



# Radical Additions onto Functionalized Chiral Cyclobutenes. Application to the Total Syntheses of Eucophylline and Eburnamine. A Biomimetic Approach Towards Leucophyllidine

Iman Traboulsi

## ► To cite this version:

Iman Traboulsi. Radical Additions onto Functionalized Chiral Cyclobutenes. Application to the Total Syntheses of Eucophylline and Eburnamine. A Biomimetic Approach Towards Leucophyllidine. Organic chemistry. Université de Bordeaux, 2020. English. NNT : 2020BORD0282 . tel-03881703

**HAL Id: tel-03881703**

**<https://theses.hal.science/tel-03881703>**

Submitted on 2 Dec 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

THÈSE PRÉSENTÉE  
POUR OBTENIR LE GRADE DE  
**DOCTEUR DE**  
**L'UNIVERSITÉ DE BORDEAUX**

ÉCOLE DOCTORALE DES SCIENCES CHIMIQUES  
SPÉCIALITÉ : CHIMIE ORGANIQUE

Par **IMAN TRABOULSI**

**Radical Additions onto Functionalized Chiral Cyclobutenes.  
Application to the Total Syntheses of Eucophylline and Eburnamine.  
A Biomimetic Approach Towards Leucophyllidine.**

Sous la direction de : Prof. Dr. Yannick LANDAIS  
Co-directeur : Dr. Frédéric ROBERT

Soutenue le 17 décembre 2020

Membres du jury :

<b>Dr. Dario M. BASSANI</b>	Université de Bordeaux	Président du jury
<b>Dr. Guillaume VINCENT</b>	Université Paris-Saclay	Rapporteur
<b>Dr. Fabrice DÉNÈS</b>	Université de Nantes	Rapporteur
<b>Dr. Géraldine MASSON</b>	ICSN, Gif-Sur-Yvette	Examinatrice
<b>Prof. Yannick LANDAIS</b>	Université de Bordeaux	Directeur de thèse
<b>Dr. Frédéric ROBERT</b>	Université de Bordeaux	Co-directeur de thèse

© 2020

Iman Traboulsi

ORCID: 0000-0002-6885-6214

All Rights Reserved

*Institut des Sciences Moléculaires (ISM – UMR 5255)*

*Bâtiment A12, Université de Bordeaux, 351 Cours de la Libération, 33405 Talence, France.*

---

# **Additions Radicalaires sur des Cyclobutènes Chiraux Fonctionnalisés. Application aux Synthèses Totales de l'Eucophylline et de l'Eburnamine. Approche Biomimétique à la Leucophyllidine**

---

**Résumé :** Cette thèse décrit une nouvelle approche à la sulfonyl-cyanation de cyclobutènes chiraux à l'aide d'un simple photosensibilisateur, le *p*-anisaldéhyde. Cette réaction a permis d'introduire un centre quaternaire tout-carboné d'une manière régio-, stéréo- et diastéréocontrôlée, *via* un processus par transfert d'énergie. Différentes stratégies d'élimination du groupement sulfonylé et d'ouverture de cycle des cyclobutanes correspondants ont ensuite été examinées afin de donner accès à une nouvelle bibliothèque de dérivés fonctionnalisés. Un processus basé sur l'utilisation de borure de nickel a permis de mettre au point une séquence en cascade en "un-pot" de réduction de la fonction nitrile / cyclisation / ouverture de cycle donnant accès à un lactame cyclique à six chaînons à partir des cyclobutanes ci-dessus. Cette chimie a été appliquée à la synthèse totale énantiosélective de l'eucophylline, le fragment sud de la leucophyllidine, un alcaloïde terpène bis-indole cytotoxique isolé de *Leuconotis griffithii* et *L. eugenifolius*. La synthèse racémique de l'éburnamine, le fragment nord, a également été réalisée en 10 étapes à partir d'un substrat commercialement disponible. Le couplage biomimétique de ces deux fragments a ensuite été examiné en utilisant un modèle de l'eucophylline.

**Mots clés :** synthèse totale, indoles alcaloïdes, cyclobutanes, ouverture de cycle, borure de nickel, chimie radicalaire, photocatalyse, synthèse asymétrique.

---

## **Radical Additions onto Functionalized Chiral Cyclobutenes. Application to the Total Syntheses of Eucophylline and Eburnamine. A Biomimetic Approach Towards Leucophyllidine**

---

**Abstract:** This Ph.D. thesis describes a new approach to the sulfonyl-cyanation of chiral cyclobutenes using *p*-anisaldehyde as a simple photosensitizer. This reaction allowed the introduction of an all-carbon quaternary stereocenter in a regio-, stereo- and diastereocontrolled manner, *via* an energy transfer process. Different strategies for the removal of the sulfonyl group and ring-opening of the corresponding cyclobutanes were then examined to provide access to a new library of functionalized derivatives. A process based on the use of nickel boride allowed the development of a "one-pot" cascade sequence of nitrile function reduction/cyclization/ring-opening giving access to a six-membered cyclic lactam from above cyclobutanes. This chemistry has been applied to the enantioselective total synthesis of eucophylline, the southern fragment of leucophyllidine, a cytotoxic bis-indole terpene alkaloid isolated from *Leuconotis griffithii* and *L. eugenifolius*. The racemic synthesis of eburnamine, the northern fragment, was also performed in 10 steps from a commercially available substrate. The biomimetic coupling of these two fragments was then examined using an eucophylline model.

**Keywords:** total synthesis, indole alkaloids, cyclobutanes, ring-opening, nickel boride, radical chemistry, photocatalysis, asymmetric synthesis.

**Institut des Sciences Moléculaire (ISM)  
Groupe de synthèse organique et substances naturelles (ORGA)  
Université de Bordeaux – CNRS-UMR 5255  
351 cours de la Libération, 33405 Talence, France**





*To the leading women in Science, who changed the standards*



## Acknowledgment

First, I would like to thank the Jury members: Dr. Guillaume Vincent, Dr. Fabrice Dénès, Dr. Géraldine Masson, and Dr. Dario M. Bassani for accepting to judge my work, for taking time to read my manuscript, and for the valuable scientific discussions we had during the Ph.D. defense.

I would like to thank my supervisor, Professor Yannick Landais, for giving me the opportunity to work on this project. Such work allowed me to invest in a well-diversified organic synthesis, to visit many chemical reactions, and to manipulate under very different conditions. This rich experience will stay with me wherever I go. Needless to say, I am not anymore that same rookie who started her research three years ago. Huge thanks also for our scientific discussions on various reactions and retrosynthetic plans. But also, for providing me with all the necessary reagents and lab materials, and two fume hoods to use as I please, a luxury I will miss dearly!

I also thank my co-supervisor, Dr. Frédéric Robert, for the positive encouragement throughout these years, and for always having faith in me. I am grateful for the time we spent analyzing complex NMR spectra and weird unexpected products, for discussing mechanisms, techniques, and ideas.

Thanks again to Dr. Dario M. Bassani for our fruitful collaboration during the mechanistic studies of the *p*-anisaldehyde photosynthesized sulfonyl-cyanation reaction. Thank you for your kind help and explanation of the photochemical principles. I valued our collaboration a lot.

Huge thanks to the Ministry of Higher Education and Research of France for the Ph.D. grant, and the University of Bordeaux and the doctoral school for giving me this opportunity and the needed facilities. Thanks to the ISM administration team, you made my Ph.D. much easier, with all the administration papers and the week-end accesses that went smoothly. I can't thank you enough. I am so grateful for the analytical platform CESAMO! You were enormously helpful. Thanks for facilitating my analyses even when it wasn't obvious and easy.

Thanks to Jonathan for the HPLC analyses and for always caring to provide all the needed materials and reagents. Also, thanks to my labmates: Claire, Damien, Martin, Camille, Gülbin, Nivesh, Suman, Govind, Anthony, Paul, Alix, Matteo, Dickson, Shuai... And all my friends in Bordeaux.

Finally, I would like to thank the French singers of the 80s and 90s, without you, my lab work wouldn't be the same. And thank you Martin and Damien for "tolerating" my singing and my music preferences. I know it wasn't your cup of tea!!



# Table of Contents

<i>Résumé de Recherche</i> .....	5
<i>List of Abbreviations, Acronyms, and Symbols</i> .....	15
<i>General Introduction</i> .....	19
1. From nature to chemotherapeutic agents: the story .....	21
2. Leucophyllidine: isolation, structure, and biological activity .....	23
3. Monoterpene indole alkaloids: origin and dimers biosynthesis .....	24
4. Initial retrosyntheses of leucophyllidine, eucophylline and eburnamine.....	28
5. Thesis outline.....	30
<i>Chapter I: Free-Radical Chemistry &amp; Photoredox Catalysis</i> .....	33
<i>Part I: Free-radical chemistry: General aspects and reactivity</i> .....	35
1. Free-radicals: a historical perspective .....	35
2. Free-radicals: concept .....	36
3. Structure of carbon-centered radicals .....	36
4. Stability of radicals .....	37
5. Polarity effect on radical reactivity .....	38
6. Radical reactions.....	40
6.1. Radical fragmentation.....	40
6.2. Radical chain reactions .....	40
6.3. Radical chain mediators.....	41
6.4. Hydrogen transfer reactions.....	41
6.5. Atom transfer reactions or halogen group transfer .....	42
6.6. Radical carbo-allylation reactions .....	43
6.7. Carbo-alkenylation and alkynylation reactions .....	44
6.8. Free-radical carbo-cyanation of olefins .....	45
6.9. Free-radical carbo-oximation reaction.....	45
7. Conclusion .....	47
<i>Part II: Photoredox catalysis: Basic concepts and applications</i> .....	48
1. Photoredox catalysis in organic synthesis.....	48
2. Photoredox catalysis: basic concepts.....	49
2.1. Nature of light.....	49
2.2. Absorption of light.....	50
2.3. Excited states .....	51
2.4. Deactivation pathways of excited states .....	51
3. Intramolecular deactivation of excited states.....	51
3.1. Jablonski-Perrin diagram .....	51
4. Intermolecular deactivation of excited states.....	52
4.1. Photoinduced electron transfer (PET).....	53
4.2. Energy transfer.....	57
5. Sulfonyl radicals in photoredox catalysis .....	60
5.1. Photocatalyzed cyanation reactions .....	60
5.2. Photoredox-catalyzed sulfonyl-cyanation of olefins .....	61
6. Conclusion .....	64
<i>Chapter II: The Chemistry of Small Rings</i> .....	65
1. Carbocyclic small-sized rings in nature.....	67
2. Geometry of small carbocyclic rings.....	68
2.1. Structure and bonding.....	69
2.2. Hybridization and molecular orbitals .....	70
2.3. Bond strengths .....	71
2.4. Energies of small carbocycles.....	72
3. Construction of cyclopropene/butene templates .....	72
3.1. Synthesis of cyclopropenes.....	73

3.2. Synthesis of cyclobutenes .....	73
<b>4. Reactivity: cyclopropene vs. cyclobutene.....</b>	<b>77</b>
4.1. Reported radical additions to cyclopropenes .....	78
4.2. Reported radical additions to cyclobutenes .....	80
<b>5. Conclusion .....</b>	<b>81</b>
<b>Chapter III: Radical Additions onto Cyclobutenes &amp; Further Derivatization .....</b>	<b>83</b>
<b>Part I: Synthesis and radical additions onto chiral cyclobutenes .....</b>	<b>85</b>
<b>1. Development of an enantioselective synthesis of cyclobutenes .....</b>	<b>85</b>
1.1. Synthesis of cyclobutene sulfides following Narasaka's procedure .....	85
1.2. Enantiomeric excess measurements.....	86
1.3. Desulfurization of cyclobutyl sulfides .....	88
<b>2. Radical additions onto enantiopure cyclobutenes.....</b>	<b>90</b>
2.1. Carbo-alkynylation of cyclobutenes .....	91
2.2. Carbo-cyanation of cyclobutenes.....	93
2.3. Atom transfer radical addition of haloalkanes onto cyclobutenes .....	94
2.4. Sulfonyl-cyanation of cyclobutenes.....	98
<b>3. Conclusion .....</b>	<b>107</b>
<b>Part II: Ring-opening studies and cyclobutane derivatives.....</b>	<b>109</b>
<b>1. Development of cyclobutane ring-opening reactions.....</b>	<b>109</b>
<b>2. Ring-opening reaction through Samarium(II) diiodide .....</b>	<b>110</b>
2.1. Samarium(II) diiodide in organic synthesis .....	111
2.2. Reported SmI <sub>2</sub> -mediated ring-opening processes .....	111
2.3. Application of SmI <sub>2</sub> -promoted reaction on sulfonyl cyclobutanes .....	114
<b>3. The Ramberg-Bäcklund Rearrangement (RBR) .....</b>	<b>115</b>
3.1. Ramberg-Bäcklund reaction in the literature .....	116
3.2. Application of the Ramberg-Bäcklund reaction .....	117
<b>4. Nitrile fragment hydrolysis and lactone synthesis .....</b>	<b>119</b>
4.1. Application of hydrolytic lactonization on $\delta$ -hydroxy nitrile <b>237</b> .....	120
4.2. RBR reaction on diol <b>255</b> .....	122
<b>5. Base-promoted sulfone elimination .....</b>	<b>122</b>
<b>6. Ring-opening reaction through ozonolysis .....</b>	<b>127</b>
6.1. Application of ozonolysis on cyclobutenes .....	128
<b>7. Ring-opening reaction through Donor-Acceptor systems.....</b>	<b>130</b>
7.1. Introduction to Donor-Acceptor (DA) ring systems .....	131
7.2. Synthesis of amino-cyclobutane precursor and attempts for the ring cleavage .....	132
7.3. Reduction of the nitrile group in cyclobutane <b>284</b> .....	133
7.4. Ring-opening investigations .....	135
<b>8. Ring-opening through the transformation of malleable functions.....</b>	<b>137</b>
8.1. Ring-opening through a hydroxide system .....	137
8.2. Addition of masked alcohol onto cyclobutene.....	138
8.3. Ring-opening through radical denitration.....	139
8.4. Ring-opening through malonyl decarboxylation .....	141
<b>9. Conclusion .....</b>	<b>148</b>
<b>Chapter IV: Total Synthesis of (+)-Eucophylline.....</b>	<b>149</b>
<b>1. Isolation, structure, and biogenesis of eucophylline .....</b>	<b>151</b>
<b>2. Reported total syntheses of eucophylline .....</b>	<b>153</b>
<b>3. Retrosynthetic strategy towards the synthesis of (+)-eucophylline .....</b>	<b>155</b>
<b>4. Cyclobutane ring-opening through nitrile-reduction, cyclization and decarboxylation .....</b>	<b>156</b>
4.1. Nickel borohydride-catalyzed reduction of cyano-cyclobutanes .....	157
4.2. Reported nickel boride-mediated ring-opening .....	162
<b>5. Attempts to access mono-ester lactams.....</b>	<b>163</b>
<b>6. Synthesis of bicyclic lactam model bearing a protected alcohol chain.....</b>	<b>164</b>
<b>7. Synthesis of bicyclic lactam model bearing a propyl chain.....</b>	<b>167</b>
<b>8. Synthesis of bicyclic lactam model bearing an ethyl side chain.....</b>	<b>169</b>

<b>9. Construction of the tetracyclic scaffold of eucophylline .....</b>	<b>174</b>
9.1. Construction of tetracyclic scaffold using <i>ortho</i> -propenylanilines.....	174
9.2. Construction of tetracyclic scaffold using amino benzonitrile <b>354</b> .....	176
<b>10. Pathways towards the vinyl-quinoline construction from the amine precursor .....</b>	<b>176</b>
10.1. Incorporation of the vinyl fragment through a diazonium salt .....	177
10.2. Incorporation of the vinyl fragment through a triflate .....	178
10.3. Incorporation of the vinyl fragment through a bromide .....	179
10.4. Suzuki coupling and <i>O</i> -demethylation .....	180
<b>11. Application towards the enantioselective synthesis of eucophylline .....</b>	<b>181</b>
<b>12. Analytical data of (+)-eucophylline .....</b>	<b>182</b>
<b>13. Summary scheme of the total synthesis of (+)-eucophylline .....</b>	<b>192</b>
<b>14. Conclusion .....</b>	<b>193</b>
<b><i>Chapter V: Total Synthesis of Eburnane Alkaloids .....</i></b>	<b><i>195</i></b>
<b>1. Eburnane-vincane alkaloids: isolation, biogenesis, and structure .....</b>	<b>197</b>
<b>2. Bioactivity and pharmacological potential of indole alkaloids .....</b>	<b>199</b>
<b>3. Common approaches towards the eburnane pentacyclic core .....</b>	<b>199</b>
<b>4. Illustration of the most popular syntheses of eburnamnine and eburnamine.....</b>	<b>201</b>
<b>5. Revised retrosynthetic strategy towards enantioselective eburnamine .....</b>	<b>207</b>
<b>6. Modified retrosynthetic strategy of eburnamine .....</b>	<b>208</b>
6.1. Synthesis of the precursors .....	209
6.2. Synthesis of hemiaminal <b>499</b> using hypervalent iodine .....	212
6.3. Synthesis of hemiaminal <b>499</b> under photooxidative conditions .....	213
6.4. Synthesis of hemiaminal <b>499</b> under basic conditions .....	215
<b>7. Construction of ring C under oxidative conditions .....</b>	<b>216</b>
<b>8. Alternative approach for the synthesis of eburnamine .....</b>	<b>217</b>
8.1. Selective reduction of the lactam's carbonyl.....	218
8.2. Synthesis of carbinolamine lactone <b>470</b> .....	220
8.3. Construction of the eburnane alkaloids .....	220
<b>9. Summary scheme of the total synthesis of (±)-eburnamine .....</b>	<b>221</b>
<b>10. Application towards the enantioselective total synthesis of eburnamine.....</b>	<b>222</b>
<b>11. Conclusion .....</b>	<b>224</b>
<b><i>Chapter VI: Biomimetic Coupling Studies Towards Leucophyllidine.....</i></b>	<b><i>227</i></b>
<b>1. Introduction.....</b>	<b>229</b>
<b>2. Biomimetic coupling in the synthesis of dimeric indole alkaloids .....</b>	<b>229</b>
<b>3. Proposed strategy for the biomimetic coupling in leucophyllidine .....</b>	<b>232</b>
<b>4. Biomimetic coupling studies .....</b>	<b>233</b>
<b><i>General Conclusion .....</i></b>	<b><i>237</i></b>
<b>1. General conclusion.....</b>	<b>239</b>
<b>2. Perspectives .....</b>	<b>244</b>
<b><i>Experimental Part.....</i></b>	<b><i>247</i></b>
<b><i>Experimental Part - General Information .....</i></b>	<b><i>249</i></b>
<b>1. Chemical reagents and apparatus .....</b>	<b>249</b>
<b>2. Visible-light irradiation system .....</b>	<b>251</b>
<b>3. UV-light irradiation system .....</b>	<b>252</b>
<b><i>Experimental Part - Chapter III.....</i></b>	<b><i>254</i></b>
<b>1. General procedures for chapter III.....</b>	<b>254</b>
<b>2. Synthesis of starting materials.....</b>	<b>258</b>
<b>3. Synthesis of alkynyl sulfides.....</b>	<b>264</b>
<b>4. Narasaka's asymmetric [2+2] cycloaddition .....</b>	<b>266</b>
<b>5. Desulfurization reaction.....</b>	<b>269</b>
<b>6. Carbo-alkynylation reaction.....</b>	<b>272</b>
<b>7. Atom transfer radical addition reaction .....</b>	<b>273</b>
<b>8. Eosin-photocatalyzed sulfonyl-cyanation reaction .....</b>	<b>277</b>
<b>9. <i>p</i>-Anisaldehyde-photosensitized sulfonyl-cyanation reaction .....</b>	<b>280</b>



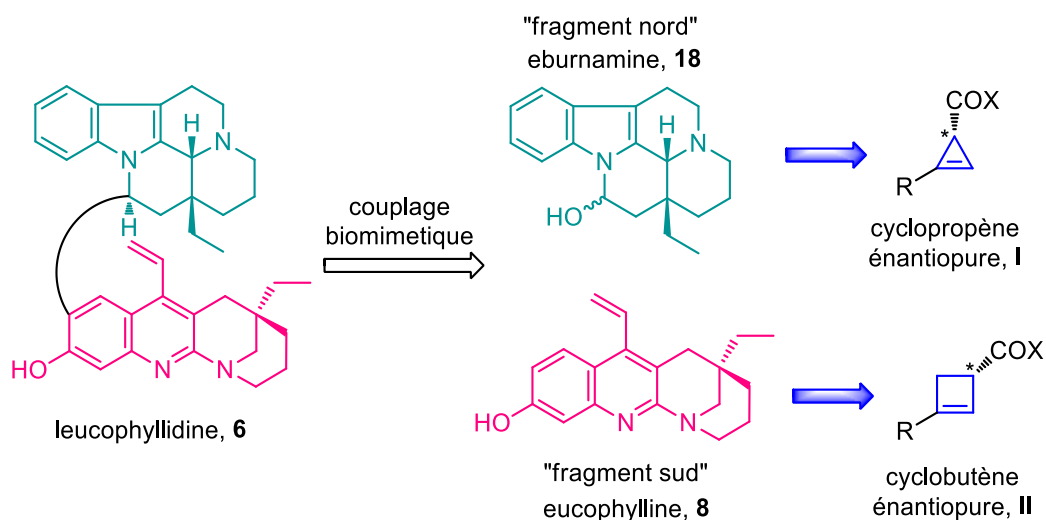
10. SmI <sub>2</sub> -mediated ring-opening reaction .....	285
11. Ramberg-Bäcklund reaction.....	291
12. Formation of lactone.....	292
13. Transesterification reaction .....	295
14. Base-mediated sulfone elimination reaction .....	296
15. Ring-opening through ozonolysis .....	299
16. 1,4-Conjugate addition to cyclobutenes .....	300
17. Enantiomeric excess measurements .....	309
18. Crystallographic data .....	317
<i>Experimental Part – Chapter IV .....</i>	<i>318</i>
1. General procedures for chapter IV .....	318
2. Synthesis of the starting materials.....	320
3. Synthesis of <i>nor</i> -ethyleucophylline .....	322
4. Synthesis of chiral azabicyclo[3.3.1]nonane skeleton models .....	325
4.1. Alcohol-protected side chain model .....	325
4.2. Propyl side chain model.....	330
5. Total synthesis of (+)-eucophylline .....	334
6. Enantiomeric excess measurements .....	347
7. Crystallographic data .....	350
<i>Experimental Part – Chapter V.....</i>	<i>351</i>
1. General procedures for chapter V.....	351
2. Synthesis of the starting materials.....	351
3. Total synthesis of (±)-eburnamine.....	351
<i>References and Notes.....</i>	<i>361</i>

## Résumé de Recherche

### **Titre : Additions Radicalaires sur des Cyclobutènes Chiraux Fonctionnalisés. Application aux Synthèses Totales de l'Eucophylline et de l'Eburnamine. Approche Biomimétique à la Leucophyllidine**

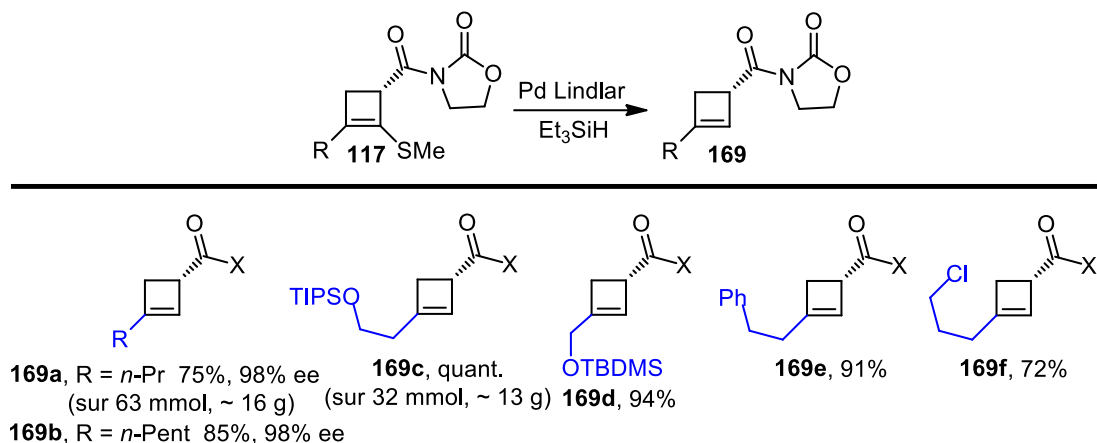
**Mots clés :** synthèse totale, indoles alcaloïdes, cyclobutanes, ouverture de cycle, borure de nickel, chimie radicalaire, photocatalyse, synthèse asymétrique.

La leucophyllidine **6**, un alcaloïde indole cytotoxique, a été isolée il y a dix ans par Kam et ses collègues<sup>1</sup> de l'écorce de tige de *Leuconotis griffithii*, une apocynacée malaise (Schéma I). Mis à part sa structure originale, les études biologiques ont montré qu'elle présente une cytotoxicité *in vitro* prononcée envers les cellules KB humaines résistantes à la vincristine ( $IC_{50} = 2,92 \mu\text{g} / \text{ml}$ ), ce qui en fait une cible potentielle comme agent antitumoral.<sup>2</sup> Cette thèse vise à élaborer la première synthèse de cet alcaloïde dimérique par le couplage biomimétique de ses deux fragments, l'éburnamine **18** et l'eucophylline **8**. Les synthèses totales de ces alcaloïdes ont été planifiées à partir de synthons cyclopropène **I** et cyclobutène **II**, respectivement. Pour atteindre cet objectif, de nouvelles méthodologies ont été développées afin d'accéder aux stéréocentres quaternaires tout-carbonés présents dans ces substrats. L'ouverture de cycle des dérivés obtenus a délivré une série de molécules chirales fonctionnalisées adaptées à leur application dans les stratégies de synthèse totale.



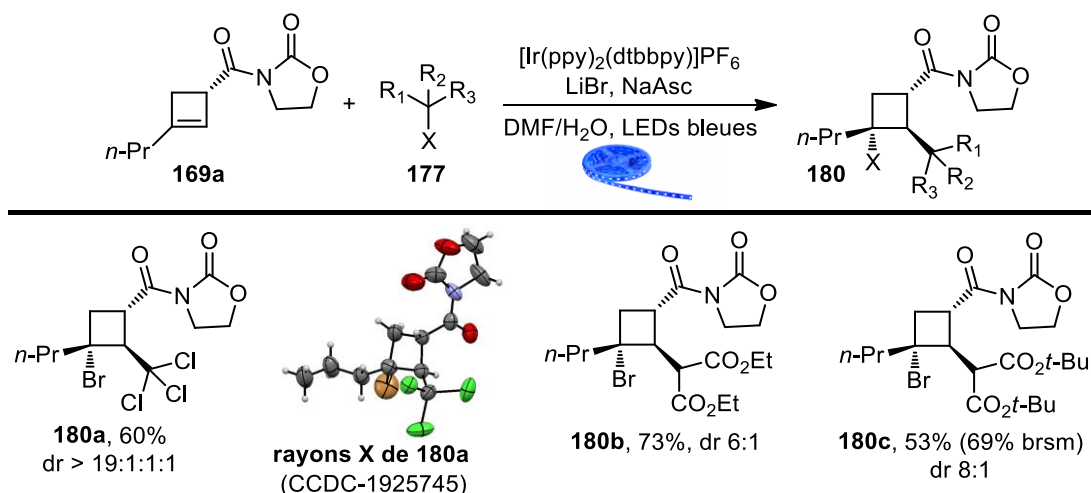
**Schéma I.** Rétrosynthèse de la leucophyllidine **6**.

Au cours de la première partie de la thèse, une synthèse énantiosélective efficace de cyclobutènes **169** a été décrite, inspirée des travaux de recherche de Narasaka et de ses collaborateurs<sup>3</sup> sur les cycloadditions [2+2] asymétriques pour fournir le cyclobutène **117**. Les cyclobutènes **169** fonctionnalisés ont été ensuite obtenus par une réaction de désulfuration sur une échelle pouvant atteindre la dizaine de grammes, avec d'excellents rendements et énantiosélectivités (Schéma II).



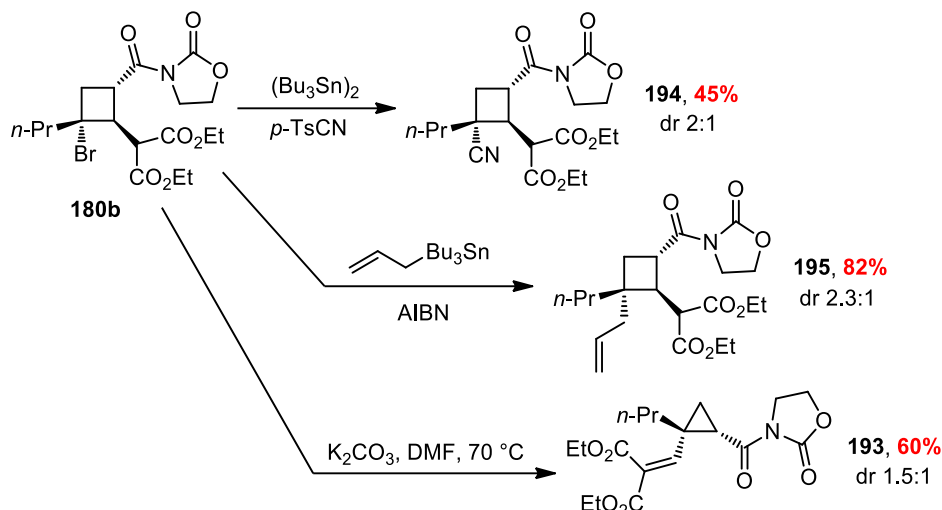
**Schéma II.** Synthèse de cyclobutènes par désulfuration. X = oxazolidinone.

La réactivité de ces cyclobutènes en conditions radicalaires a été étudiée à partir de différents types de radicaux. Dans ce contexte, les réactions de carbo-alcynylation, carbo-cyanation et d'addition de radicaux par transfert d'atome (ATRA) sur les cyclobutènes ont été étudiées. Les haloalcanes ont ainsi pu être additionnés au système  $\pi$  de cyclobutènes par réaction ATRA donnant accès aux cyclobutanes correspondants **180** avec des rendements bons à élevés (Schéma III). La diastéréosélectivité est contrôlée dans un premier temps par le groupement oxazolidinone puis ensuite par l'intermédiaire du fragment carboné additionné par voie radicalaire.



**Schéma III.** Réaction ATRA sur les cyclobutènes.

Le cyclobutène **180b** dérivé du processus ATRA a été modifié ultérieurement. Par exemple, l'atome de brome a été échangé pour un motif cyanure avec une diastéréosélectivité modeste pour donner le cyano-cyclobutane **194** en 45% de rendement (Schéma IV). De même, l'allyl cyclobutane **195** a été obtenu par échange de l'atome bromure par un groupement allyl dans les conditions de Keck.<sup>4</sup> Plusieurs essais pour ouvrir le cycle **180b** en milieu basique n'ont pas conduit aux résultats escomptés. En présence de  $K_2CO_3$ , une contraction de cycle a été observée après ouverture du cyclobutane suivie d'une cyclisation et du déplacement de l'atome de brome pour fournir le cyclopropane **193** en un rendement de 60%.

Schéma IV. Dérivés obtenus à partir du cyclobutane **180b**.

La sulfonyl-cyanation d'oléfines en utilisant l'éosine-Y comme photocatalyseur sous irradiation à la lumière visible, précédemment développée dans le groupe,<sup>5</sup> a été appliquée aux cyclobutènes. Dans ce procédé, les cyanures d'alkylsulfonyle se sont révélés d'excellents agents de transfert radicalaires pour fournir une série de dérivés polyfonctionnalisés présentant des centres quaternaires tout-carbonés, avec de bons rendements et excellentes diastéréosélectivités (Schéma V).

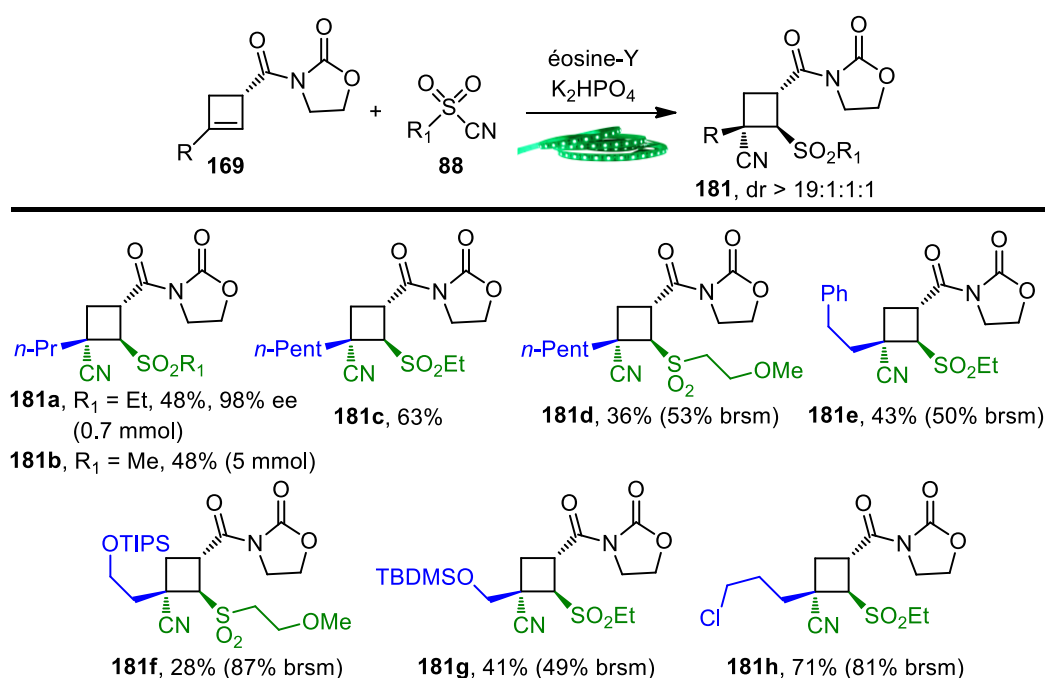
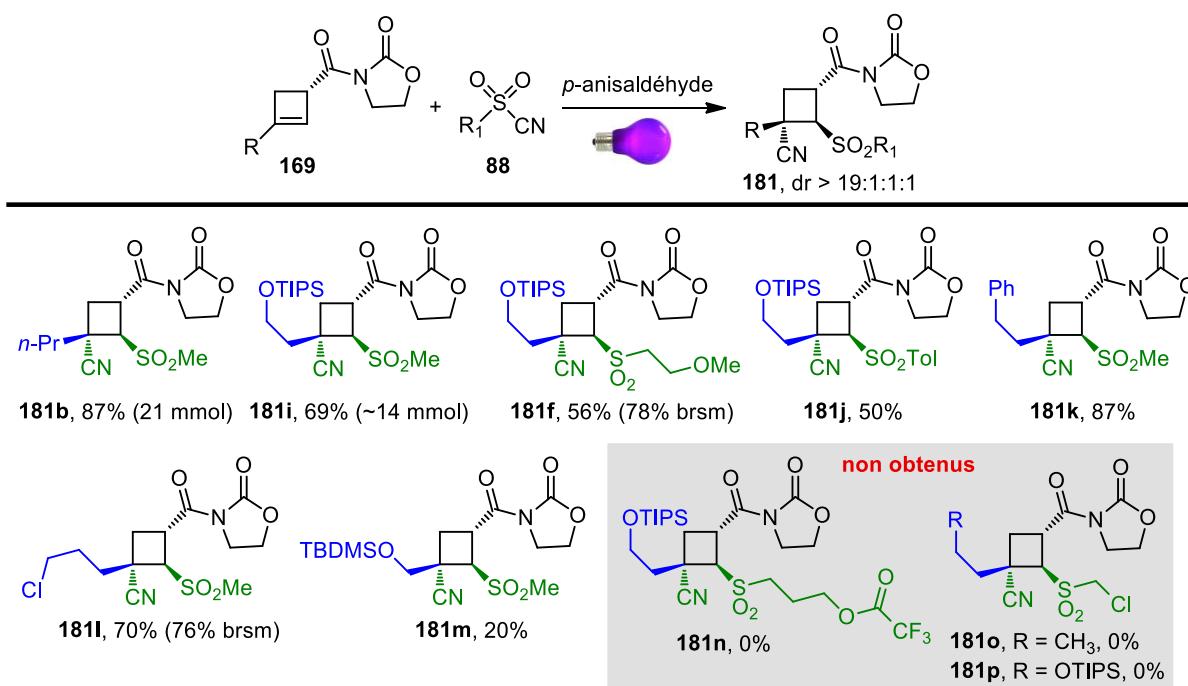


Schéma V. Sulfonyl-cyanation de cyclobutènes catalysée par l'éosine-Y.

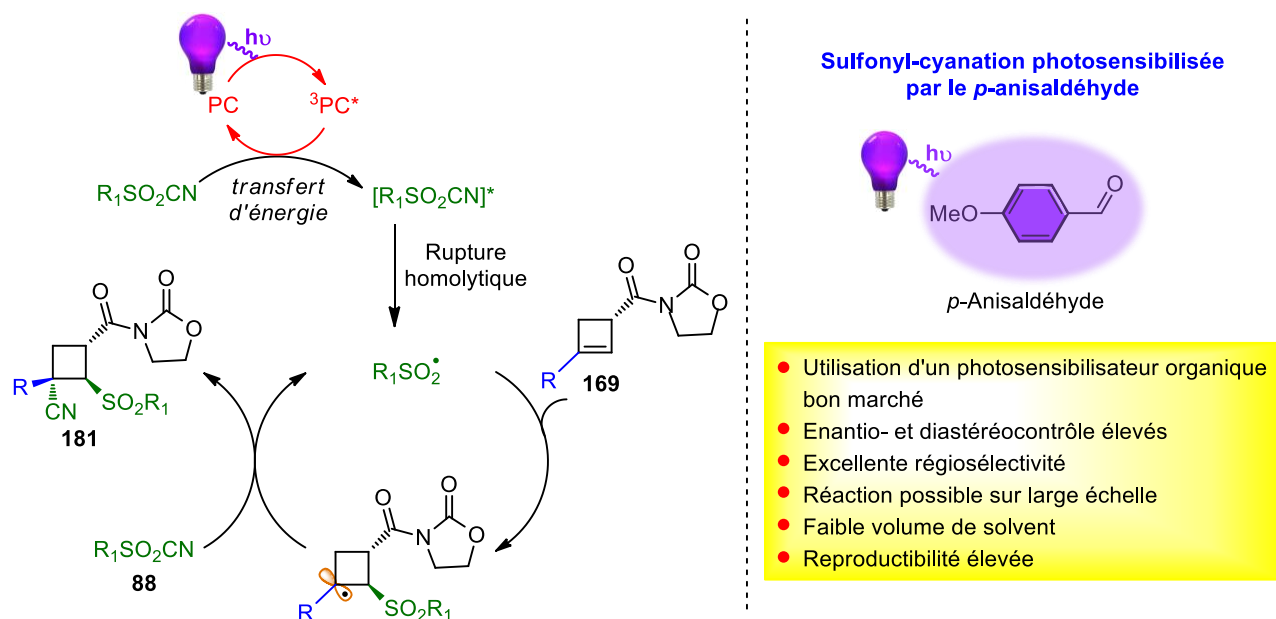
En raison de rendements modérés, une méthode de sulfonyl-cyanation plus efficace a été développée en utilisant le *p*-anisaldéhyde, comme photosensibilisateur (Schéma VI). Dans l'ensemble, les réactions sont plus propres avec ce dernier qu'avec l'éosine-Y, sont plus faciles à réaliser, ne nécessitant aucun traitement aqueux en fin de la réaction et les purifications du produit final sont plus simples même à grande échelle. Finalement, cette méthode s'est avérée compatible avec une série de groupements fonctionnels et a permis de réaliser des montées en échelle importantes

sans affecter les rendements. Par exemple, **181b** a été obtenu avec un rendement de 87% sur une échelle de 21 mmol, tandis qu'avec l'éosine-Y, le même produit a été isolé avec un rendement de 48% sur une échelle de 5 mmol.



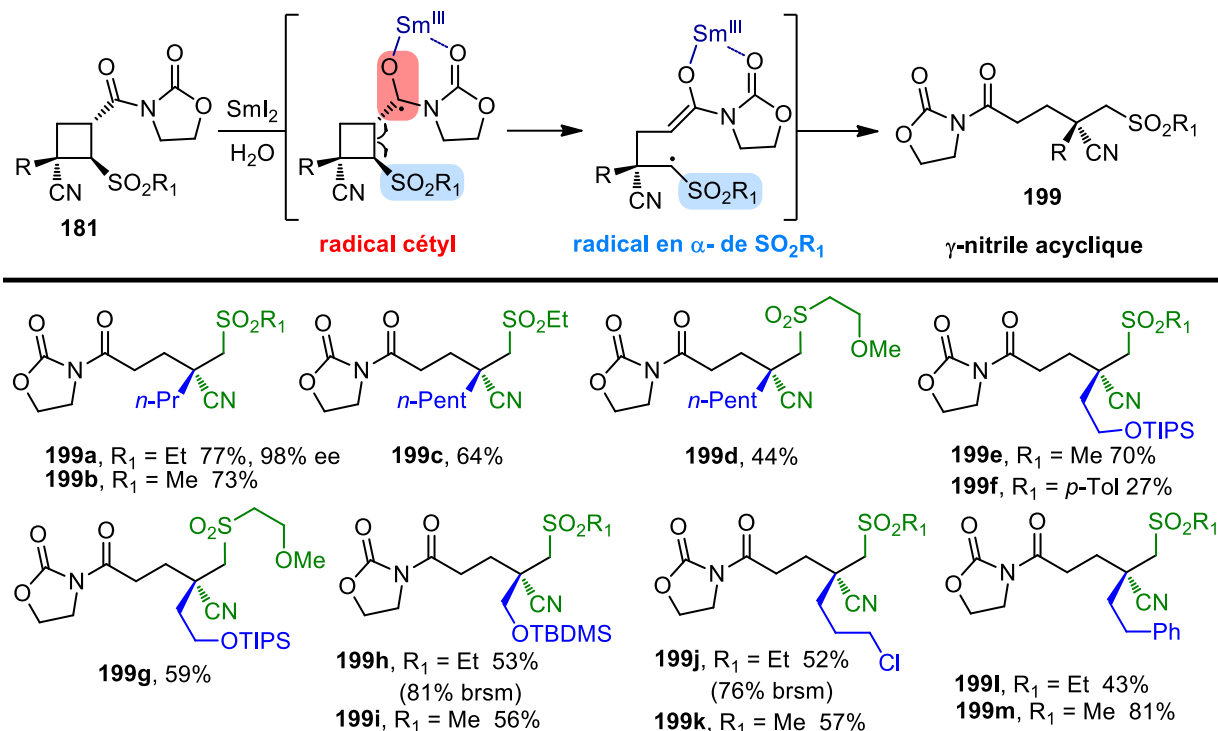
**Schéma VI.** Sulfonyl-cyanation de cyclobutènes photosensibilisée par le *p*-anisaldéhyde.

Les études mécanistiques ont montré que cette réaction procédait probablement *via* un mécanisme de transfert d'énergie impliquant l'état triplet excité du photosensibilisateur (Figure I). Ce transfert d'énergie induisant une rupture homolytique de la liaison O<sub>2</sub>S-CN à partir du sulfonylcyanure à l'état excité, pour former le radical sulfonyle. Le radical électrophile s'ajouterait alors sur l'extrémité la moins substituée de la double liaison du cyclobutène pour générer un radical β-sulfonyle. Ce dernier serait piégé par R<sub>1</sub>SO<sub>2</sub>CN, conduisant au produit attendu **181** et à un radical R<sub>1</sub>SO<sub>2</sub>•, capable de propager la réaction radicalaire en chaîne.



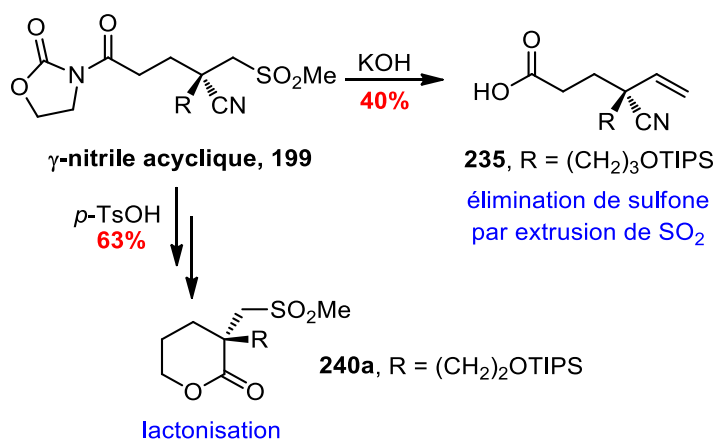
**Figure I.** Mécanisme proposé pour la sulfonyl-cyanation photosensibilisée par le *p*-anisaldéhyde.

Ces modèles polyfonctionnalisés ont ensuite été soumis à une ouverture de cycle par fragmentation radicalaire en utilisant le diiodure de samarium (Schéma VII). Les  $\gamma$ -nitriles acycliques **199** résultants ont été obtenus avec des rendements bons à élevés montrant la compatibilité de ce protocole avec une variété de substituants.



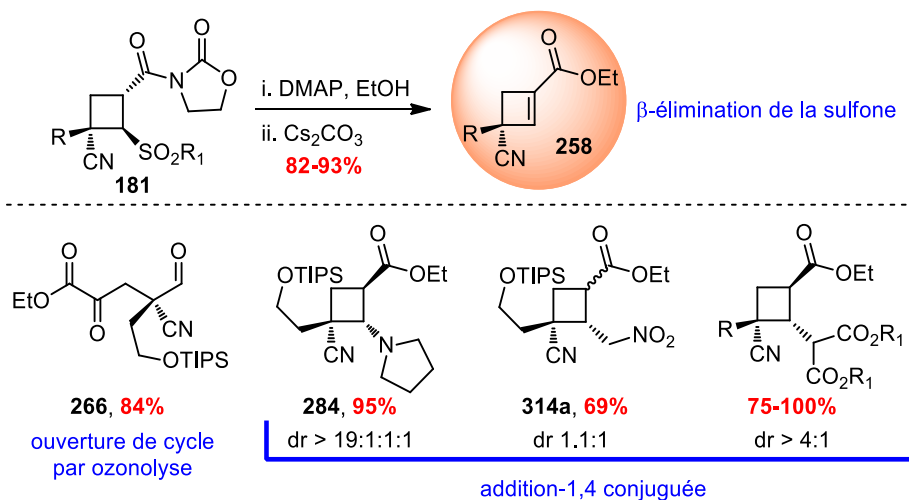
**Schéma VII.** Scope de la réaction d'ouverture de cycle médiée par  $\text{SmI}_2$ .

Les produits ouverts ont ensuite été transformés démontrant leur utilité dans la synthèse de nouveaux composés chiraux. Par exemple, le groupement sulfonyl peut être éliminé dans les conditions de réarrangement de Ramberg-Bäcklund pour fournir l'oléfine **235** avec un rendement de 40% (Schéma VIII). Bien que l'oléfine souhaitée soit obtenue, cette réaction souffre d'un problème de reproductibilité en raison des conditions dures peu compatibles avec le groupement nitrile. A partir du  $\gamma$ -nitrile acyclique **199**, une réaction de lactonisation a également été développée pour donner accès à un nouveau type de lactone **240a** portant un centre quaternaire tout-carboné, avec un rendement de 63%.



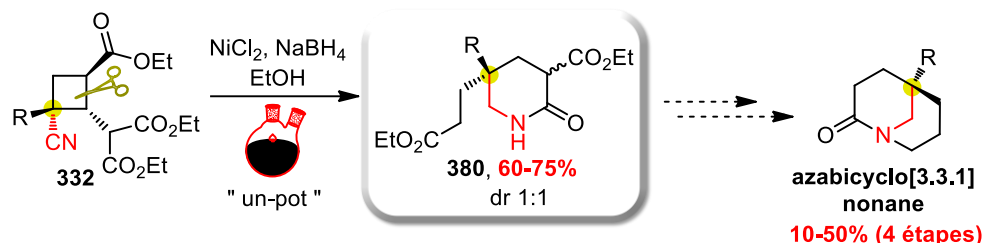
**Schéma VIII.** Dérivés du composé **199** issus de l'ouverture de cycle.

Le cyclobutane **181** a également été transformé en d'autres " synthons " utiles (Schéma IX). Par exemple, le fragment sulfone a été éliminé sous conditions basiques après plusieurs optimisations, pour donner le cyclobutène carboxylate **258** avec d'excellents rendements et reproductibilité sur une série de cyclobutanes et sur des échelles de 15-20 mmol. De nouvelles méthodes d'ouverture de cycle ont ensuite été testées sur ces cyclobutènes. Premièrement, sous des conditions d'ozonolyse, le cyclobutène carboxylate **258a** fourni le composé tricarbonyle **266** avec un rendement de 84%. Cet  $\alpha$ -cétoester-aldéhyde s'est avéré instable, et plusieurs tentatives de fonctionnalisation afin d'obtenir un dérivé stable ont échoué. Des amines, alcools, le nitrométhane ou encore des malonates ont été additionnés avec succès sur la double liaison de l'énone, pour donner les produits de Michael correspondants avec des rendements élevés à excellents. Par exemple, l'addition nucléophile d'une pyrrolidine au cyclobutène carboxylate a produit un amino-cyclobutane **284** donneur-accepteur. L'activation de ce système "push-pull" à l'aide d'un acide de Brønsted ou de Lewis n'a pas permis l'ouverture du cyclobutane en raison de la présence du fragment nitrile. La réduction de ce nitrile en amine n'a malheureusement pas contribué à favoriser l'ouverture du cycle dans le sens désiré. Le traitement des malonyl cyclobutanes en conditions basiques n'a pas non plus permis l'ouverture du cyclobutane. En général, les difficultés rencontrées lors de l'ouverture du cycle ont été attribuées à la présence du fragment nitrile sur le cyclobutane.



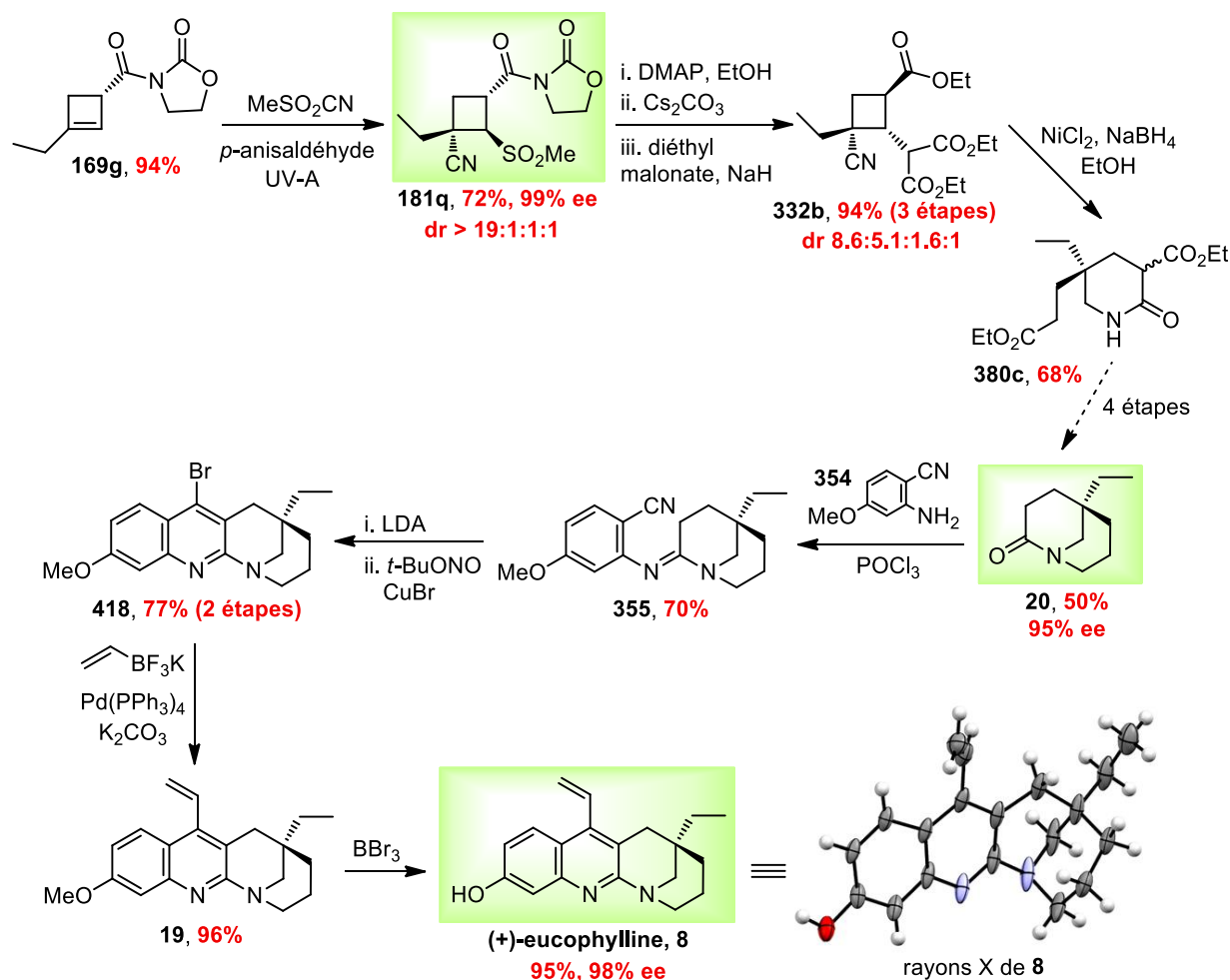
**Schéma IX.** Dérivés obtenus à partir du cyclobutane **181**.

Un dérivé de ces composés, le cyclobutyl malonate **332**, a été engagé dans une réaction de réduction en utilisant le borure de nickel comme catalyseur (Schéma X). Après optimisation, la réduction de la fonction nitrile, la cyclisation et l'ouverture du cyclobutane dans un processus en " un-pot " a été appliquée à plusieurs cyclobutanes comportant des chaînes latérales variées. Les lactames **380** résultants ont été en outre manipulés pour générer le azabicyclo[3.3.1]nonane avec des rendements faibles à modérés.



**Schéma X.** Réduction du nitrile, cyclisation et ouverture du cyclobutane, médiées par le borure de nickel.

Plus tard, la synthèse totale énantiosélective de l'eucophylline **8**, un alcaloïde comportant un squelette naphthyridine unique isolé de *Leuconotis eugenifolius*, a été envisagée basée sur la stratégie développée ci-dessus. La synthèse a été réalisée en 17 étapes à partir du but-1-yne ou 1,1-dibromobut-1-ène, avec un rendement moyen de 85% et un rendement global de 5,9% (Schéma XI). Les analyses HPLC ont confirmé l'excès énantiomérique élevé du produit naturel (ee = 98%). Dans cette synthèse, aucun groupe protecteur n'a été utilisé et seulement 9 étapes ont nécessité une purification par chromatographie. L'approche synthétique comprend la préparation d'un cyclobutène chiral permettant d'incorporer le stéréocentre quaternaire asymétrique tout-carboné selon une approche photocatalytique. Les analyses de diffraction aux rayons X ont permis d'obtenir la première structure cristalline de **8** qui a confirmé la synthèse de l'énantiomère naturel.



**Schéma XI.** Synthèse totale énantiosélective de l'eucophylline.



En parallèle, les synthèses de l'éburnamone racémique **423**, de l'*épi*-éburnamone **520**, de l'éburnamine **18** et de l'*épi*-éburnamine **424** ont été réalisées à partir de la 2-pipéridinone **379** commercialement disponible (Schéma XII). La transformation de ce lactame a permis l'élaboration de l'amine ( $\pm$ )-**517a** qui contient le centre quaternaire tout-carboné présent dans les squelettes de l'éburnane. Après plusieurs tentatives infructueuses, la synthèse totale racémique de la série éburnane a finalement été achevée, reposant sur des étapes finales établies précédemment par Wenkert.<sup>6</sup> l'éburnamine **18** et l'*épi*-éburnamine **424** ont été obtenus en 10 étapes, avec un rendement moyen d'environ 81% et un rendement global de 9,5%.

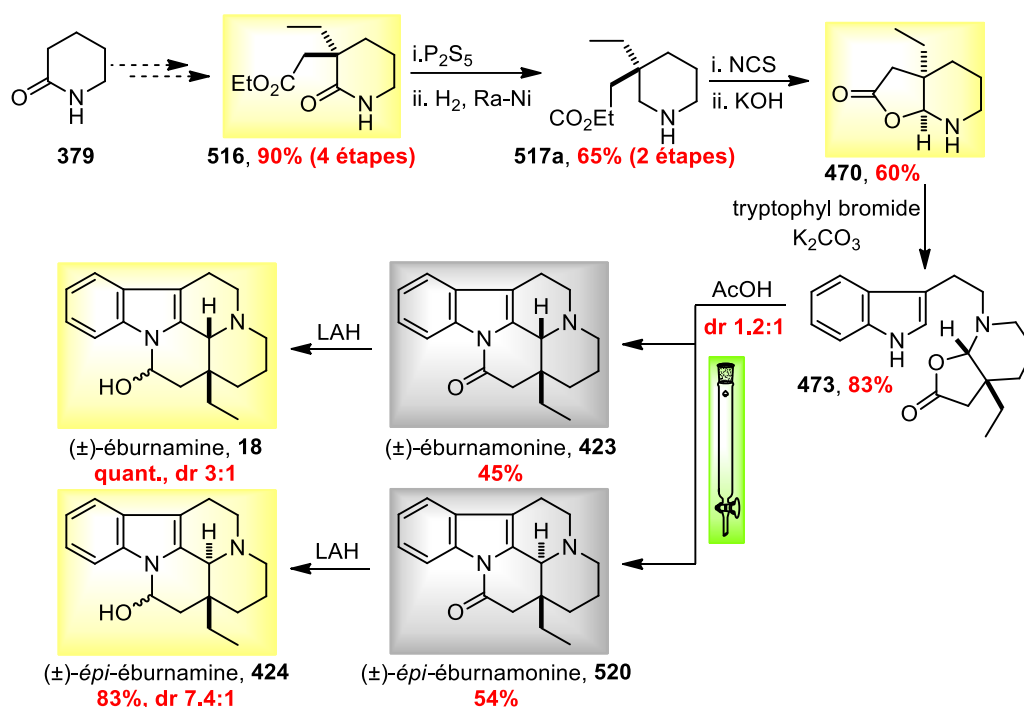


Schéma XII. Synthèse totale de l'éburnamine racémique.

La synthèse énantiosélective de (+)-**517a** envisagée à partir d'un cyclopropène chiral **31** (Schéma XIII) repose en partie sur la stratégie établie en série synthèse racémique. La synthèse de l'amine **517a** a été étudiée sur un modèle cyclopropène comportant une chaîne latérale de type propyle. Cependant, par manque de temps, l'extension de cette approche au cyclopropène **31** n'a pu être réalisée.

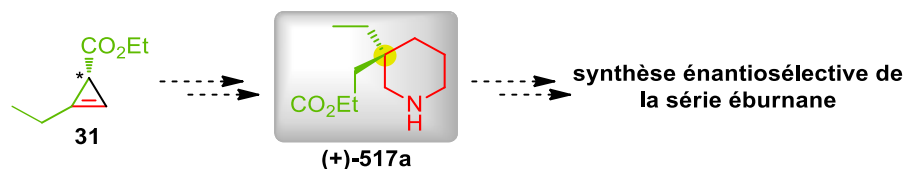
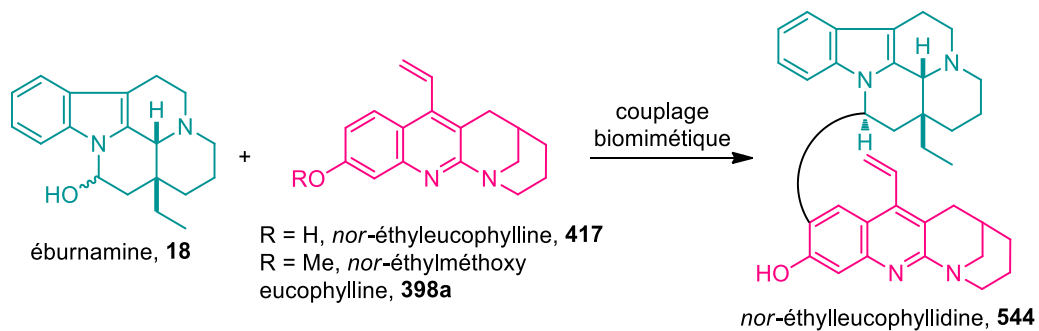


Schéma XIII. Synthèse totale énantiosélective de la série éburnane à partir d'un cyclopropène.

Enfin, la synthèse de la leucophyllidine **6** a été envisagée. Le couplage biomimétique entre ses deux fragments **8** et **18** a été étudié en utilisant l'éburnamine racémique et un modèle avancé de l'eucophylline, la *nor*-éthyleucophylline **417** (Schéma XIV). Des résultats préliminaires ont montré que le couplage en milieu faiblement acide provoque une protonation de l'azote de la *nor*-

éthyleucophylline, laquelle altère probablement la nucléophilie de l'hétérocycle et empêche le couplage.



**Schéma XIV.** Approche au couplage biomimétique et à la synthèse d'un modèle avancé de la leucophyllidine.



## List of Abbreviations, Acronyms, and Symbols

$[\alpha]_{\text{D}}^{25}$	specific rotation at 25 °C using the sodium D line
Å	ångström ( $10^{-10}$ meter)
Abs	absorbance
Ac	acetyl group
Ac <sub>2</sub> O	acetic anhydride
AcOH	acetic acid
AIBN	azobis(isobutyronitrile)
APCI	Atmospheric Pressure Chemical Ionization
aq.	aqueous
Ar	aryl group, mono or polysubstituted
atm	atmospheric pressure
ATRA	Atom Transfer Radical Addition
BDE	Bond Dissociation Energy
BF <sub>3</sub> .OEt <sub>2</sub>	boron trifluoride diethyl etherate
Bn	benzyl group
Boc	<i>tert</i> -butoxycarbonyl group
b. p.	boiling point
brsm	based on recovered starting material
<i>i</i> -Bu	<i>iso</i> -butyl
<i>n</i> -Bu	<i>normal</i> -butyl
<i>t</i> -Bu	<i>tert</i> -butyl
<i>n</i> -BuLi	<i>normal</i> -butyllithium
<i>t</i> -BuOH	<i>tert</i> -butyl alcohol
<i>t</i> -BuOK	potassium <i>tert</i> -butoxide
<i>t</i> -BuONO	<i>tert</i> -butyl nitrite
(Bu <sub>3</sub> Sn) <sub>2</sub>	bis(tributyltin)
Bz	benzoyl group
<i>c</i>	mass concentration
°C	degree Celsius
CAS	Chemical Abstracts Service
cat.	catalytic quantity/catalyst
Chz	carboxybenzyl group
CCDC	Cambridge Crystallographic Data Centre
CD	circular dichroism
CFL	Compact Fluorescent Lamp
CI	Chemical Ionization
comp. mix.	complex mixture
COSY	COrrrelation SpectroscopY
<i>m</i> -CPBA	<i>meta</i> -chloro perbenzoic acid
$\Delta/\delta$	delta
$\delta$	chemical shift
$\Delta$	refluxing conditions
$\Delta G$	Gibbs free energy
$\Delta H$	change in enthalpy
$\Phi$	diameter/quantum yield
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DEPT	Distortionless Enhancement by Polarization Transfer
DFT	Density Functional Theory
dia	diastereomer
DIBAL-H	diisobutylaluminum hydride
DIPA	diisopropylamine
DIPEA	<i>N,N'</i> -diisopropylethylamine
DMA	dimethylacetamide

---



---

<b>DMAP</b>	4-dimethylaminopyridine
<b>DME</b>	dimethoxyethane
<b>DMF</b>	dimethylformamide
<b>DMP</b>	Dess-Martin periodinane
<b>DMPU</b>	<i>N,N'</i> -dimethylpropyleneurea
<b>DMSO</b>	dimethylsulfoxide
<b>dr</b>	diastereomeric ratio
<b>DTBHN</b>	di- <i>tert</i> -butylhyponitrite
<b><math>\epsilon</math></b>	molar extinction coefficient
<b>E</b>	undefined electrophile
<b>€</b>	euro currency
<b>E<sup>0</sup></b>	standard reduction potential
<b>E<sub>ox</sub></b>	oxidation potential
<b>E<sub>red</sub></b>	reduction potential
<b>EDCI</b>	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
<b>EDG</b>	Electron Donating Group
<b>EDTA</b>	ethylenediaminetetraacetic acid
<b>ee</b>	enantiomeric excess
<b>Eq.</b>	equation
<b>eq.</b>	equivalent
<b>er</b>	enantiomeric ratio
<b>ESI</b>	ElectroSpray Ionization
<b>Et</b>	ethyl group
<b>eV</b>	electron volt
<b>EWG</b>	Electron Withdrawing Group
<b><i>F</i></b>	Faraday constant
<b><i>fac</i>-Ir</b>	<i>facial</i> -Iridium
<b>FD</b>	Field Desorption
<b>FI</b>	Field Ionization
<b>FID</b>	Flame Ionization Detector
<b><math>\gamma</math></b>	gamma
<b>GC-MS</b>	Gas Chromatography-Mass Spectrometry
<b>[H]</b>	reduction
<b>HAT</b>	Hydrogen Atom Transfer
<b>HFIP</b>	1,1,1,3,3,3-hexafluoroisopropanol
<b>Hg-h<math>\nu</math></b>	irradiation with a mercury lamp
<b>HMPA</b>	hexamethylphosphoramide
<b>HOMO</b>	Highest Occupied Molecular Orbital
<b>HPLC</b>	High-Performance Liquid Chromatography
<b>HRMS</b>	High Resolution Mass Spectrometry
<b>HSQC</b>	Heteronuclear Single Quantum Coherence
<b>h<math>\nu</math></b>	photochemical activation
<b>Hz</b>	Hertz
<b>IBX</b>	2-iodoxybenzoic acid
<b>IC<sub>50</sub></b>	half maximal inhibitory concentration
<b>IR</b>	Infrared Spectroscopy
<b><i>J</i></b>	coupling constant
<b>J</b>	Joule
<b>k</b>	rate constant
<b>kcal</b>	kilocalorie
<b>KHMDS</b>	potassium bis(trimethylsilyl)amide
<b>kJ</b>	kilojoule
<b><math>\lambda</math></b>	lambda/wavelength
<b>L<sup>*</sup></b>	Undefined chiral ligand
<b>LA</b>	Lewis acid
<b>LAH</b>	lithium aluminium hydride
<b>LDA</b>	lithium diisopropylamide
<b>LED</b>	Light-Emitting Diode
<b>LiHMDS</b>	lithium bis(trimethylsilyl)amide

---

<b>Lindlar</b>	5% Pd-CaCO <sub>3</sub> + quinoline
<b>LiTMP</b>	lithium tetramethylpiperidide
<b>LRMS</b>	Low Resolution Mass Spectrometry
<b>LUMO</b>	Lowest Unoccupied Molecular Orbital
<b><i>m</i></b>	<i>meta</i> position
<b>M</b>	concentration (mole per liter)
<b>M</b>	undefined metal
<b>MHz</b>	megahertz
<b>mmHg</b>	millimeter of mercury
<b>mmol</b>	millimole
<b>mol</b>	mole
<b>mol %</b>	molar percentage
<b>m. p.</b>	melting point
<b>Ms</b>	mesylate group
<b>MS</b>	molecular sieves
<b>MsCl</b>	methanesulfonyl chloride
<b>MW</b>	molecular weight
<b><i>v</i></b>	wavenumber
<b><i>n</i></b>	molar number
<b>NaAsc</b>	sodium L-ascorbate
<b>NCS</b>	<i>N</i> -chlorosuccinimide
<b>nd</b>	not determined
<b>nm</b>	nanometer (10 <sup>-9</sup> meter)
<b>NMO</b>	<i>N</i> -methylmorpholine <i>N</i> -oxide
<b>nOe</b>	Nuclear Overhauser Effect
<b>NOESY</b>	Nuclear Overhauser Effect Spectroscopy
<b>nr</b>	no reaction
<b>ns</b>	nanosecond
<b>Ns</b>	nosyl group
<b>Nu</b>	undefined nucleophile
<b><i>o</i></b>	<i>ortho</i> position
<b>[O]</b>	oxidation
<b>ORTEP</b>	Oak Ridge Thermal Ellipsoid Plot Program
<b><i>p</i></b>	<i>para</i> position
<b>PC</b>	photocatalyst
<b>[Pd]</b>	palladium
<b>PDC</b>	pyridinium dichromate
<b>PE</b>	petroleum ether
<b>PET</b>	Photoinduced Electron Transfer
<b>PG</b>	protecting group
<b>Ph</b>	phenyl group
<b>pH</b>	potential of Hydrogen
<b>PIDA</b>	(diacetoxyiodo)benzene
<b>PIFA</b>	(bis(trifluoroacetoxy)iodo)benzene
<b>p<i>K</i><sub>a</sub></b>	−log <sub>10</sub> ( <i>K</i> <sub>a</sub> ), the negative logarithm, to the base 10, of the acid dissociation constant ( <i>K</i> <sub>a</sub> )
<b>PPA</b>	polyphosphoric acid
<b>ppm</b>	parts per million
<b>quant.</b>	quantitative
<b>R, R<sub>n</sub>, R'</b>	undefined alkyl group
<b>Ra-Ni</b>	Raney <sup>®</sup> -nickel
<b>R<sub>f</sub></b>	retention factor
<b>rt</b>	room temperature (20-25 °C)
<b>sat.</b>	saturated
<b>S<sub>N</sub>2</b>	bimolecular nucleophilic substitution
<b>SOMO</b>	Singly Occupied Molecular Orbital
<b><i>t/tert</i></b>	<i>tertio</i>
<b>TBAF</b>	tetrabutylammonium fluoride
<b>TBDMS/TBS</b>	<i>tert</i> -butyldimethylsilyl group
<b>TBDMSCI/TBSCI</b>	<i>tert</i> -butyldimethylsilyl chloride

<b>TEMPO</b>	2,2,6,6-tetramethylpiperidine- <i>N</i> -oxy radical
<b>Tf</b>	triflate group
<b>TFA</b>	trifluoroacetic acid
<b>TFAA</b>	trifluoroacetic anhydride
<b>Tf<sub>2</sub>O</b>	triflic anhydride
<b>THF</b>	tetrahydrofuran
<b>TIPS</b>	triisopropylsilyl group
<b>TIPSCI</b>	triisopropylsilyl chloride
<b>TLC</b>	Thin Layer Chromatography
<b>TMP</b>	2,2,6,6-tetramethylpiperidine
<b>TMS</b>	trimethylsilyl group
<b>TMSCHN<sub>2</sub></b>	(trimethylsilyl)diazomethane
<b>TMSCl</b>	trimethylsilyl chloride
<b>TMSCN</b>	trimethylsilyl cyanide
<b>TOF</b>	time-of-flight
<b><i>p</i>-Tol</b>	<i>para</i> -tolyl group
<b>TPAP</b>	tetrapropylammonium perruthenate
<b>Ts</b>	tosyl group
<b>TTMS</b>	tris(trimethylsilyl)silane
<b>UV</b>	ultraviolet irradiation
<b>UV-A</b>	electromagnetic spectral range between 325 and 400 nm
<b>V-40</b>	1,1'-azobis(cyclohexanecarbonitrile)
<b>W-hν</b>	irradiation with a tungsten lamp
<b>wt. %</b>	weight percent
<b>X</b>	undefined halogen

# ***General Introduction***

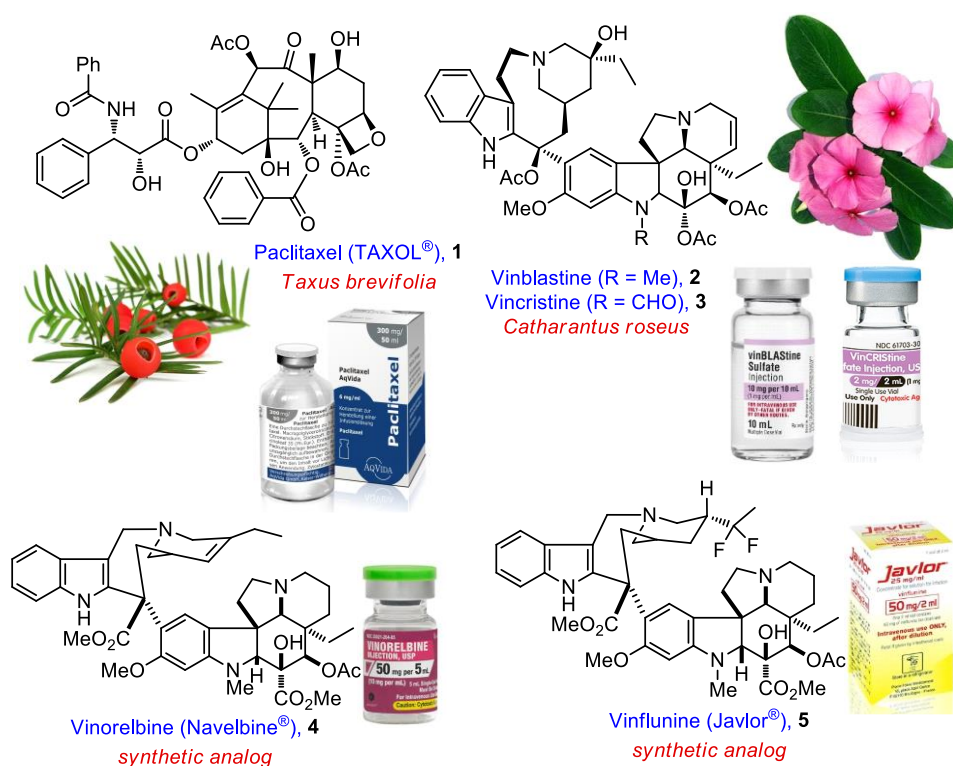




## 1. From nature to chemotherapeutic agents: the story

For centuries, scientific minds were constantly inspired and often challenged by Mother Nature, to invent in their laboratories new technologies and sophisticated architectures of high value. The chemical society, for example, showed a particular interest in recreating molecules with significant therapeutic activities. Among these, come the anti-cancer agents.

During a plant screening program for the search for potential medication, Paclitaxel (TAXOL® [Bristol-Myers Squibb Co., Princeton, NJ]) **1** was isolated in the 1960s from the bark of Pacific yew tree, *Taxus brevifolia*, and it took several years to get it in its pure form (Figure 1).<sup>7</sup> This molecule, a member of the taxanes family, presented an interesting chemical structure and a level of cytotoxicity that led to deeper investigations. Nowadays, TAXOL® is the best-selling chemotherapeutic drug ever manufactured, and it is used for the treatment of lung, breast, and ovarian cancers, as well as leukemia and Kaposi's sarcoma.<sup>8</sup>



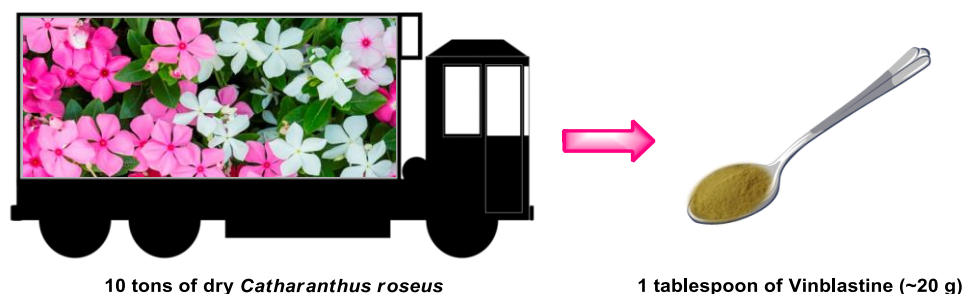
**Figure 1.** Examples of anti-cancer drugs derived from natural and synthetic sources.

Other molecules, Vinblastine (Vincal leukoblastine; Velban® or Velbé®) **2** and Vincristine (leurocristine; Oncovin®) **3** were isolated from Madagascar periwinkle, *Catharantus roseus*, previously called *Vinca rosea*. These *Vinca* alkaloids have been used over the last 50 years, for the treatment of cancer diseases including Hodgkin's disease and leukemia.<sup>9,10</sup> Inspired by their structures, Potier and co-workers<sup>11</sup> pursued the development of new synthetic analogs, by altering the original templates. Their efforts produced vinorelbine **4** (anhydrovinblastine) as the first active semi-synthetic *Vinca* alkaloid. This was later introduced to the market by the French pharmaceutical company Pierre Fabre Medicaments under the name Navelbine®, for the treatment of several types of cancers, like breast and non-small cell lung cancers. The research division of Pierre Fabre also

launched Vinflunine (Javlor<sup>®</sup>) **5**, a *gem*-difluoro derivative of vinorelbine. Preclinical results showed that vinflunine is more active than vinorelbine, vinblastine, and vincristine against many cancer cells.<sup>12</sup> This case demonstrated that the *Vinca* alkaloids drug family is a prospective area, and that the design of a new generation of alkaloids with promising pharmacological properties, is always possible.<sup>13</sup>

Other anti-cancer agents isolated from natural resources are continuously emerging, such as epothilones, camptothecin, Manzamine A, and others.<sup>14,15</sup> Some of them are already available in the market and approved by the Food and Drug Administration (FDA).<sup>16</sup>

Despite their presence in nature, these bioactive substances are often isolated in very low yields, not enough to supply the human needs and the advanced clinical trials. For instance, paclitaxel is present in the Pacific yew in a yield of 0.001% to 0.01% of the dry bark weight depending on the tree's age.<sup>17</sup> To carry out the early clinical studies of its activity, toxicity, and its drug compatibility, no less than 9,000 yew trees have been cut down in the North American forests to result in 27,000 kg of dry bark.<sup>8,18</sup> Besides, 2,500 trees would be needed to treat about 300 patients, while the number of candidates for paclitaxel therapy was estimated in tens of thousands in the 90s alone.<sup>19</sup> Similarly, the vinblastine's actual content in Madagascar periwinkles is extremely low with an average of 0.002%.<sup>20</sup> For the pharmaceutical production, approximately half a ton of dry leaves is needed to isolate, after extraction, only 1 gram of vinblastine.<sup>21</sup> For comparison, one could imagine needing a truck of 10 tons of dry *Catharanthus roseus* to provide only a tablespoon of vinblastine, the equal of 20 grams (Figure 2).



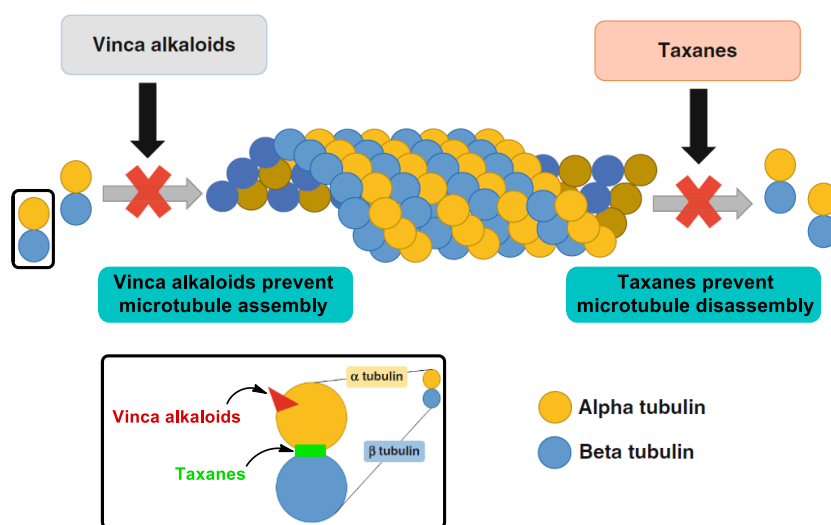
**Figure 2.** An illustration of the quantity of dry plants necessary for the isolation of 20 grams of vinblastine.

Even if the natural resources can be grown at a large scale, the production of trees of a certain age is revealed much more delicate, impracticable, and time-consuming. In addition, the isolation and purification of the abovementioned substances from many by-products, are rather tedious. Such rarity and difficulty of purification were well translated into the high cost of these chemical agents. For example, 1 kg of vinblastine **2** costs around a million-dollar or ~18 times the current price of gold per kg, while the world annual production is 12 kg. Similarly, 1 kg of vincristine **3** costs 3.5 million dollars, and the world annual production is about 1 kg.<sup>22</sup>

At this point comes the duty of chemists in developing straightforward and time- and cost-efficient strategies, to synthetically access these compounds, without depleting the ecological system. In the 1980s, chemists discovered that the leaves of the European yew (*Taxus baccata*), as abundant and renewable resources, contain a high amount of 10-deacetylbaccatin III, a structure close to

paclitaxel. This precursor was synthetically converted to paclitaxel and completely solved the supply problems.<sup>8,23</sup> In the case of vinblastine, a semi-synthesis was also optimized, combining nature's gems and chemists' creativity. Two molecules, vindoline and catharanthine, more abundant within the periwinkle of Madagascar, were efficiently coupled by means of chemical reactions, leading to the dimer alkaloid vinblastine.<sup>24,25</sup>

At the biological level, the vinca alkaloids' mode of action was found to be like the paclitaxel's in that they bind to tubulin molecules. By binding, they interrupt the microtubule dynamics during the cell division, which leads to mitosis inhibition and apoptosis.<sup>26</sup> Still, the taxanes bind at a different site than the vinca alkaloids and cause slow cell division by blocking the degradation of microtubules and preventing their shrinkage, rather than destabilizing the microtubules and inhibiting their polymerization (Figure 3).



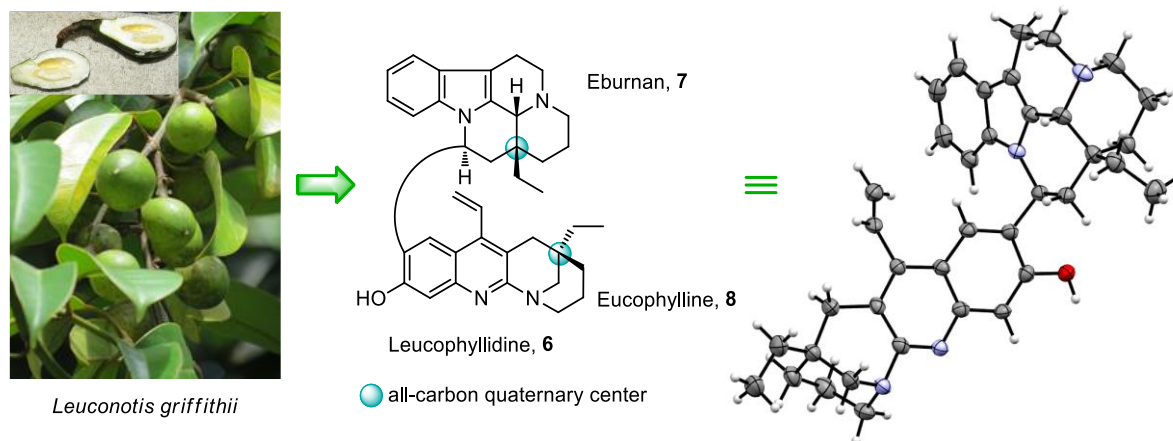
**Figure 3.** Mechanism of action of vinca alkaloids and taxanes on microtubules.<sup>26</sup>

Despite this bioactivity and the developed clinical therapies, new generations of cancer cells have been showing mutation and became more resistant to these drugs.<sup>27</sup> Herein rises the need for new analogs with enhanced activity and efficiency. As well, a better selectivity for the sick cells is required to limit the severe side effects caused by the toxicity of the current drugs. Therefore, the isolation and identification of natural products as new chemotherapeutic agents became a principal aim in this dynamic area.

## 2. Leucophyllidine: isolation, structure, and biological activity

In this context, leucophyllidine **6**, a potential therapeutic agent, was isolated a decade ago by Kam and co-workers<sup>1</sup> as a minor alkaloid from the stem-bark of Malayan *Leuconotis griffithii*, in a yield of 0.00071 g/kg. Subsequent crystallization from Et<sub>2</sub>O/EtOAc gave pale yellowish crystals with m. p. = 215-217 °C and  $[\alpha]_D = -138^\circ$  (CHCl<sub>3</sub>,  $c = 0.18$ ). X-ray studies of these crystals in combination with other spectroscopic data indicated an unprecedented structure of a bis-indole alkaloid. This dimer results in the union between an eburnan unit **7** (northern fragment) and a novel tetrahydrobenzo-[b][1,8]naphthyridine template **8** (southern fragment) (Figure 4). The chromophore

**8** was isolated a year later by Morita *et al.*<sup>2</sup> from *Leuconotis eugenifolius* and named Eucophylline.<sup>2</sup> Leucophyllidine **6** was also found in the same plant extract and was isolated in a yield of 0.044%.



**Figure 4.** Structure of leucophyllidine **6** confirmed by X-ray diffraction analysis.<sup>1</sup>

(Picture source: flickr.com)

The leucophyllidine structure was regarded as original and complex because it represents the first member of new structural bis-indole alkaloids based on the constituent monomeric units.<sup>28</sup> As well, the naphthyridine half, the eucophylline, is a new unprecedented vinylquinoline skeleton. Stereochemically, this dimeric natural product features four stereogenic centers, where two of them are all-carbon quaternary centers. These characteristics eventually, make the molecule a challenging target at the synthetic level.

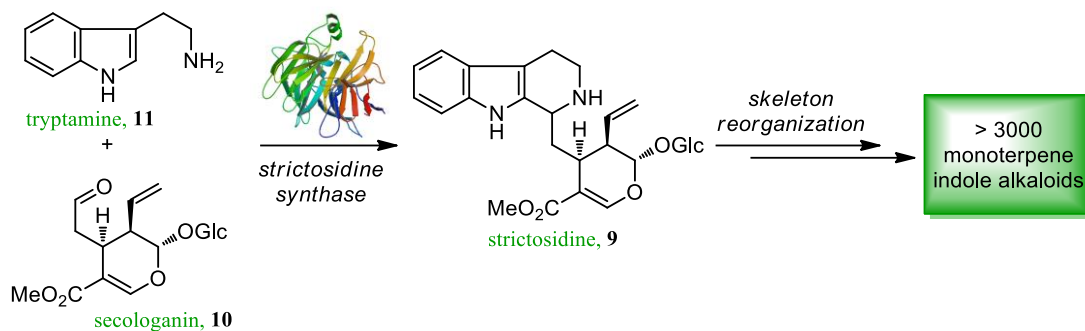
Besides its intricate architecture, the eburnan-quinoline dimer **6** exhibits a pronounced *in vitro* selective cytotoxicity towards drug-sensitive and vincristine-resistant human KB cells (VJ300), with half inhibitory concentrations (IC<sub>50</sub>) of 2.95 and 2.92 µg/mL, respectively.<sup>1</sup> Also, Morita *et al.*<sup>2</sup> found that leucophyllidine **6** inhibits the NO production stimulated by LPS dose-dependently with IC<sub>50</sub> of 7.1 µM, and shows high cell viability of J774.1 at a concentration of 7.1 µM.

### 3. Monoterpene indole alkaloids: origin and dimers biosynthesis

Leucophyllidine and dimeric alkaloids are proposed to be formed through the coupling of monomeric subunits belonging to the monoterpenoid indole alkaloids class.<sup>29</sup> This class contains over 3000 known members and more than 40 structural types. It represents one of the largest natural product families that have intriguing structural complexity and significant biological profile.<sup>30</sup> Monoterpene indole alkaloids were mainly isolated from three plant families: *Rubiaceae*/*Naucleaceae* RUB, *Loganiaceae*/*Strychnaceae* LOG, and *Apocynaceae* APO. Leucophyllidine and the before cited *Vinca* alkaloids **2** and **3** for example, belong to the latter family.

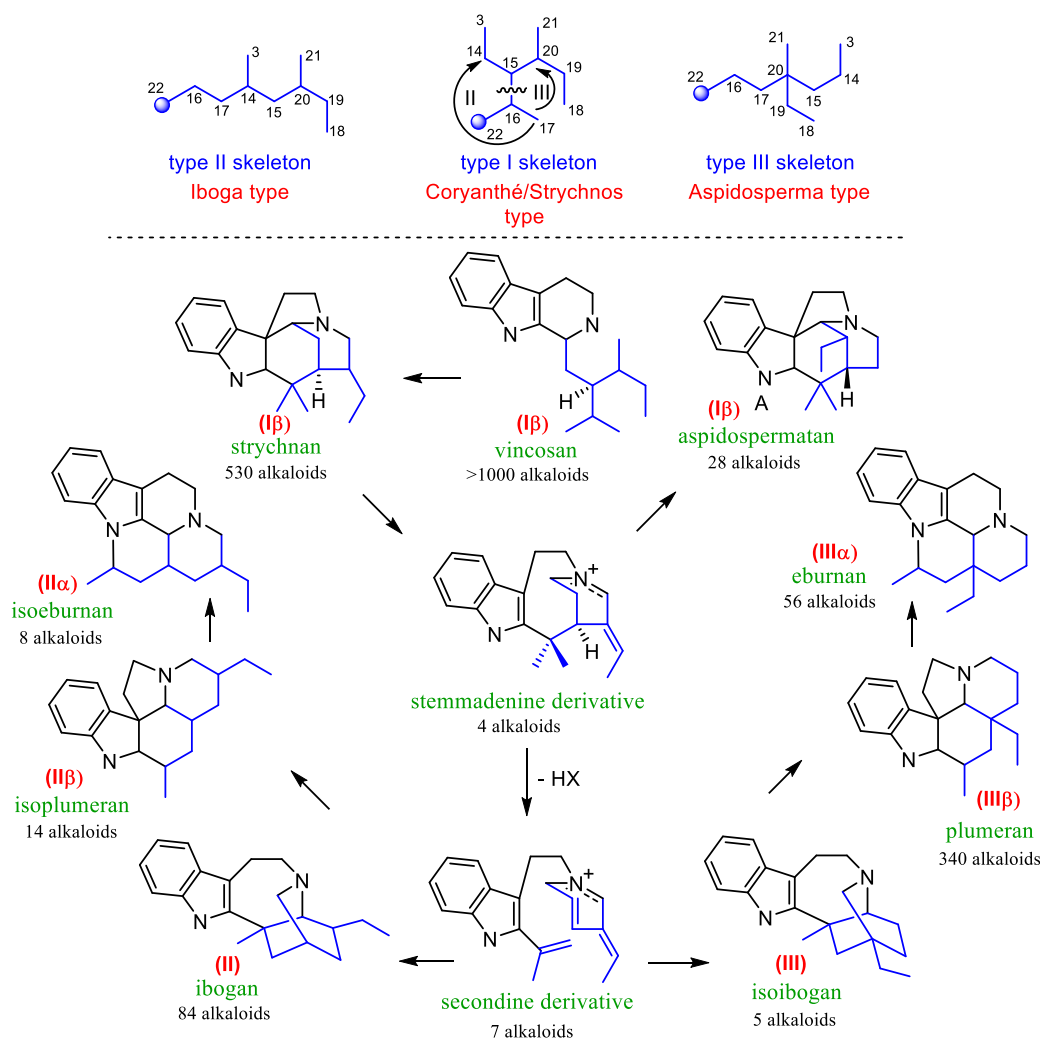
In spite of their structural diversity, the monoterpene indole alkaloids are all biosynthetically derived from a basic intermediate, strictosidine **9**. Strictosidine, in turn, is obtained by the condensation between a secoiridoid unit, secologanin **10**, and an indole segment, tryptamine **11**, through a strictosidine synthase-catalyzed Pictet-Spengler reaction (Scheme 1).<sup>30–32</sup> Both the chemo-

and stereoselectivities of the enzyme were proven to be high *in vitro* (i.e., under cell-free conditions).<sup>29</sup>



**Scheme 1.** Nature's synthesis of the key precursor of indole alkaloids.

Subsequently, strictosidine **9** undergoes controlled germination through series of cyclization, rearrangement, ring contraction, ring expansion, or oxidation reactions, to provide a collection of skeletally diverse natural products (Scheme 2).<sup>33</sup> These tryptamine-derived alkaloids can be classified into several classes based on the type of the rearranged skeleton I, II, or III. Further discussion of the structural variation of those types of alkaloids is out of the scope of this manuscript. Yet, one could appreciate the design intelligence of Mother Nature creating so many diverse structures in elegant and thought-provoking ways.



**Scheme 2.** System of monomeric indole alkaloids derived from Secologanin.<sup>29</sup>

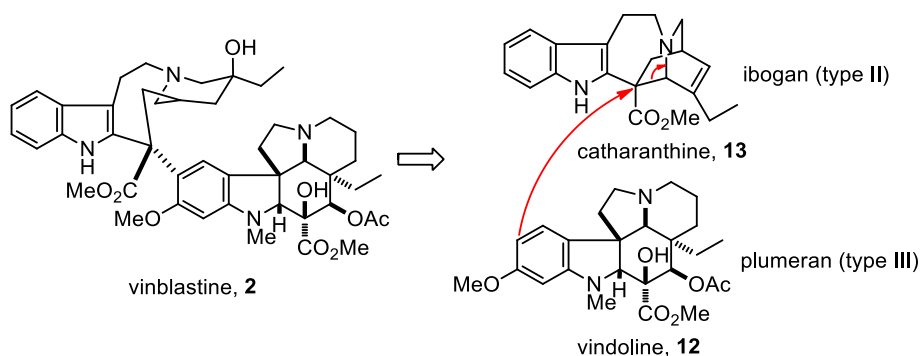
The coupling of type I, II, and III monomeric alkaloids leads to quite common heterodimeric indole alkaloids (having two different basic skeletons) and more rarely to homodimeric indole alkaloids (having the same basic skeleton). A chemotaxonomic network could be found between different monomeric indole alkaloids in plants (Table 1). This biogenetic network was established based on the three-dimensional structure, taxonomic structure, and standard reaction mechanisms. From the chemotaxonomic point of view, the presence of heterodimers proves that the different monomers coexist in the species from which they were isolated. Therefore, their biogenetic relatedness is rather evident.

	Skeleton	Homodimer	Heterodimer*
Type I	vincosan I $\alpha$	found	24
	strychnan I $\beta$	found	
	aspidospermatan I $\beta$	indirect	
Type II	ibogan II	found	4
	isoplumeran II $\beta$	not found	
	isoeburnan II $\alpha$	not found	
Type III	isoibogan III	not found	11
	plumeran III $\beta$	found	
	eburnan III $\alpha$	found	

\* number of dimeric alkaloids beside bracket

**Table 1.** Summary of the chemotaxonomic relationships between indole alkaloids.<sup>29</sup>

The presence of these intricate dimeric structures in nature led to the development of biogenetic hypotheses during the 1950s, and they were experimentally verified years later through *in vivo* feeding experiments with radioactively labeled precursors.<sup>34</sup> As well, these biogenetic pathways were often taken into serious consideration when a synthetic design is proposed. For instance, the proposed biogenetic synthesis of vinblastine **2** involves a direct coupling between vindoline **12** and catharanthine **13**, having respectively a plumeran (type III) and ibogan (type II) skeletons (Scheme 3).<sup>35</sup> This hypothesis was verified *in vivo* by the incorporation of radiolabeled precursors (tritium), as well as synthetically through several reported total syntheses.<sup>36,37</sup>

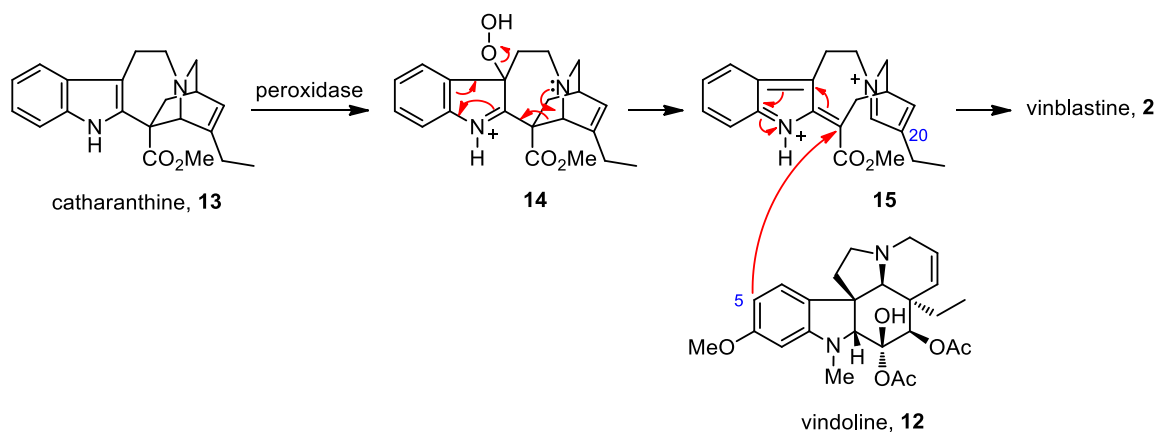


**Scheme 3.** Vinblastine biogenetic synthesis through dimerization between vindoline and catharanthine.

This coupling was proposed to result from a peroxidase-catalyzed reaction, where catharanthine **13** is oxidized into a hydroperoxide **14** (Scheme 4).<sup>38</sup> An electronic reorganization results in the departure of the hydroperoxide as a leaving group, to give an electrophilic intermediate **15**. The latter

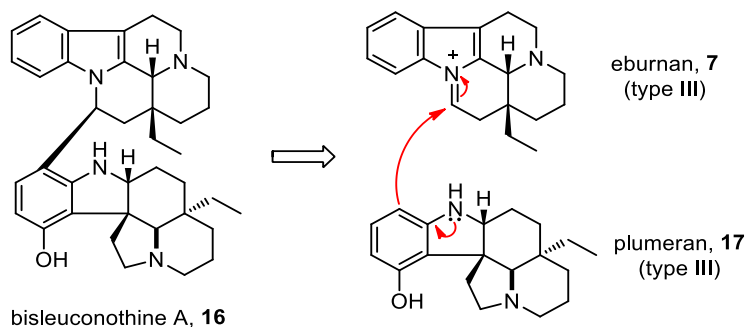


undertakes a nucleophilic addition of the C-5 center of vindoline elaborating an adduct which is later reduced by NADH (Nicotinamide Adenine Dinucleotide). Vinblastine is then obtained through oxidation at the C-20 carbon center.



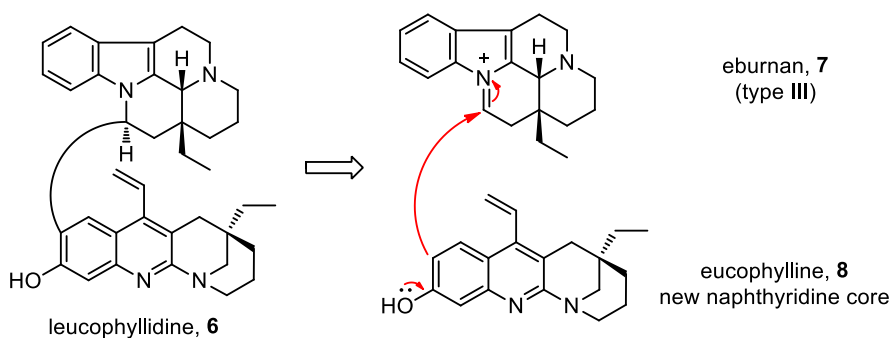
**Scheme 4.** Peroxidase-catalyzed biosynthesis of vinblastine.<sup>38</sup>

During their studies, Morita and co-workers proposed biogenetic pathways for several alkaloids through a Mannich-type coupling reaction between type I and III skeletons.<sup>39–41</sup> For example, an eburnan-aspidosperma alkaloid, bisleuconothine A **16**, isolated from *Leuconotis griffithii*, is believed to result from a Mannich-type reaction between a plumeran **17** and an eburnan **7** skeletons (Scheme 5).<sup>42</sup>



**Scheme 5.** Proposed biomimetic coupling of bisleuconothine A.<sup>42</sup>

About the leucophyllidine, the team directed by Kam proposed a similar Mannich-type coupling between the vinylquinoline alkaloid **8** and the eburnamine-type motif **7** to furnish the bis-indole **6** (Scheme 6).<sup>1</sup>

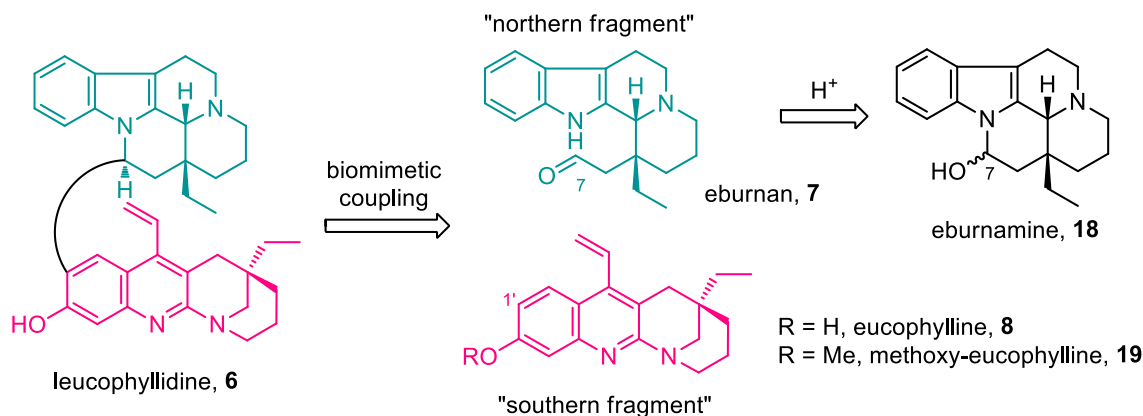


**Scheme 6.** Proposed biosynthesis of leucophyllidine, by Kam *et al.*<sup>1</sup>



#### 4. Initial retrosyntheses of leucophyllidine, eucophylline and eburnamine

The three natural substances leucophyllidine **6**, eburnan **7** and eucophylline **8** are present in the *Leuconotis* species. In addition, Morita and co-workers<sup>2</sup> isolated both leucophyllidine and eucophylline from the same source, *Leuconotis eugenifolius*. These findings altogether suggest that the biogenetic analysis proposed by Kam *et al.*,<sup>1</sup> would most probably produce leucophyllidine **6** through a Mannich-type reaction. Using acidic sources, the biomimetic coupling would proceed between the C-1' electron-rich center of eucophylline **8** and the C-7 electrophilic center of eburnan **7** (Scheme 7). The latter itself derives from eburnamine **18**. Methoxy-eucophylline **19** may also be envisioned in the coupling process as another reactive analog of **8** in the Mannich reaction.



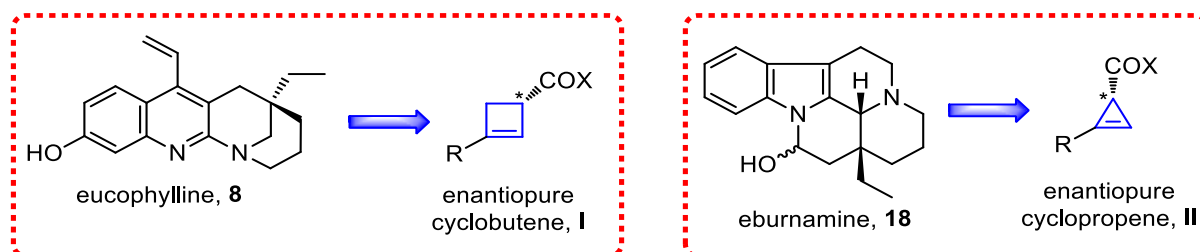
**Scheme 7.** Retrosynthesis of leucophyllidine **6**.

The fact that leucophyllidine presents a complex molecular framework with four stereocenters, requires an attentive investigation and a development of solid enantio- and diastereo-controlled strategies. Indeed, the construction of quaternary centers has been a challenging synthetic topic over the years. More specifically, all-carbon quaternary stereocenters (carbon atoms bonded to four carbon substituents) are difficult to create with high level of stereoselectivity.<sup>43–45</sup>

Such an issue is of considerable importance in the domain of the synthesis of natural molecules. In this work, it was suggested that manipulating small chiral ring systems, would allow the control of the stereochemistry of the synthesized molecules. As in cyclic systems, the diastereoselectivity is more predictable than in the acyclic counterparts.<sup>46</sup> Such rings would be functionalized through radical approaches, as suitable ways for the formation of all-carbon quaternary centers. This center would be created by the addition of a carbon fragment such as a nitrile. The corresponding compound would serve as a key precursor for a broad spectrum of synthetic applications (*e.g.*, reduction of the nitrile to access the amino-methyl group). Subsequently, the nucleophilic amino group would react with various electrophilic agents to create complex structures, such as indole rings. Apart from the interest in generating stereo-controlled all-carbon quaternary centers, the reactivity of small rings towards radical reactions will be revisited, as little is known in this domain. This would add knowledge to the already-known facts about these carbocycles.

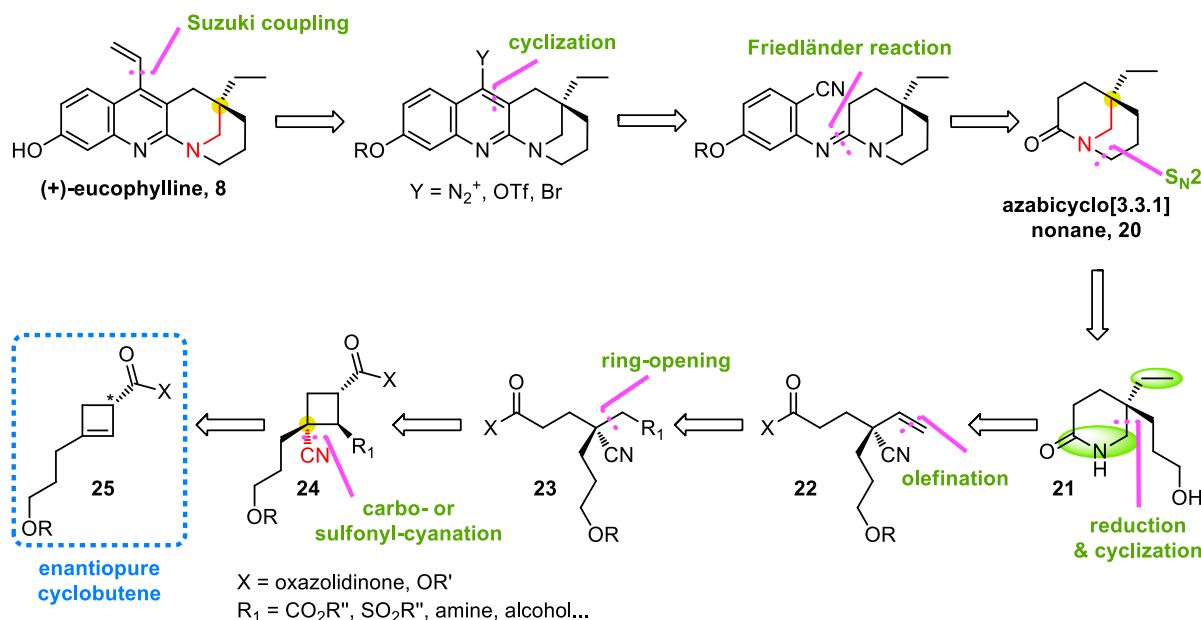
Considering the number of carbon atoms necessary to build the chiral part of eucophylline, its synthesis would be developed starting from an enantiopure cyclobutene unit **I** (Figure 5). Such a ring

is not reported in the literature; thus, the establishment of a new method to access the desired fragment will be studied first. In the meantime, the eburnamine would arise from a chiral cyclopropene analog **II**, where an efficient synthesis of a such molecule has been documented before.<sup>47</sup>



**Figure 5.** Small-ring systems as precursors for chiral natural products.

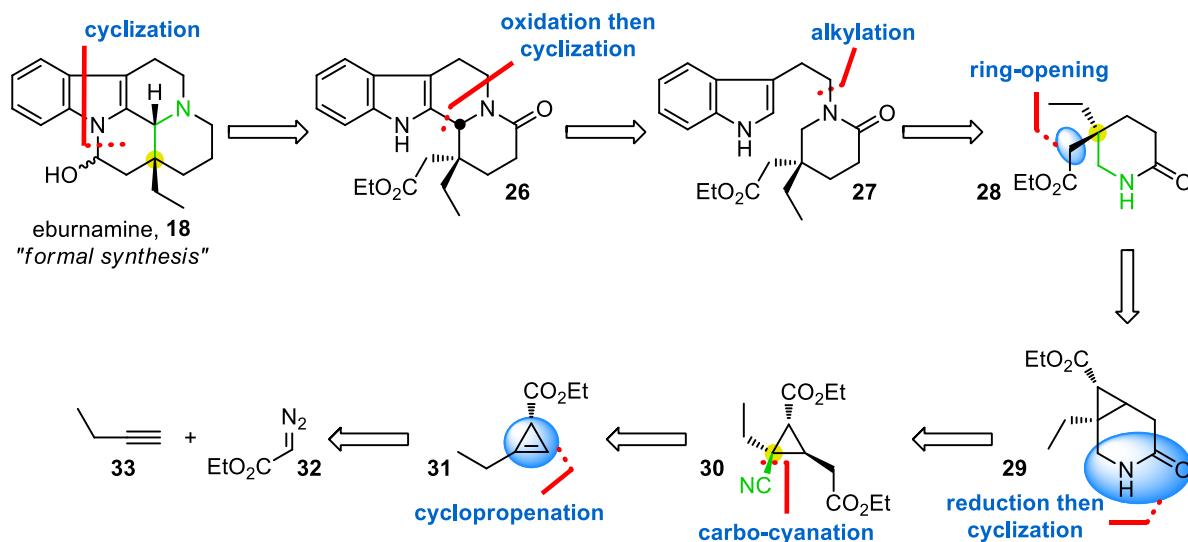
For the eucophylline, the first steps of its retrosynthesis are based on the total synthesis of the racemic form, reported by Landais *et al.*<sup>48</sup> The incorporation of a vinyl unit would be established at a late stage through a Suzuki coupling from the corresponding triflate, bromide or diazonium salt (Scheme 8). The eucophylline tetracyclic core would arise from a Friedländer-type annulation of an unusual bicyclic lactam **20** with a functionalized aniline, followed by cyclization under basic conditions. For the bicyclic lactam **20** itself, it would derive from an  $S_N2$  reaction of a post-activated alcohol **21**. The latter would be produced after the reduction of the nitrile function and a spontaneous cyclization with the carbonylated function in **22**, while the enantiopure acyclic skeleton bearing an all-carbon quaternary center **23**, would arise from a highly functionalized cyclobutane **24**. This would be constructed from a radical carbo- or sulfonyl-cyanation of an enantiopure cyclobutene **25**.



**Scheme 8.** Initial retrosynthesis of (+)-eucophylline **8**.

The beginning of the eburnamine retrosynthesis would be based on formal syntheses, by tailoring the last ring using a suitable base, followed by reduction of the molecule's carbonyl groups (Scheme 9). The tetracyclic template **26** would be synthesized by selective oxidation of the methine site  $\alpha$ - to the nitrogen. Its precursor, the ester **27**, would derive from the alkylation of a cyclic lactam **28** with

tryptophyl bromide. The lactam ring would result from a cyclopropane ring-opening of **29**, which itself comes from the nitrile reduction and cyclization of a polyfunctionalized cyclopropane **30**. The latter originates from the diastereoselective free-radical carbo-cyanation of cyclopropene **31**, thus incorporating the quaternary center bearing a nitrile functional group.<sup>47</sup> The enantiopure cyclopropene would be accessed inspired by previous reports, starting from suitable alkyne and diazoester reagents.<sup>47,49</sup>



**Scheme 9.** Initial retrosynthesis of eburnamine **18**.

## 5. Thesis outline

This Ph.D. manuscript will be presented in six chapters. The first chapter will be dedicated in its first part to the various aspects of the free-radical reactions, including the stability, structure, and reactivity of radicals. The major transformations in this field, especially the transformations involving the sulfonyl derivatives, will also be described. In the second part, however, a general overview of the photoredox catalysis concepts will be examined, followed by a brief application of this powerful tool in the elaboration of diversified synthetic architectures.

The second chapter will present the properties, reactivity, and stability of three- and four-membered ring systems. The most common pathways to access these templates will also be highlighted.

Chapter three will discuss the Ph.D.'s results on the development of an efficient approach to access a library of enantiopure cyclobutenes. The stereocontrolled functionalization of these scaffolds through various radical additions will also be presented. In this transformation, different radical traps will be tested using classic radical chemistry or the newly developed photocatalyzed radical addition reactions. The second part of this chapter will be dedicated to the formation of a broad range of skeletons as derivatives of cyclobutanes, including the investigated approaches to carbocycles ring-opening.

The fourth chapter will report the total synthesis of (+)-eucophylline, starting by the development of a chiral azabicyclo[3.3.1]nonane scaffold created from a cyclobutane unit. Such transformation

was possible thanks to the challenging nickel boride reduction reaction of the corresponding intermediate. The aspects and optimizations of this reaction will be presented in detail. Later, the completion of the natural product's synthesis will be reported, and its structural characterization will be discussed carefully.

Chapter five will describe the different strategies to access the eburnane series. The total synthesis of the eburnamine will be discussed and the pathway to access the chiral natural product from an enantiopure cyclopropene skeleton will be presented.

The sixth and final chapter deals with the biomimetic coupling of leucophyllidine and the performed coupling studies between the eburnamine and a structurally similar model of eucophylline.



# *Chapter I*

## *Free-Radical Chemistry & Photoredox Catalysis*



## Part I

### *Free-radical chemistry: General aspects and reactivity*

#### 1. Free-radicals: a historical perspective

Pioneering works on free radicals go back to the eighteenth century when Gay-Lussac reported in 1815 that heating mercuric cyanide led to the formation of cyanogen dimer, which was explained by the creation of cyanide radicals ( $\cdot\text{CN}$ ) as intermediates.<sup>50</sup> Kolbe<sup>51</sup> and Frankland<sup>52</sup> also claimed, respectively, in 1849, the formation of methyl radical ( $\cdot\text{CH}_3$ ) by decarboxylation of potassium acetate, and “ethyl” radical ( $\cdot\text{C}_2\text{H}_5$ ) from the reaction of ethyl iodide with zinc. Yet, these findings and few others,<sup>53</sup> were neglected in front of the flourishing concept of carbon tetravalency (*e.g.*, by forming four bonds) and the lack of suitable techniques for free-radical detection and isolation.

The key breakthrough came half a century later, when Gomberg<sup>54</sup> proved the existence of radical species by discovering the triphenylmethyl radical (trityl for short), the first stabilized radical example. Upon treatment with silver metal, triphenylmethyl chloride yielded a yellow solution that was attributed to the trityl radical. Its character was demonstrated by its facile reaction with oxygen to give the corresponding peroxide. However, this bold announcement faced skeptics who insisted that such trivalent carbon could not exist. Not until a decade later, the existence of this radical was confirmed by Schlenk and colleagues<sup>55</sup> through the preparation of tris(4-biphenyl)methyl radical. These two examples provided evidence for the existence of stabilized arylmethyl radicals, but aliphatic radicals (such as methyl and ethyl) were still a subject of doubt. In 1929, Paneth and his coworkers<sup>56</sup> reported the existence of alkyl radicals through their experiments of thermolysis of the vapor phase of organometallic compounds such as tetramethyllead. Shortly after, radicals were postulated as key intermediates in the mechanistic explanation of the so-called “abnormal reactions”. For instance, the Kharasch reaction and mechanism, an anti-Markovnikov addition of HBr to alkenes, became the first demonstration of a free radical chain mechanism.<sup>57</sup>

These results encouraged scientists to investigate the generation of carbon-centered radicals and the measurement of their reaction kinetics in the following decades. This was greatly helped by the development of spectroscopic methods such as Electronic spin/Paramagnetic Resonance (ESR/EPR) and Nuclear Magnetic Resonance (NMR) Spectroscopy in the 60s and 70s.<sup>58</sup> Since then, free-radical



chemistry expanded as a powerful tool in organic synthesis. Indeed, Giese described the addition of nucleophilic radicals onto unactivated olefins.<sup>59</sup> Barton also proposed new methods to produce carbon- and heteroatom-centered radicals.<sup>60,61</sup> In the 90s, Curran achieved bright syntheses of complex natural products through tandem radical cyclizations.<sup>62,63</sup> While Parker and co-workers<sup>64,65</sup> prepared (-)-morphine using a radical cascade process installing the all-carbon quaternary stereocenter and the tricyclic system of the alkaloid in a single step. Recently, the radical cascade chemistry was applied in the synthesis of 47 monoterpene alkaloids.<sup>66</sup>

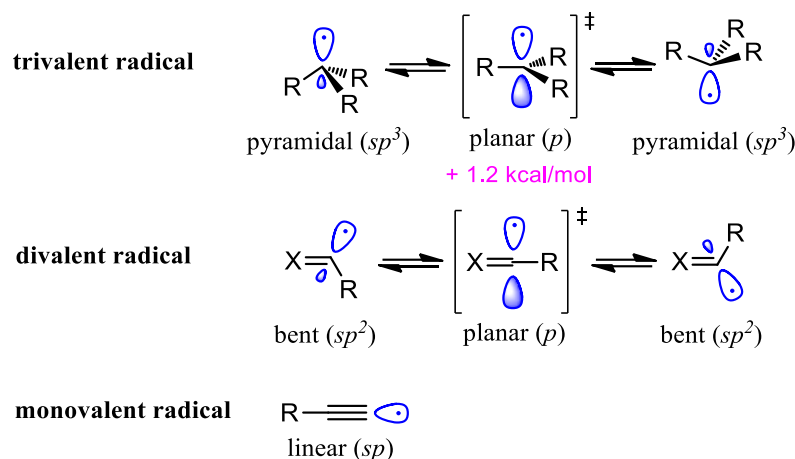
Despite its uncertain beginning, the topic of free-radicals holds today a central place in modern organic synthesis, from the fundamental studies (*e.g.*, electronic distribution of spin and charge) and the synthetic applications (novel polymers, natural products), to the elucidation of biochemical processes (photosynthesis, tissue damage, and aging process). This amplified interest demanded, therefore, more understanding of the structural and reactivity features of such species. So, what are free-radicals?

## 2. Free-radicals: concept

Free-radicals are chemical species that contain a singly occupied orbital. Generally, they tend to be very unstable and reactive. Their high reactivity is due to the unpaired electron, which has an affinity to pair with a second electron to produce a filled outer shell.<sup>67</sup> Radicals are often generated through homolytic bond cleavage, from radical initiators such as peroxides or azo-bis derivatives. The decomposition of the initiator is triggered by thermolysis (heat) or photolysis (light). Many radical reactions are chain reactions including an initiation step, a propagation step, and a termination step. The cleanness, efficiency, and selectivity of these reactions are related to the reactivity of carbon-centered radicals. This has been shown to be influenced by many factors including the structure and stability of the radical and the thermodynamic of the reaction (the energetic summary of the broken and formed bonds during the radical reaction steps).

## 3. Structure of carbon-centered radicals

In studying their structure, physical methods have provided insights that the trivalent carbon radical may adopt different geometrical configurations depending on the number and nature of the ligands attached to the radical center (Figure I.1). Specifically, the ESR spectrum of the methyl radical led to the conclusion that its structure could adopt  $sp^2$  hybridization, thus a planar structure (with angles equal to  $120^\circ$ ), or could adopt  $sp^3$  hybridization, with a pyramidal structure ( $109.5^\circ$ ) with a very low barrier of inversion (1.2 kcal/mol).<sup>68</sup>



**Figure I.1.** Structures and shapes of carbon-centered radicals.

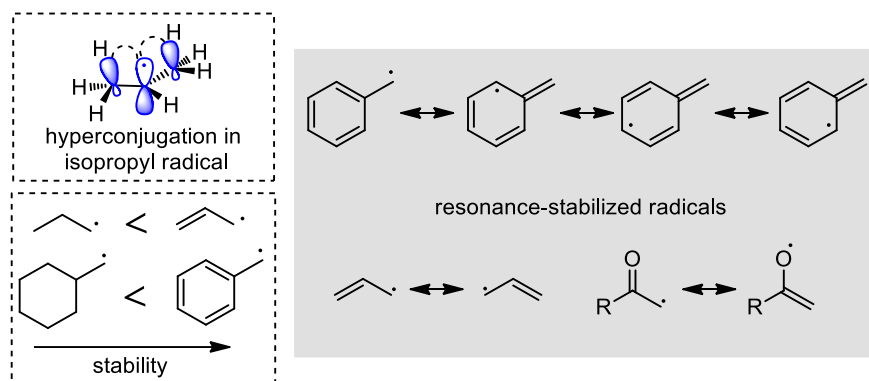
Other trivalent alkyl radicals are generally planar and are located in a  $p$  orbital. As a consequence of the planar shape, the stereochemical information is lost during the process of bond breaking/bond formation.<sup>69</sup> However, depending on the steric hindrance (constrained systems *e.g.*, adamant-1-yl radical) and the electronic character (electron-donating groups  $\alpha$ - to the radical *e.g.*, trifluoromethyl radical) of the substituent, pyramidalization of the radical may occur because the barrier of inversion slightly increases.<sup>70</sup>

For divalent radicals (*e.g.*, aryl, alkenyl, and acyl radicals), the unpaired electron resides in an  $sp^2$  orbital bent shaped, unless constrained in a small ring (*e.g.*, in phenyl radical). The inversion of this radical is possible and the transition state exhibits a linear geometry at  $C^\bullet$  with the radical in a  $p$  orbital.<sup>69</sup>

Finally, for monovalent radical species, the radical adopts a linear shape with an  $sp$  hybridized orbital.

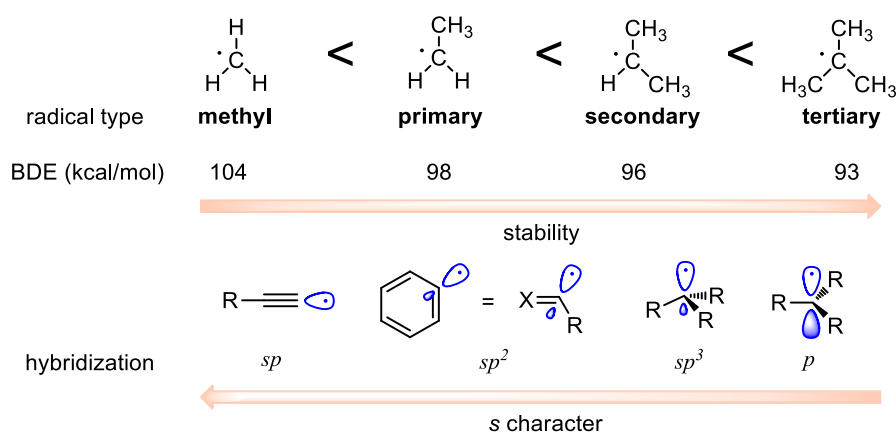
#### 4. Stability of radicals

Carbon radicals can be stabilized by both electronic and steric effects. In general, alkyl radicals are stabilized by inductive effects, hence, they obey the following order: methyl < ethyl < *i*-propyl < *t*-butyl. This phenomenon can also be explained by the hyperconjugation between the SOMO (Single Occupied Molecular Orbital) in which resides the unpaired electron, and the neighboring C-H  $\sigma$  bonding molecular orbital (Figure I.2).<sup>71</sup> Therefore, alkyl radical stability follows carbocation stability. Resonance (orbital overlap with an adjacent  $\pi$  bond or lone pair) also contributes to radical stability. Hybridization also affects radical stability; the more  $s$  character is present on the SOMO, the more the radical is destabilized. This explains the low stability of alkynyl radicals.



**Figure I.2.** Stability of radicals *via* resonance effect.

The thermodynamic stability of the radical can be estimated through the bond dissociation energy (BDE) of the R-H bond. In other words, lower is the BDE, more stable is the resulting radical (Figure I.3).<sup>58</sup>



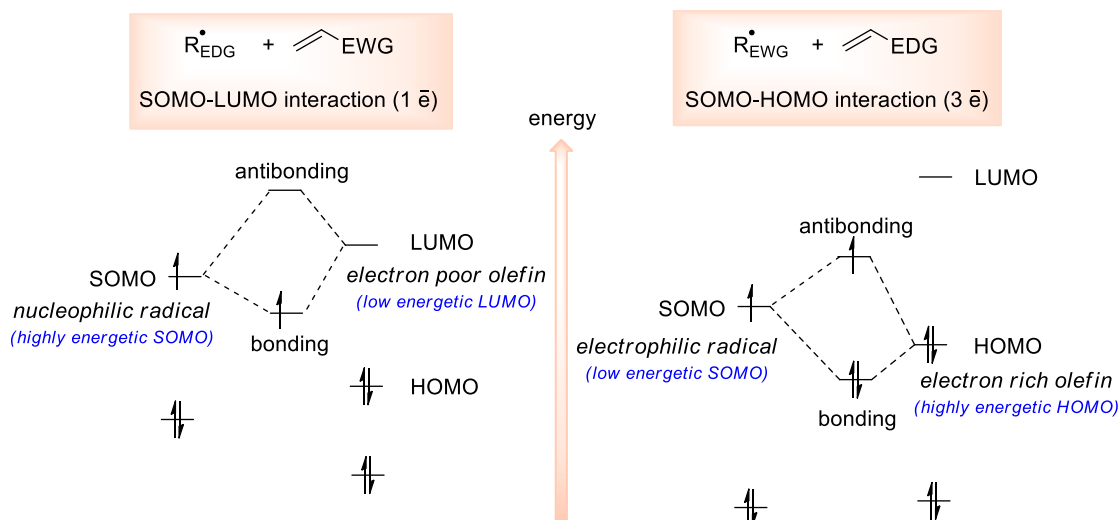
**Figure I.3.** The effect of Bond Dissociation Energy and hybridization on radical stability.

On the other hand, the kinetic stability of radicals can be influenced by the steric hindrance around the radical center. The more the radical is sterically hindered, the more it is stable and long-lived (*e.g.*, Gomberg's trityl radical). This longevity/unreactivity is explained by a combination of electronic and kinetic stabilization and low probability of recombination. This kind of radicals is often referred to by the term "persistent radicals".<sup>72</sup> Thus, the radical stability and reactivity are strongly related; the more the radical is stable, the less it is reactive.

## 5. Polarity effect on radical reactivity

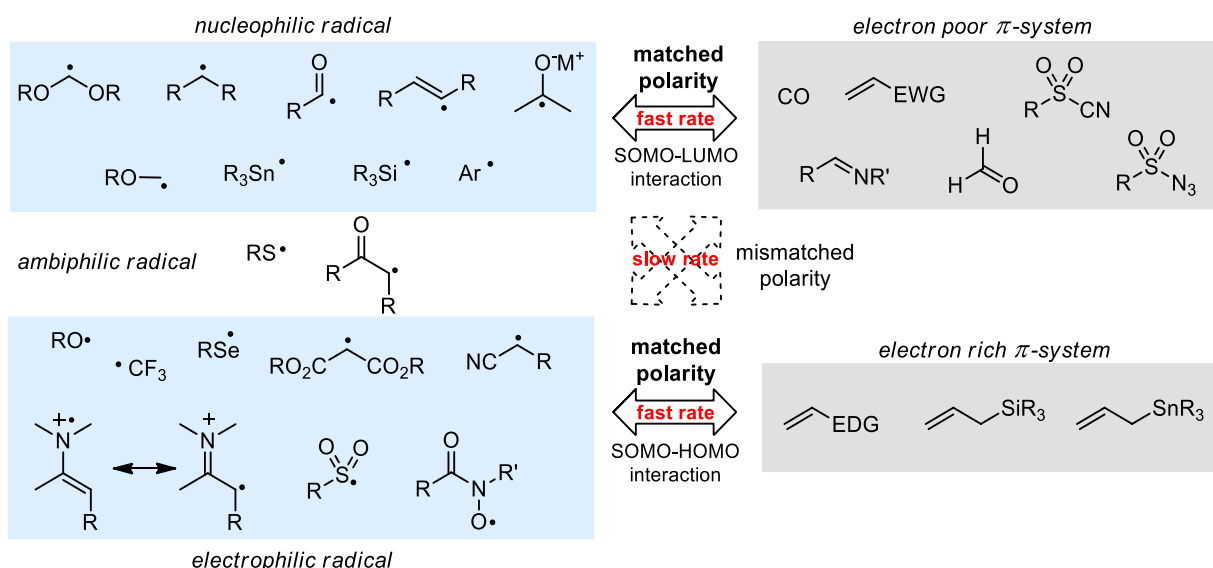
The reactivity and the successful radical addition onto  $\pi$ -systems also depend on the nature of both the radical and the unsaturated systems. In a radical addition reaction, an electrophilic radical will react faster with an electron-rich alkene, whereas a nucleophilic radical will react faster with an electron-deficient alkene. This is known as matched or complementary polarities. In the case of polarity mismatch, the reaction rate is slow. These polar effects are best explained by the frontier molecular orbitals theory (FMO)<sup>73</sup> which provides a better understanding of the radical reactivity (Figure I.4). The radical SOMO possesses energy between the HOMO (Highest Occupied Molecular

Orbital) and the LUMO (Lowest Unoccupied Molecular Orbital) of the olefin. With a nucleophilic radical (higher SOMO) and an electron-poor alkene (lower LUMO), the SOMO-LUMO interaction dominates because they are close in energy (*i.e.*, the energy barrier is small). In contrast, with an electrophilic radical and an electron-rich alkene, the SOMO-HOMO interaction is preferred. In both cases, the interaction results in a gain of energy relative to the newly formed  $\sigma$  bond at the expense of a weaker  $\pi$  bond, making the reaction thus, exothermic.



**Figure I.4.** The polar effect explained by FMO considerations.

Taking into consideration the polarity effect helps significantly in predicting and designing successful and chemoselective radical reactions. However, there are always exceptions when it comes to radical chemistry; some may arise from the borderline polarity of radical species or other components (Figure I.5).<sup>74</sup>

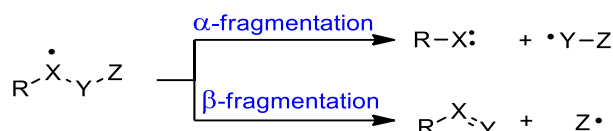


**Figure I.5.** Polarity matching between radical species and unsaturated systems.<sup>74</sup>

## 6. Radical reactions

### 6.1. Radical fragmentation

The radical fragmentation is an elementary reaction that cleaves a bond to one of the atoms adjacent to a radical center. The  $\alpha$ - and  $\beta$ -fragmentation (other names  $\alpha$ - and  $\beta$ -cleavage or scission) are usually endothermic (Scheme I.1).  $\beta$ -fragmentation, for instance, takes place when a weak  $\sigma$ -bond  $\beta$ -related to a radical center cleaves to generate two fragments; an unsaturated compound and a new radical.<sup>75</sup> Typically, this weak  $\sigma$ -bond is a carbon-heteroatom bond such as C-SR, C-SO<sub>2</sub>R, C-Br, C-I and C-SnR<sub>3</sub>.<sup>76</sup>



**Scheme I.1.** Radical fragmentation reactions.

Radical fragmentations show similar kinetic effects to those observed in radical additions. The stability of the formed radical plays an important role in the rate of fragmentation reactions. The more stable the radical is, the faster is the reaction. For instance, in the series of substituted cyclopropylcarbinyl radicals, the stability of the formed radical influences the rate of the ring-opening reaction (Table I.1). the rate constants are similar except in the case of the highly stabilized benzyl radical.<sup>77</sup>

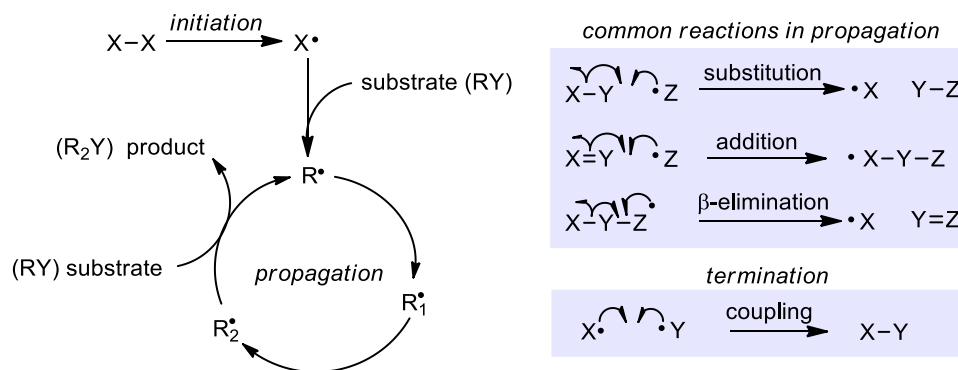
X	$k$ (s <sup>-1</sup> )	Y	$k$ (s <sup>-1</sup> )
H	$7 \times 10^7$	H	$7 \times 10^7$
Me	$4 \times 10^7$	Me	$1 \times 10^8$
OMe	$2 \times 10^7$	OMe	$1 \times 10^9$
CO <sub>2</sub> Et	$2 \times 10^8$	CO <sub>2</sub> Me	$7 \times 10^{10}$
Ph	$6 \times 10^4$	Ph	$1.5 \times 10^{11}$

**Table I.1.** Rate constants for the cyclopropylcarbinyl radical fragmentation.<sup>77</sup>

### 6.2. Radical chain reactions

Before the 1980s, the radical reactions were considered messy, unpredictable, and non-selective. Kinetic data relative to the generation and reactions of radical species were then gathered, allowing the development of controllable chemo- and regioselective chain reactions. This remarkable evolution allowed the chemistry of radical species to participate to the construction of complex building blocks for synthesis and material applications. Chain reactions are considered the major method in radical chemistry nowadays. Such reactions require the generation of a small amount of reactive radicals in the initiation phase through homolysis (thermolysis or photolysis). Once radicals are formed, they

react with the precursor generating for instance a new carbon-centered radical, which enters into the propagation cycle (Scheme I.2).



**Scheme I.2.** Mechanism of a generalized radical chain reaction.

The process of transmitting the radical character from one species to another allows the propagation of the radical chain while releasing continuously the final product. However, when odd-electron species undergo direct radical-radical recombination, the radical character is lost to form a non-radical adduct. The chain reaction is stopped and this step is called termination. In order to avoid this undesirable event, low concentrations of radicals are required, and small quantities of initiators are used. Propagation steps often involve substitution (atom abstraction), addition, or fragmentation ( $\alpha$ - and  $\beta$ -elimination) as the most common processes in radical reactions. For the reader's convenience, a non-exhaustive description of some radical processes is provided.

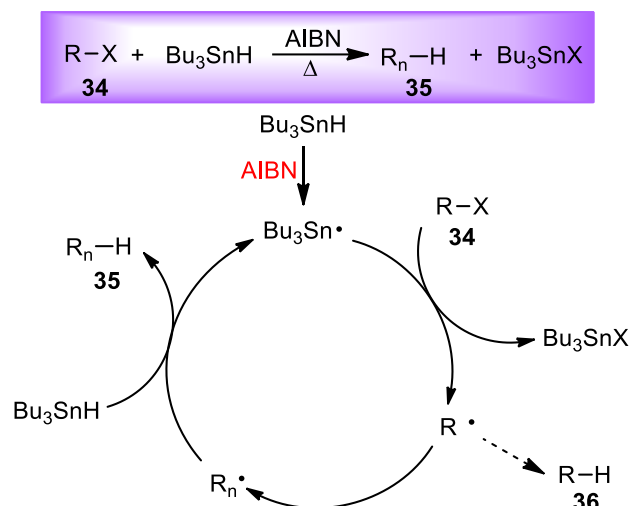
### 6.3. Radical chain mediators

The use of radical initiators is required to produce the first radicals that will enter into the propagation stage. Despite its use in sub-stoichiometric amounts, the initiator is not a catalyst because it is irreversibly transformed into radicals. Some reactions do not need an additional reagent to allow a complete conversion of the precursor (*e.g.*, Kharasch reaction), however, many reactions need an additional reagent called a radical mediator. A mediator is a reagent involved in the conversion of the precursor by sustaining the radical chain. The most popular mediators were so far the organotin compounds (tri-*n*-butyltin hydride, bis(tri-*n*-butyltin)), organosilanes (tris(trimethylsilyl)silane), germanes and boranes (triethylborane).<sup>78</sup> For clarity reasons, only the major radical processes are discussed and are categorized depending on the nature of the radical acceptor.

### 6.4. Hydrogen transfer reactions

Tri-*n*-butyltin hydride (*n*-Bu<sub>3</sub>SnH) is well known as a hydrogen donor in radical reactions. Generally, radical reactions with Bu<sub>3</sub>SnH initiated by azobisisobutyronitrile (AIBN) proceed effectively in benzene.<sup>79</sup> Upon initiation, the hydrogen abstraction of *n*-Bu<sub>3</sub>SnH leads to the tributyltin radical (Scheme I.3). In the propagation step, the mediating Bu<sub>3</sub>Sn<sup>•</sup> radical abstracts a halogen atom from the organohalide **34** to generate a carbon-centered radical R<sup>•</sup>. This radical can then be directly reduced by *n*-Bu<sub>3</sub>SnH to form the dehalogenated product R<sub>n</sub>-H **35** or can be transformed to another

radical  $R_n^\bullet$ , which is then subjected to the hydrogen transfer reaction providing the alkane **36** and a  $Bu_3Sn^\bullet$  radical, thereby closing the cycle.<sup>80,81</sup>

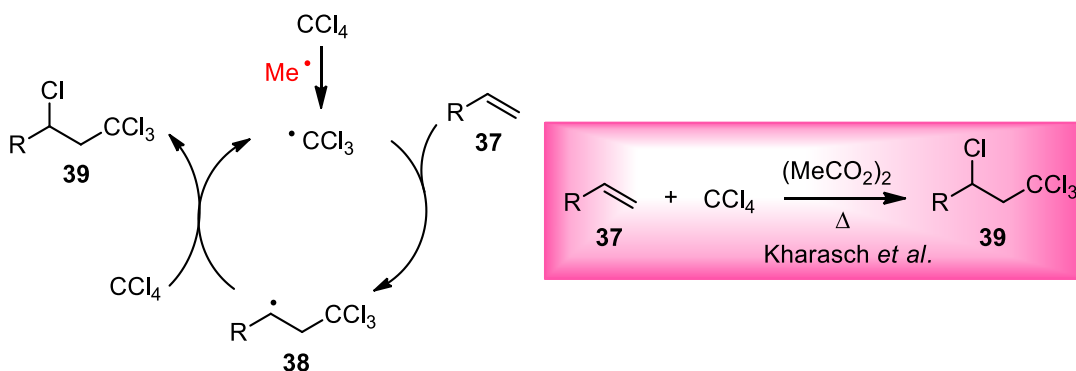


**Scheme I.3.** Generalized  $Bu_3SnH$ -mediated hydrogen transfer mechanism.

To address the toxicity issues of tin hydride and the challenging removal of its residues from organic compounds, chemists introduced other reagents as a hope to escape from “the tyranny of tin” as described by Walton.<sup>82</sup> Tris(trimethylsilyl)silane and organoboranes are among the potential replacements of tin hydride catalyst.<sup>78</sup>

### 6.5. Atom transfer reactions or halogen group transfer

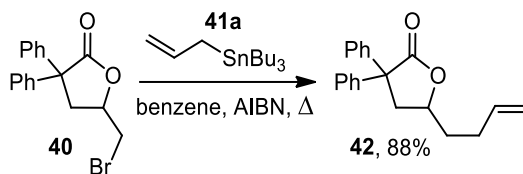
The Atom Transfer Radical Addition (ATRA) reaction was first reported by Kharasch<sup>83</sup> and later developed by Curran,<sup>84</sup> Oshima,<sup>85</sup> and others (Scheme I.4). In this reaction, electrophilic precursors such as organohalide compounds (*e.g.*,  $CCl_4$ , iodomalonate, bromomalonate...) add to the electron-rich olefins **37** in the presence or absence of tin reagents. In the example of Kharasch, diacetyl peroxide  $(MeCO_2)_2$  was used as an initiator, which upon thermolysis generated a methyl radical, which upon chlorine abstraction from  $CCl_4$  led to a  $\cdot CCl_3$  radical and promoted its addition onto the olefin's double bond. The newly generated nucleophilic radical **38** reacted then with carbon tetrachloride to deliver the ATRA product **39** and regenerate the carbon trichloride radical.



**Scheme I.4.** Mechanism of the ATRA reaction developed by Kharasch.<sup>83</sup>

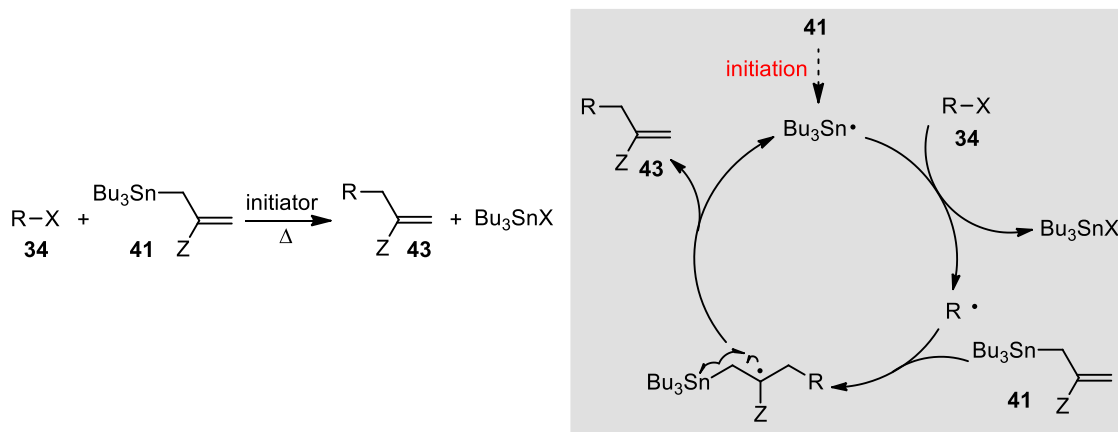
## 6.6. Radical carbo-allylation reactions

Besides the xanthate group additions developed by Zard,<sup>86</sup> the allyl addition is considered as one of the most popular group transfer reactions. The allyl group transfer from allyltrimethyltin reagent was first discovered in 1973 by Pereyre *et al.*<sup>87,88</sup> and Migita *et al.*<sup>89</sup> and developed later by Keck *et al.*<sup>90</sup> with allyltributyltin **41a** (Scheme I.5).



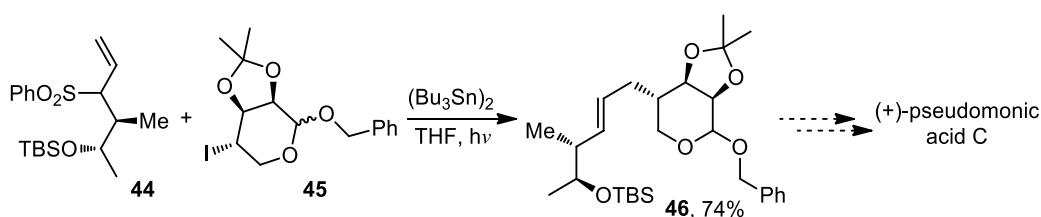
**Scheme I.5.** Allyl transfer reaction reported by Keck *et al.*<sup>90</sup>

Under refluxing conditions, a small amount of stannyl radicals are generated, which abstract the halide from the organohalide substrate **34**. The generated electrophilic radical ( $R^\bullet$ ) is later added to the allylstannane **41** to form a C-C bond followed by a  $\beta$ -elimination to provide the allylation product **43** and regenerate the stannyl radical, which in turn propagates the radical chain (Scheme I.6).



**Scheme I.6.** Mechanism of radical carbo-allylation reaction.

In this context, Russell *et al.*<sup>91</sup> reported examples of allylation reactions using vinyl thioethers, sulfoxides, and sulfones, showing the ability of these reagents to undergo fragmentation after the addition of alkyl radical onto the allyl reagent. Based on these results, Keck *et al.*<sup>92</sup> described the first application of allylsulfones fragmentation as a key step in the synthesis of the natural product (+)-pseudomonic acid C (Scheme I.7). These examples opened the way for the use of sulfone groups in radical reactions.



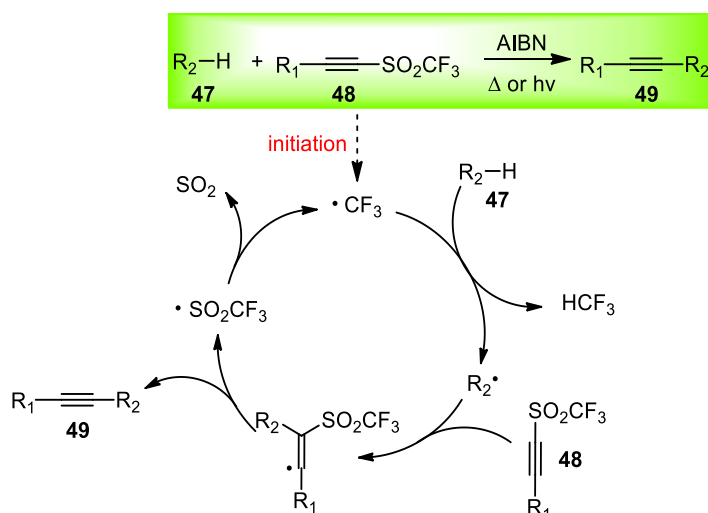
**Scheme I.7.** Application of the sulfone fragmentation as a key step in (+)-pseudomonic acid C synthesis.<sup>92</sup>



## 6.7. Carbo-alkenylation and alkynylation reactions

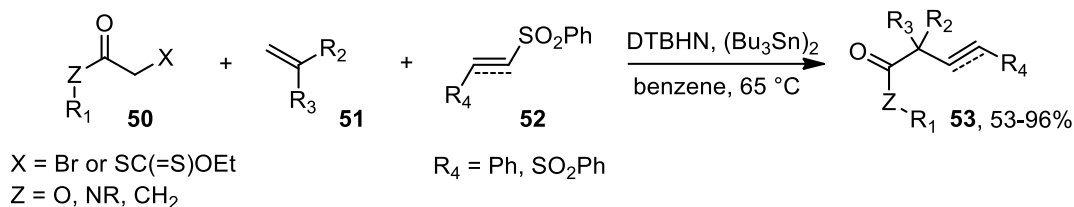
The electrophilic property of sulfonyl radicals and the easy access to a wide range of sulfone substituents motivated research groups to explore their reactivity as radical acceptors. These features were directed towards the addition of alkenyl and alkynyl groups onto olefin backbones, a challenging task that was first taken by Fuchs *et al.*<sup>93</sup> Thus, alkynyltriflone derivatives were developed as radical traps in the alkynylation of alkanes C-H bonds.

In a tin-free process, the initiator generates an electrophilic trifluoromethyl radical, which abstracts hydrogen from an alkane **47** (Scheme I.8). The resulting nucleophilic alkyl radical then adds onto the alkynyltriflone **48** followed by the  $\beta$ -fragmentation of the alkenyl radical to deliver the coupling product **49** and an unstable sulfonyl radical. The latter then undergoes  $\alpha$ -scission with loss of sulfur dioxide to generate a trifluoromethyl radical that propagates the radical chain. The  $\beta$ -fragmentation rate of sulfonyl radical depends on the stability of the intermediate.<sup>94,95</sup> These conditions allowed functionalizing poorly reactive alkanes such as cyclohexane, cycloheptane, norbornane, and adamantane. This strategy was then extended to the alkenylation and allylation of alkanes with vinyl- and allyltriflones, respectively.<sup>96–98</sup> The method, however, showed limitation by the necessity of using the CF<sub>3</sub> group in the radical acceptor backbone.



**Scheme I.8.** Mechanism of alkynylation of C-H bond, by Fuchs *et al.*<sup>93</sup>

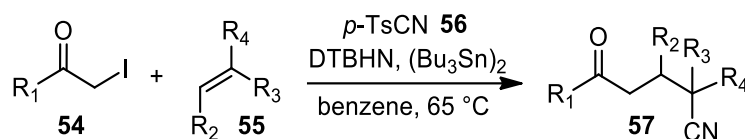
Three-components (3-MCR) carbo-alkenylation and -alkynylation of olefins were also described by Landais *et al.*<sup>99</sup> In this method, two functional groups could be added across the  $\pi$ -system of unactivated olefins **51**. Starting from a broad range of carbonyl precursors **50** (ketone, nitrile, malonate, amide) as radical precursors, the addition of the alkyl radicals on alkenyl- and alkynylsulfones **52** proceeded smoothly to deliver the unsaturated products **53** in good to excellent yields (Scheme I.9).



**Scheme I.9.** Carbo-alkynylation and alkenylation of olefins by Landais *et al.*<sup>99</sup>

### 6.8. Free-radical carbo-cyanation of olefins

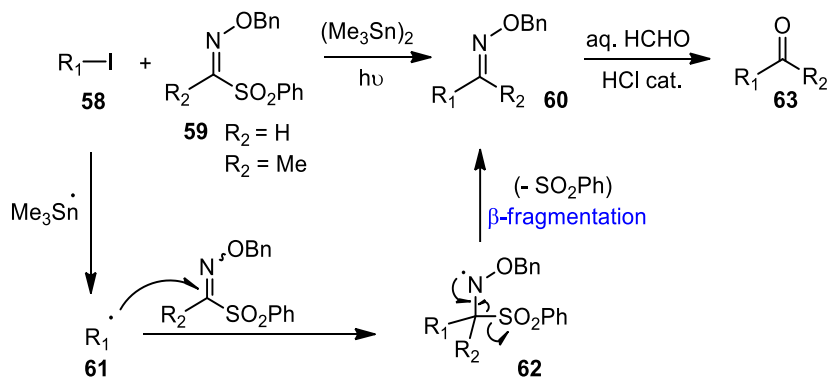
Landais and co-workers<sup>100</sup> also developed an efficient three-components carbo-cyanation reaction of olefins **55** using the commercially available tosyl cyanide **56** (Scheme I.10). Nitrile-functionalized all-carbon quaternary centers **57** were produced in good yields and this strategy was applied to a large library of olefins.



**Scheme I.10.** Free-radical carbo-cyanation of olefins, by Landais *et al.*<sup>100</sup>

### 6.9. Free-radical carbo-oximation reaction

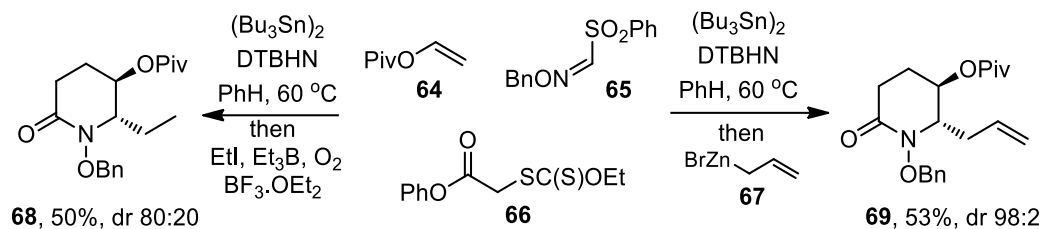
Kim *et al.*<sup>101–103</sup> were the first to use sulfonyl oximes in tin-mediated radical additions. Their studies showed that the electron density on the oxime's carbon ( $\text{C}=\text{N}$ ) is low, making them good radical traps. Hence, the less electron density on the carbon is, the better is the radical acceptor.<sup>104,105</sup> The addition of an alkyl radical **61** (generated from alkyl iodide **58**) onto a sulfonyl oxime **59** afforded, after  $\beta$ -elimination of the phenylsulfonyl radical, the alkylated oxime **60** in moderate to excellent yields (Scheme I.11). The hydrolysis of the oxime product **60** in formaldehyde and HCl gave access to the corresponding aldehyde ( $\text{R}_2 = \text{H}$ ) or ketone ( $\text{R}_2 = \text{Me}$ ). It is worth noting that the sulfone group decreases the energy difference between the SOMO of the alkyl radical and the LUMO of the radical acceptor, which in turn increases the rate of addition of the alkyl radical onto the oxime.



**Scheme I.11.** Alkylation of sulfonyl-oxime/radical acylation of alkyl halides by Kim *et al.*

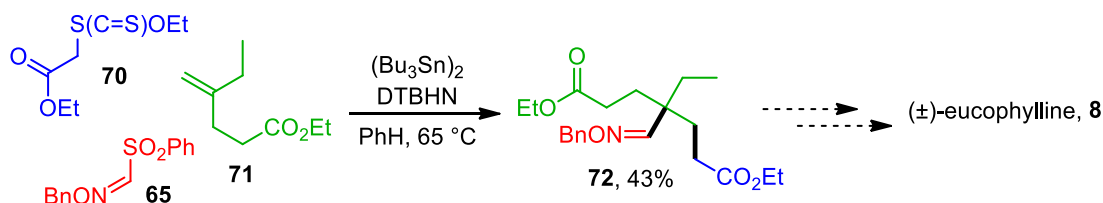
Inspired by this work, an efficient four-components radical process (4-MCR) was developed by Landais and co-workers.<sup>106</sup> Instead of hydrolyzing the oxime group, the oximated product was

allowed to react with an alkyl radical or an allylzinc reagent to afford multi-substituted piperidinones **68** and **69** in good yields and high *trans*-favored diastereoselectivity (Scheme I.12).



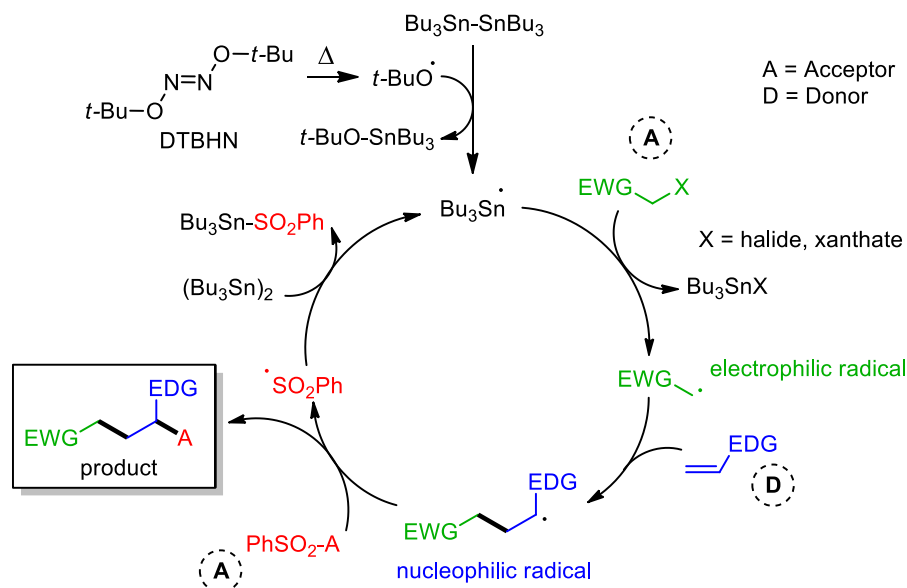
**Scheme I.12.** Synthesis of functionalized piperidinones through a 4-MCR carbo-oxidation.<sup>106</sup>

This strategy was used in the development of three-components carbo-oxidation as a key step in the total synthesis of (±)-eucophylline, proving thus, the utility of a such approach (Scheme I.13).<sup>48</sup>



**Scheme I.13.** 3-MCR carbo-oxidation as a key step in (±)-eucophylline synthesis.<sup>48</sup>

The three-components free-radical carbo-oxidation is categorized as “ADA” system (Acceptor-Donor-Acceptor system) (Figure I.6).<sup>74</sup> In this system, the tin radical abstracts a halide or a xanthate from the corresponding alkyl halide or xanthate, generating the first electrophilic alkyl radical (Acceptor). The latter then adds onto the less hindered end of an electron-rich olefin (Donor). The nucleophilic intermediate radical thus formed is then rapidly trapped by the electrophilic sulfonyl oxime (Acceptor). The sulfonyl radical, generated after β-fragmentation, propagates the chain by reacting with a stoichiometric amount of bis(tributyltin) producing new stannyl radicals that sustain the radical chain. This sequence represents a straightforward strategy to access highly substituted oximes in a one-pot operation.



**Figure I.6.** 3-MCR carbo-oxidation reaction mechanism.

## 7. Conclusion

Along this section, free-radical chemistry was briefly discussed as a central theme in organic synthesis. Its advantages reside in high functional groups tolerance, high selectivity in the presence of unprotected groups (*e.g.*, ketone, alcohol), and efficient access to complex molecular architectures, notably through well-designed cascade processes. Considering the aforementioned transformations, radical chain reactions allow the integration of a wide range of functional groups (halides, alkyl, allyl, cyanide, azide, alkene, alkyne, acyl, oxime, and xanthate...) which explain the high interest in this promising field. Yet, many of these reactions require, as propagation mediators, a stoichiometric quantity of toxic reagents such as organotin derivatives. Besides their toxicity, these mediators generate large amounts of tin residues that contaminate the final products.<sup>107,108</sup> These strategies cannot be considered for agrochemical and pharmaceutical uses, even if the results in terms of organic synthesis are excellent and efficient. Much less toxic but more effective radical mediators have been developed to replace organotins, and among them, tris(trimethylsilyl)silane, samarium (II) iodide, and triethylborane. In the last two decades, the need for greener radical transformations were at the roots of the blooming of attractive alternatives including, the photoredox catalysis, which became an increasingly important and appealing tool in organic synthesis.

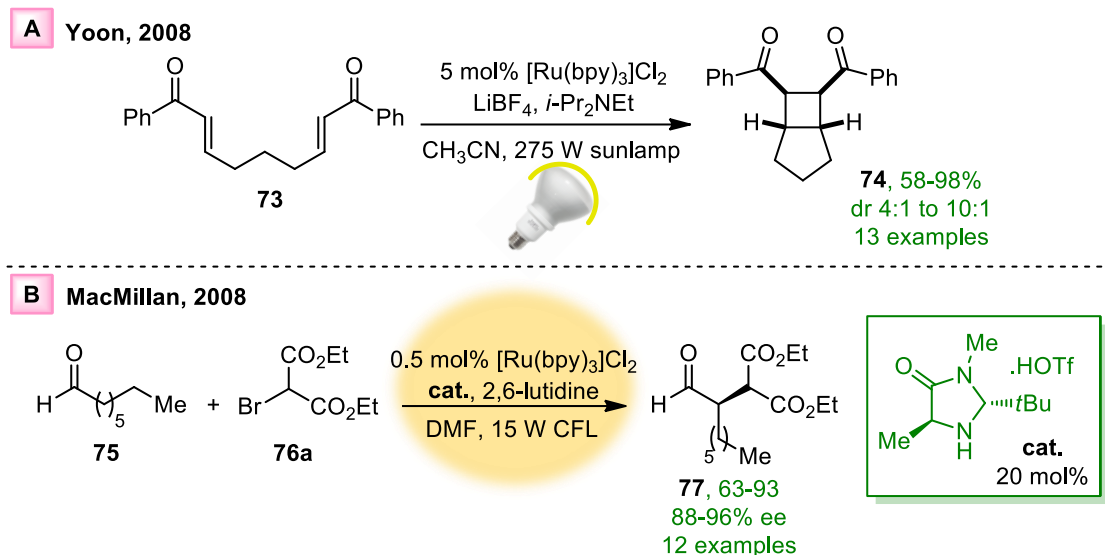
## *Part II*

### *Photoredox catalysis: Basic concepts and applications*

#### **1. Photoredox catalysis in organic synthesis**

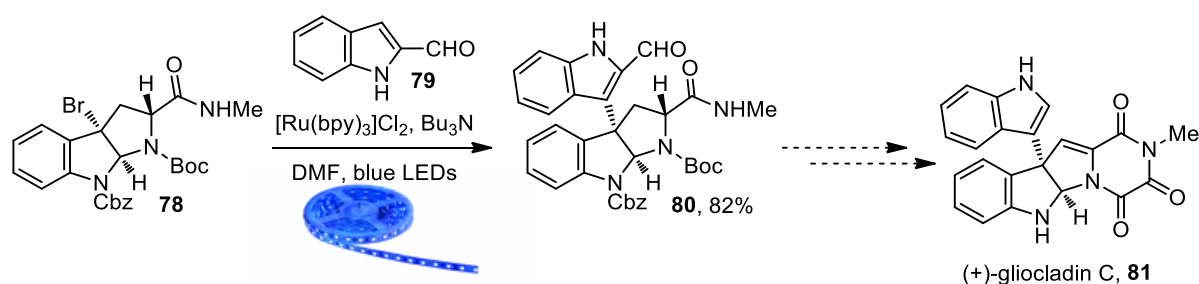
Visible light-mediated photoredox chemistry has emerged in the last decade as a powerful tool to perform organic reactions through energy transfer or single electron transfer (SET) processes, inaccessible otherwise. Since most organic molecules are transparent to visible light, bench-stable metal complexes and organic dyes were developed and used to mediate radical reactions, advantageously replacing initiators usually employed in classical radical chemistry. These photocatalysts mediate chemical transformations under very mild conditions, at room temperature, and in a green and clean manner.<sup>109</sup>

Although the first applications were described by Kellogg<sup>110</sup> and Deronzier<sup>111,112</sup> in 1978 and 1984 respectively, it was not until 2008 that the field of visible-light photocatalysis experienced a renaissance and started to receive some attention. Yoon thus, reported the intramolecular [2+2] cycloaddition of enone **73** to cyclobutane **74** by the intermediacy of [Ru(bpy)<sub>3</sub>]Cl<sub>2</sub> under visible light irradiation (Scheme I.14.A).<sup>113</sup> In the same year, MacMillan developed the enantioselective  $\alpha$ -alkylation of aldehydes **75** using a dual organo- and photoredox catalysis (Scheme I.14.B).<sup>114</sup> These reports illustrated the powerful potential of photocatalysis in organic synthesis and inspired other groups to investigate this domain profoundly.



**Scheme I.14.** Photoredox catalysis by Yoon and MacMillan.<sup>113,114</sup>

Photoredox catalysis was later studied by Stephenson and co-workers who reported its applicability in the enantioselective total synthesis of (+)-gliocladin C natural product (Scheme I.15).<sup>115</sup> Visible light was used to promote the intermolecular pyrrole-pyrroloindoline coupling reaction which delivered the advanced intermediate **80** in excellent yield.



**Scheme I.15.** Application of photoredox catalysis in the total synthesis of (+)-gliocladin C.<sup>115</sup>

## 2. Photoredox catalysis: basic concepts

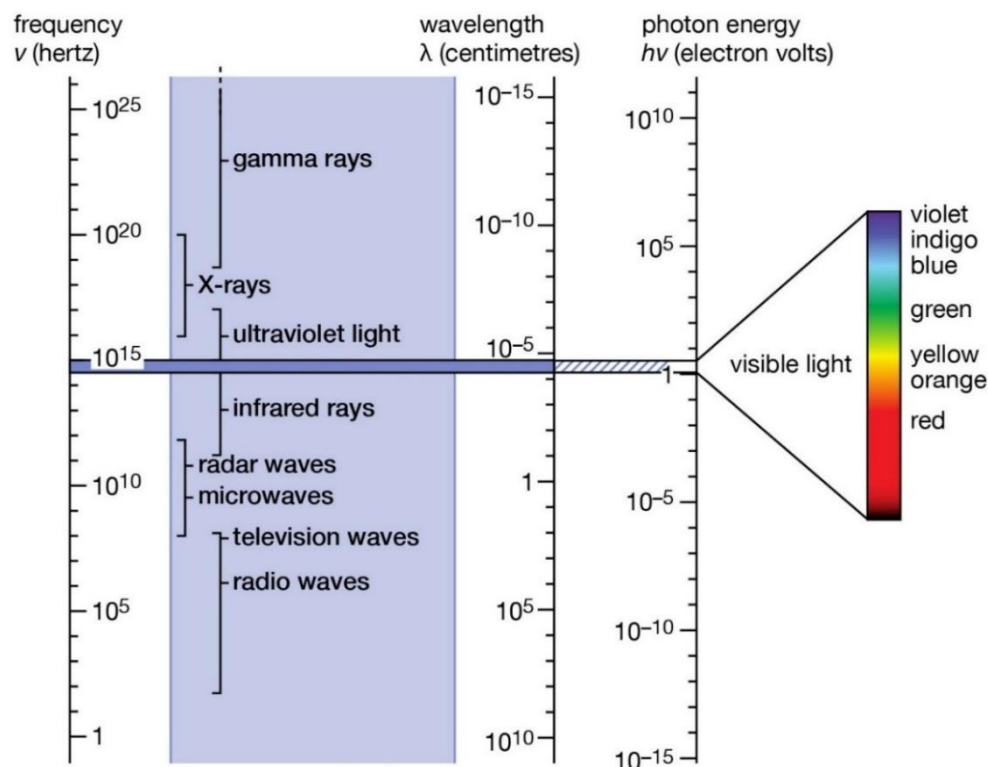
### 2.1. Nature of light

An electromagnetic radiation is characterized by a wavelength ( $\lambda$ ), a frequency ( $\nu$ ) and a velocity ( $c$ ). The relationship between these three parameters is illustrated in the equation below:

$$\lambda\nu = c \quad (\text{Eq. I.1})$$

where the velocity of light in vacuum is a constant ( $c = 2.998 \times 10^8 \text{ m.s}^{-1}$ ). The wavelength and frequency are expressed in nm and Hz, respectively. The electromagnetic radiation includes different radiations ranging from  $\gamma$ -rays to radio waves. This range is known as the electromagnetic spectrum (Figure I.7).  $\gamma$ -rays and X-rays are the most energetic radiations (high frequencies), whereas radio waves are the least energetic (low frequencies). The term “light” is used to include the near-ultraviolet (UV,  $\lambda = 200\text{-}400 \text{ nm}$ ), the visible (VIS,  $\lambda = 400\text{-}700 \text{ nm}$ ), and the near-infrared (IR,  $\lambda = 700\text{-}1000 \text{ nm}$ ) regions of the electromagnetic spectrum. These electromagnetic radiations are involved in

photochemistry, as they are capable of provoking electronic excitation or electronic deactivation of molecules.<sup>116</sup>



**Figure I.7.** Electromagnetic spectrum (source: *Encyclopædia Britannica, Inc.*).

According to the quantum theory (wave-particle duality), electromagnetic radiation can also be seen as a flux of *photons* (or *quanta*). A photon is characterized by its energy related to the frequency of the radiation,  $\nu$  according to the following equation:

$$E = h\nu = h \frac{c}{\lambda} \quad (\text{Eq. I.2})$$

where  $h$  is the Planck's constant ( $6.63 \times 10^{-34}$  J.s). Typically, using light (200 to 1000 nm range), a molecule receives energy between  $9.95 \times 10^{-19}$  and  $1.99 \times 10^{-19}$  J, which corresponds to 599 kJ and 120 kJ for one mole. These values are of the same order of magnitude of those required for the bond dissociation energies of some typical carbon-heteroatom or carbon-hydrogen bonds (e.g., 190 kJ mol<sup>-1</sup> for the Br-Br bond of Br<sub>2</sub> or 416 kJ mol<sup>-1</sup> for the C-H bond of CH<sub>4</sub>). Thus, this energy is significant to realize chemical transformations.<sup>116</sup>

## 2.2. Absorption of light

According to the Grotthuss-Draper law, only the light absorbed by an investigated species is effective. Therefore, it is important to measure the absorption of the medium to determine the energy of the light absorbed. The absorbance of the species is defined by the Beer-Lambert law (Eq. I.3). This equation describes the absorption of a monochromatic beam light by a substance dissolved in a transparent medium.

$$I = I_0 \times 10^{-\epsilon bc} \quad \text{or} \quad A = \log\left(\frac{I_0}{I}\right) = \epsilon lc \quad (\text{Eq. I.3})$$

where  $I$  is the intensity of the transmitted light,  $I_0$  is the intensity of the incident light,  $A$  is the absorbance,  $\epsilon$  is the molar absorption coefficient ( $\text{M}^{-1} \text{cm}^{-1}$ ),  $l$  is the optical path (cm) and  $c$  is the solution concentration (M).<sup>116</sup>

### 2.3. Excited states

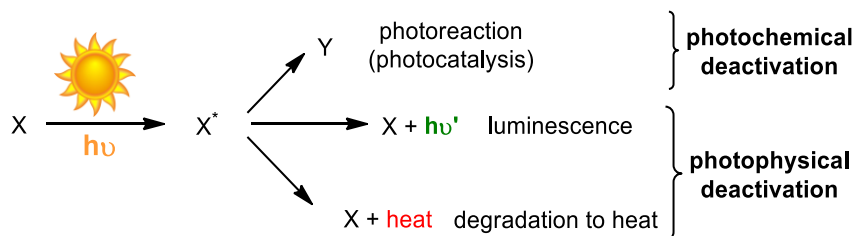
When excited by a photon with a given energy, a molecule is promoted from its initial ground state to an electronically excited state.<sup>116</sup> This phenomenon causes changes in the electronic structure of the molecule. Since the chemical and physical properties depend on the electronic structure, a molecule in the excited state holds chemical and physical properties different from that of the ground state. The excitation of a molecule  $X$  is generally expressed as:



$X$  refers to the ground state molecule,  $h\nu$  is the absorbed photon and  $X^*$  corresponds to the electronically excited state. After excitation,  $X^*$  possesses greater electronic energy than  $X$ .

### 2.4. Deactivation pathways of excited states

After reaching an excited state, a molecule  $X$  becomes reactive ( $X^*$ ) and it usually relaxes back to the ground state in a given time interval through different deactivation modes (physical or chemical) (Figure I.8).<sup>116</sup> In a photophysical process, the original molecule is recovered after returning to its ground state. This deactivation is accompanied by the emission of light (luminescence) or by the dissipation of heat. In a photochemical process, the excited species enter in chemical reactions, and a new product is formed. These processes can occur at intra- or intermolecular levels.



**Figure I.8.** Deactivation pathways of an excited state.

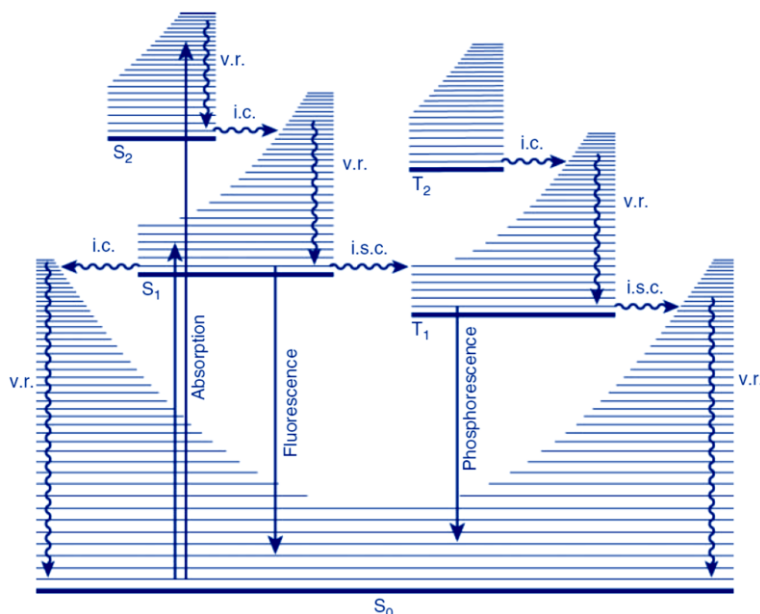
## 3. Intramolecular deactivation of excited states

### 3.1. Jablonski-Perrin diagram

The properties of excited states and their various deactivation processes are usually represented through a Jablonski diagram (Figure I.9).<sup>116</sup> The thick horizontal lines refer to the electronic states and are arranged vertically following order of increasing energy. Singlet electronic states are represented by  $S_0, S_1, S_2, S_n$ , etc. and triplet electronic states as  $T_1, T_2, T_n$ ... Only the first two excited states are shown. The thin horizontal lines correspond to the vibrational levels associated with each state and are represented as  $v = 0, v = 1, v = 2$ ... Rotational levels are not indicated. Radiative



transitions (absorption or emission of a photon) are drawn as straight arrows whereas the radiationless transitions are drawn as wavy arrows.



**Figure I.9.** Jablonski-Perrin diagram of an organic molecule.<sup>116</sup>

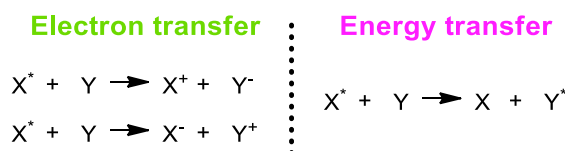
When a molecule absorbs light, it goes from the ground state  $S_0$  to a higher electronic state (excited state)  $S_n$  possessing a higher vibrational level (Franck-Condon state). This electronically excited species then disperses the additional vibrational energy (as heat) and returns to the population of  $S_1$  (Kasha's rule). This process is called vibrational relaxation (v.r.) and it usually happens in pico- to nanoseconds timescale. Relaxation from an upper excited state to a lower excited state (isoenergetic states) involves an intramolecular radiationless transition process. When the relaxation happens within the same multiplicity (spin-allowed,  $S_n \rightarrow S_1$  and  $T_n \rightarrow T_1$ ), the process is called internal conversion (i.c.). This transition happens at a rapid rate between the upper excited states ( $10^{-14}$  to  $10^{-11}$  s) because the difference in energy is relatively small, whereas it is slower between  $S_1$  and  $S_0$  ( $10^{-9}$  to  $10^{-7}$  s) due to the large energy gap. When the transition happens between isoenergetic states of different multiplicities (spin-forbidden, *e.g.*,  $S_1 \rightarrow T_1$ ), the relaxation process is called intersystem crossing (i.s.c.), and it is slower than that of the internal conversion ( $10^{-11}$  to  $10^{-8}$  s timescale).

If the transition from an excited state to the ground state was accompanied by the emission of a photon, the deactivation is called radiative and the energy excess is released as light. If the photon emission occurred between states of the same multiplicities (spin-allowed emission,  $S_1 \rightarrow S_0$ ), the transition is defined as fluorescence ( $10^{-12}$  to  $10^{-6}$  s typical timescale). When the transition occurs between states of different multiplicities (spin-forbidden emission,  $T_1 \rightarrow S_0$ ), the phenomenon is called phosphorescence ( $10^{-3}$  to  $10^2$  s typical timescale).

#### 4. Intermolecular deactivation of excited states

The deactivation of an excited state can also occur through an intermolecular interaction by the means of chemical transformations.<sup>116</sup> A molecule  $X^*$  in the excited state can be deactivated by

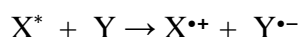
another molecule, Y through four main types of interactions: (1) collisional deactivation; (2) chemical reaction; (3) electron transfer and (4) energy transfer. Electron transfer, considered as a photophysical process, implies a photoexcited donor molecule to interact with a ground-state acceptor (Figure I.10). This involves oxidation or reduction of the species, where an ion pair is formed. During an energy transfer deactivation, the electronically excited state of a molecule (the donor) is deactivated by transferring energy to the lower electronic state of another molecule (the acceptor). The donor is known as a sensitizer and the acceptor is known as a quencher.



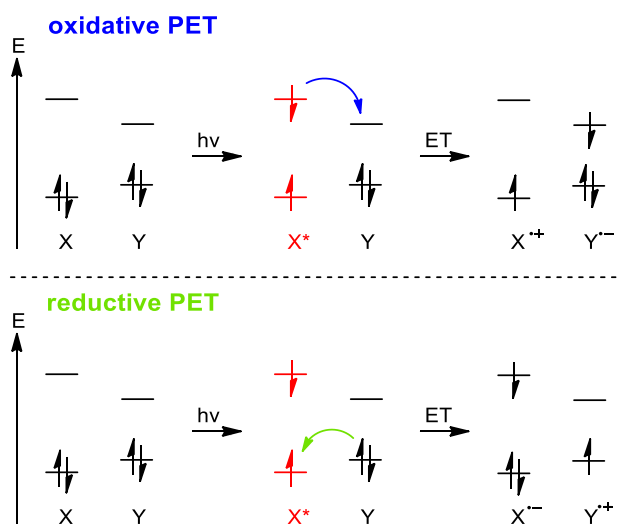
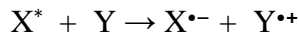
**Figure I.10.** Intermolecular deactivations.

#### 4.1. Photoinduced electron transfer (PET)

Photoinduced electron transfer (PET) corresponds to the primary photochemical process of the excited state species,  $X^*$ , where  $X^*$  can be an electron donor or an electron acceptor when reacting with another molecule, Y (Figure I.11). When  $X^*$  acts as an electron donor, it is oxidized (oxidative electron transfer):



When  $X^*$  acts as an electron acceptor, it is reduced (reductive electron transfer):



**Figure I.11.** Oxidative and reductive PET.

In a photoinduced electron transfer process, an electron is transferred between an excited-state and a ground-state species, therefore, this exchange requires orbital overlap.<sup>116</sup>

### 4.1.1. Thermodynamics of ET and PET

When designing a given reaction involving photoinduced electron transfer, it is important to know whether it is thermodynamically favored or not.<sup>117</sup> For this reason, the measurement of the reduction potentials of both the photocatalyst and the substrate is required. The obtained values can then be applied in the adequate equation. To calculate the free energy of a single electron transfer ( $\Delta G_{ET}$ ), the equation below is used:

$$\Delta G_{ET} = -F(E_{red} - E_{ox}) = -F[E_{1/2}(A/A^{\bullet-}) - E_{1/2}(D^{\bullet+}/D)] \quad (\text{Eq. I.5})$$

where  $F$  is the Faraday constant (23.061 kcal V<sup>-1</sup> mol<sup>-1</sup>),  $E_{red}$  and  $E_{ox}$  are the ground state redox potentials for species **A** (acceptor) and **D** (donor) describing the half reduction reaction for each species.  $E_{red}$ , also written as  $E_{1/2}(A/A^{\bullet-})$ , refers to the reduction potential of an acceptor **A** describing the single electron reduction according to the half-reaction  $A \rightarrow A^{\bullet-}$ .  $E_{ox}$ , also written as  $E_{1/2}(D^{\bullet+}/D)$ , corresponds to the oxidation potential of a donor **D** describing the half reduction reaction  $D^{\bullet+} \rightarrow D$ .

For a photoinduced electron transfer process, the free energy ( $\Delta G_{PET}$ ) is commonly determined by the following equation:

$$\Delta G_{PET} = -F[E_{ox}(D^{\bullet+}/D) - E_{red}(A/A^{\bullet-})] - w - E_{0,0} \quad (\text{Eq. I.6})$$

where  $w$  is an electrostatic work term and is usually omitted because the correction of  $w$  to  $\Delta G_{PET}$  is relatively small.  $E_{0,0}$  represents the excited state energy for a given catalyst. This equation is normally used in the selection of an appropriate photoredox catalyst for the desired transformation.  $\Delta G_{PET}$  is also represented by the simplified equations I.7 and I.8, in the case of an oxidant and reductant photoredox catalyst **cat\***, respectively. This allows the calculation of the excited state redox potential of the photocatalyst **cat**.

$$\Delta G_{PET} = -F[E_{red}^*(cat^*/cat^{\bullet-}) - E_{ox}(sub^{\bullet+}/sub)] \quad (\text{Eq. I.7})$$

$$\Delta G_{PET} = -F[E_{red}(sub/sub^{\bullet-}) - E_{ox}^*(cat^{\bullet+}/cat^*)] \quad (\text{Eq. I.8})$$

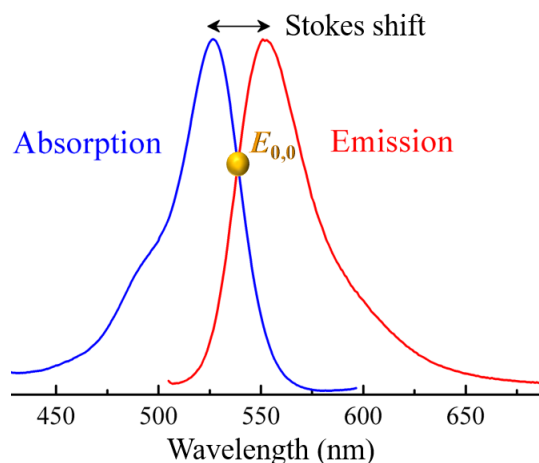
When a photoredox catalyst acts as an excited state oxidant (Eq. I.7),  $E_{red}^*$  is positive and must be more positive than the substrate **sub**  $E_{ox}$ , for the photoinduced oxidation to occur. Similarly, when a photoredox catalyst acts as an excited state reductant,  $E_{ox}^*$  is negative and must be more negative than the substrate **sub**  $E_{red}$  to be a thermodynamically favored photoinduced transfer.

The reduction potential of an excited state **cat\*** is related to its ground state reduction potentials and to the zero-zero excitation energy (in eV). This can be estimated using the equations below:

$$E_{red}^*(cat^*/cat^{\bullet-}) = E_{red}(cat/cat^{\bullet-}) + E_{0,0} \quad (\text{Eq. I.9})$$

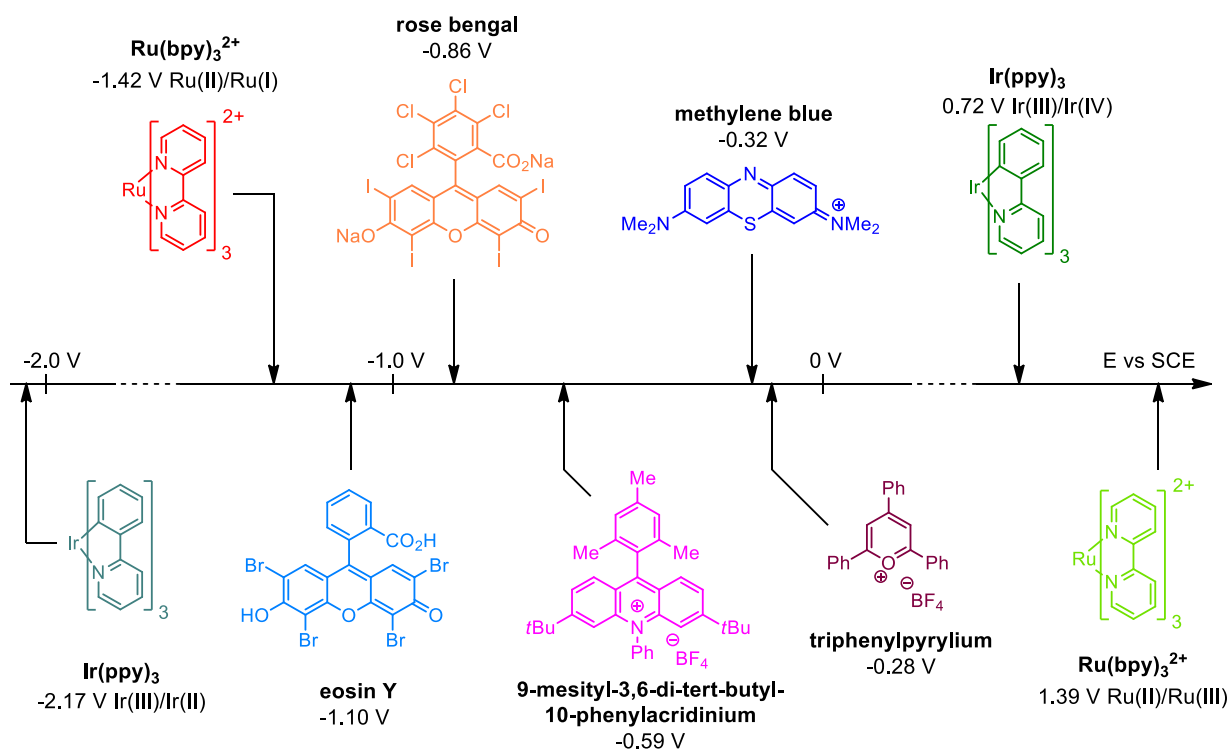
$$E_{ox}^*(cat^{\bullet+}/cat^*) = E_{ox}(cat^{\bullet+}/cat) - E_{0,0} \quad (\text{Eq. I.10})$$

$E_{0,0}$ , also written as  $E_{0,0}(cat^*/cat)$ , refers to the electronic spectroscopic energy of the excited state of a catalyst. The term **cat\*** corresponds to the  $S_1$  or  $T_1$  singlet excited states, with the corresponding  $E_{0,0}$  value ( $E_{0,0}^{S_1}$  or  $E_{0,0}^{T_1}$ ). The  $E_{0,0}$  is usually estimated by the intersection of the absorbance and the emission spectra (Figure I.12).<sup>117</sup>



**Figure I.12.** Estimation of the zero-zero excitation energy of an excited state.

Finally, the reduction potentials of the photocatalysts' and substrate's ground state are commonly measured by cyclic voltammetry (CV) (Figure I.13).<sup>118</sup>

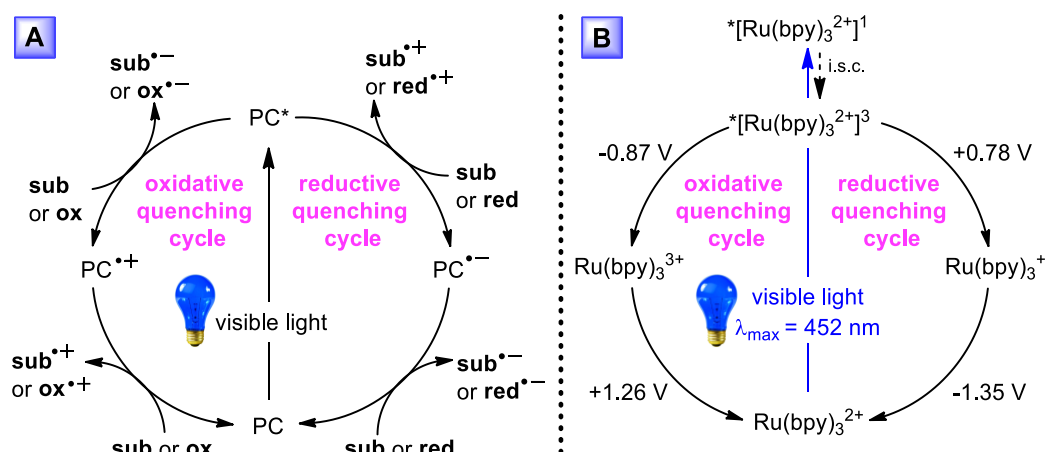


**Figure I.13.** Common photocatalysts and their reduction potentials measured by CV; potentials are reported against SCE.<sup>118</sup>

#### 4.1.2. Mechanistic schemes of photoredox catalysis

Most photoredox catalytic processes follow reductive or oxidative quenching cycles (Figure I.14.A). Upon excitation under visible light, a photocatalyst (PC) is promoted to an excited state. In an oxidative quenching cycle, the excited state **cat\*** is quenched by donating an electron to a substrate **sub** (in other words an oxidant **ox**) present in the reaction vessel. In a reductive quenching cycle, **cat\*** is quenched after accepting an electron from a substrate **sub** (in other words a reductant **red**). These redox reactions are governed by the reduction potentials of each catalytic species. This fact is

illustrated in the mechanistic cycles of the well-known photoredox catalyst, tris(2,2'-bipyridine)ruthenium(II) complex (Figure I.14.B).<sup>119</sup>

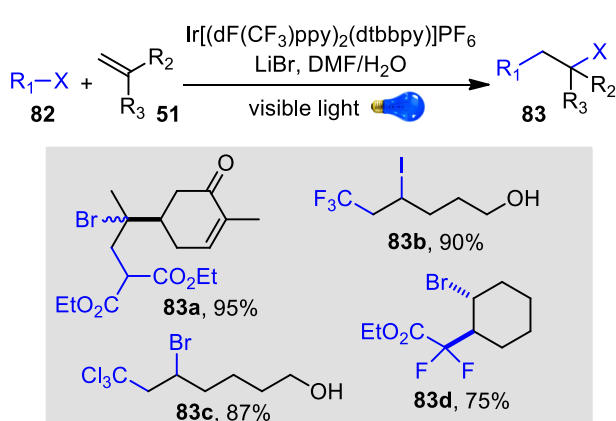


**Figure I.14.** A) Reductive and oxidative quenching cycles of a photocatalyst. B) Mechanistic cycles of [Ru(bpy)<sub>3</sub>]Cl<sub>2</sub>.<sup>119</sup>

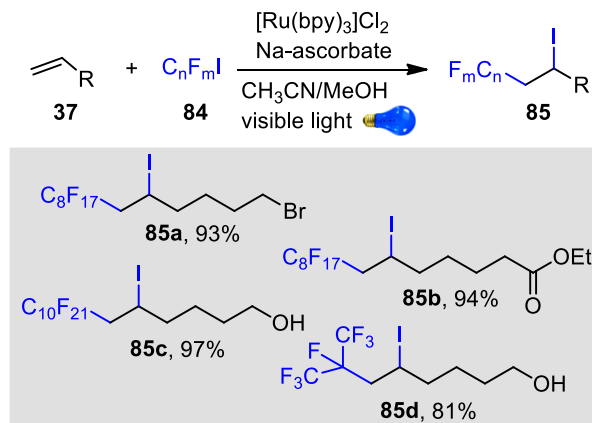
#### 4.1.3. ATRA reaction as an example of PET process

The photocatalyzed Atom Transfer Radical Addition reaction of organo-halides with  $\pi$ -systems was investigated by Stephenson's group<sup>120,121</sup> among others, using the ability of a photocatalyst to enter either in a reductive or an oxidative quenching cycle. Photoredox ATRA reactions were performed mediated by iridium Ir[(dF(CF<sub>3</sub>)ppy)<sub>2</sub>(dtbbpy)]PF<sub>6</sub> or ruthenium [Ru(bpy)<sub>3</sub>]Cl<sub>2</sub> complexes as photocatalysts, and were applied to the addition of a variety of mono- and di-substituted olefins (Scheme I.16). A wide scope of haloalkanes was isolated in excellent yields and controlled selectivity, proving the efficiency of the method.

##### Oxidative quenching cycle



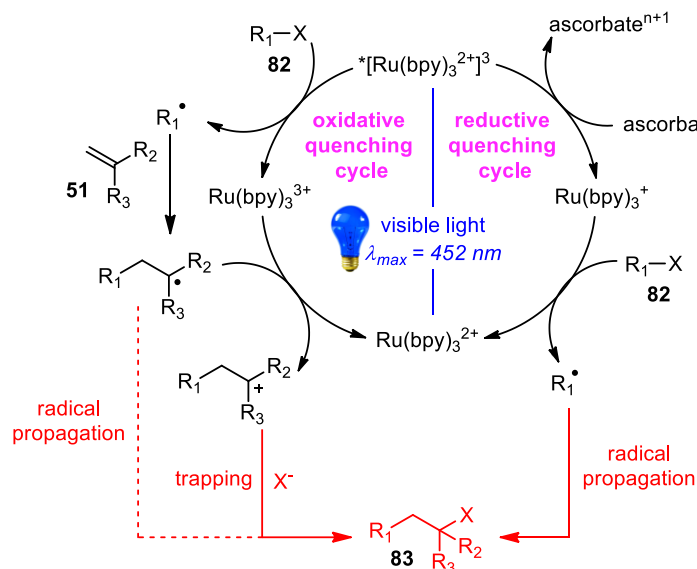
##### Reductive quenching cycle



**Scheme I.16.** Photocatalytic ATRA reported by Stephenson *et al.*<sup>120,121</sup>

Taking the example of [Ru(bpy)<sub>3</sub>]Cl<sub>2</sub> complex, its triplet excited state is reduced or oxidized depending on the reaction parameters (Figure I.15). In the reductive quenching cycle, the ascorbate acts as an electron donor and quenches the triplet excited state of [Ru(bpy)<sub>3</sub>]<sup>2+</sup>\*. The reduced catalyst [Ru(bpy)<sub>3</sub>]<sup>+</sup> with a strong reduction potential converts the alkyl halide **82** into a radical (R<sub>1</sub>•) that undergoes a radical chain mechanism to deliver the ATRA product **83**. In the oxidative quenching

cycle, the activated organohalide **82** is reduced into an electrophilic radical finally trapped by the alkene **51**. The generated nucleophilic radical may be oxidized by the photocatalyst to form a carbocation (radical-polar crossover process). The ATRA product **83** can be delivered through the trapping of the carbocation with a halide or through a radical chain process.



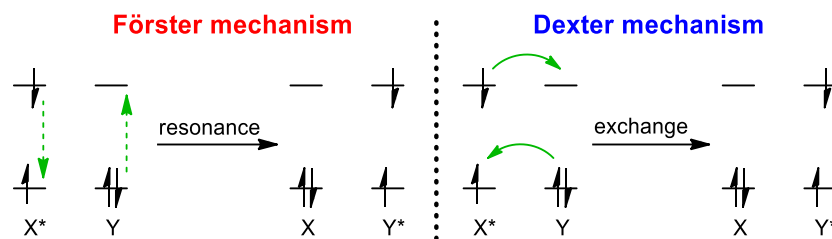
**Figure I.15.** Mechanism of the oxidative and reductive quenching cycles in ATRA reactions using  $[\text{Ru}(\text{bpy})_3]\text{Cl}_2$ .<sup>121</sup>

## 4.2. Energy transfer

The energy transfer is a process by which the excited state  $\text{X}^*$  is deactivated by interaction with a quencher  $\text{Y}$  (Eq. I.11). The excited state  $\text{Y}^*$  then undergoes deactivation through radiative or non-radiative processes (luminescence or reaction). The energy transfer process is considered favored if the energy of  $\text{Y}^*$  is lower than that of  $\text{X}^*$ .<sup>116</sup>



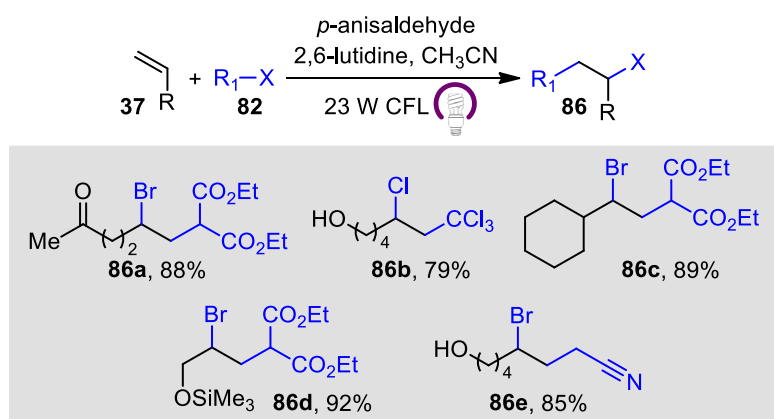
Radiative energy transfer, also called trivial energy transfer, takes place when  $\text{X}^*$  emits a photon that is reabsorbed by  $\text{Y}$ . In non-trivial energy transfer, the excited state undergoes resonant energy transfer (Förster mechanism), or electron exchange energy transfer (Dexter mechanism) (Figure I.16). In Förster Resonance Energy Transfer (FRET) mechanism, a donor initially in its electronic excited state transfers energy to an acceptor through nonradiative dipole-dipole coupling, this transfer can operate over long distances. The energy transfer through Dexter mechanism occurs when an excited electron is transferred from a donor to an acceptor through a non-radiative route. This process requires considerable overlap between the molecular orbitals of  $\text{X}$  and  $\text{Y}$ , which involves close transfer distances.



**Figure I.16.** Representation of a resonant energy transfer and an electron exchange energy transfer.<sup>116</sup>

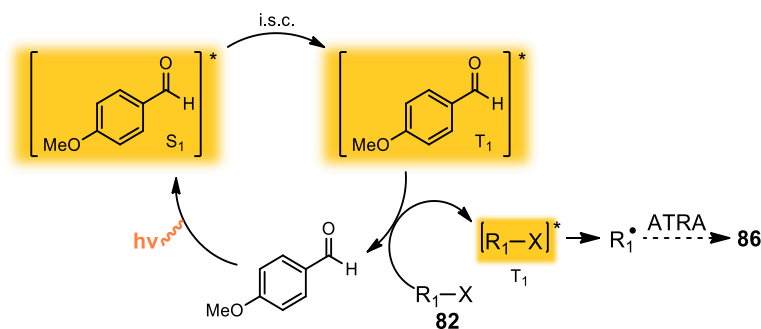
#### 4.2.1. *p*-Anisaldehyde-mediated energy transfer reaction

Melchiorre and co-workers<sup>122</sup> developed a metal-free photochemical method to perform an intermolecular ATRA reaction. They successfully engaged a simple organic molecule, *p*-anisaldehyde, in the radical addition of haloalkanes **82** onto olefins **37** in an efficient and selective manner (Scheme I.17). In their report, the reaction occurred under 23 CFL irradiation using olefins in excess, and in the presence of a base, 2,6-lutidine, as a scavenger. The optimal conditions were applied to a broad range of halides and olefins to afford the ATRA derivatives **86** in high to excellent yields.



**Scheme I.17.** Photocatalytic ATRA reported by Melchiorre *et al.*<sup>122</sup>

The mechanistic studies showed that the reaction follows an energy-transfer pathway (Figure I.17). Visible light irradiation (near UV region) promotes *p*-anisaldehyde to a singlet excited state which after intersystem crossing (i.s.c.) reaches the triplet state. The latter leads the haloalkane **82** to a triplet excited state through an energy transfer mechanism. This sensitization causes the homolytic cleavage of the C-X bond, which generates radical species, then reacting onto the alkenes'  $\pi$ -system. The bond dissociation energies of the alkyl halides used in this ATRA methodology are around 260–300 kJ.mol<sup>-1</sup>. These values are similar to the energy of the triplet excited state of *p*-anisaldehyde (300 kJ.mol<sup>-1</sup>), which is consistent with an energy transfer mechanism.



**Figure I.17.** Mechanism of an energy transfer in ATRA reactions.<sup>122</sup>

#### 4.2.2. Quantum yield of a photochemical reaction

The efficiency of a photocatalyst can be assessed by comparing the photochemical quantum efficiency for the formation of the desired product in the absence and presence of the sensitizer.<sup>116</sup> The quantum yield ( $\Phi$ ) is defined by the ratio of the number of formed products per unit of time to the number of photons absorbed per unit of time. It is expressed by the following equation:

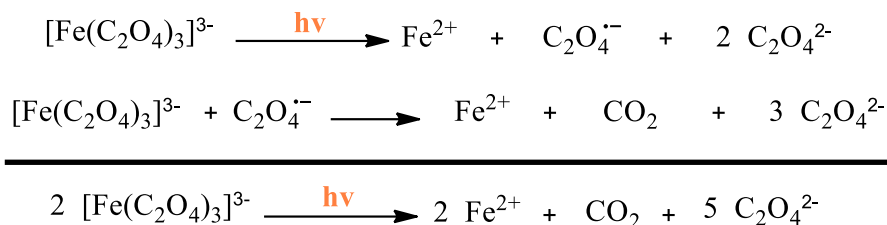
$$\Phi = \frac{n_{\text{product/s}}}{n_{\text{photons abs/s}}} \quad (\text{Eq. I.12})$$

The quantum yield is determined by irradiating the reaction vessel under a monochromatic light for a suitable time interval. Its value normally falls in the range between 0.0 and 1.0. To avoid secondary reactions, the measurement is usually limited to a conversion below 10%.

In order to calculate the quantum yield of a photochemical reaction, the number of absorbed photons on the reaction vessel has to be measured first. This measurement can be done using a chemical actinometer (potassium ferrioxalate, uranyl oxalate...) or a physical device (energy-meter, photodiode, solar cell...). A chemical actinometer, for instance, is a reference substance that undergoes a photochemical reaction with a known quantum yield. With the known quantum yield, this reaction can be used to determine the number of absorbed photons. After irradiation, the number of formed products is measured by analytical techniques (GC-MS, NMR...).

Among the chemical actinometers, potassium ferrioxalate (Parker's actinometer) is widely used as the most reliable reference for UV and visible light ( $< 420$  nm). After irradiation of the aqueous solution of  $\text{K}_3[\text{Fe}(\text{C}_2\text{O}_4)_3]$ , it decomposes into  $\text{CO}_2$  (Scheme I.18). After decomposition of  $[\text{Fe}(\text{C}_2\text{O}_4)_3]^{3-}$ , two  $\text{Fe}^{2+}$  ions are formed. The quantity of  $\text{Fe}^{2+}$  ions formed during the irradiation is then determined by adding phenanthroline which forms an orange-red complex  $[\text{Fe}(\text{phen})_3]^{2+}$  with a maximum of absorbance at  $\lambda = 510$  nm ( $\epsilon = 11100 \text{ M}^{-1} \text{ cm}^{-1}$ ). The quantity of  $\text{Fe}^{2+}$  can then be obtained by using UV-visible spectrometer and applying the Beer-Lambert law. Finally, the calculation of the quantum yield using ferrioxalate actinometer depends on the studied wavelength; for instance, the quantum yield of the formation of  $\text{Fe}^{2+}$  is 1.24 at 313 nm while it is 1.11 at 436 nm.





**Scheme I.18.** Decomposition of potassium ferrioxalate under visible light irradiation.<sup>116</sup>

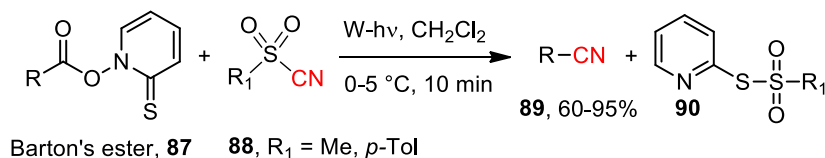
## 5. Sulfonyl radicals in photoredox catalysis

Sulfonyl derivatives have been used in organic synthesis as excellent radical traps due to their ability to undergo radical fragmentations through  $\alpha$ -scission. New photocatalytic methods were developed, especially in the last years, to activate these radical precursors under very mild conditions. Among the precursors widely used, one can cite sulfonyl halides, tri/difluoromethylsulfones, thiosulfones, sulfonyl selenides, sulfonyl azides, sulfonyl cyanides, sulfinates, etc.<sup>123</sup> In this section, only a few examples focusing on sulfonyl cyanide precursors will be described for illustrative purposes.

### 5.1. Photocatalyzed cyanation reactions

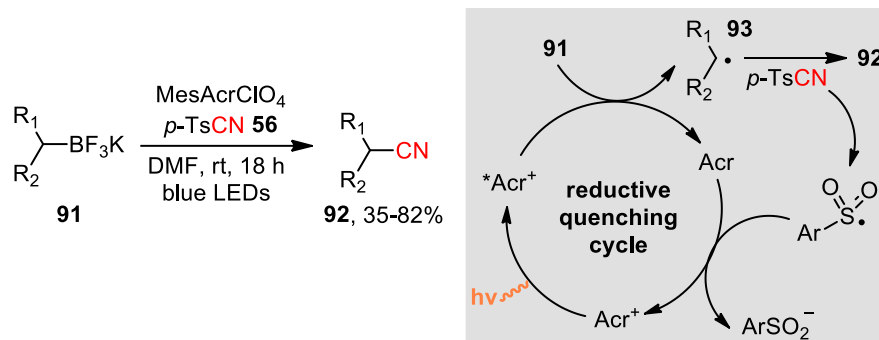
As stated in the general introduction, nitriles are considered among the most interesting functional groups in organic synthesis. The development of efficient and mild methods to introduce such a functional group onto an organic backbone is highly relevant. Sulfonyl cyanides (*p*-TsCN or MeSO<sub>2</sub>CN), trimethylsilyl cyanide (TMSCN) and cyanobenziodoxolone (CBX) are commonly used as cyanide sources and they can be activated by the means of photoredox catalysis.

Tosyl and mesyl cyanides were used by Barton and co-workers to trap the reactive carbon radical generated from acyl **87** under photochemical conditions (Scheme I.19).<sup>124</sup> This reaction afforded the nitriles **89** in high yields, better results being observed with mesyl cyanide as compared to tosyl cyanide. The generated sulfonyl radical then reacts with Barton's ester to generate **90** and a new C-centered radical R<sup>•</sup> which sustains the radical chain.



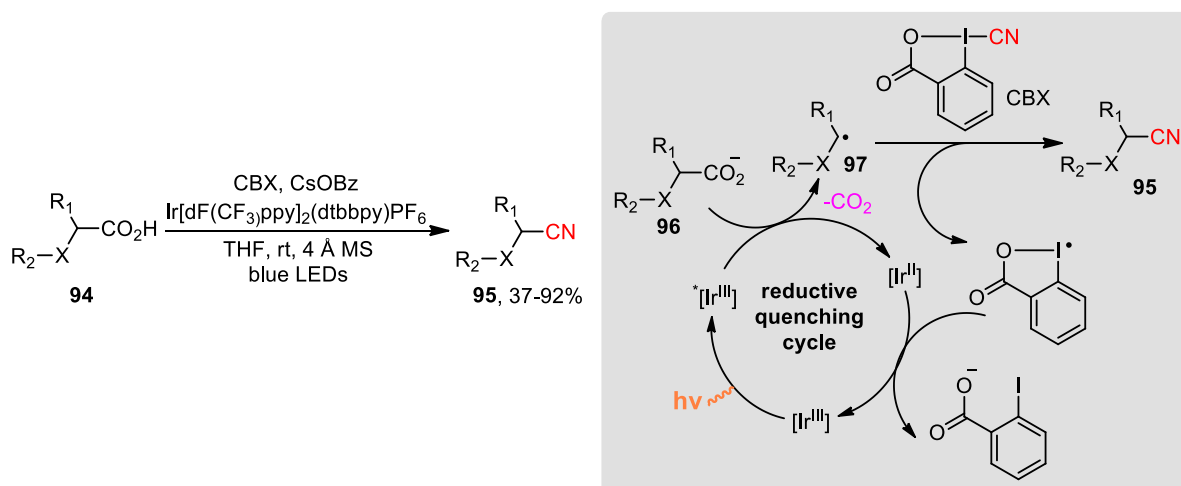
**Scheme I.19.** Photochemical cyanation reaction by Barton *et al.*<sup>124</sup>

Molander and co-workers<sup>125</sup> described the photoredox-catalyzed deboronative cyanation of alkyltrifluoroborates **91** using *p*-TsCN **56** as a cyanide source (Scheme I.20). The borate **91** follows deboronation using mesitylacridinium as a photocatalyst to generate alkyl radical **93**. The latter then reacts with the tosyl cyanide to afford the cyanide **92** in moderate to high yields. This process involves a reductive quenching cycle of the acridinium excited state. The reduced form of acridinium reduces then the sulfonyl radical into a sulfinate.



**Scheme I.20.** Photoredox-catalyzed deboronative cyanation by Molander *et al.*<sup>125</sup>

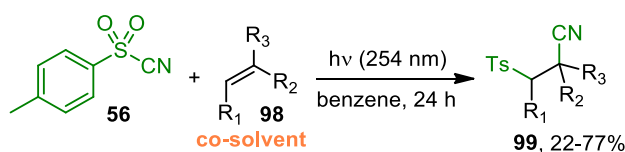
Waser and co-workers<sup>126</sup> reported a decarboxylative cyanation of carboxylic acids **94** using  $\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{dtbbpy})\text{PF}_6$  as a photocatalyst and CBX as a cyanating agent under visible light (Scheme I.21). The photocatalytic mechanism involves the reductive quenching of  $^*[\text{Ir}^{\text{III}}]$  complex by the carboxylate **96** formed *in situ* to elaborate the nucleophilic radical **97** after immediate decarboxylation. This radical is then trapped by CBX to deliver the cyanide **95** and the iodine-centered radical. The latter is later reduced by  $[\text{Ir}^{\text{II}}]$  species to regenerate the ground state photocatalyst  $[\text{Ir}^{\text{III}}]$ .



**Scheme I.21.** Decarboxylative cyanation of carboxylic acids by Waser *et al.*<sup>126</sup>

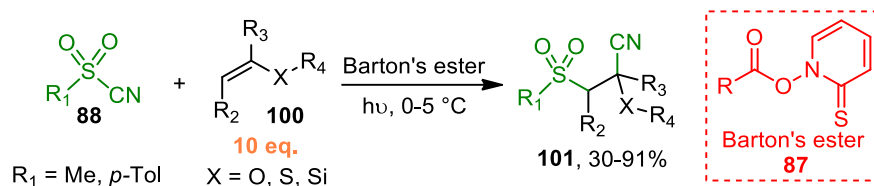
## 5.2. Photoredox-catalyzed sulfonyl-cyanation of olefins

Sulfonyl cyanides can also be activated photochemically to generate sulfonyl radicals as radical traps. The first photochemical addition of sulfonyl cyanides to olefins was reported in 1971 by Pews and co-workers (Scheme I.22).<sup>127</sup> In this report, the commercially available *p*-toluenesulfonyl cyanide **56** was used as a sulfonyl cyanide source and was added to olefins **98** under UV-activation (254 nm). In this reaction, the olefin is used as a co-solvent.



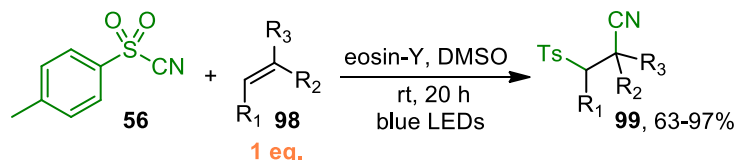
**Scheme I.22.** Photochemical sulfonyl-cyanation reported by Pews *et al.*<sup>127</sup>

The sulfonyl cyanation of olefins was also reported in 1992 by Barton and co-workers (Scheme I.23).<sup>128</sup> The photolysis of Barton's ester at low temperature gave access to a range of functionalized derivatives **101**. This method presents few drawbacks such as its restriction to electron-rich olefins **100** that are used in large excess (10 eq.) and the limitation of the sulfonyl cyanide source to mesyl and tosyl cyanides.



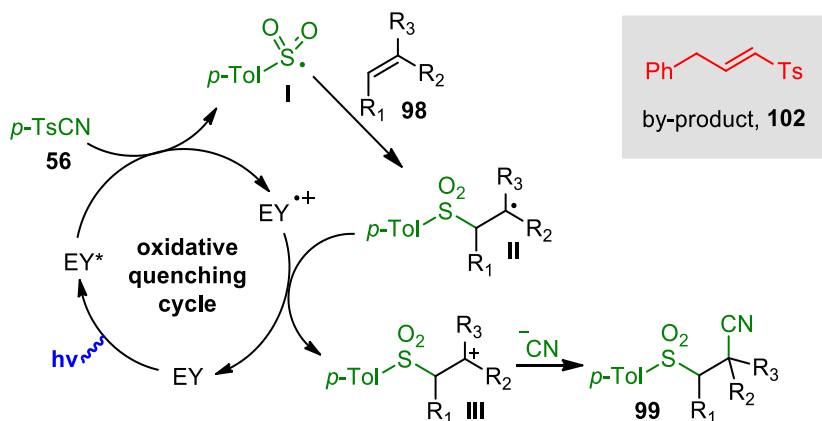
**Scheme I.23.** Reported sulfonyl-cyanation by Barton *et al.*<sup>128</sup>

Recently, Chu and co-workers<sup>129</sup> reported a visible light-mediated sulfonyl-cyanation of olefins using *p*-toluenesulfonyl cyanide **56** as a sulfonyl source (Scheme I.24). The reaction was catalyzed by eosin-Y as a cheap photocatalyst to elaborate a broad scope of  $\beta$ -sulfonyl nitriles **99** in good to high yields.



**Scheme I.24.** Eosin-mediated sulfonyl-cyanation by Chu *et al.*<sup>129</sup>

The group proposed that the reaction involves a photoinduced electron transfer mechanism through an oxidative quenching cycle (Figure I.18). After irradiation, eosin-Y underwent a photoinduced electron transfer generating a sulfonyl radical **I**. The latter added to the olefin and the new nucleophilic radical **II** underwent oxidation by the semi-oxidized eosin to form the carbocation **III**. The carbocation was later trapped by a cyanide anion to deliver the  $\beta$ -sulfonyl nitrile **99**. 5% of by-product **102** formed through elimination of the carbocation intermediate suggested a radical-polar crossover mechanism.



**Figure I.18.** Proposed mechanism of the sulfonyl-cyanation by Chu *et al.*<sup>129</sup>

[illegible]

{ 63 }

## 6. Conclusion

In the second part of this chapter, a brief overview of the basic concepts and principles of photoredox catalysis was discussed. Photoredox catalysis allows the smooth generation of radical intermediates under very mild conditions, and its impact on the development of selective radical reactions is noticeable, explaining its current blooming. Photocatalyzed reactions circumvent the use of radical mediators including tin reagents. This chemistry allows the formation of multiple chemical bonds and the assembly of structurally complex molecules in a green and economic manner, with a foreseen impact on the way of preparation of useful pharmaceuticals and agrochemical drugs. Furthermore, the sulfonyl derivatives proved to be excellent radical traps and showed their ability to generate new carbon-centered radicals under photocatalytic conditions. Photoredox catalysis represents nowadays one of the most efficient methods to initiate radical processes through electron or energy transfer.

## *Chapter II*

# *The Chemistry of Small Rings*

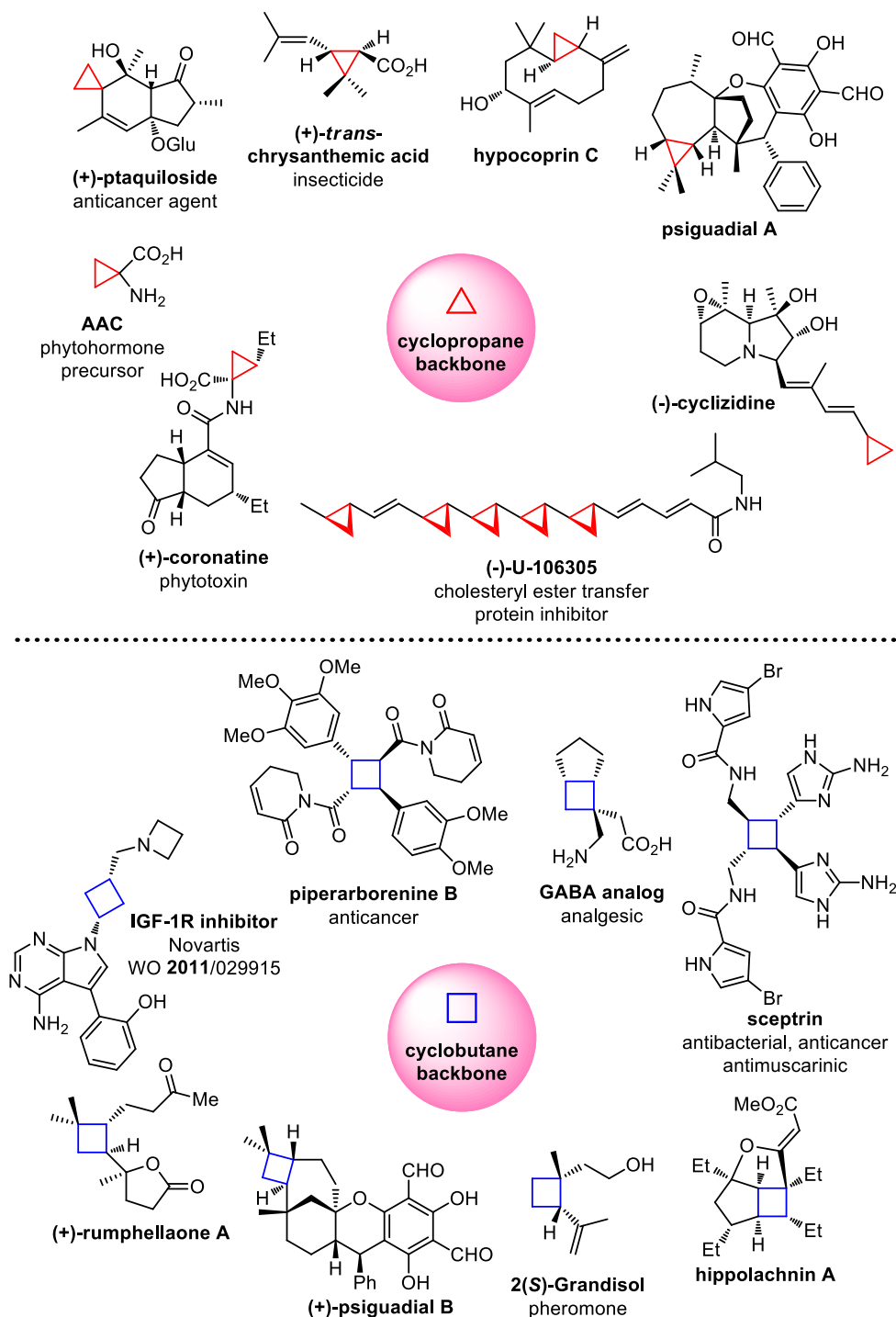


## 1. Carbocyclic small-sized rings in nature

Cyclopropanes and cyclobutanes, as the smallest monocyclic all-carbon rings, are encountered frequently in the plant kingdom, microorganisms, and marine organisms as well as in biomolecules including proteins, lipids, carbohydrates, nucleic acids, and pheromones (Figure II.1).<sup>130–135</sup> The structural novelty and potential biological properties of the cyclopropane and/or cyclobutane-containing natural products have attracted a wide interest from synthetic chemists and pharmaceutical companies.

Besides their presence in nature, small-sized rings have emerged in the past decade as extremely useful intermediates for chemical synthesis. They can be engaged in complex transformations<sup>134</sup> or submitted to ring-expansion and ring-cleavage reactions to provide a variety of carbocycles, heterocycles, and acyclic derivatives.<sup>136–138</sup> Their strained skeletons allowed their functionalization in a creative manner and inspired for the development of innovative stereoselective tactics.<sup>139–141</sup> Despite these attractive characteristics, their synthesis may still constitute a hurdle, mostly because of this same strained nature. Therefore, understanding the relationship between their geometry, electronic structure (bond lengths, angles...), strain energy on one side and their reactivity on the other side is very important for the development of new synthetic approaches.





**Figure II.1.** Selected cyclopropane/cyclobutane-containing natural products and drugs.

## 2. Geometry of small carbocyclic rings

Cyclopropane with  $C_3H_6$  molecular formula is the smallest cycloalkane. It was discovered and characterized by August Freund in 1882.<sup>142</sup> Its industrial production began around 1930 after the discovery of its very powerful anesthetic properties.<sup>143</sup> Cyclobutane, as the second smallest carbocycle with  $C_4H_8$  molecular formula, was first synthesized in 1887.<sup>144</sup> Although it has only one extra carbon atom compared to cyclopropane, this small difference has a big impact on its electronic structure and the spatial organization of atoms. Cyclobutane shows very original geometric features and reactivity pattern that lies between the “unique” cyclopropane and the “normal” cycloalkanes (Table II.1).<sup>145</sup> These main features will be discussed in the following paragraphs.

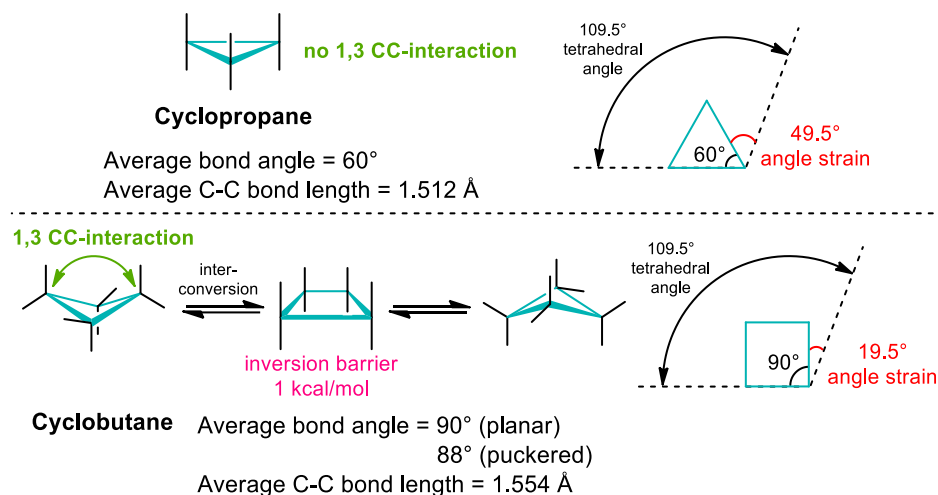
compound	bond angle (°)	bond length (Å)
cyclopropane	60	1.512
cyclobutane	88	1.554
cyclopentane	109	1.546
cyclohexane	109.5	1.536

**Table II.1.** Comparison of selected properties of cycloalkanes.

## 2.1. Structure and bonding

Because of their small ring size, cyclopropane and cyclobutane possess strained structure not encountered in bigger sized cycles. This ring strain is divided into two main contributors; the angle strain and the torsional strain.<sup>145,146</sup> The former, also called Baeyer strain, results from the compressing of the bond angles to less than the ideal 109.5° tetrahedral value. The latter, also called Pitzer strain, results from the unfavorable eclipsing of bonds on neighboring atoms (Figure II.2). The geometry of the cyclobutane holds unique features that are absent in the cyclopropane. For instance, although the cyclobutane has less angle strain than the planar cyclopropane, it has more torsional strain because of its larger number of ring hydrogens. To reduce the hydrogen-hydrogen eclipsing interactions, the cyclobutane adopts a non-planar conformation where one carbon atom rotates out of the plane by *ca* 25°. This folded conformation is not rigid, it interconverts rapidly from one bent conformation to another due to its low inversion barrier (1 kcal/mol). Although this puckering relieves some torsional strain with a global gain of around 1.5 kcal/mol, it increases the bond angle strain (the C-C-C bond angle is reduced from 90° in square planar to 88° in puckered geometry).<sup>147</sup> Thus, the equilibrium geometry is a result of the tension between these two strain terms.

Another specific feature of the cyclobutane structure is that the methylene groups are rotated inwards the concave face. Bartell and Anderson suggested that the methylene groups prefer a local  $C_{2v}$  geometry in order to favor the overlap of the “bent” bonds.<sup>148</sup> It was also observed in a variety of cyclobutane backbones that the C-C bond is long compared to a normal single bond (1.54 Å). The C-C bond lengths vary in a range of 1.521-1.606 Å depending on the substitution environment, with an average of 1.554 Å.<sup>149</sup> The long C-C bond length in cyclobutane compared to the short length in cyclopropane (1.512 Å) may be credited to the repulsive 1,3 C-C non-bonded interactions (Dunitz-Shomaker strain).<sup>150</sup> In cyclopropane, Dunitz-Shomaker strain is absent as all the carbons are bonded to each other, whereas, cyclobutane has two 1,3 C-C non-bonded repulsions with a relatively small distance between the carbons. These repulsions lead to lengthening the C-C bonds.<sup>145,147</sup>



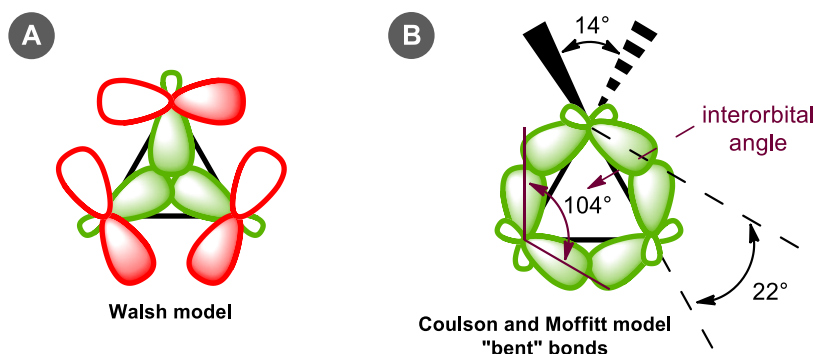
**Figure II.2.** Comparison of the angle strain in cyclopropane and cyclobutane.

## 2.2. Hybridization and molecular orbitals

The short bond lengths in cyclopropane are in part explained by the molecular orbital theory. Since the cyclopropane is an equilateral triangle with an internuclear angle of  $60^\circ$ , in order to overlap effectively, the orbitals contributing in forming the C-C bonds of the ring possess a higher  $p$ -character than those in a normal  $sp^3$  hybridization (with the ideal  $109.5^\circ$  tetrahedral angle). Consequently, the carbon orbitals forming the carbon-hydrogen bonds present more  $s$ -character (33%  $s$ -character vs. the normal value of about 25%  $s$ -character).<sup>151</sup> This increase in the  $s$ -character contributes to shortening and strengthening the C-H bonds.

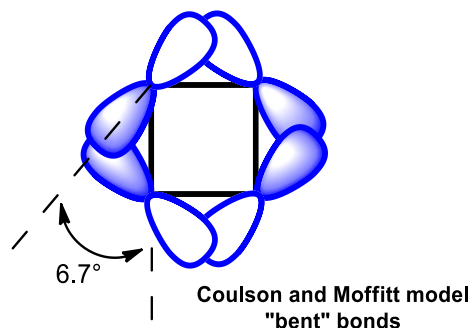
In order to understand the electronic environment and the nature of bonding in cyclopropane, two models have been proposed, the Walsh model<sup>152</sup> and the Coulson-Moffitt model<sup>153</sup> (Figure II.3). Although some divergence exists, both theories propose that the electron density between two carbon atoms in cyclopropane is the highest outside the C-C axis.<sup>154</sup> In the first model, Walsh suggested his structure based on the assumption that the carbon atoms are  $sp^2$  hybridized. In this model, the  $sp^2$  hybridized orbitals are combined with three  $p$  orbital, each one is oriented tangentially with respect to the ring (Figure II.3.A). The poor overlap of the methylene orbitals is the origin of the angular strain and the pseudo- $sp^2$  reactivity of cyclopropane.<sup>152</sup>

In the model proposed by Coulson and Moffitt,<sup>153</sup> cyclopropane is described as so-called banana bonds or bent bonds which are  $sp^3$  hybridized but with a greater  $p$ -character (Figure II.3.B). Such hybridization is required for the bond to deal with a smaller angle. In this system, the six equivalent hybrids are not pointed directly towards each other, and the interorbital angle is estimated to be  $104^\circ$  (close to  $109.5^\circ$ ). This interorbital angle corresponds to 80%  $p$ -character in the C-C bonds vs. the normal value of about 75%  $p$ -character. *Ab initio* calculations were performed to determine the bond angle bending. This may be described in terms of the angle between the C-C bond paths at the C center. Coulson and Moffitt reported that with cyclopropane, the angle deviates from the conventional angle by  $22^\circ$ . The banana-shaped bonds in cyclopropane derivatives have been observed by X-ray crystallographic studies such as in the case of certain rotanes.<sup>155,156</sup>



**Figure II.3.** Proposed bonding models for cyclopropane.

Coulson and Moffitt applied their bent bond model to cyclobutane as well (Figure II.4). They concluded that cyclobutane should be more like cyclopentane than like cyclopropane. The deviation angle for cyclobutane was determined to be inferior to the one of cyclopropane with a value of  $6.7^\circ$ .<sup>157,158</sup>



**Figure II.4.** Coulson-Moffitt model representation for cyclobutane.

### 2.3. Bond strengths

The aforementioned theoretical studies were found to be consistent with the C-H bond force constant ( $k_{\text{C-H}}$ ) and the bond dissociation energy (Table II.2).<sup>159</sup> Both are greater in cyclopropane than in cyclobutane. Concerning the latter, the properties of its C-H bonds are closer to those of the other cycloalkanes than those of cyclopropane, although there is an indication of increased *s*-character. The C-H bond lengths are therefore shortened, and the bond dissociation energy is calculated to be greater than that of cyclohexane in an order of 1.5 kcal/mol. These features confirm that cyclobutane has a hybridization between that of cyclopropane and cyclopentane, and is closer to the latter.<sup>145</sup>

compound	$k_{\text{C-H}}^a$	BDE <sup>b</sup>
cyclopropane	6.3	108.4
cyclobutane	5.1 <sup>c</sup>	99.8 <sup>c</sup>
cyclopentane	4.2 <sup>c</sup>	95.5 <sup>c</sup>
cyclohexane	5.3 <sup>c</sup>	98.4 <sup>c</sup>

**Table II.2.** Cycloalkanes C-H force constants and bond dissociation energies (BDE). <sup>a</sup> Calculated at the B3LYP/6-311+G\* level of theory. <sup>b</sup> In kcal/mol; calculated at the G3B3 level of theory. <sup>c</sup> Equatorial hydrogens.<sup>145</sup>

## 2.4. Energies of small carbocycles

Another aspect to consider is the strain energy.<sup>145,146</sup> It is defined as the difference in heat of formation between the compound of interest and that of an unstrained model. Strain energy is typically released when the constituent atoms of a given molecule are allowed to rearrange themselves in a chemical reaction. For instance, cyclohexane has no strain energy while cyclopentane has small strain energy resulting from the partial eclipsing of adjacent C-H bonds in addition to some bond angle strain (Table II.3). Cyclopropane and cyclobutane have similar strain energy (27.5 kcal/mol for cyclopropane vs. 26.3 kcal/mol for cyclobutane) with only 1.2 kcal/mol of difference. This appears hard to rationalize considering the significantly reduced C-C-C bond angles and their difference in hybridization. Dunitz and Shomaker proposed that the C-C transannular interactions absent in cyclopropane and present in cyclobutane are the reason behind this observation and contribute significantly to the structure's strain energy.<sup>147,150</sup>

compound	$\Delta H_f$	strain energy
cyclopropane	$12.7 \pm 0.1$	27.5
cyclobutane	$6.6 \pm 0.3$	26.3
cyclopentane	$-18.3 \pm 0.2$	6.3
cyclohexane	$-29.5 \pm 0.2$	0.0

**Table II.3.** Heats of formation and strain energy of some cycloalkanes, gas phase, 25 °C, kcal/mol.<sup>145</sup>

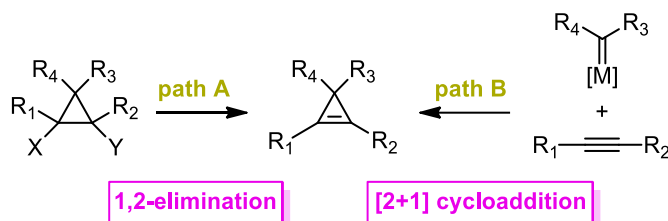
The foregoing results may explain the origin of the unusual properties and unexpected reactivity of these rings. The reactivity of the cyclopropyl ring resembles more to that of the carbon-carbon double bonds than that of a cycloalkane of a larger size. The extra energy of cyclopropane makes the C-C bond cleavage thermodynamically favorable due to the large strain release. Cyclobutane with similar strain and homolytic fragmentation energy (61 kcal/mol for cyclopropane vs. 62.5 kcal/mol for cyclobutane), however, does not possess the same reactivity and is considered inert.<sup>145</sup> Due to its decreased reactivity, the cyclobutane template has been less studied compared to its three-membered counterpart.<sup>138,160–163</sup>

## 3. Construction of cyclopropene/butene templates

Over the years, saturated small-sized rings have been synthesized through various pathways.<sup>164–166</sup> Among the main approaches is the functionalization of their corresponding olefins. This route is particularly interesting as it gives an entry to a rich library of cyclopropanes/butanes with a variety of functionalities starting from the same cyclopropene/butene precursor. Since this strategy is appealing and was adopted during this work, the main synthetic aspects of cyclopropenes/butenes will be highlighted in the next section.

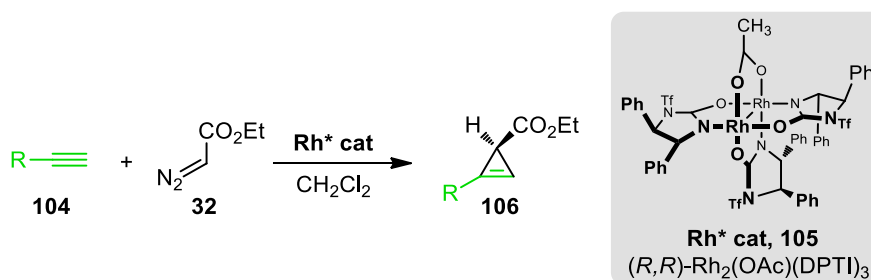
### 3.1. Synthesis of cyclopropenes

Unsaturated three-membered rings are well appreciated in organic synthesis as reactive substrates. They were synthesized through several synthetic approaches, yet two main routes were frequently employed (Scheme II.1).<sup>167,168</sup> The first one makes use of a pre-existing functionalized cyclopropane that undergoes 1,2-elimination (path A). The second route involves a [2+1] cycloaddition with alkynes (path B). This approach requires the use of highly reactive carbene intermediates, usually generated by decomposition of diazo compounds with transition metals. Although both routes are reliable, only an illustrative example of the metal-catalyzed cyclopropenation (path B) will be provided here.



**Scheme II.1.** Main synthetic routes to prepare cyclopropenes.

Among the most efficient ways to access cyclopropenyl esters, is the reaction discovered by Noels *et al.*<sup>169</sup> In this reaction, alkyl diazoacetates **32** were added to an excess of the appropriate alkyne **104** in the presence of a catalytic amount of rhodium acetate  $\text{Rh}_2(\text{OAc})_4$  to deliver the corresponding cyclopropenes **106** in excellent yields. An enantioselective version of this reaction was later developed.<sup>49,170,171</sup> Corey *et al.*<sup>49</sup> described the [2+1] cycloaddition of **32** to **104** in presence of 0.5 mol % of (*R,R*)- $\text{Rh}_2(\text{OAc})(\text{DPTI})_3$  **105** as a catalyst to obtain the enantiopure desired adducts **106** (Scheme II.2). The chiral catalyst **105** was found highly efficient in terms of selectivity, yield and reaction scope.



**Scheme II.2.** Enantioselective synthesis of cyclopropene through metal-catalyzed [2+1] cycloaddition.<sup>49</sup>

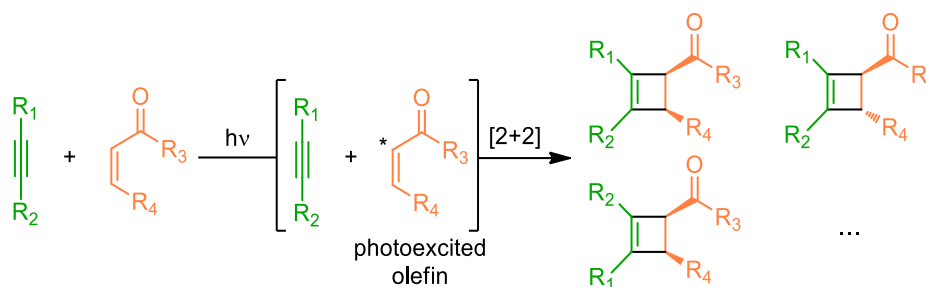
### 3.2. Synthesis of cyclobutenes

During the past decade, an increasing number of synthetic methods to prepare cyclobutene substrates have emerged. However, the access to enantioenriched cyclobutenes remains a demanding synthetic challenge.<sup>164,165,172</sup> The reported strategies are often based on the target molecule and very rarely, in order to obtain a general route to access enantiopure unsaturated four-membered rings. The [2+2] cycloaddition of alkynes with alkenes is regarded as a versatile approach to construct

cyclobutenes. This has been achieved mainly by thermal reactions *via* biradical intermediates, photoreactions, Lewis acid-catalyzed cycloadditions, and transition-metal-catalyzed reactions.<sup>164</sup> Yet, the scope is still limited. Other catalytic methods for accessing cyclobutenes were also developed, such as ring expansions,<sup>173</sup> but they will not be discussed in this chapter.

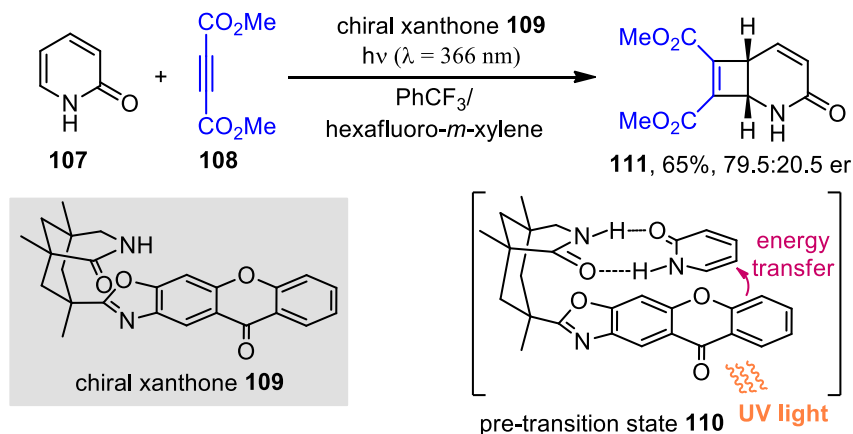
### 3.2.1. Photochemical reactions

Concerted [2+2] photocycloadditions often employ a photosensitizer (*e.g.*, benzophenone). During this process, an energy transfer occurs from an excited-state photosensitizer to a cycloaddition substrate. Such intermolecular reactions usually suffer from low yields and low selectivity due to the poor regioselectivity and poor differentiation of the enantiotopic faces of the substrate (Scheme II.3).<sup>174</sup>



**Scheme II.3.** Potential products of a photochemical [2+2] cycloaddition.

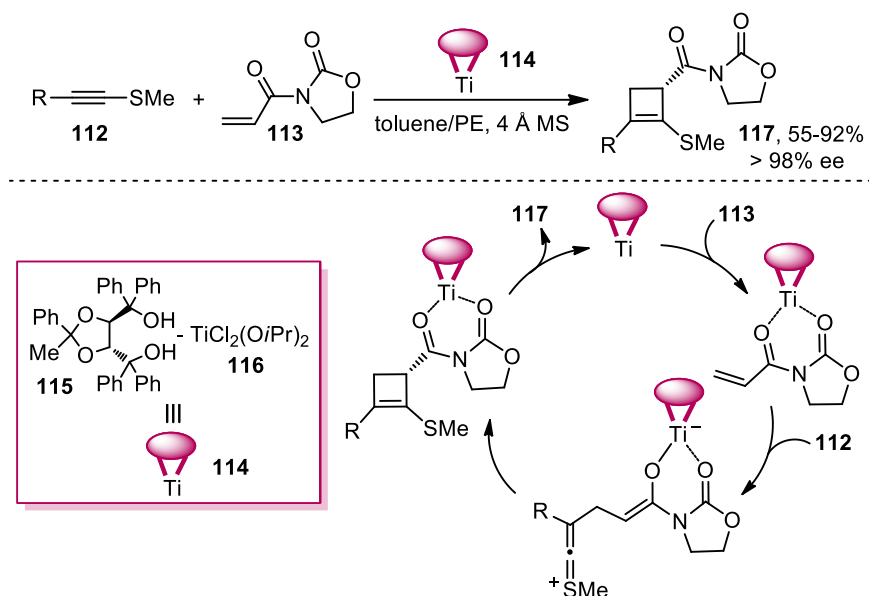
To address this issue, Bach and co-workers developed new chiral triplet sensitizers that allow enantioselective photocycloadditions to proceed. In these systems, the chiral catalyst is bound to the substrate through noncovalent interactions (hydrogen bonds). Upon excitation, the sensitizer maintains communication with the substrate and the energy transfer will favorably occur to the proximally bound substrate. Following this principle, the chiral xanthone **109** was specifically designed for the 2-pyridones **107** (Scheme II.4). Acetylenedicarboxylates **108** were thus added to the excited 2-pyridones **107**, furnishing densely functionalized scaffolds **111** with high enantioface differentiation.<sup>175</sup>



**Scheme II.4.** Intermolecular photochemical [2+2] by Bach *et al.*<sup>175</sup>

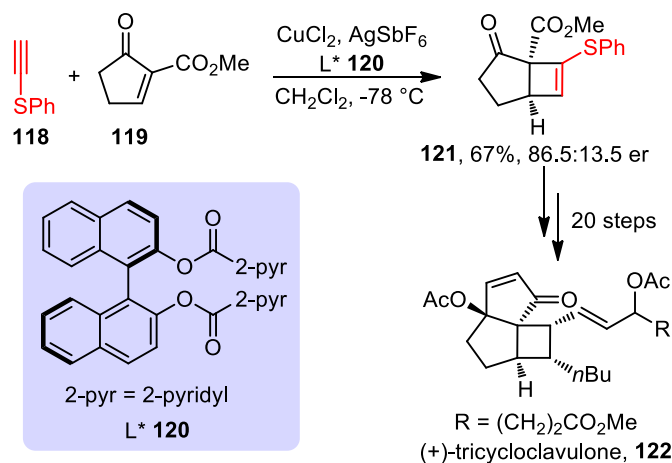
### 3.2.2. Lewis acid-catalyzed reactions

The use of Lewis acid catalysts in the catalyzed cycloadditions has proven to be effective in the enantioselective synthesis of optically pure cyclobutenes. This approach typically involves the use of polarized alkynes and follows a stepwise reaction mechanism with generation of charged intermediates. One of the most efficient methods for enantioselective syntheses of cyclobutenes was developed by Narasaka and Hayashi.<sup>3</sup> The donor-acceptor [2+2] cycloaddition involves the use of a cheap chiral titanium complex **114** as a catalyst (Scheme II.5). The derived tartaric acid ligand **116** induces high enantioselectivity in the cycloaddition of alkynylsulfides **112** with oxazolidinone enamide **113** to give the enantiomerically pure cycloadducts **117** in high yields.



**Scheme II.5.** Lewis acid-catalyzed [2+2] cycloaddition by Narasaka *et al.*<sup>3</sup>

Iguchi and co-workers<sup>176,177</sup> engaged the activated alkynylsulfide **118** in an enantioselective [2+2] cycloaddition with cyclopentenone derivative **119** (Scheme II.6). This reaction was catalyzed by the chiral ligand **120** in combination of  $\text{CuCl}_2$  and  $\text{AgSbF}_6$ . Surprisingly, more common chiral catalysts such as Ti/TADDOL and Cu/BOX were found ineffective towards this transformation. The cycloadduct intermediate **121** was used in the total synthesis of (+)-tricycloclavulone **122**.



**Scheme II.6.** Lewis acid-catalyzed [2+2] cycloaddition by Iguchi *et al.*<sup>176</sup>



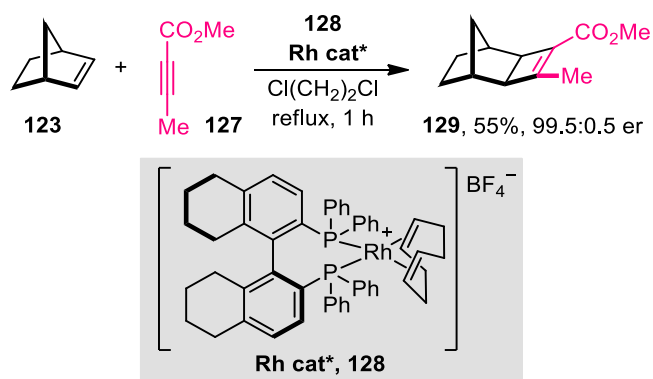
### 3.2.3. Transition metal-catalyzed reactions

[2+2] cycloaddition reactions involving nonactivated alkynes were also reported. This class of reactions is usually catalyzed by transition metals that are capable of coordinating to the  $\pi$ -binding site of the carbon-carbon double bond, permitting thus, the reaction with the nonactivated alkynes. For instance, using ruthenium complex **125**, Watanabe and co-workers<sup>178</sup> reported the cyclization of unactivated alkynes **124** with norbornene **123** to give the strained cyclobutenes **126** (Scheme II.7). It is worth noting that engaging ring-strained alkenes such as norbornene derivatives in cycloaddition reactions is one of the used strategies to make the transformation more practical.



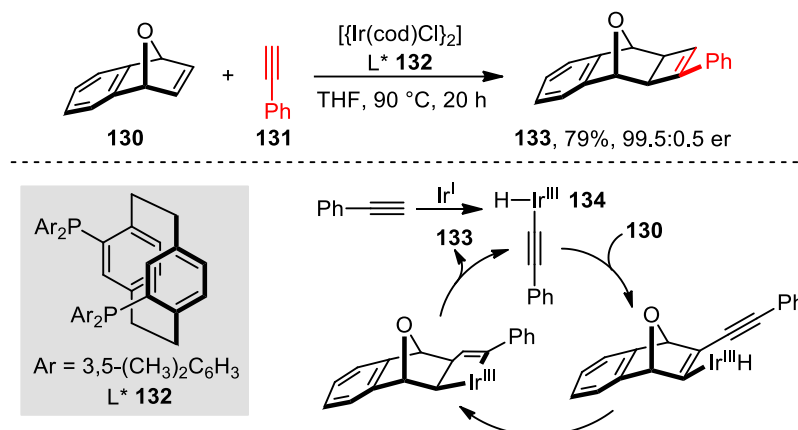
**Scheme II.7.** Metal-catalyzed [2+2] cycloaddition with norbornene.<sup>178</sup>

An enantioselective version of this reaction was later developed by Shibata and co-workers using norbornene derivative **123** as alkene source (Scheme II.8).<sup>179</sup> This reaction was promoted by the rhodium complex **128** and delivered the cyclobutene **129** in good yield and high enantioselectivity.



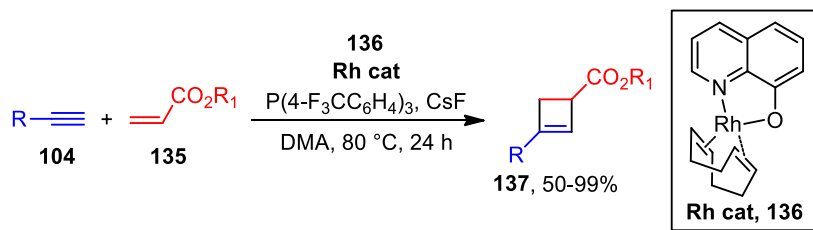
**Scheme II.8.** Rhodium-catalyzed [2+2] cycloaddition by Shibata *et al.*<sup>179</sup>

Shao and co-workers<sup>180</sup> reported an iridium-catalyzed enantioselective [2+2] cycloaddition of bicyclic alkene **130** and terminal alkyne **131** giving the corresponding ring **133** in high yield and enantioselectivity in the presence of enantiopure *para*-cyclophane **132** (Scheme II.9). Mechanistic studies proposed an oxidative addition of iridium complex to **131** to generate a [hydrido(alkyne)iridium(III)] adduct **134**. The latter then undergoes migratory insertion followed by reinsertion and reductive elimination to furnish the cyclobutene **133**.<sup>181</sup>



**Scheme II.9.** Iridium-catalyzed [2+2] cycloaddition. Cod = 1,5-cyclooctadiene.<sup>180,181</sup>

Unlike cyclopropenes, the enantioselective synthesis of cyclobutene-type **137** is rare and only one racemic method was reported to date by Sakai and co-workers (Scheme II.10).<sup>182</sup> The group reported a direct access to cyclobutene **137** through a rhodium-catalyzed intermolecular [2+2] cycloaddition of terminal alkynes **104** with electron-deficient alkenes **135**. The reaction was applied to a series of substrates and gave the corresponding cycloadducts **137** in good to high yields and excellent regioselectivity. Although the motif **137** is highly valuable, this reaction was not extended into enantioselective series and requires expensive rhodium catalyst **136** that must be prepared from  $[\text{RhCl}(\text{cod})]_2$ .

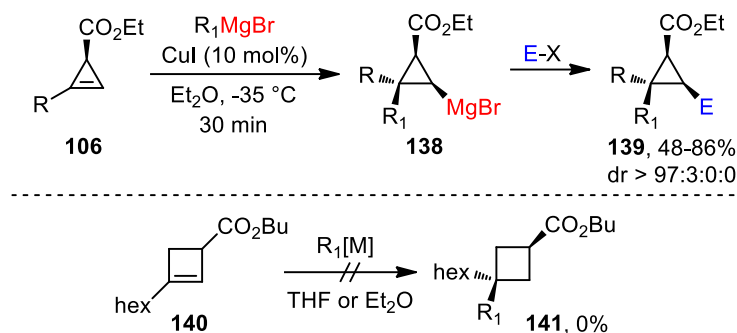


**Scheme II.10.** Rhodium-catalyzed intermolecular [2+2] cycloaddition of terminal alkynes by Sakai *et al.*<sup>182</sup>

#### 4. Reactivity: cyclopropene vs. cyclobutene

The functionalization of the above-described strained cyclopropenes/butenes was studied by many researchers, not only in order to give access to the corresponding saturated rings but also to understand the properties of their parents. Both olefin parents showed a difference in reactivity. Cyclopropene behaves as both electrophile and nucleophile.<sup>167,168,183,184</sup> The highly acidic proton of the C( $sp^2$ )-H bonds, due to the ring strain, allows easy deprotonation and further functionalization with electrophiles. The addition of organometallic species (hydrides, Grignard reagents, organocuprates, zinc reagents...) also reveals the cyclopropene's electrophilicity. One of the examples that illustrate this behavior is the results published by Marek and co-workers.<sup>185</sup> During their studies, a diastereoselective carbometalation of cyclopropenes was developed, delivering a wide scope of poly-substituted cyclopropanes bearing an all-carbon quaternary stereocenter with excellent diastereomeric ratios (Scheme II.11). The extension of the carbometalation reaction to cyclobutene ester **140** was however unsuccessful. The difference of behavior between both carbocycles **106** and

**140** towards the addition of organometallic species across the  $\pi$ -bond was rationalized by the difference in strain energy released during the carbometalation reaction (cyclopropene to cyclopropane: 30 kcal/mol; cyclobutene to cyclobutane: 6 kcal/mol).

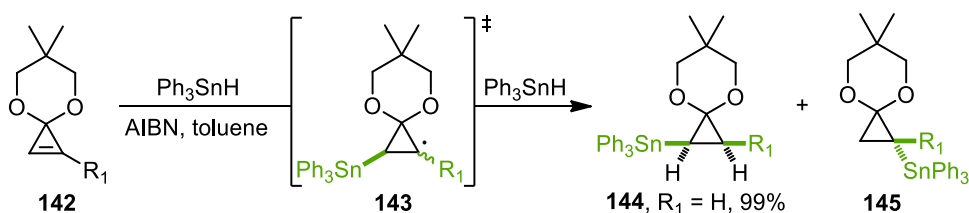


**Scheme II.11.** Carbometalation reaction of cyclopropenes and cyclobutenes by Marek *et al.*<sup>185</sup>

A similar pattern is observed with radical species. The reactivity of cyclobutenes was shown to be on the same order as that of cyclohexene ring and lower than that of cyclopropene.<sup>186</sup> Therefore, to ensure successful radical additions to cyclobutenes, highly electrophilic radicals are required. During a radical addition, the generated cyclobutyl radical located in a  $p$  orbital is less reactive than the cyclopropyl radical located in an  $sp^3$  orbital. This difference in reactivity is in contrast with the C-H bond dissociation energies.<sup>187</sup> In consistency with the main goal of this manuscript, reported examples of radical additions to cyclopropenes/butenes are provided.

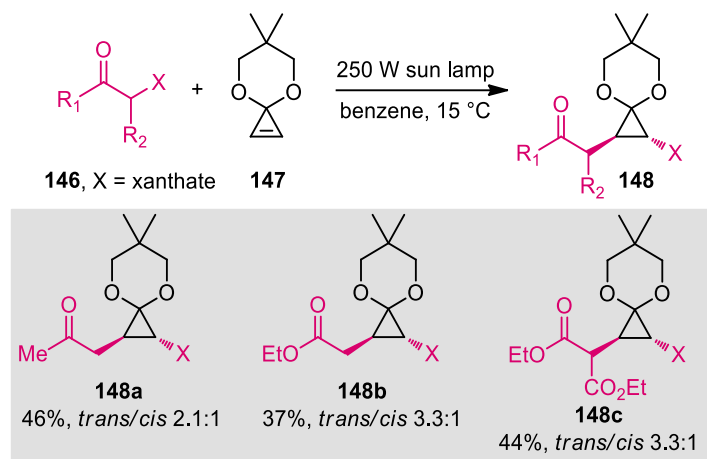
#### 4.1. Reported radical additions to cyclopropenes

The first cyclopropene strain-driven radical reaction was reported by Nakamura and co-workers in 1994 (Scheme II.12).<sup>188</sup> This reaction highlighted the efficient addition of tin radicals to the cyclopropene's  $\pi$ -system. Hydrostannation gave rise to the stannyl radical **143** which reacts further with tin hydride to give the hydrostannation adduct **144**, alongside with the tin product **145**, which is responsible for chain propagation.



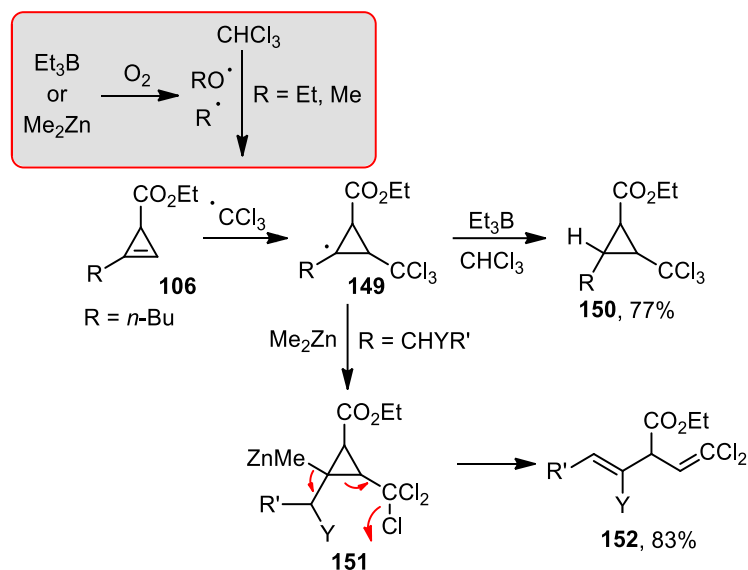
**Scheme II.12.** Hydrostannation of cyclopropenes by Nakamura *et al.*<sup>188</sup>

Saičić and co-workers<sup>186</sup> later developed new radical reactions on the same type of cyclopropenes (Scheme II.13). In this work, xanthates **146** were used as radical precursors under photochemical conditions to deliver the cyclopropanone acetals **148** in moderate yields and diastereoselectivities in favor of the *trans* isomer.



**Scheme II.13.** ATRA reactions on cyclopropenes by Saičić *et al.*<sup>186</sup>

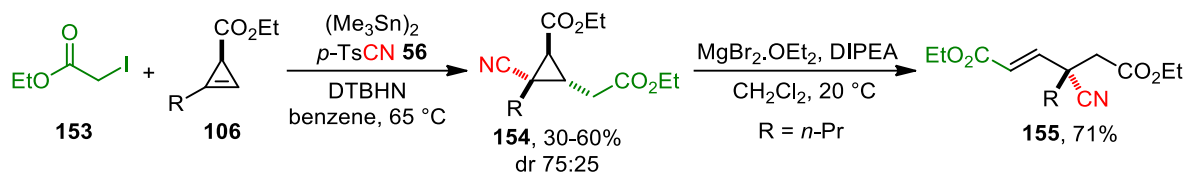
Ueda, Miyata and co-workers studied the radical addition reactions of trichloromethyl radicals on cyclopropene **106** (Scheme II.14).<sup>189</sup> In the presence of Et<sub>3</sub>B as an initiator, trichloromethyl radical is generated after abstraction of a hydrogen atom from chloroform. The addition of this radical onto the double bond delivers the cyclopropyl radical **149**. The latter abstracts a hydrogen from chloroform in the presence of Et<sub>3</sub>B to furnish trichloromethylpropane carboxylate **150** in high yield. When dimethyl zinc is used as an initiator, cyclopropylzinc **151** is formed, which further undergoes elimination and ring-opening to give the unsaturated ester **152**.



**Scheme II.14.** Addition of trichloromethyl radical to cyclopropenes.<sup>189</sup>

In order to study further the reactivity of cyclopropene-type motifs **106**, Landais and co-workers developed a radical carbo-cyanation approach to deliver polyfunctionalized cyclopropanes **154** in moderate yields and good diastereoselectivities (Scheme II.15).<sup>47</sup> This reaction used bis(trimethyltin) as a mediator and allowed the generation of an all-carbon quaternary stereocenter on cyclopropane **154**, a highly valuable synthetic intermediate. This skeleton was further modified by activation of the cyclopropyl ester group using a soft enolization process to provide the opened product **155** in high

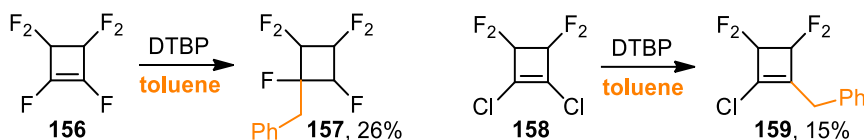
yield. This obtained building block can serve as a valuable intermediate in the enantioselective total synthesis of natural products.



**Scheme II.15.** A diastereoselective carbo-cyanation of cyclopropenes by Landais *et al.*<sup>47</sup>

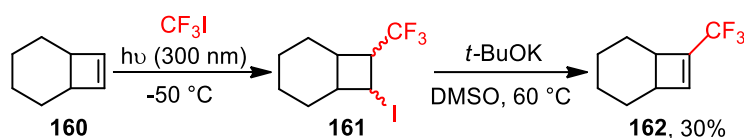
## 4.2. Reported radical additions to cyclobutenes

The radical functionalization of cyclobutenes is far less documented than that of cyclopropenes. Only a few reports have been published. Kimoto and co-workers,<sup>190</sup> for instance, reported the addition of benzyl radical to hexafluorocyclobutene **156** and 1,2-dichlorotetrafluorocyclobutene **158** using toluene and di-*t*-butyl peroxide (DTBP). Two stereoisomers of **157** were obtained in favor of the *trans* configuration in which the hydrogen and benzyl groups are on the opposite sides of the carbocycle plane (Scheme II.16).



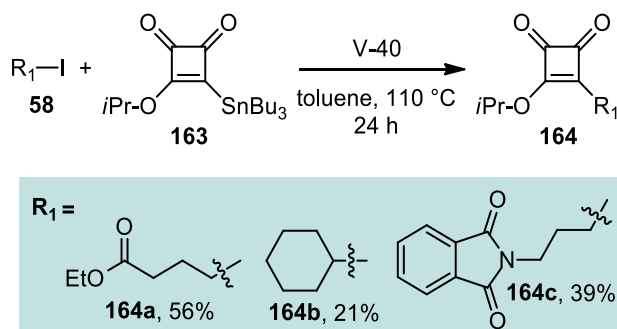
**Scheme II.16.** Addition of benzylic radical to fluorocyclobutenes by Kimoto *et al.*<sup>190</sup>

On the other hand, Leigh and co-workers<sup>191</sup> reported a photochemical addition of trifluoromethyl iodide to bicyclo[4.2.0]oct-7-ene **160** (Scheme II.17). Further transformation by eliminating the iodine atom elaborated a new trifluorocyclobutene ring **162**.



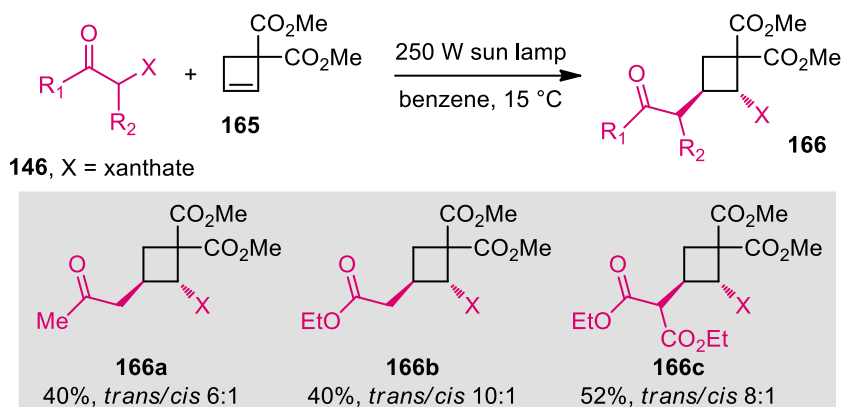
**Scheme II.17.** Photochemical addition of trifluoromethyl iodide on cyclobutene.<sup>191</sup>

Kinney described the addition of alkyl radicals to cyclobutenyl stannane **163** giving the alkyl-substituted cyclobutenediones **164** in low to moderate yields (Scheme II.18).<sup>192</sup> This methodology was applied to the synthesis of an NMDA antagonist analog.



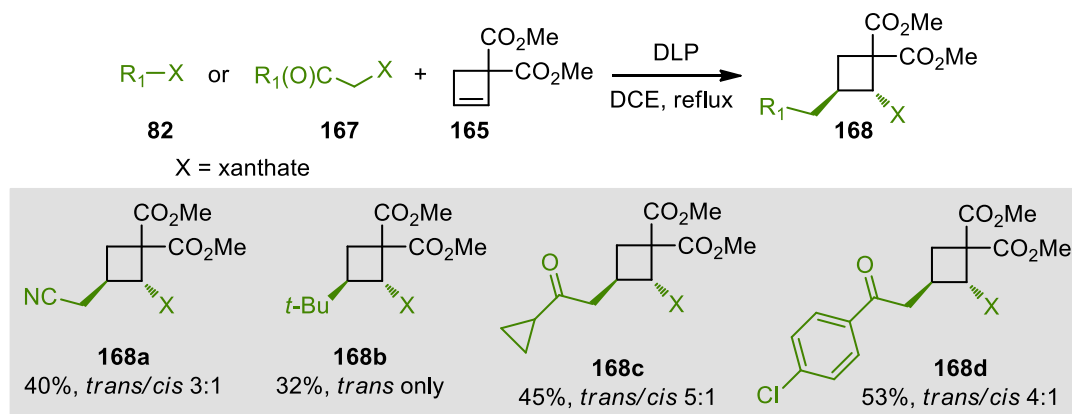
**Scheme II.18.** Addition of alkyl radicals to cyclobutenyl stannane by kinney.<sup>192</sup>

Saičić and co-workers applied their xanthate transfer radical reaction to cyclobutenes **165** (Scheme II.19).<sup>186</sup> This reaction provided the functionalized rings **166** in moderate yields and diastereoselectivities privileging the *trans* isomer as the dominant product.



**Scheme II.19.** ATRA reactions on cyclobutenes by Saičić *et al.*<sup>186</sup>

A concomitant work was published by Zard and co-workers<sup>193</sup> adding the xanthate radicals to cyclobutenes and cyclopropenes (Scheme II.20). The xanthate-transfer radical chain was promoted by lauroyl peroxide (DLP) as an initiator. Similar to Saičić, moderate yields were obtained, and the radical was added regioselectively at the less hindered site of the double bond, leading to a mixture of diastereomers with the *trans* isomer as the major product.



**Scheme II.20.** Radical additions of xanthate derivatives on cyclobutenes by Zard *et al.*<sup>193</sup>

## 5. Conclusion

In conclusion, cyclopropanes and cyclobutanes, as the most strained small rings, have emerged in the past decades as potential synthetic tools for further complex transformations in natural products and drug discovery. Their unusual bonding and ring strain, at the origin of their properties and reactivity, are used as a driving force to facilitate chemical reactions. In this context, cyclopropanes have been widely studied compared to their four-membered counterparts. Radical additions on cyclobutene rings did not attract much attention due to their low reactivity towards radicals, and also due to the restricted access to enantiopure carbocycles. The fact that the major isomer obtained in all the cases stated above was the *trans* isomer, makes the investigation of the ATRA reaction on chiral four-membered rings even more intriguing, as excellent diastereoselectivity might be achieved. For

these reasons, the development of a straightforward access to this class of olefins and the study of their reactivity towards free-radical species were envisioned during this Ph.D. thesis.

## *Chapter III*

# *Radical Additions onto Cyclobutenes & Further Derivatization*



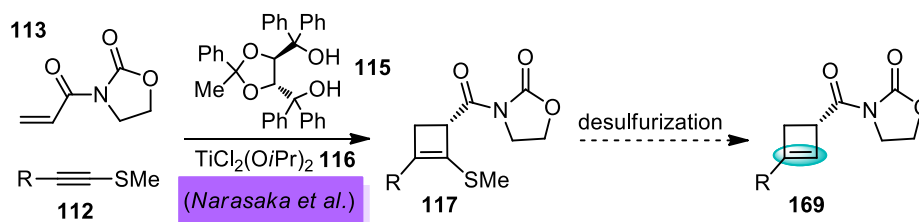


## Part I

### Synthesis and Radical Additions onto Chiral Cyclobutenes

#### 1. Development of an enantioselective synthesis of cyclobutenes

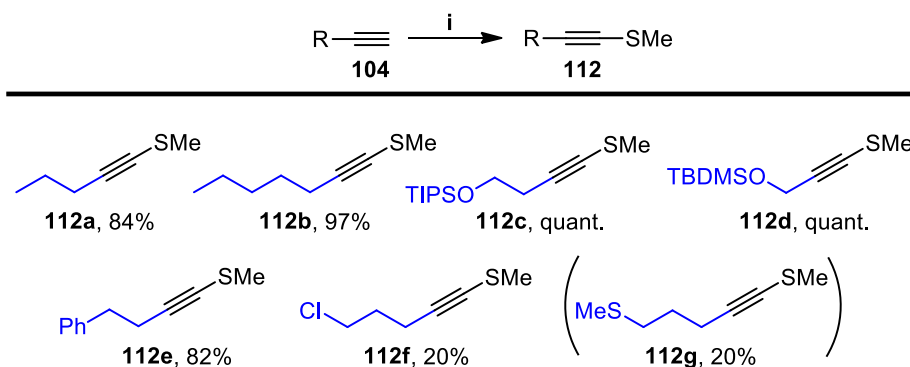
In the aim of revisiting the reactivity of unsaturated four-membered rings towards radical additions, the synthesis of a new type of chiral cyclobutenes has been looked at. Hence, a two-steps sequence was planned inspired by the work of Narasaka and co-workers.<sup>3,194–196</sup> The chiral carbocycle would be obtained through an asymmetric [2+2]-cycloaddition reaction between an  $\alpha,\beta$ -unsaturated acid derivative, the *N*-acyloxazolidinone **113**, and a series of alkynyl sulfides (Scheme III.1). This transformation would be catalyzed by a cheap chiral titanium reagent **116**, coordinated with a 1,4-diol chiral ligand **115**. A reduction of the corresponding cyclobutenyl sulfides **117** through direct desulfurization would then furnish the corresponding cyclobutenes **169**, ready for radical reactions.



**Scheme III.1.** Proposed two-steps strategy to access enantiopure cyclobutenes.

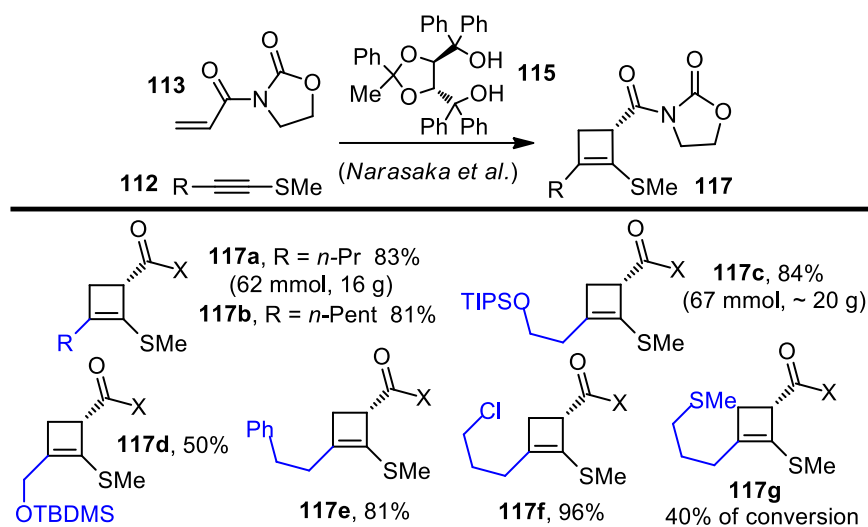
##### 1.1. Synthesis of cyclobutene sulfides following Narasaka's procedure

To access cyclobutene sulfides, a series of alkynyl sulfides **112** were first synthesized in high yields through the deprotonation of the corresponding terminal alkynes **104**, followed by the addition of dimethyl disulfide (Scheme III.2).<sup>197</sup> This reaction was found tolerant to functionalities such as silyl ethers and aryls, while with halogen, a lower yield was obtained due to the displacement of the chlorine atom by a thiomethyl group (**112f** and **112g**).



**Scheme III.2.** Synthesis of alkynyl sulfides. *Reagents and conditions:* i) 1. alkyne **104** (1.125 eq.), *n*-BuLi (1.06 eq.), THF (0.65 M), 0 °C, 30 min; 2. Me<sub>2</sub>S<sub>2</sub> (1.0 eq.), 20 °C, 2 h.

Once synthesized, the alkynes **112** were engaged in the cycloaddition reaction with *N*-acyloxazolidinone, delivering various cyclobutenes bearing functionalized side chains (Scheme III.3). All examples gave high yields even on decagram scales (**117a,c**). A moderate yield (50%) was, however, obtained with more hindered substituents (**117d**). When the alkynyl sulfide **112g** was used, the product **117g** was obtained with only 40% of conversion and was found inseparable from the *N*-acyloxazolidinone **113**. The partial conversion is probably due to the competitive coordination between the thiomethyl groups with the catalyst. Increasing the quantity of the catalyst and ligand to 0.7 and 0.77 equivalents respectively, did not increase the conversion further. Finally, although the alkynyl sulfides were used in excess, the unreacted material was recycled after purification.

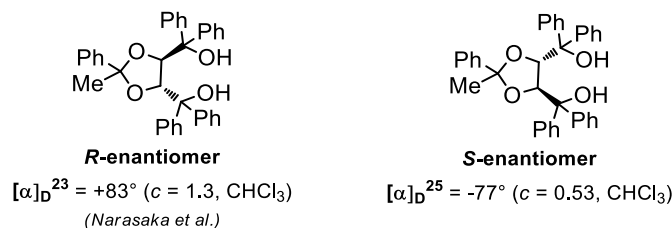


**Scheme III.3.** Synthesis of functionalized cyclobutene sulfides, based on Narasaka's protocol. *Reagents and conditions:* alkyne **112** (1.5-2.0 eq.), (*R*)-**115** (0.11 eq.), TiCl<sub>2</sub>(OiPr)<sub>2</sub> **116** (0.1 eq.), toluene (0.25 M), 4 Å MS, 0 to 20 °C, 12-66 h. X = oxazolidinone.

## 1.2. Enantiomeric excess measurements

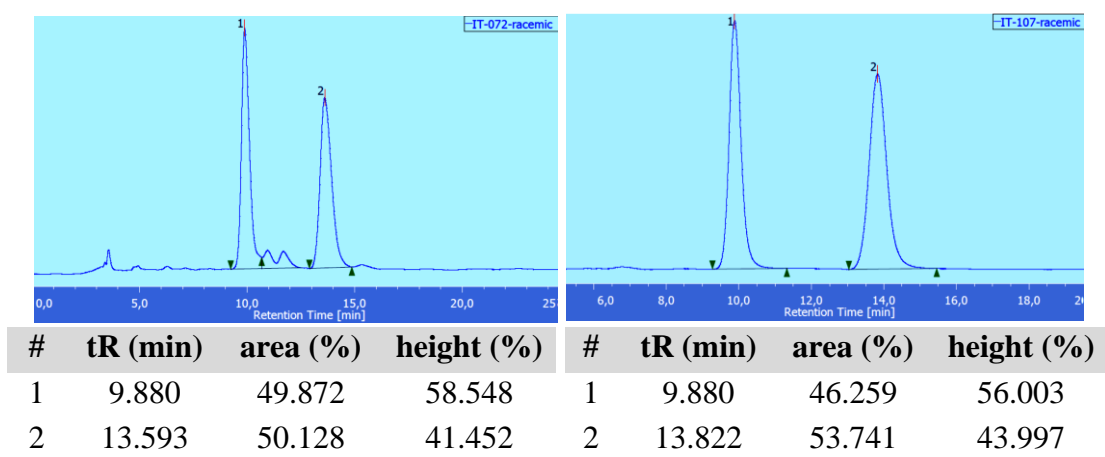
In order to estimate the enantiomeric excesses of the above cyclobutenes, it was planned to synthesize racemic cyclobutene analogs using the same route, but in the absence of the 1,4-diol ligand **115**. Under such conditions, the cyclobutenes were obtained in very low yields (8-20%) after 4 to 7 days (*data not shown*). Increasing the quantity of titanium catalyst **116** to 1 equivalent did not improve

the results. While the NMR spectra of the isolated products were clean, the HPLC profiles were complicated, and the separation of the enantiomers was not acceptable. To avoid these limitations, the ligand's enantiomer (**S**)-**115** was synthesized from (-)-dimethyl D-tartrate by the same strategy as for (**R**)-**115** (Figure III.1). Values of the optical rotation were relatively close ( $[\alpha]_{\text{D}}^{25} = -77^\circ$  ( $c = 0.53$ ,  $\text{CHCl}_3$ ) for (**S**)-**115**) versus lit.<sup>198</sup> ( $[\alpha]_{\text{D}}^{23} = +83^\circ$  ( $c = 1.3$ ,  $\text{CHCl}_3$ ) for (**R**)-**115**). All other analytical data were in agreement with those reported for the ligand (**R**)-**115**.<sup>198</sup>



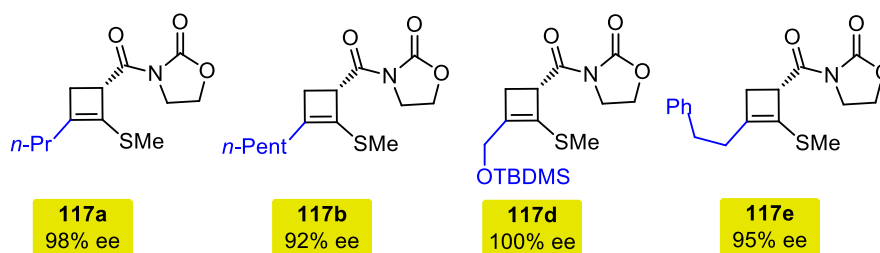
**Figure III.1.** Comparison of the optical rotation of the ligand *R*-enantiomer reported by Narasaka et al.,<sup>198</sup> and the *S*-enantiomer synthesized for this study.

With both enantiomers in hand, the racemic cyclobutenes were re-synthesized using a mixture of 50% of the (*R*)- and 50% of the (*S*)-ligands (*details are in the experimental part*). This protocol afforded the racemic samples in 35-65% yields in the expected range of time (12-48 h). The optical purity of the cyclobutenes was then determined by chiral HPLC (an analytical Chiralpak® IA column was employed). In this case, both enantiomers were successfully separated showing a more reliable HPLC trace (Figure III.2, *HPLC profiles without ligands versus with ligands*).



**Figure III.2.** HPLC trace of racemic compound **117b**, synthesized without (*left*) or with ligands (*right*). Analytical Chiralpak® IA column, *n*-hexane/ethanol 90:10, 1 mL/min, 20 °C.

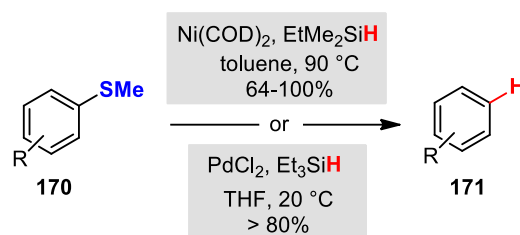
Finally, the optical purity of the synthesized cyclobutenes was determined to range between 92 and 98% (Figure III.3). For products **117c** and **117f**, the separation of the two enantiomers was not sufficient to determine the enantiomeric excess.



**Figure III.3.** Evaluation of the enantioselectivity of the cyclobutene sulfides.

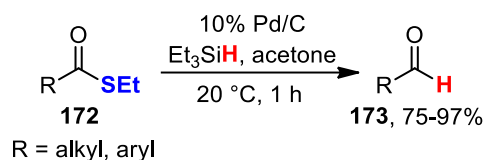
### 1.3. Desulfurization of cyclobutyl sulfides

The direct desulfurization of cyclobutenes was then investigated. The desulfurization of thiomethyl group was already reported for aromatic sulfides, using palladium or nickel catalysts and trialkylsilanes as reducing agent (Scheme III.4).<sup>199–201</sup>



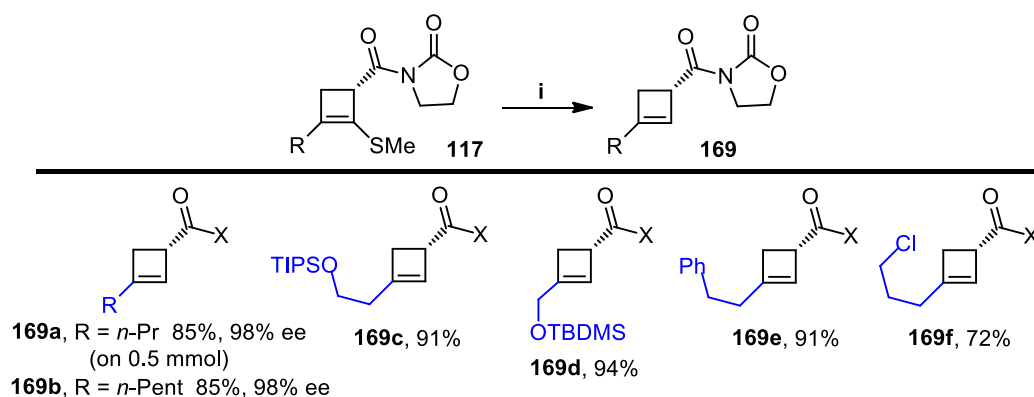
**Scheme III.4.** Reported desulfurization of aromatic sulfides.

Fukuyama, on the other hand, described the reduction of thioesters **172** into aldehydes **173** in the presence of palladium on charcoal and triethylsilane (Scheme III.5).<sup>202,203</sup>



**Scheme III.5.** Fukuyama's hydrosilylation-based reduction of thioesters.

The utility of Fukuyama's approach in organic synthesis was illustrated by the work of Evans and colleagues in their enantioselective synthesis of Altohyrtin C.<sup>204–206</sup> To avoid the over-reduction of their unsaturated thioester substrate, they conducted the reaction in the presence of Lindlar's catalyst and a sacrificial monosubstituted terminal olefin (hex-1-ene). Lindlar's catalyst, known to reduce alkynes into alkenes, seemed to be a good choice to allow the full conversion of the cyclobutyl sulfides **117**, without over-reducing the latter. Thus, the reaction was conducted at 20–25 °C using an excess of Lindlar's catalyst (10 eq.) leading to a series of cyclobutenes **169** with excellent purity and without erosion of the enantioselectivity (Scheme III.6). This method was shown to be compatible with the presence of silyl ethers, chlorides, and aryls as functional groups.

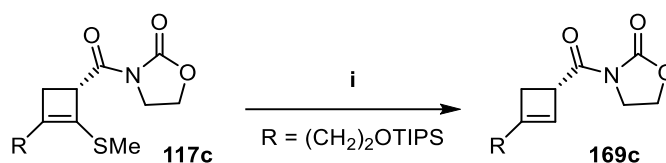


**Scheme III.6.** Reduction of cyclobutyl sulfides. *Reagents and conditions:* i) Lindlar's catalyst (10 eq.), Et<sub>3</sub>SiH (10 eq.), oct-1-ene **174** (10 eq.) acetone (0.1 M), 20 °C, 24–96 h. X = oxazolidinone.

Nevertheless, these conditions faced two problems on large scale. First, at a scale > 4 mmol, the conversion rate was very low, and the reaction took several days to reach completion (4–10 days). For

instance, on a 7 mmol scale, desulfurization of **169a** required 10 days to reach full conversion, affording the desired product in 87% yield (*data not shown*). Secondly, the use of a large excess of palladium on a large scale was not optimal, due to the high cost of the catalyst (CAS: 7440-05-3, TCI supplier: 225 €/25 g), even though the catalyst was usually recycled once or twice and reused without affecting its efficiency.

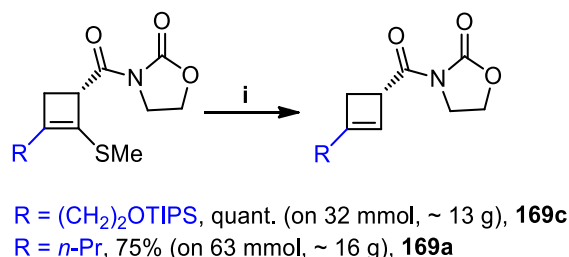
For these reasons, the model **117c** was chosen for further optimization on large scale (5 mmol of substrate). By heating at 50 °C, the reaction time decreased from 50 to 16 h without affecting the yield (Table III.1, entries 1 and 2). Similarly, subsequent decrease of the catalyst's quantity from 10.0 to 1.0 eq. led to a quantitative conversion in the same range of time (entries 3 to 7). When the reaction scale increased 6 times (32 mmol, ~ 13 g), the yield and the purity were not affected, and the desired cyclobutene **169c** was obtained in quantitative yield after 24 h (entry 8).



entry	[Pd] (eq.)	temp (°C)	time (h)	isolated yield (%)
1	10.0	20	50	91
2	10.0	50	16	94
3	5.0	50	16	94
4	3.0	50	18	93
5	2.0	50	18	quant.
6	1.5	50	18	quant.
7	1.0	50	17	quant.
8 <sup>a</sup>	1.0	50	24	quant.

**Table III.1.** Optimization of the desulfurization reaction on large scale. *Reagents and conditions:* i) Substrate (5 mmol), Lindlar's catalyst, Et<sub>3</sub>SiH (10 eq.), oct-1-ene, acetone (0.1 M). <sup>a</sup> Substrate (32.0 mmol).

These optimized conditions were also applied to the cyclobutene **117a** on 63 mmol scale (~ 16 g) leading to 75% yield of the final product **169a** after 24 h (*versus* 87% on 7 mmol scale, for 10 days at 20 °C, and in the presence of 10 eq. of palladium catalyst) (Scheme III.7).



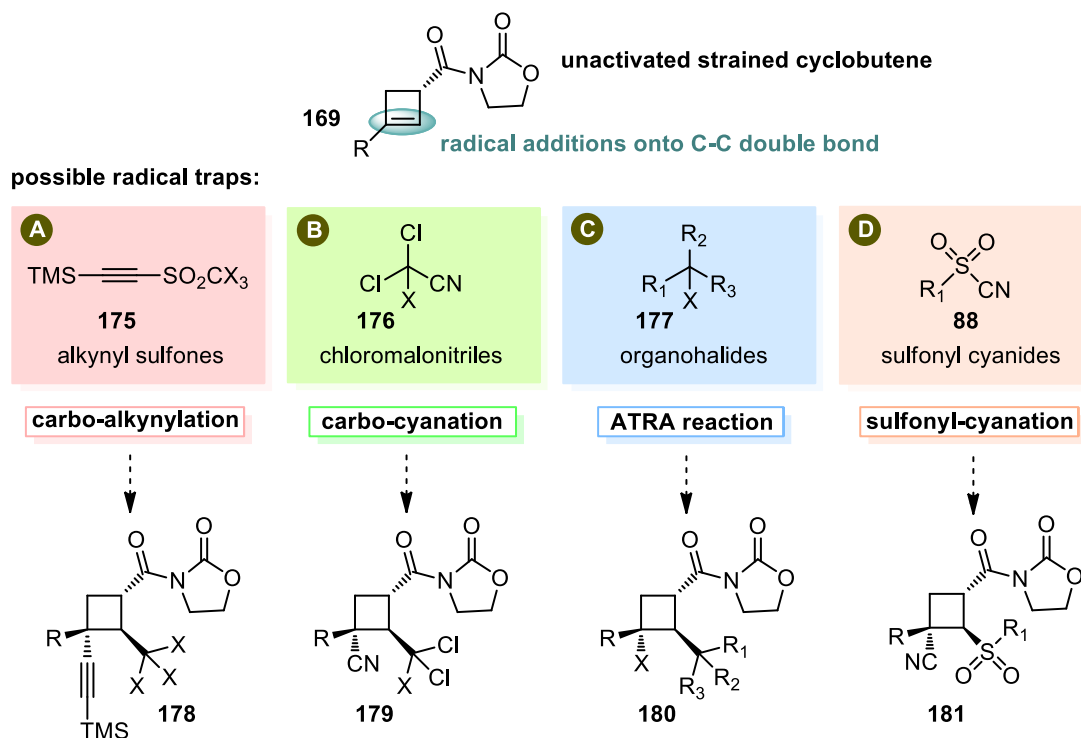
**Scheme III.7.** Optimized reduction reaction on large scale. *Reagents and conditions:* i) Lindlar's catalyst (1.0 eq.), Et<sub>3</sub>SiH (10-7 eq.), oct-1-ene (1.0 eq.), acetone (0.1-0.3 M), 50 °C, 24 h.

In conclusion, this multigram-scale reduction has demonstrated its robustness, a relatively broad scope, and reliability, even in the presence of sensitive functional groups. The developed two-steps sequence described here provides easy enantioselective access to a new type of cyclobutenes ready for further studies.

## 2. Radical additions onto enantiopure cyclobutenes

As stated before, cyclobutenes were described to react with radical traps with slow kinetics. It was envisioned to closely reexamine their behavior with highly electrophilic radical traps, reported to add successfully to acyclic alkenes. Furthermore, the radical additions onto cyclobutenes C-C double bond would be of high interest, since it would allow installing two functional groups on vicinal carbon centers in a single operation. This would furnish more complex architectures that are synthetically valuable. As a possible transformation, it was decided that the addition of two different carbon units across the cyclobutene  $\pi$ -system would also generate a very useful all-carbon quaternary stereocenter. Among useful 2-carbon units, alkynyl fragments are particularly attractive in organic synthesis, and can be introduced onto the  $\pi$ -system through a tin-free carbo-alkynylation process, as previously described by Fuchs<sup>207</sup> (Figure III.4.A). Besides alkynes, the introduction of a cyano group onto the carbon skeleton is also appealing, since this function is considered as a precursor for a variety of functional groups such as carbonyls, amines, amides, and oximes.<sup>208</sup> Its insertion onto chiral frameworks would serve for later applications in the asymmetric synthesis of indole alkaloids, the target family in this work. As a cyanide source, chloromalonitrile derivatives, for example, would act as good radical traps to deliver the carbo-cyanation products (Figure III.4.B).

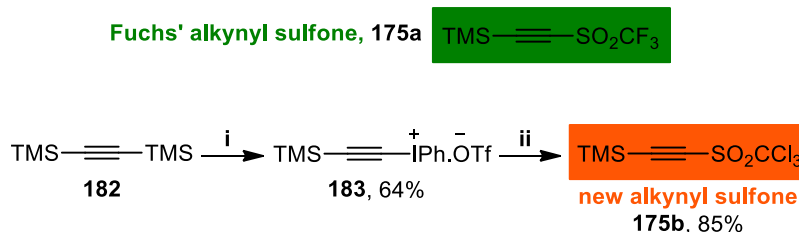
On the other side, the addition of carbon and heteroatom units across the cyclobutene  $\pi$ -bond in a one-step process is also possible. Particularly, the addition of alkyl halides onto the cyclobutenes would be investigated, through Atom Transfer Radical Addition (ATRA) processes, using suitable photocatalysts (Figure III.4.C). Further manipulations of the ATRA products would then be envisioned, by exchanging the halide groups with other substituents such as a nitrile or an alkyl, giving diversified carbocycles. The recently developed strategy of sulfonyl-cyanation by Landais *et al.*<sup>5</sup> would also be investigated on cyclobutenes (Figure III.4.D). This would install cyanide and sulfonyl fragments onto the double bond. The sulfonyl entity would be later modified leading to attractive synthons.



**Figure III.4.** Possible candidates for radical additions onto cyclobutenes.

## 2.1. Carbo-alkynylation of cyclobutenes

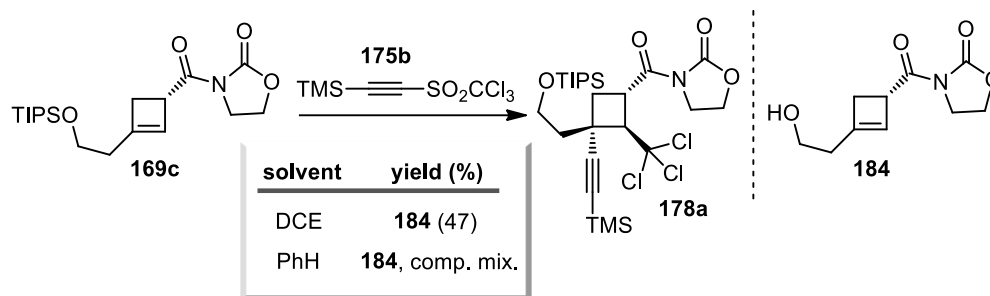
With the perspectives of adding carbon radicals onto cyclobutenes, the carbo-alkynylation was first investigated. While Fuchs studied the radical additions using trifluorosulfone **175a**, it was envisioned that the replacement of  $\text{CF}_3$  with  $\text{CCl}_3$  would be more interesting for this work purpose, as the chlorine atoms could later be transformed into other functionalities, or eliminated (Scheme III.8). The preparation of **175b** through adaptation of literature procedures<sup>207,209</sup> failed. The trichlorosulfone **175b** was finally obtained successfully in 85% yield through the intermediacy of an alkynyl-iodonium salt **183**.<sup>210,211</sup> This sulfone was found unstable on silica gel, and the pure product was obtained by trituration from diethyl ether.



**Scheme III.8.** Preparation of alkynyl sulfone **175b**. *Reagents and conditions:* i)  $(\text{CF}_3\text{CSO}_2)_2\text{O}$  (0.5 eq.), PhIO (1.0 eq.),  $\text{CH}_2\text{Cl}_2$  (1.0 M), 0 °C, 1 h; ii)  $\text{CCl}_3\text{SO}_2\text{Na}$  (1.5 eq.),  $\text{CH}_2\text{Cl}_2$  (0.1 M), 25 °C, 13 h.

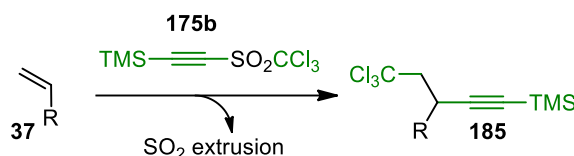
With the desired alkyne in hand, the radical addition reaction was conducted on cyclobutene **169c** in the presence of AIBN as an initiator. When DCE was used as a solvent as described by Fuchs,<sup>207</sup> only 47% of the TIPS-deprotected alcohol **184** were isolated in a relatively clean reaction (Scheme III.9). However, in benzene, a complex mixture of products was obtained, with only trace amount of **184**.





**Scheme III.9.** Attempts for carbo-alkynylation of cyclobutenes. *Reagents and conditions:* **175b** (1.5 eq.), AIBN (0.2 eq. x 4), solvent (0.1 M), 85 °C, 45 h.

To evaluate the reactivity of the newly synthesized alkynyl sulfone, the reaction was also tested targeting simpler olefins. When hex-5-en-2-one **186** was submitted to the carbo-alkynylation reaction, the desired radical transformation took place to produce the alkynyl trichloride **185a** in 77% yield (Table III.2, entry 1). With the phthalimide derivative **187**, the desired product **185b** was isolated in 55% yield (68% brsm) (entry 2). Interestingly, when the above conditions were applied to cyclopropene carboxylate **106a**, a complex mixture of products was obtained, suggesting that acid-sensitive substrates such as cyclopropanes may not be compatible with the reaction conditions (entry 3). Release of SO<sub>2</sub> may generate strong acids in the medium (in the presence of traces of moisture), also explaining the TIPS deprotection above.

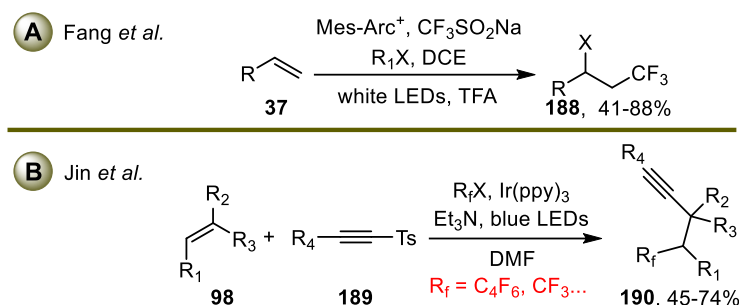


entry	starting material	desired product	yield (%)
1			77
2			55, brsm (68)
3			comp. mix.

**Table III.2.** Radical addition of alkynyl sulfone **175b** onto olefins. *Reagents and conditions:* alkynyl sulfone (1.5 eq.), AIBN (0.2 eq. x 4), DCE (0.1 M), 85 °C, 19 h.

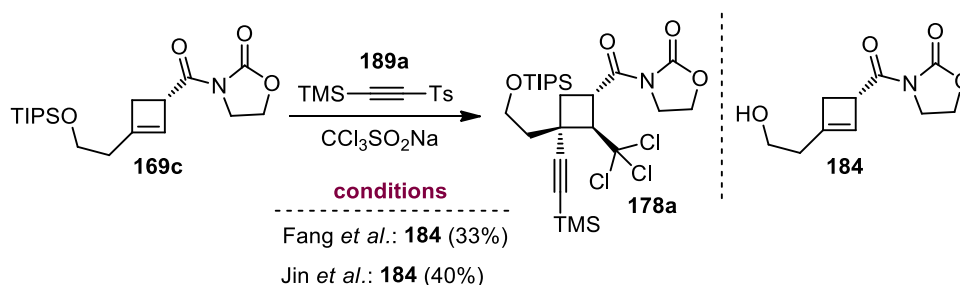
In the literature, three-components processes were also described to introduce trihalo groups and alkynyl chains onto the double bond. For instance, Fang and co-workers<sup>212</sup> introduced CF<sub>3</sub> and chlorine radicals onto olefins using *N*-methyl-9-mesityl acridinium as a photocatalyst and sodium triflate as a trifluoromethyl source (Scheme III.10.A). While Jin and colleagues<sup>213</sup> used iridium

catalyst and the alkynyl sulfones **189** to promote the fluoroalkylation of various  $\pi$ -systems (Scheme III.10.B).



**Scheme III.10.** Three-components alkynyl-trifluoroalkylation of unactivated alkenes.<sup>212,213</sup>

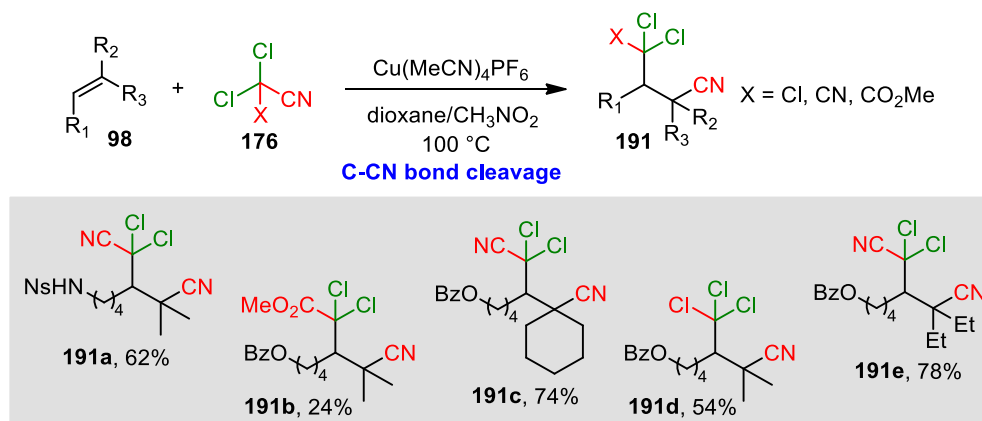
Applying the abovementioned conditions described by Fang *et al.* to *p*-tosyl alkyne **189** and trichloromethyl sulfinate ( $\text{CCl}_3\text{SO}_2\text{Na}$ ), did not afford the desired product, but only 33% of the deprotected alcohol **184** (Scheme III.11). Similarly, under Jin's conditions, the alcohol **184** was recovered in 40% yield. Again, acid-mediated deprotection of the TIPS group may be invoked here.



**Scheme III.11.** Application of Fang and Jin conditions to cyclobutene **169c**.

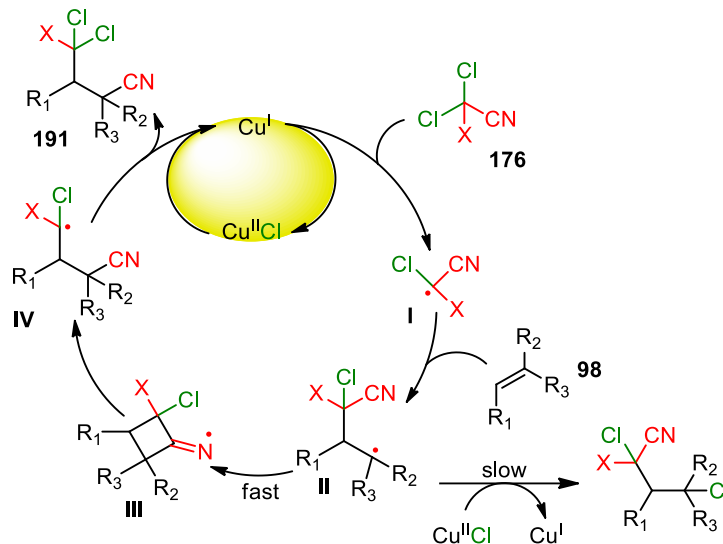
## 2.2. Carbo-cyanation of cyclobutenes

The radical carbo-cyanation of olefins using carbo-cyanides is not an easy process due to the high bond dissociation energy of the C-CN bond ( $\text{H}_3\text{C-CN}$ : 120.9 kcal/mol). Yet, Inoue and co-workers<sup>214</sup> successfully used trichloroacetonitrile in a copper-catalyzed carbo-cyanation of trisubstituted olefins (Scheme III.12). In their report, they rationalized the formation of the carbo-cyanation products **191** invoking an intramolecular nitrile transfer step, and the cleavage of the C-CN bond. This method was applied to a variety of olefins and cyanides affording the desired products in moderate to high yields.



**Scheme III.12.** Carbo-cyanation of trisubstituted olefins by Inoue *et al.*<sup>214</sup>

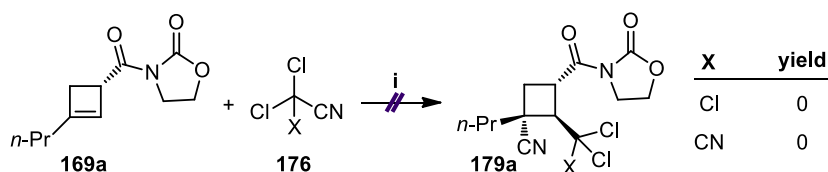
Such a transformation relies on a radical-based pathway catalyzed by Cu(I)-mediated cleavage of the C-Cl bond (Figure III.5). The generated electrophilic radical **I** reacts then selectively on the less hindered carbon of the electron-rich olefin **98**, yielding a new radical **II**. The latter undergoes intramolecular cyclization, forming the carbocyclic iminyl radical **III**. The ring-opening of the strained cyclobutane produces a more stabilized tertiary radical **IV** through 1,3-cyanide transfer. Finally, the delivery of a chlorine atom from Cu(II)Cl to **IV** yields the final product **191** and regenerates the Cu(I) catalyst.



**Figure III.5.** Proposed radical mechanism for Cu(I)-catalyzed carbo-cyanation.<sup>214</sup>

Interestingly, when trisubstituted alkenes were used as substrates, the ATRA transfer reaction on radical **II** was slow, in contrast with monosubstituted alkenes where the ATRA products were formed exclusively.

It was anticipated that this concept might work on the cyclobutenes to yield the carbo-cyanide cyclobutanes **179** bearing an all-carbon quaternary stereocenter. The application of Inoue's conditions on cyclobutene **169a**, however, did not afford the desired outcome, and the expected products were not observed (Scheme III.13). Only traces of unidentified products were isolated.



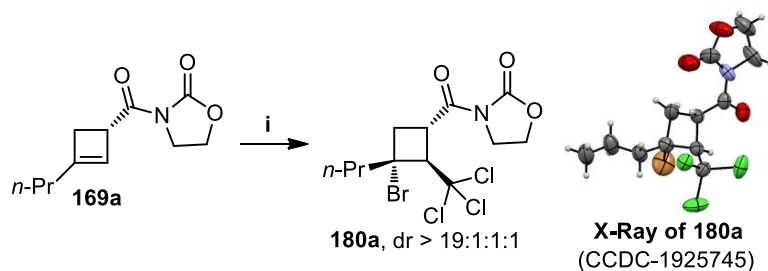
**Scheme III.13.** Attempts for carbo-cyanation of cyclobutene **169a**. Reagents and conditions: i) **176** (2.0 eq.), Cu(MeCN)<sub>4</sub>PF<sub>6</sub> (0.5 eq.), 1,4-dioxane/CH<sub>3</sub>NO<sub>2</sub>, (0.2 M), 100 °C, 48 h.

## 2.3. Atom transfer radical addition of haloalkanes onto cyclobutenes

### 2.3.1. Synthesis of halo-cyclobutanes

The classic radical chemistry was first applied to cyclobutene **169a**, using BrCCl<sub>3</sub> as a halo source and bis(tributyltin) as a chain carrier.<sup>99,215</sup> The reaction conditions delivered the expected product in 40% yield as a single diastereomer (dr > 19:1:1:1) (Table III.3, entry 1). Stephenson's<sup>121</sup> modified conditions were also investigated, giving the cyclobutane **180a** in 60% yield without

optimization (entry 2). In both cases, the stereochemistry of the cyclobutane **180a** was obtained in favor of the all-*trans*-product, as the major isomer, and was confirmed by X-ray diffraction studies (CCDC-1925745).



entry	catalyst (eq.)	additives (eq.)	solvent	yield (%)
1 <sup>a</sup>	(Bu <sub>3</sub> Sn) <sub>2</sub> (0.5)	DTBHN (0.5)	PhH	40
2 <sup>b</sup>	[Ir] (0.02)	LiBr (2.0), NaAsc (2.0)	DMF/H <sub>2</sub> O	60

**Table III.3.** ATRA reaction of  $\text{BrCCl}_3$  onto cyclobutene, and the ORTEP view of the product. [Ir] =  $[\text{Ir}(\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$ . *Reagents and conditions:* i)  $\text{BrCCl}_3$  (2.0 eq.), solvent (0.1 M), DMF/H<sub>2</sub>O: 4/1, 24 h. <sup>a</sup> 65 °C. <sup>b</sup> blue LEDs.

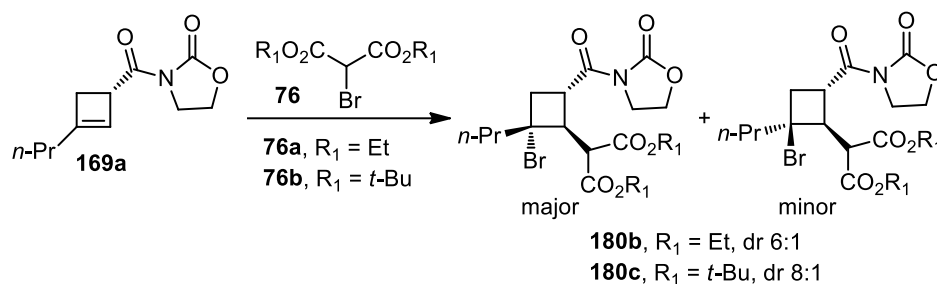
The excellent diastereocontrol was rationalized invoking the steric hindrance of the oxazolidinone moiety, leading the  $\text{Cl}_3\text{C}^\bullet$  radical to approach the less hindered face of the cyclobutene  $\pi$ -system *anti* with respect to the oxazolidinone group. The nucleophilic radical generated on the neighboring carbon then combines with the bromine atom, which approaches *trans* to the trichloromethyl group, settling the third stereocenter in a controlled mode.

Attempts to remove a chlorine atom from  $\text{CCl}_3$  through various methods (Zn dust, THF, 66 °C; Zn dust, AcOH, 116 °C; TTMSH, AIBN, PhH, 80 °C;  $\text{SmI}_2$ , H<sub>2</sub>O, THF, -78 to 20 °C) to access more various attractive synthons unfortunately failed, leading to a complex mixture of products. Although the diastereocontrol was excellent, the failure in transforming the trichloromethyl group into useful derivatives thus directed the attention towards other haloalkanes.

Dialkyl bromo-malonates became then the focal point in the following studies as efficient atom-transfer agents, first because of the known high electrophilicity of the malonyl radicals, and second, for the possible transformations that could occur on these fragments to produce intermediates of high value. Under the iridium-mediated photocatalytic conditions, diethyl malonate radicals were successfully added onto the cyclobutene **169a**, giving the functionalized cyclobutane **180b** in high yield and satisfying diastereoselectivity (Table III.4, entry 1). This confirms that such radicals are electrophilic enough to add to the unreactive  $\pi$ -bond of the four-membered ring.

Similar to the observation in the previous case, the diethyl malonate approaches *anti* relative to the oxazolidinone. However, the malonyl chain proved unable to totally control the approach of the bromine atom, as shown by the 6:1 dr in the favor of the *trans-trans* product. The bulkier di-*tert*-butyl bromo-malonate **76b**, was submitted to the same conditions to afford the cyclobutane **180c** in 53% yield (69% brsm), and with higher diastereoselectivity (dr 8:1) as expected (entry 1). The organotin conditions were also studied for comparison; in this case, the reaction furnished both cyclobutanes **180b** and **180c** in 46% and 29% yields, in 5.7:1 and 7:1 dr, respectively (entry 2).

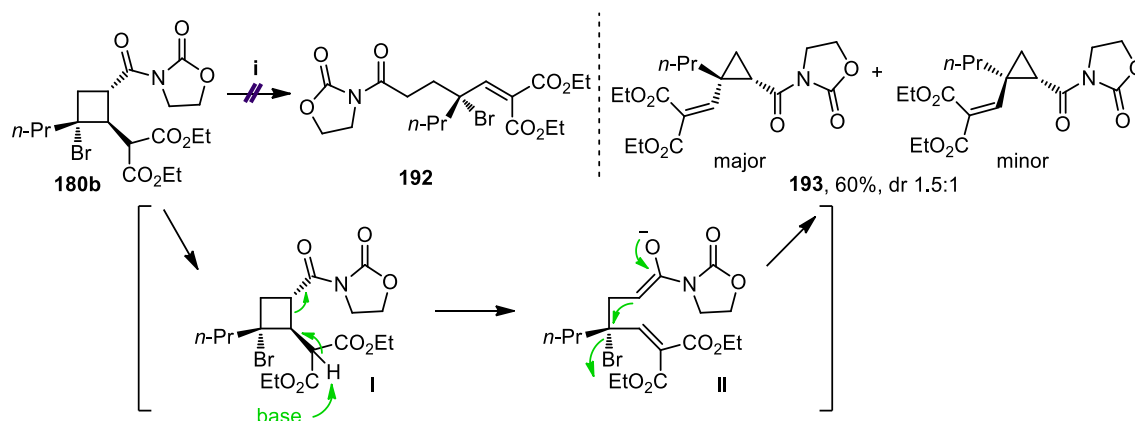
The addition of the malonyl radicals using other photocatalysts was also inspected. For instance, the cyclobutene **169a** was submitted to the modified conditions of Melchiorre.<sup>122</sup> In this reaction, 2 equivalents of di-*tert*-butyl malonate **76b** and 2,6-lutidine were used to afford the expected product **180c** in 69%, and in 7.5:1 dr (entry 3). Interestingly, when the quantity of base has halved, the yield dropped to the half as well (entry 4), while in the absence of base no reaction occurred (entry 5). These observations are in good agreement with reports by Melchiorre *et al.*,<sup>122</sup> Ramseier *et al.*,<sup>216</sup> and Nebe *et al.*,<sup>217</sup> suggesting that traces amount of acid (*e.g.*, HBr) quenches the triplet state of the aromatic carbonyl sensitizers by protonation, inhibiting the process. The reactivity of benzophenone studied by Inoue *et al.*<sup>218</sup> was also tested. In the presence of 4 equivalents of 2,6-di-*tert*-butylpyridine, the expected product **180c** was obtained in a moderate yield of 36% (entry 6), whereas, in the absence of base, no reaction occurred (entry 7).



entry	catalyst (eq.)	additives (eq.)	solvent	yield (%)	
				180b	180c
1 <sup>a</sup>	[Ir] (0.02)	LiBr (2.0), NaAsc (2.0)	DMF/H <sub>2</sub> O	73	53, brsm (69)
2 <sup>b</sup>	(Bu <sub>3</sub> Sn) <sub>2</sub> (0.5)	DTBHN (0.5)	PhH	46	29, brsm (8)
3 <sup>c</sup>	<i>p</i> -anisald. (0.2)	2,6-lutidine (2.0)	CH <sub>3</sub> CN	/	69
4 <sup>c</sup>	<i>p</i> -anisald. (0.2)	2,6-lutidine (1.0)	CH <sub>3</sub> CN	/	33, brsm (66)
5 <sup>c</sup>	<i>p</i> -anisald. (0.2)	-	CH <sub>3</sub> CN	0	0
6 <sup>c</sup>	benzoph. (0.5)	2,6-di- <i>tert</i> -butylpyridine (4.0)	CH <sub>3</sub> CN	/	36
7 <sup>c</sup>	benzoph. (0.5)	-	CH <sub>3</sub> CN	/	0

**Table III.4.** Radical additions of dialkyl bromomalonates onto cyclobutene. [Ir] = [Ir(ppy)<sub>2</sub>(dtbbpy)]PF<sub>6</sub>. *Reagents and conditions:* malonate (2.0 eq.), solvent (0.1 M), DMF/H<sub>2</sub>O: 4/1, 24 h. <sup>a</sup> blue LEDs. <sup>b</sup> 65 °C. <sup>c</sup> UV-A. dr calculated by <sup>1</sup>H and <sup>13</sup>C NMR.

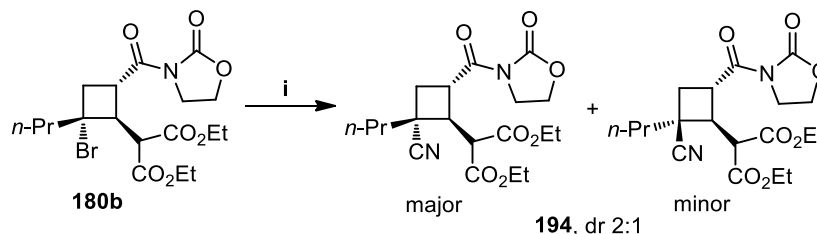
Finally, attempts to transform the cyclobutane **180c** into a useful synthon by cleaving the *tert*-butyl groups with TMSCN/TBAF, TMSCN/SnCl<sub>4</sub>, or TFA gave complex mixtures of products. Similarly, efforts to open the ring **180b** in a basic medium by deprotonation of the proton  $\alpha$ - to the diester groups using MgBr<sub>2</sub>.OEt<sub>2</sub>/DIPEA,<sup>47</sup> Et<sub>3</sub>N or NaH gave negative results and the starting material was recovered. A complex mixture was also obtained using LDA as a base. In contrast, with K<sub>2</sub>CO<sub>3</sub> in DMF at 70 °C, a ring contraction took place after displacement of the bromine atom, affording a new cyclopropane **193** in 60% yield as a mixture of two diastereomers (Scheme III.13).



**Scheme III.13.** Ring contraction of cyclobutane **180b** in the presence of potassium carbonate. *Reagents and conditions:* i)  $\text{K}_2\text{CO}_3$  (2.0 eq.), DMF (0.1 M), 70 °C, 14 h.

### 2.3.2. Bromine interchange with a cyanide substituent

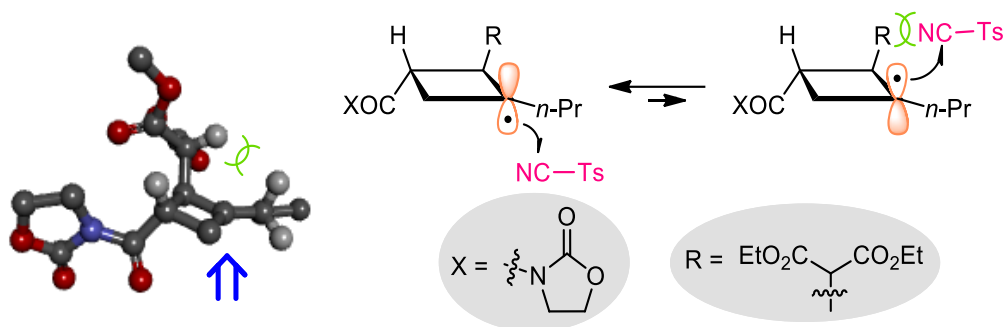
Given the unsuccessful attempts to introduce diethyl malonate/cyanide radicals onto cyclobutenes in a one-pot operation, a two-steps sequence was planned instead. The substitution of the halide atom with cyanide was investigated using bis(tributyltin), as reported by Landais *et al.*<sup>47</sup> When a stoichiometric amount of tin reagent was used in the presence of DTBHN (di-*tert*-butyl hyponitrite) in refluxing benzene, 27% of the expected product **194** was obtained with moderate diastereoselectivity (Table III.5, entry 1). When a sub-stoichiometric quantity of bis(tributyltin) was used, the yield increased to 40% (entry 2), whereas, in refluxing DCE, the desired product was isolated in a 45% yield (entry 3).



entry	( $\text{Bu}_3\text{Sn}$ ) <sub>2</sub> (eq.)	solvent	time (h)	yield (%)
1	1.0	PhH	29	27, brsm (45)
2	1.5	PhH	6	40
3	1.5	DCE	22	45

**Table III.5.** Bromine-cyanide exchange on cyclobutane **180b**. *Reagents and conditions:* *p*-TsCN (2.0 eq.), DTBHN (0.5 eq. x 2), solvent (0.1 M), reflux.

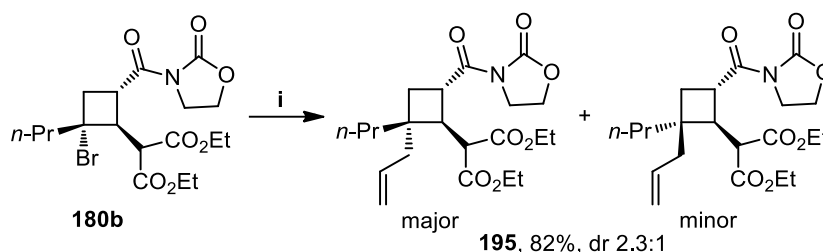
Interestingly, the diastereoselectivity dropped from 6:1 in bromo-cyclobutane **180b** to 2:1 in cyano-cyclobutane **194**. This could be rationalized by the lower steric hindrance of the cyano group as compared to bromine (the nitrile group with an A-value of 0.21 represents one of the smallest functional group in synthetic organic chemistry).<sup>219</sup> Thus, the cyanide approaches in less differentiation of both faces, in favor of the *trans* configuration (Figure III.6).



**Figure III.6.** Transition state model during the bromine-cyanide interchange on cyclobutane.

### 2.3.3. Bromine exchange with alkyl substituents

Finally, the substitution of the bromine atom with an allyl chain was also looked at, applying Keck's conditions.<sup>4</sup> This led to a clean formation of the allylated product **195** in high yield, albeit in moderate stereocontrol (Scheme III.14). As observed before, the decrease in diastereoselectivity probably results from the smaller size of the allyl fragment in comparison to the bromine atom.

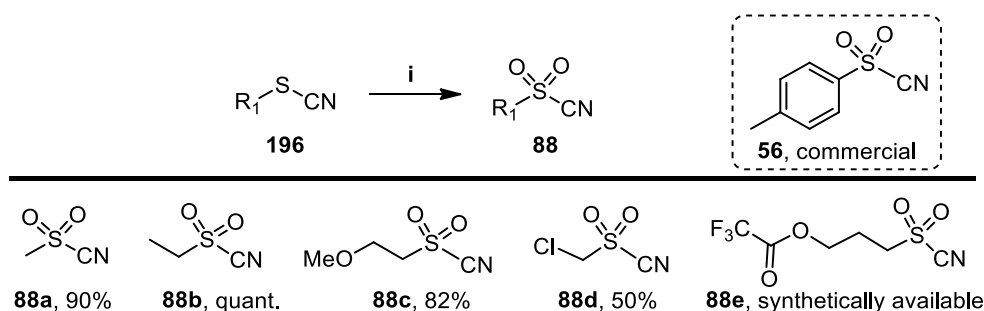


**Scheme III.14.** Cyclobutane allylation. *Reagents and conditions:* i) allyltri-*n*-butylstannane (5.0 eq.), AIBN (0.5 eq. x 3), benzene (0.1 M), 85 °C, 26 h.

## 2.4. Sulfonyl-cyanation of cyclobutenes

### 2.4.1. Eosin-mediated photocatalyzed sulfonyl-cyanation of cyclobutenes

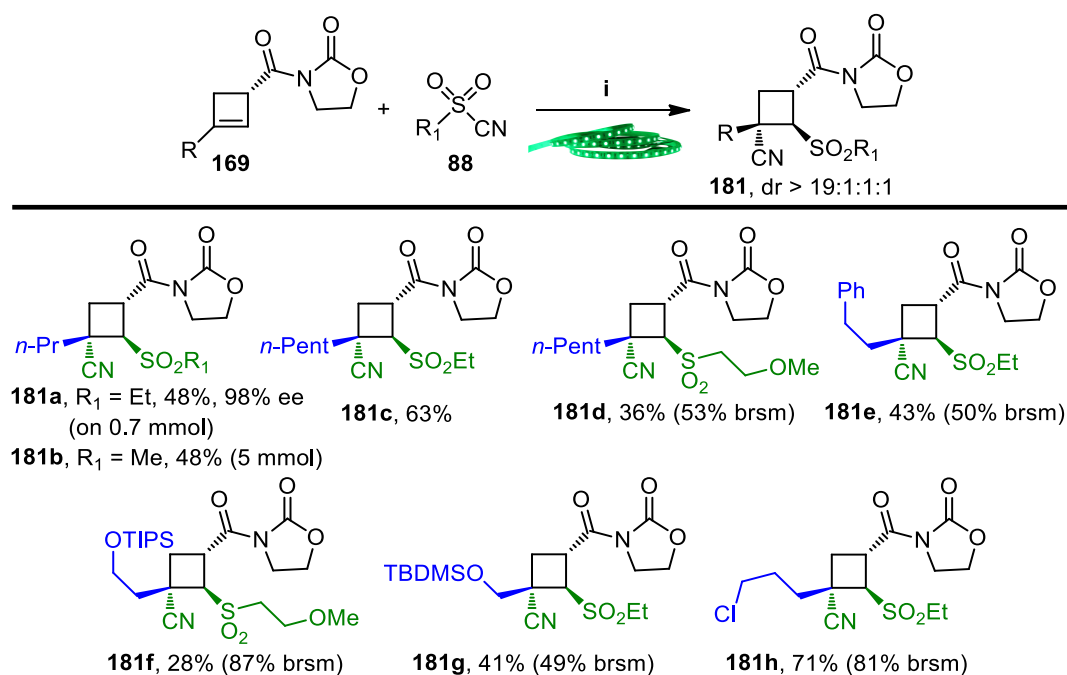
Considering that only electrophilic radicals add efficiently onto poorly reactive cyclobutene rings,<sup>5,220</sup> highly electrophilic sulfonyl radicals were also envisaged for this study. A list of sulfonyl cyanides was then selected presenting simple alkyl chains or functionalized ramifications such as aryl, ester, methoxy, chloride, and trifluoroacetate (scheme III.15). The sulfonyl cyanides **88** were prepared according to the literature<sup>5</sup> with some modifications using 5 equivalents of trifluoroacetic anhydride and hydrogen peroxide instead of 10.



**Scheme III.15.** Preparation of the selected sulfonyl cyanides. *Reagents and conditions:* i) trifluoroacetic anhydride (5.0 eq.), H<sub>2</sub>O<sub>2</sub> 50 wt. % (5.0 eq.), CH<sub>2</sub>Cl<sub>2</sub> (1.0 M), 40 min, 0 °C; then **196**, 5 h, 40 °C.



The eosin-mediated sulfonyl-cyanation of olefins described by Landais *et al.*<sup>5</sup> was then applied to a series of cyclobutenes, using green LEDs as a light source (Scheme III.16). The reaction was found compatible with different functional groups present on the side chains of the cyclobutenes and sulfones. Hence, the corresponding cyclobutanes **181** were provided in moderate to good yields with *trans* products as major isomers (dr > 19:1:1:1). The stereochemistry of the products was assigned by NMR and confirmed by X-ray diffraction analyses for some substrates.<sup>221</sup> In this transformation, the addition of the bulky sulfonyl radical occurs in an *anti*-fashion relative to the oxazolidinone fragment, followed by the addition of the cyanide group in an *anti*-manner relative to the sulfonyl moiety.



**Scheme III.16.** Eosin-mediated sulfonyl-cyanation of cyclobutenes. *Reagents and conditions:* i)  $R_1\text{SO}_2\text{CN}$  (2.0-4.0 eq.), Eosin-Y (2 mol %),  $\text{K}_2\text{HPO}_4$  (0.2 eq.), DMF (1.0 M), green LEDs, 30 °C, 24-96 h.

Although the excellent diastereocontrol was encouraging, the purification of the polar products from the eosin residues was challenging, and the yields were not satisfactory on a larger scale (> 1 mmol). Therefore, such results did not seem promising for future scale-up of the process. An alternative way to generate the electrophilic sulfonyl radicals was thus envisioned, under mild and efficient conditions.

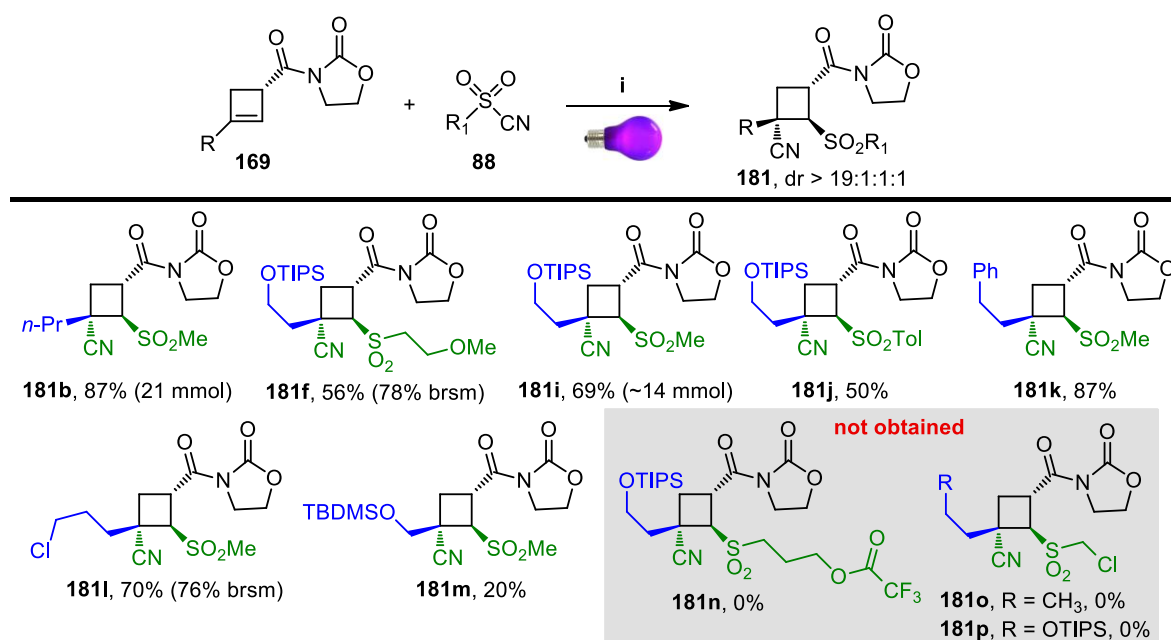
#### 2.4.2. *p*-Anisaldehyde photocatalyzed sulfonyl-cyanation of cyclobutenes

As mentioned before, the studies reported by Melchiorre *et al.*<sup>122</sup> showed that photocatalysts having high triplet energy levels<sup>222-225</sup> (around 70 kcal/mol) such as *p*-anisaldehyde and benzophenone, are able to promote the carbon-halide bond cleavage, and could be engaged in ATRA reactions. This system proved to be efficient when applied to cyclobutenes, generating cyclobutane **180c**. In addition, benzophenone was described by Inoue *et al.*<sup>218</sup> to efficiently cleave the  $\text{ToIO}_2\text{S-CN}$  bond. Therefore, it was anticipated that these simple organic photosensitizers might be able to activate the alkylsulfonyl cyanides in a similar way. Since *p*-anisaldehyde was proven to be more efficient



than benzophenone in the ATRA reaction on cyclobutene, it was chosen as a photosensitizer to conduct the following investigations.

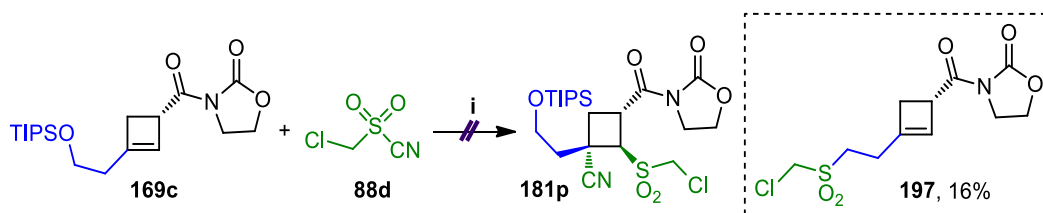
The cyclobutenes **169** were thus submitted to the sulfonyl-cyanation reaction in the presence of suitable sulfonyl cyanides **88** and a catalytic quantity of *p*-anisaldehyde in acetonitrile. After irradiation under UV-A light for the necessary amount of time, the corresponding cyclobutanes **181** were successfully obtained in good to high yields and excellent diastereocontrol, illustrating thus, the first examples of a triplet photosensitized olefin sulfonyl-cyanation (Scheme III.17). Overall, the reactions were cleaner than those with eosin-Y, easier to carry out, requiring no aqueous treatment at the end of the reaction. Moreover, purifications were more straightforward even on a large scale. Eventually, this method allowed achieving scale-ups without affecting the yields. For instance, **181b** was obtained in 87% yield on a 21 mmol scale, while with eosin-Y, the same product was isolated in 48% yield on a 5 mmol scale. As well, **181i** presenting a silyl ether entity was obtained in 69% yield on a 14 mmol scale. In general, better yields were observed using less hindered sulfonyl cyanides (MeSO<sub>2</sub>CN), while the yield decreased significantly for hindered cyclobutenes (*e.g.*, **181m** bearing a bulky TBDMS substituent). In addition, this process showed high tolerance for chains bearing a chlorine atom (**181l**), silyl ethers (**181h-j,m**), or aryls (**181k**). The reaction was not restricted to methyl or arylsulfones, but it was extended to functionalized sulfonyl cyanides (**181f**), albeit with lower efficiency. Interestingly, these mild conditions also prevent desulfonylation of the alkanesulfonyl radicals and the formation of the corresponding alkyl radicals.



**Scheme III.17.** *p*-Anisaldehyde photosensitized sulfonyl-cyanation of cyclobutenes. *Reagents and conditions:* i) R<sub>1</sub>SO<sub>2</sub>CN (2.0 eq.), *p*-anisaldehyde (0.2 eq.), CH<sub>3</sub>CN (1.0 M), UV-A (325–400 nm), 30 °C, 23–100 h.

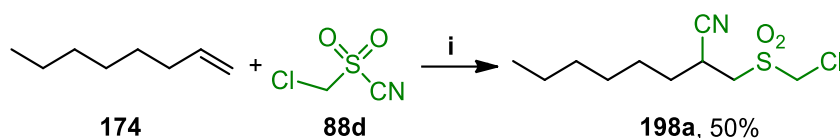
In contrast, sulfonyl cyanides **88d** and **88e** failed to react with cyclobutenes. The reaction of **88e** with **169c** gave a complex mixture of products, while the reaction of **88d** with **169a** and **169c** gave back the starting material. Unexpectedly, when the cyclobutene **169c** reacted with the sulfonyl cyanide **88d**, a side product **197** was isolated in 16% yield, alongside with 80% of the recovered starting material (Scheme III.18). During this reaction, the sulfonyl unit displaced the *O*-protected

fragment creating a C-S bond. The full analytical data confirmed the formation of the proposed structure, although the mechanism of this transformation is currently unknown.



**Scheme III.18.** Isolation of **197** as a side product of the sulfonyl-cyanation. *Reagents and conditions:* i) sulfonyl cyanide **88d** (2.0 eq.), *p*-anisaldehyde (0.2 eq.), CH<sub>3</sub>CN (1.0 M), 325-400 nm, 30 °C, 42 h.

The sulfonyl cyanide **88d**, however, was successfully added onto a simple olefin, oct-1-ene **174**, using the *p*-anisaldehyde method, to give the corresponding sulfone **198a** in a moderate yield of 50% (Scheme III.19).



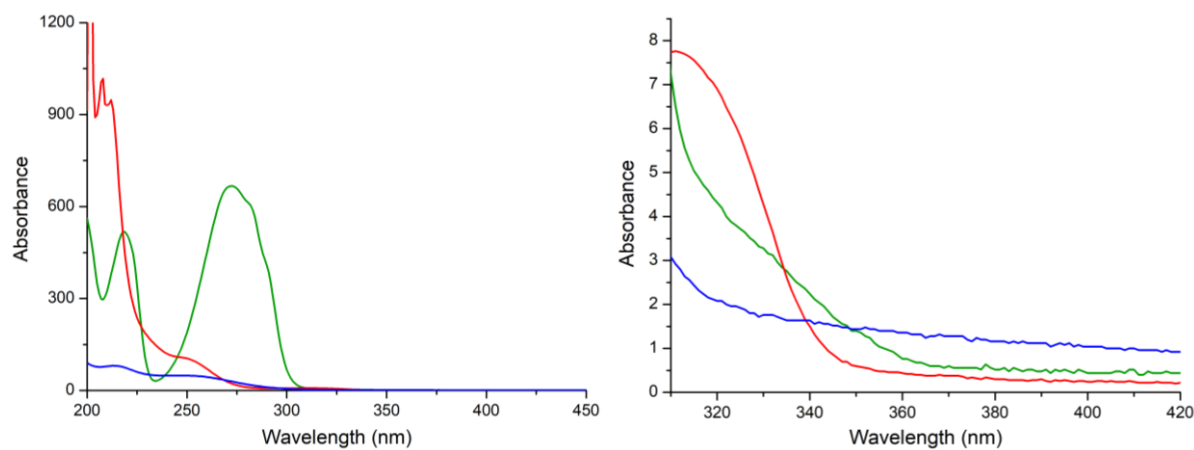
**Scheme III.19.** Addition of sulfonyl cyanide **88d** onto oct-1-ene. *Reagents and conditions:* i) **88d** (2.0 eq.), *p*-anisaldehyde (0.2 eq.), CH<sub>3</sub>CN (1.0 M), UV-A (325-400 nm), 30 °C, 67 h.

#### 2.4.2.1. Mechanistic studies

To understand the mechanistic pathway of the sulfonyl-cyanation reaction, and the efficiency of *p*-anisaldehyde as a photosensitizer, several control experiments were performed.

##### 1.2.4.2.1.1 UV-Vis absorption spectra of *p*-anisaldehyde, cyclobutene **169a** and MeSO<sub>2</sub>CN

First, in order to choose the irradiation zone adequate for the sulfonyl-cyanation, the absorption wavelength of the reagents was measured using UV-vis analyses (Figure III.7). The UV-visible spectra were recorded in acetonitrile in 1 cm path quartz cuvettes. [The concentrations of the substrates are: 10<sup>-4</sup> M for *p*-anisaldehyde and 10<sup>-3</sup> M for cyclobutene **169a** and methane sulfonyl cyanide **88a**]. The spectra show that *p*-anisaldehyde highly absorbs around the zone 200-230 and 240-300 nm, while the cyclobutene's maximal absorption is around 200-225 nm. The sulfonyl cyanide **88a** itself absorbs mostly in the zone 200-250 nm and continues absorbing in the region 360-600 nm, albeit in small amounts (*not shown*). Although the photosensitizer absorbs around 220 and 275 nm, these zones were avoided to limit the possible side reactions that might arise from the competitive absorption of cyclobutenes and reagents. Instead, the zone 325-400 nm was chosen, where the components absorb but more weakly.

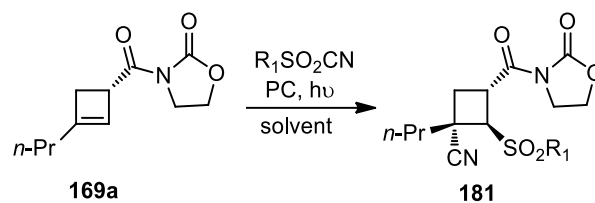


**Figure III.7.** *Left:* UV-visible absorption spectra (200-450 nm) of the sulfonyl-cyanation reactants. *Right:* zoom on the UV-visible spectra showing the absorption profiles of the reactants in the 325-400 nm zone chosen for the irradiation reaction. Curves: Green: *p*-anisaldehyde; red: cyclobutene **169a**; blue: MeSO<sub>2</sub>CN.

#### 1.2.4.2.1.2 Conditions screening

Using UV-A irradiation (325-400 nm), *p*-anisaldehyde effectively mediated the activation process of the O<sub>2</sub>S-CN bond, leading to the formation of **181b** in high yield (Table III.6, entry 3). This yield was higher than that observed with eosin-Y as a photocatalyst (entries 1 and 2). In the absence of *p*-anisaldehyde, **181b** was also formed albeit in much lower yield as a result of the direct absorption of substrates **169a** and **88a** at 325-400 nm, as seen previously in the UV-vis studies (entry 4).

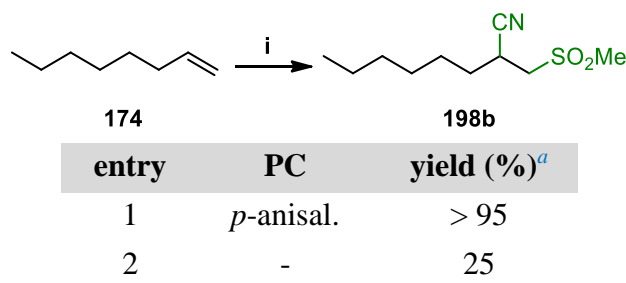
Benzophenone was also able to promote the sulfonyl-cyanation reaction, albeit less efficiently, giving the cyanosulfone **181b** in 60% yield (entry 5). With *p*-TolSO<sub>2</sub>CN as a sulfone source, the corresponding cyclobutane **181j** was obtained in a moderate yield of 50%, while only 7% of **181j** were formed in the absence of *p*-anisaldehyde (entries 6 and 7). This difference in reactivity between mesyl and tosyl cyanide was already observed by Barton under thermal conditions.<sup>226</sup> The reaction was also performed at 254 nm, leading to complete consumption of **169a** and the formation of a complex mixture of products in which **181b** was absent, in contrast to the literature's report<sup>127</sup> (entries 8 and 9). In this case, the high absorbance of the reactants at this wavelength probably favored side reactions or the decomposition of the cyclobutene. Using monochromatic wavelengths such as 334 nm, gave very low yields (entries 10 and 11), while, at 419 nm, a slightly better conversion was observed in the presence or absence of catalyst (entries 12 and 13). This observation was rationalized by the fact that MeSO<sub>2</sub>CN absorbs in this region, which probably promotes the addition reaction. At 344 nm, no reaction was observed with or without photosensitizer due to the narrow band of the light source and the insufficient energy absorbed at this wavelength (entries 14 and 15).



entry	PC <sup>a</sup>	R <sub>1</sub>	product	hν (nm) <sup>b</sup>	solvent	yield (%) <sup>c</sup>
1	eosin-Y	Et	<b>181a</b>	513	DMF	48
2	eosin-Y	Me	<b>181b</b>	513	DMF	48
3	<i>p</i> -anisal.	Me	<b>181b</b>	325-400	CD <sub>3</sub> CN	80
4	-	Me	<b>181b</b>	325-400	CD <sub>3</sub> CN	41
5	BP	Me	<b>181b</b>	325-400	CD <sub>3</sub> CN	60
6	<i>p</i> -anisal.	<i>p</i> -Tol	<b>181j</b>	325-400	CD <sub>3</sub> CN	50
7	-	<i>p</i> -Tol	<b>181j</b>	325-400	CD <sub>3</sub> CN	7
8	<i>p</i> -anisal.	Me	<b>181b</b>	254	CD <sub>3</sub> CN	- <sup>d,e</sup>
9	-	Me	<b>181b</b>	254	CD <sub>3</sub> CN	- <sup>d,e</sup>
10 <sup>f</sup>	<i>p</i> -anisal.	Me	<b>181b</b>	334	CD <sub>3</sub> CN	8
11 <sup>g</sup>	-	Me	<b>181b</b>	334	CD <sub>3</sub> CN	5
12	<i>p</i> -anisal.	Me	<b>181b</b>	419	CD <sub>3</sub> CN	26
13	-	Me	<b>181b</b>	419	CD <sub>3</sub> CN	17
14 <sup>h</sup>	<i>p</i> -anisal.	Me	<b>181b</b>	344	CD <sub>3</sub> CN	0
15 <sup>h</sup>	-	Me	<b>181b</b>	344	CD <sub>3</sub> CN	0

**Table III.6.** Conditions screening of the photocatalyzed sulfonyl-cyanation. Photocatalysts (PC): Eosin-Y (2 mol %); *p*-anisal.: *p*-anisaldehyde (20 mol %); BP: benzophenone (20 mol %), 30 °C, 24 h. <sup>a</sup> R<sub>1</sub>SO<sub>2</sub>CN (2.0 eq.). <sup>b</sup> Green LEDs (513 nm); UV-A (325-400 nm); UV-C (254 nm). <sup>c</sup> NMR yield. <sup>d</sup> Reaction performed in a quartz cell (1 cm). <sup>e</sup> Complex mixture. <sup>f</sup> 5.5 h of irradiation. <sup>g</sup> 19 h of irradiation. <sup>h</sup> 9 h of irradiation.

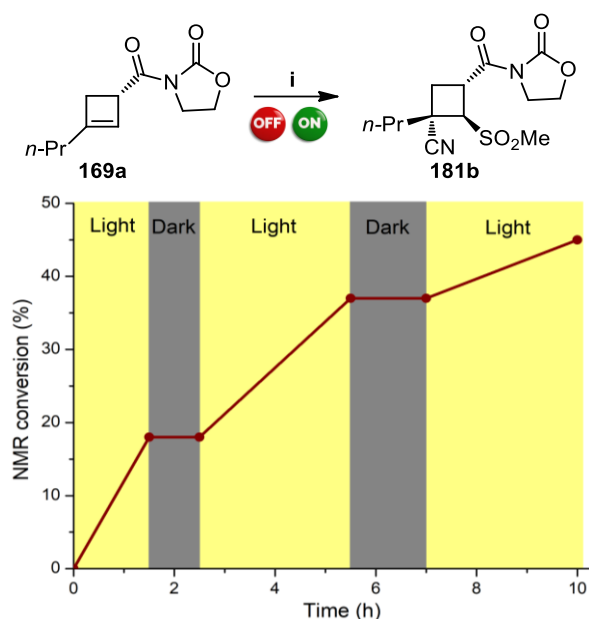
The critical role of *p*-anisaldehyde in this process was also highlighted by using oct-1-ene **174** as olefin, which does not absorb light in the 325-400 nm zone. The sulfonyl-cyanation of oct-1-ene led to the desired product **198b** with > 95% conversion (97% isolated yield) in the presence of *p*-anisaldehyde, and only 25% in its absence after 20 h of irradiation (Table III.7).



**Table III.7.** Sulfonyl-cyanation of oct-1-ene. *Reagents and conditions:* i) MeSO<sub>2</sub>CN (2.0 eq.), CD<sub>3</sub>CN (0.2 M), 325-400 nm, 30 °C, 20 h. <sup>a</sup> NMR yield.

### 1.2.4.2.1.3 Irradiation control

To investigate the importance of light in this process, an ON/OFF light experiment was performed. This experiment showed that the sulfonyl-cyanation reaction stops when the light was switched off and restarts when the light was switched on (Figure III.8).



**Figure III.8.** The effect of successive intervals of irradiation and dark periods on the reaction's kinetics. *Reagents and conditions:* i)  $\text{MeSO}_2\text{CN}$  (2.0 eq.), *p*-anisaldehyde (0.2 eq.),  $\text{CD}_3\text{CN}$  (0.2 M), 325-400 nm, 30 °C.

### 1.2.4.2.1.4 Quenching studies

When the sulfonyl-cyanation of **169a** was carried out using  $\text{MeSO}_2\text{CN}$  and *p*-anisaldehyde (20 mol %) but in the presence of a triplet quencher such as 2,5-dimethylhexa-2,4-diene (20 mol %), **181b** could not be detected after 20 h of irradiation (Table III.8, entry 1). A similar result was observed in the presence of pyridazine, which possesses a triplet-state energy lower than that of *p*-anisaldehyde (entry 2).

entry	quencher	yield (%)
1	2,5-dimethylhexa-2,4-diene	0
2	pyridazine	6

**Table III.8.** The sulfonyl-cyanation of **169a** in the presence of triplet state quenchers. *Reagents and conditions:*  $\text{MeSO}_2\text{CN}$  (2.0 eq.), *p*-anisaldehyde (0.2 eq.), quencher (20 mol %),  $\text{CD}_3\text{CN}$  (0.2 M), 325-400 nm, 30 °C, 20 h.

### 1.2.4.2.1.5 Quantum yield determination

The calculation of the quantum yield was performed by Dr. Dario M. Bassani – ISM, UMR 5255.

The quantum yields for the formation of **181b** from irradiation of acetonitrile- $d_3$  solutions of **169a** (0.16 M) and MeSO<sub>2</sub>CN (0.33 M) were carried out on an optical bench equipped with a 150 W high-pressure Hg-Xe lamp and a high-intensity monochromator set at 334 nm. The solutions (0.6 mL) were placed in Young NMR tubes that were degassed by three cycles of freeze-pump-thaw. The tubes were placed in 1 cm quartz cuvettes filled with water to minimize lensing effects and irradiated. Overall yields of **181b**, determined by <sup>1</sup>H NMR-600 MHz, were 5% (19 h irradiation) and 8% (5.5 h irradiation) in the absence and presence of *p*-anisaldehyde (33 mM), respectively. From the relative molar extinction coefficients of **169a** and *p*-anisaldehyde at 334 nm (71 and 15 L mol<sup>-1</sup> cm<sup>-1</sup>, respectively), the proportion of light absorbed by the *p*-anisaldehyde in the sensitized reaction was calculated to be 48.6% of the total incident light (evaluated to be  $7.84 \times 10^{-10}$  Einstein using ferrioxalate actinometry with  $\Phi_{\text{Fe(II)}} = 1.23$  for a 6 mM solution of potassium ferrioxalate using the same volume and irradiation geometry as the samples).

The quantum yield for the formation of **181b** upon direct irradiation of **169a** was determined to be  $\Phi_S = 0.09$  from the conversion measured in the absence of photosensitizer. In the case of the photosensitized reaction, the observed yield was corrected for the background reaction and internal filter effects, since **169a** absorbs at the excitation wavelength. The overall conversion ( $\chi_t$ ) is given by the sum of the contributions from the sensitized ( $\chi_{PS}$ ) and direct ( $\chi_S$ ) irradiation, weighted by the fraction of light absorbed by each species:

$$\chi_t = \frac{\epsilon_{PS}[PS]}{\epsilon_S[S] + \epsilon_{PS}[PS]} \chi_{PS} + \frac{\epsilon_S[S]}{\epsilon_S[S] + \epsilon_{PS}[PS]} \chi_S$$

where  $\epsilon_S$  and  $\epsilon_{PS}$  are the molar extinction coefficients at the irradiation wavelength of the substrate and photosensitizer, respectively. Similarly:

$$\text{moles of } \mathbf{181b} = I_t \left[ \frac{\epsilon_{PS}[PS]}{\epsilon_S[S] + \epsilon_{PS}[PS]} \Phi_{PS} + \frac{\epsilon_S[S]}{\epsilon_S[S] + \epsilon_{PS}[PS]} \Phi_S \right]$$

$$8\% \cdot 0.16\text{M} \cdot 0.0006\text{L} = (7.84 \cdot 10^{-10} \text{mol s}^{-1})(1.98 \cdot 10^4 \text{s})[0.54\Phi_{PS} + 0.46\Phi_S]$$

$$0.52 = 0.49\Phi_{PS} + 0.51\Phi_S$$

giving  $\Phi_{PS} = 0.96$ .

A value of 0.96 for the quantum yield of formation of **181b** from excited *p*-anisaldehyde, is close to unity. This implies that the sequence of reactions leading to the formation of **181b** is particularly efficient or that it may involve a radical chain reaction with a turnover > 1. Importantly, the transformation was found intrinsically 10-fold faster when sensitized *versus* direct irradiation.

#### 1.2.4.2.1.6 Calculation of the free energy of photo-induced electron transfer

##### Evaluation of the photo-induced electron transfer process

At first, the redox potentials of the sulfonyl cyanides were estimated through cyclic voltammetry (Table III.9):<sup>5</sup>

substrate	$E_{\text{red}}^a$ (V vs SCE)
EtSO <sub>2</sub> CN	-1.72
MeSO <sub>2</sub> CN	-1.88
<i>p</i> -TsCN	-1.34

**Table III.9.** Reduction potentials of the sulfonyl cyanides used in the control reactions. <sup>a</sup> Experiments were carried out at 25±0.5 °C using a glassy carbon working electrode, a Pt-wire counter-electrode, and Ag as a pseudo-reference electrode.

### Oxidative quenching of <sup>3</sup>BP\* and Electron Transfer (ET) to ethylsulfonyl cyanide

The free energy of a photo-induced electron transfer from benzophenone triplet state is given by the following relation:

$$\Delta G_{\text{PET}} = - \mathcal{F} [E_{\text{red}}(\text{RSO}_2\text{X}/\text{RSO}_2\text{X}^{\cdot-}) - ({}^3E_{\text{ox}}(\text{BP}^*/\text{BP}^{+\cdot}))]$$

with  ${}^3E_{\text{ox}}(\text{BP}^*/\text{BP}^{+\cdot}) = -0.61 \text{ V}^{117}$  and the Faraday constant  $\mathcal{F} = 23.061 \text{ kcal V}^{-1} \text{ mol}^{-1}$

Electron transfer to EtSO<sub>2</sub>CN ( $E_{\text{red}}(\text{RSO}_2\text{CN}/\text{RSO}_2\text{CN}^{\cdot-}) = -1.72 \text{ V (vs SCE)}$ ) and

$$\Delta G_{\text{PET}} = - \mathcal{F} [-1.72 - (-0.61)]$$

$$\Delta G_{\text{PET}} = +25.6 \text{ kcal/mol}$$

### Oxidative quenching of <sup>3</sup>An\* and Electron Transfer (ET) to ethylsulfonyl cyanide

The free energy of a photo-induced electron transfer from *p*-anisaldehyde (An) triplet state is given by the following relation:

$$\Delta G_{\text{PET}} = - \mathcal{F} [E_{\text{red}}(\text{RSO}_2\text{X}/\text{RSO}_2\text{X}^{\cdot-}) - ({}^3E_{\text{ox}}(\text{An}^*/\text{An}^{+\cdot}))]$$

with the Faraday constant  $\mathcal{F} = 23.061 \text{ kcal V}^{-1} \text{ mol}^{-1}$

and  ${}^3E_{\text{ox}}(\text{An}^*/\text{An}^{+\cdot}) = E^\circ(\text{An}/\text{An}^{+\cdot}) - E_{0,0}^T \rightarrow {}^3E_{\text{ox}}(\text{An}^*/\text{An}^{+\cdot}) = +1.64 - (+3.04) = -1.41 \text{ V}$

$E^\circ(\text{An}/\text{An}^{+\cdot}) = +1.64 \text{ V},^{227}$  and  $E_{0,0}^T = 3.04 \text{ V}.^{228}$

Electron transfer to EtSO<sub>2</sub>CN ( $E_{\text{red}}(\text{RSO}_2\text{CN}/\text{RSO}_2\text{CN}^{\cdot-}) = -1.72 \text{ V (vs SCE)}$ ) and

$$\Delta G_{\text{PET}} = - \mathcal{F} [-1.72 - (-1.41)]$$

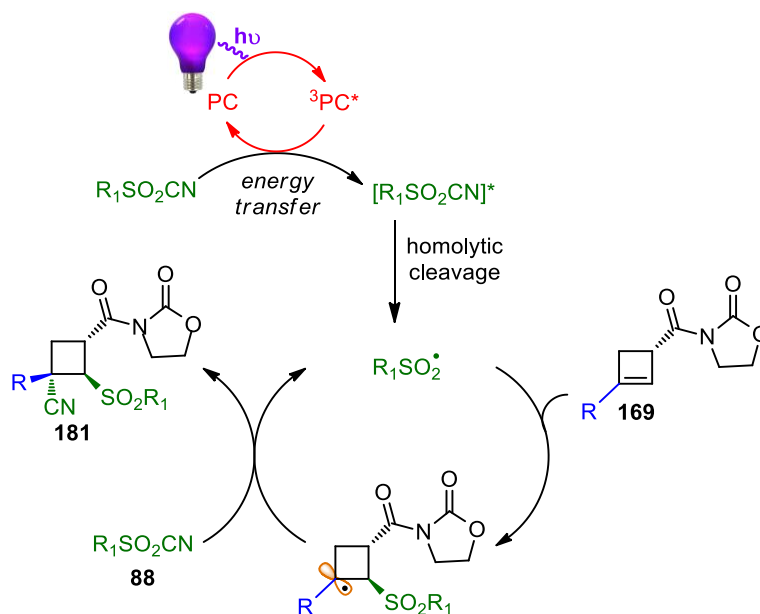
$$\Delta G_{\text{PET}} = +7.2 \text{ kcal/mol}$$

In conclusion, on the thermodynamic ground, the electron-transfer mechanism is not favored with both benzophenone and *p*-anisaldehyde.

#### 1.2.4.2.1.7 Proposed mechanism

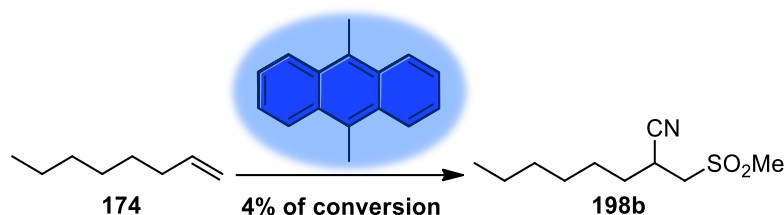
The above-mentioned results were found consistent with an energy transfer mechanism from the excited triplet state of the photosensitizer to the sulfonyl cyanide. Indeed, it is suggested that the energy transfer from the *p*-anisaldehyde<sup>229</sup> or Benzophenone<sup>230,231</sup> excited triplet state to R<sub>1</sub>SO<sub>2</sub>CN allows the generation of the sulfonyl cyanide excited triplet state (Figure III.9). This would later undergo a homolytic cleavage of the O<sub>2</sub>S–CN bond to form the sulfonyl radical. The electrophilic

radical would then add onto the less substituted end of the cyclobutene's double bond to generate a  $\beta$ -sulfonyl radical. The latter would be trapped by  $R_1SO_2CN$ , leading to the expected product and  $R_1SO_2^*$  radical, ready to sustain the radical chain reaction.



**Figure III.9.** Proposed mechanism for the *p*-anisaldehyde-photosensitized sulfonyl-cyanation.

As stated earlier, alternative mechanisms involving photo-induced electron transfer from triplet *p*-anisaldehyde or benzophenone to the sulfonyl cyanide were calculated to be thermodynamically less favorable. However, the sulfonyl-cyanation of oct-1-ene using 9,10-dimethylantracene, a strong electron donor but with a low triplet energy, led to the formation of the desired nitrile **198b** with  $\Phi = 0.13$  ( $\lambda_{\text{ex}} = 365$  nm) (Scheme III.20). This observation keeps the door open for new investigations or observations in the future.



**Scheme III.20.** Sulfonyl-cyanation of **174** in the presence of an electron donor. *Reagents and conditions:* **88a** (2.0 eq.), 9,10-dimethylantracene (0.01 eq.),  $CD_3CN/CD_2Cl_2$ : 3/2 (0.2 M), 365 nm, 30 °C, 2 h.

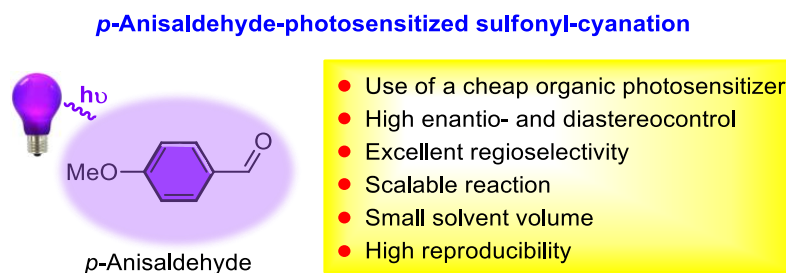
### 3. Conclusion

In the first part of this chapter, new functionalized enantiopure cyclobutenes were synthesized on decagram scale through a two-steps sequence. The first step was based on Narasaka's<sup>195</sup> early report of asymmetric [2+2]-cycloaddition to elaborate cyclobutenyl sulfides with high yields and enantiomeric excesses. These skeletons were later desulfurized to give the corresponding olefins. The  $\pi$ -system of cyclobutenes was found weakly reactive towards some electrophilic radical species. However, the malonyl radicals were successfully added onto the double bond furnishing functionalized cyclobutane rings with good yields and diastereoselectivities. Subsequent



modifications to incorporate a nitrile group in a fully enantio- and diastereocontrolled manner gave moderate results.

An unprecedented *p*-anisaldehyde-photosensitized sulfonyl-cyanation of cyclobutenes was established, allowing the addition of sulfonyl and cyanide radicals onto the cyclobutene's double bond. The mechanistic studies showed that the reaction proceeds through an energy transfer mechanism, giving the corresponding cyanosulfones in good to high yields. The sulfonyl-cyanation reaction was found ideal to incorporate a nitrile unit in a fully regio-, enantio- and diastereocontrolled manner. The sequence can be carried out on a multigram scale with excellent reproducibility, using small volumes of solvent, under mild conditions, and no workup (Figure III.10).



**Figure III.10.** *p*-Anisaldehyde as a photosensitizer in the sulfonyl-cyanation reaction.

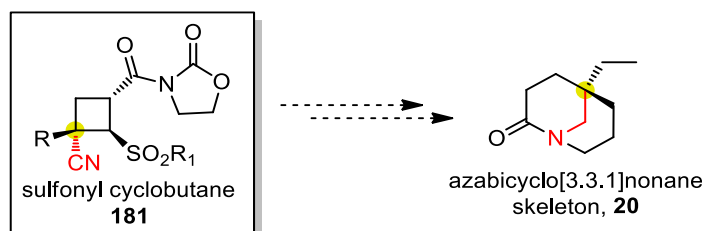
Further functionalization of the synthesized cyclobutanes was envisioned in the next part of this chapter, to elaborate these useful intermediates<sup>232,233</sup> into more complex molecular architectures.

## Part II

### Ring-Opening Studies and Cyclobutane Derivatives

#### 1. Development of cyclobutane ring-opening reactions

The successful synthesis of highly substituted cyclobutanes bearing an all-carbon quaternary center with excellent diastereocontrol is ideal for further manipulations to produce useful enantiopure derivatives. Such a backbone can be an advanced intermediate in the synthesis of azabicyclo[3.3.1]nonane **20**, a key chiral core in the total synthesis of eucophylline (Figure III.11). To achieve this goal, two modifications must be focused upon: a general method for the sulfonyl group elimination and an efficient route for the cyclobutyl ring-cleavage.

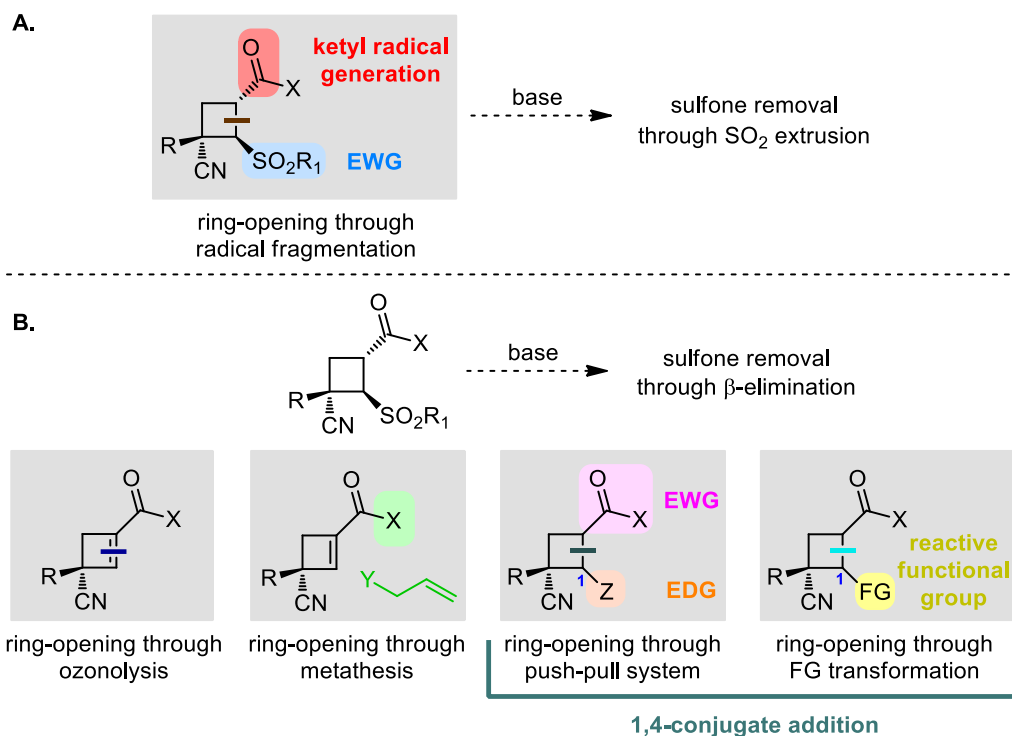


**Figure III.11.** Sulfonylcyclobutanes as key-synthons in the synthesis of azabicyclo[3.3.1]nonane, an eucophylline's intermediate.

Compared to the three-membered ring, the cleavage of the cyclobutane ring is harder due to the less important total strain within the molecule. Still, the ring-opening of the synthesized cyclobutanes can be triggered in various ways. Generating an unstable ketyl-type radical from the cyclobutyloxazolidinone would for instance induce the formation of a relatively stable radical  $\alpha$ - to the electron-withdrawing group, which could then trigger a straightforward ring fragmentation (Scheme III.21.A). The resulting acyclic chain can later be submitted to sulfone elimination using a suitable base.

In contrast, the sulfonyl group can be removed first, through an E<sub>1cb</sub>-type elimination process to generate a homochiral cyclobutene (Scheme III.21.B). The latter can be then submitted to a ring-opening procedure through ozonolysis of the double bond, a ring-opening metathesis (ROM) with an appropriate olefin, or to 1,4-addition of a nucleophile. In the latter strategy, an electron-donating group, for example, can be introduced at the C1-position to the carbonyl fragment, which might allow

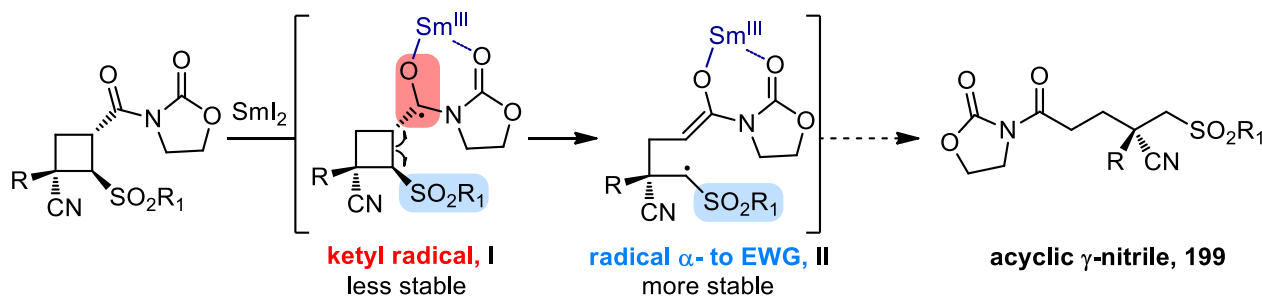
further “push-pull” process. Since both groups, the carboxylate and the nitrile, are electron-withdrawing groups in this system, conditions have to be carefully studied to favor the pull effect on the desired side. Alternatively, the 1,4-addition of different reactive fragments might, under the appropriate conditions, induce the cyclobutyl ring-opening.



**Scheme III.21.** Various pathways towards cyclobutane ring-opening and sulfone elimination.

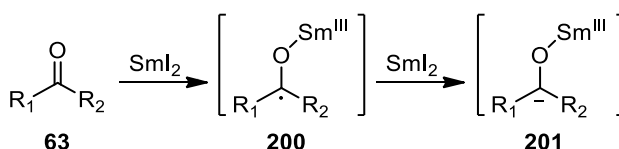
## 2. Ring-opening reaction through Samarium(II) diiodide

At first, the ring-opening process was developed through radical fragmentation. To meet this purpose, the formation of a ketyl radical species would be carried out using samarium(II) diiodide ( $\text{SmI}_2$ ), a well-known reagent for such transformation.<sup>234</sup> In the presence of  $\text{SmI}_2$  under suitable reaction conditions, a single electron would be transferred to the cyclobutane to generate a metallated ketyl radical  $\alpha$ - to the oxazolidinone fragment **I** (Scheme III.22), which would then trigger a regioselective ring cleavage leading to the formation of a radical  $\alpha$ - to the sulfone **II**. Such a process would deliver after the convenient treatment, the expected acyclic  $\gamma$ -amidonitrile **199**.



**Scheme III.22.** Cyclobutane ring opening through  $\text{SmI}_2$ -promoted radical fragmentation.

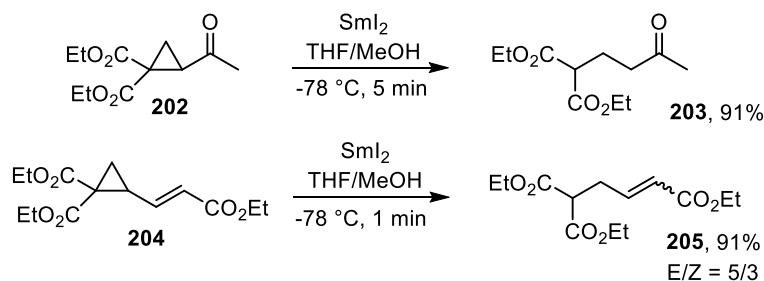
Hundreds of reactions were reported on functional groups reduction (ester, ketone, aldehyde, carboxylic acid, amide, nitrile, *N*-oxazolidinone, nitron...), carbon-carbon and carbon-heteroatom bond formation and fragmentation.<sup>238,243</sup> Reduction of carbonyl compounds using oxophilic SmI<sub>2</sub> leads to ketyl radicals, which under certain conditions are further reduced into samarium(III) enolate intermediates (Scheme III.23).<sup>241</sup> Such enolates can be quenched *in situ* with electrophiles to make new bonds, or experience rapid scission of a carbon-carbon bond  $\alpha$ - to the carbonyl group.<sup>244–249</sup> Compared to the former, the latter outcome is less documented.



**Scheme III.23.** Common mechanism of SmI<sub>2</sub>-promoted activation of carbonyl compounds.

## 2.2. Reported SmI<sub>2</sub>-mediated ring-opening processes

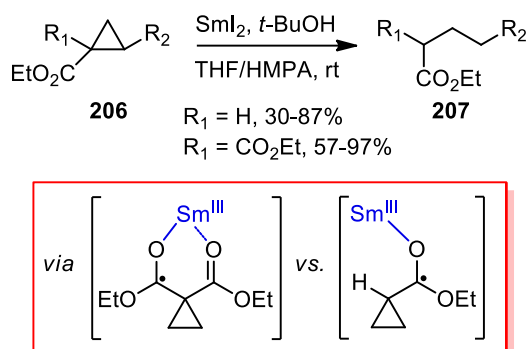
In correlation with this section, illustrative examples of the power of SmI<sub>2</sub> in the ring-opening reaction are described. Kim *et al.*<sup>250</sup> reported a reductive ring-opening of cyclopropyl ketones **202** and **204** using the samarium complex in THF/MeOH at low temperature. The introduction of an electron-withdrawing group on the vicinal position to the ketone favored the fast and selective ring cleavage (Scheme III.24).



**Scheme III.24.** SmI<sub>2</sub>-mediated ring-opening of cyclopropyl ketone.<sup>250</sup>

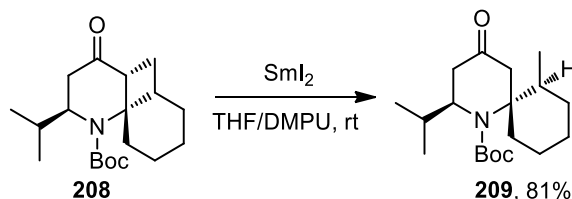
Similarly, the ring-opening of cyclopropane mono- and di-carboxylates **206** was reported by Yamashita and co-workers.<sup>251</sup> A large scope was studied in the presence of a proton source, to deliver the acyclic compounds **207** in good to high yields (Scheme III.25). This reaction showed high

regioselectivity and a satisfying tolerance for different functional groups. This also illustrates the effect of the electron-withdrawing groups on the reactivity of the three-membered carbocycle towards the ring scission.



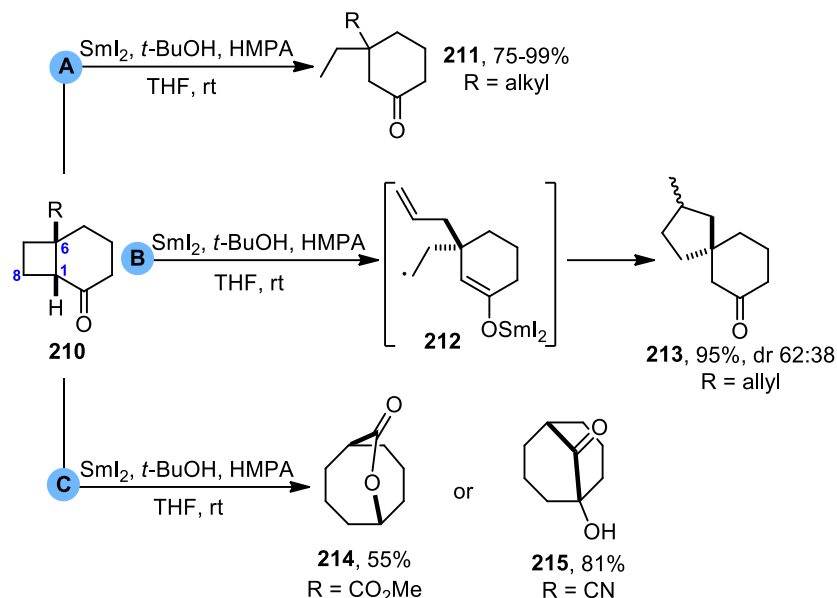
**Scheme III.25.** SmI<sub>2</sub>-mediated ring-opening of cyclopropane carboxylates.<sup>251</sup>

Although studies on SmI<sub>2</sub>-mediated cyclobutanes cleavage are less popular than cyclopropanes, reports demonstrated its feasibility and utility in the synthesis of polycyclic targets. For instance, Comins *et al.*<sup>252</sup> exposed  $\alpha$ -ketocyclobutane **208** to a single-electron transfer reaction using SmI<sub>2</sub> coordinated with a Lewis base (DMPU). This scaffold undertook facile C-C disconnection to yield 81% of azaspiro[5.5]undecane **209** as a sole product (Scheme III.26).



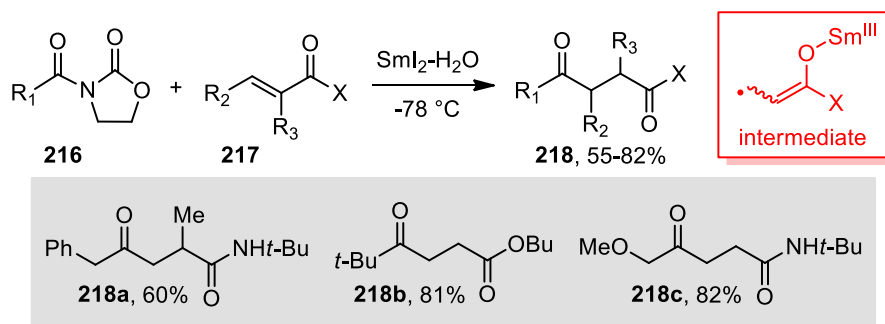
**Scheme III.26.** Synthesis of spirocycle **209** through SmI<sub>2</sub>-promoted ring-opening.<sup>252</sup>

An interesting study on the four-membered ring cleavage and expansion was described by Kakiuchi and co-workers.<sup>253</sup> Subjected to SmI<sub>2</sub>/HMPA/*t*-BuOH complex, bicyclo[4.2.0]octan-2-ones **210** met with different fates depending on their C-6 substituent. The alkyl-substituted bicyclo[4.2.0]octan-2-ones afforded the cyclohexanones **211** through the cleavage of the external C1-C8 bond (Scheme III.27.A). With an unsaturated side chain as a substituent, the radical intermediate **212** proceeded through 5-*exo*-trig cyclization to provide the spiro[4.5]decanone **213** in excellent yield (Scheme III.27.B). In contrast, in the presence of electron-withdrawing groups such as nitrile or ester, the regioselectivity was directed towards the formation of eight-membered ring derivatives **214** and **215** (Scheme III.27.C). Other examples on the ring-opening  $\alpha$ - to a ketone in unactivated cyclobutanes were also described elsewhere.<sup>243,252,254,255</sup>



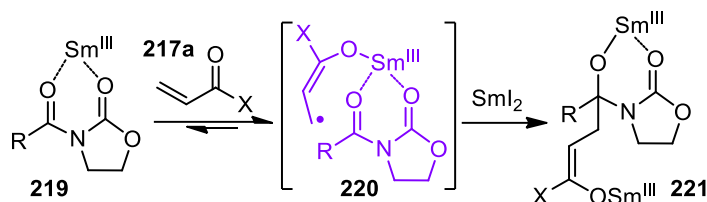
**Scheme III.27.** SmI<sub>2</sub>-mediated ring-opening reaction of bicyclo[4.2.0]octan-2-ones.<sup>253</sup>

When it comes to carbonyls next to heteroatoms such as nitrogen, the reactivity of the organosamarium was far less studied.<sup>241</sup> Yet, Skrydstrup,<sup>256</sup> Procter,<sup>257,258</sup> and others<sup>259</sup> succeeded at creating ketyl radicals from unactivated amides or *N*-acyloxazolidinones. Under suitable conditions, it was found that, when associated to water, the reductive potential of SmI<sub>2</sub> is high enough to activate the oxazolidinone entity.<sup>240</sup> But, it was also stated that Sm(II) has a high affinity (due to its oxophilic character) towards *N*-acyloxazolidinone, which coordinates with SmI<sub>2</sub> and behaves as a ligand, as observed with HMPA.<sup>256,260</sup> Skrydstrup and co-workers<sup>256,261</sup> utilized SmI<sub>2</sub> assisted by H<sub>2</sub>O to promote a radical addition of acrylates and acrylamides **217** onto *N*-acyloxazolidinones **216** (Scheme III.28). This reaction furnished a wide variety of  $\gamma$ -ketoamides and  $\gamma$ -ketoesters **218** in good to high yields.



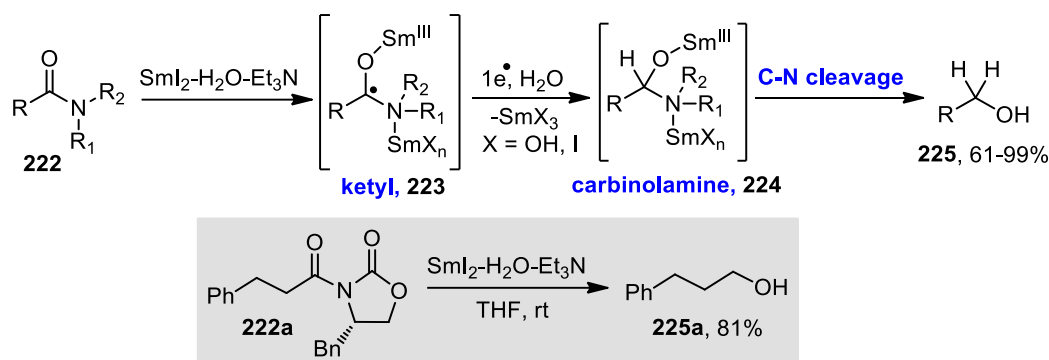
**Scheme III.28.** SmI<sub>2</sub>/H<sub>2</sub>O-mediated cross-coupling of *N*-acyloxazolidinones with acrylamides and acrylates.<sup>256,261</sup>

The mechanistic studies showed that the acrylamide/acrylate **217a** gets reduced into a radical anion after coordination with the Sm(II)-oxazolidinone complex **219** (Scheme III.29). The alkyl radical then undergoes intermolecular coupling with the *N*-acyloxazolidinone's carbonyl.<sup>256</sup> This reaction was also extended to *N*-acyloxazolidinones derived from amino acids and peptides as intermediates for more complex targets.<sup>262,263</sup>



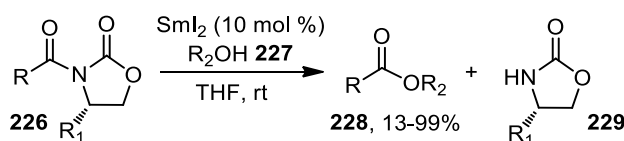
**Scheme III.29.** Mechanism of  $\text{SmI}_2$ -mediated cross-coupling of *N*-acyloxazolidinones.<sup>256</sup>

When a base such as triethylamine is added, a chemoselective reduction of unactivated amides and *N*-acyloxazolidinones into alcohols was observed (Scheme III.30).<sup>257</sup> The mechanistic data indicate that the coordination of  $\text{Sm(II)}$  to the carbonyl and the Lewis basic nitrogen facilitates the electron transfer through a ketyl-type radical **223**. After reduction into carbinolamine **224**, the organosamarium intermediate undergoes selective C-N bond scission to provide access to a library of functionalized alcohols **225** in good to high yields. Similarly, the reduction of *N*-acyloxazolidinone **222a** delivered the corresponding alcohol **225a** in a high yield.



**Scheme III.30.** Chemoselective reduction of amide derivatives to alcohol using  $\text{SmI}_2\text{-H}_2\text{O-Et}_3\text{N}$  complex.<sup>257</sup>

Interestingly, in the presence of alcohol **227** and a catalytic amount of  $\text{SmI}_2$ , unactivated Evans-type oxazolidinones **226** were converted into esters **228** through stable acyl radicals, as reported by Collin and co-workers (Scheme III.31).<sup>259</sup> This reaction was applied to a broad scope to afford the expected products without racemization. The oxazolidinone moieties **229** were also recovered in good yields.

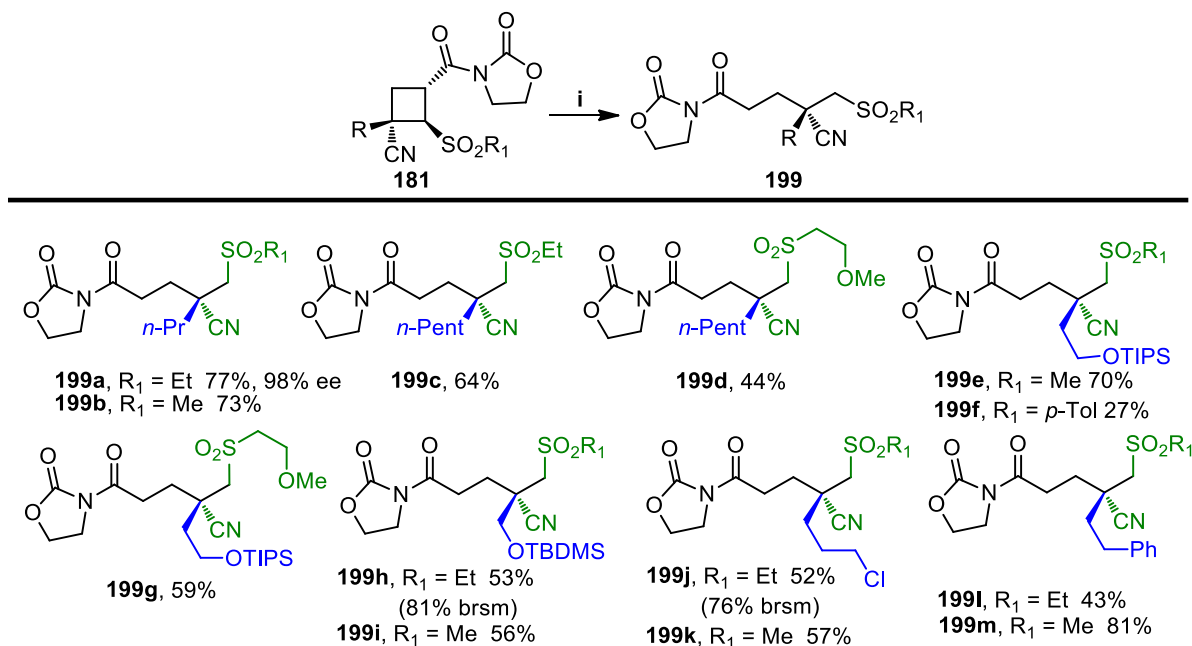


**Scheme III.31.** Conversion of *N*-acyloxazolidinones into esters using  $\text{SmI}_2$ .<sup>259</sup>

### 2.3. Application of $\text{SmI}_2$ -promoted reaction on sulfonyl cyclobutanes

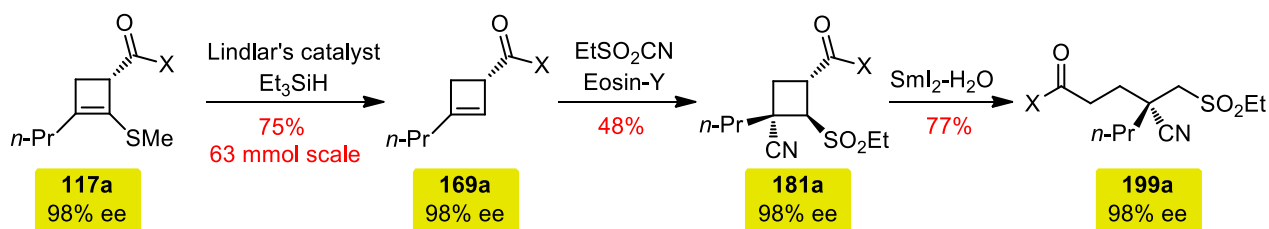
The regioselective fragmentation of cyclobutanes then proceeded using  $\text{SmI}_2\text{-H}_2\text{O}$  mixture at  $-78^\circ\text{C}$ , to give access to enantiopure nitriles **199**  $\gamma$ - to a carbonyl group in good to high yields (Scheme III.32). The reaction conditions were found to tolerate functionalized alkyl groups, such as chlorides, silyl ethers, and aryls. The reaction was also suitable for different sulfonyl chains, although better yields were observed with methylsulfones (e.g., **199m** vs **199l**). Tosyl cyclobutane **181j** on the other hand, gave the opened product **199f** in a low yield, and the crude mixture was contaminated by other

unidentified side products. This is indeed predictable since the arylsulfones are more sensitive to  $\text{SmI}_2$  reduction than the alkylsulfones.<sup>264</sup>



**Scheme III.32.** Scope of  $\text{SmI}_2$ -promoted ring-opening reaction. *Reagents and conditions:* i)  $\text{SmI}_2$  (3.5-4.5 eq.),  $\text{H}_2\text{O}$  (12.0-18.0 eq.), THF (0.1-0.2 M),  $-78^\circ\text{C}$ , 1-4.5 h.

Overall, this sequence led efficiently to cyclic and acyclic  $\beta$ -sulfonylnitriles bearing an all-carbon quaternary stereocenter, starting from simple optically pure cyclobutenes. The generality of this methodology was illustrated by its applicability to cyclobutenes bearing a variety of functionalities. The enantioselectivity of this sequence was monitored for each step after the synthesis of the racemic substrates. No racemization arose, and for the sequential substrates **117a**, **169a**, **181a** and **199a** the enantiomeric ratio exceeded 98% (Scheme III.33).



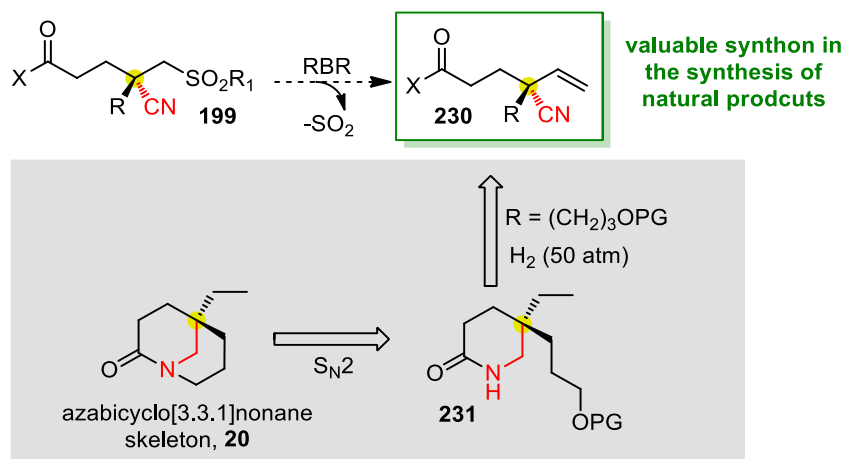
**Scheme III.33.** Evaluation of the enantioselectivity of the cyclobutenes sequence methodology. X = oxazolidinone.

### 3. The Ramberg-Bäcklund Rearrangement (RBR)

Following these results, above sulfonyl nitriles were ready for sulfonyl group elimination. It was envisioned that submitting the alkyl-sulfone **199** to the Ramberg-Bäcklund reaction conditions, would deliver the corresponding allyl-nitrile derivative **230** in an efficient and straightforward way (Scheme III.34). Such a synthon would then be prone to successive modifications, making it a valuable intermediate for the asymmetric synthesis of natural targets. For instance, hydrogenation under high pressure (*e.g.*,  $\text{H}_2$ , 50 atm, Raney<sup>®</sup>-nickel) of such an alkene with the suitable R side chain ( $R =$



(CH<sub>2</sub>)<sub>3</sub>OPG), would promote the cyclization into a six-membered ring lactam **231**, a direct precursor of the azabicyclo[3.3.1]nonane fragment of eucophylline.



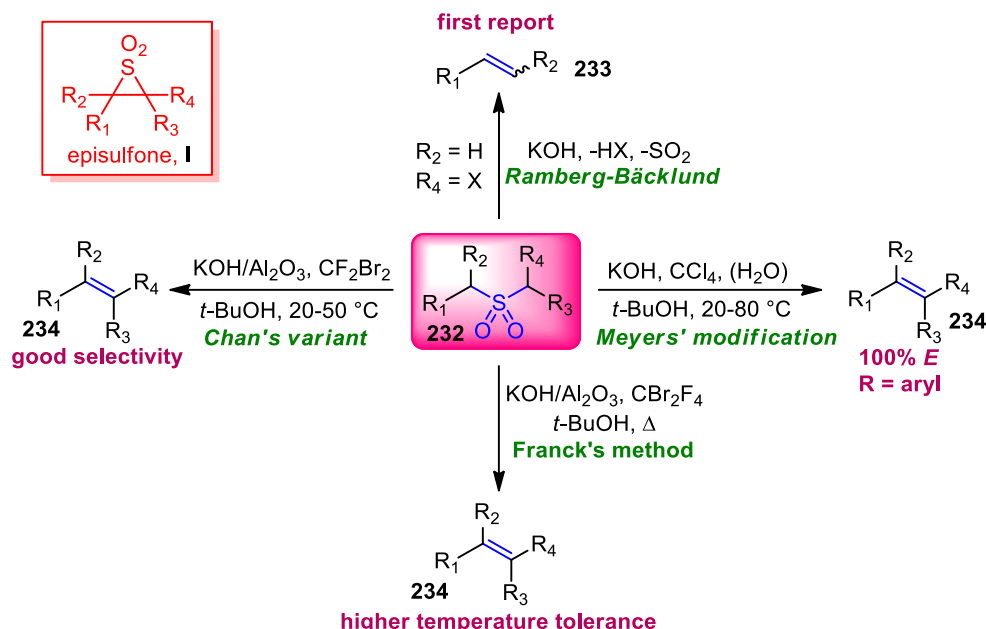
**Scheme III.34.** Sulfone elimination reaction through RBR, and utility of the allylnitrile product in the total synthesis of eucophylline. X = oxazolidinone or alkoxy group.

### 3.1. Ramberg-Bäcklund reaction in the literature

In 1940, Ramberg and Bäcklund<sup>265,266</sup> discovered that treatment of  $\alpha$ -halo-sulfones **232** with 2 *N* KOH, led to the corresponding alkenes **233** with *Z*-selectivity (Scheme III.35). The reaction was shown to proceed through the intermediate episulfone **I**, which collapses into alkene after fast SO<sub>2</sub> extrusion.

This two-steps sequence: halogenation/base-induced rearrangement being challenging (difficulties encountered in the preparation of  $\alpha$ -halosulfones), Meyers<sup>267</sup> later developed a one-pot process, where the  $\alpha$ -halo-sulfones are synthesized *in situ*.  $\alpha$ - and  $\alpha'$ -hydrogen-bearing sulfones were thus treated with an excess of powdered KOH in the presence of *t*-BuOH and CCl<sub>4</sub> as a halogenating agent. Although this chemistry gave excellent yields of regio-defined olefins **234**, it was limited to the preparation of stilbenes and 1,1-diarylalkenes.

Consequently, Chan and co-workers<sup>268</sup> proposed another method, using alumina-supported potassium hydroxide and difluorodibromomethane as base and halogen sources, respectively. This reaction was carried out at room temperature for activated substrates (*e.g.*, benzylic and allylic sulfones). However, for other substrates (alkyl sulfones), heating was essential to generate the required carbanion species which led to poor yields due to the loss of the low boiling CF<sub>2</sub>Br<sub>2</sub>. Franck and colleagues<sup>269</sup> then proposed dibromotetrafluoroethane as a less volatile alternative (C<sub>2</sub>Br<sub>2</sub>F<sub>4</sub>, 47 °C *vs.* CF<sub>2</sub>Br<sub>2</sub>, 23 °C). Examples of RBR have flourished over the years, which were notably reviewed by Taylor and Paquette.<sup>270,271</sup>

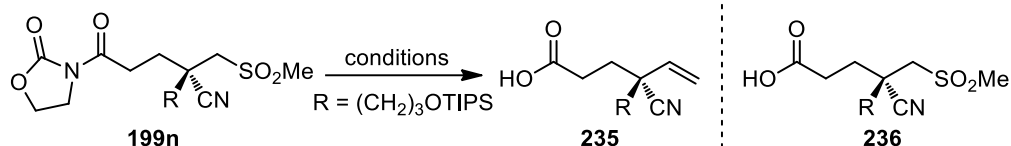


**Scheme III.35.** Ramberg-Bäcklund rearrangement and key improvements proposed by Meyers, Chan, and Franck.

### 3.2. Application of the Ramberg-Bäcklund reaction

Meyers' original conditions ( $CCl_4$ ,  $KOH$ ,  $t-BuOH/H_2O$ ) on the acyclic  $\gamma$ -nitrile **199n** as a model, gave no typical alkene signals in the  $^1H$ -NMR spectrum, the profile of which was rather complex (Table III.10, entry 1). Changing the halogen source to Chan's  $CBr_2F_2$  employed in large excess due to its volatile nature, delivered the alkene **235** in 10% yield after column chromatography (entry 2). Under such harsh conditions, the oxazolidinone-deprotection was observed to give the saponified analog **236**. Other highly polar compounds were observed on TLC resulting probably from decomposition. Under Chan's conditions ( $CBr_2F_2$ ,  $KOH/Al_2O_3$ ), a partial conversion was observed, and **235** was isolated in 18% yield alongside with 30% of the saponified starting material **236** (entry 3). When chloroform was used as a co-solvent, full conversion of the starting material was observed, however, only 23% of **235** were isolated, with many spots seen on TLC (entry 4).

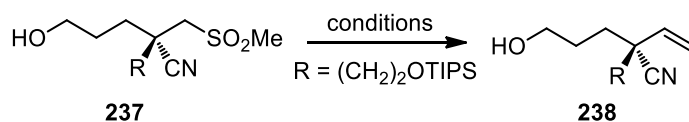
With the halogenating agents 1,2-dibromotetrachloroethane ( $C_2Br_2Cl_4$ ),<sup>272</sup> a non-volatile and ozone-friendly reagent, and hexachloroethane ( $C_2Cl_6$ )<sup>273</sup> only traces of the desired product were detected on the crude  $^1H$ -NMR (entries 5 and 6). When combining Meyers' and Chan's conditions ( $CCl_4$ ,  $KOH/Al_2O_3$ ) at  $80\text{ }^\circ C$  for 21 h, the product was isolated in 40% yield (entry 7), conditions which were not reproducible, likely as a result of the high polarity of the compounds, easily lost on column chromatography (entry 8). Unfortunately, increasing the reaction time did not afford a better yield (entry 9). Such harsh conditions are probably not compatible with the nitrile group, which may be hydrolyzed. The application of milder bases such as DBU and  $Et_3N$  did not promote any reaction even at reflux, which was somehow expected, due to the low acidity of the proton  $\alpha$ - to the sulfone (entries 10 and 11).



entry	base	[X]	solvent	temp (°C)	time (h)	yield (%)	
						235	236
1	aq. KOH	-	<i>t</i> -BuOH/ $\text{CCl}_4$	40	24	0	0
2	aq. KOH	$\text{CBr}_2\text{F}_2$	<i>t</i> -BuOH/ $\text{CH}_2\text{Cl}_2$	40	24	10	0
3	KOH/ $\text{Al}_2\text{O}_3$	$\text{CBr}_2\text{F}_2$	<i>t</i> -BuOH/ $\text{CH}_2\text{Cl}_2$	40	18	18	30
4	KOH/ $\text{Al}_2\text{O}_3$	$\text{CBr}_2\text{F}_2$	<i>t</i> -BuOH/ $\text{CHCl}_3$	40	16	23	0
5	KOH/ $\text{Al}_2\text{O}_3$	$\text{C}_2\text{Br}_2\text{Cl}_4$	<i>t</i> -BuOH/ $\text{CH}_2\text{Cl}_2$	40	6	traces	0
6	KOH/ $\text{Al}_2\text{O}_3$	$\text{C}_2\text{Cl}_6$	<i>t</i> -BuOH/ $\text{CH}_2\text{Cl}_2$	40	6	traces	0
7	KOH/ $\text{Al}_2\text{O}_3$	-	<i>t</i> -BuOH/ $\text{CCl}_4$	80	21	40	0
8	KOH/ $\text{Al}_2\text{O}_3$	-	<i>t</i> -BuOH/ $\text{CCl}_4$	80	21	27	0
9	KOH/ $\text{Al}_2\text{O}_3$	-	<i>t</i> -BuOH/ $\text{CCl}_4$	80	30	22	0
10	DBU	$\text{CBr}_2\text{F}_2$	$\text{CH}_2\text{Cl}_2$	0 to 40	7	-	-
11	$\text{Et}_3\text{N}$	$\text{CBr}_2\text{F}_2$	$\text{CH}_2\text{Cl}_2$	0 to 40	7	-	-

**Table III.10.** Conditions screening of Ramberg-Bäcklund reaction. [X] = halogen source. *Reagents and conditions:* base (2.0 eq.), KOH/ $\text{Al}_2\text{O}_3$  (250 mg/0.1 mmol of substrate). [X]:  $\text{CF}_2\text{Br}_2$  (10.0+10.0 eq.),  $\text{C}_2\text{Cl}_6$  (5.0 eq.),  $\text{C}_2\text{Br}_2\text{Cl}_4$  (2.0 eq.). Solvent: 1/1. *t*-BuOH/ $\text{CH}_2\text{Cl}_2$ /H<sub>2</sub>O 1:1:0.2.

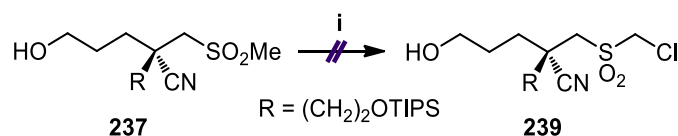
To solve the polarity problem, the oxazolidinone moiety in **199e** was reduced in the presence of  $\text{LiBH}_4$  into alcohol **237**, in 88% yield (*experimental part*). With **237** is in hand, the best conditions found previously were applied to give the expected product **238** in 35% yield, contaminated with inseparable impurities (Table III.11, entry 1). Using *t*-BuOK as a base gave only traces of the typical alkene as detected by crude  $^1\text{H}$ -NMR (entry 2). Other modified conditions ( $\text{BrCCl}_3$ , KOH/ $\text{Al}_2\text{O}_3$ ) did not afford better results (entry 3).



entry	base	solvent	temp (°C)	time (h)	yield (%)
1	KOH/ $\text{Al}_2\text{O}_3$	<i>t</i> -BuOH/ $\text{CCl}_4$	80	13	35 (not pure)
2	<i>t</i> -BuOK	<i>t</i> -BuOH/ $\text{CCl}_4$	80	39	traces
3	KOH/ $\text{Al}_2\text{O}_3$	<i>t</i> -BuOH/ $\text{BrCCl}_3$	20	22	traces

**Table III.11.** Attempts for RB reaction on alcohol sulfone. *Reagents and conditions:* *t*-BuOK (3.0 eq.), KOH/ $\text{Al}_2\text{O}_3$  (250 mg/0.1 mmol of substrate), solvent: 1/1.

Besides the high polarity of the manipulated compounds, the poor yields could also be rationalized by the lower acidity of the alkyl proton  $\alpha$ - to the sulfone compared to benzylic proton used in the original paper (benzylic  $\alpha$ -protons,  $pK_a \sim 23.4$  vs. alkyl  $\alpha$ -protons,  $pK_a \sim 31.0$ ). The halogenation process could thus be controlled by introducing a chlorine atom  $\alpha$ - to the alkyl sulfone using *n*-BuLi and  $C_2Cl_6$  as deprotonating and halogenating agents, respectively.<sup>274</sup> Yet, applying this strategy to **237** gave a complex mixture of unidentified products (Scheme III.36).

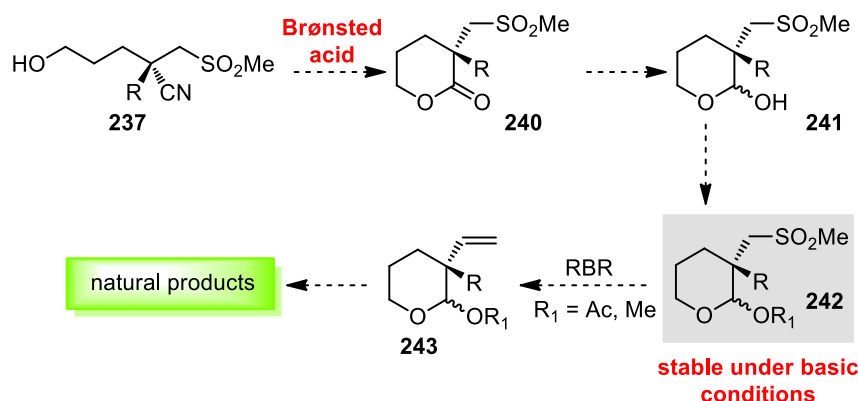


**Scheme III.36.** Attempt for halogenation of **237**. *Reagents and conditions:* i) *n*-BuLi (2.2 eq.),  $C_2Cl_6$  (3.0 eq.), THF (0.12 M), -78 to 20 °C, 3.5 h.

All the above observations suggest that in such a system, the nitrile might undergo hydrolysis or an intramolecular nucleophilic attack of the carbanion  $\alpha$ - to the sulfone, which led to look for other tactics to reach the desired goal.

#### 4. Nitrile fragment hydrolysis and lactone synthesis

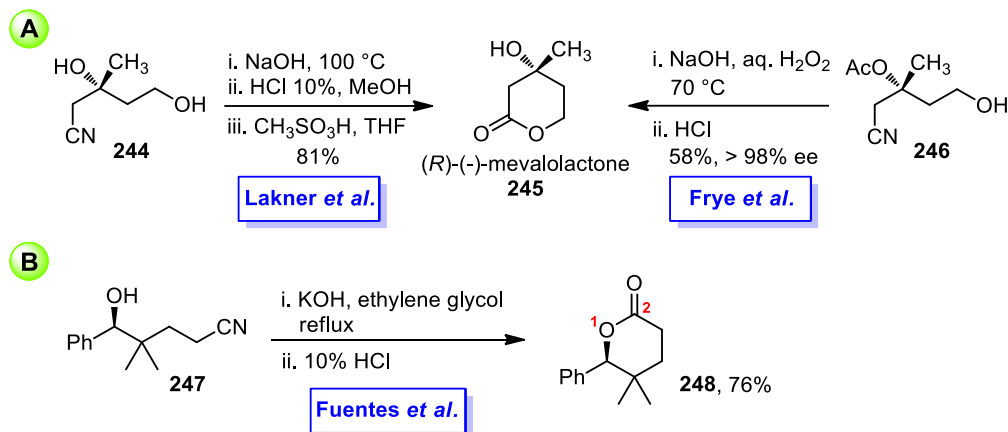
The next logical step was to transform the nitrile group under hydrolysis, reduction, or hydrogenation into a functionality compatible with the Ramberg-Bäcklund rearrangement. To start, it was planned to hydrolyze the nitrile in **237** into a carboxylic acid. This latter would be submitted *in situ* to a spontaneous nucleophilic attack of the alcohol six atoms away, to generate a  $\delta$ -lactone ring **240** (Scheme III.37). Further manipulation of the lactone framework would deliver a lactol **241**, which could evolve into an  $\alpha$ -alkoxy ether **242** under suitable conditions. This substrate would be stable under the highly basic conditions of RBR and could be submitted to the sulfone elimination to give an unsaturated  $\alpha$ -alkoxy pyran **243**. This kind of functionalized heterocycles might be an interesting intermediate in the synthesis of complex targets, such as  $\delta$ -lactone- and tetrahydropyran-containing natural products<sup>275</sup> like polyketides,<sup>276</sup> pheromones,<sup>277</sup> and anticancer agents.<sup>278</sup> For this project, pyran **243** would be a valuable synthon in the asymmetric synthesis of eburnamine **18**.<sup>279</sup>



**Scheme III.37.** Strategy towards lactone formation and further manipulation.

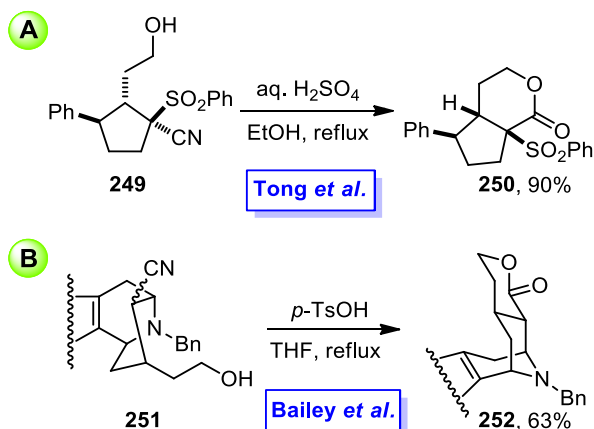
The intramolecular cyclization of a  $\delta$ -hydroxy acid is considered one of the most straightforward protocols for the synthesis of  $\delta$ -lactone frameworks.<sup>280</sup> Such lactones may also be prepared in a one-

pot process from  $\delta$ -hydroxy nitriles, after hydrolysis and subsequent lactonization under thermal acidic or basic conditions. Lakner and Frye prepared for instance the optically pure (*R*)-mevalolactone **245** using NaOH at high temperature (Scheme III.38.A).<sup>281,282</sup> Both cases afforded the expected product in high yields and excellent enantioselectivity. The Intramolecular hydrolytic cyclization of nitrile **247** in refluxing KOH went smoothly to construct O1-C2 bond in lactone **248** in 76% yield, *via* a  $\delta$ -hydroxy acid (Scheme III.38.B).<sup>283</sup>



**Scheme III.38.** Synthesis of  $\delta$ -lactones from  $\delta$ -hydroxy nitriles under thermal basic conditions.

Acid-catalyzed lactonization of  $\delta$ -hydroxy nitriles was also inspected; Tong and co-workers used aqueous sulfuric acid to promote the hydrolysis and lactonization sequence to obtain the *cis*-bicyclic lactone **250** in 90% yield (Scheme III.39.A).<sup>284</sup> The lactonization of hydroxy nitrile **251** also took place with *p*-toluenesulfonic acid in refluxing THF to give **252** in 63% yield, an advanced intermediate in the synthesis of ajmaline alkaloid (Scheme III.39.B).<sup>285</sup>

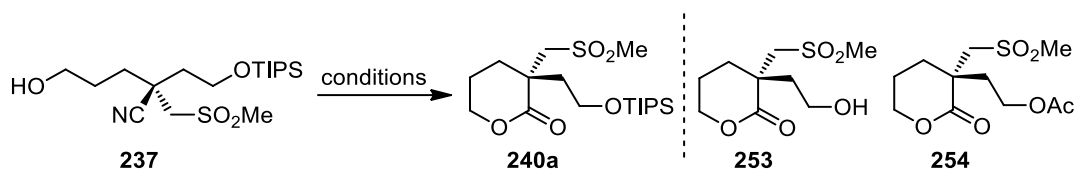


**Scheme III.39.** One-pot hydrolyzation-lactonization process under thermal acidic conditions.

#### 4.1. Application of hydrolytic lactonization on $\delta$ -hydroxy nitrile **237**

When KOH in refluxing ethylene glycol was used on nitrile **237**, only traces of the TIPS-protected lactone **253** were obtained (Table III.12, entry 1). In contrast, when the reaction was assisted with sodium hydroxide/hydrogen peroxide mixture, 56% of the deprotected lactone **253** were also obtained, alongside with 10% of the starting material (entry 2). The reprotection of **253** was carried out under standard conditions (TIPSCl, imidazole,  $\text{CH}_2\text{Cl}_2$ , 0 to 20 °C, 1.5 h) to afford **240a** in a 91% yield. In the presence of a Brønsted acid, such as aqueous sulfuric acid, complete

decomposition of the starting material was observed after 6 h (entry 3). However, with 2 equivalents of *p*-toluenesulfonic acid, 1% of the desired product **240a**, 54% of the deprotected **253**, and 1% of the starting material were isolated (entry 4). Interestingly, 10% of an acylated lactone **254** were also obtained. The formation of this product could be rationalized by the reaction of the hydroxy-lactone **253** with ethyl acetate in the presence of an excess of *p*-TsOH during the extraction process. Similarly, with a stoichiometric amount of acid, the reaction led to 1% and 54% of the desired product **240a** and the alcohol **253** respectively, alongside with 26% of the initial substrate (entry 5). Running the reaction in refluxing toluene using a Dean-Stark, produced 63% of the expected product **240a**, 26% of **253**, and 9% of the starting material in a clean fashion (entry 6). In this case, leaving the reaction for a long time did not improve the conversion of the substrate **237**.



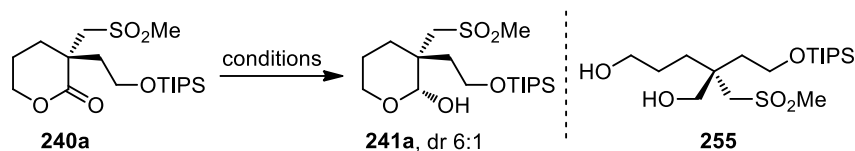
entry	reagents (eq.)	solvent <sup>a</sup>	time (h)	yield (%)			
				237	240a	253	254
1	KOH (5.0)	ethylene glycol	47	80	0	traces	-
2	NaOH, H <sub>2</sub> O <sub>2</sub>	-	22	10	0	56	-
3	H <sub>2</sub> SO <sub>4</sub> (30.0)	EtOH/H <sub>2</sub> O <sup>b</sup>	6	decomposition			
4	<i>p</i> -TsOH (2.0)	THF	24	1	1	54	10
5	<i>p</i> -TsOH (1.0)	THF	19	26	1	54	-
6	<i>p</i> -TsOH (1.0)	toluene <sup>c</sup>	48	9	63	26	-

**Table III.12.** Lactone synthesis through hydrolytic cyclization. Reactions were performed under reflux.

<sup>a</sup> Solvent (0.1 M). <sup>b</sup> EtOH/H<sub>2</sub>O: 1/2. <sup>c</sup> Dean-Stark.

From these studies, a straightforward hydrolytic cyclization of the sulfonyl nitrile **237** gave access to a substituted  $\delta$ -lactone bearing an all-carbon quaternary center. The yield obtained was considered high enough to pursue the following steps.

The lactone **240a** was then subjected to reduction under standard conditions (DIBAL-H, THF, low temperature).<sup>286</sup> With 1.5 equivalents of DIBAL-H, 9% of the expected lactol **241a** were isolated as a mixture of two diastereomers (dr 6:1), alongside with an acyclic diol **255** in 46% yield (Table III.13, entry 1). Decreasing the amount of hydride source to 1.0 eq. afforded the lactol **241a** and the diol **255** in 13% and 46%, respectively (entry 2). When modifying the workup procedure by stirring the crude mixture with the Rochelle's salt (potassium sodium tartrate) for 12 h, the diol **255** was isolated in 70% yield as the sole product (entry 3).

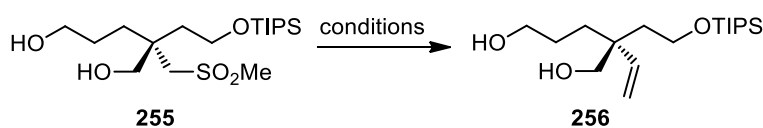


entry	DIBAL-H (eq.)	time (h)	Rochelle salt	yield (%)	
			workup	241a	255
1	1.5	1.5	stirring 30 min	9	46
2	1.0	4	stirring 30 min	13	46
3	1.0	3	stirring 12 h	0	70

**Table III.13.** Lactone reduction into lactol. *Reagents and conditions:* CH<sub>2</sub>Cl<sub>2</sub> (0.2 M), -78 to 0 °C.

#### 4.2. RBR reaction on diol 255

Before continuing the optimization measures, and with enough material in hand, the diol **255** was submitted to RBR conditions. Surprisingly, with the optimal conditions of KOH/Al<sub>2</sub>O<sub>3</sub> in *t*-BuOH/CCl<sub>4</sub>, a complex mixture of products was obtained (Table III.14, entry 1). With CBr<sub>2</sub>F<sub>2</sub> as the halogenating agent, traces of a typical double bond signal were detected, but not enough for the product to be isolated and analyzed. Other bases were then studied; both potassium hydroxide and potassium *tert*-butoxide gave a complex mixture of products (entries 3 and 4).



entry	base	[X]	solvent	temp (°C)	yield (%)
1	KOH/Al <sub>2</sub> O <sub>3</sub>	-	<i>t</i> -BuOH/CCl <sub>4</sub>	80	comp. mix.
2	KOH/Al <sub>2</sub> O <sub>3</sub>	CBr <sub>2</sub> F <sub>2</sub>	<i>t</i> -BuOH/CH <sub>2</sub> Cl <sub>2</sub>	40	traces
3	aq. KOH	CBr <sub>2</sub> F <sub>2</sub>	<i>t</i> -BuOH/CH <sub>2</sub> Cl <sub>2</sub>	20	comp. mix.
4	<i>t</i> -BuOK	CBr <sub>2</sub> F <sub>2</sub>	<i>t</i> -BuOH/CH <sub>2</sub> Cl <sub>2</sub>	20	comp. mix.

**Table III.14.** Conditions screening for the Ramberg-Bäcklund reaction. [X] = halogen source. *Reagents and conditions:* base (22.0 eq.), KOH/Al<sub>2</sub>O<sub>3</sub> (250 mg/0.1 mmol of substrate), CF<sub>2</sub>Br<sub>2</sub> (10.0+10.0 eq.), C<sub>2</sub>Cl<sub>6</sub> (5.0 eq.), solvent: 1/1, 12 h.

Accordingly, even after the modification of the substrates, RBR was still inefficient. At this stage, the elimination of the sulfone through Ramberg-Bäcklund strategy was abandoned, and shorter and more efficient routes were investigated.

#### 5. Base-promoted sulfone elimination

The complexity of applying Ramberg-Bäcklund reaction on the  $\gamma$ -nitrile substrates **199**, directed the focus towards other methods.<sup>287,288</sup> It was envisioned to eliminate the sulfone group directly from the cyclobutane **181** through a base-mediated  $\beta$ -elimination.

The reaction progress was monitored by TLC, using the substrate in 0.1 to 0.2 mmol scale. During the first attempts, no reaction was detected with DBU as a base after 24 h (Table III.15, entry 1). Similarly, screening other non-nucleophilic bases such as the organolithiums *n*-butyllithium and lithium tetramethylpiperidide, sodium hydride in THF and benzene, or caesium carbonate in DMF led to complex mixtures of unidentified products (entries 2 to 6). When LDA, Cs<sub>2</sub>CO<sub>3</sub> and phosphazene P<sub>1</sub>-*t*-Bu were used in the presence of ethanol as a solvent, the elimination of the oxazolidinone moiety was observed, and traces of the cyclobutene carboxylate **258a** were identified on crude <sup>1</sup>H-NMR (entries 7, 8, and 9), while 17% of this product were isolated using phosphazene P<sub>2</sub>-Et as a base (entry 10). In the aforementioned cases, although the full conversion of the starting material was attained, low isolated yields were obtained. The purification and analysis data did not bring useful information about the side reactions that possibly took place.

The screening then continued with sodium ethoxide in ethanol; such conditions did not afford the desired outcome, for the crude <sup>1</sup>H-NMR showed no typical double bond. After purification on silica gel, traces of product **259a** were isolated, where an ethoxy group was added to the reactive double bond (entry 11).<sup>289</sup> A different product, the β-sulfonyl ester **260a**, was also isolated in 56% yield. In this case, only the transesterification occurred with no elimination of the sulfone moiety. The quality of the sensitive sodium ethoxide was questioned, and in another try, the base was freshly prepared. These measures afforded the cyclobutene carboxylate **258a** in 8% yield after 3 h, however with 3% of product **259a**, and other degradation residues (entry 12). Although the elimination of the sulfone group was observed in this case, the yield was too low to attribute the better reactivity to the freshly prepared NaOEt.

At this point, the leaving group ability of the alkylsulfone was examined. Using the above conditions (freshly prepared NaOEt, EtOH, -78 °C) on the tosyl cyclobutane **181j** afforded the cyclobutene carboxylate **258a** in 50% yield after 2 h, in a clean fashion (*data not shown*). This unexpected result confirmed that the prepared base was of good quality and that the alkylsulfones are indeed less efficient leaving groups than the arylsulfones. Such a result contrasted with an observation reported elsewhere.<sup>290</sup> Although the result with the tosyl cyclobutane may seem more encouraging for optimization, the study was not pursued due to the moderate efficiency of the sulfonyl-cyanation step (50% yield).

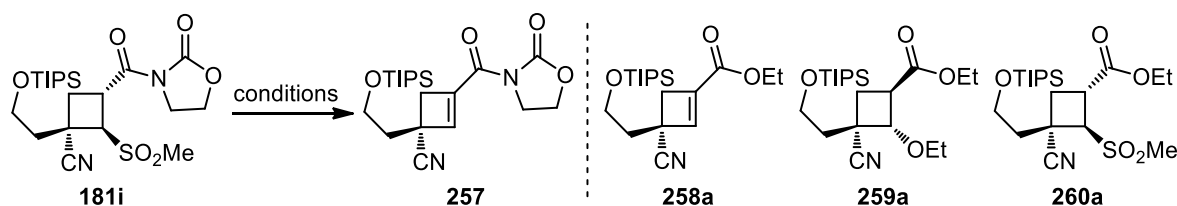
With the aim of limiting the formation of side products, an attempt with only 1 equivalent of NaOEt was made, which led only to a new product **260a** resulting from the nucleophilic displacement of the oxazolidinone. Leaving the reaction for an additional 84 h did not show any conversion, and **260a** was then isolated in 33% yield with no observation of side reactions (entry 13). It is believed, based on these results, that the β-sulfonyl ester **260a** is actually an intermediate in the reaction and that the oxazolidinone displacement occurs faster than the sulfonyl elimination.

DMF was also tried as a solvent instead of ethanol, leading to the absence of the desired product (entry 14), while the decomposition of the starting material was observed when potassium carbonate was used as a base (entry 15). With K<sub>2</sub>CO<sub>3</sub>, and in the presence of a mixture of ethanol and dichloromethane as solvents, 27% of **258a** were isolated (entry 16). In contrast, with ethanol as the



only solvent, the yield increased to 44% (entry 17). The previous experiments illustrate the important role of ethanol as a solvent in this transformation, and as noticed, during the whole screening, the initial desired product **257** was not detected. The weaker acidity of the proton  $\alpha$ - to the oxazolidinone probably explain the failure of the  $\beta$ -elimination, which only becomes efficient after formation of the ester, which is more easily converted into its enolate using a base. Performing the reaction in other alcohols such as methanol led to a complex mixture of products (entry 18).

Attempts to optimize the reaction by adding an excess of  $K_2CO_3$  resulted in the decomposition of the starting material, and only traces of **258a** were observed on the crude  $^1H$ -NMR (entry 19). Increasing the scale to 2.8 mmol of substrate under the optimal conditions, led to a lower yield of 25% (entry 20). Unexpectedly, repeating the reaction on the same scale did not give the same results; after 3 h, a complete conversion was observed with a formation of **258a** and **260a** (entry 21). Leaving the reaction for another 2 h did not improve the conversion. Thus, the reaction was stopped to prevent exposing the double bond to undesirable transformations, and **258a** and **260a** were isolated in 7 and 66%, respectively. Even though this reaction was clean, and no significant loss of material was observed, the elimination of the sulfone was found problematic on large scale. Such results are not optimal for the development of a reliable method for further use in the total synthesis strategy.

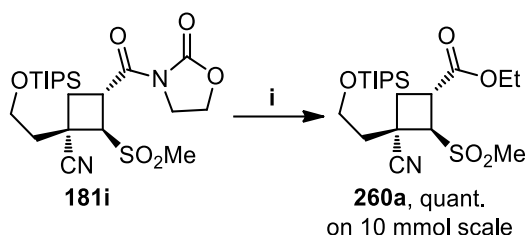


entry	base	solvent	temp (°C)	time (h)	yield (%)
1	DBU	CH <sub>2</sub> Cl <sub>2</sub>	20	24	0
2	<i>n</i> -BuLi	THF	-78	1	- <sup>a</sup>
3	LiTMP	THF	-78 to 20	5	- <sup>a</sup>
4	NaH	THF	20	20	- <sup>a</sup>
5	NaH	benzene	20	18	- <sup>a</sup>
6	Cs <sub>2</sub> CO <sub>3</sub>	DMF	70	20	- <sup>a</sup>
7	Cs <sub>2</sub> CO <sub>3</sub>	EtOH	70	3	<b>258a</b> (traces)
8	LDA	EtOH/THF	-78 to 20	5	<b>258a</b> (traces)
9	P <sub>1</sub> - <i>t</i> -Bu	EtOH	-78 to 20	6	<b>258a</b> (traces)
10	P <sub>2</sub> -Et	EtOH	-78 to 20	24	<b>258a</b> (17)
11	NaOEt	EtOH	-78 to 25	4	<b>259a</b> (traces), <b>260a</b> (56)
12	NaOEt <sup>b</sup>	EtOH	-78 to 25	3	<b>258a</b> (8), <b>259a</b> (3)
13	NaOEt <sup>c</sup>	EtOH	-78 to 25	88	<b>260a</b> (33)
14	NaOEt	DMF	-78 to 25	23	0
15	K <sub>2</sub> CO <sub>3</sub>	DMF	25	12	- <sup>a</sup>
16	K <sub>2</sub> CO <sub>3</sub>	EtOH/CH <sub>2</sub> Cl <sub>2</sub>	20	5	<b>258a</b> (27)
17	K <sub>2</sub> CO <sub>3</sub>	EtOH	20	12	<b>258a</b> (44)

18	K <sub>2</sub> CO <sub>3</sub>	MeOH	20	19	- <sup>a</sup>
19	K <sub>2</sub> CO <sub>3</sub> <sup>d</sup>	EtOH	20	12	<b>258a</b> (traces)
20 <sup>e</sup>	K <sub>2</sub> CO <sub>3</sub>	EtOH	20	3	<b>258a</b> (25)
21 <sup>e</sup>	K <sub>2</sub> CO <sub>3</sub>	EtOH	20	5	<b>258a</b> (7), <b>260a</b> (66)

**Table III.15.** Base screening for sulfone elimination reaction. *Reagents and conditions:* base (2.0 eq.), solvent (0.1 M). <sup>a</sup> Complex mixture of products. <sup>b</sup> Freshly prepared NaOEt. <sup>c</sup> NaOEt (1.0 eq.). <sup>d</sup> K<sub>2</sub>CO<sub>3</sub> (4.0 eq.). <sup>e</sup> 2.8 mmol scale.

In a desire to reduce the amount of side products and to control the behavior of this reaction, a two-steps sequence was designed for the sulfone elimination. The submission of cyclobutane **181i** to DMAP in refluxing ethanol afforded the sulfone ester **260a** in quantitative yield on a 10 mmol scale (Scheme III.40).



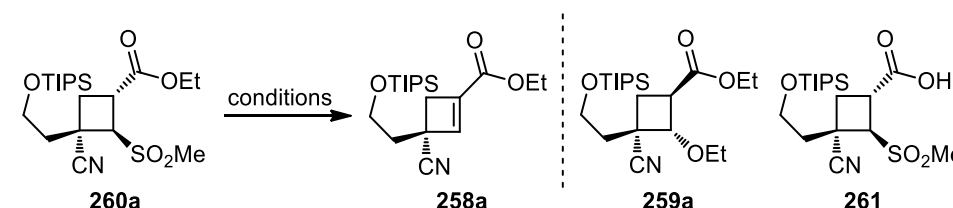
**Scheme III.40.** Transesterification of cyclobutane **181i** using DMAP. *Reagents and conditions:* i) DMAP (0.5 eq.), EtOH (0.07 M), 78 °C, 12 h.

With enough material in hand, the sulfone elimination was investigated. Taking into account the results of the earlier attempts, **260a** was first treated with 1 equivalent of K<sub>2</sub>CO<sub>3</sub> in ethanol to give 41% of the desired product after 19 h, along with 12% of unreacted starting material (Table III.16, entry 1), while, with 1 eq. of NaOEt, no reaction was observed even after 53 h (entry 2). Increasing the quantity of K<sub>2</sub>CO<sub>3</sub> to 2 eq. delivered **258a** in 66% yield on 2.4 mmol scale (entry 3), but this yield was hardly reproducible. When performing the reaction at a higher temperature the yield dropped to 46% (entry 4). With an excess of potassium bicarbonate, only 1% of **258a** was isolated with 40% of **259a** (entry 5). The formation of **259a** demonstrates the potential reactivity of the double bond toward 1,4-conjugate addition, a property that will be considered in further studies.

When DMF was used, traces of **258a** were observed without decomposition of the starting material (entry 6). Interestingly, the same conditions provoked decomposition of **181i** bearing the oxazolidinone fragment, as previously described. Changing the solvent to acetonitrile gave **258a** in a good yield of 62%, and 27% of the starting material were recovered after 46 h (entry 7). Switching to a combination of DBU and DMAP in dichloromethane afforded **258a** in 31% yield, while heating led to a decomposition (entries 8 and 9). With phosphazene P<sub>2</sub>-Et in DMF, only traces were formed with the recovery of the starting material (entry 10).

Sodium hydride was also inspected; the reaction gave **258a** in a satisfactory yield of 64% after 5 h (entry 11), along with 10% of recovered starting material. Repeating the reaction for a longer time gave, surprisingly, a lower yield of 44% (entry 12). Washing the sodium hydride with pentane under argon atmosphere prior to reaction gave however, the sulfonyl carboxylic acid **261** in 68% yield as

the sole product (entry 13), suggesting the presence of NaOH, responsible for the saponification. Submitting the substrate **260a** to caesium carbonate in dichloromethane afforded the product in traces only (entry 14), while heating at reflux increased the yield to 24% (entry 15). Further optimization by changing the solvent to DMF was performed. At room temperature, the reaction gave 41% of the product in a clean manner (entry 16). Increasing the temperature to 90 °C gave 65% of enone **258a** (entry 17), while performing the reaction at 70-75 °C led to reproducible results with 81-82% of yields (entries 18 and 19). Finally, these conditions were found reproducible also on large scale (78 and 71% on 3 and 10 mmol scale respectively).

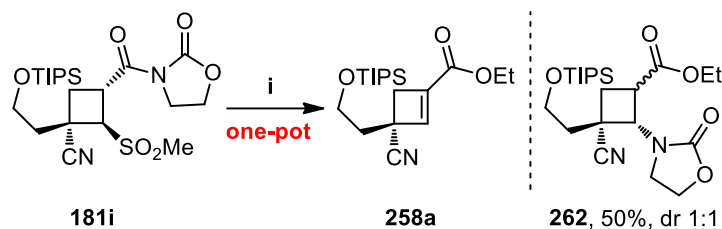


entry	base	solvent	temp (°C)	time (h)	yield (%)
1	K <sub>2</sub> CO <sub>3</sub> <sup>a</sup>	EtOH	20	19	<b>258a</b> (41, brsm 46)
2	NaOEt <sup>b</sup>	EtOH	-78 to 20	53	0
3 <sup>c</sup>	K <sub>2</sub> CO <sub>3</sub>	EtOH	20	22	<b>258a</b> (66)
4	K <sub>2</sub> CO <sub>3</sub>	EtOH	20 to 40	28	<b>258a</b> (46)
5	K <sub>2</sub> CO <sub>3</sub> <sup>d</sup>	EtOH	20	20	<b>258a</b> (1), <b>259a</b> (40)
6	K <sub>2</sub> CO <sub>3</sub>	DMF	20	16	<b>258a</b> (traces)
7	K <sub>2</sub> CO <sub>3</sub>	CH <sub>3</sub> CN	20	46	<b>258a</b> (62, brsm 85)
8	DBU/DMAP <sup>e</sup>	CH <sub>2</sub> Cl <sub>2</sub>	20	8	<b>258a</b> (31)
9	DBU/DMAP <sup>e</sup>	CH <sub>2</sub> Cl <sub>2</sub>	40	10	decomp.
10	P <sub>2</sub> -Et	DMF	-78 to 20	16	<b>258a</b> (traces)
11	NaH	THF	20	5	<b>258a</b> (64, brsm 71)
12	NaH	THF	20	16	<b>258a</b> (44)
13	NaH <sup>f</sup>	THF	20	18	<b>261</b> (68)
14	Cs <sub>2</sub> CO <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	20	17	<b>258a</b> (traces)
15	Cs <sub>2</sub> CO <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	40	21	<b>258a</b> (24)
16	Cs <sub>2</sub> CO <sub>3</sub>	DMF	20	24	<b>258a</b> (41)
17	Cs <sub>2</sub> CO <sub>3</sub>	DMF	90	21	<b>258a</b> (65)
18	Cs <sub>2</sub> CO <sub>3</sub>	DMF	75	14	<b>258a</b> (81)
19	Cs <sub>2</sub> CO <sub>3</sub>	DMF	70	14	<b>258a</b> (82)

**Table III.16.** Base screening for sulfone elimination. *Reagents and conditions:* base (2.0 eq.), solvent (0.1 M). <sup>a</sup> K<sub>2</sub>CO<sub>3</sub> (1.0 eq.). <sup>b</sup> NaOEt (1.0 eq.). <sup>c</sup> 2.4 mmol scale. <sup>d</sup> K<sub>2</sub>CO<sub>3</sub> (3.0 eq.). <sup>e</sup> DMAP (0.5 eq.). <sup>f</sup> Washed.

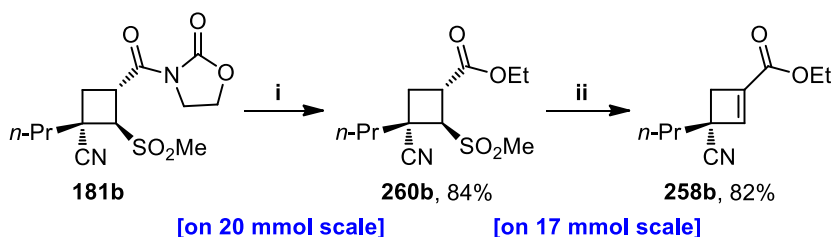
A final attempt to perform a one-pot reaction without submitting the sulfonyl ester intermediate to purification, led to the formation of **262** in 50% yield as two easily separable diastereomers, and only traces of the desired product **258a** were observed (Scheme III.41). The oxazolidinyl cyclobutane **262** was not detected before, suggesting that the nucleophilicity of the oxazolidinone may be

responsible for various side reactions and shows the high reactivity of the conjugated cyclobutene **258a**.



**Scheme III.41.** Attempts for one-pot sulfone elimination reaction. *Reagents and conditions:* i) DMAP (0.5 eq.), EtOH (0.07 M), 78 °C, 28 h; then Cs<sub>2</sub>CO<sub>3</sub> (2.0 eq.), DMF (0.1 M), 70 °C, 16 h.

The optimized conditions were then applied to the cyclobutane **181b** with a propyl side chain giving high yields. Precisely, the esterification step launched on 20 mmol scale delivered the desired ester **260b** in 84% yield (Scheme III.42), while the second step of the sequence, was performed on 17 mmol scale to give the homochiral cyclobutene **258b** in 82% yield. When the reaction was performed on a large scale, the medium was concentrated to ~ 0.4 M without affecting the yield.

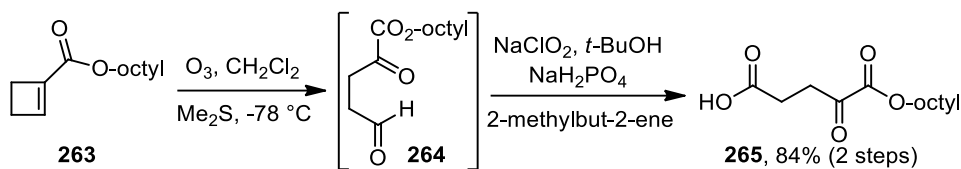


**Scheme III.42.** Application of the base-mediated sulfone elimination reaction on cyclobutane **181b**. *Reagents and conditions:* i) DMAP (0.5 eq.), EtOH (0.33 M), 78 °C, 7 h; ii) Cs<sub>2</sub>CO<sub>3</sub> (2.0 eq.), DMF (0.4 M), 70 °C, 14 h.

To sum up, the sulfone elimination was not a straightforward process, partly due to the sensitivity of the final product. The reaction time, the high temperature in certain cases, and the amount of base added were found critical. In addition, the reproducibility was challenging on large scales. The presence of the nucleophilic oxazolidinone fragment was also problematic. Finally, the best conditions include a two-steps sequence, using DMAP and Cs<sub>2</sub>CO<sub>3</sub>, respectively. With this method in hand, the potential ring-opening routes were then explored.

## 6. Ring-opening reaction through ozonolysis

Among the common methods for cycloalkenes ring-opening is the ozonolysis.<sup>291</sup> The reaction is a clean and cost-effective choice to perform a sustainable oxidative cleavage. It occurs under mild conditions, at low temperature in a dilute medium, and it is compatible with a wide range of functionalities due to its selectivity.<sup>292</sup> The only ozonolysis study on cyclobutenes was reported by Jung and Deng<sup>293</sup> using a two-steps sequence (Scheme III.43). The ketoaldehyde **264** generated from ozonolysis was submitted without purification to Pinnick conditions using sodium chlorite, to give a monoester of  $\alpha$ -ketoglutarate **265** in 84% overall yield.

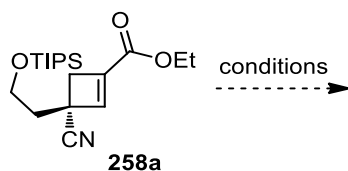


**Scheme III.43.** Cyclobutene ring-opening under ozonolytic oxidative cleavage.

### 6.1. Application of ozonolysis on cyclobutenes

In the light of this study, the cyclobutene ring **258a** was submitted to ozonolysis at low temperature, and the formed ozonide was treated with dimethyl sulfide, a mild reducing agent. The ester ketoaldehyde **266** was obtained cleanly and the full analysis confirmed the formation of the desired product in 84% crude yield (Table III.17, entry 1). This product, however, was found unstable on silica gel. In fact, after purification, the aldehyde function was missing, and a mixture of inseparable products was formed, the structure of which was found difficult to identify through  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR. The mass analysis showed only one peak with the same molecular weight as for the keto aldehyde **266** ( $\text{C}_{19}\text{H}_{32}\text{NO}_5\text{Si}$   $[\text{M}-\text{H}]^+$ , peak mass 382.20552). This suggests that the formed products are isomers, which were also detected after a few hours in the NMR tube containing the pure ozonolysis product.

Efforts were then invested to obtain more stable products. In the presence of ethanol or tosic acid in ethanol, the diethyl acetal **267** was not observed, and a complex mixture was obtained (entries 2 and 3). The investigations of Schreiber's conditions<sup>294</sup> to generate the desired acetal **268** or ester **269** all led to a mixture of decomposed products (entries 4, 5, and 6). When the workup was carried out under reductive conditions in the presence of sodium borohydride, the desired diol **270** was not observed, nor the intramolecular condensation of the alcohol (entry 7). When the isolated ketoaldehyde **266** was submitted to reduction, no product was isolated (entry 8). Under oxidative conditions in the presence of formic acid, a decomposition of the intermediate was observed (entry 9). However, under the conditions described by Jung, the same mixture of unidentified isomers observed before was obtained (entry 10). Alternatives to ozonolysis, *i.e.*, Lemieux-Von Rudloff reagent ( $\text{KMnO}_4/\text{NaIO}_4$ ),<sup>295,296</sup> or  $\text{RuO}_4$  species<sup>297,298</sup> as oxidizing agents, were also investigated, leading to the same isomers' mixture as before (entries 11 and 12).



entry	conditions	desired product	observation
1	$\text{O}_3$ , $\text{CH}_2\text{Cl}_2$ , $-78\text{ }^\circ\text{C}$ , 10 min, then $\text{Me}_2\text{S}$ (1.5 eq.), $-78$ to $20\text{ }^\circ\text{C}$ , 1 h	 266	84% crude, unstable
2	$\text{O}_3$ , $\text{CH}_2\text{Cl}_2/\text{EtOH}$ , $-78\text{ }^\circ\text{C}$ , 10 min, then $\text{Me}_2\text{S}$ (1.5 eq.), $-78$ to $20\text{ }^\circ\text{C}$ , 1 h	 267	comp. mix.

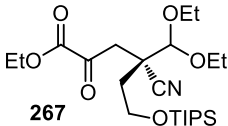
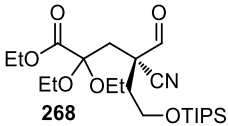
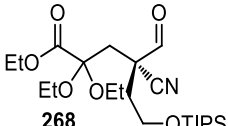
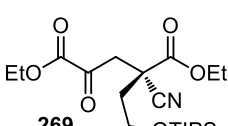
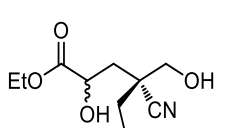
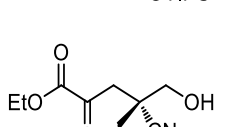
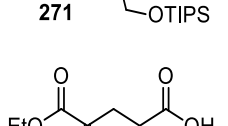
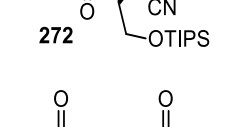
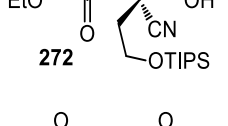
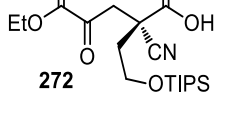
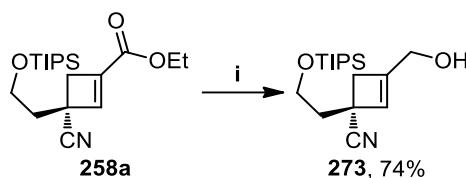
3	O <sub>3</sub> , CH <sub>2</sub> Cl <sub>2</sub> /EtOH, <i>p</i> -TsOH, -78 °C, 10 min		comp. mix.
4	O <sub>3</sub> , CH <sub>2</sub> Cl <sub>2</sub> /EtOH, then <i>p</i> -TsOH, -78 to 20 °C, then NaHCO <sub>3</sub> , then Me <sub>2</sub> S		comp. mix.
5	i. O <sub>3</sub> , CH <sub>2</sub> Cl <sub>2</sub> /EtOH, <i>p</i> -TsOH, -78 °C, 10 min. ii. Ac <sub>2</sub> O (5.0 eq.), Et <sub>3</sub> N (2.0 eq.), CH <sub>2</sub> Cl <sub>2</sub> , 0 to 20 °C		comp. mix.
6	i. O <sub>3</sub> , CH <sub>2</sub> Cl <sub>2</sub> /EtOH, -78 °C, 10 min. ii. Ac <sub>2</sub> O (5.0 eq.), Et <sub>3</sub> N (2.0 eq.), CH <sub>2</sub> Cl <sub>2</sub> , 0 to 20 °C		comp. mix.
7	i. O <sub>3</sub> , CH <sub>2</sub> Cl <sub>2</sub> , -78 °C. ii. NaBH <sub>4</sub> (3.0 eq.), THF, -78 to 20 °C, 5 h		comp. mix.
8	i. O <sub>3</sub> , CH <sub>2</sub> Cl <sub>2</sub> , Me <sub>2</sub> S, -78 °C, isolated. ii. NaBH <sub>4</sub> (1.5 eq.), THF, 0 °C, 19 h		comp. mix.
9	i. O <sub>3</sub> , CH <sub>2</sub> Cl <sub>2</sub> , -78 °C, 10 min. ii. HCO <sub>2</sub> H, 30% H <sub>2</sub> O <sub>2</sub> , 20 °C, 14 h		comp. mix.
10	O <sub>3</sub> , CH <sub>2</sub> Cl <sub>2</sub> , Me <sub>2</sub> S, -78 °C, then NaClO <sub>4</sub> , <i>t</i> -BuOH, NaH <sub>2</sub> PO <sub>4</sub> , 2-methyl-2-butene		unknown mix. of isomers
11	i. KMnO <sub>4</sub> (2.0 eq.), acetone (0.1 M). ii. H <sub>3</sub> O <sup>+</sup> , 0 °C, 5 h		unknown mix. of isomers
12	RuCl <sub>3</sub> (0.03 eq.), NaIO <sub>4</sub> (6.0 eq.), CH <sub>3</sub> CN/CCl <sub>4</sub> /H <sub>2</sub> O, 20 °C, 2 h		unknown mix. of isomers

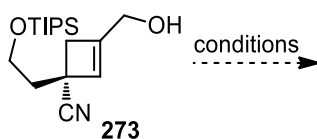
Table III.17. Attempts for cyclobutene ring-opening through ozonolysis.

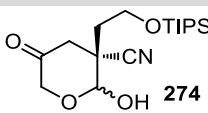
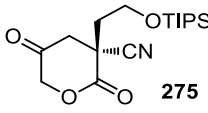
The cyclobutene **258a** was then submitted to reducing conditions using DIBAL-H, which led to the alcohol **273** in 74% yield (Scheme III.44).



**Scheme III.44.** Reduction of the ester unit of cyclobutene **258a**. *Reagents and conditions:* i) DIBAL-H (3.0 eq.), THF (0.1 M), -78 °C, 4 h.

The ozonolysis of this alcohol was then performed to give cleanly the desired product **274** as a 2.2:1 mixture of two diastereoisomers, as detected by  $^1\text{H}$ -NMR of the crude reaction mixture (Table III.18, entry 1). Purification of the crude unfortunately led to a complete decomposition on silica gel, preventing full characterization of the unstable lactol product. The ozonolysis was finally carried out, followed by a rapid oxidation in the hope of obtaining the corresponding lactone **275**. A complex mixture of products was, however, obtained (entry 2).



entry	conditions	desired product	observation
1	$\text{O}_3$ , $\text{CH}_2\text{Cl}_2$ , -78 °C, 10 min, then $\text{Me}_2\text{S}$ (1.5 eq.), -78 to 20 °C, 1 h	 <b>274</b>	very unstable
2	i. $\text{O}_3$ , $\text{CH}_2\text{Cl}_2$ , -78 °C, 10 min, then $\text{Me}_2\text{S}$ , -78 to 20 °C, 1 h. ii. DMP (1.5 eq.), pyridine (10.0 eq.), $\text{CH}_2\text{Cl}_2$ , 20 °C	 <b>275</b>	comp. mix.

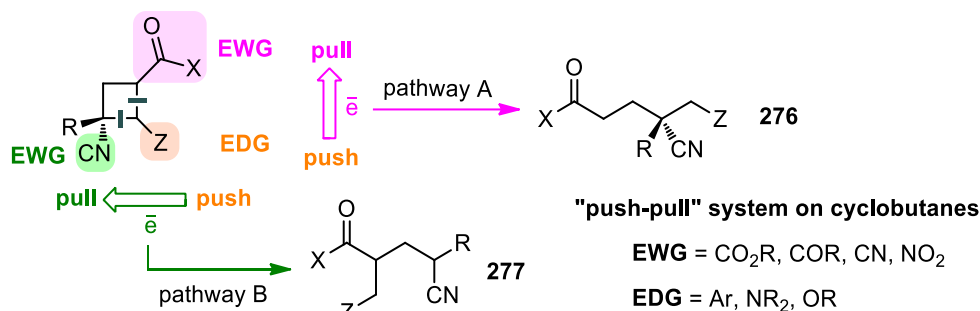
**Table III.18.** Attempts for ozonolysis on cyclobutene alcohol **273**.

Based on these results, this ring-opening strategy was abandoned and other approaches were envisioned. It is worth noting that the ring-opening metathesis (ROM) in the presence of a series of olefins was also investigated on cyclobutene carboxylate **258**, however, in all cases, the starting material was recovered (*data not shown*).

## 7. Ring-opening reaction through Donor-Acceptor systems

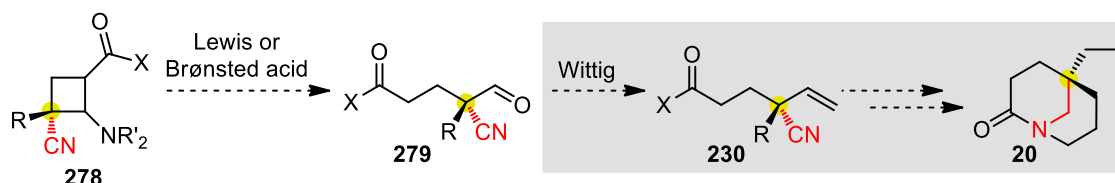
Based on the previous observations, the reactivity of the enone functionality in cyclobutene carboxylate **258a** could be utilized to promote the ring-opening through several pathways. For instance, an electron-donating fragment could be incorporated onto the cyclobutene through 1,4-conjugate addition, creating, therefore, a donor-acceptor (DA) system with the  $\text{C}(\text{O})\text{X}$  unit (Figure III.12). The constructed DA-cyclobutane might be activated later by a suitable Lewis or Brønsted acid species, to create a “push-pull” effect. Such force will weaken the adjacent C-C bond and trigger the ring cleavage to give **276** (pathway A). However, the nitrile fragment is also an EWG. push-pull in its direction would compete with the aforesaid pathway and favor the ring-opening on the undesired

side to furnish **277** (pathway B). This problem might be minimized by the use of oxophilic acids which would activate the carbonyl group to favor pathway A.



**Figure III.12.** Construction of a "push-pull" system on cyclobutanes.

It was suggested that the 1,4-addition of an amine fragment onto cyclobutene carboxylate **278** would be strong enough to create an electron-donating effect. With suitable Lewis or Brønsted acid, the ring-opening would be favored to obtain the corresponding aldehyde **279** after hydrolysis of the iminium intermediate (Scheme III.45). This aldehyde could then be a precursor of allylnitrile **230** (Wittig reaction), the previously expected target of RBR, which would eventually be transformed into the bicyclic lactam **20**.



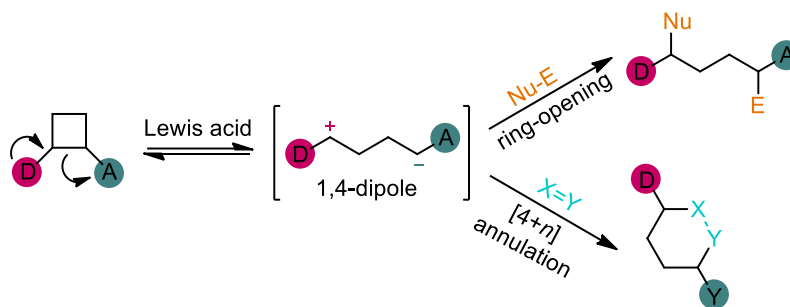
**Scheme III.45.** Ring-opening reaction of an amino-cyclobutane under acidic conditions and further modification of the produced aldehyde.

### 7.1. Introduction to Donor-Acceptor (DA) ring systems

Small-ring systems are usually stable and quite resistant to bond cleavage except when activated. The ring activation could be triggered by the vicinal incorporation of electron-donating and electron-withdrawing groups into the system, which could be referred to as a donor-acceptor (DA) system, a concept first introduced by Reissig in the 1980s.<sup>299,300</sup> Under certain conditions (usually Lewis acid), the C-C bond which link A and D becomes labile allowing various dipolar reactions to take place.<sup>301</sup> This mode of reactivity was extensively studied with cyclopropanes,<sup>136–138,160,302</sup> and recently extended to cyclobutanes.<sup>303–307</sup>

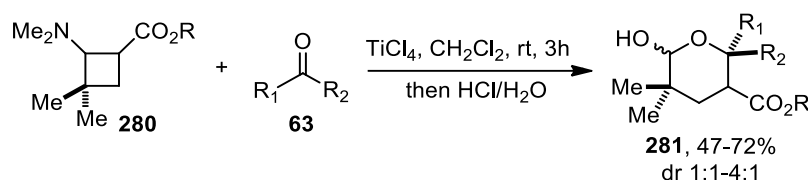
Typically, under Lewis acid conditions, donor-acceptor cyclobutanes undergo ring-opening forming reactive 1,4-zwitterionic synthons (Scheme III.46). In such a structure, the positive charge is stabilized by the donor while the negative charge is stabilized by the acceptor. These distonic ions showed high reactivity towards electrophiles, nucleophiles, and dipolarophiles.<sup>136</sup> Compared to DA-cyclopropanes, DA-cyclobutanes showed lower reactivity, partly due to their lower ring strain energy (27.5 kcal/mol for cyclopropanes vs. 26.3 kcal/mol for cyclobutanes).<sup>308</sup>





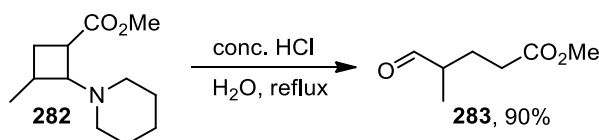
**Scheme III.46.** Reactivity pattern of DA-cyclobutenes with nucleophiles (Nu), electrophiles (E), and dipolarophiles (X=Y). D = donor, A = acceptor.

Among the donor groups, the nitrogen substituted groups were chosen extensively to activate the cyclopropanes and cyclobutenes synthons.<sup>138</sup> The first report of formal cycloaddition of DA-cyclobutenes was accomplished by Saigo *et al.* in 1991.<sup>309</sup> In this work, amino-activated cyclobutane **280** underwent Lewis acid-promoted [4+2] annulation with carbonyl compounds **63** in the presence of titanium(IV) chloride to afford tetrahydropyrans **281**, albeit in low diastereoselectivity (Scheme III.47).



**Scheme III.47.** Synthesis of tetrahydropyrans through titanium-catalyzed ring expansion of amino-cyclobutenes.<sup>309</sup>

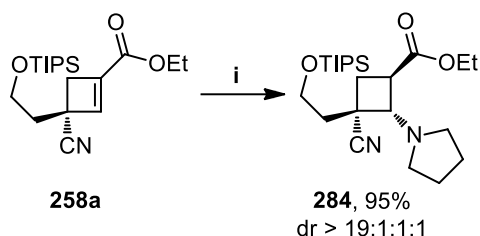
Fleming and Ware<sup>310</sup> studied the reactivity of the “push-pull” system created in the amino-cyclobutenes skeleton **282** (Scheme III.48). Under acidic conditions, the ring-opening was observed to generate after hydrolysis, the corresponding aldehyde **283** in 90% yield.



**Scheme III.48.** Ring-opening reaction of amino-cyclobutane under acidic conditions.<sup>310</sup>

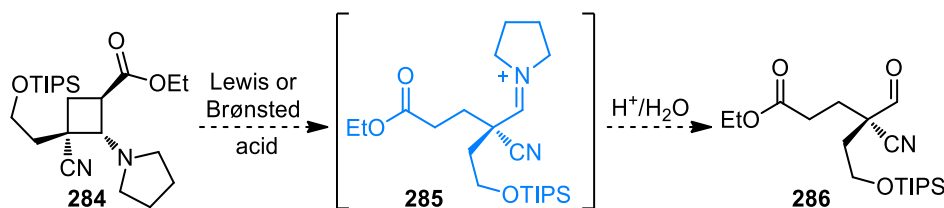
## 7.2. Synthesis of amino-cyclobutane precursor and attempts for the ring cleavage

Based on the literature survey, the introduction of a nitrogen substituent onto the cyclobutene carboxylate **258a** was envisioned through a conjugate addition. The conjugate additions of nitrogenated fragments onto cyclobutenes are well described in the literature.<sup>311–313</sup> The addition of pyrrolidine skeleton on the  $\pi$ -system delivered the *trans* tetra-substituted amino-cyclobutane **284** in excellent yield and diastereoselectivity (Scheme III.49). The nucleophilic amine was shown to approach *anti* relative to the alkyl side chain and ester. The ensuing protonation of the ester enolate finally occurs *anti* relative to the pyrrolidine ring.



**Scheme III.49.** Synthesis of DA amino-cyclobutane through 1,4-addition reaction. *Reagents and conditions:* i) pyrrolidine (4.0 eq.), THF (0.1 M), 66 °C, 5 h.

The efforts were then directed towards the ring-cleavage under acidic conditions. It was planned that under such a medium, the ring-opening would promote the formation of an iminium ion **285** which would deliver the corresponding aldehyde **286** after hydrolysis (Scheme III.50).



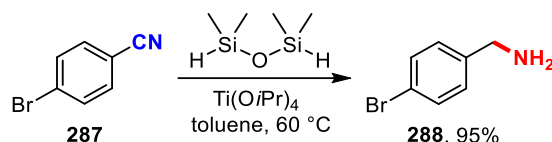
**Scheme III.50.** Envisioned acid-promoted ring-opening of amino-cyclobutane.

The activation of the DA-cyclobutane **284** in conc. HCl/H<sub>2</sub>O medium at reflux failed, however, to afford the desired transformation after 48 h (*data not shown*).

### 7.3. Reduction of the nitrile group in cyclobutane **284**

The reduction of a nitrile on an all-carbon quaternary center is somehow difficult to perform. In preliminary attempts, the standard catalytic hydrogenation was performed on substrate **284**, under atmospheric pressure or H-cube in the presence of Raney<sup>®</sup>-nickel. Such conditions proved to be insufficient for the reaction to occur as higher pressure is likely required.<sup>314</sup> Nevertheless, the lack of a suitable apparatus led to pursuing alternative methods.

In literature, nitriles are reported to be efficiently reduced into the corresponding amines through strong metal hydride donors such as aluminum hydrides, boranes,<sup>314–316</sup> and diisopropylaminoboranes in the presence of a catalytic amount of lithium borohydride.<sup>317</sup> Non-borohydride-based methods were also described through single electron transfer using the SmI<sub>2</sub>-Et<sub>3</sub>N-H<sub>2</sub>O complex.<sup>318</sup> However, all these conditions lack selectivity in the presence of an ester group. Milder methods using hydrides have also been reported for the reduction of nitriles to the corresponding amines. For instance, Laval and co-workers<sup>319</sup> investigated the reactivity of hydrosiloxanes as hydride sources, using stoichiometric amounts of 1,1,3,3-tetramethyldisiloxane (TMDS) in conjunction with titanium(IV) isopropoxide (Scheme III.51). This method was applied to a scope of aliphatic and aromatic nitriles **287** giving the corresponding amines **288** in high yields, but no example on tetrasubstituted nitriles was documented.

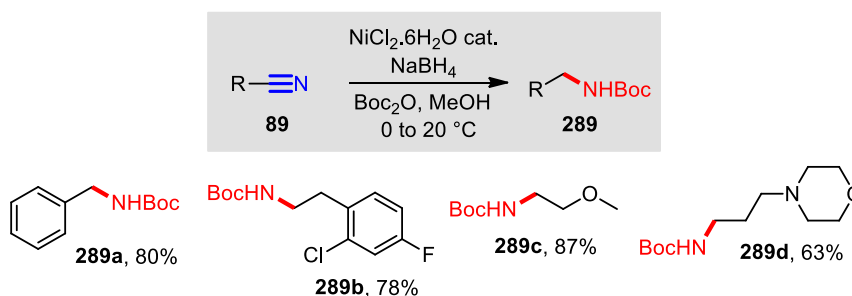


**Scheme III.51.** Reduction of nitrile group using the TMDS/ $\text{Ti}(\text{O}i\text{Pr})_4$  system.<sup>319</sup>

Applied to cyclobutane **284**, these conditions were not found suitable to reduce the desired nitrile, even at higher temperatures (80 or 120 °C).

Sodium borohydride is a milder reducing agent than the aluminum hydrides (LAH) and aminoboranes, and thus does not normally reduce nitriles. Its reducing behaviour, however, changes drastically with the addition of transition metal salts (Ni, Co, Pd, Pt, Fe), which compensates the reactivity gap between  $\text{LiAlH}_4$  and  $\text{NaBH}_4$ , creating new catalysts with various possible applications.<sup>320–322</sup> Among these, Ni(II) salts were widely used to modify the sodium borohydride's reactivity, generating *in-situ* nickel boride species ( $\text{Ni}_2\text{B}$ ) as the active catalyst.

In this area, Caddick and co-workers<sup>323</sup> reported the reduction of aliphatic and aromatic nitriles using a catalytic quantity of nickel(II) chloride (0.1 eq.) in combination with an excess of sodium borohydride (7 eq.). In the presence of di-*tert*-butyl bicarbonate (2 eq.) as a trapping agent, a broad range of nitriles **89** were converted into the corresponding primary protected amines **289** in high yields (Scheme III.52). Consequently, the isolated double bonds were hydrogenated. Amides, halogen, methoxy, and ester functional groups, however, were found tolerant under these conditions.

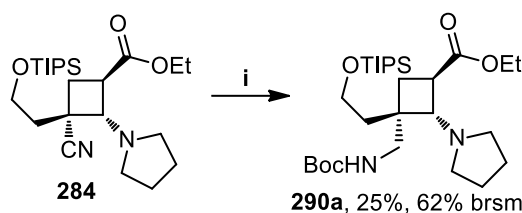


**Scheme III.52.** Reduction of nitriles to Boc-amines using nickel boride species.<sup>323</sup>

In their previous paper,<sup>324</sup> they mentioned that the formation of free primary amines using  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}/\text{NaBH}_4/\text{MeOH}$  system was challenging and dimerization of the amine products occurred. Therefore, amine traps such as acetylated compounds were necessary, and a special workup was needed. However, Khurana and Kukreja<sup>325</sup> described a successful reduction of aromatic nitriles into their corresponding primary amines, using a stoichiometric quantity of nickel chloride in conjunction with  $\text{NaBH}_4$ . The *in situ* formation of the nickel boride active catalyst was achieved in anhydrous ethanol under ambient temperature. These conditions proved to be chemoselective in the presence of halogen, methoxy, and olefinic groups, and produced primary amines in high to excellent yields, with a low percentage of amine dimers (< 10%). They explained that by using ethanol as a solvent, primary amines were obtained by a simple workup procedure.

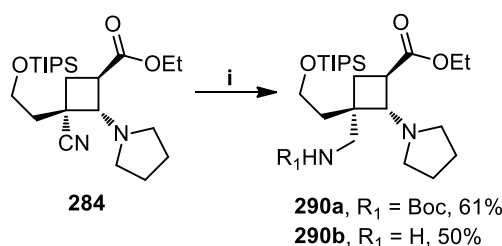
In the light of these reports, it was first intended to test Caddick's conditions<sup>323</sup> on nitrile **284** (Scheme III.53). This protocol thus allowed the isolation of the protected amino cyclobutane **290a** in an encouraging 25% yield together with 60% of unreacted starting material, highlighting the

particular reactivity of these sterically hindered nitrile towards reduction, as compared to their aliphatic and aromatic counterparts.



**Scheme III.53.** Reduction of amino-cyclobutane following Caddick's procedure. *Reagents and conditions:* i)  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$  (0.1 eq.),  $\text{NaBH}_4$  (7.0 eq.),  $\text{Boc}_2\text{O}$  (2.0 eq.) MeOH (0.13 M), 0 to 20 °C, 5 h.

It was then proposed to modify the reducing system as suggested by Khurana *et al.* The  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}/\text{NaBH}_4/\text{EtOH}$  complex was thus used to obtain free amino-cyclobutanes, and  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}/\text{NaBH}_4/\text{Boc}_2\text{O}/\text{EtOH}$  reagents system to produce the Boc-protected amino-cyclobutanes. The application of this strategy to cyclobutane **284** was found to be efficient towards the sterically hindered cyano group. In the absence or presence of Boc anhydride, the nickel boride catalyst reduced the nitrile to free or Boc-protected primary amine respectively, in good yields (Scheme III.54). In both cases, the reduction proceeded chemoselectively, and no reduction of the ester functional group was observed. Using less than a stoichiometric amount of nickel catalyst, however, afforded lower yields (for instance, with 0.8 eq. of  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ , **290b** was obtained in 40% yield).



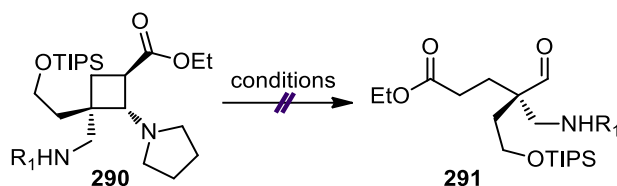
**Scheme III.54.** Reduction of **284** using nickel boride. *Reagents and conditions:* i)  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$  (1.0 eq.),  $\text{NaBH}_4$  (7.0 eq.), EtOH (0.07 M), 0 to 20 °C, 3 h. For **290a**,  $\text{Boc}_2\text{O}$  (2.0 eq.) was added.

#### 7.4. Ring-opening investigations

With the reduced amino-cyclobutanes in hand, the cyclobutane ring-opening was investigated again under acidic medium. At first, the free-amino cyclobutane **290b** was submitted to strong Brønsted acid conditions; in aqueous HCl, no ring-opening reaction was observed (Table III.19, entry 1), and heating at reflux led to the same result (entry 2). Changing to tosic acid in refluxing ethanol did not afford a better result (entry 3). In the above conditions, only traces of TIPS-deprotected alcohol were detected. Similarly, applying the first three conditions to the Boc-protected amine **290a** did not favor the ring-cleavage and only the deprotection was observed (entries 4, 5, and 6).

Switching to Lewis acids did not give successful outcomes either. The reaction with the oxophilic magnesium bromide failed at activating the DA system and gave back the starting material (entry 7). The substrate remained unchanged using the borane-THF complex under reflux (entry 8). Transition metals, *i.e.*, mild (indium triflate) or stronger (titanium derivatives) Lewis acids were, unfortunately, unreactive towards the substrate (entries 9, 10, and 11). Finally, a photocatalytic pathway was looked

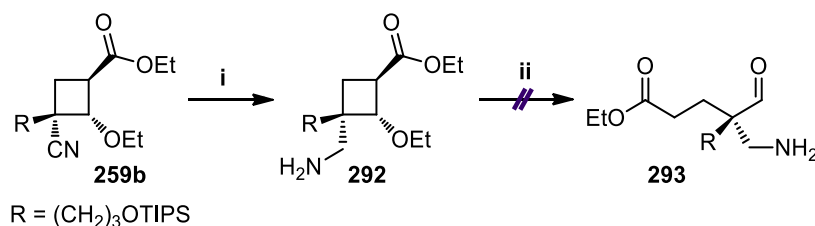
at, with the hope that, the photocatalyst would oxidize the tertiary amine into a radical cation, which would then trigger a radical fragmentation and deliver the ring-opened iminium species. The latter would furnish the corresponding aldehyde after hydrolysis. Examining this approach using iridium photocatalyst, however, gave similar results as above (entry 12).



entry	R <sub>1</sub>	acid source	solvent	temp (°C)	time (h)	yield
1	H	HCl/H <sub>2</sub> O 1:1	-	20	70	0
2	H	HCl/H <sub>2</sub> O 1:1	-	100	24	0
3	H	<i>p</i> -TsOH	EtOH	78	46	0
4	Boc	HCl/H <sub>2</sub> O 1:1	-	20	24	0
5	Boc	HCl/H <sub>2</sub> O 1:1	-	100	24	0
6	Boc	<i>p</i> -TsOH	EtOH	78	24	0
7	H	MgBr <sub>2</sub> .OEt <sub>2</sub>	EtOH	20	146	0
8	H	BH <sub>3</sub> .THF <sup>a</sup>	THF	60	6	0
9	H	In(OTf) <sub>3</sub>	EtOH	20	146	0
10	H	Ti(OiPr) <sub>4</sub>	EtOH	20	16	0
11	H	TiCl <sub>2</sub> (OiPr) <sub>2</sub>	EtOH	20	55	0
12	H	[Ir] <sup>b</sup>	CH <sub>3</sub> CN	blue LEDs	38	0

**Table III.19.** Attempts for ring cleavage of amino-cyclobutane under acidic and photocatalytic conditions. [Ir] = (Ir[dF(CF<sub>3</sub>)ppy]<sub>2</sub>(dtbpy))PF<sub>6</sub>. *Reagents and conditions:* reagent (2.0 eq.), solvent (1.0 M). <sup>a</sup> BH<sub>3</sub>.THF (5.0 eq.). <sup>b</sup> [Ir] cat. (0.01 eq.).

Although the electron-donating character of an ether group is weaker than an amine, it was reasoned that the ring-opening reaction could presumably be carried out with alkoxy groups as EDG.<sup>326</sup> The oxy-cyclobutane **259b** was subjected to nitrile reduction under the nickel boride conditions to afford the reduced cyclobutane **292** in 33% yield (Scheme III.55). The resulting product was then submitted to ring-opening under conc. HCl in water at reflux, however, no reaction was observed even after 48 h. Only some minor degradations were detected on TLC.



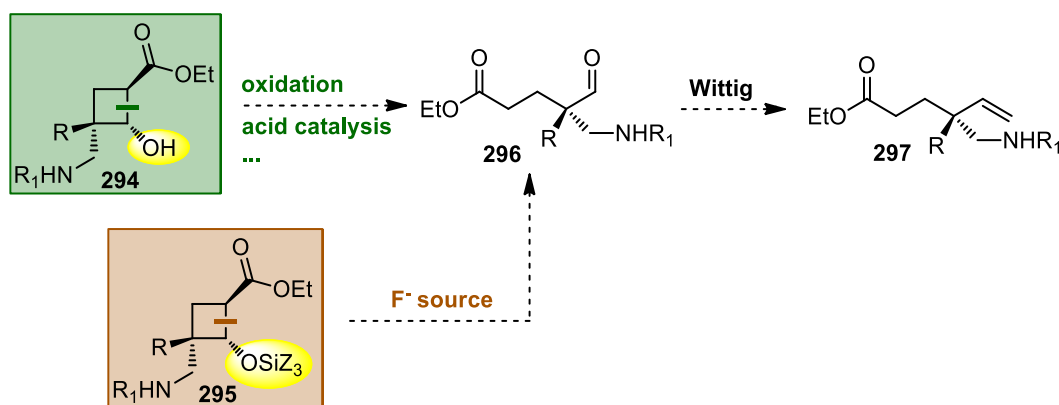
**Scheme III.55.** Reduction of oxy-cyclobutane using nickel boride and attempts for ring-opening under acidic catalysis. *Reagents and conditions:* i) NiCl<sub>2</sub>.6H<sub>2</sub>O (1.0 eq.), NaBH<sub>4</sub> (7.0 eq.), EtOH (0.1 M), 0 to 20 °C, 4 h, 33%; ii) conc. HCl, H<sub>2</sub>O, 100 °C, 48 h.

Based on the above results, it can be concluded that a single ester group as an acceptor rather than geminal diesters generally used in literature is probably insufficient to trigger the push-pull process.<sup>137</sup> This approach was thus abandoned and other plans were envisioned.

## 8. Ring-opening through the transformation of malleable functions

### 8.1. Ring-opening through a hydroxide system

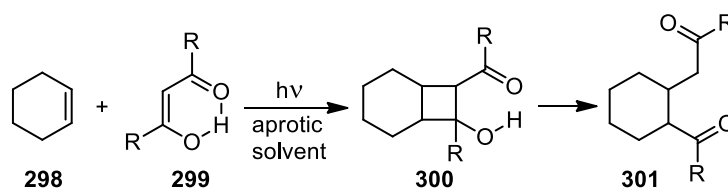
Having failed to obtain the desired aldehyde using a DA-system, it was suggested that other nucleophiles might serve to reach the expected goal. For instance, the 1,4-addition of a suitable alkoxy group as a masked alcohol might deliver a free alcohol **294**, which could then undergo oxidation, or acid catalysis to trigger the ring-opening (Scheme III.56). Also, a silanol group could be added onto the cyclobutene carboxylate, before to be activated using a fluorine source, triggering the ring-opening and generating the desired aldehyde **296**.<sup>327</sup>



**Scheme III.56.** Ring-opening through alcohol and silanol transformation.

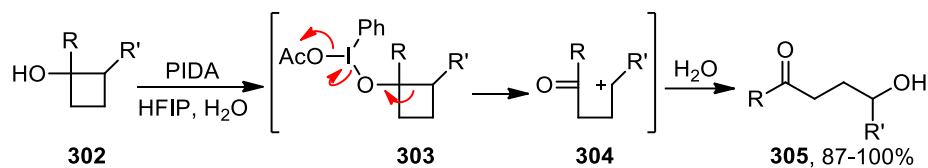
Since the nitrile reduction in the presence of the enone double bond is a challenging task,<sup>320</sup> it was planned to introduce the nucleophilic substituent first. It was also hoped to find conditions that would break the expected C-C bond in the presence of nitrile.

The synthesis and manipulation of cyclobutanols and cyclobutanones have been established in the literature.<sup>328–332</sup> Under suitable conditions, these frameworks can undergo ring cleavage, ring expansion, or functional transformation. One of the first examples of hydroxy-cyclobutane ring-opening was reported by De Mayo and co-workers (Scheme III.57).<sup>333</sup> The addition of enolized 1,3-diketones **299** onto alkenes **298** by [2+2] photo-cycloaddition, afforded acyl-cyclobutanol **300**. The De Mayo product underwent then a spontaneous retro-aldol cyclobutane cleavage to afford the diketone **301**.



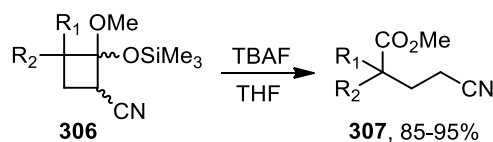
**Scheme III.57.** De Mayo reaction and spontaneous ring-opening of cyclobutane.<sup>333</sup>

Interestingly, Fujioka and co-workers<sup>334</sup> developed a strategy to open the cyclobutanol rings using hypervalent iodine reagents as oxidant. Cyclobutanols **302** underwent regioselective oxidative cleavage in the presence of PIDA, to give access to a range of  $\gamma$ -hydroxy ketones **305** in excellent yields (Scheme III.58).



**Scheme III.58.** PIDA-mediated oxidative cleavage of cyclobutanols.<sup>334</sup>

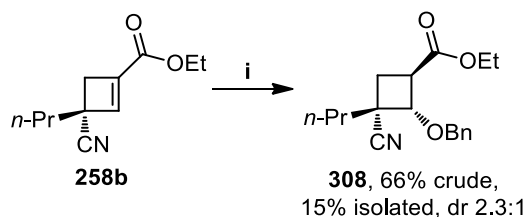
The addition of silanols into cyclobutanes was also reported in the literature.<sup>335,336</sup> For instance, Rousseau *et al.*<sup>337</sup> prepared the silyl acetals **306** in an efficient manner. In the presence of tetrabutylammonium fluoride, these molecules were transformed into the opened cyano esters **307** in excellent yields (Scheme III.59).



**Scheme III.59.** Ring-opening of cyclobutane silylacetals in the presence of TBAF.<sup>337</sup>

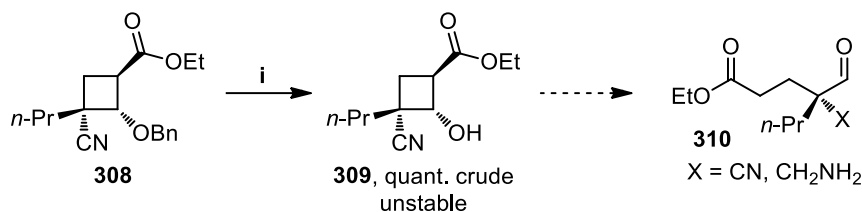
## 8.2. Addition of masked alcohol onto cyclobutene

At first, the 1,4-addition of masked alcohol onto cyclobutene **258b** was carried out with a stoichiometric amount of benzylic alcohol in the presence of sodium hydride as a base. After 2 h, the crude <sup>1</sup>H NMR showed a clean reaction, and the expected product **308** was obtained as a 2.3:1 mixture of two diastereomers. The purification of the crude mixture afforded the product **308** in only 15% yield (vs. 66% crude), as a result of degradation on silica gel (Scheme III.60).



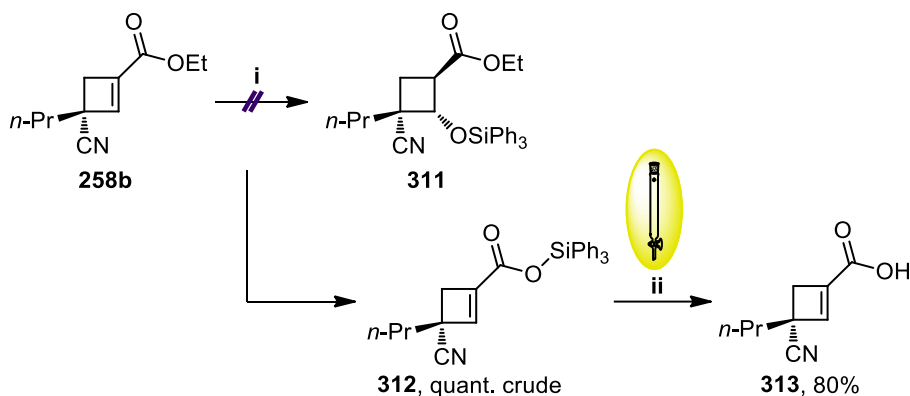
**Scheme III.60.** Conjugate addition of benzyl alcohol onto cyclobutene. *Reagents and conditions:* i) benzyl alcohol (1.0 eq.), NaH (1.0 eq.), THF (0.1 M), 0 to 20 °C, 2 h.

The crude reaction mixture was thus submitted directly to the hydrogenation in the presence of palladium on charcoal (Scheme III.61). The crude <sup>1</sup>H NMR showed the successful deprotection of the benzyl group, but the cyclobutane was found particularly unstable, preventing any further manipulation.



**Scheme III.61.** Deprotection of the benzyl group. *Reagents and conditions:* i)  $\text{H}_2$  (1 atm), Pd/C (10% wt. %), EtOH (0.08 M), 25 °C, 18 h.

A contrasting behavior was observed during the conjugate addition of nucleophilic silanols. When treated with a stoichiometric amount of triphenylsilanol, cyclobutene **258b** led cleanly to the transesterification product **312** which gave the saponified cyclobutene **313** in 80% yield after chromatography on silica gel (Scheme III.62). Surprisingly, when 2 eq. of triphenylsilanol were used in the presence of 2 eq. of sodium hydride, the desired product was not observed and only the starting material was recovered.

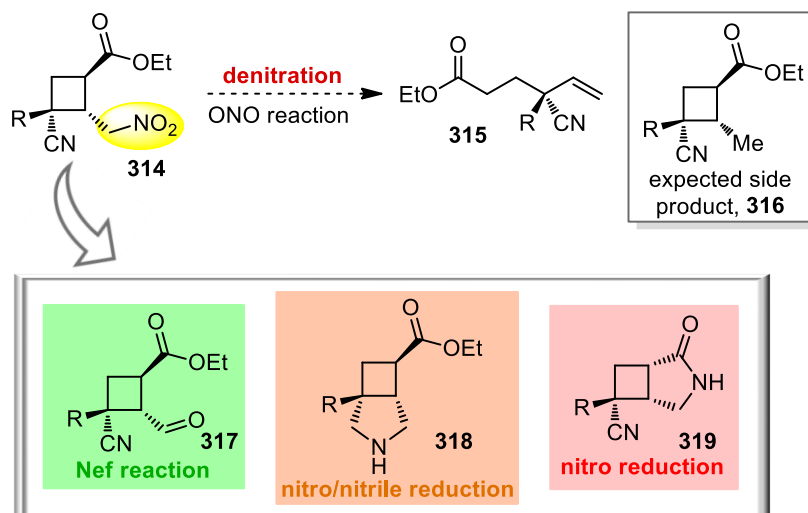


**Scheme III.62.** Silanol addition onto cyclobutenes. *Reagents and conditions:* i)  $\text{Ph}_3\text{SiOH}$  (1.0 eq.), NaH (1.1 eq.), THF (0.1 M), 0 to 20 °C, 5 h; ii) column  $\text{SiO}_2$ .

### 8.3. Ring-opening through radical denitration

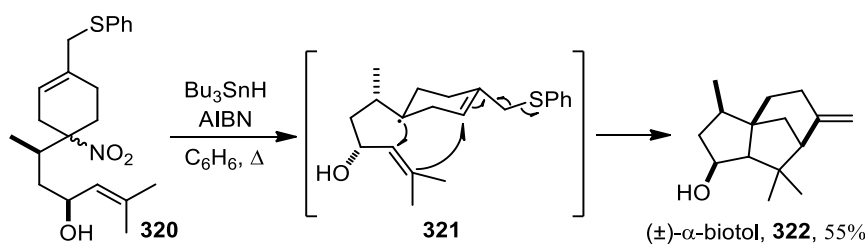
Nitroalkyl groups can also be introduced efficiently onto electron-deficient enones through 1,4-addition of nitroalkanes.<sup>338,339</sup> Application of this strategy to cyclobutene carboxylate **258** was envisaged, that would then be followed by a radical denitration (following Ono reaction). The generated primary radical would then undergo an intramolecular ring fragmentation to deliver the allyl  $\gamma$ -nitrile **315** (Figure III.13). Interestingly, nitro-cyclobutenes such as **314** would also constitute attractive intermediates for the elaboration of optically pure synthons like aldehydes **317**,<sup>340</sup> pyrrolidines **318**,<sup>341</sup> or pyrrolidinones **319**.<sup>342</sup>





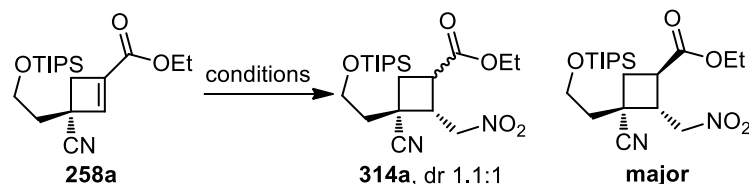
**Figure III.13.** Ring-opening of nitro-cyclobutane through denitration, and possible transformations of the nitro fragment.

The denitration of nitroalkanes in radical conditions ( $\text{Bu}_3\text{SnH/AIBN}$ ) generates a radical intermediate that can follow two fates. It may be reduced by hydrogen abstraction from the organotin reagent or react with intramolecular alkenes promoting a cyclization reaction. Chen and co-workers<sup>343</sup> for example, subjected nitro-cyclohexene **320** to Ono's conditions (Scheme III.63). The radical intermediate **321** underwent a tandem radical cyclization giving ( $\pm$ )- $\alpha$ -biotol **322** in 55% yield.



**Scheme III.63.** Synthesis of ( $\pm$ )-biotol through tandem radical cyclization.<sup>343</sup>

Cyclobutene carboxylate **258a** was submitted to Michael reaction with nitromethane. The latter may be easily deprotonated by a wide range of bases ( $\text{CH}_3\text{NO}_2$ ,  $pK_a$  10).<sup>344</sup> A preliminary study was carried out in the presence of sodium hydride and 2 equivalents of nitromethane, to give the desired product **314a** in 17% yield (Table III.20, entry 1). When the nitromethane was used as a solvent in the presence of DBU, the yield increased dramatically to 69% (entry 2). Attempts to improve the reaction by concentrating the medium to 1 M lowered the yield to 43% (entry 3). The same yield was obtained when DBU was assisted with DMAP (entry 4). However, when a mixture of nitromethane and dichloromethane was used, the yield increased to 57% (entry 5), while heating under the same conditions led to the decomposition of the substrate (entry 6). The use of DBN as a base, however, gave a low yield of 7% (entry 7). With Amberlyst® A21, 11% of **314a** were isolated (entry 8). Amberlyst® A21 was described to assist the conjugate addition of functionalized nitroalkanes to  $\alpha,\beta$ -unsaturated alkenes.<sup>345</sup> Finally, caesium fluoride proved to be as efficient as DBU and the reaction afforded the nitro cyclobutane **314a** in 64% yield (entry 9). The nitrocyclobutane **314a** was isolated as a 1.1:1 mixture of inseparable diastereomers. The complete 1D and 2D NMR analyses allowed the identification of the stereochemistry of both diastereomers.



entry	Reagent (2.0 eq.)	solvent (0.1 M)	yield (%)
1 <sup>a</sup>	NaH	THF	17
2	DBU	CH <sub>3</sub> NO <sub>2</sub>	69
3 <sup>b</sup>	DBU	CH <sub>3</sub> NO <sub>2</sub>	43
4	DBU/DMAP <sup>c</sup>	CH <sub>3</sub> NO <sub>2</sub>	43
5	DBU	CH <sub>3</sub> NO <sub>2</sub> /CH <sub>2</sub> Cl <sub>2</sub>	57
6 <sup>d</sup>	DBU	CH <sub>3</sub> NO <sub>2</sub> /CH <sub>2</sub> Cl <sub>2</sub>	- <sup>e</sup>
7	DBN	CH <sub>3</sub> NO <sub>2</sub>	7
8	Amberlyst <sup>®</sup> A21 <sup>f</sup>	CH <sub>3</sub> NO <sub>2</sub>	11
9	CsF	CH <sub>3</sub> NO <sub>2</sub>	64

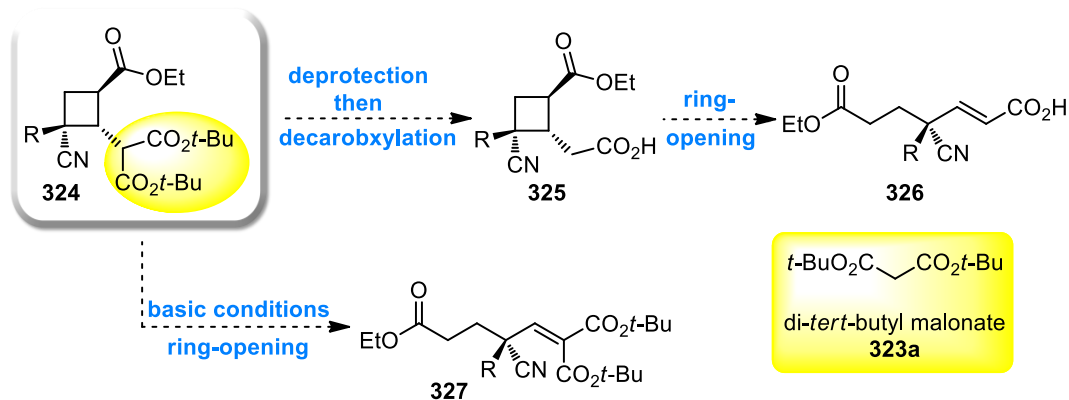
**Table III.20.** Conditions screening for the synthesis of nitro-cyclobutane. *Reagents and conditions:* 0 to 20 °C, 24 h. <sup>a</sup> CH<sub>3</sub>NO<sub>2</sub> (2.0 eq.). <sup>b</sup> CH<sub>3</sub>NO<sub>2</sub> (1.0 M). <sup>c</sup> DMAP (0.5 eq.). <sup>d</sup> 40 °C. <sup>e</sup> Complex mixture of products. <sup>f</sup> (214 mg/0.1 mmol of substrate).

The nitro adduct **314a** was then submitted to Ono's conditions;<sup>339</sup> however, only a complex mixture of products was obtained. Repeating the reaction with slow addition of the hydrogen source (Bu<sub>3</sub>SnH) using a syringe pump (1 mL/h) did not give better results.

Efforts to reduce the nitro group under several conditions (zinc dust, HCl, EtOH/H<sub>2</sub>O, 80 °C; zinc dust, acetic acid, 110 °C; iron powder, acetic acid, 110 °C) led to a complex mixture of products, while under hydrogenation in the presence of palladium on charcoal (1 atm, EtOH, 20 °C; 20 atm, EtOH, 20 °C; 20 atm, EtOH, 50 °C) no reaction was observed. Similarly, the Nef reaction in the presence of DBU in acetonitrile at 60 °C led to the decomposition of the substrate.

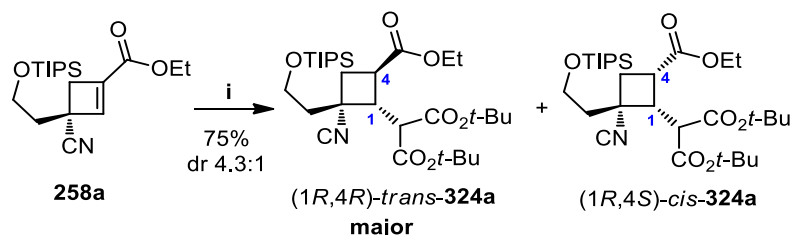
#### 8.4. Ring-opening through malonyl decarboxylation

The conjugate addition of activated methylenes onto enones is also well documented in the literature.<sup>346,347</sup> Thus, the 1,4-addition of the di-*tert*-butyl malonate **323a** was envisioned, given the role of steric interactions in the control of the diastereofacial selectivity in these systems (*vide supra*). The resulted cyclobutane would be deprotected using TFA to deliver carboxylic acid moieties, which would then decarboxylate under thermal conditions (Scheme III.64). The ring-opening process might be induced during the decarboxylation step, or later under basic conditions. Deprotonation of the acidic proton  $\alpha$ - to the malonate unit, might also deliver the corresponding acyclic system through a base-mediated ring opening.



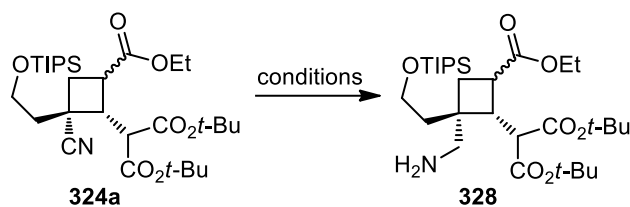
**Scheme III.64.** Ring-opening strategy of di-*tert*-butyl malonyl cyclobutane through decarboxylation or under basic conditions.

The addition reaction was conducted with di-*tert*-butyl malonate **323a** on cyclobutene **258a**, using sodium hydride as a base (Scheme III.65). The Michael product **324a** was obtained as a 4.3:1 mixture of two diastereomers, easily separable by column chromatography, in a 75% combined yield. The stereochemistry of the major component was unambiguously determined using 2D NOESY experiments, while that of the minor product, was obtained after a subsequent transformation. The NMR analyses indicates that the malonyl anion and the proton both adds *anti* to the bulky silyl ether chain (*syn* to the small nitrile group). For the minor isomer, the addition of the malonyl is also controlled by the bulky side chain but not the protonation of the enolate.



**Scheme III.65.** Synthesis of **324a**. *Reagents and conditions:* i) **323a** (1.0 eq.), NaH (1.0 eq.), THF (0.1 M), 0 to 20 °C, 4 h.

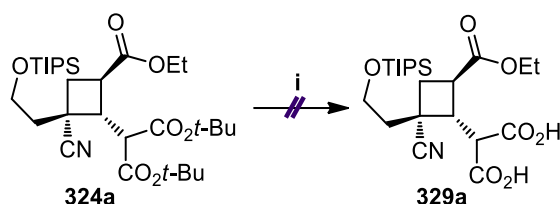
It was noticed that di-*tert*-butyl malonate **323a** possesses the same retention factor as the major cyclobutane **324a**, thus the addition of a slight excess of malonate (*e.g.*, 1.1 eq.) complicates the efficient separation. It is also worth noting that under the above conditions, the reaction proceeds cleanly, and a purification step is generally not necessary. Although the two isomers were separable, the mixture was submitted to the nitrile reduction, using nickel chloride hexahydrate conditions. The reaction afforded the reduced substrate **328** in 40% (combined yield) along with 56% of recovered starting material (Table III.21, entry 1). Cobalt chloride led to the reduced products in 35% yield with a slight loss of material (entry 2). It was suggested that the modest conversion may be related to the steric hindrance on the side of the nitrile group, making the reduction process more challenging. Nevertheless, in this case, too, both isomers were separable, and the minor diastereomer was analyzed to be (1*R*,4*S*)-*cis* by 2D NOESY NMR. The stereochemistry of its precursor minor-**324a** may then be assigned the same (1*R*,4*S*)-*cis*, based on the assumption that the Ni<sub>2</sub>B-mediated reduction occurs without epimerization.



entry	reagents (eq.)	time (h)	yield (%)
1	NiCl <sub>2</sub> .6H <sub>2</sub> O (1.0)	16	40, (91 brsm)
2	CoCl <sub>2</sub> .6H <sub>2</sub> O (1.0)	12	35, (66 brsm)

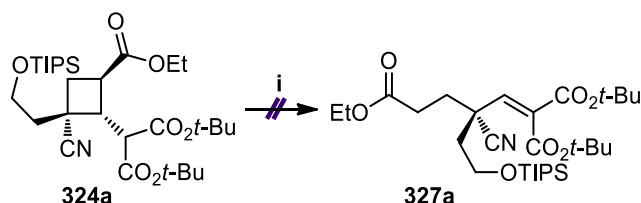
**Table III.21.** Nitrile reduction in *t*-butyl malonyl cyclobutane. *Reagents and conditions:* NaBH<sub>4</sub> (7.0 eq.), EtOH (0.07 M), 0 to 20 °C.

The cyclobutane **324a** was then submitted to deprotection of the *tert*-butyl groups using TFA, which led to a mixture of polar products, difficult to identify on the crude <sup>1</sup>H NMR spectrum. Although the *t*-butyl groups were clearly cleaved, purification of the crude mixture resulted in the isolation of only traces of unidentified products (Scheme III.66).



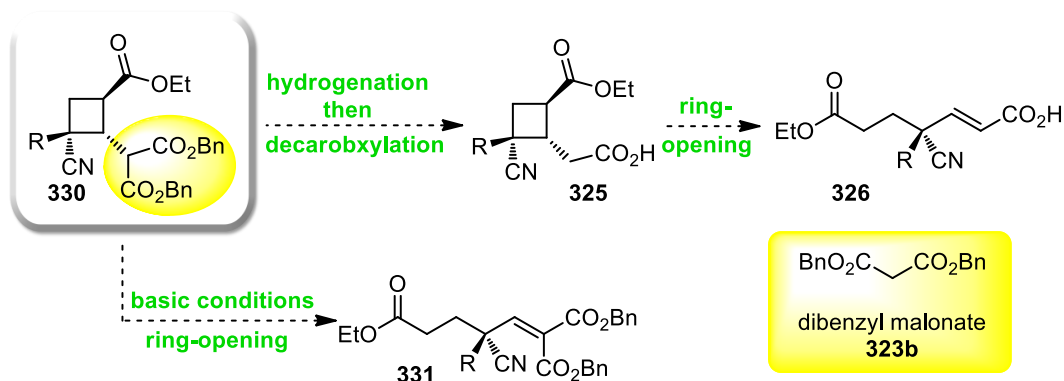
**Scheme III.66.** Deprotection attempt of *tert*-butyl fragments. *Reagents and conditions:* i) TFA/CH<sub>2</sub>Cl<sub>2</sub> (1/1), 0 to 20 °C, 4 h.

Alternatively, the base-mediated ring-opening using LDA gave a complex mixture of products (Scheme III.67).



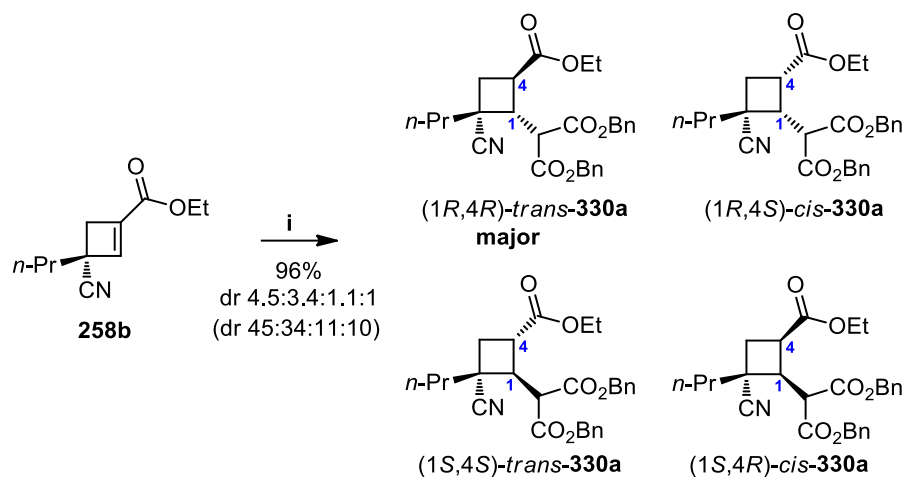
**Scheme III.67.** Attempt for base-mediated ring-opening of **324a**. *Reagents and conditions:* i) LDA (2.0 eq.), THF (0.1 M), -78 to 20 °C, 23 h.

The difficult isolation of products after the deprotection step of *t*-butyl groups led to envisage another strategy, using instead a dibenzyl malonate **323b**, the hydrogenation of which in the presence of palladium on charcoal, would afford the same diacid without side reactions. As above, the obtained cyclobutane would then be submitted to thermal conditions, to induce decarboxylation and ring-opening, directly or by the assistance of a base (Scheme III.68).



**Scheme III.68.** Ring-opening strategy of dibenzyl malonyl cyclobutane through decarboxylation or under basic conditions.

For this purpose, dibenzyl malonate **323b** was added to cyclobutene **258b** in the presence of sodium hydride. Four isomers in a 4.5:3.4:1.1:1 ratio were formed in 96% combined yield, (Scheme III.69).



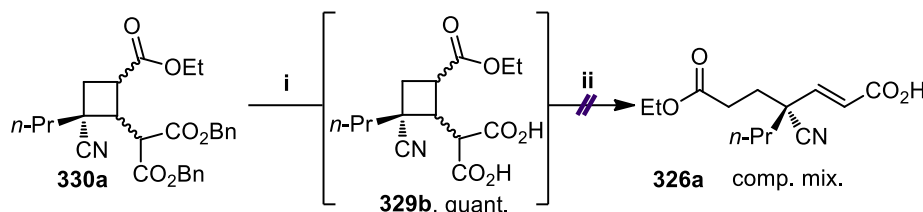
**Scheme III.69.** Synthesis of **330a**. Reagents and conditions: i) **323b** (1.0 eq.), NaH (1.0 eq.), THF (0.1 M), 0 to 20 °C, 13 h.

Unlike the former malonyl cyclobutane, these isomers were not separable using the standard column chromatography. Although the  $^1\text{H}$ ,  $^{13}\text{C}$ , and 2D NMR spectra were clear enough to attribute the signals for each isomer, this was not the case for the correlation assignments by 2D NOESY experiments. The stereochemistry of the compounds was then assigned based on the diethyl malonate analog discussed below.

Similar to what was observed with the *t*-butyl cyclobutane **324a**, the malonyl anion adds *syn* to the nitrile group, allowing the small-sized proton to approach from both sides of the ring to generate (1*R*, 4*R*)-**trans-330a** and (1*R*,4*S*)-**cis-330a** isomers, with the *trans* isomer being major. Two other isomers were also observed, albeit in lower amount, the (1*S*, 4*S*)-**trans-330a** and (1*S*,4*R*)-**cis-330a**. The lack of control at C-1 during the reaction is likely the result of the lower steric hindrance created by the dibenzyl ester units as compared to the *t*-butyl esters (A-value Ph, 3.0 kcal/mol vs. *t*-Bu, > 4.5 kcal/mol).

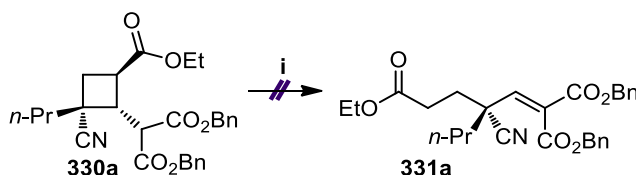
The mixture of diastereomers **330a** was deprotected using palladium on charcoal and hydrogen under atmospheric pressure (Scheme III.70). The analytical data showed that the deprotection

occurred successfully in a quantitative (crude) yield. The mixture of the carboxylic acids **329b** was then heated in toluene or DMF under reflux, leading to a complex mixture of products.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of the crude reaction mixture were particularly complex. The absence of typical double bond signals indicates that the decarboxylation/fragmentation did not occur. The addition of a base such as DBU or  $\text{Et}_3\text{N}$  did not afford better results.



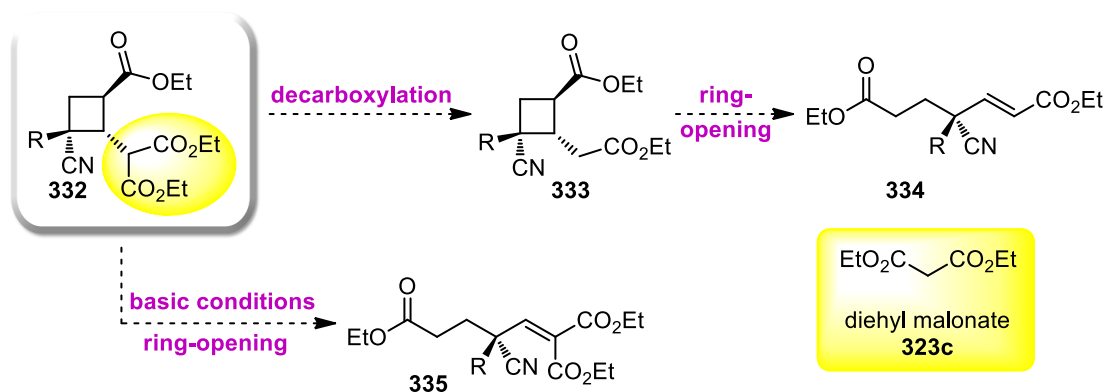
**Scheme III.70.** Attempts for decarboxylation and ring-opening of **330a**. *Reagents and conditions:* i) 10% Pd/C,  $\text{H}_2$  (1 atm), EtOH, 20 °C, 23 h; ii) toluene or DMF, 120 °C.

The ring-opening by the intermediacy of a base was also investigated. However, a complex mixture of products was obtained using LDA as a base and no typical double bond was observed (Scheme III.71). It is also worth noting that the ring-opening of the malonyl cyclobutane **330a** through radical fragmentation using  $\text{SmI}_2$  was also applied, but no reaction occurred.



**Scheme III.71.** Attempt for base-mediated ring-opening of **330a**. *Reagents and conditions:* i) LDA (2.0 eq.), THF (0.1 M), -78 to 20 °C, 20 h.

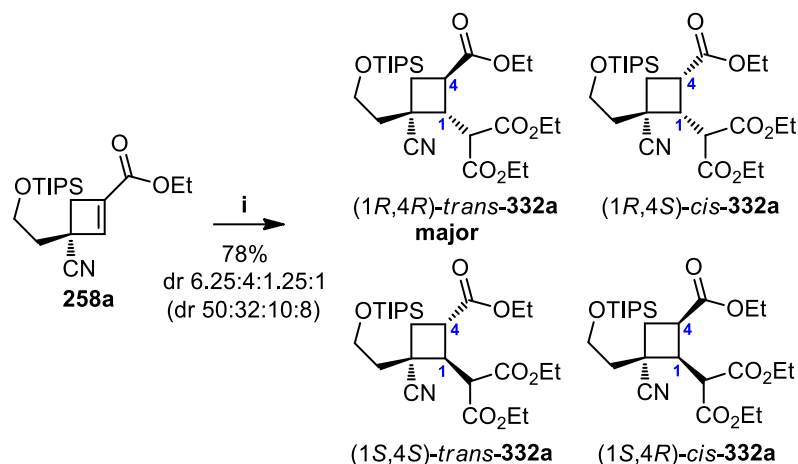
The 1,4-addition of diethyl malonate **323c** on cyclobutene was finally studied, as described above (Scheme III.72).



**Scheme III.72.** Ring-opening strategy of diethyl malonyl cyclobutane through decarboxylation or under basic conditions.

Under the same conditions as before, the conjugate addition of diethyl malonate onto cyclobutene **258a** delivered four diastereomers in a 6.25:4:1.25:1 ratio, and 78% combined yield (Scheme III.73). With a slight excess of malonate substrate, no separation from the cyclobutane was possible. However, using a strict stoichiometry, the reaction occurred cleanly, and no further purification was

required. The first three diastereomers were separable using column chromatography, while the fourth one was contaminated with a fraction of the third isomer.

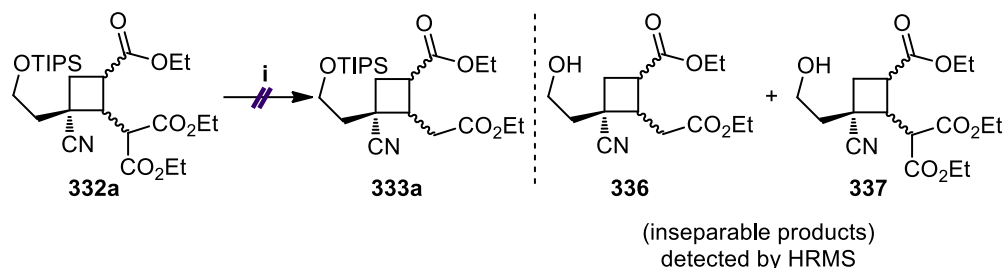


**Scheme III.73.** Synthesis of **332a**. Reagents and conditions: i) **323c** (1.0 eq.), NaH (1.0 eq.), THF (0.1 M), 0 to 20 °C, 4 h.

The correlation analyses by 2D NOESY experiments indicates that the major diastereomer possesses the (1R,4R)-*trans* configuration as explained before. The stereochemistry of the second isomer was identified as (1R,4S)-*cis* by NMR studies. For the other two isomers, the NOESY data confirmed the stereochemistry at the C-1 stereocenter to be 1S. However, the stereochemistry at C-4 was not totally clear, although the HRMS analyses confirmed that these two products are isomers of the first two. Further manipulations below, confirmed the assigned stereochemistry.

With ester **332a** in hand, it was envisioned to carry out the cyclobutane ring-opening through a Krapcho deethoxycarbonylation reaction.<sup>348,349</sup> The Krapcho decarboxylation typically involves heating the substrate in a polar aprotic solvent (DMSO...) at high temperature, in the presence of a halide anion source (NaCl, LiCl...) as a nucleophile. The Krapcho's method led to a mixture of inseparable polar products without significant loss of material. The NMR analyses presented a complex profile and the HRMS confirmed the formation of the decarboxylation product **336** by showing a peak with a chemical formula of C<sub>14</sub>H<sub>21</sub>O<sub>5</sub>NNa [M+Na]<sup>+</sup> and a mass of 306.13084 (Scheme III.74). The mass spectrometry also indicated the presence of **337** with a peak corresponding to a chemical formula of C<sub>17</sub>H<sub>25</sub>O<sub>7</sub>NNa [M+Na]<sup>+</sup> and a mass of 378.15193. At this point, with a mixture of at least eight products, it was clear that the optimization of the reaction would not be an easy task. Therefore, it was focused on the selective ring-opening through deprotonation to access a compound lacking two stereogenic centers and thus, easier to analyze. The decarboxylation process would then be optimized on a simpler acyclic system.





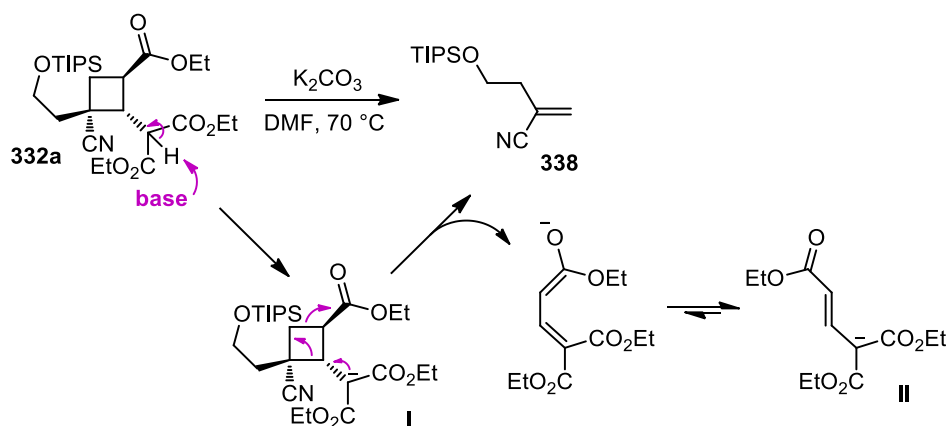
**Scheme III.74.** Decarboxylation under Krapcho's conditions. *Reagents and conditions:* i) LiCl (2.0 eq.), DMSO/H<sub>2</sub>O: 1/1, 155 °C, 24 h.

Submitting **332a** to DBU in dichloromethane did not induce any reaction (Table III.22, entry 1), whereas a strong base such as LDA, gave a complex mixture of products (entry 2). With potassium carbonate in DMF at 70 °C, an unsaturated nitrile **338** was isolated in 14% yield (entry 3).

entry	base	conditions	yield (%)
1	DBU	CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 21 h	0
2	LDA	THF, -78 to 20 °C, 24 h	comp. mix.
3	K <sub>2</sub> CO <sub>3</sub>	DMF, 70 °C, 23 h	<b>338</b> (14)

**Table III.22.** Base-mediated ring-opening of **332a**. *Reagents and conditions:* base (2.0 eq.), solvent (0.1 M).

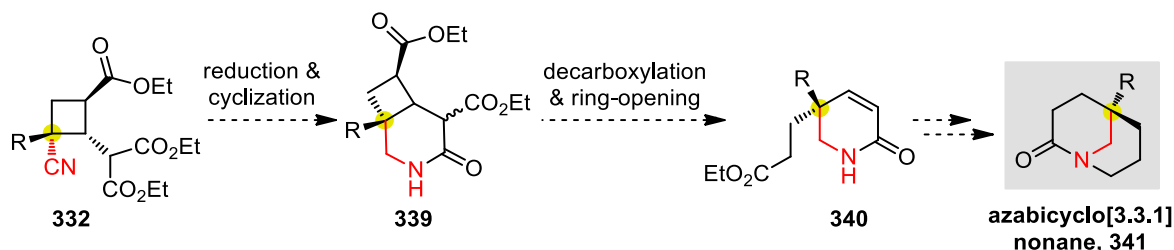
The product **338** is obtained as a result of retro [2+2] cycloaddition reaction. This suggests that the deprotonation of the malonyl moiety has occurred, followed by a fragmentation of the cyclobutane ring on the undesired side (Scheme III.75).



**Scheme III.75.** Formation of **338** through retro [2+2] cycloaddition reaction.

Based on these premises, it was proposed to modify the strategy again and to open the ring after the nitrile reduction, which should produce an amine ready to cyclize and afford a bicyclic system **339** (Scheme III.76). This intermediate would then be manipulated further through decarboxylation and cyclobutane ring-opening to give access to the azabicyclo[3.3.1]nonane skeleton.





**Scheme III.76.** Alternative ring-opening strategy through nitrile reduction and cyclization.

## 9. Conclusion

In the second part of this chapter, studies on cyclobutene/ane ring-opening were performed, leading to an efficient radical fragmentation promoted by  $\text{SmI}_2$ . Enantioenriched  $\gamma$ -nitrile systems bearing a functionalized all-carbon quaternary stereocenter were obtained in good to high yields. Efforts to remove the sulfone moiety efficiently through Ramberg-Bäcklund reaction were unsuccessful. Alternatively, the sulfonyl group was removed under basic conditions before exploring the ring-opening strategies. Ring-cleavage through ozonolysis, metathesis, or push-pull system was unsuccessful, probably due to the high functionalization of the templates under study, and the presence of a nitrile group as a strong EWG. Transformation of the nitrile into other functionalities did not solve the problem, and the four-membered ring was found inactive towards these strategies. The addition of different nucleophiles *via* 1,4-conjugate addition on the cyclobutene carboxylates with the aim of promoting the ring-opening was also deceiving.

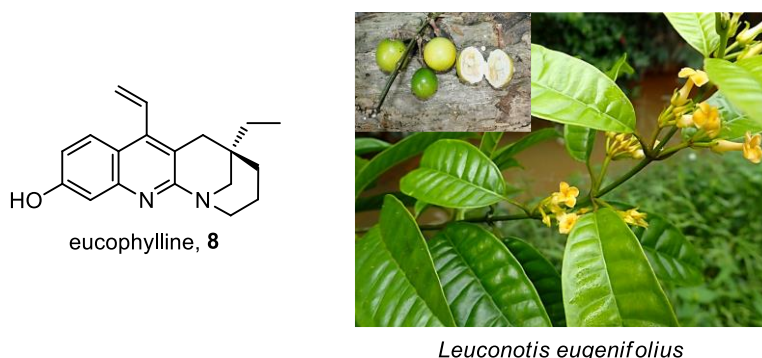
## *Chapter IV*

### *Total Synthesis of (+)-Eucophylline*



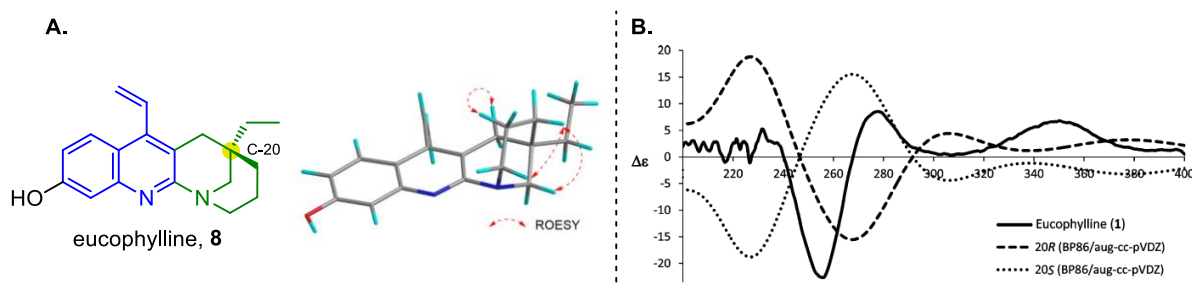
## 1. Isolation, structure, and biogenesis of eucophylline

Eucophylline **8**, a rare example of a tetracyclic vinylquinoline alkaloid, was isolated from the bark of *Leuconotis eugenifolius* species collected in Peninsular Malaysia, by extraction with methanol (Figure IV.1).<sup>2</sup> The purification of the extract allowed the isolation of eucophylline **8** as a brown powder in 0.00039% yield (1.9 mg), together with leucophyllidine, eburnamine, leuconolam, and rhazinilam alkaloids. The fact that Morita and co-workers isolated eucophylline, eburnamine and leucophyllidine alkaloids in the same extract supports the proposed biogenesis of the dimeric alkaloid **6**, involving a Mannich-type coupling between the eburnan backbone **7** and eucophylline **8**.



**Figure IV.1.** Eucophylline **8** isolated from *Leuconotis eugenifolius*.  
(Picture source: Flickr.com)

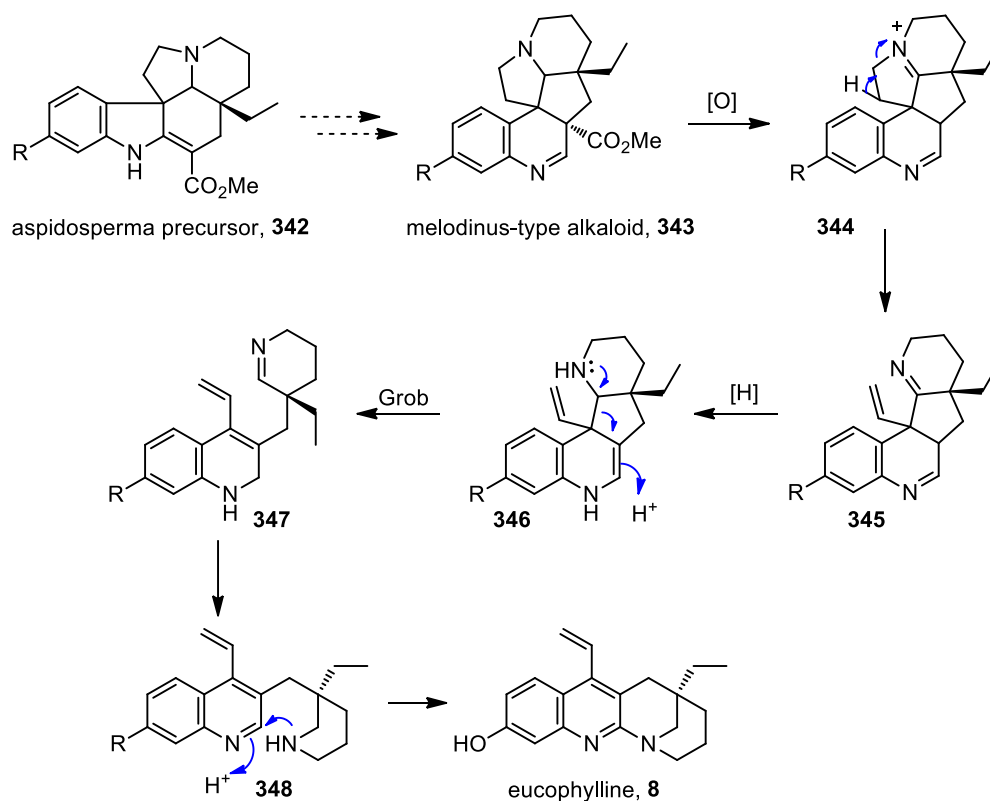
The relative structure of **8** was confirmed by a combination of NMR data analyses and ROESY correlations in computerized 3D drawing, which suggested that the piperidine ring adopts a chair conformation (Figure IV.2.A). The absolute configuration of the asymmetric C-20 center was assigned to be (*R*) by comparing the experimental circular dichroism (CD) spectra with the calculated CD spectra performed by Turbomole (Figure IV.2.B).<sup>2,350</sup>



**Figure IV.2.** A) ROESY correlations of **8**. B) Experimental and calculated CD spectra for (*R*)-**8** and (*S*)-**8**.<sup>2</sup>

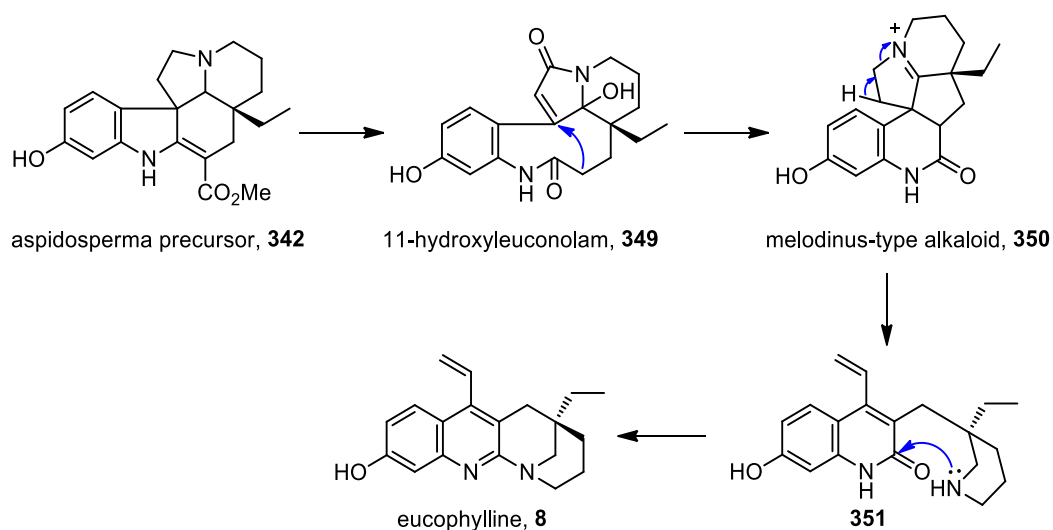
It was proposed that this unprecedented tetrahydrobenzo[*b*][1,8]naphthyridine chromophore comes from an indole precursor since *Leuconotis* species contain only monoterpenoid indole alkaloids. Kam's and Morita's groups proposed different biogenetic pathways starting from the same aspidosperma precursor. Kam and co-workers<sup>1</sup> for example, proposed the derivatization of a melodinus-type alkaloid **343** from the aspidosperma precursor **342** (Scheme IV.1). The derivative **343** undergoes decarboxylation and oxidation giving an iminium **344**. The latter evolves into the tetracyclic backbone **345** after C-N bond cleavage. The imine reduction and the Grob-like fragmentation of the resulting intermediates produce the vinyl-substituted dihydroquinoline adduct

**347.** Vinylquinoline **348** arises after aromatization and reduction. Finally, the subsequent nucleophilic addition of the piperidine nitrogen onto the pyridine ring and aromatization produce the eucophylline skeleton **8**.



**Scheme IV.1.** Proposed biogenetic pathway of eucophylline, by Kam *et al.*<sup>1</sup>

Another possible biogenetic pathway was also proposed by Morita *et al.*<sup>2</sup> The aspidosperma precursor **342** evolves into a melodinus-type alkaloid through an internal Michael addition of the leuconolam intermediate **349** (Scheme IV.2). The attack of the piperidine nitrogen onto the carbonyl promotes the ring closure to give, once dehydrated, the eucophylline scaffold **8**.



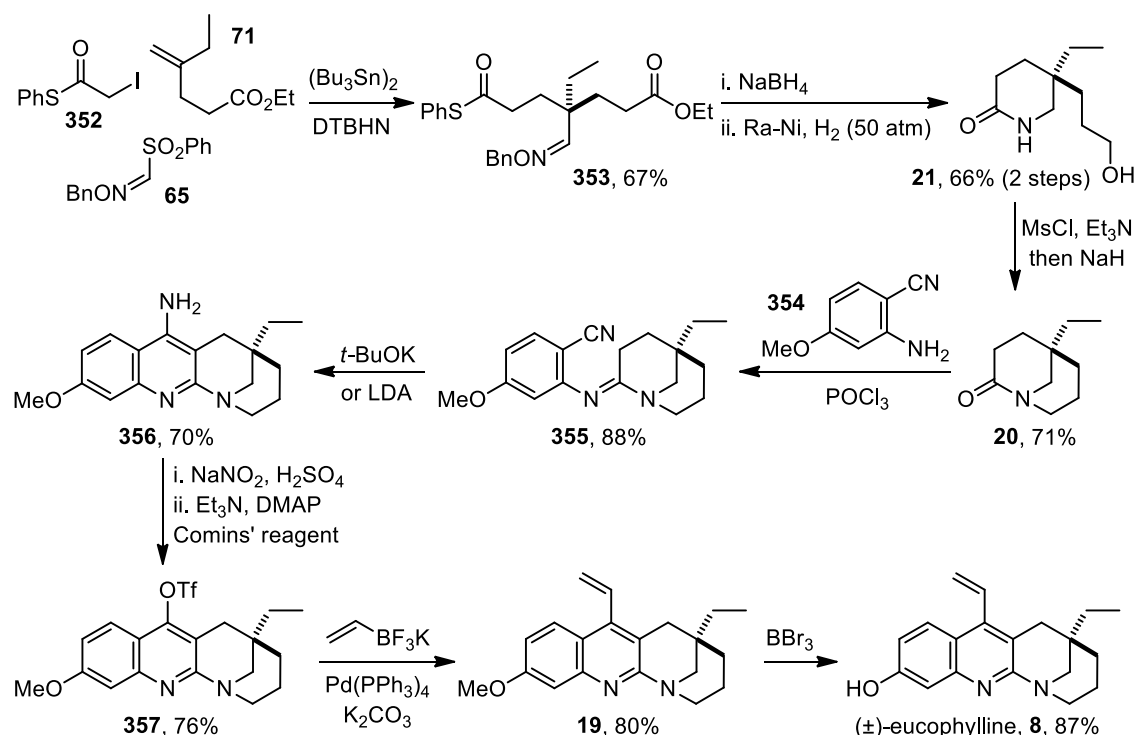
**Scheme IV.2.** Proposed biogenetic pathway of eucophylline, by Morita *et al.*<sup>2</sup>

Apart from its complex and uncommon structure, eucophylline **8** constitutes the southern fragment of the leucophyllidine bis-indole alkaloid **6**. As well, it showed high cell viability in J774.1

at a concentration of  $IC_{50}$  7.1  $\mu$ M.<sup>2</sup> Considering these features, the development of a suitable total synthesis of this strained scaffold was envisioned.

## 2. Reported total syntheses of eucophylline

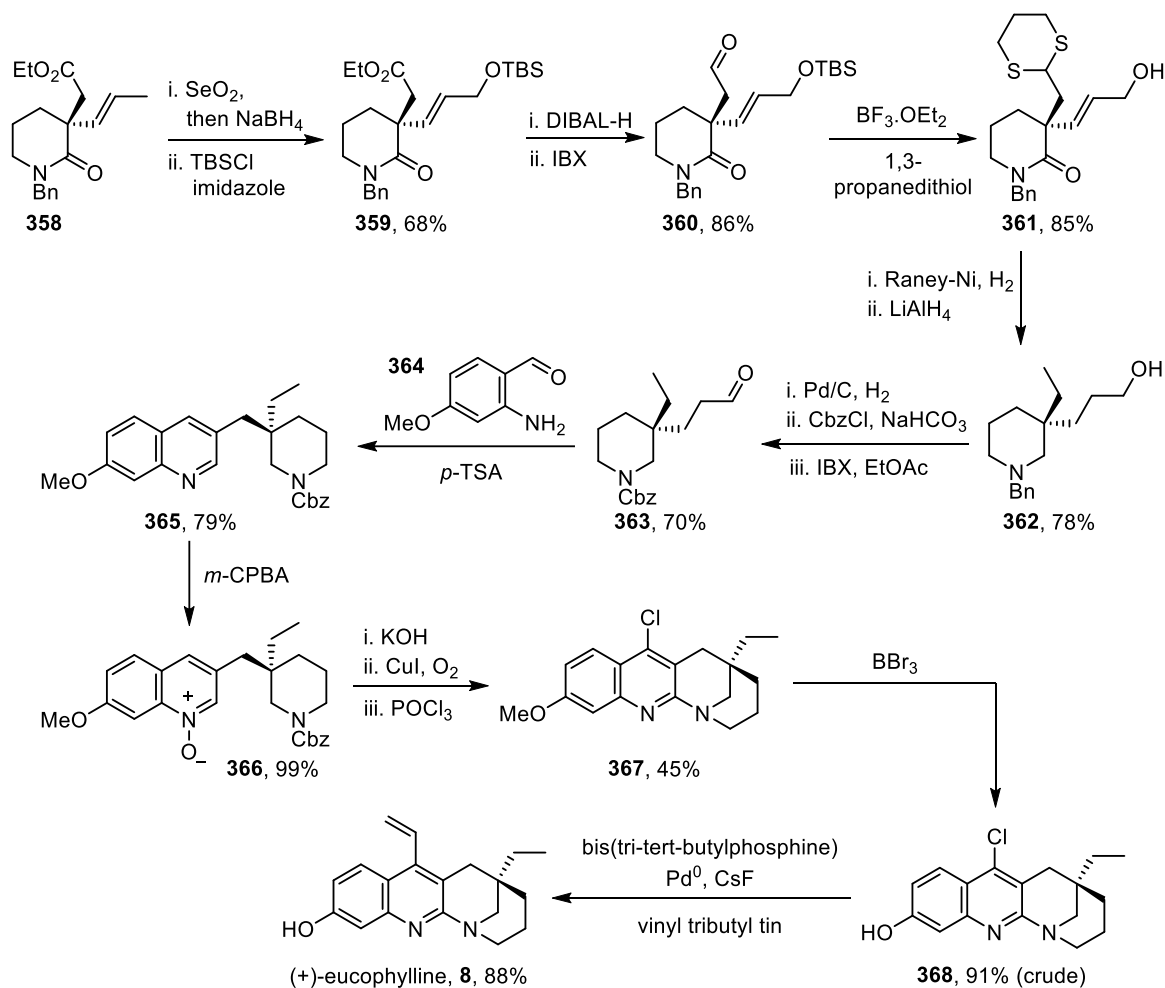
The first total synthesis of ( $\pm$ )-eucophylline **8** was accomplished by Landais and co-workers<sup>48</sup> in 10 steps and 10% overall yield from  $\alpha$ -iodothioester **352** (Scheme IV.3). The installation of the all-carbon quaternary center was based on a free radical three-component carbo-oximation process developed by the group, as the main step.<sup>351</sup> The adduct **353** was subjected to a chemoselective reduction of the thioester group into alcohol, followed by hydrogenolysis and cyclization of the oxime giving the hydroxy-lactam **21**. The hydroxyl group was then activated by a mesylate as a leaving group, facilitating the construction of the strained bicyclic lactam **20** after deprotonation of the amide. The coupling of the bridgehead lactam with benzonitrile **354** under Friedländer conditions afforded the amidine **355** in high yield. The latter underwent cyclization under basic conditions, to provide the amine **356**, which proceeded to the triflate **357** by the intermediacy of a diazonium salt. The vinyl fragment was incorporated into the tetracyclic core at this stage through a Suzuki-type coupling, affording **19** in an 80% yield. Final *O*-demethylation of the aromatic core produced the ( $\pm$ )-eucophylline **8** in 87% yield.



**Scheme IV.3.** Total synthesis of ( $\pm$ )-eucophylline by Landais and co-workers.<sup>48</sup>

On the other hand, the first enantioselective total synthesis of (+)-eucophylline was described by Pandey and co-workers<sup>352</sup> (Scheme IV.4). In their strategy, the chiral lactam **358** was subjected to allylic oxidation in the presence of selenium dioxide followed by the protection of the resulting alcohol to give **359** in 68% yield over two steps. The chemoselective reduction of the ester moiety using DIBAL-H provided a mixture of aldehyde and alcohol which was then oxidized with IBX to

furnish the aldehyde **360** as a single product. The latter was submitted to dithioacetalization giving the 1,3-dithiane **361**, which itself was desulfurized and the amide function reduced to provide the piperidine adduct **362** in 78% yield over two steps. Further manipulation and oxidation afforded the corresponding aldehyde **363** which was engaged in a Friedländer-type reaction. The quinoline adduct **365** was oxidized using *m*-CPBA to provide the *N*-oxide derivative **366** in a 99% yield. The latter proceeded with further modifications including a copper-catalyzed intramolecular cyclization to give a crude tetracyclic *N*-oxide. Upon reaction with an excess of phosphorus oxychloride, it afforded **367** in 45% yield over three steps. The phenol **368** was engaged in a Stille coupling after *O*-demethylation, to produce the (+)-eucophylline **8** in 88% yield.

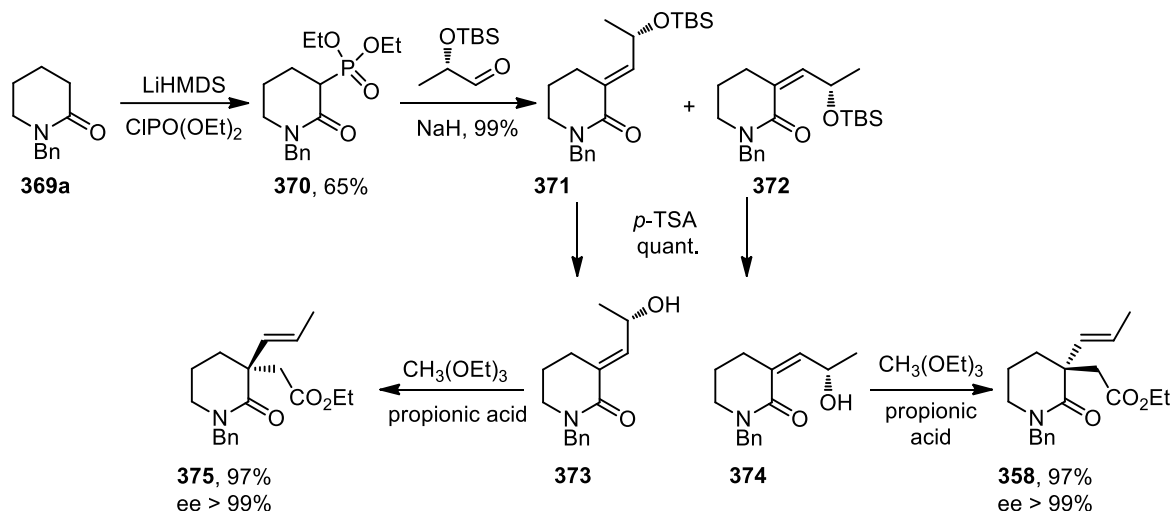


**Scheme IV.4.** Enantioselective total synthesis of (+)-eucophylline, by Pandey *et al.*<sup>352</sup>

The authors noted that the eucophylline synthesis was achieved in 11 linear steps and 7.4% overall yield starting from the lactam **358**. But, in this report, it was not taken into account the sequential steps of oxidation and reduction where the crude intermediates were isolated by extraction. As well, the synthesis begins from the enantiopure lactam **358**, which itself was constructed in several steps.

In a previous work of the group,<sup>353</sup> a method was established to install an all-carbon quaternary stereocenter at the C-3 carbon of lactams through a [3,3] sigmatropic rearrangement (Scheme IV.5). The protected piperidinone **369a** was submitted to LiHMDS in the presence of diethyl chlorophosphate to afford the alkylphosphonate **370**. The latter was engaged in Horner-Wadsworth-

Emmons (HWE) olefination with TBS-protected L-lactaldehyde to furnish the corresponding enone as a mixture of two diastereoisomers **371** and **372**. TBS-protecting groups of **371** and **372** were cleaved separately to provide the alcohols **373** and **374** in quantitative yields. These two underwent a [3,3] sigmatropic shift (Johnson-Claisen rearrangement) to furnish the enantiomeric lactams **358** and **375** with excellent yields and enantiomeric excess in four-steps sequence.



**Scheme IV.5.** Synthesis of enantiopure lactams **358** and **375** through [3,3] sigmatropic rearrangement, by Pandey *et al.*<sup>353</sup>

Based on the abovementioned statements, it is more accurate to report that the synthesis of eucophylline was accomplished in 21 steps and 4.8% overall yield from Bn-protected piperidinone **369a** (the protection step of the commercially available 2-piperidinone **376** was not reported in the article, so, the overall yield was calculated starting from **369a**).

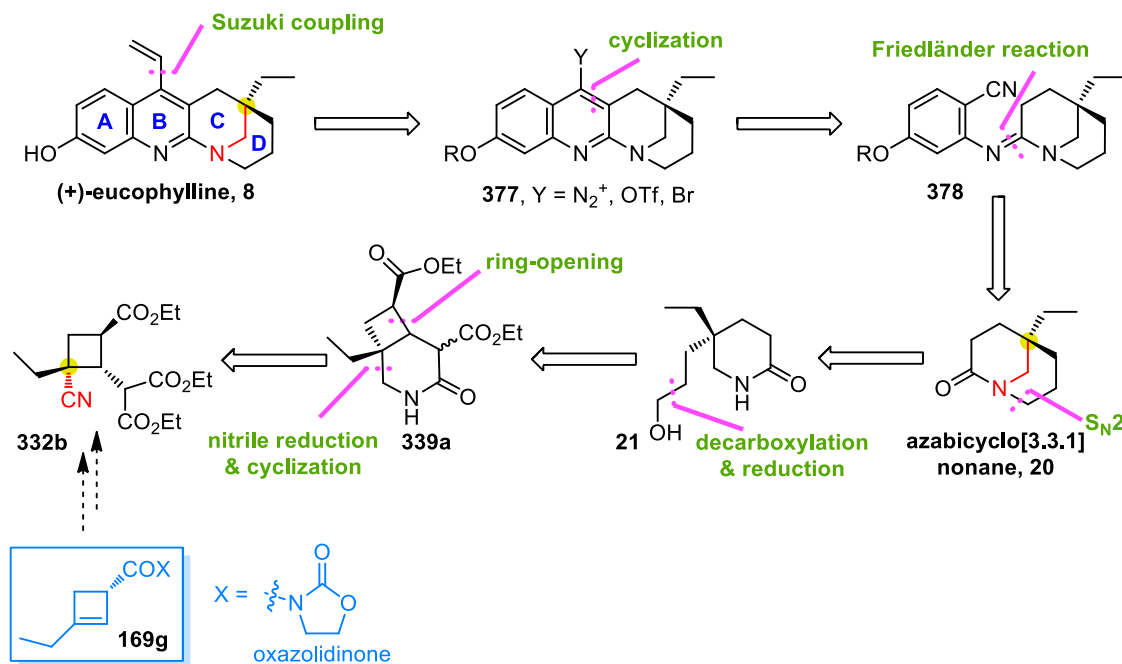
### 3. Retrosynthetic strategy towards the synthesis of (+)-eucophylline

In the course of the studies to synthesize leucophyllidine **6**, an asymmetric synthesis of the natural eucophylline **8** was intended. The key feature is the synthesis of an enantiopure 1-azabicyclo[3.3.1]nonane nucleus containing the all-carbon stereogenic quaternary center, starting from a cyclobutene backbone.

The beginning of the retrosynthesis would be based on the racemic total synthesis of eucophylline described by Landais *et al.*<sup>48</sup> The synthesis of eucophylline **8** would rely on the late incorporation of a vinyl substituent through a Suzuki-vinylation process, from the corresponding diazonium salt, triflate or bromide **377** (Scheme IV.6). The 1,8-naphthyridine scaffold of eucophylline would arise from tailoring the ring B, upon base-mediated intramolecular cyclization of an amidine **378**. The latter would be produced through a Friedländer-type annulation, after condensation of an *ortho*-aminobenzonitrile with a bridgehead lactam scaffold, 1-azabicyclo[3.3.1]nonane **20**. This amide would ascend from a nucleophilic substitution after the conversion of alcohol **21** into a mesylate. The alcohol **21** would be generated from the cyclobutyl ring-opening of **339a**, followed by decarboxylation and reduction of the ester moiety. The aforementioned cyclobutyl lactam **339a** would arise from the malonyl cyclobutane **332b** after the reduction of the nitrile unit and spontaneous cyclization with an



ester fragment. The malonyl cyclobutane **332b** itself would derive from the cyclobutene **169g** bearing an ethyl side chain, after several transformations.

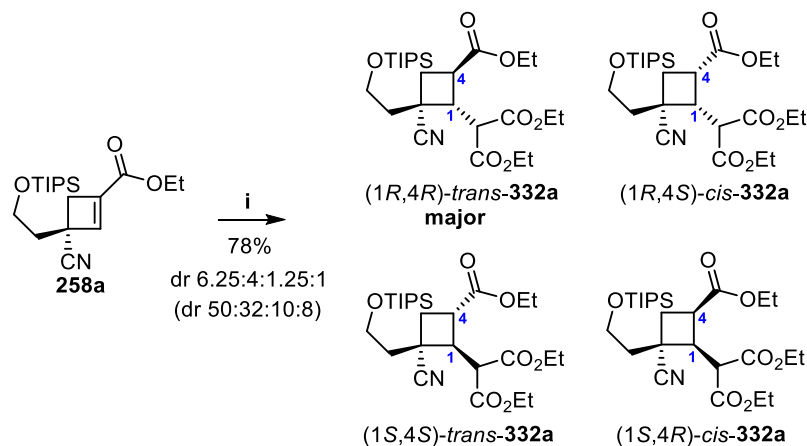


**Scheme IV.6.** Revised retrosynthesis of eucophylline through an azabicyclo[3.3.1]nonane intermediate.

Throughout this chapter, the different investigated approaches towards the development of (+)-eucophylline alkaloid **8** will be presented, relying on the established method to access the polyfunctionalized cyclobutanes. In parallel, the main highlights on the preparation of the key bridged lactam and the nickel boride reaction will be examined.

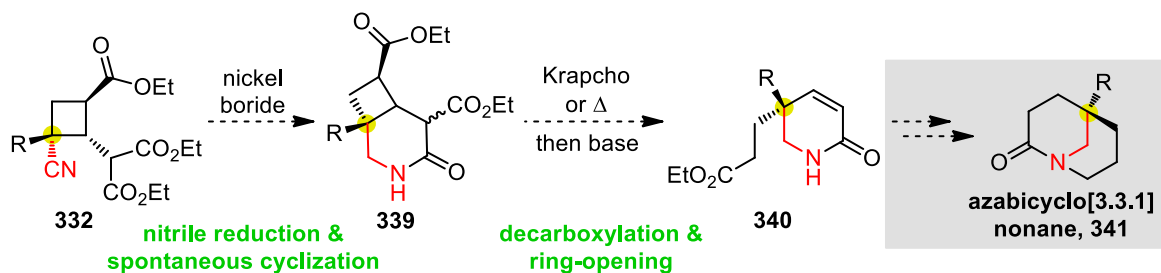
#### 4. Cyclobutane ring-opening through nitrile-reduction, cyclization and decarboxylation

In the last chapter, the development of acyclic chains from cyclobutanes bearing an all-carbon quaternary center, encountered difficulties, mainly due to the presence of a nitrile group. Alternatively, it was envisioned to open the cyclobutane ring in a different manner, starting from **332a** synthesized earlier from the addition of diethyl malonate onto cyclobutene **258a** (Scheme IV.7).



**Scheme IV.7.** Earlier synthesis of diethyl malonyl cyclobutane **332a**. *Reagents and conditions:* i) diethyl malonate (1.0 eq.), NaH (1.0 eq.), THF (0.1 M), 0 to 20 °C, 4 h.

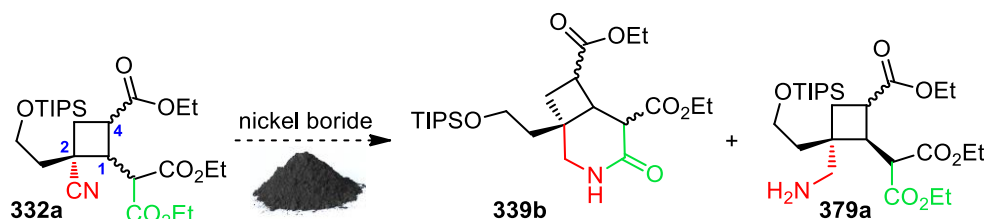
It was reasoned that the malonyl cyclobutane **332** should undergo nitrile reduction using for instance nickel boride catalyst, to deliver an amine group which would react spontaneously with a malonyl ester fragment giving a cyclic lactam fused with the cyclobutane ring **339** (Scheme IV.8). In such case, only the diastereomers with the malonyl substituent in *cis* with the nitrile group (1*R* configuration) would undergo cyclization. Since the isomers possessing such configuration are the two major isomers (~ 80% combined ratio), this plan seemed reasonable. The resulting lactam ester **339** would later be decarboxylated under Krapcho's conditions. It is supposed that at this point, the decarboxylation would induce a subsequent cleavage of the cyclobutyl ring, with the release of the total strain as a powerful driving force. Otherwise, the ring-opening would be performed after decarboxylation, using a strong base like LDA. The base would abstract the acidic proton  $\alpha$ - to the carbonyl, which would then open the four-membered ring leading to an unsaturated cyclic lactam **340**. Such moiety, would offer after reduction and cyclization, the azabicyclo[3.3.1]nonane **341**, the key core of eucophylline (compound **20** with R = Et). Although this ring-opening strategy would not deliver an acyclic chain as previously planned, at least it would give access to the azabicyclic core, allowing the pursuit of the enantioselective total synthesis of eucophylline.



**Scheme IV.8.** Ring-opening strategy through nitrile reduction, cyclization and decarboxylation process.

#### 4.1. Nickel borohydride-catalyzed reduction of cyano-cyclobutanes

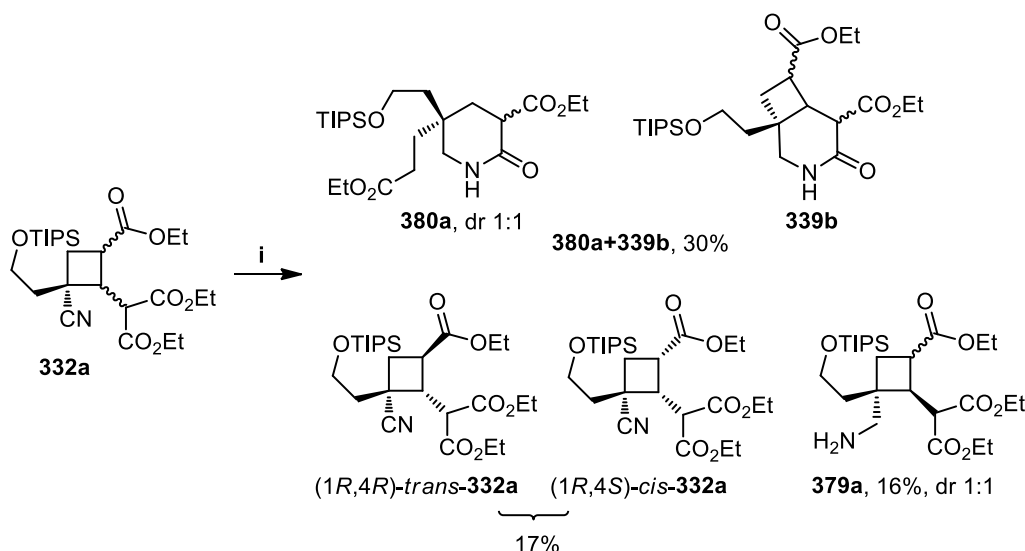
As a first attempt, it was suggested to perform the reduction reaction on the mixture **332a** issued from the addition of diethyl malonate to cyclobutene **258a**, using the *in situ* prepared nickel boride ( $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}/\text{NaBH}_4$  in EtOH). Although the major diastereomers *cis* to nitrile, (1*R*,4*R*)-*trans*-**332a** and (1*R*,4*S*)-*cis*-**332a**, were separable by column chromatography, the reaction proceeded with the mixture, as the stereochemistry stereogenic center C-4 has no influence on the final step, and it will be lost upon the ring-opening. The minor *trans*-C1-C2 isomers (1*S*,4*S*)-**332a** and (1*S*,4*R*)-**332a** were expected to be reduced but not cyclized, giving polar amines. Thus, after the reduction step, the products will be much easier to separate. Based on this rationalization, two sets of products were expected to form, the bicyclic scaffold **339b** and the amino-cyclobutane **379a** (Scheme IV.9).



**Scheme IV.9.** Designed reduction reaction of **332a** and the expected products.

However, the designed reaction gave a more complex mixture than predicted. Foremost, from the crude mixture of this reaction, a fraction was isolated in a 30% yield (Scheme IV.10). Surprisingly, it was composed of a mixture of two different and inseparable products in a 70:30 ratio ( $^1\text{H}$  NMR). Based on 1D NMR ( $^1\text{H}$ ,  $^{13}\text{C}$ , and  $^{13}\text{C}$ -DEPT-135) and 2D NMR ( $^1\text{H}$ - $^1\text{H}$  COSY and  $^1\text{H}$ - $^{13}\text{C}$  HSQC), it was proposed that the major product is the lactam **380a**, present as two diastereomers of a 1:1 ratio, with the silyl ether and the two ester groups being left intact. In fact, the  $^{13}\text{C}$ -DEPT-135 analysis of this major product presented signals for eight secondary carbons ( $\text{CH}_2$ ) and only one tertiary carbon ( $\text{CH}$ ) instead of three (*counting for one diastereomer*). Such an observation suggested immediately that the cyclobutane ring has opened. The minor product, however, was most likely to be the bicycle **339b**, also as a mixture of four diastereomers. Yet, the analysis of this product was not as clear as for the major one. The mass spectrometry analysis came later to confirm the presence of two products, where the major possesses a chemical formula of  $\text{C}_{24}\text{H}_{45}\text{NO}_6\text{SiNa}$   $[\text{M}+\text{Na}]^+$  and a peak mass of 494.28961 that correspond to the opened ring **380a**. Whereas, the minor presents two protons less with a chemical formula of  $\text{C}_{24}\text{H}_{43}\text{NO}_6\text{SiNa}$   $[\text{M}+\text{Na}]^+$  and a peak mass of 492.28949 which correspond to the fused-rings system **339b**.

From the reaction mixture, 17% of the starting material were also recovered featuring the major isomer (1*R*,4*R*)-*trans*-**332a** and the second isomer (1*R*,4*S*)-*cis*-**332a** in 30 and 70%  $^1\text{H}$  NMR ratio, respectively. As anticipated, the minor isomers (1*S*,4*S*)-*trans*-**332a**, and (1*S*,4*R*)-*cis*-**332a** were reduced to give the amino-cyclobutane **379a** as a mixture of two isomers in a 1:1 ratio ( $^{13}\text{C}$  NMR), in 16% overall yield. Since the crude NMR was too complex to analyze, the isomers' ratio was calculated after the purification step. The ratio of the amine isomers in the precursor was 1.25:1, slightly different from what obtained after reduction. This difference goes more likely to a possible loss of a small quantity during the treatment and purification step.



**Scheme IV.10.** Preliminary results of cyclobutane **332a** reduction with nickel boride. *Reagents and conditions:* i)  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$  (1.0 eq.),  $\text{NaBH}_4$  (7.0 eq.),  $\text{EtOH}$  (0.07 M).

Based on these results, it was envisioned to optimize the reaction to favor the formation of the desired lactam **380a** and drive the reaction into full conversion. As the first way of improvement, the

nature of the transition metal salt was questioned, and  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$  was replaced by  $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ . The reaction under such conditions afforded a 6% yield of lactam **380a** and cyclobutane **339b** in 80:20 ratio, respectively (Table IV.1, entry 2). 37% of the starting material were also recovered as a mixture of the two diastereomers (1*R*,4*R*)-*trans*-**332a** and (1*R*,4*S*)-*cis*-**332a** in a 42:58 ratio respectively. The reduced cyclobutane **379a** was however obtained in a correct yield of 16%. This result indicates that cobalt boride is a less powerful reductant than its nickel analog, at least in this transformation (entries 1 and 2).

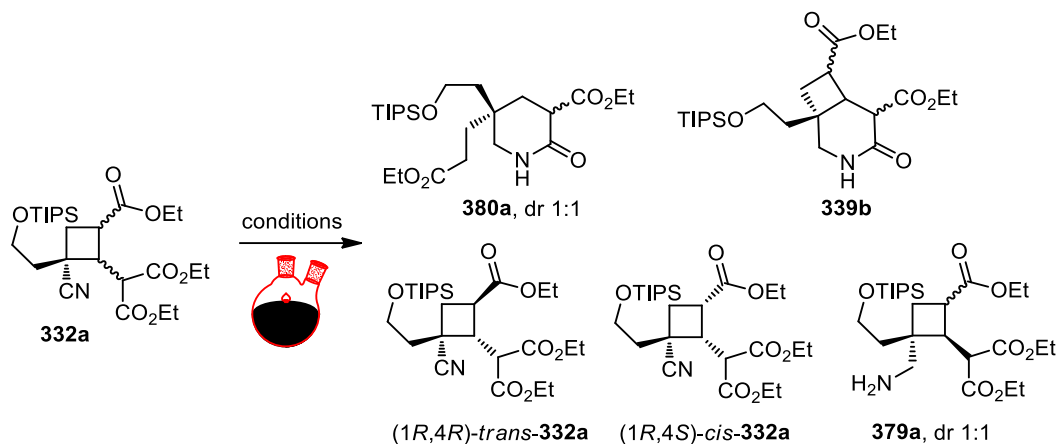
On this basis, the conditions were further optimized using nickel species, changing the nickel source. Khurana and Kukreja observed that nickel chloride hexahydrate was much less efficient than the dehydrated nickel.<sup>325</sup> For this reason, they modified the nickel chloride's surface by drying it in the oven (~ 250 °C) then under vacuum, transforming the green-colored salts into a yellow one.<sup>354</sup> This protocol was followed, and indeed, the color of the salt changed to yellow after dehydration. Yet, once the modified catalyst was used in the reaction, the lactam **380a** and cyclobutane lactam **339b** were obtained in a 9% yield, while 17% of the starting material were isolated together with 8% of the amino-cyclobutane **379a** (entry 3). Besides the low efficiency of this catalyst, an important loss of material was detected. In fact, in all previous cases, the loss of material was clear (the change of the treatment method: extraction or filtration over celite, did not show a significant improvement of the yield or recovery of the material). It is possible that depending on the nature of the nickel boride nanoparticles, unconsumed starting material may be irreversibly bonded to the catalyst's matrix, or that a large quantity of the substrate degraded.

The fact that the nickel chloride's source influences the nature of the formed nanoparticles, inspired testing the commercial anhydrous nickel chloride using the same reduction system. Interestingly, the yield increased to 53% of lactams **380a** and **339b** in 75:25 ratio, respectively (entry 4). The starting material was recovered in 23% yield. In this case, no significant loss of material of the major diastereomers was noticed. However, the cyclobutane **379a** was isolated in only 5% yield, likely due to its high polarity and difficulties during the isolation step. It is worth adding here that a few milligrams fraction with a polarity between the lactams and the amines was also isolated, the structure of which was too complex to be identified, although few signals relate to the cyclobutane core.

Using unpurified ethanol lowered the yield of lactams **380a** and **339b** to 46%, and the reduction rate was slightly retarded (entry 5), while the starting material was isolated in 21% yield with 15% of cyclobutane **379a**. This observation is in agreement with what reported by Khurana and co-workers, that the use of 95% ethanol decreased the yield of the reaction, and they insisted on working with a dry solvent. This too, shows that the quality of the solvent is a parameter to consider.

Although studying the physical properties of the generated nanoparticles is beyond the purpose of this research, it was suggested to study the influence of the stirring nature on the reactivity of the catalyst. Therefore, after setting up the reaction at 0 °C and warming it gradually to room temperature, the reaction flask was submitted to sweeping using ultrasounds to activate the nanoparticles. After 19 h, the formation of a complex mixture was detected on TLC and by NMR spectroscopy (entry 6).

Besides the mechanical stirring and under ultrasounds for a long period of time, the temperature reached 25-30 °C, which most likely affected the reactivity too. Big-sized black precipitate was also observed indicating the formation of nickel aggregates, which eventually reduced the catalyst's efficiency.



entry	salt (eq.)	NaBH <sub>4</sub> (eq.)	time (h)	yield % (ratio) <sup>a</sup>		
				380a:339b	332a(trans:cis)	379a
1	NiCl <sub>2</sub> .6H <sub>2</sub> O (1.0)	7.0	12	30 (70:30)	17 (30:70)	16
2	CoCl <sub>2</sub> .6H <sub>2</sub> O (1.0)	7.0	19	6 (80:20)	37 (42:58)	16
3 <sup>b</sup>	NiCl <sub>2</sub> .6H <sub>2</sub> O (1.0)	7.0	20	9 (72:28)	17 (52:48)	8
4	NiCl <sub>2</sub> (1.0)	7.0	21	53 (75:25)	23 (20:80)	5
5 <sup>c</sup>	NiCl <sub>2</sub> (1.0)	7.0	26	46 (67:33)	21 (14:86)	15
6 <sup>d</sup>	NiCl <sub>2</sub> (1.0)	7.0	19	complex mixture		
7	NiCl <sub>2</sub> (1.0)	7.0	39	50 (> 95:< 5)	27 (30:70)	7
8	NiCl <sub>2</sub> (2.2)	7.0	41	52 (70:30)	8 (< 5:> 95)	14
9	NiCl <sub>2</sub> (2.2)	20.0	42	54 (> 95:< 5)	6 (< 5:> 95)	6
10	NiCl <sub>2</sub> (3.0)	20.0	19	complex mixture		
11 <sup>e</sup>	NiCl <sub>2</sub> (2.2)	20.0	42	60 (100:0)	0	13
12 <sup>e</sup>	CoCl <sub>2</sub> (2.2)	20.0	43	4 (100:0)	56 (nd)	6
13 <sup>e</sup>	NiCl <sub>2</sub> (1.0)	7.0	41	52 (82:18)	3 (37:63)	16

**Table IV.1.** Screening conditions for reduction of **332a** using nickel boride. *Reagents and conditions:* EtOH (0.07 M), 0 to 20 °C. <sup>a</sup> Isolated yields, NMR ratios. <sup>b</sup> NiCl<sub>2</sub>.6H<sub>2</sub>O dried in oven. <sup>c</sup> EtOH unpurified. <sup>d</sup> Ultrasounds. <sup>e</sup> EtOH (0.025 M).

Next, the time frame was studied; doubling the reaction time did not help to fully convert the starting material, which was recovered in 27% yield as a mixture of (1*R*,4*R*)-**trans-332a** and (1*R*,4*S*)-**cis-332a** in 30:70 ratio, while cyclobutane **379a** was isolated in 7% yield (entry 7). Lactams were isolated in 50% combined yield and surprisingly, in > 95% ratio of the lactam **380a**. Only traces of the cyclobutane lactam **339b** were detected through <sup>1</sup>H NMR spectrum. Such a result suggests that the reduction step precedes the ring-opening. In addition, if the cyclobutane ring-opening occurred first, reduction of the nitrile into an amine could be followed by reaction with the ester function at C-4 leading to a six-membered ring lactam which was not detected in these experiments. In previous

experiments (such as in entry 4), the shorter reaction time led to a mixture of the cyclized lactams with or without the cyclobutane ring-opening. These data were supported by another experiment where the same result was observed; with a reaction time of ~ 22 h (on 0.29 mmol scale), a mixture of the closed- and opened-ring compounds was formed. The re-submission of this fraction to the nickel boride reducing system, gave the ring-opened lactam in a quantitative yield. This confirms that the reducing system induces the ring-opening of the cyclobutane.

In contrast, this shows that the reaction time had no influence on the full conversion of the starting material under these conditions. Thus, it was looked carefully at the amount of nickel salt present in the reaction mixture, because of the inherent instability of nickel boride. To confirm this, an experiment was conducted using 2.2 eq. of  $\text{NiCl}_2$ . A large quantity of the starting material was reduced and only 8% were recovered (entry 8). The cyclobutane **379a** itself was isolated in 14% yield. While the lactams **380a** and **379b** were isolated in 52% yield, unexpectedly, in a 70:30 ratio. This indicates that not only time is important for the ring-opening to occur, but also the nature of the nickel boride nanoparticles. Many groups pointed out the influence of the stoichiometric ratio of  $\text{NiCl}_2/\text{NaBH}_4$  on the reaction's result.<sup>320</sup> It is believed that at a specific stoichiometry, the active nickel boride nanoparticles are formed. Thus, it was decided to increase the quantity of sodium borohydride to 20 eq. to have a large excess of hydride and boron source in the medium, and compensate for the catalytic decomposition of the borohydride by the newly-formed nickel boride. Such conditions allowed obtaining the lactam **380a** in 54% yield with only traces of the lactam **339b**, yet, the full conversion of the starting material was not observed and 6% were recovered (entry 9). From the reaction mixture, cyclobutane **379a** was also isolated in 6% yield.

Increasing the amount of nickel chloride to 3 eq. to fully convert the starting material, led a complex mixture after 19 h (entry 10). At this point, it was decided to find out unambiguously whether the isomer (1*R*,4*S*)-**cis-332a** endures full reduction or not. The isolated diastereomer (1*R*,4*S*)-**cis-332a** was submitted to the reduction system used in entry 9, in the presence of 2.2 equivalents of  $\text{NiCl}_2$ . After 27 h of reaction, the opened product **380a** was obtained in 36% yield, as a mixture of 2 isomers in a ratio of 1:1 (*data not shown*). 43% of the starting material were also recovered. This confirms that this isomer is prone to reduction albeit in a much slower rate.

Knowing that it is possible to reduce the isomer (1*R*,4*S*)-**cis-332a** allowed the pursuit of the optimization. It was proposed that by changing the size of the nickel boride nanoparticles or improving their dispersity, these particles would be able to reduce the cyclobutane ring. For this reason, the concentration of the medium was questioned since such a factor would eventually change the dynamic of the medium and then, the nature of the particles.<sup>355</sup> Thus, the reaction concentration was lowered to 0.025 M, and indeed, a full conversion of the starting material occurred (entry 11). Under these conditions, the major isomers were fully transformed into the lactam **380a** in a 60% yield, while the minor isomers produced 13% of the amino-cyclobutane **379a**. In general, a concentration between 0.02 and 0.03 M was found to be optimal for this reaction.

For comparison, cobalt chloride was utilized again under the optimized conditions; a considerable difference in reactivity was noticed. Only 4% of the lactam **380a** were isolated together

with 56% of the starting material (entry 12). The latter showed the presence of both major diastereomers in approximately the same ratio (56:44), and a small quantity of the minor isomers was present. The reduced cyclobutane **379a** itself was isolated in 6% yield. The fact that **380a** was detected, indicates that the cobalt boride is also capable of opening the cyclobutane ring after the cyclization step, albeit in a much less efficient manner.

Finally, the original conditions with 1 eq. of  $\text{NiCl}_2$  were repeated in a 0.025 M concentrated medium (entry 13). Compared to entry 7, the lactams **380a** and **339b** were isolated in a similar yield of 52%, however, the ring-opening was less efficient giving both products in 82:18 ratio. In contrast, the isomer *cis* (1*R*,4*S*)-**332a** was almost completely reduced and only 3% were recovered, as compared to 27% with 0.07 M concentration. Cyclobutane **379a** was also isolated in a higher yield of 16%.

During these investigations, the precursors were purified before use, but, for later studies, it was observed that using the crude precursor had no effect on the efficiency of the reaction. Based on observations in manipulating heterogeneous catalysis, the reactions were performed from the beginning under good stirring to prevent the formation of aggregates. Sodium borohydride was the last reagent to add to the reaction mixture, which is already set at 0 °C. The formation of the characteristic borides is exothermic, and usually, it is accompanied by vigorous  $\text{H}_2$  evolution. When the reaction was carried out on a large scale (2.0-4.5 mmol),  $\text{NaBH}_4$  was added slowly for 15-20 minutes, and the reaction was set up at 0-5 °C for at least 1 hour even if no more bubbling was observed. If not, the temperature rises and an explosion happens (violent reaction).

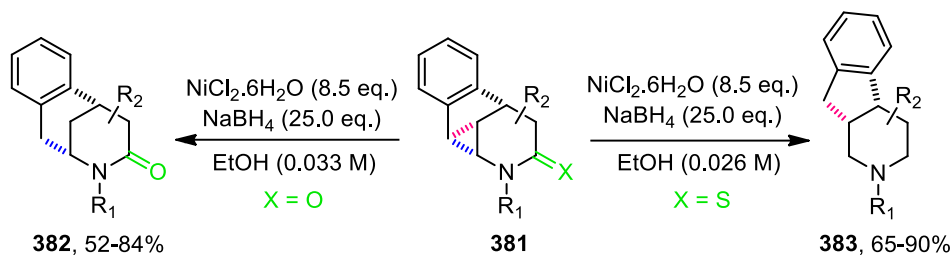
This work advocates the statements in the literature<sup>320,356,357</sup> that this reaction needs to be studied carefully, as a parameter may change the behavior of the reducing agent. Yet, this also leaves a possibility to inspire new transformations using transition metals/borohydrides to access new frameworks in an efficient way. The work on the ring-opening showed how this process is highly related to the substrate's structure and to different other factors at the same time.

Finally, for comparison consideration, the cyclobutane **332a** was submitted to hydrogenation under 20 atm using Raney<sup>®</sup>-nickel in ethanol. This reaction resulted in recovery of the starting material, and no conversion was observed (*data not shown*). Such an outcome is in agreement with the claimed higher reactivity of nickel boride compared to Raney<sup>®</sup>-nickel.<sup>358</sup>

## 4.2. Reported nickel boride-mediated ring-opening

Two months after establishing this reaction, an interesting article came to light.<sup>359</sup> The report describes the cyclopropane ring-opening of cyclopropane-fused benzomorphan substrates **381**, by the intermediacy of nickel boride (Scheme IV.11). Depending on the substitution present on the molecule (oxo or thio), a selective opening of the cyclopropane ring was observed. This method gave access to fused indenopiperidine and bridged benzomorphanone derivatives **382** and **383** starting from oxo and thio analogs of **381**, respectively. The authors mentioned that the cyclopropane ring-opening was found to be a combination of electronic effects and ring tensions resulting from the bridged structures,

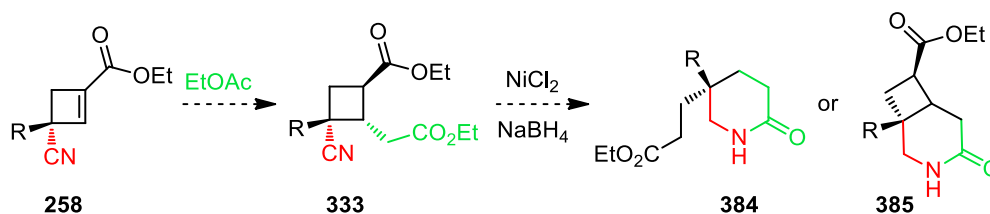
which constitute a powerful driving force towards this end. Remarkably, this reaction was performed in a concentration range of 0.026-0.033 M, the same range that was found optimal for the reduction of cyclobutanes with nickel boride.



**Scheme IV.11.** Cyclopropane ring-opening in oxo and thio benzomorphan derivatives, with nickel boride.<sup>359</sup>

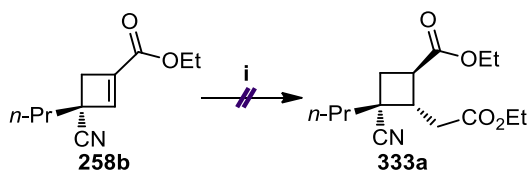
## 5. Attempts to access mono-ester lactams

Although the diester lactam **380a** was obtained in an efficient cascade sequence, this, however, requires removal of the ester  $\alpha$ - to the amide to further access the final target. Thus, it was suggested that the 1,4-addition of an ethyl acetate fragment on the cyclobutene carboxylate **258** would shorten the sequence (Scheme IV.12). Moreover, the outcome of this reaction would provide insights into the role of the ester  $\alpha$ - to the amide in lactam **380a** above.



**Scheme IV.12.** Strategy towards the synthesis of a mono-ester lactam backbone.

Foremost, an attempt to add an ethyl acetate anion to the enone **258b** was investigated using Lithium tetramethylpiperidide (LiTMP) as a non-nucleophilic base (Scheme IV.13). However, after 24 h of reaction, no conversion was observed and the starting material was recovered unchanged.



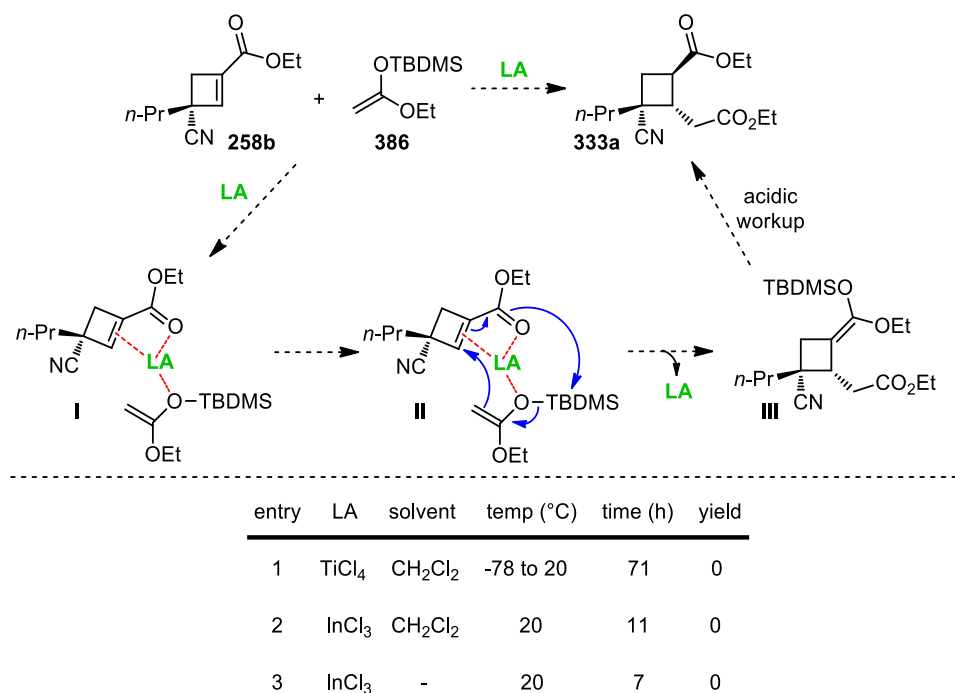
**Scheme IV.13.** Preliminary attempt for ethyl acetate addition onto enone **258**. *Reagents and conditions:* i) EtOAc (2.0 eq.), LiTMP (2.0 eq.), THF (0.1 M), 0 to 20 °C, 24 h.

It was then proposed that such a scaffold could be accessed through the Mukaiyama version of the Michael reaction.<sup>360</sup>

It was believed that the cyclobutene **258b** could be activated by coordination of a strong Lewis acid with the carbonyl functional group, facilitating the nucleophilic attack of the ketene silyl acetal **386**, and delivering the corresponding Michael adduct **333a** (Scheme IV.14). The use of titanium tetrachloride as the Lewis acid, however, did not provide any reaction even after several days, and the starting material was recovered (Scheme IV.14, entry 1). Similarly, no reaction occurred using indium trichloride<sup>361</sup> in a solvent or under neat conditions (entries 2 and 3). These results correlate



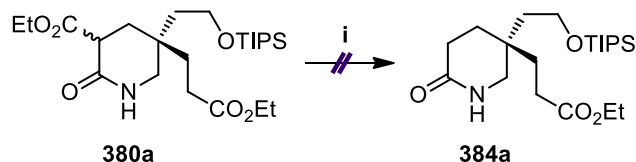
with what was observed during the studies on the “push-pull” system, and it is possible that these pseudo-acidic conditions are not strong enough to activate the enone **258b**. Thus, this strategy was not investigated further.



**Scheme IV.14.** Attempts for ethyl acetate addition onto enone **258b** through Mukaiyama-Michael reaction. *Reagents and conditions:* **386** (2.0 eq.), LA (0.2 eq.), CH<sub>2</sub>Cl<sub>2</sub> (0.1 M).

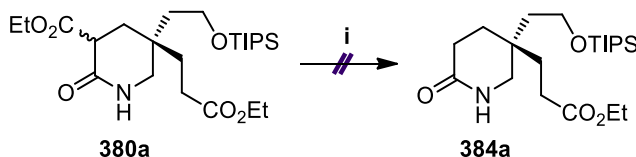
## 6. Synthesis of bicyclic lactam model bearing a protected alcohol chain

Considering the above failure, it was decided to work on diester **380a**, and more precisely on the decarboxylation of the  $\beta$ -amidoester. The Krapcho conditions<sup>348,349</sup> led only to traces of the product with other degradations (Scheme IV.15).



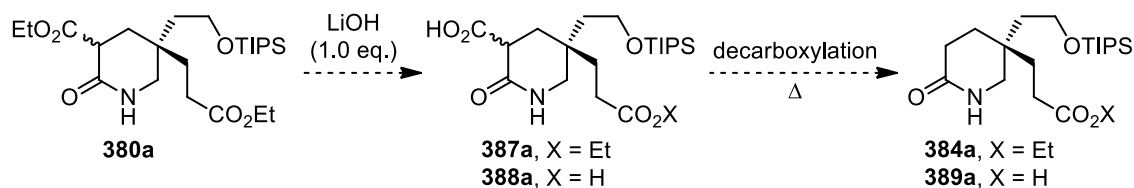
**Scheme IV.15.** Application of Krapcho's conditions to lactam **380a**. *Reagents and conditions:* i) LiCl (2.0 eq.), DMSO/H<sub>2</sub>O, 155 °C, 18 h.

During their work on the total synthesis of aspidophytine, Padwa and co-workers also observed unsatisfying results and low yields using Krapcho's conditions.<sup>362</sup> Instead, they heated an advanced intermediate in refluxing wet acetonitrile in the presence of MgI<sub>2</sub>, playing with the chelating properties of Mg(II) cations.<sup>363</sup> Unfortunately, when applied, Padwa's protocol led to no reaction and the starting material was recovered (Scheme IV.16).



**Scheme IV.16.** Application of Padwa's conditions to lactam **380a**. *Reagents and conditions:* i) MgI<sub>2</sub> (3.0 eq.), wet CH<sub>3</sub>CN (0.05 M), 82 °C, 23 h.

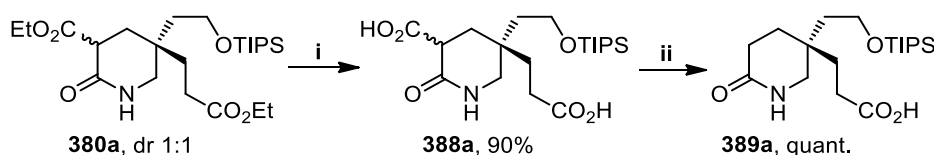
Alternatively, it was suggested to submit the diester **380a** to basic hydrolysis, generating a carboxylic acid next to the carbonyl, which would undergo decarboxylation once heated (Scheme IV.17). A selective mono-saponification was however anticipated to be challenging as shown below.



**Scheme IV.17.** Alternative hydrolysis and decarboxylation plan.

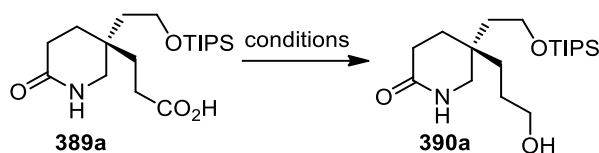
Thus, submitting the amide **380a** to 1 equivalent of lithium hydroxide led to various products, suggesting that the saponification occurred on both sites, giving a mixture of mono- and dicarboxylic acids in addition to the remaining starting material. Although these products were not isolated, the addition of another equivalent of LiOH to the reaction mixture converted the majority of the remained esters into the dicarboxylic acid. The NMR showed that a small quantity of ester signals was still present in the mixture.

Therefore, the saponification was repeated in the presence of an excess of lithium hydroxide, to afford the dicarboxylic acid **388a** as a very polar product in 90% crude yield on a 2 mmol scale (Scheme IV.18). The extraction was eventually optimized to furnish **388a** in an optimal and clean manner. The crude dicarboxylic acid **388a** was then heated in THF to afford the monocarboxylic acid **389a** in a quantitative yield. It is worth noting that **389a** was isolated by simple evaporation of THF and dryness under vacuum. A temperature of 70 °C was found to be ideal to afford the desired scaffold in a clean manner and complete conversion after 0.5–4 h, depending on the scale. If the heating proceeded for a long time (*e.g.*, > 24 h) degradation of the substrate was observed. Other solvents such as toluene or *m*-xylene afforded the desired product but less cleanly. Refluxing dichloromethane, however, did not succeed at decarboxylating the substrate **388a**.



**Scheme IV.18.** Saponification and decarboxylation of diester **380a**. *Reagents and conditions:* i) LiOH (5.0 eq.), EtOH/H<sub>2</sub>O: 4/1, 20 °C, 12 h; ii) THF (0.08 M), 70 °C, 3 h.

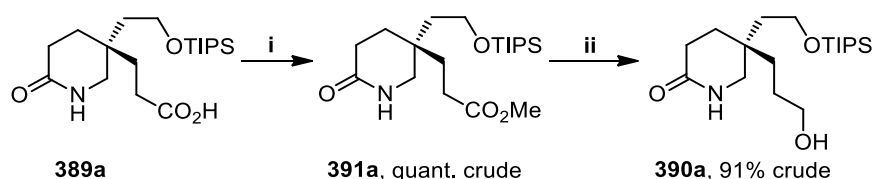
Once decarboxylated, the cyclic lactam **389a** was submitted to chemoselective reduction conditions in the presence of the amide functionality. At first, reducing the acid group into alcohol using the borane-THF complex gave only traces of the desired product (Table IV.2, entry 1). Increasing the temperature did not give better results even after 18 h (entry 2). With LAH solution, 31% of the desired alcohol were isolated (entry 3). However, when diethyl ether was used instead of THF as a solvent, the yield decreased to 21% (entry 4). Although the desired product was successfully obtained, with such a low yield the transformation was not considered efficient.



entry	reagent (eq.)	solvent	time (h)	yield (%)
1	BH <sub>3</sub> .THF (3.0)	THF	13	traces
2 <sup>a</sup>	BH <sub>3</sub> .THF (3.0)	THF	18	traces
3	LAH (1.25)	THF	12	31
4	LAH (1.25)	Et <sub>2</sub> O	12	21

**Table IV.2.** Reduction of **389a** into alcohol. *Reagents and conditions:* solvent (0.02 M), 0 to 20 °C. <sup>a</sup> 35 °C.

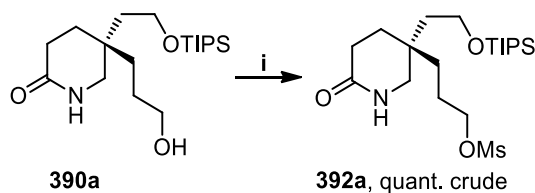
The product issued from decarboxylation was then submitted to a fast esterification using (trimethylsilyl)diazomethane, to regenerate the alkylated ester in a quantitative yield (Scheme IV.19). The ester **391** was then reduced with LAH in THF to afford the alcohol **390a** in 91% crude yield. Performing the reaction in diethyl ether as the solvent, under the optimized conditions, gave the hydroxy-lactam **390a** in 45% yield. Although organoboranes such as NaBH<sub>4</sub> and LiBH<sub>4</sub> were described to selectively reduce esters into alcohol, no reaction was observed with these reagents even after 18 h. The reported yields describe the results after optimization of the extraction protocol (*details in the experimental part*). Most importantly, these reactions were clean and no purification was needed to pursue the following steps.



**Scheme IV.19.** Esterification and reduction of **389a** into alcohol. *Reagents and conditions:* i) TMSCHN<sub>2</sub> (1.5 eq.), CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 5/1 (0.12 M), 0 to 20 °C, 1 h; ii) LAH (1.25 eq.), THF (0.02 M), 0 to 20 °C, 8 h.

It is worth mentioning that the decarboxylation-esterification-reduction process was performed by subsequent addition of reagents/concentration of solvents in a one-pot fashion without any isolation of the reaction intermediates. Thus, this sequence was considered as a one-step transformation.

The free alcohol **390a** was then activated by introducing a mesylate as a leaving group, in a quantitative yield (Scheme IV.20).



**Scheme IV.20.** Activation of free alcohol **390a** by mesylate. *Reagents and conditions:* i) MsCl (1.2 eq.), Et<sub>3</sub>N (2.0 eq.), CH<sub>2</sub>Cl<sub>2</sub> (0.09 M), 0 to 20 °C, 6 h.

This group was then submitted to displacement under the commonly reported conditions.<sup>364,365</sup> However, no reaction was observed in DMF at room temperature (Table IV.3, entry 1). When heated

at 40 °C, a partial conversion occurred to deliver the bicyclic lactam **341a** in 10% yield (entry 2). Heating at a higher temperature did not lead to a better conversion, and **341a** was isolated in a 6% yield (entry 3). Changing the solvent to THF did not produce any conversion at room temperature (entry 4), while under reflux, a decomposition of the substrate took place (entry 5).

**392a**  $\xrightarrow[\text{conditions}]{\text{NaH (1.5 eq.)}}$  **341a**

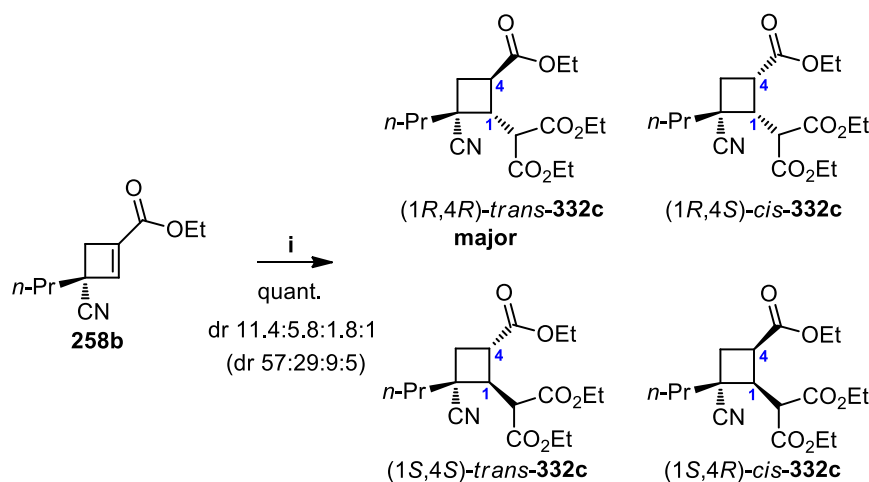
entry	solvent (0.05 M)	conditions	yield (%)
1	DMF	20 °C, 7 h	0
2	DMF	40 °C, 12 h	10
3	DMF	70 °C, 19 h	6
4	THF	20 °C, 10 h	0
5	THF	66 °C, 16 h	comp. mix.

**Table IV.3.** Synthesis of bicyclic lactam model **341a**.

This bridgehead amide (also called anti-Bredt molecule) possesses an oily aspect at room temperature but it solidifies in the freezer, a characteristic that was observed with the derivatives of this molecule.<sup>366</sup> The infrared spectrum showed a sharp, strong carbonyl absorption (stretching  $\nu_{\text{C=O}}$ ) at 1684  $\text{cm}^{-1}$ , while the  $^{13}\text{C}$  NMR for the carbonyl carbon at 184.7 ppm indicates that this lactam **341a** has a moderate distortion of the amide bond, as observed for the twisted amides reported by Buchanan and co-workers.<sup>367</sup>

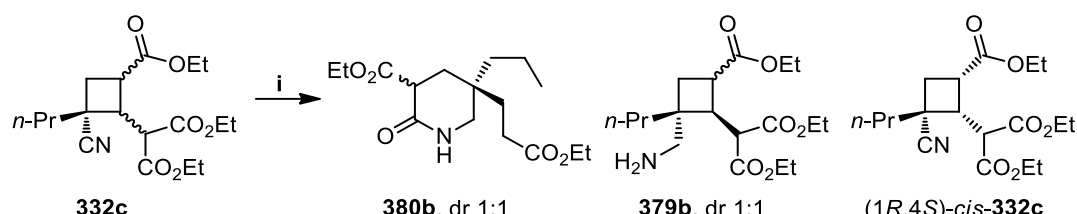
## 7. Synthesis of bicyclic lactam model bearing a propyl chain

Based on the results discussed above, another cyclobutene model was manipulated to confirm the efficiency of the developed strategy. The cyclobutene **258b** bearing a propyl side chain was submitted to 1,4-conjugate addition of diethyl malonate to deliver the cyclobutane **332c** in a quantitative yield (Scheme IV.21).



**Scheme IV.21.** Conjugate addition on cyclobutene **258b**. Reagents and conditions: i) **323c** (1.0 eq.), NaH (1.0 eq.), THF (0.1 M), 0 to 20 °C, 5 h.

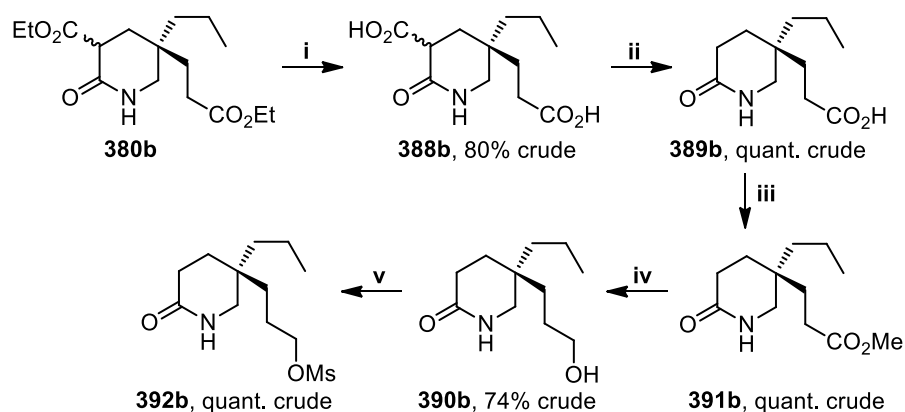
The cyclobutyl malonate **332c** was then submitted to the nickel boride's optimized conditions, to afford the lactam **380b** in 75% yield on a 4 mmol scale, alongside with the amine **379b** in 10% yield (Table IV.3, entry 1). To confirm whether the medium's concentration would have an effect on the reduction reaction of this model, the reaction was performed in a 0.07 M solution of ethanol. As expected, the products **380b** and **379b** were isolated in 44 and 10% yields respectively, altogether with the minor diastereomer (1*R*,4*S*)-**cis-332c**, which was recovered in 10% yield (entry 2). This transformation is thus relatively independent of the steric hindrance that might be created by the cyclobutane's side chain.



entry	concentration	time (h)	yield (%)
1	0.025 M	70	<b>380b</b> (75), <b>379b</b> (10)
2	0.07 M	72	<b>380b</b> (44), <b>379b</b> (10), (1 <i>R</i> ,4 <i>S</i> )- <b>cis-332c</b> (10)

**Table IV.3.** Reduction of cyclobutane **332c** using nickel boride. *Reagents and conditions:* i) NiCl<sub>2</sub> (2.2 eq.), NaBH<sub>4</sub> (20.0 eq.), EtOH, 0 to 20 °C.

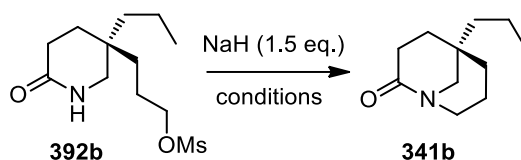
The lactam **380b** was then saponified to give the carboxylic acid **388b** in 80% crude yield (Scheme IV.22). This product was decarboxylated in refluxing THF to afford **389b** in a quantitative yield. Subsequent modification afforded the ester **391b** also in a quantitative crude yield, which was then reduced by LAH into the alcohol **390b** in 74% yield. Finally, the alcohol was activated into a better leaving group by the incorporation of a mesylate fragment, giving the mesylate lactam **392b** in a quantitative crude yield.



**Scheme IV.22.** Sequential synthesis of mesylate **392b**. *Reagents and conditions:* i) LiOH (5.0 eq.), EtOH/H<sub>2</sub>O: 3/1 (0.15 M), 20 °C, 12 h; ii) THF (0.08 M), 70 °C, 3 h; iii) TMSCHN<sub>2</sub> (1.5 eq.), CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 5/1 (0.12 M), 0 to 20 °C, 1 h; iv) LAH (1.25 eq.), THF (0.1 M), 0 to 20 °C, 3 h; v) MsCl (1.2 eq.), Et<sub>3</sub>N (2.0 eq.), CH<sub>2</sub>Cl<sub>2</sub> (0.05 M), 0 to 20 °C, 6 h.

Finally, the mesylate **392b** was submitted to nucleophilic substitution in the presence of sodium hydride. When DMF was used, a partial conversion was observed at room temperature after 24 h

(Table IV.4, entry 1). When the temperature was increased to 70 °C, a full conversion was observed after 10 h, and **341b** was isolated in 15% yield after column chromatography. The reaction was then repeated by heating directly at 70 °C. The full conversion was observed after 14 h and the purification was carried out using neutralized silica gel to isolate 40% of the bicyclic lactam **341b** over 4 steps (entry 2). When using THF as the solvent, no reaction occurred at room temperature (entry 3) nor at reflux (entry 4), and the starting material was recovered unchanged. Contrary to what was observed with lactam **341a**, no major decomposition of the substrate took place in refluxing THF.



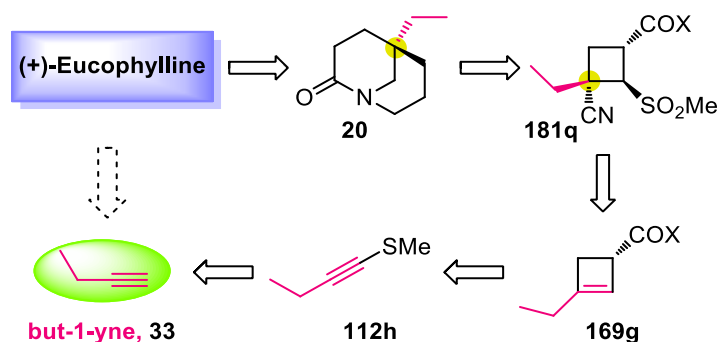
entry	solvent (0.05 M)	conditions	yield (%)
1	DMF	20 °C for 24 h, then 70 °C for 10 h	15
2	DMF	70 °C, 14 h	40
3	THF	20 °C, 16 h	0
4	THF	66 °C, 10 h	0

**Table IV.4.** Synthesis of bicyclic lactam **341b** bearing a propyl chain.

This anti-Bredt molecule possesses a low melting point as observed with lactam **341a**. The infrared spectrum showed a sharp, strong carbonyl absorption (stretching  $\nu_{C=O}$ ) at 1682  $\text{cm}^{-1}$ , and the  $^{13}\text{C}$  NMR for the carbonyl carbon at 184.7 ppm indicates too, that **341b** has a moderate distortion of the amide bond with a twist angle ( $\tau$ )  $\approx 20^\circ$ .

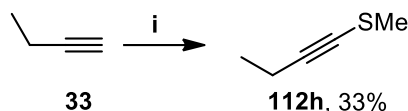
## 8. Synthesis of bicyclic lactam model bearing an ethyl side chain

To apply this developed method to the synthesis of eucophylline, a bicyclic lactam **20** bearing an ethyl side chain has to be synthesized (Scheme IV.23). This would arise from cyanosulfone **181q** with the installed quaternary center after submitting the cyclobutene **169g** to the sulfonyl-cyanation reaction. The cyclobutene bearing the ethyl side chain itself has to derive from the [2+2] cycloaddition of *N*-acyloxazolidinone with alkyne sulfide **112h**. The latter would be obtained from the corresponding alkyne, but-1-yne **33**.



**Scheme IV.23.** Possible alkyne precursor necessary for the synthesis of eucophylline. X = oxazolidinone.

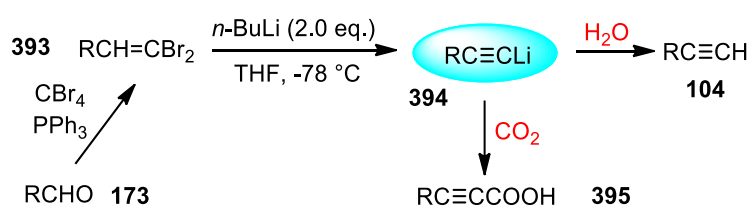
Since but-1-yne is a gas at room temperature (boiling point:  $\sim 8\text{ }^{\circ}\text{C}$ ), the reaction previously applied to introduce a thiomethyl fragment into alkynes was modified using but-1-yne in excess ( $\sim 3$  eq.) (*experimental part*). The expected product was isolated after distillation in 33% yield as a colorless liquid with a low boiling point (Scheme IV.23). The low yield was related to the traces of water possibly present in the medium, which quench the organolithium reagent. When lower stoichiometry of but-1-yne was used, only traces of the desired product were obtained.



**Scheme IV.23.** Synthesis of butyne sulfide **112h** from but-1-yne. *Reagents and conditions:* i) 1. But-1-yne (3.0 eq.), *n*-BuLi (1.06 eq.), THF (0.65 M),  $0\text{ }^{\circ}\text{C}$ , 30 min; 2.  $\text{Me}_2\text{S}_2$  (1.0 eq.),  $20\text{ }^{\circ}\text{C}$ , 2 h.

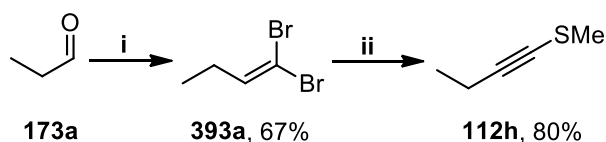
Further optimization of this method was not possible due to the lack of additional supply of but-1-yne. In fact, this reagent is highly expensive (CAS: 107-00-6; Sigma Aldrich supplier; 646 €/100 g), which restricted its use. Thus, a cheaper method was developed.

Corey and Fuchs transformed aldehydes **173** by chain extension into dibromo olefins **393** using carbon tetrabromides and triphenylphosphine (Scheme IV.24).<sup>368</sup> The brominated substrates are then transformed into lithium acetylides **394** in the presence of 2 equivalents of *n*-BuLi. Such intermediates could be transformed into the corresponding terminal alkynes **104** by quenching **394** with water, or into acetylene carboxylic acids **395** under  $\text{CO}_2$  atmosphere.



**Scheme IV.24.** Synthesis of acetylene derivatives from aldehydes.

Based on this report, it was proposed that the organolithium intermediate would react with dimethyl disulfide to generate the desired butyne sulfide. This approach was applied to propionaldehyde **173a** to generate 1,1-dibromobut-1-ene **393a** in a 67% yield (Scheme IV.25). The latter was then submitted to an excess of *n*-BuLi to generate the butynyl-lithium intermediate which was quenched *in situ* with dimethyl disulfide, furnishing the thiomethyl butyne **112h** in 80% yield. This reaction was repeated several times to give the butynyl derivative in 60-80% yield range.

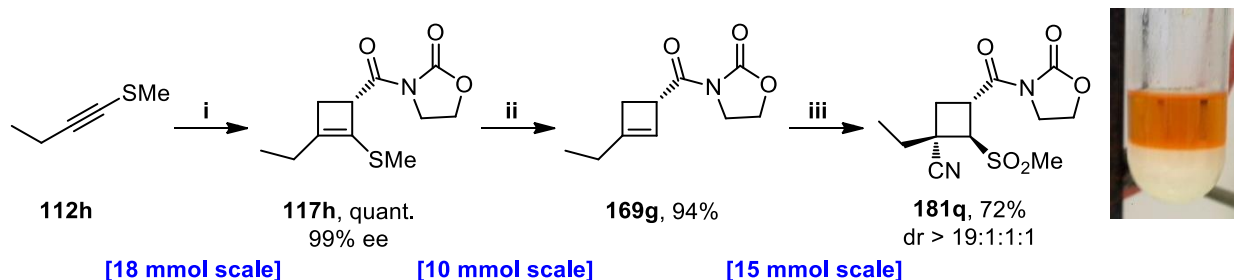


**Scheme IV.25.** Synthesis of butyne sulfide **112h** from propionaldehyde. *Reagents and conditions:* i)  $\text{CBr}_4$  (2.0 eq.),  $\text{PPh}_3$  (4.0 eq.),  $\text{CH}_2\text{Cl}_2$  (0.22 M),  $0$  to  $20\text{ }^{\circ}\text{C}$ , 3 h; ii) 1. *n*-BuLi (2.3 eq.), THF (0.65 M),  $-78\text{ }^{\circ}\text{C}$ , 1 h, then  $20\text{ }^{\circ}\text{C}$ , 1 h; 2.  $\text{Me}_2\text{S}_2$  (1.0 eq.),  $0$  to  $20\text{ }^{\circ}\text{C}$ , 2 h.

After succeeding at developing a reliable method for the synthesis of butyne sulfide **112h**, this alkyne was engaged in a [2+2]-cycloaddition with *N*-acyloxazolidinone, to deliver the chiral

thiomethyl-cyclobutene **117h** bearing an ethyl side chain, in a quantitative yield (on ~ 18 mmol scale) and an excellent enantiomeric excess of 99% (Scheme IV.26). The cyclobutene was then submitted to reduction under the optimized conditions with Lindlar's catalyst, furnishing the cyclobutene **169g** in 94% yield on a 10 mmol scale (84% yield on a 19 mmol scale after 24 h of reaction). In fact, when the reaction was left after full conversion for a longer time, traces of over-reduced cyclobutane were observed, which was not the case in previous examples. This could be rationalized by the small size of the ethyl chain, which favors the over-reduction step. This undesired transformation could be controlled when necessary, by diluting the reaction's concentration, adding more equivalents of oct-1-ene, or simply by stopping the reaction directly once finished.

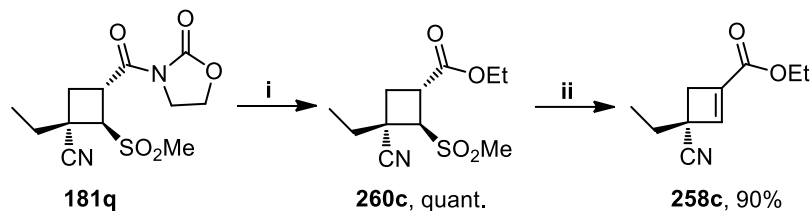
The synthesized cyclobutene **169g** was then engaged in the *p*-anisaldehyde catalyzed sulfonyl-cyanation to deliver the cyclobutane **181q** in high yield (on a 15 mmol scale) and diastereoselectivity. Interestingly, in the schlenk tube used for the reaction, the sulfonyl-cyanation product was formed as a white precipitate. Hence it was isolated from the reaction mixture by simple washing. This product was found insoluble in several solvents except dimethyl sulfoxide (and as traces in dichloromethane). It is interesting to notice how this molecule (melting point = 267 °C) has very different physical properties compared to the cyclobutane **181b** with only one carbon more on the side chain (melting point = 70 °C).



**Scheme IV.26.** Synthesis of highly functionalized cyclobutane **181q**. *Reagents and conditions:* i) 3-acryloyloxazolidin-2-one (1.0 eq.), (*R*)-**115** (0.11 eq.),  $\text{TiCl}_2(\text{OiPr})_2$  (0.1 eq.), toluene (0.25 M), 4 Å MS, 0 to 20 °C, 24 h; ii) Lindlar's catalyst (1.0 eq.),  $\text{Et}_3\text{SiH}$  (7.0 eq.), oct-1-ene (1.0 eq.), acetone (0.3 M), 50 °C, 16 h; iii)  $\text{MeSO}_2\text{CN}$  (2.0 eq.), *p*-anisaldehyde (0.2 eq.),  $\text{CH}_3\text{CN}$  (1.5 M), 325-400 nm, 48 h.

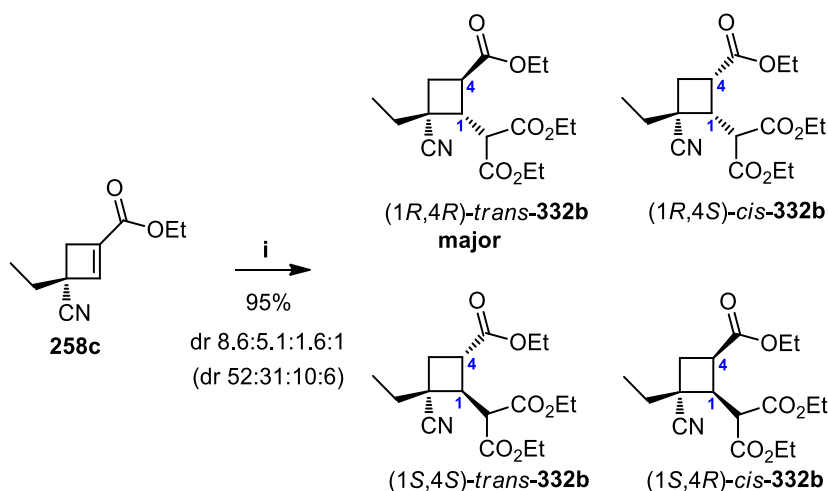
The cyclobutane **181q** was then transformed by transesterification into cyclobutane carboxylate **260c** in a quantitative yield (Scheme IV.27). Interestingly, the starting material was not soluble in ethanol even at reflux. Decreasing the reaction concentration to 0.02 M or adding a 3/1 mixture of EtOH/DMF or  $\text{CH}_2\text{Cl}_2$  did not help to solubilize the product or to accelerate the reaction. Anyway, the transformation occurs in a heterogeneous mixture to deliver the desired soluble product after 48 h. The ester **260c** was then desulfonylated under  $\text{Cs}_2\text{CO}_3$  conditions to generate the cyclobutene carboxylate **258c** in a 90% yield. Unlike the other cyclobutene carboxylates **258a** and **258b**, this product was found unstable and decomposes at room temperature after several hours. Once the product was formed, it was thus purified on short column chromatography then submitted to the next transformation without the need for storage.





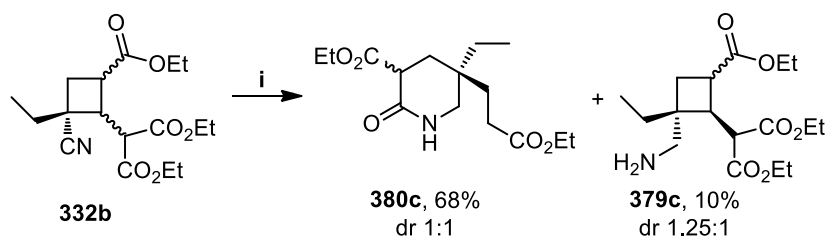
**Scheme IV.27.** Synthesis of cyclobutene carboxylate **258c**. *Reagents and conditions:* i) DMAP (0.5 eq.), EtOH (0.09 M), 78 °C, 48 h; ii) Cs<sub>2</sub>CO<sub>3</sub> (2.0 eq.), DMF (0.2 M), 70 °C, 13 h.

The addition reaction of diethyl malonate on the Michael acceptor **258c** occurred smoothly to afford the cyclobutane **332b** in 95% as a mixture of four diastereomers (Scheme IV.28). Such reaction was very clean and there was no need for purification of the crude reaction mixture. In fact, the same yields were obtained with or without purification.



**Scheme IV.28.** Conjugate addition on cyclobutene **258c**. *Reagents and conditions:* i) diethyl malonate (1.0 eq.), NaH (1.0 eq.), THF (0.1 M), 0 to 20 °C, 3 h.

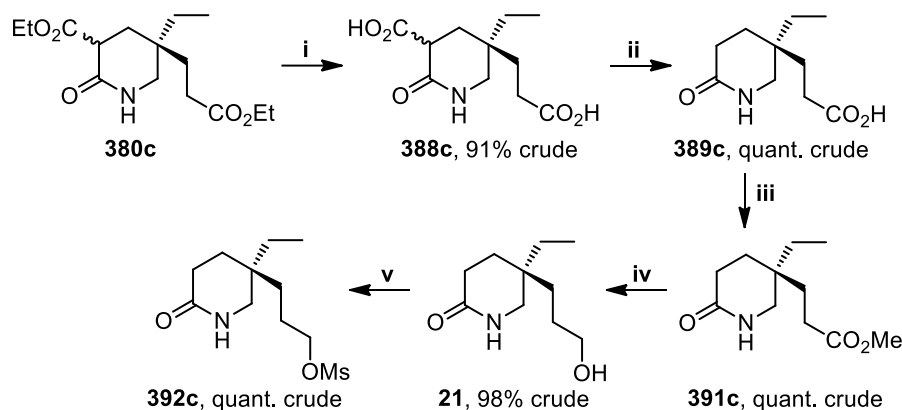
2 mmol of malonyl-cyclobutane **332b** were then submitted to the reduction/cyclization/ring-opening sequence under the optimal nickel boride conditions, to give the cyclic lactam **380c** in 68% yield together with the reduced cyclobutane **379c** in 10% yield (Scheme IV.29).



**Scheme IV.29.** Synthesis of cyclic lactam **380c** using nickel boride. *Reagents and conditions:* i) NiCl<sub>2</sub> (2.2 eq.), NaBH<sub>4</sub> (20.0 eq.), EtOH (0.025 M), 0 to 20 °C, 70 h.

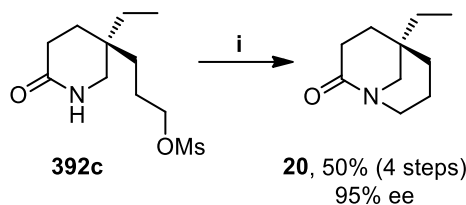
The cyclic lactam **380c** was then transformed through the above straightforward sequence into the bicyclic lactam **20** (Scheme IV.30). The saponification reaction gave the diacid **388c** in a 91% yield. In the first run, by using the same extraction method as before, **388c** was isolated in 40% yield. The re-extraction of the aqueous phase succeeded at isolating 50% of the product. This observation suggests that this product is much more polar than the other synthesized lactams **388a** and **388b**. Hence, the extraction method was optimized again, to deliver the expected yields in other runs. In

refluxing THF, the decarboxylation occurred smoothly to give the desired lactam carboxylic acid **389c** in a quantitative yield. This was then esterified quantitatively in a one-pot process, followed by the ester reduction to afford the alcohol **21** in 98% under the optimized treatment. The alcohol was then activated to give the mesylate **392c** in quantitative yield.



**Scheme IV.30.** Preparation of mesylate lactam **392c**. *Reagents and conditions:* i) LiOH (5.0 eq.), EtOH/H<sub>2</sub>O: 4/1 (0.15 M), 20 °C, 4 h; ii) THF (0.08 M), 70 °C, 3 h; iii) TMSCHN<sub>2</sub> (1.5 eq.), CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 5/1 (0.12 M), 0 to 20 °C, 1 h; iv) LAH (1.25 eq.), THF (0.035 M), 0 to 20 °C, 12 h; v) MsCl (1.1 eq.), Et<sub>3</sub>N (1.1 eq.), CH<sub>2</sub>Cl<sub>2</sub> (0.07 M), 0 to 20 °C, 3 h.

The mesylate **392c** was later submitted to nucleophilic substitution with sodium hydride in DMF. In contrast to what was observed with the other lactams, the reaction occurred at room temperature to give the bicyclic lactam **20** in 50% yield over four steps starting from **380c** (the transformation from **388c** to **21** is considered as one step since the intermediates were not isolated), and in an excellent enantiomeric excess as shown by HPLC analysis (Scheme IV.31). This reaction was repeated several times to give the bicyclic lactam in 30-50% yield range over four steps.



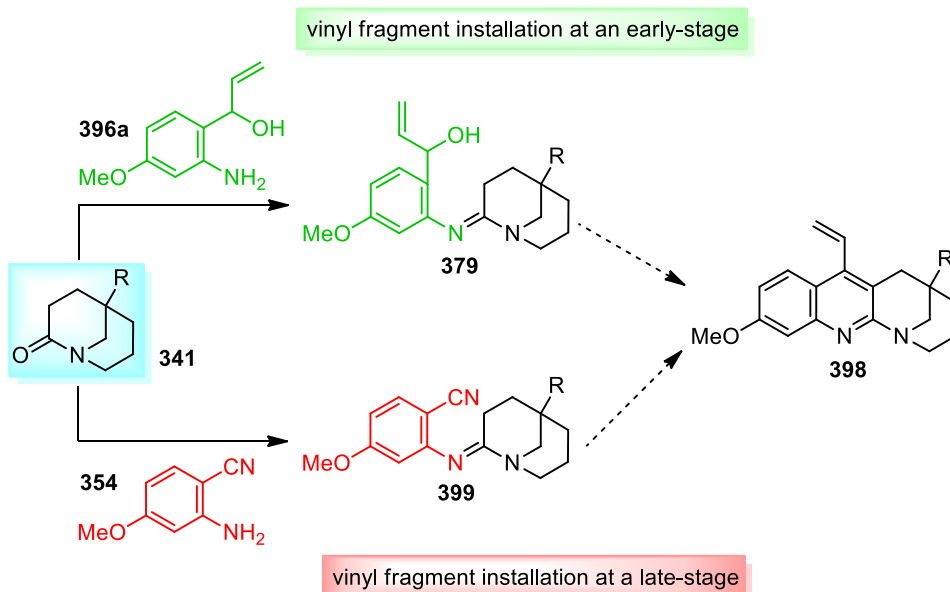
**Scheme IV.31.** Synthesis of bicyclic lactam **20**. *Reagents and conditions:* i) NaH (1.5 eq.), DMF (0.1 M), 0 to 20 °C, 12 h.

This sequence could certainly be shortened to some extent, for example, by performing a one-pot transesterification-sulfone elimination using K<sub>2</sub>CO<sub>3</sub> in ethanol, or by reducing the carboxylic acid directly into alcohol. However, the present sequence offers much better yields and reproducibility, with minimum purification steps and time consumption. Therefore, this sequence gives a straightforward access to strained chiral azabicyclo[3.3.1]nonane derivatives with different side chains. The bicyclic lactam **20** was obtained in 11 steps starting from 1,1-dibromo but-1-ene **393a** in ~ 15% overall yield. While the racemic bicyclic amide reported by Landais *et al.*<sup>48</sup> was obtained in 4 steps and 31% overall yield. The full analyses of the bicyclic lactam were in good agreement with those reported for the racemic template.

This twisted amide possesses an oily aspect at room temperature and solidifies in the freezer. So, it could not be recrystallized to be analyzed by X-ray diffraction studies. The infrared spectrum showed a sharp, strong carbonyl absorption (stretching  $\nu_{\text{C=O}}$ ) at  $1676\text{ cm}^{-1}$ , and the  $^{13}\text{C}$  NMR for the carbonyl carbon at  $184.8\text{ ppm}$  indicate that **20** has a moderate distortion of the amide bond. Hall *et al.*<sup>366</sup> reported that these lactams are hydrolyzable in water and polymerize on standing. Indeed, when leaving lactam **20** for weeks on the bench, decomposition started to occur.

## 9. Construction of the tetracyclic scaffold of eucophylline

The construction of the tetracyclic template of eucophylline from a bicyclic lactam would be achieved through a Friedländer-type annulation from an aniline derivative. Such a strategy could take place through two pathways, allowing the installation of a vinyl fragment on the tetracyclic core at an early- or a late-stage (Scheme IV.32). A propenylaniline **396a** for example, would be condensed with the bridgehead lactam **341** in the presence of a dehydrating agent to deliver the amidine intermediate **379** holding the vinyl fragment. This intermediate would undergo dehydration to deliver the methoxy-eucophylline core **398** *in situ* in a one-pot process, or in a two-steps sequence. Alternatively, a  $\text{POCl}_3$ -assisted annulation would proceed with the aminobenzoic nitrile **354** to give the amidine nitrile intermediate **399**, which would follow further treatment to allow the cyclization and the vinyl unit incorporation at a later stage.

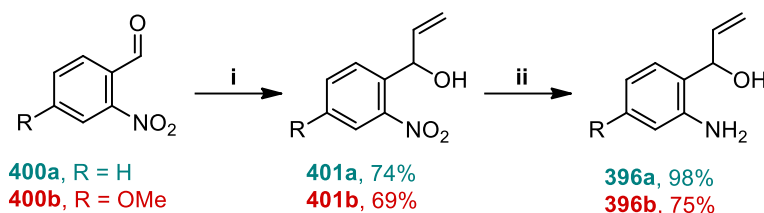


**Scheme IV.32.** Proposed pathways to access the eucophylline tetracyclic backbone, with possible incorporation of the vinyl unit at an early- or a late-stage.

### 9.1. Construction of tetracyclic scaffold using *ortho*-propenylanilines

The first envisioned pathway consists of installing the vinyl group on the aromatic backbone at an early stage. For this, the *ortho*-propenylaniline precursors were synthesized as a first step. The nitro benzaldehyde **400** was subjected to Grignard reaction using vinyl magnesium bromide as the reagent, to deliver the desired Grignard adducts **401a** and **401b** in high yields (Scheme IV.33).<sup>369–371</sup> The reduction of the nitro group was accomplished using zinc dust, giving **396a** and **396b** in 75 and

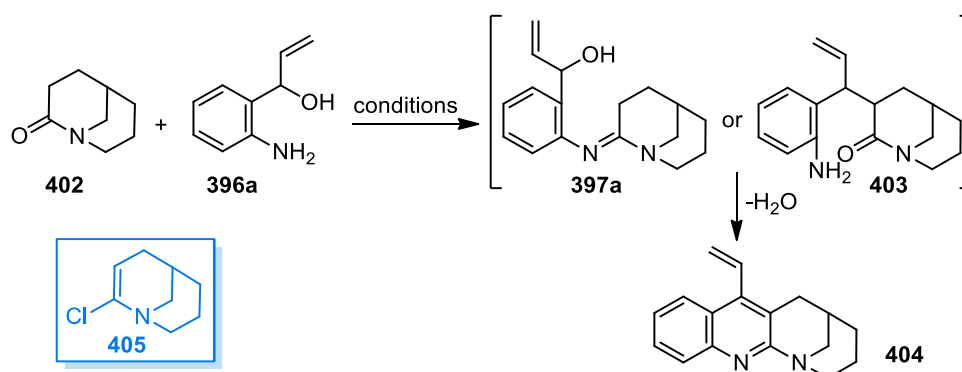
98% yields respectively.<sup>372</sup> Product **396b** was found to be more sensitive and prone to degradation than **396a**.



**Scheme IV.33.** Synthesis of propenylaniline derivatives. *Reagents and conditions:* i) vinyl magnesium bromide (1.5 eq.), THF (0.23 M), -78 to 20 °C, 12 h; ii) Zn dust (15.0 eq.), NH<sub>4</sub>Cl (5.0 eq.), EtOH/H<sub>2</sub>O: 4/1 (6.0 M), 20 °C, 7-12 h.

With the propenylaniline **396a** in hand, the POCl<sub>3</sub>-assisted Friedländer reaction was performed using the bridged lactam **402**<sup>373</sup> as a model. Under such conditions, only the  $\alpha$ -chloroenamine **405** was isolated in 15% yield (Table IV.5, entry 1). This unusually stable chloroenamine was observed by Landais *et al.* as the intermediate of the Friedländer annulation and was fully analyzed and characterized.<sup>48</sup> Although the POCl<sub>3</sub>-assisted condensation was found by the group to be optimal to favor the amidine synthesis, it was intended to investigate once more the reactivity of the bridged lactam, and the possibility to induce the condensation with the aromatic aniline.

The formation of the quinoline backbone was well reported through the modified Friedländer annulation, especially in the studies of camptothecin synthesis.<sup>374</sup> Thus, adding 4 Å molecular sieves as a dehydrating agent to drive the equilibrium towards the product formation, led to the decomposition of **396a**, while the bicyclic lactam remained intact (entry 2). In the presence of a Brønsted acid such as *p*-toluenesulfonic acid, anilines are condensed with ketones to deliver quinoline templates,<sup>375</sup> however, with the bicyclic lactam, such conditions did not work and only the decomposition of the propenylaniline was observed (entry 3). Based on this, it is clear that the propenylaniline does not survive in dehydrating or acidic conditions.



entry	reagents (eq.)	solvent <sup>a</sup>	temp (°C)	yield (%)
1	POCl <sub>3</sub> (1.1)	CH <sub>2</sub> Cl <sub>2</sub>	60	<b>405</b> (15)
2	4 Å MS	toluene	120	0
3	<i>p</i> -TsOH (0.6)	toluene	120	0

**Table IV.5.** Attempts for allyl amidine synthesis starting from bridged lactam **402**. *Reagents and conditions:* **396a** (1.5 eq.), 6-16 h. <sup>a</sup> Solvent (0.06 M).

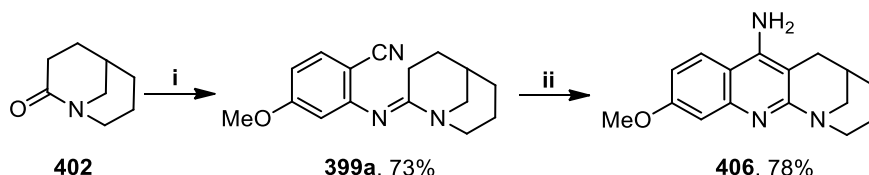
It was then suggested to perform the Friedländer annulation in a two-steps sequence starting from the  $\alpha$ -chloroenamine intermediate **405**. Under neutral conditions, no reaction was observed after 24 h, and both starting materials remained intact (Table IV.6, entry 1). Changing the solvent to toluene, while heating at a higher temperature did not lead to the desired product either (entry 2). This result shows the difference in reactivity between the propenylaniline and the *o*-aminobenzoic nitrile previously used by Landais *et al.* This might be related to steric issues, or to the lack of reactivity of the aniline **396**. Using the propenylaniline analog **396b** under neutral conditions did not lead to the desired product; instead, a mixture of decomposed products was obtained, illustrating the high instability of **396b** (entry 3). The addition of a base to promote the reaction also gave negative results (entry 4).

entry	R	reagent	solvent <sup>a</sup>	temp (°C)	yield
1	H	-	CH <sub>2</sub> Cl <sub>2</sub>	60	0
2	H	-	toluene	120	0
3	OMe	-	CH <sub>2</sub> Cl <sub>2</sub>	60	comp. mix.
4	H	[pyr.] (0.1 eq.)	CH <sub>2</sub> Cl <sub>2</sub>	60	0

**Table IV.6.** Attempts for allyl amidine synthesis starting from **405**. *Reagents and conditions:* **396** (1.5 eq.), 24 h. <sup>a</sup> Solvent (0.05 M). [pyr.] = 2,6-di-*tert*-butyl pyridine.

## 9.2. Construction of tetracyclic scaffold using amino benzonitrile **354**

After failing at developing a short pathway to access the vinyl tetracyclic core, it was planned to make the aminoquinoline instead, and incorporate the vinylic fragment at a later stage. The POCl<sub>3</sub>-assisted Friedländer reaction gave the amidine target **399a** in a high yield of 73% after a basic workup (Scheme IV.34). The connection between the rings was then achieved under *t*-BuOK conditions to deliver the amino-tetracyclic product **406** in a 78% yield.

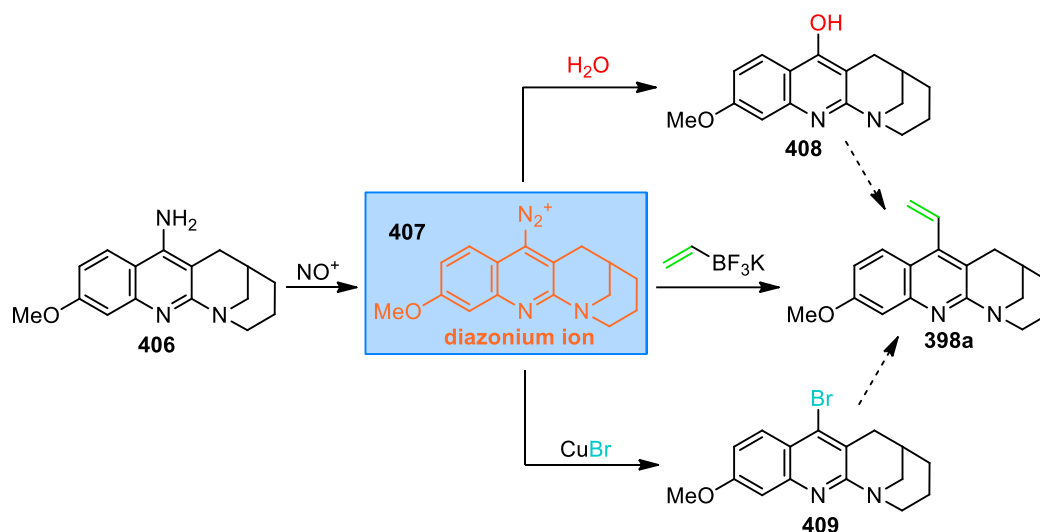


**Scheme IV.34.** Synthesis of amino-quinoline **406**. *Reagents and conditions:* i) **354** (1.5 eq.), POCl<sub>3</sub> (1.1 eq.), CH<sub>2</sub>Cl<sub>2</sub> (0.05 M), 60 to 50 °C, 24 h; ii) *t*-BuOK (2.7 eq.), THF (0.05 M), 0 to 20 °C, 15 h.

## 10. Pathways towards the vinyl-quinoline construction from the amine precursor

With the amino-naphthyridine **406** in hand, the incorporation of a vinylic fragment was planned relying on a Suzuki-type coupling.<sup>376</sup> Considering the poor nucleophilicity of the amino group, the amine fragment has to be transformed into a better leaving group such as a diazonium (Scheme

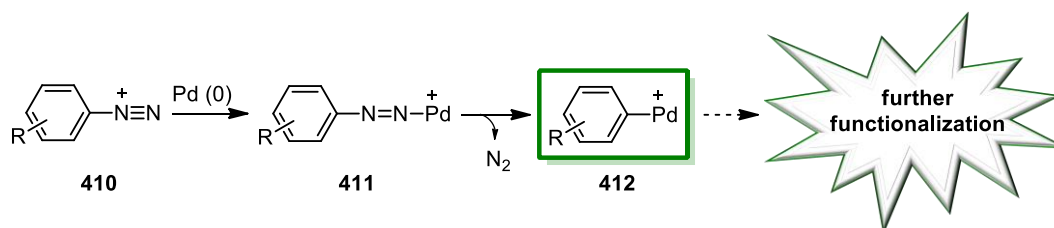
IV.35). In the reported racemic synthesis of eucophylline, this diazonium was first converted into an alcohol then a triflate, which was finally engaged in the Suzuki coupling to incorporate the vinyl substituent. An alternative pathway to access the vinyl-quinoline template might proceed through the corresponding bromo-quinoline intermediate, generated *in situ* from the diazonium salt.



**Scheme IV.35.** Possible pathways to access vinyl-quinoline **398a** through a diazonium intermediate.

### 10.1. Incorporation of the vinyl fragment through a diazonium salt

The generation of a diazonium salt is possible through a reaction of aromatic amines with nitrites ( $\text{NaNO}_2$ ) or alkyl nitrites (*t*-BuONO, isoamylONO). The arenediazonium salts such as **410**, can undergo Pd-catalyzed cross-coupling delivering complex **411** (Scheme IV.36). This can be effectively functionalized with palladium species, after the loss of nitrogen gas.<sup>377</sup> Counter-anions were described to play an important role in the stability of the diazonium salt;<sup>378–380</sup> for instance, counter-anions with low nucleophilicity such as tetrafluoroborate and hexafluoroborate among others, are often used as they can be isolated and manipulated without risk of explosion or decomposition.



**Scheme IV.36.** Palladium-catalyzed cross coupling through diazonium salts.

Based on this, the first efforts were directed towards the isolation of diazonium salts containing tetrafluoroborates as counter-anions. Using a *t*-BuONO/ $\text{BF}_3 \cdot \text{OEt}_2$  mixture in an organic solvent such as  $\text{CH}_2\text{Cl}_2$ , a characteristic red-colored diazonium salt was isolated after filtration (Table IV.7, entry 1). The infrared spectrum showed a weak peak at  $2259\text{ cm}^{-1}$  (the typical peak of a diazo fragment is usually observed between  $2250$  and  $2290\text{ cm}^{-1}$ ).<sup>381</sup> Other analytical data showed, however, that the obtained product might be the protonated amino-quinoline which was isolated in 85% yield. In fact, the HRMS analysis detected a product with a chemical formula  $\text{C}_{16}\text{H}_{20}\text{ON}_3\text{Na}$  that corresponds to

[M+Na+H<sup>+</sup>] and a mass of 293.12559. Such a result suggests that the structure **413** was probably obtained since the nitrogen center on the quinoline is the most basic site of the molecule (based on DFT calculations), yet, the structure needs to be confirmed. The obtained salt was soluble only in methanol, and the <sup>1</sup>H and <sup>13</sup>C NMR spectra were in agreement with the proposed structure. After a basic workup (sat. NaHCO<sub>3</sub>) the starting material was recovered, confirming that only protonation occurred during this reaction.

Since only a small peak characteristic of a diazonium was observed by IR, it was suggested that probably this signal is a mere artifact or only a small quantity of the diazonium was formed. To favor the formation of the desired product, an excess of acid was added, however, the same result was obtained and the salt **413** was isolated in quantitative yield (entry 2). Changing the solvent to THF or DMF did not give any reaction, and the starting material was recovered unchanged (entries 3 and 4). Changing the acid source to AcOH did not provide better results, even when excess was added (entries 5 and 6). When sodium nitrite was used in association with fluoroboric acid, only the product **413** was isolated (entries 7 and 8).

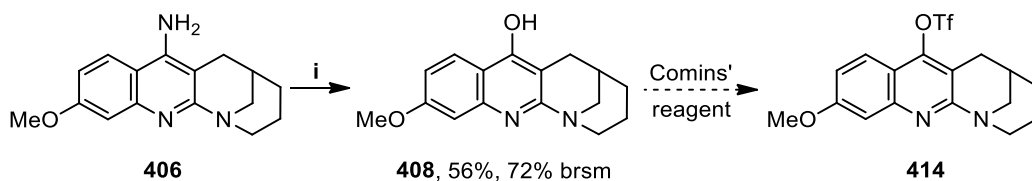
entry	X <sup>-</sup>	conditions	yield (%)
1	BF <sub>4</sub> <sup>-</sup>	<i>t</i> -BuONO (1.2 eq.), BF <sub>3</sub> ·OEt <sub>2</sub> (1.5 eq.), CH <sub>2</sub> Cl <sub>2</sub>	<b>413</b> (85)
2	BF <sub>4</sub> <sup>-</sup>	<i>t</i> -BuONO (1.2 eq.), BF <sub>3</sub> ·OEt <sub>2</sub> (10.0 eq.), CH <sub>2</sub> Cl <sub>2</sub>	<b>413</b> (quant.)
3	BF <sub>4</sub> <sup>-</sup>	<i>t</i> -BuONO (1.2 eq.), BF <sub>3</sub> ·OEt <sub>2</sub> (1.5 eq.), THF	-
4	BF <sub>4</sub> <sup>-</sup>	<i>t</i> -BuONO (1.2 eq.), BF <sub>3</sub> ·OEt <sub>2</sub> (1.5 eq.), DMF	-
5	AcO <sup>-</sup>	<i>t</i> -BuONO (1.2 eq.), AcOH (1.5 eq.), DMF	-
6	AcO <sup>-</sup>	<i>t</i> -BuONO (1.2 eq.), AcOH (4.0 eq.), DMF	-
7	BF <sub>4</sub> <sup>-</sup>	NaNO <sub>2</sub> (10.0 eq.), HBF <sub>4</sub> (50% aq., 11.2 eq.), H <sub>2</sub> O	<b>413</b> (50)
8	BF <sub>4</sub> <sup>-</sup>	NaNO <sub>2</sub> (10.0 eq.), HBF <sub>4</sub> (50% aq., 22.4 eq.), H <sub>2</sub> O	<b>413</b> (72)

**Table IV.7.** Conditions screening for the preparation of diazonium salt.

## 10.2. Incorporation of the vinyl fragment through a triflate

The unsuccessful attempts to isolate a diazonium salt led to alternatively follow the method described by Landais *et al.* and performing the coupling using a triflate.<sup>382</sup> This would be accessible after transforming the amine into an alcohol through *in situ* generation of a diazonium. The diazotation of amino-quinoline **406** was performed in the presence of an excess of sodium nitrite and sulfuric acid, followed by hydrolysis to give the hydroxy-quinoline **408** in 56% yield, together with 44% of the remaining starting material (Scheme IV.37). Increasing the quantity of the acid and nitrite sources to 10 equivalents gave similar yields, and the full conversion of the starting material was not attained. In addition, increasing the reaction time to 5 days, or decreasing the medium concentration

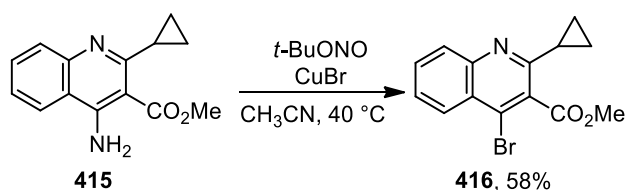
to 0.1 M gave yields between 47 and 56%, with the recovery of unreacted starting material. No significant loss of material was observed during this reaction. These results suggested to follow another route to incorporate the vinyl fragment, by first generating the corresponding bromo-quinoline through a Sandmeyer reaction. This would shorten the synthesis sequence by one step, and avoid the use of expensive Comins' reagent.<sup>383</sup>



**Scheme IV.37.** Synthesis of hydroxy-quinoline **408**. *Reagents and conditions:* i)  $\text{NaNO}_2$  (5.0 eq.),  $\text{H}_2\text{SO}_4$  (5.0 eq.),  $\text{H}_2\text{O}$  (0.48 M), 0 to 20 °C, 8 h.

### 10.3. Incorporation of the vinyl fragment through a bromide

The incorporation of a bromine atom onto the tetracyclic core is possible through the venerable Sandmeyer reaction. This reaction consists in the conversion of an aryl diazonium intermediate into an aryl halide in the presence of copper(I) salts, and likely proceeds through a radical-pathway.<sup>384–386</sup> Usually, the  $\text{NaNO}_2/\text{H}_2\text{SO}_4$  mixture is used to generate the aryl diazonium salt, which in the presence of copper(I) bromide then delivers the corresponding aryl bromide. However, it was observed in the present study, that the  $\text{NaNO}_2/\text{H}_2\text{SO}_4$  reaction conditions are inefficient, and do not provide a complete conversion of the starting material. In this context, Yagi and co-workers<sup>387</sup> reported the transformation of amino-quinoline **415** into bromo-quinoline **416** under very mild conditions, using *t*-BuONO as a nitrosyl cation source (Scheme IV.38). Such conditions seemed adequate to the tetracyclic core under study.



**Scheme IV.38.** Synthesis of bromo-quinoline **416** through Sandmeyer reaction.<sup>387</sup>

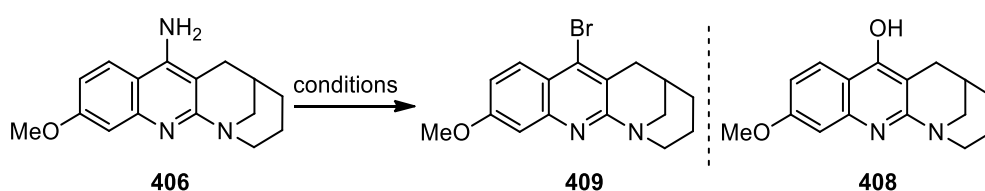
The conditions described by Yagi *et al.* were applied to the amino-quinoline **406** to deliver the brominated product **409** in 57% yield, together with 10% of unreacted starting material and another 10% of the hydroxyquinoline **408** (Table IV.8, entry 1). The fact that the phenol **408** was obtained indicates that traces of water were present in the medium, and participated in the hydrolysis of the diazonium intermediate. The traces of water may come from the solvent distilled several days before, or from the copper bromide known to be moisture- and air-sensitive.

Besides the necessity to prohibit the formation of the hydroxyquinoline **408**, optimizations are needed to fully convert the initial substrate. Usually, the reaction is completed within 3–4 h; leaving it for a longer time had no effect on the conversion of the starting material. As a precaution, the following reactions were performed in freshly distilled acetonitrile. The use of an excess of *t*-BuONO (3 eq. added in two portions within 1 h interval), led to almost complete conversion of the starting



material, and only traces of the initial substrate remaining. After column chromatography, **409** was isolated in 45% yield while the alcohol **408** was formed in 16% yield (entry 2). Once the quantity of copper bromide was increased to 2 equivalents, the starting material was fully converted, even when only 1.5 eq. of *t*-BuONO were used, giving the bromide **409** and alcohol **408** in 55 and 8% yields, respectively (entry 3). Using a different batch of copper bromide, under the same stoichiometry, afforded the desired product in 62% yield with only traces of **408** (entry 4), indicating that the quality of copper salt is an important factor.

Although a full conversion of the material was achieved, and the formation of alcohol was almost prevented, the yield was still moderate. Thus, the aqueous phase was extracted again after saturation with sodium chloride. 3% of the bromo-quinoline were recovered, indicating that a certain amount of **409** was lost during the treatment process (before extraction, the reaction mixture was filtered over celite, as described in Yagi's protocol). Therefore, it was suggested to purify the crude mixture through column chromatography directly without treatment, after removing the solvents under vacuum. This procedure increased the yield of **409** to 81%, always with traces of **408** (entry 5). When a freshly ordered bottle of copper bromide was used, the same yield of **409** was obtained, and no traces of alcohol were formed (entry 6). Decreasing the quantity to 1.8 eq., however, slightly decreased the yield to 75% (entry 7).

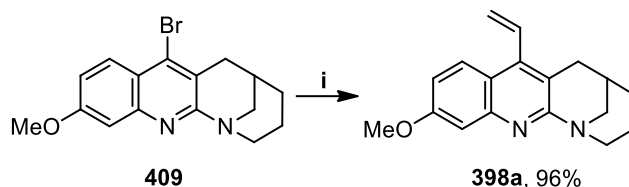


entry	CuBr (eq.)	<i>t</i> -BuONO (eq.)	workup	yield (%)		
				409	408	406
1	1.8	1.5	+	57	10	10
2	1.8	1.5 x 2	+	45	16	traces
3	2.0	1.5	+	55	8	-
4 <sup>a</sup>	2.0	1.5	+	62	traces	-
5 <sup>a</sup>	2.0	1.5	-	81	traces	-
6 <sup>b</sup>	2.0	1.5	-	81	-	-
7 <sup>b</sup>	1.8	1.5	-	75	-	-

**Table IV.8.** Conditions screening for the synthesis of bromo-quinoline **409**. *Reagents and conditions:* CH<sub>3</sub>CN (0.1 M), 40 °C, 3-4 h. <sup>a</sup> CuBr old batch. <sup>b</sup> CuBr new bottle.

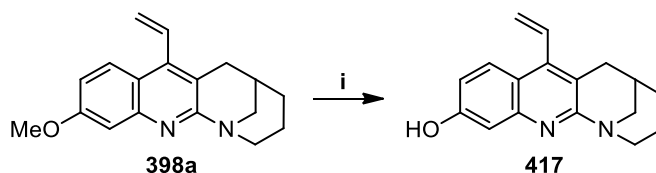
#### 10.4. Suzuki coupling and *O*-demethylation

With the bromide **409** in hand, the vinylic fragment was installed through Suzuki coupling with the commercially available potassium vinyltrifluoroborate, in the presence of potassium carbonate.<sup>382,388,389</sup> The desired vinyl naphthyridine scaffold **398a** was isolated in an excellent yield of 96% (Scheme IV.39). This reaction was repeated several times to give **398a** in yields between 80 and 100%.



**Scheme IV.39.** Synthesis of vinyl quinoline **398a** through Suzuki coupling. *Reagents and conditions:* i) Potassium vinyltrifluoroborate (1.5 eq.), Pd(PPh<sub>3</sub>)<sub>4</sub> (0.1 eq.), K<sub>2</sub>CO<sub>3</sub> (1.0 eq.), DME/H<sub>2</sub>O (0.06 M/0.12 M), 95 °C, 12 h.

Once the vinyl naphthyridine **398a** was successfully synthesized, the *O*-demethylation was achieved with BBr<sub>3</sub>. With 1.5 equivalents of BBr<sub>3</sub>, only a partial conversion was observed on TLC. During the extraction process using saturated Na<sub>2</sub>SO<sub>4</sub>, both the substrate and the product were decomposed and no trace of the typical double bond signals was found on the crude <sup>1</sup>H NMR spectrum (Table IV.9, entry 1). In a second run, a large excess of boron reagent was added to attain a full conversion after 12 h. Although the substrate was fully consumed, the final product was isolated in only 53% yield after extraction with aqueous HCl and purification on a short column (entry 2). The aqueous layer was then evaporated and analyzed after washing several times with organic solvents, showing that a quantity of the desired product went into the aqueous phase. Similarly, the extraction with a small amount of saturated NaHCO<sub>3</sub> gave a moderate yield and some quantity was lost in the aqueous phase (entry 3). Such findings are not surprising since the chromophore core **417** present both acidic and basic sites. To avoid the extraction step, a better alternative was established by quenching the reaction mixture with methanol, followed by a simple evaporation and purification. This procedure afforded the *nor*-ethyleucophylline **417** in a quantitative yield (entry 4) and was repeated several times to give **417** in yields between 82 and 100%.

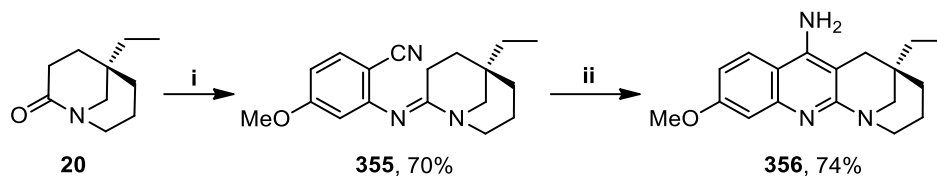


entry	BBr <sub>3</sub> (eq.)	time (h)	workup	yield (%)
1 <sup>a</sup>	1.5	16	sat. Na <sub>2</sub> SO <sub>4</sub>	decomp.
2	10.0	12	HCl (1 N)	53
3	10.0	12	sat. NaHCO <sub>3</sub>	59
4	10.0	12	MeOH	quant.

**Table IV.9.** *O*-demethylation of vinyl-quinoline **398a** with BBr<sub>3</sub>. *Reagents and conditions:* i) BBr<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub> (0.02 M), 0 to 20 °C. <sup>a</sup> Partial conversion (TLC).

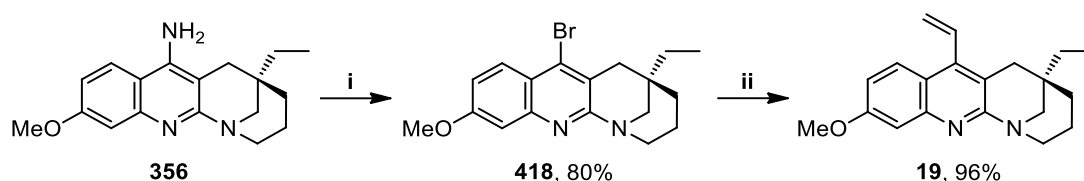
## 11. Application towards the enantioselective synthesis of eucophylline

Once the methodology was optimized on the studied model, the chiral bicyclic lactam **20** was submitted to Friedländer reaction, to generate the amidine **355** in 70% yield (Scheme IV.40). The latter was then engaged in a cyclization process using LDA, to furnish the desired amine **356** in 74% yield.



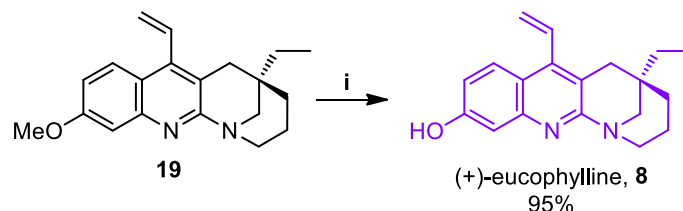
**Scheme IV.40.** Synthesis of chiral amino-quinoline **356**. *Reagents and conditions:* i) **354** (1.5 eq.), POCl<sub>3</sub> (1.1 eq. x 2), CH<sub>2</sub>Cl<sub>2</sub> (0.05 M), 60 to 50 °C, 48 h; ii) LDA (3.0 eq.), THF (0.05 M), 0 to 20 °C, 48 h.

At a later stage, the amino-quinoline **356** was transformed under Sandmeyer conditions to bromo-quinoline **418** in 80% yield, ready for the final vinylation through Suzuki coupling (Scheme IV.41). This reaction proceeded smoothly in a schlenk tube to furnish the vinyl-quinoline **19** in a 96% yield. Both reactions were repeated several times to give yields between 80 and > 95%.



**Scheme IV.41.** Synthesis of methoxy-eucophylline **19**. *Reagents and conditions:* CuBr (2.0 eq.), *t*-BuONO (1.5 eq.), CH<sub>3</sub>CN (0.1 M), 40 °C, 3 h; ii) Potassium vinyltrifluoroborate (1.5 eq.), Pd(PPh<sub>3</sub>)<sub>4</sub> (0.1 eq.), K<sub>2</sub>CO<sub>3</sub> (1.0 eq.), DME/H<sub>2</sub>O (0.06 M/0.12 M), 95 °C, 12 h.

With the methoxy-eucophylline **19** in hand, the last step of *O*-demethylation was achieved using 10 equivalents of BBr<sub>3</sub>. The (+)-eucophylline **8** was isolated in 93% yield with an observation of traces of unconverted starting material after 12 h of reaction. Increasing the quantity of BBr<sub>3</sub> to 12 eq. led to a complete conversion, and the natural product was obtained as a yellow solid in 95% yield (Scheme IV.42).



**Scheme IV.42.** Synthesis of (+)-eucophylline **8**. *Reagents and conditions:* i) BBr<sub>3</sub> (12.0 eq.), CH<sub>2</sub>Cl<sub>2</sub> (0.02 M), 0 to 20 °C, 14 h.

## 12. Analytical data of (+)-eucophylline

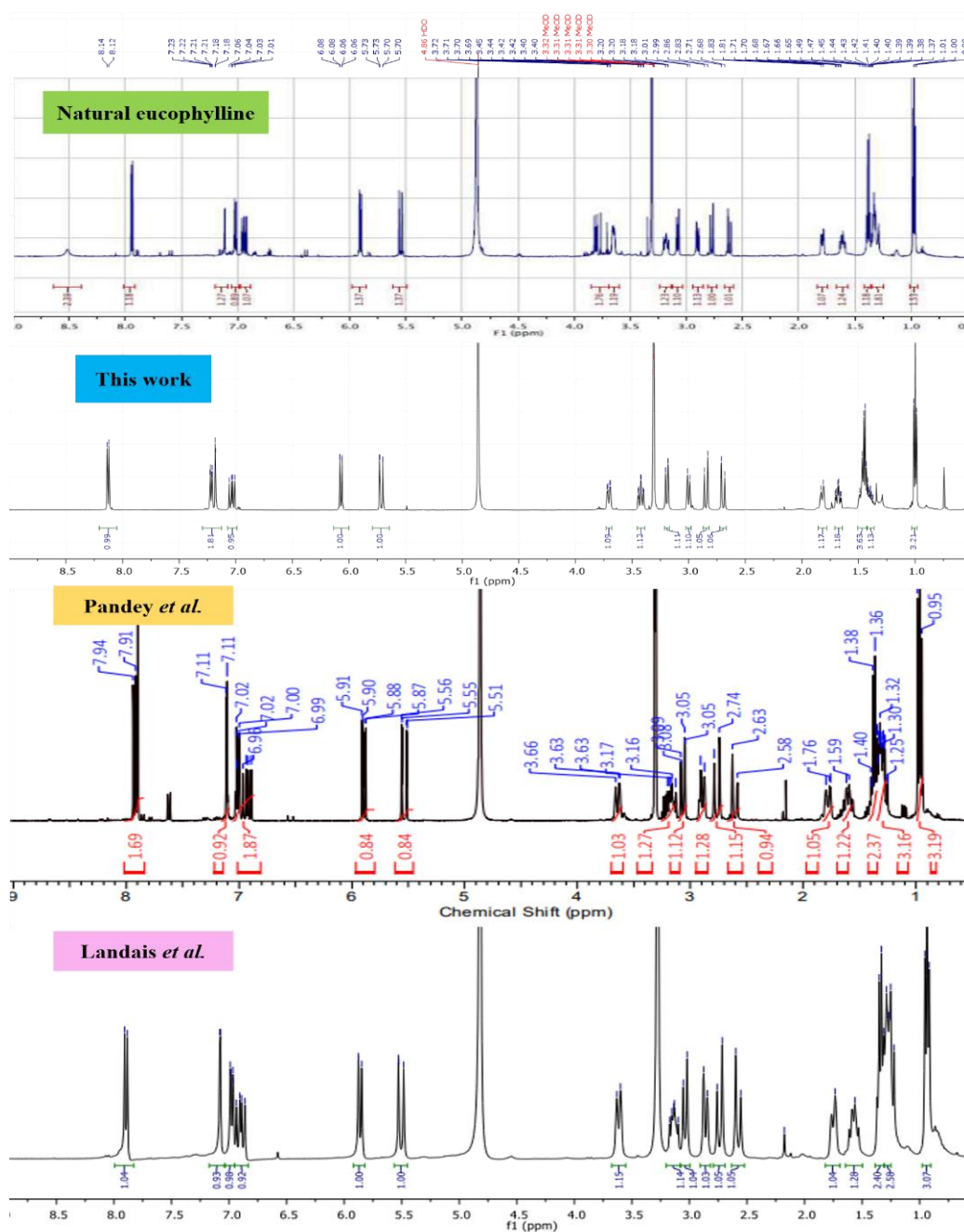
The natural product was reported to be isolated as a brownish powder from plants, as well as from the previously reported syntheses. While it was isolated as a yellow powder in its pure form, it became brownish at room temperature after a week, suggesting that the eucophylline might be prone to some oxidation.

The TLC retention factor of the product was reported to be 0.6 in CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 98/2 mixture.<sup>48,352</sup> Yet, in this work, the eucophylline was found to be much more polar and possesses an *R<sub>f</sub>* of ~ 0.2 in CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 96/4 (the *R<sub>f</sub>* was found to be between 0.19 and 0.23 with room for manipulation error). Spotting the racemic eucophylline alone and in co-spot with the chiral one, gave similar *R<sub>f</sub>*. As well, the *nor*-ethyleucophylline possesses a low *R<sub>f</sub>* value (0.11 in CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 98/2

mixture). Such a range of values might be explained by the amphoteric nature of eucophylline structure, which holds two basic amine sites and an acidic phenol entity.

The HRMS of the synthesized (+)-eucophylline ( $[M+H]^+ = 295.18018$ ) was found to be in good agreement with that reported for the authentic eucophylline ( $[M+H]^+ = 295.1816$ ).<sup>2</sup> The melting point (164.6-166.3 °C) was slightly higher than the values reported by Landais (159-160 °C)<sup>48</sup> and Pandey (158-159 °C).<sup>352</sup>

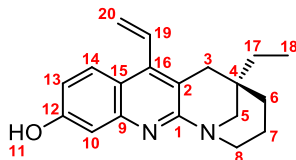
The 1D NMR ( $^1H$ ,  $^{13}C$ , and  $^{13}C$  DEPT-135) and 2D NMR ( $^1H$ - $^1H$  COSY,  $^1H$ - $^{13}C$  HSQC, and  $^1H$ - $^{13}C$  HMBC) spectroscopic data exhibit, when compared with the published data of the naturally isolated eucophylline, a slight shift in some  $^1H$ -NMR signals (Figure IV.3 and Table IV.10). The previously published  $^1H$ -NMR data of the synthetic samples showed too, some shift from the authentic product. This may be attributed to hydrogen bonding in methanol- $d_4$  and also, as mentioned above, to the amphoteric nature of eucophylline.



**Figure IV.3.** The  $^1H$  NMR spectra of natural and synthesized eucophylline, in  $CD_3OD$ .

By closely comparing the values of  $^{13}\text{C}$  NMR, a more significant shift was observed especially for the C-10 next to the alcohol fragment, which appears at 104.7 ppm instead of 109.1 ppm (Table IV.11). Pandey's  $^{13}\text{C}$  NMR results (Table IV.12) were found be closer to the natural product's data than those of this work or the  $^{13}\text{C}$  NMR reported by Landais *et al.* (Table IV.13). To check whether the product is complexed with external atoms (*e.g.*, metalloids such as boron), the eucophylline samples were extracted with HCl (1 M) or sat.  $\text{NaHCO}_3$ . In both cases, the same  $^{13}\text{C}$  NMR was obtained.

The C-10 of *nor*-ethyleucophylline **417** was found to be lower than expected as well (103.6 ppm in  $\text{CD}_3\text{OD}$ ). Analyzing *nor*-ethyleucophylline **417** in other deuterated solvents to minimize the interactions between the molecule and the solvent, showed C-10 at 103.1 and 102.7 ppm in acetonitrile- $d_3$  and dichloromethane- $d_2$ , respectively. In chloroform- $d$ , the solubility was very low precluding any analysis, while in acetone- $d_6$ , C-10 appeared at 104.5 ppm. It was envisioned that the naphthyridine nucleus might be in its protonated form. To confirm this, 0.1 eq. of *p*-TSA was added to the NMR tube (in acetone- $d_6$ ) leading to a shift of the C-10 from 104.5 to 105.7 ppm (Table IV.14), showing that the lower chemical shift is not related to the protonated nitrogen next to C-10, and that the synthesized product is not protonated.

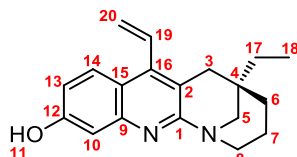


proton number	natural (+)-eucophylline <sup>2</sup> <sup>1</sup> H NMR, 700 MHz, CD <sub>3</sub> OD <sup>1</sup> H [δ, multiplet, <i>J</i> (Hz)]	this work, synthetic (+)-eucophylline <sup>1</sup> H NMR, 600 MHz, CD <sub>3</sub> OD <sup>1</sup> H [δ, multiplet, <i>J</i> (Hz)]	Δδ
<b>3a</b>	2.76 (m)	2.85 (d, <i>J</i> = 17.7 Hz)	+0.09
<b>3b</b>	2.60 (m)	2.70 (d, <i>J</i> = 17.7 Hz)	+0.1
<b>5a</b>	3.10 (d, <i>J</i> = 13.1 Hz)	3.19 (dd, <i>J</i> = 13.2, 1.9 Hz)	+0.09
<b>5b</b>	2.90 (d, <i>J</i> = 13.1 Hz)	3.00 (d, <i>J</i> = 13.1 Hz)	+0.1
<b>6a</b>	1.78 (m)	1.82 (d, <i>J</i> = 11.5 Hz)	+0.04
<b>6b</b>	1.59 (m)	1.68 (td, <i>J</i> = 13.2, 4.9 Hz)	+0.09
<b>7</b>	1.32 (m)	1.43-1.36 (m)	+0.07
<b>8a</b>	3.65 (dd, <i>J</i> = 5.5, 5.5 Hz)	3.71 (dd, <i>J</i> = 13.7, 3.5 Hz)	+0.06
<b>8b</b>	3.16 (m)	3.42 (td, <i>J</i> = 13.2, 3.7 Hz)	+0.26
<b>10</b>	7.15 (d, <i>J</i> = 2.3 Hz)	7.18 (d, <i>J</i> = 2.4 Hz)	+0.03
<b>11</b>	not seen*	not seen*	-
<b>13</b>	7.00 (d, <i>J</i> = 9.0 Hz)	7.22 (dd, <i>J</i> = 9.2, 2.4 Hz)	+0.22
<b>14</b>	7.95 (d, <i>J</i> = 9.0 Hz)	8.13 (d, <i>J</i> = 9.2 Hz)	+0.18
<b>17</b>	1.38 (q, <i>J</i> = 7.5 Hz)	1.45 (q, <i>J</i> = 7.5 Hz)	+0.07
<b>18</b>	0.96 (t, <i>J</i> = 7.5 Hz)	1.00 (t, <i>J</i> = 7.6 Hz)	+0.04
<b>19</b>	6.95 (dd, <i>J</i> = 17.9, 11.7 Hz)	7.03 (dd, <i>J</i> = 17.9, 11.9 Hz)	+0.08
<b>20a</b>	5.95 (dd, <i>J</i> = 11.7, 1.7 Hz)	6.07 (dd, <i>J</i> = 11.9, 1.4 Hz)	+0.12
<b>20b</b>	5.55 (dd, <i>J</i> = 17.9, 1.7 Hz)	5.72 (dd, <i>J</i> = 17.9, 1.4 Hz)	+0.17

Table IV.10. Comparison table of <sup>1</sup>H NMR data for natural and synthetic (+)-eucophylline.\*Signal disappears in CD<sub>3</sub>OD.

carbon number	natural (+)-eucophylline <sup>2</sup> <sup>13</sup> C NMR, 175 MHz, CD <sub>3</sub> OD <sup>13</sup> C [δ (ppm)]	this work, synthetic (+)-eucophylline <sup>13</sup> C NMR, 150 MHz, CD <sub>3</sub> OD <sup>13</sup> C [δ (ppm)]	Δδ
<b>1</b>	162.3	162.7	+0.4
<b>2</b>	122.6	123.3	+0.7
<b>3</b>	37.6	36.9	-0.7
<b>4</b>	31.7	32.4	+0.7
<b>5</b>	58.5	57.9	-0.6
<b>6</b>	37.0	36.3	-0.7
<b>7</b>	20.5	20.9	+0.4
<b>8</b>	56.8	57.8	+1.0
<b>9</b>	148.9	152.0	+3.1
<b>10</b>	109.1	104.7	-4.4
<b>12</b>	160.0	160.2	+0.2
<b>13</b>	118.8	120.4	+1.6
<b>14</b>	127.6	129.1	+1.5
<b>15</b>	120.0	119.9	-0.1
<b>16</b>	146.5	143.7	-2.8
<b>17</b>	36.1	35.6	-0.5
<b>18</b>	7.4	7.3	-0.1
<b>19</b>	133.1	132.0	-1.1
<b>20</b>	123.6	125.9	+2.3

Table IV.11. Comparison table of <sup>13</sup>C NMR data for natural and synthetic (+)-eucophylline.

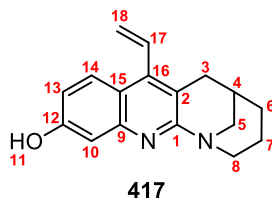


carbon number	natural (+)-eucophylline <sup>2</sup> <sup>13</sup> C NMR, 175 MHz, CD <sub>3</sub> OD <sup>13</sup> C [δ (ppm)]	synthetic (+)-eucophylline <sup>352</sup> <sup>13</sup> C NMR, 100 MHz, CD <sub>3</sub> OD <sup>13</sup> C [δ (ppm)]	Δδ
1	162.3	162.5	+0.2
2	122.6	122.7	+0.1
3	37.6	37.8	+0.2
4	31.7	31.8	+0.1
5	58.5	58.7	+0.2
6	37.0	37.2	+0.2
7	20.5	20.6	+0.1
8	56.8	56.9	+0.1
9	148.9	149.3	+0.4
10	109.1	109.5	+0.4
12	160.0	160.0	0
13	118.8	118.9	+0.1
14	127.6	127.7	+0.1
15	120.0	120.2	+0.2
16	146.5	146.4	-0.1
17	36.1	36.2	+0.1
18	7.4	7.5	+0.1
19	133.1	133.3	+0.2
20	123.6	123.6	0

**Table IV.12.** Comparison table of <sup>13</sup>C NMR data for natural and synthetic (+)-eucophylline (Pandey *et al.*).<sup>352</sup>

carbon number	natural (+)-eucophylline <sup>2</sup> <sup>13</sup> C NMR, 175 MHz, CD <sub>3</sub> OD <sup>13</sup> C [δ (ppm)]	synthetic (±)-eucophylline <sup>48</sup> <sup>13</sup> C NMR, 75 MHz, CD <sub>3</sub> OD <sup>13</sup> C [δ (ppm)]	Δδ
1	162.3	160.9	-1.4
2	122.6	117.3	-5.3
3	37.6	36.2	-1.4
4	31.7	30.2	-1.5
5	58.5	57.1	-1.4
6	37.0	34.6	-2.4
7	20.5	19.0	-1.5
8	56.8	55.3	-1.5
9	148.9	147.7	-1.2
10	109.1	107.9	-1.2
12	160.0	158.4	-1.6
13	118.8	121.1	+2.3
14	127.6	126.1	-1.5
15	120.0	118.6	-1.4
16	146.5	144.8	-1.7
17	36.1	35.6	-0.5
18	7.4	5.97	-1.43
19	133.1	131.7	-1.4
20	123.6	122.0	-1.6

**Table IV.13.** Comparison table of <sup>13</sup>C NMR data for natural and synthetic (±)-eucophylline (Landais *et al.*).<sup>48</sup>

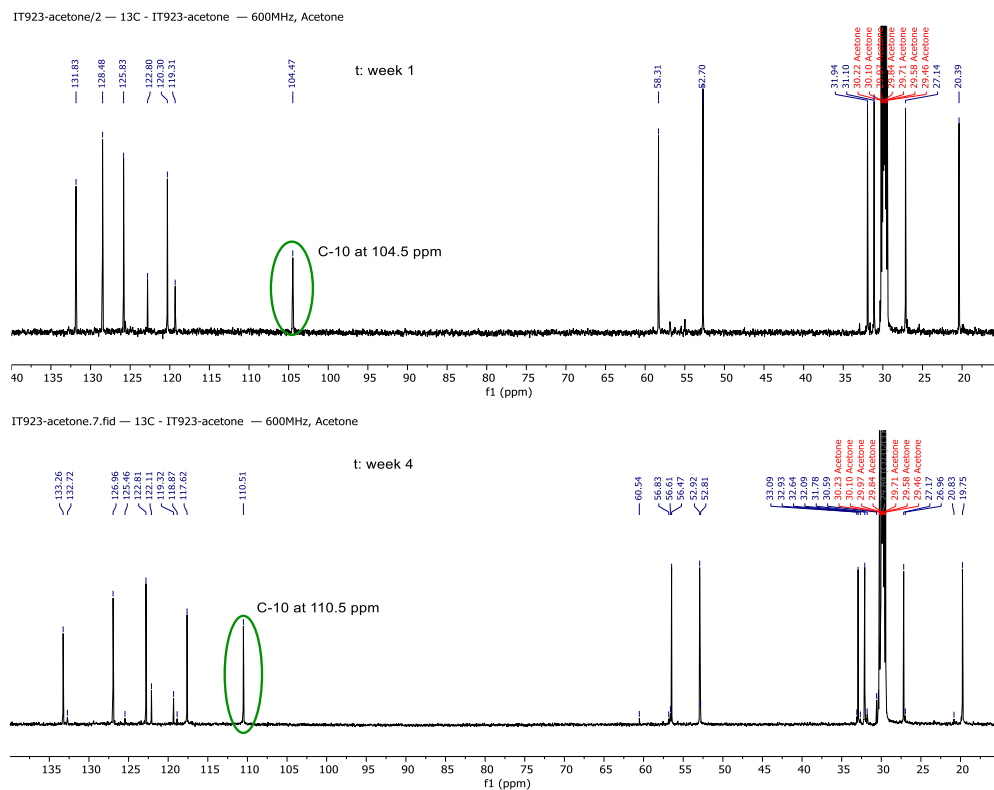


carbon number	<i>nor</i> -ethyleucophylline	with <i>p</i> -TSA	$\Delta\delta$
	$^{13}\text{C}$ NMR, 150 MHz, acetone- $d_6$ $^{13}\text{C}$ [ $\delta$ (ppm)]		
<b>1</b>	162.0	161.8	-0.2
<b>2</b>	122.8	122.6	-0.2
<b>3</b>	31.9	32.0	+0.1
<b>4</b>	27.1	27.0	-0.1
<b>5</b>	52.7	52.6	-0.1
<b>6</b>	31.1	31.2	+0.1
<b>7</b>	20.4	20.1	-0.3
<b>8</b>	58.3	57.6	-0.7
<b>9</b>	151.8	150.6	-1.2
<b>10</b>	104.5	105.7	+1.2
<b>12</b>	159.3	160.0	+0.7
<b>13</b>	120.3	120.0	-0.3
<b>14</b>	128.5	128.2	-0.3
<b>15</b>	119.3	119.2	-0.1
<b>16</b>	142.4	145.7	+3.3
<b>17</b>	131.8	132.0	+0.2
<b>18</b>	125.8	125.3	-0.5

**Table IV.14.** Comparison table of  $^{13}\text{C}$  NMR data for *nor*-ethyleucophylline in acetone- $d_6$ , without and with *p*-TSA.

When analyzing the *nor*-ethyleucophylline **417** in acetone- $d_6$  several weeks later (for the “without acid” sample, the NMR tube was prepared again), C-10 shifted to 110.5 ppm and other small peaks were detected (Figure IV.4). The explanation behind this shift is not clear. In the case of (+)-eucophylline, the C-10 chemical shift appeared at 105.8 ppm using acetone- $d_6$  as a solvent. Repeating the analyses after several weeks were not accomplished for this molecule.





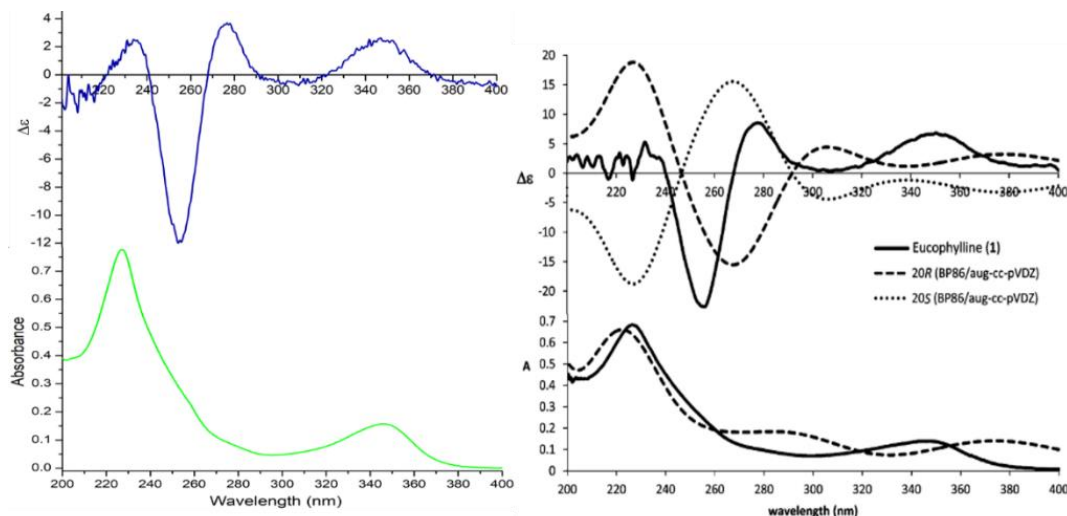
**Figure IV.4.** The  $^{13}\text{C}$  NMR spectra of **417** in acetone- $d_6$  with 26 days gap.

After leaving the NMR tube for more than 2 days, white precipitates were observed. These precipitates were not crystalline, do not deviate the polarized light, and they were not soluble in organic solvents.

Albeit the sense of the optical rotation matched what was reported in the literature, the specific optical rotation value of (+)-eucophylline was found to exhibit a higher value than that in the isolation paper:  $[\alpha]_{\text{D}}^{25} = +72.16$  ( $c = 0.53$ , MeOH) *versus* lit.<sup>2</sup>  $[\alpha]_{\text{D}}^{27} = +27$  ( $c = 0.75$ , MeOH). While Pandey found a closer value to that obtained for the authentic sample:  $[\alpha]_{\text{D}}^{19.8} = +36.102$  ( $c = 1.25$ , MeOH).<sup>352</sup> Although it has to be taken into account that the experimental values could hold  $\pm 10^\circ$  error, the results in this work were obviously much higher. Using methanol as commercially received or purified did not give different results. Attempts to measure the specific rotation in chloroform did not seem useful, due to the low solubility of eucophylline in this solvent. The measurement of the specific rotation of known molecules with reported  $[\alpha]_{\text{D}}$  values confirmed that the problem does not come from the polarimeter. For instance, the  $[\alpha]_{\text{D}}$  of the ligand **115** synthesized in chapter III, was remeasured giving the expected value.

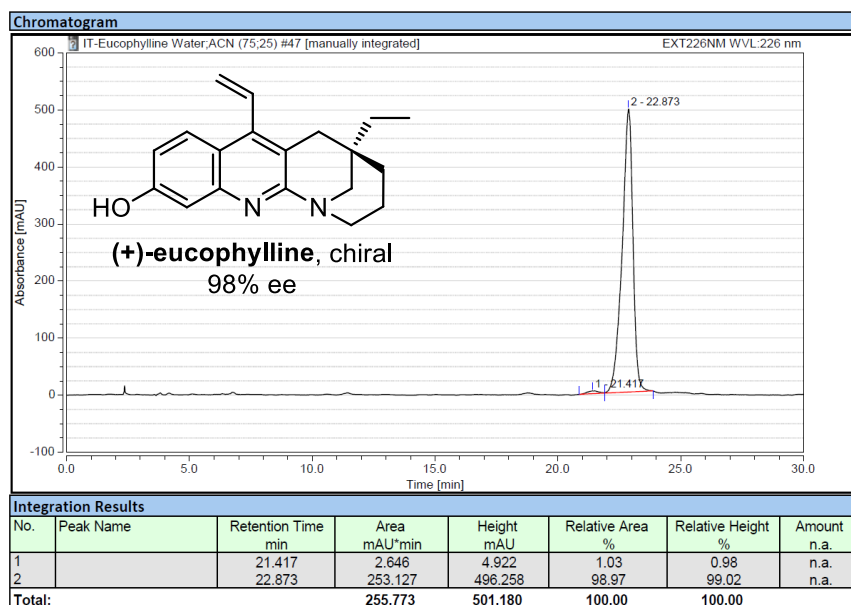
By searching in the literature for an explanation, it was found that some groups also found a difference between the  $[\alpha]_{\text{D}}$  values of their synthetic samples and the ones reported for the natural products.<sup>390,391</sup> Their explanations seem to fit this case, where the difference could be attributed to the impurities present in the isolated natural product, as seen on the reported  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra, or it could be related to the low quantity available for accurate measurement of the specific rotation (1.9 mg isolated natural product).

Circular dichroism analysis was also performed and compared with the literature data (Figure IV.5). According to the CD spectra, the absolute configuration at the C-20 position was deduced to be (*R*), as expected. The UV spectrum was also found in good agreement with that of the isolated natural eucophylline ( $\lambda_{\text{max}} = 227 \text{ nm}, 346 \text{ nm}$ ; lit.<sup>2</sup>  $\lambda_{\text{max}} = 227 \text{ nm}, 347 \text{ nm}$ ).

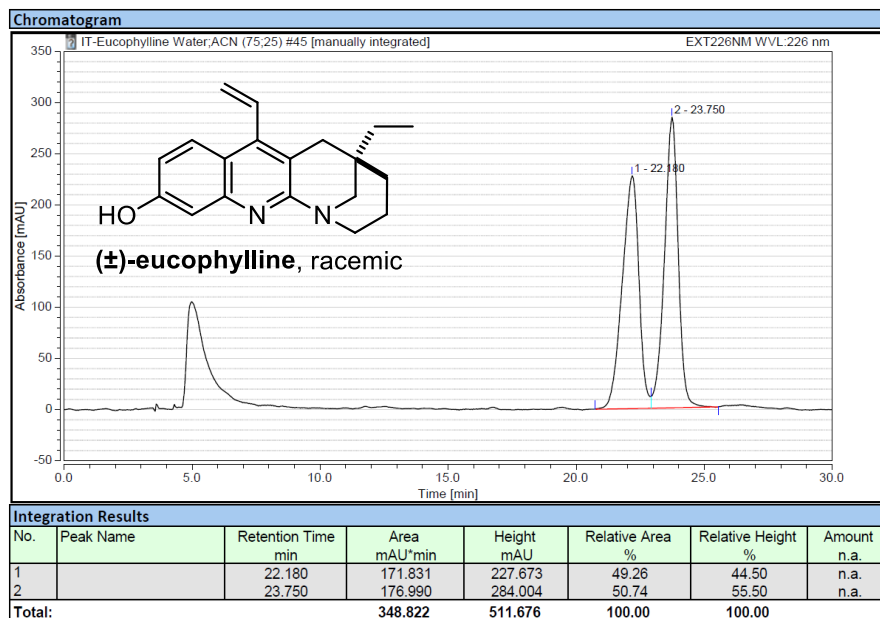


**Figure IV.5.** Comparison of CD and UV spectra of the eucophylline synthesized in this work (*left*) and the natural one<sup>2</sup> (*right*).

The (+)-eucophylline was then analyzed through HPLC, together with the racemic sample. The HPLC profile showed that (+)-**8** was synthesized in an excellent enantiomeric excess of 98% and no racemization occurred along the synthetic sequence (Figures IV.6 and IV.7). Interestingly, no separation of both enantiomers was possible using Chiralpak<sup>®</sup> IA column. As well, the HPLC analysis was successful only when pure water (osmotic water) was used. In the presence of traces of acid (TFA) or base (Et<sub>3</sub>N) several inseparable peaks (at least 4) were observed, indicating that the molecule was probably transformed into other entities.

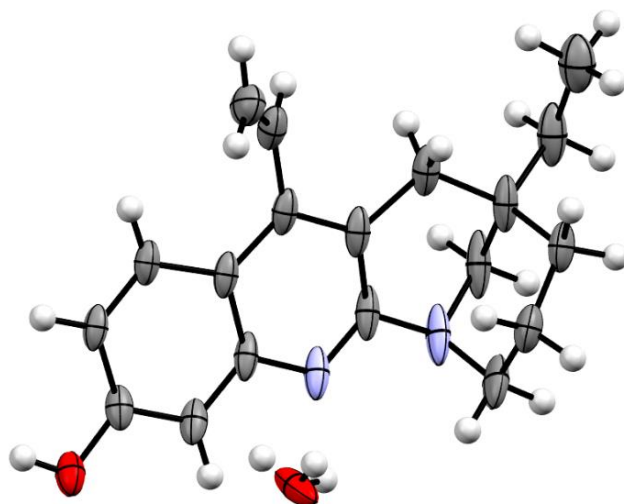


**Figure IV.6.** HPLC trace of chiral (+)-eucophylline. Analytical Phenomenex<sup>®</sup> column (Lux 5  $\mu\text{m}$  Cellulose-3, 4.6 mm $\Phi$  x 250 mmL), pure H<sub>2</sub>O/CH<sub>3</sub>CN: 75/25, 1 mL/min, 20  $^{\circ}\text{C}$ .



**Figure IV.7.** HPLC trace of (±)-eucophylline (synthesized by Landais *et al.*). Analytical Phenomenex<sup>®</sup> column (Lux 5  $\mu$ m Cellulose-3, 4.6 mm $\Phi$  x 250 mmL), pure H<sub>2</sub>O/CH<sub>3</sub>CN: 75/25, 1 mL/min, 20 °C.

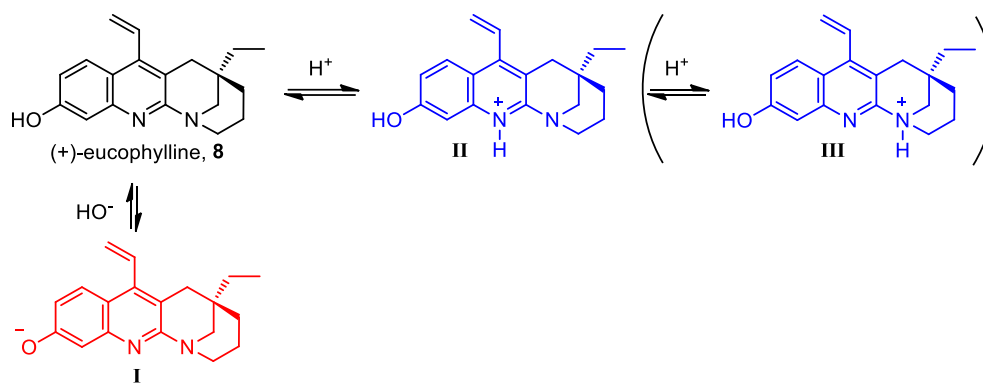
To dismiss all doubts about the structure of the tetracyclic core, crystals were grown to perform X-ray analysis. 17 solvent mixtures were tested to finally succeed at obtaining crystals suitable for X-ray diffraction analysis by diffusion from CH<sub>2</sub>Cl<sub>2</sub>/Et<sub>2</sub>O. The X-ray structure confirmed the successful synthesis of the natural enantiomer crystallized with a water molecule appearing close to the quinoline's nitrogen atom (Figure IV.8). These analyses secured the first X-ray crystal structure of **8** which nicely illustrates the overall conformation of the molecule, showing the piperidine ring in a chair conformation.



**Figure IV.8.** ORTEP view of (+)-eucophylline obtained by X-ray diffraction, crystallized with a water molecule.

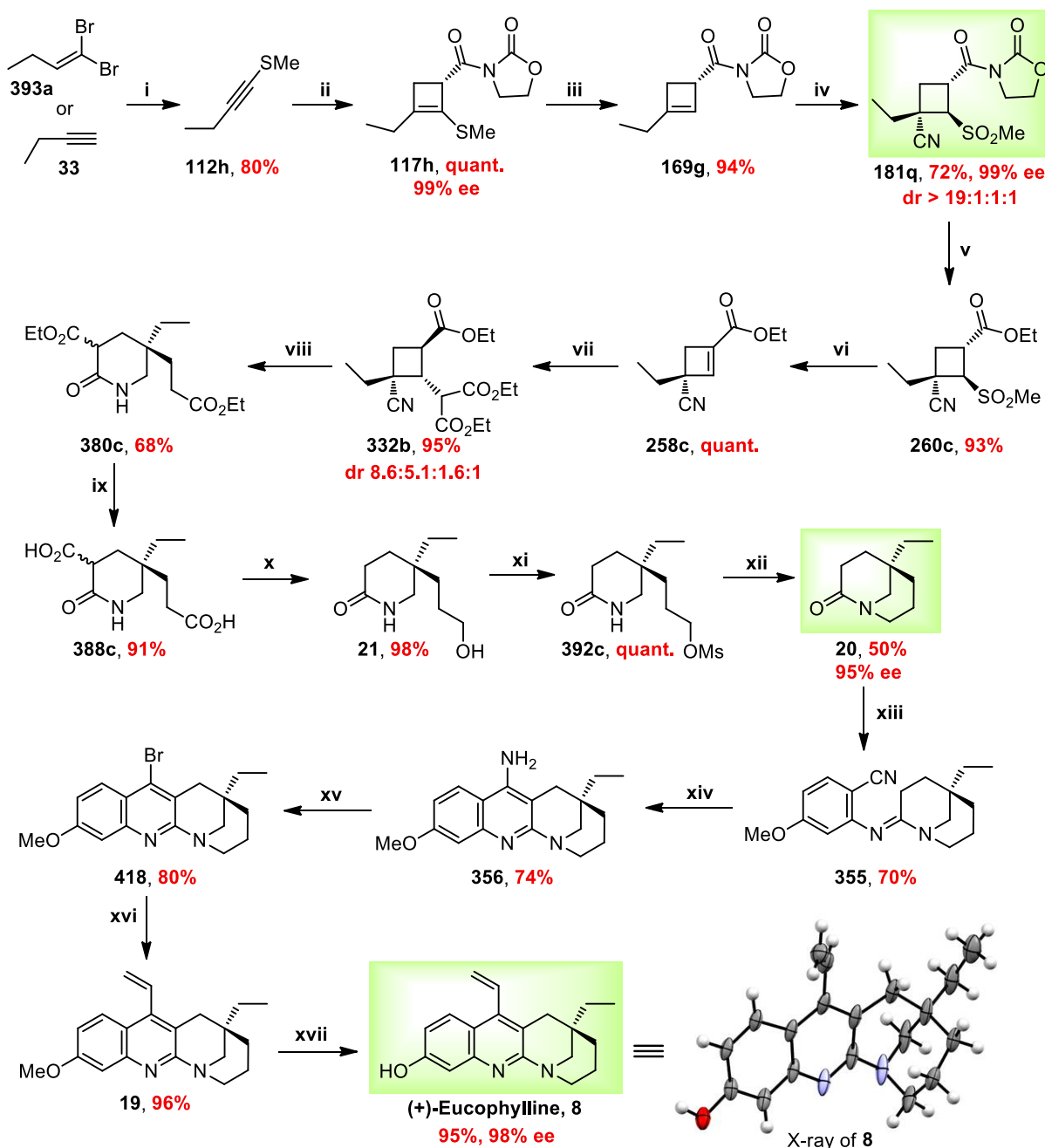
Finally, the abovementioned observations may be related to the amphoteric nature of eucophylline. In the presence of traces of acid or base, different forms could be generated (Scheme IV.43). In the presence of a base, a phenolate **I** is formed, while in the presence of acid, the protonation

of the eucophylline's nitrogens would be favored. The protonation might occur on the quinoline's nitrogen **II** or less probably on the bridgehead nitrogen **III**.



**Scheme IV.43.** Different forms of eucophylline in basic or acidic medium.

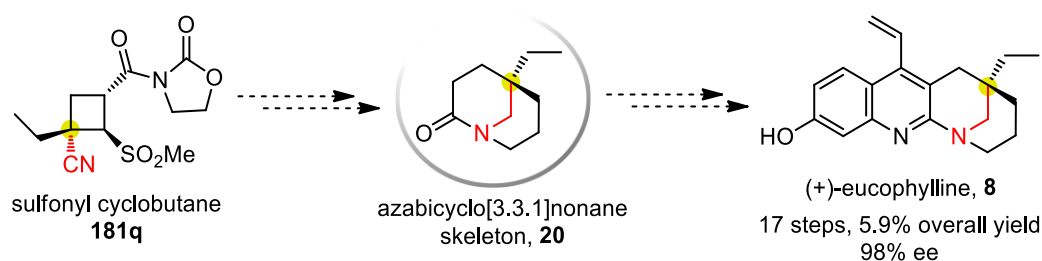
## 13. Summary scheme of the total synthesis of (+)-eucophylline



**Scheme IV.44.** Summary of the total synthesis of (+)-eucophylline. *Reagents and conditions:* i) 1. *n*-BuLi; 2. Me<sub>2</sub>S<sub>2</sub>; ii) 3-acryloyloxazolidin-2-one, (**R**)-**115**, TiCl<sub>2</sub>(OiPr)<sub>2</sub>; iii) Lindlar's catalyst, Et<sub>3</sub>SiH; iv) MeSO<sub>2</sub>CN, *p*-anisaldehyde; v) DMAP, EtOH; vi) Cs<sub>2</sub>CO<sub>3</sub>; vii) diethyl malonate, NaH; viii) NiCl<sub>2</sub>, NaBH<sub>4</sub>, EtOH; ix) LiOH; x) 1. THF, 70 °C; 2. TMSCHN<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH; 3. LAH; xi) MsCl, Et<sub>3</sub>N; xii) NaH; xiii) 2-amino-4-methoxybenzonitrile, POCl<sub>3</sub>; xiv) LDA; xv) CuBr, *t*-BuONO; xvi) potassium vinyltrifluoroborate, Pd(PPh<sub>3</sub>)<sub>4</sub>, K<sub>2</sub>CO<sub>3</sub>; xvii) BBr<sub>3</sub>.

## 14. Conclusion

In summary, this chapter disclosed the enantioselective total synthesis of natural eucophylline **8** in 17 steps starting from 1,1-dibromobut-1-ene, with an overall yield of 5.9%, and an average yield of 85%. The HPLC analysis confirmed the high enantiomeric excess of the natural product (ee = 98%). In this synthesis, no protecting groups were used and only 9 steps proceeded with purification on column chromatography. The synthetic approach features the construction of a chiral cyclobutene which was further functionalized to introduce the asymmetric all-carbon quaternary stereocenter through a photocatalytic approach (Figure IV.9). Most notably, this synthesis takes advantage of a nickel boride-mediated cascade, allowing a nitrile reduction/cyclization/ring-opening sequence in a one-pot process. This transformation gave access to a six-membered cyclic lactam starting from a cyclobutane scaffold. The lactam was further manipulated to deliver a highly strained bridgehead amide. The elaboration of the eucophylline tetracyclic core continued after several optimizations. The natural product was fully characterized and an X-ray structure confirmed its successful synthesis.



**Figure IV.9.** Total synthesis of (+)-eucophylline.



## *Chapter V*

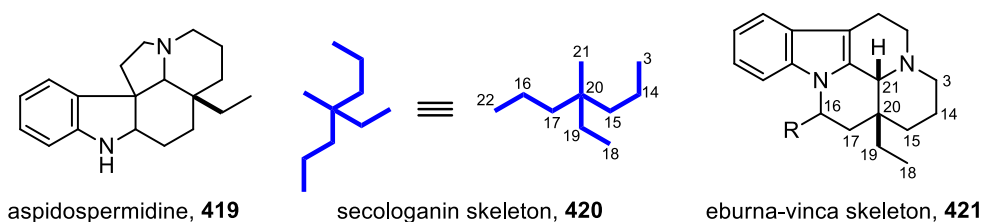
# *Total Synthesis of Eburnane Alkaloids*





## 1. Eburnane-vincane alkaloids: isolation, biogenesis, and structure

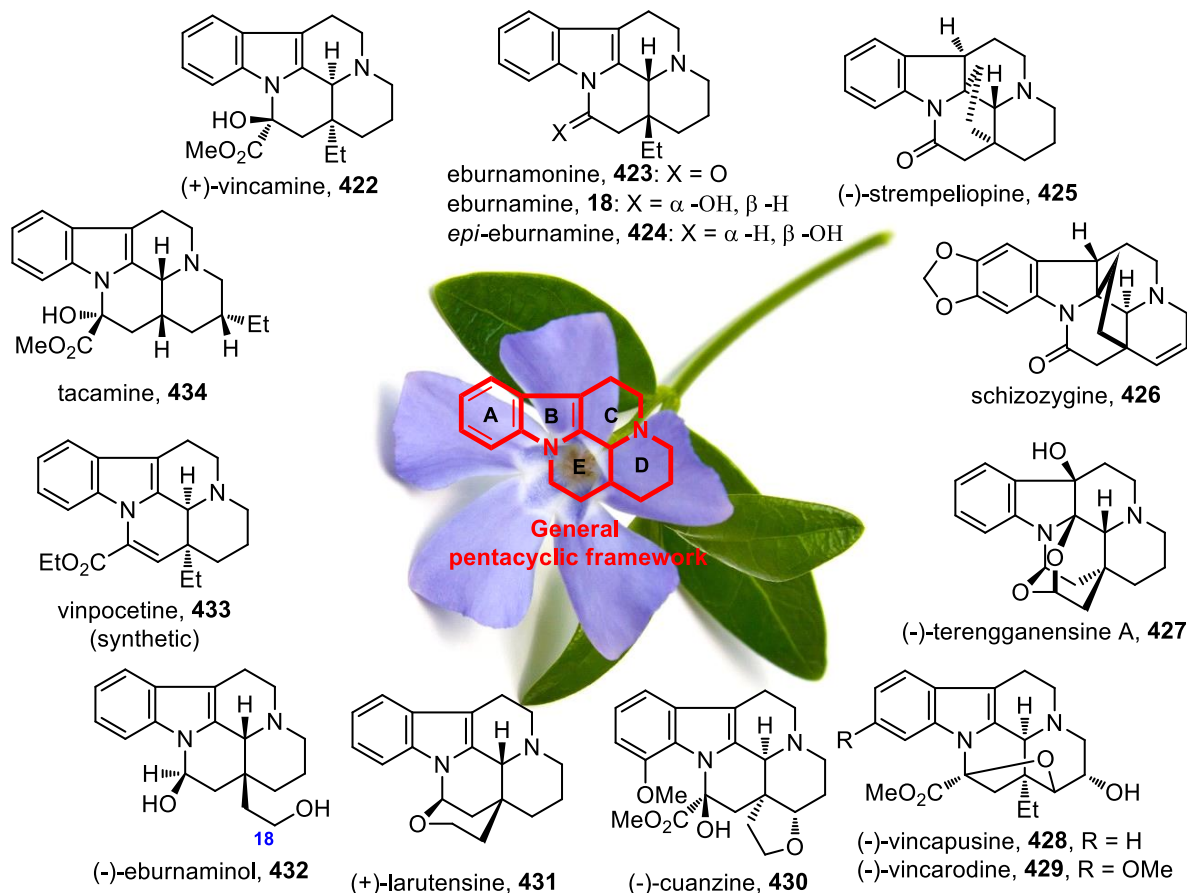
The pentacyclic northern fragment of leucophyllidine **6**, the eburnamine **18**, belongs to the eburnane-vincane family, which is a well-known group of the monoterpene indole alkaloids.<sup>392</sup> The eburnane-vincane alkaloids have been isolated from numerous species of the plant family *Apocynaceae*, but also from *Hunteria*, *Kopsia*, *Rhazya stricta*, *Leuconotis*, and *Vinca* species.<sup>393–395</sup> Their template possesses the same fundamental secologanin skeleton **420** already noted in the *Aspidosperma* series. It is, however, incorporated into the former system in a rather different fashion, which defines the backbone's architecture of the group (Figure V.1).<sup>392</sup>



**Figure V.1.** Secologanin skeleton present in aspidosperma and eburna-vinca alkaloids.

This family of approximately 35 bases, features a common pentacyclic framework,<sup>396</sup> containing either a *cis*- or *trans*-fused D/E ring system, and an all-carbon quaternary center at C-20 (Figure V.2).<sup>397</sup> The family can be divided into three major subgroups: (-)-eburnamine **18**, (+)-vincamine **422**, and (-)-strepmpeliopine **425**, which are regarded as the parent bases of the series.<sup>398–400</sup> Further functionalization of the pentacyclic core leads to a diversity of molecules.<sup>401</sup> For example, vincamine **422** has an eburnane pentacyclic core with an ester group in ring E. The same pentacyclic core is also present in eburnamonine **423** and eburnamine **18** with an amide or alcohol on ring E, respectively.<sup>402</sup> Eburnamine **18** (natural series) presents a *cis* D/E ring junction while its diastereoisomer *epi*-eburnamine **424** (unnatural series) presents a *trans* D/E ring junction.

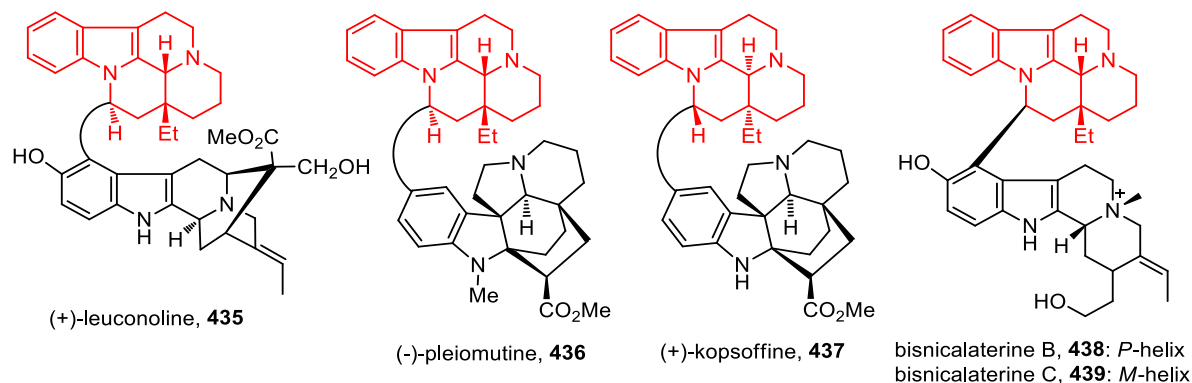
Tacamine **434** is a regioisomer of vincamine **422** with an opposite stereochemistry at the ring junctions.<sup>403</sup> Functionalization at the terminal C-18 gives rise to eburnaminol **432**, as well, further cyclization results in architecturally more complex molecules such as the hexacyclic larutensine **431** and cuanzine **430**. A different type of cyclization is observed in vincarodine **429**, a constituent of *catharanthus roseus* G. Don., and its demethoxy relative, vincapusine **428**, present in the leaves and roots of *Vinca pusilla*.<sup>404,405</sup> A more complex cyclization also occurs in schizozygine **426** derivatives and terengganensine A **427** with seven-membered rings.



**Figure V.2.** Selected examples of eburnane-vincane indole alkaloids.

Interestingly, unlike most indole alkaloids for which only one enantiomer is naturally generated by plants, the eburnane indole alkaloids show enantiodivergence. Levorotatory, dextrorotatory, and racemic forms have been isolated from plants of *Kopsia* growing in different geographical areas. For example, the (20*R*,21*R*)-enantiomers of eburnane alkaloids were exclusively found in Malaysian *Kopsia*, while the opposite enantiomers (20*S*,21*S*) were isolated from Chinese *Kopsia*.<sup>393,406</sup> These observations provide evidence for the biosynthetic pathway that could be traced to the achiral secodine intermediate.<sup>30,407–409</sup>

Speaking of the eburnane skeleton, it also constitutes the half part of several pharmacologically active bis-indole alkaloids like leuconoline **435**, pleiomutine **436**, and kopsoffine **437** (Figure V.3),<sup>410,411</sup> as well as two bis-indole alkaloids, bisnicalaterines B and C **438** and **439** consisting of eburnane- and corynanthe-type skeletons, which were isolated from the bark of *Hunteria zeylanica*. Each of them was shown to be in an atropisomeric relationship towards the other, and they showed potent vasorelaxant activity on isolated rat aorta.<sup>412</sup>



**Figure V.3.** Bis-indole alkaloids containing eburnane pentacyclic core.

## 2. Bioactivity and pharmacological potential of indole alkaloids

Since isolation, scientists gave special attention to aspidosperma-type alkaloids, not only for their sophisticated structures as mentioned above but also for the popularity of plants that produce these substances in folk medicine.<sup>413</sup> Specifically, the eburnane-vincane indole alkaloids were found to exhibit strong vasodilatation activity which brings about an enhancement of the overall cerebral blood flow.<sup>414</sup> They also exert other potent pharmacological activities on cell multiplication, the cardiovascular system, and the brain functions as cerebroprotective agents.<sup>415,416</sup>

For example, (-)-eburnamonine **423**, also known as (-)-vincamone, has been shown to prevent cerebrovascular disorders, whereas (+)-vincamine **422** (Vincarutine®) is a marketed peripheral vasodilator for treatment of primary degenerative and vascular dementia.<sup>410,415,417</sup> The pharmacological studies showed (+)-eburnamonine to be less effective than vincamine or (-)-eburnamonine. In addition to its lower toxicity, (-)-eburnamonine was found to be a more active and selective cerebral vasodilator than (+)-eburnamonine.<sup>418,419</sup>

Investigations on the chemical modification of eburnamine derivatives were aimed at finding pharmacologically more effective derivatives and safer to administer than the natural plant alkaloids themselves. Most of these derivatives were obtained by the introduction of substitutions at the aromatic ring or by functional modification at C-16 (*see Figure V.1 for the numbering*). For instance, vinpocetine **433** has been found to be pharmacologically more effective than vincamine itself.<sup>420</sup> Since its introduction to the market as a neuroprotective agent (Cavinton®), clinical studies proved the usefulness of vinpocetine in the treatment of post-ischaemic stroke disease and various disorders of cerebrovascular origin.<sup>415</sup> In 2010, Rosenberg described vinpocetine and eburnamine derivatives as having the ability to promote bone growth, thus illustrating, the wide array of potential pharmacological applications of this type of compounds.<sup>421</sup> Beyond this, it is important to develop new syntheses to obtain these substances efficiently without the necessity of extraction from natural sources.

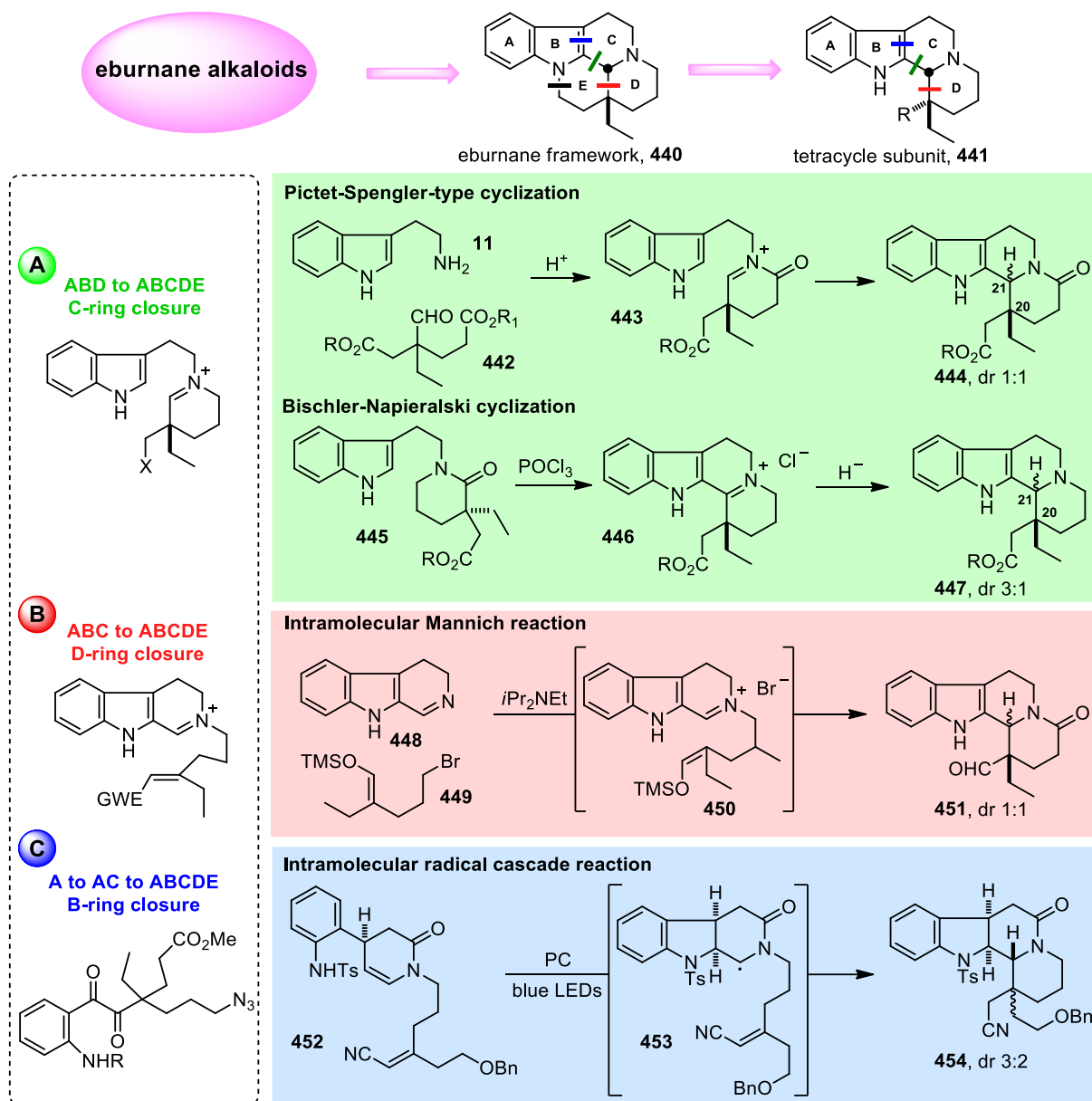
## 3. Common approaches towards the eburnane pentacyclic core

The potential pharmacological activity and the notable array of structures inherent to the eburnane-vincane alkaloids family provided the opportunity for considerable diversification in the

synthetic approaches towards these molecules.<sup>398,410</sup> Undoubtedly, it will not be possible, within the limitations in scope and length of this chapter to provide a detailed discussion of all the advances that have been made in this area. It is hoped that the present selection of the synthetic pathways will provide some appreciation of the various strategies followed during the construction of the common ABCDE pentacyclic framework. Strategically, the most common route towards this particular family is to first establish the ABCD key ring system **441** and then to complete the synthesis of the specific target by tailoring the final E-ring (Scheme V.1).<sup>422</sup>

The majority of syntheses follow the design of first building the ABD fragment of the molecule, then closing the C-ring *via* C-2/C-3 bond formation. Typically, The condensation of a tryptamine template with an aldehyde-ester **442** through Pictet-Spengler reaction,<sup>423</sup> or the intramolecular condensation of a lactam **445**, followed by reduction through Bischler-Napieralski<sup>424</sup> are among the most exploited transformations towards this end (Scheme V.1.A).<sup>408,425</sup> An inherent drawback, however, associated with these approaches, is the lack of diastereocontrol of the crucial quaternary center at C-20 and the adjacent methine at C-21. The insignificant steric difference between an ethyl and an ester group at C-20 prohibits the differentiation of the two faces of the neighboring iminium function.<sup>426</sup>

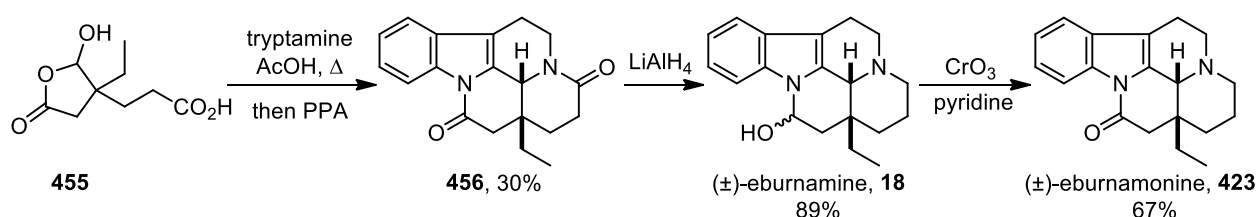
Other pathways proceeded through an easily accessible ABC nucleus, 3,4-dihydro- $\beta$ -carboline **448**, upon which the remaining rings were built (Scheme V.1.B).<sup>427,428</sup> This approach involves usually an intramolecular Mannich reaction, leading to Oppolzer's intermediate derivatives **451** with moderate diastereoselectivity.<sup>429</sup> Finally, the construction of the B ring starting from a non-indole portion was also investigated (Scheme V.1.C). The key step in the ring system assembly is a photoredox radical-based cascade approach.<sup>66,430–432</sup> Another version of this reaction type has also been developed with full diastereocontrol.<sup>433</sup> In the following section, a few examples of the most characteristic synthetic approaches of eburnamonine **423** and eburnamine **18**, will be provided for illustrative purposes.



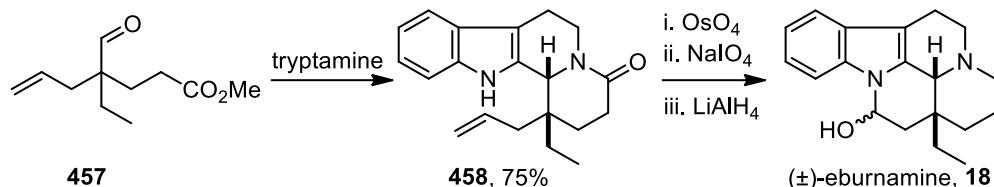
Scheme V.1. Common synthetic strategies towards eburnane indole alkaloids.

#### 4. Illustration of the most popular syntheses of eburnamine and eburnamine

The structure elucidation and the first synthesis of the eburnane series: eburnamine **18**, *epi*-eburnamine **424**, and eburnamnine **423** were achieved by Bartlett and Taylor in 1960.<sup>395,434</sup> In this synthesis, the condensation of substituted adipic acid derivative **455** with tryptamine through an acid-catalyzed ring closure afforded 3-oxoeburnaminone **456**. Reduction of the latter gave a mixture of eburnamine **18** and *epi*-eburnamine **424**, which were oxidized to eburnamnine **423** under Sarett conditions (Scheme V.2).

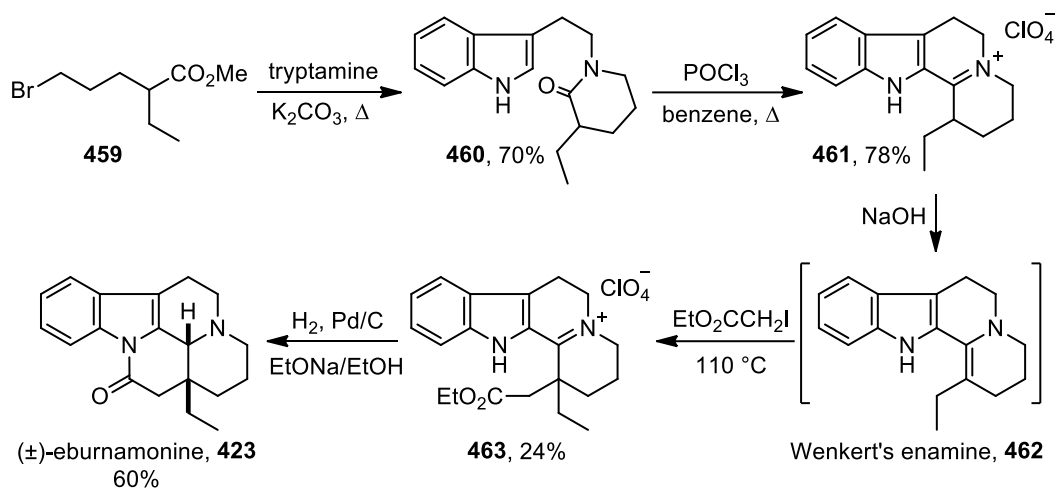
Scheme V.2. Taylor synthesis of (±)-eburnamine and (±)-eburnamnine.<sup>395,434</sup>

The Pictet-Spengler approach used by Barton and Harley-Mason, involved an unsaturated aldehyde-ester **457** as the condensing unit. The higher reactivity of the aldehydic carbonyl function privileged the reaction at this site (Scheme V.3).<sup>435</sup> The produced tetracyclic olefin **458** was subjected to oxidative scission under Lemieux-Johnson conditions, to provide the C-16 aldehyde function. Reduction then gave ( $\pm$ )-eburnamine **18**. The intermediate **458** was also used for the synthesis of aspidospermidine derivatives following the aspidosperma-eburnea rearrangement pattern.



**Scheme V.3.** Barton and Harley-Mason synthesis of ( $\pm$ )-eburnamine.<sup>435</sup>

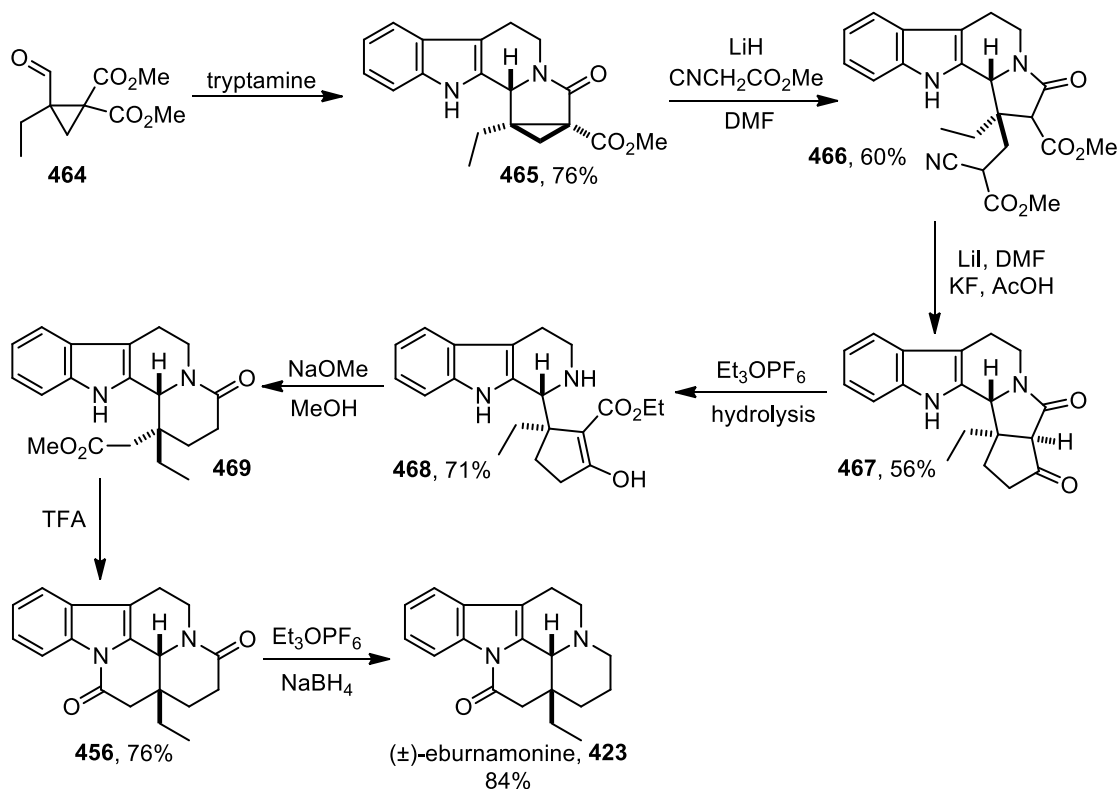
A different approach to the pentacyclic nucleus of eburnamonine was developed by Wenkert and Wickberg.<sup>408</sup> The cyclic amide **460** was prepared from the cyclization of tryptamine with bromoester **459**. The construction of the C-ring then took place under Bischler-Napieralski condensation to give iminium **461** (Scheme V.4). The enamine **462**, later known as Wenkert's enamine, was formed *in situ* under basic conditions and was alkylated with ethyl iodoacetate. The product of alkylation **463** was hydrogenated and ( $\pm$ )-eburnamonine **423** was obtained under basic conditions together with its epimer. A general study on the utility of Wenkert's enamine derivatives has been made by Wenkert for the synthesis of other indole alkaloids.<sup>436</sup>



**Scheme V.4.** Synthesis of ( $\pm$ )-eburnamonine by Wenkert and Wickberg.<sup>408</sup>

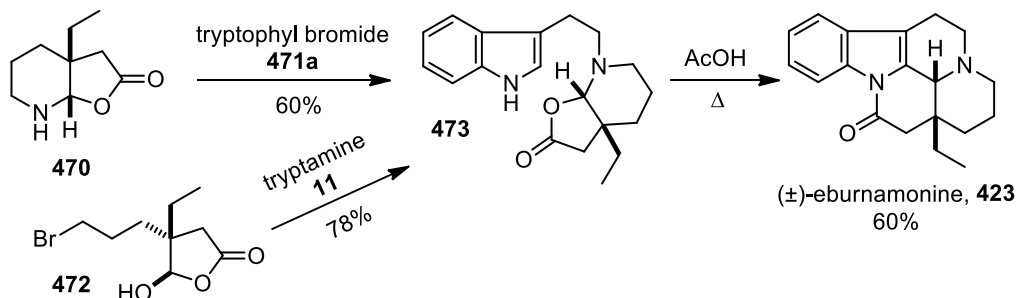
A genuine contribution of Winterfeldt *et al.*<sup>437</sup> afforded the eburnamonine **423** based on a regioselective ring-opening of a cyclopropane derivative **465** as the key intermediate (Scheme V.5). Condensation of tryptamine and cyclopropyl aldehyde ester **464** gave the pentacyclic lactam ester **465**. Only 15% of the epimer of **465** were obtained. The correct stereochemical relationship between C-20 and C-21 was thus ascertained, and this remained undisturbed during the later stages of the synthesis. The reaction of the latter with the lithium enolate of methyl cyanoacetate caused the ring-opening of the cyclopropane, leading to the tetracycle **466**. Decarboxylation and ring-closure gave oxolactam **467**. The lactam ring-opening of **467** under acidic conditions gave the  $\beta$ -oxoester **468**.

Basic and acidic treatment of the latter gave dilactam **456**, which upon reduction, afforded ( $\pm$ )-eburnamonine **423**. The asymmetric synthesis of cyclopropane **464** was described later by the group, offering an enantioselective pathway to (+)- and (-)-eburnamonine.<sup>438</sup>



**Scheme V.5.** Winterfeldt's synthesis of ( $\pm$ )-eburnamonine.<sup>437</sup>

Wenkert *et al.*<sup>6</sup> proposed a second synthesis of ( $\pm$ )-eburnamonine following two parallel routes to lead to the lactone intermediate **473** (Scheme V.6). The latter was obtained either from the alkylation of carbinolamine lactone **470** with tryptophyl bromide **471a** or from the condensation of bromolactol **472** with tryptamine **11**. Under acidic and thermal conditions, the carbinolamine lactone **473** underwent cyclization, leading directly to eburnamonine **423**. The aminolactone **470** was later used by several groups for the synthesis of eburnane family or for other synthetic purposes.<sup>410</sup> Alternative syntheses have also been described for the preparation of this aminolactone.<sup>439,440</sup>

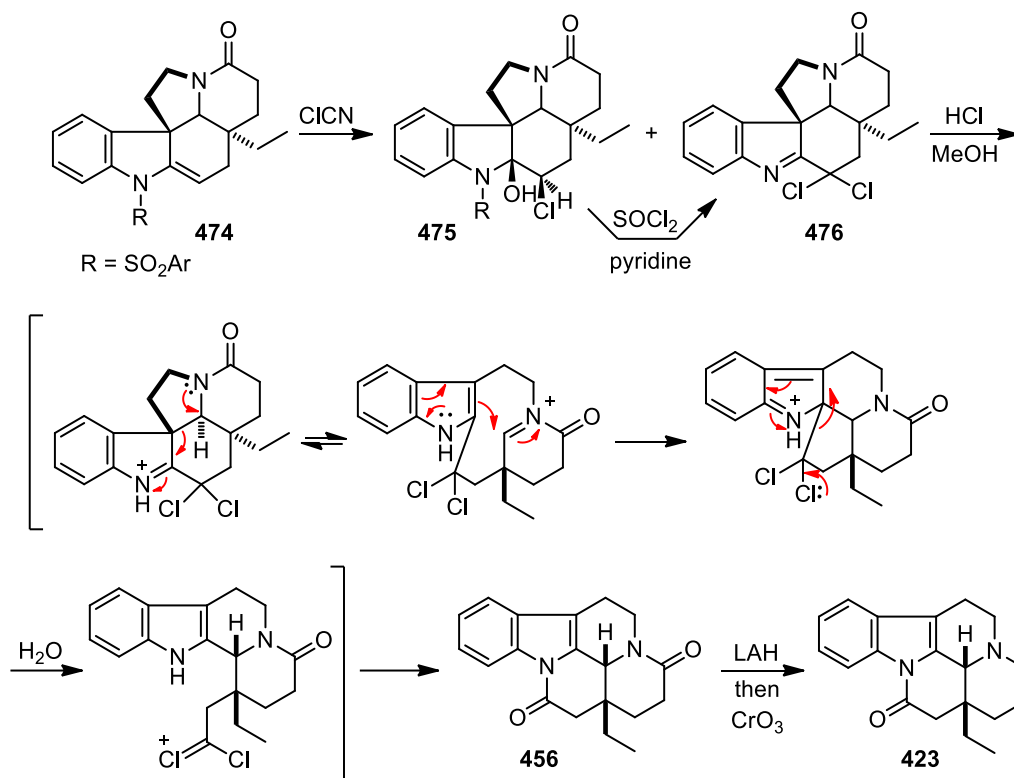


**Scheme V.6.** Synthesis of ( $\pm$ )-eburnamonine by Wenkert *et al.*<sup>6</sup>

Magnus *et al.*<sup>441</sup> based their synthesis of ( $\pm$ )-eburnamonine on the rearrangement of an aspidosperma-type intermediate (Scheme V.7). The pentacyclic amide **474** was treated with cyanogen chloride to furnish the *cis*-chlorohydrin **475** and the geminal dichloroimine **476**. Under acidic conditions, **476** rearranged rapidly by the intermediacy of acyliminium species, to 3-

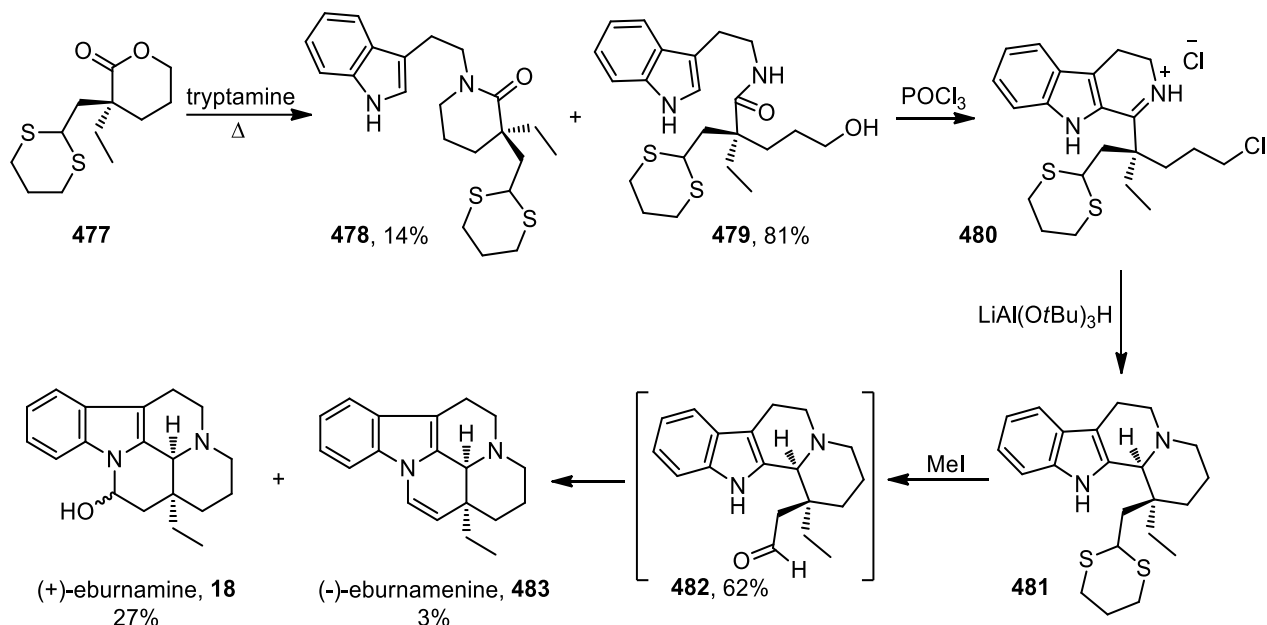


oxoeburnamonine **456**. **456** was then transformed into ( $\pm$ )-eburnamonine **423** by consecutive reduction-oxidation sequence.



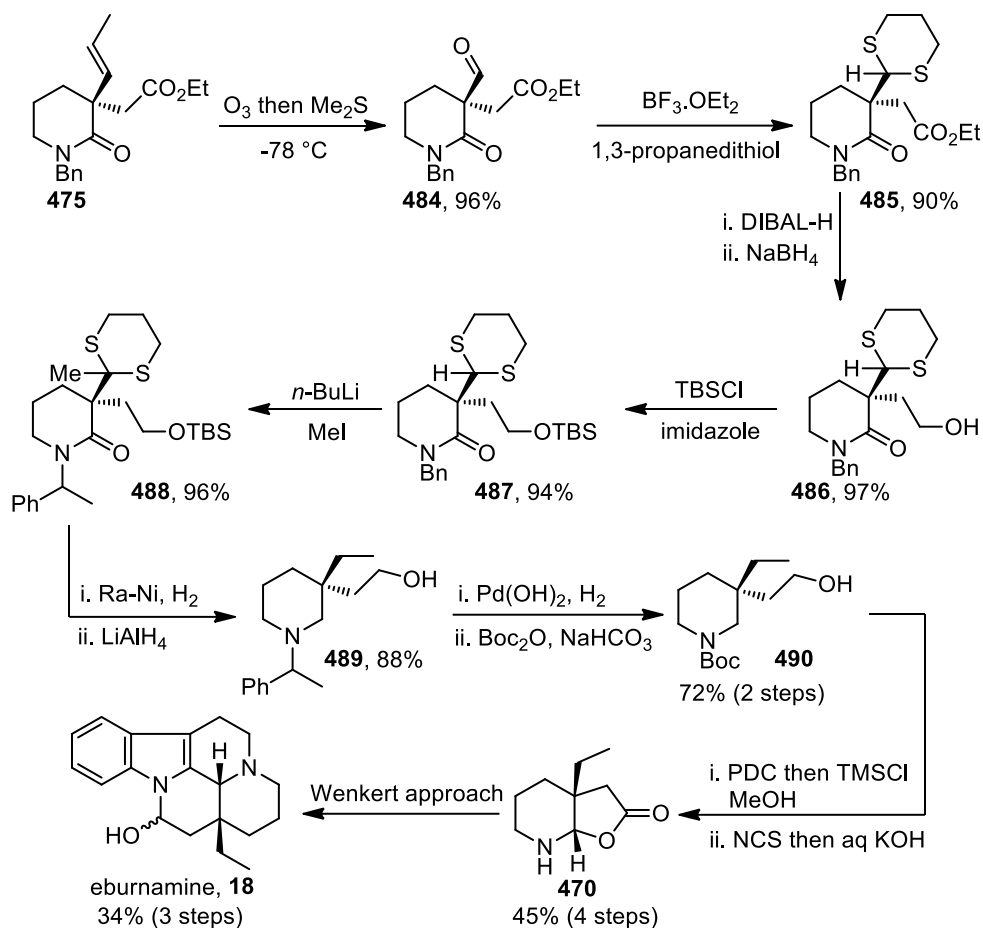
**Scheme V.7.** Synthesis of ( $\pm$ )-eburnamonine by Magnus *et al.*<sup>441</sup>

The first syntheses of the enantiopure (+)-eburnamine **18**, (-)-eburnamenine **483**, and (-)-eburnamonine **423** was reported by Takano and co-workers.<sup>442</sup> Chiral lactone **477** was synthesized in sequential reactions starting from L-glutamic acid. Its condensation with tryptamine afforded  $\delta$ -lactam **478** and the amide **479** in 14 and 81% yields, respectively (Scheme V.8). The amide **479**, cyclized under Bischler-Napieralski conditions to afford the iminium salt **480** that was reduced by a hydride source to give the tetracyclic core **481** in 62% overall yield. After hydrolysis of the dithiane group, the formed aldehyde **482** underwent spontaneous cyclization to afford (+)-eburnamine **18** and (-)-eburnamenine **483** in 27 and 3% yields, respectively. Further oxidation of (+)-eburnamine **18** with pyridinium dichromate elaborated (-)-eburnamonine **423** in a 75% yield.



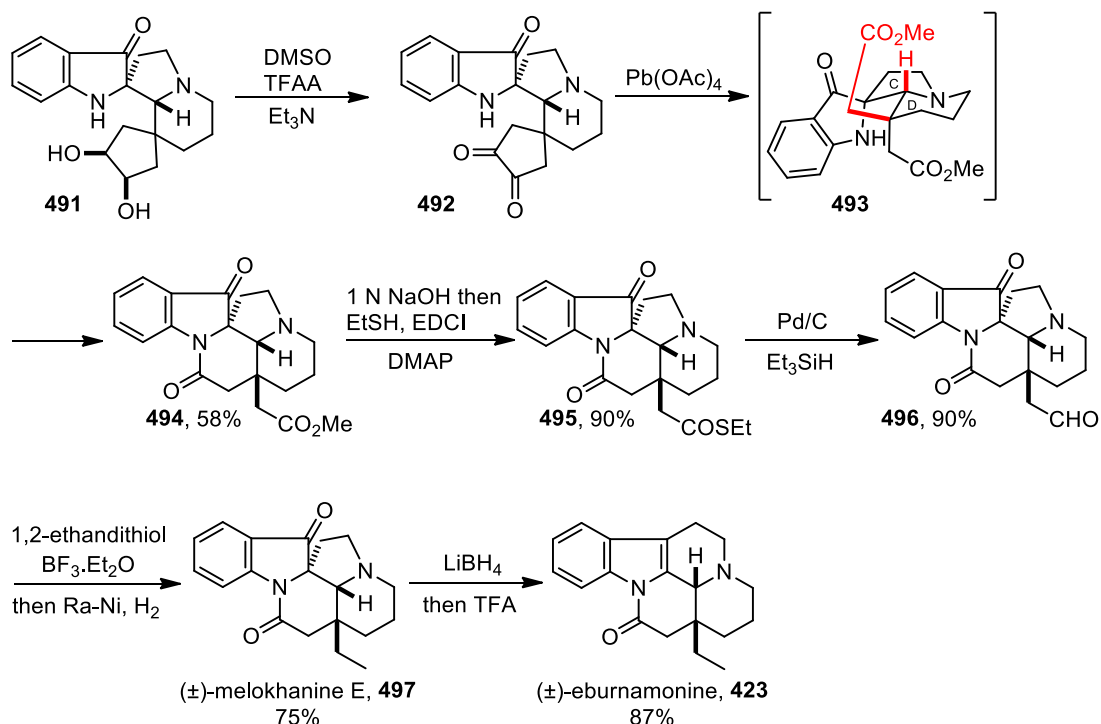
**Scheme V.8.** Takano's synthesis of (+)-eburnamine and (-)-eburnamenine.<sup>442</sup>

Pandey *et al.*<sup>352</sup> synthesized eburnamine **18** from the enantiopure lactam **475** (Scheme V.9). The latter was obtained by a similar approach to the lactam used in the eucophylline synthesis. Ozonolysis of **475** gave the aldehyde **484**, the subjecting of which to Wittig reaction was not successful. The aldehyde was then converted into a 1,3-dithiane **485** and the ester was fully reduced into the corresponding alcohol **486**. Basic treatment of the protected alcohol **487** using *n*-BuLi, followed by the addition of iodomethane furnished the methyl-1,3-dithiane **488**. This alkylation also methylated the benzylic center of the N-Bn protecting group. The piperidine **489** was obtained after reductive desulfurization of 1,3-dithiane and reduction of the amide with lithium aluminium hydride. Protecting group transformations gave the Boc-protected amide **490**. Oxidation of the alcohol with pyridinium dichromate provided the corresponding carboxylic acid. N-Boc deprotection and esterification of the acid led to the methyl ester. The chlorination of the amine followed by basic hydrolysis afforded the aminolactone **470**, a known advanced intermediate introduced by Wenkert to accomplish the total synthesis of eburnamine **18**. According to the authors, this formal synthesis proceeded through 10 linear steps and an overall yield of 7.4%. As for the eucophylline, a more realistic counting from commercially available material leads to 21 steps and a 4.6% overall yield.



**Scheme V.9.** Enantioselective synthesis of eburnamine by Pandey *et al.*<sup>352</sup>

Zhu *et al.*<sup>426</sup> addressed the long-standing issue of C-20/C-21 relative stereochemistry in the synthesis of eburnane-type alkaloids. Their approach allowed the achievement of (±)-eburnamonine **423** synthesis from (±)-melokhanine **497**. The advanced intermediate **491** was oxidized to provide the diketone **492** which, upon treatment with lead tetraacetate was converted into the pentacyclic **494** as a single diastereomer in 58% yield over two steps (Scheme V.10). The desired C-20/C-21 cis-stereochemistry was controlled by the preferred conformation of **493** in which the C/D ring adopted a trans-fused configuration. Hydrolysis of **494** followed by coupling of the resulting carboxylic acid with ethanethiol generated the thioester **495** in a 90% overall yield. Fukuyama reduction of **495** delivered the aldehyde **496**, which was converted, via a 1,3-dithiolane intermediate, into (±)-melokhanine E **497**, an antibacterial agent (MIC = 2 μM against *P. aeruginosa*) in a good overall yield. Chemoselective reduction of the latter followed by aza-pinacol rearrangement of the resulting alcohol under acidic conditions delivered (±)-eburnamonine **423** in 87% overall yield.



**Scheme V.10.** Synthesis of (±)-eburnamonine by Zhu *et al.*<sup>426</sup>

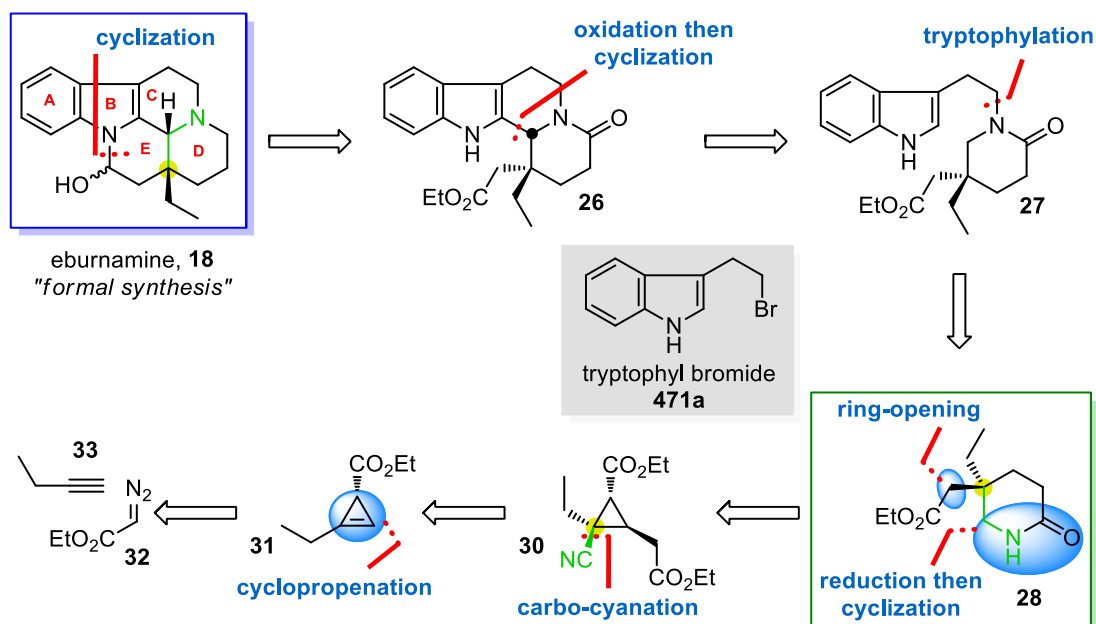
Considering the aforementioned syntheses and the literature reports, the common two pathways to access the tetracyclic core of eburnane alkaloids are either through Pictet-Spengler reaction or Bischler-Napieralski intramolecular condensation. This brief survey also showed the diversity of approaches developed to access the pentacyclic skeleton. Some of these syntheses are distinguished by the stereospecificity of the crucial constructive steps, others are characterized by their generality and versatility, whereas others followed biosynthetic pathways.

In most cases, the challenging task is to construct the non-tryptamine part in a short and efficient strategy. The construction of this non-tryptamine part usually takes at least 7 to 10 steps, except for a few examples.<sup>435</sup> To date, many approaches have been reported for the synthesis of the racemic and chiral non-tryptamine fragment, a task that will be undertaken in the following discussion.

## 5. Revised retrosynthetic strategy towards enantioselective eburnamine

Following the results obtained in chapter IV, a revised retrosynthesis of chiral eburnamine was proposed based on three connections of the indole core to tailor the C-D-E rings (Scheme V.11). Strategically, the beginning of the eburnamine retrosynthesis would be based on formal syntheses, by tailoring the last ring (ring E) using a suitable base, followed by reduction of the molecule's carbonyl groups. Installing the quaternary stereocenter at C-21 would be envisioned by selective oxidation of the site  $\alpha$ - to the ring D's nitrogen to generate an iminium ion and favors the nucleophilic attack of the indole fragment on the carbocation, tailoring thus, the C ring regioselectively. From this disconnection, the ring D would be introduced to the eburnamine's scaffold through alkylation of lactam **28** with tryptophyl bromide **471a** (or its derivatives) to form the first connection to the indole backbone. The six-membered lactam **28**, as a key intermediate, would be provided by a strategy similar to that used in the synthesis of (+)-eucophylline. Applying the nickel boride conditions to the

polyfunctionalized cyclopropane **30** would result in nitrile reduction, cyclization, and ring-opening of the three-membered carbocycle in a one-pot process. The diastereoselective free-radical carbo-cyanation of cyclopropene **31** would construct the all-carbon quaternary center bearing the nitrile functional group with good diastereocontrol to generate **30**.<sup>47</sup> The enantiopure cyclopropene **31** itself would be accessed by adapting the previous cyclopropenation reports starting from the suitable alkyne **33** and diazoester **32**. Thus, the key chiral lactam **28** would be obtained in three straightforward steps starting from but-1-yne **33**.



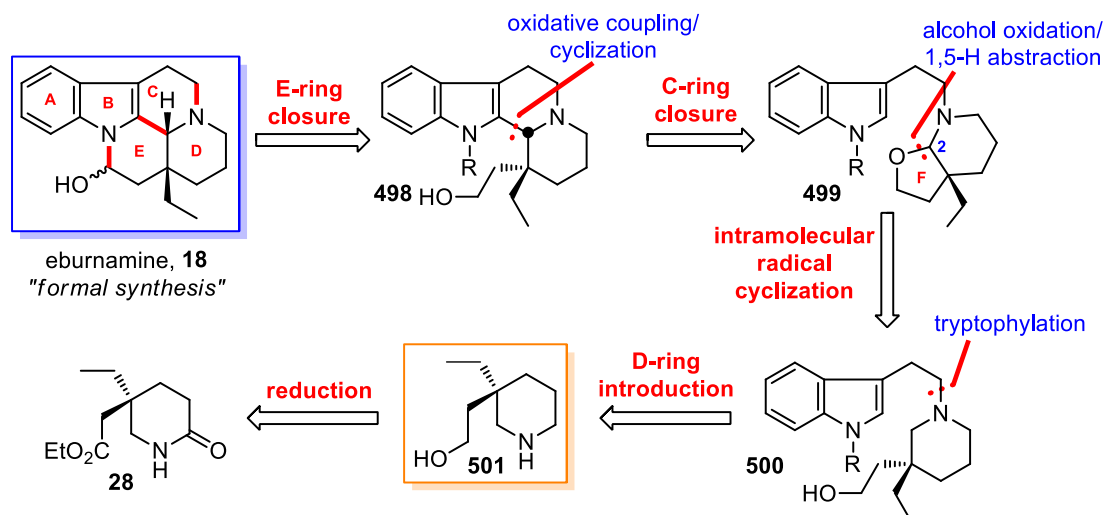
**Scheme V.11.** Revised retrosynthesis of chiral eburnamine skeleton **18**.

Although this plan seemed reasonable at the beginning, efforts to promote the alkylation of the tryptophyl bromide **417a** or its Boc protected form **471b** with a lactam model similar to **28** or with the commercially available 2-piperidinone **379** under strong basic conditions, have all failed. It was suspected that the problem may come from the protecting group; but this reaction was not studied further and the synthesis strategy was modified.

## 6. Modified retrosynthetic strategy of eburnamine

After failing at alkylating the cyclic lactam backbone, it has been proposed that the removal of the lactam's carbonyl group would help to promote the alkylation by enhancing the nucleophilicity of the nitrogen atom. Although the reduction conditions will reduce the ester group at the same time, the alkylation of **501** must then occur smoothly under mild basic conditions (Scheme V.12). The presence of the alcohol group would be used to direct the generation of an iminium ion regioselectively through a 1,5-hydrogen atom transfer (HAT). The selective generation of an alkoxy radical will be challenging due to the complexity of the molecule. However, it might be possible to induce the cyclization and therefore to generate the iminium ion under acidic conditions and subsequent nucleophilic attack of the indole ring on the cationic carbon center at C-2. The aza-

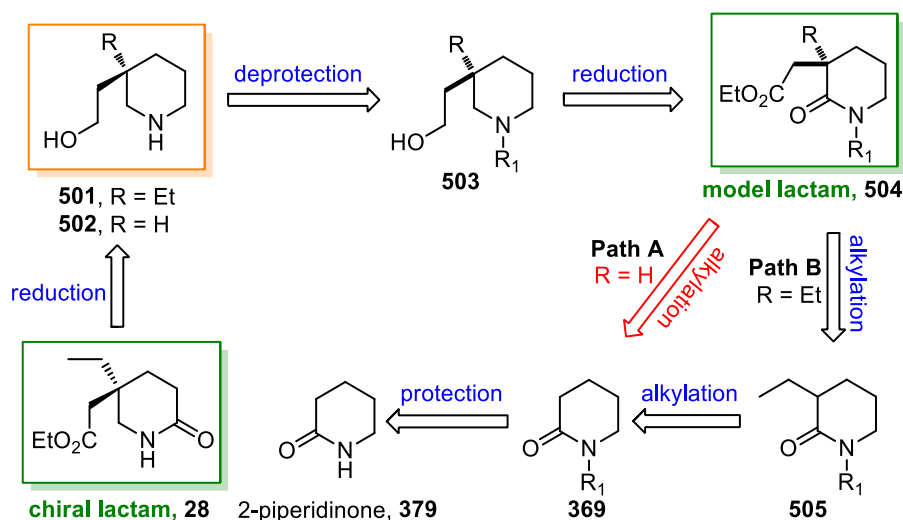
hemiacetal **498** could then be oxidized by Ley-Griffith's TPAP/NMO system with concomitant cyclization to deliver eburnamine **18** after a final reduction.



**Scheme V.12.** Modified retrosynthetic strategy of eburnamine.

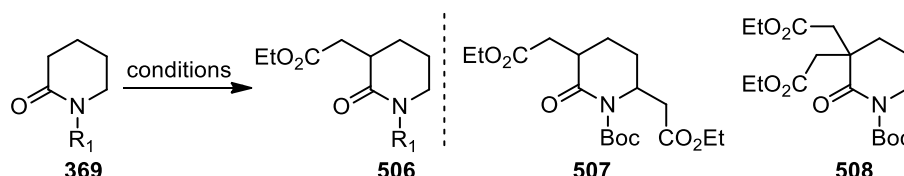
### 6.1. Synthesis of the precursors

The next step was then to synthesize a piperidine model **501** with the alcohol chain at position-3, in a short and efficient way, to elaborate enough material for further investigation (Scheme V.13). This could be accessed through path A (R = H) or B (R = Et). Path A would deliver the desired alcohol in fewer steps, while path B would give access to the racemic version of **501**, mimicking the synthesis of the enantiopure synthon. 2-piperidinone **379** would be a cheap and readily available precursor for this strategy; the presence of the carbonyl group would direct the alkylation selectively at the position-3 after deprotonation of the acidic proton  $\alpha$ - to the carbonyl; the second alkylation (path B) would also take place selectively. Although the model **504** and the chiral **28** do not have the carbonyl group on the same side, this will not be a problem since this functionality will be reduced later to deliver the protected amino-alcohol **503**. The deprotection of **503** will give access to the desired template **501** ready for further manipulation.



**Scheme V.13.** Synthetic strategies of the model study.

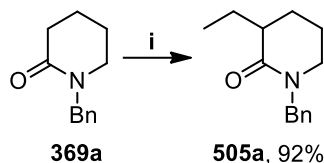
At first, the path A ( $R = H$ ) was investigated. The Boc-protected piperidinone **369b**, was chosen for the easiness of the deprotection step at a later stage. The alkylation of **369b** with ethyl bromoacetate was performed under LDA conditions, however, the reaction gave an inseparable mixture of the desired product **506** and the double alkylated one **507** (Table V.1, entry 1). Using ethyl chloroacetate as the alkylating agent was believed to help, slowing down the reaction rate and hopefully control the alkylation process. Although the reaction was much slower, it gave the same mixture of products as in the previous case (entry 2). Changing the addition order of LDA and 2-piperidinone provided also the same result (entry 3). Although the proton next to the carbonyl is supposed to be the most acidic, the presence of the Boc group activates the site next to the nitrogen (acidic proton). Therefore, two sites are activated and prone to deprotonation. It was then suggested that stirring the deprotonated product at  $-30\text{ }^{\circ}\text{C}$  before the addition of the alkylating agent, would only generate the lithium enolate. This hypothesis was confirmed; however, the double alkylated **508** was obtained (entry 4), in agreement with observations reported in the literature.<sup>443</sup> When the Bn-protected lactam **369a** was used, a complex mixture of products was obtained (entry 5), while no reaction was observed with the Bz-protected analog **369c** (entry 6). This pathway was then abandoned and the efforts directed towards path B.



entry	R <sub>1</sub>	time (h)	method	yield (%)
1	Boc	4	A	<b>506 + 507</b>
2 <sup>a</sup>	Boc	16	A	<b>506 + 507</b>
3	Boc	5	B	<b>506 + 507</b>
4	Boc	9	C	<b>508</b>
5	Bn	8	C	nd
6	Bz	6	C	nr

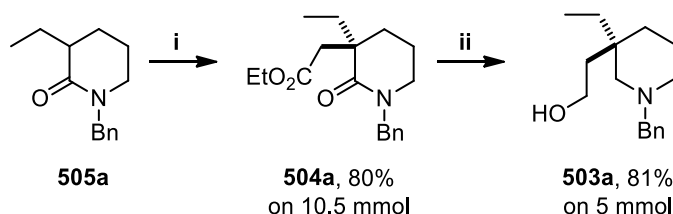
**Table V.1.** Alkylation attempts following path A. *Reagents and conditions:* ethyl bromoacetate (1.2 eq.), LDA (1.2 eq.), THF (0.1 M),  $-78$  to  $20\text{ }^{\circ}\text{C}$ . <sup>a</sup> Ethyl chloroacetate was used. **A:** Addition of LDA to **369**. Stirring at  $-78\text{ }^{\circ}\text{C}$  for 2 h, then addition of ethyl bromo/chloroacetate at  $-78\text{ }^{\circ}\text{C}$ . **B:** Addition of **369** to LDA. Stirring at  $-78\text{ }^{\circ}\text{C}$  for 2 h, then addition of ethyl bromoacetate at  $-78\text{ }^{\circ}\text{C}$ . **C:** Addition of **369** to LDA. Stirring at  $-78\text{ }^{\circ}\text{C}$  for 2 h, then at  $-30\text{ }^{\circ}\text{C}$  for 1 h. Then, addition of ethyl bromoacetate at  $-78\text{ }^{\circ}\text{C}$ .

Path B was designed as a model sequence to install the all-carbon quaternary center present in the eburnamine. Since the Boc protecting group was not the best choice to work with, the Bn-protected lactam **369a** was submitted to alkylation. The use of KHMDS as a base gave no reaction after 9 h. However, following Stoltz's procedure<sup>444</sup> using LDA, the desired product was isolated in 92% in a clean manner on a 0.5 mmol scale (Scheme V.13). Increasing the scale to 7 mmol gave **505a** in 73% without observation of undesired reactions.



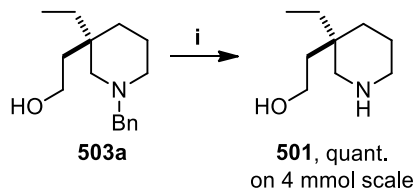
**Scheme V.13.** Monoalkylation of **369a**. *Reagents and conditions:* i) EtI (1.2 eq.), LDA (1.2 eq.), THF (0.1 M), 0 to -78 to 20 °C, 5 h.

The second alkylation with ethyl bromoacetate went smoothly following the same procedure used with ethyl iodide. The  $\alpha$ -quaternary lactam **504a** was obtained in 80% yield on 10.5 mmol scale (Scheme V.14). The reduction of the amide and ester groups with LAH under reflux afforded the alcohol **503a** in 81% yield on a 5 mmol scale.



**Scheme V.14** Sequential alkylation/reduction of the amide **505a**. *Reagents and conditions:* i) Ethyl bromoacetate (3.0 eq.), LDA (1.5 eq.), THF (0.3 M), 0 to -78 to 20 °C, 20 h. ii) LAH (4.0 eq.), THF (0.05 M), 66 °C, 12 h.

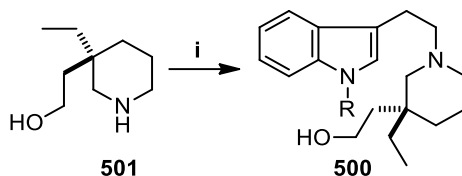
With the amino-alcohol **503a** in hand, the deprotection conditions were investigated. The best conditions were obtained under hydrogenation (1 atm) with Pearlman's catalyst in methanol at 50 °C (Scheme V.15). The reaction afforded the amino alcohol **501** in a quantitative yield on a 4 mmol scale. Other conditions were unsuccessful; no conversion was observed at 22 or 35 °C or using other solvents such as EtOAc and THF. No reaction was observed using palladium on charcoal at 22 °C.



**Scheme V.15.** Deprotection of Bn-protected alcohol **503a** under hydrogenation conditions. *Reagents and conditions:* i) H<sub>2</sub> (1 atm), Pd(OH)<sub>2</sub>/C (40 wt. %), MeOH (0.03 M), 50 °C, 48 h.

The tryptophylation of the amino-alcohol with indole **371** was then investigated to construct the molecular structure **500** necessary for the oxidation studies. The alkylation was first conducted with potassium carbonate in DMF to yield the desired product in 17% yield (Table V.2, entry 1). Better conditions using sodium carbonate as a base in refluxing acetonitrile afforded **500a** in 74% yield (entry 2). The Boc-protected tryptophyl bromide **371b** was also submitted to the alkylation with **500b** under the same conditions to afford the corresponding product in a 73% yield (entry 3). Once the amino-alcohol was alkylated as planned, the oxidation conditions were investigated.



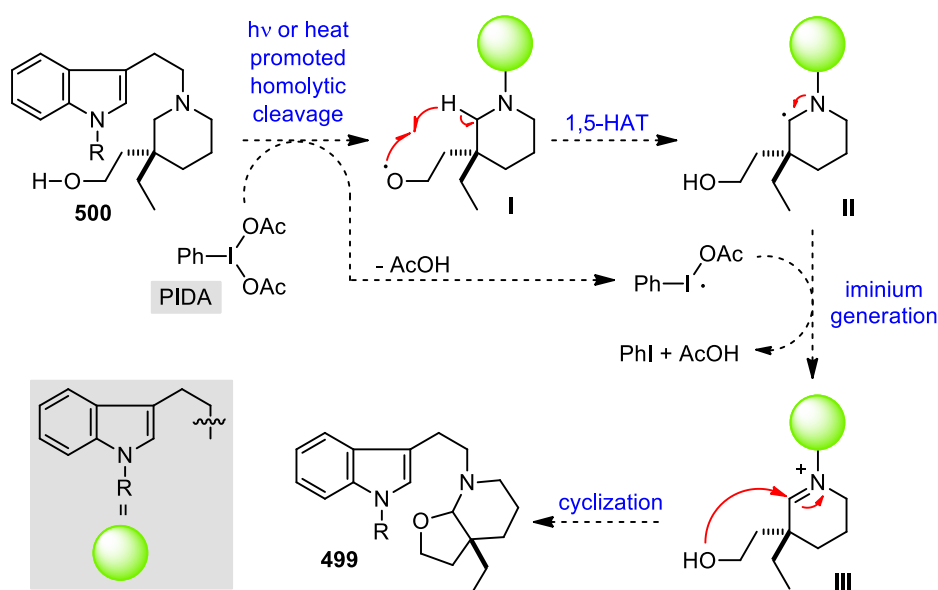


entry	R	base	conditions	yield (%)
1	H	K <sub>2</sub> CO <sub>3</sub>	DMF, 70 °C, 17 h	17
2	H	NaHCO <sub>3</sub>	CH <sub>3</sub> CN, 80 °C, 16 h	74
3 <sup>a</sup>	Boc	NaHCO <sub>3</sub>	CH <sub>3</sub> CN, 80 °C, 16 h	73

**Table V.2.** Alkylation of **501** with tryptophyl bromide. *Reagents and conditions:* i) **371a** (1.2 eq.), base (4.0 eq.), solvent (0.1 M). <sup>a</sup> Starting from **371b**.

## 6.2. Synthesis of hemiaminal **499** using hypervalent iodine

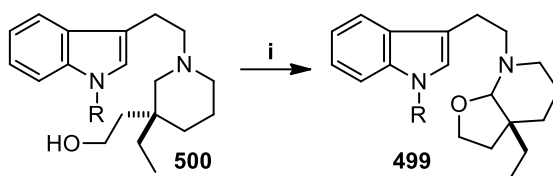
It was planned that the generation of an alkoxy radical from indole **500** could be promoted using PIDA or PIFA under irradiation or heating conditions (Scheme V.14). The 1,5-hydrogen atom transfer (1,5-HAT) reaction from the alkoxy radical (**I**) would then allow the regioselective activation of the C(sp<sup>3</sup>)-H bond next to the nitrogen. The resulting alkyl radical (**II**) would then direct the generation of an iminium ion (**III**) followed by the nucleophilic attack of the alcohol to construct the hemiaminal skeleton **499**.



**Scheme V.14.** Planned synthesis of hemiaminal **499**.

The use of PIDA or PIFA in HFIP to generate the alkoxy radical from compound **500a** led to a decomposition of the starting material after 2 h (Table V.3, entries 1 and 2). Reaction of **500a** with PIDA in acetonitrile led to no conversion with only traces of degradation (entry 3). It was thought that the generated acetic acid from PIDA might be detrimental for the reaction; for this reason, 2 equivalents of sodium carbonate were added to neutralize the mixture. Still, no reaction was observed (entry 4), nor with dichloromethane as a solvent (entry 5). In the latter case, a prolonged stirring led to complete decomposition of the starting material. To favor the iodide bond breaking in PIDA, the reaction was performed under irradiation with blue LEDs. In this case, a complete degradation of the

starting material was observed (entry 6). Adding a catalytic amount of iodine in the medium to favor the formation of the O-I bond, gave the same results (entry 7). Considering the above failure, the reaction was then performed on the Boc-protected indole **500b** to limit the side reactions. However, using PIDA or PIFA, no conversion was observed and the starting material was recovered unchanged (entries 8 and 9). When the reaction was performed with a catalytic amount of iodine under irradiation, the decomposition of the starting material was observed (entry 10). Anticipating that the electron-rich piperidine nitrogen center might be oxidized under such conditions,<sup>445</sup> efforts to generate the alkoxy radicals were then directed towards other conditions.

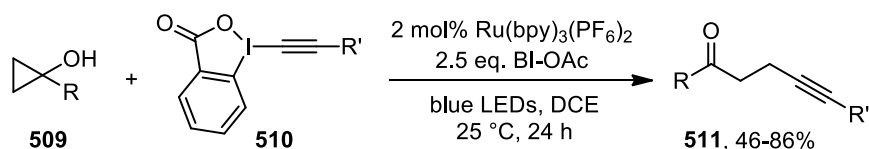


entry	R	oxidant	solvent	additive	time (h)	yield
1	H	PIDA	HFIP	-	2	decomp.
2	H	PIFA	HFIP	-	2	decomp.
3	H	PIDA	CH <sub>3</sub> CN	-	10	nr
4	H	PIDA	CH <sub>3</sub> CN	NaHCO <sub>3</sub> <sup>a</sup>	5	nr
5	H	PIDA	CH <sub>2</sub> Cl <sub>2</sub>	NaHCO <sub>3</sub> <sup>a</sup>	3 <sup>b</sup>	nr
6 <sup>c</sup>	H	PIDA	CH <sub>3</sub> CN	-	15	decomp.
7 <sup>c</sup>	H	PIDA	CH <sub>3</sub> CN	I <sub>2</sub> <sup>d</sup>	18	decomp.
8	Boc	PIDA	CH <sub>3</sub> CN	-	12	nr
9	Boc	PIFA	CH <sub>3</sub> CN	-	12	nr
10 <sup>c</sup>	Boc	PIDA	CH <sub>3</sub> CN	I <sub>2</sub> <sup>d</sup>	17	decomp.

**Table V.3.** Screening of the oxidation conditions. *Reagents and conditions:* i) oxidant (1.1 eq.), solvent (0.1 M), 20-30 °C. <sup>a</sup> NaHCO<sub>3</sub> (2.0 eq.). <sup>b</sup> Complex mixture of products after 16 h. <sup>c</sup> Blue LEDs. <sup>d</sup> I<sub>2</sub> (0.2 eq.).

### 6.3. Synthesis of hemiaminal **499** under photooxidative conditions

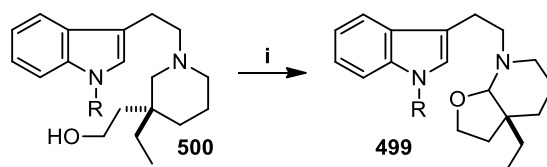
Jia and co-workers<sup>446,447</sup> succeeded at generating an alkoxy radical using mild photocatalytic conditions, in the presence of cyclic iodine(III) reagent, BI-OAc, as the iodine source (Scheme V.15). In their work, they mentioned that the cyclic iodine (III) reagents were more reactive and chemoselective compared to the non-cyclic analogs. Their methodology was applied to a wide scope of substrates giving the expected products in moderate to high yields.



**Scheme V.15.** C(*sp*<sup>3</sup>)-C(*sp*<sup>3</sup>) bond cleavage and alkynylation using cyclic iodine(III) reagents.<sup>447</sup>

It was suggested that these conditions would be able to generate an alkoxy radical in a more selective way. The alkoxy radical would then undergo 1,5-HAT to form the tetrahydrofuran ring after formation of the iminium and cyclization. However, applying their conditions to the substrate **500a**

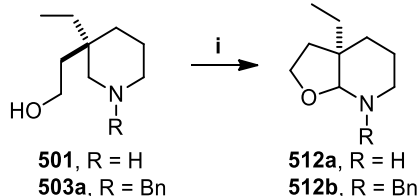
led to a complex mixture of products (Table V.4, entry 1), while the protected analog **500b** gave back the starting material (entry 2). Performing the reaction at 50 °C or in acetonitrile led also to decomposition (entries 3 and 4). Other catalysts such as [Ir(dtbbpy)(ppy)<sub>2</sub>][PF<sub>6</sub>]<sub>2</sub> and Ir(ppy)<sub>3</sub> gave back the starting material (entries 5 and 6). The presence of the *N*- piperidyl nitrogen is itself oxidizable; in order to check if the alkoxy radical is formed, TEMPO was added to the reaction mixture (entry 7). A complex mixture was however obtained with complete degradation of the starting material, which suggests that many sites are probably oxidized, leading to side reactions and degradation of the substrate.



entry	R	PC	solvent	temp (°C)	time (h)	yield
1	H	[Ru]	DCE	30	15	decomp.
2	Boc	[Ru]	DCE	30	15	nr
3	Boc	[Ru]	DCE	50	4	decomp.
4	Boc	[Ru]	CH <sub>3</sub> CN	30	14	decomp.
5	Boc	[Ir]	DCE	30	14	nr
6	Boc	Ir(ppy) <sub>3</sub>	DCE	30	14	nr
7 <sup>a</sup>	Boc	[Ru]	DCE	30	14	decomp.

**Table V.4.** Screening of the photocatalytic oxidation conditions. *Reagents and conditions:* i) PC (0.1 eq.), BI-OAc (2.5 eq.), blue LEDs. [Ru] = Ru(bpy)<sub>3</sub>(PF<sub>6</sub>)<sub>2</sub>, [Ir] = [Ir(dtbbpy)(ppy)<sub>2</sub>][PF<sub>6</sub>]<sub>2</sub>. <sup>a</sup> TEMPO (1.0 eq.).

In order to check if the reaction would occur on simpler substrates lacking the reactive indole ring, **503a** was chosen for further investigation. The reaction was performed in the presence of PIDA or PIFA, however, no reaction was observed and the starting material was recovered after column chromatography (Table V.5, entries 1 and 2). Applying the ruthenium conditions studied above led to a complex mixture of unidentified products (entry 3). The reaction with PIDA on the secondary amine **501** gave a complex mixture as expected (entry 4).



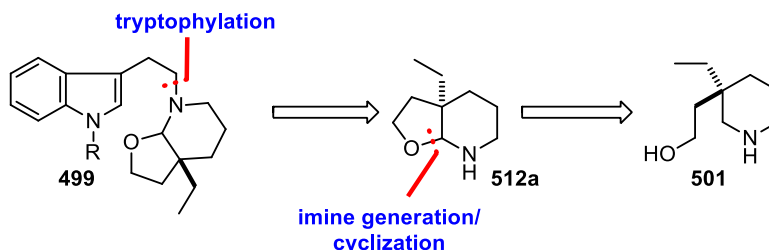
entry	R	oxidant	additive	solvent	time (h)	yield
1	Bn	PIDA	-	CH <sub>3</sub> CN	16	nr
2	Bn	PIFA	-	CH <sub>3</sub> CN	15	nr
3 <sup>a</sup>	Bn	[Ru]	BI-OAc	DCE	16	comp. mix.
4	H	PIDA	-	CH <sub>3</sub> CN	14	comp. mix.

**Table V.5.** Screening of the oxidation conditions. *Reagents and conditions:* i) oxidant (1.1 eq.), solvent (0.05 M), Ru(bpy)<sub>3</sub>(PF<sub>6</sub>)<sub>2</sub> (0.1 eq.), BI-OAc (2.5 eq.), 20-30 °C. <sup>a</sup> Blue LEDs.

As the experiments showed, the nitrogen atom on the non-indole part is most probably oxidized which makes the reactions messy and unpredictable. Another way to install the tetrahydrofuran ring was then looked for.

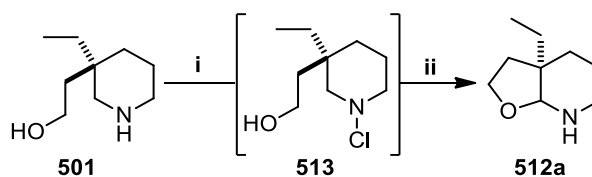
#### 6.4. Synthesis of hemiaminal **499** under basic conditions

It was proposed that the indole **499** could be obtained from the alkylation of tryptophyl bromide with furane **512a** (Scheme V.16). The latter could be constructed from alcohol **501**.



**Scheme V.16.** An alternative plan for the synthesis of **499**.

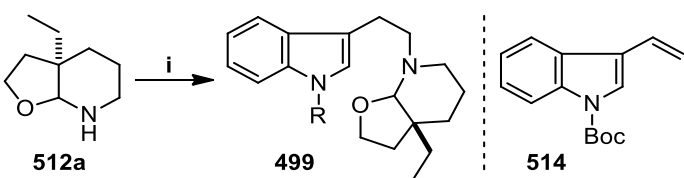
Pandey and co-workers<sup>448</sup> reported the synthesis of hemiaminal derivative **512a** in their total synthesis of leucolusine. **512a** was synthesized from the amino-alcohol **501** in two steps after *N*-chlorination followed by elimination with sodium methoxide. Applying the described conditions led only to traces of the product **512a** (Table V.6, entry 1). Repeating the reaction many times gave the same result. Increasing the amount of NCS to favor the formation of the chlorinated amine gave also traces of the product (entry 2). Changing the solvent to dichloromethane, however, gave a complex mixture of products (entry 3). Although the second step was messy, the first step using dichloromethane as a solvent gave, as described, a white semi-solid in a quantitative yield. Performing the elimination step with aqueous KOH in dioxane gave the desired product **512a** in 70% yield (entry 4). These conditions were repeated many times to furnish the product in yields between 57-72% in a clean manner. Repeating the reaction using Et<sub>2</sub>O as a solvent in the first step, gave again only traces of the desired product (entry 5).



entry	step i		step ii	3 steps yield
	NCS (eq.)	solvent	conditions	
1	1.1	Et <sub>2</sub> O	NaOMe, MeOH, 50 °C	traces
2	1.8	Et <sub>2</sub> O	NaOMe, MeOH, 50 °C	traces
3	1.8	CH <sub>2</sub> Cl <sub>2</sub>	NaOMe, MeOH, 50 °C	comp. mix.
4	1.8	CH <sub>2</sub> Cl <sub>2</sub>	KOH, dioxane, 70 °C	70%
5	1.8	Et <sub>2</sub> O	KOH, dioxane, 70 °C	traces

**Table V.6.** Screening conditions for the synthesis of **512a**. *Reagents and conditions:* i) 20 °C, 2 h. ii) NaOMe (10.0 eq.) or 20 % aq. KOH (0.2 M), 4 h.

The hemiaminal **512a** was then submitted to alkylation with tryptophyl bromide **471a**. Under the optimal condition obtained for the tryptophylation of amino-alcohol **501**, a complex mixture was obtained (Table V.7, entry 1). The reaction was then performed with sodium carbonate in refluxing dioxane, but no conversion was observed and the crude  $^1\text{H}$  NMR showed that the reactants remained unchanged (entry 2). Trying these conditions on the Boc-protected tryptophyl bromide **471b** did not afford any conversion, however, traces of the indole **514** were identified by  $^1\text{H}$  NMR (entry 3). Refluxing the mixture in  $\text{CH}_3\text{CN}$  gave the same results (entry 4) while starting from Bz-protected tryptophyl bromide **471c** led to a complex mixture of products (entry 5).

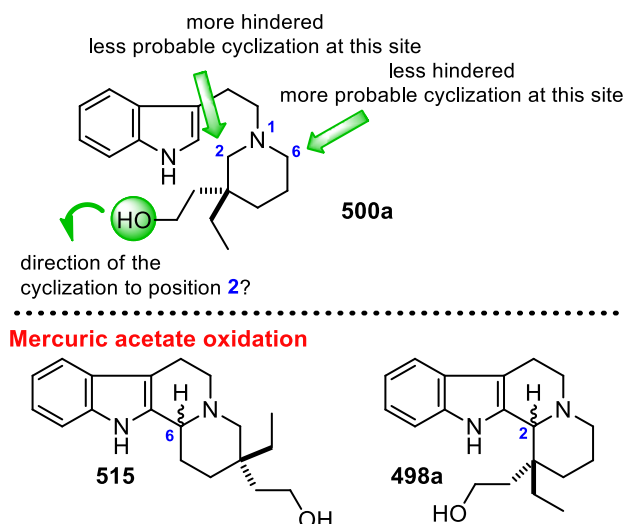


entry	R	base	solvent	yield
1	H	$\text{NaHCO}_3$	$\text{CH}_3\text{CN}$	comp. mix.
2	H	$\text{K}_2\text{CO}_3$	dioxane	nr
3	Boc	$\text{K}_2\text{CO}_3$	dioxane	nr, traces of <b>514</b>
4	Boc	$\text{K}_2\text{CO}_3$	$\text{CH}_3\text{CN}$	nr, traces of <b>514</b>
5	Bz	$\text{K}_2\text{CO}_3$	$\text{CH}_3\text{CN}$	nr

**Table V.7.** Attempts for the alkylation of **512a**. *Reagents and conditions:* i) **471** derivatives (1.2 eq.), base (4.0 eq.), solvent (0.1 M), reflux, 12 h.

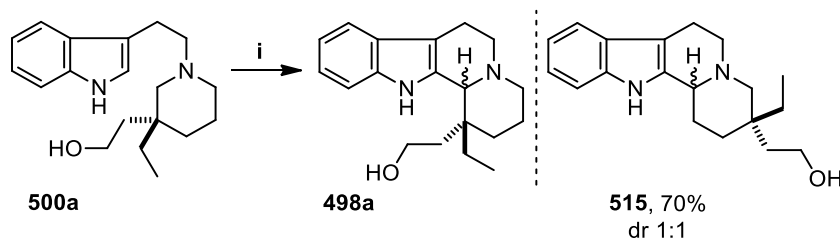
## 7. Construction of ring C under oxidative conditions

After the unsuccessful attempts to synthesize the compound **499**, it was decided to submit the indole **500a** to oxidative conditions following Fujii's procedure ( $\text{Hg}(\text{OAc})_2$ ,  $\text{NaBH}_4$ ).<sup>449</sup> It is known that oxidizing such compounds under the mercuric acetate oxidation reaction would generate regioselectively a radical on position **6**, the less hindered site of the piperidine ring (Figure V.4). This would later induce the formation of the iminium ion intermediate followed by the cyclization with the tryptophyl fragment to give the tetracycle **515**. It was however hoped, that the presence of an alcohol group five atoms away from the carbon  $\alpha$ - to the nitrogen **1** would direct the generation of the iminium ion at the position **2** instead of **6**, to finally furnish the desired tetracyclic backbone **498a**.<sup>450</sup>



**Figure V.4.** Possible cyclization under Fujii's conditions.

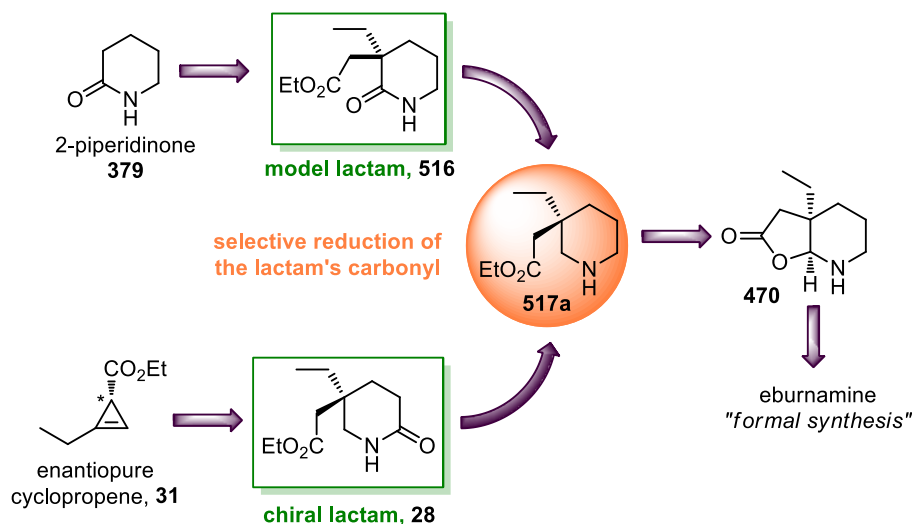
The application of this procedure delivered, however, the eburnane-type compound **515** in 70% yield as a 1:1 mixture of two separable diastereoisomers (Scheme V.17). This cyclization had placed the quaternary center away from the indole ring as originally expected.



**Scheme V.17.** Oxidation of **500a** under Fujii's conditions. *Reagents and conditions:* i) 1.  $\text{Hg}(\text{OAc})_2$  (3.0 eq.),  $\text{EDTA-Na}_2$  (3.0 eq.),  $\text{EtOH}/\text{H}_2\text{O}$ : 1/2 (0.02 M), 78 °C, 4 h. 2.  $\text{NaBH}_4$  (10.0 eq.),  $\text{CH}_2\text{Cl}_2$  (0.03 M), 0 to 20 °C, 12 h.

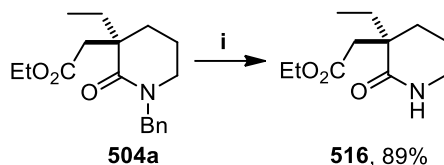
## 8. Alternative approach for the synthesis of eburnamine

It was then decided to modify the plans and to selectively reduce the lactam group without affecting the ester group present in compound **516** (Scheme V.18). This would give the amine **517a** which would be transformed later into Wenkert's lactone **470**. The latter would then be engaged in the construction of the pentacyclic core of eburnamine following Wenkert's approach.<sup>451</sup> This strategy would be also applied to the chiral lactam **20** to deliver the amine **517a** after the selective reduction of the lactam's carbonyl. The straightforward synthesis of the natural product in an enantioselective fashion will then be investigated.



### 8.1. Selective reduction of the lactam's carbonyl

The Bn-protected lactam **504a** was then submitted to hydrogenation to deprotect the benzyl group and furnish the corresponding lactam **516** in 89% yield (Scheme V.19). This reaction was repeated several times to give **516** in 70-89% yield range after 2 to 4 days.



**Scheme V.19.** Deprotection of **504a**. *Reagents and conditions:* i)  $\text{H}_2$  (1 atm),  $\text{Pd}(\text{OH})_2/\text{C}$  (50 wt. %), MeOH (0.02 M), 50 °C, 4 days.

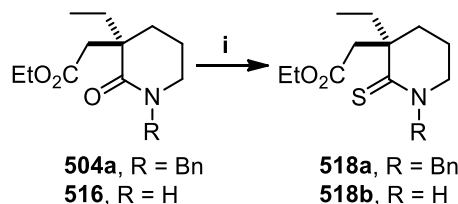
The selective reduction was performed in the presence of  $\text{BH}_3\text{-Me}_2\text{S}$ , however, no reaction was observed with both the protected **504a** and the deprotected **516**, probably due to the steric hindrance at the all-carbon quaternary stereocenter next to the carbonyl (Table V.8, entries 1 and 2). In contrast with an excess of borane, 35% of **503a** were isolated (entry 3).

entry	R	$\text{BH}_3 \cdot \text{Me}_2\text{S}$ (eq.)	yield (%)
1	H	2	0
2	Bn	2	0
3	Bn	5	<b>503a</b> (35%)

**Table V.8.** Attempts for selective reduction of the amide functional group. *Reagents and conditions:* i) THF (0.1 M), 0 to 20 °C, 24 h.

Since the selective lactam reduction was unsuccessful in the presence of the ester group, it was envisioned to remove the lactam's carbonyl after converting it to a thionyl group followed by

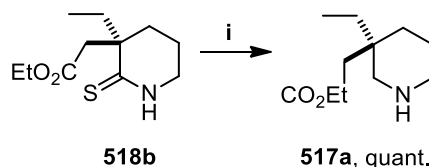
desulfurization. Thus, the lactam adduct **504a** was refluxed with Lawesson's reagent in toluene.<sup>452</sup> However, the corresponding thioamide **518a** was not detected and only the starting material was recovered (Table V.9, entry 1). Performing the reaction on the deprotected lactam **516** did not give the desired product, even in the presence of 2 eq. of Lawesson's reagent (entries 2 and 3). In the presence of 0.6 eq. of P<sub>2</sub>S<sub>5</sub> in refluxing toluene, no reaction was observed on **504a** and 70% of the starting material were recovered with the observation of some decomposition (entry 4), whereas, using an excess of P<sub>2</sub>S<sub>5</sub> led to a complete decomposition of the substrate (entry 5). In contrast with these results, when the reaction was performed on lactam **516**, 65% of the desired thiolactam **518b** were isolated (entry 6). This reaction gave the product in a 46-65% yield range due to its sensitivity. In order to optimize the yield further, the reaction was performed in benzene, but the product **518b** was isolated in 17% yield only, along with 50% of unreacted starting material (entry 7). The poor results observed with Lawesson's reagent are likely resulting from the steric hindrance next to the all-carbon quaternary stereocenter.



entry	R	[S] source (eq.)	time (h)	yield (%)
1	Bn	LR (1.0)	24	0
2	H	LR (1.0)	24	0
3	H	LR (2.0)	24	0
4	Bn	P <sub>2</sub> S <sub>5</sub> (0.6)	12	<b>504a</b> (70)
5	Bn	P <sub>2</sub> S <sub>5</sub> (1.2)	12	decomp.
6	H	P <sub>2</sub> S <sub>5</sub> (0.6)	7	<b>518b</b> (65)
7 <sup>a</sup>	H	P <sub>2</sub> S <sub>5</sub> (0.6)	10	<b>518b</b> (17), <b>516</b> (50)

**Table V.9.** Synthesis of thiolactam **518**. LR = Lawesson's reagent. *Reagents and conditions:* i) toluene (0.05 M), 110 °C. <sup>a</sup> Benzene.

With the thiolactam **518b** in hand, the desulfurization was performed under H<sub>2</sub> atmosphere in the presence of an excess of Raney<sup>®</sup>-nickel to give smoothly the desired amine **517a** in a quantitative yield in a clean manner (Scheme V.20). This product can be used in the next steps without purification. No reaction took place when a catalytic amount of Raney<sup>®</sup>-nickel was used, or in the absence of H<sub>2</sub> even when the mixture was heated at reflux.

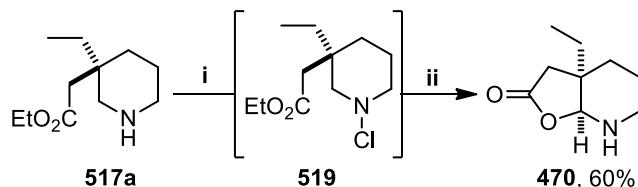


**Scheme V.20.** Desulfurization of **518b**. *Reagents and conditions:* i) H<sub>2</sub> (1 atm), Raney<sup>®</sup>-nickel (excess), THF (0.02 M), 20 °C, 12 h.



## 8.2. Synthesis of carbinolamine lactone **470**

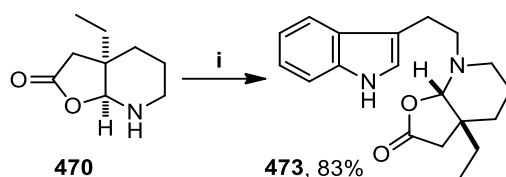
The amine **517a** was later submitted to NCS in order to obtain the *N*-chloroamine **519**, which was directly submitted to aqueous KOH in refluxing dioxane (Scheme V.21). These conditions afforded the desired carbinolamine lactone **470** in 60% yield after several optimizations of the workup procedure.



**Scheme V.21.** Synthesis of carbinolamine lactone **470**. *Reagents and conditions:* i) NCS (1.2 eq.), CH<sub>2</sub>Cl<sub>2</sub>, 20 °C, 4 h. ii) 20 % aq. KOH, dioxane (0.1 M), 100 °C, 6 h.

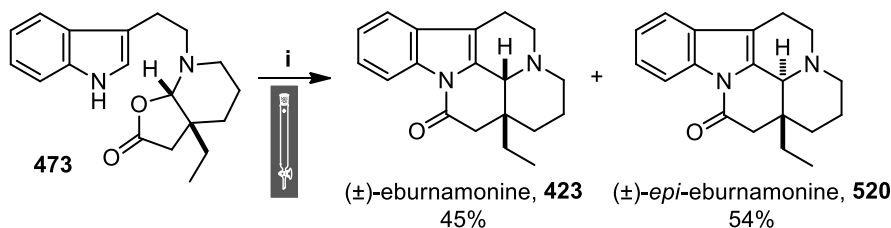
## 8.3. Construction of the eburnane alkaloids

Following the formal synthesis developed by Wenkert and co-workers,<sup>451</sup> lactone **470** was alkylated with tryptophyl bromide **471a** under basic conditions to give the corresponding indole **473** in 83% yield (Scheme V.22). The reproducibility of this reaction gave the product in 75-83% yield range.



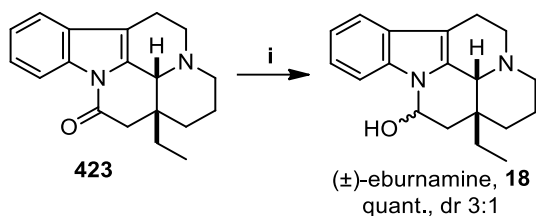
**Scheme V.22.** Synthesis of indole **473**. *Reagents and conditions:* i) tryptophyl bromide (2.0 eq.), K<sub>2</sub>CO<sub>3</sub> (3.5 eq.), dioxane (0.1 M), 100 °C, 12 h.

The lactone **473** was then refluxed in glacial acetic acid to give the (±)-eburnamonine **423** and (±)-*epi*-eburnamonine **520** in 45% and 54% respectively (87% combined yield), in 1:1.2 diastereomeric ratio (vs. dr 1:1.3 reported by Wenkert) (Scheme V.23). Unlike the report of Wenkert, the *epi*-eburnamonine **520** was the major diastereomer and not **423**. Repeating the reaction gave the same diastereomeric ratio. Both diastereoisomers were easily separable through column chromatography and the analytical data were in agreement with those reported in the literature.



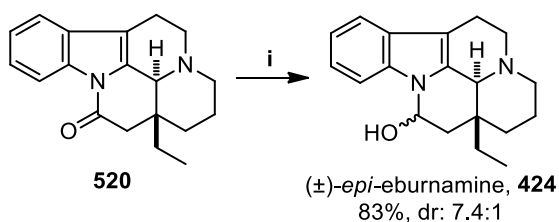
**Scheme V.23.** Synthesis of eburnamonine and *epi*-eburnamonine. *Reagents and conditions:* i) AcOH (0.04 M), 110 °C, 48 h.

Eburnamonine **423** was later submitted to the reduction conditions using LAH to give eburnamine **18** in a quantitative yield after 30 min of reaction as a mixture of two diastereomers (dr 3:1 or 75:25) (Scheme V.24).



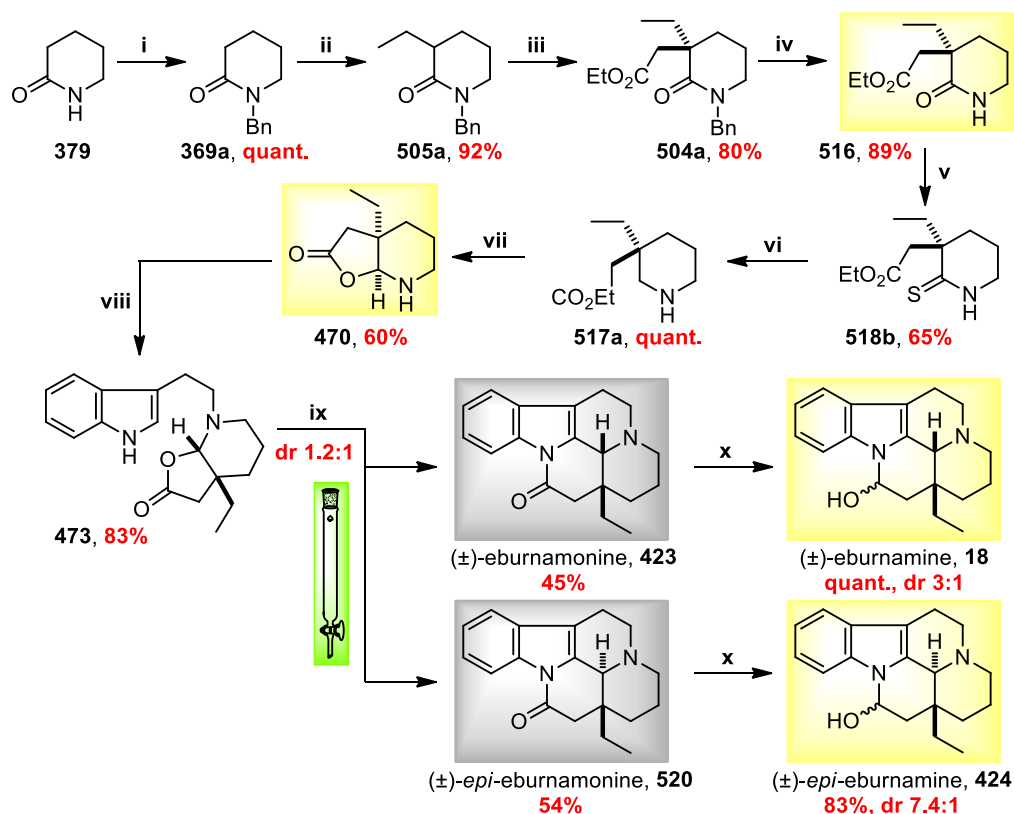
**Scheme V.24.** Synthesis of eburnamine. *Reagents and conditions:* i) LAH (2.0 eq.), THF (0.023 M), 0 °C, 30 min.

Similarly, *epi*-eburnamonine **520** was submitted to the same reaction conditions to furnish the *epi*-eburnamine **424** in 83% yield as a mixture of two diastereomers (dr 7.4:1 or 88:12) (Scheme V.25).



**Scheme V.25.** Synthesis of *epi*-eburnamine. *Reagents and conditions:* i) LAH (2.0 eq.), THF (0.023 M), 0 °C, 30 min.

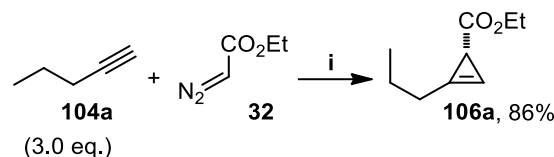
## 9. Summary scheme of the total synthesis of (±)-eburnamine



**Scheme V.26.** Summary scheme of the racemic total synthesis of eburnane series. *Reagents and conditions:* i) BnBr, NaH; ii) EtI, LDA; iii) Ethyl bromoacetate, LDA; iv) Pd(OH)<sub>2</sub>/C, 50 °C; v) P<sub>2</sub>S<sub>5</sub>; vi) H<sub>2</sub> (1 atm), Raney<sup>®</sup>-nickel; vii) 1. NCS, 2. KOH; viii) tryptophyl bromide, K<sub>2</sub>CO<sub>3</sub>; ix) AcOH, 110 °C; x) LAH.

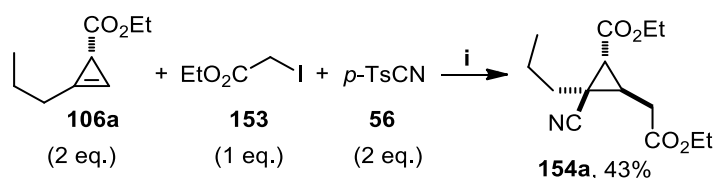
## 10. Application towards the enantioselective total synthesis of eburnamine

In order to perform the enantiomeric version of the total synthesis of eburnamine, the cyclopropene model **106a** was prepared based on the procedure reported by Landais *et al.*<sup>47</sup> The cyclopropanation of an excess of pentyne **104a** with ethyl diazoacetate **32** in the presence of a catalytic amount of rhodium acetate gave the cyclopropene **106a** in 86% yield (Scheme V.27).



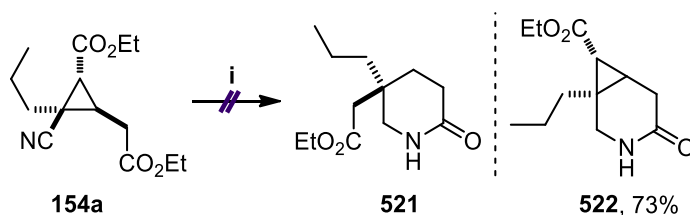
**Scheme V.27.** Synthesis of cyclopropene **106a**. *Reagents and conditions:* i)  $\text{Rh}_2(\text{OAc})_4$  (0.01 eq.),  $\text{CH}_2\text{Cl}_2$  (0.5 M), 20 °C, 14 h.

This olefin was then functionalized through the carbo-cyanation reaction<sup>47</sup> to deliver the poly-functionalized cyclopropane **154a** presenting an all-carbon quaternary center in 43% yield (Scheme V.28).



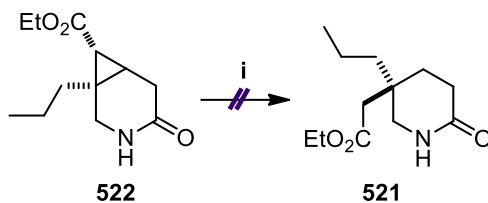
**Scheme V.28.** Carbo-cyanation reaction of cyclopropene **106a**. *Reagents and conditions:* i)  $(\text{SnMe}_3)_2$  (2.0 eq.), DTBHN (0.4 eq.), benzene (0.2 M), 65 °C, 13 h.

The nickel boride-mediated reduction reaction was then performed on cyanide **154a**. Unexpectedly, the cyclopropane fused lactam **522** was isolated in 73% yield (Scheme V.29). In this reaction, the ring-opening did not occur, contrasting with observations made in the cyclobutane series.



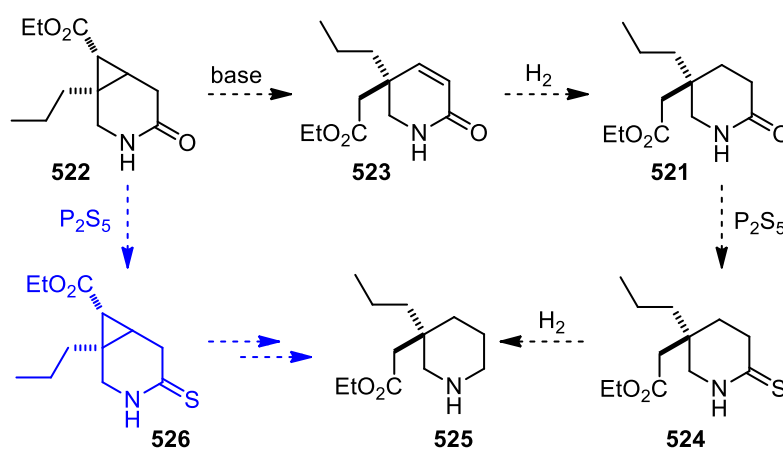
**Scheme V.29.** Nickel boride-mediated reduction reaction of cyclopropane **154a**. *Reagents and conditions:* i)  $\text{NiCl}_2$  (2.2 eq.)  $\text{NaBH}_4$  (20.0 eq.) EtOH (0.025 M), 0 to 20 °C, 48 h.

Re-submitting the cyclopropane **522** to nickel boride conditions did not provoke the ring-opening and the starting material was recovered (Scheme V.30). The absence of an ester moiety  $\alpha$ - to the carbonyl in **522** probably explains the difference in reactivity. Yet, further study is required to confirm this hypothesis.



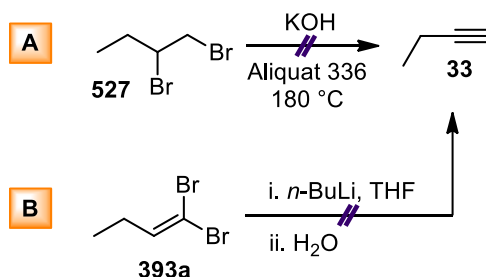
**Scheme V.30.** Attempts for cyclopropane ring-opening of **522**. *Reagents and conditions:* i)  $\text{NiCl}_2$  (2.2 eq.)  $\text{NaBH}_4$  (20.0 eq.)  $\text{EtOH}$  (0.025 M), 0 to 20 °C, 12 h.

The cyclopropane ring-opening would be possible, using a strong base such as LDA (*Dr. Nitin Dange, post-doc*). Such a base would deprotonate the proton  $\alpha$ - to the carbonyl to give the unsaturated compound **523** (Scheme V.31). After reduction of the double bond, the lactam **521** would be converted to the thiolactam **524**. Desulfurization would then deliver the amine **525**. Alternatively, treatment with  $\text{P}_2\text{S}_5$  could be applied first to cyclopropane **522**.



**Scheme V.31.** Possible transformations to access amine **525**.

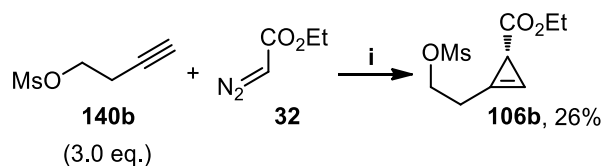
In order to move forward towards the synthesis of the desired chiral cyclopropene **31**, the cyclopropenation had to start from but-1-yne **33**. Due to its high cost, it was decided to develop a synthesis of this gas following the reaction procedure described by Szántay and co-workers<sup>453</sup> (Scheme V.32.A). However, several attempts failed to deliver the desired product, probably due to the necessity to work on a large scale. Alternatively, the use of the Corey-Fuchs reaction<sup>453</sup> did not afford the desired but-1-yne (Scheme V.32.B).



**Scheme V.32.** Attempts for but-1-yne synthesis.

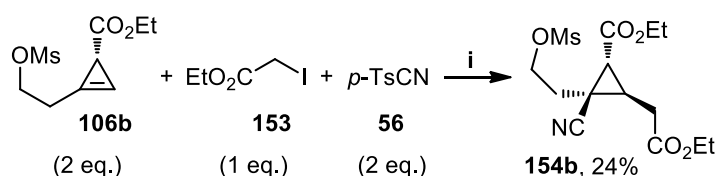
To solve this problem, it was envisioned to start from an alkyne functionalized with a good leaving group such as a mesylate, which would be easier to access and to manipulate. This leaving group would be eliminated several steps later during the nickel boride-reduction reaction. This

strategy seemed efficient since no additional steps would be needed. Based on this plan, the cyclopropenation of alkyne **140b** with ethyl diazoacetate was performed in the presence of chiral rhodium catalyst (*S,S*)-Rh<sub>2</sub>(OAc)(DPTI)<sub>3</sub> **105** (Scheme V.33). The latter was prepared in three steps starting from (1*S*,2*S*)-diphenylethanediamine. Cyclopropene **106b** was isolated in 26% yield.



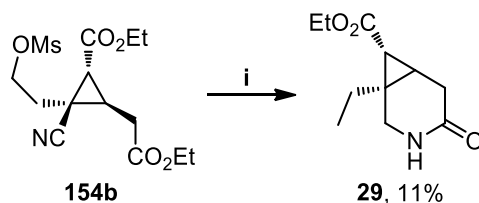
**Scheme V.33.** Synthesis of cyclopropene **106b**. *Reagents and conditions:* i) (*S,S*)-Rh<sub>2</sub>(OAc)(DPTI)<sub>3</sub> (0.05 eq.), CH<sub>2</sub>Cl<sub>2</sub> (0.5 M), 20 °C.

The carbo-cyanation of cyclopropene **106b** afforded the cyclopropane **154b** in a low yield of 24% (Scheme V.34).



**Scheme V.34.** Carbo-cyanation reaction of cyclopropene **106b**. *Reagents and conditions:* i) (SnMe<sub>3</sub>)<sub>2</sub> (2.0 eq.), DTBHN (0.4 eq.), benzene (0.2 M), 65 °C, 6 h.

The application of the reduction reaction using nickel boride catalyst gave the desired lactam **29** with the ethyl side chain as expected (Scheme V.35). However, only 11% (2 mg) were obtained with formation of a complex mixture of products. The structure of compound **29** was confirmed by mass spectrometry and <sup>1</sup>H NMR, but other analyses were not performed due to the small isolated amount. Due to the lack of time, this reaction was not studied further and the enantioselective synthesis could not be accomplished.



**Scheme V.35.** Nickel boride-mediated reduction reaction of cyclopropane **154b**. *Reagents and conditions:* i) NiCl<sub>2</sub> (2.2 eq.) NaBH<sub>4</sub> (20.0 eq.) EtOH (0.025 M), 0 to 20 °C, 12 h.

## 11. Conclusion

In this chapter, the total synthesis of racemic eburnamonine and eburnamine was investigated. This synthesis was not straightforward and the construction of the ring C of eburnamine proved to be complicated with the model under study. After several attempts, the total synthesis of (±)-eburnamonine and (±)-*epi*-eburnamonine was achieved in 9 steps in 1:1.2 diastereomeric ratio, starting from a cheap commercially available 2-piperidinone (δ-valerolactam). After an easy separation through column chromatography, these compounds were then reduced in an additional step to give eburnamine and *epi*-eburnamine, respectively. Both alkaloids were thus obtained in 10

steps sequence, in ~ 81% average yield and 9.5% overall yield. Although this synthesis was developed as an entry towards the enantioselective synthesis of eburnamine, the latter was not accomplished due to the lack of time. Yet, the required steps were developed on a similar chiral model and they can be later applied to the desired target.



## *Chapter VI*

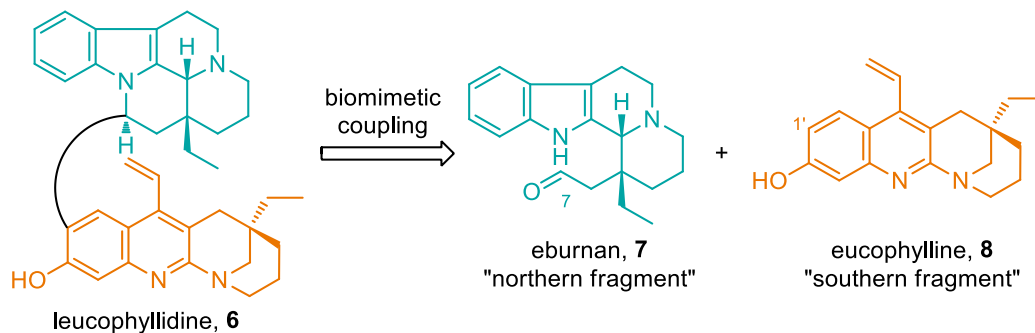
### *Biomimetic Coupling Studies Towards Leucophyllidine*





## 1. Introduction

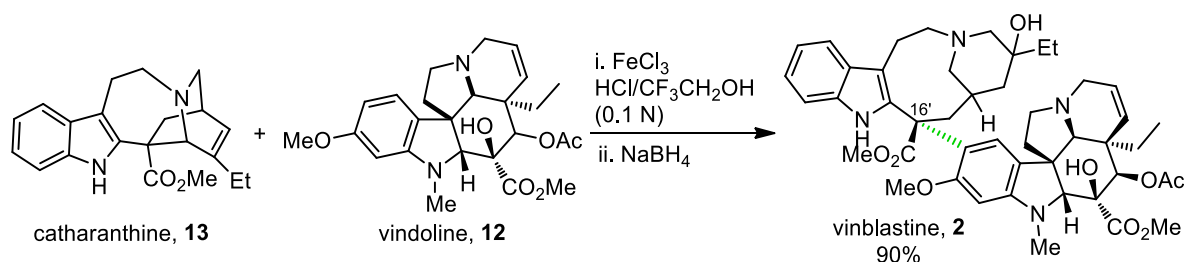
Morita and co-workers<sup>2</sup> isolated both leucophyllidine, eburnamine and eucophylline from *leuconotis eugenifolius*. This finding advocates that the biogenetic analysis proposed by Kam *et al.*,<sup>1</sup> consisting of a coupling between the two fragments, eburnan **7** and eucophylline **8**, will most probably produce leucophyllidine **6**. Monomers coupling would proceed through a Mannich-type reaction between the C-7 electrophilic center of eburnan **7** and the C-1' electron-rich center of eucophylline **8** to afford the bis-indole template of leucophyllidine (Scheme VI.1).



Scheme VI.1. Retrosynthesis of leucophyllidine.

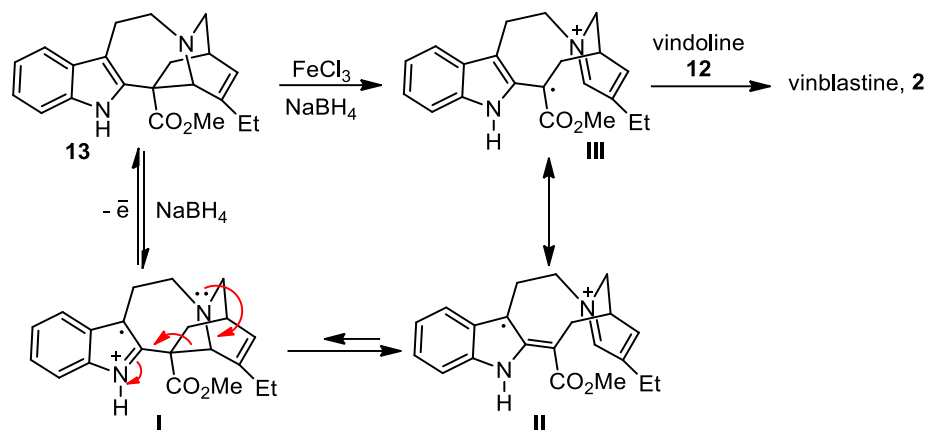
## 2. Biomimetic coupling in the synthesis of dimeric indole alkaloids

When considering the synthesis of these types of dimeric natural products, only a few syntheses were designed relying on the biomimetic couplings between two alkaloid monomers. Among the most well-known examples in the biomimetic coupling approaches is the synthesis of vinblastine **2** described by Boger and co-workers and several others before.<sup>11,37</sup> In Boger's work, the catharanthine **13** monomer was activated using Fe(III) to promote its coupling with vindoline **12**, thus providing a biomimetic access to vinblastine **2** (Scheme VI.2). This reaction showed high stereochemical selectivity to produce exclusively the natural diastereomer.



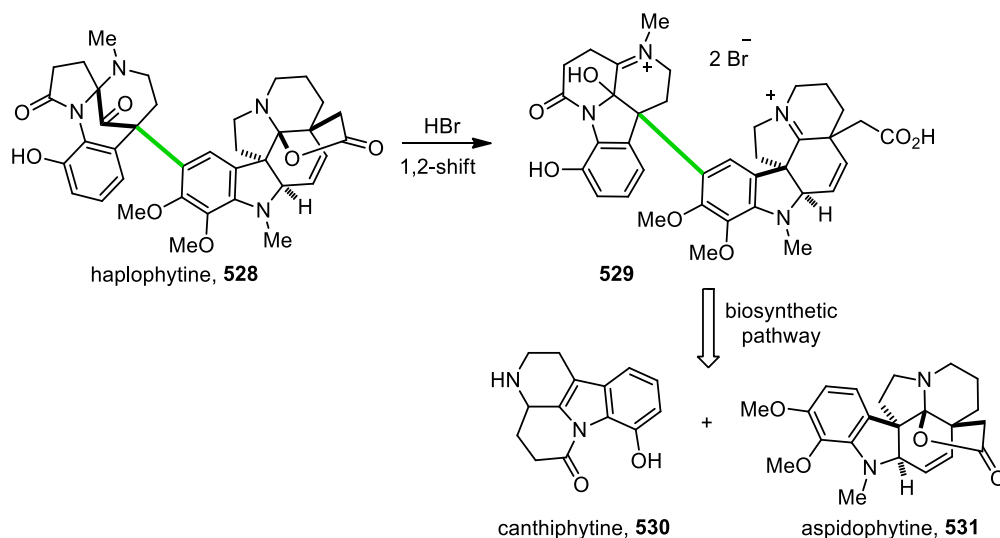
Scheme VI.2. Biomimetic approach in the total synthesis of vinblastine.<sup>37</sup>

Mechanistic studies showed that the reaction proceeds through free-radical oxidation. At first, an electrophilic radical is generated in catharanthine **13** monomer by single-electron oxidation of the indole ring by the Fe(III) salt (Scheme VI.3). Later, an intramolecular one-electron-two center bonding interaction between the radical site  $\alpha$ - to the carbomethoxy group and the iminium carbon stabilizes a conformation in which the upper face of the radical is sterically blocked. Finally, the addition of this radical to the electron-rich vindoline furnishes the natural diastereomer.<sup>454</sup>



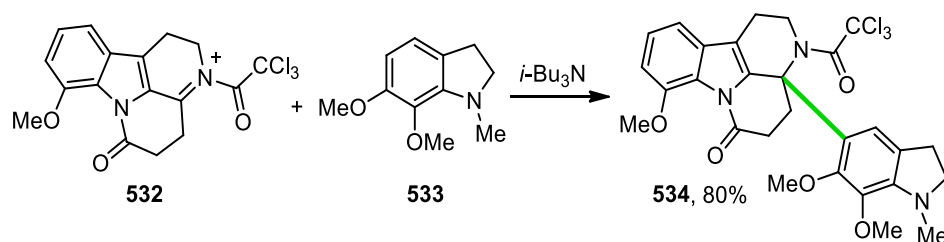
**Scheme VI.3.** Proposed mechanism for vinblastine biomimetic coupling.<sup>454</sup>

The biomimetic coupling of haplophytine **528** was also studied by several groups.<sup>455–457</sup> In this alkaloid, the coupling between its two fragments occurs on an all-carbon quaternary stereocenter, which was found challenging to construct.<sup>457</sup> Knowing that the indole fragment aspidophytine **531** was also found in the plant, it was hypothesized that the treatment of haplophytine in acidic medium results in a 1,2-cationic shift. Upon rearrangement, this generates a new bis-iminium skeleton **529** that is probably involved in the biosynthetic pathway (Scheme VI.4).



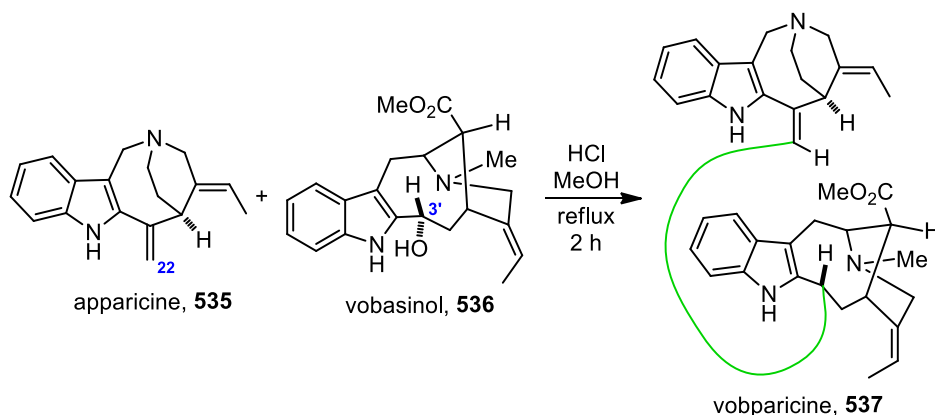
**Scheme VI.4.** Hypothetic biosynthesis of haplophytine.

During the investigations in the total synthesis of haplophytine **528**, Corey and co-workers studied the coupling process between two models of an electron-rich arene **533** and a canthiphytine derivative **532** (Scheme VI.5).<sup>457</sup> They concluded that it is not operative to generate a benzylic quaternary center under the studied conditions in order to promote this sterically unfavorable coupling.



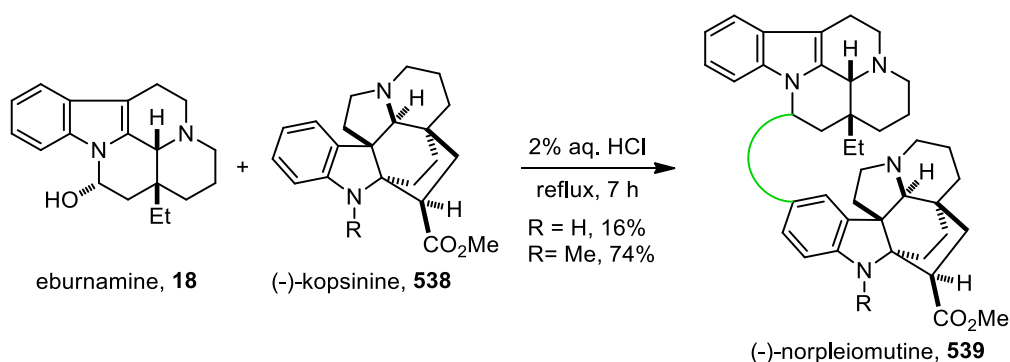
**Scheme VI.5.** Model study towards the synthesis of Haplophytine.<sup>457</sup>

Swenden and co-workers<sup>458</sup> described the biomimetic coupling of the monomer vobasinol **536** with an excess of apparicine **535** under acidic conditions to furnish the bis-indole alkaloid vobparicine **537** (Scheme VI.6). It was proposed that the coupling occurs through a reaction between the C-3' electrophilic center of vobasinol and the C-22 electron-rich center of apparicine **535**.



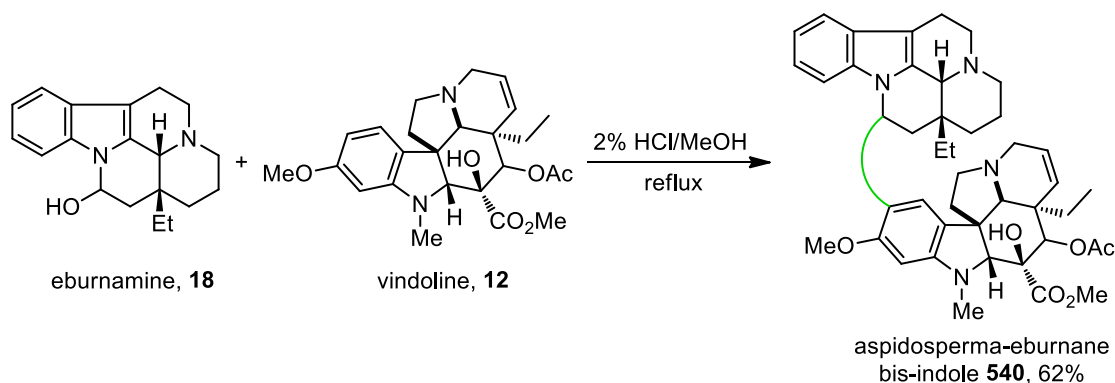
**Scheme VI.6.** Biomimetic coupling of vobparicine **537**.<sup>458</sup>

Magnus and Brown<sup>459</sup> also described the successful synthesis of (-)-norpleiomutine **539**. The synthesis of this bis-indole alkaloid occurred through the coupling between two fragments, eburnamine **18** and (-)-kopsinine **538**, in 2% aqueous HCl (Scheme VI.7).



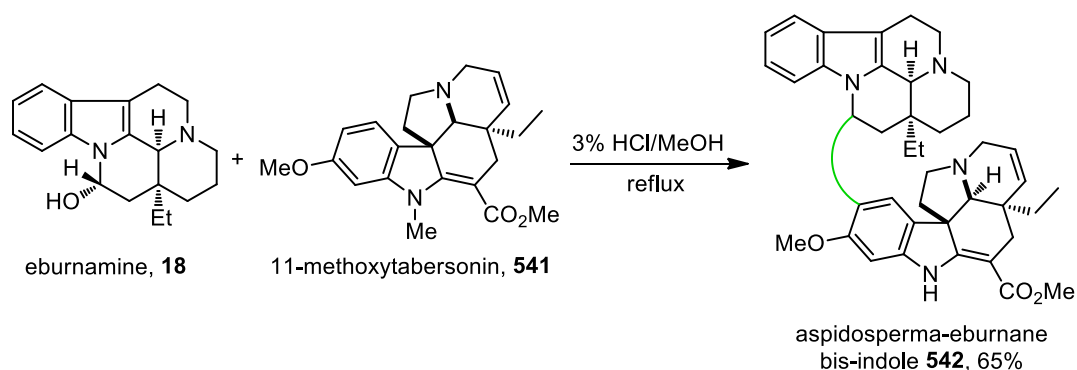
**Scheme VI.7.** Biomimetic coupling in (-)-norpleiomutine.<sup>459</sup>

Szántay and co-workers<sup>460</sup> reported the biomimetic coupling between eburnamine **18** and vindoline **12** in a mixture of HCl/MeOH to give the non-natural bis-indole aspidosperma-eburnane **540** in 62% yield, thus proving the generality of this method (Scheme VI.8).



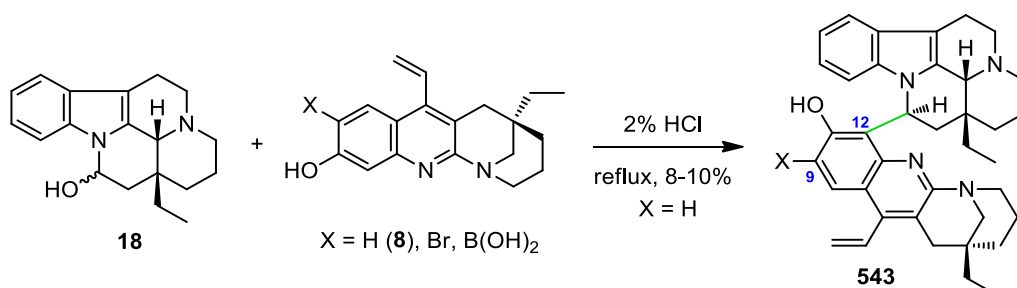
**Scheme VI.8.** Szántay biomimetic coupling in aspidosperma-eburnane bisindole **540**.<sup>460</sup>

Passarella and co-workers<sup>461</sup> reported the synthesis of aspidosperma-eburnane type alkaloid **542** in 65% yield (Scheme VI.9). This alkaloid results from the biomimetic coupling between eburnamine **18** and 11-methoxytabersonin **541** in 3% HCl/MeOH solution.



**Scheme VI.9.** Passarella biomimetic coupling in aspidosperma-eburnane bis-indole **542**.<sup>461</sup>

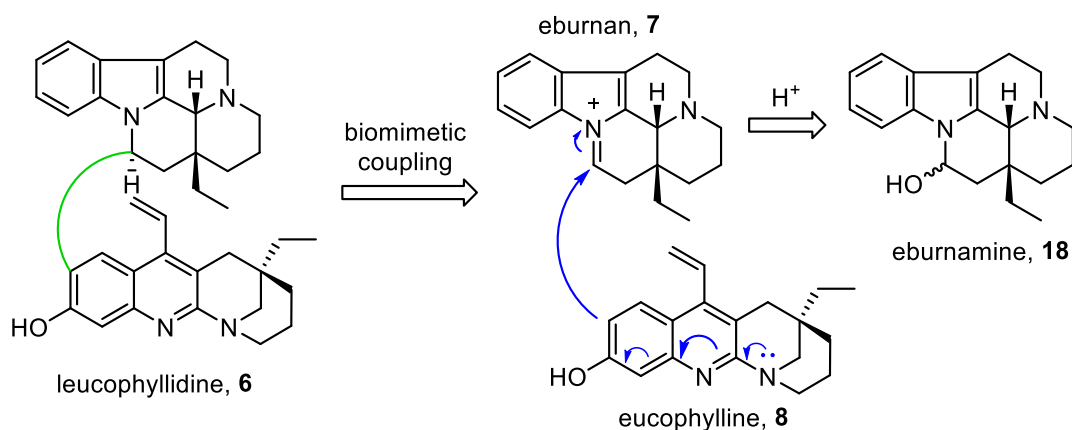
Recently, Pandey and co-workers<sup>352</sup> reported the synthesis of molecule **543**, the regioisomer of leucophyllidine **6** (Scheme VI.10). Eucophylline **8** and eburnamine **18** were heated in the presence of 2% HCl giving the wrong regioisomer **543** in 8-10% yield after 7 days. The coupling at the undesired position (C-12) was explained according to the stability of Wheland intermediates. Other attempts like the Petasis reaction with the boronic acid ( $X = \text{B}(\text{OH})_2$ ) and the reaction between the lithiated eucophylline (from lithium-halogen exchange,  $X = \text{Br}$ ) with the iminium generated *in situ* by the treatment of  $\text{BF}_3 \cdot \text{OEt}_2$  failed to give the expected result. Although a Mannich-type coupling was proposed, and in spite of the precedent from the literature, as mentioned above, the obtained results suggest that probably a more complex mechanism is involved in this dimerization.



**Scheme VI.10.** Attempts for biomimetic coupling in leucophyllidine by Pandey *et al.*<sup>352</sup>

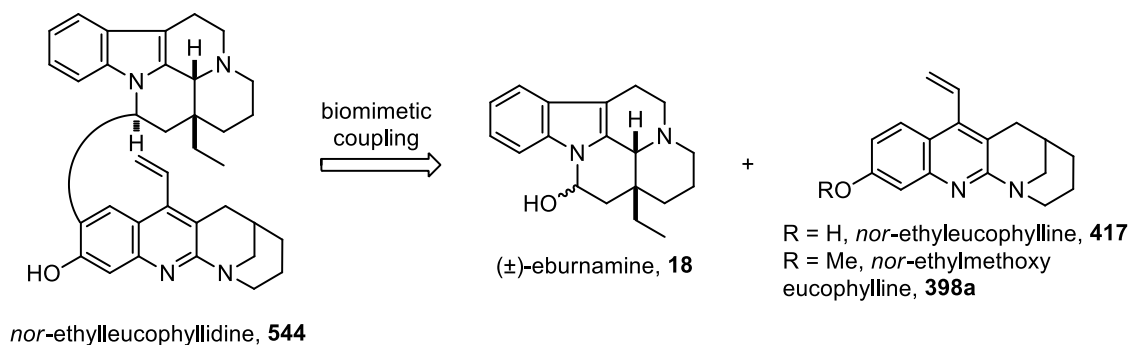
### 3. Proposed strategy for the biomimetic coupling in leucophyllidine

Based on the aforementioned biomimetic approaches, the synthesis of leucophyllidine will be first studied through a direct Mannich-type coupling between the *ortho*-phenol fragment of eucophylline **8** (or the methoxy analog) and the iminium generated from eburnamine **18** (Scheme VI.11). Triggering the complete conversion of the eburnamine **18** to the corresponding iminium **7** will be investigated under different conditions. It was anticipated that the stereochemistry might be controlled during the biomimetic coupling by the torsional effects generated at the transition state through the  $\text{CH}_2$  moiety adjacent to the iminium. The eucophylline **8** would approach the eburnan **7** from the top face of the iminium intermediate, *syn* to the ethyl group on the quaternary center, providing thus, the desired diastereomer.



**Scheme VI.11.** Proposed biomimetic coupling in leucophyllidine **6**.

Therefore, to save the available and valuable amount of eucophylline, the feasibility of this biomimetic coupling approach will be investigated through model **417** which is very similar to the south fragment, eucophylline, and the racemic eburnamine **18** (Scheme VI.12). These substrates will be tested under several reaction conditions, for which some of them were already investigated in the literature. These studies would provide information on the regio- and stereoselectivity of the coupling, as well as the nucleophilicity of the eucophylline and methoxy-eucophylline under the coupling reaction conditions. Based on these results, the coupling between the natural subunits will be performed to produce natural leucophyllidine **6**.

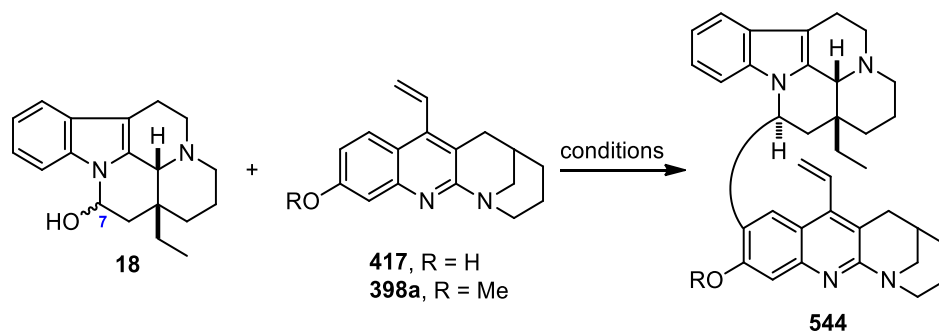


**Scheme VI.12.** Proposed model synthesis of *nor*-ethylleucophyllidine **544**.

#### 4. Biomimetic coupling studies

With the desired subunits in hand, the investigations started by first submitting the reaction to acidic conditions (Table VI.1). When the *nor*-ethylmethoxyeucophylline **398a** was used, no reaction was observed even after 6 days of heating in a 3% HCl/MeOH solution (entry 1). For the eburnamine, no change was observed on TLC, while the protonation of **398a** was detected (TLC, visualization under 360 nm), which gave back the starting material after basic workup (sat. NaHCO<sub>3</sub>). It was also suggested that probably the expected iminium was not formed efficiently under these conditions. To ensure the formation of eburnan **7**, the reaction was performed in an NMR Young tube and the eburnamine was submitted to triflic anhydride to generate the corresponding triflate (entry 2). After 5 min, as observed by <sup>1</sup>H-NMR, the proton at position-7 disappeared with the appearance of another peak at 9.5 ppm that probably corresponds to the iminium proton. Eucophylline model **398a** dissolved in CD<sub>2</sub>Cl<sub>2</sub> was then added. No reaction was observed at 25 °C after 6 h, while heating at 50 °C

provided the protonated form of **398a** in 50% of conversion after 3 days (the conversion was followed by NMR by studying the vinyl signals). After extraction with sat.  $\text{NaHCO}_3$ , the starting materials were recovered. The protonation of the model's nitrogens is caused by the generated triflic acid in the medium. This probably affects the nucleophilicity of the quinoline **398a** and circumvent the coupling process. To prevent the formation of acid in the medium, the eburnamine was treated with  $\text{MsCl}$  to form the corresponding mesylate in the presence of an excess of triethylamine as a scavenger (entry 3). Once the TLC showed total consumption of the eburnamine, model **398a** was added to the medium. No reaction was observed after 24 h, while heating at  $50\text{ }^\circ\text{C}$  for another 24 h resulted in the formation of a new product alongside the starting materials. After column chromatography, a quantity of the eucophylline model was recovered, and surprisingly, the new product was found to correspond to the vinylquinoline fragment, suggesting that some degradation took place. It was then decided to perform the reaction under mild conditions using  $\text{NaHCO}_3$  as a buffer. When model **398a** was used in  $\text{CH}_2\text{Cl}_2$  no reaction was observed and the starting materials were recovered after column chromatography (entry 4). Similarly, using the *nor*-ethyleucophylline **417** in aqueous sodium carbonate did not favor any reaction (entry 5).



entry	R	conditions	observation
1	Me	3% $\text{HCl}/\text{MeOH}$ , $70\text{ }^\circ\text{C}$ , 6 days	protonation of <b>398a</b>
2	Me	$\text{Tf}_2\text{O}$ , $\text{CD}_2\text{Cl}_2$ , 0 to $50\text{ }^\circ\text{C}$ , 3 days	protonation of <b>398a</b>
3	Me	$\text{Et}_3\text{N}$ , $\text{MsCl}$ , $\text{CH}_2\text{Cl}_2$ , 0 to $50\text{ }^\circ\text{C}$ , 2 days	decomposition of <b>398a</b>
4	Me	$\text{NaHCO}_3$ , $\text{CH}_2\text{Cl}_2$ , 20 to $50\text{ }^\circ\text{C}$ , 3 days	nr
5	H	$\text{NaHCO}_3$ , $\text{H}_2\text{O}$ , 20 to $50\text{ }^\circ\text{C}$ , 2 days	nr
6	H	$\text{Et}_3\text{N}$ , $\text{MsCl}$ , $\text{CH}_2\text{Cl}_2$ , 0 to $50\text{ }^\circ\text{C}$ , 15 days	traces of decomposition
7	H	$\text{Et}_3\text{N}$ , $\text{Tf}_2\text{O}$ , $\text{CH}_2\text{Cl}_2$ , 0 to $50\text{ }^\circ\text{C}$ , 10 days	traces of decomposition
8	H	$\text{CHCl}_3$ , 20 to $60\text{ }^\circ\text{C}$ , 10 days	nr
9	H	20% aq. $\text{KOH}$ , 20 to $100\text{ }^\circ\text{C}$ , 13 days	decomposition of <b>18</b>
10	H	mechanical stirring, neat, 2 days	nr

**Table VI.1.** Biomimetic coupling studies in **544**.

The submission of model **417** to the mesyl chloride and triflic anhydride conditions did not allow the coupling to take place, showing that this model wasn't a better choice than **398a** under these conditions (entries 6 and 7). Simple heating at reflux of both subunits **18** and **417** in chloroform for a long time, also did not give the desired outcome, and the starting materials were recovered after column chromatography (entry 8). At this point, it was decided to increase the nucleophilicity of *nor*-

ethyleucophylline template by generating the corresponding phenolate using concentrated aqueous potassium hydroxide. Under such conditions, the eburnamine backbone decomposed while the *nor*-ethyleucophylline was recovered after column chromatography (entry 9). Finally, the vigorous mechanical stirring of **18** and **417** under neat conditions did not promote the coupling and both monomers were recovered (entry 10).



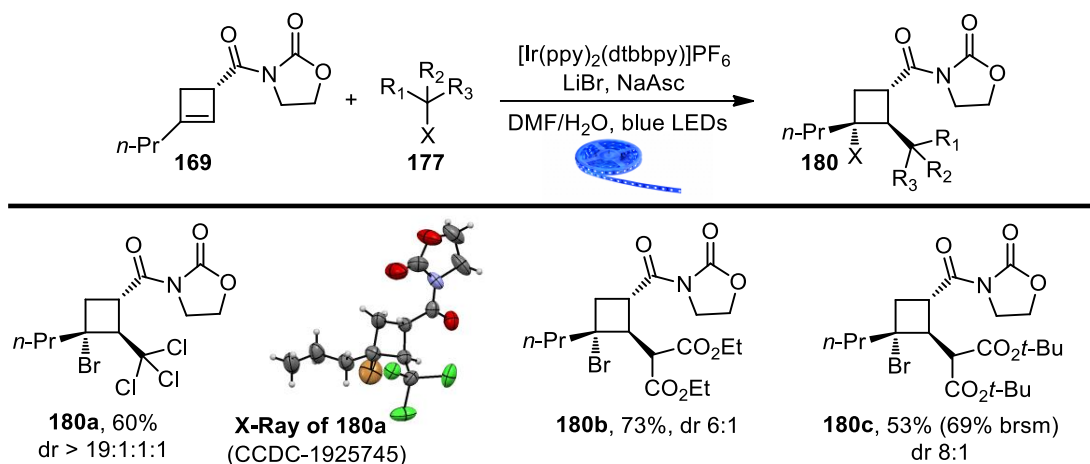


# *General Conclusion & Perspectives*

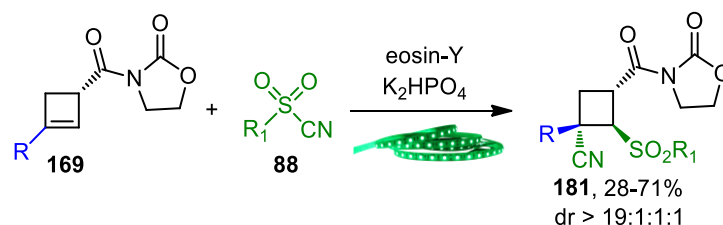


## 1. General conclusion

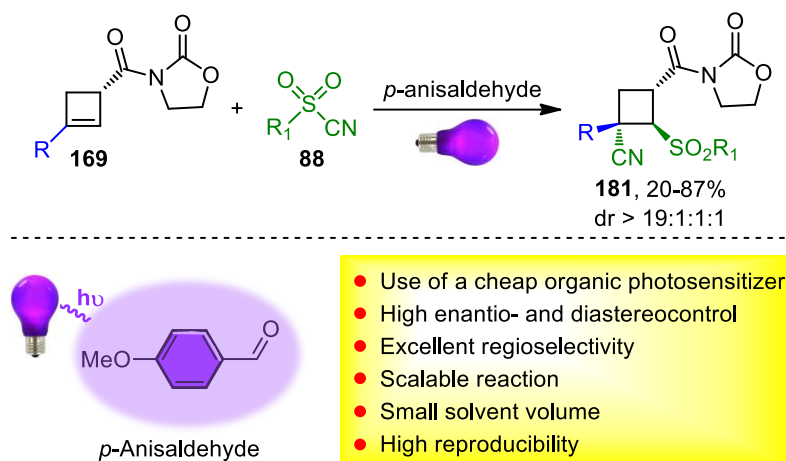
In the first part of this thesis, an efficient enantioselective synthesis of cyclobutenes was described, inspired by the research work of Narasaka and co-workers.<sup>3</sup> A series of functionalized cyclobutenes was obtained through a desulfurization reaction on scales up to 10-20 grams, in excellent yields and enantioselectivities. The reactivity of these cyclobutenes towards free-radical species was studied through the addition of various radical traps. In this context, the carbo-alkynylation, carbo-cyanation, and atom transfer radical addition (ATRA) on cyclobutenes were studied. Haloalkanes were thus shown to add to the cyclobutenes'  $\pi$ -system through ATRA reaction to give the corresponding cyclobutanes in good to high yields (Scheme VII.1). The diastereoselectivity was found to be controlled by the steric hindrance of the oxazolidinone and that of the added radical precursor.



The sulfonyl-cyanation of olefins using eosin-Y as a photocatalyst under visible light irradiation, previously developed by the group,<sup>5</sup> was applied to the four-membered rings. In this process, alkylsulfonyl cyanides were used as excellent radical traps giving a series of polyfunctionalized derivatives **181** presenting nitrile-functionalized all-carbon quaternary centers, in excellent diastereoselectivities and good yields (Scheme VII.2).

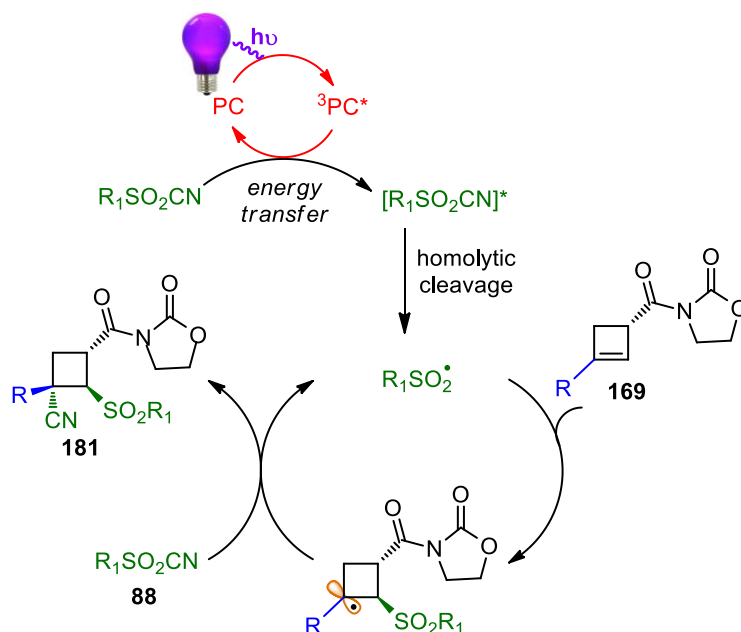


A more efficient sulfonyl-cyanation method was developed using *p*-anisaldehyde, as a photosensitizer (Scheme VII.3). Overall, the reactions were cleaner than those with eosin-Y, easier to carry out, requiring no aqueous treatment at the end of the reaction, and the purifications were more straightforward even on large scale. Eventually, this method proved to be compatible with a series of functional groups and allowed achieving scale-ups without affecting the yields.



**Scheme VII.3.** Sulfonyl-cyanation reaction of cyclobutenes using *p*-anisaldehyde as a photosensitizer.

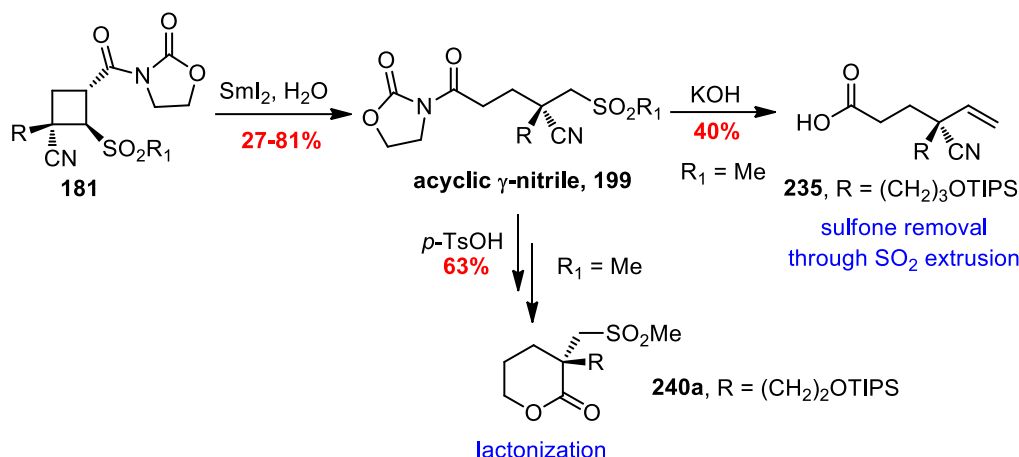
The mechanistic studies showed this reaction to follow an energy transfer mechanism from the excited triplet state of the photosensitizer to the sulfonyl cyanide (Figure VII.1). This would later undergo a homolytic cleavage of the  $\text{O}_2\text{S}-\text{CN}$  bond to form the sulfonyl radical. The electrophilic radical would then add onto the less substituted end of the cyclobutene's double bond to generate a  $\beta$ -sulfonyl radical. The latter would be trapped by  $\text{R}_1\text{SO}_2\text{CN}$ , leading to the expected product and a  $\text{R}_1\text{SO}_2^\bullet$  radical, ready to sustain the radical chain.



**Figure VII.1.** Proposed mechanism for the *p*-anisaldehyde-photosensitized sulfonyl-cyanation.

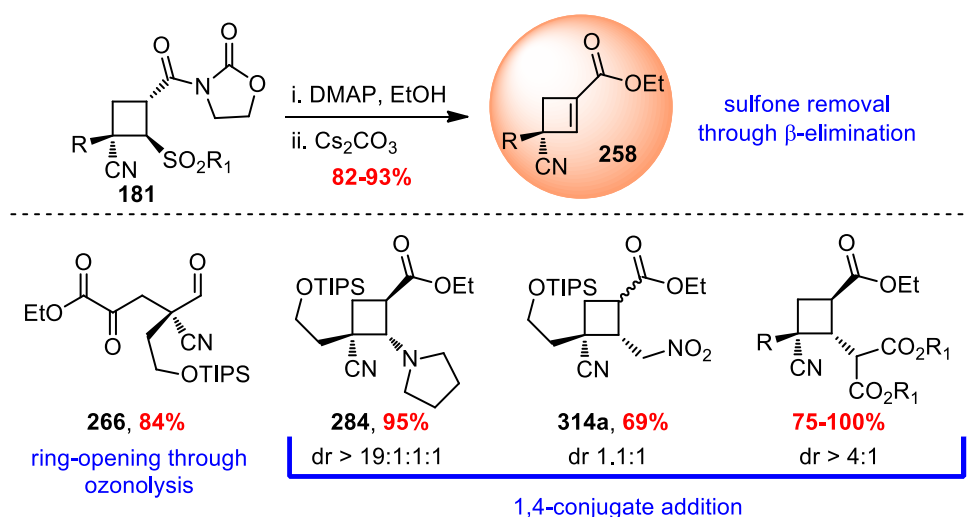
These polyfunctionalized templates were later submitted to ring-opening through radical fragmentation using samarium diiodide (Scheme VII.4). The resulting optically pure acyclic  $\gamma$ -nitriles **199** were obtained in good to high yields showing the compatibility of this procedure with a variety of substituents. The opened products were then transformed into other derivatives showing their utility to access new complex chiral compounds. For instance, the sulfone group could be eliminated under Ramberg-Bäcklund rearrangement conditions to furnish the olefin **235** in 40% yield. Although the desired olefin was obtained, this reaction suffered from problem of reproducibility due to the harsh conditions that probably hydrolyze the nitrile group. From the ring-opened nitrile **199**, a

lactonization reaction was also developed to give access to a new type of lactone **240a** bearing an all-carbon quaternary center, in 63% yield.



**Scheme VII.4.** Sml<sub>2</sub>-promoted ring-opening reaction and derivatives of the ring-opened compound **199**.

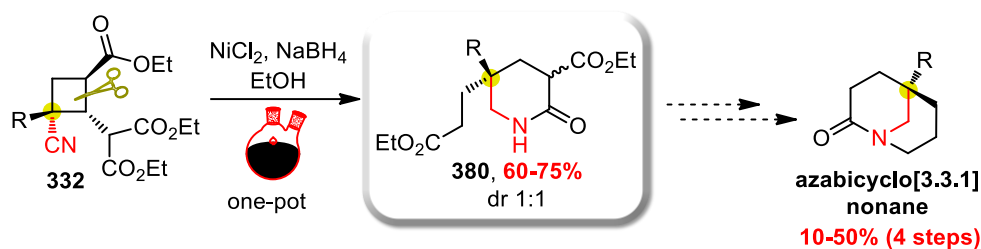
Cyclobutane **181** was also transformed into other useful templates (Scheme VII.5). For instance, the sulfone fragment was eliminated under basic conditions after several optimizations, to give the cyclobutene carboxylate **258** in excellent yields. Good reproducibility was also observed on a range of cyclobutanes on 15-20 mmol scales. These cyclobutenes were manipulated further to develop new ring-opening methods. First, under ozonolysis conditions, cyclobutene carboxylate **258a** gave the ring-opened tricarbonyl compound **266** in 84% yield. This  $\alpha$ -ketoester-aldehyde was found unstable, and several attempts to functionalize it further failed. The enone **258** was found reactive towards nucleophiles through 1,4-conjugate additions. Amine, alcohol, nitromethane, and malonate derivatives were successfully added to the enone's double bond, to give the corresponding Michael products in high to excellent yields.



**Scheme VII.5.** Derivatives obtained from cyclobutane **181**.

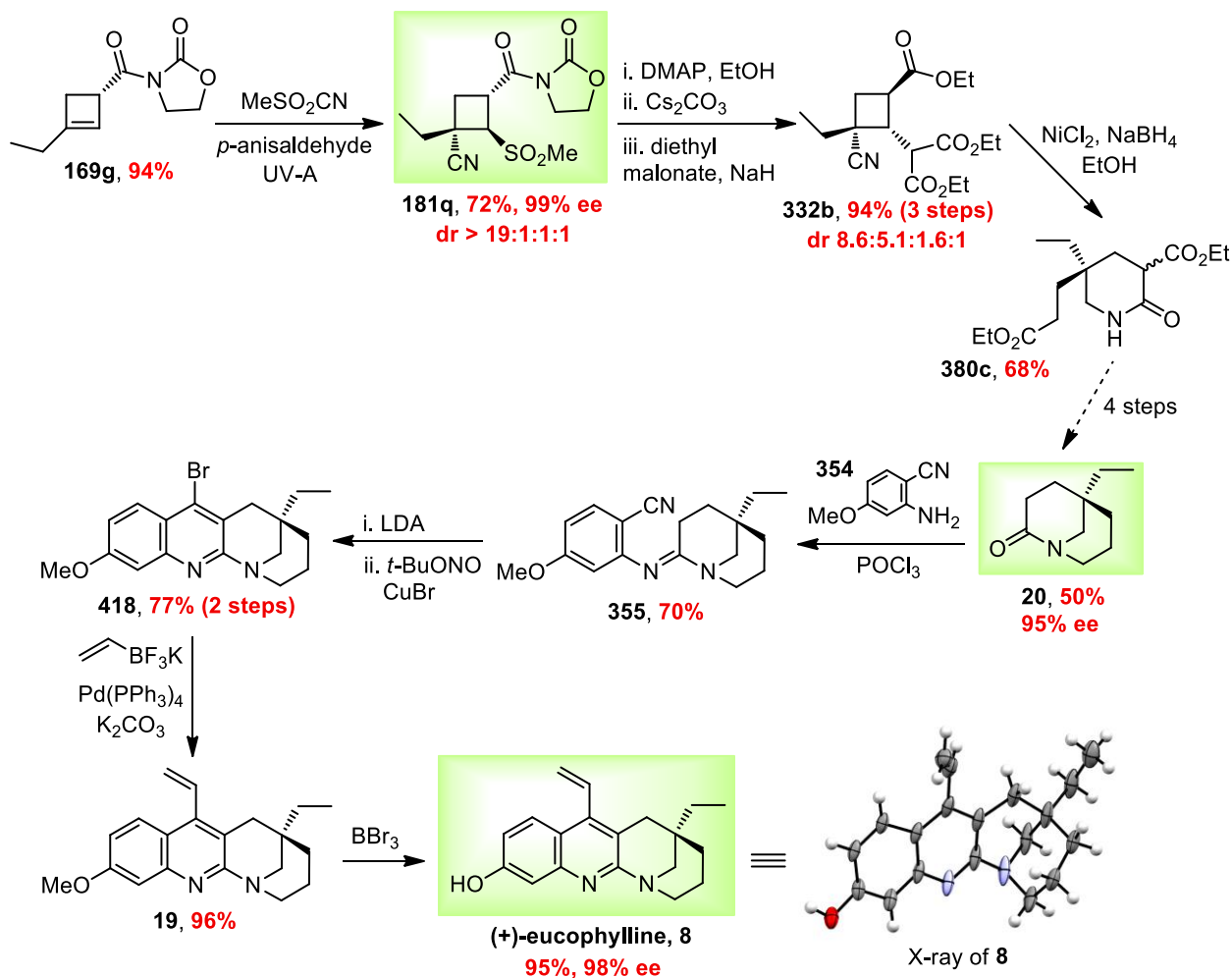
A derivative of these frameworks, the cyclobutyl malonate **332**, was engaged in a reduction reaction using nickel boride as a catalyst (Scheme VII.6). After several optimizations, a new method was established, allowing the nitrile reduction, cyclization, and cyclobutyl ring-opening in a one-pot process. This sequence was applied to a series of cyclobutanes with different functionalized side

chains. The resulting lactams **380** were further manipulated to generate the azabicyclo[3.3.1]nonane in low to moderate yields.



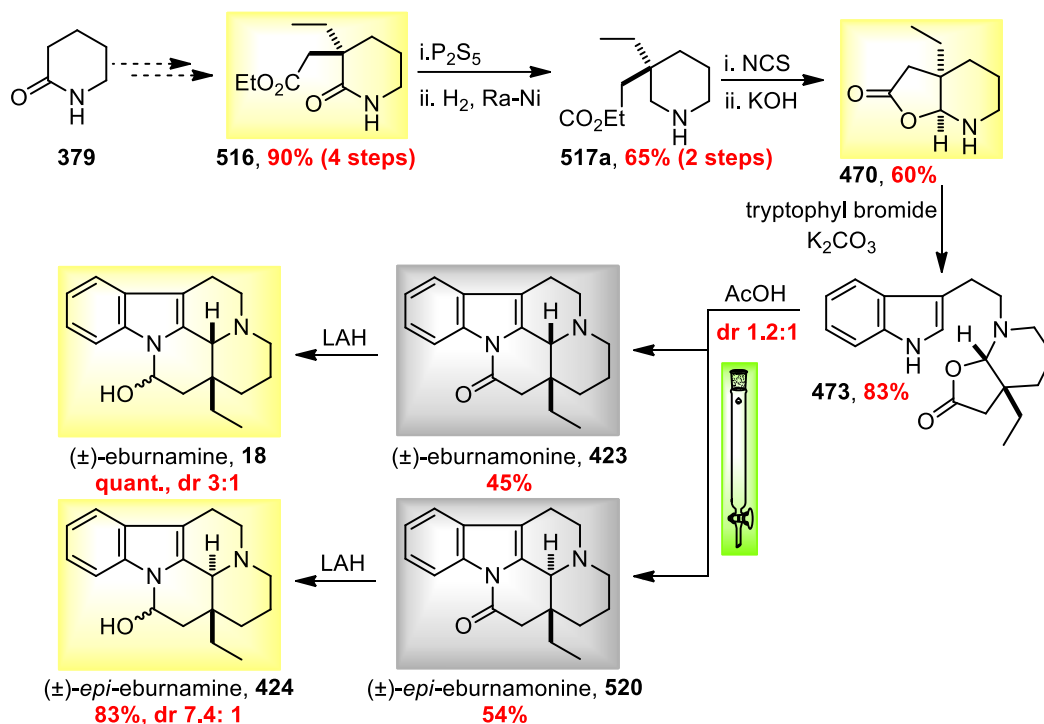
**Scheme VII.6.** Nickel boride-mediated nitrile reduction, cyclization, and cyclobutyl ring-opening.

Later, the enantioselective total synthesis of eucophylline **8**, a unique vinylnaphthyridine alkaloid isolated from *Leuconotis eugenifolius*, was planned based on the above strategy. The synthesis was accomplished in 17 steps starting from the commercially available but-1-yne or 1,1-dibromobut-1-ene, in 85% average yield, and 5.9% overall yield (Scheme VII.7). The HPLC analysis confirmed the high enantiomeric excess of the natural product (ee = 98%). In this synthesis, no protecting groups were used and only 9 steps required purification on column chromatography. The synthetic approach features the preparation of a chiral cyclobutene which was further functionalized to introduce the asymmetric all-carbon quaternary stereocenter through a photocatalytic approach. The X-ray analyses secured the first X-ray crystal structure of **8**, which confirmed the successful synthesis of the natural enantiomer.



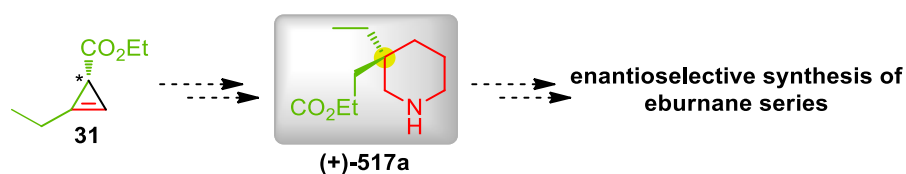
**Scheme VII.7.** Enantioselective total synthesis of (+)-eucophylline.

The synthesis of the racemic eburnamone **423**, *epi*-eburnamone **520**, eburnamine **18** and *epi*-eburnamine **424** was also accomplished starting from commercially available 2-piperidinone **379** (Scheme VII.8). The transformation of this lactam allowed the formation of the amine ( $\pm$ )-**517a** that holds the all-carbon quaternary center present in the eburnane skeletons. After several unsuccessful attempts, a racemic total synthesis of the eburnane series was finally accomplished, in which the last steps were based on Wenkert's approach.<sup>6,451</sup> Eburnamine **18** and *epi*-eburnamine **424** were both obtained in 10 steps sequence, in  $\sim 81\%$  average yield and 9.5% overall yield.



**Scheme VII.8.** Total synthesis of racemic eburnane series.

The enantioselective synthesis of (+)-**517a** was planned starting from a chiral cyclopropene **31** (Scheme VII.9). The enantioenriched eburnane series would then be prepared from (+)-**517a** based on the strategy used for the racemic synthesis before. The Synthesis of the amine **517a** was studied on a cyclopropene model with a propyl side chain. However, due to the lack of time, the extension of this work to cyclopropene **31** could not be carried out.

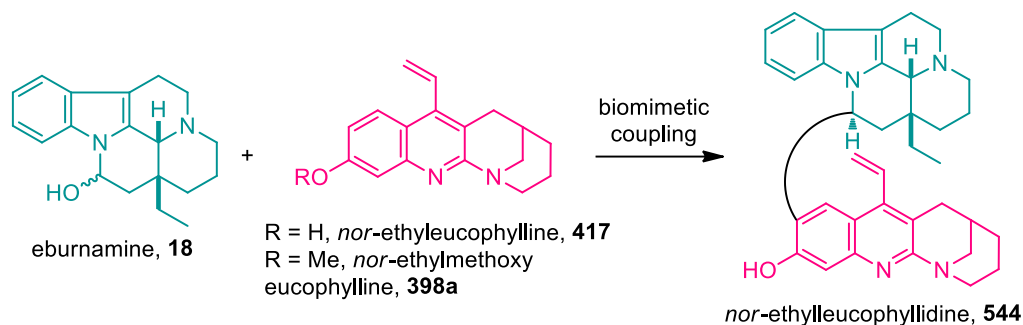


**Scheme VII.9.** Enantioselective total synthesis of the eburnane series starting from a cyclopropene ring system.

Finally, the synthesis of leucophyllidine **6**, a cytotoxic indole alkaloid isolated from the stem-bark of *Leuconotis griffithii*, was investigated. The biomimetic coupling between fragments **8** and **18** was studied using racemic eburnamine and a structurally similar model of eucophylline, the *nor*-ethyleucophylline **417** (Scheme VII.10). Preliminary results showed that the coupling in moderately acidic medium provokes protonation of the *nor*-ethyleucophylline's nitrogens, which probably alters



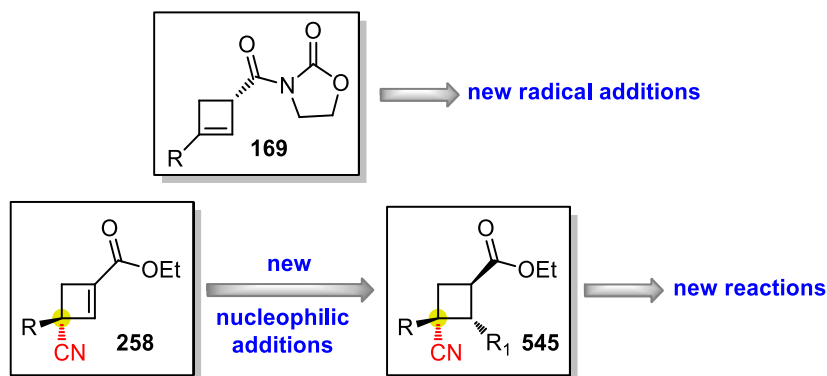
its nucleophilicity and prevents the coupling. This reaction is still under investigation and will be reported in due course.



**Scheme VII.10.** Biomimetic coupling approach towards leucophyllidine's model.

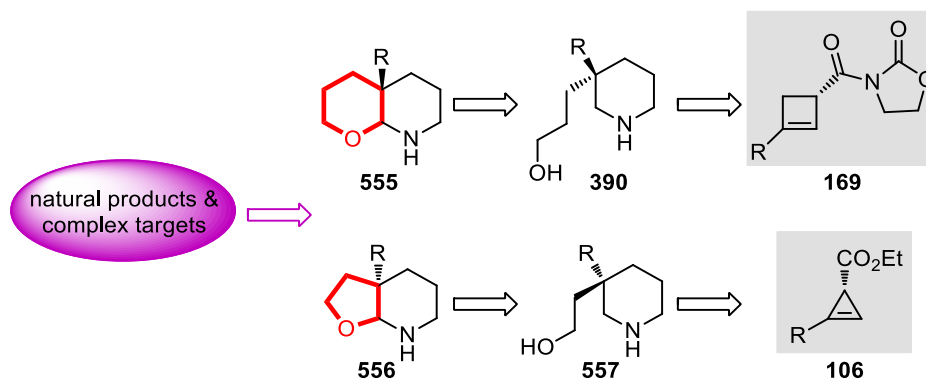
## 2. Perspectives

The strategy developed to access a new type of enantioselective cyclobutenes **169** opens the door towards new investigation areas. These carbocycles could be further studied in radical functionalization reactions to incorporate new types of radicals onto the C-C double bond (Scheme VII.11). The obtained derivatives could be manipulated further to develop new ring-opening strategies and give enantioselective access to a library of functionalized all-carbon quaternary stereocenters. The cyclobutene carboxylate **258** could also be studied further by adding different nucleophiles to the enone's double bond. A new reaction could be then designed to deliver valuable synthons for the total synthesis of indole alkaloids.



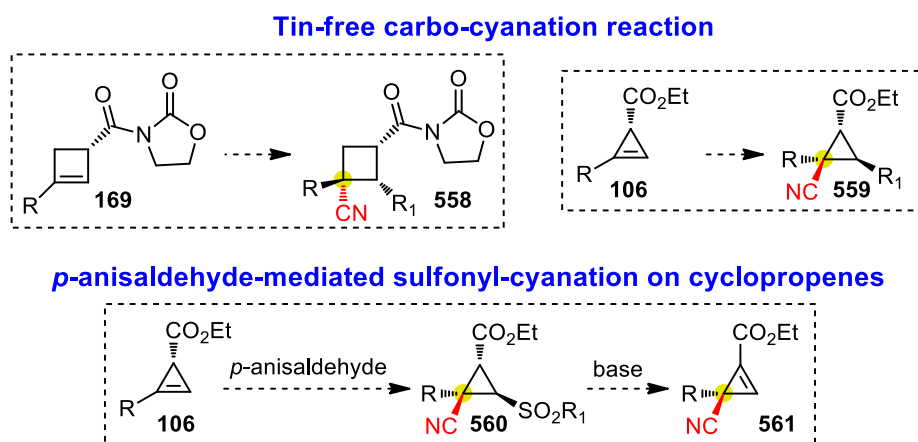
**Scheme VII.11.** Further examination of cyclobutenes **169** and **258**.

Furthermore, the amino-alcohols **390** and **557** obtained from cyclobutenes and cyclopropenes could be used in the construction of chiral pyrans **555** and furans **556**, respectively, bearing an all-carbon quaternary center (Scheme VII.12). These heterocycles could be then used as intermediates in the synthesis of complex targets or natural products.



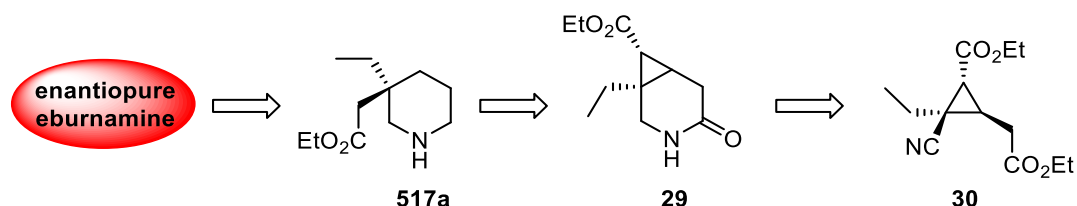
**Scheme VII.12.** Synthesis of functionalized pyrans and furans from cyclobutenes and cyclopropanes.

On the other hand, a new tin-free carbo-cyanation reaction on cyclobutenes and cyclopropanes is still needed in order to install an all-carbon quaternary center in a stereocontrolled manner, under mild and efficient conditions (Scheme VII.13). Due to the low reactivity of cyclobutenes towards radicals, such a reaction should be studied carefully to reach the desired goal. The sulfonyl-cyanation reaction could also be investigated on cyclopropanes using *p*-anisaldehyde as a photosensitizer (*preliminary results: Mr. Matteo Cayla, Master 1 internship*). Further studies towards the sulfone elimination could also be investigated under basic medium. This would offer a new pathway to access cyclopropanes/enes holding an all-carbon quaternary center in a stereocontrolled manner through a tin-free process. These studies would eventually offer access to a new library of highly valuable optically pure cyclic derivatives.



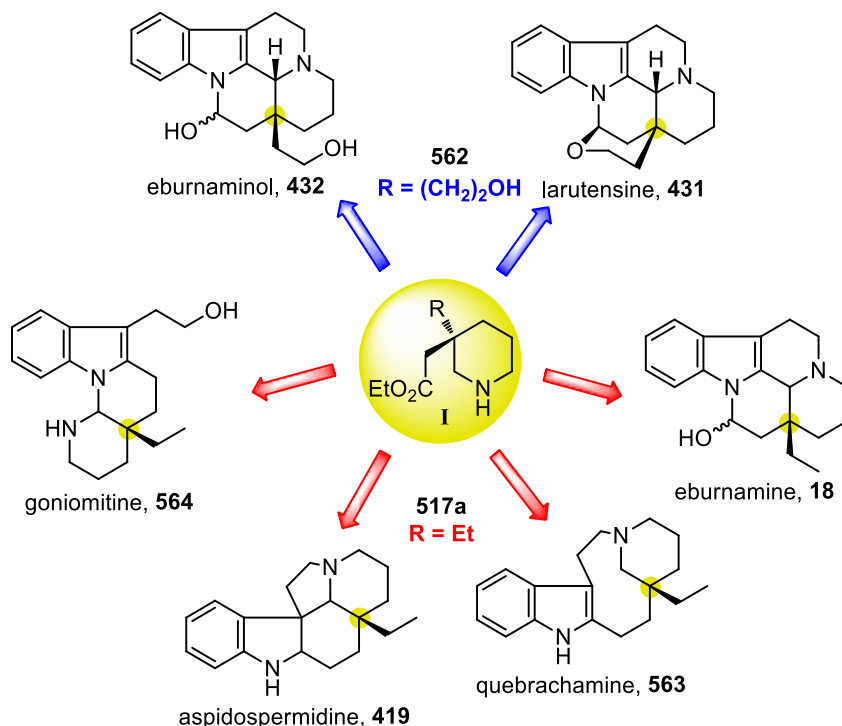
**Scheme VII.13.** Further carbo- and sulfonyl-cyanation reactions of small-sized rings.

For the enantioselective total synthesis of the eburnane series, this could be developed from cyclopropane **30** and following the strategy already applied on the cyclopropane model **154a** with a propyl side chain to generate the ester **517a** (Scheme VII.14).



**Scheme VII.14.** Enantioselective synthesis of eburnamine through a cyclopropane intermediate.

Finally, the intermediate-type **I** could also be interesting to prepare other indole alkaloids; for instance, with  $R = \text{Et}$ , amine **517a** could be used in the total synthesis of quebrachamine **563**, aspidospermidine **419** and goniomitine **564** (Figure VII.2). Whereas, starting from a cyclopropane with a functionalized side chain  $R = (\text{CH}_2)_2\text{OPG}$ , the amine **562** could be manipulated to give access to larutensine **431** and eburnaminol **432** indole alkaloids.



**Figure VII.2.** Possible use of ester **I** in the synthesis of a series of indole alkaloids.

# *Experimental Part*



## Experimental Part - General Information

### 1. Chemical reagents and apparatus

All reactions were carried out under nitrogen or argon atmosphere with dry solvents under anhydrous conditions unless otherwise noted. The glass equipment and stirring bars were stored in an oven at 180 °C or heat gun-dried and evacuated prior to use. Dichloromethane (CH<sub>2</sub>Cl<sub>2</sub>), methanol (MeOH), tetrahydrofuran (THF), diethyl ether (Et<sub>2</sub>O), and toluene were dried over activated alumina columns on MBraun Solvent Purification System (SPS-800). Anhydrous dimethylformamide (DMF) and acetone AcroSeal™ packaging stored under argon were purchased from a chemical supplier (Acros Organics). Benzene (PhH) and tetrahydrofuran used for the organolithium reactions were distilled from sodium/benzophenone. Dry chlorobenzene (PhCl), 1,2-dichloroethane (DCE), 1,2-dimethoxyethane (DME), *n*-hexane, and ethyl acetate (EtOAc) were obtained by distillation over CaH<sub>2</sub> and they were all stored over oven-activated 4 Å molecular sieves. Dry 1,4-dioxane, acetonitrile (CH<sub>3</sub>CN), and ethanol (EtOH) were obtained by distillation over CaH<sub>2</sub> and stored over oven-activated 3 Å molecular sieves. Diisopropylamine (DIPA), *N,N'*-diisopropylethylamine (DIPEA), triethylamine (Et<sub>3</sub>N), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were distilled from CaH<sub>2</sub> and stored over oven-activated 4 Å molecular sieves. 2,2,6,6-tetramethylpiperidine (TMP) was distilled from CaH<sub>2</sub>, under vacuum (0.8 mbar) at 70-80 °C and stored over oven-activated 4 Å molecular sieves. Hexamethylphosphoramide (HMPA) was distilled from CaH<sub>2</sub>, under vacuum (0.8 mbar) at 55 °C and stored over oven-activated 4 Å molecular sieves. Ti(O*i*Pr)<sub>4</sub> was distilled under vacuum (0.8 mbar) and used directly in the appropriate reaction. Triethylsilane (Et<sub>3</sub>SiH) was distilled and used directly in the appropriate reaction. Potassium carbonate (K<sub>2</sub>CO<sub>3</sub>) was dried in the oven for weeks prior to use. *n*-BuLi was titrated prior to use with *N*-benzylbenzamide (3 x).<sup>462</sup> water for reactions was purified by Millipore Direct-Q™ 3 Tap purification system, particle size 0.22 µm. Other commercial reagents were used as received without further purification unless otherwise stated.

Photochemical reactions were performed with commercial LEDs (7 W, 12 V, 500 mA) and a Rayonet® RPR-200 Photochemical Reactor (Model RPR-200, 110/227 volts, 50/60 Hz, operating temp 30-40 °C) with UV-A light (2 x RPR 3500 Å Black Light Blue, 8 W, 12-inches, or 6 x Black Light fluorescent tube 8w/08 BLB 370 nm, 12-inches), UV-C light (6 x 254 nm, Philips TUV 16 W G16T5, 12-inches), and blue light (2 x RPR 4190 Å, 12-inches).

UV-vis absorption spectra were measured on a Cary 100 Scan UV-vis spectrophotometer (Varian, USA), using quartz cuvette (1 cm light path, Hellma 110-QS) in the 200-800 nm spectral range.

Analytical thin layer chromatography (TLC) was performed using silica gel 60 F254 pre-coated plates (Merck) with visualization by ultraviolet light (mainly 254 nm). An ethanolic solution of vanillin or an aqueous solution of potassium permanganate/sodium carbonate and heat were used as developing agents. Merck silica gel (60, particle size 40-63 µm) was used for column chromatography. Diastereomers were described as mixtures, when it was not possible to separate them using classic column chromatography. Yields refer to chromatographically and spectroscopically (<sup>1</sup>H and <sup>13</sup>C NMR) homogeneous materials unless otherwise stated. Diastereomeric ratios were estimated by <sup>1</sup>H or <sup>13</sup>C NMR analyses of the crude reaction mixture after a short filtration on column unless otherwise stated.

1D and 2D NMR analyses with the specified deuterated solvents were recorded at 20 °C on a Brüker Avance I 300 (<sup>1</sup>H: 300 MHz, <sup>13</sup>C: 75.46 MHz), a Brüker Avance II 400 (<sup>1</sup>H: 400 MHz, <sup>13</sup>C: 100.75 MHz) or a Brüker Avance III 600 (<sup>1</sup>H: 600 MHz, <sup>13</sup>C: 151.13 MHz) and were calibrated using residual undeuterated solvent as an internal reference [chloroform-*d* (<sup>1</sup>H): δ = 7.26 ppm; chloroform-*d* (<sup>13</sup>C): δ = 77.16 ppm; DMSO-*d*<sub>6</sub> (<sup>1</sup>H): δ = 2.50 ppm; DMSO-*d*<sub>6</sub> (<sup>13</sup>C): δ = 39.52 ppm; methanol-*d*<sub>4</sub> (<sup>1</sup>H): δ = 3.31 ppm; methanol-*d*<sub>4</sub> (<sup>13</sup>C): δ = 49.00 ppm; acetonitrile-*d*<sub>3</sub> (<sup>1</sup>H): δ = 1.94 ppm; acetonitrile-*d*<sub>3</sub> (<sup>13</sup>C): δ = 118.26, 1.32 ppm]. The chemical shifts (δ) and coupling constants (*J*) are expressed in ppm and Hz respectively. The following abbreviations were used to describe the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, q<sub>AB</sub> = quartet in AB system, quint = quintuplet, dd =

doublet of doublet, dt = doublet of triplet, dq = doublet of quartet, td = triplet of doublet, tt = triplet of triplet, tq = triplet of quartet, qd = quartet of doublet, qq = quartet of quartet, pd = quintuplet of doublet, ddd = doublet of doublet of doublet, ddt = doublet of doublet of triplet, dtd = doublet of triplet of doublet, dqd = doublet of quartet of doublet, tdd = triplet of doublet of doublet, qdt = quartet of doublet of triplet, dddd = doublet of doublet of doublet of doublet, m = multiplet, br s = broad singlet, br = broad signal.

The mass spectrometric measurements were performed at the Centre d'Etude Structurale et d'Analyse des Molécules Organiques (CESAMO) at the Institut des Sciences Moléculaires (ISM, CNRS-UMR 5255, Talence, France). High-resolution mass spectrometry (HRMS) and low-resolution mass spectrometry (LRMS) were recorded on a QStar Elite ABSciex (ElectroSpray Ionization (ESI), Atmospheric Pressure Chemical Ionization (APCI)), on an AccuTOF JEOL (Electron Ionization (EI), Chemical Ionization (CI), Field Desorption (FD), Field Ionization (FI)), or on a Qexactive mass spectrometer (Thermo). The Qexactive instrument is equipped with an ESI source and the spectra were recorded in the negative/positive mode. The spray voltage was maintained at 3200 V and capillary temperature set at 320 °C. Samples were introduced by injection through a 20 mL sample loop into a 300 mL/min flow of methanol from the LC pump.

IR spectra were recorded between 4000 and 550  $\text{cm}^{-1}$  on a Bruker IFS55 (OPUS/IR 3.0.2) FT-IR spectrometer, using a highly polished KBr crystal plate for liquid samples (thin films), or KBr pellet for powder samples (thin and transparent pellet). Optical rotation measurements were carried out on a JASCO P-2000ST polarimeter using a sodium lamp (589 nm) at 23-25 °C, and the reported values represent the average of 15 measurements. Melting points (m. p.) were recorded on a digital Buchi B-540 melting point capillary apparatus in open capillary tubes and are uncorrected.

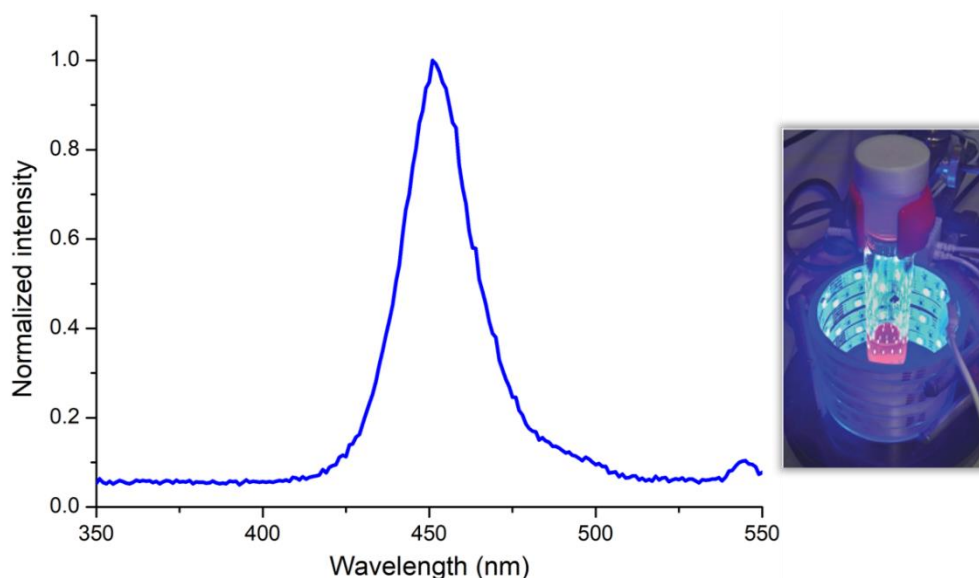
The enantiomeric excess measurements were performed on a Jasco LC-NetII/ADC HPLC using a Chiralpak® IA column (4.6 mm $\Phi$  x 250 mmL, particle size 5  $\mu\text{m}$ ) at 20 °C. For the racemic and chiral eucophylline **8**, HPLC measurements were recorded on a Thermo Scientific Dionex Ultimate 3000 Diode Array Detector, using a Phenomenex® column (Lux 5  $\mu\text{m}$  Cellulose-3, 4.6 mm $\Phi$  x 250 mmL). Circular Dichroism (CD) spectra were recorded on a JASCO J-815 instrument in the wavelength range of 200-400 nm with a data pitch of 0.1 nm at 20 °C in a 2 mm quartz cell, under nitrogen flow (99.9%).

The X-ray structure analysis measurements were carried out at the CESAMO technical center, on a Bruker APEX 2 DUO. A single crystal was mounted and immersed in a stream of nitrogen gas [ $T = 150(2)$  K]. For compound **180a**, crystallographic data were collected, using a microfocus sealed tube of Mo K $\alpha$  radiation ( $k = 0.71073$  Å) on a KappaCCD diffractometer. For eucophylline **8**, data were collected, using a microfocus sealed tube of Cu K $\alpha$  radiation ( $k = 1.54184$  Å) on a KappaCCD diffractometer. For both compounds, data collection and cell refinement were performed using APEX2 2013.10-0 (Bruker AXS Inc.), and SAINT v8.34A (Bruker AXS Inc.). Data reduction was performed using SAINT v8.34A (Bruker AXS Inc.). Correction for absorption was performed using multi-scan integration as included in SADABS V2012/1 (Bruker AXS). Structure solutions were found by charge flipping methods SUPERFLIP<sup>463</sup> or EDMA<sup>464</sup> and refined using Shelx software suite.<sup>465</sup> The program Mercury<sup>466</sup> was used for analysis and drawing figures.

## 2. Visible-light irradiation system

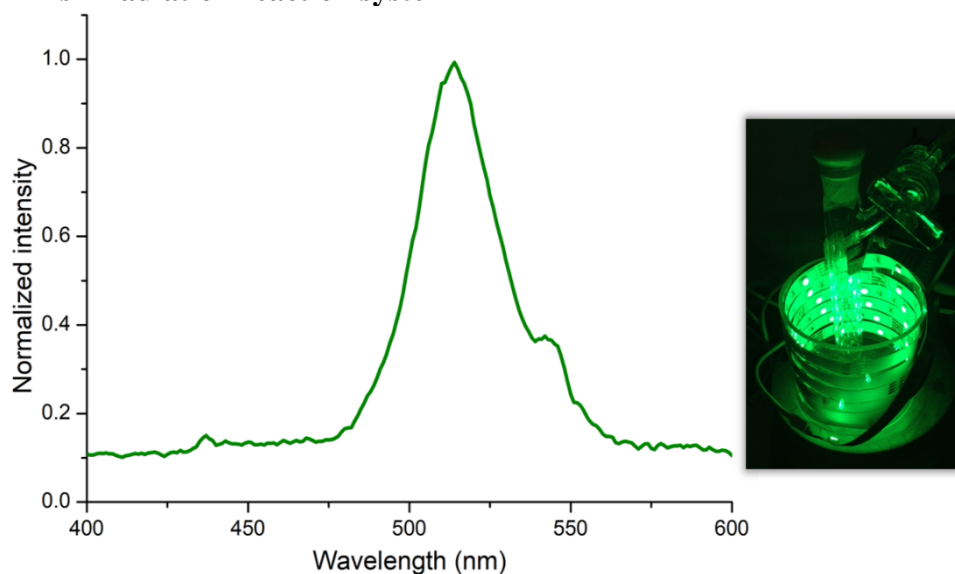
A cylindric vial, containing all the reagents, was placed in the middle of an assembly of LEDs light strip fixed on a cylindric glass (diameter: 8 cm).

### The blue LEDs-irradiation reaction system



**Figure S.1.** The emission spectrum of the commercial blue LEDs (*left*;  $\lambda_{\text{max}} = 451$  nm) and the experimental setup used in the irradiation reactions (*right*).

### The green LEDs-irradiation reaction system

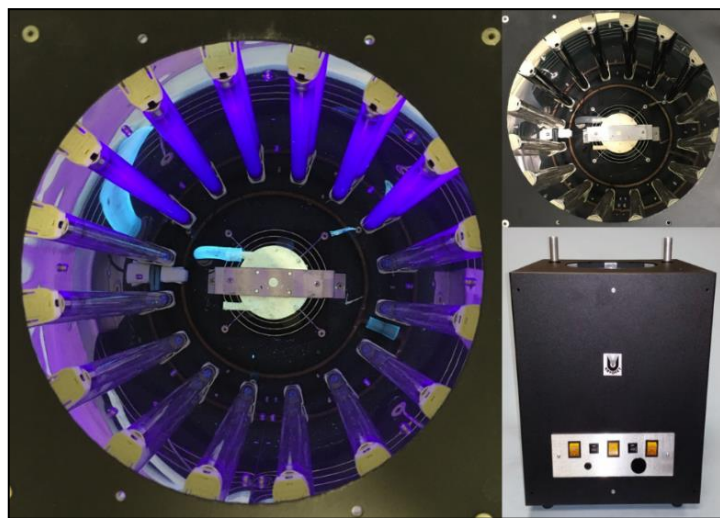


**Figure S.2.** The emission spectrum of the commercial green LEDs (*left*;  $\lambda_{\text{max}} = 513$  nm) and the experimental setup used in the irradiation reactions (*right*).



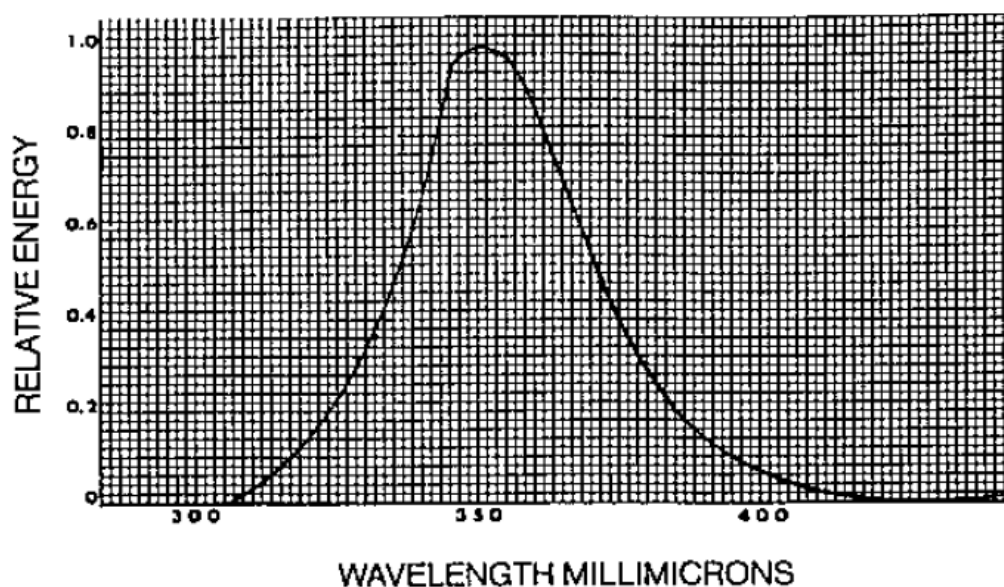
### 3. UV-light irradiation system

#### The experimental setup used for the UV-light irradiation reactions

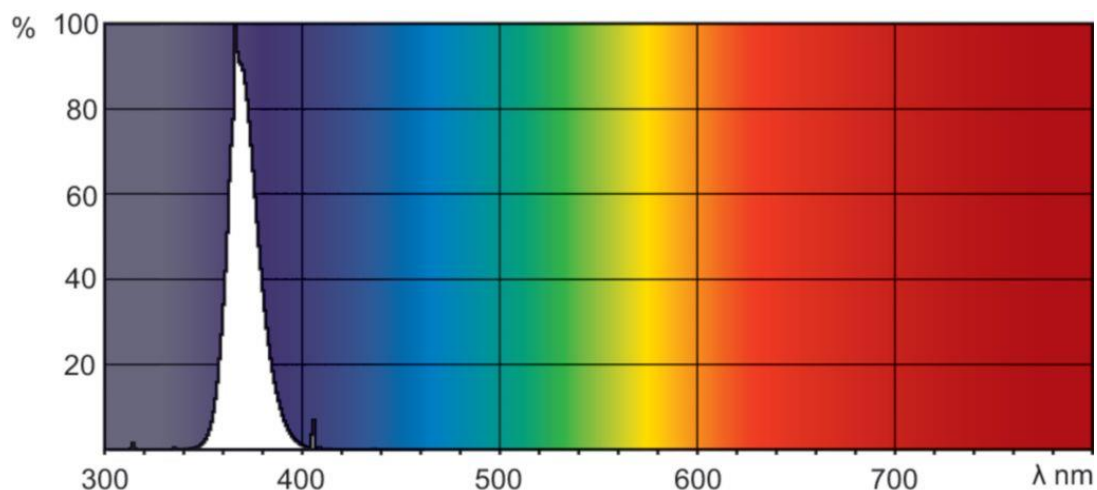


**Figure S.3.** The Rayonet Reactor<sup>®</sup> (RPR-200) used in the UV-irradiation reactions.

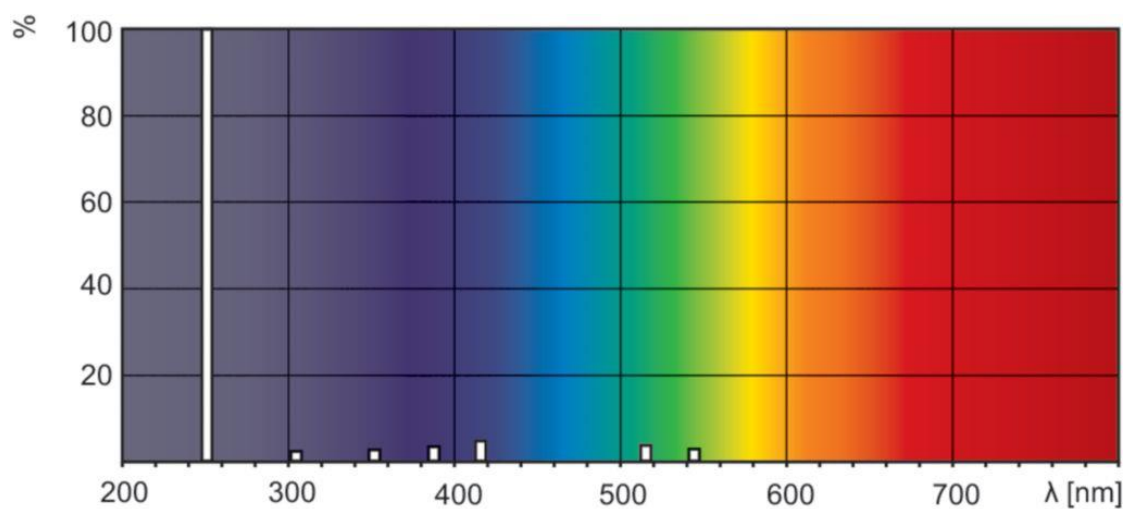
#### The emission spectrum profile of UV-A light (RPR-3500 Å lamp)



**Figure S.4.** The spectral energy distribution curve for rayonet RPR-3500 Å lamp (Scaiano, J. C. *Handbook of Organic Photochemistry, Vol. I*, CRC Press, **1989**, p. 190).

**The emission spectrum profile of UV-A light (TL 8W BLB lamp)**

**Figure S.5.** The spectral energy distribution curve for rayonet PHILIPS TL 8W BLB  
(*Lighting Philips website*).

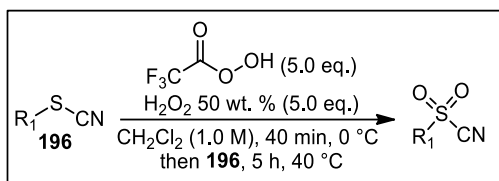
**The emission spectrum profile of UV-C light (TUV 16W G16T5 lamp)**

**Figure S.6.** The spectral energy distribution curve for rayonet PHILIPS TUV 16W G16T5  
(254 nm) (*Lighting Philips website*).

## Experimental Part - Chapter III

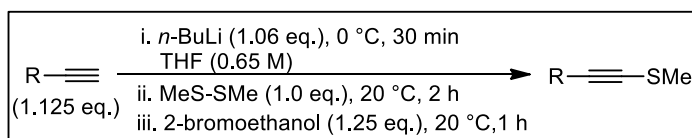
### 1. General procedures for chapter III

#### General procedure (A) for sulfonyl cyanides synthesis<sup>5</sup>



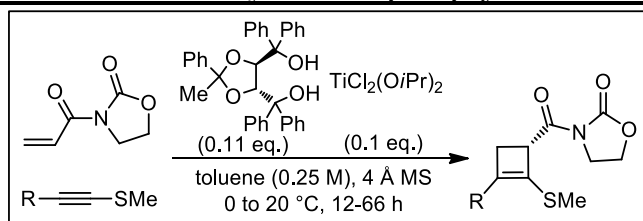
Hydrogen peroxide (50 wt. % solution in water, 5.0 eq.) was added dropwise at 0 °C to a solution of trifluoroacetic anhydride (5.0 eq.) in CH<sub>2</sub>Cl<sub>2</sub> (1.0 M) in a two-necked flask equipped with a condenser and a glass cap. After being stirred for 40 min at 0 °C, alkyl thiocyanate (1.0 eq.) was added dropwise without dilution and the reaction mixture was stirred at 40 °C silicon oil bath temperature for 5 h. At 0 °C, the reaction was quenched with water. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> and the combined organic layers were washed with water (x 2) and brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated carefully under reduced pressure (volatile). The crude was pure enough to be used directly without further purification.

#### General procedure (B) for the synthesis of alkynyl sulfides



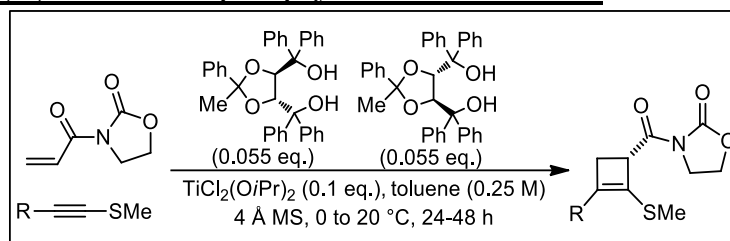
In a dried two-necked flask, the alkyne (1.125 eq.) was diluted in dry THF (0.65 M) and freshly titrated *n*-BuLi in hexane (1.06 eq.) was added dropwise at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and dimethyl disulfide (1.0 eq.) was then added. The mixture was stirred for 2 h at 20 °C and quenched with 2-bromoethanol (1.25 eq.). After stirring further for 1 h, water was added. The aqueous layer was extracted with Et<sub>2</sub>O (x 3) and the combined organic layers were washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The obtained crude mixture was then purified through column chromatography on SiO<sub>2</sub> (eluent as noted).

#### General procedure (C) for Narasaka's asymmetric [2+2] cycloaddition<sup>3</sup>



To a dried two-necked flask under inert atmosphere, TiCl<sub>2</sub>(OiPr)<sub>2</sub> (0.1 eq.) and the chiral ligand (**R**)-**115** (0.11 eq.) were introduced, followed by dry toluene (0.08 M), and the mixture was stirred for 1 h at 20 °C.

To a two-necked flask under inert atmosphere, 4 Å molecular sieves (39 mg/mmol of substrate) were introduced and activated by heat gun under vacuum. Dry toluene (0.25 M) was then added followed by the titanium complex prepared above and the reaction was transferred to 0 °C. 3-acryloyloxazolidin-2-one (1.0 eq.) and the alkynyl sulfide (2.0-1.5 eq.) were then added successively to the mixture, and the reaction was stirred till completion at 20 °C. The reaction was then quenched with sat. aqueous NaHCO<sub>3</sub> and the mixture was filtrated over a celite pad. The filtrate was extracted with EtOAc, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude mixture was purified through column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc: percentages as indicated) to obtain the desired cyclobutene.

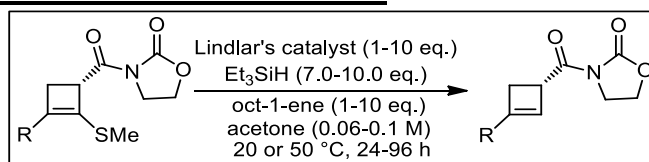
**General procedure (D) for racemic [2+2] cycloaddition reaction****Method A:** without ligands

To a two-necked flask under inert atmosphere, 4 Å molecular sieves (39 mg/mmol of substrate) were introduced and activated by heat gun under vacuum. Dry toluene (0.25 M) was added and the reaction was transferred to 0 °C.  $\text{TiCl}_2(\text{OiPr})_2$  (0.1 eq.), 3-acryloyloxazolidin-2-one (1.0 eq.) and the alkynyl sulfide (2.0-1.5 eq.) were then added successively to the mixture, and the reaction was stirred till completion at 20 °C. The reaction was quenched with sat. aqueous  $\text{NaHCO}_3$  and the mixture was filtrated over a celite pad. The filtrate was extracted with EtOAc, washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The crude mixture was purified through column chromatography on  $\text{SiO}_2$  (cyclohexane/ EtOAc) to obtain the desired cyclobutene.

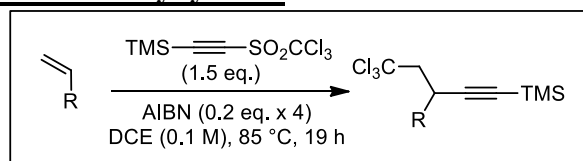
**Method B:** with chiral ligands (*R*) and (*S*).

To a dried two-necked flask under inert atmosphere,  $\text{TiCl}_2(\text{OiPr})_2$  (0.1 eq.), the chiral ligand (*S*)-**115** (0.055 eq.), and the chiral ligand (*R*)-**115** (0.055 eq.) were introduced, followed by dry toluene (0.08 M), and the mixture was stirred for 1 h at 20 °C.

To a two-necked flask under inert atmosphere, 4 Å molecular sieves (39 mg/mmol of substrate) were introduced and activated by heat gun under vacuum. Dry toluene (0.25 M) was then added followed by the titanium complex prepared above and the reaction was transferred to 0 °C. 3-acryloyloxazolidin-2-one (1.0 eq.) and the alkynyl sulfide (2.0-1.5 eq.) were then added successively to the mixture, and the reaction was stirred till completion at 20 °C. The reaction was quenched with sat. aqueous  $\text{NaHCO}_3$  and the mixture was filtrated over a celite pad. The filtrate was extracted with EtOAc, washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The crude mixture was purified through column chromatography on  $\text{SiO}_2$  (cyclohexane/ EtOAc) to obtain the desired cyclobutene.

**General procedure (E) for desulfurization reaction**

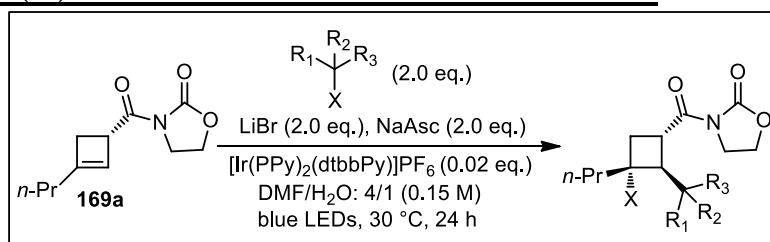
Cyclobutene (1.0 eq.) was introduced to a two-necked flask under inert atmosphere. Acetone AcroSeal™ packaging (0.06-0.1 M) was added, followed by Lindlar's catalyst (5% on calcium carbonate poisoned with Lead, 1.0-10.0 eq.), and oct-1-ene (1.0-10.0 eq.). Freshly distilled triethylsilane (10.0 eq.) was added slowly at the end. The mixture was stirred at 20 or 50 °C silicon oil bath temperature, and the evolution of the reaction was monitored until complete conversion by aliquot NMR. After completion, the product was filtrated on a celite pad and purified through column chromatography on  $\text{SiO}_2$  (cyclohexane/EtOAc: percentages as noted) to obtain the pure reduced cyclobutene.

**General procedure (F) for carbo-alkynylation**

To a dried two-necked flask equipped with a condenser and under inert atmosphere, the olefin (1.0 eq.) was introduced followed by distilled DCE (0.1 M), and the alkyne (1.5 eq.). AIBN (0.2 eq.) was added and the reaction was heated at 85 °C silicon oil bath temperature. 0.2 eq. x 4 of AIBN were

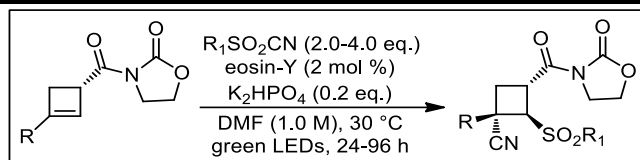
then added every 4-7 h. After 19 h, the reaction was quenched with water (3 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  (7 mL). The organic layer was washed with brine (5 mL), dried over  $\text{Na}_2\text{SO}_4$  then concentrated under reduced pressure. The crude mixture was purified through column chromatography on  $\text{SiO}_2$  (cyclohexane/EtOAc: 95/5) to afford the pure desired product.

### General procedure (G) for atom transfer radical addition reaction



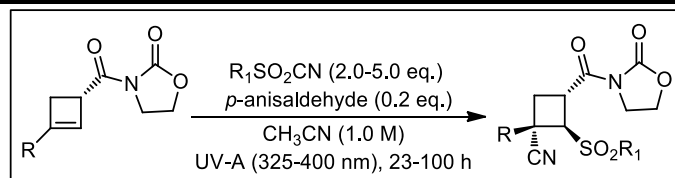
A 10 mL sealed tube was charged with cyclobutene **169a** (1.0 eq.), DMF/ $\text{H}_2\text{O}$ : 4/1 (0.15 M), halogenoalkane (2.0 eq.), sodium L-ascorbate (2.0 eq.), LiBr (2.0 eq.) and  $[\text{Ir}(\text{PPy})_2(\text{dtbbPy})]\text{PF}_6$  (0.02 eq.). The mixture was degassed by three cycles of freeze-pump-thaw and irradiated at 30 °C with blue LEDs (400-495 nm, the tube was positioned approximately 4 cm away from the light source). After completion, the reaction was quenched with water and extracted with EtOAc. The organic layer was then washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The crude mixture was purified through column chromatography on  $\text{SiO}_2$  (cyclohexane/EtOAc: eluants as noted) to afford the pure desired product.

### General procedure (H) for eosin-photocatalyzed sulfonyl-cyanation reaction<sup>5</sup>

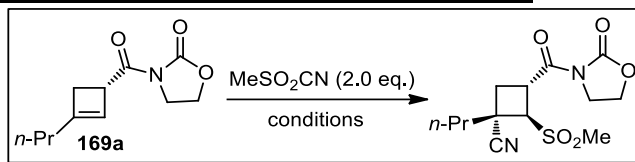


A 10 mL sealed tube equipped with a stirrer was charged with cyclobutene (1.0 eq.), DMF AcroSeal™ packaging (1.0 M), sulfonyl cyanide (2.0-4.0 eq.), eosin-Y (2 mol %) and  $\text{K}_2\text{HPO}_4$  (0.2 eq.) then the mixture was stirred 2 minutes for homogenization. The reaction mixture was degassed by argon sparging for 30 min, then it was irradiated at 30 °C under green LEDs light (500-565 nm, the tube was positioned approximately 4 cm away from the light source), and monitored by TLC. After completion, the reaction mixture was diluted with EtOAc and aqueous HCl (1.0 M). The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The crude mixture was then purified through column chromatography on  $\text{SiO}_2$  (elution solvents as noted) to afford the desired cyclobutane.

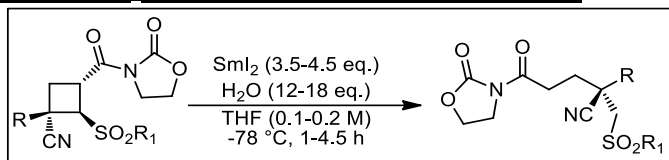
### General procedure (I) for *p*-anisaldehyde-photosensitized sulfonyl-cyanation reaction



A 10 mL side arm storage schlenk equipped with a stirrer was charged with cyclobutene (1.0 eq.), acetonitrile (1.0 M), sulfonyl cyanide (2.0-5.0 eq.) and *p*-anisaldehyde (0.2 eq.). The reaction mixture was degassed by three cycles of freeze-pump-thaw, then the tube was refilled with nitrogen. The reaction mixture was irradiated at 30 °C under UV-A light (325-400 nm, the tube was positioned approximately 10 cm away from the light source), and it was monitored by TLC under nitrogen atmosphere. After completion, the solvent was concentrated under reduced pressure and the crude mixture was purified through column chromatography on  $\text{SiO}_2$  (elution solvents as noted) to afford the desired cyclobutane.

**General procedure (J) for *p*-anisaldehyde control experiments**

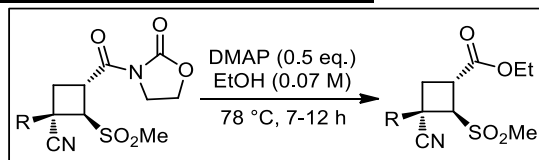
The control experiments were carried out in Young NMR tubes, on 0.1 mmol scale of **169a** in 0.5 mL CD<sub>3</sub>CN (0.2 M). Before irradiation, the mixture was degassed by three cycles of freeze-pump-thaw.

**General procedure (K) for SmI<sub>2</sub>-mediated ring-opening reaction**

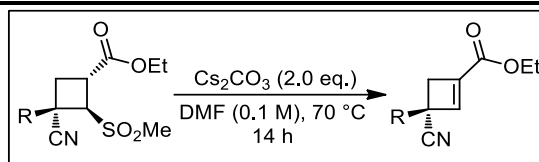
In a dried two-necked flask, the starting material (1.0 eq.) was dissolved in dry THF (0.1-0.2 M), then distilled H<sub>2</sub>O (12.0-18.0 eq.) was added. The reaction was cooled down to -78 °C and stirred 5 min at this temperature. Afterwards, SmI<sub>2</sub>/THF (3.5-4.5 eq.), was added dropwise. The dark blue color of SmI<sub>2</sub> was immediately quenched upon addition of each drop and became persistent after addition of certain volume of SmI<sub>2</sub>. The evolution of the reaction was monitored by TLC maintaining the temperature between -70 and -78 °C. After full conversion, the reaction was then quenched at -78 °C by addition of aqueous HCl (1.0 M) and air sparging for 5 min, the color changed to yellow. The reaction was then stirred at 20 °C for another 5 min, diluted with CH<sub>2</sub>Cl<sub>2</sub> and extracted with aqueous HCl (1.0 M). The aqueous phase was back-extracted with CH<sub>2</sub>Cl<sub>2</sub>, and the combined organic layers were washed with aqueous sodium thiosulfate/Rochelle salt: 1/1, and brine, then dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. Purification of the crude mixture through column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: percentages as noted) afforded the desired product.

**Preparation of 0.2 M solution of SmI<sub>2</sub>/THF:**<sup>467</sup> A two-necked flask containing Sm metal (Strem, 2.48 g, 16.5 mmol, 1.5 eq.) was flame-dried under vacuum then cooled to ambient temperature. The atmosphere was exchanged three times for argon, then freshly purified 1,2-diiodoethane (2.79 g, 11.0 mmol, 1.0 eq.) was added and the atmosphere was exchanged again three times for argon. Freshly dried THF (55.0 mL, 5.0 M) was then added and the mixture was stirred vigorously under argon. After 15 min the color turned from dark green to dark blue. After 2 h, the stirring was halted and the mixture was allowed to settle for 30 min prior to use.

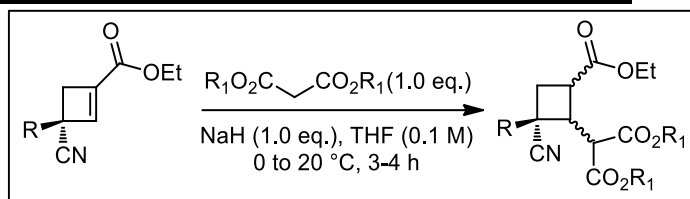
**Purification of 1,2-diiodoethane:**<sup>467</sup> 1,2-diiodoethane (25.0 g) was dissolved in Et<sub>2</sub>O (250.0 mL) and washed with saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (3 x 15 mL, aqueous solution) and distilled water (3 x 10 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under reduced pressure then dried under vacuum to give a white solid (23.0 g).

**General procedure (L) for transesterification reaction**

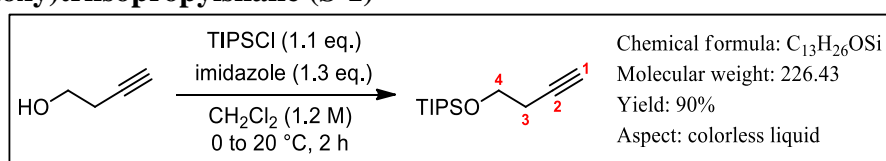
In a dried two-necked flask equipped with a condenser, the cyclobutane (1.0 eq.) was dissolved in distilled EtOH (0.07 M), then DMAP (0.5 eq.) was added and the reaction mixture was heated at 78 °C silicon oil bath temperature. The consumption of the starting material was followed by TLC, then the solvent was concentrated under reduced pressure and the crude mixture was purified through short column chromatography on SiO<sub>2</sub> (eluents as noted) to afford the pure desired product.

**General procedure (M) for base-mediated sulfone elimination reaction**

In a dried two-necked flask equipped with a condenser, the cyclobutane (1.0 eq.) was dissolved in DMF AcroSeal™ packaging (0.1 M), then  $\text{Cs}_2\text{CO}_3$  (2.0 eq.) was added and the reaction mixture was heated at 70 °C silicon oil bath temperature. The consumption of the starting material was followed by TLC, then the solvent was evaporated directly for small scales. For large scales, the reaction was washed with aqueous HCl (1.0 M) and extracted with EtOAc, washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The crude mixture was purified through short column chromatography on  $\text{SiO}_2$  (eluents as noted) to afford the desired cyclobutene.

**General procedure (N) for 1,4-conjugate addition of dialkyl malonate**

To a flame-dried two-necked flask and under inert atmosphere, dialkyl malonate (1.0 eq.) was introduced followed by dry THF (0.2 M) and the reaction was set at 0 °C. NaH (60% suspension in oil, 1.0 eq.) was added portion-wise and the reaction was stirred for 10 min at the same temperature. The cyclobutene (1.0 eq.) was dissolved in dry THF (0.17 M) and added slowly to the mixture. The reaction was stirred at 20 °C and followed by TLC. After completion, the reaction was quenched with sat.  $\text{NH}_4\text{Cl}$  and extracted with EtOAc. The organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The crude as a mixture of diastereomers was pure enough to be used directly in the next step without further purification. [Purification of the crude for analysis was accomplished through short column chromatography on  $\text{SiO}_2$  (cyclohexane/ EtOAc: eluents as noted)].

**2. Synthesis of starting materials****(but-3-yn-1-yloxy)triisopropylsilane (S-1)<sup>468</sup>**

To a dried two-necked flask under inert atmosphere and set at 0 °C, 3-buten-1-ol (9.0 mL, 119.0 mmol, 1.0 eq.) was introduced, followed by dry  $\text{CH}_2\text{Cl}_2$  (100.0 mL, 1.2 M), imidazole (10.5 g, 154.7 mmol, 1.3 eq.), and TIPSCl (28.0 mL, 130.9 mmol, 1.1 eq.) was added slowly. The mixture was stirred at 20 °C and the evolution of the reaction was followed by TLC. After 2 h, the reaction was quenched with water and extracted with  $\text{CH}_2\text{Cl}_2$ . The organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The product was purified through column chromatography on  $\text{SiO}_2$  (cyclohexane/EtOAc: 90/10 then 70/30) and was obtained as a colorless liquid (24.3 g, 90%).

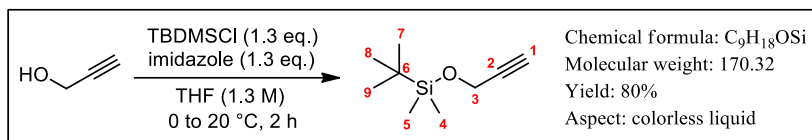
**TLC (cyclohexane/EtOAc: 80/20):**  $R_f$  = 0.88 (UV active;  $\text{KMnO}_4$ , stains yellow).

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 3.82 (t,  $J$  = 7.3 Hz, 2H, H-4), 2.43 (td,  $J$  = 7.3, 2.7 Hz, 2H, H-3), 1.95 (t,  $J$  = 2.6 Hz, 1H, H-1), 1.09-1.06 (m, 21H, H-TIPS).

The  $^1\text{H}$  NMR data are in agreement with those reported in the literature.<sup>468</sup>

**tert-butyldimethyl(prop-2-yn-1-yloxy)silane (S-2)<sup>469</sup>**





To a dried two-necked flask under inert atmosphere and set at 0 °C, prop-2-yn-1-ol (5.2 mL, 89.0 mmol, 1.0 eq.) was introduced, followed by dry THF (70.0 mL, 1.3 M), imidazole (7.9 g, 116.0 mmol, 1.3 eq.), and TBDMSCl (7.9 g, 116.0 mmol, 1.3 eq.) was added slowly. The mixture was stirred at 20 °C and the evolution of the reaction was followed by TLC. After 2 h, the reaction was quenched with water and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The product was purified through column chromatography on SiO<sub>2</sub> (pentane/EtOAc: 99/1) and was obtained as a colorless liquid (12.2 g, 80%).

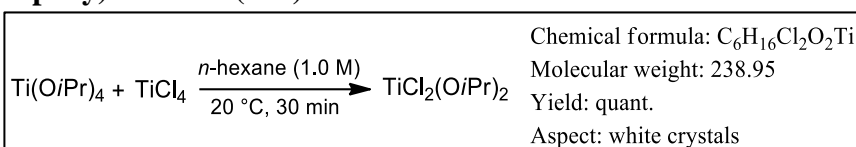
**TLC (pentane/EtOAc: 95/5):** R<sub>f</sub> = 0.56 (UV active; KMnO<sub>4</sub>, stains yellow).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ (ppm) = 4.31 (d, *J* = 2.4 Hz, 2H, H-3), 2.93 (t, *J* = 2.4 Hz, 1H, H-1), 0.91 (s, 9H, H-7, H-8, H-9), 0.13 (s, 6H, H-4, H-5).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ (ppm) = 82.5 (C-2), 72.9 (C-1), 51.6 (C-3), 25.9 (C-7, C-8, C-9), 18.4 (C-6), -5.0 (C-4, C-5).

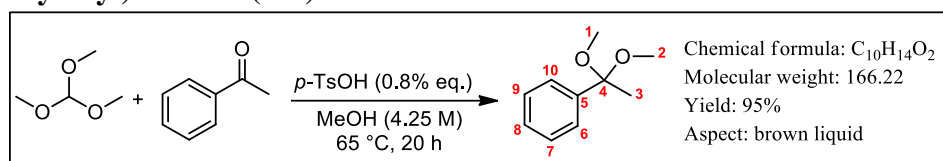
The NMR data are in agreement with those reported in the literature.<sup>469</sup>

### dichloro(diisopropoxy)titanium (116)<sup>198</sup>



To a dried flask under inert atmosphere, Ti(OiPr)<sub>4</sub> freshly distilled under vacuum (6.4 mL, 21.0 mmol, 1.05 eq.), was introduced followed by distilled *n*-hexane (20.0 mL, 1.0 M). TiCl<sub>4</sub> (2.2 mL, 20.0 mmol, 1.0 eq.) was then added dropwise at 20 °C. The color changed to pale-yellow and the solution was kept under stirring for 30 min. The stirring was then halted and the mixture was allowed to settle for 2 h at the same temperature to allow crystallization to happen. The solvent was then removed under inert atmosphere via syringe and the crystals were washed with cold hexane (3 x 3 mL) and dried under vacuum. The product (7.0 g, quant.) was obtained as white crystals and stored under argon atmosphere in the freezer.

### (1,1-dimethoxyethyl)benzene (S-3)<sup>198</sup>



To dry MeOH (40.0 mL, 4.25 M) in a two-necked flask under inert atmosphere, acetophenone (20.1 g, 170.0 mmol, 1.0 eq.) was added, followed by trimethyl orthoformate (27.3 g, 257.0 mmol, 1.5 eq.) and a catalytic amount of *p*-toluenesulfonic acid monohydrate (261.0 mg, 1.4 mmol, 0.8% eq.). The mixture was stirred at 65 °C silicon oil bath temperature for 20 h, and the reaction was followed by TLC. After completion, the solvents were evaporated, and the product was diluted in EtOAc, washed with water, then extracted. The organic layer was then washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The product (26.8 g, 95%) was obtained as a brown liquid, pure enough to be used in the next step without further purification.

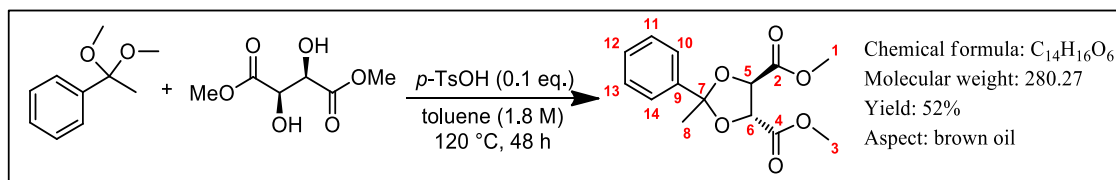
**TLC (cyclohexane/EtOAc: 90/10):** R<sub>f</sub> = 0.89 (UV active; KMnO<sub>4</sub>, stains yellow).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ (ppm) = 7.52-7.27 (m, 5H, H-6, H-7, H-8, H-9, H-10), 3.19 (s, 6H, H-1, H-2), 1.54 (s, 3H, H-3).

The <sup>1</sup>H NMR data are in agreement with those reported in the literature.<sup>198</sup>

### (4*R*,5*R*)-dimethyl 2-methyl-2-phenyl-1,3-dioxolane-4,5-dicarboxylate (S-4)<sup>198</sup>





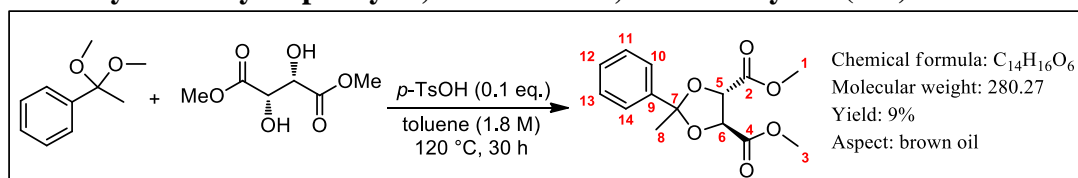
A dried two-necked flask was equipped with a condenser, and a dean stark system filled with dry toluene (10.0 mL) used to eliminate methanol. Under inert atmosphere, acetophenone dimethyl acetal (12.0 g, 72.19 mmol, 1.0 eq.) was introduced followed by dry toluene (40.0 mL, 1.8 M), (+)-dimethyl L-tartrate (12.8 g, 72.19 mmol, 1.0 eq.) and a catalytic quantity of *p*-toluenesulfonic acid monohydrate (1.37 g, 7.22 mmol, 0.1 eq.). The brown solution was stirred at 120 °C silicon oil bath temperature for 48 h and the reaction was followed by TLC. The crude mixture was diluted in ethyl acetate and washed with  $NaHCO_3$  then brine, dried over  $Na_2SO_4$  and concentrated under reduced pressure. The crude mixture was purified through column chromatography on  $SiO_2$  (cyclohexane/EtOAc: 95/5). The product (10.6 g, 52%) was obtained as a brown oil.

**TLC (cyclohexane/EtOAc: 90/10):**  $R_f$  = 0.2 (UV active;  $KMnO_4$ , stains yellow).

**$^1H$  NMR (300 MHz,  $CDCl_3$ ):**  $\delta$  (ppm) = 7.81-7.28 (m, 5H, H-10, H-11, H-12, H-13, H-14), 4.89-4.80 (m, 2H, H-5, H-6), 3.85 (s, 3H, H-1 or H-3), 3.74 (s, 3H, H-1 or H-3), 1.54 (s, 3H, H-8).

The  $^1H$  NMR data are in agreement with those reported in the literature.<sup>198</sup>

#### (4S,5S)-dimethyl 2-methyl-2-phenyl-1,3-dioxolane-4,5-dicarboxylate (S-5)

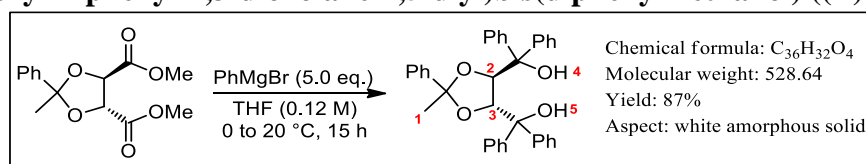


A dried two-necked flask was equipped with a condenser, and a dean stark system filled with dry toluene (10.0 mL) used to eliminate methanol. Under inert atmosphere, acetophenone dimethyl acetal (20.6 g, 124.0 mmol, 1.0 eq.) was introduced followed by dry toluene (69.0 mL, 1.8 M), (-)-dimethyl D-tartrate (22.1 g, 124.0 mmol, 1.0 eq.) and a catalytic quantity of *p*-toluenesulfonic acid monohydrate (2.36 g, 12.4 mmol, 0.1 eq.). The brown solution was stirred at 120 °C silicon oil bath temperature for 30 h and the reaction was followed by TLC. The crude mixture was diluted in ethyl acetate and washed with  $NaHCO_3$  then brine, dried over  $Na_2SO_4$  and concentrated under reduced pressure. The crude mixture was purified through column chromatography on  $SiO_2$  (cyclohexane/EtOAc: 90/10). The product (3.0 g, 9%) was obtained as a brown oil.

**TLC (cyclohexane/EtOAc: 90/10):**  $R_f$  = 0.2 (UV active;  $KMnO_4$ , stains yellow; vanillin, stains red).

**$^1H$  NMR (300 MHz,  $CDCl_3$ ):**  $\delta$  (ppm) = 7.81-7.28 (m, 5H, H-10, H-11, H-12, H-13, H-14), 4.89-4.80 (m, 2H, H-5, H-6), 3.85 (s, 3H, H-1 or H-3), 3.74 (s, 3H, H-1 or H-3), 1.54 (s, 3H, H-8).

#### ((4R,5R)-2-methyl-2-phenyl-1,3-dioxolane-4,5-diyl)bis(diphenylmethanol) ((R)-115)<sup>198</sup>



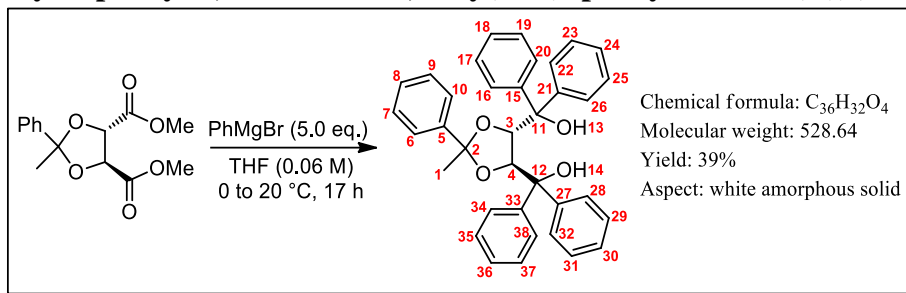
To dry THF (300.0 mL, 0.12 M) in a flame-dried flask under inert atmosphere and set at 0 °C, phenylmagnesium bromide (3.0 M in THF, 63.0 mL, 189.0 mmol, 5.0 eq.) was added. Afterwards, the prepared dioxolane S-4 (10.6 g, 37.8 mmol, 1.0 eq.) diluted in dry THF (7.0 mL) was added. The mixture was stirred for 15 h at 20 °C. After completion, the product was washed with sat.  $NH_4Cl$  and extracted with EtOAc. The organic layer was then washed with brine, dried over  $Na_2SO_4$  and concentrated under reduced pressure. The product was purified through column chromatography on  $SiO_2$  (cyclohexane/EtOAc: 90/10) to obtain it as a white amorphous solid (17.5 g, 87%).

**TLC (cyclohexane/EtOAc: 90/10):**  $R_f$  = 0.46 (UV active;  $KMnO_4$ , stains yellow; vanillin, stains red).

**$^1H$  NMR (300 MHz,  $CDCl_3$ ):**  $\delta$  (ppm) = 7.56-7.07 (m, 25H, H-Ph), 5.18 (d,  $J$  = 5.5 Hz, 1H, H-2), 5.10 (d,  $J$  = 5.5 Hz, 1H, H-3), 2.34 (s, 1H, H-5), 2.21 (s, 1H, H-4), 1.34 (s, 3H, H-1).

The  $^1\text{H}$  NMR data are in agreement with those reported in the literature.<sup>198</sup>

**((4*S*,5*S*)-2-methyl-2-phenyl-1,3-dioxolane-4,5-diyl)bis(diphenylmethanol) ((*S*)-115)**



To dry THF (136.0 mL, 0.06 M) in a two-necked flask under inert atmosphere and set at 0 °C, phenylmagnesium bromide (1.0 M in THF, 41.6 mL, 41.6 mmol, 5.0 eq.) was added. Afterwards, the prepared dioxolane **S-5** (2.33 g, 8.3 mmol, 1.0 eq.) diluted in dry THF (5 mL) was added. The mixture was stirred at 20 °C for 17 h. After completion, the product was washed with sat.  $\text{NH}_4\text{Cl}$  and extracted with EtOAc. The organic layer was then washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The product was purified through column chromatography on  $\text{SiO}_2$  (cyclohexane/EtOAc: 90/10) to obtain it as a white amorphous solid (1.7 g, 39%).

**TLC (cyclohexane/EtOAc: 90/10):**  $R_f = 0.46$  (UV active;  $\text{KMnO}_4$ , stains yellow; vanillin, stains red).

**m. p.** = 81.2–84.5 °C ( $\text{CH}_2\text{Cl}_2$ ).

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 7.56–7.07 (m, 25H, H-Ph), 5.18 (d,  $J = 5.5$  Hz, 1H, H-3), 5.10 (d,  $J = 5.5$  Hz, 1H, H-4), 2.35 (s, 1H, H-14), 2.22 (s, 1H, H-13), 1.34 (s, 3H, H-1).

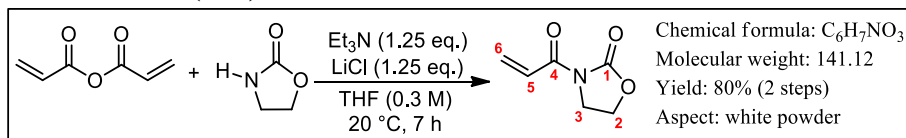
**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 145.2 (C-5), 145.2 (C-15), 145.1 (C-21), 143.5 (C-27), 143.4 (C-33), 128.6 (C-Ph), 128.4 (C-Ph), 128.2 (C-Ph), 128.18 (C-Ph), 128.1 (C-Ph), 127.7 (C-Ph), 127.6 (C-Ph), 127.4 (C-Ph), 127.35 (C-Ph), 127.3 (C-Ph), 127.1 (C-Ph), 127.0 (C-Ph), 126.9 (C-Ph), 126.6 (C-Ph), 124.8 (C-6, C-10), 111.4 (C-2), 83.3 (C-4), 81.7 (C-3), 79.0 (C-11), 78.5 (C-12), 30.1 (C-1).

**IR (solution in  $\text{CH}_2\text{Cl}_2$ , thin film, KBr):**  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 3327 (br, OH), 1494, 1445, 1170, 1039, 698.

**HRMS (TOF, ES<sup>+</sup>):** calculated for  $\text{C}_{36}\text{H}_{32}\text{O}_4\text{Na}$   $[\text{M}+\text{Na}]^+$  551.21928, **found** 551.21831.

**$[\alpha]_{\text{D}}^{25}$**  = -77 ( $c = 0.53$ ,  $\text{CHCl}_3$ ).

**3-acryloyloxazolidin-2-one (113)<sup>470</sup>**



**Synthesis of acrylic anhydride:** To acrylic acid (11.9 mL, 174.0 mmol, 1.25 eq.) in a flame-dried flask, EtOAc (500.0 mL, 0.35 M) was added and the mixture was transferred to 0 °C. Distilled triethylamine (24.3 mL, 174.0 mmol, 1.25 eq.) was then added followed by acryloyl chloride (14.1 mL, 174.0 mmol, 1.25 eq.). After 30 min at 0 °C, the reaction was stirred for another 30 min at 20 °C. A white suspension was formed, it was filtrated on Büchner, and washed with EtOAc. The filtrate was concentrated under reduced pressure to obtain the product as a pale-yellow liquid and it was directly engaged in the next step.

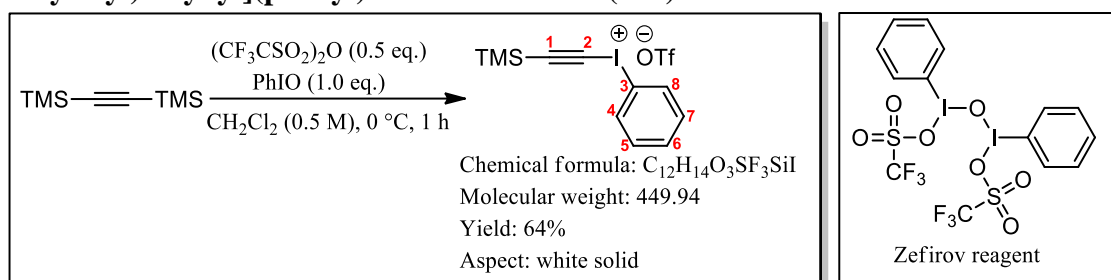
To a two-necked flask under argon and set at 0 °C, 2-oxazolidinone (12.1 g, 139.2 mmol, 1.0 eq.) was introduced to dry THF (500.0 mL, 0.3 M), then lithium chloride (3.6 mL, 174.0 mmol, 1.25 eq.), distilled triethylamine (24.3 mL, 174.0 mmol, 1.25 eq.) and the acrylic anhydride (1.25 eq.) were added. The mixture was allowed to warm up slowly to 20 °C (exothermic reaction). After 7 h, the reaction was quenched with HCl aqueous solution (100.0 mL, 1.0 M). The product was extracted with  $\text{CH}_2\text{Cl}_2$  and the organic layer was washed with sat.  $\text{NaHCO}_3$  then brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The obtained solid was washed with  $\text{Et}_2\text{O}$  (3 x 5 mL) to get a white powder (15.7 g, 80% over 2 steps). The product was obtained pure enough to be used directly in the next step.

**TLC (cyclohexane/EtOAc: 50/50):**  $R_f = 0.52$  (UV active;  $\text{KMnO}_4$ , stains yellow; vanillin stains colorless).

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 7.49 (dd,  $J$  = 17.0, 10.5 Hz, H-5), 6.55 (dd,  $J$  = 17.0, 1.8 Hz, 1H, H-6a), 5.90 (dd,  $J$  = 10.5, 1.8 Hz, 1H, H-6b), 4.44 (t,  $J$  = 8.1 Hz, 2H, H-2), 4.08 (t,  $J$  = 8.0 Hz, 2H, H-3).

The  $^1\text{H}$  NMR data are in agreement with those reported in the literature.<sup>470</sup>

**[(trimethylsilyl)ethynyl](phenyl)iodonium triflate (183)<sup>210</sup>**



To a flame-dried flask, iodosobenzene (3.4 g, 15.4 mmol, 1.0 eq.) was introduced followed by dry  $\text{CH}_2\text{Cl}_2$  (15.4 mL). The mixture was set at  $0^\circ\text{C}$ , then trifluoromethanesulfonic anhydride (1.0 M in  $\text{CH}_2\text{Cl}_2$ , 7.7 mL, 7.7 mmol, 0.5 eq.) was added slowly and the reaction was stirred at the same temperature until the suspension became a clear, homogeneous yellow solution (30 min). To the resulting Zefirov reagent, bis(trimethylsilyl)acetylene (2.6 g, 15.4 mmol, 1.0 eq.) dissolved in  $\text{CH}_2\text{Cl}_2$  (15.4 mL) was added, and the solution was stirred at  $0^\circ\text{C}$  for an additional 30 min. The solvents were concentrated under reduced pressure to give a beige solid. Trituration with  $\text{Et}_2\text{O}$  (5 x 5 mL) gave the product (4.44 g, 64%) as a white solid after drying under vacuum.

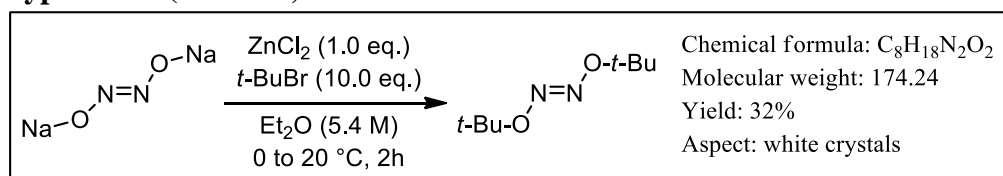
**TLC:** -

**$^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):**  $\delta$  (ppm) = 8.30 (d,  $J$  = 7.7 Hz, 1H, H-8), 7.75 (t,  $J$  = 7.1 Hz, 1H, H-4), 7.62 (t,  $J$  = 7.5 Hz, 2H, H-5, H-7), 0.18 (s, 9H, H-TMS).

**$^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO}-d_6$ ):**  $\delta$  (ppm) = 134.7 (C-4, C-8), 132.5 (C-6), 132.0 (C-5, C-7), 127.7 (C-CF<sub>3</sub>), 118.7 (C-3), 113.1 (C-2), 53.3 (C-1), -0.85 (C-TMS).

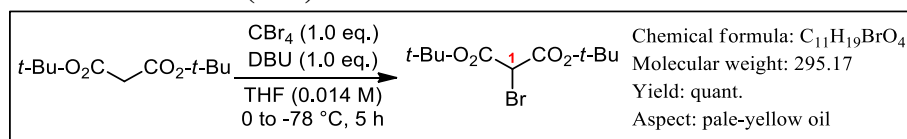
**IR (solution in MeOH, thin film, KBr):**  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 2252 (C $\equiv$ C), 2126, 1654, 1025, 824, 762, 626.

**di-*t*-butyl hyponitrite (DTBHN)<sup>471</sup>**



To a flame-dried two-necked flask,  $\text{Et}_2\text{O}$  (5.5 mL, 5.4 M) was introduced, followed by freshly distilled *t*-BuBr (34.0 mL, 296.0 mmol, 10.0 eq.).  $\text{ZnCl}_2$  (1.0 M in  $\text{Et}_2\text{O}$ , 29.6 mL, 29.6 mmol, 1.0 eq.) was added dropwise at  $0^\circ\text{C}$ , then sodium hyponitrite dried under vacuum the night before (3.14 g, 29.6 mmol, 1.0 eq.) was added portion-wise over 5 min. The reaction was stirred at  $20^\circ\text{C}$  for 2 h. The mixture was filtered on Büchner, and the filtrate was washed with water and extracted with  $\text{Et}_2\text{O}$  then dried over  $\text{Na}_2\text{SO}_4$ . The organic layer was concentrated under reduced pressure at  $20^\circ\text{C}$ , then the white solid was dissolved in minimum of pentane (10 mL) and stored in the freezer overnight. The pentane was then removed and the white crystals were weighed. The product (1.65 g, 32%) was covered with aluminium foil and stored under argon in the freezer.

**di-*tert*-butyl 2-bromomalonate (76b)<sup>472</sup>**



To a flame-dried two-necked flask, di-*tert*-butyl malonate (1.0 mL, 4.46 mmol, 1.0 eq.) was introduced to dry THF (300.0 mL, 0.014 M) at  $0^\circ\text{C}$ , then DBU (0.66 mL, 4.46 mmol, 1.0 eq.) was added slowly. The reaction was stirred at  $20^\circ\text{C}$  for 1 h, then cooled down to  $-78^\circ\text{C}$ .  $\text{CBr}_4$  (1.48 g,

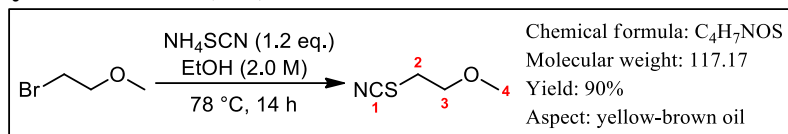
4.46 mmol, 1.0 eq.) was added and the mixture was stirred at the same temperature until completion and followed by TLC. After 5 h, the reaction was quenched with  $\text{NH}_4\text{Cl}$  and extracted with  $\text{CH}_2\text{Cl}_2$ . The organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$  then concentrated under reduced pressure. The crude was purified through column chromatography on  $\text{SiO}_2$  (cyclohexane/EtOAc: 70/30) to afford the product (1.44 g, quant.) as a pale-yellow oil.

**TLC (cyclohexane/EtOAc: 80/20):**  $R_f = 0.70$  (UV inactive;  $\text{KMnO}_4$ , stains white-yellow).

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 4.64 (s, 1H, H-1), 1.48 (s, 18H, H-*t*-Bu).

The  $^1\text{H}$  NMR data are in agreement with those reported in the literature.<sup>472</sup>

### 1-methoxy-2-thiocyanatoethane (S-6)<sup>5</sup>

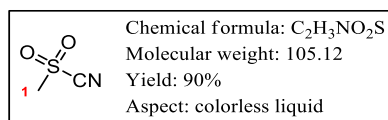


To a solution of ammonium thiocyanate (3.9 g, 51.0 mmol, 1.2 eq.) in EtOH (21.0 mL, 2.0 M) was added 1-bromo-2-methoxyethane (4.0 mL, 42.5 mmol, 1.0 eq.). The reaction mixture was heated at 78 °C silicon oil bath temperature for 14 h, then the reaction was allowed to reach 20 °C and the solid residues were filtered off and washed with  $\text{CH}_2\text{Cl}_2$ . The pooled liquids were washed with water, brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure to give the product (4.5 g, 90%) as a yellow-brown oil, pure enough to be used directly in the next step.

**TLC (cyclohexane/EtOAc: 80/20):**  $R_f = 0.43$  (UV active;  $\text{KMnO}_4$ , stains yellow).

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 3.73 (td,  $J = 5.8, 1.3$  Hz, 2H, H-3), 3.42 (d,  $J = 1.5$  Hz, 3H, H-4), 3.15 (td,  $J = 5.9, 1.4$  Hz, 2H, H-2).

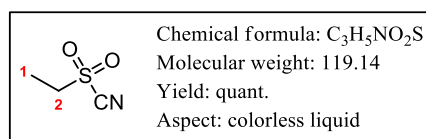
### methanesulfonyl cyanide (88a)<sup>5</sup>



Synthesized according to the general procedure (A), from hydrogen peroxide (50 wt. % solution in water, 11.9 g, 350.0 mmol, 5.0 eq.), trifluoroacetic anhydride (49.4 mL, 350.0 mmol, 5.0 eq.),  $\text{CH}_2\text{Cl}_2$  (72.0 mL, 1.0 M) and methyl thiocyanate (4.7 mL, 70.0 mmol, 1.0 eq.) to afford the product (6.7 g, 90%) as a colourless liquid.

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 3.43 (s, 3H, H-1).

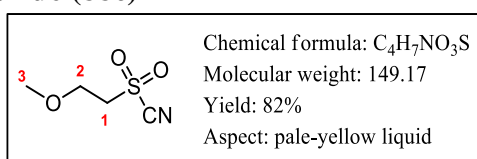
### ethanesulfonyl cyanide (88b)<sup>5</sup>



Synthesized according to the general procedure (A), from hydrogen peroxide (50 wt. % solution in water, 9.8 g, 289.0 mmol, 5.0 eq.), trifluoroacetic anhydride (40.8 mL, 289.0 mmol, 5.0 eq.),  $\text{CH}_2\text{Cl}_2$  (60.0 mL, 1.0 M), and ethyl thiocyanate (5.0 mL, 58.0 mmol, 1.0 eq.) to afford the product (7.0 g, quant.) as a colourless liquid.

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 3.43 (q,  $J = 7.4$  Hz, 2H, H-2), 1.60 (t,  $J = 7.4$  Hz, 3H, H-1).

### 2-methoxyethanesulfonyl cyanide (88c)<sup>5</sup>

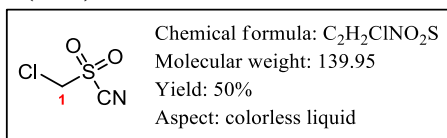


Synthesized according to the general procedure (A), from hydrogen peroxide (50 wt. % solution in water, 6.5 g, 192.0 mmol, 5.0 eq.), trifluoroacetic anhydride (27.0 mL, 192.0 mmol, 5.0 eq.),  $\text{CH}_2\text{Cl}_2$

(40.0 mL, 1.0 M), and 1-methoxy-2-thiocyanatoethane (4.5 mL, 38.4 mmol, 1.0 eq.) to afford the product (4.4 g, 82%) as a pale-yellow liquid.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 3.94 (dd,  $J$  = 5.9, 5.0 Hz, 2H, H-2), 3.63 (dd,  $J$  = 5.8, 5.0 Hz, 2H, H-1), 3.45 (s, 3H, H-3).

### chloromethanesulfonyl cyanide (88d)<sup>5</sup>

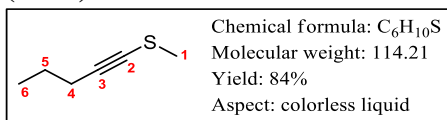


Synthesized according to the general procedure (A), from hydrogen peroxide (50 wt. % solution in water, 6.5 g, 191.0 mmol, 5.0 eq.), trifluoroacetic anhydride (27.0 mL, 191.0 mmol, 5.0 eq.), CH<sub>2</sub>Cl<sub>2</sub> (39.0 mL, 1.0 M), and chloro(thiocyanato)methane (3.0 mL, 38.2 mmol, 1.0 eq.) to afford the product (2.7 g, 50%) as a colourless liquid.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 4.81 (s, 2H, H-1).

## 3. Synthesis of alkynyl sulfides

### methyl(pent-1-yn-1-yl)sulfane (112a)



According to the general procedure (B), from pent-1-yne (6.9 g, 0.10 mol, 1.25 eq.), dry THF (100.0 mL, 0.8 M), *n*-BuLi (2.5 M in hexane, 34.4 mL, 86.0 mmol, 1.06 eq.), dimethyl disulfide (7.6 g, 81.0 mmol, 1.0 eq.), and 2-bromoethanol (7.2 mL, 0.10 mmol, 1.25 eq.). Purification through column chromatography on SiO<sub>2</sub> (pentane: 100%) afforded the product (7.7 g, 84%) as a colourless liquid.

**TLC (pentane: 100%):**  $R_f$  = 0.73 (UV active; KMnO<sub>4</sub>, stains yellow).

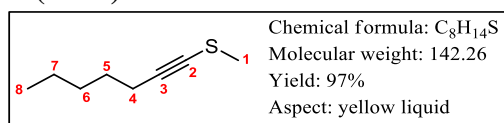
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 2.35 (s, 3H, H-1), 2.26 (t,  $J$  = 7.0 Hz, 2H, H-4), 1.53 (hex,  $J$  = 7.3 Hz, 2H, H-5), 0.97 (t,  $J$  = 7.4 Hz, 3H, H-6).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 93.3 (C-2), 70.0 (C-3), 22.3 (C-4), 22.2 (C-5), 19.5 (C-1), 13.6 (C-6).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2961 (-C-H), 2926 (-C-H), 2870 (-C-H), 1460, 1432, 1314, 974.

**LRMS (GC-MS):** calculated for C<sub>6</sub>H<sub>10</sub>S:  $m/z$ : 114 (M<sup>+</sup>, 64%), 99 (17%), 85 (100%), 67 (51%), 55 (7%), 45 (27%), 39 (11%).

### hept-1-yn-1-yl(methyl)sulfane (112b)



According to the general procedure (B), from hept-1-yne (5.8 mL, 45.0 mmol, 1.125 eq.), dry THF (60.0 mL, 0.65 M), *n*-BuLi (2.1 M in hexane, 20.0 mL, 42.4 mmol, 1.06 eq.), dimethyl disulfide (3.6 mL, 40.0 mmol, 1.0 eq.) and 2-bromoethanol (0.8 mL, 50.0 mmol, 1.25 eq.). Purification through column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc: 90/10) afforded the product (5.6 g, 97%) as a yellow liquid.

**TLC (cyclohexane/EtOAc: 50/50):**  $R_f$  = 0.85 (UV active; KMnO<sub>4</sub>, stains yellow).

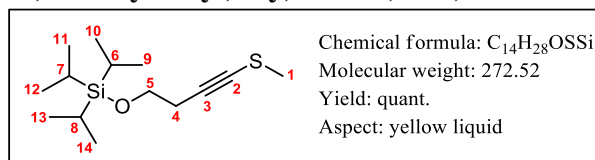
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 2.53 (s, 3H, H-1), 2.28 (t,  $J$  = 7.0 Hz, 2H, H-4), 1.56-1.46 (m, 2H, H-5), 1.41-1.26 (m, 4H, H-6, H-7), 0.93-0.87 (m, 3H, H-8).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 93.3 (C-3), 69.8 (C-2), 31.1 (C-6), 28.5 (C-5), 22.3 (C-7), 20.1 (C-1), 19.3 (C-4), 14.0 (C-8).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 3545, 2957 (-C-H), 2929 (-C-H), 2859 (-C-H), 1730, 1448, 1434, 1313, 976, 700.

**HRMS (TOF, FI+):** calculated for C<sub>8</sub>H<sub>14</sub>S [M]<sup>+</sup> 142.08162, found 142.08200.



**triisopropyl((4-(methylthio)but-3-yn-1-yl)oxy)silane (112c)**

According to the general procedure (**B**), from TIPS-protected 3-butyn-1-ol **S-1** (24.3 g, 107.4 mmol, 1.125 eq.), dry THF (150.0 mL, 0.65 M), *n*-BuLi (2.1 M in hexane, 46.0 mL, 101.2 mmol, 1.06 eq.), dimethyl disulfide (8.6 mL, 95.5 mmol, 1.0 eq.) and 2-bromoethanol (8.5 mL, 119.4 mmol, 1.25 eq.). Purification through column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc: 90/10) afforded the product (27.3 g, quant.) as a yellow liquid.

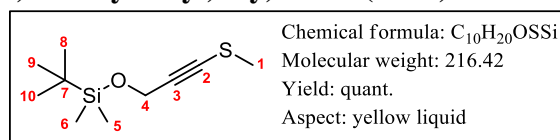
**TLC (cyclohexane/EtOAc: 90/10):** R<sub>f</sub> = 0.88 (UV active; KMnO<sub>4</sub> or vanillin, stains yellow).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ (ppm) = 3.79 (t, *J* = 7.2 Hz, 2H, H-5), 2.53 (t, *J* = 7.2 Hz, 2H, H-4), 2.34 (s, 3H, H-1), 1.17-0.94 (m, 21H, H-6, H-7, H-8, H-9, H-10, H-11, H-12, H-13, H-14).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ (ppm) = 90.2 (C-3), 71.3 (C-2), 62.3 (C-5), 24.6 (C-4), 19.2 (C-1), 18.1 (C-9, C-10, C-11, C-12, C-13, C-14), 12.1 (C-6, C-7, C-8).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):** ν<sub>max</sub> (cm<sup>-1</sup>) = 2942 (-C-H), 2866 (-C-H), 2194 (C≡C), 1463, 1113, 1070, 882, 683.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>14</sub>H<sub>28</sub>OSSiNa [M+Na]<sup>+</sup> 295.1522, **found** 295.1528.

**triisopropyl((4-(methylthio)but-3-yn-1-yl)oxy)silane (112d)**

According to the general procedure (**B**), from TBDMS-protected prop-2-yn-1-ol **S-2** (4.13 g, 24.2 mmol, 1.125 eq.), dry THF (33.0 mL, 0.65 M), *n*-BuLi (2.1 M in hexane, 10.7 mL, 22.8 mmol, 1.06 eq.), dimethyl disulfide (2.0 mL, 21.5 mmol, 1.0 eq.) and 2-bromoethanol (1.9 mL, 26.8 mmol, 1.25 eq.). Purification through column chromatography on SiO<sub>2</sub> (cyclohexane: 100%) afforded the product as a yellow liquid (5.0 g, quant.).

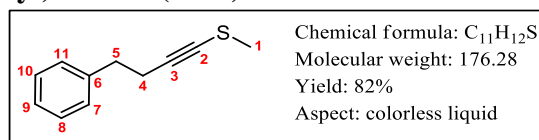
**TLC (cyclohexane/EtOAc: 90/10):** R<sub>f</sub> = 0.8 (UV active; KMnO<sub>4</sub>, stains yellow).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ (ppm) = 4.40 (s, 2H, H-4), 2.37 (s, 3H, H-1), 0.91 (s, 9H, H-8, H-9, H-10), 0.12 (s, 6H, H-5, H-6).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ (ppm) = 91.9 (C-3), 76.9 (C-2), 52.6 (C-4), 26.0 (C-8, C-9, C-10), 19.1 (C-1), 18.4 (C-7), -4.9 (C-5, C-6).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):** ν<sub>max</sub> (cm<sup>-1</sup>) = 2955, 2929 (-C-H), 2857 (-C-H), 2189 (C≡C), 1254, 1093, 836, 777.

**HRMS (TOF, FI<sup>+</sup>):** calculated for C<sub>6</sub>H<sub>9</sub>OSSi [M]<sup>+</sup> 216.10080, **found** 216.10041.

**methyl(4-phenylbut-1-yn-1-yl)sulfane (112e)**

According to the general procedure (**B**), from 4-Phenyl-1-butyne (3.0 mL, 21.0 mmol, 1.125 eq.), dry THF (29.0 mL, 0.65 M), *n*-BuLi (2.1 M in hexane, 9.5 mL, 20.0 mmol, 1.06 eq.), dimethyl disulfide (1.7 mL, 19.0 mmol, 1.0 eq.) and 2-bromoethanol (1.7 mL, 23.7 mmol, 1.25 eq.). Purification through column chromatography on SiO<sub>2</sub> (cyclohexane: 100%) afforded the product as a colourless liquid (3.1 g, 82%).

**TLC (cyclohexane: 100%):** R<sub>f</sub> = 0.28 (UV active; KMnO<sub>4</sub>, stains yellow; vanillin, stains red then yellow).

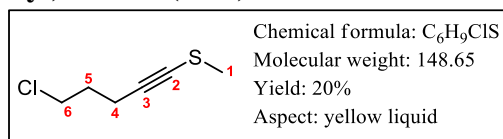
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ (ppm) = 7.33-7.27 (m, 2H, H-7, H-11), 7.25-7.18 (m, 3H, H-8, H-9, H-10), 2.84 (t, *J* = 7.5 Hz, 2H, H-4), 2.58 (t, *J* = 7.6 Hz, 2H, H-5), 2.33 (s, 3H, H-1).

**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 140.7 (C-6), 128.5 (C-7, C-11), 128.4 (C-8, C-10), 126.4 (C-9), 92.5 (C-3), 71.0 (C-2), 35.3 (C-5), 22.4 (C-1), 19.3 (C-4).

**IR (solution in  $\text{CH}_2\text{Cl}_2$ , thin film, KBr):**  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 3027, 2926 (C-H), 2189 ( $\text{C}\equiv\text{C}$ ), 1602, 1495, 1453, 1312, 1077, 976, 747, 698, 507.

**HRMS (TOF, FI+):** calculated for  $\text{C}_{11}\text{H}_{12}\text{S}$   $[\text{M}]^{+}$  176.06597, **found** 176.06600.

#### (5-chloropent-1-yn-1-yl)(methyl)sulfane (112f)



According to the general procedure (**B**), from 5-chloropent-1-yne (2.2 mL, 20.8 mmol, 1.125 eq.), dry THF (40.0 mL, 0.4 M), *n*-BuLi (2.5 M in hexane, 8.4 mL, 17.6 mmol, 1.06 eq.), dimethyl disulfide (1.5 mL, 16.6 mmol, 1.0 eq.) and 2-bromoethanol (1.5 mL, 20.8 mmol, 1.25 eq.). Purification through column chromatography on  $\text{SiO}_2$  (pentane/ $\text{Et}_2\text{O}$ : 100/0 to 99/1) afforded the product (484.0 mg, 20%) as a yellow liquid.

**TLC (cyclohexane/ $\text{EtOAc}$ : 50/50):**  $R_f$  = 0.65 (UV active;  $\text{KMnO}_4$ , stains yellow).

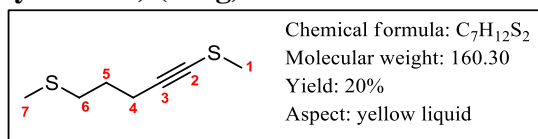
**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 3.63 (t,  $J$  = 6.4 Hz, 2H, H-6), 2.48 (t,  $J$  = 6.8 Hz, 2H, H-4), 2.35 (s, 3H, H-1), 1.95 (quint,  $J$  = 6.6 Hz, 2H, H-5).

**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 91.1 (C-3), 71.4 (C-2), 43.7 (C-6), 31.5 (C-5), 19.3 (C-1), 17.6 (C-4).

**IR (solution in  $\text{CH}_2\text{Cl}_2$ , thin film, KBr):**  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 2927 (C-H), 1725, 1446, 1175, 1045, 700.

**HRMS (TOF, FI+):** calculated for  $\text{C}_6\text{H}_9\text{ClS}$   $[\text{M}]^{+}$  148.01135, **found** 148.01150.

#### pent-1-yne-1,5-diylbis(methylsulfane) (112g)



This product was obtained as a side-product alongside with (5-chloropent-1-yn-1-yl)(methyl)sulfane **112f**, as a yellow liquid (518.0 mg, 20%).

**TLC (cyclohexane/ $\text{EtOAc}$ : 50/50):**  $R_f$  = 0.25 (UV active;  $\text{KMnO}_4$ , stains yellow).

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 2.57 (t,  $J$  = 6.4 Hz, 2H, H-6), 2.41 (t,  $J$  = 6.9 Hz, 2H, H-4), 2.34 (s, 3H, H-7), 2.08 (s, 3H, H-1), 1.78 (quint,  $J$  = 7.0 Hz, 2H, H-5).

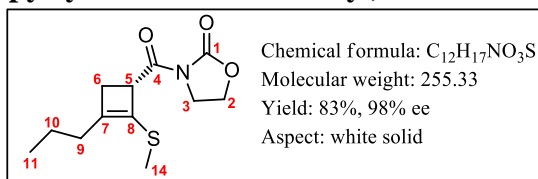
**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 92.1 (C-3), 70.8 (C-2), 33.2 (C-6), 28.1 (C-5), 19.3 (C-1), 19.2 (C-4), 15.5 (C-7).

**IR (solution in  $\text{CH}_2\text{Cl}_2$ , thin film, KBr):**  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 2920 (C-H), 2856 (C-H), 2188 ( $\text{C}\equiv\text{C}$ ), 1429, 1313, 1279, 976, 957.

**HRMS (TOF, FI+):** calculated for  $\text{C}_7\text{H}_{12}\text{S}_2$   $[\text{M}]^{+}$  160.03804, **found** 160.03850.

### 4. Narasaka's asymmetric [2+2] cycloaddition

#### (*R*)-3-(2-(methylthio)-3-propylcyclobut-2-enecarbonyl)oxazolidin-2-one (117a)



According to the general procedure (**C**), from the titanium complex:  $\text{TiCl}_2(\text{O}i\text{Pr})_2$  (1.78 g, 7.52 mmol, 0.1 eq.) and (**R**)-**115** (4.37 g, 8.27 mmol, 0.11 eq.) in dry toluene (93.0 mL, 0.08 M), 4 Å molecular sieves (1.72 g), dry toluene (170.0 mL, 0.25 M), 3-acryloyloxazolidin-2-one (10.6 g, 75.18 mmol, 1.0 eq.) and alkynyl thioether **112a** (14.6 g, 127.8 mmol, 1.7 eq.) for 40 h. Purification through

column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc: 80/20 to 60/40 to 50/50) afforded the product (16.08 g, 83%, 98% ee) as a white solid.

**TLC (pentane/EtOAc: 50/50):**  $R_f$  = 0.7 (UV active; vanillin, stains purple).

**m. p.** = 59–63 °C (pentane/EtOAc).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 4.78–4.69 (m, 1H, H-5), 4.49–4.37 (m, 2H, H-2), 4.11–3.99 (m, 2H, H-3), 2.77 (ddt,  $J$  = 12.7, 4.9, 1.2 Hz, 1H, H-6a), 2.57–2.46 (m, 1H, H-6b), 2.24 (s, 3H, H-14), 2.22–2.10 (m, 2H, H-9), 1.57–1.41 (m, 2H, H-10), 0.93 (t,  $J$  = 7.3 Hz, 3H, H-11).

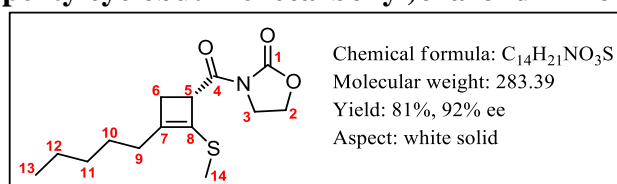
**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 173.0 (C-4), 153.6 (C-1 or C-7), 151.1 (C-1 or C-7), 129.3 (C-8), 62.4 (C-2), 44.8 (C-5), 42.8 (C-3), 33.7 (C-6), 31.0 (C-9), 20.2 (C-10), 15.9 (C-14), 14.1 (C-11).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2959 (–C–H), 2923 (–C–H), 2835 (–C–H), 1789 (4–C=O), 1770, 1679 (1–C=O), 1383, 1368, 1260, 1218, 1198.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>12</sub>H<sub>17</sub>NO<sub>3</sub>SNa [M+Na]<sup>+</sup> 278.0821, **found** 278.0811.

**[ $\alpha$ ]<sub>D</sub><sup>25</sup>** = +50.55 ( $c$  = 0.21, CHCl<sub>3</sub>).

**(R)-3-(2-(methylthio)-3-pentylcyclobut-2-enecarbonyl)oxazolidin-2-one (117b)**



According to the general procedure (C), from the titanium complex: TiCl<sub>2</sub>(OiPr)<sub>2</sub> (100.0 mg, 0.42 mmol, 0.1 eq.) and **(R)-115** (247.0 mg, 0.47 mmol, 0.11 eq.) in dry toluene (5.0 mL, 0.08 M), 4 Å molecular sieves (168.0 mg), dry toluene (17.0 mL, 0.25 M), 3-acryloyloxazolidin-2-one (600.0 mg, 4.25 mmol, 1.0 eq.) and the alkynyl thioether **112b** (900.0 mg, 6.4 mmol, 1.5 eq.) for 20 h. Purification through column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc: 80/20) afforded the product (982.0 mg, 81%, 92% ee) as a white solid.

**TLC (cyclohexane/EtOAc: 50/50):**  $R_f$  = 0.58 (UV active; vanillin, stains brown).

**m. p.** = 64–65.5 °C (pentane/EtOAc).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 4.72 (dq,  $J$  = 5.2, 1.8 Hz, 1H, H-5), 4.43 (t,  $J$  = 8.0 Hz, 2H, H-2), 4.04 (t,  $J$  = 8.4 Hz, 2H, H-3), 2.76 (dd,  $J$  = 12.7, 4.9 Hz, 1H, H-6a), 2.51 (dq,  $J$  = 12.5, 1.5 Hz, 1H, H-6b), 2.23 (s, 3H, H-14), 2.17 (t,  $J$  = 7.4 Hz, 2H, H-9), 1.44 (q,  $J$  = 7.0 Hz, 2H, H-10), 1.35–1.25 (m, 4H, H-11, H-12), 0.88 (t,  $J$  = 6.8 Hz, 3H, H-13).

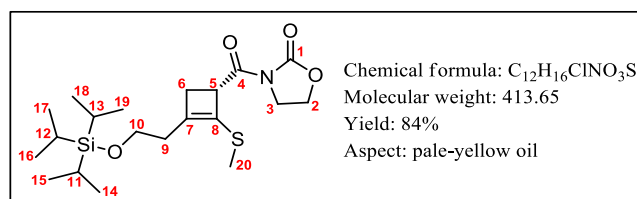
**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 172.9 (C-4), 153.6 (C-1), 151.3 (C-7), 129.0 (C-8), 62.3 (C-2), 44.8 (C-5), 42.7 (C-3), 33.7 (C-6), 31.7 (C-11 or C-12), 28.9 (C-9), 26.5 (C-10), 22.5 (C-11 or C-12), 15.9 (C-14), 14.1 (C-13).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2925 (–C–H), 1789 (4–C=O), 1771, 1679 (1–C=O), 1384, 1369, 1262, 1219, 1196, 1040, 757.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>14</sub>H<sub>21</sub>NO<sub>3</sub>SNa [M+Na]<sup>+</sup> 306.1134, **found** 306.1140.

**[ $\alpha$ ]<sub>D</sub><sup>23</sup>** = +43.55 ( $c$  = 1.93, CHCl<sub>3</sub>).

**(R)-3-(2-(methylthio)-3-(2-((triisopropylsilyl)oxy)ethyl)cyclobut-2-enecarbonyl)oxazolidin-2-one (117c)**



According to the general procedure (C), from the titanium complex: TiCl<sub>2</sub>(OiPr)<sub>2</sub> (1.34 g, 5.56 mmol, 0.1 eq.) and **(R)-115** (3.29 g, 6.23 mmol, 0.11 eq.) in dry toluene (70.0 mL, 0.08 M), 4 Å molecular sieves (2.22 g), dry toluene (224.0 mL, 0.25 M), 3-acryloyloxazolidin-2-one (8.0 g, 56.6 mmol, 1.0 eq.) and the alkynyl thioether **112c** (30.8 g, 113.2 mmol, 2.0 eq.) for 48 h. Purification through column



chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc: 90/10 to 70/30 to 50/50) afforded the product (19.6 g, 84%) as a pale-yellow oil.

**TLC (cyclohexane/EtOAc: 50/50):**  $R_f$  = 0.63 (UV active; vanillin, stains brown).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 4.73 (dq,  $J$  = 5.1, 1.8 Hz, 1H, H-5), 4.43 (t,  $J$  = 8.1 Hz, 2H, H-2), 4.04 (td,  $J$  = 5.1, 1.8 Hz, 2H, H-3), 3.80 (t,  $J$  = 6.8 Hz, 2H, H-10), 2.84 (dd,  $J$  = 8.0, 4.0 Hz, 1H, H-6a), 2.56 (d,  $J$  = 16.0 Hz, 1H, H-6b), 2.52-2.38 (m, 2H, H-9), 2.25 (s, 3H, H-20), 1.07-1.04 (m, 21H, H-11, H-12, H-13, H-14, H-15, H-16, H-17, H-18, H-19).

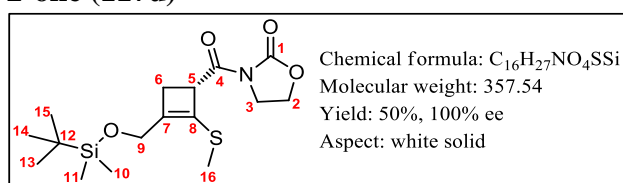
**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 172.7 (C-4), 153.9 (C-1), 148.0 (C-7), 130.6 (C-8), 62.4 (C-2), 61.3 (C-10), 45.3 (C-5), 42.7 (C-3), 34.5 (C-6), 32.9 (C-9), 18.1 (C-14, C-15, C-16, C-17, C-18, C-19), 15.8 (C-20), 12.1 (C-11, C-12, C-13).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2938 (-C-H), 1781 (4-C=O), 1696 (1-C=O), 1465, 1385, 1361, 1230, 1102, 1070, 1042, 883, 684.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>20</sub>H<sub>35</sub>NO<sub>4</sub>SSiNa [M+Na]<sup>+</sup> 436.1959, found 436.1955.

$[\alpha]_D^{23}$  = +36.16 ( $c$  = 0.13, CHCl<sub>3</sub>).

**(R)-3-(3-(((tert-butyldimethylsilyl)oxy)methyl)-2-(methylthio)cyclobut-2-enecarbonyl)oxazolidin-2-one (117d)**



According to the general procedure (C), from titanium complex: TiCl<sub>2</sub>(OiPr)<sub>2</sub> (201.0 mg, 0.85 mmol, 0.1 eq.) and (R)-115 (493.0 mg, 0.93 mmol, 0.11 eq.) in dry toluene (11.0 mL, 0.08 M), 4 Å molecular sieves (334.0 mg), dry toluene (33.0 mL, 0.25 M), 3-acryloyloxazolidin-2-one (1.2 g, 8.5 mmol, 1.0 eq.) and the alkynyl thioether 112d (2.7 g, 12.7 mmol, 1.5 eq.) for 66 h. Purification through column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc: 70/30) afforded the product (1.5 g, 50%, 100% ee) as a white solid.

**TLC (cyclohexane/EtOAc: 50/50):**  $R_f$  = 0.61 (UV active; vanillin, stains brown).

**m. p.** = 98.8-101.5 °C (pentane/EtOAc).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 4.72 (dq,  $J$  = 5.3, 1.9 Hz, 1H, H-5), 4.44 (dd,  $J$  = 8.6, 7.5 Hz, 2H, H-2), 4.24 (qq,  $J$  = 14.1, 1.3 Hz, 2H, H-9), 4.05 (dd,  $J$  = 8.6, 7.5 Hz, 2H, H-3), 2.90 (ddt,  $J$  = 12.5, 5.0, 1.2 Hz, 1H, H-6a), 2.54 (dq,  $J$  = 12.6, 1.4 Hz, 1H, H-6b), 2.25 (s, 3H, H-16), 0.90 (s, 9H, H-13, H-14, H-15), 0.08 (s, 6H, H-10, H-11).

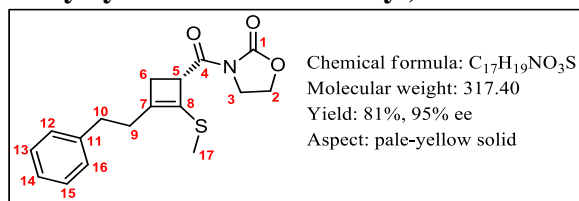
**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 172.4 (C-4), 153.5 (C-1), 145.7 (C-7), 130.6 (C-8), 62.4 (C-2), 59.3 (C-9), 44.6 (C-5), 42.7 (C-3), 32.9 (C-6), 26.0 (C-13, C-14, C-15), 18.5 (C-12), 15.2 (C-16), -5.1 (C-10, C-11).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2929 (-C-H), 1789 (4-C=O), 1682 (1-C=O), 1383, 1369, 1259, 1087, 1040, 839, 778.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>16</sub>H<sub>27</sub>NO<sub>4</sub>SSiNa [M+Na]<sup>+</sup> 380.1322, found 380.1327.

$[\alpha]_D^{23}$  = +70.91 ( $c$  = 2.46, CHCl<sub>3</sub>).

**(R)-3-(2-(methylthio)-3-phenethylcyclobut-2-enecarbonyl)oxazolidin-2-one (117e)**



According to the general procedure (C), from the titanium complex: TiCl<sub>2</sub>(OiPr)<sub>2</sub> (38.0 mg, 0.16 mmol, 0.1 eq.) and (R)-115 (93.0 mg, 0.17 mmol, 0.11 eq.) in dry toluene (2.0 mL, 0.08 M), 4 Å molecular sieves (62.0 mg), dry toluene (6.5 mL, 0.25 M), 3-acryloyloxazolidin-2-one (225.0 mg, 1.6 mmol, 1.0 eq.) and the alkynyl thioether 112e (500.0 mg, 2.8 mmol, 1.7 eq.) for 12 h. Purification

through column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc: 70/30) gave the product (423.0 mg, 81%, 95% ee) as a pale-yellow solid.

**TLC (cyclohexane/EtOAc: 50/50):**  $R_f$  = 0.52 (UV active; vanillin, stains brown).

**m. p.** = 51–52.4 °C (pentane/EtOAc).

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 7.29–7.27 (m, 2H, H-13, H-15), 7.20–7.17 (m, 3H, H-12, H-14, H-16), 4.71 (dq,  $J$  = 5.1, 1.7 Hz, 1H, H-5), 4.42 (t,  $J$  = 8.1 Hz, 2H, H-2), 4.04 (td,  $J$  = 5.1, 1.8 Hz, 2H, H-3), 2.83–2.74 (m, 3H, H-6a, H-10), 2.57–2.45 (m, 3H, H-6b, H-9), 2.16 (s, 3H, H-17).

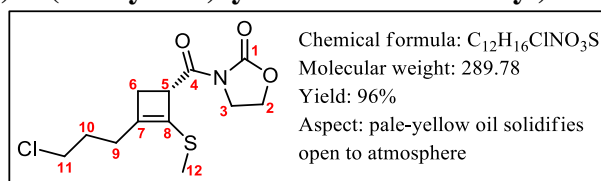
**<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 172.7 (C-4), 153.5 (C-1), 149.7 (C-7), 141.4 (C-11), 130.1 (C-8), 128.5 (C-13, C-15 or C-12, C-16), 128.4 (C-13, C-15 or C-12, C-16), 126.1 (C-14), 62.3 (C-2), 44.8 (C-5), 42.7 (C-3), 33.8 (C-6), 33.1 (C-10), 30.8 (C-9), 15.7 (C-17).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2922 (–C–H), 1778 (4–C=O), 1694 (1–C=O), 1386, 1363, 1252, 1225, 1108, 1039, 758, 701.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>17</sub>H<sub>19</sub>NO<sub>3</sub>SNa [M+Na]<sup>+</sup> 340.0977, **found** 340.0976.

**[ $\alpha$ ]<sub>D</sub><sup>23</sup>** = +30.54 ( $c$  = 2.6, CHCl<sub>3</sub>).

### (*R*)-3-(3-(3-chloropropyl)-2-(methylthio)cyclobut-2-enecarbonyl)oxazolidin-2-one (**117f**)



According to the general procedure (**C**), from the titanium complex: TiCl<sub>2</sub>(OiPr)<sub>2</sub> (14.2 mg, 0.06 mmol, 0.1 eq.) and (**R**)-**115** (35.0 mg, 0.066 mmol, 0.11 eq.) in dry toluene (0.8 mL, 0.08 M), 4 Å molecular sieves (23.0 mg), dry toluene (2.4 mL, 0.25 M), 3-acryloyloxazolidin-2-one (42.0 mg, 0.6 mmol, 1.0 eq.) and the alkynyl thioether **112f** (150.0 mg, 1.0 mmol, 1.7 eq.) for 43 h. Purification through column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc: 70/30) afforded the product (170.0 mg, 96%) as a pale-yellow oil solidifies open to atmosphere.

**TLC (cyclohexane/EtOAc: 50/50):**  $R_f$  = 0.55 (UV active; vanillin, stains brown).

**m. p.** = 63.1–64.2 °C (pentane/EtOAc).

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 4.75 (dq,  $J$  = 5.1, 1.8 Hz, 1H, H-5), 4.43 (t,  $J$  = 8.0 Hz, 2H, H-2), 4.04 (td,  $J$  = 5.1, 1.8 Hz, 2H, H-3), 3.55 (t,  $J$  = 6.6 Hz, 2H, H-11), 2.77 (ddt,  $J$  = 12.7, 4.9, 1.2 Hz, 1H, H-6a), 2.51 (dq,  $J$  = 12.6, 1.4 Hz, 1H, H-6b), 2.34 (tq,  $J$  = 8.3, 1.6 Hz, 2H, H-9), 2.25 (s, 3H, H-12), 1.97 (pd,  $J$  = 6.8, 2.3 Hz, 2H, H-10).

**<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 172.7 (C-4), 153.5 (C-1), 148.1 (C-7), 130.9 (C-8), 62.4 (C-2), 44.7 (C-5), 44.5 (C-11), 42.7 (C-3), 33.8 (C-6), 29.8 (C-10), 26.4 (C-9), 15.6 (C-12).

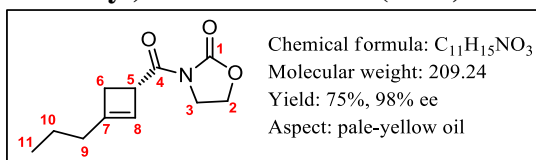
**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2923 (–C–H), 1778 (4–C=O), 1694 (1–C=O), 1387, 1363, 1253, 1227, 1109, 1040, 760.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>12</sub>H<sub>16</sub>ClNO<sub>3</sub>SNa [M+Na]<sup>+</sup> 312.0431, **found** 312.0441.

**[ $\alpha$ ]<sub>D</sub><sup>23</sup>** = +38.76 ( $c$  = 2.2, CHCl<sub>3</sub>).

## 5. Desulfurization reaction

### (*S*)-3-(3-propylcyclobut-2-enecarbonyl)oxazolidin-2-one (**169a**)



According to the general procedure (**E**), from cyclobutene **117a** (16.08 g, 62.9 mmol, 1.0 eq.), dry acetone (200.0 mL, 0.3 M), Lindlar's catalyst (6.7 g, 62.9 mmol, 1.0 eq.), oct-1-ene (9.8 mL, 62.9 mmol, 1.0 eq.) and freshly distilled triethylsilane (70.0 mL, 440.0 mmol, 7.0 eq.) at 50 °C for 24 h. Purification through column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc: 70/30 to 60/40) afforded the reduced cyclobutene (10.0 g, 75%, 98% ee) as a pale-yellow oil.

**TLC (pentane/EtOAc: 70/30):**  $R_f$  = 0.67 (UV active; vanillin, stains dark purple).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 5.80-5.78 (m, 1H, H-8), 4.46-4.38 (m, 2H, H-2), 4.36-4.30 (m, 1H, H-5), 4.06-3.98 (m, 2H, H-3), 2.81-2.73 (m, 1H, H-6a), 2.70-2.62 (m, 1H, H-6b), 2.08-1.98 (m, 2H, H-9), 1.55-1.40 (m, 2H, H-10), 0.92 (t,  $J$  = 7.4 Hz, 3H, H-11).

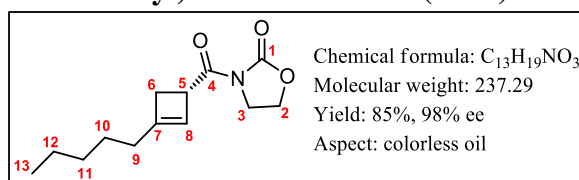
**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 173.8 (C-4), 153.5 (C-1), 152.9 (C-7), 125.2 (C-8), 62.4 (C-2), 42.7 (C-5), 42.6 (C-3), 34.8 (C-6), 33.0 (C-9), 19.8 (C-10), 14.0 (C-11).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2959 (-C-H), 2928 (-C-H), 2872 (-C-H), 1780 (4-C=O), 1694 (1-C=O), 1387, 1361, 1258, 1225.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>11</sub>H<sub>15</sub>NO<sub>3</sub>Na [M+Na]<sup>+</sup> 232.0944, **found** 232.0947.

**$[\alpha]_D^{25}$**  = -66.0 ( $c$  = 0.25, CHCl<sub>3</sub>).

**(S)-3-(3-pentylcyclobut-2-enecarbonyl)oxazolidin-2-one (169b)**



According to the general procedure (E), from cyclobutene **117b** (920.0 mg, 3.25 mmol, 1.0 eq.), dry acetone (33.0 mL, 0.1 M), Lindlar's catalyst (3.5 g, 32.5 mmol, 10.0 eq.), oct-1-ene (5.1 mL, 32.5 mmol, 5.0 eq.) and freshly distilled triethylsilane (5.2 mL, 32.5 mmol, 10.0 eq.) at 20 °C for 96 h. Purification through column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc: 80/20) afforded the reduced cyclobutene (660.0 mg, 85%, 98% ee) as a colorless oil.

**TLC (cyclohexane/EtOAc: 50/50):**  $R_f$  = 0.41 (UV active; vanillin, stains green).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 5.78 (q,  $J$  = 1.5 Hz, 1H, H-8), 4.42 (dd,  $J$  = 8.6, 7.5 Hz, 2H, H-2), 4.32 (dq,  $J$  = 4.5, 2.2, 1.4 Hz, 2H, H-5), 4.04 (dd,  $J$  = 8.4, 7.4 Hz, 2H, H-3), 2.77 (ddt,  $J$  = 13.2, 4.5, 1.1 Hz, 1H, H-6a), 2.66 (ddt,  $J$  = 13.3, 2.1, 1.2 Hz, 1H, H-6b), 2.12-1.94 (m, 2H, H-9), 1.49-1.39 (m, 2H, H-10), 1.31-1.26 (m, 4H, H-11, H-12), 0.91-0.86 (m, 3H, H-13).

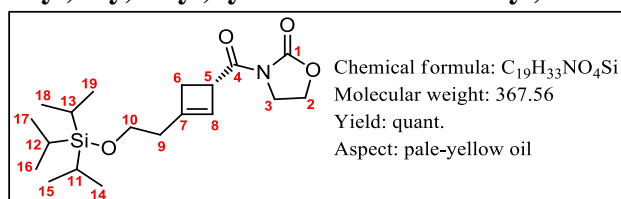
**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 173.8 (C-4), 153.5 (C-1), 153.1 (C-7), 125.0 (C-8), 62.4 (C-2), 42.7 (C-5), 42.6 (C-3), 34.8 (C-6), 31.7 (C-11), 30.9 (C-9), 26.1 (C-10), 22.6 (C-11 or C-12), 14.1 (C-13).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2927 (-C-H), 1789 (4-C=O), 1694 (1-C=O), 1480, 1385, 1229, 1108, 1041, 760.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>13</sub>H<sub>19</sub>NO<sub>3</sub>Na [M+Na]<sup>+</sup> 260.1257, **found** 260.1255.

**$[\alpha]_D^{23}$**  = -42.14 ( $c$  = 2.4, CHCl<sub>3</sub>).

**(S)-3-(3-(2-((triisopropylsilyl)oxy)ethyl)cyclobut-2-enecarbonyl)oxazolidin-2-one (169c)**



According to the general procedure (E), from cyclobutene **117c** (13.2 g, 32.0 mmol, 1.0 eq.), dry acetone (270.0 mL, 0.11 M), Lindlar's catalyst (3.4 g, 32.0 mmol, 1.0 eq.), oct-1-ene (5.0 mL, 32.0 mmol, 1.0 eq.) and freshly distilled triethylsilane (50.5 mL, 320.0 mmol, 10.0 eq.) at 50 °C for 24 h. Purification through column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc: 80/20) afforded the reduced cyclobutene (11.8 g, quant.) as a pale-yellow oil.

**TLC (cyclohexane/EtOAc: 50/50):**  $R_f$  = 0.63 (UV active; vanillin, stains purple).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 5.83 (q,  $J$  = 1.3 Hz, 1H, H-8), 4.42 (dd,  $J$  = 8.5, 7.5 Hz, 2H, H-2), 4.34 (m, 1H, H-5), 4.01 (dd,  $J$  = 8.7, 7.5 Hz, 2H, H-3), 3.80 (t,  $J$  = 7.0 Hz, 2H, H-10), 2.83 (ddt,  $J$  = 13.4, 4.6, 1.2 Hz, 1H, H-6a), 2.71 (ddt,  $J$  = 13.3, 2.1, 1.1 Hz, 1H, H-6b), 2.35-2.30 (m, 2H, H-9), 1.08-1.05 (m, 21H, H-11, H-12, H-13, H-14, H-15, H-16, H-17, H-18, H-19).

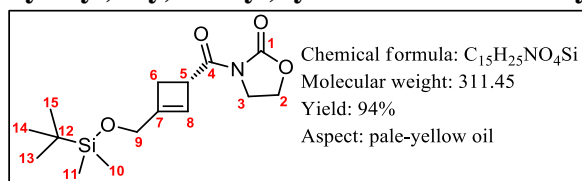
**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 173.4 (C-4), 153.3 (C-1), 149.8 (C-7), 126.5 (C-8), 62.2 (C-2), 61.1 (C-10), 43.1 (C-5), 42.5 (C-3), 35.2 (C-6), 34.5 (C-9), 18.0 (C-14, C-15, C-16, C-17, C-18, C-19), 11.9 (C-11, C-12, C-13).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2944 (-C-H), 2866 (-C-H), 1783 (4-C=O), 1695 (1-C=O), 1466, 1384, 1360, 1234, 1103, 1044, 882, 683.

**HRMS (TOF, ES+):** calculated for C<sub>19</sub>H<sub>33</sub>NO<sub>4</sub>SiNa [M+Na]<sup>+</sup> 390.2082, **found** 390.2087.

**[ $\alpha$ ]<sub>D</sub><sup>23</sup>** = -30.72 (*c* = 0.093, CHCl<sub>3</sub>).

**(S)-3-(3-(((*tert*-butyldimethylsilyl)oxy)methyl)cyclobut-2-enecarbonyl)oxazolidin-2-one (169d)**



According to the general procedure (**E**), from cyclobutene **117d** (1.5 g, 4.15 mmol, 1.0 eq.), dry acetone (70.0 mL, 0.06 M), Lindlar's catalyst (4.4 g, 41.5 mmol, 10.0 eq.), oct-1-ene (6.5 mL, 41.5 mmol, 10.0 eq.) and freshly distilled triethylsilane (6.6 mL, 41.5 mmol, 10.0 eq.) at 20 °C for 60 h. Purification through column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc: 70/30) gave the reduced cyclobutene (1.2 g, 94%) as a pale-yellow oil.

**TLC (cyclohexane/EtOAc: 50/50):** *R<sub>f</sub>* = 0.55 (UV active; vanillin, stains green).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 5.95 (q, *J* = 1.6 Hz, 1H, H-8), 4.43 (dd, *J* = 8.5, 7.6 Hz, 2H, H-2), 4.37-4.33 (m, 1H, H-5), 4.16-4.13 (m, 2H, H-9), 4.01 (dd, *J* = 8.6, 7.3 Hz, 2H, H-11), 2.83 (ddt, *J* = 13.2, 4.5, 1.2 Hz, 1H, H-6a), 2.72 (ddt, *J* = 13.3, 2.3, 1.3 Hz, 1H, H-6b), 0.90 (s, 9H, H-13, H-14, H-15), 0.06 (s, 6H, H-10, H-11).

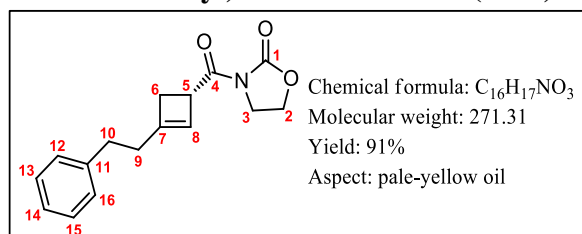
**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 173.1 (C-4), 153.4 (C-1), 150.7 (C-7), 125.8 (C-8), 62.4 (C-2), 61.3 (C-9), 43.0 (C-5), 42.6 (C-3), 33.1 (C-6), 26.0 (C-13, C-14, C-15), 18.5 (C-12), -5.2 (C-10, C-11).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 3441, 2930 (-C-H), 2857 (-C-H), 1779 (4-C=O), 1695 (1-C=O), 1472, 1387, 1257, 1091, 1042, 840, 777.

**HRMS (TOF, ES+):** calculated for C<sub>15</sub>H<sub>25</sub>NO<sub>4</sub>SiNa [M+Na]<sup>+</sup> 334.1445, **found** 334.1440.

**[ $\alpha$ ]<sub>D</sub><sup>23</sup>** = -19.82 (*c* = 8.5, CHCl<sub>3</sub>).

**(S)-3-(3-phenethylcyclobut-2-enecarbonyl)oxazolidin-2-one (169e)**



According to the general procedure (**E**), from cyclobutene **117e** (1.06 g, 3.34 mmol, 1.0 eq.), dry acetone (28.0 mL, 0.12 M), Lindlar's catalyst (3.5 g, 33.4 mmol, 10.0 eq.), oct-1-ene (2.6 mL, 16.7 mmol, 5.0 eq.) and freshly distilled triethylsilane (5.3 mL, 33.4 mmol, 10.0 eq.) at 20 °C for 46 h. Purification through column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc: 80/20) afforded the reduced cyclobutene (828.0 mg, 91%) as a pale-yellow oil.

**TLC (cyclohexane/EtOAc: 50/50):** *R<sub>f</sub>* = 0.41 (UV active; vanillin, stains green).

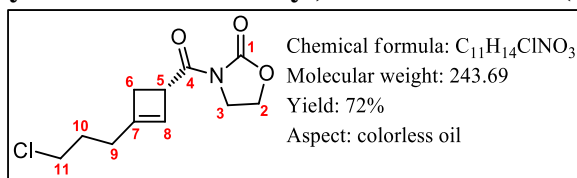
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 7.31-7.28 (m, 2H, H-13, H-15), 7.21-7.16 (m, 3H, H-12, H-14, H-16), 5.84 (q, *J* = 1.6 Hz, 1H, H-8), 4.46-4.39 (m, 2H, H-2), 4.35 (dq, *J* = 4.4, 2.2, 1.0 Hz, 1H, H-5), 4.02 (dd, *J* = 8.6, 7.4 Hz, 2H, H-3), 2.83-2.75 (m, 3H, H-6a, H-10), 2.71-2.67 (m, 1H, H-6b), 2.42-2.38 (m, 2H, H-9).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 173.6 (C-4), 153.5 (C-1), 152.1 (C-7), 141.7 (C-11), 128.5 (C-12, C-16), 128.4 (C-13, C-15), 126.0 (C-14), 125.8 (C-8), 62.4 (C-2), 42.8 (C-5), 42.6 (C-3), 34.9 (C-6), 32.8 (C-10), 32.7 (C-9).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2922 (-C-H), 1779 (4-C=O), 1694 (1-C=O), 1385, 1259, 1111, 1042, 759, 701.

**HRMS (TOF, ES+):** calculated for C<sub>16</sub>H<sub>17</sub>NO<sub>3</sub>Na [M+Na]<sup>+</sup> 294.1100, **found** 294.1108.

**[ $\alpha$ ]<sub>D</sub><sup>23</sup>** = -35.51 (*c* = 2.26, CHCl<sub>3</sub>).

**(S)-3-(3-(3-chloropropyl)cyclobut-2-enecarbonyl)oxazolidin-2-one (117f)**

According to the general procedure (**E**), from cyclobutene **117f** (883.0 mg, 3.05 mmol, 1.0 eq.), dry acetone (31.0 mL, 0.1 M), Lindlar's catalyst (3.2 g, 30.5 mmol, 10.0 eq.), oct-1-ene (2.4 mL, 15.3 mmol, 5.0 eq.) and freshly distilled triethylsilane (4.9 mL, 30.5 mmol, 10.0 eq.) at 20 °C for 26 h. Purification through column chromatography on  $SiO_2$  (cyclohexane/EtOAc: 70/30) gave the reduced cyclobutene (530.0 mg, 72%) as a colorless oil.

**TLC (cyclohexane/EtOAc: 50/50):**  $R_f$  = 0.47 (UV active; vanillin, stains green).

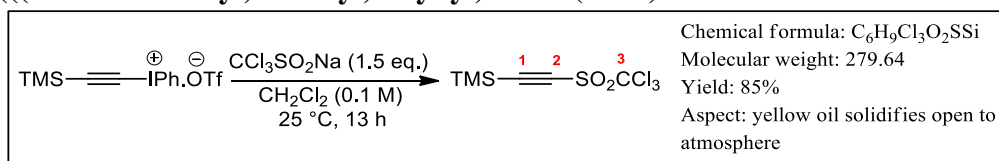
**$^1H$  NMR (300 MHz,  $CDCl_3$ ):**  $\delta$  (ppm) = 5.83 (q,  $J$  = 1.4 Hz, 1H, H-8), 4.42 (t,  $J$  = 8.1 Hz, 2H, H-2), 4.35-4.30 (m, 1H, H-5), 4.00 (t,  $J$  = 8.1 Hz, 2H, H-3), 3.55 (t,  $J$  = 6.6 Hz, 2H, H-11), 2.80-2.75 (m, 1H, H-6a), 2.70-2.63 (m, 1H, H-6b), 2.25-2.18 (m, 2H, H-9), 1.92 (quint,  $J$  = 6.7 Hz, 2H, H-10).

**$^{13}C$  NMR (75 MHz,  $CDCl_3$ ):**  $\delta$  (ppm) = 173.4 (C-4), 153.4 (C-1), 150.9 (C-7), 126.3 (C-8), 62.4 (C-2), 44.5 (C-5), 42.7 (C-11), 42.6 (C-3), 34.7 (C-6), 29.4 (C-10), 28.1 (C-9).

**IR (solution in  $CH_2Cl_2$ , thin film, KBr):**  $\nu_{max}$  ( $cm^{-1}$ ) = 2933 (C-H), 1779 (4-C=O), 1692 (1-C=O), 1634, 1478, 1374, 1228, 1110, 1042, 984, 870, 760.

**HRMS (TOF, ES<sup>+</sup>):** calculated for  $C_{11}H_{14}ClNO_3Na$   $[M+Na]^+$  266.0554, **found** 266.0561.

$[\alpha]_D^{23}$  = -46.46 ( $c$  = 1.66,  $CHCl_3$ ).

**6. Carbo-alkynylation reaction****trimethyl(((trichloromethyl)sulfonyl)ethynyl)silane (175b)**

To a dried two-necked flask under inert atmosphere, **183** (1.9 g, 4.2 mmol, 1.0 eq.) was introduced followed by  $CH_2Cl_2$  (42.0 mL, 0.1 M), then  $CCl_3SO_2Na$  (1.3 g, 6.3 mmol, 1.5 eq.) was added. The reaction mixture was stirred at 25 °C for 13 h then extracted with water (2 x 3 mL) and  $CH_2Cl_2$  (2 x 5 mL). The combined organic layers were washed with brine, dried over  $Na_2SO_4$  and concentrated under reduced pressure. The crude was obtained as a yellow oil that solidifies open to atmosphere. After trituration with  $Et_2O$ , the product (1.0 g, 85%) was obtained pure enough to be used directly in the next step without further purification. The product was stored under inert atmosphere in the freezer.

**TLC:** -

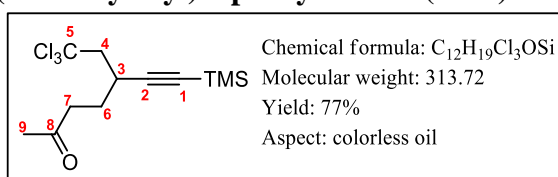
**m. p.** = 85-90.2 °C ( $CH_2Cl_2$ ).

**$^1H$  NMR (300 MHz,  $CDCl_3$ ):**  $\delta$  (ppm) = 0.34 (s, 9H, H-TMS).

**$^{13}C$  NMR (75 MHz,  $CDCl_3$ ):**  $\delta$  (ppm) = 112.0 (C-1), 104.2 (C-3), 88.6 (C-2), -1.3 (C-TMS).

**IR (solution in  $CH_2Cl_2$ , thin film, KBr):**  $\nu_{max}$  ( $cm^{-1}$ ) = 2978 (C-H), 2129 (C $\equiv$ C), 1358, 851, 820, 571.

**HRMS (TOF, ES<sup>+</sup>):** not detected.

**5-(2,2,2-trichloroethyl)-7-(trimethylsilyl)hept-6-yn-2-one (185a)**



According to the general procedure (F), from 5-hexen-2-one (11.0  $\mu$ L, 0.1 mmol, 1.0 eq.), distilled DCE (1.0 mL, 0.1 M), **175b** (42.0 mg, 0.15 mmol, 1.5 eq.) and AIBN (3.3 mg, 0.02 mmol, 0.2 eq.). The crude mixture was purified to afford the pure product (24.0 mg, 77%) as a colorless oil.

**TLC (cyclohexane/EtOAc: 70/30):**  $R_f$  = 0.76 (UV active;  $\text{KMnO}_4$ , stains yellow).

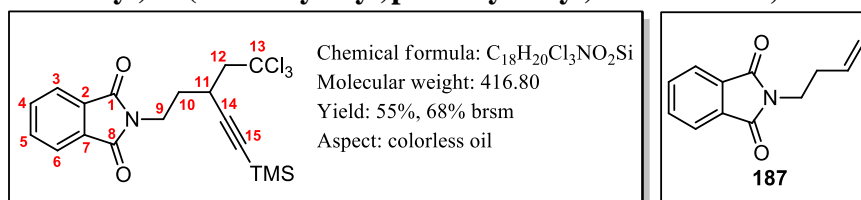
**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 3.04 (dd,  $J$  = 14.3, 7.5 Hz, 1H, H-7a), 2.98-2.87 (m, 2H, H-3), 2.76 (dd,  $J$  = 14.4, 3.2 Hz, 1H, H-7b), 2.67 (t,  $J$  = 7.4 Hz, 2H, H-4), 2.18 (s, 3H, H-9), 2.05-1.89 (m, 1H, H-6a), 1.81-1.65 (m, 1H, H-6b), 0.14 (s, 9H, H-TMS).

**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 207.8 (C-8), 107.2 (C-2), 98.3 (C-5), 88.3 (C-1), 59.6 (C-7), 40.9 (C-4), 30.3 (C-9), 30.2 (C-3), 29.2 (C-6), 0.08 (C-TMS).

**IR (solution in  $\text{CH}_2\text{Cl}_2$ , thin film, KBr):**  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 2960 (C-H), 2170 ( $\text{C}\equiv\text{C}$ ), 1718 (C=O), 1362, 1376, 1250, 843, 760, 706.

**HRMS (TOF, ES $^+$ ):** not detected.

## 2-(3-(2,2,2-trichloroethyl)-5-(trimethylsilyl)pent-4-yn-1-yl)isoindoline-1,3-dione (**185b**)



According to the general procedure (F), from the olefin **187** (50.0 mg, 0.25 mmol, 1.0 eq.), distilled DCE (2.5 mL, 0.1 M), **175b** (104.0 mg, 0.37 mmol, 1.5 eq.) and AIBN (8.0 mg, 0.05 mmol, 0.2 eq.). The crude mixture was purified to afford the pure product (57.0 mg, 55%, 68% brsm) as a colorless oil.

**TLC (cyclohexane/EtOAc: 70/30):**  $R_f$  = 0.76 (UV active;  $\text{KMnO}_4$ , stains yellow).

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 7.85 (dd,  $J$  = 5.5, 3.0 Hz, 2H, H-3, H-6), 7.71 (dd,  $J$  = 5.4, 3.1 Hz, 2H, H-4, H-5), 4.02-3.77 (m, 2H, H-9), 3.09 (dd,  $J$  = 14.1, 7.3 Hz, 1H, H-12a), 3.06-2.97 (m, 1H, H-11), 2.83 (dd,  $J$  = 14.1, 3.2 Hz, 1H, H-12b), 2.16-1.88 (m, 2H, H-10), 0.09 (s, 9H, H-TMS).

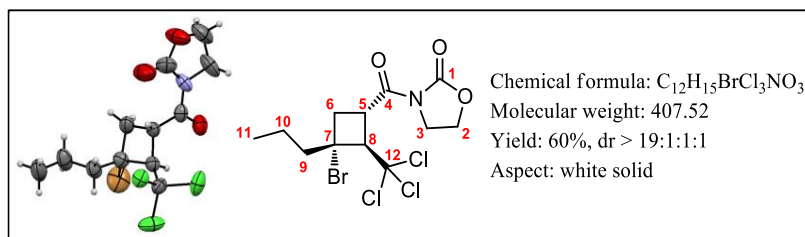
**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 168.3 (C-1, C-8), 134.1 (C-4, C-5), 132.2 (C-2, C-7), 123.4 (C-3, C-6), 106.5 (C-14), 98.2 (C-13), 88.4 (C-15), 59.2 (C-12), 36.0 (C-9), 33.7 (C-10), 28.9 (C-11), -0.05 (C-TMS).

**IR (solution in  $\text{CH}_2\text{Cl}_2$ , thin film, KBr):**  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 2961 (C-H), 2172 ( $\text{C}\equiv\text{C}$ ), 1714 (C=O), 1398, 1376, 1249, 844, 760, 719.

**HRMS (TOF, ES $^+$ ):** calculated for  $\text{C}_{18}\text{H}_{20}\text{Cl}_3\text{NO}_2\text{SiNa}$   $[\text{M}+\text{Na}]^+$  438.02211, found 438.02199.

## 7. Atom transfer radical addition reaction

### 3-((1S,2S,3R)-3-bromo-3-propyl-2-(trichloromethyl)cyclobutanecarbonyl)oxazolidin-2-one (**180a**)



According to the general procedure (G), from cyclobutene **169a** (100.0 mg, 0.48 mmol, 1.0 eq.), DMF (2.0 mL),  $\text{H}_2\text{O}$  (0.5 mL),  $\text{BrCCl}_3$  (0.1 mL, 0.96 mmol, 2.0 eq.), sodium L-ascorbate (190.0 mg, 0.96 mmol, 2.0 eq.), LiBr (83.0 mg, 0.96 mmol, 2.0 eq.) and  $[\text{Ir}(\text{PPy})_2(\text{dtbbPy})]\text{PF}_6$  (9.0 mg, 9.6  $\mu$ mol, 0.02 eq.). The crude mixture was purified through column chromatography on  $\text{SiO}_2$  (cyclohexane/EtOAc: 80/20) to afford the product (117.0 mg, 60%, dr > 19:1:1:1) as a white solid.

**TLC (cyclohexane/EtOAc: 50/50):**  $R_f$  = 0.57 (UV active; vanillin, stains green).

**m. p.** = 138-141  $^\circ\text{C}$  ( $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ ).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 4.73 (d,  $J$  = 9.5 Hz, 1H, H-8), 4.59 (q,  $J$  = 9.4 Hz, 1H, H-5), 4.50-4.42 (m, 2H, H-2), 4.11-4.03 (m, 2H, H-3), 2.87 (dd,  $J$  = 13.2, 4.9 Hz, 1H, H-6a), 2.55 (dd,  $J$  = 12.0, 9.0 Hz, 1H, H-6b), 2.27-2.05 (m, 2H, H-9), 1.77-1.64 (m, 1H, H-10a), 1.50-1.36 (m, 1H, H-10b), 1.01 (t,  $J$  = 7.3 Hz, 3H, H-11).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 170.7 (C-4), 153.2 (C-1), 96.8 (C-12), 67.8 (C-8), 63.4 (C-7), 62.4 (C-2), 42.8 (C-3), 39.8 (C-6), 39.2 (C-9), 38.3 (C-5), 19.7 (C-10), 14.0 (C-11).

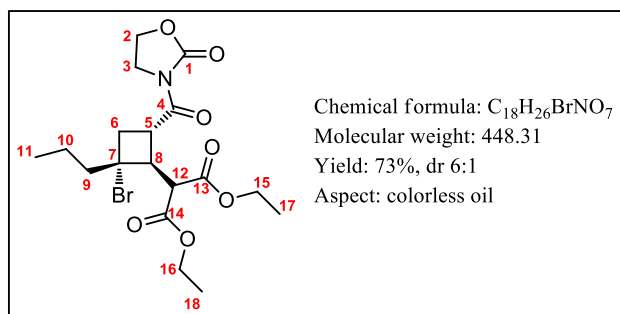
**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2963 (-C-H), 1782 (4-C=O), 1698 (1-C=O), 1389, 1271, 1223, 1116, 1041, 774.

**HRMS (TOF, ES+):** calculated for C<sub>12</sub>H<sub>15</sub>BrCl<sub>3</sub>NO<sub>3</sub>Na [M+Na]<sup>+</sup> 427.9193, **found** 427.9195.

**$[\alpha]_D^{23}$**  = +47.92 ( $c$  = 1.8, CHCl<sub>3</sub>).

**X-Ray crystallography:** the compound **180a** was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (1 mL), followed by slow diffusion (CH<sub>2</sub>Cl<sub>2</sub>/Et<sub>2</sub>O) in a container pierced with an 18 Gauge needle, at 20 °C for 3 days. The crystal suitable for X-ray crystallographic analysis was obtained as a thin translucent crystal.

**diethyl 2-((1*S*,2*R*,4*S*)-2-bromo-4-(2-oxooxazolidine-3-carbonyl)-2-propylcyclobutyl)malonate (180b)**



According to the general procedure (**G**), from cyclobutene **169a** (227.0 mg, 1.0 mmol, 1.0 eq.), DMF (3.5 mL), H<sub>2</sub>O (0.8 mL), bromo diethylmalonate **76a** (0.35 mL, 2.0 mmol, 2.0 eq.), sodium L-ascorbate (396.0 mg, 2.0 mmol, 2.0 eq.), LiBr (173.0 mg, 2.0 mmol, 2.0 eq.) and [Ir(PPy)<sub>2</sub>(dtbbPy)]PF<sub>6</sub> (9.0 mg, 10.0  $\mu$ mol, 0.02 eq.). The crude mixture was purified through column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc: 70/30 to 60/40) to afford the mixture of diastereomers (326.0 mg, 73%, dr 6:1) as a colorless oil.

**TLC (cyclohexane/EtOAc: 60/40):**  $R_f$  = 0.35 (UV active; KMnO<sub>4</sub>, stains yellow).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 4.53-4.30 (m, 3H, H-2, H-5), 4.17 (q,  $J$  = 7.1 Hz, 2H, H-15), 4.10-3.94 (m, 6H, H-3, H-12, H-16), 3.23 (t,  $J$  = 10.4 Hz, 1H, H-8), 2.91-2.79 (m, 0.28H, H-6 minor dia), 2.66 (dd,  $J$  = 12.6, 8.7 Hz, 1H, H-6a), 2.50 (dd,  $J$  = 12.7, 9.5 Hz, 1H, H-6b), 2.08-1.98 (m, 1H, H-9a), 1.84-1.73 (m, 1H, H-9b), 1.61-1.33 (m, 2H, H-10), 1.26-1.16 (m, 7H, H-17, H-18), 0.97 (t,  $J$  = 7.2 Hz, 0.6H, H-11 minor dia), 0.90 (t,  $J$  = 7.3 Hz, 3H, H-11).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**

**Major diastereomer (trans):**

$\delta$  (ppm) = 172.9 (C-4), 168.1 (C-13), 167.7 (C-14), 153.5 (C-1), 71.6 (C-7), 62.2 (C-2), 61.7 (C-15), 61.5 (C-16), 56.0 (C-12), 48.6 (C-8), 47.3 (C-9), 42.7 (C-3), 40.1 (C-6), 37.5 (C-5), 18.6 (C-10), 14.0 (C-17), 13.9 (C-18), 13.8 (C-11).

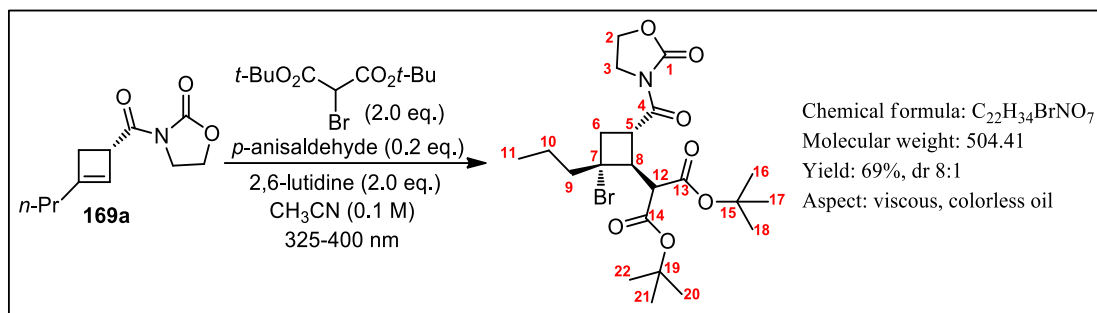
**Minor diastereomer (cis):**

$\delta$  (ppm) = 172.0 (C-4), 167.9 (C-13), 167.1 (C-14), 154.0 (C-1), 71.6 (C-7), 62.3 (C-2), 61.9 (C-15), 61.0 (C-16), 53.2 (C-12), 51.5 (C-8), 42.9 (C-9), 39.5 (C-3), 39.4 (C-6), 38.2 (C-5), 19.2 (C-10), 14.0 (C-17), 13.9 (C-17), 13.8 (C-11).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2965 (-C-H), 2937 (-C-H), 1778 (4-C=O), 1769 (13-C=O, 14-C=O), 1695 (1-C=O), 1479, 1428, 1462, 1445, 1242, 1037, 760, 734.

**HRMS (TOF, ES+):** calculated for C<sub>18</sub>H<sub>26</sub>BrNO<sub>7</sub>Na [M+Na]<sup>+</sup> 470.0784, **found** 470.0773.

**di-*tert*-butyl 2-((1*S*,2*R*,4*S*)-2-bromo-4-(2-oxooxazolidine-3-carbonyl)-2-propylcyclobutyl)malonate (180c)**



A 10 mL sealed tube was charged with cyclobutene **169a** (58.0 mg, 0.27 mmol, 1.0 eq.), acetonitrile (2.7 mL, 0.1 M), di-*tert*-butyl 2-bromomalonate **76b** (163.0 mg, 0.55 mmol, 2.0 eq.), 2,6-lutidine (0.06 mL, 0.55 mmol, 2.0 eq.) and *p*-anisaldehyde (7.0  $\mu$ L, 0.054 mmol, 0.2 eq.). The reaction mixture was degassed by three cycles of freeze-pump-thaw, then the tube was refilled with nitrogen. The reaction mixture was irradiated at 30 °C under UV-A light (325-400 nm, the tube was positioned approximately 10 cm away from the light source), and it was monitored by TLC under nitrogen atmosphere. After completion, the solvents were concentrated under reduced pressure and the crude mixture was purified through column chromatography on  $SiO_2$  (cyclohexane/EtOAc: 70/30 to 60/40) to afford the desired product (94.0 mg, 69%, dr 8:1) as a viscous, colorless oil.

**TLC (cyclohexane/EtOAc: 60/40):**  $R_f$  = 0.5 (UV active;  $KMnO_4$ , stains yellow; vanillin, stains blue then brown).

**$^1H$  NMR (300 MHz,  $CDCl_3$ ):**  $\delta$  (ppm) = 4.53 (q,  $J$  = 9.1 Hz, 1H, H-5 major), 4.46-4.41 (m, 0.24H, H-2 minor, H-5 minor), 4.36 (t,  $J$  = 8.3 Hz, 2H, H-2 major), 4.11-3.93 (m, 2.16H, H-3 major, H-3 minor), 3.82 (d,  $J$  = 11.2 Hz, 1H, H-12 major), 3.49 (d,  $J$  = 11.7 Hz, 0.08H, H-12 minor), 3.13 (dd,  $J$  = 11.2, 9.5 Hz, 1H, H-8 major), 2.89 (ddd,  $J$  = 11.5, 9.9, 1.7 Hz, 0.08H, H-8 minor), 2.64-2.54 (m, 2.16H, H-6 major, H-6 minor), 2.38-2.27 (m, 0.14H, H-9a minor), 2.26-2.16 (m, 0.16H, H-9b minor), 2.13-2.01 (m, 1H, H-9a major), 1.88-1.74 (m, 1H, H-9b major), 1.69-1.49 (m, 2.16H, H-10 major, H-10 minor), 1.47 (s, 0.72H, H-16 minor, H-17 minor, H-18 minor), 1.45 (s, 9H, H-16 major, H-17 major, H-18 major), 1.38 (s, 9.72H, H-20 major, H-21 major, H-22 major, H-20 minor, H-21 minor, H-22 minor), 0.92 (t,  $J$  = 7.3 Hz, 3.24H, H-11 major, H-11 minor).

**$^{13}C$  NMR (150 MHz,  $CDCl_3$ ):**

**Major diastereomer (trans):**

$\delta$  (ppm) = 173.2 (C-4), 167.6 (C-13), 167.1 (C-14), 153.6 (C-1), 82.0 (C-15), 81.6 (C-19), 71.8 (C-7), 62.1 (C-2), 58.0 (C-12), 49.5 (C-8), 47.5 (C-9), 42.3 (C-3), 39.8 (C-6), 37.3 (C-5), 27.9 (C-16, C-17, C-18, C-20, C-21, C-22), 18.7 (C-10), 13.8 (C-11).

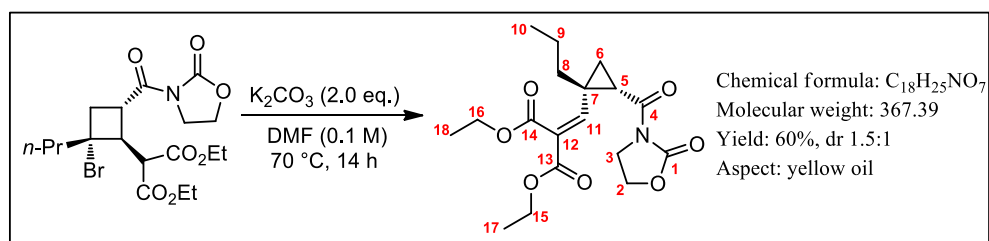
**Minor diastereomer (cis):**

$\delta$  (ppm) = 172.3 (C-4), 167.3 (C-13), 166.4 (C-14), 153.9 (C-1), 82.1 (C-15), 81.5 (C-19), 71.8 (C-7), 62.1 (C-2), 58.5 (C-12), 48.6 (C-8), 46.8 (C-9), 42.8 (C-3), 40.1 (C-6), 37.4 (C-5), 28.3 (C-16, C-17, C-18), 27.9 (C-20, C-21, C-22), 19.3 (C-10), 14.0 (C-11).

**IR (solution in  $CH_2Cl_2$ , thin film, KBr):**  $\nu_{max}$  ( $cm^{-1}$ ) = 2974 (-C-H), 2937 (-C-H), 1779 (4-C=O), 1725 (13-C=O, 14-C=O), 1695 (1-C=O), 1478, 1389, 1367, 1272, 1162, 1041, 846, 761, 707.

**HRMS (TOF, ES+):** calculated for  $C_{22}H_{34}BrNO_7Na$   $[M+Na]^+$  526.14109, found 526.14051.

### diethyl 2-(((1*S*,2*S*)-2-(2-oxooxazolidine-3-carbonyl)-1-propylcyclopropyl)methylene)malonate (**193**)



To a dried schlenk, **180b** (30.0 mg, 0.066 mmol, 1.0 eq.) was introduced, followed by dry DMF (0.7 mL, 0.1 M) and  $K_2CO_3$  (18.0 mg, 0.13 mmol, 2.0 eq.). The reaction mixture was then heated at 70 °C silicon oil bath temperature. After 14 h, the reaction was quenched with aqueous HCl (1.0 M) and



extracted with EtOAc. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude mixture was purified through column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc: 70/30) to afford the product (15.0 mg, 60%, dr 1.5:1) as a yellow oil.

**TLC (cyclohexane/EtOAc: 60/40):**  $R_f$  = 0.44 (UV active; KMnO<sub>4</sub>, stains yellow; vanillin stains colorless).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 7.14 (s, 0.63H, H-11 minor), 6.94 (s, 1H, H-11 major), 4.52-4.38 (m, 3.5H, H-2 major, H-2 minor), 4.37-4.16 (m, 7H, H-15 major, H-15 minor, H-16 major, H-16 minor), 4.14-3.93 (m, 3.5H, H-3 major, H-3 minor), 3.39 (dd,  $J$  = 7.9, 5.7 Hz, 1H, H-5 major), 3.09 (dd,  $J$  = 8.1, 6.5 Hz, 0.7H, H-5 minor), 1.81-1.55 (m, 6H, H-6a major, H-6 minor, H-8 major, H-8 minor), 1.53-1.40 (m, 4.5H, H-6b major, H-9 major, H-9 minor), 1.39-1.22 (m, 10H, H-17 major, H-17 minor, H-18 major, H-18 minor), 0.96-0.84 (m, 5H, H-10 major, H-10 minor).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**

**Major diastereomer:**

$\delta$  (ppm) = 170.0 (C-4), 165.8 (C-13), 163.8 (C-14), 154.0 (C-1), 146.2 (C-11), 131.3 (C-12), 62.1 (C-2), 61.6 (C-15), 61.5 (C-16), 43.1 (C-3), 40.7 (C-6), 33.9 (C-7), 27.8 (C-5), 22.1 (C-8), 20.4 (C-9), 14.2 (C-10, C-17, C-18).

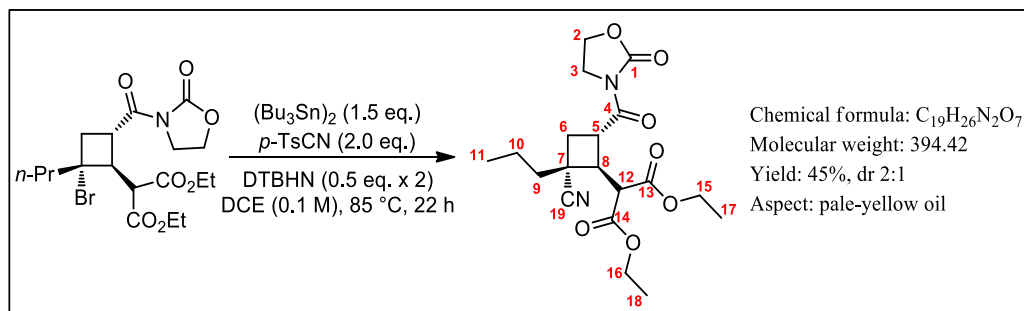
**Minor diastereomer:**

$\delta$  (ppm) = 170.2 (C-4), 165.6 (C-13), 163.8 (C-14), 153.7 (C-1), 148.1 (C-11), 129.9 (C-12), 62.0 (C-2), 61.6 (C-15), 61.5 (C-16), 43.0 (C-3), 33.3 (C-7), 33.2 (C-6), 27.0 (C-5), 20.7 (C-8), 20.3 (C-9), 14.2 (C-10, C-17, C-18).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2961 (-C-H), 2935 (-C-H), 1778 (4-C=O), 1728 (13-C=O, 14-C=O), 1688 (1-C=O), 1383, 1243, 1217, 1039, 760, 734.

**HRMS (TOF, ES+):** calculated for C<sub>18</sub>H<sub>25</sub>NO<sub>7</sub>Na [M+Na]<sup>+</sup> 390.15232, **found** 390.15122.

**diethyl 2-((1S,2R,4S)-2-cyano-4-(2-oxooxazolidine-3-carbonyl)-2-propylcyclobutyl)malonate (194)**



To a dried two-necked flask equipped with a condenser, the cyclobutane **180b** (40.0 mg, 0.09 mmol, 1.0 eq.) was introduced, followed by dry DCE (0.5 mL, 0.2 M) then (Bu<sub>3</sub>Sn)<sub>2</sub> (0.07 mL, 0.13 mmol, 1.5 eq.), and the mixture was degassed through argon bubbling for 10 min. To this solution was added a degassed (argon bubbling for 10 min) solution of DTBHN (8.0 mg, 0.045 mmol, 0.5 eq.) and *p*-TsCN (33.0 mg, 0.18 mmol, 2.0 eq.) in DCE (0.5 mL, 0.2 M) dropwise, and the reaction mixture was heated at 85 °C silicon oil bath temperature. After 5 h, another 0.5 eq. of DTBHN was added and the heating continued and the reaction completion was followed by TLC. After 22 h, the solvent was concentrated under reduced pressure and the crude mixture was purified through column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc: 70/30 to 60/40) to afford the product (16.0 mg, 45%, dr 2:1) as a pale-yellow oil.

**TLC (cyclohexane/EtOAc: 60/40):**  $R_f$  = 0.16 (UV inactive; KMnO<sub>4</sub>, stains yellow after long heating; or vanillin, stains yellow after long heating).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 4.53-4.34 (m, 3.5H, H-2 major, H-2 minor, H-5 minor), 4.32-4.17 (m, 4H, H-15 major, H-15 minor, H-5 major), 4.16-3.94 (m, 6H, H-16 major, H-16 minor, H-3 major, H-3 minor), 3.88 (d,  $J$  = 11.8 Hz, 0.5H, H-12 minor), 3.77 (dd,  $J$  = 12.0, 9.8 Hz, 1H, H-8 major), 3.56 (d,  $J$  = 12.0 Hz, 1H, H-12 major), 3.31 (dd,  $J$  = 12.1, 9.3 Hz, 0.5H, H-8 minor), 2.77-2.57 (m, 1.5H, H-6a major, H-6a minor), 2.36-2.20 (m, 1.5H, H-6b major, H-6b minor), 1.79-1.48 (m, 6H, H-9 major, H-9 minor, H-10 major, H-10 minor), 1.38-1.17 (m, 9H, H-17 major, H-17 minor, H-18 major, H-18 minor), 1.02 (t,  $J$  = 7.1 Hz, 3H, H-11 major), 0.94 (t,  $J$  = 7.1 Hz, 3H, H-11 minor).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):****Major diastereomer (trans):**

$\delta$  (ppm) = 171.9 (C-4), 167.5 (C-13), 167.0 (C-14), 153.8 (C-1), 122.2 (C-19), 62.4 (C-2), 62.3 (C-15), 62.1 (C-16), 51.5 (C-12), 43.9 (C-8), 42.8 (C-3), 40.7 (C-7), 37.6 (C-5), 33.1 (C-9), 32.4 (C-6), 18.5 (C-10), 14.1 (C-17), 14.0 (C-18), 13.7 (C-11).

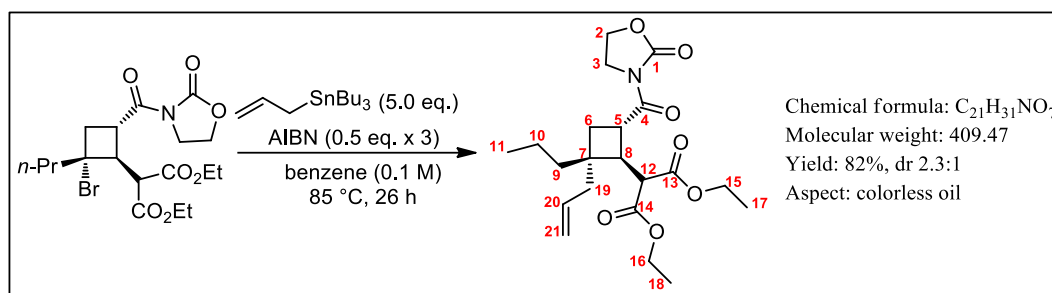
**Minor diastereomer (cis):**

$\delta$  (ppm) = 172.5 (C-4), 167.6 (C-13), 167.5 (C-14), 153.5 (C-1), 121.6 (C-19), 62.4 (C-2), 62.3 (C-15), 62.0 (C-16), 54.1 (C-12), 44.7 (C-8), 42.8 (C-3), 38.9 (C-7), 37.4 (C-5), 33.3 (C-9), 32.4 (C-6), 18.2 (C-10), 14.1 (C-17), 13.9 (C-17), 13.7 (C-11).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2957 (-C-H), 2922 (-C-H), 2232 (C≡N), 1778 (4-C=O), 1730 (13-C=O, 14-C=O), 1697 (1-C=O), 1388, 1283, 1227, 1036, 864, 760.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>19</sub>H<sub>26</sub>N<sub>2</sub>O<sub>7</sub>Na [M+Na]<sup>+</sup> 417.16322, found 417.16328.

**diethyl 2-((1*S*,2*R*,4*S*)-2-allyl-4-(2-oxooxazolidine-3-carbonyl)-2-propylcyclobutyl)malonate (195)**



To a dried two-necked flask equipped with a condenser, **180b** (830.0 mg, 1.85 mmol, 1.0 eq.) was introduced, followed by distilled benzene (18.5 mL, 0.1 M), allyltributylstannane (2.8 mL, 9.25 mmol, 5.0 eq.) and AIBN (152.0 mg, 0.92 mmol, 0.5 eq.) and the reaction mixture was heated at 85 °C silicon oil bath temperature. Another 0.5 eq. x 2 of AIBN were added with 5 h interval, and the reaction evolution was followed by TLC. After 26 h, the solvents were concentrated under reduced pressure and the crude mixture was purified through column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc: 80/20 to 70/30) to afford the product (618.0 mg, 82%, dr 2.3:1) as a colorless oil.

**TLC (cyclohexane/EtOAc: 60/40):**  $R_f$  = 0.30 (UV active; KMnO<sub>4</sub>, stains yellow; vanillin stains black).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 5.92-5.67 (m, 1.45H, H-20 major, H-20 minor), 5.19-4.95 (m, 3H, H-21 major, H-21 minor), 4.46-4.28 (m, 3H, H-2 major, H-2 minor), 4.23-4.12 (m, 4.5H, H-15 major, H-15 minor, H-5 major, H-5 minor), 4.11-3.90 (m, 6H, H-3 major, H-3 minor, H-16 major, H-16 minor), 3.61 (d,  $J$  = 11.9 Hz, 1H, H-12 major), 3.56 (d,  $J$  = 11.9 Hz, 0.45H, H-12 minor), 3.32-3.23 (m, 1.5H, H-8 major, H-8 minor), 2.46-2.20 (m, 2H, H-19 major), 2.18-2.08 (m, 1H, H-19 minor), 2.08-1.87 (m, 3H, H-6 major, H-6 minor), 1.56-1.30 (m, 6H, H-9 major, H-9 minor, H-10 major, H-10 minor), 1.28-1.17 (m, 9H, H-17 major, H-17 minor, H-18 major, H-18 minor), 0.97-0.82 (m, 4.5H, H-11 major, H-11 minor).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):****Major diastereomer (trans):**

$\delta$  (ppm) = 174.5 (C-4), 168.7 (C-13), 168.6 (C-14), 153.7 (C-1), 134.4 (C-20), 118.0 (C-21), 62.1 (C-2), 61.5 (C-15, C-16), 52.3 (C-12), 43.2 (C-8), 42.8 (C-3), 41.3 (C-9), 41.0 (C-7), 38.8 (C-19), 36.6 (C-5), 31.4 (C-6), 17.3 (C-10), 14.7 (C-11), 14.1 (C-17), 14.0 (C-18).

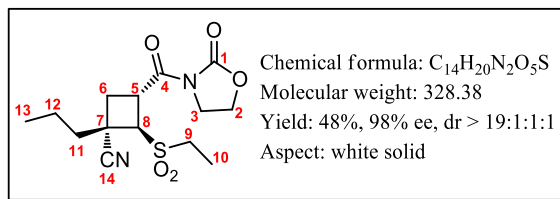
**Minor diastereomer (cis):**

$\delta$  (ppm) = 174.4 (C-4), 168.7 (C-13), 168.6 (C-14), 153.7 (C-1), 134.8 (C-20), 117.8 (C-21), 62.1 (C-2), 61.5 (C-15, C-16), 52.2 (C-12), 43.2 (C-8), 42.8 (C-3), 42.6 (C-19), 41.3 (C-9), 41.0 (C-7), 36.5 (C-5), 31.0 (C-6), 17.3 (C-10), 15.0 (C-11), 14.1 (C-17), 14.0 (C-17).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2965 (-C-H), 2937 (-C-H), 1778 (4-C=O), 1726 (13-C=O, 14-C=O), 1701 (1-C=O), 1387, 1269, 1226, 1039, 760, 734.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>21</sub>H<sub>31</sub>NO<sub>7</sub>Na [M+Na]<sup>+</sup> 432.19927, found 432.19885.

## 8. Eosin-photocatalyzed sulfonyl-cyanation reaction

**(1*S*,2*R*,3*R*)-2-(ethylsulfonyl)-3-(2-oxooxazolidine-3-carbonyl)-1-propylcyclobutanecarbonitrile (181a)**

According to the general procedure (**H**), from cyclobutene **169a** (150.0 mg, 0.7 mmol, 1.0 eq.), dry DMF (0.7 mL, 1.0 M), ethanesulfonyl cyanide **88b** (341.0 mg, 2.87 mmol, 4.0 eq.), eosin-Y (9.2 mg, 14.3 μmol, 2 mol %) and K<sub>2</sub>HPO<sub>4</sub> (24.9 mg, 143.0 μmol, 0.2 eq.) for 60 h. Purification through column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc: 50/50) afforded the product (114.0 mg, 48%, 98% ee, dr > 19:1:1:1) as a white solid.

**TLC (cyclohexane/EtOAc: 50/50):** R<sub>f</sub> = 0.38 (UV inactive; KMnO<sub>4</sub>, stains white).

**m. p.** = 132-136 °C (EtOAc).

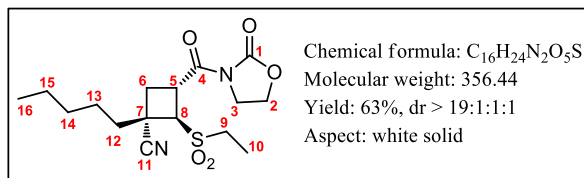
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ (ppm) = 4.59 (d, *J* = 9.9 Hz, 1H, H-8), 4.48 (dd, *J* = 8.5, 7.8 Hz, 2H, H-2), 4.44 (q, *J* = 9.8 Hz, 1H, H-5), 4.05-4.01 (m, 2H, H-3), 3.05-2.98 (m, 1H, H-9a), 2.96-2.86 (m, 1H, H-9b), 2.83-2.78 (m, 1H, H-6a), 2.44 (ddd, *J* = 11.4, 9.5, 1.5 Hz, 1H, H-6b), 2.33-2.25 (m, 1H, H-11a), 2.10 (ddd, *J* = 13.9, 12.1, 4.6 Hz, 1H, H-11b), 1.60-1.43 (m, 2H, H-12), 1.41 (t, *J* = 7.5 Hz, 3H, H-10), 1.03 (t, *J* = 7.3 Hz, 3H, H-13).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ (ppm) = 170.1 (C-4), 152.9 (C-1), 121.3 (C-14), 62.9 (C-2), 57.5 (C-8), 48.9 (C-9), 42.5 (C-3), 38.4 (C-5), 36.1 (C-7), 33.3 (C-11), 33.0 (C-6), 18.7 (C-12), 13.9 (C-13), 6.2 (C-10).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):** ν<sub>max</sub> (cm<sup>-1</sup>) = 2966 (-C-H), 2877 (-C-H), 2237 (C≡N), 1782 (4-C=O), 1691 (1-C=O), 1468, 1391, 1317, 1286, 1229, 1130, 1041.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>14</sub>H<sub>20</sub>N<sub>2</sub>O<sub>5</sub>SNa [M+Na]<sup>+</sup> 351.0981, **found** 351.0985.

[α]<sub>D</sub><sup>25</sup> = +97.71 (*c* = 0.3, CHCl<sub>3</sub>).

**(1*S*,2*R*,3*R*)-2-(ethylsulfonyl)-3-(2-oxooxazolidine-3-carbonyl)-1-pentylcyclobutanecarbonitrile (181c)**

According to the general procedure (**H**), from cyclobutene **169b** (150.0 mg, 0.63 mmol, 1.0 eq.), dry DMF (0.7 mL, 1.0 M), ethanesulfonyl cyanide **88b** (225.0 mg, 1.89 mmol, 3.0 eq.), eosin-Y (8.0 mg, 0.012 mmol, 2 mol %) and K<sub>2</sub>HPO<sub>4</sub> (22.0 mg, 0.13 mmol, 0.2 eq.) for 24 h. Purification through column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 60/40) afforded the product (143.0 mg, 63%, dr > 19:1:1:1) as a white solid.

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 50/50):** R<sub>f</sub> = 0.62 (UV inactive; KMnO<sub>4</sub>, stains white).

**m. p.** = 122.7-125 °C (Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>).

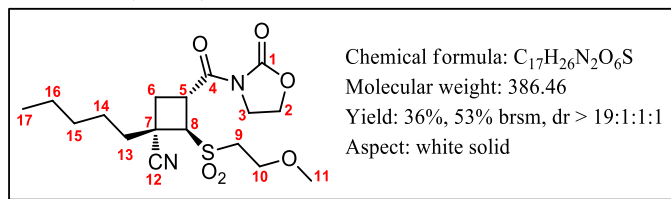
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ (ppm) = 4.59 (d, *J* = 9.8 Hz, 1H, H-8), 4.52-4.38 (m, 3H, H-2, H-5), 4.03 (dd, *J* = 8.7, 7.4 Hz, 2H, H-3), 3.08-2.77 (m, 3H, H-6a, H-9), 2.43 (ddd, *J* = 11.3, 9.5, 1.4 Hz, 1H, H-6b), 2.35-2.26 (m, 1H, H-12a), 2.17-2.04 (m, 1H, H-12b), 1.51-1.28 (m, 9H, H-10, H-13, H-14, H-15), 0.90 (t, *J* = 7.0 Hz, 3H, H-16).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ (ppm) = 170.0 (C-4), 153.0 (C-1), 121.3 (C-11), 62.9 (C-2), 57.4 (C-8), 48.8 (C-9), 42.4 (C-3), 38.4 (C-5), 36.1 (C-7), 33.2 (C-6), 31.4 (C-14), 31.0 (C-12), 25.0 (C-13), 22.6 (C-15), 14.0 (C-16), 6.1 (C-10).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):** ν<sub>max</sub> (cm<sup>-1</sup>) = 2931 (-C-H), 2237 (C≡N), 1783 (4-C=O), 1692 (1-C=O), 1392, 1318, 1230, 1132, 1041, 736.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>16</sub>H<sub>24</sub>N<sub>2</sub>O<sub>5</sub>SNa [M+Na]<sup>+</sup> 379.1298, **found** 379.1311.

[α]<sub>D</sub><sup>23</sup> = +86.15 (*c* = 1.13, CHCl<sub>3</sub>).

**(1*S*,2*R*,3*R*)-2-((2-methoxyethyl)sulfonyl)-3-(2-oxooxazolidine-3-carbonyl)-1-pentylcyclobutanecarbonitrile (181d)**

According to the general procedure (**H**), from cyclobutene **169b** (160.0 mg, 0.7 mmol, 1.0 eq.), acetone (0.7 mL, 1.0 M), sulfonyl cyanide **88c** (190.0 mg, 1.35 mmol, 2.0 eq.), eosin-Y (9.0 mg, 13.4 μmol, 2 mol %) and K<sub>2</sub>HPO<sub>4</sub> (23.0 mg, 0.13 mmol, 0.2 eq.) for 96 h. Purification through column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 90/10) afforded the product (94.0 mg, 36% yield, 53% brsm, dr > 19:1:1:1) as a white solid. 31% of the starting material were recovered.

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 50/50):** R<sub>f</sub> = 0.57 (UV inactive; KMnO<sub>4</sub>, stains white).

**m. p.** = 132.4–134 °C (Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>).

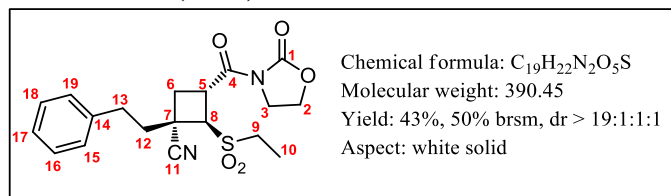
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ (ppm) = 4.89 (d, *J* = 9.8 Hz, 1H, H-8), 4.54–4.44 (m, 3H, H-2, H-5), 4.04 (dd, *J* = 8.6, 7.4 Hz, 2H, H-3), 3.85–3.80 (m, 2H, H-10), 3.42 (s, 3H, H-11), 3.40–3.33 (m, 1H, H-9a), 3.13–3.05 (m, 1H, H-9b), 2.76 (dd, *J* = 12.8, 8.9 Hz, 1H, H-6a), 2.40 (ddd, *J* = 11.3, 9.4, 1.4 Hz, 1H, H-6b), 2.34–2.23 (m, 1H, H-13a), 2.07 (ddd, *J* = 15.1, 11.5, 3.9 Hz, 1H, H-13b), 1.39–1.37 (m, 4H, H-14, H-15, H-16), 0.90 (t, *J* = 7.0 Hz, 3H, H-17).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ (ppm) = 170.0 (C-4), 153.0 (C-1), 121.3 (C-12), 65.9 (C-10), 62.9 (C-2), 60.3 (C-8), 59.4 (C-11), 55.1 (C-9), 42.5 (C-3), 37.8 (C-5), 36.4 (C-7), 33.0 (C-6), 31.5 (C-13), 31.2 (C-15), 25.0 (C-14), 22.6 (C-16), 14.0 (C-17).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):** ν<sub>max</sub> (cm<sup>-1</sup>) = 2930 (–C–H), 2236 (C≡N), 2180, 1783 (4–C=O), 1694 (1–C=O), 1391, 1321, 1228, 1131, 1116, 1041, 759.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>17</sub>H<sub>26</sub>N<sub>2</sub>O<sub>6</sub>SNa [M+Na]<sup>+</sup> 409.1403, **found** 409.1400.

[α]<sub>D</sub><sup>23</sup> = +91.56 (*c* = 0.073, CHCl<sub>3</sub>).

**(1*S*,2*R*,3*R*)-2-(ethylsulfonyl)-3-(2-oxooxazolidine-3-carbonyl)-1-phenethylcyclobutanecarbonitrile (181e)**

According to the general procedure (**H**), from cyclobutene **169e** (300.0 mg, 1.1 mmol, 1.0 eq.), dry DMF (1.1 mL, 1.0 M), ethanesulfonyl cyanide **88b** (394.0 mg, 3.3 mmol, 3.0 eq.), eosin-Y (14.0 mg, 0.022 mmol, 2 mol %) and K<sub>2</sub>HPO<sub>4</sub> (38.0 mg, 0.22 mmol, 0.2 eq.) for 48 h. Purification through column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 60/40) afforded the product (185.0 mg, 43%, 50% brsm, dr > 19:1:1:1) as a white solid. 14% of the starting material were recovered.

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 50/50):** R<sub>f</sub> = 0.57 (UV active; KMnO<sub>4</sub>, stains white).

**m. p.** = 61.5–63 °C (Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>).

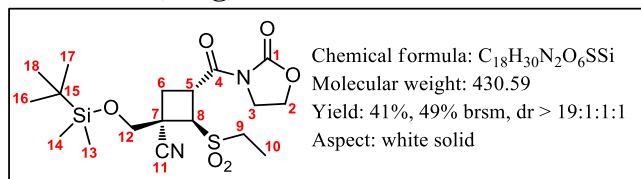
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ (ppm) = 7.33–7.21 (m, 5H, H-15, H-16, H-17, H-18, H-19), 4.65 (d, *J* = 9.7 Hz, 1H, H-8), 4.52–4.42 (m, 3H, H-2, H-5), 4.01 (t, *J* = 8.3 Hz, 2H, H-3), 3.07–2.61 (m, 7H, H-6a, H-9, H-12, H-13), 2.52–2.44 (m, 1H, H-6b), 1.41 (t, *J* = 7.5 Hz, 3H, H-10).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ (ppm) = 170.0 (C-4), 152.8 (C-1), 139.5 (C-14), 128.7 (C-15, C-19), 128.6 (C-16, C-18), 126.6 (C-17), 121.0 (C-11), 62.9 (C-2), 57.4 (C-8), 48.8 (C-9), 42.4 (C-3), 38.4 (C-5), 36.0 (C-7), 33.3 (C-6), 33.0 (C-13), 31.6 (C-12), 6.1 (C-10).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):** ν<sub>max</sub> (cm<sup>-1</sup>) = 2941 (–C–H), 2238 (C≡N), 1783 (4–C=O), 1692 (1–C=O), 1391, 1316, 1229, 1132, 1040, 758, 735, 702.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>19</sub>H<sub>22</sub>N<sub>2</sub>O<sub>5</sub>SNa [M+Na]<sup>+</sup> 413.1141, **found** 413.1149.

[α]<sub>D</sub><sup>23</sup> = +47.98 (*c* = 1.93, CHCl<sub>3</sub>).

**(1*S*,2*R*,3*R*)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-(ethylsulfonyl)-3-(2-oxooxazolidine-3-carbonyl)cyclobutanecarbonitrile (181g)**

According to the general procedure (**H**), from cyclobutene **169d** (150.0 mg, 0.5 mmol, 1.0 eq.), dry DMF (0.5 mL, 1.0 M), ethanesulfonyl cyanide **88b** (172.0 mg, 1.44 mmol, 3.0 eq.), eosin-Y (6.0 mg, 9.6 μmol, 2 mol %) and K<sub>2</sub>HPO<sub>4</sub> (17.0 mg, 0.096 mmol, 0.2 eq.) for 30 h. Purification through column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 90/10) afforded the product (100.0 mg, 41%, 49% brsm, dr > 19:1:1:1) as a white solid. 15% of the starting material were recovered.

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 50/50):** R<sub>f</sub> = 0.65 (UV inactive; KMnO<sub>4</sub>, stains white).

**m. p.** = 129-131 °C (Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>).

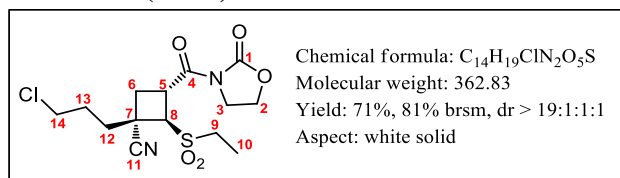
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ (ppm) = 4.66 (d, *J* = 9.7 Hz, 1H, H-8), 4.57-4.46 (m, 3H, H-2, H-5), 4.34 (d, *J* = 10.4 Hz, 1H, H-12a), 4.11-4.01 (m, 3H, H-3, H-12b), 3.11 (quint, *J* = 7.2 Hz, 1H, H-9), 2.89 (dd, *J* = 11.8, 10.1 Hz, 1H, H-6a), 2.43 (ddd, *J* = 11.8, 9.3, 0.9 Hz, 1H, H-6b), 1.43 (t, *J* = 7.5 Hz, 3H, H-10), 0.92 (s, 9H, H-16, H-17, H-18), 0.14 (s, 6H, H-13, H-14).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ (ppm) = 170.0 (C-4), 153.0 (C-1), 120.5 (C-11), 62.9 (C-2), 62.0 (C-12), 56.5 (C-8), 48.5 (C-9), 42.5 (C-3), 38.4 (C-7), 37.3 (C-5), 31.1 (C-6), 25.8 (C-16, C-17, C-18), 18.4 (C-15), 6.2 (C-10), -5.3 (C-13 or C-14), -5.4 (C-13 or C-14).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):** ν<sub>max</sub> (cm<sup>-1</sup>) = 2955 (-C-H), 2931 (-C-H), 2242 (C≡N), 1786 (4-C=O), 1693 (1-C=O), 1391, 1311, 1229, 1130, 1108, 1041, 838, 781.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>18</sub>H<sub>30</sub>N<sub>2</sub>O<sub>6</sub>SSiNa [M+Na]<sup>+</sup> 453.1486, **found** 453.1476.

[α]<sub>D</sub><sup>23</sup> = +28.72 (*c* = 1.13, CHCl<sub>3</sub>).

**(1*S*,2*R*,3*R*)-1-(3-chloropropyl)-2-(ethylsulfonyl)-3-(2-oxooxazolidine-3-carbonyl)cyclobutanecarbonitrile (181h)**

According to the general procedure (**H**), from cyclobutene **169f** (150.0 mg, 0.62 mmol, 1.0 eq.), dry DMF (0.6 mL, 1.0 M), ethanesulfonyl cyanide **88b** (294.0 mg, 2.5 mmol, 4.0 eq.), eosin-Y (8.0 mg, 12.3 μmol, 2 mol %) and K<sub>2</sub>HPO<sub>4</sub> (21.0 mg, 0.12 mmol, 0.2 eq.) for 42 h. Purification through column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 60/40) afforded the product (160.0 mg, 71%, 81% brsm, dr > 19:1:1:1) as a white solid. 12% of the starting material were recovered.

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 50/50):** R<sub>f</sub> = 0.57 (UV inactive; KMnO<sub>4</sub>, stains white).

**m. p.** = 66.2-68.5 °C (Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ (ppm) = 4.61 (d, *J* = 9.8 Hz, 1H, H-8), 4.54-4.41 (m, 3H, H-2, H-5), 4.05 (dd, *J* = 9.0, 7.5 Hz, 2H, H-3), 3.65-3.60 (m, 2H, H-14), 3.07-2.80 (m, 3H, H-6a, H-9), 2.55-2.44 (m, 2H, H-12a, H-6b), 2.36-2.26 (m, 1H, H-12b), 2.16-2.02 (m, 1H, H-13a), 1.98-1.83 (m, 1H, H-13b), 1.43 (t, *J* = 7.5 Hz, 3H, H-10).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ (ppm) = 169.9 (C-4), 152.8 (C-1), 120.7 (C-11), 62.9 (C-2), 57.2 (C-8), 48.9 (C-9), 43.7 (C-14), 42.4 (C-3), 38.5 (C-5), 35.9 (C-7), 33.3 (C-6), 28.9 (C-13), 28.6 (C-12), 6.2 (C-10).

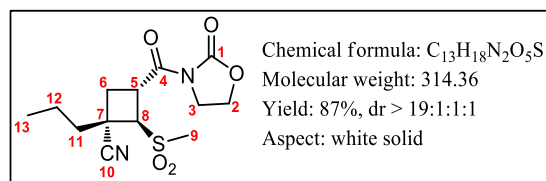
**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):** ν<sub>max</sub> (cm<sup>-1</sup>) = 2950 (-C-H), 2238 (C≡N), 1782 (4-C=O), 1692 (1-C=O), 1391, 1316, 1229, 1131, 1040, 759, 733.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>14</sub>H<sub>19</sub>ClN<sub>2</sub>O<sub>5</sub>SNa [M+Na]<sup>+</sup> 385.0595, **found** 385.0603.

[α]<sub>D</sub><sup>23</sup> = +63.53 (*c* = 1.13, CHCl<sub>3</sub>).

**9. *p*-Anisaldehyde-photosensitized sulfonyl-cyanation reaction**



**(1*S*,2*R*,3*R*)-2-(methylsulfonyl)-3-(2-oxooxazolidine-3-carbonyl)-1-propylcyclobutanecarbonitrile (181b)**

According to the general procedure (**I**), from cyclobutene **169a** (4.4 g, 21.0 mmol, 1.0 eq.), acetonitrile (10.0 mL, 2.1 M), methanesulfonyl cyanide **88a** (4.4 g, 42.0 mmol, 2.0 eq.) and *p*-anisaldehyde (0.5 mL, 4.2 mmol, 0.2 eq.) for 72 h. Purification through column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 90/10) afforded the product (5.77 g, 87%, dr > 19:1:1:1) as a white solid.

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 50/50):** R<sub>f</sub> = 0.45 (UV inactive; KMnO<sub>4</sub>, stains white).

**m. p.** = 66–70 °C (EtOAc).

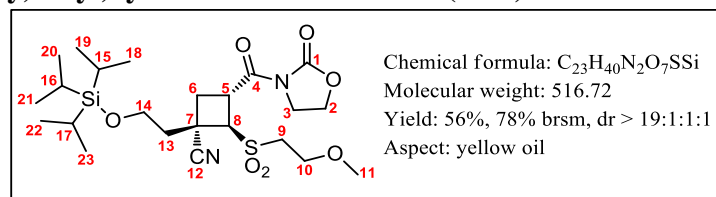
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ (ppm) = 4.64 (d, *J* = 9.8 Hz, 1H, H-8), 4.52–4.36 (m, 3H, H-5, H-2), 4.07–3.99 (m, 2H, H-3), 2.92 (s, 3H, H-9), 2.87–2.73 (m, 1H, H-6a), 2.46 (ddd, *J* = 11.4, 9.6, 1.4 Hz, 1H, H-6b), 2.32–2.01 (m, 2H, H-11), 1.65–1.35 (m, 2H, H-12), 1.02 (t, *J* = 7.3 Hz, 3H, H-13).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ (ppm) = 170.0 (C-4), 153.0 (C-1), 121.3 (C-10), 63.0 (C-2), 59.7 (C-8), 42.50 (C-9), 42.46 (C-3), 38.7 (C-5), 35.9 (C-7), 33.1 (C-6), 32.8 (C-11), 18.6 (C-12), 13.9 (C-13).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):** ν<sub>max</sub> (cm<sup>-1</sup>) = 2964 (–C–H), 2932 (–C–H), 2876 (–C–H), 2237 (C≡N), 1782 (4–C=O), 1691 (1–C=O), 1391, 1315, 1287, 1228, 1146, 1133, 1040, 759.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>13</sub>H<sub>18</sub>N<sub>2</sub>O<sub>5</sub>SSiNa [M+Na]<sup>+</sup> 337.0828, found 337.0833.

[α]<sub>D</sub><sup>25</sup> = +89.21 (*c* = 0.27, CHCl<sub>3</sub>).

**(1*R*,2*R*,3*R*)-2-((2-methoxyethyl)sulfonyl)-3-(2-oxooxazolidine-3-carbonyl)-1-(2-((triisopropylsilyl)oxy)ethyl)cyclobutanecarbonitrile (181f)**

According to the general procedure (**I**), from cyclobutene **169c** (200.0 mg, 0.54 mmol, 1.0 eq.), acetonitrile (0.5 mL, 1.0 M), sulfonyl cyanide **88c** (383.0 mg, 2.72 mmol, 5.0 eq.) and *p*-anisaldehyde (13.0 μL, 0.108 mmol, 0.2 eq.) for 47 h. 73% of conversion of the starting material was observed. Purification through column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 80/20) afforded the product (157.0 mg, 56%, 78% brsm, dr > 19:1:1:1) as a yellow oil.

Another method to obtain the product **181f**:

According to the general procedure (**H**), from cyclobutene **169c** (260.0 mg, 0.7 mmol, 1.0 eq.), dry acetone (0.7 mL, 1.0 M), sulfonyl cyanide **88c** (203.0 mg, 1.36 mmol, 2.0 eq.), eosin-Y (9.0 mg, 13.6 μmol, 2 mol %) and K<sub>2</sub>HPO<sub>4</sub> (24.0 mg, 0.136 mmol, 0.2 eq.) for 90 h. Purification through column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 80/20) afforded the product (105.0 mg, 28%, 87% brsm) as a yellow oil. 67% of the starting material were recovered.

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 50/50):** R<sub>f</sub> = 0.62 (UV inactive; KMnO<sub>4</sub>, stains white).

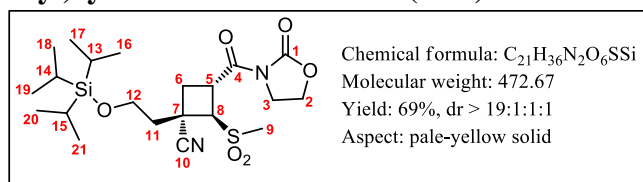
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ (ppm) = 4.92 (d, *J* = 9.9 Hz, 1H, H-8), 4.59–4.44 (m, 3H, H-2, H-5), 4.09–3.99 (m, 4H, H-3, H-14), 3.85–3.80 (m, 2H, H-10), 3.42 (s, 3H, H-11), 3.40–3.34 (m, 1H, H-9a), 3.21 (dd, *J* = 10.6, 9.6 Hz, 1H, H-6a), 3.08 (ddd, *J* = 15.1, 5.7, 4.2 Hz, 1H, H-9b), 2.49–2.41 (m, 3H, H-6b, H-13), 1.08–1.04 (m, 21H, H-15, H-16, H-17, H-18, H-19, H-20, H-21, H-22, H-23).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ (ppm) = 170.2 (C-4), 152.7 (C-1), 121.0 (C-12), 65.9 (C-10), 62.7 (C-2), 60.8 (C-8), 60.6 (C-14), 59.4 (C-11), 55.1 (C-9), 42.5 (C-3), 37.8 (C-5), 35.2 (C-7), 33.7 (C-6), 33.3 (C-13), 18.1 (C-18, C-19, C-20, C-21, C-22, C-23), 11.9 (C-15, C-16, C-17).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):** ν<sub>max</sub> (cm<sup>-1</sup>) = 2943 (–C–H), 2867 (–C–H), 2238 (C≡N), 1785 (4–C=O), 1694 (1–C=O), 1390, 1322, 1226, 1116, 1040, 882, 759, 684.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>23</sub>H<sub>40</sub>N<sub>2</sub>O<sub>7</sub>SSiNa [M+Na]<sup>+</sup> 539.2228, **found** 539.2231.  
[ $\alpha$ ]<sub>D</sub><sup>23</sup> = +38.33 (*c* = 0.086, CHCl<sub>3</sub>).

**(1*R*,2*R*,3*R*)-2-(methylsulfonyl)-3-(2-oxooxazolidine-3-carbonyl)-1-(2-((triisopropylsilyl)oxy)ethyl)cyclobutanecarbonitrile (181i)**



According to the general procedure (**I**), from cyclobutene **169c** (5.0 g, 13.6 mmol, 1.0 eq.), acetonitrile (10.0 mL, 1.3 M), methanesulfonyl cyanide **88a** (2.8 g, 27.2 mmol, 2.0 eq.) and *p*-anisaldehyde (0.33 mL, 2.72 mmol, 0.2 eq.) for 91 h. Purification through column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 90/10) afforded the product (4.5 g, 69%, dr > 19:1:1:1) as a pale-yellow solid.

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 50/50):** R<sub>f</sub> = 0.68 (UV inactive; KMnO<sub>4</sub>, stains red-white).

**m. p.** = 70.6–73.5 °C (pentane/EtOAc).

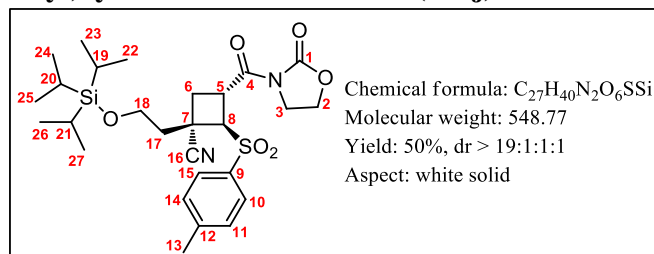
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 4.66 (d, *J* = 9.8 Hz, 1H, H-8), 4.53–4.43 (m, 3H, H-2, H-5), 4.06–3.99 (m, 4H, H-3, H-12), 3.28 (dd, *J* = 11.7, 10.2 Hz, 1H, H-6a), 2.92 (s, 3H, H-9), 2.54–2.45 (m, 3H, H-6b, H-11), 1.08–1.05 (m, 21H, H-13, H-14, H-15, H-16, H-17, H-18, H-19, H-20, H-21).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 170.1 (C-4), 152.7 (C-1), 121.0 (C-10), 62.8 (C-2), 60.6 (C-8), 60.3 (C-12), 42.6 (C-9), 42.5 (C-3), 38.6 (C-5), 34.8 (C-7), 33.9 (C-6), 33.0 (C-11), 18.1 (C-16, C-17, C-18, C-19, C-20, C-21), 11.9 (C-13, C-14, C-15).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\text{max}}$  (cm<sup>-1</sup>) = 2944 (–C–H), 2867 (–C–H), 2237 (C≡N), 1786 (4–C=O), 1692 (1–C=O), 1390, 1316, 1227, 1131, 1040, 882, 759, 683.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>21</sub>H<sub>36</sub>N<sub>2</sub>O<sub>6</sub>SSiNa [M+Na]<sup>+</sup> 495.1955, **found** 495.1956.  
[ $\alpha$ ]<sub>D</sub><sup>23</sup> = +78.37 (*c* = 0.1, CHCl<sub>3</sub>).

**(1*R*,2*R*,3*R*)-3-(2-oxooxazolidine-3-carbonyl)-2-tosyl-1-(2-((triisopropylsilyl)oxy)ethyl)cyclobutanecarbonitrile (181j)**



According to the general procedure (**I**), from cyclobutene **169c** (800.0 mg, 2.2 mmol, 1.0 eq.), acetonitrile (2.2 mL, 1.0 M), *p*-toluenesulfonyl cyanide (790.0 mg, 4.4 mmol, 2.0 eq.) and *p*-anisaldehyde (0.05 mL, 0.44 mmol, 0.2 eq.) for 71 h. Purification through column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc: 80/20 to 50/50) afforded the product (600.0 mg, 50%, dr > 19:1:1:1) as a white solid.

**TLC (cyclohexane/EtOAc: 70/30):** R<sub>f</sub> = 0.22 (UV active; KMnO<sub>4</sub>, stains white).

**m. p.** = 81.2–84.3 °C (CH<sub>2</sub>Cl<sub>2</sub>).

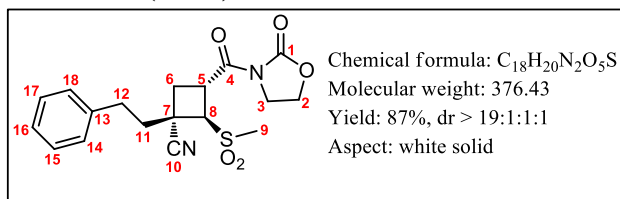
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 7.77 (d, *J* = 8.3 Hz, 2H, H-10, H-15), 7.36 (d, *J* = 8.0 Hz, 2H, H-11, H-14), 4.76–4.60 (m, 2H, H-5, H-8), 4.42 (ddd, *J* = 8.6, 7.3, 2.1 Hz, 2H, H-2), 4.05–3.76 (m, 4H, H-3, H-18), 3.17 (dd, *J* = 11.8, 9.6 Hz, 1H, H-6a), 2.62 (ddd, *J* = 13.7, 8.2, 5.5 Hz, 1H, H-17a), 2.48–2.33 (m, 5H, H-6b, H-17b, H-13), 1.09–1.01 (m, 21H, H-19, H-20, H-21, H-22, H-23, H-24, H-25, H-26, H-27).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 169.3 (C-4), 152.8 (C-1), 145.6 (C-12), 135.4 (C-9), 130.1 (C-11, C-14), 128.2 (C-10, C-15), 120.8 (C-16), 62.9 (C-2), 61.4 (C-8), 60.9 (C-18), 42.3 (C-3), 36.7 (C-5), 35.1 (C-7), 33.9 (C-6, C-17), 21.6 (C-13), 18.0 (C-22, C-23, C-24, C-25, C-26, C-27), 11.8 (C-19, C-20, C-21).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2944 (-C-H), 2867 (-C-H), 2237 (C≡N), 1784 (4-C=O), 1697 (1-C=O), 1390, 1322, 1150, 1111, 1040, 882, 672.

**HRMS (TOF, ES+):** calculated for C<sub>27</sub>H<sub>40</sub>N<sub>2</sub>O<sub>6</sub>SSiNa [M+Na]<sup>+</sup> 571.2268, **found** 571.2278.  
[ $\alpha$ ]<sub>D</sub><sup>25</sup> = +159.39 (*c* = 0.073, CHCl<sub>3</sub>).

**(1*S*,2*R*,3*R*)-2-(methylsulfonyl)-3-(2-oxooxazolidine-3-carbonyl)-1-phenethylcyclobutanecarbonitrile (181k)**



According to the general procedure (**I**), from cyclobutene **169e** (150.0 mg, 0.55 mmol, 1.0 eq.), acetonitrile (0.55 mL, 1.0 M), methanesulfonyl cyanide **88a** (116.0 mg, 1.1 mmol, 2.0 eq.) and *p*-anisaldehyde (13.0  $\mu$ L, 0.11 mmol, 0.2 eq.) for 23 h. Purification through column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 90/10) afforded the product (180.0 mg, 87%, dr > 19:1:1:1) as a white solid.  
**TLC (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 50/50):** R<sub>f</sub> = 0.48 (UV active; KMnO<sub>4</sub>, stains white).

**m. p.** = 166.6-169 °C (Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 7.34-7.22 (m, 5H, H-14, H-15, H-16, H-17, H-18), 4.65 (d, *J* = 9.8 Hz, 1H, H-8), 4.54-4.42 (m, 3H, H-2, H-5), 4.08-4.02 (m, 2H, H-3), 2.93 (s, 3H, H-9), 2.90-2.61 (m, 4H, H-6a, H-11a, H-12), 2.51-2.36 (m, 2H, H-6b, H-11b).

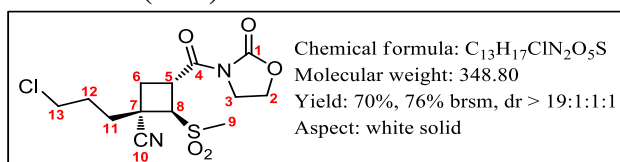
**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 169.8 (C-4), 152.9 (C-1), 139.5 (C-13), 128.7 (C-14, C-18), 128.6 (C-15, C-17), 126.6 (C-16), 121.0 (C-10), 62.9 (C-2), 59.7 (C-8), 42.9 (C-9), 42.4 (C-3), 38.7 (C-5), 36.0 (C-7), 33.3 (C-6), 32.9 (C-11 or C-12), 31.7 (C-11 or C-12).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2926 (-C-H), 2237 (C≡N), 1782 (4-C=O), 1692 (1-C=O), 1390, 1314, 1228, 1133, 1039, 756.

**HRMS (TOF, ES+):** calculated for C<sub>18</sub>H<sub>20</sub>N<sub>2</sub>O<sub>5</sub>SSNa [M+Na]<sup>+</sup> 399.0985, **found** 399.0993.

[ $\alpha$ ]<sub>D</sub><sup>23</sup> = +61.25 (*c* = 0.12, CHCl<sub>3</sub>).

**(1*S*,2*R*,3*R*)-1-(3-chloropropyl)-2-(methylsulfonyl)-3-(2-oxooxazolidine-3-carbonyl)cyclobutanecarbonitrile (181l)**



According to the general procedure (**I**), from cyclobutene **169f** (220.0 mg, 0.9 mmol, 1.0 eq.), acetonitrile (0.9 mL, 1.0 M), methanesulfonyl cyanide **88a** (189.0 mg, 1.8 mmol, 2.0 eq.) and *p*-anisaldehyde (21.0  $\mu$ L, 0.18 mmol, 0.2 eq.) for 100 h. 91% of conversion of the starting material was observed. Purification through column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 90/10) afforded the product (217.0 mg, 70%, 76% brsm, dr > 19:1:1:1) as a white solid.

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 50/50):** R<sub>f</sub> = 0.44 (UV inactive; KMnO<sub>4</sub>, stains white).

**m. p.** = 133-136 °C (Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 4.66 (d, *J* = 9.8 Hz, 1H, H-8), 4.53-4.39 (m, 3H, H-2, H-5), 4.04 (dd, *J* = 8.7, 7.4 Hz, 2H, H-3), 3.68-3.53 (m, 2H, H-13), 2.94 (s, 3H, H-9), 2.86-2.79 (m, 1H, H-6a), 2.53-2.41 (m, 2H, H-6b, H-11a), 2.30-2.26 (m, 1H, H-11b), 2.10-2.03 (m, 1H, H-12a), 1.94-1.90 (m, 1H, H-12b).

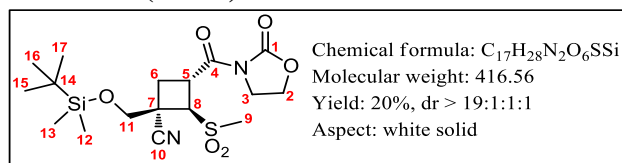
**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 169.7 (C-4), 152.9 (C-1), 120.7 (C-10), 63.0 (C-2), 59.5 (C-8), 43.7 (C-13), 42.5 (C-9), 42.4 (C-3), 38.7 (C-5), 35.4 (C-7), 33.2 (C-6), 28.7 (C-12), 28.6 (C-11).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2962 (-C-H), 2238 (C≡N), 1781 (4-C=O), 1692 (1-C=O), 1391, 1314, 1229, 1228, 1133, 1039, 759.

**HRMS (TOF, ES+):** calculated for C<sub>13</sub>H<sub>17</sub>ClN<sub>2</sub>O<sub>5</sub>SSNa [M+Na]<sup>+</sup> 371.0438, **found** 371.0439.

[ $\alpha$ ]<sub>D</sub><sup>23</sup> = +15.39 (*c* = 0.1, CHCl<sub>3</sub>).



**(1*S*,2*R*,3*R*)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-(methanesulfonyl)-3-(2-oxooxazolidine-3-carbonyl)cyclobutanecarbonitrile (181m)**

According to the general procedure (**I**), from cyclobutene **169d** (208.0 mg, 0.6 mmol, 1.0 eq.), acetonitrile (0.6 mL, 1.0 M), methanesulfonyl cyanide **88a** (135.0 mg, 1.28 mmol, 2.0 eq.) and *p*-anisaldehyde (16.0  $\mu$ L, 0.13 mmol, 0.2 eq.) for 100 h. Purification through column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 90/10) afforded the product (55.0 mg, 20%, dr > 19:1:1:1) as a white solid. **TLC** (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: **70/30**): R<sub>f</sub> = 0.60 (UV inactive; KMnO<sub>4</sub>, stains white).

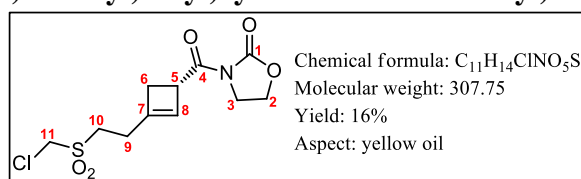
**m. p.** = 141.3–144.2 °C (Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>).

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 4.70 (d, *J* = 9.7 Hz, 1H, H-8), 4.54–4.45 (m, 3H, H-2, H-5), 4.35 (d, *J* = 10.4 Hz, 1H, H-11a), 4.08–4.01 (m, 3H, H-3, H-11b), 3.08 (s, 3H, H-9), 2.92–2.81 (m, 1H, H-6a), 2.45 (dd, *J* = 11.8, 9.5 Hz, 1H, H-6b), 0.91 (s, 9H, H-15, H-16, H-17), 0.14 (s, 6H, H-12, H-13).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 169.7 (C-4), 153.0 (C-1), 120.5 (C-10), 62.9 (C-2), 62.0 (C-11), 58.7 (C-8), 42.5 (C-3), 42.0 (C-9), 38.4 (C-7), 37.3 (C-5), 31.0 (C-6), 25.8 (C-15, C-16, C-17), 18.4 (C-14), -5.4 (C-12, C-13).

**IR** (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):  $\nu_{\text{max}}$  (cm<sup>-1</sup>) = 2931 (–C–H), 2242 (C $\equiv$ N), 1784 (4-C=O), 1694 (1-C=O), 1391, 1309, 1144, 1112, 838, 781, 759.

**HRMS** (TOF, ES<sup>+</sup>): calculated for C<sub>17</sub>H<sub>28</sub>N<sub>2</sub>O<sub>6</sub>SSiNa [M+Na]<sup>+</sup> 439.1329, **found** 439.1334. [ $\alpha$ ]<sub>D</sub><sup>23</sup> = +31.8 (*c* = 0.06, CHCl<sub>3</sub>).

**(*S*)-3-(3-(2-((chloromethyl)sulfonyl)ethyl)cyclobut-2-enecarbonyl)oxazolidin-2-one (197)**

According to the general procedure (**I**), from cyclobutene **169c** (250.0 mg, 0.68 mmol, 1.0 eq.), acetonitrile (0.7 mL, 1.0 M), sulfonyl cyanide **88d** (200.0 mg, 1.36 mmol, 2.0 eq.) and *p*-anisaldehyde (16.0  $\mu$ L, 0.136 mmol, 0.2 eq.) for 42 h. Purification through column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 90/10) afforded the product (34.0 mg, 16%) as a yellow oil. 80% of the starting material were recovered.

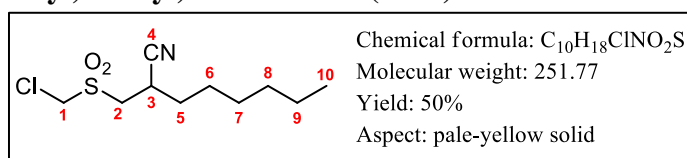
**TLC** (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: **90/10**): R<sub>f</sub> = 0.27 (UV inactive; KMnO<sub>4</sub>, stains white).

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 5.94–5.92 (m, 1H, H-8), 4.43 (t, *J* = 8.1 Hz, 2H, H-2), 4.39–4.36 (m, 1H, H-5), 4.28–4.16 (m, 4H, H-10, H-11), 4.04 (t, *J* = 8.1 Hz, 2H, H-3), 2.85 (dd, *J* = 13.3, 4.6 Hz, 1H, H-6a), 2.75 (dd, *J* = 13.3, 1.9 Hz, 1H, H-6b), 2.52 (t, *J* = 6.5 Hz, 2H, H-9).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 172.9 (C-4), 153.3 (C-1), 147.0 (C-7), 128.4 (C-8), 66.3 (C-11), 62.3 (C-2), 59.7 (C-10), 43.1 (C-5), 42.4 (C-3), 35.0 (C-6), 31.5 (C-9).

**IR** (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):  $\nu_{\text{max}}$  (cm<sup>-1</sup>) = 2935 (–C–H), 1777 (4-C=O), 1691 (1-C=O), 1477, 1388, 1363, 1260, 1227, 1136, 1114, 1040, 971, 760.

**HRMS** (TOF, ES<sup>+</sup>): calculated for C<sub>11</sub>H<sub>14</sub>ClNO<sub>5</sub>SNa [M+Na]<sup>+</sup> 330.0173, **found** 330.0172. [ $\alpha$ ]<sub>D</sub><sup>23</sup> = -31.70 (*c* = 0.06, CHCl<sub>3</sub>).

**2-(((chloromethyl)sulfonyl)methyl)octanenitrile (198a)**

According to the general procedure (**I**), from oct-1-ene (0.1 mL, 0.66 mmol, 1.0 eq.), acetonitrile (0.7 mL, 1.0 M), sulfonyl cyanide **88d** (139.0 mg, 1.0 mmol, 2.0 eq.) and *p*-anisaldehyde (16.0  $\mu$ L, 0.13 mmol, 0.2 eq.) for 67 h. Purification through column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 90/10) afforded the product (83.0 mg, 50%) as a pale-yellow solid.

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 70/30):** *R<sub>f</sub>* = 0.57 (UV inactive; KMnO<sub>4</sub>, stains red-white).

**m. p.** = 62.6-65.2 °C (pentane/EtOAc).

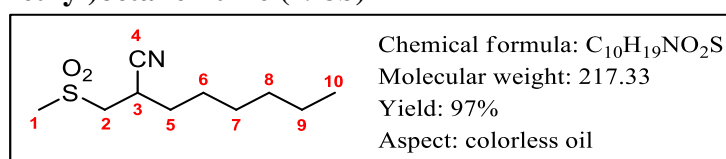
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 4.69 (d, *J* = 13.0 Hz, 1H, H-2a), 4.50 (dd, *J* = 13.0 Hz, 1H, H-2b), 3.73-3.65 (m, 1H, H-1a), 3.29-3.14 (m, 2H, H-1b, H-3), 1.84-1.76 (m, 2H, H-5), 1.56 (dq, *J* = 13.8, 7.4 Hz, 2H, H-6), 1.38-1.28 (m, 6H, H-7, H-8, H-9), 0.90 (t, *J* = 6.6 Hz, 3H, H-10).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 119.2 (C-4), 56.6 (C-2), 50.8 (C-1), 32.1 (C-5), 31.5 (C-7 or C-8 or C-9), 28.5 (C-7 or C-8 or C-9), 26.8 (C-6), 26.3 (C-3), 22.5 (C-7 or C-8 or C-9), 14.1 (C-10).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2955 (-C-H), 2930 (-C-H), 2245 (C $\equiv$ N), 1463, 1328, 1147, 1122.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>10</sub>H<sub>18</sub>ClNO<sub>2</sub>SNa [M+Na]<sup>+</sup> 274.0638, **found** 274.0648.

## 2-((methylsulfonyl)methyl)octanenitrile (**198b**)



According to the general procedure (**I**), from oct-1-ene (15.0  $\mu$ L, 0.1 mmol, 1.0 eq.), acetonitrile (0.5 mL, 0.2 M), methanesulfonyl cyanide **88a** (21.0 mg, 0.2 mmol, 2.0 eq.) and *p*-anisaldehyde (2.4  $\mu$ L, 0.02 mmol, 0.2 eq.) for 24 h. Purification through column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>: 100%) afforded the product (21.0 mg, 97%) as a colorless oil.

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 90/10):** *R<sub>f</sub>* = 0.53 (UV inactive; KMnO<sub>4</sub>, stains white-red).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 3.41 (dd, *J* = 14.1, 9.1 Hz, 1H, H-2a), 3.29-3.18 (m, 1H, H-3), 3.13 (dd, *J* = 4.4, 0.9 Hz, 1H, H-2b), 3.09 (s, 3H, H-1), 1.84-1.70 (m, 2H, H-5), 1.66-1.22 (m, 8H, H-6, H-7, H-8, H-9), 0.89 (t, *J* = 6.7 Hz, 3H, H-10).

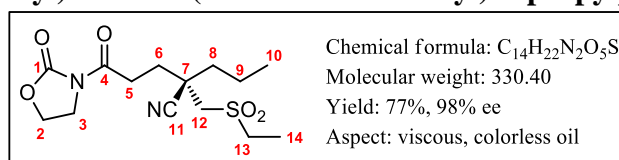
**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 119.8 (C-4), 56.3 (C-2), 42.2 (C-1), 32.2 (C-5), 31.5 (C-8), 28.5 (C-7), 26.8 (C-3, C-6), 22.6 (C-9), 14.1 (C-10).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2930 (-C-H), 2859 (-C-H), 2244 (C $\equiv$ N), 1303, 1134, 968, 513.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>10</sub>H<sub>19</sub>NO<sub>2</sub>SNa [M+Na]<sup>+</sup> 240.10287, **found** 240.10240.

## 10. SmI<sub>2</sub>-mediated ring-opening reaction

### (*S*)-2-((ethylsulfonyl)methyl)-5-oxo-5-(2-oxooxazolidin-3-yl)-2-propylpentanenitrile (**199a**)



According to the general procedure (**K**), from cyclobutane **181a** (82.0 mg, 0.24 mmol, 1.0 eq.), dry THF (2.4 mL, 0.1 M), distilled H<sub>2</sub>O (~ 78.0  $\mu$ L, 4.32 mmol, 18.0 eq.) and SmI<sub>2</sub>/THF (0.15 M, 6.4 mL, 0.96 mmol, 4.0 eq.) for 30 min. Purification of the crude mixture through column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 50/50) afforded the product (61.0 mg, 77%, 98% ee) as a viscous, colorless oil.

**TLC (EtOAc: 100%):** *R<sub>f</sub>* = 0.53 (UV inactive; KMnO<sub>4</sub>, stains white).

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 4.42 (t, *J* = 8.1 Hz, 2H, H-2), 4.01 (t, *J* = 8.1 Hz, 2H, H-3), 3.33-3.26 (m, 2H, H-12), 3.16-3.10 (m, 4H, H-5, H-13), 2.39-2.26 (m, 2H, H-6), 2.02-1.95 (m, 1H, H-8a), 1.89-1.81 (m, 1H, H-8b), 1.58-1.50 (m, 2H, H-9), 1.41 (t, *J* = 7.5 Hz, 3H, H-14), 0.99 (t, *J* = 7.3 Hz, 3H, H-10).

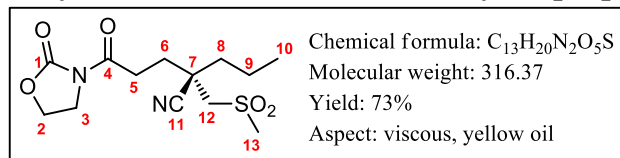
**$^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 171.4 (C-4), 153.8 (C-1), 120.9 (C-11), 62.4 (C-2), 54.3 (C-12), 50.1 (C-13), 42.6 (C-3), 39.0 (C-7), 38.6 (C-8), 30.7 (C-5, C-6), 18.1 (C-9), 13.9 (C-10), 6.6 (C-14).

**IR (solution in  $\text{CH}_2\text{Cl}_2$ , thin film, KBr):**  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 2966 (C-H), 2937 (C-H), 2877 (C-H), 2237 ( $\text{C}\equiv\text{N}$ ), 1777 (4-C=O), 1699 (4-C=O), 1392, 1365, 1313, 1134, 1041.

**HRMS (TOF, ES $^+$ ):** calculated for  $\text{C}_{14}\text{H}_{22}\text{N}_2\text{O}_5\text{SNa}$   $[\text{M}+\text{Na}]^+$  353.1142, found 353.1145.

$[\alpha]_{\text{D}}^{25} = -0.56$  ( $c = 0.24$ ,  $\text{CHCl}_3$ ).

**(S)-2-((methylsulfonyl)methyl)-5-oxo-5-(2-oxooxazolidin-3-yl)-2-propylpentanenitrile (199b)**



According to the general procedure (**K**), from cyclobutane **181b** (66.4 mg, 0.21 mmol, 1.0 eq.), dry THF (2.1 mL, 0.1 M), distilled  $\text{H}_2\text{O}$  (46.0  $\mu\text{L}$ , 2.5 mmol, 12.0 eq.) and  $\text{SmI}_2/\text{THF}$  (0.16 M, 5.3 mL, 0.84 mmol, 4.0 eq.) for 1 h. Purification of the crude mixture through column chromatography on  $\text{SiO}_2$  ( $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ : 70/30) afforded the product (48.0 mg, 73%) as a viscous, yellow oil.

**TLC ( $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ : 70/30):**  $R_f = 0.16$  (UV inactive;  $\text{KMnO}_4$ , stains white).

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 4.42 (t,  $J = 8.1$  Hz, 2H, H-2), 4.00 (t,  $J = 8.1$  Hz, 2H, H-3), 3.36 (s, 2H, H-12), 3.11 (t,  $J = 7.9$  Hz, 2H, H-5), 3.06 (s, 3H, H-13), 2.39-2.18 (m, 2H, H-6), 2.02-1.74 (m, 2H, H-8), 1.60-1.45 (m, 2H, H-9), 0.98 (t,  $J = 7.2$  Hz, 3H, H-10).

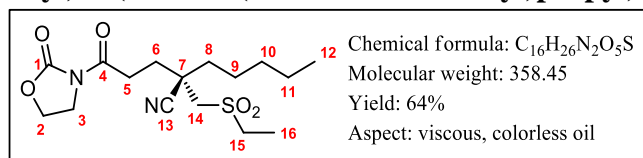
**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 171.4 (C-4), 153.8 (C-1), 120.9 (C-11), 62.4 (C-2), 57.3 (C-12), 43.5 (C-13), 42.6 (C-3), 38.9 (C-7), 38.5 (C-8), 30.6 (C-5 or C-6), 30.5 (C-5 or C-6), 17.9 (C-9), 13.9 (C-10).

**IR (solution in  $\text{CH}_2\text{Cl}_2$ , thin film, KBr):**  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 2966 (C-H), 2933 (C-H), 2876 (C-H), 2237 ( $\text{C}\equiv\text{N}$ ), 1777 (4-C=O), 1697 (1-C=O), 1391, 1365, 1311, 1226, 1138, 1040, 761.

**HRMS (TOF, ES $^+$ ):** calculated for  $\text{C}_{13}\text{H}_{20}\text{N}_2\text{O}_5\text{SNa}$   $[\text{M}+\text{Na}]^+$  339.0985, found 339.0988.

$[\alpha]_{\text{D}}^{25} = -11.24$  ( $c = 0.25$ ,  $\text{CHCl}_3$ ).

**(S)-2-((ethylsulfonyl)methyl)-2-(3-oxo-3-(2-oxooxazolidin-3-yl)propyl)heptanenitrile (199c)**



According to the general procedure (**K**), from cyclobutane **181c** (50.0 mg, 0.14 mmol, 1.0 eq.), dry THF (1.4 mL, 0.1 M), distilled  $\text{H}_2\text{O}$  (45.0  $\mu\text{L}$ , 2.5 mmol, 18.0 eq.) and  $\text{SmI}_2/\text{THF}$  (0.11 M, 4.5 mL, 0.5 mmol, 3.5 eq.) for 3 h. Purification of the crude mixture through column chromatography on  $\text{SiO}_2$  ( $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ : 50/50) afforded the product (32.0 mg, 64%) as a viscous, colorless oil.

**TLC ( $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ : 50/50):**  $R_f = 0.48$  (UV inactive;  $\text{KMnO}_4$ , stains white).

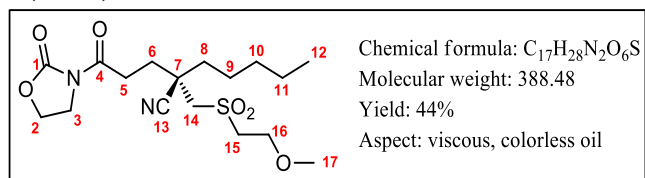
**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 4.43 (dd,  $J = 8.7, 7.5$  Hz, 2H, H-2), 4.03 (dd,  $J = 8.7, 7.5$  Hz, 2H, H-3), 3.29 (q<sub>AB</sub>,  $J = 1.3$  Hz, 2H, H-14), 3.19-3.09 (m, 4H, H-5, H-15), 2.42-2.24 (m, 2H, H-6), 2.07-1.95 (m, 1H, H-8a), 1.91-1.81 (m, 1H, H-8b), 1.57-1.49 (m, 2H, H-9), 1.42 (t,  $J = 7.5$  Hz, 3H, H-16), 1.40-1.32 (m, 4H, H-10, H-11), 0.94-0.85 (m, 3H, H-12).

**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 171.4 (C-4), 153.7 (C-1), 120.9 (C-13), 62.4 (C-2), 54.3 (C-14), 50.1 (C-15), 42.6 (C-3), 39.1 (C-7), 36.6 (C-8), 31.5 (C-10), 30.7 (C-5, C-6), 24.3 (C-9), 22.4 (C-11), 14.0 (C-12), 6.6 (C-16).

**IR (solution in  $\text{CH}_2\text{Cl}_2$ , thin film, KBr):**  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 2932 (C-H), 2236 ( $\text{C}\equiv\text{N}$ ), 1778 (4-C=O), 1699 (1-C=O), 1391, 1314, 1227, 1134, 1040, 760.

**HRMS (TOF, ES $^+$ ):** calculated for  $\text{C}_{16}\text{H}_{26}\text{N}_2\text{O}_5\text{SNa}$   $[\text{M}+\text{Na}]^+$  381.1454, found 381.1460.

$[\alpha]_{\text{D}}^{23} = -1.03$  ( $c = 1.4$ ,  $\text{CHCl}_3$ ).

**(S)-2-(((2-methoxyethyl)sulfonyl)methyl)-2-(3-oxo-3-(2-oxooxazolidin-3-yl)propyl)heptanenitrile (199d)**

According to the general procedure (**K**), from cyclobutane **181d** (78.0 mg, 0.2 mmol, 1.0 eq.), dry THF (2.0 mL, 0.1 M), distilled  $H_2O$  (43.0  $\mu L$ , 2.4 mmol, 12.0 eq.) and  $SmI_2/THF$  (0.2 M, 4.5 mL, 0.91 mmol, 4.5 eq.) for 3.5 h. Purification of the crude mixture through column chromatography on  $SiO_2$  ( $CH_2Cl_2/EtOAc$ : 80/20) afforded the product (34.0 mg, 44%) as a viscous, colorless oil.

**TLC** ( $CH_2Cl_2/EtOAc$ : 50/50):  $R_f$  = 0.53 (UV inactive;  $KMnO_4$ , stains white).

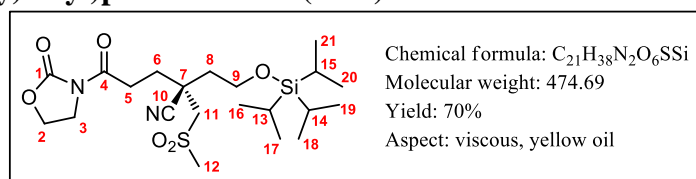
**$^1H$  NMR** (300 MHz,  $CDCl_3$ ):  $\delta$  (ppm) = 4.43 (dd,  $J$  = 8.6, 7.4 Hz, 2H, H-2), 4.02 (dd,  $J$  = 8.6, 7.4 Hz, 2H, H-3), 3.83-3.79 (m, 2H, H-16), 3.51-3.49 (m, 2H, H-14), 3.41 (s, 3H, H-17), 3.28 (dd,  $J$  = 5.9, 4.4 Hz, 2H, H-15), 3.20-3.12 (m, 2H, H-5), 2.35-2.27 (m, 2H, H-6), 2.07-1.97 (m, 1H, H-8a), 1.89-1.79 (m, 1H, H-8b), 1.59-1.43 (m, 2H, H-9), 1.36-1.28 (m, 4H, H-10, H-11), 0.98-0.80 (m, 3H, H-12).

**$^{13}C$  NMR** (75 MHz,  $CDCl_3$ ):  $\delta$  (ppm) = 171.5 (C-4), 153.6 (C-1), 120.9 (C-13), 66.3 (C-16), 62.4 (C-2), 59.3 (C-17), 57.3 (C-14), 56.2 (C-15), 42.6 (C-3), 39.2 (C-7), 36.7 (C-8), 31.5 (C-10 or C-11), 30.9 (C-5 or C-6), 30.8 (C-5 or C-6), 24.3 (C-9), 22.5 (C-10 or C-11), 14.0 (C-12).

**IR** (solution in  $CH_2Cl_2$ , thin film, **KBr**):  $\nu_{max}$  ( $cm^{-1}$ ) = 2931 (C-H), 2179 ( $C\equiv N$ ), 1778 (4-C=O), 1699 (1-C=O), 1391, 1319, 1224, 1115, 1040.

**HRMS** (TOF, **ES**<sup>+</sup>): calculated for  $C_{17}H_{28}N_2O_6SNa$   $[M+Na]^+$  411.1571, found 411.1577.

$[\alpha]_D^{23}$  = -8.18 ( $c$  = 0.08,  $CHCl_3$ ).

**(R)-2-(((methanesulfonyl)methyl)-5-oxo-5-(2-oxooxazolidin-3-yl)-2-(2-((triisopropylsilyl)oxy)ethyl)pentanenitrile (199e)**

According to the general procedure (**K**), from cyclobutane **181i** (1.43 g, 3.0 mmol, 1.0 eq.), dry THF (15.0 mL, 0.2 M), distilled  $H_2O$  (1.0 mL, 54.0 mmol, 18.0 eq.) and  $SmI_2/THF$  (0.2 M, 65.0 mL, 13.0 mmol, 4.3 eq.) for 1 h. Purification of the crude mixture through column chromatography on  $SiO_2$  ( $CH_2Cl_2/EtOAc$ : 80/20) afforded the product (993.0 mg, 70%) as a viscous, yellow oil.

**TLC** ( $CH_2Cl_2/EtOAc$ : 80/20):  $R_f$  = 0.42 (UV inactive;  $KMnO_4$ , stains white).

**$^1H$  NMR** (400 MHz,  $CDCl_3$ ):  $\delta$  (ppm) = 4.44 (dd,  $J$  = 8.6, 7.6 Hz, 2H, H-2), 4.07-3.99 (m, 3H, H-9, H-3), 3.75 (d,  $J$  = 14.9 Hz, 1H, H-11a), 3.45 (d,  $J$  = 14.9 Hz, 1H, H-11b), 3.19 (t,  $J$  = 7.9 Hz, 2H, H-5), 3.08 (s, 3H, H-3a, H-12), 2.96-2.83 (m, 1H, H-3b), 2.59-2.47 (m, 1H, H-6a), 2.42-2.33 (m, 1H, H-6b), 2.26-2.16 (m, 1H, H-8a), 2.13-2.07 (m, 1H, H-8b), 1.11-1.03 (m, 21H, H-13, H-14, H-15, H-16, H-17, H-18, H-19, H-20, H-21).

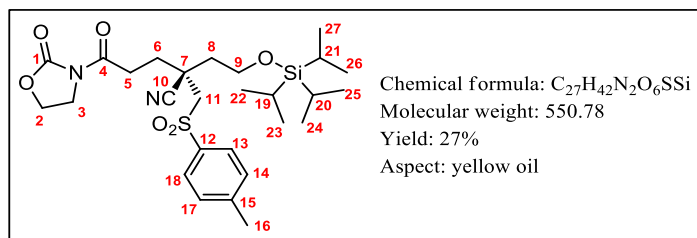
**$^{13}C$  NMR** (75 MHz,  $CDCl_3$ ):  $\delta$  (ppm) = 171.3 (C-4), 153.7 (C-1), 120.5 (C-10), 62.4 (C-2), 60.2 (C-9), 58.6 (C-11), 43.5 (C-12), 42.6 (C-3), 38.5 (C-7), 38.2 (C-8), 31.3 (C-6), 30.7 (C-5), 18.1 (C-16, C-17, C-18, C-19, C-20, C-21), 11.9 (C-13, C-14, C-15).

**IR** (solution in  $CH_2Cl_2$ , thin film, **KBr**):  $\nu_{max}$  ( $cm^{-1}$ ) = 2943 (C-H), 2867 (C-H), 2238 ( $C\equiv N$ ), 1776 (4-C=O), 1699 (1-C=O), 1391, 1312, 1226, 1141, 1040, 883, 761, 684.

**HRMS** (TOF, **ES**<sup>+</sup>): calculated for  $C_{21}H_{38}N_2O_6SSiNa$   $[M+Na]^+$  497.2123, found 497.2115.

$[\alpha]_D^{23}$  = -34.28 ( $c$  = 0.093,  $CHCl_3$ ).

**(R)-5-oxo-5-(2-oxooxazolidin-3-yl)-2-(2-((triisopropylsilyl)oxy)ethyl)-2-(tosylmethyl)-2-((triisopropylsilyl)oxy)ethyl)pentanenitrile (199f)**



According to the general procedure (**K**), from cyclobutane **181j** (379.0 mg, 0.69 mmol, 1.0 eq.), dry THF (3.5 mL, 0.2 M), distilled  $H_2O$  (0.22 mL, 12.4 mmol, 18.0 eq.) and  $SmI_2/THF$  (0.2 M, 15.5 mL, 3.1 mmol, 4.5 eq.) for 3 h. Purification of the crude mixture through column chromatography on  $SiO_2$  ( $CH_2Cl_2/EtOAc$ : 95/5 to 90/10 to 80/20) afforded the product (102.0 mg, 27%) as a yellow oil.

**TLC** ( $CH_2Cl_2/EtOAc$ : **70/30**):  $R_f$  = 0.68 (UV active;  $KMnO_4$ , stains white).

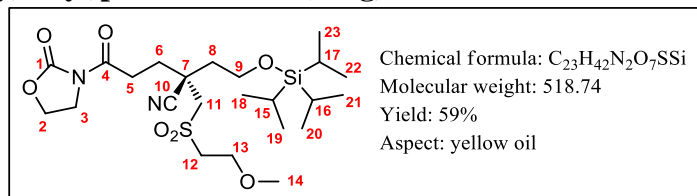
**$^1H$  NMR** (300 MHz,  $CDCl_3$ ):  $\delta$  (ppm) = 7.83-7.80 (m, 2H, H-13, H-18), 7.36 (d,  $J$  = 8.0 Hz, 2H, H-14, H-17), 4.42 (dd,  $J$  = 8.7, 7.4 Hz, 2H, H-2), 4.06-3.95 (m, 4H, H-3, H-9), 3.70 (d,  $J$  = 14.7 Hz, 1H, H-11a), 3.47 (d,  $J$  = 14.6 Hz, 1H, H-11b), 3.19 (t,  $J$  = 7.9 Hz, 2H, H-5), 2.61-2.38 (m, 5H, H-6, H-16), 2.23 (ddd,  $J$  = 14.6, 7.1, 4.9 Hz, 1H, H-8a), 2.09 (ddd,  $J$  = 14.6, 5.9, 4.7 Hz, 1H, H-8b), 1.09-0.99 (m, 21H, H-19, H-20, H-21, H-22, H-23, H-24, H-25, H-26, H-27).

**$^{13}C$  NMR** (75 MHz,  $CDCl_3$ ):  $\delta$  (ppm) = 171.4 (C-4), 153.7 (C-1), 145.5 (C-15), 137.5 (C-12), 130.1 (C-13, C-15), 128.1 (C-14, C-17), 120.2 (C-10), 62.3 (C-2), 60.2 (C-9), 59.5 (C-11), 42.6 (C-3), 39.0 (C-7), 38.5 (C-8), 31.4 (C-6), 30.8 (C-5), 21.8 (C-16), 18.0 (C-22, C-23, C-24, C-25, C-26, C-27), 11.9 (C-19, C-20, C-21).

**IR** (solution in  $CH_2Cl_2$ , thin film, **KBr**):  $\nu_{max}$  ( $cm^{-1}$ ) = 2943 (-C-H), 2866 (-C-H), 2236 ( $C\equiv N$ ), 1780 (4-C=O), 1701 (1-C=O), 1390, 1320, 1225, 1151, 734.

**HRMS** (TOF, **ES**<sup>+</sup>): calculated for  $C_{27}H_{42}N_2O_6SSiNa$   $[M+Na]^+$  573.24251, found 573.24086.  $[\alpha]_D^{25}$  = -123.12 ( $c$  = 0.66,  $CHCl_3$ ).

**(R)-2-(((2-methoxyethyl)sulfonyl)methyl)-5-oxo-5-(2-oxooxazolidin-3-yl)-2-(2-((triisopropylsilyl)oxy)ethyl)pentanenitrile (199g)**



According to the general procedure (**K**), from cyclobutane **181f** (203.0 mg, 0.39 mmol, 1.0 eq.), dry THF (2.0 mL, 0.2 M), distilled  $H_2O$  (0.13 mL, 7.02 mmol, 18.0 eq.) and  $SmI_2/THF$  (0.2 M, 8.7 mL, 1.75 mmol, 4.5 eq.) for 4.5 h. Purification of the crude mixture through column chromatography on  $SiO_2$  ( $CH_2Cl_2/EtOAc$ : 90/10 to 80/20) afforded the product (119.0 mg, 59%) as a yellow oil.

**TLC** ( $CH_2Cl_2/EtOAc$ : **70/30**):  $R_f$  = 0.58 (UV inactive;  $KMnO_4$ , stains white).

**$^1H$  NMR** (300 MHz,  $CDCl_3$ ):  $\delta$  (ppm) = 4.42 (dd,  $J$  = 8.6, 7.4 Hz, 2H, H-2), 4.05-3.98 (m, 4H, H-3, H-9), 3.82 (ddd,  $J$  = 5.7, 4.1, 1.4 Hz, 2H, H-13), 3.63 (s, 2H, H-11), 3.41 (s, 3H, H-14), 3.37-3.15 (m, 4H, H-5, H-12), 2.42 (dd,  $J$  = 8.7, 7.1 Hz, 2H, H-6), 2.33-2.11 (m, 2H, H-8), 1.09-1.04 (m, 21H, H-15, H-16, H-17, H-18, H-19, H-20, H-21, H-22, H-23).

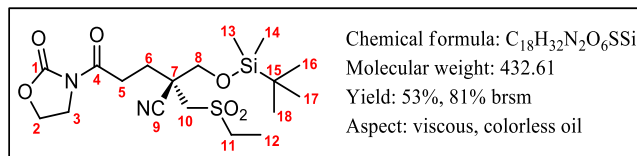
**$^{13}C$  NMR** (75 MHz,  $CDCl_3$ ):  $\delta$  (ppm) = 171.4 (C-4), 153.6 (C-1), 120.7 (C-10), 66.2 (C-13), 62.3 (C-2), 59.9 (C-9), 59.3 (C-14), 58.1 (C-11), 56.2 (C-12), 42.6 (C-3), 38.8 (C-8), 37.9 (C-7), 31.5 (C-6), 30.9 (C-5), 18.1 (C-18, C-19, C-20, C-21, C-22, C-23), 11.9 (C-15, C-16, C-17).

**IR** (solution in  $CH_2Cl_2$ , thin film, **KBr**):  $\nu_{max}$  ( $cm^{-1}$ ) = 2943 (-C-H), 2867 (-C-H), 2237 ( $C\equiv N$ ), 1780 (4-C=O), 1701 (1-C=O), 1390, 1320, 1224, 1114.

**HRMS** (TOF, **ES**<sup>+</sup>): calculated for  $C_{23}H_{42}N_2O_7SSiNa$   $[M+Na]^+$  541.2374, found 541.2351.  $[\alpha]_D^{25}$  = -34.57 ( $c$  = 0.086,  $CHCl_3$ ).

**(S)-2-(((tert-butyldimethylsilyl)oxy)methyl)-2-((ethylsulfonyl)methyl)-5-oxo-5-(2-oxooxazolidin-3-yl)pentanenitrile (199h)**





According to the general procedure (**K**), from cyclobutane **181g** (140.0 mg, 0.32 mmol, 1.0 eq.), dry THF (3.2 mL, 0.1 M), distilled  $H_2O$  (69.0  $\mu L$ , 4.3 mmol, 12.0 eq.) and  $SmI_2/THF$  (0.15 M, 8.6 mL, 1.3 mmol, 4.0 eq.) for 2.5 h. Purification of the crude mixture through column chromatography on  $SiO_2$  ( $CH_2Cl_2/EtOAc$ : 95/5) afforded the product (74.0 mg, 53%, 81% brsm) as a viscous, colorless oil. 36% of the starting material were recovered.

**TLC** ( $CH_2Cl_2/EtOAc$ : 50/50):  $R_f$  = 0.42 (UV inactive;  $KMnO_4$ , stains white).

**$^1H$  NMR** (300 MHz,  $CDCl_3$ ):  $\delta$  (ppm) = 4.42 (t,  $J$  = 8.1 Hz, 2H, H-2), 4.02 (t,  $J$  = 8.1 Hz, 2H, H-3), 3.95 (q,  $J$  = 13.3 Hz, 2H, H-8), 3.36 (q<sub>AB</sub>,  $J$  = 1.6 Hz, 2H, H-10), 3.19-3.15 (m, 4H, H-5, H-11), 2.39-2.34 (m, 1H, H-6a), 2.18-2.22 (m, 1H, H-6b), 1.41 (t,  $J$  = 7.4 Hz, 3H, H-12), 0.90 (s, 9H, H-16, H-17, H-18), 0.11 (d,  $J$  = 2.9 Hz, 6H, H-13, H-14).

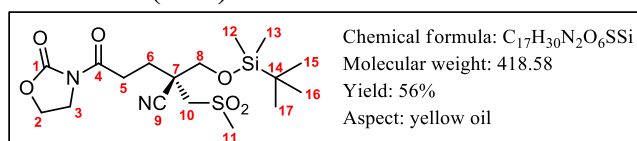
**$^{13}C$  NMR** (75 MHz,  $CDCl_3$ ):  $\delta$  (ppm) = 171.4 (C-4), 153.7 (C-1), 119.7 (C-9), 65.1 (C-8), 62.4 (C-2), 52.2 (C-10), 49.9 (C-11), 42.6 (C-3), 41.5 (C-7), 30.8 (C-5), 28.1 (C-6), 25.8 (C-16, C-17, C-18), 18.3 (C-15), 6.7 (C-12), -5.4 (C-13 or C-14), -5.5 (C-13 or C-14).

**IR** (solution in  $CH_2Cl_2$ , thin film, **KBr**):  $\nu_{max}$  ( $cm^{-1}$ ) = 2930 (-C-H), 2241 ( $C\equiv N$ ), 1779 (4-C=O), 1700 (1-C=O), 1390, 1315, 1257, 1227, 1123, 1040, 840, 781.

**HRMS** (TOF, **ES**<sup>+</sup>): calculated for  $C_{18}H_{32}N_2O_6SSiNa$   $[M+Na]^+$  455.1642, found 455.1648.

$[\alpha]_D^{23}$  = -9.14 ( $c$  = 1.2,  $CHCl_3$ ).

**(S)-2-(((tert-butyldimethylsilyl)oxy)methyl)-2-((methylsulfonyl)methyl)-5-oxo-5-(2-oxooxazolidin-3-yl)pentanenitrile (199i)**



According to the general procedure (**K**), from cyclobutane **181m** (44.0 mg, 0.1 mmol, 1.0 eq.), dry THF (0.5 mL, 0.2 M), distilled  $H_2O$  (32.0  $\mu L$ , 1.8 mmol, 18.0 eq.) and  $SmI_2/THF$  (0.2 M, 2.3 mL, 0.47 mmol, 4.5 eq.) for 3 h. Purification of the crude mixture through column chromatography on  $SiO_2$  ( $CH_2Cl_2/EtOAc$ : 80/20) afforded the product (23.5 mg, 56%) as a yellow oil.

**TLC** ( $CH_2Cl_2/EtOAc$ : 80/20):  $R_f$  = 0.37 (UV inactive;  $KMnO_4$ , stains white).

**$^1H$  NMR** (300 MHz,  $CDCl_3$ ):  $\delta$  (ppm) = 4.44 (dd,  $J$  = 8.7, 7.5 Hz, 2H, H-2), 4.01-4.05 (m, 2H, H-3), 3.99 (d,  $J$  = 10.0 Hz, 1H, H-8a), 3.91 (d,  $J$  = 10.0 Hz, 1H, H-8b), 3.41 (q,  $J$  = 13.3 Hz, 2H, H-10), 3.19 (ddd,  $J$  = 8.4, 6.6, 2.8 Hz, 2H, H-5), 3.09 (s, 3H, H-11), 2.39-2.35 (m, 1H, H-6a), 2.21 (ddd,  $J$  = 14.4, 8.9, 6.8 Hz, 1H, H-6b), 0.91 (s, 9H, H-15, H-16, H-17), 0.12 (d,  $J$  = 2.9 Hz, 6H, H-12, H-13).

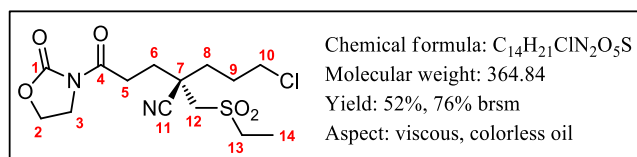
**$^{13}C$  NMR** (75 MHz,  $CDCl_3$ ):  $\delta$  (ppm) = 171.4 (C-4), 153.7 (C-1), 119.6 (C-9), 64.9 (C-8), 62.4 (C-2), 55.9 (C-10), 43.9 (C-11), 42.6 (C-3), 41.4 (C-7), 30.6 (C-5), 28.2 (C-6), 25.8 (C-15, C-16, C-17), 18.3 (C-14), -5.3 (C-12, C-13).

**IR** (solution in  $CH_2Cl_2$ , thin film, **KBr**):  $\nu_{max}$  ( $cm^{-1}$ ) = 2930 (-C-H), 2867 (-C-H), 2237 ( $C\equiv N$ ), 1778 (4-C=O), 1701 (1-C=O), 1390, 1312, 1257, 1237, 1116, 840, 781.

**HRMS** (TOF, **ES**<sup>+</sup>): calculated for  $C_{17}H_{30}N_2O_6SSiNa$   $[M+Na]^+$  441.1486, found 441.1466.

$[\alpha]_D^{25}$  = -29.70 ( $c$  = 0.053,  $CHCl_3$ ).

**(R)-2-(3-chloropropyl)-2-((ethylsulfonyl)methyl)-5-oxo-5-(2-oxooxazolidin-3-yl)pentanenitrile (199j)**



According to the general procedure (**K**), from cyclobutane **181h** (60.0 mg, 0.16 mmol, 1.0 eq.), dry THF (1.6 mL, 0.1 M), distilled H<sub>2</sub>O (52.0  $\mu$ L, 2.9 mmol, 18.0 eq.) and SmI<sub>2</sub>/THF (0.15 M, 4.0 mL, 0.6 mmol, 3.5 eq.) for 2.5 h. Purification of the crude mixture through column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 90/10) afforded the product (30.0 mg, 52%, 76% brsm) as a viscous, colorless oil. 34% of the starting material were recovered.

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 60/40):**  $R_f$  = 0.34 (UV inactive; KMnO<sub>4</sub>, stains white).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 4.44 (dd,  $J$  = 8.7, 7.4 Hz, 2H, H-2), 4.04 (t,  $J$  = 8.0 Hz, 2H, H-3), 3.64–3.58 (m, 2H, H-10), 3.31 (s, 2H, H-12), 3.24–3.09 (m, 4H, H-5, H-13), 2.45–2.30 (m, 2H, H-6), 2.30–2.20 (m, 1H, H-8a), 2.15–1.99 (m, 3H, H-8b, H-9), 1.44 (t,  $J$  = 7.5 Hz, 3H, H-14).

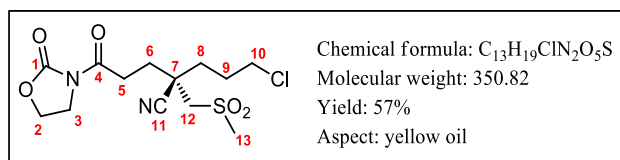
**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 171.2 (C-4), 153.7 (C-1), 120.3 (C-11), 62.4 (C-2), 54.1 (C-12), 50.2 (C-13), 43.9 (C-10), 42.6 (C-3), 38.8 (C-7), 34.1 (C-8), 30.9 (C-5 or C-6), 30.7 (C-5 or C-6), 27.9 (C-9), 6.7 (C-14).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2937 (–C–H), 2238 (C $\equiv$ N), 1777 (4–C=O), 1698 (1–C=O), 1392, 1313, 1228, 1134, 1040, 760, 733.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>14</sub>H<sub>21</sub>ClN<sub>2</sub>O<sub>5</sub>Na [M+Na]<sup>+</sup> 387.0751, found 387.0752.

$[\alpha]_D^{23}$  = –5.81 ( $c$  = 1.2, CHCl<sub>3</sub>).

**(R)-2-(3-chloropropyl)-2-((methylsulfonyl)methyl)-5-oxo-5-(2-oxooxazolidin-3-yl)pentanenitrile (199k)**



According to the general procedure (**K**), from cyclobutane **181i** (200.0 mg, 0.57 mmol, 1.0 eq.), dry THF (2.8 mL, 0.2 M), distilled H<sub>2</sub>O (0.18 mL, 10.26 mmol, 18.0 eq.) and SmI<sub>2</sub>/THF (0.2 M, 12.5 mL, 2.5 mmol, 4.5 eq.) for 1.5 h. Purification of the crude mixture through column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 80/20 to 70/30) afforded the product (114.0 mg, 57%) as a yellow oil.

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 60/40):**  $R_f$  = 0.27 (UV inactive; KMnO<sub>4</sub>, stains white).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 4.43 (dd,  $J$  = 8.7, 7.5 Hz, 2H, H-2), 4.02 (dd,  $J$  = 8.7, 7.5 Hz, 2H, H-3), 3.59 (t,  $J$  = 5.9 Hz, 2H, H-10), 3.40 (d,  $J$  = 2.3 Hz, 2H, H-12), 3.14 (t,  $J$  = 10.0 Hz, 2H, H-5), 3.07 (s, 3H, H-13), 3.34–3.28 (m, 2H, H-6), 2.25–2.11 (m, 1H, H-8a), 2.07–1.97 (m, 3H, H-8b, H-9).

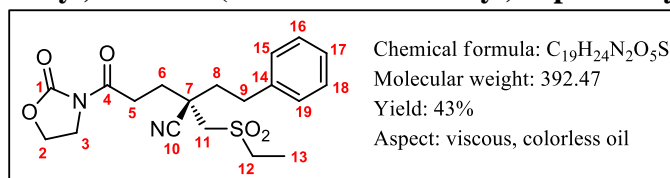
**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 171.2 (C-4), 153.8 (C-1), 120.4 (C-11), 62.4 (C-2), 57.0 (C-12), 44.0 (C-10), 43.6 (C-13), 42.6 (C-3), 38.5 (C-7), 33.8 (C-8), 30.6 (C-5 or C-6), 30.5 (C-5 or C-6), 27.7 (C-9).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2967 (–C–H), 2930 (–C–H), 2238 (C $\equiv$ N), 1775 (4–C=O), 1697 (1–C=O), 1392, 1309, 1139, 760.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>13</sub>H<sub>20</sub>ClN<sub>2</sub>O<sub>5</sub>S [M+H]<sup>+</sup> 351.0775, found 351.0782.

$[\alpha]_D^{25}$  = –1.47 ( $c$  = 0.01, CHCl<sub>3</sub>).

**(S)-2-((ethylsulfonyl)methyl)-5-oxo-5-(2-oxooxazolidin-3-yl)-2-phenethylpentanenitrile (199l)**



According to the general procedure (**K**), from cyclobutane **181e** (95.0 mg, 0.24 mmol, 1.0 eq.), dry THF (2.4 mL, 0.1 M), distilled H<sub>2</sub>O (78.0  $\mu$ L, 4.3 mmol, 18.0 eq.) and SmI<sub>2</sub>/THF (0.15 M, 5.6 mL, 0.84 mmol, 3.5 eq.) for 1.5 h. Purification of the crude mixture through column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 60/40) afforded the product (40.0 mg, 43%) as a viscous, colorless oil.

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 50/50):**  $R_f$  = 0.42 (UV active; KMnO<sub>4</sub>, stains white).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 7.34–7.19 (m, 5H, H-15, H-16, H-17, H-18, H-19), 4.44 (dd,  $J$  = 8.7, 7.5 Hz, 2H, H-2), 4.04 (dd,  $J$  = 8.7, 7.5 Hz, 2H, H-3), 3.36 (q<sub>AB</sub>,  $J$  = 1.3 Hz, 2H, H-11), 3.22

(t,  $J = 7.8$  Hz, 2H, H-5), 3.13 (q,  $J = 7.5$  Hz, 2H, H-12), 2.88 (ddd,  $J = 10.2, 5.9, 3.7$  Hz, 2H, H-9), 2.55-2.32 (m, 3H, H-6, H-8a), 2.18 (ddd,  $J = 14.1, 10.8, 6.2$  Hz, 1H, H-8b), 1.44 (t,  $J = 7.5$  Hz, 3H, H-13).

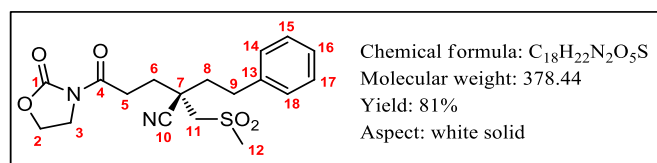
**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 171.3 (C-4), 153.7 (C-1), 139.7 (C-14), 128.8 (C-15, C-19), 128.6 (C-16, C-18), 126.6 (C-17), 120.6 (C-10), 62.4 (C-2), 53.8 (C-11), 50.2 (C-12), 42.6 (C-3), 39.3 (C-7), 38.4 (C-8), 31.2 (C-5 or C-6 or C-9), 30.9 (C-5 or C-6 or C-9), 30.7 (C-5 or C-6 or C-9), 6.7 (C-13).

**IR (solution in  $\text{CH}_2\text{Cl}_2$ , thin film, KBr):**  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 2932 (C-H), 2237 ( $\text{C}\equiv\text{N}$ ), 1777 (4-C=O), 1699 (1-C=O), 1391, 1314, 1227, 1135, 1040, 759, 734, 703.

**HRMS (TOF, ES+):** calculated for  $\text{C}_{19}\text{H}_{24}\text{N}_2\text{O}_5\text{SNa}$   $[\text{M}+\text{Na}]^+$  415.1298, found 415.1296.

$[\alpha]_{\text{D}}^{23} = -23.07$  ( $c = 1.2$ ,  $\text{CHCl}_3$ ).

**(S)-2-((methylsulfonyl)methyl)-5-oxo-5-(2-oxooxazolidin-3-yl)-2-phenethylpentanenitrile (199m)**



According to the general procedure (**K**), from cyclobutane **181k** (100.0 mg, 0.26 mmol, 1.0 eq.), dry THF (2.6 mL, 0.1 M), distilled  $\text{H}_2\text{O}$  (56.0  $\mu\text{L}$ , 3.12 mmol, 12.0 eq.) and  $\text{SmI}_2/\text{THF}$  (0.2 M, 5.3 mL, 1.06 mmol, 4.0 eq.) for 2 h. Purification of the crude mixture through column chromatography on  $\text{SiO}_2$  ( $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ : 70/30) afforded the product (80.0 mg, 81%) as a white solid.

**TLC ( $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ : 50/50):**  $R_f = 0.37$  (UV active;  $\text{KMnO}_4$ , stains white).

**m. p.** = 139-142  $^\circ\text{C}$  ( $\text{CH}_2\text{Cl}_2$ ).

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 7.33-7.21 (m, 5H, H-14, H-15, H-16, H-17, H-18), 4.43 (t,  $J = 8.1$  Hz, 2H, H-2), 4.02 (t,  $J = 8.1$  Hz, 2H, H-3), 3.44 (s, 2H, H-11), 3.19 (t,  $J = 7.8$  Hz, 2H, H-5), 3.07 (s, 3H, H-12), 2.89-2.82 (m, 2H, H-9), 2.49-2.29 (m, 3H, H-6, H-8a), 2.17 (ddd,  $J = 14.1, 10.0, 7.0$  Hz, 1H, H-8b).

**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 171.3 (C-4), 153.7 (C-1), 139.7 (C-13), 128.8 (C-14, C-18), 128.6 (C-15, C-17), 126.7 (C-16), 120.6 (C-10), 62.4 (C-2), 56.8 (C-11), 43.7 (C-12), 42.6 (C-3), 39.2 (C-7), 38.4 (C-8), 31.0 (C-5 or C-6 or C-9), 30.8 (C-5 or C-6 or C-9), 30.7 (C-5 or C-6 or C-9).

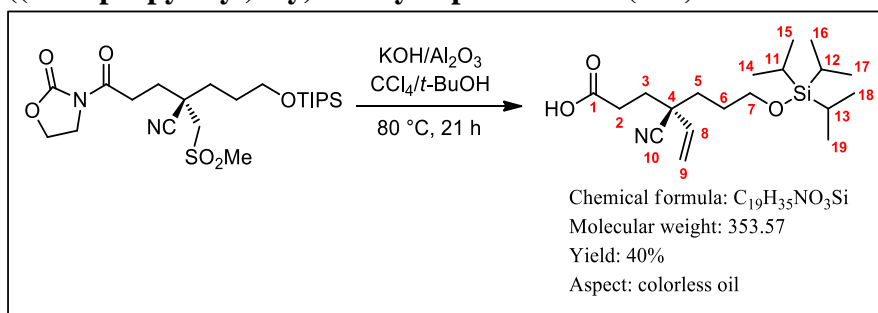
**IR (solution in  $\text{CH}_2\text{Cl}_2$ , thin film, KBr):**  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 2930 (C-H), 2237 ( $\text{C}\equiv\text{N}$ ), 1776 (4-C=O), 1698 (1-C=O), 1391, 1311, 1226, 1140, 1039, 759, 735, 702.

**HRMS (TOF, ES+):** calculated for  $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_5\text{SNa}$   $[\text{M}+\text{Na}]^+$  401.1141, found 401.1135.

$[\alpha]_{\text{D}}^{23} = -1.94$  ( $c = 0.086$ ,  $\text{CHCl}_3$ ).

## 11. Ramberg-Bäcklund reaction

**(R)-4-cyano-7-((triisopropylsilyl)oxy)-4-vinylheptanoic acid (235)**



In a dried two-necked flask, **199n** (61.0 mg, 0.12 mmol, 1.0 eq.) was diluted in  $\text{CCl}_4/t\text{-BuOH}$ : 1/1 (2.2 mL, 0.05 M).  $\text{KOH}/\text{Al}_2\text{O}_3$  (308.0 mg, 250 mg/0.1 mmol of substrate) was added and the reaction mixture was stirred at 80  $^\circ\text{C}$  silicon oil bath temperature for 21 h. The reaction was quenched with aqueous  $\text{HCl}$  (1.0 M) and the aqueous layer was extracted with  $\text{EtOAc}$  (x 3). The combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The



obtained crude mixture was purified through column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 98/2) to afford the alkene as a colorless oil (17.0 mg, 40%).

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 90/10):** *R<sub>f</sub>* = 0.43 (UV active; KMnO<sub>4</sub>, stains yellow).

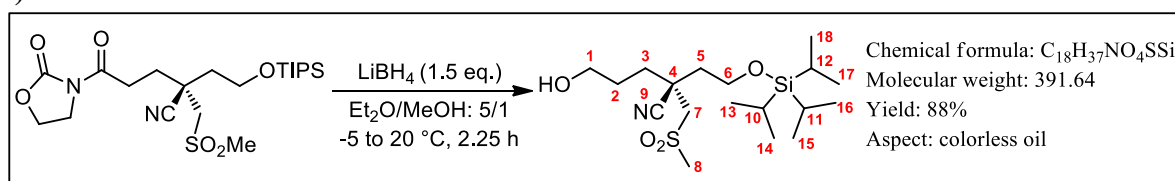
**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 5.52 (dd, *J* = 17.0, 0.6 Hz, 1H, H-9a), 5.47-5.39 (m, 1H, H-8), 5.35 (dd, *J* = 10.0, 0.6 Hz, 1H, H-9b), 3.75-3.68 (m, 2H, H-7), 2.56 (ddd, *J* = 16.7, 11.0, 5.6 Hz, 1H, H-2a), 2.51-2.45 (m, 1H, H-2b), 2.11 (ddd, *J* = 14.0, 10.8, 5.5 Hz, 1H, H-3a), 1.94-1.80 (m, 2H, H-3b, H-5a), 1.76-1.61 (m, 3H, H-5b, H-6), 1.13-1.00 (m, 21H, H-11, H-12, H-13, H-14, H-15, H-16, H-17, H-18, H-19).

**<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 177.2 (C-1), 136.0 (C-8), 120.5 (C-10), 118.4 (C-9), 62.6 (C-7), 45.7 (C-4), 35.7 (C-5), 33.4 (C-3), 29.8 (C-2), 28.7 (C-6), 18.2 (C-14, C-15, C-16, C-17, C-18, C-19), 12.1 (C-11, C-12, C-13).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 3200 (br, OH), 2944 (-C-H), 2892 (-C-H), 2867 (-C-H), 2238 (C≡N), 1716 (1-C=O), 1462, 1104.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>19</sub>H<sub>35</sub>NO<sub>3</sub>SiNa [M+Na]<sup>+</sup> 376.2278, found 376.2278.

**(*R*)-5-hydroxy-2-((methylsulfonyl)methyl)-2-(2-((triisopropylsilyl)oxy)ethyl)pentanenitrile (237)**



In a dried two-necked flask, **199e** (993.0 mg, 2.09 mmol, 1.0 eq.) was dissolved in dry Et<sub>2</sub>O/MeOH: 5/1 (18.9/3.7 mL, 0.1 M), then the reaction was cooled down to -5 °C. LiBH<sub>4</sub> (68.4 mg, 3.14 mmol, 1.5 eq.) was added and the mixture was stirred for 5 min at the same temperature then at 20 °C. A complete conversion was observed after 2.25 h. Aqueous HCl (1.0 M) was added at 0 °C, then the product was extracted with EtOAc. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. Purification through column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 90/10 to 70/30) afforded the product (726.0 mg, 88%) as a colorless oil.

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 50/50):** *R<sub>f</sub>* = 0.35 (UV inactive; KMnO<sub>4</sub>, stains white-red).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 4.12-3.97 (m, 2H, H-6), 3.80-3.70 (m, 3H, H-1, H-7a), 3.39 (d, *J* = 14.9 Hz, 1H, H-7b), 3.07 (s, 3H, H-8), 2.29-2.03 (m, 4H, H-3, H-5), 1.86-1.76 (m, 2H, H-2), 1.53 (t, *J* = 5.2 Hz, 1H, OH), 1.11-1.07 (m, 21H, H-10, H-11, H-12, H-13, H-14, H-15, H-16, H-17, H-18, H-19).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 120.9 (C-9), 62.0 (C-1), 60.3 (C-6), 59.0 (C-7), 43.5 (C-8), 38.7 (C-4), 38.6 (C-3), 33.3 (C-5), 27.7 (C-2), 18.1 (C-13, C-14, C-15, C-16, C-17, C-18), 11.9 (C-10, C-11, C-12).

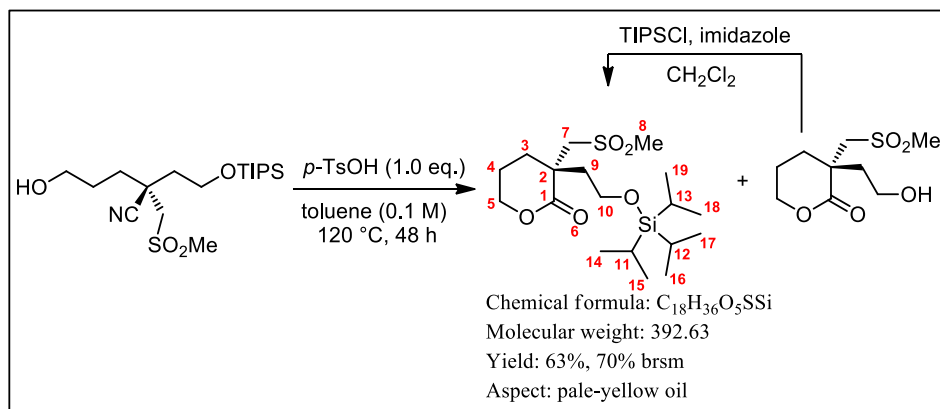
**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 3340 (br, OH), 2943 (-C-H), 2867 (-C-H), 2238 (C≡N), 1463, 1310, 1140, 1107, 883, 683.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>18</sub>H<sub>37</sub>NO<sub>4</sub>SSiNa [M+Na]<sup>+</sup> 414.2104, found 414.2104.

**[ $\alpha$ ]<sub>D</sub><sup>25</sup> = -0.91** (*c* = 0.106, CHCl<sub>3</sub>).

## 12. Formation of lactone

**(*R*)-3-((methylsulfonyl)methyl)-3-(2-((triisopropylsilyl)oxy)ethyl)tetrahydro-2*H*-pyran-2-one (240a)**



To a dried two-necked flask equipped with a condenser and a dean stark system filled with dry toluene, **237** (222.0 mg, 0.57 mmol, 1.0 eq.) dissolved in dry toluene (5.7 mL, 0.1 M) was introduced, followed by *p*-TsOH.H<sub>2</sub>O (108.0 mg, 0.57 mmol, 1.0 eq.). The mixture was heated at 120 °C silicon oil bath temperature, then the solvent was concentrated under reduced pressure and the crude was purified through column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 99/1 to 95/5 to 90/10) to afford the product (142.0 mg, 63%, 70% brsm) as a pale-yellow oil. 9% of the starting material were recovered.

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 90/10):**  $R_f$  = 0.88 (UV inactive; KMnO<sub>4</sub>, stains white-red).

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 4.47 (td,  $J$  = 9.4, 3.6 Hz, 1H, H-5a), 4.31 (q,  $J$  = 8.3 Hz, 1H, H-5b), 3.70 (td,  $J$  = 5.9, 1.2 Hz, 2H, H-10), 3.40 (q<sub>AB</sub>,  $J$  = 14.6 Hz, 2H, H-7), 2.99 (s, 3H, H-8), 2.96-2.88 (m, 1H, H-9a), 2.29 (ddd,  $J$  = 13.4, 8.0, 3.6 Hz, 1H, H-9b), 1.89-1.80 (m, 2H, H-4), 1.70-1.53 (m, 2H, H-3), 1.11-1.02 (m, 21H, H-11, H-12, H-13, H-14, H-15, H-16, H-17, H-18, H-19).

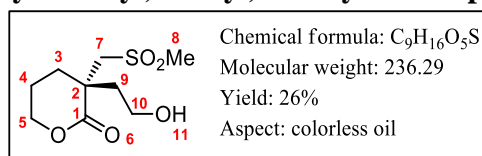
**<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 178.9 (C-1), 65.9 (C-5), 62.6 (C-10), 59.2 (C-7), 44.8 (C-2), 44.1 (C-8), 34.0 (C-4), 30.9 (C-9), 27.6 (C-3), 18.1 (C-14, C-15, C-16, C-17, C-18, C-19), 12.0 (C-11, C-12, C-13).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2942 (-C-H), 2866 (-C-H), 1767 (1-C=O), 1462, 1307, 1138, 1106, 882, 681.

**HRMS (TOF, APCI+):** calculated for C<sub>18</sub>H<sub>37</sub>O<sub>5</sub>SSi [M+H]<sup>+</sup> 393.2125, found 393.2137.

$[\alpha]_D^{25}$  = -33.73 ( $c$  = 0.08, CHCl<sub>3</sub>).

### (*R*)-3-(2-hydroxyethyl)-3-((methylsulfonyl)methyl)tetrahydro-2*H*-pyran-2-one (**253**)



The hydroxypyranone was obtained as a side product alongside with TIPS-protected lactone **240a**, as a colorless oil (35.0 mg, 26%).

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 95/5):**  $R_f$  = 0.26 (UV inactive; KMnO<sub>4</sub>, stains white).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 4.46 (td,  $J$  = 9.4, 3.7 Hz, 1H, H-5a), 4.32 (dt,  $J$  = 9.1, 8.1 Hz, 1H, H-5b), 3.65 (t,  $J$  = 6.0 Hz, 2H, H-10), 3.40 (q<sub>AB</sub>,  $J$  = 9.9 Hz, 2H, H-7), 3.00 (s, 3H, H-8), 2.97-2.83 (m, 1H, H-9a), 2.32 (ddd,  $J$  = 13.5, 7.9, 3.7 Hz, 1H, H-9b), 1.90-1.78 (m, 3H, H-4, H-11), 1.71-1.56 (m, 2H, H-3).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 178.8 (C-1), 66.0 (C-5), 62.0 (C-10), 58.8 (C-7), 44.7 (C-2), 44.0 (C-8), 33.5 (C-4), 31.3 (C-9), 27.1 (C-3).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 3426 (br, OH), 2928 (-C-H), 1757 (1-C=O), 1299, 1136, 1026.

**HRMS (TOF, APCI-):** calculated for C<sub>9</sub>H<sub>15</sub>O<sub>5</sub>S [M-H]<sup>+</sup> 235.0645, found 235.0642.

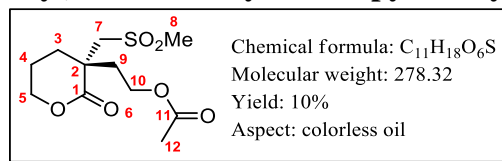
$[\alpha]_D^{25}$  = -30.75 ( $c$  = 0.49, CHCl<sub>3</sub>).

### Reprotection of the hydroxypyranone **253**:

To a dried two-necked flask under inert atmosphere and set to 0 °C, hydroxypyranone **253** (66.0 mg, 0.28 mmol, 1.0 eq.) was introduced, followed by dry CH<sub>2</sub>Cl<sub>2</sub> (0.6 mL, 0.5 M), imidazole (25.0 mg,

0.36 mmol, 1.3 eq.), and TIPSCl (65.0  $\mu$ L, 0.3 mmol, 1.1 eq.) was added slowly. The mixture was stirred at 20 °C and the evolution of the reaction was followed by TLC. After 1.5 h, the reaction was quenched with water and extracted with  $\text{CH}_2\text{Cl}_2$ . The organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The crude mixture was purified through column chromatography on  $\text{SiO}_2$  ( $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ : 90/10) and the desired product (100.0 mg, 91%) was obtained as a pale-yellow oil.

**(*R*)-2-(3-((methylsulfonyl)methyl)-2-oxotetrahydro-2*H*-pyran-3-yl)ethyl acetate (**254**)**



To a dried two-necked flask equipped with a condenser, **237** (300.0 mg, 0.76 mmol, 1.0 eq.) dissolved in dry THF (7.6 mL, 0.1 M) was introduced, followed by *p*-TsOH. $\text{H}_2\text{O}$  (291.0 mg, 1.53 mmol, 2.0 eq.). The mixture was heated at 66 °C silicon oil bath temperature for 24 h. The solvent was then concentrated under reduced pressure and the crude mixture was purified through column chromatography on  $\text{SiO}_2$  ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ : 99/1 to 95/5) to afford the acetylated product **254** (29.0 mg, 10%) as a colorless oil, with **240a** (2.5 mg, 1%) and **253** (97.0 mg, 54%). 1% of the starting material was recovered.

**TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ : 96/4):**  $R_f$  = 0.6 (UV inactive;  $\text{KMnO}_4$ , stains white).

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 4.45 (td,  $J$  = 9.4, 3.7 Hz, 1H, H-5a), 4.30 (q,  $J$  = 8.6 Hz, 1H, H-5b), 4.05 (t,  $J$  = 5.9 Hz, 2H, H-10), 3.37 (q<sub>AB</sub>,  $J$  = 9.9 Hz, 2H, H-7), 2.98 (s, 3H, H-8), 2.95-2.85 (m, 1H, H-9a), 2.33-2.24 (m, 1H, H-9b), 2.03 (s, 3H, H-12), 1.93-1.61 (m, 4H, H-4, H-3).

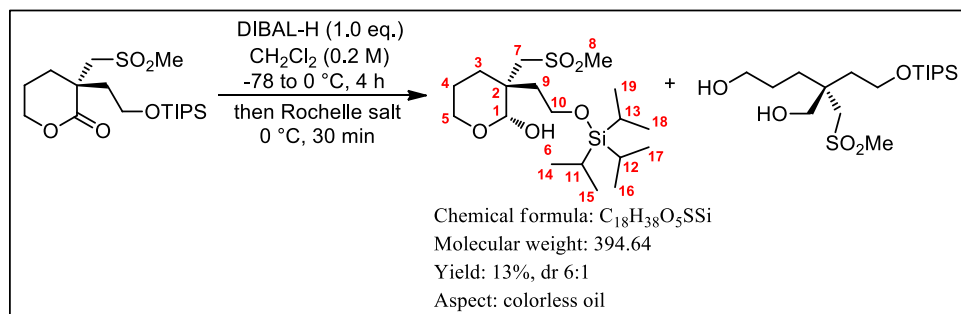
**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 178.3 (C-1), 171.0 (C-11), 65.9 (C-5), 63.6 (C-10), 58.5 (C-7), 44.5 (C-2), 44.0 (C-8), 33.5 (C-4), 31.3 (C-9), 23.5 (C-3), 21.0 (C-12).

**IR (solution in  $\text{CH}_2\text{Cl}_2$ , thin film, KBr):**  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 2928 (C-H), 1757 (1-C=O, 11-C=O), 1299, 1136, 1026.

**HRMS (TOF, ES<sup>+</sup>):** calculated for  $\text{C}_{11}\text{H}_{18}\text{O}_6\text{SNa}$   $[\text{M}+\text{Na}]^+$  301.0716, found 301.0722.

$[\alpha]_{\text{D}}^{25}$  = -49.73 ( $c$  = 0.093,  $\text{CHCl}_3$ ).

**(3*R*)-3-((methylsulfonyl)methyl)-3-(2-((triisopropylsilyl)oxy)ethyl)tetrahydro-2*H*-pyran-2-ol (**241a**)**



In a dried two-necked flask, **240a** (224.0 mg, 0.57 mmol, 1.0 eq.) was dissolved in dry  $\text{CH}_2\text{Cl}_2$  (2.8 mL, 0.2 M) then the reaction mixture was cooled down to -78 °C. DIBAL-H (1.0 M in hexane, 0.6 mL, 0.57 mmol, 1.0 eq.) was added dropwise at this temperature. After 30 min the reaction mixture was stirred at 0 °C for another 4 h. Rochelle salt (10.0 mL) was then added at 0 °C, and the mixture was stirred for 30 min then extracted with EtOAc. Purification through column chromatography on  $\text{SiO}_2$  ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ : 99/1) afforded the product (30.0 mg, 13%, dr 6:1) as a colorless oil.

**TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ : 95/5):**  $R_f$  = 0.45 (UV inactive;  $\text{KMnO}_4$ , stains white).

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 5.33 (s, 1H, H-1, major diastereomer), 5.30 (s, 0.16H, H-1, minor diastereomer), 4.11 (td,  $J$  = 8.0, 5.2 Hz, 1H, H-5a), 3.91 (q,  $J$  = 8.3 Hz, 1H, H-5b), 3.76-3.65 (m, 2H, H-10), 3.40 (q,  $J$  = 11.6 Hz, 2H, H-7), 3.13-3.04 (m, 1H, H-6), 2.97 (s, 3H, H-8), 2.01-1.96 (m, 2H, H-9), 1.82-1.66 (m, 4H, H-3, H-4), 1.10-1.03 (m, 21H, H-11, H-12, H-13, H-14, H-15, H-16, H-17, H-18, H-19).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):****Major diastereomer:**

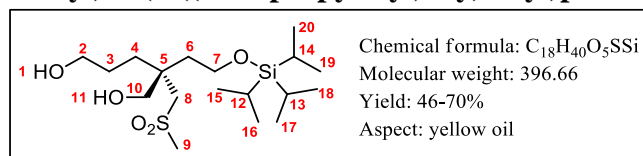
$\delta$  (ppm) = 101.5 (C-1), 65.9 (C-5), 63.3 (C-10), 57.0 (C-7), 49.5 (C-2), 44.0 (C-8), 33.4 (C-4), 29.4 (C-9), 28.0 (C-3), 18.1 (C-14, C-15, C-16, C-17, C-18, C-19), 12.1 (C-11, C-12, C-13).

**Minor diastereomer:**

$\delta$  (ppm) = 100.9 (C-1), 66.0 (C-5), 63.6 (C-10), 56.7 (C-7), 50.5 (C-2), 44.3 (C-8), 33.6 (C-4), 28.7 (C-9), 27.9 (C-3), 18.1 (C-14, C-15, C-16, C-17, C-18, C-19), 12.1 (C-11, C-12, C-13).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 3445 (br, OH), 2943 (-C-H), 2866 (-C-H), 1462, 1303, 1135, 1102, 882, 681.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>18</sub>H<sub>38</sub>O<sub>5</sub>SSiNa [M+Na]<sup>+</sup> 417.2101, **found** 417. 2118.

**(R)-2-((methylsulfonyl)methyl)-2-(2-(((triisopropylsilyl)oxy)ethyl)pentane-1,5-diol (255)**

The diol **255** was obtained as a side product alongside with the lactol **241a** as a yellow oil (105.0 mg, 46%).

**Another method to synthesize the diol 255:**

In a dried two-necked flask, **240a** (39.0 mg, 0.1 mmol, 1.0 eq.) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL, 0.2 M) then the reaction mixture was cooled down to -78 °C. DIBAL-H (1.0 M in hexane, 0.1 mL, 0.1 mmol, 1.0 eq.) was added dropwise at this temperature. After 30 min the reaction mixture was stirred at 0 °C for another 2.5 h. Rochelle salt (5.0 mL) was then added at 0 °C, and the mixture was stirred for 12 h at 20 °C then extracted with EtOAc. Purification through column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 99/1) afforded the product (28.0 mg, 70%) as a yellow oil.

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 95/5):**  $R_f$  = 0.38 (UV inactive; KMnO<sub>4</sub>, stains white).

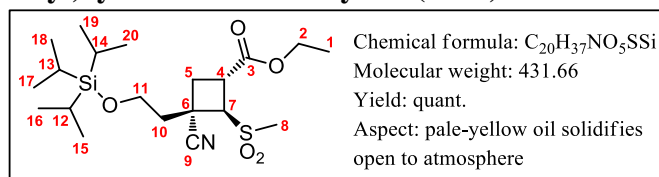
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 3.79-3.74 (m, 2H, H-7), 3.70-3.62 (m, 4H, H-2, H-10), 3.33 (d,  $J$  = 14.0 Hz, 1H, H-8a), 3.17 (d,  $J$  = 14.0 Hz, 1H, H-8b), 2.96 (s, 3H, H-9), 2.02 (br s, 1H, H-11), 1.90-1.76 (m, 2H, H-6), 1.68-1.48 (m, 4H, H-3, H-4), 1.09-1.00 (m, 21H, H-12, H-13, H-14, H-15, H-16, H-17, H-18, H-19, H-20).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 66.8 (C-10), 63.5 (C-2), 58.5 (C-7), 57.8 (C-8), 44.1 (C-9), 42.3 (C-5), 31.0 (C-6), 33.3 (C-4), 26.5 (C-3), 18.1 (C-15, C-16, C-17, C-18, C-19, C-20), 12.0 (C-12, C-13, C-14).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 3406 (br, OH), 2943 (-C-H), 2867 (-C-H), 1462, 1296, 1131, 1106, 882, 682.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>18</sub>H<sub>40</sub>O<sub>5</sub>SSiNa [M+Na]<sup>+</sup> 419.2257, **found** 419.2261.

$[\alpha]_D^{25}$  = -99.47 ( $c$  = 0.066, CHCl<sub>3</sub>).

**13. Transesterification reaction****(1R,2R,3R)-ethyl 3-cyano-2-(methylsulfonyl)-3-(2-(((triisopropylsilyl)oxy)ethyl)cyclobutanecarboxylate (260a)**

According to the general procedure (**L**), from cyclobutane **181i** (4.6 g, 9.74 mmol, 1.0 eq.), distilled EtOH (50.0 mL, 0.2 M), and DMAP (595.0 mg, 4.87 mmol, 0.5 eq.) for 12 h. Purification through short column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc: 70/30) afforded the desired product (4.27 g, quant.) as a pale-yellow oil solidifies open to atmosphere.

**TLC (cyclohexane/EtOAc: 70/30):**  $R_f$  = 0.4 (UV inactive; KMnO<sub>4</sub>, stains red-white).

**m. p.** = 50.8-53.5 °C (pentane/EtOAc).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 4.33 (d,  $J$  = 9.6 Hz, 1H, H-7), 4.22 (qd,  $J$  = 7.1, 1.0 Hz, 2H, H-2), 4.03-3.98 (m, 2H, H-11), 3.69 (q,  $J$  = 9.8 Hz, 1H, H-4), 3.02-2.95 (m, 4H, H-8, H-5a), 2.68 (dd,  $J$  = 11.9, 9.8 Hz, 1H, H-5b), 2.43 (t,  $J$  = 6.0 Hz, 2H, H-10), 1.29 (t,  $J$  = 7.1 Hz, 3H, H-1), 1.11-0.97 (m, 21H, H-12, H-13, H-14, H-15, H-16, H-17, H-18, H-19, H-20).

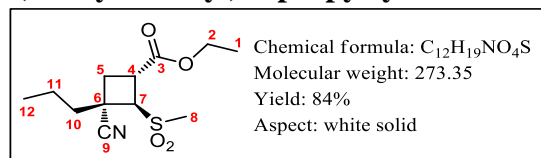
**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 170.9 (C-3), 120.7 (C-9), 62.3 (C-2), 62.1 (C-7), 60.7 (C-11), 42.3 (C-8), 37.0 (C-4), 34.9 (C-6), 33.0 (C-5), 32.6 (C-10), 18.1 (C-15, C-16, C-17, C-18, C-19, C-20), 14.2 (C-1), 11.9 (C-12, C-13, C-14).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2944 (-C-H), 2867 (-C-H), 2238 (C $\equiv$ N), 1735 (3-C=O), 1464, 1315, 1237, 1148, 1132, 1103, 882, 744, 683.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>20</sub>H<sub>37</sub>NO<sub>5</sub>SSiNa [M+Na]<sup>+</sup> 454.20539, found 454.20525.

**$[\alpha]_D^{25}$**  = -108.25 ( $c$  = 0.1, CHCl<sub>3</sub>).

#### (1*R*,2*R*,3*S*)-ethyl 3-cyano-2-(methylsulfonyl)-3-propylcyclobutanecarboxylate (260b)



According to the general procedure (**L**), from cyclobutane **181b** (6.31 g, 20.0 mmol, 1.0 eq.), distilled EtOH (60.0 mL, 0.33 M), and DMAP (1.22 g, 10.0 mmol, 0.5 eq.) for 7 h. Purification through short column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc: 70/30) afforded the desired product (4.57 g, 84%) as a white solid.

**TLC (cyclohexane/EtOAc: 70/30):**  $R_f$  = 0.81 (UV inactive; KMnO<sub>4</sub>, stains red-white).

**m. p.** = 112.4-114.7 °C (pentane/EtOAc).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 4.32-4.18 (m, 3H, H-2, H-7), 3.68 (q,  $J$  = 9.7 Hz, 1H, H-4), 2.97 (s, 3H, H-8), 2.69-2.61 (m, 1H, H-5a), 2.58-2.49 (m, 1H, H-5b), 2.36-2.23 (m, 1H, H-10a), 2.04 (ddd,  $J$  = 13.8, 11.8, 4.7 Hz, 1H, H-10b), 1.69-1.36 (m, 2H, H-11), 1.30 (t,  $J$  = 7.1 Hz, 3H, H-1), 1.04 (t,  $J$  = 7.3 Hz, 3H, H-12).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 170.7 (C-3), 120.9 (C-9), 62.1 (C-2), 61.7 (C-7), 42.2 (C-8), 37.1 (C-4), 35.8 (C-6), 32.7 (C-10), 31.7 (C-5), 18.5 (C-11), 14.1 (C-1), 13.9 (C-12).

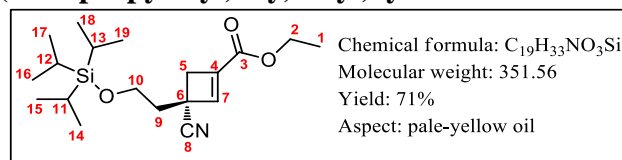
**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2966 (-C-H), 2876 (-C-H), 2237 (C $\equiv$ N), 1733 (3-C=O), 1314, 1148, 1037, 756.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>12</sub>H<sub>19</sub>NO<sub>4</sub>SiNa [M+Na]<sup>+</sup> 296.0927, found 296.0923.

**$[\alpha]_D^{25}$**  = +12.46 ( $c$  = 0.14, CHCl<sub>3</sub>).

## 14. Base-mediated sulfone elimination reaction

#### (*S*)-ethyl 3-cyano-3-(2-((triisopropylsilyl)oxy)ethyl)cyclobut-1-enecarboxylate (258a)



According to the general procedure (**M**), from cyclobutane **260a** (4.27 g, 9.9 mmol, 1.0 eq.), dry DMF (50.0 mL, 0.2 M), and Cs<sub>2</sub>CO<sub>3</sub> (6.4 g, 19.8 mmol, 2.0 eq.) for 14 h. Purification through short column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc: 90/10) afforded the desired cyclobutene (2.5 g, 71%) as a pale-yellow oil.

**TLC (cyclohexane/EtOAc: 80/20):**  $R_f$  = 0.75 (UV active; KMnO<sub>4</sub>, stains yellow).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 6.77 (s, 1H, H-7), 4.22 (q,  $J$  = 16.6 Hz, 2H, H-2), 3.95-3.97 (m, 2H, H-10), 3.21 (d,  $J$  = 13.8 Hz, 1H, H-5a), 2.90 (d,  $J$  = 13.8 Hz, 1H, H-5b), 2.11-1.94 (m, 2H, H-9), 1.30 (t,  $J$  = 7.1 Hz, 3H, H-1), 1.10-1.05 (m, 21H, H-11, H-12, H-13, H-14, H-15, H-16, H-17, H-18, H-19).



**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 161.7 (C-3), 144.2 (C-7), 139.2 (C-4), 120.2 (C-8), 61.1 (C-2), 60.7 (C-10), 41.3 (C-5), 38.8 (C-9), 37.4 (C-6), 18.1 (C-14, C-15, C-16, C-17, C-18, C-19), 14.3 (C-1), 12.0 (C-11, C-12, C-13).

**IR (solution in  $\text{CH}_2\text{Cl}_2$ , thin film, KBr):**  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 2944 (C-H), 2867 (C-H), 2234 ( $\text{C}\equiv\text{N}$ ), 1727 (3-C=O), 1464, 1319, 1106, 882, 735, 682.

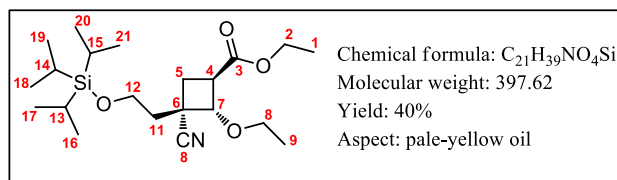
**HRMS (TOF, ES $^+$ ):** calculated for  $\text{C}_{19}\text{H}_{33}\text{NO}_3\text{SiNa}$   $[\text{M}+\text{Na}]^+$  374.2121, **found** 374.2126.

$[\alpha]_{\text{D}}^{25} = -31.53$  ( $c = 0.1$ ,  $\text{CHCl}_3$ ).

### Procedure for “one-pot” base-mediated sulfone elimination reaction:

In a dried two-necked flask, the cyclobutane **181i** (105.0 mg, 0.22 mmol, 1.0 eq.) was dissolved in distilled EtOH (2.2 mL, 0.1 M), then  $\text{K}_2\text{CO}_3$  (61.5 mg, 0.44 mmol, 2.0 eq.) was added and the reaction mixture was stirred at 20 °C for 12 h. After completion, the solvent was concentrated under reduced pressure and the crude mixture was purified through short column chromatography on  $\text{SiO}_2$  (cyclohexane/EtOAc: 95/5) to afford the desired cyclobutene **258a** (34.0 mg, 44%) as a pale-yellow oil.

### (1*R*,2*S*,3*R*)-ethyl 3-cyano-2-ethoxy-3-(2-((triisopropylsilyl)oxy)ethyl)cyclobutanecarboxylate (**259a**)



In a dried two-necked flask, the cyclobutane **181i** (515.0 mg, 1.2 mmol, 1.0 eq.) was dissolved in distilled EtOH (12.0 mL, 0.1 M), then  $\text{K}_2\text{CO}_3$  (497.5 mg, 3.6 mmol, 3.0 eq.) was added at 0 °C and the reaction mixture was allowed to warm to 20 °C. After 47 h, total consumption of the starting material was observed. The solvent was concentrated under reduced pressure and the crude mixture was purified through column chromatography on  $\text{SiO}_2$  (cyclohexane/EtOAc: 95/5 to 90/10) to afford the side product (190.0 mg, 40%) as a pale-yellow oil. Only 1% (5.0 mg) of the desired product **258a** was isolated.

**TLC (cyclohexane/EtOAc: 80/20):**  $R_f = 0.68$  (UV inactive;  $\text{KMnO}_4$ , stains yellow).

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 4.16 (qd,  $J = 7.2, 1.1$  Hz, 2H, H-2), 3.96-3.86 (m, 3H, H-7, H-12), 3.58 (q,  $J = 7.0$  Hz, 2H, H-8), 3.28-3.19 (m, 1H, H-4), 2.52 (ddd,  $J = 12.0, 9.6, 0.9$  Hz, 1H, H-5a), 2.11-1.92 (m, 3H, H-5b, H-11), 1.25 (dt,  $J = 8.9, 7.1$  Hz, 6H, H-1, H-9), 1.13-1.02 (m, 21H, H-13, H-14, H-15, H-16, H-17, H-18, H-19, H-20, H-21).

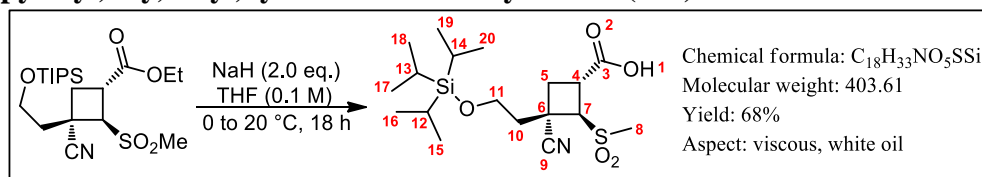
**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 172.3 (C-3), 120.7 (C-10), 79.6 (C-7), 65.4 (C-8), 61.1 (C-12), 60.2 (C-2), 44.2 (C-4), 41.5 (C-6), 40.2 (C-11), 28.7 (C-5), 18.1 (C-16, C-17, C-18, C-19, C-20, C-21), 15.2 (C-9), 14.3 (C-1), 12.0 (C-13, C-14, C-15).

**IR (solution in  $\text{CH}_2\text{Cl}_2$ , thin film, KBr):**  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 2943 (C-H), 2867 (C-H), 2236 ( $\text{C}\equiv\text{N}$ ), 1733 (3-C=O), 1463, 1199, 1108, 882, 683.

**HRMS (TOF, ES $^+$ ):** calculated for  $\text{C}_{21}\text{H}_{39}\text{NO}_4\text{SiNa}$   $[\text{M}+\text{Na}]^+$  420.25406, **found** 420.25397.

$[\alpha]_{\text{D}}^{25} = -27.93$  ( $c = 0.18$ ,  $\text{CHCl}_3$ ).

### (1*R*,2*R*,3*R*)-3-cyano-2-(methylsulfonyl)-3-(2-((triisopropylsilyl)oxy)ethyl)cyclobutanecarboxylic acid (**261**)



In a dried two-necked flask, the cyclobutane **260a** (311.0 mg, 0.72 mmol, 1.0 eq.) was dissolved in dry THF (7.2 mL, 0.1 M), then NaH (60% suspension in oil, 26.0 mg, 1.08 mmol, 2.0 eq.) was added at 0 °C. The reaction was stirred at 20 °C for 18 h, then quenched with sat.  $\text{NaHCO}_3$  (2 mL) and

extracted with EtOAc (5 mL). The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude mixture was washed with CH<sub>2</sub>Cl<sub>2</sub> and dried under vacuum to afford the side-product (200.0 mg, 68%) as a viscous white oil.

**TLC:** -

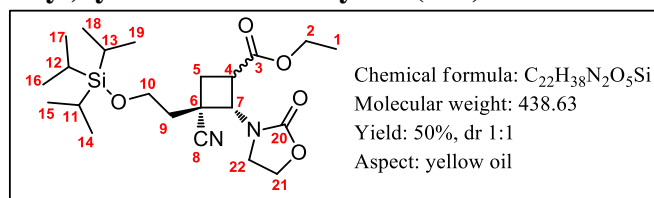
**<sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD):**  $\delta$  (ppm) = 5.99 (d,  $J$  = 9.7 Hz, 1H, H-7), 5.65-5.48 (m, 2H, H-11), 5.00 (q,  $J$  = 9.9 Hz, 1H, H-4), 4.59 (s, 3H, H-8), 4.41-4.33 (m, 1H, H-5a), 4.11 (dd,  $J$  = 11.5, 9.9 Hz, 1H, H-5b), 3.97 (t,  $J$  = 6.1 Hz, 2H, H-10), 2.68-2.65 (m, 21H, H-12, H-13, H-14, H-15, H-16, H-17, H-18, H-19, H-20).

**<sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>OD):**  $\delta$  (ppm) = 177.8 (C-3), 122.6 (C-9), 64.7 (C-7), 61.7 (C-11), 42.3 (C-8), 41.2 (C-4), 34.6 (C-6), 34.5 (C-5, C-10), 18.5 (C-15, C-16, C-17, C-18, C-19, C-20), 13.0 (C-12, C-13, C-14).

**IR (solution in MeOH, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 3422 (br, OH), 2943 (-C-H), 2867 (-C-H), 2236 (C $\equiv$ N), 1597 (3-C=O), 1462, 1412, 1305, 1144, 882, 682.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>18</sub>H<sub>33</sub>NO<sub>5</sub>SSiNa [M+Na]<sup>+</sup> 426.17409, **found** 426.17289.  $[\alpha]_D^{25}$  = +76.1 ( $c$  = 0.08, MeOH).

**(2*S*,3*S*)-ethyl 3-cyano-2-(2-oxooxazolidin-3-yl)-3-(2-((triisopropylsilyl)oxy)ethyl)cyclobutanecarboxylate (262)**



According to the general procedure (**L**), from cyclobutane **181i** (1.0 g, 2.11 mmol, 1.0 eq.), distilled EtOH (30.0 mL, 0.07 M), and DMAP (128.0 mg, 1.05 mmol, 0.5 eq.) for 16 h. the solvents were evaporated under reduced pressure, then the crude cyclobutane (1.17 g, 2.72 mmol, 1.0 eq.) was dissolved in dry DMF (27.2 mL, 0.1 M), then Cs<sub>2</sub>CO<sub>3</sub> (1.77 g, 5.44 mmol, 2.0 eq.) was added and the reaction mixture was heated at 70 °C silicon oil bath temperature. The consumption of the starting material was followed by TLC. After 16 h, the solvent was concentrated under reduced pressure and the crude as a mixture of two diastereomers (dr 1:1) was purified through column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc: 80/20) to afford the first diastereomer (304.0 mg, 25%) and the second diastereomer (300.0 mg, 25%) as yellow oils.

**For the first diastereomer (trans diastereomer):**

**TLC (cyclohexane/EtOAc: 70/30):**  $R_f$  = 0.47 (UV inactive; KMnO<sub>4</sub>, stains yellow).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 4.46-4.38 (m, 3H, H-7, H-21), 4.25-4.14 (m, 3H, H-2, H-22a), 3.92-3.88 (m, 2H, H-10), 3.79-3.70 (m, 1H, H-22b), 3.63-3.53 (m, 1H, H-4), 2.59 (ddd,  $J$  = 12.1, 9.2, 0.8 Hz, 1H, H-5a), 2.28 (dd,  $J$  = 12.1, 10.5 Hz, 1H, H-5b), 2.16 (dt,  $J$  = 14.4, 4.4 Hz, 1H, H-9a), 2.07-1.97 (m, 1H, H-9b), 1.27 (t,  $J$  = 7.1 Hz, 3H, H-1), 1.09-1.04 (m, 21H, H-11, H-12, H-13, H-14, H-15, H-16, H-17, H-18, H-19).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 170.6 (C-3), 157.8 (C-20), 121.8 (C-8), 62.7 (C-21), 61.5 (C-2), 60.0 (C-10), 57.6 (C-7), 42.6 (C-22), 41.6 (C-4), 40.5 (C-9), 39.9 (C-6), 31.0 (C-5), 18.1 (C-14, C-15, C-16, C-17, C-18, C-19), 14.2 (C-1), 12.0 (C-11, C-12, C-13).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2943 (-C-H), 2867 (-C-H), 2233 (C $\equiv$ N), 1753 (br, 3-C=O, 20-C=O), 1463, 1419, 1224, 1103, 882, 683.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>22</sub>H<sub>38</sub>N<sub>2</sub>O<sub>5</sub>SiNa [M+Na]<sup>+</sup> 461.2442, **found** 461.2436.  $[\alpha]_D^{25}$  = -29.52 ( $c$  = 0.27, CHCl<sub>3</sub>).

**For the second diastereomer (cis diastereomer):**

**TLC (cyclohexane/EtOAc: 70/30):**  $R_f$  = 0.32 (UV inactive; KMnO<sub>4</sub>, stains yellow).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 4.47 (d,  $J$  = 10.2 Hz, 1H, H-7), 4.38 (t,  $J$  = 8.1 Hz, 2H, H-21), 4.24-4.11 (m, 3H, H-2, H-4), 4.00 (dd,  $J$  = 7.3, 4.8 Hz, 2H, H-10), 3.75-3.64 (m, 2H, H-22), 2.77-2.60 (m, 1H, H-5a), 2.44 (ddd,  $J$  = 11.6, 10.4, 1.4 Hz, 1H, H-5b), 2.20-2.11 (m, 1H, H-9a), 1.87 (dtd,  $J$  = 13.7, 4.6, 1.2 Hz, 1H, H-9b), 1.27 (t,  $J$  = 7.1 Hz, 3H, H-1), 1.10-1.05 (m, 21H, H-11, H-12, H-13, H-14, H-15, H-16, H-17, H-18, H-19).

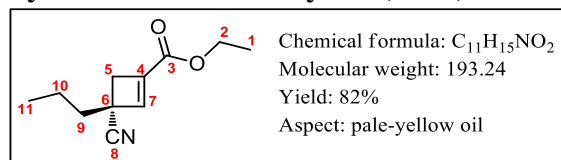
**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 171.5 (C-3), 157.7 (C-20), 121.5 (C-8), 62.2 (C-21), 61.5 (C-2), 60.5 (C-10), 58.3 (C-7), 45.8 (C-22), 37.9 (C-4), 36.9 (C-6), 32.9 (C-9), 30.2 (C-5), 18.1 (C-14, C-15, C-16, C-17, C-18, C-19), 14.2 (C-1), 12.0 (C-11, C-12, C-13).

**IR (solution in  $\text{CH}_2\text{Cl}_2$ , thin film, KBr):**  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 2943 (C-H), 2867 (C-H), 2233 ( $\text{C}\equiv\text{N}$ ), 1753 (br, 3-C=O, 20-C=O), 1463, 1419, 1224, 1103, 882, 683.

**HRMS (TOF, ES $^+$ ):** calculated for  $\text{C}_{22}\text{H}_{38}\text{N}_2\text{O}_5\text{SiNa}$   $[\text{M}+\text{Na}]^+$  461.2442, found 461.2436.

$[\alpha]_{\text{D}}^{25} = -12.07$  ( $c = 0.2$ ,  $\text{CHCl}_3$ ).

### (*R*)-ethyl 3-cyano-3-propylcyclobut-1-enecarboxylate (**258b**)



According to the general procedure (**M**), from cyclobutane **260b** (4.57 g, 16.7 mmol, 1.0 eq.), dry DMF (35.0 mL, 0.4 M), and  $\text{Cs}_2\text{CO}_3$  (10.88 g, 33.4 mmol, 2.0 eq.) for 14 h. Purification through short column chromatography on  $\text{SiO}_2$  (cyclohexane/EtOAc: 80/20) afforded the desired cyclobutene (2.65 g, 82%) as a pale-yellow oil.

**TLC (cyclohexane/EtOAc: 50/50):**  $R_f = 0.61$  (UV active;  $\text{KMnO}_4$ , stains yellow).

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 6.70 (s, 1H, H-7), 4.20 (dq,  $J = 7.2$ , 0.6 Hz, 2H, H-2), 3.18 (d,  $J = 13.8$  Hz, 1H, H-5a), 2.74 (d,  $J = 13.7$  Hz, 1H, H-5b), 1.81-1.73 (m, 2H, H-9), 1.65-1.50 (m, 2H, H-10), 1.28 (td,  $J = 7.1$ , 0.7 Hz, 3H, H-1), 1.00 (t,  $J = 7.3$  Hz, 3H, H-11).

**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 161.6 (C-3), 143.5 (C-7), 140.3 (C-4), 120.5 (C-8), 61.1 (C-2), 40.8 (C-5), 38.9 (C-6), 38.3 (C-9), 19.8 (C-10), 14.3 (C-1), 14.0 (C-11).

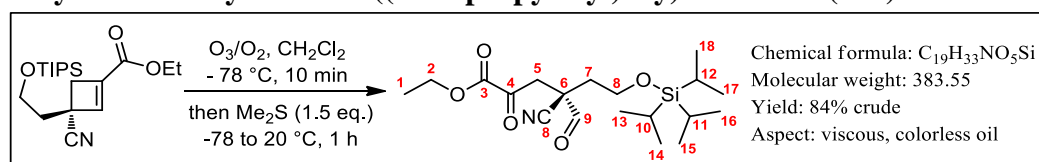
**IR (solution in  $\text{CH}_2\text{Cl}_2$ , thin film, KBr):**  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 2964 (C-H), 2876 (C-H), 2234 ( $\text{C}\equiv\text{N}$ ), 1725 (3-C=O), 1620, 1465, 1370, 1321, 1282, 1233, 1153, 1096.

**HRMS (TOF, ES $^+$ ):** calculated for  $\text{C}_{11}\text{H}_{15}\text{NO}_2\text{Na}$   $[\text{M}+\text{Na}]^+$  216.0995, found 216.0986.

$[\alpha]_{\text{D}}^{25} = +64.76$  ( $c = 0.22$ ,  $\text{CHCl}_3$ ).

## 15. Ring-opening through ozonolysis

### (*S*)-ethyl 4-cyano-4-formyl-2-oxo-6-((triisopropylsilyl)oxy)hexanoate (**266**)



A solution of the cyclobutene **258a** (50.0 mg, 0.14 mmol, 1.0 eq.) in  $\text{CH}_2\text{Cl}_2$  (5.0 mL, 0.028 M) was cooled to  $-78^\circ\text{C}$  and  $\text{O}_3/\text{O}_2$  was bubbled through it until the solution turned blue (10 min). The residual ozone was then discharged by bubbling with oxygen until it became clear again (5 min). Dimethyl sulfide (15.0  $\mu\text{L}$ , 0.21 mmol, 1.5 eq.) was added and the reaction mixture was warmed to  $20^\circ\text{C}$  with continuous stirring for another 1 h. The solvents were concentrated under reduced pressure to obtain the crude product as a viscous, colorless oil (45.0 mg, 84% crude, not stable in isolated form).

**TLC (cyclohexane/EtOAc: 60/40):**  $R_f = 0.37$  (UV inactive;  $\text{KMnO}_4$ , stains yellow).

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 9.84 (s, 1H, H-9), 4.34 (q,  $J = 7.1$  Hz, 2H, H-2), 4.04 (qd,  $J = 10.8$ , 3.2 Hz, 1H, H-8a), 3.91 (ddd,  $J = 10.9$ , 4.6, 3.6 Hz, 1H, H-8b), 3.65 (d,  $J = 19.4$  Hz, 1H, H-5a), 3.55 (dd,  $J = 19.4$ , 1.0 Hz, 1H, H-5b), 2.62 (s, DMSO), 2.22 (ddd,  $J = 13.9$ , 10.3, 4.6 Hz, 1H, H-7a), 1.98 (dt,  $J = 13.8$ , 3.3 Hz, 1H, H-7b), 1.37 (t,  $J = 7.1$  Hz, 3H, H-1), 1.10-1.05 (m, 21H, H-10, H-11, H-12, H-13, H-14, H-15, H-16, H-17, H-18).

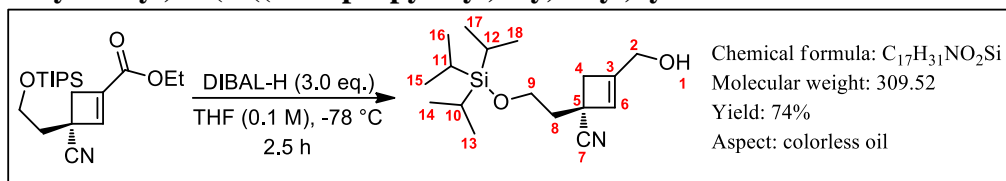
**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 193.2 (C-9), 189.0 (C-4), 159.5 (C-3), 118.4 (C-8), 63.3 (C-2), 59.4 (C-8), 47.4 (C-5), 46.5 (C-7), 41.1 (C-6), 39.9 (DMSO), 18.0 (C-13, C-14, C-15, C-16, C-17, C-18), 14.0 (C-1), 12.0 (C-10, C-11, C-12).



**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 3430, 2948 (-C-H), 2867 (-C-H), 2237 (C≡N), 1732 (3-C=O), 1636 (9-C=O), 1462, 1107, 913, 744.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>19</sub>H<sub>34</sub>NO<sub>5</sub>Si [M+H]<sup>+</sup> 384.22008, **found** 384.21958.

**(S)-3-(hydroxymethyl)-1-(2-(((triisopropylsilyl)oxy)ethyl)cyclobut-2-enecarbonitrile (273)**



In a dried two-necked flask, the cyclobutene **258a** (100.0 mg, 0.28 mmol, 1.0 eq.) was dissolved in dry THF (2.8 mL, 0.1 M), then the reaction mixture was cooled to -78 °C. DIBAL-H (1.0 M in hexane, 0.85 mL, 0.85 mmol, 3.0 eq.) was added and the consumption of the starting material was followed by TLC. After 2.5 h, Rochelle salt (3.0 mL) was added and the reaction mixture was stirred for 5 min then extracted with EtOAc. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated. The crude mixture was purified through column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc: 90/10) to afford the desired product (64.0 mg, 74%) as a colorless oil.

**TLC (cyclohexane/EtOAc: 70/30):** R<sub>f</sub> = 0.33 (UV active; KMnO<sub>4</sub>, stains yellow).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 6.07 (t, *J* = 1.7 Hz, 1H, H-6), 4.17 (s, 2H, H-2), 3.95 (t, *J* = 6.0 Hz, 2H, H-9), 3.01 (dt, *J* = 13.6, 1.3 Hz, 1H, H-4a), 2.72 (dt, *J* = 13.7, 1.3 Hz, 1H, H-4b), 1.99 (td, *J* = 6.0, 2.8 Hz, 2H, H-8), 1.10-1.05 (m, 21H, H-10, H-11, H-12, H-13, H-14, H-15, H-16, H-17, H-18).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 150.1 (C-6), 129.6 (C-3), 121.9 (C-7), 60.9 (C-9), 60.8 (C-2), 41.7 (C-4), 39.5 (C-8), 37.6 (C-5), 18.1 (C-13, C-14, C-15, C-16, C-17, C-18), 12.0 (C-10, C-11, C-12).

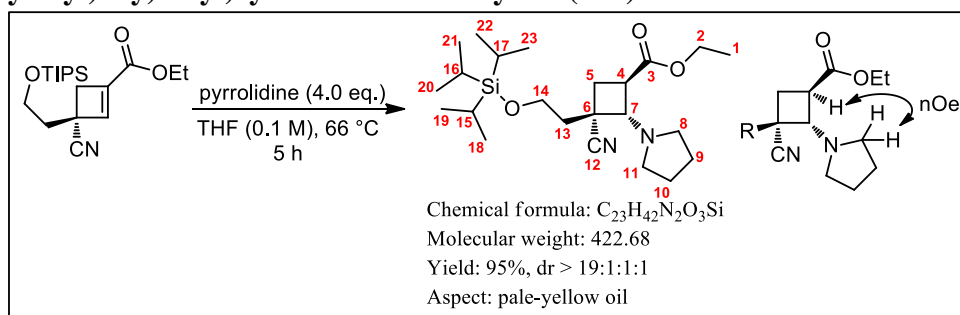
**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 3435 (br, OH), 2943 (-C-H), 2866 (-C-H), 2232 (C≡N), 1462, 1108, 882, 682.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>17</sub>H<sub>31</sub>NO<sub>2</sub>SiNa [M+Na]<sup>+</sup> 332.20163, **found** 332.20079.

$[\alpha]_D^{25}$  = +41.69 (*c* = 0.086, CHCl<sub>3</sub>).

## 16. 1,4-Conjugate addition to cyclobutenes

**(1R,2S,3S)-ethyl 3-cyano-2-(pyrrolidin-1-yl)-3-(2-(((triisopropylsilyl)oxy)ethyl)cyclobutanecarboxylate (284)**



In a dried two-necked flask, cyclobutene **258a** (211.0 mg, 0.6 mmol, 1.0 eq.) was dissolved in dry THF (6.0 mL, 0.1 M) and pyrrolidine (0.2 mL, 2.4 mmol, 4.0 eq.) was added. The reaction mixture was stirred at 66 °C silicon oil bath temperature for 5 h. The mixture was then cooled down to 20 °C and the solvent was concentrated under reduced pressure. The obtained crude mixture was purified through column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc: 80/20) to afford the product (242.0 mg, 95%, dr > 19:1:1:1) as a pale-yellow oil.

**TLC (cyclohexane/EtOAc: 80/20):** R<sub>f</sub> = 0.66 (UV active; KMnO<sub>4</sub>, stains white).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 4.15 (qq, *J* = 7.0, 3.7 Hz, 2H, H-2), 3.96-3.83 (m, 2H, H-14), 3.25 (dt, *J* = 10.3, 8.9 Hz, 1H, H-4), 2.99 (d, *J* = 8.6 Hz, 1H, H-7), 2.61-2.53 (m, 5H, H-5a, H-8, H-11), 2.21 (dd, *J* = 12.0, 10.3 Hz, 1H, H-5b), 2.09-1.89 (m, 2H, H-13), 1.81-1.77 (m, 4H, H-9, H-

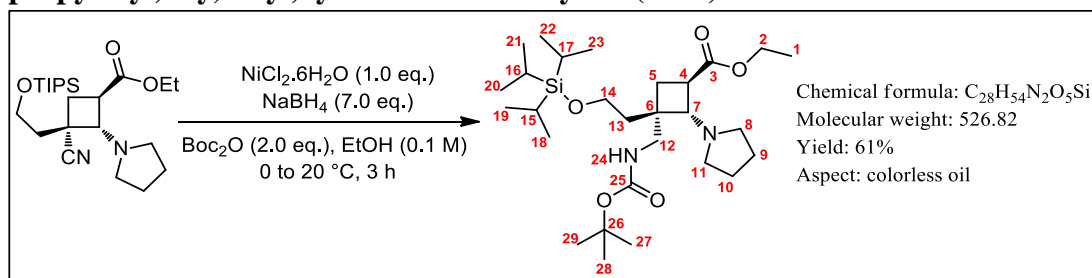
10), 1.25 (t,  $J = 7.1$  Hz, 3H, H-1), 1.08-1.05 (m, 21H, H-15, H-16, H-17, H-18, H-19, H-20, H-21, H-22, H-23).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) = 173.0 (C-3), 121.8 (C-12), 69.4 (C-7), 61.0 (C-2), 60.2 (C-14), 51.5 (C-8, C-11), 41.3 (C-4), 40.9 (C-13), 39.1 (C-6), 31.2 (C-5), 23.6 (C-9, C-10), 18.1 (C-18, C-19, C-20, C-21, C-22, C-23), 14.3 (C-1), 12.0 (C-15, C-16, C-17).

IR (solution in  $\text{CH}_2\text{Cl}_2$ , thin film, KBr):  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 2945 (C-H), 2867 (C-H), 2237 ( $\text{C}\equiv\text{N}$ ), 1732 (3-C=O), 1463, 1104, 883, 682.

HRMS (TOF, ES $^+$ ): calculated for  $\text{C}_{23}\text{H}_{43}\text{N}_2\text{O}_3\text{SiNa}$   $[\text{M}+\text{Na}]^+$  423.3037, found 423.3049.  $[\alpha]_{\text{D}}^{25} = -86.42$  ( $c = 0.066$ ,  $\text{CHCl}_3$ ).

**(1*R*,2*S*,3*R*)-ethyl 3-(((*tert*-butoxycarbonyl)amino)methyl)-2-(pyrrolidin-1-yl)-3-(2-((triisopropylsilyl)oxy)ethyl)cyclobutanecarboxylate (290a)**



In a dried two-necked flask, cyclobutane **284** (166.0 mg, 0.4 mmol, 1.0 eq.) was dissolved in distilled EtOH (4.0 mL, 0.1 M) and the reaction mixture was cooled down to 0 °C.  $\text{Boc}_2\text{O}$  (0.18 mL, 0.8 mmol, 2.0 eq.) and  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$  (93.0 mg, 0.4 mmol, 1.0 eq.) were added, followed by portion-wise addition of  $\text{NaBH}_4$  (106.0 mg, 2.8 mmol, 7.0 eq.) then the reaction mixture was stirred at 20 °C for 3 h. The solvent was evaporated, then the crude was dissolved in EtOAc and filtrated over a celite pad. The filtrate was evaporated and the crude mixture was purified through column chromatography on  $\text{SiO}_2$  (cyclohexane/EtOAc: 80/20) to afford the product (128.0 mg, 61%) as a colorless oil.

TLC (cyclohexane/EtOAc: 70/30):  $R_f = 0.47$  (UV inactive;  $\text{KMnO}_4$ , stains yellow).

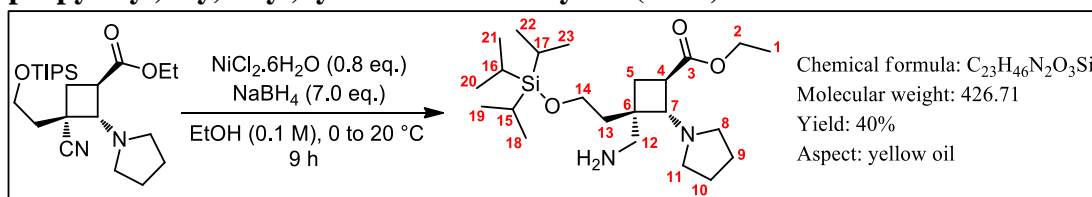
$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) = 6.00 (br s, 1H, H-24), 4.09 (qdt,  $J = 7.1, 2.4, 1.1$  Hz, 2H, H-2), 3.71 (t,  $J = 6.4$  Hz, 2H, H-14), 3.41 (dd,  $J = 14.2, 6.2$  Hz, 1H, H-12a), 3.24 (dd,  $J = 14.1, 6.0$  Hz, 1H, H-12b), 2.97 (q,  $J = 9.1$  Hz, 1H, H-4), 2.81 (d,  $J = 8.5$  Hz, 1H, H-7), 2.42-2.35 (m, 4H, H-8, H-11), 1.99 (t,  $J = 10.5$  Hz, 1H, H-5a), 1.85-1.64 (m, 7H, H-5b, H-9, H-10, H-13), 1.41 (s, 9H, H-27, H-28, H-29), 1.21 (tt,  $J = 7.1, 1.1$  Hz, 3H, H-1), 1.07-1.02 (m, 21H, H-15, H-16, H-17, H-18, H-19, H-20, H-21, H-22, H-23).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) = 174.7 (C-3), 156.6 (C-25), 78.6 (C-26), 70.6 (C-7), 60.5 (C-2), 59.7 (C-14), 52.6 (C-8, C-11), 44.3 (C-12), 42.9 (C-13), 41.6 (C-6), 40.1 (C-4), 28.5 (C-27, C-28, C-29), 28.0 (C-5), 23.4 (C-9, C-10), 18.1 (C-18, C-19, C-20, C-21, C-22, C-23), 14.3 (C-1), 12.0 (C-15, C-16, C-17).

IR (solution in  $\text{CH}_2\text{Cl}_2$ , thin film, KBr):  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 3385, 2940 (C-H), 2866 (C-H), 1714 (3-C=O), 1500 (25-C=O), 1248, 1173, 882.

HRMS (TOF, ES $^+$ ): calculated for  $\text{C}_{28}\text{H}_{55}\text{N}_2\text{O}_5\text{Si}$   $[\text{M}+\text{H}]^+$  527.38748, found 527.38611.  $[\alpha]_{\text{D}}^{25} = -25.8$  ( $c = 0.106$ ,  $\text{CHCl}_3$ ).

**(1*R*,2*S*,3*R*)-ethyl 3-(aminomethyl)-2-(pyrrolidin-1-yl)-3-(2-((triisopropylsilyl)oxy)ethyl)cyclobutanecarboxylate (290b)**



In a dried two-necked flask, cyclobutane **284** (242.0 mg, 0.57 mmol, 1.0 eq.) was dissolved in distilled EtOH (5.7 mL, 0.1 M) and the reaction mixture was cooled down to 0 °C.  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$  (109.0 mg, 0.45 mmol, 0.8 eq.) was added followed by portion-wise addition of  $\text{NaBH}_4$  (151.0 mg, 3.99 mmol,

7.0 eq.), then the reaction mixture was stirred at 20 °C for 9 h. The solvent was evaporated, then the crude mixture was dissolved in EtOAc and filtrated over a celite pad. The filtrate was concentrated under reduced pressure and the crude mixture was purified through column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 95/5) to afford the product (98.0 mg, 40%) as a yellow oil.

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 90/10):** *R<sub>f</sub>* = 0.38 (UV inactive; KMnO<sub>4</sub>, stains yellow).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ (ppm) = 4.13 (qd, *J* = 7.1, 2.2 Hz, 2H, H-2), 3.78-3.74 (m, 2H, H-14), 3.25-3.09 (m, 4H, H-4, H-7, H-12), 2.68-2.62 (m, 4H, H-8, H-11), 2.27 (dd, *J* = 11.8, 10.0 Hz, 1H, H-5a), 1.98-1.85 (m, 2H, H-13), 1.83-1.73 (m, 5H, H-5b, H-9, H-10), 1.24 (t, *J* = 7.1 Hz, 3H, H-1), 1.12-1.04 (m, 21H, H-15, H-16, H-17, H-18, H-19, H-20, H-21, H-22, H-23).

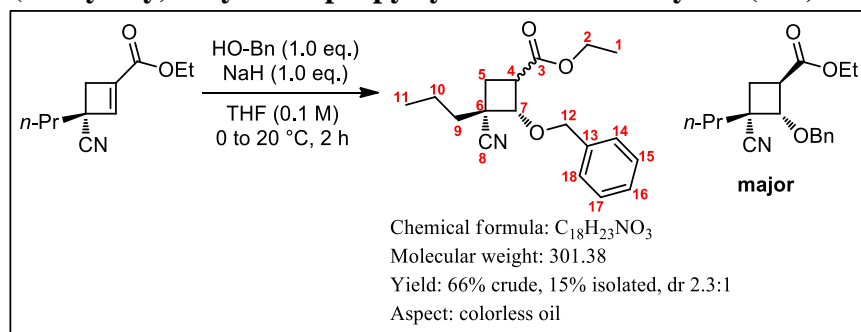
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ (ppm) = 174.0 (C-3), 69.9 (C-7), 60.0 (C-2), 59.6 (C-14), 53.0 (C-8, C-11), 45.6 (C-12), 41.8 (C-4), 41.0 (C-13), 39.7 (C-6), 28.8 (C-5), 23.4 (C-9, C-10), 18.2 (C-18, C-19, C-20, C-21, C-22, C-23), 14.3 (C-1), 12.0 (C-15, C-16, C-17).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):** *v*<sub>max</sub> (cm<sup>-1</sup>) = 2943 (-C-H), 2866 (-C-H), 1729 (3-C=O), 1464, 1097, 882, 684.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>23</sub>H<sub>47</sub>N<sub>2</sub>O<sub>3</sub>Si [M+H]<sup>+</sup> 427.33505, **found** 427.33459.

[α]<sub>D</sub><sup>25</sup> = -45.88 (*c* = 0.053, CHCl<sub>3</sub>).

### (2*S*,3*S*)-ethyl 2-(benzyloxy)-3-cyano-3-propylcyclobutanecarboxylate (308)



According to the general procedure (N), from benzyl alcohol (20.0 μL, 0.2 mmol, 1.0 eq.), dry THF (1.0 mL, 0.2 M), NaH (60% suspension in oil, 8.0 mg, 0.2 mmol, 1.0 eq.) and the cyclobutene **258b** (39.0 mg, 0.2 mmol, 1.0 eq.) in dry THF (1.1 mL, 0.17 M) for 2 h. The crude as a mixture of diastereomers (40.0 mg, 66% crude, dr 2.3:1) was obtained as a colorless oil and was pure enough to be used directly in the next step without further purification. [Purification of the crude for analysis was accomplished through column chromatography on SiO<sub>2</sub> (cyclohexane/ethyl acetate: 90/10), and only 9.0 mg (15%) were recuperated. The product is not stable on column].

**TLC (cyclohexane/EtOAc: 90/10):** *R<sub>f</sub>* = 0.29 (UV active; KMnO<sub>4</sub>, stains yellow).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ (ppm) = 7.40-7.27 (m, 6.5H, H-Ph dia-1/dia-2), 4.62 (s, 2H, H-12 dia-1), 4.60 (d, *J* = 6.7 Hz, 0.3H, H-12a), 4.48 (d, *J* = 8.1 Hz, 0.3H, H-12b), 4.26-4.06 (m, 2.6H, H-2 dia-1/dia-2), 3.94 (d, *J* = 7.8 Hz, 1H, H-7 dia-1), 3.87 (d, *J* = 7.7 Hz, 0.3H, H-7 dia-2), 3.58 (q, *J* = 7.0 Hz, 0.3H, H-4 dia-2), 3.36-3.07 (m, 1.3H, H-4 dia-1, H-5a dia-2), 2.55-2.44 (m, 1H, H-5a dia-1), 2.30-2.11 (m, 1H, H-5b dia-1), 1.89-1.37 (m, 5.5H, H-5b dia-2, H-9 dia-1/dia-2, H-10 dia-1/dia-2), 1.34-1.18 (m, 4H, H-1 dia-1/dia-2), 1.02 (t, *J* = 7.1 Hz, 1H, H-11 dia-2), 0.94 (td, *J* = 7.2, 3.3 Hz, 3H, H-11 dia-1).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**

**Major diastereomer, dia-1:**

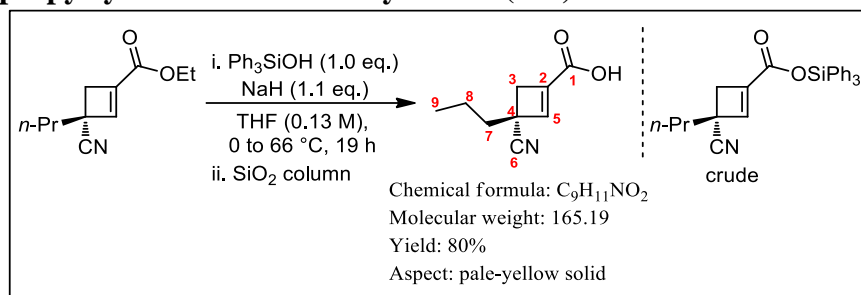
δ (ppm) = 172.2 (C-3), 137.0 (C-13), 128.6 (C-15, C-17), 128.1 (C-16), 128.0 (C-14, C-18), 121.1 (C-8), 79.1 (C-7), 71.6 (C-12), 61.2 (C-2), 43.4 (C-9), 43.1 (C-6), 39.7 (C-4), 28.2 (C-5), 18.7 (C-10), 14.3 (C-1), 14.0 (C-11).

**Minor diastereomer, dia-2:**

δ (ppm) = 171.8 (C-3), 136.9 (C-13), 128.7 (C-15, C-17), 128.2 (C-16), 127.8 (C-14, C-18), 122.6 (C-8), 78.2 (C-7), 72.2 (C-12), 61.2 (C-2), 43.8 (C-9), 43.4 (C-6), 38.0 (C-4), 27.1 (C-5), 18.4 (C-10), 14.3 (C-1), 14.0 (C-11).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):** *v*<sub>max</sub> (cm<sup>-1</sup>) = 2962 (-C-H), 2874 (-C-H), 2234 (C≡N), 1731 (3-C=O), 1454, 1197, 1129, 741, 698.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>18</sub>H<sub>23</sub>NO<sub>3</sub>Na [M+Na]<sup>+</sup> 324.15701, **found** 324.15635.

**(R)-3-cyano-3-propylcyclobut-1-enecarboxylic acid (313)**

To a flame-dried two-necked flask equipped with a condenser, and under inert atmosphere,  $Ph_3SiOH$  (71.5 mL, 0.258 mmol, 1.0 eq.) was introduced followed by dry THF (1.0 mL, 0.26 M) and the reaction was set at 0 °C. NaH (60% suspension in oil, 11.3 mg, 0.28 mmol, 1.1 eq.) was added portion-wise and the reaction was stirred for 10 min at the same temperature. **258b** (50.0 mg, 0.258 mmol, 1.0 eq.) was dissolved in THF (1.0 mL, 0.26 M) and added slowly to the mixture, the color changed to yellow. The reaction was stirred at 20 °C for 3 h then at 66 °C silicon oil bath temperature for 16 h. The reaction was quenched with aqueous HCl (1.0 M) and extracted with EtOAc. The organic layer was washed with brine, dried over  $Na_2SO_4$  and concentrated under reduced pressure. The crude mixture (114.0 mg, quant.) was obtained as a yellow solid, and purified through column chromatography on  $SiO_2$  (cyclohexane/ethyl acetate: 80/20) to give the saponified product (34.0 mg, 80%) as a pale-yellow solid.

**TLC (cyclohexane/EtOAc: 80/20):**  $R_f = 0$  (UV active;  $KMnO_4$ , stains white).

**m. p.** = 79.2–84.0 °C ( $CH_2Cl_2$ ).

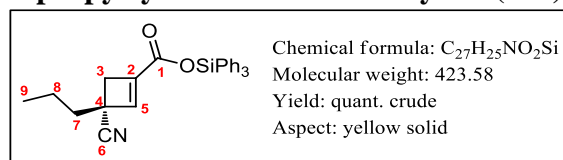
**$^1H$  NMR (300 MHz,  $CDCl_3$ ):**  $\delta$  (ppm) = 9.56 (br s, 1H, OH), 6.87 (s, 1H, H-5), 3.20 (d,  $J = 13.8$  Hz, 1H, H-3a), 2.76 (d,  $J = 13.7$  Hz, 1H, H-3b), 1.90–1.71 (m, 2H, H-7), 1.66–1.50 (m, 2H, H-8), 1.00 (t,  $J = 7.3$  Hz, 3H, H-9).

**$^{13}C$  NMR (75 MHz,  $CDCl_3$ ):**  $\delta$  (ppm) = 161.1 (C-1), 146.6 (C-5), 139.5 (C-2), 120.0 (C-6), 40.6 (C-3), 39.0 (C-4), 38.1 (C-7), 19.8 (C-8), 19.9 (C-9).

**IR (solution in  $CH_2Cl_2$ , thin film, KBr):**  $\nu_{max}$  ( $cm^{-1}$ ) = 3083 (br, OH), 2964 (–C–H), 2876 (–C–H), 2237 ( $C\equiv N$ ), 1710 (1–C=O), 1623, 1417, 1281, 1230, 1187, 741.

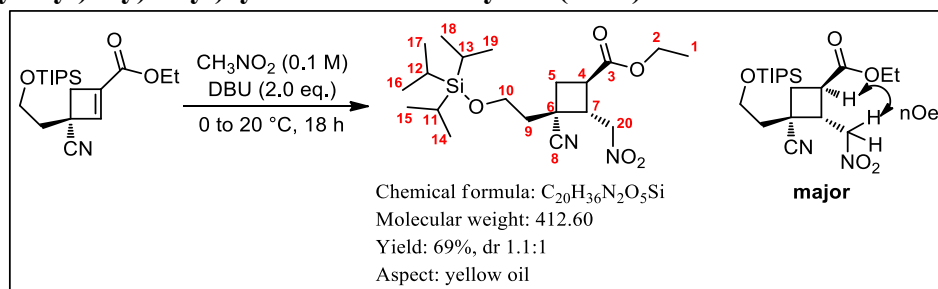
**HRMS (TOF, ES $^+$ ):** calculated for  $C_9H_{10}NO_2$   $[M-H]^+$  164.07170, found 164.07120.

$[\alpha]_D^{25} = +60.40$  ( $c = 0.23$ ,  $CHCl_3$ ).

**(R)-triphenylsilyl 3-cyano-3-propylcyclobut-1-enecarboxylate (312)**

**TLC (cyclohexane/EtOAc: 80/20):**  $R_f = 0.63$  (UV active;  $KMnO_4$ , stains white).

**$^1H$  NMR (300 MHz,  $CDCl_3$ ):**  $\delta$  (ppm) = 7.67–7.57 (m, 2H, H-Ph), 7.48–7.31 (m, 8H, H-Ph), 7.25–7.20 (m, 5H, H-Ph), 6.85 (s, 1H, H-5), 3.20 (d,  $J = 13.8$  Hz, 1H, H-3a), 2.76 (d,  $J = 13.8$  Hz, 1H, H-3b), 1.82–1.73 (m, 2H, H-7), 1.67–1.48 (m, 2H, H-8), 0.99 (t,  $J = 7.3$  Hz, 3H, H-9).

**(2S,3S)-ethyl-3-cyano-2-(nitromethyl)-3-((triisopropylsilyl)oxy)ethylcyclobutanecarboxylate (314a)**

In a dried two-necked flask, the cyclobutene **258a** (50.0 mg, 0.14 mmol, 1.0 eq.) was dissolved in distilled nitromethane (1.4 mL, 0.1 M), and the mixture was set at 0 °C, then DBU (0.04 mL, 0.28 mmol, 2.0 eq.) was added and the reaction was stirred at 20 °C. After 18 h, the solvent was concentrated under reduced pressure and the crude was directly purified through short column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc: 95/5 to 85/15) to afford the mixture of diastereomers as a yellow oil (40.0 mg, 69%, dr 1.1:1).

**TLC (cyclohexane/EtOAc: 80/20):**  $R_f$  = 0.45 (UV inactive; KMnO<sub>4</sub>, stains yellow).

**Major diastereomer (*trans*):**

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 4.84 (dd,  $J$  = 14.3, 7.1 Hz, 1H, H-20a), 4.78 (dd,  $J$  = 15.5, 6.2 Hz, 1H, H-20b), 4.23–4.13 (m, 2H, H-2), 3.96–3.89 (m, 2H, H-10), 3.36–3.30 (m, 1H, H-7), 3.16 (q,  $J$  = 9.6 Hz, 1H, H-4), 2.75–2.68 (m, 1H, H-5a), 2.50–2.46 (m, 1H, H-5b), 2.16–1.98 (m, 2H, H-9), 1.30–1.24 (m, 3H, H-1), 1.09–1.05 (m, 21H, H-11, H-12, H-13, H-14, H-15, H-16, H-17, H-18, H-19).

**<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 171.8 (C-3), 120.8 (C-8), 75.4 (C-20), 61.8 (C-2), 60.6 (C-10), 43.6 (C-7), 40.9 (C-4), 39.1 (C-9), 37.8 (C-6), 33.0 (C-5), 18.1 (C-14, C-15, C-16, C-17, C-18, C-19), 14.2 (C-1), 12.0 (C-11, C-12, C-13).

**Minor diastereomer (*cis*):**

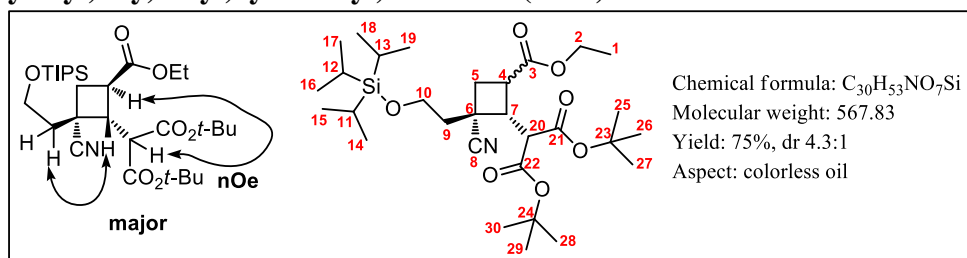
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 4.94 (dd,  $J$  = 15.5, 8.8 Hz, 1H, H-20a), 4.64 (dd,  $J$  = 14.3, 7.6 Hz, 1H, H-20b), 4.23–4.13 (m, 2H, H-2), 3.96–3.89 (m, 2H, H-10), 3.53–3.51 (m, 1H, H-7), 3.43 (td,  $J$  = 9.5, 5.8 Hz, 1H, H-4), 2.91 (dd,  $J$  = 12.9, 5.5 Hz, 1H, H-5a), 2.56–2.51 (m, 1H, H-5b), 2.16–1.98 (m, 2H, H-9), 1.30–1.24 (m, 3H, H-1), 1.09–1.05 (m, 21H, H-11, H-12, H-13, H-14, H-15, H-16, H-17, H-18, H-19).

**<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 171.6 (C-3), 120.1 (C-8), 72.8 (C-20), 61.6 (C-2), 60.4 (C-10), 41.0 (C-7), 40.6 (C-4), 37.8 (C-6), 36.6 (C-9), 34.3 (C-5), 18.1 (C-14, C-15, C-16, C-17, C-18, C-19), 14.2 (C-1), 12.0 (C-11, C-12, C-13).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2941 (–C–H), 2870 (–C–H), 2232 (C≡N), 1733 (3–C=O), 1557, 1464, 1380, 1189, 1102, 883.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>20</sub>H<sub>36</sub>N<sub>2</sub>O<sub>5</sub>SiNa [M+Na]<sup>+</sup> 435.22857, found 435.22840.

**di-*tert*-butyl 2-((1*R*,2*S*)-2-cyano-4-(ethoxycarbonyl)-2-((triisopropylsilyl)oxy)ethyl)cyclobutyl)malonate (**324a**)**



According to the general procedure (N), from di-*tert*-butyl malonate **323a** (0.12 mL, 0.55 mmol, 1.0 eq.), dry THF (2.7 mL, 0.2 M), NaH (60% suspension in oil, 22.0 mg, 0.55 mmol, 1.0 eq.) and the cyclobutene **258a** (195.0 mg, 0.55 mmol, 1.0 eq.) in dry THF (3.2 mL, 0.17 M) for 4 h. The crude as a mixture of two diastereomers (dr 4.3:1) was purified through column chromatography on SiO<sub>2</sub> (cyclohexane/ethyl acetate: 98/2) to afford the major diastereomer (190.0 mg, 61%) and the minor diastereomer with traces of the major diastereomer (44.0 mg, 14%) as a colorless oil.

**For the major diastereomer (1*R*,4*R*)-*trans*-**324a**:**

**TLC (cyclohexane/EtOAc: 90/10):**  $R_f$  = 0.44 (UV inactive; KMnO<sub>4</sub>, stains yellow).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 4.13 (q,  $J$  = 7.1 Hz, 2H, H-2), 3.88 (dd,  $J$  = 7.4, 4.7 Hz, 2H, H-10), 3.65 (d,  $J$  = 11.5 Hz, 1H, H-20), 3.23 (dd,  $J$  = 11.6, 9.0 Hz, 1H, H-7), 3.10 (q,  $J$  = 9.3 Hz, 1H, H-4), 2.69 (dd,  $J$  = 12.2, 9.2 Hz, 1H, H-5a), 2.46 (dd,  $J$  = 12.2, 9.5 Hz, 1H, H-5b), 2.25 (dt,  $J$  = 14.1, 4.6 Hz, 1H, H-9a), 2.09–2.00 (m, 1H, H-9b), 1.46 (s, 9H, H-25, H-26, H-27), 1.43 (s, 9H, H-28, H-29, H-30), 1.24 (t,  $J$  = 7.1 Hz, 3H, H-1), 1.07–1.04 (m, 21H, H-11, H-12, H-13, H-14, H-15, H-16, H-17, H-18, H-19).



**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 172.9 (C-3), 166.7 (C-21), 166.2 (C-22), 121.5 (C-8), 82.5 (C-23), 82.4 (C-24), 61.0 (C-2), 60.5 (C-10), 56.6 (C-20), 44.4 (C-7), 40.9 (C-9), 39.3 (C-4), 38.1 (C-6), 34.6 (C-5), 28.0 (C-25, C-26, C-27), 27.9 (C-28, C-29, C-30), 18.1 (C-14, C-15, C-16, C-17, C-18, C-19), 14.2 (C-1), 12.0 (C-11, C-12, C-13).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2943 (-C-H), 2868 (-C-H), 2232 (C $\equiv$ N), 1735 (br, 3-C=O, 21-C=O, 22-C=O), 1463, 1369, 1254, 1165, 1143, 1105, 883, 683.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>30</sub>H<sub>53</sub>NO<sub>7</sub>SiNa [M+Na]<sup>+</sup> 590.3483, **found** 590.3477.

$[\alpha]_{\text{D}}^{25}$  = -25.55 ( $c$  = 0.16, CH<sub>3</sub>Cl).

**For the minor diastereomer (1*R*,4*S*)-cis-324a:**

**TLC (cyclohexane/EtOAc: 90/10):**  $R_f$  = 0.34 (UV inactive; KMnO<sub>4</sub>, stains yellow).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 4.15 (q,  $J$  = 7.2 Hz, 2H, H-2), 4.02-3.86 (m, 2H, H-10), 3.71 (dd,  $J$  = 11.8, 9.7 Hz, 1H, H-7), 3.32 (d,  $J$  = 11.8 Hz, 1H, H-20), 3.00 (q,  $J$  = 9.6 Hz, 1H, H-4), 2.68-2.59 (m, 2H, H-5), 1.99-1.85 (m, 2H, H-9), 1.50 (s, 9H, H-25, H-26, H-27), 1.42 (s, 9H, H-28, H-29, H-30), 1.30-1.24 (m, 3H, H-1), 1.09-1.04 (m, 21H, H-11, H-12, H-13, H-14, H-15, H-16, H-17, H-18, H-19).

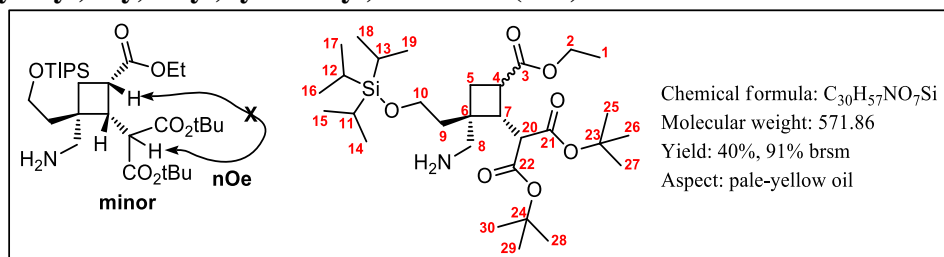
**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 172.3 (C-3), 166.2 (C-21), 166.1 (C-22), 122.2 (C-8), 83.1 (C-23), 82.7 (C-24), 61.1 (C-2), 60.5 (C-10), 54.2 (C-20), 44.1 (C-7), 39.1 (C-4), 33.5 (C-9), 33.3 (C-6), 33.0 (C-5), 28.0 (C-25, C-26, C-27), 27.9 (C-28, C-29, C-30), 18.1 (C-14, C-15, C-16, C-17, C-18, C-19), 14.2 (C-1), 12.0 (C-11, C-12, C-13).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2943 (-C-H), 2867 (-C-H), 2234 (C $\equiv$ N), 1733 (br, 3-C=O, 21-C=O, 22-C=O), 1462, 1369, 1255, 1149, 1104, 882, 683.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>30</sub>H<sub>53</sub>NO<sub>7</sub>SiNa [M+Na]<sup>+</sup> 590.3483, **found** 590.3470.

$[\alpha]_{\text{D}}^{25}$  = -1.27 ( $c$  = 0.1, CH<sub>3</sub>Cl).

**di-*tert*-butyl 2-((1*R*,2*S*)-2-(aminomethyl)-4-(ethoxycarbonyl)-2-((triisopropylsilyl)oxy)ethyl)cyclobutyl)malonate (328)**



In a dried two-necked flask, the cyclobutane **324a** (120.0 mg, 0.21 mmol, 1.0 eq.) was dissolved in distilled EtOH (2.1 mL, 0.1 M) and the reaction mixture was cooled down to 0 °C. NiCl<sub>2</sub>·6H<sub>2</sub>O (50.0 mg, 0.21 mmol, 1.0 eq.) was added followed by portion-wise addition of NaBH<sub>4</sub> (55.0 mg, 1.48 mmol, 7.0 eq.) then the reaction mixture was stirred at 20 °C for 16 h. The solvent was concentrated under reduced pressure, then the crude mixture was dissolved in EtOAc and filtrated over a celite pad. The filtrate was evaporated and the crude mixture was purified through column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 95/5) to afford the major diastereomer (30.8 mg, 26%) and the minor diastereomer (17.0 mg, 14%) with traces of the major diastereomer as a pale-yellow oil. 56% of the starting material were recovered.

**For the major diastereomer (1*R*,4*R*)-trans-328:**

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 95/5):**  $R_f$  = 0.32 (UV inactive; KMnO<sub>4</sub>, stains yellow).

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 4.14-4.05 (m, 2H, H-2), 3.85-3.82 (m, 1H, H-10a), 3.76-3.72 (m, 1H, H-10b), 3.37-3.34 (m, 1H, H-20), 3.17 (d,  $J$  = 13.2 Hz, 1H, H-8a), 3.05-3.00 (m, 2H, H-7, H-8b), 2.91 (q,  $J$  = 9.2 Hz, 1H, H-4), 2.43 (br s, 1H, H-5a), 2.08-1.99 (m, 2H, H-5b, H-9a), 1.95-1.91 (m, 1H, H-9b), 1.44 (s, 9H, H-25, H-26, H-27), 1.40 (s, 9H, H-28, H-29, H-30), 1.23-1.20 (m, 3H, H-1), 1.16-1.10 (m, 3H, H-11, H-12, H-13), 1.07-1.05 (m, 18H, H-14, H-15, H-16, H-17, H-18, H-19).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 174.1 (C-3), 168.3 (C-21), 166.5 (C-22), 82.7 (C-23), 82.2 (C-24), 60.6 (C-2), 59.6 (C-10), 54.1 (C-20), 46.2 (C-7), 43.6 (C-8), 42.8 (C-9), 40.8 (C-4), 37.8 (C-

6), 31.0 (C-5), 28.0 (C-25, C-26, C-27), 27.9 (C-28, C-29, C-30), 18.1 (C-14, C-15, C-16, C-17, C-18, C-19), 14.2 (C-1), 11.8 (C-11, C-12, C-13).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2941 (-C-H), 2867 (-C-H), 1730 (br, 3-C=O, 21-C=O, 22-C=O), 1462, 1368, 1256, 1156, 1097, 882, 685.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>30</sub>H<sub>58</sub>NO<sub>7</sub>Si [M+H]<sup>+</sup> 572.3977, **found** 572.3969.

$[\alpha]_{\text{D}}^{25} = -3.17$  ( $c = 0.12$ , CH<sub>3</sub>Cl).

**For the minor diastereomer (1*R*,4*S*)-cis-328:**

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 95/5):**  $R_f = 0.24$  (UV inactive; KMnO<sub>4</sub>, stains yellow).

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 4.20-4.08 (m, 1H, H-2a), 4.06-3.98 (m, 1H, H-2b), 3.90-3.87 (m, 1H, H-10a), 3.79-3.73 (m, 2H, H-10b, H-20), 3.37-3.23 (m, 2H, H-7, H-8a), 3.19-3.06 (m, 2H, H-4, H-8b), 2.53-2.44 (m, 1H, H-9a), 2.38 (q,  $J = 10.3, 9.4$  Hz, 1H, H-5a), 2.20-2.10 (m, 1H, H-5b), 1.52-1.48 (m, 1H, H-9b), 1.45-1.41 (m, 18H, H-25, H-26, H-27, H-28, H-29, H-30), 1.26-1.21 (m, 3H, H-1), 1.16-1.10 (m, 3H, H-11, H-12, H-13), 1.06-1.02 (m, 18H, H-14, H-15, H-16, H-17, H-18, H-19).

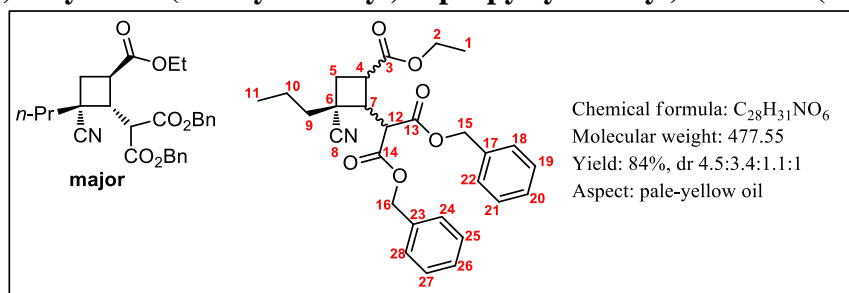
**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 174.7 (C-3), 170.0 (C-21), 166.0 (C-22), 83.7 (C-23), 82.4 (C-24), 61.0 (C-2), 59.3 (C-10), 51.8 (C-20), 49.5 (C-8), 42.9 (C-7), 40.5 (C-6), 35.0 (C-4), 33.7 (C-9), 30.5 (C-5), 28.0 (C-25, C-26, C-27), 27.9 (C-28, C-29, C-30), 18.1 (C-14, C-15, C-16, C-17, C-18, C-19), 14.1 (C-1), 11.8 (C-11, C-12, C-13).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2941 (-C-H), 2867 (-C-H), 1727 (br, 3-C=O, 21-C=O, 22-C=O), 1462, 1369, 1254, 1165, 1144, 1100, 882, 683.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>30</sub>H<sub>58</sub>NO<sub>7</sub>Si [M+H]<sup>+</sup> 572.3977, **found** 572.3964.

$[\alpha]_{\text{D}}^{25} = -7.12$  ( $c = 0.12$ , CH<sub>3</sub>Cl).

#### dibenzyl 2-((2*R*)-2-cyano-4-(ethoxycarbonyl)-2-propylcyclobutyl)malonate (330a)



According to the general procedure (N), from dibenzyl malonate (1.19 g, 4.2 mmol, 1.0 eq.), dry THF (21.0 mL, 0.2 M), NaH (60% suspension in oil, 168.0 mg, 4.2 mmol, 1.0 eq.) and cyclobutene **258b** (818.0 mg, 4.2 mmol, 1.0 eq.) in dry THF (25.0 mL, 0.17 M) for 4 h. The crude as a mixture of diastereomers (1.69 g, 84%, dr 4.5:3.4:1.1:1) was obtained as a pale-yellow oil and was pure enough to be used directly in the next step without further purification. [Purification of the crude for analysis was accomplished through column chromatography on SiO<sub>2</sub> (cyclohexane/ethyl acetate: 80/20)].

**TLC (cyclohexane/EtOAc: 80/20):**  $R_f = 0.48$  (UV active; KMnO<sub>4</sub>, stains yellow).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 7.31-7.01 (m, 22H, H-Ph all dia), 5.17-4.65 (m, 9H, H-15 all dia, H-16 all dia), 4.31-4.17 (m, 0.75H, H-12 dia-2), 4.12-3.88 (m, 3.75H, H-2 all dia), 3.83 (dd,  $J = 11.2, 2.5$  Hz, 1H, H-7 dia-1), 3.79-3.62 (m, 0.44H, H-12 dia-3/dia-4), 3.53-3.43 (m, 0.25H, H-7 dia-3), 3.34-2.85 (m, 4H, H-4 all dia, H-7 dia-2/dia-4, H-12 dia-1), 2.70-2.43 (m, 2.1H, H-5a all dia), 2.32-2.04 (m, 2.2H, H-5b all dia), 1.84-1.55 (m, 2.1H, H-9a all dia), 1.55-1.00 (m, 13.6H, H-1 all dia, H-9b all dia, H-10 all dia), 0.96-0.65 (m, 7H, H-11 all dia).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**

**For the major diastereomer, dia-1, (1*R*,4*R*)-trans-330a:**

$\delta$  (ppm) = 172.5 (C-3), 167.0 (C-13), 166.6 (C-14), 135.0 (C-17, C-23), 128.9-128.2 (m, C-Ph), 121.6 (C-8), 67.8 (C-15), 67.6 (C-16), 61.2 (C-2), 54.5 (C-12), 44.7 (C-7), 40.4 (C-9), 39.5 (C-6), 38.4 (C-4), 33.1 (C-5), 18.2 (C-10), 14.2 (C-1), 13.8 (C-11).

**For the second major diastereomer, dia-2, (1*R*,4*S*)-cis-330a:**

$\delta$  (ppm) = 172.1 (C-3), 167.5 (C-13), 166.8 (C-14), 135.1 (C-17), 135.0 (C-23), 128.9-128.2 (m, C-Ph), 121.1 (C-8), 67.9 (C-15), 67.7 (C-16), 61.4 (C-2), 51.8 (C-12), 43.2 (C-7), 41.2 (C-9), 39.3 (C-6), 37.0 (C-4), 32.5 (C-5), 18.2 (C-10), 14.1 (C-1), 13.9 (C-11).

**For the minor diastereomer, dia-3, (1*S*,4*S*)-trans-330a:**

$\delta$  (ppm) = 172.4 (C-3), 167.0 (C-13), 166.6 (C-14), 135.3 (C-17, C-23), 128.9-128.2 (m, C-Ph), 121.6 (C-8), 67.8 (C-15), 67.6 (C-16), 61.2 (C-2), 51.7 (C-12), 44.8 (C-7), 41.7 (C-9), 39.5 (C-6), 38.4 (C-4), 33.1 (C-5), 18.3 (C-10), 14.1 (C-1), 13.8 (C-11).

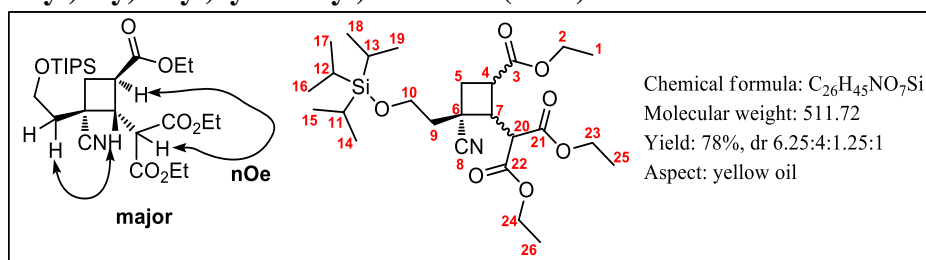
**For the minor diastereomer, dia-4, (1*S*,4*R*)-cis-330a:**

$\delta$  (ppm) = 172.1 (C-3), 166.8 (C-13), 166.4 (C-14), 135.5 (C-17, C-23), 128.9-128.2 (m, C-Ph), 121.1 (C-8), 67.9 (C-15), 67.7 (C-16), 61.4 (C-2), 49.5 (C-12), 43.9 (C-7), 41.7 (C-9), 39.5 (C-6), 36.9 (C-4), 32.4 (C-5), 18.2 (C-10), 14.0 (C-1), 13.8 (C-11).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2961 (-C-H), 2835 (-C-H), 2231 (C≡N), 1733 (br, 3-C=O, 13-C=O, 14-C=O), 1455, 1378, 1180, 1157, 745, 697.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>28</sub>H<sub>31</sub>NO<sub>6</sub>Na [M+Na]<sup>+</sup> 500.20436, found 500.20368.

**diethyl 2-((2*S*)-2-cyano-4-(ethoxycarbonyl)-2-(2-((triisopropylsilyl)oxy)ethyl)cyclobutyl)malonate (332a)**



According to the general procedure (N), from diethyl malonate **323c** (0.25 mL, 1.7 mmol, 1.0 eq.), dry THF (8.5 mL, 0.2 M), NaH (60% suspension in oil, 68.0 mg, 1.7 mmol, 1.0 eq.) and cyclobutene (600.0 mg, 1.7 mmol, 1.0 eq.) in dry THF (10.0 mL, 0.17 M) for 4 h. The crude as a mixture of diastereomers (680.0 mg, 78%, dr 6.25:4:1.25:1) was obtained as a yellow oil and was pure enough to be used directly in the next step without further purification. [Purification of the crude for analysis was accomplished through column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc: 85/15)].

**For the major diastereomer (1*R*,4*R*)-trans-332a:**

**TLC (cyclohexane/EtOAc: 90/10):**  $R_f$  = 0.31 (UV inactive; KMnO<sub>4</sub>, stains yellow).

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 4.24-4.17 (m, 2H, H-2), 4.17-4.10 (m, 4H, H-23, H-24), 3.90-3.86 (m, 2H, H-10), 3.82 (d,  $J$  = 11.5 Hz, 1H, H-20), 3.27 (dd,  $J$  = 11.4, 9.4 Hz, 1H, H-7), 3.16 (q,  $J$  = 9.5 Hz, 1H, H-4), 2.69 (dd,  $J$  = 12.3, 9.3 Hz, 1H, H-5a), 2.49 (dd,  $J$  = 12.3, 9.8 Hz, 1H, H-5b), 2.21 (dt,  $J$  = 14.1, 4.5 Hz, 1H, H-9a), 2.05-2.00 (m, 1H, H-9b), 1.28-1.23 (m, 9H, H-1, H-25, H-26), 1.08-1.04 (m, 21H, H-11, H-12, H-13, H-14, H-15, H-16, H-17, H-18, H-19).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 172.5 (C-3), 167.4 (C-21), 167.0 (C-22), 121.4 (C-8), 62.0 (C-23, C-24), 61.1 (C-2), 60.5 (C-10), 54.5 (C-20), 44.6 (C-7), 40.8 (C-9), 39.4 (C-4), 38.4 (C-6), 34.5 (C-5), 18.1 (C-14, C-15, C-16, C-17, C-18, C-19), 14.3 (C-1), 14.1 (C-25), 14.0 (C-26), 12.0 (C-11, C-12, C-13).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2948 (-C-H), 2868 (-C-H), 2232 (C≡N), 1740 (br, 3-C=O, 21-C=O, 22-C=O), 1465, 1374, 1306, 1250, 1178, 1103, 1031, 883, 684.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>26</sub>H<sub>45</sub>NO<sub>7</sub>SiNa [M+Na]<sup>+</sup> 534.2857, found 534.2843.

$[\alpha]_D^{25}$  = -15.12 ( $c$  = 0.16, CH<sub>3</sub>Cl).

**For the second major diastereomer (1*R*,4*S*)-cis-332a:**

**TLC (cyclohexane/EtOAc: 90/10):**  $R_f$  = 0.27 (UV inactive; KMnO<sub>4</sub>, stains yellow).

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 4.24-4.18 (m, 5H, H-20, H-23, H-24), 4.17-4.10 (m, 2H, H-2), 3.91-3.89 (m, 2H, H-10), 3.38-3.32 (m, 2H, H-4, H-7), 2.77 (dd,  $J$  = 13.1, 3.8 Hz, 1H, H-5a), 2.64-2.57 (m, 1H, H-5b), 2.13 (dt,  $J$  = 14.1, 4.6 Hz, 1H, H-9a), 2.02-1.97 (m, 1H, H-9b), 1.30-1.25 (m, 9H, H-1, H-25, H-26), 1.13-1.04 (m, 21H, H-11, H-12, H-13, H-14, H-15, H-16, H-17, H-18, H-19).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 172.3 (C-3), 167.8 (C-21), 167.0 (C-22), 120.9 (C-8), 62.2 (C-23), 62.0 (C-24), 61.3 (C-2), 60.5 (C-10), 51.8 (C-20), 43.1 (C-7), 41.5 (C-9), 38.3 (C-4), 37.9 (C-



6), 33.4 (C-5), 18.1 (C-14, C-15, C-16, C-17, C-18, C-19), 14.2 (C-1), 14.1 (C-25), 14.0 (C-26), 12.0 (C-11, C-12, C-13).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2948 (-C-H), 2868 (-C-H), 2232 (C≡N), 1740 (br, 3-C=O, 21-C=O, 22-C=O), 1465, 1374, 1306, 1250, 1178, 1103, 1031, 883, 684.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>26</sub>H<sub>45</sub>NO<sub>7</sub>SiNa [M+Na]<sup>+</sup> 534.2857, **found** 534.2843.

$[\alpha]_{\text{D}}^{25}$  = -10.03 (*c* = 0.08, CH<sub>3</sub>Cl).

**For the minor diastereomer (1*S*,4*S*)-*trans*-332a:**

**TLC (cyclohexane/EtOAc: 90/10):** *R<sub>f</sub>* = 0.26 (UV inactive; KMnO<sub>4</sub>, stains yellow).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 4.31-4.19 (m, 2H, H-2), 4.14 (qd, *J* = 7.2, 3.1 Hz, 4H, H-23, H-24), 3.99-3.88 (m, 2H, H-10), 3.74 (dd, *J* = 11.9, 9.8 Hz, 1H, H-7), 3.51 (d, *J* = 11.8 Hz, 1H, H-20), 3.04 (q, *J* = 9.5 Hz, 1H, H-4), 2.66 (d, *J* = 9.5 Hz, 1H, H-5a), 2.16-1.76 (m, 3H, H-5b, H-9), 1.32-1.22 (m, 9H, H-1, H-25, H-26), 1.13-1.01 (m, 21H, H-11, H-12, H-13, H-14, H-15, H-16, H-17, H-18, H-19).

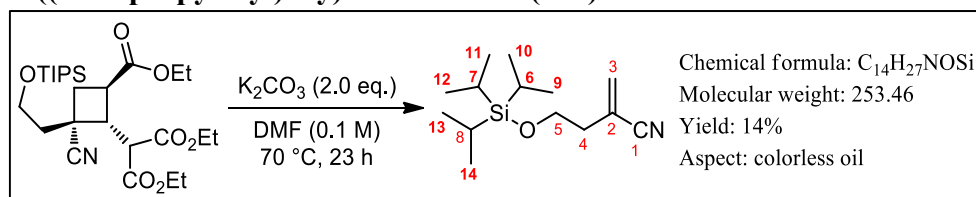
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 172.0 (C-3), 166.9 (C-21), 166.8 (C-22), 121.8 (C-8), 62.3 (C-23), 62.1 (C-24), 61.2 (C-2), 60.5 (C-10), 51.9 (C-20), 44.3 (C-7), 38.9 (C-4), 33.4 (C-9), 33.2 (C-6), 33.1 (C-5), 18.1 (C-14, C-15, C-16, C-17, C-18, C-19), 14.2 (C-1), 14.1 (C-25), 14.0 (C-26), 12.0 (C-11, C-12, C-13).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2943 (-C-H), 2867 (-C-H), 2232 (C≡N), 1735 (br, 3-C=O, 21-C=O, 22-C=O), 1464, 1370, 1234, 1183, 1101, 1033, 882, 683.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>26</sub>H<sub>45</sub>NO<sub>7</sub>SiNa [M+Na]<sup>+</sup> 534.2857, **found** 534.2843.

$[\alpha]_{\text{D}}^{25}$  = -0.99 (*c* = 0.25, CHCl<sub>3</sub>).

## 2-methylene-4-((triisopropylsilyl)oxy)butanenitrile (338)



In a dried two-necked flask, the cyclobutane **332a** (58.0 mg, 0.11 mmol, 1.0 eq.) was dissolved in dry DMF (1.1 mL, 0.1 M), and K<sub>2</sub>CO<sub>3</sub> (32.0 mg, 0.22 mmol, 2.0 eq.) was added at the end. The reaction mixture was stirred at 70 °C silicon oil bath temperature for 23 h, then aq. HCl (1.0 M) (3 mL) was added and the reaction was extracted with EtOAc (7 mL). The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude mixture was purified through column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc: 90/10) to afford the side product (4.0 mg, 14%) as a colorless oil.

**TLC (cyclohexane/EtOAc: 70/30):** *R<sub>f</sub>* = 0.8 (UV active; KMnO<sub>4</sub>, stains yellow).

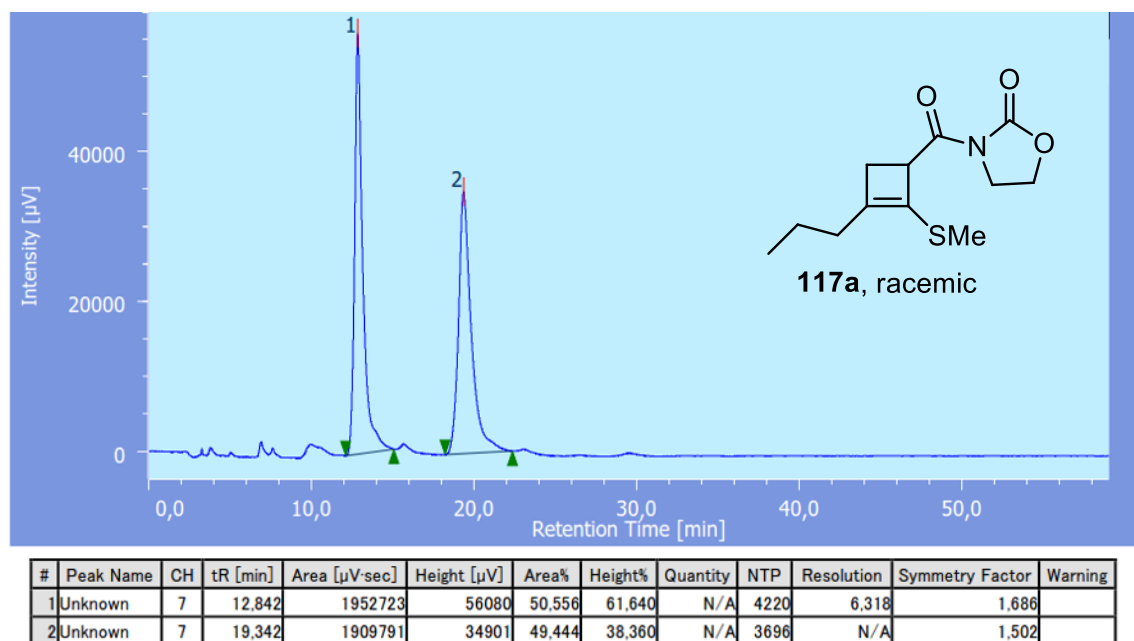
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 5.92 (s, 1H, H-3a), 5.80 (s, 1H, H-3b), 3.88 (t, *J* = 6.1 Hz, 2H, H-5), 2.47 (tdd, *J* = 6.1, 1.4, 0.7 Hz, 2H, H-4), 1.08-1.03 (m, 21H, H-6, H-7, H-8, H-9, H-10, H-11, H-12, H-13, H-14).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 132.3 (C-3), 120.6 (C-1), 118.8 (C-2), 60.9 (C-5), 38.3 (C-4), 18.1 (C-9, C-10, C-11, C-12, C-13, C-14), 12.0 (C-6, C-7, C-8).

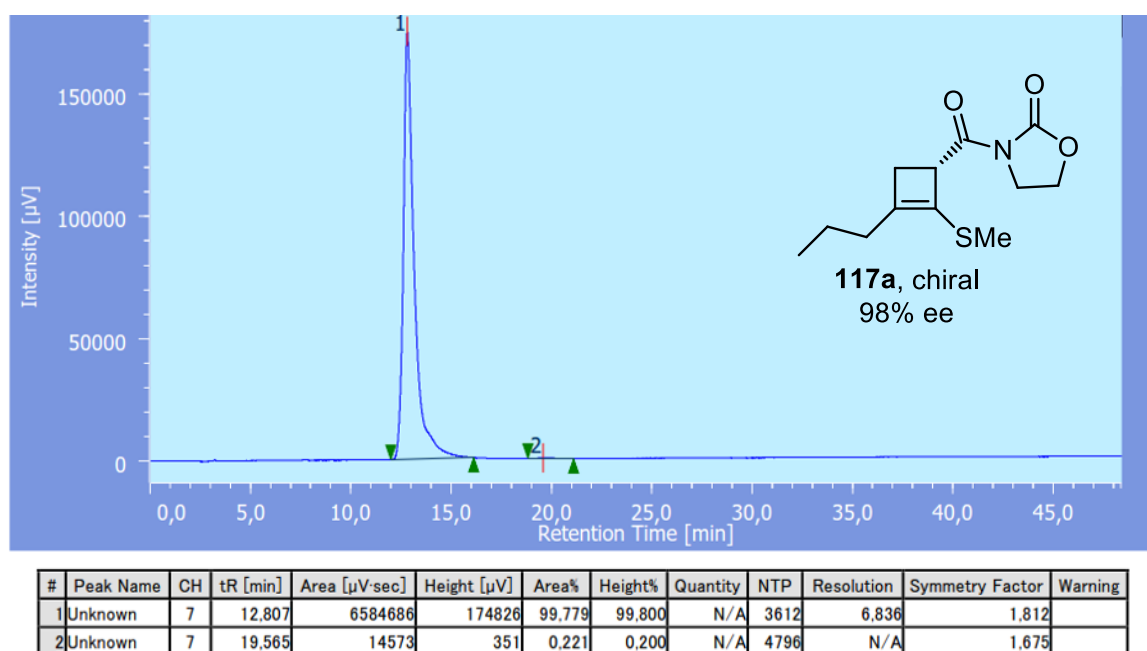
**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2944 (-C-H), 2867 (-C-H), 2225 (C≡N), 1463, 1111, 882, 682.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>14</sub>H<sub>27</sub>NOSiNa [M+Na]<sup>+</sup> 276.1754, **found** 276.1748.

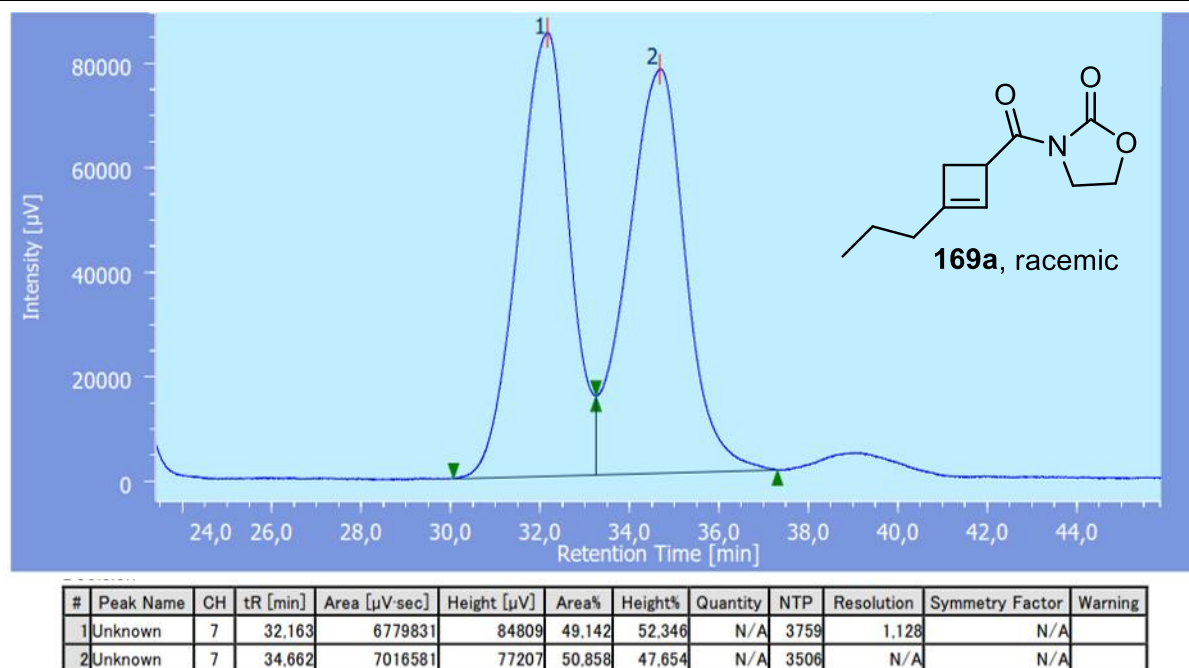
## 17. Enantiomeric excess measurements



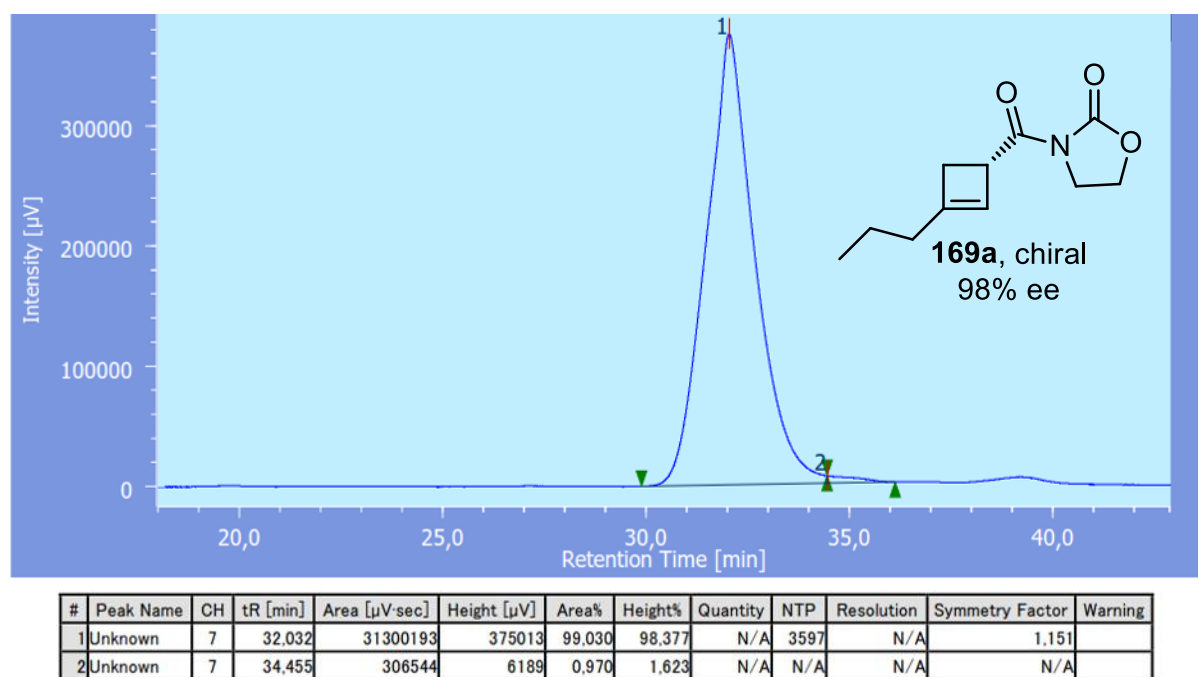
**Figure S.7.** HPLC trace of racemic compound **117a**, synthesized according to the general procedure (D) – method A. Analytical Chiralpak® IA column (4.6 mmΦ x 250 mmL, particle size 5 µm), *n*-hexane/ethanol: 90/10, 1 mL/min, 20 °C.



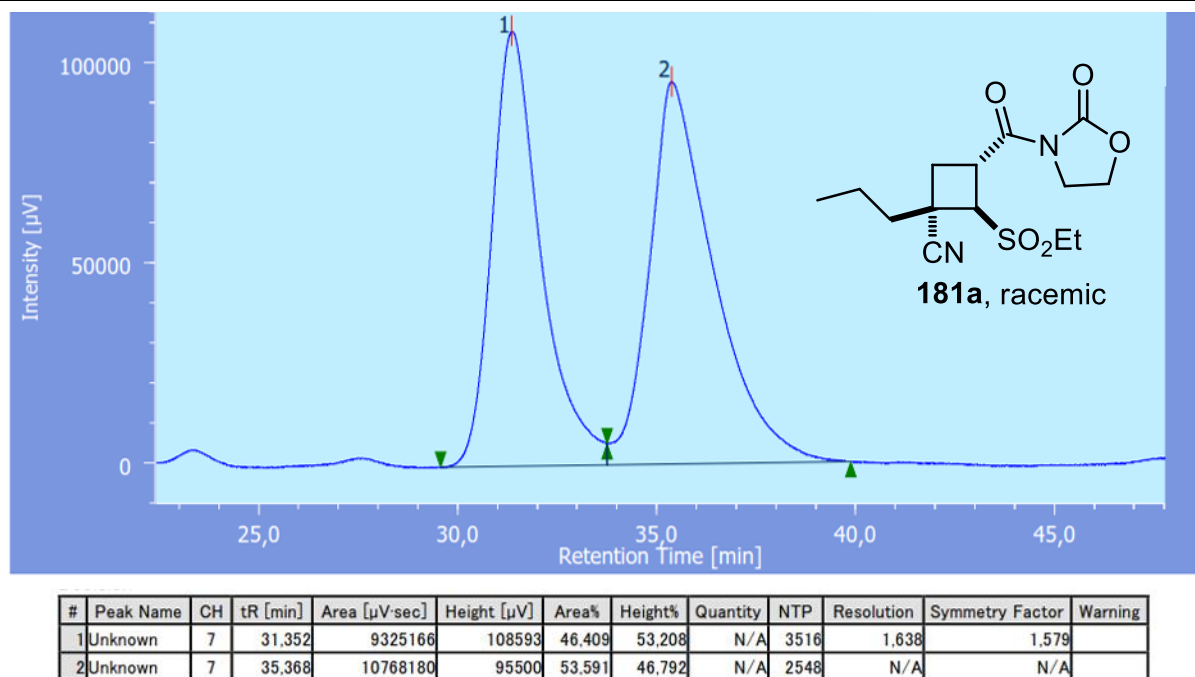
**Figure S.8.** HPLC trace of chiral compound **117a**. Analytical Chiralpak® IA column (4.6 mmΦ x 250 mmL, particle size 5 µm), *n*-hexane/ethanol: 90/10, 1 mL/min, 20 °C.



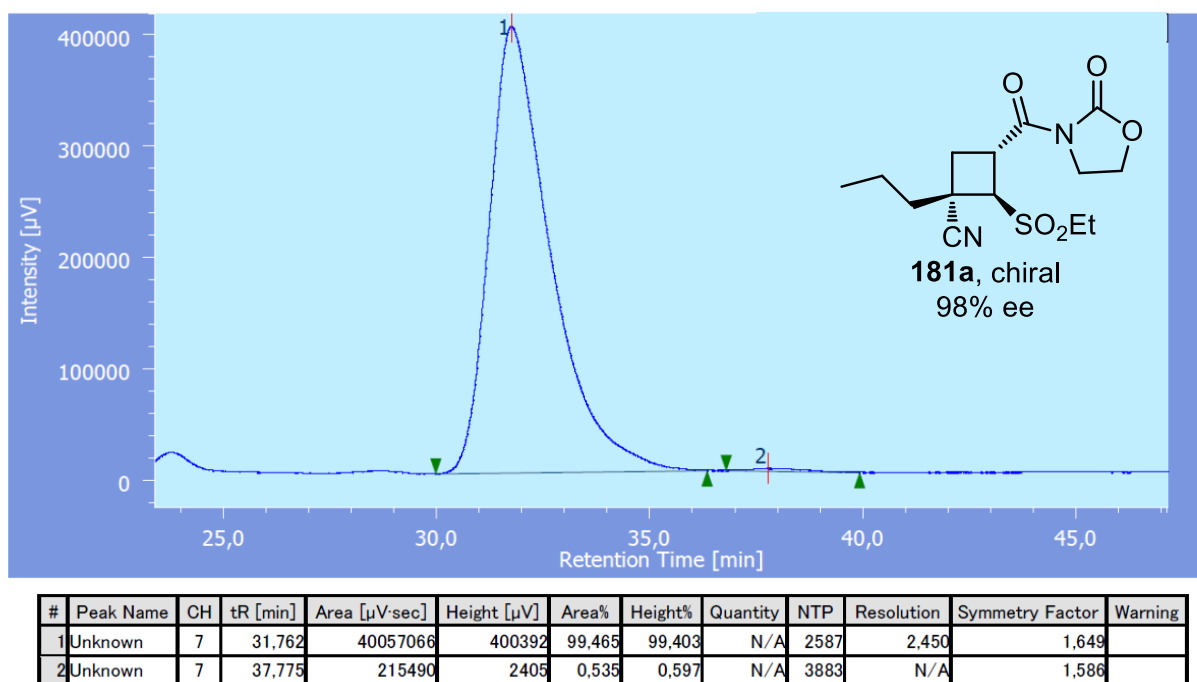
**Figure S.9.** HPLC trace of racemic compound **169a**. Analytical Chiralpak® IA column (4.6 mmΦ x 250 mmL, particle size 5 μm), *n*-hexane/ethanol: 90/10, 1 mL/min, 20 °C.



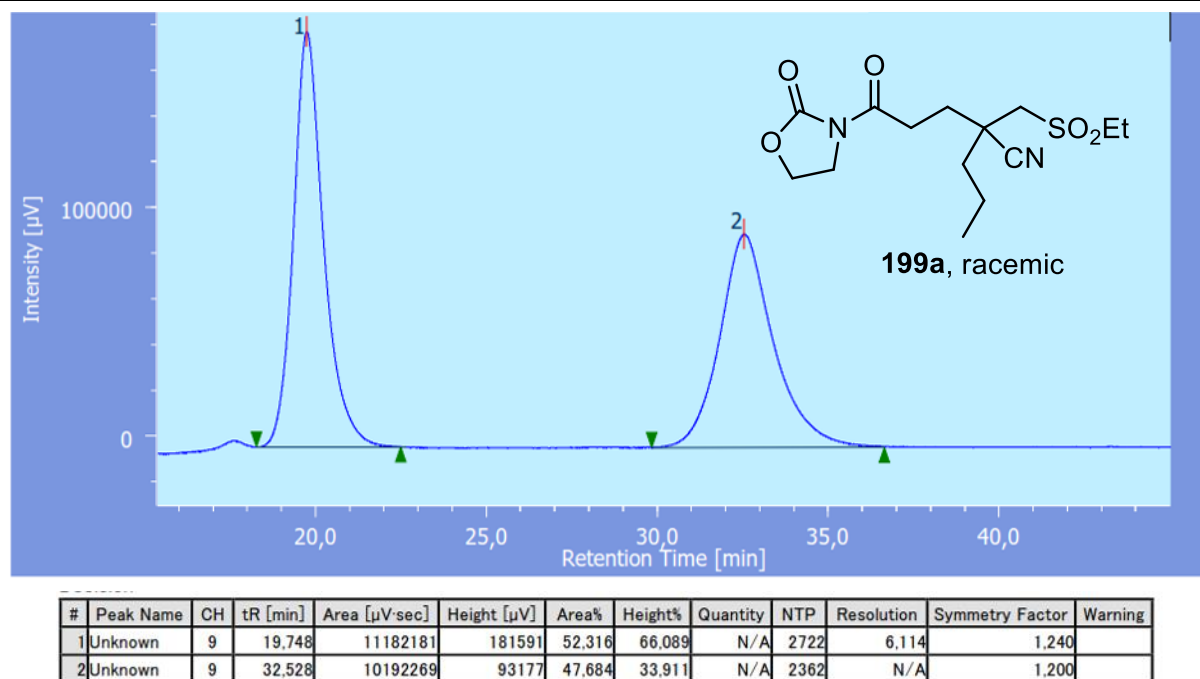
**Figure S.10.** HPLC trace of chiral compound **169a**. Analytical Chiralpak® IA column (4.6 mmΦ x 250 mmL, particle size 5 μm), *n*-hexane/ethanol: 90/10, 1 mL/min, 20 °C.



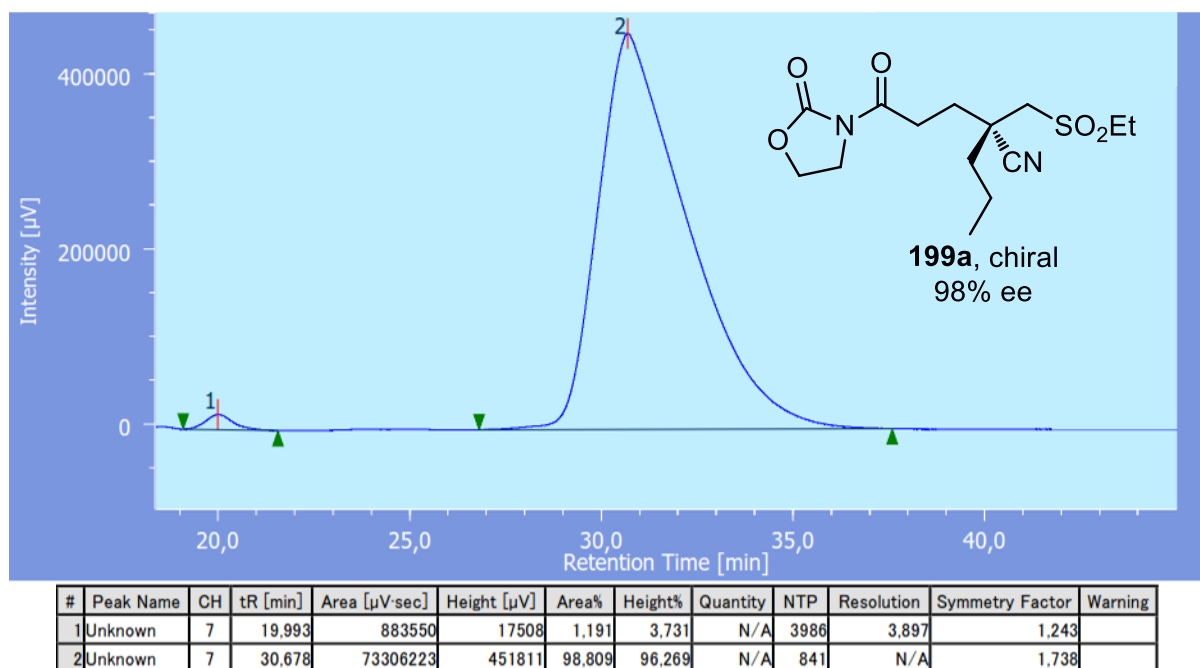
**Figure S.11.** HPLC trace of racemic compound **181a**. Analytical Chiralpak® IA column (4.6 mmΦ x 250 mmL, particle size 5 µm), *n*-hexane/ethanol: 75/25, 1 mL/min, 20 °C.



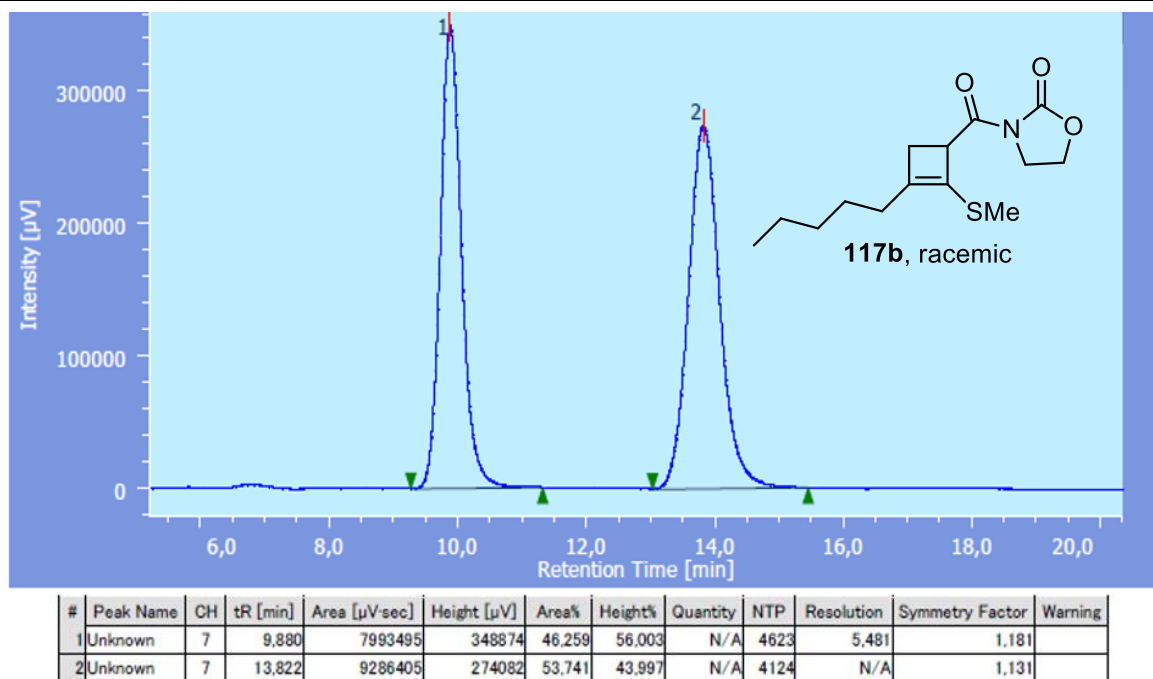
**Figure S.12.** HPLC trace of chiral compound **181a**. Analytical Chiralpak® IA column (4.6 mmΦ x 250 mmL, particle size 5 µm), *n*-hexane/ethanol: 75/25, 1 mL/min, 20 °C.



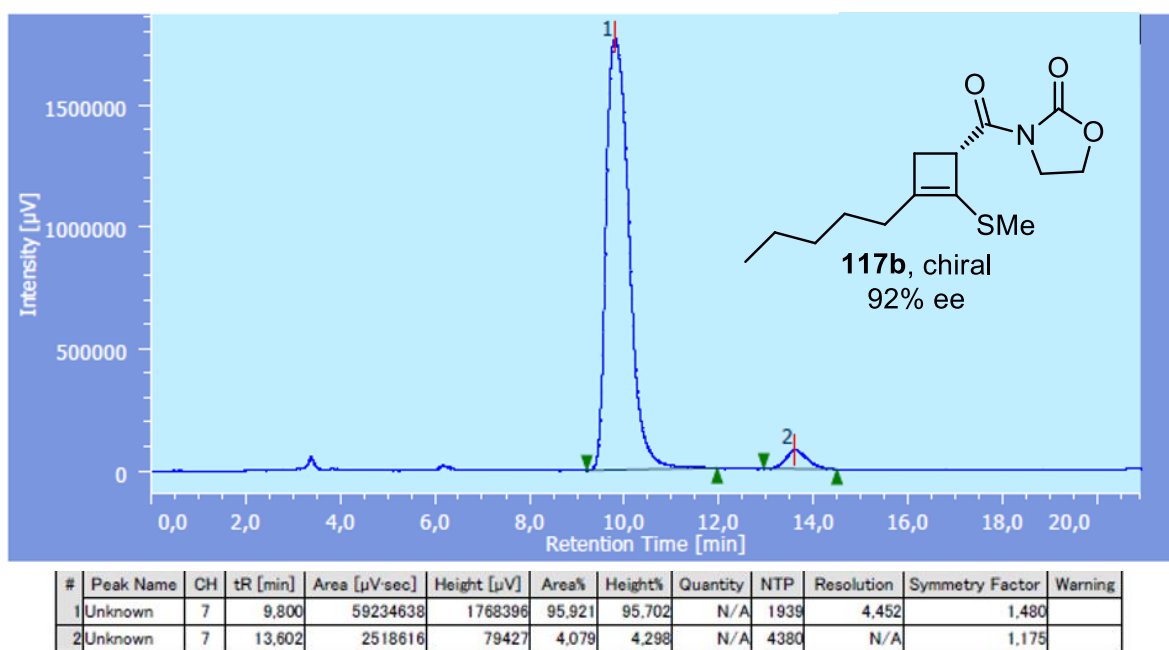
**Figure S.13.** HPLC trace of racemic compound **199a**. Analytical Chiralpak® IA column (4.6 mmΦ x 250 mmL, particle size 5 μm), ethanol: 100%, 1 mL/min, 20 °C.



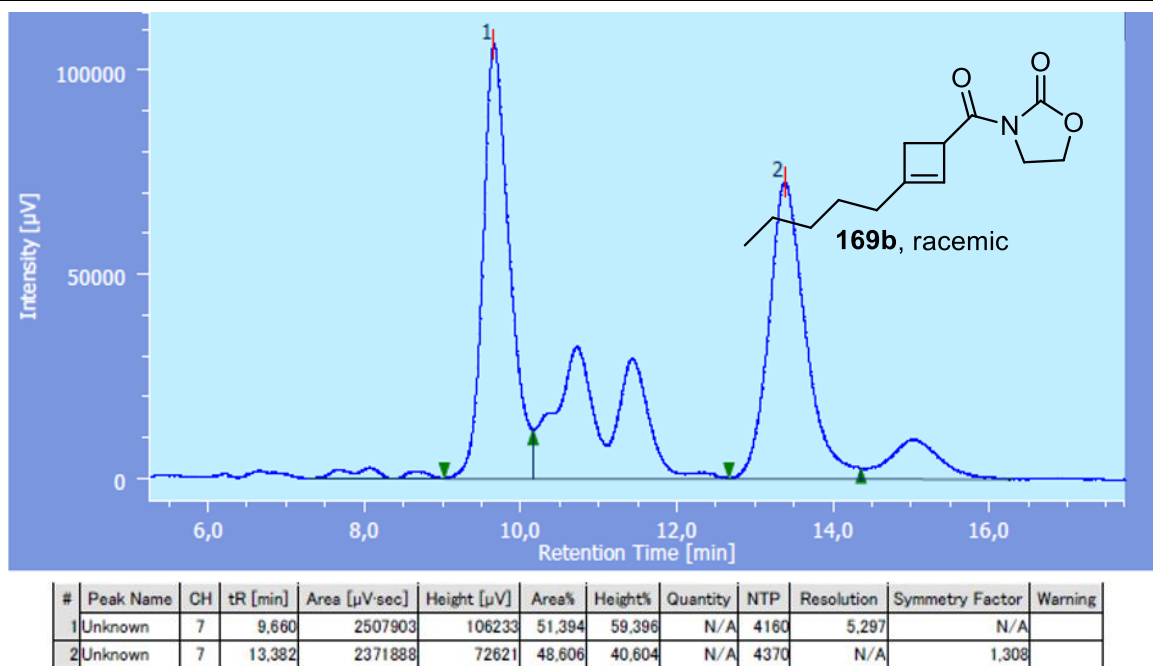
**Figure S.14.** HPLC trace of chiral compound **199a**. Analytical Chiralpak® IA column (4.6 mmΦ x 250 mmL, particle size 5 μm), ethanol: 100%, 1 mL/min, 20 °C.



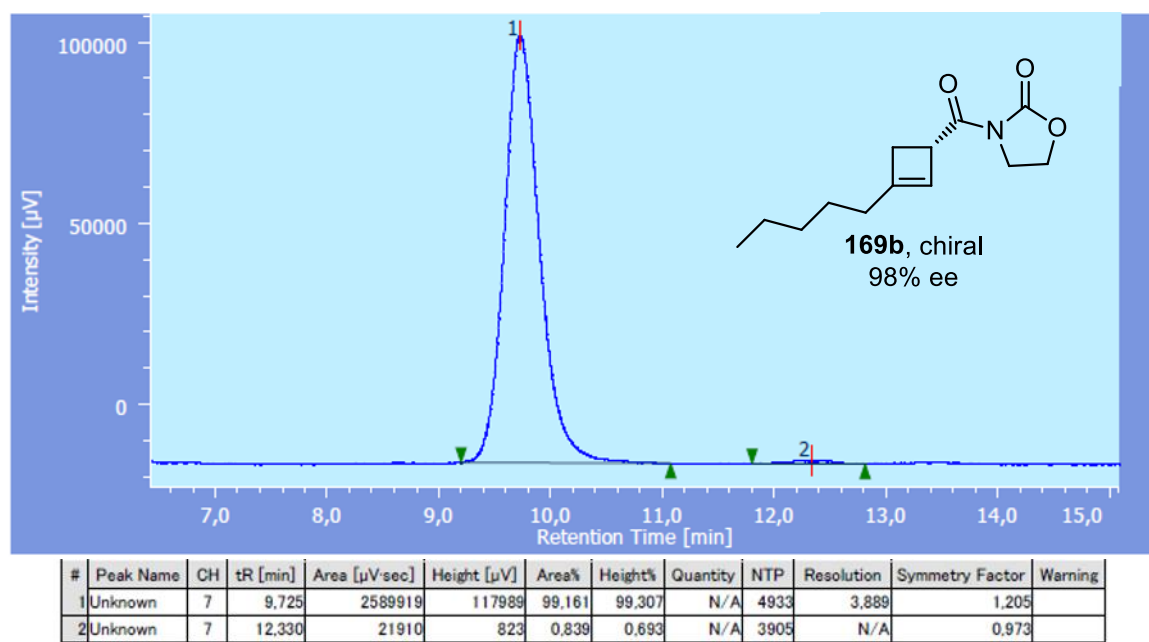
**Figure S.15.** HPLC trace of racemic compound **117b**, synthesized according to the general procedure (D) – method B. Analytical Chiralpak® IA column (4.6 mmΦ x 250 mmL, particle size 5 µm), *n*-hexane/ethanol: 90/10, 1 mL/min, 20 °C.



**Figure S.16.** HPLC trace of chiral compound **117b**. Analytical Chiralpak® IA column (4.6 mmΦ x 250 mmL, particle size 5 µm), *n*-hexane/ethanol: 90/10, 1 mL/min, 20 °C.

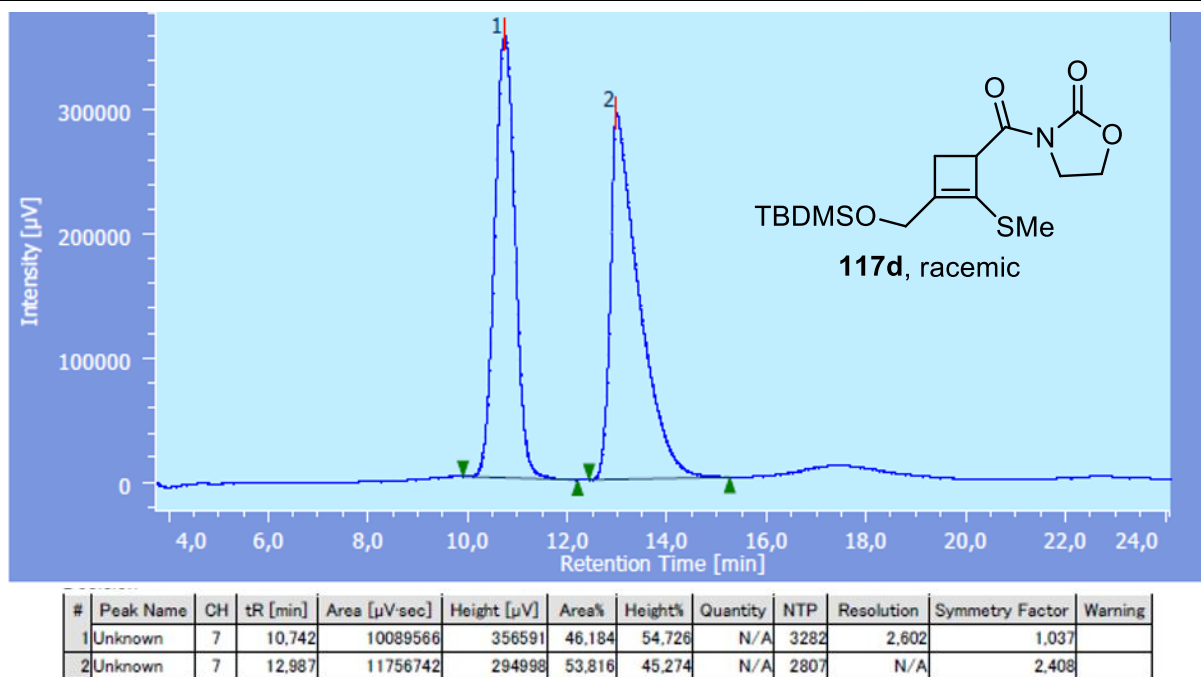


**Figure S.17.** HPLC trace of racemic compound **169b**. Analytical Chiralpak® IA column (4.6 mmΦ x 250 mmL, particle size 5 μm), *n*-hexane/ethanol: 90/10, 1 mL/min, 20 °C.

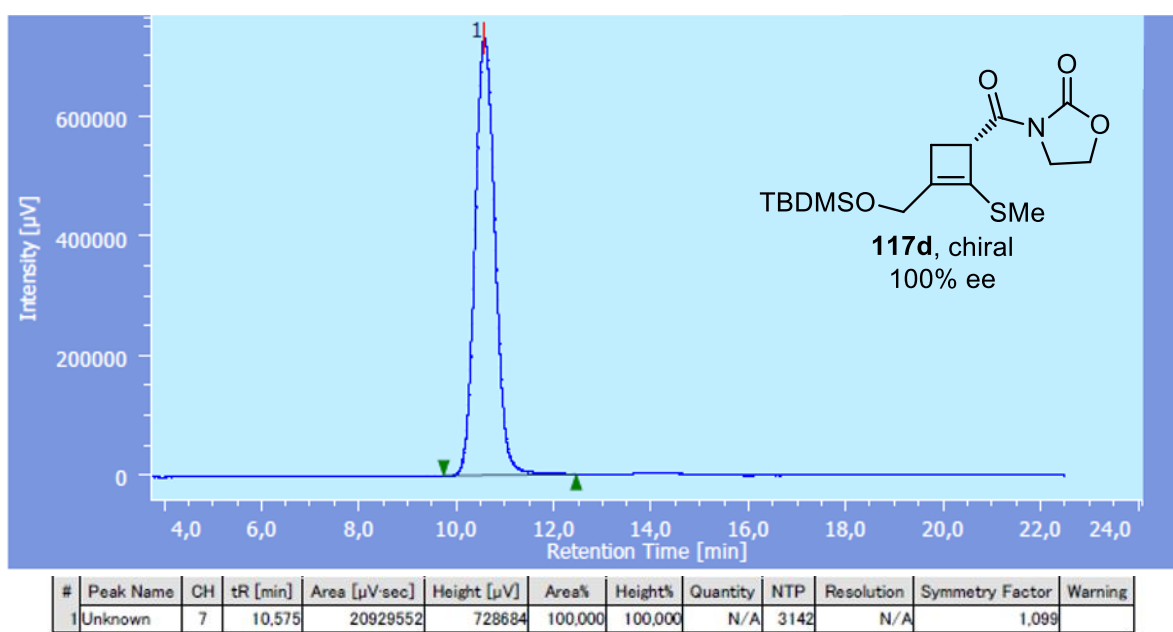


**Figure S.18.** HPLC trace of chiral compound **169b**. Analytical Chiralpak® IA column (4.6 mmΦ x 250 mmL, particle size 5 μm), *n*-hexane/ethanol: 90/10, 1 mL/min, 20 °C.



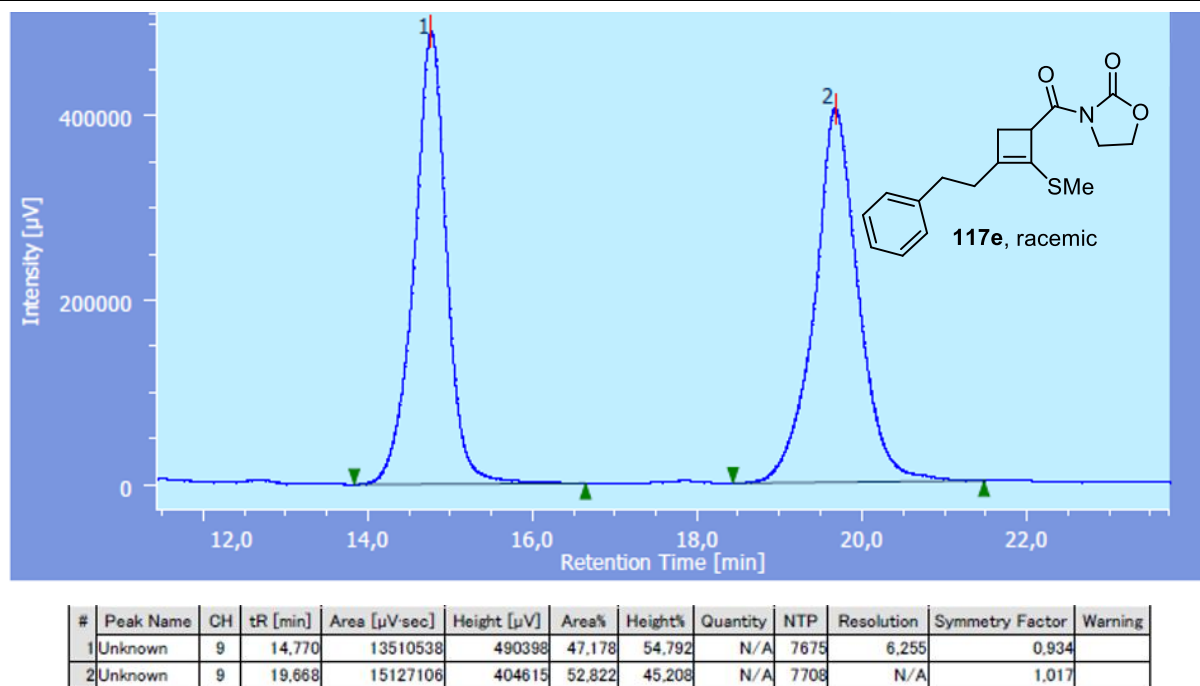


**Figure S.19.** HPLC trace of racemic compound **117d**, synthesized according to the general procedure (**D**) – **method B**. Analytical Chiralpak® IA column (4.6 mmΦ x 250 mmL, particle size 5 µm), *n*-hexane/ethanol: 95/5, 1 mL/min, 20 °C.

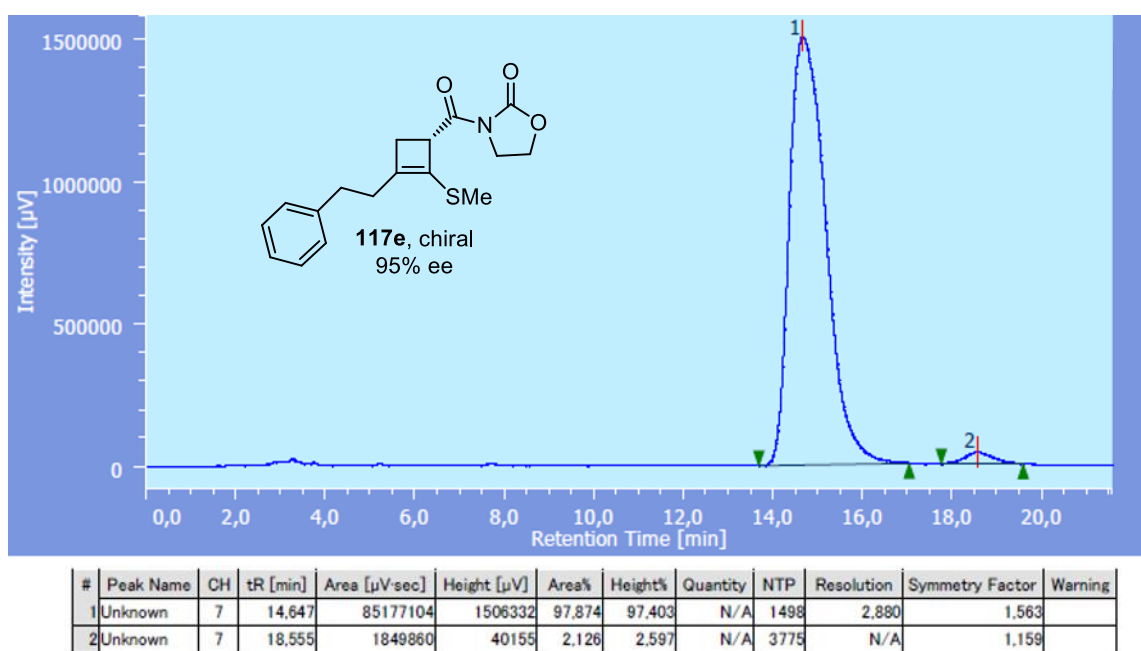


**Figure S.20.** HPLC trace of chiral compound **117d**. Analytical Chiralpak® IA column (4.6 mmΦ x 250 mmL, particle size 5 µm), *n*-hexane/ethanol: 95/5, 1 mL/min, 20 °C.



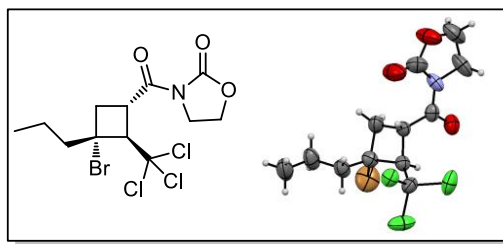


**Figure S.21.** HPLC trace of racemic compound **117e**, synthesized according to the general procedure (D) – method B. Analytical Chiralpak® IA column (4.6 mmΦ x 250 mmL, particle size 5 µm), *n*-hexane/ethanol: 85/15, 1 mL/min, 20 °C.



**Figure S.22.** HPLC trace of chiral compound **117e**. Analytical Chiralpak® IA column (4.6 mmΦ x 250 mmL, particle size 5 µm), *n*-hexane/ethanol: 85/15, 1 mL/min, 20 °C.

## 18. Crystallographic data

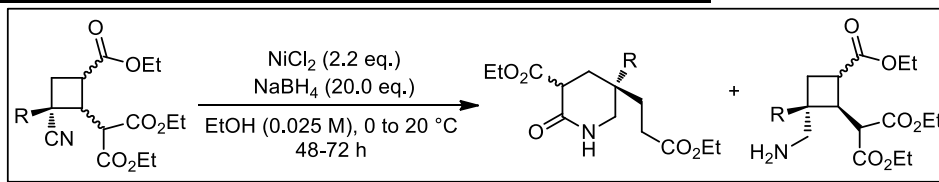
**3-((1*S*,2*S*,3*R*)-3-bromo-3-propyl-2-(trichloromethyl)cyclobutanecarbonyl)oxazolidin-2-one (180a)**

Empirical Formula	C <sub>12</sub> H <sub>15</sub> BrCl <sub>3</sub> NO <sub>3</sub>
Formula Weight	407.51
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, P 21 21 21
Unit cell dimensions	a = 10.4994(13) Å      α = 90°
	b = 12.2463(15) Å      β = 90°
	c = 12.3909(15) Å      γ = 90°
Volume	1593.2(3) Å <sup>3</sup>
Z, Calculated density	4, 1.699 Mg/m <sup>3</sup>
Absorption coefficient	3.088 mm <sup>-1</sup>
F(000)	816
Crystal size	0.200 x 0.100 x 0.050 mm
Theta range for data collection	2.543 to 27.187°
Limiting indices	-13 ≤ h ≤ 13, -12 ≤ k ≤ 15, -15 ≤ l ≤ 15
Reflections collected / unique	26735 / 3543 [R(int) = 0.0438]
Completeness to theta = 25.242	99.9%
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Data / restraints / parameters	3543 / 0 / 182
Goodness-of-fit on F <sup>2</sup>	1.030
Final R indices [I > 2σ(I)]	R <sub>I</sub> = 0.0227, wR <sub>2</sub> = 0.0440
R indices (all data)	R <sub>I</sub> = 0.0290, wR <sub>2</sub> = 0.0454
Absolute structure parameter	0.004(4)
Extinction coefficient	n/a
Largest diff. peak and hole	0.258 and -0.372 e.Å <sup>-3</sup>
CCDC number	1925745

## Experimental Part – Chapter IV

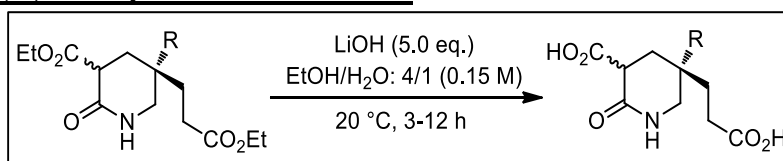
### 1. General procedures for chapter IV

#### General procedure (A) for nickel-catalysed lactamization reaction



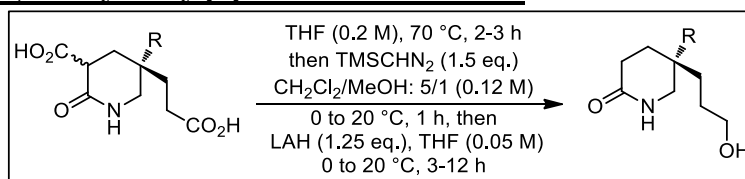
To a flame-dried flask and under inert atmosphere, the crude cyclobutane **332** (1.0 eq.) was introduced followed by anhydrous  $\text{NiCl}_2$  (2.2 eq.), then freshly distilled EtOH (0.025 M). The reaction was set at 0 °C and  $\text{NaBH}_4$  (20.0 eq.) was added portion-wise for 5-10 min depending on the scale. The reaction was warmed up slowly to 20 °C and kept under vigorous stirring for the indicated time. After total consumption of the starting material as shown by TLC, the reaction mixture was concentrated under reduced pressure, then diluted with EtOAc and extracted with aqueous HCl (0.4 M). The aqueous phase was charged with 2 spoons of NaCl then extracted twice with EtOAc. The combined organic layers were washed with minimum quantity of brine (20 mL), dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The crude mixture was purified through column chromatography on  $\text{SiO}_2$  ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ : eluants as noted) to afford the pure desired product and the reduced amine. The product was stored under inert atmosphere in the freezer.

#### General procedure (B) for saponification reaction



To a dried flask under inert atmosphere, the starting material (1.0 eq.) was introduced, followed by EtOH/ $\text{H}_2\text{O}$ : 4/1 (0.15 M) then LiOH (5.0 eq.). The reaction was stirred at 20 °C and followed by TLC. After completion, the solvents were evaporated and the reaction was diluted with water and extracted with EtOAc. The aqueous layer was acidified with concentrated HCl till pH = 1, then charged with 2 spoons of NaCl and extracted with EtOAc (4 x). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The crude was used directly in the next step without further purification. The product was stored under inert atmosphere in the freezer.

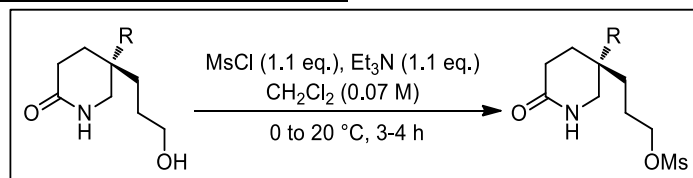
#### General procedure (C) for hydroxy piperidinone formation



To a flame-dried flask equipped with a condenser and under inert atmosphere, the crude diacid (1.0 eq.) was introduced, followed by dry THF (0.2 M). The reaction was heated at 70 °C for 2-3 h, then cooled down to 20 °C. The solvent was concentrated under reduced pressure then the crude mixture (1.0 eq.) was set under inert atmosphere and dissolved in dry  $\text{CH}_2\text{Cl}_2/\text{MeOH}$ : 5/1 (0.12 M).  $\text{TMSCHN}_2$  (2.0 M in hexane, 1.5 eq.) was added at 0 °C and the mixture was stirred at 20 °C for 1 h. The reaction was quenched with AcOH (0.3 eq.) and stirred for 2 min then the solvents were concentrated under reduced pressure. [Purification of the crude for analysis was accomplished through short column chromatography on  $\text{SiO}_2$  ( $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_4\text{OH}$ : 98/1/1 to 95/4/1)]. The crude mixture (1.0 eq.) was set again under inert atmosphere and dissolved in dry THF (0.05 M) then LAH (1.0 M in Et<sub>2</sub>O, 1.25 eq.) was added dropwise at 0 °C. The reaction was warmed up slowly to 20 °C and followed by TLC. After completion, it was diluted with EtOAc and extracted with

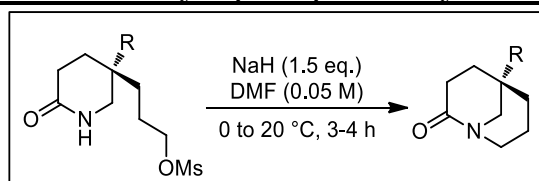
minimum amount of water (5-10 mL). The aqueous phase was saturated with 2 spoons of NaCl and extracted with EtOAc (5 x). The combined organic layers were washed with brine (5-10 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude was used directly in the next step without further purification. [Purification of the crude for analysis was accomplished through short column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>4</sub>OH: 95/4/1)]. The product was stored under inert atmosphere in the freezer.

#### **General procedure (D) for mesylate formation**<sup>48</sup>



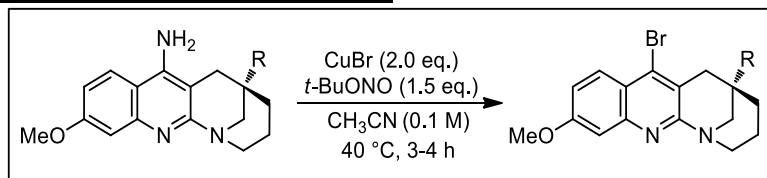
To a flame-dried flask and under inert atmosphere, the hydroxy piperidinone (1.0 eq.) was introduced followed by dry CH<sub>2</sub>Cl<sub>2</sub> (0.07 M) and the reaction was set at 0 °C. MsCl (1.1 eq.) was added slowly followed by distilled Et<sub>3</sub>N (1.1 eq.) and the reaction was stirred at 20 °C for 3-4 h and followed by TLC. After completion, the reaction was quenched with minimum amount of water (5-10 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The aqueous phase was saturated with 2 spoons of NaCl and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x). The combined organic layers were washed with brine (5 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude mixture was used directly in the next step without further purification. [Purification of the crude for analysis was accomplished through short column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>4</sub>OH: 95/4/1)]. The product was stored under inert atmosphere in the freezer.

#### **General procedure (E) for chiral azabicyclo[3.3.1]nonane synthesis**<sup>48</sup>



To a flame-dried two-necked flask and under inert atmosphere, DMF AcroSeal™ packaging (0.1 M) was introduced and the reaction was set at 0 °C. NaH (60% suspension in oil, 1.5 eq.) was added followed by dropwise addition of the mesylate (1.0 eq.) dissolved in DMF (0.1 M), then the mixture was stirred at 20 °C for 3-4 h. After completion, the reaction was quenched with minimum amount of water (5 mL) and extracted with EtOAc. The aqueous phase was saturated with 2 spoons of NaCl and extracted with EtOAc (2 x). The combined organic layers were washed with brine (5 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated carefully under reduced pressure. The crude was purified through short column chromatography on SiO<sub>2</sub> (eluants as noted) to afford the pure desired product. The product was stored under inert atmosphere in the freezer.

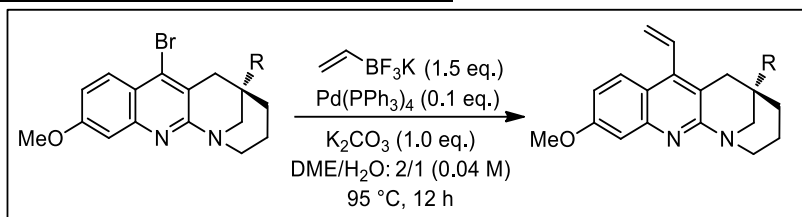
#### **General procedure (F) for Sandmeyer reaction**



To a flame-dried 10 mL schlenk tube equipped with a Teflon stopcock, the amino quinoline (1.0 eq.) was introduced, followed by CuBr (2.0 eq.), and the atmosphere was exchanged with vacuum/argon (3 x). Freshly distilled CH<sub>3</sub>CN (0.1 M) and *t*-BuONO (1.5 eq.) were added respectively and the black mixture was stirred at 40 °C silicon oil bath temperature for 3-4 h. After completion, the solvents were concentrated under reduced pressure and the crude mixture was purified through column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>4</sub>OH: percentages as noted) to afford the pure desired

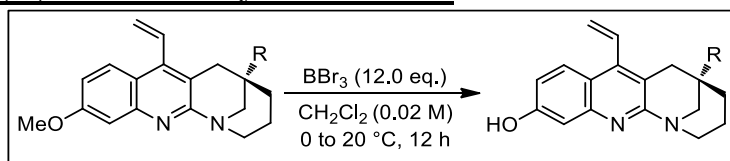
product. [All the solvents used for purification were distilled prior to use to remove the traces of impurities present in the commercial bottles].

### General procedure (G) for Suzuki coupling reaction



To a flame-dried 10 mL schlenk tube equipped with a Teflon stopcock, the bromoquinoline (1.0 eq.) was introduced, followed by Potassium vinyltrifluoroborate (1.5 eq.) and anhydrous (oven dried)  $K_2CO_3$  (1.0 eq.) and the atmosphere was exchanged with vacuum/argon (3 x). Freshly distilled DME (0.06 M) and distilled  $H_2O$  (0.12 M) were added respectively and the mixture was degassed through argon bubbling for 30 min.  $Pd(PPh_3)_4$  (0.1 eq.) was then added and the reaction mixture was stirred at 95 °C silicon oil bath temperature for 12 h. After completion, the solvents were concentrated under reduced pressure and the crude mixture was purified through micro-column chromatography on  $SiO_2$  ( $CH_2Cl_2/MeOH$ : 99/0 to 99/1 to 98/2) to afford the pure desired product as a yellow viscous oil. The purity of the column fractions was checked through the UV different wavelengths (254 nm and 365 nm). At 365 nm,  $PPh_3$  residues appear dark blue, the desired product appears light blue sky, and the starting material is inactive. [All the solvents used for purification were distilled to remove the traces of impurities present in the commercial bottles].

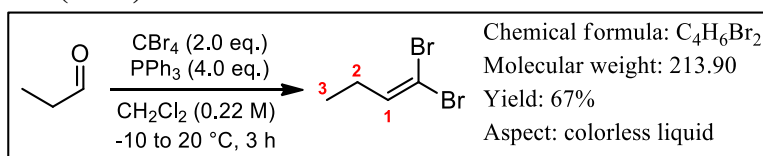
### General procedure (H) for *O*-demethylation reaction



To a flame-dried flask and under inert atmosphere, the vinyl quinoline (1.0 eq.) was introduced, and the atmosphere was exchanged with vacuum/argon (3 x).  $CH_2Cl_2$  freshly distilled from  $CaH_2$  (0.02 M) was added and the reaction mixture was set at 0 °C.  $BBr_3$  (1.0 M in  $CH_2Cl_2$ , 12.0 eq.) was then added dropwise, the color changed to yellow then brown with observation of orange precipitate. The reaction mixture was allowed to warm up slowly and stirred at 20 °C for 12 h. After completion, the reaction was quenched at 0 °C with dropwise addition of MeOH (0.1-0.2 mL), the addition of MeOH may continue till the disappearance of the white fume and the solubilization of the precipitate. the solvents were concentrated under reduced pressure and the crude mixture was purified through micro-column chromatography on  $SiO_2$  ( $CH_2Cl_2/MeOH$ : 99/1 to 98/2) to afford the pure desired product as a yellow solid. The purity of the column fractions was checked through the UV different wavelengths (254 nm and 365 nm). At 365 nm, the desired product appears light blue sky. On TLC, when concentrated, the product appears yellow. [All the solvents used for purification were distilled to remove the traces of impurities present in the commercial bottles].

## 2. Synthesis of the starting materials

### 1,1-dibromobut-1-ene (393a)<sup>368</sup>



To a flame-dried two-necked flask, dry  $CH_2Cl_2$  (300.0 mL, 0.22 M) was introduced and the reaction was set at -10 °C (ice/acetone bath: 1/1).  $CBr_4$  (45.0 g, 136.0 mmol, 2.0 eq.) was added, followed by  $PPh_3$  (70.8 g, 270.0 mmol, 4.0 eq.), and the color turned to brown with orange precipitate. The mixture was stirred at the same temperature for 40 min, then propionaldehyde AcroSeal™ packaging stored

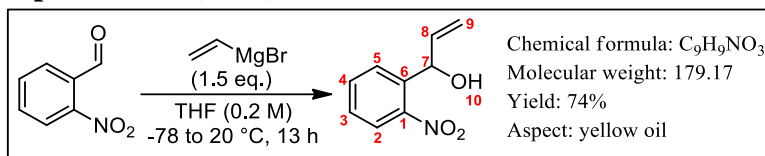
under argon (4.9 mL, 67.5 mmol, 1.0 eq.) was added dropwise and the mixture was stirred for further 2.5 h at 0 °C, then allowed to warm to 20 °C. The solvents were concentrated under reduced pressure at 25-30 °C. the solid residue was washed with pentane, filtered through a silica plug, and the filtrate was concentrated under reduced pressure. The crude mixture was purified through short column chromatography on SiO<sub>2</sub> (pentane: 100%). The product was concentrated carefully under reduced pressure (volatile) to afford the product (9.6 g, 67%) as a colorless liquid and stored under argon in the freezer.

**TLC (cyclohexane: 100%):**  $R_f$  = 0.71 (UV active; KMnO<sub>4</sub>, stains yellow).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 6.39 (t,  $J$  = 7.2 Hz, 1H, H-1), 2.11 (quint,  $J$  = 7.5 Hz, 2H, H-2), 1.03 (t,  $J$  = 7.6 Hz, 3H, H-3).

The <sup>1</sup>H NMR data are in agreement with those reported in the literature.<sup>368</sup>

### 1-(2-nitrophenyl)prop-2-en-1-ol (401a)<sup>473</sup>



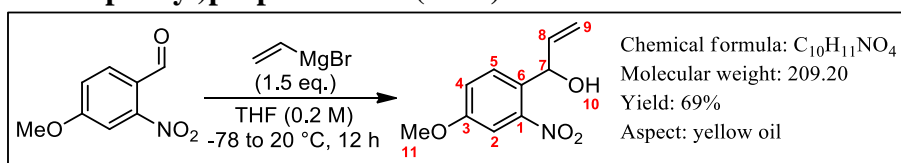
To a flame-dried flask, 2-nitrobenzaldehyde (184.0 mg, 1.2 mmol, 1.0 eq.) was introduced and the atmosphere was exchanged with argon/vacuum (3 x). Dry THF (6.0 mL, 0.2 M) was added then the reaction was set at -78 °C. Vinylmagnesium bromide (1.0 M in THF, 1.82 mL, 1.82 mmol, 1.5 eq.) was added slowly and the reaction was stirred for 1 h at the same temperature, then at 20 °C for 12 h. The reaction was quenched with aqueous HCl (0.01 N) and extracted with EtOAc, the organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude mixture was purified through column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc: 90/10) to afford the product (160.0 mg, 74%) as a yellow oil. The product was stored under inert atmosphere in the freezer.

**TLC (cyclohexane/EtOAc: 80/20):**  $R_f$  = 0.36 (UV active; KMnO<sub>4</sub>, stains yellow).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 7.92 (dd,  $J$  = 8.1, 1.4 Hz, 1H, H-2), 7.77 (dd,  $J$  = 7.8, 1.5 Hz, 1H, H-3), 7.64 (td,  $J$  = 7.6, 1.3 Hz, 1H, H-5), 7.45 (td,  $J$  = 7.6, 1.3 Hz, 1H, H-4), 6.09 (ddd,  $J$  = 17.2, 10.4, 5.2 Hz, 1H, H-8), 5.80 (t,  $J$  = 4.9 Hz, 1H, H-7), 5.43 (dt,  $J$  = 17.2, 1.4 Hz, 1H, H-9a), 5.27 (dt,  $J$  = 10.4, 1.4 Hz, 1H, H-9b), 2.52 (d,  $J$  = 4.6 Hz, 1H, H-10).

The <sup>1</sup>H NMR data are in agreement with those reported in the literature.<sup>473</sup>

### 1-(4-methoxy-2-nitrophenyl)prop-2-en-1-ol (401b)



To a flame-dried flask, 4-methoxy-2-nitrobenzaldehyde (100.0 mg, 0.55 mmol, 1.0 eq.) was introduced and the atmosphere was exchanged with argon/vacuum (3 x). Dry THF (2.7 mL, 0.2 M) was added then the reaction was set at -78 °C. Vinylmagnesium bromide (1.0 M in THF, 0.82 mL, 0.82 mmol, 1.5 eq.) was added slowly and the reaction was stirred for 1 h at the same temperature, then at 20 °C for 11 h. The reaction was quenched with aqueous HCl (0.01 N) and extracted with EtOAc, the organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude mixture was purified through short column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc: 80/20) to afford the product (75.0 mg, 69%) as a yellow oil. The product was stored under inert atmosphere in the freezer.

**TLC (cyclohexane/EtOAc: 80/20):**  $R_f$  = 0.30 (UV active; KMnO<sub>4</sub>, stains white).

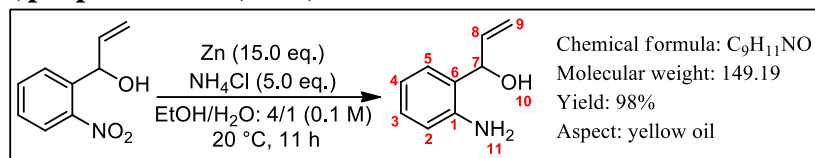
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 7.63 (d,  $J$  = 8.7 Hz, 1H, H-5), 7.42 (d,  $J$  = 2.7 Hz, 1H, H-2), 7.17 (dd,  $J$  = 8.7, 2.7 Hz, 1H, H-4), 6.06 (ddd,  $J$  = 17.2, 10.5, 5.0 Hz, 1H, H-8), 5.71 (t,  $J$  = 4.9 Hz, 1H, H-7), 5.41 (dt,  $J$  = 17.2, 1.5 Hz, 1H, H-9a), 5.25 (dt,  $J$  = 10.5, 1.4 Hz, 1H, H-9b), 3.87 (s, 3H, H-11), 2.52 (d,  $J$  = 4.6 Hz, 1H, H-10).

**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 158.6 (C-3), 147.2 (C-1), 137.1 (C-8), 128.5 (C-5), 126.1 (C-6), 115.1 (C-4), 114.9 (C-9), 109.2 (C-2), 69.7 (C-7), 56.0 (C-11).

**IR (solution in  $\text{CH}_2\text{Cl}_2$ , thin film, KBr):**  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 3387 (br, OH), 2926 (-C-H), 1620, 1529, 1352, 1242, 1033.

**HRMS (TOF, ES $^+$ ):** calculated for  $\text{C}_{10}\text{H}_{11}\text{NO}_4\text{Na}$   $[\text{M}+\text{Na}]^+$  232.05803, **found** 232.05793.

### 1-(2-aminophenyl)prop-2-en-1-ol (396a)<sup>372</sup>



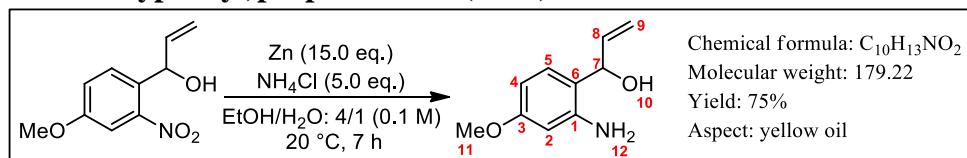
To a dried flask, **401a** (160.0 mg, 0.89 mmol, 1.0 eq.) was introduced followed by EtOH/ $\text{H}_2\text{O}$ : 4/1 (8.8 mL, 0.1 M),  $\text{NH}_4\text{Cl}$  (242.0 mg, 4.45 mmol, 5.0 eq.), and Zn dust (876.0 mg, 13.4 mmol, 15.0 eq.). The reaction was stirred at 20 °C for 11 h, then the ethanol was concentrated under reduced pressure and the reaction was diluted with  $\text{CH}_2\text{Cl}_2$  then filtered over a short celite pad. The filtrate was then extracted with  $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ , and the organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The crude mixture was purified through column chromatography on  $\text{SiO}_2$  (cyclohexane/EtOAc: 90/10 to 80/20) to afford the product (130.0 mg, 98%) as a yellow oil. The product was stored under inert atmosphere in the freezer.

**TLC (cyclohexane/EtOAc: 80/20):**  $R_f$  = 0.17 (UV active, appears fluorescent;  $\text{KMnO}_4$ , stains yellow; vanillin, stains red-brown then green after 5 min).

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 7.19-7.02 (m, 2H, H-3, H-5), 6.80-6.61 (m, 2H, H-2, H-4), 6.21 (ddd,  $J$  = 17.2, 10.4, 5.3 Hz, 1H, H-8), 5.40 (dt,  $J$  = 17.2, 1.5 Hz, 1H, H-9a), 5.29 (dt,  $J$  = 10.4, 1.5 Hz, 1H, H-9b), 5.25 (d,  $J$  = 5.3 Hz, 1H, H-7), 4.14 (br s, 2H, H-11), 2.13 (br s, 1H, H-10).

The  $^1\text{H}$  NMR data are in agreement with those reported in the literature.<sup>372</sup>

### 1-(2-amino-4-methoxyphenyl)prop-2-en-1-ol (396b)



To a dried flask, **401b** (65.0 mg, 0.31 mmol, 1.0 eq.) was introduced followed by EtOH/ $\text{H}_2\text{O}$ : 4/1 (3.0 mL, 0.1 M),  $\text{NH}_4\text{Cl}$  (84.4 mg, 1.55 mmol, 5.0 eq.), and Zn dust (305.0 mg, 4.66 mmol, 15.0 eq.). The reaction was stirred at 20 °C for 7 h, then the ethanol was concentrated under reduced pressure and the reaction was diluted with  $\text{CH}_2\text{Cl}_2$  then filtered over a short celite pad. The filtrate was then extracted with  $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ , and the organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The crude mixture was purified through column chromatography on  $\text{SiO}_2$  (cyclohexane/EtOAc: 80/20) to afford the product (42.0 mg, 75%) as a yellow oil. The product was stored under inert atmosphere in the freezer, degradation of the product was observed within 24 h at 20 °C.

**TLC (cyclohexane/EtOAc: 70/30):**  $R_f$  = 0.44 (UV active, appears fluorescent;  $\text{KMnO}_4$ , stains yellow).

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 7.05 (d,  $J$  = 8.3 Hz, 1H, H-5), 6.29 (dd,  $J$  = 8.3, 2.5 Hz, 1H, H-4), 6.25-6.10 (m, 2H, H-2, H-8), 5.39 (dt,  $J$  = 8.4, 1.5 Hz, 1H, H-9a), 5.34 (dt,  $J$  = 8.5, 1.6 Hz, 1H, H-9b), 5.23-5.17 (m, 1H, H-7), 4.19 (s, 2H, H-12), 3.81 (s, 3H, H-11), 1.99 (d,  $J$  = 4.6 Hz, 1H, H-10).

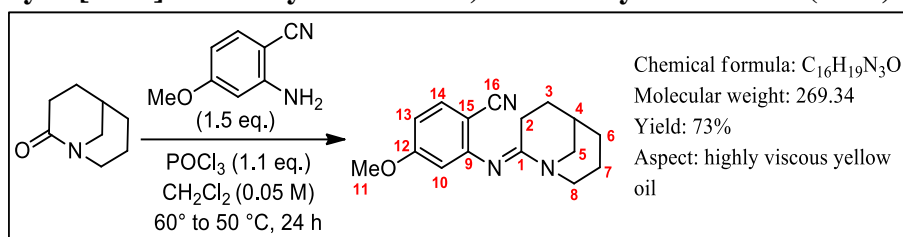
**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 160.5 (C-3), 146.6 (C-1), 138.6 (C-8), 129.3 (C-5), 115.3 (C-6, C-9), 103.5 (C-4), 102.5 (C-2), 74.1 (C-7), 53.5 (C-11).

**IR (solution in  $\text{CH}_2\text{Cl}_2$ , thin film, KBr):**  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 3371 (br, OH), 2930 (-C-H), 1608, 1509, 1209, 1169, 731.

**HRMS (TOF, ES $^+$ ):** calculated for  $\text{C}_{10}\text{H}_{12}\text{NO}$   $[\text{M}+\text{H}-\text{H}_2\text{O}]^+$  162.09134, **found** 162.09103.

## 3. Synthesis of *nor*-ethyleucophylline

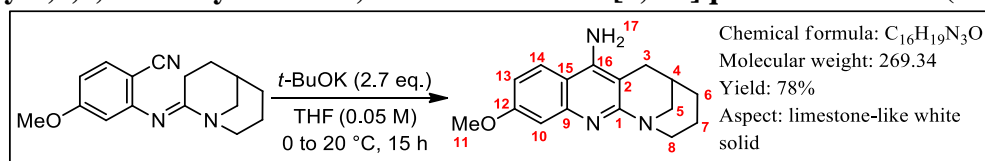


**(E)-2-(1-azabicyclo[3.3.1]nonan-2-ylideneamino)-4-methoxybenzonitrile (399a)**<sup>48</sup>

To a flame-dried two-necked flask equipped with a condenser, the bicyclic lactam **402** (87.0 mg, 0.62 mmol, 1.0 eq.) was introduced followed by dry CH<sub>2</sub>Cl<sub>2</sub> (6.2 mL, 0.1 M), and POCl<sub>3</sub> (64.0 μL, 0.68 mmol, 1.1 eq.) was added dropwise. The reaction was stirred at 60 °C silicon oil bath temperature and the starting material consumption was followed by TLC. After 7 h, the reaction was cooled down to 20 °C and 2-amino-4-methoxybenzonitrile **354** (137.0 mg, 0.93 mmol, 1.5 eq.) dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (5.8 mL, 0.1 M), was added dropwise. The reaction was stirred at 50 °C for 17 h, then the solvents were concentrated under reduced pressure and ice water (2.0 mL) was added to the reaction. The aqueous layer was basified with sat. NaHCO<sub>3</sub> till pH = 8, then extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude mixture was purified through column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc/NH<sub>4</sub>OH: 90/9/1) to afford the product (122.0 mg, 73%) as a highly viscous yellow oil.

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 80/20):** R<sub>f</sub> = 0.67 (UV active; KMnO<sub>4</sub>, stains yellow).

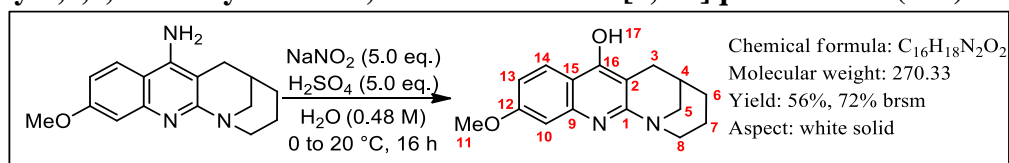
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ (ppm) = 7.46 (d, *J* = 8.7 Hz, 1H, H-14), 6.57 (dd, *J* = 8.7, 2.5 Hz, 1H, H-13), 6.32 (s, 1H, H-10), 4.31 (d, *J* = 13.1 Hz, 1H, H-8a), 3.81 (s, 3H, H-11), 3.31 (d, *J* = 13.6 Hz, 1H, H-5a), 3.04-2.95 (m, 2H, H-5b, H-8b), 2.50-2.08 (m, 5H, H-2, H-3a, H-6), 1.97-1.71 (m, 1H, H-3b), 1.62-1.56 (m, 1H, H-4), 1.51-1.31 (m, 2H, H-7).

**10-methoxy-3,4,5,6-tetrahydro-2H-1,5-methanoazocino[2,3-*b*]quinolin-7-amine (406)**<sup>48</sup>

To a flame-dried two-necked flask, the amidine **399a** (119.0 mg, 0.44 mmol, 1.0 eq.) was introduced followed by dry THF (9.0 mL, 0.05 M), and the reaction was set at 0 °C. *t*-BuOK (133.0 mg, 1.19 mmol, 2.7 eq.) was then added, and the color changed immediately to yellow-orange. The resulting solution was allowed to warm up slowly to 20 °C and stirred for 15 h. The reaction was quenched with sat. NaHCO<sub>3</sub> and extracted with EtOAc. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude mixture was purified through a short column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>4</sub>OH: 97/2/1 to 95/4/1) to afford the product (92.0 mg, 78%) as a limestone-like white solid. The product was stored under inert atmosphere in the freezer.

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>4</sub>OH: 96/3/1):** R<sub>f</sub> = 0.05 (UV active, appears fluorescent; KMnO<sub>4</sub>, stains yellow after long heating).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ (ppm) = 7.56 (d, *J* = 9.1 Hz, 1H, H-14), 7.21 (d, *J* = 1.8 Hz, 1H, H-10), 6.98-6.94 (m, 1H, H-13), 4.66 (br s, 2H, H-17), 3.88 (s, 3H, H-11), 3.76 (dd, *J* = 13.7, 4.6 Hz, 1H, H-8a), 3.36 (d, *J* = 13.2 Hz, 1H, H-5a), 3.23 (td, *J* = 13.3, 3.3 Hz, 1H, H-8b), 3.12 (d, *J* = 13.2 Hz, 1H, H-5b), 2.91 (dd, *J* = 16.4, 8.0 Hz, 1H, H-3a), 2.38 (d, *J* = 16.2 Hz, 1H, H-3b), 2.25 (br, 1H, H-4), 2.04-1.92 (m, 1H, H-6a), 1.77 (d, *J* = 13.6 Hz, 1H, H-6b), 1.56-1.32 (m, 1H, H-7a), 1.25-1.19 (m, 1H, H-7b).

**10-methoxy-3,4,5,6-tetrahydro-2H-1,5-methanoazocino[2,3-*b*]quinolin-7-ol (408)**<sup>48</sup>

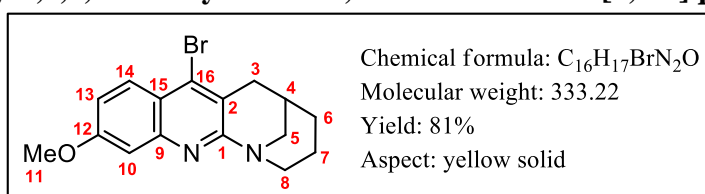


To a dried two-necked flask, the amino quinoline **406** (65.0 mg, 0.24 mmol, 1.0 eq.) was introduced followed by H<sub>2</sub>O (0.5 mL, 0.48 M), and the reaction was set at 0 °C. H<sub>2</sub>SO<sub>4</sub> (64.0 µL, 1.2 mmol, 5.0 eq.) was then added, and NaNO<sub>2</sub> (82.8 mg, 1.2 mmol, 5.0 eq.) dissolved in H<sub>2</sub>O (1.9 mL, 0.12 M) was added dropwise. The mixture color changed to intense red with observation of bubbles, and the reaction was allowed to warm up slowly to 20 °C. After 10 min the color disappeared. The resulting mixture was stirred at the same temperature for 16 h. The reaction was then basified at 0 °C till pH = 9 with sat. NaHCO<sub>3</sub> and extracted with EtOAc. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude mixture was purified through column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>4</sub>OH: 98/1/1 to 94/5/1) to afford the product (36.0 mg, 56%, 72% brsm) as a white solid.

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>4</sub>OH: 96/3/1):** *R<sub>f</sub>* = 0.11 (UV active, appears fluorescent; KMnO<sub>4</sub>, stains yellow).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ (ppm) = 8.27 (d, *J* = 8.9 Hz, 1H, H-14), 7.93 (br s, 1H, H-17), 6.87 (dd, *J* = 9.0, 2.3 Hz, 1H, H-10), 6.59 (d, *J* = 2.4 Hz, 1H, H-13), 3.86 (s, 3H, H-11), 3.35 (dd, *J* = 13.2, 4.5 Hz, 1H, H-8a), 3.19 (dd, *J* = 13.0, 2.6 Hz, 2H, H-5a, H-8b), 3.03 (d, *J* = 12.8 Hz, 1H, H-5b), 2.90 (dd, *J* = 17.8, 7.8 Hz, 1H, H-3a), 2.54 (d, *J* = 17.7 Hz, 1H, H-3b), 2.20 (br, 1H, H-4), 1.95-1.74 (m, 1H, H-6a), 1.72-1.57 (m, 2H, H-6b, H-7a), 1.35-1.19 (m, 1H, H-7b).

#### 7-bromo-10-methoxy-3,4,5,6-tetrahydro-2H-1,5-methanoazocino[2,3-*b*]quinoline (**409**)



According to the general procedure (**F**), from the amino quinoline **406** (25.0 mg, 0.092 mmol, 1.0 eq.), CuBr (26.6 mg, 0.185 mmol, 2.0 eq.), CH<sub>3</sub>CN (0.1 mL, 0.1 M) and *t*-BuONO (16.0 µL, 0.138 mmol, 1.5 eq.) for 4 h. The crude mixture was purified through column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>4</sub>OH: 98/1/1) to afford the desired product (25.0 mg, 81%) as a yellow solid.

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>4</sub>OH: 95/4/1):** *R<sub>f</sub>* = 0.42 (UV active; KMnO<sub>4</sub>, stains red-yellow then intense yellow after 5 min).

**m. p.** = 83.0-86.6 °C (CH<sub>2</sub>Cl<sub>2</sub>/pentane).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ (ppm) = 8.01 (d, *J* = 9.2 Hz, 1H, H-14), 7.24 (d, *J* = 2.5 Hz, 1H, H-10), 7.13 (dd, *J* = 9.2, 2.6 Hz, 1H, H-13), 3.92 (s, 3H, H-11), 3.80 (dd, *J* = 14.0, 4.6 Hz, 1H, H-8a), 3.41 (dt, *J* = 13.4, 2.3 Hz, 1H, H-5a), 3.32 (td, *J* = 13.3, 3.3 Hz, 1H, H-8b), 3.20 (dd, *J* = 18.4, 8.2 Hz, 1H, H-3a), 3.11 (d, *J* = 13.4 Hz, 1H, H-5b), 2.79 (dd, *J* = 18.2, 2.1 Hz, 1H, H-3b), 2.29 (br s, 1H, H-4), 2.11-1.93 (m, 1H, H-6a), 1.93-1.71 (m, 1H, H-6b), 1.47-1.33 (m, 1H, H-7a), 1.35-1.24 (m, 1H, H-7b).

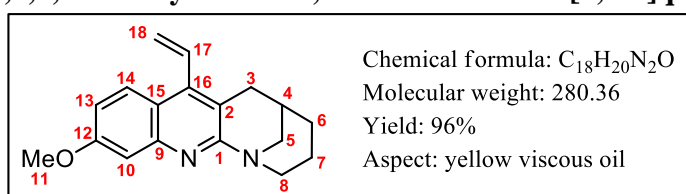
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ (ppm) = 162.3 (C-1), 160.8 (C-9), 148.0 (C-12), 136.0 (C-16), 127.3 (C-14), 125.6 (C-15), 121.0 (C-2), 118.9 (C-10), 106.5 (C-13), 56.3 (C-5), 55.6 (C-11), 52.5 (C-8), 35.5 (C-3), 31.5 (C-6), 26.8 (C-4), 19.1 (C-7).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):** *v*<sub>max</sub> (cm<sup>-1</sup>) = 2925 (-C-H), 2853 (-C-H), 1619, 1582, 1485, 1446, 1365, 1226, 1161, 1014, 791.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>16</sub>H<sub>18</sub>BrN<sub>2</sub>O [M+H]<sup>+</sup> 333.06080, **found** 333.05933.

**calculated** for C<sub>16</sub>H<sub>17</sub>BrN<sub>2</sub>ONa [M+Na]<sup>+</sup> 355.04274, **found** 355.04126.

#### 10-methoxy-7-vinyl-3,4,5,6-tetrahydro-2H-1,5-methanoazocino[2,3-*b*]quinoline (**398a**)<sup>48</sup>



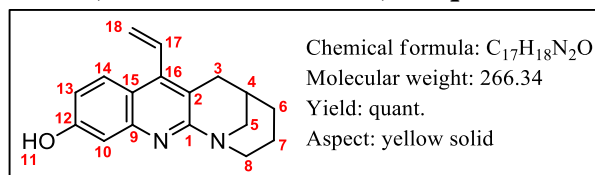
According to the general procedure (**G**), from the bromoquinoline **409** (40.0 mg, 0.12 mmol, 1.0 eq.), potassium vinyltrifluoroborate (24.0 mg, 0.18 mmol, 1.5 eq.), anhydrous K<sub>2</sub>CO<sub>3</sub> (16.5 mg,

0.12 mmol, 1.0 eq.), freshly distilled DME (2.0 mL, 0.06 M), distilled H<sub>2</sub>O (1.0 mL, 0.12 M) and Pd(PPh<sub>3</sub>)<sub>4</sub> (13.8 mg, 0.012 mmol, 0.1 eq.) for 12 h. The crude mixture was purified through column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 98/2 to 96/4) to afford the pure desired product (32.0 mg, 96%) as a yellow viscous oil.

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>4</sub>OH: 94/5/1):** R<sub>f</sub> = 0.37 (UV active; KMnO<sub>4</sub>, stains intense yellow).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ (ppm) = 7.91 (d, *J* = 9.2 Hz, 1H, H-14), 7.27 (d, *J* = 2.6 Hz, 1H, H-13), 7.03 (dd, *J* = 9.2, 2.7 Hz, 1H, H-10), 6.85 (dd, *J* = 17.9, 11.7 Hz, 1H, H-17), 5.84 (dd, *J* = 11.7, 1.8 Hz, 1H, H-18a), 5.54 (dd, *J* = 17.9, 1.8 Hz, 1H, H-18b), 3.91 (s, 3H, H-11), 3.80 (dd, *J* = 13.7, 4.6 Hz, 1H, H-8a), 3.40 (dt, *J* = 13.3, 2.3 Hz, 1H, H-8b), 3.28 (td, *J* = 13.2, 3.4 Hz, 1H, H-5a), 3.20-3.05 (m, 2H, H-5b, H-3a), 2.63 (dd, *J* = 18.0, 2.0 Hz, 1H, H-3b), 2.20 (br s, 1H, H-4), 2.06-1.91 (m, 1H, H-6a), 1.84-1.71 (m, 1H, H-6b), 1.50-1.20 (m, 2H, H-7).

#### 7-vinyl-3,4,5,6-tetrahydro-2H-1,5-methanoazocino[2,3-*b*]quinolin-10-ol (417)



According to the general procedure (H), from vinyl quinoline **398a** (9.0 mg, 0.032 mmol, 1.0 eq.), CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL, 0.02 M) and BBr<sub>3</sub> (1.0 M in CH<sub>2</sub>Cl<sub>2</sub>, 0.32 mL, 0.32 mmol, 10.0 eq.). The crude mixture was purified through short column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 99/1 to 98/2) to afford the pure desired product (9.0 mg, quant.) as a yellow solid.

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 98/2):** R<sub>f</sub> = 0.11 (UV active; KMnO<sub>4</sub>, stains yellow).

**m. p.** = 149.3-150.2 °C (evaporation from CH<sub>2</sub>Cl<sub>2</sub>).

**<sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD):** δ (ppm) = 8.14 (d, *J* = 9.2 Hz, 1H, H-14), 7.23 (dd, *J* = 9.2, 2.3 Hz, 1H, H-13), 7.19 (d, *J* = 2.4 Hz, 1H, H-10), 7.04 (dd, *J* = 17.9, 11.9 Hz, 1H, H-17), 6.08 (dd, *J* = 11.9, 1.3 Hz, 1H, H-18a), 5.73 (dd, *J* = 17.9, 1.4 Hz, 1H, H-18b), 3.74 (d, *J* = 13.8 Hz, 1H, H-8a), 3.61-3.44 (m, 2H, H-5a, H-8b), 3.28-3.16 (m, 2H, H-3a, H-5b), 2.77 (d, *J* = 18.0 Hz, 1H, H-3b), 2.40 (br s, 1H, H-4), 2.21-2.01 (m, 1H, H-6a), 1.83 (d, *J* = 13.9 Hz, 1H, H-6b), 1.51-1.34 (m, 2H, H-7).

**<sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>OD):** δ (ppm) = 166.5 (C-1), 159.6 (C-12), 153.6 (C-9), 142.3 (C-16), 131.8 (C-17), 129.4 (C-14), 126.5 (C-18), 123.4 (C-2), 120.9 (C-13), 119.9 (C-15), 103.4 (C-10), 58.5 (C-5), 53.0 (C-8), 32.0 (C-3), 31.4 (C-6), 27.5 (C-4), 20.5 (C-7).

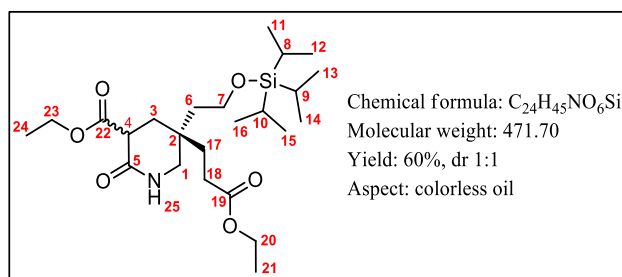
**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):** ν<sub>max</sub> (cm<sup>-1</sup>) = 3370 (br, OH), 3060, 2929 (-C-H), 2853 (-C-H), 1632, 1578, 1581, 1370, 1255, 1238, 1169, 1011, 732.

**HRMS (TOF, ES+):** calculated for C<sub>17</sub>H<sub>19</sub>N<sub>2</sub>O [M+H]<sup>+</sup> 267.14919, found 267.14900.

## 4. Synthesis of chiral azabicyclo[3.3.1]nonane skeleton models

### 4.1. Alcohol-protected side chain model

#### (5*R*)-ethyl 5-(3-ethoxy-3-oxopropyl)-2-oxo-5-(2-((triisopropylsilyl)oxy)ethyl)piperidine-3-carboxylate (580a)



According to the general procedure (A), from the crude cyclobutane **332a** (50.0 mg, 0.1 mmol, 1.0 eq.), anhydrous NiCl<sub>2</sub> (28.0 mg, 0.21 mmol, 2.2 eq.), freshly distilled EtOH (4.0 mL, 0.025 M), and NaBH<sub>4</sub> (72.0 mg, 1.94 mmol, 20.0 eq.) for 42 h. The crude mixture was purified through column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 98/2 to 95/5 to 90/10) to afford the desired mixture of

diastereomers **580a** (28.0 mg, 60%, dr 1:1) as a colorless oil, and the reduced amine **379a** (6.5 mg, 13%, isolated dr 1:1) as a colorless oil.

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 90/10):**  $R_f$  = 0.48 (UV inactive; KMnO<sub>4</sub>, stains white).

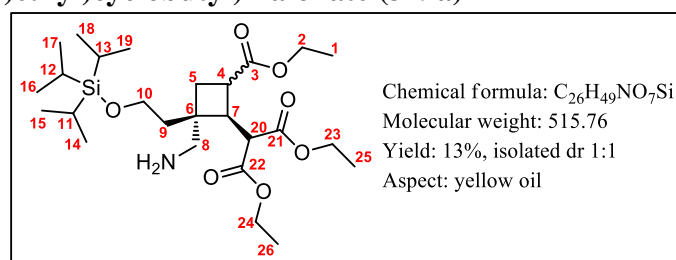
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 5.70 (br s, 2H, H-25 dia-1/dia-2), 4.32-4.01 (m, 8H, H-20 dia-1/dia-2, H-23 dia-1/dia-2), 3.79 (dt,  $J$  = 8.9, 6.1 Hz, 4H, H-7 dia-1/dia-2), 3.60-3.30 (m, 3H, H-4 dia-1/dia-2, H-1a dia-1), 3.29-3.03 (m, 3H, H-1b dia-1, H-1 dia-2), 2.43-2.22 (m, 4H, H-18 dia-1/dia-2), 2.16-1.51 (m, 12H, H-3 dia-1/dia-2, H-6 dia-1/dia-2, H-17 dia-1/dia-2), 1.32-1.23 (m, 12H, H-21 dia-1/dia-2, H-24 dia-1/dia-2), 1.11-1.01 (m, 42H, dia-1/dia-2: H-8, H-9, H-10, H-11, H-12, H-13, H-14, H-15, H-16).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 173.2 (C-19 dia-1), 173.1 (C-19 dia-2), 170.8 (C-22 dia-1), 170.7 (C-22 dia-2), 168.1 (C-5 dia-1), 167.8 (C-5 dia-2), 61.7 (C-23 dia-1), 61.6 (C-23 dia-2), 60.8 (C-20 dia-1), 60.7 (C-20 dia-2), 59.4 (C-7 dia-1), 59.1 (C-7 dia-2), 51.5 (C-1 dia-1), 51.4 (C-1 dia-2), 46.1 (C-4 dia-1), 46.0 (C-4 dia-2), 39.6 (C-6 dia-1), 34.8 (C-6 dia-2), 34.6 (C-3 dia-1), 34.3 (C-3 dia-2), 34.1 (C-2 dia-1/dia-2), 32.4 (C-17 dia-1), 28.9 (C-18 dia-1), 28.8 (C-18 dia-2), 27.7 (C-17 dia-2), 18.2 (dia-1: C-11, C-12, C-13, C-14, C-15, C-16), 18.1 (dia-2: C-11, C-12, C-13, C-14, C-15, C-16), 14.3 (C-21 dia-1/dia-2), 14.2 (C-24 dia-1/dia-2), 12.0 (dia-1/dia-2: C-8, C-9, C-10).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2941 (-C-H), 2867 (-C-H), 1734 (19-C=O, 22-C=O), 1667 (5-C=O), 1465, 1182, 1034, 882, 681.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>24</sub>H<sub>45</sub>NO<sub>6</sub>SiNa [M+Na]<sup>+</sup> 494.2892, found 494.2894.

**diethyl 2-((1*S*,2*S*)-2-(aminomethyl)-4-(ethoxycarbonyl)-2-(2-((triisopropylsilyl)oxy)ethyl)cyclobutyl)malonate (**379a**)**



The reduced amine (6.5 mg, 14%, isolated dr 1:1) was obtained as a yellow oil, as a side product alongside with the cyclized product.

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 90/10):**  $R_f$  = 0.27 (UV inactive; KMnO<sub>4</sub>, stains yellow).

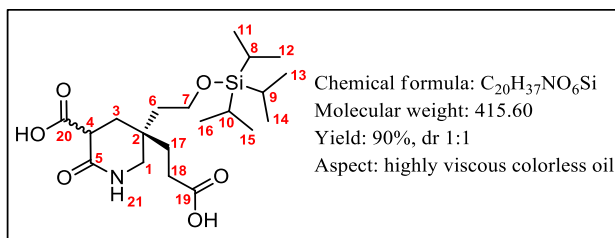
**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 4.25-4.17 (m, 12H, dia-1/dia-2: H-2, H-23, H-24), 3.97 (m, 1H, H-20 dia-1), 3.83-3.73 (m, 4H, H-10 dia-1/dia-2), 3.51 (d,  $J$  = 11.9 Hz, 1H, H-20 dia-2), 3.31-3.27 (m, 3H, H-4 dia-1, H-7 dia-1/dia-2), 3.08-2.85 (m, 5H, H-4 dia-2, H-8 dia-1/dia-2), 2.27-2.11 (m, 4H, H-5 dia-1, H-5a dia-2, H-9a dia-1), 2.01 (t,  $J$  = 9.8 Hz, 1H, H-5b dia-2), 1.81 (dt,  $J$  = 13.6, 5.6 Hz, 1H, H-9a dia-2), 1.68-1.57 (m, 2H, H-9b dia-1, H-9b dia-2), 1.28-1.22 (m, 18H, dia-1/dia-2: H-1, H-25, H-26), 1.06-1.03 (m, 42H, dia-1/dia-2: H-11, H-12, H-13, H-14, H-15, H-16, H-17, H-18, H-19).

**<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 174.7 (C-3 dia-1), 173.5 (C-3 dia-2), 170.3 (C-21 dia-1), 169.3 (C-21 dia-2), 167.6 (C-22 dia-1), 167.3 (C-22 dia-2), 62.5 (C-2 dia-1), 62.3 (C-2 dia-2), 61.9 (C-23 dia-1), 61.8 (C-23 dia-2), 61.0 (C-24 dia-1), 60.9 (C-24 dia-2), 59.5 (C-10 dia-1), 59.3 (C-10 dia-2), 52.4 (C-20 dia-2), 50.0 (C-20 dia-1), 49.9 (C-8 dia-1), 49.0 (C-8 dia-2), 43.2 (C-7 dia-1), 42.7 (C-7 dia-2), 37.0 (C-4 dia-2), 35.6 (C-4 dia-1), 34.2 (C-9 dia-2), 33.6 (C-9 dia-1), 30.2 (C-6 dia-1/dia-2), 30.1 (C-5 dia-1), 29.8 (C-5 dia-2), 18.2 (dia-1: C-14, C-15, C-16, C-17, C-18, C-19), 18.1 (dia-2: C-14, C-15, C-16, C-17, C-18, C-19), 14.3 (C-1 dia-1), 14.2 (C-1 dia-2), 14.1 (C-25 dia-1/dia-2), 14.0 (C-26 dia-1/dia-2), 12.0 (dia-1: C-11, C-12, C-13), 11.9 (dia-2: C-11, C-12, C-13).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2941 (-C-H), 2866 (-C-H), 1730 (br, 3-C=O, 21-C=O, 22-C=O), 1463, 1372, 1250, 1181, 1097, 882, 683.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>26</sub>H<sub>50</sub>NO<sub>7</sub>Si [M+H]<sup>+</sup> 516.3351, found 516.3336.

**(5*R*)-5-(2-carboxyethyl)-2-oxo-5-(2-((triisopropylsilyl)oxy)ethyl)piperidine-3-carboxylic acid (**388a**)**



According to the general procedure (B), from **380a** (859.0, 1.83 mmol, 1.0 eq.), EtOH/H<sub>2</sub>O: 4/1 (12.0 mL, 0.15 M) and LiOH (219.0 mg, 9.15 mmol, 5.0 eq.) for 12 h. The crude mixture of diastereomers (681.0 mg, 90%, dr 1:1) was obtained as a highly viscous colorless oil and was used directly in the next step without further purification.

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/AcOH: 90/9/1):** R<sub>f</sub> = 0 (UV inactive; KMnO<sub>4</sub>, stains yellow-white).

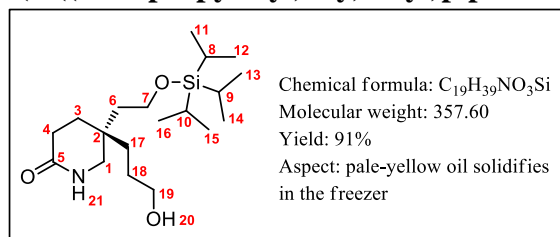
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ (ppm) = 6.80 (br s, 1H, H-21 dia-1), 6.66 (br s, 1H, H-21 dia-2), 3.86-3.75 (m, 4H, H-7 dia-1/dia-2), 3.50-3.13 (m, 6H, H-1 dia-1/dia-2, H-4 dia-1/dia-2), 2.44-1.59 (m, 16H, dia-1/dia-2: H-3, H-6, H-17, H-18), 1.11-1.01 (m, 42H, dia-1/dia-2: H-8, H-9, H-10, H-11, H-12, H-13, H-14, H-15, H-16).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ (ppm) = 178.0 (C-19 dia-1), 177.9 (C-19 dia-2), 172.0 (C-20 dia-1), 171.7 (C-20 dia-2), 170.4 (C-5 dia-1), 167.0 (C-5 dia-2), 59.2 (C-7 dia-1), 59.0 (C-7 dia-2), 42.2 (C-1 dia-1), 42.0 (C-1 dia-2), 39.3 (C-4 dia-1/dia-2), 39.0 (C-6 dia-1), 38.7 (C-6 dia-2), 35.3 (C-3 dia-1/dia-2), 31.0 (C-2 dia-1/dia-2), 28.4 (C-18 dia-1/dia-2), 27.2 (C-17 dia-1/dia-2), 18.2 (dia-1/dia-2: C-11, C-12, C-13, C-14, C-15, C-16), 12.0 (dia-1/dia-2: C-8, C-9, C-10).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):** ν<sub>max</sub> (cm<sup>-1</sup>) = 3218 (br, OH), 2940 (-C-H), 2867 (-C-H), 1733 (19-C=O, 20-C=O), 1668 (5-C=O), 1465, 1180, 1038, 882.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>20</sub>H<sub>37</sub>NO<sub>6</sub>SiNa [M+Na]<sup>+</sup> 438.2282, found 438.2270.

#### (R)-5-(3-hydroxypropyl)-5-(2-((triisopropylsilyl)oxy)ethyl)piperidin-2-one (**390a**)



According to the general procedure (C), from the crude diacid **388a** (368.0 mg, 0.88 mmol, 1.0 eq.) and dry THF (10.0 mL, 0.08 M) for 3 h. The crude mixture **389a** (337.0 mg, quant.) was obtained as a highly viscous white oil. The esterification reaction was accomplished from the crude **389a** (442.0 mg, 1.2 mmol, 1.0 eq.) in CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 5/1 (10.0 mL, 0.12 M), TMSCHN<sub>2</sub> (2.0 M in hexane, 0.9 mL, 1.8 mmol, 1.5 eq.), and AcOH (0.02 mL, 0.36 mmol, 0.3 eq.). The crude **391a** (476.0 mg, quant.) was obtained as a pale-yellow oil. The reduction reaction was accomplished from the crude **391a** (476.0 mg, 1.23 mmol, 1.0 eq.) in dry THF (24.6 mL, 0.05 M), and LAH (1.0 M in Et<sub>2</sub>O, 1.54 mL, 1.54 mmol, 1.25 eq.) for 8 h. The crude **390a** (400.0 mg, 91%) was obtained as yellow oil and was used directly in the next step without further purification. [Purification of the crude for analysis afforded the alcohol as a pale-yellow oil solidifies in the freezer].

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 90/10):** R<sub>f</sub> = 0.22 (UV inactive; KMnO<sub>4</sub>, stains yellow).

**m. p.** = 63.6-69.0 °C (EtOAc).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ (ppm) = 5.65 (br s, 1H, H-21), 3.77 (t, *J* = 6.5 Hz, 2H, H-19), 3.65 (br s, 2H, H-7), 3.22 (dd, *J* = 12.2, 2.1 Hz, 1H, H-1a), 3.09 (dd, *J* = 11.9, 2.6 Hz, 1H, H-1b), 2.45-2.31 (m, 2H, H-4), 1.79-1.49 (m, 8H, H-3, H-6, H-17, H-18), 1.09-1.03 (m, 21H, H-8, H-9, H-10, H-11, H-12, H-13, H-14, H-15, H-16).

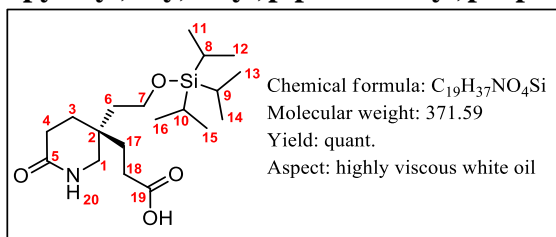
**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ (ppm) = 172.2 (C-5), 63.2 (C-19), 59.5 (C-7), 52.0 (C-1), 37.3 (C-6), 33.6 (C-2), 30.7 (C-4), 30.6 (C-3), 28.0 (C-17), 26.7 (C-18), 18.2 (C-11, C-12, C-13, C-14, C-15, C-16), 12.0 (C-8, C-9, C-10).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):** ν<sub>max</sub> (cm<sup>-1</sup>) = 3292 (br, OH), 2941 (-C-H), 2866 (-C-H), 1660 (5-C=O), 1463, 1097, 1068, 883, 682.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>19</sub>H<sub>39</sub>NO<sub>3</sub>SiNa [M+Na]<sup>+</sup> 380.2591, **found** 380.2577.  
**[α]<sub>D</sub><sup>25</sup>** = -1.55 (*c* = 0.12, CHCl<sub>3</sub>).

### Isolation of the intermediates

#### **(S)-3-(6-oxo-3-(2-(((triisopropylsilyl)oxy)ethyl)piperidin-3-yl)propanoic acid (389a)**



**TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/AcOH: 90/9/1):** R<sub>f</sub> = 0 (UV inactive; KMnO<sub>4</sub>, stains yellow, drags on TLC).

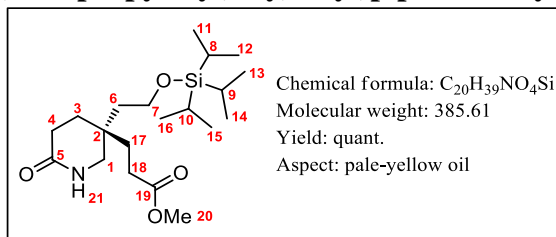
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ (ppm) = 6.87 (br s, 1H, H-20), 3.78 (t, *J* = 6.3 Hz, 2H, H-7), 3.22-3.08 (m, 2H, H-1), 2.45-2.26 (m, 3H, H-4, H-18a), 1.91-1.56 (m, 5H, H-3, H-17, H-18b), 1.07-1.03 (m, 21H, H-8, H-9, H-10, H-11, H-12, H-13, H-14, H-15, H-16).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ (ppm) = 177.9 (C-19), 173.8 (C-5), 59.2 (C-7), 51.3 (C-1), 37.1 (C-6), 33.3 (C-2), 29.9 (C-4), 29.4 (C-3), 28.7 (C-17), 27.5 (C-18), 18.1 (C-11, C-12, C-13, C-14, C-15, C-16), 12.0 (C-8, C-9, C-10).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):** ν<sub>max</sub> (cm<sup>-1</sup>) = 3215 (br, OH), 2941 (-C-H), 2866 (-C-H), 1704 (19-C=O), 1655 (5-C=O), 1462, 1097, 883, 682.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>19</sub>H<sub>37</sub>NO<sub>4</sub>SiNa [M+Na]<sup>+</sup> 394.2384, **found** 394.2376.  
**[α]<sub>D</sub><sup>25</sup>** = +7.81 (*c* = 0.33, CHCl<sub>3</sub>) crude value.

#### **(S)-methyl 3-(6-oxo-3-(2-(((triisopropylsilyl)oxy)ethyl)piperidin-3-yl)propanoate (391a)**



**TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 95/5):** R<sub>f</sub> = 0.32 (UV inactive; KMnO<sub>4</sub>, stains yellow).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ (ppm) = 6.61 (br s, 1H, H-21), 3.77-3.73 (m, 2H, H-7), 3.65-3.64 (s, 3H, H-20), 3.16 (d, *J* = 12.4 Hz, 1H, H-1a), 3.05 (d, *J* = 12.1 Hz, 1H, H-1b), 2.39-2.22 (m, 4H, H-4, H-18), 1.89-1.52 (m, 6H, H-3, H-6, H-17), 1.13-0.95 (m, 21H, H-8, H-9, H-10, H-11, H-12, H-13, H-14, H-15, H-16).

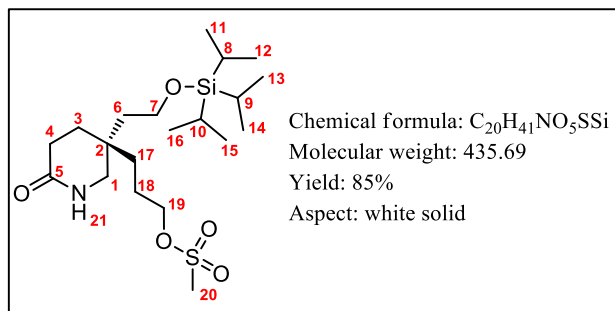
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ (ppm) = 173.8 (C-19), 172.3 (C-5), 59.2 (C-7), 51.8 (C-1), 51.5 (C-20), 36.8 (C-6), 33.4 (C-2), 30.3 (C-4), 29.8 (C-3), 28.6 (C-17), 27.9 (C-18), 18.1 (C-11, C-12, C-13, C-14, C-15, C-16), 12.0 (C-8, C-9, C-10).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):** ν<sub>max</sub> (cm<sup>-1</sup>) = 2942 (-C-H), 2866 (-C-H), 1738 (19-C=O), 1683 (5-C=O), 1462, 1250, 1171, 1097, 882, 682.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>20</sub>H<sub>39</sub>NO<sub>4</sub>SiNa [M+Na]<sup>+</sup> 408.2537, **found** 408.2540.  
**[α]<sub>D</sub><sup>25</sup>** = +18.88 (*c* = 0.08, CHCl<sub>3</sub>).

#### **(R)-3-(6-oxo-3-(2-(((triisopropylsilyl)oxy)ethyl)piperidin-3-yl)propyl methanesulfonate (392a)**





According to the general procedure (**D**), from the hydroxy piperidinone **390a** (400.0 mg, 1.12 mmol, 1.0 eq.), dry CH<sub>2</sub>Cl<sub>2</sub> (12.0 mL, 0.09 M), MsCl (0.1 mL, 1.34 mmol, 1.2 eq.) and distilled Et<sub>3</sub>N (0.31 mL, 2.24 mmol, 2.0 eq.) for 6 h. The crude mixture (420.0 mg, 85%) was obtained as a yellow oil and was used directly in the next step without further purification. [Purification of the crude for analysis was accomplished through short column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>4</sub>OH: 95/4/1) to afford the product as a white solid]. Traces of TIPS group deprotection were observed.

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 90/10):** R<sub>f</sub> = 0.57 (UV inactive; KMnO<sub>4</sub>, stains white-red).

**m. p.** = 55-56.1 °C (CH<sub>2</sub>Cl<sub>2</sub>).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ (ppm) = 5.65 (br s, 1H, H-21), 4.22 (t, *J* = 6.2 Hz, 2H, H-19), 3.77 (t, *J* = 6.3 Hz, 2H, H-7), 3.23 (dd, *J* = 12.0, 1.7 Hz, 1H, H-1a), 3.11 (dd, *J* = 11.9, 2.6 Hz, 1H, H-1b), 3.01 (s, 3H, H-20), 2.48-2.28 (m, 2H, H-4), 1.79-1.53 (m, 8H, H-3, H-6, H-17, H-18), 1.08-1.06 (m, 21H, H-8, H-9, H-10, H-11, H-12, H-13, H-14, H-15, H-16).

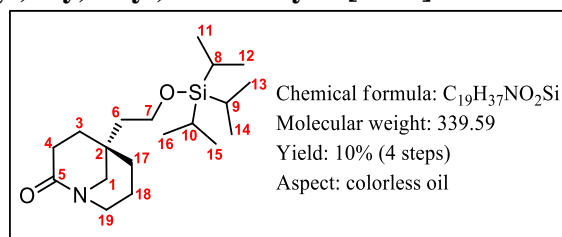
**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ (ppm) = 171.9 (C-5), 69.9 (C-19), 59.3 (C-7), 51.7 (C-1), 37.5 (C-20), 37.0 (C-6), 33.6 (C-2), 30.6 (C-4), 30.5 (C-3), 28.0 (C-17), 23.6 (C-18), 18.2 (C-11, C-12, C-13, C-14, C-15, C-16), 12.0 (C-8, C-9, C-10).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):** ν<sub>max</sub> (cm<sup>-1</sup>) = 2941 (-C-H), 2866 (-C-H), 1663 (5-C=O), 1464, 1174, 1097, 1070, 995, 883, 682.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>20</sub>H<sub>41</sub>NO<sub>5</sub>SSiNa [M+Na]<sup>+</sup> 458.2366, found 458.2356.

[α]<sub>D</sub><sup>25</sup> = -2.23 (*c* = 0.12, CHCl<sub>3</sub>).

**(5R)-5-(2-((triisopropylsilyl)oxy)ethyl)-1-azabicyclo[3.3.1]nonan-2-one (341a)**



According to the general procedure (**E**), from the mesylate **392a** (40.0 mg, 0.09 mmol, 1.0 eq.), DMF (1.8 mL, 0.05 M) and NaH (60% suspension in oil, 5.5 mg, 0.137 mmol, 1.5 eq.). The mixture was stirred at 20 °C for 7 h then 40 °C for 12 h. The crude mixture was purified through short column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc: 50/50) to afford the pure desired product (3.0 mg, 10% over 4 steps) as a colorless oil. Traces of TIPS group deprotection were observed. The product was stored under inert atmosphere in the freezer.

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 95/5):** R<sub>f</sub> = 0.48 (UV inactive; KMnO<sub>4</sub>, stains yellow after long heating).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ (ppm) = 4.11 (dd, *J* = 13.0, 5.5 Hz, 1H, H-19a), 3.81 (td, *J* = 6.6, 1.5 Hz, 2H, H-7), 3.30 (d, *J* = 13.5 Hz, 1H, H-1a), 2.84-2.66 (m, 2H, H-1b, H-19b), 2.51 (td, *J* = 13.7, 8.3 Hz, 1H, H-4a), 2.31 (dd, *J* = 14.3, 4.9 Hz, 1H, H-4b), 2.03 (ddd, *J* = 14.0, 8.3, 1.4 Hz, 1H, H-3a), 1.81-1.62 (m, 1H, H-18a), 1.61-1.36 (m, 6H, H-3b, H-6, H-17, H-18b), 1.13-1.02 (m, 21H, H-8, H-9, H-10, H-11, H-12, H-13, H-14, H-15, H-16).

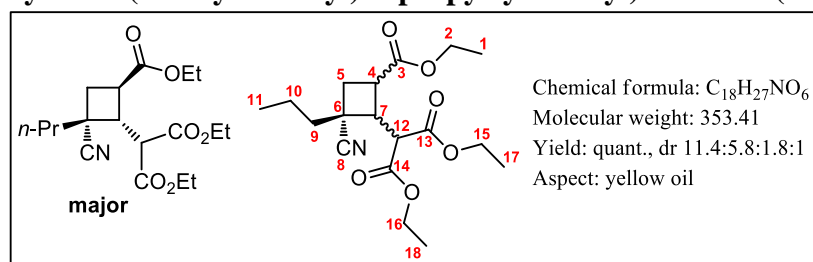
**<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):** δ (ppm) = 184.7 (C-5), 59.6 (C-7), 57.7 (C-1), 50.9 (C-19), 43.7 (C-6), 37.0 (C-2), 36.3 (C-17), 33.7 (C-4), 30.5 (C-3), 21.7 (C-18), 18.2 (C-11, C-12, C-13, C-14, C-15, C-16), 12.0 (C-8, C-9, C-10).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):** ν<sub>max</sub> (cm<sup>-1</sup>) = 2940 (-C-H), 2865 (-C-H), 1684 (5-C=O), 1460, 1375, 1096, 1069, 883, 681.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>19</sub>H<sub>37</sub>NO<sub>2</sub>SiNa [M+Na]<sup>+</sup> 362.24858, **found** 362.24823.  
**[α]<sub>D</sub><sup>25</sup>** = +50.35 (*c* = 0.33, CHCl<sub>3</sub>).

## 4.2. Propyl side chain model

### diethyl 2-((2*R*)-2-cyano-4-(ethoxycarbonyl)-2-propylcyclobutyl)malonate (332c)



According to the general procedure (N) in chapter III, from diethyl malonate (0.6 mL, 4.14 mmol, 1.0 eq.), dry THF (20.7 mL, 0.2 M), NaH (60% suspension in oil, 165.0 mg, 4.14 mmol, 1.0 eq.) and cyclobutene **258b** (800.0 mg, 4.14 mmol, 1.0 eq.) in dry THF (24.3 mL, 0.17 M) for 4 h. The crude as a mixture of diastereomers (1.5 g, quant., dr 11.4:5.8:1.8:1) was obtained as a yellow oil and was pure enough to be used directly in the next step without further purification. [Purification of the crude for analysis was accomplished through column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc: 90/10)].

**TLC (cyclohexane/EtOAc: 80/20):** R<sub>f</sub> = 0.48 (UV active; KMnO<sub>4</sub>, stains yellow).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ (ppm) = 4.34-4.06 (m, 12H, H-2 all dia, H-15 all dia, H-16 all dia, H-12 dia-2), 3.90 (d, *J* = 12.5 Hz, 0.1H, H-12 dia-4), 3.85 (d, *J* = 9.5 Hz, 0.1H, H-7 dia-4), 3.80 (d, *J* = 11.3 Hz, 1H, H-12 dia-1), 3.73 (dd, *J* = 11.7, 9.8 Hz, 0.2H, H-7 dia-3), 3.49 (d, *J* = 11.8 Hz, 0.17H, H-12 dia-3), 3.43-3.26 (m, 1.2H, H-7 dia-2, H-4 dia-2, H-4 dia-4), 3.22 (dd, *J* = 11.2, 9.1 Hz, 1H, H-7 dia-1), 3.13 (q, *J* = 9.1 Hz, 1H, H-4 dia-1), 3.00 (q, *J* = 9.6 Hz, 0.15H, H-4 dia-3), 2.75 (dd, *J* = 12.6, 4.1 Hz, 0.6H, H-5a dia-2, H-5a dia-4), 2.62 (dd, *J* = 11.9, 9.1 Hz, 1.14H, H-5a dia-1, H-5a dia-3), 2.44-2.31 (m, 0.14H, H-5b dia-4), 2.32-2.17 (m, 2H, H-5b dia-1, H-5b dia-2, H-5b dia-3), 2.07-1.98 (m, 2H, H-9a dia-1, H-9a dia-2, H-9a dia-3, H-9a dia-4), 1.74-1.33 (m, 7H, H-9b all dia, H-10 all dia), 1.34-1.19 (m, 20H, H-1 all dia, H-17 all dia, H-18 all dia), 1.07-0.86 (m, 6.2H, H-11 all dia).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**

**For the major diastereomer, dia-1, (1*R*,4*R*)-*trans*-332c:**

δ (ppm) = 172.6 (C-3), 167.3 (C-13), 167.0 (C-14), 121.7 (C-8), 62.0 (C-15, C-16), 61.2 (C-2), 54.6 (C-12), 44.6 (C-7), 40.6 (C-9), 39.5 (C-6), 38.3 (C-4), 33.0 (C-5), 18.2 (C-10), 14.2 (C-1), 14.1 (C-17, C-18), 13.9 (C-11).

**For the second diastereomer, dia-2, (1*R*,4*S*)-*cis*-332c:**

δ (ppm) = 172.2 (C-3), 167.8 (C-13), 167.1 (C-14), 121.2 (C-8), 62.3 (C-15), 61.9 (C-16), 61.3 (C-2), 51.8 (C-12), 43.2 (C-7), 41.5 (C-9), 39.2 (C-6), 37.0 (C-4), 32.3 (C-5), 18.3 (C-10), 14.1 (C-1), 14.0 (C-17, C-18), 13.9 (C-11).

**For the third diastereomer, dia-3, (1*S*,4*S*)-*trans*-332c:**

δ (ppm) = 172.0 (C-3), 167.3 (C-13), 166.9 (C-14), 122.2 (C-8), 62.3 (C-15), 62.1 (C-16), 60.5 (C-2), 51.9 (C-12), 43.7 (C-7), 40.6 (C-9), 39.0 (C-4), 34.7 (C-6), 33.3 (C-5), 18.4 (C-10), 14.3 (C-1), 14.0 (C-11, C-17, C-18).

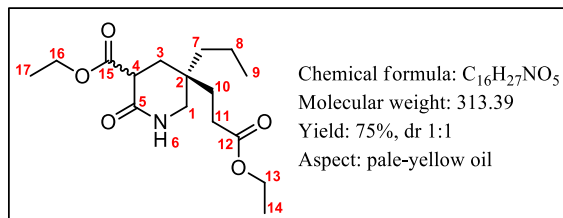
**For the minor diastereomer, dia-4, (1*S*,4*R*)-*cis*-332c:**

δ (ppm) = 173.4 (C-3), 167.4 (C-13), 166.9 (C-14), 123.2 (C-8), 62.4 (C-15, C-16), 60.5 (C-2), 49.6 (C-12), 42.3 (C-7), 41.8 (C-9), 37.7 (C-4), 36.8 (C-6), 32.6 (C-5), 18.0 (C-10), 14.0 (C-1, C-11, C-17, C-18).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):** ν<sub>max</sub> (cm<sup>-1</sup>) = 2970 (-C-H), 2875 (-C-H), 2231 (C≡N), 1734 (br, 3-C=O, 13-C=O, 14-C=O), 1466, 1372, 1301, 1245, 1181, 1032, 860.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>18</sub>H<sub>27</sub>NO<sub>6</sub>Na [M+Na]<sup>+</sup> 376.17306, **found** 376.17224.

### (5*R*)-ethyl 5-(3-ethoxy-3-oxopropyl)-2-oxo-5-propylpiperidine-3-carboxylate (380b)



According to the general procedure (A), from the crude cyclobutane **332c** (1.44 g, 4.07 mmol, 1.0 eq.), anhydrous  $NiCl_2$  (1.16 g, 8.95 mmol, 2.2 eq.), freshly distilled EtOH (162.0 mL, 0.025 M), and  $NaBH_4$  (3.04 g, 81.4 mmol, 20.0 eq.) for 70 h. The crude mixture was purified through column chromatography on  $SiO_2$  ( $CH_2Cl_2/MeOH$ : 95/5 to 90/10) to afford the desired mixture of diastereomers (965.0 mg, 75%, dr 1:1) as a pale-yellow oil, and the reduced amine **379b** (150.0 mg, 10%, isolated dr 1:1) as a viscous yellow oil.

**TLC** ( $CH_2Cl_2/MeOH$ : 90/10):  $R_f$  = 0.57 (UV inactive;  $KMnO_4$ , stains white).

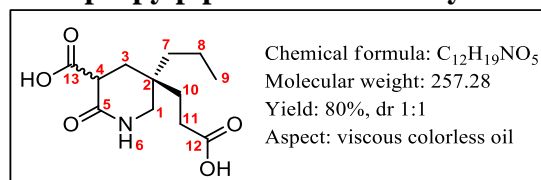
**$^1H$  NMR** (400 MHz,  $CDCl_3$ ):  $\delta$  (ppm) = 5.88 (br s, 2H, H-6 dia-1/dia-2), 4.27-4.17 (m, 4H, H-11 dia-1/dia-2), 4.17-4.11 (m, 4H, H-16 dia-1/dia-2), 3.42-3.33 (m, 2H, H-4 dia-1/dia-2), 3.18 (dd,  $J$  = 11.9, 8.3 Hz, 2H, H-1a dia-1/dia-2), 3.02 (ddd,  $J$  = 12.3, 4.3, 1.9 Hz, 2H, H-1b dia-1/dia-2), 2.36-2.13 (m, 4H, H-11 dia-1/dia-2), 2.02-1.87 (m, 4H, H-3 dia-1/dia-2), 1.84-1.73 (m, 2H, H-10 dia-1), 1.69 (dtd,  $J$  = 9.7, 6.8, 2.3 Hz, 2H, H-10 dia-2), 1.44-1.33 (m, 2H, H-7 dia-1), 1.33-1.19 (m, 18H, H-7 dia-2, H-8 dia-1/dia-2, H-14 dia-1/dia-2, H-17 dia-1/dia-2), 0.95-0.90 (m, 6H, H-9 dia-1/dia-2).

**$^{13}C$  NMR** (100 MHz,  $CDCl_3$ ):  $\delta$  (ppm) = 173.3 (C-12 dia-1), 173.2 (C-12 dia-2), 170.8 (C-15 dia-1/dia-2), 168.0 (C-5 dia-1/dia-2), 61.7 (C-16 dia-1/dia-2), 60.9 (C-13 dia-1), 60.8 (C-13 dia-2), 51.1 (C-1 dia-1), 51.0 (C-1 dia-2), 46.1 (C-4 dia-1), 46.0 (C-4 dia-2), 39.5 (C-7 dia-2), 34.6 (C-7 dia-1), 34.4 (C-2 dia-1/dia-2), 34.3 (C-3 dia-1), 34.2 (C-3 dia-2), 32.0 (C-10 dia-2), 28.8 (C-11 dia-1), 28.7 (C-11 dia-2), 27.4 (C-10 dia-1), 16.5 (C-8 dia-1), 16.4 (C-8 dia-2), 14.8 (C-9 dia-1/dia-2), 14.3 (C-14 dia-1/dia-2), 14.2 (C-17 dia-1/dia-2).

**IR** (solution in  $CH_2Cl_2$ , thin film, KBr):  $\nu_{max}$  ( $cm^{-1}$ ) = 2958 (-C-H), 2935 (-C-H), 2873 (-C-H), 1734 (12-C=O, 15-C=O), 1674 (5-C=O), 1466, 1371, 1282, 1181, 1034, 731.

**HRMS** (TOF, ES+): calculated for  $C_{16}H_{27}NO_5Na$   $[M+Na]^+$  336.17814, found 336.17700.

#### (5R)-5-(2-carboxyethyl)-2-oxo-5-propylpiperidine-3-carboxylic acid (**388b**)



According to the general procedure (B), from **380b** (571.0, 1.82 mmol, 1.0 eq.), EtOH/ $H_2O$ : 4/1 (12.0 mL, 0.15 M) and LiOH (218.0 mg, 9.1 mmol, 5.0 eq.) for 4 h. The crude mixture of diastereomers (375.0 mg, 80%, dr 1:1) was obtained as a viscous colorless oil and was used directly in the next step without further purification.

**TLC** ( $CH_2Cl_2/MeOH/AcOH$ : 90/9/1):  $R_f$  = 0 (UV inactive;  $KMnO_4$ , stains yellow-white).

**$^1H$  NMR** (300 MHz,  $CD_3OD$ ): For dia-1 and dia-2:  $\delta$  (ppm) = 3.03 (s, 2H, H-1), 2.39-2.15 (m, 3H, H-4, H-11), 1.79-1.60 (m, 4H, H-3, H-10), 1.41-1.24 (m, 4H, H-7, H-8), 0.98-0.92 (m, 3H, H-9).

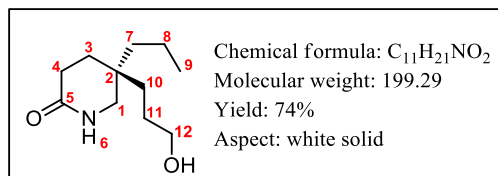
**$^{13}C$  NMR** (100 MHz,  $CD_3OD$ ):  $\delta$  (ppm) = 177.2 (C-12 dia-1/dia-2), 174.1 (C-13 dia-1/dia-2), 171.2 (C-5 dia-1/dia-2), 51.4 (C-1 dia-1), 51.2 (C-1 dia-2), 48.5 (C-4 dia-1/dia-2), 40.2 (C-7 dia-1), 35.7 (C-7 dia-2), 35.3 (C-2 dia-1/dia-2), 35.0 (C-3 dia-1/dia-2), 32.9 (C-10 dia-1), 29.2 (C-11 dia-1), 29.1 (C-11 dia-2), 28.5 (C-10 dia-2), 17.3 (C-8 dia-1), 17.2 (C-8 dia-2), 15.0 (C-9 dia-1/dia-2).

**IR** (solution in  $CH_2Cl_2$ , thin film, KBr):  $\nu_{max}$  ( $cm^{-1}$ ) = 3219 (br, OH), 2957 (-C-H), 2872 (-C-H), 1716 (12-C=O, 13-C=O), 1635 (5-C=O), 1468, 1410, 1288, 807.

**HRMS** (TOF, ES+): calculated for  $C_{12}H_{19}NO_5Na$   $[M+Na]^+$  280.11554, found 280.11507.

#### (R)-5-(3-hydroxypropyl)-5-propylpiperidin-2-one (**390b**)





According to the general procedure (C), from the crude diacid **388b** (350.0 mg, 1.36 mmol, 1.0 eq.) and dry THF (6.0 mL, 0.08 M) for 3 h. The crude mixture **389b** (313.0 mg, quant.) was obtained as a white solid. The esterification reaction was accomplished from the crude **389b** (245.0 mg, 1.15 mmol, 1.0 eq.) in  $CH_2Cl_2$ /MeOH: 5/1 (10.2 mL, 0.12 M), TMSCHN<sub>2</sub> (2.0 M in hexane, 0.86 mL, 1.72 mmol, 1.5 eq.), and AcOH (0.02 mL, 0.345 mmol, 0.3 eq.). The crude **391b** (291.0 mg, quant.) was obtained as a pale-yellow oil solidifies open to atmosphere. The reduction reaction was accomplished from the crude **391b** (271.0 mg, 1.19 mmol, 1.0 eq.) in dry THF (24.0 mL, 0.05 M), and LAH (1.0 M in Et<sub>2</sub>O, 1.5 mL, 1.49 mmol, 1.25 eq.) for 6 h. The crude **390b** (145.0 mg, 74%) was obtained as pale-yellow viscous oil and was used directly in the next step without further purification. [Purification of the crude for analysis afforded the alcohol as a white solid].

**TLC ( $CH_2Cl_2$ /MeOH: 90/10):**  $R_f$  = 0.4 (UV inactive; KMnO<sub>4</sub>, stains yellow).

**m. p.** = 96.5-99.5 °C ( $CH_2Cl_2$ ).

**<sup>1</sup>H NMR (300 MHz,  $CDCl_3$ ):**  $\delta$  (ppm) = 6.02 (s, 1H, H-6), 3.64 (t,  $J$  = 6.1 Hz, 2H, H-12), 3.05 (d,  $J$  = 2.5 Hz, 2H, H-1), 2.37-2.32 (m, 2H, H-4), 1.64 (t,  $J$  = 7.0 Hz, 2H, H-3), 1.54-1.18 (m, 8H, H-7, H-8, H-10, H-11), 0.92 (t,  $J$  = 6.9 Hz, 3H, H-9).

**<sup>13</sup>C NMR (75 MHz,  $CDCl_3$ ):**  $\delta$  (ppm) = 173.0 (C-5), 63.3 (C-12), 51.6 (C-1), 37.1 (C-7), 33.9 (C-2), 30.5 (C-10), 30.2 (C-3), 27.9 (C-4), 26.5 (C-11), 16.5 (C-8), 14.9 (C-9).

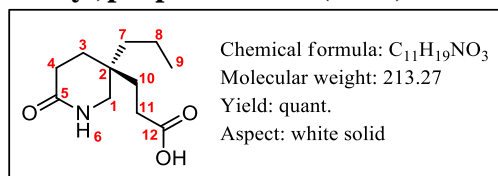
**IR (solution in  $CH_2Cl_2$ , thin film, KBr):**  $\nu_{max}$  (cm<sup>-1</sup>) = 3294 (br, OH), 2938 (-C-H), 2871 (-C-H), 1655 (5-C=O), 1495, 1410, 1364, 1059, 731.

**HRMS (TOF, ES<sup>+</sup>):** calculated for  $C_{11}H_{21}NO_2Na$   $[M+Na]^+$  222.14645, **found** 222.14609.

$[\alpha]_D^{25}$  = +3.29 ( $c$  = 0.10,  $CHCl_3$ ).

### Isolation of the intermediates

#### (S)-3-(6-oxo-3-propylpiperidin-3-yl)propanoic acid (389b)



**TLC ( $CH_2Cl_2$ /MeOH/AcOH: 90/9/1):**  $R_f$  = 0 (UV inactive; KMnO<sub>4</sub>, stains yellow, drags on TLC).

**m. p.** = 111.7-113.6 °C (EtOAc/pentane).

**<sup>1</sup>H NMR (300 MHz,  $CDCl_3$ ):**  $\delta$  (ppm) = 7.13 (br s, 1H, H-6), 3.06 (d,  $J$  = 2.5 Hz, 2H, H-1), 2.37 (t,  $J$  = 7.0 Hz, 2H, H-4), 2.27 (td,  $J$  = 7.3, 2.1 Hz, 2H, H-11), 1.75 (dd,  $J$  = 9.2, 7.1 Hz, 2H, H-3), 1.64 (t,  $J$  = 7.0 Hz, 2H, H-10), 1.38-1.17 (m, 4H, H-7, H-8), 0.95-0.90 (m, 3H, H-9).

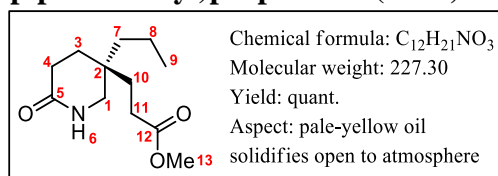
**<sup>13</sup>C NMR (75 MHz,  $CDCl_3$ ):**  $\delta$  (ppm) = 178.1 (C-12), 174.3 (C-5), 51.0 (C-1), 36.9 (C-7), 33.6 (C-2), 29.6 (C-10), 29.1 (C-3), 28.6 (C-4), 27.4 (C-11), 16.4 (C-8), 14.8 (C-9).

**IR (solution in  $CH_2Cl_2$ , thin film, KBr):**  $\nu_{max}$  (cm<sup>-1</sup>) = 3280 (br, OH), 2933 (-C-H), 2872 (-C-H), 1704 (12-C=O), 1636 (5-C=O), 1497, 1410, 1307, 1227, 802.

**HRMS (TOF, ES<sup>+</sup>):** calculated for  $C_{11}H_{19}NO_3Na$   $[M+Na]^+$  236.12571, **found** 236.12523.

$[\alpha]_D^{25}$  = +9.84 ( $c$  = 0.16,  $CHCl_3$ ) crude value.

#### (S)-methyl 3-(6-oxo-3-propylpiperidin-3-yl)propanoate (391b)



**TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 90/10):**  $R_f$  = 0.55 (UV inactive; KMnO<sub>4</sub>, stains yellow).

**m. p.** = 64.1-66.2 °C (CH<sub>2</sub>Cl<sub>2</sub>).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 6.76 (br s, 1H, H-6), 3.67 (s, 3H, H-13), 3.03 (d,  $J$  = 2.5 Hz, 2H, H-1), 2.33 (t,  $J$  = 7.0 Hz, 2H, H-11), 2.28-2.18 (m, 2H, H-4), 1.77-1.66 (m, 2H, H-3), 1.61 (td,  $J$  = 7.0, 3.2 Hz, 2H, H-10), 1.37-1.15 (m, 4H, H-7, H-8), 0.95-0.88 (m, 3H, H-9).

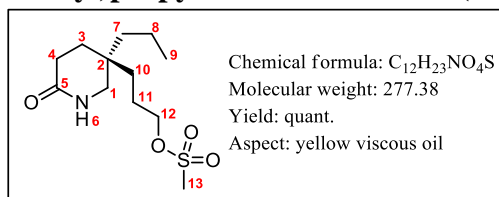
**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 173.9 (C-12), 172.9 (C-5), 51.9 (C-13), 51.1 (C-1), 36.6 (C-7), 33.7 (C-2), 30.0 (C-10), 29.5 (C-3), 28.5 (C-4), 27.7 (C-11), 16.4 (C-8), 14.8 (C-9).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2955 (-C-H), 2872 (-C-H), 1736 (12-C=O), 1664 (5-C=O), 1436, 1302, 1196, 1168, 727.

**HRMS (TOF, ES+):** calculated for C<sub>12</sub>H<sub>21</sub>NO<sub>3</sub>Na [M+Na]<sup>+</sup> 250.14136, **found** 250.14050.

$[\alpha]_D^{25}$  = +5.28 ( $c$  = 0.11, CHCl<sub>3</sub>).

**(R)-3-(6-oxo-3-propylpiperidin-3-yl)propyl methanesulfonate (392b)**



According to the general procedure (**D**), from the hydroxy piperidinone **390b** (138.0 mg, 0.69 mmol, 1.0 eq.), dry CH<sub>2</sub>Cl<sub>2</sub> (10.0 mL, 0.07 M), MsCl (60.0  $\mu$ L, 0.82 mmol, 1.2 eq.) and distilled Et<sub>3</sub>N (0.14 mL, 1.03 mmol, 1.5 eq.) for 5 h. The crude (200.0 mg, quant.) was obtained as a yellow viscous oil and was used directly in the next step without further purification. [Purification of the crude for analysis was accomplished through short column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>4</sub>OH: 95/4/1) to afford the product as a pale-yellow viscous oil].

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 90/10):**  $R_f$  = 0.59 (UV inactive; KMnO<sub>4</sub>, stains white-red).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 5.81 (br s, 1H, H-6), 4.22 (t,  $J$  = 6.3 Hz, 2H, H-12), 3.05 (t,  $J$  = 2.5 Hz, 2H, H-1), 3.01 (s, 3H, H-13), 2.34 (t,  $J$  = 7.0 Hz, 2H, H-4), 1.77-1.63 (m, 3H, H-3a, H-11), 1.52-1.14 (m, 7H, H-3b, H-7, H-8, H-10), 0.93 (t,  $J$  = 6.8 Hz, 3H, H-9).

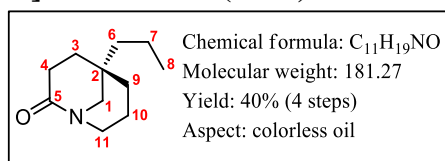
**<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 172.1 (C-5), 70.0 (C-12), 51.5 (C-1), 37.6 (C-13), 36.9 (C-7), 34.0 (C-2), 30.3 (C-3, C-10), 27.9 (C-4), 23.5 (C-11), 16.5 (C-8), 14.9 (C-9).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2956 (-C-H), 2872 (-C-H), 1655 (5-C=O), 1469, 1350, 1173, 1102, 974, 829, 528.

**HRMS (TOF, ES+):** calculated for C<sub>12</sub>H<sub>23</sub>NO<sub>4</sub>SNa [M+Na]<sup>+</sup> 300.12400, **found** 300.12296.

$[\alpha]_D^{25}$  = +3.70 ( $c$  = 0.18, CHCl<sub>3</sub>).

**(5R)-5-propyl-1-azabicyclo[3.3.1]nonan-2-one (341b)**



According to the general procedure (**E**), from the mesylate **392b** (50.0 mg, 0.18 mmol, 1.0 eq.), DMF (0.9 mL, 0.2 M) and NaH (60% suspension in oil, 11.0 mg, 0.27 mmol, 1.5 eq.). The mixture was stirred at 70 °C for 14 h. The crude was purified through short column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc/NH<sub>4</sub>OH: 70/29/1) to afford the pure desired product (13.0 mg, 40% 4 steps) as a colorless oil. The product was stored under inert atmosphere in the freezer.

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 90/10):**  $R_f$  = 0.54 (UV inactive; KMnO<sub>4</sub>, stains yellow after long heating).

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 4.11 (ddd,  $J$  = 13.1, 5.6, 1.5 Hz, 1H, H-11a), 3.18 (d,  $J$  = 13.3 Hz, 1H, H-1a), 2.72 (td,  $J$  = 12.6, 3.4 Hz, 1H, H-11b), 2.66 (d,  $J$  = 13.4 Hz, 1H, H-1b), 2.46 (td,  $J$  = 13.6, 13.2, 8.4 Hz, 1H, H-4a), 2.30 (ddd,  $J$  = 14.3, 5.7, 1.3 Hz, 1H, H-4b), 1.89 (ddd,  $J$  = 14.0, 8.4, 1.3 Hz, 1H, H-3a), 1.75-1.64 (m, 1H, H-10a), 1.54-1.48 (m, 1H, H-9a), 1.47-1.38 (m, 3H, H-3b, H-9b, H-10b), 1.38-1.31 (m, 1H, H-7a), 1.31-1.21 (m, 3H, H-6, H-7b), 0.92 (t,  $J$  = 7.0 Hz, 3H, H-8).

**<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 184.7 (C-5), 57.6 (C-1), 51.0 (C-11), 43.6 (C-6), 36.9 (C-2), 36.6 (C-9), 33.6 (C-4), 30.0 (C-3), 21.6 (C-10), 16.7 (C-7), 14.9 (C-8).

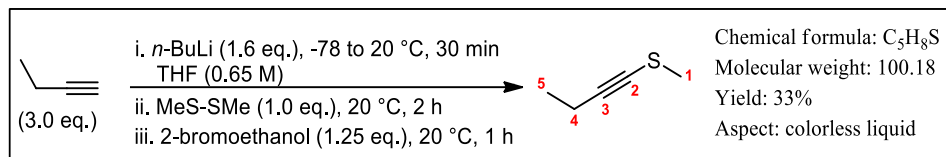
**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2954 (-C-H), 2932 (-C-H), 1682 (5-C=O), 1458, 1377, 1127, 965, 744.

**HRMS (TOF, ES+):** calculated for C<sub>11</sub>H<sub>19</sub>NONa [M+Na]<sup>+</sup> 204.13589, found 204.13572.  
[ $\alpha$ ]<sub>D</sub><sup>25</sup> = +15.3 (*c* = 0.06, CHCl<sub>3</sub>).

## 5. Total synthesis of (+)-eucophylline

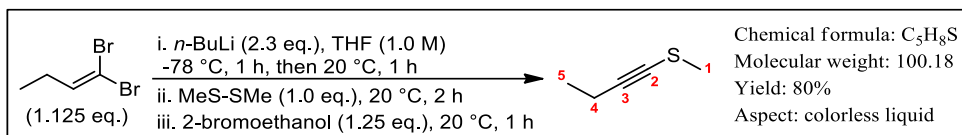
### but-1-yn-1-yl(methyl)sulfane (112h)

#### Method A:



In a dried two-necked flask, approximately 4 g of acetone (approximative mass of the alkyne) were weighed and the level of the solvent was marked. The solvent was then removed and the flask was equipped with a cold trap condenser. The system was flame-dried, set under inert atmosphere then at -78 °C (acetone/dry ice bath, the trap was also filled with acetone and dry ice). The butyne gas bottle was equipped with a manometer and connected to an 18G needle. The gas flow was allowed to pass through the tubing before connecting the bottle to the reaction setup. 1-butyne **33** (~ 6.4 mL, 3.8 g, 72.0 mmol, ~ 3.0 eq.) was then condensed in the flask for 5 min to reach the predetermined mark. Once finished, the bottle was disconnected and dry THF (30.0 mL, 0.65 M) previously cooled to 0 °C was added, followed by dropwise addition of *n*-BuLi (1.8 M in hexane, 17.7 mL, 32.0 mmol, 1.6 eq.). The reaction mixture was then stirred at 0 °C for 30 min, then dimethyl disulfide (1.8 mL, 20.0 mmol, 1.0 eq.) was added slowly, and the reaction mixture was stirred at 20 °C for 2 h. The reaction was then quenched with 2-bromoethanol (1.8 mL, 25.0 mmol, 1.25 eq.) at 0 °C then stirred at 20 °C for 1 h. Water was added and the reaction mixture was extracted with Et<sub>2</sub>O. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and distilled to remove the solvents. The crude was purified through column chromatography on SiO<sub>2</sub> (pentane/Et<sub>2</sub>O: 98/2) then the fractions were distilled to remove the solvents, and the pure product (670.0 mg, 33%) was obtained as a colorless liquid.

#### Method B:



To a flame-dried two-necked flask, THF (40.0 mL, 1.0 M) was introduced, and the reaction was set at -78 °C. 1,1-dibromobut-1-ene **393a** (9.5 g, 44.8 mmol, 1.125 eq.) was added slowly, then *n*-BuLi (1.8 M in hexane, 51.0 mL, 91.5 mmol, 2.3 eq.) was added dropwise, the color changed to dark orange. The reaction mixture was stirred at -78 °C for 1 h, then at 20 °C for another 1 h. Dimethyl disulfide (3.6 mL, 39.8 mmol, 1.0 eq.) was later added slowly at 0 °C, and the reaction mixture was stirred at 20 °C for 2 h (formation of suspension was observed). The reaction was quenched with 2-bromoethanol (3.5 mL, 49.7 mmol, 1.25 eq.) at 0 °C then stirred at 20 °C for 1 h. Water was added and the reaction mixture was extracted with Et<sub>2</sub>O. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and distilled to remove the solvents. The crude was purified through column chromatography on SiO<sub>2</sub> (pentane: 100%) then the fractions were distilled to remove the solvents, and the pure product (3.6 g, 80%) was obtained as a colorless liquid.

**TLC (cyclohexane: 100%):** R<sub>f</sub> = 0.64 (UV active; KMnO<sub>4</sub>, stains yellow).

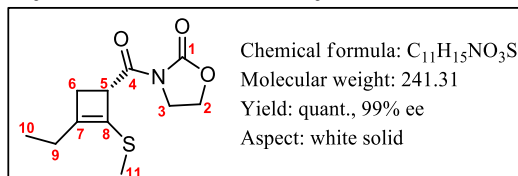
**b. p.** = 105-110 °C.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 2.35 (s, 3H, H-1), 2.30 (q, *J* = 7.5 Hz, 2H, H-4), 1.14 (t, *J* = 7.5 Hz, 3H, H-5).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 94.6 (C-3), 69.4 (C-2), 19.4 (C-4), 14.0 (C-1, C-5).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2956 (-C-H), 2929 (-C-H), 2866 (-C-H), 2306 (C≡C).

**HRMS (TOF, ES+):** not detected.

**(R)-3-(3-ethyl-2-(methylthio)cyclobut-2-enecarbonyl)oxazolidin-2-one (117h)**

According to the general procedure (C) in chapter III, from the titanium complex: TiCl<sub>2</sub>(OiPr)<sub>2</sub> (416.0 mg, 1.75 mmol, 0.1 eq.) and **(R)-115** (1.02 g, 1.93 mmol, 0.11 eq.) in dry toluene (21.8 mL, 0.08 M), 4 Å molecular sieves (397.0 mg), dry toluene (70.0 mL, 0.25 M), 3-acryloyloxazolidin-2-one (2.48 g, 17.6 mmol, 1.0 eq.) and alkynyl thioether **112h** (3.0 g, 29.9 mmol, 1.7 eq.) for 24 h. Purification through column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc: 70/30 to 60/40) afforded the product (4.6 g, quant., 99% ee) as a white solid.

**TLC (cyclohexane/EtOAc: 60/40):** R<sub>f</sub> = 0.42 (UV active; vanillin, stains brown).

**m. p.** = 78.2-82.1 °C (pentane/EtOAc).

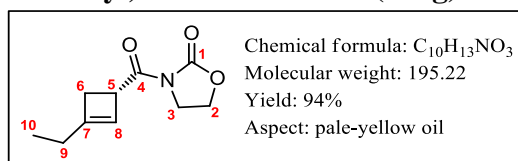
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ (ppm) = 4.70 (dq, *J* = 5.2, 1.8 Hz, 1H, H-5), 4.43 (dd, *J* = 8.6, 7.5 Hz, 2H, H-2), 4.04 (dd, *J* = 8.6, 7.6 Hz, 2H, H-3), 2.77 (ddt, *J* = 12.7, 4.9, 1.2 Hz, 2H, H-6a), 2.50 (dq, *J* = 12.7, 1.4 Hz, 1H, H-6b), 2.26-2.15 (m, 5H, H-9, H-11), 1.04 (t, *J* = 7.6 Hz, 3H, H-10).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ (ppm) = 172.9 (C-4), 153.5 (C-1), 151.9 (C-7), 128.2 (C-8), 62.4 (C-2), 44.6 (C-5), 42.7 (C-3), 33.3 (C-6), 22.3 (C-9), 15.8 (C-11), 11.3 (C-10).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):** ν<sub>max</sub> (cm<sup>-1</sup>) = 2919 (-C-H), 1791 (4-C=O), 1681 (1-C=O), 1384, 1371, 1263, 1196, 1039, 757.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>11</sub>H<sub>15</sub>NO<sub>3</sub>Na [M+Na]<sup>+</sup> 264.06649, **found** 264.06593.

[α]<sub>D</sub><sup>25</sup> = +81.37 (*c* = 0.2, CHCl<sub>3</sub>).

**(S)-3-(3-ethylcyclobut-2-enecarbonyl)oxazolidin-2-one (169g)**

According to the general procedure (E) in chapter III, from cyclobutene **117h** (2.5 g, 10.3 mmol, 1.0 eq.), dry acetone (34.0 mL, 0.3 M), Lindlar's catalyst (1.1 g, 10.3 mmol, 1.0 eq.), oct-1-ene (1.6 mL, 10.3 mmol, 1.0 eq.) and freshly distilled Et<sub>3</sub>SiH (11.5 mL, 72.1 mmol, 7.0 eq.) at 50 °C for 16 h. Purification through column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc: 70/30) gave the reduced cyclobutene (1.9 g, 94%) as a pale-yellow oil.

**TLC (cyclohexane/EtOAc: 60/40):** R<sub>f</sub> = 0.45 (UV active; vanillin, stains dark green).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ (ppm) = 5.79 (q, *J* = 1.6 Hz, 1H, H-8), 4.42 (dd, *J* = 8.6, 7.6 Hz, 2H, H-2), 4.33-4.31 (m, 1H, H-5), 4.02 (dd, *J* = 8.7, 7.4 Hz, 2H, H-3), 2.77 (ddt, *J* = 13.2, 4.5, 1.2 Hz, 1H, H-6a), 2.66 (dq, *J* = 13.3, 1.3 Hz, 1H, H-6b), 2.15-1.97 (m, 2H, H-9), 1.03 (t, *J* = 7.5 Hz, 3H, H-10).

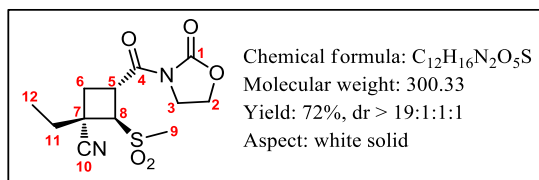
**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ (ppm) = 173.8 (C-4), 154.2 (C-7), 153.3 (C-1), 124.2 (C-8), 62.4 (C-2), 42.6 (C-5), 42.5 (C-3), 34.6 (C-6), 24.1 (C-9), 10.6 (C-10).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):** ν<sub>max</sub> (cm<sup>-1</sup>) = 2966 (-C-H), 2922 (-C-H), 1780 (4-C=O), 1693 (1-C=O), 1479, 1387, 1362, 1260, 1225, 1112, 1038, 840, 760.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>10</sub>H<sub>13</sub>NO<sub>3</sub>Na [M+Na]<sup>+</sup> 218.07876, **found** 218.07774.

[α]<sub>D</sub><sup>25</sup> = +9.22 (*c* = 0.2, CHCl<sub>3</sub>).

**(1S,2R,3R)-1-ethyl-2-(methylsulfonyl)-3-(2-oxooxazolidine-3-carbonyl)cyclobutanecarbonitrile (181q)**



According to the general procedure (**I**) in chapter III, from cyclobutene **169g** (3.0 g, 15.3 mmol, 1.0 eq.), acetonitrile (10.0 mL, 1.5 M), methanesulfonyl cyanide **88a** (3.2 g, 30.6 mmol, 2.0 eq.) and *p*-anisaldehyde (0.37 mL, 3.06 mmol, 0.2 eq.) for 48 h. A white precipitate was formed in the schlenk, the solvent was removed using a Pasteur pipette and the precipitate was washed with CH<sub>3</sub>CN (3 x 0.5 mL), then dried under vacuum to afford the product (3.32 g, 72%, dr > 19:1:1:1) as a white solid.

**TLC:** -

**m. p.** = 266.3-267.8 °C (CH<sub>2</sub>Cl<sub>2</sub>).

**<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>):** δ (ppm) = 4.76 (d, *J* = 9.4 Hz, 1H, H-8), 4.41 (t, *J* = 8.0 Hz, 2H, H-2), 4.29 (q, *J* = 9.7 Hz, 1H, H-5), 3.90 (t, *J* = 8.0 Hz, 2H, H-3), 3.00 (s, 3H, H-9), 2.56 (dd, *J* = 9.8, 2.7 Hz, 2H, H-6), 2.24-2.07 (m, 1H, H-11a), 2.11-2.00 (m, 1H, H-11b), 1.02 (t, *J* = 7.3 Hz, 3H, H-12)

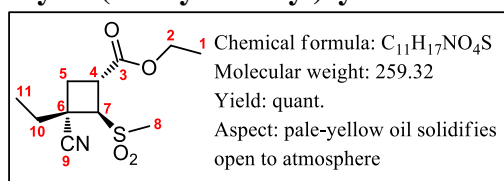
**<sup>13</sup>C NMR (150 MHz, DMSO-*d*<sub>6</sub>):** δ (ppm) = 169.2 (C-4), 153.3 (C-1), 121.0 (C-10), 63.0 (C-2), 58.1 (C-8), 42.4 (C-3), 41.2 (C-9), 37.4 (C-5), 35.7 (C-7), 31.7 (C-6), 24.3 (C-11), 9.0 (C-12).

**IR (KBr pellet):** ν<sub>max</sub> (cm<sup>-1</sup>) = 2991 (-C-H), 2977 (-C-H), 2244 (C≡N), 1787 (4-C=O), 1684 (1-C=O), 1477, 1393, 1306, 1205, 1132, 1039, 971, 760, 538.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>12</sub>H<sub>16</sub>N<sub>2</sub>O<sub>5</sub>SNa [M+Na]<sup>+</sup> 323.06721, found 323.06562.

[α]<sub>D</sub><sup>25</sup> = +25.06 (*c* = 0.13, CHCl<sub>3</sub>).

**(1R,2R,3S)-ethyl 3-cyano-3-ethyl-2-(methylsulfonyl)cyclobutanecarboxylate (260c)**



According to the general procedure (**L**) in chapter III, from cyclobutane **181q** (1.67 g, 5.56 mmol, 1.0 eq.), distilled EtOH (60.0 mL, 0.09 M), and DMAP (340.0 mg, 2.78 mmol, 0.5 eq.) for 48 h. Purification through short column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 90/10) afforded the desired product (1.44 g, quant.) as a pale-yellow oil solidifies open to atmosphere.

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 70/30):** R<sub>f</sub> = 0.82 (UV inactive; KMnO<sub>4</sub>, stains red-white).

**m. p.** = 73.9-76.8 °C (CH<sub>2</sub>Cl<sub>2</sub>/pentane).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ (ppm) = 4.30 (d, *J* = 9.6 Hz, 1H, H-7), 4.24 (q, *J* = 7.1 Hz, 2H, H-2), 3.67 (q, *J* = 9.7 Hz, 1H, H-4), 2.97 (s, 3H, H-8), 2.67-2.59 (m, 1H, H-5a), 2.52 (dd, *J* = 11.8, 10.0 Hz, 1H, H-5b), 2.44-2.32 (m, 1H, H-10a), 2.20-2.05 (m, 1H, H-10b), 1.30 (t, *J* = 7.1 Hz, 3H, H-1), 1.11 (t, *J* = 7.4 Hz, 3H, H-11).

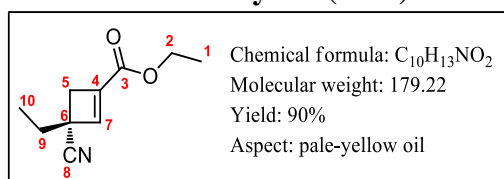
**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ (ppm) = 170.7 (C-3), 120.7 (C-9), 62.2 (C-2), 61.7 (C-7), 42.3 (C-8), 37.1 (C-4), 36.7 (C-6), 31.2 (C-5), 24.4 (C-10), 14.2 (C-1), 9.2 (C-11).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):** ν<sub>max</sub> (cm<sup>-1</sup>) = 2977 (-C-H), 2238 (C≡N), 1732 (3-C=O), 1311, 1249, 1146, 1130, 1041, 969, 756.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>11</sub>H<sub>17</sub>NO<sub>4</sub>SNa [M+Na]<sup>+</sup> 282.07694, found 282.07705.

[α]<sub>D</sub><sup>25</sup> = +32.62 (*c* = 0.16, CHCl<sub>3</sub>).

**(R)-ethyl 3-cyano-3-ethylcyclobut-1-enecarboxylate (258c)**





According to the general procedure (M) in chapter III, from cyclobutane **260c** (1.61 g, 6.2 mmol, 1.0 eq.), dry DMF (30.0 mL, 0.2 M), and Cs<sub>2</sub>CO<sub>3</sub> (12.4 g, 4.0 mmol, 2.0 eq.) for 13 h. Purification through short column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>: 100%) afforded the desired cyclobutene (1.0 g, 90%) as a pale-yellow oil. The product was concentrated carefully under reduced pressure, and stored under inert atmosphere in the freezer.

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 70/30):** R<sub>f</sub> = 0.9 (UV active; KMnO<sub>4</sub>, stains yellow).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ (ppm) = 6.74 (s, 1H, H-7), 4.23 (q, *J* = 7.1 Hz, 2H, H-2), 3.17 (d, *J* = 13.8 Hz, 1H, H-5a), 2.73 (d, *J* = 13.8 Hz, 1H, H-5b), 1.93-1.73 (m, 2H, H-9), 1.31 (t, *J* = 7.1 Hz, 3H, H-1), 1.14 (t, *J* = 7.4 Hz, 3H, H-10).

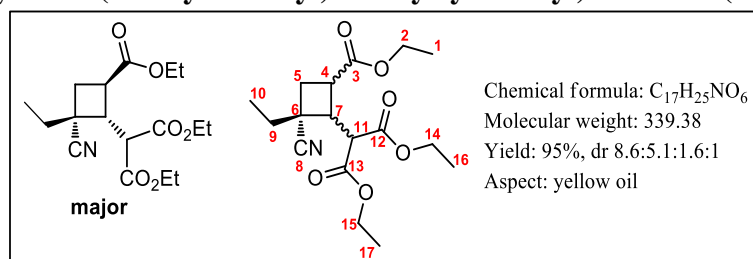
**<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):** δ (ppm) = 161.6 (C-3), 143.3 (C-7), 140.5 (C-4), 120.3 (C-8), 61.1 (C-2), 40.2 (C-5), 38.7 (C-6), 29.7 (C-9), 14.3 (C-1), 10.5 (C-10).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):** ν<sub>max</sub> (cm<sup>-1</sup>) = 2974 (-C-H), 2939 (-C-H), 2234 (C≡N), 1724 (3-C=O), 1461, 1317, 1278, 1240, 1153, 735.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>10</sub>H<sub>13</sub>NO<sub>2</sub>Na [M+Na]<sup>+</sup> 202.08385, found 202.08332.

[α]<sub>D</sub><sup>25</sup> = +5.98 (*c* = 0.08, CHCl<sub>3</sub>).

### diethyl 2-((2*R*)-2-cyano-4-(ethoxycarbonyl)-2-ethylcyclobutyl)malonate (**332b**)



According to the general procedure (N) in chapter III, from diethyl malonate (0.37 mL, 2.45 mmol, 1.0 eq.), dry THF (12.2 mL, 0.2 M), NaH (60% suspension in oil, 98.0 mg, 2.45 mmol, 1.0 eq.) and cyclobutene **258c** (440.0 mg, 2.45 mmol, 1.0 eq.) in dry THF (14.4 mL, 0.17 M) for 3 h. The crude as a mixture of diastereomers (788.0 mg, 95%, dr 8.6:5.1:1.6:1) was obtained as a yellow oil and was pure enough to be used directly in the next step without further purification. [Purification of the crude for analysis was accomplished through short column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc: 80/20)].

**TLC (cyclohexane/EtOAc: 70/30):** R<sub>f</sub> = 0.51 (UV active; KMnO<sub>4</sub>, stains yellow).

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):** δ (ppm) = 4.33-4.06 (m, 12H, all dia: H-2, H-14, H-15; H-11 dia-2), 3.89 (d, *J* = 12.5 Hz, 0.1H, H-11 dia-4), 3.87-3.80 (m, 0.1H, H-7 dia-4), 3.80 (d, *J* = 11.5 Hz, 1H, H-11 dia-1), 3.77-3.72 (m, 0.14H, H-7 dia-3), 3.48 (d, *J* = 11.9 Hz, 0.16H, H-11 dia-3), 3.41 (td, *J* = 9.8, 3.9 Hz, 0.1H, H-4 dia-4), 3.35-3.27 (m, 1.3H, H-7 dia-2, H-4 dia-2), 3.22 (dd, *J* = 11.5, 9.1 Hz, 1H, H-7 dia-1), 3.12 (q, *J* = 9.3 Hz, 1H, H-4 dia-1), 2.98 (q, *J* = 9.6 Hz, 0.13H, H-4 dia-3), 2.77-2.71 (m, 0.7H, H-5a dia-2), 2.71-2.67 (m, 0.1H, H-5a dia-4), 2.65-2.56 (m, 1.4H, H-5a dia-1, H-5a dia-3), 2.35 (dd, *J* = 12.7, 3.7 Hz, 0.1H, H-5b dia-4), 2.27-2.20 (m, 2H, H-5b dia-1, H-5b dia-2, H-5b dia-3), 2.08-1.97 (m, 2H, H-9a dia-1, H-9a dia-2, H-9a dia-3), 1.93 (dd, *J* = 13.5, 7.1 Hz, 0.1H, H-9a dia-4), 1.76-1.61 (m, 2.5H, all dia: H-9b), 1.32-1.23 (m, 20H, all dia: H-1, H-16, H-17), 1.06-0.99 (m, 6H, all dia: H-10).

**<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):**

**For the major diastereomer, dia-1, (1*R*,4*R*)-*trans*-332b:**

δ (ppm) = 172.6 (C-3), 167.3 (C-12), 167.0 (C-13), 121.5 (C-8), 62.0 (C-14, C-15), 61.2 (C-2), 54.7 (C-11), 44.3 (C-7), 40.3 (C-6), 38.1 (C-4), 32.3 (C-5), 31.7 (C-9), 14.2 (C-1), 14.1 (C-16, C-17), 9.0 (C-10).

**For the second diastereomer, dia-2, (1*R*,4*S*)-*cis*-332b:**

δ (ppm) = 172.2 (C-3), 167.8 (C-12), 167.1 (C-13), 121.0 (C-8), 62.2 (C-14), 61.9 (C-15), 61.3 (C-2), 51.8 (C-11), 42.9 (C-7), 39.0 (C-6), 36.8 (C-4), 32.5 (C-5), 31.7 (C-9), 14.1 (C-1, C-16, C-17), 9.1 (C-10).

**For the third diastereomer, dia-3, (1*S*,4*S*)-*trans*-332b:**

$\delta$  (ppm) = 172.0 (C-3), 167.3 (C-12), 166.9 (C-13), 122.0 (C-8), 62.3 (C-14), 62.1 (C-15), 61.2 (C-2), 51.9 (C-11), 43.6 (C-7), 40.0 (C-6), 37.6 (C-4), 32.0 (C-5), 24.4 (C-9), 14.1 (C-1, C-16, C-17), 9.1 (C-10).

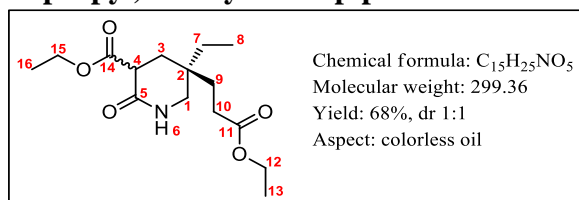
**For the minor diastereomer, dia-4, (1*S*,4*R*)-cis-332b:**

$\delta$  (ppm) = 173.4 (C-3), 167.4 (C-12), 166.9 (C-13), 123.0 (C-8), 62.4 (C-14, C-15), 61.2 (C-2), 49.7 (C-11), 42.1 (C-7), 40.0 (C-6), 35.6 (C-4), 31.2 (C-5), 24.2 (C-9), 14.1 (C-1, C-16, C-17), 8.7 (C-10).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2981 (-C-H), 2940 (-C-H), 2232 (C≡N), 1738 (br, 3-C=O, 12-C=O, 13-C=O), 1464, 1373, 1308, 1253, 1237, 1187, 1037, 862.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>17</sub>H<sub>26</sub>NO<sub>6</sub> [M+H]<sup>+</sup> 340.17546, found 340.17429.

**(5*R*)-ethyl 5-(3-ethoxy-3-oxopropyl)-5-ethyl-2-oxopiperidine-3-carboxylate (580c)**



According to the general procedure (A), from the crude cyclobutane **332b** (698.0 mg, 2.05 mmol, 1.0 eq.), anhydrous NiCl<sub>2</sub> (585.7 mg, 4.52 mmol, 2.2 eq.), freshly distilled EtOH (82.0 mL, 0.025 M), and NaBH<sub>4</sub> (1.53 g, 41.0 mmol, 20.0 eq.) for 70 h. The crude mixture was purified through column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 95/5 to 90/10) to afford the desired mixture of diastereomers (420.0 mg, 68%, dr 1:1) as a colorless oil, and the reduced amine (70.0 mg, 10%, isolated dr 1.25:1) as a yellow oil.

**Scale-up reaction:**

According to the general procedure (A), from the crude cyclobutane **332b** (1.4 g, 4.0 mmol, 1.0 eq.), anhydrous NiCl<sub>2</sub> (1.14 g, 8.8 mmol, 2.2 eq.), freshly distilled EtOH (160.0 mL, 0.025 M), and NaBH<sub>4</sub> (2.99 g, 80.0 mmol, 20.0 eq.) for 70 h. The crude mixture was purified through column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 98/2 to 95/5 to 90/10) to afford the desired mixture of diastereomers (744.0 mg, 62%, 77% brsm, dr 1:1) as a colorless oil, and the reduced amine (150.0 mg, 11%, isolated dr 1.25:1) as a yellow oil. 21% of the starting material were recovered and engaged again in the reduction reaction.

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 90/10):** R<sub>f</sub> = 0.62 (UV inactive; KMnO<sub>4</sub>, stains white).

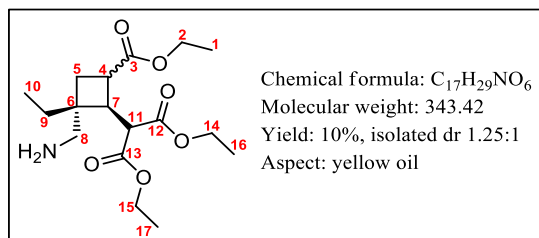
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 5.78 (br s, 2H, H-6 dia-1/dia-2), 4.31-4.18 (m, 4H, H-12 dia-1/dia-2), 4.14 (qd,  $J$  = 7.1, 1.9 Hz, 4H, H-15 dia-1/dia-2), 3.44-3.31 (m, 2H, H-4 dia-1/dia-2), 3.18 (d,  $J$  = 12.3 Hz, 2H, H-1a dia-1/dia-2), 3.07-2.96 (m, 2H, H-1b dia-1/dia-2), 2.31-2.19 (m, 4H, H-10 dia-1/dia-2), 1.97-1.88 (m, 4H, H-9 dia-1/dia-2), 1.82-1.74 (m, 2H, H-3 dia-1), 1.73-1.65 (m, 2H, H-3 dia-2), 1.51-1.41 (m, 2H, H-7 dia-2), 1.39-1.32 (m, 2H, H-7 dia-1), 1.28 (dtd,  $J$  = 9.1, 7.1, 1.5 Hz, 12H, H-13 dia-1/dia-2, H-16 dia-1/dia-2), 0.87 (td,  $J$  = 7.5, 3.4 Hz, 6H, H-8 dia-1/dia-2).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 173.3 (C-11 dia-1), 173.2 (C-11 dia-2), 170.9 (C-14 dia-1), 170.8 (C-14 dia-2), 168.3 (C-5 dia-1/dia-2), 61.6 (C-15 dia-1/dia-2), 60.8 (C-12 dia-1), 60.7 (C-12 dia-2), 50.7 (C-1 dia-1), 50.5 (C-1 dia-2), 46.0 (C-4 dia-1/dia-2), 34.3 (C-2 dia-1), 34.2 (C-2 dia-2), 34.0 (C-10 dia-1), 33.7 (C-10 dia-2), 31.3 (C-3 dia-2), 29.4 (C-7 dia-1), 28.7 (C-9 dia-1), 28.5 (C-9 dia-2), 26.7 (C-3 dia-1), 24.5 (C-7 dia-2), 14.3 (C-13 dia-1/dia-2), 14.2 (C-16 dia-1/dia-2), 7.5 (C-8 dia-1/dia-2).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2970 (-C-H), 2939 (-C-H), 2878 (-C-H), 1734 (11-C=O, 14-C=O), 1674 (5-C=O), 1465, 1372, 1302, 1276, 1182, 1034, 861, 737.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>15</sub>H<sub>25</sub>NO<sub>5</sub>Na [M+Na]<sup>+</sup> 322.16249, found 322.16092.

**diethyl 2-((1*S*,2*R*)-2-(aminomethyl)-4-(ethoxycarbonyl)-2-ethylcyclobutyl)malonate (379c)**



The reduced amine **379c** (70.0 mg, 10%, isolated dr 1.25:1) was obtained as a yellow oil, as a side product alongside with the cyclized product.

**TLC** ( $CH_2Cl_2/MeOH$ : 90/10):  $R_f$  = 0.23 (UV inactive;  $KMnO_4$ , stains yellow).

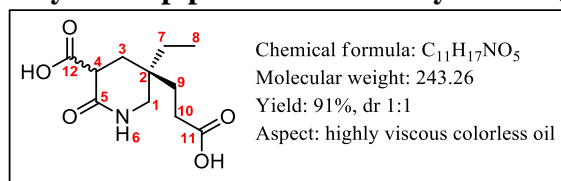
**$^1H$  NMR** (300 MHz,  $CDCl_3$ ):  $\delta$  (ppm) = 4.32-3.97 (m, 15H, dia-1/dia-2: H-2, H-14, H-15, H-11 dia-1), 3.58 (d,  $J$  = 11.7 Hz, 1H, H-11 dia-2), 3.41-2.82 (m, 10H, H-4 dia-1/dia-2, H-7 dia-1/dia-2, H-8 dia-1/dia-2), 2.22-2.06 (m, 2H, H-5 dia-1), 1.99-1.87 (m, 3H, H-5 dia-2, H-9a dia-1), 1.70-1.54 (m, 3H, H-9b dia-1, H-9 dia-2), 1.46 (q,  $J$  = 7.1 Hz, 7H, H-1 dia-1/dia-2), 1.32-1.17 (m, 14H, H-16 dia-1/dia-2, H-17 dia-1/dia-2), 1.01 (t,  $J$  = 7.3 Hz, 3H, H-10 dia-1), 0.97-0.80 (m, 4H, H-10 dia-2).

**$^{13}C$  NMR** (75 MHz,  $CDCl_3$ ):  $\delta$  (ppm) = 174.2 (C-3 dia-1), 173.9 (C-3 dia-2), 167.2 (C-12 dia-1/dia-2, C-13 dia-1/dia-2), 63.3 (C-2 dia-1), 63.2 (C-2 dia-2), 62.2 (C-14 dia-1), 62.1 (C-14 dia-2), 61.2 (C-15 dia-1), 61.0 (C-15 dia-2), 54.3 (C-8 dia-1), 52.0 (C-11 dia-2), 49.5 (C-11 dia-1), 45.0 (C-8 dia-2), 43.3 (C-7 dia-1), 41.6 (C-7 dia-2), 40.3 (C-6 dia-1/dia-2), 36.3 (C-4 dia-1), 35.0 (C-4 dia-2), 30.4 (C-5 dia-1), 29.8 (C-5 dia-2), 23.5 (C-9 dia-1/dia-2), 14.3 (C-16 dia-1), 14.2 (C-16 dia-2), 14.0 (C-17 dia-1/dia-2), 11.8 (C-1 dia-1), 11.6 (C-1 dia-2), 7.8 (C-10 dia-1), 7.2 (C-10 dia-2).

**IR** (solution in  $CH_2Cl_2$ , thin film, KBr):  $\nu_{max}$  ( $cm^{-1}$ ) = 2980 (-C-H), 2940 (-C-H), 1731 (br, 3-C=O, 12-C=O, 13-C=O), 1464, 1447, 1373, 1301, 1185, 1029, 861.

**HRMS** (TOF, ES<sup>+</sup>): calculated for  $C_{17}H_{30}NO_6$   $[M+H]^+$  344.20676, found 344.20637.

#### (5R)-5-(2-carboxyethyl)-5-ethyl-2-oxopiperidine-3-carboxylic acid (**388c**)



According to the general procedure (**B**), from **380c** (271.0, 0.9 mmol, 1.0 eq.), EtOH/ $H_2O$ : 4/1 (3.5 mL, 0.15 M) and LiOH (108.0 mg, 4.5 mmol, 5.0 eq.) for 4 h. The crude mixture of diastereomers (200.0 mg, 91%, dr 1:1) was obtained as a highly viscous colorless oil and was used directly in the next step without further purification.

**TLC** ( $CH_2Cl_2/MeOH/AcOH$ : 90/9/1):  $R_f$  = 0 (UV inactive;  $KMnO_4$ , stains yellow-white).

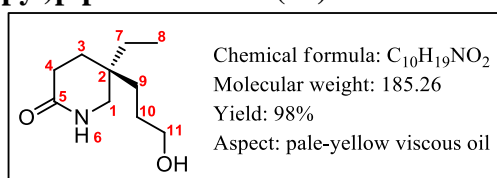
**$^1H$  NMR** (400 MHz,  $CD_3OD$ ): For dia-1 and dia-2:  $\delta$  (ppm) = 3.44-3.36 (m, 1H, H-4), 3.12 (d,  $J$  = 12.8 Hz, 1H, H-1a), 3.07-2.99 (m, 1H, H-1b), 2.35-2.21 (m, 2H, H-10), 2.07-1.99 (m, 1H, H-3a), 1.93-1.83 (m, 1H, H-3b), 1.80-1.61 (m, 2H, H-9), 1.52-1.33 (m, 2H, H-7), 0.89 (td,  $J$  = 7.5, 5.1 Hz, 3H, H-8).

**$^{13}C$  NMR** (100 MHz,  $CD_3OD$ ):  $\delta$  (ppm) = 177.2 (C-11 dia-1/dia-2), 174.1 (C-12 dia-1/dia-2), 171.2 (C-5 dia-1/dia-2), 51.2 (C-1 dia-1), 50.9 (C-1 dia-2), 48.4 (C-4 dia-1), 47.9 (C-4 dia-2), 35.3 (C-2 dia-1/dia-2), 34.7 (C-3 dia-1), 34.5 (C-3 dia-2), 32.2 (C-9 dia-1), 30.1 (C-7 dia-1), 29.1 (C-10 dia-1), 29.0 (C-10 dia-2), 27.9 (C-9 dia-2), 25.5 (C-7 dia-2), 7.6 (C-8 dia-1/dia-2).

**IR** (solution in  $CH_2Cl_2$ , thin film, KBr):  $\nu_{max}$  ( $cm^{-1}$ ) = 3282 (br, OH), 2923 (-C-H), 2853 (-C-H), 1711 (11-C=O, 12-C=O), 1637 (5-C=O), 1463, 1310, 1233, 732.

**HRMS** (TOF, ES<sup>+</sup>): calculated for  $C_{11}H_{17}NO_5Na$   $[M+Na]^+$  266.09989, found 266.09857.

#### (R)-5-ethyl-5-(3-hydroxypropyl)piperidin-2-one (**21**)





According to the general procedure (C), from the crude diacid **388c** (303.0 mg, 1.24 mmol, 1.0 eq.) and dry THF (15.5 mL, 0.08 M) for 3 h. The crude mixture **389c** (250.0 mg, quant.) was obtained as a colorless viscous oil. The esterification reaction was accomplished from the crude **389c** (407.0 mg, 2.04 mmol, 1.0 eq.) in CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 5/1 (17.0 mL, 0.12 M), TMSCHN<sub>2</sub> (2.0 M in hexane, 1.5 mL, 3.06 mmol, 1.5 eq.), and AcOH (0.035 mL, 0.612 mmol, 0.3 eq.). The crude **391c** (435.0 mg, quant.) was obtained as a pale-yellow oil. The reduction reaction was accomplished from the crude **391c** (300.0 mg, 1.4 mmol, 1.0 eq.) in dry THF (40.0 mL, 0.035 M), and LAH (1.0 M in Et<sub>2</sub>O, 1.75 mL, 1.75 mmol, 1.25 eq.) for 12 h. The crude **21** (257.0 mg, 98%) was obtained as pale-yellow viscous oil and was used directly in the next step without further purification. [Purification of the crude for analysis afforded the alcohol as a pale-yellow viscous oil].

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 90/10):**  $R_f$  = 0.32 (UV inactive; KMnO<sub>4</sub>, stains yellow).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 5.65 (br s, 1H, H-6), 3.65 (br s, 2H, H-11), 3.05 (d,  $J$  = 2.6 Hz, 2H, H-1), 2.35 (t,  $J$  = 7.0 Hz, 2H, H-4), 1.64 (t,  $J$  = 7.0 Hz, 2H, H-3), 1.54-1.29 (m, 6H, H-7, H-9, H-10), 0.85 (t,  $J$  = 7.5 Hz, 3H, H-8).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 172.9 (C-5), 63.1 (C-11), 51.2 (C-1), 33.8 (C-2), 29.8 (C-9), 29.7 (C-3), 27.9 (C-4), 27.0 (C-7), 26.4 (C-10), 7.6 (C-8).

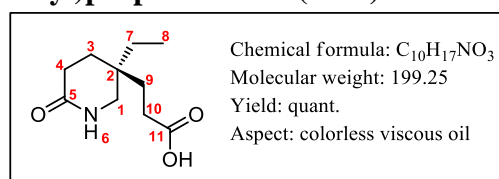
**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 3309 (br, OH), 2938 (-C-H), 2871 (-C-H), 1654 (5-C=O), 1496, 1464, 1410, 1308, 1061, 732.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>10</sub>H<sub>19</sub>NO<sub>2</sub>Na [M+Na]<sup>+</sup> 208.13080, **found** 208.12978.

$[\alpha]_D^{25}$  = +7.73 ( $c$  = 0.11, CHCl<sub>3</sub>).

### Isolation of the intermediates

#### (S)-3-(3-ethyl-6-oxopiperidin-3-yl)propanoic acid (**389c**)



**TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/AcOH: 90/9/1):**  $R_f$  = 0 (UV inactive; KMnO<sub>4</sub>, stains yellow, drags on TLC).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 7.73 (br s, 1H, H-6), 3.05 (s, 2H, H-1), 2.41-2.18 (m, 4H, H-4, H-10), 1.73-1.60 (m, 4H, H-3, H-9), 1.45-1.31 (m, 2H, H-7), 0.85 (t,  $J$  = 7.4 Hz, 3H, H-8).

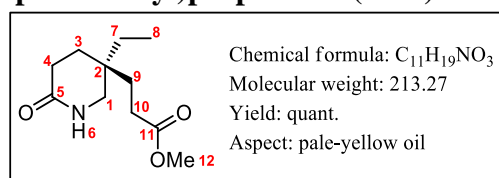
**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 178.1 (C-11), 174.4 (C-5), 50.7 (C-1), 33.5 (C-2), 29.2 (C-9), 28.5 (C-3), 28.4 (C-4), 27.4 (C-10), 26.9 (C-7), 7.5 (C-8).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 3277 (br, OH), 2938 (-C-H), 2878 (-C-H), 1712 (11-C=O), 1638 (5-C=O), 1496, 1231, 807.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>10</sub>H<sub>17</sub>NO<sub>3</sub>Na [M+Na]<sup>+</sup> 222.11006, **found** 222.10980.

$[\alpha]_D^{25}$  = +7.16 ( $c$  = 0.26, CHCl<sub>3</sub>) crude value.

#### (S)-methyl 3-(3-ethyl-6-oxopiperidin-3-yl)propanoate (**391c**)



**TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 90/10):**  $R_f$  = 0.5 (UV inactive; KMnO<sub>4</sub>, stains yellow).

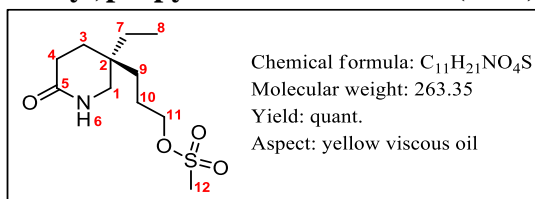
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 6.90 (br s, 1H, H-6), 3.64 (s, 3H, H-12), 3.00 (s, 2H, H-1), 2.39-2.05 (m, 4H, H-4, H-10), 1.74-1.51 (m, 4H, H-3, H-9), 1.36 (hept,  $J$  = 7.2 Hz, 2H, H-7), 0.81 (t,  $J$  = 7.5 Hz, 3H, H-8).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 173.9 (C-5, C-11), 51.8 (C-12), 50.7 (C-1), 33.6 (C-2), 29.6 (C-9), 28.8 (C-3), 28.3 (C-4, C-10), 26.5 (C-7), 7.4 (C-8).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2947 (-C-H), 2877 (-C-H), 1736 (11-C=O), 1663 (5-C=O), 1463, 1436, 1309, 1196, 1170, 790.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>11</sub>H<sub>20</sub>NO<sub>3</sub> [M+H]<sup>+</sup> 214.14377, **found** 214.14352.  
 [ $\alpha$ ]<sub>D</sub><sup>25</sup> = +6.88 (*c* = 0.16, CHCl<sub>3</sub>).

**(R)-3-(3-ethyl-6-oxopiperidin-3-yl)propyl methanesulfonate (392c)**



According to the general procedure (**D**), from the hydroxy piperidinone **21** (257.0 mg, 1.38 mmol, 1.0 eq.), dry CH<sub>2</sub>Cl<sub>2</sub> (20.0 mL, 0.07 M), MsCl (0.11 mL, 1.52 mmol, 1.1 eq.) and distilled Et<sub>3</sub>N (0.2 mL, 1.52 mmol, 1.1 eq.) for 3 h. The crude (365.0 mg, quant.) was obtained as a yellow viscous oil and was used directly in the next step without further purification. [Purification of the crude for analysis was accomplished through short column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>4</sub>OH: 95/4/1) to afford the product as a pale-yellow viscous oil].

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 90/10):** R<sub>f</sub> = 0.50 (UV inactive; KMnO<sub>4</sub>, stains white-red).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 5.90 (br s, 1H, H-6), 4.22 (t, *J* = 6.3 Hz, 2H, H-11), 3.05 (d, *J* = 2.4 Hz, 2H, H-1), 3.01 (s, 3H, H-12), 2.34 (t, *J* = 7.1 Hz, 2H, H-4), 1.74-1.60 (m, 4H, H-3, H-10), 1.51-1.35 (m, 4H, H-7, H-9), 0.85 (t, *J* = 7.5 Hz, 3H, H-8).

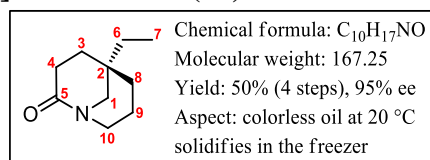
**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 172.2 (C-5), 70.0 (C-11), 51.1 (C-1), 37.6 (C-12), 33.9 (C-2), 29.8 (C-9), 29.6 (C-3), 27.9 (C-4), 26.8 (C-7), 23.4 (C-10), 7.6 (C-8).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2943 (-C-H), 2879 (-C-H), 1652 (5-C=O), 1467, 1347, 1201, 1049, 974, 831, 529.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>11</sub>H<sub>21</sub>NO<sub>4</sub>SNa [M+Na]<sup>+</sup> 286.10835, **found** 286.10793.

[ $\alpha$ ]<sub>D</sub><sup>25</sup> = +2.46 (*c* = 0.4, CHCl<sub>3</sub>).

**(5R)-5-ethyl-1-azabicyclo[3.3.1]nonan-2-one (20)**



According to the general procedure (**E**), from the mesylate **392c** (70.0 mg, 0.26 mmol, 1.0 eq.), DMF (2.6 mL, 0.1 M) and NaH (60% suspension in oil, 16.0 mg, 0.39 mmol, 1.5 eq.). The mixture was stirred at 20 °C for 12 h. The crude was purified through short column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc/NH<sub>4</sub>OH: 70/29/1) to afford the pure desired product (22.0 mg, 50% over 4 steps, 95% ee) as a colorless oil at 20 °C solidifies in the freezer. The product was stored under inert atmosphere in the freezer.

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 95/5):** R<sub>f</sub> = 0.41 (UV inactive; KMnO<sub>4</sub>, stains yellow after long heating).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 4.17-4.05 (m, 1H, H-10a), 3.19 (d, *J* = 13.1 Hz, 1H, H-1a), 2.79-2.67 (m, 1H, H-10b), 2.65 (d, *J* = 13.4 Hz, 1H, H-1b), 2.47 (td, *J* = 13.5, 8.3 Hz, 1H, H-4a), 2.31 (ddd, *J* = 14.2, 5.7, 1.2 Hz, 1H, H-4b), 1.88 (ddd, *J* = 14.0, 8.3, 1.5 Hz, 1H, H-3a), 1.78-1.59 (m, 1H, H-9a), 1.53-1.23 (m, 6H, H-3b, H-6, H-8, H-9b), 0.89 (t, *J* = 7.4 Hz, 3H, H-7).

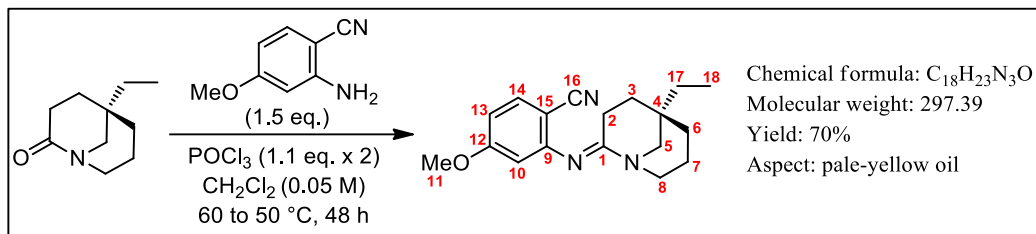
**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 184.8 (C-5), 57.4 (C-1), 51.0 (C-10), 37.0 (C-2), 36.3 (C-8), 33.7 (C-4), 33.5 (C-6), 29.6 (C-3), 21.7 (C-9), 7.8 (C-7).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2929 (-C-H), 2865 (-C-H), 1676 (5-C=O), 1459, 1355, 1175, 957, 826, 746.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>10</sub>H<sub>18</sub>NO [M+H]<sup>+</sup> 168.13829, **found** 168.13809.

[ $\alpha$ ]<sub>D</sub><sup>25</sup> = +8.75 (*c* = 0.18, CHCl<sub>3</sub>).

**2-((E)-((5R)-5-ethyl-1-azabicyclo[3.3.1]nonan-2-ylidene)amino)-4-methoxybenzonitrile (355)**



To a flame-dried two-necked flask equipped with a condenser, the bicyclic lactam **20** (49.0 mg, 0.29 mmol, 1.0 eq.) was introduced followed by dry  $CH_2Cl_2$  (3.0 mL, 0.1 M), and  $POCl_3$  (30.0  $\mu$ L, 0.328 mmol, 1.1 eq.) was added dropwise. The reaction was stirred at 60 °C silicon oil bath temperature and the starting material consumption was followed by TLC. After 12 h, another 1.1 eq. of  $POCl_3$  were added and the heating continued for another 12 h. After total consumption of the starting material, the reaction was cooled down to 20 °C and 2-amino-4-methoxybenzonitrile (66.0 mg, 0.44 mmol, 1.5 eq.) dissolved in dry  $CH_2Cl_2$  (2.0 mL, 0.1 M), was added dropwise. The reaction was stirred at 50 °C for 24 h, then the solvents were concentrated under reduced pressure and ice water (2.0 mL) was added to the reaction. The aqueous layer was basified with sat.  $NaHCO_3$  till pH = 8, then extracted with  $CH_2Cl_2$ . The organic layer was washed with brine, dried over  $Na_2SO_4$  and concentrated under reduced pressure. The crude mixture was purified through column chromatography on  $SiO_2$  ( $CH_2Cl_2$ /EtOAc/ $NH_4OH$ : 99/0/1 to 90/9/1) to afford the product (60.0 mg, 70%) as a pale-yellow oil.

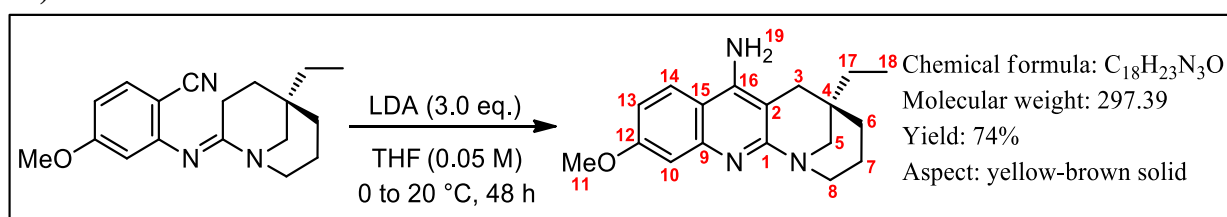
**TLC ( $CH_2Cl_2$ /MeOH: 98/2):**  $R_f$  = 0.51 (UV active;  $KMnO_4$ , stains yellow after long heating).

**$^1H$  NMR (600 MHz,  $CDCl_3$ ):**  $\delta$  (ppm) = 7.46 (d,  $J$  = 8.6 Hz, 1H, H-14), 6.57 (dd,  $J$  = 8.8, 2.4 Hz, 1H, H-13), 6.31 (s, 1H, H-10), 4.30 (dd,  $J$  = 13.1, 5.1 Hz, 1H, H-8a), 3.81 (s, 3H, H-11), 3.15 (d,  $J$  = 13.4 Hz, 1H, H-5a), 2.90 (t,  $J$  = 12.6 Hz, 1H, H-8b), 2.65 (d,  $J$  = 13.4 Hz, 1H, H-5b), 2.34 (dd,  $J$  = 15.0, 5.3 Hz, 1H, H-3a), 2.28-2.12 (m, 2H, H-6), 1.74 (dd,  $J$  = 13.9, 7.7 Hz, 1H, H-3b), 1.60 (d,  $J$  = 13.4 Hz, 1H, H-2a), 1.52-1.36 (m, 3H, H-2b, H-7), 1.31-1.25 (m, 2H, H-17), 0.87 (t,  $J$  = 7.5 Hz, 3H, H-18).

**$^{13}C$  NMR (150 MHz,  $CDCl_3$ ):**  $\delta$  (ppm) = 170.3 (C-1), 163.6 (C-9), 156.6 (C-12), 134.4 (C-14), 118.9 (C-16), 109.4 (C-10), 107.3 (C-13), 97.4 (C-15), 56.9 (C-5), 55.6 (C-11), 53.8 (C-8), 36.5 (C-3), 35.7 (C-4), 33.8 (C-17), 29.4 (C-6), 26.4 (C-7), 20.8 (C-2), 7.7 (C-18).

$[\alpha]_D^{25}$  = +50.38 ( $c$  = 0.24,  $CHCl_3$ ).

**(5*R*)-5-ethyl-10-methoxy-3,4,5,6-tetrahydro-2*H*-1,5-methanoazocino[2,3-*b*]quinolin-7-amine (356)**



**LDA preparation:** To a flame-dried flask, freshly distilled DIPA (68.0  $\mu$ L, 0.48 mmol, 1.1 eq.) was introduced followed by dry THF (2.0 mL, 0.22 M) and the reaction was set at 0 °C.  $n$ -BuLi (1.4 M in hexane, 0.30 mL, 0.44 mmol, 1.0 eq.) was added dropwise. The reaction was stirred at 20 °C for 30 min.

To a flame-dried flask and under inert atmosphere, **355** (38.0 mg, 0.127 mmol, 1.0 eq.) was introduced, followed by dry THF (2.4 mL, 0.05 M) and the reaction was set at 0 °C. LDA prepared above (0.22 M, 1.74 mL, 0.38 mmol, 3.0 eq.) was added dropwise and the reaction was warmed up slowly to 20 °C. After 48 h, the reaction was quenched at 0 °C with sat.  $NH_4Cl$  (0.1 mL) and extracted with  $H_2O$  (0.5 mL)/EtOAc. The aqueous phase was extracted twice and the combined organic layers were dried over  $Na_2SO_4$  and concentrated under reduced pressure. The crude mixture was purified through short column chromatography on  $SiO_2$  ( $CH_2Cl_2$ /MeOH/ $NH_4OH$ : 98/1/1 to 97/2/1) to afford the product (28.0 mg, 74%) as a yellow-brown solid. The product was stored under inert atmosphere in the freezer. [All the solvents used for extraction and purification were distilled to remove the traces of impurities present in the commercial bottles].

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>4</sub>OH: 94/5/1):**  $R_f$  = 0.20 (UV active, appears fluorescent; KMnO<sub>4</sub>, stains yellow after long heating).

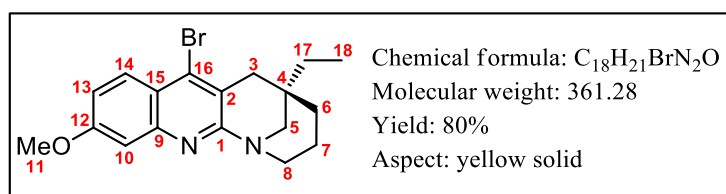
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 7.54 (d,  $J$  = 9.1 Hz, 1H, H-14), 7.21 (d,  $J$  = 2.6 Hz, 1H, H-13), 6.97 (dd,  $J$  = 9.1, 2.6 Hz, 1H, H-10), 4.56 (br s, 2H, H-19), 3.89 (s, 3H, H-11), 3.78-3.69 (m, 1H, H-8a), 3.13 (td,  $J$  = 12.9, 3.4 Hz, 1H, H-5a), 3.04 (dd,  $J$  = 13.1, 1.7 Hz, 1H, H-8b), 2.93 (dd,  $J$  = 13.0, 1.9 Hz, 1H, H-5b), 2.50 (dd,  $J$  = 16.2, 1.5 Hz, 1H, H-3a), 2.31 (dd,  $J$  = 16.1, 1.7 Hz, 1H, H-3b), 1.96-1.65 (m, 1H, H-6a), 1.63-1.50 (m, 1H, H-6b), 1.38 (q,  $J$  = 7.5 Hz, 2H, H-17), 1.33-1.21 (m, 2H, H-7), 0.97 (t,  $J$  = 7.5 Hz, 3H, H-18).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 162.1 (C-1), 160.2 (C-9), 148.5 (C-12), 146.8 (C-16), 120.8 (C-14), 115.9 (C-10), 111.1 (C-15), 107.1 (C-13), 105.4 (C-2), 57.9 (C-5), 55.5 (C-11), 55.1 (C-8), 36.5 (C-3), 35.4 (C-17), 33.5 (C-6), 30.5 (C-4), 19.6 (C-7), 7.4 (C-18).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2929 (-C-H), 2854 (-C-H), 1621, 1573, 1458, 1334, 1242, 1165, 1030, 731.

**$[\alpha]_D^{25}$**  = +101.69 ( $c$  = 0.33, CHCl<sub>3</sub>).

**(5R)-7-bromo-5-ethyl-10-methoxy-3,4,5,6-tetrahydro-2H-1,5-methanoazocino[2,3-*b*]quinoline (418)**



According to the general procedure (F), from the amino quinoline **356** (12.0 mg, 0.04 mmol, 1.0 eq.), CuBr (11.5 mg, 0.08 mmol, 2.0 eq.), CH<sub>3</sub>CN (0.4 mL, 0.1 M) and *t*-BuONO (7.1  $\mu$ L, 0.06 mmol, 1.5 eq.) for 3 h. The crude mixture was purified through micro-column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/NH<sub>4</sub>OH: 98/1) to afford the desired product (11.5 mg, 80%) as a yellow solid.

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>4</sub>OH: 95/4/1):**  $R_f$  = 0.48 (UV active; KMnO<sub>4</sub>, stains red-yellow then intense yellow after 5 min).

**m. p.** = 62.2-64.9 °C (CH<sub>2</sub>Cl<sub>2</sub>/pentane).

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 8.00 (d,  $J$  = 9.2 Hz, 1H, H-14), 7.25 (d,  $J$  = 2.5 Hz, 1H, H-13), 7.13 (dd,  $J$  = 9.3, 2.5 Hz, 1H, H-10), 3.92 (s, 3H, H-11), 3.77 (d,  $J$  = 14.0 Hz, 1H, H-8a), 3.19 (td,  $J$  = 12.9, 3.4 Hz, 1H, H-8b), 3.07 (d,  $J$  = 13.3 Hz, 1H, H-5a), 2.91 (d,  $J$  = 13.3 Hz, 1H, H-5b), 2.80 (d,  $J$  = 18.0 Hz, 1H, H-3a), 2.70 (d,  $J$  = 18.1 Hz, 1H, H-3b), 1.80 (d,  $J$  = 12.8 Hz, 1H, H-6a), 1.60-1.55 (m, 1H, H-6b), 1.40 (q,  $J$  = 7.6 Hz, 2H, H-17), 1.37-1.29 (m, 2H, H-7), 1.00 (t,  $J$  = 7.5 Hz, 3H, H-18).

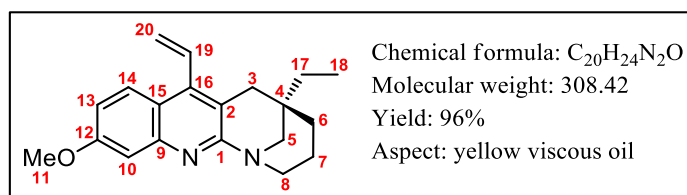
**<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 162.2 (C-1), 160.8 (C-9), 148.1 (C-12), 135.9 (C-16), 127.3 (C-14), 125.7 (C-15), 121.0 (C-2), 119.0 (C-10), 106.5 (C-13), 57.7 (C-5), 56.0 (C-8), 55.7 (C-11), 40.1 (C-3), 36.1 (C-6), 35.0 (C-17), 31.6 (C-4), 19.7 (C-7), 7.4 (C-18).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2929 (-C-H), 2856 (-C-H), 1618, 1582, 1486, 1446, 1366, 1229, 1147, 1030, 891, 800.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>18</sub>H<sub>22</sub>BrN<sub>2</sub>O [M+H]<sup>+</sup> 361.09100, found 361.09065.

**$[\alpha]_D^{25}$**  = +132.10 ( $c$  = 0.06, CHCl<sub>3</sub>).

**(5R)-5-ethyl-10-methoxy-7-vinyl-3,4,5,6-tetrahydro-2H-1,5-methanoazocino[2,3-*b*]quinoline (19)**



According to the general procedure (G), from the bromoquinoline **418** (10.0 mg, 0.027 mmol, 1.0 eq.), potassium vinyltrifluoroborate (5.6 mg, 0.04 mmol, 1.5 eq.), anhydrous K<sub>2</sub>CO<sub>3</sub> (3.7 mg, 0.027 mmol, 1.0 eq.), freshly distilled DME (0.45 mL, 0.06 M), distilled H<sub>2</sub>O (0.22 mL, 0.12 M) and

$\text{Pd(PPh}_3)_4$  (3.1 mg, 2.7  $\mu\text{mol}$ , 0.1 eq.) for 12 h. The crude mixture was purified through micro-column chromatography on  $\text{SiO}_2$  ( $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_4\text{OH}$ : 99/0/1 to 98/1/1) to afford the pure desired product (8.0 mg, 96%) as a yellow viscous oil.

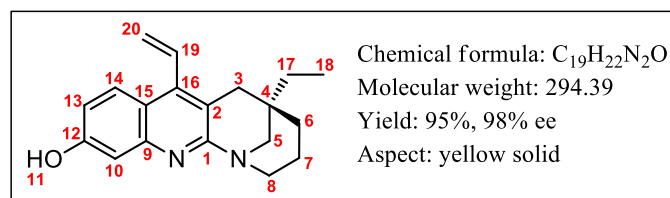
**TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_4\text{OH}$ : 95/4/1):**  $R_f$  = 0.42 (UV active;  $\text{KMnO}_4$ , stains intense yellow).

**$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 7.92 (d,  $J$  = 9.2 Hz, 1H, H-14), 7.27 (d,  $J$  = 2.6 Hz, 1H, H-13), 7.03 (dd,  $J$  = 9.2, 2.6 Hz, 1H, H-10), 6.84 (dd,  $J$  = 18.0, 11.7 Hz, 1H, H-19), 5.84 (dd,  $J$  = 11.8, 1.9 Hz, 1H, H-20a), 5.54 (dd,  $J$  = 17.9, 2.0 Hz, 1H, H-20b), 3.92 (s, 3H, H-11), 3.77 (d,  $J$  = 12.3 Hz, 1H, H-8a), 3.19 (td,  $J$  = 13.1, 3.4 Hz, 1H, H-8b), 3.07 (d,  $J$  = 13.1 Hz, 1H, H-5a), 2.94 (d,  $J$  = 13.2 Hz, 1H, H-5b), 2.72 (d,  $J$  = 17.6 Hz, 1H, H-3a), 2.55 (d,  $J$  = 17.8 Hz, 1H, H-3b), 1.76 (d,  $J$  = 13.5 Hz, 1H, H-6a), 1.64-1.57 (m, 1H, H-6b), 1.35 (q,  $J$  = 7.6 Hz, 2H, H-17), 1.33-1.22 (m, 2H, H-7), 0.96 (t,  $J$  = 7.6 Hz, 3H, H-18).

**$^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 161.8 (C-1), 160.1 (C-9), 148.5 (C-12), 143.7 (C-16), 132.1 (C-19), 126.1 (C-14), 122.7 (C-20), 121.9 (C-15), 119.3 (C-2), 117.6 (C-10), 106.7 (C-13), 57.7 (C-5), 55.8 (C-8), 55.5 (C-11), 36.8 (C-3), 36.3 (C-6), 35.3 (C-17), 30.8 (C-4), 19.7 (C-7), 7.3 (C-18).

$[\alpha]_{\text{D}}^{25}$  = +118.57 ( $c$  = 0.16,  $\text{CHCl}_3$ ).

**(5*R*)-5-ethyl-7-vinyl-3,4,5,6-tetrahydro-2*H*-1,5-methanoazocino[2,3-*b*]quinolin-10-ol ((+)-Eucophylline), 8**



According to the general procedure (**H**), from vinyl quinoline **19** (10.0 mg, 0.032 mmol, 1.0 eq.),  $\text{CH}_2\text{Cl}_2$  (1.6 mL, 0.02 M) and  $\text{BBr}_3$  (1.0 M in  $\text{CH}_2\text{Cl}_2$ , 0.39 mL, 0.39 mmol, 12.0 eq.). The crude mixture was purified through micro-column chromatography on  $\text{SiO}_2$  ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ : 99/1 to 98/2) to afford the pure desired product (9.0 mg, 95%, 98% ee) as a yellow solid.

**TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ : 96/4):**  $R_f$  = 0.20 (UV active;  $\text{KMnO}_4$ , stains yellow).

**m. p.** = 164.6-166.3  $^\circ\text{C}$  (evaporation from  $\text{CH}_2\text{Cl}_2$ ).

**$^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{OD}$ ):**  $\delta$  (ppm) = 8.13 (d,  $J$  = 9.2 Hz, 1H, H-14), 7.22 (dd,  $J$  = 9.2, 2.4 Hz, 1H, H-13), 7.18 (d,  $J$  = 2.4 Hz, 1H, H-10), 7.03 (dd,  $J$  = 17.9, 11.9 Hz, 1H, H-19), 6.07 (dd,  $J$  = 11.9, 1.4 Hz, 1H, H-20a), 5.72 (dd,  $J$  = 17.9, 1.4 Hz, 1H, H-20b), 3.71 (dd,  $J$  = 13.7, 3.5 Hz, 1H, H-8a), 3.42 (td,  $J$  = 13.2, 3.7 Hz, 1H, H-8b), 3.19 (dd,  $J$  = 13.2, 1.9 Hz, 1H, H-5a), 3.00 (d,  $J$  = 13.1 Hz, 1H, H-5b), 2.85 (d,  $J$  = 17.7 Hz, 1H, H-3a), 2.70 (d,  $J$  = 17.7 Hz, 1H, H-3b), 1.82 (d,  $J$  = 11.5 Hz, 1H, H-6a), 1.68 (td,  $J$  = 13.2, 4.9 Hz, 1H, H-6b), 1.45 (q,  $J$  = 7.5 Hz, 2H, H-17), 1.43-1.36 (m, 2H, H-7), 1.00 (t,  $J$  = 7.6 Hz, 3H, H-18).

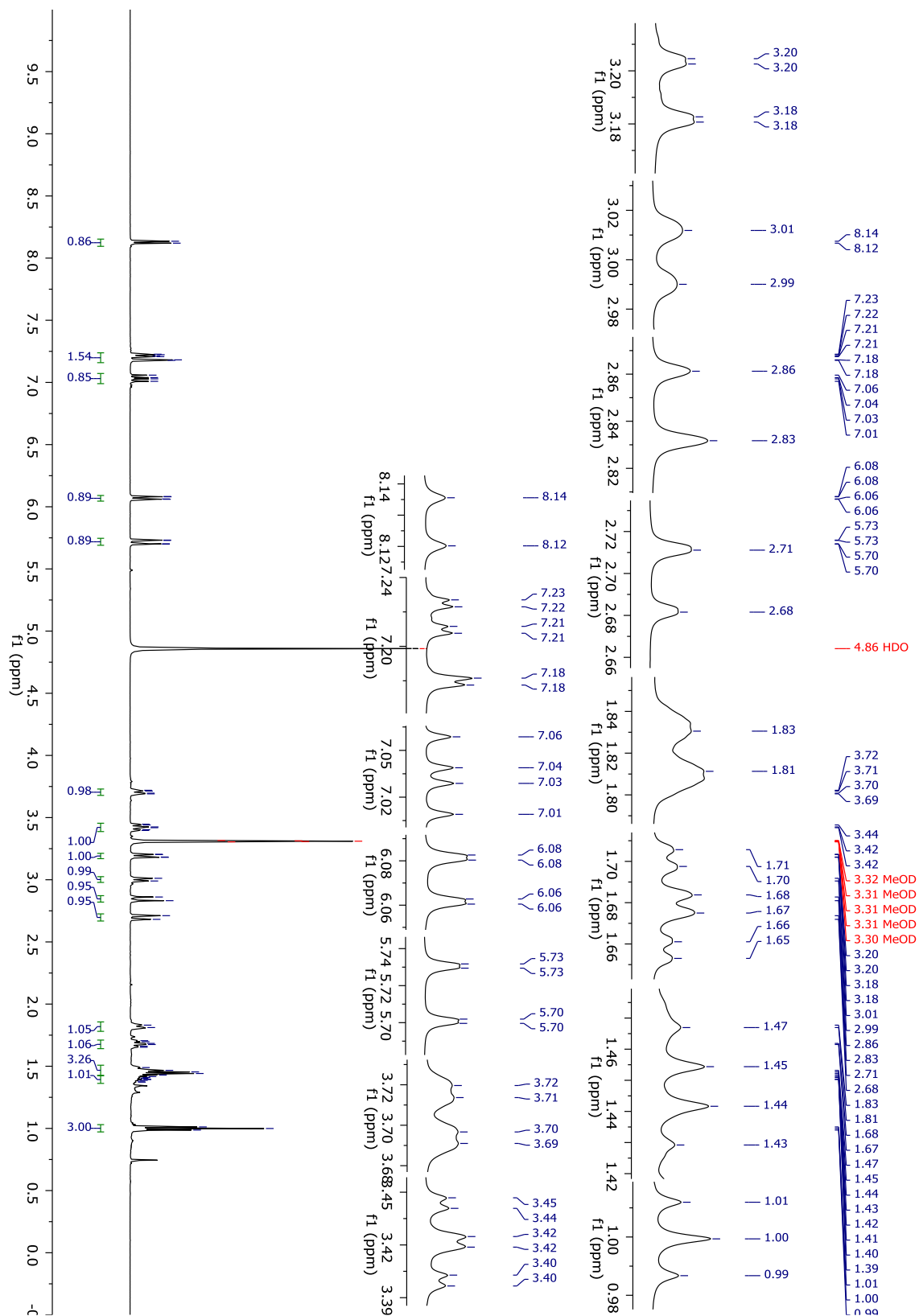
**$^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{OD}$ ):**  $\delta$  (ppm) = 162.7 (C-1), 160.2 (C-12), 152.0 (C-9), 143.7 (C-16), 132.0 (C-19), 129.1 (C-14), 125.9 (C-20), 123.3 (C-2), 120.4 (C-13), 119.9 (C-15), 104.7 (C-10), 57.9 (C-5), 57.8 (C-8), 36.9 (C-3), 36.3 (C-6), 35.6 (C-17), 32.4 (C-4), 20.9 (C-7), 7.3 (C-18).

**IR (solution in  $\text{CH}_2\text{Cl}_2$ , thin film, KBr):**  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 3413 (br, OH), 3267 (br, OH), 3064, 2931 (-C-H), 2853 (-C-H), 1627, 1578, 1453, 1368, 1251, 1234, 1166.

**HRMS (TOF, ES $^+$ ):** calculated for  $\text{C}_{19}\text{H}_{23}\text{N}_2\text{O}$   $[\text{M}+\text{H}]^+$  295.18049, **found** 295.18018.

$[\alpha]_{\text{D}}^{25}$  = +72.16 ( $c$  = 0.53, MeOH).





**Figure S.23.**  $^1\text{H}$  NMR spectrum of (+)-eucophylline in  $\text{CD}_3\text{OD}$ , 600 MHz.

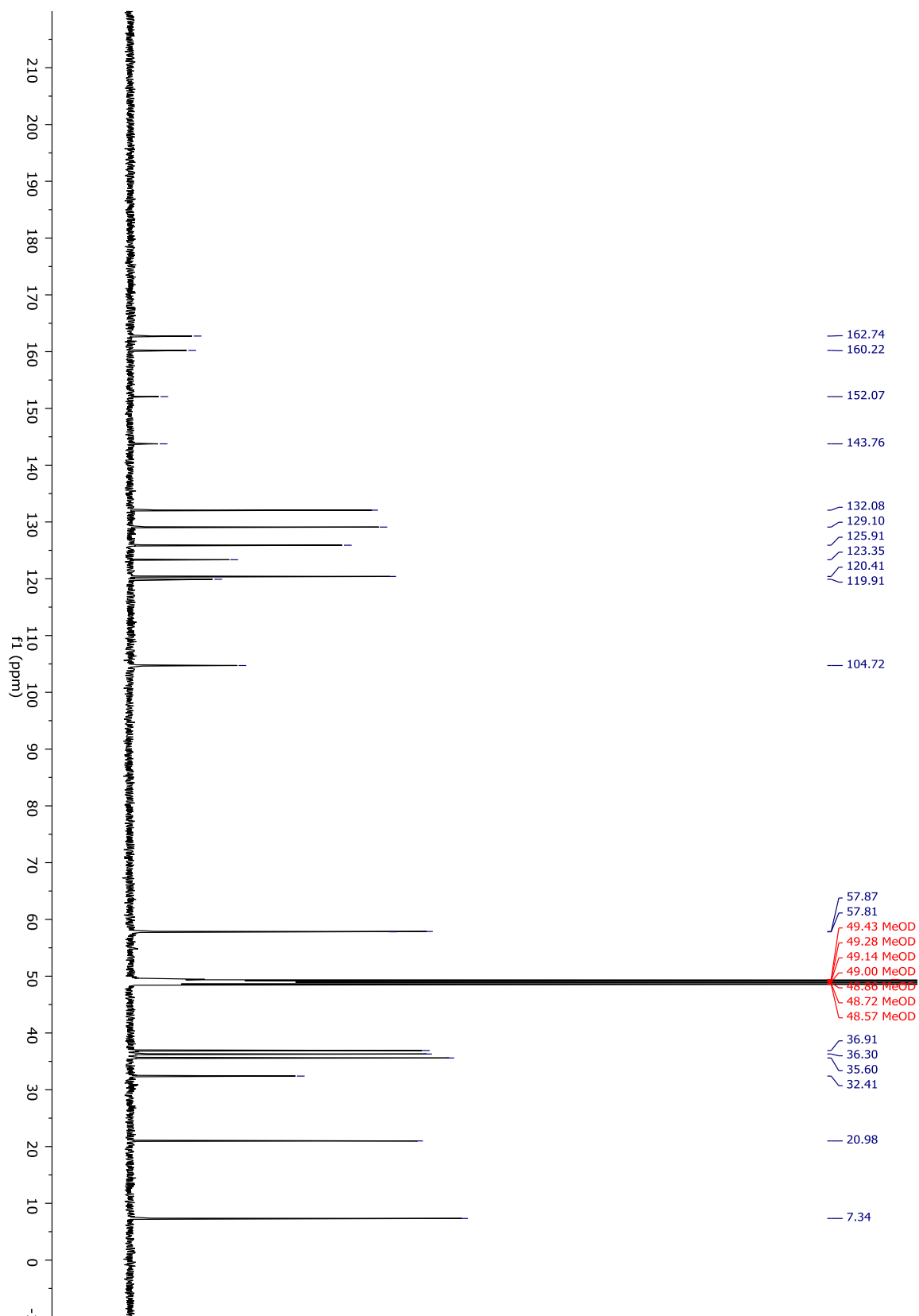
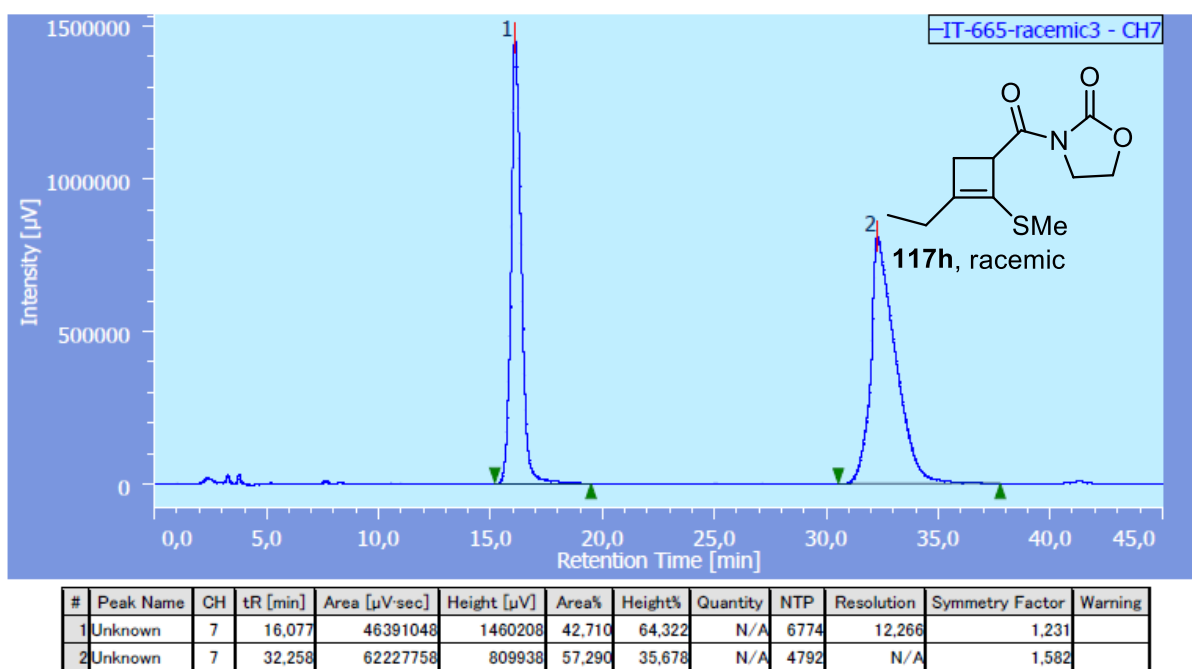
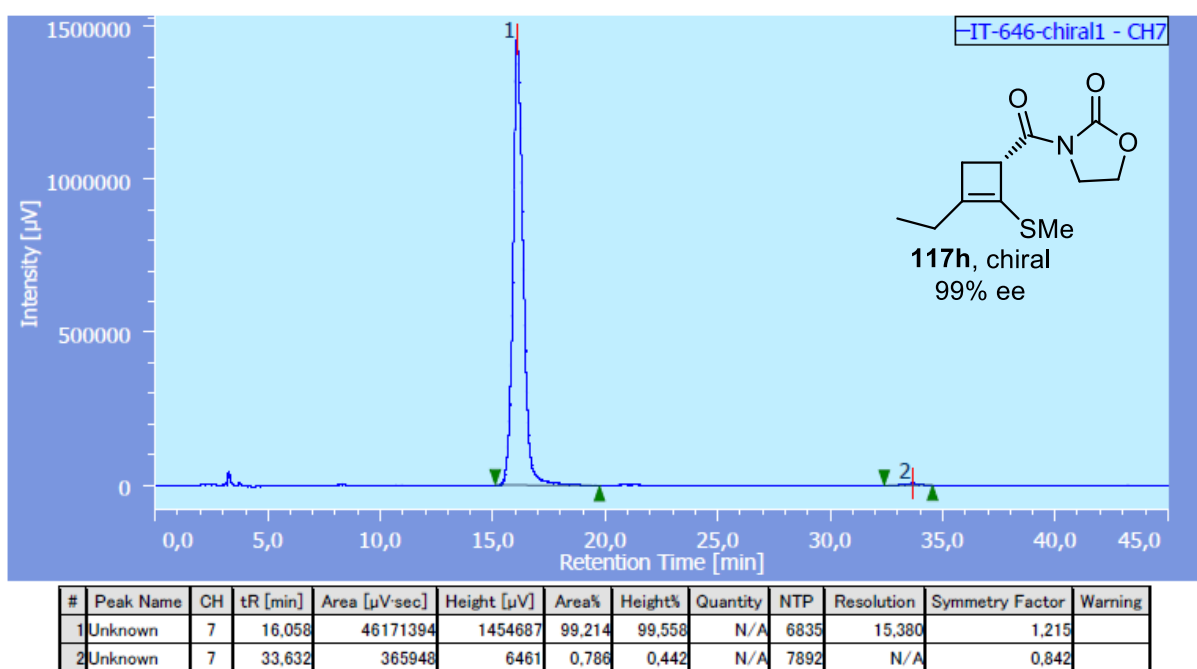


Figure S.24. <sup>13</sup>C NMR spectrum of (+)-eucophylline in CD<sub>3</sub>OD, 600 MHz.

## 6. Enantiomeric excess measurements

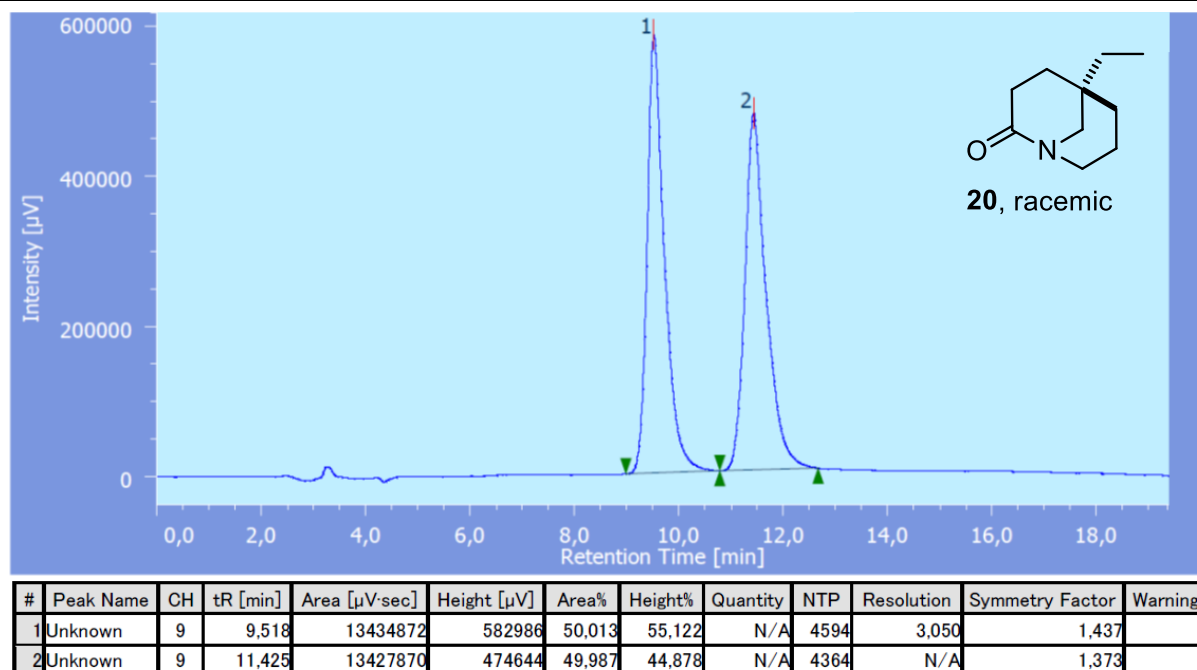


**Figure S.25.** HPLC trace of racemic compound **117h**, synthesized according to the general procedure (D) – method B in chapter III. Analytical Chiralpak® IA column (4.6 mmΦ x 250 mmL, particle size 5 μm), *n*-hexane/ethanol: 90/10, 1 mL/min, 20 °C.

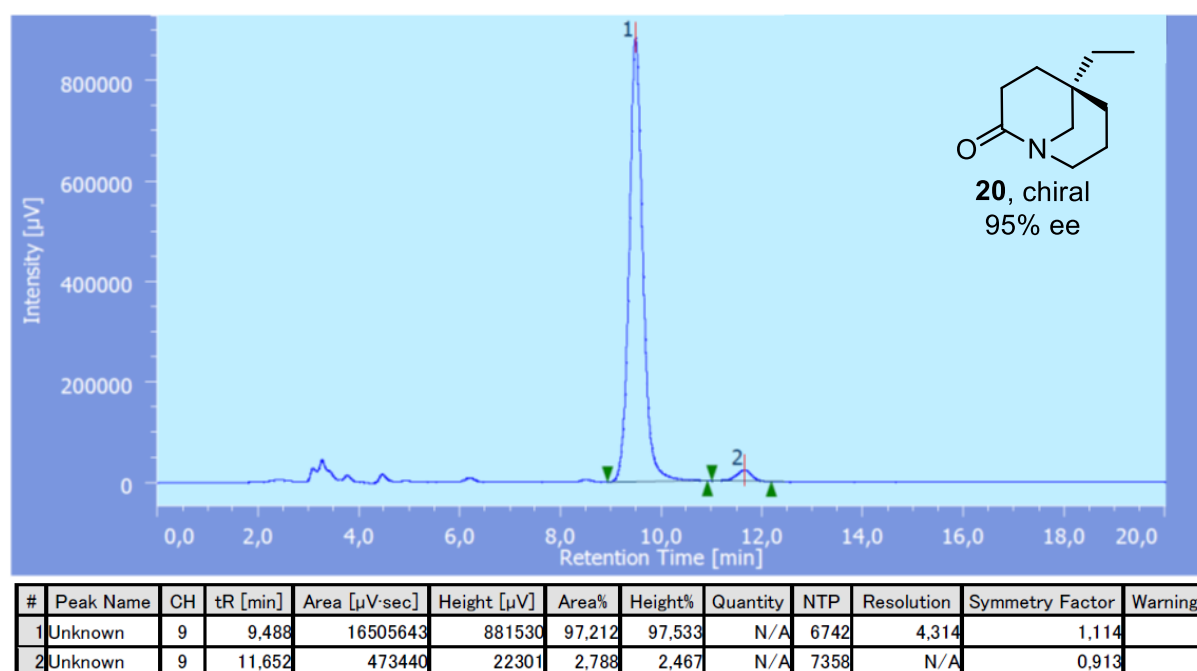


**Figure S.26.** HPLC trace of chiral compound **117h**. Analytical Chiralpak® IA column (4.6 mmΦ x 250 mmL, particle size 5 μm), *n*-hexane/ethanol: 90/10, 1 mL/min, 20 °C.

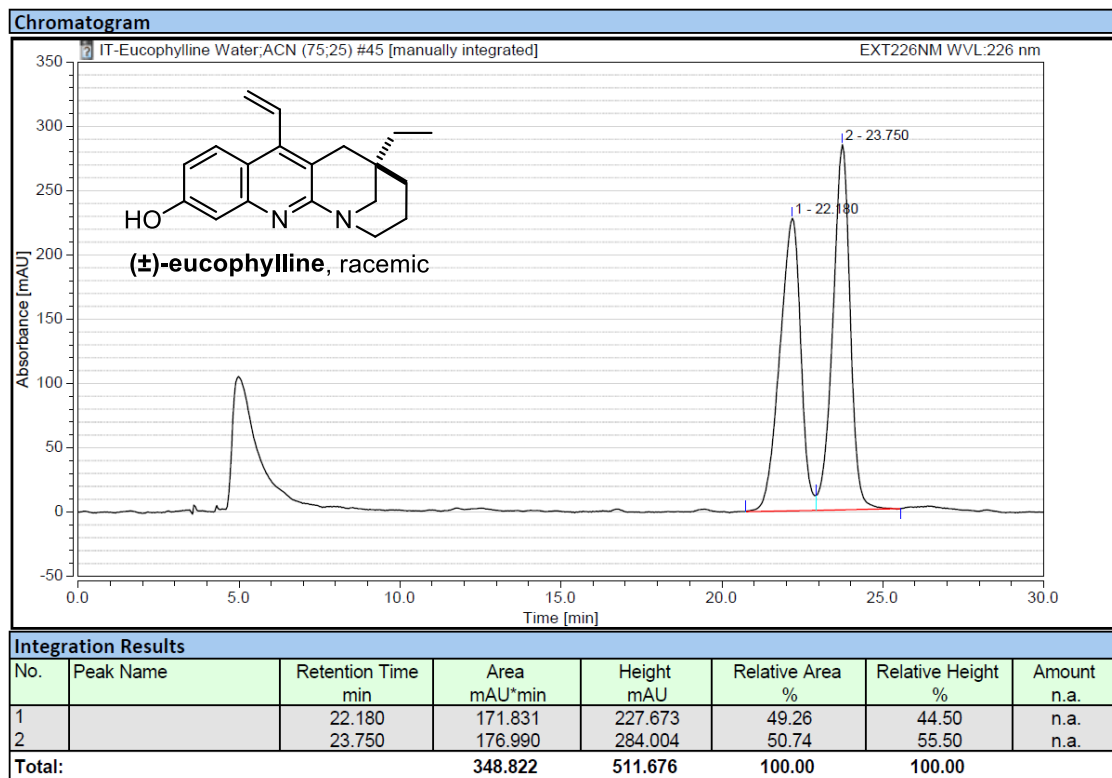




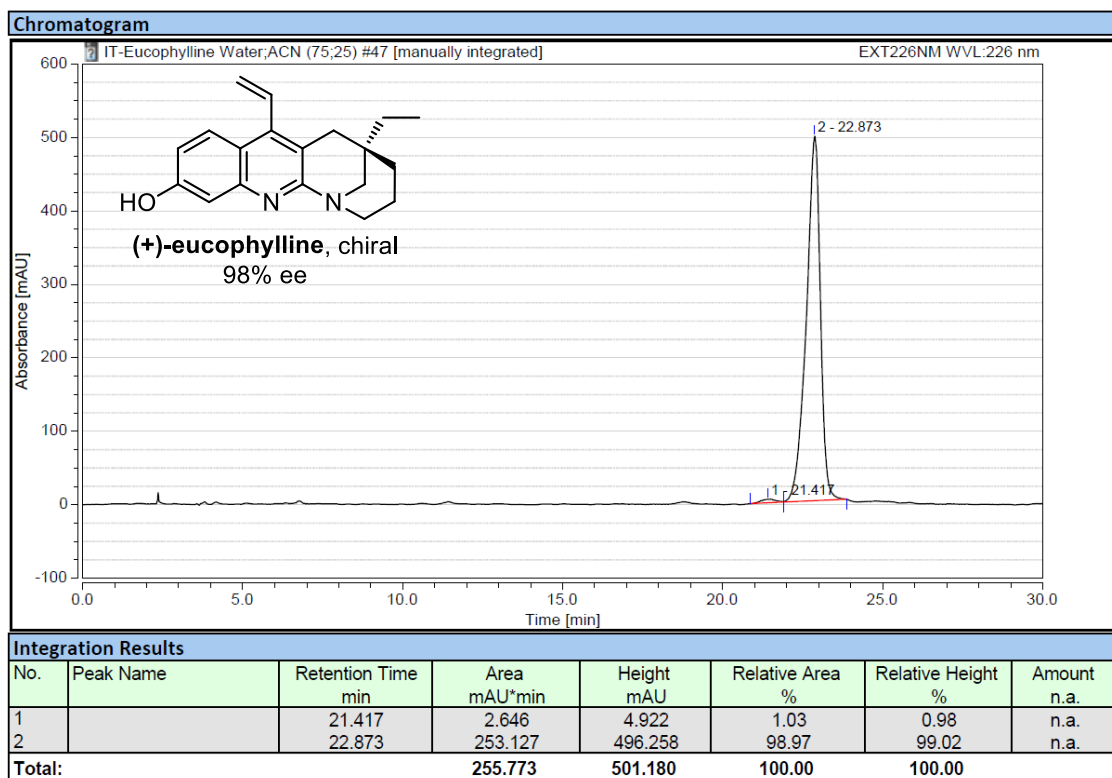
**Figure S.27.** HPLC trace of racemic compound **20**.<sup>48</sup> Analytical Chiralpak® IA column (4.6 mmΦ x 250 mmL, particle size 5 μm), *n*-hexane/ethanol: 90/10, 1 mL/min, 20 °C.



**Figure S.28.** HPLC trace of chiral compound **20**. Analytical Chiralpak® IA column (4.6 mmΦ x 250 mmL, particle size 5 μm), *n*-hexane/ethanol: 90/10, 1 mL/min, 20 °C.



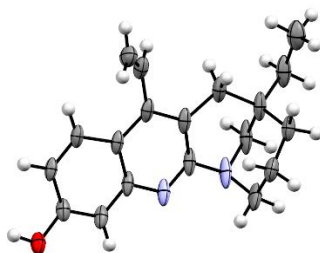
**Figure S.29.** HPLC trace of racemic **eucophylline**.<sup>48</sup> Analytical Phenomenex® column (Lux 5  $\mu$ m Cellulose-3, 4.6 mm $\Phi$  x 250 mmL), pure H<sub>2</sub>O/CH<sub>3</sub>CN: 75/25, 1 mL/min, 20 °C.



**Figure S.30.** HPLC trace of chiral (+)-**eucophylline**. Analytical Phenomenex® column (Lux 5  $\mu$ m Cellulose-3, 4.6 mm $\Phi$  x 250 mmL), pure H<sub>2</sub>O/CH<sub>3</sub>CN: 75/25, 1 mL/min, 20 °C.

## 7. Crystallographic data

**(5*R*)-5-ethyl-7-vinyl-3,4,5,6-tetrahydro-2*H*-1,5-methanoazocino[2,3-*b*]quinolin-10-ol**  
**((+)-Eucophylline), 8**



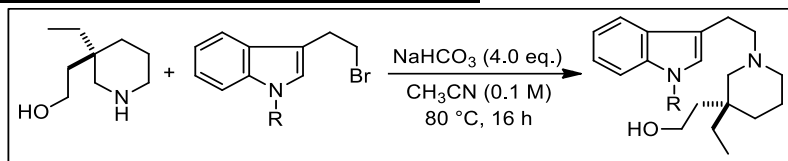
Crystal data and structure refinement for it924 crystallized with a water molecule (omitted for clarity).

Empirical Formula	C <sub>19</sub> H <sub>24</sub> N <sub>2</sub> O <sub>2</sub>
Formula Weight	312.40
Temperature	150(2) K
Wavelength	1.54184 Å
Crystal system, space group	Trigonal, P 3 <sub>2</sub> 2 1
Unit cell dimensions	a = 10.18330(10) Å    α = 90°
	b = 10.18330(10) Å    β = 90°
	c = 27.7910(4) Å    γ = 120°
Volume	2495.81(6) Å <sup>3</sup>
Z, Calculated density	6, 1.247 Mg/m <sup>3</sup>
Absorption coefficient	0.644 mm <sup>-1</sup>
F(000)	1008
Crystal size	0.100 x 0.080 x 0.060 mm
Theta range for data collection	5.015 to 66.713°
Limiting indices	-12 ≤ h ≤ 12, -12 ≤ k ≤ 12, -32 ≤ l ≤ 21
Reflections collected / unique	63512 / 2920 [R(int) = 0.0631]
Completeness to theta = 66.713	99.3 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7527 and 0.6735
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Data / restraints / parameters	2920 / 6 / 220
Goodness-of-fit on F <sup>2</sup>	1.019
Final R indices [I > 2σ(I)]	R <sub>I</sub> = 0.0517, wR <sub>2</sub> = 0.1223
R indices (all data)	R <sub>I</sub> = 0.0589, wR <sub>2</sub> = 0.1283
Absolute structure parameter	0.07(10)
Extinction coefficient	0.0037(6)
Largest diff. peak and hole	0.182 and -0.226 e.Å <sup>-3</sup>

## Experimental Part – Chapter V

### 1. General procedures for chapter V

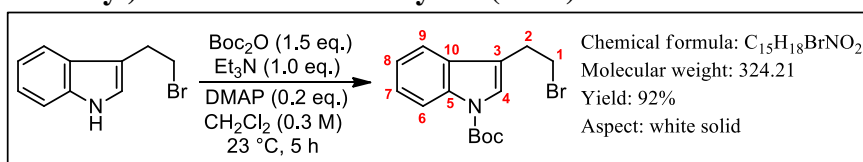
#### General procedure (A) for indole alkylation reaction



To a flame-dried two-necked flask equipped with a condenser and under inert atmosphere, the amino alcohol **501** (1.0 eq.) was introduced followed by tryptophyl bromide (1.2 eq.),  $\text{NaHCO}_3$  (4.0 eq.) and distilled  $\text{CH}_3\text{CN}$  (0.1 M). The reaction mixture was vigorously stirred at 80 °C. After 16 h, the reaction was cooled to 20 °C, then extracted with  $\text{H}_2\text{O}/\text{EtOAc}$ . The organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The crude mixture was purified through short column chromatography on  $\text{SiO}_2$  ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ : 95/5 to 90/10) to afford the pure desired product.

### 2. Synthesis of the starting materials

#### *tert*-butyl 3-(2-bromoethyl)-1*H*-indole-1-carboxylate (**371b**)<sup>474</sup>



To a flame-dried two-necked flask under inert atmosphere, 3-(2-bromoethyl)indole (500.0 mg, 2.23 mmol, 1.0 eq.) was introduced, followed by di-*tert*-butyl dicarbonate (730.0 mg, 3.34 mmol, 1.5 eq.), DMAP (54.0 mg, 0.44 mmol, 0.2 eq.) and dry  $\text{CH}_2\text{Cl}_2$  (7.4 mL, 0.3 M).  $\text{Et}_3\text{N}$  (0.31 mL, 2.23 mmol, 1.0 eq.) was added at 23 °C and the reaction mixture was stirred for 5 h. The reaction was then quenched with water and extracted with  $\text{CH}_2\text{Cl}_2$ . The organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The crude mixture was purified through short column chromatography on  $\text{SiO}_2$  (cyclohexane/ $\text{EtOAc}$ : 80/20) to afford the desired product (668.0 mg, 92%) as a white solid.

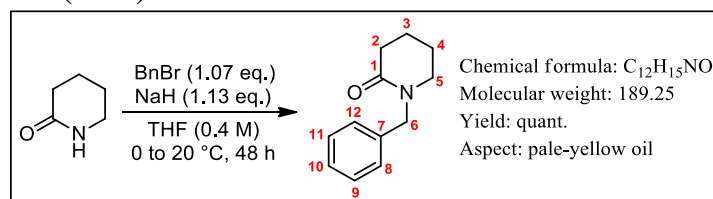
**TLC (cyclohexane/ $\text{EtOAc}$ : 80/20):**  $R_f$  = 0.64 (UV active;  $\text{KMnO}_4$ , stains yellow).

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 8.14 (d,  $J$  = 8.2 Hz, 1H, H-9), 7.52 (ddd,  $J$  = 7.6, 1.5, 0.7 Hz, 1H, H-6), 7.48 (s, 1H, H-4), 7.37-7.22 (m, 2H, H-7, H-8), 3.64 (t,  $J$  = 7.5 Hz, 2H, H-1), 3.31-3.23 (m, 2H, H-2), 1.67 (s, 9H, H-*t*-butyl).

The  $^1\text{H}$  NMR data are in agreement with those reported in the literature.<sup>474</sup>

### 3. Total synthesis of (±)-eburnamine

#### 1-benzylpiperidin-2-one (**369a**)<sup>444</sup>



To a flame-dried two-necked flask under inert atmosphere, dry THF (44.0 mL, 1.0 M) was introduced followed by NaH (60% dispersion in mineral oil, 1.98 g, 49.7 mmol, 1.13 eq.) at 0 °C (ice/water bath). 2-Piperidinone (4.38 g, 44.0 mmol, 1.0 eq.) dissolved in THF (66.6 mL, 0.66 M) was added rapidly dropwise and the reaction mixture was warmed up slowly to 20 °C. After 15 min, a thick white gel was formed, the mixture was stirred further for 2 h then BnBr (~ 5.6 mL, 47.08 mmol, 1.07

eq.) was added dropwise and the reaction evolution was monitored by TLC. After 48 h, the mixture was quenched with sat.  $\text{NH}_4\text{Cl}$  and extracted with  $\text{Et}_2\text{O}$ . The organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The crude mixture was purified through short column chromatography on  $\text{SiO}_2$  (cyclohexane/ $\text{EtOAc}$ : 80/20 to 50/50) to afford the desired product (8.34 g, quant.) as a pale-yellow oil.

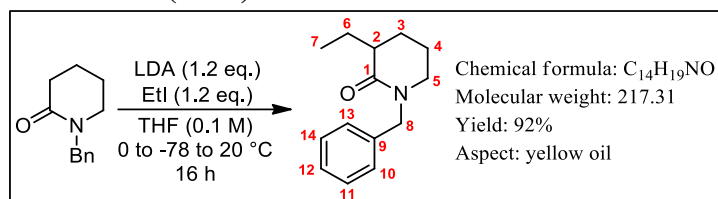
**TLC (cyclohexane/ $\text{EtOAc}$ : 50/50):**  $R_f$  = 0.16 (UV active;  $\text{KMnO}_4$ , stains white).

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 7.38-7.20 (m, 5H, H-Ph), 4.60 (s, 2H, H-6), 3.24-3.13 (m, 2H, H-5), 2.51-2.40 (m, 2H, H-2), 1.90-1.68 (m, 4H, H-3, H-4).

**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 170.0 (C-1), 137.4 (C-7), 128.6 (C-9, C-11), 128.2 (C-8, C-12), 127.4 (C-10), 50.2 (C-6), 47.4 (C-5), 32.6 (C-2), 23.3 (C-4), 21.5 (C-3).

The NMR data are in agreement with those reported in the literature.<sup>444</sup>

### 1-benzyl-3-ethylpiperidin-2-one (505a)<sup>444</sup>



The compound **505a** was prepared adapting the literature procedure.<sup>444</sup> To a flame-dried flask under inert atmosphere, freshly distilled diisopropylamine (0.23 mL, 1.65 mmol, 1.1 eq.) was added, followed by dry THF (3.0 mL, 0.5 M) and the solution was cooled to 0 °C (ice/water bath). *n*-BuLi (1.9 M in hexane, 0.8 mL, 1.5 mmol, 1.0 eq.) was added rapidly dropwise and the faint yellow solution was stirred at the same temperature for 20 min. Meanwhile, in another flame-dried flask, the protected lactam **369a** (100.0 mg, 0.52 mmol, 1.0 eq.) was dissolved in dry THF (5.2 mL, 0.1 M) and the solution was cooled to 0 °C. The freshly prepared LDA (0.5 M, 1.24 mL, 0.62 mmol, 1.2 eq.) was then added rapidly dropwise to the lactam solution at 0 °C and the reaction mixture was stirred for 45 min. The mixture was then cooled to -78 °C (dry ice/acetone bath) and iodoethane (0.05 mL, 0.624 mmol, 1.2 eq.) was added dropwise. After 5 min, the yellow solution was placed in an ice/water bath and the temperature was warmed slowly to 20 °C. After 16 h, the reaction was quenched with  $\text{NH}_4\text{Cl}$  and extracted with  $\text{Et}_2\text{O}$ . The organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The crude mixture was purified through short column chromatography on  $\text{SiO}_2$  (cyclohexane/ $\text{EtOAc}$ : 80/20 to 70/30) to afford the desired product (103.0 mg, 92%) as a yellow oil. The product was stored under argon in the freezer.

#### Scale-up reaction:

Following the same procedure above, from diisopropylamine (4.7 mL, 33.4 mmol, 1.1 eq.), dry THF (19.0 mL, 1.6 M), *n*-BuLi (1.8 M in hexane, 16.9 mL, 30.4 mmol, 1.0 eq.), the protected lactam **369a** (4.5 g, 23.77 mmol, 1.0 eq.) in dry THF (225.0 mL, 0.1 M) and iodoethane (2.3 mL, 28.5 mmol, 1.2 eq.) for 16 h, to afford the desired product (3.6 g, 70%, quant. brsm).

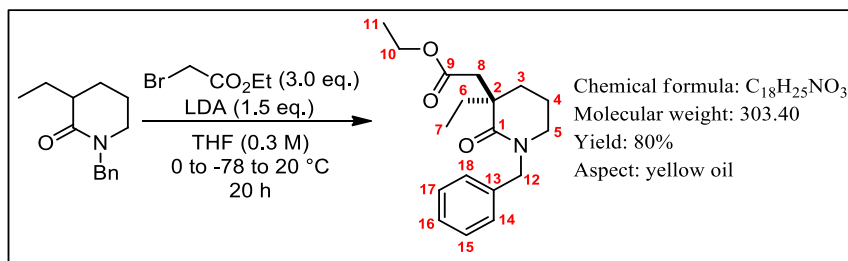
**TLC (cyclohexane/ $\text{EtOAc}$ : 50/50):**  $R_f$  = 0.50 (UV active;  $\text{KMnO}_4$ , stains white).

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 7.37-7.19 (m, 5H, H-Ph), 4.59 (s, 2H, H-8), 3.19 (dd,  $J$  = 7.1, 4.9 Hz, 2H, H-5), 2.31 (tdd,  $J$  = 9.1, 5.8, 4.2 Hz, 1H, H-2), 2.09-1.78 (m, 3H, H-3a, H-4a, H-6a), 1.77-1.47 (m, 3H, H-3b, H-4b, H-6b), 0.97 (t,  $J$  = 7.4 Hz, 3H, H-7).

**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 172.8 (C-1), 137.7 (C-9), 128.7 (C-11, C-13), 128.1 (C-10, C-14), 127.3 (C-12), 50.4 (C-8), 47.6 (C-5), 43.1 (C-2), 25.9 (C-3), 25.0 (C-6), 21.8 (C-4), 11.6 (C-7).

The NMR data are in agreement with those reported in the literature.<sup>444</sup>

### ethyl 2-(1-benzyl-3-ethyl-2-oxopiperidin-3-yl)acetate (504a)



To a flame-dried flask under inert atmosphere, freshly distilled diisopropylamine (2.8 mL, 19.8 mmol, 1.1 eq.) was added, followed by dry THF (18.0 mL, 1.0 M) and the solution was cooled to 0 °C (ice/water bath). *n*-BuLi (1.8 M in hexane, 10.0 mL, 18.0 mmol, 1.0 eq.) was added rapidly dropwise and the faint yellow solution was stirred at the same temperature for 20 min. Meanwhile, in another flame-dried flask, the mono-alkylated lactam **505a** (2.3 g, 10.5 mmol, 1.0 eq.) was dissolved in dry THF (35.0 mL, 0.3 M) and the solution was cooled to 0 °C. The freshly prepared LDA (1.0 M in THF, ~ 16.0 mL, 15.75 mmol, 1.5 eq.) was then added rapidly dropwise to the lactam solution at 0 °C and the reaction mixture was stirred for 45 min. The mixture was then cooled to -78 °C (dry ice/acetone bath) and ethyl bromoacetate (3.5 mL, 31.5 mmol, 3.0 eq.) was added dropwise. After 5 min, the yellow solution was placed in an ice/water bath and the temperature was warmed slowly to 20 °C. After 20 h, the reaction was quenched with NH<sub>4</sub>Cl and extracted with Et<sub>2</sub>O. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude mixture was purified through column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc: 90/10 to 80/20) to afford the desired product (2.59 g, 80%) as a yellow oil. The product was stored under argon in the freezer.

**TLC (cyclohexane/EtOAc: 50/50):** R<sub>f</sub> = 0.58 (UV active; KMnO<sub>4</sub>, stains white).

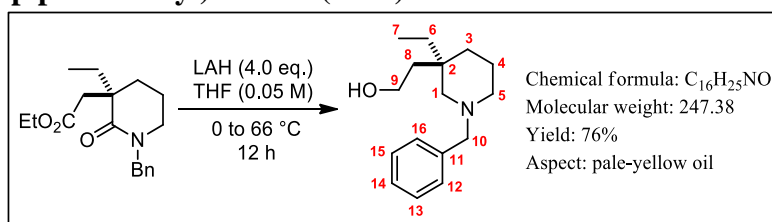
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ (ppm) = 7.34-7.22 (m, 5H, H-Ph), 4.79 (d, *J* = 14.7 Hz, 1H, H-12a), 4.41 (d, *J* = 14.7 Hz, 1H, H-12b), 4.16-4.06 (m, 2H, H-10), 3.35-3.26 (m, 1H, H-5a), 3.21-3.13 (m, 1H, H-5b), 2.99 (d, *J* = 16.1 Hz, 1H, H-8a), 2.35 (d, *J* = 16.1 Hz, 1H, H-8b), 2.09-1.93 (m, 1H, H-6a), 1.90-1.63 (m, 5H, H-3, H-4, H-6b), 1.23 (t, *J* = 7.1 Hz, 3H, H-11), 0.91 (t, *J* = 7.5 Hz, 3H, H-7).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ (ppm) = 174.4 (C-9), 172.2 (C-1), 137.8 (C-13), 128.6 (C-15, C-17), 128.2 (C-14, C-18), 127.3 (C-16), 60.3 (C-10), 50.6 (C-12), 47.6 (C-5), 43.7 (C-2), 42.3 (C-8), 31.7 (C-3), 29.1 (C-6), 19.8 (C-4), 14.3 (C-11), 8.7 (C-7).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):** ν<sub>max</sub> (cm<sup>-1</sup>) = 2965 (-C-H), 2939 (-C-H), 1732 (9-C=O), 1636 (1-C=O), 1454, 1185, 1033, 701.

**HRMS (TOF, ES+):** calculated for C<sub>18</sub>H<sub>25</sub>NO<sub>3</sub>Na [M+Na]<sup>+</sup> 326.17266, found 326.17237.

## 2-(1-benzyl-3-ethylpiperidin-3-yl)ethanol (**503a**)



To a flame-dried two-necked flask equipped with a condenser and under inert atmosphere, the starting material **504a** (1.4 g, 4.6 mmol, 1.0 eq.) was added, followed by dry THF (90.0 mL, 0.05 M) and the solution was cooled to 0 °C (ice/water bath). LAH (1.0 M in Et<sub>2</sub>O, 18.4 mL, 18.4 mmol, 4.0 eq.) was added dropwise and the light-yellow solution was stirred at the same temperature for 5 min, then heated at 66 °C silicon oil bath temperature. The reaction completion was followed by TLC, and after 12 h, the solution became colorless. The reaction was quenched carefully at 0 °C by dropwise addition of EtOAc (5 mL), then water (5 mL). Once no more bubbles were observed, water (10 mL) was added again and the mixture was filtered to remove the white suspension. The crude mixture was extracted after addition of EtOAc (20 mL), then the organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude mixture was purified through column chromatography on SiO<sub>2</sub> (cyclohexane/EtOAc: 90/10 to 80/20 to 60/40) to afford the desired product (866.0 mg, 76%) as a pale-yellow oil. The product was stored under argon in the freezer.



**TLC (cyclohexane/EtOAc: 50/50):**  $R_f$  = 0.19 (UV active;  $\text{KMnO}_4$ , stains white).

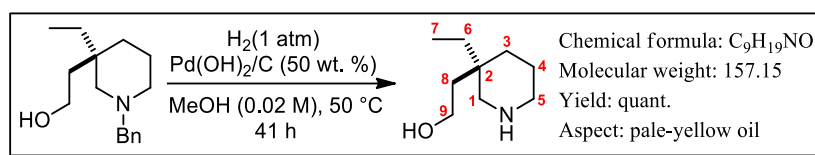
**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 7.38-7.19 (m, 5H, H-Ph), 3.75 (ddd,  $J$  = 11.6, 8.7, 4.0 Hz, 1H, H-9a), 3.69-3.64 (m, 1H, H-9b), 3.64 (d,  $J$  = 12.8 Hz, 1H, H-10a), 3.27 (d,  $J$  = 12.8 Hz, 1H, H-10b), 2.75 (d,  $J$  = 9.1 Hz, 1H, H-5a), 2.67 (d,  $J$  = 11.5 Hz, 1H, H-1a), 1.87 (d,  $J$  = 11.7 Hz, 1H, H-1b), 1.82-1.48 (m, 6H, H-3a, H-4, H-5b, H-8), 1.33-1.12 (m, 3H, H-3b, H-6), 0.81 (t,  $J$  = 7.5 Hz, 3H, H-7).

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 137.4 (C-11), 129.5 (C-13, C-15), 128.4 (C-12, C-16), 127.4 (C-14), 64.2 (C-1), 63.8 (C-10), 59.5 (C-9), 53.2 (C-5), 40.2 (C-8), 36.0 (C-2), 35.2 (C-6), 33.6 (C-3), 22.7 (C-4), 7.6 (C-7).

**IR (solution in  $\text{CH}_2\text{Cl}_2$ , thin film, KBr):**  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 3349 (br, OH), 2932 (C-H), 1453, 1043, 741, 698.

**HRMS (TOF, ES $^+$ ):** calculated for  $\text{C}_{16}\text{H}_{26}\text{NO}$   $[\text{M}+\text{H}]^+$  248.20089, found 248.20065.

## 2-(3-ethylpiperidin-3-yl)ethanol (501)



To a flame-dried flask equipped with a condenser and under inert atmosphere, the starting material **503a** (770.0 mg, 3.1 mmol, 1.0 eq.) dissolved in MeOH (160.0 mL, 0.02 M) was introduced, and the corresponding solution was degassed by argon bubbling for 15 min using a metallic needle, which was passed through the condenser.  $\text{Pd}(\text{OH})_2/\text{C}$  (385.0 mg, 50 wt. %) was added and the solution was then bubbled with  $\text{H}_2$  for 15 min. Then, the  $\text{H}_2$  balloon was replaced with a new one and the reaction mixture was heated at 50 °C under vigorous stirring. After 41 h, the reaction mixture was filtered through a celite pad, and the solvents were concentrated under reduced pressure to afford the desired product (500.0 mg, quant.) as a pale-yellow oil, pure enough to be used in the next step without further purification. The product was stored under argon in the freezer.

**TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ : 90/10):**  $R_f$  = 0 (UV inactive;  $\text{KMnO}_4$ , stains yellow-white).

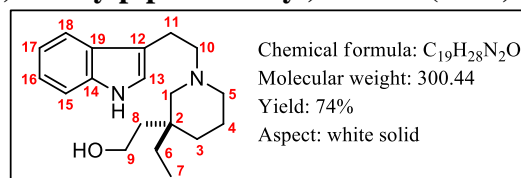
**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 4.07 (br s, 1H, NH), 3.80-3.54 (m, 2H, H-9), 2.98 (dt,  $J$  = 11.4, 4.3 Hz, 1H, H-5a), 2.83 (d,  $J$  = 11.9 Hz, 1H, H-1a), 2.54 (td,  $J$  = 11.2, 3.2 Hz, 1H, H-5b), 2.37 (d,  $J$  = 11.9 Hz, 1H, H-1b), 1.81-1.64 (m, 2H, H-4a, H-8a), 1.60-1.46 (m, 3H, H-3a, H-4b, H-8b), 1.29-1.19 (m, 3H, H-3b, H-6), 0.79 (t,  $J$  = 7.5 Hz, 3H, H-7).

**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 59.1 (C-9), 55.6 (C-1), 46.6 (C-5), 39.3 (C-8), 35.2 (C-2), 34.1 (C-3), 33.9 (C-6), 22.7 (C-4), 7.5 (C-7).

**IR (solution in  $\text{CH}_2\text{Cl}_2$ , thin film, KBr):**  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 3311 (br, OH), 2931 (C-H), 2855 (C-H), 1466, 1422, 1279, 1048.

**HRMS (TOF, ES $^+$ ):** calculated for  $\text{C}_9\text{H}_{20}\text{NO}$   $[\text{M}+\text{H}]^+$  158.15394, found 158.15388.

## 2-(1-(2-(1H-indol-3-yl)ethyl)-3-ethylpiperidin-3-yl)ethanol (500a)



According to the general procedure (A), from **501** (127.0 mg, 0.8 mmol, 1.0 eq.), **371a** (217.0 mg, 0.97 mmol, 1.2 eq.),  $\text{NaHCO}_3$  (267.0 mg, 3.2 mmol, 4.0 eq.) and  $\text{CH}_3\text{CN}$  (8.0 mL, 0.1 M) to afford the desired product (179.0 mg, 74%) as a white solid.

**TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ : 90/10):**  $R_f$  = 0.14 (UV active;  $\text{KMnO}_4$ , stains white; vanillin, stains purple).

**m. p.** = 122.4-124.5 °C ( $\text{CH}_2\text{Cl}_2$ ).

**$^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):**  $\delta$  (ppm) = 7.56 (d,  $J$  = 7.7 Hz, 1H, H-18), 7.35 (d,  $J$  = 8.0 Hz, 1H, H-15), 7.13-7.08 (m, 2H, H-13, H-16), 7.06-6.98 (m, 1H, H-17), 3.67 (td,  $J$  = 7.0, 1.9 Hz, 2H, H-9), 3.03 (dd,  $J$  = 9.9, 6.3 Hz, 2H, H-11), 2.83-2.78 (m, 3H, H-10, H-5a), 2.66 (d,  $J$  = 11.5 Hz, 1H, H-1a),

2.53 (br s, 1H, H-5b), 2.38 (d,  $J = 12.0$  Hz, 1H, H-1b), 1.75-1.57 (m, 4H, H-4, H-8), 1.51-1.31 (m, 4H, H-3, H-6), 0.88 (t,  $J = 7.5$  Hz, 3H, H-7).

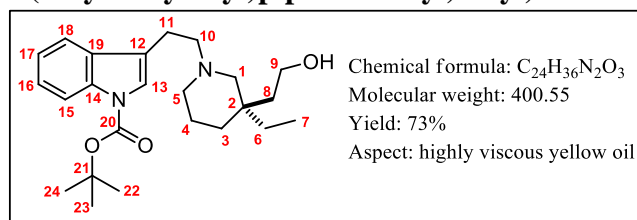
**$^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ ):**  $\delta$  (ppm) = 138.1 (C-14), 128.6 (C-19), 123.2 (C-13), 122.3 (C-16), 119.6 (C-17), 119.2 (C-18), 113.2 (C-12), 112.2 (C-15), 63.7 (C-1), 60.8 (C-10), 59.0 (C-9), 55.5 (C-5), 38.9 (C-8), 36.5 (C-2), 34.3 (C-3), 23.1 (C-11), 22.6 (C-4), 7.7 (C-7).

*Note: C-6 was not seen, in HSQC the H-6 correlates with 29.9 ppm in  $^{13}\text{C}$  NMR, however, no peak is observed in this place (baseline).*

**IR (solution in  $\text{CH}_2\text{Cl}_2$ , thin film, KBr):**  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 3262 (br, OH), 2925 (-C-H), 2853 (-C-H), 1457, 740.

**HRMS (TOF, ES $^{+}$ ):** calculated for  $\text{C}_{19}\text{H}_{29}\text{N}_2\text{O}$   $[\text{M}+\text{H}]^{+}$  301.22854, found 301.22711.

***tert*-butyl 3-(2-(3-ethyl-3-(2-hydroxyethyl)piperidin-1-yl)ethyl)-1*H*-indole-1-carboxylate (500b)**



According to the general procedure (A), from **501** (141.0 mg, 0.89 mmol, 1.0 eq.), Boc-protected tryptophyl bromide **371b** (381.0 mg, 1.17 mmol, 1.2 eq.),  $\text{NaHCO}_3$  (299.0 mg, 3.56 mmol, 4.0 eq.) and  $\text{CH}_3\text{CN}$  (9.0 mL, 0.1 M) to afford the desired product (260.0 mg, 73%) as a highly viscous yellow oil. 100.0 mg of Boc-protected tryptophyl bromide **371b** were recovered.

**TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ : 90/10):**  $R_f = 0.42$  (UV active;  $\text{KMnO}_4$ , stains white; vanillin, stains purple).

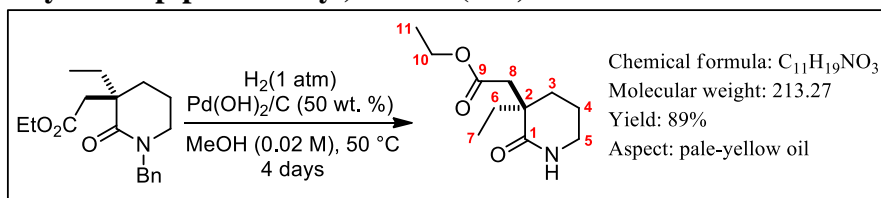
**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 8.11 (d,  $J = 8.1$  Hz, 1H, H-18), 7.54-7.51 (m, 1H, H-15), 7.40 (s, 1H, H-13), 7.30 (td,  $J = 7.4, 1.2$  Hz, 1H, H-17), 7.22 (td,  $J = 7.4, 1.2$  Hz, 1H, H-16), 3.80 (ddd,  $J = 12.3, 8.6, 3.9$  Hz, 1H, H-9a), 3.69 (dt,  $J = 11.6, 5.3$  Hz, 1H, H-9b), 3.03-2.90 (m, 3H, H-5a, H-11), 2.81-2.65 (m, 3H, H-1a, H-10), 2.09-1.74 (m, 4H, H-1b, H-4a, H-5b, H-8a), 1.65 (s, 9H, H-*t*-butyl), 1.62-1.52 (m, 3H, H-3a, H-4b, H-8b), 1.36-1.14 (m, 4H, H-3b, H-6), 0.83 (t,  $J = 7.5$  Hz, 3H, H-7).

**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  (ppm) = 149.8 (C-20), 135.5 (C-14), 130.5 (C-19), 124.4 (C-17), 122.8 (C-13), 122.5 (C-16), 119.0 (C-15), 118.5 (C-12), 115.3 (C-18), 83.5 (C-21), 63.7 (C-1), 59.4 (C-9), 58.5 (C-10), 53.9 (C-5), 39.9 (C-8), 36.1 (C-2), 34.9 (C-6), 33.5 (C-3), 28.3 (C-22, C-23, C-24), 22.7 (C-4), 22.2 (C-11), 7.6 (C-7).

**IR (solution in  $\text{CH}_2\text{Cl}_2$ , thin film, KBr):**  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 3395 (br, OH), 2933 (-C-H), 1730 (20-C=O), 1453, 1373, 1256, 1158, 1086, 746.

**HRMS (TOF, ES $^{+}$ ):** calculated for  $\text{C}_{24}\text{H}_{37}\text{N}_2\text{O}_3$   $[\text{M}+\text{H}]^{+}$  401.27987, found 401.27978.

**(*R*)-ethyl 2-(3-ethyl-2-oxopiperidin-3-yl)acetate (516)**



To a flame-dried flask equipped with a condenser and under inert atmosphere, the starting material **504a** (500.0 mg, 1.6 mmol, 1.0 eq.) dissolved in MeOH (80.0 mL, 0.02 M) was introduced, and the corresponding solution was degassed by argon bubbling for 15 min using a metallic needle, which was passed through the condenser.  $\text{Pd}(\text{OH})_2/\text{C}$  (250.0 mg, 50 wt. %) was added and the solution was then bubbled with  $\text{H}_2$  for 15 min. Then, the  $\text{H}_2$  balloon was replaced with a new one and the reaction mixture was heated at 50 °C under vigorous stirring. After 4 days, the reaction mixture was filtered through a celite pad, and the solvents were concentrated under reduced pressure to afford the desired product (300.0 mg, 89%) as a pale-yellow oil, pure enough to be used in the next step without further purification. The product was stored under argon in the freezer.

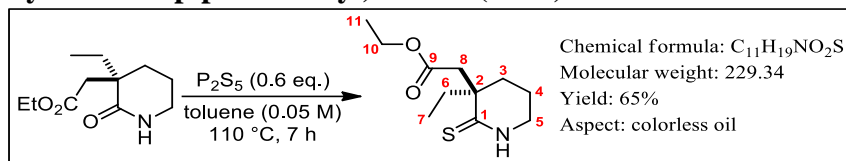
**TLC (cyclohexane/EtOAc: 50/50):**  $R_f = 0.17$  (UV inactive;  $\text{KMnO}_4$ , stains white).



**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2924 (-C-H), 2853 (-C-H), 1734 (9-C=O), 1657 (1-C=O), 1466, 1403, 1180, 1042, 645.

**HRMS (TOF, ES+):** calculated for C<sub>11</sub>H<sub>19</sub>NO<sub>3</sub>Na [M+Na]<sup>+</sup> 236.12571, **found** 236.12574.

**(R)-ethyl 2-(3-ethyl-2-thioxopiperidin-3-yl)acetate (518b)**



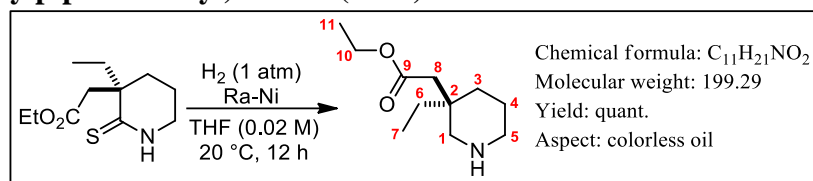
To a flame-dried two-necked flask equipped with a condenser and under inert atmosphere, the starting material **516** (100.0 mg, 0.43 mmol, 1.0 eq.) was added, followed by dry toluene (8.6 mL, 0.05 M) then crystallized P<sub>2</sub>S<sub>5</sub> (58.0 mg, 0.25 mmol, 0.6 eq.). The yellow mixture was heated at 110 °C for 7 h then cooled to 20 °C and the solvents were rapidly concentrated under reduced pressure. The crude mixture was quickly purified through column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 100/0 to 90/10) to afford the desired product (65.0 mg, 65%) as a colorless oil. The product is unstable and it was used directly in the next step.

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc: 50/50):** R<sub>f</sub> = 0.72 (UV inactive; KMnO<sub>4</sub>, stains brown).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2924 (-C-H), 2853 (-C-H), 1731 (9-C=O), 1563, 1462, 1357, 1183.

**HRMS (TOF, ES+):** calculated for C<sub>11</sub>H<sub>19</sub>NO<sub>2</sub>SNa [M+Na]<sup>+</sup> 252.10287, **found** 252.10293.

**(R)-ethyl 2-(3-ethylpiperidin-3-yl)acetate (517a)**



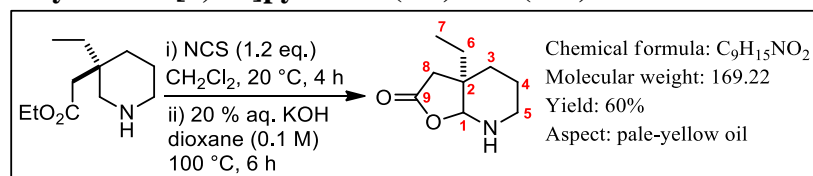
In a flame-dried flask and under inert atmosphere, Raney<sup>®</sup>-nickel (pinch, excess) was washed with THF (5 x). The starting material **518b** (65.0 mg, 0.28 mmol, 1.0 eq.) dissolved in THF (14.0 mL, 0.02 M) was degassed by argon bubbling for 15 min then introduced to the reaction flask. The corresponding mixture was then bubbled with H<sub>2</sub> for 15 min. The H<sub>2</sub> balloon was replaced with a new one and the reaction mixture was left under vigorous stirring at 20 °C for 12 h. The reaction mixture was filtered through a celite pad, and the solvents were concentrated under reduced pressure to afford the desired product (57.0 mg, quant.) as a colorless oil, and used directly in the next step without further purification.

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 90/10):** R<sub>f</sub> = 0 (UV inactive; KMnO<sub>4</sub>, stains white).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2923 (-C-H), 2853 (-C-H), 1732 (9-C=O), 1467, 1258, 1044, 762.

**HRMS (TOF, ES+):** calculated for C<sub>11</sub>H<sub>22</sub>NO<sub>2</sub> [M+H]<sup>+</sup> 200.16451, **found** 200.16447.

**(3aR)-3a-ethylhexahydrofuro[2,3-b]pyridin-2(3H)-one (470)**



To a flame-dried flask under inert atmosphere, the starting material **517a** (105.0 mg, 0.53 mmol, 1.0 eq.) was introduced followed by dry CH<sub>2</sub>Cl<sub>2</sub> (4.0 mL, 0.13 M) and the solution was cooled to 0 °C (ice/water bath). NCS (79.0 mg, 0.59 mmol, 1.1 eq.) was then added and the mixture was stirred at 20 °C for 4 h. The reaction was quenched with sat. NaHCO<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude mixture was then dissolved in 1,4-dioxane (3.5 mL) and 20% aq. KOH (2.5 mL) was added and the reaction mixture was heated at 100 °C for 6 h. The solvents were concentrated under reduced pressure

and the pH was adjusted to 8 at 0 °C using conc. HCl then sat. NaHCO<sub>3</sub> and extracted with EtOAc. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford the desired product (55.0 mg, 60%) as a pale-yellow oil, and used directly in the next step without further purification.

**TLC (EtOAc: 100%):**  $R_f$  = 0.14 (UV inactive; KMnO<sub>4</sub>, stains yellow).

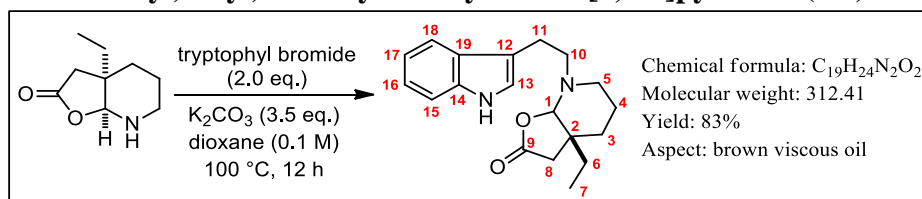
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 5.11 (s, 1H, H-1), 2.98 (td,  $J$  = 11.3, 2.8 Hz, 1H, H-5a), 2.83-2.75 (m, 1H, H-5b), 2.41 (d,  $J$  = 16.5 Hz, 1H, H-8a), 2.20 (d,  $J$  = 16.6 Hz, 1H, H-8b), 1.85-1.35 (m, 6H, H-3, H-4, H-6), 0.90 (t,  $J$  = 7.5 Hz, 3H, H-7).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 175.5 (C-9), 97.2 (C-1), 43.7 (C-2), 40.9 (C-5), 38.7 (C-8), 28.3 (C-3), 26.3 (C-6), 20.5 (C-4), 9.1 (C-7).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2938 (-C-H), 2862 (-C-H), 1746 (9-C=O), 1448, 1193, 1119, 698.

**HRMS (TOF, ES+):** calculated for C<sub>9</sub>H<sub>16</sub>NO<sub>2</sub> [M+H]<sup>+</sup> 170.11756, found 170.11742.

**(3a*R*)-7-(2-(1*H*-indol-3-yl)ethyl)-3a-ethylhexahydrofuro[2,3-*b*]pyridin-2(3*H*)-one (473)**



To a flame-dried two-necked flask equipped with a condenser and under inert atmosphere, the lactone **470** (40.0 mg, 0.23 mmol, 1.0 eq.) was introduced followed by tryptophyl bromide **371a** (105.0 mg, 0.47 mmol, 2.0 eq.), K<sub>2</sub>CO<sub>3</sub> (111.0 mg, 0.8 mmol, 3.5 eq.) and 1,4-dioxane (2.3 mL, 0.1 M). The reaction mixture was vigorously stirred at 100 °C. After 12 h, the reaction was cooled to 20 °C, then the solvents were concentrated under reduced pressure. The crude mixture was purified through short column chromatography on SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 100/0 to 98/2 to 95/5) to afford the pure desired product (60.0 mg, 83%) as a brown viscous oil.

**TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 90/10):**  $R_f$  = 0.35 (UV active; vanillin, stains purple).

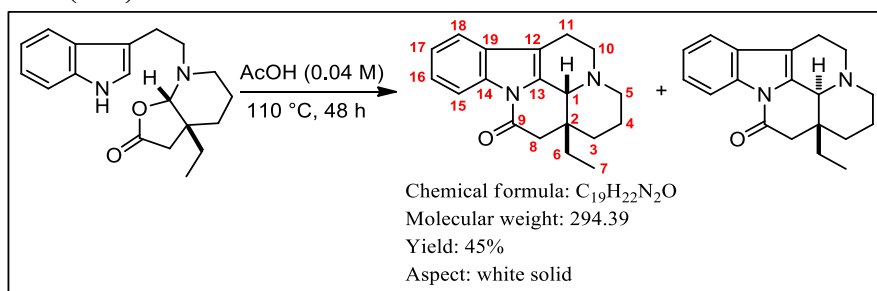
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 8.13 (s, 1H, NH), 7.62-7.58 (m, 1H, H-18), 7.36 (dt,  $J$  = 8.1, 1.0 Hz, 1H, H-15), 7.19 (dtd,  $J$  = 8.1, 7.0, 1.3 Hz, 1H, H-13), 7.11 (dtd,  $J$  = 8.0, 7.0, 1.1 Hz, 1H, H-16), 7.00 (d,  $J$  = 2.2 Hz, 1H, H-17), 5.09 (s, 1H, H-13), 3.25-3.13 (m, 1H, H-10a), 3.11-2.94 (m, 3H, H-10b, H-11), 2.87-2.73 (m, 2H, H-5), 2.38 (d,  $J$  = 16.5 Hz, 1H, H-8a), 2.20 (d,  $J$  = 16.5 Hz, 1H, H-8b), 1.71-1.51 (m, 3H, H-3a, H-4), 1.41-1.24 (m, 3H, H-3b, H-6), 0.83 (t,  $J$  = 7.5 Hz, 3H, H-7).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 175.9 (C-9), 136.3 (C-14), 127.6 (C-19), 122.0 (C-13), 121.7 (C-16), 119.3 (C-17), 118.8 (C-18), 113.9 (C-12), 111.2 (C-15), 102.8 (C-1), 56.0 (C-10), 44.3 (C-5), 43.4 (C-2), 41.7 (C-8), 27.7 (C-3), 26.3 (C-6), 23.7 (C-11), 20.8 (C-4), 9.0 (C-7).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2926 (-C-H), 2849 (-C-H), 1742 (9-C=O), 1456, 1180, 1028, 720.

**HRMS (TOF, ES+):** calculated for C<sub>19</sub>H<sub>25</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> 313.19105, found 313.19041.

**(4<sup>1</sup>*R*,13a*R*)-13a-ethyl-2,3,5,6,13,13a-hexahydro-1*H*-indolo[3,2,1-*de*]pyrido[3,2,1-*ij*][1,5]naphthyridin-12(4<sup>1</sup>*H*)-one (±)-eburnamonine (423)**



To a flame-dried two-necked flask equipped with a condenser and under inert atmosphere, the lactone **473** (40.0 mg, 0.128 mmol, 1.0 eq.) was introduced followed by AcOH (3.0 mL, 0.04 M) and the

reaction mixture was heated at 110 °C. After 48 h, the solvents were concentrated under reduced pressure and the crude mixture was purified through column chromatography on SiO<sub>2</sub> (CHCl<sub>3</sub>: 100%) to afford (±)-eburnamonine **423** (15.0 mg, 45%) as a white solid alongside with (±)-*epi*-eburnamonine **520** (18.0 mg, 54%) as a pale-yellow solid.

**TLC (EtOAc: 100%):**  $R_f$  = 0.14 (UV active; KMnO<sub>4</sub>, stains yellow).

**m. p.** = 196-199 °C (CH<sub>2</sub>Cl<sub>2</sub>).

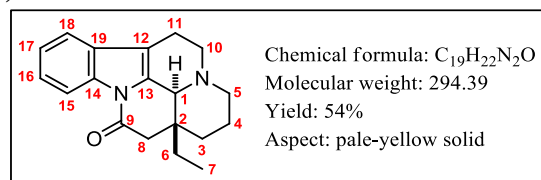
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 8.41-8.34 (m, 1H, H-15), 7.45-7.42 (m, 1H, H-18), 7.35-7.28 (m, 2H, H-16, H-17), 4.03 (s, 1H, H-1), 3.40-3.22 (m, 2H, H-10), 2.98-2.85 (m, 1H, H-11a), 2.64 (q,  $J$  = 16.8, 11.5 Hz, 2H, H-6), 2.50-2.40 (m, 2H, H-11b, H-8a), 2.16-1.97 (m, 1H, H-8b), 1.91-1.58 (m, 2H, H-5), 1.53-1.37 (m, 3H, H-4, H-3a), 1.05 (td,  $J$  = 13.6, 3.8 Hz, 1H, H-3b), 0.94 (t,  $J$  = 7.6 Hz, 3H, H-7).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 167.7 (C-9), 134.3 (C-14), 131.9 (C-13), 130.1 (C-19), 124.5 (C-16), 124.0 (C-17), 118.2 (C-18), 116.4 (C-15), 112.7 (C-12), 57.8 (C-1), 50.8 (C-10), 44.5 (C-5), 44.4 (C-8), 38.6 (C-2), 28.5 (C-3), 27.0 (C-6), 20.7 (C-4), 16.6 (C-11), 7.8 (C-7).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2931 (-C-H), 2857 (-C-H), 1702 (9-C=O), 1454, 1373, 1332, 1173, 749.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>19</sub>H<sub>23</sub>N<sub>2</sub>O [M+H]<sup>+</sup> 295.18049, found 295.17976.

(4<sup>1</sup>*S*,13*aR*)-13*a*-ethyl-2,3,5,6,13,13*a*-hexahydro-1*H*-indolo[3,2,1-*de*]pyrido[3,2,1-*ij*][1,5]naphthyridin-12(4<sup>1</sup>*H*)-one  
(±)-*epi*-eburnamonine (**520**)



**TLC (EtOAc: 100%):**  $R_f$  = 0.57 (UV active; KMnO<sub>4</sub>, stains yellow).

**m. p.** = 122.1-125.5 °C (CH<sub>2</sub>Cl<sub>2</sub>).

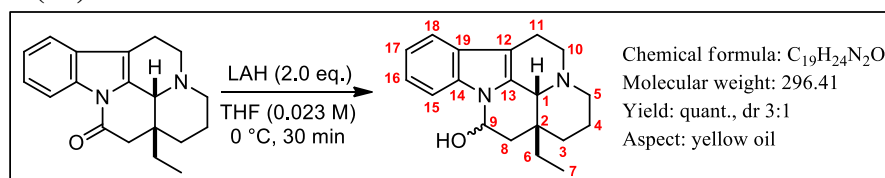
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 8.34-8.31 (m, 1H, H-15), 7.43-7.39 (m, 1H, H-18), 7.32-7.23 (m, 2H, H-16, H-17), 3.17-3.02 (m, 3H, H-1, H-10), 2.80 (d,  $J$  = 16.7 Hz, 1H, H-11a), 2.68-2.64 (m, 1H, H-11b), 2.59-2.50 (m, 1H, H-5a), 2.41-2.27 (m, 2H, H-5b, H-8a), 1.91-1.88 (m, 2H, H-6, H-8b), 1.69-1.55 (m, 2H, H-4), 1.24-1.13 (m, 1H, H-3a), 0.91-0.72 (m, 4H, H-3b, H-7).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):**  $\delta$  (ppm) = 167.7 (C-9), 135.2 (C-14), 130.0 (C-13), 130.0 (C-19), 124.2 (C-16), 124.0 (C-17), 118.2 (C-18), 116.3 (C-15), 113.1 (C-12), 66.1 (C-1), 55.5 (C-10), 52.5 (C-5), 44.4 (C-8), 39.6 (C-2), 31.9 (C-3), 21.6 (C-6), 21.3 (C-4), 20.8 (C-11), 7.5 (C-7).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):**  $\nu_{\max}$  (cm<sup>-1</sup>) = 2930 (-C-H), 2858 (-C-H), 1699 (9-C=O), 1453, 1373, 1331, 1173, 751.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>19</sub>H<sub>23</sub>N<sub>2</sub>O [M+H]<sup>+</sup> 295.18049, found 295.17976.

(4<sup>1</sup>*R*,13*aR*)-13*a*-ethyl-2,3,4<sup>1</sup>,5,6,12,13,13*a*-octahydro-1*H*-indolo[3,2,1-*de*]pyrido[3,2,1-*ij*][1,5]naphthyridin-12-ol  
(±)-eburnamine (**18**)



To a flame-dried two-necked flask and under inert atmosphere, (±)-eburnamonine **423** (14.0 mg, 0.047 mmol, 1.0 eq.) was introduced, followed by dry THF (2.0 mL, 0.023 M) and the solution was cooled to 0 °C (ice/water bath). LAH (1.0 M in Et<sub>2</sub>O, 0.1 mL, 0.1 mmol, 2.0 eq.) was added dropwise and the light-yellow solution was stirred at the same temperature for 30 min. The reaction was quenched carefully at 0 °C by dropwise addition of EtOAc (1 mL) then brine (1 mL). The organic

layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford the eburnamine **18** (14.0 mg, quant., dr: 3:1) as a yellow oil.

**TLC (EtOAc: 100%):** R<sub>f</sub> = 0.13 (UV active; KMnO<sub>4</sub>, stains yellow).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ (ppm) = 7.77-7.71 (m, 0.75H, H-18), 7.53-7.39 (m, 1.43H, H-15), 7.23-7.11 (m, 2.12H, H-16, H-17), 6.07 (d, *J* = 4.6 Hz, 0.25H, H-9 minor dia), 5.61 (dd, *J* = 9.6, 5.2 Hz, 0.75H, H-9 major dia), 3.91 (s, 1H, H-1), 3.37-3.18 (m, 2H, H-10), 3.00-2.89 (m, 1H, H-11a), 2.71-2.52 (m, 2H, H-11b, H-5a), 2.44-2.28 (m, 2H, H-5b, H-8a), 2.14-1.96 (m, 2H, H-4a, H-8b), 1.63-1.53 (m, 2H, H-4b, H-3a), 1.29-1.20 (m, 3H, H-3b, H-6), 0.99-0.80 (m, 3H, H-7).

**Major diastereomer:**

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ (ppm) = 136.8 (C-14), 132.6 (C-13), 128.6 (C-19), 121.5 (C-16), 120.3 (C-17), 118.1 (C-18), 112.3 (C-15), 105.6 (C-12), 76.6 (C-9), 58.9 (C-1), 50.9 (C-10), 44.4 (C-5), 43.5 (C-8), 36.9 (C-2), 28.7 (C-3), 25.1 (C-6), 20.5 (C-4), 16.9 (C-11), 7.7 (C-7).

**Minor diastereomer:**

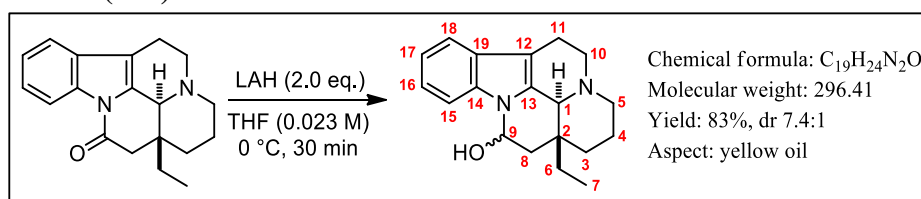
**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ (ppm) = 134.9 (C-14), 131.0 (C-13), 128.9 (C-19), 121.4 (C-16), 128.2 (C-17), 118.6 (C-18), 110.0 (C-15), 105.5 (C-12), 74.7 (C-9), 59.4 (C-1), 51.4 (C-10), 44.9 (C-5), 40.0 (C-8), 34.7 (C-2), 30.0 (C-3), 26.5 (C-6), 20.9 (C-4), 16.8 (C-11), 7.7 (C-7).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):** ν<sub>max</sub> (cm<sup>-1</sup>) = 3327 (br, OH), 2929 (-C-H), 2853 (-C-H), 1456, 1320, 1061, 739.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>19</sub>H<sub>23</sub>N<sub>2</sub>O [M-H]<sup>+</sup> 295.18159, found 295.18150.

calculated for C<sub>19</sub>H<sub>25</sub>N<sub>2</sub>O [M+H]<sup>+</sup> 297.19614, found 297.19544.

**(4<sup>1</sup>S,13aR)-13a-ethyl-2,3,4<sup>1</sup>,5,6,12,13,13a-octahydro-1H-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridin-12-ol**  
**(±)-*epi*-eburnamine (424)**



To a flame-dried two-necked flask and under inert atmosphere, (±)-*epi*-eburnamone **520** (24.0 mg, 0.08 mmol, 1.0 eq.) was introduced, followed by dry THF (3.4 mL, 0.023 M) and the solution was cooled to 0 °C (ice/water bath). LAH (1.0 M in Et<sub>2</sub>O, 0.16 mL, 0.16 mmol, 2.0 eq.) was added dropwise and the light-yellow solution was stirred at the same temperature for 30 min. The reaction was quenched carefully at 0 °C by dropwise addition of EtOAc (1 mL) then brine (1 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford the *epi*-eburnamine **424** (20.0 mg, 83%, dr: 7.4:1) as a yellow oil.

**TLC (EtOAc: 100%):** R<sub>f</sub> = 0.55 (UV active; KMnO<sub>4</sub>, stains yellow).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ (ppm) = 7.69-7.59 (m, 1H, H-18), 7.51-7.40 (m, 1H, H-15), 7.23-7.07 (m, 2H, H-16, H-17), 5.96 (d, *J* = 5.1 Hz, 0.18H, H-9 minor diastereomer), 5.59 (dd, *J* = 9.2, 5.7 Hz, 0.82H, H-9 major diastereomer), 3.97-3.83 (m, 0.18H, H-1 minor diastereomer), 3.79-3.52 (m, 0.82H, H-1 major diastereomer), 3.18-2.97 (m, 2H, H-10), 2.97-2.79 (m, 1H, H-5a), 2.79-2.60 (m, 1H, H-5b), 2.54-2.40 (m, 2H, H-11), 2.36-2.12 (m, 1H, H-8a), 2.01-1.60 (m, 4H, H-3a, H-4, H-8b), 1.63-1.50 (m, 2H, H-3b, H-6a), 1.19-1.00 (m, 1H, H-6b), 0.76 (t, *J* = 7.6 Hz, 3H, H-7).

**IR (solution in CH<sub>2</sub>Cl<sub>2</sub>, thin film, KBr):** ν<sub>max</sub> (cm<sup>-1</sup>) = 3323 (br, OH), 2929 (-C-H), 2853 (-C-H), 1456, 1320, 1302, 1061, 737.

**HRMS (TOF, ES<sup>+</sup>):** calculated for C<sub>19</sub>H<sub>23</sub>N<sub>2</sub>O [M-H]<sup>+</sup> 295.18159, found 295.18137.

calculated for C<sub>19</sub>H<sub>25</sub>N<sub>2</sub>O [M+H]<sup>+</sup> 297.19614, found 297.19532.



## References and Notes

- 1 Gan, C. Y.; Robinson, W. T.; Etoh, T.; Hayashi, M.; Komiyama, K.; Kam, T. S. *Org. Lett.* **2009**, *11*, 3962–3965.
- 2 Deguchi, J.; Shoji, T.; Nugroho, A. E.; Hirasawa, Y.; Hosoya, T.; Shiota, O.; Awang, K.; Hadi, A. H. A.; Morita, H. *J. Nat. Prod.* **2010**, *73*, 1727–1729.
- 3 Hayashi, Y.; Narasaka, K. *Chemistry Letters* **1990**, 1295–1298.
- 4 Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 5829–5831.
- 5 Pirenne, V.; Kurtay, G.; Voci, S.; Bouffier, L.; Sojic, N.; Robert, F.; Bassani, D. M.; Landais, Y. *Org. Lett.* **2018**, *20*, 4521–4525.
- 6 Wenkert, E.; Hudlicky, T.; Showalter, H. D. H. *J. Am. Chem. Soc.* **1978**, *100*, 4893–4894.
- 7 Martin, V. *Semin. Oncol. Nurs.* **1993**, *9*, 2–5.
- 8 Goodman, J.; Walsh, V. *The Story of Taxol: Nature and Politics in the Pursuit of an Anti-Cancer Drug*, Cambridge University Press, **2001**.
- 9 Svoboda, G. H.; Blake, D. A. In *The Catharanthus alkaloids: Botany, chemistry, pharmacology, and clinical use*, Marcel Dekker, Inc., New-York, **1975**, pp 45–83.
- 10 Schmeller, T.; Wink, M. In *Alkaloids*, Springer US, **1998**, pp 435–459.
- 11 Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y.; Potier, P. *Tetrahedron* **1980**, *36*, 3053–3060.
- 12 Kruczynski, A.; Hill, B. T. *Crit. Rev. Oncol. Hematol.* **2001**, *40*, 159–173.
- 13 Fahy, J.; Duflos, A.; Ribet, J.-P.; Jacquesy, J.-C.; Berrier, C.; Jouannetaud, M.-P.; Zunino, F. *J. Am. Chem. Soc.* **1997**, *119*, 8576–8577.
- 14 Forli, S. *Curr. Top. Med. Chem.* **2014**, *14*, 2312–2321.
- 15 Hunt, J. T. *Mol. Cancer Ther.* **2009**, *8*, 275–281.
- 16 Drugs@FDA: FDA-Approved Drugs <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>.
- 17 Kathiravan, G.; Bhuvaneshwari, V.; Kramony, E.; Sureban, S.; Sree, H. *J. Basic Clin. Pharm.* **2013**, *4*, 14.
- 18 Hartzell, H. *The Yew Tree: A Thousand Whispers*, Hulgosi Books, **1991**.
- 19 Folkemer, M.; Bennett, S. *J. Natl. Cancer Inst.* **1992**, *84*, 479–480.
- 20 Husain, A. *Status Report on Cultivation of Medicinal Plants in NAM Countries*, Publication and Information Directorate, **1992**.
- 21 Noble, R. L. *Biochem. Cell Biol.* **1990**, *68*, 1344–1351.
- 22 De Luca, V.; Laflamme, P. *Curr. Opin. Plant Biol.* **2001**, *4*, 225–233.
- 23 Isah, T. *Br. J. Pharm. Res.* **2015**, *6*, 214–227.
- 24 Magnus, P.; Mendoza, J. S.; Stamford, A.; Ladlow, M.; Willis, P. *J. Am. Chem. Soc.* **1992**, *114*, 10232–10245.
- 25 Ataei-Azimi, A.; Delnavaz, H. B.; Ebrahimzadeh, H.; Majd, A. *Afric. J. Biotechnol.* **2008**, *7*, 2834–2839.
- 26 Kim, K. W.; Roh, J. K.; Wee, H. J.; Kim, C. *Cancer Drug Discov. Sci. Hist.* **2016**, 1–276.
- 27 Krause, W. *Cancer Drug Resist.* **2019**, 82–106.
- 28 Kam, T.-S.; Choo, Y.-M. In *The alkaloids*, Academic Press, **2006**, pp 181–337.
- 29 Szabó, L. F. *Molecules* **2008**, *13*, 1875–1896.
- 30 O'Connor, S. E.; Maresh, J. J. *Nat. Prod. Rep.* **2006**, *23*, 532–547.
- 31 Ma, X.; Panjikar, S.; Koepke, J.; Loris, E.; Stöckigt, J. *Plant Cell* **2006**, *18*, 907–920.
- 32 Barleben, L.; Panjikar, S.; Ruppert, M.; Koepke, J.; Stöckigt, J. *Plant Cell* **2007**, *19*, 2886–2897.
- 33 Xu, Z.; Wang, Q.; Zhu, J. *Chem. Soc. Rev.* **2018**, *47*, 7882–7898.
- 34 Stöckigt, J.; Ruppert, M. In *Comprehensive Natural Products Chemistry*, Elsevier, **1999**, pp 109–138.
- 35 Daddona, P. E.; Hutchinson, C. R. *J. Am. Chem. Soc.* **1974**, *96*, 6806–6807.
- 36 Langlois, N.; Gueritte, F.; Langlois, Y.; Potier, P. *J. Am. Chem. Soc.* **1976**, *98*, 7017–7024.
- 37 Ishikawa, H.; Colby, D. A.; Seto, S.; Va, P.; Tam, A.; Kakei, H.; Rayl, T. J.; Hwang, I.; Boger, D. L. *J. Am. Chem. Soc.* **2009**, *131*, 4904–4916.
- 38 Goodbody, A.; Endo, T.; Vukovic, J.; Misawa, M. *Planta Med.* **1988**, *54*, 210–214.
- 39 Zaima, K.; Hirata, T.; Hosoya, T.; Hirasawa, Y.; Koyama, K.; Rahman, A.; Kusumawati, I.; Zaini, N. C.; Shiro, M.; Morita, H. *J. Nat. Prod.* **2009**, *72*, 1686–1690.
- 40 Nugroho, A. E.; Hirasawa, Y.; Kawahara, N.; Goda, Y.; Awang, K.; Hadi, A. H. A.; Morita, H. *J. Nat. Prod.* **2009**, *72*, 1502–1506.
- 41 Nugroho, A. E.; Hirasawa, Y.; Hosoya, T.; Awang, K.; Hadi, A. H. A.; Morita, H. *Tetrahedron Lett.* **2010**, *51*, 2589–2592.
- 42 Hirasawa, Y.; Shoji, T.; Arai, T.; Nugroho, A. E.; Deguchi, J.; Hosoya, T.; Uchiyama, N.; Goda, Y.;

- Awang, K.; Hadi, A. H. A.; Shiro, M.; Morita, H. *Bioorganic Med. Chem. Lett.* **2010**, *20*, 2021–2024.
- 43 Fuji, K. *Chem. Rev.* **1993**, *93*, 2037–2066.
- 44 Christoffers, J.; Mann, A. *Angew. Chemie Int. Ed.* **2001**, *40*, 4591–4597.
- 45 Christoffers, J.; Baro, A. *Quaternary Stereocenters*, Wiley-VCH Verlag GmbH & Co., **2005**.
- 46 Patil, K.; Sibi, M. P. In *Quaternary Stereocenters*, Wiley-VCH Verlag GmbH & Co., **2006**, pp 287–313.
- 47 Dange, N. S.; Robert, F.; Landais, Y. *Org. Lett.* **2016**, *18*, 6156–6159.
- 48 Hassan, H.; Mohammed, S.; Robert, F.; Landais, Y. *Org. Lett.* **2015**, *17*, 4518–4521.
- 49 Lou, Y.; Horikawa, M.; Kloster, R. A.; Hawryluk, N. A.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 8916–8918.
- 50 Gay-Lussac, H. L. *Ann. Chim.* **1815**, *95*, 172.
- 51 Kolbe, H. *Ann. der Chemie und Pharm.* **1849**, *69*, 257–294.
- 52 Frankland, E. *Justus Liebigs Ann. Chem.* **1849**, *71*, 171–213.
- 53 Tidwell, T. T. In *The history of free radical chemistry*, John Wiley & Sons, Ltd., **2012**, pp 1–35.
- 54 Gomberg, M. *J. Am. Chem. Soc.* **1900**, *22*, 757–771.
- 55 Schlenk, W.; Weickel, T.; Herzenstein, A. *Justus Liebig's Ann. der Chemie* **1910**, *372*, 1–20.
- 56 Paneth, F.; Hofeditz, W. *Chem. Ber.* **1929**, *62*, 1335–1347.
- 57 Kharasch, M. S.; Engelmann, H.; Mayo, F. R. *J. Org. Chem.* **1937**, *2*, 288–302.
- 58 Forbes, M. D. E. *Carbon-Centered Free Radicals and Radical Cations*, John Wiley & Sons, Inc., **2010**.
- 59 Giese, B. *Angew. Chemie* **1985**, *97*, 555–567.
- 60 Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901–3924.
- 61 Barton, D. H. R.; Parekh, S. I. *Half a Century of Free Radical Chemistry*, Cambridge University Press, **1993**.
- 62 Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237–1286.
- 63 Curran, D. P.; Rakiewicz, D. M. *Tetrahedron* **1985**, *41*, 3943–3958.
- 64 Parker, K. A.; Fokas, D. *J. Am. Chem. Soc.* **1992**, *114*, 9688–9689.
- 65 Parker, K. A.; Fokas, D. *J. Org. Chem.* **2006**, *71*, 449–455.
- 66 Liu, X. Y.; Qin, Y. *Acc. Chem. Res.* **2019**, *52*, 1877–1891.
- 67 Togo, H. *Advanced Free Radical Reactions for Organic Synthesis*, Elsevier Science, **2004**.
- 68 Karplus, M.; Fraenkel, G. K. *J. Chem. Phys.* **1961**, *35*, 1312–1323.
- 69 Sherburn, M. S. In *Encyclopedia of Radicals in Chemistry, Biology and Materials*, John Wiley & Sons, Ltd., **2012**, pp 1–23.
- 70 Carey, F. A.; Sunberg, R. J. *Advanced Organic Chemistry Part A*, Springer, **2007**.
- 71 Walton, J. C.; Nonhebel, D. C. *Free-Radical Chemistry; Structure and Mechanism*, Cambridge University Press, **1974**.
- 72 Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1976**, *9*, 13–19.
- 73 Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*, John Wiley & Sons, Ltd., **1976**.
- 74 Godineau, E.; Landais, Y. *Chem. - A Eur. J.* **2009**, *15*, 3044–3055.
- 75 Rosenstein, I. J. In *Radicals in Organic Synthesis*, Wiley-VCH Verlag GmbH, **2001**, pp 50–71.
- 76 Bertrand, M. P.; Ferreri, C. In *Radicals in Organic Synthesis*, Wiley-VCH Verlag GmbH, **2001**, pp 485–504.
- 77 Newcomb, M. In *Encyclopedia of Radicals in Chemistry, Biology and Materials*, John Wiley & Sons, Ltd., **2012**.
- 78 Chatgililoglu, C.; Ferreri, C.; Landais, Y.; Timokhin, V. I. *Chem. Rev.* **2018**, *118*, 6516–6572.
- 79 Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*, Pergamon Press, Oxford, **1986**.
- 80 Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc. Perkin Trans. 1* **1975**, 1574.
- 81 Barton, D. H. R.; Crich, D.; Motherwell, W. B. *J. Chem. Soc. Chem. Commun.* **1983**, 939.
- 82 Baguley, P. A.; Walton, J. C. *Angew. Chemie Int. Ed.* **1998**, *37*, 3072–3082.
- 83 Kharasch, M. S.; Jensen, E. V.; Urry, W. H. *Science* **1945**, *102*, 128.
- 84 Curran, D. P.; Chen, M. H.; Spletzer, E.; Seong, C. M.; Chang, C. T. *J. Am. Chem. Soc.* **1989**, *111*, 8872–8878.
- 85 Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K.; Omoto, K.; Fujimoto, H. *J. Org. Chem.* **2001**, *66*, 7776–7785.
- 86 Quiclet-Sire, B.; Zard, S. Z. *Chim. Int. J. Chem.* **2012**, *66*, 404–412.
- 87 Grignon, J.; Pereyre, M. *J. Organomet. Chem.* **1973**, *61*, C33.
- 88 Grignon, J.; Servens, C.; Pereyre, M. *J. Organomet. Chem.* **1975**, *96*, 225.
- 89 Kosugi, M.; Kurino, K.; Takayama, K.; Migita, T. *J. Organomet. Chem.* **1973**, *56*, C11–C13.
- 90 Keck, G. E.; Enholm, E. J.; Yates, J. B.; Wiley, M. R. *Tetrahedron* **1985**, *41*, 4079–4094.



- 91 Russell, G. A.; Tashtoush, H.; Ngoviwatchai, P. *J. Am. Chem. Soc.* **1984**, *106*, 4622–4623.
- 92 Keck, G. E.; Tafesh, A. M. *J. Org. Chem.* **1989**, *54*, 5845–5846.
- 93 Gong, J.; Fuchs, P. L. *J. Am. Chem. Soc.* **1996**, *118*, 4486–4487.
- 94 Timokhin, V. I.; Gastaldi, S.; Bertrand, M. P.; Chatgililoglu, C. *J. Org. Chem.* **2003**, *68*, 3532–3537.
- 95 Chatgililoglu, C.; Mozziconacci, O.; Tamba, M.; Bobrowski, K.; Kciuk, G.; Bertrand, M. P.; Gastaldi, S.; Timokhin, V. I. *J. Phys. Chem. A* **2012**, *116*, 7623–7628.
- 96 Xiang, J.; Evarts, J.; Rivkin, A.; Curran, D. P.; Fuchs, P. L. *Tetrahedron Lett.* **1998**, *39*, 4163–4166.
- 97 Xiang, J.; Fuchs, P. L. *J. Am. Chem. Soc.* **1996**, *118*, 11986–11987.
- 98 Xiang, J.; Jiang, W.; Fuchs, P. L. *Tetrahedron Lett.* **1997**, *38*, 6635–6638.
- 99 Liautard, V.; Robert, F.; Landais, Y. *Org. Lett.* **2011**, *13*, 2658–2661.
- 100 Hassan, H.; Pirenne, V.; Wissing, M.; Khiar, C.; Hussain, A.; Robert, F.; Landais, Y. *Chem. - A Eur. J.* **2017**, *23*, 4651–4658.
- 101 Kim, S.; Lee, I. Y.; Yoon, J.-Y.; Oh, D. H. *J. Am. Chem. Soc.* **1996**, *118*, 5138–5139.
- 102 Kim, S.; Yoon, J.-Y. *J. Am. Chem. Soc.* **1997**, *119*, 5982–5983.
- 103 Kim, S.; Song, H.-J.; Choi, T.-L.; Yoon, J.-Y. *Angew. Chemie Int. Ed.* **2001**, *40*, 2524–2526.
- 104 Kim, S.; Sub Yoon, K.; Suk Kim, Y. *Tetrahedron* **1997**, *53*, 73–80.
- 105 Kim, S.; Kim, Y.; Yoon, K. S. *Tetrahedron Lett.* **1997**, *38*, 2487–2490.
- 106 Godineau, E.; Landais, Y. *J. Am. Chem. Soc.* **2007**, *129*, 12662–12663.
- 107 Le Grogne, E.; Chrétien, J.-M.; Zammattio, F.; Quintard, J.-P. *Chem. Rev.* **2015**, *115*, 10207–10260.
- 108 Ferreira, M.; Blanco, L.; Garrido, A.; Vieites, J. M.; Cabado, A. G. *J. Agric. Food Chem.* **2013**, *61*, 4195–4203.
- 109 Yoon, T. P. *ACS Catal.* **2013**, *3*, 895–902.
- 110 Hedstrand, D. M.; Kruizinga, W. H.; Kellogg, R. M. *Tetrahedron Lett.* **1978**, *19*, 1255–1258.
- 111 Cano-Yelo, H.; Deronzier, A. *Tetrahedron Lett.* **1984**, *25*, 5517–5520.
- 112 Cano-Yelo, H.; Deronzier, A. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1093–1098.
- 113 Ischay, M. A.; Anzovino, M. E.; Du, J.; Yoon, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 12886–12887.
- 114 Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77–80.
- 115 Furst, L.; Narayanam, J. M. R.; Stephenson, C. R. J. *Angew. Chemie Int. Ed.* **2011**, *50*, 9655–9659.
- 116 Balzani, V.; Ceroni, P.; Juris, A. *Photochemistry and Photophysics. Concepts, Research, Applications*, Wiley-VCH, Weinheim, **2014**.
- 117 Romero, N. A.; Nicewicz, D. A. *Chem. Rev.* **2016**, *116*, 10075–10166.
- 118 Roth, H.; Romero, N.; Nicewicz, D. A. *Synlett* **2015**, *27*, 714–723.
- 119 Tucker, J. W.; Stephenson, C. R. J. *J. Org. Chem.* **2012**, *77*, 1617–1622.
- 120 Nguyen, J. D.; Tucker, J. W.; Konieczynska, M. D.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2011**, *133*, 4160–4163.
- 121 Wallentin, C. J.; Nguyen, J. D.; Finkbeiner, P.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2012**, *134*, 8875–8884.
- 122 Arceo, E.; Montroni, E.; Melchiorre, P. *Angew. Chemie - Int. Ed.* **2014**, *53*, 12064–12068.
- 123 Zhu, J.; Yang, W.-C.; Wang, X.; Wu, L. *Adv. Synth. Catal.* **2018**, *360*, 386–400.
- 124 Barton, D. H. R.; Jaszberenyi, J. C.; Theodorakis, E. A. *Tetrahedron Lett.* **1991**, *32*, 3321–3324.
- 125 Heitz, D. R.; Rizwan, K.; Molander, G. A. *J. Org. Chem.* **2016**, *81*, 7308–7313.
- 126 Le Vaillant, F.; Wodrich, M. D.; Waser, J. *Chem. Sci.* **2017**, *8*, 1790–1800.
- 127 Pews, R. G.; Evans, T. E. *J. Chem. Soc. D Chem. Commun.* **1971**, *3*, 1397–1398.
- 128 Barton, D. H. R.; Jaszberenyi, J. C.; Theodorakis, E. A. *Tetrahedron* **1992**, *48*, 2613–2626.
- 129 Sun, J.; Li, P.; Guo, L.; Yu, F.; He, Y.-P.; Chu, L. *Chem. Commun.* **2018**, *54*, 3162–3165.
- 130 Fan, Y. Y.; Gao, X. H.; Yue, J. M. *Sci. China Chem.* **2016**, *59*, 1126–1141.
- 131 Beniddir, M. A.; Evanno, L.; Joseph, D.; Skiredj, A.; Poupon, E. *Nat. Prod. Rep.* **2016**, *33*, 820–842.
- 132 Dembitsky, V. M. *J. Nat. Med.* **2008**, *62*, 1–33.
- 133 Li, J.; Gao, K.; Bian, M.; Ding, H. *Org. Chem. Front.* **2019**, *7*, 136–154.
- 134 Ebner, C.; Carreira, E. M. *Chem. Rev.* **2017**, *117*, 11651–11679.
- 135 Chen, D. Y. K.; Pouwer, R. H.; Richard, J. A. *Chem. Soc. Rev.* **2012**, *41*, 4631–4642.
- 136 Schneider, T. F.; Kaschel, J.; Werz, D. B. *Angew. Chemie - Int. Ed.* **2014**, *53*, 5504–5523.
- 137 Vemula, N.; Pagenkopf, B. L. *Org. Chem. Front.* **2016**, *3*, 1205–1212.
- 138 De Nanteuil, F.; De Simone, F.; Frei, R.; Benfatti, F.; Serrano, E.; Waser, J. *Chem. Commun.* **2014**, *50*, 10912–10928.
- 139 Hoz, S. *The Chemistry of the Cyclopropyl Group*, John Wiley & Sons, Ltd., **1987**.
- 140 Lebel, H.; Marcoux, J. F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977–1050.
- 141 Trost, B. M. In *Small Ring Compounds in Organic Synthesis I. Topics in Current Chemistry*, Vol. 133, Springer, Berlin, Heidelberg, **1986**, pp 3–82.



- 142 Freund, A. *J. für Prakt. Chemie* **1882**, 26, 367–377.
- 143 Hass, H. B.; McBee, E. T.; Hinds, G. E. *Ind. Eng. Chem.* **1936**, 28, 1178–1181.
- 144 Perkin, W. H. *J. Chem. Soc., Trans.* **1887**, 51, 1–28.
- 145 Wiberg, K. B. In *The Chemistry of Cyclobutanes*, John Wiley & Sons, Ltd., **2005**, pp 1–15.
- 146 Wiberg, K. B. *Angew. Chemie Int. Ed. English* **1986**, 25, 312–322.
- 147 Bauld, N. L.; Cessac, J.; Holloway, R. L. *J. Am. Chem. Soc.* **1977**, 99, 8140–8144.
- 148 Bartell, L. S.; Andersen, B. *J. Chem. Soc. Chem. Commun.* **1973**, 786.
- 149 Allen, F. H. *Acta Crystallogr. Sect. B Struct. Sci.* **1984**, 40, 64–72.
- 150 Dunitz, J. D.; Schomaker, V. *J. Chem. Phys.* **1952**, 20, 1703–1707.
- 151 Weigert, F. J.; Roberts, J. D. *J. Am. Chem. Soc.* **1967**, 89, 5962–5963.
- 152 Walsh, A. D. *Trans. Faraday Soc.* **1949**, 45, 179–190.
- 153 Coulson, C. A.; Moffitt, W. E. *London, Edinburgh, Dublin Philos. Mag. J. Sci.* **1949**, 40, 1–35.
- 154 Rashid, Z.; Broer, R.; Van Lenthe, J. H.; Havenith, R. W. A. In *Structure, Bonding and Reactivity of Heterocyclic Compounds. Topics in Heterocyclic Chemistry, Vol. 38*, Springer, Berlin, Heidelberg, **2014**, pp 103–128.
- 155 Boese, R.; Miebach, T.; De Meijere, A. *J. Am. Chem. Soc.* **1991**, 113, 1743–1748.
- 156 Chakrabarti, P.; Seiler, P.; Dunitz, J. D.; Schluter, A. D.; Szeimies, G. *J. Am. Chem. Soc.* **1981**, 103, 7378–7380.
- 157 Wiberg, K. B.; Bader, R. F. W.; Lau, C. D. H. *J. Am. Chem. Soc.* **1987**, 109, 985–1001.
- 158 Hoffmann, R.; Davidson, R. B. *J. Am. Chem. Soc.* **1971**, 93, 5699–5705.
- 159 Coulson, C. A. *Valence*, Clarendon Press, Oxford, **1952**.
- 160 Cavitt, M. A.; Phun, L. H.; France, S. *Chem. Soc. Rev.* **2014**, 43, 804–818.
- 161 Namyslo, J. C.; Kaufmann, D. E. *Chem. Rev.* **2003**, 103, 1485–1537.
- 162 Seiser, T.; Saget, T.; Tran, D. N.; Cramer, N. *Angew. Chemie - Int. Ed.* **2011**, 50, 7740–7752.
- 163 Campbell, M. J.; Johnson, J. S.; Parsons, A. T.; Pohlhaus, P. D.; Sanders, S. D. *J. Org. Chem.* **2010**, 75, 6317–6325.
- 164 Xu, Y.; Conner, M. L.; Brown, M. K. *Angew. Chemie - Int. Ed.* **2015**, 54, 11918–11928.
- 165 Poplata, S.; Tröster, A.; Zou, Y. Q.; Bach, T. *Chem. Rev.* **2016**, 116, 9748–9815.
- 166 Wu, W.; Lin, Z.; Jiang, H. *Org. Biomol. Chem.* **2018**, 16, 7315–7329.
- 167 Vicente, R. *Synth.* **2016**, 48, 2343–2360.
- 168 Zhu, Z. Bin; Wei, Y.; Shi, M. *Chem. Soc. Rev.* **2011**, 40, 5534–5563.
- 169 Petiniot, N.; Anciaux, A. J.; Noels, A. F.; Hubert, A. J.; Teyssié, P. *Tetrahedron Lett.* **1978**, 19, 1239–1242.
- 170 Doyle, M. P.; Ene, D. G.; Peterson, C. S.; Lynch, V. *Angew. Chemie Int. Ed.* **1999**, 38, 700–702.
- 171 Protopopova, M. N.; Doyle, M. P.; Mueller, P.; Ene, D. *J. Am. Chem. Soc.* **1992**, 114, 2755–2757.
- 172 Misale, A.; Niyomchon, S.; Maulide, N. *Acc. Chem. Res.* **2016**, 49, 2444–2458.
- 173 Kleinbeck, F.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, 131, 9178–9179.
- 174 Regan, A. C. In *Comprehensive Organic Functional Group Transformations, Vol. 1*, Elsevier, Oxford, **1995**, pp 516–519.
- 175 Maturi, M. M.; Bach, T. *Angew. Chemie - Int. Ed.* **2014**, 53, 7661–7664.
- 176 Ito, H.; Hasegawa, M.; Takenaka, Y.; Kobayashi, T.; Iguchi, K. *J. Am. Chem. Soc.* **2004**, 126, 4520–4521.
- 177 Takenaka, Y.; Ito, H.; Hasegawa, M.; Iguchi, K. *Tetrahedron* **2006**, 62, 3380–3388.
- 178 Mitsudo, T.; Naruse, H.; Kondo, T.; Ozaki, Y.; Watanabe, Y. *Angew. Chemie Int. Ed. English* **1994**, 33, 580–581.
- 179 Shibata, T.; Takami, K.; Kawachi, A. *Org. Lett.* **2006**, 8, 1343–1345.
- 180 Fan, B. M.; Li, X. J.; Peng, F. Z.; Zhang, H. Bin; Chan, A. S. C.; Shao, Z. H. *Org. Lett.* **2010**, 12, 304–306.
- 181 Hu, J.; Yang, Q.; Yu, L.; Xu, J.; Liu, S.; Huang, C.; Wang, L.; Zhou, Y.; Fan, B. *Org. Biomol. Chem.* **2013**, 11, 2294.
- 182 Sakai, K.; Kochi, T.; Kakiuchi, F. *Org. Lett.* **2013**, 15, 1024–1027.
- 183 Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, 107, 3117–3179.
- 184 Archambeau, A.; Miege, F.; Meyer, C.; Cossy, J. *Acc. Chem. Res.* **2015**, 48, 1021–1031.
- 185 Didier, D.; Delaye, P. O.; Simaan, M.; Island, B.; Eppe, G.; Eijssberg, H.; Kleiner, A.; Knochel, P.; Marek, I. *Chem. - A Eur. J.* **2014**, 20, 1038–1048.
- 186 Ferjančič, Z.; Čeković, Ž.; Saičić, R. N. *Tetrahedron Lett.* **2000**, 41, 2979–2982.
- 187 Feng, Y.; Liu, L.; Wang, J. T.; Zhao, S. W.; Guo, Q. X. *J. Org. Chem.* **2004**, 69, 3129–3138.
- 188 Yamago, S.; Ejiri, S.; Nakamura, E. *Chem. Lett.* **1994**, 23, 1889–1892.
- 189 Ueda, M.; Doi, N.; Miyagawa, H.; Sugita, S.; Takeda, N.; Shinada, T.; Miyata, O. *Chem. Commun.*

- 2015**, *51*, 4204–4207.
- 190 Kimoto, H.; Muramatsu, H.; Inukai, K. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2815–2816.
- 191 Leigh, W. J.; Zheng, K.; Nguyen, N.; Werstiuk, N. H.; Ma, J. *J. Am. Chem. Soc.* **1991**, *113*, 4993–4999.
- 192 Kinney, W. A. *Tetrahedron Lett.* **1993**, *34*, 2715–2718.
- 193 Legrand, N.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **2000**, *41*, 9815–9818.
- 194 Hayashi, Y.; Narasaka, K. *Chemistry Letters* **1989**, 793–796.
- 195 Narasaka, K.; Hayashi, Y.; Shimadzu, H.; Niihata, S. *J. Am. Chem. Soc.* **1992**, *114*, 8869–8885.
- 196 Hayashi, Y.; Niihata, S.; Narasaka, K. *Chemistry Letters* **1990**, 2091–2094.
- 197 Hu, L.; Gui, Q.; Chen, X.; Tan, Z.; Zhu, G. *J. Org. Chem.* **2016**, *81*, 4861–4868.
- 198 Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340–5345.
- 199 Matsumura, T.; Niwa, T.; Nakada, M. *Tetrahedron Lett.* **2012**, *53*, 4313–4316.
- 200 Barbero, N.; Martin, R. *Org. Lett.* **2012**, *14*, 796–799.
- 201 Becker, S.; Fort, Y.; Caubere, P. *J. Org. Chem.* **1990**, *55*, 6194–6198.
- 202 Fukuyama, T.; Lin, S. C.; Li, L. *J. Am. Chem. Soc.* **1990**, *112*, 7050–7051.
- 203 Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Lin, S. C.; Li, L.; Fukuyama, T. *J. Braz. Chem. Soc.* **1998**, *9*, 381–387.
- 204 Evans, D. A.; Trotter, B. W.; Coleman, P. J.; Côté, B.; Dias, L. C.; Rajapakse, H. A.; Tyler, A. N. *Tetrahedron* **1999**, *55*, 8671–8726.
- 205 Evans, D. A.; Trotter, B. W.; Côté, B.; Coleman, P. J. *Angew. Chemie Int. Ed. English* **1997**, *36*, 2741–2744.
- 206 Evans, D. A.; Wood, M. R.; Trotter, B. W.; Richardson, T. I.; Barrow, J. C.; Katz, J. L. *Angew. Chemie Int. Ed.* **1998**, *37*, 2700–2704.
- 207 Xiang, J. S.; Mahadevan, A.; Fuchs, P. L. *J. Am. Chem. Soc.* **1996**, *118*, 4284–4290.
- 208 Patai, S.; Rappoport, Z. *The Chemistry of the Cyano Group*, John Wiley & Sons, Ltd., **1970**.
- 209 Jiang, H.; He, Y.; Cheng, Y.; Yu, S. *Org. Lett.* **2017**, *19*, 1240–1243.
- 210 Bachi, M. D.; Bar-Ner, N.; Crittell, C. M.; Stang, P. J.; Williamson, B. L. *J. Org. Chem.* **1991**, *56*, 3912–3915.
- 211 Zhang, Y. F.; Kirchmeier, R. L.; Shreeve, J. M. *Inorg. Chem.* **1992**, *31*, 492–494.
- 212 Fang, J.; Wang, Z. K.; Wu, S. W.; Shen, W. G.; Ao, G. Z.; Liu, F. *Chem. Commun.* **2017**, *53*, 7638–7641.
- 213 Jin, W.; Wu, M.; Xiong, Z.; Zhu, G. *Chem. Commun.* **2018**, *54*, 7924–7927.
- 214 Kamijo, S.; Yokosaka, S.; Inoue, M. *Tetrahedron Lett.* **2012**, *53*, 4324–4327.
- 215 Ovadia, B.; Robert, F.; Landais, Y. *Chim. Int. J. Chem.* **2016**, *70*, 34–42.
- 216 Ramseier, M.; Senn, P.; Wirz, J. *J. Phys. Chem. A* **2003**, *107*, 3305–3315.
- 217 Nebe, M. M.; Loeper, D.; Fürmeyer, F.; Opatz, T. *European J. Org. Chem.* **2018**, *2018*, 2471–2476.
- 218 Hoshikawa, T.; Yoshioka, S.; Kamijo, S.; Inoue, M. *Synthesis* **2013**, *45*, 874–887.
- 219 Schneider, H. J.; Hoppen, V. *J. Org. Chem.* **1978**, *43*, 3866–3873.
- 220 Chatgililoglu, C.; Mozziconacci, O.; Tamba, M.; Bobrowski, K.; Kciuk, G.; Bertrand, M. P.; Gastaldi, S.; Timokhin, V. I. *J. Phys. Chem. A* **2012**, *116*, 7623–7628.
- 221 Pirenne, V.; Traboulsi, I.; Rouvière, L.; Lusseau, J.; Massip, S.; Bassani, D. M.; Robert, F.; Landais, Y. *Org. Lett.* **2020**, *22*, 575–579.
- 222 Albin, A. *Synthesis* **1981**, *1981*, 249–264.
- 223 Lu, Z.; Yoon, T. P. *Angew. Chemie - Int. Ed.* **2012**, *51*, 10329–10332.
- 224 Farney, E. P.; Yoon, T. P. *Angew. Chemie - Int. Ed.* **2014**, *53*, 793–797.
- 225 Alonso, R.; Bach, T. *Angew. Chemie - Int. Ed.* **2014**, *53*, 4368–4371.
- 226 Barton, D. H. R.; Jaszberenyi, J. C.; Theodorakis, E. A. *Tetrahedron Lett.* **1991**, *32*, 2585–2588.
- 227 Kochi, J. K. In *Comprehensive Organic Synthesis*, Elsevier, **1991**.
- 228 Montalti, M.; Credi, A.; Prodi, L.; Gandolfi, M. T. *Handbook of Photochemistry*, CRC Press, **2006**.
- 229 Gorner, H.; Kuhn, H. J. *J. Phys. Chem.* **1986**, *90*, 5946–5955.
- 230 Yang, N. C.; Kimura, M.; Eisenhardt, W. *J. Am. Chem. Soc.* **1973**, *95*, 5058–5060.
- 231 Koyanagi, M.; Goodman, L. *J. Chem. Phys.* **1971**, *55*, 2959–2976.
- 232 Theodoropoulou, M. A.; Nikitas, N. F.; Kokotos, C. G. *Beilstein J. Org. Chem.* **2020**, *16*, 833–857.
- 233 Liu, L.; Si, M.; Han, S.; Zhang, Y.; Li, J. *Org. Chem. Front.* **2020**, *7*, 2029–2034.
- 234 Coote, S. C.; Flowers, R. A.; Skrydstrup, T.; Procter, D. J. In *Encyclopedia of Radicals in Chemistry, Biology and Materials*, John Wiley & Sons, Ltd., **2012**, pp 1–52.
- 235 Namy, J. L.; Girard, P.; Kagan, H. B. *Nouv. J. Chim.* **1977**, *1*, 5.
- 236 Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693–2698.
- 237 Girard, P.; Kagan, H. B.; Caro, P. E. *Nouv. J. Chim.* **1981**, *5*, 479.

- 238 Procter, D. J.; Flowers, R. A., II; Skrydstrup, T. *Organic Synthesis Using Samarium Diiodide: A Practical Guide*, Royal Society of Chemistry, Cambridge, **2009**.
- 239 Prasad, E.; Flowers, R. A. *J. Am. Chem. Soc.* **2005**, *127*, 18093–18099.
- 240 Szostak, M.; Spain, M.; Parmar, D.; Procter, D. J. *Chem. Commun.* **2012**, *48*, 330–346.
- 241 Szostak, M.; Spain, M.; Procter, D. J. *J. Am. Chem. Soc.* **2014**, *136*, 8459–8466.
- 242 Nicolaou, K. C.; Ellery, S. P.; Chen, J. S. *Angew. Chemie - Int. Ed.* **2009**, *48*, 7140–7165.
- 243 Szostak, M.; Fazakerley, N. J.; Parmar, D.; Procter, D. J. *Chem. Rev.* **2014**, *114*, 5959–6039.
- 244 Batey, R. A.; Motherwell, W. B. *Tetrahedron Lett.* **1991**, *32*, 6211–6214.
- 245 Enholm, E. J.; Schreier, J. A. *J. Org. Chem.* **1995**, *60*, 1110–1111.
- 246 Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1991**, *56*, 4112–4120.
- 247 Batey, R. A.; Harling, J. D.; Motherwell, W. B. *Tetrahedron* **1996**, *52*, 11421–11444.
- 248 Boffey, R. J.; Santagostino, M.; Kilburn, J. D.; Boffey, R. J.; Whittingham, W. G. *Chem. Commun.* **1998**, 1875–1876.
- 249 Boffey, R. J.; Whittingham, W. G.; Kilburn, J. D. *J. Chem. Soc. Perkin Trans. 1* **2001**, 487–496.
- 250 Kim, Y. H.; Lee, I. S. *Heteroat. Chem.* **1992**, *3*, 509–512.
- 251 Yamashita, M.; Okuyama, K.; Ohhara, T.; Kawasaki, I.; Sakai, K.; Nakata, S.; Kawabe, T.; Kusumoto, M.; Ohta, S. *Chem. Pharm. Bull.* **1995**, *43*, 2075–2081.
- 252 Sahn, J. J.; Comins, D. L. *J. Org. Chem.* **2010**, *75*, 6728–6731.
- 253 Kakiuchi, K.; Minato, K.; Tsutsumi, K.; Morimoto, T.; Kurosawa, H. *Tetrahedron Lett.* **2003**, *44*, 1963–1966.
- 254 Takatori, K.; Ota, S.; Tendo, K.; Matsunaga, K.; Nagasawa, K.; Watanabe, S.; Kishida, A.; Kogen, H.; Nagaoka, H. *Org. Lett.* **2017**, *19*, 3763–3766.
- 255 Comins, D. L.; Zhang, Y. M.; Zheng, X. *Chem. Commun.* **1998**, *4*, 2509–2510.
- 256 Hansen, A. M.; Lindsay, K. B.; Sudhadevi Antharjanam, P. K.; Karaffa, J.; Daasbjerg, K.; Flowers, R. A.; Skrydstrup, T. *J. Am. Chem. Soc.* **2006**, *128*, 9616–9617.
- 257 Szostak, M.; Spain, M.; Eberhart, A. J.; Procter, D. J. *J. Am. Chem. Soc.* **2014**, *136*, 2268–2271.
- 258 Huang, H. M.; Procter, D. J. *Angew. Chemie - Int. Ed.* **2017**, *56*, 14262–14266.
- 259 Magnier-Bouvier, C.; Reboule, I.; Gil, R.; Collin, J. *Synlett* **2008**, 1211–1215.
- 260 Prasad, E.; Flowers, R. A. *J. Am. Chem. Soc.* **2002**, *124*, 6895–6899.
- 261 Jensen, C. M.; Lindsay, K. B.; Taaning, R. H.; Karaffa, J.; Hansen, A. M.; Skrydstrup, T. *J. Am. Chem. Soc.* **2005**, *127*, 6544–6545.
- 262 Karaffa, J.; Lindsay, K. B.; Skrydstrup, T. *J. Org. Chem.* **2006**, *71*, 8219–8226.
- 263 Mittag, T.; Christensen, K. L.; Lindsay, K. B.; Nielsen, N. C.; Skrydstrup, T. *J. Org. Chem.* **2008**, *73*, 1088–1092.
- 264 Keck, G. E.; Savin, K. A.; Weglarz, M. A. *J. Org. Chem.* **1995**, *60*, 3194–3204.
- 265 Ramberg, L.; Bäcklund, B. *Ark. Kemi, Miner. Geol.* **1940**, *13A*, 1–50.
- 266 Ramberg, L.; Bäcklund, B. *Chem. Abstr.* **1940**, *34*, 4725.
- 267 Meyers, C. Y.; Malte, A. M.; Matthews, W. S. *J. Am. Chem. Soc.* **1969**, *91*, 7510–7512.
- 268 Chan, T.; Fong, S.; Li, Y.; Man, T.; Poon, C. J. *Chem. Soc., Chem. Commun.*, **1994**, 1771–1772.
- 269 Yang, G.; Franck, R. W.; Byun, H.-S.; Bittman, R.; Samadder, P.; Arthur, G. *Org. Lett.* **1999**, *1*, 2149–2151.
- 270 Taylor, R. J. K. *Chem. Commun.* **1999**, 217–227.
- 271 Paquette, L. A. In *Organic Reactions*, John Wiley & Sons, Inc., **1977**, pp 1–71.
- 272 Söderman, S. C.; Schwan, A. L. *J. Org. Chem.* **2012**, *77*, 10978–10984.
- 273 Vedejs, E.; Singer, S. P. *J. Org. Chem.* **1978**, *43*, 4831–4837.
- 274 Vacher, B.; Samat, A.; Allouche, A.; Laknifil, A.; Baldyl, A.; Chanon, M. *Tetrahedron* **1988**, *44*, 2925–2932.
- 275 Marco, J. A.; Carda, M. In *Natural Lactones and Lactams*, Wiley-VCH Verlag GmbH & Co. KGaA, **2013**, pp 51–100.
- 276 Paterson, I.; Lam, N. Y. S. *J. Antibiot.* **2018**, *71*, 215–233.
- 277 Mori, K. *Tetrahedron* **1989**, *45*, 3233–3298.
- 278 Florence, G. J.; Gardner, N. M.; Paterson, I. *Nat. Prod. Rep.* **2008**, *25*, 342.
- 279 Gilchrist, T. L. *Heterocyclic Chemistry*, John Wiley & Sons, **1997**.
- 280 Collins, I. *J. Chem. Soc. - Perkin Trans. 1* **1998**, 1869–1888.
- 281 Lakner, F. J.; Hager, L. P. *J. Org. Chem.* **1996**, *61*, 3923–3925.
- 282 Frye, S. V.; Eliel, E. L. *J. Org. Chem.* **1985**, *50*, 3402–3404.
- 283 Fuentes, J. A.; Phillips, S. D.; Clarke, M. L. *Chem. Cent. J.* **2012**, *6*, 1–6.
- 284 Tong, B. M. K.; Chen, H.; Chong, S. Y.; Heng, Y. L.; Chiba, S. *Org. Lett.* **2012**, *14*, 2826–2829.
- 285 Bailey, P. D.; Beard, M. A.; Cresswell, M.; Dang, H. P. T.; Pathak, R. B.; Phillips, T. R.; Price, R. A.

- Tetrahedron Lett.* **2013**, *54*, 1726–1729.
- 286 Crimmins, M. T.; Siliphaivanh, P. *Org. Lett.* **2003**, *5*, 4641–4644.
- 287 Nájera, C.; Yus, M. *Tetrahedron* **1999**, *55*, 10547–10658.
- 288 Simpkins, N. S. *Sulphones in Organic Synthesis (Tetrahedron Organic Chemistry Series)*, Pergamon Press, **1993**.
- 289 Bordwell, F. G.; Chapman, R. D.; McKellin, W. H. *J. Am. Chem. Soc.* **1954**, *76*, 3637–3639.
- 290 Delaunay, J.; Orliac, A.; Simonet, J. *Tetrahedron Lett.* **1995**, *36*, 2083–2084.
- 291 Fisher, T. J.; Dussault, P. H. *Tetrahedron* **2017**, *73*, 4233–4258.
- 292 Bailey, P. S. *Ozonation in Organic Chemistry. Vol. I. Olefinic Compounds*, Academic Press, **1978**.
- 293 Jung, M. E.; Deng, G. *J. Org. Chem.* **2012**, *77*, 11002–11005.
- 294 Schreiber, S. L.; Claus, R. E.; Reagan, J. *Tetrahedron Lett.* **1982**, *23*, 3867–3870.
- 295 Lemieux, R. U.; Rudloff, E. Von. *Can. J. Chem.* **1955**, *33*, 1701–1709.
- 296 Dash, S.; Patel, S.; Mishra, B. K. *Tetrahedron* **2009**, *65*, 707–739.
- 297 Schwab, W.; Jäger, V. *Angew. Chemie Int. Ed. English* **1981**, *20*, 603–605.
- 298 Nunez, M. T.; Martin, V. S. *J. Org. Chem.* **1990**, *55*, 1928–1932.
- 299 Reissig, H.-U.; Hirsch, E. *Angew. Chemie Int. Ed. English* **1980**, *19*, 813–814.
- 300 Böhm, I.; Hirsch, E.; Reissig, H.-U. *Angew. Chemie Int. Ed. English* **1981**, *20*, 574–574.
- 301 Reissig, H.-U. *Topics in Current Chemistry, Vol. 144*, Springer, Berlin, Heidelberg, **1988**, pp 73–135.
- 302 Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151–1196.
- 303 Reissig, H.-U.; Zimmer, R. *Angew. Chemie - Int. Ed.* **2015**, *54*, 5009–5011.
- 304 Moustafa, M. M. A. R.; Pagenkopf, B. L. *Org. Lett.* **2010**, *12*, 4732–4735.
- 305 Moustafa, M. M. A. R.; Stevens, A. C.; Machin, B. P.; Pagenkopf, B. L. *Org. Lett.* **2010**, *12*, 4736–4738.
- 306 Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 14202–14203.
- 307 Stevens, A. C.; Palmer, C.; Pagenkopf, B. L. *Org. Lett.* **2011**, *13*, 1528–1531.
- 308 Wang, L.; Tang, Y. *Isr. J. Chem.* **2016**, *56*, 463–475.
- 309 Shimada, S.; Saigo, K.; Nakamura, H.; Hasegawa, M. *Chemistry Letters* **1991**, 1149–1152.
- 310 A. C. Ware, *Approaches to carbons 6-14 of Ebelactone A using silicon, Ph.D. thesis*, University of Cambridge, **1988**.
- 311 Dowling, M. S.; Vanderwal, C. D. *J. Org. Chem.* **2010**, *75*, 6908–6922.
- 312 Charnay-Pouget, F.; Frank, M.; Baltaze, J. P.; Pereira, E.; Aitken, D. J. *Arkivoc* **2012**, *2012*, 80–93.
- 313 Fleming, I.; Rowley, M. *Tetrahedron* **1986**, *42*, 3181–3198.
- 314 Trost, B. M.; Fleming, I. *Comprehensive Organic Synthesis, Vol. 8*, Pergamon, Oxford, **1991**.
- 315 Seyden-Penne, J. *Reduction by Alumino and Borohydrides in Organic Synthesis, 2nd Ed.*, Wiley-VCH, **1997**.
- 316 Walker, E. R. H. *Chem. Soc. Rev.* **1976**, *5*, 23.
- 317 Haddenham, D.; Pasumansky, L.; DeSoto, J.; Eagon, S.; Singaram, B. *J. Org. Chem.* **2009**, *74*, 1964–1970.
- 318 Szostak, M.; Sautier, B.; Spain, M.; Procter, D. J. *Org. Lett.* **2014**, *16*, 1092–1095.
- 319 Laval, S.; Dayoub, W.; Favre-Reguillon, A.; Berthod, M.; Demonchaux, P.; Mignani, G.; Lemaire, M. *Tetrahedron Lett.* **2009**, *50*, 7005–7007.
- 320 Ganem, B.; Osby, J. O. *Chem. Rev.* **1986**, *86*, 763–780.
- 321 Itsuno, S.; Sakurai, Y.; Ito, K. *Synthesis* **1988**, *1988*, 995–996.
- 322 Suzuki, N.; Kaneko, Y.; Tsukanaka, T.; Nomoto, T.; Ayaguchi, Y.; Izawa, Y. *Tetrahedron* **1985**, *41*, 2387–2392.
- 323 Caddick, S.; Judd, D. B.; Lewis, A. K. D. K.; Reich, M. T.; Williams, M. R. V. *Tetrahedron* **2003**, *59*, 5417–5423.
- 324 Caddick, S.; Alexandra, A. K.; Judd, D. B.; Williams, M. R. V. *Tetrahedron Lett.* **2000**, *41*, 3513–3516.
- 325 Khurana, J. M.; Kukreja, G. *Synth. Commun.* **2002**, *32*, 1265–1269.
- 326 Feng, L. W.; Ren, H.; Xiong, H.; Wang, P.; Wang, L.; Tang, Y. *Angew. Chemie - Int. Ed.* **2017**, *56*, 3055–3058.
- 327 DiLauro, A. M.; Seo, W.; Phillips, S. T. *J. Org. Chem.* **2011**, *76*, 7352–7358.
- 328 Sato, M.; Ohuchi, H.; Abe, Y.; Kaneko, C. *Tetrahedron: Asymmetry* **1992**, *3*, 313–328.
- 329 Hasegawa, T.; Arata, Y.; Kageyama, A. *Tetrahedron Lett.* **1983**, *24*, 1995–1996.
- 330 Hasegawa, T.; Arata, Y.; Endoh, M.; Yoshioka, M. *Tetrahedron* **1985**, *41*, 1667–1673.
- 331 Heng, R.; Zard, S. Z. *Tetrahedron Lett.* **2015**, *56*, 3679–3682.
- 332 Secci, F.; Frongia, A.; Piras, P. P. *Molecules* **2013**, *18*, 15541–15572.
- 333 De Mayo, P.; Takeshita, H. *Can. J. Chem.* **1963**, *41*, 440–449.
- 334 Fujioka, H.; Komatsu, H.; Miyoshi, A.; Murai, K.; Kita, Y. *Tetrahedron Lett.* **2011**, *52*, 973–975.

- 335 Kuwajima, I.; Azegami, I. *Tetrahedron Lett.* **1979**, 20, 2369–2372.
- 336 Gembus, V.; Karmazin, L.; Pira, S.; Uguen, D. *Bull. Chem. Soc. Jpn.* **2018**, 91, 319–336.
- 337 Rousseau, G.; Quendo, A. *Tetrahedron* **1992**, 48, 6361–6370.
- 338 Patai, S. *The Chemistry of Amino, Nitroso, Nitro and Related Groups*, John Wiley & Sons, Inc., **1996**.
- 339 Ono, N. *The Nitro Group in Organic Synthesis*, Wiley-VCH, **2001**.
- 340 Noland, W. E. *Chem. Revs.* **1955**, 1899, 137–155.
- 341 Malek M., A.; Blanchard, P.; Fourrey, J.-L.; Robert-Gero, M. *Tetrahedron Lett.* **1990**, 31, 7003–7006.
- 342 Hagen, T. J.; Bergmanis, A. A.; Kramer, S. W.; Fok, K. F.; Schmelzer, A. E.; Pitzele, B. S.; Swenton, L.; Jerome, G. M.; Kornmeier, C. M.; Moore, W. M.; Branson, L. F.; Connor, J. R.; Manning, P. T.; Currie, M. G.; Hallinan, E. A. *J. Med. Chem.* **1998**, 41, 3675–3683.
- 343 Chen, Y.-J.; Chang, W.-H. *J. Org. Chem.* **1996**, 61, 2536–2539.
- 344 Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, 105, 933–971.
- 345 Ballini, R.; Petrini, M.; Rosini, G. *Synthesis* **1987**, 1987, 711–713.
- 346 Wang, W.; Ye, L.; Shi, Z.; Zhao, Z.; Li, X. *RSC Adv.* **2018**, 8, 41699–41704.
- 347 Yamaguchi, M.; Shiraishi, T.; Hiramata, M. *J. Org. Chem.* **1996**, 61, 3520–3530.
- 348 Krapcho, A. P. *Synthesis* **1982**, 1982, 805–822.
- 349 Krapcho, A. P. *Synthesis* **1982**, 1982, 893–914.
- 350 Nugroho, A. E.; Morita, H. *J. Nat. Med.* **2014**, 68, 1–10.
- 351 Landais, Y.; Robert, F.; Godineau, E.; Huet, L.; Likhite, N. *Tetrahedron* **2013**, 69, 10073–10080.
- 352 Pandey, G.; Mishra, A.; Khamrai, J. *Org. Lett.* **2017**, 19, 3267–3270.
- 353 Pandey, G.; Khamrai, J.; Mishra, A. *Org. Lett.* **2018**, 20, 166–169.
- 354 Vorotyntsev, A. V.; Petukhov, A. N.; Vorotyntsev, I. V.; Sazanova, T. S.; Trubyanov, M. M.; Kopersak, I. Y.; Razov, E. N.; Vorotyntsev, V. M. *Appl. Catal. B Environ.* **2016**, 198, 334–346.
- 355 Prathap, K. J.; Wu, Q.; Olsson, R. T.; Dinér, P. *Org. Lett.* **2017**, 19, 4746–4749.
- 356 Wade, R. C.; Holah, D. G.; Hughes, A. N.; Hui, B. C. *Catal. Rev.* **1976**, 14, 211–246.
- 357 Khurana, J. M.; Gogia, A. *Org. Prep. Proced. Int.* **1997**, 29, 1–32.
- 358 Paul, R.; Buisson, P.; Joseph, N. *Ind. Eng. Chem.* **1952**, 44, 1006–1010.
- 359 Idzik, T. J.; Myk, Z. M.; Sośnicki, J. G. *J. Org. Chem.* **2019**, 84, 8046–8066.
- 360 Narasaka, K.; Soai, K.; Mukaiyama, T. *Chem. Lett.* **1974**, 3, 1223–1224.
- 361 Loh, T. P.; Wei, L. L. *Tetrahedron* **1998**, 54, 7615–7624.
- 362 England, D. B.; Padwa, A. *J. Org. Chem.* **2008**, 73, 2795–2802.
- 363 Mejía-Oneto, J. M.; Padwa, A. *Helv. Chim. Acta* **2008**, 91, 285–302.
- 364 Li, Z.; Zhang, S.; Wu, S.; Shen, X.; Zou, L.; Wang, F.; Li, X.; Peng, F.; Zhang, H.; Shao, Z. *Angew. Chemie - Int. Ed.* **2013**, 52, 4117–4121.
- 365 Jing, P.; Yang, Z.; Zhao, C.; Zheng, H.; Fang, B.; Xie, X.; She, X. *Chem. - A Eur. J.* **2012**, 18, 6729–6732.
- 366 Hall, H. K.; Shaw, R. G.; Deutschmann, A. *J. Org. Chem.* **1980**, 45, 3722–3724.
- 367 Buchanan, G. L.; Kitson, D. H.; Mallinson, P. R.; Sim, G. A.; White, D. N. J.; Cox, P. J. *J. Chem. Soc. Perkin Trans. 2* **1983**, 1709.
- 368 Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769–3772.
- 369 Carrión, M. D.; Chayah, M.; Entrena, A.; López, A.; Gallo, M. A.; Acuña-Castroviejo, D.; Camacho, M. E. *Bioorg. Med. Chem.* **2013**, 21, 4132–4142.
- 370 Mason, J. J.; Bergman, J. *Org. Biomol. Chem.* **2007**, 5, 2486.
- 371 Tebikachew, B. E.; Börjesson, K.; Kann, N.; Moth-Poulsen, K. *Bioconj. Chem.* **2018**, 29, 1178–1185.
- 372 Cheng-Sánchez, I.; Carrillo, P.; Sánchez-Ruiz, A.; Martínez-Poveda, B.; Quesada, A. R.; Medina, M. A.; López-Romero, J. M.; Sarabia, F. J. *J. Org. Chem.* **2018**, 83, 5365–5383.
- 373 Steliou, K.; Poupart, M. A. *J. Am. Chem. Soc.* **1983**, 105, 7130–7138.
- 374 Chen, L.; Chen, F. E. *Synlett* **2017**, 28, 1134–1150.
- 375 Chavan, S. P.; Pasupathy, K.; Venkatraman, M. S.; Kale, R. R. *Tetrahedron Lett.* **2004**, 45, 6879–6882.
- 376 Darses, S.; Michaud, G.; Genêt, J. P. *Tetrahedron Lett.* **1998**, 39, 5045–5048.
- 377 Canning, P. S. J.; Maskill, H.; McCrudden, K.; Sexton, B. *Bull. Chem. Soc. Jpn.* **2002**, 75, 789–800.
- 378 Mo, F.; Dong, G.; Zhang, Y.; Wang, J. *Org. Biomol. Chem.* **2013**, 11, 1582–1593.
- 379 Felpin, F. X.; Nassar-Hardy, L.; Le Callonnec, F.; Fouquet, E. *Tetrahedron* **2011**, 67, 2815–2831.
- 380 Bonin, H.; Fouquet, E.; Felpin, F. X. *Adv. Synth. Catal.* **2011**, 353, 3063–3084.
- 381 Hubbard, A.; Okazaki, T.; Laali, K. K. *J. Org. Chem.* **2008**, 73, 316–319.
- 382 Molander, G. A.; Rivero, M. R. *Org. Lett.* **2002**, 4, 107–109.
- 383 Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, 33, 6299–6302.
- 384 Sandmeyer, T. *Berichte der Dtsch. Chem. Gesellschaft* **1884**, 17, 2650–2653.

- 385 Sandmeyer, T. *Berichte der Dtsch. Chem. Gesellschaft* **1884**, 17, 1633–1635.
- 386 Hodgson, H. H. *Chem. Rev.* **1947**, 40, 251–277.
- 387 Yagi, Y.; Kimura, H.; Arimitsu, K.; Ono, M.; Maeda, K.; Kusuhara, H.; Kajimoto, T.; Sugiyama, Y.; Saji, H. *Org. Biomol. Chem.* **2015**, 13, 1113–1121.
- 388 Molander, G. A.; Bernardi, C. R. *J. Org. Chem.* **2002**, 67, 8424–8429.
- 389 Darses, S.; Michaud, G.; Genêt, J.-P. *Tetrahedron Lett.* **1998**, 39, 5045–5048.
- 390 Yang, Z. P.; He, Q.; Ye, J. L.; Huang, P. Q. *Org. Lett.* **2018**, 20, 4200–4203.
- 391 Piemontesi, C.; Wang, Q.; Zhu, J. *Angew. Chemie - Int. Ed.* **2016**, 55, 6556–6560.
- 392 Kutney, J. P. In *Total Synthesis of Natural Products*, Vol. 3, John Wiley & Sons, Inc., **2007**, pp 273–438.
- 393 Mokřý, J.; Kompiš, I.; Spiteller, G. *Collect. Czechoslov. Chem. Commun.* **1967**, 32, 2523–2531.
- 394 Kompis, I.; Hesse, M.; Schmid, H. *Lloydia* **1971**, 34, 269–291.
- 395 Bartlett, M. F.; Taylor, W. I. *Tetrahedron Lett.* **1959**, 1, 20–22.
- 396 Wieland, T.; Neeb, E. *Justus Liebigs Ann. Chem.* **1956**, 600, 161–175.
- 397 Le Men, J.; Taylor, W. I. *Experientia* **1965**, 21, 508–510.
- 398 Saxton, J. E. In *Chemistry of Heterocyclic Compounds: Indoles, Part Four, The Monoterpenoid Indole Alkaloids*, Vol. 25, John Wiley & Sons, Inc., **2008**, pp 439–465.
- 399 Cava, M. P.; Tjoa, S. S.; Ahmed, Q. A.; Da Rocha, A. I. *J. Org. Chem.* **1968**, 33, 1055–1059.
- 400 Awang, K.; Païs, M.; Sévenet, T.; Schaller, H.; Nasir, A. M.; Hadi, A. H. A. *Phytochemistry* **1991**, 30, 3164–3167.
- 401 Hava, M. In *The Catharanthus alkaloids: Botany, chemistry, pharmacology, and clinical use*, Marcel Dekker, **1973**, p 305.
- 402 Ho, T. L.; Chen, C. K. *Helv. Chim. Acta* **2005**, 88, 2764–2770.
- 403 Lounasmaa, M.; Din Belle, D.; Tolvanen, A. *Heterocycles* **1999**, 51, 1125.
- 404 Svoboda, G. H.; Gorman, M.; Barnes, A. J.; Oliver, A. T. *J. Pharm. Sci.* **1962**, 51, 518–523.
- 405 Mitra, A. K.; Patra, A.; Mukhopadhyay, A. K. *Phytochemistry* **1981**, 20, 865–866.
- 406 Chong, K. W.; Yeap, J. S. Y.; Lim, S. H.; Weber, J. F. F.; Low, Y. Y.; Kam, T. S. *J. Nat. Prod.* **2017**, 80, 3014–3024.
- 407 Kutney, J. P.; Beck, J. F.; Nelson, V. R.; Sood, R. S. *J. Am. Chem. Soc.* **1971**, 93, 255–257.
- 408 Wenkert, E.; Wickberg, B. *J. Am. Chem. Soc.* **1965**, 87, 1580–1589.
- 409 Wenkert, E.; Wickberg, B. *J. Am. Chem. Soc.* **1962**, 84, 4914–4919.
- 410 Lounasmaa, M.; Tolvanen, A. In *The Alkaloids: Chemistry and Pharmacology*, Elsevier Inc., **1992**, pp 1–116.
- 411 Feng, X. Z.; Kan, C.; Husson, H. P.; Potier, P.; Kan, S. K.; Lounasmaa, M. *J. Nat. Prod.* **1984**, 47, 117–122.
- 412 Hirasawa, Y.; Hara, M.; Nugroho, A. E.; Sugai, M.; Zaima, K.; Kawahara, N.; Goda, Y.; Awang, K.; Hadi, A. H. A.; Litaudon, M.; Morita, H. *J. Org. Chem.* **2010**, 75, 4218–4223.
- 413 Sévenet, T.; Allorge, L.; David, B.; Awang, K.; Hamid, A.; Hadi, A.; Kan-Fan, C.; Quirion, J.-C.; Remy, F.; Schaller, H.; Teo, L. E. *J. Ethnopharmacol.* **1994**, 41, 147–183.
- 414 Taylor, W. I.; Farnsworth, N. R. *The Vinca Alkaloids: Botany, Chemistry and Pharmacology*, Marcel Dekker, **1973**.
- 415 Vas, Á.; Gulyás, B. *Med. Res. Rev.* **2005**, 25, 737–757.
- 416 Nemes, A.; Szántay jr, C.; Czibula, L.; Greiner, I. *Arkivoc* **2008**, 2008, 154.
- 417 Czibula, L.; Nemes, A.; Visky, G.; Farkas, M.; Szombathelyi, Z.; Kárpáti, E.; Sohár, P.; Kessel, M.; Kreidl, J. *Liebigs Ann. der Chemie* **1993**, 1993, 221–229.
- 418 Linée, P.; Lacroix, P.; Le Polles, J. B.; Auroousseau, M.; Boulu, R.; Van den Driessche, J.; Albert, O. *Eur. Neurol.* **1978**, 17, 113–120.
- 419 Vereczkey, L.; Tamás, J.; Czira, G.; Szporny, L. *Arzneimittelforschung.* **1980**, 30, 1860–1865.
- 420 Lörincz, Cs.; Szász, K.; Kisfaludy, L. *Arzneimittelforschung.* **1976**, 26, 1907.
- 421 Ellies, D.; Rosenberg, W. US2010000 3324 (A1), **2010**.
- 422 Desmaële, D.; Mekouar, K.; D'Angelo, J. *J. Org. Chem.* **1997**, 62, 3890–3901.
- 423 Pictet, A.; Spengler, T. *Berichte der Dtsch. Chem. Gesellschaft* **1911**, 44, 2030–2036.
- 424 Bischler, A.; Napieralski, B. *Berichte der Dtsch. Chem. Gesellschaft* **1893**, 26, 1903–1908.
- 425 Kuehne, M. E. *J. Am. Chem. Soc.* **1964**, 86, 2946–2946.
- 426 Li, G.; Piemontesi, C.; Wang, Q.; Zhu, J. *Angew. Chemie - Int. Ed.* **2019**, 58, 2870–2874.
- 427 Atta-ur-Rahman. *J. Chem. Soc. Perkin Trans. 1* **1972**, 731.
- 428 Smith, M. W.; Ferreira, J.; Hunter, R.; Venter, G. A.; Su, H. *Org. Lett.* **2019**, 21, 8740–8745.
- 429 Oppolzer, W.; Hauth, H.; Pfäffli, P.; Wenger, R. *Helv. Chim. Acta* **1977**, 60, 1801–1810.
- 430 Zhou, Q.; Dai, X.; Song, H.; He, H.; Wang, X.; Liu, X. Y.; Qin, Y. *Chem. Commun.* **2018**, 54, 9510–

- 9512.
- 431 Wang, X. *Chem* **2017**, 2, 749–750.
- 432 Wang, X.; Xia, D.; Qin, W.; Zhou, R.; Zhou, X.; Zhou, Q.; Liu, W.; Dai, X.; Wang, H.; Wang, S.; Tan, L.; Zhang, D.; Song, H.; Liu, X. Y.; Qin, Y. *Chem* **2017**, 2, 803–816.
- 433 Xu, Z.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2013**, 135, 19127–19130.
- 434 Bartlett, M. F.; Taylor, W. I. *J. Am. Chem. Soc.* **1960**, 82, 5941–5946.
- 435 Barton, J. E. D.; Harley-Mason, J. *Chem. Commun.* **1965**, 298–299.
- 436 Wenkert, E. *Acc. Chem. Res.* **1968**, 1, 78–81.
- 437 Klatte, F.; Rosentreter, U.; Winterfeldt, E. *Angew. Chemie* **1977**, 89, 916–917.
- 438 Hakam, K.; Thielmann, M.; Thielmann, T.; Winterfeldt, E. *Tetrahedron* **1987**, 43, 2035–2044.
- 439 Imanishi, T.; Miyashita, K.-I.; Nakai, A.; Inoue, M.; Hanaoka, M. *Chem. Pharm. Bull.* **1983**, 31, 1191–1198.
- 440 Shono, T.; Matsumura, Y.; Ogaki, M.; Onomura, O. *Chem. Lett.* **1987**, 16, 1447–1450.
- 441 Magnus, P.; Pappalardo, P.; Southwell, I. *Tetrahedron* **1986**, 42, 3215–3222.
- 442 Takano, S.; Yonaga, M.; Morimoto, M.; Ogasawara, K. *J. Chem. Soc. Perkin Trans. 1* **1985**, 305–309.
- 443 Liu, L. T.; Hong, P. C.; Huang, H. L.; Chen, S. F.; Wang, C. L. J.; Wen, Y. S. *Tetrahedron Asymmetry* **2001**, 12, 419–426.
- 444 Xing, X.; O'Connor, N. R.; Stoltz, B. M. *Angew. Chemie - Int. Ed.* **2015**, 54, 11186–11190.
- 445 Ishikawa, H.; Takayama, H.; Aimi, N. *Tetrahedron Lett.* **2002**, 43, 5637–5639.
- 446 Martin, A.; Salazar, J. A.; Suárez, E. *J. Org. Chem.* **1996**, 61, 3999–4006.
- 447 Jia, K.; Zhang, F.; Huang, H.; Chen, Y. *J. Am. Chem. Soc.* **2016**, 138, 1514–1517.
- 448 Pandey, G.; Khamrai, J. *Asian J. Org. Chem.* **2016**, 5, 621–624.
- 449 Lounasmaa, M.; Karvinen, E. *Tetrahedron* **1991**, 41, 6371–6380.
- 450 Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, 93, 1307–1370.
- 451 Wenkert, E.; Hudlicky, T. *J. Org. Chem.* **1988**, 53, 1953–1957.
- 452 Pedersen, B. S.; Lawesson, S.-O. *Tetrahedron* **1979**, 35, 2433–2437.
- 453 Vinczer, P.; Kovacs, T.; Novak, L.; Szántay, C. *Org. Prep. Proced. Int.* **1989**, 21, 232–237.
- 454 Gotoh, H.; Sears, J. E.; Eschenmoser, A.; Boger, D. L. *J. Am. Chem. Soc.* **2012**, 134, 13240–13243.
- 455 Ueda, H.; Satoh, H.; Matsumoto, K.; Sugimoto, K.; Fukuyama, T.; Tokuyama, H. *Angew. Chemie Int. Ed.* **2009**, 48, 7600–7603.
- 456 Nicolaou, K. C.; Dalby, S. M.; Li, S.; Suzuki, T.; Chen, D. Y. K. *Angew. Chemie - Int. Ed.* **2009**, 48, 7616–7620.
- 457 Rege, P. D.; Tian, Y.; Corey, E. J. *Org. Lett.* **2006**, 8, 3117–3120.
- 458 Van Beek, T. A.; Verpoorte, R.; Svendsen, A. B. *Tetrahedron Lett.* **1984**, 25, 2057–2060.
- 459 Magnus, P.; Brown, P. J. *Chem. Soc., Chem. Commun.* **1985**, 1985, 184–186.
- 460 Honty, K.; Szántay, C.; Kolonits, P.; Demeter, Á.; Szántay, C. *Tetrahedron* **1993**, 49, 10421–10426.
- 461 Danieli, B.; Lesma, G.; Palmisano, G.; Passarella, D.; Pyuskyulev, B.; Ngoc, T. M. *J. Org. Chem.* **1994**, 59, 5810–5813.
- 462 Burchat, A. F.; Chong, J. M.; Nielsen, N. J. *Organomet. Chem.* **1997**, 542, 281–283.
- 463 Palatinus, L.; Chapuis, G. *J. Appl. Crystallogr.* **2007**, 40, 786–790.
- 464 Palatinus, L.; Prathapa, S. J.; Van Smaalen, S. *J. Appl. Crystallogr.* **2012**, 45, 575–580.
- 465 Sheldrick, G. M. *Acta Crystallogr. Sect. A Found. Crystallogr.* **2008**, 64, 112–122.
- 466 Macrae, C. F.; Bruno, I. J.; Chisholm, J. A.; Edgington, P. R.; McCabe, P.; Pidcock, E.; Rodriguez-Monge, L.; Taylor, R.; Van de Streek, J.; Wood, P. A. *J. Appl. Crystallogr.* **2008**, 41, 466–470.
- 467 Farney, E. P.; Feng, S. S.; Schäfers, F.; Reisman, S. E. *J. Am. Chem. Soc.* **2018**, 140, 1267–1270.
- 468 Liang, S.; Jasinski, J.; Hammond, G. B.; Xu, B. *Org. Lett.* **2015**, 17, 162–165.
- 469 Zhu, D.; Chen, L.; Zhang, H.; Ma, Z.; Jiang, H.; Zhu, S. *Angew. Chemie Int. Ed.* **2018**, 57, 12405–12409.
- 470 Evans, D. A.; Miller, S. J.; Lectka, T.; Von Matt, P. *J. Am. Chem. Soc.* **1999**, 121, 7559–7573.
- 471 Boukouvalas, J.; Cren, S.; Renaud, P. In *Encyclopedia of Reagents for Organic Synthesis*, John Wiley & Sons, Ltd., **2007**.
- 472 Betz, P.; Krueger, A. *ChemPhysChem* **2012**, 13, 2578–2584.
- 473 Carrión, M. D.; Chayah, M.; Entrena, A.; López, A.; Gallo, M. A.; Acuña-Castroviejo, D.; Camacho, M. E. *Bioorganic Med. Chem.* **2013**, 21, 4132–4142.
- 474 Fuentes, L.; Hernández-Juarez, M.; Terán, J.; Quintero, L.; Sartillo-Piscil, F. *Synlett* **2013**, 24, 878–882.

