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Total synthesis of eucophylline: a free-radical approach towards total synthesis of cytotoxic leucophyllidine

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

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SPÉCIALITÉ : CHIMIE ORGANIQUE

Par Haitham HASSAN

**TOTAL SYNTHESIS OF EUCOPHYLLINE.
A FREE-RADICAL APPROACH TOWARDS
TOTAL SYNTHESIS OF CYTOTOXIC LEUCOPHYLLIDINE**

Sous la direction du Prof. Yannick LANDAIS
(co-directeur : Dr. Frédéric ROBERT)

Soutenue le 23.09.2016

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Synthèse totale de l'Eucophylline. Approches radicalaires vers la synthèse totale de la Leucophyllidine

Résumé : La thèse décrit la première synthèse totale de l'Eucophylline, le fragment sud de l'alkaloïde Leucophyllidine récemment isolé à partir de *Leuconotis griffithii* et *L. eugenifolius*. La synthèse en 10 étapes comprend une nouvelle méthode d'accès au squelette azabicyclo[3.3.1]nonane par un processus de carbo-oximation radicalaire d'oléfines à trois composants. Au cours de ces études, nous avons également isolé des énamines présentant des stabilités inhabituelles résultant de leur conformation bicyclique tendue. La synthèse de la partie éburnane, le fragment nord de la Leucophyllidine, a été réalisée grâce à une nouvelle réaction radicalaire de carbo-cyanation à trois composants. Cette réaction radicalaire s'est révélée efficace pour installer le groupement fonctionnel nitrile sur des oléfines, et éventuellement former des centres quaternaires, notamment dans des structures complexes, puisqu'une bonne tolérance aux différents groupes fonctionnels a été observée. Le couplage biomimétique entre le squelette éburnane et l'Eucophylline a finalement été étudié en utilisant des modèles de structure similaire. Les résultats préliminaires de cette étude ont montré que l'absence d'effet *gem*-diméthyle dans le modèle éburnane empêche probablement la formation de l'imine cyclique, intermédiaire-clé dans le couplage désiré.

Mots clés : Eucophylline, Synthèse totale, alcaloïdes bisindoliques, carbo-cyanation, amides contraints.

Total Synthesis of Eucophylline. A free-Radical Approach towards Total Synthesis of Cytotoxic Leucophyllidine

Abstract: The thesis describes the first total synthesis of Eucophylline, the south fragment of the Leucophyllidine alkaloid recently isolated from *Leuconotis griffithii* and *L. eugenifolius*. The 10-step synthesis encompasses a new straightforward method to access to the azabicyclo[3.3.1]nonane skeleton through a free-radical three-component olefinic carbo-oximation process. During these studies, we also isolated enamines exhibiting unusual stabilities resulting from their strained bicyclic conformation. The synthesis of the Eburnane part, the north fragment of Leucophyllidine, was developed relying on a new free-radical three-component Carbo-Cyanation reaction. This new reaction showed high tolerance toward different functional groups and provided an efficient mean to install the nitrile group in complex structures and to introduce quaternary centers. The biomimetic coupling between the Eburnane and Eucophylline fragments was finally studied using structurally similar models. Preliminary results of this model study showed that absence of a *gem*-dimethyl effect in the Eburnane model probably prevents the formation of the cyclic imine, key intermediate for the desired coupling.

Keywords: Eucophylline, Total synthesis, Bisindole alkaloids, Carbo-Cyanation, Twisted amides.

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List of Abbreviations

Ac:	Acetyl
MeCN:	Acetonitrile
atm:	Atmospher
AIBN:	Azobis(isobutyronitrile)
ACCN:	1,1'-Azobis(cyclohexane-1-carbonitrile)
aq:	Aqueous
Ar:	Aromatic
BDE	Bond Dissociation Energy
β:	Beta
9-BBN:	9-Borabicyclo[3.3.1]nonane
BINAP:	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyle
Boc:	Di- <i>tert</i> -butyloxycarbonyl
Bn:	Benzyl
Bz:	Benzoyl
<i>i</i> -Bu:	<i>iso</i> -butyl
<i>n</i> -Bu:	butyl
<i>s</i> -Bu:	<i>sec</i> -butyl
<i>t</i> -Bu:	<i>tert</i> -butyl
CAN:	Ceric ammonium nitrate
Cbz:	Carboxybenzoyl
COSY:	CORrelation SpectroscopY
CSA:	Camphorsulfonic acid
3-CR:	Three-components reaction
4-CR:	Four-components reaction
DBU:	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM:	Dichloromethane
DCC:	Dicyclohexacarbodiimide
DCE:	Dichloroethane
DEAD:	Diethyl azodicarboxylate
DIAD:	Diisopropyl azodicarboxylate
DIPEA:	(<i>N,N'</i> -diisopropylethylamine)
d.r.:	Diastereomeric ratio
DMAP:	Dimethylaminopyridine
DME:	Dimethoxyethane
DMF:	Dimethylformamide
DMSO:	Dimethylsulfoxide
DTBHN:	Di- <i>tert</i> -butylhyponitrite
DTBP:	Di- <i>tert</i> -butyl peroxide
DIBAL-H	Diisobutylaluminium hydride
Drierite	Calcium sulfate
E, E ⁺ :	Electrophile
ee.:	Enantiomeric excess
eq.:	Equivalent
Et:	Ether
Et ₃ B:	Triethylborane
EtOH:	Ethanol
Et ₃ N:	Triethylamine
Et ₂ O:	Diethyl ether
EtOAc:	Ethyl acetate

EWG:	Electron Withdrawing Group
EDG:	Electron Donating Group
FMO:	Frontier Molecular Orbitals
Florisol:	Synthetic magnesium silicate
g:	Gram
h:	Hour
IC ₅₀ :	half maximal inhibitory concentration
Im:	Imidazole
IR:	Infra-red spectroscopy
HOBT:	Hydroxybenzotriazole
HOMO:	Highest Occupied Molecular Orbital
HMPA:	Hexamethylphosphoramide
HSQC:	Heteronuclear Single Quantum Coherence
KHMDS:	Potassium bis(trimethylsilyl)amide
kcal:	Kilocalories
kg:	Kilogram
LDA:	Lithium diisopropylamide
LUMO:	Lowest Unoccupied Molecular Orbital
LA:	Lewis Acid
LB:	Lewis Base
LAH:	Lithium aluminium hydride
LG:	Leaving group
MCR	Multi-Component Reactions
Me:	Methyl
Ms:	Mesylate
MOM:	Methoxymethyl acetal
M:	Concentration (mole per liter)
MCRs:	Multicomponent reactions
<i>m</i> -CPBA	<i>meta</i> -chloro perbenzoic acid
MeOH:	Methanol
mg:	Milligram
mmHg:	Millimeter of mercury
MS:	Molecular sieves
MW:	Molecular weight
NBS:	N-bromosuccinimide
NIS:	N-iodosuccinimide
NMR:	Nuclear magnetic resonance
Nu, Nu ⁻ :	Nucleophilic
<i>o</i> - :	<i>Ortho</i>
ONs:	Nosylate = para nitrobenzenesulfonyl
<i>p</i> - :	<i>Para</i>
PTSA:	<i>para</i> -toluenesulfonic acid
PG:	Protecting Group
Ph:	Phenyl
Piv:	Pivlate
PMB:	<i>para</i> -Methoxybenzyl ether
<i>i</i> -Pr:	<i>iso</i> -propyl
Py:	pyridine
Quant.:	Quantitative
Red-Al	Sodium bis(2-methoxyethoxy)aluminium hydride
Rf:	Retention Factor
rt:	Room temperature

SOMO:	Singly Occupied Molecular Orbital
τ :	Torsional angle
χ_N :	Pyramidalization at nitrogen
<i>t</i> = <i>tert</i> -	<i>Tertio</i>
TBDPS:	<i>Tert</i> -butyldiphenylsilyl
TBDMS:	<i>Tert</i> -butyldimethylsilyl
TBAF:	Tetra- <i>n</i> -butylammonium fluoride
<i>t</i> -BuOK:	Potassium <i>tert</i> -butoxide
TEMPO:	2,2,6,6-Tetramethylpiperidine-N-oxy radical
THF:	Tetrahydrofuran
TLC:	Thin layer chromatography
TFA:	Trifluoroacetic acid
Tf:	Triflate
TMS:	Trimethyl silyl
TTMS:	Tris(trimethylsilyl)silyl
TPAP:	Tetrapropylammonium perruthenate
<i>p</i> -Tol:	<i>para</i> -Tolyl
Ts:	Tosyl

Résumé en Français

Cette thèse décrit la première synthèse totale de l'Eucophylline, alcaloïde isolé récemment de *Leuconotis eugenifolius*, et présentant un motif vinylquinoléine unique incorporant un système bicyclique. Une approche vers la synthèse totale de la Leucophyllidine, un nouvel alcaloïde bisindolique cytotoxique isolé de *Leuconotis griffithii* est également décrite. Dans les deux synthèses, nous nous sommes appuyés sur de nouvelles réactions radicalaires multi-composants, montrant l'utilité et l'efficacité des radicaux libres dans l'élaboration de structures complexes et la construction de centres quaternaires.

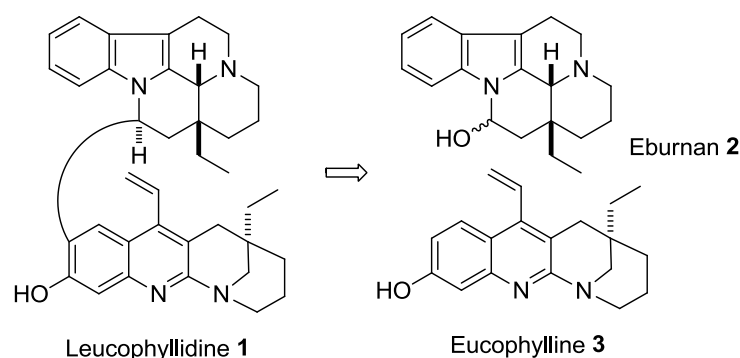


Schéma I. La Structure de Leucophyllidine et Eucophylline.

La première synthèse totale de l'Eucophylline a été réalisée en 10 étapes et un rendement global de 10%, avec, comme réaction-clé, un processus de carbo-oximation radicalaire récemment développé au laboratoire et mettant en jeu un précurseur de radicaux de type α -iodothioester **337**, une oléfine riche en électron **252** et une sulfonyloxime **233**. Cette réaction clé nous a permis d'introduire le centre quaternaire de l'Eucophylline et de concevoir un nouvel accès direct au squelette azabicyclo[3.3.1]nonane de manière efficace (Schéma II).

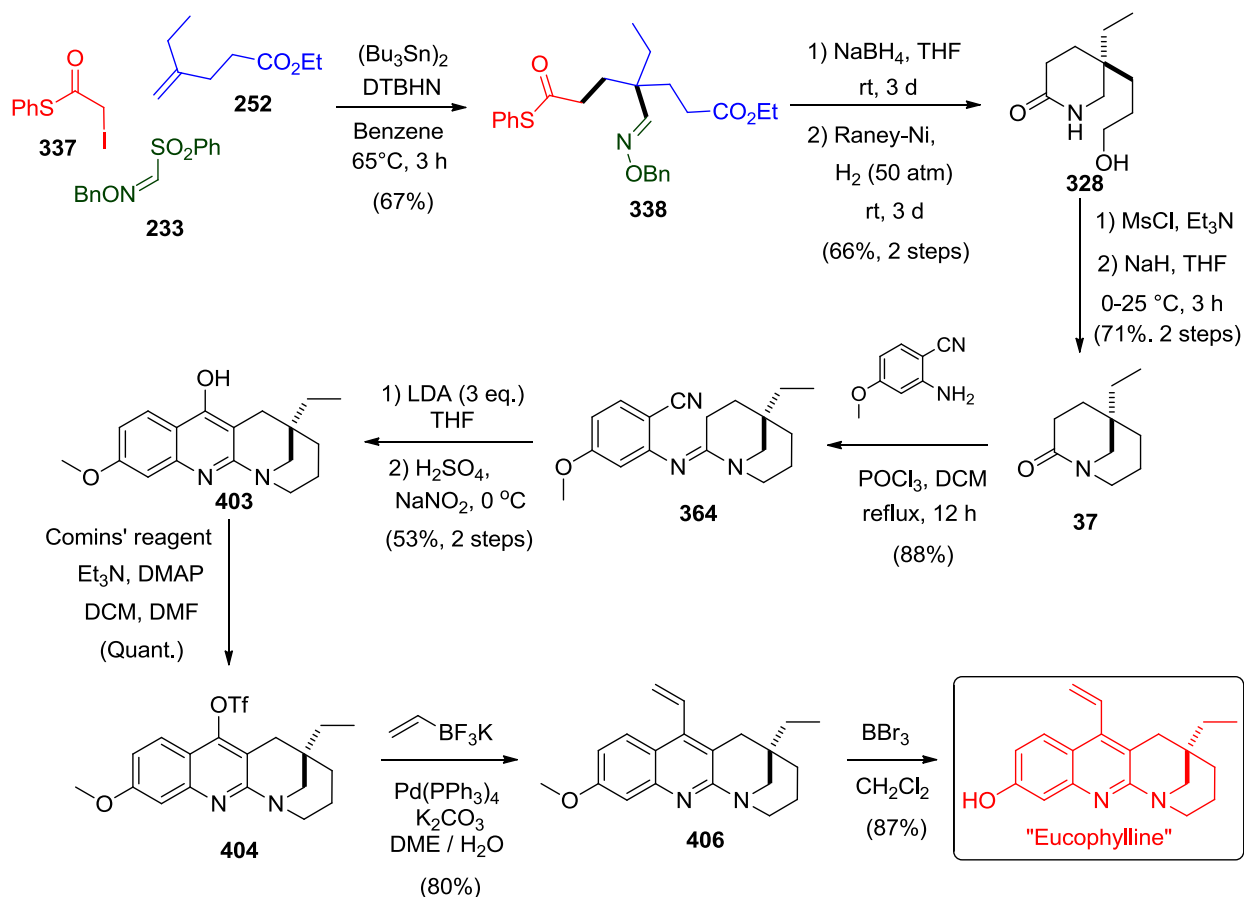
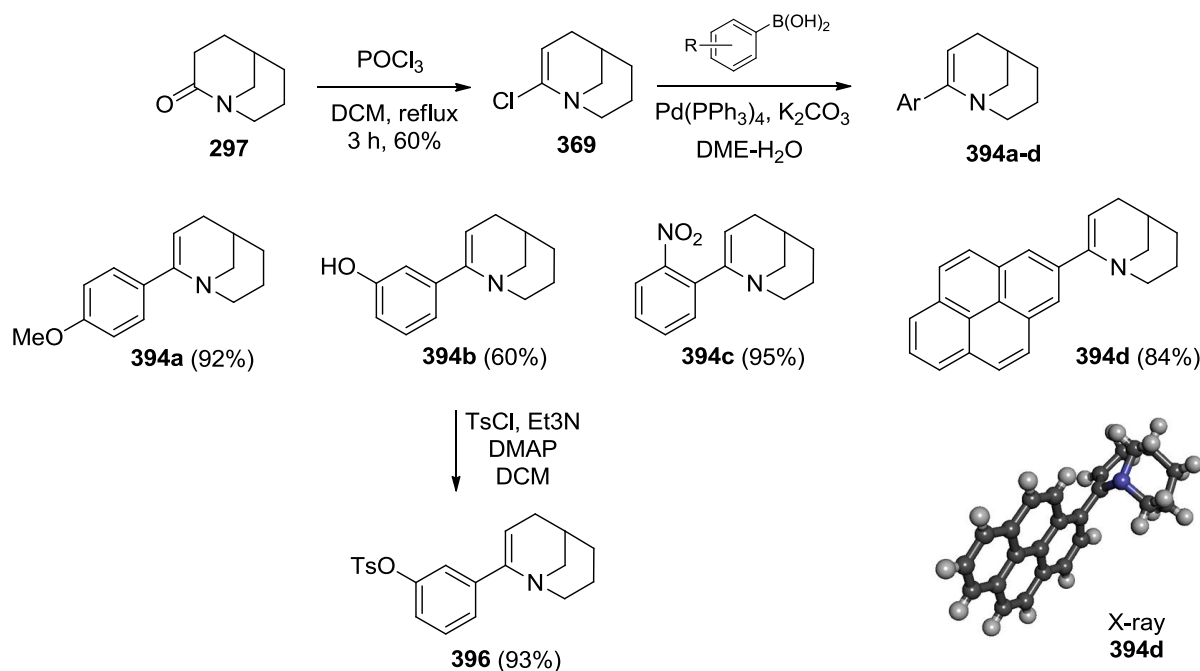
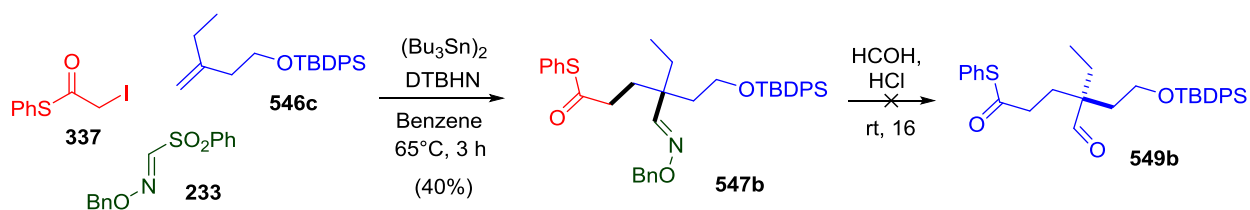


Schéma II. Synthèse de l'Eucophylline.

Lors de l'étude de la réaction entre les lactames bicycliques pontés avec des nucléophiles, nous avons montré que des intermédiaires α -chloroénamines remarquablement stables sont formés. La réactivité unique de la fonction amide, présente dans les lactames bicycliques, nous a permis d'isoler et de fonctionnaliser ces α -chloroénamines bicycliques **369**, illustrant l'importance de la conjugaison entre la paire d'électrons sur l'azote et le système π de l'énamine (Schéma III).

Schéma III. α -chloroénamine **369**, L'isolement et La Fonctionnalisation.

Lors de la synthèse du motif éburnane **2**, le fragment nord de la Leucophyllidine, le processus de carbo-oximation, très utile lors de la synthèse de Eucophylline, s'est avéré beaucoup moins efficace, en raison probablement de l'encombrement stérique autour du radical nucléophile qui gêne le piégeage de ce radical par la sulfonyloxime. De plus, la conversion de l'oxime **546b** en aldéhyde **549b** ne s'est pas avérée très efficace dans les différentes conditions testées (Schéma IV).

Schéma IV. Processus Carbo-Oximation avec l'oléfine **546c**.

A la recherche d'un groupe fonctionnel équivalent à un aldéhyde et compatible avec les processus radicalaires multi-composants, nous avons développé une nouvelle réaction radicalaire de carbo-cyanation. Les conditions de cette réaction ont montré une tolérance élevée vis-à-vis des différents précurseurs de radicaux et des oléfines. Par ailleurs, l'accepteur radicalaire, le cyanure de *p*-toluènesulfonyl **570**, est disponible commercialement et permet d'éviter les synthèses souvent longues et fastidieuses des autres accepteurs de sulfonyl. La valeur A du groupe nitrile (0.21) explique probablement la facilité de ce petit groupement à réagir avec les radicaux nucléophiles, même ceux encombrés (Schéma V).

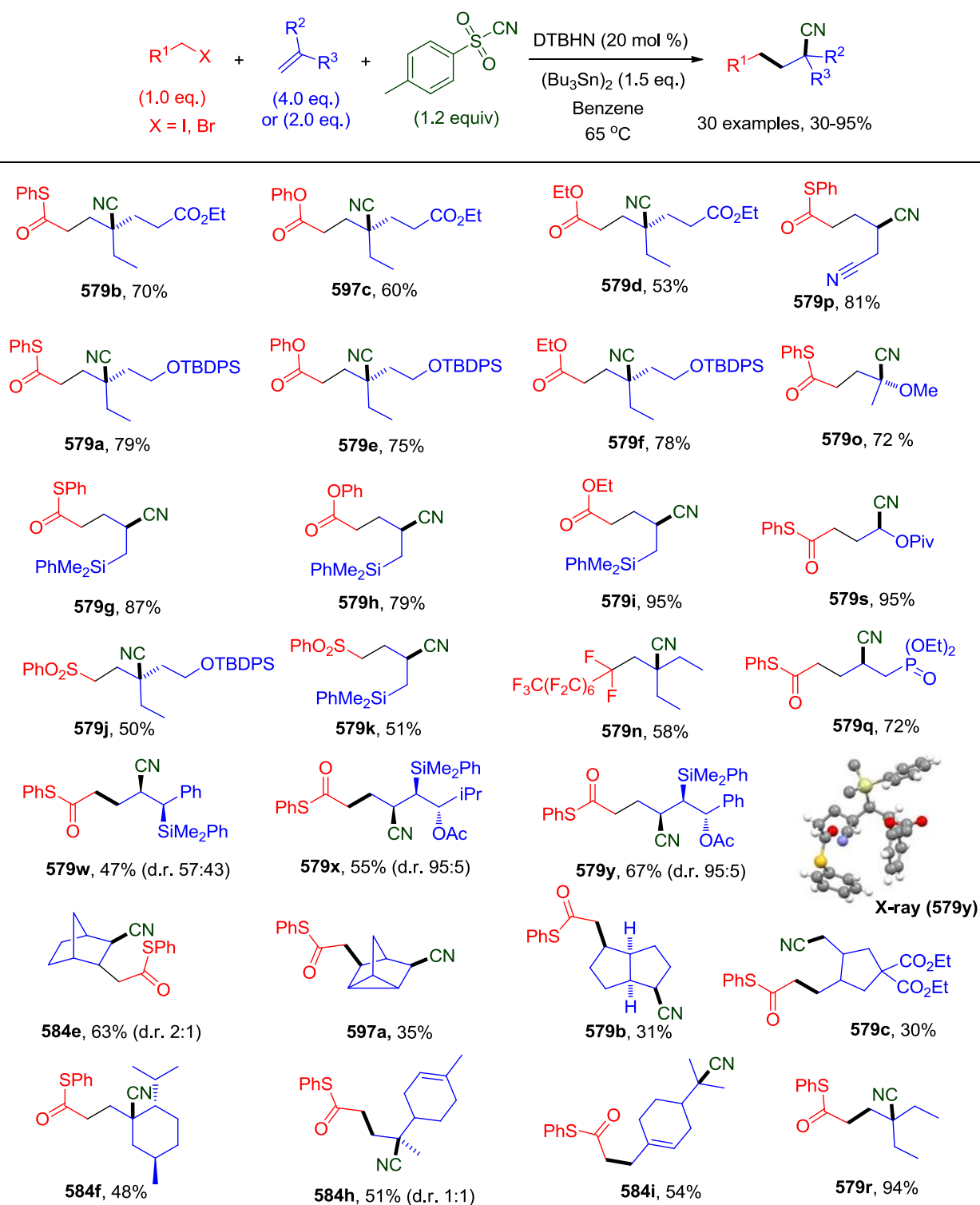
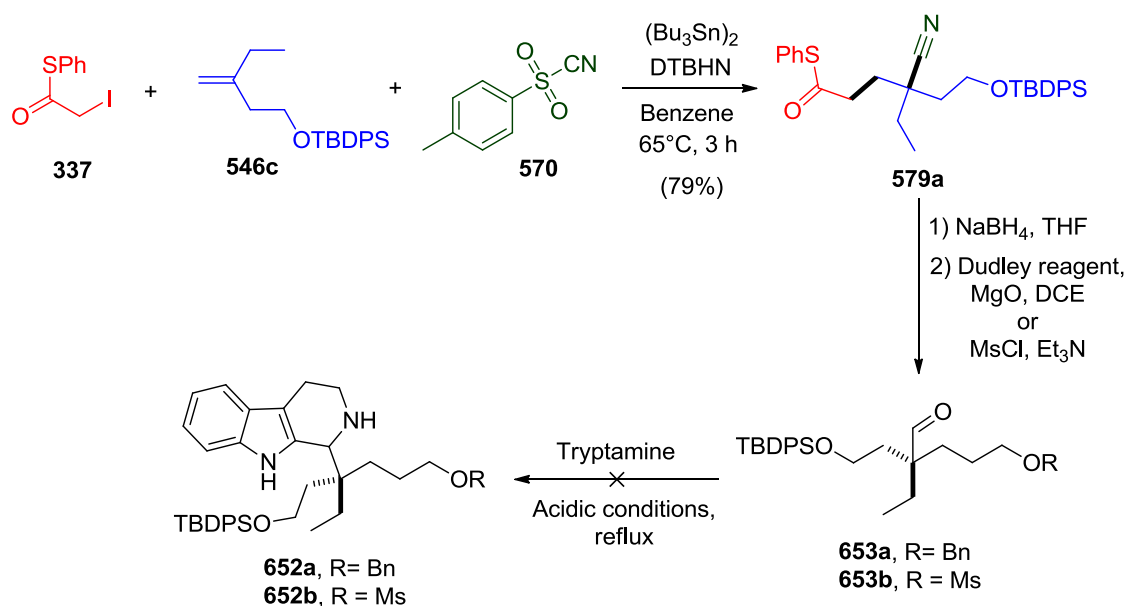


Schéma V. Champ d'application de la réaction de carbo-cyanation.

Sur la base de cette réaction de carbo-cyanation, deux approches ont été développées afin d'accéder au motif éburnane **2**, le fragment nord de la Leucophyllidine **1**. La première met en jeu une réaction de Pictet-Spengler entre la tryptamine et l'aldéhyde **653a-b** entièrement fonctionnalisé, et obtenu à partir du nitrile **579a** correspondant. Malheureusement, la réaction n'a pas conduit au produit attendu, les aldéhydes étant difficiles à isoler sous forme pure (Schéma VI).

Schéma VI. Synthèse d'un Eburnane via réaction de Pictet-Spengler avec aldéhydes **653a-b**.

Pendant, le chauffage à température élevée d'un mélange d'aldéhyde masqué sous forme lactol **639** et de tryptamine permet d'obtenir un produit de Pictet-Spengler, dont le centre quaternaire est sur une position inattendue. La formation de ce produit tétracyclique peut être rationalisée par l'encombrement stérique au voisinage de la fonction aldéhyde. Le produit formé résulte probablement d'une migration d'iminium par une réaction rédox interne (Schéma VII).

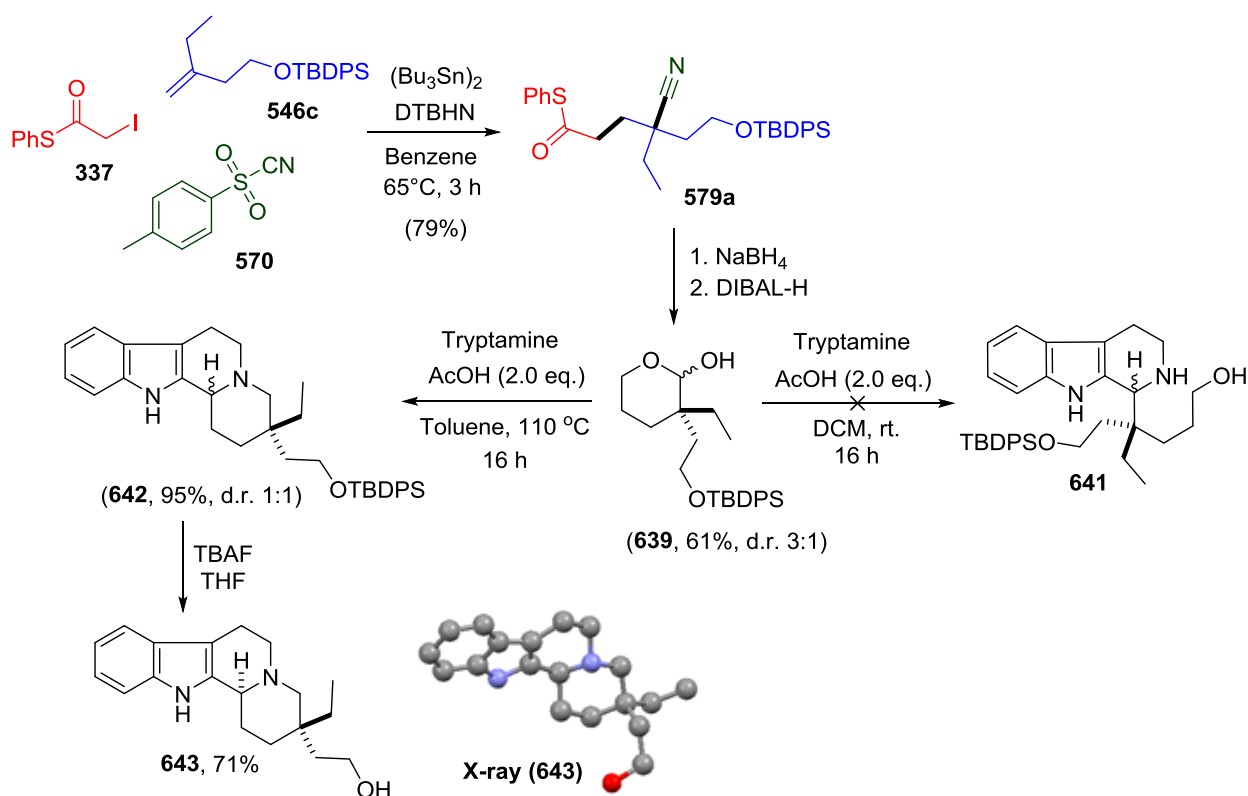


Schéma VII. Synthèse d'un Eburnane via une migration d'iminium.

La seconde approche est basée sur la condensation de Bischler-Napieralski. Le même produit de carbo-cyanation **579a**, que celui utilisé auparavant, constitue le précurseur-clé de cette approche. La réduction du groupe thioester en aldéhyde **654** a ainsi permis, dans des conditions réductrices, la réaction de ce dernier avec la tryptamine pour donner l'amine secondaire **655**. L'addition nucléophile de cette amine sur le nitrile a conduit au lactame **659**, intermédiaire-clé pour la condensation de Bischler-Napieralski. Malheureusement, la présence de l'alcool libre sur le lactame **659** produit un hémiaminal **662** au lieu de l'alcool tétracyclique attendu. La protection de l'alcool libre, suivie de la réaction de Bischler-Napieralski a finalement donné le produit tétracyclique **668** désiré mais avec un rendement faible et de manière peu reproductible (Schéma VIII).

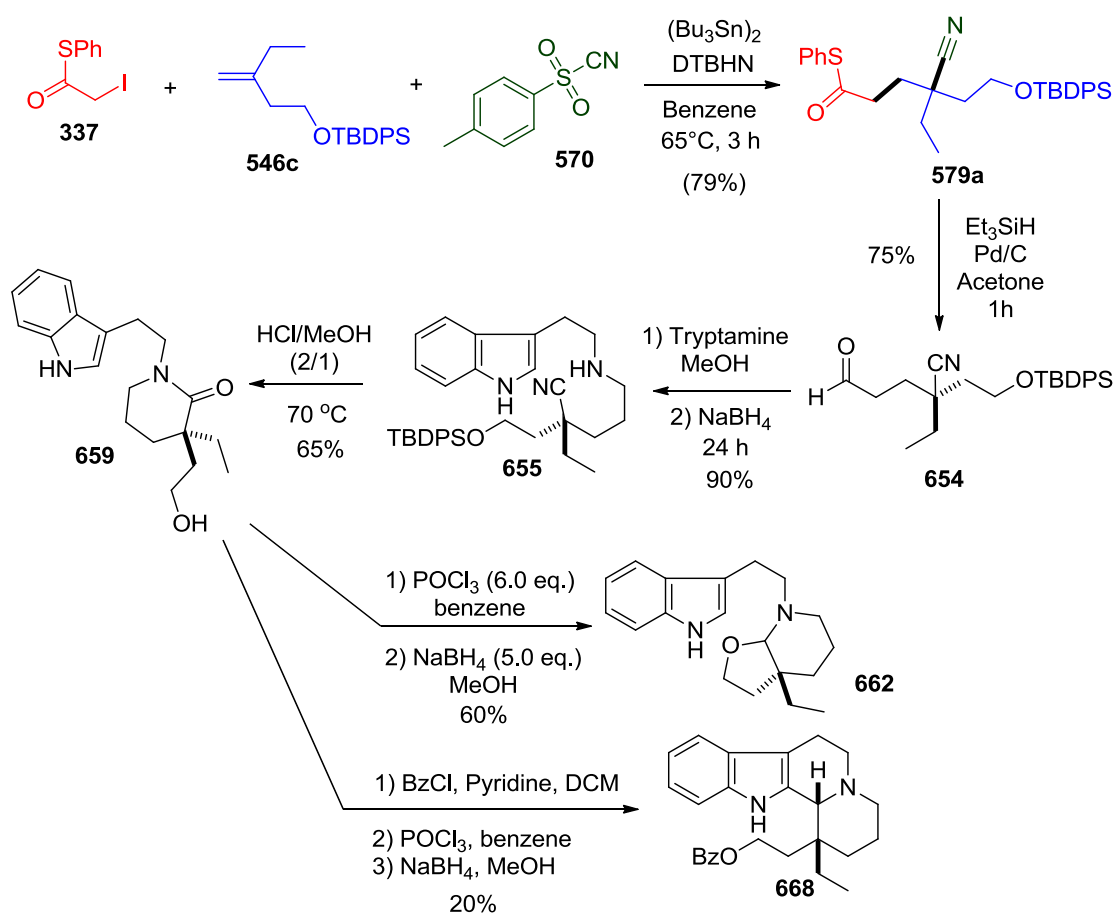


Schéma VIII. Synthèse d'un Eburnane via réaction de Bischler-Napieralski.

Le couplage biomimétique entre le motif éburnane **2** et l'Eucophylline **3** a été étudié à partir de modèles simplifiés. Ces derniers sont accessibles en un nombre d'étapes limitées à partir de matières premières disponibles dans le commerce. Les résultats préliminaires de cette étude de modèle ont montré que l'absence d'effet gem-diméthyle dans le modèle nord défavorise la formation de l'imine cyclique essentielle pour la réaction de couplage désirée (Schéma IX).

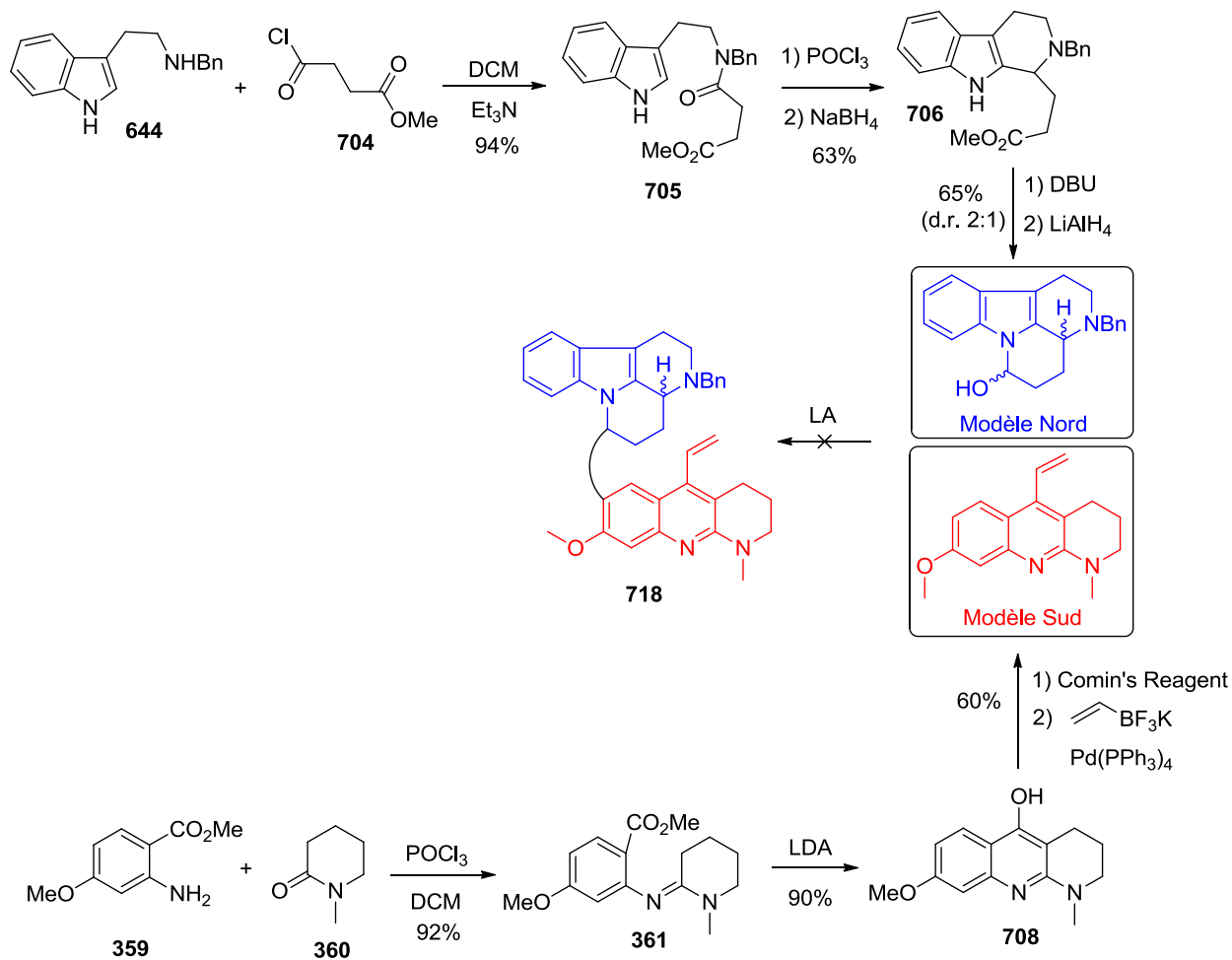


Schéma IX. Etude modèle du couplage biomimétique.

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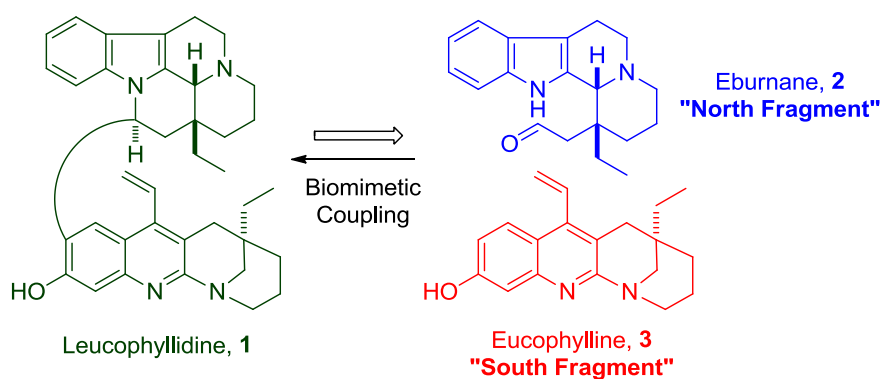
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Introduction

Introduction

In search for potent and natural anticancer agents, Leucophyllidine **1**, an unprecedented bisindole alkaloid, stands out as a promising chemotherapeutic agent that deserve deep attention. Leucophyllidine is a cytotoxic dimeric terpene bisindole alkaloid recently isolated by *Kam* and co-workers from the EtOH extract of the stem-bark of Malaysian Apocynaceae plant, *Leuconotis griffithii*.¹ This unprecedented bisindole alkaloid is constituted by an eburnane unit **2** and a novel tetrahydrobenzo-[b][1,8]naphthyridine ring system **3**, recently isolated by *Morita et al.* from *Leuconotis eugenifolius* and named Eucophylline.² This complex alkaloid exhibits pronounced *in vitro* cytotoxicity towards drug-sensitive as well as vincristine-resistant (VJ300) human KB cells with IC₅₀ values of 2.95 and 2.92 µg/mL respectively. In addition, Leucophyllidine inhibits NO production stimulated by LPS dose-dependently with IC₅₀ 7.1 µM. Both compounds, Leucophyllidine and Eucophylline, showed high cell viability in J774.1 cells at concentration of IC₅₀ 7.1 µM.



Scheme 1. Leucophyllidine and Eucophylline Structure.

1. Dimeric indole Alkaloids

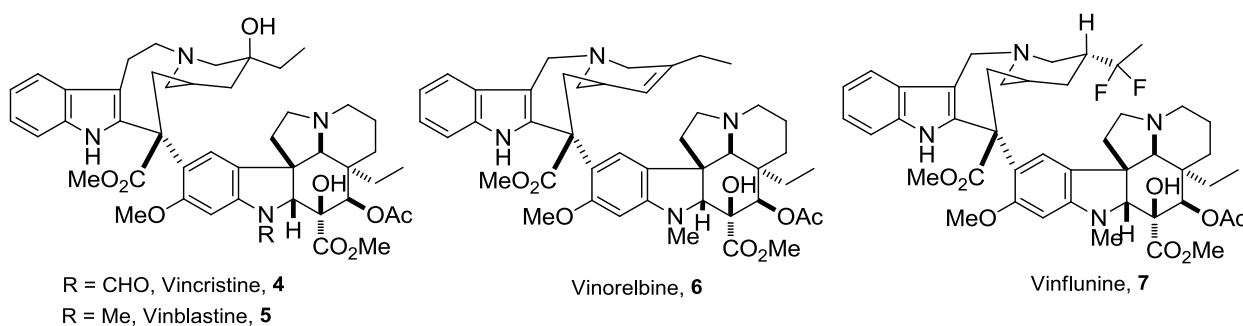
Terpene indole alkaloids, including their dimeric forms constitute a family of more than 3000 members, in which only a few exhibit physiological effects on mammals. Amongst the dimeric members, vinca alkaloids vincristine **4** and vinblastine **5** (Scheme 2), isolated for *Catharanthus roseus*,³ are the most well-known, the former is being used in the treatment of leukemia, while the latter was found active against Hodgkin's disease. Vinorelbine **6** (Navelbine®), a semi-synthetic vinca alkaloid obtained through extraction from catharanthus, was later introduced on the market by

¹ Gan, C.-Y. R., W. T.; Etoh, T.; Hayashi, M.; Komiyama, K.; Kam, T.-S. *Org. Lett.* **2009**, *11*, 3962-3965.

² Jun Deguchi, T. S., Alfarius E. Nugroho, Yusuke Hirasawa, Takahiro Hosoya, Osamu Shirota,; Khalijah Awang, A. H. A. H., and Hiroshi Morita *J. Nat. Prod.* **2010**, *73*, 1727-1729.

³ (a) Svoboda, G. H.; Blake, D. A. *The phytochemistry and pharmacology of Catharanthus roseus* in: Taylor, W. I.; Farnsworth, N. R. Eds. *The Catharanthus alkaloids*. Marcel Dekker, Inc., New-York, **1975**, 45-83; (b) Schmeller, T., Wink, M. *Utilization of alkaloids in modern medicine*, in: Roberts, M. F., Wink, M. Eds. *Alkaloids. Biochemistry, ecology and medicinal applications*. Plenum Press, New-York, **1998**, 435-459.

Potier and co-workers for the treatment of several types of cancers, including breast and non-small cell lung cancers.⁴ However, all these compounds are rather expensive. For instance, 1 kg of Vinblastine **6** costs around a million \$ and the annual production in the world is 12 kg. Similarly, 1 kg of Vincristine **4** costs 3.5 million \$, while the world annual production is about 1 kg, emphasizing on the difficulty to isolate and purify these dimeric alkaloids from the numerous by-products in the plant.⁵ These few indicators illustrate the value of such natural products but also their limited availability. Moreover, resistance tends to appear and research for new analogues becomes a priority. Promising fluorinated analogues of the above vinca alkaloids, including Vinflunine **7** have recently been launched and have shown anti-angiogenic activity, indicating that unusual functionalization of these dimeric indole alkaloids may still be a prospective area.⁶



Scheme 2. Dimeric Indole Alkaloids.

1.1 Biogenetic Pathways

Dimeric alkaloids are formed via the coupling of monomeric subunits belonging to the monoterpenoid indole alkaloids class.⁷ There are 2500 indole alkaloids isolated originally from three families of plants (*Rubiaceae/Naucleaceae*, *Loganiaceae/Strychnaceae* and *Apocynaceae*) (Scheme 3). Leucophyllidine and the above vinca alkaloids belong to the latter family. These alkaloids are issued from secologanin **8** and tryptamine **9**. This reaction is catalyzed by an enzyme, the strictosidine synthase, leading to strictosidine **10**, the basic monomeric alkaloid intermediate in the biosynthesis of indole alkaloids.⁸

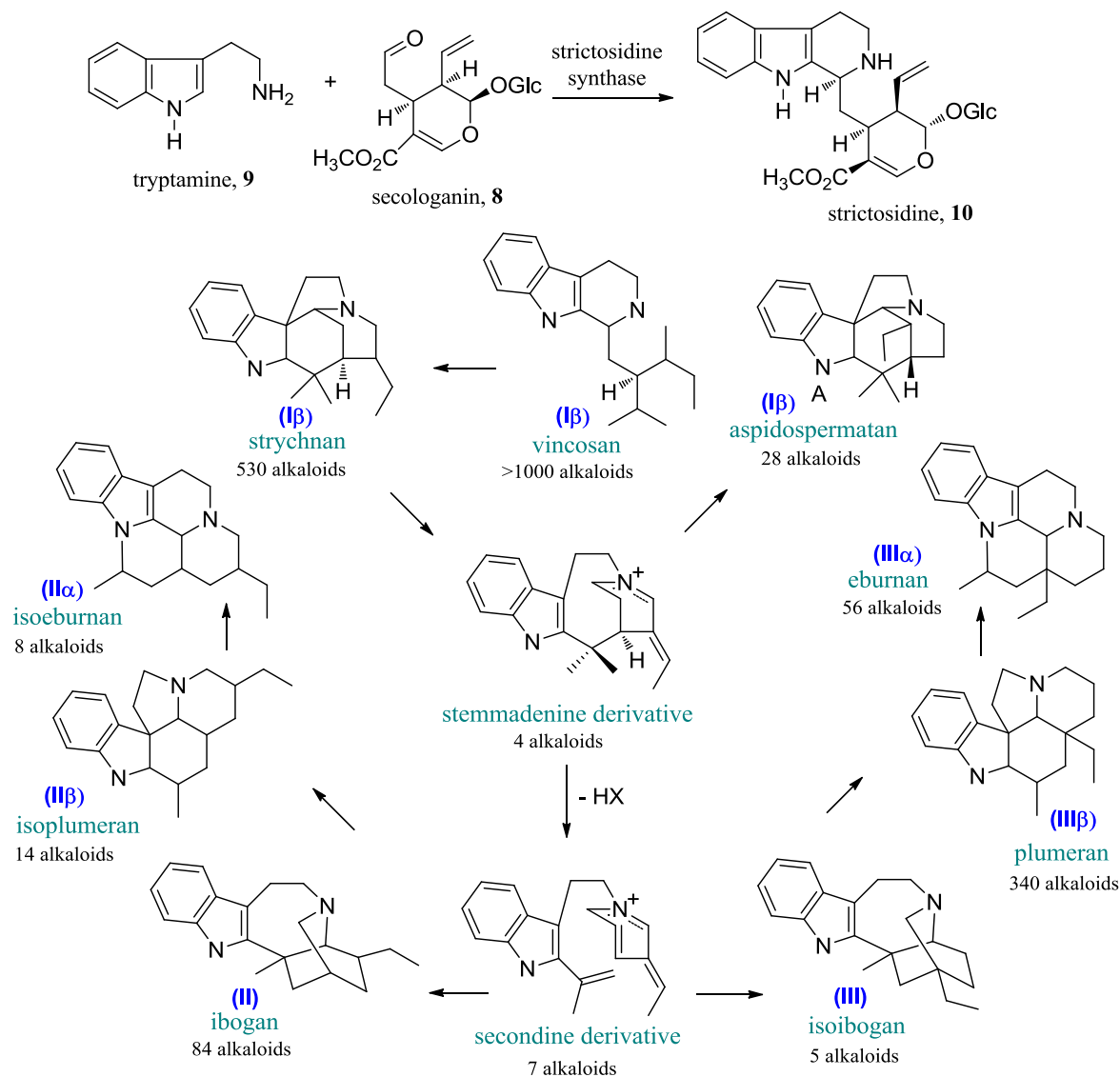
⁴ Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y.; Potier, P. *Tetrahedron* **1980**, *36*, 3053-3060.

⁵ DeLuca, V.; Laflamme, P. *Curr. Opi. Plant Biol.* **2001**, *4*, 225-233.

⁶ 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.

⁷ Szabo, L. F. *Molecules*, **2008**, *13*, 1875-1896.

⁸ Barleben, L.; Panjikar, S.; Ruppert, M.; Koepke, J.; Stöckigt, J. *The Plant Cell* **2007**, *19*, 2886-2897.



Scheme 3. System of Indole Alkaloids Derived from Secologanin.

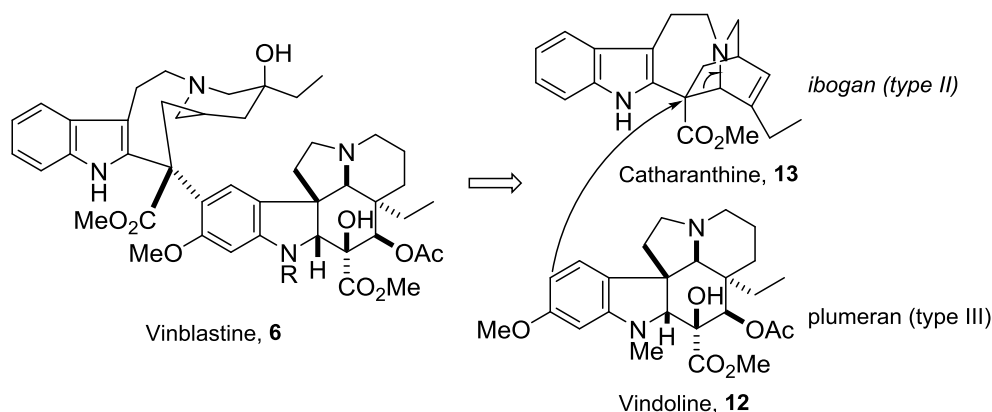
As shown above (Scheme 3), these monomeric alkaloids can be classified into several classes based in the type of skeleton I, II or III resulting from the further rearrangement of strictosidine. Rearrangement, ring contraction or extension may lead to more complex alkaloids. Depending on these different skeletons, dimers could be formed from the coupling of two monomeric indole alkaloids which will lead to more common heterodimeric indole alkaloids than homodimeric ones. Chemotaxonomic network could be found in the plant between these different alkaloids. Table 1 gives a summary about this network.

	Skeleton	Homodimer	Heterodimer*
Type I	vincosan I α	found	69] 8] 24]
	strychnan I β	found	
	aspidospermatan I β	indirect	
Type II	ibogan II	found	36] 4]
	isoplumeran II β	not found	
	isoeburnan II α	not found	
Type III	isoibogan III	not found	11]
	plumeran III β	found	
	eburnan III α	found	

* number of dimeric alkaloids beside bracket

Table 1. Summary of Chemotaxonomic Relationships between Indole Alkaloids.

As an archetypal example of such dimers, the synthesis of Vinblastine **6** was proposed, after a biogenetic analysis, to result from a direct coupling between a plumeran (type III) skeleton, represented by Vindoline **12**, and an ibogan (type II) skeleton, represented by catharanthine **13** (Scheme 4). This hypothesis,⁹ verified *in vivo*, has since been used by several synthetic chemists in their total synthesis plans.^{10,11}



Scheme 4. Vinblastine Biogenetic synthesis.

Recently Morita studied the biogenetic hypothesis that showed a Mannich-type coupling reaction between type I and III skeletons.¹²

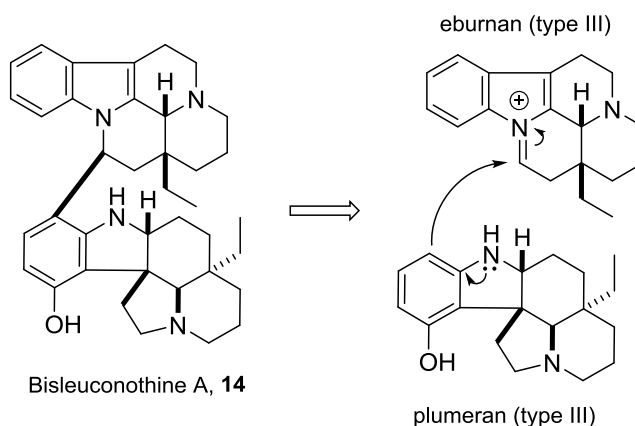
For example, Bisleuconothine A **14**, recently isolated from *Leuconotis griffithii*, showed this type of coupling (Scheme 5).¹³

⁹ Daddona, P. E.; Hutchinson, C. R. *J. Am. Chem. Soc.* **1974**, *96*, 6806-6807.

¹⁰ Langlois, N.; Gueritte, F.; Langlois, Y.; Potier, P. *J. Am. Chem. Soc.* **1976**, *98*, 7017-7024.

¹¹ 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.

¹² (a) Nugroho, A. E.; Hirasawa, Y.; Kawahara, N.; Goda, Y.; Awang, K.; Hadi, A. H.; Morita, H. *J. Nat. Prod.* **2009**, *72*, 1502-1506; (b) Zaima, K.; Hirata, T.; Hosoya, T.; Hurasawa, Y.; Koyama, K.; Rahman, A.; Kusumawati, I.; Zaini, N. C.; Shiro, M.; Morita, H. *J. Nat. Prod.* **2009**, *72*, 1686-1690; (c) Nugroho, A. E.; Hirasawa, Y.; Hosoya, T.; Awang, K.; Hadi, A. H.; Morita, H. *Tetrahedron Lett.* **2010**, *51*, 2589-2592.



Scheme 5. Bisleuconothine A Biogenetic Hypothesis.

2. Isolation and structure of Leucophyllidine and Eucophylline

Leucophyllidine **1** was isolated as a minor alkaloid from the EtOH extract of the stem-bark of *Leuconotis griffithii* in yield of 7.10 mg/Kg. It was obtained after several chromatographic fractionation of the basic fraction from the EtOH, then crystallization from Et₂O-EtOAc. The structure of Leucophyllidine was established unambiguously through X-ray diffraction studies (Figure 1).¹

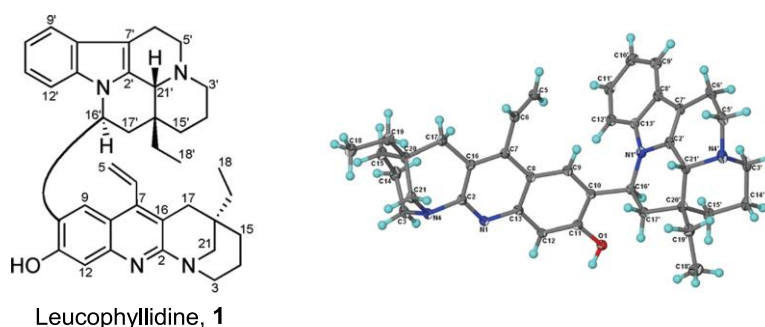


Figure 1. Leucophyllidine Structure.

While isolation of the tetracyclic vinylquinoline alkaloid, Eucophylline **3**, was achieved from the alkaloidal fraction prepared from a MeOH extract of the bark of *Leuconotis eugenifolius*.² This fraction was introduced to Sephadex LH-20, silica gel, and amino silica gel columns and ODS HPLC to give Eucophylline **3** (1.9 mg; 0.00039%) along with Leucophyllidine, Eburnamine, Leuconolam, and Rhazinilam. Eucophylline **3** is a brown powder with molecular formula C₁₉H₂₂N₂O, which was determined by HRESITOFMS. The relative structure of **3** was assigned by ROESY correlations as shown in computer generated 3D drawing. The ROESY correlations suggested that the piperidine ring of **3** adopts a chair conformation (Figure 2). The absolute

¹³ 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. *Bioorg. & Med. Chem. Lett.* **2010**, *20*, 2021-2024.

configuration of C-20 was assigned by comparing the experimental CD Spectra (Circular dichroism calculation) with the calculate CD spectra performed by Turbomole 6.1(Figure 3).¹⁴

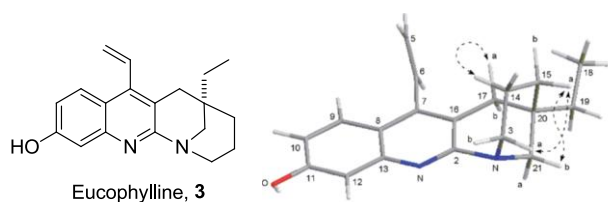


Figure 2. Eucophylline Structure.

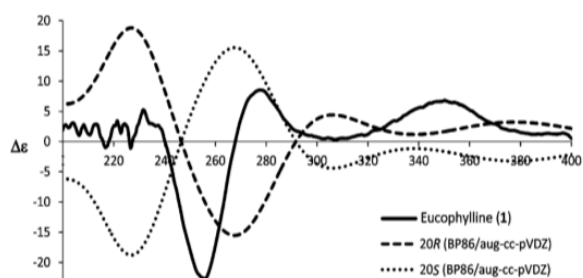


Figure 3. Experimental and calculated CD spectra for (R)-3 and (S)-3.

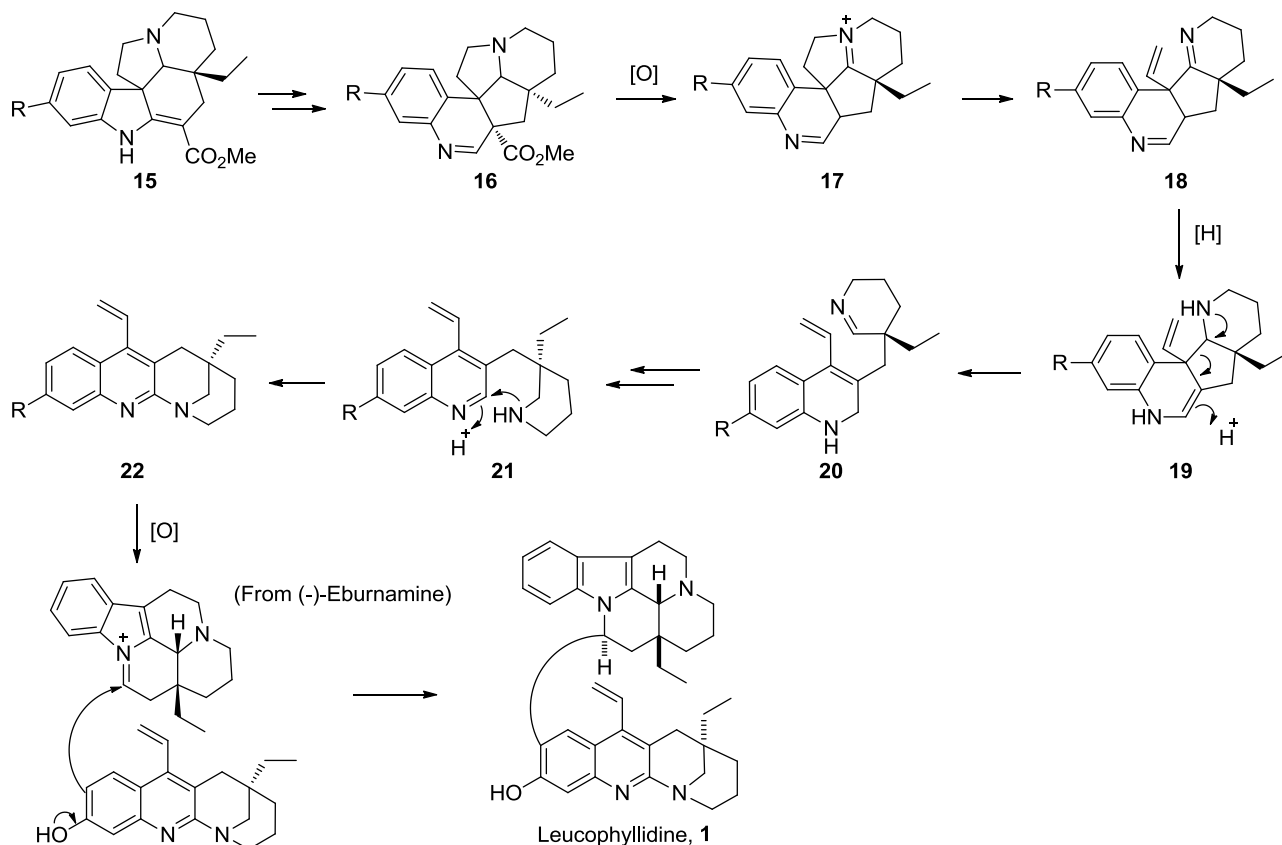
3. Biogenetic Pathways to Leucophyllidine and Eucophylline

Since Leucophyllidine has an unprecedented structure, new biogenic pathways had to be proposed. The originality of Leucophyllidine structure stems from two points. The first one is that Leucophyllidine represents the first member of new structural bisindole alkaloids based on the constituent monomeric halves.¹⁵ The second point is the vinylquinoline half, Eucophylline, constituted from a new unprecedented tetrahydrobenzo[b][1,8]naphthyridine skeleton. So the proposed biogenetic pathway is based on the fact that all the alkaloids present in *Leuconotis* are monoterpenoid indoles. A first proposed biogenetic pathway starts from the *Aspidosperma* precursor **15**.¹ This pathway was corrected later after an error in the configuration of the *Aspidosperma* precursor **15** (Scheme 6).¹⁶

¹⁴ Nugroho, A. E.; Morita, H. *J. Nat. Med.* **2014**, *68*, 1-10.

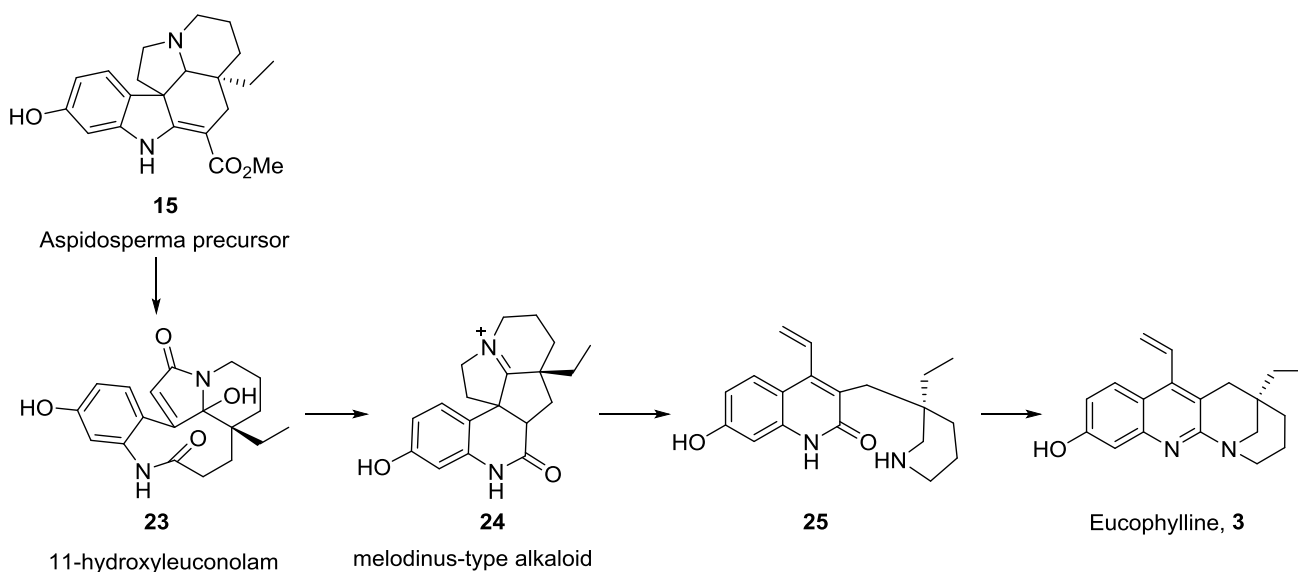
¹⁵ Kam, T. S.; Choo, Y. M. *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: Amsterdam, **2006**; Vol. 63, pp 181-337.

¹⁶ Gan, C.-Y.; Low, Y.-Y.; Robinson, W. T.; Komiyama, K.; Kam, T.-S. *Phytochemistry*. **2010**, *71*, 1365-1370.



Scheme 6. Possible Biogenetic Pathway to Leucophyllidine.

Nevertheless, another possible biogenetic pathway was proposed by Morita *et al.*² This pathway relies on the biogenesis of Aspidosperma precursor **15** to Leuconolam derivative through melodinus-type alkaloid. Such transformation could be possible through an internal Michael addition. After ring closure, Eucophylline could be formed by the attack of piperidine NH onto the carbonyl then dehydration, (Scheme 7).



Scheme 7. Possible Biogenetic Pathway to Eucophylline.

4. Biological Activity of Leucophyllidine and Eucophylline

Vinca alkaloid members showed a wide range of biological activity. Beside their fascinating complex structure, they proved themselves as potent chemotherapeutic agents towards the most dangerous and frightening disease, cancer. The most recognized members of this family, Vinblastine **5** and Vincristine **4**, have been used for cancer treatment over the last 50 years. Their biological effects depend on the perturbations in the microtubule dynamics that lead to inhibition of mitosis in cancer cells. Both Vinblastine and Vincristine are efficacious clinical drugs and are used in combination therapies for treatment of Hodgkin's disease, testicular cancer, ovarian cancer, breast cancer, head and neck cancer, and non-Hodgkin's lymphoma or in the curative treatment regimens for childhood lymphocytic leukemia and Hodgkin's disease.¹⁷ Despite this activity and clinical therapies and due to the mutation of cancer cells, a new generation of this cancer cells becomes more resistant to those medications. Chemists also developed new anticancer agents such as Fluorovinblastine that showed better activity and selectivity for these cells (Figure 4).

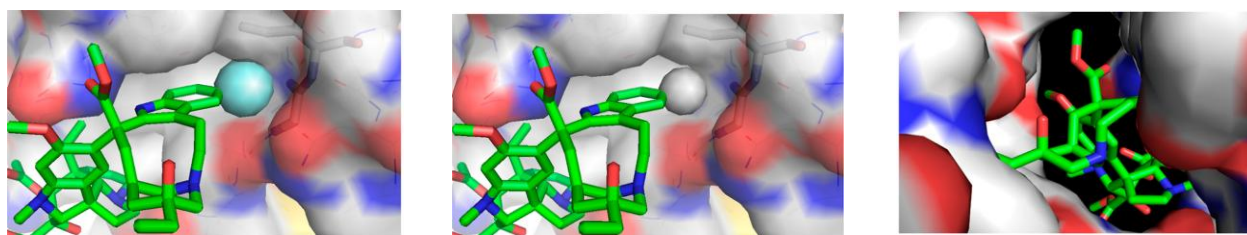
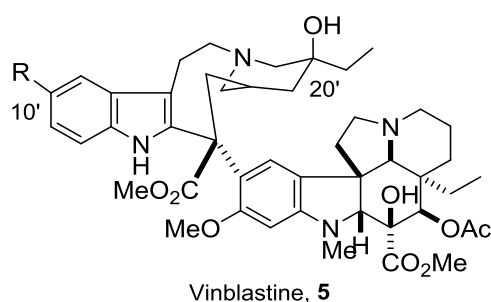


Figure 4. Space filling model of the fluorovinblastine binding site (R = F, left), (R = H, middle). X-ray structure of vinblastine bound to tubulin highlighting the region surrounding vinblastine C20' site (right image).

With the increasing demand for more efficient and targetable antitumor agents, Leucophyllidine **1** stands out as a promising agent. It has already shown a promising *in vitro* cytotoxicity toward vincristine-resistant human KB cells with IC₅₀ of less than 3 $\mu\text{g}/\text{mol}$.¹ While the level of activity is not outstanding, the selectivity toward resistant cells is of considerable interest. Morita *et al.*² also evaluated the effect of expression on iNOS protein in J774.1 cells stimulated by LPS by using western blotting analysis. When the cells were stimulated by LPS, iNOS protein in the cells was overexpressed, subjected to overproduction of NO. They found that Leucophyllidine **1** decreased the

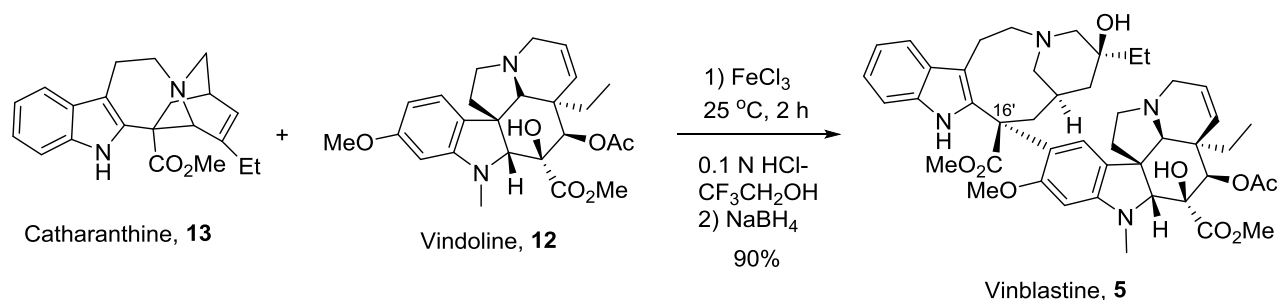
¹⁷ Sears, J. E.; Boger, D. L. *Acc. Chem. Res.* **2015**, *48*, 653-662.

iNOS protein expression dose-dependently. Besides that, Leucophyllidine **1** and Eucophylline **3** showed high cell viability of J774.1 at concentration of 7.1 μM .²

Based on the previously mentioned facts, Leucophyllidine **1** is a particular promising anticancer target, which retained our attention for two important reasons; Firstly, its selectivity and pronounced cytotoxicity and secondly, the unusual quinoline sub-structure that opens new perspectives for the discovery of potent drugs in cancer chemotherapy.

5. Synthetic approaches to dimeric indole alkaloids

The key step for forming the bisindole alkaloids is a biomimetic coupling between the two alkaloid monomers. Despite the logic of this disconnection, it has only scarcely been explored. We will discuss below only few examples that show the importance of biomimetic coupling in synthesis of bisindole alkaloids. One of the most important examples for the biomimetic approaches has been proposed by Boger and co-workers.¹¹ They were able, through Fe(III) mediated-coupling of Catharanthine **13** and Vindoline **12**, to provide a straightforward and biomimetic access to vinblastine **5** (Scheme 8).

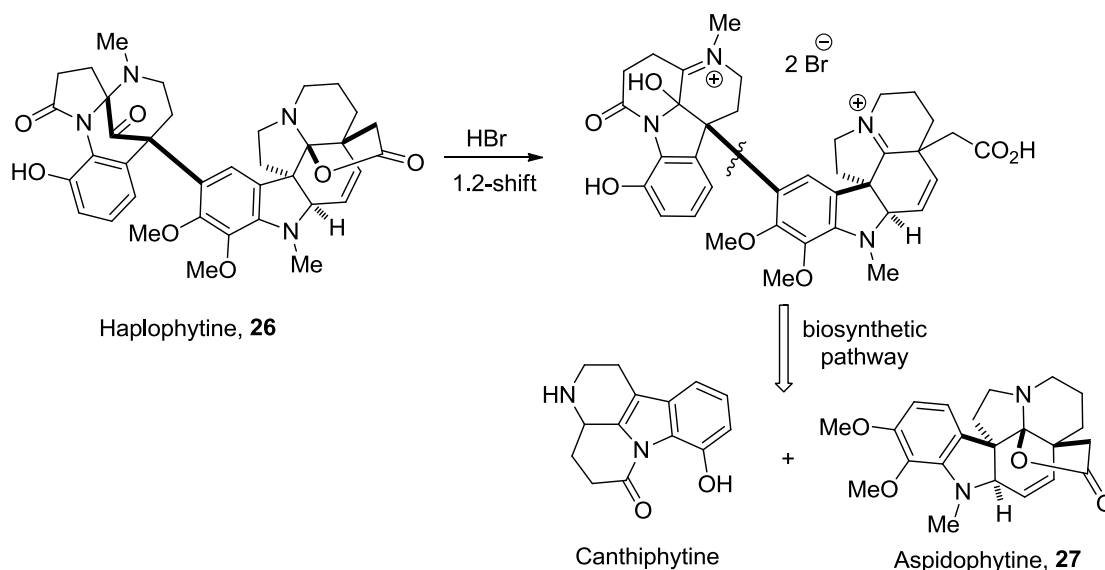


Scheme 8. Biomimetic Approach of Total Synthesis of Vinblastine.

Recently, Haplophytine **26** attracted the attention of several groups.¹⁸ This alkaloid is composed of two subunits linked by a quaternary carbon center. Recent investigations by Corey *et al.*¹⁹ on the biomimetic approach to the core of Haplophytine showed that the formation of this quaternary center was very challenging. Haplophytine is composed of two indole moieties; one of them is Aspidophytine **27** that is also present in the plant. Acidic treatment of Haplophytine results in a 1,2-cationic shift that generates upon rearrangement a new bis-iminium skeleton, which contain two indole fragments that are probably involved in the biosynthetic pathway (Scheme 9).

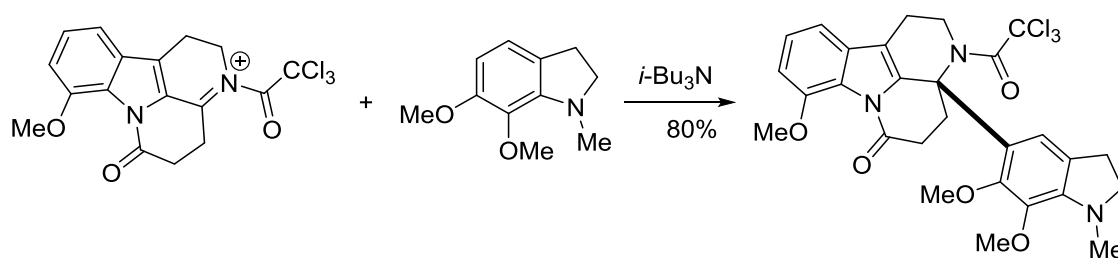
¹⁸ (a) Ueda, H.; Satoh, H.; Matsumoto, K.; Sugimoto, K.; Fukuyama, T.; Tokuyama, H. *Angew. Chem. Int. Ed.* **2009**, *48*, 7600-7603. (b) Nicolaou, K. C.; Dalby, S. M.; Li, S.; Suzuki, T.; Chen, D. Y. K. *Angew. Chem. Int. Ed.* **2009**, *48*, 7616-7620.

¹⁹ Rege, P. D.; Tian, Y.; Corey, E. J. *Org. Lett.* **2006**, *8*, 3117-3120.



Scheme 9. Hypothetic Haplophytine Biosynthesis.

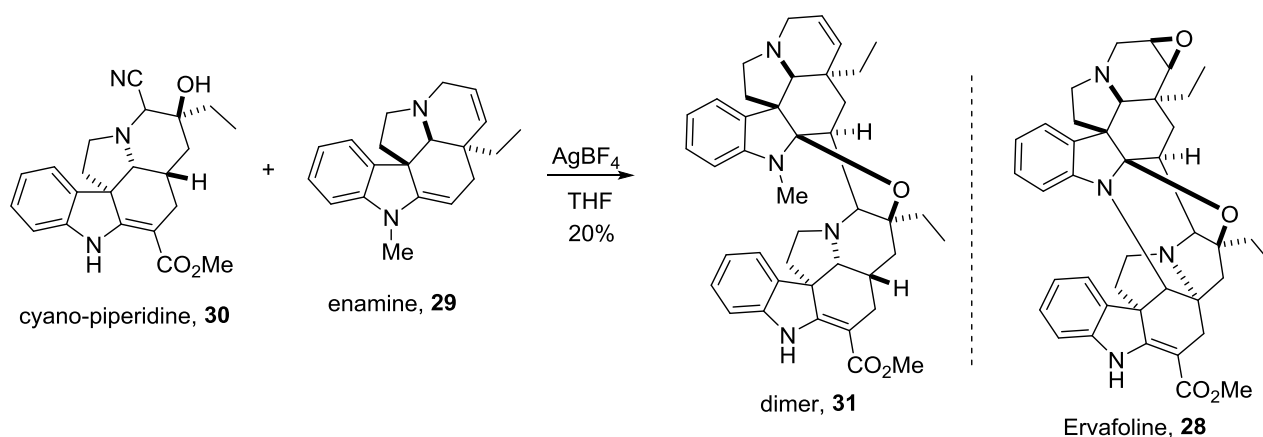
Based on these premises, Corey investigated coupling models between electron-rich arenes and Canthiphytine derivatives (Scheme 10). Several tries finally showed that biomimetic coupling is not operative to generate the benzylic quaternary center under the studied conditions, also pointing out the difficulties in finding proper conditions to initiate this sterically unfavorable coupling.



Scheme 10. Model Study on Biomimetic approach to access Haplophytine.

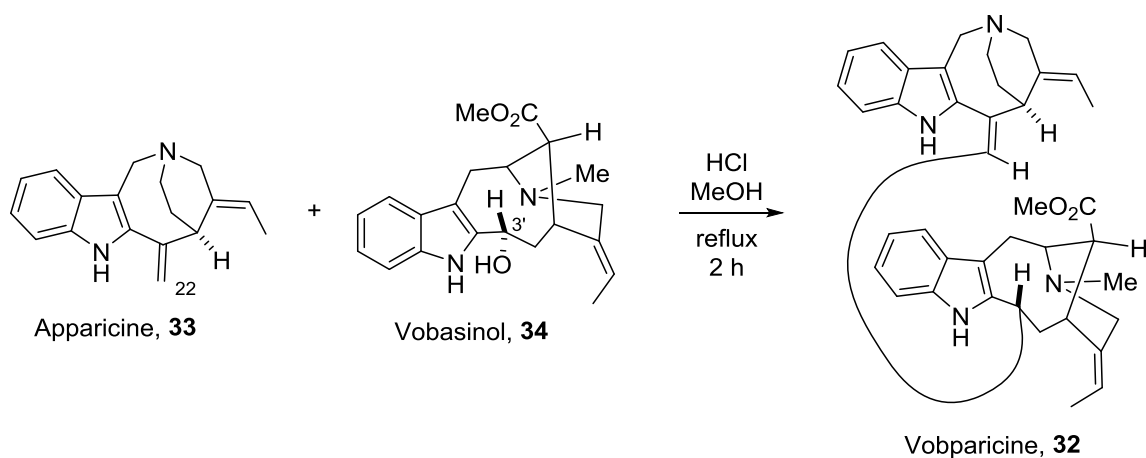
One of the important strategies in this kind of couplings is enamine-iminium chemistry. Such a process is very common in the biosynthesis of other classes of natural products. Based on this fact, Husson *et al.*²⁰ investigated the biomimetic approaches to link monomeric indole units to access the dimeric structure of natural product Ervafoline **28**. Thus, authors demonstrated that α -cyano-piperidines are equivalent and stable forms of iminium salts. So they allowed the enamine **29** to react with α -cyano-piperidine **30** in presence of AgBF_4 to afford the dimer **31** in 20% yield. This reaction paved the way to access Ervafoline **28** and demonstrated the possible biogenetic pathway formation of two of the three bonds in Ervafoline **28** (Scheme 11).

²⁰ Henriques, A.; Husson, H.-P. *Tetrahedron lett.* **1981**, *22*, 567-570.



Scheme 11. Enamine-iminium Biomimetic Approach toward Ervafoline.

Despite the apparent complexity of these biomimetic couplings, they may be very easy in some cases. For example, Vobparicine **32** results from the union of the two monoterpene indole alkaloids, Apparicine **33** and Vobasinol **34**. Biomimetically, treatment of Vobasinol with an excess of Apparicine under acidic conditions effectively led to Vobparicine (Scheme 12).²¹ The coupling was speculated to occur through the reaction at C-3' electrophilic center of Vobasinol and C-22 electron-rich center of Apparicine.

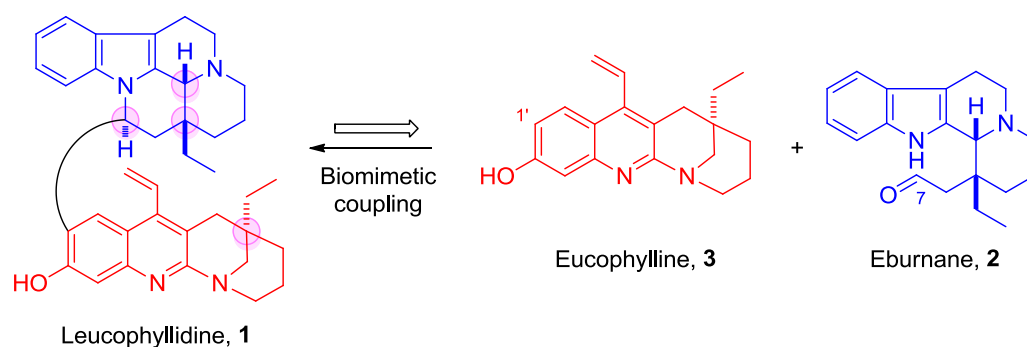


Scheme 12. Biomimetic Coupling of Vobparicine.

6. General Retrosynthesis of Leucophyllidine and Eucophylline

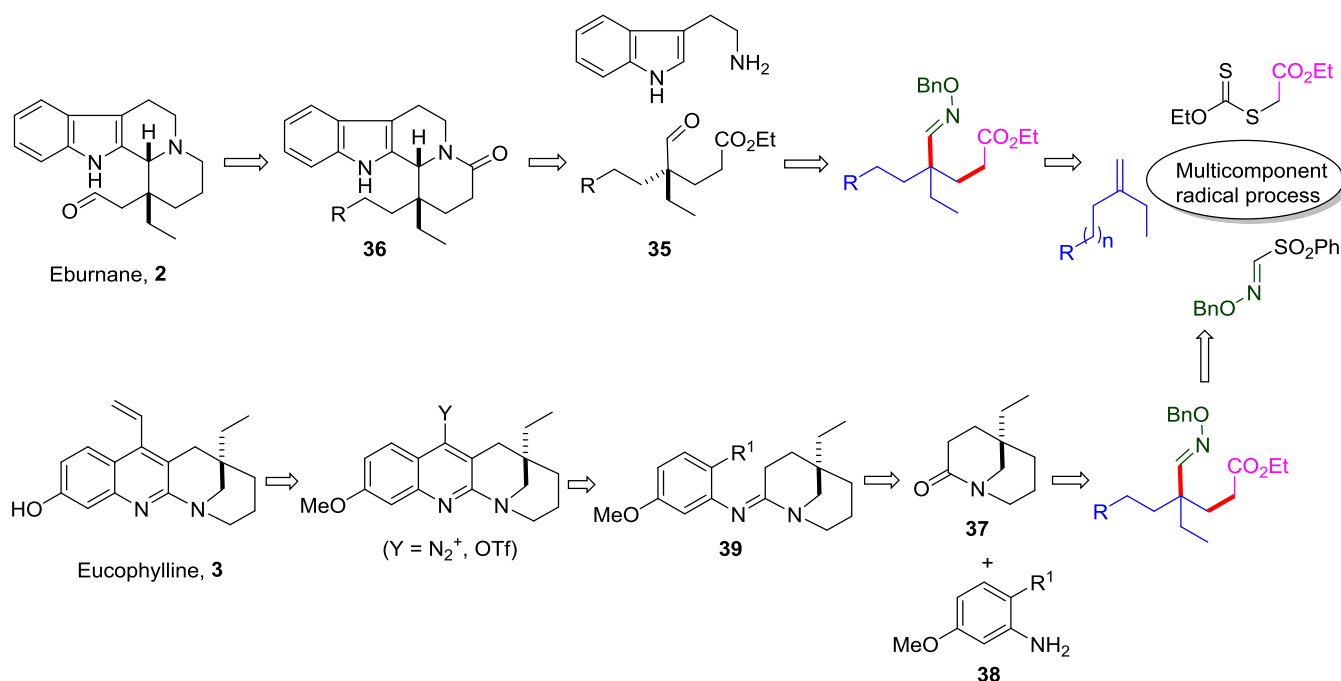
In view of aforementioned facts, it is clear that Leucophyllidine **1** may be resulted from the biomimetic coupling between the Eburnane **2** and Eucophylline **3** through a Mannich type reaction between the C-7 electrophilic center of Eburnane and the C-1' electron-rich center of Eucophylline. This assumption, which is in good agreement with the proposed biogenic pathway by Kim 1, constitutes our first step in the retrosynthesis of Leucophyllidine (Scheme 13).

²¹ Van Beek, T. A.; Verpoorte, R.; Baerheim Swenden, A. *Tetrahedron Lett.* **1984**, *25*, 2057-2060.



Scheme 13. Retrosynthesis of Leucophyllidine.

Not only Leucophyllidine attracted our attention biologically, as mentioned before, but also chemically. It is a very attracting target for chemists for many reasons. Firstly, the biomimetic coupling between its two fragments is very motivating. As in general, biomimetic couplings in this type of natural products did not receive the appropriate attention and sufficient studies. Secondly, two of the four stereogenic centers in both fragments are all-carbon quaternary centers which installation constitutes a challenging task. Thirdly, the original bicyclic system in Eucophylline is one of the major challenges in this natural product synthesis. Finally, our group has a special interest in this molecule as the proposed retrosynthesis analysis rely on multi-component free radical reactions for both fragments, which were recently developed in the group (Scheme 14).^{22, 23}

Scheme 14. General Retrosynthesis of Eburnane **2** & Eucophylline **3**

²² Godineau, E.; Landais, Y. *J. Am. Chem. Soc.* **2007**, *129*, 12662-12663.

²³ Landais, Y.; Robert, F.; Godineau, E.; Huet, L.; Likhite, N., *Tetrahedron*, **2013**, *69*, 10073-10080.

The key step in the construction of the quaternary centers in both fragments, Eburnane and Eucophylline, is the multi-component free radical carbo-oximation reaction between the appropriate olefin, a sulfonyloxime and a xanthate ester (Scheme 14).

In case of Eburnane retrosynthesis, the oxime functional group will be later hydrolyzed to aldehyde **35**, which will be allowed to react with tryptamine under Pictet-Spengler reaction conditions to afford the tetracyclic lactam **36**. The latter will hopefully give, through a sequence of transformations, a straightforward access to Eburnane **2** (Scheme 14).

In the case of Eucophylline retrosynthesis, the fully functionalized oxime will be subjected to sequences of reductions and post activation of the free alcohol, followed by cyclization to afford the bicyclic lactam. This lactam will be coupled with a functionalized aniline **38** under Vilsmeier reaction conditions to afford amidine **39**, which after cyclization and installation of the vinyl group will eventually lead to the desired natural product, Eucophylline **3** (Scheme 14).

This dissertation is composed of four chapters. We will discuss in the first one, various aspects of free radical reactions, including the stability of radicals and multi-component reactions along with their development in the group.

The second chapter will focus on the total synthesis of Eucophylline, starting by optimization of the key free radical carbo-oximation reaction, followed by the elaboration of the bicyclic lactam and the mechanism of the formation of these bicyclic systems under Vilsmeier-type reaction conditions. Finally, completion of the total synthesis of Eucophylline will be discussed.

In chapter three, the synthesis of Eburnane through different pathways will be investigated along with the development of the new carbo-cyanation reaction. The scope of this new reaction and its advantages will be screened in details, followed by its application in the Eburnane synthesis.

Finally, in chapter four, the preliminary studies about the biomimetic coupling between Eburnane half and Eucophylline on model compounds, which were accessed easily, will be presented.

Chapter one

Free Radical Multi-Component Chemistry

1.1. Introduction to Radical Chemistry

It is actually two centuries, since the first carbon radical was discovered. Gay-Lussac in 1815 reported the formation of cyanogen (the dimer of $\cdot\text{CN}$) by heating mercuric cyanide.²⁴ After this experiment, numerous experiments involving pyrolysis of organometallic compounds were done notably by Bunsen,²⁵ Frankland,²⁶ and Wurtz²⁷ in the 1840s. All of these experiments proposed the idea of the existence of carbon radicals, but there were no available physical methods to detect these radicals. Till 1900, when Gomberg reported the preparation of triphenylmethyl radical,²⁸ the first stable and free trivalent carbon radical.

A lot of scientific doubt pushed more scientists to prove the existence of carbon radicals,²⁹ until 1929, when Paneth and Hofeditz clearly reported the existence of alkyl radicals through their experiments of thermolysis of vapor phase of $\text{Pb}(\text{CH}_3)_4$ and other organometallic compounds.³⁰ Moreover, Staudinger in 1920 suggested that free radicals were involved in polymerization reactions of olefins.³¹ After that, Flory came out with a definitive paper on the kinetics of vinyl polymerization reactions, which confirmed the nature of these reactions as free radical propagations.³² Since then, great spurts in polymer industrial growth were achieved.

In the middle of the last century, with beginning of spectroscopic era, the discoveries of NMR and EPR and commercialization of them had a great effect on development of the radical chemistry. As a result of this development, Giese was able to add nucleophilic radicals onto unactivated olefins.³³ Barton also used thiohydroxamates in generating radicals and trapping them by other radical traps.³⁴ More than 80000 publications appeared focusing on EPR spectroscopy of radicals and more than half of those publications were devoted to carbon-centered radicals.

All of these important observation and reactions, besides the fact that radical chemistry has great compatibility with different functional groups with broad chemoselectivity, prompted synthetic chemists to use radical chemistry. Radical processes turned out to be important tools, which

²⁴ Gay-Lussac, H. L. *Ann. Chim.* **1815**, 95, 172.

²⁵ Bunsen, R. H. *Justus Liebigs Ann. Chim.* **1842**, 42, 27.

²⁶ Frankland, E. *Ann. Chem. Pharm.* **1849**, 71, 213.

²⁷ Wurtz, C. A. *Compt. Rend.* **1854**, 40, 1285.

²⁸ Gomberg, M. *J. Am. Chem. Soc.* **1900**, 22, 757-771.

²⁹ Forbes, M. D. E. in *Carbon Centered Free Radicals and Radical Cation*, John Wiley and Sons, **2010**, p. 1

³⁰ Paneth, F.; Hofeditz, W. *Chem. Ber.* **1929**, 62, 1335.

³¹ Staudinger, Ber. *Dtsch. Chem. Ges.* **1920**, 53, 1073.

³² Bloch, F. *Phys. Rev.* **1946**, 70, 460.

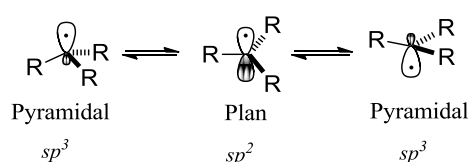
³³ Giese, B. *Angew. Chem.* **1985**, 97, 555.

³⁴ Barton, D. H. R.; Parekh, S. I., *Half a Century of Radical Chemistry*, Cambridge University Press, Cambridge, **1993**, p. 49.

facilitates greatly the access to many important targets and natural products.³⁵ Along this chapter, the fundamentals of radical chemistry and multicomponent free radical reactions will be highlighted.

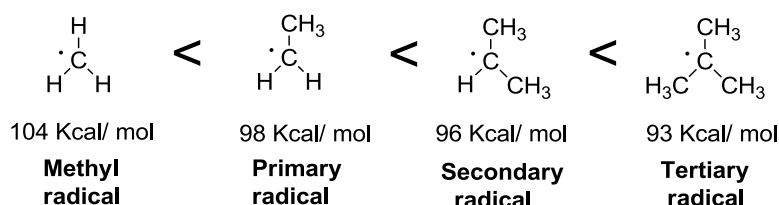
1.1.1. Structure and Stability of Radicals

The carbon-centered radical (R_3C^\bullet) may adopt several geometrical configurations. This trivalent radical may change its configuration from pyramidal to planar. This change is quite rapid and is affected by the type of substituents on the carbon bearing the radical. Trivalent radicals can thus change their hybridization from sp^3 to sp^2 depending on the nature of the substituent. For example, in the case of the methyl radical, the radical appears as planar as the barrier of inversion is very small (Scheme 15).



Scheme 15. Radical Geometrical Configurations.

In the other side, the pyramidal structure of the radical increases in the following order: Ethyl < *i*-propyl < *t*-butyl. This phenomenon could be explained by the fact that the hyperconjugation between the SOMO and σ orbital of C-H bond stabilizes the pyramidal structure (Scheme 16).³⁶



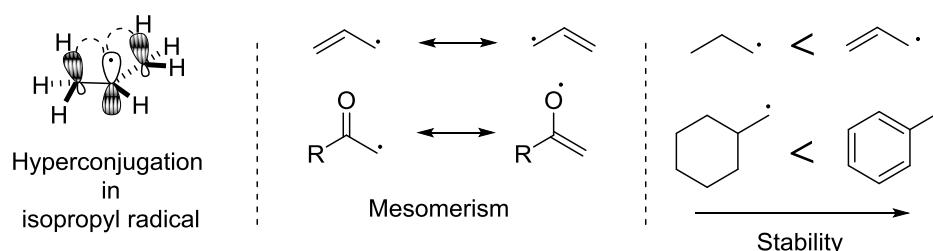
Scheme 16. Stability of Radicals Species.

Not only the pyramidal structure is favored in case of conjugation with adjacent C-H bonds, but also when the carbon bearing radical has π -donor substituents. For example, when fluorine or oxygen is one of the substituents on the carbon bearing the radical, the radical will be pyramidal. This could be rationalized due to the repulsion between the p orbital of the radical and the lone pair of oxygen or fluorine. That explains why $^\bullet CF_3$ is a pyrimadized radical.

³⁵ (a) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237-1286 ; (b) Quiclet-Sire, B.; Zard, S. Z. *Beilstein J. Org. Chem.* **2013**, *9*, 557-576.

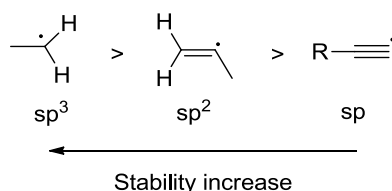
³⁶ Carey, F. A.; Sunberg, R. J. in *Advanced Organic Chemistry Part A*, Springer, New York, **2007**, pp. 980-988.

The stability of a radical depends on thermodynamic and kinetic factors. The principal thermodynamic factor is hyperconjugation and delocalization of radical through mesomeric structures (Scheme 17).



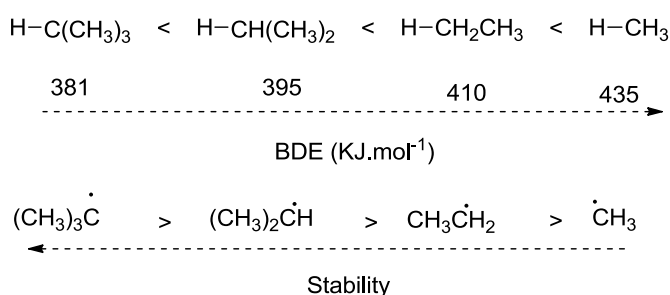
Scheme 17. Stability of Radicals.

Hybridization also has an influence on the stability of the radical. The more *s* character is present on the SOMO, the more the radical is destabilized. This could explain the fact that alkyl radicals are more stable than vinyl and alkynyl radicals (Scheme 18).



Scheme 18. Hybridization effect in radical stability.

The thermodynamic stability of the radical R^\bullet could be measured through the bond dissociation energy of the R-H bond (BDE). In other words, the radical is formed more easily, if BDE of the broken bond is small (Scheme 19).²⁹



Scheme 19. Relation between BDE and radical stability.

On the other hand, kinetic factors that affect the stability of radicals are more influenced by the steric hindrance around the radical center. The more the radical is sterically hindered, the more it is stable and long lived. For this reasons, Gomberg²⁸ was able to detect triphenylmethyl radical.

Stability and reactivity are strongly related. The more the radical is stable, the less it is reactive. The reactivity of different radical types will be discussed below.

1.1.2. Reactivity of Radicals

The reactivity of radicals can be determined through two important points. The first, which we discussed in the last section, is the stability of the generated radicals, in other words the structural factors. The second point, that we are going to discuss in this section, is the thermodynamic of the reaction; the energetic summary of the broken and formed bonds during the radical reactions steps.

From a thermodynamic point of view, the energy summary will give an idea if this reaction is possible or not. For example, the addition of a C-centered radical onto an olefin is possible, and as a result a gain in energy relative to the new formed σ bond will suggest that this reaction is exothermic. In the most cases, radical reactions are exothermic.

According to Hammond's postulate, in radical transformations, the transition state energy is close to the energy of the reaction components. Based on that, the Frontier Molecular Orbital theory (FMO)³⁷ can be applied, providing a satisfying explanation of the radical reactivity.

Let us consider a reaction between a radical R^\bullet and an olefin. The radical electron in SOMO can interact with HOMO or LUMO orbitals of the olefin. Based on the difference of energy between these orbitals (SOMO and HOMO or LUMO of olefin) the reactivity between the two molecules can be described. The rate of addition of the C-centered radical onto the olefin will depend on the energy difference between the SOMO orbital of the radical and the orbitals HOMO or LUMO of the olefin. The closer the orbitals (i.e. energy barrier is small), the faster is the reaction. In all cases, there are two scenarios for this interaction (Figure 5):

1. A carbon radical that have electron donating groups (a nucleophilic radical) will have highly energetic SOMO orbital and then will add more easily to an energetically low LUMO orbital of an electron poor olefin (substituted by electron withdrawing groups).
2. In contrast, a C-centered radical having electron withdrawing groups (electrophilic radical) will add more favorably to an electron rich olefin through an interaction between the low energetic SOMO orbital of the radical and the highly energetic HOMO orbital of the olefin.

³⁷ Fleming, I. in *Frontier Orbitals and Organic Chemical Reactions*, Wiley, New-York, **1976**, 5, 182-186.

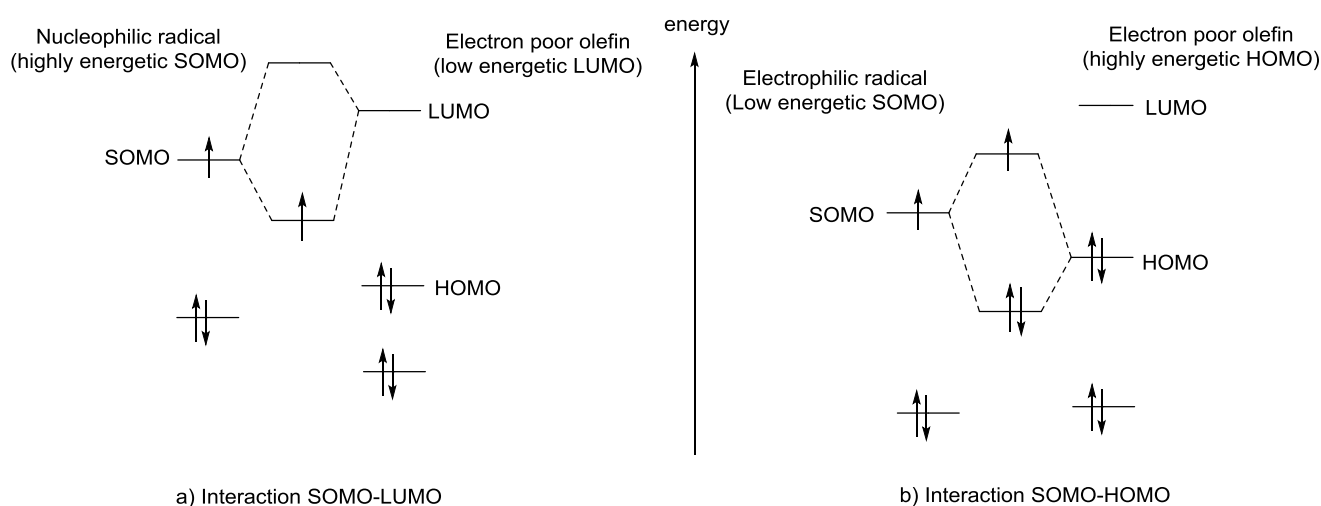
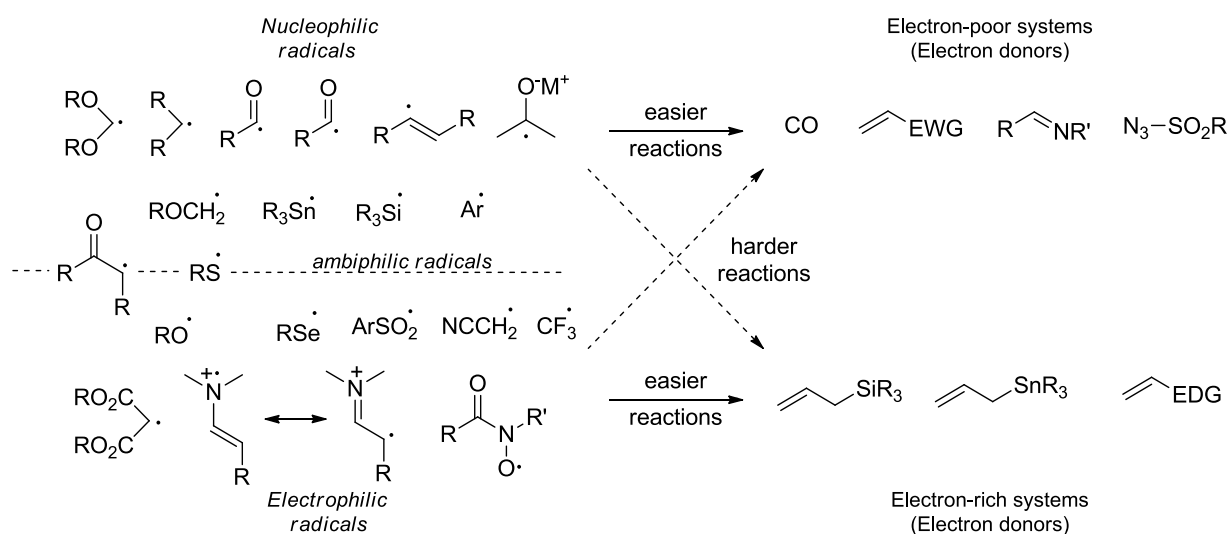


Figure 5. Orbital interactions between radical and olefin.

From the aforementioned details, it is important to understand the behavior of the radical to classify them according to their polarities or according to the used substrates. In (Scheme 20), the different types of radicals and radical acceptors are categorized according to their polarities.³⁸



Scheme 20. Polarity of Different Radical Systems.

It is worth noticing that this classification is just to guide chemists to design their radical reactions taking into consideration the possible species that could react together. However, once the radical is generated, it is highly reactive and could react with different classes of radical acceptors. For example, an electrophilic radical may react with an electron-poor olefin, if there is no other choice. And in this case, the reaction will occur with a slow rate.

³⁸ Godineau, E.; Landais, Y. *Chem. Eur. J.* **2009**, *15*, 3044-3055.

1.2. Multi-component Reactions

In the beginning of 1990s, with the appearance of high-throughput screening in the pharmaceutical industry, the use of multi-component reactions (MCRs) became an important and attractive synthetic strategy. MCRs provide an easy and rapid access to large libraries of organic compounds with diverse substitution patterns.

MCRs are generally defined as reactions in which more than two reactants combine to form a product, which retains the majority of the atoms of the starting materials. The history of MCRs returns back over 150 years with the Strecker (1850),³⁹ Hantzsch (1882),⁴⁰ Biginelli (1891),⁴¹ Mannich (1912)⁴² and Passerini (1921)⁴³ reactions. In the second half of the last century, in part due to the seminal contributions from Ugi (1959),⁴⁴ MCRs began to show its power in the synthesis of libraries of compounds. Since then, they became one of the cornerstones of combinatorial chemistry.

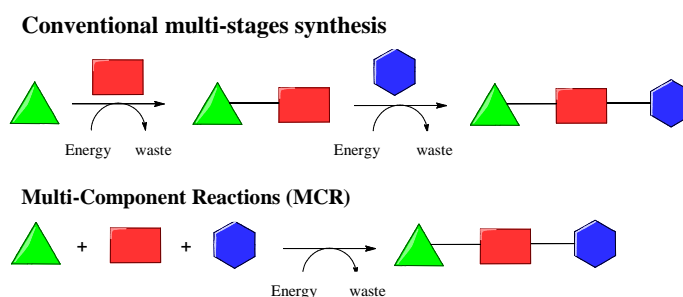


Figure 6. Graphical scheme illustrating the differences between conventional multi-stages synthesis and MCRs.

³⁹ (a) Strecker, A. *Justus Liebigs Ann. Chem.* **1850**, 75, 27-51 ; (b) Strecker, A., *Ann. Chem. Pharm.* **1850**, 91, 349.

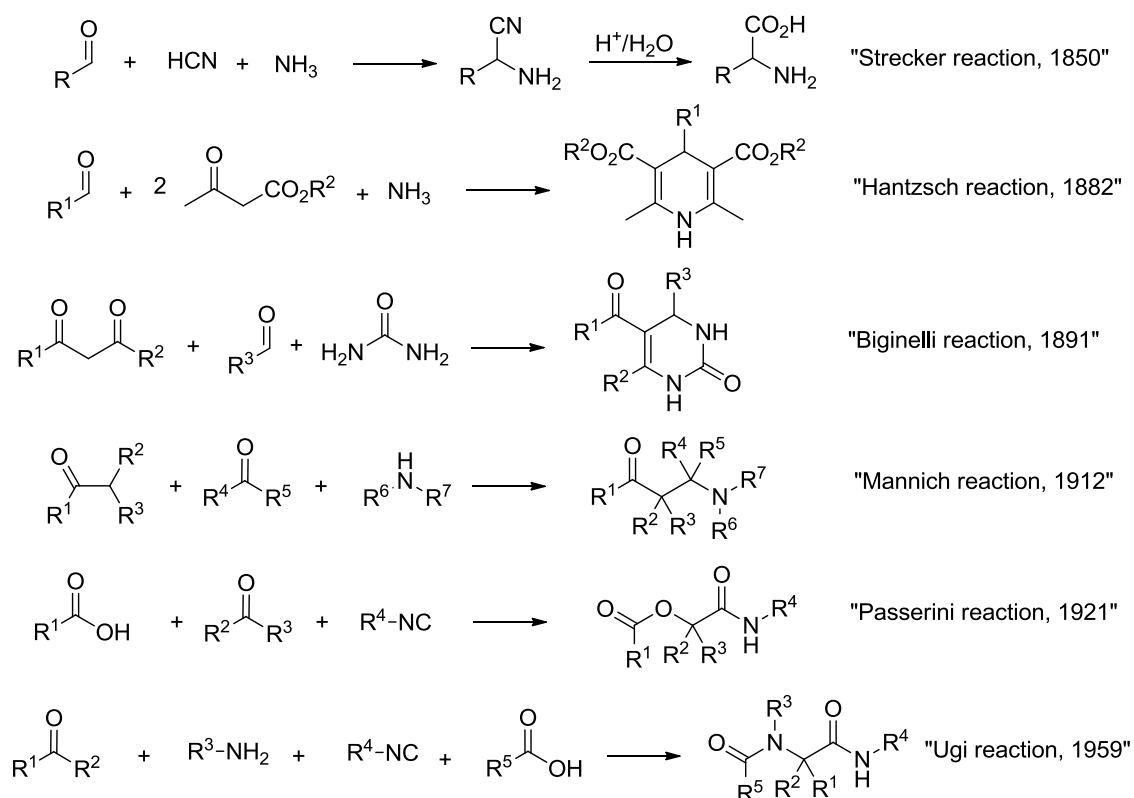
⁴⁰ Hantzsch, A. *Justus Liebigs Ann. Chem.* **1882**, 215, 1-82.

⁴¹ (a) Biginelli, P. *Ber. Dtsch. Chem. Ges.* **1891**, 24, 2962 ; (b) Biginelli, P. *Ber. Dtsch. Chem. Ges.* **1893**, 26, 447.

⁴² Mannich, C.; Krösche, W. *Arch. Pharm.* **1912**, 250, 647-667.

⁴³ Passerini, M. *Gazz. Chim. Ital.* **1921**, 51, 181-189.

⁴⁴ (a) Ugi, I.; Meyr, R.; Fetzer, U.; Steinbrucker, C. *Angew. Chem.* **1959**, 71, 386 ; (b) Ugi, I.; Steinbrucker, C.; *Angew. Chem.* **1960**, 72, 267-268.



Scheme 21. History of MCRs.

MCRs fit well with green chemistry concepts.⁴⁵ As they respect the atom-, step- and energy-efficient synthesis rules. It is no longer sufficient to “make the molecule”, but chemists have to synthesize it in an environmentally benign manner, with a minimal amount of resources, energy and wastes. MCRs can also give access to complex structures in a simple and efficient one-pot process. For example, the synthesis of piperazine-2-carboxamide (the central part of Crixivan®, protease inhibitor for treatment of HIV) was achieved by a 4CR-Ugi reaction. The synthesis of nifedipine (Adalat®, a highly active calcium antagonist) was also made through a one-step 3CR-Hantzsch reaction and is a striking example of the power of MCRs.⁴⁶

By integrating the advantages of MCRs such as selectivity, efficiency, compatibility and tolerance to different functional groups with the broad chemoselectivity of radical reactions, very powerful synthetic tools could be developed to access more complex targets in an efficient manner. During the following part of this chapter, we will overview the development of free radical multi-component reactions.

⁴⁵ (a) Cioc, R.; Ruijter, E.; Orru, R. *Green chem.* **2014**, *16*, 2958-2975; (b) Trost, B. *Science* **1991**, *254*, 1471-1477; (c) Noyori, R., *Chem. Commun.* **2005**, *14*, 1807-1811.

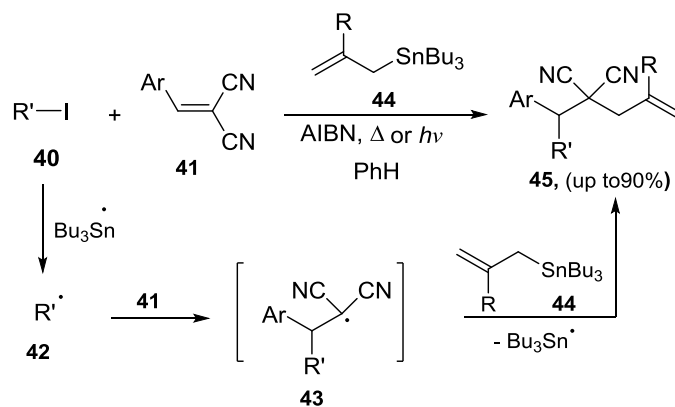
⁴⁶ Zhu, J.; Bienayme, H. *Multicomponent Reactions*, Wiley-VCH: Weinheim, **2005**.

1.3. Free-Radical Multi-Component Reactions

Radical MCRs are highly convergent processes which lead to complex structures, starting from simple and readily available materials. To design successful radical MCR, the polarities of the generated radicals during the reaction course must be taken in consideration. The polarity of radicals generated during each individual step, given by the classification depicted in (Scheme 20), must be chosen carefully to avoid the formation of undesired products. The collected data about radical kinetics and stabilities during last decades (additions, abstraction, fragmentations, etc.) helped greatly in predicting and designing radical MCRs.

1.3.1. Radical Carbo-allylation Reactions

One of the first radical MCRs, developed in 1988 by Mizuno *et al.*⁴⁷ involved the addition of nucleophilic radical **42** to the electron poor olefin **41** to form a C-C bond. Radical **42** was generated from the corresponding alkyl iodide by the abstraction of iodine with $\text{Bu}_3\text{Sn}^\bullet$. As a result, the newly generated electrophilic radical **43** could be trapped by the electron rich allylstannane **44** to form another C-C bond, followed by a β -elimination and regeneration of tin radical, which in turn propagates the radical chain. The reaction ended up successfully with the desired product **45** in excellent yields (Scheme 22).

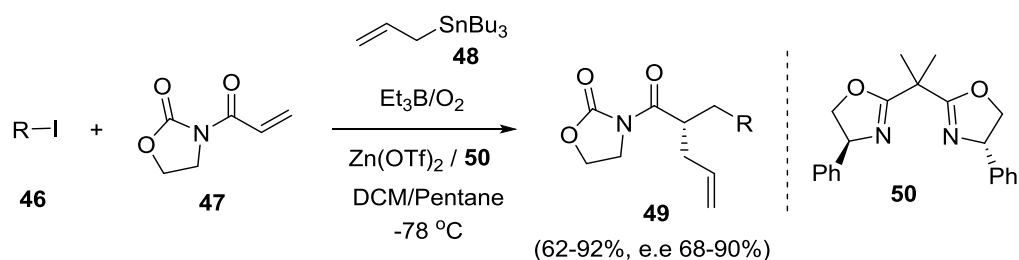


Scheme 22. Carbo-allylation Reaction of Mizuno and Otsuji.

In 1995 Porter and coworkers⁴⁸ developed the first asymmetric radical carbo-allylation (also the first asymmetric MCR) by the addition of an alkyl radical, generated from the corresponding iodide **46**, on an oxazolidinone derived from an acrylate **47** (Evans' oxazolidinone) in the presence of a Lewis acid and a chiral ligand, a bisoxazoline (BOX) **50**. The generated intermediate radical was trapped by an allylstannane **48** to form the desired products **49** in very good yields and enantiomeric excesses (Scheme 23).

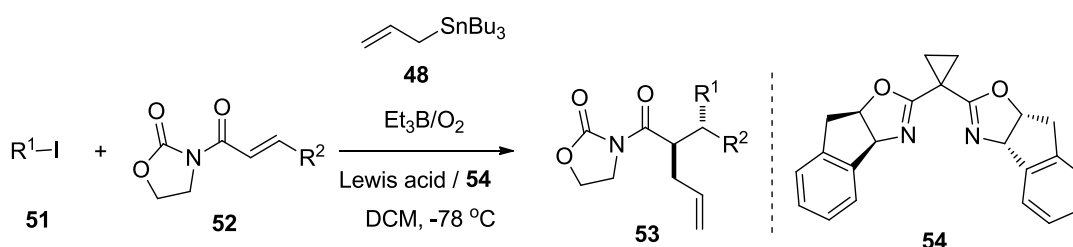
⁴⁷ Mizuno, K.; Ikeda, M.; Toda, S.; Otsuji, Y. *J. Am. Chem. Soc.* **1988**, *110*, 1288-1290.

⁴⁸ Wu, J. H.; Radinov, R.; Porter, N. A. *J. Am. Chem. Soc.* **1995**, *117*, 11029-11030.



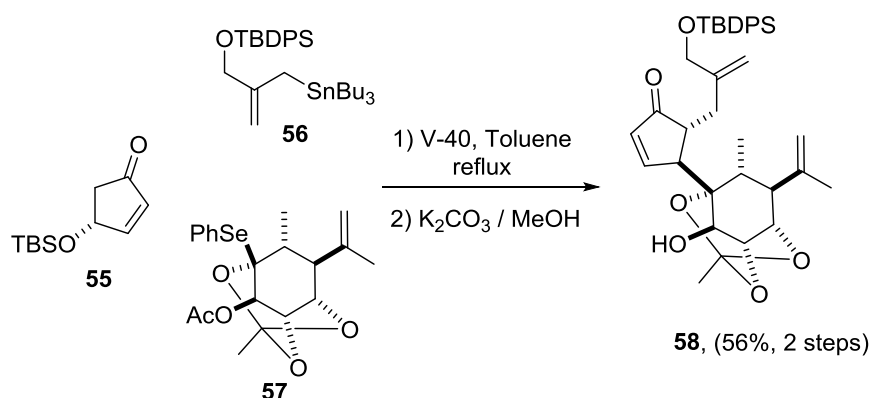
Scheme 23. Enantioselective Radical Addition of Porter.

Few years later, Sibi *et al.*⁴⁹ reinvestigated the previous reaction and was able to create two chiral centers with perfect control of stereochemistry. The major discovery was the replacement of the Lewis acid from MgI to $\text{Cu}(\text{OTf})_2$, that allowed to obtain the other diastereomer with the same ligand (Scheme 24).



Scheme 24. Asymmetric Radical Addition of Sibi.

The recent synthesis of diterpenoid **58**, showed the power, efficiency and compatibility of this radical MCRs to access complicated functionalized systems. In 2013, Inoue *et al.*⁵⁰ initiated the radical addition of selenyl compound **57** on the olefin **55** by V-40. The resulting electron-deficient α -carbonyl radical was added to the electron-rich tin reagent **56** leading to adduct **58**. After deacetylation and elimination of TBDSOH with alkaline methanol, the desired product was obtained in 56% yield (Scheme 25).



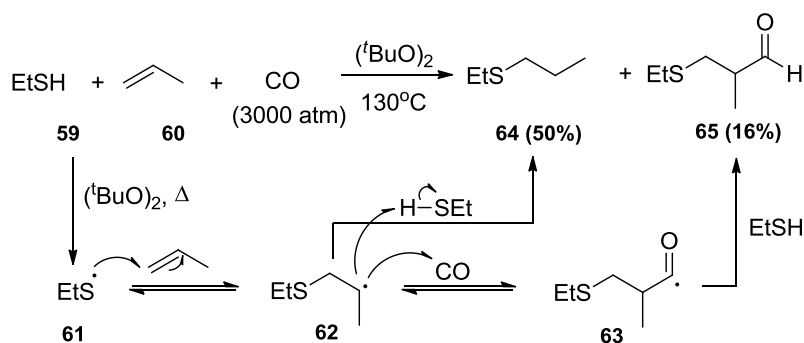
Scheme 25. Synthesis of Diterpenoid by Carbo-allylation Reaction.

⁴⁹ (a) Sibi, M. P.; Chen, J. *J. Am. Chem. Soc.* **2001**, *123*, 9472-9473; (b) Sibi, M. P.; Manyem, S.; Subramanian, R. *Tetrahedron* **2003**, *59*, 10575-10580.

⁵⁰ Murai, K.; Katoh, S.-i.; Urabe, D.; Inoue, M. *Chem. Sci.* **2013**, *4*, 2364-2368.

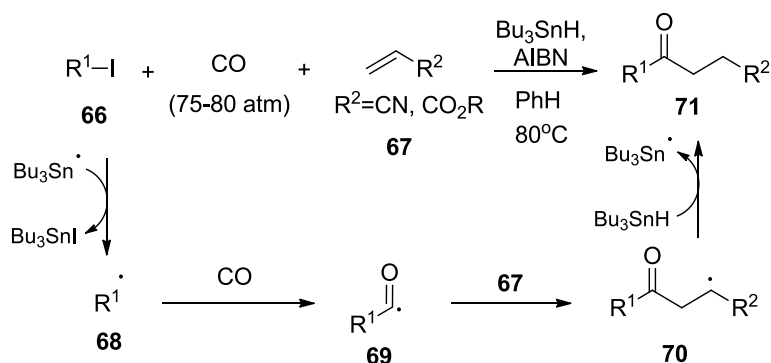
1.3.2. Carbonylative Radical Reaction

Depending on the fact that carbon monoxide is a good radical acceptor, Lipscomb *et al.*⁵¹ in 1956 were able to develop the first radical MCR by using high pressure of CO. Thus, through the radical addition of a thiyl radical **61** onto propene **60**, the resulting radical **62** reacted with CO as the third component to form an acyl radical, which upon abstraction of hydrogen from the thiol gave the product **65** in low yield. This could be rationalized due to the formation of a sulfide side product **64** (Scheme 26). Later Tsuji was able to improve the yields by using $[\text{Co}_2(\text{CO})_8]$ as a catalyst.⁵²



Scheme 26. Thiocarbonylation of Olefins.

More efficient processes were developed by Ryu and Sonoda to synthesize unsymmetrical ketones by using CO in radical MCR.⁵³ Thus, by initiating the radical chain with AIBN, the alkyl radical **68**, generated from the corresponding iodide **66**, added to CO to form the nucleophilic acyl radical **69** which in turn reacted with the electron deficient olefins **67** to form the radical **70**, which was finally reduced by tin hydride to form the product **71** in good yield (Scheme 27).



Scheme 27. Carbonylation radical MCR by Ryu.

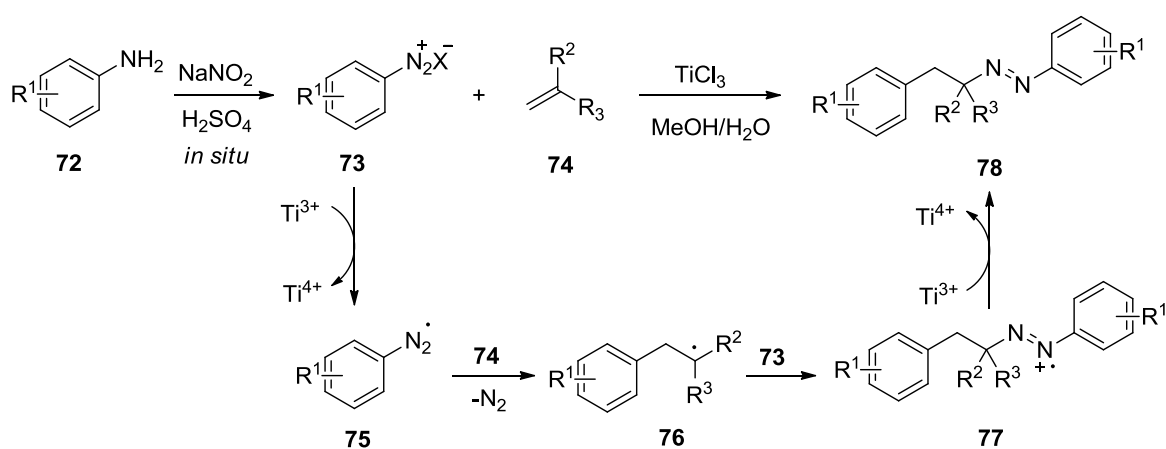
⁵¹ Foster, R. E.; Larchar, A. W.; Lipscomb, R. D.; McKusick, B. C. *J. Am. Chem. Soc.* **1956**, *78*, 5606-5611.

⁵² Susuki, T.; Tsuji, J. *J. Org. Chem.* **1970**, *35*, 2982-2986.

⁵³ (a) Ryu, I.; Uehara, S.; Hirao, H.; Fukuyama, T. *Org. Lett.* **2008**, *10*, 1005-1008 ; (b) Kawamoto, T.; Uehara, S.; Hirao, H.; Fukuyama, T.; Matsubara, H.; Ryu, I. *J. Org. Chem.* **2014**, *79*, 3999-4007.

1.3.3. Arylation radical reaction

Aryl radicals, generated from the corresponding aryl diazonium salts, have been known for the last century.⁵⁴ The well-known Meerwein reaction which involves the addition of aryl diazonium salts (ArN_2X) to an electron-poor alkene, paved the way towards the development of aryl radical reactions.⁵⁵ More recently, Heinrich *et al.*⁵⁶ were able to develop successfully carbo-diazenylation reactions of olefins. Starting from aryl diazonium salts **73**, which were reduced by TiCl_3 to aryl radical **75** with evolution of N_2 , the aryl radicals could add onto olefins **74** to form the nucleophilic intermediate radical **76**, which was trapped directly by another molecule of aryl diazonium salts **73**. The final product **78** was obtained in excellent yield after electron transfer to Ti^{III} (Scheme 28).



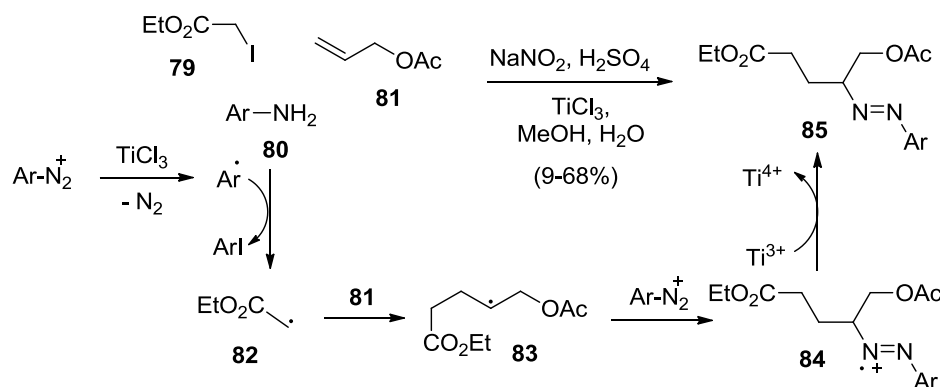
Scheme 28. carbo-diazenylation Reaction of Heinrich.

To increase the impact of these aryl radicals, the same group remarkably developed a three-component carbo-diazenylation reaction that involved addition of an aliphatic radical to diazonium salts. They used alkyl iodide derivatives **79** as a third component in this reaction. The reaction started by generation of the aryl radical, which abstracted iodine to generate the electrophilic radical **82** which in turn added to the olefin **81**. The intermediate nucleophilic radical **83** was then trapped by the diazonium salt to give intermediate **84** which is reduced by TiCl_3 to give the product **85** in good yield (Scheme 29).

⁵⁴ Galli, C. *Chem. Rev.* **1988**, *88*, 765-792.

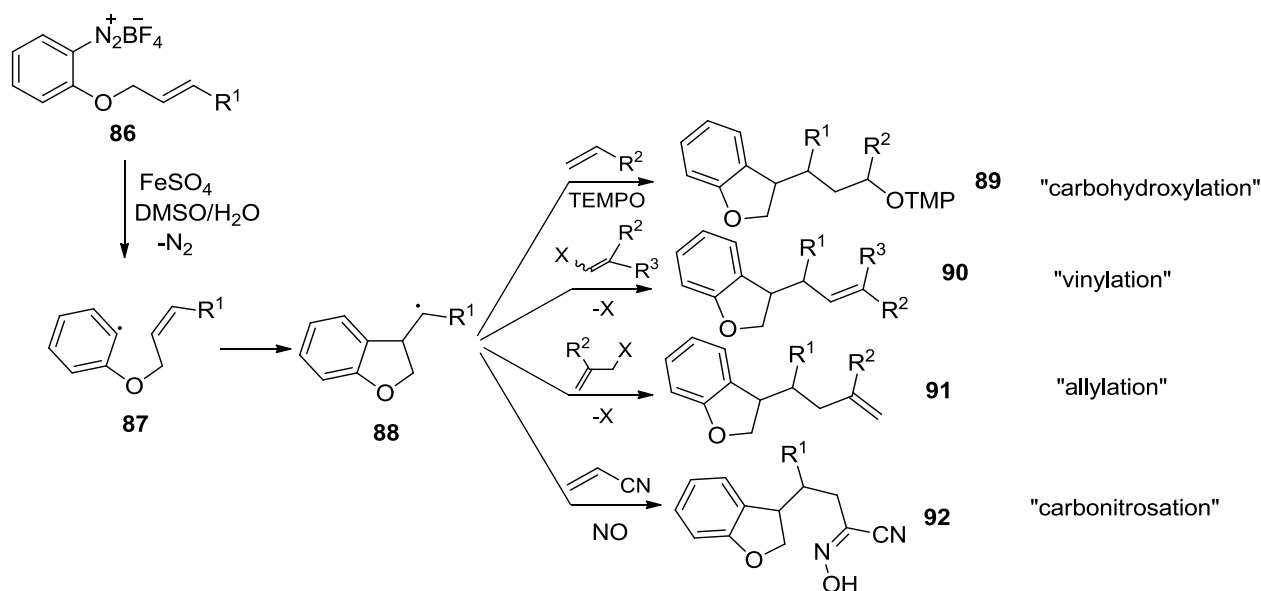
⁵⁵ Heinrich, M. R. *Chem. Eur. J.* **2009**, *15*, 820-833.

⁵⁶ Heinrich, M. R.; Blank, O.; Wölfel, S. *Org. Lett.* **2006**, *8*, 3323-3325.



Scheme 29. 3-CR-alkylcarbodiazenylation Reaction of Heinrich.

In a fruitful cooperation between Landais and Heinrich groups, they were able to develop the carbodiazenylation reaction that involved an intramolecular radical cyclization of diazonium-substituted allyl phenyl ethers, followed by radical trapping through carbohydroxylation, carbonitrosation, vinylation, and allylation reactions (Scheme 30).⁵⁷



Scheme 30. Cyclization Reactions with further Radical Functionalization.

1.3.4. Carbo-phosphorylation Radical Reaction

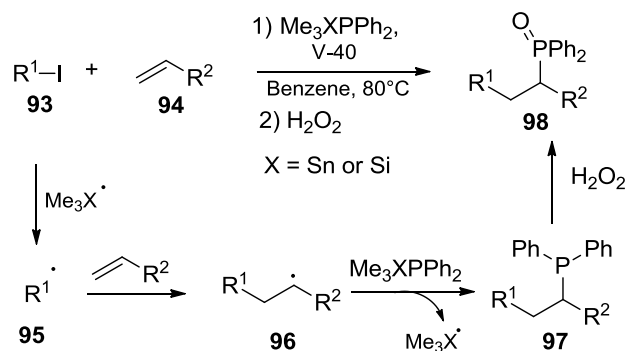
Introducing phosphorus-containing substituents onto organic structures constitutes an important challenge that organic chemist have faced for a long time.⁵⁸ Recently, Studer *et al.*⁵⁹ were able to

⁵⁷ Jasch, H.; Landais, Y.; Heinrich, M. R. *Chem. Eur. J.* **2013**, *19*, 8411-8416.

⁵⁸ (a) Barton, D. H. R.; Bridon, D.; Zard, S. *Tetrahedron Lett.* **1986**, *27*, 4309-4312; (b) Ding, B.; Bentrude, W. G. *J. Am. Chem. Soc.* **2003**, *125*, 3248-3259; (c) Sato, A.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2006**, *128*, 4240-4241; (d) Wada, T.; Kondoh, A.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2008**, *10*, 1155-1157; (e) Shirai, T.; Kawaguchi, S.-I.; Nomoto, A.; Ogawa, A. *Tetrahedron Lett.* **2008**, *49*, 4043-4046; (f) Cossairt, B. M.; Cummins, C. C. *New J. Chem.* **2010**, *34*, 1533-1536; (g) Leca, D.; Fensterbank, L.; Lacôte E.; Malacria, M. *Chem. Soc. Rev.* **2005**, *34*, 858-865.

⁵⁹ (a) Vaillard, S. E.; Mück-Lichtenfeld, C.; Grimme, S.; Studer, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 6533-6539; (b) Lamas, M.-C.; Studer, A. *Org. Lett.* **2011**, *13*, 2236-2239.

develop a 3CR-carbo-phosphorylation reaction, through addition of alkyl radicals **95**, generated from the corresponding iodide **93**, to unactivated olefins **94**. The generated nucleophilic radical was trapped later by $\text{Me}_3\text{SiPPh}_2$ or $\text{Me}_3\text{SnPPh}_2$ to liberate silyl or stannyl radicals, which then propagate the radical chain. The phosphane product thus obtained was oxidized *in situ* by H_2O_2 to form phosphinyl oxide product **98** (Scheme 31).



Scheme 31. Carbo-phosphorylation Reaction.

1.3.5. Radical Addition to Imines

The reactivity of imines motivated a lot of chemists to explore the possibility to use them as radical acceptors. However, due to the easy hydrolysis of imines and the possibility of tautomerism, oxime ethers and hydrazones were more attractive. The aminyl radicals that are formed from the radical addition on imines are less stable than those resulting from additions to oxime ethers or hydrazones. From a kinetic point of view, the radical addition to imines is relatively slow as compared to addition onto oxime and hydrazone. The reason is that the electron density on oxime's or hydrazones's carbon ($\text{C}=\text{N}$) is low (the less electron density on carbon, the better radical acceptor). Accordingly the reactivity of these functional groups could be ordered as follows: hydrazone > oxime > imine.⁶⁰ Radical version of the Strecker and Mannich reactions were however developed recently.

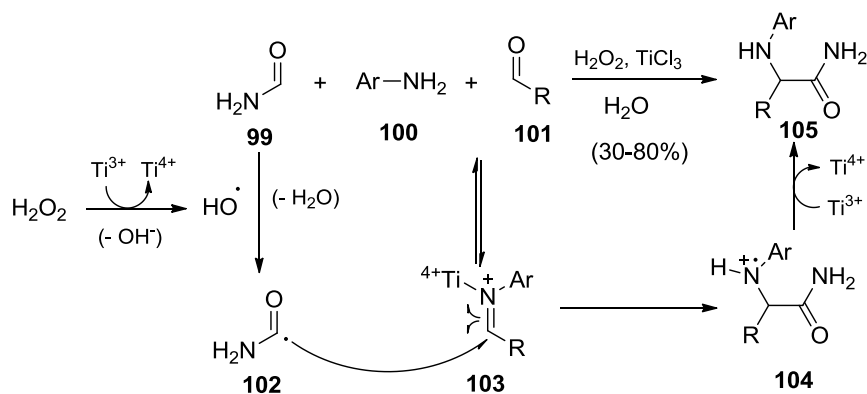
1.3.5.1. Radical Strecker Reaction

The ionic version of the Strecker reaction, first developed about two centuries ago, gives an access to α -amino acids or amides after hydrolysis of α -aminonitriles. Recently, Porta *et al.*⁶¹ developed the radical version of this reaction. The reaction starts by the formation of a hydroxyl radical through the reduction of hydrogen peroxide by Ti^{III} . This highly reactive radical then abstracts a hydrogen from amide **99** to form the nucleophilic formamidyl radical **102** which in turn adds to the *in situ*

⁶⁰ (a) Kim, S.; Sub Yoon, K.; Suk Kim, Y. *Tetrahedron* **1997**, *53*, 73-80 ; (b) Kim, S.; Kim, Y.; Yoon, K. S. *Tetrahedron Lett.* **1997**, *38*, 2487-2490.

⁶¹ Canella, R.; Clerici, A.; Panzeri, W.; Pastori, N.; Punta, C.; Porta, O. *J. Am. Chem. Soc.* **2006**, *128*, 5358 - 5359

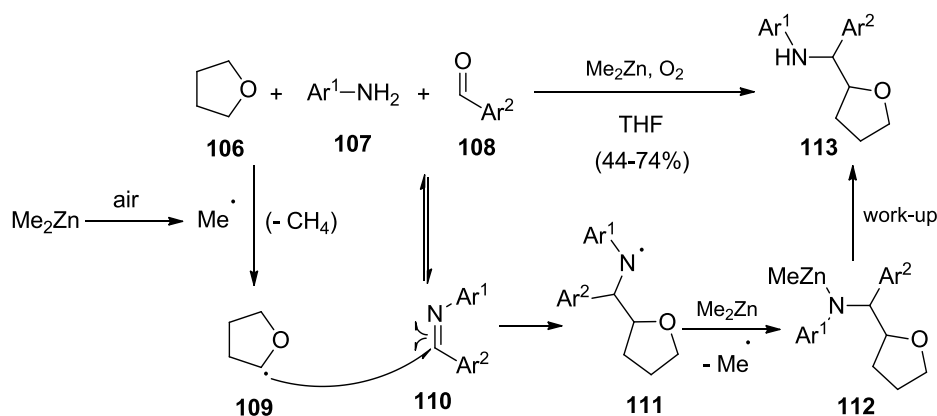
generated iminium (from condensation of amine **100** and aldehyde **101** in presence of Ti^{IV}). The resulting cationic radical **104** is finally reduced by Ti^{III} to form an α -aminoamide **105** (Scheme 32). This method provides an efficient and wide access to different aliphatic and aromatic α -aminoamides in one-pot and in mild conditions. The same group later extended this methodology to ketones.⁶²



Scheme 32. Strecker Reaction in Radical Version.

1.3.5.2. Radical Mannich Reaction

Similarly to the previous reaction, a radical version of the Mannich reaction was developed by Tomioka in 2003.⁶³ The reaction was initiated by dimethylzinc and oxygen. This generates a methyl radical, which can abstract hydrogen α -to the oxygen of THF **106**. The radical thus formed then adds to the imine **110** generated *in situ* (resulted from condensation of amine **107** and aldehyde **108**) to give the aminyl radical **111**. This radical in turn reacts by homolytic substitution on dimethylzinc to give the zincate derivative **112** along with a methyl radical which sustains the radical chain. Treatment of the zincate derivative eventually afforded β -aminoether **113** in good yields (Scheme 33).

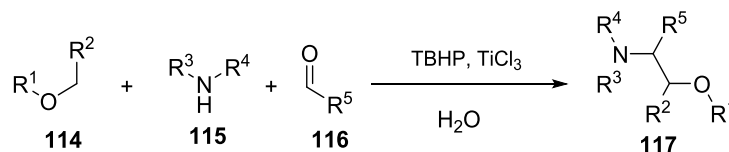


Scheme 33. Mannich Reaction in Radical Version of Tomioka.

⁶² Pastori, N.; Greco, C.; Clerici, A.; Punta, C.; Porta, O. *Org. Lett.* **2010**, *12*, 3898-3901.

⁶³ Yamada, K.-I.; Yamamoto, Y.; Tomioka, K. *Org. Lett.* **2003**, *5*, 1797-1799.

Later, Porta *et al.*⁶⁴ developed another radical version of the Mannich reaction using the system Ti^{III}/Ti^{IV} described above. The *tert*-butyl hydroperoxide (TBHP) was used as a source of *tert*-butoxy radical, which can abstract hydrogens in α -position of heteroatoms. The nucleophilic α -alkoxyalkyl radical thus generated can attack the generated *in situ* iminium to form aminoalcohols or aminoethers (Scheme 34).



Scheme 34. Mannich Reaction in Radical Version of Porta.

1.4. Radical-Ionic Multi-component Reactions

Reducing or oxidizing radicals formed in the reaction medium can generate respectively anions or cations which may be trapped in classical ionic reactions. Following this idea, several research groups developed MCRs that combine radical and ionic mechanisms. This is generally featured by the metallic species which can selectively reduce or oxidize the formed radicals. During the following section, the different radical-ionic MCRs will be highlighted.

1.4.1. Radical-anionic MCRs

In this type of reactions, the formed radical is reduced by metal species having reducing properties to create a nucleophilic species which may then react with an electrophile in a standard ionic process. Researchers developed numerous tandem processes from this type by involving different metals species such as Cr,⁶⁵ Co,⁶⁶ Pd,⁶⁷ Sm⁶⁸ and Ti.⁶⁹ Among all of these metal species, boron and zinc derivatives received more attention due to their commercial availability. One of the leading examples in this type of reactions is the one developed by Mukaiyama in 1973 using $(nBu)_3B$.⁷⁰ The reaction starts with the decomposition of $(nBu)_3B$ in the presence of O_2 to give the butyl radical which adds onto the Michael acceptor **118** to generate the enoyl radical **120**. The latter then reacts with another molecule of Bu_3B to give a boron enolate and a butyl radical, which propagate the radical chain. This enolate **121** reacts finally with benzaldehyde to give the aldol adduct **122** in good yield and moderate diastereoselectivity (Scheme 35).

⁶⁴ (a) Clerici, A.; Canella, R.; Pastori, N.; Panzeri, W.; Porta, O. *Tetrahedron* **2006**, *62*, 5986-5994; (b) Clerici, A.; Ghilardi, A.; Pastori, N.; Punta, C.; Porta, O. *Org. Lett.* **2008**, *10*, 5063-5066; (c) Spaccini, R.; Ghilardi, A.; Pastori, N.; Clerici, A.; Punta, C.; Porta, O. *Tetrahedron* **2010**, *66*, 2044-2052.

⁶⁵ Takai, K.; Matsukawa, N.; Takahashi, A.; Fujii, T. *Angew. Chem. Int. Ed.* **1998**, *37*, 152-155.

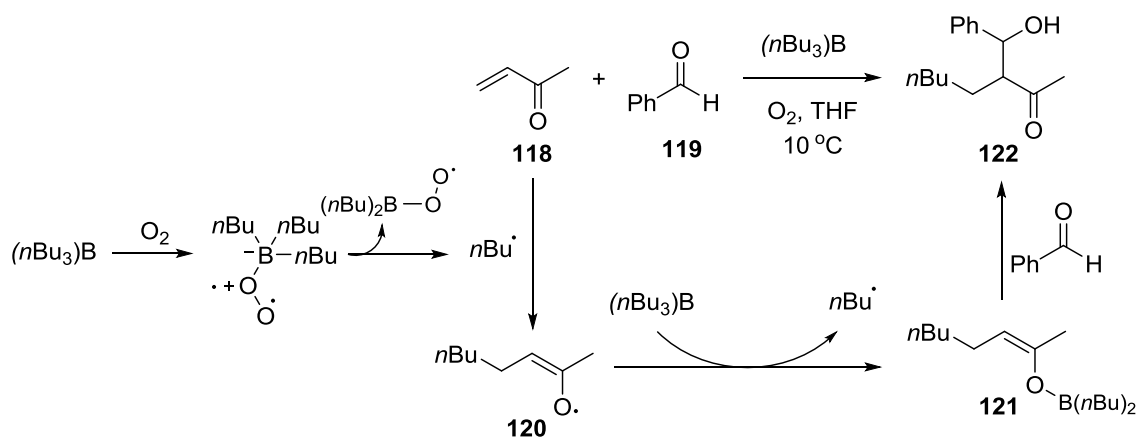
⁶⁶ Mizutani, K.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2003**, *5*, 3959-3961.

⁶⁷ Takai, K.; Ueda, T.; Ikeda, N.; Moriwake, T. *J. Org. Chem.* **1996**, *61*, 7990-7991.

⁶⁸ Szostak, M.; Fazakerley, N. J.; Parmar, D.; Procter, D. J. *Chem. Rev.* **2014**, *114*, 5959-6039.

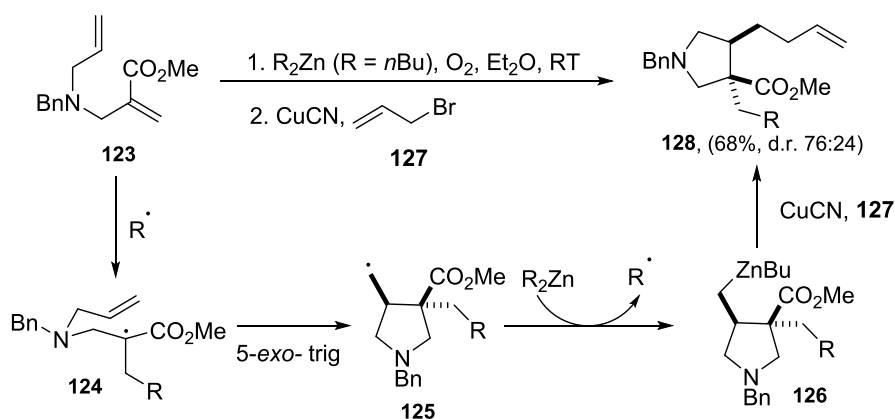
⁶⁹ Nii, S.; Terao, J.; Kambe, N. *J. Org. Chem.* **2000**, *65*, 5291-5297.

⁷⁰ Mukaiyama, T.; Inomata, K.; Muraki, M. *J. Am. Chem. Soc.* **1973**, *95*, 967-968.



Scheme 35. Radical-anionic MCR of Mukaiyama.

More recently, Chemla *et al.*⁷¹ exploited rate differences to design MCR cascade reaction. First, an alkyl radical, formed from the decomposition of dialkylzinc with oxygen was shown to add onto the double bond system of **123**. This triggered a 5-*exo*-trig radical cyclization which is faster than the reduction of the enolate radical. Finally, homolytic substitution at the zinc center forms a zincate derivative **126** and an alkyl radical, which propagate the radical chain. A transmetalation of zinc with copper eventually initiates a S_N2 displacement of an allyl bromide **127** to give substituted pyrrolidines **128** in good yields and moderate diastereoselectivity (Scheme 36).



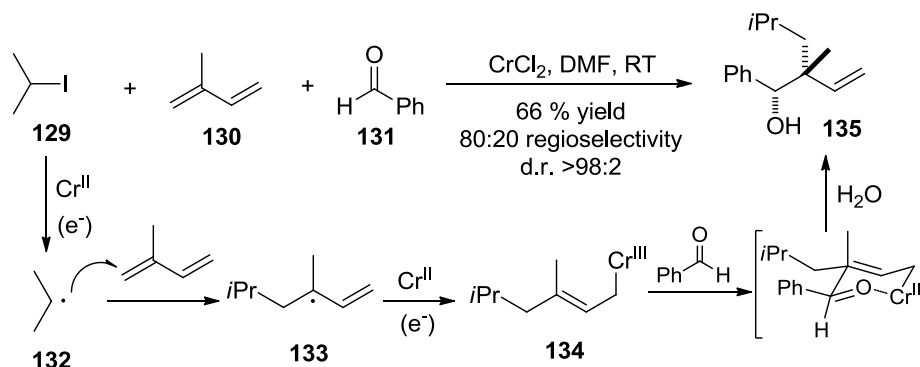
Scheme 36. Tandem Radical-anionic MCR of Chemla.

Another radical anionic MCR mediated Cr^{II} was described by Takai group.⁷² It relies on the fact that single electron transfers (SET) in the presence of Cr^{II} salts are much faster with allylic radicals than with secondary or tertiary alkyl radicals. Thus, they developed 3-CR radical anionic reactions involving CrCl₂, which reduces isopropyl iodide **129** through a one-electron reduction with Cr^{II} ion, to form the isopropyl radical **132** which may then add regioselectively to 1,3-diene **130**. Finally, SET from Cr^{II} salt to the resulting allylic radical **133** forms allylchromium species **134** which add to

⁷¹ (a) Denes, F.; Chemla, F.; Normant, J. F. *Angew. Chem. Int. Ed.* **2003**, *42*, 4043-4046; (b) Denes, F.; Cutri, A.; Perez-Luna, A.; Chemla, F. *Chem. Eur. J.* **2006**, *12*, 6506-6513; (c) Perez-Luna, A.; Botuha, C.; Ferreira, F.; Chemla, F. *Chem. Eur. J.* **2008**, *14*, 8784-8788.

⁷² Takai, K.; Matsukawa, N.; Takahashi, A.; Fujii, T. *Angew. Chem. Int. Ed.* **1998**, *37*, 152-155.

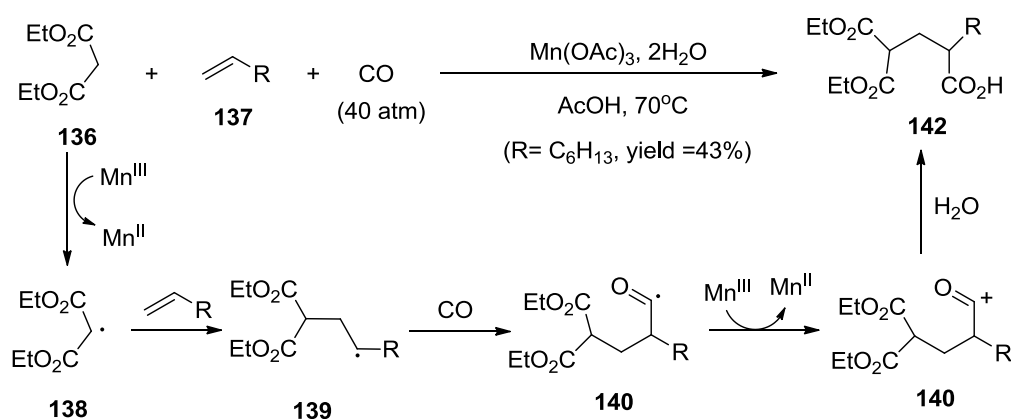
benzaldehyde, affording homoallylic alcohol **135** in good yield and excellent diastereoselectivity (Scheme 37).



Scheme 37. Radical-Anionic MCR mediated by Cr^{II} .

1.4.2. Radical-cationic MCRs

Applying the same concept than with the radical-anionic MCRs, the radical-cationic MCRs rely on the capacity of the metal to oxidize the formed radical selectively and generate a true electrophile. The common oxidants used in this type of processes are Mn or Ce. In case of Mn, and based on the work developed by Corey,⁷³ Fristad,⁷⁴ and Snider,⁷⁵ Ryu and Alper were able to oxidize the acyl radical by Mn^{III} .⁷⁶ They used Mn^{III} to do two tasks in this reaction. The first task is to generate an electrophilic malonyl radical **138** from malonate **136**, which adds to olefin **137**. The second task is to oxidize the acyl radical **140**, resulting from the reaction of radical **139** with carbon monoxide, into an acylium cation **140**. This cation is immediately trapped by the nucleophilic water to give the carboxylic acid **142** (Scheme 38).



Scheme 38. Radical-Cationic MCRs mediated by Mn^{III} .

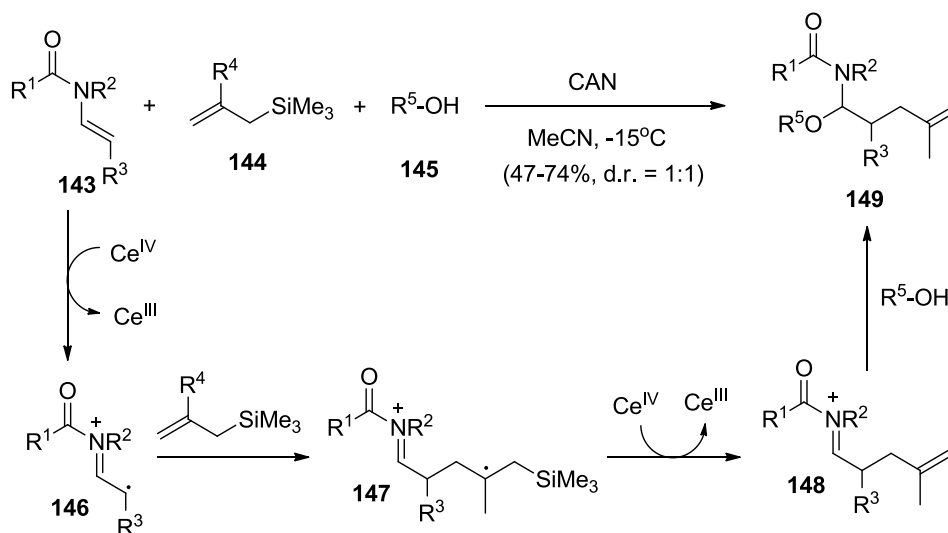
⁷³ Corey, E. J.; Kang, M. *J. Am. Chem. Soc.* **1984**, *106*, 5384-5385.

⁷⁴ Ernst, A. B.; Fristad, W. E. *Tetrahedron Lett.* **1985**, *26*, 376-3764.

⁷⁵ Snider, B. B.; Mohan, R.; Kates, S. A. *J. Org. Chem.* **1985**, *50*, 3659-3661.

⁷⁶ (a) Ryu, I.; Alper, H. *J. Am. Chem. Soc.* **1993**, *115*, 7543-7544; (b) Okuro, K.; Alper, H. *J. Org. Chem.* **1996**, *61*, 5312-5315.

More recently, Masson and coworkers⁷⁷ used CAN [$\text{Ce}(\text{NH}_4)_2(\text{NO}_3)_6$] as oxidant to generate cationic radical from enamide **143**. This radical could react with allylsilane **144** to give radical **147**, which is oxidized by Ce^{IV} followed by elimination of the silicon group to give iminium **148**. The new iminium **148** is trapped by an alcohol **145** to give β -allylated α -amidoethers **149** in good yields (Scheme 39).



Scheme 39. Radical-cationic MCRs of Masson.

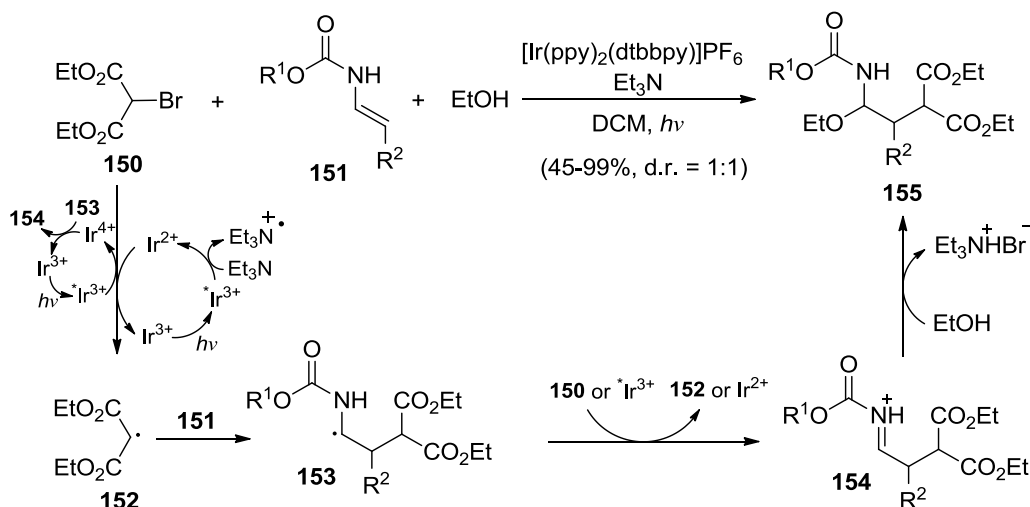
1.4.3. Photoredox-catalyzed Radical MCRs.

Since the beginning of the last century, scientists try to use sunlight to develop organic reactions. But the major obstacle they faced is that most organic molecules are not able to absorb sunlight. Therefore, chemists developed photocatalysts, which are able to absorb the light and transfer this energy to perform chemical transformations. Researchers found that the most efficient catalysts are based on ruthenium (II) and iridium (III). With the idea in mind to use light to initiate radical-ionic processes, Masson's group studied oxyalkylation of ene-carbamates in the presence of iridium (III).⁷⁸ They proposed two mechanisms for generating the radical and oxidizing it. The first mechanism, proposed the formation of the electrophilic malonyl radical through transfer of one electron from $\text{Ir}^{\text{(III)*}}$ to bromomalonate **150**. This radical attacks an ene-carbamate **151** to form the nucleophilic radical **153**, that is oxidized quickly by $\text{Ir}^{\text{(III)*}}$ into an *N*-acyliminium cation **154**. This cation is then trapped by an alcohol to form α -amidoethers **155** (Scheme 40). This oxidative mechanism did not rationalize the role of Et_3N in the reaction. So the second mechanism proposed a reductive pathway, starting by reduction of $\text{Ir}^{\text{(III)*}}$ to $\text{Ir}^{\text{(II)}}$ by Et_3N . Bromomalonate **150** could be reduced to the electrophilic malonyl radical **152** by $\text{Ir}^{\text{(II)}}$. After addition of this radical to the ene-carbamate **151**, the generated α -aminyl radical **153** could be oxidized either by the bromomalonate

⁷⁷ Bekkaye, M.; Masson, G. *Org. Lett.* **2014**, *16*, 1510-1513.

⁷⁸ Courant, T.; Masson, G. *Chem. Eur. J.* **2012**, *18*, 423-427.

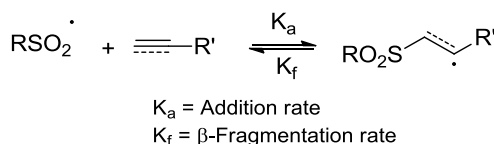
150 or by $\text{Ir}^{\text{(III)*}}$ to give an *N*-acyliminium cation **154** that was trapped by the alcohol to form α -amidoethers **155** (Scheme 40).



Scheme 40. Photo-redox Radical MCR.

1.5. Free-Radical Multi-component Reactions with Sulfonyl Derivatives

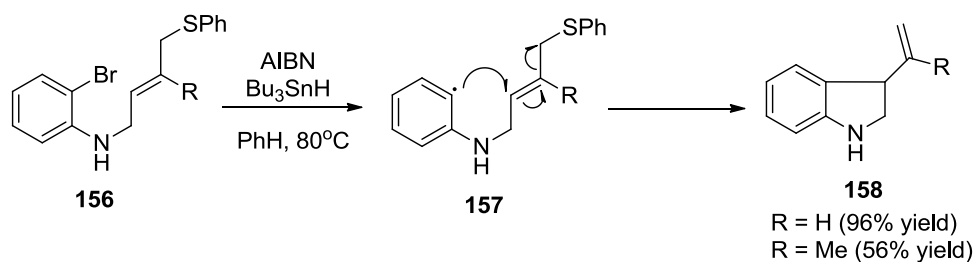
The electrophilic nature of sulfonyl radicals, their availability and easy preparation made them good candidates for radical MCRs. Their electrophilicity allowed the addition of the sulfonyl radical to electron rich olefins and alkynes, the process being governed by the reversibility of the reaction and the ratio between the rate of addition and rate of β -fragmentation (Scheme 41).



Scheme 41. Addition / Fragmentation Rate.

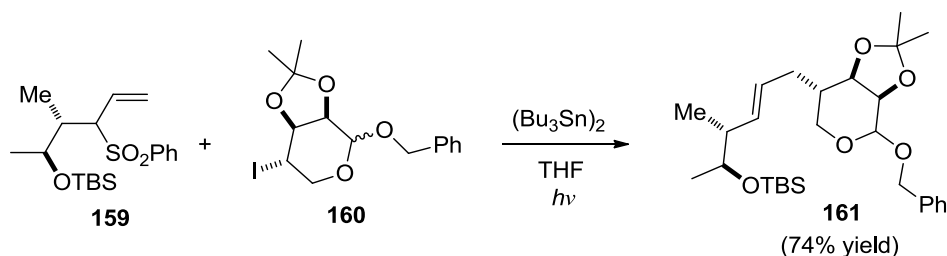
Ueno *et al.*⁷⁹ first used allylthioethers as allylation agents to cyclize bromoaniline derivatives **156**. The reaction was initiated by AIBN, which abstracted the hydrogen of Bu_3SnH to generate the tin radical. The latter then abstracted bromine to generate the intermediate radical **157**. Cyclization of the latter, followed by fragmentation of the phenylthiyl radical afforded the cyclized product **158** (Scheme 42).

⁷⁹ Ueno, Y.; Chino, K.; Okawara, M. *Tetrahedron Lett.* **1982**, *23*, 2575-2576.



Scheme 42. Fragmentation of Phenylthiyl Radical.

Later, Russell showed the utility of vinyl thioethers, sulfoxides and sulfones in allylation reactions, and their ability to fragment and afford the substituted olefins after the addition of alkyl radical.⁸⁰ As an application of these sulfones fragmentations, Keck *et al.*⁸¹ were the first to use allylsulfones in synthesis of natural products (Scheme 43).



Scheme 43. Sulfone Fragmentation (Key step in synthesis of (+)-Pseudomonic Acid C).

Through such examples, researchers shed light on the utility of these sulfones in radical reactions. In the next part of this chapter, we will focus on the development of sulfonyl derivatives in free radical MCRs.⁸²

1.5.1. Kinetic Aspects

The reversibility of the addition process of sulfonyl radicals to olefins depends on the rate of β -fragmentation of this radical as shown above (Scheme 41).

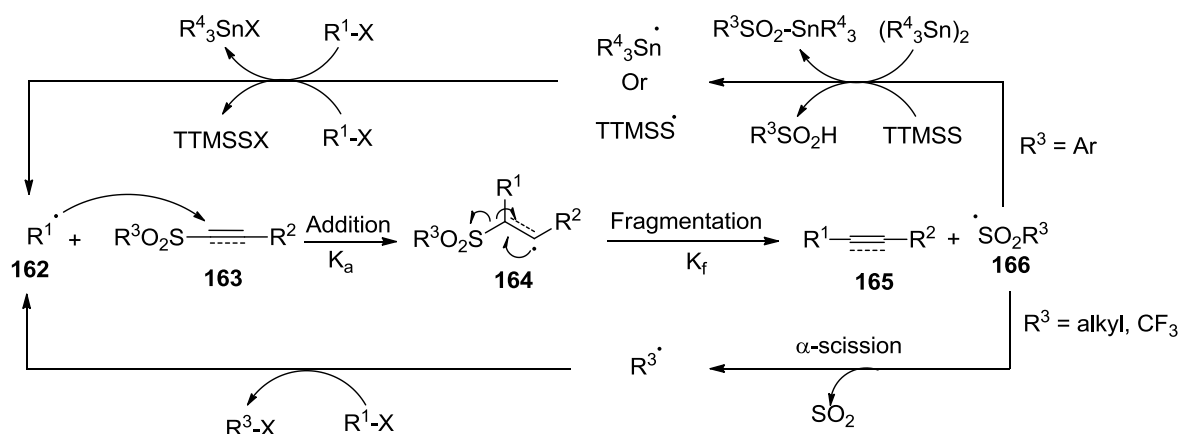
Addition of nucleophilic radical R^1 to α -position of sulfone **163** provide an alkyl or a vinyl radical which may fragment to provide the alkene or alkyne **165** and a sulfonyl radical **166**. The rate of β -fragmentation of sulfonyl radical **166** is depending on the stability of the intermediate radical **164** (Scheme 44).⁸³

⁸⁰ Russell, G. A.; Tashtoush, H.; Ngoviwatchai, P. *J. Am. Chem. Soc.* **1984**, *106*, 4622-4623.

⁸¹ Keck, G. E.; Tafesh, A. M. *J. Org. Chem.* **1989**, *54*, 5845-5846.

⁸² Ovadia, B.; Robert, F.; Landais, Y. *Chimia* **2016**, *70*, 34-42.

⁸³ (a) Timokhin, V. I.; Gastaldi, S.; Bertrand, M. P.; Chatgililoglu, C. *J. Org. Chem.* **2003**, *68*, 3532-3537; (b) 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.



The generated sulfonyl radical **166** may then evolve through two ways depending on R^3 substituent. When R^3 is an aryl group, arylsulfonyl radicals are known to be relatively stable and cannot fragment (under the reaction conditions) and sustain the radical chain. Then, they will react with other radical chain propagator like tin derivatives or with other less toxic species like silane derivatives (e.g. TTMSS: $(Me_3Si)_3SiH$) which was developed by Chatgililoglu.⁸⁴ It is worth noticing that in case of TTMSS, the concentration of the silane should be lower than the concentration of sulfone derivatives, otherwise the reduction product will be the only isolable product. When R^3 is an alkyl group, alkylsulfonyl radicals are less stable and tend to undergo α -scission with extrusion of SO_2 to generate alkyl radicals which can also propagate the radical chain. Zard *et al.*⁸⁵ showed that ethyl radical, which is generated from ethylsulfonyl radical after SO_2 extrusion, could propagate the radical chain in the absence of tin reagents. Also, when R^3 is CF_3 group, trifluoromethanesulfonyl radical decomposes very quickly to form the electrophilic trifluoromethyl radical (Scheme 44).⁸⁶ Fuchs *et al.*⁸⁷ used this phenomenon to propagate and sustain a radical reactions through electrophilic trifluoromethyl radical which could rapidly abstract hydrogen from alkane or from position α to oxygen of an ether and generate nucleophilic radical which add to the starting triflone and sustain the radical chain.

⁸⁴ Chatgililoglu, C.; Alberti, A.; Ballestri, M.; Macciantelli, D.; Curran, D. P. *Tetrahedron Lett.* **1996**, *37*, 6391-6394.

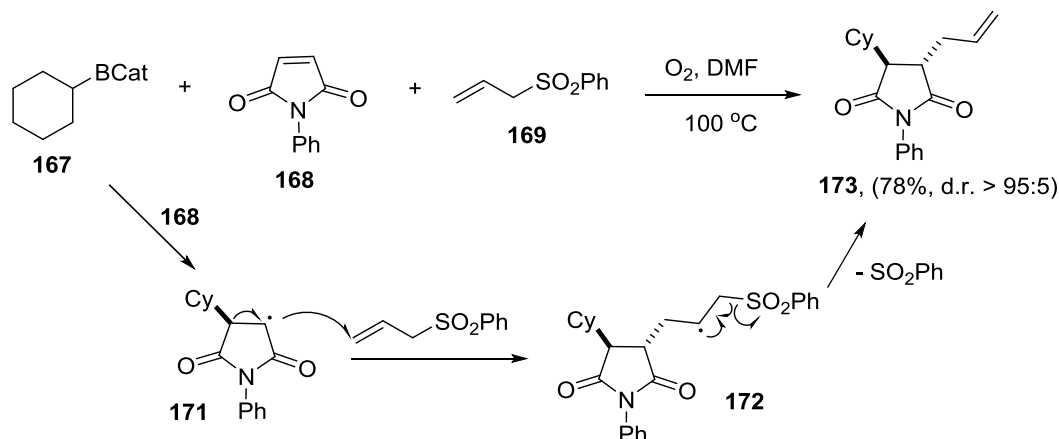
⁸⁵ (a) Le Guyader, F.; Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *J. Am. Chem. Soc.* **1997**, *119*, 7410-7411 ; (b) Bertrand, F.; Quiclet-Sire, B.; Zard, S. Z. *Angew. Chem. Int. Ed.* **1999**, *38*, 1943-1946.

⁸⁶ (a) Langlois, B.; Laurent, E.; Roidot, N. *Tetrahedron Lett.* **1991**, *32*, 7525-7528 ; (b) Langlois, B.; Laurent, E.; Roidot, N. *Tetrahedron Lett.* **1992**, *33*, 1291-1294.

⁸⁷ (a) Gong, J.; Fuchs, P. L. *J. Am. Chem. Soc.* **1996**, *118*, 4486-4487; (b) Xiang, J.; Fuchs, P. L. *J. Am. Chem. Soc.* **1996**, *118*, 11986-11987; (c) Xiang, J.; Jiang, W.; Gong, J.; Fuchs, P. L. *J. Am. Chem. Soc.* **1997**, *119*, 4123-4129; (d) Xiang, J.; Everts, J.; Rivkin, A.; Curran, D. P.; Fuchs, P. L. *Tetrahedron Lett.* **1998**, *39*, 4163-4166; (e) Xiang, J. S.; Fuchs, P. L. *Tetrahedron Lett.* **1996**, *37*, 5269-5272; (f) Xiang, J.; Jiang, W.; Fuchs, P. L. *Tetrahedron Lett.* **1997**, *38*, 6635-6638; (g) Xiang, J.; Fuchs, P. L. *Tetrahedron Lett.* **1998**, *39*, 8597-8600.

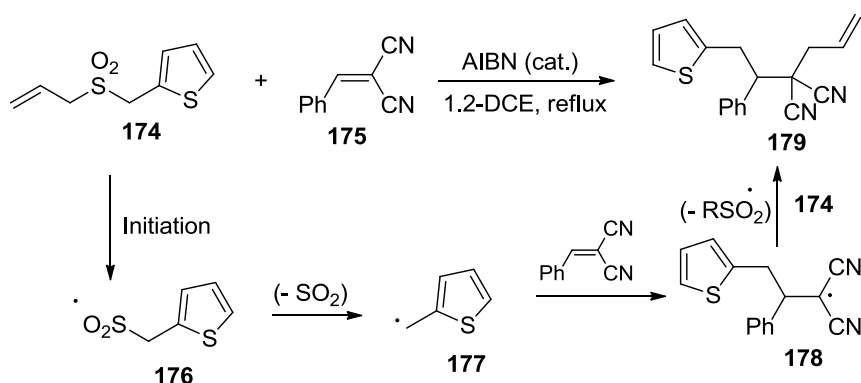
1.5.2. Carbo-allylation depending on Sulfonyl Radical

Renaud *et al.*⁸⁸ provide recently a nice example of the utility of allylsulfones, using organoboranes derivatives as radical precursors. The reaction starts by the addition of nucleophilic alkyl radical, resulting from the corresponding catecholborane **167**, to the electron poor olefin to give the electrophilic radical intermediate **171** which is trapped by the allylsulfone **169** to give the allylated product **173** and phenylsulfonyl radical that sustains the radical chain by reacting with the starting borane **167** (Scheme 45).



Scheme 45. Carbo-allylation MCRs with sulfone.

Zard *et al.*⁸⁹ also developed allylthiophenemethylsulfone **174**, which undergoes α -scission to give the nucleophilic radical **177**. This radical adds onto the electron poor olefin **175** to give the electrophilic radical **178**, which is finally trapped by another molecule of sulfone **174** to give the allylated product **179** (Scheme 46).



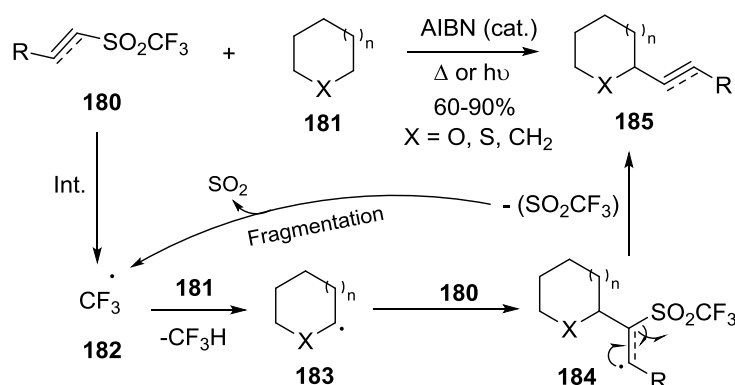
Scheme 46. Carbo-allylation MCRs with allylalkylsulfone.

⁸⁸ Schaffner, A. P.; Sarkunam, K.; Renaud, P. *Helv. Chim. Acta* **2006**, *89*, 2450-2461.

⁸⁹ Bertrand, F.; Le Guyader, F.; Liguori, L.; Ouvry, G.; Quiclet-Sire, B.; Seguin, S.; Zard, S. *Z. C. R. Acad. Sci., Ser. IIC: Chem.* **2001**, *4*, 547-555.

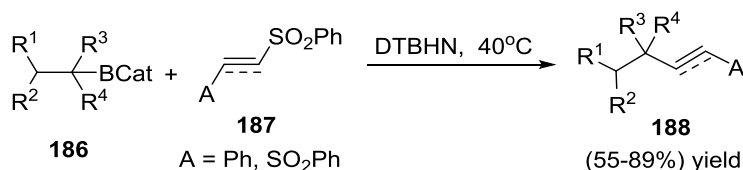
1.5.3. Carbo-alkenylation and alkynylation

Addition of alkenyl or alkynyl groups across olefin backbones remained for a long time a difficult task. Pioneering studies in this direction came from Fuchs *et al.*⁸⁷ who incorporated alkenyl or alkynyl groups to ethers or alkanes **181** using vinyl- and alkynyltriflone derivatives **180**. The radical process starts by a C-H abstraction by the very electrophilic trifluoromethyl radical **182**. The resulting nucleophilic alkyl radical **183** then adds onto the alkenyl- or alkynyltriflone **180**, followed by the β -elimination of the unstable trifluoromethanesulfonyl radical, which decomposes into SO₂ and the trifluoromethyl radical **182** that sustains the radical chain (Scheme 47).



Scheme 47. Alkenylation and Alkynylation by triflones.

More recently, Renaud *et al.*⁹⁰ developed a carbo-alkenylation and alkynylation of various olefins using organoboranes as a source of alkyl radicals. The reaction starts with the hydroboration of the corresponding olefins and formation of intermediates **186**. The alkyl radicals, generated by addition of sulfonyl radical or *t*-butoxide radical (from DTBHN initiator) onto the borane, then add onto the sulfone derivatives **187** to give, after β -elimination of the phenylsulfonyl moiety, the alkenylated or alkynylated products **188** in good yields (Scheme 48).



Scheme 48. Carbo-alkenylation and alkynylation from corresponding catecholboranes.

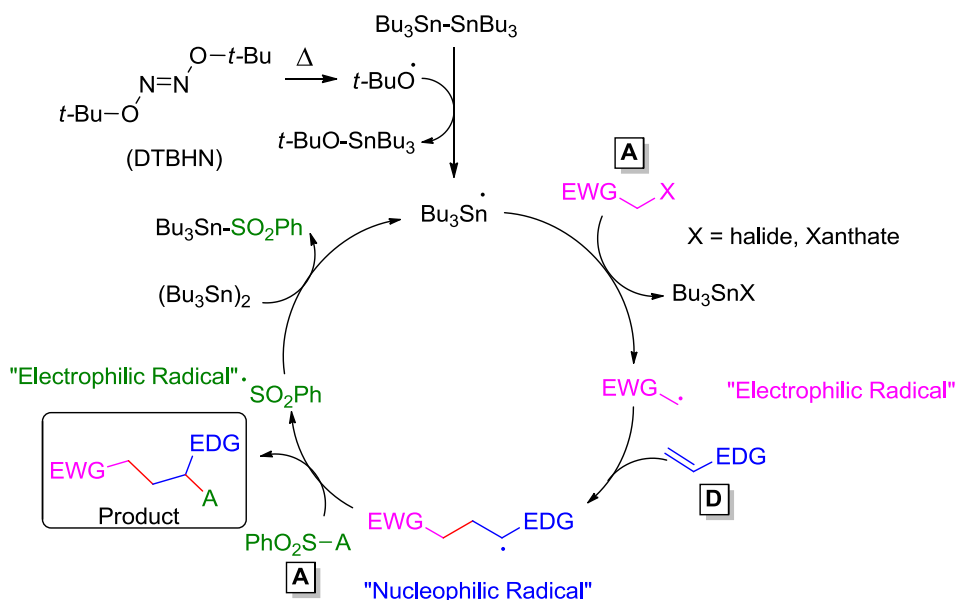
The last two examples showed the progress in the alkenylation and alkynylation of olefins. But these methods showed some limitations either for using CF₃ group in the first example or using catecholboranes in the second one. Recently our group developed new free-radical three-component carbo-alkenylation and alkynylation of olefins in which two functional groups could be added across the π -system of unactivated olefins.⁹¹

⁹⁰ Schaffner, A. P.; Darmency, V.; Renaud, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 5847-5849.

⁹¹ Liautard, V.; Robert, F.; Landais, Y. *Org. Lett.* **2011**, *13*, 2658-2661.

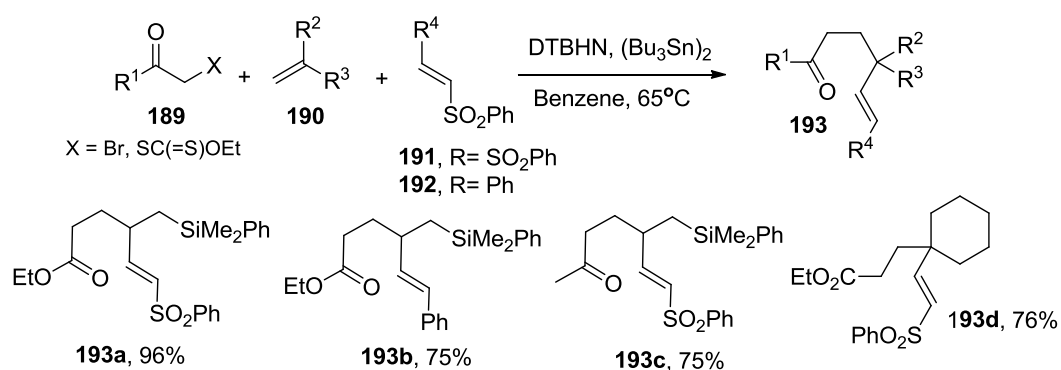
The reaction between the three components was categorized as “ADA” free radical multi-component system (Acceptor, Donor, Acceptor systems).³⁸ In this system, the first electrophilic radical (acceptor), generated from the corresponding xanthates or alkyl halides after abstraction of halide or xanthate by tin radical, add to the less hindered end of an electron-rich olefin (donor). The newly formed nucleophilic radical can then be trapped by the electrophilic sulfone derivatives (acceptor). The sulfonyl radical, generated after β -fragmentation, propagate the chain by reacting with stoichiometric amount of hexabutylditin (Scheme 49).

Based on this mechanism, our group developed several reactions changing the nature of the sulfone acceptor. For instance Landais *et al.* developed Carbo-alkenylation, -alkynylation and oximation. In this section carbo-alkenylation, alkynylation will be discussed in more detail.



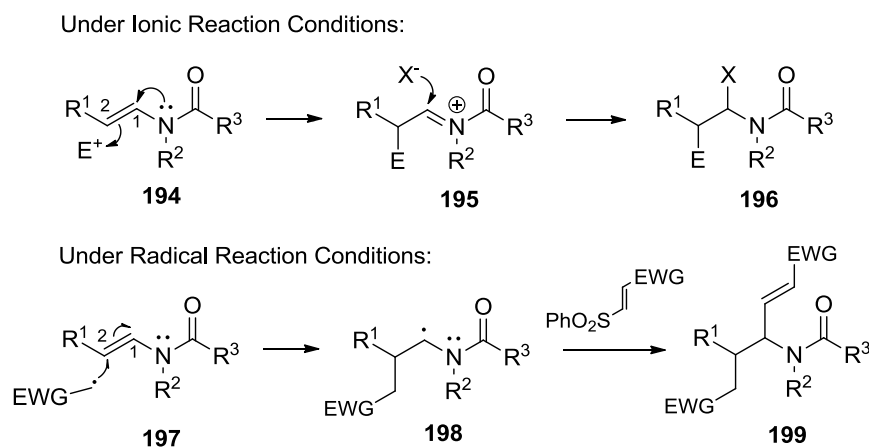
Scheme 49. Free-Radical three-component Mechanism

For carbo-alkenylation, the use of ethylene bisphenylsulfone **191** as a sulfone acceptor provided the alkenylated products **193a,c,d** in excellent yield. In contrast, styrylsulfone **192** gave also the expected products **193b** but in slightly lower yields. This could be rationalized based on the fact that styrylsulfone **192** is less electrophilic than bisphenylsulfone **191**. As expected, electron-rich olefins (e.g. allylsilanes or vinyl ethers) are more reactive in this reaction comparing to other alkenes. This shows the importance of polarity effects on the reactivity of olefins. One of the advantages of this reaction is the easy setup of quaternary centers which can give the access to valuable structures in one step and formation of two C-C bonds. It is also worth noticing that the nature of radical precursor **189** (xanthate or alkyl halide) may be also be varied, extending the reaction scope. For instance, varying **189** can give access to ketones, nitriles, amides or malonates in good yields (Scheme 50).

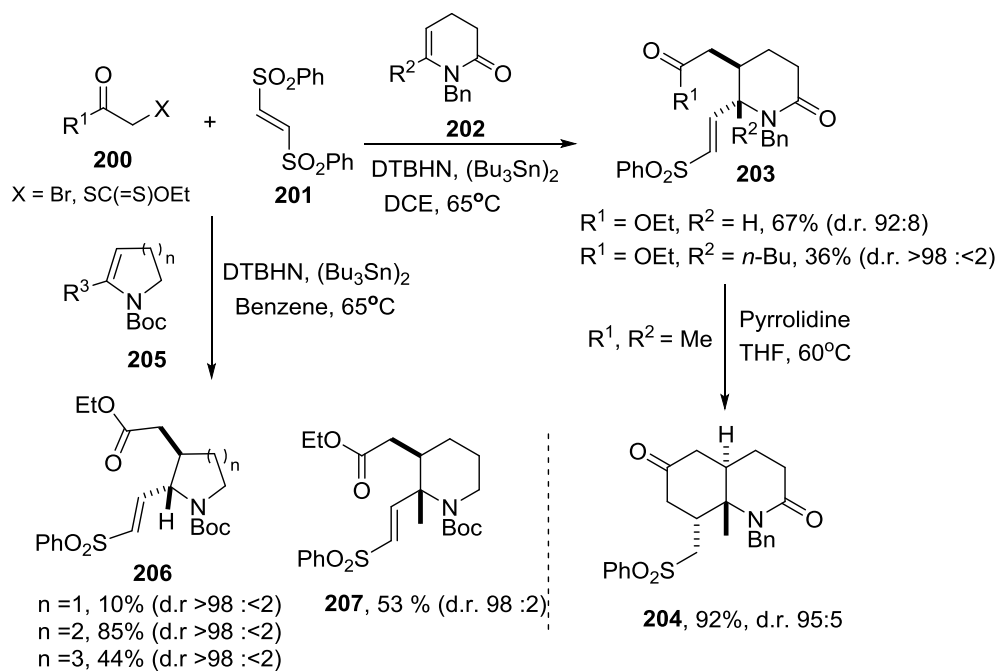


Scheme 50. Examples for Carbo-alkenylation MCRs.

Landais *et al.*⁹² extended this carbo-alkenylation reaction to include cyclic and acyclic enamides and ene-carbamates. These reactions gave access to highly functionalized amides and carbamates with good diastereocontrol. Enamides and ene-carbamates show, under ionic conditions, nucleophilic then electrophilic reactivity on the C(2) and C(1) carbons respectively. Under radical conditions, the electrophilic radical adds effectively on C(2) which lead to an electron-rich radical intermediate. This intermediate can then be trapped by an electrophilic sulfone (Scheme 51). The radical and ionic reactivities of enamides and ene-carbamates are thus complementary. Free-radical carbo-alkenylation reactions on enamide **202** afford lactams **203** which can be functionalized easily, as shown in (Scheme 51), with the elaboration of the core of some alkaloids from Lycopodium family.

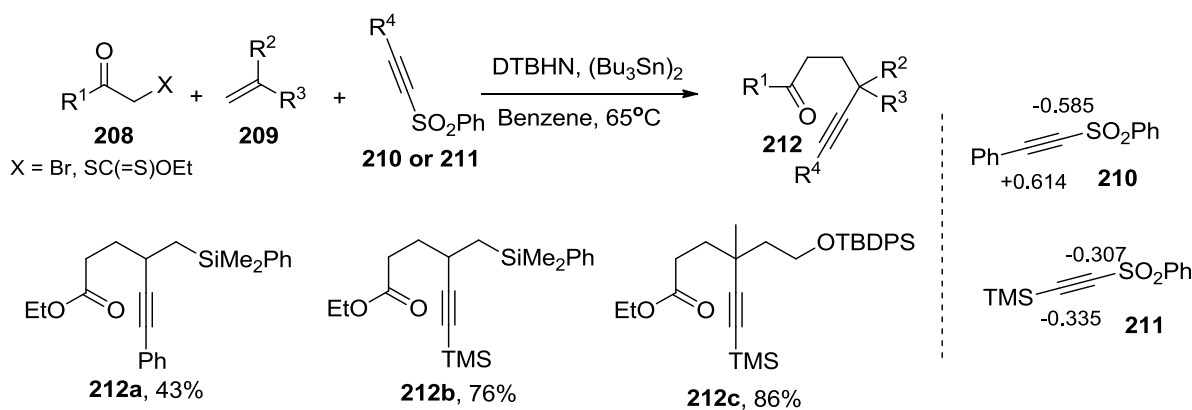


⁹² Poittevin, C.; Liautard, V.; Beniazza, R.; Robert, F.; Landais, Y. *Org. Lett.* **2013**, *15*, 2814-2817.



Scheme 51. Carbo-alkenylation MCR on Enamides and Ene-carbamates.

Similarly, Free radical carbo-alkynylation MCRs were developed in our group starting from alkynylsulfone **210**, **211**. The yields are in general good, but it was observed that the yields are better with alkynylsulfone **211** bearing a trimethylsilyl group. This may be due to the low polarization in silylalkynyl sulfone as compared to alkynylsulfone **210** (Scheme 52).



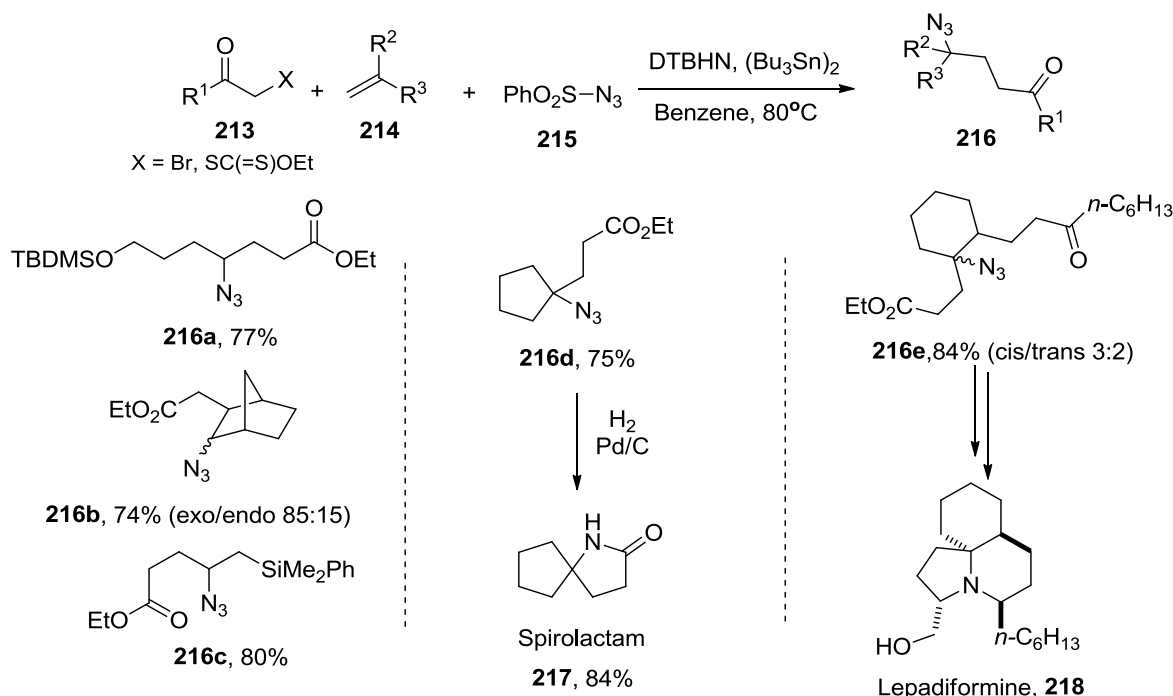
Scheme 52. Examples for Carbo-alkynylation MCRs.

The Mulliken population analysis, studied by DFT calculations, showed a partial negative charge on the alkyne carbon center α - to the sulfone. The high polarization in case of alkynylsulfone **210** leads to mismatch reactivity towards the electron-poor radical species, generated from the radical precursor **208**, which explain the modest yields in this cases. In contrast, little or no polarization was observed on silylalkyne **211**, which may be due to the strong π -d interaction between silicon (a π -acceptor) and the carbon center (Scheme 52).⁹¹

1.5.4. Carbo-azidation

Renaud *et al.*⁹³ were the first to report the use of sulfonylazides as radical traps. With systems similar to the ones used in carbo-alkenylation, they were able to form C-C bond and C-N bond in one pot. In the same way, the electrophilic radicals, generated from corresponding alkyl halides **213**, could add to the electron-rich olefins **214** to afford the nucleophilic radical which in turn was trapped by sulfonylazide **215** to finally give the azide product **216** in excellent yields (Scheme 53).

The potentiality of this reaction is illustrated with the straightforward synthesis of Lepadiformine **218**, the tricyclic core being elaborated in only two steps using a carbo-azidation reaction as a key step. Access to spiro lactams **217** was also easily achieved through a of carbo-azidation/reduction sequence (Scheme 53).⁹⁴



Scheme 53. Examples for Carbo-azidation MCRs.

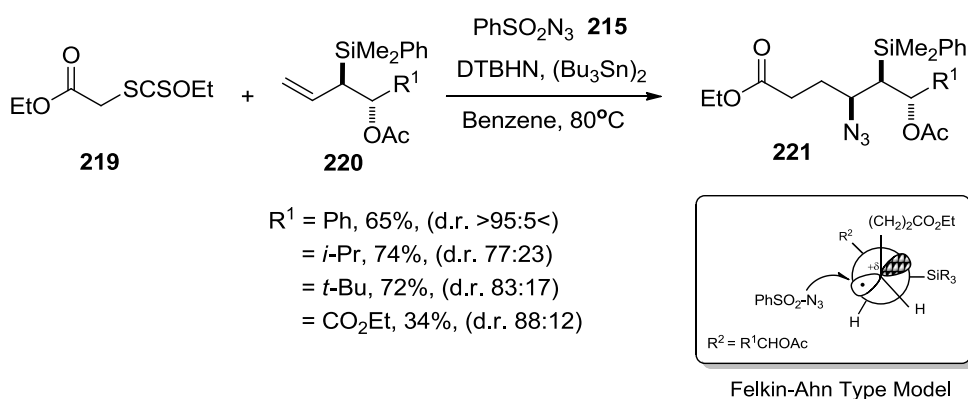
In a fruitful cooperation between Renaud and Landais teams, the stereocontrol in carbo-azidation reaction of acyclic chiral allylsilanes was investigated.⁹⁵ Addition of xanthate derivatives **219** onto the electron-rich chiral allylsilanes afforded the β -silyl radicals, which were trapped by sulfonylazide **215** to give β -azidosilanes with high level of diastereocontrol (up to 95:5 in favor of *syn* isomer).

⁹³ Ollivier, C.; Renaud, P. *J. Am. Chem. Soc.* **2001**, *123*, 4717-4727

⁹⁴ (a) Panchaud, P.; Ollivier, C.; Renaud, P.; Zigmantas, S. *J. Org. Chem.* **2004**, *69*, 2755-2759; (b) Schär, P.; Renaud, P. *Org. Lett.* **2006**, *8*, 1569-1571; (c) Lapointe, G.; Schenk, K.; Renaud, P. *Org. Lett.* **2011**, *13*, 4774-4777; (d) Lapointe, G.; Schenk, K.; Renaud, P. *Chem. Eur. J.* **2011**, *17*, 3207-3212.

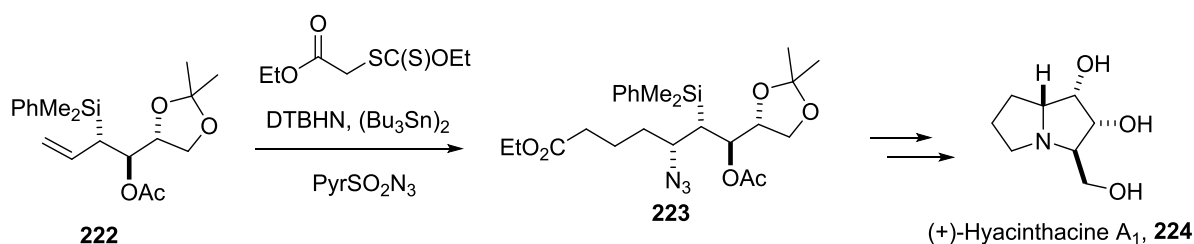
⁹⁵ Chabaud, L.; Landais, Y.; Renaud, P.; Robert, F.; Castet, F.; Lucarini, M.; Schenk, K. *Chem. Eur. J.* **2008**, *14*, 2744-2756.

The level of diastereocontrol depends on the nature of the silicon group and on the R¹ substituent. This diastereocontrol could be rationalized through Felkin-Ahn type model, which suggested pyramidalized transitional state and quasi-staggered confirmation to avoid gauche interactions between the most hindered groups SiR₃ and (CH₂)₂CO₂Et. According to that, the sulfonyl azide is believed to approach *anti* relative to the bulky silicon group from the side of the smallest H substituent. The formation of minor diastereomer would result from an approach of sulfonylazide **215** *anti* relative to the silicon group, but closer to the bulky R² substituent. It is also worth noticing that in such transition state, the developing positive charge β to silicon is best stabilized by overlapping with the quasi coplanar electron-rich C-Si bond (silicon β-effect) (Scheme 54).



Scheme 54. Carbo-azidation MCRs with Chiral Allylsilanes.

As an application of this methodology, the first diastereoselective total synthesis of the potent glycosidase inhibitor (+)-Hyacinthacine A₁ **224** was established.⁹⁶ Based on the stereocontrolled carbo-azidation reaction of chiral allylsilane **222** as key step, the authors established their synthesis (Scheme 55).

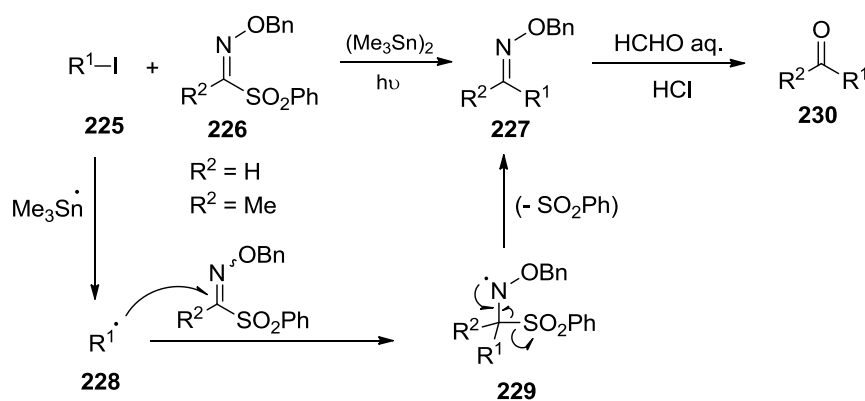
Scheme 55. Total Synthesis of Hyacinthacine A₁

⁹⁶ Chabaud, L.; Landais, Y.; Renaud, P. *Org. Lett.* **2005**, *7*, 2587-2590.

1.5.5. Carbo-oximation

Kim *et al.*⁹⁷ first showed that sulfonyloximes are good radical traps. They demonstrated that the addition of alkyl radical **228**, generated from the corresponding alkyl halide **225**, onto sulfonyloxime **226** affords, after β -elimination of the phenylsulfonyl radical, the alkylated oxime **227** (Scheme 56).

These oximes are very useful intermediates for the synthesis of the corresponding carbonyls. Actually Kim's first trials⁹⁷ were to develop radical mediated acylation reactions. But due to the reversible addition of alkyl radicals to C=O as a consequence of the higher π -bond strength of the C=O bond, these trials were unsuccessful. Therefore, sulfonyloximes, are excellent surrogates of carbonyl radical acceptors. Based on this methodology, the hydrolysis of oxime **227** in formaldehyde and HCl gave access to the corresponding aldehyde or ketone **230** depending on the R² substituent (Scheme 56).



Scheme 56. Alkylation of Sulfonyloxime / Indirect Way of Radical Acylation.

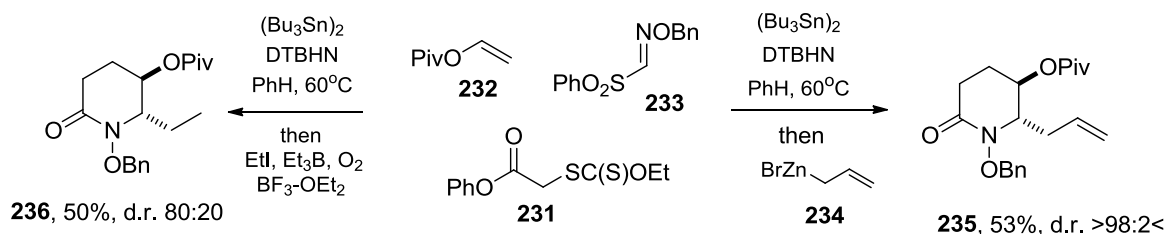
It is worth noticing that, using a sulfone in this reaction is crucial for two reasons. First, the sulfone group decreases the energy difference between the SOMO of the alkyl radical and the LUMO of the radical acceptor, which in turn will increase the rate of addition of the alkyl radical to the oxime. This feature was not present when a PhS was used instead of a PhSO₂ group. The second point concerns the radical chain propagation through the reaction of the β -fragmented sulfone with bis(trialkyl)tin that showed much better efficacy than the propagation through a phenyl-thio radical.

Recently our laboratory devised a sequential four component carbo-oximation reaction.⁹⁸ Instead of hydrolyzing the oxime group, the oximated product was allowed to react with alkyl radical or allylzinc reagent. Thus, the electrophilic radical, generated from the corresponding xanthate **231**,

⁹⁷ (a) Kim, S.; Lee, I. Y.; Yoon, J. Y.; Oh, D. H. *J. Am. Chem. Soc.* **1996**, *118*, 5138-5139; (b) Kim, S.; Yoon, J.-Y. *J. Am. Chem. Soc.* **1997**, *119*, 5982-5983; (c) Kim, S.; Song, H.-J.; Choi, T.-L.; Yoon, J. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 2524-2526; (d) Kim, S.; Yoon, J. Y.; Lee, I. Y. *Synlett* **1997**, 475-476; (e) Kim, S.; Lee, I. Y. *Tetrahedron Lett.* **1998**, *39*, 1587-1590.

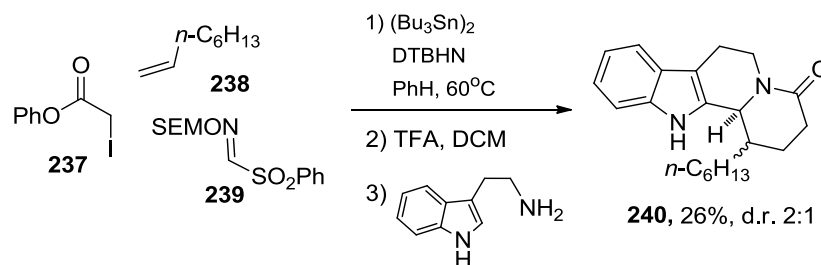
⁹⁸ Godineau, E.; Landais, Y. *J. Am. Chem. Soc.* **2007**, *129*, 12662-12663.

adds to electron-rich olefin **232** to generate the nucleophilic intermediate radical which is rapidly trapped by the electrophilic sulfonyloxime **233** to afford, after reaction with an alkyl radical or an allylzinc reagent, the lactamized products **235**, **236** in good yields and high diastereoselectivity (Scheme 57). This sequence represents a straightforward strategy to access to highly substituted piperidinones with up to three stereogenic centers generated in a one-pot operation.



Scheme 57. Carbo-oximation MCRs/Cyclization Sequence.

Our group also devised new oximes that showed better synthetic utility.⁹⁹ For instance the SEM-sulfonyl oxime **239**, was found to be slightly more reactive than the OBn-sulfonyl oxime **233**. Thus smoother hydrolysis of this new oxime, after the 3CR-carbo-oximation reaction, afforded an efficient access to an aldehyde, which underwent Pictet-Spengler/lactamization sequence to give a rapid and high yielding access to the tetracyclic core **240** of eburnane alkaloids (Scheme 58).



Scheme 58. Carbo-oximation MCR with SEM-Sulfonyloxime/PicteteSpengler/lactamization cascade.

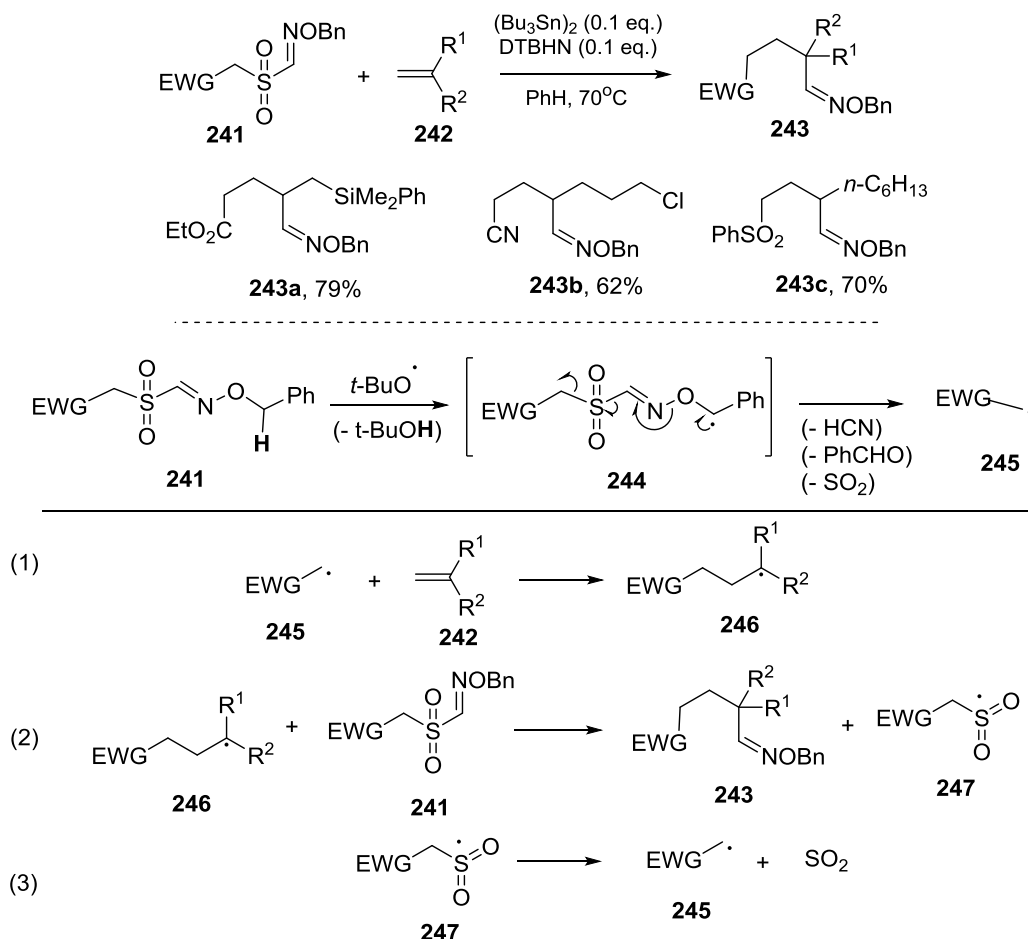
Considering the aforementioned reactions, the sulfonyl radical plays an essential role in chain propagation through its reaction with bis(trialkyl)tin derivatives. Thus, using stoichiometric amount of tin derivatives is required. But tin derivatives have drawbacks beside their toxicity.¹⁰⁰ The large amount of tin derivatives used in these reactions to sustain radical chain, generates large amounts of tin residue which contaminate the final products.

To avoid using tin derivatives in MCRs, our group devised new bifunctional reagents which incorporate both the oxime function and the radical precursor. The behavior of these bifunctional

⁹⁹ Landais, Y.; Robert, F.; Godineau, E.; Huet, L.; Likhite, N., *Tetrahedron*, **2013**, *69*, 10073-10080.

¹⁰⁰ (a) Le Grogne, E.; Chrétien, J.-M.; Zammattio, F.; Quintard, J.-P. *Chem. Rev.* **2015**, *115*, 10207-10260; (b) Ferreira, M.; Blanco, L.; Garrido, A.; Vieites, J. M.; Cabado, A. G. *J. Agric. Food Chem.* **2013**, *61*, 4195-4203.

reagents relies on the α -scission of the alkylsulfonyl radical intermediate.¹⁰¹ These new reagents play two roles in MCRs. First, they act as a source of electrophilic radicals, which add to the electron-rich olefin. Then, they can be trapped by the resulting nucleophilic radicals generated during the MCRs processes (Scheme 59).



Scheme 59. 2CR-Carbo-oximation Process.

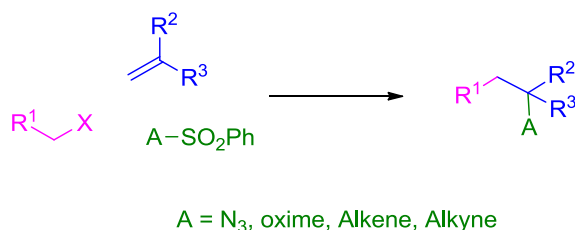
Although the process can be carried out under tin-free conditions, a catalytic amount of $(\text{Bu}_3\text{Sn})_2$ was shown to increase the reaction yield. The initiation mechanism is interesting and starts by the abstraction of one of the two benzylic hydrogen atoms by the *t*-BuO radical, followed by the β -fragmentation of the generated benzylic radical to release benzaldehyde, HCN and SO_2 and give the electrophilic radical **245**. The latter then adds to the electron-rich olefin **242**, generating the nucleophilic radical **246** which was trapped by the starting oxime **241** to afford the product **243**.

According to this reaction mechanism, tin is not required in this reaction and its role in catalytic amount is not yet clear. It is envisioned that the tin nucleophilic radical could attack the sulfonyloxime **243** to generate a stabilized alkoxyaminy radical, followed by a β -fragmentation to generate the electrophilic radical **245** more efficiently (Scheme 59).

¹⁰¹ Ovadia, B.; Robert, F.; Landais, Y. *Org. Lett.* **2015**, *17*, 1958-1961.

1.6. Conclusion

Along this chapter, we presented the state of the art in multi-component radical reactions. The combination of radical processes and multicomponent reactions showed its efficiency to access complex structures and form several bonds in one step. With this free radical MCRs, C-C, C-N, C-Cl bonds and different functional groups could be installed in one step and in an efficient way. We showed also the utility of sulfonyl radicals in MCRs and how they can propagate the radical chain, increase the rate of the reactions and integrate wide range of functional groups (azide, alkene, alkyne, oxime and alkyl). Moreover, the pronounced impact of these MCRs was highlighted through the synthesis of several natural products, which show that this synthetic tool may be utile in total synthesis of the natural products that will be presented in this dissertation, Leucophyllidine and Eucophylline. In the next chapter, we will focus on the optimization of the carbo-oximation MCR process and show how it was used to elaborate Eucophylline.



Scheme 60. Free Radical MCRs.

Chapter two
Total Synthesis of Eucophylline

2.1. Introduction

Eucophylline **3**,¹⁰² the recently isolated tetracyclic vinylquinoline alkaloid from *Leuconotis eugenifolius*, retained our attention. This new skeleton has an unprecedented tetrahydrobenzo[b][1,8]naphthyridine chromophore, which posed questions about its biogenetic pathway. The access to the naphthyridine core which incorporates a bicyclic system with an ethyl group on the all-carbon quaternary stereocenter represents a challenging issue for organic chemists. The synthesis of bicyclic systems, like the one present in Eucophylline, has not been well-reported before. Only few methods reported the synthesis of simple bicyclic systems without any substitution on the bridgehead carbon, making our mission more challenging. Besides, the synthesis of Eucophylline, the south fragment of Leucophyllidine **1**, will pave the way for the total synthesis of cytotoxic bisindole alkaloid, Leucophyllidine. All of these motifs prompted us to develop an access to Eucophylline.

Along this chapter, the efforts towards total synthesis of Eucophylline will be presented, relying on the recently developed carbo-oximation reaction. In parallel, deep focus on the bridgehead bicyclic lactams and a remarkably stable bicycle α -chloroamine will be discussed.

2.2. Retrosynthesis Analysis

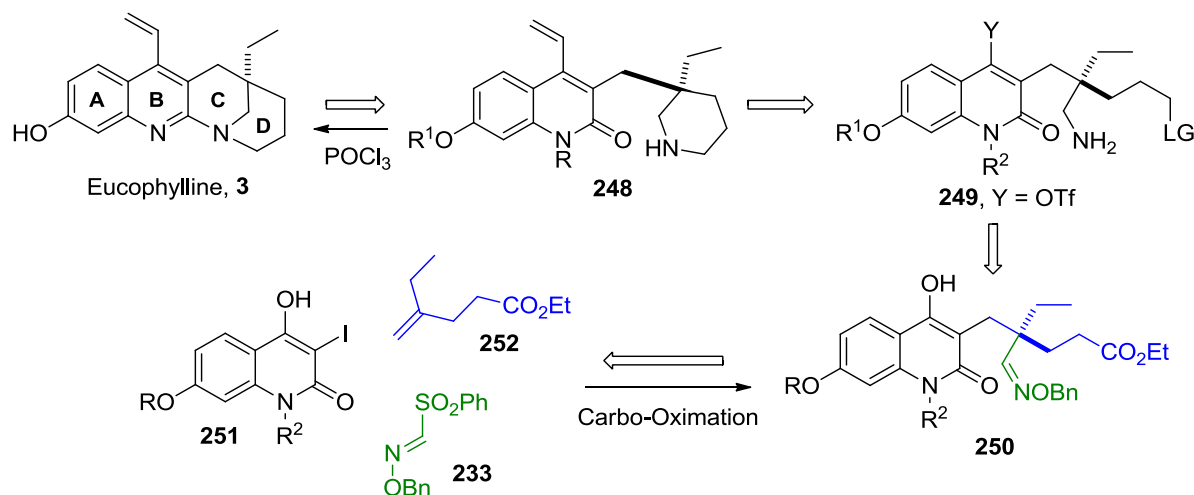
The retrosynthesis analysis of Eucophylline is centralized around the synthesis of a challenging bicyclic system, the synthesis of which will be based on the recently developed free radical carbo-oximation multi-component reaction.¹⁰³ Two different disconnection strategies were proposed:

1. Iodoquinoline Strategy.

In this approach, the tetracyclic vinylquinoline could be formed after the reaction between piperidine NH and quinoline amide in **248** under Vilsmeier reaction conditions to form cycle **C**. The piperidine ring **D** would in turn be formed from the cyclization of a free amine on an alcohol, activated as a mesylate, both amine and alcohol being formed by reductions of respectively an oxime and an ester. The quaternary center would be accessed relying on the free radical carbo-oximation reaction between the iodoquinoline **251**, sulfonyl oxime **233**, and olefin **252**. The reactive vinylic fragment could be introduced after formation of piperidine cycle **D** through a Suzuki coupling (Scheme **61**). It is worth noting that this approach is very similar to the proposed biogenetic pathway proposed by Morita and coworkers.¹⁰²

¹⁰² Deguchi, J.; Shoji, T.; Nugroho, A. E.; Hirasawa, Y.; Hosoya, T.; Shirota, O.; Awang, K.; Hadi, A. H. A.; Morita H. *J. Nat. Prod.* **2010**, *73*, 1727-1729.

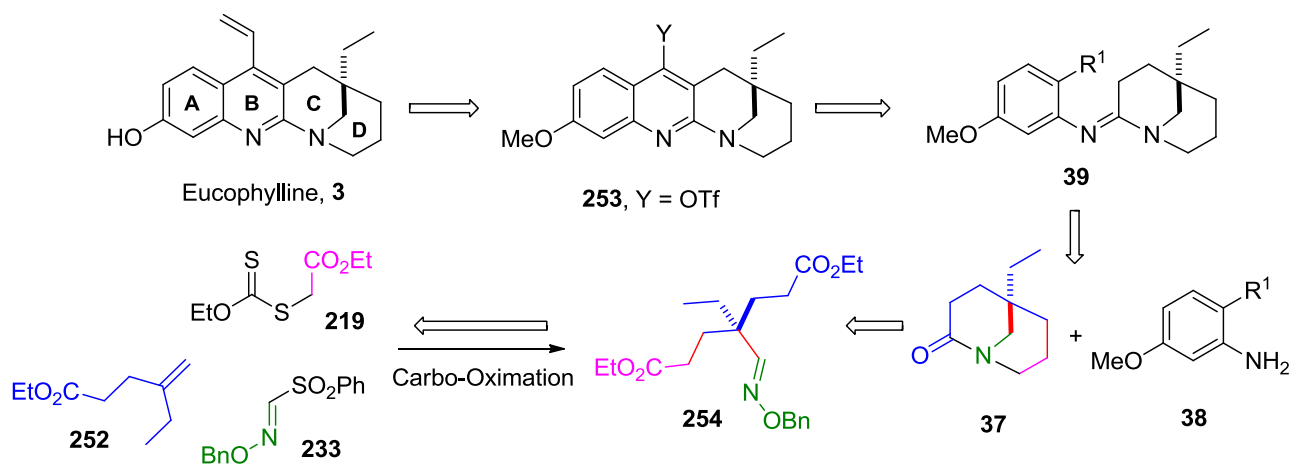
¹⁰³ Landais, Y.; Robert, F.; Godineau, E.; Huet, L.; Likhite, N. *Tetrahedron* **2013**, *69*, 10073-10080.



Scheme 61. Disconnection Approach of Eucophylline through Iodoquinoline.

2. Azabicyclo[3.3.1]nonane Strategy

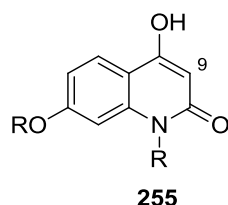
In this approach, the reactive vinylic fragment would be introduced in a late stage of the synthesis through a Suzuki coupling after formation of tetracyclic vinylquinoline **253**. This tetracycle would be formed from the base-mediated cyclization of amidine **254** (Friedländer type cyclization), which in turn would be formed from the coupling between simple trisubstituted aniline **38** and the azabicyclo[3.3.1]nonane **37**. This bicycle **37** would be accessed after reduction of the fully functionalized oxime **254**, followed by lactamization and cyclization. The oxime **254** could be synthesized relying on the free radical carbo-oximation reaction between the sulfonyl oxime **233**, xanthate ester **219** and olefin **252** (Scheme 62)



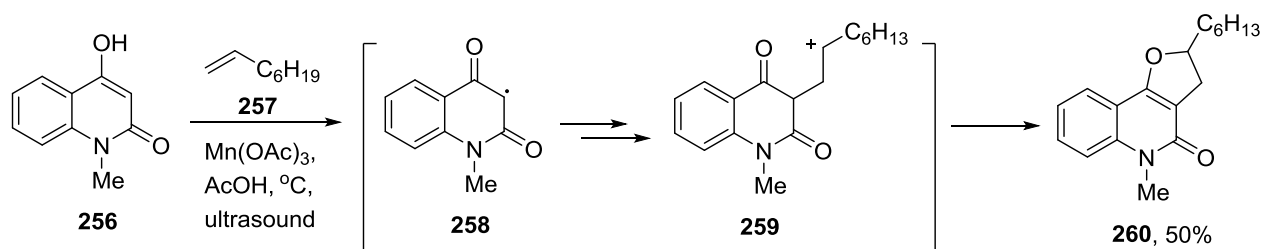
Scheme 62. Disconnection Approach of Eucophylline through Azabicyclo[3.3.1]nonane.

2.3. First Strategy: Iodoquinoline Strategy.

Two questions had to be answered following this strategy. Would it be possible to generate a stable radical at C-9 of quinoline **255** and would this radical be electrophilic enough to add onto an electron-rich olefin?



The pioneering work by Parsons *et al.*¹⁰⁴ in generating radical in C-9 position of quinoline derivatives like **256** was a promising start for our approach. This group was able to alkylate quinoline **256** by olefin **257** through a reaction mediated by manganese (III) acetate in AcOH. The reaction started by initial oxidation of **256** to form radical **258** through formation of a manganese (III) enolate, which is favored in this type of reactions.¹⁰⁵ Then, the electrophilic radical **258** added to the electron-rich olefin **257** to form the secondary radical, which was oxidized by another equivalent of manganese (III) to generate cation **259**. This cation was trapped by the enol hydroxyl group to form the five-membered ring **260** (Scheme 63).



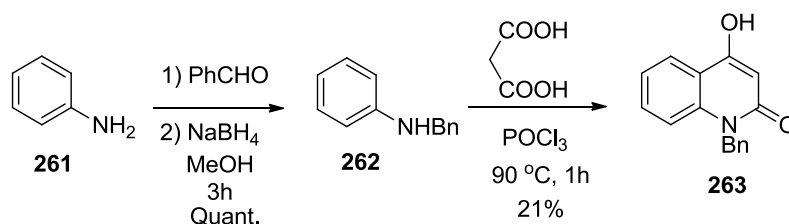
Scheme 63. Alkylation of Quinoline through manganese(III)-promoted Radical Addition Reaction.

Based on these promising results, a quinoline model was synthesized and tested under carbonylation reaction conditions. Therefore, the quinoline **263** was synthesized from the readily available aniline through protection of the free amine by a benzyl group, followed by a reaction with malonic acid to give the desired quinoline **263** in low yield (Scheme 64).¹⁰⁶

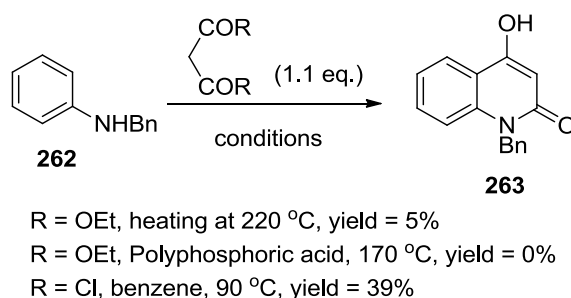
¹⁰⁴ (a) Bar, G.; Parsons, A. F.; Thomas, C. B. *Tetrahedron Lett.* **2000**, *41*, 7751-7755; (b) Bar, G.; Parsons, A. F.; Thomas, C. B. *Tetrahedron* **2001**, *57*, 4719-4728.

¹⁰⁵ Snider, B. B. *Chem. Rev.* **1996**, *96*, 339-364.

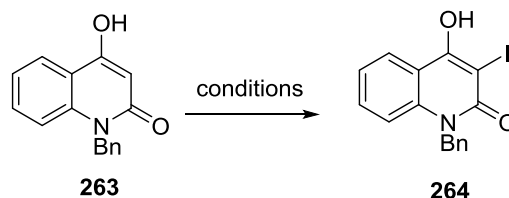
¹⁰⁶ (a) Pirrung, M. C.; Blume, F. J. *Org. Chem.* **1999**, *64*, 3642-3649; (b) Kappa, T.; Aigner, R.; Hohengassner, P.; Stadlbauer, W. *J. Prakt. Chem.* **1994**, *336*, 596-601; (c) Blackburn, C.; LaMarche, M. J.; Brown, J.; Che, J. L.; Cullis, C.A.; Lai, S.; Manguire, M.; Marsilje, T.; Geddes, B.; Govek, E.; Kadambi, V.; Doherty, C.; Dayton, B.; Brodjian, S.; Marsh, K. C.; Collins, C. A.; Kym, P. R. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2621-2627.

Scheme 64. Synthesis of 1-benzyl-4-hydroxyquinolin-2(1*H*)-one.

Trials to improve the efficiency of the last step, either by reacting benzyl protected aniline with diethylmalonate¹⁰⁷ or by reacting with malonyl chloride,¹⁰⁸ did not improve the yield significantly (Scheme 65).

Scheme 65. Synthesis of 1-benzyl-4-hydroxyquinolin-2(1*H*)-one through malonyl derivatives.

This synthesis has not been optimized further since the goal was just to investigate the feasibility of this approach. With this hydroxyquinoline in hand, the next step was the iodination of this quinoline **263** through the reaction either with iodine and periodic acid in EtOH or by NIS in MeCN. The yields in both cases were low (Scheme 66).¹⁰⁹



Conditions (A): I₂ (0.5 eq.), H₅IO₆ (0.11 eq.), EtOH, r.t. 3 h, yield = 21%.

Conditions (B): NIS (1.1 eq.), TFA (1.1 eq.), MeCN, yield = 23%.

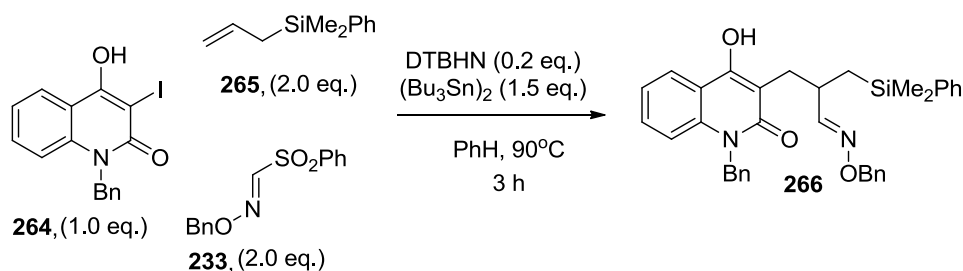
Scheme 66. Iodination of 1-benzyl-4-hydroxyquinolin-2(1*H*)-one.

With the iodoquinoline **264** in hand, we tested the first free-radical multi-component carbonylation process.¹⁰³ For this test, the electron-rich allylsilane **265** was used, with sulfonyloxime **233** in benzene. The reaction was initiated by the DTBHN/(Bu₃Sn)₂ system (Scheme 67).

¹⁰⁷ Mohamed, E. A. *J. Chem. Soc. Pak.* **1991**, *13*, 166-168.

¹⁰⁸ Sheibani, H.; Mosslemine, M. H.; Behzadi, S.; Islami, M. R.; Saidi, K. *Synthesis* **2006**, *3*, 435-438.

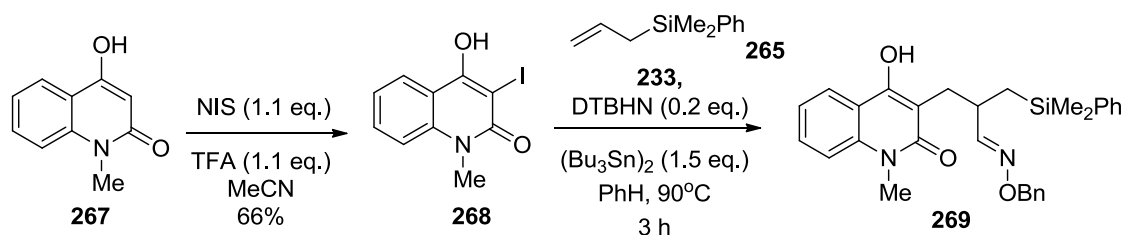
¹⁰⁹ (a) Barr, S. A.; Neville, C. F.; Grundon, M. F.; Boyd, D. R.; Malone, J. F.; Evans, T. A. *J. Chem. Soc. Perkin Trans. 1* **1995**, 445-452; (b) Reisch, J.; Nordhaus, P. *Monatshefte für Chemie*, **1994**, *125*, 225-231; (c) Bossharth, E.; Desbordes, P.; Monteiro, N.; Balme, G. *Tetrahedron Lett.* **2009**, *50*, 614-616.



Scheme 67. Carbo-oximation MCR with 1-benzyl-4-hydroxy-3-iodoquinolin-2(1H)-one.

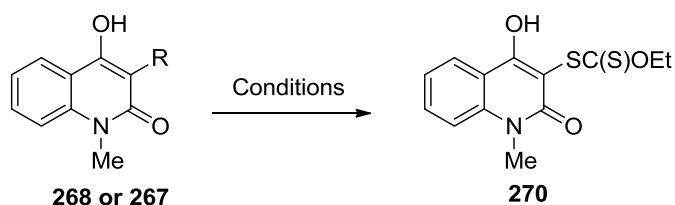
Unfortunately, the reaction was not successful; the starting iodoquinoline **264** was consumed, but no major product could be isolated. The presence of a benzyl group which could generate benzyl radical and lead to undesired products may have caused this failure.

In order to save time and efforts, we turned our attention to the commercially available methyl protected quinoline **267**. Iodination of methyl quinoline derivative **267** by NIS in MeCN worked well with yield up to 66%, in good agreement with the previously reported product.^{109a} With this iodinated quinoline **268**, the carbo-oximation reaction was tested again with allylsilane **265** and sulfonyl oxime **233** (Scheme 68), but again, the reaction was not successful.



Scheme 68. Iodination & Carbo-Oximation of 4-hydroxy-1-methylquinolin-2(1H)-one.

Further trials to prepare xanthate quinoline derivative **270**, either from the corresponding iodoquinoline **268** or from quinoline derivative **267**, by reaction with bi-xanthate¹¹⁰ were unfortunately not successful (Scheme 69).

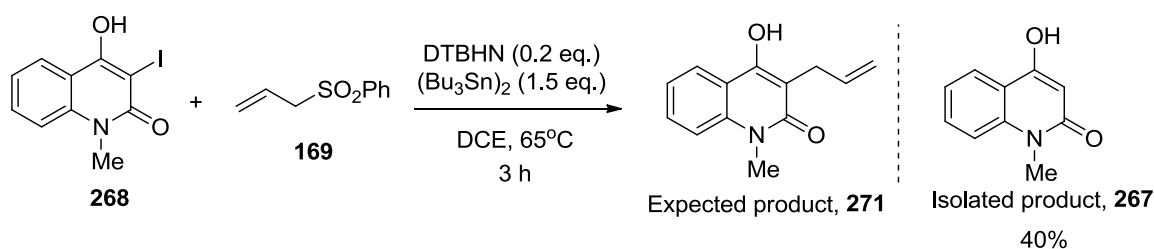


Condition (A) ; R = I; KSC(S)OEt, Acetone, Yield (0%)
 Conditions (B); R=H; (SC(S)OEt)₂, NaH, THF, -78°C- r.t., Yield (0%)

Scheme 69. Preparation of Xanthate Quinoline Derivative **270**.

¹¹⁰ (a) Shi, L.; Chapman, T. M.; Beckman, E. J. *Macromolecules* **2003**, *36*, 2563-2567; (b) Gagosz, F.; Zard, S. Z. *Synlett* **2003**, *3*, 387-389.

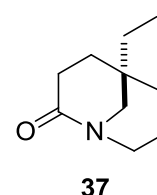
There are two reasons which could explain the failure of these carbo-oximation MCRs. The first one could be the electrophilicity of the generated radical in quinoline ring, too low to add efficiently onto the electron-rich allylsilane. This explanation was supported by the results obtained from the free-radical two-component reaction between this quinoline **268** and allylsulfone **169** (Scheme 70). Interestingly, instead of obtaining the allylated quinoline **271**, the de-iodinated quinoline **267** was the only isolated product in 40% yield. This reaction showed that the generated radical in C-9 position of quinoline ring is likely not electrophilic enough to add onto the π -system of olefins. The second reason could be the free alcohol group, which showed in some cases incompatibility with this type of free-radical reactions.¹⁰³



Based on these results and assumptions, we decided to focus our attention on the second proposed strategy for accessing Eucophylline. It was envisioned that this strategy could provide a general and straightforward access for preparing bicyclic lactams and therefore an entry to the natural product Eucophylline **3**.

2.4. Second Strategy: Azabicyclo[3.3.1]nonane Strategy

The key intermediate in this strategy is the bicyclic lactam **37** that contains the all-carbon stereogenic quaternary center. The synthesis of bicyclic systems, like the one present in Eucophylline, has not been well-reported before. Only few methods reported the synthesis of simple bicyclic systems without substitution in the bridgehead carbon.



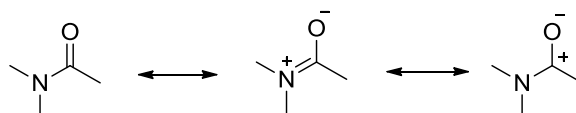
In the following part we will shed light on the chemistry of bicyclic bridgehead lactams and the chemistry of twisted and strained amides.

2.4.1. Bicyclic Bridgehead Lactams

The low reactivity of amides usually stems from the planarity of the N-C=O system. This planar geometry allows strong resonance interaction between n_N and $\pi^*_{C=O}$ orbitals and hence more stability (Scheme 71). But some deviation of this planarity was observed in peptides, small molecules and in bicyclic systems.¹¹¹ The normal properties of amide bonds include (i) the relatively

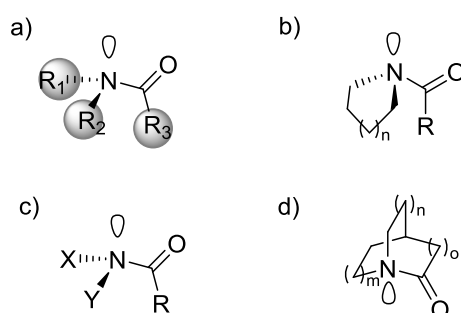
¹¹¹ (a) Chalupský, J.; Vondrášek, J.; Špirko, V. *J. Phys. Chem. A* **2008**, *112*, 693-699; (b) Mannfors, B. E.; Mirkin, N. G.; Palmo, K.; Krimm, S. *J. Phys. Chem. A* **2003**, *107*, 1825-1832.

short N-C(O) bond, (ii) high rotational barrier for cis-trans isomerization (typically 15-20 kcal/mol), (iii) low reactivity of carbonyl group towards nucleophilic addition and hydrolysis, and (iv) the lower carbonyl IR stretching frequencies and more upfield shifts in ^{13}C NMR spectra as compared to other carbonyl groups.¹¹²



Scheme 71. Resonance of the Amide Bonds.

The deviation from these standards opened a new interesting area in amide chemistry, *i.e.* the distorted amide chemistry.¹¹³ These distorted amides show deviations from the standard planar geometry leading to a variation in their physical and chemical properties and reactivities. Aubé and Szostak¹¹² classified these distorted amides, according to the spatial arrangement of substituents around the amide bond, into four classes: (a) the strict repulsion between the substituents, (b) conformational effects (ring or allylic strain), (c) the electronic delocalization (in which an electronegative substituent of the amide affect the electron environment around the amide bond), and (d) steric restriction (Scheme 72).



Scheme 72. Types of distorted amide bonds: (a) steric repulsion; (b) conformational effects; (c) anomeric amides; (d) steric restriction.

Out of these four classes, the geometrically restricted amides (bridged twisted amides; type (d) in Scheme 72) are specifically interesting because these bridgehead lactams does not suffer from extreme steric hindrance around the amide bond or from the complicated electronic influence of the amide substituents. Moreover, bridgehead amides could be easily modified and diversified as compared to other classes of distorted amides; therefore they represent one of easiest and most straightforward methods to construct non-planar amides.¹¹⁴

¹¹² Szostak, M.; Aubé, J. *Chem. Rev.* **2013**, *113*, 5701-5765.

¹¹³ Yamada, S. in *The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science*, Wiley-Interscience, **2000**, p. 215.

¹¹⁴ Szostak, M.; Aubé, J. *Org. Biomol. Chem.* **2011**, *9*, 27-35.

In these bicyclic bridgehead lactams, the non-planar geometry of the amide bond implies that the lone pair of electrons on nitrogen is not any more in conjugation with the adjacent π orbitals of the carbonyl group.¹¹³ This has a strong influence on these amide properties as compared to those of planar amides. These twisted amides are more reactive towards amide hydrolysis and nucleophilic attack on the carbonyl carbon.¹¹⁵ Also, they have different reactive sites for amide protonation and alkylation reactions. Consequently, spectroscopic and physical properties are completely different from those of planar amides.¹¹⁶ The importance of these twisted amides has been extended to the peptide chemistry. As they are analogues to the transition state encountered by peptides amide bonds during a *cis-trans* isomerization, they can give more insight into the important feature of protein folding.¹¹⁷

2.4.1.1. General Properties of Bridgehead Lactams

In this section we will focus on the physical properties of bridgehead lactams including the degree of distortion, bond lengths and spectroscopic properties. Also a comparison between these lactams and their counterparts in bridgehead olefins will be discussed.

a) Distortion Parameters.

In 1971, Winkler and Dunitz introduced three independent parameters to measure and quantify the distortion degree of amide bonds.¹¹⁸ These parameters are: (i) twist angle (τ) which describes the magnitude of rotation around the N-C(O) bond, (ii) pyramidalization at nitrogen (χ_N), and (iii) pyramidalization at carbon (χ_C). The last two parameters, describe the tetrahedral character of the nitrogen and carbon atoms respectively (Figure 7).

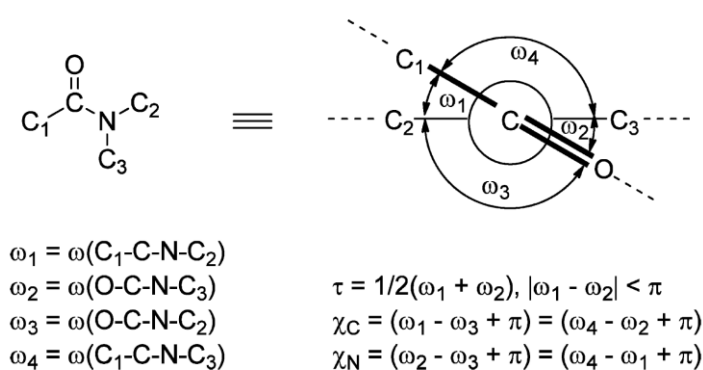


Figure 7. Winkler–Dunitz Distortion Parameters of Amide Bonds.

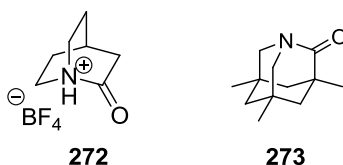
¹¹⁵ Brown, R. *Studies in Amide Hydrolysis: The Acid, Base, and Water Reactions. In The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science*; Greenberg, A., Breneman, C. M., Liebman, J. F., Eds.; Wiley: New York, **2000**, p.85.

¹¹⁶ Greenberg, A.; Thomas, T. D.; Bevilacqua, C. R.; Coville, M.; Ji, D.; Tsai, J. C.; Wu, G. *J. Org. Chem.* **1992**, *57*, 7093-7099.

¹¹⁷ Cox, C.; Lectka, T. *Acc. Chem. Res.* **2000**, *33*, 849-858.

¹¹⁸ Winkler, F. K.; Dunitz, J. D. *J. Mol. Biol.* **1971**, *59*, 169-182.

When the twist angle (τ) is 0° , the amide bond is planar without a tetrahedral character for nitrogen and carbon since $\chi_N = \chi_C = 0^\circ$. In contrast, when twist angle (τ) is 90° , then the N-C(O) bond is orthogonal and $\chi_N = \chi_C = 60^\circ$ for fully pyramidalized amide bonds. Till now, only two bridged lactams with perfectly perpendicular amide bonds have been confirmed structurally (Scheme 73).^{119,120} The other bridgehead lactams showed distorted geometries of amide bonds characterized by medium τ and χ_N values.



Scheme 73. Examples for Fully Orthogonal Bridgehead Lactams.

It also worth notice that, for most of the reported bridgehead lactams, the χ_C values are close to 0° regardless to the degree of distortion. This fact reflects the tendency of these lactams to be in the amino ketone resonance form.¹²¹

Also the distortion of amides could be quantified by the sum of three bond angles at nitrogen (θ) (Figure 7).¹²² For instance, the ideally sp^3 hybridized atom have $\theta = 328.4^\circ$, while the sp^2 atom have $\theta = 360.0^\circ$.

Moreover, Yamada proposed a qualitative description of the distorted amides based on the twist angle and pyramidalization of the nitrogen atom.¹¹³ Therefore, he classified the twisted amides into three classes: (i) Type A amides: which have perpendicularly twisted N-C(O) bonds and non-pyramidalized nitrogen atoms, (ii) Type B amides: which have planar N-C(O) bonds and sp^3 nitrogen atoms, and (iii) Type C amides: which have perpendicularly twisted N-C(O) bonds and pyramidalized nitrogen atoms.

b) Bond Lengths in Bridgehead Lactams.

As the distortion of amide bonds increase, the length of N-C(O) bond increase significantly and C=O bond shortens slightly. These observations showed the tendency of twisted amides to be in the amino- ketone resonance form and also indicate the gradual pyramidalization of the nitrogen

¹¹⁹ Tani, K.; Stoltz, B. M. *Nature* **2006**, *441*, 731-734.

¹²⁰ Kirby, A. J.; Komarov, I. V.; Feeder, N. *J. Chem. Soc., Perkin Trans. 2* **2001**, 522-529.

¹²¹ Wiberg, K. *Origin of the Amide Rotational Barrier*. In *The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science*; Greenberg, A., Breneman, C. M., Liebman, J. F., Eds.; Wiley: New York, **2000**, p. 33.

¹²² Otani, Y.; Nagae, O.; Naruse, Y.; Inagaki, S.; Ohno, M.; Yamaguchi, K.; Yamamoto, G.; Uchiyama, M.; Ohwada, T. *J. Am. Chem. Soc.* **2003**, *125*, 15191-15199.

atom.¹²³ The obvious example for this phenomenon is 1-aza-2-adamantanone **273**, in which the N-C(O) bond is 1.475 Å, longer than that of the corresponding *N*-methyl- δ -valerolactam by 0.15 Å. As a result, the C=O bond length is 1.196 Å, 0.037 Å shorter than for the planar analogue.¹²⁰

c) Spectroscopic Properties of Bridgehead Lactams.

The spectroscopic properties of these lactams exhibit values in the region between normal ketones and planar lactams. Therefore, the infrared carbonyl stretching frequencies of amide bonds are characterized by increased $\nu_{\text{C=O}}$ values and more downfield $^{13}\text{C=O}$ resonance compared to planar amides.¹²⁴ For example, the perfectly twisted amide **273**, showed $\nu_{\text{C=O}}$ at 1732 cm^{-1} in IR and 200.0 ppm in ^{13}C NMR, which showed how these amides behave like amino-ketone rather than amide groups.

d) Similarities between Bridgehead lactams and Bridgehead Olefins.

Bridgehead lactams are also known as anti-Bredt lactams. This is due to the partial double bond character that appears during the resonating forms of these amides.¹²⁵ In general, Bredt's rule states that a double bond cannot be placed at the bridgehead of a bridged ring system, unless the rings are large enough.¹²⁶ Generally, bridgehead lactams are more stable and easier to prepare than the corresponding bridgehead olefins because the amide nitrogen atom can adopt sp^3 geometry in the amino-ketone resonance without violating the octet rule.¹¹²

In 1981, Schleyer proposed the olefin strain energy parameter, which is defined as the difference between the strain energy of the olefin and that of its parent hydrocarbon and is directly related to the enthalpy of hydrogenation.¹²⁷ From this parameter, he showed that the bridgehead olefins with olefin strain energy below 17 kcal/mol could be isolated. Olefins with strain energy between 17 and 21 kcal/mol could be observed. But, those with olefin strain energy higher than 21 kcal/mol are classified as unstable. In comparison between bridgehead lactams and their analogues of bridgehead olefins, it is obvious that the highly strained bridgehead lactams are stable enough for isolation comparing to their analogues of bridgehead olefins (Scheme 74).



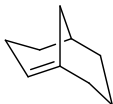

¹²³ Kirby, A. J.; Komarov, I. V.; Kowski, K.; Rademacher, P. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1313-1316.

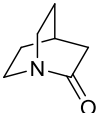
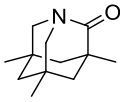
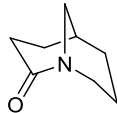
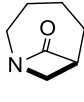
¹²⁴ Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectroscopic Identification of Organic Compounds*; John Wiley and Sons: New York, **1991**.

¹²⁵ Lease, T. G.; Shea, K. J. A. *Compilation and Analysis of Structural Data of Distorted Bridgehead Olefins and Amides*. In *Advances in Theoretically Interesting Molecules*; JAI Press Inc.: Greenwich, CT, **1992**; Vol. 2.

¹²⁶ Bredt, J. *Justus Liebigs Ann. Chem.* **1924**, 437, 1-13.

¹²⁷ Maier, W. F.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1981**, 103, 1891-1900.

Bridgehead Olefins				
Olefin Strain Energy	40.4 Kcal/mol	39.5 Kcal/mol	15.2 Kcal/mol	37.8 Kcal/mol

Bridgehead Lactams				
Year of isolation	1959, 2006	1998	1980	1986

Scheme 74. Comparison between Bridgehead Olefins and Bridgehead Lactams.

It is also worth noticing that prior to Schleyer olefin strain energy, Fawcett proposed an empirical parameter to predict violations of Bredt's rule.¹²⁸ This parameter was the *S* value which represents the sum of atoms contained in all the bridges of the bicyclic system. For example, a bicyclo[3.2.1]octane has an *S* value of 6. Therefore, according to Fawcett's generalization, bridged bicyclic systems with bridgehead double bonds with an *S* value ≥ 9 have the potential to be isolated. While systems with *S* = 7 could be observed but not isolated. Whereas those with *S* = 6 could be entertained as fleeting intermediates. In the same period, Prelog proposed that only bicyclo[5.3.1] or larger systems (*S* ≥ 9) could contain a stable bridgehead double bond.¹²⁹

2.4.1.2. Synthesis of Bridgehead Lactams

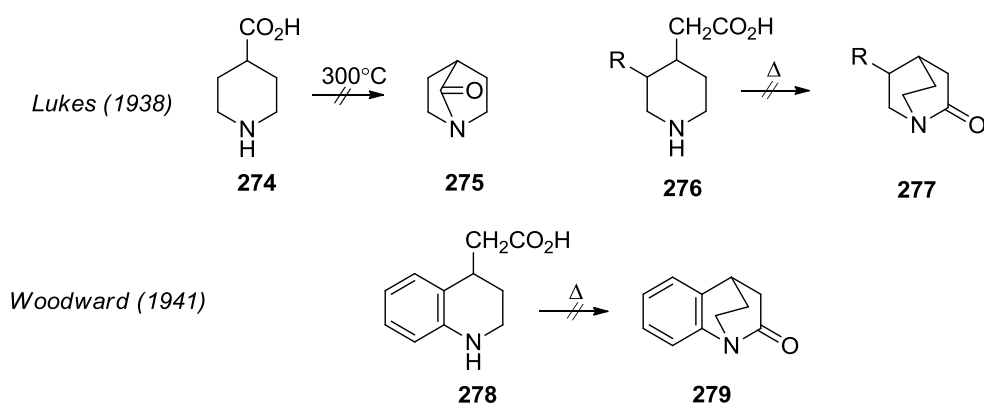
The challenging synthesis of strained bicyclic bridgehead lactams attracted organic chemist since beginning of the last century. After Bredt stated his rule, Lukes tried to prepare the bridgehead lactams **275**, **277** through condensation under thermal conditions, but without success. Then, he proposed that such amides with nitrogen atom at the bridgehead position would be sterically impossible to generate (Scheme 74).¹³⁰ In the same era, Woodward also tried and failed to synthesize related bicyclic 2-quinuclidones **279**.¹³¹ However, he concluded that such compounds would constitute a new type of amino-ketone.

¹²⁸ Fawcett, F. S. *Chem. Rev.* **1950**, *47*, 219–274.

¹²⁹ (a) Prelog, V.; Ruzicka, L.; Barman, P.; Frenkiel, L. *Helv. Chim. Acta* **1948**, *31*, 92–97; (b) Prelog, V.; Barman, P.; Zimmermann, M. *Helv. Chim. Acta* **1949**, *32*, 1284–1296; (c) Prelog, V. *J. Chem. Soc.* **1950**, 420–428.

¹³⁰ Lukes, R. *Collect. Czech. Chem. Commun.* **1938**, *10*, 148–152.

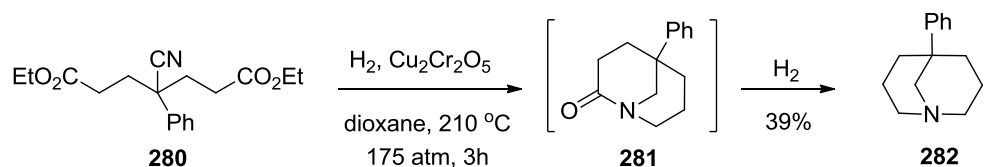
¹³¹ Doering, W. E.; Chanley, J. D. *J. Am. Chem. Soc.* **1946**, *68*, 586–588.



Scheme 74. Early Trials towards Synthesis of Bridgehead Lactams.

Since then, many attempts to synthesize these different types of bridgehead lactams were developed.¹¹⁴ Only the efforts done for the synthesis of bicyclic[3.3.1] bridgehead lactams present in Eucophylline will be presented.

In 1949, Walker *et al.*¹³² reported the formation of 1-azabicyclo[3.3.1]nonan-2-one derivative **281** during their studies on the hydrogenation reactions catalyzed by copper chromite. The reaction underwent intramolecular condensation of the cyano diester **280** to the bridgehead lactam **281**, which was further reduced under the reaction conditions to 1-azabicyclo[3.3.1]nonane **282** in 39% yield (Scheme 75). Actually, this synthesis was the first to report the formation of bicyclo[3.3.1] bridgehead lactam with substitution in the bridgehead carbon.

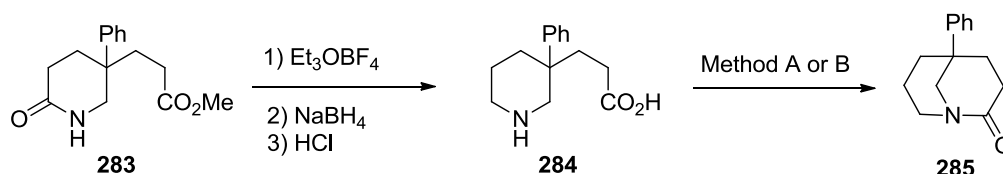


Scheme 75. Walker Synthesis of 1-azabicyclo[3.3.1]nonane.

Later in 1981, Buchanan and coworkers developed their synthesis by using a gem-dialkyl effect to facilitate the cyclization to the bridgehead amide **285** through substrate **284**. Activating the carboxylic acid as an acyl chloride followed by condensation with the secondary amine or by thermal cyclization under high vacuum afforded the 1-azabicyclo[3.3.1]nonan-2-one derivative **285** but in low yield, showing the difficulties to achieve the synthesis of these strained bridgehead lactams through this approach (Scheme 76).¹³³

¹³² Badger, G. M.; Cook, J. W.; Walker, T. J. *Chem. Soc.* **1949**, 1141-1144.

¹³³ (a) Buchanan, G. L. *J. Chem. Soc. Chem. Commun.* **1981**, 814-815; (b) Buchanan, G. L. *J. Chem. Soc. Perkin Trans. 1*, **1984**, 2669-2670.

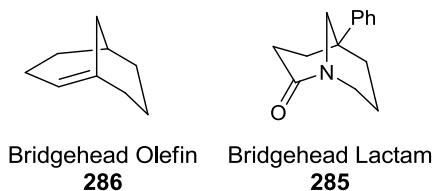


Method **A**: 1) SOCl_2 , Et_3N , 2) Et_3N , C_6H_6 , r.t., Yield = 10 % from **283**.

Method **B**: 210-230 °C, 0.1 mmHg, Yield = 17% from **283**.

Scheme 76. Buchanan Synthesis of 1-azabicyclo[3.3.1]nonan-2-one.

Buchanan showed that a bridgehead lactam like **285** exists in a chair-boat conformation, like the anti-Bredt olefin bicyclo[3.3.1]non-1-ene **286**. These compounds favor a *trans* double bond in the larger ring (Scheme 77).¹³⁴ The X-ray of lactam **285** reported by Buchanan showed $\tau = 20.8^\circ$; $\chi_{\text{N}} = 48.8^\circ$ and $\chi_{\text{C}} = 5.9^\circ$ while the bond lengths were $\text{N-C(O)} = 1.374\text{\AA}$; $\text{C=O} = 1.201\text{\AA}$. All of these parameters beside the IR stretching $\nu_{\text{C=O}} = 1695\text{ cm}^{-1}$ indicate that this lactam showed a moderate distortion of the amide bond.¹³⁵



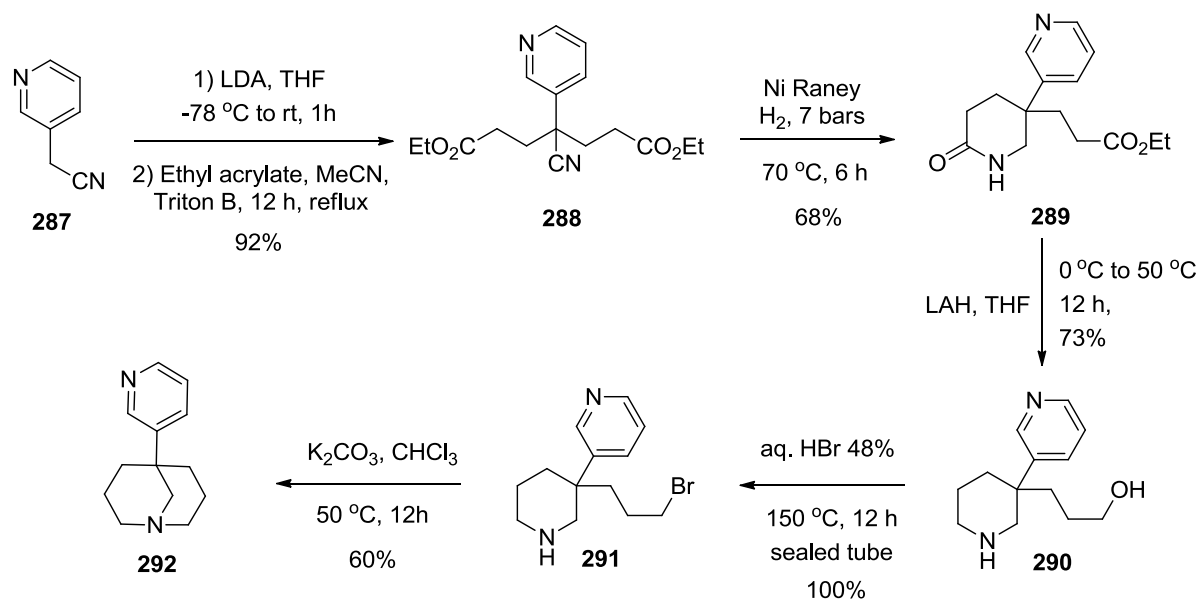
Scheme 77. Chair-boat Conformation of Bridgehead Olefin and Lactam.

More recently, an exploratory unit in Sanofi Aventis R&D developed a sequence to access 1-azabicyclo[3.3.1]nonane derivative **292** with a pyridinyl substituent at the bridgehead carbon.¹³⁶ Starting from the pyridinyl acetonitrile **297** and after deprotonation α - to the nitrile group and alkylation by ethyl acrylate, the cyano diester **288** was obtained in excellent yield. The cyano diester **288** was then hydrogenated into an amine, which lactamized directly with one of the two esters to give the first lactam cycle **290**. The reduction of both the ester and amide followed by the conversion of the free alcohol into a bromide allowed the final cyclization to give the azabicyclo[3.3.1]nonane **292** in excellent yield (Scheme 78). It is worth noticing that depending on this approach, it would be possible to access azabicyclo[3.3.1]nonan-2-one derivatives with substitution in bridgehead position.

¹³⁴ Warner, P. M. *Chem. Rev.* **1989**, 89, 1067-1093.

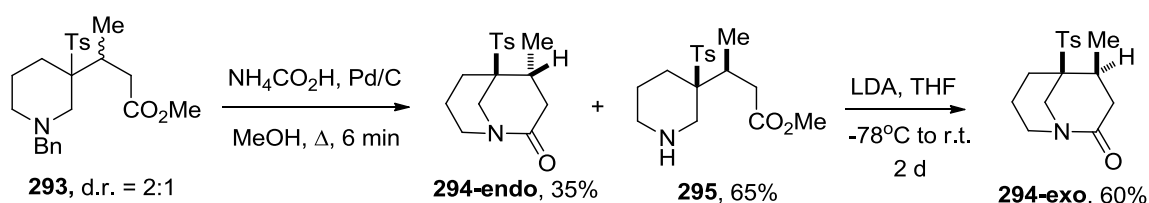
¹³⁵ Buchanan, G. L.; Kitson, D. H.; Mallinson, P. R.; Sim, G. A.; White, D. N. J.; Cox, P. J. *J. Chem. Soc. Perkin Trans. 2* **1983**, 1709-1712.

¹³⁶ Slowinski, F.; Ben Ayad, O.; Vache, J.; Saady, M.; Leclerc, O.; Lochead, A. *J. Org. chem.* **2011**, 76, 8336-8346.



Scheme 78. Synthesis of pyridinyl azabicyclo[3.3.1]nonane derivative.

In another synthesis of a bicyclo[3.3.1] bridgehead lactam with substituent at the bridgehead carbon, Najera showed that there was a difference in the cyclization rate between diastereoisomeric amino esters **293** to form bridgehead lactams. The *endo*-lactam **294** was obtained quantitatively during the removal of the benzyl group, while the amino lactam **295** did not cyclize spontaneously under this reaction conditions and the corresponding *exo*-lactam **294** was obtained in a separate step after treatment of the amino ester with LDA. It was also observed that the *endo*-lactam **294** exists in a twist boat-boat conformation due to the steric interactions between the axial methyl group and an axial hydrogen atom. Interestingly, the *exo*-lactam **294** adopts the common chair-boat conformation, known for this type of bridgehead lactams (Scheme 79).¹³⁷

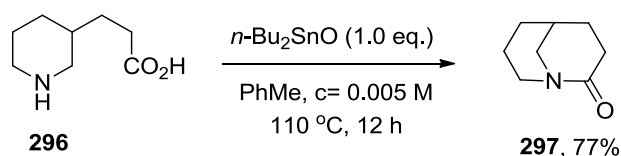


Scheme 79. Najera Synthesis of 1-azabicyclo[3.3.1]nonan-2-one derivative.

The synthesis of simple bicyclo[3.3.1] bridgehead lactams without substituent at the bridgehead carbon was developed by Steliou in 1983 by promoting the difficult lactamization by di-*n*-butyltin oxide under high dilution to afford the desired bridgehead lactam **297** in 77% yield (Scheme 80).¹³⁸

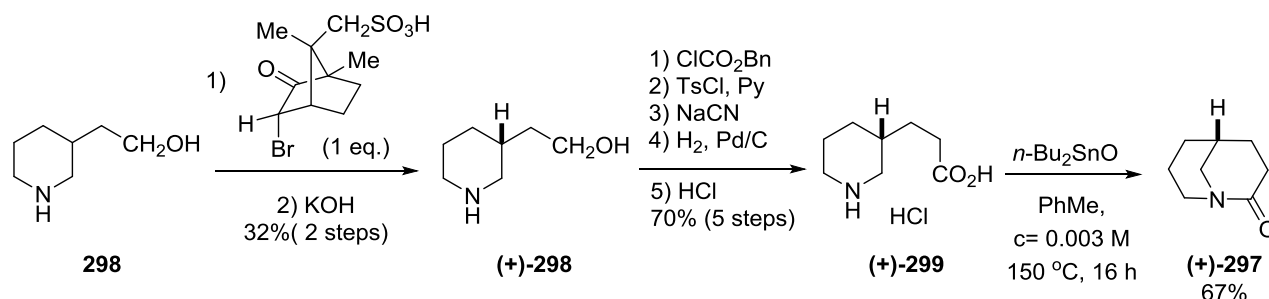
¹³⁷ Alonso, D. A.; Costa, A.; Mancheno, B.; Najera, C. *Tetrahedron* **1997**, *53*, 4791-4814.

¹³⁸ Steliou, K.; Poupart, M. A. *J. Am. Chem. Soc.* **1983**, *105*, 7130-7138.



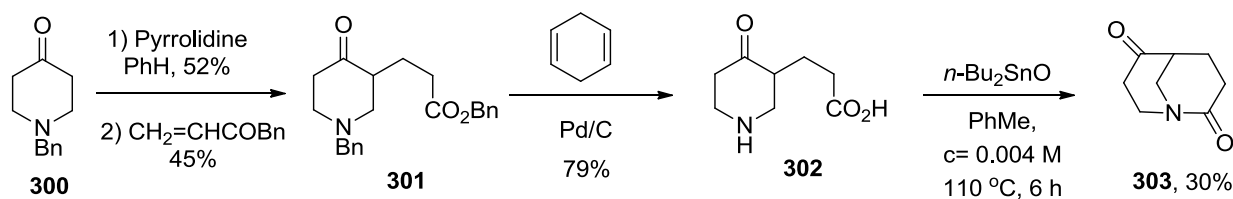
Scheme 80. Steliou Synthesis of 1-azabicyclo[3.3.1]nonan-2-one.

This tin-mediated lactamization has been used by Gerlach to prepare the enantiomerically enriched bridged lactam (+)-**297**.¹³⁹ After reaction of piperidine alcohol **298** with bromocamphorsulfonic acid, the enantiomerically enriched alcohol (+)-**298** was obtained. A homologation reaction, *via* the replacement of an activated alcohol by a cyano group, was used to prepare the desired piperidine carboxylic acid (+)-**299**. The di-*n*-butyltin oxide reagent could then facilitate the lactamization giving the enantiomerically enriched bridged lactam (+)-**297** in good yield (Scheme 81).



Scheme 81. Gerlach Synthesis of enantiomerically enriched 1-azabicyclo[3.3.1]nonan-2-one derivative.

Later, Sim used the same efficient promoter, Bu_2SnO , in the synthesis of the closely related bridgehead lactam **303**, albeit in moderate yield (Scheme 82).¹⁴⁰ The important information obtained from this synthesis is the distortion parameters. The X-ray structure of lactam **303** showed the following parameters: $\tau = 16.3^\circ$; $\chi_N = 49.1^\circ$ and $\chi_c = 5.8^\circ$ while the bond lengths were $\text{N-C(O)} = 1.377\text{\AA}$ and $\text{C=O} = 1.217\text{\AA}$. These parameters, associated with an IR stretching $\nu_{\text{C=O}}$ at 1680 cm^{-1} , are very similar to those of lactam **285**, reported by Buchanan. These two bridgehead lactams confirmed that lactams with N-C(O) bond placed at one of the larger bridges are characterized by large χ_N values and moderate twist angles.

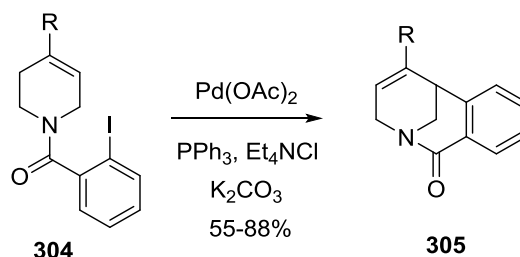


Scheme 82. Sim Synthesis of 1-azabicyclo[3.3.1]nonan-2-one derivative.

¹³⁹ Brehm, R.; Ohnhäuser, D.; Gerlach, H. *Helv. Chim. Acta* **1987**, *70*, 1981-1987.

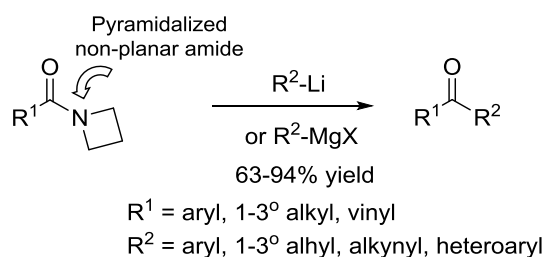
¹⁴⁰ McCabe, P. H.; Milne, N. J.; Sim, G. A. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1459-1462.

Another strategy depending on Heck reaction to synthesize the bridged lactams was developed by Grigg.¹⁴¹ With a catalyst system consisting of Pd(OAc)₂ and PPh₃, the cyclization of amide substrates **304** occurred in high yield to generate a variety of bridgehead lactams **305** (Scheme 83).



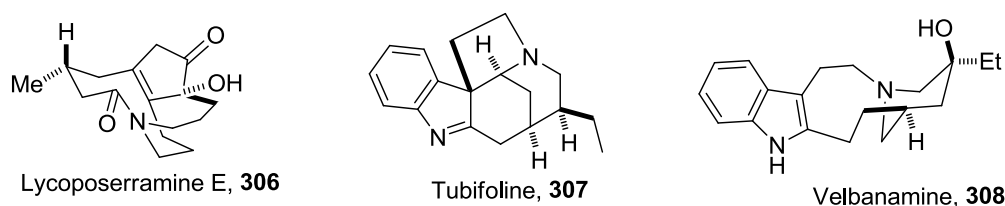
Scheme 83. Grigg Synthesis of Bridged Lactams via Heck Reaction.

To sum up this part, twisted amides have unique features that combine the ketone and amine properties depending on the degree of distortion they exhibit. As an application for this twisted amides properties, recently Szostak developed chemoselective ketone synthesis by the addition of organometallics to *N*-acylazetidines.¹⁴² This reaction showed how to activate the inert amide bonds under mild reactions to give useful chemical transformations (Scheme 84).



Scheme 84. Szostak Ketone Synthesis from Twisted Amides.

Also bridgehead lactams and bicyclic systems with different bicyclic ring sizes are present in many natural products (Scheme 85).¹¹²



Scheme 85. Bridgehead Lactams and Bicyclic Systems with Different Bicyclic Ring Sizes in Natural Products.

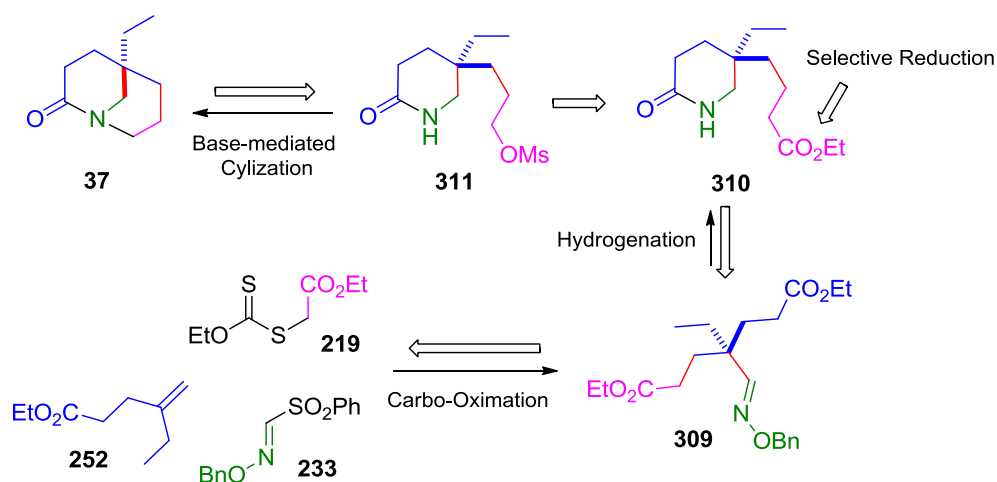
In the following part, our efforts to access the bicyclo[3.3.1] bridgehead nitrogen system which is present in Eucophylline, will be discussed through a general strategy relaying on the recently developed free-radical carbo-oximation multicomponent reaction.

¹⁴¹ (a) Grigg, R.; Sridharan, V.; Stevenson, P.; Worakun, T. *J. Chem. Soc., Chem. Commun.* **1986**, 1697-1699; (b) Grigg, R.; Santhakumar, V.; Sridharan, V.; Stevenson, P.; Teasdale, A.; Thorntonpett, M.; Worakun, T. *Tetrahedron* **1991**, 47, 9703-9720.

¹⁴² Liu, C.; Achtenhagen, M.; Szostak, M. *Org. Lett.* **2016**, 18, 2375-2378.

2.4.2. Synthesis of the Azabicyclo[3.3.1]nonane

Relying on the recently developed free-radical carbo-oximation reaction, it was reasoned that the bicyclic system in Eucophylline could be accessed through a straightforward sequence depicted below (Scheme 86). The initial retrosynthesis analysis depends on olefin **252**, sulfonyloxime **233** and the xanthate ester **219**, which will undergo a carbo-oximation reaction to construct the desired quaternary center. The diester benzyl oxime ether **309** will be subjected to hydrogenation under high pressure to give the free amine, which will lactamize directly to give the piperidinone **310**. After chemoselective reduction of the ester and activation of the generated alcohol as a mesylate, the base-mediated cyclization will eventually lead to the desired bicyclic lactam **37** (Scheme 86).



Scheme 86. Retrosynthesis Analysis of Azabicyclo[3.3.1]nonane.

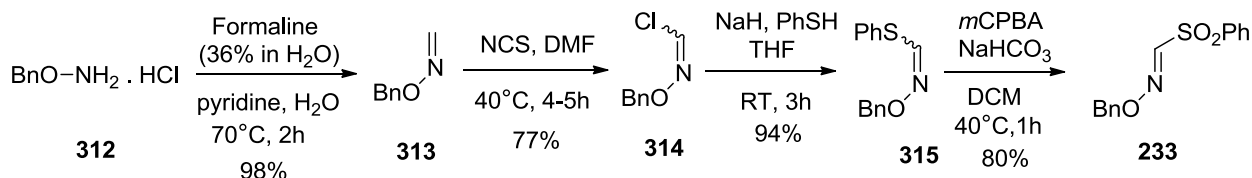
2.4.2.1. Carbo-oximation MCR with ethyl 4-methylenehexanoate **252**

To start this synthesis, the starting materials sulfonyloxime **233** and olefin **252** were synthesized according the following sequences.

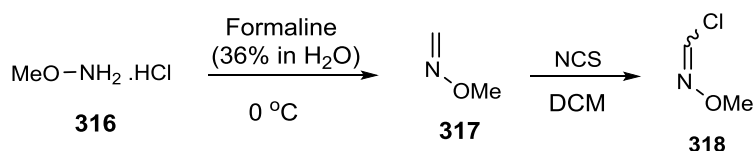
1. Sulfonyl oxime **233**:

The sulfonyl oxime, the radical trap in this carbo-oximation process, is prepared according to Kim's procedure.¹⁴³ Starting from the commercially available *O*-benzylhydroxylamine hydrochloride **312** and through condensation with formaldehyde followed by chlorination, compound **314** was obtained in excellent yield. The introduction of the sulfonyl group was carried out through two steps *via* the intermediate thio-oxime ether **315**, followed by oxidation to give the desired sulfonyloxime **315** in 57% overall yield and in a 15 g scale (Scheme 87).

¹⁴³ Kim, S.; Lee, I. Y.; Yoon, J.-Y.; Oh, D. H. *J. Am. Chem. Soc.* **1996**, 118, 5138-5139.

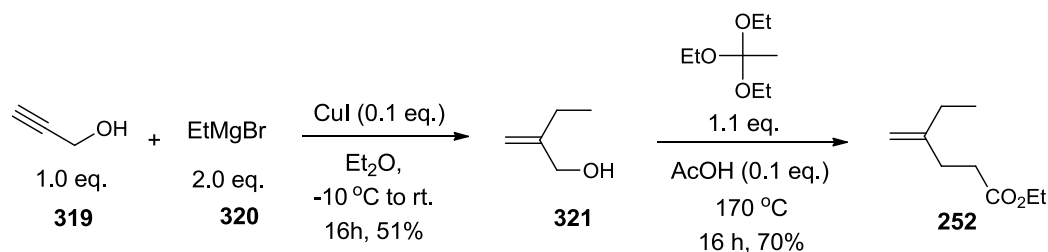
Scheme 87. Preparation of sulfonyloxime **215**.

As free-radical multi-component reactions are very sensitive to steric hindrance, a smaller oxime precursor could be also interesting. The easiest modification was the replacement of the benzyl group, with a methyl group. Thus, through a similar sulfonyloxime **233** synthesis pathway, the commercially available methoxyamine hydrochloride **316** was condensed with formaldehyde at 0°C. Unfortunately, due to the volatility of the formaldehyde *O*-methyloxime (b.p. = 12-12.5°C/760 mmHg)¹⁴⁴, the product **317** could not be isolated. Attempts at chlorinating formaldehyde *O*-methyloxime **317** by NCS *in situ* were not more successful (Scheme 88).

Scheme 88. Preparation of Formaldehyde *O*-methyloxime.

2. Olefin **252**: ethyl 4-methylenehexanoate

The electron-rich olefin, the second component in this carbo-oximation process, was prepared in two steps from the cheap and commercially available propargyl alcohol **319** by reaction with EtMgBr in the presence of copper iodide as a catalyst and an active stirring.¹⁴⁵ The second step is a Johnson-Claisen rearrangement, proceeding through the reaction of the prepared allylic alcohol **321** with triethyl orthoacetate in the presence of catalytic amount of acetic acid in refluxing toluene, giving the desired olefin **252** in 36% overall yield and in a 5 g scale (Scheme 89).¹⁴⁶

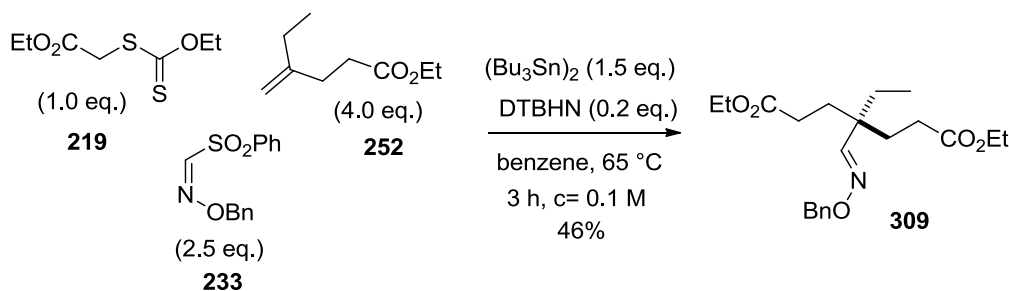
Scheme 89. Synthesis of Olefin **252**.

¹⁴⁴ Jensen, K. A.; Buss, L.; Holm, A. *Acta. Chem. Scand. B*, **1977**, *31*, 28-30.

¹⁴⁵ (a) Duboudin, J. G.; Jousseau, B. *J. Organomet. Chem.* **1979**, *168*, 1-11; (b) Barile, F.; Bassetti, M.; D'Annibale, A.; Gerometta, R.; Palazzi, M. *Eur. J. Org. Chem.* **2011**, *32*, 6519-6526.

¹⁴⁶ Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.-T.; Faulkner, D. J.; Petersen, M. *R. J. Am. Chem. Soc.* **1970**, *92*, 741-743.

With these three components in hand, the first attempt of a carbo-oximation process was carried out. The electrophilic radical, generated by the action of DTBHN/(Bu₃Sn)₂ on the corresponding xanthate ester, added to the less substituted end of the electron-rich olefin **252** to give the nucleophilic tertiary radical, which in turn was trapped by sulfonyl oxime **233**, to give the desired product **309** in 46% (Scheme 90). It also worth noticing that addition of DTBHN was repeated every 1.5 h till consumption of starting xanthate ester since DTBHN decomposes with half life time of 29 min at 65 °C.^{147,148}



Scheme 90. Carbo-oximation MCR with Olefin **252**.

The moderate yield prompted us to study the reaction mechanism more carefully and start a reaction optimization to increase the yield of this key reaction. Therefore, we first tried to increase the amount of olefin **252** (up to 10 eq.) since the concentration of the electron-rich olefin as compared to sulfonyloxime is crucial in this reaction. Unfortunately, the yield did not improve by increasing the olefin concentration. The byproduct **322**, which results from the addition of electrophilic radical to sulfonyloxime, implies that either the olefin **252** is not electron-rich enough to attack this radical or the sulfonyloxime **233** concentration is too high allowing considerable part (15%) of the electrophilic radical to add on it (table 2).

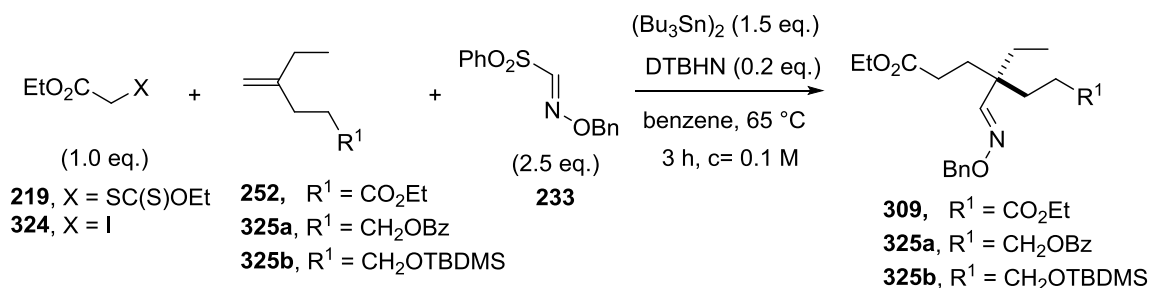
Attempts to increase the reaction yield also included changing the olefin **252** for other olefins **325a,b** having the same number of carbons. Thus, in entry (3, 4, table 2), yields of carbo-oximation reactions, with olefins bearing an alcohol protected as benzoate or silyl ether, were not improved. As in (entry 3, table 2), no trace of product was observed. Instead, the reduction product **323**, resulting from the reduction of the nucleophilic radical, was the major isolable product along with many other unidentified byproducts. In entry 4, the silyl protected olefin **325b** gave the expected product **326b**, but in very low yield along with the byproduct **323**.

Our attention was then directed to the xanthate ester part. It was reported that in some cases the xanthate part, which reacts with tin gives numerous tin residues, which complicates the separation and purification of the product.¹⁰³ It is also known that the iodine tin bond is strong and that iodine-

¹⁴⁷ H. Kiefer, T. G. T aylor, *Tetrahedron Lett.* **1966**, 7, 6163-6168.

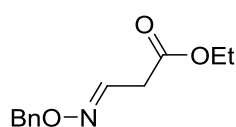
¹⁴⁸ J. Cooper, A. Hudson, R. A. Jackson, *J. Chem. Soc. Perkin Trans. 2* **1973**, 1056-1060.

tin residues are solids which could facilitate the isolation of the product.¹⁴⁹ Based on this premises, α -iodoethylester **324** was used instead of xanthate ester (entry **5**, table **2**). Surprisingly, despite of the formation of the expected iodine-tin solid residues that gave cleaner reaction, the yield decreased dramatically to 26% (entry **5**, table **2**).

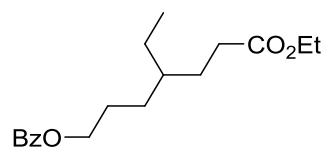


Entry	X	R ¹	Olefin N. of Eq.	Yield (%)
1	SC(S)OEt	CO ₂ Et	4.0	46 ^a
2	SC(S)OEt	CO ₂ Et	10.0	35 ^a
3	SC(S)OEt	CH ₂ OBz	4.0	0 ^b
4	SC(S)OEt	CH ₂ OTBDMS	4.0	10 ^a
5	I	CO ₂ Et	4.0	26

Table **2**. ^a with formation of the byproduct **322** in 15%. ^b formation of reduction product **323**



Addition of electrophilic radical to sulfonyloxime byproduct, **322**

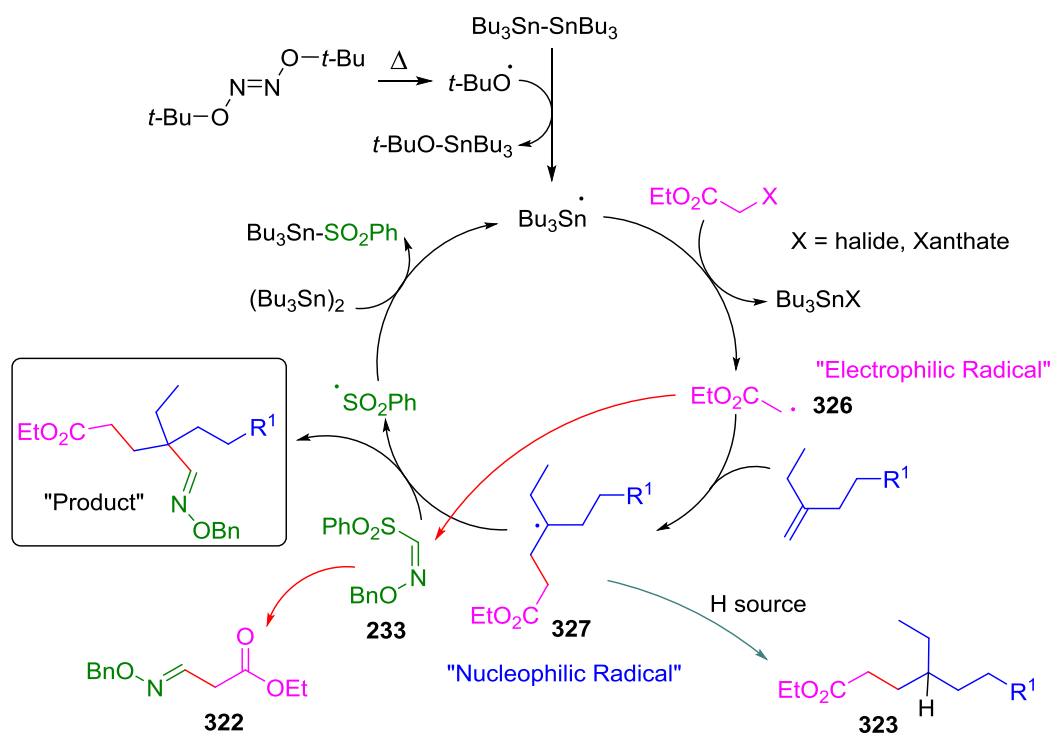


Reduction product, **323**

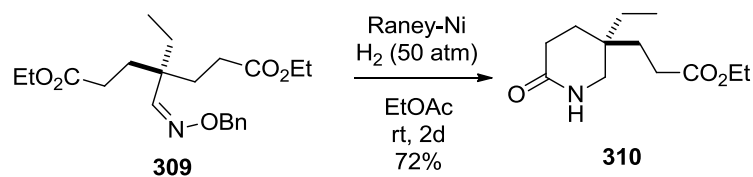
The proposed reaction mechanism for the formation of the product **309**, byproduct **322** and reduction product **323** is shown in (Scheme **91**). The expected product is formed after a sequence of two σ -bonds formation. The first results from the addition of an electrophilic radical **326**, onto the electron-rich olefin. While the second bond was formed after trapping of the nucleophilic radical **327** by sulfonyl oxime **233**, ending up with the formation of the desired product. The reaction starts by the decomposition of DTBHN (half life time of 29 min at 65 °C) into *tert*-butoxyl radicals which react with hexabutyldistannane to give tributylstannyl radical which propagate the chain.

The byproduct **322** was formed after addition of the electrophilic radical **326** to sulfonyloxime **233**, followed by β -fragmentation of the sulfonyl radical, which sustains the radical chain. This product is formed in specific cases when the second component, the olefin, is not electron-rich enough or sterically too hindered. On the other hand, the reduction product **323** may be formed when the sterically hindered tertiary nucleophilic radical abstracts hydrogen from tin residues or any other source. At this point the radical chain is broken, stopping the reaction.

¹⁴⁹ Le Grogne, E.; Chrétien, J.-M.; Zammattio, F.; Quintard, J.-P. *Chem. Rev.* **2015**, *115*, 10207-10260



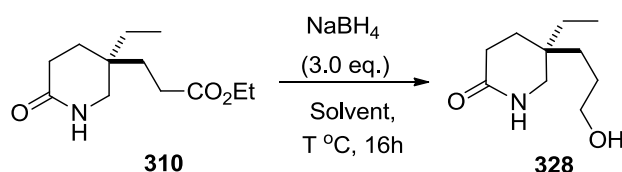
Despite the rather low yield of the carbo-oximation reaction, the total synthesis of Eucophylline was pursued. So with the MCR product **309** in hand, the hydrogenation of the oxime into an amine accompanied by direct lactamization with one of the two esters would give the piperidinone ring **310**. Thus, the hydrogenation of benzyl oxime ether **309** using Raney nickel under 50 atm of hydrogen pressure for 3 days afforded the desired piperidinone ring **310** in 72% yield without observation of the corresponding imide (Scheme 92).¹⁵⁰ The formation of the imide (through a double cyclization) under these conditions seems difficult because further ring closure in system like **310** is not favored, in good agreement with early studies of Buchanan.¹³⁵



The challenging chemoselective reduction of ethyl ester into the corresponding alcohol in the presence of an amide group led to some difficulties (Scheme 93). By using NaBH₄ in different combinations of solvent (table 3), no trace of the desired product was observed. The described condition for reduction of ethyl ester into the corresponding alcohol in the presence of amide is NaBH₄ in mixture of THF/MeOH (1:1) at 65 °C was not successful and starting piperidinone ester

¹⁵⁰ Gualtierotti, J.-B.; Pasche, D.; Wang, Q.; Zhu, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 9926-9930.

was degraded.¹⁵¹ Milder conditions were tried, but unfortunately, all of them failed. The typical reducing agents for ethyl ester group are LiAlH_4 or DIBAL-H, but these agents will also reduce the amide functional group, a reaction we wanted to avoid.



Scheme 93. Chemoselective Reduction of Ester **310**.

Entry	Solvent	Temp. °C	Yield (%)
1	THF/MeOH (1:1)	65	0
2	THF/MeOH (1:1)	r.t.	0
3	MeOH	r.t.	0
4	THF	r.t.	0
5	THF	65	0

Table 3. Screening of reduction solvents and temperature.

Soon after our work on this part of the project, Kerr *et al.*¹⁵² reported the reduction of a similar system using about 40 eq. of NaBH_4 , added in portions every 10 minutes under MeOH reflux.

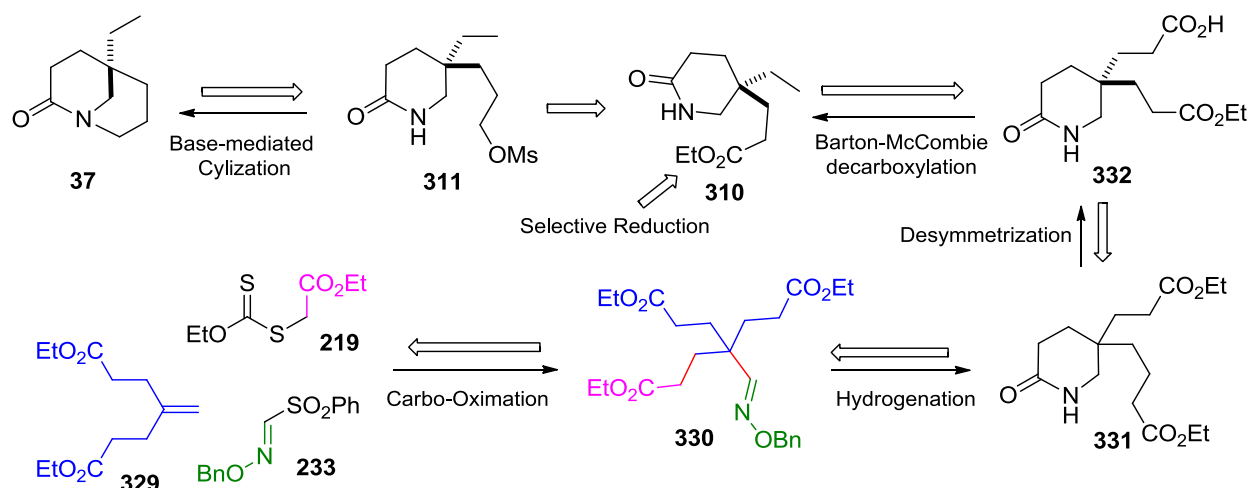
2.4.2.2. Carbo-oximation MCR with diethyl 4-methyleneheptanedioate **329**

At this point, an olefin like **329** was found to be a promising equivalent to the olefin **252**. Interestingly, this olefin **329** will also be of interest in the context of the development of an asymmetric synthesis of Eucophylline. Consequently, a little modification in the disconnection approach was introduced. Since an extra ester group will be present in the final compound, this ester will give us a chance to desymmetrize the prochiral diester **331** by hydrolyzing it into the corresponding acid, which will then be decarboxylated later using Barton decarboxylation,¹⁵³ installing the desired all-carbon quaternary stereogenic center (Scheme **94**).

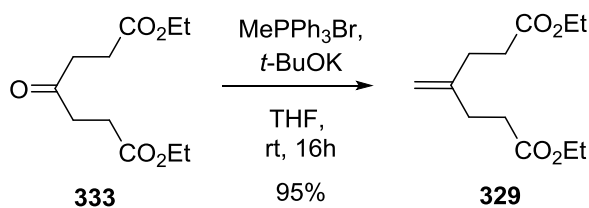
¹⁵¹ Seyden-Penne, J.; Curran, D. P. *Reductions by the alumino- and borohydrides in organic synthesis*; Wiley-VCH: New York, **1997**.

¹⁵² Grover, H. K.; Kerr, M. A. *Synlett* **2015**, 26, 815-819.

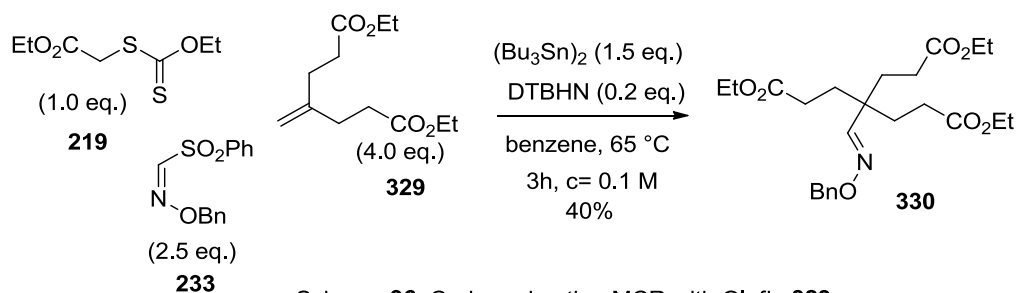
¹⁵³ Barton, D. H. R.; Crich, D.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1983**, 939-941.

Scheme 94. Retrosynthesis Analysis of Azabicyclo[3.3.1]nonane Relying on Diester Olefin **329**.

Thus, the diester olefin **329** was prepared from the corresponding commercially available ketone **333**, through a Wittig olefination reaction by methyltriphenylphosphonium bromide in nearly quantitative yield (Scheme 95).¹⁵⁴

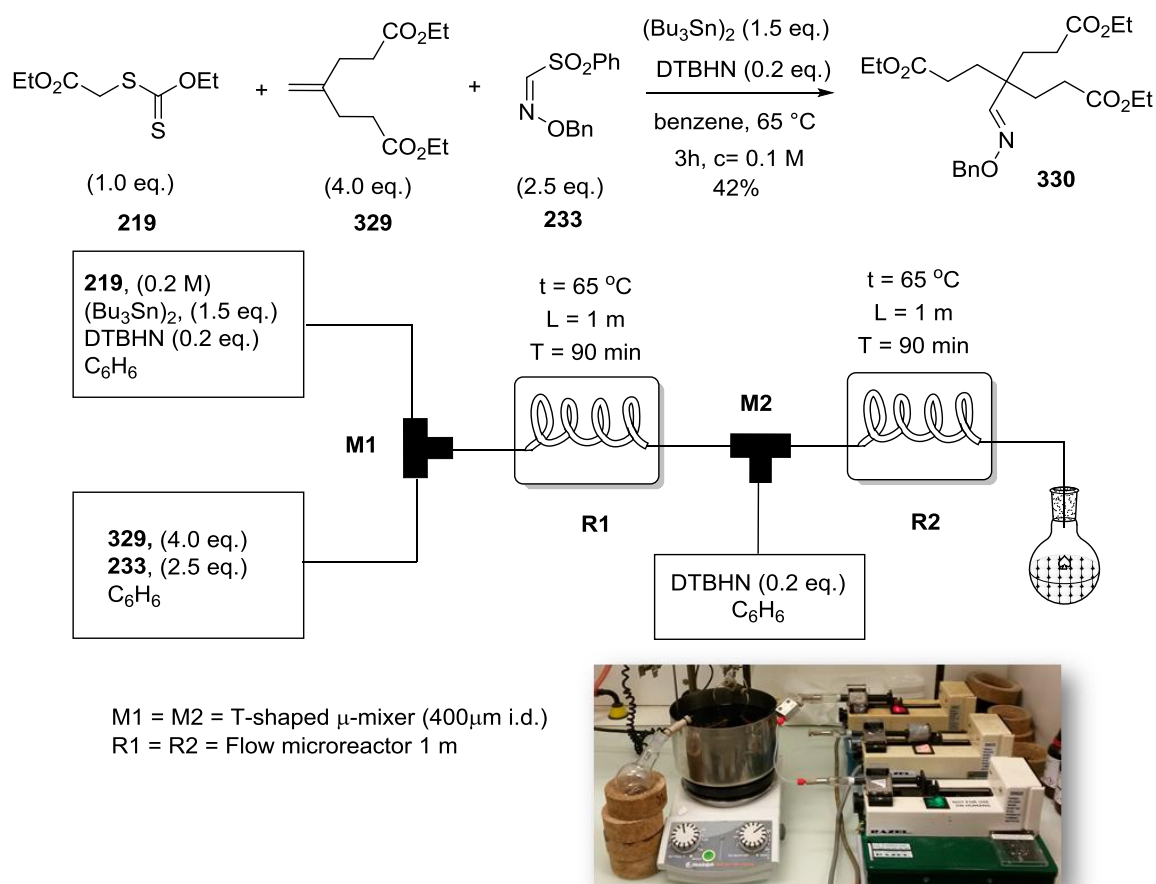
Scheme 95. Synthesis of diester olefin **329**.

With this diester olefin **329** in hand, the carbo-oximation process was carried out. Unfortunately, the yield (40%) was also modest (Scheme 96).

Scheme 96. Carbo-oximation MCR with Olefin **329**.

In a fruitful cooperation between our group and Ryu group, we tried to improve the yield of this reaction by the use of continuous flow chemistry. A visiting PhD student, Mr. Takenori Totoki, tried to perform the three-component carbo-oximation reaction under flow microreactor conditions.

¹⁵⁴ Harada, K.; Imai, A.; Uto, K.; Carter, R. G.; Kubo, M.; Hioki, H.; Fukuyama, Y. *Org. Lett.* **2011**, 13, 988-991.

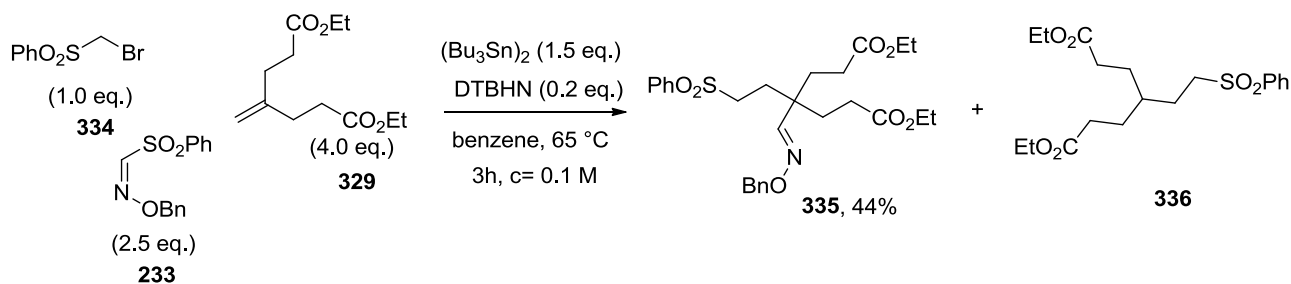
Scheme 97. Carbo-oximation MCR with Olefin **329** under Microreactor Flow Technology.

In this process, a benzene solution of xanthate ester **219**, $(\text{Bu}_3\text{Sn})_2$ and DTBHN was mixed with a benzene solution of diester olefin **329** and sulfonyl oxime **233** in the first T-shaped micromixer (**M1**, stainless-steel made, 400 μm channel diameter). The reaction was allowed to pass through the microreactor (**R1**) with a residence time of 90 min at 65°C. Another addition of DTBHN was mixed with the reaction flow through (**M2**) and the reaction flow was allowed to pass through microreactor (**R2**) for another 90 min at 65°C. After collection of the reaction flow, the crude mixture was concentrated and chromatographed to afford the desired diester product in 42% yield (Scheme 97). Since the yields being similar between the flow technique and the batch system, this process was abandoned.

At this point, a small modification of the approach was envisaged and the xanthate ester was replaced by α -bromosulfone **334** (Scheme 98).¹⁵⁵ The expected MCR product **335** with two esters and a sulfone group could be subjected to desulfonylation reaction, after formation of the piperidinone ring, by Al(Hg) amalgam to give the quaternary center with the desired ethyl group.¹⁵⁶ But again, the carbo-oximation reaction with α -bromosulfone **334** led to a modest yield (44%). The reduction product **336** was also observed in this reaction.

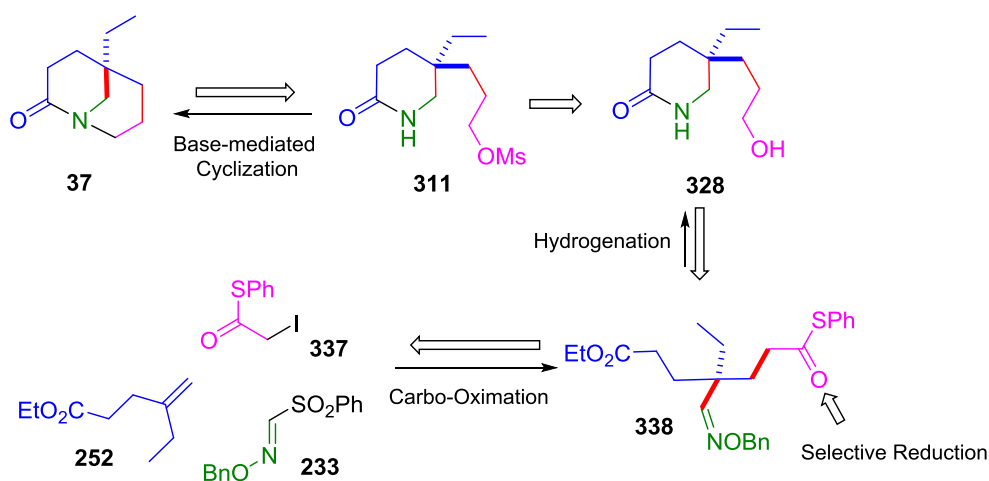
¹⁵⁵ Makosza, M.; Golinski, J.; Baran, J. *J. Org. Chem.* **1984**, *49*, 1488-1494.

¹⁵⁶ Kajiwara, Y.; Scott, A. I. *Tetrahedron Lett.* **2002**, *43*, 8795-8496.

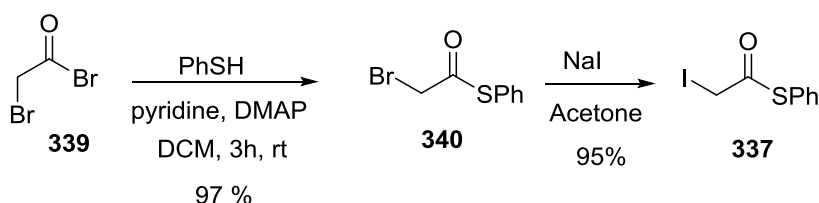
Scheme 98. Carbo-oximation MCR with α -bromosulfone **334**.

2.4.2.3. Carbo-oximation MCR with α -Iodothioester **337**

To avoid the chemoselectivity problems that appeared during the reduction of ethyl ester in the presence of amide functional group in piperidinone like **310**, our efforts were directed towards another functional group that could be reduced under milder conditions. The thioester group appeared to be a good candidate for this purpose. Again, a small modification to our original disconnection approach was added. Depending on the versatility of carbo-oximation reaction, α -iodothioester **337** will be used instead of xanthate or iodide ethyl ester **219**, **324** (Scheme 99)

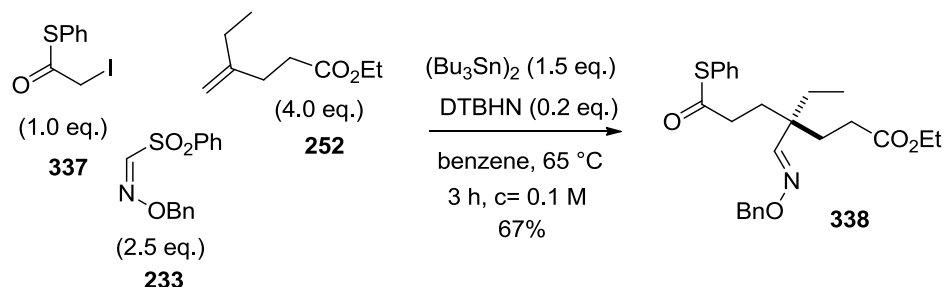
Scheme 99. Retrosynthesis Analysis of Azabicyclo[3.3.1]nonane Relying on α -iodothioester **337**.

Therefore, α -iodothioester **337** was synthesized according to the procedure described by Coltart *et al.*¹⁵⁷ from the corresponding 2-bromoacetyl bromide **339**. After reaction of **339** with thiophenol, the bromide atom was exchanged by iodine under Finkelstein reaction conditions (Scheme 100).

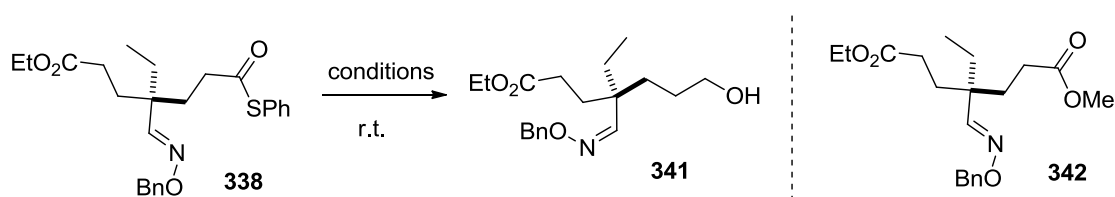
Scheme 100. Preparation of α -iodothioester **337**.

¹⁵⁷ Yost, J. M.; Alfie, R. J.; Tarsis, E. M.; Chong, I.; Coltart, D. M. *chem. Comm.* **2011**, 47, 571-572.

The first carbo-oximation reaction with α -iodothioester **337** was promising. The reaction worked efficiently, under the same reaction conditions than before, in good and reproducible 67% yield (Scheme **101**). It is worth noticing that, this reaction also worked well in large scale (5 g of isolated pure product) with the possibility to recover the excess of olefin **252** and oxime **233**. The reaction is also clean and the product is easier to isolate as compared to the reaction with xanthate ester **219**.

Scheme **101**. Carbo-oximation MCR with α -Iodothioester **337**.

The key carbo-oximation step being optimized with the installation of a thioester group, a chemoselective reduction of this thioester group to alcohol was then attempted before the reduction of the oxime (with subsequent cyclization to the amide). Therefore, the reduction of thioester **338** by NaBH_4 to the corresponding alcohol **341** in MeOH gave the expected product in moderate yield (42%) in combination with the trans-esterification byproduct **342**. To avoid the formation of the undesired trans-esterification byproduct **342** the solvent was changed to THF. The reaction worked better (80%) but slower due to the low solubility of NaBH_4 in THF. Attempts to increase the solubility of NaBH_4 by cation exchange with *n*-tetrabutylammonium chloride decreased the yield significantly to 47% (Scheme **102**).¹⁵⁸

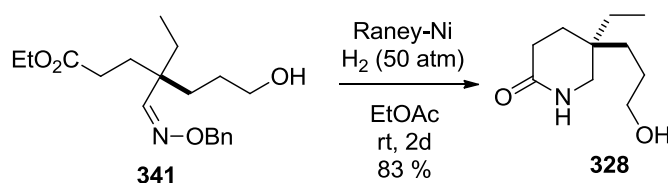


Entry	Conditions	Yield (%)
1	NaBH_4 (5.0 eq.), MeOH, 3 h	42
2	NaBH_4 (5.0 eq.), THF, 3 d	80
3	NaBH_4 (5.0 eq.), $(n\text{Bu})_4\text{NCl}$ (5.0 eq.), THF, 3 h	47

Scheme **102**. Chemoselective Reduction of Thioester **338**.

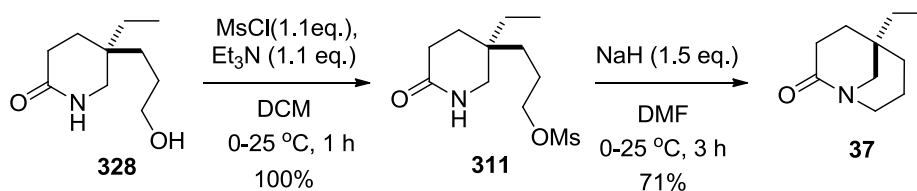
¹⁵⁸ Nagao, Y.; Ikeda, T.; Inoue, T.; Yagi, M.; Shiro, M.; Fujita, E. *J. Org. Chem.* **1985**, *50*, 4072-4080.

The hydrogenation of benzyl oxime ether **341** over Raney Nickel under 50 atm. of hydrogen for 3 days gave the free amine which cyclized directly onto the ethyl ester, affording the hydroxy-lactam **328** (Scheme 103).¹⁵⁹



Scheme 103. Hydrogenation of Benzyl Oxime Ether **341**.

After the quantitative activation of the free alcohol as a mesylate, the lactam **311** was submitted to sodium hydride promoting the cyclization, giving the bicyclic lactam **37** in 71% yield (Scheme 104).¹⁶⁰



Scheme 104. Synthesis of Bicyclic Lactam **37**.

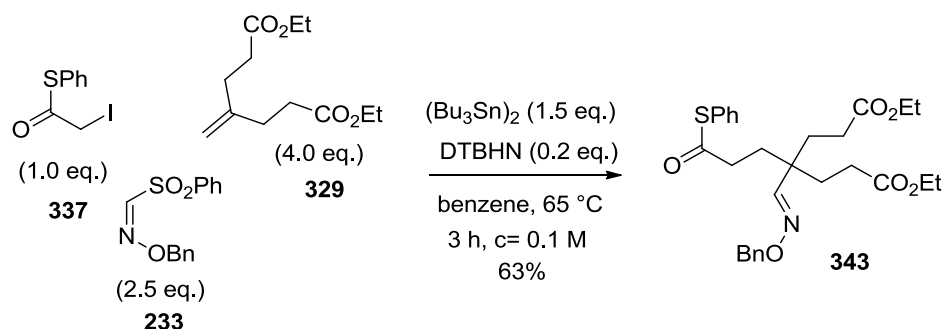
This short sequence provides a new straightforward access to this strained bicyclic amide in four steps and 31% overall yield. This oily bicyclic lactam could not be recrystallized, but the IR stretching $\nu_{C=O}$ at 1678 cm^{-1} and the ^{13}C NMR for the carbonyl carbon at 184.4 ppm indicate that this lactam **37** showed a moderate distortion of the amide bond, very similarly to the twisted amide **285** reported by Buchanan,¹³⁵ which suggests that the twist angle (τ) is around 20° .

2.4.2.4. Desymmetrization of Prochiral Esters

With the idea to develop an asymmetric synthesis of Eucophylline, the carbo-oximation reaction was also run between the potentially successful radical precursor, α -iodoester **337**, the symmetrical diester olefin **329** and the sulfonyl oxime **233** to afford the prochiral product **343** in a satisfactory 63% yield (Scheme 105).

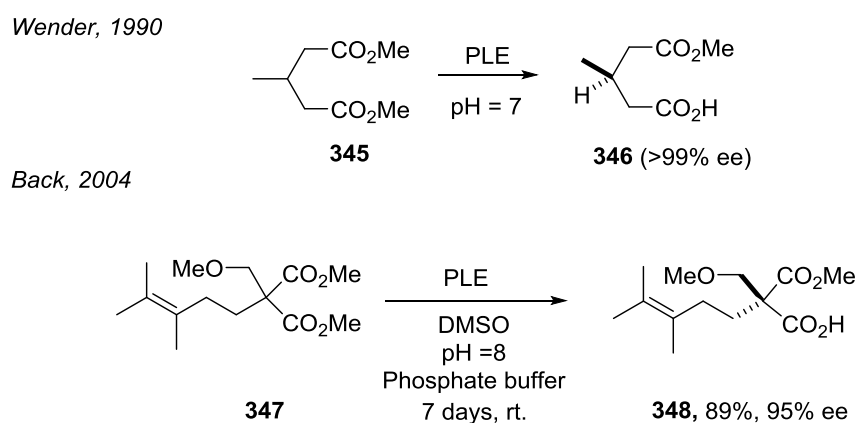
¹⁵⁹ Zhang, F.-G.; Yang, Q.-Q.; Xuan, J.; Lu, H.-H.; Duan, S.-W.; Chen, J.-R.; Xiao, W.-J. *Org. Lett.* **2010**, *12*, 5636-5639.

¹⁶⁰ (a) Li, Z.; Zhang, S.; Wu, S.; Shen, X.; Zou, L.; Wang, F.; Li, X.; Peng, F.; Zhang, H.; Shao, Z. *Angew. Chem. Int. Ed.* **2013**, *52*, 4117-4121; (b) Jing, P.; Yang, Z.; Zhao, C.; Zheng, H.; Fang, B.; Xie, X.; She, X. *Chem. Eur. J.* **2012**, *18*, 6729-6732.

Scheme 105. Carbo-oximation MCR with Diester Olefin **329**.

At this stage, the prochiral quaternary carbon could be made stereogenic by hydrolyzing one of the two esters to afford the corresponding acid ester **344**, the acid chain being transformed in an ethyl group through a Barton decarboxylation.¹⁵³ This mono-hydrolysis of the diester could be done enantioselectively by the use of enzymes (bio-catalyzed desymmetrization).

The advantage of an enzymatic desymmetrization is the ability to obtain the desired enantiomer with yield up to 100% in comparison with kinetic resolution where only 50% of the initial matter is transformed into the desired enantiomer.¹⁶¹ One of the most common enzymes used to desymmetrize a diester by mono-hydrolysis is the Pig Liver Esterase (PLE). PLE is one of the hydrolytic enzymes with the better synthetic potential.¹⁶² It has been used for many desymmetrizations of diester. For example, Wender *et al.*¹⁶³ used PLE to desymmetrize the prochiral diester **345** into the acid ester **346** in >99% ee (Scheme 106). More recently, Back and coworkers were able to desymmetrize diester **347** by partial hydrolysis with PLE to afford the acid ester **348** in 89% yield and 95% ee (Scheme 106).¹⁶⁴



Scheme 106. Examples of PLE Desymmetrizations.

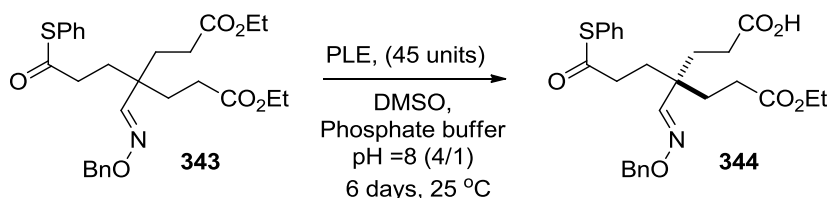
¹⁶¹ Palomo, J. M.; Cabrera, Z. *Curr. Org. Synth.*, **2012**, *9*, 791-805.

¹⁶² Lam, L. K. P.; Hui, R. A. H. F.; Jones, J. B. *J. Org. Chem.* **1986**, *51*, 2047-2050.

¹⁶³ Wender, P. A.; Singh, S. K. *Tetrahedron Lett.* **1990**, *31*, 2517-2520.

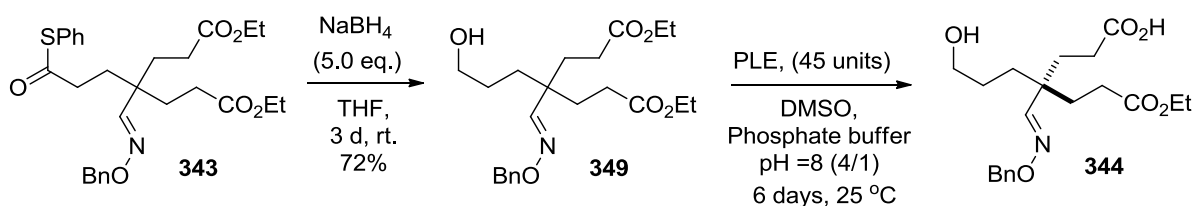
¹⁶⁴ Back, T. G.; Wulff, J. E. *Angew. Chem. Int. Ed.* **2004**, *43*, 6493-6496.

Based on these premises, the first desymmetrization trial was done with the prochiral diester **343**. The diester **343** was dissolved in a mixture of DMSO/phosphate buffer pH = 8 (4/1), then 45 units of PLE were added in three portions every 2 days to the reaction mixture. The temperature of the reaction was kept at 25°C and stirred for 6 days. Unfortunately, the acid ester **344** was not observed under these conditions and the only isolated product was the starting diester **343** (Scheme 107).



Scheme 107. Desymmetrization of Prochiral Diester **343**.

The anticipated difficult differentiation between the two ethyl esters and thioester groups¹⁶⁵ prompted us to engage the chemoselective reduction of the thioester **343** into the corresponding alcohol diester **349**. The enzymatic desymmetrization was repeated on the new diester under the same conditions but unfortunately, after 6 days, the only isolated product was also the starting material **343** (Scheme 108).



Scheme 108. Desymmetrization of Prochiral Diester Alcohol **349**.

As this stage, we gave up our wish to develop an enantioselective route to the bicycle[3.3.1]nonane and reported our attention to the elaboration in racemic series of the quinoline core of Eucophylline.

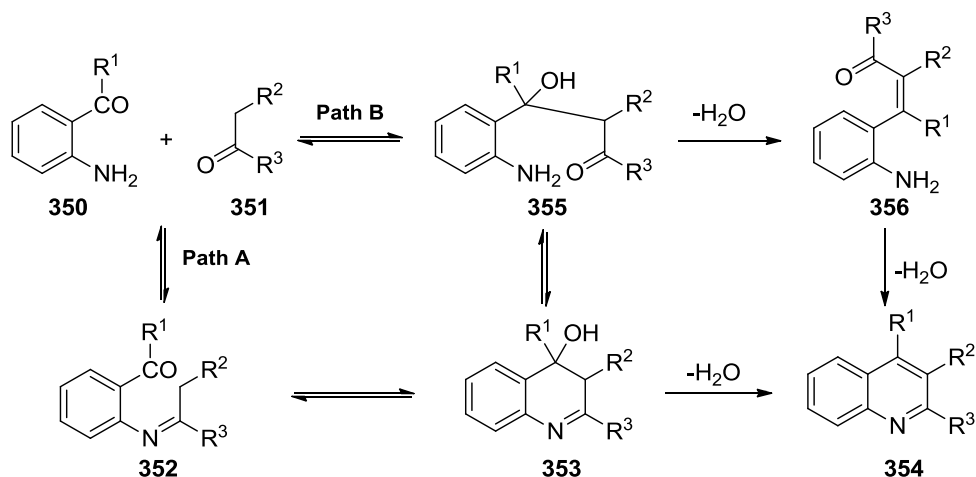
2.4.3. Synthesis of Quinoline Tetracyclic Core

One of the simplest methods to construct the quinoline ring system is the Friendländer reaction, based on an acid- or base-promoted condensation between an aromatic 2-amino-substituted carbonyl compound and an appropriately substituted carbonyl derivative containing a reactive α -methylene group.¹⁶⁶ The Friendländer reaction mechanism may be explained through two different possible pathways. The first one, starting from 2-amino-substituted aromatic carbonyl compound **350** and the carbonyl partner **351**, involves the formation of the Schiff base **352** followed by an intramolecular

¹⁶⁵ Toone, E. J.; Werth, M. J.; Jones, J. B. *J. Am. Chem. Soc.* **1990**, *112*, 4946-4952.

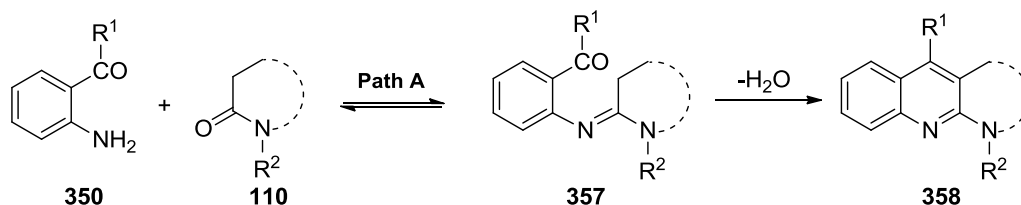
¹⁶⁶ Marco-Contelles, J.; Pérez-Mayoral, E.; Samadi, A.; Carreiras, M. D. C.; Soriano, E. *Chem. Rev.* **2009**, *109*, 2652-2671.

aldol reaction to give the hydroxyl imine **353** (path A). The second proposed mechanism suggests that under typically acidic [H_2SO_4 , HCl , $p\text{-TsOH}$] or basic (NaOH) conditions, the intermolecular aldol reaction is the first step and is followed by the formation of the Schiff base (path B). The dehydration (that may also happen before the formation of the Schiff base), then produces the expected quinoline **354** (Scheme 109).



Scheme 109. Possible Mechanisms of the Friedländer Reaction.

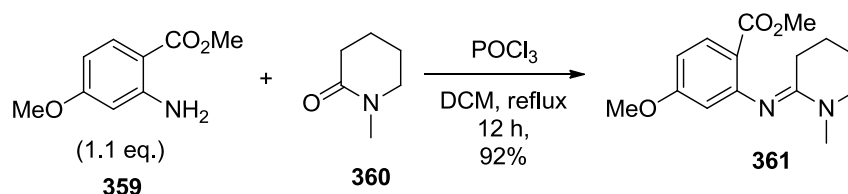
The synthesis of a 2-amino substituted quinoline would involve, when following the path A, the formation of an intermediate amidine (Scheme 110).



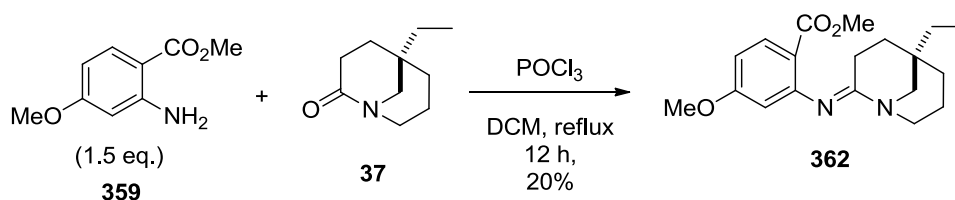
Scheme 110. Proposed Synthesis for a 2-amino Substituted Quinoline.

But in contrast with the condensation between an amine and a ketone, the formation of an amidine cannot proceed by direct condensation of an amine with an amide. This condensation has to be triggered by a strong dehydrating agent. The coupling between the amides and anilines is known to proceed under Vilsmeier reaction conditions by the mediation of POCl_3 .¹⁶⁷ The preliminary coupling between the monocyclic lactam **360** with the substituted aniline **359**, prepared from the commercially available nitro-benzoic acid, afforded the desired amidine **361** in 92% yield (Scheme 111).

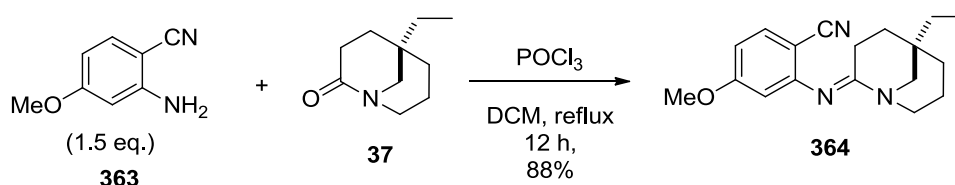
¹⁶⁷ Lucas-Lopez, C.; Patterson, S.; Blum, T.; Straight, A. F.; Toth, J.; Slawin, A. M. Z.; Mitchison, T. J.; Sellers, J. R.; Westwood, N. J. *Eur. J. Org. Chem.* **2005**, 9, 1736-1740.

Scheme 111. Reaction of Aniline **359** with monocyclic Lactam **360**.

However, an extension of this procedure to the coupling between our bicyclic lactam **37** and the same aniline **359** was disappointing. The reaction worked with a poor yield and led to a lot of degradation. The product was also difficult to isolate in a pure form (Scheme 112). This difference in reactivity may be explained by the particular reactivity of the twisted amide or by the steric hindrance.

Scheme 112. Reaction of Aniline **359** with Bicyclic Lactam **37**.

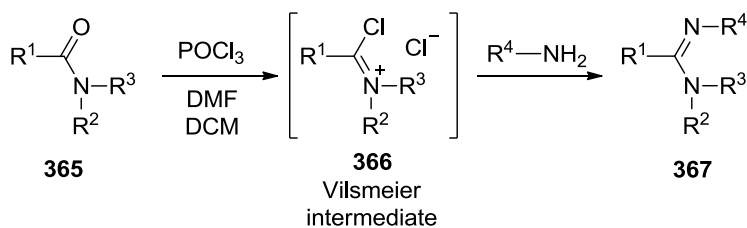
To reduce the steric hindrance that may impede with the coupling, the methyl ester group in aniline **359** was replaced by a nitrile group. The nitrile group is very small with A value = 0.21 which will help in reducing the steric hindrance in this coupling process.¹⁶⁸ Consequently, the cyano aniline **363** was introduced to react with bicyclic lactam **37** in the presence of POCl_3 . Pleasingly, the reaction worked well this time to give amidine **364** in 88% yield (Scheme 113).

Scheme 113. Reaction of Cyano-aniline **363** with Bicyclic Lactam **37**.

2.4.3.1. Mechanistic insights

The reaction between amides or lactams and POCl_3 is well-known to afford the corresponding α -chloroiminiums, often called Vilsmeier intermediates, which then react efficiently with nucleophiles, including amines to form amidines (Scheme 114).¹⁶⁷

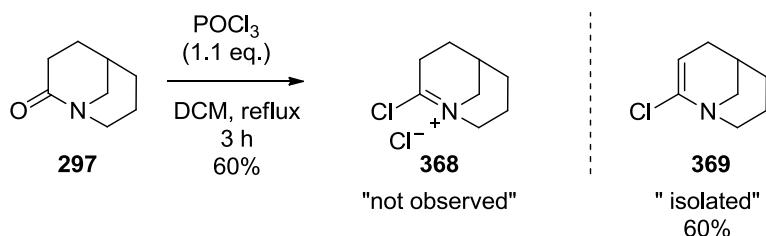
¹⁶⁸ (a) Boiadjev, S. E.; Lightner, D. A. *J. Am. Chem. Soc.* **2000**, *122*, 11328-11339; (b) Jensen, F. R.; Bushweller, C. H.; Beck, B. H. *J. Am. Chem. Soc.* **1969**, *91*, 344-351; (c) Schneider, H. J.; Hoppen, V. J. *Org. Chem.* **1978**, *43*, 3866-3873; (d) Winstein, S.; Holness, N. J. *J. Am. Chem. Soc.* **1955**, *77*, 5562-5578.



Scheme 114. Synthesis of amidines via Vilsmeier intermediate.

But in the case of highly strained bridgehead lactams, the formation of iminium species, like Vilsmeier-Haack intermediate **366**, is not favored according to Bredt's rule. This hypothesis prompted us to investigate the mechanism of this reaction.

In an attempt to try to observe the Vilsmeier-Haack intermediate, the bicyclic lactam model **297**, prepared following a Steliou procedure,¹³⁸ was treated with POCl_3 in dry DCM under reflux for 3 h. The Vilsmeier-Haack intermediate **368** could not be observed from the reaction but surprisingly, a remarkably stable bicyclic α -chloroenamine **369** could be isolated after column chromatography. In an optimized synthesis, after basic treatment of the reaction mixture with 30% NaOH till pH = 8, followed by extraction by DCM, the crude mixture is purified by column chromatography, and the bicyclic α -chloroenamine **369** could be isolated in 60% yield (Scheme 115). This result prompted us to study more in depth the chemistry of this α -chloroenamine.

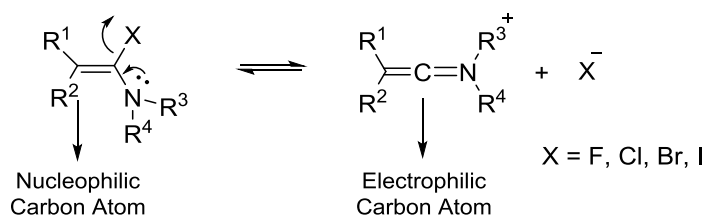
Scheme 115. Synthesis of α -chloroenamine **369**.

The remarkable stability of this bicyclic α -chloroenamine questioned us about the general stability of chloroenamines and how these chloroenamines may be synthesized. Some answers are provided in the following lines.

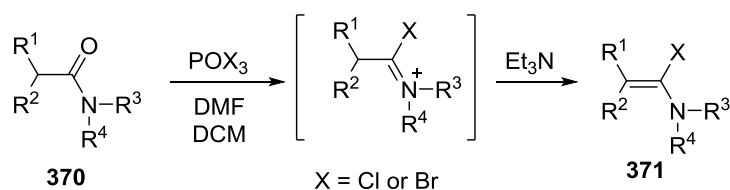
1. Synthesis of α -chloroenamines.

In general, α -haloenamines behave as ambiphilic molecules and react as nucleophilic reagents at the β -carbon atom of the enamine function, but also show electrophilic reactivity at the α -carbon atom through the intermediate formation of a keteniminium salt (Scheme 116).¹⁶⁹

¹⁶⁹ Ghosez, L.; George-Koch, I.; Patiny, L.; Houtekie, M.; Bovy, P.; Nshimyumukiza, P.; Phan, T. *Tetrahedron* **1998**, *54*, 9207-9222.

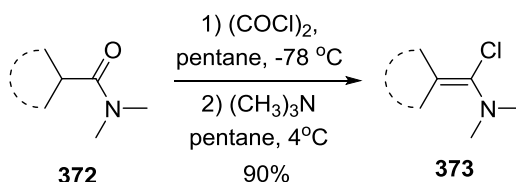
Scheme 116. α -Haloenamine Reactivity.

By tuning the ambiphilicity of α -haloenamines through variation of the nature of the halogen atom or the amine substituents, a controllable unique reactivity of enamines could be obtained. Ghosez *et al.* pioneered the synthesis and isolation of α -haloenamines.¹⁷⁰ In 1969, this group was able to synthesize α -chloroenamines from the corresponding tertiary amides **370** by reacting them with phosgene followed by dehydrochlorination of the intermediate chloroiminium with triethylamine. Later, the same group used less toxic chlorinating agents like phosphorous oxychloride or oxybromide (to obtain α -bromo enamines) (Scheme 117).

Scheme 117. Synthesis of α -Haloenamine.

It is worth noticing that all of the reactions reported must be run under strict anhydrous conditions and that these α -haloenamines must be kept away from moisture, since they are very sensitive to any traces of water and degrade rapidly.¹⁷¹

In 2011, Kingsbury *et al.* reported the formation of α -chloroenamines **373** from the corresponding amides **372** by the reaction with oxalyl chloride. The reaction was performed under anhydrous conditions at -78°C and the dehydrochlorination was done with dry Me_3N . The work up, isolation and storage of this enamine were performed under glovebox conditions. The strict anhydrous conditions reflect the high instability of these enamines (Scheme 118).¹⁷²

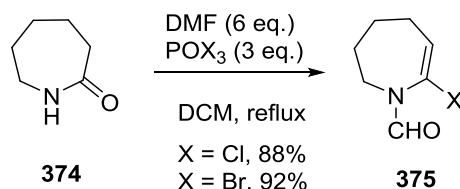
Scheme 118. Synthesis of α -chloroenamine **373**.

¹⁷⁰ (a) Ghosez, L.; Haveaux, B.; Viehe, H. G. *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 454-455; (b) Ghosez, L.; Notté, P.; Bernard-Henriet, C.; Maurin, R. *Heterocycles* **1981**, *15*, 1179-1185. (c) Martin, M. L.; Ricolleau, G.; Poignant, S.; Martin, G. J. *J. Chem. Soc., Perkin Trans. 2* **1976**, 182-186; (d) Marchand-Brynaert, J.; Ghosez, L. *J. Am. Chem. Soc.* **1972**, *94*, 2869-2870.

¹⁷¹ Haveaux, B.; Dekoker, A.; Rens, M.; Sidani, A. R.; Toye, J.; Ghosez, L. *Org. Synth.* **1979**, *59*, 26.

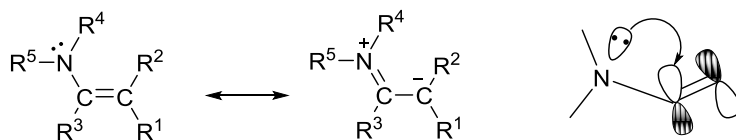
¹⁷² O'Brien, J. M.; Kingsbury, J. S. *J. Org. Chem.* **2011**, *76*, 1662-1672.

More recently, Sarpong and coworkers reported the synthesis of α -haloeneformamides **375** from the corresponding caprolactam **374** through the reaction with POCl_3 or POBr_3 .¹⁷³ The important factor that allowed this group to isolate this enamine easily is the presence of a formyl group, an electron withdrawing substituent on the nitrogen atom. But it has also been noticed that these enamines are not stable for long time outside the fridge (Scheme **119**).

Scheme **119**. Synthesis of α -Haloeneformamides **375**.

2. Stability of α -chloroenamines.

From the previous examples, it is clear that isolation of this type of enamines in general is not an easy task. The reactivity of enamines, in general, stems from the conjugation between the olefinic π -bond of the α,β -carbons and the lone pair of nitrogen (Scheme **120**). Normally, an amine has a pyramidal geometry with bond angles around the nitrogen of 109.5° . The lone pair of electrons on the sp^3 -hybridized nitrogen may overlap with the p-orbitals of the π -bond, giving a high nucleophilic character to the β -carbon.¹⁷⁴

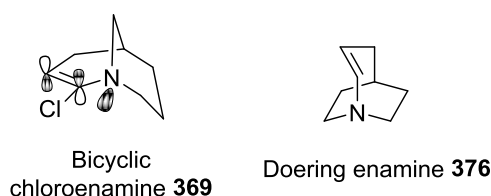
Scheme **120**. Normal Enamine Reactivity.

This reactivity is then governed by the degree of conjugation of the lone pair with the π -system and this conjugation may be influenced by electronic and steric factors.¹⁷⁴ Thus, the presence of an electron-withdrawing group on nitrogen will significantly alter the reactivity, exemplified by the possible isolation of α -haloeneformamides **375**. Also, any variation of the coplanar conformation will have a strong effect on the system properties as it is the case in our bicyclic system where the nitrogen lone pair is forced to be quasi orthogonal to the enamine π -system (Scheme **121**). This has also been observed by Doering *et al.* with the stable 1-azabicyclo[3.2.2]non-3-en **376**, in which, orthogonal enamine is forced by the bicyclic system to place the nitrogen in a pyramidal geometry with its lone pair perpendicular to the olefinic π bond, conferring the π -system a more standard olefinic character.¹⁷⁵

¹⁷³ Beng, T. K.; Wilkerson-Hill, S. M.; Sarpong, R. *Org. Lett.* **2014**, *16*, 916-919.

¹⁷⁴ *Enamines: Synthesis, Structure and Reactions*; Cook, A. G., Ed.; Marcel Dekker: New-York and London, **1969**.

¹⁷⁵ Doering, W. v. E.; Birladeanu, L.; Andrews, D. W.; Pagnotta, M. *J. Am. Chem. Soc.* **1985**, *107*, 428-435.

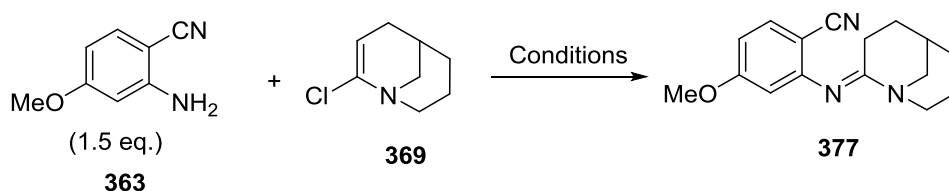


Scheme 121. Orthogonal Enamines .

2.4.3.2. Coupling Reaction Mechanism

Based on these results and observations, the next question that arose was the possible involvement of this α -chloroenamine **369** as an intermediate in the coupling reaction between the bicyclic lactam **37** and aniline **363**. The purified α -chloroenamine **369** was thus allowed to react with *ortho*-cyanoaniline **363** in presence of catalytic amount of TFA. The reaction worked well and the amidine **377** was isolated in 84% yield confirming that the α -chloroenamine **369** is a key reaction intermediate.

Moreover, to draw a mechanism of this reaction, the role of TFA was investigated. Therefore, the reaction was repeated under neutral condition, with just the α -chloroenamine **369** and *ortho*-cyanoaniline **363** in refluxing DCM. Surprisingly, the reaction worked well with a similar same yield (77%). The reaction was also performed under basic condition by addition of 2,6-di-*tert*-butyl pyridine and the same amidine was obtained with the same yield (80%) (Scheme 122). These observations showed that acid and bases are not essential, their role remaining unclear.

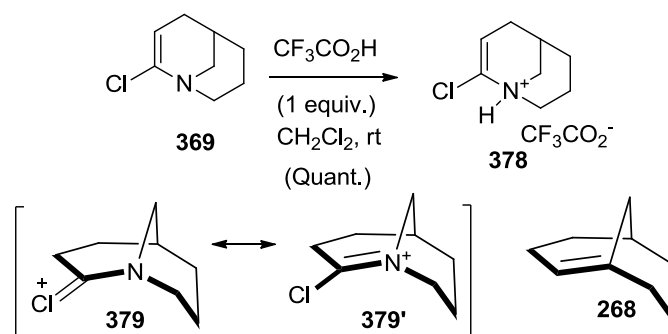


Entry	Conditions	Yield (%)
1	TFA (0.1 eq.), DCM, reflux, 12 h	84
2	DCM, reflux, 12 h	77
3	(Me ₃ C) ₂ C ₅ H ₃ N (0.1 eq.), DCM, reflux, 12 h	80

Scheme 122. Reaction of Cyano-aniline **363** with Bicyclic α -Chloroenamine **369**.

Treatment of α -chloroenamine **369** with TFA did not give the corresponding α -chloroiminium, but led to the kinetic protonation at the nitrogen center with the formation of α -chloroenaminium salt **378** in quantitative yield (Scheme 123). A ¹³C NMR analysis of this salt showed a shifting of the α -carbon of the enamine from 138 ppm to 122 ppm, due to the modification of the electronic environment around this carbon by protonation of neighboring nitrogen. When allowed to react with *ortho*-cyanoaniline **363**, this α -chloroenaminium salt **378** afforded the amidine **377** in 59%. An *in*

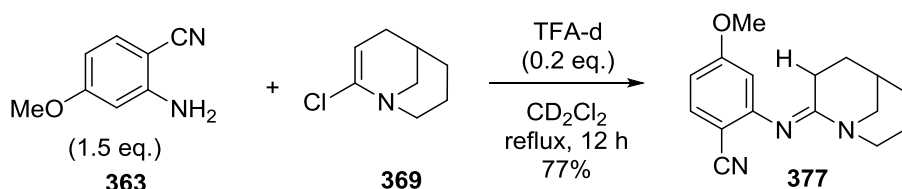
situ prototropy in **369** could provide intermediates **379** or **379'**, able to react further with aniline **363**. The analogous bridgehead alkene **368**, which has been isolated by Marshall *et al.* is reasonably stable and supports the assumption of the formation of an iminium as an intermediate in the reaction.¹⁷⁶



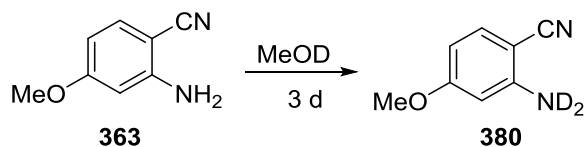
Scheme 123. Kinetic Protonation.

Surprisingly, when chloroenamine **369** was heated in water at 60°C for 3 h, it was completely recovered, after extraction from DCM, without any degradation or decomposition, in sharp contrast with what is usually observed with “planar” enamines.^{169,172}

We also searched for the source of hydrogen that adds onto the β -carbon of enamine (C-2), using deuterated substrates or reagents. First, the use of sub-stoichiometric amount of deuterated trifluoroacetic acid in deuterated DCM catalyzed the reaction but without any change in the amidine ¹H NMR, indicating no incorporation of deuterium in the final product (Scheme 124).

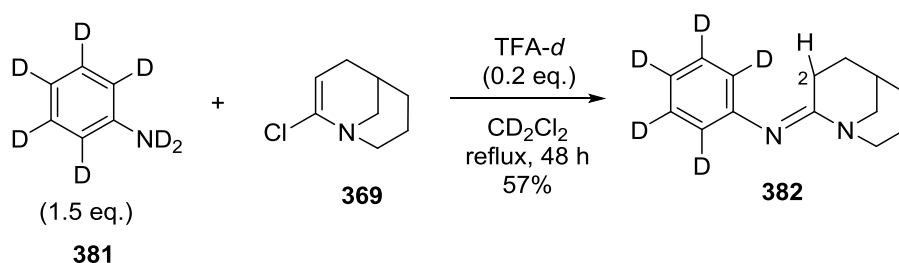
Scheme 124. Coupling Reaction between α -chloroenamine and Aniline **363** in deuterated conditions.

This sub-stoichiometric amount being not optimal to observe a decrease in the CH₂ integration, the aniline was stirred in deuterated methanol to study the exchange of hydrogens with deuteriums. However, the isolation of fully deuterated aniline was not successful (Scheme 125).

Scheme 125. Deuterium Exchange in Aniline **363**.

¹⁷⁶ (a) Marshall, J. A.; Faubl, H. *J. Am. Chem. Soc.* **1967**, *89*, 5965-5966; (b) Wiseman, J. R. *J. Am. Chem. Soc.* **1967**, *89*, 5966-5968.

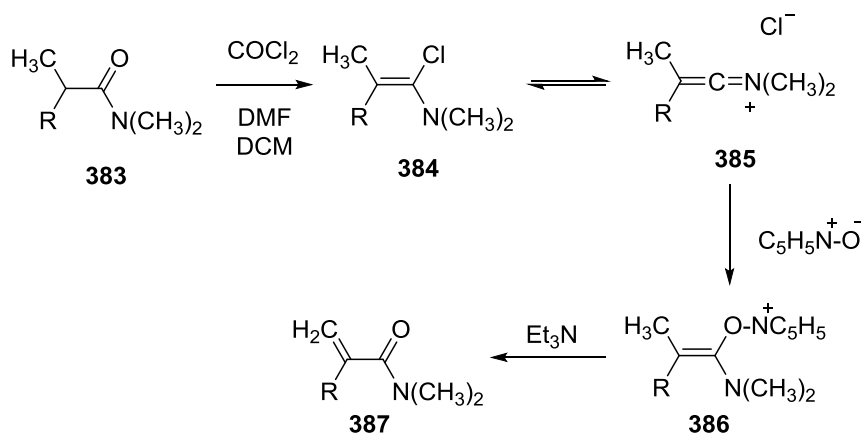
The fully deuterated aniline- d_7 **381** being commercially available, it was mixed with the α -chloroenamine **369** and a catalytic amount of TFA- d in CD_2Cl_2 . The amidine **382** was isolated in lower yield (57%) but without any incorporation of deuterium at C-2 (Scheme **126**), the structure of this amidine being established though extensive 1H and ^{13}C NMR studies and confirmed by HRMS.



Scheme **126**. Coupling Reaction between α -chloroenamine and Aniline- d_7 **381** in deuterated conditions.

All of these attempts to explore the mechanism probably failed because the C-2 protons are readily exchangeable and the coupling requires an aqueous basic workup and a chromatography on silica gel, conditions that also favor deuterium-hydrogen exchanges.

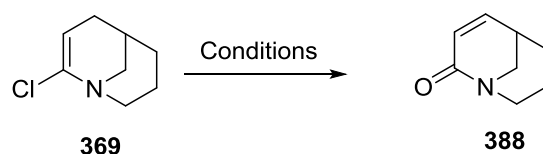
Ghosez and coworkers described the α,β -dehydration of tertiary carboxyamides **383** by pyridine N -oxide though the α -chloroenamine intermediate **384**. The reaction probably involved ionization of α -chloroenamine **384** to the corresponding ketene-iminium chloride **385** followed by the addition of pyridine N -oxide. A base mediated 1,4-elimination produced finally an α,β -unsaturated amide **387** (Scheme **127**).¹⁷⁷



Scheme **127**. α,β -Dehydrogenation of Tertiary Carboxyamides by Ghosez

In an analogous fashion, these conditions were applied to our α -chloroenamine, but the reaction did not proceed and the starting material was recovered (Scheme **128**).

¹⁷⁷ Da Costa, R.; Gillard, M.; Falmagne, J. B.; Ghosez, L. *J. Am. Chem. Soc.* **1979**, *101*, 4381-4383.

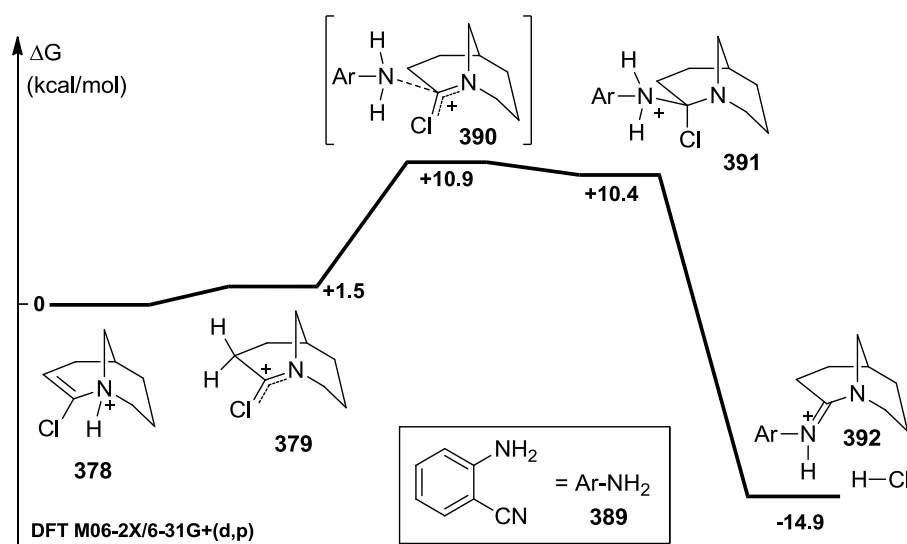


Entry	Conditions	Yield (%)
1	C ₅ H ₅ N-O (1.0 eq.), Et ₃ N (2.5 eq.), r.t., 2 h	S.M.
2	C ₅ H ₅ N-O (1.0 eq.), Et ₃ N (2.5 eq.), 65°C, 16 h	S.M.

Scheme 128. Reaction of α -chloroenamine **369** with Pyridine *N*-oxide.

These results confirm that our α -chloroenamine cannot form, as expected, a keteniminium intermediate and that the coupling with the aniline should follow another pathway.

To have some insight into the mechanism of the amidine formation, DFT computational studies were performed by Dr Frédéric ROBERT. Starting from the protonated α -chloroenamine **378**, it appeared that the α -chloroiminium form **379** is only 1.5 kcal/mol higher, indicating that these two species should be in equilibrium. The α -cyanoaniline would then approach on the upper face to give the addition product **391**. The formation of the final amidine **392**, obtained after loss of HCl, was found highly exothermic, rationalizing the reaction pathway (Scheme 129). It is also worth noticing that whereas the transition state for aniline attack **390** was relatively low (+10.9 kcal/mol), the equivalent transition state with water attacking the chloroiminium was found much higher (+31.2 kcal/mol), possibly explaining the surprising stability of the α -chloroenamine in hot water.

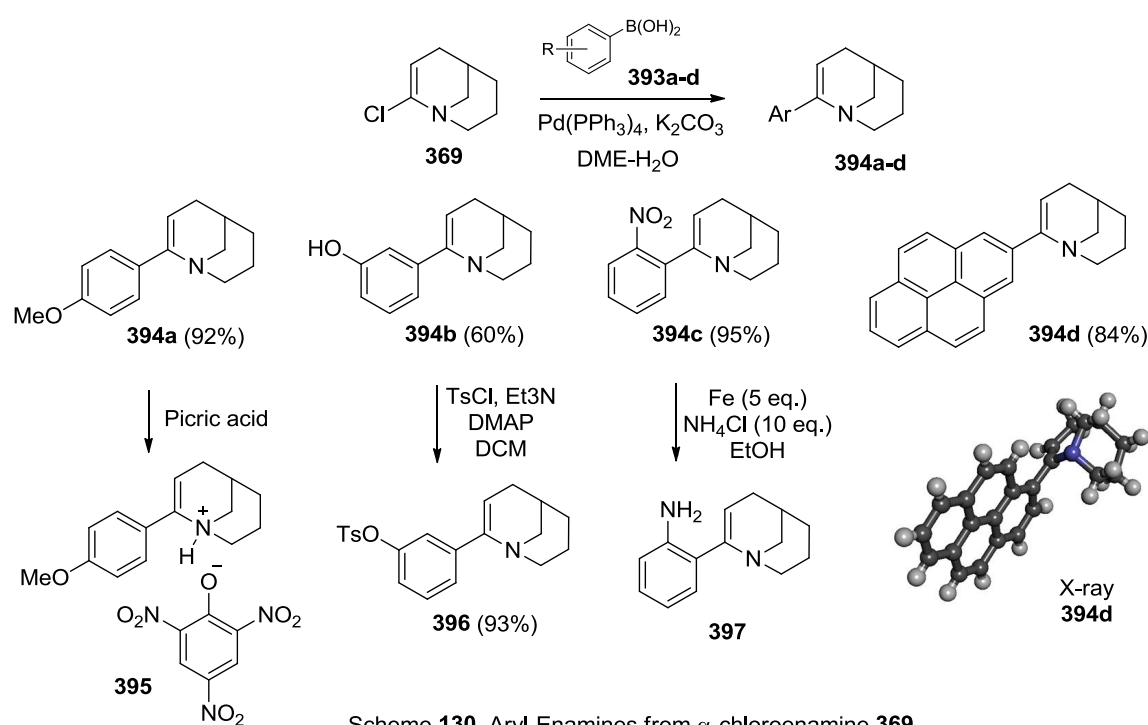


Scheme 129. Rationalization of the Amidine Formation Mechanism by DFT Calculations.

2.4.3.3. Reactions with the α -Chloroenamine

The stability of this α -chloroenamine and its bicyclic architecture motivated us to try to functionalize them and explore their unique reactivity. In order to test if the α -chloroenamine would behave like a vinylic chloride, Pd-catalyzed reactions with boronic acids (Suzuki coupling) have

been tested.¹⁷³ Thus aryl boronic acids **393a-d** were allowed to react with α -chloroenamine under Pd-catalysis to afford the corresponding bicyclic aryl-enamines **394a-d** in good to excellent yields. Further functionalization of these arylenamines was performed. For instance, in order to obtain a solid enamine ready for X-ray diffraction studies, arylenamine **394a** was reacted with picric acid, but the only isolated solid product was the picric acid. Arylenamine **394b** was protected as a tosylate, which worked well in 93%, but unfortunately the compound **396** was also oil. When the nitro group in aryl-enamine **394c** was subjected to iron reduction to give the corresponding amine, the reaction unfortunately did not work. Finally, the pyrene-enamine **394d** was isolated in solid form which gave us the opportunity to start X-ray diffraction studies. Crystallographic data indicate that the bicyclic system enforces the nitrogen lone pair to be quasi orthogonal to the enamine π -system, explaining the unusual stability of such enamines and chloroenamines (Scheme 130).

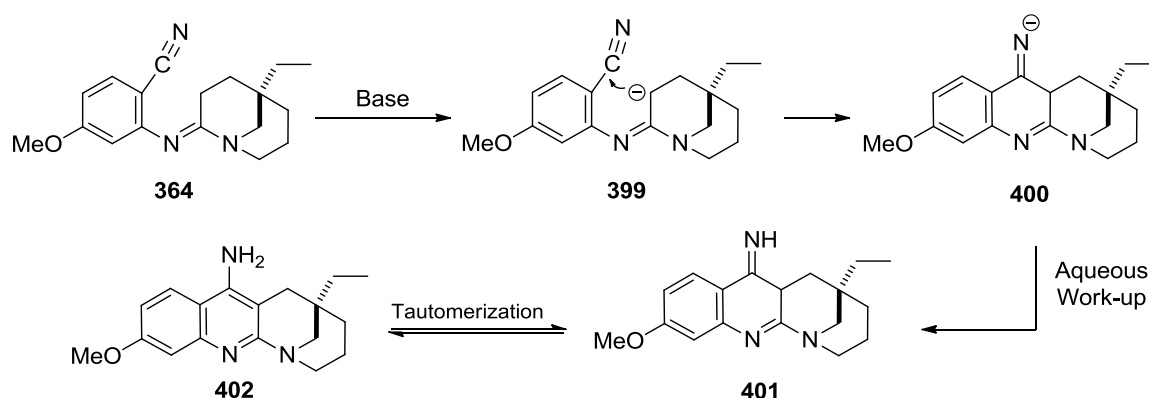


Epoxidation of the enamine provides some insights into the reactivity of the enamine double bond. Thus, arylenamine **394a** was allowed to react with *m*-CPBA in DCM for 2 days. But our attempt to epoxidize the enamine double bond was not successful and the only isolated product was the starting material (Scheme 131). The poor nucleophilicity of the double bond as compared to that of normal enamines explains this lack of reactivity.



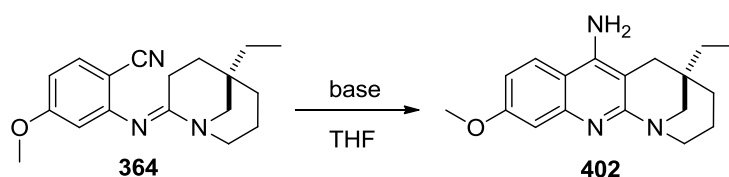
2.4.4. Elaboration of Eucophylline

To complete the synthesis of Eucophylline, we needed to elaborate the last ring (noted B) in the naphthyridine core. This cyclization could be mediated by a strong base to abstract the more acidic proton, in α -position to the amidine, generating a carbanion which could attack the nitrile group to form the ring. After a work-up and tautomerization, the amino naphthyridine skeleton **402** should be obtained (Scheme 132).



Scheme 132. Mechanism of Amidine Cyclization.

Therefore, with amidine **364** in hand, the cyclization was tried by using *t*-BuOK. The primary results were disappointing, as the expected product **402** was formed in only 20% along with recovered starting amidine. Extended reaction time did not improve the yield to a large extent (entry 2, table 4). The reaction was nevertheless clean with only the product and the starting material. The use of a stronger base, LDA, gave much better results (table 4). After some optimizations, the best results were obtained by preparing very concentrated LDA and running the reaction at room temperature, conditions that gave the desired product in 70% yield (Scheme 133).

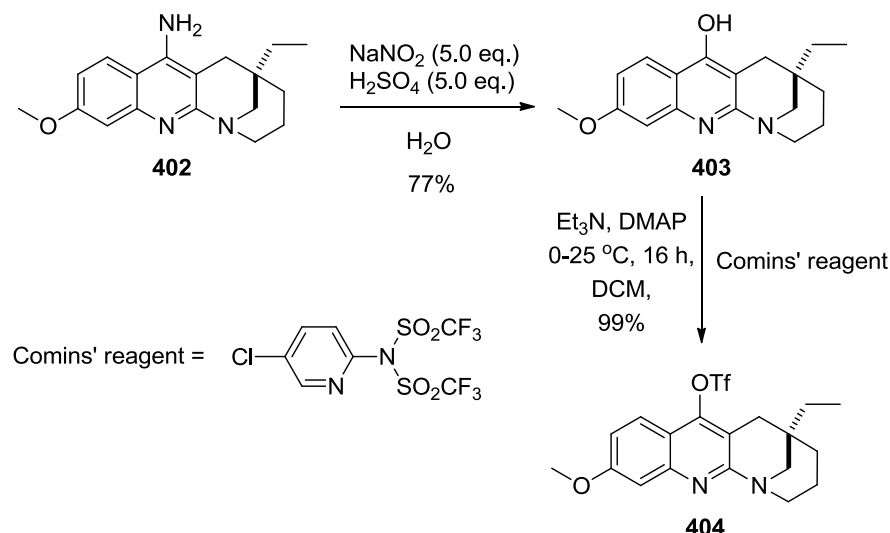


Scheme 133. Cyclization of Amidine **364**.

Entry	base	Base Eq.	Temp. °C	time	Yield% (a)
1	<i>t</i> -BuOK	2.65	25	3	20(59)
2	<i>t</i> -BuOK	2.65	25	16	21(53)
3	LDA	2.65	-78	3	44(79)
4	LDA	3	-78	3	35(64)
5	LDA(neat)	3	25	3	56(88)
6	LDA(neat)	3	25	16	70

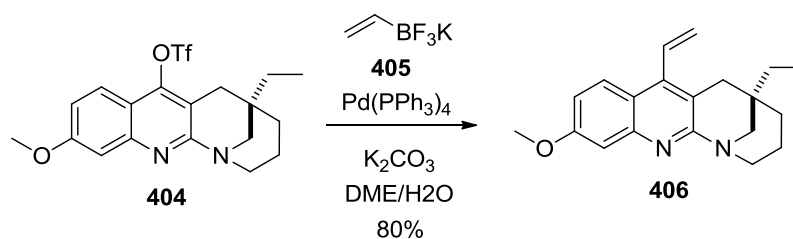
Table 4. Optimization of Amidine Cyclization. (a) brsm

With this amino naphthyridine **402** in hand, the installation of vinylic fragment was planned relying on a Suzuki coupling with diazonium salts derived from this amino naphthyridine **402**.¹⁷⁸ Due to the modest yields obtained with model compounds, an alternative strategy using triflate was developed. Therefore, the diazotation of the amino naphthyridine **402** was performed in sodium nitrite and sulfuric acid, followed by hydrolysis to give the corresponding alcohol **403**. After reaction of the latter with Comins' reagent,¹⁷⁹ the corresponding triflate **404** was obtained in quantitative yield (Scheme 134).



Scheme 134. Converting Amino Group to Triflate in Naphthyridine **402**.

With this triflate **404** in hand, the installation of vinylic moiety was carried out through the Suzuki coupling with commercially available vinyl trifluoroborate **405** in the presence of potassium carbonate to afford the desired vinyl naphthyridine **406** in 80% yield (Scheme 135).¹⁸⁰



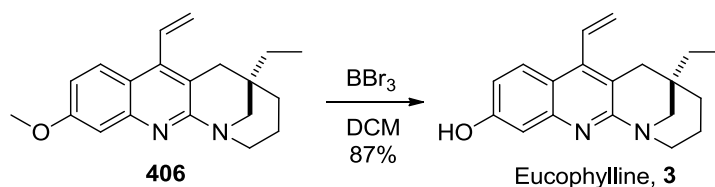
Scheme 135. Synthesis of Vinyl Naphthyridine through Suzuki Coupling.

To achieve the synthesis of Eucophylline **3**, *O*-demethylation of vinyl naphthyridine **406** was performed with BBr_3 which worked in an excellent 87% yield (Scheme 136).

¹⁷⁸ Darses, S.; Michaud, G.; Genet, J. P. *Eur. J. Org. Chem.* **1999**, 1999, 1875-1883.

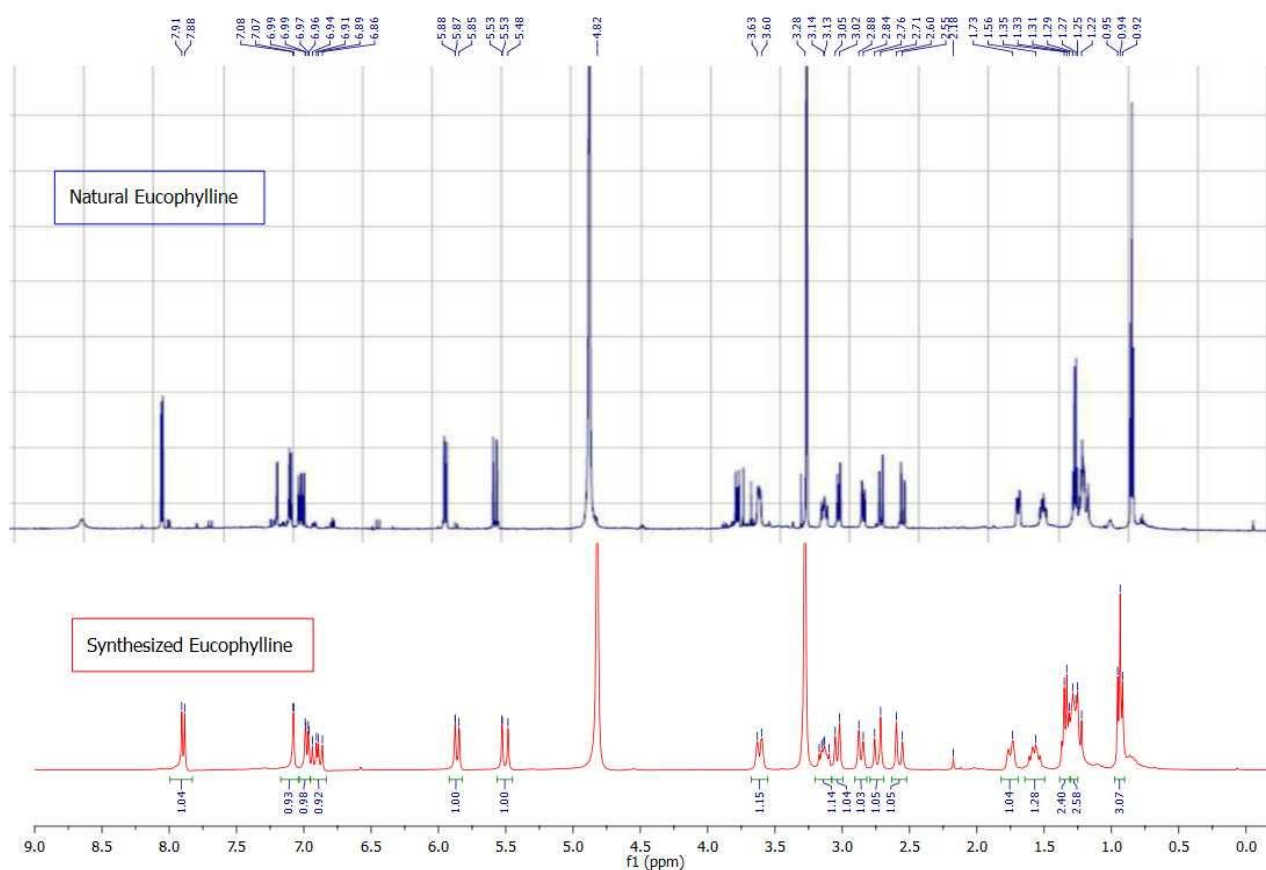
¹⁷⁹ Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, 33, 6299-6302.

¹⁸⁰ (a) Molander, G. A.; Rodriguez Rivero, M. *Org. Lett.* **2002**, 4, 107-109; (b) Darses, S.; Michaud, G.; Genet, J. P. *Tetrahedron Lett.* **1998**, 39, 5045-5048.



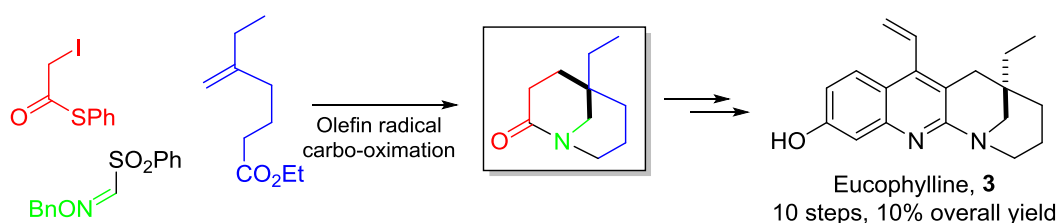
Scheme 136. Elaboration of Eucophylline 3.

The synthesized (\pm)-Eucophylline analytical data are in good agreement with those found for the natural product isolated by Morita *et al.*¹⁰² The ^1H NMR spectra of both natural and synthesized Eucophylline showed good agreement (Figure 8). Also the ^{13}C NMR is in good agreement with the one reported for natural Eucophylline. HRMS of the synthesized Eucophylline is $[\text{M}+\text{H}]^+ = 295.1814$ in good agreement with that reported for natural Eucophylline 295.1816.

Figure 8. The ^1H NMR spectra of both natural and synthesized Eucophylline.

2.5. Conclusion

In summary, the first total synthesis of Eucophylline **3**, the south half of Leucophyllidine **1**, has been reported in 10 steps from α -iodothioester **337** and in a 10% overall yield relying on the recently developed carbo-oximation free radical reaction. This total synthesis also includes a new straightforward method to access the azabicyclo[3.3.1]nonane skeleton. The unique reactivity of twisted amides, present in the bicyclic lactams, allowed us to isolate and functionalize a remarkably stable bicyclic α -chloroenamine intermediate, illustrating again the importance of the conjugation of the nitrogen's lone-pair electron position in the reactivity of amides and enamines. This total synthesis, the study on the bridgehead bicyclic lactam and α -chloroenamine intermediate were the topic of a recently published article in *Organic Letters* in 2015.¹⁸¹



Scheme 137. Total Synthesis of Eucophylline.

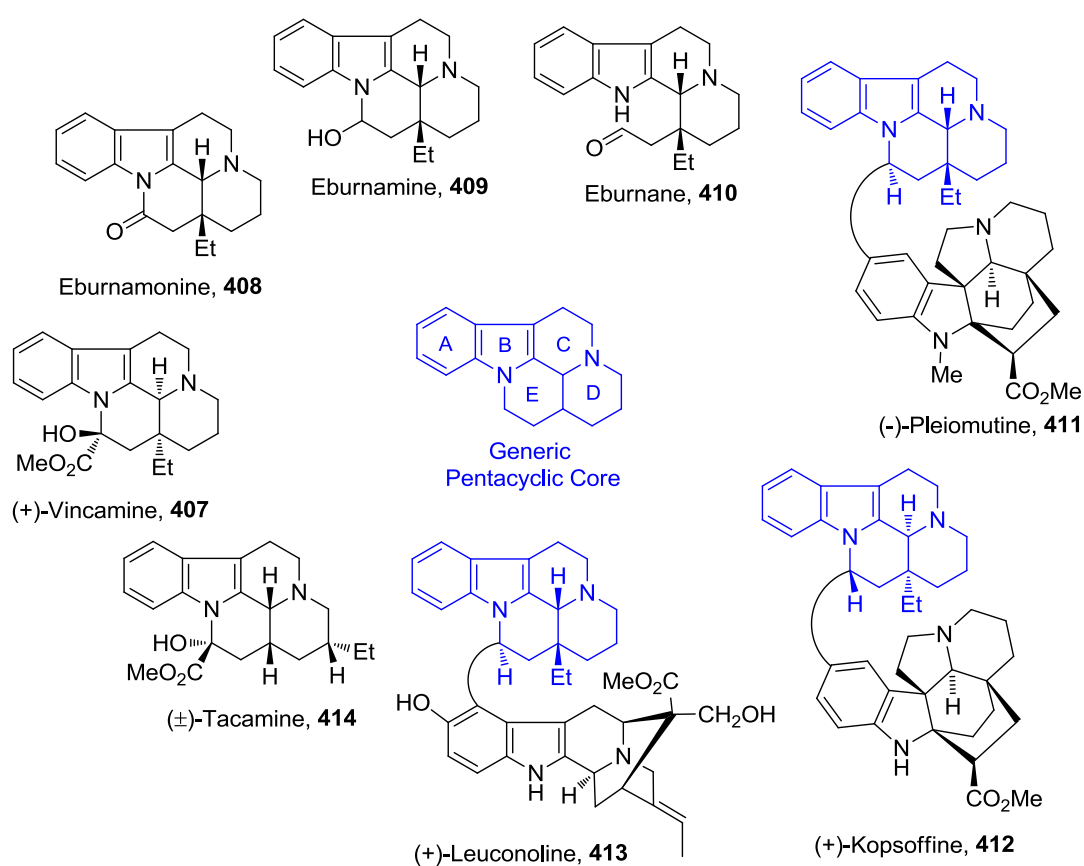
¹⁸¹ Hassan, H.; Mohammed, S.; Robert, F.; Landais, Y. *Org. Lett.* **2015**, *17*, 4518-4521.

Chapter Three

Eburnane Synthesis

3.1. Introduction

Eburnane **2**, the north fragment of Leucophyllidine **1**, is a pentacyclic indole alkaloid with a skeleton present in many vinca alkaloids, mainly isolated from the plant family Apocyanaceae.¹⁸² For example, Vincamine **407**, which is known for its cerebral vasodilatory pharmacological activities, has an Eburnane pentacyclic core with an ester group in ring E.¹⁸³ The same pentacyclic core is also present in Eburnamonine **408** and Eburnamine **409** with amide or alcohol in ring E respectively,¹⁸⁴ and the structurally related Tacamine **414**.¹⁸⁵ Eburnane skeleton also constitutes the half part of several pharmacologically active bisindole alkaloids like Pleiomutine **411**, Kopsoffine **412** and Leuconoline **413** (Scheme 138).^{186,187}



Scheme 138. Eburnane Pentacyclic core / Examples in natural products.

¹⁸² England, D. B.; Padwa A. *J. Org. Chem.* **2008**, *73*, 2792-2802.

¹⁸³ Hava, M. The Pharmacology of Vinca species and their Alkaloids, *The Vinca Alkaloids*; Taylor, W. I., Farnsworth, N. R., Eds.; Marcel Dekker: New York, **1973**; Chapter 6, p 305.

¹⁸⁴ Ho, T.-L.; Chen, C.-K. *Helv. Chim. Acta* **2005**, *88*, 2764-2770.

¹⁸⁵ Van Beek, T. A.; Verpoorte, R.; Baerheim, Svendsen, A. *Tetrahedron* **1984**, *40*, 737-748.

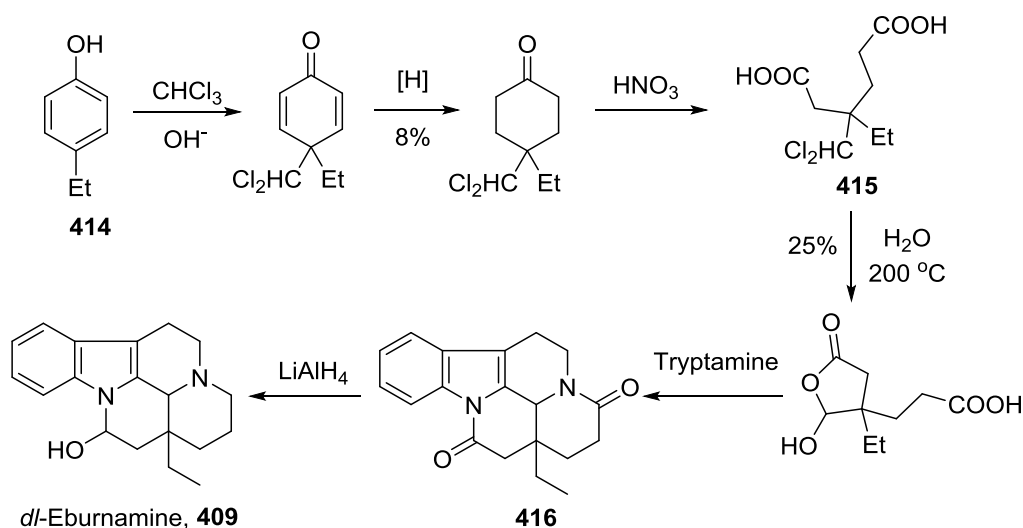
¹⁸⁶ Lounasmaa, M.; Tolvanen, A. The alkaloids; Cordell G. A., Ed.; Academic press, New York, **1992**, Vol. 42, chapter 1.

¹⁸⁷ (a) Feng, X. Z.; Kan, C.; Husson, H.-P.; Potier, P.; Kan, S.-K.; Lounasmaa, M. *J. Nat. Prod.* **1984**, *47*, 117-122; (b) Gan, C.-Y.; Low, Y.-Y.; Robinson, W. T.; Komiyama, K.; Kam, T.-S. *Phytochemistry* **2010**, *71*, 1365-1370.

Since isolation of these Eburnane-type alkaloids, organic chemists developed numerous syntheses for constructing its pentacyclic core. Most of these syntheses were based on condensation of aldehydes with tryptamine under Pictet-Spengler reaction conditions or on Bischler-Napieralski intramolecular condensations. In the following part, a survey on the synthesis of this indole pentacyclic structures will be reviewed.

3.2. Review on the synthesis of Eburnane Pentacyclic Core

One of the first syntheses of Eburnamine **409** has been done in 1960 by Taylor.¹⁸⁸ In this synthesis, the condensation of β -ethyl- β -formyladipic acid **415**, prepared from *p*-ethyl phenol **414** under Reimer-Tiemann reaction conditions, with tryptamine afforded the eburnamonine lactam **416**. This lactam **416** was reduced to the corresponding eburnamine **409** in poor yields for the ring closure (25%) and Reimer-Tiemann reaction (8%) (Scheme 139).

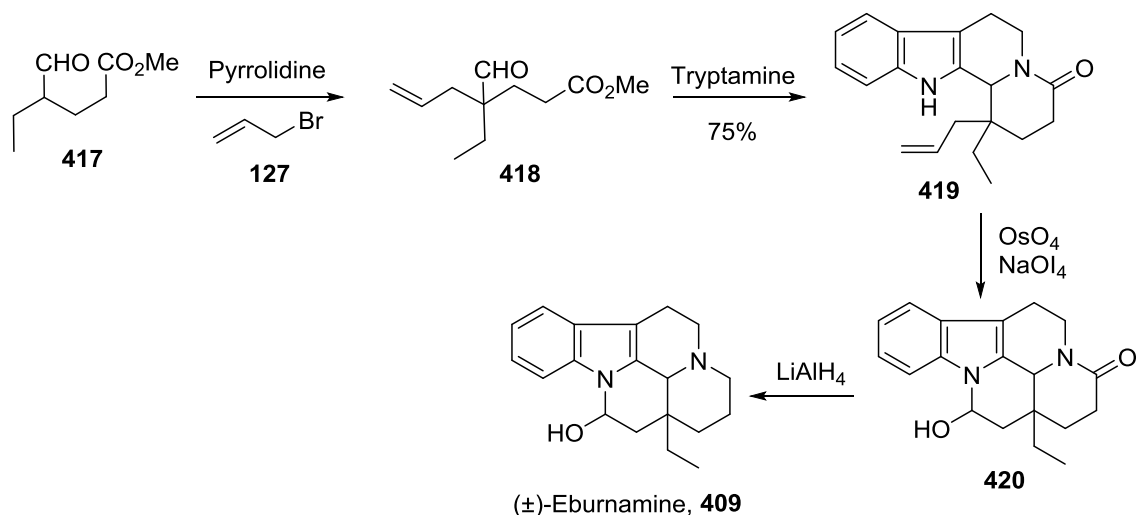


Scheme 139. Taylor Synthesis of *dl*-Eburnamine.

In 1965, Harley–Mason developed a synthesis for (\pm)-Eburnamine.¹⁸⁹ The synthesis of the non-tryptamine part of this indole alkaloid was based on alkylation of the pyrrolidine enamine intermediate, derived from methyl 4-formyl-hexanoate **417**, with allyl bromide **127** (Stork reaction conditions) to afford the desired aldehyde **418**. This aldehyde was condensed with tryptamine under Pictet-Spengler reaction conditions to give (\pm)-Eburnamine lactam **420** that was reduced later to give the (\pm)-Eburnamine **409** (Scheme 140).

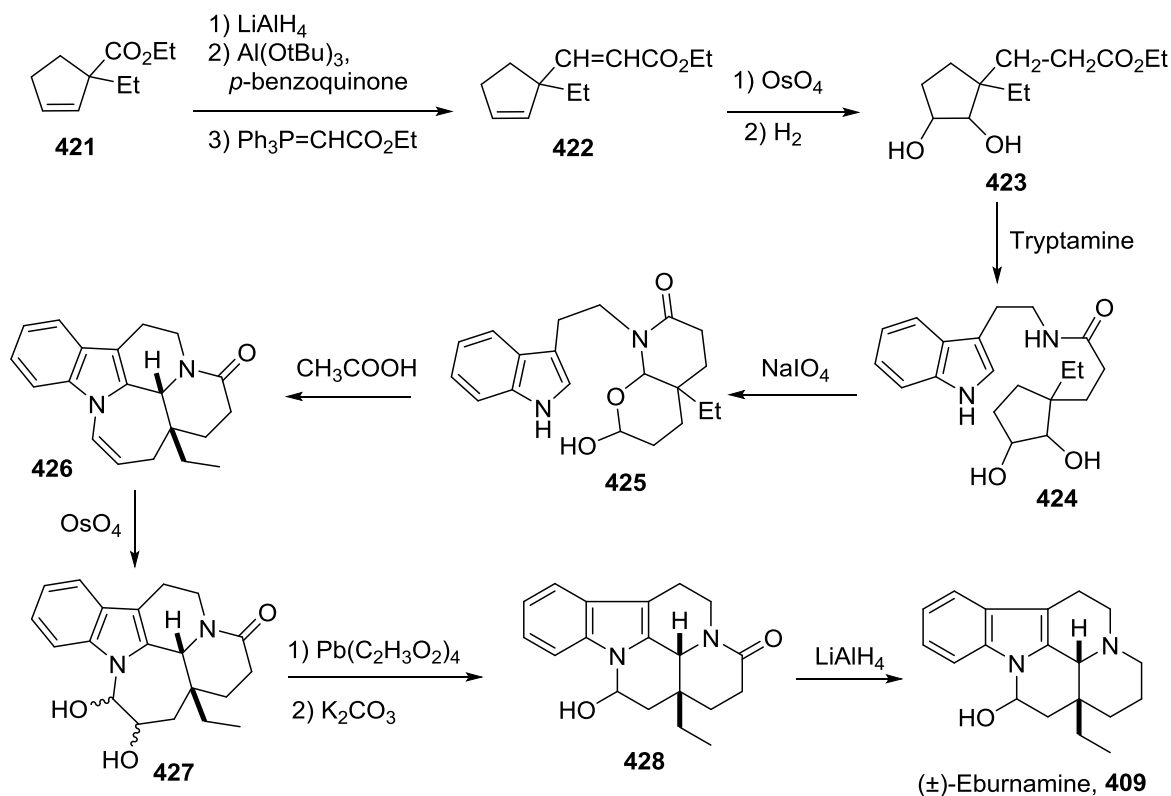
¹⁸⁸ Bartlett, M. F.; Taylor, W. I. *J. Am. Chem. Soc.* **1960**, *82*, 5941-5946.

¹⁸⁹ Barton, J. E. D.; Harley-Mason, J. *Chem. Commun.* **1965**, 298-299.



Scheme 140. Harley-Mason Synthesis of (±)-Eburnamine.

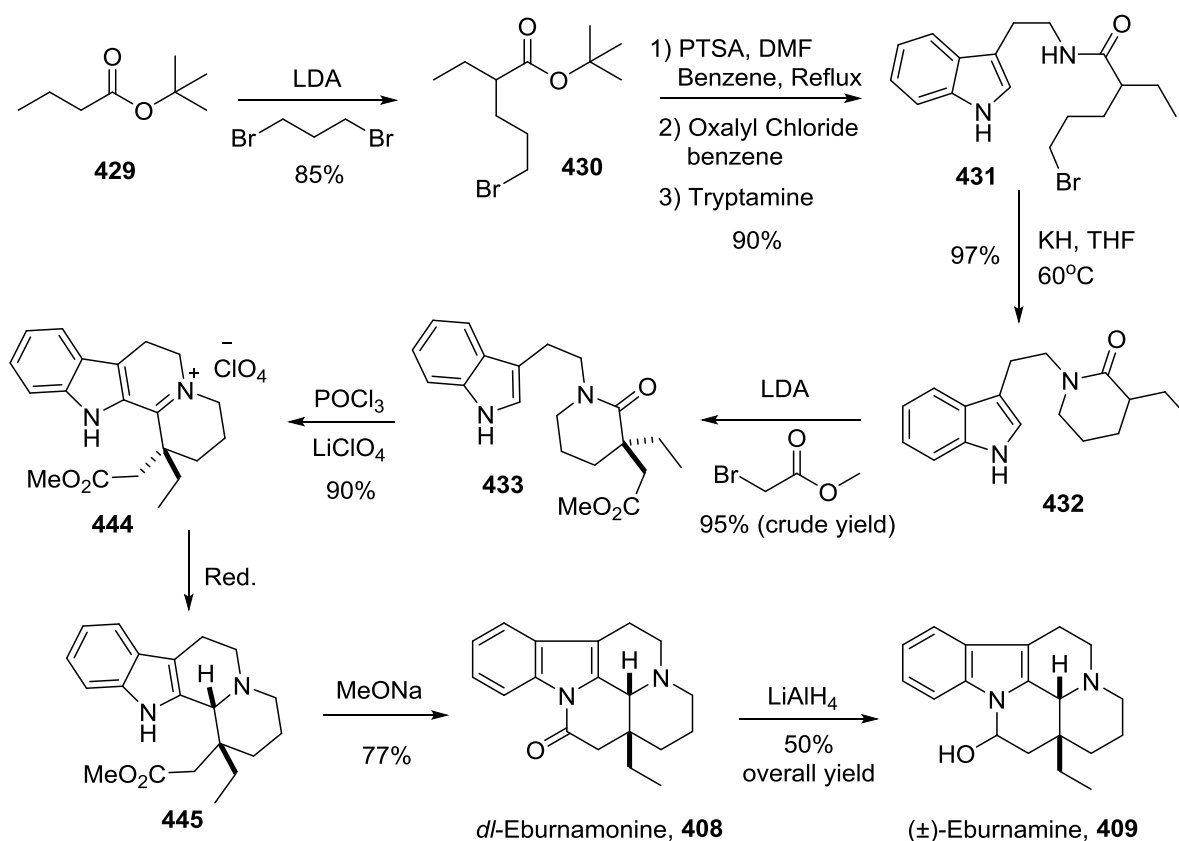
Later, in 1969 Saxton *et al.*¹⁹⁰ prepared the non-tryptamine part **423** in 5 steps from ester **421**. After reaction between tryptamine and ester **423**, the tryptamide **424** was oxidized by NaIO₄, undergoing cyclization in glacial acetic acid to give the pentacyclic core **426**. (±)-Eburnamine **409** was isolated after a sequence of functional group transformations (Scheme 141).



Scheme 141. Saxton Synthesis of (±)-Eburnamine.

¹⁹⁰ (a) Gibson, K. H.; Saxton, J. E. *J. Chem. Soc. D* **1969**, 799; (b) Gibson, K. H.; Saxton, J. E. *J. Chem. Soc., Perkin Trans. 1*, **1972**, 2776-2787.

In 1979, Schlessinger *et al.*¹⁹¹ developed another pathway to access *dl*-Eburnamonine **408** and (\pm)-Eburnamine **409** through Bischler-Napieralski intramolecular condensation. The construction of the first quaternary center was achieved by deprotonation of amide **432** α -carbon followed by alkylation with methylbromoacetate to afford a single product in 95%. The Bischler cyclization of lactam **433** to the corresponding tetracyclic salt, followed by the reduction of the imine by a hydride source gave the tetracyclic product **445**. Base-mediated cyclization, followed by reduction of this Eburnamonine **408** by LiAlH_4 afforded the corresponding (\pm)-Eburnamine **409** (Scheme 142).



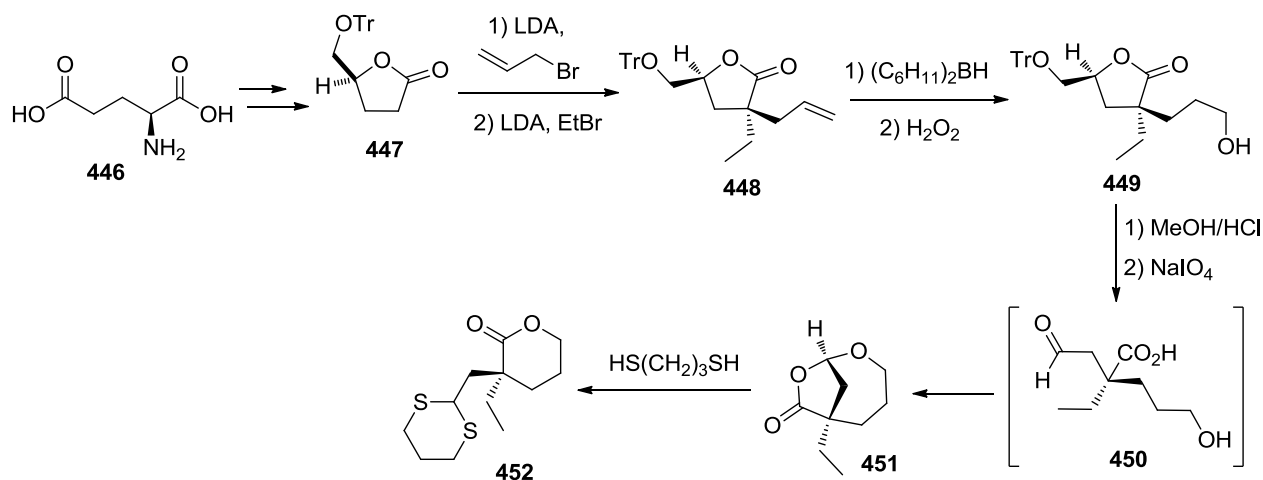
Scheme 142. Schlessinger Synthesis of *dl*-Eburnamonine and (\pm)-Eburnamine.

In 1985, Takano and coworkers synthesized for the first time enantiopure (+)-Eburnamine, (-)-Eburnamenine, and (-)-Eburnamonine starting from L-glutamic acid **446**.¹⁹² Therefore, after double alkylation of lactone **447**, first by allyl bromide, then by ethyl bromide, the dialkyl lactone **448** was synthesized as a single product. This lactone **448** was functionalized to access the non-tryptamine part required for the synthesis of this series of indole natural products. Therefore, hydroboration of vinylic position by dicyclohexylborane and oxidation by H_2O_2 afforded the primary alcohol **449**. After detritylation and cleavage of the 1,2-glycol, the expected aldehyde **450** was obtained. This

¹⁹¹ Herrmann, J. L.; Cregge, R. J.; Richman, J. E.; Kieczkowski, G. R.; Normandin, S. N.; Quesada, M. L.; Semmelhack, C. L.; Poss, A. J.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1979**, *101*, 1540-1544.

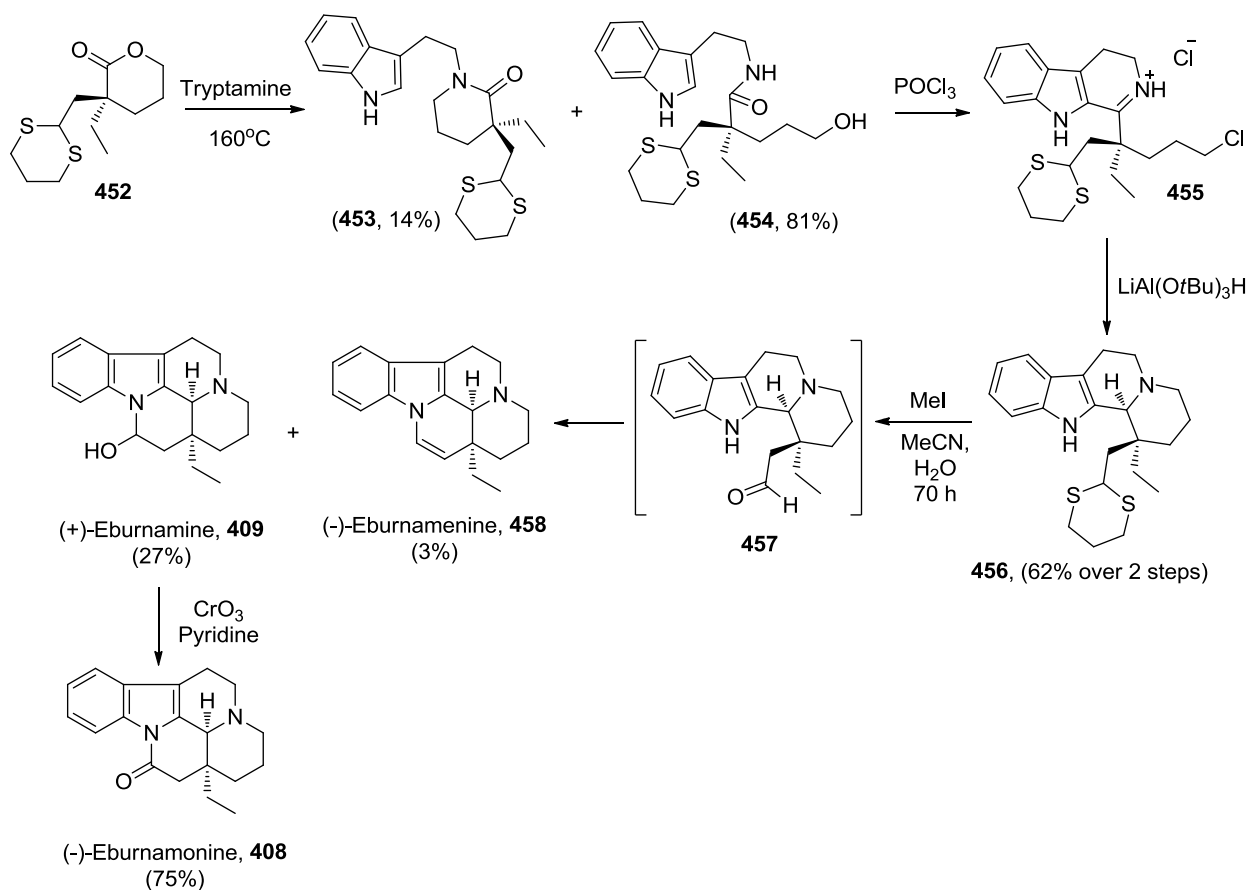
¹⁹² Takano, S.; Yonaga, M.; Morimoto, M.; Ogasawara, K. *J. Chem. Soc., Perkin Trans. 1*, **1985**, 305-309.

aldehyde underwent spontaneous reaction to furnish the bicyclo[3.2.1]nonane acetal **451**. This bicyclic compound **451** was treated with propane-1,3-dithiol to give the key dithiane-lactone **452** (Scheme 143).



Scheme 143. Takano Synthesis of Lactone **452**.

Condensation of lactone **452** with tryptamine at $160^\circ C$ afforded the amide **454** and δ -lactam **453** in 81 and 14% yields respectively. The amide **454** was then allowed to cyclize under Bischler-Napieralski reaction conditions to afford the iminium salt **455**, which was reduced by $LiAl(OtBu)_3H$ to give the tetracyclic core **456** in 62% overall yield and with the desired configuration. After hydrolysis of the dithiane group, the aldehyde **457** formed underwent spontaneous cyclization to afford (+)-Eburnamine **409** and (-)-Eburnamenine **458** in 27 and 3% yields respectively. Further transformation of (+)-eburnamine **409** to (-)-Eburnamonine **408** could be achieved by oxidation with pyridinium dichromate (Scheme 144).

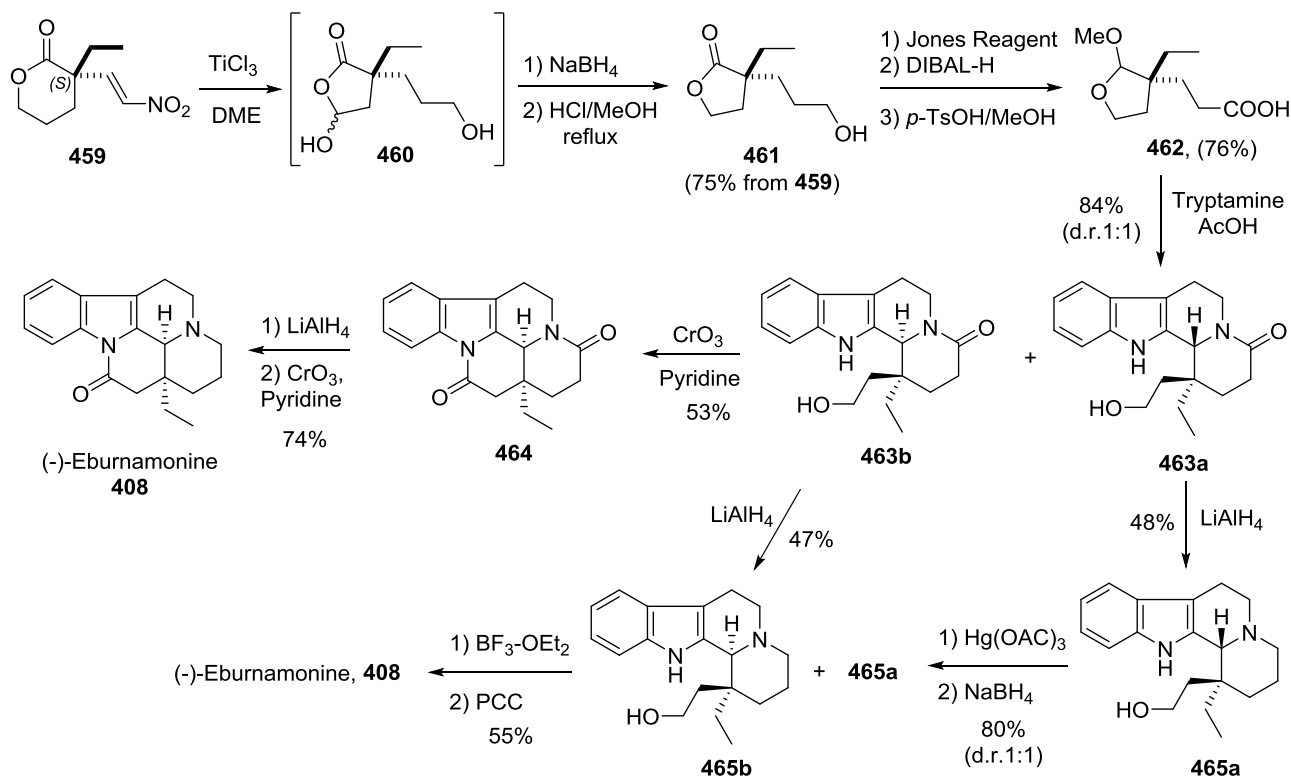


Scheme 144. Takano Synthesis of (+)-Eburnamine, (-)-Eburnamenine, and (-)-Eburnamonine.

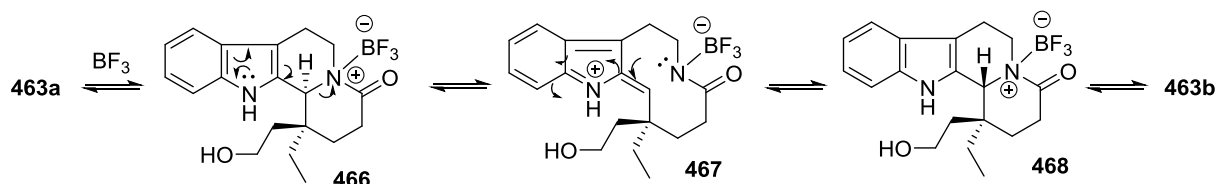
Five years later, Fuji *et al.*¹⁹³ developed an enantioselective synthesis of (-)-Eburnamonine **408** from the chiral (*S*)-lactone **459**. Therefore, the reductive denitration of **459** in DME afforded hemiacetal **460**. Reduction of **460** followed by refluxing in HCl/MeOH gave γ -lactone **461** in 75% overall yield. The desired non-tryptamine unit was obtained after three steps from lactone **461**. γ -Lactone **461** was thus subjected to Jones oxidation, DIBAL-H reduction and acid treatment in MeOH to afford the desired lactone **462**. Refluxing the latter with tryptamine in AcOH under Pictet-Spengler reaction conditions proceeded smoothly to afford an approximately 1:1 mixture of the two diastereoisomers **463a** and **463b**. After enrichment of the desired diastereoisomer **463b** by recrystallization, the dilactam **464** was obtained by Sarett oxidation. Reduction of this dilactam and oxidation of eburnamine afforded (-)-Eburnamonine **408** in 74% yield. The other diastereoisomer **463a** formed from Pictet-Spengler reaction could serve as an intermediate for the synthesis of (-)-Eburnamonine **408**, as the **463a** and **463b** were shown to establish an equilibrium with an approximate 1:1 ratio in the presence of $\text{BF}_3\text{-OEt}_2$ (equation 1). Therefore, an alternative synthesis of (-)-Eburnamonine **408** was developed through oxidation of **465a** by $\text{Hg}(\text{OAc})_2$ followed by reduction of the iminium with

¹⁹³ (a) Node, M.; Nagasawa, H.; Fuji, K. *J. Org. Chem.* **1990**, *55*, 517-521; (b) Node, M.; Nagasawa, H.; Fuji, K. *J. Am. Chem. Soc.* **1987**, *109*, 7901-7905.

NaBH₄ to give the 1:1 mixture of **465a** and its epimer **465b**. This epimer **465b** was oxidized by PCC, after treating by BF₃-OEt₂, to afford the desired (-)-Eburnamonine **408** (Scheme 145).



Scheme 145. Fuji Synthesis of (-)-Eburnamonine **408**.

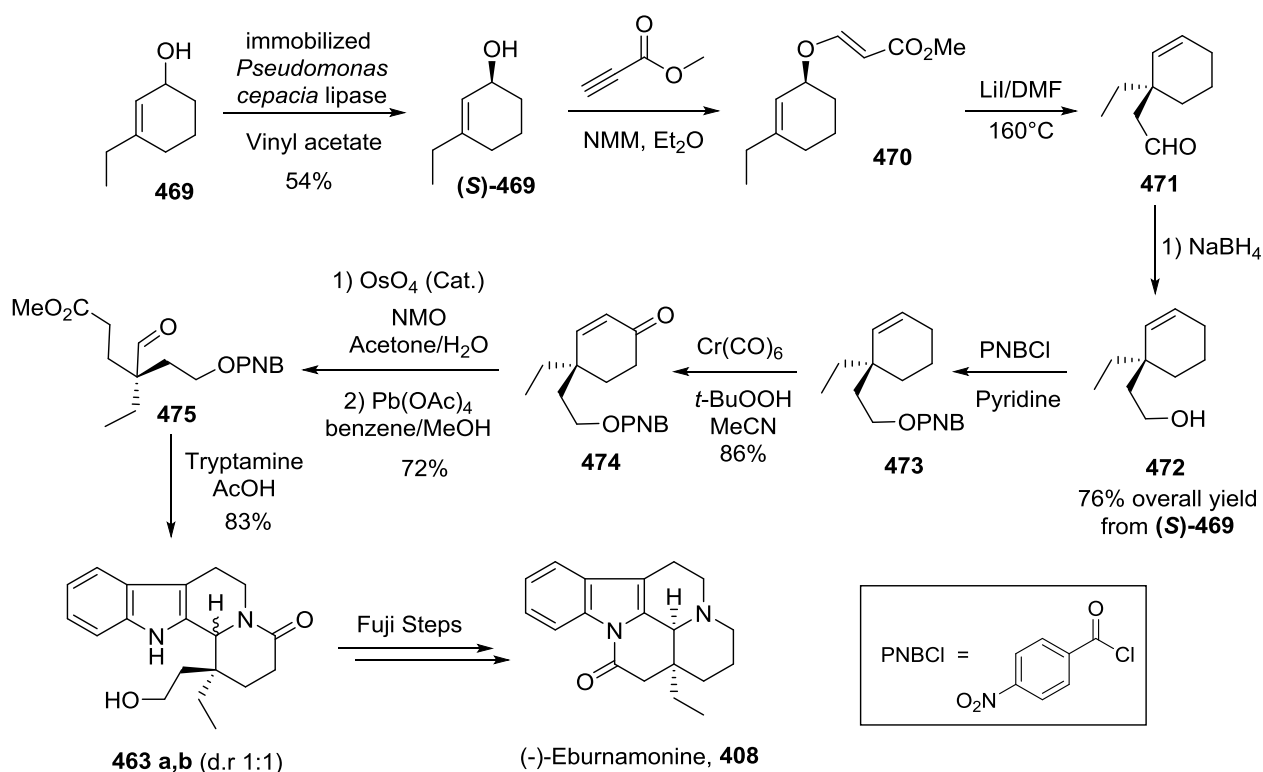


Equation 1. Epimerization step

In 1994, Palmisano *et al.*¹⁹⁴ accessed (-)-eburnamonine **408** through a [3,3]-allyl vinyl ether-type rearrangement (Claisen rearrangement) of the enantiopure β -alkoxy acrylate **470**. Preparation of β -alkoxy acrylate **470** started from achiral hydroxyl compound **469**, which underwent enzyme kinetic resolution by immobilized *Pseudomonas cepacia* lipase in neat vinyl acetate to give (*S*)-**469**. The latter then reacted with methyl propiolate to give **470**. After tandem decarboxylation-rearrangement sequence of **470**, the aldehyde **471** was obtained. Reduction of this aldehyde to alcohol **472** and protection of this alcohol as a 4-methoxybenzyl ether (PMB), followed by allylic oxidation by Cr(CO)₆ / *t*-BuOOH gave enone **474**. Osmylation of this enone by OsO₄ and *N*-methylmorpholine *N*-oxide (NMO) followed by glycol cleavage with Pb(OAc)₄ gave the expected aldehyde **475** in 72%. Refluxing this aldehyde with tryptamine in AcOH gave the tetracyclic lactam **463a,b** in (d.r.

¹⁹⁴ Palmisano, G.; D'Anniballe, P.; Santagostino, M. *Tetrahedron* **1994**, 50, 9487-9494.

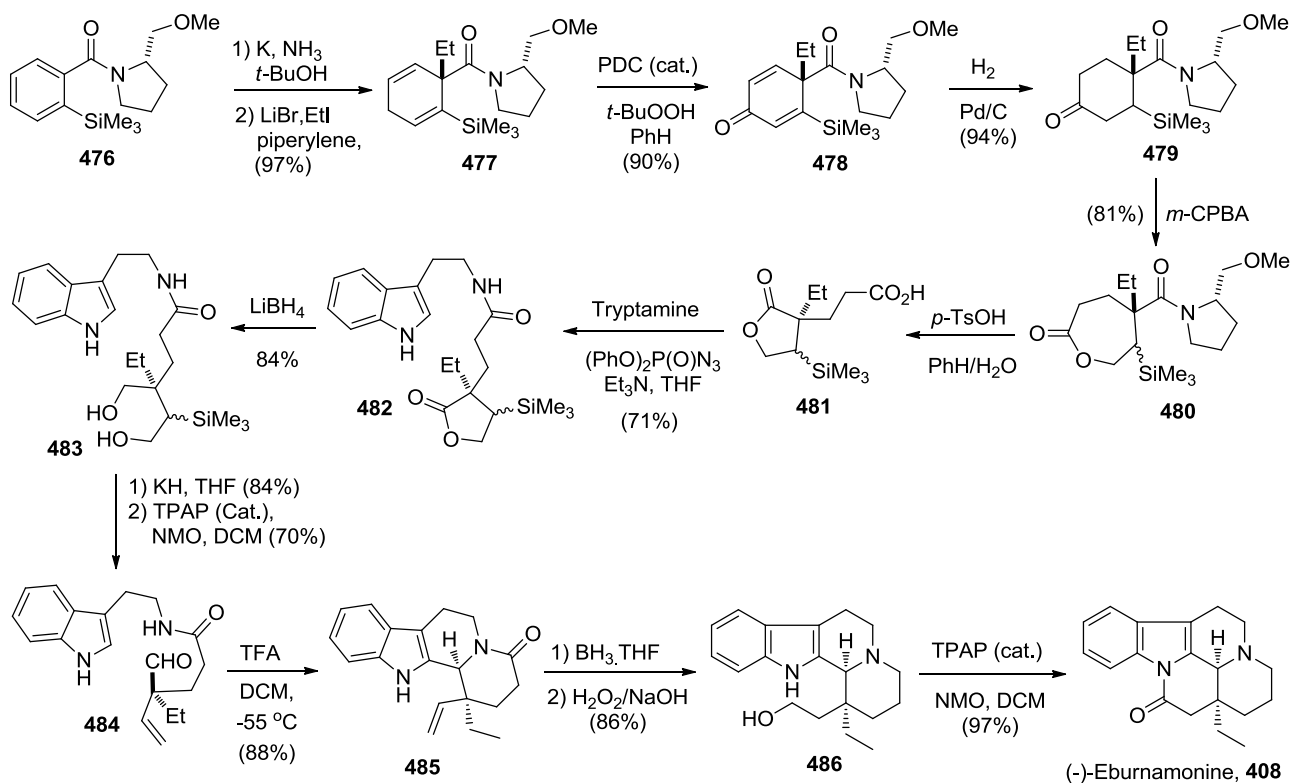
1:1) (Scheme 146). Isolation of the desired diastereoisomer and re-equilibration of the tetracyclic epimer **463b** by using BF_3 -etherate (according to Fuji's method) was performed. The tetracyclic lactam underwent the same steps as mentioned in Fuji's approach (*vide supra*).



Scheme 146. Plamisano Synthesis of (-)-Eburnamonine **408**.

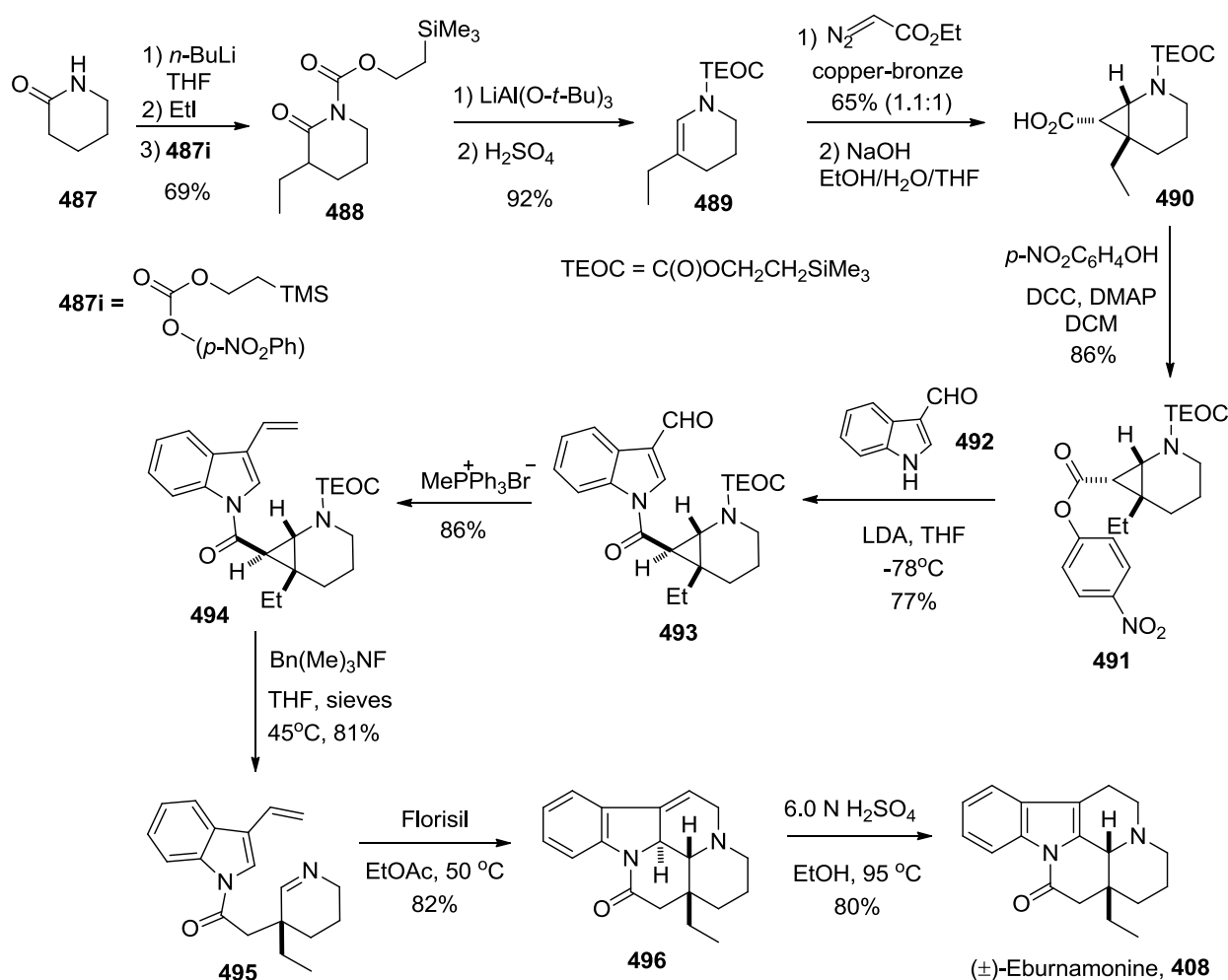
Later, Schultz and coworkers developed an asymmetric synthesis of (-)-eburnamonine **408**, relying on the asymmetric Birch reduction-alkylation of chiral benzamides.¹⁹⁵ Therefore, Birch reduction-ethylation sequence of **476** gave the desired cyclohexadiene **477**. Allylic oxidation of **477**, followed by hydrogenation and Baeyer-Villiger oxidation afforded the caprolactone **480**. This lactone **480** was converted to butyrolactone carboxylic acid **481** by treatment with *p*-TsOH. This acid was coupled with tryptamine to afford the amide **482**. Reduction of lactone **482** to diol **483** followed by KH -induced elimination of Me_3SiOH to give alkene and oxidation of the remaining alcohol to aldehyde gave **484**, ready for Pictet-Spengler reaction. Cyclization of this aldehyde under Pictet-Spengler conditions in the presence of TFA afforded the tetracyclic lactam **485**. The high diastereoselectivity of the reaction was ascribed to π - π interaction between the C-1 β -vinyl substituent and the indole moiety of the acyl iminium ion intermediate which, in turn, helped to deliver the indole unit to the β -face of the iminium unit. This tetracyclic lactam **485** reacted with $\text{BH}_3 \cdot \text{THF}$, followed by $\text{H}_2\text{O}_2/\text{NaOH}$ to give the amino alcohol **486**. Oxidation of this alcohol by a catalytic amount of TPAP led to (-)-Eburnamonine **408** in 12 steps from chiral benzamide **476** and in 17% overall yield (Scheme 147).

¹⁹⁵ Schultz, A. G.; Pettus, L. *J. Org. Chem.* **1997**, *62*, 6855-6861.

Scheme 147. Schultz Synthesis of (-)-Eburnamonine **408**.

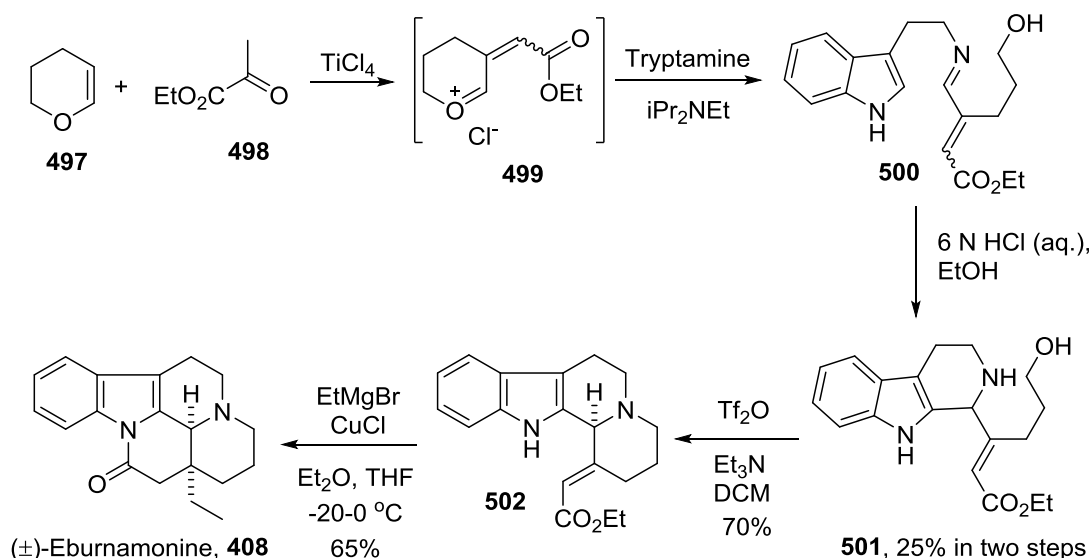
In a unique approach to access (±)-Eburnamonine, Grieco *et al.*¹⁹⁶ developed a [4+2] intramolecular imino Diels-Alder reaction of vinyl indole into imine to give the tetracyclic core of Eburnamonine, which was then rapidly converted into (±)-Eburnamonine. Lactam **487** was doubly alkylated, first on the α -carbon to lactam by ethyl iodide and then on the lactam's nitrogen by a 2-(trimethylsilyl)ethyl-4-nitrophenyl carbonate **487i**. This alkylated lactam **488** was reduced and dehydrogenated to give enamine **489**, which underwent cyclopropanation with ethyl diazoacetate to give *exo* and *endo* cyclopropanes **490** in a 1.1:1 ratio. Saponification of the *endo*-cyclopropane and coupling with indole **492** gave the amide **493**. Methylenation of aldehyde **493** and liberation of imine through reaction with Bn(Me)₃NF gave the key vinyl-imine **495** in 81%. The imino Diels-Alder reaction was performed in the presence of Florisil at 50°C in EtOAc to give the desired tetracyclic core of Eburnamonine **496** in 82%. Dehydration of **496** with H₂SO₄ in EtOH gave (±)-Eburnamonine **408** in 11 steps from δ -valerolactam **487** and 16% overall yield (Scheme 148).

¹⁹⁶ Grieco, P. A.; Kaufman, M. D. *J. Org. Chem.* **1999**, *64*, 7586-7593.

Scheme 148. Grieco Synthesis of (±)-Eburnamonine **408**.

In 2000, Ghosh and coworkers developed a short synthesis of (±)-Eburnamonine through a key step involving a TiCl₄ promoted three-component coupling of dihydropyran **497**, ethyl glyoxylate **498** and tryptamine.¹⁹⁷ Therefore, in a one-pot reaction, the ethyl glyoxylate **498** reacted with dihydropyran **497** in the presence of TiCl₄ to give the corresponding oxonium ion. The latter then reacted *in situ* with tryptamine to give the key imine **500** in a 1.2:1 *E/Z* ratio. The crude imine **500** was treated with 6 N HCl to give the amino alcohol **501** as a single diastereomer in 25% yield over two steps. It is believed that the cyclization occurred only on the *E*-isomer while the *Z*-isomer might have decomposed under the acidic reaction conditions. Treatment of amino alcohol **501** with triflic anhydride gave the tetracyclic core of Eburnane **502**. Installation of the ethyl group through the reaction with EtMgBr, followed by cyclization gave the (±)-Eburnamonine **408** in 11% overall yield (Scheme 149).

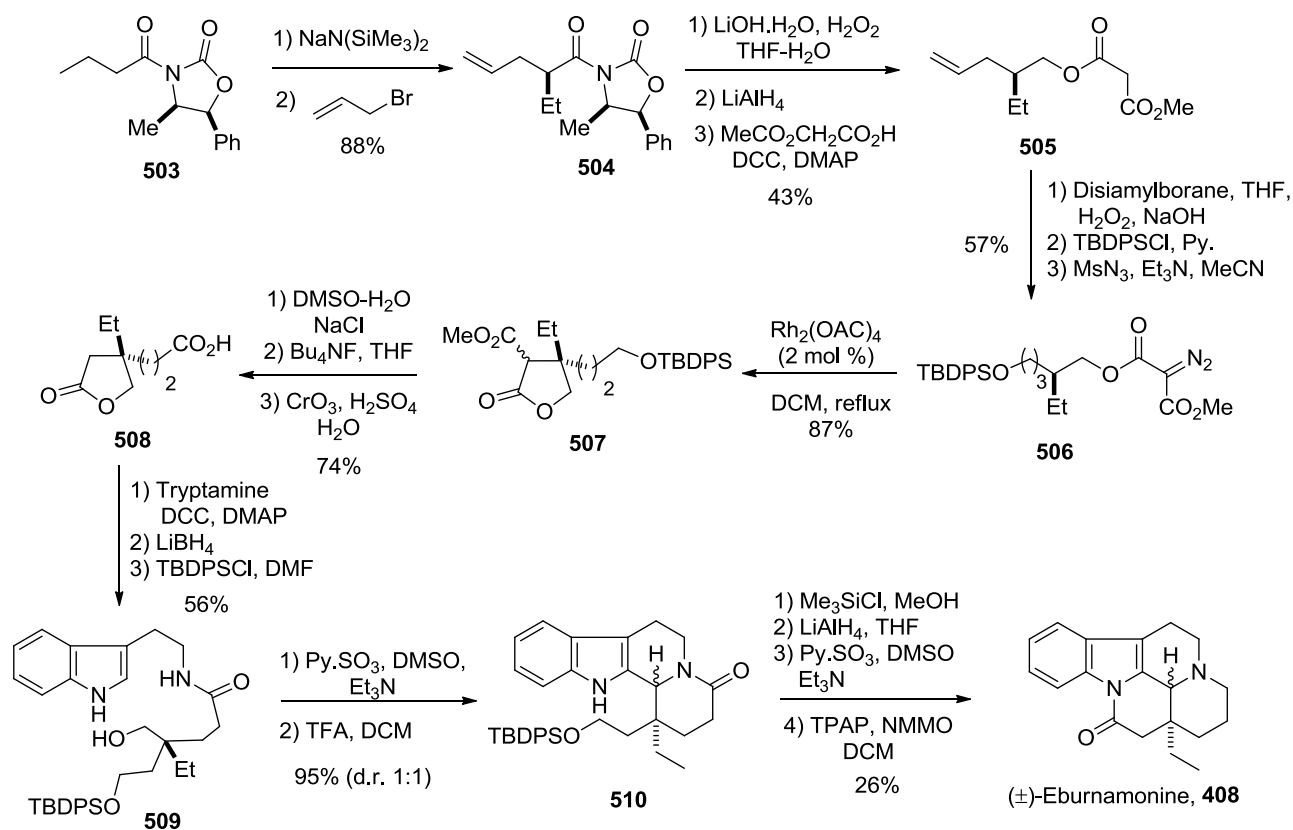
¹⁹⁷ Ghosh, A. K.; Kawahama, R. *J. Org. Chem.* **2000**, *65*, 5433-5435.



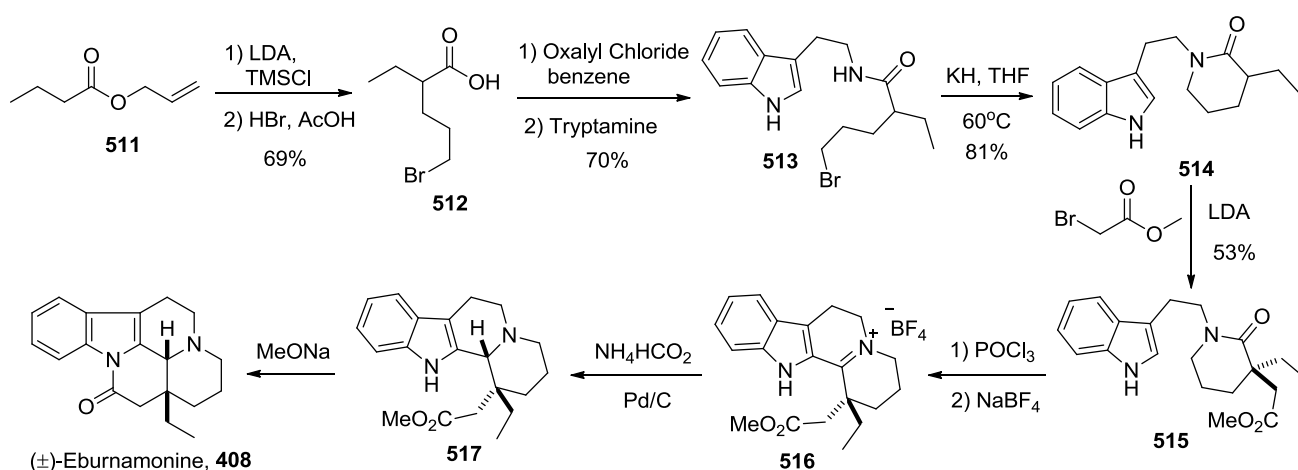
Scheme 149. Ghosh Synthesis of (±)-Eburnamonine 408.

Later, Wee and coworkers developed an asymmetric synthesis of (-)-Eburnamonine and (+)-*epi*-Eburnamonine relying on acid 508.¹⁹⁸ The (*S*)-508 was prepared from the *N*-butanoyloxazolidinone 503 through a sequence of functional group transformations with a tertiary C-H insertion of a rhodium-carbene as the key step. The synthesis relied on the fact that dirhodium(II)-carbenoid insertion into configurationally defined tertiary carbon stereocenters was stereospecific and occurred with retention of configuration. Therefore the diazomalonate 506 was treated with Rh₂(OAc)₄ to give lactone 507 in high regioselectivity and excellent yield. After conversion of the protected alcohol 507 into an acid 508, the condensation of 508 with tryptamine to form amide followed by reduction of lactone into diol and protection of the less hindered alcohol gave 509. Oxidation of free alcohol in 509 gave the desired aldehyde, which underwent Pictet-Spengler reaction to give the tetracyclic lactam 510 as a 1:1 mixture of two diastereoisomers. (±)-Eburnamonine 408 was accessed, after functional group transformations, in 21 steps and 1.9% overall yield (Scheme 150).

¹⁹⁸ Wee, A. G. H.; Yu, Q. *J. Org. Chem.* **2001**, *66*, 8935-8943.

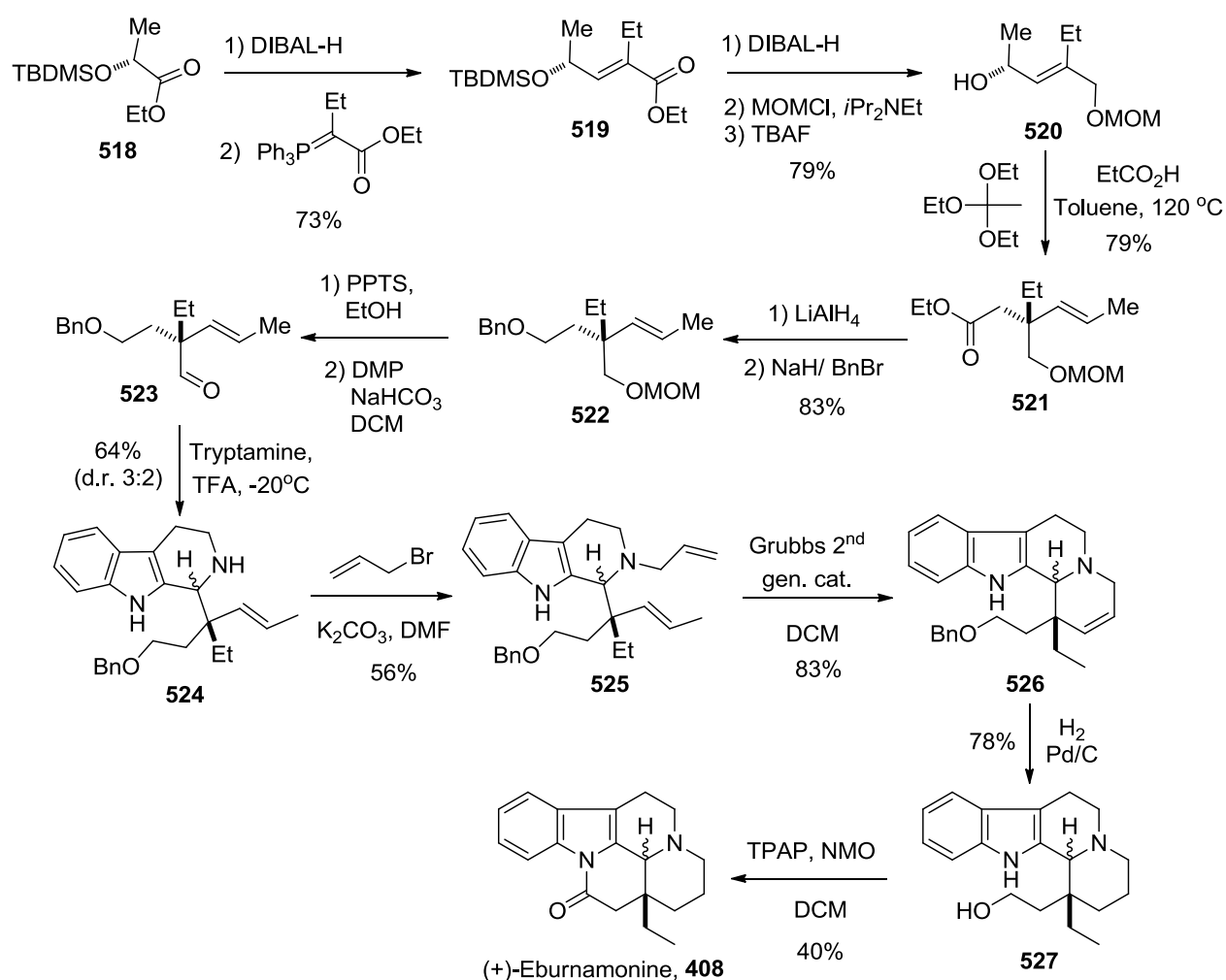
Scheme 150. Wee Synthesis of (±)-Eburnamonine **408**.

In 2012, Westwood *et al.*¹⁹⁹ modified Schlessinger approach to access (±)-Eburnamonine. First, the acid **512** was synthesized in two steps and in 69% yield. Reduction of imine **516** was then carried out more conveniently through a transfer hydrogenation by ammonium formate instead of H_2 gas hydrogenation (Scheme 151).

Scheme 151. Westwood Synthesis of (±)-Eburnamonine **408**.

¹⁹⁹ Lancefield, C. S.; Zhou, L.; Lébl, T.; Slawin, A. M. Z.; Westwood, N. J. *Org. Lett.* **2012**, *14*, 6166-6169.

Very recently, Prasad developed a new sequence to access (+)-Eburnamonine.²⁰⁰ The non-tryptamine part was accessed starting from L-ethyl lactate **518** and through formation of the chiral quaternary center by a Johnson-Claisen rearrangement. After functional group transformations, aldehyde **523** underwent Pictet-Spengler reaction with tryptamine to give the desired product **524** as a 3:2 mixture of two diastereoisomers. Allylation of **524** afforded a separable mixture of two *N*-allyl carbolines **525**, from which the major isomer was isolated in 56% yield. Construction of the tetracyclic core of eburnane **526** was achieved after treating the diene **525** with the Grubbs second-generation catalyst. At the end, (+)-Eburnamonine was isolated in 3.2% overall yield after 15 steps (Scheme 152).



Scheme 152. Prasad Synthesis of (+)-Eburnamonine **408**.

To sum up this review, the common two pathways to access the tetracyclic core of Eburnane are either through the Pictet-Spengler reaction between an aldehyde and tryptamine or through Bischler-Napieralski intramolecular condensations between lactams and the tryptamine indole fragments. In

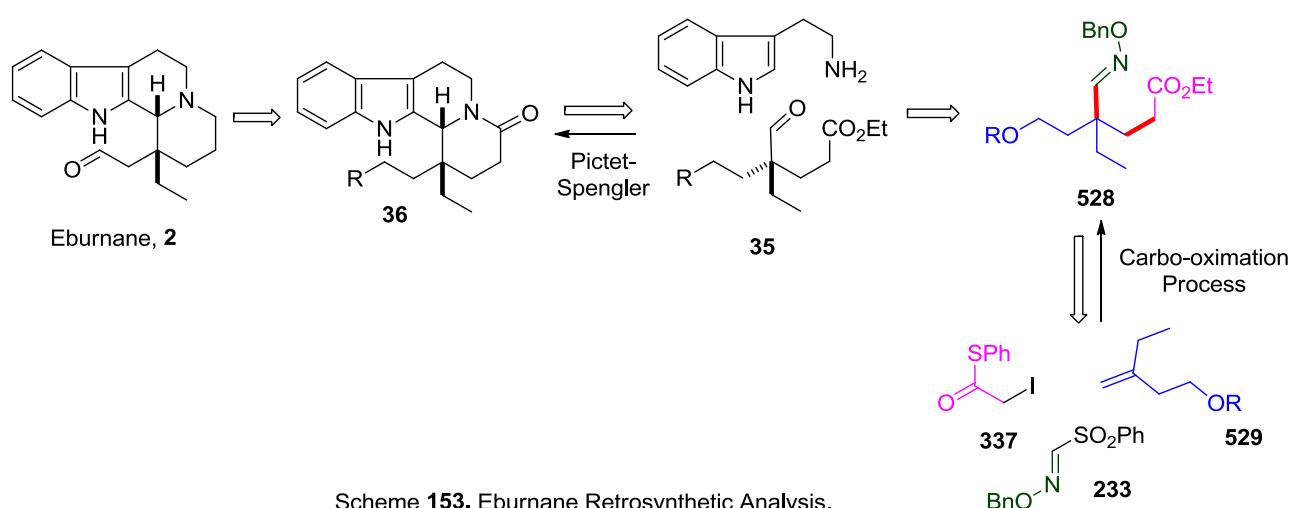
²⁰⁰ (a) Nidhiry, J. E.; Prasad, K. R. *Tetrahedron* **2013**, *69*, 5525-5536; (b) Prasad, K. R.; Nidhiry, J. E. *Synlett* **2012**, *23*, 1477-1480.

both pathways, the challenging task is to construct the non-tryptamine part in a short and efficient sequence. As shown in the previous syntheses, construction of this non-tryptamine part took at least from 7 to 10 steps, except for a few examples.^{189, 197} Nevertheless, controlling the stereochemical outcome in the Pictet-Spengler or Bischler-Napieralski intramolecular condensations cannot be achieved through these syntheses. The most satisfactory results were observed for the synthesis of (-)-Eburnamonine **408** by Fuji through the enrichment of desired diastereoisomer through epimerization mediated by $\text{BF}_3 \cdot \text{Et}_2\text{O}$.¹⁹³

In the following part, the construction of the non-tryptamine part will be discussed relying on a short sequence using free radical processes. Furthermore, two different strategies to access eburnane **2**, the north fragment of Leucophyllidine **1**, will be shown in the remaining part of this chapter.

3.3 Eburnane Retrosynthetic Analysis

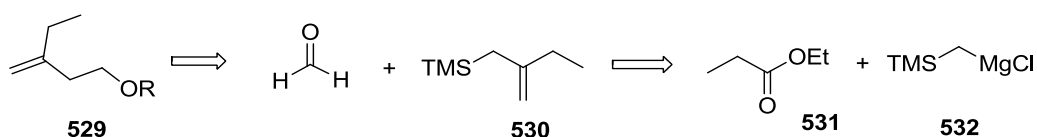
The retrosynthetic analysis of Eburnane proposed first the disconnection between the tryptamine and aldehyde **35**. Therefore, the key reaction for constructing the tetracyclic core **36** will be a Pictet-Spengler reaction between this aldehyde and tryptamine. The challenging task is to construct this aldehyde in a short and straightforward manner. Thus, this approach will be based on the free radical carbo-oximation process between radical precursor **337**, olefin **529** and sulfonyl oxime **233** to construct the quaternary center bearing the oxime function group. This oxime **528** could be hydrolysed later in one step to the desired aldehyde **35**. Through this approach, the non-tryptamine part of Eburnane could be constructed in two steps only (Scheme 153).



3.4. Synthesis of the non-tryptamine part of Eburnane

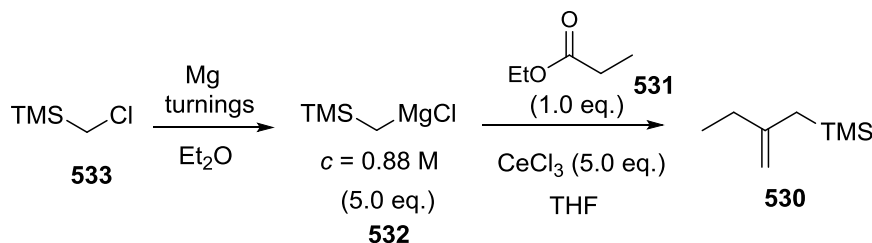
3.4.1. Through free-radical carbo-oximation process

Similarly to the total synthesis of Eucophylline **3**, the construction of the quaternary center in this non-tryptamine part **35** was based on the free-radical carbo-oximation reaction between xanthate ethyl ester **337**, olefin **529** and sulfonyl oxime **233**. The olefin was not commercially available but its synthesis has been reported in the literature. Thus, the first attempt at synthesizing the latter was based on Bunnelle method to convert ester **531** to allylsilane **530**.²⁰¹ This allylsilane could later react with formaldehyde to give the desired alkene (Scheme **154**).²⁰²



Scheme **154**. Retrosynthesis of Olefin **529** through Bunnelle Method.

Therefore, the commercially available ethyl propionate **531** was allowed to react with TMSCH₂MgCl Grignard reagent, which was prepared from the corresponding TMSCH₂Cl. The reaction is mediated by CeCl₃, which was powdered and dried at 150°C under vacuum overnight. Trials to prepare this allylsilane **530** under these conditions were not successful.



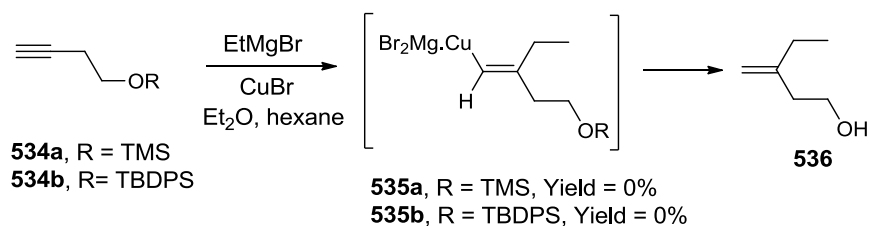
Scheme **155**. Synthesis of Olefin **529** through Bunnelle Method.

Another direct method was reported by Normant *et al.* for synthesizing this alkene.²⁰³ In this approach, the Grignard reagent EtMgBr was added to protected alcohols **534a-b** to give the desired alkene **536** in 85%. Unfortunately, this method proved to be non-reproducible in our hands, neither with TMS-protected alcohol nor with TBDPS-protected one (Scheme **156**).

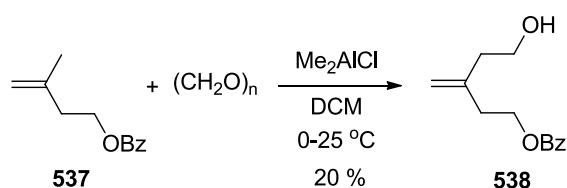
²⁰¹ Narayanan, B. A.; Bunnelle, W. H. *Tetrahedron Lett.* **1987**, 28, 6261-6264.

²⁰² Paterson, I.; Cumming, J. G.; Smith, J. D.; Ward, R. A. *Tetrahedron Lett.* **1994**, 35, 441-444.

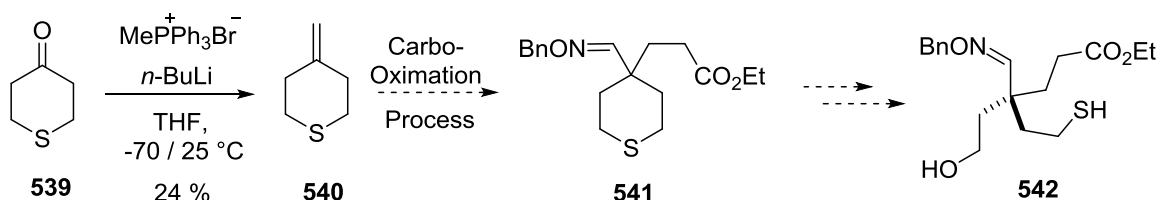
²⁰³ Alexakis, A.; Normant, J. F. *J. Organometallic Chem.* **1975**, 96, 471-485.

Scheme 156. Synthesis of Olefin **536** through Normant Method.

Also, another method was reported to synthesize olefin **538** through carbonyl-ene reaction between protected isopentenyl alcohol **537** and paraformaldehyde.²⁰⁴ Therefore, benzoate protected isopentenyl alcohol **537** was reacted with paraformaldehyde in presence of Me_2AlCl as a Lewis acid to give the desired olefin **538** albeit in low yield (20%) (Scheme 157).

Scheme 157. Synthesis of Olefin **538** through carbonyl-ene Method.

The low yield of the previous reaction prompted us to find another procedure to circumvent the use of this olefin. Therefore, it was envisioned that thiopyran alkene **540** could be an attractive equivalent for the above olefin, as it could undergo, after carbo-oximation process, a ring opening to give the desired non-tryptamine part (as proposed in Scheme 158). Thus, dihydrothiopyranone **539** was allowed to undergo a Wittig reaction to give the corresponding alkene **540**, which was isolated, albeit in low yield (24%).²⁰⁵ This isolated alkene was volatile, very smelly and degraded quickly outside the fridge. As a consequence, we did not have the opportunity to run the carbo-oximation process with this olefin (Scheme 158).

Scheme 158. Synthesis of Thiopyran alkene **540** / Proposed Pathway to non-tryptamine Part.

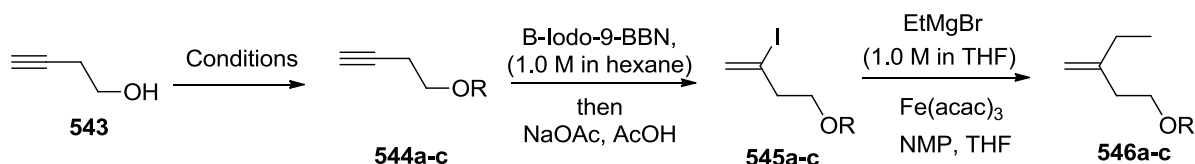
Finally, olefins **546** could be synthesized based on the reported method by Kitching *et al.* in two steps from the corresponding protected 3-Butyn-1-ol **544a-c**.²⁰⁶ Therefore, the commercially

²⁰⁴ Alonso, F.; Rodríguez-Fernández, M.; Sánchez, D.; Yus, M. *Eur. J. Org. Chem.* **2011**, 6459-6469.

²⁰⁵ Paquette, L. A.; Underiner, T. L.; Gallucci, J. C. *J. Org. Chem.* **1992**, *57*, 86-96.

²⁰⁶ (a) Hayes, P. Y.; Chow, S.; Rahm, F.; Bernhardt, P. V.; De Voss, J. J.; Kitching, W. *J. Org. Chem.* **2010**, *75*, 6489-6501; (b) Hayes, P. Y.; Kitching, W. *J. Am. Chem. Soc.* **2002**, *124*, 9718-9719.

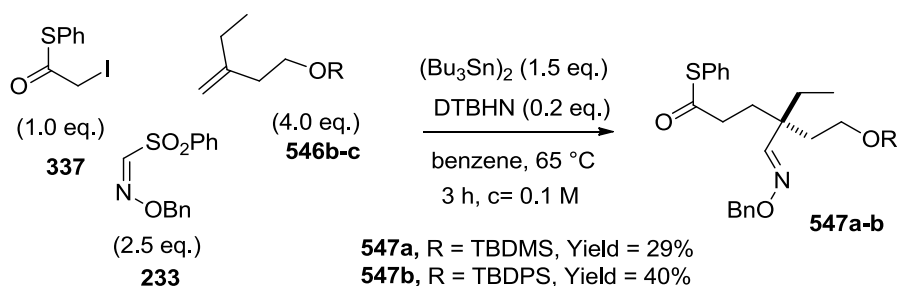
available and cheap 3-butyn-1-ol **543** was protected as a *p*-methoxyphenylether and was allowed to undergo iodination reaction with B-iodo-9-BBN. Unfortunately, the reaction was not successful, the product being probably degraded during the workup. Therefore, the protecting group was changed to a TBDMS group, which gave better results but still with moderate yields for the iodination step and addition of EtMgBr. This moderate yield may be due to deprotection of the weak silyl ether group during isolation of the product. Finally, changing the protecting group to the more stable TBDPS silyl ether gave excellent yields in both steps (Scheme 159)



Entry	Conditions (Yield)	R	Iodination step Yield (%)	Grignard addition Yield (%)
a	4-MePhenol, PPh ₃ , DEAD, THF, 16h (38%)	PMP	0	N/A
b	TBDMSCI, DIPEA, DCM, 3h (91%)	TBDMS	45	54
c	TBDPSCI, Imidazole, DCM, 3h (Quant.)	TBDPS	94	87

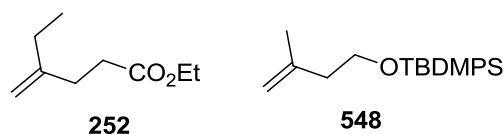
Scheme 159. Synthesis of Olefins **546**.

With these two protected olefins **546b** and **546c** in hand, the first carbo-oximation process was examined, by using the optimal conditions developed during the total synthesis of Eucophylline **3** (see chapter two, Scheme 101). Therefore, α -iodo thioester, sulfonyl oxime and olefin **546b** or olefin **546c** were allowed to undergo the free-radical carbo-oximation process to give the desired oxime **547a-b** in 29% and 40% yield respectively (Scheme 160).

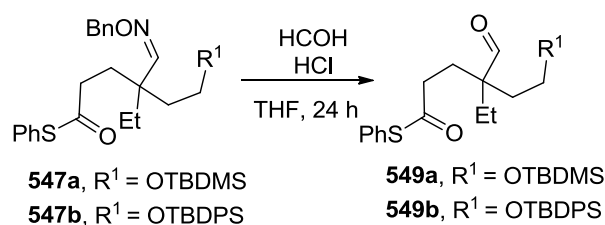
Scheme 160. Carbo-oximation MCR with α -Iodothioester **337** and Olefins **546b**, **546c**.

These modest yields with both olefins **546b-c** showed that the generated nucleophilic radical intermediates in these cases are sterically quite hindered. By comparing these results with those observed with olefin **252**, used in total synthesis of Eucophylline (carbo-oximation process 67%), it is assumed that with one less carbon on the side chain of the olefin, the generated nucleophilic radical could suffer from steric hindrance which may affect its approach towards the sulfonyl oxime

233. Also, the carbo-oximation process with olefin **548**, with a methyl substituent in the olefinic carbon instead of ethyl, worked in 76%,²⁰⁷ showing that a slight change in the steric environment might have a dramatic effect on the yields of our radical reaction.



With these two oximes in hand, the next step was the hydrolysis of the oxime functional group into an aldehyde, which could be performed according to the reported procedure on secondary oximes.²⁰⁷ Therefore, oximes **547a-b** were allowed to react with formaldehyde in presence of HCl. Unfortunately, the expected aldehydes **549a-b**, were not detected under these conditions.



Scheme **161**. Hydrolysis of oxime benzyl ethers.

It was reported that the hydrolysis of SEM-protected oximes is easier than for benzyloximes.²⁰⁷ At this point, we however decided to change our strategy and search for another group that could be compatible with free-radical processes and easily introduced on this quaternary center with better yields. Furthermore, this group has to be convertible to aldehyde in an easy and reliable manner.

3.4.2. Through Carbo-alkenylation Free-radical process

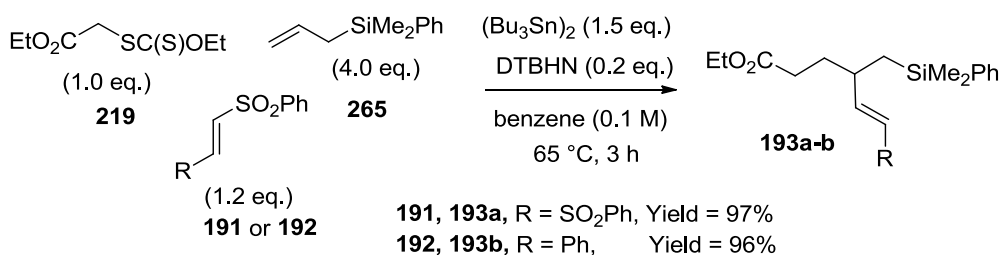
According to the previous requirements, we figured out that carbo-alkenylation process could be suitable for our purpose. First, this process was demonstrated to be very successful with a wide range of olefins.²⁰⁸ Second, the only modification in our retrosynthesis analysis would be the sulfonyl acceptor, which will be replaced by the commercially available vinyl bisphenylsulfone **191** or styrylsulfone **192**. Third and more importantly, the installed double bond could be cleaved easily under Lemieux–Johnson oxidation²⁰⁹ conditions into the desired aldehyde.

Therefore, to test the viability of this approach, the carbo-alkenylation process between the xanthate ethyl ester **219**, vinyl bisphenylsulfone **191** or styrylsulfone **192** and the available allylsilane **265** was performed to give the desired products **193a-b** in excellent yields (Scheme **162**).²⁰⁸

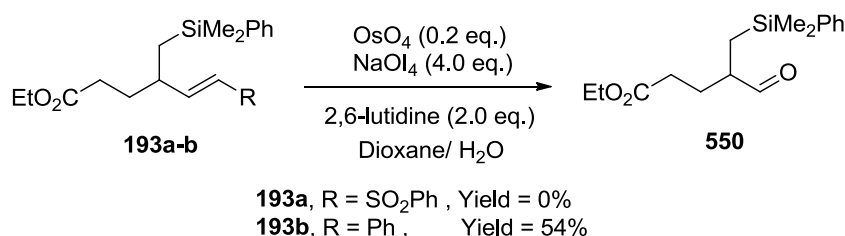
²⁰⁷ Landais, Y.; Robert, F.; Godineau, E.; Huet, L.; Likhite, N., *Tetrahedron*, **2013**, *69*, 10073-10080.

²⁰⁸ Liautard, V.; Robert, F.; Landais, Y. *Org. Lett.* **2011**, *13*, 2658-2661.

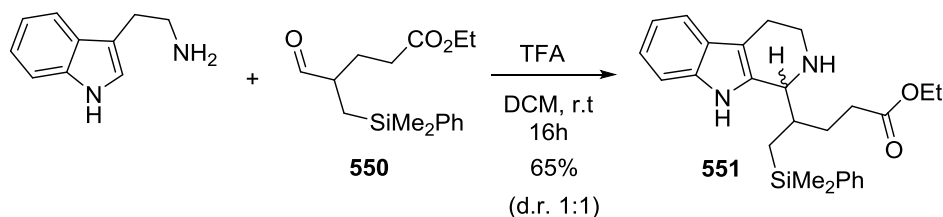
²⁰⁹ Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z., *Org. Lett.* **2004**, *6*, 3217–3219.

Scheme 162. Carbo-alkenylation MCR with Sulfonyl Acceptors **191** or **192**.

The Lemieux–Johnson oxidation of the double bond in carbo-alkenylation product **193a**, under standard conditions (OsO_4 , NaIO_4), was not successful.²¹⁰ This was attributed to the electron-withdrawing effect of the sulfone. In contrast, this reaction worked well in case of carbo-alkenylation product **193b** in 54% isolated yield (Scheme 163).

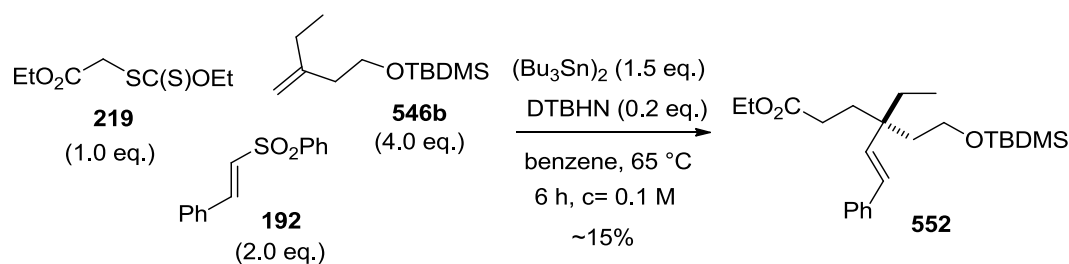
Scheme 163. Lemieux-Johnson oxidation of **193a,b**

With this aldehyde **550** in hand, the Pictet-Spengler reaction with tryptamine was performed in the presence of 2.0 equiv. of TFA in DCM at room temperature for 16 h. The reaction worked well, leading to the expected product **551** in 65% isolated yield as a 1:1 mixture of two diastereoisomers (Scheme 164).

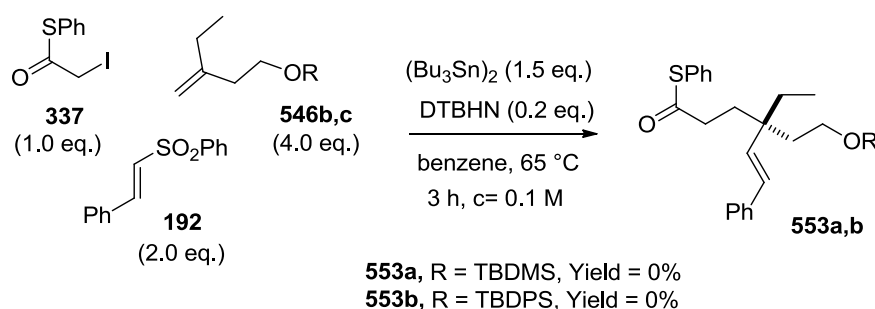
Scheme 164. Pictet-Spengler reaction with aldehyde **550**.

With these promising results in hand, this strategy was extended to olefins **546b** assigned for synthesis of Eburnane **2**. Therefore, the carbo-alkenylation process between the xanthate ethyl ester **219**, styrylsulfone **192** and the olefin **546b** was performed. Surprisingly, only traces of the product **552** was observed and the isolation of the product in pure form was not successful (~15% yield) (Scheme 165).

²¹⁰ Mohan, P.; Koushik, K.; Fuertes, M. J. *Tetrahedron Lett.* **2012**, *53*, 2730-2732.

Scheme 165. Carbo-alkenylation MCR with Olefin **546b**.

Then, we tested the more reactive α -iodothioester **337** instead of xanthate ethyl ester **219**. Unfortunately, the desired product was not detected and the reaction mixture was very complex. The same result was also observed in case of olefin **546c** (Scheme 166).

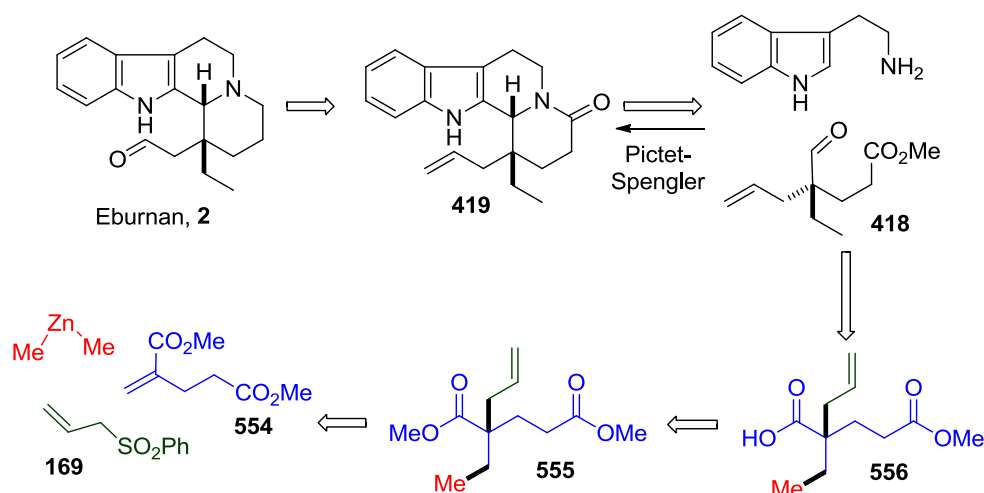
Scheme 166. Carbo-alkenylation MCR with α -iodothioester.

With these disappointing results in carbo-alkenylation approach, we began to think about different multi-component free-radical processes, which could be used to give a rapid access to Eburnane.

3.4.3. Use of dimethyl zinc as chain carrier

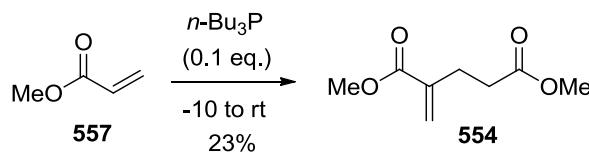
To take the advantage of multicomponent free radical processes in constructing quaternary centers in one step, our retrosynthesis was adapted to fit the idea of using methyl radicals as chain carrier. Therefore, the modified retrosynthetic analysis proposed the use of dimethyl zinc to generate a nucleophilic methyl radical which would add onto activated olefin **554**, forming an electrophilic radical, which could finally be trapped by allyl sulfone **169**. After construction of the desired quaternary center, the two methyl esters could be discriminated in a later stage based on the reported method by Tello-Aburto *et al.*²¹¹ Then, the acid **556** could be converted into aldehyde **418**, which could undergo a Pictet-Spengler reaction with tryptamine to give the tetracyclic lactam core of Eburnane. Hopefully, Eburnane **2** could be accessed after reduction of lactam and oxidation of the double bond.

²¹¹ Tello-Aburto, R.; Lucero, A. N.; Rogelj, S. *Tetrahedron Lett.* **2014**, *55*, 6266-6268.



Scheme 167. Modified Retrosynthesis Analysis of Eburnane.

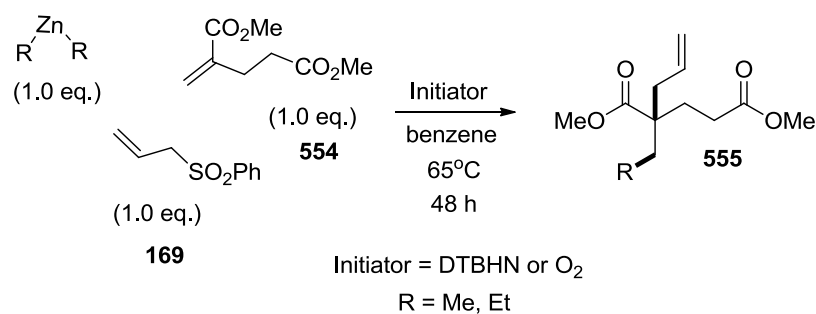
Therefore, our synthetic approach started with a Rauhut–Currier reaction²¹² of methyl acrylate **557**, in presence of catalytic amount of tributyl phosphine, to give the desired diester olefin **554** in 23% yield. It is worth noticing that the quality of tributyl phosphine is essential here for the efficiency and yield of this reaction (Scheme 168).

Scheme 168. Synthesis of Olefin **554**.

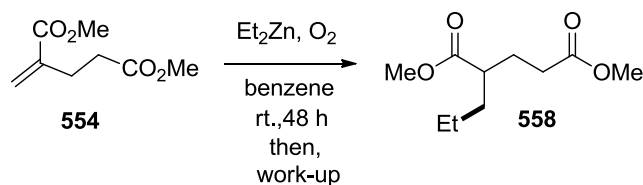
With this olefin in hand, the multi-component radical approach was tested. Therefore, olefin **554**, dimethyl zinc and allylsulfone **169** were allowed to react under DTBHN initiation in benzene. The starting olefin had not been consumed after 24 h, and then another addition of DTBHN was performed. Unfortunately, the reaction mixture solidified after 2 days, which likely indicates a polymerization of the starting materials. To avoid this undesired polymerization, the reaction was repeated under the same conditions, but through initiation with O₂. After 3 days of heating at 65°C and adding O₂ through a syringe pump, the starting material had not been consumed.

Repeating the reaction by using the more stable diethyl zinc reagent did not give the expected product and the starting olefin had not been consumed after 3 days (Scheme 169).

²¹² Aroyan, C. E.; Dermenci, A.; Miller, S. J. *Tetrahedron* **2009**, *65*, 4069–4084.

Scheme 169. Dialkyl Zinc Radical MCR with olefin **554**.

One of the possible reasons that made this reaction difficult is the presence of two olefins in the reaction mixture (olefin **554** and allylsulfone **169**). Therefore, to examine the reactivity of olefin **554** towards the addition of methyl or ethyl radicals, generated from organozinc species, a two component radical aerobic reaction between olefin **554** and diethyl zinc was performed. In this trial the starting olefin **554** was consumed, but the reaction mixture was very messy with a lot of side products. (Scheme 170).

Scheme 170. Diethyl Zinc Radical 2-CR with olefin **554**.

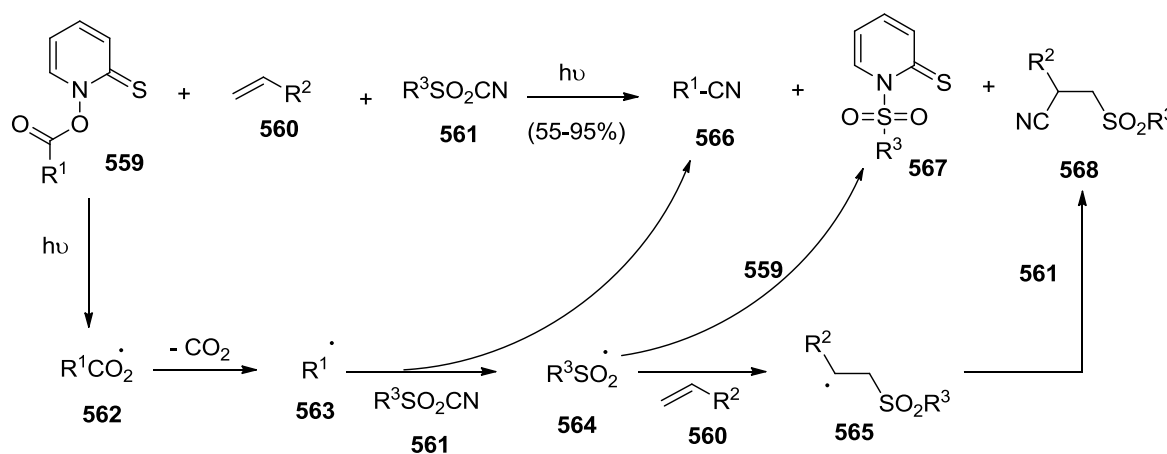
The key idea in our approach to access eburnane is to construct the non-tryptamine aldehyde in two steps relying on the multi-component free radical processes. At that point, we were searching for a group that is compatible with free-radical processes, convertible to aldehyde in an easy and reliable manner and small enough to be installed on a quaternary center without suffering from steric hindrance. A cyano group was found to be an ideal candidate for this task. The construction of the non-tryptamine part based on the introduction of a cyano group will be discussed in the following section.

3.4.4. Through a Free-Radical Carbo-cyanation process

The nitrile group is a convenient equivalent the formyl functional group. Simple reduction of nitrile by using DIBAL-H could easily give the desired aldehyde ready for the Pictet-Spengler reaction. Besides that, the nitrile group with an A-value of 0.21 represents one of the smallest functional

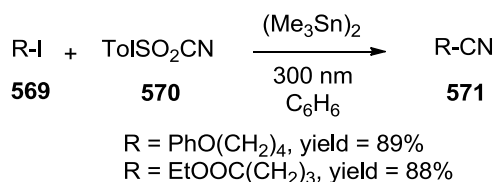
group in synthetic organic chemistry.²¹³ Questions that arose were its compatibility with free-radical multi-component processes and the nature of the appropriate cyanating agent.

A literature review on the radical processes involving nitrile transfer to carbon radicals was overviewed. Hence, in 1992 Barton *et al.*²¹⁴ reported the decarboxylative cyanation of Barton's ester and addition of sulfonyl cyanide **561** onto olefins. The reaction started by photolysis of Barton's ester **559** to generate the corresponding carbon radicals **563** through the primarily formed carboxyl radicals **562**. These carbon radicals **562** could be trapped by sulfonyl cyanides **561** to give nitriles **566** and sulfonyl radicals **564**. These sulfonyl radicals may also add onto olefins **560** to give intermediate radical **565** which was trapped again with another molecule of sulfonyl cyanides **561** (Scheme **171**).



Scheme **171**. Barton's Nitrile Transfer to Carbon Radicals.

In 2002, Kim *et al.*²¹⁵ studied cyanation of alkyl halides through a tin-mediated radical cyanation process of primary alkyl iodides **569** with *p*-toluenesulfonyl cyanide **570** under radiation at 300 nm to give the desired nitrile **571** in excellent yields (Scheme **172**).



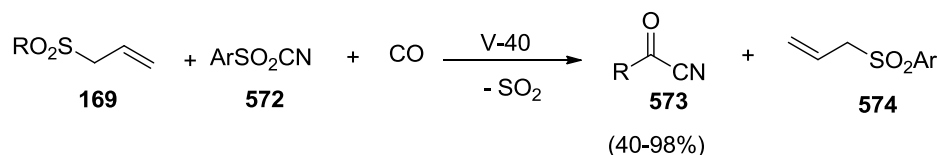
Scheme **172**. Kim's Cyanation of Primary Alkyl Iodides.

²¹³ (a) Boiadjiev, S. E.; Lightner, D. A. *J. Am. Chem. Soc.* **2000**, *122*, 11328-11339; (b) Jensen, F. R.; Bushweller, C. H.; Beck, B. H. *J. Am. Chem. Soc.* **1969**, *91*, 344-351; (c) Schneider, H. J.; Hoppen, V. J. *Org. Chem.* **1978**, *43*, 3866-3873; (d) Winstein, S.; Holness, N. J. *J. Am. Chem. Soc.* **1955**, *77*, 5562-5578.

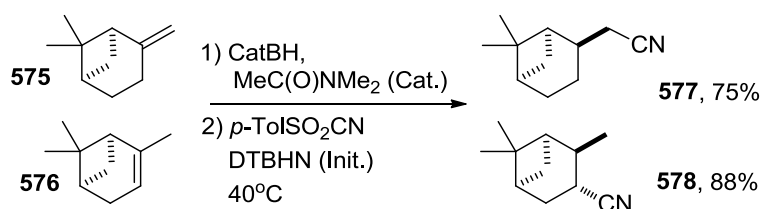
²¹⁴ (a) Barton, D. H. R.; Jaszberenyi, J. C.; Theodorakis, E. A. *Tetrahedron* **1992**, *48*, 2613-2626; (b) Barton, D. H. R.; Jaszberenyi, J. C.; Theodorakis, E. A. *Tetrahedron Lett.* **1991**, *32*, 3321-3324.

²¹⁵ Kim, S.; Song, H.-J. *Synlett* **2002**, *12*, 2110-2112.

Few years later, Kim and coworkers reported a new radical approach for the synthesis of aliphatic acyl cyanides based on a tin-free radical cyanocarbonylation, using alkylallylsulfone, arylsulfonyl cyanide **572** and CO (Scheme **173**).²¹⁶

Scheme **173**. Kim's Cyanocarbonylation.

Recently, Renaud and coworkers reported a cyanation process by using *p*-toluenesulfonyl cyanide **570**.²¹⁷ Therefore, olefins **575**, **576** were hydroborated with catecholborane followed by treatment with *p*-toluenesulfonyl cyanide in the presence of a radical initiator (DTBHN or O₂) to give the corresponding nitriles **577**, **578** in excellent yields (Scheme **174**).

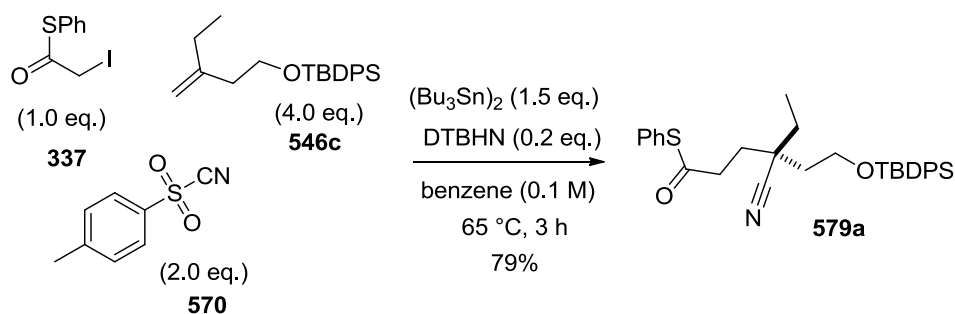
Scheme **174**. Renaud Cyanation Process.

From the aforementioned examples, the nitrile group proved to be compatible with free-radical processes and showed high efficacy and tolerance in these reactions. Besides that, the common cyanating agent used in these radical processes is *p*-toluenesulfonyl cyanide **570**, which is a cheap and commercially available starting material.

Therefore, based on these premises, we decided to extend our 3-CR free radical process to include the new three component free-radical carbo-cyanation process. Thus, this new reaction, run with the same optimal reaction conditions used for carbo-oximation process, was very successful. The α -iodothioester **337** was allowed to react with olefin **546c** and *p*-toluenesulfonyl cyanide **570** to give the expected nitrile **579a** in 79% (Scheme **175**). This is to be compared with the 40% yield obtained with the same olefin and thioester, when using the corresponding sulfonyloxime.

²¹⁶ Kim, S.; Cho, C. H.; Kim, S.; Uenoyama, Y.; Ryu, I. *Synlett* **2005**, 3160-3162.

²¹⁷ Schaffner, A.-P.; Darmency, V.; Renaud, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 5847-5849.

Scheme 175. Carbo-Cyanation MCR with α -Iodothioester **337** and Olefins **546c**.

This new and efficient reaction prompted us to study the scope and limitation of this process, which will be discussed in the following part.

3.4.4.1. Carbo-cyanation Reaction Scope & Limitations

The above efficient carbo-cyanation process suggested that this reaction could be extended to different radical precursors and olefinic partners. Therefore, with the available radical precursors and olefins present in our laboratory, an extensive study on the scope of this reaction was performed (Scheme 176).

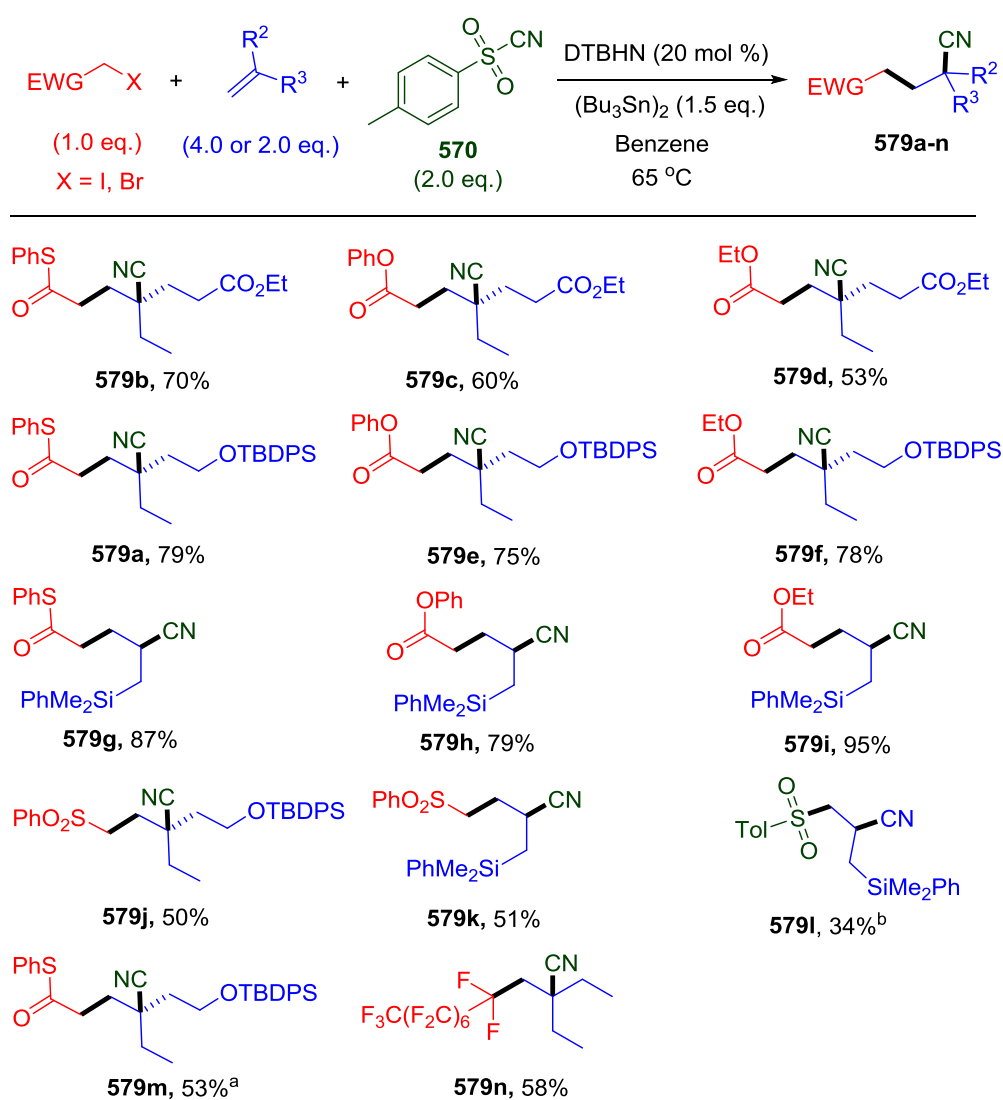
First, different radical precursors were allowed to react with olefin **252**, used in synthesis of Eucophylline. In general, yields were very good and reproducible. Therefore, α -iodoester **337** led to the best results with this olefin as compared to those of α -iodophenol ester **580** and α -iodoethyl ester **324**. This comparison was extended also to olefins **546c** and allylsilane **265**. It is also worth noticing that the carbo-cyanation process worked with only (2.0 eq.) of olefin **546b** and gave the expected product in good yield.

Secondly, the radical precursor was changed to α -bromosulfone **334** which reacted with olefins **546c** and allylsilane **265** to give the expected products **579j** and **579k** in moderate yields. It is known that α -bromosulfone **334** is not a very reactive radical precursor; however it showed moderate yields in these carbo-cyanation processes. It is worth noticing that side-product **579l** was isolated in the carbo-cyanation process between α -bromosulfone **334** and the reactive allylsilane **265**. This product may be formed due to the slow addition of α -bromosulfone **334** onto allylsilane **265**. This slow addition gave the opportunity to *p*-toluenesulfonyl cyanide **570** to add across the double bond of allylsilane **265** and form **579l** in 34% yield (based on the *p*-toluenesulfonyl cyanide). Similar observations have been made on analogous poorly reactive radical precursors.

Third, the radical precursor was also changed to the perfluorooctyl iodide **581**, which added effectively to the olefin **582** and gave the fluorinated nitrile product **579n** in good yield. This

reaction paved the way for the construction of pharmacologically active fluorinated structures, bearing nitrile functional group, in one step and in an efficient manner.

This scope showed the generality of these multi-component free-radical processes. Radical precursors, bearing electron withdrawing groups, add onto different electron-rich olefins, the new generated radicals being trapped by sulfonyl acceptor, in good to excellent yields.



^a with 2.0 eq. of olefin.

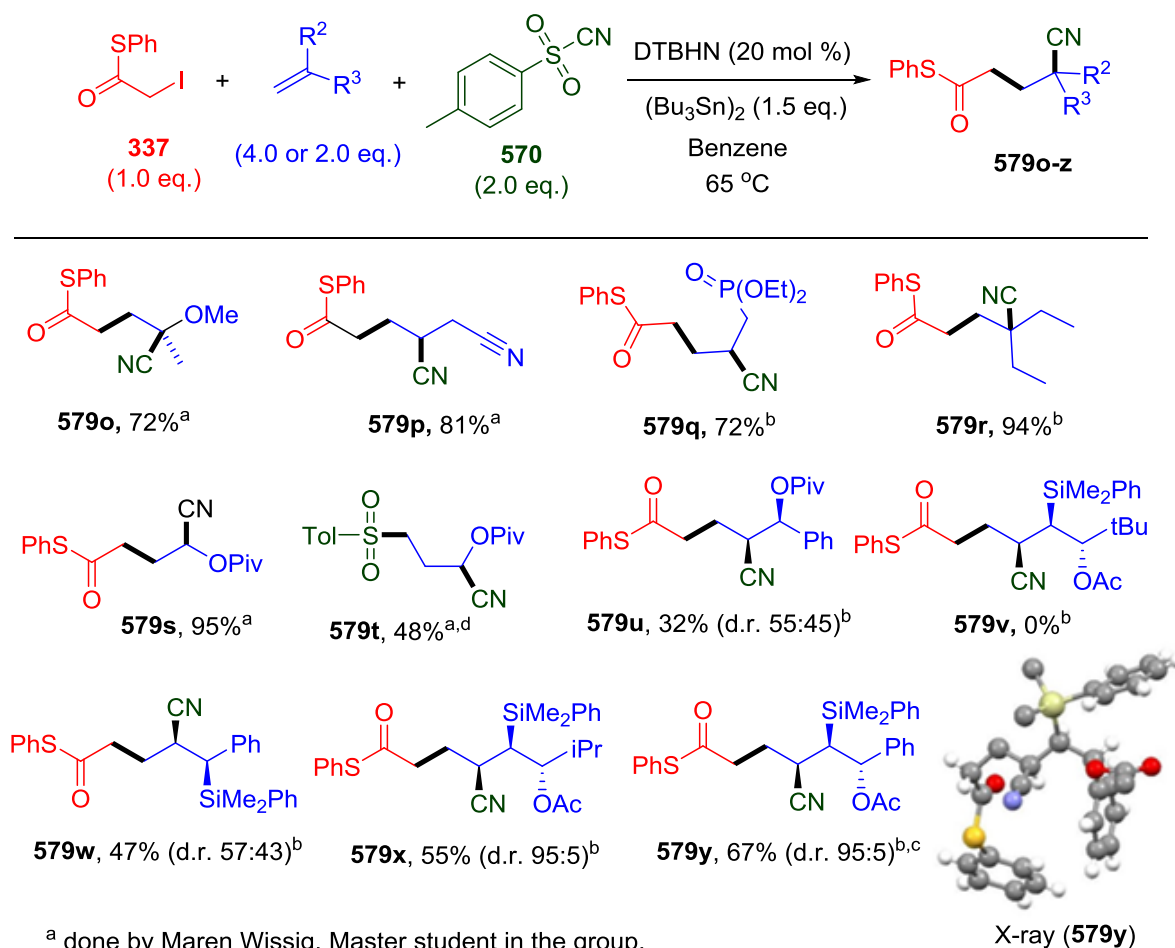
^b isolated as side product of addition of *p*-toluenesulfonyl cyanide **570** to allylsilane **265**.

Scheme 176. Carbo-Cyanation Scope / Radical precursors.

In the other side, the scope of this efficient reaction with different olefins was studied. Therefore, the more reactive radical precursor, α -iodoester **337** was allowed to react with different olefins bearing different functional groups (Scheme 177).

The reaction showed high tolerance towards different functional groups. For instance, the reaction worked well with olefins bearing protected alcohols, nitriles, phosphates and alkyl chains to give the

expected products in excellent yields. It is worth noticing that in case of *O*-pivalate olefin **583**, the side product **579t** was isolated in 48% (based on the *p*-toluenesulfonyl cyanide) along with the desired product **579s**. This side product results from addition of the extra equivalents of *p*-toluenesulfonyl cyanide **570** to this electron-rich olefin **583**.



^a done by Maren Wissig, Master student in the group.

^b done by Chahinaz Khiar, internship in the group.

^c 2.0 eq. of olefin.

^d isolated as side product of addition of *p*-toluenesulfonyl cyanide **570** to olefin **583**.

Scheme 177. Carbo-Cyanation Scope / Olefins.

In cooperation with Ms. Maren Wissig, master student in the group, the scope of the carbo-cyanation reaction with chiral allylsilanes was performed. The reaction also showed high tolerance towards chiral allylsilanes. The expected products were formed in very good yields and high diastereocontrol (Scheme 177). For instance, the products **579x**, **579y** with *i*-Pr, and phenyl groups in the terminal end of allylsilanes, showed high diastereocontrol up to (95:5). The absolute configuration of **579y** was assigned by X-ray crystallography. Similarly to carbo-azidation process, the level of diastereocontrol depends on the nature of the silicon group and on the substituents at the terminal end of allylsilanes (R). This diastereocontrol could be rationalized through a Felkin-Ahn type model (Figure 9), with a pyramidalized transition state and quasi-staggered conformation to avoid gauche

interactions between the most hindered groups SiR_3 and $(\text{CH}_2)_2\text{C}(\text{O})\text{SPh}$. According to that, the *p*-toluenesulfonyl cyanide **570** is believed to approach *anti* relative to the bulky silicon group and from the side of the smallest H substituent.

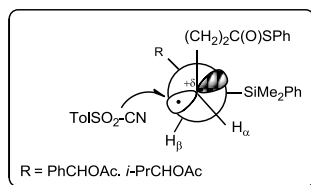


Figure 9. Felkin-Ahn Type Model of **579x** and **579y**.

But surprisingly, with the bulky *t*-Bu group, at the same terminal position, the reaction did not work and the desired product **579v** was not observed.

Nevertheless, when the size of the substituents on the stereogenic center was decreased as in **579u** and **579w**, the diastereocontrol decreased dramatically. This may be explained by the new alternative approach of the cyanide group from the side of the medium-sized phenyl group (Figure 10).

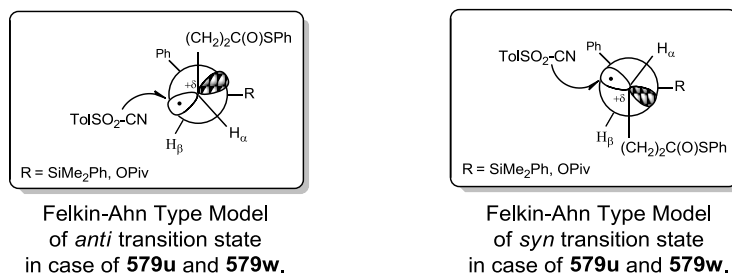


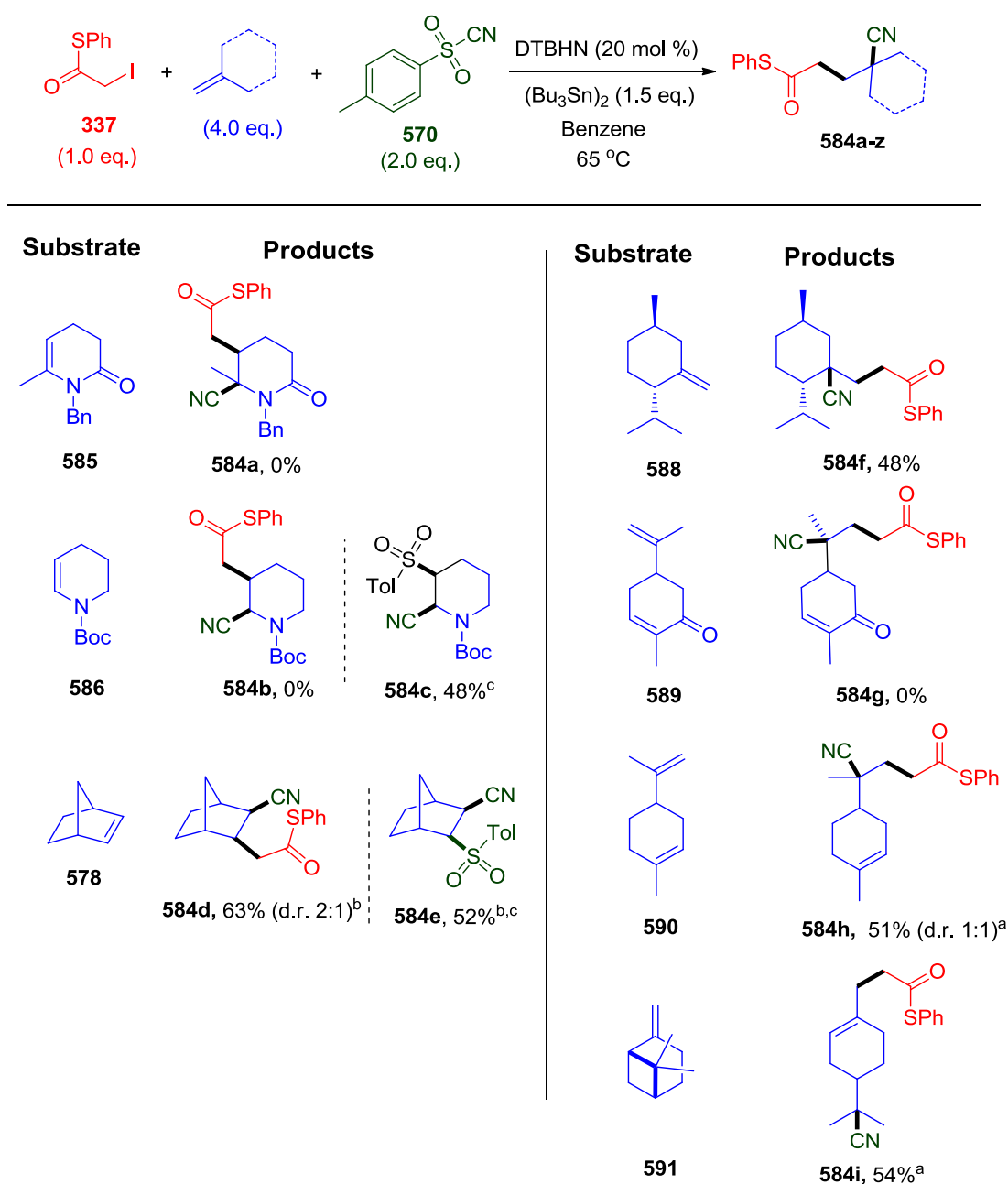
Figure 10. Felkin-Ahn Type Model of **579u** and **579w**.

These results showed that the small size of the cyano substituent likely plays an important role in the efficacy of this reaction and in the stereocontrol achieved with chiral allylsilanes.

The extension of the scope of this carbo-cyanation process to include addition of nitrile onto double bonds in complex structures was also studied. Therefore, α -iodoester **337** was allowed to react with different enamines, terpenes, dienes and bicyclic systems (Scheme 178).

The carbo-cyanation process with enamines did not afford the expected product. In case of **585**, the desired product **584a** had not been observed and instead a degradation of the starting materials was observed. Similarly, nitrile product **584b** had not been observed under the carbo-cyanation process conditions. Instead, the side-product **584c** was observed as a major product in this case and isolated in 48% yield (based on the *p*-toluenesulfonyl cyanide). This side product was probably formed through addition of *p*-toluenesulfonyl cyanide **570** onto the enamine double bond. Degradation of

the product is believed to occur due to the presence of the amide group or the carbamate functional groups, which would favor elimination of the nitrile. This observation showed the limitation of carbo-cyanation process with enamines (Scheme 178).



^a done by Maren Wissig, Master student in the group.

^b done by Chahinaz Khiar, Internship in the group.

^c isolated as side product of addition of *p*-toluenesulfonyl cyanide **570** to the double bond.

Scheme 178. Carbo-Cyanation Scope / Complex Structures.

In cooperation with Ms. Chahinaz Khiar, who did her internship in the group, the scope of the carbo-cyanation reaction with bicyclic compounds was studied. Thus, norbornene **587** reacted under carbo-cyanation reaction conditions and gave the expected nitrile product **584d** in very good yield and two separable diastereoisomers in a 2:1 ratio. The sulfone side product **584e**, resulting from the addition

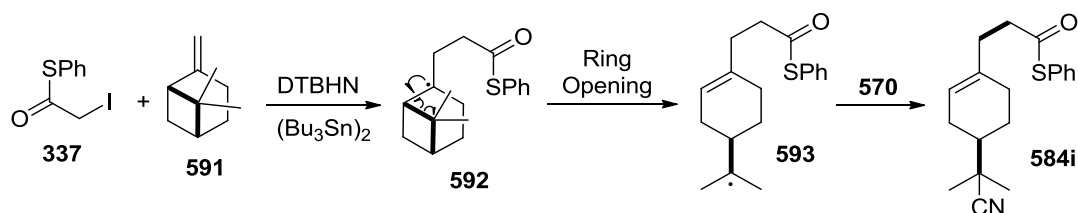
of *p*-toluenesulfonyl cyanide **570** onto the norbornene double bond, was also isolated in 52% (based on the *p*-toluenesulfonyl cyanide). The formation of this side product was observed when using (4.0 eq.) of norbornene **587** (Scheme **178**).

Extension of this scope to include terpenes was also studied. Therefore, the carbo-cyanation process between α -iodoester **337** and terpenes (*R*-Limonene **590**, β -Pinene **591**, *R*-Carvone **589** and Menthol **588**²¹⁸) gave the expected products in moderate yields (Scheme **178**).

In case of *R*-Limonene **590**, the carbo-cyanation process gave the desired nitrile product **584h** in moderate yield. The cyclization onto the endocyclic double bond is unfavoured and the carbo-cyanation process occurs on the more accessible 1,1-disubstituted alkene to give the expected product **584h** in moderate yield.

In the case of *R*-Carvone **589**, the presence of ketone functional group apparently altered the carbo-cyanation process. No traces of the expected product **584g** were observed.

The carbo-cyanation process with β -Pinene **591** afforded the nitrile product **584i**, after rearrangement, in moderate yield. This reaction showed that ring opening is faster than the intermolecular trapping of the nucleophilic radical (Scheme **179**).²¹⁹

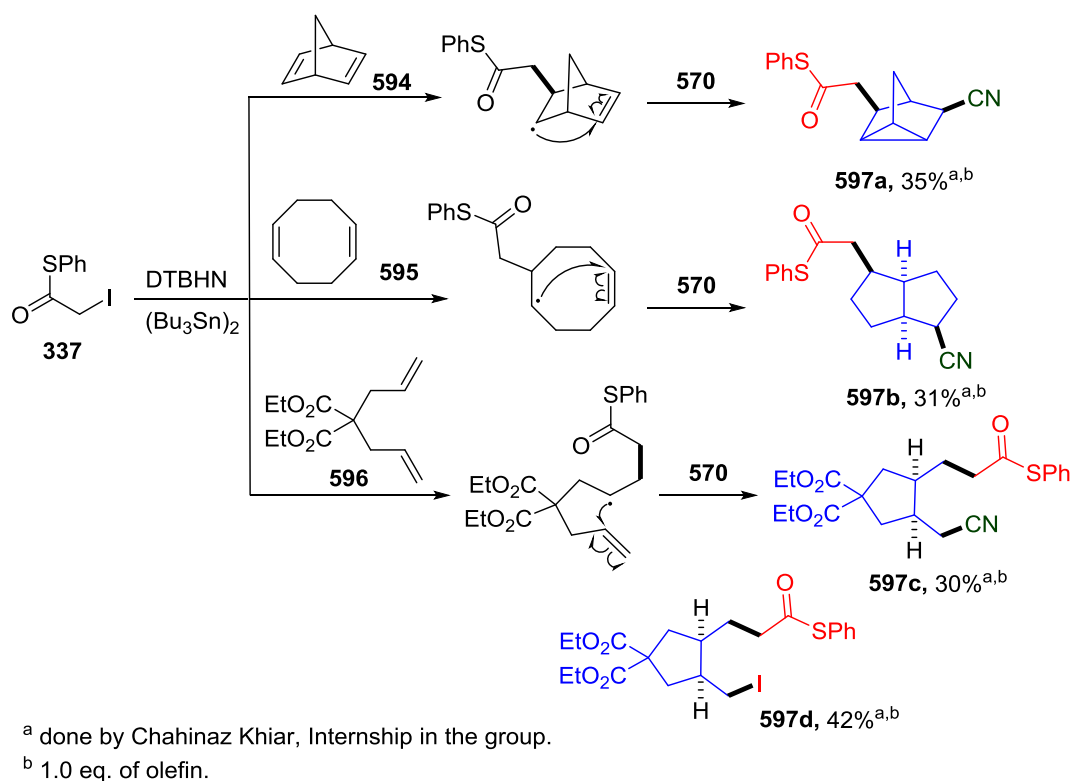


Scheme **179**. Carbo-Cyanation MCR with β -Pinene.

The carbo-cyanation reaction was extended also to dienes. Therefore, the carbo-cyanation reaction with norbornadiene **594** led to the product **597a** after cyclization of the formed radical onto the second double bond. Diene **595** was also allowed to undergo carbo-cyanation process to give the bicyclo[3.3.0]octane **597b** in modest yield. Besides, carbo-cyanation process with diene **596** also afforded the cyclized nitrile product **597c** in modest yield. It is noteworthy that all of these nitrile products **597a-c** were isolated as single diastereomers.

²¹⁸ Fernandes, R. A.; Chaudhari, D. A. *Eur. J. Org. Chem.* **2012**, 2012, 1945-1952.

²¹⁹ Oldroyd, D. M.; Fisher, G. S.; Goldblatt, L. A. *J. Am. Chem. Soc.* **1950**, 72, 2407-2410.



Scheme 179. Carbo-cyanation Radical Clock Mechanism.

The reactivity observed with dienes above showed that the intramolecular cyclization of the formed nucleophilic radical onto the second double bond is faster than the intermolecular addition onto *p*-toluenesulfonyl cyanide **570**.²²⁰ For example, diene **595** underwent 5-*exo-trig* cyclization onto the second double bond to give the bicyclo[3.3.0]octane **597b**. Similarly, diene **596** underwent 5-*exo-trig* cyclization to give the trisubstituted cyclopentane **597c**. While diene **594** underwent 3-*exo-trig* to give disubstituted tricyclo[2.2.1.0]heptane **597a**.

It is also worth noticing that the transfer product **597d** was observed in case of diene **596** along with the expected nitrile product **597c**. The carbo-cyanation reactions with dienes were performed with equimolar ratio of the three components, in order to avoid the presence of the sulfone addition side products, generated from addition of the *p*-toluenesulfonyl radical onto the double bond. Although carbo-cyanation processes with dienes gave access, in one step, to complex functionalized structures, it was generally observed that the yields in these processes were quite modest.

To summarize this scope, the free-radical carbo-cyanation multicomponent process showed high tolerance to different functional groups with good to excellent yields. The small size of the cyano group plays an important role during the control of the stereochemistry in chiral allylsilanes and for the easy installation of this chemically important functional group on the most hindered olefins. The elaboration of all-carbon quaternary centers by using this carbo-cyanation process proved to be very

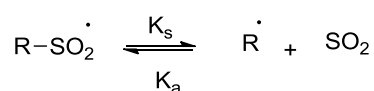
²²⁰ Villa, G.; Povie, G.; Renaud, P. *J. Am. Chem. Soc.* **2011**, *133*, 5913-5920.

efficient; giving access to fully functionalized quaternary centers in very good yields. However, the carbo-cyanation process showed some limitations with enamines and ketones. Nevertheless, this carbo-cyanation process gave access to different complex functionalized structures in only one step.

3.4.4.2 .Towards Tin-Free Carbo-Cyanation MCRs.

Organotin reagents showed high efficiency to mediate the radical reactions. But these reagents have perceived toxicity and it is difficult to remove their residues from the final products.²²¹ These disadvantages have proved to be a serious hurdle to industrial applications. Therefore, few approaches were developed to design free-radical reaction without tin mediation.

In 1997, Zard *et al.*²²² developed allylation reaction of olefins based on the thermal decomposition of ethyl-allylsulfones **598**. The principle idea in this approach is based on the possible α -scission of alkylsulfonyl radicals with the formation of the alkyl radical and extrusion of SO₂. The α -scission reaction is reversible and the rate of this scission depends on the stability of the formed alkyl radical (Scheme **180**).



K_s= rate of α -scission.
K_a= rate of association

Scheme **180**. Reversibility of α -scission

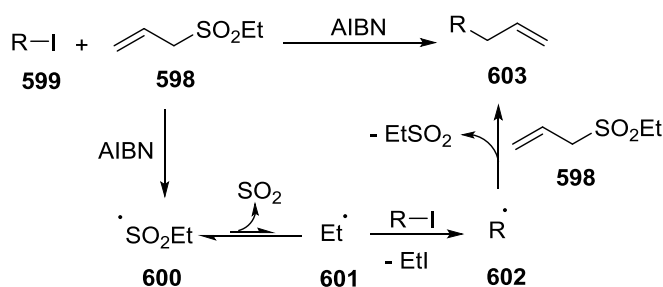
Generally, the equilibrium is shifted towards the formation of the alkylsulfonyl radical. And the more stable the alkyl radical, the higher the rate of elimination of SO₂, shifting the equilibrium to the right. For example, the rate of α -scission in the case of benzylsulfonyl radical is $2 \cdot 10^8 \text{ s}^{-1}$ (295°K).²²³ However, in case of an arylsulfonyl radical, the formation of the highly energetic aryl radical is not favored. Therefore, these types of aryl sulfonyl radicals do not undergo α -scission process.

Based on this, Zard and his coworkers used ethyl sulfonyl radical **600**, generated from the addition of an initiator onto allylsulfone **598**, which undergoes an α -scission process, thus generating an alkyl radical after elimination of SO₂. This alkyl radical then abstracts iodine from the alkyl iodate **599** and generates radical **602**. The latter then adds onto the allylsulfone **598** and liberates ethylsulfonyl radical which can propagate the radical chain (Scheme **181**).

²²¹ (a) Le Grogneec, E.; Chrétien, J.-M.; Zammattio, F.; Quintard, J.-P. *Chem. Rev.* **2015**, *115*, 10207-10260; (b) Ferreira, M.; Blanco, L.; Garrido, A.; Vieites, J. M.; Cabado, A. G. *J. Agric. Food Chem.* **2013**, *61*, 4195-4203.

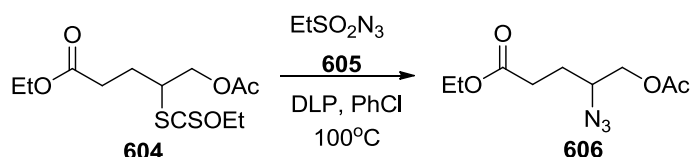
²²² Le Guyader, F.; Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *J. Am. Chem. Soc.* **1997**, *119*, 7410-7411.

²²³ Chatgililoglu, C.; Lunazzi, L.; Ingold, K. U. *J. Org. Chem.* **1983**, *48*, 3588-3589.

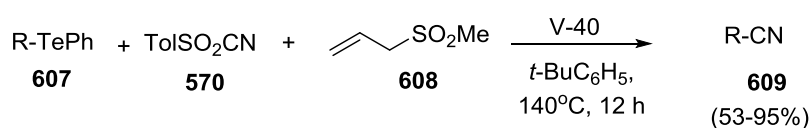


Scheme 181. Zard allylation with ethyl-allylsulfone.

More recently, Renaud *et al.*²²⁴ relied on the same α -scission process to develop azidation reactions of iodate or xanthate derivatives **604** by using ethylsulfonylazide **605**. The azide part of this reagent **605** acts as a radical acceptor and the ethyl radical, generated after extrusion of SO_2 , propagate the radical chain (Scheme 182).

Scheme 182. Renaud azidation reaction by EtSO_2N_3 .

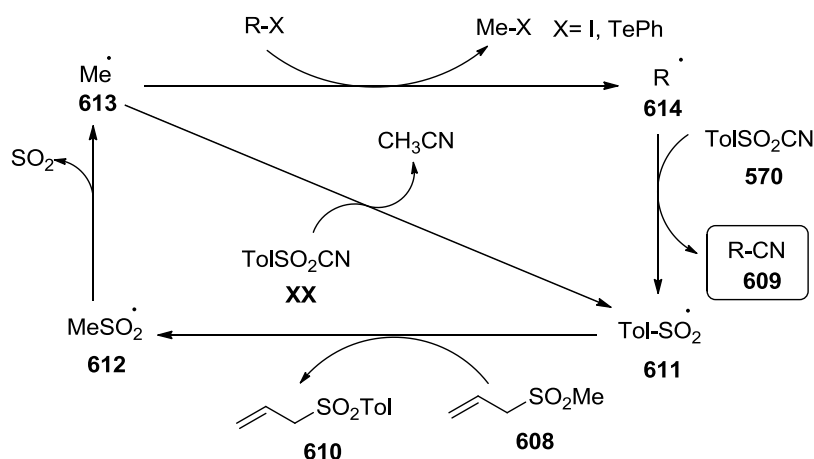
Kim also developed a tin-free radical cyanation process using methylallylsulfone **608**.²¹⁵ In this approach, primary alkyl phenyl telluride derivatives **607** were used instead of alkyl iodides. This is due to the much faster transfer of the phenyl telluride group to the methyl radical than the corresponding iodine atom transfer. Thus, treatment of alkyl phenyl tellurides **607** with *p*-toluenesulfonyl cyanide **570**, methylallylsulfone **608** and V-40 in *t*-butylbenzene gave the corresponding nitriles in excellent yields (Scheme 183).



Scheme 183. Kim's Tin-Free Cyanation of Primary Alkyl Iodides.

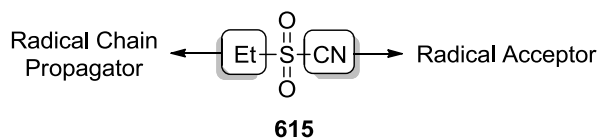
The mechanism of this tin-free reaction involved the use of methylallylsulfone **608** as a source of methyl radical **613** for iodine or phenyl telluride transfer. The addition of *p*-toluenesulfonyl cyanide to methyl allyl sulfone **608** would produce methanesulfonyl radical **612** which will thermally decompose to give the desired methyl radical **613**. This methyl radical would undergo the iodine atom or phenyl telluride transfer to give the alkyl radical **614**, which would add to *p*-toluenesulfonyl cyanide **570** and give the nitrile product **609**. Also, this methyl radical might add to *p*-toluenesulfonyl cyanide **570** to generate *p*-toluenesulfonyl radical **611**, which propagate the chain (Scheme 184).

²²⁴ (a) Ollivier, C.; Renaud, P. *J. Am. Chem. Soc.* **2000**, *122*, 6496-6497; (b) Ollivier, C.; Renaud, P. *J. Am. Chem. Soc.* **2001**, *123*, 4717-4727.

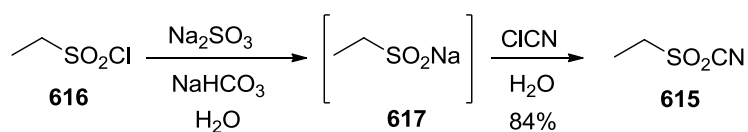


Scheme 184. Kim's Tin-Free Cyanation Mechanism.

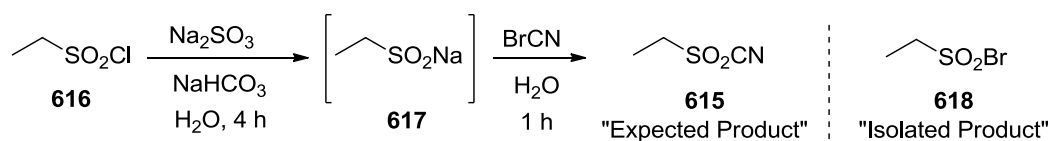
From the aforementioned approaches and relying on the success of 3-CR-carbo-cyanation process, we tried to synthesize the ethylsulfonyl cyanide **615** to develop a tin-free carbo-cyanation process. In this reagent the nitrile part would act as radical acceptor and the ethyl radical, generated after extrusion of SO₂, would propagate the radical chain.



The first reported method to synthesize this bifunctional reagent was from ethylsulfinic acid sodium salt **617** and cyanogen chloride. Therefore, ethylsulfonyl chloride **616** was treated with sodium sulfite and sodium bicarbonate to give the ethylsulfinic acid sodium salt **617**, which was further reacted with cyanogen chloride to afford ethylsulfonyl cyanide **615** (Scheme 185).²²⁵

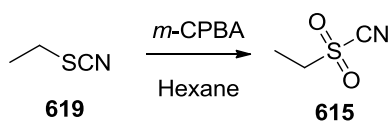
Scheme 185. Synthesis of ethylsulfonyl cyanide **615**, by ClCN

We tried to avoid the use of the highly dangerous cyanogen chloride by using the less toxic cyanogen bromide. Therefore, the last sequence was repeated by using cyanogen bromide. Unfortunately, the only isolated product was ethylsulfonyl bromide **618** (Scheme 186).

Scheme 186. Synthesis of ethylsulfonyl cyanide **615**, by BrCN

²²⁵ (a) M. S. A. Vrijland, *Org. Synth.* **1977**, *57*, 88; (b) Kim, S.; Lim, K.-C.; Kim, S. *Chem. Asian J.* **2008**, *3*, 1692-1701

Another method was reported for the synthesis of ethylsulfonyl cyanide **615** through oxidation of ethyl thiocyanate **619** by *m*-CPBA.²²⁶ The reported reaction worked only in 6% isolated yield. Our efforts to reproduce this reaction were unfortunately not successful (Scheme **187**).

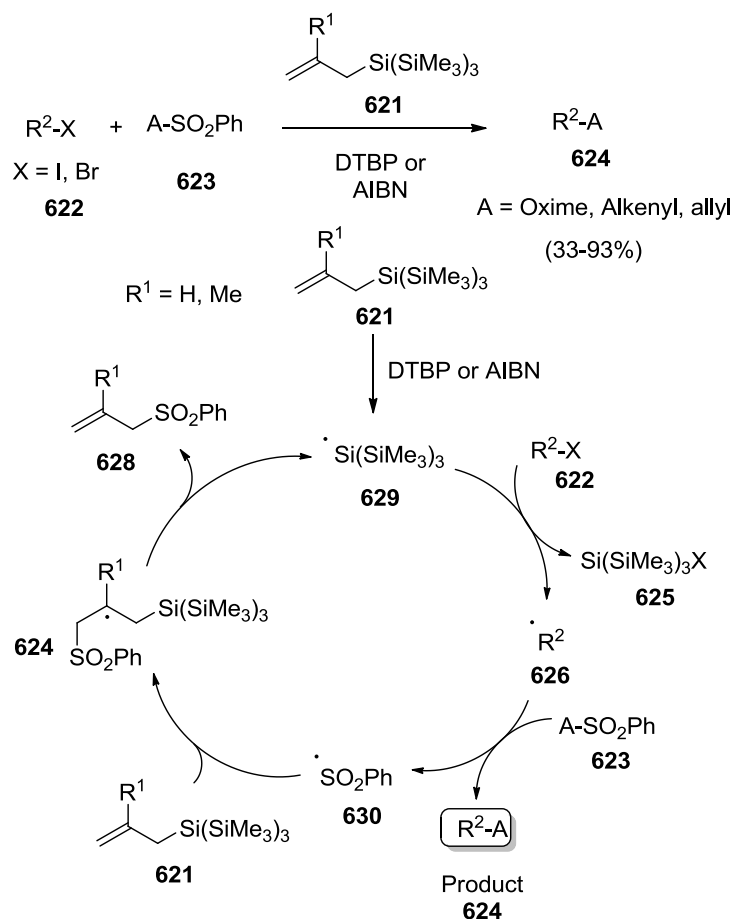


Scheme **187**. Oxidation of ethyl thiocyanate **619**.

It was envisioned that another cyanating agent would be able to perform the same task. $(\text{Me}_3\text{Si})_3\text{SiCN}$ **620** could be a source of electrophilic nitrile and the $(\text{Me}_3\text{Si})_3\text{Si}$ part could propagate the radical chain. This hypothesis is based on the results obtained in the group with allyl(tristrimethylsilyl)silane **621** which was used to propagate the radical chain in 2-CR carbonylation, alkenylation, and allylation process.²²⁷ The mechanism of this TTMS propagation starts with generation of TTMS radical from the corresponding allyl(tristrimethylsilyl)silane **621** followed by halogen abstraction from alkyl halide **622** by the $(\text{Me}_3\text{Si})_3\text{Si}$ radical **629**. The generated nucleophilic alkyl radical **626** adds onto the sulfonyl acceptor **623** to afford the desired product **624** and release of phenylsulfonyl radical **630**. The latter can then react with the electron-rich allyl(tristrimethylsilyl)silane **621** to generate the allylsulfone **628** and regenerate TTMS radical **629**, which sustains the radical chain (Scheme **188**).

²²⁶ Pews, R. G.; Corson, F. P. *J. Chem. Soc. D., Chem. Comm.* **1969**, 1187.

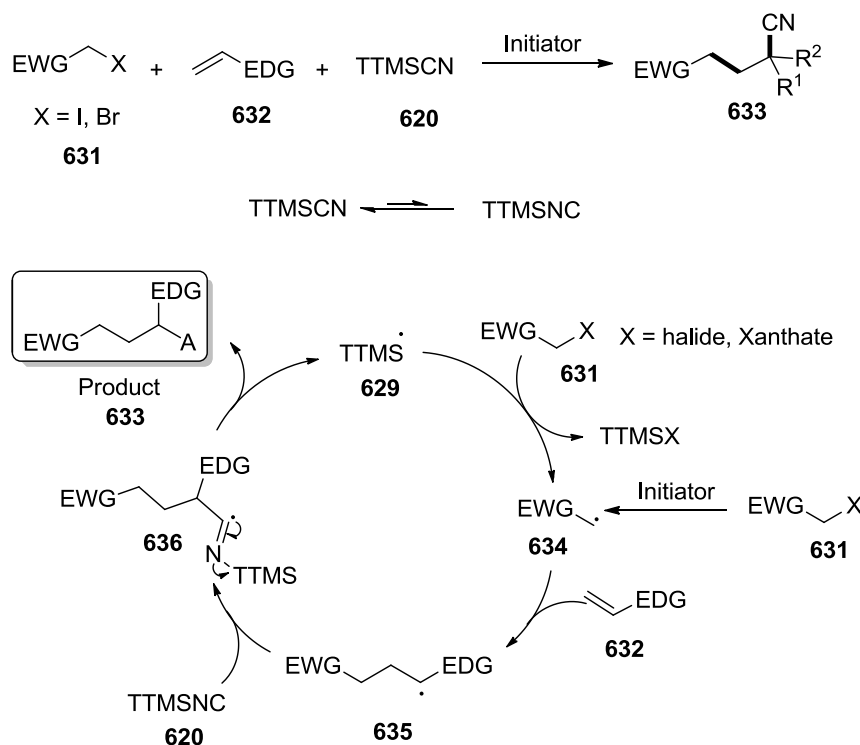
²²⁷ Rouquet, G.; Robert, F.; Méreau, R.; Castet, F.; Landais, Y. *Chem. Eur. J.* **2011**, *17*, 13904-13911.



Scheme 188. Tin-Free Oximation, Alkenylation, and Allylation of alkyl halides.

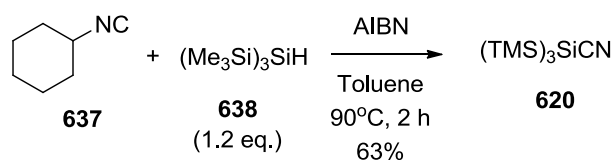
Based on these observations, our hypothesis for $(Me_3Si)_3SiCN$ started by generation of the electrophilic radical **634**, generated from the corresponding radical precursor **631** by action of AIBN. This electrophilic radical will add on the electron-rich olefin **632** to give the nucleophilic radical **635**. The latter will then add onto the electrophilic nitrile carbon of $(Me_3Si)_3SiCN$ **620** and liberate the $(Me_3Si)_3Si$ radical **629**, which will abstract the halide from the starting alkyl halide **631** and sustain the radical chain (Scheme 189). The problem with this approach is the much lower electrophilic character of the silylcyanide as compared to sulfonylcyanide. However, silylcyanides R_3SiCN are in equilibrium with silylisonitriles R_3SiNC with a large predominance (> 95%) of the cyanide form.²²⁸ It was then being imagined that the nucleophilic alkyl radical could however react with the isonitrile form even if its concentration in the medium is likely very low. β -Elimination of the $(Me_3Si)_3Si$ radical would then sustain the radical chain.

²²⁸ Seckar, J. A.; Thayer, J. S. *Inorg. Chem.* **1976**, *15*, 501-504.



Scheme 189. Hypothesis Tin-Free Carbo-cyanation process by TTMSCN.

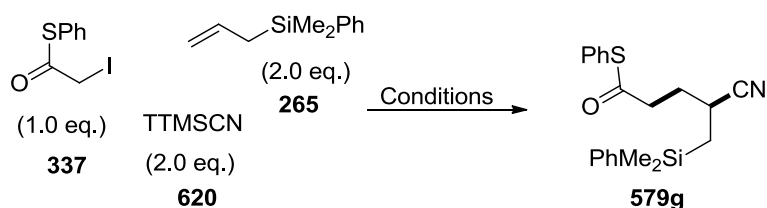
Therefore, the cyanating agent $(\text{Me}_3\text{Si})_3\text{SiCN}$ **620** was synthesized according to the reported method from the corresponding cyclohexyl isocyanide **637**.²²⁹ Cyclohexyl isocyanide **637** was then refluxed in toluene with $(\text{Me}_3\text{Si})_3\text{SiH}$ **638** in presence of AIBN to give the corresponding $(\text{Me}_3\text{Si})_3\text{SiCN}$ **620** in 63% (Scheme 190).



Scheme 190. Synthesis of TTMSCN.

Then, this cyanating agent was allowed to react with the more reactive α -iodoester **337** and electron-rich allylsilane **265** in presence of AIBN as an initiator (Scheme 191). Unfortunately, the expected product **579g** was not observed despite the full consumption of α -iodoester **337**. This reaction was repeated again with di-*tert*-butyldiazene as an initiator, but the same negative result was observed. Then, the reaction was repeated again by applying the standard condition for this carbo-cyanation process by mediation of DTBHN/ $(\text{Bu}_3\text{Sn})_2$. The reaction did not give the desired product too and only complex mixtures of by-products were observed (Scheme 191).

²²⁹ North, M. *Science of Synthesis*; Thieme Chemistry, **2002**, 499-511.



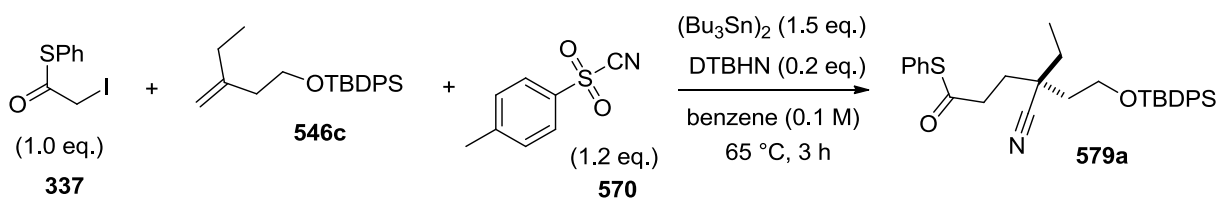
Entry	Conditions	Yield (%)
1	AIBN (0.2 eq.), benzene, 90 °C, 3 h	N/A
2	<i>t</i> -BuN=N <i>t</i> -Bu (0.2 eq. x 3), benzene, 90 °C, 16 h	N/A
3	DTBHN (0.2 eq. x 3), (Bu ₃ Sn) ₂ (1.5 eq.), benzene, 65 °C, 6 h	N/A

Scheme 191. Carbo-Cyanation MCR with TTMSCN

At this point, we gave up the tin-free radical carbo-cyanation process and reported our attention to the synthesis of Eburnane **2** relying on the carbo-cyanation under standard tin-conditions. In the following section, elaboration of Eburnane **2** through two different approaches will be introduced.

3.5. Elaboration of Eburnane

Relying on the carbo-cyanation process developed above, our efforts to elaborate eburnane started with attempts at reducing the number of equivalents of olefin used in this carbo-cyanation process. Using equimolar amounts of this olefin will make this synthesis more efficient. Therefore, the carbo-cyanation process between equimolar amounts of α -iodo thioester **337**, olefin **546c** and *p*-toluenesulfonyl cyanide **570** was performed. The desired product was isolated in somewhat lower yield (50%). Therefore, the reaction was repeated with 2.0 equivalents of olefin **546c** and the desired product was isolated with almost the same yield observed when the reaction was performed with 4.0 equivalents (Scheme 192).



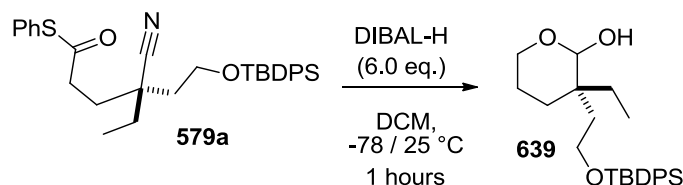
Entry	Olefin No. of. Eq.	Yield (%)
1	1.0 eq.	50%
2	2.0 eq.	75%
3	4.0 eq.	79%

Scheme 192. Olefin Optimization of Carbo-Cyanation MCR.

It is worth noticing that this reaction could be scaled up to 5 grams of isolated pure product in a reproducible manner.

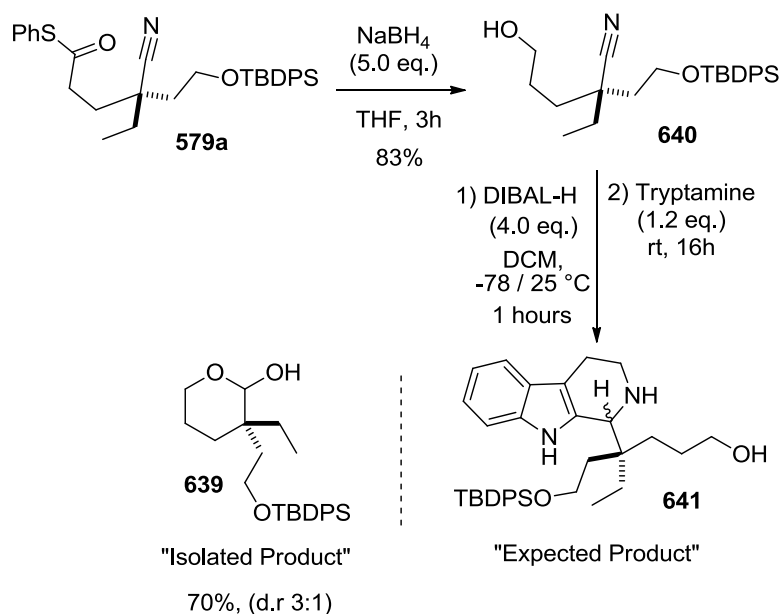
3.5.1. Synthesis of Eburnane through Pictet-Spengler Approach

With nitrile product **579a** in hand, our efforts were directed as to reduce the nitrile group into an aldehyde, which could be used as the non-tryptamine part for Pictet-Spengler reaction. Therefore, nitrile **579a** was reduced into an aldehyde by DIBAL-H, which also reduced the thioester group into the corresponding alcohol, to form the expected lactol **639**. Unfortunately, the starting material was consumed but no major product could be isolated from the reaction mixture (Scheme **193**).



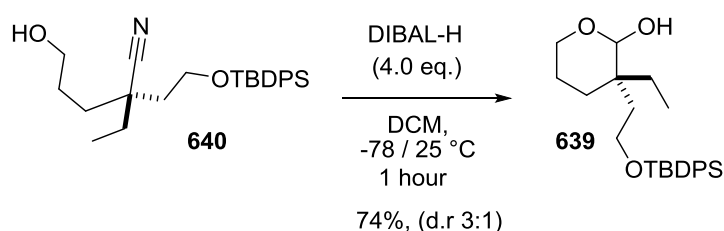
Scheme **193**. Reduction of Nitrile and Thioester to form Lactol **639**

With the aim to access the tricyclic core of Eburnane **641** directly, a stepwise reduction sequence of thioester and nitrile was developed. First, the thioester group in **579a** was reduced to alcohol by NaBH_4 . The reaction worked well and the desired alcohol **640** was isolated in very good yield (83%). Second, the nitrile group in **640** was reduced by DIBAL-H. Then, instead of hydrolyzing the formed imine by water to form aldehyde, we tried to trap this imine directly by tryptamine to form the tricyclic Pictet-Spengler product **641**. This sequence failed and the lactol **639** was the only isolated product (in 70% yield). The trapping of imine by tryptamine was not successful probably due to presence of DIBAL aluminum residues in the reaction medium (Scheme **194**).



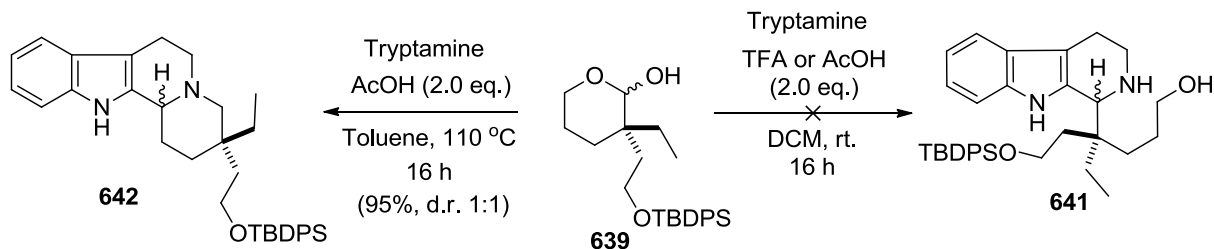
Scheme **194**. Reduction Sequence of Thioester and Nitrile / Pictet-Spengler Cyclization.

When then performed separately the DIBAL-H reduction of nitrile into aldehyde, followed by *in situ* cyclization, which gave the lactol **639** in 74% yield and a 3:1 diastereomeric ratio (Scheme 195).



Scheme 195. DIBAL-H Reduction of Nitrite.

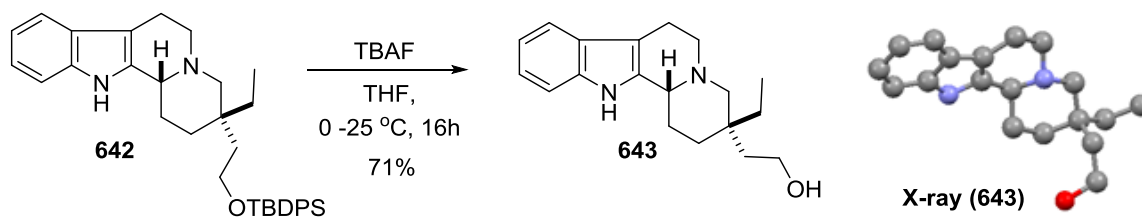
With lactol **639** in hand, the Pictet-Spengler reaction between this masked aldehyde and tryptamine was attempted. Therefore, lactol **639** was treated with tryptamine under acidic conditions in DCM at room temperature. Unfortunately, the Pictet-Spengler product **641** was not observed neither in presence of TFA nor AcOH. But surprisingly, when the reaction was performed in toluene under reflux at 110°C for 16 h and in the presence of AcOH,²³⁰ the tetracyclic core of an Eburnane-type compound **642** was isolated in 95% yield as a 1:1 mixture of two separable diastereoisomers. However, as shown later by X-ray diffraction studies, this cyclization had placed the quaternary center away from the indole ring (Scheme 196).



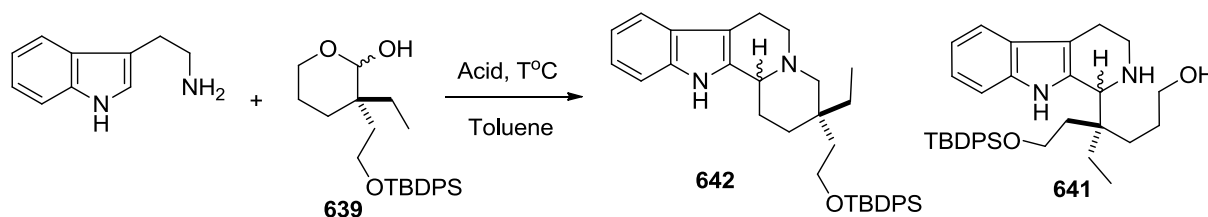
Scheme 196. Pictet-Spengler reaction with Lactol **639**.

The formation of this isomer of Eburnane **642** was not expected. To confirm the structure of the tetracyclic core of **642**, one of the two diastereoisomers was allowed to undergo deprotection of the silyl ether group by TBAF to give the hydroxyl-free tetracyclic core of eburnane **643**, with inverted quaternary center, in 71% yield. The structure of this tetracyclic core was confirmed by X-ray diffraction studies (Scheme 197).

²³⁰ Pancrazi, A.; Kervagoret, J.; Khuong-Huu, Q. *Tetrahedron Lett.* **1991**, *32*, 4303-4306.

Scheme 197. Deprotection of Silyl Ether Group in Tetracyclic Core **642**.

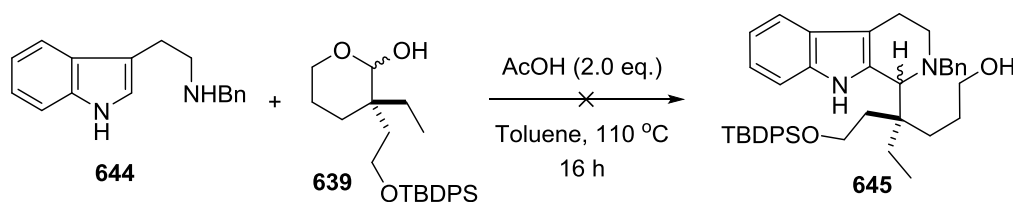
The unexpected formation of **642** prompted us to investigate the possible mechanism of its formation. Therefore, different acids were used instead of AcOH to explore the role of the acid during this reaction. In parallel, the screen of acids was performed at different temperatures. Therefore, (*R*)-BINOL-phosphate, TFA, AcOH were screened at 60, 90, 110 °C. Under all of these conditions, no traces of the desired product **641** or the unexpected tetracyclic product **642** were observed, except when AcOH and (*R*)-BINOL-phosphate were used at 110°C. In case of (*R*)-BINOL-phosphate at 110°C, a partial conversion of lactol towards the formation of tetracyclic core **642** was observed with formation of one diastereoisomer more than the other (Table 5).



Entry	Acid (eq.)	Temperature (°C)	Product 642 (%)	Product 641 (%)
1	AcOH (2.0 eq.)	60	N/A	N/A
2	AcOH (2.0 eq.)	90	N/A	N/A
3	AcOH (2.0 eq.)	110	95 (d.r. 1:1)	N/A
4	AcOH (0.2 eq.)	110	N/A	N/A
5	TFA (0.2 eq.)	60	N/A	N/A
6	TFA (0.2 eq.)	90	N/A	N/A
7	TFA (0.2 eq.)	110	N/A	N/A
8	(<i>R</i>)-BINOL-phosphate (0.2 eq.)	60	N/A	N/A
9	(<i>R</i>)-BINOL-phosphate (0.2 eq.)	90	N/A	N/A
10	(<i>R</i>)-BINOL-phosphate (0.2 eq.)	110	Partial conversion	N/A

Table 5. Acid and temperature Screen for reaction between lactol **639** and tryptamine

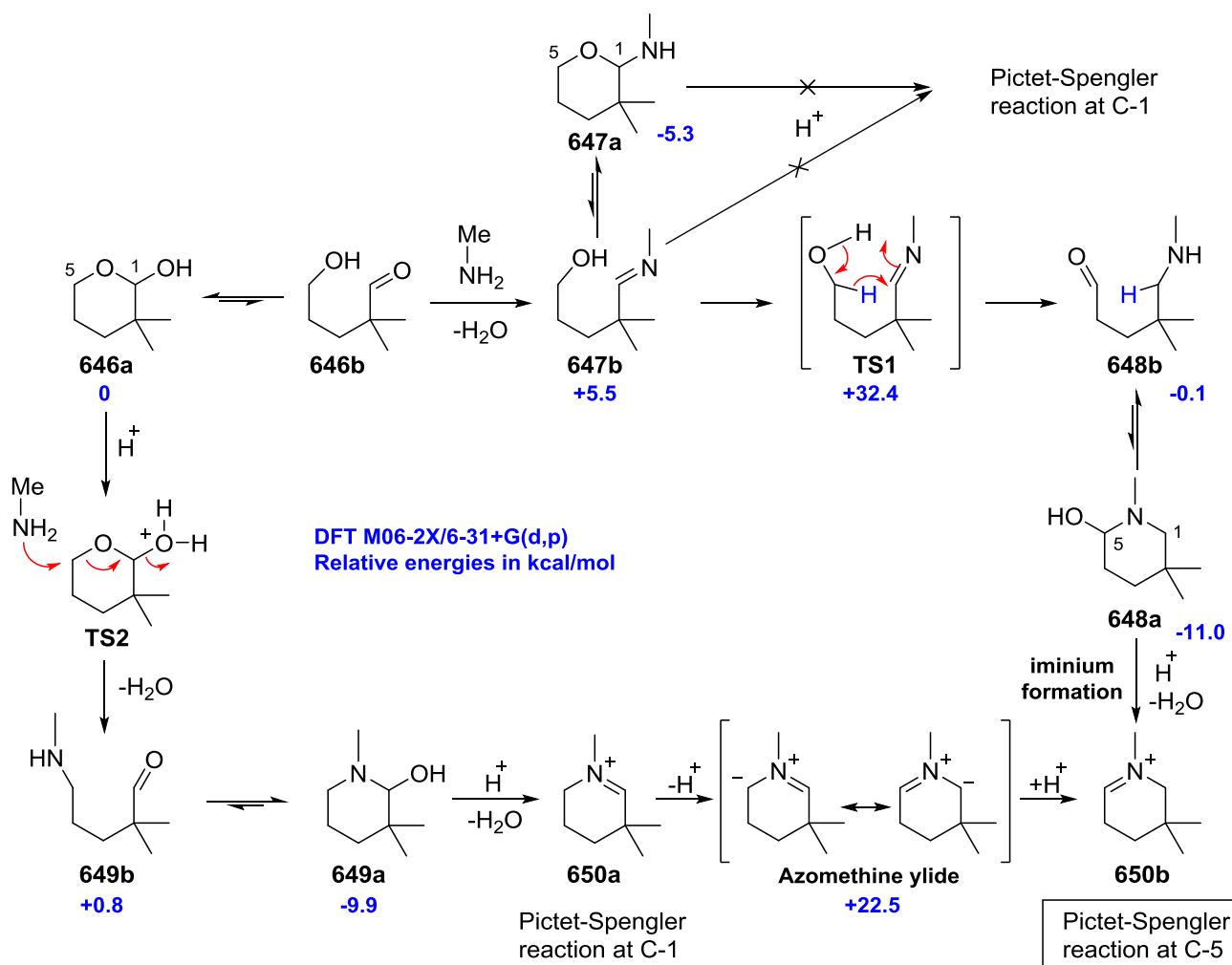
Furthermore, the reaction between benzyl protected tryptamine **644** and lactol **639** under the same conditions than those used in formation of tetracyclic product **642**, did not give the Pictet-Spengler product **645** (Scheme 198).

Scheme 198. Reaction between Benzyl Protected Tryptamine and Lactol **639**.

Based on preliminary DFT studies, performed with a dimethyl lactol model **646a** and methylamine, two viable routes could be possible for explaining this reactivity (Scheme 199). The first pathway would imply the expected formation of the normal iminoalcohol **647b** from the open form of the lactol **646b**. But rather than being involved in a Pictet-Spengler reaction at C-1 (may be for steric reasons), an intramolecular hydride transfer could transform the iminoalcohol into a more stable aminoaldehyde **648b** which can also cyclize in an even more stable hemiaminal **648a**, ready for a Pictet-Spengler reaction at C-5.

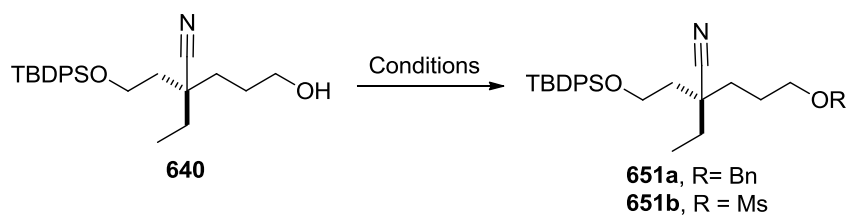
The other possible route would imply of the protonated lactol at C-5 to give the aminoaldehyde **649b** and its cyclized hemiaminal form **649a** (a nucleophilic substitution at the more sterically hindered C-1 would also give **647a**). At this stage, the formation of the iminium would involve a Pictet-Spengler reaction at C-1. A direct thermal 1,3-hydride shift, that would transform the iminium **650a** into **650b**, should be antarafacial thus forbidden. But a deprotonation at the acidic C-5 position of **650a** could form an azomethine ylide which would form the rearranged iminium **650b** by reprotonation at C-1, **650b** being the precursor the observed tetracyclic eburnane **642**. Iminium migrations of this type have been extensively used by Seidel *et al.* in total synthesis in so-called internal-redox Mannich reactions.²³¹ Both routes would be energetically feasible and the process would be governed by the stability increase of the hemiaminal **648a** compared to the other hemiaminal **649a**, both in equilibrium with their corresponding iminiums.

²³¹ (a) Ma, L.; Seidel, D. *Chem. Eur. J.* **2015**, *21*, 12908–12913; (b) Seidel, D. *Acc. Chem. Res.* **2015**, *48*, 317–328.

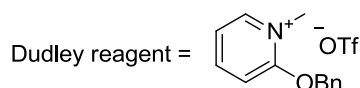
Scheme 199. Proposed Mechanism of Formation of Tetracyclic Core of Eburnane **642**

It was then envisioned that the reaction of tryptamine with the free aldehyde instead of lactol **639** would be more reliable. After an attempt to protect alcohol **640** with a benzyl group using benzyl bromide, the protection was performed with Dudley's benzylation reagent²³² to give the desired benzyl protected alcohol **651a** in 82% yield. The free alcohol **640** was also protected as a mesylate, which might be useful for a potent cyclization with the secondary amine resulting from the Pictet-Spengler reaction (Scheme 200).

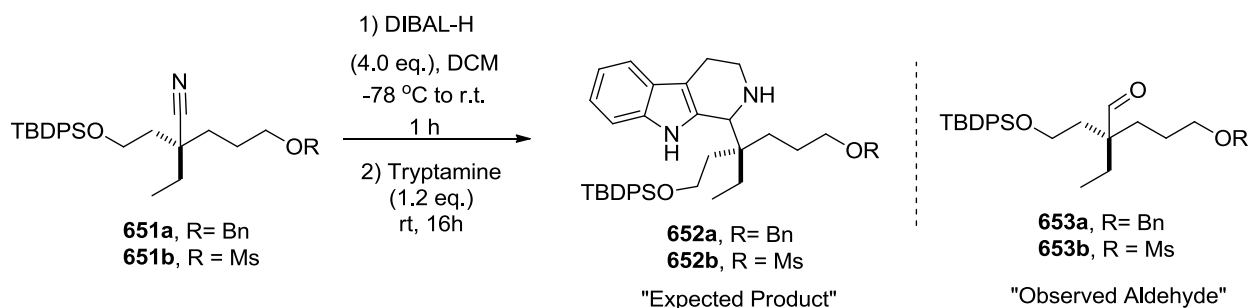
²³² Poon, K. W. C.; House, S. E.; Dudley, G. B. *Synlett* **2005**, 2005, 3142-3144.



Entry	Conditions	Yield (%)
1	BnBr, NaH, THF, 16h	N/A
2	Dudley reagent, MgO (2.0 eq.), DCE, Reflux, 24 h	82
3	MsCl, Et ₃ N, DCM, rt, 3 h	Quant.

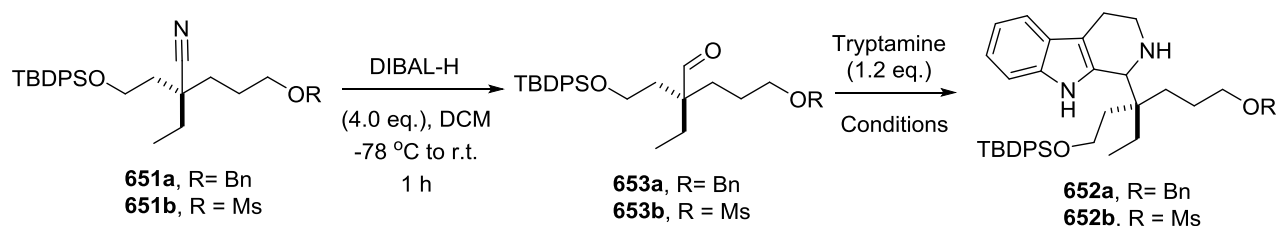
Scheme 200. Protection of Alcohol **640**.

With these protected alcohols in hand and similarly to the previous idea of nitrile reduction / Pictet-Spengler cyclization sequence, the nitrile group in **651a-b** was reduced by DIBAL-H. Then, instead of hydrolyzing the formed imine by water to form aldehyde, this imine was trapped directly by tryptamine to form the tricyclic Pictet-Spengler product **652a-b**. Unfortunately, the desired Pictet-Spengler products **652a-b** were not observed, and only traces of the corresponding aldehydes **653a-b** were detected (Scheme 201).



Scheme 201. Reduction of Nitrile / Pictet-Spengler Cyclization Sequence.

Again a stepwise sequence was developed to give the Pictet-Spengler products **652a-b**. First, nitriles **651a-b** were reduced to aldehydes by DIBAL-H. Our efforts to chromatography the formed aldehyde were not successful. But, the crude aldehyde seemed to be pure enough to undergo the next reaction. Second, aldehydes **653a-b** were allowed to react with tryptamine under the acidic conditions of Pictet-Spengler reaction. The desired products were not observed neither by using TFA at room temperature nor by using AcOH at 110°C.



Entry	Conditions	Yield (%)
1	TFA (2.0 eq.), DCM, 16 h	S.M.
2	AcOH (2.0 eq.), DCM, 16 h	S.M.
3	AcOH (2.0 eq.), Toluene, 110°C, 16 h	S.M.

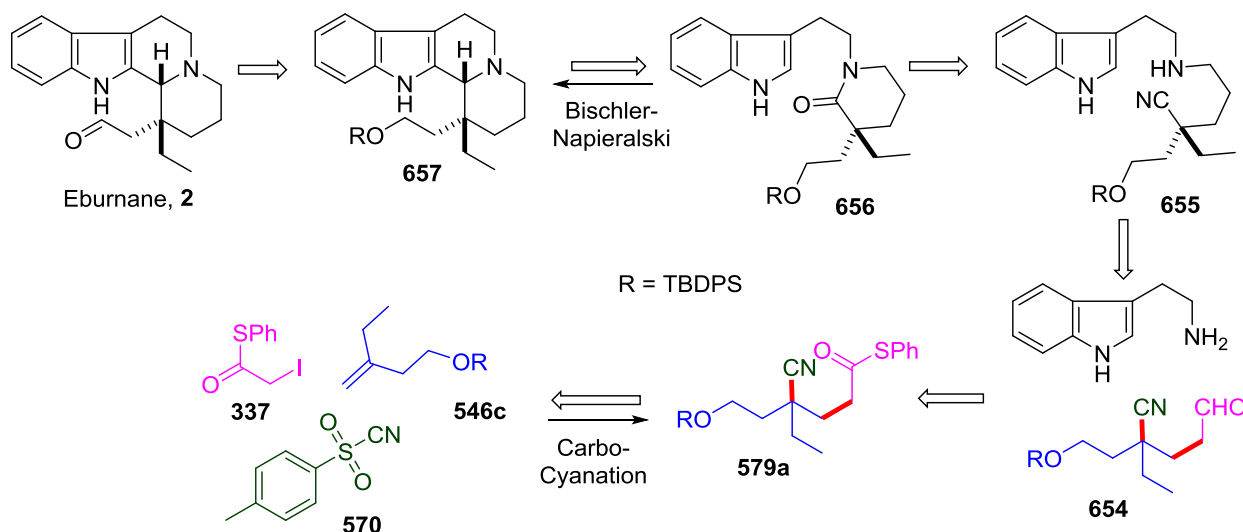
Scheme 202. Reduction of Nitrile by DIBAL-H followed by Pictet-Spengler Cyclization.

These reactions were not successful, which may be due to the presence of DIBAL aluminum residues in the reaction medium, preventing the attack of tryptamine on the aldehyde from occurring. A solution to this problem thus had to be found.

Another pathway to access the eburnane **2** was envisioned relying on the Bischler-Napieralski intramolecular condensation. In the following section the details of this approach will be discussed.

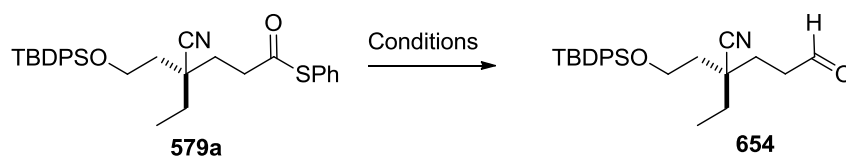
3.5.2. Synthesis of Eburnane through Bischler-Napieralski Approach

In this approach, the same key carbo-cyanation reaction and product **579a** were employed. The nitrile product **579a** bearing a thioester group could undergo a chemoselective reduction of the thioester into the aldehyde **654**. This aldehyde **654** could react with tryptamine under reductive conditions to give the secondary amine **655**, which could cyclize onto the nitrile to give the key amide intermediate **656**. The Bischler-Napieralski intramolecular condensation between this amide and tryptamine indole should hopefully give the desired tetracyclic core of Eburnane **657**. Deprotection of the alcohol, followed by oxidation to aldehyde could give a straightforward sequence to Eburnane **2** (Scheme 203).



Scheme 203. Eburnane Retrosynthesis through Bischler-Napieralski Reaction.

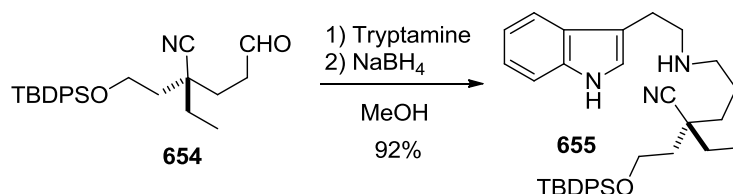
Therefore, the thioester group in the nitrile product **579a** was reduced to the corresponding aldehyde **654** either by Et_3SiH ²³³ or by Bu_3SnH ²³⁴ with a better yield when Et_3SiH was used (Scheme 204).



Entry	Conditions	Yield (%)
1	Et_3SiH (3.0 eq.), Pd/C (5.0 mol%), Aceton, rt, 1 h	75%
2	Bu_3SnH (3.0 eq.), $\text{Pd}[\text{C}_6\text{H}_5_3\text{I}]_4$ (0.4 mol%), Benzene, rt, 16 h	41%

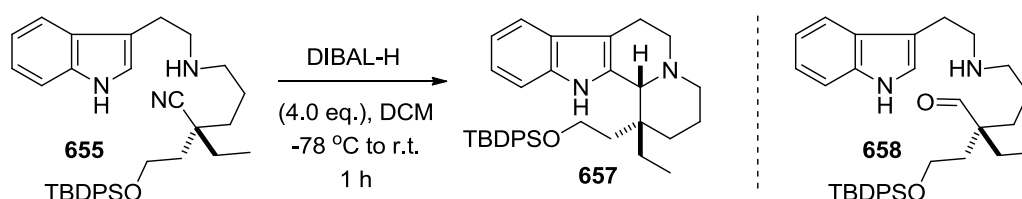
Scheme 204. Reduction of Thioester to aldehyde.

The aldehyde **654** was then allowed to react with tryptamine under reductive conditions to give the secondary amine **655** in 92% yield (Scheme 205).



Scheme 205. Reductive Amination of Tryptamine and Aldehyde **654**.

With this secondary amine **655** in hand, our first approach was to reduce the nitrile group by DIBAL-H to imine and hopefully this imine could be trapped *in situ* by the secondary amine. But unfortunately the desired tetracyclic product **657**, resulting from the Pictet-Spengler cyclization, was not observed. Instead, only traces of the corresponding aldehyde **658** were observed (Scheme 206).



Scheme 206. Reduction of Nitrile **655**.

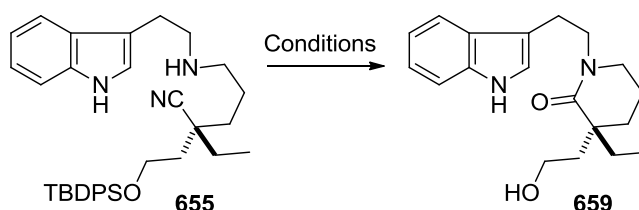
Therefore, the alternative pathway was the cyclization of this secondary amine onto the nitrile group to form the amide **656**. Different reaction conditions were tested to perform this cyclization. Refluxing the nitrile **655** in a mixture of EtOH and H_2O was attempted first.²³⁵ Unfortunately the

²³³ Fukuyama, T.; Lin, S. C.; Li, L. *J. Am. Chem. Soc.* **1990**, *112*, 7050-7051

²³⁴ Kuniyasu, H.; Ogawa, A.; Sonoda, N. *Tetrahedron Lett.* **1993**, *34*, 2491-2494.

²³⁵ Vitry, C.; Vasse, J.-L.; Dupas, G.; Levacher, V.; Quéguiner, G.; Bourguignon, J. *Tetrahedron* **2001**, *57*, 3087-3098.

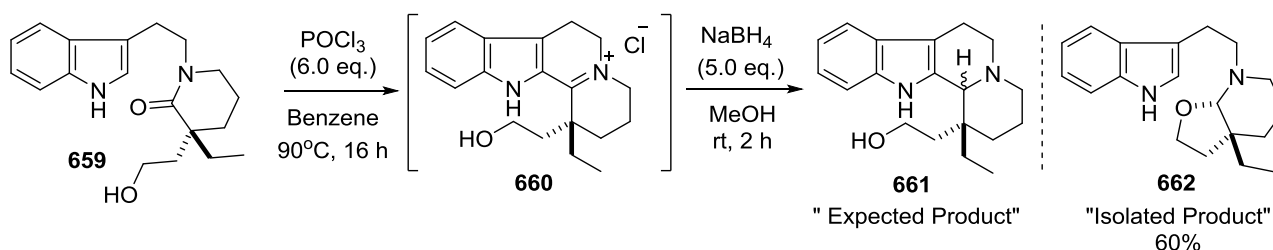
desired amide **656** was not observed and the only isolated product was the starting nitrile **655**. Refluxing the nitrile **655** in mixture of MeOH/H₂O in the presence of LiOH did not give the amide **656** either. Finally, refluxing the nitrile **655** in a mixture of HCl / MeOH (2/1) gave the desired amide group but with deprotection of the silyl ether group under these harsh acidic conditions. Consequently, the hydroxy-lactam **659** was isolated in 65% yield (Scheme 207).²³⁶ The reaction went probably through hydrolysis of the nitrile into a primary amide or an acid, which then reacted with secondary amine to form the amide product.²³⁷



Entry	Conditions	Yield (%)
1	EtOH/H ₂ O (95/5), 80°C, 48 h	S.M.
2	LiOH (excess), MeOH/H ₂ O (2/1), rt, 6 days	S.M.
3	HCl/MeOH (2/1), 70°C, 16 h	65%

Scheme 207. Cyclization of 2nd Amine into Nitrile.

The cyclic amide was thus ready for the Bischler-Napieralski intramolecular condensation, which is usually mediated by POCl₃ to form a tetracyclic intermediate imine **660**, followed by its reduction by NaBH₄. Therefore hydroxyl lactam **659** was subjected to Bischler-Napieralski reaction conditions, but unfortunately, instead of isolating the tetracyclic alcohol **661**, the only isolated product was hemiaminal **662** (Scheme 208).

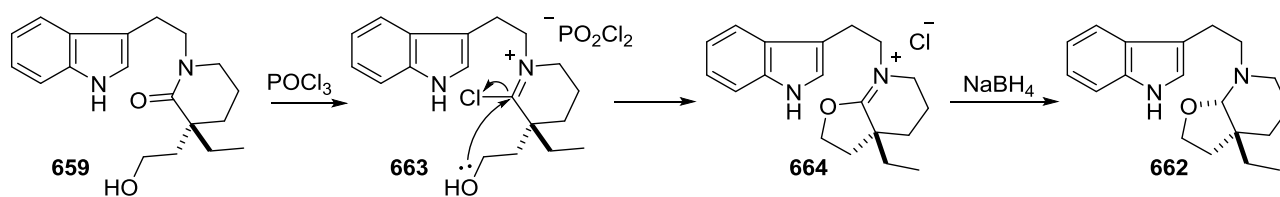


Scheme 208. Bischler-Napieralski Reaction on Lactam **659** and Formation of Hemiaminal **626**

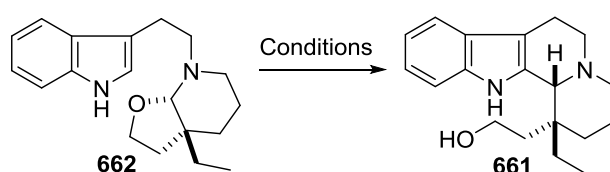
The hemiaminal **662** was probably generated from chloroiminium **663** formed through reaction of amide **659** with POCl₃. Chloroiminium **663** could be trapped by the free alcohol faster than the tryptamine indole (Scheme 209). After reduction of iminium **664** by NaBH₄, the hemiaminal **662** could be formed. This side reaction has already been observed by Schultz and Pettus.¹⁹⁵

²³⁶ Lounasmaa, M.; Miikki, L.; Tolvanen, A. *Tetrahedron* **1996**, *52*, 9925-9930.

²³⁷ Li, X.; Li, Z.; Deng, H.; Zhou, X. *Tetrahedron Lett.* **2013**, *54*, 2212-2216.

Scheme 209. Proposed Mechanism of Formation of Hemiaminal **662**.

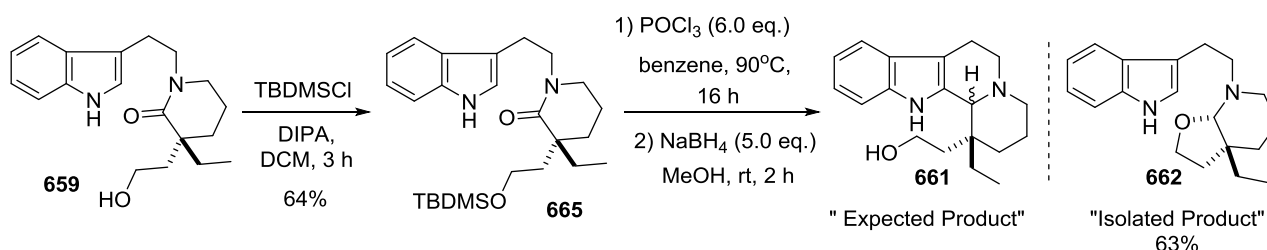
Our efforts to open hemiaminal **662** and form the hydroxyl-free tetracyclic core **661** were not successful, neither by refluxing in toluene in the presence of acetic acid, nor by using TMSOTf. Instead, decomposition of the starting hemiaminal was observed under these conditions (Scheme **210**).



Entry	Conditions	Yield (%)
1	AcOH (2.0 eq.), Toluene, 110 °C, 72 h	N/A
2	TMSOTf (3.0 eq.), DCM, rt, 16 h	N/A

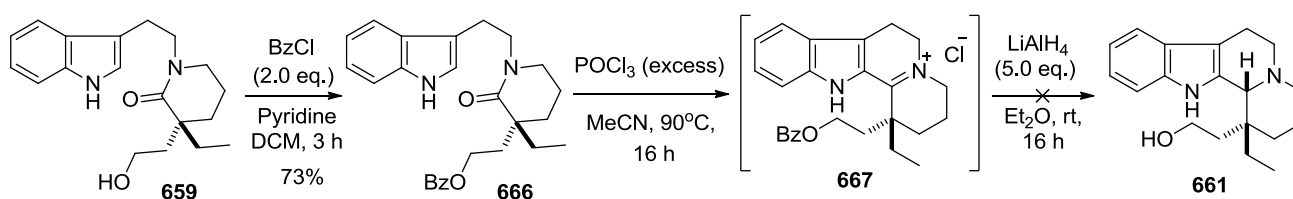
Scheme 210. Trials to open Hemiaminal **662**.

Therefore, to avoid the formation of the undesired hemiaminal **662**, the free alcohol **659** was protected before applying Bischler-Napieralski reaction conditions. First, the free alcohol **659** was protected as a TBDMS ether. The idea here was to protect the free alcohol temporarily during the Bischler-Napieralski reaction, this group being then removed under the harsh reaction conditions to give the desired hydroxyl-free tetracyclic core. But unfortunately, the deprotection of silyl ether group was faster than the Bischler-Napieralski cyclization and again the hemiaminal **662** was the major isolated product (Scheme **211**).

Scheme 211. Protection by TBDMSCl / Bischler-Napieralski Reaction of Lactam **665**.

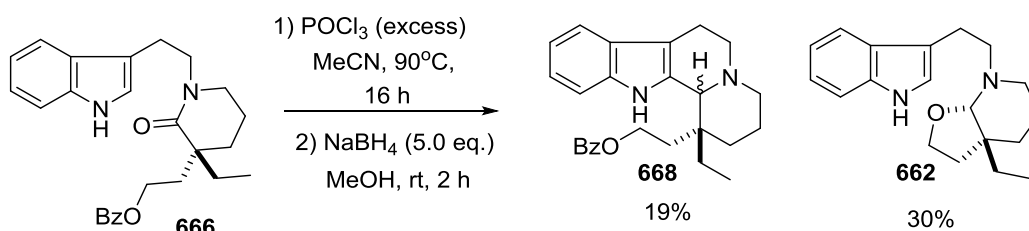
It was then envisioned that the free alcohol **659** should be protected with a stronger protecting group. A benzoate protecting group was thus designed as it is quite stable under acidic conditions and most importantly, it could be removed during the reduction of Bischler-Napieralski iminium and

give the desired free alcohol. Hydroxy lactam **659** was thus protected as a benzoate, and the Bischler-Napieralski reaction conditions applied to form iminium **667**, the latter being then reduced by excess LiAlH_4 to remove the benzoate protecting group. Unfortunately, the reaction did not work and only degradation was observed under these conditions (Scheme **212**).



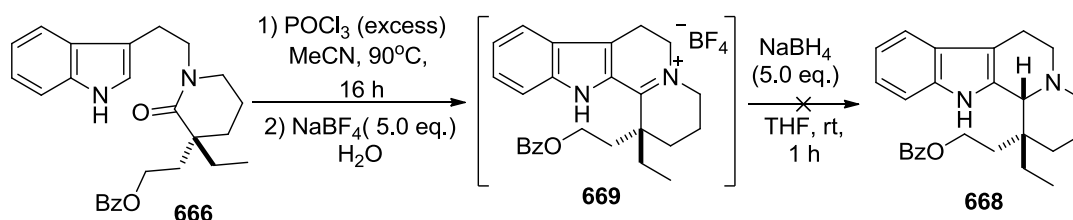
Scheme **212**. Protection By BzCl / Bischler-Napieralski Reaction of Lactam **666**.

Then, the standard Bischler-Napieralski reaction conditions were applied on the benzoate protected hydroxy lactam **666**. Lactam **666** was thus refluxed with POCl_3 in MeCN for 16 h, followed by reduction of the generated imine by NaBH_4 to give the desired tetracyclic core of Eburnane **668** in 19%, along with hemiaminal **662** in 30% (Scheme **213**).



Scheme **213**. Bischler-Napieralski Reaction of Lactam **666**.

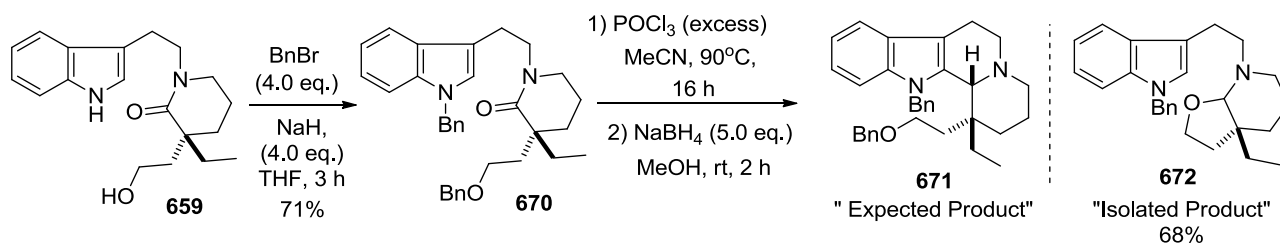
The hemiaminal **662** was probably formed due to the partial deprotection of the benzoate under the highly acidic POCl_3 -mediated cyclization conditions. Our efforts to increase the yield of tetracyclic core **668** and avoid the formation of hemiaminal **662** were not successful. Thus, isolation of the iminium **667** by treating it with NaBF_4 then reduction of this imine by NaBH_4 in THF did not improve the yield at all (Scheme **214**).¹⁹⁹



Scheme **214**. Bischler-Napieralski Reaction of Lactam **666** / Isolation and reduction of imine.

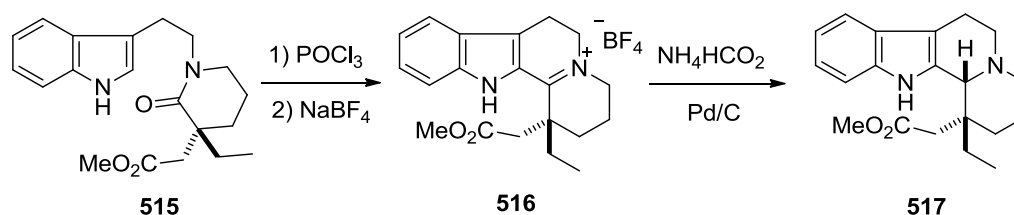
The protecting group was then changed for a more robust one. The benzyl protecting group was thus used instead of a benzoate. Thus, treating hydroxy lactam **659** with BnBr protected both the alcohol function and the indole NH. Bischler-Napieralski reaction conditions were applied again on the

benzyl protected lactam **670**, but unfortunately, the only isolated product was the hemiaminal **672** (Scheme 215).



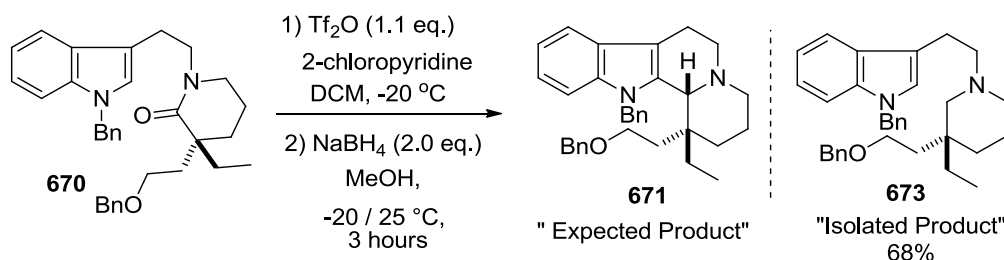
Scheme 215. Protection By BnBr / Bischler-Napieralski Reaction of Lactam **670**

The formation of hemiaminal **672** also resulted from the deprotection of the benzyl alcohol **670** and attack of the free alcohol on the iminium intermediate. Westwood *et al.*¹⁹⁹ performed this Bischler-Napieralski / reduction sequence with methyl ester group **515** in the position of the protected alcohol (Scheme 216). The presence of a methyl ester group in this position is likely more compatible with HCl released during POCl₃-mediated cyclizations.



Scheme 216. Bischler-Napieralski / Reduction Sequence of Westwood.

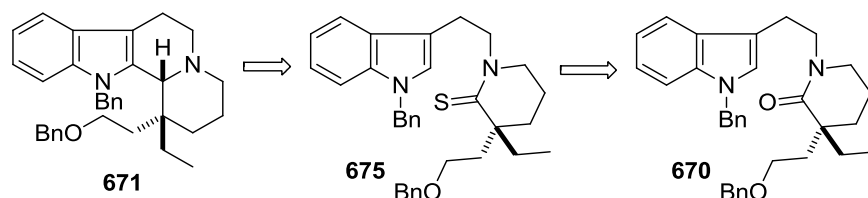
Another method was envisioned to obtain the desired tetracyclic core of eburnane. Instead of using POCl₃, which produces a very acidic medium under high temperatures, triflic anhydride could react with amide **670** to form an iminium triflate which hopefully could be trapped by tryptamine.²³⁸ Amide **670** was thus treated with triflic anhydride in the presence of 2-chloropyridine, followed by addition of NaBH₄ to reduce the generated iminium. Unfortunately, the only isolated product was **673** which resulted from the reduction of the iminium triflate (Scheme 217).



Scheme 217. Cyclization of amide **670** by Tf₂O.

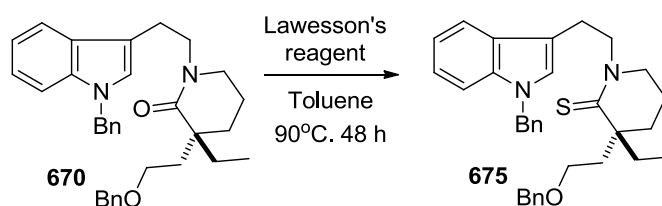
²³⁸ (a) Nicolaou, K. C.; Dalby, S. M.; Majumder, U. *J. Am. Chem. Soc.* **2008**, *130*, 14942-14943; (b) Chen, Z.; Zhou, S.; Jia, Y. *J. Org. Chem.* **2015**, *80*, 12545-12551.

These different attempts thus showed how hard is the cyclization of this lactam. This difficulty may be attributed to the steric hindrance around the amide bond. Another approach for the cyclization was thus planned, involving the conversion of the amide **670** to a thioamide **675**, followed by formation of iminium by sulfur alkylation. The tetracyclic core of Eburnane **671** could then be accessed after reduction of the final iminium (Scheme **218**).



Scheme **218**. Retrosynthesis based on thioamide **675**.

Therefore, amide **670** was refluxed with Lawesson's reagent in toluene.²³⁹ Unfortunately, the corresponding thioamide **675** was not observed and the only isolated product was the starting material (Scheme **21**).

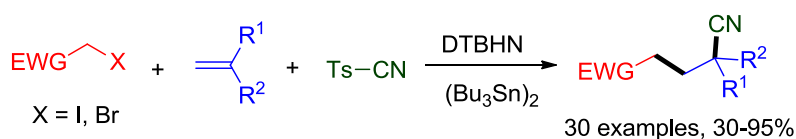


Scheme **219**. Reaction of amide **670** with Lawesson's reagent.

²³⁹ Kirillova, M. S.; Muratore, M. E.; Dorel, R.; Echavarren, A. M. *J. Am. Chem. Soc.* **2016**, *138*, 3671-3674.

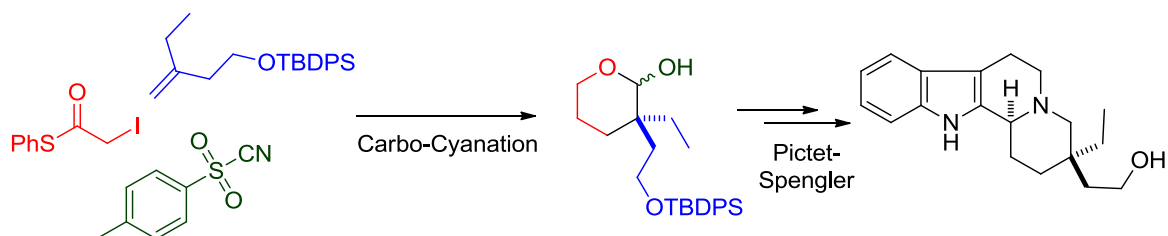
3.6. Conclusion

In summary, during the course of the total synthesis of the Leucophyllidine's north fragment, Eburnane **2**, the key carbo-oximation reaction assigned for this total synthesis showed some limitations, mainly due to steric factors. Consequently, a novel free-radical carbo-cyanation process was developed, which showed better yields and a higher tolerance for the substitution of the different radical precursors and olefins. The small size of the nitrile helped in the development of the carbo-cyanation process with different chiral allylsilanes, bicyclic systems and terpenes. This process could also be used in the elaboration of cyclic and acyclic systems bearing fully functionalized quaternary centers in very good yields.



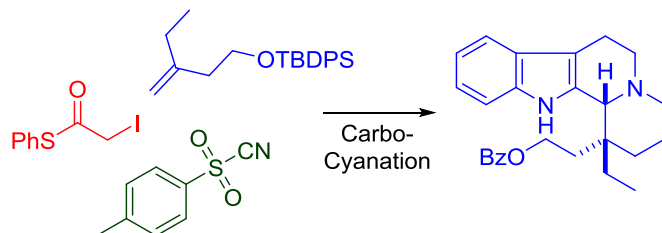
Scheme 220. Carbo-cyanation MCR.

Relying on this carbo-cyanation process, two different approaches were developed to access the Eburnane core. The first one, through Pictet-Spengler reaction, ended up with the unexpected formation of an eburnane-like tetracyclic core with a quaternary center away from the indole ring.



Scheme 221. Unexpected Formation of an Eburnane-like Tetracyclic Core.

While the second approach, based on the Bischler-Napieralski reaction, afforded an access to the eburnane skeleton albeit in low and non-reproducible yield.



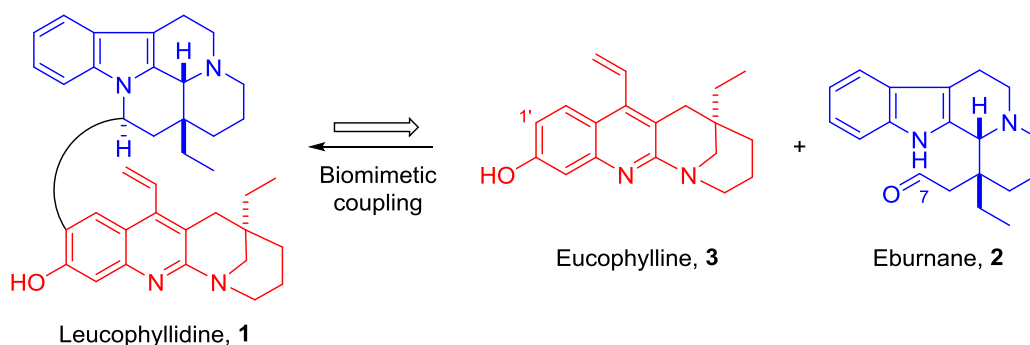
Scheme 222. Elaboration of Eburnane through Bischler-Napieralski Reaction.

Chapter Four

Preliminary Results on Biomimetic Coupling

4.1. Introduction

Since the three components Leucophyllidine **1**, Eburnane **2** and Eucophylline **3** are all present in the plant, the biogenetic analysis proposed by Kam *et al.*¹, then assumed that a coupling between the two monomers, Eburnane **2** and Eucophylline **3**, will likely issue Leucophyllidine **1**. This is the focal point in our retrosynthesis analysis of Leucophyllidine. Coupling the north fragment, Eburnane, and the south fragment, Eucophylline, will hopefully afford the unique bisindole structure of Leucophyllidine. This coupling will proceed through a Mannich type reaction between the C-7 electrophilic center of Eburnane and C-1' electron-rich center of Eucophylline.

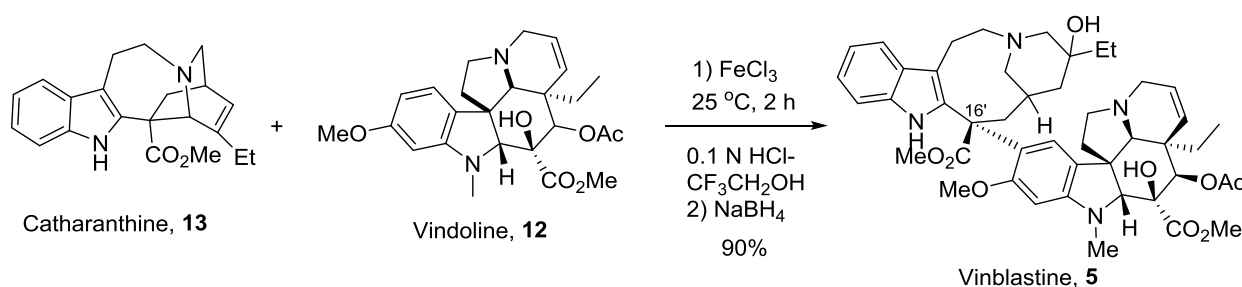


Scheme 223. Retrosynthesis of Leucophyllidine.

In general, biomimetic couplings in these types of natural products have received modest attention. Only few syntheses were designed relying on the biomimetic couplings in synthesis of bisindole-like structures. In the following part a literature survey about biomimetic couplings in synthesis of natural products will be highlighted.

4.2. Biomimetic Coupling in Synthesis of Natural Products

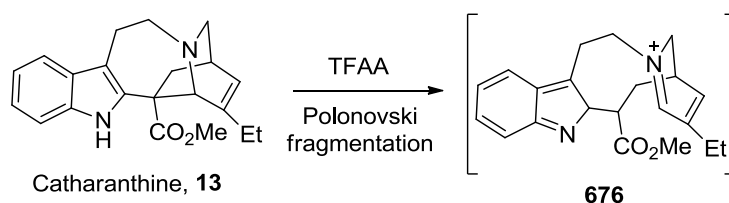
The synthesis of Vinblastine **5** constitutes one of the most well-known syntheses, relying on a biomimetic coupling between two monomeric alkaloids. Boger *et al.*²⁴⁰ thus developed Fe(III) mediated-coupling of Catharanthine **13** and Vindoline **12**, to provide a straightforward and biomimetic access to Vinblastine **5** (Scheme 224).



Scheme 224. Biomimetic Approach of Total Synthesis of Vinblastine.

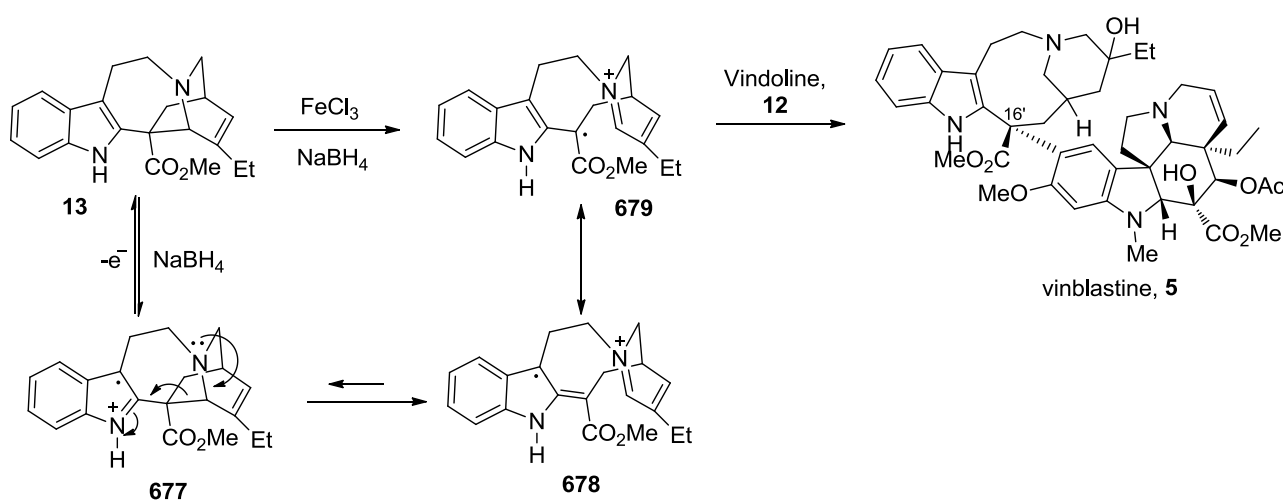
²⁴⁰ Ishikawa, H.; Colby, D. A.; Seto, S.; Va, P.; Tam, A.; Kakei, H.; Rayl, T. J.; Hwang, I.; Boger, D. L. *J. Am. Chem. Soc.* **2009**, *131*, 4904-4916.

Since the introduction of this coupling reaction by Potier and Kutney,²⁴¹ some features of the mechanism were not well understood. For instance, The Fe(III)-promoted coupling reaction displays high stereochemical selectivity, producing exclusively the natural diastereomer, which could not be rationalized based on the traditional Polonovski fragmentation (Scheme 225).²⁴²



Scheme 225. Polonovski Fragmentation.

The initial studies on the mechanism of this coupling revealed that it is a free-radical oxidation reaction. The reaction is initiated by generation of an electrophilic radical in catharanthine **13** fragment. This radical is generated by a single electron oxidation of the indole ring by the Fe(III) salt. An intramolecular one-electron-two center bonding interaction between the radical site α to the carbomethoxy group and the iminium carbon may stabilize a conformation in which the upper face of the radical is sterically blocked. Hence, addition of this radical to electron-rich vindoline will lead exclusively to the formation of the natural stereoisomer. This proposal suggests that the initial indole radical cation **677** and its fragmented cation radical **678** possess a unique stability, persistence, electrophilic character, and conformational properties to effectively react selectively with vindoline (Scheme 226).²⁴³



Scheme 226. Proposed Mechanism for Vinblastine Biomimetic Coupling.

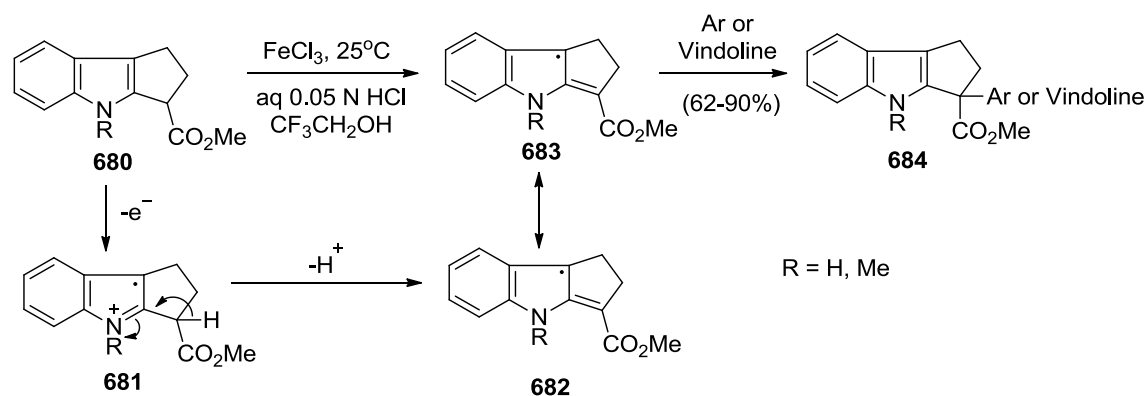
This mechanism was built based on initial results obtained from the mechanistic model study on simplified indoles **680**. In Catharanthine **13**, the free indole NH would be required. The reaction is

²⁴¹ Vukovic, J.; Goodbody, A. E.; Kutney, J. P.; Misawa, M. *Tetrahedron* **1988**, *44*, 325-331.

²⁴² Langlois, N.; Gueritte, F.; Langlois, Y.; Potier, P. *J. Am. Chem. Soc.* **1976**, *98*, 7017-7024.

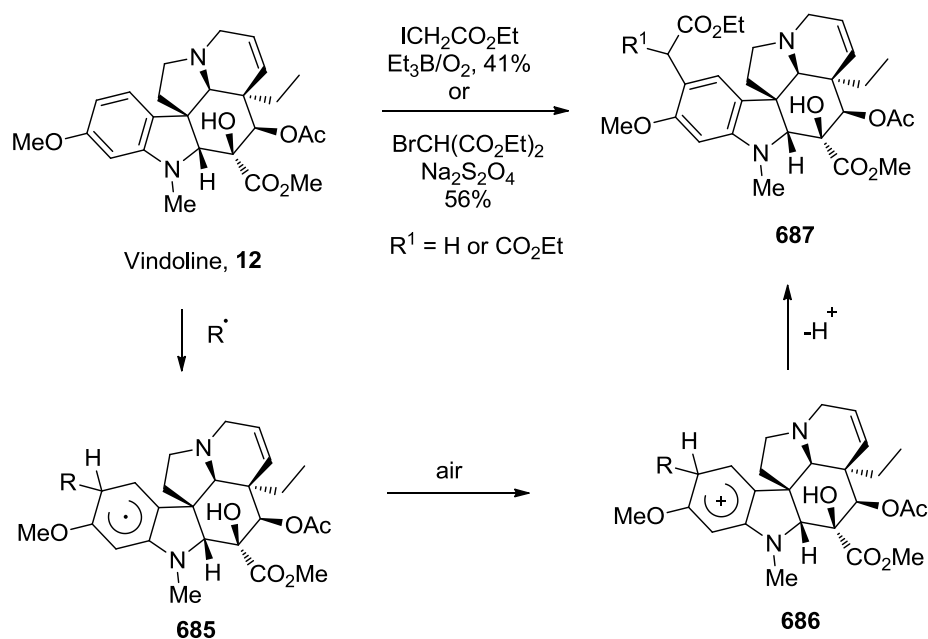
²⁴³ Gotoh, H.; Sears, J. E.; Eschenmoser, A.; Boger, D. L. *J. Am. Chem. Soc.* **2012**, *134*, 13240-13243.

proceeding through a neutral azabenzofulvene. The protonation of the tertiary amino group may stop its competitive single electron oxidation. In contrast, in the case of simplified indoles **680**, the coupling with electron-rich aromatics, or with Vindoline, afforded the expected coupling products in good yields, which indicates that removal of the tertiary amino group as well as *N*-methylation did not preclude coupling with Vindoline **12** (Scheme 227). All of these observations indicate that Fe(III)-mediated oxidation is sufficient for the coupling reaction to occur and reveal that the reaction does not require the presence of the indole free NH or the participation of Catharanthine tertiary amino group. Therefore, since the reaction no longer requires the reduction of catharanthine-derived iminium ion in the reaction product, NaBH₄ is no longer required for the reductive workup of this reaction. For sure, in the case of simplified indoles **680**, the reaction provided a mixture of diastereomer, which confirms that the C16' stereochemistry set in vinblastine Fe(III)-promoted coupling reaction is principally controlled by Catharanthine.

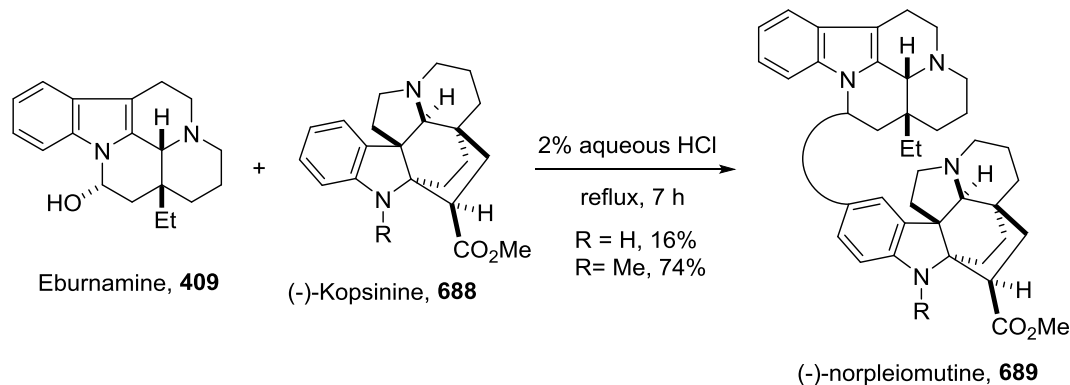


Scheme 227. Mechanistic Model study on Fe(III)-promoted Coupling.

Moreover, it was confirmed that Vindoline **12** is susceptible to aromatic substitution by electrophilic carbon radicals. Treatment of Vindoline **12** with the radical generated from radical precursor ICH₂CO₂Et or BrCH(CO₂Et)₂ gave the aromatic substitution products **687**, arising from the addition of the electrophilic radical to vindoline aromatic ring, followed by rearomatization through air oxidation (Scheme 228). The electrophilic radical substitution reaction of Vindoline **12** in protic solvents supported the fact that Fe(III)-promoted reactions with Catharanthine in water follow a radical pathway rather than a route involving an azabenzofulvene intermediate, as previously suggested.

Scheme 228. Electrophilic Radical Substitution Reaction of Vindoline **12**.

In 1985, Magnus and Brown developed a biomimetic coupling reaction between Eburnamine **409** and (-)-Kopsinine **688** by refluxing the two fragments in 2% aqueous HCl to afford the bisindole alkaloid, (-)-norpleiomutine **689** (Scheme 229).²⁴⁴

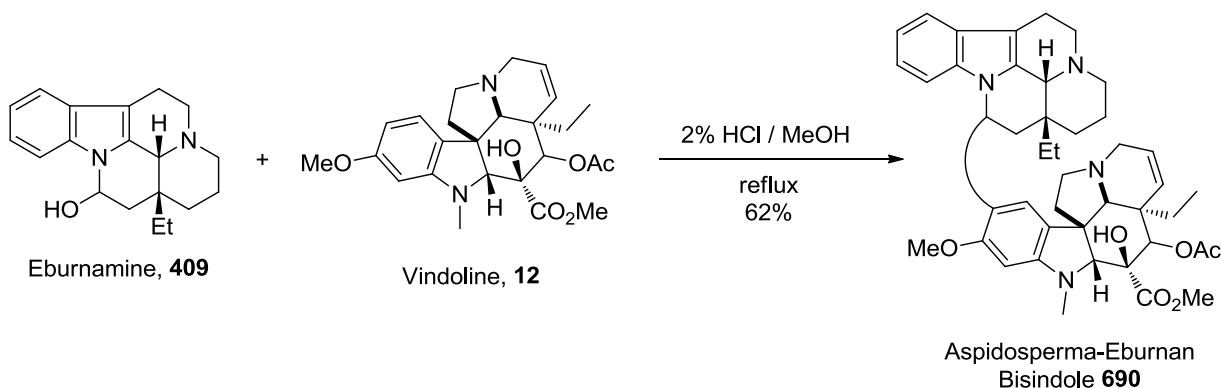


Scheme 229. Biomimetic Coupling in (-)-norpleiomutine.

In 1993, Szántay *et al.*²⁴⁵ also developed a biomimetic coupling between Eburnamine **409** and Vindoline **12** in a mixture of HCl / MeOH to give the Aspidosperma-Eburnane Bisindole **690** (Scheme 230). In this example, the authors showed the possibility to couple two different alkaloidal monomers to form a non-natural bisindole structure, which suggests a generality for this type of biomimetic couplings.

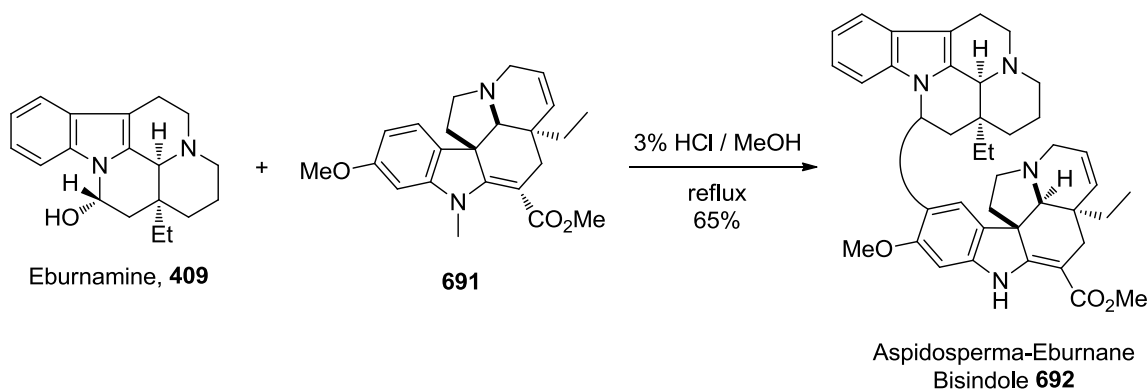
²⁴⁴ Magnus, P.; Brown, P. *J. Chem. Soc., Chem. Commun.* **1985**, 184-186

²⁴⁵ Honty, K.; Szántay, C. Jr.; Kolonits, P.; Demeter, Á.; Szántay, C. *Tetrahedron* **1993**, 49, 10421-10426.



Scheme 230. Szántay Biomimetic Coupling.

In 1994, Passarella *et al.*²⁴⁶ developed a biomimetic coupling between eburnamine **409** and 11-methoxytabersonin **691** in the course of a model study to access modified Vinblastine-type antitumor alkaloids. The coupling was performed in 3% HCl / MeOH solution to give the binary alkaloid **692** in 65% yield (Scheme 231).

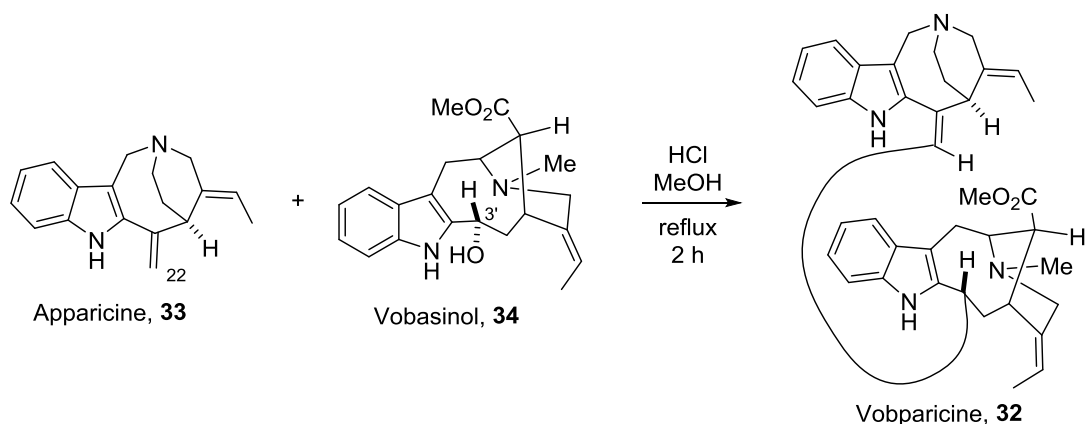


Scheme 231. Passarella Biomimetic Coupling.

Despite the apparent complexity of these biomimetic couplings, they may be very easy in some cases. For example, Vobparicine **32** results from the union of the two monoterpene indole alkaloids, Apparicine **33** and Vobasinol **34**. Thus, treatment of Vobasinol with an excess of Apparicine under acidic conditions effectively led to Vobparicine (Scheme 232).²⁴⁷ The coupling was speculated to occur through the reaction between the C-3' electrophilic center of Vobasinol and the C-22 electron-rich center of Apparicine.

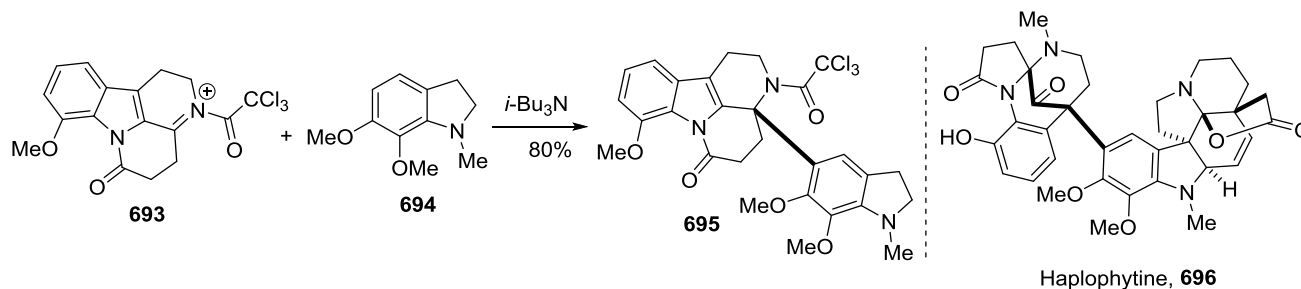
²⁴⁶ Danieli, B.; Lesma, G.; Palmisano, G.; Passarella, D.; Pyuskyulev, B.; Ngoc, T. M. *J. Org. Chem.* **1994**, *59*, 5810-5813.

²⁴⁷ Van Beek, T. A.; Verpoorte, R.; Baerheim Swenden, A. *Tetrahedron Lett.* **1984**, *25*, 2057-2060.



Scheme 232. Biomimetic Coupling of Vobparicine

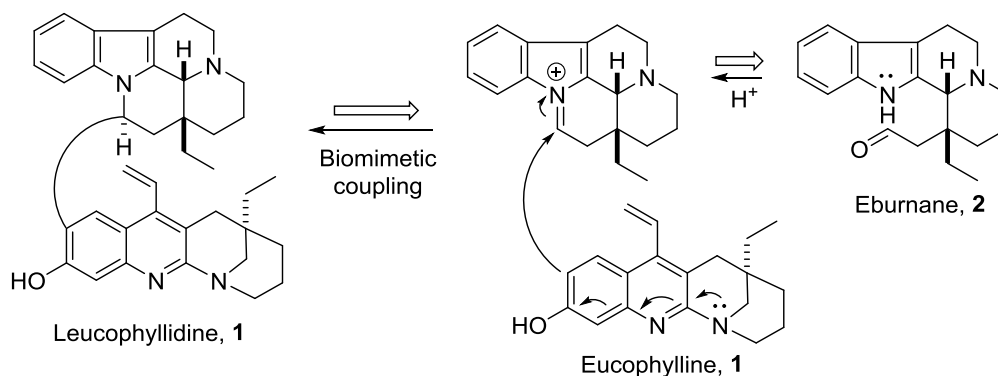
In the course of the total synthesis of Haplophytine **696**, Corey and his coworkers investigated coupling models between electron-rich arenes and Canthiphytine derivatives (Scheme 233).²⁴⁸ Several trials finally showed that biomimetic coupling is not operative to generate the benzylic quaternary center under the studied conditions, pointing out the difficulties in finding proper conditions to initiate this sterically unfavorable coupling.



Scheme 233. Model Study on Biomimetic approach to access Haplophytine.

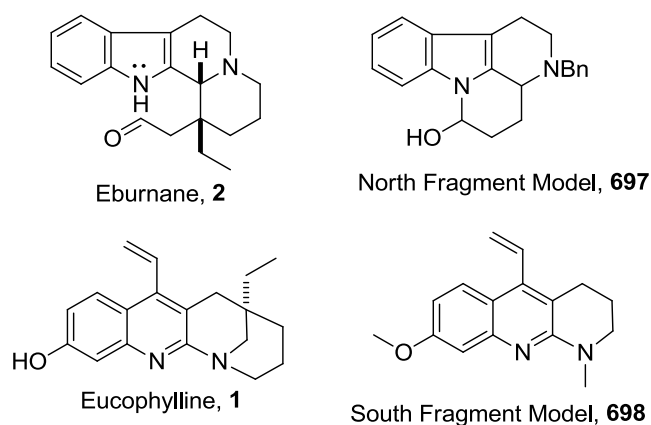
From the aforementioned examples and based on the retrosynthesis analysis of Leucophyllidine, the final step in the total synthesis of this bisindole alkaloid **1** will be the biomimetic coupling between the Eburnane **2** and Eucophylline **3**, which would involve a direct Mannich-type coupling between the *ortho*-phenol moiety of Eucophylline **3** and a putative iminium generated from the north Eburnane **2** (Scheme 234).

²⁴⁸ Rege, P. D.; Tian, Y.; Corey, E. J. *Org. Lett.* **2006**, *8*, 3117-3120.

Scheme 234. Proposed Biomimetic Coupling in Leucophyllidine **1**.

The regioselectivity of the process should be governed both by the *ortho*-phenol group, and by the strongly donating ability of the aminoquinoline moiety (Scheme 234). The stereocontrol arising during the biomimetic coupling will be studied carefully. It is believed that the stereochemistry of the newly created stereogenic center should be governed by the torsional effects generated at the transition state through the CH₂ moiety adjacent to the iminium. Approach of the Eucophylline **3** from the top face of the iminium intermediate, *syn* to the ethyl group on the quaternary center, leads to a staggered conformation, providing the new stereocenter with the desired configuration. *A priori*, this approach is similar to what is observed during the biosynthesis of these alkaloids. In contrast, the approach from the bottom face suffers from torsional strain.

Therefore, to save the available and valuable amounts of Eburnane and Eucophylline, the feasibility of this biomimetic coupling approach will be investigated firstly through models **697**, **698** which are very similar to the north fragment, Eburnane, and south fragment, Eucophylline, respectively (Scheme 235). These models will be tested under several reaction conditions, for which exist some precedents in the literature. These preliminary experiments should provide further insight into the regio- and stereoselectivity of the final coupling. These studies will also provide information on the stability of the Eucophylline vinyl moiety under the coupling reaction conditions (and ultimately indicate if this group must be installed before or after the coupling). Based on these results, the coupling between Eburnane **2** and Eucophylline **3** will be performed to furnish the natural Leucophyllidine **1**.

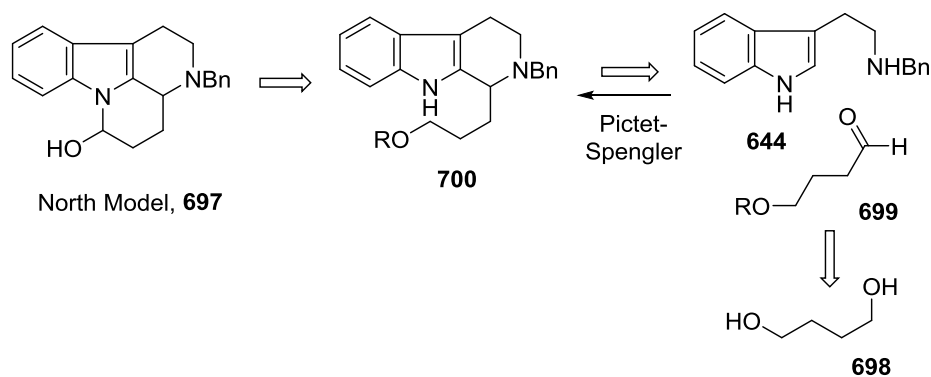
Scheme 235. North and South Models **697**, **698**.

In the following section, synthesis of the north fragment model **697** and the south one **698** will be discussed firstly, before presentation of preliminary results on the biomimetic coupling approach.

4.3. Synthesis of North Fragment Model.

4.3.1. Through Pictet-Spengler Reaction.

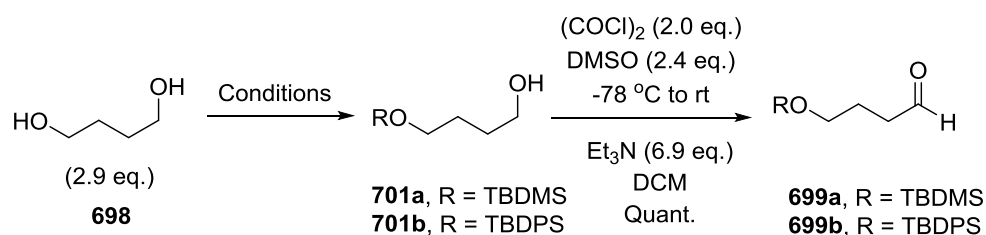
The north model **697** was designed to be very similar to the Eburnane **2** and could be accessed in a short and straightforward sequence. Therefore, the retrosynthesis analysis of this model will not differ so much from the one proposed for Eburnane **2**. Thus, the tetracyclic model **697** could be accessed through a base-mediated cyclization of the tricyclic Pictet-Spengler product **700**, which in turn could be accessed from Pictet-Spengler reaction between benzyl protected tryptamine **644** and aldehyde **699**. This aldehyde **699** could be accessed from the corresponding commercially available diol **698** (Scheme 236).



Scheme 236. Retrosynthesis Analysis of North Model through Pictet-Spengler .

The starting point was the synthesis of aldehyde **699**. Commercially available diol **698** was mono-protected as TBDMS or TBDPS groups, followed by Swern oxidation of the free alcohol to give

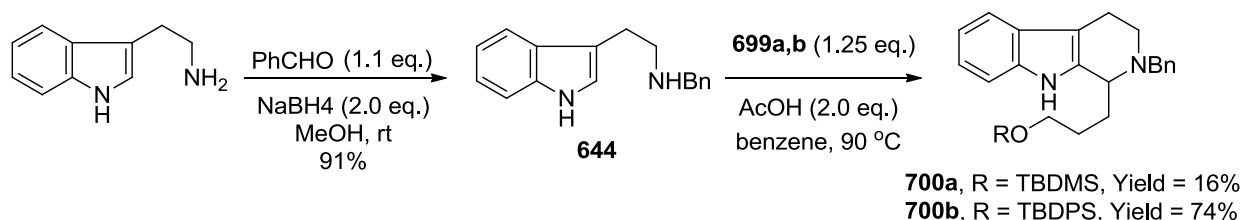
aldehydes **699a-b** (Scheme 237).²⁴⁹ It is worth noticing that, the purification of these aldehydes through column chromatography was not successful, however the crude product is pure enough to be used in the next step without further purifications.



Entry	Conditions	Yield (%)
1	TBDMSCl (1.0 eq.), DIPA (3.16 eq.), DCM, rt, 3 h	68%
2	TBDMPCl (1.0 eq.), DIPA (3.16 eq.), DCM, rt, 3 h	73%

Scheme 237. Preparation of Aldehydes **699a,b**.

In the meantime, the tryptamine NH_2 was protected by a benzyl group under reductive conditions to give the benzylated tryptamine **644** (Scheme 238).²⁵⁰ The latter was allowed to react with aldehydes **699a-b** under Pictet-Spengler reaction conditions to give the tetrahydro- β -carboline **700a-b** (scheme 236).²⁵¹ It was noticed that in case of $\text{R} = \text{TBDMS}$, the yield was quite modest. This was attributed to degradation of the silyl ether group during the silica chromatography of the product.

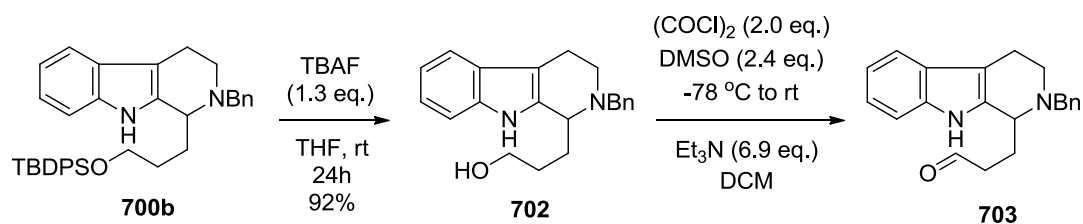
Scheme 238. Pictet-Spengler reaction with Aldehydes **699a,b**.

Then, to elaborate the tetracyclic model **697**, the removal of silyl ether group from **700b** was performed with TBAF, followed by oxidation of the so-formed free alcohol **702** to aldehyde through a Swern reaction. Unfortunately, the oxidation step was not successful and instead a degradation of the product **703** was observed (Scheme 239).

²⁴⁹ Commandeur, M.; Commandeur, C.; Cossy, J. *Org. Lett.* **2011**, *13*, 6018-6021.

²⁵⁰ Huang, D.; Xu, F.; Lin, X.; Wang, Y. *Chem. Eur. J.* **2012**, *18*, 3148-3152.

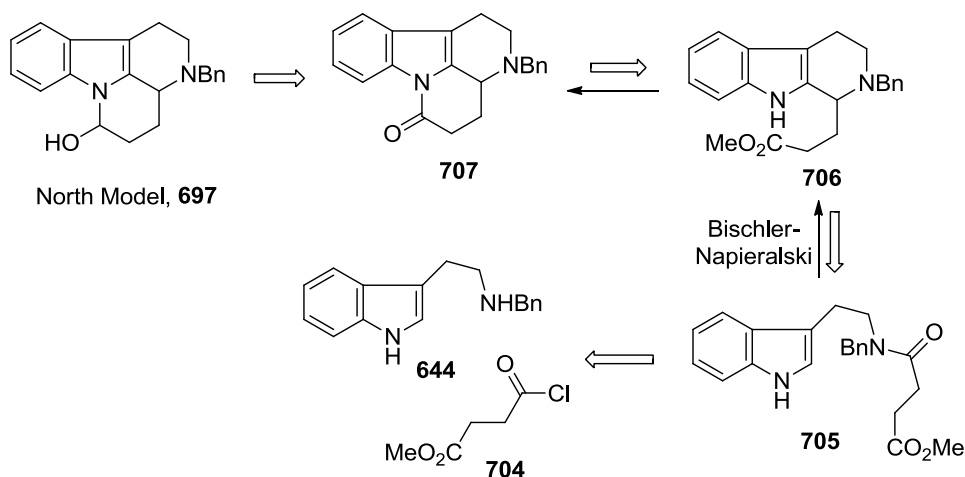
²⁵¹ (a) Soe, T.; Kawate, T.; Fukui, N.; Nakagawa, M. *Tetrahedron Lett.* **1995**, *36*, 1857-1860; (b) Sewgobind, N. V.; Wanner, M. J.; Ingemann, S.; de Gelder, R.; van Maarseveen, J. H.; Hiemstra, H. *J. Org. Chem.* **2008**, *73*, 6405-6408.

Scheme 239. Deprotection and Oxidation of **700b**.

At that point, and to save time and materials, another easier and shorter pathway to access this tetracyclic model **697** was envisioned. In the following section the synthesis of model **697** through Bischler-Napieralski reaction will be discussed.

4.3.2. Through Bischler-Napieralski Reaction

In this approach, the tetracyclic Model **697** was accessed based on the Bischler-Napieralski condensation between the amide group and the tryptamine indole in compound **705**. This amide could be accessed through the reaction between the benzyl protected tryptamine **644** and the commercially available acid chloride **704**. After construction of the tricyclic core **706**, the base mediated cyclization of indole NH into the methyl ester group will afford the tetracyclic lactam **707** which should be easily reduced to the corresponding tetracyclic amino-alcohol **697** (Scheme 240).

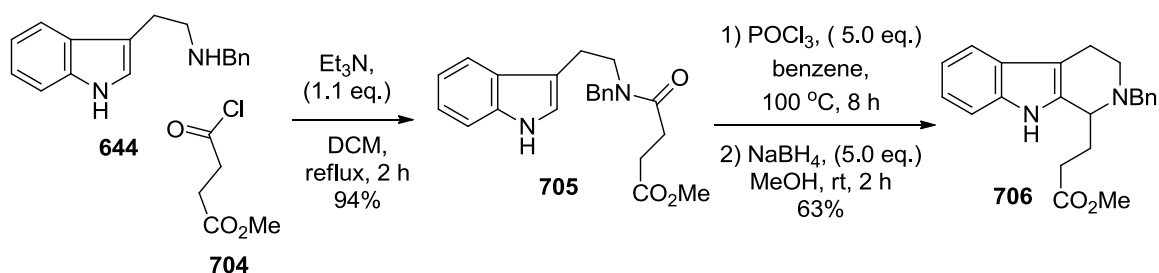


Scheme 240. Retrosynthesis Analysis of North Model through Bischler-Napieralski

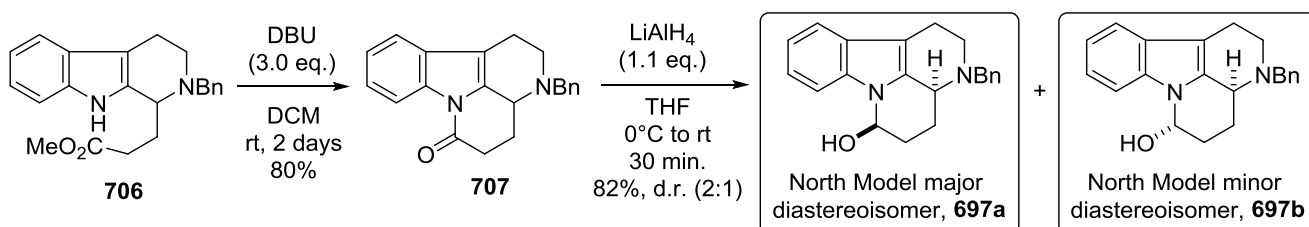
Acid chloride **704** was condensed with benzyl protected tryptamine **644** in the presence of Et_3N to afford amide **705** in excellent yield (94%).²⁵² This amide was then cyclized into tryptamine indole under Bischler-Napieralski reaction conditions to give the tetrahydro- β -carboline **706** in 63% yield (Scheme 241).²⁵³

²⁵² Stoit, A. R.; Pandit, U. K. *Tetrahedron* **1988**, *44*, 6187-6195.

²⁵³ Hoefgen, B.; Decker, M.; Mohr, P.; Schramm, A. M.; Rostom, S. A. F.; El-Subbagh, H.; Schweikert, P. M.; Rudolf, D. R.; Kassack, M. U.; Lehmann, J. *J. Med. Chem.* **2006**, *49*, 760-769.

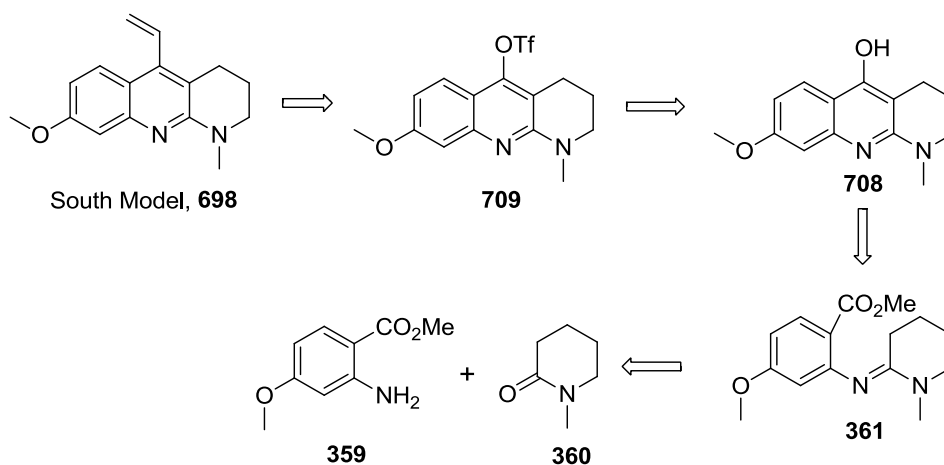
Scheme 241. Synthesis of Tricyclic Core **706**.

With this indole tricycle in hand, the cyclization between indole NH and the methyl ester group was performed in the presence of DBU to form the tetracyclic lactam **707** in 80% yield.²⁴⁸ This lactam was then reduced into the corresponding amino-alcohol by using LiAlH_4 , to give the desired product **697a,b** in 82% yield as a 2:1 mixture of two separable diastereoisomers (Scheme 242).

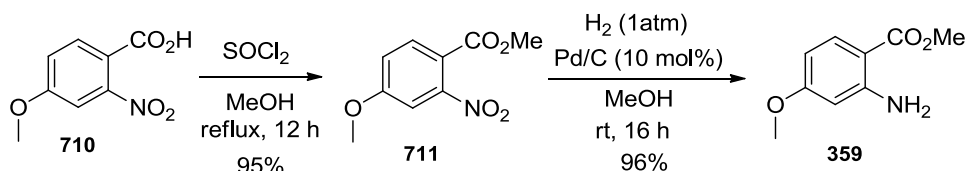
Scheme 242. Elaboration of the North Model **697a-b**.

4.4. Synthesis of the South Fragment Model.

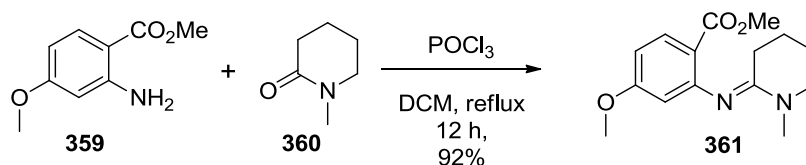
Similarly to the north fragment, the south model was designed to be very similar to Eucophylline **3** and to be accessed in a short and straightforward manner. Therefore, the bicyclic lactam, used in the synthesis of Eucophylline, will be replaced with the commercially available monocyclic lactam **360**. This lactam will be coupled with the trisubstituted aniline **359** to give amidine **361**, which will undergo the same steps, followed in the elaboration of Eucophylline, to give the tricyclic model **698** (Scheme 243).

Scheme 243. Retrosynthesis Analysis of South Model **698**.

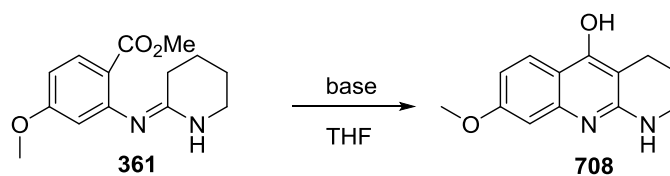
The starting point was the synthesis of the trisubstituted aniline **359**. Commercially available *p*-methoxy-2-nitrobenzoic acid **710** was esterified first, by using thionyl chloride in refluxing methanol to give methyl ester derivative **711** in nearly quantitative yield. Subsequently, the nitro group was reduced into an amino-group under hydrogen pressure in the presence of palladium on charcoal to give the desired trisubstituted aniline **359** in 96% yield (Scheme 244).²⁵⁴

Scheme 244. Synthesis of trisubstituted Aniline **359**.

The trisubstituted aniline was then coupled with monocyclic lactam **360** in the presence of POCl₃ to give the desired amidine **361** in 92% yield (Scheme 245).²⁵⁵ It is worth noticing that the reaction was clean and the product isolated in very pure form after a simple basic work-up and no chromatography.

Scheme 245. Formation of Amidine **361**.

With this amidine in hand, the base-mediated cyclization to elaborate the tricyclic model was performed in the presence of different bases. The first attempt was made by using *t*-BuOK as a base. Unfortunately, the product was not formed and instead degradation of the starting material was observed. By changing the base to LiHMDS, the desired product was isolated, albeit in modest yield. Finally, an excess of LDA in THF gave the desired product **708** in 90% yield (Scheme 246).



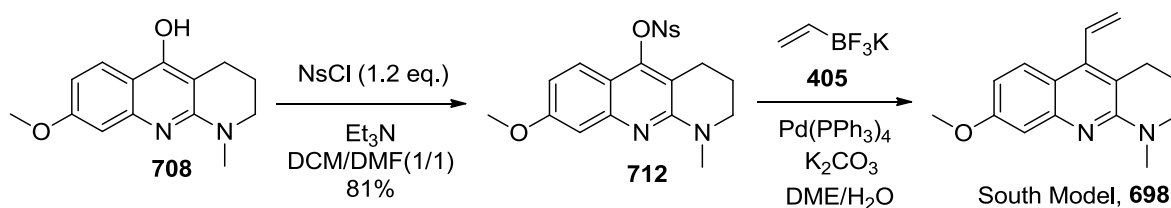
Entry	Conditions	Yield (%)
1	<i>t</i> -BuOK (2.65 eq.), rt, 16 h	N/A
2	LiHMDS (3.0 eq.), rt, 16 h	44%
3	LDA (2.65 eq.), -78°C to rt, 16 h	90%

Scheme 246. Cyclization of Amidine **361**.

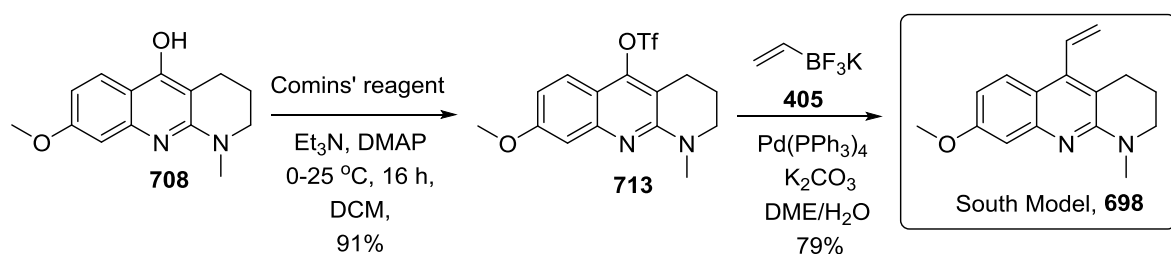
²⁵⁴ Gaillard, P.; Pomel, V.; Jeanclaude-Etter, I.; Dorbais, J.; Klicic, J.; Montagne, C. *PCT Int, Appl.*, WO 2008/101979 A1, **2008**.

²⁵⁵ Lucas-Lopez, C.; Patterson, S.; Blum, T.; Straight, A. F.; Toth, J.; Slawin, A. M. Z.; Mitchison, T. J.; Sellers, J. R.; Westwood, N. J. *Eur. J. Org. Chem.* **2005**, 9, 1736-1740.

The next step was the installation of the vinyl moiety. The hydroxyl group in tricyclic **708** was converted to a more reactive leaving group. Thus, our first attempts were directed as to avoid the use of the expensive Comins' reagent, as in the synthesis of Eucophylline. So the hydroxyl group in **708** was converted to a nosylate, by reacting **708** with nosyl chloride in the presence of Et₃N, which gave the desired nosylate in 81% yield. Then, the installation of the vinyl moiety was tested by reacting nosylate **712** with the vinyl trifluoroborate **405** under Suzuki coupling conditions.²⁵⁶ Unfortunately, the vinyl quinoline **698** was not observed under these conditions (Scheme 247).

Scheme 247. Suzuki coupling with Nosylate **712**.

The installation of the vinyl moiety was thus performed following the procedure already designed for the synthesis of Eucophylline. Thus, the hydroxyl group in **708** was converted to a triflate, by reacting **708** with Comins' reagent to give the desired triflate in 91% yield. The vinyl group was then installed through a Suzuki coupling with vinyl trifluoroborate **405** to give the desired vinyl quinoline **698** in 79% yield (Scheme 248).²⁵⁷

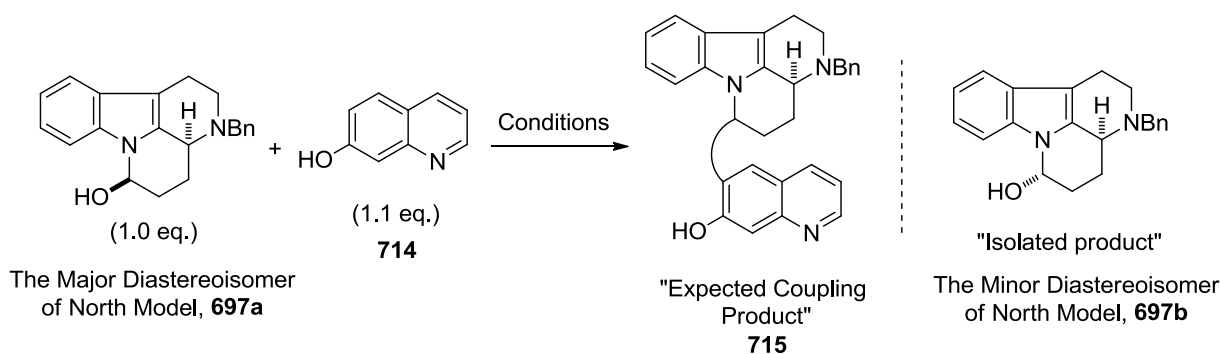
Scheme 248. Suzuki coupling with Triflate **713**.

4.4. Biomimetic Coupling

With these two models in hand, the biomimetic coupling between was studied. Since the idea was to generate the imine in the north model and trap it with electron-rich arenes, our first attempt was carried out with commercially available electron-rich quinolinol **714**, which will be used as a south fragment model. Therefore, the north model **697a** was allowed to react with quinolinol **714** under different acidic conditions (Table 6).

²⁵⁶ Cheval, N. P.; Dikova, A.; Blanc, A.; Weibel, J.-M.; Pale, P. *Chem. Eur. J.* **2013**, *19*, 8765-8768.

²⁵⁷ (a) Molander, G. A.; Rodriguez Rivero, M. *Org. Lett.* **2002**, *4*, 107-109; (b) Darses, S.; Michaud, G.; Genêt, J. P. *Tetrahedron Lett.* **1998**, *39*, 5045-5048.



Entry	Reagent / (eq.)	Additives / (eq.)	Solvent	Temperature °C	Time	Results
1	BF ₃ . Et ₂ O (1.5 eq.)	---	THF	r.t.	24 h	The minor diastereoisomer of the north fragment 697b and the starting quinolinol 714 .
2	BF ₃ . Et ₂ O (5.0 eq.)	TFAA (1.0 eq.)	MeOH	r.t.	40 h	The minor diastereoisomer of the north fragment 697b and the starting quinolinol 714 .
3	FeCl ₃ (5.0 eq.)	---	MeOH	r.t.	24 h	The minor diastereoisomer of the north fragment 697b and the starting quinolinol 714 .
4	FeCl ₃ (5.0 eq.)	TFAA (1.0 eq.)	MeOH	r.t.	24 h	The minor diastereoisomer of the north fragment 697b and the starting quinolinol 714 .
5	TiCl ₄ (5.0 eq.)	----	MeOH	r.t.	40 h	The minor diastereoisomer of the north fragment 697b and the starting quinolinol 714 .
6	TiCl ₄ (5.0 eq.)	TFAA (1.0 eq.)	MeOH	r.t.	40 h	The minor diastereoisomer of the north fragment 697b and the starting quinolinol 714 .
7	HCl (3%)	---	MeOH	70	24 h	Degradation of the North model and isolation of the starting quinolinol 714
8	TFAA (5.0 eq)	---	MeOH	r.t.	40 h	The minor diastereoisomer of the north fragment 697b and the starting quinolinol 714 .
9	----	---	THF/ H ₂ O 1/2	100	7 days	The minor diastereoisomer of the north fragment 697b and the starting quinolinol 714 .
10 ^a	----	---	THF/ H ₂ O 1/2	100	1 days	The major diastereoisomer of the north fragment 697a and the starting quinolinol 714 .

Table 6. Screening Different Acidic Conditions for Biomimetic Coupling between North Model **697a-b** and Quinolinol **714**. ^a using the minor diastereoisomer of the North Model.

Firstly, the major diastereoisomer of the north model **697a** was reacted with quinolinol **714** in the presence of BF₃-etherate as a Lewis acid. Unfortunately, the coupling product **715** was not observed under these conditions (entry 1, Table 6), and instead the minor diastereoisomer of the north fragment **697b** and quinolinol **714** were the only isolated products.²⁵⁸ Repeating the reaction with addition of TFAA (trifluoroacetic anhydride) (entry 2, Table 6) to enhance the formation of imine, did not improve the situation and the same result was observed.

Then, the Lewis acid was changed to FeCl₃ but unfortunately also the result did not change at all and the only isolated products were the minor diastereoisomer **697b** of the north fragment and quinolinol

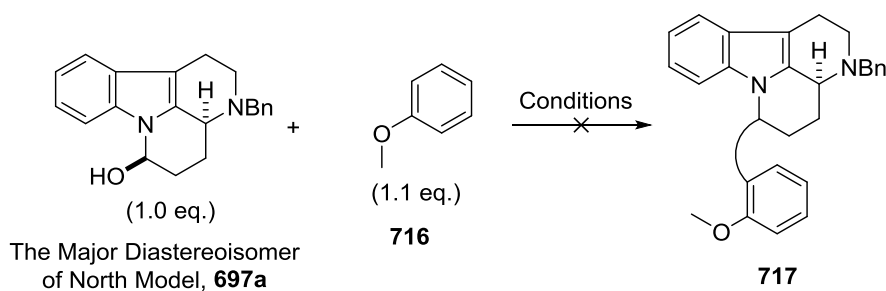
²⁵⁸ Kitamura, T.; Harano, K.; Hisano, T. *Chem. pharm. Bull.* **1992**, *40*, 2255-2261.

714 (entry **3**, Table **6**). The Lewis acid was changed to TiCl_4 but, again also the same negative results were observed (entry **5**, Table **6**).

As illustrated above with the reported couplings from the literature, the coupling was also performed in HCl acidified solutions.²⁵⁹ Our coupling conditions were thus performed in methanolic solution of HCl under reflux for several days (entry **7**, Table **6**). Unfortunately, the desired coupling product **715** was not observed and instead degradation of the starting north Model was observed, beside the isolation of quinolinol **714**. Changing the acid to be TFAA, did not also lead to the desired product and again the only isolated products were the minor diastereoisomer of the north fragment **697b** and quinolinol **714** (entry **8**, Table **6**).

A recently reported method showed that imines could be trapped by electron-rich arenes just by heating them in a mixture of THF and H_2O .²⁶⁰ Therefore, the major diastereoisomer of the north model **697a** was heated with quinolinol **714** in a 2:1 THF/ H_2O mixture. Unfortunately, the same negative results were observed (entry **9**, Table **6**). Starting with the minor diastereoisomer of the north model **697b**, the only isolated product was the major diastereoisomer of the same model **697a**.

Another electron-rich arene was used instead of quinolinol **714**. Anisole **716** was thus allowed to react with the major diastereoisomer of the north model **697a** under acidic conditions. Unfortunately, no traces of the desired product **717** was observed and the north model was decomposed under HCl/MeOH reaction conditions or in TFAA/TMSOTf medium (Scheme **249**).



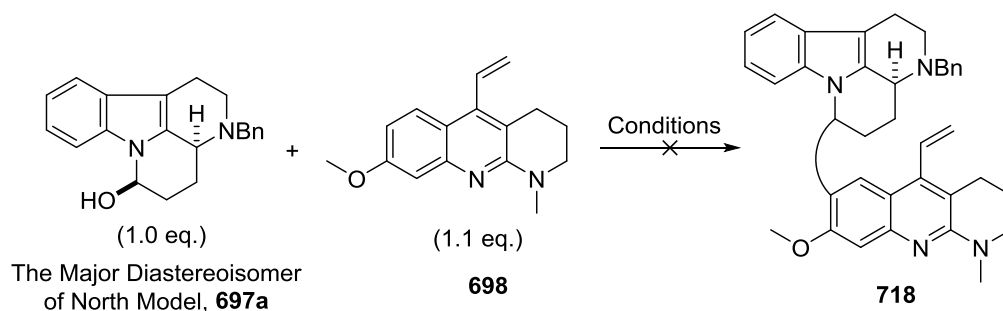
Entry	Conditions	Yield (%)
1	HCl/MeOH, 70°C, 3 days	N/A
2	TFAA (1.0 eq.), TMSOTf (0.5 eq.), drierite (excess), -30°C to rt, 4 days	N/A

Scheme **249**. Attempts in Biomimetic Coupling between North Model **697a** and Anisole.

²⁵⁹ (a) Buchi, G.; Manning, R. E.; Monti, S. A. *J. Am. Chem. Soc.* **1964**, *86*, 4631-4641; (b) Thomas, D. W.; Achenbach, H.; Biemann, K. *J. Am. Chem. Soc.* **1966**, *88*, 1537-1544.

²⁶⁰ Nguyen, T. B.; Lozach, O.; Surpateanu, G.; Wang, Q.; Retailleau, P.; Iorga, B. I.; Meijer, L.; Guéritte, F. *J. Med. Chem.* **2012**, *55*, 2811-2819.

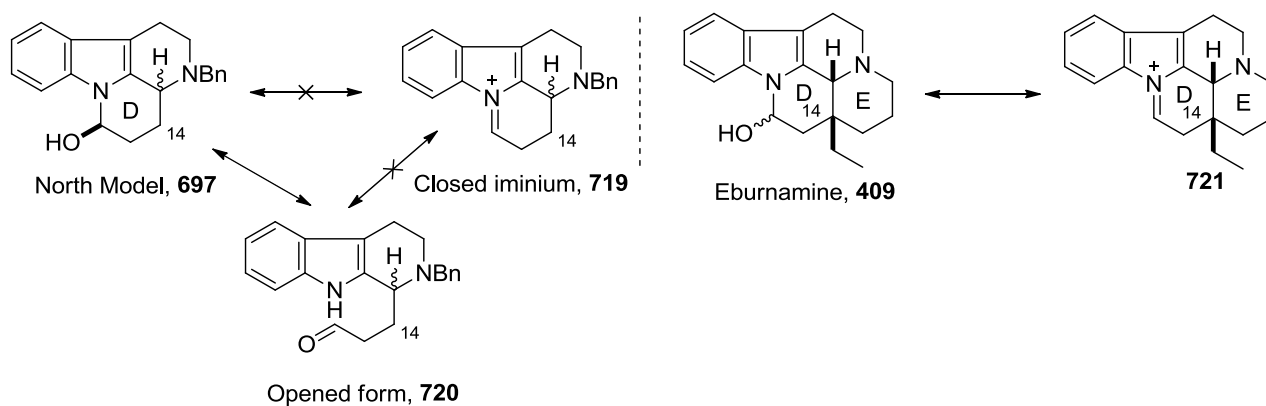
The coupling between the major diastereoisomer of the north model **697a** and the south model **698** was also tested. In this trial, the most common and frequently cited procedure that described this type of couplings was followed.²⁵⁹ The coupling reaction was performed in a methanoic HCl solution at 65°C for 6 days. Unfortunately, no traces of the desired coupling product **718** were observed and instead degradation of the north model **697a** was observed along with isolation of the south model **698**. Repeating the reaction under dry conditions using TMSOTf in anhydrous DCM did not lead to the formation of the desired coupling product **718** (Scheme 250).



Entry	Conditions	Yield (%)
1	HCl (5%), MeOH, 65 °C, 6 days	N/A
2	HCl (37%), MeOH, 65 °C, 6 days	N/A
3	TMSOTf (1.1 eq.), DCM, rt, 3 days	N/A

Scheme 250. Trials in Biomimetic Coupling between North Model **697a** and South Model **698**.

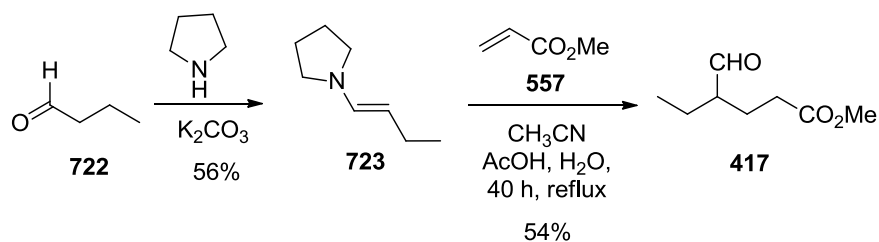
After these disappointing results, our attention was directed towards the reactivity of the north model **697a,b** under these acidic conditions. The careful analysis of this model showed that the absence of *gem*-dimethyl effect at C-14 (as in natural Eburnamine) probably led ring D to stand essentially in its opened form under acidic conditions, the concentration of the real cyclic iminium **719**, essential for the coupling, being thus very low. This hypothesis was reinforced by the formation, in some cases, of the other diastereoisomer of the north model which showed that cyclic and opened forms are in equilibrium. The comparison between this model **697** and Eburnamine **409** showed that in Eburnamine **409** there is an ethyl group at C-14 beside fused rings D and E, likely forcing closure of ring D and formation of iminium **721**. This *gem*-dimethyl effect facilitates the coupling with Eburnamine **409**, a feature that is absent in model **697** (Scheme 251).

Scheme 251. Imine Formation in North Model **697** and Eburnamine **409**.

At that point, it was thus essential to use the real Eburnane **2** to test this biomimetic coupling. To access Eburnane **2** in a short sequence, it was envisioned to follow Harley–Mason sequence which represents one of the shortest pathways to access Eburnane from inexpensive and available starting materials.²⁶¹ In the following section, synthesis of Eburnane **2** through Harley–Mason sequence will be discussed.

4.6. Elaboration of Eburnane through Stork Reaction

Relying on the Stork reaction between commercially available butanal **722** and methyl acrylate **557**, the non-tryptamine part of Eburnane could be accessed in two steps from inexpensive starting materials. Following to the literature procedure,²⁶² the pyrrolidine enamine of butanal **723** was prepared in 56% yield by the reaction of butanal **722** with pyrrolidine in the presence of potassium carbonate. This enamine was then allowed to undergo Michael addition with methyl acrylate **557** to give the aldehyde ester **417** in 54% yield (Scheme 252).

Scheme 252. Stork Reaction with Butanal **722**.

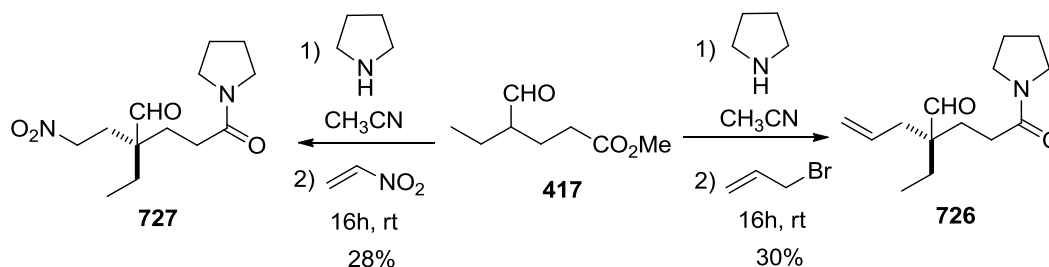
By repeating the same steps than before, aldehyde ester **417** reacted with pyrrolidine to form the intermediate enamine **724**. This enamine **724** was allowed to undergo a nucleophilic addition with either allyl bromide **127** or nitroethene **725**, generated *in situ* by thermolysis of nitroethyl acetate.²⁶³

²⁶¹ Barton, J. E. D.; Harley-Mason, J. *Chem. Commun.* **1965**, 298-299.

²⁶² (a) Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2872-2873. (b) Norman, M. H.; Heathcock, C. H. *J. Org. Chem.* **1988**, *53*, 3370-3371.

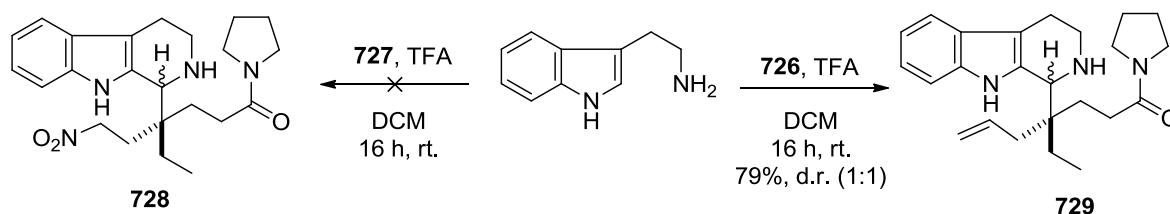
²⁶³ Flaugh, M. E.; Crowell, T. A.; Clemens, J. A.; Sawyer, B. D. *J. Med. Chem.* **1979**, *22*, 63-69.

Both reactions worked, but unfortunately, the methyl ester part of the formed aldehydes was transesterified by pyrrolidine to give aldehyde amides **726** and **727** in 30% and 28% yields respectively (Scheme 253). It is worth noticing that, the isolated aldehyde amide **726** was not described in the Harley–Mason synthesis, who obtained the aldehyde-ester **418**.²⁶¹



Scheme 253. Preparation of the non-Tryptamine Aldehydes.

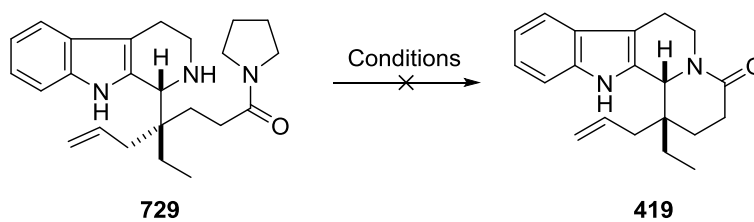
Since the aim was just to test the biomimetic coupling with easily prepared Eburnane **2**, we proceeded directly to the following step. Therefore, Pictet-Spengler reactions between tryptamine and aldehydes **727** and **726** were performed in the presence of TFA in DCM at room temperature. With the aldehyde **727**, the Pictet-Spengler product **728** was not observed, while with aldehyde **726**, the cyclized product **729** was isolated in 79% yield as a 1:1 mixture of diastereomers (Scheme 254).

Scheme 254. Pictet-Spengler reactions with Aldehydes **726**, **727**.

With the Pictet-Spengler product **729** in hand, the intramolecular transamidation reaction between the secondary amine and the amide was tried under different acidic and basic conditions. First, **729** was treated with DBU for 2 days, but the desired tetracyclic lactam **419** was not observed. The same result was also observed when treating **729** with sodium methoxide. Changing to acidic conditions, did not change the outcome. For instance, treating **729** with boric acid in water or in DCE under reflux did not lead to the desired product **419**.²⁶⁴ Similarly, using aluminum chloride as a Lewis acid according to a reported method, did not give the tetracyclic lactam **419** (Scheme 255).²⁶⁵

²⁶⁴ Nguyen, T. B.; Sorres, J.; Tran, M. Q.; Ermolenko, L.; Al-Mourabit, A. *Org. Lett.* **2012**, *14*, 3202-3205.

²⁶⁵ Bon, E.; Bigg, D. C. H.; Bertrand, G. *J. Org. Chem.* **1994**, *59*, 4035-4036.



Entry	Conditions	Yield (%)
1	DBU (3.0 eq.), DCM, 48 h, rt	S.M.
2	MeONa (3.0 eq.), MeOH, 3 days, rt.	S.M.
3	B(OH) ₃ (0.1 eq.), H ₂ O, 16h, 120°C	S.M.
4	B(OH) ₃ (2.0 eq.), DCE, 16h, 85°C	S.M.
5	AlCl ₃ (2.0 eq.), DCE, 16h, 85°C	N/A

Scheme 255. Transamidation Reaction of **729**

At this stage and due to time constraints, we abandoned this route to access Eburnane **2**. A recently appointed PhD student in the group will continue investigating this biomimetic coupling.

4.7. Conclusion

In this chapter, we initiated preliminary studies on the proposed biomimetic coupling, leading to Leucophyllidine. North and south models were designed with structures as close as possible to the Eburnane and Eucophylline skeletons. These models were accessed easily through short sequences of reactions from commercially available and inexpensive starting materials. The north model **697a-b** led to some disappointing results under acidic conditions due to the absence of *gem*-dimethyl in its skeleton, which disfavor the formation of the cyclic imine required in the coupling. Interestingly, the south fragment model **698** showed high stability under harsh acidic conditions and the vinyl moiety incorporated in this model was not affected by these reaction conditions, suggesting that the future coupling might be realized after its incorporation.

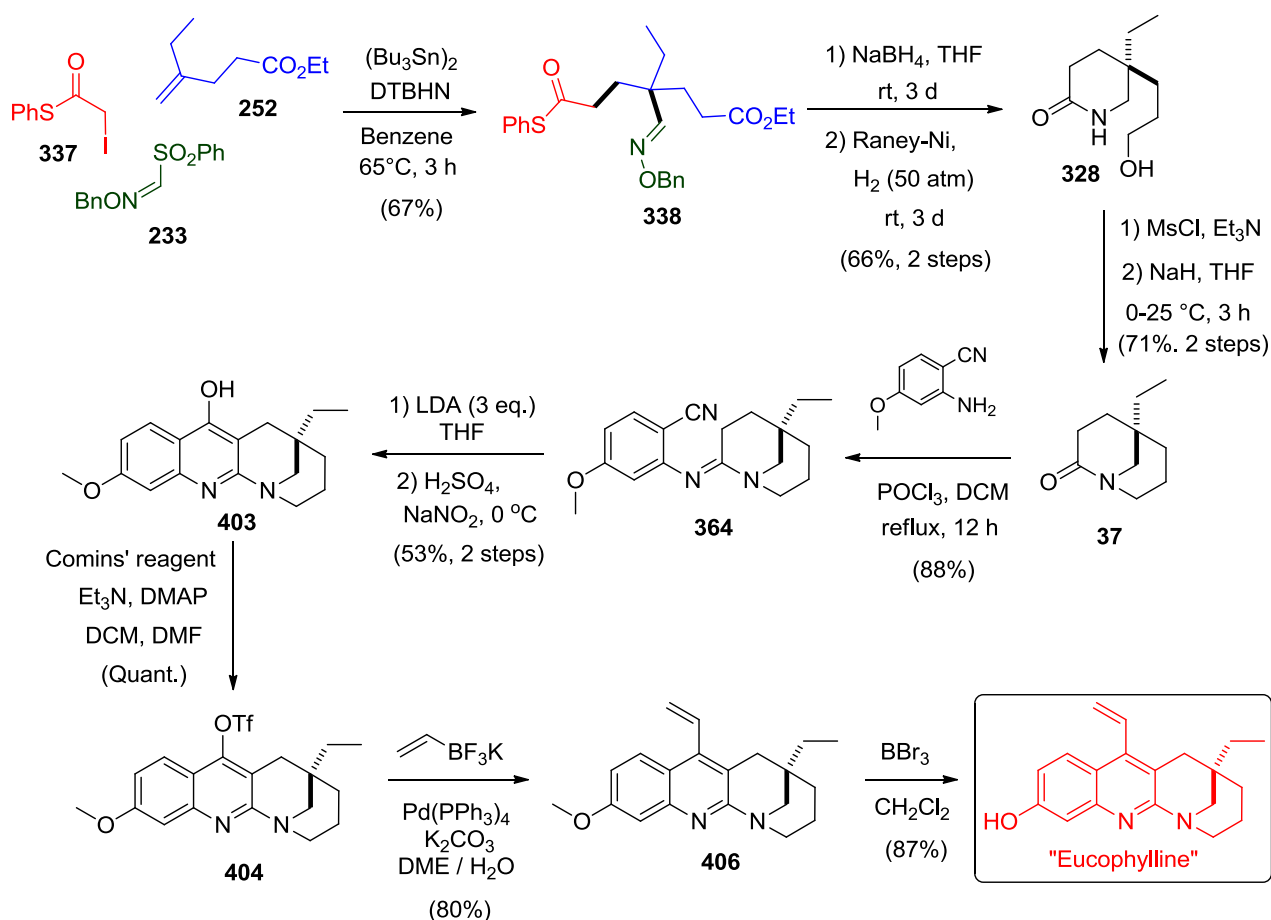
Our efforts to elaborate Eburnane **2** fragment through Stork reaction, which was guided by Harley–Mason precedent, could not be reproduced according to the literature report. The final transamidation reaction proved to be impossible under the reaction conditions tested, thus preventing us from obtaining the desired eburnane fragment.

Conclusion & Perspectives

1. Conclusion

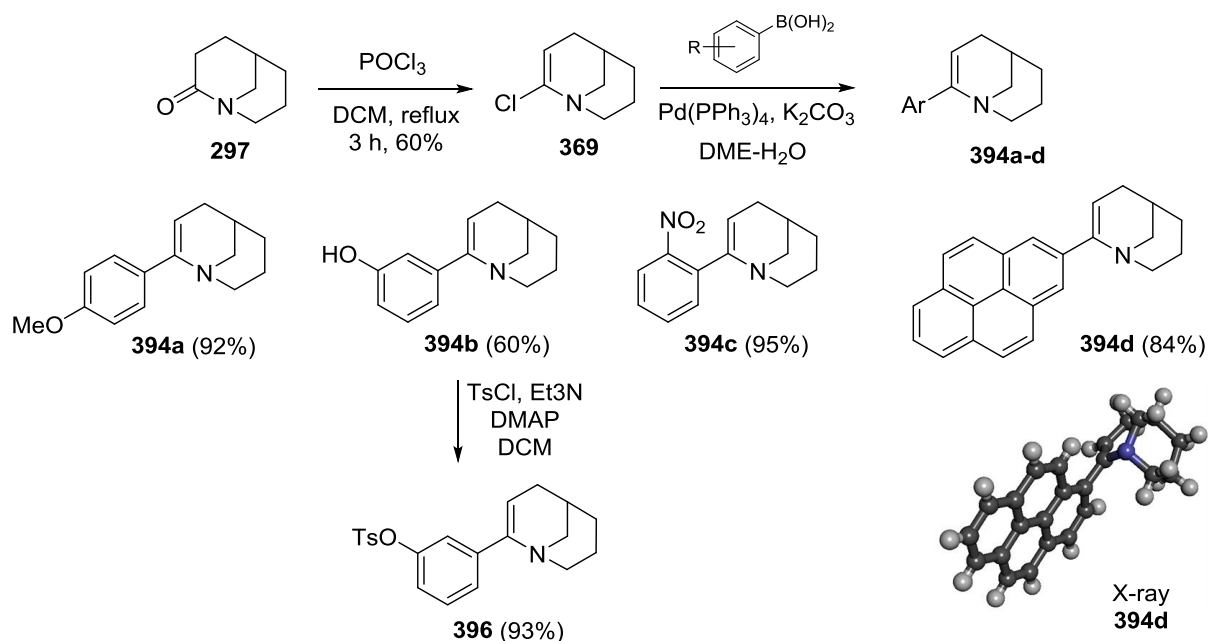
Along this dissertation, we described the first total synthesis of Eucophylline, a unique vinyl quinoline alkaloid incorporating a bicyclic system, which was recently isolated from *Leuconotis eugenifolius*. We also described an approach towards the total synthesis of cytotoxic Leucophyllidine, a new bisindole alkaloid isolated from *Leuconotis griffithii* exhibiting a promising and selective anti-cancer activity. In both syntheses, we relied on new free-radical multi-component reactions, showing through them the utility and effectiveness of free-radical reactions in accessing complex structures and constructing quaternary centers through short sequences.

The first total synthesis of Eucophylline was achieved in 10 steps and 10% overall yield based on the recently developed free-radical multi-component carbo-oximation reaction between radical precursor α -iodoester **337**, the electron-rich olefin **252** and sulfonyl oxime **233**. This key reaction allowed us to construct the quaternary center in Eucophylline and devise a new straightforward access to the azabicyclo[3.3.1]nonane skeleton with an efficient and short sequence of reactions (Scheme 256).



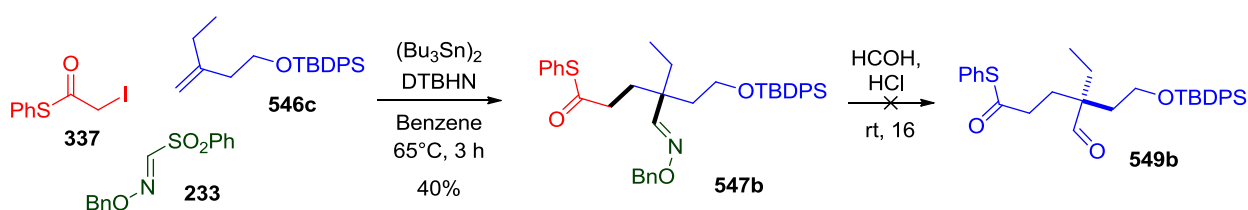
Scheme 256. Synthesis of Eucophylline.

In the course of our investigations on the reactivity of bridgehead bicyclic lactams under Vilsmeier-type conditions, we observed that these reactions went through the intermediacy of a remarkably stable α -chloroenamines. The unique reactivity of these twisted amides allowed us to isolate and functionalize the stable bicyclic α -chloroenamine intermediate **369**, illustrating the absence of conjugation between the nitrogen's lone-pair and the enamine double bond (Scheme 257).



Scheme 257. α -chloroenamine **369**, Isolation and Functionalization.

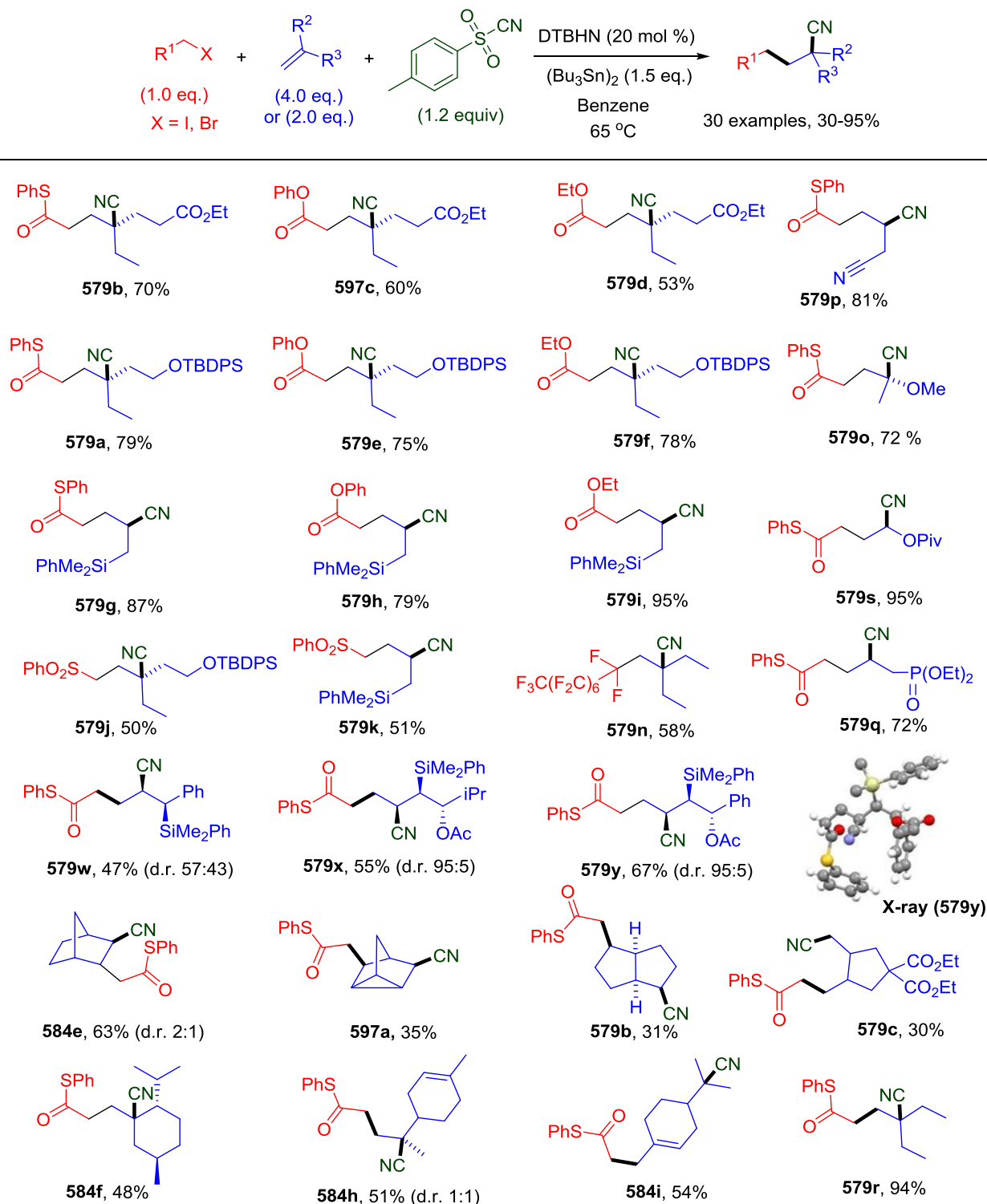
In the synthesis of Eburnane **2**, the north fragment of Leucophyllidine, the carbo-oximation process, which showed its efficiency in synthesis of Eucophylline, did not display the same efficiency during the construction of the non-tryptamine part of Eburnane, likely as a result of an increased steric hindrance around the generated nucleophilic radical that complicated the trapping of this radical by sulfonyl oxime. Furthermore, the conversion of the oxime **547b** to aldehyde **549b** was not reliable under the used conditions (Scheme 258).



Scheme 258. Carbo-Oximation process with Olefin **546c**.

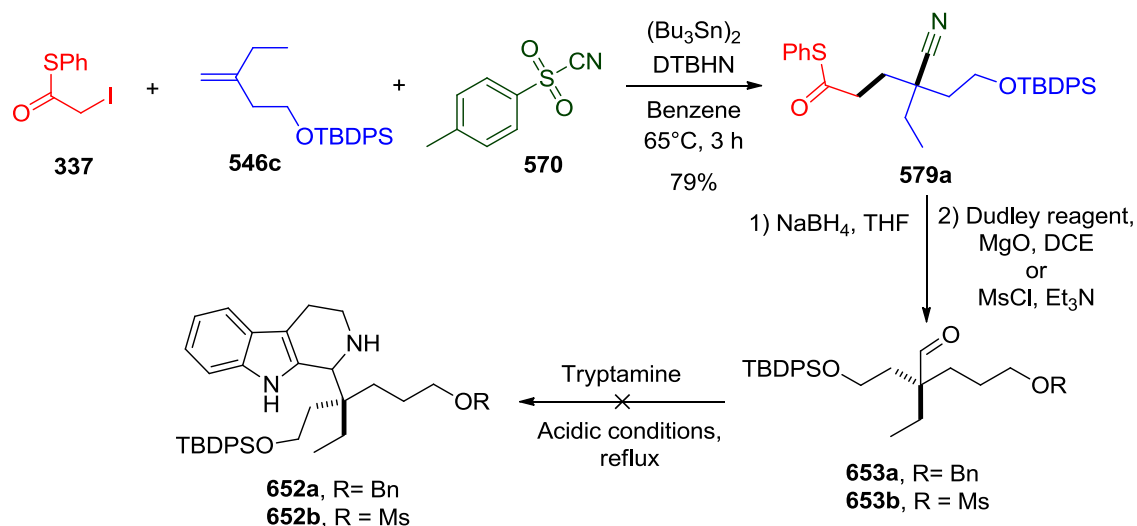
In search for a functional group equivalent to an aldehyde and compatible with free-radical multi-component processes, we came out with the new three-component carbo-cyanation free-radical reaction. This reaction showed high tolerance towards different radical precursors, different olefins and structures containing double bonds. Besides that, the *p*-toluenesulfonyl cyanide **570**, the sulfonyl acceptor, is commercially available, which is not the case for other sulfonyl acceptors. The

small A-value of the nitrile group (0.21) allowed the nucleophilic radical, generated after the first step of the multi-component radical process, to attack easily the small nitrile acceptor to afford the desired MCR product. This process provides easy and efficient way to construct fully functionalized quaternary centers in very good yields and in only one step (Scheme 259).



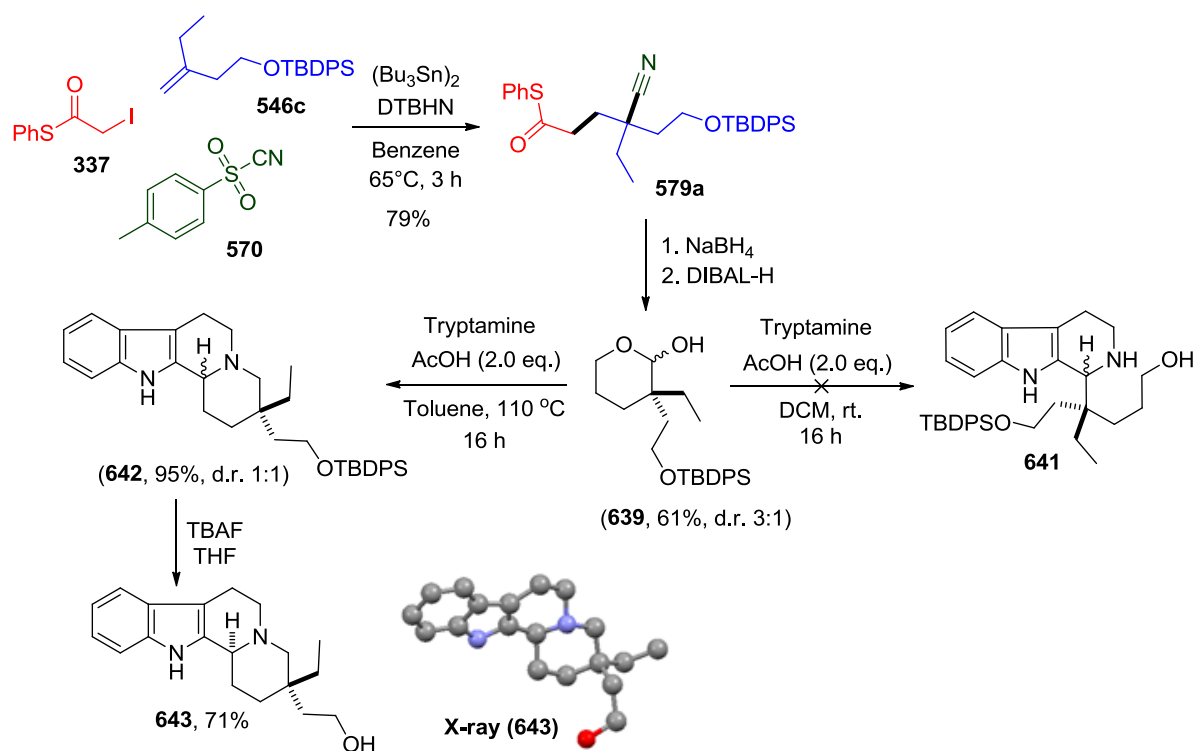
Scheme 259. Olefin Carbo-Cyanation Scope.

Relying on this efficient carbo-cyanation reaction, two approaches were developed to access Eburnane **2**, the north fragment of Leucophyllidine **1**. The first one was based on a Pictet-Spengler reaction between tryptamine and a fully functionalized aldehyde **653a-b**, obtained from the corresponding nitrile product **579a**. The reaction was not successful with real aldehydes due to the difficulties encountered to isolate them in pure form (Scheme **260**).



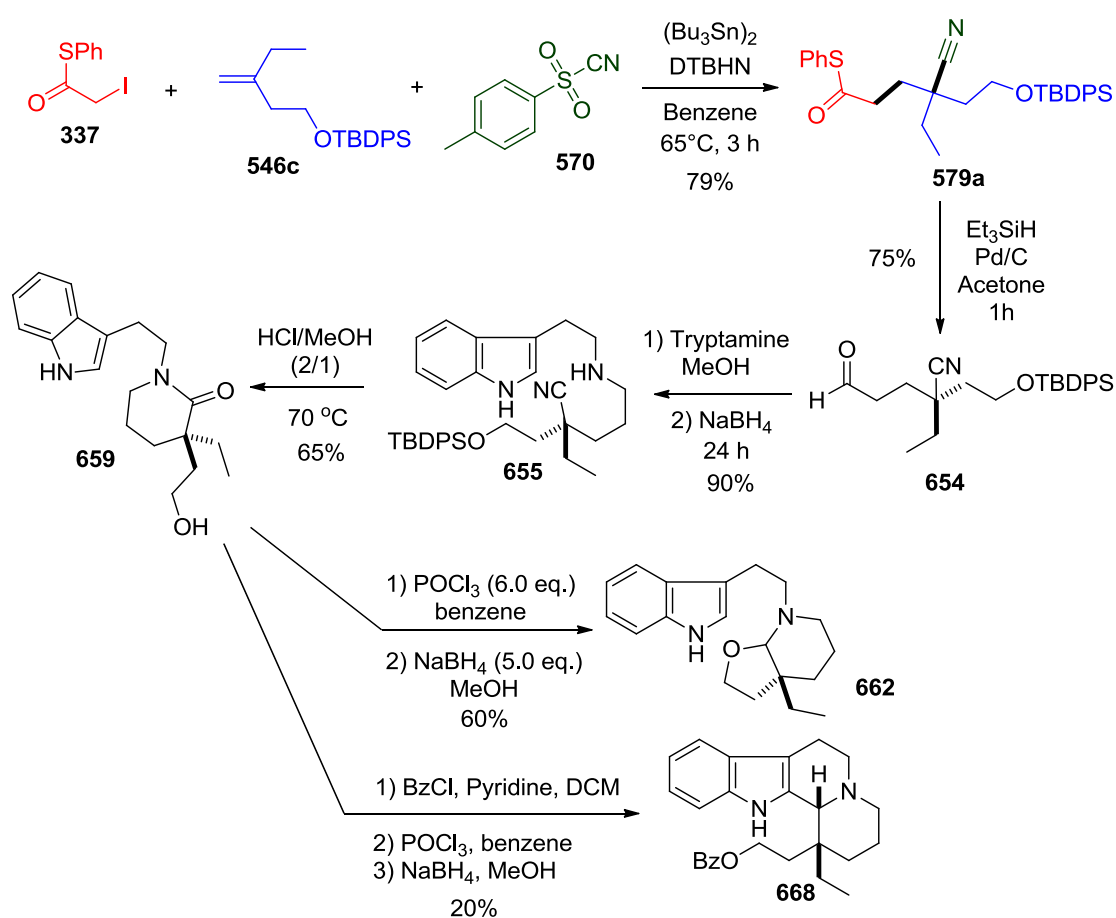
Scheme **260**. Synthesis of Eburnane / Pictet-Spengler reaction with real aldehydes **653a-b**.

However, the masked aldehyde, lactol **639**, gave a Pictet-Spengler product **642**, after refluxing at high temperature with tryptamine, having an unexpected structure. The formation of this tetracyclic product was rationalized based on a redox-Mannich process (Scheme **261**).



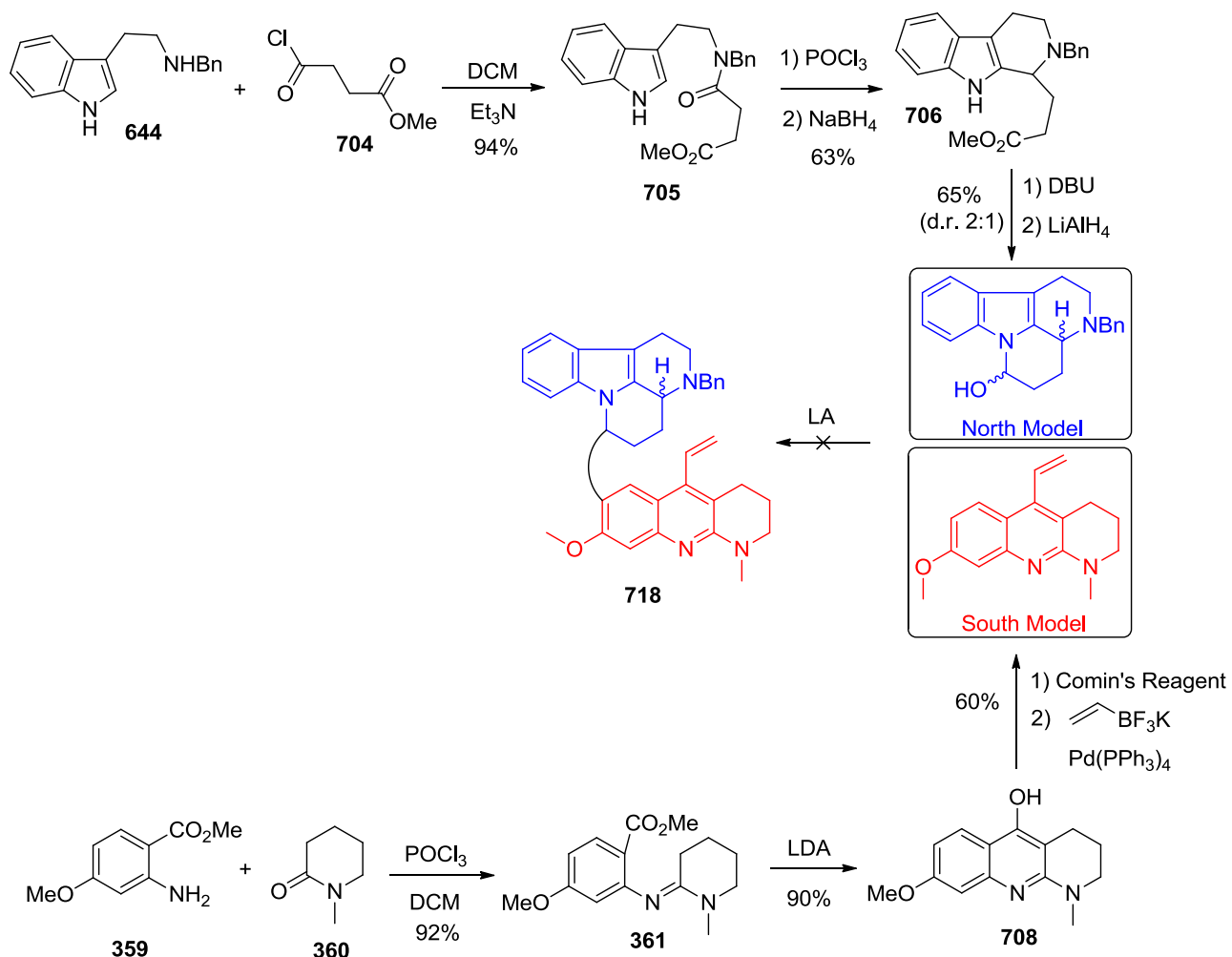
Scheme **261**. Synthesis of Eburnane / Pictet-Spengler reaction with masked aldehyde **639**.

The second approach was based on the Bischler-Napieralski condensation. Therefore, the same carbo-cyanation product **579a**, used before, was the key precursor in this approach. Playing with the reactivity of the thioester group allowed us to get access to aldehyde **654**, which reacted under reductive conditions with tryptamine to give the secondary amine **655**. Cyclization of this secondary amine onto the nitrile group gave the lactam **659**, designed for Bischler-Napieralski condensation. Unfortunately, the presence of a free alcohol in lactam **659** gave the hemiaminal **662** instead of the expected tetracyclic alcohol. Protection of this free alcohol and applying Bischler-Napieralski reaction conditions gave the desired tetracyclic product **668** albeit in low and non-reproducible yield (Scheme 262).



Scheme 262. Synthesis of Eburnane / Bischler-Napieralski Reaction.

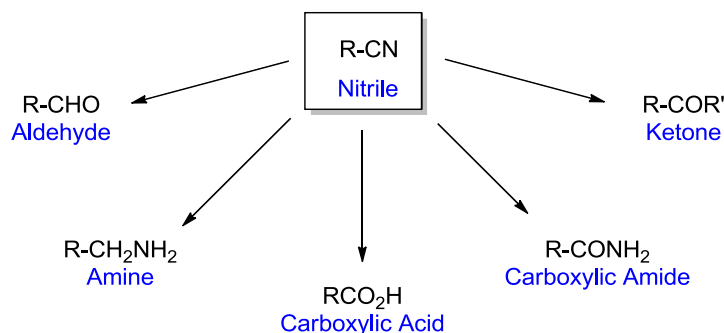
The biomimetic coupling between the Eburnane **2** and Eucophylline **3** was finally studied using structurally similar models. The latter were accessed very easily in a limited number of steps from commercially available starting materials. Preliminary results on this model study showed that absence of *gem*-dimethyl effect in the north model **697** probably prevents the formation of the cyclic imine, crucial intermediate in the desired coupling (Scheme 263).



Scheme 263. Model Study on Biomimetic Coupling.

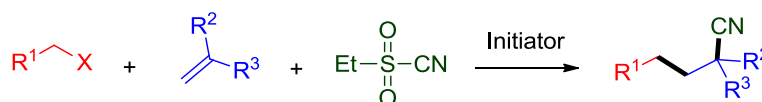
2. Perspectives

The new free-radical carbo-cyanation reaction, which showed high tolerance to different functional groups, provided an efficient procedure to install the nitrile group in complex structures and formation of quaternary centers. This opens the door to the use of this reaction widely in synthetic organic chemistry. The nitrile group is a C-1 equivalent and could be easily converted to a wide range of functional groups (aldehyde, amine, carboxylic acid, carboxylic amide, and ketone), through well-known reactions.



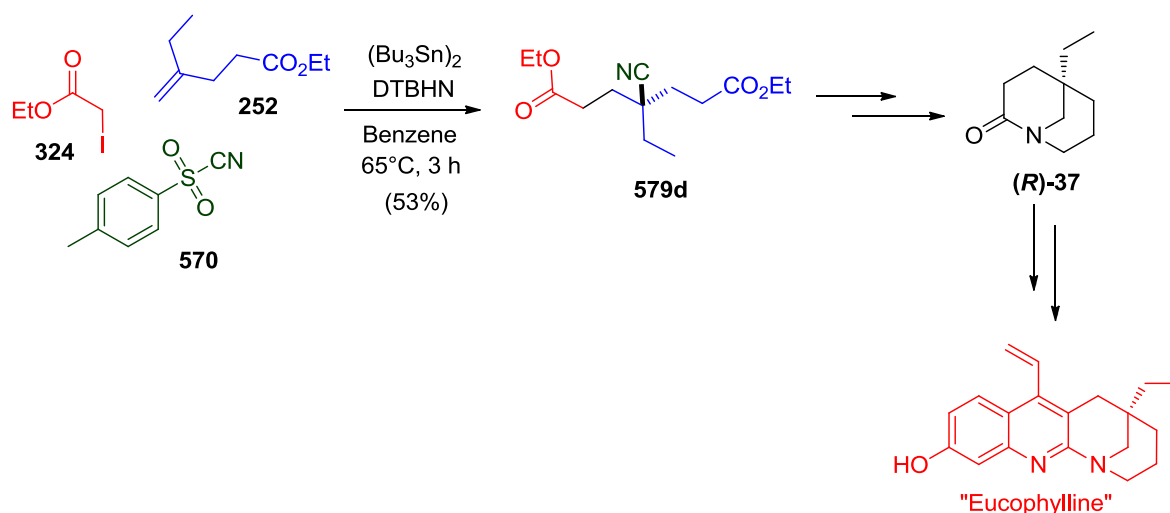
Scheme 264. Converting Nitrile to Different Functional Groups.

To increase the impact of this reaction and avoid using equimolar amounts of tin species, the development of a tin-free version of this reaction would deserve considerable interest. Synthesizing the key ethylsulfonyl cyanide and tuning the right conditions will hopefully lead to an environmental more benign reaction.



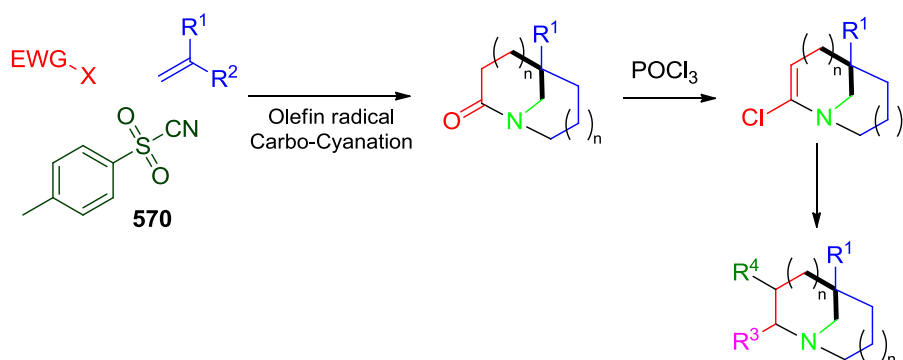
Scheme 265. Tin-Free Carbo-Cyanation Reaction.

The enantioselective synthesis of Eucophylline could also be accessed relying on this carbo-cyanation reaction and on the nitrile product **597d**. Reduction of prochiral nitrile **549d** to amine and “desymmetrizing” cyclization of this amine onto one of the two esters could possibly give an access to the desired chiral center in the bicyclic system of Eucophylline.



Scheme 266. Approach towards the Enantioselective Synthesis of Eucophylline.

This carbo-cyanation reaction and the new straightforward sequence, used in construction of azabicyclo[3.3.1]nonane **37**, open the door for constructing and functionalizing nitrogen bridgehead bicycles with different sizes relying on versatility of the carbo-cyanation MCR. Moreover, taking benefit from the reactivity of twisted amides present in these bicyclic systems, their functionalization should give rise to bicyclic enamines, generated by reaction with POCl_3 .²⁶⁶ The stability of these enamines will depend on the ring size of bicyclic systems (Scheme 267).

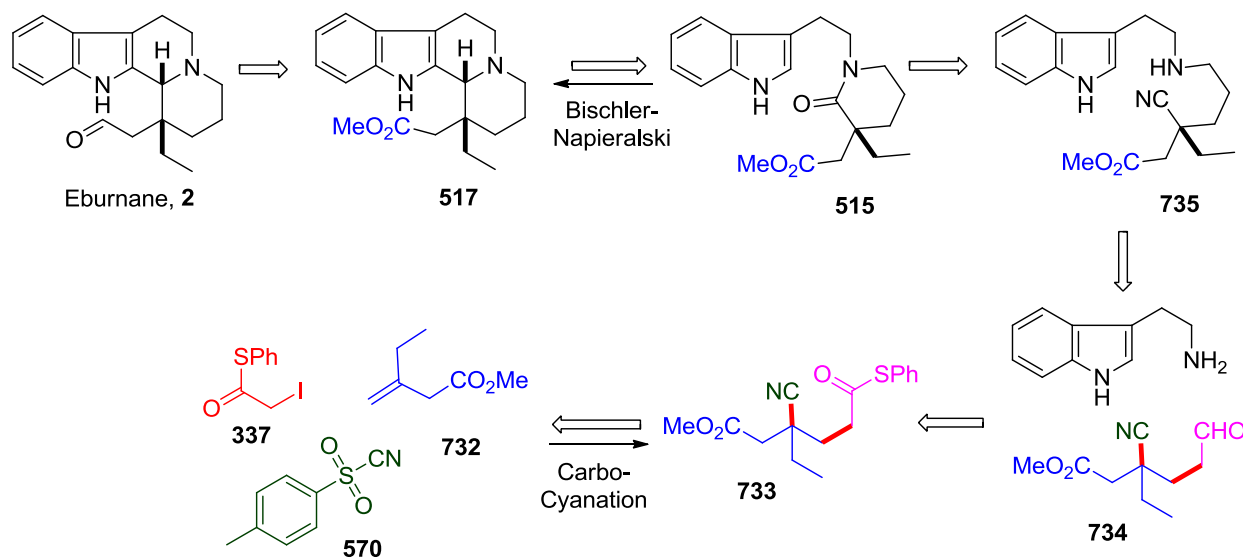


Scheme 267. Carbo-Cyanation MCR in Constructing and Functionalizing of Different Bicyclic Systems.

On the Eburnane side, the use of olefin **732** in the carbo-cyanation process will hopefully lead to a product bearing a methyl ester in the side chain of lactam **515**, which will be more reliable and

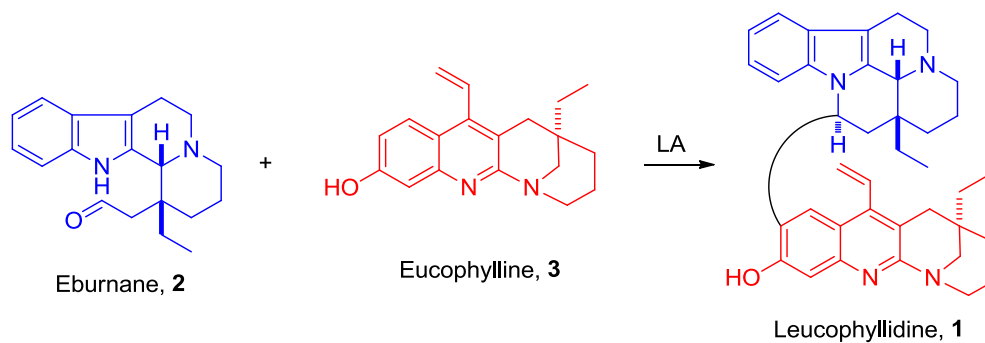
²⁶⁶ (a) Bassler, D. P.; Spence, L.; Alwali, A.; Beale, O.; Beng, T. K. *Org. Biomol. Chem.*, **2015**, *13*, 2285-2292; (b) Beng, T. K.; Wilkerson-Hill, S. M.; Sarpong, R. *Org. Lett.* **2014**, *16*, 916-919; (c) Haveaux, B.; Dekoker, A.; Rens, M.; Sidani, A. R.; Toye, J.; Ghosez, L. *Org. Synth.* **1979**, *59*, 26.

compatible for the Bischler-Napieralski reaction, leading to better and reproducible yields (Scheme 268).²⁶⁷



Scheme 268. Eburnane Retrosynthesis through Bischler-Napieralski Reaction and Olefin **732**.

Finally, after elaboration of Eburnane **2**, the biomimetic coupling could hopefully be performed in moderately acidic medium taking in the consideration the possible protonation of the Eucophylline nitrogens which could alter the nucleophilicity of Eucophylline and abort the coupling.



Scheme 269. Biomimetic Coupling Approach in Leucophyllidine.

²⁶⁷ (a) Herrmann, J. L.; Cregge, R. J.; Richman, J. E.; Kieczkowski, G. R.; Normandin, S. N.; Quesada, M. L.; Semmelhack, C. L.; Poss, A. J.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1979**, *101*, 1540-1544; (b) Lancefield, C. S.; Zhou, L.; Lébl, T.; Slawin, A. M. Z.; Westwood, N. J. *Org. Lett.* **2012**, *14*, 6166-6169.

Experimental Part

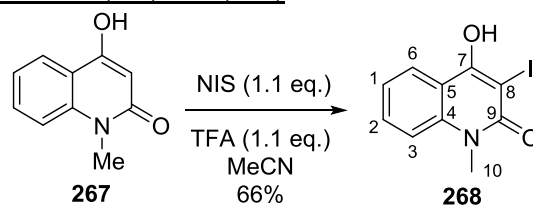
General information

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions unless otherwise noted. Dichloromethane, MeOH, THF and toluene were dried over activated alumina columns on MBraun Solvent Purification System (SPS-800). Benzene was distilled from Na/benzophenone, 1,2-dichloroethane and acetonitrile was distilled from CaH₂. All commercial reagents were used as received without further purification unless otherwise stated. Diisopropylamine, Et₃N, isopropylcyclohexylamine, TMEDA were distilled from KOH. *n*BuLi was titrated using *N*-benzylbenzamide.²⁶⁸ Yields refer to chromatographically and spectroscopically (¹H and ¹³C NMR) homogeneous materials unless otherwise stated.

¹H NMR and ¹³C NMR were recorded on a Bruker DPX 200 (¹H: 200 MHz, ¹³C: 50 MHz), a Bruker Avance 300 (¹H: 300 MHz, ¹³C: 75.46 MHz) using CDCl₃ as internal reference unless otherwise indicated. The chemical shifts (δ) and coupling constants (J) are expressed in ppm and Hz respectively. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, quint = quintuplet, hex = hexuplet. FT-IR spectra were recorded on a Perkin-Elmer Spectrum 100 using a ZnSe crystal ATR accessory. HRMS were recorded with a Waters Q-TOF 2 spectrometer in the electrospray ionization (ESI) mode. Analytical thin layer chromatography was performed using silica gel 60 F254 pre-coated plates (Merck) with visualization by ultraviolet light, potassium permanganate. Fluka silica gel 60 (230-400 mesh) was used for flash chromatography.

²⁶⁸ Burchat, A. F.; Chong, J. M.; Nielsen, N. *J. Organomet. Chem.* **1997**, *542*, 281-283.

Experimental Part for Chapter Two

4-Hydroxy-3-iodo-1-methylquinolin-2(1H)-one (268)

To a solution of quinolinone **267** (50 mg, 0.28 mmol) in dry CH₃CN (10 mL), TFA (0.02 mL, 0.314 mmol, 1.1 eq.) was added. The reaction mixture was stirred at room temperature for 5 min after that NIS (70.64 mg, 0.314 mmol, 1.1 eq.) was added. The reaction was stirred at room temperature for 24 h. After that, the reaction was stopped and the solvent was removed under reduced pressure. The residue was treated with 10 % sodium thiosulfate solution (10 mL) and the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over Na₂SO₄ and the solvent was removed under reduced pressure to afford dark brown oil which was purified by chromatography on silica gel (PE/EtOAc 95/5). The desired compound **268** was obtained as yellow solid (57 mg, 66%).

Mp = 170°C (DCM).

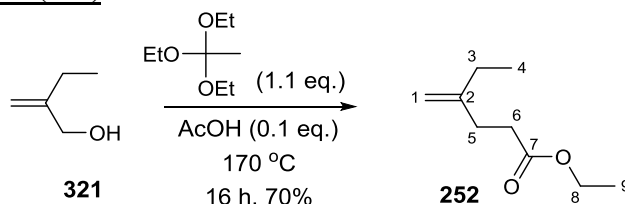
R_f = 0.45 (PE/EtOAc 50/50).

IR (KBr) ν_{max} (cm⁻¹) = 3349, 2976, 2928, 1647, 1540, 1088, 1044.

H NMR (CDCl₃, 300 MHz): δ (ppm) = 8.05-8.02 (dd, 1H, *J* = 12, 15, 78 Hz, H-1), 7.66-7.61 (m, 1H, H-2), 7.39-7.36 (d, 1H, *J* = 9 Hz, H-6), 7.28-7.23 (dd, 1H, *J* = 9.9, .0.9, 15.3 Hz, H-3), 3.78 (s, 3H, H-10).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 177.4 (C-9), 160.4 (C-7), 139.3 (C-4), 132.0 (C-2), 124.1 (C-3), 122.2 (C-1), 114.1 (C-6), 113.9 (C-5), 77.7 (C-8), 31.4 (C-10).

HRMS (ESI): [M+Na]⁺ C₁₀H₈NO₂NaI: calcd. 323.9492, found 323.9481.

Ethyl 4-methylenehexanoate (252)

In two necked round bottom flask equipped with Dean Stark apparatus connected with a reflux condenser, a solution of alcohol **321** (2.65 g, 30.84 mmol, 1 eq.), triethyl-orthoacetate (6.21 mL, 33.92 mmol, 1.1 eq.) and acetic acid (0.17 mL, 3.084 mmol, 0.1 eq.) were added. The reaction mixture was refluxed at 170°C for 12h. The solvent was evaporated under vacuum then the crude material was purified by chromatography on silica gel using (PE/EtOAc 98/2). The olefin **252** was obtained as colorless oil (3.360 g, 70%).

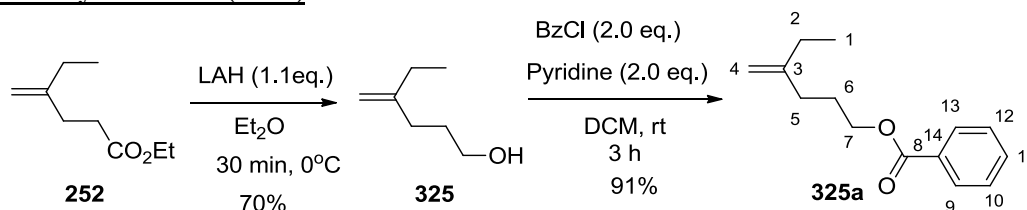
R_f = 0.52 (Pentane/Et₂O 98/2).

IR (ATR) ν_{max} (cm⁻¹) = 3253, 2976, 2928, 2856, 1730, 1621, 1457, 1261, 1091.

H NMR (CDCl₃, 300 MHz): δ (ppm) = 4.74-4.68 (m, 2H, H-1), 4.11 (q, 2H, *J* = 7.2 Hz, H-8), 2.46-2.30 (m, 4H, H-5 and H-6), 2.02 (q, 2H, *J* = 7.5 Hz, H-3), 1.24 (t, 3H, *J* = 7.2 Hz, H-9), 1.02 (t, 3H, *J* = 7.5 Hz, H-4).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 173.3 (C-7), 149.7 (C-2), 107.9 (C-1), 60.2 (C-8), 32.7 (C-5), 31.1 (C-6), 28.8 (C-3), 14.2 (C-9), 12.26 (C-4).

HRMS (ESI): [M+H]⁺ C₉H₁₆O₂: calcd. 156.11503, found 156.11532.

4-Methylenehexyl benzoate (325a)

To a solution of suspended LiAlH₄ (134 mg; 3.52 mmol, 1.1 eq.) in dry Et₂O (30 mL), olefin **252** (500 mg, 3.20 mmol, 1.0 eq.) was diluted in dry Et₂O (10 mL) and added dropwise to the reaction mixture at 0°C. The reaction was stirred at this temperature for 30 min. After that, the reaction was quenched by addition of drops

of concentrated solution of NH_4Cl at 0°C . The formed solids were filtered off and the filtrate was concentrated under reduced pressure to afford alcohol **325** which is used directly in the next step without further purification.

To a solution of alcohol **325** (250 mg, 2.18 mmol, 1.0 eq.) in dry DCM (5 mL), benzoyl chloride (0.50 mL, 4.37 mmol, 2.0 eq.) and pyridine (0.35 mL, 4.37 mmol, 2.0 eq.) were added. The reaction was stirred at room temperature for 3 h. After that, the reaction was diluted by H_2O (5 mL) and the organic layer was separated and washed with solution of 5% HCl followed by saturated aqueous solution of NaHCO_3 . The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum to afford faint yellow oil which was purified by chromatography on silica gel (PE/EtOAc 95/5). The desired protected alcohol **325a** was obtained as colorless oil (434 mg, 91%).

$R_f = 0.72$ (PE/EtOAc 95/5).

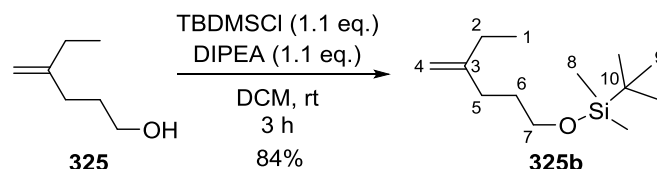
IR (ATR) ν_{max} (cm^{-1}) = 3067, 2964, 2928, 1716, 1645, 1601, 1452, 1268, 1113.

¹H NMR (CDCl_3 , 300 MHz): δ (ppm) = 8.07-8.04 (m, 2H, H-11 and H-12), 7.58-7.50 (m, 1H, H-10), 7.47-7.41 (m, 2H, H-9 and H-13), 4.78-4.76 (m, 2H, H-4), 4.33 (t, 2H, $J = 6.6$ Hz, H-7), 2.19 (t, 2H, $J = 7.5$ Hz, H-5), 2.06 (q, 2H, $J = 7.5$ Hz, H-2), 1.97-1.87 (m, 2H, H-6), 1.05 (t, 3H, $J = 7.5$ Hz, H-1)

¹³C NMR (CDCl_3 , 75 MHz): δ (ppm) = 166.5 (C-8), 150.1 (C-3), 132.8 (C-11), 130.4 (C-14), 129.6 (C-10 and C-12), 128.2 (C-9 and C-13), 108.3 (C-4), 64.6 (C-7), 32.5 (C-5), 28.7 (C-6), 26.8 (C-2), 12.3 (C-1).

HRMS (ESI): $[\text{M}+\text{H}]^+$ $\text{C}_{14}\text{H}_{18}\text{O}_2\text{Na}$: calcd. 241.1199, found 241.1190.

Tert-butyl dimethyl((4-methylenehexyl)oxy)silane (325b)



To a solution of alcohol **325** (250 mg, 2.18 mmol, 1.0 eq.) in dry DCM (10 mL), TBDMSCl (0.41 mL, 2.40 mmol, 1.1 eq.) and DIPEA (0.39 mL, 2.40 mmol, 1.1 eq.) were added. The reaction was stirred at room temperature for 3 h. After that, the reaction was diluted by saturated solution of NH_4Cl (10 mL) and the organic layer was separated and dried over Na_2SO_4 and concentrated under vacuum to afford faint yellow oil which was purified by chromatography on silica gel (pentane/ Et_2O 95/5). The desired protected alcohol **325b** was obtained as colorless oil (419 mg, 84%).

$R_f = 0.81$ (pentane/ Et_2O 95/5).

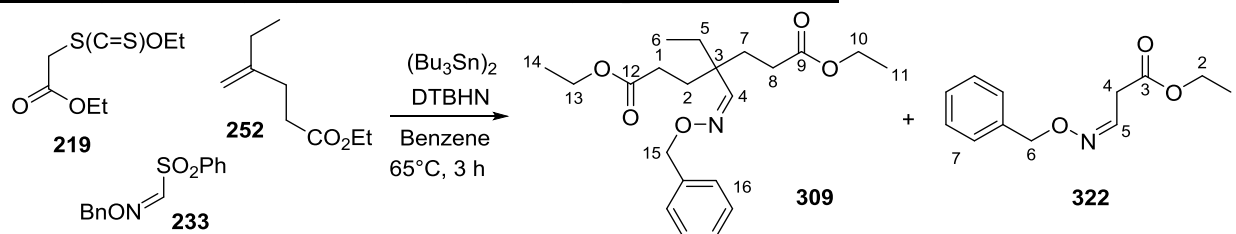
IR (ATR) ν_{max} (cm^{-1}) = 2933, 2854, 1613, 1584, 1535, 1461, 1349.

¹H NMR (CDCl_3 , 300 MHz): δ (ppm) = 4.71-4.70 (m, 2H, H-4), 3.61 (t, 2H, $J = 6.3$ Hz, H-7), 2.09-1.99 (m, 4H, H-5 and H-6), 1.68-1.63 (m, 2H, H-2), 1.03 (t, 3H, $J = 7.5$ Hz, H-1), 0.90 (s, 9H, H-9), 0.05 (s, 6H, H-8).

¹³C NMR (CDCl_3 , 75 MHz): δ (ppm) = 151.2 (C-3), 107.5 (C-4), 62.9 (C-7), 32.3 (C-5), 31.0 (C-6), 28.8 (C-2), 25.9 (C-9), 18.3 (C-10), 12.3 (C-1), -5.2 (C-8).

HRMS (ESI): $[\text{M}+\text{H}]^+$ $\text{C}_{13}\text{H}_{28}\text{OSiNa}$: calcd. 228.1909, found 228.1923.

(E)-Diethyl 4-(((benzyloxy)imino)methyl)-4-ethylheptanedioate (309)



To a solution of xanthate **219** (243.3 mg, 1.16 mmol, 1 eq.) in dry degassed benzene (11.6 mL), olefin **252** (730 mg, 4.67 mmol, 4 eq.), oxime²⁶⁹ **233** (804.1 mg, 2.33 mmol, 2.5 eq.), di(tributyl)tin (1.01g, 0.175 mmol, 1.5 eq.) and 20 mol% of DTBHN (40.7 mg, 0.23 mmol) were added. The reaction mixture was stirred for 1.5 h at 65°C . The reaction progress was monitored by TLC and further additions of DTBHN (20 mol%, 40.7 mg, 0.23 mmol) were done. The yellow reaction mixture was concentrated under reduced pressure and the residue purified by chromatography on silica gel (PE/EtOAc 95/5). The desired compound **309** was obtained as colorless oil (205 mg, 46%).

²⁶⁹ Kim, S.; Lee, I. Y.; Yoon, J. Y.; Oh, D. H. *J. Am. Chem. Soc.* **1996**, *118*, 5138.

$R_f = 0.5$ (PE/EtOAc 90/10).

IR (ATR) ν_{\max} (cm⁻¹) = 2965, 1733, 1260, 1182, 1027, 800.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 7.45-7.29 (m, 5H, H-16), 7.21 (s, 1H, H-4), 5.09 (s, 2H, H-15), 4.15 (q, 4H, $J = 6.9$ Hz, H-13 and H-10), 2.29-2.17 (m, 4H, H-1 and H-8), 1.86-1.74 (m, 4H, H-2 and H-7), 1.47 (q, 2H, $J = 7.5$ Hz, H-5), 1.29 (t, 6H, $J = 7.2$ Hz, H-11 and H-14), 0.84 (t, 3H, $J = 7.2$ Hz, H-6).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 173.6 (C-9 and C-12), 155.5 (C-4), 137.8 (C-16), 128.5 (C-16), 128.4 (C-16), 127.9 (C-16), 75.9 (C-15), 60.6 (C-10 and C-13), 41.9 (C-1 and C-8), 29.4 (C-2 and C-7), 28.9 (C-5), 27.3 (C-3), 14.3 (C-11 and C-14), 7.7 (C-6).

HRMS (ESI): [M+Na]⁺ C₂₁H₃₁NO₃Na: calcd. 400.2094, found 400.2104.

Ethyl 3-((benzyloxy)imino)propanoate (322)

(*E/Z* ratio 65/35)

$R_f = 0.71$ (PE/EtOAc 90/10).

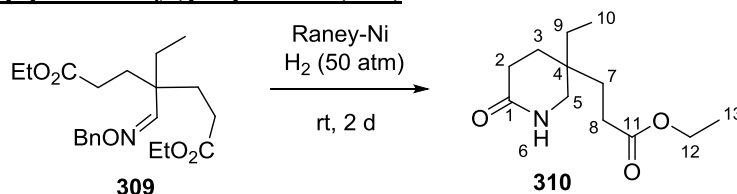
IR (ATR) ν_{\max} (cm⁻¹) = 3087, 3063, 3031, 2924, 2869, 1738, 1631, 1454, 1396, 1181, 1094.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 7.61 (t, 1H, $J = 6.3$ Hz, H-5, *Z*-isomer), 7.43-7.31 (m, 5H, H-7), 7.7 (t, 1H, $J = 4.8$ Hz, H-5, *E*-isomer), 5.18, 5.13 (s, 2H, H-6, *E/Z*), 4.21 (qd, 2H, $J = 7.2$ Hz, H-2), 3.45, 3.29 (d, 2H, $J = 4.8, 6.3$ Hz, H-4, *E/Z*), 1.30 (td, 3H, $J = 7.2$ Hz, H-1, *E/Z*).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 169.2 (C-3*E*), 144.3 (C-5*Z*), 143.8 (C-5*E*), 137.5 (C-7), 128.4 (C-7), 128.2 (C-7), 128.0 (C-7), 127.9 (C-7), 76.1 (C-6*E*), 75.9 (C-6*Z*), 61.2 (C-2*Z*), 61.1 (C-2*E*), 35.2 (C-4*Z*), 31.6 (C-4*E*), 14.2 (C-1*EZ*).

HRMS (ESI): [M+Na]⁺ C₁₂H₁₅NO₃Na: calcd. 244.0944, found 244.0954.

Ethyl 3-(3-ethyl-6-oxopiperidin-3-yl)propanoate (310)



To a solution of MCR product **309** (200 mg, 0.960 mmol, 1 eq.) in EtOAc (10 mL), a pinch of Raney nickel catalyst (slurry in water) was added. The reaction mixture was subjected to high pressure of hydrogen (50 atm.) with stirring for 2 days at room temperature. The reaction mixture was then filtered through a short pad of celite and the solvent was concentrated under reduced pressure to give the crude product which was purified by chromatography on silica gel (DCM/MeOH 95/5). The desired piperidinone **310** was obtained as a white solid (157 mg, 72%).

Mp = 62-64°C (DCM).

$R_f = 0.4$ (DCM/ MeOH 95/5).

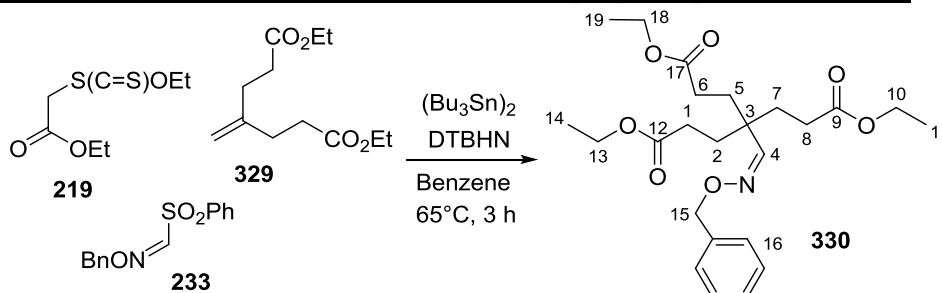
IR (KBr) ν_{\max} (cm⁻¹) = 3219, 2939, 1731, 1661, 1308, 1185.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 7.12 (br, 1H, NH), 4.06 (q, 2H, $J = 10.8$ Hz, H-12), 2.96 (d, 2H, $J = 3.3$ Hz, H-5), 2.36-2.07 (m, 4H, H-2, H-8), 1.76-1.48 (m, 4H, H-3, H-7), 1.44-1.26 (m, 2H, H-9), 1.19 (t, 3H, $J = 7.2$ Hz, H-13), 0.78 (t, 3H, $J = 7.2$ Hz, H-10).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 173.4 (C-11), 172.6 (C-1), 60.6 (C-12), 50.6 (C-5), 33.6 (C-4), 29.6 (C-9), 28.8 (C-7, C-3), 28.6 (C-11), 27.7 (C-8), 26.5 (C-2), 14.2 (C-13), 7.4 (C-10).

HRMS (ESI): [M+Na]⁺ C₁₂H₂₁NO₃Na: calcd. 250.1413, found 250.1420.

(*Z*)-diethyl 4-(((benzyloxy)imino)methyl)-4-(3-ethoxy-3-oxopropyl)heptanedioate (330)



To a solution of xanthate **219** (100 mg, 0.425 mmol, 1 eq.) in dry degassed benzene (4.2 mL), olefin **329** (388.4 mg, 1.70 mmol, 4 eq.), oxime **233** (292.8 mg, 1.06 mmol, 2.5 eq.), di(tributyl)tin (370.1 mg, 0.63

mmol, 1.5 eq.) and 20 mol% of DTBHN (14.8 mg, 0.08 mmol) were added. The reaction mixture was stirred for 1.5 h at 65°C. The reaction progress was monitored by TLC and further additions of DTBHN (20 mol%, 14.8 mg, 0.08 mmol) were made. The yellow reaction mixture was concentrated under reduced pressure and the residue purified by chromatography on silica gel (PE/EtOAc 80/20). The desired compound **330** was obtained as colorless oil (88.0 mg, 40%).

$R_f = 0.53$ (PE/EtOAc 80/20).

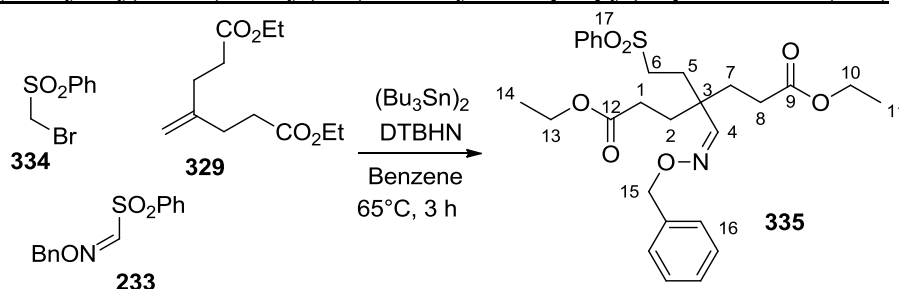
IR (ATR) ν_{\max} (cm⁻¹) = 2987, 1730, 1468, 1326, 1179, 1038, 1027

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 7.42-7.22 (m, 5H, H-16), 7.17 (s, 1H, H-4), 5.06 (s, 2H, H-15), 4.12 (qd, 6H, $J = 1.2, 7.2$ Hz, H10, H13 and H18), 2.22 (t, 6H, $J = 7.8, 8.7$ Hz, H-1, H-8, and H-6), 1.76 (t, 6H, $J = 8.7, 7.8$ Hz, H-2, H-5 and H-7), 1.26 (td, 9H, $J = 1.2, 7.2$ Hz, H-11, H-14 and H-19).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 173.2 (C-9, C-12, C-17), 154.4 (C-4), 137.5 (C-16), 128.5 (C-16), 128.4 (C-16), 127.9 (C-16), 75.9 (C-15), 60.5 (C-10, C-13, C-18), 41.3 (C-3), 29.5 (C-1, C-6, C-8), 28.6 (C-2, C-5, C-7), 14.2 (C-11, C-14, C-19).

HRMS (ESI): [M+Na]⁺ C₂₄H₃₅NO₇Na: calcd. 472.2311, found 472.2317.

(Z)-diethyl 4-(((benzyloxy)imino)methyl)-4-(3-ethoxy-3-oxopropyl)heptanedioate (335)



To a solution of bromosulfone **334** (341.6 mg, 1.45 mmol, 1 eq.) in dry degassed benzene (14.5 mL), olefin **329** (1.32 g, 5.81 mmol, 4 eq.), oxime **233** (1.0 g, 3.6 mmol, 2.5 eq.), di(tributyl)tin (1.26 g, 2.17 mmol, 1.5 eq.) and 20 mol% of DTBHN (50.6 mg, 0.29 mmol) were added. The reaction mixture was stirred for 1.5 h at 65°C. The reaction progress was monitored by TLC and further additions of DTBHN (20 mol%, 50.6 mg, 0.29 mmol) were made. The yellow reaction mixture was concentrated under reduced pressure and the residue purified by chromatography on silica gel (PE/EtOAc 80/20). The desired compound **335** was obtained as colorless oil (322 mg, 44%).

$R_f = 0.39$ (PE/EtOAc 80/20).

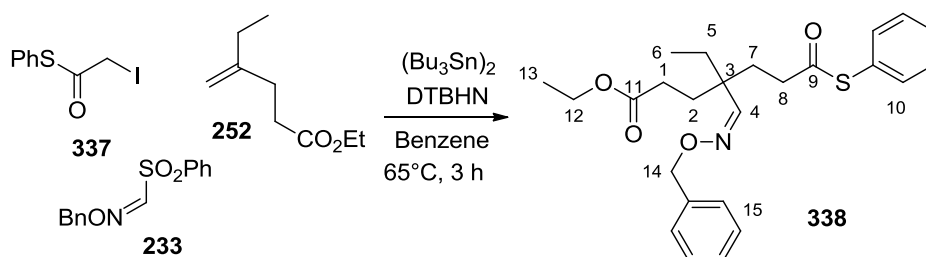
IR (ATR) ν_{\max} (cm⁻¹) = 2928, 2869, 1726, 1587, 1448, 1377, 1306, 1177.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 8.46-8.43 (m, 2H, H_{ar}), 8.28-8.13 (m, 3H, H_{ar}), 7.93-7.84 (m, 5H, H_{ar}), 7.66 (s, 1H, H-4), 5.57 (s, 2H, H-15), 4.68 (q, 4H, $J = 7.2$ Hz, H-10, H-13), 3.60-3.55 (m, 2H, H-6), 2.74-2.68 (m, 4H, H-1, H-8), 2.43-2.38 (m, 2H, H-5), 2.31-2.25 (m, 4H, H-2, H-7), 1.83 (t, 6H, $J = 6.9$ Hz, H-11, H-14).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 172.7 (C-9, C-12), 153.2 (C-4), (138.9, 137.3, 133.7, 129.3, 128.4, 128.0 (C-16, C17)), 76.0 (C-15), 60.7 (C-10, C-13), 51.1 (C-6), 41.0 (C-5), 29.8 (C-1, C-8), 28.3 (C-2, C-7), 26.7 (C-3), 14.1 (C11, C-14).

HRMS (ESI): [M+Na]⁺ C₂₇H₃₅NO₇NaS: calcd. 540.2026, found 540.2017.

(E)-Ethyl 4-(((benzyloxy)imino)methyl)-4-ethyl-7-oxo-7-(phenylthio)heptanoate (338)



To a solution of α -iodo thioester²⁷⁰ **337** (108 mg, 0.388 mmol, 1 eq.) in dry benzene (3.8 mL), olefin **252** (242 mg, 1.55 mmol, 4 eq.), oxime **233** (267 mg, 0.97 mmol, 2.5 eq.), di(tributyl)tin (338 mg, 0.58 mmol, 1.5 eq.)

²⁷⁰ Yost, J. M.; Alfie, R. J.; Tarsis, E. M.; Chong, I.; Coltart, D. M., *Chem. Commun.* **2011**, 47, 571.

were added, the reaction mixture was degassed for 20 min. The reaction was initiated by adding 20 mol% of DTBHN (13.5 mg, 0.07 mmol). The reaction mixture was then stirred for 1.5 h at 65 °C. The reaction progress was monitored by TLC and another addition of DTBHN (20 mol%, 13.5 mg, 0.07 mmol) was done then the reaction mixture was stirred for another 1.5 h at 65 °C. During the reaction progress a white precipitate was formed in the reaction medium. After 3h, the mixture was concentrated under reduced pressure and the residue purified by chromatography on silica gel with (PE/EtOAc 95/5). The desired compound **338** was obtained as colorless oil (115 mg, 67%).

$R_f = 0.27$ (PE/EtOAc 90/10).

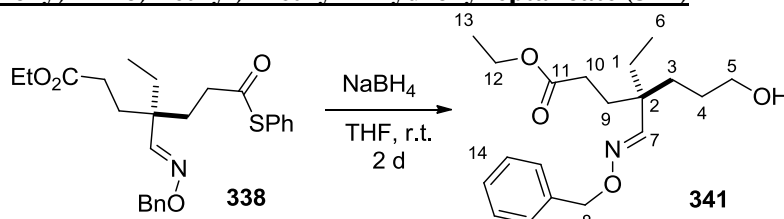
IR (ATR) ν_{\max} (cm⁻¹) = 2956, 2928, 2861, 1732, 1708, 1605, 1581, 1536, 1454, 1440

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 7.40-7.35 (m, 10H, H-10, H-15), 7.18 (s, 1H, H-4), 5.07 (s, 2H, H-14), 4.12 (q, 2H, $J = 7.0$ Hz, H-12), 2.61-2.53 (m, 2H, H-1), 2.22-2.17 (m, 2H, H-8), 1.88-1.77 (m, 4H, H-2, H-7), 1.46 (q, 2H, $J = 7.4$ Hz, H-5), 1.26 (t, 3H, $J = 7.2$ Hz, H-13), 0.82 (t, 3H, $J = 7.6$ Hz, H-6).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 197.1 (C-9), 173.4 (C-11), 155.1 (C-4), (137.7, 134.5, 129.4, 129.2, 128.5, 128.4, 127.9, 127.8 (C-10, C-15)), 75.9 (C-14), 60.5 (C-12), 41.9 (C-1), 38.3 (C-3), 29.6 (C-8), 29.4 (C-2), 28.8 (C-7), 27.4 (C-5), 14.3 (C-13), 7.6 (C-6).

HRMS (ESI): $[M+Na]^+ C_{25}H_{31}NO_4SNa$: calcd. 464.1866, found 464.1874.

(E)-Ethyl 4-(((benzyloxy)imino)methyl)-4-ethyl-7-hydroxyheptanoate (341)



To a solution of compound **338** (95 mg, 0.21 mmol) in dry THF (3 mL), was added at 0 °C NaBH₄ (24 mg, 0.63 mmol, 5.0 eq.). The reaction was stirred at r.t. for 2 days. After removal of THF under reduced pressure, the residue was quenched by adding NH₄Cl and extracted 3 times with EtOAc. The combined organic layer was washed by brine and dried over Na₂SO₄. The solvent was removed under reduced pressure and the crude yellow oil was purified by chromatography on silica gel (PE/EtOAc 70/30). The desired compound **341** was obtained as colorless oil (34 mg, 80%).

$R_f = 0.58$ (PE/EtOAc 70/30).

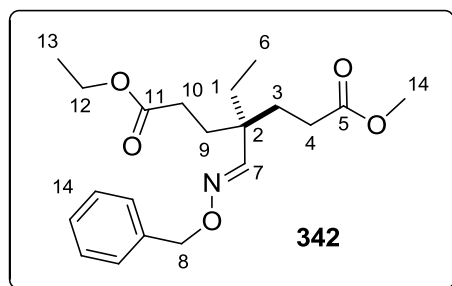
IR (ATR) ν_{\max} (cm⁻¹) = 3408, 3083, 3063, 3031, 2932, 2869, 1732, 1611, 1538, 1496, 1454, 1373.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 7.35-7.28 (m, 5H, H-14), 7.19 (s, 1H, H-7), 5.04 (s, 2H, H-8), 4.11 (q, 2H, $J = 7.2$ Hz, H-12), 3.57 (br s, 2H, H-5), 2.21-2.16 (m, 2H, H-10), 1.78-1.72 (m, 2H, H-4), 1.45-1.44 (m, 6H, H-9, H-3, H-1), 1.25 (t, 3H, $J = 7.2$ Hz, H-13), 0.79 (t, 3H, $J = 7.5$ Hz, H-6).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 173.7 (C-11), 156.3 (C-7), (137.7, 128.3, 127.8 (C-14)), 75.6 (C-8), 63.0 (C-5), 60.4 (C-12), 41.9 (C-2), 30.1 (C-4), 29.6 (C-10), 28.8 (C-3), 27.5 (C-9), 26.6 (C-1), 14.2 (C-13), 7.6 (C-6).

HRMS (ESI): $[M+Na]^+ C_{19}H_{29}NO_4Na$: calcd. 358.1988, found 358.1979.

(E)-1-Ethyl 7-methyl 4-(((benzyloxy)imino)methyl)-4-ethylheptanedioate (342)



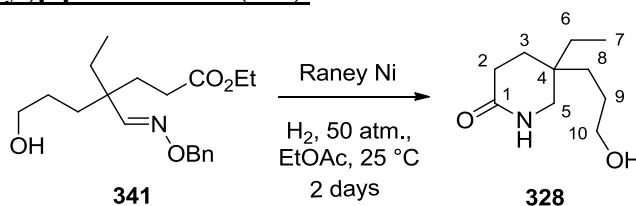
Isolated as a trans-esterification by-product during the reduction of **338** by NaBH₄ in MeOH.

IR (ATR) ν_{\max} (cm⁻¹) = 3063, 3031, 2928, 2876, 1734, 1605, 1496, 1452, 1438 1375.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 7.35-7.28 (m, 5H, H-14), 7.17 (s, 1H, H-7), 5.05 (s, 2H, H-8), 4.11 (q, 2H, $J = 7.2$ Hz, H-12), 3.66 (s, 3H, H-14), 2.24-2.16 (m, 4H, H-10, H-4), 1.78-1.72 (m, 4H, H-3, H-9), 1.43 (q, 2H, $J = 7.2$ Hz, H-1), 1.25 (t, 3H, $J = 7.2$ Hz, H-13), 0.80 (t, 3H, $J = 7.5$ Hz, H-6).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 173.9 (C-11), 173.5 (C-5), 155.3 (C-7), (137.7, 128.3, 127.8 (C-14)), 75.8 (C-8), 60.4 (C-12), 51.6 (C-14), 41.9 (C-2), 29.3 (C-4), 29.2 (C-10), 28.7 (C-3), 28.5 (C-9), 27.7 (C-1), 14.2 (C-13), 7.6 (C-6).

HRMS (ESI): $[M+Na]^+ C_{20}H_{29}NO_5Na$: calcd. 386.1937, found 386.1929.

5-Ethyl-5-(3-hydroxypropyl)piperidin-2-one (328).

To a solution of alcohol **328** (100 mg, 0.29 mmol, 1 eq.) in EtOAc (5 mL), a pinch of Raney nickel catalyst (slurry in water) was added. The reaction mixture was subjected to high pressure of hydrogen (50 atm.) with stirring for 2 days at room temperature. The reaction mixture was filtered through a short pad of celite and the solvent was concentrated under reduced pressure to give the crude product which was purified by chromatography on silica gel (DCM/MeOH 95/5). The desired compound **341** was obtained as a white solid (46 mg, 83%).

Mp = 110-111 °C (DCM).

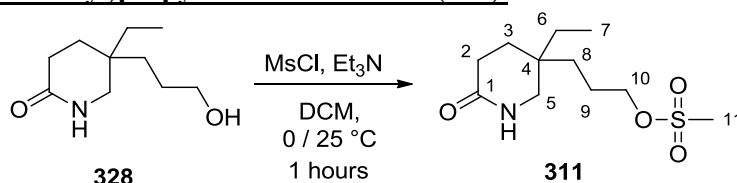
R_f = 0.31 (DCM/ MeOH 95/5).

IR (KBr) ν_{max} (cm⁻¹) = 3321, 2960, 2924, 2865, 1655, 1538, 1496, 1450, 1407, 1383.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 6.49 (br s, 1H, NH), 3.63-3.58 (m, 2H, H-10), 3.01 (d, 2H, *J* = 2.7 Hz, H-5), 2.35-2.28 (m, 2H, H-2), 1.60 (t, 2H, *J* = 6.9 Hz, H-3), 1.46-1.36 (m, 6H, H-8, H-9, H-6), 0.82 (t, 3H, *J* = 7.5 Hz, H-7).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 173.0 (C-1), 62.8 (C-10), 50.9 (C-5), 33.7 (C-2), 33.6 (C-9), 29.6 (C-3), 27.7 (C-4), 26.9 (C-8), 26.3 (C-6), 7.4 (C-7).

HRMS (ESI): [M+Na]⁺ C₁₀H₁₉NO₂Na: calcd. 208.1308, found 208.1316.

3-(3-Ethyl-6-oxopiperidin-3-yl)propyl methanesulfonate (311).

To a solution of hydroxy-lactam **328** (26 mg, 0.14 mmol) in dry DCM (3 mL), were added at 0 °C, MsCl (17.7 mg, 0.154 mmol, 1.1 eq.) and Et₃N (0.02 mL, 0.154 mmol, 1.1 eq.). The reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was then treated with a concentrated solution of NH₄Cl and extracted by DCM. The combined organic layers were dried over Na₂SO₄ and the solvent was removed under reduced pressure. The crude white solid was purified by chromatography on silica gel (DCM/MeOH 95/5). The desired compound **311** was obtained as a white solid (37 mg, 100%).

Mp = 105-106 °C (DCM).

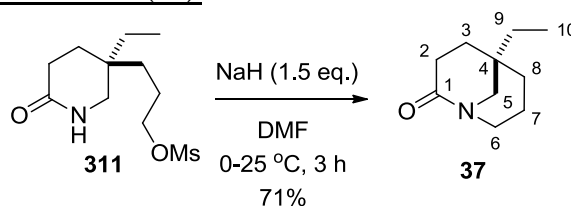
R_f = 0.54 (DCM/ MeOH 95/5).

IR (KBr) ν_{max} (cm⁻¹) = 3416, 3293, 3190, 3047, 2992, 2960, 2932, 2869, 1668, 1506, 1474, 1437, 1409.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 6.19 (br s, 1H, NH), 4.22 (t, 2H, *J* = 6.3 Hz, H-10), 3.04 (d, 2H, *J* = 3 Hz, H-5), 3.01 (s, 3H, H-11), 2.33 (t, 2H, *J* = 7.2 Hz, H-2), 1.68-1.63 (m, 4H, H-9, H-3), 1.46-1.39 (m, 4H, H-8, H-6), 0.84 (t, 3H, *J* = 7.5 Hz, H-7).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 172.5 (C-1), 70.1 (C-10), 50.7 (C-5), 37.3 (C-11), 33.6 (C-4), 29.6 (C-2), 29.4 (C-3), 27.7 (C-9), 26.6 (C-6), 23.2 (C-8), 7.4 (C-7).

HRMS (ESI): [M+Na]⁺ C₁₁H₂₁NO₄NaS: calcd. 286.1083, found 286.1082.

5-Ethyl-1-azabicyclo[3.3.1]nonan-2-one (37).

To a solution of NaH (31.4 mg, 0.78 mmol, 1.5 eq.) in dry DMF (10 mL), was added dropwise at 0 °C, mesylate **311** (138 mg, 0.52 mmol). The reaction mixture was stirred at room temperature for 3 h, and then quenched through addition of a saturated solution of NH₄Cl. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over Na₂SO₄ and the solvent removed under reduced pressure.

The crude yellow oil was purified by chromatography on silica gel (PE/EtOAc 50/50). The desired compound **37** was obtained as colorless oil (62 mg, 71%).

$R_f = 0.79$ (PE/EtOAc 50/50).

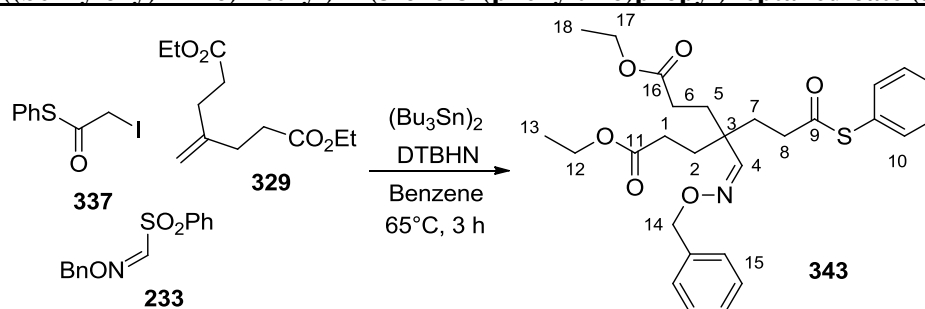
IR (KBr) ν_{\max} (cm^{-1}) = 3400, 2928, 2853, 1678, 1540, 1492, 1456, 1375, 1341.

^1H NMR (CDCl_3 , 300 MHz): δ (ppm) = 4.11 (ddd, 1H, $J = 1.2, 5.4, 13.8$ Hz, H-6a), 3.19 (d, 1H, $J = 15$ Hz, H-5a), 2.74 (dt, 1H, $J = 3.3, 12.3$ Hz, H-6b), 2.66 (d, 1H, $J = 13.5$ Hz, H-5b), 2.52-2.41 (m, 1H, H-8a), 2.31 (ddd, 1H, $J = 1.2, 5.7, 14.4$ Hz, H-8b), 1.88 (ddd, 1H, $J = 1.2, 8.1, 13.8$ Hz, H-2a), 1.75-1.60 (m, 1H, H-7a), 1.43-1.25 (m, 6H, H-2b, H-7b, H-3, H-9), 0.89 (t, 3H, $J = 7.2$ Hz, H-10).

^{13}C NMR (CDCl_3 , 75 MHz): δ (ppm) = 184.4 (C-1), 57.3 (C-5), 50.9 (C-6), 36.9 (C-4), 36.1 (C-3), 33.5 (C-8), 33.3 (C-9), 29.4 (C-2), 21.5 (C-7), 7.7 (C-10).

HRMS (ESI): $[\text{M}+\text{Na}]^+ \text{C}_{10}\text{H}_{17}\text{NONa}$: calcd. 190.1202, found 190.1209.

(Z)-diethyl 4-(((benzyloxy)imino)methyl)-4-(3-oxo-3-(phenylthio)propyl)heptanedioate (343)



To a solution of α -iodothioester **337** (100 mg, 0.35 mmol, 1 eq.) in dry benzene (3.5 mL), olefin **329** (328.3 mg, 1.43 mmol, 4 eq.), oxime **233** (247.5 mg, 0.89 mmol, 2.5 eq.), di(tributyl)tin (312.9 mg, 0.53 mmol, 1.5 eq.) were added, the reaction mixture was degassed for 20 min. The reaction was initiated by adding 20 mol% of DTBHN (12.53 mg, 0.07 mmol). The reaction mixture was then stirred for 1.5 h at 65°C. The reaction progress was monitored by TLC and another addition of DTBHN (20 mol%, 12.53 mg, 0.07 mmol) was done then the reaction mixture was stirred for another 1.5 h at 65 °C. During the reaction progress a white precipitate was formed in the reaction medium. After 3h, the mixture was concentrated under reduced pressure and the residue purified by chromatography on silica gel with (PE/EtOAc 95/5). The desired compound **343** was obtained as colorless oil (116 mg, 63%).

$R_f = 0.24$ (PE/EtOAc 90/10).

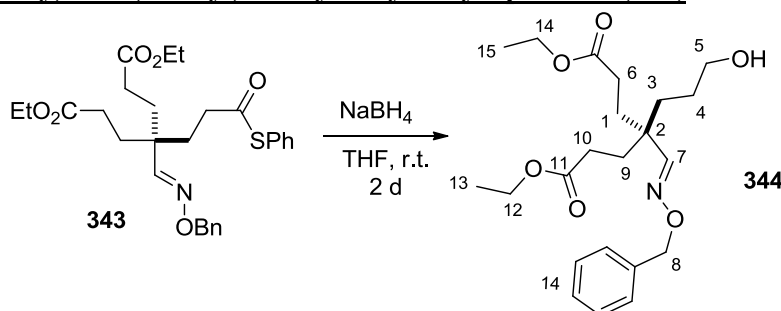
IR (ATR) ν_{\max} (cm^{-1}) = 3003, 2956, 2928, 2873, 1730, 1607, 1583, 1496, 1452, 1440, 1419, 1375.

^1H NMR (CDCl_3 , 300 MHz): δ (ppm) = 7.44-7.39 (m, 10H, H-10, H-15), 7.21 (s, 1H, H-4), 5.11 (s, 2H, H-14), 4.12 (q, 4H, $J = 7.0$ Hz, H-12, H-17), 2.64-2.59 (m, 2H, H-1), 2.29-2.13 (m, 4H, H-8, H-6), 1.89-1.78 (m, 6H, H-2, H-5, H-7), 1.30 (t, 6H, $J = 7.2$ Hz, H-13).

^{13}C NMR (CDCl_3 , 75 MHz): δ (ppm) = 196.8 (C-9), 173.0 (C-11), 154.1(C-4), (137.7, 134.5, 129.4, 129.2, 128.5, 128.4, 127.9, 127.8 (C-10, C-15)), 75.9 (C-14), 60.5 (C-12, C-17), 41.9 (C-8), 38.3 (C-3), 29.7 (C-7), 29.7(C-1, C-6), 28.5 (C-2, C-5), 14.3 (C-13, C-18).

HRMS (ESI): $[\text{M}+\text{Na}]^+ \text{C}_{28}\text{H}_{35}\text{NO}_6\text{NaS}$: calcd. 536.2077, found 536.2083.

(E)-Ethyl 4-(((benzyloxy)imino)methyl)-4-ethyl-7-hydroxyheptanoate (344)



To a solution of compound **343** (100 mg, 0.19 mmol) in dry THF (9 mL), was added at 0 °C NaBH_4 (36.8 mg, 0.95 mmol, 5.0 eq.). The reaction was stirred at r.t. for 3 days. After removal of THF under reduced pressure, the residue was quenched by adding NH_4Cl and extracted 3 times with EtOAc. The combined organic layer was washed by brine and dried over Na_2SO_4 . The solvent was removed under reduced pressure

and the crude yellow oil was purified by chromatography on silica gel (PE/EtOAc 50/50). The desired compound **344** was obtained as colorless oil (57 mg, 72%).

$R_f = 0.51$ (PE/EtOAc 50/50).

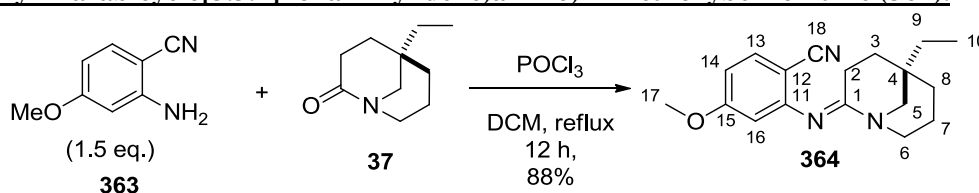
IR (ATR) ν_{\max} (cm⁻¹) = 3465, 3030, 2926, 2873, 1731, 1496, 1455, 1420, 1370.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 7.34-7.29 (m, 5H, H-14), 7.17 (s, 1H, H-7), 5.03 (s, 2H, H-8), 4.11 (q, 4H, $J = 7.2$ Hz, H-12, H-14), 3.56 (br t, 2H, H-5), 2.22-2.17 (m, 4H, H-6, H-10), 1.78-1.72 (m, 4H, H-1, H-9), 1.45-1.44 (m, 4H, H-4, H-3), 1.24 (t, 6H, $J = 7.2$ Hz, H-13, H-15).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 173.4 (C-11), 155.3 (C-7), (137.5, 128.4, 128.83, 127.8 (C-14)), 75.8 (C-8), 62.8 (C-5), 60.55 (C-12, C-14), 41.4 (C-2), 30.1 (C-4), 29.8 (C-10, C-6), 28.7 (C-9, C-1), 26.4 (C-3), 14.2 (C-13, C-15).

HRMS (ESI): $[M+Na]^+$ C₂₂H₃₃NO₆Na : calcd. 430.2200, found 430.2194.

(E)-2-((5-Ethyl-1-azabicyclo[3.3.1]nonan-2-ylidene)amino)-4-methoxybenzonitrile (364).



To a solution of bicyclic lactam **37** (50 mg, 0.29 mmol, 1.0 eq.) in dry DCM (3.0 mL), POCl₃ (0.030 mL, 0.328 mmol, 1.1 eq.) was added. The mixture was refluxed at 60°C for 3 h till consumption of the bicyclic lactam (checked by TLC). Then the reaction was cooled down to room temperature and a solution of aniline **363** (66.4 mg, 0.448 mmol, 1.5 eq.) in DCM (2.0 mL) was added dropwise. The reaction mixture was heated under reflux for 12 h. Then the solvent was evaporated under reduced pressure and the yellow oily residue was treated by an ice-cold H₂O and basified with a 30% NaOH solution up to pH = 8. The aqueous layer was extracted by DCM and the combined organic layers were washed with brine and dried over Na₂SO₄. The solvents were removed under reduced pressure and the crude yellow oil was purified by chromatography on silica gel (DCM/MeOH 99/01). The desired amidine **364** was obtained as yellow oil (78 mg, 88%).

$R_f = 0.62$ (DCM/MeOH 99/01).

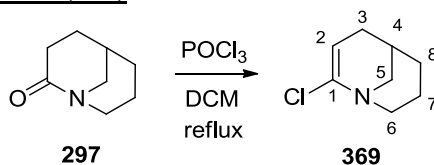
IR (ATR) ν_{\max} (cm⁻¹) = 3361, 2959, 2928, 2853, 2214, 1627, 1593, 1563, 1488, 1456, 1375.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 7.41 (d, 1H, $J = 8.7$ Hz, H-13), 6.53 (dd, 1H, $J = 2.4, 8.7$ Hz, H-14), 6.26 (d, 1H, $J = 1.8$ Hz, H-16), 4.25 (dd, 1H, $J = 4.8, 12.9$ Hz, H-6a), 3.75 (s, 3H, H-17), 3.12-2.80 (m, 2H, H-6b, H-5a), 2.60 (d, 1H, $J = 13.5$ Hz, H-5a), 2.28-2.12 (m, 3H, H-3, H-8a), 1.70 (dd, 1H, $J = 7.2, 13.8$ Hz, H-8b), 1.57-1.30 (m, 4H, H-2, H-7), 1.23 (q, 2H, $J = 6.9$ Hz, H-9), 0.82 (t, 3H, $J = 7.2$ Hz, H-10).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 170.1 (C-1), 163.4 (C-11), 156.4 (C-15), 134.2 (C-13), 118.8 (CN), 109.2 (C-14), 107.1 (C-16), 97.1 (C-12), 56.7 (C-5), 55.4 (C-17), 53.5 (C-6), 36.3 (C-3), 35.5 (C-9), 33.6 (C-8), 29.1 (C-4), 26.2 (C-7), 20.6 (C-2), 7.5 (C-10).

HRMS (ESI): $[M+H]^+$ C₁₈H₂₄N₃O : calcd. 298.1913, found 298.1910.

2-Chloro-1-azabicyclo[3.3.1]non-2-ene (369)



In a 10 mL two-necked round bottom flask equipped with a reflux condenser, bicyclic piperidinone **267** (60 mg, 0.43 mmol) was dissolved in dry DCM (3 mL). POCl₃ (0.044 mL, 0.47 mmol, 1.1 eq.) was introduced dropwise to the reaction mixture, which was then heated under reflux for 3 h. POCl₃ (0.044 mL; 0.47 mmol; 1.1 eq.) was then added again and the reaction mixture refluxed for another 3h, until complete consumption of piperidinone. The heating was stopped and the reaction mixture allowed to cool to room temperature. The solvent was removed under vacuum and the remaining yellow oil was dissolved in an ice. The mixture was then treated with a 30% solution of NaOH until pH = 8. Then the aqueous layer was extracted by DCM (3x). The combined organic layers were washed with brine and dried over Na₂SO₄. The solvent was removed and the crude yellow oil was purified through column chromatography (PE/EtOAc 95/5) to afford chloroenamine **369** as faint yellow oil with characteristic menthol like smell (40 mg, 60%).

$R_f = 0.71$ (PE/EtOAc 95/5).

IR (ATR) ν_{\max} (cm⁻¹) = 2932, 2865, 1641, 1444, 1363, 1339, 1330, 1308, 1266, 1238, 1218.

$^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ (ppm) = 5.58 (t, 1H, J = 3.6 Hz, H-2), 3.30 (dd, 1H, J = 3, 14.1 Hz, H-6a), 3.13 (dd, 1H, J = 1.2, 12.6 Hz, H-5a), 3.04 (dd, 1H, J = 1.8, 12.6 Hz, H-5a), 2.84-2.74 (m, 1H, H-6b), 2.41-2.31 (m, 1H, H-8a), 1.95-1.61 (m, 5H, H-4, H-3, H-7a, H-8b), 1.33-1.24 (m, 1H, H-7a).

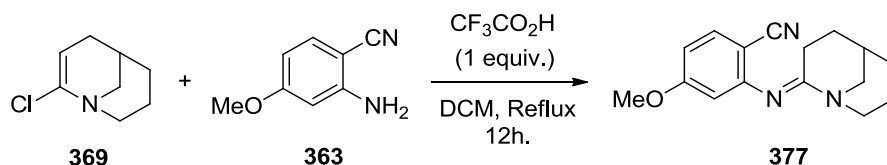
$^{13}\text{C NMR}$ (CDCl_3 , 75 MHz): δ (ppm) = 138.6 (C-1), 116.4 (C-2), 55.6 (C-5), 48.5 (C-6), 31.5 (C-4), 31.1 (C-8), 26.0 (C-3), 17.6 (C-7).

$^{13}\text{C NMR}$ (CD_2Cl_2 , 75 MHz): δ (ppm) = 138.9 (C-1), 116.2 (C-2), 55.5 (C-5), 48.4 (C-6), 31.4 (C-4), 31.0 (C-8), 26.2 (C-3), 17.6 (C-7).

HRMS (EI): $[\text{M}]^+$ $\text{C}_8\text{H}_{12}\text{ClN}$: calcd. 157.06583, found 157.06618.

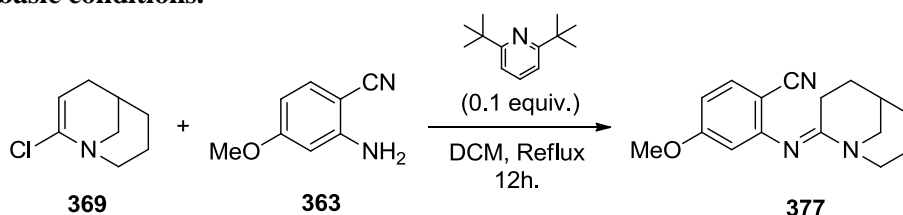
Reactions of chloroamine with aromatic anilines

a. Under acidic conditions.



To a solution of chloroamine **369** (30 mg, 0.19 mmol, 1.0 eq.) in dry DCM (2.5 mL), methoxyaminobenzonitrile **363** (42.2 mg, 0.285 mmol, 1.5 eq.) and TFA (1.4 μL , 0.019 mmol, 0.1 eq.) were added. The reaction mixture was heated under reflux for 12 h. Then the solvent was evaporated under reduced pressure and the yellow oily residue was treated by an ice-cold H_2O and basified with a 30% NaOH solution up to pH = 8. The aqueous layer was extracted by DCM and the combined organic layers were washed with brine and dried over Na_2SO_4 . The solvents were removed under reduced pressure and the crude yellow oil was purified by chromatography on silica gel (DCM/MeOH 99/1) to afford amidine **377** as yellow oil (43 mg, 84%).

b. Under basic conditions.

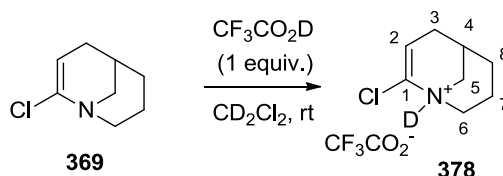


To a solution of chloroamine **369** (25 mg, 0.158 mmol, 1.0 eq.) in dry DCM (2 mL), methoxyaminobenzonitrile **363** (35.2 mg, 0.237 mmol, 1.5 eq.) and 2,6-di-*tert*-butyl pyridine (3.5 μL , 0.015 mmol, 0.1 eq.) were added. The reaction mixture was heated under reflux for 12 h. Then the solvent was evaporated under reduced pressure and the yellow oily residue was treated by an ice-cold H_2O and basified with a 30% NaOH solution up to pH = 8. The aqueous layer was extracted by DCM and the combined organic layers were washed with brine and dried over Na_2SO_4 . The solvents were removed under reduced pressure and the crude yellow oil was purified by chromatography on silica gel (DCM/MeOH 99/1) to afford amidine **377** as yellow oil (34 mg, 80%).

c. Under neutral conditions.



To a solution of chloroamine **369** (25 mg, 0.158 mmol, 1.0 eq.) in dry DCM (2 mL), methoxyaminobenzonitrile **363** (35.2 mg, 0.237 mmol, 1.5 eq.) was added. The reaction mixture was heated under reflux for 12 h. Then the solvent was evaporated under reduced pressure and the yellow oily residue was treated by an ice-cold H_2O and basified with a 30% NaOH solution up to pH = 8. The aqueous layer was extracted by DCM and the combined organic layers were washed with brine and dried over Na_2SO_4 . The solvents were removed under reduced pressure and the crude yellow oil was purified by chromatography on silica gel (DCM/MeOH 99/1) to afford amidine **377** as a yellow oil (33 mg, 77%).

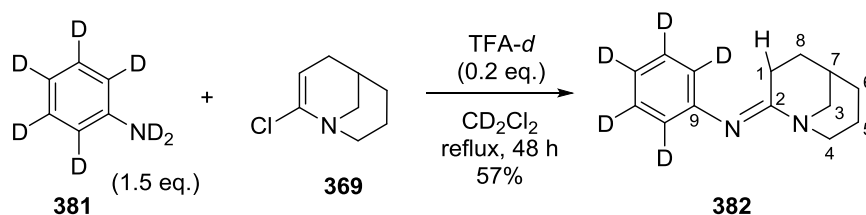
Kinetic protonation of chloroenamine**2-Chloro-1-azabicyclo[3.3.1]non-2-en-1-ium 2,2,2-trifluoroacetate (378)**

In a NMR tube, bicyclic chloroenamine **369** (10 mg, 0.06 mmol, 1.0 eq.) was dissolved in dry CD_2Cl_2 (0.5 mL). Deuterated trifluoroacetic acid (TFA-*d*) (4.8 μL , 0.06 mmol, 1.0 eq.) was then introduced dropwise to the reaction mixture to provide the desired enamine salt which was directly subjected to NMR studies. The solvent was then removed under reduced pressure and the crude reaction product submitted to high resolution mass spectroscopy.

$^1\text{H NMR}$ (CD_2Cl_2 , 300 MHz): δ (ppm) = 11.7 (s, 1H, CF_3COOH), 6.36 (t, 1H, $J = 4.2$ Hz, H-2), 3.62-3.58 (m, 1H, H-6a), 3.61 (m, 3H, H-6b, H-5), 3.49-3.39 (m, 1H, H-4), 2.70 (ddd, 1H, $J = 3.3, 7.2, 19.8$ Hz H-8a), 2.47-2.41 (m, 1H, H-8b), 2.24-2.22 (m, 1H, H-7a), 2.00-1.82 (m, 3H H-7b, H-3).

$^{13}\text{C NMR}$ (CD_2Cl_2 , 75 MHz): δ (ppm) = 159.8 (q, CF_3CO , $J = 39.75$ Hz), 128.4 (C-2), 122.8 (C-1) 115.1 (q, CF_3 , $J = 285$ Hz), 54.7 (C-5), 50.6 (C-6), 29.7 (C-4), 28.6 (C-8), 22.9 (C-3), 15.5 (C-7).

HRMS (ESI): $[\text{M}]^+ \text{C}_8\text{H}_{13}\text{ClN}^+$: calcd. 158.0731, found 158.0724.

Reaction of bicyclic enamine 369 with aniline-*d*₇

To a solution of chloroenamine **369** (50 mg, 0.31 mmol, 1.0 eq.) in dry CD_2Cl_2 (2.5 mL), aniline-*d*₇ **381** (31.77 mg, 0.317 mmol, 1.0 eq.) and TFA-*d* (2.4 μL , 0.031 mmol, 0.1 eq.) were added. The reaction mixture was heated under reflux for 48 h. Then the solvent was evaporated under reduced pressure and the yellow oily residue was treated by an ice-cold H_2O and basified with a 30% NaOH solution up to pH = 8. The aqueous layer was extracted by DCM and the combined organic layers were washed with brine and dried over Na_2SO_4 . The solvents were removed under reduced pressure and the crude yellow oil was purified by chromatography on silica gel (DCM/MeOH 99/1) to afford amidine **382** as a faint yellow oil (40 mg, 57%).

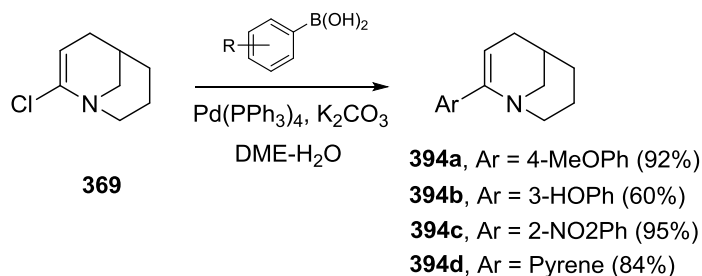
$R_f = 0.27$ (DCM/MeOH 99/1).

IR (ATR) ν_{max} (cm^{-1}) = 2929, 2854, 1633, 1563, 1456, 161, 1351, 1339, 1253, 1170.

$^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ (ppm) = 4.26-4.20 (dd, 1H, $J = 4.2, 12.9$ Hz, H-3), 3.37-3.32 (m, 1H, H-3), 3.00-2.95 (m, 2H, H-4), 2.57-2.51 (m, 1H, H-6), 2.17-1.92 (m, 5H, H-8, H-6, H-5), 1.89-1.77 (m, 1H, H-7), 1.59-1.54 (m, 2H, H-1).

$^{13}\text{C NMR}$ (CDCl_3 , 75 MHz): δ (ppm) = 169.5 (C-2), 150.5 (C-9), (128.6, 128.3, 128.0, 122.0, 121.4, 121.1, 120.8 C-Ar.), 54.2 (C-3), 51.9 (C-4), 31.2 (C-7), 28.3 (C-6), 25.1 (C-8), 24.4 (C-5), 19.5 (C-1)

HRMS (CI): $[\text{M}+\text{H}]^+ \text{C}_{14}\text{H}_{14}\text{D}_5\text{N}_2$: calcd. 220.1707, found 220.1710.

General procedure for Suzuki coupling with α -chloroenamine

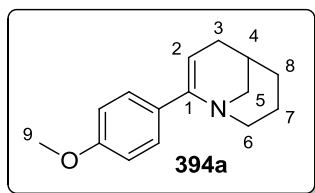
To a solution of the chloroenamine **369** (1 eq.) in freshly distilled DME (0.019 M) and H_2O (0.054 M), were added the boronic acid derivative (1.5 eq.) and K_2CO_3 (1 eq.). The flask containing the reaction mixture was flashed with argon for 30 min, then $\text{Pd}(\text{PPh}_3)_4$ (0.1 eq.) was added. The reaction mixture was heated at

95°C for 3 h, then cooled down to room temperature and the solvent was evaporated under vacuum. The residue was diluted with DCM and water and the aqueous layer was extracted with DCM. The combined extracts were dried over Na₂SO₄ and solvents were evaporated under vacuum. The crude product was purified by flash chromatography on silica gel.

2-(4-Methoxyphenyl)-1-azabicyclo[3.3.1]non-2-ene (394a)

Synthesized according to the general procedure above, from a mixture of chloroenamine **369** (30 mg, 0.190 mmol, 1 eq.) in DME (10 mL) and H₂O (3.5 mL), 4-methoxyphenylboronic acid **393a** (43.3 mg, 0.28 mmol, 1.5 eq.), K₂CO₃ (26.3 mg, 0.190 mmol, 1 eq.) and Pd(PPh₃)₄ (22 mg, 0.019 mmol, 0.1 eq.). The crude product was purified by chromatography on silica gel (PE/EtOAc 95/5) to give the enamine **394a** as yellow oil (40 mg, 92%).

R_f = 0.42 (PE/EtOAc 95/5).



IR (ATR) ν_{\max} (cm⁻¹) = 2997, 2921, 2900, 2855, 1630, 1607, 1575, 1507, 1461, 1441, 1369, 1354, 1321, 1298, 1269, 1254.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 7.50 (d, 2H, *J* = 9 Hz, Ar), 6.86 (d, 2H, *J* = 8.7 Hz, Ar), 5.85 (t, 1H, *J* = 3.6 Hz, H-2), 3.81 (s, 3H, H-9), 3.19 (m, 1H, H-6a), 3.00 (dd, 1H, *J* = 1.2, 12.3 Hz, H-5a), 2.89-2.72 (m, 2H, H-6b, H-5b), 2.58-2.48 (m, 1H, H-4), 2.02-1.94 (m, 2H, H-8), 1.83-1.65 (m, 3H, H-7, H-3a), 1.16-1.12 (m, 1H, H-3b).

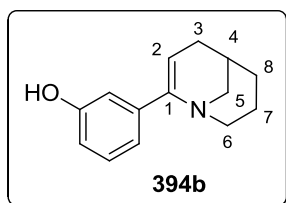
¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 159.1 (C-1), 146.3 (C-1), (130.0, 127.1, 114.3, 113.5 (C-Ar)), (C-2), 55.2 (C-9), 54.3 (C-5), 49.3 (C-6), 31.9 (C-4), 31.0 (C-8), 26.5 (C-3), 18.1 (C-7).

HRMS (ESI): [M+H]⁺ C₁₅H₂₀NO : calcd. 230.1539, found 230.1543.

3-(1-Azabicyclo[3.3.1]non-2-en-2-yl)phenol (394b)

Synthesized according to the general procedure above, from a mixture of chloroenamine **369** (30 mg, 0.190 mmol, 1 eq.) in DME (10 mL) and H₂O (3.5 mL), 3-hydroxyphenylboronic acid **393b** (39.4 mg, 0.28 mmol, 1.5 eq.), K₂CO₃ (26.3 mg, 0.19 mmol, 1 eq.) and Pd(PPh₃)₄ (22 mg, 0.019 mmol, 0.1 eq.). The crude product was purified by chromatography on silica gel (PE/EtOAc 80/20) to give the enamine **394b** as yellow oil (24.5 mg, 60%).

R_f = 0.40 (PE/EtOAc 80/20).



IR (ATR) ν_{\max} (cm⁻¹) = 3354, 2927, 2855, 2825, 1631, 1579, 1480, 1445, 1369, 1355, 1323, 1281, 1245, 1218.

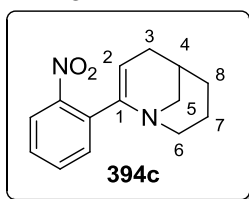
¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 7.17-7.07 (m, 3H, Ar), 6.75-6.72 (m, 1H, Ar), 5.99 (t, 1H, *J* = 3.9 Hz, H-2), 5.12 (br s, 1H, OH), 3.18 (dd, 1H, *J* = 1.2, 12.3 Hz, H-6a), 2.99 (d, 1H, *J* = 12.6 Hz, H-5a), 3.00-2.81 (m, 3H, H-6b, H-5b, H-4), 2.56-2.49 (m, 1H, H-8a), 2.03-1.95 (m, 2H, H-8b, H-7a), 1.81-1.65 (m, 3H, H-7b, H-3).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 155.8 (C-1), (149.9, 139.8, 129.3, 118.4, 117.0, 114.5 (C-Ar)), 112.9 (C-2), 54.2 (C-5), 49.4 (C-6), 31.7 (C-4), 31.0 (C-8), 26.3 (C-3), 18.0 (C-7).

HRMS (ESI): [M+H]⁺ C₁₄H₁₈NO : calcd. 216.1382, found 216.1375.

2-(2-nitrophenyl)-1-azabicyclo[3.3.1]non-2-ene (394c)

Synthesized according to the general procedure above, from a mixture of chloroenamine **369** (34 mg, 0.21 mmol, 1 eq.) in DME (11.3 mL) and H₂O (3.8 mL), 2-nitrophenylboronic acid **393c** (54 mg, 0.32 mmol, 1.5 eq.), K₂CO₃ (29.8 mg, 0.21 mmol, 1 eq.) and Pd(PPh₃)₄ (24.9 mg, 0.021 mmol, 0.1 eq.). The crude product was purified by chromatography on silica gel (PE/EtOAc 80/20) to give the enamine **394c** as deep yellow oil (50 mg, 95%).



R_f = 0.52 (PE/EtOAc 95/05).

IR (ATR) ν_{\max} (cm⁻¹) = 3057, 3035, 2927, 2857, 1637, 1604, 1574, 1529, 1459, 1445, 1366, 1332, 1322.

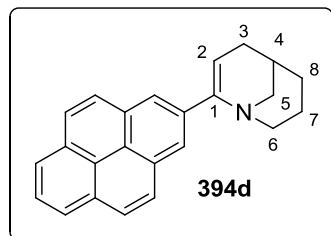
¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 7.58 (m, 1H, Ar), 7.45 (m, 2H, Ar), 7.36 (m, 1H, Ar), 5.86 (t, 1H, *J* = 3.6 Hz, H-2, H-6a), 3.01 (dd, 1H, *J* = 1.5, 12.3 Hz, H-5a), 2.90 (d, 1H, *J* = 12.3 Hz, H-6b), 2.60 (m, 3H, H-5b, H-4, H8a), 1.99 (m, 2H, H-8b, H-7a), 1.74 (m, 3H, H-7b, H-3).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 149.7 (C-1), (144.3, 134.2, 131.4, 130.7, 128.2, 123.5 (C-Ar)), 121.0 (C-2), 53.7 (C-5), 49.4 (C-6), 31.7 (C-4), 30.9 (C-8), 26.2 (C-3), 18.0 (C-7).

HRMS (ESI): [M+H]⁺ C₁₄H₁₆N₂O₂ : calcd. 245.1284, found 245.1286.

2-(Pyren-1-yl)-1-azabicyclo[3.3.1]non-2-ene (394d)

Synthesized according to the general procedure above, from a mixture of chloroenamine **369** (35 mg, 0.22 mmol, 1 eq.) in DME (11 mL) and H₂O (4 mL), pyrene-1-boronic acid **393d** (82 mg, 0.33 mmol, 1.5 eq.), K₂CO₃ (30.6 mg, 0.22 mmol, 1 eq.) and Pd(PPh₃)₄ (25.6 mg, 0.022 mmol, 0.1 eq.). The crude product was purified by chromatography on silica gel (PE/EtOAc 95/5) to give the desired enamine **394c** as a yellow solid (60 mg, 84%).



Mp = 55 °C (DCM/Hexane)

R_f = 0.40 (PE/EtOAc 95/5).

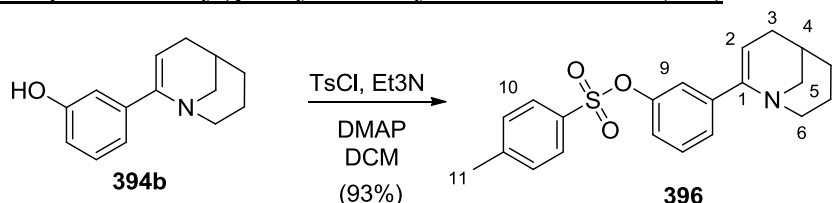
IR (KBr) ν_{\max} (cm⁻¹) = 3040, 2923, 2855, 2824, 1630, 1601, 1583, 1504, 1488, 1457, 1444, 1415.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 8.66 (d, 1H, *J* = 9.3 Hz, Ar), 8.18-7.96 (m, 8H, Ar), 5.92 (t, 1H, *J* = 3.6 Hz, H-2), 3.44-3.33 (m, 2H, H-6), 2.83-2.75 (m, 2H, H-5), 2.73-2.63 (m, 1H, H-4), 2.25 (dd, 1H, *J* = 3.9, 18.9 Hz, H-8a), 2.18-2.06 (m, 2H, H-8b, H-7a), 2.00-1.88 (m, 2H, H-7b, H-3a), 1.33-1.29

(m, 1H, H-3b).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 146.9 (C-2), (135.4, 131.3, 131.0, 130.8, 129.8, 127.6, 127.4, 127.2, 126.9, 125.8, 124.8, 127.7, 124.3 (C-Ar)), 121.8 (C-2), 54.4 (C-5), 49.2 (C-6), 31.9 (C-4), 31.3 (C-8), 26.4 (C-3), 18.5 (C-7).

HRMS (ESI): [M+H]⁺ C₂₄H₂₂N : calcd. 324.1746, found 324.1746.

3-(1-Azabicyclo[3.3.1]non-2-en-2-yl)phenyl 4-methylbenzenesulfonate (396)

To a solution of enamine **394b** (10 mg, 0.46 mmol, 1.0 eq.) in dry DCM (2.5 mL), were added at 0 °C, TsCl (9.74 mg, 0.051 mmol, 1.1 eq.), Et₃N (0.6 μ L, 0.04 mmol, 1.0 eq.) and DMAP (0.5 mg, 0.004 mmol, 0.1 eq.). The reaction mixture was stirred at 25 °C for 16 h. The reaction mixture was then treated with a concentrated solution of NH₄Cl and extracted by DCM. The combined organic layers were dried over Na₂SO₄ and the solvent was removed under reduced pressure. The crude white solid was purified by chromatography on silica gel (PE/EtOAc 9/1). The desired compound **396** was obtained as a colorless oil (16 mg, 93%).

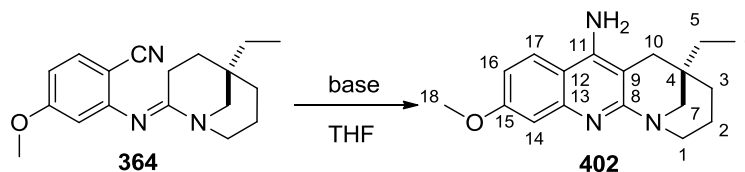
R_f = 0.62 (PE/EtOAc 9/1).

IR (ATR) ν_{\max} (cm⁻¹) = 2927, 2856, 1631, 1598, 1575, 1444, 1372, 1190, 1178

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 7.71-7.69 (m, 2H, H-9, H-10), 7.45-7.42 (m, 1H, H-9, H-10), 7.30-7.28 (m, 2H, H-9, H-10), 6.89-6.86 (m, 1H, H-9, H-10), 5.89 (t, 1H, *J* = 3.6 Hz, H-2), 3.14-3.09 (m, 1H, H-5), 2.91-2.87 (m, 1H, H-5), 2.74-2.54 (m, 3H, H-6, H-3), 2.43 (s, 3H, H-11), 2.03-1.91 (m, 4H, H-3, H-8, H7), 1.75-1.64 (m, 2H, H-7, H-4).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 149.9 (C-1), (140.2, 129.8, 129.6, 129.1, 128.6, 128.4, 124.3, 121.0, 119.9 (C-Ar)), 117.4 (C-2), 54.2 (C-5), 49.3 (C-6), 31.8 (C-4), 31.0 (C-8), 26.4 (C-3), 21.7 (C-11), 18.0 (C-7).

HRMS (ESI): [M+H]⁺ C₂₁H₂₄NO₃S: calcd. 370.1471, found 370.1474.

5-Ethyl-10-methoxy-3,4,5,6-tetrahydro-2H-1,5-methanoazocino[2,3-b]quinolin-7-amine (402)

In a 25 mL two necked round bottom flask (flame-dried and equipped with an inlet for argon) was added *n*-BuLi (0.39 mL, 0.72 mmol, 3.0 eq.), then freshly distilled diisopropylamine (DIPA) (0.10 mL, 0.75 mmol, 3.1 eq.) at r.t. During addition of DIPA, the reaction mixture forms a colorless gel. The reaction mixture was then diluted with dry THF (0.5 mL) and stirred for 30 min at r.t. Amidine **364** (72 mg, 0.24 mmol, 1.0 eq.) was dissolved in dry THF (2.5 mL) and introduced dropwise to the reaction mixture (which became clear deep yellow). The reaction mixture was allowed to react overnight at r.t., then was quenched with a few drops

of a NH_4Cl solution. THF was then evaporated under reduced pressure. The residue was diluted with a NH_4Cl solution and extracted with DCM. The combined organic layers were washed with brine and dried over Na_2SO_4 . The solvent was concentrated under reduced pressure and the residue purified by chromatography on silica gel (DCM/MeOH/ NH_4OH 95/4/1) to give **402** as a faint brown solid (50 mg, 70%).

Mp = 212°C (DCM).

R_f = 0.45 (DCM/MeOH/ NH_4OH 95/4/1).

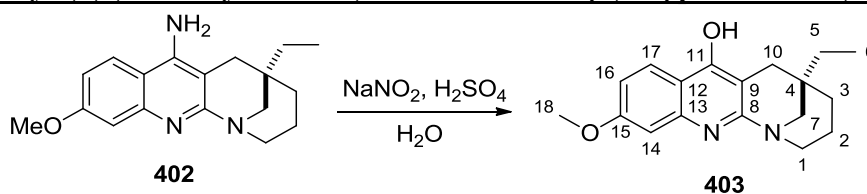
IR (KBr) ν_{max} (cm^{-1}) = 3325, 2964, 2924, 2857, 1661, 1639, 1597, 1540, 1496, 1452, 1405, 1387, 1260.

¹H NMR (CDCl_3 , 300 MHz): δ (ppm) = 7.66 (d, 1H, J = 9 Hz, H-17), 7.26 (d, 1H, H-14), 6.94 (dd, 1H, J = 2.4, 9 Hz, H-16), 5.03 (br s, 2H, NH), 3.86 (s, 3H, H-18), 3.77-3.72 (m, 1H, H-1), 3.12 (dt, 1H, J = 3.6, 13.2 Hz, H-1), 3.01 (d, 1H, J = 13.5 Hz, H-7a), 2.86 (d, 1H, J = 13.2 Hz, H-7b), 2.47 (d, 1H, J = 16.5 Hz, H-3a), 2.28 (d, 1H, J = 16.2 Hz, H-3b), 1.73-1.24 (m, 4H, H-2, H-10), 1.36 (q, 2H, J = 7.8 Hz, H-5), 0.95 (t, 3H, J = 7.2 Hz, H-6).

¹³C NMR (CDCl_3 , 75 MHz): δ (ppm) = 162.1 (C-8), 160.1 (C-11), 148.4 (C-13), 146.8 (C-15), 120.8 (C-17), 115.7 (C-16), 111.0 (C-12), 106.9 (C-14), 105.2 (C-9), 57.8 (C-7), 55.3 (C-18), 55.0 (C-1), 36.3 (C-10), 35.2 (C-5), 33.3 (C-3), 30.3 (C-4), 19.4 (C-2), 7.2 (C-6).

HRMS (ESI): $[\text{M}+\text{H}]^+$ $\text{C}_{18}\text{H}_{24}\text{N}_3\text{O}$: calcd. 298.1919, found 298.1916.

5-Ethyl-10-methoxy-3,4,5,6-tetrahydro-2H-1,5-methanoazocino[2,3-b]quinolin-7-ol (**403**)



To a solution of the amine **402** (78 mg, 0.262 mmol, 1 eq.) and H_2SO_4 (0.07 mL, 1.31 mmol, 5 eq.), NaNO_2 (90 mg, 1.31 mmol, 5 eq.) in H_2O (2 mL) was added dropwise at 0°C. Stirring was then continued for 12 h at room temperature. A 20% NaOH solution was added dropwise at 0°C until pH = 9. The aqueous layer was then extracted with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by chromatography on silica gel (DCM/MeOH/ NH_4OH 96/3/1) to give **403** as a white solid (60 mg, 77% yield).

Mp = >300°C (DCM).

R_f = 0.47 (DCM / MeOH / NH_4OH 95/4/1).

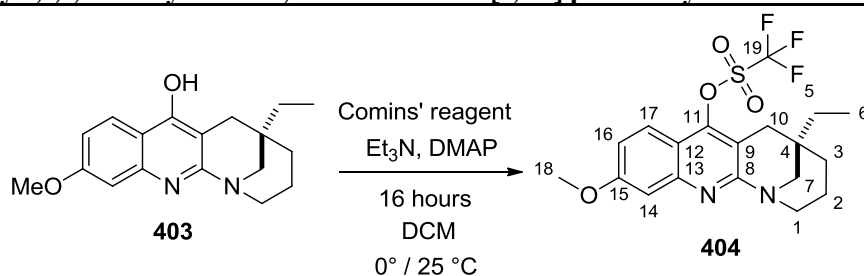
IR (KBr) ν_{max} (cm^{-1}) = 3435, 3225, 3003, 3063, 2933, 2850, 2797, 1629, 1605, 1558, 1500, 1480, 1422.

¹H NMR (CD_3OD , 300 MHz): δ (ppm) = 8.12 (d, 1H, J = 9 Hz, H-17), 6.93 (dd, 1H, J = 2.4, 9 Hz, H-14), 6.88 (d, 1H, J = 2.4 Hz, H-16), 3.90 (s, 3H, H-18), 3.44-3.33 (m, 1H, H-1a), 3.25-3.15 (m, 1H, H-1b), 2.99 (d, 1H, J = 12.9 Hz, H-7a), 2.85 (d, 1H, J = 14.1 Hz, H-7b), 2.55 (d, 2H, J = 17.4 Hz, H-3a), 2.44 (d, 1H, J = 17.4 Hz, H-3b), 1.82-1.79 (m, 1H, H-10a), 1.57-1.54 (m, 2H, H-2), 1.38 (q, 2H, J = 7.5 Hz, H-5), 1.30 (s, 1H, H-10b), 1.00 (t, 3H, J = 7.5 Hz, H-6).

¹³C NMR (CD_3OD , 75 MHz): δ (ppm) = (162.7, 126.2, 113.2, 111.3, 97.4 (Ar)), 57.8 (C-7), 54.6 (C-18), 53.8 (C-1), 35.7 (C-5), 34.5 (C-3), 31.6, 31.5, 30.3, 29.3, 22.4, 18.9 (C-2), 13.0, 5.9 (C-6).

HRMS (ESI): $[\text{M}+\text{Na}]^+$ $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_2\text{Na}$: calcd. 321.1573, found 321.1578.

5-Ethyl-10-methoxy-3,4,5,6-tetrahydro-2H-1,5-methanoazocino[2,3-b]quinolin-7-yltrifluoro-methanesulfonate (**404**)



To a solution of phenol **403** (44 mg, 0.14 mmol, 1 eq.) in dry DCM (7 mL), triethylamine (0.030 mL, 0.22 mmol, 1.5 eq.) and DMAP (9 mg, 0.073 mmol, 0.5 eq.) were added at 0°C and the reaction mixture was stirred for 30 min. The color during this period changed from colorless to deep yellow. Comins' reagent (115.8 mg, 0.29 mmol, 2 eq.) was added and the reaction mixture was stirred for 16 h at r.t. A 30% ammonium hydroxide solution was added until pH = 13 and the organic solvents were evaporated under

vacuum. The residue was then diluted with EtOAc and saturated NaCl solution, the organic layer was separated and dried over Na₂SO₄. The solvent was concentrated under reduced pressure and the crude material purified by chromatography on silica gel (DCM/MeOH 98/2) to give triflate **404** as a white solid (63 mg, 99%).

Mp = 112–113°C (DCM).

R_f = 0.53 (DCM/MeOH 98/2).

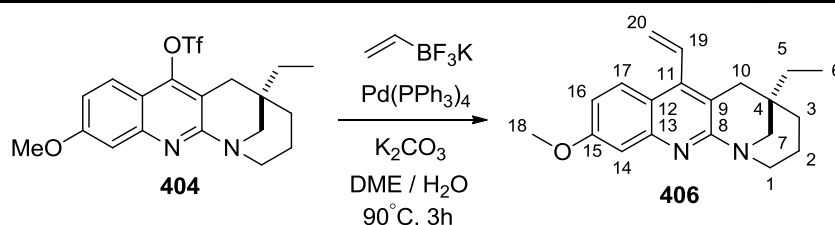
IR (KBr) ν_{\max} (cm⁻¹) = 2963, 2935, 2857, 1625, 1562, 1524, 1497, 1449, 1410, 1372, 1333, 1233, 1208.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 7.83 (d, 1H, *J* = 9.3 Hz, H-17), 7.30 (d, 1H, *J* = 2.4 Hz, H-14), 7.17 (dd, 1H, *J* = 2.4, 9.3 Hz, H-16), 3.91 (s, 3H, H-18), 3.76 (d, 1H, *J* = 12.9 Hz, H-1a), 3.21–3.14 (m, 1H, H-1b), 3.12 (dd, 1H, *J* = 1.5, 13.5 Hz, H-7a), 2.97 (br s, 1H, H-7b), 2.89 (d, 1H, *J* = 18.6 Hz, H-3a), 2.78 (d, 1H, *J* = 19.2 Hz, H-3b), 1.80 (d, 1H, *J* = 13.2 Hz, H-10a), 1.61–1.56 (m, 1H, H-2a), 1.38 (q, 2H, *J* = 7.5 Hz, H-5), 1.33–1.23 (m, 2H, H-10b, H-2b), 0.96 (t, 3H, *J* = 7.5 Hz, H-6).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 163.6 (C-8), 161.3 (C-11), 150.1 (C-13), 147.5 (C-15), 121.8 (C-17), 119.7 (C-16), 118.1 (C-19), 115.4 (C-12), 114.6 (C-14), 106.4 (C-9), 57.4 (C-7), 56.2 (C-18), 55.6 (C-1), 35.6 (C-10), 34.9 (C-5), 32.8 (C-3), 29.9 (C-4), 19.5 (C-2), 7.0 (C-6).

HRMS (ESI): [M+H]⁺ C₁₉H₂₂F₃N₂O₄S: calcd. 431.1246, found 431.1232.

5-Ethyl-10-methoxy-7-vinyl-3,4,5,6-tetrahydro-2H-1,5-methanoazocino[2,3-b]quinolone (**406**)



To a solution of the triflate **404** (63 mg, 0.146 mmol, 1 eq.) in freshly distilled DME (7 mL) and H₂O (2.5 mL), vinyl potassium trifluoroborate **405** (31 mg, 0.21 mmol, 1.5 eq.) and K₂CO₃ (20 mg, 0.186 mmol, 1 eq.) were added. The flask containing the reaction mixture was flashed with argon for 30 min, then Pd(PPh₃)₄ (17 mg, 0.014 mmol, 0.1 eq.) was added. The reaction mixture was heated at 95°C for 3 h. The reaction mixture was then cooled down to room temperature and the solvent evaporated under vacuum. The product was purified by chromatography on silica gel (EtOAc 100%) to give **406** as yellow oil (36 mg, 80%).

R_f = 0.3 (EtOAc 100%).

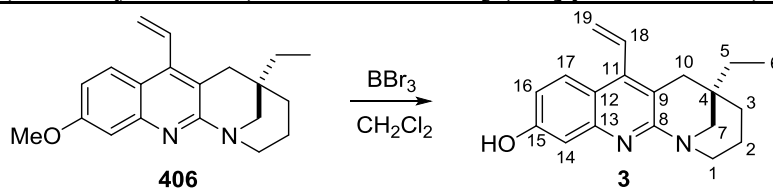
IR (ATR) ν_{\max} (cm⁻¹) = 3054, 2925, 2855, 1621, 1561, 1501, 1451, 1424, 1269, 1264, 1228, 1160.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 7.91 (d, 1H, *J* = 9.3 Hz, H-17), 7.27 (d, 1H, *J* = 2.7 Hz, H-14), 7.02 (dd, 1H, *J* = 2.7, 9.3 Hz, H-16), 6.83 (dd, 1H, *J* = 11.7, 18 Hz, H-19), 5.83 (dd, 1H, *J* = 1.8, 11.7 Hz, H-20a), 5.53 (dd, 1H, *J* = 1.8, 18 Hz, H-20b), 3.90 (s, 3H, H-18), 3.84–3.73 (m, 1H, H-1a), 3.24–3.12 (m, 1H, H-1b), 3.06 (dd, 1H, *J* = 1.8, 13.2 Hz, H-7a), 2.93 (dd, 1H, *J* = 1.5, 13.2 Hz, H-7b), 2.71 (d, 1H, *J* = 17.7 Hz, H-3a), 2.54 (dd, 1H, *J* = 1.5, 17.7 Hz, H-3b), 1.80–1.25 (m, 4H, H-2, H-10), 1.35 (q, 2H, *J* = 7.5 Hz, H-5), 0.94 (t, 3H, *J* = 7.5 Hz, H-6).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 161.6 (C-8), 160.0 (C-11), 148.4 (C-13), 143.6 (C-15), 131.9 (C-19), 126.0 (C-20), 122.6 (C-17), 121.8 (C-16), 119.2 (C-12), 117.5 (C-14), 106.5 (C-9), 57.6 (C-7), 55.7 (C-18), 55.4 (C-1), 36.6 (C-10), 36.1 (C-5), 35.1 (C-3), 30.6 (C-4), 19.5 (C-2), 7.2 (C-6).

HRMS (ESI): [M+H]⁺ C₂₀H₂₄N₂O₂: calcd. 331.1780, found 331.1774.

5-Ethyl-7-vinyl-3,4,5,6-tetrahydro-2H-1,5-methanoazocino[2,3-b]quinolin-10-ol (Eucophylline, (**3**))



To a cold (0 °C) stirred solution of compound **406** (26 mg, 0.083 mmol) in dry DCM (1 mL) under argon, was added a 1M solution of BBr₃ in DCM (0.126 mL, 0.126 mmol). The cooling bath was then removed and the resulting solution was stirred at room temperature for 16 h. The reaction mixture was then cooled to 0°C, quenched and neutralized with saturated aqueous Na₂CO₃ (1 mL). The organic layer was separated and dried over Na₂SO₄. The resulting crude product was purified through column chromatography (DCM/MeOH 98/2)

to afford Eucophylline **3** as a faint yellow solid (21.5 mg, 87%). Spectroscopic data are in good agreement with those of the natural product described by Morita *et al.*²

Mp = 159-160°C.

R_f = 0.60 (DCM/MeOH 98/2).

IR (KBr) ν_{\max} (cm⁻¹) = 3353, 3058, 2925, 2857, 1618, 1575, 1496, 1449, 1368, 1343, 1264, 1236, 1162.

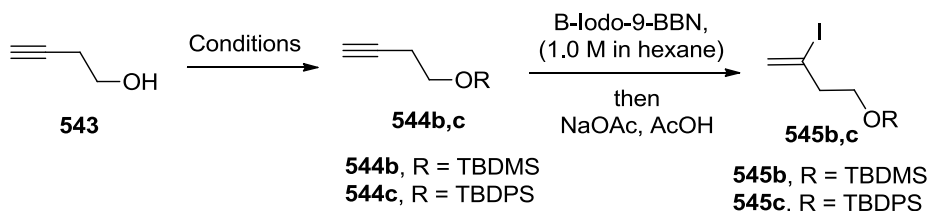
¹H NMR (CD₃OD, 400 MHz): δ (ppm) = 7.90 (d, 1H, *J* = 9.2 Hz, H-17), 7.08 (d, 1H, *J* = 2.0 Hz, H-14), 6.98 (dd, 1H, *J* = 2, 9.2 Hz, H-16), 6.90 (dd, 1H, *J* = 11.6, 18 Hz, H-18), 5.87 (d, 1H, *J* = 11.6 Hz, H-19a), 5.51 (dd, 1H, *J* = 18 Hz, H-19b), 3.62 (d, 1H, *J* = 12.8 Hz, H-1a), 3.20-3.14 (m, 1H, H-1b), 3.04 (d, 1H, *J* = 12.8 Hz, H-7a), 2.86 (d, 1H, *J* = 13.2 Hz, H-7b), 2.74 (d, 1H, *J* = 17.6 Hz, H-3a), 2.58 (d, 1H, *J* = 18 Hz, H-3b), 1.76-1.73 (m, 1H, H-10a), 1.61-1.53 (m, 1H, H-10b), 1.33 (q, 2H, *J* = 7.2 Hz, H-5), 1.22 (m, 2H, H-10b, H-2b), 0.94 (t, 3H, *J* = 7.2 Hz, H-6).

¹³C NMR (CD₃OD, 75 MHz): δ (ppm) = 160.9 (C-8), 158.4 (C-11), 147.7 (C-13), 144.8 (C-15), 131.7 (C-18), 126.1 (C-19), 122.0 (C-17), 121.1 (C-16), 118.6 (C-12), 117.3 (C-17), 107.9 (C-9), 57.1 (C-7), 55.3 (C-1), 36.2 (C-10), 35.6 (C-5), 34.6 (C-3), 30.2 (C-4), 19.0 (C-2), 5.97 (C-6).

HRMS (ESI): [M+H]⁺ C₁₉H₂₃N₂O : calcd. 295.1804, found 295.1814.

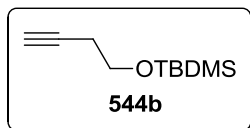
Experimental Part for Chapter Three

Olefins (545b-c)



Protection of alkyne:

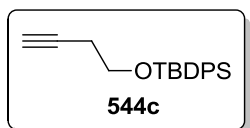
(But-3-yn-1-yloxy)(*tert*-butyl)dimethylsilane (**544b**)



To a solution of 3-butyn-1-ol **543** (3.0 g, 42.8 mmol, 1.0 eq.) and *i*-Pr₂NEt (7.78 mL, 47.08 mmol, 1.1 eq.) in DCM (65 mL), was added TBDMSCl (8.15 mL, 47.08 mmol, 1.1 eq.) to The resulting slurry at 0 °C. The reaction mixture was allowed to warm up 25 °C and stirred at that temperature for 3 h. Then, the reaction was quenched with a saturated aqueous solution of NH₄Cl (10 mL) and the separated

aqueous layer was extracted with CH₂Cl₂ (3×20 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude protected alcohol **544b** (7.71 g, 91%, brown oil) was used directly in the next step without further purifications.

(But-3-yn-1-yloxy)(*tert*-butyl)diphenylsilane (**544c**)



To a solution of 3-butyn-1-ol **543** (2.5 g, 35.7 mmol, 1.0 eq.) and imidazole (2.55 g, 35.7 mmol, 1.05 eq.) in DCM (200 mL), was added TBDPSCl (9.27 mL, 35.7 mmol, 1.1 eq.) to The resulting slurry at 0 °C. The reaction mixture was allowed to warm up 25 °C and stirred at that temperature for 16 h. Then, the reaction mixture was filtered

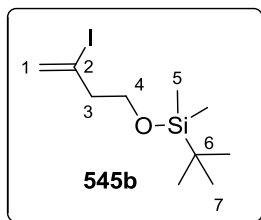
through a plug of silica gel eluting with DCM. The solvent was concentrated under reduced pressure. The crude protected alcohol **544c** (11 g, quant., colorless oil) was used directly in the next step without further purifications.

General Procedure:

To a stirred solution of alkyne **544b** or **544c** (1.0 eq.) in dry hexane, B-iodo-9-BBN (1.2 eq., 1.0 M in hexane) was added at 0 °C. The reaction mixture was allowed to slowly warm to room temperature and stirred for 16 h. the boron adduct was hydrolysed by the addition of NaOAc (1.2 eq.), followed by AcOH (3.5 eq.) and the reaction was stirred for 1 h. Then, the solution was diluted with hexane and washed with water, saturated NaHCO₃ and water respectively. The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure. The crude oil was purified by chromatography on silica gel.

***Tert*-butyl((3-iodobut-3-en-1-yl)oxy)dimethylsilane (545b)**

Synthesized according to the general procedure above from alkyne **544b** (1000 mg, 5.42 mmol, 1.0 eq.) in dry hexane (40 mL) and B-iodo-9-BBN (6.5 mL, 6.50 mmol, 1.2 eq., 1.0 M in hexane). The hydrolysed was performed by NaOAc (534 mg, 6.50 mmol, 1.2 eq.), followed by AcOH (1.1 mL, 18.99 mmol, 3.5 eq.). The crude brownish oil was purified by chromatography on silica gel (Pentane/Et₂O 95/5). The desired compound **545b** was obtained as colorless oil (765 mg, 45%).



$R_f = 0.99$ (Pentane/Et₂O 95/5).

IR (ATR) ν_{\max} (cm⁻¹) = 3413, 3064, 2931, 1456, 1427, 1258, 1107.

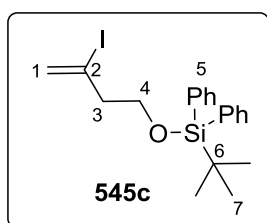
¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 6.08 (dq, 1H, $J = 1.2, 2.7$ Hz H-1a), 5.76 (d, 1H, $J = 1.5$ Hz, H-1b), 3.72 (t, 2H, $J = 6.3$ Hz, H-4), 2.63 (td, 2H, $J = 1.2, 6.6$ Hz, H-3), 0.89 (s, 9H, H-7), 0.07 (s, 6H, H-7)

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 127.4 (C-1), 97.8 (C-2), 61.7 (C-4), 48.4 (C-3), 30.3 (C-6), 25.8 (C-7), -5.2 (C-5).

HRMS (CI): $[M-H]^+$ C₁₀H₂₁IOSi: found 310.92.

***Tert*-butyl((3-iodobut-3-en-1-yl)oxy)diphenylsilane (545c)**

Synthesized according to the general procedure above from alkyne **544c** (3000 mg, 9.72 mmol, 1.0 eq.) in dry hexane (120 mL) and B-iodo-9-BBN (11.67 mL, 11.67 mmol, 1.2 eq., 1.0 M in hexane). The hydrolysed was performed by NaOAc (11.67 mg, 6.50 mmol, 1.2 eq.), followed by AcOH (0.67 mL, 11.67 mmol, 3.5 eq.). The crude brownish oil was purified by chromatography on silica gel (Pentane/Et₂O 95/5). The desired alkene **545c** was obtained as colorless oil (3.98 g, 94%).



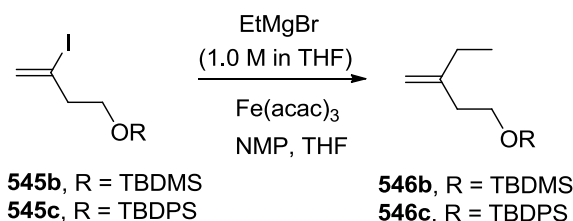
$R_f = 0.79$ (PE/EtOAc 98/2).

IR (ATR) ν_{\max} (cm⁻¹) = 3071, 3049, 2999, 2921, 2858, 1615, 1589, 1471, 1462, 1471, 1428.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 7.77-7.74 (m, 4H, Ar), 7.50-7.45 (m, 6H, Ar). 6.17-6.16 (m, 1H, H-1a), 5.85 (m, 1H, H-1b), 3.85 (t, 2H, $J = 6.3$ Hz, H-4), 2.69 (td, 2H, $J = 0.9, 6.0$ Hz, H-3), 1.12 (s, 9H, H-7).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = (135.6, 133.6, 129.7, 127.7 (C-Ar)), 127.5 (C-1), 107.6 (C-2), 62.3 (C-4), 48.2 (C-3), 41.9 (C-6), 26.8 (C-7).

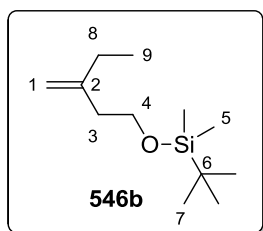
HRMS (ESI): $[M+Na]^+$ C₂₀H₂₅ONaSi: calcd. 459.0611, found 459.0611.

Olefins (546b-c)**General Procedure:**

To a solution containing **546b** or **546c** (1.0 eq.), Fe(acac)₃ (3% mol), in a mixture NMP and dry THF was added dropwise a solution of EtMgBr (1 M in THF) over 5 min. The temperature was maintained in between -5°C and 0°C during the addition. Stirring was continued for 15 min, and the reaction mixture was hydrolyzed at -10°C with aqueous HCl (10%). The reaction was diluted by ether, and then the organic layer was separated washed with saturated NaHCO₃ and water respectively. The combined organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure. The crude faint yellow oil was purified by chromatography on silica gel.

Tert-butyl dimethyl((3-methylenepentyl)oxy)silane (546b)

Synthesized according to the general procedure above from a solution containing **545b** (730 mg, 2.338 mmol, 1.0 eq.), Fe(acac)₃ (25 mg, 0.069 mmol, 3% mol), in a mixture NMP (0.632 mL) and dry THF (22 mL) and by addition of EtMgBr (2.57 mL, 2.57 mmol, 1.1 eq., 1 M in THF). The reaction mixture was hydrolyzed at -10°C with aqueous (80 ml) HCl (10%). The crude faint yellow oil was purified by chromatography on silica gel (Pentane/Et₂O 95/5). The desired alkene **546b** was obtained as colorless oil (272 mg, 54%).



$R_f = 0.85$ (PE/EtOAc 98/2).

IR (ATR) ν_{\max} (cm^{-1}) = 3073, 2960, 1645, 1595, 1471, 1259, 1097.

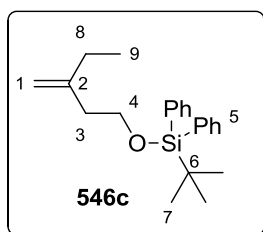
$^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ (ppm) = 4.77-4.75 (m, 1H, H1a), 4.72-4.71 (m, 1H, H1b), 3.70 (t, 2H, $J = 7.2$ Hz, H-4), 2.25 (t, 2H, $J = 7.5$ Hz, H-3), 2.04 (q, 2H, $J = 7.2$ Hz, H-8), 1.02 (t, 3H, $J = 7.5$ Hz, H-9), 0.89 (s, 9H, H-7).

$^{13}\text{C NMR}$ (CDCl_3 , 75 MHz): δ (ppm) = 148.5 (C-2), 109.1 (C-1), 62.5 (C-4), 39.6 (C-3), 29.25 (C-6), 25.8 (C-7), 18.3 (C-8), 12.3 (C-9), -5.2 (C-5).

HRMS (CI): $[\text{M}-\text{H}]^+ \text{C}_{12}\text{H}_{26}\text{IOSi}$: found 213.14.

Tert-butyl((3-methylenepentyl)oxy)diphenylsilane (546c)

Synthesized according to the general procedure above from a solution containing **545c** (3.85g, 8.82 mmol, 1.0 eq.), $\text{Fe}(\text{acac})_3$ (93.02 mg, 0.263 mmol, 3% mol), in a mixture NMP (2.38 mL) and dry THF (82 mL) and by addition of EtMgBr (9.70 mL, 9.70 mmol, 1.1 eq., 1 M in THF). The reaction mixture was hydrolyzed at -10°C with aqueous (80 ml) HCl (10%). The crude faint yellow oil was purified by chromatography on silica gel (Pentane/ Et_2O 95/5). The desired alkene **546c** was obtained as colorless oil (2.59 g, 87%).



$R_f = 0.77$ (PE/EtOAc 98/2).

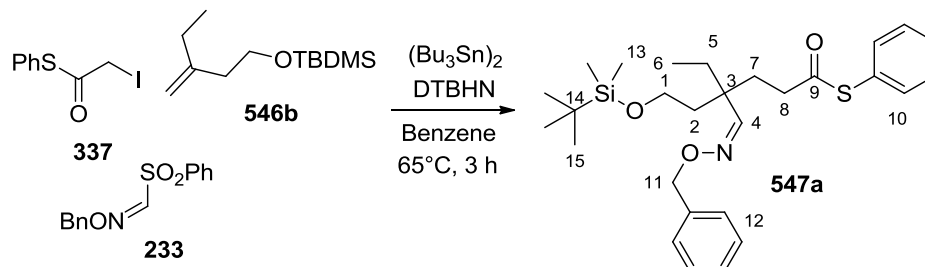
IR (ATR) ν_{\max} (cm^{-1}) = 3051, 3072, 2962, 2932, 2858, 1645, 1590, 1463, 1472, 1428, 1390.

$^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ (ppm) = 7.76-7.72 (m, 4H, Ar), 7.51-7.40 (m, 6H, Ar), 4.81-4.80 (m, 1H, H1a), 4.77-4.75 (m, 1H, H1b), 3.81 (t, 2H, $J = 7.2$ Hz, H-4), 2.36 (t, 2H, $J = 6.9$ Hz, H-3), 2.04 (q, 2H, $J = 7.5$ Hz, H-8), 1.11 (s, 9H, H-7), 1.03 (t, 3H, $J = 7.5$ Hz, H-9).

$^{13}\text{C NMR}$ (CDCl_3 , 75 MHz): δ (ppm) = 148.5 (C-2), (135.6, 134.0, 129.5, 127.6 (C-Ar)), 109.1 (C-1), 63.1 (C-4), 39.3 (C-3), 29.0 (C-6), 26.8 (C-7), 19.2 (C-8), 12.2 (C-9).

HRMS (ESI): $[\text{M}+\text{Na}]^+ \text{C}_{22}\text{H}_{30}\text{ONaSi}$: calcd. 361.1962, found 361.1958.

S-Phenyl 4-(((benzyloxy)imino)methyl)-6-((tert-butyl dimethylsilyl)oxy)-4-ethylhexanethioate (547a)



To a solution of α -iodoester **337** (81.06 mg, 0.29 mmol, 1 eq.) in dry benzene (2.9 mL), olefin **546b** (250 mg, 1.16 mmol, 4 eq.), oxime **233** (200.6 mg, 0.72 mmol, 2.5 eq.), di(tributyl)tin (253.6 mg, 0.43 mmol, 1.5 eq.) were added, the reaction mixture was degassed for 20 min. The reaction was initiated by adding 20 mol% of DTBHN (10.16 mg, 0.05 mmol). The reaction mixture was then stirred for 1.5 h at 65°C . The reaction progress was monitored by TLC and another addition of DTBHN (20 mol%, 10.16 mg, 0.05 mmol) was done then the reaction mixture was stirred for another 1.5 h at 65°C . During the reaction progress a white precipitate was formed in the reaction medium. After 3h, the mixture was concentrated under reduced pressure and the residue purified by chromatography on silica gel with (PE/EtOAc 95/5). The desired compound **547a** was obtained as colorless oil (42 mg, 29%).

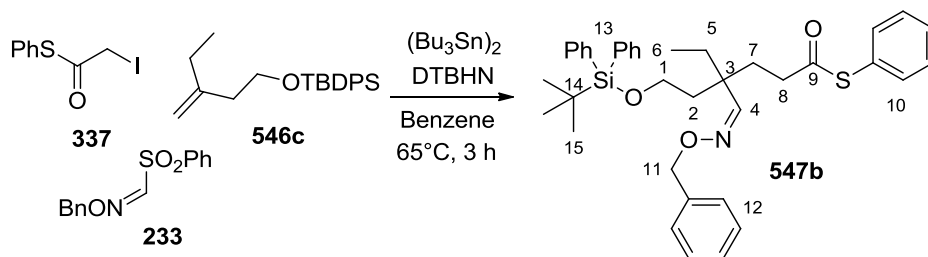
$R_f = 0.61$ (PE/EtOAc 95/05).

IR (ATR) ν_{\max} (cm^{-1}) = 2923, 2869, 1708, 1613, 1566, 1501, 1432, 1415

$^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ (ppm) = 7.42-7.31 (m, 10H, Ar), 7.27 (s, 1H, H-4), 5.09 (s, 2H, H-11), 3.64 (t, 2H, $J = 10.5$ Hz, H-1), 2.65-2.57 (m, 2H, H-8), 1.92-1.83 (m, 2H, H-7), 1.70 (t, 2H, $J = 10.2$ Hz, H-2), 1.53-1.44 (m, 2H, H-5), 0.91 (s, 9H, H-15), 0.84 (t, 3H, $J = 11.1$ Hz, H-6), 0.06 (s, 6H).

$^{13}\text{C NMR}$ (CDCl_3 , 75 MHz): δ (ppm) = 197.1 (C-9), 156.0 (C-4), (137.7, 134.5, 129.3, 129.1, 128.3, 128.8, 127.8 (C-Ar)), 75.7 (C-11), 41.5 (C-1), 38.5 (C-8), 37.3 (C-7), 30.2 (C-2), 27.9 (C-3), 25.9 (C-15), 18.3 (C-5), 7.7 (C-6), -5.3 (C-13).

HRMS (ESI): $[\text{M}+\text{Na}]^+ \text{C}_{28}\text{H}_{41}\text{NO}_3\text{NaSSi}$: calcd. 522.2474, found 522.2466.

S-Phenyl 4-(((benzyloxy)imino)methyl)-6-((*tert*-butyldimethylsilyl)oxy)-4-ethylhexanethioate (547b**)**

To a solution of α -iodo thioester **337** (81.06 mg, 0.29 mmol, 1 eq.) in dry benzene (2.9 mL), olefin **546c** (394.7 mg, 1.16 mmol, 4 eq.), oxime **233** (200.6 mg, 0.72 mmol, 2.5 eq.), di(tributyl)tin (253.6 mg, 0.43 mmol, 1.5 eq.) were added, the reaction mixture was degassed for 20 min. The reaction was initiated by adding 20 mol% of DTBHN (10.16 mg, 0.05 mmol). The reaction mixture was then stirred for 1.5 h at 65°C . The reaction progress was monitored by TLC and another addition of DTBHN (20 mol%, 10.16 mg, 0.05 mmol) was done then the reaction mixture was stirred for another 1.5 h at 65°C . During the reaction progress a white precipitate was formed in the reaction medium. After 3h, the mixture was concentrated under reduced pressure and the residue purified by chromatography on silica gel with (PE/EtOAc 95/5). The desired compound **547b** was obtained as colorless oil (72 mg, 40%).

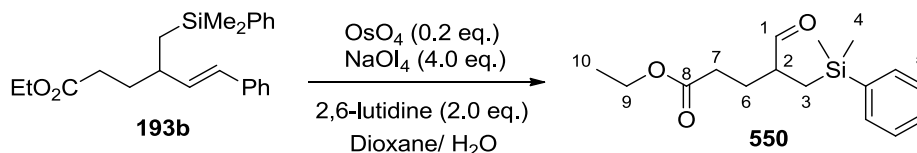
$R_f = 0.59$ (PE/EtOAc 95/05).

IR (ATR) ν_{max} (cm^{-1}) = 3070, 3032, 2960, 2931, 2880, 2857, 1711, 1588, 1472, 1454, 1441, 1428.

^1H NMR (CDCl_3 , 300 MHz): δ (ppm) = 7.59-7.56 (m, 4H, Ar), 7.32-7.24 (m, 16H, Ar), 7.11 (s, 1H, H-4), 4.95 (s, 2H, H-11), 3.57 (t, 2H, $J = 6.9$ Hz, H-1), 2.43-2.37 (m, 2H, H-8), 1.75-1.68 (m, 2H, H-7), 1.63 (t, 2H, $J = 7.2$ Hz, H-2), 1.34 (q, 2H, $J = 6.3$ Hz, H-5), 0.96 (s, 9H, H-15), 0.64 (t, 3H, $J = 7.5$ Hz H-6).

^{13}C NMR (CDCl_3 , 75 MHz): δ (ppm) = 197.2 (C-9), 155.9 (C-4), (137.7, 135.6, 134.5, 133.6, 129.7, 129.3, 129.1, 128.3, 127.8, 127.7 (C-Ar)), 75.7 (C-11), 59.9 (C-1), 41.5 (C-8), 38.4 (C-7), 37.0 (C-2), 30.1 (C-3), 27.7 (C-15), 26.8 (C-15), 7.7 (C-6).

HRMS (ESI): $[\text{M}+\text{Na}]^+ \text{C}_{38}\text{H}_{45}\text{NO}_3\text{NaSi}$: calcd. 646.2781, found 646.2798.

Ethyl 5-(dimethyl(phenyl)silyl)-4-formylpentanoate (550**)**

To a solution of **193b** (100 mg, 0.272 mmol, 1.0 eq.) in (3:1) mixture of dioxane and water (2.0 mL) was added 2,6-lutidine (0.063 mL, 0.54 mmol, 2.0 eq.), sodium periodate (233 mg, 1.09 mmol, 4.0 eq.) and osmium tetroxide solution in *t*-butanol (0.0039 mL, 0.371 mmol, 0.2 eq., 2.5 Wt %) sequentially. The reaction mixture was stirred at room temperature for 2 days. The reaction mixture was diluted by DCM (5 mL) and the organic layer was separated. The combined organic layer was dried over MgSO_4 and the solvent was removed under reduced pressure. The crude faint yellow oil was purified by chromatography on silica gel with (PE/EtOAc 95/5). The desired aldehyde **550** was obtained as colorless oil (43 mg, 54%).

$R_f = 0.37$ (PE/EtOAc 95/05).

IR (ATR) ν_{max} (cm^{-1}) = 3068, 2961, 1732, 1427, 1375, 1250.

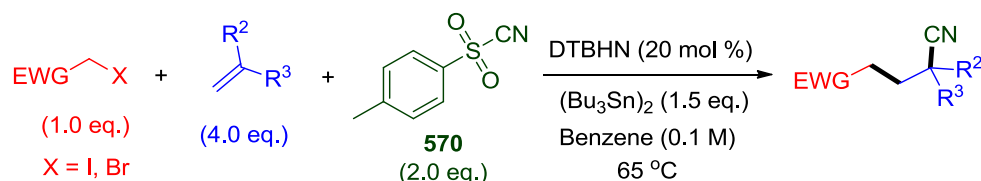
^1H NMR (CDCl_3 , 300 MHz): δ (ppm) = 9.50 (d, 1H, $J = 2.7$ Hz, H-1), 7.58-7.51 (m, 2H, Ar), 7.43-7.37 (m, 3H), 4.13 (q, 2H, $J = 7.2$ Hz, H-9), 2.57-2.19 (m, 3H, H-7, H-2), 2.00-1.72 (m, 2H, H-6), 1.26 (t, 3H, $J = 7.2$ Hz, H-10), 1.20-1.13 (m, 1H, H-3), 0.88-0.81 (m, 1H, H-3), 0.37 (s, 6H, H-4)

^{13}C NMR (CDCl_3 , 75 MHz): δ (ppm) = 203.7 (C-1), 172.9 (C-8), (133.5, 129.2, 128.0, 127.9, 127.8 (C-Ar)), 60.5 (C-9), 47.15 (C-2), 31.4 (C-7), 26.4 (C-6), 15.2 (C-3), 14.2 (C-10), -2.3 (C-4)

HRMS (ESI): $[\text{M}+\text{Na}]^+ \text{C}_{16}\text{H}_{24}\text{O}_3\text{NaSi}$: calcd. 315.1386, found 315.1399.

Carbo-Cyanation Reaction

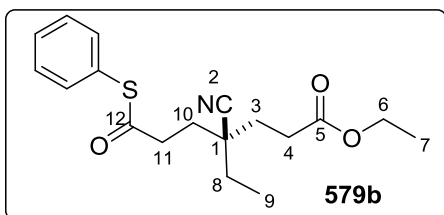
General Procedure:



To a solution of radical precursor (1.0 eq.) in dry benzene (1.0 M), olefin (4.0 or 2.0 eq.), *p*-toluenesulfonyl cyanide **570** (2.0 eq.), di(tributyl)tin (1.5 eq.) were added, the reaction mixture was degassed for 20 min. Then, the reaction was initiated by adding DTBHN (20 mol%). The reaction mixture was then stirred for 1.5 h at 65°C. The reaction progress was monitored by TLC and another addition of DTBHN (20 mol%) was done then the reaction mixture was stirred for another 1.5 h at 65 °C. After 3h, the mixture was concentrated under reduced pressure and the residue purified by chromatography on silica gel.

Ethyl 4-cyano-4-ethyl-7-oxo-7-(phenylthio)heptanoate (**579b**)

Synthesized according to the general procedure from α -iodophenylester **337** (133.5 mg, 0.48 mmol, 1.0 eq.), olefin **252** (300 mg, 1.92 mmol, 4.0 eq.), *p*-toluenesulfonyl cyanide **570** (173.9 mg, 0.96 mmol, 2.0 eq.), di(tributyl)tin (417 mg, 0.72 mmol, 1.5 eq.) and DTBHN (16.7 mg, 0.09 mmol). The crude faint yellow oil was purified by chromatography on silica gel (PE/EtOAc 90/10). The desired nitrile product **579b** was obtained as yellow oil (112 mg, 70%).



$R_f = 0.25$ (PE/EtOAc 90/10).

IR (ATR) ν_{\max} (cm^{-1}) = 3062, 2974, 2939, 2233, 1731, 1714, 1584, 1478, 1422, 1379, 1304.

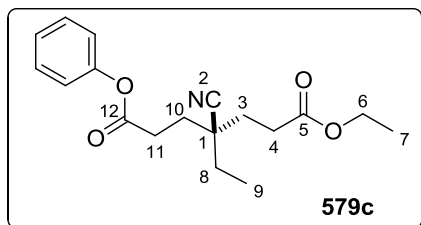
^1H NMR (CDCl_3 , 300 MHz): δ (ppm) = 7.40-7.34 (m, 5H, Ar), 4.14 (q, 2H, $J = 6.9$ Hz, H-6), 2.83-2.78 (m, 2H, H-4), 2.47-2.42 (m, 2H, H-11), 1.99-1.91 (m, 4H, H-3, H-10), 1.63 (q, 2H, $J = 7.5$ Hz, H-8), 1.25 (t, 3H, $J = 7.2$ Hz, H-7), 1.03 (t, 3H, $J = 7.5$ Hz, H-9).

^{13}C NMR (CDCl_3 , 75 MHz): δ (ppm) = 195.9 (C-12), 172.1 (C-5), (134.4, 129.6, 129.2, 127.1 (C-Ar), 122.1 (CN), 60.9 (C-6), 40.2 (C-1), 38.6 (C-4), 30.5 (C-3), 30.4 (C-10), 29.5 (C-11), 28.8 (C-8), 14.1 (C-7), 8.6 (C-9).

HRMS (ESI): $[\text{M}+\text{Na}]^+ \text{C}_{18}\text{H}_{23}\text{NO}_3\text{NaS}$: calcd. 356.1290, found 356.1286.

1-Ethyl 7-phenyl 4-cyano-4-ethylheptanedioate (**579c**)

Synthesized according to the general procedure from α -iodophenylester **580** (62 mg, 0.33 mmol, 1.0 eq.), olefin **252** (150 mg, 0.96 mmol, 4.0 eq.), *p*-toluenesulfonyl cyanide **570** (119.5 mg, 0.66 mmol, 2.0 eq.), di(tributyl)tin (208.9 mg, 0.36 mmol, 1.5 eq.) and DTBHN (8.3 mg, 0.04 mmol). The crude faint green oil was purified by chromatography on silica gel (PE/EtOAc 90/10). The desired nitrile product **579c** was obtained as faint green oil (46 mg, 60%).



$R_f = 0.29$ (PE/EtOAc 90/10).

IR (ATR) ν_{\max} (cm^{-1}) = 3064, 2960, 2232, 1757, 1732, 1593, 1493, 1456, 1420, 1379.

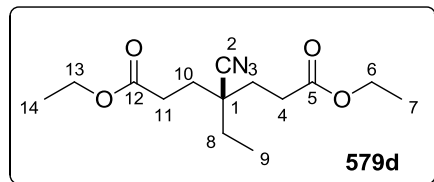
^1H NMR (CDCl_3 , 300 MHz): δ (ppm) = 7.41-7.07 (m, 5H, Ar), 4.16 (q, 2H, $J = 6.9$ Hz, H-6), 2.77-2.72 (m, 2H, H-4), 2.52-2.47 (m, 2H, H-11), 2.03-1.97 (m, 4H, H-3, H-10), 1.66 (q, 2H, $J = 7.5$ Hz, H-8), 1.27 (t, 3H, $J = 7.2$ Hz, H-7), 1.07 (t, 3H, $J = 7.5$ Hz, H-9).

^{13}C NMR (CDCl_3 , 75 MHz): δ (ppm) = 172.2 (C-5), 170.8 (C-12), (150.4, 129.5, 126.0, 121.4 (C-Ar), 122.2 (CN), 60.9 (C-6), 40.2 (C-1), 30.4 (C-4), 30.3 (C-3), 29.7 (C-10), 29.5 (C-11), 28.9 (C-8), 14.1 (C-7), 8.6 (C-9).

HRMS (ESI): $[\text{M}+\text{Na}]^+ \text{C}_{18}\text{H}_{23}\text{NO}_4\text{Na}$: calcd. 340.1519, found 340.1514.

Diethyl 4-cyano-4-ethylheptanedioate (579d)

Synthesized according to the general procedure from α -iodoethylester **324** (72 mg, 0.33 mmol, 1.0 eq.), olefin **252** (210.2 mg, 1.34 mmol, 4.0 eq.), *p*-toluenesulfonyl cyanide **570** (119.5 mg, 0.66 mmol, 2.0 eq.), di(tributyl)tin (292.8 mg, 0.50 mmol, 1.5 eq.) and DTBHN (11.7 mg, 0.06 mmol). The crude faint green oil was purified by chromatography on silica gel (PE/EtOAc 80/20). The desired nitrile product **579d** was obtained as faint green oil (48 mg, 53%).



$R_f = 0.66$ (PE/EtOAc 80/20).

IR (ATR) ν_{\max} (cm^{-1}) = 3452, 2979, 2943, 2887, 2232, 1739, 1732, 1463, 1455, 1422, 1379, 1304, 1256.

$^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ (ppm) = 4.08 (q, 4H, $J = 7.2$ Hz, H-6, H-13), 2.42-2.36 (m, 4H, H-4, H-11), 1.88-1.82 (m, 4H, H-3, H-10), 1.57 (q, 2H, $J = 5.1$ Hz, H-8), 1.20 (t, 6H, $J = 7.2$ Hz, H-7, H-14),

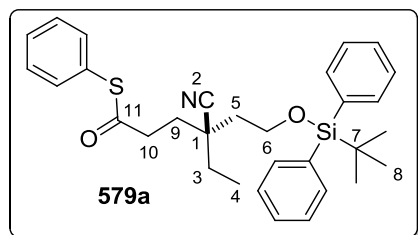
0.97 (t, 3H, $J = 7.2$ Hz, H-9).

$^{13}\text{C NMR}$ (CDCl_3 , 75 MHz): δ (ppm) = 172.2 (C-5, C-12), 122.3 (CN), 60.8 (C-6, C-13), 40.2 (C-1), 30.3 (C-4, C-11), 29.5 (C-3, C-10), 28.8 (C-8), 14.1 (C-7, C-14), 8.5 (C-9).

HRMS (ESI): $[\text{M}+\text{Na}]^+ \text{C}_{14}\text{H}_{23}\text{NO}_4\text{Na}$: calcd. 292.1519, found 292.1526.

S-Phenyl 6-((*tert*-butyldiphenylsilyloxy)-4-cyano-4-ethylhexanethioate (579a)

Synthesized according to the general procedure from α -iodothioester **337** (200 mg, 0.71 mmol, 1.0 eq.), olefin **546c** (973.9 mg, 2.87 mmol, 4.0 eq.), *p*-toluenesulfonyl cyanide **570** (257.3 mg, 1.42 mmol, 2.0 eq.), di(tributyl)tin (625.8 mg, 1.07 mmol, 1.5 eq.) and DTBHN (25.0 mg, 0.14 mmol). The crude faint yellow oil was purified by chromatography on silica gel (PE/EtOAc 95/05). The desired nitrile product **579a** was obtained as colorless oil (292 mg, 79%).



$R_f = 0.31$ (PE/EtOAc 95/05).

IR (ATR) ν_{\max} (cm^{-1}) = 3071, 2932, 2879, 2858, 2233, 1713, 1589, 1471, 1443, 1425, 1391, 1361.

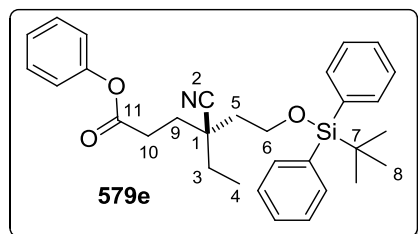
$^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ (ppm) = 7.68-7.65 (m, 3H, Ar), 7.45-7.37 (m, 12H, Ar), 3.81 (t, 2H, $J = 6.6$ Hz, H-6), 2.80-2.74 (m, 2H, H-10), 2.02-1.97 (m, 2H, H-9), 1.83 (t, 2H, $J = 6.9$ Hz, H-5), 1.64 (q, 2H, $J = 7.5$ Hz, H-3), 1.06 (s, 9H, H-8), 0.97 (t, 2H, $J = 7.5$ Hz, H-4)

$^{13}\text{C NMR}$ (CDCl_3 , 75 MHz): δ (ppm) = 196.0 (C-11), (135.5, 134.8, 134.4, 133.1, 129.8, 129.5, 129.2, 127.8 (C-Ar)), 122.6 (CN), 60.0 (C-6), 39.4 (C-1), 38.9 (C-10), 37.3 (C-5), 31.2 (C-9), 29.7 (C-7), 29.3 (C-3), 26.8 (C-3), 8.70 (C-4).

HRMS (ESI): $[\text{M}+\text{Na}]^+ \text{C}_{31}\text{H}_{37}\text{NO}_2\text{NaSiS}$: calcd. 538.2206, found 538.2203.

Phenyl 6-((*tert*-butyldiphenylsilyloxy)-4-cyano-4-ethylhexanoate (579e)

Synthesized according to the general procedure from α -iodophenylester **580** (38.7 mg, 0.14 mmol, 1.0 eq.), olefin **546c** (200 mg, 0.59 mmol, 4.0 eq.), *p*-toluenesulfonyl cyanide **570** (50.7 mg, 0.28 mmol, 2.0 eq.), di(tributyl)tin (128.5 mg, 0.22 mmol, 1.5 eq.) and DTBHN (5.1 mg, 0.02 mmol). The crude faint yellow oil was purified by chromatography on silica gel (PE/EtOAc 95/05). The desired nitrile product **579e** was obtained as colorless oil (55 mg, 75%).



$R_f = 0.48$ (PE/EtOAc 95/05).

IR (ATR) ν_{\max} (cm^{-1}) = 3072, 3048, 2965, 2932, 2884, 2858, 2233, 1760, 1593, 1494, 1471, 1428, 1391, 1306.

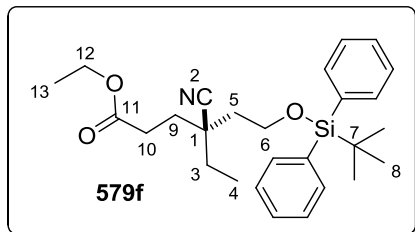
$^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ (ppm) = 7.69-7.66 (m, 4H, Ar), 7.47-7.34 (m, 9H, Ar), 7.25-7.20 (m, 1H, Ar), 7.08-7.05 (m, 1H, Ar), 3.86-3.82 (m, 2H, H-6), 2.72-2.67 (m, 2H, H-10), 2.09-2.03 (m, 2H, H-9), 1.90-1.85 (m, 2H, H-5), 1.68 (q, 2H, $J = 7.5$ Hz, H-3), 1.06 (s, 9H, H-8), 1.01 (t, 2H, $J = 7.2$ Hz, H-4)

$^{13}\text{C NMR}$ (CDCl_3 , 75 MHz): δ (ppm) = 170.9 (C-11), (150.5, 135.5, 129.8, 129.4, 127.8, 125.9, 121.4, 115.2 (C-Ar)), 122.7 (CN), 60.0 (C-6), 39.5 (C-1), 37.3 (C-5), 30.9 (C-9), 29.8 (C-10), 29.7 (C-7), 29.4 (C-3), 26.8 (C-3), 8.70 (C-4).

HRMS (ESI): $[\text{M}+\text{Na}]^+ \text{C}_{31}\text{H}_{37}\text{NO}_3\text{NaSi}$: calcd. 522.2434, found 522.2423.

Ethyl 6-((tert-butyl)diphenylsilyloxy)-4-cyano-4-ethylhexanoate (579f)

Synthesized according to the general procedure from α -iodoethyl ester **324** (31.6 mg, 0.14 mmol, 1.0 eq.), olefin **546c** (200 mg, 0.59 mmol, 4.0 eq.), *p*-toluenesulfonyl cyanide **570** (50.7 mg, 0.28 mmol, 2.0 eq.), di(tributyl)tin (128.5 mg, 0.22 mmol, 1.5 eq.) and DTBHN (5.1 mg, 0.02 mmol). The crude faint yellow oil was purified by chromatography on silica gel (PE/EtOAc 90/10). The desired nitrile product **579f** was obtained as colorless oil (52 mg, 78%).



R_f = 0.63 (PE/EtOAc 90/10).

IR (ATR) ν_{\max} (cm⁻¹) = 3047, 3068, 2961, 2932, 2892, 2857, 2232, 1736, 1471, 1460, 1472, 1390.

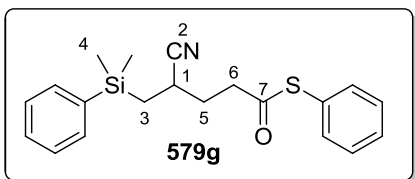
¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 7.68-7.65. (m, 3H, Ar), 7.47-7.36 (m, 7H), 4.14 (q, 2H, J = 7.2 Hz, H-12), 3.81 (t, 2H, J = 6.6 Hz, H-6), 2.44-2.39 (m, 2H, H-10), 1.96-1.91 (m, 2H, H-9), 1.83 (t, 2H, J = 6.6 Hz, H-5), 1.63 (q, 2H, J = 7.5 Hz, H-3), 1.25 (t, 3H, J = 6.9 Hz, H-13), 1.05 (s, 9H, H-8), 0.97 (t, 3H, J = 7.5 Hz, H-4).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 172.3 (C-11), (135.5, 133.1, 129.8 J = 6.9 Hz, 127.8 (C-Ar)), 122.8 (CN), 60.7 (C-12), 60.0 (C-6), 39.4 (C-1), 37.3 (C-5), 31.0 (C-9), 29.7 (C-10), 29.3 (C-3), 26.7 (C-8), 19.0 (C-7), 14.1 (C-13), 8.6 (C-4)

HRMS (ESI): [M+Na]⁺ C₂₇H₃₇NO₃NaSi: calcd. 474.2434, found 474.2428.

S-Phenyl 4-cyano-5-(dimethyl(phenyl)silyl)pentanethioate (579g)

Synthesized according to the general procedure from α -iodoethioester **337** (100 mg, 0.35 mmol, 1.0 eq.), allylsilane **265** (253.6 mg, 1.43 mmol, 4.0 eq.), *p*-toluenesulfonyl cyanide **570** (126.8 mg, 0.70 mmol, 2.0 eq.), di(tributyl)tin (312.9 mg, 0.53 mmol, 1.5 eq.) and DTBHN (12.5 mg, 0.07 mmol). The crude faint yellow oil was purified by chromatography on silica gel (PE/EtOAc 95/05). The desired nitrile product **579g** was obtained as colorless oil (111 mg, 87%).



R_f = 0.33 (PE/EtOAc 95/05).

IR (ATR) ν_{\max} (cm⁻¹) = 3069, 3056, 3022, 2929, 2956, 2236, 1704, 1585, 1478, 1441, 1427, 1410, 1362, 1327.

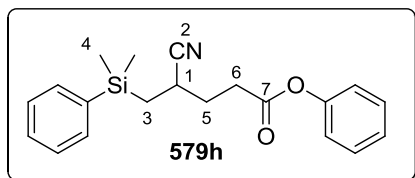
¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 7.58-7.43 (m, 10H, Ar), 2.90-2.79 (m, 2H, H-6), 2.75-2.59 (m, 1H, H-1), 2.03-1.93 (m, 2H, H-5), 1.13-0.93 (m, 2H, H-3), 0.47-0.44 (d, 6H, J = 9.9 Hz, H-4)

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 196.1 (C-7), (137.1, 134.5, 133.5, 129.64, 129.61, 129.3, 128.1, 127.2 (C-Ar)), 122.3 (CN), 40.5 (C-6), 31.1 (C-5), 26.5 (C-1), 20.0 (C-3), (-2.3, -3.0 (C-4).

HRMS (ESI): [M+Na]⁺ C₂₀H₂₃NONaSiS: calcd. 376.1161, found 376.1168.

Phenyl 4-cyano-5-(dimethyl(phenyl)silyl)pentanoate (579h)

Synthesized according to the general procedure from α -iodophenylester **580** (37.1 mg, 0.14 mmol, 1.0 eq.), allylsilane **265** (100 mg, 0.56 mmol, 4.0 eq.), *p*-toluenesulfonyl cyanide **570** (50.7 mg, 0.28 mmol, 2.0 eq.), di(tributyl)tin (123.4 mg, 0.21 mmol, 1.5 eq.) and DTBHN (4.9 mg, 0.02 mmol). The crude faint yellow oil was purified by chromatography on silica gel (PE/EtOAc 95/05). The desired nitrile product **579h** was obtained as colorless oil (38 mg, 79%).



R_f = 0.28 (PE/EtOAc 95/05).

IR (ATR) ν_{\max} (cm⁻¹) = 3070, 3047, 3017, 2957, 2926, 2236, 1760, 1593, 1493, 1455, 1427, 1378, 1317.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 7.54-7.51 (m, 2H, Ar), 7.40-7.35 (m, 5H, Ar), 7.23-7.21 (m, 1H, Ar), 7.05-7.02 (m, 2H, Ar), 2.81-2.64 (m, 3H, H-1, H-6), 2.05-1.88 (m, 2H, H-5), 1.32-1.23 (m, 1H, H-3a), 1.34-1.06 (dd, 1H, J = 5.7, 14.7 Hz, H-3b) 0.45-0.41 (d, 6H, J = 12.0 Hz, H-4)

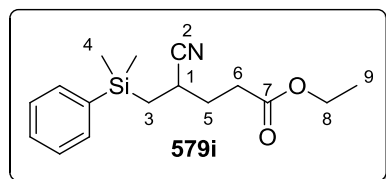
¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 170.8 (C-7), (150.4, 137.0, 133.5, 129.5, 129.4, 128.1, 126.0, 121.4 (C-Ar)), 122.4 (CN), 31.5 (C-6), 30.6 (C-5), 26.5 (C-1), 20.0 (C-3), (-2.3, -3.0 (C-4).

HRMS (ESI): [M+Na]⁺ C₂₀H₂₃NO₂NaSi: calcd. 360.1390, found 360.1406.

Ethyl 4-cyano-5-(dimethyl(phenyl)silyl)pentanoate (579i)

Synthesized according to the general procedure from α -iodoethyl ester **324** (55 mg, 0.25 mmol, 1.0 eq.), allylsilane **265** (181.1 mg, 1.02 mmol, 4.0 eq.), *p*-toluenesulfonyl cyanide **570** (90.6 mg, 0.5 mmol, 2.0 eq.), di(tributyl)tin (223.6 mg, 0.38 mmol, 1.5 eq.) and DTBHN (8.9 mg, 0.05 mmol). The crude faint yellow oil

was purified by chromatography on silica gel (PE/EtOAc 95/05). The desired nitrile product **579i** was obtained as colorless oil (71 mg, 95%).



$R_f = 0.56$ (PE/EtOAc 95/05).

IR (ATR) ν_{\max} (cm^{-1}) = 3070, 3070, 3958, 2939, 2236, 1739, 1590, 1449, 1427, 1395, 1377, 1317, 1252.

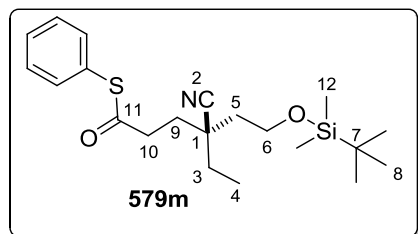
^1H NMR (CDCl_3 , 300 MHz): δ (ppm) = 7.33-7.29 (m, 2H, Ar), 7.20-7.15 (m, 3H, Ar), 3.91 (q, 2H, $J = 7.2$ Hz, H-8), 2.46-2.39 (m, 3H, H-1, H-1), 2.34-2.18 (m, 2H, H-6), 1.76-1.61 (m, 2H, H-5), 1.06-0.98 (m, 4H, H-3a, H-9), 0.88-0.82 (dd, 1H, $J = 5.7, 14.7$ Hz, H-3b), 0.23-0.20 (d, 6H, $J = 11.1$ Hz, H-4)

^{13}C NMR (CDCl_3 , 75 MHz): δ (ppm) = 172.1 (C-7), (137.1, 133.5, 129.5, 128.0 (C-Ar)), 122.5 (CN), 60.6 (C-8), 31.4 (C-6), 30.8 (C-5), 26.5 (C-1), 19.9 (C-3), 14.1 (C-9), (-2.3, -3.1 (C-4).

HRMS (ESI): $[\text{M}+\text{Na}]^+$ $\text{C}_{16}\text{H}_{23}\text{NO}_2\text{NaSi}$: calcd. 312.1390, found 312.1396.

S-Phenyl 6-((tert-butyl dimethylsilyl)oxy)-4-cyano-4-ethylhexanethioate (579m)

Synthesized according to the general procedure from α -iodothioester **337** (291.8 mg, 1.04 mmol, 1.0 eq.), olefin **546b** (450 mg, 2.09 mmol, 4.0 eq.), *p*-toluenesulfonyl cyanide **570** (376.9 mg, 2.08 mmol, 2.0 eq.), di(tributyl)tin (913.1 mg, 1.57 mmol, 1.5 eq.) and DTBHN (36.5 mg, 0.20 mmol). The crude faint yellow oil was purified by chromatography on silica gel (PE/EtOAc 95/05). The desired nitrile product **579m** was obtained as colorless oil (244 mg, 60%).



$R_f = 0.45$ (PE/EtOAc 95/05).

IR (ATR) ν_{\max} (cm^{-1}) = 3062, 2954, 2930, 2883, 2857, 2232, 1709, 1584, 1471, 1463, 1441, 1410, 1389, 1361.

^1H NMR (CDCl_3 , 300 MHz): δ (ppm) = 7.41 (s, 5H, Ar), 3.80 (t, 2H, $J = 6.6$ Hz, H-6), 2.87-2.81 (m, 2H, H-10), 2.07-2.01 (m, 2H, H-9), 1.84-1.79 (m, 2H, H-9), 1.68 (q, 2H, $J = 7.5$ Hz, H-3), 1.04 (t, 3H, $J = 7.2$ Hz, H-4), 0.90 (s, 9H, H-8), 0.77 (s, 6H, H-12).

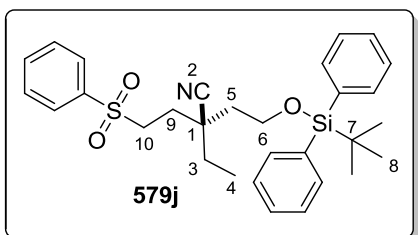
^{13}C NMR (CDCl_3 , 75 MHz): δ (ppm) = 196.1 (C-11), (136.5, 134.5, 129.5, 129.2 (C-Ar)), 122.7 (CN), 59.3 (C-6), 39.6 (C-1), 38.9 (C-10), 37.6 (C-5), 31.2 (C-9), 29.4 (C-3), 28.9 (C-7), 25.9 (C-8), 8.70 (C-4), -5.4 (C-12)

HRMS (ESI): $[\text{M}+\text{Na}]^+$ $\text{C}_{21}\text{H}_{33}\text{NO}_2\text{NaSiS}$: calcd. 414.1893, found 414.1892.

4-((tert-Butyldiphenylsilyl)oxy)-2-ethyl-2-(2-(phenylsulfonyl)ethyl)butanenitrile (579j)

Synthesized according to the general procedure from α -bromosulfone **334** (34.72 mg, 0.14 mmol, 1.0 eq.), olefin **546c** (200 mg, 0.59 mmol, 4.0 eq.), *p*-toluenesulfonyl cyanide **570** (53.52 mg, 0.29 mmol, 2.0 eq.), di(tributyl)tin (128.5 mg, 0.22 mmol, 1.5 eq.) and DTBHN (5.1 mg, 0.02 mmol). The crude faint yellow oil was purified by chromatography on silica gel (PE/EtOAc 80/20). The desired nitrile product **579j** was obtained as colorless oil (38 mg, 50%).

$R_f = 0.37$ (PE/EtOAc 80/20).



IR (ATR) ν_{\max} (cm^{-1}) = 3071, 2959, 2932, 2883, 2858, 2234, 1462, 1447, 1428, 1308, 1149.

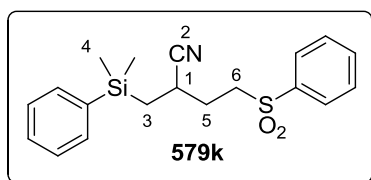
^1H NMR (CDCl_3 , 300 MHz): δ (ppm) = 7.89-7.56 (m, 2H, Ar), 7.67-7.53 (m, 7H, Ar), 7.44-7.36 (m, 6H, Ar), 3.75 (t, 2H, $J = 6.6$ Hz, H-6), 3.18-3.13 (m, 2H, H-10), 2.07-2.01 (m, 2H, H-5), 1.80-1.76 (m, 2H, H-9), 1.68-1.57 (m, 2H, H-3), 1.04 (s, 9H, H-8), 0.92 (t, 3H, $J = 7.8$ Hz, H-4)

^{13}C NMR (CDCl_3 , 75 MHz): δ (ppm) = (138.6, 135.5, 134.0, 133.0, 129.9, 129.4, 128.0, 127.8 (C-Ar)), 121.9 (CN), 59.8 (C-6), 52.0 (C-10), 39.0 (C-1), 37.4 (C-5), 29.3 (C-3), 28.7 (C-9), 26.7 (C-8), 19.0 (C-7), 8.5 (C-4)

HRMS (ESI): $[\text{M}+\text{Na}]^+$ $\text{C}_{30}\text{H}_{37}\text{NO}_3\text{NaSiS}$: calcd. 542.2155, found 542.2135.

2-((Dimethyl(phenyl)silyl)methyl)-4-(phenylsulfonyl)butanenitrile (579k)

Synthesized according to the general procedure from α -bromosulfone **334** (60.4 mg, 0.25 mmol, 1.0 eq.), allylsilane **265** (181.3 mg, 1.02 mmol, 4.0 eq.), *p*-toluenesulfonyl cyanide **570** (93.15 mg, 0.51 mmol, 1.2 eq.), di(tributyl)tin (223.6 mg, 0.38 mmol, 1.5 eq.) and DTBHN (8.9 mg, 0.05 mmol). Three additions of DTBHN were added in this reaction. The crude faint yellow oil was purified by chromatography on silica gel (PE/EtOAc 80/20). The desired nitrile product **579k** was obtained as colorless oil (47 mg, 51%).



$R_f = 0.37$ (PE/EtOAc 80/20).

IR (ATR) ν_{\max} (cm^{-1}) = 3069, 2956, 2924, 2871, 2854, 2237, 1586, 1447, 1427, 1377, 1308, 1377, 1308.

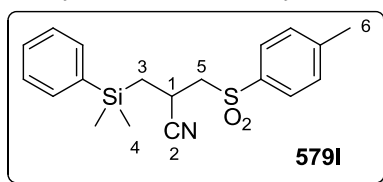
$^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ (ppm) = 7.88-7.85 (m, 2H, Ar), 7.60- 7.38 (m, 8H, Ar), 3.29-3.08 (m, 2H, H-6), 2.68-2.63 (m, 1H, H-1), 2.07-1.93 (m, 2H, H-5), 1.21-1.16 (m, 1H, H-3a), 1.05-0.98 (dd, 1H, $J = 5.4$, 14.7 Hz, H-3b), 0.42-0.38 (d, 6H, $J = 12$ Hz, H-4).

$^{13}\text{C NMR}$ (CDCl_3 , 75 MHz): δ (ppm) = (138.7, 136.6, 134.0, 133.5, 129.7, 128.5, 128.2, 127.9 (C-Ar)), 121.5 (CN), 53.5 (C-6), 28.7 (C-5), 26.2 (C-1), 19.9 (C-3), (-2.4, -3.2 (C-4).

HRMS (ESI): $[\text{M}+\text{Na}]^+$ $\text{C}_{19}\text{H}_{23}\text{NO}_2\text{NaSiS}$: calcd. 380.1111, found 380.1114.

3-(Dimethyl(phenyl)silyl)-2-(tosylmethyl)propanenitrile (579l)

Isolated as a side-product in the previous reaction. It was formed as result from the addition of the extra equivalents of *p*-toluenesulfonyl cyanide **590** into allylsilane **265**. It is faint yellow oil, isolated in (66 mg, 34% yield based on Tosyl-CN **570**).



$R_f = 0.39$ (PE/EtOAc 80/20).

IR (ATR) ν_{\max} (cm^{-1}) = 3069, 3049, 3021, 2955, 2926, 2242, 1596, 1447, 1427, 1409, 1380, 1323, 1304.

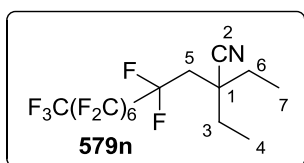
$^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ (ppm) = 7.53-7.06 (m, 9H, Ar), 3.18-3.13 (m, 1H, H-5a), 2.95-2.88 (m, 2H, H-1, H-5b), 2.25 (s, 3H, H-6), 1.82-1.07 (m, 2H, H-3), 0.24-0.20 (d, 6H, $J = 12.9$ Hz, H-4)

$^{13}\text{C NMR}$ (CDCl_3 , 75 MHz): δ (ppm) = (145.6, 136.3, 135.2, 133.6, 130.2, 129.7, 129.3, 128.2 (C-Ar)), 120.2 (CN), 59.7 (C-6), 22.4 (C-1), 21.7 (C-6), 20.1 (C-3) (-2.4, -3.4 (C-4).

HRMS (ESI): $[\text{M}+\text{Na}]^+$ $\text{C}_{19}\text{H}_{23}\text{NO}_2\text{NaSiS}$: calcd. 380.1111, found 380.1110.

2,2-Diethyl-4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecanenitrile (579n)

Synthesized according to the general procedure from perfluorooctyl iodide **581** (80 mg, 0.146 mmol, 1.0 eq.), olefin **582** (49.33 mg, 0.586 mmol, 4.0 eq.), *p*-toluenesulfonyl cyanide **570** (31.86 mg, 0.175 mmol, 1.2 eq.), di(tributyl)tin (127.5 mg, 0.21 mmol, 1.5 eq.) and DTBHN (5.1 mg, 0.02 mmol). The crude faint yellow oil was purified by chromatography on silica gel (PE/EtOAc 98/02). The desired nitrile product **579n** was obtained as colorless oil (45 mg, 58%).



$R_f = 0.32$ (PE/EtOAc 98/02).

IR (ATR) ν_{\max} (cm^{-1}) = 2956, 2924, 2857, 2237, 1720, 1582, 1479, 1460, 1441, 1374, 1290.

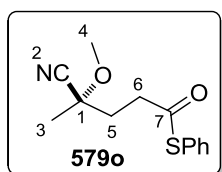
$^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ (ppm) = 2.36 (t, 2H, $J = 19.2$ Hz, H-5), 1.84 (q, 4H, $J = 7.5$ Hz H-3, H-6), 1.08 (t, 6H, $J = 7.5$ Hz, H-4, H-7).

$^{13}\text{C NMR}$ (CDCl_3 , 75 MHz): δ (ppm) = (129.4, 129.1, 126.9, 124.9 (C-F)), 121.6 (CN), 38.5 (C-1), (34.7, 34.4, 34.1 (C-5)), 29.2 (C-3, C-6), 8.5 (C-4, C-7).

HRMS (ESI): $[\text{M}+\text{Na}]^+$ $\text{C}_{15}\text{H}_{12}\text{NF}_{17}\text{Na}$: calcd. 552.0590, found 552.0609.

S-Phenyl 4-cyano-4-methoxypentanethioate (579o)

Synthesized according to the general procedure from α -iodoethioester **337** (80 mg, 0.287 mmol, 1.0 eq.), olefin **730** (82.9 mg, 1.15 mmol, 4.0 eq.), *p*-toluenesulfonyl cyanide **570** (104.3 mg, 0.57 mmol, 2.0 eq.), di(tributyl)tin (250.3 mg, 0.43 mmol, 1.5 eq.) and DTBHN (10.0 mg, 0.05 mmol). The crude faint yellow oil was purified by chromatography on silica gel (PE/EtOAc 95/05). The desired nitrile product **579o** was obtained as colorless oil (51 mg, 72%).



$R_f = 0.26$ (PE/EtOAc 95/05).

IR (ATR) ν_{\max} (cm^{-1}) = 3061, 2987, 2956, 2934, 2875, 2834, 2237, 1707, 1478, 1441, 1378, 1279.

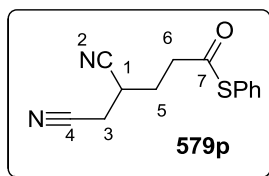
$^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ (ppm) = 7.34 (s, 5H, Ar), 3.36 (s, 3H, H-4), 2.88-2.77 (m, 2H, H-6), 2.15-2.09 (m, 2H, H-5), 1.47 (s, 3H, H-3).

$^{13}\text{C NMR}$ (CDCl_3 , 75 MHz): δ (ppm) = 196.0 (C-7), (134.5, 129.5, 129.2, 127.2 (C-Ar)), 119.0 (CN), 73.7 (C-1), 53.3 (C-4), 38.0 (C-6), 35.0 (C-5), 23.4 (C-3).

HRMS (ESI): $[\text{M}+\text{Na}]^+$ $\text{C}_{13}\text{H}_{15}\text{NO}_2\text{NaS}$: calcd. 272.0715, found 272.0707.

S-Phenyl 4,5-dicyanopentanethioate (579p)

Synthesized according to the general procedure from α -iodoethioester **337** (80 mg, 0.287 mmol, 1.0 eq.), allyl cyanide **731** (77.19 mg, 1.15 mmol, 4.0 eq.), *p*-toluenesulfonyl cyanide **570** (104.3 mg, 0.57 mmol, 2.0 eq.), di(tributyl)tin (250.3 mg, 0.43 mmol, 1.5 eq.) and DTBHN (10.0 mg, 0.05 mmol). The crude faint yellow oil was purified by chromatography on silica gel (PE/EtOAc 70/30). The desired nitrile product **579p** was obtained as colorless oil (57 mg, 81%).



$R_f = 0.5$ (PE/EtOAc 70/30).

IR (ATR) ν_{\max} (cm⁻¹) = 3060, 2930, 2875, 0857, 2247, 1701, 1478, 1440, 1419.

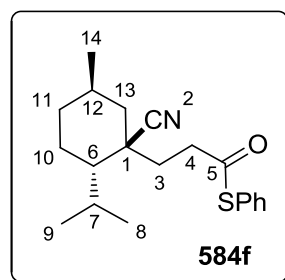
¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 7.45-7.40 (m, 5H, Ar), 3.16 (m, 1H, H-1), 3.01-2.85 (m, 2H, H-7), 2.70 (d, 2H, $J = 6.3$ Hz, H-3), 2.22-2.01 (m, 2H, H-5).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 196.1 (C-7), (134.5, 129.9, 129.4, 126.7 (C-Ar)), 118.2 (C-2), 115.3 (C-4), 39.5 (C-6), 27.6 (C-5), 26.9 (C-1), 21.0 (C-3).

HRMS (ESI): [M+Na]⁺ C₁₃H₁₂N₂ONaS: calcd. 267.0562, found 267.0567.

S-Phenyl 3-((2S,5R)-1-cyano-2-isopropyl-5-methylcyclohexyl)propanethioate (584f)

Synthesized according to the general procedure from α -iodoethioester **337** (91.3 mg, 0.328 mmol, 1.0 eq.), terpene **588** (200 mg, 1.31 mmol, 4.0 eq.), *p*-toluenesulfonyl cyanide **570** (119 mg, 0.65 mmol, 2.0 eq.), di(tributyl)tin (285.7 mg, 0.492 mmol, 1.5 eq.) and DTBHN (11.4 mg, 0.06 mmol). The crude faint yellow oil was purified by chromatography on silica gel (PE/EtOAc 98/02). The desired nitrile product **584f** was obtained as colorless oil (52 mg, 48%).



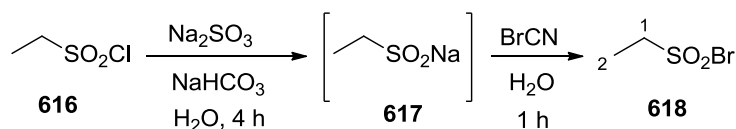
$R_f = 0.23$ (PE/EtOAc 98/02).

IR (ATR) ν_{\max} (cm⁻¹) = 3061, 2955, 2929, 2870, 2228, 1709, 1478, 1456, 1441, 1414, 1390.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 7.34 (s, 5H, Ar), 2.87-2.64 (m, 2H, H-4), 2.02-1.84 (m, 4H, H-13, H-11), 1.71-1.66 (m, 1H, H-3a), 1.53-1.08 (m, 6H, H-3b, H-10, H-12, H-6, H-7), 0.99-0.97 (d, $J = 6.9$ Hz, H-14), 0.82-0.80 (m, 6H, H-8, H-9)

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 196.5 (C-5), (134.5, 129.6, 129.2, 127.2 (C-Ar), 124.6 (CN), 49.2 (C-6), 42.2 (C-4), 41.9 (C-1), 39.2 (C-13), 34.3 (C-11), 29.1 (C-12), 26.2 (C-7), 24.3 (C-10), 23.6 (C-3), 21.9 (C-9), 21.8 (C-8), 19.5 (C-14)

HRMS (ESI): [M+Na]⁺ C₂₀H₂₇NONaS: calcd. 352.1705, found 352.1713.

Ethanesulfonyl bromide (618)

A mixture of Na₂SO₃ (1.260 g, 10 mmol, 1.0 eq.), and NaHCO₃ (1.680 g, 20 mmol, 2.0 eq.) in H₂O (40 mL) was stirred and degassed before addition of ethylsulfonyl chloride **616** (1.28 g, 10 mmol, 1.0 eq.). The reaction was stirred at room temperature for 26 h. After that, cyanogen bromide (2.183 g, 20 mmol, 2.0 eq.) was added to the reaction mixture in one portion with vigorous stirring at 0 °C and then the reaction mixture was stirred for 1 h at this temperature. The mixture was extracted with DCM (40 mL) and the aqueous layer was extracted again with EtOAc, then the organic extracts were washed with brine and dried over Na₂SO₄. The solvent was removed under reduced pressure and the crude yellow oil was purified by chromatography on silica gel (PE/EtOAc 90/10). Ethanesulfonyl bromide **618** was obtained as colorless oil (917 mg, 53%) instead of the desired ethanesulfonyl cyanide.

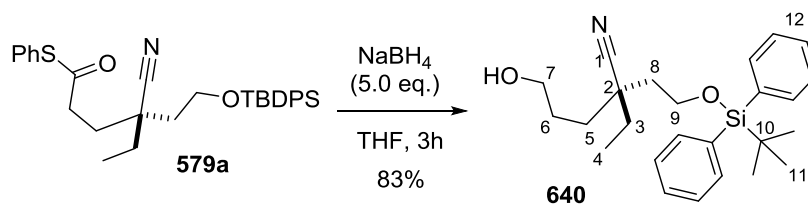
$R_f = 0.70$ (PE/EtOAc 90/10).

IR (ATR) ν_{\max} (cm⁻¹) = 2985, 2944, 2924, 2878, 1455, 1400.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 3.73 (q, 2H, $J = 6.9$ Hz, H-1), 1.45 (t, 3H, $J = 7.5$ Hz, H-2).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 64.2 (C-1), 9.6 (C-2).

HRMS (CI): [M+H]⁺ C₂H₅O₂SBr : calcd. 172.92, found 172.9, 174.9 two isotopes of bromine.

2-(2-((*tert*-Butyldiphenylsilyloxy)ethyl)-2-ethyl-5-hydroxypentanenitrile (640)

To a solution of nitrile **579a** (555 mg, 1.07 mmol) in dry THF (36.8 mL), was added at 0 °C NaBH₄ (203 mg, 5.38 mmol, 5.0 eq.). The reaction was stirred at r.t. for 3 h. After removal of THF under reduced pressure, the residue was quenched by adding NH₄Cl and extracted 3 times with EtOAc. The combined organic layer was washed by brine and dried over Na₂SO₄. The solvent was removed under reduced pressure and the crude yellow oil was purified by chromatography on silica gel (PE/EtOAc 70/30). The desired compound **640** was obtained as colorless oil (367 mg, 83%).

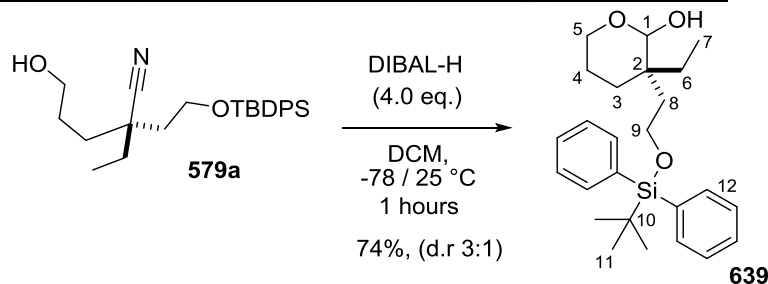
R_f = 0.66 (PE/EtOAc 70/30).

IR (ATR) ν_{max} (cm⁻¹) = 3452, 3068, 3047, 2939, 3883, 3853, 2232, 1591, 1471, 1458, 1430, 1391, 1363, 1309.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 7.68-7.65 (m, 4 H, Ar), 7.44-7.37 (m, 6H, Ar), 3.83 (t, 2H, *J* = 6.9 Hz, H-7), 3.61 (t, 2H, *J* = 4.5 Hz, H-9), 1.84 (t, 2H, *J* = 6.6 Hz, H-8), 1.66- 1.59 (m, 7H, H-3, H-5, H-6, OH), 1.05 (s, 9H, H-11), 0.96 (t, 3H, *J* = 7.2 Hz).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = (135.5, 133.3, 129.8, 127.7(C-Ar)), 123.4 (CN), 62.4 (C-7), 60.1 (C-9), 39.5 (C-8), 37.4 (C-2), 32.3 (C-6), 29.3 (C-10), 27.5 (C-5), 26.8 (C-11), 19.1 (C-3), 8.7 (C-4).

HRMS (ESI): [M+Na]⁺ C₂₅H₃₅NO₂NaSi: calcd. 432.2329, found 432.2321.

3-(2-((*tert*-Butyldiphenylsilyloxy)ethyl)-3-ethyltetrahydro-2H-pyran-2-ol (639)

To a solution of nitrile **579a** (150 mg, 0.366 mmol, 1.0 eq.) in dry DCM (18 mL) under inert conditions, DIBAL-H (1.46 mL, 1.46 mmol, 4.0 eq., 1 M in DCM) was added dropwise to the reaction mixture at -78 °C. The reaction was stirred for 1 h at room temperature. Then, the reaction was quenched with 1 M HCl (3 mL) at 0 °C. The mixture was then stirred for 15 min at room temperature then Na₂SO₄ was added to the reaction mixture and the stirred for another 15 min. Then solids were filtered through celite and the residue was concentrated under reduced pressure. The resulting crude colorless oil was purified by chromatography on silica gel (PE/EtOAc 80/20) to give lactol **639** as colorless oil (111.7 mg, 74%, d.r. 3:1).

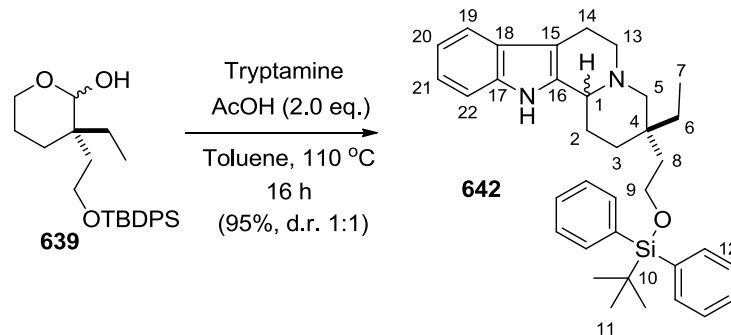
R_f = 0.63 (PE/EtOAc 80/20).

IR (ATR) ν_{max} (cm⁻¹) = 3370, 3071, 3049, 3017, 1471, 1460, 1428, 1390, 1361, 1261, 1111, 1085.

¹H NMR (CDCl₃, 200 MHz): δ (ppm) = 7.76-7.68 (m, 4H, Ar), 7.47-7.37 (m, 6H, Ar), 5.44-5.39 (d, 1H, *J* = 9 Hz, OH), 4.63 (d, 0.25H, *J* = 3.2 Hz, m H-1), 4.44 (d, 0.75H, *J* = 3.2 Hz, M H-1), 4.12-4.02 (m, 1H, H-9a), 3.75-3.46 (m, 3H, H-9b, H-5), 2.24 (ddd, 1H, *J* = 4.8, 9.8, 15 Hz, H-8a), 1.69-1.17 (m, 7H, H-3, H-4, H-8b, H-6), 1.07 (s, 9H, H-11), 0.77 (t, 3H, *J* = 7.6 Hz).

¹³C NMR (CDCl₃, 50 MHz): δ (ppm) = (135.7, 135.6, 133.4, 132.6, 132.5, 129.9, 129.7, 127.8, 127.7, (C-Ar)), 100.3, 99.6 (C-1), 65.4, 63.6 (C-9), 40.0, 38.9 (C-5), 36.1 (C-2), 33.0, 32.59 (C-8), 29.6 (C-10), 26.8, 26.6 (C-11), 26.2 (C-3), 21.5 (C-4), 19.1, 19.0 (C-6), 7.0, 6.9 (C-7).

HRMS (ESI): [M+Na]⁺ C₂₅H₃₆O₃NaSi: calcd. 435.2325, found 435.2317.

3-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-3-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine (642)

To a solution of tryptamine (45.19 mg; 0.28 mmol, 1.2 eq.) in dry toluene (5 mL), lactol **639** (97 mg; 0.23 mmol, 1.0 eq.) was dissolved in dry toluene (4 mL) and added to the reaction mixture. The reaction was stirred at room temperature for 30 min. At the end of 30 min. AcOH (0.026 mL; 0.47 mmol; 2.0 eq.) was added. Then the reaction was refluxed at 110 °C overnight. Then, the solvent was removed and the residue was diluted with sat. NaHCO₃ solution (to neutralize AcOH monitored by pH paper), and EtOAc. The organic layer was separated and washed with and brine solution (~5 mL). The combined organic layers were dried over MgSO₄ and the solvent was removed under reduced pressure. The crude product was purified by silica gel (60 Å) flash column (PE/EtOAc 90/10) to give tetracyclic product **642** as brown oil (120 mg, 95%, d.r. 1:1).

The first diastereoisomer (642a):

R_f = 0.58 (PE/EtOAc 90/10).

IR (ATR) ν_{\max} (cm⁻¹) = 3241, 3070, 2961, 2930, 2856, 1632, 1589, 1460, 1427, 1389, 1327, 1265.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 7.73-7.68 (m, 4H, Ar), 7.47-7.27 (m, 8H, Ar), 7.12-7.06 (m, 2H, Ar), 3.73 (t, 2H, *J* = 10.8 Hz, H-9), 3.10-3.05 (br d, 1H, *J* = 15.3 Hz, H-1), 2.93-2.86 (m, 2H, H-13a, H-14a), 2.71-2.50 (m, 3H, H-13b, H-14b, H-5a), 2.12-2.07 (m, 1H, H-5b), 1.86-1.43 (m, 7H, H-2, H-3, H-8, NH), 1.26-1.17 (m, 2H, H-6), 1.07 (s, 9H, H-11), 0.69 (t, 3H, *J* = 11.1 Hz).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = (135.9, 315.6, 135.4, 135.9, 129.6, 127.6, 127.4, 121.1, 119.3, 118.0, 110.7, 108.2 (C-Ar)), 64.7 (C-5), 60.3 (C-1), 60.0 (C-9), 53.6 (C-13), 40.5 (C-8), 35.4 (C-4), 33.5 (C-3), 29.2 (C-10), 26.8 (C-11), 26.2 (C-2), 25.3 (C-6), 21.7 (C-14), 7.6 (C-7)

HRMS (ESI): [M+H]⁺ C₃₅H₄₅N₂OSi: calcd. 537.3285, found 537.3295.

The second diastereoisomer (642b):

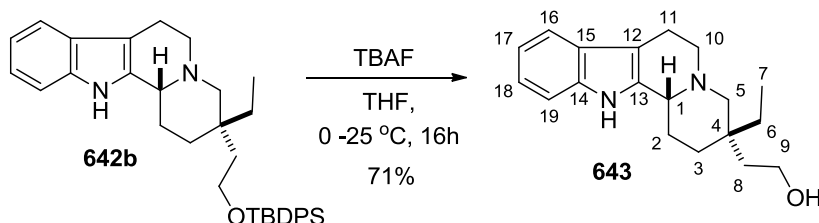
R_f = 0.45 (PE/EtOAc 90/10).

IR (ATR) ν_{\max} (cm⁻¹) = 3051, 2962, 2935, 2905, 2801, 1619, 1587, 1260, 1088, 1026.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 7.74-7.64 (m, 5H, Ar), 7.50-7.30 (m, 7H, Ar), 7.17-7.07 (m, 2H, Ar), 3.76-3.62 (m, 2H, H-9), 3.11-3.08 (br d, 1H, *J* = 10.5 Hz, H-1), 2.68-2.64 (m, 2H, H-13a, H-14a), 2.58-2.49 (m, 1H, H-13b), 2.05-1.79 (m, 4H, H-5, H-3), 1.69-1.56 (m, 3H, H-2a, H-8a, NH), 1.26-1.17 (m, 4H, H-2b, H-8b, H-6), 1.06-1.03 (m, 9H, H-11), 0.78 (t, 3H, *J* = 7.5 Hz).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = (135.9, 135.6, 1333.9, 129.9, 129.4, 127.8, 127.5, 121.1, 119.3, 118.0, 110.7, 108.3 (C-Ar)), 65.07 (C-5), 60.6 (C-9), 60.3 (C-1), 53.6 (C-13), 35.3 (C-8), 34.3 (C-4), 34.1 (C-3), 31.5 (C-6), 29.2 (C-10), 26.8 (C-11), 26.2 (C-2), 21.7 (C-14), 7.4 (C-7).

HRMS (ESI): [M+Na]⁺ C₃₅H₄₄N₂ONaSi: calcd. 559.3115, found 559.3110.

3-Ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-3-yl)ethanol (643)

To a solution of the second diastereoisomer of tetracyclic protected alcohol **642b** (50 mg; 0.093 mmol) in dry THF (7 mL) was added TBAF (0.139 mL; 0.139, 1.5 eq., 1 M in THF) at 0 °C. The reaction mixture was stirred at room temperature overnight. The solvent was removed and the residue was diluted with EtOAc and saturated solution of NaHCO₃. The organic layer was separated and washed with and brine solution (~5 mL). The combined organic layers were dried over MgSO₄ and the solvent was removed under reduced pressure.

The crude product was purified by silica gel (60 Å) column (DCM/MeOH 95/5) to give tetracyclic product **643** as white solid (19.8 mg, 71%).

$R_f = 0.58$ (PE/EtOAc 90/10).

Mp = 167 °C (DCM).

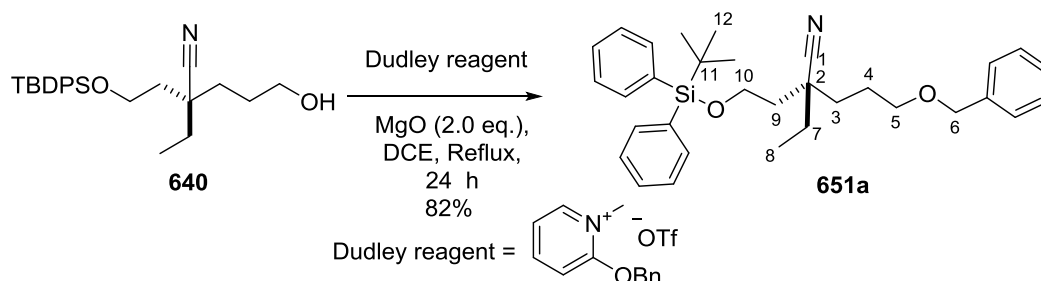
IR (ATR) ν_{\max} (cm⁻¹) = 3234, 3054, 2956, 2918, 2854, 1624, 1592, 1432.

¹H NMR (CDCl₃, 600 MHz): δ (ppm) = 8.04 (br s, 1H, NH), 7.43 (d, 1H, $J = 7.8$ Hz, H-19), 7.35 (d, 1H, $J = 3.9$ Hz, H-16), 7.14-7.11 (m, 1H, H-18), 7.08-7.05 (m, 1H, H-17), 3.62 (br s, 2H, H-9), 3.26 (d, 1H, $J = 11.4$ Hz, H-1), 3.08-3.05 (m, 1H, H-11a), 2.99-2.96 (m, 1H, H-10a), 2.84 (d, 1H, H-5a), 2.73-2.70 (dd, 1H, $J = 4.2, 15$ Hz, H-11), 2.67- 2.63 (td, 1H, $J = 4.2, 11.4$ Hz, H-10), 2.21 (d, 1H, $J = 11.4$ Hz, H-5b), 2.11 (br d, 1H, $J = 13.2$ Hz, H-2a), 1.19 (br s, 1H, OH), 1.65-1.60 (m, 3H, H-2b, H-8), 1.38-1.25 (m, 4H, H-3, H-6), 0.85 (t, 3H, $J = 3.6$ Hz, H-7).

¹³C NMR (CDCl₃, 150 MHz): δ (ppm) = (136.1, 133.9, 127.1, 121.5, 119.5, 118.1, 111.0, 108.0 (C-Ar)), 64.8 (C-5), 59.9 (C-1), 59.2 (C-9), 53.3 (C-10), 40.2 (C-8), 36.1 (C-6), 35.9 (C-4), 33.4 (C-3), 27.6 (C-2), 21.2 (C-11), 7.5 (C-7)

HRMS (ESI): $[M+Na]^+ C_{19}H_{26}N_2ONa$: calcd. 321.1937, found 321.1941.

5-(Benzyloxy)-2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-2-ethylpentanenitrile (**651a**)



A solution of alcohol **640** (159 mg; 0.388 mmol, 0.1 eq.), Dudley reagent (271.2 mg, 0.77 mmol, 2.0 eq.) and MgO (31.29 mg, 0.77 mmol, 2.0 eq.) in dry DCE (4 mL) was refluxed at 80 °C for 24 h. Then, the reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel (60 Å) flash column (PE/EtOAc 95/5) to give tetracyclic product **651a** as yellow oil (160 mg, 72%).

$R_f = 0.51$ (PE/EtOAc 95/05).

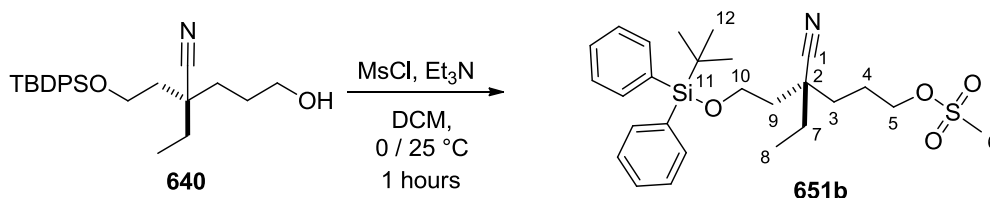
IR (ATR) ν_{\max} (cm⁻¹) = 3070, 3051, 3025, 2230, 1589, 1472, 1455, 1427, 1390, 1361, 1308, 1262.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 7.74-7.71 (m, 4H, Ar), 7.49-7.36 (m, 11H, Ar), 4.53 (s, 2H, H-6), 3.57 (t, 2H, $J = 6.9$ Hz, H-10), 3.50 (t, 2H, $J = 5.4$ Hz, H-5), 1.90 (t, 2H, $J = 6.6$ Hz, H-9), 1.72-1.66 (m, 6H, H-3, H-4, H-7), 1.11 (s, 9H, H12), 1.01 (t, 3H, $J = 7.2$ Hz, H-8).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = (138.3, 135.5, 134.8, 133.3, 129.8, 129.6, 128.4, 127.7, 127.6 (C-Ar)), 123.5 (CN), 72.9 (C-6), 60.8 (C-5), 60.2 (C-10), 39.5 (C-9), 37.5 (C-4), 32.8 (C-3), 29.3 (C-11), 26.8 (C-12), 24.7 (C-2), 19.1 (C-7), 8.7 (C-8).

HRMS (ESI): $[M+Na]^+ C_{32}H_{41}NO_2NaSi$: calcd. 522.2798, found 522.2783.

6-((*tert*-Butyldiphenylsilyl)oxy)-4-cyano-4-ethylhexyl methanesulfonate (**651b**)



To a solution of alcohol **640** (150 mg, 0.366 mmol, 1.0 eq.) in dry DCM (7.5 mL), were added at 0 °C, MsCl (0.034 mL, 0.439 mmol, 1.2 eq.) and Et₃N (0.076 mL, 0.549 mmol, 1.5 eq.). The reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was then treated with a concentrated solution of NH₄Cl and extracted by DCM. The combined organic layers were dried over Na₂SO₄ and the solvent was removed under reduced pressure. The crude yellow oil was purified by chromatography on silica gel (PE/EtOAc 70/30). The desired compound **651b** was obtained as a yellow oil (178 mg, quant.).

$R_f = 0.69$ (PE/EtOAc 70/30).

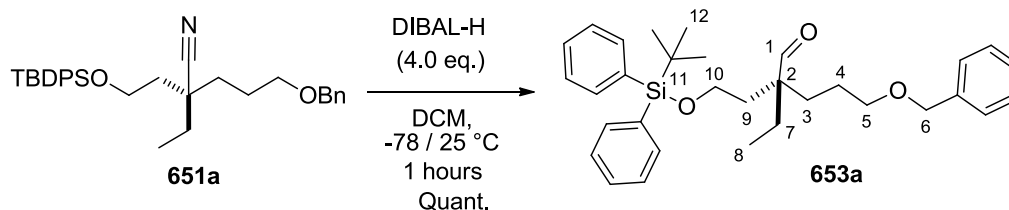
IR (ATR) ν_{\max} (cm⁻¹) = 3068, 2956, 2934, 2858, 2232, 1472, 1428, 1357, 1176.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 7.68-7.64 (m, 4H, Ar), 7.44-7.37 (m, 6H, Ar), 4.19 (t, 2H, *J* = 5.7 Hz, H-5), 3.80 (t, 2H, *J* = 6.9 Hz, H-10), 2.98 (s, 3H, H-6), 1.83 (t, 2H, *J* = 6.9 Hz, H-9), 1.70-1.66 (m, 6H, H-3, H-4, H-7), 1.05 (s, 9H, H12), 0.96 (t, 3H, , *J* = 7.5 Hz, H-8).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = (135.5, 1333.1, 129.8, 127.8 (C-Ar)), 123.0 (CN), 69.0 (C-5), 60.9 (C-10), 39.4 (C-9), 37.4 (C-6), 37.3 (C-4) 32.8 (C-3), 29.3 (C-11), 26.8 (C-12), 24.7 (C-2), 19.1 (C-7), 8.7 (C-8).

HRMS (ESI): [M+Na]⁺ C₂₆H₃₇NO₄NaSiS: calcd. 510.2104, found 510.2095.

5-(Benzyloxy)-2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-2-ethylpentanal (653a)

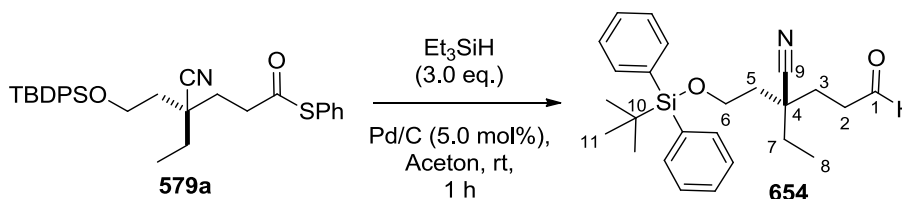


To a solution of nitrile **651a** (100 mg, 0.200 mmol, 1.0 eq.) in dry DCM (10 mL) under inert conditions, DIBAL-H (0.80 mL, 0.80 mmol, 4.0 eq., 1 M in DCM) was added dropwise to the reaction mixture at -78 °C. The reaction was stirred for 1 h at room temperature. Then, the reaction was quenched with 1M HCl (3 mL) at 0 °C. The mixture was then stirred for 15 min at room temperature then Na₂SO₄ was added to the reaction mixture and the stirred for another 15 min. Then solids were filtered through celite and the residue was concentrated under reduced pressure. The resulting crude colorless oil **653a** (100 mg) was used directly in the next step without further purification.

IR (ATR) ν_{\max} (cm⁻¹) = 3069, 3047, 3030, 1724, 1664, 1471, 1455, 1427, 1361, 1111.

HRMS (ESI): [M+Na]⁺ C₃₂H₄₂O₃NaSi: calcd. 525.2795, found 525.2778.

2-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-2-ethyl-5-oxopentanenitrile (654)



Under very dry conditions and Argon atmosphere, place 10% Pd on carbon (15.49 mg; 0.05 eq.) and evacuate the system and flash it with Argon gas. Then thio-ester **579a** (1.5 g; 2.9) was dissolved in acetone (37.5 mL) and added to the reaction flask. The mixture was stirred for 5 minutes and then freshly distilled Et₃SiH (1.40, 8.72mmol, 3.0 eq.) was added. After 5 minutes of addition of Et₃SiH, hydrogen bubbles start to appear in the reaction mixture, it is an indicator that the reaction worked. The stirring was continued for 1 h. Then, the reaction mixture was filtered through celite and the solvent was removed under reduced pressure. The crude colorless oil was purified by chromatography on silica gel (PE/EtOAc 80/20). The desired aldehyde **654** was obtained as a colorless oil (190 mg, 75%).

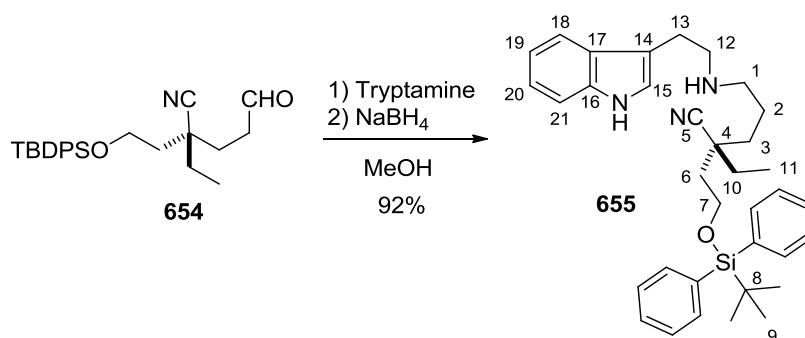
R_f = 0.30(PE/EtOAc 90/10).

IR (ATR) ν_{\max} (cm⁻¹) = 3071, 3051, 2933, 2858, 2726, 2231, 1726, 1589, 1473, 1462, 1428, 1390.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 9.7 (br t, 1H, H-1), 7.67-7.64 (m, 4H, Ar), 7.43-7.39 (m, 6H, Ar), 3.82-3.78 (m, 2H, H-6), 2.58-2.53 (m, 2H, H-5), 1.93-1.87 (m, 2H, H-2), 1.84-1.83 (m, 2H, H-3), 1.63-1.58 (m, 2H, H-7), 1.05 (s, 9H, H-11), 0.97 (t, 3H, *J* = 6.9 Hz, H-8).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 200.0 (C-1), (135.5, 133.1, 129.8, 127.8 (C-Ar)), 122.8 (CN), 60.0 (C-6), 39.3(C-5), 37.3 (C-2), 29.4 (C-10), 28.0 (C-3), 26.7 (C-11), 24.5(C-4), 19.0 (C-7), 8.7 (C-8)

HRMS (ESI): [M+Na]⁺ C₂₅H₃₃NO₂NaSi: calcd. 430.2172, found 430.2177.

5-((2-(1H-Indol-3-yl)ethyl)amino)-2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-2-ethylpentanenitrile (655)

To a solution of tryptamine (236.2 mg; 1.47 mmol, 1.1 eq.) on dry MeOH (3 mL), aldehyde **654** (545 mg; 1.33 mmol, 1.0 eq) was dissolved in dry MeOH (15 ml) and added to the reaction mixture. The reaction was allowed to react overnight. Then, the reaction was cooled to 0°C and NaBH₄ (101 mg, 2.67 mmol, 2.0 eq.) was added to the reaction mixture in two portions. Then the reaction was allowed to warm to room temperature and stirred for another 4 h. The solvent was removed and the residue was diluted with EtOAc and quenched with saturated aqueous NaHCO₃. The organic layer was separated, washed with brine and dried over Na₂SO₄. The solvent was removed under reduced pressure and the crude product was purified by silica gel (60 Å) flash column (DCM/MeOH 90/10) to give **655** as yellow heavy oil (679 mg, 92%).

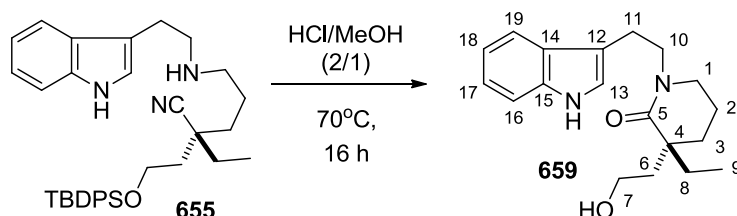
$R_f = 0.55$ (DCM/MeOH 90/10).

IR (ATR) ν_{\max} (cm⁻¹) = 3413, 3122, 2938, 2232, 1590, 1455, 1265, 1107.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 8.14 (br s, 1H, NH-indole), 7.68-7.61 (m, 5H, Ar), 7.42-7.33 (m, 7H, Ar), 7.19-7.11 (m, 2H, Ar), 7.02-7.01 (m, 1H, Ar), 3.78 (t, 2H, *J* = 6.9 Hz, H-7), 3.00-2.95 (m, 4H, H-1, H-12), 2.60-2.59 (m, 2H, H-13), 2.30 (br s, 1H, NH), 1.79 (t, 2H, *J* = 6.9 Hz, H-6), 1.58-1.52 (m, 6H, H-2, H-3, H-10), 1.05 (s, 9H, H-9), 0.92 (t, 3H, *J* = 7.2 Hz, H-11).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = (136.4, 135.5, 1333.3, 129.8, 127.7, 127.3, 122.1, 122.0, 119.3, 118.8, 113.4, 111.2 (C-Ar)), 123.5 (CN), 60.2 (C-7), 49.6 (C-12), 49.3 (C-1), 39.5 (C-6), 37.4 (C-3), 33.6 (C-2), 29.2 (C-8), 26.8 (C-9), 25.4 (C-13), 24.5 (C-4), 19.1 (C-10), 8.7 (C-11)

HRMS (ESI): [M+H]⁺ C₃₅H₄₆N₃OSi : calcd. 552.3404, found 552.3393.

1-(2-(1H-Indol-3-yl)ethyl)-3-ethyl-3-(2-hydroxyethyl)piperidin-2-one (659)

A solution of nitrile **655** (366 mg; 0.66 mmol, 1.0 eq.) in a (2/1) mixture of HCl (37%) / MeOH (21 mL) was refluxed for 16h. Then, MeOH was removed under reduced pressure, and the residue was basified to pH = 10 by a solution of NaOH (50%). The aqueous layer was extracted by EtOAc and the combined organic layers were washed with brine and dried over Na₂SO₄. The solvent was removed under reduced pressure and the crude product was purified by silica gel (60 Å) flash column (DCM/MeOH 90/10) to give **659** as brown oil (136 mg, 65%).

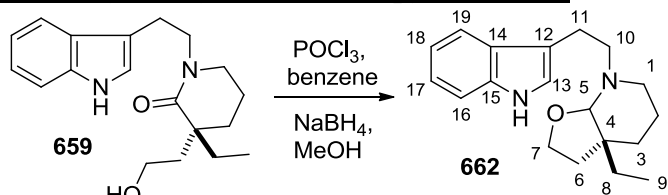
$R_f = 0.52$ (DCM/MeOH 90/10).

IR (ATR) ν_{\max} (cm⁻¹) = 3280, 3055, 2937, 2862, 1755, 1607, 1493, 1457, 1358, 1264, 1231, 1201.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 8.67 (br s, 1H, NH), 7.65-7.62 (d, 1H, *J* = 7.5 Hz, H-19), 7.36-7.33 (m, 1H, H-13), 7.16-7.00 (m, 3H, H-16, H-17, H-18), 3.86-3.84 (m, 1H, H-7a), 3.68-3.57 (m, 3H, H-7b, H-10), 3.17-3.14 (m, 2H, H-2), 3.00 (t, 2H, *J* = 7.2 Hz, H-11), 1.85-1.49 (m, 9H, H-2, H-3, H-8, H-6, OH), 0.82 (t, 3H, *J* = 7.5 Hz, H-9).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 176.2 (C-5), (136.3, 127.4, 122.4, 121.7, 119.1, 118.6, 112.5, 111.3 (C-Ar)), 58.9 (C-7), 49.2 (C-10), 48.9 (C-1), 43.9 (C-4), 40.3 (C-6), 31.2 (C-3), 29.7 (C-2), 22.9 (C-11), 19.3 (C-8), 8.2 (C-9)

HRMS (ESI): [M+Na]⁺ C₁₉H₂₆N₂O₂Na : calcd. 337.1886, found 337.1895.

7-(2-(1H-Indol-3-yl)ethyl)-3a-ethyloctahydrofuro[2,3-b]pyridine (662)

To solution of hydroxy-lactam **659** (60 mg; 0.19 mmol, 1.0 eq.) in dry benzene (4 ml), POCl₃ (0.10 ml; 1.14 mmol; 6 eq.) was added dropwise. The reaction mixture was refluxed at 90 °C for 24h. Then, the solvent was removed reduced pressure and the residue was placed under high vacuum for 15 min. then, dry MeOH (5 ml) was added to the reaction mixture under Argon atmosphere and the reaction mixture was cooled to 0 °C in ice bath. NaBH₄ (36.1 mg; 0.95 mmol; 5.0 eq.) was added to the reaction mixture in two portions. The reaction was stirred at room temperature for 1 h. Then, the solvent was removed under reduced pressure and the residue was diluted with EtOAc (5 mL) and saturated solution of NaHCO₃ (5 ml) till pH = 9. The aqueous layer was extracted with EtOAc (3x5 mL). The combined organic layers were washed with brine and dried over Na₂SO₄. The solvent was removed under reduced pressure and the crude product was purified by silica gel (60 Å) flash column (DCM/MeOH 98/2) to give hemiaminal **662** as brown oil (35 mg, 60%).

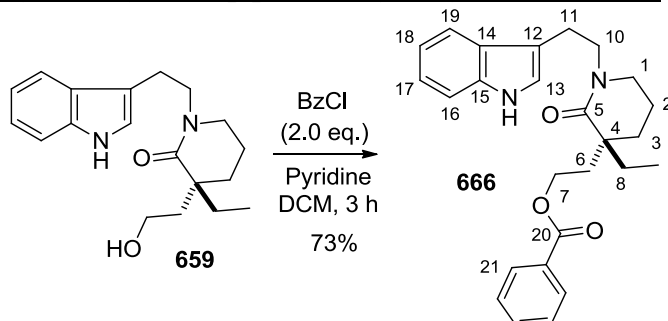
R_f = 0.38 (DCM/MeOH 98/2).

IR (ATR) ν_{\max} (cm⁻¹) = 3417, 3281, 3056, 2932, 2875, 2858, 1755, 1620, 1455, 1355, 1265, 1225.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 8.17 (br s, 1H, NH), 7.68-7.65 (d, 1H, *J* = 7.8 Hz, H-19), 7.39-7.36 (m, 1H, H-13), 7.23-7.11 (m, 3H, H-16, H-17), 7.05 (d, 1H, *J* = 2.1 Hz, H-18), 4.31 (s, 1H, H-5), 4.01-3.77 (m, 2H, H-7), 3.13-3.00 (m, 4H, H-10- H-11), 2.84-2.77 (m, 1H, H-1a), 2.70-2.66 (m, 1H, H-1b), 1.84-1.54 (m, 8H, H-2, H-3, H-6, H-8), 0.92 (t, 3H, *J* = 7.5 Hz, H-9).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = (136.1, 127.7, 121.7, 121.5, 119.0, 118.9, 114.7, 110.9 (C-Ar)), 97.7 (C-5), 63.2 (C-7), 55.5 (C-10), 45.1 (C-1), 41.3 (C-4), 36.2 (C-6), 27.1 (C-3), 26.7 (C-2), 23.9 (C-11), 21.3 (C-8), 9.1 (C-9).

HRMS (ESI): [M+H]⁺ C₁₉H₂₇N₂O : calcd. 229.2117, found 299.2117.

2-(1-(2-(1H-Indol-3-yl)ethyl)-3-ethyl-2-oxopiperidin-3-yl)ethyl benzoate (666)

To a solution of alcohol **659** (135 mg, 0.42 mmol, 1.0 eq.) in dry DCM (10 mL), pyridine (0.069 mL, 0.85 mmol, 2.0 eq.) was added at 0 °C. After that, BzCl (0.099 mL, 0.85mmol, 2.0 eq.) was added to the resulting slurry at 0 °C. The reaction mixture was allowed to warm up to room temperature and stirred at that temperature for 3 h. Then, the reaction mixture was diluted by water (5 mL) and the aqueous layer was separated and washed with DCM. The combined organic layers were washed with 5% HCl, saturated solution of NaHCO₃ and brine respectively. The combined organic layers were dried over Na₂SO₄ and the solvent was removed under reduced pressure. The crude product was purified by silica gel (60 Å) flash column (PE/EtOAc 70/30) to give protected product **666** as brown oil (131 mg, 73%).

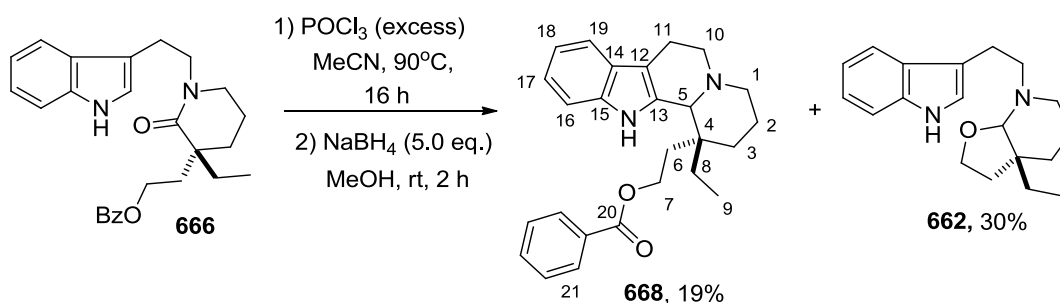
R_f = 0.53 (PE/EtOAc 98/2).

IR (ATR) ν_{\max} (cm⁻¹) = 3272, 3058, 2939, 2870, 1714, 1614, 1493, 1455, 1357, 1240, 1315, 1275.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 8.48 (br s, 1H, NH), 8.05-8.02 (m, 2H, Ar), 7.68-7.65 (m, 1H, Ar), 7.56-7.51 (m, 1H, Ar), 7.45-7.33 (m, 3H, Ar), 7.19-7.08 (m, 2H, Ar), 7.04-7.03 (d, 1H, *J* = 2.1 Hz, Ar), 4.42-4.35 (m, 2H, H-7), 3.70-3.64 (m, 2H, H-10), 3.20-3.19 (m, 2H, H-1), 3.02 (t, 2H, *J* = 7.2 Hz, H-11), 2.26 (m, 1H, H-6a), 1.96-1.71 (m, 7H, H-2, H-3, H-6b, H-8), 0.89 (t, 3H, *J* = 7.5 Hz, H-9).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 173.7 (C-5), 166.7 (C-20), (136.3, 132.9, 130.3, 129.5, 128.3, 127.4, 122.3, 121.8, 119.1, 118.7, 112.8, 111.2 (C-Ar)), 62.3 (C-7), 48.8 (C-10), 48.5(C-1), 43.8 (C-4), 36.7 (C-6), 31.7 (C-3), 29.6 (C-2), 23.9 (C-11), 19.8 (C-8), 8.6 (C-9).

HRMS (ESI): [M+Na]⁺ C₂₆H₃₀N₂O₃Na : calcd. 441.2148, found 411.2137.

2-(1-Ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-1-yl)ethyl benzoate (666)

To solution lactam **666** (43 mg; 0.10 mmol, 1.0 eq.) in dry MeCN (3 ml), POCl₃ (0.29 ml; 3.12 mmol; 30.4 eq.) was added dropwise. The reaction mixture was refluxed at 90 °C for 24h. Then, the solvent was removed reduced pressure and the residue was placed under high vacuum for 15 min. then, dry MeOH (5 ml) was added to the reaction mixture under Argon atmosphere and the reaction mixture was cooled to 0 °C in ice bath. NaBH₄ (19.4 mg; 0.51 mmol; 5.0 eq.) was added to the reaction mixture in two portions. The reaction was stirred at room temperature for 1 h. Then, the solvent was removed under reduced pressure and the residue was diluted with EtOAc (5 mL) and saturated solution of NaHCO₃ (5 ml) till pH = 9. The aqueous layer was extracted with EtOAc (3x5 mL). The combined organic layers were washed with brine and dried over Na₂SO₄. The solvent was removed under reduced pressure and the crude product was purified by silica gel (60 Å) flash column (PE/EA 80/20) to give Eburnan **668** as brown oil (8 mg, 19%) and hemiaminal **662** (13 mg, 30%).

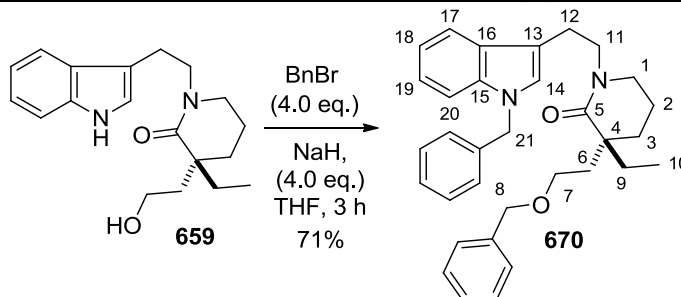
$R_f = 0.68$ (PE/EA 80/20).

IR (ATR) ν_{\max} (cm⁻¹) = 3344, 3064, 2926, 2857, 2750, 1702, 1621, 1602, 1582, 1524, 1462, 1451.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 10.1 (br s, 1H, NH), 8.16-8.13 (m, 2H, Ar), 7.76-7.46 (m, 8H, Ar), 7.37-7.32 (m, 1H, Ar), 7.17-7.08 (m, 3H, Ar), 5.12 (m, 1H, H-7a), 4.43-4.34 (m, 1H, H-7b), 3.84-3.61 (m, 1H, H-10a), 3.39 (s, 1H, H-5), 3.00-2.87 (m, 4H, H-10b, H1, H11a), 2.68-2.60 (m, 2H, H-11b, H-6a), 2.43-2.33 (m, 2H, H-6b, H3a), 1.87-1.61 (m, 5H, H2, H-3b, H-8), 0.67 (t, 3H, $J = 7.8$ Hz, H-9).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 176.2 (C-20), (144.5, 1333.4, 129.8, 129.5, 128.5, 128.2, 126.5, 121.0, 118.8, 117.5, 115.4, 111.4, 111.3 (C-Ar)), 66.8 (C-5), 62.9 (C-7), 56.9 (C-10), 54.0 (C-1), 39.3 (C-4), 36.1 (C-6), 31.1 (C-3), 29.7 (C-2), 25.2 (C-11), 22.2 (C-8), 7.03 (C-9).

HRMS (ESI): [M+H]⁺ C₂₆H₃₁N₂O₂ : calcd. 403.2380, found 403.2395.

1-(2-(1-Benzyl-1H-indol-3-yl)ethyl)-3-(2-(benzyloxy)ethyl)-3-ethylpiperidin-2-one (570).

To a suspension of NaH (30.5 mg; 0.76 mmol, 4.0 eq.) in dry THF (2.0 mL), hydroxy-lactam **659** (60 mg; 0.19 mmol, 1.0 eq.) was dissolved in dry THF (1.2 mL) and added to the reaction mixture at 0 °C. The reaction mixture was stirred at this temperature for 30 min and then BnBr (0.09 mL, 0.76 mmol, 4.0 eq.) was added to the reaction mixture. The reaction was stirred for 16h at room temperature. Then, the solvent was removed under reduced pressure and the residue was diluted by EtOAc and quenched by saturated solution of NaHCO₃. The organic layer was separated and washed with brine then dried over Na₂SO₄. The solvent was removed under reduced pressure and the crude product was purified by silica gel (60 Å) flash column (PE/EA 70/30) to give protected alcohol **670** as brown oil (67 mg, 71%).

$R_f = 0.61$ (PE/EA 70/30).

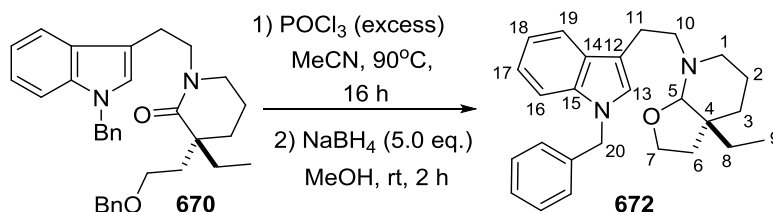
IR (ATR) ν_{\max} (cm⁻¹) = 2962, 2909, 2857, 1626, 1488, 1462, 1445, 1413, 1260.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) 7.70-7.67 (m, 1H, Ar), 7.33-7.09 (m, 13H, Ar), 6.93(s, 1H, Ar), 5.25 (s, 2H, H-21), 4.46 (d, 2H, $J = 1.2$ Hz, H-8), 3.68-3.54 (m, 4H, H-7, H-11), 3.16-3.13 m, 2H, J-1), 2.98 (t, 2H, $J = 7.5$ Hz, H-12), 2.11-2.01 (m, 2H, H-6), 1.83-1.69 (m, 5H, H-2, H-3, H-9a), 1.57-1.48 (m, 1H, H-9b), 0.84 (t, 3H, $J = 7.2$ Hz, H-10).

^{13}C NMR (CDCl_3 , 75 MHz): δ (ppm) = 174.0 (C-5), (138.5, 137.6, 136.6, 128.7, 128.3, 128.1, 127.6, 127.5, 127.4, 126.8, 126.1, 121.7, 119.1, 119.0, 112.6, 109.6 (C-Ar)), 72.9 (C-8), 67.5 (C-7), 49.8 (C-11), 49.0 (C-21), 48.8 (C-1), 43.9 (C-4), 37.8 (C-6), 31.5 (C-3), 23.1 (C-12), 19.8 (C-9), 8.6 (C-10).

HRMS (ESI): $[\text{M}+\text{Na}]^+$ $\text{C}_{33}\text{H}_{38}\text{N}_2\text{O}_2\text{Na}$: calcd. 517.2825, found 517.2805.

7-(2-(1-Benzyl-1H-indol-3-yl)ethyl)-3a-ethyloctahydrofuro[2,3-b]pyridine (672)



To solution of lactam **670** (15 mg; 0.03 mmol, 1.0 eq.) in dry MeCN (1 ml), POCl_3 (0.08 ml; 0.9 mmol; 30.4 eq.) was added dropwise. The reaction mixture was refluxed at 90 °C for 24h. Then, the solvent was removed reduced pressure and the residue was placed under high vacuum for 15 min. then, dry MeOH (1 ml) was added to the reaction mixture under Argon atmosphere and the reaction mixture was cooled to 0 °C in ice bath. NaBH_4 (5.7 mg; 0.15 mmol; 5.0 eq.) was added to the reaction mixture in two portions. The reaction was stirred at room temperature for 1 h. Then, the solvent was removed under reduced pressure and the residue was diluted with EtOAc (5 mL) and saturated solution of NaHCO_3 (5 ml) till pH = 9. The aqueous layer was extracted with EtOAc (3x5 mL). The combined organic layers were washed with brine and dried over Na_2SO_4 . The solvent was removed under reduced pressure and the crude product was purified by silica gel (60 Å) flash column (PE/EtOAc 80/20) to give hemiaminal **672** as brown oil (8 mg, 60%).

R_f = 0.60 (PE/EtOAc 80/20).

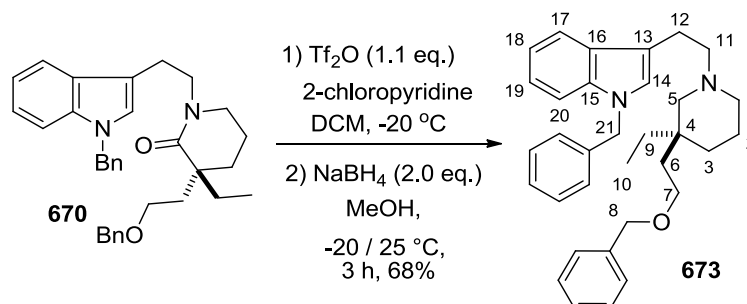
IR (ATR) ν_{max} (cm^{-1}) = 3060, 2962, 2926, 2857, 1726, 1673, 1617, 1454, 1413, 1378, 1331.

^1H NMR (CDCl_3 , 600 MHz): δ (ppm) = 7.65-7.64 (d, 1H, J = 4.2 Hz, Ar), 7.31-7.29 (m, 2H, Ar), 7.28-7.25 (m, 2H, Ar), 7.18-7.10 (m, 4H, Ar), 7.01-6.98 (m, 1H, Ar), 5.28 (s, 2H, H-20), 4.25 (s, 1H, H-5), 3.92-3.89 (m, 1H, H-7a), 3.83-3.80 (m, 1H, H-7b), 3.07-2.87 (m, 4H, H-10, H-1), 2.77-2.74 (m, 1H, H-11a), 2.64-2.60 (m, 1H, H-11b), 2.09-2.06 (m, 2H, H-6), 1.67-1.59 (m, 6H, H-2, H-3, H-8), 0.90-0.85 (m, 3H, H-9).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) = (135.2, 128.6, 127.4, 126.8, 125.7, 127.0, 125.0, 124.7, 121.5, 119.1, 118.7, 114.1, 109.4 (C-Ar)), 94.6 (C-5), 63.2 (C-7), 55.5 (C-10), 49.8 (C-20), 45.1 (C-1), 41.2 (C-4), 36.2 (C-6), 27.1 (C-3), 26.7 (C-2), 23.6 (C-11), 21.3 (C-8), 9.1 (C-9).

HRMS (ESI): $[\text{M}+\text{Na}]^+$ $\text{C}_{26}\text{H}_{32}\text{N}_2\text{ONa}$: calcd. 411.2406, found 411.2408.

1-Benzyl-3-(2-(3-(2-(benzyloxy)ethyl)-3-ethylpiperidin-1-yl)ethyl)-1H-indole (673)



To a stirred solution of amide **670** (36 mg, 0.07 mmol, 1.0 eq.) and 2-Cl-pyridine (8.2 μL , 0.08 mmol, 1.2 eq.) in dry DCM (3 mL) at -20 °C was added Tf_2O (13.29 μL , 0.08 mmol, 1.1 eq.). The reaction mixture was stirred for 10 min at -20 °C and 1.5 h at room temperature by which time a deep brown color had formed. The mixture was cooled to -20 °C again, and the solution of NaBH_4 (5.5 mg, 0.14 mmol, 2.0 eq.) in MeOH (1.4 mL) was then added dropwise over 5 min. The color rapidly disappeared, and the reaction mixture was stirred for further 1 h. the reaction mixture was quenched with saturated Na_2CO_3 solution (5 mL) and diluted with DCM (10 mL). The organic layer was separated, and the aqueous layer was extracted with DCM (3x10 mL). The combined organic layers were washed with brine and dried over Na_2SO_4 . Then, the solvent was removed under reduced pressure and the crude product was purified by silica gel (60 Å) flash column (DCM/MeOH 95/05) to give compound **673** as yellow oil (23 mg, 68%).

R_f = 0.61 (DCM/MeOH 95/05).

IR (ATR) ν_{max} (cm^{-1}) = 3054, 3029, 2963, 2929, 2854, 2802, 1661, 1627, 1614, 1495, 1467, 1454.

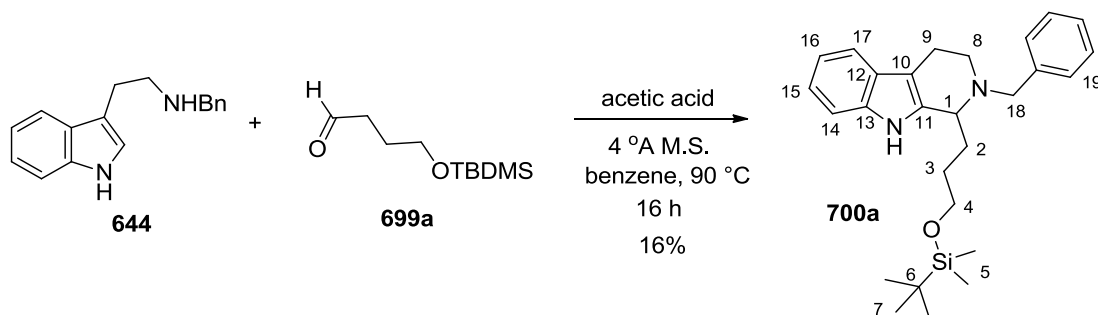
¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 7.61-7.59 (m, 1H, Ar), 7.34-7.29.1 (m, 61h, Ar), 7.24-7.08 (7H, Ar), 6.97-6.93 (m, 1H, Ar), 5.26 (s, 2H, H-21), 4.48 (s, 2H, H-8), 3.52 (t, 2H, *J* = 6.9 Hz, H-7), 3.01-2.95 (m, 2H, H-11), 2.78-2.69 (m, 2H, H-1), 1.75-1.36 (m, 12H, H-12, H-2, H-3, H-5, H-6, H-9), 0.85 (t, 3H, *J* = 7.5 Hz, H-10).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = (138.5, 137.6, 136.5, 128.7, 128.4, 128.3, 127.9, 127.7, 127.6, 127.5, 126.8, 126.0, 121.7, 118.9, 117.2, 109.6 (C-Ar)), 93.0 (C-8), 67.5 (C-7), 66.5 (C-5), 59.5 (C-11), 54.8 (C-1), 49.8 (C-21), 41.2 (C-4), 35.5 (C-6), 27.0 (C-3), 23.4 (C-2), 22.6 (C-11), 19.5 (C-8), 7.46 (C-9).

HRMS (ESI): [M+Na]⁺ C₃₃H₄₀N₂ONa: calcd. 503.3032, found 503.3027.

Experimental Part for Chapter Four

2-Benzyl-1-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (700a)



A solution of *N*-benzyltryptamine **644** (200 mg; 0.79 mmol; 1.0eq.) in dry benzene (9 mL) was refluxed at 90 °C. After 5 min, aldehyde **699a** (485 mg; 0.239 mmol; 3 eq.) was added to the reaction mixture. After 30 min, acetic acid (0.5 mL; 8.72 mmol; 10.9 eq.) was added to the reaction mixture. The reaction was stirred under reflux overnight at 90 °C. After that, the reaction was allowed to cool to room temperature and the solvent was removed under reduced pressure. After that NaHCO₃ (2 % solution) was added to the residue dark brown oil, then the mixture was extracted with DCM (3 x 10 mL). The combined organic layers were dried over Na₂SO₄, and the solvent was removed under reduced pressure to afford dark brown oil. The crude brown oil was purified by chromatography on silica gel (PE/EtOAc 90/10). The desired compound **770a** was obtained as yellow oil (60 mg, 16%).

R_f = 0.47 (PE/EtOAc 95/05).

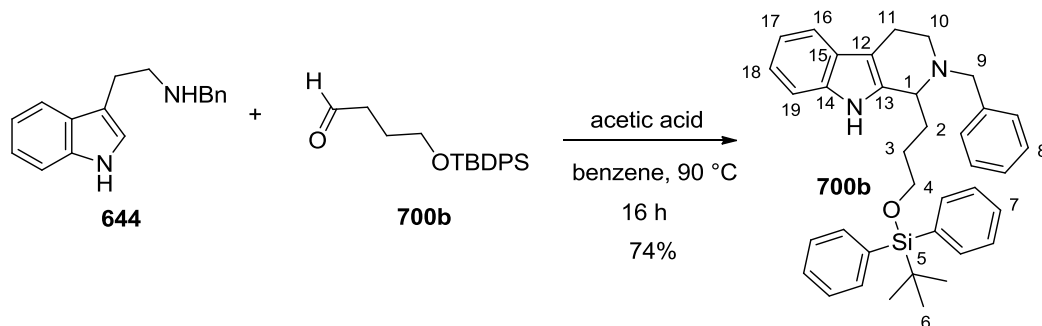
IR (ATR) *v*_{max} (cm⁻¹) = 3408, 3060, 3029, 2926, 2739, 1682, 1636, 1622, 1604, 1587, 1544, 1494, 1470, 1387

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 8.37 (br s, 1H, NH), 7.55 (d, 1H, *J* = 7.5 Hz, Ar.), 7.41-7.26 (m, 6H, Ar.), 7.20-7.12 (m, 2H, Ar.), 3.86-3.57 (m, 4H, H-18, H-4,), 3.35-3.25 (m, 1H, H-1), 3.00-2.88 (m, 2H, H-8), 2.66-2.58 (m, 1H, H-9), 2.01-1.61 (m, 5H, H-2, H-3, H-9), 0.91 (s, 9H, H-7), 0.07 (s, 6H, H-5).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = (139.9, 135.7, 135.5, 128.8, 128.3, 127.4, 126.9, 121.2, 119.1, 118.0, 110.7, 107.5 (C-Ar)), 63.7 (C-1), 57.3 (C-4), 55.9 (C-18), 45.0 (C-8), 31.8 (C-2), 29.0 (C-6), 26.0 (C-7), 18.4 (C-9), -5.2 (C-5).

HRMS (ESI): [M+H]⁺ C₂₇H₃₉N₂OSi: calcd. 435.2826, found 435.2824.

2-Benzyl-1-(3-((*tert*-butyldiphenylsilyl)oxy)propyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (700b)



A solution of *N*-benzyltryptamine **644** (200 mg; 0.79 mmol; 1.0eq.) in dry benzene (9 mL) was refluxed at 90 °C. After 5 min, aldehyde **699b** (326.1 mg; 0.99 mmol; 1.25 eq.) was added to the reaction mixture. After 30 min, acetic acid (0.09 mL; 1.58 mmol; 2.0 eq.) was added to the reaction mixture. The reaction was stirred under reflux overnight at 90 °C. After that, the reaction was allowed to cool to room temperature and the

solvent was removed under reduced pressure. After that NaHCO_3 (2 % solution) was added to the residue dark brown oil, then the mixture was extracted with DCM (3 x 10 ml). The combined organic layers were dried over Na_2SO_4 , and the solvent was removed under reduced pressure to afford dark brown oil. The crude brown oil was purified by chromatography on silica gel (PE/EtOAc 90/10). The desired compound **700b** was obtained as yellow oil (330 mg, 74%).

$R_f = 0.62$ (PE/EtOAc 95/05).

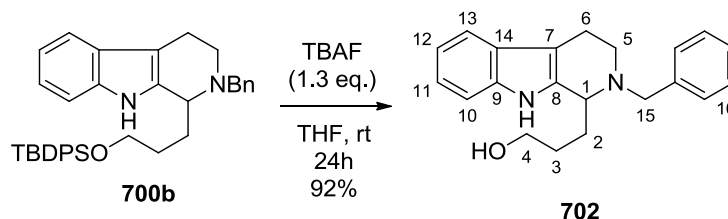
IR (ATR) ν_{max} (cm^{-1}) = 3408, 3063, 2928, 2853, 1607, 1587, 1538, 1429, 1325.

^1H NMR (CDCl_3 , 300 MHz): δ (ppm) = 7.77 (br s, 1H, NH), 7.67-7.10 (m, 19 H, Ar.), 3.84-3.61 (m, 4H, H-4, H-9), 3.29-3.16 (m, 1H, H-1), 2.96-2.84 (m, 2H, H-10), 2.66-2.54 (m, 1H, H-11), 1.93-1.86 (m, 2H, H-11, H-2), 1.79-1.66 (m, 3H, H-2, H-3), 1.05 (s, 9H, H-6).

^{13}C NMR (CDCl_3 , 75 MHz): δ (ppm) = (139.9, 135.8, 135.6, 135.4, 133.9, 133.8, 129.7, 128.9, 128.2, 127.4, 126.9, 121.3, 119.2, 118.0, 110.7, 107.9 (C-Ar)), 64.0 (C-1), 57.3 (C-4), 56.2 (C-9), 45.1 (C-10), 30.8 (C-2), 28.8 (C-5), 27.0 (C-6), 19.3 (C-11).

HRMS (ESI): $[\text{M}+\text{Na}]^+ \text{C}_{37}\text{H}_{42}\text{N}_2\text{OSiNa}$: calcd. 558.3061, found 558.3058.

3-(2-Benzyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)propan-1-ol (702)



To a solution of tricyclic **700b** (1,210 g; 2.16 mmol) in dry THF (25 mL), TBAF (2.82 ml; 2.815 mmol; 1.3 eq., 1M in THF) was added. The reaction was stirred at room temperature for 24h. After that, the reaction was quenched by drops of saturated aqueous NH_4Cl and the solvent was removed under vacuum. The residue was diluted with EtOAc and saturated aqueous NH_4Cl . Then the organic layer was separated and the aqueous layer was washed three times with EtOAc. The combined organic layers were dried over Na_2SO_4 , and the solvent was removed under reduced pressure to afford brown oil. The crude brown oil was purified by chromatography on silica gel (DCM/MeOH 95/05). The desired compound **702** was obtained as brown oil (331 mg, 92%).

$R_f = 0.38$ (DCM/MeOH 95/05).

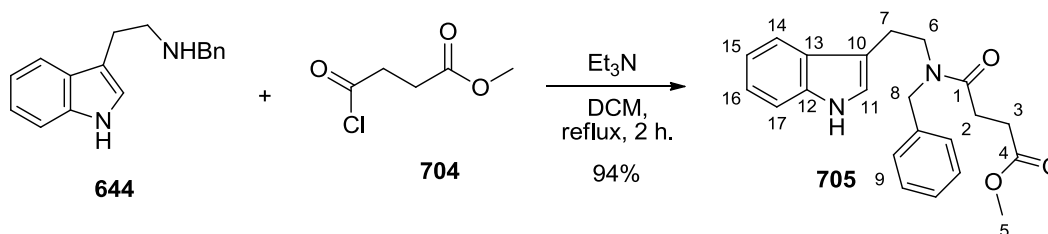
IR (ATR) ν_{max} (cm^{-1}) = 3272, 3059, 2930, 1683, 1621, 1585, 1495, 1454.

^1H NMR (CDCl_3 , 300 MHz): δ (ppm) = 8.26 (br s, 1H, NH), 7.56-7.15 (m, 9H, Ar.), 3.94-3.78 (m, 3H, H-15, H-4), 3.74-3.70 (m, 1H, H-4), 3.60-3.52 (m, 1H, H-1), 3.33-3.32 (m, 1H, H-5), 3.01-3.23 (m, 2H, H-5, H-6), 2.69-2.63 (m, 1H, H-6), 2.15-2.10 (m, 1H, H-2), 2.01-1.90 (m, 2H, H-2, H-3), 1.71-1.64 (m, 1H, H-3)

^{13}C NMR (CDCl_3 , 75 MHz): δ (ppm) = (137.4, 136.0, 133.9, 129.7, 128.4, 127.5, 127.0, 121.6, 119.4, 118.1, 110.8, 107.2 (C-Ar)), 62.7 (C-4), 57.7 (C-1), 57.3 (C-15), 43.2 (C-5), 33.2 (C-2), 30.2 (C-3), 17.2 (C-6)

HRMS (ESI): $[\text{M}+\text{Na}]^+ \text{C}_{21}\text{H}_{24}\text{N}_2\text{ONa}$: calcd. 343.1780, found 343.1788.

Methyl 4-((2-(1H-indol-3-yl)ethyl)(benzyl)amino)-4-oxobutanoate (705)



To a solution of *N*-benzyltryptamine **644** (9.88 g; 39.47 mmol; 1.0 eq.) in dry DCM (130 mL), Et_3N (6.46 mL; 46.5 mmol; 1.1 eq.) was added. Then Methyl-4-chloro-4-oxobutanoate **704** (6.73 g; 43.41 mmol; 1.1 eq.) was dissolved in DCM (3 mL) and cautiously dropped into the reaction mixture under vigorous stirring. The reaction mixture was heated under reflux for 2 h. After that, the reaction was allowed to cool to room temperature and treated with 1% HCl. The organic layer was separated, washed with brine and dried over Na_2SO_4 . The solvent was removed under reduced pressure to afford white solid. The crude white solid was purified by chromatography on silica gel (PE/EtOAc 50/50). The desired compound **705** was obtained as white needles (13.5 g, 94%).

R_f = 0.48 (DCM/MeOH 95/05).

Mp = 102-103 °C (DCM)

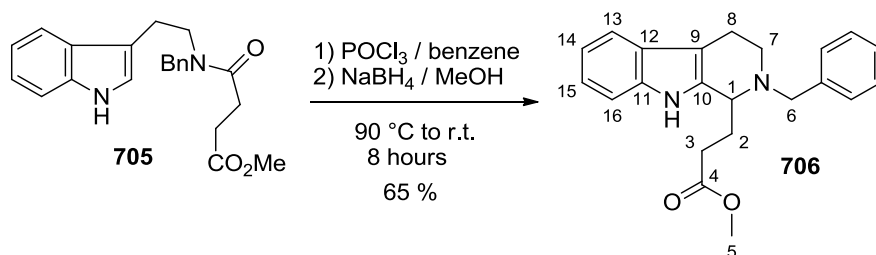
IR (KBr) ν_{max} (cm⁻¹) = 3439, 3263, 3056, 2953, 1728, 1627, 1486, 1435, 1412, 1384, 1263, 1230.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 8.37 (br d, 1H, J = 27.6 Hz, NH), 7.61-7.53 (m, 1H, H-14), 7.41-7.10 (m, 8H, Ar), 7.01-6.96 (m, 1H, Ar), 4.67 (s, 1H, H-8), 4.48 (s, 1H, H-8), 3.74 (d, 3H, J = 7.8 Hz, H-5), 3.70-3.69 (m, 1H, H-3), 3.62-3.57 (m, 1H, H-3), 3.09-3.03 (m, 2H, H-2), 2.78- 2.63 (m, 4H, H6, H7).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 173.6 (C-4), 171.6 (C-1), (137.7, 136.8, 136.3, 128.9, 128.6, 128.1, 127.6, 127.3, 126.4, 122.2, 113.1, 112.1, 111.5, 111.2 (C-Ar), (51.8 , 51.7 (C-5)), 48.7 (C-6), 47.8, 47.5 (C-8), (29.4, 29.2 (C-3)), (28.3, 27.8 (C-2)), (24.4, 23.5 (C-7)).

HRMS (ESI): [M+Na]⁺ C₂₂H₂₄N₂O₃Na : calcd. 387.1679, found 387.1675.

Methyl 3-(2-benzyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)propanoate (706)



To a solution of amide **705** (11.245 g; 30.86 mmol) in 300 ml dry benzene under Ar-atmosphere, POCl₃ (20 ml; 216 mmol; 7 eq.) was added dropwise to the reaction mixture. The reaction mixture was refluxed at 90 °C. The reaction was mentored by TLC and after consumption of the starting material, the solvent was removed and placed under vacuum for 15 min. Dry MeOH (400 ml) was added to the reaction mixture under Ar-atmosphere. The reaction was cooled to 0 °C in ice bath. (5.8 g; 154.3 mmol; 5 eq) of NaBH₄ was added in two portions to the reaction mixture. After that the solvent was removed and the residue was diluted with 50 ml DCM. The reactive materials were quenched by adding (50 ml) saturated solution of NH₄Cl. The aqueous layer was extracted with DCM (3x50 ml). The combined organic layers were washed with NaHCO₃, dried over Na₂SO₄ and concentrated under reduced pressure to afford dark green oil. The crude oil was purified by chromatography on silica gel (PE/EtOAc 80/20). The desired compound **706** was obtained as faint yellow oil (6.95 g, 65%).

R_f = 0.70 (PE/EtOAc 8/2).

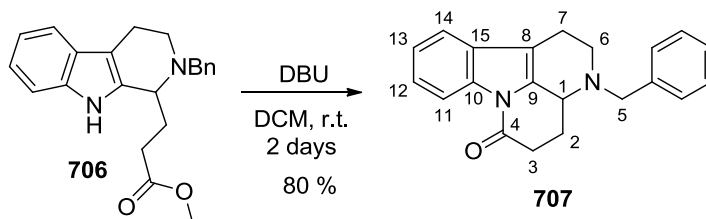
IR (ATR) ν_{max} (cm⁻¹) = 3392, 3097, 2916, 2853, 1726, 1619, 1601, 1494, 1452.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 8.06 (br s, 1H, NH), 7.55-7.51 (m, 1H, Ar), 7.36-7.08 (m, 8H, Ar), 3.75 (s, 2H, H-6), 3.96-3.63 (m, 1H, H-1), 3.60 (s, 3H, H-5), 3.30-3.16 (m, 1H, H-7), 3.01-2.85 (m, 2H, H-3), 2.69-2.34 (m, 3H, H-7, H-8), 2.13-2.00 (m, 2H, H-2).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 174.6 (C-4), (139.6, 136.0, 134.4, 129.1, 128.2, 127.2, 127.0, 121.5, 119.3, 118.1, 110.9, 108.1 (C-Ar), 57.4 (C-6), 55.4 (C-1), 51.6 (C-5), 44.7 (C-7), 30.5 (C-2), 29.3 (C-3), 17.9 (C-8).

HRMS (ESI): [M+Na]⁺ C₂₂H₂₄N₂O₂Na : calcd. 371.1729, found 371.1721.

3-Benzyl-3,3a,4,5-tetrahydro-1H-indolo[3,2,1-de][1,5]naphthyridin-6(2H)-one (707)



To a solution of ester **706** (6.65 g; 19.09 mmol; 1.0 eq.) in dry DCM (230 mL), DBU (8.55 ml; 57.26 mmol; 3 eq.) was added at r.t. The reaction was stirred at r.t. for 2 days. After that, the solvent was removed under reduced pressure. The residue was treated by 10 % CuCO₄ solution and then extracted with DCM. The combined organic layer was dried over Na₂SO₄ and concentrated under vacuum to afford dark green oil. The crude oil was purified by chromatography on silica gel (PE/EtOAc 70/30). The desired compound **707** was obtained as gray green solid (4.83 g, 80%).

R_f = 0.78 (PE/EtOAc 7/7).

Mp = 173-175 °C (EtOAc)

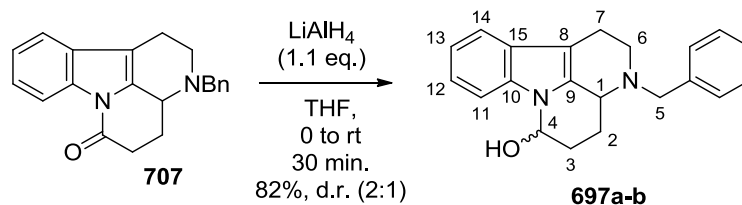
IR (KBr) ν_{\max} (cm⁻¹) = 3390, 3082, 2964, 2920, 2886, 2808, 1701, 1640, 1601, 1495, 1474, 1457, 1383.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 8.42-8.39 (m, 1H, H-11), 7.24-7.25 (m, 8H, Ar), 4.23 (d, 1H, *J* = 13.5 Hz, H-5a), 3.56-3.52 (m, 1H, H-1), 3.40 (d, 1H, *J* = 13.5 Hz, H-5b), 3.21 (dd, 1H, *J* = 5.7, 11.4 Hz, H-6a), 2.92-2.90 (m, 1H, H-7a), 2.87-2.70 (m, 2H, H-3), 2.64-2.63 (m, 1H, H-7b), 2.59-2.48 (m, 2H, H-6a, H-2b), 1.90 (qd, 1H, *J* = 4.5, 12.9 Hz, H-2b).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 168.1 (C-4), (138.5, 135.0, 134.6, 129.4, 128.8, 128.4, 127.2, 124.4, 123.9, 118.1, 116.2 (C-Ar)), 113.5 (C-11), 57.7 (C-5), 57.2 (C-1), 50.1 (C-6), 32.9 (C-3), 27.5 (C-2), 21.3 (C-7).

HRMS (ESI): [M+H]⁺ C₂₁H₂₁N₂ONa : calcd. 317.1653, found 317.1662.

3-benzyl-2,3,3a,4,5,6-hexahydro-1H-indolo[3,2,1-de][1,5]naphthyridin-6-ol (697a-b)



To a solution of LiAlH₄ (26.39 mg; 0.69 mmol; 1.1 eq.) in dry THF (3 mL) under inert conditions, amide **1** (200 mg; 0.63 mmol; 1.0 eq.) in dry THF (7 mL) was added dropwise at 0 °C. The reaction was stirred for 30 min at 0 °C. After 30 min, the excess LiAlH₄ in the reaction mixture was quenched by adding H₂O (2 mL) carefully and dropwise. After that the formed solid was filtered and washed with EtOAc. The filtrate was concentrated under reduced pressure. The residue was treated with DCM and washed with brine. The organic layer was dried over Na₂SO₄ and concentrated under vacuum to afford foamy light faint brown solid. The crude solid was purified by chromatography on silica gel (pentane/Et₂O 50/50). The desired compound **71** was obtained as faint yellow solid in two diastereoisomers (d.r. 2:1) (166 mg, 85%).

First diastereoisomer (697a):

R_f = 0.62 (PE/EtOAc 50/50).

Mp = 149-150 °C (EtOAc)

IR (KBr) ν_{\max} (cm⁻¹) = 3416, 3039, 2956, 2892, 2841, 2924, 1645, 1605, 1494, 1454, 1427, 1401, 1383, 1310.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 7.67 (d, 1H, *J* = 6.9 Hz, H-11), 7.44-7.26 (m, 6H, Ar), 7.18-7.10 (m, 2H, Ar), 5.49-5.44 (m, 1H, H-4), 4.15 (d, 1H, *J* = 13.5 Hz, H-5a), 3.41-3.33 (m, 1H, H-1), 3.14 (dd, 1H, *J* = 5.7, 11.7 Hz, H-5b), 2.83-2.73 (m, 2H, H-6a), 2.63-2.58 (m, 1H, H-7a), 2.52-2.46 (m, 2H, H-3), 2.31-2.26 (m, 1H, H-6b), 1.76-1.64 (m, 1H, H-7b), 1.47-1.35 (m, 1H, H-2), 0.91-0.84 (m, 1H, H-2).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = (138.6, 137.9, 129.0, 126.4, 128.1, 127.2, 121.6, 120.3, 118.2, 115.5, 111.9, 107.3 (C-Ar)), 78.7 (C-4), 58.4 (C-5), 57.4 (C-1), 50.2 (C-6), 33.1 (C-3), 26.2 (C-2), 21.3 (C-7).

HRMS (ESI): [M+Na]⁺ C₂₁H₂₂N₂ONa : calcd. 341.1624, found 341.1637.

Second diastereoisomer (697b):

R_f = 0.5 (PE/EtOAc 50/50).

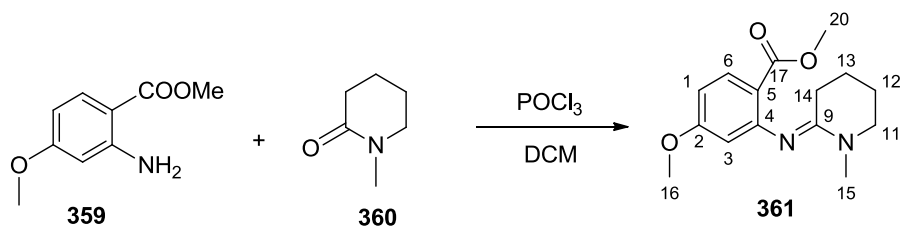
Mp = 136-138 °C (EtOAc)

IR (KBr) ν_{\max} (cm⁻¹) = 3432, 3079, 3059, 3023, 2956, 2920, 2853, 2825, 1617, 1492, 1460, 1440, 1337, 1236.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 7.46-7.29 (m, 7H, Ar), 7.22-7.10 (m, 2H, Ar), 6.00 (s, 1H, H-4), 4.23 (d, 1H, *J* = 13.5 Hz, H-5a), 3.54 (br d, 1H, *J* = 9 Hz, H-1), 3.38 (d, 1H, *J* = 13.2 Hz, H-5b), 3.22 (dd, 1H, *J* = 5.7, 11.7 Hz, H-6a), 2.91-2.79 (m, 1H, H-7a), 2.69-2.48 (m, 2H, H-3, H), 3.34-3.15 (m, 3H, H-6b, H7b, H-2), 1.99-1.85 (m, 1H, H-2).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = (136.1, 129.2, 128.7, 128.4, 121.7, 121.6, 120.4, 118.6 (C-Ar)), 110.2 (C-11), 66.0 (C-4), 58.9 (C-5), 56.9 (C-1), 49.4 (C-6), 30.2 (C-3), 21.2 (C-2), 19.7 (C-7).

HRMS (ESI): [M+Na]⁺ C₂₁H₂₃N₂ONa : calcd. 319.1804, found 319.1813.

(E)-Methyl 4-methoxy-2-((1-methylpiperidin-2-ylidene)amino)benzoate (361)

To a solution of 1-methylpiperidin-2-one **360** (563 mg; 4.97 mmol) in dry DCM (29 mL), POCl₃ (0.46 mL; 4.97 mmol) was added dropwise. The reaction was stirred for 3 h. at room temperature. After that, trisubstituted aniline **359** (820 mg, 4.52 mmol) was dissolved in dry DCM (20 mL) and introduced to the reaction mixture. The reaction was refluxed for 12 h. After that, the reaction was allowed to cool to room temperature and the solvent was removed under reduced pressure. Then the remaining yellow oil was dissolved in 3M HCl. and extracted with DCM (3 x 50 ml). The DCM layers were concentrated under vacuum and the resulting faint yellow oil was carried through the above procedure for more three times. The combined aqueous layers were basified with 1 M NaOH till pH = 8. After that the aqueous layer was extracted with Ethyl acetate (3 x 100 ml). The combined ethyl acetate layers were dried over Na₂SO₄ and the solvent was removed under vacuum. The desired compound **361** was obtained as faint yellow solid (1.14 g, 78%).

R_f = 0.58 (DCM/MeOH 95/05).

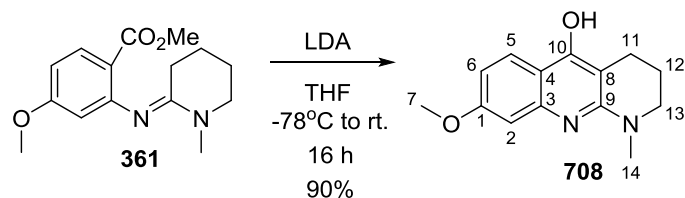
Mp = 64-66 °C (DCM)

IR (KBr) ν_{\max} (cm⁻¹) = 301, 2982, 2949, 2837, 1717, 1671, 1625, 1596, 1557, 1488, 1460, 1320.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) 7.80 (d, *J* = 6 Hz, 1H, H-3), 7.48 (dd, *J* = 3, 9 Hz, 1H, H-1), 6.26 (d, *J* = 3 Hz, 1H, H-6), 3.79 (s, 3H, H-20), 3.75 (s, 3H, H-8), 3.27 (t, *J* = 6 Hz, 2H, H-11), 3.02 (s, 3H, H-16), 2.14 (t, 2H, *J* = 6 Hz, H-13); 1.79 (m, 2H, H-12); 1.62 (m, 2H, H-14).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 166.8 (C-10), 163.10 (C-17), 156.9 (C-2), 155.7 (C-4), 132.9 (C-6), 114.6 (C-1), 108.2 (C-3), 107.9 (C-5), 55.2 (C-20), 51.2 (C-16), 50.6 (C-11), 37.3 (C-15), 26.9 (C-14), 23.7 (C-13), 21.2 (C-12).

HRMS (ESI): [M+Na]⁺ C₁₅H₀N₂O₃Na : calcd. 299.1366 found 299.1359.

8-Methoxy-1-methyl-1,2,3,4-tetrahydrobenzo[b][1,8]naphthyridin-5-ol (708)

In 25 mL dry round bottom two-necked flask, *n*-BuLi (0.514 mL; 0.9047 mmol, 2.5 eq., 1.7 M in THF) was placed. After that freshly distilled diisopropylamine (0.135 mL; 0.95 mmol, 2.65 eq.) was added very drop wisely to reaction mixture. (LDA begin to form as a gel). After that, dry THF (2 mL) was added to the reaction mixture. The reaction mixture was cooled to -78°C. Amidine **361** (100 mg; 0.361 mmol) was dissolved in dry THF (2 ml) and introduced drop wisely to the reaction mixture. The reaction was allowed to react for 3h at -78°C and then was allowed to warm up to room temperature overnight. Then, the reaction was quenched with a few drops of a NH₄Cl solution. THF was then evaporated under reduced pressure. The residue was diluted with a NH₄Cl saturated solution and extracted with DCM. The combined organic layers were washed with brine and dried over Na₂SO₄. The solvent was concentrated under reduced pressure and the residue purified by chromatography on silica gel (DCM/MeOH 95/5) to give **708** as a faint pink solid (79.5 mg, 90%).

Mp = > 300°C (DCM).

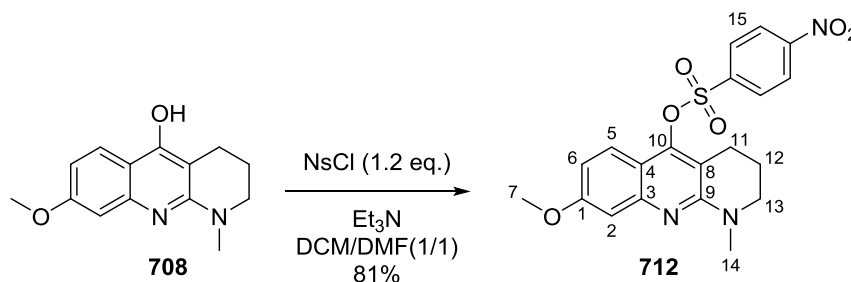
R_f = 0.50 (DCM/MeOH 95/5).

IR (KBr) ν_{\max} (cm⁻¹) = 3071, 2943, 2848, 1632, 1591, 1548, 1500, 1469, 1390, 1338, 1314, 1278.

¹H NMR (MeOH, 300 MHz): δ (ppm) = 8.03-8.00 (d, 1H, *J* = 8.7 Hz, H-5), 7.07 (d, 1H, *J* = 2.1 Hz, H-2), 6.87-6.83 (dd, 1H, *J* = 2.4, 8.7 Hz, H-6), 3.88 (s, 3H, H-7), 3.44 (t, 2H, *J* = 5.4 Hz, H-13), 3.20 (s, 3H, H-14), 2.69 (t, 2H, *J* = 6.3 Hz, H-11), 1.99-1.91(m, 2H, H-12).

¹³C NMR (MeOH, 75 MHz): δ (ppm) = (161.3, 155.7, 150.0, 121.9, 125.6, 111.5, 105.4, 98.2 (C-Ar)), 54.5 (C-7), 49.3 (C-14), 43.2 (C-13), 21.9 (C-11) 20.7(C-12).

HRMS (ESI): [M+Na]⁺ C₁₄H₁₆N₂O₂Na : calcd. 267.1103, found 267.1113.

8-Methoxy-1-methyl-1,2,3,4-tetrahydrobenzo[b][1,8]naphthyridin-5-yl 4-nitrobenzenesulfonate (712)

To a solution of phenol **708** (100 mg, 0.40 mmol, 1 eq.) in dry DCM / DMF (15 mL 2/1), triethylamine (0.073 mL, 0.532 mmol, 1.3 eq.) was added and the reaction mixture was stirred for 30 min. The color during this period changed from colorless to deep yellow. NsCl (117.9 mg, 0.532 mmol, 1.3 eq.) was added and the reaction mixture was stirred for 3 h at r.t. The solvents were removed under reduced pressure and the crude material purified by chromatography on silica gel (PE/EtOAc 50/50) to give nosylate **712** as orange solid (143 mg, 81%).

$R_f = 0.31$ (PE/EtOAc 50/50).

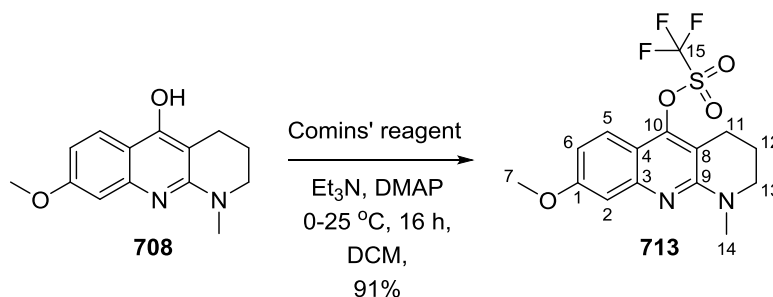
Mp = 202-203°C (DCM).

IR (KBr) ν_{\max} (cm⁻¹) = 3440, 3111, 2956, 2936, 2849, 1631, 1617, 1555, 1534, 1464, 1448, 1395, 1365.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 8.42 (d, 2H, $J = 1.8$ Hz, Ar), 8.17 (d, 1H, $J = 1.8$ Hz, Ar), 7.06 (br s, 1H, Ar), 6.96 (d, 1H, $J = 9.0$ Hz, H-2), 6.59-6.55 (dd, 1H, $J = 2.4, 9.0$ Hz, H-6), 3.89 (s, 3H, H-7), 3.50 (t, 2H, $J = 5.7$ Hz, H-13), 3.32 (s, 3H, H-14), 2.89 (t, 2H, $J = 6.3$ Hz, H-11), 2.00-1.92 (m, 2H, H-12).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = (160.9, 151.0, 142.0, 129.7, 124.5, 122.1, 113.7, 111.5, 105.3 (C-Ar)), 55.3 (C-7), 49.8 (C-14), 37.2 (C-13), 23.2 (C-11), 20.6 (C-12).

HRMS (ESI): $[M+H]^+$ C₂₀H₂₀N₃O₆S : calcd. 430.1067, found 430.1075.

8-Methoxy-1-methyl-1,2,3,4-tetrahydrobenzo[b][1,8]naphthyridin-5-yltrifluoromethane sulfonate (713)

To a solution of phenol **708** (400 mg, 0.286 mmol, 1 eq.) in dry DCM / DMF (30 mL 2/1), triethylamine (0.35 mL, 0.429 mmol, 1.5 eq.) and DMAP (14.7 mg, 0.81 mmol, 0.5 eq.) were added at 0°C and the reaction mixture was stirred for 30 min. The color during this period changed from colorless to deep yellow. Comins' reagent (224.6 mg, 0.572 mmol, 1.5 eq.) was added and the reaction mixture was stirred for 16 h at r.t. A 30% ammonium hydroxide solution was added until pH = 13 and the organic solvents were evaporated under vacuum. The residue was then diluted with EtOAc and saturated NaCl solution, the organic layer was separated and dried over Na₂SO₄. The solvent was concentrated under reduced pressure and the crude material purified by chromatography on silica gel (PE/EtOAc 7/3) to give triflate **713** as brown oil (535 mg, 87%).

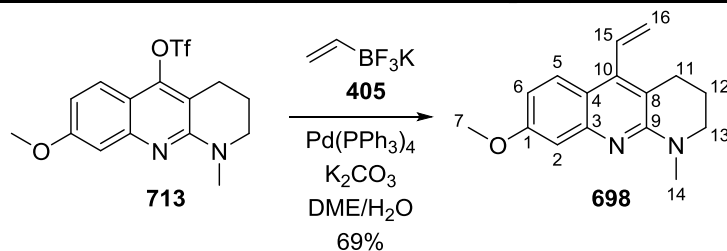
$R_f = 0.76$ (PE/EtOAc 7/3).

IR (ATR) ν_{\max} (cm⁻¹) = 3090, 2901, 2853, 1613, 1511, 1483, 1443, 1372.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 7.66-7.63 (d, 1H, $J = 9.0$ Hz, H-5), 7.09 (d, 1H, $J = 2.4$ Hz, H-2), 6.93-6.89 (dd, 1H, $J = 2.4, 9.0$ Hz, H-6), 3.94 (s, 3H, H-7), 3.52 (t, 2H, $J = 5.7$ Hz, H-13), 3.33 (s, 3H, H-14), 2.98 (t, 2H, $J = 6.0$ Hz, H-11), 2.04-2.00 (m, 2H, H-12).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = (161.3, 155.7, 150.0, 148.6, 128.8, 121.9, 120.7 (C-Ar)), 116.4 (C-15), (114.5, 111.1, 110.7, 105.4 (C-Ar)), 55.4 (C-7), 49.6 (C-14), 37.2 (C-13), 22.8 (C-11), 20.5 (C-12).

HRMS (ESI): $[M+H]^+$ C₁₅H₁₆N₂O₄F₃S : calcd. 377.0777, found 377.0784.

8-Methoxy-1-methyl-5-vinyl-1,2,3,4-tetrahydrobenzo[b][1,8]naphthyridine (698)

To a solution of the triflate **713** (140 mg, 0.37 mmol, 1 eq.) in freshly distilled DME (14 mL) and H₂O (7 mL), vinyl potassium trifluoroborate (55.07 mg, 0.39 mmol, 1.05 eq.) and K₂CO₃ (51.4 mg, 0.372 mmol, 1 eq.) were added. The flask containing the reaction mixture was flashed with argon for 30 min, then Pd(PPh₃)₄ (4.9 mg, 0.01 mmol, 0.1 eq.) was added. The reaction mixture was heated at 95°C for 3 h. The reaction mixture was then cooled down to room temperature and the solvent evaporated under vacuum. The product was purified by chromatography on silica gel (PE/EtOAc 80/20) to give **698** as yellow oil (75 mg, 79%).

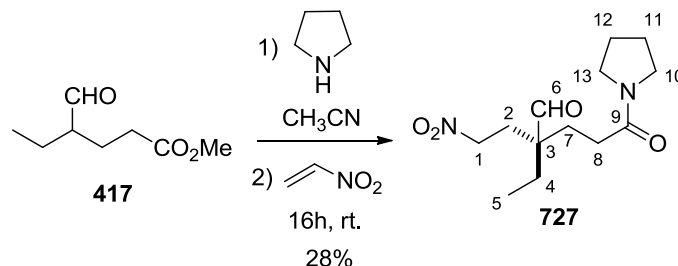
$R_f = 0.45$ (PE/EtOAc 80/20).

IR (ATR) ν_{max} (cm⁻¹) = 3079, 2939, 2839, 1615, 1584, 1562, 1509, 1463, 1449, 1423, 1401, 1343.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 7.66-7.63 (d, 1H, $J = 9.0$ Hz, H-5), 7.06 (d, 1H, $J = 2.4$ Hz, H-2), 6.85-6.75 (m, 2H, H-6, H-15), 5.76-5.71 (dd, 1H, $J = 1.8, 11.4$ Hz, H-16a), 5.43-5.36 (dd, 1H, $J = 2.1, 18.0$ Hz, H-16b), 3.90 (s, 3H, H-7), 3.43 (t, 2H, $J = 5.7$ Hz, H-13), 3.28 (s, 3H, H-14), 2.82 (t, 2H, $J = 6.3$ Hz, H-11), 1.98-1.90 (m, 2H, H-12).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = (160.0, 155.3, 148.6, 141.2, 132.4, 125.9 (C-Ar)), 121.8 (C-15), (116.4, 144.7, 105.6 (C-Ar)), 112.9 (C-16) 55.3 (C-7), 50.0 (C-14), 37.0 (C-13), 26.0 (C-11), 21.6 (C-12).

HRMS (ESI): [M+H]⁺ C₁₆H₁₉N₂O: calcd. 255.1491, found 255.1490.

2-Ethyl-2-(2-nitroethyl)-5-oxo-5-(pyrrolidin-1-yl)pentanal (727)**Preparation of 2-nitroethyl acetate:**

A solution of (0.5 g) of NaOAc in (2.4 mL, 25.55 mmol) of Ac₂O was maintained at a temperature of 35 °C using a cold H₂O bath, as 2 g (1.1 mol) of 2-nitroethanol was added over a period of 30 min. (Caution: The temperature of this reaction must be carefully controlled. If allowed to exceed 60 °C, a violent decomposition may occur). When the reaction temperature no longer tended to rise, the bath was removed and the solution was allowed to stir overnight. The solution was then poured into a large volume of cold H₂O and extracted with three portions of DCM. The extracts were washed with NaCl solution and dried over Na₂SO₄. Evaporation of the solvent under reduced pressure afforded yellow oil (3.052 g, quant. yield). The crude oil was used directly in the next step.

Preparation of enamine:

To a solution of pyrrolidine (0.15 mL, 1.89 mmol, 1.0 eq.), aldehyde **417** (300 mg, 1.89 mmol, 1.0 eq.) in dry toluene (42 mL) *p*-toluene sulfonic acid (0.6 mL, 0.4 mol%) was added. The reaction mixture was refluxed at 110°C for 5h using dean's stark apparatus. Then solvent was removed with a rotary evaporator, and the resulting crude product was used directly in the next step.

Preparation of aldehyde 727:

A solution of 2-nitroethyl acetate (315 mg, 2.36 mmol, 1.25 eq.), in CH₃CN (2 mL) was added to a crude solution of the enamine of **417** (400 mg, 1.89 mmol, 1.0 eq.) in CH₃CN (6 mL). The reaction was maintained at room temperature for 2 h. After 2 h, HCl (5% aqueous solution, 8 mL) was added and the resulting mixture was extracted with EtOAc (3 x 5mL). The combined organic extracts were washed with saturated NaHCO₃ solution and then brine, dried over MgSO₄. The solvent was concentrated under reduced pressure and the crude material purified by chromatography on silica gel (EtOAc 100%) to give aldehyde **727** as colorless oil (144 mg, 28%).

$R_f = 0.42$ (EtOAc 100%),

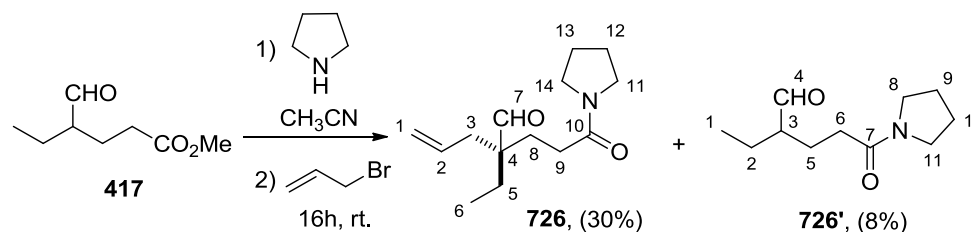
IR (ATR) ν_{\max} (cm⁻¹) = 3420, 2968, 2932, 2876, 1718, 1629, 1550, 1440, 1383, 1383, 1363.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 9.36 (s, 1H, H-6), 4.38-4.28 (m, 2H, H-1), 3.40-3.30 (m, 4H, H-10, H-13), 2.26-2.07 (m, 4H, H-2, H-8), 1.97-1.75 (m, 6H, H-7, H-11, H-12), 1.63-1.47 (m, 2H, H-4), 0.83 (t, 3H, $J = 7.5$ Hz, H-5).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 204.3 (C-6), 169.7 (C-9), 71.2 (C-1), 50.6 (C-3), 46.5 (C-10), 45.8 (C-13), 28.3 (C-8), 27.2 (C-7), 27.0 (C-2), 25.9 (C-12), 25.2 (C-11), 24.2 (C-4), 7.7 (C-5).

HRMS (ESI): $[M+Na]^+$ C₁₃H₂₂N₂O₄Na: calcd. 293.1471, found 293.1472.

2-Ethyl-2-(3-oxo-3-(pyrrolidin-1-yl)propyl)pent-4-enal (726)



Preparation of enamine:

To a solution of pyrrolidine (0.15 mL, 1.89 mmol, 1.0 eq.), aldehyde **417** (300 mg, 1.89 mmol, 1.0 eq.) in dry toluene (42 mL) *p*-toluene sulfonic acid (0.6 mL, 0.4 mol%) was added. The reaction mixture was refluxed at 110°C for 5h using dean's stark apparatus. Then solvent was removed with a rotary evaporator, and the resulting crude product was used directly in the next step.

Preparation of aldehyde 726:

A solution of allyl bromide **127** (1.11 mL, 12.7 mmol, 3.55 eq.), in dry CH₃CN (2 mL) was added to a crude solution of the enamine of **417** (900 mg, 3.59 mmol, 1.0 eq.) in dry CH₃CN (6 mL). The reaction was maintained at room temperature for 2 h. After 2 h, HCl (5% aqueous solution, 8 mL) was added and the resulting mixture was extracted with EtOAc (3 x 5mL). The combined organic extracts were washed with saturated NaHCO₃ solution and then brine, dried over MgSO₄. The solvent was concentrated under reduced pressure and the crude material purified by chromatography on silica gel (EtOAc 100%) to give aldehyde **726** as colorless oil (154 mg, 30%) and aldehyde **726'** (112 mg, 8%).

$R_f = 0.62$ (EtOAc 100%).

IR (ATR) ν_{\max} (cm⁻¹) = 3077, 2964, 2878, 2703, 1722, 1634, 1446, 1344, 1260.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 9.44 (s, 1H, H-7), 5.73-5.59 (m, 1H, H-2), 5.12-5.05 (m, 1H, H-1), 3.43 (t, 2H, $J = 6.9$ Hz, H-11), 3.34 (t, 2H, $J = 6.6$ Hz, H-14), 2.28-2.23 (m, 2H, H-9), 2.12-2.07 (m, 2H, H-3), 1.94-1.79 (m, 6H, H-8, H12, H13), 1.63-1.48 (m, 2H, H-5), 0.81(t, 3H, $J = 7.5$ Hz, H-6).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 206.3 (C-7), 170.6 (C-10), 132.7 (C-2), 118.5 (C-1), 51.7 (C-4), 46.5 (C-11), 45.7 (C-14), 35.1 (C-3), 28.9 (C-9), 27.1 (C-8), 26.0 (C-5), 24.7 (C-11), 24.3 (C-14), 7.8 (C-6).

HRMS (ESI): $[M+Na]^+$ C₁₄H₂₃NO₂Na: calcd. 260.1621, found 260.1623.

2-Ethyl-5-oxo-5-(pyrrolidin-1-yl)pentanal (726')

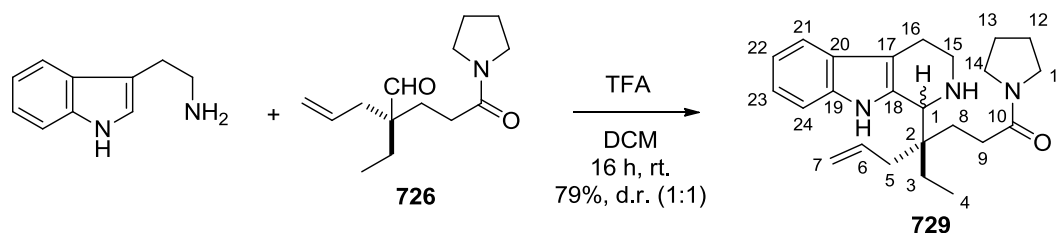
$R_f = 0.62$ (EtOAc 100%).

IR (ATR) ν_{\max} (cm⁻¹) = 3048, 2964, 2874, 1721, 1631, 1441, 1343, 1267.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 9.54 (m, 1H, H-4), 3.41-3.31 (m, 4H, H-8, H-11), 2.25-2.17 (m, 3H, H-6, H-9), 1.99-1.74 (m, 6H, H-9, H-10, H-5), 1.71-1.59 (m, 1H, H-2a), 1.56-1.44 (m, 1H, H-2b), 0.89(t, 3H, $J = 7.2$ Hz, H-1).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 205.1 (C-4), 170.5 (C-7), 52.8 (C-3), 46.4(C-11), 45.5 (C-8), 31.7 (C-6), 25.9 (C-9), 24.3 (C-10), 23.2 (C-5), 22.0 (C-2), 11.3 (C-1)

HRMS (ESI): $[M+Na]^+$ C₁₁H₁₉NO₂Na: calcd. 220.1308, found 220.1309.

4-Ethyl-1-(pyrrolidin-1-yl)-4-(2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)hept-6-en-1-one (729)

To a solution of tryptamine (44.5 mg; 0.27 mmol, 1.1 eq.) in dry DCM (7.5 mL), aldehyde **726** (60 mg; 0.25 mmol, 1.0 eq.) was dissolved in dry DCM (2.0 mL) and introduced to the reaction mixture. The reaction was stirred at room temperature for 2 h. At the end of 2.0 h, the reaction mixture was cooled to 0 °C in an ice bath and TFA (0.04 mL; 0.50 mmol; 2.0 eq.) was added. The reaction mixture was stirred for about 30 min at 0 °C. The ice bath was removed after 30 min and the reaction mixture was stirred at room temperature for about 16 hours. Then, the reaction was quenched with sat. NaHCO₃ solution, to neutralize TFA (monitored by pH paper). The reaction mass was diluted with methylene chloride and the organic layer was washed with water (~5 mL) and brine solution (~5 mL). The combined organic layer was dried over MgSO₄ and the solvent was concentrated under reduced pressure and the crude material purified by chromatography on silica gel (EtOAc 100%) to give Pictet-Spengler product **729** as brown solid (76 mg, 79%, d.r. (1:1)).

R_f = 0.39 (DCM/MeOH 95/5).

Mp = 135 °C (DCM).

IR (KBr) ν_{max} (cm⁻¹) = 3185, 3071, 2970, 2877, 1608, 1473, 1444, 1340.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 9.89 (br s, 2H, NH), 7.55-7.48 (m, 3H, Ar), 7.20-7.07 (m, 3H, Ar), 6.04-5.90 (m, 1H, H-6), 5.85-5.71 (m, 1H, H-6), 5.22-5.12 (m, 2H, H-7), 5.02-4.96 (m, 2H, H-7), 4.16 (s, 2H, H-1), 3.54-3.34 (m, 9H, H-11, H-14), 2.93-2.76 (m, 6H), 2.58-2.09 (m, 12H), 1.97-1.81 (m, 10H), 1.67-1.50 (m, 4H, H-3), 1.01 (t, 3H, *J* = 7.2 Hz, H-4), 0.79 (t, 3H, *J* = 7.2 Hz, H-4).

¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = (172.7, 172.4, (C-10)), (136.1, 135.5, 135.4, 134.1, 133.9, 126.9, 126.8, 121.1, 118.7, 117.6, 117.5, 117.4, 111.5, 111.3, 111.1 (C-Ar)), (58.4, 58.0 (C-1)), 46.8, 46.7, 45.8, 43.9, 43.8, 43.3, 43.2, 40.9, 39.6, 29.9, 29.7, 28.7, 28.7, 28.1, 27.2, 25.9, 24.45, 24.40, (23.3, 23.2 (C-3)), (8.5, 8.3 (C-4)).

HRMS (ESI): [M+H]⁺ C₂₄H₃₄N₃O: calcd. 380.2696, found 380.2695.