



HAL
open science

Photochemistry and cascade reactions: access to propellanes and natural products

Youssef Nassar

► **To cite this version:**

Youssef Nassar. Photochemistry and cascade reactions: access to propellanes and natural products. Organic chemistry. Université de Lyon, 2020. English. NNT : 2020LYSE1186 . tel-03395419

HAL Id: tel-03395419

<https://theses.hal.science/tel-03395419v1>

Submitted on 22 Oct 2021

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

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

N°d'ordre NNT : xxx



THESE de DOCTORAT DE L'UNIVERSITE DE LYON

opérée au sein de
l'Université Claude Bernard Lyon 1

Ecole Doctorale N° 206
Chimie, Procédés, Environnement

Spécialité de doctorat : Chimie

Discipline : Chimie Organique

Soutenue publiquement le 26/10/2020, par :

Youssef Nassar

Photochimie et Réactions en Cascade: Accès aux Propellanes et aux Produits Naturels

Devant le jury composé de :

Aitken, David	Professeur, Univ. Paris Saclay	Rapporteur
Py, Sandrine	Directeur de Recherche CNRS, Univ. Grenoble-Alpes	Rapporteur
Andrioletti, Bruno	Professeur, Univ. Lyon 1	Examineur
Cossy, Janine	Professeure, ESPCI PARIS – PSL	Examinatrice
Piva, Olivier	Professeur, Univ. Lyon 1	Directeur de thèse

UNIVERSITE CLAUDE BERNARD – LYON 1

Président de l'Université	M. Frédéric FLEURY
Président du Conseil Académique	M. Hamda BEN HADID
Vice-Président du Conseil d'Administration	M. Didier REVEL
Vice-Président du Conseil des Etudes et de la Vie Universitaire	M. Philippe CHEVALLIER
Vice-Président de la Commission de Recherche	M. Jean-François MORNEX
Directeur Général des Services	M. Damien VERHAEGHE

COMPOSANTES SANTE

Faculté de Médecine Lyon-Est –Claude Bernard	Doyen : M. Gilles RODE
Faculté de Médecine et Maïeutique Lyon Sud Charles. Mérieux	Doyenne : Mme Carole BURILLON
UFR d'Odontologie	Doyenne : Mme Dominique SEUX
Institut des Sciences Pharmaceutiques et Biologiques	Directrice : Mme Christine VINCIGUERRA
Institut des Sciences et Techniques de la Réadaptation	Directeur : M. Xavier PERRO
Département de Formation et Centre de Recherche en Biologie Humaine	Directrice: Mme Anne-Marie SCHOTT

COMPOSANTES & DEPARTEMENTS DE SCIENCES & TECHNOLOGIE

UFR Biosciences	Directrice : Mme Kathrin GIESELER
Département Génie Electrique et des Procédés (GEP)	Directrice : Mme Rosaria FERRIGNO
Département Informatique	Directeur : M. Behzad SHARIAT
Département Mécanique	Directeur : M. Marc BUFFAT
UFR -Faculté des Sciences	Directeur : M. Bruno ANDRIOLETTI
UFR (STAPS)	Directeur : M. Yannick VANPOULLE
Observatoire de Lyon	Directrice : Mme Isabelle DANIEL
Ecole Polytechnique Universitaire Lyon 1	Directeur : Emmanuel PERRIN
Ecole Supérieure de Chimie, Physique, Electronique (CPE Lyon)	Directeur : Gérard PIGNAULT
Institut Universitaire de Technologie de Lyon 1	Directeur : M. Christophe VITON
Institut de Science Financière et d'Assurances	Directeur : M. Nicolas LEBOISNE
ESPE	Administrateur Provisoire : M. Pierre CHAREYRON

Résumé

L'augmentation remarquable du nombre de nouveaux médicaments cibles peut se traduire directement par une demande de nouvelles méthodes pour construire rapidement de petites molécules très pures qui possèdent un niveau de complexité structurelle toujours croissant. Ces processus doivent également être plus efficaces, plus propres pour l'environnement et conduire à une plus grande diversité structurelle en peu de temps. Ces besoins ont conduit au développement de nouvelles stratégies, qui ont aidé à produire des composés à un rythme plus élevé que ce que l'on pensait possible auparavant. La photochimie ainsi que les réactions en cascade font partie de ces stratégies dans lesquelles elles sont très recherchées pour leur efficacité à construire un certain nombre de liaisons et de cycles et à augmenter la complexité moléculaire des produits qui en résultent. Cette thèse rapporte l'utilisation de la photochimie et des réactions en cascade pour la synthèse de structures complexes, telles que des propellanes et de certains produits naturels. Le chapitre 1 donne un aperçu de la conception et de la synthèse des α - (hydroxyméthyl) cycloalcanols et le chapitre 2 décrit l'utilisation de la photo-hydroxymethylation pour synthèse des éléments constitutifs du propellane. Les chapitres 3 à 5 concernent la synthèse de divers systèmes de cycles de propellane avec une architecture structurelle esthétiquement attrayante alors que, le dernier chapitre donne brièvement nos tentatives vers la synthèse totale de cordycol, le monomère de l'idesolide et d'un analogue.

Mots-clefs:

Photochimie – Réactions en cascade – Propellanes – Spirocycles – Synthèse totale – Cordycol – Lactones.

Abstract

The remarkable increase in the number of new drug targets can be directly translated into a demand for new methods to rapidly construct highly pure small molecules that possess an ever-increasing level of structural complexity. These processes are also required to be more efficient, environmentally cleaner, and lead to greater structural diversity in a short time. Such needs have driven the development of novel strategies, which have helped to produce compounds at a greater rate than previously thought possible. Photochemistry as well as cascade reactions are part of these strategies in which they are highly desired for their efficiency in building a number of bonds and rings and increasing the molecular complexity in the ensuing products. This PhD thesis aims to provide applications of photochemistry and cascade reactions for the synthesis of intricate structures, such as propellanes and certain natural products. Chapter 1 gives an overview of the design and synthesis of α -(hydroxymethyl)cycloalkanols and Chapter 2 provides the use of photohydroxymethylation for the synthesis of propellane building blocks. Chapters 3-5 relate to the synthesis of diverse propellane ring-systems with aesthetically appealing structural architecture. Whereas, the last chapter briefly gives our attempts toward the total synthesis of cordycol, idesolide monomer and analogue.

Keywords:

Photochemistry – Cascade reactions – Propellanes – Spirocycles – Total synthesis – Cordycol – Lactones.

Acknowledgments

This thesis is the output of a series of efforts from a life-changing experience, called PhD. In these three years, I could have never climbed this mountain without the help and support of special people to whom I am extremely grateful.

First and foremost, I would like to express my deepest appreciation to my advisor **Pr. Olivier Piva** for his major contribution to the work. His passion for organic chemistry, consistent supervision, and patience have inspired and motivated me to move forward with my project. He has literally made this journey adventurous and meaningful, and for that, I am profoundly grateful.

I would like to thank our group members, **Dr. Béatrice Pelotier** and **Dr. Fabienne Fache** for their infinite help inside and outside the lab. They have believed in me, and that was enough to build and develop a strong sense of trust in the group. Moreover, they have taught me French and colored my PhD with beautiful moments that I will never forget in my life.

Special thanks to “Ministère de l'Enseignement Supérieur et de la Recherche” (**MESR**) for the PhD grant, without their investment, this PhD would not have been possible.

I would also like to thank my committee members, **Pr. David Aitken**, **Dr. Sandrine Py**, **Pr. Bruno Andrioletti** and **Pr. Janine Cossy** for accepting our invitation and for editing and proof-reading the manuscript. It will be a great honor for me to present them my PhD work and acquire their feedback.

I owe my sincere gratitude to the thesis monitoring committee members (CST), **Pr. Peter Goekjian**, **Pr. Benoît Joseph** and **Pr. Abder Amgoune** for their precious advice and comments about the PhD project for the first- and second-year PhD.

A big thank you to my master II advisor at ENS de Lyon **Dr. Christophe Bucher** who empowered me with his passion for chemistry and taught me the basic methods of organic and electrochemical labs.

Special thanks to **Lucas Bolomier**, **Lucie Guillaume**, **Maxime Llobet** et **Alexandre Perera** who participated, throughout their internships, in the work of the second chapter concerning the photohydroxymethylation reaction of different terpenones.

I would like also to thank **Arnaud Comte** and **Anne Baudouin** for fruitful discussions, analyses, and ideas in parts of Chapter 4.

Family and friends...

Fortunately, I have also the privilege of having a lovely family and friends who had a fundamental role in getting me through the PhD process successfully:

My mother **Nasima** and my father **Mohammad**, there is no way to thank you for everything you have done for me. Simply, thanks for being always present and doing the (im)possible to keep me going further. You are inspiring. My brothers, **Shadi**, **Yehya**, **Feras** and **Ali**, thanks for your trust in my life choices and your support. You are everything to me, and I'm so lucky to be your brother. My grandparents **Sobhiyya** and **Ahmad**, and my relatives **Ali**, **Nabegh** and **Nelli El-kadri** and your families, thanks for your special support. That means a lot to me.

My best friends **Ali Soulieman** and **Johannes Schwartz**, thank you for not making distance a big deal of our friendship. Thank you for inspiring and helping me throughout this journey.

My Friends during my PhD...

Aurélie Rago, thank you for helping me and teaching me your French culture (language, food, and lifestyle..). **Benjamin Ourri** and **Alexandre Heloin**, thank you for empowering and motivating me (we really laughed a lot during my second year). **Nour Halawani**, **Hussien Banjak**, **Ali Khanafer**, **Shagor Chowdhury** and **Sary Abou Derhamine**, thank you for making me feel as if I am back home. **Nicolas Brevet** and your family, thank you for your special invitations to Savigney (you are such an amazing and lovely family). **Nadjib Khene**, thank you for sharing my last months in this PhD, you are just awesome. A big thank you to my colleagues at **CSAP**, **LCO2** and **CASYEN** groups for sharing special moments during my second year.

Last but not least, **Yassin Hussien** and **Khadija Rahhal**, you would have been so happy and proud of me if you were still alive. In loving you, I am gifted with memories that can never die. Thank you for everything.

Villeurbanne, on 17/07/2020,

Youssef

“To my family and my country Lebanon”

Abbreviations

Δ	heat
δ	chemical shift in parts per million
μ	micro
[α]	specific rotation
$^{\circ}\text{C}$	degrees Celsius
Ac	acetyl
aq.	aqueous
Ar	aryl
atm.	atmosphere
Boc	tert-butoxycarbonyl
n-Bu	butyl
t-Bu	tert-butyl
cat.	catalytic
COSY	correlation spectroscopy
DCM	dichloromethane
dr	diastereomeric ratio
DEPT	distortionless enhancement by polarization transfer
DMEA	N,N-dimethylethanolamine
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
<i>ee</i>	enantiomeric excess
equiv. = eq.	equivalent(s)
ESI	electrospray ionization
Et	ethyl
<i>et al.</i>	et alia
g	gram(s)
h	hour(s)
HMBC	heteronuclear multiple bond correlation

HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectroscopy
HSQC	heteronuclear single quantum correlation
Hz	Hertz
IR	infrared
LUMO	lowest unoccupied molecular orbital
M	molar
<i>m</i>	meta
<i>m</i>-CPBA	meta-chloroperoxybenzoic acid
Me	methyl
min.	minute(s)
mol	mole(s)
MOM	methoxymethyl
m.p.	melting point
m/z	mass-to-charge ratio
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser spectroscopy
Nu	nucleophile
<i>o</i>	ortho
<i>p</i>	para
Ph	phenyl
R	undefined substituent
R_f	retention factor
r.t.	room temperature
T	temperature
<i>tert</i>	tertiary
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
UV	ultraviolet

Table of Contents

Résumé.....	IV
Abstract.....	V
Acknowledgments.....	VII
Abbreviations	I
Table of Contents.....	I
Ch. I: Design and Synthesis of α-(Hydroxymethyl)cycloalkanols	3
1. Introduction.....	3
2. Occurrence	3
2.1. Aminocarbasugars	4
2.2. Terpenoids	4
2.3. Miscellaneous.....	7
3. Synthesis	9
3.1. Synthesis of α -(hydroxymethyl)cycloalkanols from ketones.....	9
3.2. Synthesis of α -(hydroxymethyl)cycloalkanols from epoxides	20
3.3. Synthesis of α -(hydroxymethyl)cycloalkanols from alkenes	23
3.4. Miscellaneous synthesis of α -(hydroxymethyl)-cycloalkanols	27
4. Conclusion	30
5. References	30
Ch. II: Photochemical Hydroxymethylation	38
1. Introduction.....	38
2. Preparation of different α -substituted β -ketoesters.....	39
3. Preparation of the photocatalyst.....	41
4. Photochemical hydroxymethylation of alkyl oxocycloalkanecarboxylates 160b-d	42
5. Photochemical hydroxymethylation of α -substituted alkyl 2-oxocycloalkanecarboxylates: access to bicyclic γ -lactones.....	43
5.1. Synthesis of propargyl bicyclic γ -lactones.....	44
5.1. Synthesis of an allyl bicyclic γ -lactone	46
6. Photochemical hydroxymethylation of miscellaneous α -substituted alkyl 2-oxocycloalkanecarboxylates	52

7. Photochemical hydroxymethylation of various terpenoids	55
6. Camphorquinone	56
8. An alternative method to photochemical hydroxymethylation	58
9. Conclusion	60
10. References.....	60
Ch. III: Propellanes – from Allyl Bicyclic β-Hydroxy-γ-Lactones.....	63
1. Introduction.....	63
1.1. Nomenclature.....	63
1.2. History.....	64
2. General properties	65
2.1. Strain.....	65
2.2. Reactivity and reactions of propellanes.....	66
3. Occurrence in natural products	66
4. Synthesis of propellanes: general overview	68
5. Applications of different propellanes	70
6. Our main objective.....	72
7. Structural Features and Retrosynthetic Analysis of the Substituted [3,3,3]- Propellanes	73
8. Synthesis of Substituted [3,3,3]Propellanes	74
8.1. Preparation of iodo[3,3,3]propellanes 231a-b.....	74
8.2. Preparation of substituted [3,3,3]propellanes from 231a-b	77
8.3. Further functionalization of our propellane ring system	82
8.4. Preparation of triazolo[3,3,3]propellanes <i>via</i> click reaction.....	83
8.5. Synthesis of unusual bis-triazolo[3,3,3]propellane via double-click reaction.....	90
9. A new approach toward unsaturated [5,3,3]propellano-bis lactone	92
10. Conclusion.....	94
11. References.....	94
Ch. IV: Propellanes – from Propargyl Bicyclic β-Hydroxy-γ-Lactones	100
1. Introduction.....	100
2. Oxaspiro[<i>n</i> ,3,3]propellanes	101
2.1. Spiropropellanes.....	101
2.2. General retrosynthetic analysis of oxaspiro[<i>n</i> ,3,3]propellanes	102
2.3. Formation of exocyclic enol ethers	103

2.4.	Spirocyclopropanyl[n,3,3]propellanes.....	107
2.5.	Spiro-oxetanyl[n,3,3]propellanes.....	109
2.6.	Oxaspirolactone[n,3,3]propellanes.....	123
2.7.	Further oxaspiro[n,3,3]propellanes!.....	133
3.	Miscellaneous propellanes obtained from propargyl bicyclic γ -lactone.....	134
3.1.	PTAD-based [6,4,3]propellanes.....	134
3.2.	Iodo-DHP[4,3,3]propellane.....	143
4.	General conclusion.....	147
5.	References.....	147
Ch. V:	Hexahydroindeno[2,1-c]pyran-based Propellanes.....	153
1.	Introduction.....	153
2.	Indenopyrans: a brief overview.....	154
2.1.	Nomenclature.....	154
2.2.	Occurrence.....	155
2.3.	Synthesis.....	156
3.	Hexahydroindeno[2,1-c]pyran-based Propellanes: Our work.....	160
3.1.	Key features and retrosynthetic analysis.....	160
3.2.	Results and discussion.....	161
3.3.	Characterization of the isolated indenopyran-based propellanes.....	175
4.	Conclusion.....	180
5.	References.....	180
Ch. VI:	Toward the Total Synthesis of Cordycol, Idesolide Monomer and Analogue.....	184
	Cordycol.....	184
1.	Introduction.....	184
2.	Results and discussion.....	187
	Idesolide monomer and analogues.....	189
3.	General Conclusion.....	193
4.	References.....	193
	General Conclusion and Perspective.....	196
	Appendix.....	198
1.	Experimental part.....	198
1.1.	General working methods.....	198

Chapter I

Design and Synthesis of α -
(Hydroxymethyl)cycloalkanols

Ch. I: Design and Synthesis of α -(Hydroxymethyl)cycloalkanols

1. Introduction

α -(Hydroxymethyl)cycloalkanols, as polar cyclic scaffolds, are found in a wide spectrum of compounds of natural or synthetic origins. Structurally, they are saturated cyclic hydrocarbons with characteristic vicinal diols acting as a reactive functional group for distinct chemical or biological activities (Figure 1). In recent years, a significant number of natural products possessing an α -(hydroxymethyl)cycloalkanol moiety, have been isolated from diverse sources, including marine organisms, fungi, insects and plants. On the other hand, α -(hydroxymethyl)cycloalkanols have been synthesized as potent intermediates in the total synthesis of some natural products to access further complex structures using a minimal number of steps. Accordingly, a number of methods and strategies have been developed to access these compounds.

Here, we review and collate the occurrence, synthesis and reactivity of α -(hydroxymethyl)cycloalkanols, as well as their relevance to medicinal chemistry programs. Advances up to late 2019 are covered, focusing on more recent studies but also detailing previous work that still remains compelling in the synthesis of distinct α -(hydroxymethyl)cycloalkanol derivatives.

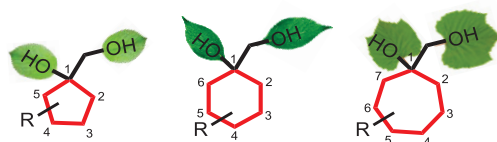


Figure 1. The most common α -(hydroxymethyl)cycloalkanol ring systems.

2. Occurrence

α -(Hydroxymethyl)cycloalkanols are quite common in nature, and it appears that their core structure mainly comprises 5 to 7 membered ring. This section aims to provide various information by focusing on the most often encountered, striking, and recent examples of structures of this kind that were isolated from aminocarbasugars, terpenoids and other miscellaneous natural products.

2.1. Aminocarbasugars

Perhaps the most well-known examples of aminocarbasugars are pactamycin derivatives **1a-d** possessing the α -(hydroxymethyl)cyclopentanol core (Figure 2). Pactamycin **1a** is a structurally unique chemical compound isolated from the soil bacterium *Streptomyces pactum*. Despite its potent antimicrobial, antitumor, antiviral and antiprotozoal activities,^[1] **1a** was not considered to be a viable drug due to its broad cytotoxicity. However, in 2011, TM-025 **1b**, obtained by bioengineering, exhibited an improved profile displaying a greater cytotoxicity against *Plasmodium falciparum* as compared to mammalian cells. Similarly, Jogyamycin **1c**, another natural product analogue, showed potent antimalarial and antitrypanosomal activities, with IC₅₀ values of 1.5 and 12.3 nM, respectively.^[2] These analogues, including de-6MSA-pactamycin **1d**, are structurally less complex and more stable than pactamycin **1a**.

Unsurprisingly, new examples of such structures are still being discovered in diverse natural products, such as trehazolin derivatives **2a-d** (Figure 2). **2d**, isolated from a culture broth of *Micromonospora strain*,^[3] is a slow and tight-binding inhibitor of the enzyme trehalase.^[4] The hydroxyl groups in this compound, providing hydrogen bonding with the active sites, are considered to be topologically essential for such firm binding.^[5] Due to this inhibitory effect, **2d** has been used to control sheath blight of rice, caused by the plant pathogenic fungus *Rhizoctonia solani*, and it thus has potential fungicidal activity.^[3a] Additionally, trehazolin analogues have important implications in immunology, virology, and oncology.^[6] For instance, the IC₅₀ values for the biological activity of compounds **2a** and **2b** toward rat intestinal maltase were 4.2 and 1.5 mg/mL, respectively.^[7]

Other classes of aminocarbasugars may contain the α -(hydroxymethyl)cyclohexanol motif. For example, valioline **3a** is related to C₇N aminocyclitols.^[8] It was first isolated in 1984 from the fermentation broth of *Streptomyces hygroscopicus subsp. Limoneus*.^[9] **3a** and its N-substituted derivatives have potent D-glucosidase inhibitory activity. One of these derivatives, voglibose **3b** (AO-128) is used as an effective drug for oral administration in clinics for controlling diabetes mellitus.^[10]

2.2. Terpenoids

The chemical structures of some isolated terpenoids, possessing α -(hydroxymethyl)cycloalkanol subunits, are shown in Figure 3. Structurally, they are saturated and unsaturated with varying degrees of oxygenation, including oxiranes, ketones, and carboxylic acid derivatives.

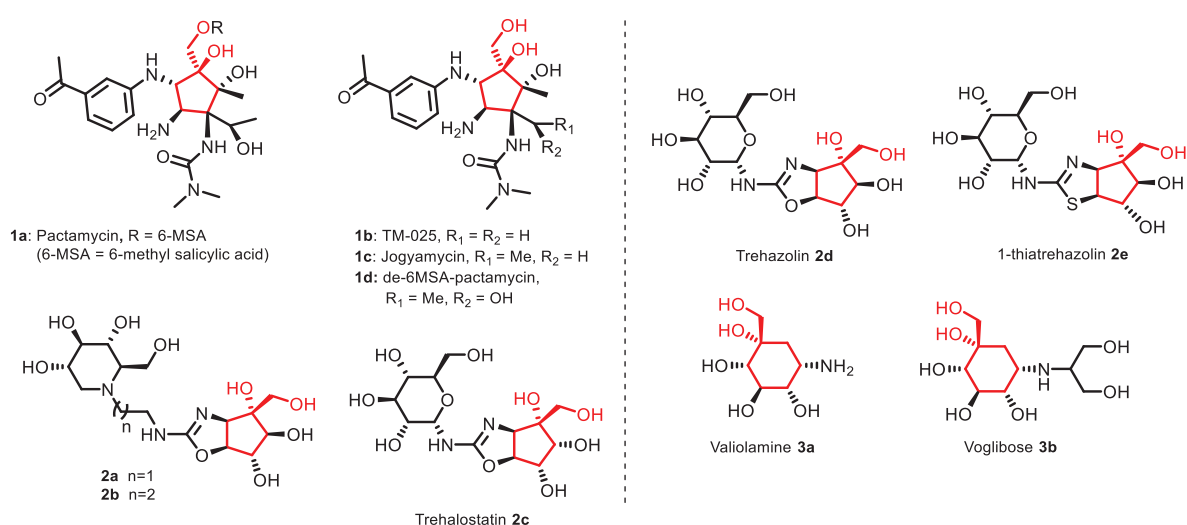


Figure 2. Structures of some aminocyclitols with different α -(hydroxymethyl)cycloalkanol subunits.

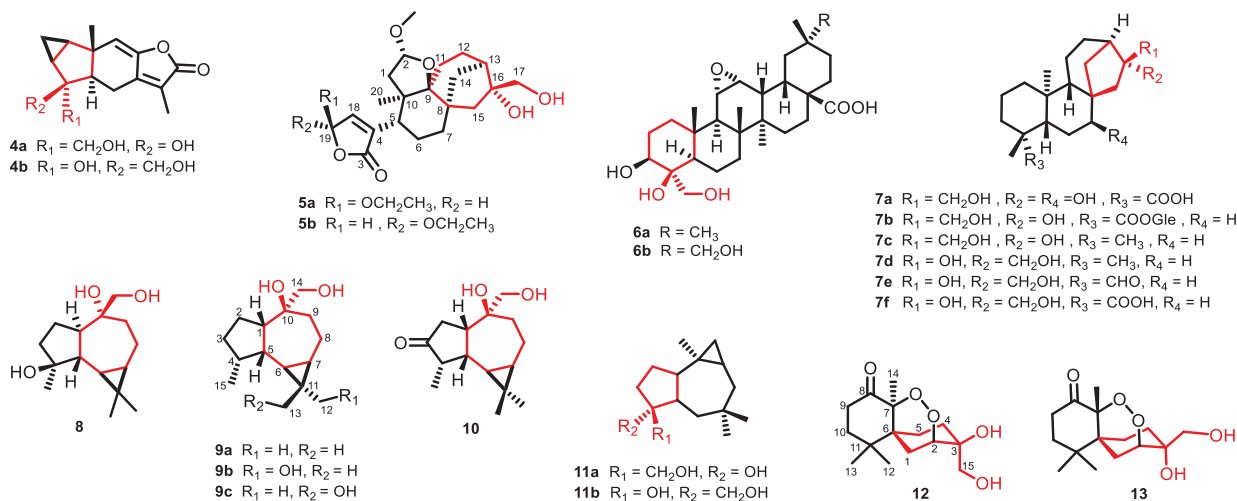


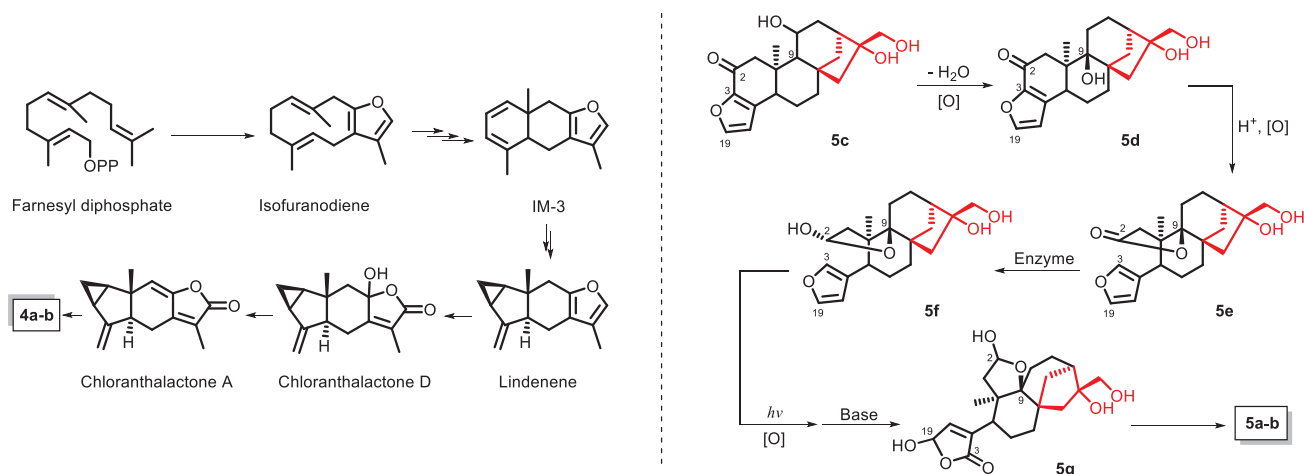
Figure 3. α -(hydroxymethyl)cycloalkanol core in different terpenoids. (Gle = β -D-glucopyranosyl).

In term of studying the inhibitory effect of some terpenoids on nitric oxide production in LPS-induced RAW 264.7 macrophages, different research groups have endeavoured the activity of α -(hydroxymethyl)cycloalkanols such as chlorajaponol F **4a**, shizukanolide E **4b**, frutilactones A **5a** and B **5b**, paeononoides D **6a** and E **6b**, *ent*-kaurane diterpenoids **7a-f**.

Chlorajaponol F **4a** and shizukanolide E **4b** are lindenane sesquiterpenoid isolated from *Chloranthus japonicus* Sieb. exhibiting no significant effects on the inhibition of nitric oxide release.^[11] Similarly, 2,3-*seco* cafestol-type diterpenoid epimers, frutilactones A **5a** and B **5b**, described by Shen and coworkers in 2015,^[12] showed no cytotoxicities (IC₅₀ >100 μ M) and weak

anti-inflammation activities. However, two new pentacyclic triterpenoids, paeonenoides D **6a** and E **6b**, recently isolated by Zou and coworkers from the roots of *Paeonia lactiflora*, exhibited inhibitory activities against NO production in LPS-induced RAW 264.7 macrophages and they showed modest cytotoxic activities against HL-60, Hep-G2, and SK-OV-3 cell lines.^[13]

The possible biosynthetic pathways of **4a-b** and **5a-b** are described in Scheme 1. A series of cyclization reactions of isofuranodiene, reported by Zhuo and coworkers,^[11] afforded lindenene *via* IM-3, which was then converted to chloranthalactones D and A. The latter compounds were proposed to be direct biosynthetic precursors of **4a-b** due to the structural relationship of these three compounds. On the other hand, **5a-b** were formed *via* ketal reaction between 9-OH and 2-carbonyl of **5d**, followed by bond breaking between C-2 and C-3, oxidation of the furan ring, methylation of 2-OH and ethylation of 19-OH. Hence, compounds **5a-b** were obtained as C-19 epimers (Scheme 1).^[12]



Scheme 1. Plausible biogenetic pathways of compounds **4a-b** and **5a-b**.

In 2014, *ent*-kaurane diterpenoids **7a-f** were isolated by Kim and coworkers from the fruits of *Annona glabra*, known as “alligator apple”.^[14] The two *ent*-kauranes **7a** and **7e** showed significant inhibitory NO production.^[14a] Previously, compound **7f** was reported for the first time in 1983 from the aerial parts of *Helianthus strumosus* without investigating its biological activity.^[15] Twelve years later, Wu *et al.*^[16] isolated **7f** from the edible fruits of *Annona squamosa* or “sugar-apples” revealing its significant activity against HIV replication in H9 lymphocyte cells.

Other terpenoids with similar α -(hydroxymethyl)cycloheptanol core has appeared in various aromadendrane sesquiterpenoids. Such structures are characterized by a dimethyl cyclopropane

ring fused to a hydroazulene skeleton (**8**, **9a-c** and **10**).^[17] For instance, pipelol A **8** was described for the first time in 2002 by Masuoka and coworkers.^[18] It has been derived from the aerial part of *Piper elongatum*. After 12 years, **8** was then isolated by Wu *et al.*^[19] from the leaves of *Desmos cochinchinensis* var. *fulvescens* B_{AN}. Unfortunately, no related bioactivities were reported.

In the process of isolating metabolites *via* biotransformation, De Lima and coworkers^[20] identified two other allo-aromadendranes; 10 β ,13,14-trihydroxy-allo-aromadendrane **9b** and 10 β ,12,14-trihydroxy-allo-aromadendrane **9c**. The process has been carried out from the natural product **9a** which was isolated from *Pulicaria paludosa* and *Duguetia glabriuscula*.^[20-21] **9a** was subjected to a series of microbial transformations using *Beauvaria densa* CMC 3240, *Beauvaria bassiana* ATCC7159 and *Curvularia lunata* NRRL 2380, to regioselectively oxidize the geminal methyl groups on the cyclopropane ring producing triols **9b-c**.^[20] In 2008, Yue *et al.*^[22] isolated Dysodensiol F **10**, another allo-aromadendrane sesquiterpenoid, its structure was closely related to **9a**. The only difference is the presence of a C-3 ketone group in **10** instead of a C-3 methylene in **9a**.

Anjaneyulu and colleagues^[23] isolated two new sesquiterpenoids **11a-b** during their investigation of biologically active metabolites from the Gulf of Mannar. Although the molecular skeleton was not considerably changed, these compounds are not related to the previously mentioned aromadendrane family. (*9S*)-africaene-9,15-diol **11a** and (*9R*)-africanene-9,15-diol **11b**, were then isolated by Qin and coworkers from another marine soft coral *Sinularia numerosa*. The latter compound was found to possess inhibitory activities against bacteria *S. aureus* and *E. coli*.^[24]

Terpene endoperoxides, having an α -(hydroxymethyl)cyclohexanol motif, constitute an important subunit that confers various bioactivities. For instance, endoperoxides **12** and **13** selectively exhibited cytotoxicity toward HL-60 cell line with the SI values of 4.4 and 64.0, respectively.^[25]

Merulin A **12** (C-3 epimer) was first isolated by Pudhom and coworkers^[26] in 2010 from an endophytic fungus of *Xylocarpus granatum*. Six years later, Kittakoop *et al.*^[25] reported both compounds merulins A **12** and 7-epi-merulin B **13** from another endophytic fungi *Pseudolagarobasidium acaciicola*.

2.3. Miscellaneous

The chemical structures of some isolated α -(hydroxymethyl)cycloalkanols, found in miscellaneous families of natural products, are shown in Figure 4. Plicatic acid **14**, possessing α -(hydroxymethyl)cyclohexanol core accompanied with two aromatics; 3-methoxy-4-

hydroxyphenyl and 3,4-dihydroxy-5-methoxyphenyl, was isolated in 1959 by MacLean and coworkers^[27] from western red cedar (*Thuja plicata*). As a lignan acid, **14** has been identified as the causative agent of occupational asthma.^[28] Furthermore, it has been shown to cause inflammatory and allergic reactions, including increased concentrations of immunoglobulins, histamine, leukotrienes, eosinophil, and T-cell levels in the blood.^[29] Another lignan, **15** or 17-hydroxyangeloylgomisin Q, is among the few examples of natural products that comprise the α -(hydroxymethyl)cyclooctanol skeleton. It was isolated from the leaves and stems of *Schisandra chinensis* collected in the Yabuli mountain area of Heilongjiang province in China. It was evaluated for its anti-HIV-1 activity.^[30] Since then, **15** has not been reported by any research group. In the investigation to determine natural lipids from *Sulfolobus acidocaldarius* N-8, Sugai and coworkers have reported the structure of the major glycolipid (GL-1a) **16a**. More than 70% of the lipids in this species were composed of a polar group linked with calditoglycerocaldarchaeol **16b** possessing the α -(hydroxymethyl)cyclopentanol moiety called calditol.^[31]

Three cyclopentenoid antibiotics, pentenomycin (I) **17a**, pentenomycin (II) **17b**, and dehydropentenomycin (I) **18**, comprising α -(hydroxymethyl)cyclopentenol subunit, have been reported several times. Pentenomycins (I) and (II) were isolated by Umino and coworkers^[32] in 1973 from culture broths of *Streptomyces eurythermus*. Five years later, A. B. Smith III *et al.*^[33] reported the isolation of antibiotic G-2201-C **18**, a simple oxidation product of pentenomycin (I), from *Streptomyces cattleya* which has been termed dehydropentenomycin (I). The interest of various research groups in these synthetic targets was prompted by their demonstrated activity against Gram-positive and Gram-negative bacteria including *Neisseria gonorrhoea*^[33] as well as by the potential pharmacological importance of the cyclopentenone structural unit which has been suggested to be the reactive functionality in a variety of structurally complex antitumor agents.^[34]

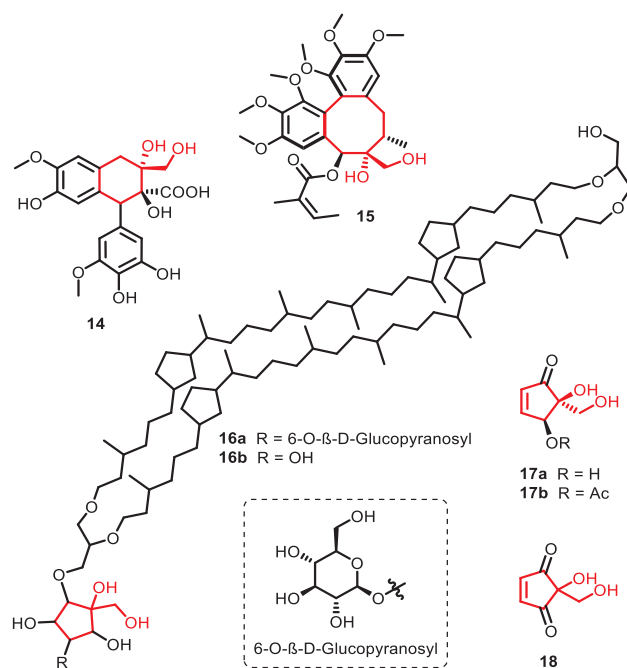


Figure 4. α -(hydroxymethyl)cycloalkanol-containing natural products.

3. Synthesis

For decades, the synthesis of α -(hydroxymethyl)cycloalkanols was considered as an access to highly functionalized molecular structures. For this reason, synthetic chemists have accessed such congeners *via* distinct strategies. In this section, some representative examples have been provided and correspondingly categorized into different subclasses (Figure 5). Rather than providing an extensive account of all the synthetic routes leading to such derivatives, the objective of this section is to give an overview of each of these subclasses by highlighting the key steps for the synthesis of α -(hydroxymethyl)cycloalkanols-containing compounds.

3.1. Synthesis of α -(hydroxymethyl)cycloalkanols from ketones

Based on nucleophilic hydroxymethylation:

Via silyl reagents: Nucleophilic hydroxymethylation of cyclic ketones *via* silyl reagents was shown to be a robust method in the synthesis of α -(hydroxymethyl)cycloalkanols. The preparation of such reagents relies on the creation of silyl carbanions. These carbanions are usually generated in four different ways: (1) Grignard reagent formation from the corresponding trialkyl halosilane; (2) deprotonation by lithiating reagent such as butyllithium; (3) metal-heteroatom (S, Sn, Si, Se) exchange reaction; (4) addition of alkyllithium to vinylsilane.^[35]

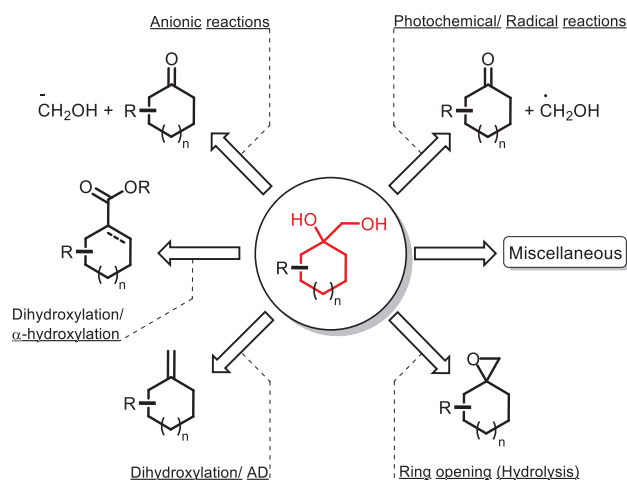
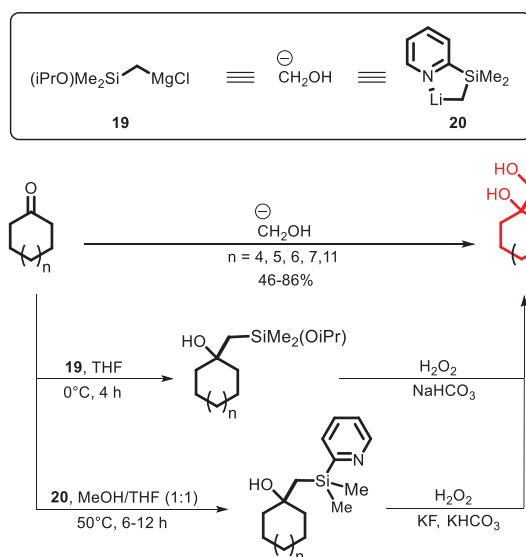


Figure 5. Different routes for the synthesis of α -(hydroxymethyl)cycloalkanols.

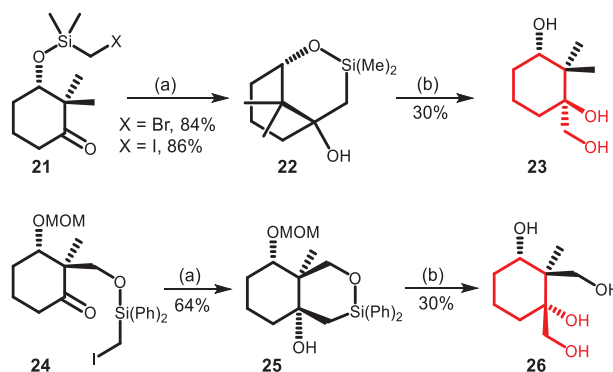
In 1984, Ishida and coworkers^[36] described an efficient umpolung method using the (isopropoxy-dimethylsilyl)methyl Grignard reagent **19** as a hydroxymethyl anion equivalent in conjunction with the oxidative cleavage of the silicon-carbon bond in the Grignard addition product (Scheme 2). The primary product contains a hydroxy-silicon moiety which might undergo elimination, known as the Peterson elimination,^[37] to form the corresponding olefin; however, under H_2O_2 oxidation conditions, the oxidative cleavage of the silicon-carbon bond preferentially proceeds, without any elimination, to form the corresponding 1,2-diol derivative in high yields.^[38] Unsurprisingly, **19** is considered to be one of the most interesting reagents since it contains both a carbon nucleophilic center and a leaving group on silicon, but it is quite stable as it can be stored in THF even at room temperature; the isopropoxyl group is probably bulky enough to prevent the intermolecular nucleophilic substitution at the silicon.

An efficient methodology has been reported by Yoshida *et al.* for the deprotonation of a methyl group on silicon. It was found that the deprotonation ($t\text{-BuLi}/\text{Et}_2\text{O}/-78^\circ\text{C}$) occurs with 2-pyridyltrimethyl-silane but not with other related silanes such as phenyltrimethyl-silane, 3-pyridyltrimethylsilane, and 4-pyridyltrimethylsilane. It seems that this deprotonation proceeded through the agency of the complex-induced proximity effect (CIPE) of a 2-pyridyl group on silicon. (2-Pyridyldimethylsilyl)-methylolithium **20** was found to react with ketones in good to excellent yields. The resultant adducts were further oxidized with $\text{H}_2\text{O}_2/\text{KF}$ to give the corresponding alcohols. Thus, this two-step transformation provides an efficient method for the nucleophilic hydroxymethylation.^[35, 38b]

Following previous studies on intermolecular nucleophilic hydroxymethylation, Nakada *et al.* has developed silicon-tethered intramolecular nucleophilic additions of a hydroxymethyl unit to ketones.^[39] This method would be a good solution to the stereoselective generation of the chiral tertiary alcohol. That is, as shown in Scheme 3, the anion generated from **21** or **24** by the halogen–lithium exchange reaction could react intramolecularly with the adjacent ketone to afford the relative tertiary alcohols **22** and **25**. Since the desired products were thus prepared in good yields, **22** and **25** were then converted to the corresponding triols **23** and **26** under Tamao's conditions.^[38b] The products obtained by this protocol were successfully converted to chiral A-ring moieties of Taxol.^[39]

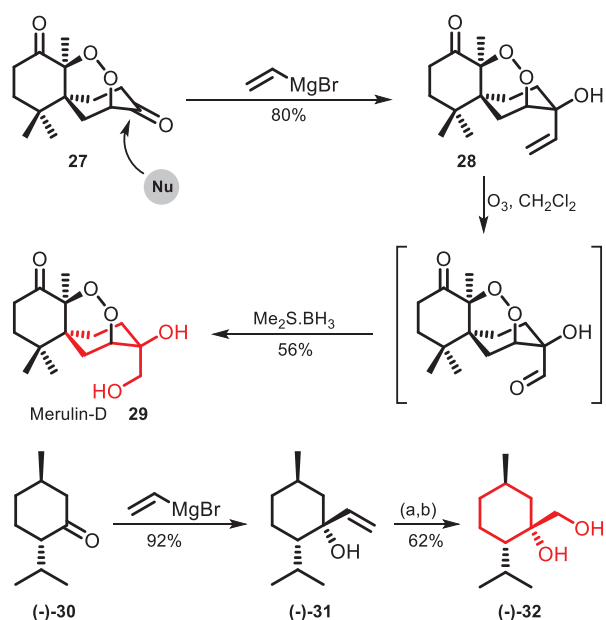


Scheme 2. Nucleophilic hydroxymethylation *via* silyl reagents.



Scheme 3. Silicon-tethered intramolecular nucleophilic additions. Reagents and conditions: (a) *t*-BuLi, THF, -78 °C, 5 min.; (b) H₂O₂, KHCO₃, KF, THF/MeOH (1:1), r.t., 10 h.

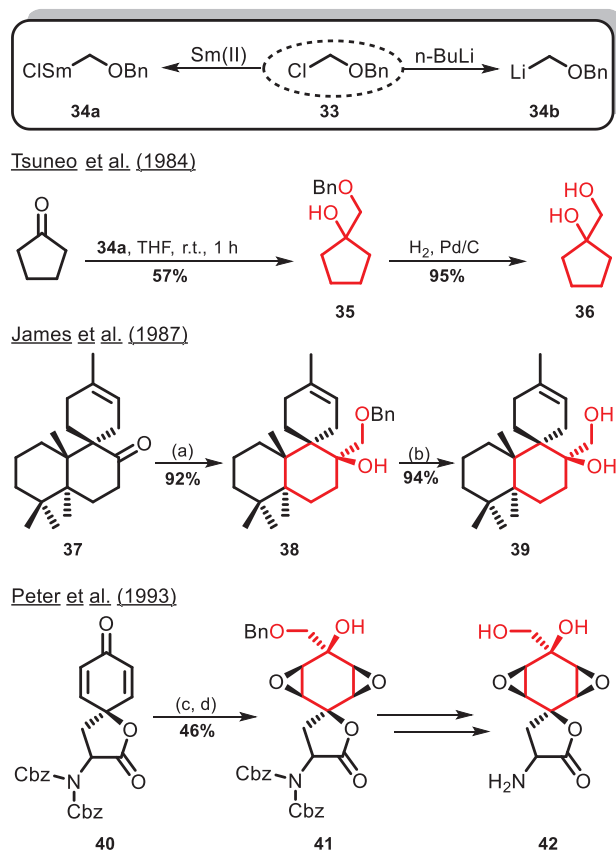
Via vinyl reagents: A classic example where the nucleophilic hydroxymethylation *via* vinyl magnesium bromide, producing α -(hydroxymethyl)cycloalkanols, can be found in the total synthesis of (\pm)-merulin D **29**.^[40] Upon exposure of **27** to $\text{CH}_2=\text{CHMgBr}$, the vinyl group added exclusively from the less hindered face, leading to **28** in 80% yield (Scheme 4). Ozonolysis of alkene **28** followed by sequential reduction of the intermediate ozonide and the aldehyde with Me_2S and $\text{Me}_2\text{S}\cdot\text{BH}_3$, respectively, led to merulin-D **29**. A similar strategy has been described by Fuganti and coworkers in 2008.^[41] 1,2-nucleophilic addition on menthone (-)-**30** afforded vinyl menthol (-)-**31** which was then converted to the corresponding diol (-)-**32** *via* reductive ozonolysis (Scheme 4).



Scheme 4. Preparation of merulin-D **29** and diol (-)-**32** using nucleophilic hydroxymethylation *via* vinyl reagents. Conditions: (a) O_3 , $\text{MeOH}/\text{CH}_2\text{Cl}_2$, $-70\text{ }^\circ\text{C}$; (b) NaBH_4 , MeOH , r.t.

Via benzyl chloromethyl ether reagents: a complementary approach for the hydroxymethylation of carbonyl compounds has been reported by Imamoto *et al.*^[42] (Scheme 5). The first trial was conducted with the reaction of simple aliphatic ketones with benzyl chloromethyl ether **33**, and then with cyclic ketones (cyclopentanone) in the presence of SmI_2 in tetrahydrofuran. The reaction proceeded rapidly at room temperature, and the addition product **35** was isolated in moderate yield. Subsequently, **35** was subjected to hydrogenolysis to yield diol **36**.

In 1987, White and coworkers described an efficient conversion of a tricyclic ketone **37**, already prepared from geraniol,^[43] to (\pm)-2-desoxystemodinone **43** (Figure 6).^[44] Although the sterically encumbered keto group of **37** resisted the attack by many nucleophilic reagents (methylolithium, for example, led only to enolate formation), benzyl chloromethyl ether **33** in the presence of samarium diiodide reacted with this ketone to give compound **38** in virtually quantitative yield. Reductive debenzoylation of **38** afforded the desired diol **39** in 94% yield.



Scheme 5. Nucleophilic hydroxymethylation *via* benzyl chloromethyl ether reagents. Conditions: (a) BnOCH_2Cl , SmI_2 , THF, 25 °C, 20 h; (b) Na/NH_3 , THF; (c) BnOCH_2Li , THF, -100 °C; (d) *m*-CPBA, 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide, CCl_4 , 70 °C.

Another application of this method has been revealed by Wipf and coworkers^[45] in 1993 in the total synthesis of aranorosin **44**; a structurally unique antibiotic isolated by Fehlhaber *et al.*^[46] from a fungal strain, *Pseudoarachniotus roseus* (Figure 6). The addition of (benzyloxy)methyl-lithium **34b**^[47] occurred chemoselectively in a 1,2-fashion at the dienone moiety of compound **40** and resulted in the formation of an approximately 5:1 mixture of quite sensitive bis-allylic alcohols

which were immediately subjected to bis-epoxidation with *m*-CPBA furnishing diepoxy alcohol **41** in 46% overall yield from dienone **40**. Further treatment of **41** with Pd(OH)₂ on carbon in methanol under an atmosphere of H₂ led to **42**.^[45]

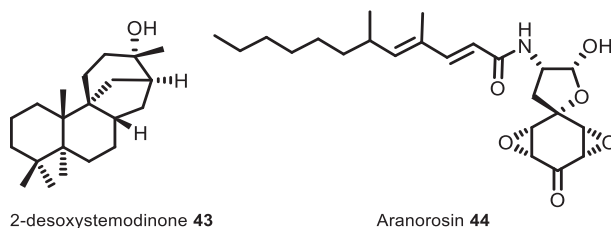
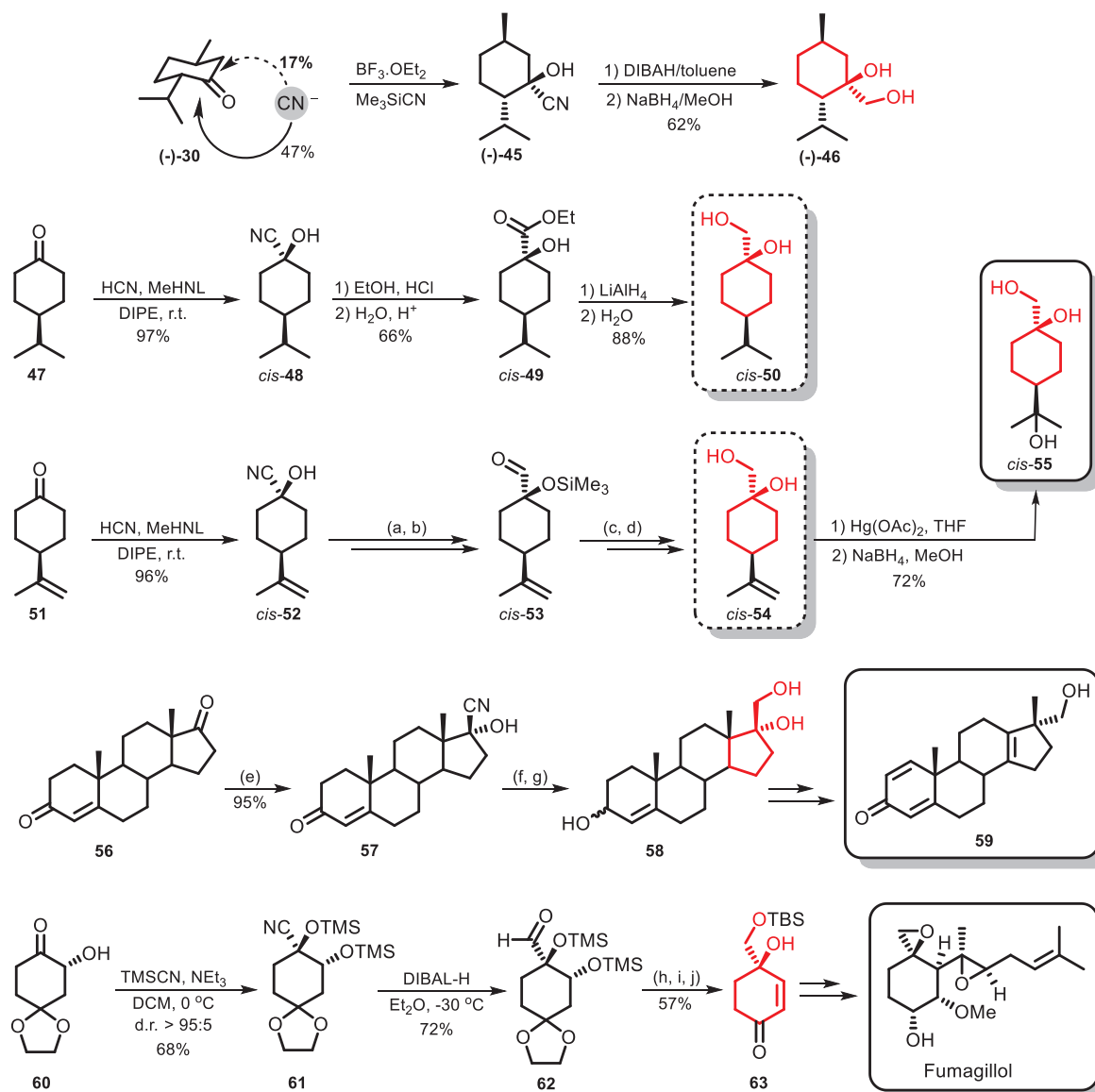


Figure 6. The chemical structures of **43** and **44**.

Via cyanide reagents: Although cyanide is highly toxic, synthetic demands and cost concerns have led to its examination for nucleophilic hydroxymethylation reactions. It can be simply added to a carbonyl group to furnish the corresponding cyanohydrin, which can be converted to vicinal diol *via* hydrolysis followed by standard reduction. For instance, Fuganti has shown that the addition of trimethylsilyl cyanide to menthone (-)-**30** has afforded the axial addition product; cyanohydrin (-)-**45** (Scheme 6).^[41] Further reaction with DIBAH gave the corresponding hydroxy-aldehyde that was treated with sodium borohydride to give the suitable diol (-)-**46**; epimer of (-)-**32**.^[41]

In 2005, Kobler *et al.*^[49] have also described the stereoselective synthesis of monoterpenediols **50**, **54** and **55**; 4-alkyl-1-hydroxymethyl cyclohexanols, isolated from *Pseudomonas mandocina*, urine of rats after treatment with β -Myrcen and *Cynanchum hancockianum-SF* respectively (Scheme 6).^[50] All the three compounds were supposed to be retrosynthetically derived from cyanohydrins of the corresponding 4-alkylcyclohexanones. The enzymatic-catalyzed chemical addition of HCN to **47** was performed under optimized conditions using (S)-MeHNL of high *cis* selectivity.^[51] The cyanohydrin *cis*-**48** was obtained almost quantitatively in a *cis/trans*-ratio of 96:4. Dissolving *cis*-**48** in a saturated solution of HCl in absolute ethanol and heating for 16 hours resulted in the ester *cis*-**49**. The hydrogenation of the latter compound with LiAlH₄ gave the final product *cis*-**50**. On the other hand, the monoterpene *cis*-p-menthane-1,7,8-triol **54**, has been synthesized following a similar synthetic approach. Starting from **51**,^[52] cyanohydrin *cis*-**52** was obtained in 99% yield with a *cis/trans*-ratio of 96:4. Before reduction of the nitrile function, the hydroxyl group of *cis*-**52** was protected with a trimethylsilyl group.^[53] Reduction with DIBAL-H was performed affording “aminoalane” as an intermediate, which was then transformed to the aldehyde *cis*-**53** by careful treatment with diluted sulfuric acid. The hydrogenation of the O-protected aldehyde^[54] *cis*-

53 followed by deprotection with TBAF yielded *cis*-**54**; precursor of the farnesylprotein transferase inhibitor XR3054.^[55] The regioselective hydroxylation of the olefinic double bond of *cis*-**54** was performed with mercury(II) acetate and subsequent demercuration with an alkaline sodium borohydride solution giving the natural product *cis*-**55**.^[56]



Scheme 6. Nucleophilic hydroxymethylation *via* cyanide reagents. Conditions: (a) Me_3SiCl , imidazole, DMF, 0 °C, 87%; (b) DIBAL-H, Et_2O , 0 °C, 70%; (c) NaBH_4 , EtOH , 0 °C, 91%; (d) TBAF, THF, 0 °C, 70%; (e) NaCN , AcOH , MeOH ; (f) HCl (6 M); (g) LiAlH_4 , Et_2O , 0 °C; (h) DIBAL-H, CH_2Cl_2 , 0 °C; (i) Amberlyst-15, THF, H_2O , 60 °C; then silica gel; (j) TBSCl , NEt_3 , DMAP, CH_2Cl_2 , (57% over three steps).

This strategy has been also described by Parr and coworkers in their synthesis of 20 α OH-NorMD **59**,^[57] a long-term metabolite that has been previously detected in urine samples.^[58] Starting with androst-4-ene-3,17-dione **56**, the formation of androstane-dione cyanohydrin **57** was achieved by reaction with sodium cyanide in methanol and glacial acetic acid as described by Nitta *et al.* (Scheme 6).^[59] Hydrolysis of **57** in hydrochloric acid (6 M) within 24 h yielded the corresponding carboxylic acid which was then reduced with lithium aluminium hydride resulting in two isomers of 17 β -hydroxymethyl-androst-4-ene-3 ξ ,17 α -diol **58**. Dehydrogenation of the latter compound with DDQ followed by Wagner–Meerwein rearrangement using hydrochloric acid yielded the desired steroid **59**.

In 2006, Hayashi *et al.*^[60] reported the first catalytic asymmetric synthesis of (-)-fumagillol, FR65814 and other congeners. Structurally, these compounds are all related to the fumagillin family, they are comprised of a cyclohexane framework, two epoxides, and five or six contiguous stereogenic centers, three or four of which are situated on the cyclohexane ring (Figure 7).^[61] The authors described the access to the spiro epoxide of fumagillol using nucleophilic hydroxymethylation *via* cyanide reagents (Scheme 6). The synthesis started from readily available cyclohexanone derivative to prepare compound **60** in two steps. The latter compound was then converted into **61** by treatment with TMSCN and catalytic Et₃N with high diastereoselectivity.^[62] The reduction of **61** was accomplished with two successive treatments of DIBAL-H to afford the primary alcohol through the isolable intermediate **62**. After acid-induced deprotection of the ketal and silyl groups and elimination of the resulting secondary alcohol, the primary alcohol was protected as a TBS ether to yield enone **63** (41% over four steps). The latter compound was then transformed to fumagillol in 8 consecutive steps.

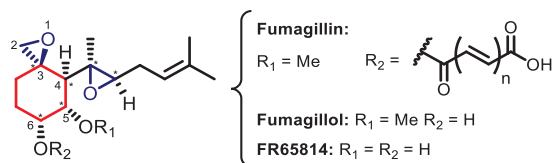


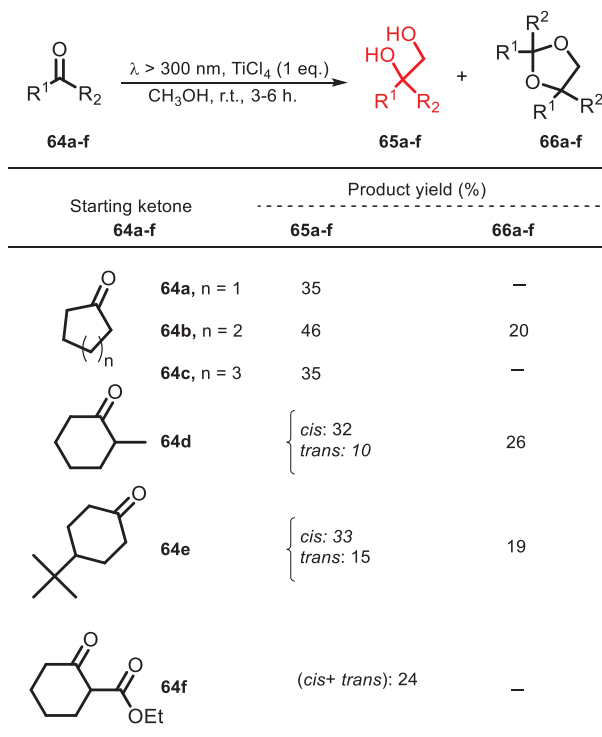
Figure 7. The chemical structure of fumagillin, fumagillol and FR65814.

Based on photochemical transformations:

Despite moderate yields, photochemical hydroxymethylation has shown a major advantage over the previously mentioned processes; it converts cyclic ketones directly to their corresponding α -

(hydroxymethyl)cycloalkanols. This method has been studied by Sato *et al.* in detail for a series of substrates and applied in a two-step synthesis of the pheromone frontalin (Figure 8).^[63]

When saturated ketones **64 a-f** were irradiated in methanol in the presence of TiCl₄, 1,2-diols **65a-f** were obtained as main products (Scheme 7).



Scheme 7. Photoredox-catalyzed hydroxymethylation of cyclic ketones.

In some cases, ketals **66** were also isolated as by-products, which result from subsequent condensation of the primary products **65** with the starting ketones. In case of substituted cyclohexanones **64d-e**, the products were obtained as stereoisomeric mixtures; the major isomeric components in the products **65d-e** were *cis*-isomers, hence, the preferential course of the photoreaction is the attack by the hydroxymethyl group from the side opposite to the alkyl substituents. Unlike the methyl or tert-butyl group, which favour the *anti*-attack, the ethoxy carbonyl group of ketoester **64f** favours the *syn*-attack to furnish compounds **65f** and **67** with higher *trans* ratios. (Scheme 7, Figure 8) According to the authors, the preferential *syn*-attack in this case can be attributed to the access of titanium to the reaction site on the same side as the ethoxy carbonyl group due to the coordination to the ester moiety. These results would be a support for the proposal that the present photoreaction proceeds within the coordination sphere of the

titanium ion. Beside compounds **65f** and **67**, the photoreaction of **64f** afforded compound **68** (Figure 8); a by-product from the intramolecular reaction between the carbonyl and the ethyl ester groups, followed by dehydration.

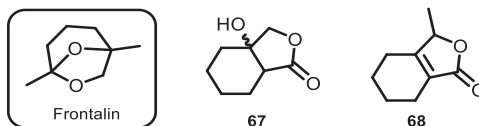
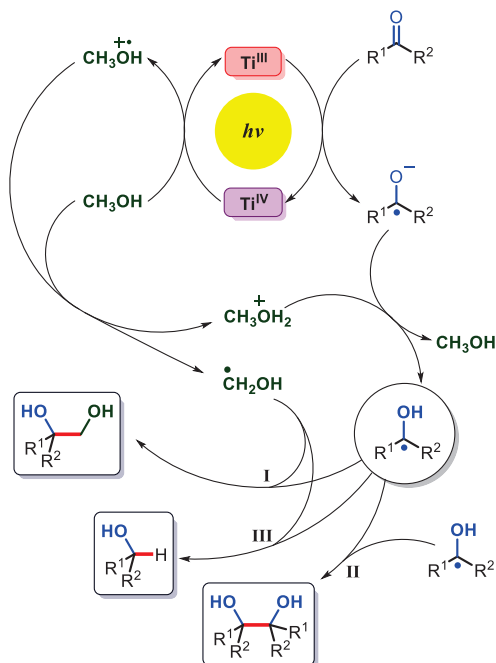


Figure 8. The chemical structure of frontalin, **67** and **68**.

In 2014, Griesbeck and Reckenthäler^[64] investigated the homogeneous titanium-catalyzed as well as the heterogeneous semiconductor particle-catalyzed photochemical hydroxymethylation of ketones by methanol to evaluate the most active photocatalyst system. The study focused on aromatic and aliphatic open chain ketones as substrates more than cyclic ones. When irradiated at 254 nm in the presence of $\text{TiCl}_2(\text{OiPr})_2$ in methanol, cyclohexanone **64b** has been sluggishly converted to the corresponding 1,2-diol **65b** (9%) and ketal **66b** (29%). These results show that ketal formation becomes more significant when the reaction mixture is allowed to stand for a long time. Additionally, **64b** and other aliphatic ketones did not show any conversion under heterogeneous TiO_2 photolyses.



Scheme 8. Mechanism of the photoredox-catalyzed hydroxymethylation.

The authors described three competitive pathways: hydroxymethylation (route (I)), pinacolization (route (II)) and reduction (route (III)) (Scheme 8).^[65] The crucial primary step for all processes is methanol oxidation. By using appropriate reaction conditions, every route can be switched on exclusively. Hydroxymethylation is favored if both hydroxyalkyl radicals are generated in proximity by a coupled electron transfer/ back transfer process. According to this expectation, the optimal conditions for route (I) are fulfilled for $\text{TiCl}_2(\text{OR})_2$; a species that is capable of oxidizing methanol in the excited state and simultaneously acting as a ground-state Lewis acid that complexes the carbonyl compound. A much weaker Lewis acid such as $\text{Ti}(\text{OR})_4$ is capable of methanol oxidation but prefers hydrogen transfer at the first or second oxidation event. The pinacolization route (II) is favored for heterogeneous and dye-catalyzed conditions. Interestingly, the combination of TiO_2 P25 with an organic dye favours largely the reduction route (III).^[66]

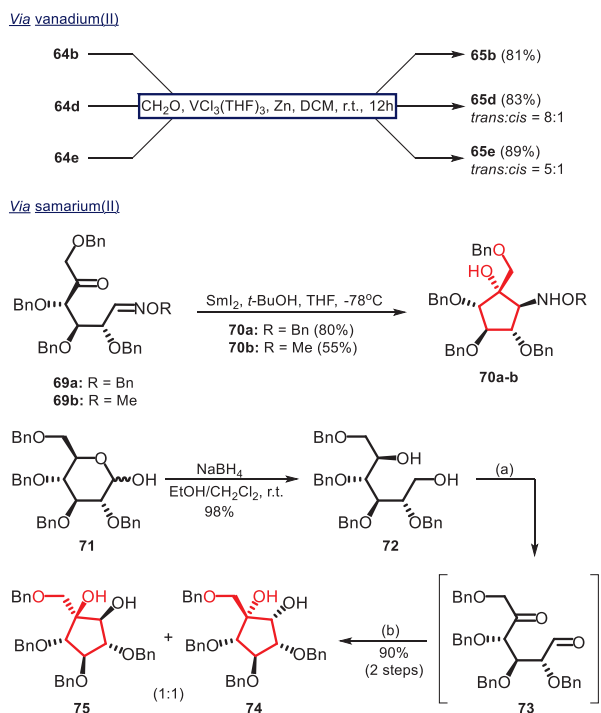
Based on radical addition via metal reagents:

Several reports on intermolecular and intramolecular radical pinacol couplings of cyclic ketones have been published by different research groups. A simple, and direct approach to hydroxymethylation of carbonyls would involve the intermolecular pinacol cross-coupling of ketones with formaldehyde. Clerici and Porta^[67] have shown the viability of such reaction in the course of their extensive studies on the reductive coupling chemistry of aqueous titanium(III) reagents. However, this method exhibited limited scope with respect to carbonyl substrates.

Later on, Park and Pedersen^[68] reported a general and practical method for the direct hydroxymethylation of aldehydes and ketones with paraformaldehyde. The reaction is promoted by vanadium (II) ions which are generated from the reduction of $\text{VCl}_3(\text{THF})_3$ with zinc dust (Scheme 9). Several ketones were examined using the outlined conditions, and in all cases excellent yields of the desired products were obtained. Moreover, stereoselective addition to two different substituted cyclohexanones **64d-e** was observed. In both cases, the major diastereoisomer is that expected from reaction on the least hindered face of the ketone.

Alternative reagents were also considered to establish intramolecular radical pinacol couplings.^[69] For instance, samarium diiodide or tributyltin hydride were used to offer straightforward and selective access to cyclitols and aminocyclitols starting from protected sugars (described in Section 2.1). Marco-Contelles *et al.*^[70] reported the intramolecular radical cyclization of a ketoimine ether **69a** derived from D-glucose (Scheme 9). This reaction, using SmI_2 , gave **70a** in good yield as the only diastereoisomer.^[71] Similarly, Chiara and coworkers^[72] achieved a short and very efficient

synthesis of trehazolamine starting from readily available hemiacetal **71**. Sodium borohydride reduction afforded D-glucitol derivative **72** quantitatively, which was then converted to **73** via Swern oxidation. The dropwise addition of the latter compound to a freshly prepared solution of SmI_2 in THF at low temperature afforded a 1:1 mixture of cyclic diols **74** and **75** in excellent yield.



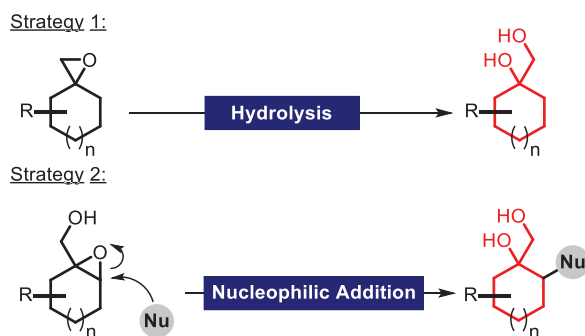
Scheme 9. Hydroxymethylation *via* radical addition reactions. Reagents and conditions : (a) (i) $(\text{COCl})_2$, DMSO, THF, -65°C , (ii) Et_3N , -65°C to r.t.; (b) SmI_2 , THF/*t*-BuOH, -50°C to r.t.

3.2. Synthesis of α -(hydroxymethyl)cycloalkanols from epoxides

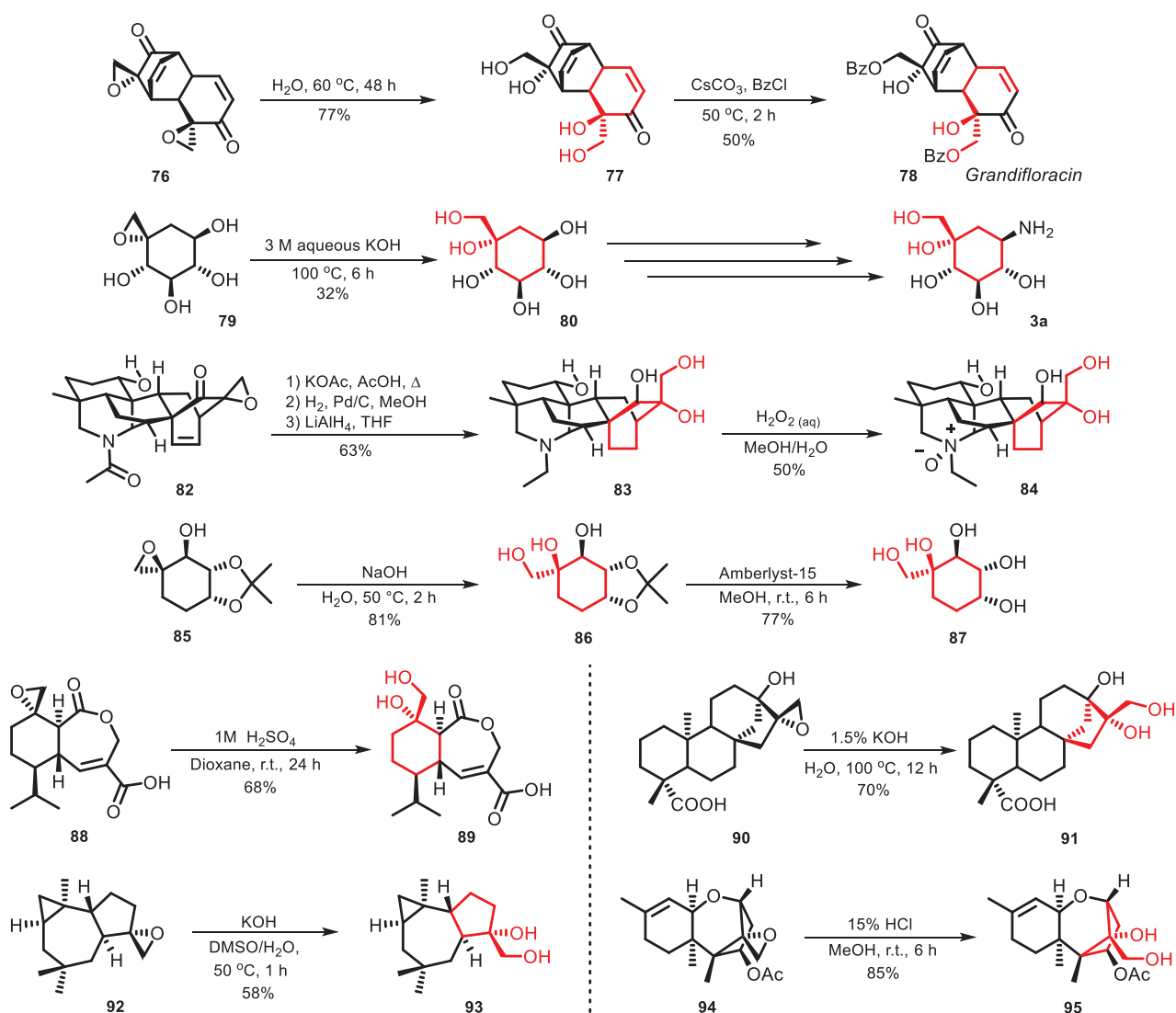
Epoxides are widely employed in the synthesis of α -(hydroxymethyl)cycloalkanols due to their ability to react with a broad variety of nucleophiles.^[73] Their ring-opening reactions provide two robust strategies for the synthesis of such products, which are represented by hydrolysis and nucleophilic addition reactions (Scheme 10).

Strategy 1

Hydrolysis of *spiro*-epoxides^[74] has been well established for the total synthesis of natural α -(hydroxymethyl)cycloalkanols. For instance, it was reported in the total synthesis of (\pm)-grandifloracin **78**,^[75] (-)-valiolamine **81**,^[76] cochlearenine **83**,^[77] paniculamine **84**,^[77] pseudo- β -fructopyranose **87**,^[78] koningic acid derivative **89**,^[79] 13 α ,16 α ,17-tri-hydroxy-*ent*-kaur-19-oic acid **91**,^[80] africane-9,15-diol **93**,^[81] and trichodermin derivative **95**^[82] (Scheme 11).



Scheme 10. Two different strategies for the synthesis of α -(hydroxymethyl)-cycloalkanols starting from epoxides.

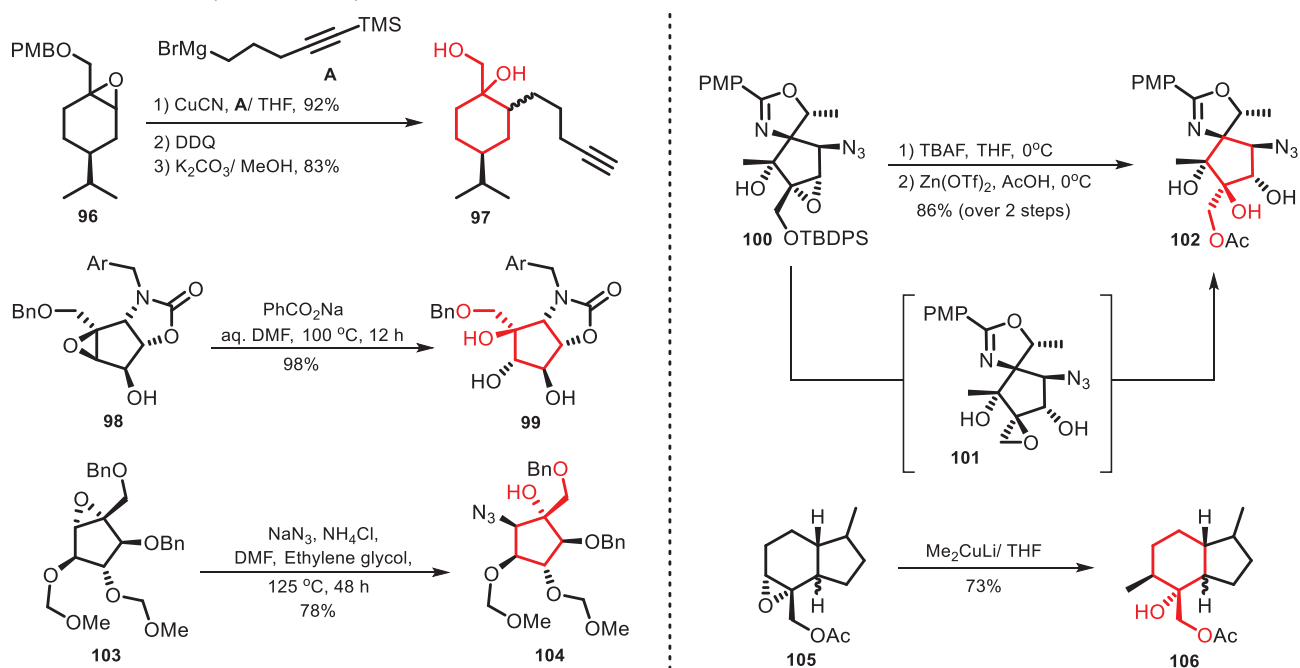


Scheme 11. Examples of the *spiro* oxirane–opening step in the synthesis of various natural products.

Moreover, this strategy has been employed in the synthesis of diverse intermediates which serve as building blocks for further synthesis.^[83] In most of the cases, the oxirane hydrolysis was catalyzed by either acids or bases. However, Stoltz and coworkers showed the possibility of milder epoxide opening without the use of solid or solid supported Lewis acids; the bisspiroepoxide **76** was subjected to gentle heating in water furnishing the tetraol **77** which was then directly converted to grandifloracin **78**.^[75, 84]

Strategy 2

(Oxabicyclo[*n.m.o*]alkan-1-yl)methanol derivatives are important starting material for the synthesis of functionalized α -(hydroxymethyl)cycloalkanols. A large variety of nucleophiles could be used to open the oxirane ring furnishing a vast spectrum of valuable intermediates. For instance, Forsyth *et al.* described the stereoselective synthesis of spirobicyclic sesquiterpenes through a key intermediate **97** (Scheme 12).^[85]



Scheme 12. Selected examples of nucleophilic addition reactions on different (oxabicyclo[*n.m.o*]alkan-1-yl)methanol derivatives.

The authors reported the copper-assisted opening of the epoxide **96** using the Grignard reagent prepared from 1-(trimethylsilyl)-5-bromo-1-pentyne **A** and CuCN. Further treatment with DDQ and methanolysis gave diol **97** in 76% overall yield.

Other nucleophilic addition reactions have been tested on complex structures like hydroxylation at the α -position of the epoxide. Knapp *et al.*^[86] reported the hydrolysis of the epoxide **98** at the least substituted position using sodium benzoate in aqueous DMF at high temperature. However, during their total synthesis of pactamycin, Hanessian and coworkers described the “inversion” of the epoxide **100** which was achieved by treatment of the corresponding primary alcohol with Zn(OTf)₂ in AcOH to give the triol **102**.^[87] Presumably, this arose from the spiroepoxide **101** which underwent solvolysis to afford the primary acetate as in **102**. Nucleophiles like azide and methide were also used for the same purpose to furnish a variety of useful intermediates (**104** and **106**).^[87-88]

3.3. Synthesis of α -(hydroxymethyl)cycloalkanols from alkenes

The oxidative functionalization of alkenes is among the most extensively investigated synthetic transformations in organic chemistry. Simple alkene dihydroxylation is one of these reactions that serve as the cornerstone of many complex-molecule syntheses.^[89] Such reaction can be performed using different stereochemical pathways: *anti*-dihydroxylation or *syn*-dihydroxylation. The opening of epoxides follows the *anti*-dihydroxylation mechanism, while potassium permanganate or osmium tetroxide produce the *syn*-dihydroxyl-ated products.

Referring to *syn*-dihydroxylation, the Upjohn condition allows a *syn*-selective preparation of 1,2-diols from alkenes by the use of osmium tetroxide as a catalyst and a stoichiometric amount of a cooxidant such as NMO. The toxic and volatile OsO₄ can also be prepared *in situ* by the oxidation of K₂OsO₂(OH)₄ with NMO.^[90] Moreover, the use of chiral amines enables enantioselective conversions, such as (DHQ)₂-PHAL and (DHQD)₂-PHAL in the Sharpless Dihydroxylation. This procedure is performed with an osmium catalyst and a stoichiometric oxidant (e.g. K₃Fe(CN)₆ or NMO); it is carried out in a buffered solution to ensure a stable pH, since the reaction proceeds more rapidly under slightly basic conditions. These reagents are also available as stable, prepackaged mixtures (AD-mix α and AD-mix β) for either enantiopreference (Figure 9).^[90a, 90f, 91] Rather than providing an extensive account of all the dihydroxylation methodologies, the objective of this section is to give an overview of the large manifold of structures subjected to such reaction providing various α -(hydroxymethyl)cycloalkanols. The section will be divided into two subgroups describing two distinct synthetic strategies (Scheme 13).

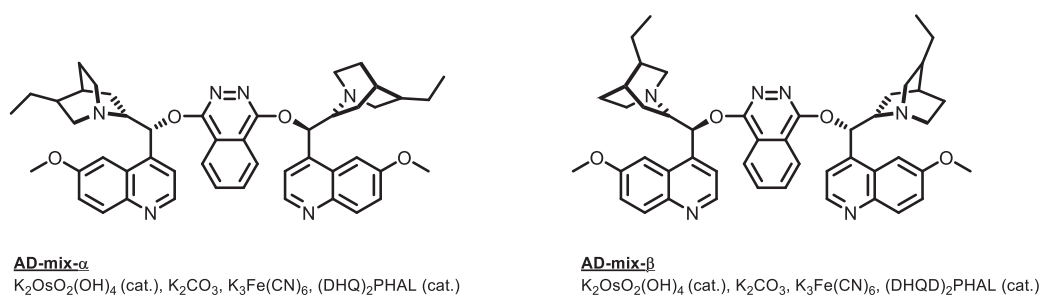
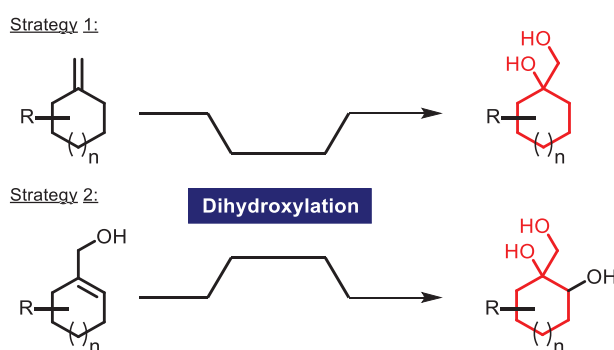


Figure 9. The essential reagents for Sharpless asymmetric dihydroxylation reactions such as AD-mix α and AD-mix β .



Scheme 13. Different strategies for the synthesis of α -(hydroxymethyl)cycloalkanols starting from alkenes.

Strategy 1

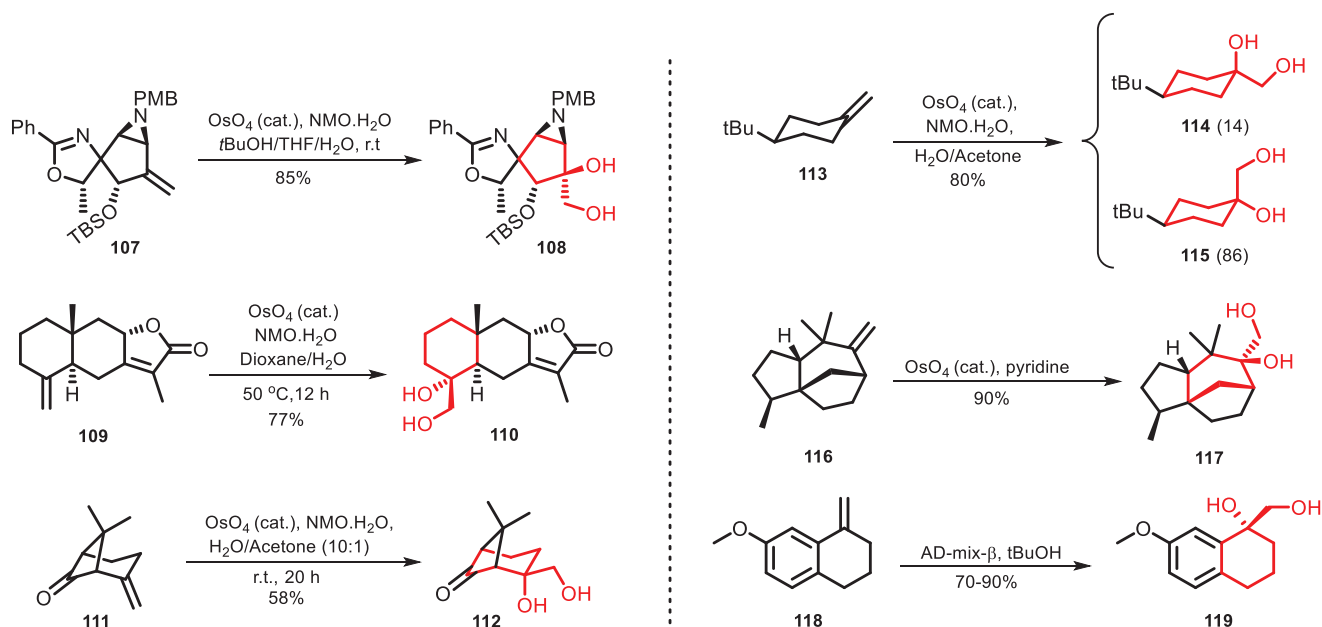
This strategy is based on simple dihydroxylation of methylenecycloalkane derivatives using one of the mentioned methodologies in the previous section. Consequently, access to several natural products, like pactalactam, atractylenolides and taxoids, has mainly relied on this route (Scheme 14). In 2019, Kim and coworkers have accomplished the first total synthesis of pactalactam; a minor component of the metabolite of the same genus culture broth as that of pactamycin.^[92] Thanks to the neighboring siloxy group and the methyl group on oxazoline, the substrate-dependent dihydroxylation of **107** using OsO_4 without chiral ligands provided an inseparable mixture of two diols **108**. The diols were subjected to further transformations before reaching the targeted molecule.^[1b]

Similarly, Ramesh and Mehta reported the total synthesis of seven bioactive atractylenolide-type eudesmanolides including atractylenolide (IV) **110** via an efficient catalytic OsO_4 -mediated dihydroxylation of atractylenolide (II) **109**.^[93] Diol **112** has been also synthesized using Upjohn condition in good yield. The study was carried out by Hebrault and Uguen showing the possibility

to expand efficiently the cyclohexanone ring of 6-pinanone derivatives, which was an essential part of their planned synthesis of taxoids.^[94]

With respect to advanced methodological studies, in their evaluation of σ - σ^* and torsional effects in the osmylation of 4-tert-butylmethylenecyclohexane derivatives, Vedejs and coworkers revealed the effect of the tert-butyl group as well as other substituents on the attack of OsO₄ to the double bond. Steric hindrance has shown a considerable effect on the ratio of the corresponding diastereoisomers in each case (**114**, **115**).^[95]

In addition to total synthesis of natural products and methodologies, such strategy has been also used either to confirm the structure of a rearrangement product (**117**)^[96] or to furnish key intermediates in a drug candidate synthesis (**119**).^[97]



Scheme 14. Selected examples of *syn*-dihydroxylation of some methylenecycloalkane derivatives.

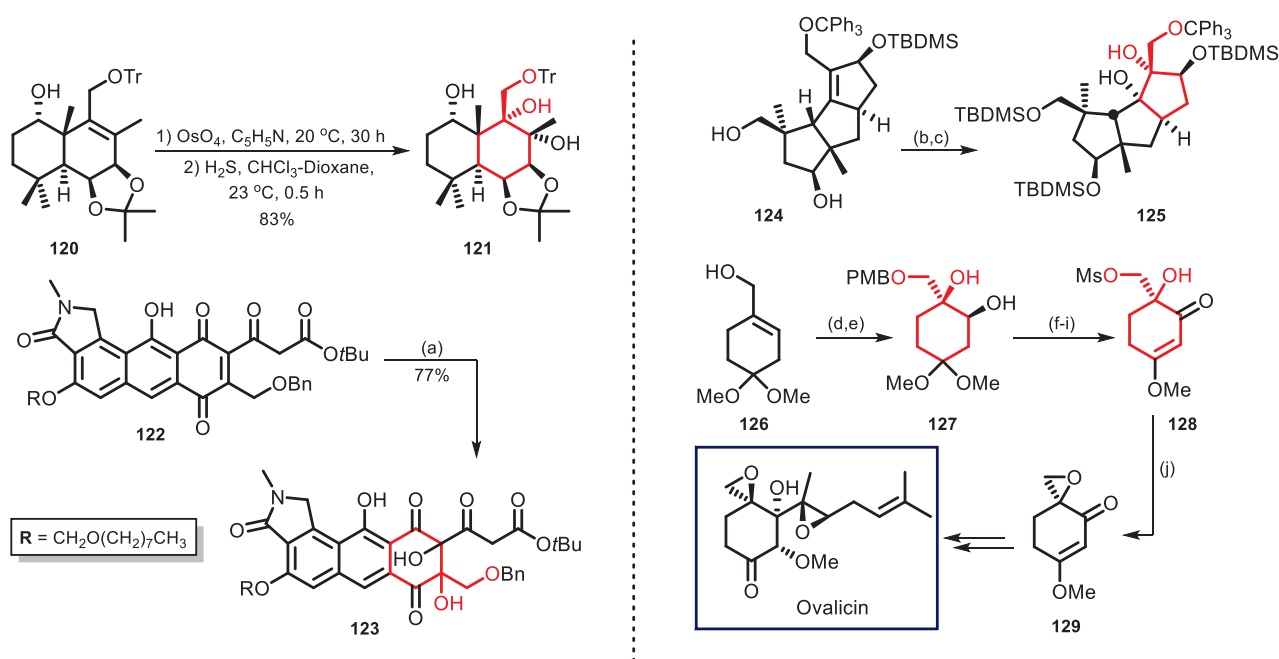
Strategy 2

The second strategy is based on *syn*-dihydroxylation of cyclo-alkenylmethanol derivatives, (Scheme 15). Although it has not been extensively described in the literature, this synthetic pathway has shown major advantage to furnish directly α -(hydroxymethyl) cycloalkane-1,2-diols. The strategy has been employed in the total synthesis of forskolin,^[98] lactonamycinone,^[99] ovalicin^[100] and some capnellols.^[101]

In 1987, Hashimoto and coworkers reported the total synthesis of the diterpene forskolin, isolated from the roots of an Indian herb *Coleus forskohlii*. The authors reported the treatment of **109** with

a stoichiometric amount of osmium tetroxide providing exclusively the desired $8\alpha,9\alpha$ -diol **121**. The latter compound was then transformed over 17 steps before reaching the targeted molecule.^[102] Treatment of **122** and **124** with similar dihydroxylation conditions led to their corresponding diols **123** and **125**. The latter compounds were building blocks for the total synthesis of lactonamycinone, and capnellol derivative respectively.^[103]

This strategy has been also applied by Corey *et al.*^[100b] to synthesize a significant building block **129** for the total synthesis of ovalicin (Scheme 15). The known allylic alcohol **126** was converted to compound **127** in two steps *via* alcohol protection followed by asymmetric dihydroxylation. Oxidation of the secondary alcohol, elimination of one molecule of MeOH, removal of the enantioselectivity-enhancing ester unit, followed by conversion of the primary alcohol into a mesylate, resulted in hydroxymesylate enone **128**. Finally, the latter compound was treated with base to yield enantiopure **129**.^[100b]

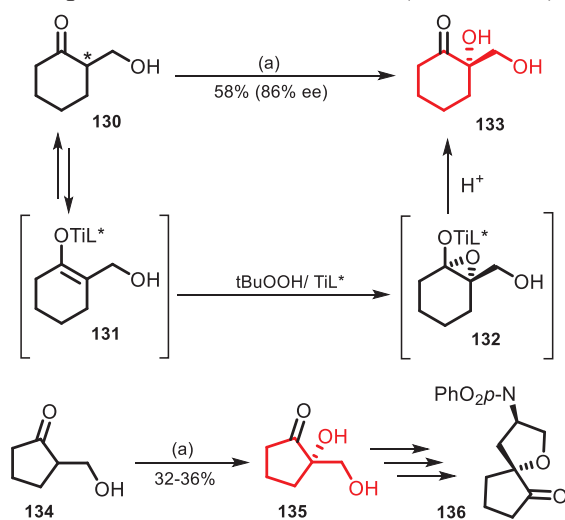


Scheme 15. Selected examples of *syn*-dihydroxylation of some cycloalkenylmethanol derivatives. Reagents and conditions: (a) 1) OsO₄, TMEDA, DCM; 2) HCl (1M), NaHSO₃, THF; (b) TBDMSCl, imidazole, DMF, r.t., 98%; (c) 1) OsO₄, pyridine; 2) NaHSO₃, 70 °C, 67%; (d) *p*-methoxybenzoyl chloride, NEt₃, DMAP, 23 °C, 98%; (e) K₂OsO₄, (DHQ)₂PHAL, K₃Fe(CN)₆, K₂CO₃, CH₃SO₂NH₂, tBuOH, H₂O, 0 °C, 93%, >99% *ee*; (f) oxalyl chloride, DMSO, NEt₃, CH₂Cl₂, -78 to 23 °C, 87%; (g) TsOH, CH₂Cl₂, 23 °C, 93%; (h) K₂CO₃, MeOH, 23 °C, 93%; (i) MsCl, NEt₃, CH₂Cl₂, -78 to 23 °C; (j) NaOH, 23 °C, 82% over two steps.

3.4. Miscellaneous synthesis of α -(hydroxymethyl)-cycloalkanols

α -hydroxylation of 2-hydroxymethyl ketones:

The two-step procedure of enolate generation and subsequent oxidation of the resulting double bond has been known in organic chemistry for decades. The first catalytic α -hydroxylations were reported in 1988 by Shioiri *et al.*^[104] They observed moderate to good enantioselectivities in the oxidation of branched ketones in the presence of alkaline peroxide solution and catalytic amounts of cinchona-based chiral phase transfer catalysts. However, in 1993, Sharpless group succeeded in the asymmetric dihydroxylation of silyl enol ethers. This method proved to be quite general and broadly applicable for the synthesis of a variety of enantiomerically enriched acyloins.^[105] This procedure has been further elaborated by different research groups for various applications.^[106] In 1997, Lopp and coworkers^[107] described the direct oxidation of 2-(hydroxymethyl) cyclohexanone **130** under Sharpless oxidation conditions (Scheme 16).



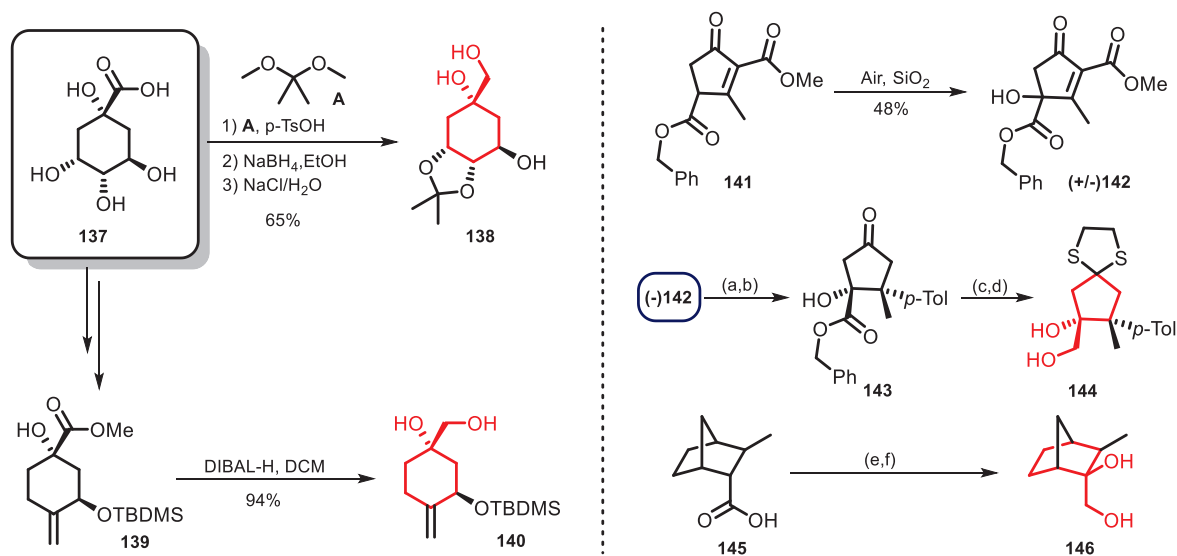
Scheme 16. α -hydroxylation of 2-hydroxymethyl ketones **133** and **136** under Sharpless oxidation conditions. Reagents and conditions (a) Ti(OiPr)₄/(+)-DET, *t*-BuOOH, -20 °C- r.t., app. 46 h. [(+)-DET = L* = Diethyl tartrate].

The presence of β -hydroxyl group and the branching of the substrate in α -position favored the formation of the allylic enolates **131** particularly. Then the oxidation of the formed allylic unit proceeded *via* the Sharpless oxidation mechanism, resulting in the epoxide **132**. This epoxide rearranged in acidic media furnishing α,β -dihydroxyketone **133**. Consequently, the stereoselectivity of hydroxylation varied from 87-97% *ee* in the best examples.

Although the current approach has not been widely applied for the syntheses of α -(hydroxymethyl)cycloalkanols, Chavre *et al.* reported such strategy for their stereoselective synthesis of 2-oxaspiro[*m,n*]alkane derivatives **136** (Scheme 16). Starting from hydroxymethyl ketone **134**, they synthesize dihydroxyketone **135** in moderate yield with low optical purity (39% *ee*).^[108]

Reduction of α -hydroxycycloalkane-carboxylic acid derivatives:

The crucial step in this strategy relies on the preparation of the starting material (α -hydroxycycloalkane-carboxylic acids). In some cases, such compounds occur naturally like quinic acid **137** (Scheme 17) which is considered as a versatile chiral starting material for the synthesis of different pharmaceuticals.^[109] For instance, Metaferia and coworkers reported the synthesis of a variety of substrate-mimic mycothiol analogs through compound **138** starting from this acid **137**.^[110] Similarly, Sibilska *et al.* described the synthesis and biological activity of vitamin D analogue reaching compound **139** (6-step synthesis from quinic acid) which was then reduced to its corresponding diol **140**.^[111]



Scheme 17. Reduction of some α -hydroxycycloalkane-carboxylic acid derivatives. Reagents and conditions: (a) (*p*-Tol)₂Zn, Ni(acac)₂, Et₂O, 20h, r.t., 50%; (b) NaI, DMSO, 100 °C, 3h, 89%; (c) (CH₂SH)₂, BF₃·Et₂O, DCM, r.t. 1h, 70%; (d) LiAlH₄, EtO₂, 0.5 h, 52%; (e) 1) *n*-BuLi, DIPA, THF, 0 °C, 15 min, 2) DMPU, THF, r.t.-50°C, 3 h, 3) Triethyl phosphite, dry O₂, -90 °C, 3h, 60%; (f) LiAlH₄, THF, r.t.- reflux, 2h, 98%.

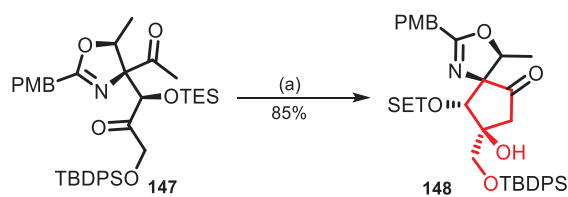
Apart from the use of quinic acid as a starting material, various research groups have prepared α -hydroxycycloalkane-carboxylic acids chemically using classical methods. For example, compound **142**, has been easily obtained *via* air-oxidation during silica gel column chromatography of the starting material **141**. On the other hand, optically pure **142**, a starting material of diol **144**, was obtained by microbial reduction using *Rhodotorula rubra* CCY 20-7-1. **144** was then used in the formal synthesis of cuparene and laurene reported by Sakai's group in 1987.^[112]

Upon their total synthesis of the fragrances (Z)- β -santalol and (E)- β -santalol, and their enantiomers, Krotz and Helmchen used also the current strategy for the preparation of intermediate **146**. The crucial step was the oxidation of the dianions of the carboxylic acid **145**, generated by deprotonation with lithium diisopropylamide (LDA). The resulting α -peroxide was then reduced *in situ* with triethyl phosphite to furnish α -hydroxycarboxylic acid intermediate. The latter was also reduced *via* LiAlH₄ to offer diol **146**.^[113]

Mukaiyama-type intramolecular aldol condensation

In 2012, Hanessian *et al.* described total synthesis of pactamycin and pactamycate.^[114] A nine-step sequence starting with L-threonine led to the PMP-oxazoline derivative **147** (Scheme 18) which was then subjected to a highly stereoselective Mukaiyama-type intramolecular aldol condensation, proceeding *via* a presumed Ti-coordinated Si-enol ether or the corresponding Ti-enolate. The resulting building block **148** was obtained as a shelf-stable crystalline product.

Such strategy has not been extensively used in the literature for the formation of α -(hydroxymethyl)cycloalkanols, but it is considered as a promising pathway for the synthesis of diastereoselective products with high yields.

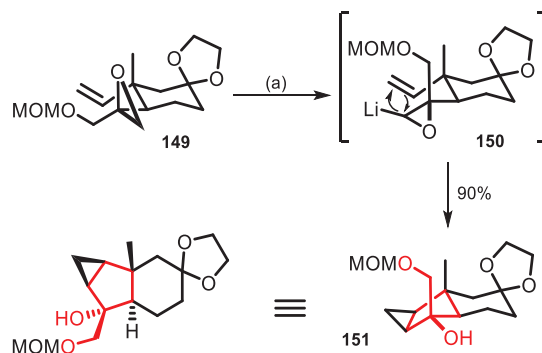


Scheme 18. Intramolecular aldol condensation of **147**. (a) DIPEA, TiCl₄, TMSCl, CH₂Cl₂, 0 °C.

Bicyclization reaction

Treatment of **149** with lithium 2,2,6,6-tetramethylpiperidide (LTMP) smoothly generated the 3/5/6 tricyclic compound **151** in 90% yield (Scheme 19).^[115] The latter compound was then used as a

building block for several unsymmetric and asymmetric total synthesis, such as chloranthalactone A, onoseriolide, bolivianine, and isobolivianine.^[116] It is worth noting that replacing the methoxymethyl (MOM) protective group by a tert-butyldimethyl-silyl (TBS) group in **149** failed to realize the intramolecular cyclopropanation, with a complex mixture formed.^[115] Despite its efficiency in the synthesis of fused α -(hydroxymethyl)cycloalkanols, such strategy is still considered to be rare in the literature.



Scheme 19. Bicyclization reaction of **149**. (a) LTMP, *t*-BuOMe, -78 °C- r.t.

4. Conclusion

This review has systematically given an overview about α -(hydroxymethyl)cycloalkanols; their occurrence and the existing methodologies for their synthesis. From the simple antibiotic G-2201-C to the sophisticated bioactive pactamycin, from the anti-HIV-1 activity of hydroxyangeloylgomisins Q to the diabetes controlling effect of voglibose, natural α -(hydroxymethyl)cycloalkanols isolated from various sources (plants, animals, and microbes) have shown wide and interesting bioactivities, providing great possibilities for drug design and discovery. Although these molecules are not well classified, many chemists have endeavored to develop concise, practical, and short routes toward them for years. The synthetic studies demonstrated herein, not only display the power of classical and current synthetic methods, but they also exhibit the colorful creativity of relevant chemists. Numerous challenges remain in synthesis and reactivity of α -(hydroxymethyl)cycloalkanols, and further exciting developments can be expected in coming years.

5. References

- [1] a) W. Lu, N. Roongsawang, T. Mahmud, *Chem. Biol.* **2011**, *18*, 425-431; b) T. Kim, S. Matsushita, S. Matsudaira, T. Doi, S. Hirota, Y. Park, M. Igarashi, M. Hatano, N. Ikeda, J. Ham, *Org. Lett.* **2019**, *21*, 3554-3557; c) J. Su, D. Olson, S. Ting, J. Du Bois, *J. Org. Chem.* **2018**, *83*, 7121-7134.

- [2] a) M. E. Abugrain, W. Lu, Y. Li, J. D. Serrill, C. J. Brumsted, A. R. Osborn, A. Alani, J. E. Ishmael, J. X. Kelly, T. Mahmud, *ChemBioChem*. **2016**, *17*, 1585-1588 b) M. Iwatsuki, A. Nishihara-Tsukashima, A. Ishiyama, M. Namatame, Y. Watanabe, S. Handasah, H. Pranamuda, B. Marwoto, A. Matsumoto, Y. Takahashi, K. Otoguro, S. Ōmura, *J. Antibiot.* **2012**, *65*, 169-171; c) R. Rodrigues, Y. Lazib, J. Maury, L. Neuville, D. Leboeuf, P. Dauban, B. Darses, *Org. Chem. Front.* **2018**, *5*, 948-953.
- [3] a) O. Ando, H. Satake, K. Itoi, A. Sato, M. Nakajima, S. Takahashi, H. Haruyama, Y. Ohkuma, T. Kinoshita, R. Enokita, *J. Antibiot.* **1991**, *44*, 1165-1168; b) O. Ando, M. Nakajima, K. Hamano, K. Itoi, S. Takahashi, Y. Takamatsu, A. Sato, R. Enokita, T. Okazaki, H. Haruyama, *J. Antibiot.* **1993**, *46*, 1116-1125.
- [4] a) N. Asano, A. Kato, Y. Yokoyama, M. Miyauchi, M. Yamamoto, H. Kizu, K. Matsui, *Carbohydr. Res.* **1996**, *284*, 169-178; b) O. Ando, M. Nakajima, M. Kifune, H. Fang, K. Tanzawa, *Biochim. Biophys. Acta* **1995**, *1244*, 295-302.
- [5] a) A. El Nemr, E. S. H. El Ashry, *Adv. Carbohydr. Chem. Biochem.* **2011**, *65*, 45-114; b) C. Uchida, H. Kitahashi, S. Watanabe, S. Ogawa, *J. Chem. Soc., Perkin Trans. 1* **1995**, *13*, 1707-1717.; c) A. El Nemr, E. S. H. El Ashry, in *Adv. Carbohydr. Chem. Biochem.*, Vol. 65 (Ed.: D. Horton), Elsevier, **Amsterdam**, **2011**, pp. 45-114.
- [6] A. Elbein, *Annu. Rev. Biochem* **1987**, *56*, 497-534.
- [7] A. El Nemr, E. S. H. El Ashry, in *Heterocycles from Carbohydrate Precursors*, Vol 7 (Ed.: E. S. H. El Ashry), Springer, Heidelberg, **2007**, pp. 249-285.
- [8] a) T. Mahmud, *Nat. Prod. Rep.* **2003**, *20*, 137-166; b) O. Arjona, A. M. Gomez, J. C. Lopez, J. Plumet, *Chem. Rev.* **2007**, *107*, 1919-2036.
- [9] Y. Kameda, N. Asano, M. Yoshikawa, M. Takeuchi, T. Yamaguchi, K. Matsui, S. Horii, H. Fukase, *J. Antibiot.* **1984**, *37*, 1301-1307.
- [10] H. Fukase, S. Horii, *J. Org. Chem.* **1992**, *57*, 3642-3650.
- [11] Z-G. Zhuo, G-Z. Wu, X. Fang, X-H. Tian, H-Y. Dong, X-K. Xu, H-L. Li, N. Xie, W-D. Zhang, Y-H. Shen, *Fitoterapia* **2017**, *119*, 90-99..
- [12] C-P. Shen, J-G. Luo, M-H. Yang, L-Y. Kong, *Tetrahedron Lett.* **2015**, *56*, 1328-1331.
- [13] Q. Fu, L. Qiu, H-M. Yuan, T. Yu, L. Zou, *Helv. Chim. Acta* **2016**, *99*, 46-49.
- [14] a) F. A. Macías, A. López, R. M. Varela, A. Torres, J. M. G. Molinillo, *J. Chem. Ecol.* **2008**, *34*, 65-69; b) Q-B. Han, M-L. Li, S-H. Li, Y-K. Mou, Z-W. Lin, H-D. Sun, *Chem. Pharm. Bull.* **2003**, *51*, 790-793; c) N. X. Nhiem, N. T. Thu Hien, B. H. Tai, H. Le Tuan Anh, D. T. T. Hang, T. H. Quang, P. Van Kiem, C. Van Minh, W. Ko, S. Lee, H. Oh, S. H. Kim, Y. H. Kim, *Bioorg. Med. Chem. Lett.* **2015**, *25*, 254-258..
- [15] W. Herz, P. Kulanthaivel, *Phytochemistry* **1984**, *23*, 1453-1459.
- [16] Y-C. Wu, Y-C. Hung, F-R. Chang, M. Cosentino, H-K. Wang, K-H. Lee, *J. Nat. Prod.* **1996**, *59*, 635-637.
- [17] K. Mitachi, T. Yamamoto, F. Kondo, T. Shimizu, M. Miyashita, K. Tanino, *Chem. Lett.* **2010**, *39*, 630-632.
- [18] C. Masuoka, M. Ono, Y. Ito, M. Okawa, T. Nohara, *Chem. Pharm. Bull.* **2002**, *50*, 1413-1415.

- [19] T-Y. Wu, Y-B Cheng, F-T. Cheng, Y-M. Hsu, T. Tran Dinh, F-R. Chang, Y-C. Wu, *Helv. Chim. Acta* **2014**, *97*, 1714-1718.
- [20] D. P. de Lima, A. J. Carnell, S. M. Roberts, *J. Chem. Res.* **1999**, 396-397.
- [21] A. San Feliciano, M. Medarde, M. Gordaliza, E. Del Olmo, J. M. G. del Corral, *Phytochemistry* **1989**, *28*, 2717-2721..
- [22] B-J. Xie, S-P. Yang, J-M. Yue, *Phytochemistry* **2008**, *69*, 2993-2997..
- [23] A. S. R. Anjaneyulu, P. M. Gowri, M. V. R. Krishna Murthy, *J. Nat. Prod.* **1999**, *62*, 1600-1604.
- [24] M. Qin, X. Li, B. Wang, *Chin. J. Chem.* **2012**, *30*, 1278-1282.
- [25] M. Wibowo, V. Prachyawarakorn, T. Aree, C. Mahidol, S. Ruchirawat, P. Kittakoop, *Phytochemistry* **2016**, *122*, 126-138.
- [26] S. Chokpaiboon, D. Sommit, T. Teerawatananon, N. Muangsin, T. Bunyapaiboonsri, K. Pudhom, *J. Nat. Prod.* **2010**, *73*, 1005-1007.
- [27] J. A. F. Gardner, G. M. Barton, H. Maclean, *Can. J. Chem.* **1959**, *37*, 1703-1709..
- [28] M. Chan-Yeung, P. C. Giclas, P. M. Henson, *J. Allergy Clin. Immun.* **1980**, *65*, 333-337.
- [29] a) S. Vedal, M. Chan-Yeung, D. A. Enarson, H. Chan, E. Dorken, K. S. Tse, *J. Allergy Clin. Immun.* **1986**, *78*, 1103-1109; b) M. Chan-Yeung, *J. Allergy Clin. Immun.* **1982**, *70*, 32-37.
- [30] Y. Shi, W. Zhong, H. Chen, R. Wang, S. Shang, C. Liang, Z. Gao, Y. Zheng, W. Xiao, H. Sun, *Chin. J. Chem.* **2014**, *32*, 734-740.
- [31] a) M. De Rosa, A. Gambacorta, B. Nicolaus, J. D. Bu'Lock, *Phytochemistry* **1980**, *19*, 821-825; b) M. De Rosa, A. Gambacorta, B. Nicolaus, B. Chappe, P. Albrecht, *Biochim. Biophys. Acta* **1983**, *753*, 249-256.
- [32] a) T. Date, K. Aoe, K. Kotera, K. Umio, *Chem. Pharm. Bull.* **1974**, *22*, 1963-1967; b) K. Umio, T. Furama, N. Matzuzawa, Y. Awataguchi, Y. Ito, *Chem. Pharm. Bull.* **1974**, *22*, 1233-1238.
- [33] a) S. J. Branca, A. B. Smith III, *J. Am. Chem. Soc.* **1978**, *100*, 7767-7768; b) N. T. Keen, S. Tamaki, D. Kobayashi, D. Trollinger, *Gene* **1988**, *70*, 191-197.
- [34] K-H. Lee, I. H. Hall, E-C. Mar, C. O. Starnes, S. ElGebaly, T. G. Waddell, R. I. Hadgraft, C. G. Ruffner, I. Weidner, *Science* **1977**, *196*, 533-536.
- [35] K. Itami, T. Kamei, K. Mitsudo, T. Nokami, J. Yoshida, *J. Org. Chem.* **2001**, *66*, 3970-3976.
- [36] K. Tamao, N. Ishida, *Tetrahedron Lett.* **1984**, *25*, 4245-4248.
- [37] a) M. Das, D. F. O'Shea, *Org. Lett.* **2016**, *18*, 336-339; b) T. A. Hamlin, C. B. Kelly, R. M. Cywar, N. E. Leadbeater, *J. Org. Chem.* **2014**, *79*, 1145-1155.
- [38] a) K. Tamao, N. Ishida, T. Tanaka, M. Kumada, *Organometallics* **1983**, *2*, 1694-1696; b) K. Tamao, *Proc. Jpn Acad., Ser. B* **2008**, *84*, 123-133.
- [39] a) M. Utsugi, Y. Kamada, H. Miyamoto, M. Nakada, *Tetrahedron Lett.* **2007**, *48*, 6868-6872; b) M. Iwamoto, M. Miyano, M. Utsugi, H. Kawada, M. Nakada, *Tetrahedron Lett.* **2004**, *45*, 8647-8651.
- [40] H-J. Chen, Y. Wu, *Org. Lett.* **2015**, *17*, 592-595.
- [41] C. Fuganti, D. Joulain, F. Maggioni, L. Malpezzi, S. Serra, A. Vecchione, *Tetrahedron Asymmetry* **2008**, *19*, 2425-2437.

- [42] T. Imamoto, T. Takeyama, M. Yokoyama, *Tetrahedron Lett.* **1984**, *25*, 3225-3226.
- [43] J. D. White, R. W. Skeeane, G. L. Trammell, *J. Org. Chem.* **1985**, *50*, 1939-1948.
- [44] a) J. D. White, T. C. Somers, *J. Am. Chem. Soc.* **1987**, *109*, 4424-4426; b) R. B. Kelly, M. L. Harley, S. J. Alward, R. N. Rej, G. Gowda, A. Mukhopadhyay, P. S. Manchand, *Can. J. Chem.* **1983**, *61*, 269-275.
- [45] P. Wipf, Y. Kim, P. C. Fritch, *J. Org. Chem.* **1993**, *58*, 7195-7203.
- [46] H. W. Fehlhaber, H. Kogler, T. Mukhopadhyay, E. K. S. Vijayakumar, K. Roy, R. H. Rupp, B. N. Ganguli, *J. Antibiot.* **1988**, *41*, 1785-1794..
- [47] a) W. C. Still, *J. Am. Chem. Soc.* **1978**, *100*, 1481-1487; b) C. R. Johnson, J. R. Medich, *J. Org. Chem.* **1988**, *53*, 4131-4133.
- [48] a) S. E. Chillous, D. J. Hart, D. K. Hutchinson, *J. Org. Chem.* **1982**, *47*, 5418-5420; b) V. Dimitrov, S. Panev, *Tetrahedron Asymmetry* **2000**, *11*, 1513-1516.
- [49] C. Kobler, F. Effenberger, *Eur. J. Chem.* **2005**, *11*, 2783-2787.
- [50] a) Y. Tsukamoto, S. Nonomura, H. Sakai, *Agric. Biol. Chem.* **1977**, *41*, 435-444; b) Y. Konda, Y. Toda, H. Takayanagi, H. Ogura, Y. Harigaya, H. Lou, X. Li, M. Onda, *J. Nat. Prod.* **1992**, *55*, 1118-1123; c) T. Ishikawa, J. Kitajima, Y. Tanaka, *Chem. Pharm. Bull.* **1998**, *46*, 1603-1606; d) K. M. Madyastha, V. Srivatsan, *Xenobiotica* **1987**, *17*, 539-549.
- [51] F. Effenberger, J. Roos, C. Kobler, H. Bühler, *Can. J. Chem.* **2002**, *80*, 671-679.
- [52] M. E. Jung, C. A. McCombs, Y. Takeda, Y-G. Pan, *J. Am. Chem. Soc.* **1981**, *103*, 6677-6685..
- [53] R. F. G. Fröhlich, A. A. Zabelinskaja-Mackova, M. H. Fechter, H. Griengl, *Tetrahedron Asymmetry* **2003**, *14*, 355-362.
- [54] J. L. García Ruano, C. García Paredes, C. Hamdouchi, *Tetrahedron Asymmetry* **1999**, *10*, 2935-2944.
- [55] a) M. J. Donaldson, V. Skoumas, M. Watson, P. A. Ashworth, H. Ryder, M. Moore, R. C. Coombes, *Eur. J. Cancer* **1999**, *35*, 1014-1019; b) R. M. Carman, A. C. Garner, *Aust. J. Chem.* **1996**, *49*, 741-749.
- [56] a) G. Blay, V. Bargues, L. Cardona, B. García, J. R. Pedro, *Tetrahedron* **2001**, *57*, 9719-9725; b) C. H. Heathcock, R. Ratcliffe, *J. Am. Chem. Soc.* **1971**, *93*, 1746-1757.
- [57] M-K. Parr, A. Zöllner, G. Fußhöller, G. Opfermann, N. Schlörer, M. Zorio, M. Bureik, W. Schänzer, *Toxicol. Lett.* **2012**, *213*, 381-391.
- [58] W. Schänzer, H. Geyer, G. Fußhöller, N. Halatcheva, M. Kohler, M-K. Parr, S. Guddat, A. Thomas, M. Thevis, *Rapid Commun. Mass Spectrom.* **2006**, *20*, 2252-2258.
- [59] I. Nitta, S. Fujimori, H. Ueno, *Bull. Chem. Soc. Jpn.* **1985**, *58*, 978-980.
- [60] J. Yamaguchi, M. Toyoshima, M. Shoji, H. Kakeya, H. Osada, Y. Hayashi, *Angew. Chem. Int. Ed.* **2006**, *45*, 789-793.
- [61] a) J. Yamaguchi, Y. Hayashi, *Chem. Eur. J.* **2010**, *16*, 3884-3901; b) D. Ingber, T. Fujita, S. Kishimoto, K. Sudo, T. Kanamaru, H. Brem, J. Folkman, *Nature* **1990**, *348*, 555-557.
- [62] M. Suzuki, Y. Morita, H. Koyano, M. Koga, R. Noyori, *Tetrahedron* **1990**, *46*, 4809-4822.

- [63] a) P. Ambrosi, A. Arnone, P. Bravo, L. Bruché, A. De Cristofaro, V. Francardi, M. Frigerio, E. Gatti, G. S. Germinara, W. Panzeri, F. Pennacchio, C. Pesenti, G. Rotundo, P. F. Roversi, C. Salvadori, F. Viani, M. Zanda, *J. Org. Chem.* **2001**, *66*, 8336-8343; b) T. Sato, H. Kaneko, S. Yamaguchi, *J. Org. Chem.* **1980**, *45*, 3778-3782.
- [64] A. G. Griesbeck, M. Reckenthäler, *Beilstein J. Org. Chem.* **2014**, *10*, 1143-1150.
- [65] M. Bowker, *Green Chem.* **2011**, *13*, 2235-2246.
- [66] S. Kohtani, E. Yoshioka, K. Saito, A. Kudo, H. Miyabe, *J. Phys. Chem.* **2012**, *116*, 17705-17713.
- [67] A. Clerici, O. Porta, *J. Org. Chem.* **1989**, *54*, 3872-3878.
- [68] J. Park, S. F. Pedersen, *Tetrahedron* **1992**, *48*, 2069-2080.
- [69] a) B. Giese, B. Kopping, T. Göbel, J. Dickhaut, G. Thoma, K. J. Kulicke, F. Trach, *Org. React. Wiley*, Hoboken, **1996**, *48*, pp. 303-856; b) D. S. Hays, G. C. Fu, *J. Am. Chem. Soc.* **1995**, *117*, 7283-7284; c) G. A. Molander, C. Kenny, *J. Am. Chem. Soc.* **1989**, *111*, 8236-8246
- [70] J. Marco-Contelles, P. Gallego, M. Rodríguez-Fernández, N. Khiar, C. Destabel, M. Bernabé, A. Martínez-Grau, J. L. Chiara, *J. Org. Chem.* **1997**, *62*, 7397-7412.
- [71] A. Boiron, P. Zillig, D. Faber, B. Giese, *J. Org. Chem.* **1998**, *63*, 5877-5882.
- [72] I. Storch de Gracia, H. Dietrich, S. Bobo, J. L. Chiara, *J. Org. Chem.* **1998**, *63*, 5883-5889.
- [73] a) J. Gorzynski Smith, *Synthesis* **1984**, *1984*, 629-656; b) A. Padwa, S. S. Murphree, *Arkivoc* **2006**, 6-33.
- [74] S. P. Tanis, M. C. McMills, P. M. Herrinton, *J. Org. Chem.* **1985**, *50*, 5887-5889.
- [75] M. Bergner, D. C. Duquette, L. Chio, B. M. Stoltz, *Org. Lett.* **2015**, *17*, 3008-3010.
- [76] S. Ogawa, Y. Ohishi, M. Asada, A. Tomoda, A. Takahashi, Y. Ooki, M. Mori, M. Itoh, T. Korenaga, *Org. Biomol. Chem.* **2004**, *2*, 884-889.
- [77] a) K. G. M. Kou, S. Kulyk, C. J. Marth, J. C. Lee, N. A. Doering, B. X. Li, G. M. Gallego, T. P. Lebold, R. Sarpong, *J. Am. Chem. Soc.* **2017**, *139*, 13882-13896; b) K. G. M. Kou, B. X. Li, J. C. Lee, G. M. Gallego, T. P. Lebold, A. G. DiPasquale, R. Sarpong, *J. Am. Chem. Soc.* **2016**, *138*, 10830-10833.
- [78] S. Ogawa, Y. Uematsu, S. Yoshida, N. Sasaki, T. Suami, *J. Carbohydr. Chem.* **1987**, *6*, 471-478.
- [79] N. J. Rahier, N. Molinier, C. Long, S. K. Deshmukh, A. S. Kate, P. Ranadive, S. A. Verekar, M. Jiotode, R. R. Lavhale, P. Tokdar, A. Balakrishnan, S. Meignan, C. Robichon, B. Gomes, Y. Aussagues, A. Samson, F. Sautel, C. Bailly, *Biorg. Med. Chem.* **2015**, *23*, 3712-3721.
- [80] R. N. Khaibullin, I. Y. Strobukina, V. E. Kataev, O. A. Lodochnikova, A. T. Gubaidullin, A. A. Balandina, S. K. Latypov, *Russ. J. Org. Chem.* **2010**, *46*, 1006-1012.
- [81] Y. Matsuda, Y. Endo, Y. Saikawa, M. Nakata, *J. Org. Chem.* **2011**, *76*, 6258-6263.
- [82] J. L. Cheng, Y. Zhou, J. H. Zhao, C. Zhang, F. C. Lin, *Chin. Chem. Lett.* **2010**, *21*, 1037-1040.
- [83] a) N. Pérez-Hernández, M. Febles, C. Pérez, R. Pérez, M. L. Rodríguez, C. Foces-Foces, J. D. Martín, *J. Org. Chem.* **2006**, *71*, 1139-1151; b) W. J. Choi, Y. J. Ko, G. Chandra, H. W. Lee, H. O. Kim, H. J. Koh, H. R. Moon, Y. H. Jung, L. S. Jeong, *Tetrahedron* **2012**, *68*, 1253-1261; c) X-F. Zhu, F. Nydegger, A. Gossauer, *Helv. Chim. Acta* **2004**, *87*, 2245-2265; d) F. Cachoux, M. Ibrahim-Ouali, M. Santelli, *Synlett* **2002**, *2002*, 1987-1990; e) K. Oumzil, M. Ibrahim-Ouali, M. Santelli, *Steroids* **2006**, *71*, 886-894; f) W. Adam, E. Crämer, *Chem. Ber.* **1987**, *120*, 1921-1924.

- [84] S. Kohtani, E. Yoshioka, K. Saito, A. Kudo, H. Miyabe, *J. Phys. Chem. C* **2012**, *116*, 17705-17713.
- [85] H. Huang, C. J. Forsyth, *J. Org. Chem.* **1995**, *60*, 2773-2779.
- [86] S. Knapp, A. Purandare, K. Rupitz, S. G. Withers, *J. Am. Chem. Soc.* **1994**, *116*, 7461-7462.
- [87] S. Hanessian, R. R. Vakiti, S. Dorich, S. Banerjee, F. Lecomte, J. R. DelValle, J. Zhang, B. Deschênes-Simard, *Angew. Chem. Int. Ed.* **2011**, *50* 3497-3500.
- [88] a) Y. Kobayashi, H. Miyazaki, M. Shiozaki, *J. Am. Chem. Soc.* **1992**, *114*, 10065-10066; b) N. Ohyabu, T. Nishikawa, M. Isobe, *J. Am. Chem. Soc.* **2003**, *125*, 8798-8805; c) G. Yue, L. Yang, C. Yuan, B. Du, B. Liu, *Tetrahedron* **2012**, *68*, 9624-9637.
- [89] M. Schwarz, O. Reiser, *Angew. Chem. Int. Ed.* **2011**, *50*, 10495-10497.
- [90] a) D. Deubel, G. Frenking, *Acc. Chem. Res.* **2003**, *36*, 645-651; b) G. Molander, R. Figueroa, *Org. Lett.* **2006**, *8*, 75-78; c) K-i. Fujita, S. Umeki, H. Yasuda, *Synlett* **2013**, *24*, 947-950.; d) S. V. Ley, C. Ramarao, A-L. Lee, N. Østergaard, S. C. Smith, I. M. Shirley, *Org. Lett.* **2003**, *5*, 185-187; e) . M. Choudary, N. S. Chowdari, K. Jyothi, M. L. Kantam, *J. Am. Chem. Soc.* **2002**, *124*, 5341-5349; f) Y. Monguchi, F. Wakayama, H. Takada, Y. Sawama, H. Sajiki, *Synlett* **2015**, *26*, 700-704.
- [91] a) G. M. Mehlretter, S. Bhor, M. Klawonn, C. Doebler, U. Sundermeier, M. Eckert, H-C. Militzer, M. Beller, *Synthesis* **2003**, 295-301; b) L. C. Branco, C. A. M. Afonso, *J. Org. Chem.* **2004**, *69*, 4381-4389; c) M. H. Junttila, O. E. O. Hormi, *J. Org. Chem.* **2009**, *74*, 3038-3047.; d) M. H. Junttila, O. E. O. Hormi, *J. Org. Chem.* **2004**, *69*, 4816-4820.
- [92] a) S. I. Elshahawi, K. A. Shaaban, M. K. Kharel, J. S. Thorson, *Chem. Soc. Rev.* **2015**, *44*, 7591-7697; b) K. L. Rinehart Jr, D. D. Weller, C. J. Pearce, *J. Nat. Prod.* **1980**, *43*, 1-20; c) T. Kim, S. Matsushita, S. Matsudaira, T. Doi, S. Hirota, Y. T. Park, M. Igarashi, M. Hatano, N. Ikeda, J. Ham, M. Nakata, *Org. Lett.* **2019**, *21*, 3554-3557.
- [93] S. Ramesh, G. Mehta, *Tetrahedron Lett.* **2015**, *56*, 5545-5548.
- [94] D. Hébrault, D. Uguen, A. De Cian, J. Fischer, *Tetrahedron Lett.* **1998**, *39*, 6703-6706.
- [95] E. Vedejs, W. H. Dent III, *J. Am. Chem. Soc.* **1989**, *111*, 6861-6862.
- [96] M. K. Sharma, M. G. Banwell, A. C. Willis, *Asian J. Org. Chem.* **2014**, *3*, 632-637.
- [97] D. Ainge, D. Ennis, M. Gidlund, M. Stefinovic, L-M. Vaz, *Org. Proc. Res. Dev.* **2003**, *7*, 198-201.
- [98] K. B. Seamon, W. Padgett, J. W. Daly, *Proc. Natl. Acad. Sci.* **1981**, *78*, 3363-3367..
- [99] X. Zhang, L. B. Alemany, H-P. Fiedler, M. Goodfellow, R. J. Parry, *Antimicrob. Agents Chemother.* **2008**, *52*, 574-585.
- [100] a) E. J. Corey, J. P. Dittami, *J. Am. Chem. Soc.* **1985**, *107*, 256-257; b) E. J. Corey, A. Guzman-Perez, M. C. Noe, *J. Am. Chem. Soc.* **1994**, *116*, 12109-12110.
- [101] R. D. Little, G. L. Carroll, J. L. Petersen, *J. Am. Chem. Soc.* **1983**, *105*, 928-932.
- [102] S-i. Hashimoto, S. Sakata, M. Sonogawa, S. Ikegami, *J. Am. Chem. Soc.* **1988**, *110*, 3670-3672.
- [103] a) T. Mase, M. Shibasaki, *Tetrahedron Lett.* **1986**, *27*, 5245-5248; b) T. Siu, C. D Cox, S. J. Danishefsky, *Angew. Chem. Int. Ed.* **2003**, *45*, 5629-5634.
- [104] M. Masui, A. Ando, T. Shioiri, *Tetrahedron Lett.* **1988**, *29*, 2835-2838.

- [105] K. Morikawa, J. Park, P. G. Andersson, T. Hashiyama, K B.. Sharpless, *J. Am. Chem. Soc.* **1993**, *115*, 8463-8464.
- [106] a) M. Schulz, R. Kluge, M. Schüßler, G. Hoffmann, *Tetrahedron* **1995**, *51*, 3175-3180; b) D. Gala, D. J. DiBenedetto, I. Mergelsberg, M. Kugelman, S. Research, *Tetrahedron Lett.* **1996**, *37*, 8117-8120; c) N. Komiya, S. Noji, S-I. Murahashi, *Tetrahedron Lett.* **1998**, *39*, 7921-7924; d) B. Plietker, *Tetrahedron Asymmetry* **2005**, *16*, 3453-3459.
- [107] M. Lopp, A. Paju, T. Kanger, T. Pehk, *Tetrahedron Lett.* **1997**, *38*, 5051-5054.
- [108] a) S. N. Chavre, P. R. Ullapu, S-J. Min, J. K. Lee, A. N. Pae, Y. Kim, Y. S. Cho, *Org. Lett.* **2009**, *11*, 3834-3837; b) A. Paju, T. Kanger, T. Pehk, M. Lopp, *Tetrahedron* **2002**, *58*, 7321-7326.
- [109] A. Barco, S. Benetti, C. De Risi, P. Marchetti, G. P. Pollini, V. Zanirato, *Tetrahedron Asymmetry* **1997**, *8*, 3515-3545.
- [110] B. B. Metaferia, S. Ray, J. A. Smith, C. A. Bewley, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 444-447.
- [111] I. Sibilska, K. M. Barycka, R. R. Sicinski, L. A. Plum, H. F. DeLuca, *J. Steroid Biochem. Mol. Biol.* **2010**, *121*, 51-55
- [112] K. Okano, H. Suemune, K. Sakai, *Chem. Pharm. Bull.* **1988**, *36*, 1379-1385.
- [113] A. Krotz, G. Helmchen, *Tetrahedron Asymmetry* **1990**, *1*, 537-540.
- [114] S. Hanessian, R. R. Vakiti, S. Dorich, S. Banerjee, B. Deschênes-Simard, *J. Org. Chem.* **2012**, *77*, 9458-9472.
- [115] G. Yue, L. Yang, C. Yuan, X. Jiang, B. Liu, *Org. Lett.* **2011**, *13*, 5406-5408.
- [116] B. Du, C. Yuan, T. Yu, L. Yang, Y. Yang, B. Liu, S. Qin, *Chem. Eur. J.* **2014**, *20*, 2613-2622.

Chapter II

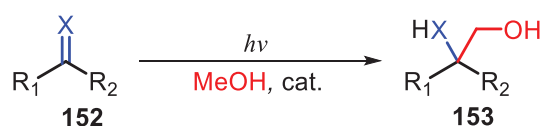
Photochemical

Hydroxymethylation

Ch. II: Photochemical Hydroxymethylation

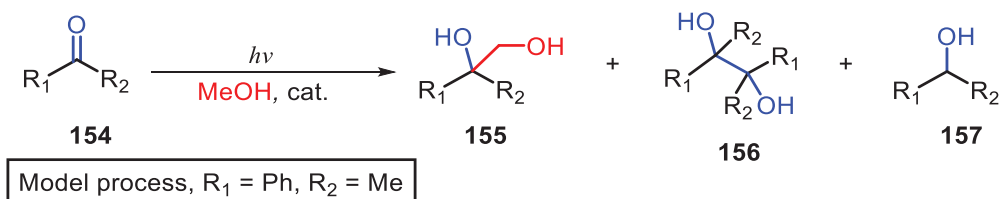
1. Introduction

As shown in Chapter one, photochemical hydroxymethylation of carbonyl compounds has been studied in a series of papers by different research groups. It has been shown that carbonyl compounds^[1] **152** as well as imines^[2] couple with methanol to give 1,2-diols or 1,2-amino alcohols, respectively, when irradiated in the presence of stoichiometric or sub-stoichiometric amounts of titanium tetrachloride (Scheme 1). To run these reactions to completion, not less than 0.5 equivalents of TiCl_4 are necessary. Furthermore, the addition of TiCl_4 to methanol solutions is ponderous and it is unclear what species is catalytically active.



Scheme 1. Photohydroxymethylation of carbonyl compounds and imines ($\text{X} = \text{O}$ or NR).^[3]

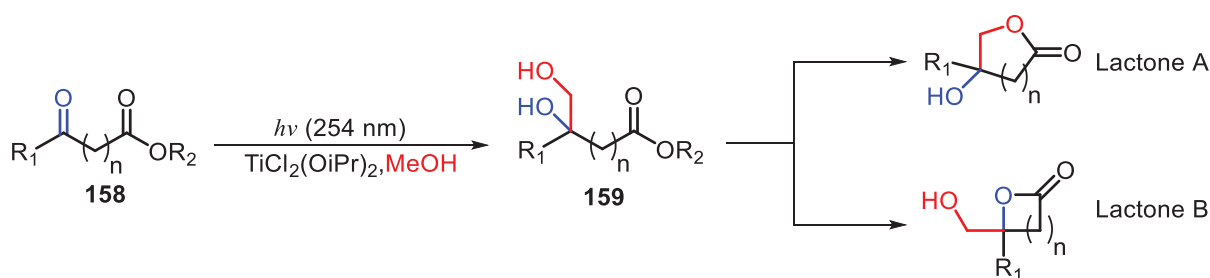
To evaluate the nature of the active catalytic species in the photochemical homogenous titanium-catalyzed hydroxymethylation and to develop a truly catalytic process, Griesbeck and Reckenthäler^[3] used a model reaction for catalyst screening (acetophenone/methanol) and applied the optimal homogenous reaction conditions to other ketones and ketoesters.



Scheme 2. Photocatalyzed ketone/methanol reaction.^[3]

Various monomeric titanium complexes were applied to the type $\text{TiCl}_n(\text{OiPr})_{4-n}$ ($n = 0, 1, 2, 3$)^[4] in the model reaction (Scheme 2). In the absence of any titanium species, photolysis at 254 and 300 nm, respectively, led only to trace amounts of the hydroxymethylation product **155** via a (triplet carbonyl) excited-state hydrogen-transfer process. In the presence of the tetraalkoxide $\text{Ti}(\text{OiPr})_4$, only the reduction product **157** was detected which demonstrates that chlorotitanium

complexes are crucial for the desired reaction path. $\text{TiCl}(\text{OiPr})_3$ showed no activity at all, meaning that no further ligand exchange to a tetraalkoxide derivatives did occur from this complex. With TiCl_4 and TiCl_3OiPr , compound **155** was obtained in moderate yield. However, the optimal results regarding reaction time and yields were observed with $\text{TiCl}_2(\text{OiPr})_2$. The irradiation of different aliphatic and aromatic ketones with the latter catalyst in methanol led to the desired compound **155** (38-60% yield). These conditions were also applied to ketoester substrates **158**, allowing the formation of lactones from the corresponding hydroxymethylation products **159** (Scheme 3). Lactone A was isolated for $n = 1$ or 2 (54-56% yield), whereas Lactone B was obtained for $n = 3$ (28% yield).



Scheme 3. Photohydroxymethylation and subsequent lactonization of keto esters.^[3]

Despite their fruitful efforts, the authors did not report the investigation of any cyclic β -ketoester under such conditions. Furthermore, the reaction has not been applied to natural cyclic ketones yet. For these reasons, we wanted to investigate the subject precisely by considering these two points. Our main objective was also to furnish bicyclic γ -lactones that could be used to rapidly access a wide variety of complex structures.

2. Preparation of different α -substituted β -ketoesters

To expand the scope of our study, it was necessary to prepare different α -substituted alkyl 2-oxocycloalkanecarboxylates *via* α -alkylation reaction. Such types of reactions are well-known, and various theories have been proposed and examined. Problems arise from the bidentate nature of the anion, which may react at both the oxygen center^[5] or at the carbon one.^[6] A polar aprotic medium, a large counterion, low concentrations of the anion, a hard leaving group, and an alkylating agent of low $\text{S}_{\text{N}}2$ reactivity are usually suggested to favor *O*-alkylation; the *C*-alkylation requiring, of course, opposite conditions. Thus, good yields of *C*-alkylated products are obtained, employing unhindered primary halides. In such cases, the reaction of the enol rather than the

enolate anion with a carbonium ion or carbonium ion-like species is the preferred route.^[7]

The α -substituted derivatives **161a-o** were prepared using commercially available alkyl 2-oxocycloalkanecarboxylates **160a-d**. The details of α -alkylation reactions are shown in Table 1.

Table 1. Alkylation of β -ketoesters **160a-d**.



Entry	SM ^a	n	R ₁	Condition ^b	Product	R ₂	t (h) ^c	%Yield ^d
1	160b	0	Et	A	161a	Methyl	48	83
2	160d	1	Et	A	161b	Methyl	40	97
3	160a	0	Me	A	161c	Benzyl	20	77
4	160b	0	Et	A	161d	Benzyl	22	90
5	160d	1	Et	A	161e	Benzyl	22	75
6	160a	0	Me	A	161f	Allyl	48	69
7	160b	0	Et	A	161g	Allyl	25	62
8	160c	1	Me	A	161h	Allyl	76	53
9	160d	1	Et	A	161i	Allyl	26	77
10	160a	0	Me	B	161j	Propargyl	20	97
11	160b	0	Et	B	161k	Propargyl	19	97
12	160c	1	Me	B	161l	Propargyl	21	76
13	160d	1	Et	B	161m	Propargyl	28	85
14	160b	0	Et	A	161n	-CH ₂ -CO ₂ Et	18	84
15	160a	0	Me	A	161o	-CH ₂ -C(CH ₃)=CH ₂	20	85

^aStarting material; ^bcond. (A) i) NaH, THF, 0 °C, 30 min., ii) R₂Br, THF, 0 °C to r.t.; ^bcond. (B) i) *t*-BuOK, *t*-BuOH, r.t., 30 min, ii) propargyl-Br (80% in toluene), reflux (85- 90 °C); ^creaction time; ^disolated yield.

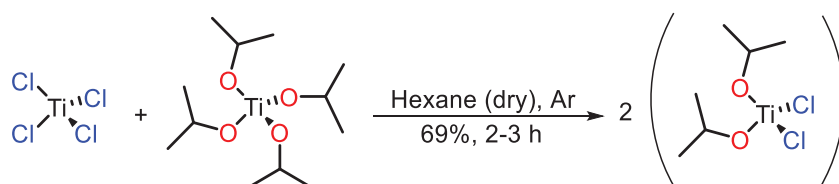
In most of the cases, the chosen β -ketoester was added to a stirred suspension of NaH in THF at 0°C, which was accompanied by an instantaneous change of color from white turbid to dark yellow. The dropwise addition of the corresponding alkyl bromide turned the mixture orange turbid of increasing intensity over time (Condition A). However, another reaction condition, of high efficiency, was exclusively used to prepare the α -propargyl adducts. Refluxing the given ketoester with propargyl bromide and potassium *tert*-butoxide afforded the thermodynamically

preferred α -substituted derivatives (Condition B).^[8]

In general, the formed products were obtained from moderate to excellent yields (53%- 97%) over 18 to 76 hours, depending on the nature of alkylating agents and the used condition. Reactions of **160a-d** with allyl bromide were relatively longer than those with other alkyl bromide derivatives (Entries 6-9). However, the best results, in terms of reaction time and isolated yields, were achieved when the reactions of ketoesters **160a-b** were carried out with propargyl bromide under condition B (Entries 10-11). It is noteworthy that the nature of the starting material, which only differs in terms of ester moiety and ring size, has also shown an unexpected impact on the reaction yield. For instance, when treated under similar conditions with benzyl bromide, compounds **160a-b** afforded different results (Entries 3-4). Likewise, **160a,c**, of 5- and 6- membered rings respectively, gave different reaction yields of their α -substituted counterparts when treated with propargyl bromide under condition B (Entries 10,12). So far, there is no experimental explanation for the obtained difference.

3. Preparation of the photocatalyst

With the α -substituted alkyl 2-oxocycloalkanecarboxylates **161a-o** in hand, we turned our attention to the preparation of the photocatalyst dichlorotitanium diisopropoxide $\text{TiCl}_2(\text{OiPr})_2$. The reagent can be obtained commercially from different chemical suppliers, but it is highly recommended to prepare it freshly from readily available $\text{Ti}(\text{OiPr})_4$ and TiCl_4 .^[9] Upon contact with humid air, titanium tetrachloride forms spectacular opaque clouds of titanium dioxide (TiO_2) and hydrated hydrogen chloride. For this reason, the reaction between both titanium compounds was carried under a dry and inert atmosphere. The resulting colorless crystals can be handled on-air for weighting and can be kept in a closed container for a long period without losing its performance.

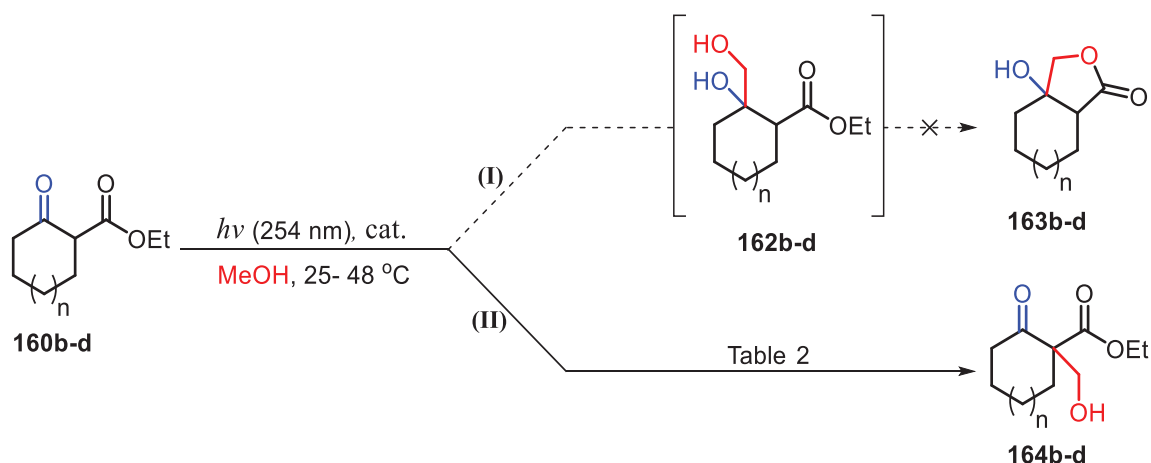


Scheme 4. Preparation of dichlorotitanium diisopropoxide $\text{TiCl}_2(\text{OiPr})_2$.

4. Photochemical hydroxymethylation of alkyl oxocycloalkanecarboxylates **160b-d**

The study began by testing ethyl 2-oxocycloalkanecarboxylates **160b-d** under similar conditions reported by Griesbeck and Reckenthäler.^[3] Either Ti(OiPr)₄ or TiCl₂(OiPr)₂ was used as a photocatalyst with the chosen substrate in methanol (Table 2). The whole mixture was then irradiated in quartz tubes by UV light (254 nm) under an inert atmosphere. The slightly yellowish initial solution turns yellow-orange over time indicating the formation of reduced titanium species. After irradiation for a specific period, it was expected to observe the formation of γ -lactones **163b-d** from the corresponding hydroxymethylation products **162b-d** (route I). The irradiation of ketoester **160d** for 4 hours without any titanium catalysis gave no reaction neither at 254 nm nor at 366 nm. This result is in contradiction with the photochemical lactonization of dihydroxy ester, which was obtained by Kagan and coworkers^[10] in 1969, upon irradiation of ethyl acetoacetate in alcohol.

Table 2. Hydroxymethylation reaction on two different positions.



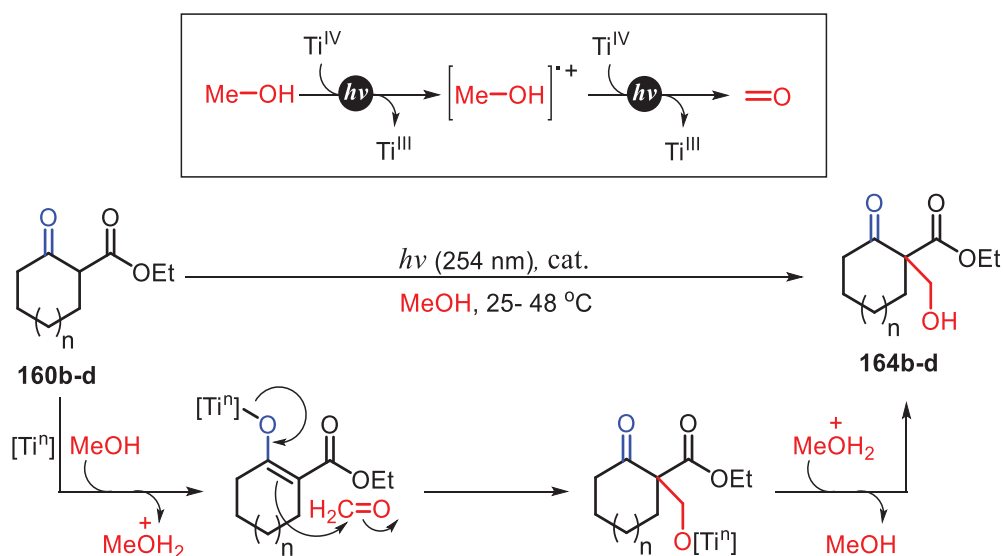
Entry	SM ^a	n	Catalyst	Product	t(h) ^b	%Yield ^c
1	160d	1	—	—	4	— ^d
2	160b	0	Ti(OiPr) ₄	164b	6	41
3	160d	1	Ti(OiPr) ₄	164d	5	38
4	160b	0	TiCl ₂ (OiPr) ₂	164b	24-72	— ^e
5	160d	1	TiCl ₂ (OiPr) ₂	164d	4	40

^a[**160b-d**] = 0.125 M. ^bIrradiation time. ^cIsolated yield. ^dno reaction neither at 254 nm nor at 366nm. ^edecomposition.

Unpredictively, hydroxymethylation took place at the α -position of the used ketoester (route II) to afford hydroxymethyl adducts **164b-d**. Moderate yields with incomplete conversions of these compounds were obtained when irradiating **160b-d** with $\text{Ti}(\text{OiPr})_4$ or $\text{TiCl}_2(\text{OiPr})_2$ for a short period (4- 6 h, Entries 2, 3, 5, Table 2). In contrast, the irradiation of **160b** with $\text{TiCl}_2(\text{OiPr})_2$ for 24 or 72 hours led to the decomposition of the whole mixture (Entry 4, Table 2).

The most probable explanation of this reaction (route II) relies on methanol oxidation, which is the crucial primary step in the process (Scheme 5). The used photocatalyst is capable of oxidizing methanol into formaldehyde in the excited state and simultaneously acting as a ground-state Lewis acid that complexes the carbonyl compound. Consequently, aldolization reaction could easily take place at this level to afford aldols **164b-d**.

By taking a closer look at literature, several research groups reported such type of hydroxymethylation using formaldehyde sources and metal complexes, such as Pd(II)-BINAP,^[11] Ni₂-Schiff base complex,^[12] and Fe(acac)₃.^[13]



Scheme 5. Suggested Mechanism for the formation of aldols **164b-d**.

5. Photochemical hydroxymethylation of α -substituted alkyl 2-oxocycloalkanecarboxylates: access to bicyclic γ -lactones.

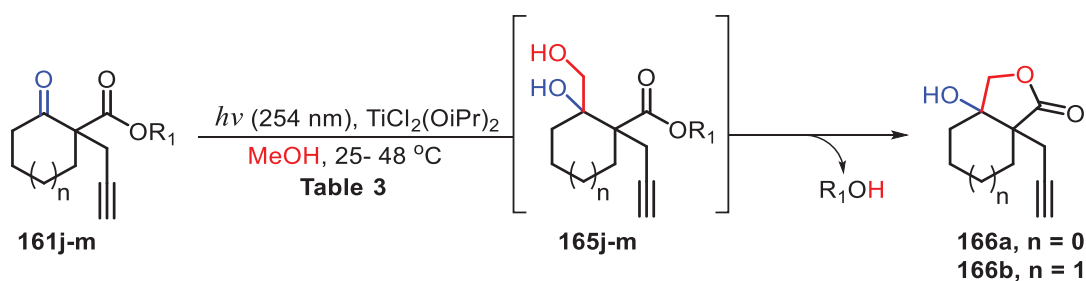
α -Alkylation of cyclic β -ketoesters does not only protect the α -position from unwanted enolization but also may add new functionality for further cyclization. In this section, the synthetic challenges

of some significant bicyclic γ -lactones, which are included in the subsequent chapters, will be highlighted, and alternative processes for their preparation will be discussed shortly.

5.1. Synthesis of propargyl bicyclic γ -lactones

A screen of photochemical reaction conditions on **161j-m** has been conducted in the presence of $\text{TiCl}_2(\text{OiPr})_2$ under an inert atmosphere, varying both the irradiation wavelength and the reaction time as shown in Table 3. Irradiation of ketoesters **161k,l** at 300 nm for 24 to 70 hours led to traces of **166a** with a negligible conversion of the starting material (^1H NMR analysis) (Entries 2, 8).

Table 3. Photochemical hydroxymethylation reaction of **161j-m**.



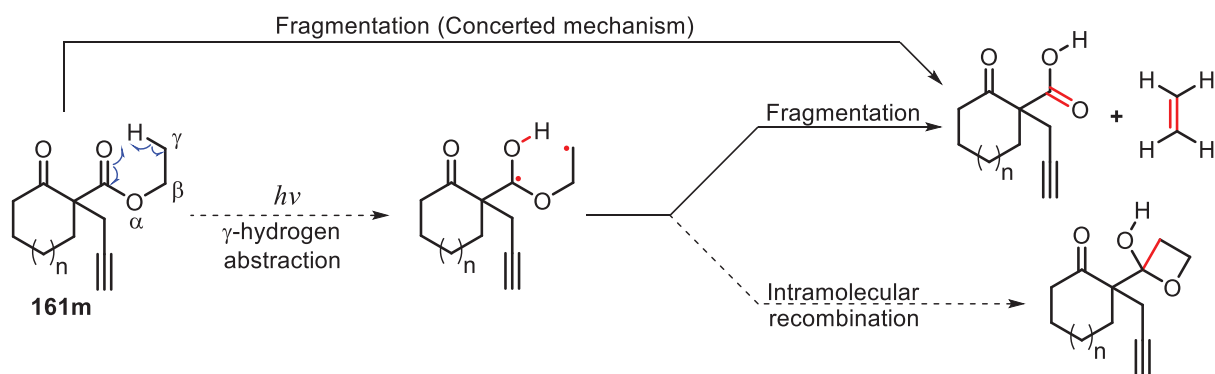
Entry	SM ^a	n	R ₁	t (h) ^b	λ (nm) ^c	Product	%Yield ^d
1	161k	0	Et	24	380-700	166a	- ^e
2	161k	0	Et	24	300	166a	Traces
3	161k	0	Et	38	254	166a	7
4	161k	0	Et	48	254	166a	12
5	161k	0	Et	118	254	166a	12
6	161j	0	Me	44	254	166a	13
7	161j	0	Me	48	254	166a	13
8	161l	1	Me	70	300	166b	Traces
9	161m	1	Et	64	254	166b	19
10	161m	1	Et	48	254	166b	19
11	161l	1	Me	48	254	166b	21

^a[161j-m] = 0.1- 0.125 M. ^bIrradiation time. ^cIrradiation wavelength. ^dIsolated yield. ^eNo reaction.

Similarly, no reaction of **161k** was observed when exposed to visible light for 24 hours (Entry 1). However, when irradiated at 254 nm for 48 hours, the yield of the appropriate bicyclic γ -lactone

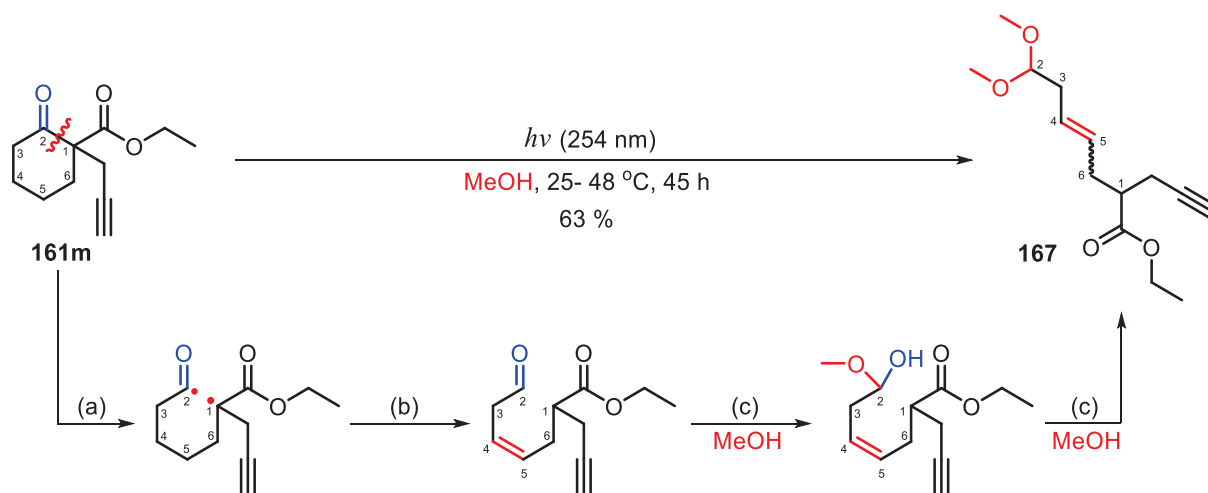
161l rose to 21% with a conversion of 60% of the starting material (Entry 11). By applying these conditions to ketoesters **161j-k**, the yield decreased by nearly half (Entries 4-7).

Presumably, the 6-membered ring has a greater impact on the stabilization of the generated hydroxymethyl radical, thus increasing the rate of coupled electron transfer with oxidized methanol. This hypothesis may explain the yield gap between the 5- and 6-membered ring adducts during the photochemical process. Moreover, it has been supposed that the ethyl ester group could influence the yield due to secondary reactions, such as intramolecular abstraction of a γ -hydrogen known as Norrish type II (Scheme 6).^[14] In contrary to this hypothesis, **161j-k** were isolated in similar yields (12- 13%) when irradiated under the same reaction condition (Entries 4, 7), likewise, **161l-m** (19-21% yield) (Entries 10, 11), meaning that there is no real impact of ethyl ester on the reaction yield.



Scheme 6. The presumed photochemical transformation of **161m** *via* Norrish type II reaction.

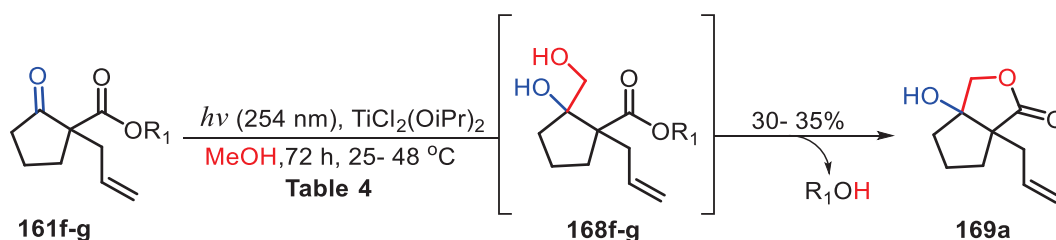
In light of these results, we suspected that the starting material **161j-m** might be a source of undesired reactivity under the applied conditions. To evaluate the nature of this reactivity, a control reaction has been tested in which the optimal conditions were applied to ketoester **161m** in the absence of titanium catalysis (Scheme 7). Instead of the expected lactone **166b**, compound **167** was isolated as a mixture of inseparable *E/Z* isomers in 63 % yield after 45 hours of continuous irradiation. This product unambiguously results from a homolytic α -cleavage (Norrish type I),^[15] followed by a hydrogen abstraction and ketal formation *via* subsequent condensation of the formed primary aldehyde formed with the solvent. By comparing this result to those obtained using titanium catalysis, we were convinced about the reactivity of ketoesters **2a-d** upon such conditions. Consequently, we sought to improve the yield of the entire transformation by following an alternative method shown at the end of this chapter.



Scheme 7. Photochemical irradiation of **161m** in methanol in the absence of titanium catalysis. Reactions: (a) homolytic α -cleavage (Norrish type I); (b) hydrogen abstraction. (c) ketal formation *via* subsequent condensation with methanol.

5.1. Synthesis of an allyl bicyclic γ -lactone

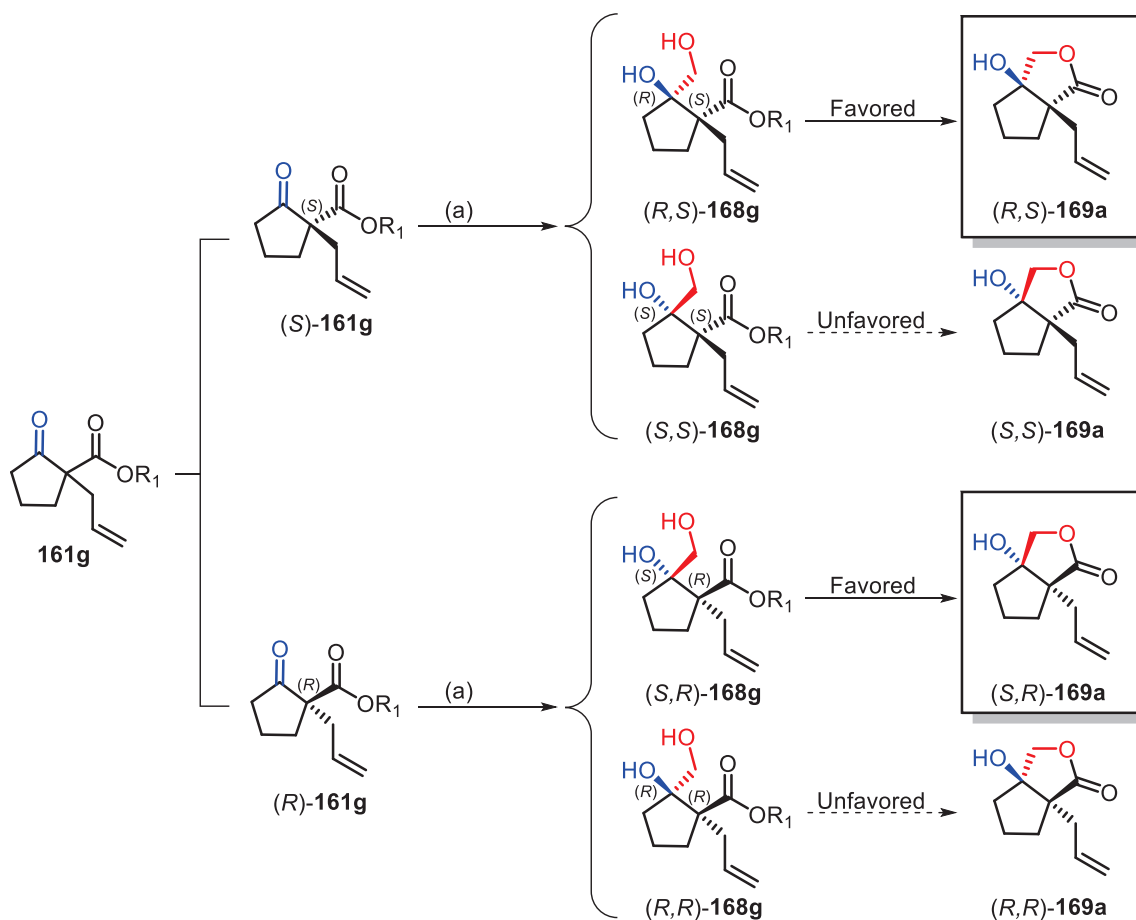
To explore the reaction with different substrates, we turned our attention to the allyl ketoesters **161f-g**, which were subjected to similar reaction conditions used to prepare the bicyclic γ -lactones **166a-b**. In contrary to the photohydroxymethylation of propargyl adducts, this reaction was different in terms of irradiation time and reaction yield (scheme 8). When irradiated at 254 nm for 72 hours in methanol, **161f-g** afforded heavy black-violet crude mixture. Its extraction from titanium salts followed by chromatography gave the bicyclic γ -lactone **169a** in a 30- 35% yield. Tuning some parameters like the molar ratio of the catalyst, substrate concentration and reaction time improved neither the reaction yield nor the conversion of the starting ketoester, but rather



Scheme 8. Photochemical hydroxymethylation of allyl ketoesters **161f-g**.

made them worse in some cases. For instance, using 0.75- 1 equivalent of $\text{TiCl}_2(\text{OiPr})_2$, instead of 0.5 equivalent, led to considerable degradation of the reaction mixture over continuous irradiation.

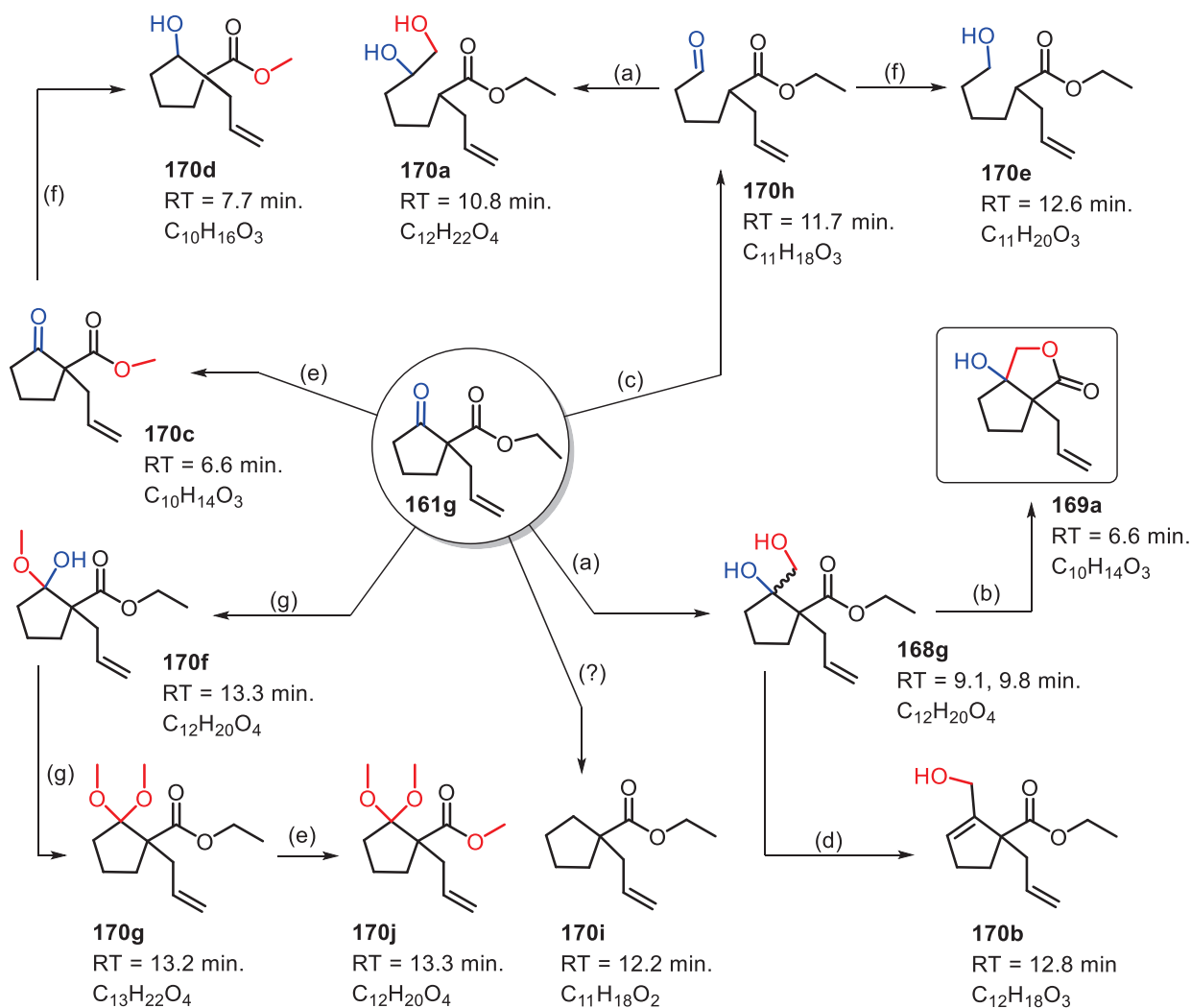
By taking a closer look to the reaction sequence, the formed diols **168f-g** were supposed to undergo further *syn*-cyclization when the hydroxymethyl group is on the same side to that of the adjacent ester. However, *anti*-cyclization would be unfavored at this level, due to ring strain. By considering the rate of hydroxymethylation of both enantiomers (*S*)-**161g** and (*R*)-**161g** to be the same, we proposed the formation of four stereoisomers of diol **168g**, in which two of them would cyclize to afford lactones (*R,S*)-**169a** and (*S,R*)-**169a**. Whereas, diols (*R,R*)-**168g** and (*S,S*)-**168g** would be blocked without any further lactonization (Scheme 9).



Scheme 9. Favored vs. unfavored *in situ* lactonization starting from racemic starting material **161g**. (a) *hν* (254 nm), $\text{TiCl}_2(\text{OiPr})_2$, MeOH, 72 h, 25- 48 °C.

Our attempts to isolate the uncyclized diols and other byproducts from the reaction mixture have been challenging, due to purification difficulties. However, thanks to UPLC-HRMS analysis, we were able to conclude 13 structures out of 21, resulting from the crude sample of **161g** after irradiation for 72 hours. A series of presumed transformations of these structures are shown in

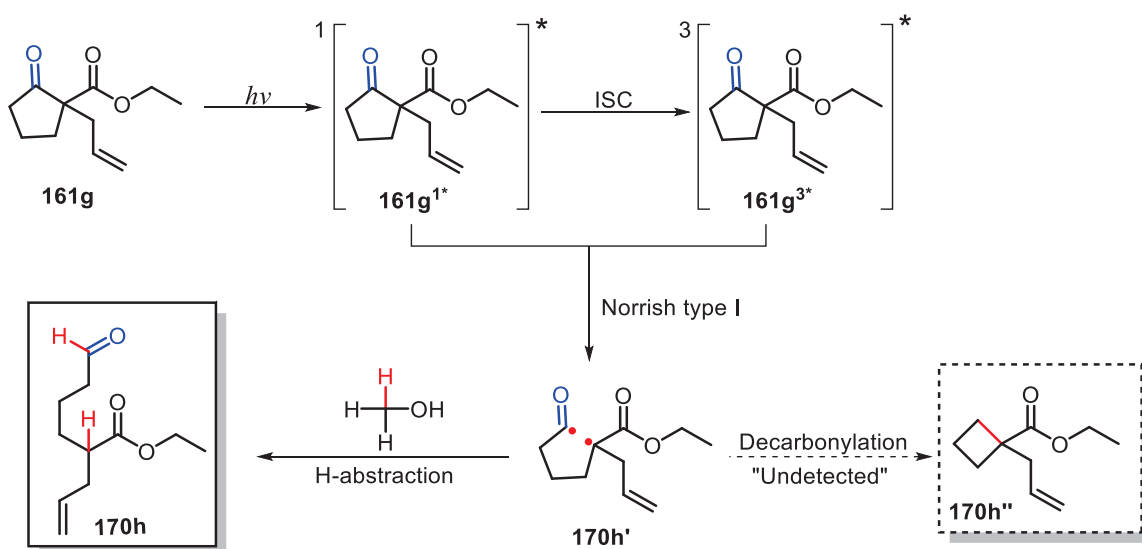
Scheme 10. The performed analysis revealed different photochemical and thermal side reactions that led to a variety of cyclic and acyclic compounds. For example, hydroxymethylation, photoreduction and homolytic α -cleavage (Norrish type I) were the dominant photochemical processes. On the other hand, transesterification, nucleophilic addition, and elimination were the major thermal reactions after long reaction time at elevated temperature.



Scheme 10. Some concluded structures and presumed transformations from UPLC-HRMS analysis. Column conditions: Luna Omega C18, 5cm \times 2.1cm; 1.6 μ m; mobile phase: (A) Ultrapure water + 0.1% formic acid, (B) Methanol + 0.1% formic acid; Flow rate: 500 μ L/min; Injection volume: 3 μ L. Reactions: (a) Photochemical hydroxymethylation; (b) *In situ* lactonization; (c) Homolytic α -cleavage (Norrish type I) followed by hydrogen abstraction; (d) Alcohol elimination; (e) Transesterification; (f) Ketone reduction; (g) Nucleophilic addition of methanol.

Here is a brief overview of the major photochemical and thermal processes: Photohydroxymethylation: This reaction resulted in the formation of diols **168g**, which were then transformed according to their stereochemistry to two different compounds **169a** and **170b** (Mechanism is clarified in Chapter 1).

Norrish type I/ Homolytic α -cleavage and hydrogen abstraction: Homolytic cleavage of the α -bond, often followed by decarbonylation, is one of the most common reactions of excited ketones. This process can be accompanied by competing processes, and its quantum yield is directly related to the stability of the radicals formed. In general, the n,π^* excited ketones undergo much faster cleavage than those with the lowest π,π^* excited state, because the σ -orbital of a bond being cleaved overlaps with the half-vacant n -orbital on the oxygen atom.^[16]

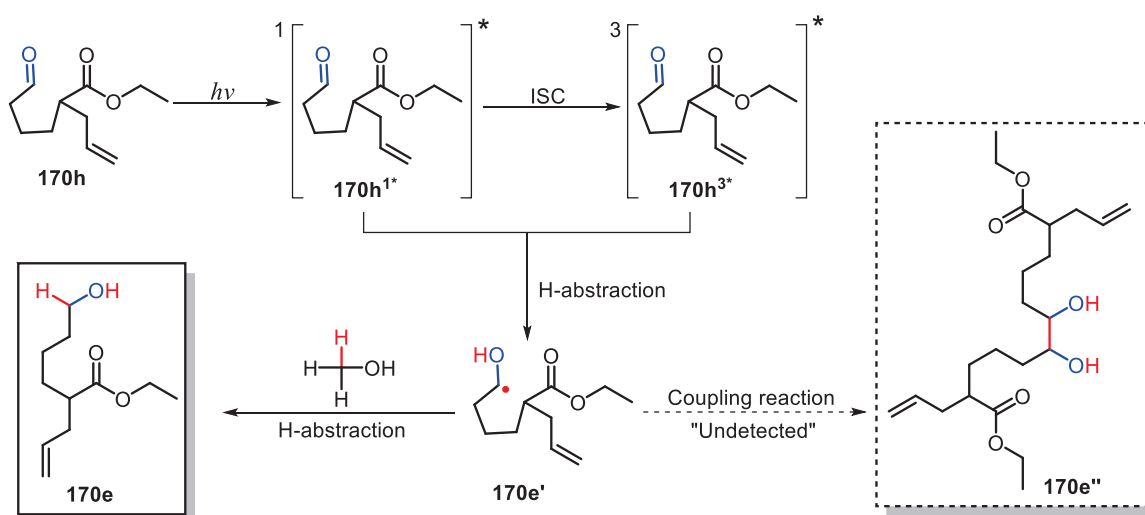


Scheme 11. Photochemical route for the detected compound **170h** via Norrish type I reaction (ISC = intersystem crossing).

Normally, the energy barriers for such cleavage in aliphatic n,π^* ketones in solutions range from nearly 0 to 65 kJ/mol, depending on the ketone structure and the spin multiplicity of the excited state.^[17] In the case of cyclic ketones, the release of the ring-strain energy during α -cleavage increases the exothermicity of the process.^[18] The cleavage rate constants of singlet n,π^* excited ketones are usually high ($k_I = 10^8$ – 10^9 s⁻¹) and they compare with those of intersystem crossing, whereas, triplet n,π^* state cleavage reactions (typically for aromatic ketones) are more efficient due to the longer triplet lifetimes and relatively large cleavage rate constants.^[29] In our case, ketoester **161g** might have undergone such cleavage after being excited photochemically to its

singlet or triplet states, (Scheme 11). Subsequent hydrogen abstraction from the solvent could then explain the formation of acyclic aldehyde **170h**. However, the suggested decarbonylation product **170h''** has not been detected.

Photoreduction: In a classical photoreduction reaction, an excited carbonyl compound, such as a ketone, undergoes hydrogen abstraction from a hydrogen donor to form the ketyl radicals, which subsequently abstract another hydrogen atom from the environment or recombine to form either alcohols or diols (Scheme 12).^[20] Photoreduction of aliphatic ketones may involve both singlet and triplet excited states, but the quantum yield for product formation *via* singlet is usually low because other competing processes, such as radical pair recombination, are involved. However, the rapid intersystem crossing (ISC) in aryl ketones allows triplet reactivity. Ketones with n,π^* lowest triplets, having an unpaired electron localized in an n-orbital on oxygen, are far more reactive than those with π,π^* lowest triplets.^[21]

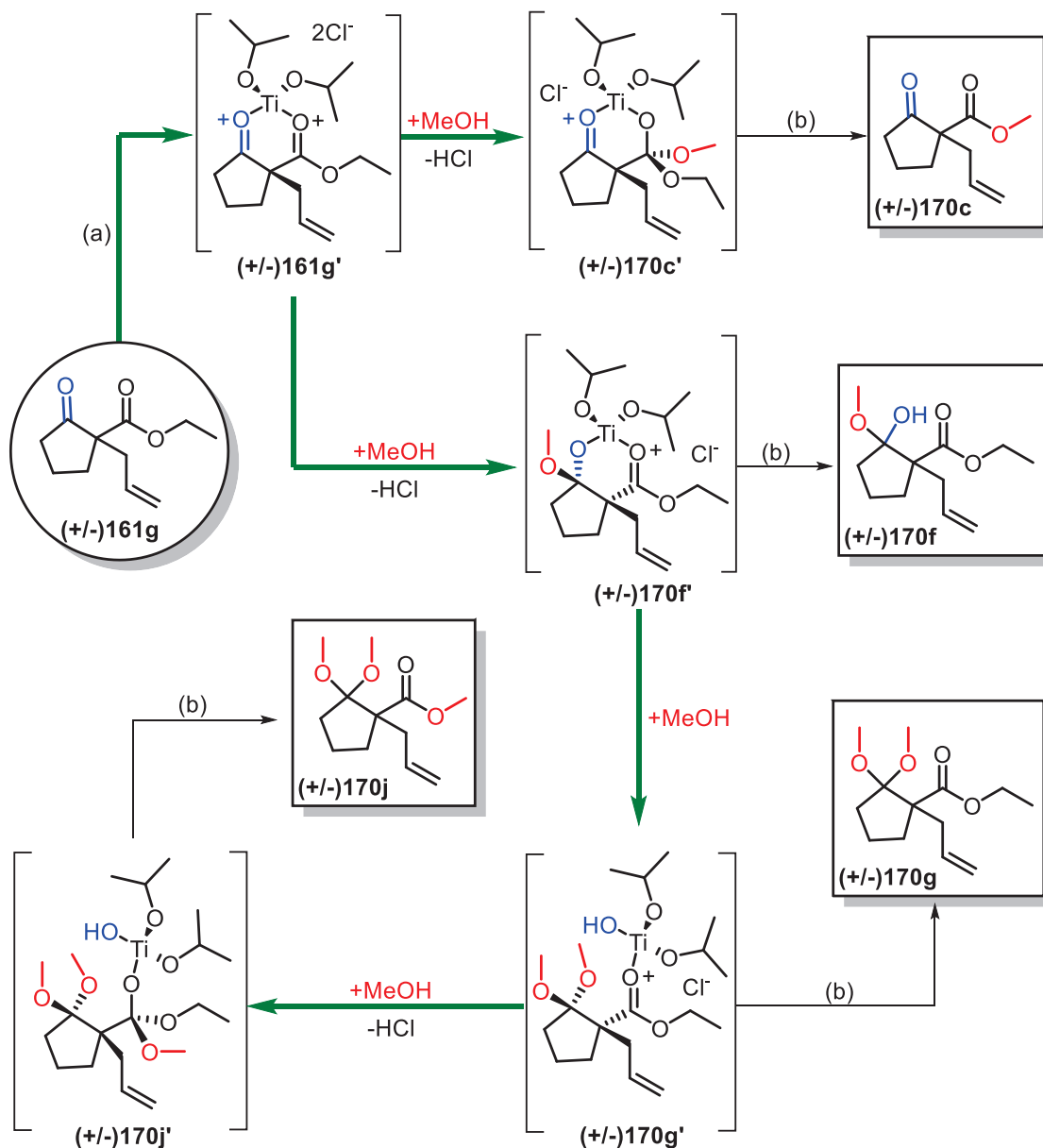


Scheme 12. Photoreduction of **170h** (ISC = intersystem crossing).

In the current study, the product of Norrish type I **170h** is suggested to be the mother structure of **170e** through a hydroxymethyl radical intermediate **170e'**. On the other hand, the coupling reaction of **170e'** by self-recombination, leading to diol **170e''**, was undetected.

Transesterification: $\text{Ti}(\text{O}i\text{Pr})_4$, as well as other titanium(IV) alkoxides, has been recommended as an exceptionally mild and efficient transesterification catalyst which can be used with many acid-sensitive substrates.^[22] The alcohol solvent employed in such processes does not need to be anhydrous, nor identical to the OR group of the titanate, because the exchange of these moieties is

generally slow compared to the transesterification reaction. This process might explain the formation of methyl esters **170c** and **170j** starting from ethyl esters **161g** and **170g** respectively (Scheme 13).



Scheme 13. Proposed thermal catalyzed processes including transesterification and nucleophilic addition of methanol upon irradiation of **161g**. (a) standard photochemical conditions; (b) Hydrolysis.

Acetalization: Titanium (IV)-catalyzed formation of acetal **170g** from hemiacetal **170f** is detailed in Scheme 13. The successive nucleophilic addition of methanol to ketoester **161g** might pass through the proposed titanium complex **170 f'**, which could either give the detected hemiacetal

product **170f** by hydrolysis or undergoes further methanol addition to afford complex **170g**'. The latter could be hydrolyzed at this level to furnish the detected acetal **170g**. It is noteworthy that there has been unambiguous competition between different thermal processes, particularly between acetalization and transesterification as demonstrated.

Even though titanium catalysis was behind the desired hydroxymethylation reaction, it was the major active species for some undesired thermal and photochemical processes. Other factors, such as long irradiation time, solvent polarity and sensitivity of the starting material, might have also been contributed to such unwanted reactions. Accordingly, this analysis can help us to better understanding the behavior of different chemical species throughout photochemical irradiation.

6. Photochemical hydroxymethylation of miscellaneous α -substituted alkyl 2-oxocycloalkanecarboxylates

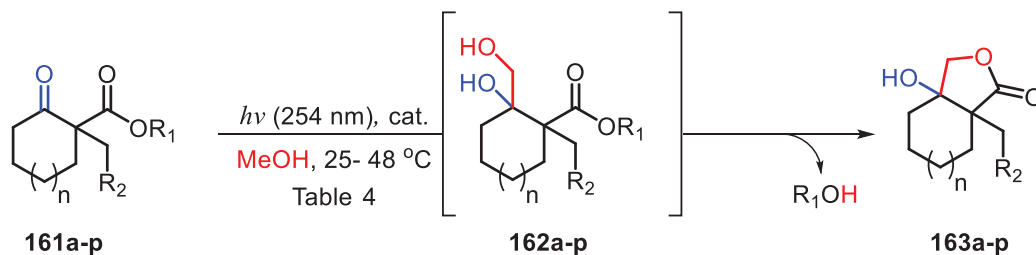
To extend the scope of the current photochemical hydroxymethylation, different α -alkylated starting ketoesters, with aliphatic or aromatic α -substituents, have been irradiated under the used optimal conditions with slight changes when needed.

As it can easily be noticed from Table 4, the attempts to get a variety of bicyclic γ -lactones have failed in almost all entries. When irradiated at 254 nm for 4 to 5 hours in the presence of $\text{TiCl}_2(\text{OiPr})_2$, traces of volatile lactone **163b** was obtained with the sluggish conversion of the starting material (Entry 3). Despite elongated irradiation time (72 hours), the reaction yield of lactone **163a** did not improve, but rather degradation took place and made the purification step more difficult (Entry 2). The decomposition of the reaction mixture was also observed when benzyl ketoester **161d** was continuously irradiated from 24 to 72 hours (Entries 6-7). In general, neither benzyl nor alkylacetyl bicyclic lactones **163d-p** were detected even after varying several reaction parameters (irradiation time, titanium catalysis, R_1 group...). However, despite being impure, methylbutenyl lactone **163o** was obtained in 10 to 16% yield, opening a new set of questions concerning its formation.

Several proposals, derived from previously obtained results and from that of Table 4, represent a reasonable explanation for such reactions. The volatility of certain products, such as lactones **163a-b**, might be a piece of evidence for the low reaction yield, but this fact cannot be generalized for other cases. For instance, propargyl bicyclic lactones **166a-b** were already isolated and they were not volatile. Presumably, intramolecular radical reactions were preferred to that of intermolecular

hydroxymethylation with oxidized methanol. Hence, the main reason behind the observed degradation and, in turn, the low reaction yield, could be the photochemical competitive reactions arising from α -cleavage (Scheme 14). After being formed, the free acyl radical possibly plays a significant role in the photodecomposition of the molecule from which it might be created.

Table 4. Photochemical hydroxymethylation reaction of **161a-p**.

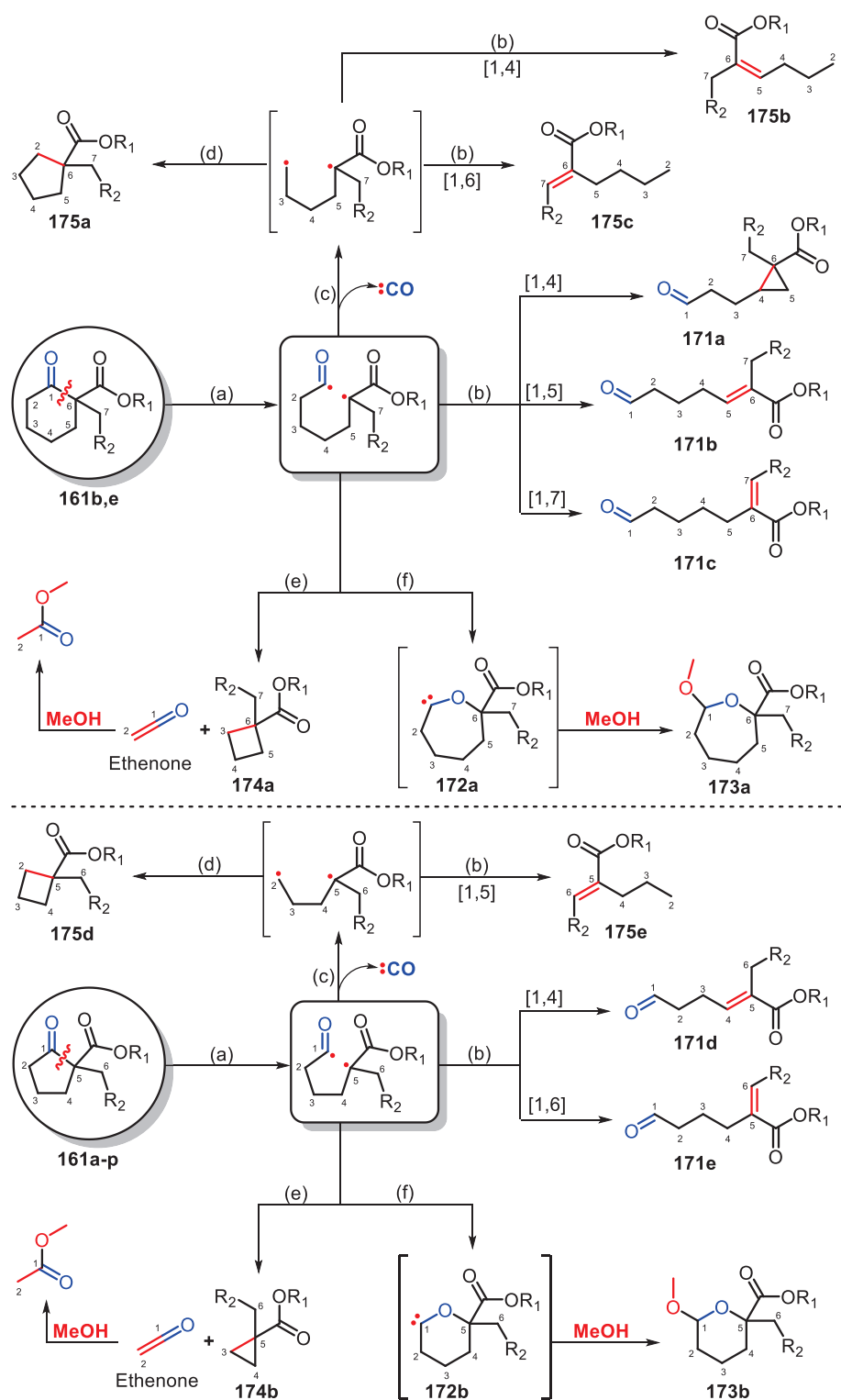


Entry	SM ^a	n	R ₁	R ₂	t (h) ^b	Catalyst ^g	Product	%Yield ^c
1	161a	0	Et	H	6	Ti(OiPr) ₄	163a ^d	- ^e
2	161a	0	Et	H	72	TiCl ₂ (OiPr) ₂	163a ^d	<10 ^f
3	161b	1	Et	H	4-5	TiCl ₂ (OiPr) ₂	163b ^d	<10
4	161d	0	Et	Ph	3	-	163d	- ^e
5	161d	0	Et	Ph	66	Ti(OiPr) ₄	163d	0
6	161d	0	Et	Ph	24	TiCl ₂ (OiPr) ₂	163d	^f
7	161d	0	Et	Ph	72	TiCl ₂ (OiPr) ₂	163d	^f
8	161e	1	Et	Ph	10	TiCl ₂ (OiPr) ₂	163e	- ^e
9	161n	0	Et	COOEt	86	TiCl ₂ (OiPr) ₂	163n	0
10	161o	0	Me	C(Me)=CH ₂	72	TiCl ₂ (OiPr) ₂	163o	10-16
11	161p	0	Me	COOMe ^h	72	TiCl ₂ (OiPr) ₂	163p	0

^a[**161a-b**]= 0.125 M. ^bIrradiation time; ^cIsolated yield; ^dHighly volatile; ^eNo reaction to slight conversion; ^fDegradation; ^g0.5 equivalence; ^hIrradiated at 300 nm.

Subsequently, this radical undergoes [1,*n*]- hydrogen atom abstraction from the environment to form compounds **171a-e**. In contrast to **161a-b**, the rate of [1,7] H-abstraction is suggested to be higher than that of [1,4], [1,5] and [1,6] in the case of compounds **161d-p**. These adducts possess different R₂ substituents, such as phenyl, alkylacetyl, and methylbutenyl, which can stabilize the radical at C₇, thus affording unsaturated esters **171c,e**.

Exhaustive photolysis of the starting ketoesters **161a-p** in methanol might also afford **173a-b**, products of ring expansion reaction through oxacarbene intermediates **172a-b**. However, the formation of compounds **174a-b** and ethenone is not expected, due to the instability of the primary



Scheme 14. Suggested photochemical side reactions of α -substituted ketoesters **161a-p**. (a) α -cleavage/Norrish type 1; (b) Hydrogen abstraction; (c) Decarbonylation; (d) Recombination; (e) Ketene formation; (f) Ring expansion.

radical intermediates. Another possible photochemical side reaction might be the decarbonylation of acyl radicals. The rate of this reaction is primarily related to the stability of the corresponding alkyl radicals formed.^[23] In our case, decarbonylation could have resulted in the formation of primary radicals, which are unstable enough to undergo further reactions. Therefore, we did not expect the construction of compounds **175a-e**.

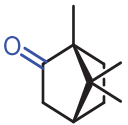
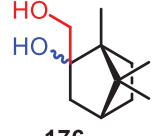
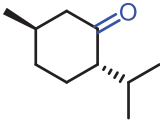
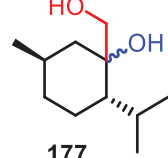
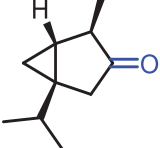
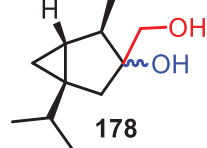
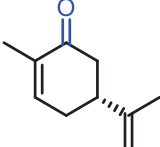
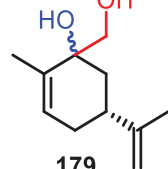
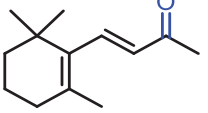
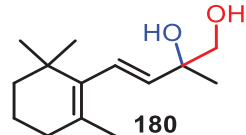
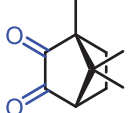
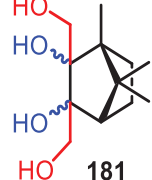
7. Photochemical hydroxymethylation of various terpenoids

As a partial replacement to fossil fuel-based routes, plant-based chemicals are increasingly being evaluated as chemical building blocks to other chemicals.^[24] This trend potentially opens the door to new sustainable alternatives for reducing dependence on fossil feedstocks as well as for reducing greenhouse gas emissions all along the production chains, thus enlarging the impact of natural products to areas beyond drug, perfume, and food industries.^[25]

Besides the recovery of valuable molecules from wastes, the development of synthetic methods for the large-scale production of molecules, which are not highly abundant in wastes, is emerging. The study herein focused on the photochemical hydroxymethylation of cyclic terpene ketones to obtain new functionalized compounds of high value. The chosen commercially available terpenoid has been irradiated at 254 nm in methanol by varying both the titanium catalysis and the irradiation time as detailed in Table 5. Upon long irradiation time (>67 hours), regardless of titanium catalyst, most of the experimented substrates underwent excessive degradation and hence their analysis was so complicated (Entries 1-5). In contrast, short irradiation time (<11 hours) with TiCl₄ resulted in a sluggish conversion of the starting material (Entries 1-3, 6). Unfortunately, the desired hydroxymethylation product was detected only in a few experiments from low to moderate yields. For example, traces of diol **176** was obtained after irradiating (+)-camphor from 3 to 6 hours in the presence of TiCl₄, and the use of other catalysts did not improve the reaction yield (Entry 1). Best results were obtained with menthone after its irradiation for 72 hours in the presence of TiCl₂(OiPr)₂ to afford diol **177** in 54% yield (dr 7:1) (Entry 1). By trying the same reaction for 137 hours, **177** was hardly isolated in 16% yield due to excessive degradation of the reaction mixture. In case of thuyone, similar results were obtained when irradiated with either TiCl₄ or TiCl₂(OiPr)₂ for 10 or 68 hours, respectively. The resulting diol **178** was then isolated in 20% to 23% yield (dr 3:1) as a pale-yellow oil. The low diastereoselectivity in this reaction can be related to the enantiopurity of the starting material. Apart from cyclic terpene ketones, we wanted to

reinvestigate the photochemical behavior of (-)-carvone, β -ionone, and isophorone, possessing an enone as a common functional group, under similar reaction conditions. The photoinduced addition of alcohols to enones dates back to 1957 when, in connection with a synthesis of terebic acid, Schenck *et al.* added isopropanol to maleic acid.^[26] Twenty years later, Sato *et al.*^[27] reported that α,β -unsaturated ketones, when irradiated in alcohol in the presence of titanium (IV) chloride,

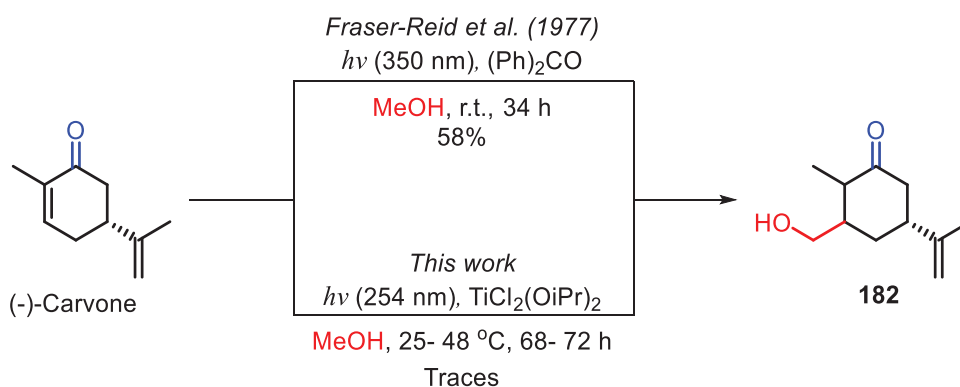
Table 5. Photochemical hydroxymethylation of different ketones.

SM ^a	Structure	t (h) ^b	Catalyst	Product	%Yield ^c
1 (+)-Camphor		3-6	TiCl ₄	 176	8
		72	Ti(OiPr) ₄		-
		3	TiCl ₂ (OiPr) ₂		-
		30	TiCl ₂ (OiPr) ₂		-
		72	TiCl ₂ (OiPr) ₂		- ^e
2 Menthone		3	TiCl ₄	 177	-
		72	Ti(OiPr) ₄		-
		12	TiCl ₂ (OiPr) ₂		29
		72	TiCl ₂ (OiPr) ₂		54 ^d
		137	TiCl ₂ (OiPr) ₂		16 ^e
3 Thuyone		10	TiCl ₄	 178	23
		9	TiCl ₂ (OiPr) ₂		-
		68	TiCl ₂ (OiPr) ₂		20 ^e
4 (-)-Carvone		48	TiCl ₂ (OiPr) ₂	 179	- ^f
		67	TiCl ₂ (OiPr) ₂		- ^e
5 β -Ionone		67	TiCl ₂ (OiPr) ₂	 180	- ^e
6 Camphorquinone		5	TiCl ₄	 181	-

^aStarting material; ^bIrradiation time; ^cIsolated yield; ^ddr (7: 1); ^eDegradation; ^f1,4-addition product was isolated.

underwent different types of reactions with a formation of a C-C bond between the carbonyl carbon atom and the α -carbon atom of the chosen alcohol (1,2 addition).

The photoinduced addition of alcohols to enones dates back to 1957 when, in connection with a synthesis of terebic acid, Schenck *et al.* added isopropanol to maleic acid.^[26] Twenty years later, Sato *et al.*^[27] reported that α,β -unsaturated ketones, when irradiated in alcohol in the presence of titanium (IV) chloride, underwent different types of reactions with a formation of a C-C bond between the carbonyl carbon atom and the α -carbon atom of the chosen alcohol (1,2 addition). However, 1,4 addition was observed in the uranyl chloride-catalyzed reactions. In the same year, Fraser-Reid and coworkers reported the photochemical induced conjugate addition of simple alcohols to a variety of α -enones. The authors described the irradiation of carvone for 34 hours in methanol in the presence of benzophenone to give its corresponding keto alcohol **182** in moderate yield (58%) (Scheme 15).^[28]



Scheme 15. The photochemically induced conjugate addition of methanol to (-)-carvone.

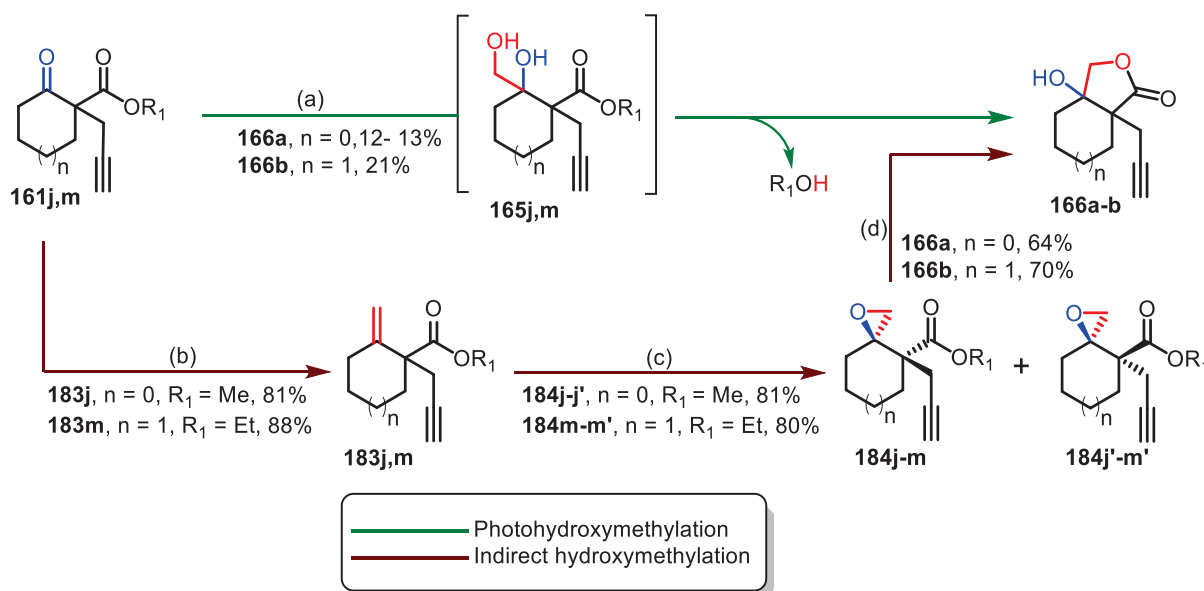
To explore the type of reactions taking place upon the irradiation of the experimented enones, we intended to isolate one of the formed products from the degraded mixture of carvone. Instead of the 1,2 addition product, the corresponding 1,4 addition product **182** was obtained in trace amount (Scheme 15). Likewise, methanol is expected to be added in a 1,4 manner to β -ionone which was completely degraded after 67 hours of continuous irradiation, thus making its analysis easier said than done. Finally, camphorquinone degraded into 4 nonpolar compounds after 5 hours of continuous irradiation. Presumably, the formed products are due to the Norrish type 1 reaction (detailed in the previous section).

According to the results mentioned above, despite similar reaction conditions, different outcomes were observed upon the irradiation of different terpenoids. Therefore, the structure of the used

substrate determines its stability and, in turn, its intramolecular or intermolecular reactivity. Moreover, it can be concluded that chlorotitanium catalysts are crucial for the desired reaction path because $\text{Ti}(\text{OiPr})_4$ showed no activity when experimented (Entries 1-2).

8. An alternative method to photochemical hydroxymethylation

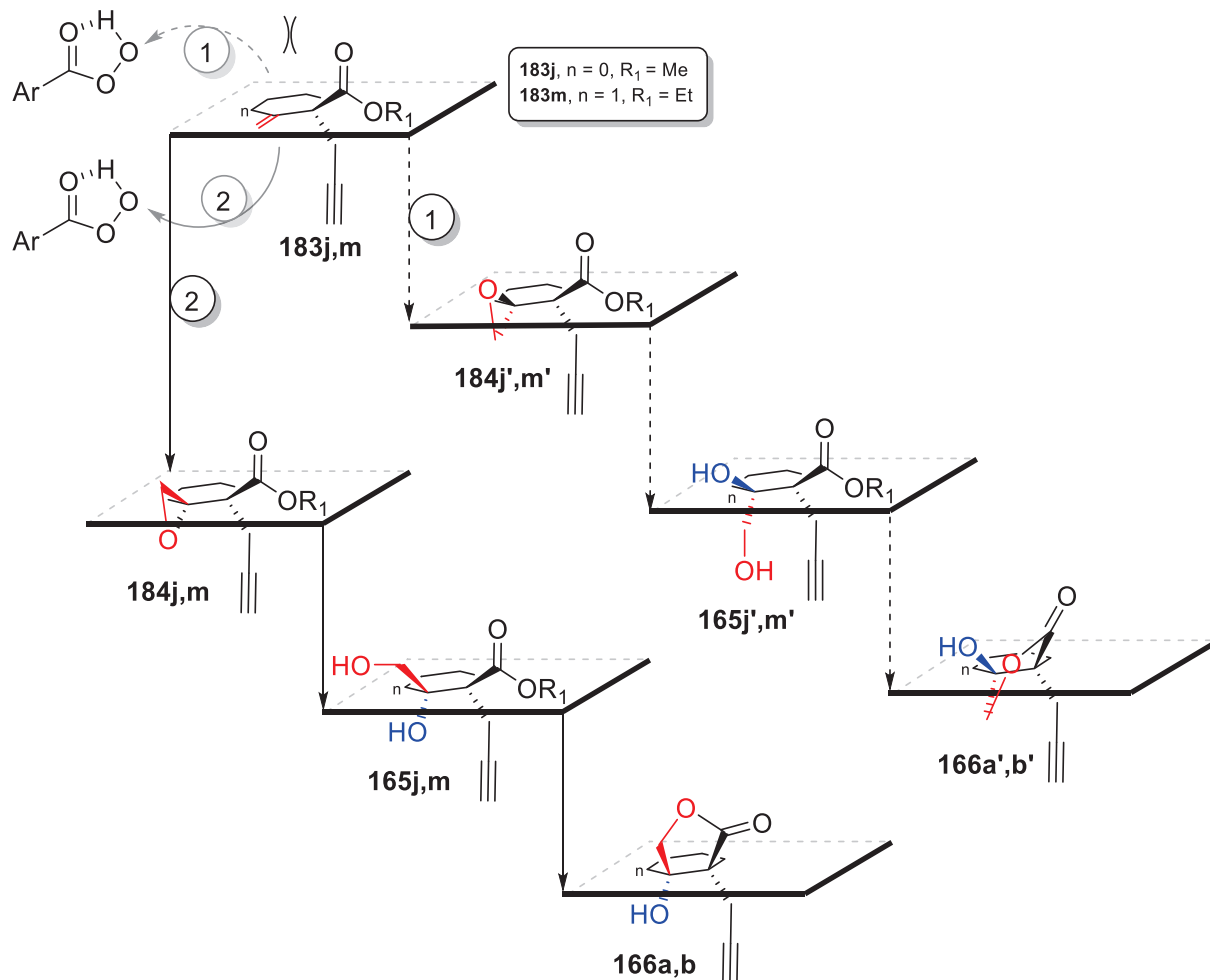
As noticed from the previous experiments, photochemical hydroxymethylation has not proven to be as efficient as other synthetic strategies used for the same purpose (Chapter 1). For this reason, we sought to improve the yield of the entire transformation by following an indirect strategy. Because further exploitation of the synthesized propargyl bicyclic γ -lactones was anticipated for the synthesis of novel molecular skeletons, the alternative method was first applied on propargyl ketoesters **161j,m** (Scheme 16).



Scheme 16. Photohydroxymethylation vs indirect hydroxymethylation starting from **161j,m**. Reagents and conditions: (a) $h\nu$ (254 nm), $\text{TiCl}_2(\text{OiPr})_2$, MeOH, 25- 48 °C, 48- 72 h; (b) MePPh_3Br , $t\text{-BuOK}$, toluene, r.t., 21- 24 h; (c) $m\text{-CPBA}$, DCM, r.t., 17- 23 h; (d) H_2O : DCM (2: 1), HCl (cat.), 70 °C, 4-5 h.

This new synthetic plan started from the formation of unsaturated esters **183j,m** that can readily be prepared *via* a classical Wittig reaction in good yields.^[29] Epoxidation of **183m** with $m\text{-CPBA}$ in CH_2Cl_2 at room temperature furnished a separable mixture of diastereomeric oxiranes **184m/184m'** in 80% yield (1.6:1, determined by ^1H NMR analysis of the crude reaction product). The same experimental protocol was then repeated with **183j**. We also observed the formation of an inseparable mixture of diastereoisomers **184j/184j'** (2.3:1) in 81% yield. The presence of an

ester group close to the double bond contributes to enhance the diastereoselectivity of this epoxidation (Scheme 17).



Scheme 17. Stereochemistry of the indirect hydroxymethylation.

The spiroepoxide moieties of compounds **184j** and **184m** were then opened by gentle heating in a mixture of water and dichloromethane (2:1) in the presence of catalytic amounts of HCl over 4-5 h. The primary alcohol of the corresponding hydroxymethylation products **165j,m** was trapped by the adjacent ester moiety *via in situ* lactonization, thereby affording 5- and 6-membered ring lactones **166a** and **166b** in 64% and 70% yield respectively. By comparing the indirect strategy with the photochemical one, it has been shown that the range of the overall yield of **166a,b** for the former route (~39% yield) is higher than that obtained from the photochemical pathway (12-21%

yield). However, in terms of purification effort and manipulation time, the photochemical step was preferred over the three-step sequence.

9. Conclusion

In summary, photochemical hydroxymethylation has been reviewed and studied on different α -substituted ketoesters and cyclic terpenic ketones. In most of the cases, the reaction was carried out at 254 nm in methanol in the presence of different titanium (IV) catalysts at 25- 48 °C. Bicyclic γ -lactones were obtained from their corresponding ketoesters *via* hydroxymethylation followed by *in situ* lactonization. These compounds are of high interest for the synthesis of novel propellanes as detailed in the subsequent chapters. Despite low reaction yields, sluggish conversion of the starting material and excessive degradation of the reaction mixture, this strategy remains as an efficient tool for the rapid synthesis of valuable building blocks in organic chemistry.

10. References

- [1] a) T. Sato, S. Yamaguchi, H. Kaneko, *Tetrahedron Lett.* **1979**, *20*, 1863-1864; b) T. Sato, H. Kaneko, S. Yamaguchi, *J. Org. Chem.* **1980**, *45*, 3778-3782.
- [2] A. G. Griesbeck, S. Buhr, J. Lex, *Tetrahedron Lett.* **1998**, *39*, 2535-2536.
- [3] A. G. Griesbeck, M. Reckenthäler, *Beilstein J. Org. Chem.* **2014**, *10*, 1143-1150.
- [4] a) M. Kamigaito, M. Sawamoto, T. Higashimura, *Macromolecules* **1995**, *28*, 5671-5675; b) M. T. Reetz, J. Westermann, R. Steinbach, B. Wenderoth, R. Peter, R. Ostarek, S. Maus, *Chem. Ber.* **1985**, *118*, 1421-1440.
- [5] W. J. Le Noble, *Synthesis* **1970**, 1-6.
- [6] A. Brandstorm, G. Strandlund, *Acta Chem. Scand. B* **1978**, *B32*, 489-498.
- [7] S. Benetti, R. Romagnoli, C. De Risi, G. Spalluto, V. Zanirato, *Chem. Rev.* **1995**, *95*, 1065-1114.
- [8] a) N. T. Tzvetkov, P. A. Waske, B. Neumann, H. G. Stammler, J. Mattay, *Tetrahedron Lett.* **2008**, *49*, 1710-1713; b) K. Mori, M. Matsui, *Tetrahedron* **1966**, *22*, 879-884.
- [9] M. Peifer, R. Berger, V. W. Shurtleff, J. C. Conrad, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2014**, *136*, 5900-5903.
- [10] S. P. Singh, J. Kagan, *Chem. Commun.* **1969**, 1121-1121.
- [11] I. Fukuchi, Y. Hamashima, M. Sodeoka, *Adv. Synth. Catal.* **2007**, *349*, 509-512.
- [12] S. Mouri, Z. Chen, S. Matsunaga, M. Shibasaki, *Chem. Commun.* **2009**, 5138-5140.
- [13] V. Lecomte, C. Bolm, *Adv. Synth. Catal.* **2005**, *347*, 1666-1672.
- [14] J. C. Scaiano, E. A. Lissi, M. V. Encina, *Res. Chem. Intermed.* **1978**, *2*, 139-196.
- [15] J. N. Pitts, F. E. Blacet, *J. Am. Chem. Soc.* **1950**, *72*, 2810-2811.

- [16] a) W. M. Jackson, H. Okabe, *Adv. Photochem.* **1986**, *13*, pp. 1-94 ;b) F. D. Lewis, J. G. Magyar, *J. Org. Chem.* **1972**, *37*, 2102-2107.
- [17] P. Klán, J. Wirz, *Photochemistry of organic compounds: From concepts to practice*, John Wiley & Sons, Chichester, **2009**.
- [18] E. W-G.Diau, C. K. Kötting, A. H. Zewail, *ChemPhysChem* **2001**, *2*, 294-309.
- [19] F. Lewis, J. Magyar, *J. Am. Chem. Soc.* **1973**, *95*, 5973-5976.
- [20] G. Ciamician, P. Silber, *Chem. Ber.* **1900**, *33*, 2911–2913.
- [21] P. Wagner, B. S. Park, in *Organic photochemistry, Vol. 11*, CRC Press, Ed. A. Padwa, New York, **1991**, pp. 227-366.
- [22] a) R. Imwinkelried, M. Schiess, D. Seebach, *Org. Synth.* **1987**, *65*, 230-235; b) N. L’Hermite, J. Peyrat, P. Hildgen, J. Brion, M. Alami, *Synthesis* **2008**, 1049-1060; c) M. Mader, P. Helquist, *Tetrahedron Lett.* **1988**, *29*, 3049-3052.
- [23] M. Garcia-Garibay, L. Campos, in *Handbook of Organic Photochemistry and Photobiology*, CRC Press LLC, Boca Raton, **2004**, pp. 1–41.
- [24] A. Corma, S. Iborra, A. Velty, *Chem. Rev.* **2007**, *107*, 2411-2502.
- [25] G. Rubulotta, E. Quadrelli, in *Stud. Surf. Sci. Catal., Vol. 178* (Eds.: S. Albonetti, S. Perathoner, E. A. Quadrelli), Elsevier, **2019**, pp. 215-229.
- [26] G. O. Schenck, G. Koltzenburg, H. Grossmann, *Angew. Chem.* **1957**, *69*, 177-178.
- [27] T. Sato, S. Yoshiie, T. Imamura, K. Hasegawa, M. Miyahara, S. Yamamura, O. Ito, *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2714-2730.
- [28] B. Fraser-Reid, N. L. Holder, D. R. Hicks, D. L. Walker, *Can. J. Chem.* **1977**, *55*, 3978-3985.
- [29] H-Y. Lee, D. K. Moon, J. S. Bahn, *Tetrahedron Lett.* **2005**, *46*, 1455-1458.

Chapter III

Propellanes— from Allyl Bicyclic
 β -Hydroxy- γ -Lactones

Ch. III: Propellanes— from Allyl Bicyclic β -Hydroxy- γ -Lactones

1. Introduction

Propellane is a unique class of polycyclic hydrocarbons, whose skeleton consists of three rings of carbon or hetero atoms sharing a common central single covalent bond.^[1] The name was stemmed primarily from a supposed analogy of the molecule to a propeller: namely, the rings would be the propellers' blades, and the shared C–C bond would be its axis (Figure 1).

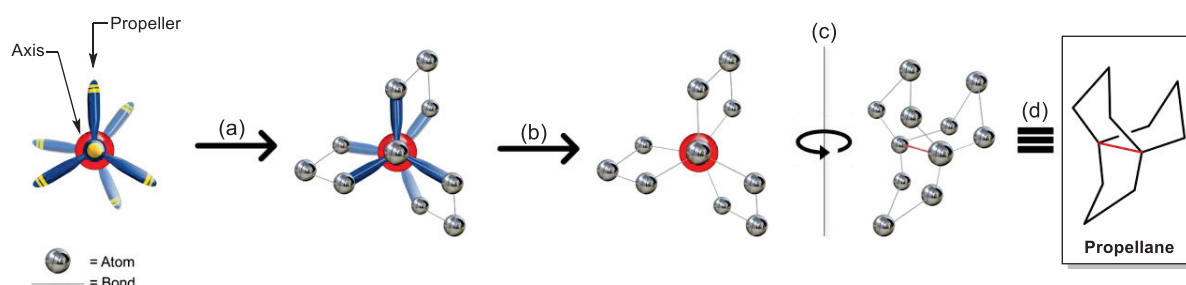


Figure 1. A supposed resemblance of propellane to a propeller. (a) Atom distribution; (b) Propellers removal; (c) Rotation by 45°; (d) Structural equivalence in organic chemistry.

1.1. Nomenclature

In 1966, Bloomfield and Irelan reported a synthesis of [4.4.2]propellane **185f** (Figure 2) and used the term “propellerane” in this context,^[2] but the editors did not accept this nomenclature^[3] and the compound was reported as 9,10-dihydro-9,10-ethanonaphthalene. In the same year, Ginsburg and co-workers introduced the name “propellane” in a paper about the syntheses of a variety of different structures, without editorial dissent.^[4]

Accordingly, $[x.y.z]$ propellane means the member of the family whose rings have x , y , and z carbon or heteroatoms, without counting the two bridgeheads. The minimum value for x , y , and z is 1, meaning a 3-carbon ring. There is no structural ordering between the rings, so, for example, [1.3.2]propellane is the same substance as [3.2.1]propellane. Therefore, it is customary to sort the indices in decreasing order, $x \geq y \geq z$ (Figure 2).

This nomenclature is more easily understood than that of the systematic IUPAC. For example, the systematic name for [1.1.1]propellane is tricyclo[1.1.1.0^{1,3}]pentane. In other words, an $[i.j.k]$ propellane would have the systematic name tricyclo[$i.j.k.0^{1,i+2}$]($i+j+k+2$)ane.^[1a, 5]

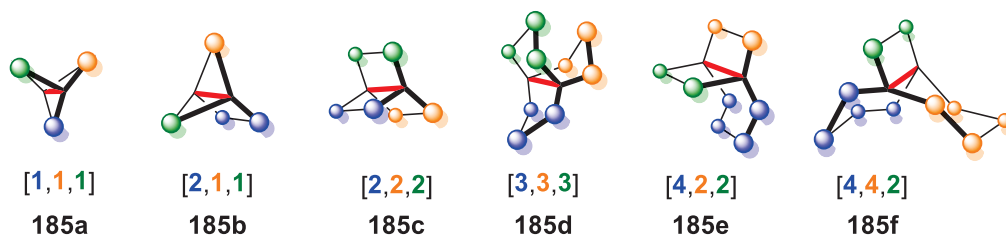
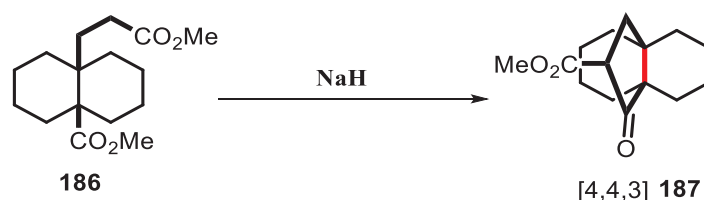


Figure 2. Different propellane ring systems **185a-f**.

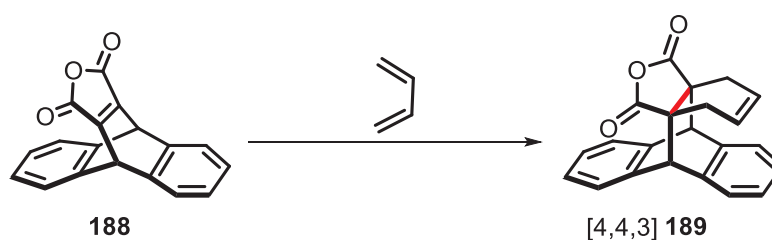
1.2. History

Although David Ginsburg has been one of the main contributors to propellane chemistry, he was not the first one to design their synthesis. The first planned synthesis of a propellane—without coining the name—was executed by Günther Snatzke at the University of Bonn in 1965 (Scheme 1). The uniqueness of three rings fused by one common bond was highlighted in the publication title: “Compounds with three rings bridging one C-C bond, part I”.^[6]



Scheme 1. First designed synthesis of a propellane ring-system by Snatzke and Zanati.

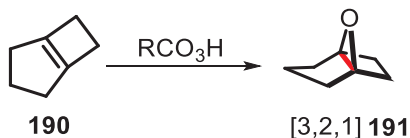
However, propellanes started to appear in the literature long before 1965.^[7] Diels and Friedrichsen, initially focusing on [4+2] cycloaddition reactions, came upon the first propellane compounds in 1934 by the reaction of the bridged maleic anhydride **188** with various 1,3-dienes,^[8] for example, 1,3-butadiene, as shown in Scheme 2.



Scheme 2. The first synthesis of a propellane by Diels and Friedrichsen in 1934.

The first small-ring [4.2.2]propellanes **185e** (Figure 2) were obtained by Wittig and Mayer from *in situ* generated cyclohexyne, which underwent tetramerization *via* bicyclohexene-annelated cyclobutadienes.^[9] Five years later, Wiberg and coworkers synthesized [3,2,1]propellane **191** from the epoxidation of bicyclo[3.2.0]hept-1(5)-ene **190** (Scheme 3).^[10] Since then, because of their

aesthetically appealing structural architecture, the term propellane has begun to emerge in the literature to occupy a special place in synthetic organic chemistry.



Scheme 3. The first synthesis of a small-ring propellane by Wiberg in 1968.

2. General properties

2.1. Strain

In the propellanes with small cycles, the two carbon atoms at the ends of the axial bond will be highly deformed, and their bonds may even assume an inverted tetrahedral geometry (Figure 3).

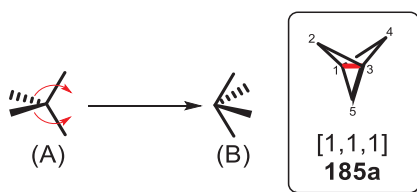
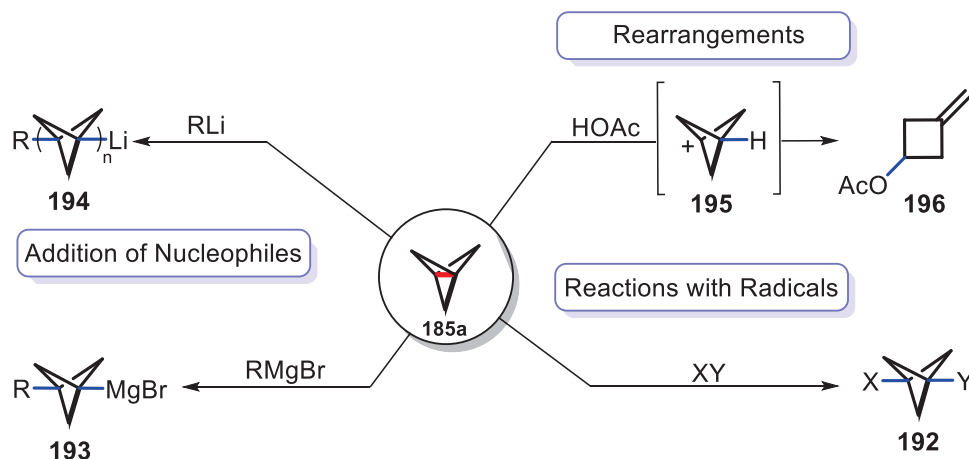


Figure 3. Severe distortion of idealized tetrahedral geometry in [1,1,1]propellane. (A) tetrahedral geometry; (B) Inverted tetrahedral geometry.

From a theoretical point of view, the most interesting propellane is [1.1.1]propellane **185a** (Figure 3). The reports of the first modeling studies concluded that **185a** should be more stable than the corresponding diradical that lacks the conjoining bond.^[11] However, the researchers were uncertain that **185a** could ever exist. A decade later, Wiberg and Walter reported the synthesis and isolation of this surprisingly stable molecule, [1.1.1]propellane.^[12] The nature of the central bond of the molecule has been the subject of many studies. The theoretical and experimental results of many different research groups agree on the special nature of the bond.^[13] Some groups have questioned the existence of the central bond,^[11, 14] but Wiberg, Bader, and Lau argue cogently that the bond definitely exists between the bridgehead carbon atoms with a bond order of 0.73.^[15] The controversy regarding the central bond revolves around different explanations of similar experimental facts and theoretical results of the nature of the bonding interaction. In addition to Wiberg's results, other theories have also been suggested.^[16] To date, because of inconsistent data, the true nature of the central bond remains uncertain.

2.2. Reactivity and reactions of propellanes

In general, strain relief is the main driving force controlling the reactivity of **185a** and allowing the bridgehead atoms to acquire the favored non-inverted geometry. This occurs by breaking the central propellane bond to yield a bicyclo[1.1.1]pentyl moiety. Under some conditions a bridging bond is broken in addition to the central bond, thereby yielding three- or four-membered-ring derivatives.^[1a] Reactions with radicals proceed rapidly, almost without the occurrence of oligomerization under appropriate reaction conditions (**192**, Scheme 4).^[17] Similarly, additions of nucleophiles to [1.1.1]propellane **185a** exhibit essentially a comparable picture to that of radical additions. For example, the addition of Grignard reagents proceeds rather slowly to yield the monomeric bicyclo[1.1.1]pentylmagnesium bromide **193**.^[18] In contrast, the addition of lithium organyl compounds often leads to bicyclo[1.1.1]pentyllithium oligomers **194**.^[19] Finally, the rearrangement of **185a** has been observed under acidic conditions,^[12, 20] elevated temperatures,^[21] and in the presence of various transition metals.^[17b] For instance, when protonated by acetic acid, **185a** led to 3-acetoxymethylenecyclobutane **196** by rearrangement of the initially formed bicyclo[1.1.1]pentyl bridgehead cation **195** to the 3-methylenecyclobutyl cation before its trapping with an acetate anion.^[12, 20]



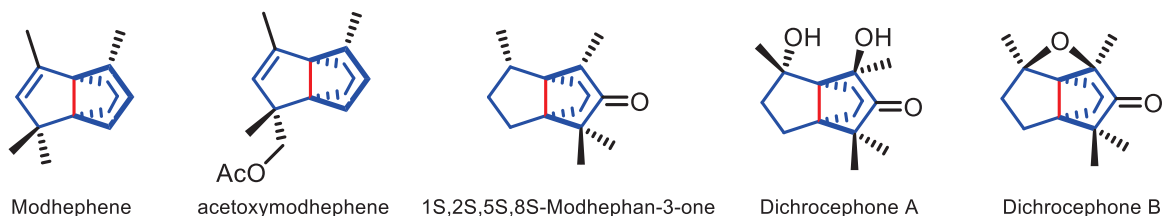
Scheme 4. Reactivity and reactions of [1,1,1]propellane **185a**. Reagents: XY = I₂, BrCCl₃, PhSH, ^tBuOCl, PhSSPh.^[22]

3. Occurrence in natural products

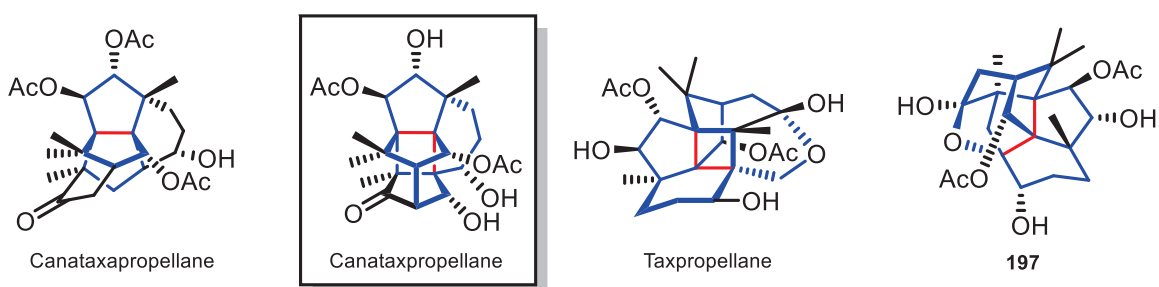
Ginsburg^[23] and Wiberg^[24] have reviewed the syntheses and the theoretical studies of propellanes extensively, Wiberg concentrating on the small-ring propellanes and Ginsburg on the medium-sized rings. In his book entitled 'Propellanes', Ginsburg even describes the syntheses and

structures of natural products possessing the propellane structure.^[25] More recently, this subject has also caught attention in different reviews reported by Bräse^[1a, 26] and Koskinen.^[27]

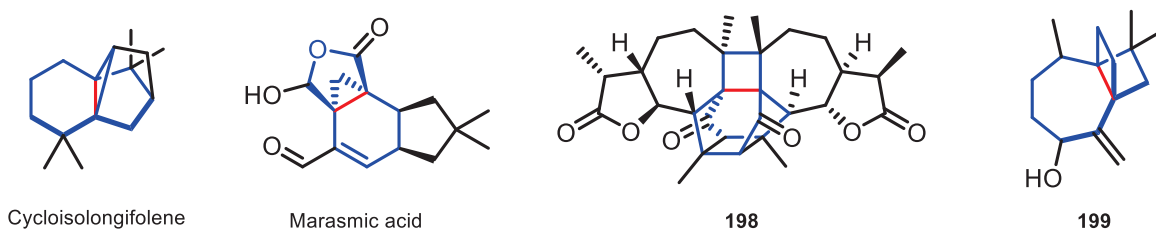
[3.3.3]propellane



Taxane-related propellanes



Propellanes with cyclopropane and cyclobutane rings



Propellane Alkaloids

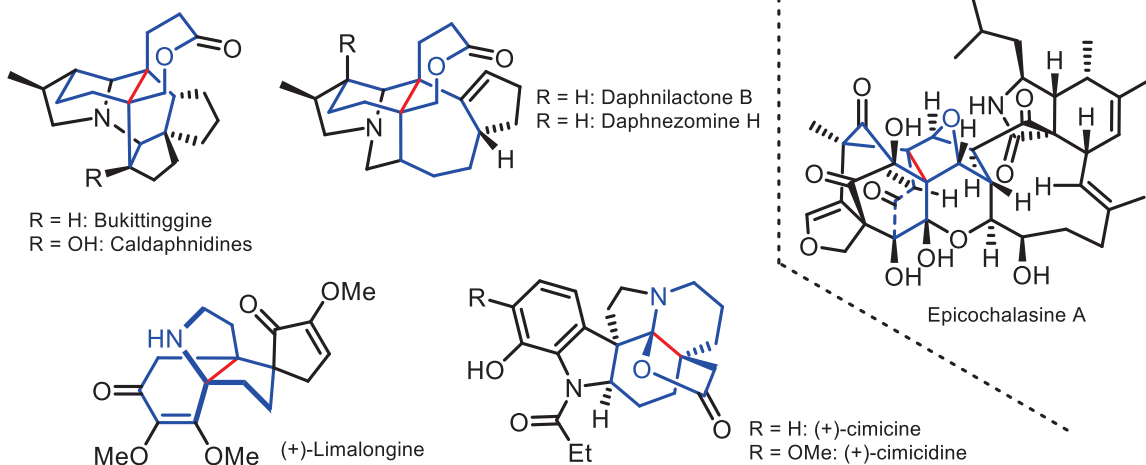


Figure 4. Natural products with propellane substructures.

Indeed, propellane structures, with varied complexity are present in many different classes of natural products as shown in Figure 4. As theoretical studies have focused on small-ring propellanes containing more than one three- or four-membered ring, in the known natural products only one of the rings is “small”, the rest being four- to eight-membered.^[27] Although propellanes with larger ring sizes, do not share the same properties of their counterparts with smaller rings,^[28] they have equally fascinated many organic chemists by the originality of their structures and by the challenge that their syntheses represent.

The chosen propellanes in Figure 4 represent a mini set of a wide library of natural propellanes. [3,3,3]Propellanes, such as modhephene and its derivatives,^[29] have been well studied by different research groups. Some of these propellanes have recently proven to be of high interest in the construction of 2D materials and hold great promise for further applications in this field.^[26] Similarly, the isolation of a new taxane, canataxapropellane, bearing a unique [3.3.3] propellane-type structure provides a new ambitious synthetic target.^[30] For instance, in 2020, Gaich *et al.*^[31] from the University of Konstanz have synthesized its analogue: canataxapropellane for the first time, opening the door toward the synthesis of other parent structures.

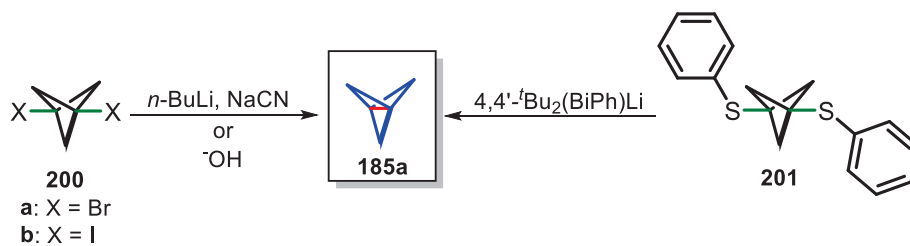
Natural products containing a propellane core in which the smallest ring is either a cyclopropane or an epoxide are relatively frequent in nature (e.g. marasmic acid).^[32] In addition, propellane alkaloids,^[1a] and even more complex and impressive structures like epicochalsine A,^[33] have caught the attention of chemists in the last decades.

4. Synthesis of propellanes: general overview

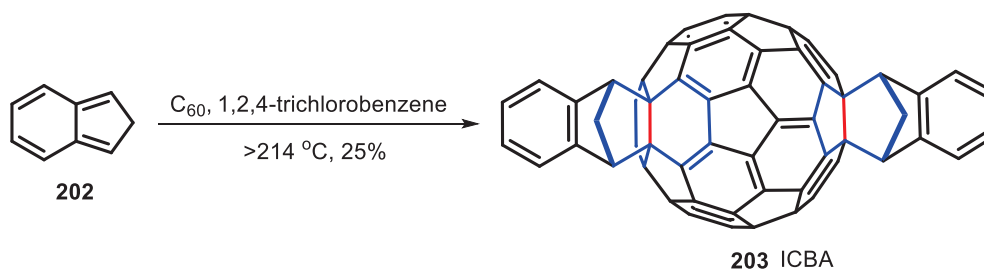
Different methods have been developed for various propellanes. In general, three principally different pathways have been used: a) elimination across the two bridgehead atoms of a bicyclo[*n.m.o*]alkane; b) cycloaddition to a bicyclo-[*n,m,o*]alk-1,*n*-ene with a central tetrasubstituted double bond; c) ring formation for a third bridge across the bridgehead positions in a bicyclo[*n,m,o*]alkane. Miscellaneous other approaches have been employed in specific individual cases (Scheme 5).^[26, 34]

Elimination across the two bridgehead positions in a bicyclo[*n.m.o*]alkane: For example, the first syntheses of [1.1.1]propellane **185a** has been achieved starting from **200a** by treatment with *n*-butyllithium^[35] or from the diiodide **200b** by nucleophilic attack of hydroxide^[36] or cyanide ions.^[37] Alternatively, **185a** can be prepared from the corresponding dithioethers, like, **201**.^[38]

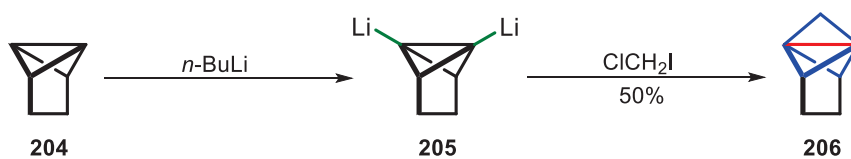
a) Elimination across the two bridgehead atoms of a bicyclo[*n.m.o*]alkane



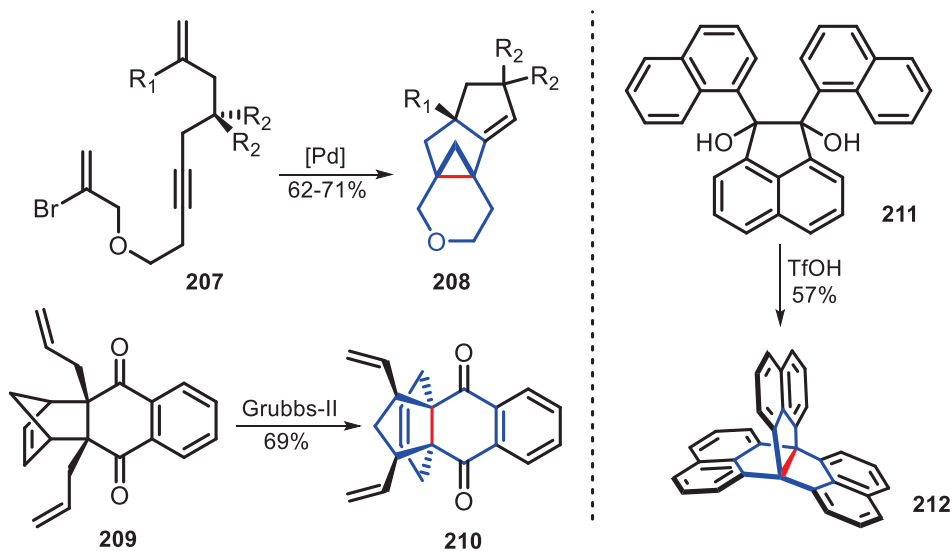
b) Cycloaddition to a bicyclo-[*n.m.o*]alk-1,*n*-ene with a central tetrasubstituted double bond



c) Ring formation for a third bridge across the bridgehead positions in a bicyclo[*n.m.o*]alkane



d) Miscellaneous



Scheme 5. Different methods for the synthesis of [*n,m,o*]propellanes.

Cycloadditions to bicyclo[*n.m.o*]alk-1,*n*-enes: In most cases, cycloadditions of a diene or a carbene to allotropes of carbon, such as C₆₀ or carbon nanotubes (CNT), were employed. For example, Hou and co-workers^[39] prepared the indene-C₆₀-bisadduct ICBA **203**, using this strategy, starting from indene, which equilibrates with isoindene **202** and C₆₀.^[40]

Ring closure of a third bridge in a bicyclo[*n.m.o*]alkane derivative: A third bridge can easily be closed across the bridgehead positions of bicyclobutanes to form propellanes through deprotonation to 1,2-dilithiated intermediates, which are converted in one step into the corresponding propellane by treatment with biselectrophiles, as shown in Scheme 5 for the bridged propellane **206**.^[41]

Miscellaneous reactions leading to [*n.m.o*]propellanes: Despite the mentioned methods, propellane synthesis is still a challenging task. Therefore, no generally applicable method can be utilized for this purpose. However, several miscellaneous reactions, such as palladium-catalyzed domino transformations,^[34, 42] Weiss reaction,^[43] ring-rearrangement metathesis,^[44] and cationic domino cyclization,^[45] were used to prepare a variety of impressive propellane structures.

5. Applications of different propellanes

Products containing a propellane-type substructure may show interesting pharmacological properties as well as applications in material sciences. Some examples selected from the recent literature are presented in Figure 5.

The synthetic amantadine-related propellanes **214-219**, prepared by Vázquez and coworkers,^[46] were tested and show potential anti-influenza A properties.^[46] In addition to these compounds, the same research group reported several other azapropellanes with notable antiviral activities, such as **221** and **222**, which showed promising inhibitory activities against the V27A mutant form of influenza A.^[47] The submicromolar activity of **220** against influenza A/H1N1 without cytotoxicity is also worth mentioning.^[48] The group of Wünsch has also been interested in the design of new amantadine analogues.^[49] In this respect, they reported the synthesis of various [4.3.3]propellanes from a common precursor **223**. These synthetic compounds were tested for their binding affinities to the σ_1 and σ_2 receptors.^[49] The highest binding affinity was observed for **225c**, with a *K_i* value of 77 nM for the σ_1 receptor.^[49] Agonists of such receptors are of potential interest in many diseases, including Alzheimer's disease and schizophrenia.

Medicinally Relevant Compounds:

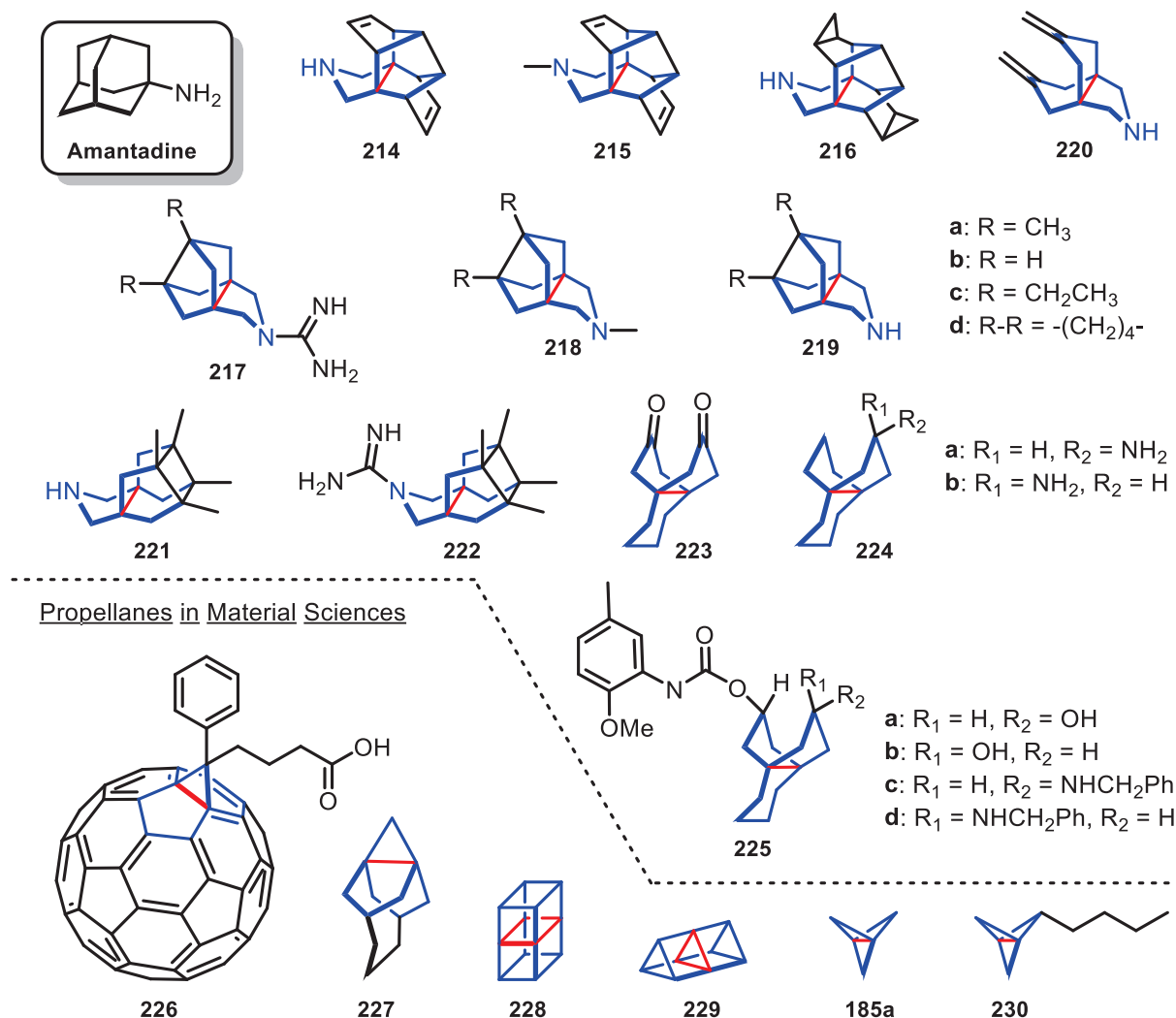


Figure 5. Propellanes with interesting applications in medicinal or material sciences.

Apart from medicinal chemistry, propellanes have also been important subunits in material sciences.^[1a] The exceptional reactivity of the central bond in the highly strained [1.1.1]propellanes (e.g. **185a**^[50] and **230**^[17c]) also makes these compounds prone to undergo polymerization. The resulting rigid and bulky bicyclo[1.1.1]pentyl units are of great interest in material sciences and can only be generated from [1.1.1]propellane starting materials, without excessive synthetic effort. As fullerene derivatives play a pivotal role in the development of modern organic molecular electronics (solar cells, OLEDs), numerous derivatives with propellane moieties (e.g. **203**^[40] (Scheme 5) and **226**^[51] (Figure 5)) have been prepared. Although this moiety does not influence the properties of the materials, it is a common linking unit in fullerene chemistry.

Other propellane skeletons would be the higher analogues of prismanes, such as biscubane- C_{12} **228**,^[52] bistrisprismane- C_9 **229**.^[52a] According to quantum mechanical computations, such oligo[n]prismanes should be auxetic materials, that is, would become thicker when stretched and thinner when compressed, at the molecular level.^[52a]

6. Our main objective

Small-ring propellanes have caught the attention as “spring-loaded” electrophiles in strain-release reactions to access nonclassical bioisosteres, such as [1.1.1]bicyclopentanes.^[53] Larger propellanes

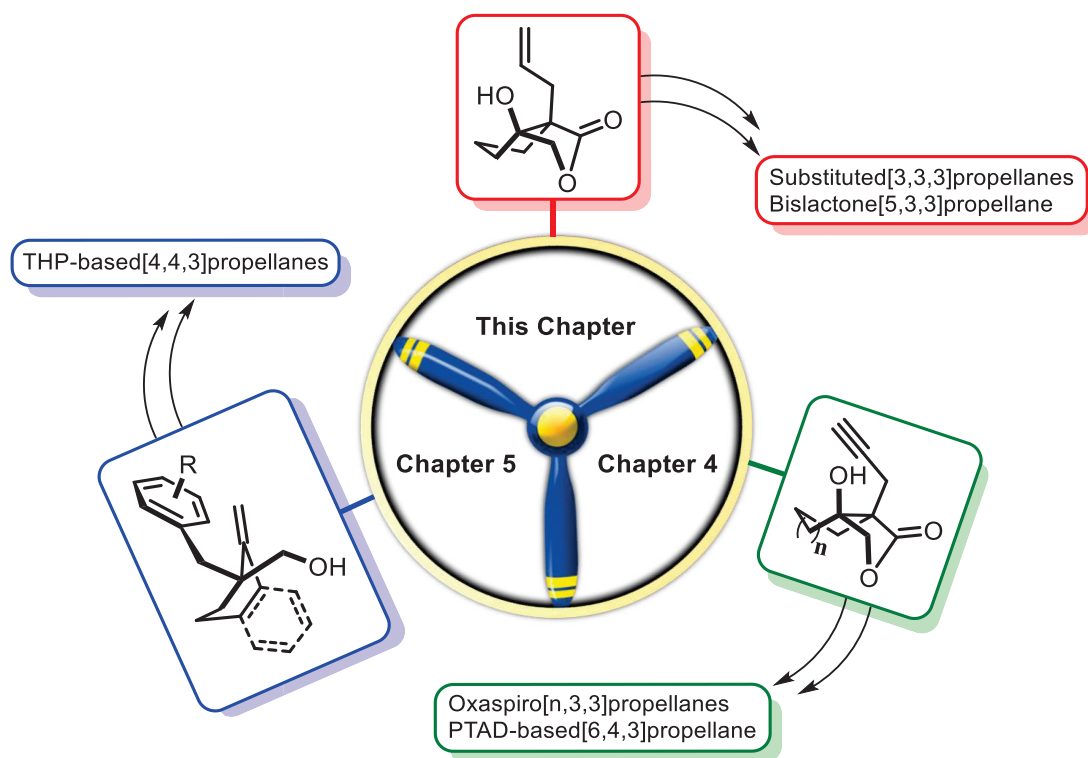


Figure 6. Outline of different propellanes classified according to their mother structure.

on the other hand, have received much less attention in drug design,^[49] probably due to the lack of general methods for their preparation.^[54] The main challenge in the synthesis of these polycyclic systems lies in the construction of the adjacent quaternary bridgehead carbon atoms. Throughout the following chapters, we will escape the “flatland” structures by describing different approaches to the synthesis of highly functionalized $[n,m,o]$ propellanes. The structural architecture of such polycycles was designed to include subunits that are frequently found in biologically potent natural

products (Figure 6). In this chapter, various [n,3,3]propellanes, prepared from allyl bicyclic hydroxy lactone, will be highlighted and discussed.

7. Structural Features and Retrosynthetic Analysis of the Substituted [3,3,3]-Propellanes

The designed [3,3,3]propellane comprises a tricyclic [5,5,5] heteroatom framework (Figure 7). It is functionalized and oxidized (one lactone, one ether, and a Y group), containing six CH₂ groups (C3, C4, C5, C8, C10, and C12). Among the features distinguishing the compound's structural complexity are the three stereocenters including two quaternary centers (C2 and C1), which reside at the propellane bridge.

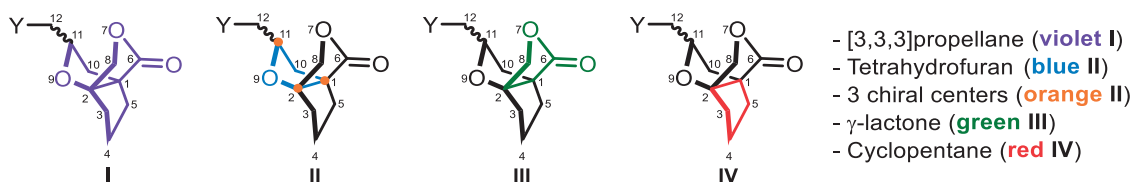
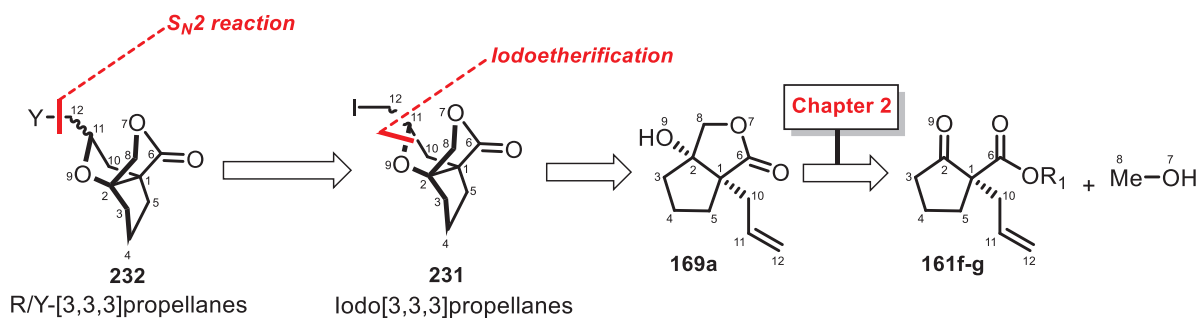


Figure 7. Key features of the designed propellanes (Y = heteroatom).

Because of the distinctive and intricate structural features displayed by the designed propellanes, the retrosynthetic analysis (Scheme 6) required a completely different strategy than those mentioned in Section 4.



Scheme 6. Retrosynthetic analysis of substituted [3,3,3]propellanes.

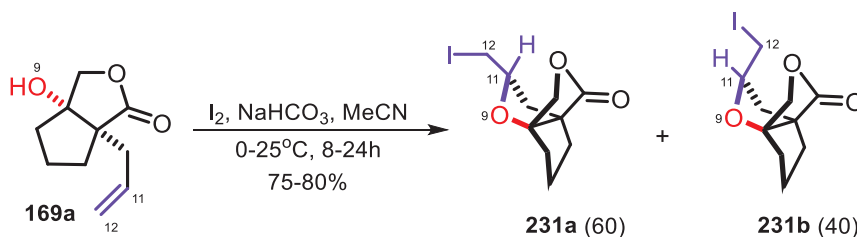
Our analysis leads to iodo[3,3,3]propellane **231** by disconnecting the Y group in **232** through nucleophilic substitution reactions. This transformation would furthermore lead to a family of substituted propellanes by changing the nature of the reacting nucleophile. Propellane **231** could be efficiently obtained by iodoetherification of the allyl bicyclic lactone **169a**, including the introduction of the tertiary stereocenter at C11. Disconnection of **169a** has already been discussed in Chapter 2, and represents by far the biggest synthetic challenge in this synthesis, as it requires

a transformation capable of not only establishing one more quaternary stereocenter at C2 but at the same time closing a lactone ring.

8. Synthesis of Substituted [3,3,3]Propellanes

8.1. Preparation of iodo[3,3,3]propellanes **231a-b**

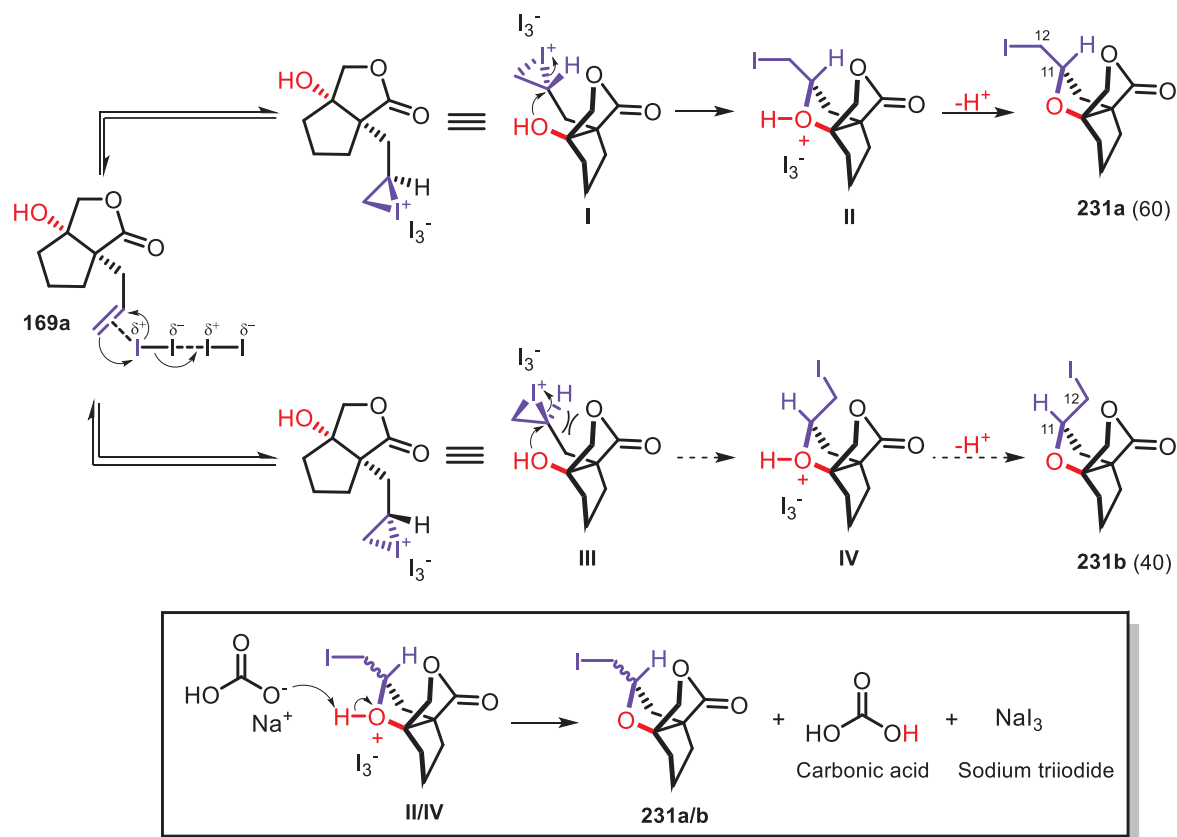
Intramolecular iodoetherification of allyl bicyclic γ -lactone **169a** was done under previously reported kinetic conditions.^[55] The substrate, dissolved in acetonitrile, was treated with iodine (3 equiv.) at 0°C or at room temperature in the presence of NaHCO₃ (3 equiv.) with efficient stirring. Generally, the reaction was clean, and only two spots attributable to the product mixture **231a-b** were observed on silica gel TLC (petroleum ether- ethyl acetate). After workup, the two components were separated by flash chromatography for a total of 75-80% recovery of pure products (1.5:1) (Scheme 7). Similar results were obtained in the absence of sodium bicarbonate, but the cyclization was slower.



Scheme 7. Access to iodo[3,3,3]propellanes **231a-b** via iodoetherification reaction of **169a**.

The mechanism and the stereochemistry of the iodoetherification reaction can be demonstrated as shown in Scheme 8. The three-membered cyclic iodonium salts **I** and **III**, produced *in situ* from the reaction of the terminal alkene with electrophilic iodine species, were opened by the corresponding tertiary alcohol to give **II** and **IV** respectively.^[56] The latter intermediates were then deprotonated by NaHCO₃, thus affording iodo[3,3,3]propellanes **231a-b**. It should be noted that no 6-membered-ring products were ever observed in this system, which means that the 5-*exo-tet* reaction is more favored under kinetic conditions.^[57] The next issue addressed was that of the stereochemical outcome at C11. The formation of **231a** was slightly more favored than its isomer **231b** with a ratio of 1.5:1. Although it is not considerable, the observed diastereoselectivity can be explained by comparing the stability of the transition states **I** and **III**. The conformation of cyclic iodonium in **III** resides toward the lactone moiety, which is more sterically hindered than its counterpart in state **II**. Therefore, the formation of iodonium **I** is relatively more favored than

that of **II**, which explains the obtained result.



Scheme 8. Proposed mechanism and stereochemistry of the iodoetherification reaction.

NMR analysis:

1H and ^{13}C resonances of **231a** and **231b** are presented in Tables 1 and 2 respectively. In general, the 1H signals were assigned from chemical shifts and multiplicities, except for protons H3, H10, and H12 which were assigned using 2D COSY, HSQC, and HMBC. These experiments were also used in combination with DEPT for ^{13}C NMR assignments.

From Table 1, the lactone and alkyl rings region in **231a-b** generally show slight variations in 1H NMR spectra ($\Delta\delta < \pm 0.1-0.2$ ppm). However, larger variations were observed for protons H10, H11, and H12. In **231a**, the deshielded proton (H11) at 3.86 ppm couples with two methylene groups to give a dddd with close coupling constants (4.5-5.1 Hz), except for one doublet which registered 9.9 Hz. After being assigned from their multiplicities, this high coupling constant corresponds to the correlation between H11 and H10e, which might be the result of the present conformation of the THF ring. On the other hand, H11 in **231b** appears at 4.22-4.09 ppm, but its

correlation with other neighboring protons was difficult to be assigned by the present multiplicities in 1D NMR. Consequently, a 2D COSY experiment was done to show strong cross-peaks between H11/H10 and H11/H12.

From Table 2, the carbon chemical shifts show weak variations between the isomers **231a-b**. In both cases, the highest deshielded carbon was that of the lactone moiety (C6) ($\Delta\delta= 0.1$ ppm), whereas the most shielded one was related to the α -iodo carbon (C12) ($\Delta\delta= 0$ ppm).^[58]

Table 1. ¹H NMR assignments of compounds **231a-b**. ^a(300 MHz, CDCl₃).

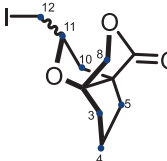

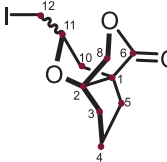
	<i>H3</i>	<i>H4</i>	<i>H5</i>	<i>H8</i>	<i>H10</i>	<i>H11</i>	<i>H12</i>	
231a^a	a: 2.28-2.15 m	2.12-1.77 m	2.12-1.77 m	a: 4.38 d	a: 2.64 dd	3.86 dddd,	a: 3.39 dd	
	e: 2.12-1.96 m			$J_{8a-8e}=10.6$	$J_{10a-10e}=13.0$	$J_{11-10e}=9.9$	$J_{12a-12e}=10.6$	
				e: 4.29 d	$J_{10a-11}=5.0$	$J_{11-10a}=5.0$	$J_{12a-11}=4.5$	
				$J_{8e-8a}=10.6$	e: 1.76 dd	$J_{11-12a}=4.5$	e: 3.36 dd	
				$J_{10e-10a}=13.0$	$J_{11-12e}=5.1$	$J_{12e-12a}=10.6$		
				$J_{10e-11}=9.9$		$J_{12e-11}=5.1$		
231b^a	2.13-1.40 m	2.13-1.40 m	2.13-1.40 m	a: 4.51 d	2.38-2.22 m	4.22-4.09 m	a: 3.26 dd	
				$J_{8a-8e}=10.3$			$J_{12a-12e}=5.6$	
				e: 4.20 d			$J_{12a-11}=2.1$	
				$J_{8e-8a}=10.3$			e: 3.24 dd	
						$J_{12e-12a}=5.6$		
						$J_{12e-11}=2.1$		

Table 2. ¹³C NMR assignments of compounds **231a-b**. ^a(101 MHz, CDCl₃).

	<i>C1</i>	<i>C2</i>	<i>C3</i>	<i>C4</i>	<i>C5</i>	<i>C6</i>	<i>C8</i>	<i>C10</i>	<i>C11</i>	<i>C12</i>	
231a^a	61.9	97.7	39.1	27.5	36.4	180.0	78.2	44.5	79.4	7.0	
231b^a	61.8	98.0	37.7	26.3	36.1	179.9	77.6	43.8	80.9	7.0	

The relative stereochemistry between **231a** and **231b** has been determined by 2D NOESY experiments as shown in Figure 8. The signals of the proton H11 in **231a** (~3.9 ppm) gives strong NOE cross-peaks with the neighboring protons H10 (2.6, 1.8 ppm) and H12 (~3.3 ppm) in addition to a weak cross peak with H8 (4.4- 4.2 ppm) related to the lactone ring. However, H11 in **231b** (~4.2 ppm) correlates with the alkyl protons (H3 and H5 (2- 1.7 ppm)), but not with H8 (4.5- 4.1 ppm). Therefore, H11 resides toward the lactone moiety away from the alkyl group in **231a** while the inverse is true for **231b**. In conclusion, a combination of 1D and 2D NMR analyses revealed the complete assignment and the exact stereochemistry of iodo[3,3,3]propellanes **231a-b**.

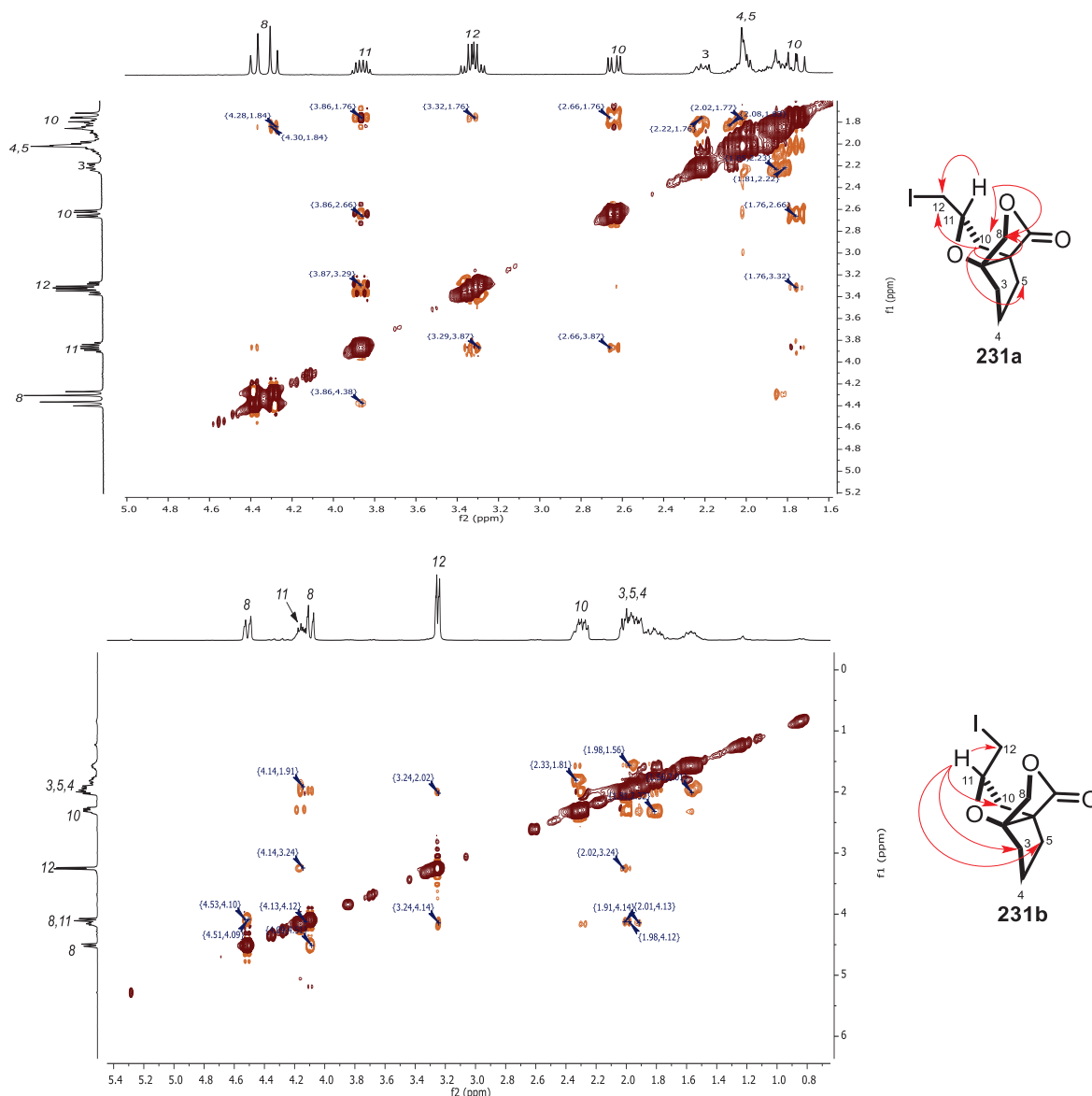


Figure 8. 2D NOESY NMR of **231a** and **231b** (CDCl_3).

8.2. Preparation of substituted [3,3,3]propellanes from **231a-b**

With iodo[3,3,3]propellanes **231a-b** in hands, we turned our attention toward their functionalization *via* nucleophilic substitution reactions. For this purpose, a variety of different nucleophiles have been examined under previously reported conditions, and the obtained results are shown in Table 3. In general, heteroatom-nucleophiles, such as azide and thiocyanate, were more efficient than carbon-nucleophiles. The best results were attained when the chosen substrate was reacted with KSCN in refluxed acetonitrile for 15-16 hours (entries 4 and 11).^[59] However, when acetonitrile was replaced with ethanol, the yield of the substituted product **233a** dropped to

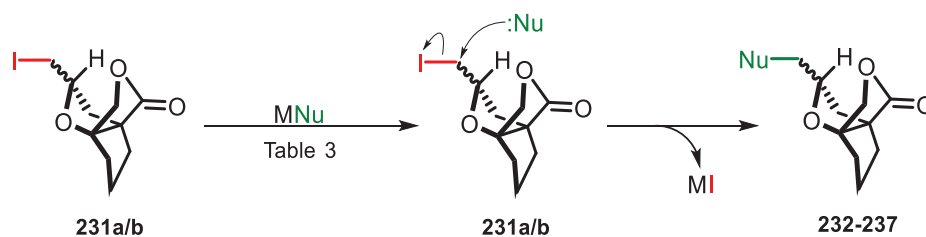
25%, and hence the reaction time was much longer (Entry 3). This result was expected because of the anion-dipole interaction between ethanol and thiocyanate which would negatively affect the substitution process.

In the case of NaN_3 , satisfactory yields of the substituted products **232a-b** were also obtained when the reaction was carried out in DMF at 60°C for 15- 24 hours (Entries 2 and 10).^[60] Indeed, it should be noted that there has been a small difference between the isolated yield of **232a** (Entry 2, 86%) and that obtained for its diastereoisomer **232b** (Entry 10, 76%). Thus, the reactivity of azide toward **231a** is higher than that with **231b**. Under similar reaction conditions, when dichloromethane was mixed with dimethylformamide in a ratio of 6:4, no reaction was observed until we evaporated dichloromethane from the reaction mixture (Entry 1). Hence, the reaction proceeds better with homogenous polar aprotic solvents.

Apart from NaN_3 and KSCN , it has to be said that the substitution reactions with other nucleophiles have been less successful. For instance, when refluxed in DMF for 24 hours, the reaction between **231a** and phthalimide did not afford the substitution product **236a** but rather a mixture of unknown compounds (Entry 8).^[61] However, when phthalimide was replaced with its potassium salt and refluxed in acetonitrile instead of DMF for 38 hours, **236a-b** were isolated in low yield as a chromatographically inseparable diastereoisomers (1:1) (Entry 9). Presumably, the anchimeric assistance of the phthalimide group is behind the obtained result as demonstrated in Scheme 9.^[62] The process might have passed through intermediates I, II, and III, having resonance structures, before losing the stereochemistry of the reactant at C11.

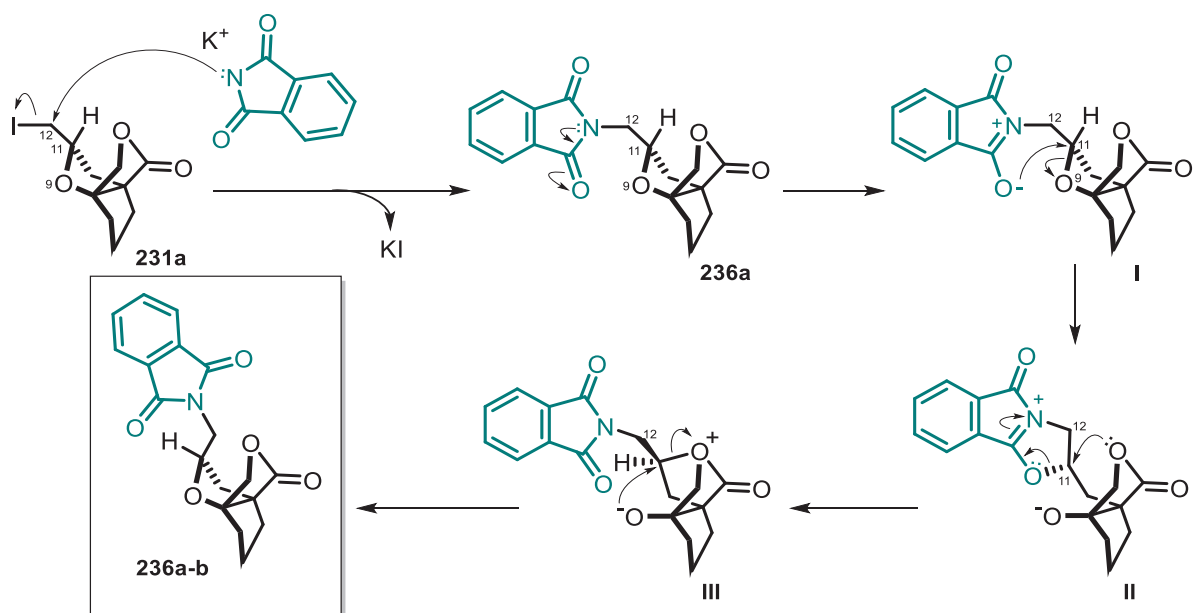
When **231a-b** were reacted with NaCN in DMSO at 40-140°C, a complete conversion to only one less polar compound was monitored by TLC (entries 5 and 12). After quantitative isolation of the obtained product, the recorded ¹HNMR spectrum showed the appearance of two singlets at 1.88 and 4.77 ppm indicating the presence of a methyl group, and an alkene moiety, respectively. Moreover, the multiplet of H11, as well as both AB systems at C10 and C12 were disappeared. Based on these results and other spectroscopic data, instead of the expected nitriles **234a-b**, the product was the unsaturated [3,3,3]propellane **238** (Figure 9). A plausible reaction mechanism is proposed where cyanide may abstract a proton to give the *exo* enol ether propellane **239**, which isomerizes to the more stable *endo* isomer **238** (Scheme 10).

Table 3. Nucleophilic substitution reactions of **231a-b** with different nucleophiles.



Entry	SM ^a	MNu ^a	Solvent	T (°C)	t (h) ^b	%Yield ^c
1	231a	NaN ₃	DMF:DCM (4:6)	60	72	- (232a)
2	231a	NaN ₃	DMF	60	15	86 (232a)
3	231a	KSCN	EtOH	80	68	25 (233a)
4	231a	KSCN	MeCN	90 ^d	16	91 (233a)
5	231a	NaCN	DMSO	40	24	- (234a)
6	231a		^t BuOH	85 ^d	23	- ^e (235a)
7	231a		THF	0- r.t.	96	- ^e (235a)
8	231a		DMF	160 ^d	24	- (236a)
9	231a		MeCN	90 ^d	38	16 (236a-b)
10	231b	NaN ₃	DMF	60	24	76 (232b)
11	231b	KSCN	MeCN	90 ^d	15	94 (233b)
12	231b	NaCN	DMSO	140	0.5	- (234b)
13	231b		THF	0- r.t.	4.5	- ^f (237b)

^aStarting material; ^bReaction time; ^cIsolated yield; ^dReflux; ^eNo reaction; ^fDecomposition.



Scheme 9. The proposed anchimeric assistance mechanism of **236a** (Triple inversion process).

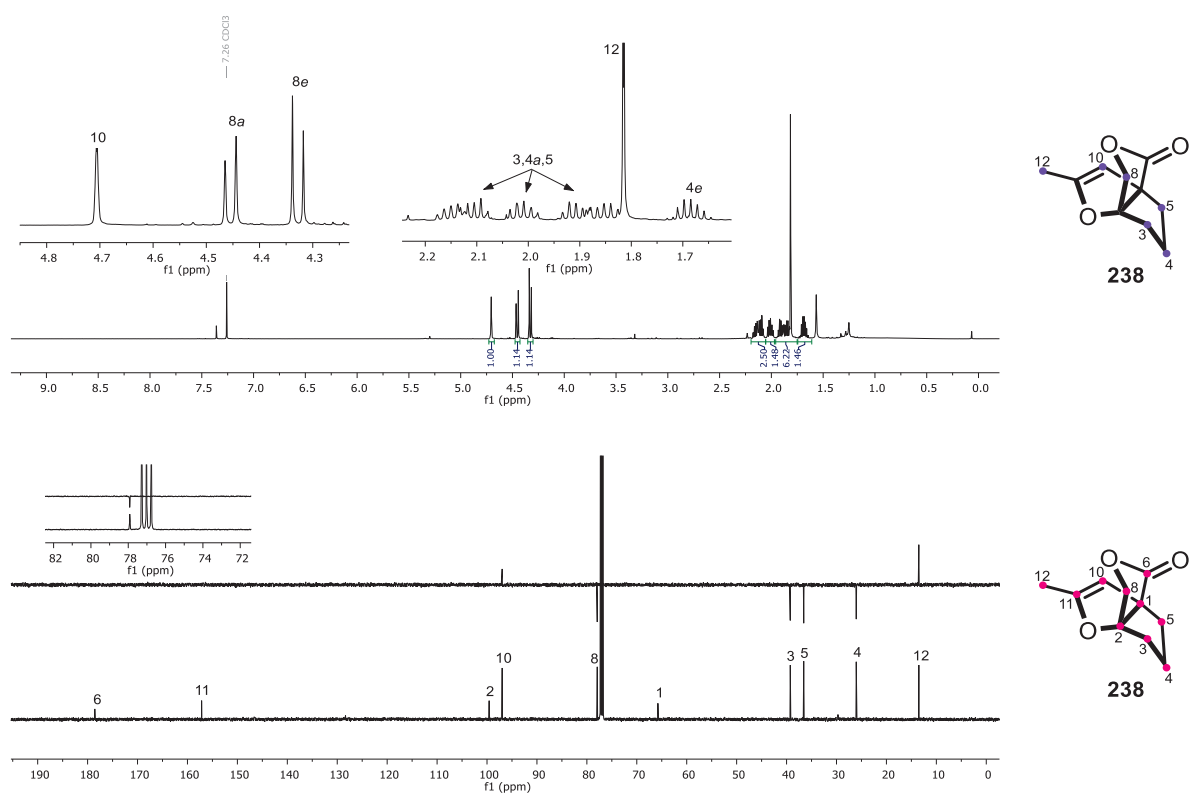
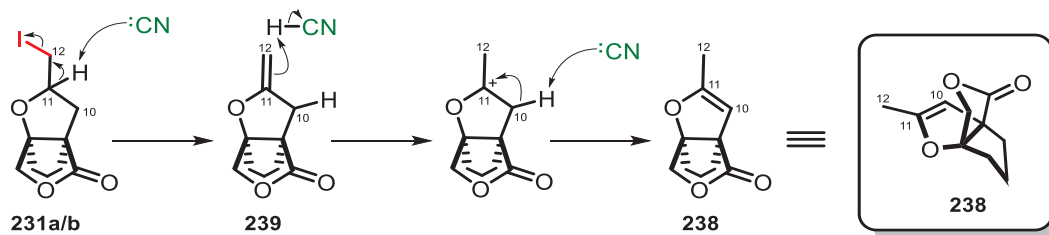


Figure 9. NMR analysis of **238**. From top to bottom: ^1H NMR (500 MHz, CDCl_3), ^{13}C NMR (126 MHz, CDCl_3), DEPT-135 (126 MHz, CDCl_3).



Scheme 10. Proposed reaction mechanism for the formation of **238**.

Finally, either no reaction or complete decomposition of the starting material was observed from the reaction of **231a/b** with diethyl malonate or methyl acetoacetate respectively (Entries 6, 7, and 13). Thus, our attempts to functionalize our propellane ring system with C-nucleophiles were not fortunate.

NMR analysis of the substituted [3,3,3]propellanes **232** and **233**:

Table 4 shows the proton chemical shifts of **232a-b** and **233a-b** in CDCl_3 and the effects due to their substituents. Table 2 shows the corresponding carbon-13 chemical shifts. The most significant feature among the proton data is the shift of the H12a and H12e signals upon X substitution. As expected, such protons are slightly more deshielded in azido propellanes **232a-b** than their counterparts in thiocyno propellanes **233a-b** ($\Delta\delta \sim 0.2\text{-}0.4$ ppm). Unambiguously, this difference in the chemical shift can be related to the higher electron-withdrawing ability of azide with respect to thiocyanate.

From Table 2, the carbon attached directly to the substituent (C12) was more highly deshielded in **232a-b** than that of **233a-b** ($\Delta\delta \sim 10\text{-}11$ ppm). However, sluggish variations have been observed for the rest of the peaks ($\Delta\delta \sim 1\text{-}4$ ppm). These results overlap with those obtained from proton-NMR, thus confirming the effect of the substituent on the chemical shift of the neighboring protons and carbon atoms.

Table 4. ^1H NMR assignments of compounds **232-233**. $^a(300\text{ MHz, CDCl}_3)$.

	H3	H4	H5	H8	H10	H11	H12
	a: 2.26-2.13 m	2.07-1.75 m	2.07-1.75 m	a: 4.36 d	a: 2.46 dd	4.15 dddd	a: 3.57 dd
	e: 2.07-1.75 m			$J_{8a-8e}=10.6$	$J_{10a-10e}=12.9$	$J_{11-10e}=?$	$J_{12a-12e}=13.3$
232a^a				e: 4.28 d	$J_{10a-11i}=5.2$	$J_{11-10a}=5.2$	$J_{12a-11i}=3.2$
				$J_{8e-8a}=10.6$	e: 1.76 dd	$J_{11-12a}=3.2$	e: 3.21 dd
					$J_{10e-10a}=12.9$	$J_{11-12e}=4.8$	$J_{12e-12a}=13.3$
					$J_{10e-11i}=?$		$J_{12e-11i}=4.8$

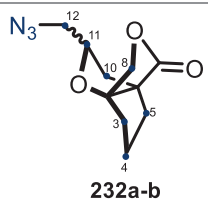
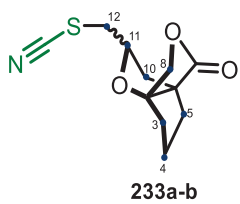
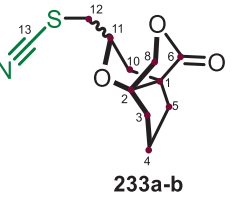
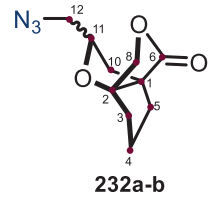
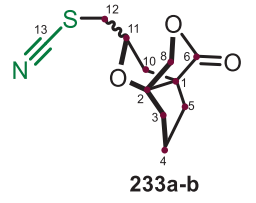
232b^a	a: 2.45-2.33 m	a: 2.13-1.40 m	2.11-1.77 m	a: 4.52 dd	a: 2.18 dd	4.35 dddd	a: 3.49 dd	 232a-b
	e: 2.11-1.77 m	e: 1.71-1.51 m		$J_{8a-8e}=10.3$	$J_{10a-10e}=13.1$	$J_{11-10e}=9.1$	$J_{12a-12e}=13.1$	
				$J_{8a-3}=0.9$	$J_{10a-11i}=6.2$	$J_{11-10a}=6.2$	$J_{12a-11i}=3.5$	
				e: 4.12 d	e: 1.14 dd	$J_{11-12a}=3.5$	e: 3.24 dd	
			$J_{8e-8a}=10.3$	$J_{10e-10a}=13.1$	$J_{11-12e}=5.7$	$J_{12e-12a}=13.1$		
				$J_{10e-11i}=9.1$		$J_{12e-11i}=5.7$		
233a^a	a: 2.18-2.09 m	2.02-1.74 m	2.02-1.74 m	a: 4.38 dd	a: 2.63 dd	4.23 dddd	a: 3.36 dd	 233a-b
	e: 2.02-1.89 m			$J_{8a-8e}=10.7$	$J_{10a-10e}=12.9$	$J_{11-10e}=9.6$	$J_{12a-12e}=13.7$	
				e: 4.32 d	$J_{10a-11i}=5.0$	$J_{11-10a}=5.0$	$J_{12a-11i}=4.3$	
				$J_{8e-8a}=10.7$	e: 1.14 dd	$J_{11-12a}=4.3$	e: 3.07 dd	
				$J_{10e-10a}=12.9$	$J_{11-12e}=5.4$	$J_{12e-12a}=13.7$		
				$J_{10e-11i}=9.6$		$J_{12e-11i}=5.4$		
233b^a	a: 2.43-2.32 m	a: 2.05-1.80 m	2.05-1.80 m	a: 4.53 dd	a: 2.32 dd	4.45 dddd	a: 3.23 dd	 233a-b
	e: 2.05-1.80 m	e: 1.66-1.52 m		$J_{8a-8e}=10.5$	$J_{10a-10e}=13.2$	$J_{11-10e}=10.1$	$J_{12a-12e}=13.6$	
				$J_{8a-3}=0.9$	$J_{10a-11i}=5.6$	$J_{11-10a}=5.6$	$J_{12a-11i}=4.5$	
				e: 4.11 d	e: 2.07 dd	$J_{11-12a}=4.5$	e: 3.06 dd	
			$J_{8e-8a}=10.5$	$J_{10e-10a}=13.2$	$J_{11-12e}=6.6$	$J_{12e-12a}=13.6$		
				$J_{10e-11i}=10.1$		$J_{12e-11i}=6.6$		

Table 5. ¹³C NMR assignments of compounds **232-233**. ^a(101 MHz, CDCl₃).

	<i>C1</i>	<i>C2</i>	<i>C3</i>	<i>C4</i>	<i>C5</i>	<i>C6</i>	<i>C8</i>	<i>C10</i>	<i>C11</i>	<i>C12</i>	<i>C13</i>	
232a^a	61.7	97.6	39.0	27.3	36.3	180.0	78.0	40.4	79.8	52.3	-	 232a-b
232b^a	61.6	97.9	37.4	26.3	36.1	180.0	77.5	40.4	80.4	53.1	-	
233a^a	61.9	97.8	36.8	27.4	36.4	179.5	77.9	38.9	78.5	42.2	111.9	 233a-b
233b^a	61.7	98.1	36.9	26.3	36.0	179.6	77.2	37.2	79.3	42.2	111.7	

8.3. Further functionalization of our propellane ring system

Despite attempts to increase the scope of functionalization of our propellane ring system, substitution reactions on iodo[3,3,3]propellanes **231a-b** have directly shown its limitations. To solve this problem, we decided to explore the chemistry of the obtained substituted products. In other words, further transformations of azido/thiocyano propellanes **232-233** would permit rapid and ready access to a variety of highly functionalized propellane scaffolds (Figure 10).

Although thiocyanates have been intensively used as precursors for other sulfur-based functional groups^[63] (thiols,^[64] thioethers,^[65] disulfides^[66]...), our interest was to continue to expand the use of azido propellanes **232a-b** in the syntheses of novel triazolo propellanes *via* click reaction.^[67]

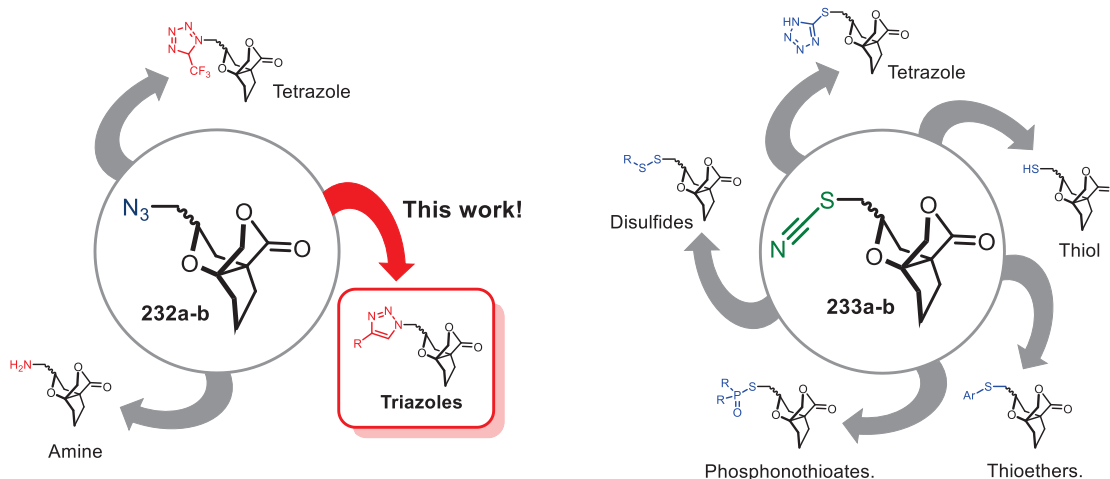


Figure 10. Some suggested transformations of **232a-b** and **233a-b**

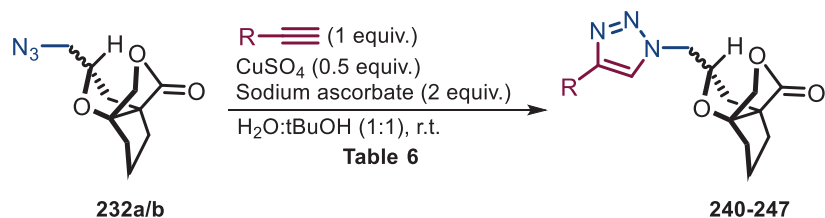
8.4. Preparation of triazolo[3,3,3]propellanes *via* click reaction

Click chemistry is a chemical philosophy proposed by Sharpless in 2001 and describes chemistry tailored to generate substances quickly and reliably by joining small units together,^[68] which has some advantages as it is fast, effective, reliable, selective, etc., and is widely used in new drug research and biochemistry.^[69] One of the most popular reactions within the click chemistry philosophy is the Huisgen 1,3-dipolar cycloaddition reaction of azide and alkyne using a Cu(I) catalyst at room temperature, which has attracted more and more attention because of simple reaction conditions, high yields (no by-products), easy purification, etc.^[70]

To demonstrate the capability of our azido propellanes as a platform starting material for the preparation of functionalized propellanes, different alkynes were allowed to react with **232a-b** *via* the click reaction catalyzed by CuSO₄-sodium ascorbate in H₂O: *t*-BuOH (1:1) at room temperature. Table 6 gives an overview of the results obtained from this reaction. In a typical reaction, the resulting suspension from the reactants was stirred vigorously at room temperature in an air atmosphere for the time specified. At the end of the reaction, the mixture was diluted with ethyl acetate and shaken with a saturated solution of ammonium chloride. The organic layer was then dried, concentrated, and purified, to give the desired 1,4-substituted triazole. Excellent results were achieved when the click reaction of either of the two isomers **232a/b** were carried out with phenyl acetylenes **248**, **252**, **253**, or **254** (Entries 1, 5-9), thus providing the corresponding 1,4-

triazolo propellanes in 81-97% yield. Good yields were also obtained with other phenyl acetylenes, such as **255** (Entry 10) as well as with aliphatic terminal alkyne **249** (Entry 2). Hence, the reaction has not shown any preferences among the used alkynes.

Table 6. Copper-catalyzed dipolar cycloaddition reaction of azides **232a/b** with different alkynes **248-255**.



Entry	SM ^a	Alkyne	t (h) ^b	%Yield ^c
1	232a	248	24	91 (240a)
2	232a	249	92	77 (241a)
3	232a	250	89	22 (242a)
4	232a	251	16	48 (243a)
5	232a	252	15	94 (244a)
6	232a	253	14	97 (245a)
7	232b		17	81 (245b)
8	232a	254	16	81 (246a)
9	232b		18	88 (246b)
10	232b	255	17	62 (247b)

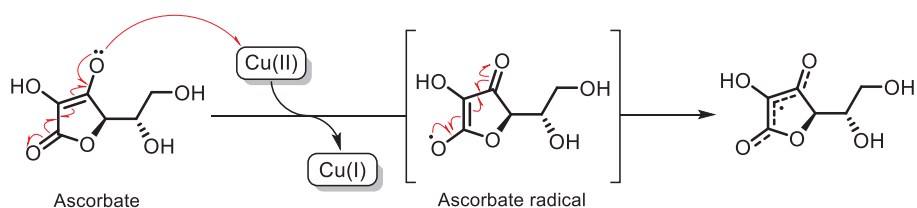
^aStarting material; ^bReaction time; ^cIsolated yield.

However, the reaction of **232a** with dimethylphenylsilyl acetylene **250** or with 4-ethynylacetophenone **251** furnished propellanes **242a** or **243a** in low to moderate yields (entries

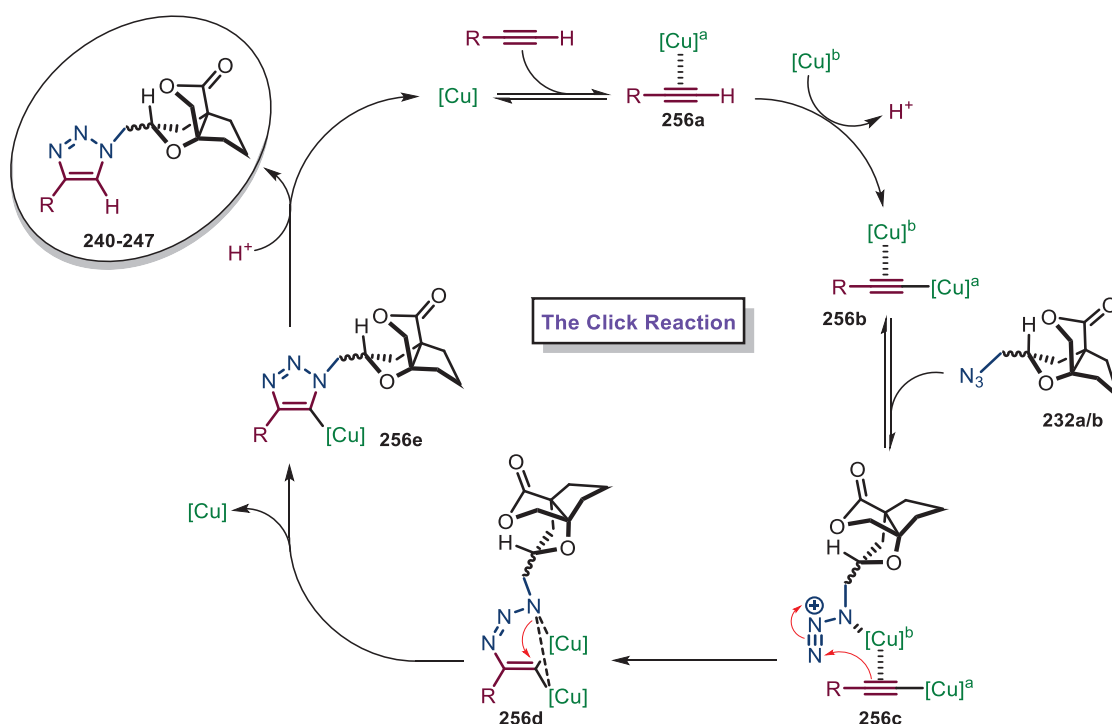
3 and 4). Presumably, the DMPS group of **250** acts as a sterically hindered moiety for the cycloaddition step (demonstrated in the subsequent section), explaining the low yield of **242a**.

Mechanistic considerations:

The first mechanism proposed for the click reaction included one catalytic copper atom, but experimental evidence of the possible involvement of polynuclear copper(I) intermediates has been much more relevant.^[71] Accordingly, a catalytic cycle has been suggested for our system as shown in Scheme 12. Initially, the active Cu(I) catalyst can be generated from Cu(II) salts, such as CuSO₄, using sodium ascorbate as a reducing agent (Scheme 11).



Scheme 11. Reduction of Cu(II) by sodium ascorbate.



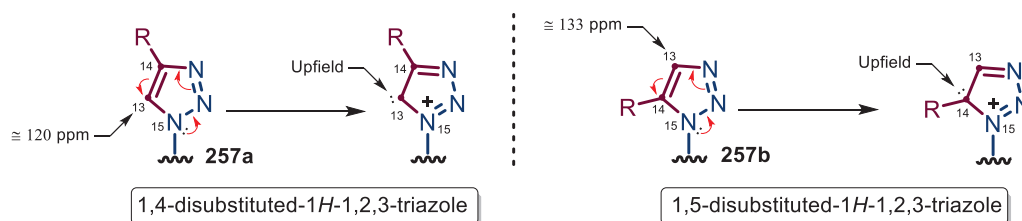
Scheme 12. An outline of the proposed catalytic cycle involving a bimetallic mechanism.

Formation of copper(I) acetylide **256a** is presumed to be the first step which probably occurs through a π -alkyne copper complex intermediate. π -Coordination of alkyne to copper(I)

significantly acidifies terminal hydrogen of the alkyne, bringing it into the proper range to be deprotonated in an aqueous medium and resulting in the formation of a σ -acetylide **256b**. The azide is then activated by coordination to copper, forming intermediate **256c**. At that point, the first C–N bond-forming event takes place, and a strained six-membered copper metallacycle **256d** forms. Finally, ring contraction to the copper triazolide **256e** is followed by protonolysis that delivers the triazole product and closes the catalytic cycle.

NMR analysis:

^1H and ^{13}C NMR assignments of triazolo propellanes **240-247** are presented in Tables 7A-B and 8A-B respectively. Generally, the used copper-catalyzed reaction is regioselective and gives 1,4-disubstituted-1*H*-1,2,3-triazoles. The latter compounds can easily be distinguished from the isomeric 1,5-disubstituted-1*H*-1,2,3-triazoles by simple one-dimensional ^{13}C NMR spectroscopy (Scheme 13). For instance, the C13 signal of **257a** and **257b** appears at $\delta \sim 120$ ppm and 133 ppm respectively.^[72] In our case, the C13 signals of the isolated compounds showed up in a range between 119.1 and 122.2 ppm, whereas, the neighboring C14 resonates between 154.1- 148.4 ppm (Tables 8A-B). Therefore, these results confirm the presence of the expected 1,4-disubstituted-1*H*-1,2,3-triazoles.



Scheme 13. The upfield position in 1,4/5-disubstituted-1*H*-1,2,3-triazoles due to resonance donation from the nitrogen N15.

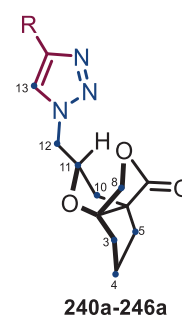
Apart from the slight variations in the ^1H and ^{13}C chemical shifts among the obtained derivatives, there exist some characteristic features that reveal the effect of the triazole moiety on the propellane core structure. Probably, the most interesting feature is the downfield shift of H12 (4.49- 4.71 ppm) in **240-247**. These protons became even more deshielded than H8 (4.10-4.50 ppm) and H11 (4.29-4.52 ppm), which was not the case previously with iodo-, azido- and thiocyno propellanes. Therefore, the triazole group exhibited a stronger electron-withdrawing effect on protons H12, thus increasing their frequencies. This effect was negligible on other protons, except

for H11 in **245b-247b** ($\delta \sim 4.52$ ppm) (Table 7B). On the other hand, the ^{13}C NMR chemical shift of C12 in triazolo propellanes was higher than that of C12 in iodo- and thiocyno- analogues ($\Delta\delta \sim +45$ ppm and $+10$ ppm respectively), but comparable to that of azido propellanes ($\Delta\delta \sim -0.7$ ppm). The substituent at C14 has also given an unambiguous influence in the ^1H NMR chemical shift, especially on protons H12 and H13. For instance, the electron-withdrawing groups 3,5-bis(trifluoromethyl)phenyl in **245a-b** and 4-acetylphenyl in **243a** made these protons more deshielded than their counterparts in other compounds. In contrast, the butyl chain in **241a** and the dimethylphenylsilyl group in **242a** made them the most shielded among their analogues (Tables 7A-B).

2D NMR experiments have also contributed to assigning the obtained triazolo propellanes. For instance, a COSY experiment has been done on compound **242a** revealing strong correlations between protons H10/ H11 and H11/H12, thus confirming the NMR assignments from previous analysis with iodo-, azido- and thiocyno-propellanes. Moreover, a NOESY experiment of the same compound has been carried to verify close spatial proximity among protons H12/H13, H11//H13 (a weak cross peak) in addition to the previously reported correlation in the propellane core (Figure 11). Again, these results ensure the presence of the 1,4-disubstituted triazoles and give a piece of additional evidence about the stereochemical configuration at C11.

Table 7A. ^1H NMR assignments of compounds **240a-246a**. (300 MHz,^a 500 MHz,^b CDCl_3).

	H3	H4	H5	H8	H10	H11	H12	H13
240a^b	a: 2.09-2.00 m	1.94-1.60 m	1.94-1.60 m	a: 4.34 d	a: 2.57 dd	4.37 dddd	a: 4.66 dd	7.88 s
	e: 1.94-1.60 m			$J_{8a-8e}=10.6$	$J_{10a-10e}=13.1$	$J_{11-10e}=?$	$J_{12a-12e}=14.6$	
				e: 4.27 d	$J_{10a-11}=5.1$	$J_{11-10a}=5.1$	$J_{12a-11}=3.2$	
				$J_{8e-8a}=10.6$	e: 1.68 dd	$J_{11-12a}=3.2$	e: 4.56 dd	
241a^a	a: 2.03-1.94 m	1.94-1.55 m	1.94-1.55 m	a: 4.33 d	a: 2.53 dd	4.29 dddd	a: 4.56 dd	7.37 s
	e: 1.94-1.55 m			$J_{8a-8e}=10.1$	$J_{10a-10e}=13.1$	$J_{11-10e}=?$	$J_{12a-12e}=14.5$	
				e: 4.26 d	$J_{10a-11}=5.1$	$J_{11-10a}=5.1$	$J_{12a-11}=3.6$	
				$J_{8e-8a}=10.1$	e: 1.70 dd	$J_{11-12a}=3.6$	e: 4.49 dd	
242a^b	1.91-1.44 m	1.91-1.44 m	1.91-1.44 m	a: 4.30 d	a: 2.51 dd	4.30 dddd	a: 4.61 dd	7.56 s
				$J_{8a-8e}=10.5$	$J_{10a-10e}=13.2$	$J_{11-10e}=11.4$	$J_{12a-12e}=14.4$	
				e: 4.24 d	$J_{10a-11}=5.1$	$J_{11-10a}=5.1$	$J_{12a-11}=4.0$	
				$J_{8e-8a}=10.5$	e: 1.53 dd	$J_{11-12a}=4.0$	e: 4.57 dd	
				$J_{10e-10a}=13.2$	$J_{11-12e}=3.7$	$J_{12e-12a}=14.4$		
				$J_{10e-11}=11.4$		$J_{12e-11}=3.7$		



243a^a	a: 2.11-1.98 m	1.98-1.61 m	1.98-1.61 m	a: 4.37 d	a: 2.60 dd	4.35 dddd	a: 4.71 dd	7.98 s
	e: 1.98-1.61 m			$J_{8a-8e}=10.6$	$J_{10a-10e}=13.1$	$J_{11-10e}=11.4$	$J_{12a-12e}=14.5$	
				e: 4.29 d	$J_{10a-11}=5.1$	$J_{11-10a}=5.1$	$J_{12a-11}=3.2$	
				$J_{8e-8a}=10.6$	e: 1.65 dd	$J_{11-12a}=3.2$	e: 4.58 dd	
				$J_{10e-10a}=13.1$	$J_{11-12e}=5.1$	$J_{12e-12a}=14.5$		
				$J_{10e-11}=11.4$		$J_{12e-11}=5.1$		
244a^a	a: 2.10-1.97 m	1.97-1.64 m	1.97-1.64 m	a: 4.34 d	a: 2.59 dd	4.36 dddd	a: 4.67 dd	7.88 s
	e: 1.97-1.64 m			$J_{8a-8e}=10.7$	$J_{10a-10e}=13.1$	$J_{11-10e}=11.5$	$J_{12a-12e}=14.5$	
				e: 4.27 d	$J_{10a-11}=5.1$	$J_{11-10a}=5.1$	$J_{12a-11}=3.2$	
				$J_{8e-8a}=10.7$	e: 1.64 dd	$J_{11-12a}=3.2$	e: 4.55 dd	
				$J_{10e-10a}=13.1$	$J_{11-12e}=5.1$	$J_{12e-12a}=14.5$		
				$J_{10e-11}=11.5$		$J_{12e-11}=5.1$		
245a^a	a: 2.13-2.00 m	2.00-1.68 m	2.00-1.68 m	a: 4.34 d	a: 2.64 dd	4.38 dddd	a: 4.74 dd	7.84 s
	e: 2.00-1.68 m			$J_{8a-8e}=10.7$	$J_{10a-10e}=13.1$	$J_{11-10e}=11.5$	$J_{12a-12e}=14.5$	
				e: 4.29 d	$J_{10a-11}=5.0$	$J_{11-10a}=5.0$	$J_{12a-11}=3.2$	
				$J_{8e-8a}=10.7$	e: 1.69 dd	$J_{11-12a}=3.2$	e: 4.56 dd	
				$J_{10e-10a}=13.1$	$J_{11-12e}=5.6$	$J_{12e-12a}=14.5$		
				$J_{10e-11}=11.5$		$J_{12e-11}=5.6$		
246a^a	a: 2.10-1.97 m	1.95-1.61 m	1.95-1.61 m	a: 4.35 d	a: 2.57 dd	4.36 dddd	a: 4.64 dd	7.74 s
	e: 1.95-1.61 m			$J_{8a-8e}=10.6$	$J_{10a-10e}=13.1$	$J_{11-10e}=11.4$	$J_{12a-12e}=14.5$	
				e: 4.27 d	$J_{10a-11}=5.1$	$J_{11-10a}=5.1$	$J_{12a-11}=3.4$	
				$J_{8e-8a}=10.6$	e: 1.64 dd	$J_{11-12a}=3.4$	e: 4.55 dd	
				$J_{10e-10a}=13.1$	$J_{11-12e}=4.7$	$J_{12e-12a}=14.5$		
				$J_{10e-11}=11.4$		$J_{12e-11}=4.7$		

Table 7B. ¹H NMR assignments of compounds **245b-247b**. (300 MHz, ^a CDCl₃).

	<i>H3</i>	<i>H4</i>	<i>H5</i>	<i>H8</i>	<i>H10</i>	<i>H11</i>	<i>H12</i>	<i>H13</i>
245b^a	a: 2.45-1.32 m	2.10-1.48 m	2.10-1.48 m	a: 4.52 d	a: 2.32 dd	4.52 dddd	a: 4.76 dd	7.85 s
	e: 2.10-1.48 m			$J_{8a-8e}=10.4$	$J_{10a-10e}=13.1$	$J_{11-10e}=9.7$	$J_{12a-12e}=13.5$	
				e: 4.15 d	$J_{10a-11}=5.3$	$J_{11-10a}=5.3$	$J_{12a-11}=2.3$	
				$J_{8e-8a}=10.4$	e: 2.00 dd	$J_{11-12a}=2.3$	e: 4.48 dd	
				$J_{10e-10a}=13.1$	$J_{11-12e}=?$	$J_{12e-12a}=13.5$		
				$J_{10e-11}=9.7$		$J_{12e-11}=?$		
246b^a	a: 2.44-1.32 m	2.06-1.48 m	2.06-1.48 m	a: 4.49 d	a: 2.28 dd	4.51 dddd	a: 4.63 dd	7.72 s
	e: 2.06-1.48 m			$J_{8a-8e}=10.4$	$J_{10a-10e}=13.1$	$J_{11-10e}=9.8$	$J_{12a-12e}=13.4$	
				e: 4.10 d	$J_{10a-11}=5.1$	$J_{11-10a}=5.1$	$J_{12a-11}=2.8$	
				$J_{8e-8a}=10.4$	e: 1.97 dd	$J_{11-12a}=2.8$	e: 4.43 dd	
				$J_{10e-10a}=13.1$	$J_{11-12e}=?$	$J_{12e-12a}=13.4$		
				$J_{10e-11}=9.8$		$J_{12e-11}=?$		
247b^a	a: 2.47-1.35 m	2.07-1.47 m	2.07-1.47 m	a: 4.50 d	a: 2.31 dd	4.52 dddd	a: 4.68 dd	7.78 s
	e: 2.07-1.47 m			$J_{8a-8e}=10.4$	$J_{10a-10e}=13.1$	$J_{11-10e}=9.9$	$J_{12a-12e}=13.5$	
				e: 4.13 d	$J_{10a-11}=5.1$	$J_{11-10a}=5.1$	$J_{12a-11}=2.6$	
				$J_{8e-8a}=10.4$	e: 1.96 dd	$J_{11-12a}=2.6$	e: 4.44 dd	
				$J_{10e-10a}=13.1$	$J_{11-12e}=?$	$J_{12e-12a}=13.5$		
				$J_{10e-11}=9.9$		$J_{12e-11}=?$		

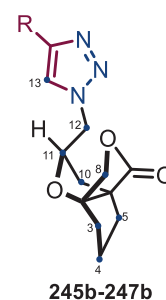


Table 8A. ¹³C NMR assignments of compounds **240a-246a**. (300 MHz, ^a 400 MHz, ^b 500 MHz, ^c CDCl₃).

	<i>C1</i>	<i>C2</i>	<i>C3-5</i>	<i>C6</i>	<i>C8</i>	<i>C10</i>	<i>C11</i>	<i>C12</i>	<i>C13</i>	<i>C14</i>
240a^a	61.6	97.7	39.0, 27.1, 36.1	179.5	77.9	40.2	78.8	51.7	121.1	147.8
241a^b	61.5	97.7	39.0, 27.1, 36.1	179.5	77.9	40.2	78.9	51.4	122.2	148.4
242a^c	61.6	97.6	38.9, 26.9, 36.1	179.5	77.9	39.9	78.7	50.8	?	145.1
243a^b	61.6	97.8	39.0, 27.2, 36.1	179.4	77.9	40.3	78.8	51.9	122.0	146.7
244a^b	61.6	97.7	39.0, 27.1, 36.1	179.4	77.9	40.3	78.8	51.8	121.1	146.8
245a^b	61.6	97.9	39.0, 27.2, 36.1	179.3	77.8	40.5	78.8	52.2	122.1	145.1
246a^c	61.6	97.6	39.0, 27.1, 36.1	179.6	77.9	40.4	78.9	51.5	119.6	148.3

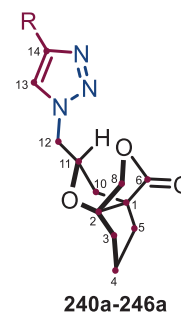
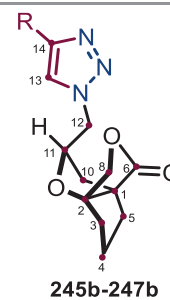


Table 8B. ¹³C NMR assignments of compounds **245b-247b**. (101 MHz,^a 126 MHz,^b CDCl₃).

	<i>C1</i>	<i>C2</i>	<i>C3-5</i>	<i>C6</i>	<i>C8</i>	<i>C10</i>	<i>C11</i>	<i>C12</i>	<i>C13</i>	<i>C14</i>
245b^a	61.4	98.3	37.0 26.2 35.8	179.5	77.2	40.7	79.5	53.1	121.6	145.2
246b^a	61.3	98.1	37.1 26.2 35.8	179.6	77.2	40.8	79.8	52.7	119.1	148.4
247b^b	61.3	98.1	37.1 26.2 35.8	179.6	77.2	40.8	79.7	52.8	119.8	147.8



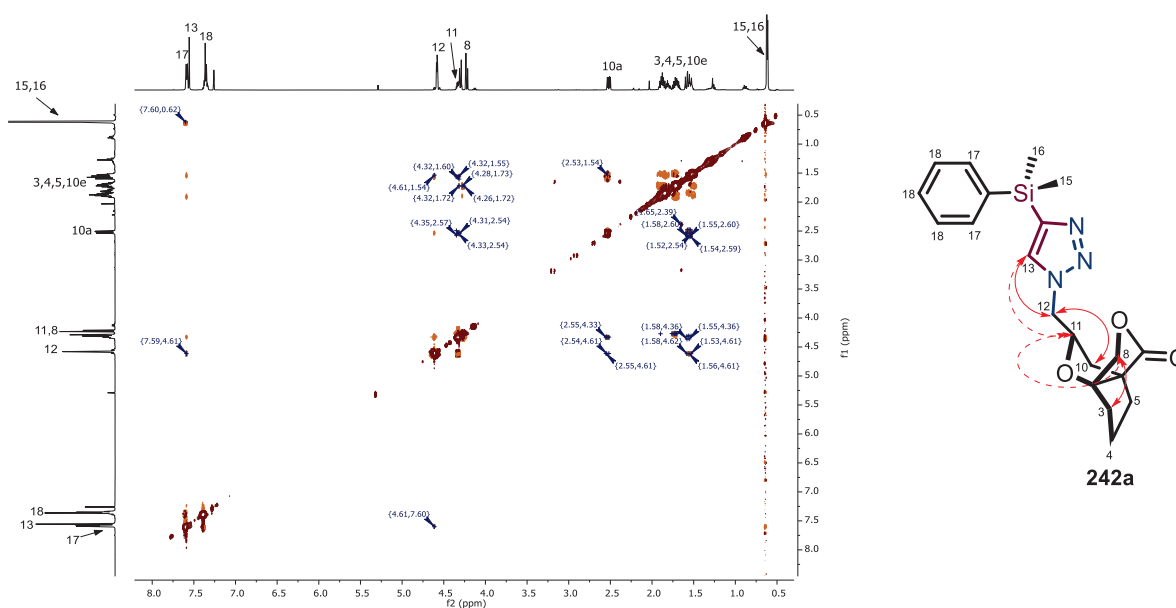
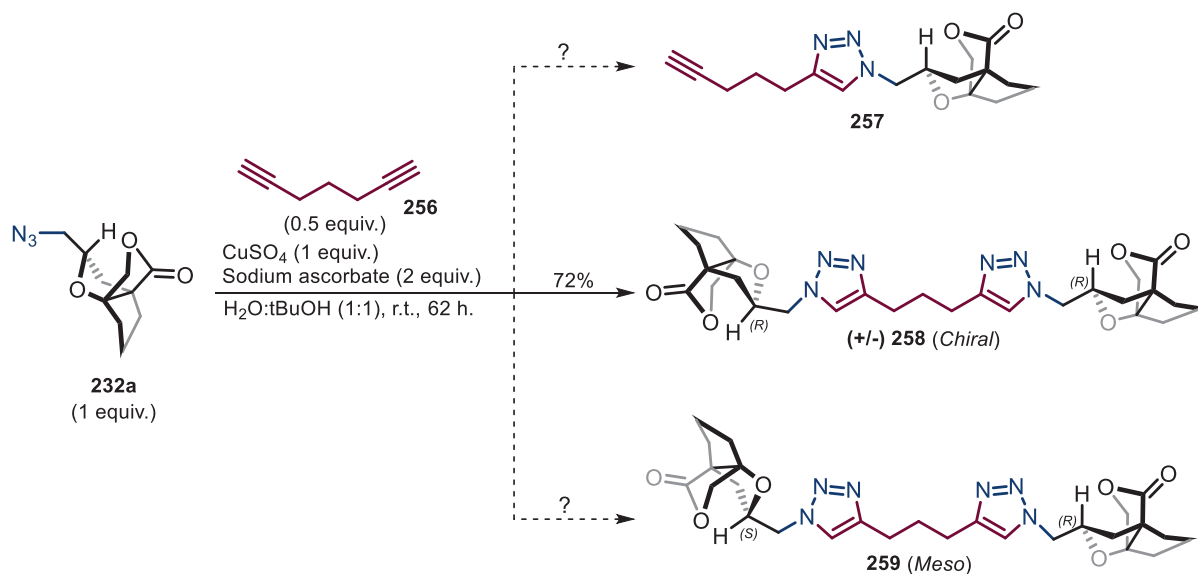


Figure 11. 2D NOESY NMR of **242a** (500 MHz, CDCl_3).

8.5. Synthesis of unusual bis-triazolo[3,3,3]propellane *via* double-click reaction

To explore the synthesis of bis-triazolo[3,3,3]propellane *via* double-click reaction, azido propellane **232a** was allowed to react with 0.5 equivalent of 1,6-heptadiyne **256** under similar reaction conditions used to prepare compounds **240-247** (Scheme 14). After 62 hours from launching the reaction, highly polar compounds have appeared on the baseline of the TLC plate (Petroleum ether: ethyl acetate 30:70). Subsequent treatment of the reaction crude, including a classical work-up followed by simple filtration over silica gel, yielded a mixture of pale-yellow oil accompanied with minuscule white solid clusters. While trying to dissolve a part of this mixture for NMR characterization, we noticed that the white solid was insoluble in deuterated chloroform. We took advantage of this insolubility to separate both compounds by successive washing off the mixture with chloroform, and hence no further chromatographic purification has been required.

The 1D NMR spectra of the oily product were highly comparable to those obtained previously from the mono-click reactions (Figure 12). For instance, the ^1H NMR spectrum revealed the characteristic peak of the triazole group H13 at 7.38 ppm, in addition to the distinctive signals of the propellane subunit H8, H11, and H12 in a range between 4.10 and 4.61 ppm. Similarly, ^{13}C NMR, accompanied by DEPT-135, showed all the signals of the triazolo propellane system in addition to 2 CH_2 peaks between 23 ppm and 30 ppm. With further HRMS analysis, the most likely product was suggested to be one of the double-click compounds **258** or **259**.



Scheme 14. Results from the CuAAC of **232a** with 1,6-heptadiyne **256**.

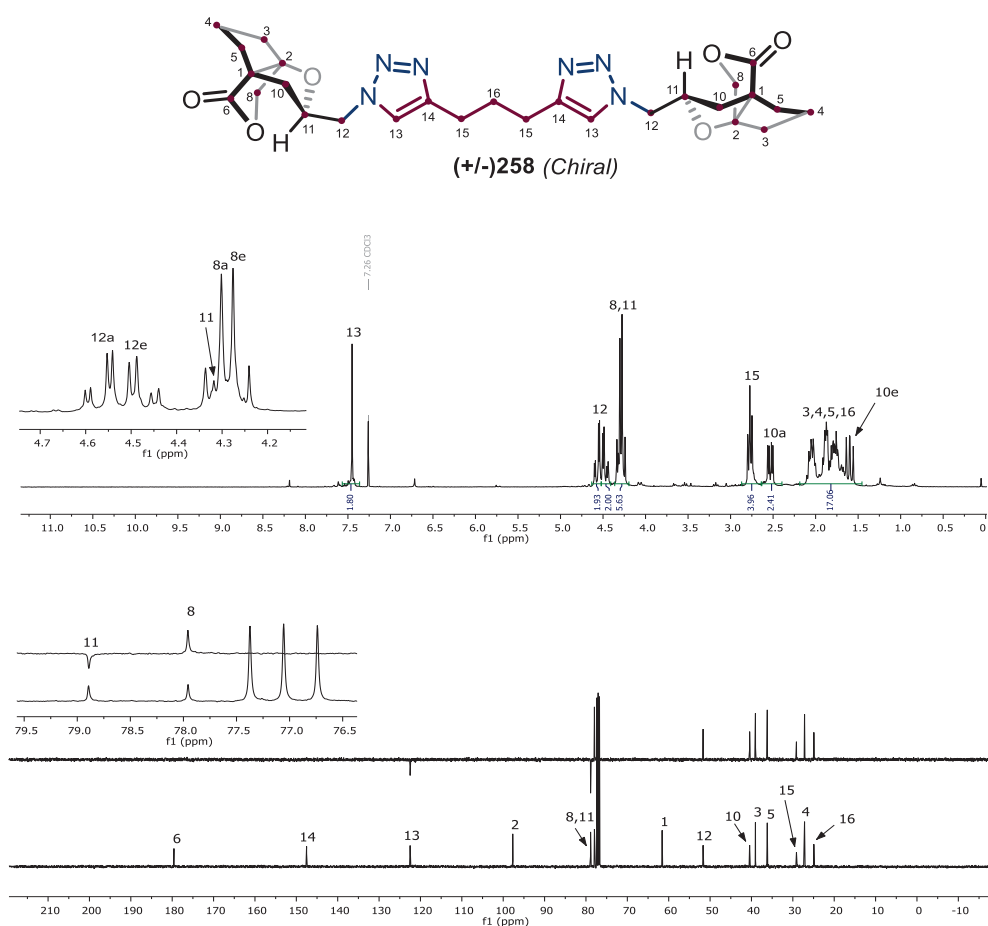


Figure 12. 1D NMR analysis of **258**; Top: ¹H NMR (500 MHz, CDCl₃), bottom: ¹³C NMR (126 MHz, CDCl₃).

After examining its optical activity, the obtained product was chiral ($[\alpha]_D^{20} +4.6^\circ$ ($c = 1.3$, DCM)), thus indicating the presence of the bis-triazolo[3,3,3]propellane **258**. Presumably, the mono-click product **257**, once it is formed, can transmit chirality to the alkyne group in the second click process, and hence resulting in a higher population of one conformation over another. Further studies in the future, such as molecular modeling combined with solid-state structures, may help determine the real mechanism of such process. Finally, the insolubility of the white residual solid, obtained from the reaction mixture, made it hard to determine its structure, which could be either **257** or **259**.

9. A new approach toward unsaturated [5,3,3]propellano-bislactone

So far, allyl bicyclic γ -lactone **169a** has been an excellent building block to easily access a variety of substituted [3,3,3]propellanes. To expand the use of **169a** in the construction of other ring systems, we herein report a simple and convenient methodology for the synthesis of unsaturated propellano-bislactones **263** (Figure 13). The beautiful structural architecture of such propellanes and the important biological properties of polylactones have also attracted the attention of several research groups. For instance, Ginsburg^[73] and Satyanarayana^[74] have reported the synthesis of bis-lactones **260-261** and **262** respectively (Figure 13). Compounds **260** and **261** were established using *Baeyer-Villiger* oxidation of the title compound,^[73] whereas **262** was prepared using acetates of the Baylis-Hillman adducts.^[74]

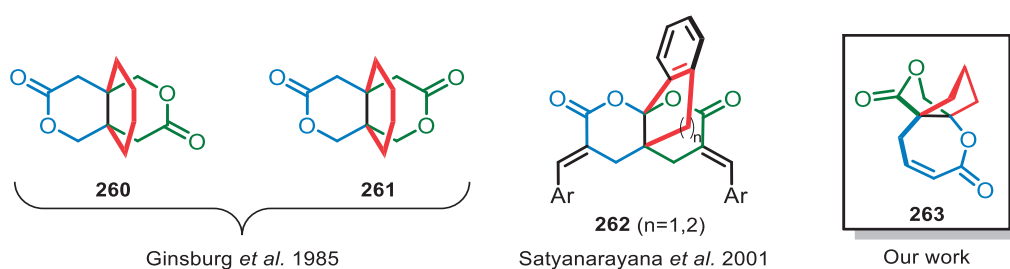


Figure 13. Some propellano-bislactones found in the literature **260-262** in addition to our designed ring system **263**.

The designed [5,3,3]propellano-bislactone **263** comprises a tricyclic [7,5,5] heteroatom framework (Figure 14). It includes one γ -lactone, in addition to 6,7-dihydro-2(5*H*)-oxepinone subunit. Theoretically, the α,β -unsaturated system could be used for further functionalization, making it an important feature for the compound's future utility.

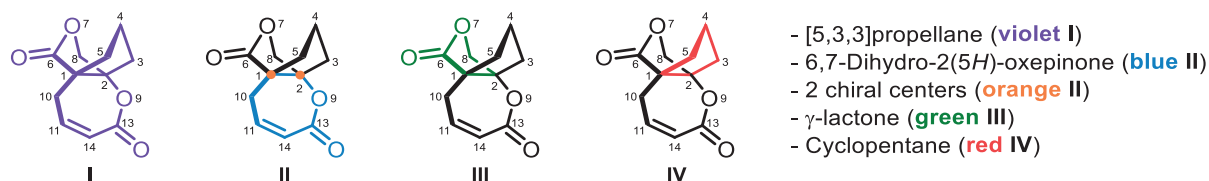


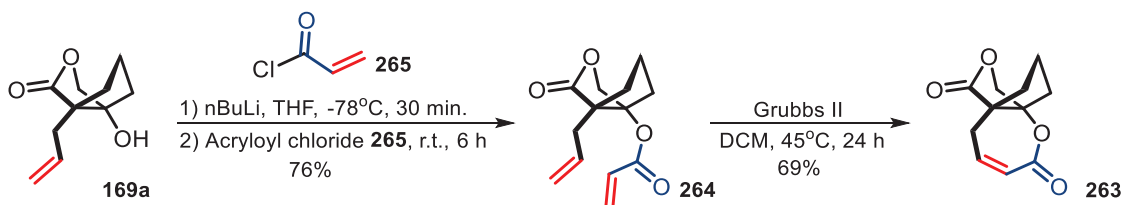
Figure 14. Key features of the designed [5,3,3]propellano-bis lactone **263**.

By analyzing the retrosynthetic pathway of **263**, the unsaturation between C11 and C14 could be obtained by ring-closing metathesis^[44] of **264**, which can be derived from the readily prepared bicyclic γ -lactone **169a** via classical esterification with acryloyl chloride **265** at O9 (Scheme 15).



Scheme 15. Retrosynthetic analysis of **263**.

The synthetic pathway for compounds **264** and **263** is presented in Scheme 16. Deprotonation of **169a** with *n*-BuLi at low temperatures followed by dropwise addition of acryloyl chloride **265** gave the bis-alkene product **264** in 76% yield. The latter compound was then refluxed with Grubbs 2 catalyst (10 mol%) in dichloromethane for one day before affording the desired [5,3,3]propellano-bis lactone **263** in 69% yield. The ¹H NMR of the final product was compared to that of **264** as shown in Figure 15. The characteristic signals of protons H12 and H15 corresponding to the terminal alkenes of **264** (5.00-6.58 ppm) have disappeared in the spectrum of **263**. Moreover, the doublet of doublet of H14 in **264** became a doublet in **263**, and H11 came to be more deshielded in **263**. All these arguments, in addition to MS spectroscopy, ensure the suggested structure of **263**.



Scheme 16. Synthesis of **263**.

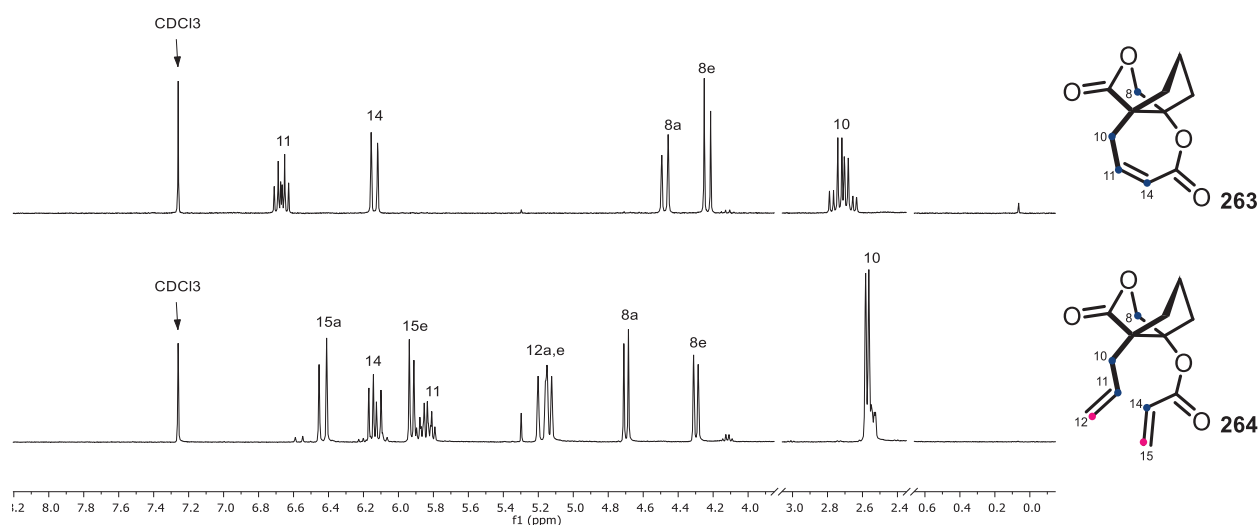


Figure 15. Some characteristic signals of compounds **263** and **264** taken from their related ^1H NMR spectra.

10. Conclusion

As presented, carbocyclic and heterocyclic propellanes occupy a special place in synthetic organic chemistry because of their aesthetically appealing structural architecture. In this work, we presented a brief overview of the synthesis of such propellanes and their occurrence in material sciences, natural products, and medicinal chemistry. We also reported the synthetic feasibility of highly functionalized [3,3,3]propellanes and [5,3,3]propellano-bis lactone from the already prepared allyl bicyclic γ -lactone **169a**. To ensure their suggested molecular structure, all the obtained compounds were fully characterized and assigned using 1D and/or 2D NMR experiments in addition to mass spectroscopy. In the subsequent chapters, many other stunning syntheses of new propellane families will also be reported and discussed in detail.

11. References

- [1] a) A. M. Dilmaç, E. Spuling, A. de Meijere, S. Bräse, *Angew. Chem. Int. Ed.* **2017**, *56*, 5684-5718; b) A. Osmont, L. Catoire, I. Gökalp, *Energy Fuels* **2008**, *22*, 2241-2257; c) J. Altman, E. Babad, J. Itzhaki, D. Ginsburg, *Tetrahedron* **1966**, *22*, 279-304.
- [2] J. J. Bloomfield, J. S. Irelan, *Tetrahedron Lett.* **1966**, *7*, 2970-2973.
- [3] A. Nickon, E. Silversmith, *Organic chemistry: The name game*, Pergamon New York, **1987**.
- [4] A. J. Pihko, A. M. Koskinen, *Tetrahedron* **2005**, *61*, 8769-8807.
- [5] K. B. Wiberg, *Chem. Rev.* **1989**, *89*, 975-983.
- [6] G. Snatzke, G. Zanati, *Justus Liebigs Ann. Chem.* **1965**, *684*, 62-78.

- [7] a) M. P. Cava, R. L. Shirley, *J. Org. Chem.* **1961**, *26*, 2212-2215; b) G. Stork, J. Tsuji, *J. Am. Chem. Soc.* **1961**, *83*, 2783-2784; c) T. A. Geissman, G. A. Ellestad, *Tetrahedron Lett.* **1962**, *3*, 1083-1088; d) J. K. Williams, R. E. Benson, *J. Am. Chem. Soc.* **1962**, *84*, 1257-1258; e) D. E. Applequist, R. Searle, *J. Am. Chem. Soc.* **1964**, *86*, 1389-1391.
- [8] O. Diels, W. Friedrichsen, *Liebigs Ann. Chem.* **1934**, *513*, 145–155.
- [9] G. Wittig, U. Mayer, *Chem. Ber.* **1963**, *96*, 342-348.
- [10] K. B. Wiberg, J. E. Hiatt, G. Burgmaier, *Tetrahedron Lett.* **1968**, *9*, 5855-5857.
- [11] a) M. D. Newton, J. M. Schulman, *J. Am. Chem. Soc.* **1972**, *94*, 773-778; b) W. D. Stohrer, R. Hoffmann, *J. Am. Chem. Soc.* **1972**, *94*, 779-786.
- [12] K. B. Wiberg, F. H. Walker, *J. Am. Chem. Soc.* **1982**, *104*, 5239-5240.
- [13] a) P. Chakrabarti, P. Seiler, J. D. Dunitz, A. D. Schluter, G. Szeimies, *J. Am. Chem. Soc.* **1981**, *103*, 7378-7380; b) J. E. Jackson, L. C. Allen, *J. Am. Chem. Soc.* **1984**, *106*, 591-599; c) K. B. Wiberg, *Chem. Rev.* **1989**, *89*, 975-983.
- [14] a) J. D. Dunitz, P. Seiler, *J. Am. Chem. Soc.* **1983**, *105*, 7056-7058; b) N. D. Epiotis, *J. Am. Chem. Soc.* **1984**, *106*, 3170-3174.
- [15] K. B. Wiberg, R. F. Bader, C. B. Lau, *J. Am. Chem. Soc.* **1987**, *109*, 1001-1012.
- [16] a) M. L. Herr, *Tetrahedron* **1977**, *33*, 1897-1903; b) K. Mlinaric-Majerski, Z. Majerski, *J. Am. Chem. Soc.* **1983**, *105*, 7389-7395; c) I. Lee, K. Yang, H. S. Kim, *Tetrahedron* **1985**, *41*, 5007-5010; d) T. Kar, K. Jug, *Chem. Phys. Lett.* **1996**, *256*, 201-206.
- [17] a) E. W. Della, P. E. Pigou, C. H. Schiesser, D. K. Taylor, *J. Org. Chem.* **1991**, *56*, 4659-4664; b) K. B. Wiberg, S. T. Waddell, *J. Am. Chem. Soc.* **1990**, *112*, 2194-2216; c) P. Kaszynski, J. Michl, *J. Org. Chem.* **1988**, *53*, 4593-4594; d) P. Kaszynski, J. Michl, *J. Am. Chem. Soc.* **1988**, *110*, 5225-5226; e) K. D. Bunker, N. W. Sach, Q. Huang, P. F. Richardson, *Org. Lett.* **2011**, *13*, 4746-4748.
- [18] a) J. D. Daniel Rehm, B. Ziemer, G. Szeimies, *Eur. J. Org. Chem.* **1999**, 2079-2085; b) M. Messner, S. I. Kozhushkov, A. de Meijere, *Eur. J. Org. Chem.* **2000**, 1137-1155.
- [19] M. D. Levin, P. Kaszynski, J. Michl, *Chem. Rev.* **2000**, *100*, 169-234.
- [20] K. B. Wiberg, C. M. Hadad, S. Sieber, P. V. R. Schleyer, *J. Am. Chem. Soc.* **1992**, *114*, 5820-5828.
- [21] a) J. Belzner, G. Szeimies, *Tetrahedron Lett.* **1986**, *27*, 5839-5842; b) A. B. Pierini, H. F. Reale, J. A. Medrano, *J. Mol. Struct.* **1986**, *148*, 109-118.
- [22] J. Turkowska, J. Durkaab, D. Gryko, *Chem. Commun.* **2020**, *56*, 5718-5734.
- [23] a) D. Ginsburg, *Acc. Chem. Res.* **1969**, *2*, 121-128; b) D. Ginsburg, *Acc. Chem. Res.* **1972**, *5*, 249–256; c) D. Ginsburg, *Top. Curr. Chem.* **1987**, *137*, 1–17.
- [24] a) K. B. Wiberg, *Acc. Chem. Res.* **1984**, *17*, 379–386; b) K. B. Wiberg, *Acc. Chem. Res.* **1996**, *29*, 229–234.
- [25] D. Ginsburg, Verlag Chemie, Weinheim, **1975**, p. 272.
- [26] A. M. Dilmaç, T. Wezeman, R. M. Bär, S. Bräse, *Nat. Prod. Rep.* **2020**, *37*, 224-245.
- [27] A. J. Pihko, A. M. Koskinen, *Tetrahedron* **2005**, *61*, 8769-8808.

- [28] a) A. Ioffe, V. Svyatkin, O. Nefedov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1988**, 37; b) T. Shubina, P. Gunchenko, T. Vigovskaya, P. Schreiner, A. Yurchenko, A. Fokin, *Theor. Exp. Chem.* **2002**, 38, 229-236; c) V. Polo, J. Andres, B. Silvi, *J. Comput. Chem.* **2007**, 28, 857-864.
- [29] a) F. Bohlmann, J. Jakupovic, *Phytochemistry* **1980**, 19, 259-265; b) F. Bohlmann, N. Le Van, T. V. Pham, J. Jacupovic, A. Schuster, V. Zabel, W. H. Watson, *Phytochemistry* **1979**, 18, 1831-1834.
- [30] Q. W. Shi, F. Sauriol, O. Mamer, L. O. Zamir, *Chem. Commun.* **2003**, 68-69.
- [31] F. Schneider, K. Samarin, S. Zanella, T. Gaich, *Science* **2020**, 367, 676-681.
- [32] S. R. Wilson, R. B. Turner, *J. Org. Chem.* **1973**, 38, 2870-2873.
- [33] H. Zhu, C. Chen, Q. Tong, X. N. Li, J. Yang, Y. Xue, Z. Luo, J. Wang, G. Yao, Y. Zhang, *Angew. Chem. Int. Ed.* **2016**, 55, 3486-3490.
- [34] F. E. Meyer, P. Parsons, A. J. De Meijere, *J. Org. Chem.* **1991**, 56, 6487-6488.
- [35] K. B. Wiberg, F. H. Walker, *J. Am. Chem. Soc.* **1982**, 104, 5239-5240.
- [36] K. B. Wiberg, N. McMurdie, *J. Am. Chem. Soc.* **1991**, 113, 8995-8996.
- [37] F. Alber, G. Szeimies, *Chem. Ber.* **1992**, 125, 757-758.
- [38] K. B. Wiberg, S. T. Waddell, *Tetrahedron Lett.* **1988**, 29, 289-292.
- [39] Y. He, H. Y. Chen, J. Hou, Y. Li, *J. Am. Chem. Soc.* **2010**, 132, 1377-1382.
- [40] a) A. Duarte-Ruiz, K. Wurst, B. Kräutler, *Helv. Chim. Acta* **2001**, 84, 2167-2177; b) C. Li, J. Zhang, X. Liu, Y. Zhou, D. Sun, P. Cheng, B. Zhang, Y. Feng, *RSC advances* **2014**, 4, 40758-40762; c) W. T. Su, M. Watanabe, Y. J. Chang, P. T. Chou, A. Ghosh, T. J. Chow, *Tetrahedron Lett.* **2015**, 56, 1092-1095.
- [41] J. Belzner, B. Gareiß, K. Polborn, W. Schmid, K. Semmler, G. Szeimies, *Chem. Ber.* **1989**, 122, 1509-1529.
- [42] a) G. Dyker, J. Körning, P. G. Jones, P. Bubenitschek, *Angew. Chem. Int. Ed.* **1993**, 32, 1733-1735; b) G. Dyker, J. Körning, P. Jones, P. Bubenitschek, *ChemInform* **1994**, 25, 116-122.
- [43] a) U. Weiss, J. M. Edwards, *Tetrahedron Lett.* **1968**, 9, 4885-4887; b) R. W. Weber, J. M. Cook, *Can. J. Chem.* **1978**, 56, 189-192; c) H. Torres-Gómez, K. Lehmkuhl, B. Frehland, C. Daniliuc, D. Schepmann, C. Ehrhardt, B. Wünsch, *Biorg. Med. Chem.* **2015**, 23, 4277-4285.
- [44] a) N. Holub, S. Blechert, *Chem. Asian J.* **2007**, 2, 1064-1082; b) S. Kotha, R. Gunta, *Beilstein J. Org. Chem.* **2015**, 11, 1727-1731.
- [45] T. Kubo, S. Miyazaki, T. Kodama, M. Aoba, Y. Hirao, H. Kurata, *Chem. Commun.* **2015**, 51, 3801-3803.
- [46] a) M. D. Duque, C. Ma, E. Torres, J. Wang, L. Naesens, J. Juárez-Jiménez, P. Camps, F. J. Luque, W. F. DeGrado, R. A. Lamb, L. H. Pinto, *J. Med. Chem.* **2011**, 54, 2646-2657; b) M. Rey-Carrizo, E. Torres, C. Ma, M. Barniol-Xicota, J. Wang, Y. Wu, L. Naesens, W. F. DeGrado, R. A. Lamb, L. H. Pinto, *J. Med. Chem.* **2013**, 56, 9265-9274; c) E. Torres, M. D. Duque, E. Vanderlinden, C. Ma, L. H. Pinto, P. Camps, M. Froeyen, S. Vázquez, L. Naesens, *Antiviral Res.* **2013**, 99, 281-291.
- [47] M. Rey-Carrizo, M. Barniol-Xicota, C. Ma, M. Frigolé-Vivas, E. Torres, L. Naesens, S. Llabrés, J. Juárez-Jiménez, F. G. Luque, W. F. DeGrado, R. A. Lamb, *J. Med. Chem.* **2014**, 57, 5738-5747.
- [48] E. Torres, R. Leiva, S. Gazzarrini, M. Rey-Carrizo, M. Frigolé-Vivas, A. Moroni, L. Naesens, S. Vázquez, *Med. Chem. Lett.* **2014**, 5, 831-836.

- [49] H. Torres-Gómez, K. Lehmkuhl, D. Schepmann, B. Wünsch, *Eur. J. Med. Chem.* **2013**, *70*, 78-87.
- [50] P. Kaszynski, A. C. Friedli, J. Michl, *J. Am. Chem. Soc.* **1992**, *114*, 601-620.
- [51] P. M. Warner, *J. Am. Chem. Soc.* **1994**, *116*, 11059-11066.
- [52] a) R. M. Minyaev, V. I. Minkin, T. N. Griбанова, A. G. Starikov, R. Hoffmann, *J. Org. Chem.* **2003**, *68*, 8588-8594; b) E. T. Seidl, H. F. Schaefer, *J. Am. Chem. Soc.* **1991**, *113*, 1915-1917.
- [53] R. Gianatassio, J. M. Lopchuk, J. Wang, C. M. Pan, L. R. Malins, L. Prieto, T. A. Brandt, M. R. Collins, G. M. Gallego, N. W. Sach, J. E. Spangler, *Science* **2016**, *351*, 241-246.
- [54] R. Nakajima, N. Yamamoto, S. Hirayama, T. Iwai, A. Saitoh, Y. Nagumo, H. Fujii, H. Nagase, *Biorg. Med. Chem.* **2015**, *23*, 6271-6279.
- [55] a) M. Labelle, Y. Guindon, *J. Am. Chem. Soc.* **1989**, *111*, 2204-2210; b) Y. Tamaru, M. Hojo, S. Kawamura, S. Sawada, Z. Yoshida, *J. Org. Chem.* **1987**, *52*, 4062-4072.
- [56] a) A. M. Sanseverino, F. M. Silva, J. Jones Jr, M. C. Mattos, *Quim. Nova* **2001**, *24*, 637-645; b) A. M. Sanseverino, M. C. de Mattos, *Synthesis* **1998**, *11*, 1584-1586.
- [57] C. Chatgililoglu, C. Ferreri, M. Lucarini, A. Venturini, A. A. Zavitsas, *Chem. Eur. J.* **1997**, *3*, 376-387.
- [58] a) A. Marker, D. Doddrell, N. V. Riggs, *J. Chem. Soc.* **1972**, *10*, 724-725; b) H. Spiesecke, W. G. Schneider, *J. Chem. Phys.* **1961**, *35*, 722-731.
- [59] Z. Benfodda, F. Guillen, H. Arnion, A. Dahmani, H. Blancou, *Heteroat. Chem.* **2009**, *20*, 355-361.
- [60] H. Thomanek, S. T. Schenk, E. Stein, K. H. Kogel, A. Schikora, W. Maison, *Org. Biomol. Chem.* **2013**, *11*, 6994-7003.
- [61] J. Mulzer, A. Angermann, W. Münch, G. Schlichthörl, A. Hentzschel, *Liebigs Ann. Chem.* **1987**, 7-14.
- [62] R. A. Jackson, K. U. Ingold, D. Griller, A. S. Nazran, *J. Am. Chem. Soc.* **1985**, *107*, 208-211.
- [63] T. Castanheiro, J. Suffert, M. Donnard, M. Gulea, *Chem. Soc. Rev.* **2016**, *45*, 494-505.
- [64] A. W. Erian, S. M. Sherif, *Tetrahedron* **1999**, *55*, 7957-8024.
- [65] F. Ke, Y. Qu, Z. Jiang, Z. Li, D. Wu, X. Zhou, *Org. Lett.* **2011**, *13*, 454-457.
- [66] X. Lu, H. Wang, R. Gao, D. Sun, X. Bi, *RSC Adv.* **2014**, *4*, 28794.
- [67] H. C. Kolb, M. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004-2021.
- [68] H. C. Kolb, K. B. Sharpless, *Drug Discov. Today* **2003**, *8*, 1128-1137.
- [69] a) C. R. Becer, R. Hoogenboom, U. S. Schubert, *Angew. Chem. Int. Ed.* **2009**, *48*, 4900-4908; b) C. E. Hoyle, C. N. Bowman, *Angew. Chem. Int. Ed.* **2010**, *49*, 1540-1573; c) B. S. Sumerlin, A. P. Vogt, *Macromolecules* **2010**, *43*, 1-13.
- [70] a) K. D. Hanni, D. A. Leigh, *Chem. Soc. Rev.* **2010**, *39*, 1240-1251; b) C. O. Kappe, E. Van der Eycken, *Chem. Soc. Rev.* **2010**, *39*, 1280-1290.
- [71] a) B. T. Worrell, J. A. Malik, V. V. Fokin, *Science* **2013**, *340*, 457-460; b) V. O. Rodionov, V. V. Fokin, M. G. Finn, *Angew. Chem. Int. Ed.* **2005**, *44*, 2210-2215; c) V. O. Rodionov, S. I. Presolski, D. Díaz Díaz, V. V. Fokin, M. G. Finn, *J. Am. Chem. Soc.* **2007**, *129*, 12705-12712; d) G. C. Kuang, P. M. Guha, W. S. Brotherton, J. T. Simmons, L. A. Stankee, B. T. Nguyen, R. J. Clark, L. Zhu, *J. Am. Chem. Soc.* **2011**, *133*, 13984-14001.

- [72] X. Creary, A. Anderson, C. Brophy, F. Crowell, Z. Funk, *J. Org. Chem.* **2012**, *77*, 8756-8761.
- [73] P. Ashkenazi, M. Kapon, U. Piantini, W. Philipsborn, D. Ginsburg, *Helv. Chim. Acta* **1985**, *68*, 614-617.
- [74] D. Basavaiah, T. Satyanarayana, *Org. Lett.* **2001**, *3*, 3619-3622.

Chapter IV

Propellanes— from Propargyl Bicyclic
 β -Hydroxy- γ -Lactones

Ch. IV: Propellanes—from Propargyl Bicyclic β -Hydroxy- γ -Lactones

1. Introduction

Over the history of organic chemistry, molecules with unusual three-dimensional structures have frequently attracted the attention of chemists as possible synthetic targets.^[1] Among such structures, propellanes are one of the most recognizable. The development of efficient synthetic strategies to such ring systems from commercially available starting materials involving environmentally benign processes is worthy of systematic investigation. To this end, our efforts are directed to design diverse $[n,m,o]$ propellanes that exhibit a broad range of structural diversities. In the previous chapter, many functionalized propellanes have been reported from the common bicyclic intermediate **169a** (Figure 1). The presence of hydroxyl and allyl group, bonded to two vicinal quaternary carbons each, has promoted speedy access to a third ring and hence furnishing the desired propellane skeleton. This exceptional importance of the designed allyl bicyclic γ -lactone led us to investigate the chemistry of some analogs. Throughout this chapter, we explore the feasibility of the readily prepared propargyl bicyclic γ -lactones **166a-b** for the synthesis of rich variety of novel propellanes (Figure 1). In this regard, several approaches to oxaspiro $[n,3,3]$ -propellanes, besides other miscellaneous scaffolds, will be discussed in detail.

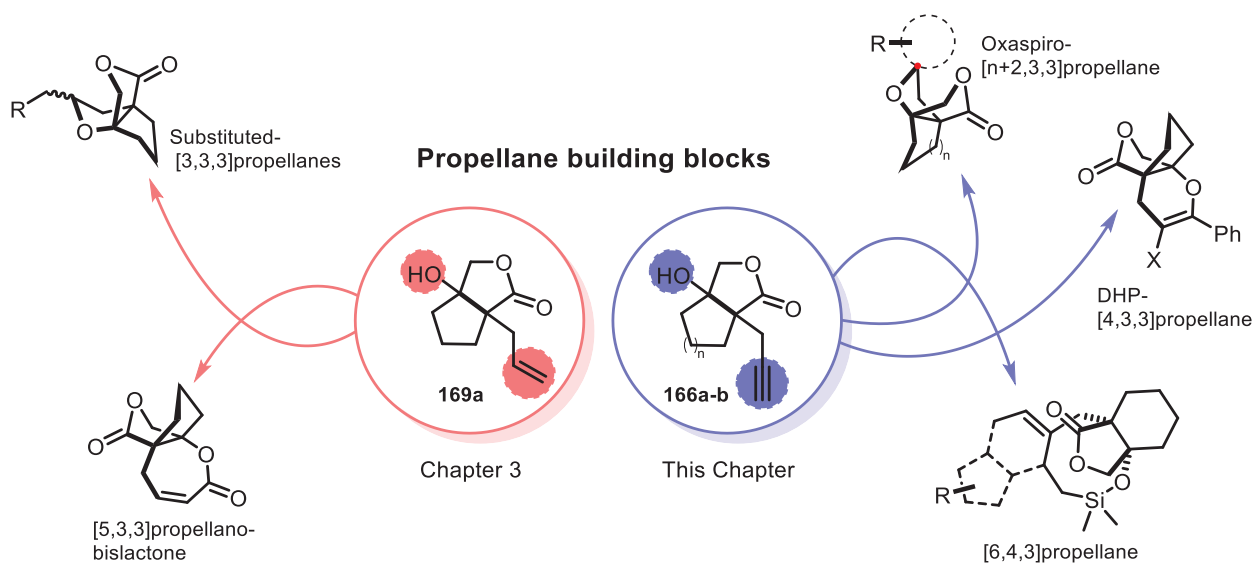


Figure 1. The rich variety of propellanes resulting from the bicyclic intermediates **169a** and **166a-b**.

2. Oxaspiro[*n*,3,3]propellanes

2.1. Spiropropellanes

Spirocyclic compounds are molecules containing two rings connected through a single shared atom (the spiroatom). Since first postulated by von Baeyer in 1900,^[2] such privileged structures have been found to occur in many natural and non-natural products.^[2-3] A rigid structure can be expected when the spirane skeleton consists of small or medium-sized rings. The resulting rigidity provides a stiff framework for the attachment of pharmacophoric groups or a rigid framework for metal coordination. Moreover, spirocycles have a high sp^3/sp^2 ratio by nature, a feature that is of increasing importance in the design of biologically active molecules with improved properties.^[2-3] In spiranes with no annular heteroatom, four carbon atoms are bonded directly to the quaternary spirocarbon. But in several spirane structures, a heteroatom, instead of a carbon atom, is linked directly to the spiranic center. When the heteroatom is oxygen, the nomenclature of the system will then be preceded by *oxa* to become “oxaspiro[*n,m*]alkane”, with *n* and *m* being the number of annular atoms in each cycle without counting the spiroatom. However, when two oxygens are bonded directly to the spirocarbon, a spiroketal thus results.^[4]

Spirocycles can be accompanied by a wide range of molecular structures.^[4b] They might be merged with propellanes to form a nonclassical family of organic compounds, spiropropellanes. The main interest in such derivatives is their exceptional rigidity, induced by their fascinating structural architecture, which could be behind important biological properties.

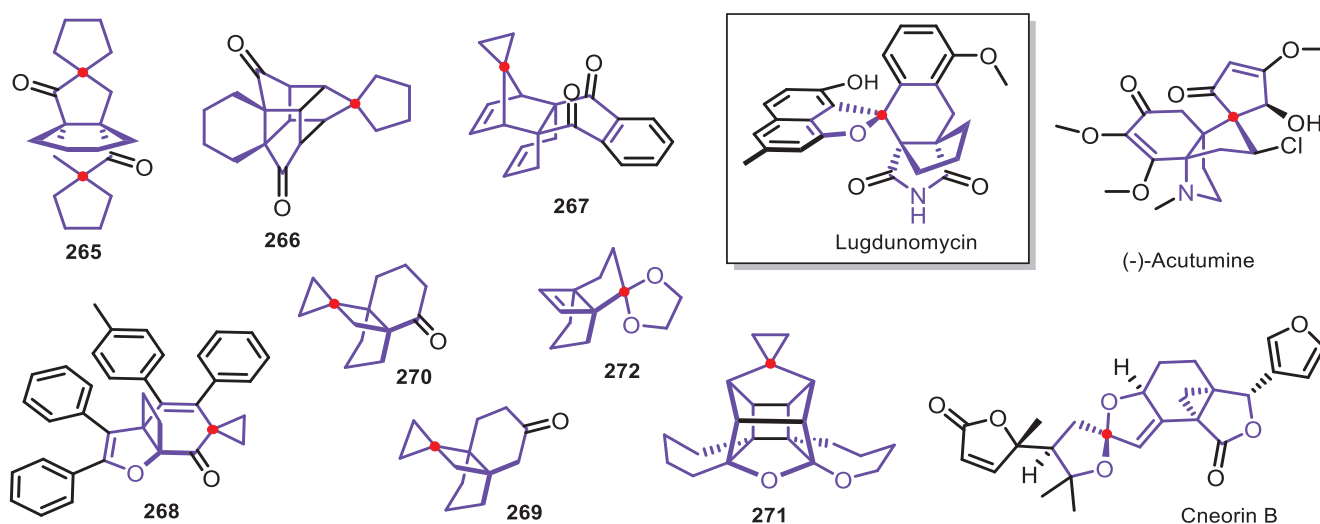


Figure 2. Some natural and non-natural products containing the spiro[*n,m,o*]propellane motif.

Such framework can occur naturally to give unprecedented chemical compounds. Recently, Wu and coworkers^[5] discovered Lugdunomycin, exhibiting unique structural characteristics, including the oxaspiro[4,3,3]propellane motif (Figure 2). Other natural products like (–)-acutumine^[6] and cneorin B^[7] analogues presented spiro[4,3,3]propellane and spiroketal[4,3,1]propellane, respectively, in their core structure. Non-natural compounds, comprising the spiropropellane skeleton, were also described by different research groups, but not extensively. Probably, the most well-known scaffolds are those functionalized cage propellanes and *D3*-trishomocubanes containing spiro linkage, such as **266**,^[8] **271**^[9] and their analogues, reported by Kotha *et al.* in a series of publications.^[4b, 10] Other miscellaneous approaches were also reported for the synthesis of **265**,^[11] **267**,^[12] **268**,^[13] **269**,^[14] **270**^[14] and **272**.^[15]

Despite the promises that these structures hold in terms of future applications, no studies have been dedicated to the detailed account of the synthetic strategies and applications of this family of compounds. Thus, we aimed to provide diverse spiropropellanes, focusing on oxaspiro[*n*,3,3]propellanes, by using different strategies for each (Figure 3). In this regard, this section covers the synthetic efforts made to access these polycyclic scaffolds with a strong focus on **274** and **275** (Figure 3). For better clarity, the synthetic approaches are sorted based on the number of annular atoms “A” attached to the common propellane subunit (**273-276**).

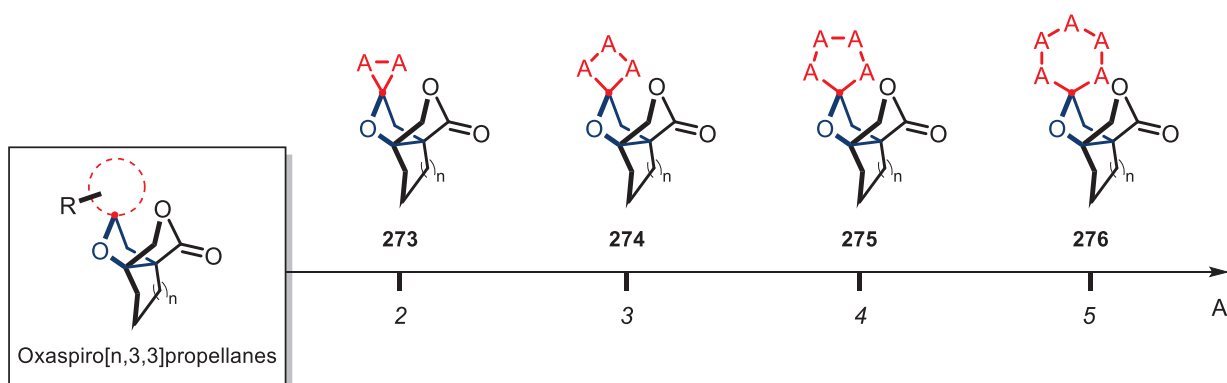
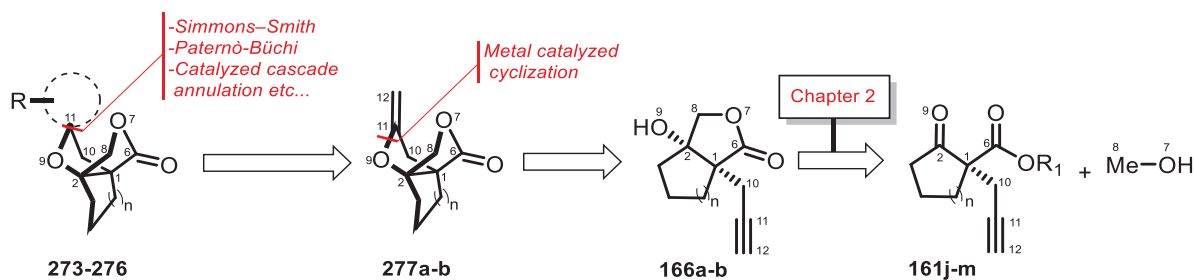


Figure 3. Our designed oxaspiro[*n*,3,3]propellanes (A = carbon or oxygen).

2.2. General retrosynthetic analysis of oxaspiro[*n*,3,3]propellanes

Oxaspiro[*n*,3,3]propellanes **273-276** can be envisioned through different cyclization reactions of the *exo* enol ether propellanes **277a-b**. Such reactions may include cyclopropanation (Simmons-

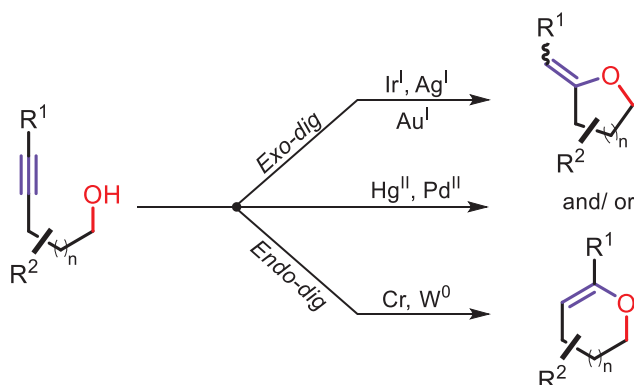


Scheme 1. General retrosynthetic analysis of oxaspiro[*n*,3,3]propellanes **273-276**.

Smith reaction), [2+2] photochemical cycloaddition (Paternò-Büchi reaction), acid-catalyzed cascade annulation, and others. The key intermediates **277a-b** can both be formed via metal-catalyzed cyclization of **166a-b**. Finally, the latter bicyclic γ -lactones have been prepared in a two-step sequence as already discussed in Chapter 2.

2.3. Formation of exocyclic enol ethers

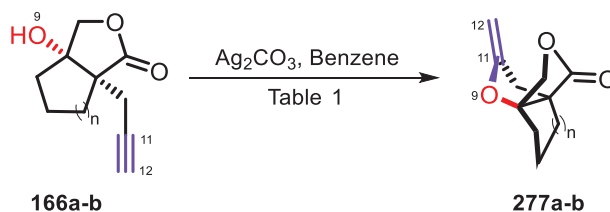
Due to their synthetic value, numerous routes have been developed for the synthesis of tetrahydrofuran and pyrane motifs.^[16] Among these methods, the cyclization of acetylenic alcohols is one of the most rapid and convenient. Such cyclizations are usually performed through metal catalysis, and the obtained products are a result of either an *exo*-dig or an *endo*-dig annulation, or both (Scheme 2). Earlier versions were based on intramolecular oxymercuration starting from acetylenic alcohols, usually leading to the corresponding exocyclic enol ether.^[17] Later, the palladium(II) catalyzed version was pioneered by Utimoto *et al.*, but a mixture of *exo*- and *endo*-dig products could be obtained.^[18] Silver (I),^[19] gold(I),^[20] and iridium(I)^[21] catalyzed exclusively and efficiently the formation of exocyclic enol ethers.



Scheme 2. Formation of tetrahydrofurans and pyranes through metal-catalyzed cyclization of acetylenic alcohols.

However, chromium, tungsten and molybdenum catalysts led, in the presence of a base, to endocyclic enol ethers.^[22] To convert the propargyl bicyclic γ -lactones **166a-b** into their corresponding exocyclic enol ethers **277a-b**, silver-catalyzed cyclization^[19] was considered, and a series of conditions were tested (Table 1).

Table 1. Ag (I) catalyzed cyclization: formation of propellanes **277a-b**.



Entry	SM ^a	n	[166a] (mM)	T (°C)	t (h) ^b	Product	%Yield ^c
1 ^d	166a	1	30	r.t.	46	277a	46
2 ^d	166a	1	64	60	15	277a	54
3 ^d	166a	1	80	60	24	277a	49
4 ^d	166b	2	60	60	19	277b	51
5 ^d	166b	2	80	60	24	277b	64

^aStarting material; ^bReaction time; ^cIsolated yield; ^dAll reactions were carried out in the presence of silver carbonate (20 mol%) in benzene.

Pleasingly, the ring closure proceeded smoothly to give 2-methylenetetrahydrofuran moiety, thereby leading to less polar products **277a-b**. The yield of the reaction has been optimized *via* tuning some parameters like the molar ratio of the chosen substrate, temperature, and reaction time. At room temperature, the reaction proceeded slowly for 46 h, yielding only 46 % of the desired product **277a** (Entry 1). The best results were achieved when lactones **166a** (64 mM) (Entry 2) and **6b** (80 mM) (Entry 5) were carried out in the presence of Ag₂CO₃ (20 mol%) in benzene at 60°C, thus providing the corresponding propellanes **277a** and **277b** in 54% and 64% yield respectively. The related ¹H NMR spectra of the latter compounds are presented in Figure 4. As expected, the methylenide protons H12a,e have appeared as two signals around 4.40-4.59 and 3.75-3.90 ppm. These protons couple with each other ($J < 2$ Hz), as well as with the allylic protons H10a-e ($\delta \sim 2.91$ -2.10 ppm) *via* a long-range coupling ($^4J = 1.5$ Hz). Such arguments, in combination with ¹³C NMR assignments and HRMS, ensure the claimed structures of **277a-b**.

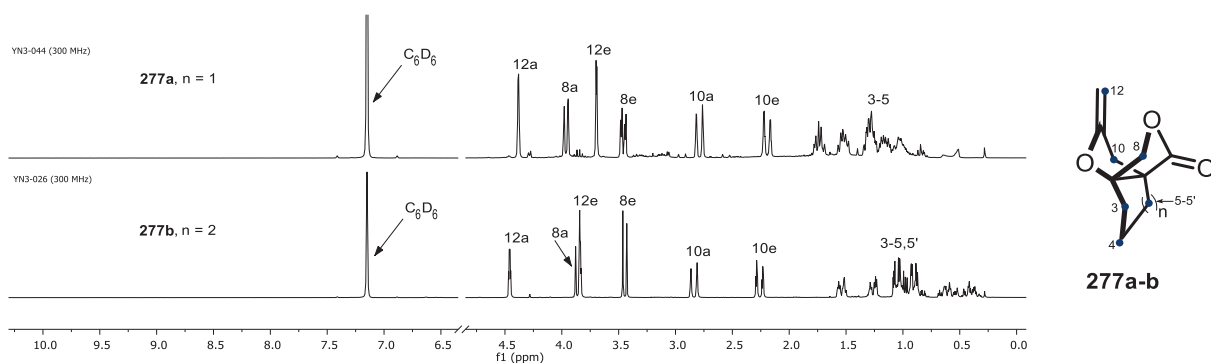
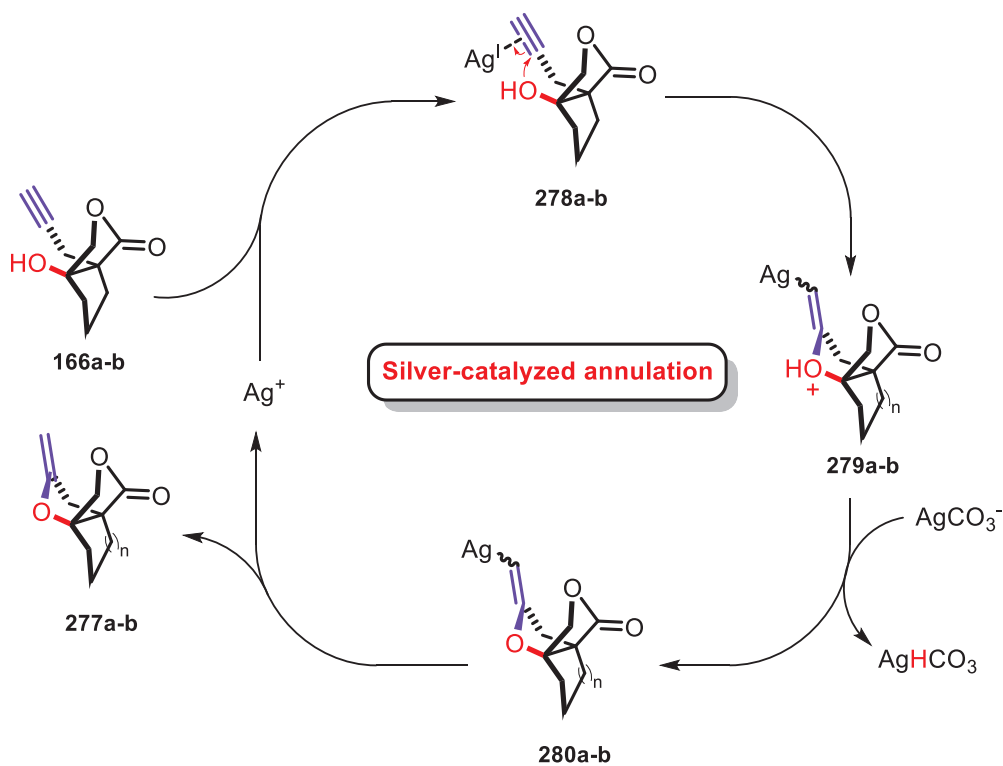


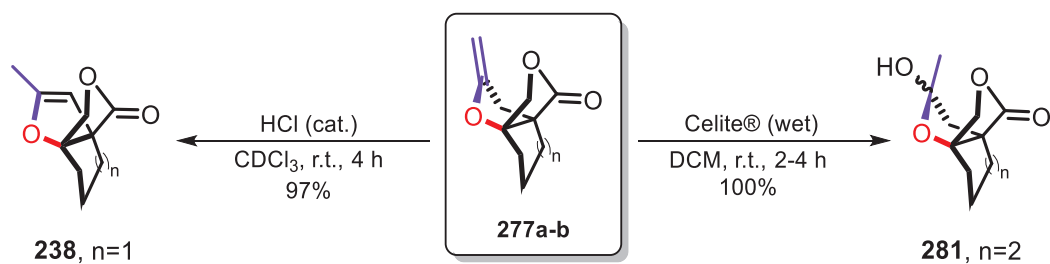
Figure 4. ^1H NMR spectra of **277a-b**.

From a mechanistic point of view, the results summarized above suggest a cyclization based on activation of the acetylenic moiety through Ag^{I} -coordination (**278a-b** in Scheme 3), which would induce a nucleophilic addition of the neighboring alcohol group. This cyclization would then lead to a protonated alkoxy organosilver intermediates **279a-b**, which could be converted to their neutral counterparts **280a-b** *via* deprotonation by silver carbonate. Finally, hydrolysis of the carbon–Ag bond would liberate the desired exocyclic enol ethers **277a-b** and regenerate the silver catalyst.



Scheme 3. Proposed mechanism for the silver-catalyzed annulation of **166a-b**.

Stability test of compounds **277a-b**



Scheme 4. Further undesired transformations of **277a-b**.

To investigate the stability of the obtained propellanes **277a-b**, catalytic amounts of HCl were dissolved in a solution of **277a** in deuterated chloroform at ambient temperature (Scheme 4). Four hours later, a quantitative isomerization to its *endo* enol ether counterpart **238** has been observed by ^1H NMR analysis. While the 2-methylenetetrahydrofuran protons have completely disappeared from the spectrum of **238**, new signals became to appear at 4.70 and 1.80 ppm related to the 5-methyl-2,3-dihydrofuran motif (Figure 5). It should be noted that **238** has been previously isolated from the reaction of iodo propellanes **231a-b** with sodium cyanide (Chapter 3), which helped us to recognize the structure more swiftly.

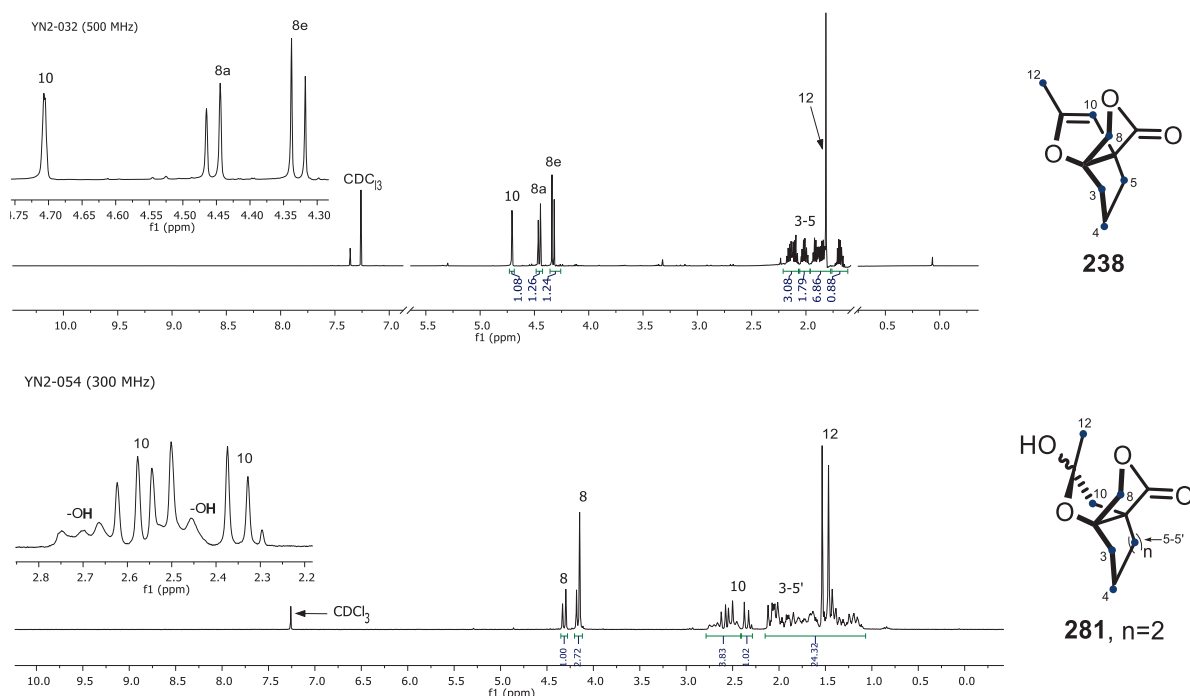


Figure 5. ^1H NMR spectra of **238** and **281**.

The structural assignments of **273a-b** are presented in Tables 2 and 3. The ^1H NMR chemical shifts of both compounds are similar with slight variation for protons H8 and H10 ($\Delta\delta \sim 0.15$ ppm). One peculiar feature has appeared in both spectra which is the upfield shift of the cyclopropane protons

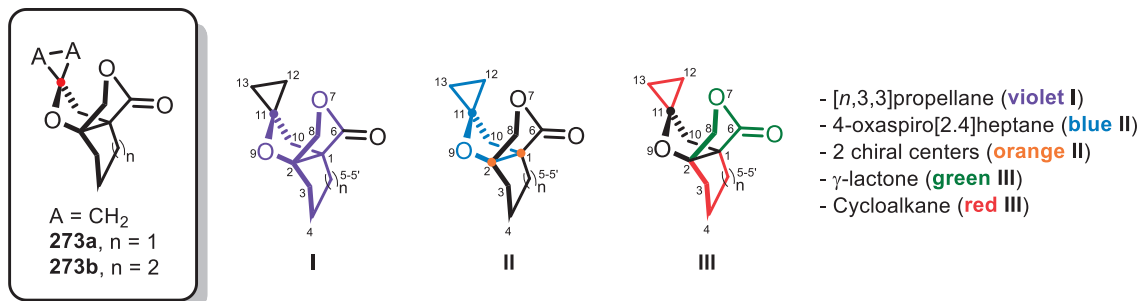


Figure 6. Key features of the designed oxaspirocyclopropane[n,3,3]propellanes **273a-b**.

Table 2. ^1H NMR assignments of compounds **273a-b** (300 MHz, CDCl₃).

	H3-5,5'	H8	H10	H12a	H12e	H13a	H13e
273a (n=1)	2.18 – 1.70 m	a: 4.44 d	2.23 s	a: 0.93 ddd	e: 0.80 ddd	a: 0.61 ddd	e: 0.48 ddd
		$J_{8a-8e}=10.2$		$J_{12a-12e}=11.5$	$J_{12e-12a}=11.5$	$J_{13a-13e}=10.4$	$J_{13e-13a}=10.4$
		e: 4.22 d		$J_{12a-13a}=5.6$	$J_{12e-13a}=6.3$	$J_{13a-12a}=5.6$	$J_{13e-12a}=6.5$
273b (n=2)	2.13-1.16 m	a: 4.25 d	a: 2.38 d	a: 0.88 ddd	e: 0.79 ddd	a: 0.58 ddd	e: 0.51 ddd
		$J_{8a-8e}=10.2$	$J_{10a-10e}=12.4$	$J_{12a-12e}=11.5$	$J_{12e-12a}=11.5$	$J_{13a-13e}=10.8$	$J_{13e-13a}=10.8$
		e: 4.18 d	e: 2.31 d	$J_{12a-13a}=5.4$	$J_{12e-13a}=6.6$	$J_{13a-12a}=5.3$	$J_{13e-12a}=6.6$
	$J_{8e-8a}=10.2$	$J_{10e-10a}=12.4$	$J_{12a-13e}=6.7$	$J_{12e-13e}=5.3$	$J_{13a-12e}=6.7$	$J_{13e-12e}=5.4$	

273a-b

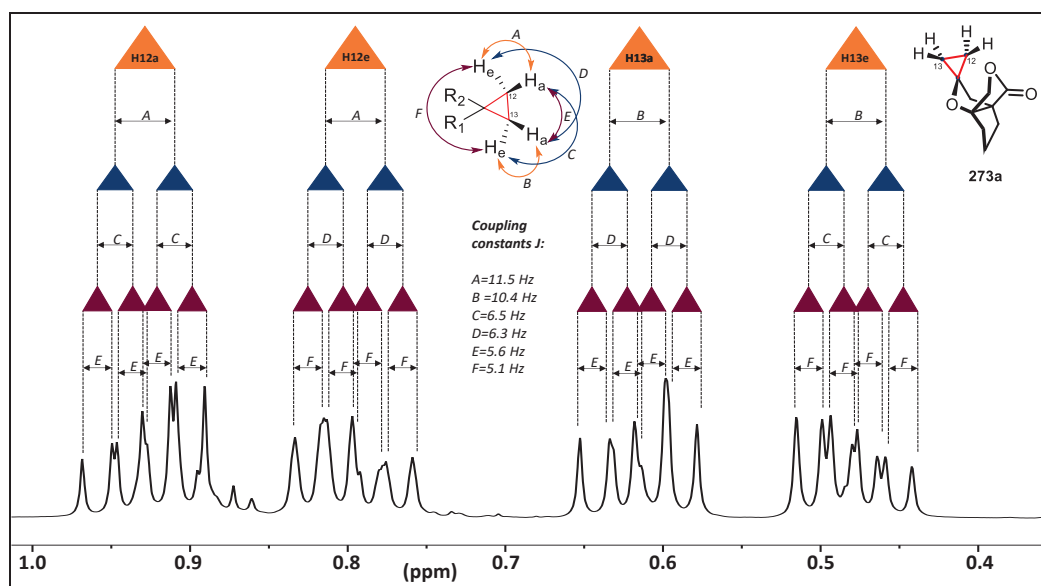


Figure 7. ^1H NMR analysis of protons H12 and H13 of **273a**.

Table 3. ^{13}C NMR assignments of compounds **273a-b** (76 MHz, CDCl_3).

	C1	C2	C3	C4	C5-5'	C6	C8	C10	C11	C12	C13
273a	62.4	97.3	38.8	27.1	36.3	180.7	78.4	43.7	65.6	10.6	7.2
273b	52.9	85.6	29.2	22.4	28.5 20.2	181.3	72.4	39.2	62.4	10.9	10.8



H12 and H13 (δ 0.93–0.43 ppm). It appears that the highly shielded position of such protons is well studied and conventionally accounted for in two ways.^[23] According to the first explanation, it is the anisotropy of the C–C bond, just opposite to CH_2 group in a three-membered ring, that shields the cyclopropane hydrogens. In the second explanation, an aromatic-like ring current involving the six electrons in the three C–C bonds (σ aromaticity) shields cyclopropane protons. Further insight into the origin of chemical shift values was obtained by theoretical studies revealing the shielding pattern arising from the cyclopropane framework in response to the applied magnetic field.^[24] By taking a closer look at the ^1H signals of H12 and H13, it is almost clear that each proton couples with its geminal and vicinal counterparts to give a ddd. For instance, the corresponding peaks of H12 and H13 in **273a** have appeared as four separate ddd between 0.41 and 0.97 ppm (Figure 7).

Assignments from ^{13}C NMR reveal the characteristic peaks of the cyclopropane motif which include two shielded methylene groups (C12 and C13; δ 7.2- 10.9 ppm) and one deshielded quaternary carbon (C11; δ 65.6 ppm) (Table 3). The rest of the signals of the propellane framework have remained similar to those obtained from the substituted scaffolds in Chapter 3.

2.5. Spiro-oxetanyl[*n*,3,3]propellanes

After being inspired by the fascinating combination of our propellane core structure with cyclopropane in the preceding section, we wanted to establish the oxaspiro[3,4]octane motif by forming a spiro-four-membered ring at position 11 (Figure 8). Among the extensive range of strained four-membered heterocycles, oxetane has been chosen for its high priority and significance to a broad range of chemical and biological applications.^[25] The designed propellanes thus comprise the dioxaspiro[3,4]octane motif with its three contiguous stereocenters, including one spiroatom (C11), which resides between the oxetane motif and the [*n*,3,3]propellane framework (Figure 8). To minimize the complexity of the system, no additional chiral centers were

included in the oxetane ring, and hence simple and similar aryl substituents were used at C13. The resulting molecular design is novel and, to the best of our knowledge, no similar merging between propellanes and oxetanes had ever been reported in the literature.

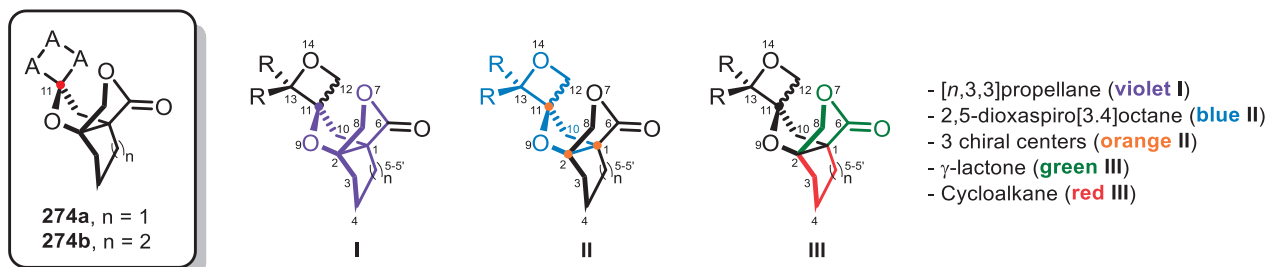
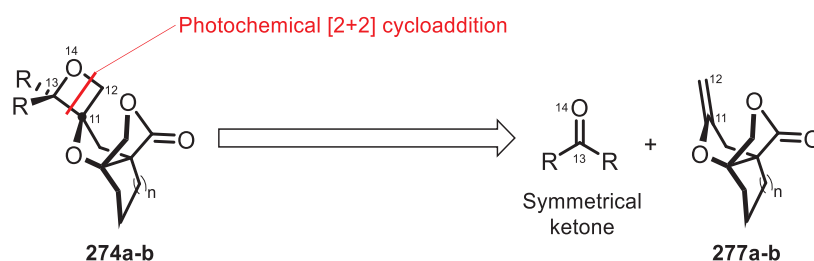


Figure 8. Key features of the designed oxaspiro-oxetanyl[n,3,3]propellanes **286-292**.

Retrosynthetic analysis: By considering the instability of the starting *exo* enol ethers **277a-b**, the retrosynthetic analysis of the designed propellanes required an appropriate and efficient strategy that could furnish the oxetane motif in a single operation. Accordingly, both the C11–C13 and C12–O14 bonds were envisioned to be established *via* the Paternò–Büchi reaction. In other words, they can be furnished by a photochemical [2+2] cycloaddition between **277a-b** and symmetrical ketone (Scheme 6).



Scheme 6. Retrosynthetic analysis of **274a-b**.

Over many years, the light-induced Paternò–Büchi reaction between carbonyls and olefins has been exploited for oxetane synthesis.^[26] For instance, this reaction was used as a key tool in the total synthesis of merrilactone A,^[27] (+)-Preussin,^[28] iridoids,^[29] and many other natural products.^[30] A series of comprehensive reviews published on the topic of the Paternò–Büchi reaction are cited here.^[30-31]

Techniques and methods:^[32] To achieve such type of transformation, several specific requirements have to be fulfilled. The chemical reagent (initiator) is light; therefore, the reaction vessel and any

optical components (lenses) should be transparent to the wavelength range of interest. The chosen products or intermediates formed in the course of the reaction may absorb at the wavelengths of irradiation. When their concentrations increase during the conversion, reaction efficiency may decrease and eventually stop. Side-reactions may be eliminated in some cases by decreasing the reactant concentration, which also improves light penetration within the sample, but as a result larger volume of the reaction mixture will be necessary. Since dioxygen is an efficient triplet quencher,^[33] it should usually be removed from the solution before irradiation. The most common procedures are purging the solution with argon or nitrogen for several minutes before or during irradiation (which, at the same time, serves to mix the solution constantly) or the more rigorous but demanding freeze–pump–thaw method. The latter process requires several cycles of freezing the solution in liquid nitrogen, evacuation using a high vacuum pump and subsequent thawing when the vacuum inlet is closed, in order to remove completely all dissolved gases. The glass vessel with the frozen solution can then be torch sealed or closed with a good PTFE stopcock.^[32]

Photochemical reactor: Such photochemistry can be carried out in a photoreactor of *external configuration*.^[34] This arrangement is very simple; the solution is held outside the source of irradiation. One option is to use an immersion well as shown in Figure 9, but the sample is placed in a separate vessel nearby. An external configuration reactor consisting of the reaction sample placed in the middle of an array of UV lamps (Rayonet) is also commercially available.

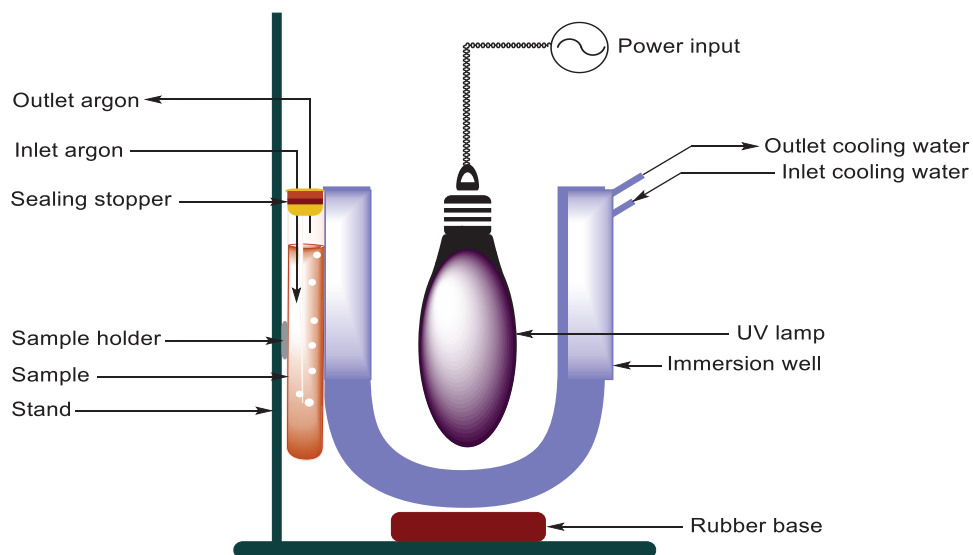


Figure 9. Photoreactor setup for the Paternò–Büchi reaction.

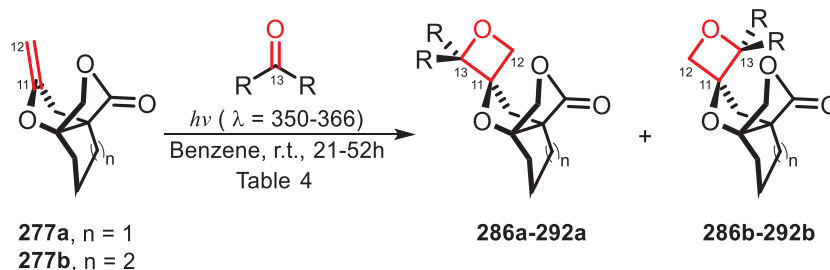
Synthesis: To examine the feasibility of our *exo* enol ethers **277a-b** as a platform starting material for the synthesis of diverse oxaspiro-oxetanyl[*n*,3,3]propellanes, different symmetrical benzophenone derivatives were allowed to react with **277a-b** under UV light ($\lambda \sim 350\text{-}366$ nm) in benzene. Initially, a series of reactions has been tested in the Rayonet ($\lambda \sim 350$ nm) at 48°C. Unfortunately, these attempts turned out to be unsuccessful due to partial isomerization of the starting material and the formation of dissociated products. At that time, we chose to repeat the same reactions, but at room temperature. Hence, we used another photoreactor of external configuration as already shown in Figure 9. Accordingly, the progress of the reactions has been followed by thin-layer chromatography (TLC) at different intervals of time. Based on the observed TLC, the irradiation was stopped as soon as the degradation of the formed products started to appear. As a result, no complete conversion of the starting materials has been attained in any of the studied cases. However, isomerization of the enol ethers **277a-b** and degradation of the formed products were less considerable than those observed from the reactions in the Rayonet at more elevated temperatures. Therefore, as reported in the literature by different research groups,^[35] the progress of such type of photochemical reactions is highly influenced by the temperature.

Upon purification of the desired adducts, triethylamine (1 vol%) was added to the appropriate eluent to neutralize silica gel and thereby avoid any possible transformations under acidic medium. For the same reason, similar precautions were taken for the NMR analysis where deuterated chloroform was either treated over alumina or replaced by deuterated benzene to analyze the crude or the purified samples. In doing so, we ensured that the work-up procedures had no effect on the obtained results.

Table 4 summarizes the performed photochemical cycloadditions of **277a-b** with symmetrical ketones **282-285**. In most of the cases, a separable 3:1 or 4:1 mixture of stereoisomers was mainly obtained as determined from ¹H NMR analysis of the crude mixture. The R_f of the major isomer was nearly similar to that of a bunch of other minor products, thus making its purification a very challenging task. This can explain the missing data in the results of some entries in Table 4. The best result was achieved when **277a** was irradiated in the presence of benzophenone **282** for 30 hours yielding the desired propellanes **286a/b** (3:1) in 56% yield (Entry 1). Under the same conditions, compounds **288**, **290**, and **291** were obtained in similar yields (45-50%) and still with low selectivities (Entries 3, 5 and 6). On the other hand, only the minor isomer was isolated when **277a** was irradiated with either dimethoxybenzophenone **283** (Entry 2) or dichlorobenzophenone

285 (Entry 4). The latter cases were accompanied by slight dissociations of products having similar polarities to that of the major isomer thereby making the purification process and even the NMR analysis highly difficult.

Table 4. Photochemical [2+2] cycloaddition of **277a/b** with different ketones **282-285**.



Entry	Enol ether ^a	Ketone ^a	R	t (h) ^b	Adducts	%Yield ^c
1	277a	282	Ph	30	286a/b (3:1) ^f	56
2	277a	283	4-OMe-Ph	30	287b	17 ^{eh}
3	277a	284	4-F-Ph	30	288a/b (3:1) ^f	45 ^h
4	277a	285	4-Cl-Ph	30	289b	19 ^{e,h}
5	277b	282	Ph	32	290a/b (4:1) ^f	49
6	277b	283	4-OMe-Ph	52	291a/b (4:1)	50 ^h
7	277b	284	4-F-Ph	48	292a/b (3:1) ^f	26 ^{e,g,h}

^aStarting material; ^bReaction time; ^cIsolated yield; ^eIsolated yield of a single diastereoisomer; ^fCrude ratio; ^gIsolated yield of **293a**; ^hSlight dissociation.

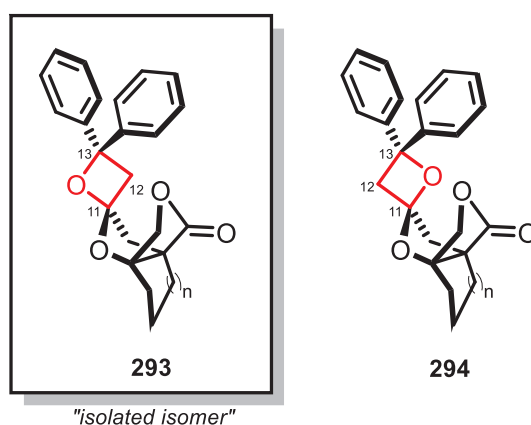
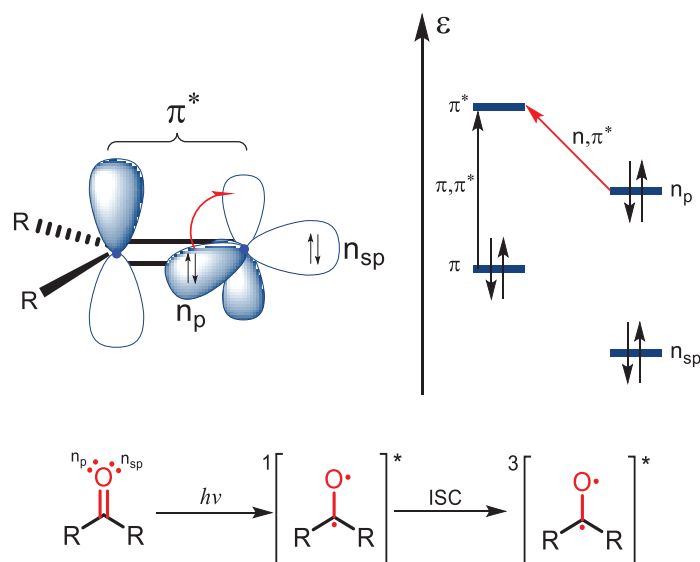


Figure 10. Structure and stereochemistry of regioisomers **293** and **294**

To evaluate the nature of the resulting side reactions, we were able to isolate a by-product in trace

amounts from Entry 1. By comparing its NMR data to those of spiro-oxetanes **286a-b**, it turned out to be one of their regioisomers **293** having the [4,5]-spiroketal motif (Figure 10). Careful analysis of 1D and 2D NMR data revealed the stereochemistry at C11 and allowed the complete assignments of the corresponding protons and carbons.

Reaction mechanism: As is generally known, carbonyl compounds have two nonbonding lone pairs on the oxygen atom occupying two nondegenerate n_p and n_{sp} orbitals (Scheme 7).^[32, 36] For simple ketones, the first ionization potential is attributed to the transition of one electron from n_p showing that this orbital, although located on a more electronegative atom, is higher in energy than the π bonding orbital. The n_p, π^* state is well represented by a biradical-like structure because of the presence of an unpaired electron in a nonbonding orbital (Scheme 7). Normally, this state rapidly undergoes an intersystem crossing (ISC) from a singlet (S_1) to a triplet (T_1) state since they are very close in energy. For aromatic ketones, the energies of $T_1(n_p, \pi^*)$ and $T_1(\pi, \pi^*)$ are also very close, therefore, the ISC from $S_1(n_p, \pi^*)$ to $T_1(\pi, \pi^*)$ is feasible. In fact, the nature of the substituents on the aromatic ring and the solvent may define which of these two triplet states is the lowest in energy. For example, the $T_1(\pi, \pi^*)$ is usually favored for ketones possessing electron donating groups,^[37] and hence, they undergo the Paternò-Büchi reaction with higher quantum yields than those which react in their n_p, π^* state.^[38]

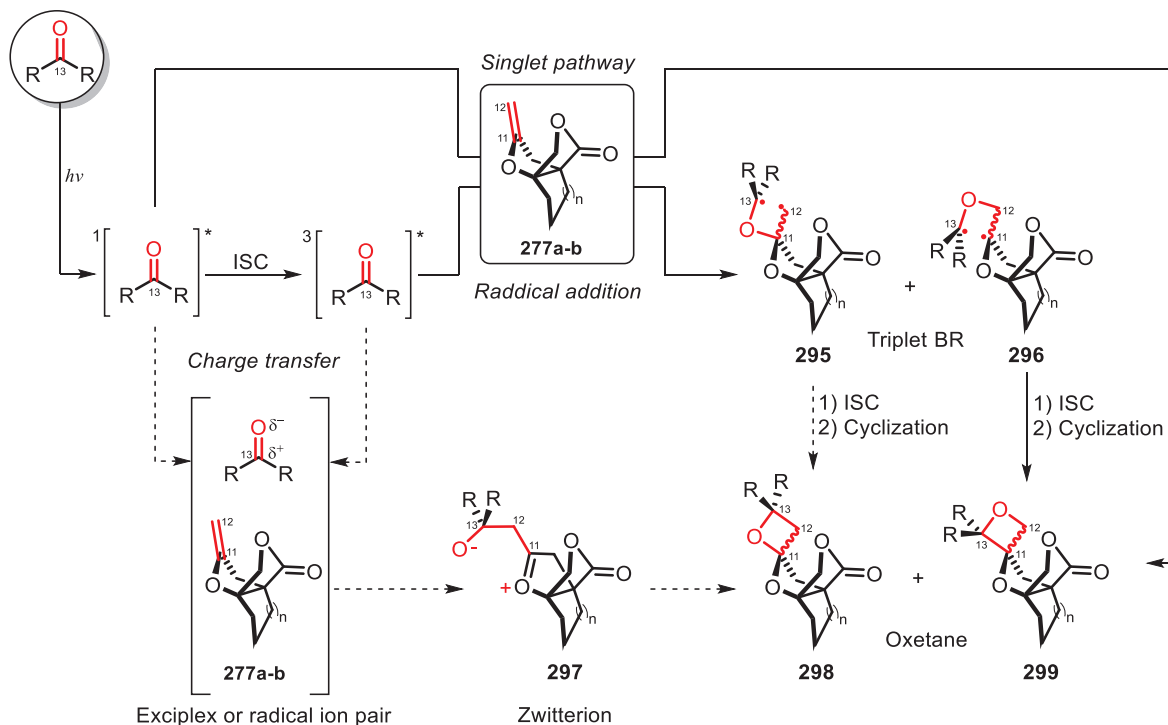


Scheme 7. MOs involved in the possible transitions and excited states of photoexcited carbonyl compounds.

Once they have been formed, both singlet and triplet excited species are known to produce cycloadducts. However, the scope and regio- and stereoselectivity of this process depend on the reactant multiplicity.^[39] The reaction may involve a concerted or a stepwise mechanism via 1,4-biradical intermediates (BR). Exciplex, radical ion pair, and zwitterion intermediate formation prior to oxetane cyclization have also been noted in some cases.^[40] This transformation may compete with inter-/intramolecular hydrogen abstraction or α -cleavage of the carbonyl moiety or with the reactions involving the alkene molecule.

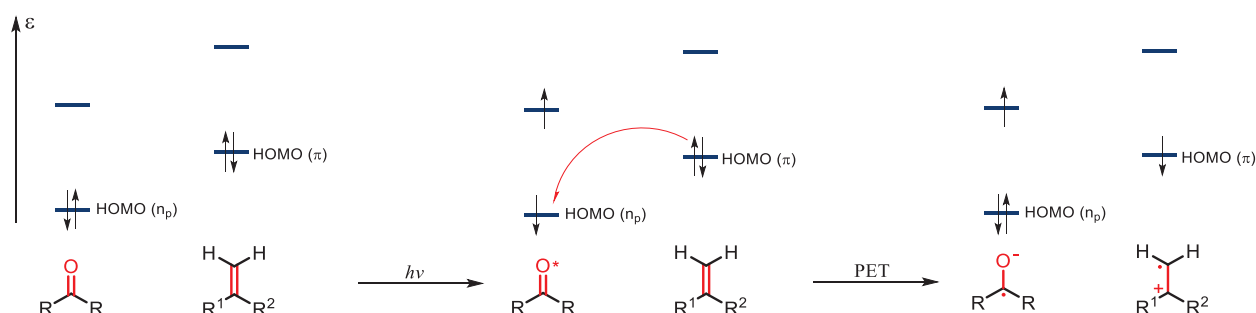
In light of the results obtained from Table 4, it is most likely that the reaction has proceeded to the stage where triplet 1,4-biradical intermediates **295** and **296** were formed (Scheme 8). The latter intermediate has a tertiary radical at the α -position of a heteroatom compared to a primary alkyl radical in **295**. Consequently, the oxetane will mainly be generated from the diradical possessing the longest lifetime, so from the most stable diradical **296**. This can explain the formation of **299** as a major product after a second ISC followed by a subsequent cyclization.

On the other hand, the formation of the minor product **298** might have also proceeded through a photoinduced electron transfer mechanism (PET) through a zwitterion intermediate **297**.^[40] The PET is induced by the interaction between the semi-occupied n_p orbital of the oxygen atom of the



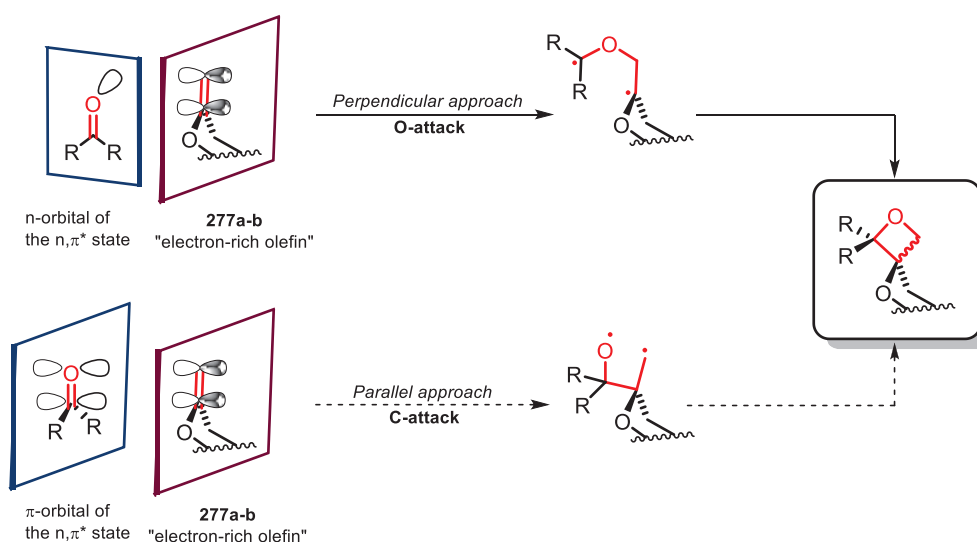
Scheme 8. Proposed reaction pathways to the obtained oxetanes **298** and **299**.

carbonyl compound in its triplet n_p, π^* state, and the π orbital (HOMO) of the alkene (Scheme 9). Apparently, the highly energetic HOMO of the used alkene **277a-b** induced the electron transfer to the n_p orbital of the reacted carbonyl compound forming oxetane **298** via a concerted or quasi-concerted mechanism.^[41]



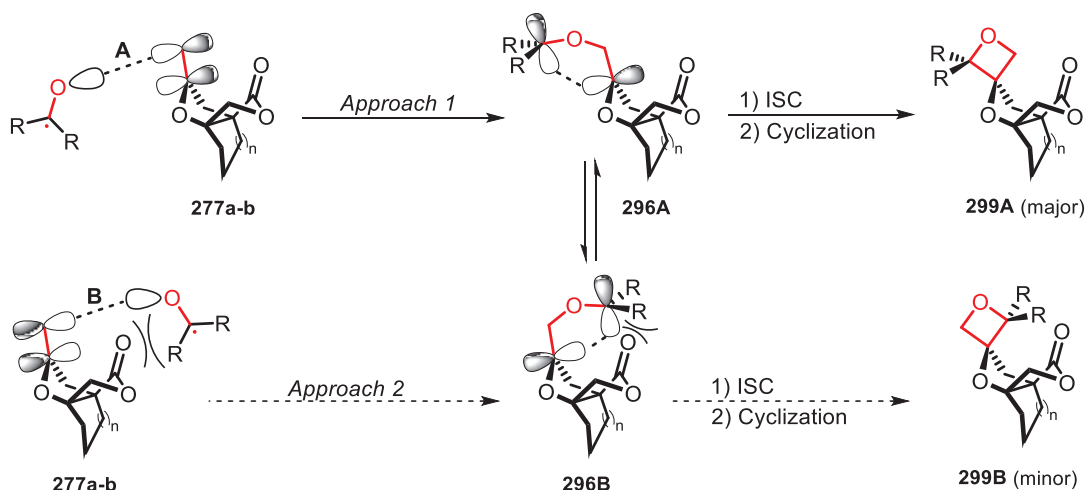
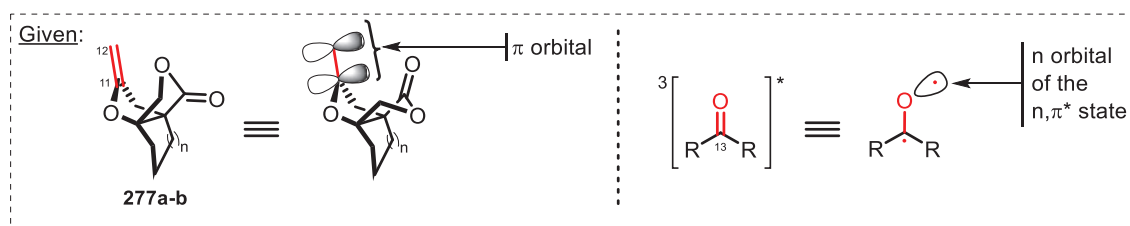
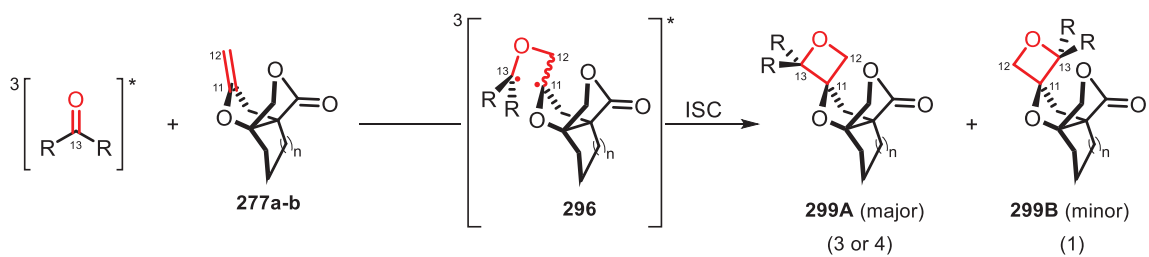
Scheme 9. The PET mechanism of the Paternò-Büchi reaction that may explain the formation of **298**.

Stereoselectivity: First, it should be noted that electron-rich alkenes, such as **277a-b**, preferentially interact with the electrophilic half-filled n-orbital on the oxygen atom, which is perpendicular to the π -plane (perpendicular approach), whereas electron-deficient alkenes attack either the oxygen atom or the nucleophilic carbon atom (parallel approach). The observed photoproduct stereochemistry cannot, however, distinguish between these mechanisms; but certain analysis reveals that the O-atom attack is favored *via* a perpendicular approach (Scheme 10).^[32, 42]



Scheme 10. The attack of an excited carbonyl compound by an electron-rich alkene **277a-b**.

The mechanisms described above allow the understanding, or even the prediction, of the preferential stereoselectivity observed in most of the cases studied in Table 4. Such selectivity can be rationalized by considering two different conformations **296A** and **296B** (Scheme 11). Both, having the two spin-bearing p-orbitals orthogonal and close in space to each other, are suitable for efficient ISC and C-C bond formation. Initially, the ketone *n*-orbital, which is perpendicular to the π -plane of the alkene, approaches either from outside the propellane core structure forming **296A** or from the lactone site forming **296B**. Hence, it is obvious that **296A** is sterically more favorable than **296B** because of the absence of the remarkable hindrance between the γ -lactone motif and the R group. This can explain the slight stereoselectivity obtained for oxetanes **299A** and **299B**.



Scheme 11. Diastereoselectivity in the cycloadditions of **277a-b** with symmetrical ketones.

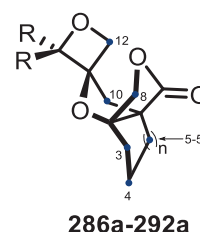
NMR analysis:

Tables 5 and 6 show the characteristic proton chemical shifts of **286-292** in C₆D₆ and their corresponding coupling constants. The expected structures possess three main AB systems residing on the oxygen-containing rings. Their related protons have appeared in the range from 1.43 to 4.66 ppm. Among these protons, H12a,e were the most deshielded (4.01-4.66 ppm), followed by H8a,e (3.33-4.05 ppm). Therefore, H10a,e, the least deshielded protons (1.43-2.91 ppm), can be correlated to the THF ring. On the other hand, according to the previously assigned scaffolds, the lactone AB system showed high geminal couplings (10.2-10.6 Hz) which are comparable to those observed from H8a,e (10.1-10.7 Hz) and higher than those from H12a,e (5.8-6.3 Hz). Consequently, H8a,e and H12a,e can be correlated to the lactone and the oxetane AB systems respectively (Figure 11).

The derived $\Delta\delta$ of protons H8, H10 and H12 between some of the obtained diastereoisomers are represented in Table 7. The slight variations of H10 ($\Delta\delta \sim 0.01$ - 0.12 ppm), observed in the studied isomers, can be related to the similar effect exerted by the R group on H10a or H10e in each diastereoisomer. However, the absolute value of $\Delta\delta$ increases for the oxetane protons H12 ($\Delta\delta \sim 0.14$ - 0.36 ppm) due to the different environments facing both protons in the AB system in each isomer. In other words, these protons could be situated toward either the alkyl ring in one isomer or the lactone group in the other one. Other considerable variations have been observed for the lactone protons H8 ($\Delta\delta \sim 0.13$ - 0.56 ppm), which might be resulted from the presence or absence of the shielding effect by the benzene ring on the lactone AB system in each conformation.

Table 5. ¹H NMR assignments of compounds **286a-292a** ^a(300 MHz, C₆D₆).

	H3-5,5'	H8a	H8e	H10a	H10e	H12a	H12e
286a R = Ph n = 1	1.76-0.87 m	a: 3.63 d $J_{8a\ 8e}=10.7$	e: 3.33 d $J_{8e-8a}=10.7$	a: 2.57 d $J_{10a-10e}=13.5$	e: 1.68 d $J_{10e-10a}=13.5$	a: 4.45 d $J_{12a-12e}=5.8$	e: 4.31 d $J_{12e-12a}=5.8$
287a R = 4-OMePh n = 1	-	a: 3.79 d $\delta J_{8a\ 8e}=10.3$	e: 3.54 d $J_{8e-8a}=10.3$	-	-	a: 4.57 d $J_{12a-12e}=6.1$	e: 4.39 d $J_{12e-12a}=6.1$
288a R = 4-F-Ph n = 1	1.55-0.94 m	a: 3.63 d $J_{8a\ 8e}=10.7$	e: 3.35 d $J_{8e-8a}=10.7$	a: 2.48 d $J_{10a-10e}=10.8$	e: 1.43 d $J_{10e-10a}=10.8$	a: 4.34 d $J_{12a-12e}=6.0$	e: 4.23 d $J_{12e-12a}=6.0$
290a R = Ph n = 2	1.53-0.66 m	a: 3.70 d $J_{8a\ 8e}=10.3$	e: 3.40 d $J_{8e-8a}=10.3$	a: 2.44 d $J_{10a-10e}=13.5$	e: 2.00 d $J_{10e-10a}=13.5$	a: 4.59 d $J_{12a-12e}=5.8$	e: 4.54 d $J_{12e-12a}=5.8$
291a R = 4-OMePh n = 2	1.57-0.70 m	a: 3.75 d $J_{8a\ 8e}=10.2$	e: 3.42 d $J_{8e-8a}=10.2$	a: 2.55 d $J_{10a-10e}=13.5$	e: 2.05 d $J_{10e-10a}=13.5$	a: 4.66 d $J_{12a-12e}=6.0$	e: 4.62 d $J_{12e-12a}=6.0$



292a	1.52-0.91	a: 3.77 d	e: 3.39 d	a: 2.67 d	e: 1.45 d	a: 4.44 d	e: 4.15 d
R = 4-F-Ph	m	$J_{8a\ 8e}=10.4$	$J_{8e-8a}=10.4$	$J_{10a-10e}=14.7$	$J_{10e-10a}=14.7$	$J_{12a-12e}=6.3$	$J_{12e-12a}=6.3$
n = 2							

Table 6. ^1H NMR assignments of compounds **286b-291b** ^a(300 MHz, C_6D_6).

	H3-5,5'	H8a	H8e	H10a	H10e	H12a	H12e
286b	1.87-0.80 m	a: 4.05 d	e: 3.34 d	a: 2.48 d	e: 1.71 d	a: 4.47 d	e: 4.15 d
R = Ph		$J_{8a\ 8e}=10.2$	$J_{8e-8a}=10.2$	$J_{10a-10e}=14.5$	$J_{10e-10a}=14.5$	$J_{12a-12e}=6.1$	$J_{12e-12a}=6.1$
n = 1							
287b	1.91-0.77 m	a: 4.04 d	e: 4.38 d	a: 2.55 d	e: 1.79 d	a: 4.54 d	e: 4.26 d
R = 4-OMePh		$J_{8a\ 8e}=10.2$	$J_{8e-8a}=10.2$	$J_{10a-10e}=14.5$	$J_{10e-10a}=14.5$	$J_{12a-12e}=6.2$	$J_{12e-12a}=6.2$
n = 1							
288b	1.87-0.80 m	a: 3.96 d	e: 3.33 d	a: 2.27 d	e: 1.65 d	a: 4.35 d	e: 4.06 d
R = 4-F-Ph		$J_{8a\ 8e}=10.1$	$J_{8e-8a}=10.1$	$J_{10a-10e}=14.3$	$J_{10e-10a}=14.3$	$J_{12a-12e}=6.3$	$J_{12e-12a}=6.3$
n = 1							
289b	1.70-0.75 m	a: 3.95 d	e: 3.32 d	a: 2.26 d	e: 1.59 d	a: 4.31 d	e: 4.01 d
R = 4-Cl-Ph		$J_{8a\ 8e}=10.3$	$J_{8e-8a}=10.3$	$J_{10a-10e}=14.8$	$J_{10e-10a}=14.8$	$J_{12a-12e}=6.3$	$J_{12e-12a}=6.3$
n = 1							
290b	1.88-0.76 m	a: 3.84 d	e: 3.39 d	a: 2.86 d	e: 1.48 d	a: 4.54 d	e: 4.25 d
R = Ph		$J_{8a\ 8e}=10.3$	$J_{8e-8a}=10.3$	$J_{10a-10e}=14.7$	$J_{10e-10a}=14.7$	$J_{12a-12e}=6.1$	$J_{12e-12a}=6.1$
n = 2							
291b	1.53-0.67 m	a: 3.89 d	e: 3.42 d	a: 2.91 d	e: 1.57 d	a: 4.60 d	e: 4.32 d
R = 4-OMePh		$J_{8a\ 8e}=10.1$	$J_{8e-8a}=10.1$	$J_{10a-10e}=14.7$	$J_{10e-10a}=14.7$	$J_{12a-12e}=6.2$	$J_{12e-12a}=6.2$
n = 2							

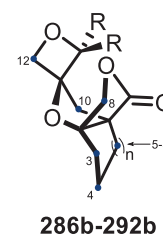


Table 7. The $|\Delta\delta|$ values of protons H8, H10 and H12 between some of the obtained diastereoisomers.

	$ \Delta\delta\ \text{H8} $	$ \Delta\delta\ \text{H10} $	$ \Delta\delta\ \text{H12} $
286a/b	0.22	0.06	0.14
R = Ph, n = 1			
287a/b	0.56	-	0.16
R = 4-OMePh, n = 1			
288a/b	0.31	0.01	0.16
R = 4-F-Ph, n = 1			
290a/b	0.13	0.1	0.34
R = Ph, n = 2			
291a/b	0.14	0.12	0.36
R = 4-OMePh, n = 2			

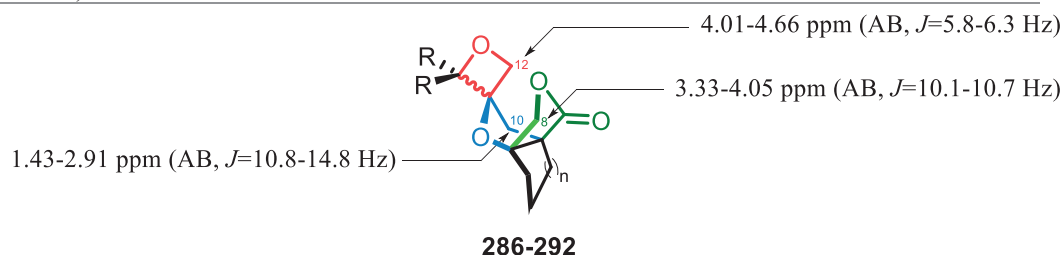
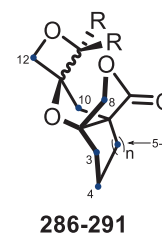


Figure 11. General ^1H NMR assignments of compounds **286-292**.

The detailed ^{13}C NMR assignments of propellanes **286-292** are presented in Tables 8-9 and summarized in Figure 12. The oxetane ring includes two quaternary carbons C11 (86.4-92.3 ppm) and C13 (86.6-96.0 ppm) in addition to a secondary carbon C12 (79.8-82.1 ppm). These carbons were assigned using further 1D and 2D NMR experiments, such as DEPT-135 and HSQC, while the rest of the propellane core peaks were realized by comparing the obtained spectra to those of the previously analyzed scaffolds. One of the main features presented in these analogues is the downfield shift of the spiroatom C11 in comparison with what has been observed in the spirocyclopropanes **273a-b** ($\Delta\delta \sim 24.0\text{-}26.7$ ppm).

By comparing the carbon chemical shifts of the isolated diastereoisomers, no significant variations have been identified ($\Delta\delta \sim 0\text{-}2$ ppm) (Table 10). Likewise, the benzophenone substituents exhibited negligible effects on the studied carbon skeleton. However, the six-membered ring scaffolds **290-292** showed remarkable variations with respect to their five-membered ring counterparts **286-289**. Once again, this ensures that the electron distribution in the propellane system could be altered by the size of the alkyl ring.

	C1	C2	C3	C4	C5-5'	C6	C8	C10	C11	C12	C13
288a	59.6	97.8	37.9	27.1	35.1	178.4	77.5	45.9	89.9	79.8	93.7
290a	50.1	95.1	30.7	22.6	27.4 19.7	179.1	71.3	40.2	86.5	81.1	86.6
291a	50.2	95.3	30.7	22.6	27.4 19.7	179.2	71.4	40.3	86.4	81.2	86.9
292a	51.6	95.8	29.0	22.2	27.4 19.3	179.3	69.8	39.6	86.9	82.0	87.1

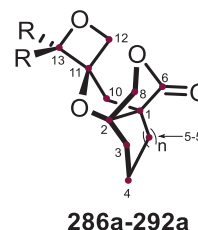


Table 8. ^{13}C NMR assignments of compounds **288a-292a** (500 MHz, C_6D_6).

	C1	C2	C3	C4	C5-5'	C6	C8	C10	C11	C12	C13
286b	60.3	98.5	38.0	25.7	35.5	178.4	76.3	45.0	91.7	80.5	95.7
287b	60.5	98.5	38.2	22.8	35.81	178.7	76.5	45.2	92.3	80.4	96.0
288b	60.2	98.5	37.8	25.6	35.4	178.3	76.1	44.9	91.3	80.5	95.0
289b	60.3	98.6	37.8	26.8	35.3	178.2	76.1	44.7	91.2	80.6	94.7
290b	51.6	96.4	29.0	22.2	27.6 19.4	179.4	69.9	40.0	86.9	82.1	87.3
291b	51.6	96.5	29.1	22.3	27.6 19.5	179.5	70.0	40.0	86.9	82.1	87.4

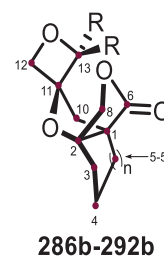


Table 9. ^{13}C NMR assignments of compounds **286b-291b** (500 MHz, C_6D_6).

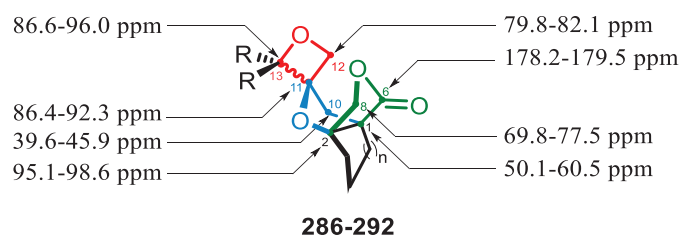


Figure 12. General ^{13}C NMR assignments of compounds **286-292**.

	$ \Delta\delta \text{ C1} $	$ \Delta\delta \text{ C2} $	$ \Delta\delta \text{ C6} $	$ \Delta\delta \text{ C8} $	$ \Delta\delta \text{ C10} $	$ \Delta\delta \text{ C11} $	$ \Delta\delta \text{ C12} $	$ \Delta\delta \text{ C13} $
288a/b	0.7	0.7	0	1.2	0.9	1.8	0.7	2
290a/b	1.5	1.3	0.3	1.4	0.2	0.4	1	0.7
291a/b	1.4	1.2	0.3	1.4	0.3	0.5	0.9	0.5

288-291

Table 10. The $|\Delta\delta|$ values of the characteristic carbons between some of the obtained diastereoisomers.

2D NMR analysis:

The results obtained from 1D NMR experiments were then verified using further 2D NMR analysis. For instance, in addition to the proton splitting patterns in the ^1H NMR spectrum, the three major AB systems in the common quadracyclic core of the obtained compounds have been confirmed by COSY analysis (H8a/ H8e, H10a/ H10e and H12a/ H12e). Moreover, the 2D HSQC correlations of these systems (H8/C8, H10/C10 and H12/C12) have also supported the achieved ^{13}C NMR assignments shown in the previous section (Figure 13).

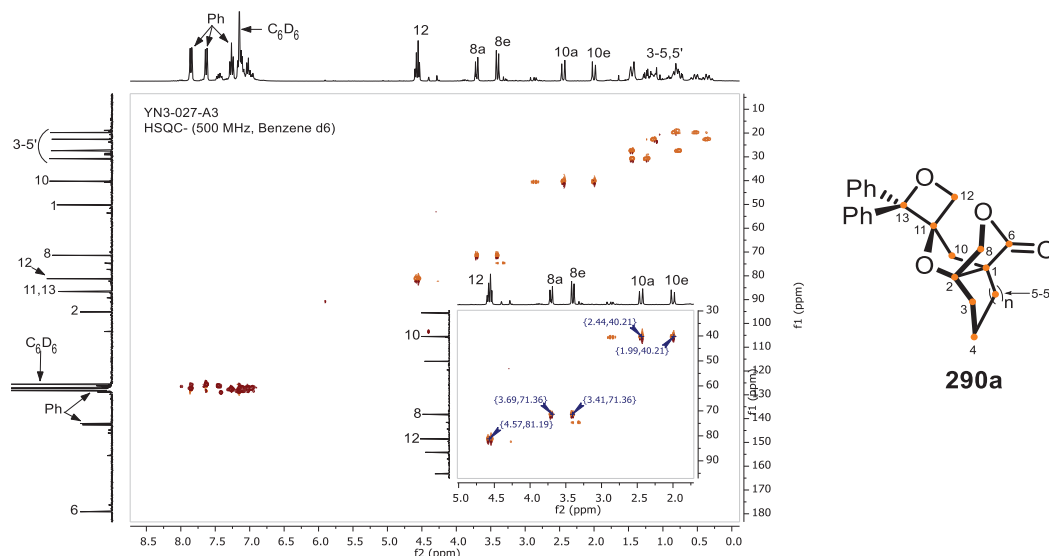


Figure 13. 2D HSQC NMR of **290a** (500 MHz, C_6D_6).

The relative stereochemistry between the isolated diastereoisomers has been determined by 2D NOESY experiments as shown in Figure 14. The signals of the phenyl protons in **290a** (~7.03-7.75 ppm) give strong NOE cross-peaks with the alkyl ring protons (H3 and H5') (0.22-1.56 ppm) in addition to other cross-peaks with the oxetane protons H12 (4.55 ppm) and the THF ones H10 (1.94-2.50 ppm). However, the alkyl ring protons H3-H5 (0.97- 1.21 ppm) in **286b** correlates with the oxetane protons H12 (4.09-4.51 ppm) but not with the phenyl ones (6.90-7.80 ppm). Therefore, the phenyl rings reside toward the alkyl ring away from the γ -lactone group in **290a**, while the inverse is true for **286b**.

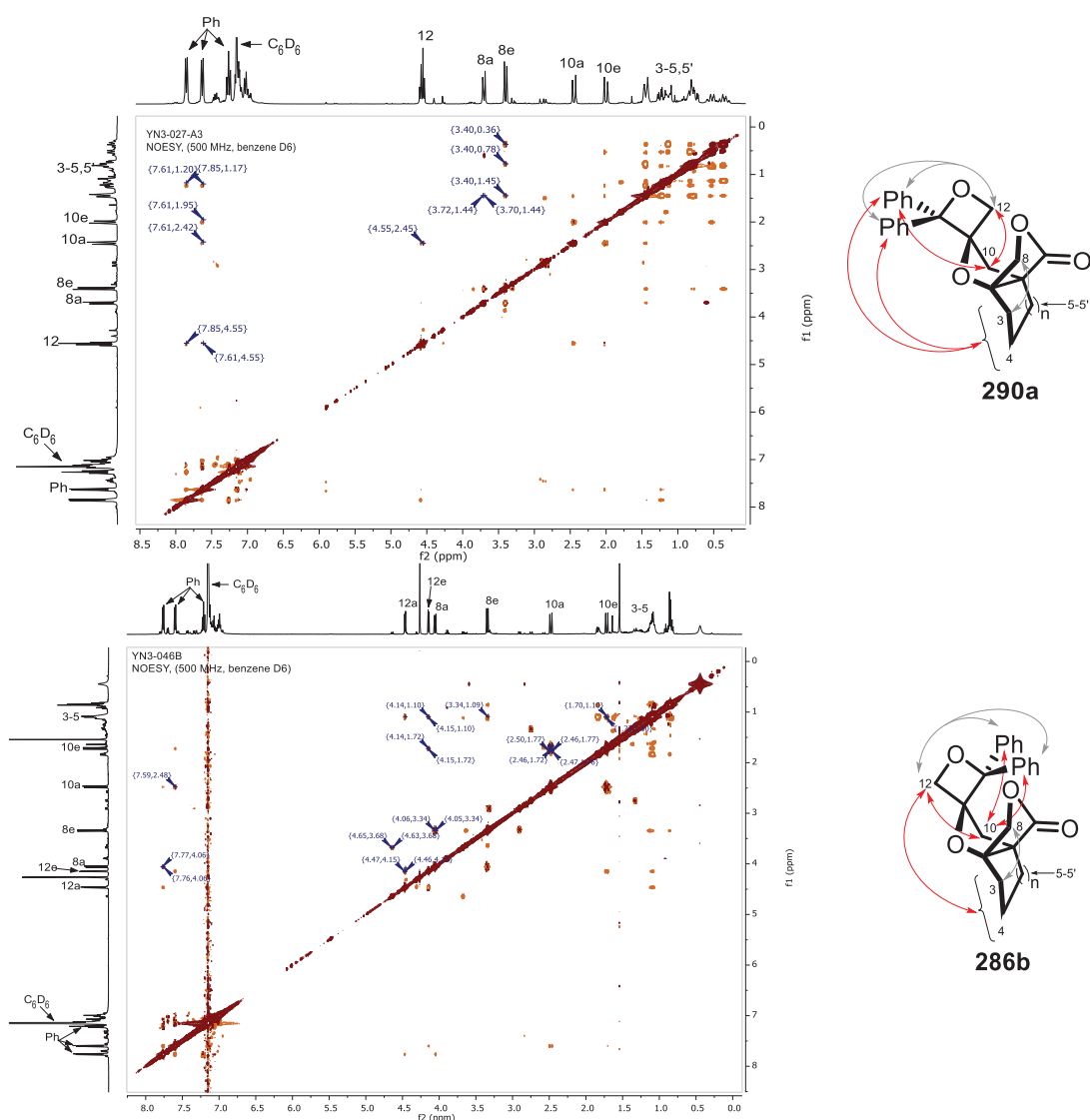


Figure 14. 2D NOESY NMR of **290a** (up) and **286b** (down) (500 MHz, C_6D_6).

2.6. Oxaspirolactone[*n*,3,3]propellanes

Natural and synthetic organic molecules with a novel biological profile or physicochemical properties are the longstanding inspiration for synthetic organic chemists. Such molecules could enhance the curiosity to develop synthetic methodologies to access them or their key functional motifs. Among these motifs, oxaspirolactones, a spiroketal subclass,^[43] are encountered in a significant number of products that have been isolated from diverse natural and synthetic sources (Figure 15).^[44] Inherent three-dimensional architectures, molecular rigidity and Michael acceptor properties (in the case of unsaturated oxaspirolactones) are primarily responsible for their biochemical and physicochemical properties.^[44]

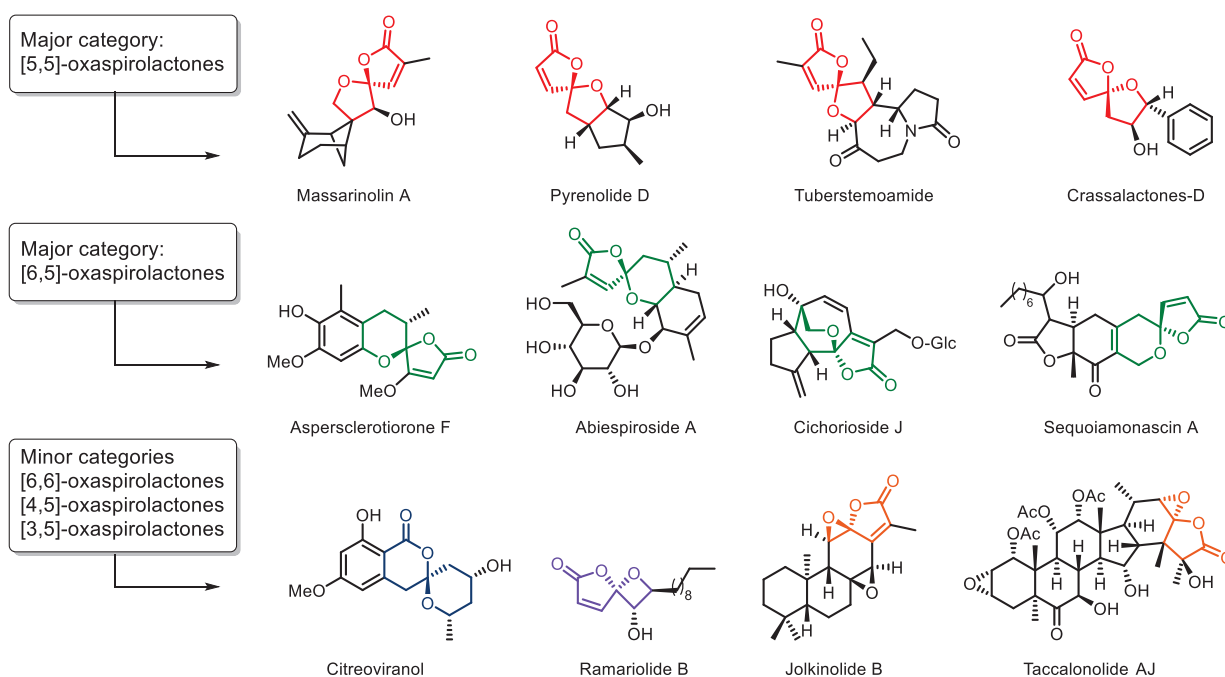


Figure 15. Natural products containing oxaspirolactone moiety.

In this section, for ease of understanding, all oxaspirolactones are designated as [*m*,*n*]-oxaspirolactones instead of complex IUPAC nomenclature. In a given scaffold, with or without unsaturation, “*m*” and “*n*” refer to the ring size of the corresponding cyclic ether and the lactone ring respectively. Oxaspirolactone-containing products are systematically classified into various categories based on their ring sizes and their frequency of disclosure in the literature as shown in Figure 16.^[44] Oxaspirolactones possessing [5,5] and [6,5] ring systems with a butyrolactone scaffold were well studied and resulted in expeditious chemistry, this is because most of the natural products fall into one of these skeletal classes. The minor category documented was [5,6], [6,6],

[3,5] and [4,5]-oxaspirolactones. Few other miscellaneous oxaspirolactones possessing [3,4],^[44-45] [5,4],^[46] [7,5],^[47] [4,6],^[48] and [6,7]^[49] ring systems were also found in the literature, but with very limited chemistry.

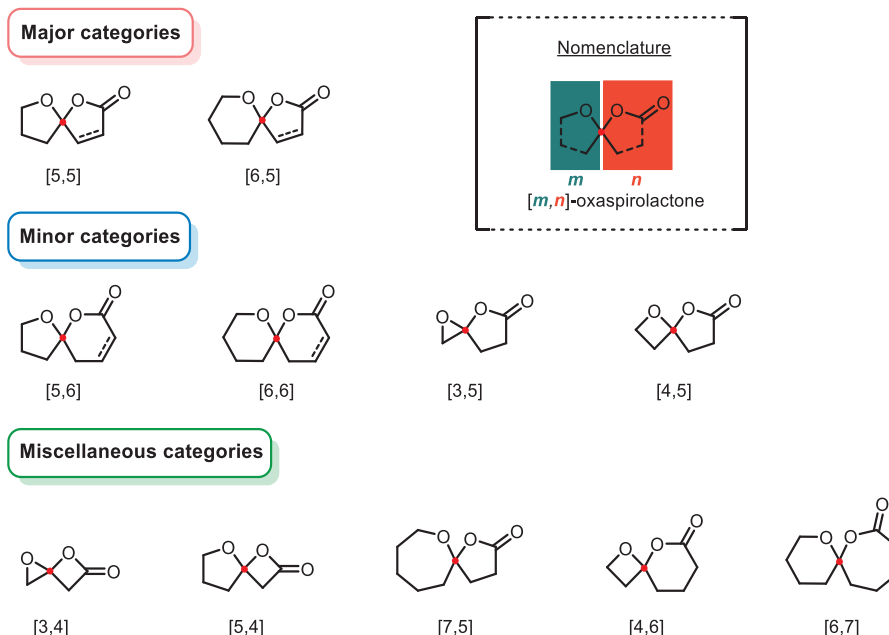


Figure 16. Various categories of oxaspirolactones and customary nomenclature.

Being inspired by the emerging importance of oxaspirolactones, we turned our attention toward the synthesis of oxaspirolactone[*n*,3,3]propellanes. The successful attempts in the last two sections to access the spiro- 3- and 4-membered rings at C11 of the common propellane core structure led us to endeavor the formation of spiro- 5-membered ring at the same position. Therefore, the designed products would then be [5,5]-oxaspirolactone[*n*,3,3]propellanes (Figure 17). In addition to the regular features presented in our propellane skeleton, the designed molecules are comprised of the characteristic unsaturated [5,5]-oxaspirolactone motif.

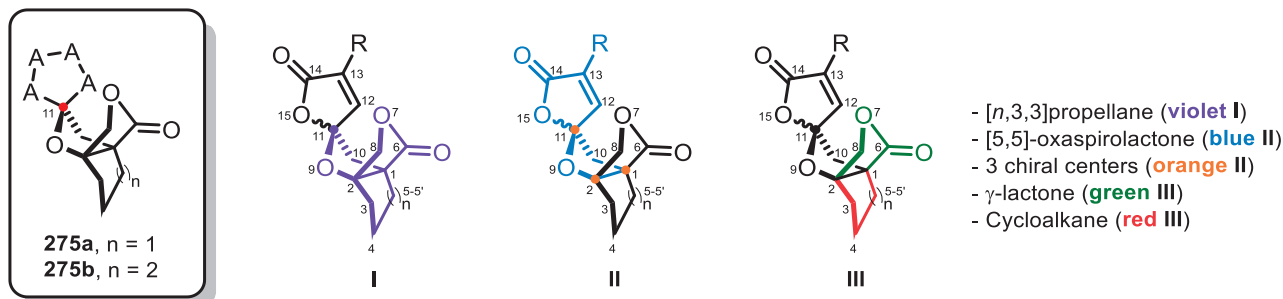
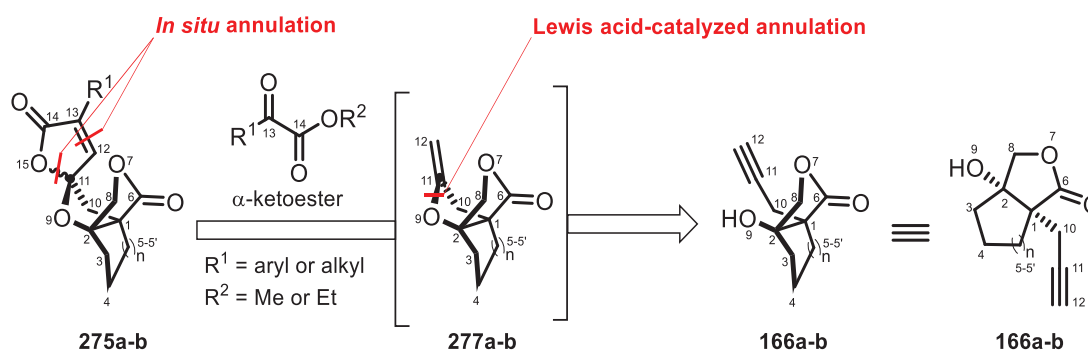


Figure 17. Key features of the designed [5,5]-oxaspirolactone[*n*,3,3]propellanes.

This reaction was expected to proceed through initial formation of exocyclic enol-ether **A** followed by annulation with pre-activated α -ketoesters **B** to give **D** *via* aldol-type addition and cyclization through oxocarbenium species **C**. Dehydration of intermediate **D** and intramolecular transesterification step *via* **E** furnishes oxaspirolactones **302**. Diverse [5,5]-oxaspirolactones with a high degree of substitution (alkyl, aryl, and alkenyl) on the butenolide ring and a large substrate scope (42 examples) were prepared in moderate to excellent yields (35–80%) in CH_2Cl_2 under ambient reaction conditions.

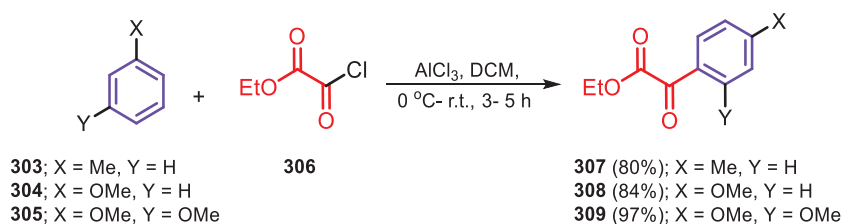
Retrosynthetic analysis: By considering the cascade annulation reaction above, the designed [5,5]-oxaspirolactone scaffolds **275a-b** were then envisioned to be prepared in only one step starting from the propargyl bicyclic γ -lactones **166a-b** (Scheme 13). Contrary to what has been already observed in the synthesis of spiro-cyclopropanes **273a-b** and spiro-oxetanes **286-292**, this strategy does not require the preparation and isolation of the *exo* enol ethers **277a-b**. The latter compounds were predicted to be formed *in situ* as already shown in Scheme 12 (Intermediate A).



Scheme 13. Retrosynthetic analysis of oxaspirolactone[*n*,3,3]propellanes **275a-b**.

- Preparation of α -ketoesters **307-309**

Before examining the reactivity of alkynols **166a-b** under the mentioned cascade annulation conditions, it was necessary to encounter the synthesis of various α -ketoesters besides the commercially available ones. The first attempts were achieved starting from acetophenone derivatives with selenium dioxide in refluxed alcohol or pyridine as mentioned in the literature.^[51] Unfortunately, the experiments did not work properly and we struggled to isolate even traces of the desired products. For this reason, we turned our attention toward the Friedel-Crafts reaction between distinct aromatics **303-305** and mono-ethyl oxalyl chloride **306** (Scheme 14).^[52]



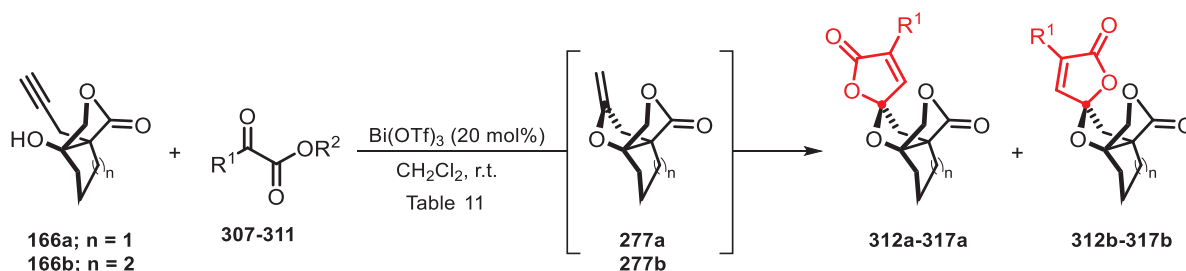
Scheme 14. Friedel-Crafts reaction between different aromatics and mono-ethyl oxalyl chloride **304**.

Consequently, α -ketoesters **307-309** were obtained from their corresponding aromatics in relatively short periods (3-5h) and satisfactory yields (80-97%).

Synthesis of [5,5]-oxaspirolactone[*n*,3,3]propellanes

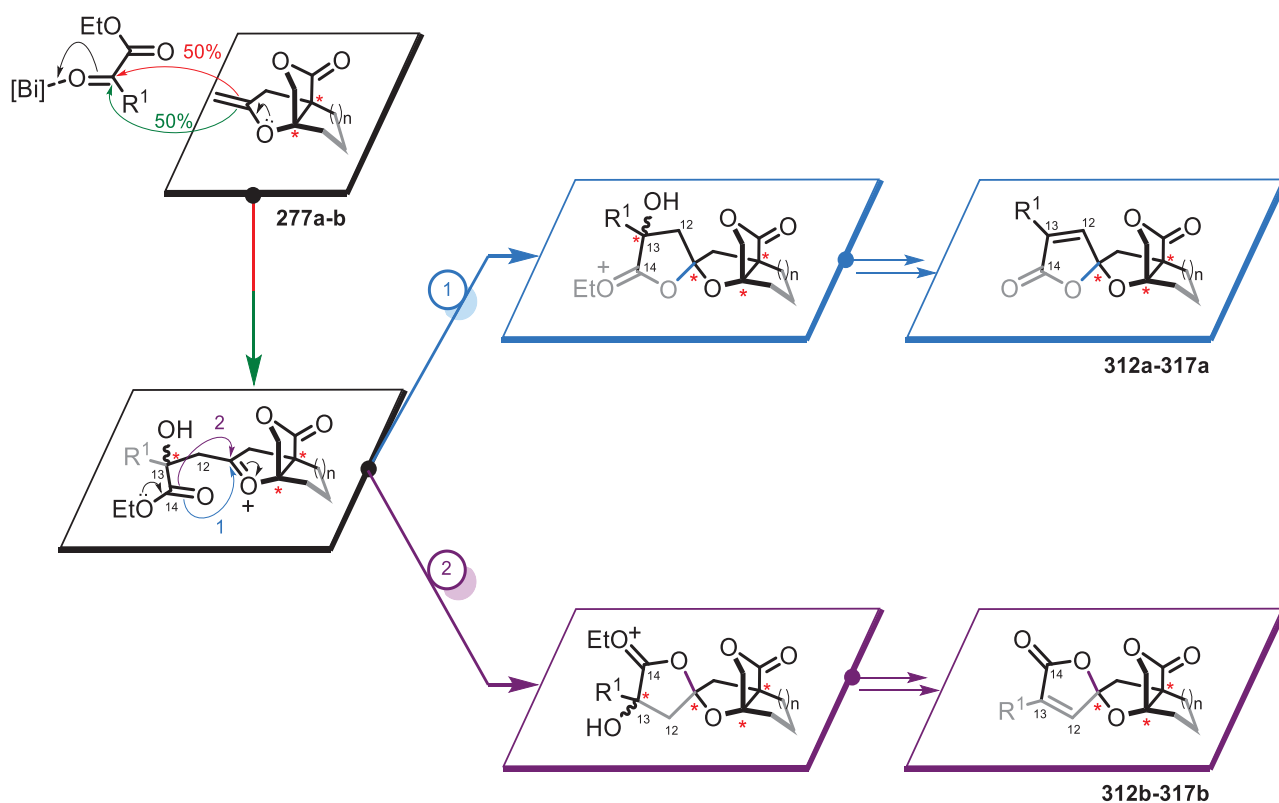
To explore the feasibility of the strategy proposed by Kontham and coworkers, the reaction between alkynol **166a/166b** (1 equiv.) and the chosen α -ketoester **307-311** (1 equiv.) was performed with commercially available Bi(OTf)₃ (20 mol%) in anhydrous dichloromethane at room temperature (Table 11). Pleasingly, in most of the cases, both starting materials were completely consumed in 16-25 hours and gave a mixture of diastereoisomers of the desired unsaturated γ -spiroketal- γ -lactones **312-317**. Condensation of **166b** was first tested with commercially available esters **310** and **311** and delivered the expected spiro products **312** and **313** in 86 and 61% yield respectively. In both cases, a 1:1 mixture of diastereoisomers was observed.

Table 11. Lewis acid-catalyzed intermolecular cascade annulation of alkynols **166a/b** with α -ketoesters **307-311**. ^a Reaction time, ^b Isolated yield.



Entry	Alkynol	Ketoester	R ¹	R ²	t (h) ^a	Adducts	Yield (%) ^b
1	166b	310	Me	Me	25	312a-b (1:1)	86
2	166b	311	Ph	Me	21	313a-b (1:1)	61
3	166b	307	4-Me-Ph	Et	18	314a-b (1:1)	74
4	166a	308	4-MeOPh	Et	16	315a-b (1:1)	69
5	166b	308	4-MeOPh	Et	19	316a-b (1:1)	87
6	166b	309	2,4-(MeO) ₂ Ph	Et	18	317a-b (1:1)	37

This lack of diastereoselectivity could be correlated to the distance between the newly created spiranic center and the two already existing ones. It could be related as well to the absence of any stereogenic center in the chosen ketoesters (Scheme 15). To enhance the scope of the reaction, additional α -ketoesters **307-309** were tested under the conditions already used. Compounds **314-316** were isolated in similar yields and still in poor selectivities. Interestingly, the diastereoisomers were usually separable by flash-chromatography, except for **315a** and **315b**. In the case of the bis(methoxy)phenyl derivative **309**, the yield of the reaction leading to **317** was significantly reduced to 37%. Presumably, the *ortho*-substituent on the aryl group could disfavor the condensation of the enol ether **277b** on the carbonyl group for both steric hindrance and electronic reasons. In summary, we have successfully prepared six novel [5,5]-oxaspirolactone[*n*,3,3]-propellanes, in only one step, from propargyl bicyclic γ -lactones **166a-b**.



Scheme 15. The lack of selectivity in the synthesis of **312-317**.

NMR analysis: To ensure the proposed molecular structures of the obtained compounds, several NMR experiments were performed. Tables 12 and 13, partially summarized in

Figure 18, represent the ^1H NMR assignments of **312-317**. Generally, in addition to the regular peaks of the propellane ring system, the [5,5]-oxaspirolactone motif reveals a deshielded proton H12 in the range between 6.62 and 7.35 ppm. In the case where R^1 is a methyl group (**312a-b**), H12 presents a long-range coupling to give a quartet (~ 6.62 ppm, $^4J = 1.6$ Hz). However, when R^1 is an aromatic ring, H12 becomes slightly more deshielded ($\Delta\delta \sim 0.34$ - 0.73 ppm) and gives a singlet around 6.97-7.35 ppm. The presence of the [5,5]-oxaspirolactone motif was further verified by ^{13}C NMR analysis as shown in Tables 14 and 15. The chemical shifts of the distinctive quaternary center C11 (109.6-111.1 ppm) were similar to what have been observed in the literature for ketal carbons in oxaspirolactones.^[53] Moreover, the appearance of another two quaternary centers and one primary carbon in the range between 130.9 and 171.1 ppm justifies the presence of an α,β -unsaturated system related to a furanone subunit (Figure 18). These arguments, in addition to 2D NMR, IR and HRMS data (shown in the appendix), confirm the assumed structures of **312-317**.

Table 12. ^1H NMR assignments of compounds **312a-317a** (300 MHz, CDCl_3).

	H3-5,5'	H8a	H8e	H10a	H10e	H12
312a $\text{R}^1 = \text{Me}$ $n = 2$	2.15-1.37 m	a: 4.28 d $J_{8a\ 8e} = 10.7$	e: 4.26 d $J_{8e\ 8a} = 10.7$	a: 2.87 d $J_{10a\ 10e} = 14.7$	e: 2.66 d $J_{10e\ 10a} = 14.7$	6.62 q $J_{12\text{-Me}} = 1.6$
313a $\text{R}^1 = \text{Ph}$ $n = 2$	2.21-1.35 m	a: 4.32 d $J_{8a\ 8e} = 10.7$	e: 4.25 d $J_{8e\ 8a} = 10.7$	a: 2.99 d $J_{10a\ 10e} = 14.8$	e: 2.73 d $J_{10e\ 10a} = 14.8$	7.08 s
314a $\text{R}^1 = 4\text{-Me-Ph}$ $n = 2$	2.23-1.18 m	a: 4.32 d $J_{8a\ 8e} = 10.7$	e: 4.26 d $J_{8e\ 8a} = 10.7$	a: 2.98 d $J_{10a\ 10e} = 14.8$	e: 2.73 d $J_{10e\ 10a} = 14.8$	7.03 s
316a $\text{R}^1 = 4\text{-MeO-Ph}$ $n = 2$	2.21-1.25 m	a: 4.32 d $J_{8a\ 8e} = 10.8$	e: 4.26 d $J_{8e\ 8a} = 10.8$	a: 2.98 d $J_{10a\ 10e} = 14.5$	e: 2.74 d $J_{10e\ 10a} = 14.5$	6.96 s
317a $\text{R}^1 = 2,4\text{-(MeO)}_2\text{-Ph}$, $n = 2$	2.26-1.37 m	a: 4.34 d $J_{8a\ 8e} = 10.8$	e: 4.23 d $J_{8e\ 8a} = 10.8$	a: 3.00 d $J_{10a\ 10e} = 14.8$	e: 2.70 d $J_{10e\ 10a} = 14.8$	7.35 s

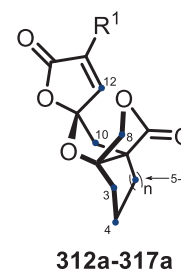
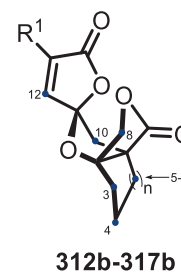


Table 13. ^1H NMR assignments of compounds **312b-317b** (300 MHz, CDCl_3).

	H3-5,5'	H8a	H8e	H10a	H10e	H12
312b $\text{R}^1 = \text{Me}$ $n = 2$	2.19-1.19 m	a: 4.44 d $J_{8a\ 8e} = 10.7$	e: 4.21 d $J_{8e\ 8a} = 10.7$	a: 2.66 d $J_{10a\ 10e} = 13.5$	e: 2.45 d $J_{10e\ 10a} = 13.5$	6.62 q $J_{12\text{-Me}} = 1.6$
313b $\text{R}^1 = \text{Ph}$ $n = 2$	2.20-1.52 m	a: 4.48 d $J_{8a\ 8e} = 10.6$	e: 4.25 d $J_{8e\ 8a} = 10.6$	a: 2.73 d $J_{10a\ 10e} = 13.6$	e: 2.57 d $J_{10e\ 10a} = 13.6$	7.10 s
314b $\text{R}^1 = 4\text{-Me-Ph}$ $n = 2$	2.12-1.26 m	a: 4.41 d $J_{8a\ 8e} = 10.9$	e: 4.18 d $J_{8e\ 8a} = 10.9$	a: 2.65 d $J_{10a\ 10e} = 13.5$	e: 2.49 d $J_{10e\ 10a} = 13.5$	6.98 s
316b $\text{R}^1 = 4\text{-MeO-Ph}$ $n = 2$	2.17-1.37 m	a: 4.49 d $J_{8a\ 8e} = 10.8$	e: 4.24 d $J_{8e\ 8a} = 10.7$	a: 2.72 d $J_{10a\ 10e} = 13.7$	e: 2.54 d $J_{10e\ 10a} = 13.7$	6.97 s



317b	2.19-1.19	a: 4.50 d	e: 4.24 d	a: 2.71 d	e: 2.54 d	7.35 s
R ¹ = 2,4-(MeO) ₂ -Ph, n = 2	m	J _{8a-8c} = 11.0	J _{8e-8a} = 11.0	J _{10a-10e} = 14.3	J _{10e-10a} = 14.3	

Table 14. ¹³C NMR assignments of compounds **312a-317a** (126 MHz, CDCl₃).

	C1	C2	C3-4	C5-5'	C6	C8	C10	C11	C12	C13	C14
312a	52.3	89.0	28.4 22.8	28.0 19.6	180.3	70.9	40.8	111.1	145.0	131.8	171.1
313a	52.5	89.3	28.4 22.8	28.01 19.6	180.3	70.9	41.0	110.3	143.2	132.7	168.9
314a	52.5	89.2	28.4 22.8	28.0 19.6	180.3	70.9	41.1	110.3	142.2	132.6	169.0
316a	52.5	89.1	28.5 22.8	28.0 19.6	180.4	70.9	41.1	110.3	140.8	132.1	169.3
317a	52.5	89.0	28.5 22.8	28.2 19.6	180.6	71.0	41.4	110.6	144.2	130.9	170.2

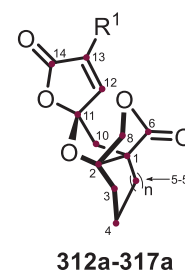


Table 15. ¹³C NMR assignments of compounds **312b-317b** (126 MHz, CDCl₃).

	C1	C2	C3-4	C5-5'	C6	C8	C10	C11	C12	C13	C14
312b	50.4	88.8	31.0 21.2	28.3 19.5	179.0	73.5	42.3	110.3	143.4	134.0	170.1
313b	50.5	89.1	31.0 21.4	28.3 19.6	179.1	73.1	42.4	109.6	141.8	134.7	167.8
314b	50.5	89.0	31.1 21.3	28.3 19.6	179.1	73.2	42.5	109.6	140.7	134.6	168.0
316b	50.5	88.9	31.1 21.3	28.3 19.6	179.1	73.2	42.6	109.6	139.1	134.1	168.1
317b	50.6	88.6	31.1 21.2	28.4 19.6	179.2	73.3	42.7	109.7	142.5	131.1	169.0

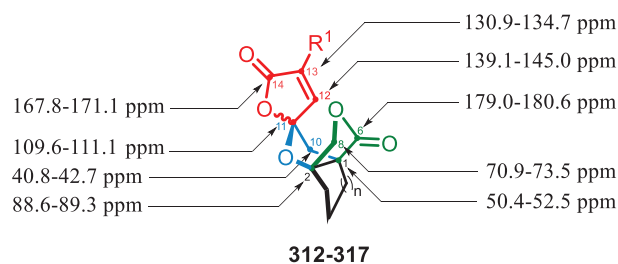
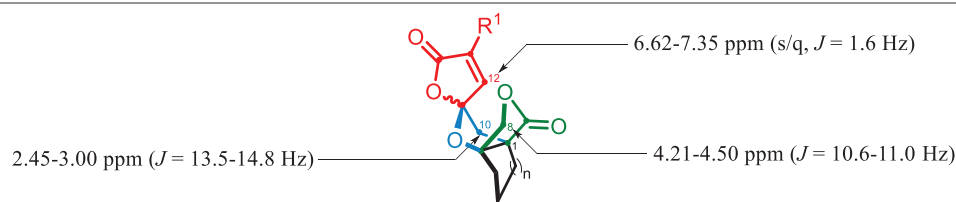
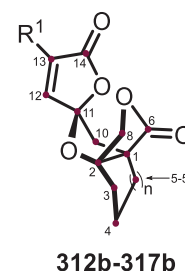
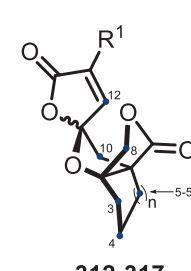


Figure 18. General ¹H NMR (up) and ¹³C NMR (down) assignments of compounds **312-317**.

Based on the calculated $|\Delta\delta|$ in Tables 16 and 17, no significant variations were observed for neither protons ($\Delta\delta \sim 0-0.29$ ppm) nor carbons ($\Delta\delta \sim 0.2-2.6$ ppm) between the diastereoisomers. Likewise, the effect of the substituent on the furanone subunit has not been remarkable as predicted.

Table 16. The $|\Delta\delta|$ values of the characteristic protons between the obtained isomers **312-317**.

	$ \Delta\delta \text{ H8} $	$ \Delta\delta \text{ H10} $	$ \Delta\delta \text{ H12} $
312a/b	0.06	0.21	0
313a/b	0.08	0.21	0.02
314a/b	0.06	0.29	0.05
316a/b	0.08	0.23	0.01
317a/b	0.09	0.23	0



312-317

Table 17. The $|\Delta\delta|$ values of the characteristic carbons between the obtained diastereoisomers **312-317**.

	$ \Delta\delta \text{ C1} $	$ \Delta\delta \text{ C2} $	$ \Delta\delta \text{ C6} $	$ \Delta\delta \text{ C8} $	$ \Delta\delta \text{ C10} $	$ \Delta\delta \text{ C11} $	$ \Delta\delta \text{ C12} $	$ \Delta\delta \text{ C13} $	$ \Delta\delta \text{ C14} $
312a/b	1.9	0.2	1.3	2.6	1.5	0.8	1.6	2.2	1
313a/b	2	0.2	1.2	2.2	1.4	0.7	1.4	2	1.1
314a/b	2	0.2	0.3	1.2	2.3	1.4	0.7	1.5	2
316a/b	2	0.2	1.3	2.3	1.5	0.7	1.7	2	1.2
317a/b	1.9	0.4	1.4	2.3	1.3	0.9	1.7	0.2	1.2



312-317

The stereochemistry of the isolated diastereoisomers was determined by using 2D NOESY experiments (Figure 19). According to the given data, there is no direct evidence about the configuration at the spiroatom C11. Proton H12 does not show any remarkable cross-peaks with neither lactone B nor the alkyl group. Nevertheless, H12 gives a strong NOE cross-peaks with the neighboring phenyl protons in addition to either H10a (in the case of **313a**) or H10e (in the case of **313b**). Moreover, the latter proton shows a clear correlation with the alkyl ring in both spectra. Hence, the first evidence is that H10a and H10e reside toward lactone B and the alkyl group

respectively. Consequently, when H12 correlates with H10a and not H10e, H12 then resides toward lactone B and not the alkyl ring to give the same configuration as **313a**. The inverse is true for **313b**. Other less important correlations, such as H8/H3 and H8/H10, have appeared in both spectra without supporting any evidence about the proposed stereochemistry.

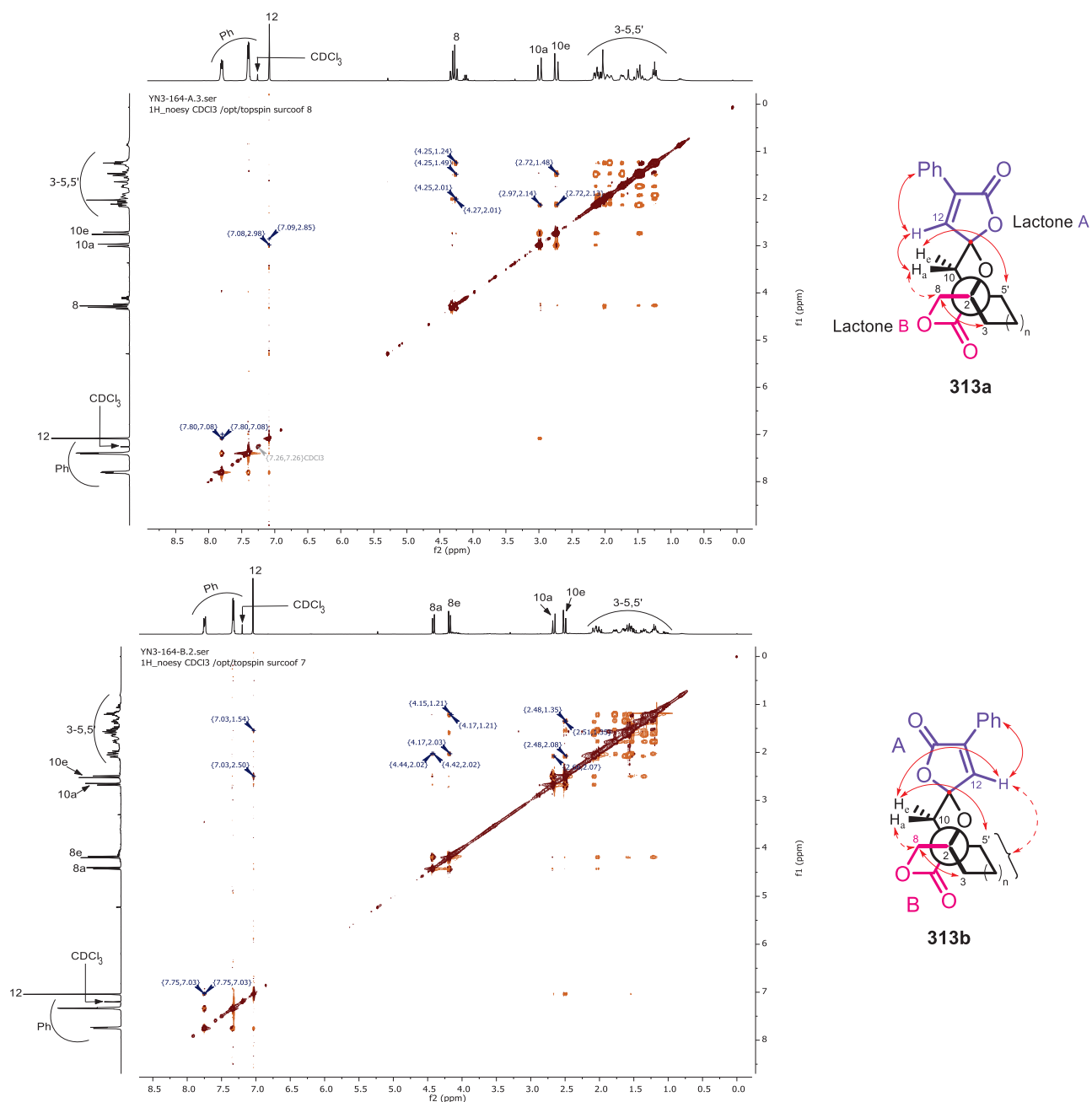


Figure 19. 2D NOESY NMR of **313a** (up) and **313b** (down) (500 MHz, CDCl₃).

2.7. Further oxaspiro[*n*,3,3]propellanes!

So far, three novel categories of oxaspiro[*n*,3,3]propellanes have been developed; **273**, **274** and **275** (Figure 20). Based on the number of annular atoms “A” in the designed spirocyclic system, **276** was envisioned as the next molecular target. Unfortunately, all attempts toward its synthesis were challenging. At first, we endeavored the hetero–Diels–Alder condensation between the electron-rich enol ethers **277a-b** and electron-poor acrolein derivatives (Scheme 16).^[54] The reactions did not work even after varying conditions. Presumably, the long reaction times favored the polymerization of acrolein and the complete isomerization of the used enol ether **277a/b** before proceeding with the desired transformation. Other attempts to furnish such spirocycles were achieved using the [4 + 2] cycloaddition between the chosen enol ether **277a** and Sc(III)-catalyzed *o*-quinone methide intermediate.^[55] The desired product **276B** was then isolated in low yield (15%) due to the acidity effect of Sc(III) on the isomerization of the starting material. Despite these unsatisfactory results, further future investigations could eventually be promising to construct **276** and even larger spirocycles *via* alternative methods.

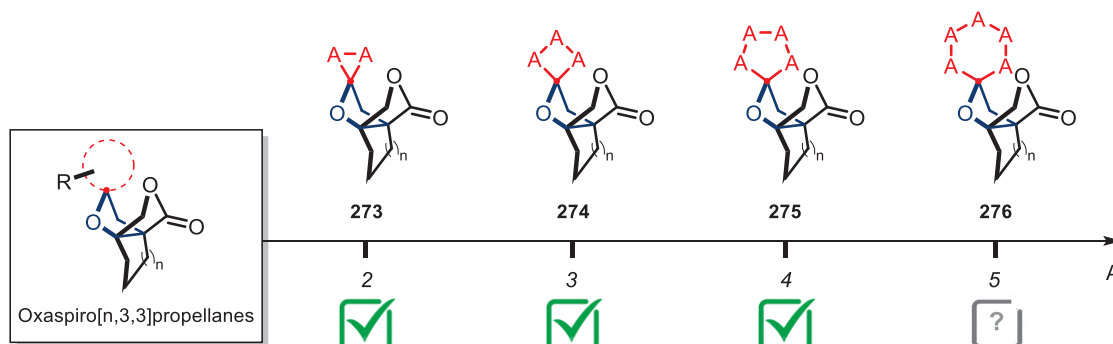
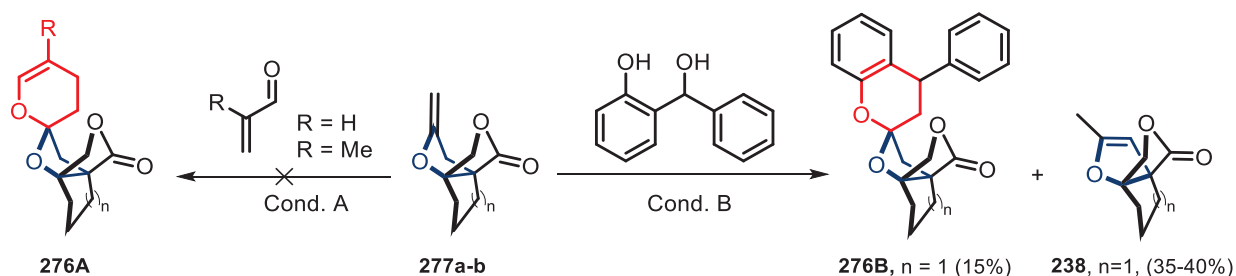


Figure 20. The achievements in the synthesis of novel oxaspiro[*n*,3,3]propellanes based on the annular atoms A.



Scheme 16. Attempts to furnish **276A-B**. Reagents and conditions: Cond. A: ZnCl₂/hydroquinone, benzene, r.t., 5-10 days; Cond. B: Sc(OTf)₃, CH₂Cl₂, r.t. 20 h.

3. Miscellaneous propellanes obtained from propargyl bicyclic γ -lactone

Besides the furnished oxaspiro[*n*,3,3]propellanes, other ring systems have been constructed from the same common building blocks; propargyl bicyclic γ -lactones **166a-b**. The aim behind these studies was to provide additional propellanes that are amenable to further derivatizations, which render them useful as central units in fragment-based drug discovery or as ligand scaffolds. Herein, we describe new approaches to the synthesis of PTAD-based [6,4,3]propellanes and iodo-DHP[4,3,3]propellanes.

3.1. PTAD-based [6,4,3]propellanes

Triazolinedione (RTAD, R = M for methyl, and R = Ph for phenyl) is a strong electron acceptor and one of the most powerful enophiles as well as dienophiles (Figure 21).^[56] RTADs afford ene products (*N*-allylurazoles)^[57] or [2 + 2] adducts (1,2-diazetidines)^[58] with alkenes and undergo DA reactions with conjugated dienes.^[59] The latter class of reactions is useful in characterizing dienes,^[60] protecting diene moieties,^[61] isolating dienes from complex reaction mixtures,^[62] and trapping unstable or volatile intermediates.^[63] On the other hand, the most important trend in the utilization of RTADs adducts is the preparation of strained polycyclic systems.^[64] Consequently, many previously difficult-to-obtain classes of organic substances have been furnished by means of this compound.^[65] The hydrolysis of the imide group in 1,4 cycloadducts affords azo compounds which are labile and readily split out a molecule of nitrogen to give the corresponding hydrocarbons upon heating or photolysis.^[65b]

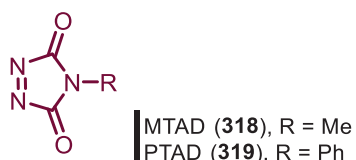


Figure 21. RTADs structure.

RTADs have also been used to prepare intricate cage structures from propellanes.^[65a, 66] For instance, David Ginsburg and coworkers have reported a number of PTAD-based propellanes, such as **320-323**,^[66a, 67] in a series of successive articles after studying the steric course of the Diels-Alder reaction between certain propellanes and PTAD (Figure 22). As reported, some of these products and analogues were obtained on a large scale and then used for the preparation of strained systems.^[66d, 66e] This was discussed in detail in the review reported by Korobitsyna *et al.*^[65a]

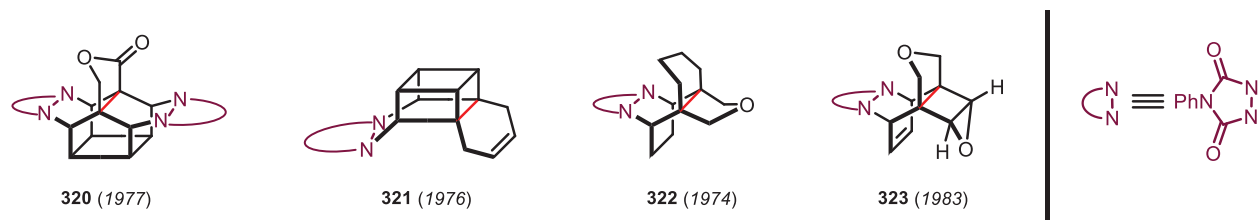


Figure 22. Some PTAD-based propellanes reported by Ginsburg and coworkers.

As far as we were concerned about introducing new subunits to our propellane scaffolds, we were interested to furnish a new PTAD-based propellane, with a higher degree of complexity, starting from the propargyl bicyclic γ -lactone **166b**. The designed structure is comprised of a [6,4,3]propellane subunit, in which the largest ring is a 1,2-oxasilocane group (Figure 23). In addition to the propellane bridge-head carbons C1 and C2, the hexacyclic framework includes an extra stereogenic center at position C17. The latter carbon with C18 both are directly connected to the urazole functionality *via* nitrogen atoms N19 and N20 respectively.

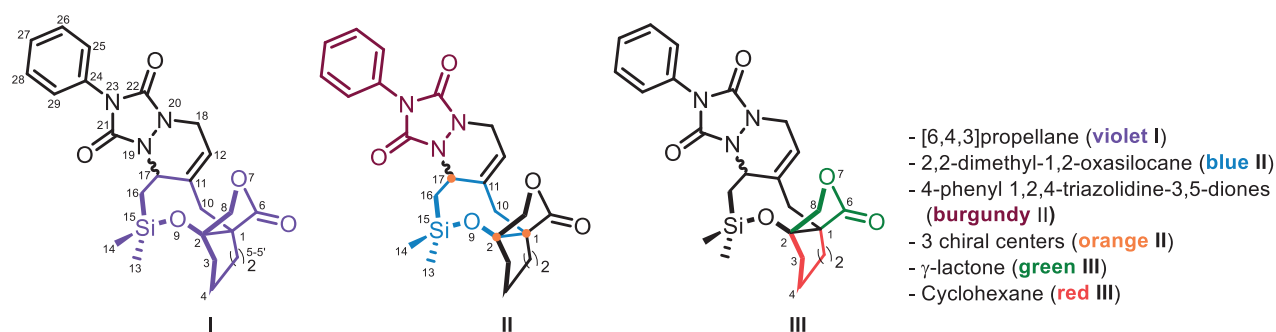
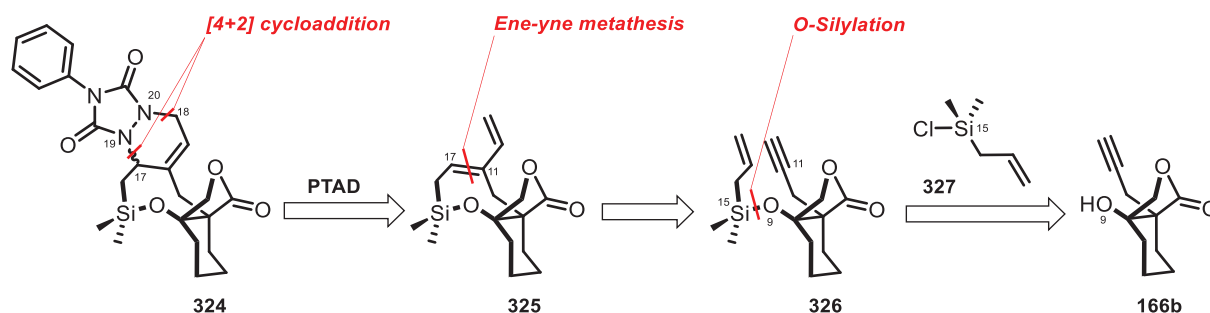


Figure 23. Key features of the designed PTAD-based propellane.

The retrosynthetic analysis of the designed compound **324** is presented in Scheme 17. Our analysis leads to PTAD and diene **325** by disconnecting C17-N19 and C18-N20 in **324** through Diels-Alder

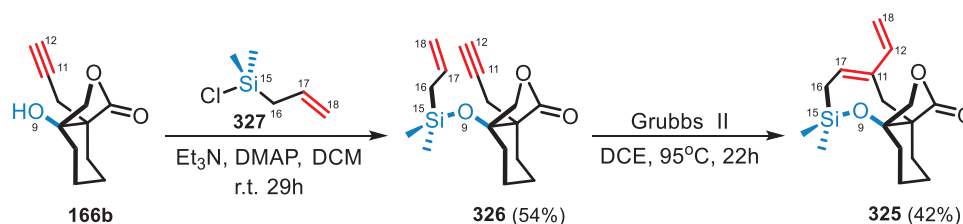


Scheme 17. Retrosynthesis of **324**.

reaction. Propellane **325** could be obtained by ring-closing enyne metathesis (RCEYM) of **326**, including the introduction of the 1,3-butadiene group and thus representing by far the most challenging step in this synthesis. Enyne **326** can eventually be prepared *via a* silylation reaction between the starting propargyl bicyclic γ -lactone **166b** and allyldimethylchlorosilane **327**.

Synthesis of diene **325**

The enyne containing an allylsilane group **326** was easily obtained from propargylic alcohol **166b** and allyldimethylchlorosilane **327** (1.1 eq.) in the presence of triethylamine (2 eq.) and a catalytic amount of 4-dimethylaminopyridine (DMAP) in dichloromethane for 29 hours at room temperature (Scheme 18).^[68] Eventually, the product **326** was then chromatographed and isolated in a 54% yield. As already demonstrated in the literature,^[69] the Lewis base (DMAP) is believed to react with silyl chloride to form silyl pyridinium ion pairs, whose subsequent reaction with the alcohol substrate yields the silyl ether products together with the protonated (and thus deactivated) pyridine base.^[70] Reactivation of the catalyst then requires the action of an auxiliary base such as Et₃N.^[71] For the synthesis of diene **325**, compound **326** was then subjected to ring-closing enyne metathesis (Scheme 18). The latter reaction was achieved within 20–22 hours at 95°C using 3 mol% of Grubbs II catalyst and the metathesis product **325** was isolated in 42% yield. The poor recovery of **325** was due to its decomposition over silica during the flash chromatography, but not to a low conversion of **326**.



Scheme 18. The three-step synthesis of diene **325** starting from propargyl bicyclic γ -lactone **166b**.

The NMR chemical shifts of the isolated compound **325** were compared to that of the starting material **326** as shown in Figures 24 and 25. The most characteristic feature in the ¹H NMR spectrum of **325** is the absence of the alkynyl proton H12 signal and the appearance of a new doublet of doublet around 6.30 ppm which couples with H18a ($J = 17.3$ Hz) and H18b ($J = 11.2$ Hz). This indicates that H12 has been converted from an alkynyl proton in **326** to a vinyl one in **325**. Moreover, the spectrum reveals a slight downfield shift of proton H17 ($\Delta\delta \sim 0.2$ ppm) which

becomes a triplet ($J = 8.0$ Hz) in **325** after being a multiplet in **326**. Therefore, H17 is not coupling with H18 anymore, but still coupling with its neighboring allylic protons H16. These arguments have been verified by ^{13}C NMR signals which were assigned by the help of 2D HSQC analysis (Figure 25). The signals of the alkynyl carbons C11 ($\delta = 80.3$ ppm) and C12 ($\delta = 70.9$ ppm) in **326** have completely disappeared in the spectrum of **325**. However, new peaks have appeared in **325** at 135.4 and 139.2 ppm related to a quaternary carbon (C11) and a primary one (C12) respectively. This ensures that both C11 and C12 have become sp^2 carbon atoms in **325**. All these pieces of evidence, in addition to MS, ensure the suggested structure of **325**.

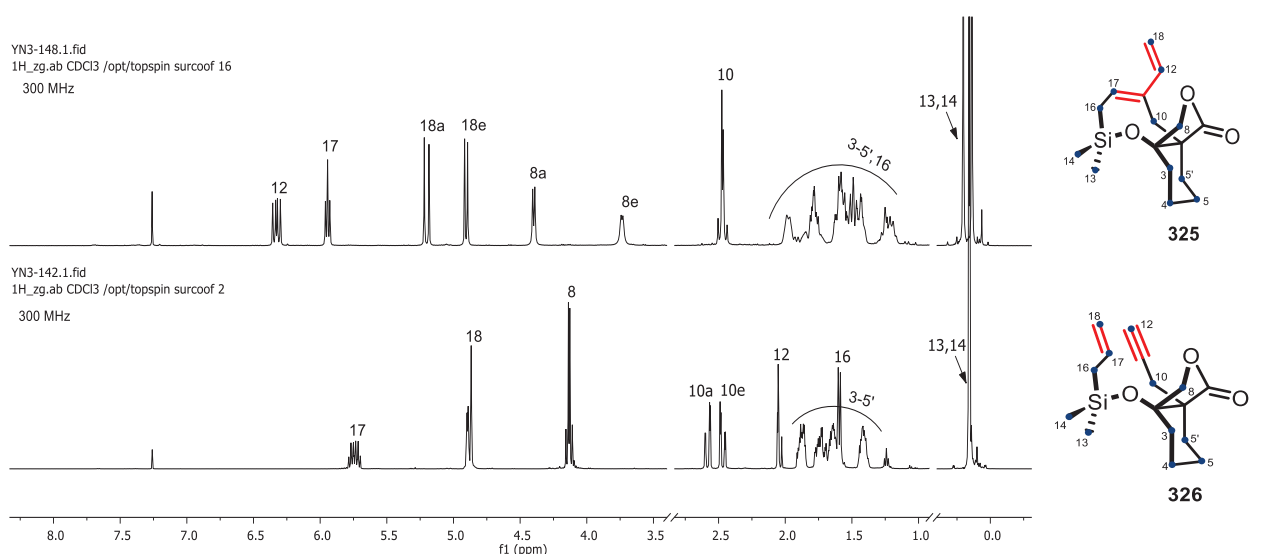


Figure 24. Comparing the ^1H NMR spectrum of **325** with that of **326**.

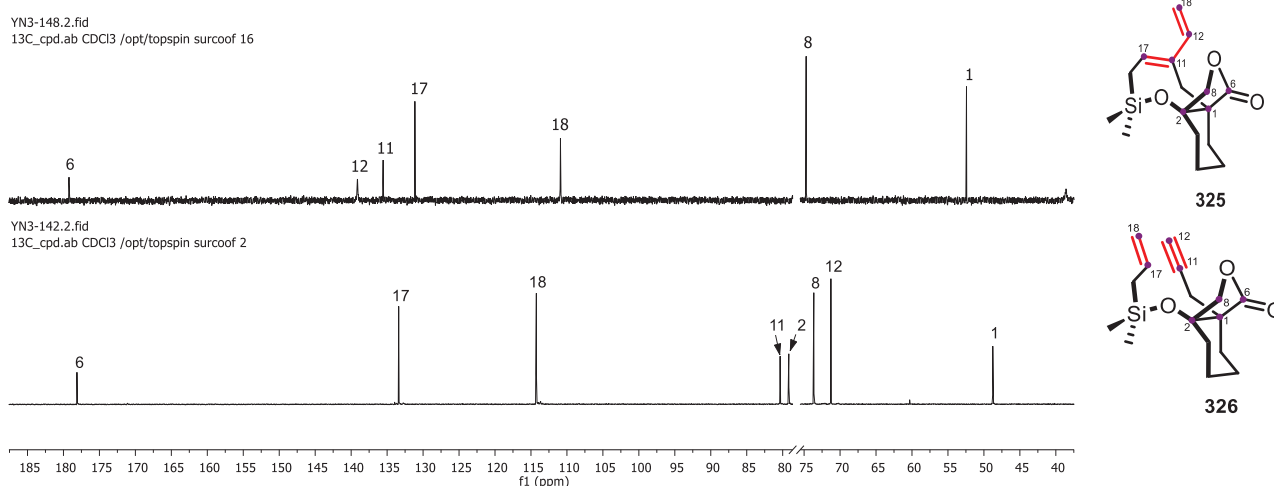
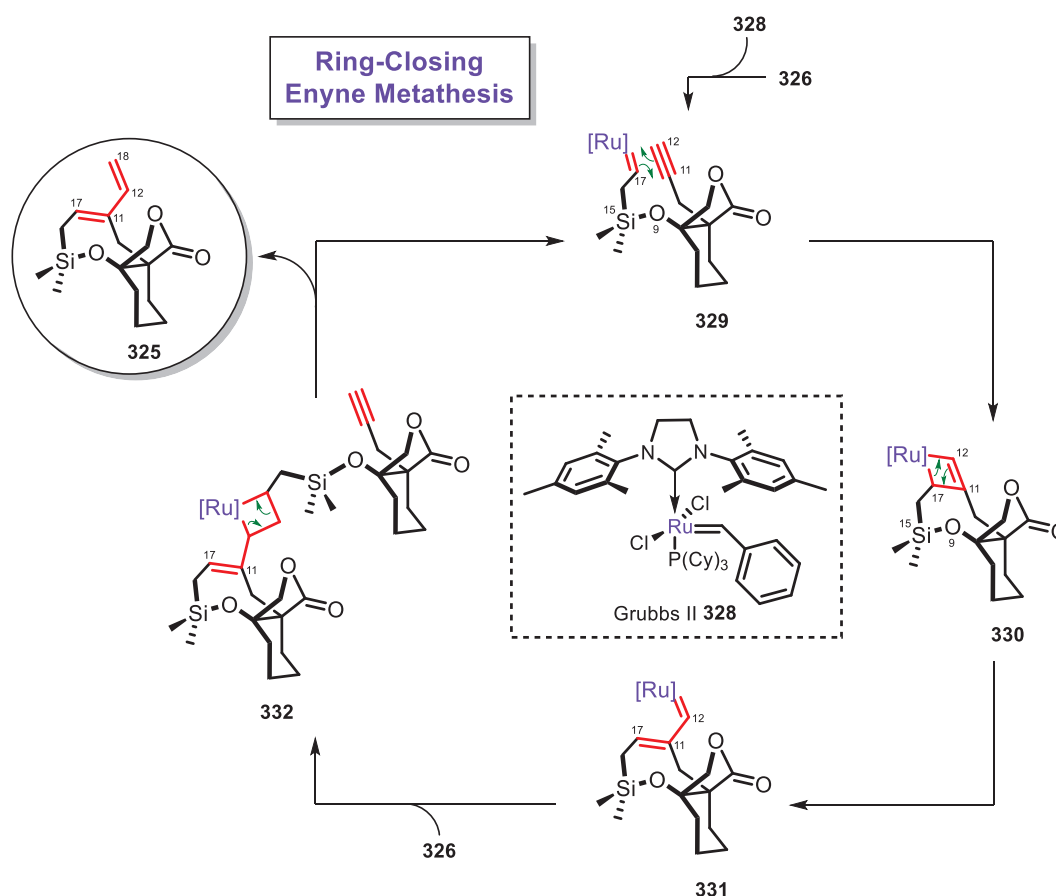


Figure 25. Comparing the characteristic ^{13}C NMR peaks of **325** with that of **326**.

Mechanism of RCEYM:

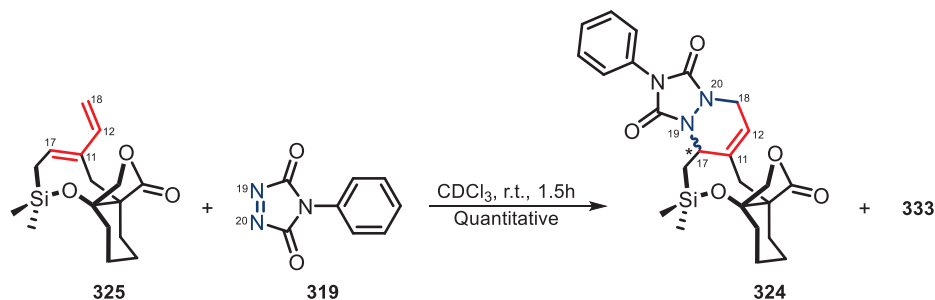
Based on what has already been described by Lippstreu and Staub,^[72] intramolecular enyne metathesis would proceed via a [2+2]-cycloaddition of a ruthenium–carbene complex **328** with the alkene part of enyne **326** to afford a new ruthenium carbene complex **329** (Scheme 18). The latter species reacts with the alkyne part to produce ruthenacyclobutene **330**, and its subsequent ring-opening gives ruthenium carbene **331**, which undergoes [2+2]-cycloaddition with the alkene part of enyne **326** to produce ruthenacyclobutane **332**. Ring-opening of **332** gives diene **325**, and the ruthenium carbene complex **329** is regenerated.^[73]



Scheme 18. Proposed mechanism of ring-closing enyne metathesis leading to **325**.

Synthesis of PTAD-based propellane **324**:

The metathesis product **325** which presents a 1,3-diene unit is well suited for a Diels–Alder reaction. After 1.5 hours of agitation in deuterated chloroform at room temperature, the dienes **325** in the presence of one equivalent of 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) led to the Diels–Alder product **324** and its “conformer” **333** in quantitative yield (Scheme 19).



Scheme 19. Diels–Alder reaction between diene **325** and PTAD **319**.

The NMR analysis of the crude reveals a complete conversion of the starting materials to a 2.5:1 mixture of **324** and **333** of similar chemical shifts (Figure 26). The major product **324** exhibits two main AB systems related to protons H8 (4.00- 4.33 ppm, $J = 10.6$ Hz) and H10 (2.31- 3.02 ppm, $J = 15.1$ Hz), which are comparable with the systems of previously obtained *exo* enol ether propellane **277b** shown at the beginning of this chapter. In addition to the most deshielded phenyl protons H25-H29 (7.28-7.59 ppm), a broad multiplet appears at 5.89 ppm which is most likely related to the vinyl proton H12. The latter gives three intense cross-peaks in COSY experiment, two related to allyl protons H18 that are situated next to the lactone AB system (3.99-4.42 ppm)

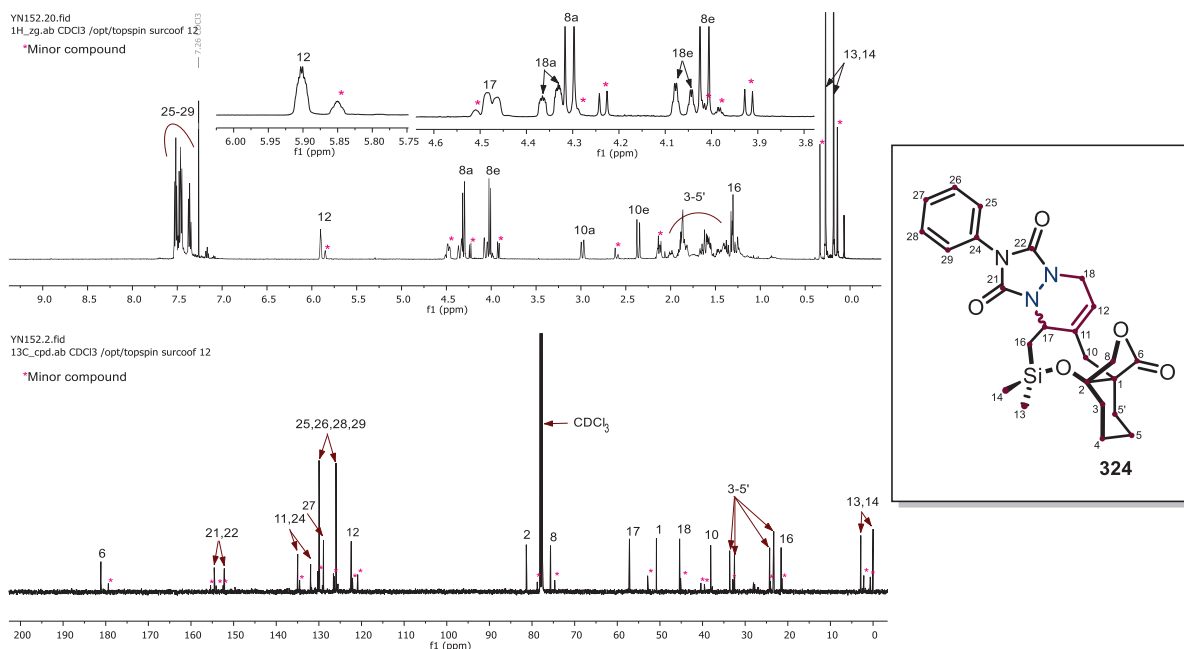


Figure 26. ^1H and ^{13}C NMR assignments of **324**.

and the other one with H10a (Figure 25). On the other hand, COSY correlation of another broad signal, observed around 4.48 ppm, gives only one cross-peak with the α -silyl protons H16. Presumably, this proton belongs to the stereogenic center at position 17.

The above arguments have been verified by ^{13}C NMR analysis (Figure 26). The presence of another minor product **333** made the analysis more challenging. Thus, further 2D NMR experiments, such as DEPT-135, HSQC and HMBC, were needed to completely assign the carbons of **324**. In addition to the phenyl ring signals, the urazole unit gives two peaks at 152.1 and 154.5 ppm related to C21 and C22 respectively, which were far enough to be correlated by any proton in the performed HMBC analysis. On the other hand, the alkene carbons C11 and C12, appearing at 134.9 and 122.4 ppm respectively, were assigned by the observed HMBC correlation with their neighboring allyl and homoallyl protons H10 and H16-H18 (Figure 25). The rest of the carbon skeleton, including the lactone, alkyl ring and dimethylsilyl group (C1-C10, C13 and C14), was assigned based on the ^{13}C chemical shifts of the starting material **325**.

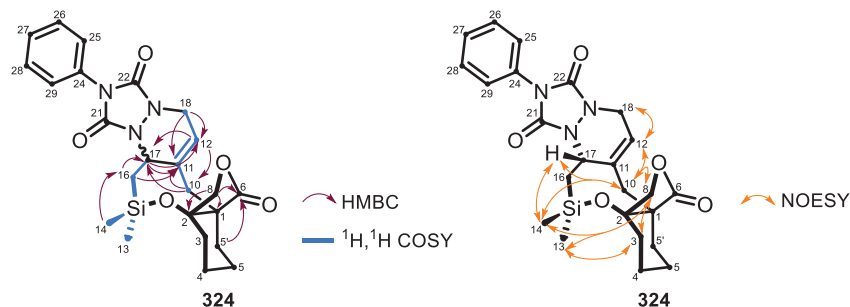


Figure 25. Key COSY, HMBC and NOESY features of **324**.

The stereochemistry of **324** at position 17 has been deduced from 2D NOESY experiment (Figure 25). Proton H17 gives strong cross-peaks with H10e and H14 but not with H10a or H13. Indeed, the latter protons correlate with the alkyl ring, which is not the case of their counterpart protons H10e and H14. Moreover, the lactone proton H8e, which shows less correlation with the alkyl ring than H8a, gives an intense cross peak with H10e and a weak one with H14. These arguments suggest that H17, with H8e, H10e and H14, is situated toward the lactone ring and not toward the alkyl group.

After a complete NMR analysis of **324**, we turned our attention back to the resulting minor product **333**. According to electrospray ionization mass spectrometry (ESI-MS), the molecular mass of **333** appears to be the same as that of **324**. Furthermore, most of the ^1H and ^{13}C chemical shifts of **333**

are positioned next to their corresponding peaks of **324** (Figure 26). This can also be seen in ^{29}Si NMR spectrum where two peaks related to the deshielded silicon atoms of **324** and **333** ($\Delta\delta \sim 3.2$ ppm) are situated in the silane region (Figure 26).^[74] Apparently, compound **333** is either the relative diastereoisomer or the rotamer of **324**. However, NOESY correlations of **333** have not supported any evidence about the presence of a new configuration at position 17 which could have been opposite to that observed in **324**. Therefore, **324** and **333** are possibly conformational isomers and not diastereoisomers.

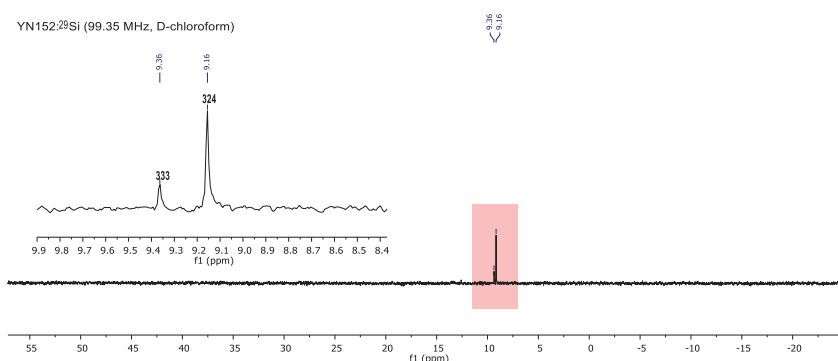


Figure 26. Decoupled ^{29}Si NMR of a mixture of **324** and **333**.

In general, equilibrating species, such as rotamers are most often distinguished from nonequilibrating diastereomers by techniques such as variable-temperature (VT) NMR,^[75] selective chemical-exchange NMR,^[76] solvent switching,^[77] or the introduction of a complexing agent.^[78] In our case, we were curious to examine the effect of temperature on the observed chemical shifts of **324** and **333**, thereby, a VT NMR experiment has been conducted on the crude mixture as shown in Figure 27. The ^1H NMR spectrum of this mixture in CDCl_3 at 260 K showed that the relative proportion of the major and minor compounds was 3.00:1.00. Upon increasing the temperature, and by using H12 and H17 signals as markers, **324** and **333** were independently detected since they were in slow exchange. At 320 K, the signals of the two compounds moved even closer but were still detected. Eventually, the two signals coalesced to a single peak at ca. 5.88 ppm at a coalescence temperature, T_c , of 330 K.

The free energy of activation for the interconversion between the two unequally populated compounds **324** and **333** can then be calculated using Eyring's equations (**a** and **b**) as modified by Shanan-Atidi and Bar-Eli:^[79]

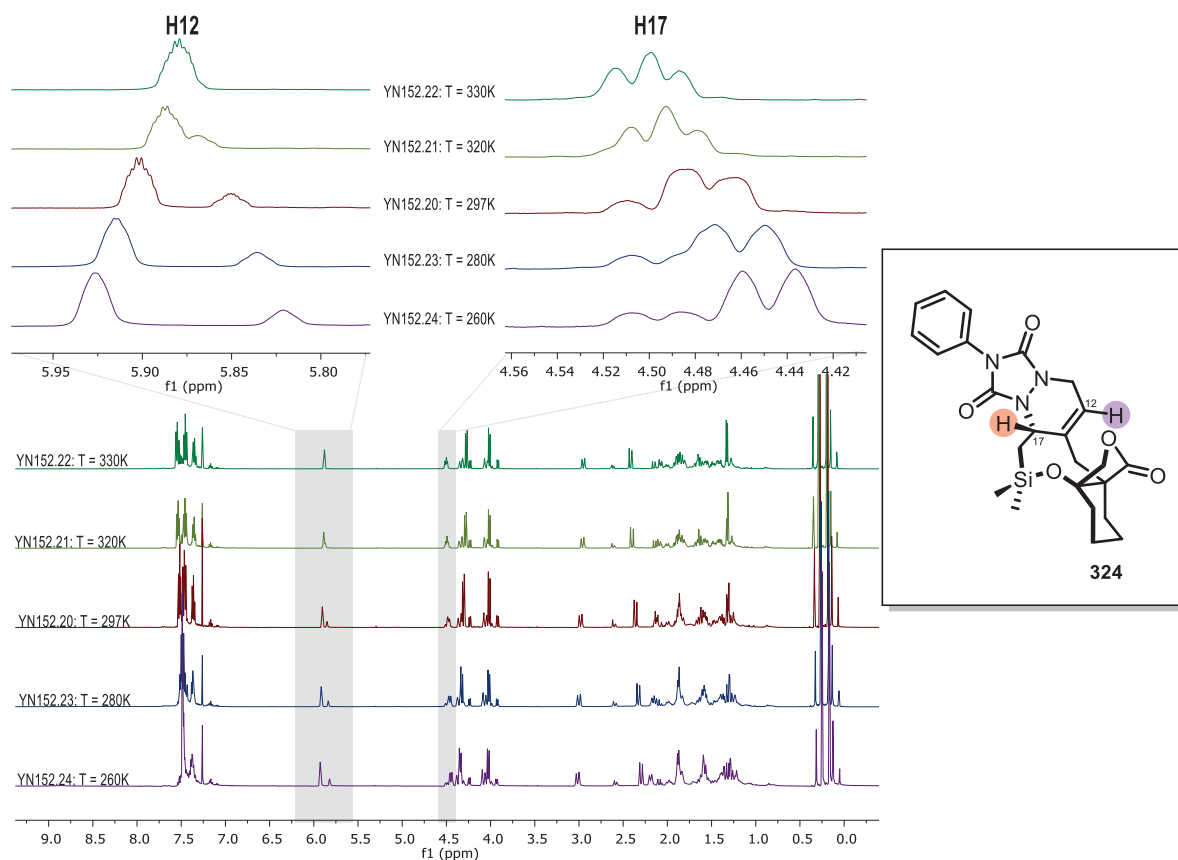


Figure 27. Effect of temperature on H12 and H17 in the ^1H NMR (500 MHz, CDCl_3) spectrum.

$$\Delta G_{\ddagger A}^{\ddagger} = 4.57Tc \{10.62 + \log [X/2\pi (1 - \Delta P)] + \log (Tc/ \Delta\nu)\} \quad (\text{a})$$

$$\Delta G_{\ddagger B}^{\ddagger} = 4.57Tc \{10.62 + \log [X/2\pi (1 + \Delta P)] + \log (Tc/ \Delta\nu)\} \quad (\text{b})$$

where $X = 2\pi\tau\Delta\nu$ and $\Delta P = P_A - P_B$.

P_A and P_B represent the population of the conformers A and B ($P_A > P_B$, $P_A + P_B = 1$), respectively, and τ is the mean lifetime. Tc and $\Delta\nu$ are the coalescence temperature and the chemical shift difference between conformers A and B, respectively. X is obtained using equation (c):

$$P_A - P_B = \Delta P = [(X^2 - 2)/3]^{3/2} * 1/X \quad (\text{c})$$

From the ^1H NMR spectrum at 260 K, the frequency difference, $\Delta\nu$, between the H12 signals was 52.73 Hz (52.73 s^{-1}). The Coalescence Temperature, Tc , was 330 K.

$$\Delta P = 0.77 - 0.23 = [(X^2 - 2)/3]^{3/2} * 1/X$$

$$X = 2.35$$

$$\Delta G_{\ddagger A}^{\ddagger} = 4.57(330) \{10.62 + \log [2.35/2\pi (1 - 0.54)] + \log (330/52.73)\}$$

$$= 16063 \text{ cal.mol}^{-1} \quad (1 \text{ cal.mol}^{-1} = 4.184 \text{ J.mol}^{-1})$$

$$\begin{aligned}
 &= \sim 67.2 \text{ kJ.mol}^{-1} \\
 \Delta G_{\ddagger B} &= 4.57(330) \{10.62 + \log [2.35/2\pi (1 + 0.54)] + \log (330/52.73)\} \\
 &= 16\,855 \text{ cal.mol}^{-1} \\
 &= \sim 70.5 \text{ kJ.mol}^{-1} \\
 \Delta G &= \Delta G_{\ddagger B} - \Delta G_{\ddagger A} = \sim 3.3 \text{ kJ.mol}^{-1}
 \end{aligned}$$

The VT ^1H NMR studies confirmed the hypothesis that the doubling of signals in the ^1H and ^{13}C NMR spectra at 262 K was due to the presence of two conformational isomers **324** and **333** separated by a relatively high energy barrier.

The data derived from the NOESY spectrum suggested that the conformation of the oxasilocane unit might be behind the formed isomers.^[80] Strong cross-peaks were observed in **324** between H12 and the respective alkyl ring protons H3-H5', which was not the case in **333**. This observation, in addition to other minor arguments, indicated that the preferred geometry of the oxasilocane unit is the one which is oriented toward the cyclohexyl group and not the lactone ring. Further investigation in the future, such as molecular modeling combined with X-ray Diffraction, may explain the observed stereochemistry and help determine the exact structure of each conformer.

3.2. Iodo-DHP[4,3,3]propellane

Today, it is safe to say that transition-metal catalyzed cross-coupling reactions were key discoveries for a conceptual revolution that occurred in organic chemistry in recent years.^[81] In one important reaction type, a main group organometallic compound of the type R-M (R = organic fragment, M = main group center) reacts with an organic halide of the type R'-X with formation of a new carbon-carbon bond in the product R-R'.^[82] Besides their wide and versatile range of applications in pharmaceuticals^[81a] and polymer chemistry,^[83] cross-coupling reactions provide new avenues for molecular diversity.^[84] Such heterogeneity can be achieved by allowing the reaction of certain R-M with different R'-X, or the inverse way. We herein report a new iodo-propellane as an important R'-X precursor for further diversity-oriented synthesis. The designed adduct is a [4,3,3]propellane that includes the regular lactone and alkyl ring, used in the core structure of the described propellanes in this chapter, in addition to 5-iodo-6-phenyl-dihydropyran unit (Figure 28). The latter exhibits vinyl iodide at position 11, which could serve as a key functionality for the future synthesis of various alkyl- or aryl-DHP[4,3,3]propellanes *via* cross-

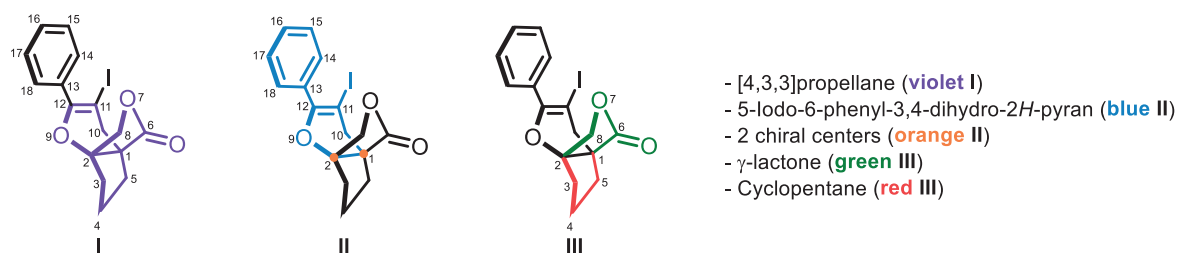
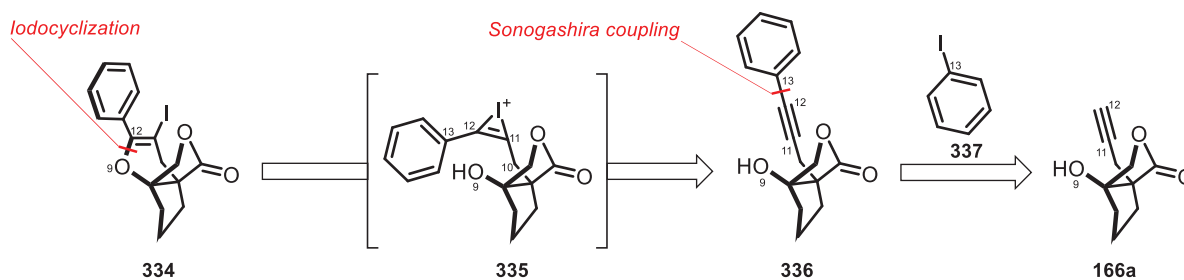


Figure 28. Key features of the designed iodo-DHP[4,3,3]propellane.

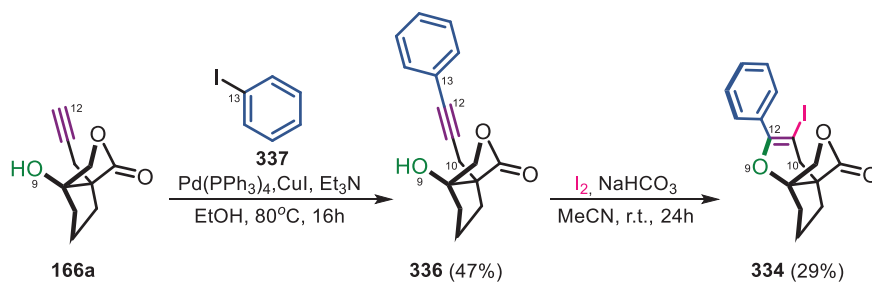
coupling reactions.

The retrosynthetic analysis of the designed structure is shown in Scheme 20. The DHP unit in **334** was envisioned to be derived from the nucleophilic attack of the hydroxyl group, or O₉, on the iodonium cycle at position 12 in **335**. The latter intermediate could be generated from the *in situ* coordination of I⁺ to the alkyne of the Sonogashira product **336** at positions 11 and 12.



Scheme 20. Retrosynthesis of **334**.

Accordingly, the synthesis of **334** commenced with the cross-coupling reaction of the readily prepared starting material **166a** and iodobenzene **337** in the presence of catalytic amounts of Pd(PPh₃)₄ and CuI (Scheme 21).^[85] The desired product **336**, having an R_f value similar to that of **166a**, was then purified over silica gel (Petroleum ether/ethyl acetate 65:35), concentrated and isolated in 47% yield. Eventually, the electrophilic cyclization of the obtained compound was



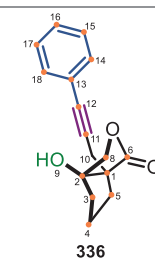
Scheme 21. Synthesis of **334**.

initiated with NaHCO₃ as base and I₂ as an electrophilic source to give the *6-endo-dig* product **334** in a 29% yield.^[86] In addition to the HRMS data, the formation of the dihydropyran unit in **334** was easily observed in the NMR analysis as shown in Table 18. Protons H10, close to the triple bond in **336**, were shifted downfield in **334** ($\Delta\delta \sim 3.12$ ppm). Moreover, the protic hydrogen of the hydroxyl group in **336** (~ 2.60 ppm) has disappeared in **334**. The cyclization has also been verified by ¹³C NMR data where the sp carbons C11 and C12, appearing at 85.3 and 85.0 ppm respectively, were remarkably shifted downfield in **334** ($\Delta\delta \sim 5.1- 67.1$ ppm) indicating the presence of the vinyl iodide group.

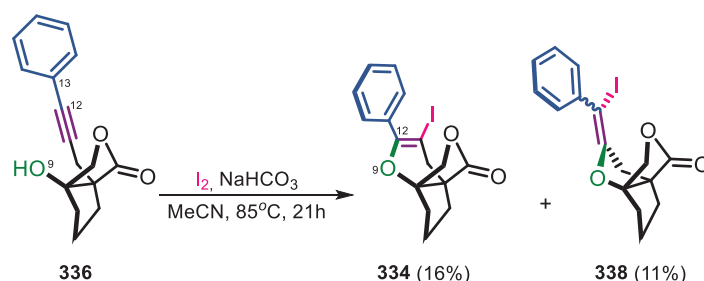
Table 18. ¹H and ¹³C NMR of **334** and **336** in CDCl₃. (^aMay be interchanged, ^b300 MHz, ^c126 MHz).

¹ H NMR ^b	H3-5	H8a	H8e	OH	H10a	H10e	H14-H18
336	1.15-2.26 m	a: 4.32 d <i>J</i> _{8a-8e} =10.0	e: 4.24 d <i>J</i> _{8e-8a} =10.0	2.60 s	a: 2.91 d <i>J</i> _{10a-10e} =16.9	e: 2.79 d <i>J</i> _{10e-10a} =16.9	7.45-7.22 m
334	1.20-2.34 m	a: 4.46 d <i>J</i> _{8a-8e} =10.1	e: 4.28 d <i>J</i> _{8e-8a} =10.1	-	a: 3.14 d <i>J</i> _{10a-10e} =16.6	e: 2.83 d <i>J</i> _{10e-10a} =16.6	7.52-7.32 m

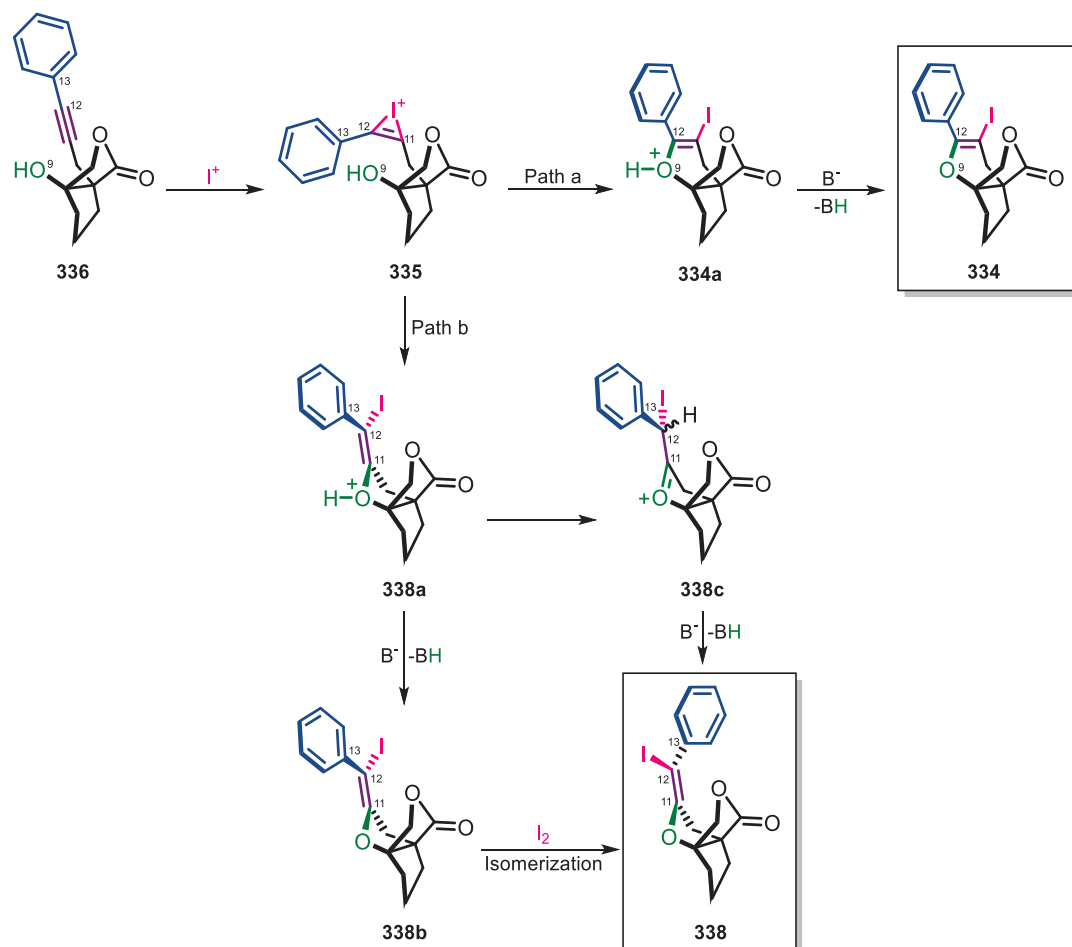
¹³ C NMR ^c	C1	C2	C3-C5	C6	C8	C10	C11	C12	C13	C14-C18
336	55.1	84.0 ^a	36.3 22.5 22.7	180.1	78.5	42.2	85.3	85.0 ^a	122.2	128.4 128.6 131.6
334	54.8	92.7 ^a	37.4 36.4 37.4	178.9	75.8	66.4	90.1 ^a	152.1	136.3	127.9 129.1 129.2



Another experiment, similar to the previous one, has been conducted at a higher temperature (Scheme 21). We found that this iodocyclization also proceeded to afford **334**, but in lower yield (16%). Furthermore, we observed the formation of regioisomer **338**, or the *5-exo-dig* product, in 11% yield. On the basis of these observations, the reaction mechanism can be proposed by referring to the one mentioned in the literature for another family of compounds (Scheme 22).^[86a]



Scheme 21. Synthesis of **334** at 85°C.



Scheme 22. Proposed mechanistic pathways for the iodocyclization of **336**.^[86a]

Coordination of an I^+ equivalent to the alkyne leads to electrophilic activation of the alkyne carbon-carbon triple bond generating iodonium intermediate **335**. Nucleophilic attack by the hydroxyl group may then take place by either of two intramolecular cyclization modes (*anti-6-endo-dig* or *anti-5-exo-dig*, paths a and b, respectively) to give intermediates **334a** or **338a**, respectively. Deprotonation of intermediate **334a** leads to the iodo-DHP[4,3,3]propellane **334** that was isolated as the major product in the performed experiments. Although the exact configuration of the alkene unit in **338** has not been verified, presumably, isomerization of the initially formed *E*-isomer **338b** led to the more stable *Z*-isomer **338**. A few examples of the isomerization of substituted *cis* alkenes to the more stable corresponding *trans* isomers in the presence of iodine are known.^[87] To demonstrate the feasibility of the isomerization, a mixture of **338** and **338b** was subjected to simple heating and partial isomerization was observed. Based on the 1H NMR spectral data, the ratio of

cis:trans was found to be 2.2:1 before heating and 1:1.7 after heating. The possibility that E-Z isomerization occurs through the formation of intermediate **338c** (deriving from **338a** via proton shift) followed by stereospecific deprotonation cannot be ruled out, however.

4. General conclusion

Throughout this chapter, we highlighted most of the accomplishments that have been done in propellane synthesis from a common propargyl bicyclic γ -lactone precursor. The study was mainly focused on oxaspiro[*n*,3,3]propellanes, which have been categorized based on their number of annular atoms attached to the common propellane subunit. The described oxaspirocyclopropane, oxaspiro-oxetane and oxaspirolactone adducts were all prepared thermally or photochemically from *exo* enol ether propellanes, which have proven to be highly useful for construction of remarkably strained and rigid molecular frameworks. Besides the furnished oxaspiro[*n*,3,3]propellanes, other miscellaneous ring systems have been constructed from the same bicyclic building blocks, such as PTAD-based [6,4,3]propellane and iodo-DHP[4,3,3]propellane that can be used as future parent structures for further transformations.

5. References

- [1] a) I. V. Komarov, *Russ. Chem. Rev.* **2001**, *70*, 991-1016; b) P. K. Mykhailiuk, *Org. Biomol. Chem.* **2019**, *17*, 2839-2849; c) Q. Wang, H. Geng, W. Chai, X. Zeng, M. Xu, C. Zhu, R. Fu, R. Yuan, *Eur. J. Org. Chem.* **2014**, *2014*, 6850-6853.
- [2] a) K. Undheim, *Synthesis* **2014**, *46*, 1957-2006; b) Y. Zheng, C. M. Tice, S. B. Singh, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3673-3682; c) V. A. D'yakonov, O. G. A. Trapeznikova, A. de Meijere, U. M. Dzhemilev, *Chem. Rev.* **2014**, *114*, 5775-5814; d) E. Chupakhin, O. Babich, A. Prosekov, L. Asyakina, M. Krasavin, *Molecules* **2019**, *24*, 4165; e) R. Rios, *Chem. Soc. Rev.* **2012**, *41*, 1060-1074.
- [3] A. Baeyer, *Ber Dtsch Chem Ges* **1900**, *33*, 3771-3775.
- [4] a) J. A. Palmes, A. Aponick, *Synthesis* **2012**, *44*, 3699-3721; b) S. Kotha, M. Meshram, Y. Dommaraju, *Chem. Rec.* **2018**, *18*, 1613-1632.
- [5] C. Wu, H. U. van der Heul, A. V. Melnik, J. Lübben, P. C. Dorrestein, A. J. Minnaard, Y. H. Choi, G. P. van Wezel, *Angew. Chem.* **2019**, *131*, 2835-2840.
- [6] a) S. M. King, N. A. Calandra, S. B. Herzon, *Angew. Chem. Int. Ed.* **2013**, *52*, 3642-3645; b) K. Goto, H. Sudzuki, *Bull. Chem. Soc. Jpn.* **1929**, *4*, 220-224; c) K. Goto, M. Tomita, Y. Okamoto, Y. Sasaki, K. Matoba, *Proc. Jpn Acad.* **1966**, *42*, 1181-1184; d) K. Goto, M. Tomita, Y. Okamoto, T. Kikuchi, K. Osaki, M. Nishikawa, K. Kamiya, Y. Sasaki, K. Matoba, *Proc. Jpn Acad.* **1967**, *43*, 499-504; e) M. Tomita, Y. Okamoto, T. Kikuchi, K. Osaki, M. Nishikawa, K. Kamiya, Y. Sasaki, K. Matoba, K. Goto, *Tetrahedron Lett.* **1967**, *8*, 2421-2424; f) M. Tomita, Y. Okamoto, T. Kikuchi, K.

- Osaki, M. Nishikawa, K. Kamiya, Y. Sasaki, K. Matoba, K. Goto, *Tetrahedron Lett.* **1967**, *8*, 2425-2430.
- [7] A. M. P. Koskinen, A. J. Pihko, *Arkivoc* **2008**, *17*, 20-35.
- [8] S. Kotha, S. R. Cheekatla, *Tetrahedron* **2019**, *75*, 84-93.
- [9] S. Kotha, S. R. Cheekatla, D. S. Mhatre, *Synthesis* **2017**, *49*, 5339-5350.
- [10] a) S. Kotha, M. Saifuddin, R. Ali, G. Sreevani, *Beilstein J. Org. Chem.* **2015**, *11*, 1367-1372; b) S. Kotha, S. R. Cheekatla, D. S. Mhatre, *Synthesis* **2017**, *49*, 5339-5350.
- [11] S. Kotha, R. Ali, A. K. Chinnam, *Tetrahedron Lett.* **2014**, *55*, 4492-4495.
- [12] a) S. Kotha, R. Gunta, *Beilstein J. Org. Chem.* **2016**, *12*, 1877-1883; b) S. Kotha, R. Gunta, *Beilstein J. Org. Chem.* **2015**, *11*, 1727-1731.
- [13] M. Miao, J. Cao, J. Zhang, X. Huang, L. Wu, *J. Org. Chem.* **2013**, *78*, 2687-2692.
- [14] K. Kakiuchi, T. Tadaki, Y. Tobe, Y. Odaira, *Chem. Lett.* **1985**, *14*, 1565-1568.
- [15] a) R. L. Cargill, J. R. Damewood, M. M. Cooper, *J. Am. Chem. Soc.* **1966**, *88*, 1330-1331; b) R. C. Cargill, P. de Mayo, A. C. Miller, K. R. Neuberger, D. M. Pond, J. Saltiel, M. F. Tchir, *Mol. Photochem.* **1969**, *1*, 301-317.
- [16] J. C. Harmange, B. Figadère, *Tetrahedron: Asymmetry* **1993**, *4*, 1711-1754.
- [17] a) R. H. Wiley, C. H. Jarboe, F. N. Hayes, *J. Am. Chem. Soc.* **1957**, *79*, 2602-2605; b) M. Riediker, J. Schwartz, *J. Am. Chem. Soc.* **1982**, *104*, 5842-5844; c) M. Suzuki, A. Yanagisawa, R. Noyori, *Tetrahedron Lett.* **1983**, *24*, 1187-1188.
- [18] a) K. Utimoto, *Pure Appl. Chem.* **1983**, *55*, 1845-1852; b) P. Compain, J. Goré, J. M. Vatéle, *Tetrahedron* **1996**, *52*, 10405-10416.
- [19] V. Dalla, P. Pale, *Tetrahedron Lett.* **1994**, *35*, 3525-3528.
- [20] H. Harkat, J. M. Weibel, P. Pale, *Tetrahedron Lett.* **2007**, *48*, 1439-1442.
- [21] E. Genin, S. Antoniotti, V. Michelet, J. P. Genêt, *Angew. Chem. Int. Ed.* **2005**, *44*, 4949-4953.
- [22] F. E. McDonald, M. M. Gleason, *J. Am. Chem. Soc.* **1996**, *118*, 6648-6659.
- [23] a) G. Tóth, *Magn. Reson. Chem.* **2001**, *39*, 656-656; b) J. B. Lambert, E. P. Mazzola, C. D. Ridge, *Nuclear magnetic resonance spectroscopy: An introduction to principles, applications, and experimental methods*, John Wiley & Sons, Upper Saddle River, **2004**.
- [24] M. Baranac-Stojanović, M. Stojanović, *J. Org. Chem.* **2013**, *78*, 1504-1507.
- [25] G. Wuitschik, E. M. Carreira, B. r. Wagner, H. Fischer, I. Parrilla, F. Schuler, M. Rogers-Evans, K. Müller, *J. Med. Chem.* **2010**, *53*, 3227-3246.
- [26] J. A. Bull, R. A. Croft, O. A. Davis, R. Doran, K. F. Morgan, *Chem. Rev.* **2016**, *116*, 12150-12233.
- [27] J. Iriondo-Alberdi, J. E. Perea-Buceta, M. F. Greaney, *Org. Lett.* **2005**, *7*, 3969-3971.
- [28] T. Bach, H. Brummerhop, *Angew. Chem. Int. Ed.* **1998**, *37*, 3400-3402.
- [29] R. K. Chaudhuri, T. Ikeda, C. R. Hutchinson, *J. Am. Chem. Soc.* **1984**, *106*, 6004-6006.
- [30] M. Fréneau, N. Hoffmann, *Photochem. Rev.* **2017**, *33*, 83-108.

- [31] a) M. Abe, *J. Chin. Chem. Soc.* **2008**, *55*, 479-486; b) M. D'auria, R. Racioppi, *Molecules* **2013**, *18*, 11384-11428; c) M. D'Auria, R. Racioppi, *Curr. Org. Chem.* **2009**, *13*, 939; d) B. Eftekhari-Sis, M. Zirak, *Chem. Rev.* **2015**, *115*, 151-264; e) T. Bach, *Liebigs Ann.* **1997**, *1997*, 1627-1634; f) Y. Inoue, *Chem. Rev.* **1992**, *92*, 741-770; g) N. Hoffmann, *Chem. Rev.* **2008**, *108*, 1052-1103; h) T. Bach, *Synthesis* **1998**, *1998*, 683-703; i) F. Mueller, J. Mattay, *Chem. Rev.* **1993**, *93*, 99-117; j) A. G. Griesbeck, M. Abe, S. Bondock, *Acc. Chem. Res.* **2004**, *37*, 919-928.
- [32] P. Klán, J. Wirz, *Photochemistry of organic compounds: From concepts to practice*, John Wiley & Sons, Chichester, **2009**.
- [33] a) W. Adam, *Chem. unserer Zeit* **1981**, *15*, 190-196; b) A. Greer, *Acc. Chem. Res.* **2006**, *39*, 797-804.
- [34] J. F. Rabek, *Experimental methods in photochemistry and photophysics*, John Wiley & Sons, New York, **1982**.
- [35] a) H. Buschmann, H. D. Scharf, N. Hoffmann, M. W. Plath, J. Runsink, *J. Am. Chem. Soc.* **1989**, *111*, 5367-5373; b) N. Kaur, M. Devi, Y. Verma, P. Grewal, P. Bhardwaj, N. Ahlawat, N. K. Jangid, *Curr. Green Chem.* **2019**, *6*, 155-183; c) W. Adam, V. R. Stegmann, S. Weinkötz, *J. Am. Chem. Soc.* **2001**, *123*, 2452-2453; d) W. Adam, V. R. Stegmann, *J. Am. Chem. Soc.* **2002**, *124*, 3600-3607.
- [36] a) B. Wardle, *Principles and applications of photochemistry*, John Wiley & Sons, Hoboken, **2009**; b) E. V. Anslyn, D. A. Dougherty, *Modern physical organic chemistry*, University science books, Sausalito, **2006**.
- [37] a) D. E. Damschen, C. D. Merritt, D. L. Perry, G. W. Scott, L. D. Talley, *J. Phys. Chem.* **1978**, *82*, 2268-2272; b) J. A. Dantas, J. T. M. Correia, M. W. Paixao, A. G. Corrêa, *J. Photochem.* **2019**, *3*, 506-520.
- [38] N. C. Yang, R. L. Loeschen, D. Mitchell, *J. Am. Chem. Soc.* **1967**, *89*, 5465-5466.
- [39] A. G. Griesbeck, M. Abe, S. Bondock, *Acc. Chem. Res.* **2004**, *37*, 919-928.
- [40] a) S. C. Freilich, K. S. Peters, *J. Am. Chem. Soc.* **1981**, *103*, 6255-6257; b) S. C. Freilich, K. S. Peters, *J. Am. Chem. Soc.* **1985**, *107*, 3819-3822.
- [41] Y. Zhang, J. Xue, Y. Gao, H. K. Fun, J. H. Xu, *J. Chem. Soc.* **2002**, 345-353.
- [42] N. J. Turro, G. L. Farrington, *J. Am. Chem. Soc.* **1980**, *102*, 6051-6055.
- [43] a) F. Perron, K. F. Albizati, *Chem. Rev.* **1989**, *89*, 1617-1661; b) R. Quach, D. F. Chorley, M. A. Brimble, *Org. Biomol. Chem.* **2014**, *12*, 7423-7432; c) F. M. Zhang, S. Y. Zhang, Y. Q. Tu, *Nat. Prod. Rep.* **2018**, *35*, 75-104.
- [44] S. S. Thorat, R. Kontham, *Org. Biomol. Chem.* **2019**, *17*, 7270-7292.
- [45] a) R. J. Duffy, K. A. Morris, D. Romo, *J. Am. Chem. Soc.* **2005**, *127*, 16754-16755; b) R. J. Duffy, K. A. Morris, R. Vallakati, W. Zhang, D. Romo, *J. of Org. Chem.* **2009**, *74*, 4772-4781.
- [46] P. V. Murphy, T. J. O'Sullivan, N. W. Geraghty, *J. Chem. Soc., Perkin Trans. 1* **2000**, 2109-2119.
- [47] Y. Bai, D. C. Davis, M. Dai, *J. Org. Chem.* **2017**, *82*, 2319-2328.
- [48] a) K. Maruyama, T. Ogawa, Y. Kubo, *Chem. Lett.* **1980**, *9*, 343-344; b) W. Adam, U. Kliem, E. M. Peters, K. Peters, H. G. von Schnering, *J. Prakt. Chem.* **1988**, *330*, 391-405.
- [49] a) J. A. Ashenhurst, L. Isakovic, J. L. Gleason, *Tetrahedron* **2010**, *66*, 368-378; b) D. H. Lukamto, M. J. Gaunt, *J. Am. Chem. Soc.* **2017**, *139*, 9160-9163.

- [50] D. A. Kambale, S. S. Thorat, M. S. Pratapure, R. G. Gonnade, R. Kontham, *Chem. Commun.* **2017**, 53, 6641-6644.
- [51] a) J. Schäfer, E. J. Corey, *J. Org. Chem.* **1959**, 24, 1825-1825; b) J. Zhuang, C. Wang, F. Xie, W. Zhang, *Tetrahedron* **2009**, 65, 9797-9800.
- [52] S. Xie, D. Li, H. Huang, F. Zhang, Y. Chen, *J. Am. Chem. Soc.* **2019**, 141, 16237-16242.
- [53] D. A. Kambale, S. S. Thorat, M. S. Pratapure, R. G. Gonnade, R. Kontham, *Chem. Commun.* **2017**, 53, 6641-6644.
- [54] R. E. Ireland, D. Häbich, *Tetrahedron Lett.* **1980**, 21, 1389-1392.
- [55] M. Liang, S. Zhang, J. Jia, C. H. Tung, J. Wang, Z. Xu, *Org. Lett.* **2017**, 19, 2526-2529.
- [56] a) C. Moody, in *Adv. Heterocycl. Chem.*, Vol. 30, Elsevier, **1982**, pp. 1-45; b) M. N. Alberti, M. Orfanopoulos, *Org. Lett.* **2009**, 11, 1659-1662.
- [57] G. C. Vougioukalakis, M. Orfanopoulos, *Synlett* **2005**, 2005, 713-731.
- [58] a) D. K. Kim, K. E. O'Shea, *J. Am. Chem. Soc.* **2004**, 126, 700-701; b) J. Sivaguru, T. Poon, C. Hooper, H. Saito, M. R. Solomon, S. Jockusch, W. Adam, Y. Inoue, N. J. Turro, *Tetrahedron* **2006**, 62, 10647-10659; c) T. Fischer, U. Kunz, S. E. Lackie, C. Cohrs, D. D. Palmer, M. Christl, *Angew. Chem. Int. Ed.* **2002**, 41, 2969-2971; d) L. A. Paquette, P. Webber, I. Simpson, *Org. Lett.* **2003**, 5, 177-180.
- [59] a) W. Adam, J. Glaeser, K. Peters, M. Prein, *J. Am. Chem. Soc.* **1995**, 117, 9190-9193; b) M. Fujita, H. Matsushima, T. Sugimura, A. Tai, T. Okuyama, *J. Am. Chem. Soc.* **2001**, 123, 2946-2957.
- [60] a) V. M. Kobal, D. T. Gibson, R. E. Davis, A. Garza, *J. Am. Chem. Soc.* **1973**, 95, 4420-4421; b) K. L. Hoffmann, G. Maas, M. Regitz, *J. Org. Chem.* **1987**, 52, 3851-3857.
- [61] a) D. H. R. Barton, A. Gunatilaka, *J. Chem. Soc.* **1976**, 1, 821; b) R. I. Yakhimovich, N. F. Fursaeva, V. E. Pashinnik, *Chem. Nat. Prod.* **1985**, 21, 98-103.
- [62] M. L. Poutsma, P. A. Ibarbia, *J. Am. Chem. Soc.* **1971**, 93, 440-450.
- [63] A. P. Henderson, E. Mutlu, A. Leclercq, C. Bleasdale, W. Clegg, R. A. Henderson, B. T. Golding, *Chem. Commun.* **2002**, 1956-1957.
- [64] a) D. Kaufmann, A. de Meijere, *Tetrahedron Lett.* **1979**, 20, 779-782; b) L. A. Paquette, *J. Am. Chem. Soc.* **1970**, 92, 5765-5767.
- [65] a) I. K. Korobitsyna, A. V. Khalikova, L. L. Rodina, N. P. Shusherina, *Chem. Heterocycl. Compd.* **1983**, 19, 117-136; b) T. J. Katz, N. Acton, *J. Am. Chem. Soc.* **1973**, 95, 2738-2739.
- [66] a) C. Amith, D. Ginsburg, *Tetrahedron* **1974**, 30, 3415-3422; b) J. Kettenring, D. Ginsburg, *Tetrahedron* **1984**, 40, 5269; c) M. Korat, D. Ginsburg, *Tetrahedron* **1973**, 29, 2373-2381; d) T. Ibata, Y. Isogami, H. Tamura, *Chem. Lett.* **1988**, 17, 1551-1554; e) I. Agmon, P. Ashkenazi, M. Kaftory, *Acta Cryst.* **1992**, 48, 1479-1484.
- [67] a) J. Kalo, J. M. Photis, L. A. Paquette, E. Vogel, D. Ginsburg, *Tetrahedron* **1976**, 32, 1013-1014; b) J. Kalo, D. Ginsburg, J. J. Bloomfield, *Tetrahedron* **1978**, 34, 2153-2154; c) P. Ashkenazi, M. Peled, E. Vogel, D. Ginsburg, *Tetrahedron* **1979**, 35, 1321-1327; d) P. Ashkenazi, M. Kaftory, T. Sayraç, G. Maier, D. Ginsburg, *Helv. Chim. Acta* **1983**, 66, 2709-2711.
- [68] D. Sémeril, M. Cléran, A. J. Perez, C. Bruneau, P. H. Dixneuf, *J. Mol. Catal. A Chem.* **2002**, 190, 9-25.

- [69] S. K. Chaudhary, O. Hernandez, *Tetrahedron Lett.* **1979**, *20*, 99-102.
- [70] a) P. Patschinski, C. Zhang, H. Zipse, *J. Org. Chem.* **2014**, *79*, 8348-8357; b) K. Akiba, Y. Iseki, M. Wada, *Tetrahedron Lett.* **1982**, *23*, 3935-3936.
- [71] P. Patschinski, C. Zhang, H. Zipse, *J. Org. Chem.* **2014**, *79*, 8348-8357.
- [72] J. J. Lippstreu, B. F. Straub, *J. Am. Chem. Soc.* **2005**, *127*, 7444-7457.
- [73] M. Mori, *Adv. Synth. Catal.* **2007**, *349*, 121-135.
- [74] a) J. Schraml, J. Vcelak, V. Chvalovsky, G. Engelhardt, *Collect. Czechoslov. Chem. Commun.* **1976**, *41*, 3758-3770; b) G. Engelhardt, H. Jancke, *Polym. Bull.* **1981**, *5*, 577-584; c) E. Williams, J. Cargioli, *Annu. Rep. NMR Spect.* **1979**, *9*, 221-319; d) R. K. Harris, R. H. Newman, *Org. Magn. Reson.* **1977**, *9*, 426-431.
- [75] J. H. Frank, Y. L. Powder-George, R. S. Ramsewak, W. F. Reynolds, *Molecules* **2012**, *17*, 7914-7926.
- [76] D. X. Hu, P. Grice, S. V. Ley, *J. Org. Chem.* **2012**, *77*, 5198-5202.
- [77] a) R. A. Al-Horani, U. R. Desai, *Tetrahedron* **2012**, *68*, 2027-2040; b) A. B. Smith III, J. J. Chroma, Q. Han, J. Barbosa, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1697-1702.
- [78] a) A. R. Modarresi-Alam, P. Najafi, M. Rostamizadeh, H. Keykha, H. R. Bijanzadeh, E. Kleinpeter, *J. Org. Chem.* **2007**, *72*, 2208-2211; b) M. J. Deetz, J. E. Fahey, B. D. Smith, *J. Phys. Org. Chem.* **2001**, *14*, 463-467; c) A. L. Moraczewski, L. A. Banaszynski, A. M. From, C. E. White, B. D. Smith, *J. Org. Chem.* **1998**, *63*, 7258-7262.
- [79] H. Shanan-Atidi, K. H. Bar-Eli, *J. Phys. Chem.* **1970**, *74*, 961-963.
- [80] a) P. W. Pakes, T. C. Rounds, H. L. Strauss, *J. Phys. Chem.* **1981**, *85*, 2469-2475; b) J. E. Anderson, E. S. Glazer, D. L. Griffith, R. Knorr, J. D. Roberts, *J. Am. Chem. Soc.* **1969**, *91*, 1386-1395; c) O. V. Dorofeeva, V. S. Mastryukov, N. L. Allinger, A. Almenningen, *J. Phys. Chem.* **1985**, *89*, 252-257.
- [81] a) C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 5062-5085; b) C. Bolm, ACS Publications, **2012**.
- [82] A. O. King, N. Yasuda, in *Organometallics in process chemistry*, Springer, Heidelberg, **2004**, pp. 205-245.
- [83] J. H. Kim, J. W. Kim, M. Shokouhimehr, Y. S. Lee, *J. Org. Chem.* **2005**, *70*, 6714-6720.
- [84] I. Hussain, J. Capricho, M. A. Yawer, *Adv. Synth. Catal.* **2016**, *358*, 3320-3349.
- [85] a) M. V. Karkhelikar, R. R. Jha, B. Sridhar, P. R. Likhar, A. K. Verma, *Chem. Commun.* **2014**, *50*, 8526-8528; b) B. Dulla, S. K. Kolli, U. R. Chamakura, G. S. Deora, R. R. Raju, M. Pal, *Synth. Commun.* **2014**, *44*, 1466-1474.
- [86] a) R. Mancuso, S. Mehta, B. Gabriele, G. Salerno, W. S. Jenks, R. C. Larock, *J. Org. Chem.* **2010**, *75*, 897-901; b) V. Vijay, M. V. Karkhelikar, B. Sridhar, N. Mirzadeh, S. Bhargava, P. R. Likhar, *Org. Biomol. Chem.* **2016**, *14*, 288-295; c) T. Okitsu, A. Namura, S. Kondo, S. Tada, M. Yanagida, A. Wada, *Org. Chem. Front.* **2020**, *7*, 879-884.
- [87] a) W. J. Muizebelt, R. J. F. Nivard, *Chem. Commun.* **1965**, 148-149; b) N. Windmon, V. Dragojlovic, *Tetrahedron Lett.* **2008**, *49*, 6543-6546.

Chapter V

Hexahydroindeno[2,1-*c*]pyran-based
Propellanes

Ch. V: Hexahydroindeno[2,1-c]pyran-based Propellanes

1. Introduction

So far, the synthesis of diverse propellane ring systems from similar building blocks has been described in the preceding chapters (three and four). Most of these structures were associated with elaborated motifs as promising features for possible future applications. To expand our investigations and explore additional families of such 3D-structures, we were curious about starting from precursors different to those used in the previous chapters. For this reason, we endeavored new access for the synthesis of a unique family of indenopyran-based propellanes from aldehydes and *exo*-olefinic alcohol (Figure 1). Throughout this chapter, besides the bibliographical part, the new approach will be discussed and covered in detail.

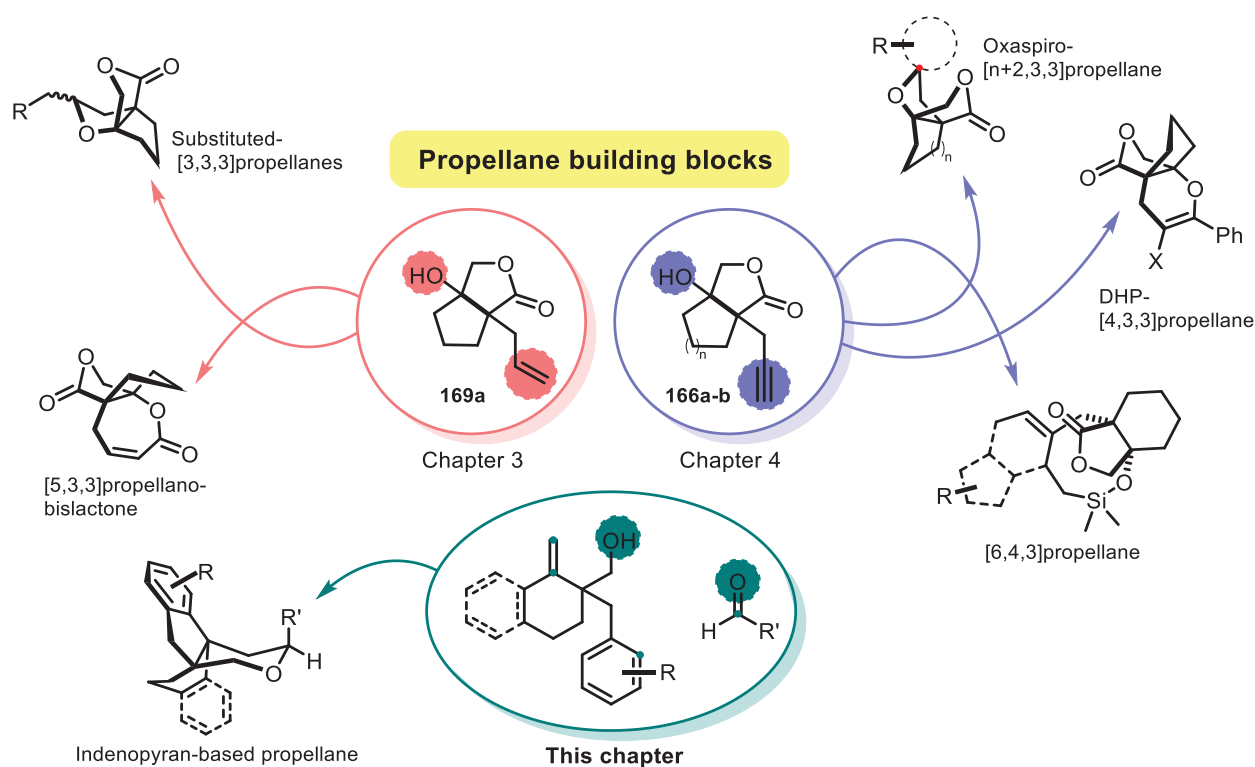


Figure 1. Alternative precursors for the propellane synthesis in this chapter.

2. Indenopyrans: a brief overview

2.1. Nomenclature

Indenopyrans are functionalized oxygen-containing heterocycles consisting of fused indene and pyran units.^[1] In addition to the variability of substituents and the localization of the oxygen atom in the pyran subunit, the position and the number of unsaturations provide wide diversity and complexity in this tricyclic system. A selection of structures, names and standard numbering of some indenopyrans are presented in Figure 2. The nomenclature usually starts with an ascending order of the numbers related to the positions of hydrogen atoms in the cyclopenta[*n*]pyran subunit. By convention, the numbering is chosen to give the lowest locant either to the oxygen atom or to

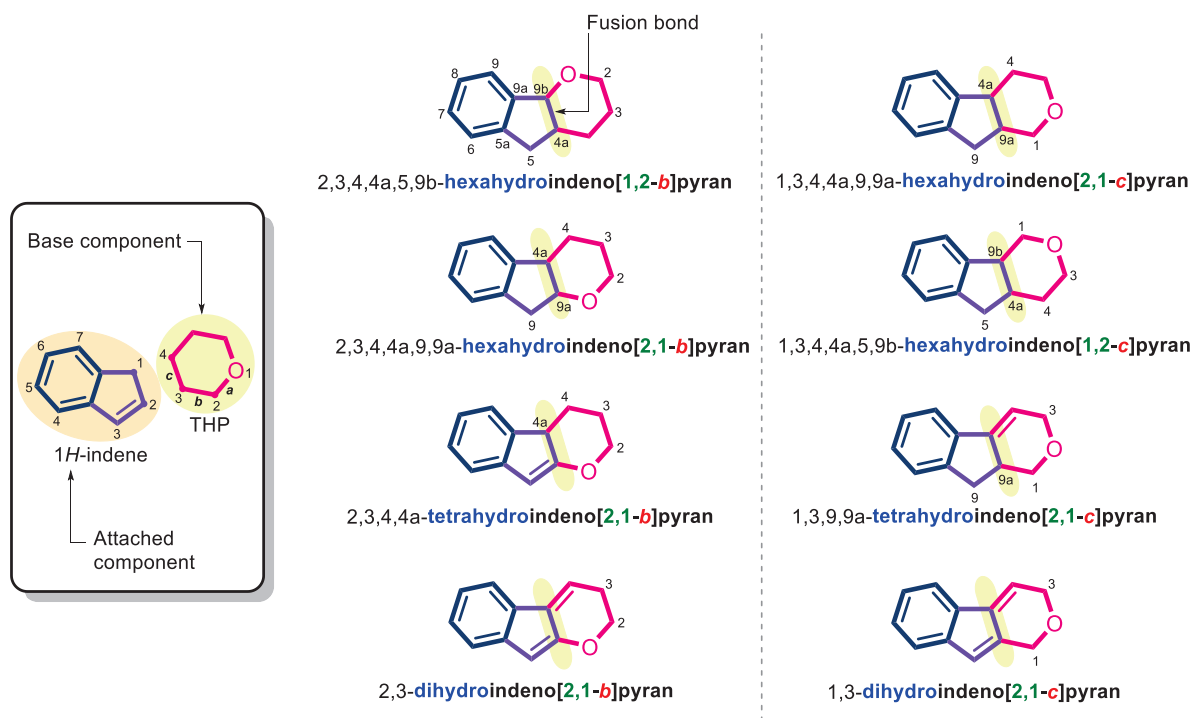


Figure 2. A selection of structures, names and standard numbering of some indenopyrans.*

*The base component is always a heterocyclic system, *i.e.* “pyran”. Therefore, the attached component is “indene”. However, in such names, the prefix is generated by replacing the terminal ‘e’ in the name of the attached component by ‘o’, *i.e.* “indeno”. In the name ‘indeno[1,2-*b*]pyran’, the numbers signify the positions of the first-named heterocycle, numbered as if it were a separate entity, which are the points of ring fusion; the italic letter, ‘*b*’ in this case, designates the side of the second named heterocycle to which the other ring is fused, the lettering deriving from the numbering of that heterocycle as a separate entity, that is, side “*a*” is between atoms 1 and 2, side “*b*” is that between atoms 2 and 3, and so on. Note that the order of the numbers ‘2,1-’ is related to the position of the oxygen atom with respect to the fusion bond. In other words, the first number represents the position on the fusion bond which is closer to the oxygen atom of the pyran unit.^[2]

the neighboring carbon directly attached to the indene group. The rest of the name is written in the following pattern:

Name of fused heterocycle = *prefix* + [*alphabet*] + *suffix*
= Attached component + [Fused bond] + Base component
= indeno[*n,m-b/c*]pyran

2.2. Occurrence

Indenopyrans, as oxygen-containing heterocycles, exhibit inherent biological profiles and interesting structural features.^[1, 3] These compounds have been found in a variety of natural products, including brazilin and its derivatives, cephanolides, nodulisporic acids and others (Figure 3).

- Brazilin and its derivatives: brazilin is a red dye precursor obtained from the heartwood of several species of tropical hardwoods, principally brazilwood and sappanwood.^[4] The extracts of the latter are used in traditional Asian medicine and have been the subject of continuous and extensive biological studies.^[5] Accordingly, brazilin has been studied for the treatment of diabetes,^[6] arthritis,^[7] and various cancer types.^[5a, 8] When oxidized by contact with atmospheric oxygen or other chemical oxidants, brazilin transforms into brazilein A^[9] with a loss of two hydrogen atoms to form a carbonyl group. In this way, it is similar to hematoxylin in behavior and structure; the latter possesses an additional hydroxyl group.^[10]
- Norditerpenoids cephanolides: plants of the *Cephalotaxaceae* family produce an extensive array of structurally diverse natural products with a variety of biological properties, particularly potent antitumor activity.^[11] In 2017, Yue and co-workers isolated new structurally unique norditerpenoids cephanolides A–D from *Cephalotaxus sinensis*, a finding which sheds light on plausible biosynthetic scenarios among this large family.^[12] Compared with other cephalotaxus diterpenoids, cephanolides A–D represent the first examples that have a rarely encountered aromatic benzenoid ring in this family.^[13]
- Nodulisporic acids: comprise a group of secondary metabolites isolated from the endophytic fungus *Hypoxylon pulicidum* (previously known as *Nodulisporium* sp.) that exhibit potent insecticidal activities.^[14] These biological effects arise from the specific activation of a subset of ligand-gated chloride ion channels found in arthropods, but not in mammals, resulting in a potentially useful selectivity profile.^[15] Detailed investigations of nodulisporic acids as a starting point for the development of new anti-flea medications for companion animals have

been performed, resulting in the identification of promising lead compounds.^[16] In addition to the common indoloterpenoid core, these natural products contain an indenopyran motif found in other members of the paxilline family, such as the janthitrems^[17] and shearinines.^[18]

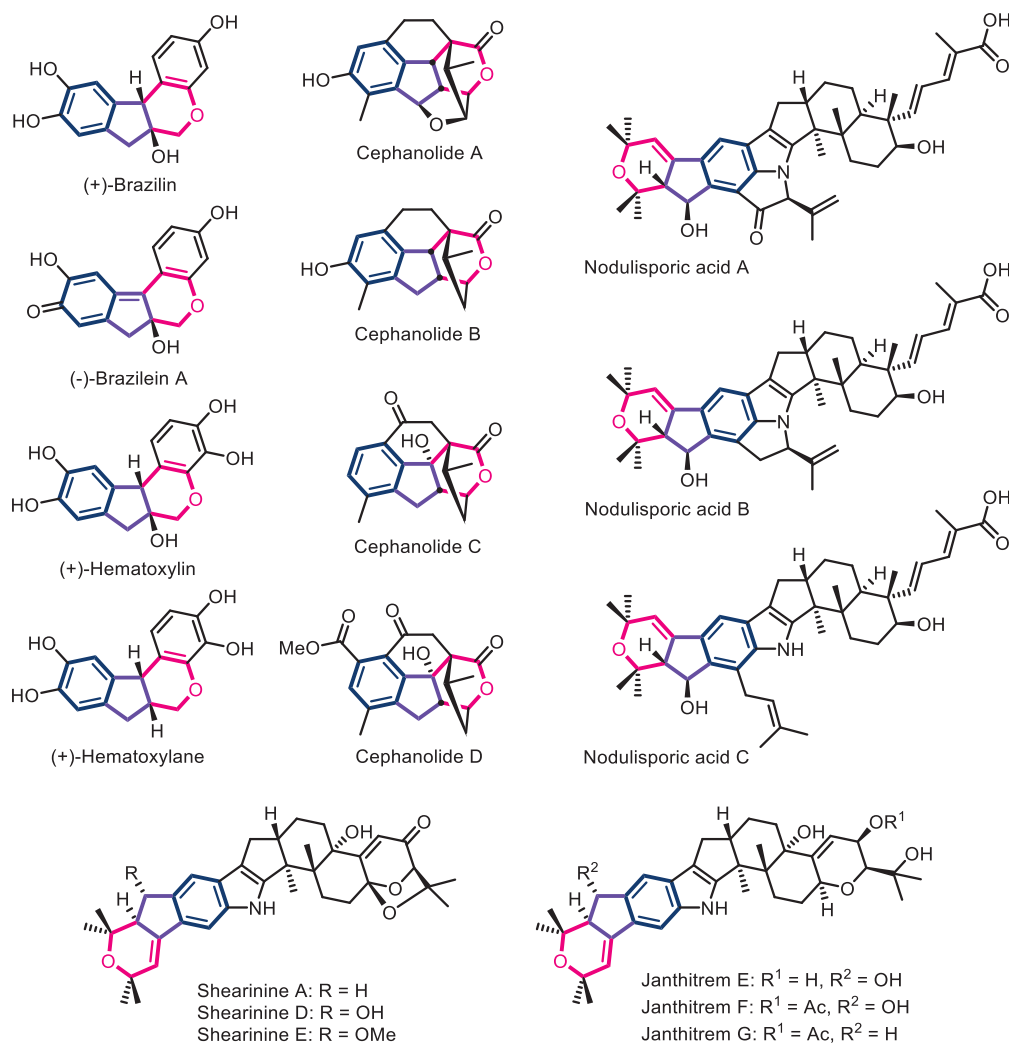
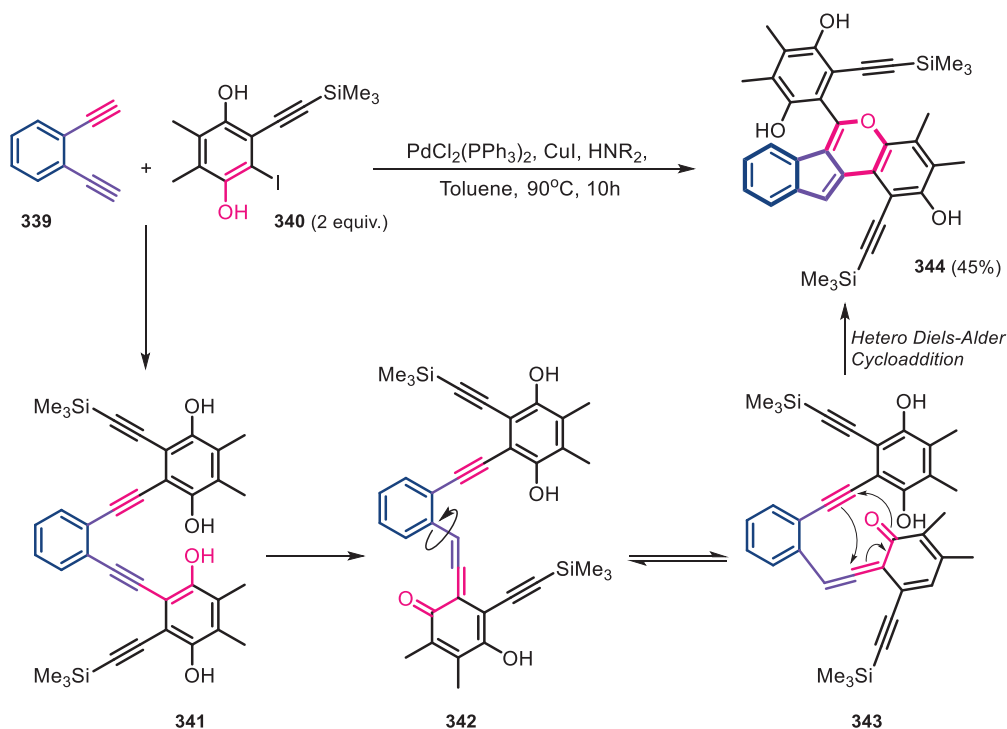


Figure 3. Some indenopyran-based natural products.

2.3. Synthesis

The combination of the challenging indenopyran core with the stereochemical requirements has fascinated many chemists and driven several groups to undertake synthetic efforts towards these compounds. Apart from stepwise syntheses, tandem reactions are extremely useful for the synthesis of such heterocycles.

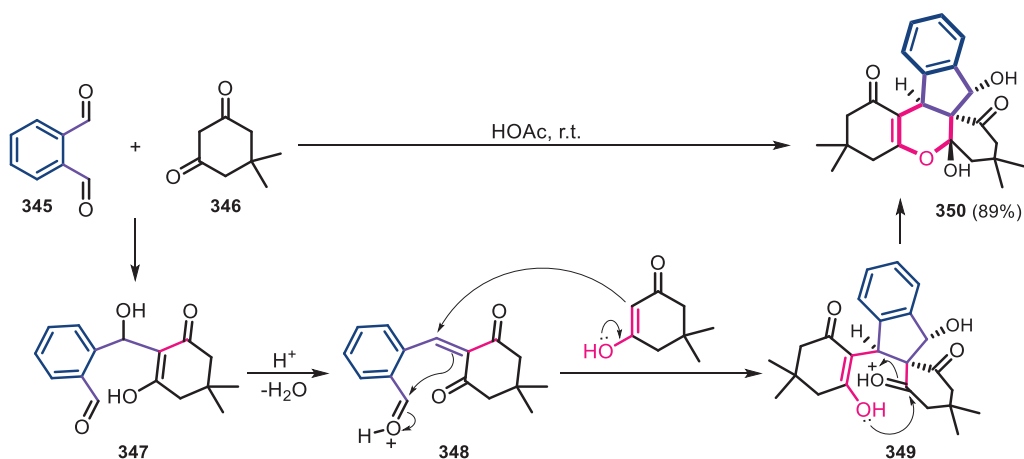
In the course of investigating various cycloalkynes^[19] and cyclodiyne^[20] with different substituted benzene rings, Youngs and coworkers reported an intramolecular acetylene-zipper type bicyclization to form an indenopyran ring system (Scheme 1).^[21]



Scheme 1. Palladium-copper catalyzed intramolecular acetylene-zipper type bicyclization by Youngs and coworkers.^[21]

Treatment of *o*-diethynylbenzene **339** with two equivalents of **340** in the presence of the Pd(II)/Cu(I) catalyst in diisopropylamine-toluene as solvent under reflux (10h, 90°C) afforded an unusual product **344** as a yellow solid in 45% isolated yield. Mechanistically it can be proposed that the one-pot synthesis of the conjugated compound **344**, having the indenopyran unit, is a result of a tandem reaction beginning with Sonogashira/Hagihara coupling^[22] to form intermediate **341**. The latter compound is likely to undergo base-catalyzed tautomerization of one of the hydroquinones to a ketylallene intermediate such as **342**. A [4 + 2] intramolecular hetero cycloaddition of **342** would result in the formation of the observed product **344**. Intermediate **342** may be held in conformation **343** by hydrogen bonding between the OH of the hydroquinone and the oxygen of the ketylallene moiety. This proximity effect would promote the [4 + 2] cycloaddition.

In 2013, Tu and coworkers reported a multi-component domino reaction (MDR) for the stereoselective synthesis of hexahydroindeno[2,1-c]pyran derivatives (Scheme 2).^[23] As described by the authors, the reaction was easy to perform by mixing *o*-phthalaldehyde **345** with cyclic 1,3-dicarbonyls **346** in acetic acid at room temperature. Up to two new rings and four sigma-bonds were built in these MDRs to afford **350** without using any metal catalysts. On the basis of experimental results, a putative reaction mechanism was proposed as shown in Scheme 2.



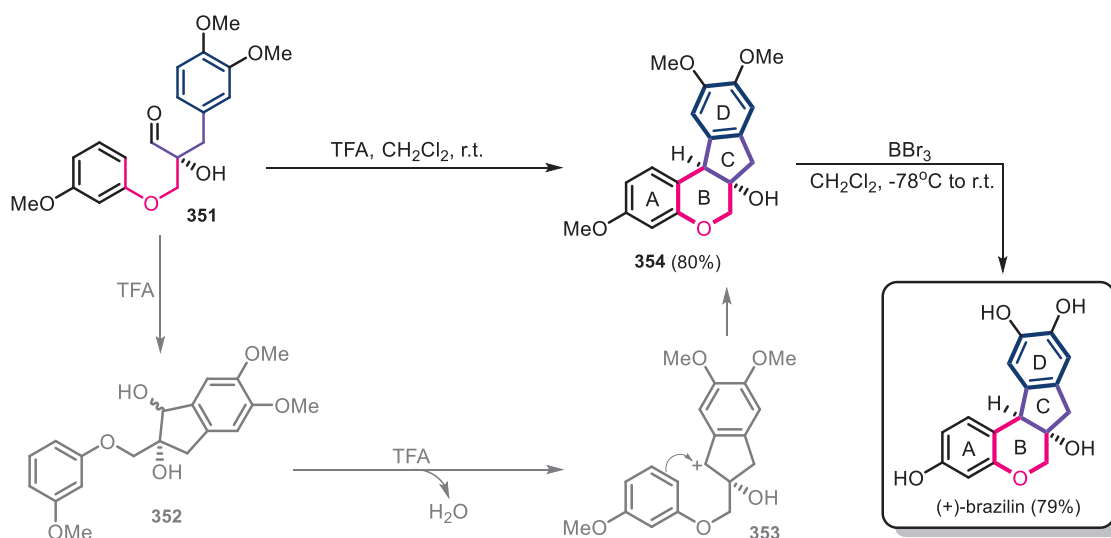
Scheme 2. Bis-cyclizations of *o*-phthalaldehyde with cyclic 1,3-dione by Tu *et al.*

First, *o*-phthalaldehyde undergoes an aldol condensation with 5,5-dimethylcyclohexane-1,3-dione (dimedone) **346** to afford intermediate **347**, followed by intramolecular dehydration to yield **348**. Then, domino Michael addition and cyclization with the second molecule of **346** occur, affording intermediate **349**. The latter is converted into final polycyclic indenopyrans **350** via second intramolecular hemiketalization.

Besides other examples,^[13a, 18c] domino Prins/Friedel-Crafts cyclization is a powerful strategy for the stereoselective synthesis of fused heterocycles.^[24] It has been successfully employed for the synthesis of several natural products.^[25] Recently, a few methods have been reported for the synthesis of tetrahydrofuran derivatives through a Prins cyclization, wherein a five-membered oxocarbenium ion is trapped with different nucleophiles.^[26] However, apart from recent investigations,^[3, 27] the formation of a five-membered ring fused tetrahydropyran system has not yet been fully explored through a domino Prins cyclization.

In 2020, Wang and coworkers described a concise and practical strategy for the synthesis of (+)-brazilin in overall 40% yield within 7 steps, and their synthetic approach was easily scaled up to a gram level with high yield. The synthetic route involved a one-pot intramolecular tandem

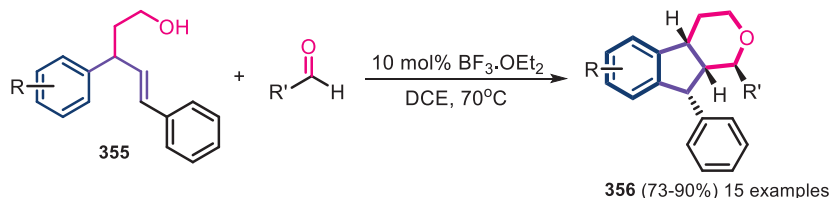
Prins/Friedel-Crafts reaction as the key transformation in the construction of the hybrid chromane and indane framework (Scheme 3).^[27a] In the presence of TFA, the desired product **354** was smoothly obtained in 80% yield in one-step,^[27b, 28] in which the C ring might have been first formed (**352**).^[29] Subsequently, under the control of the quaternary carbon center, the B ring was then constructed with the desired cis-fused rings. Finally, under the treatment of boron tribromide,^[30] the methoxy groups of **354** were successfully removed to deliver the desired natural product (+)-brazilin in 79%.



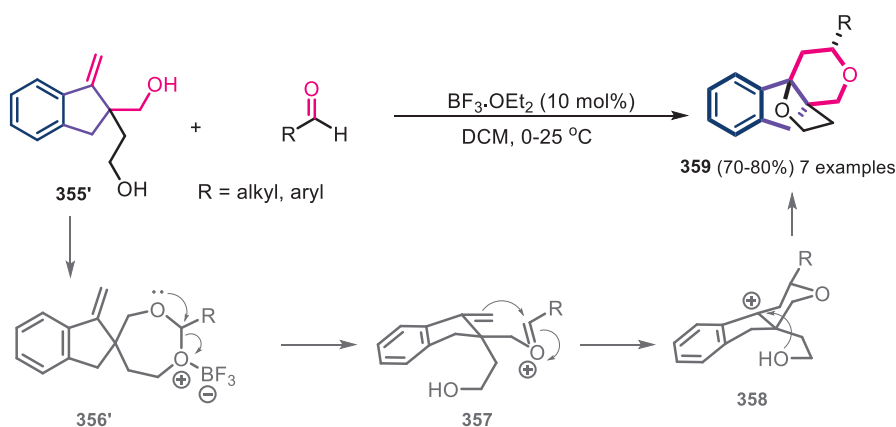
Scheme 3. One-pot intramolecular tandem Prins/Friedel-Crafts reaction in the synthesis of (+)-brazilin.

Five years before publishing the mentioned work above, Reddy and coworkers reported two papers about the stereoselective synthesis of indenopyrans *via* tandem Prins/Friedel-Crafts cyclization.^[3, 27b] In the first one,^[27b] the authors described the synthesis of hexahydroindeno[2,1-*c*]pyran scaffolds through a domino cyclization of (*E*)-3,5-diphenylpent-4-en-1-ol **355** with aldehydes using $\text{BF}_3 \cdot \text{OEt}_2$ at 70°C (Scheme 4). This method provides direct access to biologically relevant indenopyran scaffolds with four contiguous stereogenic centers in a single step. In the second paper,^[31] Reddy *et al.* reported a similar cascade process for the synthesis of indeno[2,1-*c*]pyran and cyclopenta[*c*]pyran derivatives from aldehydes and *exo*-olefinic diols **355'** (Scheme 5). As it can be noticed, the obtained products are related to indenopyran-based propellanes, which is a rare family of organic compounds. However, for unknown reasons, the term “propellane” has not even been mentioned in this paper. Mechanistically, the authors assumed that the reaction proceeds through the formation of an oxocarbenium ion from cyclic acetal **356'**, which is derived from

aldehyde and unsaturated diol **355'**. A subsequent attack of *exo*-olefin on the oxocarbenium ion generates a more stable tertiary-carbocation (**357-358**), which is simultaneously trapped with a tethered hydroxyl group to afford the desired product **359**.



Scheme 4. Prins/Friedel–Crafts cyclization of (*E*)-3,5-diphenylpent-4-en-1-ol.



Scheme 5. Synthesis of indeno[2,1-*c*]pyran scaffolds from aldehydes and *exo*-olefinic diols.

3. Hexahydroindeno[2,1-*c*]pyran-based Propellanes: Our work

3.1. Key features and retrosynthetic analysis

Inspired by the previous work about Prins reaction achieved in our group,^[32] we herein report a short access toward indenopyran-based propellanes via Prins-driven cyclization (Figure 4). The designed family possesses a complex rigid quadracyclic or pentacyclic carbon skeleton featuring a [4,4,3]propellane bearing three stereogenic centers (A-ring), and a hexahydroindeno[2,1-*c*]pyran unit with different substituents in A and C rings. These fascinating architectural attributes, as well as the promising biological activity of indenopyrans, have made such structures attractive and challenging targets for synthesis.

We envisioned the five-membered ring of the indane fragment in **360** to be derived from an *in situ* Friedel-Crafts reaction of **361**, which comes from the Prins cyclization between *exo*-olefinic alcohol **363** and the corresponding aldehyde (Scheme 6). This cascade reaction could, therefore,

construct the C5-C6 and C4-C3 bonds and access the indenopyran motif in one-step. Finally, the *exo*-olefinic alcohol **363** could be obtained from readily available starting materials **365-367** via a sequence of classical reactions.

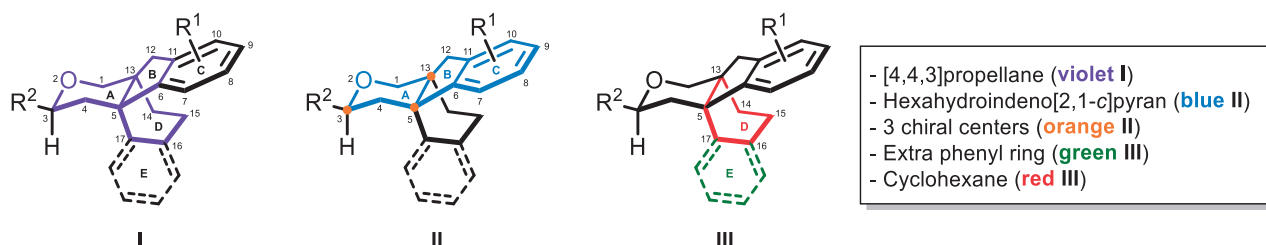
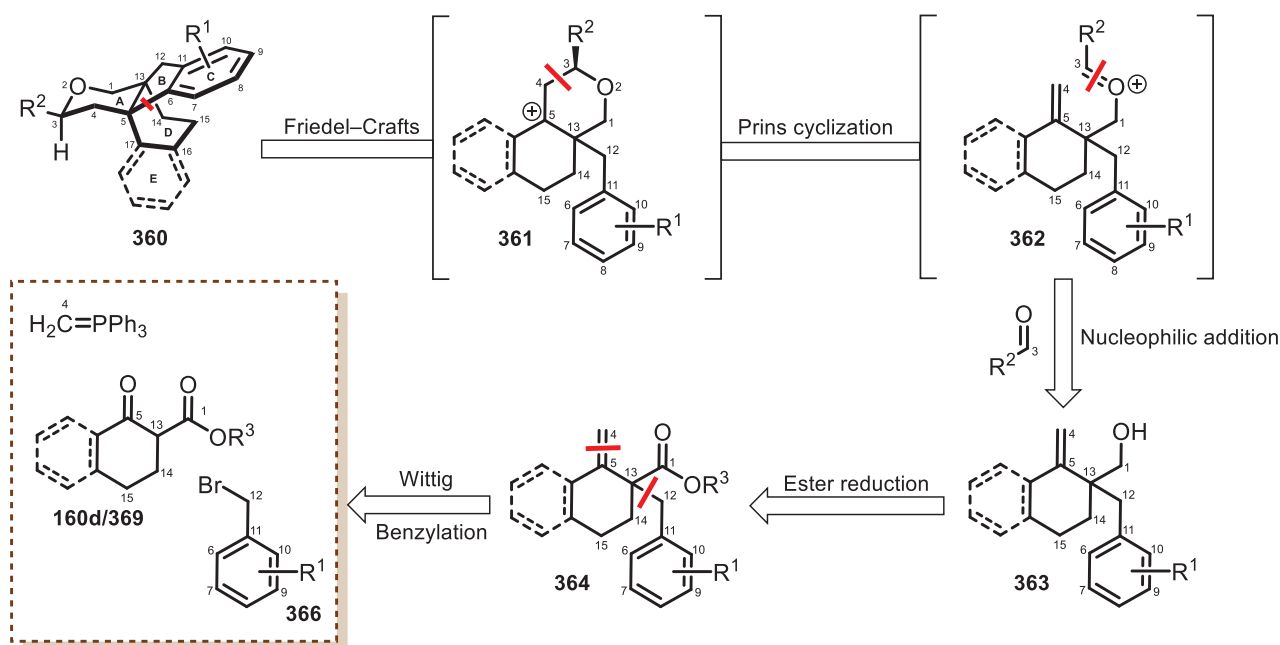


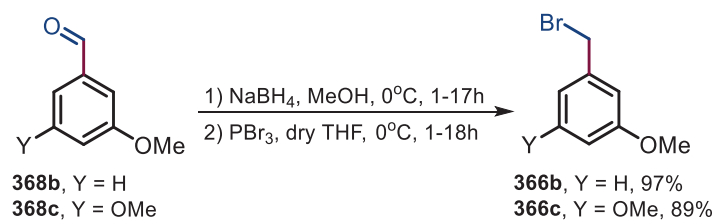
Figure 4. Key features of the designed hexahydroindeno[2,1-*c*]pyran-based [4,4,3]propellanes.



Scheme 6. Retrosynthetic analysis of compound **360**.

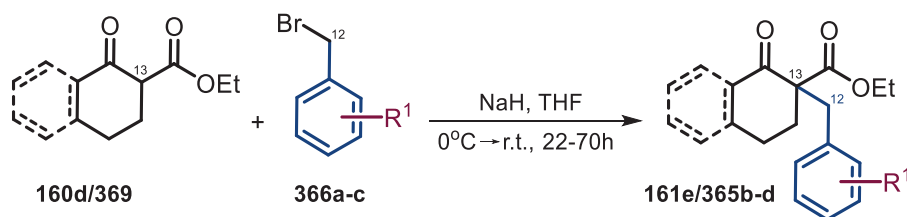
3.2. Results and discussion

Our synthetic studies commenced with the preparation of benzyl bromide derivatives **366b-c** (Scheme 7). Commercially available benzaldehydes **368b-c** underwent reduction with sodium borohydride^[33] and subsequent bromination with PBr_3 ^[34] to deliver **366b-c** in 89-97% yield over two steps. Besides benzyl bromide **366a**, the obtained products **366b-c** were used as alkylating reagents for the substitution reaction of β -ketoesters **160d** and **369** (Table 1).^[35] To our delight, the reaction proceeded at room temperature to afford the corresponding α -substituted ketoesters from low to good yields. Notably, the alkylation with the prepared benzyl bromide derivatives



Scheme 7. Synthesis of benzyl bromide derivatives **366b-c**.

Table 1. Benzylation of different β -ketoesters.^a



Entry	Ketoester	Benzyl bromide	t (h) ^b	Product (Yield) ^c
1			22	161e (75%)
2			70	365b (32%)
3			60	365c (43%)
4			63	365d (55%)

^aAll products were characterized by ^1H and ^{13}C NMR spectroscopy; ^breaction time; ^cyield refers to pure products isolated after column chromatography.

366b-c took a longer time than that with benzyl bromide **366a**, and hence the desired products **365b-d** (Entries 2-4) were isolated in lower yields compared to **161e** (Entry 1). This can be related to the lower electrophilicity of the benzylic carbon of the electron-rich derivatives which leads to a lower reactivity of the corresponding benzyl bromide towards substitution reactions.

With substantial amounts of the obtained ketoesters, we were in a position to prepare the *exo*-olefinic alcohol derivatives, the precursors of the Prins/Friedel-Crafts cyclization (Table 2).

Table 2. Preparation of *exo*-olefinic alcohol derivatives **363a-d**.^a

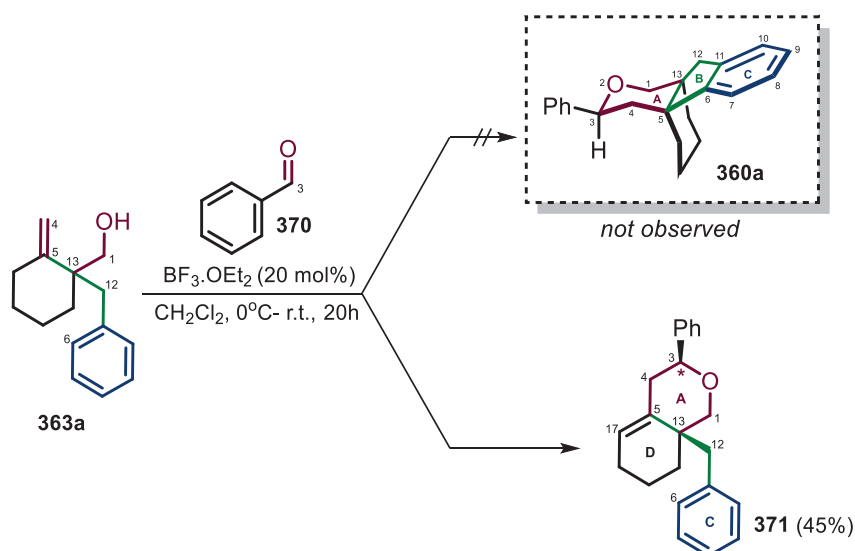
Entry	Ketoester	<i>Exo</i> -olefinic ester	t (h) ^b	Product (Yield) ^c
1	161e	 364a	1.5	363a (55%)
2	365b	 364b	18	363b (35%)
3	365c	 364c	11	363c (21%)
4	365d	 364d	6.5	363d (58%)

^aAll products were characterized by NMR spectroscopy; ^breaction time of both steps; ^cisolated yield of a two-step synthesis.

Treatment of the chosen ketoester **161e/365b-d** with a suspension of methyltriphenylphosphonium bromide and potassium *tert*-butoxide in anhydrous toluene under argon resulted in the formation of the corresponding *exo*-olefinic ester (**364a-d**).^[36] In each case, after being extracted and dried, the crude mixture was subjected to reduction by lithium aluminium hydride to furnish the desired *exo*-olefinic alcohol after hydrolysis in a 35-58% overall yield.^[37] It should be noted that this two-step sequence, which required only one chromatographic purification, made the synthesis of **363a-d** much easier to access.

Prins/Friedel–Crafts cyclization: the first scenario:

With the key intermediates **363a-d** in hand, we subsequently focused our attention on the construction of *cis*-fused pyran and indane framework of the A and B rings. Our first attempt has been achieved on the simplest substrate **363a** (Scheme 8). To a stirred solution of the latter *exo*-olefinic alcohol and benzaldehyde **370** in dichloromethane was added BF₃·OEt₂ (20 mol%) at 0°C under an inert atmosphere,^[38] and the reaction mixture was kept stirring at room temperature. By following the reaction progress, a major product has appeared on the TLC plate (Petroleum ether/Ethyl acetate (85:15)) just one hour after launching the reaction. This was also accompanied by a complete conversion of the starting material. After being isolated in a 45% yield, we assumed the formed product was the desired indenopyran **360a**. However, besides the characteristic AB systems at positions 1 and 12, and the ABX system at position 4, the corresponding ¹H NMR



Scheme 8. First attempt towards the synthesis of indenopyran-based propellane.

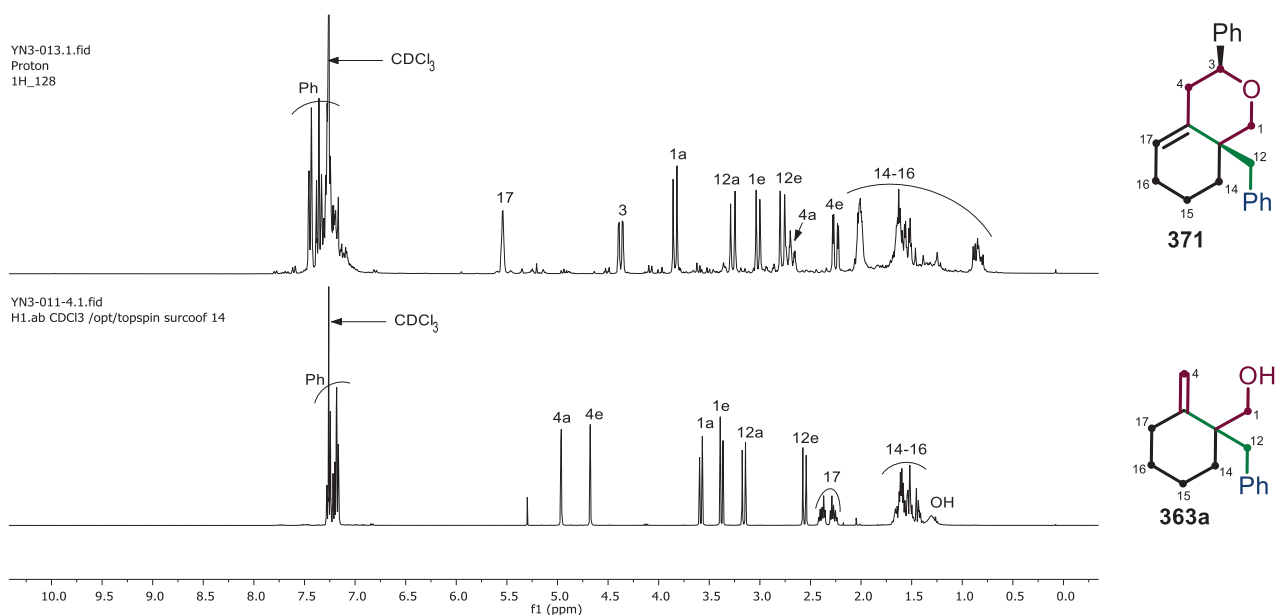
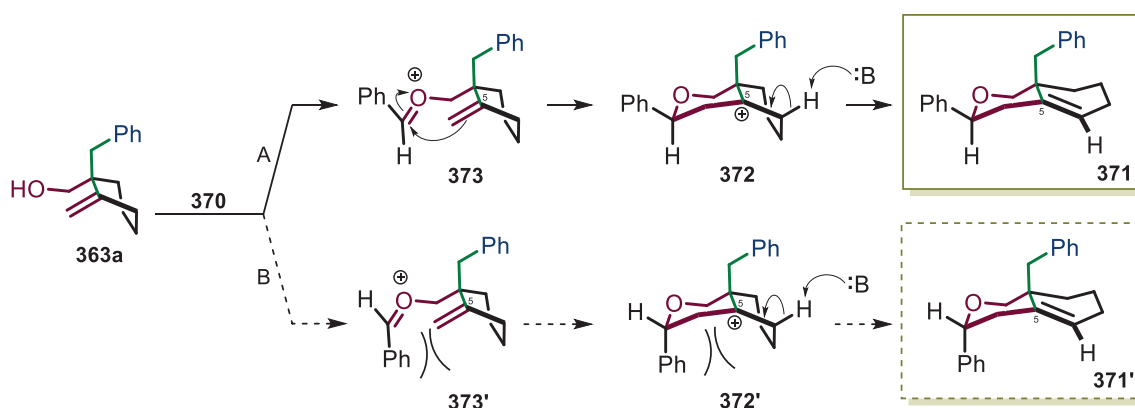


Figure 5. ^1H NMR (500 MHz) analysis of isochromene **371** compared to that of *exo*-olefinic alcohol **363a**.

spectrum recorded an extra signal at 5.53 ppm related to one alkene proton (Figure 5).

Moreover, ^{13}C NMR and DEPT-135 analysis reveal the presence of two peaks at 122.7 and 142.9 ppm correlated to a primary and quaternary carbon respectively. Although these arguments exclude the fact that Friedel-Crafts reaction has occurred between C6 and C5, they ensure the presence of a double bond in the D-ring between C5 and C17, thereby indicating the formation of isochromene **371**. It should be noted that the latter compound was diastereoisomerically pure, but unfortunately, it was difficult at that level to determine the real configuration at C3 in the pyran ring. For this reason, a plausible reaction pathway has been proposed as shown in Scheme 8.

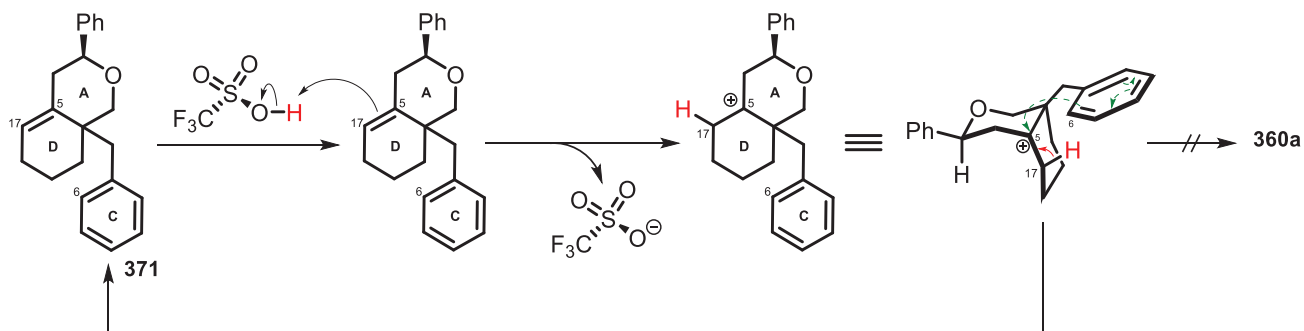
The aldehyde is activated by $\text{BF}_3 \cdot \text{OEt}_2$ for nucleophilic attack by the homoallylic alcohol **363a** to



Scheme 8. A plausible reaction pathway leading to isochromene **371**.

form an acetal, which after decomposition gives oxocarbenium ion **373/373'**. A subsequent attack of *exo*-olefin on the oxocarbenium ion generates a more stable tertiary-carbocation **372/372'**, which is simultaneously followed by a proton elimination to afford the isolated isochromene **370/370'**. By taking a closer look at both paths A and B, it can be noticed that the *exo*-olefin attacks preferentially in the transition state **373** and not **373'**. Therefore, the less hindered conformation of **373** results in an equatorial position of the phenyl group in **372** instead of an axial one in **372'**, which explains the relative configuration assigned to C3 in **371**.^[27b]

Within this context, we thought about how the Friedel-Crafts cyclization might be favoured to allow the formation of the B-ring in **360a** from **371**. We expected that the regeneration of the carbocation at C5 would give another chance for this cyclization to take place. For this reason, isochromene **371** was stirred in the presence of triflic acid in deuterated chloroform at room temperature for 16 hours (Scheme 9). Unfortunately, no reaction has occurred, not even after further heating (~ 40°C) for 3 more hours. Seemingly, the phenyl ring (Ring-C) of **371** was not electron-rich enough to quench the generated carbocation.



Scheme 9. A plausible reaction pathway for the regeneration of carbocation in **371** by means of triflic acid.

Prins/Friedel–Crafts cyclization: the second scenario

Our strategy in the second scenario was based on reinforcing the intramolecular Friedel-Crafts cyclization to furnish the required indenopyran motif. Besides using an electron-rich C-ring as an activated aryl group, it was necessary to further stabilize the generated carbocation at position 5 without expecting any competitive E₁ elimination reaction between C5 and C17. For this reason, precursor **363b**, having an aromatic system fused to the D-ring at C16-C17 bond, was the best candidate for this attempt (Figure 6).

Under similar reaction conditions to those used for **363a**, *exo*-olefinic alcohol **363b** was reacted with *p*-chlorobenzaldehyde at -78°C → r.t. for 5 hours (Scheme 10). Although we observed remark-

able degradation of the reaction mixture over silica gel, we were able to isolate the desired indenopyran-based propellane **360b** in 29% yield. The molecular formula of $C_{28}H_{27}ClO_3$ was established for **360b** by the (+)-HRESIMS ion at m/z 447.1720 $[M + H]^+$ (calcd for $C_{28}H_{28}ClO_3$, 447.1721). In addition to the characteristic AB and ABX systems of the pyran and indane unit at positions 1, 4 and 12, the 1H NMR spectrum of **360b** showed that the two methoxy groups of the C-ring appeared at different chemical shifts (3.70 and 3.92 ppm), which means the symmetry of this phenyl ring was broken (Figure 7). Moreover, the relatively shielded signals of the C-ring between 6.27 and 6.35 ppm were correlated to two protons, instead of three, which signifies that this ring became tetra-substituted. Further NMR analyses were carried out as shown in Figure 8. The DEPT-135 data revealed the presence of two methyl groups, five sp^3 methylenes, one sp^3 methine, two sp^3 quaternary carbon atoms, and three substituted benzene motifs (Figure 8).

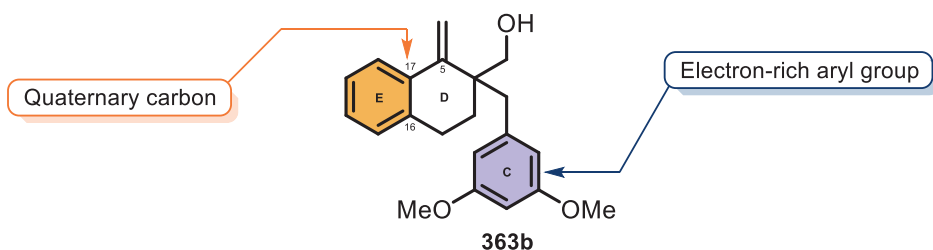
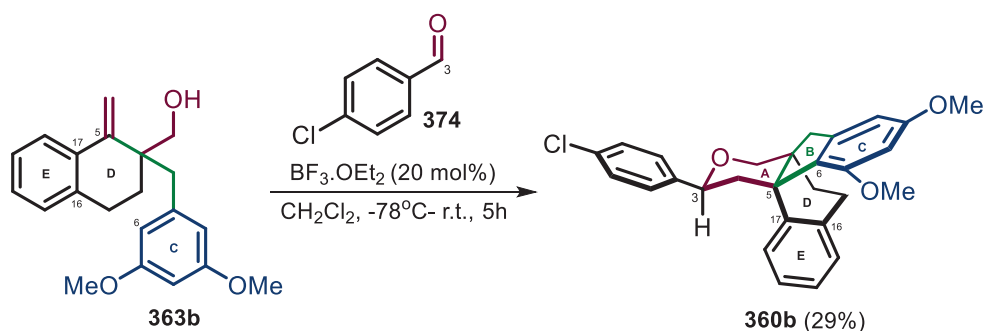


Figure 6. Key features of precursor **363b**.



Scheme 10. Second attempt towards the synthesis of indenopyran-based propellane.

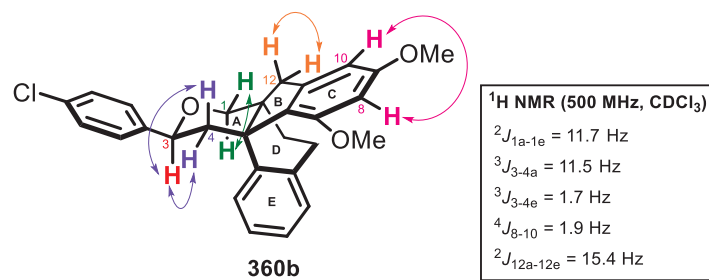


Figure 7. Major and minor 1H NMR correlation in the indenopyran motif of the isolated propellane **360b**.

By taking a closer look at the aryl region, 14 peaks related to 8 quaternary and 10 primary phenyl carbon atoms showed up between 122 and 163 ppm. These signals could be correlated to the sp^2 carbon atoms presented by the three substituted benzene rings. Therefore, based on the mentioned arguments, the results ensure the suggested structure of **360b**.

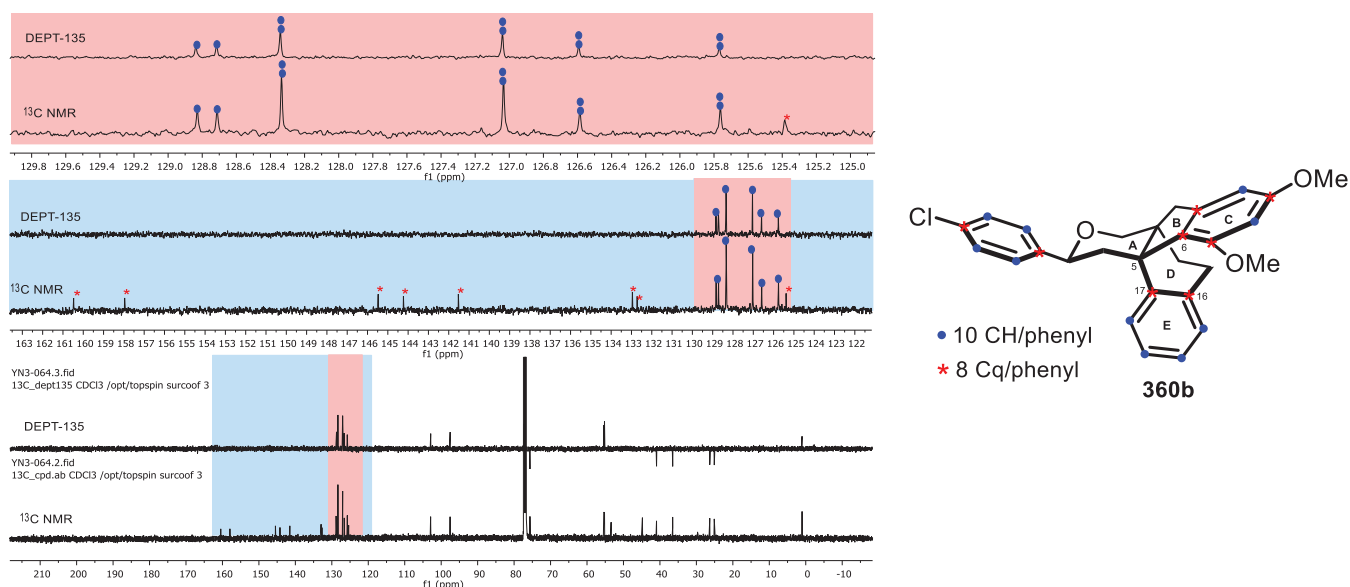
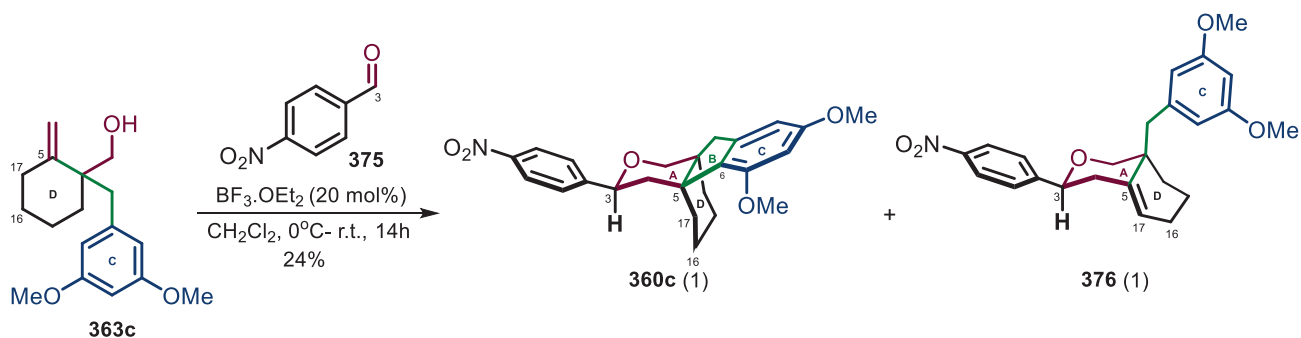


Figure 8. ^{13}C NMR analysis of the isolated indenopyran-based propellane **360b** (500 MHz).

Prins/Friedel–Crafts cyclization: the third scenario

On the basis of the above result, thanks to the presence of the fused E-ring, it seems that avoiding the formation of the elimination intermediate and stabilizing the carbocation at position 5 facilitated the cascade reaction and made it go faster. However, the observed degradation and the low reaction yield led us to explore other types of precursors. In this attempt, the reaction was extended to **363c** which is similar to **363b**, but without an additional fused E-ring (Scheme 11). After 14 hours from the treatment of **363c** with *p*-nitrobenzaldehyde under the used conditions, two inseparable compounds (namely **360c** and **376**) in 1:1 ratio were isolated by flash chromatography. It should be noted that degradation of the crude mixture over silica gel was also observed this time, but far less than that of the previous experiment. This suggested that the E-ring of **363b** was behind the considerable degradation observed in the preceding attempt.

As a result of a ^1H NMR experiment (Figure 9), the desired propellane **360c** was distinguished by its characteristic signals at 3.74 and 3.78 ppm related to the two methoxy groups and by the shielded phenyl protons of the C-ring at 6.37 and 6.44 ppm. Moreover, the accompanied



Scheme 11. Third attempt towards the synthesis of indenopyran-based propellane.

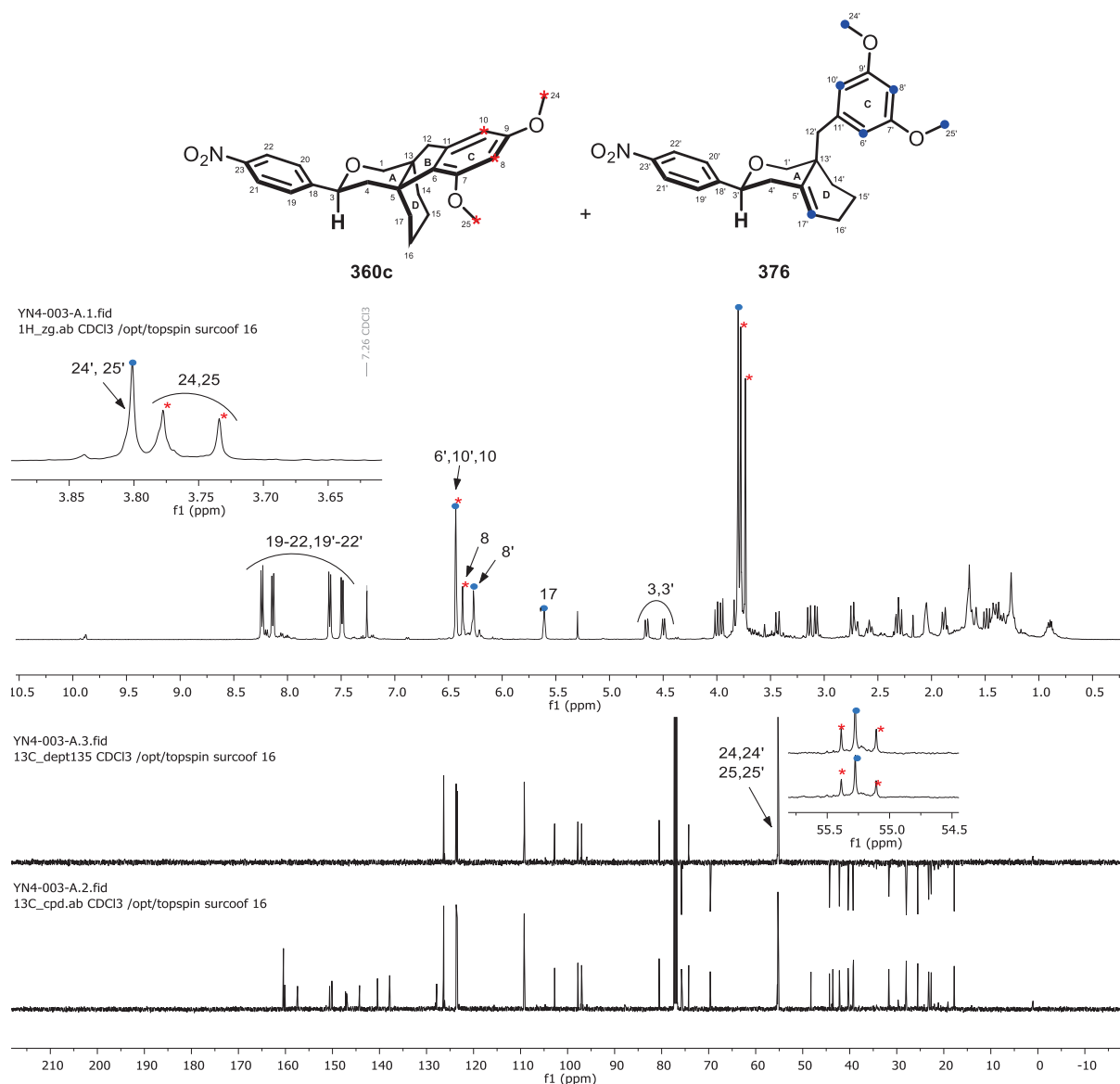


Figure 9. NMR analysis of the inseparable mixture of the desired indenopyran-based propellane **360c** and its isochromene counterpart **376** (500 MHz).

isochromene counterpart **376** was identified by the signal of the vinyl proton H17' at 5.60 ppm and by its equivalent methoxy groups that appeared as one singlet at 3.80 ppm. These arguments were then verified by ^{13}C NMR and DEPT-135 analysis where the methoxy groups of both compounds appeared as 3 peaks at 55.1, 55.3 and 55.4 ppm. This revealed the presence of a symmetrical and unsymmetrical C-ring related to **376** and **360c** respectively.

After the structural elucidation of **360c** and **376**, the plan was to go back and repeat what we had done in the first scenario by treating the isochromene with a Brønsted acid to regenerate the carbocation at position 5', and thereby promote the B-ring formation. However, this time the situation was different; isochromene **376** was accompanied by its propellane counterpart **360c**. For this reason, to better understand the reaction course, the reaction was conducted in the presence of deuterated trifluoroacetic acid in deuterated chloroform at room temperature (Figure 10).

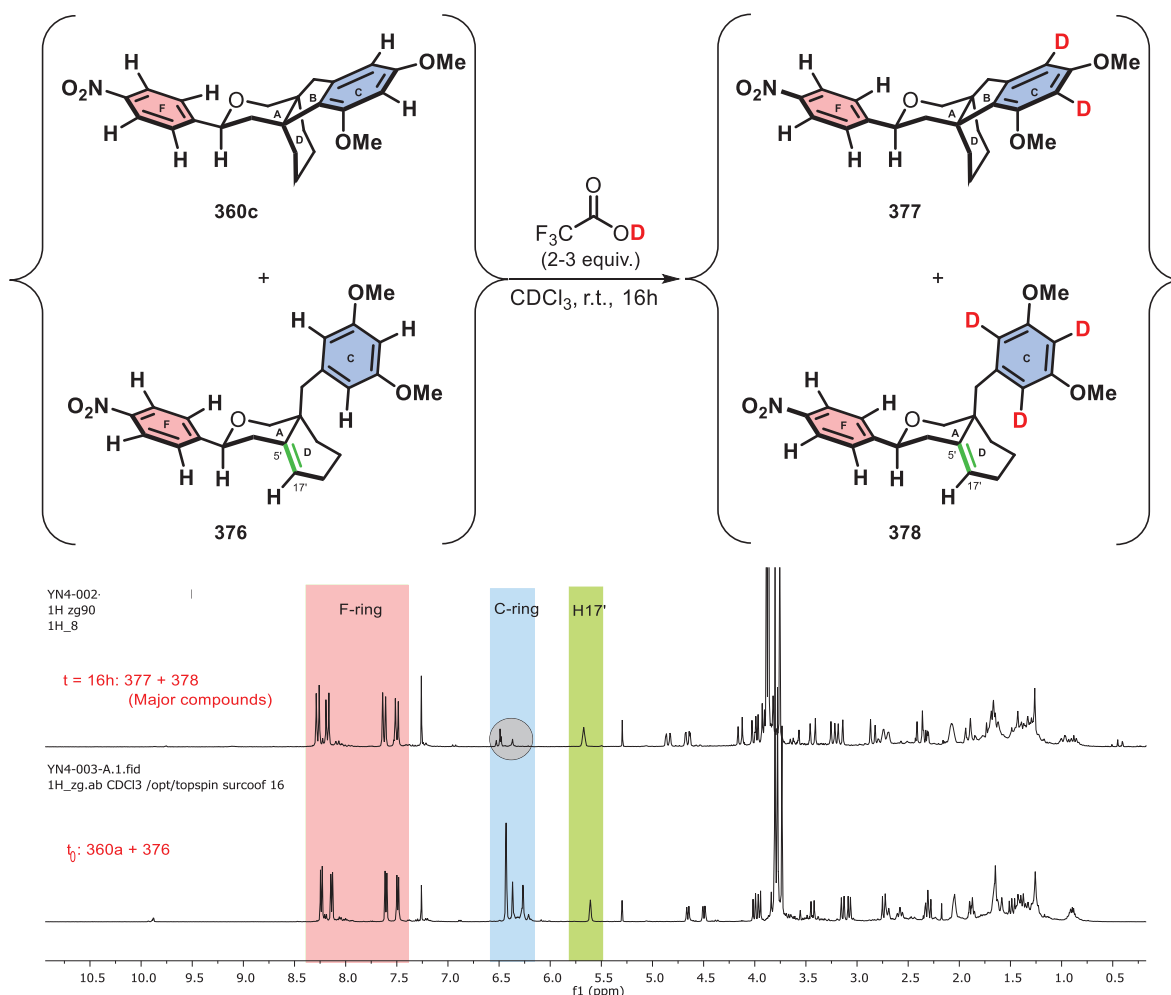


Figure 10. H–D exchange of the aromatic C-ring with CF_3COOD and the corresponding ^1H NMR (500 MHz) at t_0 and $t = 16\text{h}$.

After 16 hours from starting the reaction, the ^1H NMR analysis showed that both compounds **360c** and **376** underwent H–D exchange smoothly at the ortho and para positions to the methoxy groups of the corresponding aromatic C-ring. This result is consistent with what was reported in the literature.^[39] However, neither the electron-poor F-ring protons nor H17' showed any H–D exchange. The fact that deuteration occurred only on electron-rich aromatic rings, confirms that the mechanism of deuteration proceeded through an electrophilic aromatic substitution mechanism. Moreover, the absence of H17'–D exchange showed that the unsaturation in the D-ring was not touched by a Brønsted acid. Therefore, the attempt to regenerate the carbocation at C5', and thereby the B-ring formation of **376** failed.

Prins/Friedel–Crafts cyclization: the last scenario

So far, the problem of degradation has been resolved by avoiding any substrate with a fused E-ring. Furthermore, we concluded that the presence of an electron-rich C-ring is necessary for the C5-C6 bond formation *via* the Friedel-Crafts reaction. However, according to the last two scenarios, the low reaction yield of the desired indenopyran-based propellane suggested the possibility of a steric hindrance between the methoxy group at C7 and the D-ring (Figure 11).

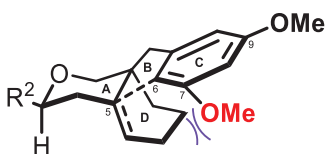


Figure 11. The suggested steric hindrance between the methoxy group (position 7) and the D-ring.

On this basis, we were curious to start from *exo*-olefinic alcohol **363d** having no methoxy group at position 7. Thus, we attempted its condensation with different benzaldehyde derivatives using $\text{BF}_3 \cdot \text{OEt}_2$ (20 mol%) at room temperature (Table 3). Interestingly, the reaction proceeded smoothly with benzaldehydes substituted with electron-withdrawing groups to offer the desired propellanes **379-385** from moderate to very good yields. As observed on a TLC plate, the first stage of each example was characterized by the formation of an intermediate, which was then transformed over time into a 2.0-3.5:1 mixture of separable regioisomers.

The nature of the substituents on the aromatic ring showed some effects on the reaction yield. For instance, results from weakly and moderately deactivated aldehydes, such as methyl 4-formylbenzoate (Entry 7), fluoro-, chloro- and bromo-substituted benzaldehyde (entries 2-4) were better than those obtained with strongly deactivating groups (entries 5 and 6). Except for simple

benzaldehyde (Entry 1), major degradations were observed with weakly activating groups, such as naphthyl (Entry 8) and toluoyl substituent (Entry 9).

Table 3. Synthesis of hexahydroindeno[2,1-*c*]pyran-based propellanes.

Entry	Aldehyde	R ²	t (h) ^a	Adducts	%yield ^b
1 ^c	370	Ph	21	379a-b (3.5:1)	46
2	387	4-F-C ₆ H ₄	20	380a-b (3.0:1)	68
3	374	4-Cl-C ₆ H ₄	57	381a-b (2.0:1)	69
4	388	4-Br-C ₆ H ₄	15	382a-b (3.6:1)	57
5 ^c	389	4-CF ₃ -C ₆ H ₄	70	383a-b (3.1:1)	41
6	375	4-NO ₂ -C ₆ H ₄	15	384a-b (3.0:1)	53
7	390	4-CO ₂ Me-C ₆ H ₄	19	385a-b (2.3:1)	72
8	391	1-naphthyl	15	-	- ^d
9	392	4-Me-C ₆ H ₄	15	-	- ^{d e}

^aReaction time; ^bisolated yield. ^cthe isochromene intermediate was isolated and characterized; ^ddegradation over silica; ^etraces.

To differentiate the isolated regioisomers, it was essential to look over the NMR correlation of the corresponding aromatic C-ring protons. Figure 12 represents an example of the characteristic ¹H NMR signals related to these protons in the nitro-adducts **384a-b**. As it can be noticed, H8 in **384a**, appearing as a doublet of doublets at 6.72 ppm, couples with H7 and H10 in a short- (³J = 8.4 Hz) and long- (⁴J = 2.3 Hz) range correlation respectively. However, the central C-ring proton H7 in **384b** gave two long-range correlations with H6 (³J = 7.4 Hz) and H8 (³J = 8.3 Hz). Based on this analysis, the major isomer is the one with the C5-C6 bond and not that with the C5-C10 bond. Therefore, the hypothesis concerning the steric hindrance between the C-methoxy group and the D-ring was ultimately validated.

After the structural differentiation of both regioisomers, we turned our attention to investigate the reaction mechanism (Scheme 12). Similar to that mentioned in the first scenario, the attack of *exo*-olefin on the oxocarbenium ion in **393** might be behind the formation of intermediate **394**. At this level, the generated carbocation could be trapped by the C-ring at C6 or C10 *via* a Friedel-Crafts reaction to afford the desired indenopyran-based propellanes **396** and **397** as a major and minor

product respectively. Based on previous observations, the reaction pathway could have also passed through an isochromene intermediate **395**, a product of proton elimination at position 17. To verify this proposal, we repeated entries 1 and 5 from Table 3 and we stopped the reaction at early stages (3-7 hours) (Figure 13).

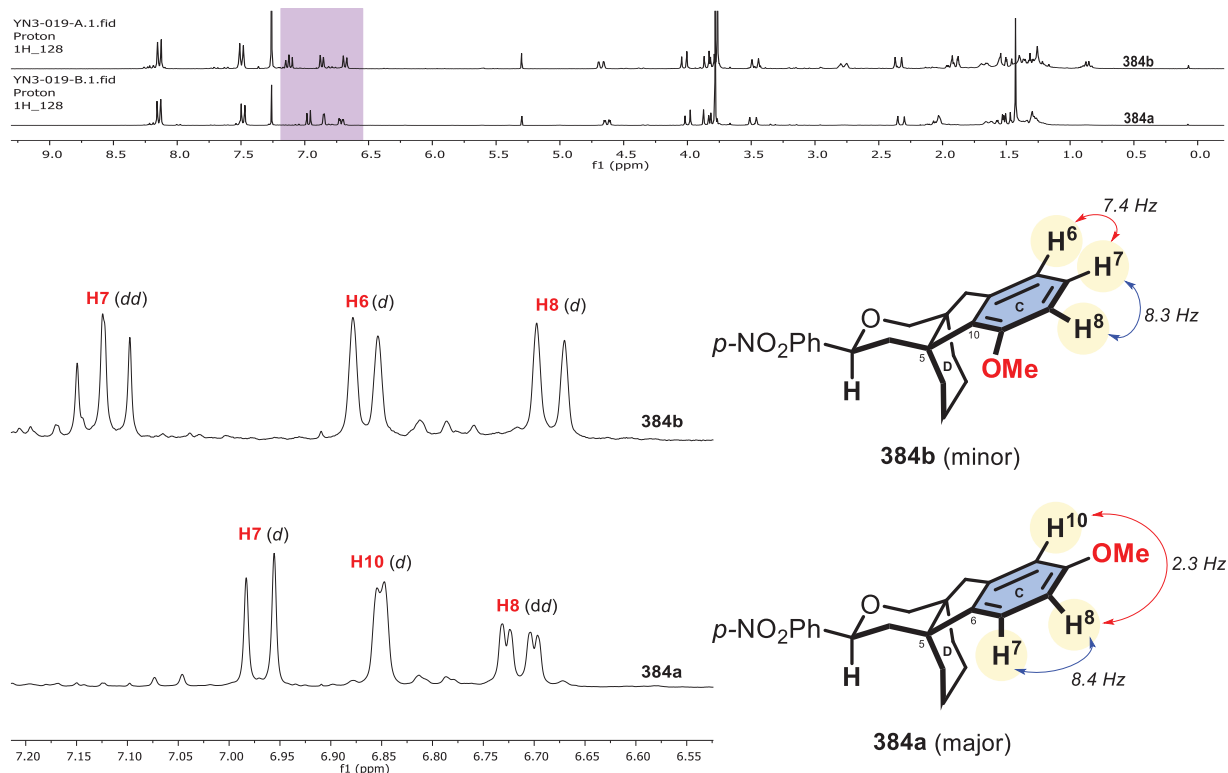
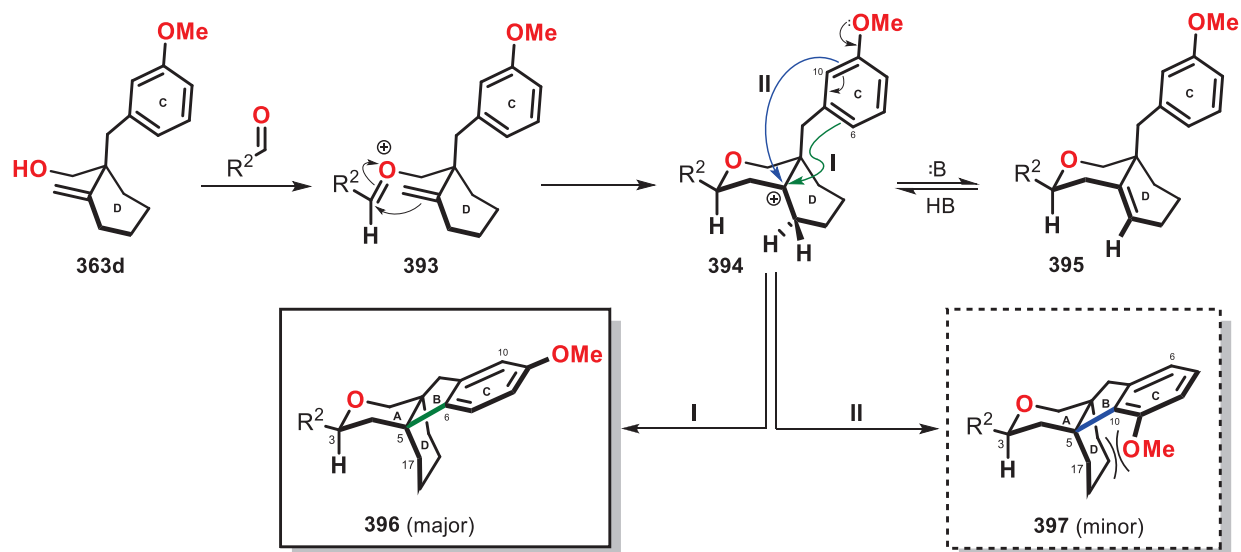


Figure 12. Differentiation of regioisomers by NMR analysis of the corresponding aromatic C-ring protons.



Scheme 12. Plausible reaction mechanism.

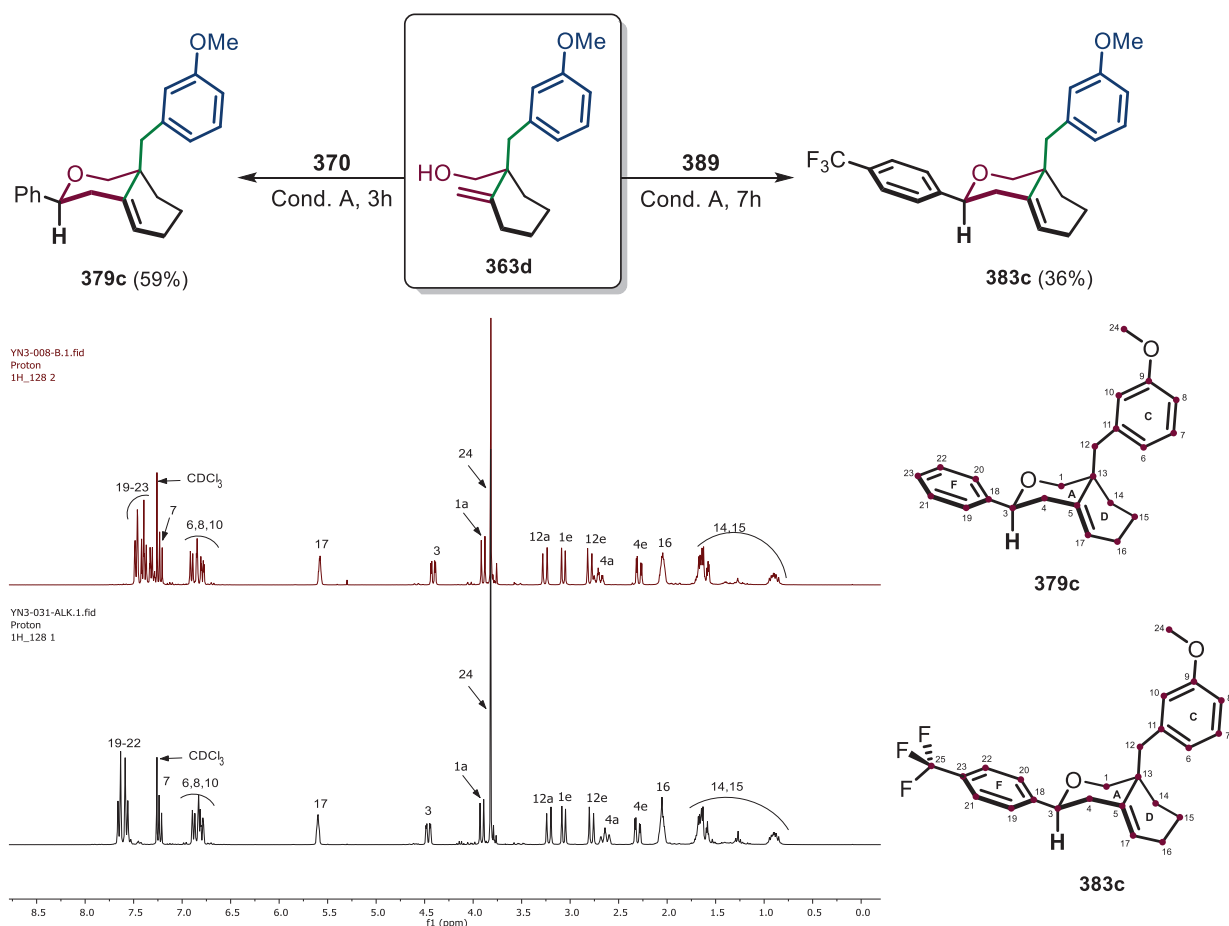


Figure 13. Isolation and ^1H NMR assignment of isochromenes **379c** and **383c**. (Cond. A: $\text{BF}_3 \cdot \text{OEt}_2$ (20 mol%), CH_2Cl_2 , 0°C - r.t.).

As expected by these control experiments, the isolated major products were isochromenes **379c** and **383c** which were easily identified by the characteristic ^1H NMR chemical shifts of their corresponding vinyl protons at position 17. Furthermore, the latter compounds were each treated with conditions A for a long period to afford their corresponding propellanes **379a-b** and **383a-b** (qualitative analysis). Back to Scheme 12, it can be said that isochromene product **395** was formed faster than its indenopyran counterparts **396** and **397**, and hence the activation energy of **395** was suggested to be lower than those of **396** and **397**. In such a case **395** can be considered as the kinetic product and is favoured under kinetic control, whereas **396** and **397** are thermodynamic products and are favoured under thermodynamic control.

3.3. Characterization of the isolated indenopyran-based propellanes

^1D NMR:

The chemical structures of the isolated hexahydroindeno[2,1-*c*]pyran-based propellanes **379-385** were defined by the ^{13}C NMR data and HRESIMS analysis. The ^1H NMR of the characteristic indenopyran-based propellane skeleton (A-D ring) revealed the presence of two main AB systems at positions 1 and 12 in addition to one ABX system at position 4 (tables 4 and 6). The most deshielded proton of these systems was correlated to H3 (X of the ABX system) and appeared as a doublet of doublets ($^3J = 1.9\text{--}12.0$ Hz) in the range between 4.45 and 4.63 ppm. However, the neighboring protons H4a,e were the most shielded protons and showed up in the alkyl region between 1.26 and 2.70 ppm. Besides the already characterized three phenyl protons at positions 7, 8 and 10 (or 6) in the aromatic C-ring (Figure 12), the methoxy group H24 appeared as a singlet around 3.60–3.80 ppm. Finally, the alkyl D-ring was distinguished by its six shielded protons situated between 1.25 and 2.01 ppm.

By comparing the ^1H NMR chemical shifts among isomers of different substituents on the *para* position of the aromatic F-ring (R^2 -group), no major variations were noticed in the indenopyran-based propellane framework. Likewise, apart from the aromatic C-ring protons, the difference in the chemical shift between each couple of regioisomers gave minor deviations ($|\Delta\delta| \sim 0.01\text{--}0.14$ ppm) especially for protons H1, H3 and H12 (Table 8). However, $|\Delta\delta|$ increased slightly for H4a,e (0.11-0.27 ppm), possibly because of the effect of the methoxy group position in the aromatic C-ring which is characteristic for each isomer.

The detailed ^{13}C NMR assignments of propellanes **379-385** are presented in Tables 5, 7 and the $|\Delta\delta|$ values of carbon atoms C1, C3 and C7-C9 between some of the obtained regioisomers are

summarized in Table 9. Similar to what was observed by the ^1H NMR analysis, altering the F-ring substituent at the *para* position also has no effect on the carbon skeleton of the indenopyran subunit. However, by comparing each pair of isomers, the main features presented were the chemical shifts of the aromatic C-ring carbon atoms. For instance, remarkable variation for C7 ($|\Delta\delta| \sim 5.7\text{-}5.9$ ppm), situated at *meta* position relative to the methoxy group, was noticed as a result of its shielded position in **379a-385a** (121.8–121.19 ppm) and slightly deshielded position in **379b-385b** (127.8–127.9 ppm). However, other neighboring carbon atoms, such as C8 and C9, showed slighter variation ($|\Delta\delta| \sim 1.9\text{-}2.6$ ppm), but still more considerable than those of the carbon atoms in the rest of the propellane skeleton. Therefore, the electron density on the aromatic C-ring might have been altered distinctively based on the formed C5-C6 or C5-C10 bond.

2D NMR:

Table 4. ^1H NMR assignments of compounds **279a-385a** (300 MHz/500MHz, CDCl_3).

	H1	H3	H4	H7	H8	H10	H12
379a	a: 3.91 d	4.45 dd	1.55-1.26	6.88 d	6.69 dd	6.76 d	a: 3.45 d
R² = Ph	$J_{1a-1e}=12.0$	$J_{3-4a}=11.3$		$J_{7-8}=8.2$	$J_{8-7}=8.2$	$J_{10-8}=2.5$	$J_{12a-12e}=15.1$
	e: 3.74 d	$J_{3-4e}=2.6$			$J_{8-10}=2.5$		e: 2.23 d
	$J_{1a-1e}=12.0$						$J_{12e-12a}=15.1$
380a	a: 3.99 d	4.51 dd	1.61-1.49	6.95 d	6.71 dd	6.85 d	a: 3.52 d
R² = 4-F-Ph	$J_{1a-1e}=12.1$	$J_{3-4a}=10.4$		$J_{7-8}=8.1$	$J_{8-7}=8.1$	$J_{10-8}=2.4$	$J_{12a-12e}=15.4$
	e: 3.82 d	$J_{3-4e}=3.3$			$J_{8-10}=2.4$		e: 2.31 d
	$J_{1a-1e}=12.1$						$J_{12e-12a}=15.4$
381a	a: 3.99 d	4.51 dd	1.55-1.47	6.88 d	6.62 dd	6.76 d	a: 3.51 d
R² = 4-Cl-Ph	$J_{1a-1e}=12.3$	$J_{3-4a}=8.4$		$J_{7-8}=8.2$	$J_{8-7}=8.2$	$J_{10-8}=2.3$	$J_{12a-12e}=15.0$
	e: 3.83 d	$J_{3-4e}=5.0$			$J_{8-10}=2.3$		e: 2.31 d
	$J_{1a-1e}=12.3$						$J_{12e-12a}=15.0$
382a	a: 3.98 d	4.49 dd	1.53-1.43	6.96 d	6.62 dd	6.76 d	a: 3.50 d
R² = 4-Br-Ph	$J_{1a-1e}=12.1$	$J_{3-4a}=8.5$		$J_{7-8}=8.3$	$J_{8-7}=8.3$	$J_{10-8}=2.3$	$J_{12a-12e}=15.3$
	e: 3.81 d	$J_{3-4e}=5.5$			$J_{8-10}=2.3$		e: 2.30 d
	$J_{1a-1e}=12.1$						$J_{12e-12a}=15.3$
383a	a: 4.00 d	4.58 dd	1.50-1.26	6.96 d	6.71 dd	6.85 d	a: 3.50 d
R² = 4-CF₃-Ph	$J_{1a-1e}=12.1$	$J_{3-4a}=8.8$		$J_{7-8}=8.2$	$J_{8-7}=8.2$	$J_{10-8}=2.4$	$J_{12a-12e}=15.3$
	e: 3.84 d	$J_{3-4e}=5.3$			$J_{8-10}=2.4$		e: 2.31 d
	$J_{1a-1e}=12.1$						$J_{12e-12a}=15.3$
384a	a: 4.00 d	4.63 dd	1.51-1.31	6.97 d	6.71 dd	6.85 d	a: 3.49 d
R² = 4-NO₂-Ph	$J_{1a-1e}=12.4$	$J_{3-4a}=11.5$		$J_{7-8}=8.4$	$J_{8-7}=8.4$	$J_{10-8}=2.3$	$J_{12a-12e}=15.9$
	e: 3.86 d	$J_{3-4e}=2.9$			$J_{8-10}=2.3$		e: 2.32 d
	$J_{1a-1e}=12.4$						$J_{12e-12a}=15.9$
385a	a: 3.99 d	4.58 dd	1.52-1.27	6.96 d	6.71 dd	6.85 d	a: 3.51 d
R² = 4-CO₂Me-Ph	$J_{1a-1e}=12.1$	$J_{3-4a}=8.1$		$J_{7-8}=8.2$	$J_{8-7}=8.2$	$J_{10-8}=2.4$	$J_{12a-12e}=15.2$
	e: 3.86 d	$J_{3-4e}=5.9$			$J_{8-10}=2.4$		e: 2.31 d
	$J_{1a-1e}=12.1$						$J_{12e-12a}=15.2$

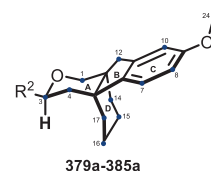
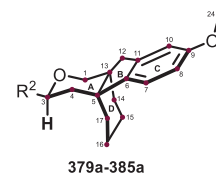


Table 5. ¹³C NMR assignments of compounds **279a-385a** (75 MHz/101 MHz/ 126 MHz, CDCl₃).

	C1	C3	C12,C4	C5,C13	C7	C8	C9	C10	C14-C17	C24
379a R² = Ph	70.1	75.5	46.0, 41.4	46.4, 44.3	121.9	111.6	158.7	112.1	31.4, 28.4, 22.6, 22.3	55.3
380a R² = 4-F-Ph	70.1	74.8	46.0, 41.3	46.4, 44.2	121.8	111.6	158.7	112.1	31.3, 28.3, 22.5, 22.3	55.3
381a R² = 4-Cl-Ph	70.0	74.8	46.0, 41.3	46.4, 44.2	121.8	111.6	158.7	112.1	31.3, 28.3, 22.5, 22.3	55.3
382a R² = 4-Br-Ph	70.0	74.8	45.9, 41.3	46.4, 44.2	121.8	111.6	158.7	112.1	31.3, 28.3, 22.5, 22.3	55.3
383a R² = 4-CF₃-Ph	70.1	74.9	46.1, 41.2	46.4, 44.1	121.9	111.7	158.8	112.2	31.4, 28.4, 22.6, 22.4	55.4
384a R² = 4-NO₂-Ph	69.9	74.5	46.1, 41.2	46.4, 44.1	121.9	111.7	158.8	112.1	31.2, 28.3, 22.5, 22.2	55.3
385a R² = 4- CO₂Me-Ph	70.0	75.1	46.0, 41.3	46.4, 44.2	121.9	111.6	158.7	112.1	31.3, 28.3, 22.5, 22.3	55.3

**Table 6.** ¹H NMR assignments of compounds **279b-385b** (300 MHz/500MHz, CDCl₃).

	H1	H3	H4	H6	H7	H8	H12
380b R² = 4-F-Ph	a: 3.94 d <i>J</i> _{1a-1e} =12.3 e: 3.80 d <i>J</i> _{1a-1e} =12.3	4.56 dd <i>J</i> _{3-4a} =11.8 <i>J</i> _{3-4e} =1.9	a: 1.82 <i>J</i> _{4a-4e} =13.8 e: 1.49 <i>J</i> _{4a-3} =11.8	6.79 d <i>J</i> ₆₋₇ =7.5	7.13 dd <i>J</i> ₇₋₆ =7.5 <i>J</i> ₇₋₈ =8.2	6.60 d <i>J</i> ₈₋₇ =8.2	a: 3.49 d <i>J</i> _{12a-12e} =12.3 e: 2.32 d <i>J</i> _{12e-12a} =12.3
381b R² = 4-Cl-Ph	a: 4.01 d <i>J</i> _{1a-1e} =12.1 e: 3.79 d <i>J</i> _{1a-1e} =12.1	4.55 dd <i>J</i> _{3-4a} =11.9 <i>J</i> _{3-4e} =2.2	a: 1.87 <i>J</i> _{4a-4e} =13.9 e: 1.53 <i>J</i> _{4a-3} =11.2	6.87 d <i>J</i> ₆₋₇ =7.3	7.12 dd <i>J</i> ₇₋₆ =7.3 <i>J</i> ₇₋₈ =8.2	6.68 d <i>J</i> ₈₋₇ =8.2	a: 3.49 d <i>J</i> _{12a-12e} =13.2 e: 2.32 d <i>J</i> _{12e-12a} =13.2
382b R² = 4-Br-Ph	a: 4.00 d <i>J</i> _{1a-1e} =12.2 e: 3.78 d <i>J</i> _{1a-1e} =12.2	4.53 dd <i>J</i> _{3-4a} =11.9 <i>J</i> _{3-4e} =2.0	a: 1.80 <i>J</i> _{4a-4e} =? e: 1.45 <i>J</i> _{4a-3} =11.9	6.78 d <i>J</i> ₆₋₇ =7.6	7.05 dd <i>J</i> ₇₋₆ =7.6 <i>J</i> ₇₋₈ =8.3	6.68 d <i>J</i> ₈₋₇ =8.3	a: 3.48 d <i>J</i> _{12a-12e} =12.2 e: 2.31 d <i>J</i> _{12e-12a} =12.2
383b R² = 4-CF₃-Ph	a: 3.95 d <i>J</i> _{1a-1e} =12.1 e: 3.72 d <i>J</i> _{1a-1e} =12.1	4.56 dd <i>J</i> _{3-4a} =11.2 <i>J</i> _{3-4e} =1.6	a: 1.83 <i>J</i> _{4a-4e} =? e: 1.47 <i>J</i> _{4a-3} =11.2	6.79 d <i>J</i> ₆₋₇ =7.3	7.05 dd <i>J</i> ₇₋₆ =7.3 <i>J</i> ₇₋₈ =8.2	6.61 d <i>J</i> ₈₋₇ =8.2	a: 3.42 d <i>J</i> _{12a-12e} =13.1 e: 2.26 d <i>J</i> _{12e-12a} =13.1
384b R² = 4-NO₂-Ph	a: 3.94 d <i>J</i> _{1a-1e} =12.2 e: 3.85 d <i>J</i> _{1a-1e} =12.2	4.60 dd <i>J</i> _{3-4a} =11.7 <i>J</i> _{3-4e} =1.9	a: 1.84 <i>J</i> _{4a-4e} =13.9 e: 1.43 <i>J</i> _{4a-3} =11.7	6.79 d <i>J</i> ₆₋₇ =7.4	7.06 dd <i>J</i> ₇₋₆ =7.4 <i>J</i> ₇₋₈ =8.3	6.62 d <i>J</i> ₈₋₇ =8.3	a: 3.47 d <i>J</i> _{12a-12e} =12.2 e: 2.35 d <i>J</i> _{12e-12a} =12.2
385b R² = 4-CO₂Me- Ph	a: 3.95 d <i>J</i> _{1a-1e} =12.1 e: 3.72 d <i>J</i> _{1a-1e} =12.1	4.56 dd <i>J</i> _{3-4a} =12.0 <i>J</i> _{3-4e} =2.2	a: 1.82 <i>J</i> _{4a-4e} =13.8 e: 1.47 <i>J</i> _{4a-3} =12.0	6.79 d <i>J</i> ₆₋₇ =7.4	7.05 dd <i>J</i> ₇₋₆ =7.4 <i>J</i> ₇₋₈ =8.2	6.61 d <i>J</i> ₈₋₇ =8.2	a: 3.43 d <i>J</i> _{12a-12e} =13.2 e: 2.26 d <i>J</i> _{12e-12a} =13.2

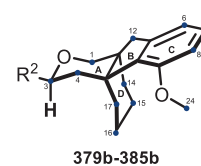
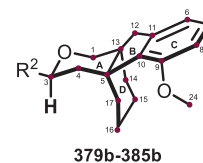
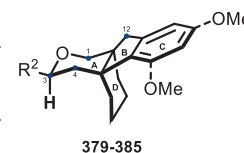


Table 7. ^{13}C NMR assignments of compounds **279b-385b** (300 MHz/500MHz, CDCl_3).

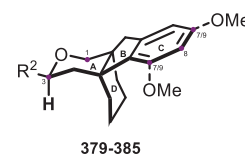
	C1	C3	C12,C4	C5,C13	C6	C7	C8	C9	C14-C17	C24
380b $\text{R}^2 = 4\text{-F-Ph}$	69.7	74.4	43.9, 41.7	48.9, 43.4	118.7	127.6	109.1	156.8	31.7, 27.9, 23.3, 22.6	55.1
381b $\text{R}^2 = 4\text{-Cl-Ph}$	69.7	74.3	43.8, 41.7	48.9, 43.4	118.7	127.6	109.1	156.8	31.7, 27.9, 23.3, 22.6	55.1
382b $\text{R}^2 = 4\text{-Br-Ph}$	69.7	74.4	43.8, 41.7	48.9, 43.4	118.7	127.6	109.1	156.8	31.7, 27.9, 23.3, 22.6	55.1
383b $\text{R}^2 = 4\text{-CF}_3\text{-Ph}$	69.6	74.6	43.8, 41.7	48.9, 43.4	118.7	127.8	109.1	156.8	31.7, 27.9, 23.3, 22.6	55.1
384b $\text{R}^2 = 4\text{-NO}_2\text{-Ph}$	69.6	74.1	43.9, 41.6	48.9, 43.4	118.7	127.8	109.1	156.8	31.6, 27.9, 23.2, 22.6	55.1
385b $\text{R}^2 = 4\text{-CO}_2\text{Me-Ph}$	69.6	74.6	43.8, 41.7	48.9, 43.4	118.7	127.6	109.1	156.8	31.7, 27.9, 23.3, 22.6	55.1

**Table 8.** The $|\Delta\delta|$ values of protons H1, H3, H4 and H12 between the obtained regioisomers.

	$ \Delta\delta \text{ H1} $	$ \Delta\delta \text{ H3} $	$ \Delta\delta \text{ H4} $	$ \Delta\delta \text{ H12} $
380a/b	a: 0.05 e: 0.02	0.05	~ 0.11	a: 0.03 e: 0.01
381a/b	a: 0.02 e: 0.04	0.04	~ 0.19	a: 0.02 e: 0.01
382a/b	a: 0.02 e: 0.03	0.04	~ 0.15	a: 0.02 e: 0.01
383a/b	a: 0.05 e: 0.12	0.02	~ 0.27	a: 0.08 e: 0.05
384a/b	a: 0.06 e: 0.01	0.03	~ 0.23	a: 0.02 e: 0.02
385a/b	a: 0.04 e: 0.14	0.02	~ 0.25	a: 0.08 e: 0.05

**Table 9.** The $|\Delta\delta|$ values of carbon atoms C1, C3 and C7-C9 between some of the obtained regioisomers.

	$ \Delta\delta \text{ C1} $	$ \Delta\delta \text{ C3} $	$ \Delta\delta \text{ C7} $	$ \Delta\delta \text{ C8} $	$ \Delta\delta \text{ C9} $
380a/b	0.4	0.4	5.8	2.5	1.9
381a/b	0.3	0.5	5.8	2.5	1.9
382a/b	0.3	0.4	5.8	2.5	1.9
384a/b	0.3	0.4	5.9	2.6	2.0
385a/b	0.4	0.5	5.7	2.5	1.9



In addition to the proton splitting patterns in the ^1H NMR spectrum, the three major systems in the A- and B-ring were confirmed by COSY analysis (H1a/ H1e, H3/ H4a, H3/ H4e, H4a/ H4e, H12a/

H12e) as a supplementary 2D NMR experiment (Figure 14 (left)). Moreover, the 2D HSQC correlations of these systems have also supported the achieved ^{13}C NMR assignments as shown in the previous section. However, the configuration at position 3 was determined by the 2D NOESY experiment as shown in Figure 14 (right). The signal of the benzyl proton H3 in **384b** (~4.69 ppm) gave strong NOE cross-peaks with H4a (~4.02 ppm) and H1a (~1.90 ppm) in addition to a weak correlation with H4b (~3.84 ppm). Likewise, H1a gave strong cross-peaks with two protons that are most likely to be those at position 14 of the alkyl D-ring. Although its geminal proton H1e correlates with one of these alkyl protons, it showed weak cross-peaks with the benzyl protons at position 12. This suggested that H3, H4a and H1a reside toward the alkyl D-ring, whereas H1e and H4e were more directed toward the indane subunit. This proposal was then verified by the major cross peak observed between H4e and H12a revealing the correct configuration at position 3, and thereby supported the given mechanisms in the first and last scenarios.

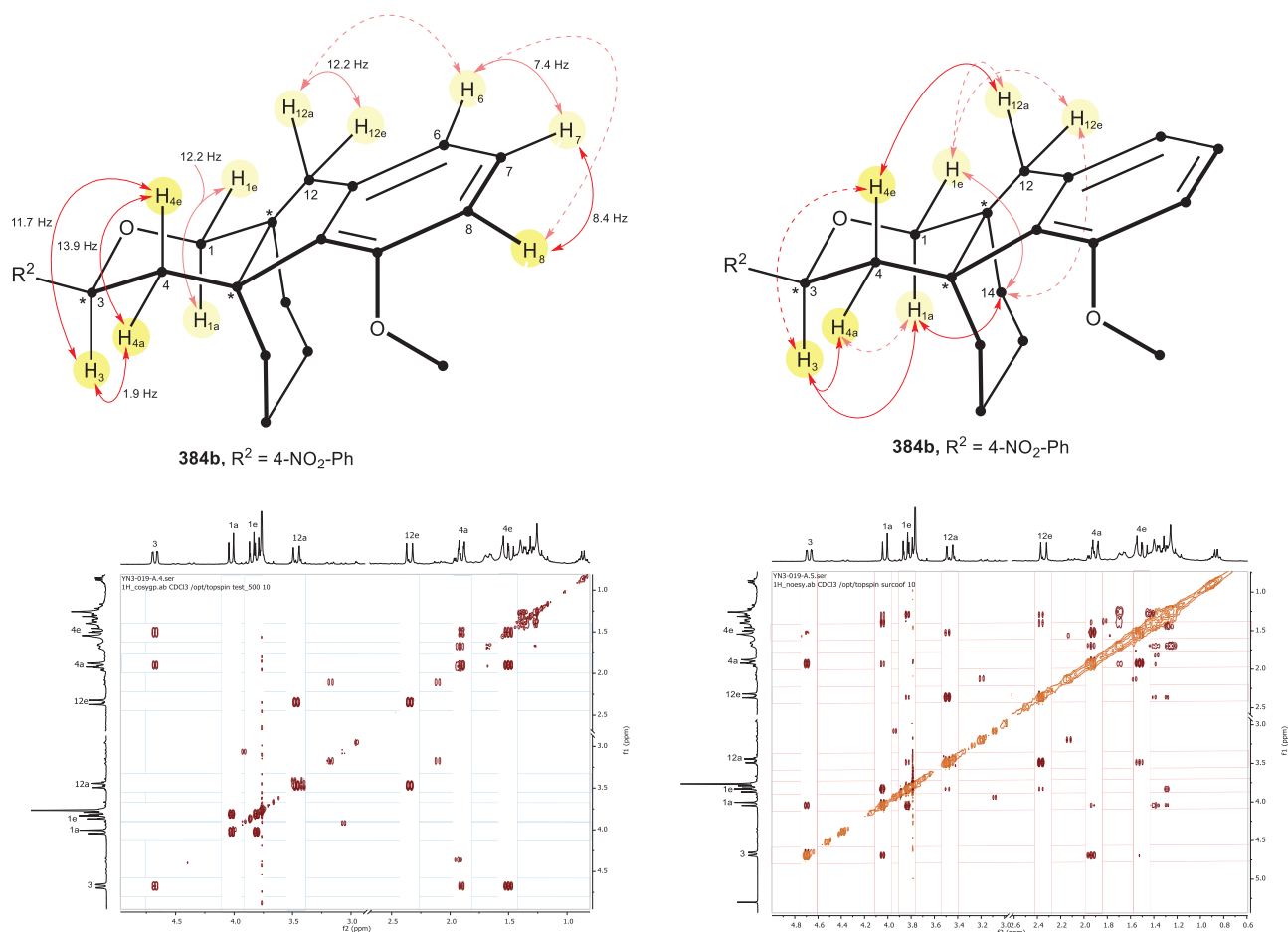


Figure 14. 2D COSY (left) and NOESY (right) NMR of **384b** (500 MHz, CDCl_3).

4. Conclusion

In summary, we have achieved the synthesis of novel and complex hexahydroindeno[2,1-*c*]pyran-based [4,4,3]propellanes in only four or five steps from aldehydes and *exo*-olefinic alcohol derivatives. The synthesis featured a Prins/Friedel-Crafts cascade annulation reaction, which enabled a rapid construction of the common indenopyran subunit. We anticipate that the synthetic strategy described herein may find further use in the preparation of other complex and diverse indenopyran-based propellanes.

5. References

- [1] A. P. Diac, A. M. Țepeș, A. Soran, I. Grosu, A. Terec, J. Roncali, E. Bogdan, *Beilstein J. Org. Chem.* **2016**, *12*, 825-834.
- [2] a) R. Gupta, M. Kumar, V. Gupta, in *Heterocyclic chemistry*, Springer, Amsterdam, **1998**, pp. 3-38; b) T. Eicher, S. Hauptmann, A. Speicher, John Wiley & Sons, New Jersey, **2013**, pp. 10-40; c) D. Hellwinkel, Springer, Amsterdam, **2001**, pp. 53-121; d) D. Kumar, V. Singh, *Int. J. Res. Sci. Technol.* **2014**, *3*, 25-28.
- [3] B. V. Subba Reddy, N. Prudhvi Raju, B. J. Someswarao, B. Reddy, B. Sridhar, K. Marumudid, A. Kunward, *Org. Biomol. Chem.* **2015**, *13*, 4733-4736.
- [4] R. W. Dapson, C. L. Bain, *Biotech. Histochem.* **2015**, *90*, 401-423.
- [5] a) V. Arredondo, D. E. Roa, E. S. Gutman, N. O. Huynh, D. L. Van Vranken, *J. Org. Chem.* **2019**, *84*, 14745-14759; b) N. P. Nirmal, M. S. Rajput, R. G. Prasad, M. Ahmad, *Asian Pac. J. Trop. Med.* **2015**, *8*, 421-430; c) L. G. Lin, Q. Y. Liu, Y. Ye, *Planta Med.* **2014**, *80*, 1053-1066; d) B. M. Abegaz, J. Mutanyatta-Comar, M. Nindi, *Nat. Prod. Commun.* **2007**, *2*, 475-498.
- [6] Z. Y. Li, Y. Zheng, Y. Chen, M. Pan, S. B. Zheng, W. Huang, Z. H. Zhou, H. Y. Ye, *Inflammation* **2017**, *40*, 1365-1374.
- [7] E. G. Jung, K. I. Han, S. G. Hwang, H. J. Kwon, B. B. Patnaik, Y. H. Kim, M. D. Han, *BMC complementary Alter. Med.* **2015**, *15*, 1-11.
- [8] a) Z. J. He, F. Y. Zhu, S. S. Li, L. Zhong, H. Y. Tan, K. Wang, *Food Chem. Toxicol.* **2017**, *101*, 55-66; b) D. Y. Lee, M. K. Lee, G. S. Kim, H. J. Noh, M. H. Lee, *Molecules* **2013**, *18*, 2449-2457; c) B. Kim, S. H. Kim, S. J. Jeong, E. J. Sohn, J. H. Jung, M. H. Lee, S. H. Kim, *J. Agric. Food Chem.* **2012**, *60*, 9882-9889.
- [9] M. Ye, W. D. Xie, F. Lei, Z. Meng, Y. N. Zhao, H. Su, L. J. Du, *Int. Immunopharmacol.* **2006**, *6*, 426-432.
- [10] a) A. H. Fischer, K. A. Jacobson, J. Rose, R. Zeller, *Cold Spring Harb. Prot.* **2008**, 986; b) Y. Melander, K. G. Wingstrand, *Stain Technol.* **1953**, *28*, 217-223; c) R. D. Cardiff, C. H. Miller, R. J. Munn, *Cold Spring Harb. Prot.* **2014**, 411; d) M. Titford, *Biotech. Histochem.* **2005**, *80*, 73-78; e) B. D. Llewellyn, *Biotech. Histochem.* **2009**, *84*, 159-177.
- [11] H. Abdelkafi, B. Nay, *Nat. Prod. Rep.* **2012**, *29*, 845-869.

- [12] Y. Y. Fan, J. B. Xu, H. C. Liu, L. S. Gan, J. Ding, J. M. Yue, *J. Nat Prod.* **2017**, *80*, 3159-3166.
- [13] a) L. Xu, C. Wang, Z. Gao, Y. M. Zhao, *J. Am. Chem. Soc.* **2018**, *140*, 5653-5658; b) E. M. Carreira, M. A. Imhof, *Synfacts* **2018**, *14*, 666.
- [14] a) J. G. Ondeyka, G. L. Helms, O. D. Hensens, M. A. Goetz, D. L. Zink, A. Tsipouras, W. L. Shoop, L. Slayton, A. W. Dombrowski, J. D. Polishook, D. A. Ostlind, *J. Am. Chem. Soc.* **1997**, *119*, 8809-8816; b) O. D. Hensens, J. G. Ondeyka, A. W. Dombrowski, D. A. Ostlind, D. L. Zink, *Tetrahedron Lett.* **1999**, *40*, 5455-5458; c) J. G. Ondeyka, A. M. Dahl-Roshak, J. S. Tkacz, D. L. Zink, M. Zakson-Aiken, W. L. Shoop, M. A. Goetz, S. B. Singh, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2941-2944; d) J. G. Ondeyka, K. Byrne, D. Vesey, D. L. Zink, W. L. Shoop, M. A. Goetz, S. B. Singh, *J. Nat. Prod.* **2003**, *66*, 121-124; e) S. B. Singh, J. G. Ondeyka, H. Jayasuriya, D. L. Zink, S. N. Ha, A. Dahl-Roshak, J. Greene, J. A. Kim, M. M. Smith, W. L. Shoop, *J. Nat. Prod.* **2004**, *67*, 1496-1506.
- [15] S. W. Ludmerer, V. A. Warren, B. S. Williams, Y. Zheng, D. C. Hunt, M. B. Ayer, M. A. Wallace, A. G. Chaudhary, M. A. Egan, P. T. Meinke, D. C. Dean, *Biochemistry* **2002**, *41*, 6548-6560.
- [16] P. T. Meinke, S. L. Colletti, M. H. Fisher, M. J. Wyvrat, T. L. Shih, M. B. Ayer, C. Li, J. Lim, D. Ok, S. Salva, L. M. Warmke, *J. Med. Chem.* **2009**, *52*, 3505-3515.
- [17] A. L. Wilkins, C. O. Miles, R. M. Ede, R. T. Gallagher, S. C. Munday, *J. Agric. Food Chem.* **1992**, *40*, 1307-1309.
- [18] a) G. N. Belofsky, J. B. Gloer, D. T. Wicklow, P. F. Dowd, *Tetrahedron* **1995**, *51*, 3959-3968; b) M. Xu, G. Gessner, I. Groth, C. Lange, A. Christner, T. Bruhn, Z. Deng, X. Li, S. H. Heinemann, S. Grabley, *Tetrahedron* **2007**, *63*, 435-444; c) N. A. Godfrey, D. J. Schatz, S. V. Pronin, *J. Am. Chem. Soc.* **2018**, *140*, 12770-12774.
- [19] a) M. Chakraborty, C. A. Tessier, W. G. Youngs, *J. Org. Chem.* **1999**, *64*, 2947-2949; b) J. D. Kinder, C. A. Tessier, W. J. Youngs, *Synlett* **1993**, 149-150; c) W. J. Youngs, J. D. Kinder, J. D. Bradshaw, C. A. Tessier, *Organometallics* **1993**, *12*, 2406-2407.
- [20] K. P. Baldwin, A. J. Matzger, D. A. Scheiman, C. A. Tessier, K. P. C. Vollhardt, W. J. Youngs, *Synlett* **1995**, 1215.
- [21] M. Chakraborty, D. B. McConville, T. Saito, H. Meng, P. L. Rinaldi, C. A. Tessier, W. J. Youngs, *Tetrahedron Lett.* **1998**, *39*, 8237-8240.
- [22] K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, *93*, 4467.
- [23] X. T. Zhu, H. W. Xu, B. Jiang, J. Y. Liu, S. J. Tu, *Tetrahedron Lett.* **2013**, *54*, 6341-6344.
- [24] a) B. S. Reddy, P. Borkar, J. S. Yadav, B. Sridhar, R. Gree, *J. Org. Chem.* **2011**, *76*, 7677-7690; b) B. S. Reddy, P. S. Reddy, J. S. Yadav, B. Sridhar, *Tetrahedron Lett.* **2013**, *54*, 1392-1396; c) A. K. Ghosh, C. Keyes, A. M. Veitschegger, *Tetrahedron Lett.* **2014**, *55*, 4251-4254; d) C. Lalli, P. Van de Weghe, *Chem. Commun.* **2014**, *50*, 7495-7498.
- [25] a) B. Li, Y. C. Lai, Y. Zhao, Y. H. Wong, Z. L. Shen, T. P. Loh, *Angew. Chem. Int. Ed.* **2012**, *51*, 10619-10623; b) X. F. Yang, M. Wang, Y. Zhang, C. J. Li, *Synlett* **2005**, 1912-1916.
- [26] a) B. V. S. Reddy, M. R. Reddy, B. Sridhar, K. K. Singarapu, *Org. Biomol. Chem.* **2014**, *12*, 4754-4762; b) S. N. Chavre, H. Choo, J. K. Lee, A. N. Pae, Y. Kim, Y. S. Cho, *J. Org. Chem.* **2008**, *73*, 7467-7471.

- [27] a) S. Huang, W. Ou, W. Li, H. Xiao, Y. Pang, Y. Zhou, X. Wang, X. Yang, L. Wang, *Tetrahedron Lett.* **2020**, *61*, 152052; b) B. S. Reddy, G. N. Reddy, M. R. Reddy, J. K. Lakshmi, B. Jagadeesh, B. Sridhar, *Asian J. Org. Chem.* **2015**, *4*, 1266-1272.
- [28] a) E. Fenster, C. Fehl, J. Aubé, *Org. Lett.* **2011**, *13*, 2614-2617; b) R. J. Hinkle, S. E. Lewis, *Org. Lett.* **2013**, *15*, 4070-4073.
- [29] a) X. Wang, H. Zhang, X. Yang, J. Zhao, C. Pan, *Chem. Commun.* **2013**, *49*, 5405-5407; b) L. Q. Li, M. M. Li, K. Wang, H. B. Qin, *Tetrahedron Lett.* **2013**, *54*, 6029-6031.
- [30] A. H. Clark, J. D. McCorvy, J. M. Conley, W. K. Williams, M. Bekkam, V. J. Watts, D. E. Nichols, *Bioorg. Med. Chem.* **2012**, *20*, 6366-6374.
- [31] B. V. Reddy, N. Raju, B. Someswarao, B. J. Reddy, B. Sridhar, K. Marumudid, A. Kunward, *Org. Biomol. Chem.* **2015**, *13*, 4733-4736.
- [32] a) D. Clarisse, B. Pelotier, O. Piva, F. Fache, *Chem. Commun.* **2012**, *48*, 157-159; b) M. A. Hiebel, B. Pelotier, O. Piva, *Tetrahedron* **2007**, *63*, 7874-7878; c) F. Fache, M. Muselli, O. Piva, *Synlett* **2013**, *24*, 1781-1784; d) L. Raffier, F. Izquierdo, O. Piva, *Synthesis* **2011**, *2011*, 4037-4044; e) C. Segovia, F. Fache, B. Pelotier, O. Piva, *ChemistrySelect* **2019**, *4*, 3191-3194.
- [33] M. Periasamy, N. Sanjeevakumar, P. O. Reddy, *Synthesis* **2012**, *44*, 3185-3190.
- [34] T. Khomenko, A. Zakharenko, T. Odarchenko, H. J. Arabshahi, V. Sannikova, O. Zakharova, D. Korchagina, J. Reynisson, K. Volcho, N. Salakhutdinov, *Bioorg. Med. Chem.* **2016**, *24*, 5573-5581.
- [35] Y. Fukuyama, H. Yuasa, Y. Tono, K. Harada, M. Wada, Y. Asakawa, T. Hashimoto, *Tetrahedron* **2001**, *57*, 9299-9307.
- [36] H. Y. Lee, D. K. Moon, J. S. Bahn, *Tetrahedron Lett.* **2005**, *46*, 1455-1458.
- [37] R. F. Nystrom, W. G. Brown, *J. Am. Chem. Soc.* **1947**, *69*, 1197-1199.
- [38] T. Kotipalli, D. R. Hou, *Org. Lett.* **2018**, *20*, 4787-4790.
- [39] a) K. Wähälä, T. Mäkelä, R. Bäckström, G. Brunow, T. Hase, *J. Chem. Soc. Perkin Trans. I* **1986**, 95-98; b) D. Munz, M. Webster-Gardiner, R. Fu, T. Strassner, W. A. Goddard III, T. B. Gunnoe, *ACS Catal.* **2015**, *5*, 769-775; c) R. Giles, G. Ahn, K. W. Jung, *Tetrahedron Lett.* **2015**, *56*, 6231-6235.

Chapter VI

Toward the Total Synthesis
of Cordycol, Idesolide Monomer
and Analogues

Ch. VI: Toward the Total Synthesis of Cordycol, Idesolide Monomer and Analogue

Cordycol

1. Introduction

Angiogenesis is the process by which new blood vessels form, allowing the delivery of oxygen and nutrients to the body's tissues (Figure 1). It is a vital function, required for growth and development as well as the healing of wounds.^[1] But it also plays an important role in the formation of cancer because, like any other body part, tumors need a blood supply to thrive and grow.^[2] In the early 1970s, the late investigator Judah Folkman first reported research showing that the formation of cancer depends on angiogenesis. Since then, many antiangiogenic compounds have been developed to stop cancers from growing or progressing — the idea being that choking off the blood supply would starve the tumor.^[3]

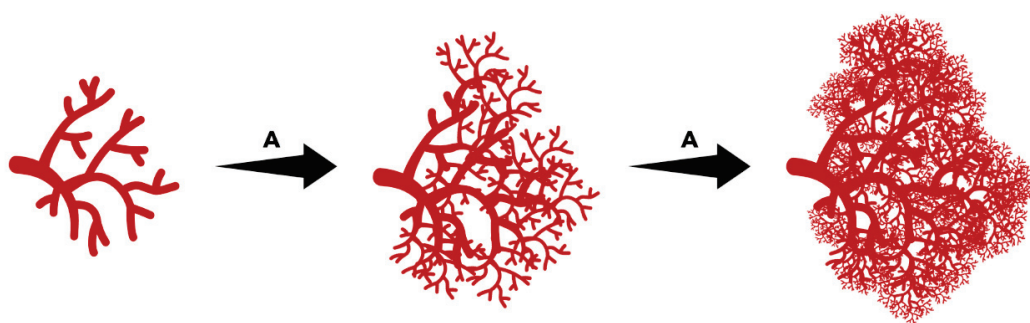


Figure 1. The process of angiogenesis (A) in the blood vessels.

Today there are about a dozen antiangiogenic cancer drugs that have been approved by the US Food and Drug Administration, such as bevacizumab (Avastin®),^[4] which is used in the treatment of glioblastoma brain tumors and kidney, lung, and colorectal cancers. There are other antiangiogenic drugs in use as well, including several for treating kidney cancer.^[5] In addition, there are many experimental angiogenesis inhibitors in clinical development.

Fumagillin **398** (Figure 2), isolated in 1949 by Elbe and Hanson^[6] from the microbial organism *Aspergillus fumigatus*, was originally described as an antimicrobial agent, but in 1990, it was

reported to be a potent, selective inhibitor of angiogenesis.^[7] Semisynthetic compounds, such as TNP-470 **399**,^[7a] and CKD-732 **401**,^[8] underwent trials for the treatment of a variety of cancers. Ovalicin **405**^[9] also inhibits angiogenesis and is more stable than **398** or **399**, whereas 5-demethylovalicin **406**,^[10] isolated in 2002, was found to be as potent angiogenesis inhibitor as **405**. Chlovalicin **407** was isolated together with **405** from *Sporothrix* sp. FO-4649 1 by Omura.^[11] Compounds **398**, **399**, and **405** have been shown to specifically bind to type 2 methionine aminopeptidase (MetAP2).^[12]

In 2004, Osada, Kakeya, and co-workers isolated RK-805 **404** from the fungus *Neosartora* sp.^[13] and RK-95113 **402** from *Aspergillus fumigatus* var. *fumigatus* sp.,^[14] both of which are inhibitors of angiogenesis. Although all these natural products are anti-angiogenesis compounds, FR65814 **403**,^[15] despite its similar structure, displays a completely different biological activity, that of an immunosuppressant. Later on, fumagillin **398** has been found to reverse the growth inhibitory activity of Viral protein R (Vpr) in yeast and human cells and to inhibit the HIV-1 infection of human macrophages.^[16]

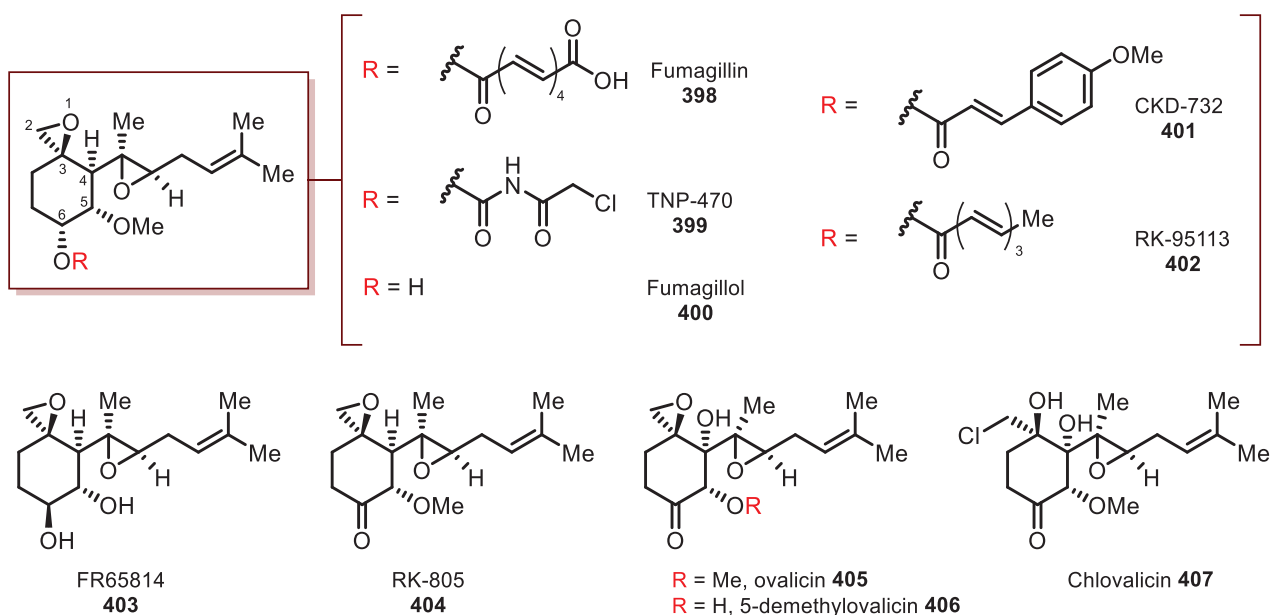


Figure 2. Fumagillin and ovalicin analogues.

In 2013, Li and coworkers reported the isolation and characterization of a new fumagillol analogue, cordycol **408**, in addition to three new unusual spiro[4.5]decane sesquiterpenes **409-411** from cultured mycelia of *Cordyceps ophioglossoides* (Figure 3).^[17] The cytotoxic activities were also evaluated, compounds **408** and **411** showing their IC₅₀ values in the range of 12 – 33 mg/ml against

HeLa and HepG2. In addition, they were not harmful towards normal liver cell lines LO2, showing IC_{50} values above 80 mg/ml. Therefore, the activities of **408** and **411** suggested that they could be promising lead compounds to treat human hepatic carcinoma.

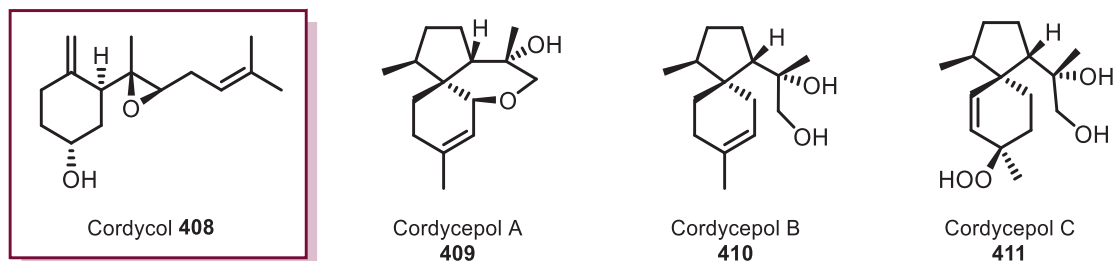


Figure 3. The structure of cordycol and cordycepol A-C.

Structurally, cordycol is comprised of a cyclohexane framework, one epoxide (C7-C8), a hydroxyl group at C5 and four stereogenic centers, two of which are situated on the cyclohexane ring (Figure 4). These interesting attributes, as well as the biological activities, have made **408** an attractive and challenging target for total synthesis. From the viewpoint of the synthetic chemist, this molecule also provides an ideal platform for the development of new synthetic strategies and the discovery of novel synthetic methodologies. Herein we describe a new approach toward the total synthesis of cordycol from abundant and inexpensive starting materials.

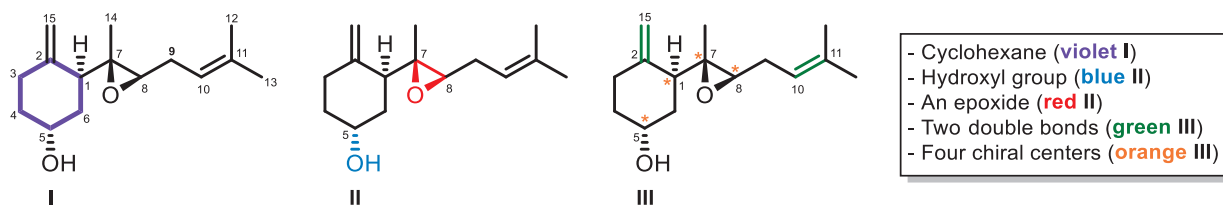
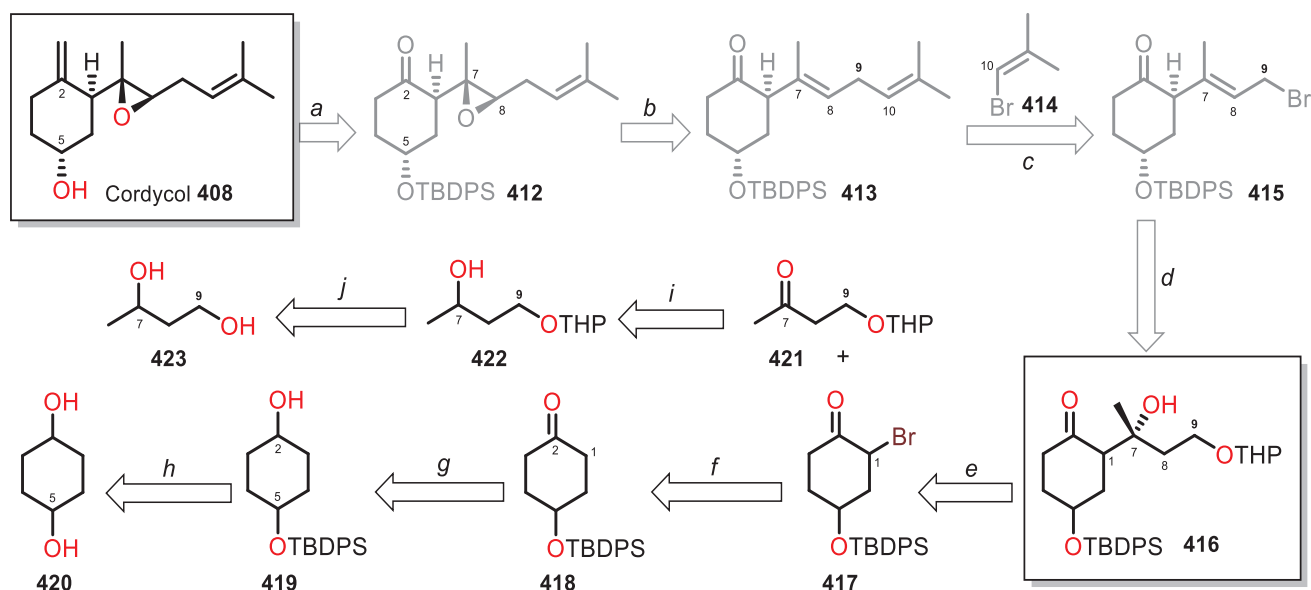


Figure 4. Key features of cordycol.

Our strategy, based upon the retrosynthetic analysis outlined in Scheme 1, features a key intermediate **416** that could be used as a building block to furnish the major functionalities of cordycol at C1, C2 and C5. For instance, **416** could be transformed, *via* a series of reactions, to establish diene **413**, which is similar to intermediates obtained by Sorensen^[18] and Eustache^[19] during their total synthesis of fumagillol **400**. After selective epoxidation at alkene C7-C8, Wittig reaction at C2 and alcohol deprotection at C5, **413** might afford the targeted structure of cordycol. Consequently, we envisaged that **416** could be synthesized from the samarium iodide-promoted Reformatsky reaction between α -bromoketone **417** and **421** to set up C1-C7 bond.

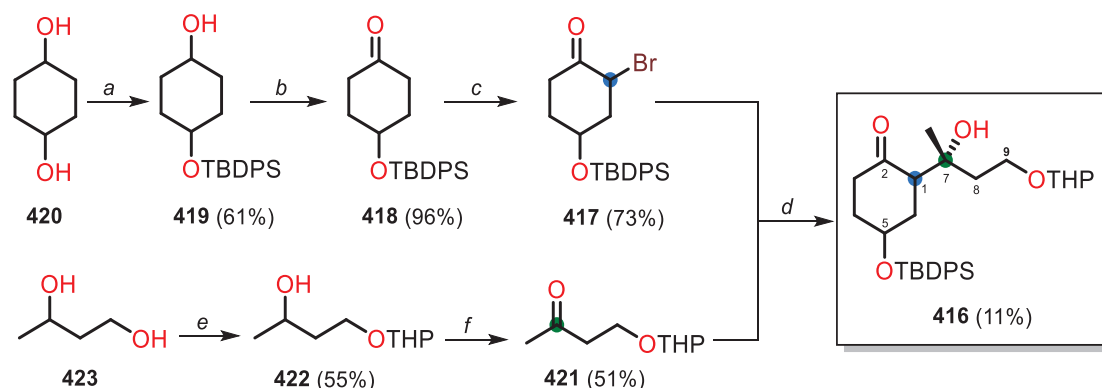


Scheme 1. Our retrosynthetic analysis of Cordycol. Reactions; *a*: (i) Wittig reaction (C2), (ii) alcohol deprotection (C5); *b*: epoxidation (C7-C8); *c*: Negishi coupling (C9-C10); *d*: (i) dehydration reaction (C1-C7 double bond formation), (ii) photochemical 1,5 hydrogen shift (double bond migration (C7-C8)) (if necessary), (iii) alcohol deprotection (C9), (iiii) Appel reaction (C9); *e*: samarium iodide-promoted Reformatsky reaction (C1-C7); *f*: α -bromination (C1); *g*: alcohol oxidation (C2); *h*: alcohol protection (C5); *i*: alcohol oxidation (C7); *j*: alcohol protection (C9).

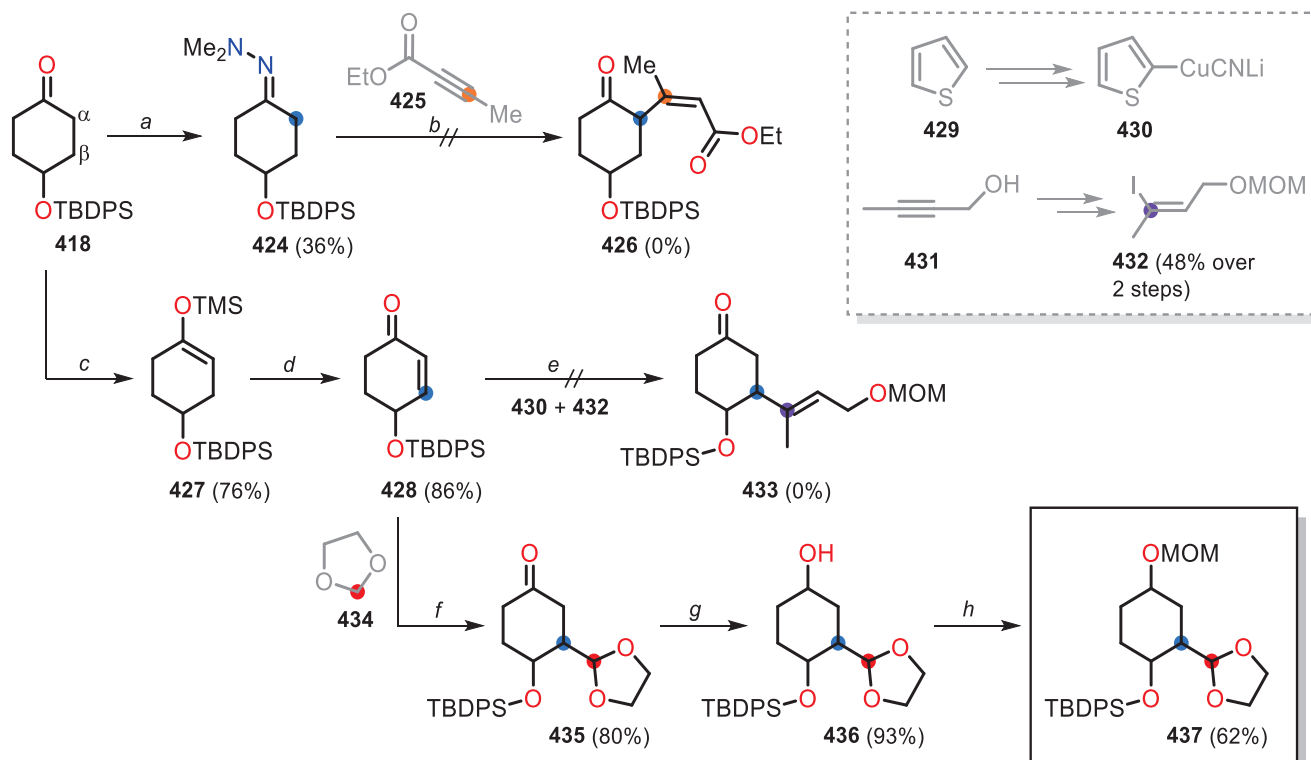
2. Results and discussion

Our synthetic studies commenced with the preparation of α -bromoketone **417** (Scheme 2). Commercially available 1,4-cyclohexanediol **420** underwent selective protection of one of the presented hydroxyl groups at C2 and C5 to give the mono-protected alcohol **419**. The latter compound was oxidized to afford ketone **418** in 96% yield, which was then exposed to *N*-bromosuccinimide before delivering **417** as a mixture of diastereoisomers in a ratio of 2.4:1. In parallel, ketone **421** was prepared in a two-step synthesis from 1,3-butanediol *via* alcohol protection at C9 followed by alcohol oxidation at C7.

Having compounds **417** and **421** in hand, we turned our attention toward a coupling reaction that can lead to C1-C7 bond formation. The intermolecular Reformatsky-type coupling of α -haloketones with ketones traditionally requires harsh Lewis acids or elevated temperatures to obtain a serviceable yield of the desired product.^[20] However, the diiodosamarium method used by Jamison and coworkers^[21] revealed an efficient coupling between acyclic α -chloro- or α -bromoketones with a variety of carbonyl compounds to form the β -hydroxyketones with excellent



Scheme 2. Synthesis of **416**. Reactions and conditions: (a) TBDPS-Cl, imidazole, THF, r.t., 20h, 61%; (b) PCC, CH₂Cl₂, r.t., 16h, 96%; (c) NBS, TsOH (10 mol%), CH₂Cl₂, 0°C- reflux (45°C), 17h, 73%; (d) SmI₂ (0.1M in THF), THF, -78– 0°C, 2h, 11%; (e) 3,4-dihydropyran, PPTs (10 mol%), dry CH₂Cl₂, 24h, 55%; (f) PCC, pyridine, Celite, CH₂Cl₂, 16 h, 51%.



Scheme 3. Attempts for α - or β - functionalization of **418**. Reactions and conditions: (a) Dean- Stark, NH₂-NMe₂, TFA, benzene, 100 °C, 4h, 36%; (b) *i.* LDA, THF, -78°C, *ii.* THF, -78– 0°C, 0%; (c) TMSCl, NaI, Et₃N, THF, r.t., 12h, 76%; (d) Pd(OAc)₂, MeCN, r.t., 5h, 86%; (e) n-BuLi, -78°C- r.t., 1 h, 0%; (f) *h* ν (366 nm), 1,3-dioxolane, benzophenone, r.t., 20h, 80%; (g) NaBH₄, MeOH, r.t., 15 min., 93%; (h) dimethoxymethane, LiBr, TsOH, r.t., 20h, 62%.

diastereoselectivity. Unfortunately, the treatment of α -bromoketone **417** with the carbonyl electrophile **421** in a solution of diiodosamarium in tetrahydrofuran afforded the desired product **416** with a low yield. The major side reaction was the debromination of **417** to give the starting ketone **418** in 30% yield. This process is initiated by initial electron transfer from SmI₂ to either the bromide substituent at the α position or the carbonyl moiety. A second reduction immediately follows, after which either protonation or elimination-tautomerization affords **418**.^[22]

As a result, we wanted to endeavor other synthetic routes to functionalize either position α or position β of **418** (Scheme 3). Attempts to obtain the 1,4-adduct **426** from the Michael addition of dimethyl hydrazine intermediate **424** with ethyl 2-butynoate **425** were all failed. Similarly, the 1,4-addition on the already synthesized enone **428** using vinyl iodide **432** and the lower order mixed cuprate, derived from CuCN and 2-lithiothiophene (i.e., 2-ThCu(CN)Li **430**),^[23] was found to be unsuccessful. However, the photoinduced Michael-type radical addition of 1,3-dioxolane **434** on **428** furnished the β -functionalized product **435** in 80% yield.^[24] The latter compound was then converted in two steps to afford **437**, a trisubstituted cyclohexane product, which might be useful for the future synthesis of cordycol **408**.

Idesolide monomer and analogues

Idesia polycarpa Maxim. is a deciduous tree of the Flacourtiaceae family.^[25] This tree is native to some Asian countries such as Korea, China, Japan, and Taiwan.^[26] In Korea, the seeds of this tree have been used as an insecticide, and the leaves have been known to have hemostatic activity.^[26] In 2005, Kim and coworkers reported the isolation of (-)-idesolide from the fruit of this plant.^[26] The discovered compound is a hemiketal/ketal dimer of methyl 1-hydroxy-6-oxo-2-cyclohexenecarboxylate **438** which has also been isolated from several sources, including *Idesia polycarpa* and *Salix subserrata* (Figure 5).^[27] Both (-)-idesolide and **438** inhibit lipopolysaccharide-induced NO production in BV2 microglia at micromolar concentrations.^[26, 27c] The 1-hydroxy-6-oxo-2-cyclohexenecarboxylate motif is also a significant unit of various willow and poplar glycosides that are related to the discovery and development of aspirin.^[28] It is a component of salicortin,^[29] idescarpin,^[25] tremulacin,^[29] cochinchiside B,^[30] and 4-hydroxytremulacin (Figure 5).^[27b] Although the structures of salicortin and tremulacin were assigned in 1970,^[29] the synthesis of the densely functionalized 1-hydroxy-6-oxo-2-cyclohexenecarboxylate moiety has not been reported until 2007.^[31] Prompted by the unique structure and the interesting biological activity of

438, we also embarked on toward its total synthesis using the photo-deconjugation reaction and ring-closing metathesis as key transformations.

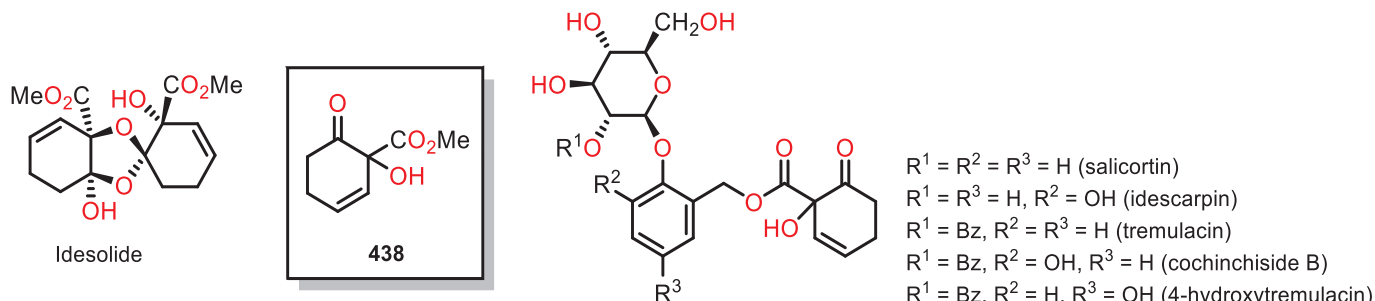
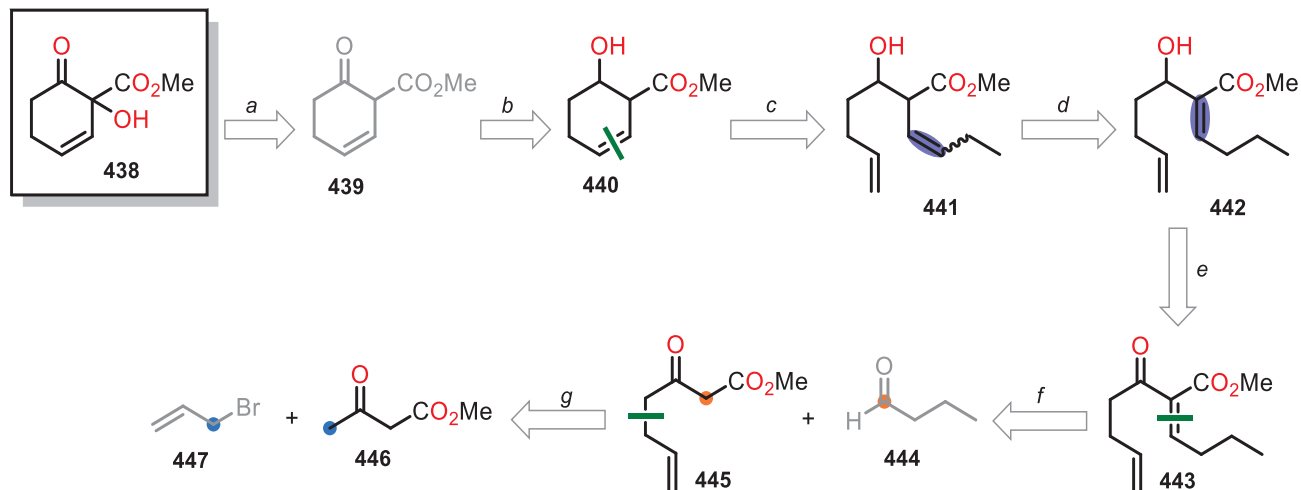


Figure 5. Some naturally occurring 1-hydroxy-6-oxo-2-cyclohexenecarboxylate esters.

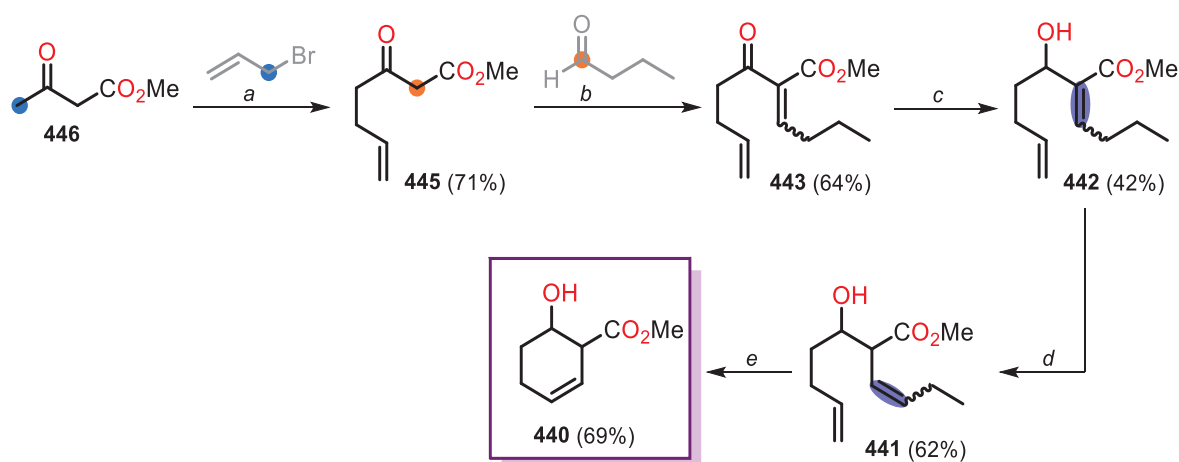
Our retrosynthetic analysis of **438** is shown in Scheme 4. Assuming that **438** might be formed from the unsaturated ketoester **439** *via* metal-catalyzed α -hydroxylation,^[32] we set the preparation of **440** as our major task. Compound **440** would be obtainable by ring-closing metathesis of **441**, which in turn could be derived from readily available starting material *via* photo-deconjugation reaction, ketone reduction, Knoevenagel condensation and subsequent α -allylation of methyl acetoacetate **446**.



Scheme 4. Retrosynthetic analysis of **438**. Reactions; *a*: α -hydroxylation reaction; *b*: alcohol oxidation; *c*: ring-closing metathesis (RCM); *d*: photo-deconjugation reaction; *e*: Luche reduction; *f*: Knoevenagel condensation; *g*: ketone allylation.

According to our synthetic plan, the γ -position of methyl acetoacetate **446** was functionalized by an allyl group using the standard methodology described by Huckin and Weiler to afford compound **445** in 71% yield (Scheme 5).^[33] The latter was then subjected to a Knoevenagel

condensation with butyraldehyde **444** to give diene **443** in 64% yield as a mixture of separable isomers. At this level, all attempts to deconjugate the introduced double bond at the α -position of ketoester **443** were unsuccessful (Table 1). Generally, degradation of the reaction mixture (entries 1, 2 and 5) and/or *E/Z* isomerization (entries 3 and 4) were the only observed processes at 254 and 300 nm respectively. We assumed that the ketone group in compound **443** further stabilized the double bond in the α -position and blocked the photo-deconjugation step. For this reason, we wanted to reduce **443** under Luche conditions and retest the photochemical process.^[34]



Scheme 5. Synthesis of intermediate **440**. Reactions and conditions: (a) *i.* NaH, THF, 0°C, *ii.* n-BuLi, -78°C, *iii.* allyl bromide, 2h, (71%); (b) *i.* LiBr, Ac₂O, *ii.* butyraldehyde, 80°C–r.t., (64%); (c) NaBH₄, CeCl₃·7H₂O, MeOH, 0°C/r.t., (42%); (d) *hν* (254 nm), CH₂Cl₂, *N,N*-DMEA (10 mol%), 48°C, 1h (62%); (e) Grubbs I catalyst (7%), CH₂Cl₂ 40°C, 25h, (69%).

Table 1. The unsuccessful attempts to photo-deconjugate the tested unsaturated- β -ketoesters.

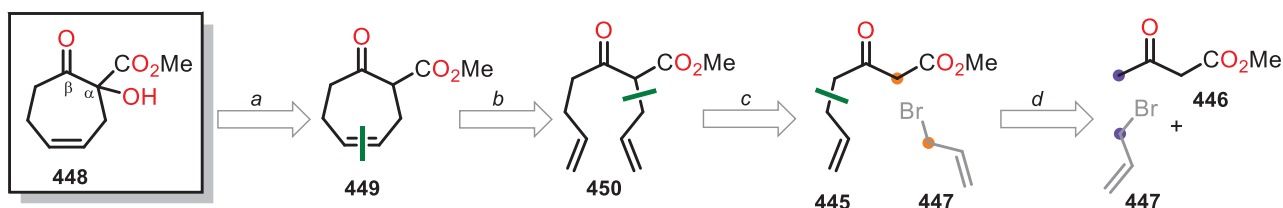
Table 1

Entry	R	R'	Solvent	Time (h) ^a	λ (nm) ^b	Additive	Result
1	Me	Et	CH ₂ Cl ₂	4	254	<i>N,N</i> -DMEA ^c	– ^d
2	Me	Et	CH ₂ Cl ₂	1	254	<i>N,N</i> -DMEA ^c	– ^d
3	(CH ₂) ₂ CH=CH ₂	Me	CHCl ₃	14	300	<i>N,N</i> -DMEA ^c	<i>E/Z</i> Isomerization
4	(CH ₂) ₂ CH=CH ₂	Me	CH ₂ Cl ₂	4.5	300	<i>N,N</i> -DMEA ^c	<i>E/Z</i> Isomerization
5	(CH ₂) ₂ CH=CH ₂	Me	CH ₂ Cl ₂	6.5	254	<i>N,N</i> -DMEA ^c	– ^{d,e}

^aIrradiation time; ^bIrradiation wavelength; ^c*N,N*-dimethylethylamine; ^ddegradation by Norrish type I; ^e*E/Z* Isomerization.

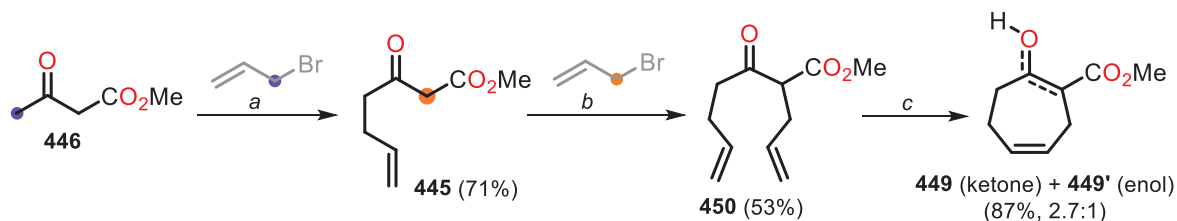
Fortunately, when irradiated at 254 nm in the presence of catalytic amounts of *N,N*-dimethylethylamine in dichloromethane for 4 hours, **442** afforded the deconjugated product **441** as a mixture of diastereoisomers in 62% yield. A subsequent ring-closing metathesis of **441** furnished the targeted intermediate **440** which might easily be converted to the final product.

One of the proposed unnatural analogues of idesolide monomer **438** could be compound **448** (Scheme 6). This congener is an unsaturated α -hydroxy β -ketoester comprised of a 7-membered ring with the double bond being at two carbon atoms from the α -position of the ester group. We assumed that **448** might be derived from ketoester **449**, which was already described in the literature as a starting material for the total synthesis of aspterric acid.^[35] We envisioned the synthesis of this intermediate from **450** *via* ring-closing metathesis. The latter compound could be prepared by the classical double allylation process from the same starting materials as those used in the previous synthesis of **440**.



Scheme 6. Retrosynthetic analysis of **448**. Reactions; *a*: α -hydroxylation reaction; *b*: ring-closing metathesis (RCM); *c* = *d*: ketone allylation.

We started this short synthesis from readily prepared unsaturated ketoester **446** which was converted to diene **450** *via* a second allylation reaction (Scheme 7). A subsequent ring-closing metathesis (RCM) afforded **449** and its tautomer **449'** in 87% yield. One more step from the latter intermediates could furnish the targeted congener **448**.



Scheme 7. Synthesis of intermediate **451**. Reactions and conditions: (a) *i.* NaH, THF, 0°C, *ii.* *n*-BuLi, -78°C, *iii.* allyl bromide, 2h, (71%); (b) *i.* NaH, THF, 0°C, *ii.* allyl bromide, r.t., 2h, (53%); (c) Grubbs I catalyst (7 mol%), CH₂Cl₂, r.t. 24h, (87%).

3. General Conclusion

Throughout this chapter, we described our attempts toward the total synthesis of cordycol, idesolide monomer and one of its analogues. The preparation of a trisubstituted cyclohexane intermediate in the cordycol synthesis featured photoinduced Michael-type radical addition of 1,3-dioxolane on a readily prepared enone. This reaction served as a key element to functionalize the cyclohexane core with a third substituent, and hence opened the door for further installation of the required functionalities in the targeted molecule. On the other hand, the construction of significant intermediates for the synthesis of natural idesolide monomer and its proposed unnatural analogue was developed from readily cheap starting material *via* ring-closing metathesis and photo-deconjugation reaction as key steps. Further investigation on the α -hydroxylation reaction could expand the synthetic scope and therefore complete the synthesis of the addressed compounds.

4. References

- [1] a) J. Folkman, *Annu. Rev. Med.* **2006**, *57*, 1-18; b) W. Risau, *Nature* **1997**, *386*, 671-674.
- [2] a) J. Folkman, *J. Natl. Cancer Inst.* **1990**, *82*, 4; b) R. S. Kerbel, *N. Engl. J. Med.* **2008**, *358*, 2039-2049; c) L. Østergaard, A. Tietze, T. Nielsen, K. Drasbek, K. R. Mouridsen, S. N. Jespersen, M. R. Horsman, *Cancer Res.* **2013**, *73*, 5618-5624.
- [3] a) T. C. Tran, B. Sneed, J. Haider, D. Blavo, A. White, T. Aiyejorun, T. C. Baranowski, A. L. Rubinstein, T. N. Doan, R. Dingleline, E. M. Sandberg, *Cancer Res.* **2007**, *67*, 11386-11392; b) M. Demeule, J. Michaud-Levesque, B. Annabi, D. Gingras, D. Boivin, S. Lamy, Y. Bertrand, R. Beliveau, *Curr. Med. Chem. Anticancer Agents* **2002**, *2*, 441-463; c) A. Claes, P. Wesseling, J. Jeuken, C. Maass, A. Heerschap, W. P. Leenders, *Mol. Cancer Ther.* **2008**, *7*, 71-78; d) C. Wang, W. Tao, Y. Wang, J. Bikow, B. Lu, A. Keating, S. Verma, T. G. Parker, R. Han, X. Y. Wen, *Eur. Urol.* **2010**, *58*, 418-426; e) R. P. Gonzalez, A. Leyva, M. O. Moraes, *Biol. Pharm. Bull.* **2001**, *24*, 1097-1101; f) A. P. Hall, F. R. Westwood, P. F. Wadsworth, *Toxicol. Pathol.* **2006**, *34*, 131-147; g) P. Nowak-Sliwinska, J. R. van Beijnum, A. Casini, A. A. Nazarov, G. Wagnieres, H. van den Bergh, P. J. Dyson, A. W. Griffioen, *J. Med. Chem.* **2011**, *54*, 3895-3902; h) M. Deckers, G. van der Pluijm, S. Dooijewaard, M. Kroon, V. van Hinsbergh, S. Papapoulos, C. Löwik, *Lab. Invest.* **2001**, *81*, 5-15; i) G. Colombo, B. Margosio, L. Ragona, M. Neves, S. Bonifacio, D. S. Annis, M. Stravalaci, S. Tomaselli, R. Giavazzi, M. Rusnati, *J. Biol. Chem.* **2010**, *285*, 8733-8742; j) J. Yatsunami, S. Hayashi, *Anticancer Res.* **2001**, *21*, 4253-4258; k) I. Sogno, N. Vannini, G. Lorusso, R. Cammarota, D. M. Noonan, L. Generoso, M. B. Sporn, A. Albini, in *Cancer prevention ii*, Springer, Amsterdam, **2009**, pp. 209-212; l) A. López-Jiménez, M. García-Caballero, M. A. Medina, A. R. Quesada, *Eur. J. Nut.* **2013**, *52*, 85-95; m) M. K. Shanmugam, S. Warriar, A. P. Kumar, G. Sethi, F. Arfuso, *Curr. Vasc. Pharmacol.* **2017**, *15*, 503-519; n) K. Senthilkumar, J. Venkatesan, P. Manivasagan, S. K. Kim, *Environ. Toxicol. Pharmacol.* **2013**, *36*, 1097-1108; o) R. Mukherjee, M. Jaggi, P. Rajendran, M. J. Siddiqui, S. K. Srivastava, A. Vardhan, A. C. Burman, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2181-2184.
- [4] a) S. J. Bakri, M. R. Snyder, J. M. Reid, J. S. Pulido, R. J. Singh, *Ophthalmol.* **2007**, *114*, 855-859; b) T. Shih, C. Lindley, *Clin. Ther.* **2006**, *28*, 1779-1802; c) F. Bock, J. Onderka, T. Dietrich, B. r. Bachmann, F. E. Kruse, M. Paschke, G. Zahn, C. Cursiefen, *Invest. Ophthalmol. Vis. Sci.* **2007**, *48*,

- 2545-2552; d) S. D. Zondor, P. J. Medina, *Ann. Pharmacother.* **2004**, *38*, 1258-1264; e) L. M. Ellis, P. Kirkpatrick, *Nat. Rev. Drug Discov.* **2005**, *4*, 51-54.
- [5] Y. Allory, S. Culine, A. De La Taille, *Pathobiology* **2011**, *78*, 90-98.
- [6] a) F. R. Hanson, T. E. Eble, *J. Bacteriol.* **1949**, *58*, 527; b) T. E. Eble, F. R. Hanson, *Antibiot. Chemothe.* **1951**, *1*, 54-58.
- [7] a) D. Ingber, T. Fujita, S. Kishimoto, K. Sudo, T. Kanamaru, H. Brem, J. Folkman, *Nature* **1990**, *348*, 555-557; b) J. Y. Kwon, H. W. Jeong, H. K. Kim, K. H. Kang, Y. H. Chang, K. S. Bae, J. D. Choi, U. C. Lee, K. H. Son, B. M. Kwon, *J. Antibiot.* **2000**, *53*, 799-806.
- [8] S. S. Jew, C. H. Yoo, D. Y. Lim, H. Kim, I. Mook-Jung, J. M. Whan, H. Choi, Y. H. Jung, H. Park, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1495-1495.
- [9] H. P. Sigg, H. P. Weber, *Helv. Chim. Acta* **1968**, *51*, 1395.
- [10] K. H. Son, J. Y. Kwon, H. W. Jeong, H. K. Kim, C. J. Kim, Y. H. Chang, J. D. Choi, B. M. Kwon, *Bioorg. Med. Chem.* **2002**, *10*, 185-188.
- [11] a) M. Hayashi, Y. P. Kim, S. Takamatsu, S. Preeprame, T. Komiyama, R. Masuma, H. Tanaka, K. Komiyama, S. Omura, *J. Antibiot.* **1996**, *49*, 631-634; b) S. Takamatsu, Y. P. Kim, T. Komiyama, T. Sunazuka, M. Hayashi, H. Tanaka, K. Komiyama, S. Omura, *J. Antibiot.* **1996**, *49*, 635-638.
- [12] a) E. C. Griffith, Z. Su, B. E. Turk, S. Chen, Y. H. Chang, Z. Wu, K. Biemann, J. O. Liu, *Chem. Biol.* **1997**, *4*, 461-471; b) N. Sin, L. Meng, M. Q. W. Wang, J. J. Wen, W. G. Bornmann, C. M. Crews, *Proc. Natl. Acad. Sci.* **1997**, *94*, 6099-6103.
- [13] Y. Asami, H. Kakeya, R. Onose, Y. H. Chang, M. Toi, H. Osada, *Tetrahedron* **2004**, *60*, 7085-7091.
- [14] Y. Asami, H. Kakeya, G. Okada, M. Toi, H. Osada, *J. Antibiot.* **2006**, *59*, 724-728.
- [15] H. Hantanaka, T. Kino, M. Hashimoto, Y. Tsurumi, A. Kuroda, H. Tanaka, T. Gato, M. Okuhara, *J. Antibiot.* **1988**, *41*, 999-1008.
- [16] N. Watanabe, Y. Nishihara, T. Yamaguchi, A. Koito, H. Miyoshi, H. Kakeya, H. Osada, *FEBS Lett.* **2006**, *580*, 2598-2602.
- [17] Y. Sun, Z. Zhao, Q. Feng, Q. Xu, L. Lü, J. K. Liu, L. Zhang, B. Wu, Y. Q. Li, *Helv. Chim. Acta* **2013**, *96*, 76-84.
- [18] a) D. A. Vosburg, S. Weiler, E. J. Sorensen, *Angew. Chem. Int. Ed.* **1999**, *38*, 971-974; b) D. A. Vosburg, S. Weiler, E. J. Sorensen, *Chirality* **2003**, *15*, 156-166.
- [19] J. G. Boiteau, P. Van de Weghe, J. Eustache, *Org. Lett.* **2001**, *3*, 2737-2740.
- [20] a) Y. Aoyagi, M. Yoshimura, M. Tsuda, T. Tsuchibuchi, S. Kawamata, H. Tateno, K. Asano, H. Nakamura, M. Obokata, A. Ohta, *J. Chem. Soc., Perkin Trans. 1* **1995**, 689-692; b) D. A. Evans, A. H. Hoveyda, *J. Am. Chem. Soc.* **1990**, *112*, 6447-6449.
- [21] B. A. Sparling, R. M. Moslin, T. F. Jamison, *Org. Lett.* **2008**, *10*, 1291-1294.
- [22] A. S. Kende, J. S. Mendoza, *Tetrahedron Lett.* **1991**, *32*, 1699-1702.
- [23] B. H. Lipshutz, M. Koerner, D. A. Parker, *Tetrahedron Lett.* **1987**, *28*, 945-948.
- [24] Q. Glenadel, Y. Nassar, L. Raffier, S. Veys, O. Piva, *Tetrahedron* **2018**, *74*, 5367-5373.
- [25] C. J. Chou, L. C. Lin, W. J. Tsai, S. Y. Hsu, L. K. Ho, *J. Nat. Prod.* **1997**, *60*, 375-377.

- [26] S. H. Kim, S. H. Sung, S. Y. Choi, Y. K. Chung, J. Kim, Y. C. Kim, *Org. Lett.* **2005**, *7*, 3275-3277.
- [27] a) O. A. Ekabo, N. R. Farnsworth, T. Santisuk, V. A. Reutrakul, *J. Nat. Prod.* **1993**, *56*, 699-707; b) B. Rasmussen, A. J. Nkurunziza, M. Witt, H. A. Oketch-Rabah, J. W. Jaroszewski, D. Stærk, *J. Nat. Prod.* **2006**, *69*, 1300-1304; c) S. H. Kim, Y. P. Jang, S. H. Sung, Y. C. Kim, *Planta Med.* **2007**, *73*, 167-169.
- [28] J. G. Mahdi, A. J. Mahdi, A. J. Mahdi, I. D. Bowen, *Cell Prolif.* **2006**, *39*, 147-155.
- [29] a) I. A. Pearl, S. F. Darling, *Tetrahedron Lett.* **1970**, *11*, 3827-3830; b) I. A. Pearl, S. F. Darling, *Phytochemistry* **1971**, *10*, 3161-3166.
- [30] T. Ishikawa, K. Nishigaya, K. Takami, H. Uchikoshi, I. S. Chen, I. L. Tsai, *J. Nat. Prod.* **2004**, *67*, 659-663.
- [31] A. M. Richardson, C. H. Chen, B. B. Snider, *J. Org. Chem.* **2007**, *72*, 8099-8102.
- [32] J. Christoffers, A. Baro, T. Werner, *Adv. Syn. Catal.* **2004**, *346*, 143-151.
- [33] a) S. N. Huckin, L. Weiler, *J. Am. Chem. Soc.* **1974**, *96*, 1082-1087; b) P. Deslongchamps, D. D. Rowan, N. Pothier, J. K. Saunders, *Can. J. Chem.* **1981**, *59*, 1122-1131; c) S. Benetti, R. Romagnoli, C. De Risi, G. Spalluto, V. Zanirato, *Chem. Rev.* **1995**, *95*, 1065-1114.
- [34] J. L. Luche, *J. Am. Chem. Soc.* **1978**, *100*, 2226-2227.
- [35] T. Harayama, K. Sakurai, K. Tanaka, Y. Hashimoto, H. Fukushi, Y. Inubushi, *Chem. Pharm. Bull.* **1987**, *35*, 1434-1442.

General Conclusion and Perspective

In conclusion, this thesis reports the synthesis of novel and intricate structures *via* photochemistry and cascade reactions. The use of photo-hydroxymethylation, along with other methodologies, to access α -(hydroxymethyl)cycloalkanols has been reviewed and applied on different terpenones and α -substituted β -ketoesters. The isolated products from the latter cyclic derivatives were found to undergo *in situ* lactonization providing bicyclic γ -lactones. These compounds were of high interest for the synthesis of diverse propellanes as detailed in chapters 3 and 4. For instance, from an allyl bicyclic γ -lactone, we reported the synthetic feasibility of highly functionalized [3,3,3]propellanes and [5,3,3]propellano-bislactone. However, from a propargyl bicyclic γ -lactone, the study was mainly focused on oxaspiro[*n*,3,3]propellanes, which have been categorized based on their number of annular atoms attached to the common propellane subunit. Besides the furnished oxaspiro[*n*,3,3]propellanes, other miscellaneous ring systems have been constructed from the same bicyclic building blocks, such as PTAD-based [6,4,3]propellane and iodo-DHP[4,3,3]propellane that can be used as future parent structures for further transformations. We have also achieved the synthesis of novel and complex hexahydroindeno[2,1-*c*]pyran-based [4,4,3]propellanes in only four or five steps from aldehydes and *exo*-olefinic alcohol derivatives *via* a Prins/Friedel-Crafts cascade annulation reaction. The reaction was optimized by analyzing different synthetic scenarios to ultimately reach a collection of indenopyran-based propellanes. Finally, we presented our attempts toward the total synthesis of cordycol, idesolide monomer and analogues. The final products were not attained, but we were able to isolate significant intermediates using photoinduced Michael-type radical addition, ring-closing metathesis and photo-deconjugation reaction as key steps. Further biological tests of the isolated products could be useful for promising applications.

Appendix

Appendix

1. Experimental part

1.1. General working methods

The analytical data were obtained with the help of the following types of equipment:

NMR spectroscopy: ^1H and ^{13}C NMR spectra were acquired on a Bruker Avance 300 (300 MHz), 400 (400 MHz), or 500 (500 MHz). in CDCl_3 as a solvent. The chemical shifts were reported relative to CDCl_3 ($\delta = ^1\text{H}$: 7.26 ppm, ^{13}C : 77.16 ppm). The multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, p = quintuplet, brd = broad. The spectra were evaluated with the software MestReNova.

Mass spectra: were obtained on an electrospray (ESI) (Spectromètre amaZon SL Bruker or Spectromètre QTOF Impact II - Bruker).

IR spectra: were measured on a JASCO FT/IR-4100 Spectrometer. Characteristic absorption bands are displayed in wavenumbers $\tilde{\nu}$ in cm^{-1} and were analyzed with the software Spectral Manager from JASCO.

Melting points: were measured on a B-540 from the company BÜCHI.

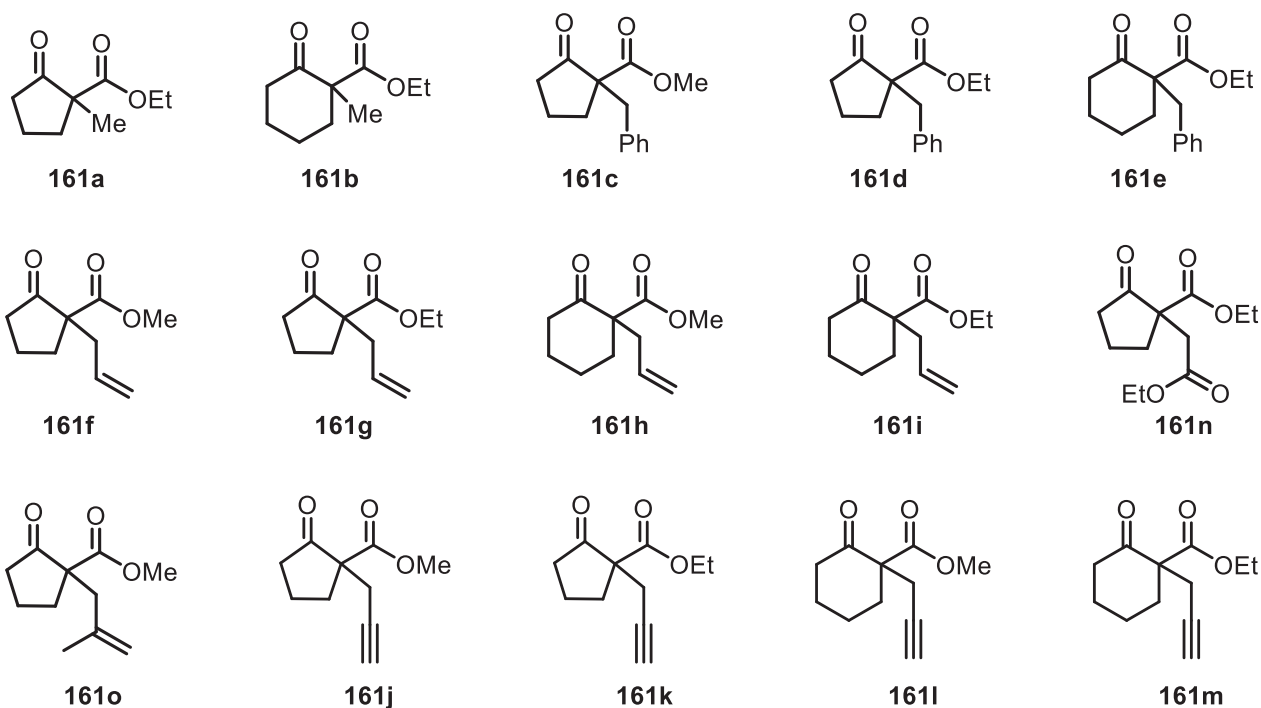
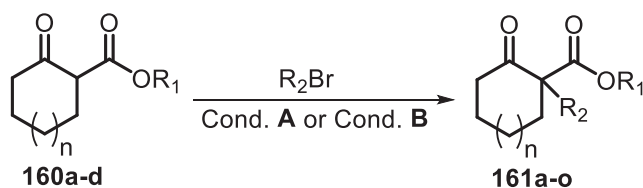
Chromatography: Reaction progress was monitored by thin-layer chromatography on aluminium backed silica gel plates (silica gel 60 with fluorescent indicator UV_{254} from Macherey-Nagel (MN)), visualizing with UV light ($\lambda = 254 \text{ nm}$). The plates were developed using KMnO_4 dip solution (3.0 g potassium permanganate, 5.0 mL NaOH-solution (5 w/w), 300 mL dest. water), cer dip solution (5.0 g phosphomolybdic acid, 16.0 mL conc. sulfuric acid, 200 mL dest. water, 2.0 g cer(IV)-sulfate) or an anisaldehyde solution (450 mL ethanol, 25.0 mL anisaldehyde, 25.0 mL conc. sulfuric acid, 8.0 mL acetic acid). Flash chromatography was performed using silica gel M60 from Macherey-Nagel (MN) (particle size: 40-63 μm).

Reagents and Solvents: Reactions with air or moisture-sensitive substances were, if not otherwise indicated, carried out under an argon atmosphere with the help of the Schlenk technique. All other reagents and solvents were used as purchased from commercial suppliers unless otherwise noted. Anhydrous solvents were purified with the solvent purification system PURE SOLV (Innovative Technology (it)). Water-free DMF was purchased from Acros Organics in AcroSeal-bottles under Argon atmosphere with molecular sieves (4 Å). The solvents (ethyl acetate, petroleum ether, pentane) used for column chromatography and workup were purified from commercially available

technical grade solvents by distillation under reduced pressure with the help of rotatory evaporators (BÜCHI) at 40 °C water bath temperature. Compound names are derived from Chemdraw and are not necessarily identical to the IUPAC nomenclature.

Chapter 2

❖ α -substituted β -ketoesters 161a-o



1.1.1. General procedure: Condition A

To a suspension of 60% sodium hydride in THF was added a solution of cyclic β -ketoesters in THF at 0 °C and the mixture was stirred for 3 hours. To this solution was added allyl bromide and then the mixture was stirred at room temperature for 3 hours. The reaction mixture was quenched by adding water, extracted with ether, washed with aqueous NaHCO_3 solution and then dried over

MgSO₄. Evaporation of the solvent gave a crude mixture, which was chromatographed on silica gel to give the desired product.^[1]

▪ Ethyl 1-methyl-2-oxocyclopentane-1-carboxylate **161a**

C₉H₁₄O₃ (170.21), colorless oil, yield: 83% (1.9 g isolated from ethyl cyclopentanonecarboxylate (2.1 g)). *R_f* = 0.350 (silica gel, Petroleum ether: EtOAc (95:5)). ¹H NMR (300 MHz, CDCl₃) δ 4.14 (q, *J* = 7.1 Hz, 2H), 2.58 – 2.22 (m, 3H), 2.11 – 1.78 (m, 3H), 1.29 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H). *Spectroscopic data matches that reported in the literature.*^[2]

▪ Ethyl 1-methyl-2-oxocyclohexane-1-carboxylate **161b**

C₁₀H₁₆O₃ (184.24), colorless oil; yield: 97% (2.1 g isolated from ethyl cyclohexanonecarboxylate (2.0 g)). *R_f* = 0.475 (silica gel, Petroleum ether: EtOAc (95:5)). ¹H NMR (300 MHz, CDCl₃) δ 4.24 – 4.15 (q, *J* = 7.1 Hz, 2H), 2.54 – 2.42 (m, 3H), 2.05 – 1.98 (m, 1H), 1.78 – 1.60 (m, 3H), 1.49 – 1.42 (m, 1H), 1.28 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H) ppm. *Spectroscopic data matches that reported in the literature.*^[3]

▪ Methyl 1-benzyl-2-oxocyclopentane-1-carboxylate **161c**

C₁₄H₁₆O₃ (232.28), pale yellow oil; yield: 77% (2.5 g isolated from methyl cyclopentanonecarboxylate (2.0 g)). *R_f* = 0.388 (silica gel, Petroleum ether: EtOAc (85:15)). ¹H NMR (300 MHz, CDCl₃) δ 7.36 – 7.07 (m, 5H), 3.74 (s, 3H), 3.24 (d, *J* = 12.2 Hz, 1H), 3.13 (d, *J* = 12.2 Hz, 1H), 2.52 – 2.31 (m, 2H), 2.15 – 2.82 (m, 3H), 1.70 – 1.53 (m, 1H). *Spectroscopic data matches that reported in the literature.*^[4]

▪ Ethyl 1-benzyl-2-oxocyclopentane-1-carboxylate **161d**

C₁₅H₁₈O₃ (246.31), colorless oil; yield: 90% (2.8 g isolated from ethyl cyclopentanonecarboxylate (2.0 g)). *R_f* = 0.353 (silica gel, Petroleum ether: EtOAc (90:10)). ¹H NMR (300 MHz, CDCl₃) δ 7.38–7.09 (m, 5H), 4.20 (q, *J* = 7.0 Hz, 2H), 3.25 (d, *J* = 13.6 Hz, 1H), 3.15 (d, *J* = 13.6 Hz, 1H), 2.5–2.3 (m, 2H), 2.13–1.83 (m, 3H), 1.70– 1.55 (m, 1H), 1.28 (t, *J* = 6.8 Hz, 3H). *Spectroscopic data matches that reported in the literature.*^[5]

▪ Ethyl 1-benzyl-2-oxocyclohexane-1-carboxylate **161e**

C₁₆H₂₀O₃ (260.33), colorless oil; yield: 75% (2.3 g isolated from ethyl cyclohexanonecarboxylate (2.0 g)). **R_f** = 0.413 (silica gel, Petroleum ether: EtOAc (90:10)). **¹H NMR** (300 MHz, CDCl₃) δ 7.18 (dd, *J* = 18.0, 6.7 Hz, 3H), 7.09 (d, *J* = 6.8 Hz, 2H), 4.06 (q, *J* = 6.8 Hz, 2H), 3.28 (d, *J* = 13.7 Hz, 1H), 2.85 (d, *J* = 13.7 Hz, 1H), 2.51–2.31 (m, 3H), 1.97 (m, 1H), 1.76–1.51 (m, 3H), 1.43 (m, 1H), 1.14 (t, *J* = 6.8 Hz, 3H). *Spectroscopic data matches that reported in the literature.*^[6]

▪ Methyl 1-allyl-2-oxocyclopentane-1-carboxylate **161f**

C₁₀H₁₄O₃ (182.22), colorless oil; yield: 69% (1.8 g isolated from methyl cyclopentanonecarboxylate (2.0 g)). **R_f** = 0.35 (silica gel, Petroleum ether: EtOAc (90:10)). **¹H NMR** (300 MHz, CDCl₃) δ 5.75–5.54 (m, 1H), 5.16–4.99 (m, 2H), 3.68 (s, 3H), 2.73–2.58 (m, 1H), 2.53–2.10 (m, 4H), 2.09–1.79 (m, 3H). *Spectroscopic data matches that reported in the literature.*^[1]

▪ Ethyl 1-allyl-2-oxocyclopentane-1-carboxylate **161g**

C₁₁H₁₆O₃ (196.25), pale yellow oil; yield: 62% (1.56 g isolated from Ethyl cyclopentanonecarboxylate (2 g)), **R_f** = 0.375 (silica gel, Petroleum ether: EtOAc (90:10)). **¹H NMR** (300 MHz, CDCl₃) δ = 5.68 (ddt, *J* = 16.5, 10.3, 7.3, 1H), 5.14–5.04 (m, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 2.65 (ddt, *J* = 13.9, 7.2, 1.2 Hz, 1H), 2.51–2.29 (m, 3H), 2.29–2.15 (m, 1H), 2.07–1.86 (m, 3H), 1.23 (t, *J* = 7.1 Hz, 3H). *Spectroscopic data matches that reported in the literature.*^[7]

▪ Methyl 1-allyl-2-oxocyclohexane-1-carboxylate **161h**

C₁₁H₁₆O₃ (196.25), colorless oil; yield: 53% (2.0 g isolated from methyl cyclohexanonecarboxylate (3.0 g)). **R_f** = 0.400 (silica gel, Petroleum ether: EtOAc (92:8)). **¹H NMR** (300 MHz, CDCl₃) δ = 5.73 (m, 1H), 5.04 (m, 1H), 4.99 (m, 1H), 3.69 (s, 3H), 2.59 (ddt, *J* = 13.9, 6.8, 1.2 Hz, 1H), 2.52–2.38 (m, 3H), 2.37–2.25 (ddt, *J* = 13.9, 8.0, 0.9 Hz, 1H), 2.05–1.92 (m, 1H), 1.81–1.53 (m, 3H), 1.52–1.38 (m, 1H). *Spectroscopic data matches that reported in the literature.*^[8]

▪ Ethyl 1-allyl-2-oxocyclohexane-1-carboxylate **161i**

C₁₂H₁₈O₃ (210.27), colorless oil; yield: 77% (1.9 g isolated from ethyl cyclohexanonecarboxylate (2 g)). **R_f** = 0.400 (silica gel, Petroleum ether: EtOAc (90:10)). **¹H NMR** (300 MHz, CDCl₃) δ = 5.57–5.66 (m, 1H), 5.01 (d, *J* = 9.5 Hz, 1H), 5.02 (d, *J* = 17.0 Hz, 1H), 4.08 (q, *J* = 7.0 Hz, 2H), 2.58 (dd, *J* = 13.5, 7.0 Hz, 1H), 2.26–2.40 (m, 3H), 2.12–2.19 (m, 1H), 1.82–1.99 (m, 3H), 1.17 (t, *J* = 7.0 Hz, 3H). *Spectroscopic data matches that reported in the literature.*^[9]

▪ Ethyl 1-(2-ethoxy-2-oxoethyl)-2-oxocyclopentane-1-carboxylate **161n**

C₁₂H₁₈O₅ (242.27), pale yellow oil; yield: 84% (2.6 g isolated from ethyl cyclopentanonecarboxylate (2.0 g)). $R_f = 0.388$ (silica gel, Petroleum ether: EtOAc (85:15)). ¹H NMR (300 MHz, CDCl₃) δ 4.16 (q, $J = 6.8$ Hz, 2H), 4.11 (q, $J = 7.0$ Hz, 2H), 2.97 (d, $J = 16.7$ Hz, 1H), 2.81 (d, $J = 16.7$ Hz, 1H), 2.63 – 4.36 (m, 3H), 2.19 – 1.94 (m, 3H), 1.23 (t, $J = 6.8$ Hz, 3H), 1.23 (t, $J = 7.0$ Hz, 3H). *Spectroscopic data matches that reported in the literature.*^[10]

▪ Methyl 1-(2-methylallyl)-2-oxocyclopentane-1-carboxylate **161o**

C₁₁H₁₆O₃ (196.25), colorless oil; yield: 85% (2.3 g isolated from methyl cyclopentanonecarboxylate (2.0 g)). $R_f = 0.363$ (silica gel, Petroleum ether: EtOAc (90:10)). ¹H NMR (300 MHz, CDCl₃) δ 4.84 (s, 1H), 4.70 (s, 1H), 3.71 (s, 3H), 2.83 (d, $J = 14.5$ Hz, 1H), 2.67 – 2.50 (m, 1H), 2.47 – 2.20 (m, 2H), 2.28 (d, $J = 14.5$ Hz, 1H), 2.07 – 2.83 (m, 3H) 1.64 (s, 3H). *Spectroscopic data matches that reported in the literature.*^[11]

1.1.2. General procedure: Condition B

To a suspension of potassium *tert*-butoxide (49.1 mmol, 1.2 equiv.) in *tert*-butanol (200.0 ml) was added a solution of the chosen cyclic β-ketoester (42.8 mmol, 1.0 equiv.) in *tert*-butanol at room temperature and the mixture was stirred for 30 minutes. To this solution was added propargyl bromide (80% in toluene) (49.1 mmol, 1.2 equiv.) and then the mixture was refluxed for 4 hours. The reaction mixture was quenched by adding water, extracted with ether, washed with aqueous NaHCO₃ solution, and then dried over MgSO₄. Evaporation of the solvent gave a crude mixture, which was chromatographed on silica gel to give the desired α-propargyl β-ketoester.^[12]

▪ Methyl 2-oxo-1-(prop-2-yn-1-yl)cyclopentane-1-carboxylate **161j**

C₁₀H₁₂O₃ (180.20), yellow oil; yield: 97% (8.4 g from methyl cyclopentanonecarboxylate (6.9 g)). $R_f = 0.375$ (silica gel, Petroleum ether: EtOAc (88:12)). ¹H NMR (300 MHz, CDCl₃) δ 3.71 (s, 3H), 2.71 (dd, $J = 2.6, 1.2$ Hz, 2H), 2.57 – 2.40 (m, 2H), 2.29 (m, 2H), 2.06 (m, 2H), 1.97 (t, $J = 2.7$ Hz, 1H). *Spectroscopic data matches that reported in the literature.*^[13]

▪ Ethyl 2-oxo-1-(prop-2-yn-1-yl)cyclopentane-1-carboxylate **161k**

C₁₁H₁₄O₃ (194.23), yellow oil; yield: 97% (4.8 g from ethyl cyclopentanonecarboxylate (4.0 g)). $R_f = 0.350$ (silica gel, Petroleum ether: EtOAc (92:8)). ¹H NMR (300 MHz, CDCl₃) δ 4.16 (q, $J = 7.1$ Hz, 2H), 2.71 (dd, $J = 2.7, 1.5$ Hz, 2H), 2.57 – 2.40 (m, 2H), 2.37 – 2.18 (m, 2H), 2.18 – 1.99

(m, 2H), 1.97 (t, $J = 2.7$ Hz, 1H), 1.25 (t, $J = 7.1$ Hz, 3H). *Spectroscopic data matches that reported in the literature.*^[14]

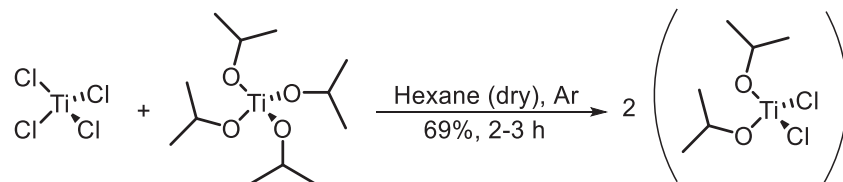
▪ Methyl 2-oxo-1-(prop-2-yn-1-yl)cyclohexane-1-carboxylate **161l**

$C_{11}H_{14}O_3$ (194.23), yellow oil; yield: 76% (1.9 g from methyl cyclohexanonecarboxylate (2.0 g)). $R_f = 0.35$ (silica gel, Petroleum ether: EtOAc (90:10)). 1H NMR (300 MHz, $CDCl_3$) δ 3.71 (s, 3H), 2.70 (d, $J = 2.7$ Hz, 2H), 2.85 – 2.14 (m, 4H), 2.03 (t, $J = 2.7$ Hz, 1H), 1.91 – 1.45 (m, 4H). *Spectroscopic data matches that reported in the literature.*^[15]

▪ Ethyl 2-oxo-1-(prop-2-yn-1-yl)cyclohexane-1-carboxylate **161m**

$C_{12}H_{16}O_3$ (208.26), colourless oil; yield: 85% (4.2 g from ethyl cyclohexanonecarboxylate (4.0 g)). $R_f = 0.378$ (silica gel, Petroleum ether: EtOAc (95:5)). 1H NMR (400 MHz, $CDCl_3$) δ 4.24 (q, $J = 7.1$ Hz, 2H), 2.82 – 2.71 (dd, $J = 17.0, 2.7$ Hz, 1H), 2.70 (dq, $J = 13.7, 3.3$ Hz, 1H), 2.58 (dd, $J = 17.0, 2.7$ Hz, 1H), 2.48 (m, 2H), 2.14 – 1.98 (m, 2H), 1.83 (m, 2H), 1.74 – 1.56 (m, 2H), 1.29 (t, $J = 7.1$ Hz, 3H). *Spectroscopic data matches that reported in the literature.*^[16]

❖ Dichlorotitanium diisopropoxide $TiCl_2(OiPr)_2$

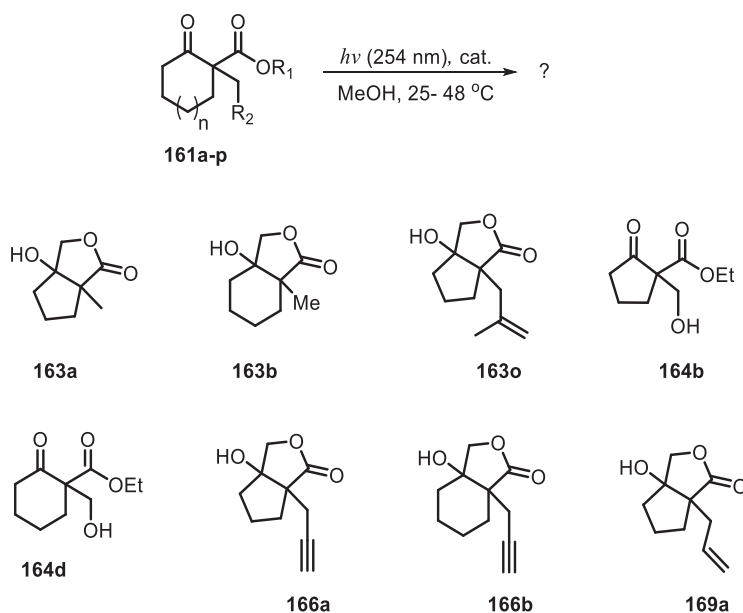


Preparation: The reagent can either be obtained commercially or prepared by the reaction of $TiCl_4$ and $Ti(OiPr)_4$. As the quality of commercially supplied $TiCl_2(OiPr)_2$ can be variable, it is recommended to prepare the reagent freshly. To a solution of distilled $Ti(OiPr)_4$ (6.4 mL, 21.0 mmol, 1.1 equiv.) in a flame-dried Schlenk flask under an atmosphere of dry N_2 was added dry hexanes (20.0 mL), followed by the dropwise addition of $TiCl_4$ (2.2 mL, 20.0 mmol, 1.0 equiv.) at room temperature. The warm solution was stirred for 15 minutes then left for crystallization (usually 2–3 hours). The colorless crystals were separated from the supernatant liquid by decantation under a stream of dry N_2 and washed with dry hexanes (5×2 mL). Drying in vacuum afforded the title compound (6.5 g, 69% yield) as colorless crystals. $TiCl_2(OiPr)_2$ can be handled on-air for weighing and can be kept in a closed container for several months without loss in

performance. Upon extended exposure to moisture, crystals of $\text{TiCl}_2(\text{OiPr})_2$ turn from a sticky paste into a liquid.^[17]

❖ *Titanium-catalyzed photochemical hydroxymethylation*

General procedure: Argon gas was passed through a solution of the chosen α -propargyl β -ketoester (5.2 mmol, 1.0 equiv.) in methanol (51.5 ml) containing titanium (IV) catalyst ($\text{TiCl}_2(\text{OiPr})_2$) (2.6 mmol, 0.5 equiv.) for 15 min. The degassed solution was irradiated with UV light (254 nm) for 48-72 h at 40-48°C. After irradiation, the solution was concentrated, poured into water, and extracted four times with ethyl acetate. The organic phase was dried over MgSO_4 and the solvent was removed under reduced pressure. The residual was purified via column chromatography.^[18]



▪ 3a-hydroxy-6a-methylhexahydro-1H-cyclopenta[c]furan-1-one **163a**

$\text{C}_8\text{H}_{12}\text{O}_3$ (156.18), colourless oil (volatile); yield: ~7% (16 mg isolated from **161a** (255 mg)). $R_f = 0.275$ (silica gel, Petroleum ether: EtOAc (6:40)). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 4.17 (d, $J = 7.0$ Hz, 1H), 4.13 (d, $J = 7.0$ Hz, 1H), 2.93 (brd, 1H), 1.94 – 1.55 (m, 6H), 1.15 (s, 3H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 182.7, 84.4, 77.56, 55.4, 40.6, 38.0, 22.6, 17.1.

▪ 3a-hydroxy-7a-methylhexahydroisobenzofuran-1(3*H*)-one **163b**

C₉H₁₄O₃ (170.21), colourless oil (volatile); yield: 5-10% (12-25 mg from **161b** (276 mg)). *R_f* = 0.275 (silica gel, Petroleum ether: EtOAc (65:35)). ¹H NMR (300 MHz, CDCl₃) δ 4.24 (d, *J* = 9.6 Hz, 1H), 4.05 (d, *J* = 9.6 Hz, 1H), 2.11 (brd, 1H), 1.86 – 1.31 (m, 8H), 1.21 (s, 3H).

▪ 3a-hydroxy-6a-(2-methylallyl)hexahydro-1*H*-cyclopenta[*c*]furan-1-one **163o**

C₁₁H₁₆O₃ (196.25), colorless oil; yield: 12% (~35 mg from **161o** (294 mg)). *R_f* = 0.325 (silica gel, Petroleum ether: EtOAc (70:30)). ¹H NMR (300 MHz, CDCl₃) δ 4.95 (s, 1H), 4.90 (s, 1H), 4.28 (d, *J* = 9.8 Hz, 1H), 4.09 (d, *J* = 9.8 Hz, 1H), 2.74 (d, *J* = 14.2 Hz, 1H), 2.64 (d, *J* = 14.2 Hz, 1H), 2.31 – 1.63 (m, 6H), 1.66 (s, 3H).

▪ Ethyl 1-(hydroxymethyl)-2-oxocyclopentane-1-carboxylate **164b**

C₉H₁₄O₄ (186.21), colourless oil; yield: 41% (115 mg from ethyl cyclopentanonecarboxylate (234 mg)). *R_f* = 0.375 (silica gel, Petroleum ether: EtOAc (60:40)). ¹H NMR (300 MHz, CDCl₃) δ 4.18 (q, *J* = 6.7 Hz, 2H), 3.95-3.78 (m, 2H), 3.03 (br s, 1H), 2.57-1.95 (m, 6H), 1.25 (t, *J* = 6.7 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 214.9, 171.1, 89.9, 63.4, 61.6, 61.4, 38.3, 30.7, 19.5, 13.8 ppm. *Spectroscopic data matches that reported in the literature.*^[19]

▪ Ethyl 1-(hydroxymethyl)-2-oxocyclohexane-1-carboxylate **164d**

C₁₀H₁₆O₄ (200.23), colourless oil; yield: 38% (114 mg from ethyl cyclohexanonecarboxylate (225 mg)). *R_f* = 0.375 (silica gel, Petroleum ether: EtOAc (65:35)). ¹H NMR (400 MHz, CDCl₃) δ 4.24 (q, *J* = 7.1 Hz, 2 H), 3.82, 3.69 (AB, *J* = 11.4 Hz, 2 H), 2.23-2.93 (m, 4H), 1.95-2.12 (m, 1 H), 1.40-1.84 (m, 4H), 1.28 (t, *J* = 7.1 Hz, 3 H). ¹³C NMR (101 MHz, CDCl₃) 211.3, 171.5, 66.5, 62.5, 61.7, 40.9, 32.7, 26.8, 21.8, 14.0. *Spectroscopic data matches that reported in the literature.*^[20]

▪ 3a-hydroxy-6a-(prop-2-yn-1-yl)hexahydro-1*H*-cyclopenta[*c*]furan-1-one **166a**

C₁₀H₁₂O₃ (180.20), pale orange oil; yield: 12% (520 mg from **161j** (4.81 g)). *R_f* = 0.35 (silica gel, Petroleum ether: EtOAc (64:36)). ¹H NMR (500 MHz, CDCl₃) δ 4.32 (d, *J* = 9.9 Hz, 1H), 4.24 (d, *J* = 9.9 Hz, 1H), 2.70 (dd, *J* = 16.9, 2.7 Hz, 1H), 2.60 (dd, *J* = 16.9, 2.7 Hz, 1H), 2.55 (s, 1H), 2.22 (t, *J* = 2.7 Hz, 1H), 2.22 – 2.10 (m, 2H), 2.08 – 1.94 (m, 2H), 1.90 – 1.80 (m, 1H), 1.54 – 1.40 (m, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 180.0, 84.8, 80.6, 78.5, 72.0, 54.6, 42.2, 36.2, 22.4, 21.7. **HRMS** (ESI): *m/z* [M + Na]⁺ calcd for C₁₀H₁₂NaO₃ : 203.0679; found 203.0672.

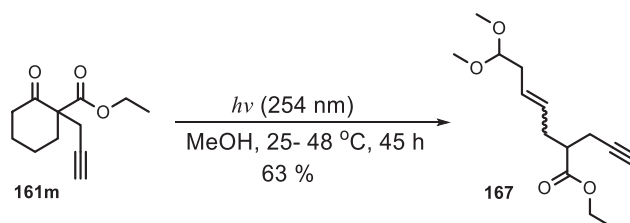
- 3a-hydroxy-7a-(prop-2-yn-1-yl)hexahydroisobenzofuran-1(3H)-one **166b**

$C_{11}H_{14}O_3$ (194.23), yellow-orange oil; yield: 21% (782 mg from **161I** (4.0 g)). $R_f = 0.288$ (silica gel, Petroleum ether: EtOAc (65:35)). 1H NMR (300 MHz, $CDCl_3$) δ 4.17 (d, $J = 9.6$ Hz, 1H), 4.06 (d, $J = 9.6$ Hz, 1H), 2.62 – 2.52 (d, $J = 2.8$ Hz, 2H), 2.50 (brd, 1H), 2.09 (t, $J = 2.8$ Hz, 1H), 2.02 – 1.52 (m, 6H), 1.52 – 1.24 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.8, 80.4, 76.9, 74.1, 72.4, 47.9, 32.8, 31.0, 22.4, 20.8, 20.7. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{11}H_{14}NaO_3$: 217.0835; found 217.0838.

- 6a-allyl-3a-hydroxyhexahydro-1H-cyclopenta[c]furan-1-one **169a**

$C_{10}H_{14}O_3$ (182.22), yellow oil; yield: 32% (0.174 g isolated from **161f** (0.546 g)). $R_f = 0.400$ (silica gel, Petroleum ether: EtOAc (65:35)). 1H NMR (300 MHz, $CDCl_3$) δ 5.92 (dddd, $J = 17.0, 10.1, 7.8, 6.8$ Hz, 1H), 5.34 – 5.12 (m, 2H), 4.23 (d, $J = 9.7$ Hz, 1H), 4.11 (d, $J = 9.7$ Hz, 1H), 2.64 – 2.40 (m, 2H), 2.22 – 2.01 (m, 2H), 1.96 – 1.71 (m, 3H), 1.66 – 1.32 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.6, 133.8, 119.5, 84.9, 77.5, 55.6, 42.5, 36.6, 36.4, 22.8. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{10}H_{14}NaO_3$: 205.0835; found 205.0830.

- *Uncatalyzed photochemical hydroxymethylation*



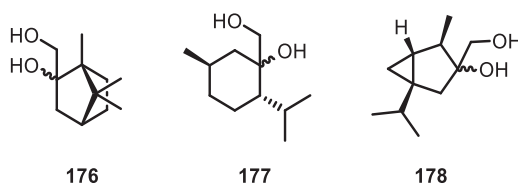
Procedure: Argon gas was passed through a solution of the chosen α -propargyl β -ketoester **161m** (1.5 mmol, 1.0 equiv.) in methanol (15 ml) for 15 min. The degassed solution was irradiated with UV light (254 nm) for 45 h at 40 °C. After irradiation, the solution was concentrated, poured into water, and extracted four times with ethyl acetate. The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residual was purified via column chromatography.^[18]

- Ethyl 7,7-dimethoxy-2-(prop-2-yn-1-yl)hept-4-enoate **167**

$C_{14}H_{22}O_4$ (254.15), pale yellow oil; yield: 63% (240 mg from **161m** (312 g)). $R_f = 0.775$ (silica gel, Petroleum ether: EtOAc (65:35)). *E*-isomer: 1H NMR (300 MHz, $CDCl_3$) δ 5.72 – 5.53 (dt, $J = 15.41, 6.42$ Hz, 1H), 5.53 – 5.32 (dt, $J = 15.41, 8.16$ Hz, 1H), 4.37 – 4.32 (t, $J = 5.72$ Hz, 1H),

4.21 – 4.06 (q, $J = 7.18$ Hz, 2H), 3.30 – 3.27 (s, 6H), 3.22 – 3.09 (q, $J = 7.21$ Hz, 1H), 2.65 – 2.34 (m, 2H), 2.22 – 2.03 (m, 2H), 1.96 (t, $J = 2.54$ Hz, 1H), 1.73 – 1.59 (m, 2H), 1.32 – 1.15 (t, $J = 7.18$ Hz, 3H). *Z*-isomer: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 5.72 – 5.53 (m, 1H), 5.53 – 5.32 (m, 1H), 4.37 – 4.32 (t, $J = 3.45$ Hz, 1H), 4.21 – 4.06 (q, $J = 7.18$ Hz, 2H), 3.60 – 3.48 (m, 1H), 3.32 – 3.29 (s, 6H), 2.65 – 2.34 (m, 2H), 2.22 – 2.03 (m, 2H), 1.96 (t, $J = 2.54$ Hz, 1H), 1.73 – 1.59 (m, 2H), 1.32 – 1.15 (t, $J = 7.18$ Hz, 3H). *E*-isomer: $^{13}\text{C NMR}$ (76 MHz, CDCl_3) δ 172.7, 133.5, 126.4, 103.8, 81.2, 69.9, 60.8, 52.7, 48.0, 31.8, 27.5, 21.9, 14.1. *Z*-isomer: $^{13}\text{C NMR}$ (76 MHz, CDCl_3) δ 172.5, 133.0, 126.2, 103.8, 81.2, 69.8, 60.9, 52.6, 43.1, 32.1, 22.9, 21.9, 14.1. **HRMS** (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{14}\text{H}_{22}\text{NaO}_4$: 277.1410; found 277.1409.

❖ Photochemical hydroxymethylation of various terpenoids



(The same procedure as previously described)

▪ (1*R*,2*S*)-2-(Hydroxymethyl)-1,7,7-trimethyl-bicyclo[2.2.1]heptan-2-ol **176**

$\text{C}_{11}\text{H}_{20}\text{O}_2$ (184.28), white solid; yield: 8% (26 mg isolated from (+)-camphor (153 mg)). $R_f = 0.357$ (silica gel, Petroleum ether: EtOAc (60:40)). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 80.52, 69.31, 52.09, 49.30, 44.45, 42.46, 29.58, 26.82, 21.55, 21.23, 10.91. *Spectroscopic data matches that reported in the literature.*^[21]

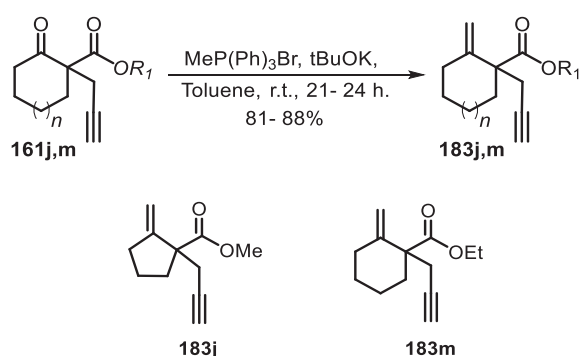
▪ (2*S*,5*R*)-1-(hydroxymethyl)-2-isopropyl-5-methylcyclohexan-1-ol **177**

$\text{C}_{11}\text{H}_{22}\text{O}_2$ (186.30), colorless solid; yield: 54% of **177'**/**177''** (7.1:1.0) (131 mg isolated from menthone (200 mg)). **177'**: $R_f = 0.413$ (silica gel, Pentane: EtOAc (73:27)). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 3.72 (d, $J = 10.9$ Hz, 1H), 3.43 (d, $J = 10.9$ Hz, 1H), 2.15 – 1.98 (m, 1H), 1.87 – 1.35 (m, 9H), 1.23 – 1.10 (m, 1H), 1.07 – 0.76 (m, 9H). $^{13}\text{C NMR}$ (76 MHz, CDCl_3) δ 76.9, 59.1, 53.9, 46.9, 35.0, 32.4, 30.1, 24.8, 24.7, 24.0, 22.3, 19.4. **177''**: $R_f = 0.225$ (silica gel, Pentane: EtOAc (73:27)). $^{13}\text{C NMR}$ (76 MHz, CDCl_3) δ 77.1, 59.6, 48.2, 43.4, 41.0, 30.9, 29.0, 25.9, 25.4, 22.7, 22.1, 20.8. *Spectroscopic data matches that reported in the literature.*^[22]

▪ (1*S*,4*R*,5*R*)-3-(hydroxymethyl)-1-isopropyl-4-methylbicyclo[3.1.0]hexan-3-ol **178**

$C_{11}H_{20}O_2$ (184.28), pale-yellow oil; yield: 20% (one isomer) (48 mg isolated from Thuyone (200 mg)). $R_f = 0.250$ (silica gel, Petroleum ether: EtOAc (70:30)). 1H NMR (300 MHz, $CDCl_3$) δ 3.42 (d, $J = 10.9$ Hz, 1H), 3.36 (d, $J = 10.9$ Hz, 1H), 2.05 – 1.54 (m, 7H), 1.37 – 1.17 (m, 2H), 1.12 – 0.72 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 86.4, 70.0, 43.6, 41.5, 33.7, 33.4, 30.2, 22.6, 20.2, 19.9, 15.5.

❖ Olefinic esters **183j,m**



General Procedure: To a well-stirred suspension of methyltriphenylphosphonium bromide (5.5 mmol, 2.0 equiv.) in anhydrous toluene (12.0 ml), under argon, was added *t*-BuOK (5.5 mmol, 2.0 equiv.). The mixture was stirred at room temperature for one hour, then a solution of the chosen α -propargyl β -ketoester (2.8 mmol, 1.0 equiv.) in toluene was added dropwise. The mixture was kept stirring for 20-23 hours. After being poured to cold ether/water (1:1), the mixture was extracted by EtOAc, washed, dried, and chromatographed on silica gel to give the desired olefinic esters **183j,m**.^[23]

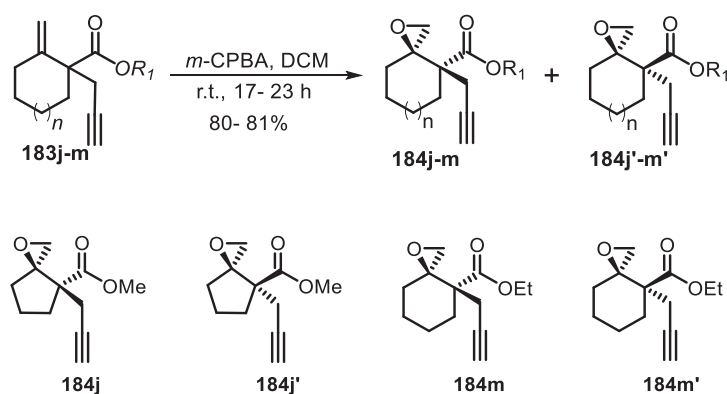
▪ Methyl 2-methylene-1-(prop-2-yn-1-yl)cyclopentane-1-carboxylate **183j**

$C_{11}H_{14}O_2$ (178.23), pale yellow oil; yield: 81% (0.398 mg from **161j** (0.500 g)). $R_f = 0.675$ (silica gel, Petroleum ether: EtOAc (80:20)). 1H NMR (400 MHz, $CDCl_3$) δ 5.06 (t, $J = 2.1$ Hz, 1H), 5.04 (t, $J = 2.1$ Hz, 1H), 3.70 (s, 3H) 2.77 (dd, $J = 16.7, 2.6$ Hz, 1H), 2.50 – 2.42 (dd, $J = 16.7, 2.6$ Hz, 1H), 2.46 – 2.35 (m, 3H), 1.97 (m, 1H), 1.93 (t, $J = 2.6$ Hz, 1H), 1.90 – 1.78 (m, 1H), 1.72 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7, 153.8, 108.0, 81.6, 69.3, 55.4, 52.3, 35.4, 34.0, 27.9, 24.1. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{11}H_{14}NaO_2$: 201.0886; found 201.0894.

▪ Ethyl 2-methylene-1-(prop-2-yn-1-yl)cyclohexane-1-carboxylate **183m**

$C_{13}H_{18}O_2$ (206.29), yellow oil; yield: 88% (0.871 g from **161m** (1 g)). $R_f = 0.788$ (silica gel, Petroleum ether: EtOAc (80:20)). 1H NMR (300 MHz, $CDCl_3$) δ 4.93 (s, 1H), 4.83 (s, 1H), 4.20 (q, $J = 7.0$ Hz, 2H), 2.71 (dd, $J = 16.5, 2.5$ Hz, 1H), 2.55 (dd, $J = 16.5, 2.5$ Hz, 1H), 2.30 (m, 2H), 2.18 – 2.05 (m, 1H), 2.03 (t, $J = 2.5$ Hz, 1H), 1.78 – 1.56 (m, 3H), 1.53 – 1.31 (m, 2H), 1.26 (t, $J = 7.0$ Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 148.3, 109.2, 80.3, 71.1, 60.9, 52.4, 35.0, 34.5, 27.8, 26.8, 22.9, 14.2. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{13}H_{18}NaO_2$: 229.119901; found 229.119978.

▪ Spiroepoxides **184j-j'** and **184m-m'**



General Procedure: *m*-CPBA (3.4 mmol, 3.0 equiv.) has been added in one portion to a solution of the chosen olefinic ester (1.1 mmol, 1.0 equiv.) at room temperature in DCM (12.0 ml). The resulting solution has been kept stirring for 17-23 hours before its classical work up.^[24]

▪ Methyl 4-(prop-2-yn-1-yl)-1-oxaspiro[2.4]heptane-4-carboxylate **184j-j'**

$C_{11}H_{14}O_3$ (194.23), pale yellow oil; yield: 81% (175 mg from **183j** (200 mg)). $R_f(2 \text{ diastereoisomers}) = 0.375$ (silica gel, Petroleum ether: EtOAc (90:10)). The ratio of the two inseparable diastereoisomers **184j/184j'** is 2.3:1. **184j**: 1H NMR (300 MHz, $CDCl_3$) δ 3.65 (s, 3H), 2.82 (d, $J = 4.6$ Hz, 1H), 2.78 (d, $J = 4.6$ Hz, 1H), 2.46 – 2.36 (dd, $J = 16.9, 2.7$ Hz, 1H), 2.33 – 2.23 (dd, $J = 16.9, 2.7$ Hz, 1H), 2.15 – 1.84 (m, 4H), 1.89 – 1.85 (t, $J = 2.7$ Hz, 1H) 1.82 – 1.63 (m, 2H). **184j'**: 1H NMR (300 MHz, $CDCl_3$) δ 3.64 (s, 3H), 2.88 (d, $J = 4.3$ Hz, 1H), 2.74 (d, $J = 4.3$ Hz, 1H), 2.56 (dd, $J = 16.8, 2.8$ Hz, 1H), 2.39 (dd, $J = 16.8, 2.8$ Hz, 1H), 2.14 – 1.92 (m, 4H), 1.89 (t, $J = 2.8$, Hz, 1H), 1.83 – 1.64 (m, 2H). **184j**: ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6, 79.3,

67.6, 65.2, 51.7, 50.3, 48.6, 33.7, 31.4, 20.4, 20.0. **184j'**: ^{13}C NMR (126 MHz, CDCl_3) δ 170.2, 78.6, 68.1, 66.0, 52.3, 50.2, 47.7, 31.7, 31.0, 22.8, 20.2. **HRMS** (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{11}\text{H}_{14}\text{NaO}_3$: 217.0111; found 217.0123.

▪ Ethyl (3*S*,4*R*)-4-(prop-2-yn-1-yl)-1-oxaspiro[2.5]octane-4-carboxylate **184m**

$\text{C}_{13}\text{H}_{18}\text{O}_3$ (222.28), colourless oil; yield: 50% (0.755 g from **183m** (1.0 g)). R_f = 0.650 (silica gel, Petroleum ether: EtOAc (90:10)). ^1H NMR (300 MHz, CDCl_3) δ 4.22 (q, J = 7.1 Hz, 2H), 3.18 (d, J = 4.0 Hz, 1H), 2.59 (d, J = 4.0 Hz, 1H), 2.41 (dd, J = 16.8, 2.7 Hz, 1H), 2.36 – 2.25 (m, 1H), 2.21 (dd, J = 16.8, 2.7 Hz, 1H), 2.03 – 1.9 (t, J = 2.7 Hz, 1H), 2.03 – 1.86 (m, 1H), 1.77 – 1.37 (m, 6H), 1.28 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 172.9, 80.2, 71.1, 60.9, 59.5, 52.2, 50.1, 32.9, 32.7, 23.3, 23.1, 22.9, 14.2. **HRMS** (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{13}\text{H}_{18}\text{NaO}_3$: 245.1148; found 245.1148.

▪ Ethyl (3*R*,4*R*)-4-(prop-2-yn-1-yl)-1-oxaspiro[2.5]octane-4-carboxylate **184m'**

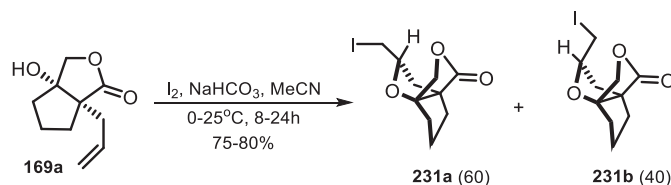
$\text{C}_{13}\text{H}_{18}\text{O}_3$, (222.28), white solid; yield: 30% (0.38 g from **183m** (1.0 g)). R_f = 0.525 (silica gel, Petroleum ether: EtOAc (90:10)). ^1H NMR (300 MHz, CDCl_3) δ 4.21 (q, J = 7.1 Hz, 2H), 3.02 (d, J = 4.3 Hz, 1H), 2.65 (dd, J = 16.6, 2.7 Hz, 1H), 2.48 (d, J = 4.3 Hz, 1H), 2.48 – 2.30 (dd, J = 16.6, 2.7 Hz, 1H), 2.01 (t, J = 2.7 Hz, 1H), 1.86 – 1.41 (m, 8H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 172.4, 79.7, 71.1, 61.0, 59.9, 50.4, 50.2, 32.4, 31.4, 24.4, 23.1, 21.6, 14.1. **HRMS** (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{13}\text{H}_{18}\text{NaO}_3$: 245.1148; found 245.1148.

▪ Epoxide opening of **184j,m**

To a suspension of the chosen spiroepoxide (0.8 mmol, 1.0 equiv.) in $\text{H}_2\text{O}:\text{CH}_2\text{Cl}_2$ (1:1) (6.0 mL) was added HCl (15 mol%) at 70 °C for 4-5 h. After completion, the mixture was extracted with EtOAc, washed with brine, dried over MgSO_4 , and then concentrated to give the crude product. Purification by silica gel flash column chromatography provided the desired bicyclic lactone.^[25] **166a**: 64% yield (66 mg isolated from **184j** (110 mg)). **166b**: 70% yield (107 mg isolated from **184m** (175 mg)).

Chapter 3

❖ Iodoetherification



General Procedure: Iodine (2.39g, 9.45 mmol) was added in one portion to a solution of alcohol **169a** (0.572g, 3.124 mmol) and sodium hydrogen carbonate (0.82, 9.88 mmol) in acetonitrile (80 mL) at room temperature. The mixture was stirred in the dark for 24 h before quenching with an aqueous saturated solution of sodium thiosulfate (20 mL). The acetonitrile was removed under reduced pressure and the residue partitioned between ethyl acetate (20 mL) and water (20 mL). The aqueous phase was further extracted with ethyl acetate and the combined organic extracts dried with $MgSO_4$, filtered, and concentrated. The crude residue was purified by flash chromatography to give the two iodinated cyclized diastereoisomers **231a** and **231b** (60:40) of 75% yield.^[26]

- (2*R*,3*aS*)-2-(iodomethyl)tetrahydro-4*H*-3*a*,6*a*-(methanooxymethano)cyclopenta[*b*]furan-9-one **231a**

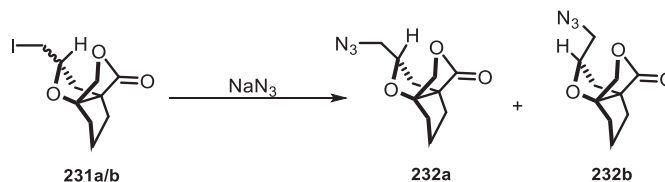
$C_{10}H_{13}IO_3$ (308.12), white solid; yield: 45% (0.436 g isolated from **169a** (0.572 g)). $R_f = 0.388$ (silica gel, Petroleum ether: EtOAc (75:25)). 1H NMR (300 MHz, $CDCl_3$) δ 4.38 (d, $J = 10.6$ Hz, 1H), 4.29 (d, $J = 10.6$ Hz, 1H), 3.86 (dq, $J = 10.0, 5.0$ Hz, 1H), 3.32 (m, 2H), 2.64 (dd, $J = 12.9, 5.0$ Hz, 1H), 2.21 (dd, $J = 12.6, 5.4$ Hz, 1H), 2.04 (dd, $J = 14.0, 3.7$ Hz, 3H), 1.95 – 1.68 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.0, 97.7, 79.4, 78.2, 61.9, 44.5, 39.1, 3.4, 27.4, 7.0. HRMS (ESI): m/z [$M + Na^+$] calcd for $C_{10}H_{13}INaO_3$: 330.9802; found 330.9787.

- (2*S*,3*aS*)-2-(iodomethyl)tetrahydro-4*H*-3*a*,6*a*-(methanooxymethano)cyclopenta[*b*]furan-9-one **231b**

$C_{10}H_{13}IO_3$ (308.12), yellow liquid; yield: 30% (0.288 g isolated from **169a** (0.572 g)) $R_f = 0.363$ (silica gel, Petroleum ether: EtOAc (75:25)). 1H NMR (300 MHz, $CDCl_3$) δ 4.55 – 4.46 (dd, $J = 10.3, 2.5$ Hz, 1H), 4.56 – 4.45 (m, 1H), 4.23 – 4.13 (dd, $J = 10.3, 2.4$ Hz, 1H), 3.25 (d, $J = 5.6$ Hz, 2H), 2.29 (m, 2H), 2.07 – 1.73 (m, 5H), 1.57 (ddd, $J = 6.9, 6.1, 4.3$ Hz, 1H). ^{13}C NMR (101 MHz,

CDCl₃) δ = 179.9, 98.0, 80.9, 77.6, 61.8, 43.8, 37.7, 36.1, 26.3, 7.0. **HRMS** (ESI): m/z [M+ Na⁺] calcd for C₁₀H₁₃INaO₃ : 330.9802; found 330.9797.

❖ **Preparation of azido[3,3,3]propellanes 232a and 232b**



231a (0.5g, 1.62 mmol) was dissolved in DMF (80 ml) and NaN₃ (1g, 16.2 mmol) was added to the mixture. After stirring for 15 h at 60 °C, ethyl acetate (60 mL) was added. The organic phase was washed three times with a saturated solution of ammonium chloride (30 mL) and a saturated NaCl solution (30 mL). The organic layer was then dried over MgSO₄, filtered, concentrated, and then chromatographed over silica gel to give the title compound **232a**. A similar procedure was then used to prepare **232b**.^[27]

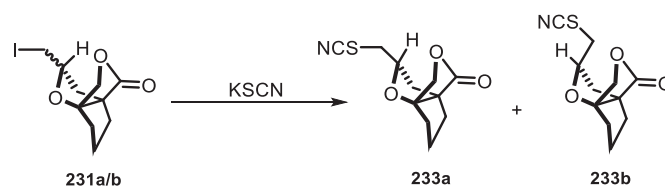
- (2*R*,3*aS*)-2-(azidomethyl)tetrahydro-4*H*-3*a*,6*a*-(methanooxymethano)cyclopenta[*b*]furan-9-one **232a**

C₁₀H₁₃N₃O₃ (223.23), white solid; yield: 86% (0.311 g isolated from **231a** (0.500 g)), R_f = 0.378 (silica gel, Petroleum ether:EtOAc (75:25)). ¹H NMR (300 MHz, CDCl₃) δ 4.36 (d, J = 10.6 Hz, 1H), 4.28 (d, J = 10.6 Hz, 1H), 4.15 (m, 1H), 3.57 (dd, J = 13.3, 3.2 Hz, 1H), 3.21 (dd, J = 13.3, 4.8 Hz, 1H), 2.46 (dd, J = 12.9, 5.2 Hz, 1H), 2.26 – 2.09 (m, 1H), 2.09 – 1.72 (m, 6H). ¹³C NMR (75 MHz, CDCl₃) δ 180.02, 97.62, 79.86, 78.06, 61.77, 52.37, 40.49, 39.09, 36.35, 27.35. **HRMS** (ESI): m/z [M + Na⁺] calcd for C₁₀H₁₃N₃NaO₃ : 246.0849 ; found 246.0841

- (2*S*,3*aS*)-2-(azidomethyl)tetrahydro-4*H*-3*a*,6*a*-(methanooxymethano)cyclopenta[*b*]furan-9-one **232b**

C₁₀H₁₃N₃O₃ (223.23), pale-yellow oil; yield: 76% (0.106 g isolated from **231b** (0.192 g)). R_f = 0.338 (silica gel, Petroleum ether: EtOAc (73:27)). ¹H NMR (300 MHz, CDCl₃) δ 4.52 (dd, J = 10.3, 0.9 Hz, 1H), 4.39 – 4.28 (m, 1H), 4.12 (d, J = 10.3 Hz, 1H), 3.49 (dd, J = 13.1, 3.5 Hz, 1H), 3.29 (dd, J = 13.1, 5.7 Hz, 1H), 2.43 – 2.30 (m, 1H), 2.20 – 1.75 (m, 6H), 1.69 – 1.5 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 180.02, 97.96, 80.45, 77.51, 61.65, 53.18, 40.42, 37.47, 36.16, 26.36. **HRMS** (ESI): m/z [M + Na⁺] calcd for C₁₀H₁₃N₃NaO₃ : 246.0849; found 246.0838.

❖ Preparation of Thiocyno[3,3,3]propellanes **233a** and **233b**



To a solution of iodo[3,3,3]propellane (**231a** or **231b**) (1 equiv.) dissolved in acetonitrile, potassium thiocyanate (5 equiv.) was added. The reaction mixture was refluxed for 15 hours. After cooling, the reaction mixture was concentrated by reduced pressure. The residue was dissolved in EtOAc and washed successively with water and brine. The organic layer was then dried over anhydrous MgSO_4 , filtered, concentrated, and purified over silica gel to yield the corresponding thiocyno[3,3,3]propellanes **233a** or **233b**.^[28]

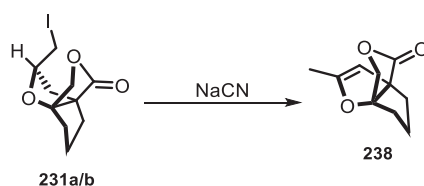
- (2*R*,3*aS*)-2-(thiocyanatomethyl)tetrahydro-4*H*-3*a*,6*a*-(methanooxymethano)cyclopenta[*b*]-furan-9-one **233a**

$\text{C}_{11}\text{H}_{13}\text{NO}_3\text{S}$ (239.29), pale-yellow oil; yield: 91% (57 mg isolated from **231a** (80 mg)). $R_f = 0.35$ (silica gel, Petroleum ether: EtOAc (60:40)). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 4.38 (d, $J = 10.7$ Hz, 1H), 4.32 (d, $J = 10.7$ Hz, 1H), 4.32 – 4.25 (m, 1H), 3.36 (dd, $J = 13.7, 4.3$ Hz, 1H), 3.07 (dd, $J = 13.7, 5.4$ Hz, 1H), 2.63 (dd, $J = 12.9, 5.0$ Hz, 1H), 2.24 – 2.16 (m, 1H), 2.08 – 1.93 (m, 3H), 1.93 – 1.79 (m, 3H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 179.50, 111.94, 97.82, 78.58, 77.96, 61.99, 42.25, 38.99, 36.83, 36.40, 27.45. **HRMS** (ESI): m/z [$\text{M} + \text{Na}^+$] calcd for $\text{C}_{11}\text{H}_{13}\text{NNaO}_3\text{S}$: 262.0508; found 262.0501.

- (2*S*,3*aS*)-2-(thiocyanatomethyl)tetrahydro-4*H*-3*a*,6*a*-(methanooxymethano)cyclopenta[*b*]-furan-9-one **233b**

$\text{C}_{11}\text{H}_{13}\text{NO}_3\text{S}$ (239.29), yellow oil; yield: 94% (43 mg isolated from **231b** (60 mg)). $R_f = 0.375$ (silica gel, Petroleum ether: EtOAc (60:40)). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ = 4.53 (dd, $J = 10.5, 0.9$ Hz, 1H), 4.45 (dddd, $J = 10.1, 6.5, 5.6, 4.5$ Hz, 1H), 4.11 (d, $J = 10.5$ Hz, 1H), 3.23 (dd, $J = 13.6, 4.5$ Hz, 1H), 3.06 (dd, $J = 13.6, 6.6$ Hz, 1H), 2.42 – 2.34 (m, 1H), 2.32 (dd, $J = 13.2, 5.6$ Hz, 1H), 2.12 – 1.79 (m, 5H), 1.66 – 1.53 (m, 1H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 179.67, 111.72, 98.17, 79.35, 77.25, 61.78, 42.26, 37.20, 36.95, 36.01, 26.32. **HRMS** (ESI): m/z [$\text{M} + \text{Na}^+$] calcd for $\text{C}_{11}\text{H}_{13}\text{NNaO}_3\text{S}$: 262.0508; found 262.0506.

❖ Formation of *endo* enol ether [3,3,3]propellane **239**



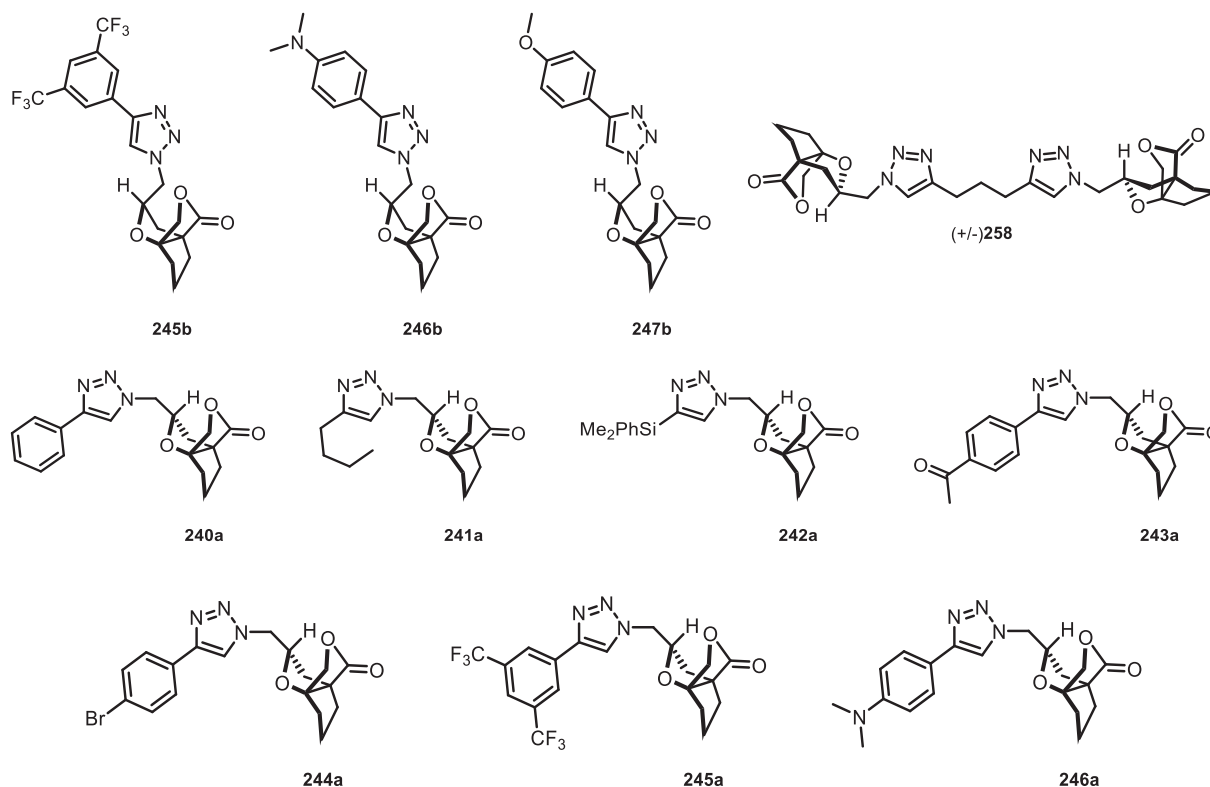
Procedure: **231b** (93 mg, 0.302 mmol) was added to a rapidly stirred partially soluble mixture of sodium cyanide (22 mg, 0.452 mmol) in dimethyl sulfoxide (15 ml). The temperature of the mixture was kept at 140°C for 15 minutes in which the reaction was complete. The brown reaction mixture was cooled, diluted with water, and extracted with ether (3 x 15 ml). The pale-yellow ether extracts were then dried, concentrated, and purified over silica gel to give the unexpected compound **239**.^[29]

- (3*aS*,6*aR*)-2-methyl-5,6-dihydro-4*H*-3*a*,6*a*-(methanooxymethano)cyclopenta[*b*]furan-9-one **239**

$C_{10}H_{12}O_3$ (180.20), colorless liquid; highly volatile; yield: 53% (29 mg isolated from **231b** (93 mg)). $R_f = 0.370$ (silica gel, Petroleum ether: EtOAc (85:15)). 1H NMR (500 MHz, $CDCl_3$) δ 4.71 (d, $J = 0.9$ Hz, 1H), 4.45 (d, $J = 10.3$ Hz, 1H), 4.33 (d, $J = 10.3$ Hz, 1H), 2.19 – 2.05 (m, 2H), 2.01 (dd, $J = 13.7, 6.9$ Hz, 1H), 1.95 – 1.82 (m, 2H), 1.81 (d, $J = 1.1$ Hz, 3H), 1.68 (dt, $J = 12.8, 6.5$ Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.5, 157.1, 99.5, 96.9, 77.9, 65.7, 39.2, 36.5, 26.0, 13.5. HRMS (ESI): m/z [$M + H^+$] calcd for $C_{10}H_{13}O_3$: 181.0859; found 181.0856.

❖ Preparation of triazolo[3,3,3]propellanes *via* click reaction

General procedure: a reaction vessel was charged in air with the azide (1.0 equiv.), copper(II) sulfate pentahydrate (0.5 equiv.), Na ascorbate (2 equiv.), and the neat alkyne (3.0 equiv.). To this was added 1:1 water/*tert*-butanol solution. The resulting suspension stirred vigorously at room temperature in an air atmosphere for the time specified. The mixture was diluted with EtOAc and shaken with a saturated solution of ammonium chloride. The organic layer was dried over ($MgSO_4$) and concentrated under reduced pressure. The residue was purified using a conventional flash chromatography as specified, to give the desired 1,4-substituted triazole.^[30]



- (2*R*,3*aS*)-2-((4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)tetrahydro-4*H*-3*a*,6*a*-(methanooxymethano)cyclopenta[*b*]furan-9-one **240a**

$C_{18}H_{19}N_3O_3$ (325.37), white solid; yield: 91% (58 mg isolated from **232a** (44 mg)). $R_f = 0.402$ (silica gel, Petroleum ether: EtOAc (40:60)). 1H NMR (500 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.85 – 7.79 (m, 2H), 7.43 (t, $J = 7.6$ Hz, 2H), 7.34 (d, $J = 7.4$ Hz, 1H), 4.66 (dd, $J = 14.6, 3.2$ Hz, 1H), 4.56 (dd, $J = 14.6, 5.0$ Hz, 1H), 4.37 (m, 1H), 4.34 (d, $J = 10.6$ Hz, 1H), 4.27 (d, $J = 10.6$ Hz, 1H), 2.57 (dd, $J = 13.1, 5.1$ Hz, 1H), 2.09 – 2.00 (m, 1H), 1.94 – 1.60 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.5, 147.8, 130.4, 128.8, 128.2, 125.7, 121.1, 97.7, 78.8, 77.9, 61.6, 51.7, 40.2, 39.0, 36.1, 27.1. IR (neat, cm^{-1}) 3148, 2968, 2905, 1762, 1075, 760. HRMS (ESI): m/z [$M + Na^+$] calcd for $C_{18}H_{19}N_3NaO_3$: 348.1319; found 348.1311.

- (2*R*,3*aS*)-2-((4-butyl-1*H*-1,2,3-triazol-1-yl)methyl)tetrahydro-4*H*-3*a*,6*a*-(methanooxymethano)cyclopenta[*b*]furan-9-one **241a**

$C_{16}H_{23}N_3O_3$ (305.38), pale yellow solid; yield: 77% (52 mg isolated from **232a** (50 mg)). $R_f = 0.405$ (silica gel, Petroleum ether: EtOAc (40:60)). 1H NMR (300 MHz, $CDCl_3$) δ 7.37 (s, 1H), 4.56 (dd, $J = 14.5, 3.6$ Hz, 1H), 4.49 (dd, $J = 14.5, 4.5$ Hz, 1H), 4.36 – 4.22 (m, 1H), 4.33 (d, $J =$

10.1 Hz, 1H), 4.26 (d, $J = 10.1$ Hz, 1H), 2.76 – 2.66 (m, 2H), 2.53 (dd, $J = 13.1, 5.1$ Hz, 1H), 1.72 (m, 9H), 1.47 – 1.27 (m, 2H), 0.93 (t, $J = 7.3$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 179.5, 148.4, 122.1, 97.6, 78.9, 77.9, 61.5, 51.4, 40.2, 39.0, 36.1, 31.5, 27.1, 25.3, 22.2, 13.8. IR (neat, cm^{-1}) 3117, 2927, 1752, 1126, 1011. HRMS (ESI): m/z [$\text{M} + \text{Na}^+$] calcd for $\text{C}_{16}\text{H}_{23}\text{N}_3\text{NaO}_3$: 328.1632; found 328.1622.

- (2*R*,3*aS*)-2-((4-(dimethyl(phenyl)silyl)-1*H*-1,2,3-triazol-1-yl)methyl)tetrahydro-4*H*-3*a*,6*a*-(methanooxymethano)cyclopenta[*b*]furan-9-one **242a**

$\text{C}_{20}\text{H}_{25}\text{N}_3\text{O}_3\text{Si}$ (383.52), white solid; yield: 22% (18 mg isolated from **232a** (50 mg)). $R_f = 0.350$ (silica gel, Petroleum ether: EtOAc (40:60)). ^1H NMR (500 MHz, CDCl_3) δ 7.60 – 7.54 (m, 2H), 7.56 (s, 1H), 7.41 – 7.32 (m, 3H), 4.61 (dd, $J = 14.4, 4.0$ Hz, 1H), 4.57 (dd, $J = 14.4, 3.7$ Hz, 1H), 4.30 (m, 1H), 4.30 (d, $J = 10.5$ Hz, 1H), 4.24 (d, $J = 10.5$ Hz, 1H), 2.51 (dd, $J = 13.2, 5.1$ Hz, 1H), 1.93 – 1.75 (m, 2H), 1.74 – 1.62 (m, 2H) 1.57 – 1.42 (m, 2H), 0.62 (s, 3H), 0.6 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 179.5, 160.7, 145.1, 137.1, 133.8, 133.8, 131.5, 129.4, 127.9, 97.6, 78.7, 77.9, 61.6, 50.8, 50.7, 39.9, 38.9, 36.1, 26.9, -2.4, -2.5. HRMS (ESI): m/z [$\text{M} + \text{Na}^+$] calcd for $\text{C}_{20}\text{H}_{25}\text{N}_3\text{NaO}_3\text{Si}$: 406.1557; found 406.1557.

- (2*R*,3*aS*)-2-((4-(4-acetylphenyl)-1*H*-1,2,3-triazol-1-yl)methyl)tetrahydro-4*H*-3*a*,6*a*-(methanooxymethano)cyclopenta[*b*]furan-9-one **243a**

$\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_4$ (367.41), white solid; yield: 48% (39 mg isolated from **232a** (50 mg)). $R_f = 0.375$ (silica gel, Petroleum ether: EtOAc (30:70)). ^1H NMR (300 MHz, CDCl_3) δ 8.07 – 8.00 (d, $J = 8.7$ Hz, 2H), 7.98 (s, 1H), 7.94 (d, $J = 8.7$ Hz, 2H), 4.71 (dd, $J = 14.5, 3.2$ Hz, 1H), 4.58 (dd, $J = 14.5, 5.1$ Hz, 1H), 4.44 – 4.32 (m, 1H), 4.40 – 4.32 (d, $J = 10.6$ Hz, 1H), 4.29 (d, $J = 10.6$ Hz, 1H), 2.64 (s, 3H), 2.65-2.59 (dd, $J = 13.1, 5.1$ Hz, 1H), 2.12 – 1.59 (m, 7H). ^{13}C NMR (101 MHz, CDCl_3) δ 197.4, 179.4, 146.7, 136.6, 134.8, 129.0, 125.6, 122.0, 97.8, 78.8, 77.9, 61.6, 51.9, 40.3, 39.0, 36.1, 27.2, 26.6. IR (neat, cm^{-1}) 3084, 2966, 2900, 1750, 1674, 1066. HRMS (ESI): m/z [$\text{M} + \text{Na}^+$] calcd for $\text{C}_{20}\text{H}_{21}\text{N}_3\text{NaO}_4$: 390.1424; found 390.1418.

- (2*R*,3*aS*)-2-((4-(4-bromophenyl)-1*H*-1,2,3-triazol-1-yl)methyl)tetrahydro-4*H*-3*a*,6*a*-(methanooxymethano)cyclopenta[*b*]furan-9-one **244a**

$\text{C}_{18}\text{H}_{18}\text{BrN}_3\text{O}_3$ (404.26), white solid; yield: 94% (86 mg isolated from **232a** (50 mg)). $R_f = 0.425$ (silica gel, Petroleum ether: EtOAc (30:70)). ^1H NMR (300 MHz, CDCl_3) δ 7.88 (s, 1H), 7.74 –

7.66 (d, $J = 8.75$ Hz, 2H), 7.59 – 7.51 (d, $J = 8.75$ Hz, 2H), 4.67 (dd, $J = 14.5, 3.2$ Hz, 1H), 4.55 (dd, $J = 14.5, 5.1$ Hz, 1H), 4.41 – 4.22 (m, 1H), 4.34 (d, $J = 10.70$ Hz, 1H), 4.27 (d, $J = 10.70$ Hz, 1H), 2.59 (dd, $J = 13.1, 5.1$ Hz, 1H), 2.10 – 1.97 (m, 1H), 1.97 – 1.53 (m, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 179.4, 146.8, 132.0, 129.4, 127.2, 122.1, 121.1, 97.7, 78.8, 77.9, 61.6, 51.8, 40.3, 39.0, 36.1, 27.1. IR (neat, cm^{-1}) 3135, 2958, 1758, 1018, 815. HRMS (ESI): m/z [$\text{M} + \text{Na}^+$] calcd for $\text{C}_{18}\text{H}_{18}\text{BrN}_3\text{NaO}_3$: 426.0424; found 426.0417.

▪ (2*R*,3*aS*)-2-((4-(3,5-bis(trifluoromethyl)phenyl)-1*H*-1,2,3-triazol-1-yl)methyl)tetrahydro-4*H*-3*a*,6*a*-(methanooxymethano)cyclopenta[*b*]furan-9-one **245a**
 $\text{C}_{20}\text{H}_{17}\text{F}_6\text{N}_3\text{O}_3$ (461.36), white solid; yield: 97% (100 mg isolated from **232a** (50 mg)). $R_f = 0.35$ (silica gel, Petroleum ether: EtOAc (60:40)). ^1H NMR (300 MHz, CDCl_3) δ 8.31 (s, 1H), 8.26 (s, 1H), 8.05 (s, 1H), 7.84 (s, 1H), 4.74 (dd, $J = 14.5, 3.2$ Hz, 1H), 4.56 (dd, $J = 14.5, 5.6$ Hz, 1H), 4.38 (m, 1H), 4.34 (d, $J = 10.7$ Hz, 1H), 4.29 (d, $J = 10.7$ Hz, 1H), 2.64 (dd, $J = 13.1, 5.0$ Hz, 1H), 2.14 – 1.62 (m, 7H). ^{13}C NMR (101 MHz, CDCl_3) δ 179.3, 145.1, 132.8, 132.6, 132.5, 132.1, 131.8, 127.2, 125.5, 124.5, 122.0, 121.8, 121.7, 121.6, 121.6, 97.9, 78.8, 77.8, 77.2, 61.6, 52.2, 40.5, 39.0, 36.1, 29.6, 27.2. ^{19}F NMR (282 MHz, CDCl_3) δ -62.99. IR (neat, cm^{-1}) 3138, 2945, 1766, 1275, 1126. HRMS (ESI): m/z [$\text{M} + \text{Na}^+$] calcd for $\text{C}_{20}\text{H}_{17}\text{F}_6\text{N}_3\text{NaO}_3$: 484.1066; found 484.1051.

▪ (2*S*,3*aS*)-2-((4-(3,5-bis(trifluoromethyl)phenyl)-1*H*-1,2,3-triazol-1-yl)methyl)tetrahydro-4*H*-3*a*,6*a*-(methanooxymethano)cyclopenta[*b*]furan-9-one **245b**
 $\text{C}_{20}\text{H}_{17}\text{F}_6\text{N}_3\text{O}_3$ (461.36), colorless oil; yield: 81% (69 mg isolated from **232b** (41 mg)). $R_f = 0.5$ (silica gel, Petroleum ether: EtOAc (50:50)). ^1H NMR (300 MHz, CDCl_3) δ 8.28 (s, 1H), 8.28 (s, 1H), 8.06 (s, 1H), 7.85 (s, 1H), 4.76 (dd, $J = 13.5, 2.3$ Hz, 1H), 4.63 – 4.45 (m, 3H), 4.15 (d, $J = 10.4$ Hz, 1H), 2.47 – 2.28 (m, 2H), 2.13 – 1.78 (m, 5H), 1.71 – 1.50 (m, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 179.5, 145.2, 132.7, 132.6, 132.4, 132.1, 131.7, 127.2, 125.6, 124.5, 121.8, 121.7, 121.6, 121.6, 121.5, 98.3, 79.5, 77.2, 61.4, 53.1, 40.7, 37.0, 35.8, 26.2. HRMS (ESI): m/z [$\text{M} + \text{Na}^+$] calcd for $\text{C}_{20}\text{H}_{17}\text{F}_6\text{N}_3\text{NaO}_3$: 484.1066; found 484.1043.

- (2*R*,3*aS*)-2-((4-(4-(dimethylamino)phenyl)-1*H*-1,2,3-triazol-1-yl)methyl)tetrahydro-4*H*-3*a*,6*a*-(methanooxymethano)cyclopenta[*b*]furan-9-one **246a**

$C_{20}H_{24}N_4O_3$ (368.44), pink solid; yield: 81% (67 mg isolated from **232a** (50 mg)). $R_f = 0.325$ (silica gel, Petroleum ether: EtOAc (30:70)). 1H NMR (300 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.70 (d, $J = 8.9$ Hz, 2H), 6.77 (d, $J = 8.9$ Hz, 2H), 4.64 (dd, $J = 14.5, 3.4$ Hz, 1H), 4.55 (dd, $J = 14.6, 4.7$ Hz, 1H), 4.37 – 4.29 (m, 1H), 4.36 – 4.33 (d, $J = 10.6$ Hz, 1H), 4.29 – 4.26 (d, $J = 10.6$ Hz, 1H), 2.99 (s, 6H), 2.57 (dd, $J = 13.1, 5.1$ Hz, 1H), 2.04 (dd, $J = 12.6, 6.9$ Hz, 1H), 1.96 – 1.54 (m, 6H). ^{13}C NMR

(126 MHz, $CDCl_3$) δ 179.6, 150.4, 148.3, 126.6, 122.4, 119.6, 112.4, 97.6, 78.9, 77.9, 61.6, 51.5, 40.4, 40.2, 39.0, 36.1, 27.1. IR (neat, cm^{-1}) 3140, 2958, 2900, 1760, 1618, 1018, 808. HRMS (ESI): m/z [$M + H^+$] calcd for $C_{20}H_{25}N_4O_3$: 369.1921; found 369.1913.

- (2*S*,3*aS*)-2-((4-(4-(dimethylamino)phenyl)-1*H*-1,2,3-triazol-1-yl)methyl)tetrahydro-4*H*-3*a*,6*a*-(methanooxymethano)cyclopenta[*b*]furan-9-one **246b**

$C_{20}H_{24}N_4O_3$ (368.44), pink solid; yield: 88% (58 mg isolated from **232b** (40 mg)). $R_f = 0.375$ (silica gel, Petroleum ether: EtOAc (20:80)). 1H NMR (300 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.71–7.68 (d, $J = 8.9$ Hz, 2H), 6.77 (d, $J = 8.9$ Hz, 2H), 4.63 (dd, $J = 13.4, 2.8$ Hz, 1H), 4.57 – 4.37 (m, 3H), 4.10 (d, $J = 10.4$ Hz, 1H), 2.99 (s, 6H), 2.38 (ddd, $J = 8.0, 6.7, 1.8$ Hz, 1H), 2.28 (dd, $J = 13.1, 5.1$ Hz, 1H), 1.90 (m, 5H), 1.67 – 1.46 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.6, 150.4, 148.4, 126.7, 119.1, 118.6, 112.4, 98.0, 79.8, 77.2, 61.3, 52.7, 40.8, 40.4, 37.1, 35.8, 26.2. IR (neat, cm^{-1}) 3140, 2967, 2900, 1760, 1618, 1066. HRMS (ESI): m/z [$M + Na^+$] calcd for $C_{20}H_{24}N_4NaO_3$: 391.1741; found 391.1737.

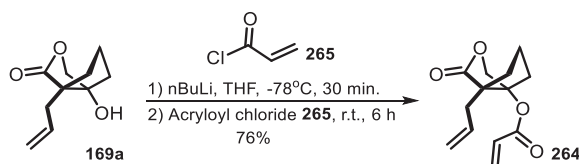
- (2*S*,3*aS*)-2-((4-(4-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)methyl)tetrahydro-4*H*-3*a*,6*a*-(methanooxymethano)cyclopenta[*b*]furan-9-one **247b**

$C_{19}H_{21}N_3O_4$ (355.39), yellow oil; yield: 62% (65 mg isolated from **232b** (66 mg)). $R_f = 0.425$ (silica gel, Petroleum ether: EtOAc (30:70)). 1H NMR (300 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.73 – 7.77 (d, $J = 8.9$ Hz, 2H), 6.99 (d, $J = 8.9$ Hz, 2H), 4.68 (dd, $J = 13.5, 2.6$ Hz, 1H), 4.60 – 4.41 (m, 3H), 4.13 (d, $J = 10.4$ Hz, 1H), 3.85 (s, 3H), 2.47 – 2.35 (m, 1H), 2.31 (dd, $J = 13.1, 5.1$ Hz, 1H), 2.10 – 1.75 (m, 5H), 1.56 (ddd, $J = 12.8, 6.2,$

1.8 Hz, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ 179.6, 159.6, 147.8, 127.0, 123.1, 119.8, 114.2, 98.1, 79.7, 77.2, 61.3, 55.3, 52.8, 40.8, 37.1, 35.8, 26.2. HRMS (ESI): m/z $[\text{M} + \text{Na}^+]$ calcd for $\text{C}_{19}\text{H}_{21}\text{N}_3\text{NaO}_4$: 378.1424; found 378.1418.

- (2R,2'R,3aS,3a'S)-2,2'-((propane-1,3-diylbis(1H-1,2,3-triazole-4,1-diyl))bis(methylene))bis-(tetrahydro-4H-3a,6a-(methanooxymethano)cyclopenta[b]furan-9-one) **258**
 $\text{C}_{27}\text{H}_{34}\text{N}_6\text{O}_6$ (538.61), yellow oil; yield: 72% (70 mg isolated from **232a** (81 mg)). $R_f = 0$ (silica gel, Petroleum ether: EtOAc (30:70)). $[\alpha]_D^{20} +4.6^\circ$ ($c = 1.3$, DCM). ^1H NMR (300 MHz, CDCl_3) δ 7.45 (s, 2H), 4.57 (dd, $J = 14.6, 3.7$ Hz, 2H), 4.47 (dd, $J = 14.6, 4.9$ Hz, 2H), 4.32 (d, $J = 10.6$ Hz, 2H), 4.26 (d, $J = 10.6$ Hz, 2H), 4.36 – 4.22 (m, 2H), 2.77 (t, $J = 7.4$ Hz, 4H), 2.58 – 2.48 (dd, $J = 13.2, 4.9$ Hz, 2H), 2.14 – 1.62 (m, 14H), 1.65 – 1.53 (dd, $J = 13.2, 11.4$ Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 179.5, 147.5, 122.5, 97.7, 78.8, 77.9, 61.5, 51.7, 51.6, 40.4, 40.4, 39.0, 36.1, 29.1, 27.1, 24.9. HRMS (ESI): m/z $[\text{M} + \text{Na}^+]$ calcd for $\text{C}_{27}\text{H}_{34}\text{N}_6\text{NaO}_6$: 561.2432; found 561.2435.

❖ Preparation of the bis-alkene product **264**

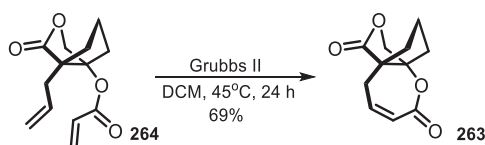


Procedure: To a solution of **169a** (200 mg, 1.1 mmol) in dry THF (60 mL) under an inert atmosphere at -78°C was added n-BuLi (98 mg, 1.5 mmol). After 30 minutes, acryloyl chloride (0.18 ml, 2.2 mmol) was added dropwise, and the resulting mixture was stirred for an additional 6 hours at room temperature. The reaction mixture was quenched by slow addition of water at 0°C , extracted with ether, washed with aqueous ammonium chloride solution, and then dried over MgSO_4 . Evaporation of the solvent gave a crude mixture, which was chromatographed on silica gel to give the desired product.

- (6a*S*)-6a-allyl-1-oxotetrahydro-1*H*-cyclopenta[*c*]furan-3a(3*H*)-yl acrylate **264**
 $\text{C}_{13}\text{H}_{16}\text{O}_4$ (236.27), colorless oil; yield: 76% (197 mg isolated from **169a** (200 mg)). $R_f = 0.525$ (silica gel, Petroleum ether: EtOAc (80:20)). ^1H NMR (300 MHz, CDCl_3) δ 6.46 (dd, $J = 17.2, 1.3$ Hz, 1H), 6.22 – 6.09 (dd, $J = 17.2, 10.3$ Hz, 1H), 5.95 (dd, $J = 10.3, 1.3$ Hz, 1H), 5.93 – 5.78

(m, 1H), 5.25 – 5.13 (m, 2H), 4.72 (d, $J = 10.6$ Hz, 1H), 4.32 (dd, $J = 10.6, 1.6$ Hz, 1H), 2.60 (d, $J = 7.3$ Hz, 1H), 2.60 (m, 1H), 2.30 – 2.01 (m, 2H), 1.92 – 1.77 (m, 2H), 1.62 – 1.43 (m, 1H), 0.88 (d, $J = 7.3$ Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 178.5, 166.5, 135.3, 131.3, 128.2, 115.7, 76.8, 72.4, 59.6, 37.3, 33.8, 27.4, 17.0. **HRMS** (ESI): m/z $[\text{M} + \text{Na}^+]$ calcd for $\text{C}_{13}\text{H}_{16}\text{NaO}_4$: 259.0941; found 259.0945.

❖ Preparation of [5,3,3]propellano-bis lactone **263**

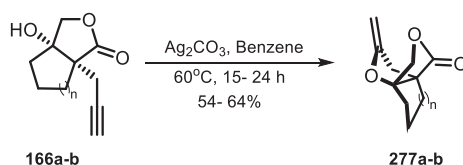


Procedure: To a stirred solution of **264** (80 mg, 0.338 mmol) in deoxygenated dichloromethane (100 ml), Grubbs II catalyst (28 mg, 10 mol%) was added in one portion. The reaction mixture was then refluxed for 24 hours before being treated and purified to offer the desired product.^[31]

▪ (5a*S*)-7,8-dihydro-6*H*-5a,8a-(methanooxymethano)cyclopenta[*b*]oxepine-2,11(5*H*)-dione **263** $\text{C}_{11}\text{H}_{12}\text{O}_4$ (208.21), brown solid; yield: 69% (48 mg isolated from **264** (80 mg)). $R_f = 0.375$ (silica gel, Petroleum ether: EtOAc (60:40)). ^1H NMR (300 MHz, CDCl_3) δ 6.72 – 6.61 (dt, $J = 11.5, 6.7$ Hz, 1H), 6.14 (d, $J = 11.5$ Hz, 1H), 4.47 (d, $J = 11.0$ Hz, 1H), 4.22 (d, $J = 11.0$ Hz, 1H), 2.81 – 2.61 (m, 2H), 2.29 – 2.17 (m, 2H), 2.06 – 1.81 (m, 2H), 1.52 – 1.36 (m, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 178.3, 167.1, 144.8, 121.7, 78.9, 72.0, 59.2, 36.9, 33.0, 27.8, 17.4. **HRMS** (ESI): m/z $[\text{M} + \text{Na}^+]$ calcd for $\text{C}_{11}\text{H}_{12}\text{NaO}_4$: 231.0628; found 231.0628.

Chapter 4

❖ Preparation of exo enol ether propellanes **277a-b**

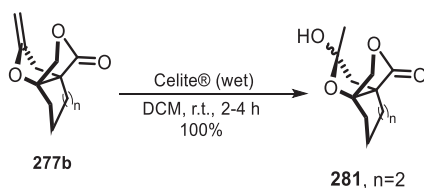


General Procedure: To a stirred solution of the chosen alkynol (1.0 mmol, 1.0 equiv.) in benzene (15.0 ml), was added at room temperature silver carbonate (0.2 mmol, 0.2 equiv.). The mixture was heated at 60°C until TLC showed the disappearance of the starting acetylenic alcohol. The heterogeneous mixture, which gradually turned from green to brown then black, was filtered over Celite and concentrated in vacuo. The resulting crude mixture was then purified using column chromatography to afford the corresponding α -methylene heterocycle. (Remark: Triethylamine (1.0 vol%) was added to the used eluent before each purification to neutralize silica).^[32]

▪ (6a*S*)-2-methylenetetrahydro-4*H*-3a,6a-(methanooxymethano)cyclopenta[*b*]furan-9-one **277a** C₁₀H₁₂O₃ (180.20), pale yellow oil; yield: 54 % (278 mg from **166a** (520 mg)). $R_f = 0.35$ (silica gel, Petroleum ether: EtOAc (85:15)). ¹H NMR (400 MHz, DMSO) δ 4.39 (s, 2H), 4.18 (dd, $J = 3.7, 1.7$ Hz, 1H), 3.86 (dd, $J = 3.7, 1.7$ Hz, 1H), 2.95 (dt, $J = 16.7, 1.5$ Hz, 1H), 2.85 (dt, $J = 16.7, 1.7$ Hz, 1H), 2.03 (m, 2H), 1.96 – 1.84 (m, 3H), 1.82 – 1.70 (m, 1H). ¹H NMR (300 MHz, C₆D₆) δ 4.38 (d, $J = 2.0$ Hz, 1H), 3.96 (dd, $J = 10.4, 1.7$ Hz, 1H), 3.70 (d, $J = 2$ Hz, 1H), 3.46 (dd, $J = 10.4, 3.9$ Hz, 1H), 2.79 (d, $J = 16.7$ Hz, 1H), 2.19 (d, $J = 16.7$, 1H), 1.81 – 1.64 (m, 1H), 1.53 (m, 1H), 1.36 – 0.88 (m, 4H). ¹³C NMR (101 MHz, DMSO) δ 179.1, 162.0, 99.9, 81.9, 76.0, 59.0, 39.1, 36.3, 34.6, 26.3. ¹³C NMR (101 MHz, C₆D₆) δ 178.0, 161.8, 99.3, 82.4, 75.8, 58.9, 39.7, 37.2, 35.7, 26.2. HRMS (ESI): m/z [M + H]⁺ calcd for C₁₀H₁₃O₃ : 181.0859; found 181.0860.

▪ (7a*S*)-2-methylenehexahydro-3a,7a-(methanooxymethano)benzofuran-10-one **277b** C₁₁H₁₄O₃ (194.23), pale yellow oil; yield: 51% (357 mg from **166b** (700 mg)). $R_f = 0.375$ (silica gel, Petroleum ether: EtOAc (80:20)). ¹H NMR (300 MHz, C₆D₆) δ 4.34 (d, $J = 10.5$ Hz, 1H), 4.28 (dt, $J = 1.3, 2.2$ Hz, 1H), 4.21 (d, $J = 10.5$ Hz, 1H), 3.91 (dt, $J = 1.3, 2.2$ Hz, 1H), 2.99 (dt, $J = 16.4, 2.2$ Hz, 1H), 2.78 (dt, $J = 16.4, 2.2$ Hz, 1H), 2.00 (m, 2H), 1.88 – 1.73 (m, 1H), 1.73 – 1.07 (m, 5H). ¹³C NMR (101 MHz, CDCl₃) δ 179.8, 158.2, 87.8, 82.7, 71.3, 50.2, 35.1, 29.1, 28.0, 22.5, 20.0. HRMS (ESI): m/z [M + Na]⁺ calcd for C₁₁H₁₄NaO₃ : 217.0835; found 217.0834.

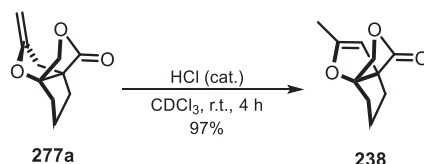
❖ Preparation of propellanes **281**



The chosen *exo* enol ether **8b** adduct (0.1 mmol, 1.0 equiv.) was added in one portion to a suspension of wet Celite® (100 mg) in dichloromethane (7 ml). After stirring for 4 h at room temperature, the reaction mixture was filtered, extracted and purified over silica gel to afford a mixture of inseparable diastereoisomers of the corresponding hemiacetal propellanes **9b-b'**.^[33]

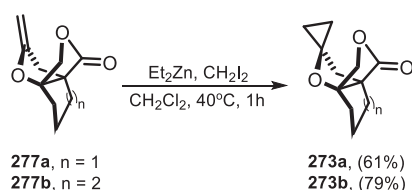
▪ 2-hydroxy-2-methylhexahydro-3a,7a-(methanooxymethano)benzofuran-10-one **281**.
 $C_{11}H_{16}O_4$ (212,25), White solid; yield: 100% (20 mg from **277b** (19 mg)). $R_f(2 \text{ diastereoisomers}) = 0.350$ (silica gel, Petroleum ether: EtOAc (50:50)). The ratio of the two inseparable diastereoisomers is 1:1. **281'**: 1H NMR (300 MHz, $CDCl_3$) δ 4.36 – 4.28 (d, $J = 10.36$ Hz, 1H), 4.20 – 4.13 (d, $J = 10.36$ Hz, 1H), 2.78 – 2.63 (brd, OH), 2.65 – 2.55 (d, $J = 14.40$ Hz, 1H), 2.40 – 2.30 (d, $J = 14.40$ Hz, 1H), 1.98 – 1.27 (m, 8H), 1.54 (s, 3H). **281''**: 1H NMR (300 MHz, $CDCl_3$) δ 4.15 (s, 2H), 2.56 – 2.48 (d, $J = 13.03$ Hz, 1H), 2.56 – 2.42 (brd, OH), 2.15 – 2.05 (d, $J = 13.03$ Hz, 1H), 1.47 (s, 3H), 2.02 – 1.06 (m, 8H). **281'**: ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.4, 105.4, 86.7, 73.5, 52.5, 44.5, 31.2, 29.6, 28.2, 23.1, 19.8. **281''**: ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.1, 104.0, 86.4, 71.5, 50.8, 44.4, 29.8, 28.2, 28.1, 21.8, 19.8. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{11}H_{16}NaO_4$: 235.0941; found 235.0934.

❖ Preparation of propellanes **238**



A catalytic amount of HCl (~10 mol%) was dissolved in a solution of the corresponding *exo* enol ether adduct **277a** (1 equiv.) in deuterated chloroform (0.07 M) at ambient temperature. Four hours later, a quantitative isomerization to its counterpart *endo* enol ether adduct **238** has been observed by 1H NMR analysis. (Spectral data has already been described in Chapter 3).

❖ Preparation of oxaspirocyclopropane[*n*,3,3]propellanes **273a-b**



General Procedure: The chosen *exo* enol ether adduct (0.7 mmol, 1.0 equiv.), methylene iodide (3.4 mmol, 5.0 equiv.), and diethylzinc (1 M in hexane) (4.8 mmol, 7.0 equiv.) were stirred at reflux in anhydrous dichloromethane (8.0 ml) for 1 hour. After completion, the reaction mixture was quenched by adding water, extracted with diethyl ether, washed with aqueous NaHCO₃ solution, and then dried over MgSO₄. Evaporation of the solvent gave a crude mixture, which was chromatographed on silica gel to give the desired oxaspirocyclopropane [n,3,3]propellane.^[34]

- Dihydro-3'*H*,4'*H*-spiro[cyclopropane-1,2'-[3a,6a](methanooxymethano)cyclopenta[*b*] furan]-9'-one **273a**

C₁₁H₁₄O₃ (194.23), colourless oil; yield: 61% (80 mg from **277a** (123 mg)). *R_f* = 0.370 (silica gel, Petroleum ether: EtOAc (82:18)). ¹H NMR (300 MHz, CDCl₃) δ 4.47–4.41 (d, *J* = 10.20 Hz, 1H), 4.22–4.18 (d, *J* = 10.20 Hz, 1H), 2.23 (s, 2H), 2.18–1.70 (m, 6H), 0.98–0.87 (ddd, *J* = 11.51, 6.58, 5.67 Hz, 1H), 0.85–0.75 (ddd, *J* = 11.51, 6.36, 5.10 Hz, 1H), 0.66–0.56 (ddd, *J* = 10.47, 6.36, 5.10 Hz, 1H), 0.53–0.43 (ddd, *J* = 10.47, 6.58, 5.67 Hz, 1H). ¹³C NMR (76 MHz, CDCl₃) δ 180.7, 97.3, 78.4, 65.6, 62.4, 43.7, 38.8, 36.3, 27.1, 10.6, 7.2. HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₁H₁₄NaO₃: 217.0835; found 217.0837.

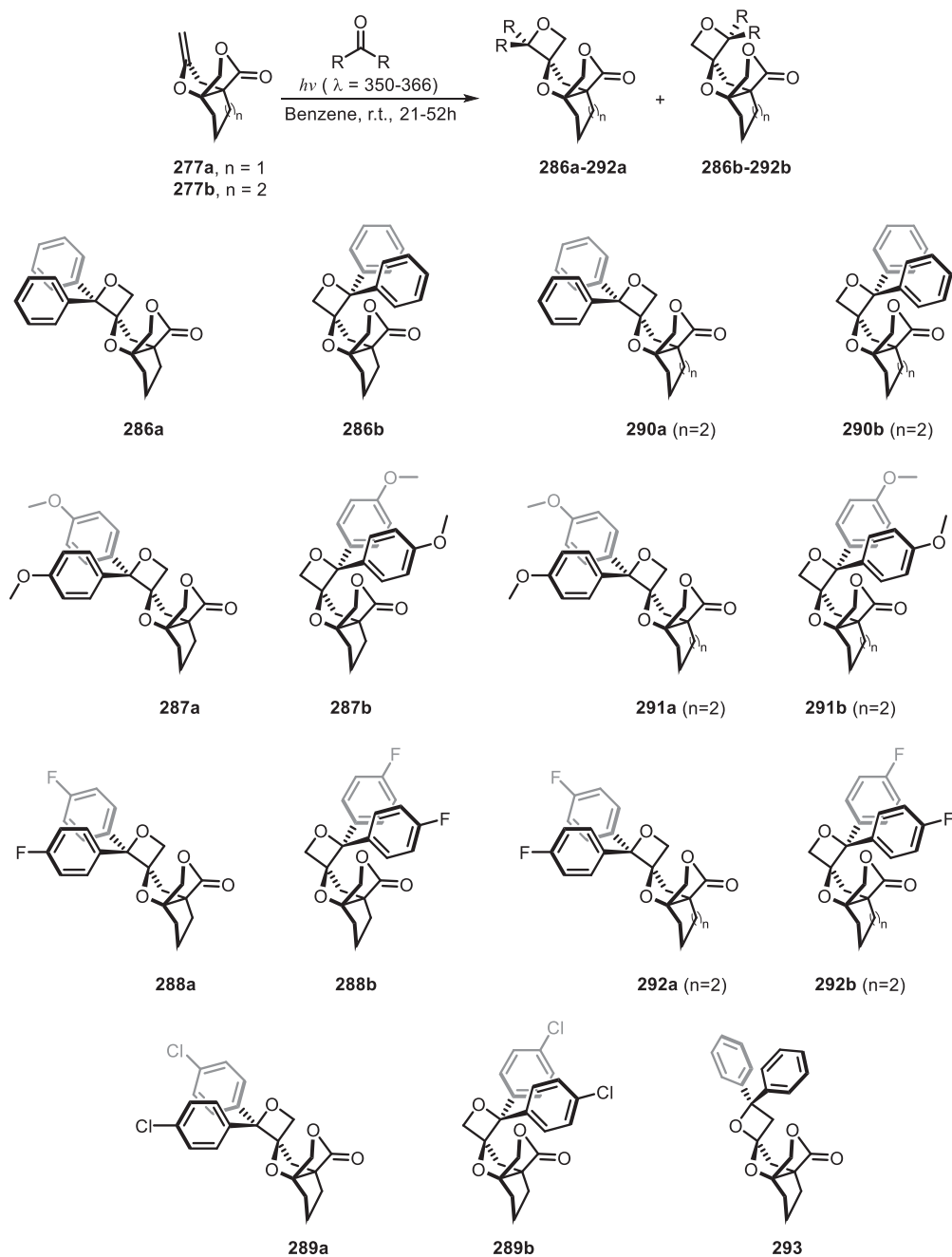
- Tetrahydro-3'*H*-spiro[cyclopropane-1,2'-[3a,7a](methanooxymethano)benzofuran]-10'-one **273b**

C₁₂H₁₆O₃ (208.26), colourless oil; yield: 79% (91 mg from **277b** (108 mg)). *R_f* = 0.375 (silica gel, Petroleum ether: EtOAc (80:20)). ¹H NMR (500 MHz, CDCl₃) δ 4.26–4.19 (d, *J* = 10.50 Hz, 1H), 4.19–4.13 (d, *J* = 10.50 Hz, 1H), 2.40–2.33 (d, *J* = 12.44 Hz, 1H), 2.33–2.26 (d, *J* = 12.44 Hz, 1H), 2.12–1.99 (m, 1H), 1.88–1.11 (m, 7H), 0.90–0.84 (ddd, *J* = 11.50, 6.72, 5.44 Hz, 1H), 0.81–0.74 (ddd, *J* = 11.50, 6.68, 5.33 Hz, 1H), 0.60–0.53 (ddd, *J* = 10.84, 6.72, 5.33 Hz, 1H), 0.52–0.46 (ddd, *J* = 10.84, 6.68, 5.44 Hz, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 181.3, 85.6, 72.4, 62.4, 52.9, 39.2, 29.2, 28.5, 22.4, 20.2, 10.9, 10.8. HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₂H₁₆NaO₃: 231.0992; found 231.0997.

❖ Paterno-Büchi reaction

Exo enol-ether propellane derivative (1 equivalent) was dissolved in benzene (0.06 M) in the presence of the carbonyl compound (1.5 equivalent). The mixture was flushed with argon for 1 hour and, then, irradiated at 350 nm at room temperature. At the end of the reaction, the removal

of the solvent yielded a crude product that was chromatographed on silica gel. The elution with petroleum ether/ethyl acetate in the presence of 1% of triethylamine gave pure products.^[35]



- **286**

Yield: 56% (97 mg from **277a** (86 mg)) (System of isomers **286a/286b** (3:1)).

- (3*R*,6*a*'*S*)-2,2-diphenyldihydro-3'*H*,4'*H*-spiro[oxetane-3,2'-[3*a*,6*a*](methanooxymethano)cyclopenta[*b*]furan]-9'-one **286a**

$C_{23}H_{22}O_4$ (362.43), colorless oil; $R_f = 0.350$ (silica gel, Petroleum ether: EtOAc: Et₃N (82:17:1)). ¹H NMR (300 MHz, C₆D₆) δ 7.80 (d, *J* = 8.2 Hz, 2H), 7.56 (d, *J* = 8.2 Hz, 2H), 7.15 (m, 3H), 7.06 (m, 3H), 4.45 (d, *J* = 5.8 Hz, 1H), 4.31 (d, *J* = 5.8 Hz, 1H), 3.63 (d, *J* = 10.7 Hz, 1H), 3.33 (d, *J* = 10.7 Hz, 1H), 2.57 (d, *J* = 13.5 Hz, 1H), 1.68 (d, *J* = 13.5 Hz, 1H), 1.76-0.87 (m, 6H). HRMS (ESI): *m/z* [M + Na⁺] calcd for $C_{23}H_{22}NaO_4$: 385.1410; found 385.1412.

- (3*S*,6*a*'*S*)-2,2-diphenyldihydro-3'*H*,4'*H*-spiro[oxetane-3,2'-[3*a*,6*a*](methanooxymethano)cyclopenta[*b*]furan]-9'-one **286b**

$C_{23}H_{22}O_4$ (362.43), colorless oil; $R_f = 0.450$ (silica gel, Petroleum ether: EtOAc: Et₃N (82:17:1)). ¹H NMR (500 MHz, C₆D₆) δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.60 (d, *J* = 8.2 Hz, 2H), 7.21 (m, 3H), 6.99 (m, 3H), 4.47 (d, *J* = 6.1 Hz, 1H), 4.15 (d, *J* = 6.1 Hz, 1H), 4.05 (d, *J* = 10.2 Hz, 1H), 3.34 (d, *J* = 10.2 Hz, 1H), 2.48 (d, *J* = 14.5 Hz, 1H), 1.71 (d, *J* = 14.5 Hz, 1H), 1.87-0.80 (m, 6H). ¹³C NMR (126 MHz, C₆D₆) δ 178.4, 142.0, 141.8, 131.7, 129.8, 128.3, 128.2, 127.3, 127.0, 126.5, 125.4, 98.5, 95.7, 91.7, 80.5, 76.3, 60.3, 45.0, 38.0, 35.5, 25.7. HRMS (ESI): *m/z* [M + Na⁺] calcd for $C_{23}H_{22}NaO_4$: 385.1410; found 385.1412.

- (2*R*,3*a*'*R*)-4,4-diphenyldihydro-3'*H*,4'*H*-spiro[oxetane-2,2'-[3*a*,6*a*](methanooxymethano)cyclopenta[*b*]furan]-9'-one **293**

$C_{23}H_{22}O_4$ (362.43), white solid; $R_f = 0.320$ (silica gel, Petroleum ether: EtOAc: Et₃N (82:17:1)). ¹H NMR (500 MHz, C₆D₆) δ 7.46 (d, *J* = 7.54 Hz, 2H), 7.27 (d, *J* = 7.54 Hz, 2H), 7.16-7.08 (m, 6H), 4.02 (d, *J* = 10.2 Hz, 1H), 3.44 (d, *J* = 10.2 Hz, 1H), 3.16 (d, *J* = 12.3 Hz, 1H), 2.90 (d, *J* = 12.3 Hz, 1H), 2.24 (d, *J* = 13.8 Hz, 1H), 1.93 (d, *J* = 13.8 Hz, 1H), 2.24-0.96 (m, 6H). ¹³C NMR (126 MHz, C₆D₆) δ 178.6, 146.3, 145.5, 128.1, 127.9, 127.7, 127.6, 127.0, 126.9, 125.7, 125.5, 112.6, 98.2, 80.2, 76.9, 59.9, 48.4, 46.7, 38.8, 35.6, 25.8. HRMS (ESI): *m/z* [M + Na⁺] calcd for $C_{23}H_{22}NaO_4$: 385.1410; found 385.1412.

- **287**

Yield: 17% of **287b** (40 mg from **277a** (100 mg)) (System of isomers **287a/287b** (?:?)).

- (3*R*,6*a'**S*)-2,2-bis(4-methoxyphenyl)dihydro-3'*H*,4'*H*-spiro[oxetane-3,2'-[3*a*,6*a*](methanooxymethano)cyclopenta[*b*]furan]-9'-one **287a**

C₂₅H₂₆O₆ (422.48), **R_f** = 0.350 (silica gel, Petroleum ether: EtOAc: Et₃N (75:24:1)).

- (3*S*,6*a'**S*)-2,2-bis(4-methoxyphenyl)dihydro-3'*H*,4'*H*-spiro[oxetane-3,2'-[3*a*,6*a*](methanooxymethano)cyclopenta[*b*]furan]-9'-one **287b**

C₂₅H₂₆O₆ (422.48), white solid; **R_f** = 0.238 (silica gel, Petroleum ether: EtOAc: Et₃N (75:24:1)).

¹H NMR (300 MHz, C₆D₆) δ 7.71 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.66 (d, *J* = 8.8 Hz, 2H), 4.54 (d, *J* = 6.2 Hz, 1H), 4.26 (d, *J* = 6.2 Hz, 1H), 4.04 (d, *J* = 10.2 Hz, 1H), 4.38 (d, *J* = 10.2 Hz, 1H), 3.29 (s, 3H), 3.26 (s, 3H), 2.55 (d, *J* = 14.5 Hz, 1H), 1.79 (d, *J* = 14.5 Hz, 1H), 1.91-0.77 (m, 6H). **¹³C NMR** (101 MHz, C₆D₆) δ 178.7, 159.1, 159.0, 134.3, 134.1, 128.2, 127.8, 127.6, 127.2, 113.8, 113.4, 113.0, 98.5, 96.0, 92.3, 80.4, 76.5, 60.5, 54.6, 54.4, 45.2, 38.2, 35.8, 25.8. **HRMS** (ESI): *m/z* [M + Na⁺] calcd for C₂₅H₂₆NaO₆ : 445.1622; found 445.1625.

- **288**

Yield: 45% (86 mg from **277a** (87 mg)) (System of isomers **288a/288b** (3:1)).

- (3*R*,6*a'**S*)-2,2-bis(4-fluorophenyl)dihydro-3'*H*,4'*H*-spiro[oxetane-3,2'-[3*a*,6*a*](methanooxymethano)cyclopenta[*b*]furan]-9'-one **288a**

C₂₃H₂₀F₂O₄ (398.41), colorless oil; **R_f** = 0.488 (silica gel, Petroleum ether: EtOAc: Et₃N (75: 24: 1)). **¹H NMR** (500 MHz, C₆D₆) δ 7.55-7.48 (m, 2H), 7.27-7.21 (m, 2H), 6.92-6.84 (m, 2H), 6.81-6.74 (m, 2H), 4.34 (d, *J* = 6.0 Hz, 1H), 4.23 (d, *J* = 6.0 Hz, 1H), 3.63 (d, *J* = 10.7 Hz, 1H), 3.35 (d, *J* = 10.7 Hz, 1H), 2.48 (d, *J* = 10.8 Hz, 1H), 1.43 (d, *J* = 10.8 Hz, 1H), 1.55-0.94 (m, 6H). **¹³C NMR** (126 MHz, C₆D₆) δ 178.4, 163.2, 163.2, 161.3, 161.2, 128.5, 128.5, 115.2, 115.0, 114.5, 114.3, 97.8, 93.7, 89.9, 79.8, 77.5, 59.6, 45.9, 37.9, 35.1, 27.1. **HRMS** (ESI): *m/z* [M + Na⁺] calcd for C₂₃H₂₀F₂NaO₄ : 421.1222; found 421.1214.

- (3*S*,6*a'**S*)-2,2-bis(4-fluorophenyl)dihydro-3'*H*,4'*H*-spiro[oxetane-3,2'-[3*a*,6*a*](methanooxymethano)cyclopenta[*b*]furan]-9'-one **288b**

C₂₃H₂₀F₂O₄ (398.41), yellow oil; **R_f** = 0.363 (silica gel, Petroleum ether: EtOAc: Et₃N (75: 24: 1)). **¹H NMR** (500 MHz, C₆D₆) δ 7.51-7.44 (m, 2H), 7.33-7.27 (m, 2H), 6.69-6.83 (m, 2H), 6.83-

6.76 (m, 2H), 4.35 (d, $J = 6.3$ Hz, 1H), 4.06 (d, $J = 6.3$ Hz, 1H), 3.96 (d, $J = 10.1$ Hz, 1H), 3.33 (d, $J = 10.1$ Hz, 1H), 2.27 (d, $J = 14.3$ Hz, 1H), 1.65 (d, $J = 14.3$ Hz, 1H), 1.87-0.80 (m, 6H). ^{13}C NMR (126 MHz, C_6D_6) δ 178.3, 163.1, 161.19, 137.4, 137.2, 128.3, 127.9, 127.6, 127.3, 115.1, 114.5, 98.5, 95.0, 91.3, 80.5, 76.1, 60.2, 44.9, 37.8, 35.4, 25.6. HRMS (ESI): m/z [$\text{M} + \text{Na}^+$] calcd for $\text{C}_{23}\text{H}_{20}\text{F}_2\text{NaO}_4$: 421.1222; found 421.1214.

- **289**

Yield: 19% of **289b** (36 mg from **277a** (80 mg)) (System of isomers **289a/289b** (?:?)).

- (3*R*,6*a'**S*)-2,2-bis(4-chlorophenyl)dihydro-3'*H*,4'*H*-spiro[oxetane-3,2'-[3*a*,6*a*](methanooxymethano)cyclopenta[*b*]furan]-9'-one **289a**

$\text{C}_{23}\text{H}_{20}\text{Cl}_2\text{O}_4$ (431.31); $R_f = 0.425$ (silica gel, Petroleum ether: EtOAc: Et₃N (75:24:1)).

- (3*S*,6*a'**S*)-2,2-bis(4-chlorophenyl)dihydro-3'*H*,4'*H*-spiro[oxetane-3,2'-[3*a*,6*a*](methanooxymethano)cyclopenta[*b*]furan]-9'-one **289b**

$\text{C}_{23}\text{H}_{20}\text{Cl}_2\text{O}_4$ (431.31), white solid; $R_f = 0.325$ (silica gel, Petroleum ether: EtOAc: Et₃N (75:24:1)). ^1H NMR (300 MHz, C_6D_6) δ 7.44-6.84 (m, 8H), 4.31 (d, $J = 6.3$ Hz, 1H), 4.01 (d, $J = 6.3$ Hz, 1H), 3.95 (d, $J = 10.3$ Hz, 1H), 3.32 (d, $J = 10.3$ Hz, 1H), 2.26 (d, $J = 14.8$ Hz, 1H), 1.59 (d, $J = 14.8$ Hz, 1H), 1.70 – 0.75 (m, 6H). ^{13}C NMR (126 MHz, C_6D_6) δ 178.2, 139.9, 139.8, 133.6, 133.2, 127.9, 127.6, 98.6, 94.7, 91.2, 80.6, 76.1, 60.3, 44.7, 37.8, 35.3, 26.8. HRMS (ESI): m/z [$\text{M} + \text{Na}^+$] calcd for $\text{C}_{23}\text{H}_{20}\text{Cl}_2\text{NaO}_4$: 453.0631; found 453.0631.

- **290**

Yield: 49% (93 mg from **277b** (97 mg)) (System of isomers **290a/290b** (4:1)).

- (3*R*,7*a'**S*)-2,2-diphenyltetrahydro-3'*H*-spiro[oxetane-3,2'-[3*a*,7*a*](methanooxymethano)benzofuran]-10'-one **290a**

$\text{C}_{24}\text{H}_{24}\text{O}_4$ (376.45), white solid; $R_f = 0.388$ (silica gel, Petroleum ether: EtOAc: Et₃N (75:24:1)). ^1H NMR (300 MHz, C_6D_6) δ 7.90-7.80 (d, $J = 7.9$ Hz, 2H), 7.66-7.59 (d, $J = 7.9$ Hz, 2H), 7.33-7.21 (m, 3H), 7.20-7.06 (m, 3H), 4.59 (d, $J = 5.8$ Hz, 1H), 4.54 (d, $J = 5.8$ Hz, 1H), 3.70 (d, $J = 10.3$ Hz, 1H), 3.40 (d, $J = 10.3$ Hz, 1H), 2.44 (d, $J = 13.5$ Hz, 1H), 2.00 (d, $J = 13.5$ Hz, 1H), 1.53-0.66 (m, 8H). ^{13}C NMR (126 MHz, C_6D_6) δ 179.1, 142.6, 142.0, 128.2, 127.9, 127.6, 127.1, 126.9,

125.5, 95.1, 86.6, 86.5, 81.1, 71.3, 50.1, 40.2, 30.7, 27.4, 22.6, 19.7. **HRMS** (ESI): m/z $[M + Na^+]$ calcd for $C_{24}H_{24}NaO_4$: 399.1567; found 399.1566.

- (3*S*,7*a'**S*)-2,2-diphenyltetrahydro-3'*H*-spiro[oxetane-3,2'-
[3*a*,7*a*](methanooxymethano)benzofuran]-10'-one **290b**

$C_{24}H_{24}O_4$ (376.45), colorless oil; R_f = 0.313 (silica gel, Petroleum ether: EtOAc: Et₃N (75:24:1)).

¹H NMR (500 MHz, CDCl₃) δ 7.90-7.82 (m, 4H), 7.30-7.20 (m, 4H), 7.10-6.94 (m, 2H), 4.54 (d, J = 6.1 Hz, 1H), 4.25 (d, J = 6.1 Hz, 1H), 3.84 (d, J = 10.3 Hz, 1H), 3.39 (d, J = 10.3 Hz, 1H), 2.86 (d, J = 14.7 Hz, 1H), 1.48 (d, J = 14.7 Hz, 1H), 1.88-0.76 (m, 8H). **¹³C NMR** (101 MHz, C₆D₆) δ 179.4, 142.8, 142.2, 131.7, 129.8, 128.4, 127.2, 126.7, 126.2, 125.6, 96.4, 87.3, 86.9, 82.1, 69.9, 51.6, 40.0, 29.0, 27.6, 26.8, 22.2, 19.4. **HRMS** (ESI): m/z $[M + Na^+]$ calcd for $C_{24}H_{24}NaO_4$: 399.1567; found 399.1566.

- **291**

Yield: 50% (101 mg from **277b** (90 mg)) (System of isomers **291a/291b** (4:1)).

- (3*R*,7*a'**S*)-2,2-bis(4-methoxyphenyl)tetrahydro-3'*H*-spiro[oxetane-3,2'-
[3*a*,7*a*](methanooxymethano)benzofuran]-10'-one **291a**

$C_{26}H_{28}O_6$ (436.50), Pale yellow oil; R_f = 0.363 (silica gel, Petroleum ether: EtOAc: Et₃N (71:28:1)). **¹H NMR** (300 MHz, C₆D₆) δ 7.79 (d, J = 8.7 Hz, 2H), 7.57 (d, J = 8.7 Hz, 2H), 6.91 (d, J = 8.7 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 4.66 (d, J = 6.0 Hz, 1H), 4.62 (d, J = 6.0 Hz, 1H), 4.75 (d, J = 10.2 Hz, 1H), 4.42 (d, J = 10.2 Hz, 1H), 3.31 (s, 3H), 3.27 (s, 3H), 2.55 (d, J = 13.5 Hz, 1H), 2.05 (d, J = 13.5 Hz, 1H), 1.57 – 0.70 (m, 8H). **¹³C NMR** (126 MHz, C₆D₆) δ 179.2, 159.0, 158.9, 135.0, 134.2, 128.4, 127.9, 127.9, 127.6, 127.2, 113.5, 113.0, 95.3, 86.9, 86.4, 81.2, 71.4, 54.4, 50.2, 40.3, 30.7, 27.4, 22.6, 19.7. **HRMS** (ESI): m/z $[M + Na^+]$ calcd for $C_{26}H_{28}NaO_6$: 459.1778; found 459.1779.

- (3*S*,7*a'**S*)-2,2-bis(4-methoxyphenyl)tetrahydro-3'*H*-spiro[oxetane-3,2'-
[3*a*,7*a*](methanooxymethano)benzofuran]-10'-one **291b**

$C_{26}H_{28}O_6$ (436.50), colorless oil; R_f = 0.300 (silica gel, Petroleum ether: EtOAc: Et₃N (71:28:1)).

¹H NMR (300 MHz, C₆D₆) δ 7.80 (d, J = 8.8 Hz, 2H), 7.77 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 4.60 (d, J = 6.2 Hz, 1H), 4.32 (d, J = 6.2 Hz, 1H), 3.89 (d, J =

10.1 Hz, 1H), 3.42 (d, $J = 10.1$ Hz, 1H), 3.28 (s, 3H), 3.24 (s, 3H), 2.91 (d, $J = 14.7$ Hz, 1H), 1.57 (d, $J = 14.7$ Hz, 1H), 1.53-0.67 (m, 8H). ^{13}C NMR (101 MHz, C_6D_6) δ 179.5, 159.0, 158.7, 135.3, 134.4, 127.8, 127.5, 127.2, 113.8, 113.0, 96.5, 87.4, 86.9, 82.1, 70.0, 54.3, 51.6, 40.0, 29.1, 27.6, 22.3, 19.5. HRMS (ESI): m/z [$\text{M} + \text{Na}^+$] calcd for $\text{C}_{26}\text{H}_{28}\text{NaO}_6$: 459.1778; found 459.1779.

- **292**

Yield: 26% of **292a** (44 mg from **277b** (81 mg)) (System of isomers **292a/292b** (3:1)).

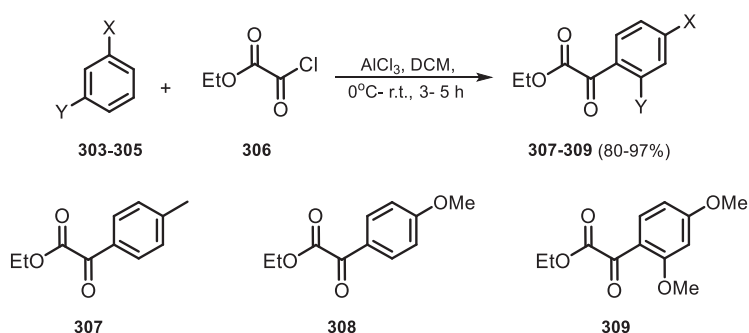
- (3*R*,7*a*'*S*)-2,2-bis(4-fluorophenyl)tetrahydro-3'*H*-spiro[oxetane-3,2'-[3*a*,7*a*](methanooxymethano)benzofuran]-10'-one **292a**

$\text{C}_{24}\text{H}_{22}\text{F}_2\text{O}_4$ (412.43), white solid; $R_f = 0.488$ (silica gel, Petroleum ether: EtOAc: Et_3N (75:24:1)). ^1H NMR (500 MHz, C_6D_6) δ 7.65-7.53 (m, 4H), 6.96-6.83 (m, 4H), 4.44 (d, $J = 6.3$ Hz, 1H), 4.15 (d, $J = 6.3$ Hz, 1H), 3.77 (d, $J = 10.4$ Hz, 1H), 3.39 (d, $J = 10.4$ Hz, 1H), 2.67 (d, $J = 14.7$ Hz, 1H), 1.45 (d, $J = 10.4$ Hz, 1H), 1.52-0.91 (m, 8H). ^{13}C NMR (126 MHz, C_6D_6) δ 179.3, 163.2, 163.0, 161.2, 161.1, 138.3, 138.3, 137.5, 137.5, 128.0, 127.9, 127.8, 127.6, 115.3, 115.1, 114.4, 114.3, 95.8, 87.1, 86.9, 82.0, 69.8, 51.6, 39.6, 29.0, 27.4, 22.2, 19.3. HRMS (ESI): m/z [$\text{M} + \text{Na}^+$] calcd for $\text{C}_{24}\text{H}_{22}\text{F}_2\text{NaO}_4$: 435.1378; found 435.1377.

- (3*S*,7*a*'*S*)-2,2-bis(4-fluorophenyl)tetrahydro-3'*H*-spiro[oxetane-3,2'-[3*a*,7*a*](methanooxymethano)benzofuran]-10'-one **292b**

$\text{C}_{24}\text{H}_{22}\text{F}_2\text{O}_4$ (412.43), $R_f = 0.375$ (silica gel, Petroleum ether: EtOAc: Et_3N (75:24:1)).

❖ Friedel–Crafts reaction



General Procedure: In a three-necked round-bottomed flask mounted with a cooling system under inert conditions, AlCl_3 (22 mmol, 2.2 equiv.) was suspended in CH_2Cl_2 (20 mL) at 0°C . To this

mixture mono-ethyl oxalyl chloride (22 mmol, 2.2 equiv.) was added dropwise over 15 min. at 0 °C an arene (10 mmol, 1.0 equiv.) was added dropwise in about 10 min., then the solution was stirred at r.t. for 2 h. After completion of the reaction, as determined by TLC, the mixture was cooled and carefully added 20 g of crushed ice and 20 mL of concentrated hydrochloric acid. Extraction was performed with CH₂Cl₂ (3 x 50 mL), the organic layer was collected and washed with 1 N NaOH (50 mL) and brine (50 mL). After the organic layer was separated and dried over Na₂SO₄, the solvent was evaporated, and the crude ethyl ester product was purified by column chromatography.^[36]

▪ Ethyl 2-oxo-2-(p-tolyl)acetate **307**

C₁₁H₁₂O₃ (192.21), colourless oil; yield: 80% (500 mg from toluene (300 mg)). *R_f* = 0.475 (silica gel, Petroleum ether: EtOAc (90:10)). ¹H NMR (300 MHz, CDCl₃) δ 7.93 – 7.86 (d, *J* = 7.91 Hz, 2H), 7.33 – 7.27 (d, *J* = 7.91 Hz, 2H), 4.44 (q, *J* = 7.04 Hz, 2H), 2.46 – 2.37 (s, 3H), 1.41 (t, *J* = 7.04 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 186.1, 164.0, 146.2, 130.1, 130.0, 129.6, 62.2, 21.9, 14.1. Spectroscopic data were in agreement with those previously reported in the literature.^[36]

▪ Ethyl 2-(4-methoxyphenyl)-2-oxoacetate **308**

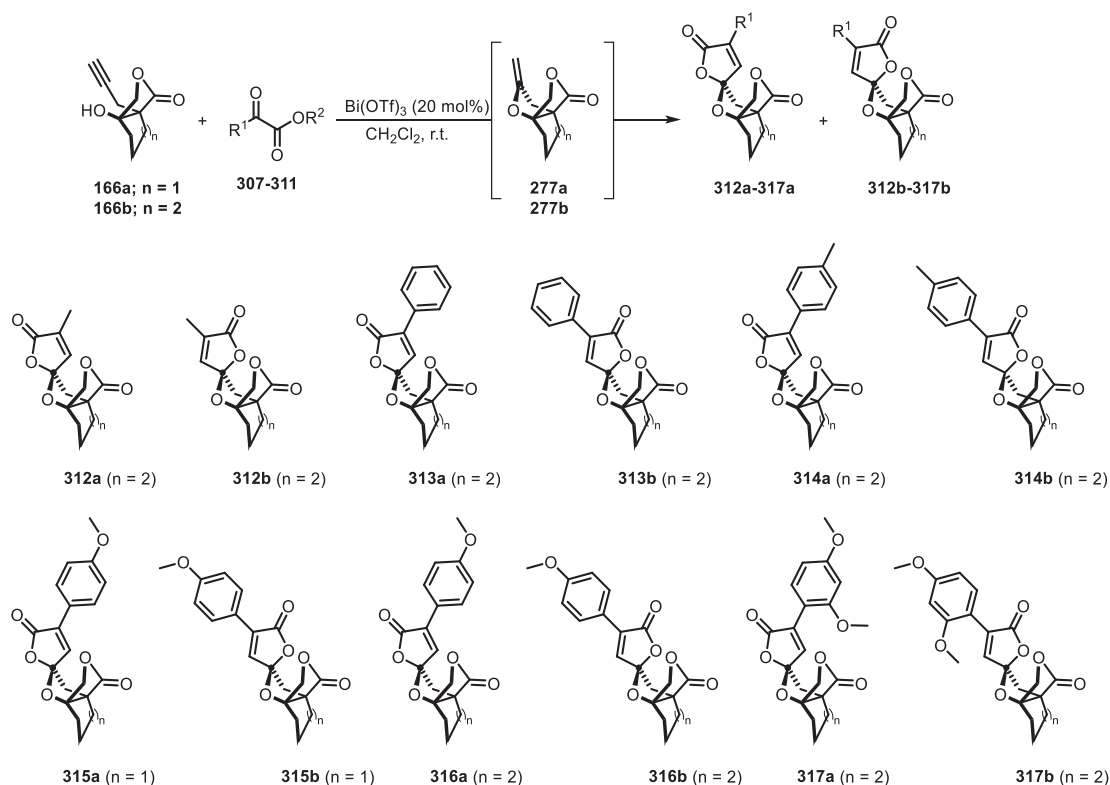
C₁₁H₁₂O₄ (208.21), yellow oil; yield: 84% (323 mg from anisole (200 mg)). *R_f* = 0.35 (silica gel, Pentane: EtOAc (85:15)). ¹H NMR (300 MHz, CDCl₃) δ 8.00 – 7.92 (d, *J* = 8.97 Hz, 2H), 6.97 – 6.89 (d, *J* = 8.97 Hz, 2H), 4.40 (q, *J* = 7.15 Hz, 2H), 3.85 (s, 3H), 1.38 (t, *J* = 7.15 Hz, 3H). ¹³C NMR (76 MHz, CDCl₃) δ 184.9, 165.0, 164.1, 132.5, 125.4, 114.2, 62.1, 55.6, 14.1. Spectroscopic data were in agreement with those previously reported in the literature.^[36]

▪ Ethyl 2-(2,4-dimethoxyphenyl)-2-oxoacetate **309**

C₁₂H₁₄O₅ (238.24), violet oil; yield: 97% (630 mg from 1,3-dimethoxybenzene (375 mg)). *R_f* = 0.370 (silica gel, Petroleum ether: EtOAc (75:25)). ¹H NMR (300 MHz, CDCl₃) δ 7.91 (d, *J* = 8.8 Hz, 1H), 6.60 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.44 (d, *J* = 2.3 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.89 (s, 3H), 3.85 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 185.0, 166.7, 166.0, 162.3, 132.9, 115.8, 106.7, 98.1, 61.6, 55.9, 55.7, 14.1. Spectroscopic data were in agreement with those previously reported in the literature.^[37]

❖ Lewis acid-catalyzed intermolecular cascade annulation of alkynols **166a/b** with α -ketoesters **307-311**.

General Procedure: The chosen alkynol (0.66 mmol, 1.0 equiv.) and α -ketoester (0.66 mmol, 1.0 equiv.) were taken into a single neck round bottom flask, then dissolved in anhydrous CH_2Cl_2 (5.0 ml). $\text{Bi}(\text{OTf})_3$ (0.13 mmol, 20 mol%) was then added under an argon atmosphere at room temperature (r.t.). The resulting reaction mixture was stirred at r.t. for respective reaction time. After completion of the reaction (typically after 14 h, monitored by TLC, visualized using UV and KMnO_4 staining solutions) the reaction was quenched with a saturated aqueous NaHCO_3 solution, then extracted with CH_2Cl_2 (2x10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , and filtered through sintered glass funnel. The filtrate was concentrated under reduced pressure and purified using silica-gel column chromatography to afford the corresponding oxaspirolactone[n,3,3]propellanes.^[38]



• **312**

Yield: 86% (117 mg from **166b** (100 mg)) (System of isomers **312a/312b** (1:1)).

- (2*S*,7*a'**S*)-4-methyl-4',5',6',7'-tetrahydro-3'*H*,5*H*-spiro[furan-2,2'-[3*a*,7*a*](methanooxymethano)benzofuran]-5,10'-dione **312a**

$C_{14}H_{16}O_5$ (264.28), white solid; $R_f = 0.688$ (silica gel, Petroleum ether: EtOAc (50:50)). **m.p.** = 145–147 °C. 1H NMR (300 MHz, $CDCl_3$) δ 6.62 (q, $J = 1.66$ Hz, 1H), 4.32 – 4.24 (d, $J = 10.74$ Hz, 1H), 4.24 – 4.21 (d, $J = 10.74$ Hz, 1H), 2.91 – 2.83 (d, $J = 14.71$ Hz, 1H), 2.67 – 2.58 (d, $J = 14.71$ Hz, 1H), 2.15 – 1.83 (m, 5H), 1.90 – 1.87 (d, $J = 1.66$ Hz, 3H), 1.53 – 1.37 (m, 3H). ^{13}C NMR (76 MHz, $CDCl_3$) δ 180.3, 171.1, 145.0, 131.8, 111.1, 89.0, 70.9, 52.3, 40.8, 28.4, 28.0, 22.8, 19.6, 10.1. **IR**: $\tilde{\nu} = 3081, 2960, 2861, 2170, 1977, 1760, 1460, 768$ cm^{-1} . **HRMS** (ESI): m/z $[M + Na]^+$ calcd for $C_{14}H_{16}NaO_5$: 287.0890; found 287.0890.

- (2*R*,7*a'**S*)-4-methyl-4',5',6',7'-tetrahydro-3'*H*,5*H*-spiro[furan-2,2'-[3*a*,7*a*](methanooxymethano)benzofuran]-5,10'-dione **312b**

$C_{14}H_{16}O_5$ (264.28), white solid; $R_f = 0.219$ (silica gel, Petroleum ether: EtOAc (50:50)). **m.p.** = 194–196 °C. 1H NMR (300 MHz, $CDCl_3$) δ 6.64 – 6.60 (q, $J = 1.60$ Hz, 1H), 4.48 – 4.40 (d, $J = 10.67$ Hz, 1H), 4.25 – 4.16 (d, $J = 10.67$ Hz, 1H), 2.68 – 2.59 (d, $J = 13.49$ Hz, 1H), 2.48 – 2.39 (d, $J = 13.49$ Hz, 1H), 2.19 – 1.98 (m, 2H), 1.96 – 1.86 (d, $J = 1.60$ Hz, 3H), 1.84 – 1.45 (m, 5H), 1.29 – 1.19 (m, 1H). ^{13}C NMR (76 MHz, $CDCl_3$) δ 179.0, 170.1, 143.4, 134.0, 110.3, 88.8, 73.5, 50.4, 42.3, 31.0, 28.3, 21.2, 19.5, 10.5. **IR**: $\tilde{\nu} = 2930, 2865, 2170, 1976, 1766, 1449, 766$ cm^{-1} . **HRMS** (ESI): m/z $[M + Na]^+$ calcd for $C_{14}H_{16}NaO_5$: 287.0890; found 287.0890.

- **313**

Yield: 61% (102 mg from **166b** (100 mg)) (System of isomers **313a/313b** (1:1)).

- (2*S*,7*a'**S*)-4-phenyl-4',5',6',7'-tetrahydro-3'*H*,5*H*-spiro[furan-2,2'-[3*a*,7*a*](methanooxymethano)benzofuran]-5,10'-dione **313a**

$C_{19}H_{18}O_5$ (326.35), white solid; $R_f = 0.488$ (silica gel, Petroleum ether: EtOAc (50:50)). **m.p.** = 168–170 °C. 1H NMR (300 MHz, $CDCl_3$) δ 7.84 – 7.75 (m, 2H), 7.44 – 7.35 (m, 3H), 7.08 (s, 1H), 4.35 – 4.29 (d, $J = 10.70$ Hz, 1H), 4.28 – 4.22 (d, $J = 10.70$ Hz, 1H), 3.04 – 2.94 (d, $J = 14.84$ Hz, 1H), 2.77 – 2.69 (d, $J = 14.84$ Hz, 1H), 2.21 – 1.86 (m, 4H), 1.78 – 1.35 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.3, 168.9, 143.2, 132.7, 130.0, 128.7, 128.3, 127.5, 110.3, 89.3, 70.9, 52.5, 41.0, 28.4, 28.0, 22.8, 19.6. **IR**: $\tilde{\nu} = 2937, 2170, 1977, 1767, 1460, 779$ cm^{-1} . **HRMS** (ESI): m/z $[M + Na]^+$ calcd for $C_{19}H_{18}NaO_5$: 349.1046; found 349.1043.

➤ (2*R*,7*a*'*S*)-4-phenyl-4',5',6',7'-tetrahydro-3'*H*,5*H*-spiro[furan-2,2'-

[3*a*,7*a*](methanooxymethano)benzofuran]-5,10'-dione **313b**

C₁₉H₁₈O₅ (326.35), pale yellow solid; **R_f** = 0.363 (silica gel, Petroleum ether: EtOAc (50:50)). **m.p.** = 200–202 °C. **¹H NMR** (300 MHz, CDCl₃) δ 7.86–7.76 (m, 2H), 7.44–7.35 (m, 3H), 7.10 (s, 1H), 4.51–4.45 (d, *J* = 10.63 Hz, 1H), 4.27–4.22 (d, *J* = 10.63 Hz, 1H), 2.77–2.69 (d, *J* = 13.59 Hz, 1H), 2.60–2.53 (d, *J* = 13.59 Hz, 1H), 2.20–2.01 (m, 3H), 1.90–1.77 (m, 1H), 1.75–1.52 (m, 4H). **¹³C NMR** (101 MHz, CDCl₃) δ 179.1, 167.8, 141.8, 134.7, 130.0, 128.7, 128.5, 127.5, 109.6, 89.1, 73.1, 50.5, 42.4, 31.0, 28.3, 21.4, 19.6. **IR**: $\tilde{\nu}$ = 3080, 2942, 2866, 2170, 1977, 1762, 1496, 747 cm⁻¹. **HRMS** (ESI): *m/z* [M + Na]⁺ calcd for C₁₉H₁₈NaO₅: 349.1046; found 349.1043.

• **314**

Yield: 74% (128 mg from **166b** (100 mg)) (System of isomers **314a/314b** (1:1)).

• (2*S*,7*a*'*S*)-4-(*p*-tolyl)-4',5',6',7'-tetrahydro-3'*H*,5*H*-spiro[furan-2,2'-

[3*a*,7*a*](methanooxymethano)benzofuran]-5,10'-dione **314a**

C₂₀H₂₀O₅ (340.38), white solid; **R_f** = 0.625 (silica gel, Petroleum ether: EtOAc (65:35)). **m.p.** = 140–142 °C. **¹H NMR** (500 MHz, CDCl₃) δ 7.73–7.68 (d, *J* = 8.27 Hz, 2H), 7.22–7.18 (d, *J* = 8.27 Hz, 2H), 7.03 (s, 1H), 4.34–4.29 (d, *J* = 10.70 Hz, 1H), 4.27–4.24 (d, *J* = 10.70 Hz, 1H), 3.00–2.95 (d, *J* = 14.80 Hz, 1H), 2.75–2.70 (d, *J* = 14.80 Hz, 1H), 2.36 (s, 3H), 2.23–1.87 (m, 4H), 1.77–1.69 (m, 1H), 1.54–1.40 (m, 2H), 1.30–1.18 (m, 1H). **¹³C NMR** (126 MHz, CDCl₃) δ 180.3, 169.0, 142.2, 140.3, 132.6, 129.4, 127.4, 125.4, 110.3, 89.2, 70.9, 52.5, 41.1, 28.4, 28.0, 22.8, 21.4, 19.6. **IR**: $\tilde{\nu}$ = 2937, 1976, 1766, 1126, 821.69 cm⁻¹. **HRMS** (ESI): *m/z* [M + Na]⁺ calcd for C₂₀H₂₀NaO₅: 363.1203; found 363.1191.

• (2*R*,7*a*'*S*)-4-(*p*-tolyl)-4',5',6',7'-tetrahydro-3'*H*,5*H*-spiro[furan-2,2'-

[3*a*,7*a*](methanooxymethano)benzofuran]-5,10'-dione **314b**

C₂₀H₂₀O₅ (340.38), white solid; **R_f** = 0.240 (silica gel, Petroleum ether: EtOAc (65:35)). **m.p.** = 197–199 °C. **¹H NMR** (500 MHz, CDCl₃) δ 7.67–7.62 (d, *J* = 7.91 Hz, 2H), 7.15–7.11 (d, *J* = 7.91 Hz, 2H), 6.98 (s, 1H), 4.43–4.39 (d, *J* = 10.98 Hz, 1H), 4.20–4.15 (d, *J* = 10.98 Hz, 1H), 2.68–2.62 (d, *J* = 13.47 Hz, 1H), 2.52–2.47 (d, *J* = 13.47 Hz, 1H), 2.29 (s, 3H), 2.12–1.98 (m, 2H), 1.82–1.72 (m, 1H), 1.68–1.47 (m, 4H), 1.39–1.26 (m, 1H). **¹³C NMR** (126 MHz, CDCl₃)

δ 179.1, 168.0, 140.7, 140.3, 134.6, 129.4, 127.4, 125.7, 109.6, 89.0, 73.2, 50.5, 42.5, 31.1, 28.3, 21.4, 21.3, 19.6. **IR:** $\tilde{\nu}$ = 2945, 2169, 1976, 1764, 962, 661 cm^{-1} . **HRMS** (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{20}\text{NaO}_5$: 363.1203; found 363.1191.

- **315**

Yield: 69% (99 mg isolated from **166a** (76 mg)) (System of isomers **315a/315b** (1:1)).

- (2*S*,6*a'**S*)-4-(4-methoxyphenyl)-5',6'-dihydro-3'*H*,4'*H*,5'*H*-spiro[furan-2,2'-[3*a*,6*a*](methanooxymethano)cyclopenta[*b*]furan]-5,9'-dione **315a**

$\text{C}_{19}\text{H}_{18}\text{O}_6$ (342.35), orange oil; R_f = 0.775 (silica gel, Pentane: EtOAc (54:46)). **¹H NMR** (500 MHz, CDCl_3) δ 8.05 – 7.96 (d, J = 8.80 Hz, 2H), 7.26 (s, 1H), 7.00 – 6.95 (d, J = 8.28 Hz, 2H), 4.56 – 4.51 (d, J = 10.21 Hz, 1H), 4.31 – 4.26 (d, J = 10.21 Hz, 1H), 3.89 (s, 3H), 3.16 – 3.09 (d, J = 16.80 Hz, 1H), 2.93 – 2.85 (d, J = 16.80 Hz, 1H), 2.31 – 2.7. (m, 6H). **¹³C NMR** (126 MHz, CDCl_3) δ 180.5, 165.0, 164.1, 132.2, 131.8, 128.5, 109.1, 97.4, 80.0, 62.1, 55.6, 41.9, 39.9, 38.4, 36.7, 29.7, 27.1. **HRMS** (ESI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{19}\text{O}_6$: 343.1176; found 343.1177 and m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{18}\text{NaO}_6$: 365.0996; found 365.0994.

- (2*R*,6*a'**S*)-4-(4-methoxyphenyl)-5',6'-dihydro-3'*H*,4'*H*,5'*H*-spiro[furan-2,2'-[3*a*,6*a*](methanooxymethano)cyclopenta[*b*]furan]-5,9'-dione **315b**

$\text{C}_{19}\text{H}_{18}\text{O}_6$ (342.11), yellow solid; R_f = 0.350 (silica gel, Pentane: EtOAc (54:46)). **m.p.** = 195–197 °C. **¹H NMR** (500 MHz, CDCl_3) δ 7.81 – 7.78 (d, J = 8.28 Hz, 2H), 7.06 (s, 1H), 6.95 – 6.90 (d, J = 8.28 Hz, 2H), 4.74 – 4.69 (d, J = 11.88 Hz, 1H), 4.34 – 4.69 (d, J = 11.88 Hz, 1H), 3.84 (s, 3H), 2.87 – 2.79 (d, J = 13.68 Hz, 1H), 2.37 – 2.32 (d, J = 13.68 Hz, 1H), 2.31 – 2.7. (m, 6H). **¹³C NMR** (126 MHz, CDCl_3) δ 178.6, 168.1, 161.1, 137.6, 129.1, 120.9, 114.2, 113.8, 100.2, 78.6, 61.0, 55.3, 48.8, 46.7, 39.7, 37.2, 27.3. **IR:** $\tilde{\nu}$ = 2952, 1981, 1760, 1617, 1268, 827 cm^{-1} . **HRMS** (ESI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{19}\text{O}_6$: 343.1176; found 343.1177 and m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{18}\text{NaO}_6$: 365.0996; found 365.0994.

- **316**

Yield: 87% (146 mg from **166b** (91 mg)) (System of isomers **316a/316b** (1:1)).

- (2*S*,7*a*'*S*)-4-(4-methoxyphenyl)-4',5',6',7'-tetrahydro-3'*H*,5*H*-spiro[furan-2,2'-[3*a*,7*a*](methanooxymethano)benzofuran]-5,10'-dione **316a**

C₂₀H₂₀O₆ (356.37), white solid; **R_f** = 0.775 (silica gel, Petroleum ether: EtOAc (50:50)). **m.p.** = 161–163 °C. **¹H NMR** (500 MHz, CDCl₃) δ 7.81 – 7.76 (d, *J* = 9.05 Hz, 2H), 6.96 (s, 1H), 6.94 – 6.89 (d, *J* = 9.05 Hz, 2H), 4.34 – 4.30 (d, *J* = 10.84 Hz, 1H), 4.28 – 4.24 (d, *J* = 10.84 Hz, 1H), 3.83 (s, 3H), 3.00 – 2.95 (d, *J* = 14.51 Hz, 1H), 2.75 – 2.70 (d, *J* = 14.51 Hz, 1H), 2.21 – 2.05 (m, 2H), 2.03 – 1.89 (m, 2H), 1.75 (m, 1H), 1.54 – 1.43 (m, 2H), 1.25 (m, 1H). **¹³C NMR** (126 MHz, CDCl₃) δ 180.4, 169.2, 160.9, 140.8, 132.1, 129.0, 120.8, 114.1, 110.3, 89.1, 70.9, 55.3, 52.5, 41.1, 28.5, 28.0, 22.8, 19.6. **IR**: $\tilde{\nu}$ = 2947, 2160, 1978, 1772, 1630, 1511, 1001, 849 cm⁻¹. **HRMS** (ESI): *m/z* [M + Na]⁺ calcd for C₂₀H₂₀NaO₆: 379.1152; found 379.1145.

- (2*R*,7*a*'*S*)-4-(4-methoxyphenyl)-4',5',6',7'-tetrahydro-3'*H*,5*H*-spiro[furan-2,2'-[3*a*,7*a*](methanooxymethano)benzofuran]-5,10'-dione **316b**

C₂₀H₂₀O₆ (356.37), pale yellow solid; **R_f** = 0.425 (silica gel, Petroleum ether: EtOAc (50:50)). **m.p.** = 201–203 °C. **¹H NMR** (500 MHz, CDCl₃) δ 7.82 – 7.78 (d, *J* = 8.80 Hz, 2H), 6.97 (s, 1H), 6.94 – 6.89 (d, *J* = 8.80 Hz, 2H), 4.51 – 4.46 (d, *J* = 10.75 Hz, 1H), 4.26 – 4.22 (d, *J* = 10.75 Hz, 1H), 3.83 (s, 3H), 2.74 – 2.70 (d, *J* = 13.67 Hz, 1H), 2.56 – 2.52 (d, *J* = 13.67 Hz, 1H), 2.17 – 2.04 (m, 2H), 1.87 – 1.78 (m, 1H), 1.72 – 1.55 (m, 4H), 1.46 – 1.37 (m, 1H). **¹³C NMR** (126 MHz, CDCl₃) δ 179.1, 168.1, 161.0, 139.1, 134.1, 129.0, 121.1, 114.1, 109.6, 88.9, 73.2, 55.3, 50.5, 42.6, 31.1, 28.3, 21.3, 19.6. **IR**: $\tilde{\nu}$ = 2949, 1977, 1764, 1612, 1268, 824 cm⁻¹. **HRMS** (ESI): *m/z* [M + Na]⁺ calcd for C₂₀H₂₀NaO₆: 379.1152; found 379.1145.

- **317**

Yield: 37% (61 mg from **166b** (82 mg)) (System of isomers **317a/317b** (1:1)).

- (2*S*,7*a*'*S*)-4-(2,4-dimethoxyphenyl)-4',5',6',7'-tetrahydro-3'*H*,5*H*-spiro[furan-2,2'-[3*a*,7*a*](methanooxymethano)benzofuran]-5,10'-dione **317a**

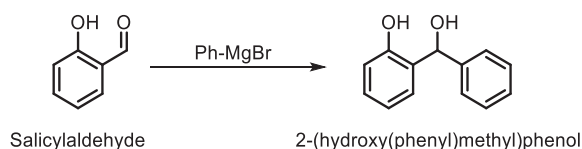
C₂₁H₂₂O₇ (386.40), white solid; **R_f** = 0.613 (silica gel, Petroleum ether: EtOAc (50:50)). **¹H NMR** (300 MHz, CDCl₃) δ 8.27 – 8.18 (d, *J* = 8.72 Hz, 1H), 7.35 (s, 1H), 6.53 – 6.50 (dd, *J* = 8.72, 2.47 Hz, 1H), 6.50 – 6.46 (d, *J* = 2.47 Hz, 1H), 4.37 – 4.30 (d, *J* = 10.75 Hz, 1H), 4.25 – 4.21 (d, *J* = 10.75 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.04 – 2.95 (d, *J* = 14.78 Hz, 1H), 2.74 – 2.65 (d, *J* = 14.78 Hz, 1H), 2.26 – 2.09 (m, 2H), 2.03 – 1.83 (m, 2H), 1.65 – 1.37 (m, 4H). **¹³C NMR** (126

MHz, CDCl₃) δ 180.6, 170.2, 161.8, 159.8, 144.2, 130.9, 127.2, 110.6, 110.4, 104.3, 98.5, 89.0, 71.0, 55.4, 55.4, 52.5, 41.4, 28.5, 28.2, 22.8, 19.6. **HRMS** (ESI): m/z [M + Na]⁺ calcd for C₂₁H₂₂NaO₇ : 409.1258; found 409.1251.

- (2*R*,7*a*'*S*)-4-(2,4-dimethoxyphenyl)-4',5',6',7'-tetrahydro-3'*H*,5*H*-spiro[furan-2,2'-[3*a*,7*a*](methanooxymethano)benzofuran]-5,10'-dione **317b**

C₂₁H₂₂O₇ (386.40), pale yellow solid; **R_f** = 0.313 (silica gel, Petroleum ether: EtOAc (50:50)). **¹H NMR** (300 MHz, CDCl₃) δ 8.30 – 8.22 (d, J = 9.00 Hz, 1H), 7.35 (s, 1H), 6.57 – 6.51 (dd, J = 9.00, 2.57 Hz, 1H), 6.51 – 6.47 (d, J = 2.57 Hz, 1H), 4.53 – 4.46 (d, J = 11.03 Hz, 1H), 4.27 – 4.20 (d, J = 11.03 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 2.75 – 2.66 (d, J = 14.29 Hz, 1H), 2.58 – 2.49 (d, J = 14.29 Hz, 1H), 2.19 – 2.04 (m, 2H), 1.76 – 1.52 (m, 4H), 1.35 – 1.19 (m, 2H). **¹³C NMR** (126 MHz, CDCl₃) δ 179.2, 169.0, 161.8, 159.7, 142.5, 131.1, 129.2, 110.7, 109.7, 104.3, 98.6, 88.6, 73.3, 55.4, 55.4, 50.6, 42.7, 31.1, 28.4, 21.2, 19.6. **HRMS** (ESI): m/z [M + Na]⁺ calcd for C₂₁H₂₂NaO₇ : 409.1258; found 409.1251.

❖ Preparation of 2-(hydroxy(phenyl)methyl)phenol



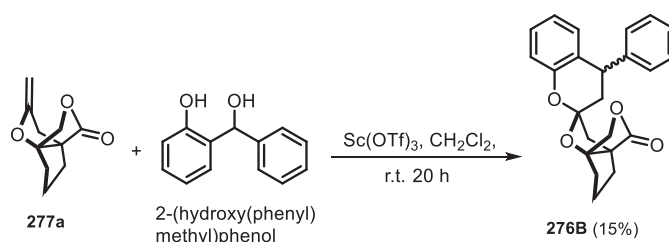
To a solution of magnesium (23.0 mmol) and a granule of I₂ in anhydrous Et₂O (10 ml) was added dropwise a solution of bromobenzene (23.0 mmol) in anhydrous Et₂O (6 ml), controlling the speed to maintain ether boiling. After adding, the system was refluxed for 30 min. Then cooled to 0 °C, a solution of salicylaldehyde (5.73 mmol) in THF (6 ml) was added dropwise to the mixture in 15 min, and then the system was refluxed for a subsequent 30 min. After refluxing, saturated NH₄Cl was added dropwise to the system at 0 °C, then the resulting solution was extracted with Et₂O (20 ml × 3). The combined organic extracts were dried with anhydrous sodium sulphate and concentrated in vacuo. The residue was chromatographed on silica gel to give 1a 2-(hydroxy(phenyl)methyl)phenol.^[39]

- 2-(hydroxy(phenyl)methyl)phenol

$C_{13}H_{12}O_2$ (200.24), white solid; yield: 75% (860 mg isolated from salicylaldehyde (700 mg)); $R_f = 0.738$ (silica gel, Petroleum ether: EtOAc (75:25)). 1H NMR (300 MHz, $CDCl_3$) δ 7.91 (s, 1 H), 7.32-7.29 (m, 5 H), 7.14-7.12 (m, 1 H), 6.85-6.76 (m, 3 H), 5.91 (d, $J = 2.70$ Hz, 1 H), 3.35 (d, $J = 2.70$ Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 142.0, 129.1, 128.6, 128.3, 127.9, 127.3, 126.8, 120.1, 116.9, 76.1. *Spectroscopic data matches that reported in the literature.*^[39]

❖ Spiroketal 276B

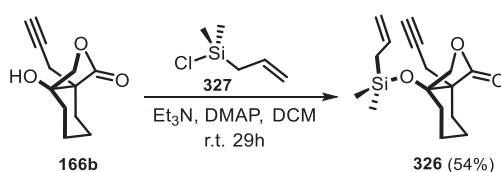
To a mixture of 2-(hydroxy(phenyl)methyl)phenol (0.07 mmol), **277a** (0.166 mmol) and $Sc(OTf)_3$ (0.03 mmol, 40 mol %) under argon atmosphere, 2 mL of dry DCM was added. The reaction system was stirred at room temperature for 20 hours. After the reaction was completed (determined by TLC analysis), the reaction mixture was filtered and evaporated under reduced pressure, and purified by column chromatography to give the desired product **276B**.^[40]



- (2*S*,4*R*,6*a'**S*)-4-phenyl-5',6'-dihydro-3'*H*,4'*H*-spiro[chromane-2,2']-[3*a*,6*a*](methanooxymethano)cyclopenta[*b*]furan]-9'-one **276B**

$C_{23}H_{22}O_4$ (362.43), white oil; yield: 15% (9 mg isolated from **277a** (30 mg)). $R_f = 0.125$ (silica gel, Petroleum ether: EtOAc: Et_3N (75:24:1)). 1H NMR (300 MHz, C_6D_6) δ 7.18-6.81 (m, 9H), 4.60 (d, $J = 10.3$ Hz, 1H), 3.70 (d, $J = 10.3$ Hz, 1H), 3.76 (dd, $J = 9.5, 7.2$ Hz, 1H), 2.24 (dd, $J = 13.4, 9.5$ Hz, 1H), 1.95 (dd, $J = 13.4, 7.2$ Hz, 1H), 1.74-1.02 (m, 8H).

❖ O-Silylation reaction of 166b

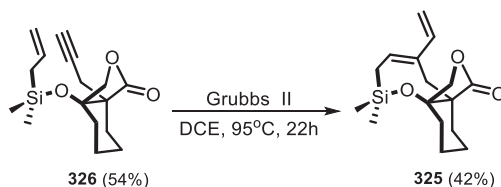


Compound **327** (0.17 ml, 1.13 mmol) was added dropwise to a stirred solution of propargylic alcohol **166b** (1.03 mmol), NEt₃ (0.29 ml, 2.06 mmol) and DMAP (13 mg, 0.10 mmol) in CH₂Cl₂ (10 ml). The reaction mixture was stirred at room temperature for 29 h. Distilled water (2 ml) was then added to the reaction, the aqueous layer was extracted with CH₂Cl₂ (10 ml). The combined organic layers were dried with MgSO₄ and filtered. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography to afford **326**.^[41]

- (3a*S*)-3a-((allyldimethylsilyl)oxy)-7a-(prop-2-yn-1-yl)hexahydroisobenzofuran-1(3H)-one **326**

C₁₆H₂₄O₃Si (292.45), yellow oil; yield: 54% (162 mg isolated from **166b** (200 mg)). *R_f* = 0.350 (silica gel, Petroleum ether: EtOAc (93:7)). ¹H NMR (500 MHz, CDCl₃) δ 5.74 (m, 1H), 4.88 (dd, *J* = 15.6, 1.4 Hz, 1H), 4.88 (d, *J* = 11.5, 1.4 Hz, 1H), 4.15 (d, *J* = 9.2 Hz, 1H), 4.12 (d, *J* = 9.2 Hz, 1H), 2.58 (dd, *J* = 17.5, 2.8 Hz, 1H), 2.47 (dd, *J* = 17.5, 2.8 Hz, 1H), 2.05 (t, *J* = 2.7 Hz, 1H), 1.93-1.83 (m, 2H), 1.80-1.57 (m, 6H), 1.47-1.35 (m, 2H), 0.16 (s, 3H), 0.15 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 178.1, 133.4, 114.3, 80.4, 79.2, 73.7, 71.3, 48.8, 33.4, 29.7, 25.9, 22.1, 21.1, 21.1, 0.1, 0.0. HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₆H₂₄NaO₃Si : 315.1387; found 315.1382.

❖ Synthesis of diene **325**



To a round-bottom flask under an argon atmosphere, Grubbs II (7.40 mg, 3 mol%), enyne **326** (85 mg, 0.29 mol) and 87 ml of degassed dichloromethane were introduced. The reaction mixture was then heated at 95°C for 22 hours. The solvent was then removed under vacuum and the crude product was purified by flash chromatography to give diene **325**.^[41-42]

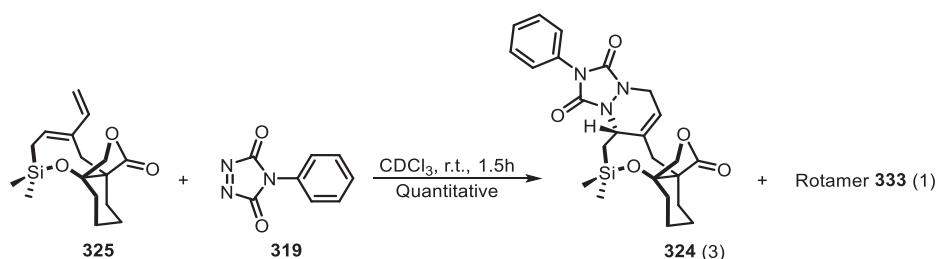
- (10a*S,E*)-2,2-dimethyl-5-vinyl-3,6,7,8,9,10-hexahydro-2H-6a,10a-(methanooxymethano)benzo[*g*][1,2]oxasilocin-13-one **325**

C₁₆H₂₄O₃Si (292.45), pale orange oil; yield: 42% (36 mg isolated from **326** (85 mg)). *R_f* = 0.350 (silica gel, Petroleum ether: EtOAc (95:5)). ¹H NMR (500 MHz, CDCl₃) δ 6.33 (dd, *J* = 17.8, 11.0 Hz, 1H), 5.94 (t, *J* = 8.3 Hz, 1H), 5.20 (d, *J* = 17.7 Hz, 1H), 4.91 (d, *J* = 11.0 Hz, 1H), 4.40 (d, *J* =

8.4 Hz, 1H), 3.74 (d, $J = 8.4$ Hz, 1H), 2.49 (d, $J = 14.4$ Hz, 1H), 2.45 (d, $J = 14.4$ Hz, 1H), 2.04-1.13 (m, 10H), 0.13 (s, 3H), 0.20 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 178.1, 137.9, 134.4, 130.0, 109.7, 77.3, 73.5, 51.3, 37.5, 30.3, 24.9, 21.7, 20.6, 19.6, 0.0, -0.2. HRMS (ESI): m/z [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{16}\text{H}_{24}\text{NaO}_3\text{Si}$: 315.1387; found 315.1382.

❖ PTAD-based [6,4,3]propellane

To a solution of diene **325** (26.0 mg, 1.0 equiv.) in deuterated chloroform (0.7 ml), 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) (16.3 mg, 1.1 equiv.) was added in one portion. The obtained solution was kept stirring at room temperature for 1.5 hours which was accompanied by a radical change in color (from red to brown). The reaction mixture was then filtered and characterized without further purification. NMR analysis revealed a complete conversion of the starting material to **324** and its rotamer **333** in a ratio of 3:1.^[43]



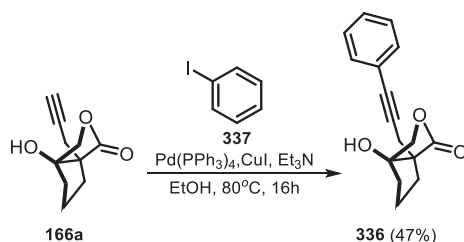
- (7a*R*,10a*S*)-9,9-dimethyl-5-phenyl-2,7a,8,11,12,13,14,15-octahydro-4*H*,9*H*-10a,14a-(methanooxymethano)benzo[7,8][1,2]oxasilocino[4,5-*c*][1,2,4]triazolo[1,2-*a*]pyridazine-4,6,16(5*H*)-trione **324/333**

$\text{C}_{24}\text{H}_{29}\text{N}_3\text{O}_5\text{Si}$ (467.60), pale green oil; 96% (40 mg isolated from **325** (26 mg)). **324**: ^1H NMR (500 MHz, CDCl_3) δ 7.54-7.34 (m, 5H), 5.90 (brd, 1H), 4.48 (brd, 1H), 4.38-4.31 (dd, $J = 16.2$, 1.7 Hz, 1H), 4.10-4.03 (dd, $J = 16.2$, 1.7 Hz, 1H), 4.33-4.28 (d, $J = 9.7$ Hz, 1H), 4.03-3.99 (d, $J = 9.7$ Hz, 1H), 3.01-2.95 (d, $J = 14.9$ Hz, 1H), 2.39-2.32 (d, $J = 14.9$ Hz, 1H), 2.19-1.20 (m, 8H), 1.38-1.28 (m, 2H), 0.27 (s, 3H), 0.18 (s, 3H). **333**: ^1H NMR (500 MHz, CDCl_3) δ 7.54-7.34 (m, 5H), 5.85 (brd, 1H), 4.50 (brd, 1H), 4.33-4.28 (m, 1H), 4.02-3.97 (m, 1H), 4.25-4.21 (d, $J = 8.3$ Hz, 1H), 3.94-3.91 (d, $J = 8.3$ Hz, 1H), 2.64-2.56 (d, $J = 15.5$ Hz, 1H), 2.15-2.09 (d, $J = 15.5$ Hz, 1H), 2.19-1.20 (m, 8H), 1.38-1.28 (m, 2H), 0.33 (s, 3H), 0.14 (s, 3H). **324**: ^{13}C NMR (126 MHz, CDCl_3) δ 181.1, 154.5, 152.1, 134.9, 131.9, 129.9, 128.9, 126.0, 125.9, 81.3, 75.6, 57.1, 50.8, 45.3, 38.1, 33.6, 32.5, 24.2, 23.3, 21.5, 2.8, 0.0. **333**: ^{13}C NMR (126 MHz, CDCl_3) δ 179.3, 155.4, 152.4

134.5, 130.2, 129.97, 129.94, 126.5, 126.4, 78.7, 74.6, 52.9, 45.3, 45.1, 39.57, 32.9, 32.5, 24.2, 24.1, 23.3, 21.4, 2.1, 0.6. **HRMS** (ESI): m/z $[M + Na]^+$ calcd for $C_{24}H_{29}N_3NaO_5Si$: 490.1769; found 490.1768.

❖ Sonogashira coupling of **166a** with iodobenzene

A mixture of iodobenzene (2.15 mmol), $Pd(PPh_3)_4$ (0.007 mmol), CuI (0.064 mmol), and triethylamine (1.71 mmol) in EtOH (20 mL) was stirred for 30 min under a nitrogen atmosphere. To this mixture was added alkyne **166a** (1.07 mmol) slowly, and the mixture was refluxed. The reaction was monitored by thin-layer chromatography (TLC). The mixture was then cooled to room temperature and filtered through celite; EtOH was removed under reduced pressure. The residue was diluted with water (50 mL) and extracted with EtOAc (3×25 mL). The organic layers were collected, combined, washed with water (2×25 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated. The residue thus obtained was purified by column chromatography to afford the title compound **336**.^[44]

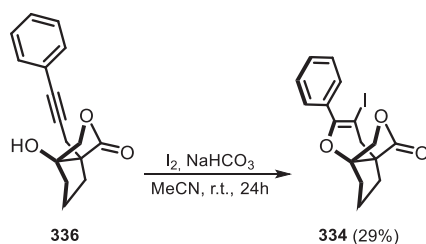


▪ (6a*S*)-3a-hydroxy-6a-(3-phenylprop-2-yn-1-yl)hexahydro-1H-cyclopenta[*c*]furan-1-one **336** $C_{16}H_{16}O_3$ (256.30), yellow oil; yield: 47% (128 mg isolated from **166a** (194 mg)). $R_f = 0.413$ (silica gel, Petroleum ether: EtOAc (65:35)). **1H NMR** (300 MHz, $CDCl_3$) δ 7.45-7.22 (m, 5H), 4.32 (d, $J = 10.0$ Hz, 1H), 4.24 (d, $J = 10.0$ Hz, 1H), 2.91 (d, $J = 16.9$ Hz, 1H), 2.79 (d, $J = 16.9$ Hz, 1H), 2.60 (s, 1H), 2.26-1.15 (m, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 180.1, 131.6, 128.6, 128.4, 122.2, 85.3, 85.0, 84.0, 78.5, 55.1, 42.2, 36.3, 22.7, 22.2. **HRMS** (ESI): m/z $[M + Na]^+$ calcd for $C_{16}H_{16}NaO_3$: 279.0992; found 279.0992.

❖ Preparation of iodo-DHP[4,3,3]propellane **334**

To a solution of **336** (70.0 mg, 0.27 mmol) in CH_3CN (20 mL) was added $NaHCO_3$ (69.0 mg, 0.82 mmol), followed by I_2 (208.0 mg, 0.82 mmol) at room temperature with stirring. The resulting mixture was allowed to stir at room temperature for 24 hours. The excess I_2 was removed by adding

a saturated aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$, followed by stirring for 5-10 min. The phases were separated, and the aqueous phase was extracted with Et_2O ($2 \times 10 \text{ mL}$). The combined organic phases were dried (Na_2SO_4) and concentrated under vacuum. The crude products were purified by column chromatography to give **334**.^[45]

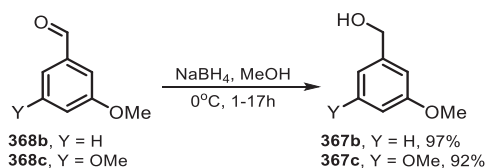


- (4*aS*)-3-iodo-2-phenyl-6,7-dihydro-4*H*,5*H*-4*a*,7*a*-(methanooxymethano)cyclopenta[*b*]pyran-10-one **334**

$\text{C}_{16}\text{H}_{15}\text{IO}_3$ (382.20), yellow-orange oil; yield: 29% (30 mg isolated from **336** (70 mg)). $R_f = 0.338$ (silica gel, Petroleum ether: EtOAc (85:15)). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.52-7.32 (m, 5H), 4.46 (d, $J = 10.1 \text{ Hz}$, 1H), 4.28 (d, $J = 10.1 \text{ Hz}$, 1H), 3.14 (d, $J = 16.6 \text{ Hz}$, 1H), 2.83 (d, $J = 16.6 \text{ Hz}$, 1H), 1.20-2.34 (m, 6H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 178.9, 152.1, 136.3, 129.2, 129.1, 127.2, 92.7, 90.1, 75.8, 66.4, 54.8, 37.4, 37.4, 36.4. **HRMS** (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{16}\text{H}_{15}\text{INaO}_3$: 404.9958; found 404.9951.

Chapter 5

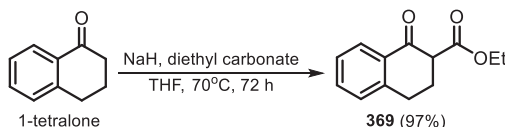
- Preparation of benzylic alcohol derivatives **367b-c**



General procedure: the selected aldehyde (1 eq.) was dissolved in MeOH (0.2 M) and cooled to 0°C . NaBH_4 (2.5 eq.) was added in portions over a period of 30 min and stirred further for 30 min at 25°C . MeOH was removed under reduced pressure, then water and ethyl acetate were added. The organic layer was separated and washed with saturated NaCl, dried (Na_2SO_4) and evaporated. After column chromatography on silica gel, the desired alcohol was isolated.^[46]

2H), 6.32 (t, $J = 2.1$ Hz, 1H), 4.36 (s, 2H), 3.71 (s, 6H). *Spectroscopic data matches that reported in the literature.*^[51]

▪ **Preparation of β -ketoester 369**



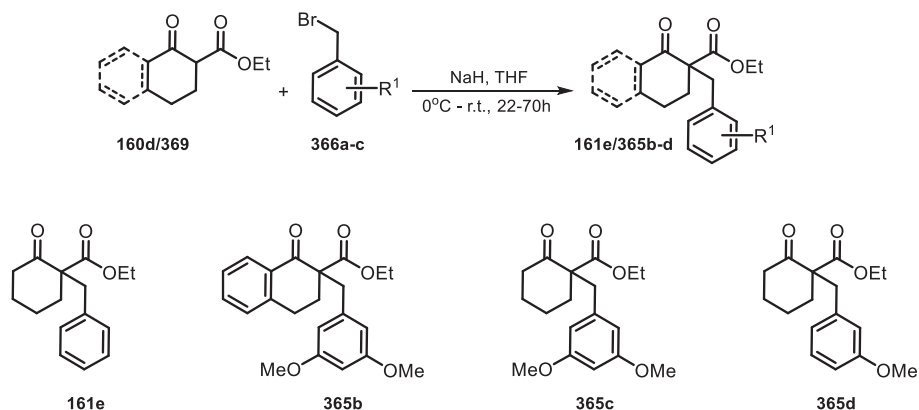
A three-necked round-bottomed flask equipped with an overhead stirrer and a dropping funnel was charged with NaH (60% mineral oil dispersion, 54.72 mmol). To this was added THF (50 mL) and diethyl carbonate (6.56 mL, 54.72 mmol). The mixture was warmed to 70°C with vigorous stirring, whereupon 1-tetralone (3.6 mL, 27.36 mmol) was added dropwise over 1 hour. After a further 72 hours, the mixture was cooled, quenched by dropwise addition of glacial acetic acid, and poured into H₂O. The mixture was extracted to EtOAc and the combined extracts washed with H₂O, dried (MgSO₄) and concentrated in vacuo. The crude product was purified by column chromatography to give **369**.^[52]

➤ Ethyl 1-tetralone-2-carboxylate **369**

C₁₃H₁₄O₃ (218.25), dark brown oil; yield: 97% (5.8 g isolated from α -tetralone (4 g)). $R_f = 0.688$ (silica gel, Petroleum ether: EtOAc (85:15)). $^1\text{H NMR}$ (500 MHz, CDCl₃) δ 12.56 (s, 1H), 7.83 (dd, $J = 7.6, 1.2$ Hz, 1H), 7.32-7.25 (m, 2H), 7.18 (d, $J = 7.0$ Hz, 1H), 4.33-4.24 (m, 2H), 2.82 (dd, $J = 9.0, 6.6$ Hz, 2H), 2.59 (dd, $J = 9.0, 6.6$ Hz, 2H), 1.37 (t, $J = 7.2$ Hz, 3H). Minor peaks due to the keto-tautomer observed at δ 8.07 (dd, $J = 7.8, 0.8$ Hz, 1H), 7.50 (td, $J = 7.6, 1.2$ Hz, 1H), 3.61 (dd, $J = 10.6, 4.8$ Hz, 1H), 3.09-2.96 (m, 2H), 2.54-2.46 (m, 1H), 2.40-2.33 (m, 1H), 1.32 (t, $J = 7.2$ Hz, 3H). $^{13}\text{C NMR}$ (101 MHz, CDCl₃) δ 172.7, 165.0, 139.3, 130.4, 130.0, 127.4, 126.8, 124.2, 97.0, 60.5, 27.7, 20.5, 14.3. Minor peaks due to the keto-tautomer observed at 193.3, 170.2, 143.7, 133.8, 131.7, 128.8, 127.6, 126.5, 61.2, 54.6, 27.6, 26.3, 14.1. *Spectroscopic data matches that reported in the literature.*^[52]

❖ Benzoylation of β -ketoester

Procedure: Same as that reported in Chapter 2.^[1]



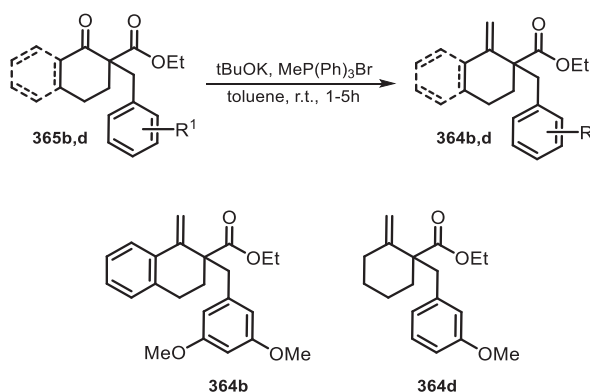
▪ Ethyl 2-(3,5-dimethoxybenzyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate **365b**
 $C_{13}H_{14}O_3$ (218.25), yellow oil; yield: 33% (82 mg isolated from **369** (687 mg)). $R_f = 0.788$ (silica gel, petroleum ether: EtOAc (80:20)). 1H NMR (300 MHz, $CDCl_3$) δ 8.07 (dd, $J = 7.9, 1.5$ Hz, 1H), 7.44 (td, $J = 7.5, 1.5$ Hz, 1H), 7.30 (d, $J = 7.9$ Hz, 1H), 7.16 (d, $J = 7.5$ Hz, 1H), 6.38 (d, $J = 2.3$ Hz, 2H), 6.30 (t, $J = 2.3$ Hz, 1H), 4.13 (q, $J = 7.1$ Hz, 2H), 3.73 (s, 6H), 3.45 (d, $J = 13.6$ Hz, 1H), 3.21 (d, $J = 13.6$ Hz, 1H), 3.08 (m, 1H), 2.84 (m, 1H), 2.48 (m, 1H), 1.99 (m, 1H), 1.15 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.6, 171.5, 160.4, 143.2, 138.8, 133.4, 132.3, 128.6, 128.1, 126.6, 108.8, 98.7, 61.5, 58.5, 55.2, 40.1, 30.3, 26.0, 14.02. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{44}H_{48}NaO_{10}$: 759.3140; found 759.3127.

▪ Ethyl 1-(3,5-dimethoxybenzyl)-2-oxocyclohexane-1-carboxylate **365c**
 $C_{18}H_{24}O_5$ (320.39), colorless oil; yield: 43% (405 mg isolated from **160d** (500 mg)). $R_f = 0.375$ (silica gel, petroleum ether: EtOAc (85:15)). 1H NMR (300 MHz, $CDCl_3$) δ 6.31 (dd, $J = 2.8, 2.7$ Hz, 2H), 6.27 (t, $J = 2.8$ Hz, 1H), 4.13 (q, $J = 7.1$ Hz, 2H), 3.74 (s, 6H), 2.45 (m, 2H), 2.57-2.47 (m, 2H), 2.05-1.93 (m, 5H), 1.27 (m, 1H), 1.20 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.2, 171.0, 160.4, 138.9, 108.9, 98.6, 62.2, 61.3, 55.2, 41.3, 40.7, 35.9, 27.6, 22.5. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{18}H_{24}NaO_5$: 343.1516; found 343.1517.

▪ Ethyl 1-(3-methoxybenzyl)-2-oxocyclohexane-1-carboxylate **365d**
 $C_{17}H_{22}O_4$ (290.36), colorless oil; yield: 55% (469 mg isolated from ethyl 2-cyclohexanonecarboxylate (500 mg)). $R_f = 0.370$ (silica gel, petroleum ether: EtOAc (90:10)).

¹H NMR (300 MHz, CDCl₃) δ 7.15 – 6.96 (dd, *J* = 8.2, 8.0, 1H), 6.75 – 6.55 (m, 3H), 4.13 – 3.92 (q, *J* = 7.1 Hz, 2H), 3.77 – 3.61 (s, 3H), 3.27 – 3.12 (d, *J* = 13.4 Hz, 1H), 2.87 – 2.72 (d, *J* = 13.4 Hz, 1H), 2.46 – 2.23 (m, 3H), 1.94 (m, 1H), 1.73 – 1.27 (m, 4H), 1.19 – 1.02 (t, *J* = 7.1 Hz, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ 207.2, 171.0, 159.2, 138.1, 128.9, 122.7, 116.2, 111.9, 62.0, 61.2, 55.1, 41.2, 40.4, 35.9, 27.6, 22.5, 13.9. **HRMS** (ESI): *m/z* [M + Na]⁺ calcd for C₁₇H₂₂NaO₄: 313.1410; found 313.1410.

❖ **Wittig reaction: isolation of intermediates 364b,d**



General procedure: To a well stirred suspension of methyltriphenylphosphonium bromide (2.0 equiv.) in anhydrous toluene under argon was added tBuOK (2.0 equiv.). The mixture was stirred at room temperature for 2 hours then the solution of the desired ketone (1.0 equiv., 1.24 M) in toluene was added. The mixture was then stirred for one more hour. After being poured to cold ether water, the mixture was extracted by ethyl acetate, then dried over MgSO₄. Evaporation of the solvent gave a crude mixture, which was chromatographed on silica gel to give the desired product.^[23]

- Ethyl 2-(3,5-dimethoxybenzyl)-1-methylene-1,2,3,4-tetrahydronaphthalene-2-carboxylate

364b

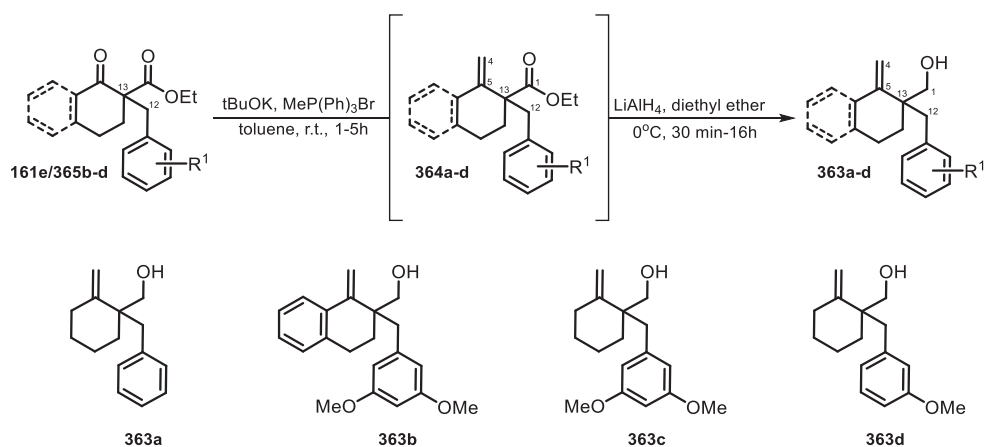
C₂₃H₂₆O₄ (366.46), white solid; yield: 71% (35 mg isolated from **365b** (50 mg)). *R_f* = 0.373 (silica gel, petroleum ether: EtOAc (90:10)). **¹H NMR** (300 MHz, CDCl₃) δ 7.55 – 7.45 (m, 1H), 7.15 – 7.05 (m, 2H), 7.05 – 6.97 (m, 1H), 6.29 (d, *J* = 2.2 Hz, 1H), 6.29 (s, 1H), 6.27 (d, *J* = 2.2 Hz, 1H), 5.59 (s, 1H), 5.26 (s, 1H), 4.06 (q, *J* = 7.1, 2H), 3.67 (s, 6H), 3.37 (d, *J* = 13.9 Hz, 1H), 2.97 – 2.65 (m, 2H), 2.77 (d, *J* = 13.9 Hz, 1H), 2.28 – 2.11 (m, 1H), 1.70 (ddd, *J* = 13.7, 8.0, 5.8 Hz, 1H), 1.11 (t, *J* = 7.1 Hz, 3H). **¹³C NMR** (76 MHz, CDCl₃) δ 174.5, 160.3, 146.2, 139.8, 136.5, 134.8, 128.4,

127.8, 126.2, 125.6, 110.8, 108.4, 98.4, 60.7, 55.2, 51.7, 43.3, 29.1, 26.3, 14.0. **HRMS** (ESI): m/z $[M + Na]^+$ calcd for $C_{23}H_{26}NaO_4$: 389.1723; found 389.1719.

▪ Ethyl 1-(3-methoxybenzyl)-2-methylenecyclohexane-1-carboxylate **364d**

$C_{23}H_{26}O_4$ (366.46), colorless oil; yield: 75% (223 mg isolated from **365d** (300 mg)). $R_f = 0.475$ (silica gel, petroleum ether: EtOAc (95:5)). **1H NMR** (300 MHz, $CDCl_3$) δ 7.08 (dd, $J = 8.2, 8.0$ Hz, 1H), 6.67 (dt, $J = 8.0, 2.8$ Hz, 1H), 6.58 (m, 2H), 4.89 (d, $J = 1.3$ Hz, 1H), 4.88 (d, $J = 1.3$ Hz, 1H), 4.12 – 3.95 (q, $J = 7.1$ Hz, 2H), 3.70 (s, 3H), 3.24 (d, $J = 13.1$ Hz, 1H), 2.72 (d, $J = 13.1$ Hz, 1H), 2.29 (m, 1H), 2.14 – 1.98 (m, 1H), 1.90 (m, 1H), 1.73 – 1.43 (m, 3H), 1.40 – 1.29 (m, 2H), 1.23 – 1.05 (t, $J = 7.1$ Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 173.9, 159.2, 150.9, 138.9, 128.8, 122.6, 116.1, 111.7, 108.3, 60.4, 55.1, 53.5, 43.1, 35.3, 34.5, 28.2, 23.0, 14.1. **HRMS** (ESI): m/z $[M + Na]^+$ calcd for $C_{18}H_{24}NaO_3$: 311.1618; found 311.1610.

❖ Reduction of exo-olefinic ester derivatives **363a-d**



General procedure: to a well stirred solution of an exo-olefinic ester (or its crude mixture in case if it is not isolated) (1.0 equiv., 0.5 M) in anhydrous diethyl ether under argon was added $LiAlH_4$ (2.0 equiv.) at 0 °C. The mixture was then stirred for 1.5-18 hours. At the end of the reaction, water was added to decompose the excess of the reagent. It is important to ensure that all the excess reagent is destroyed before continuing. The organic layer was separated and washed with sulfuric acid (0.1M), saturated NaCl, dried (Na_2SO_4) and evaporated. After column chromatography on silica gel, the desired alcohol was isolated.

▪ (1-benzyl-2-methylenecyclohexyl)methanol **363a**

$C_{15}H_{20}O$ (216.32), colorless oil; yield: 55% (for 2 steps) (1.01 g isolated from **161e** (2.2 g)). $R_f = 0.638$ (silica gel, petroleum ether: EtOAc (85:15)). 1H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.07 (m, 5H), 4.96 (d, $J = 1.2$ Hz, 1H), 4.68 (d, $J = 1.2$ Hz, 1H), 3.58 (d, $J = 11.0$ Hz, 1H), 3.38 (d, $J = 11.0$ Hz, 1H), 3.16 (d, $J = 13.1$ Hz, 1H), 2.56 (d, $J = 13.1$ Hz, 1H), 2.45 – 2.32 (m, 1H), 2.32 – 2.20 (m, 1H), 1.75 – 1.38 (m, 6H), 1.38 – 1.19 (Brd, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.0, 138.1, 130.6, 127.7, 126.0, 109.9, 64.4, 44.9, 40.0, 33.9, 33.6, 27.8, 21.8. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{15}H_{20}NaO$: 239.1406; found 239.1403.

▪ (2-(3,5-dimethoxybenzyl)-1-methylene-1,2,3,4-tetrahydronaphthalen-2-yl)methanol **363b**

$C_{21}H_{24}O_3$ (324.42), brown oil; yield: 35% (154 mg isolated from **365b** (500 mg)). $R_f = 0.600$ (silica gel, petroleum ether: EtOAc (60:40)). 1H NMR (300 MHz, $CDCl_3$) δ 7.67 – 7.58 (m, 1H), 7.23 – 7.18 (m, 2H), 7.15 – 7.08 (m, 1H), 6.33 (d, $J = 1.0$ Hz, 3H), 5.70 (s, 1H), 5.00 (s, 1H), 3.75 (s, 6H), 3.64 (d, $J = 11.0$ Hz, 1H), 3.58 (d, $J = 11.0$ Hz, 1H), 2.97 (d, $J = 13.2$ Hz, 1H), 2.85 (m, 2H), 2.69 (d, $J = 13.2$ Hz, 1H), 1.91 – 1.79 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.2, 147.3, 140.3, 136.4, 135.0, 128.7, 127.7, 126.3, 125.4, 109.8, 108.7, 98.1, 66.6, 55.2, 43.6, 40.7, 29.9, 25.8. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{21}H_{24}NaO_3$: 347.1618; found 347.1618.

▪ (1-(3,5-dimethoxybenzyl)-2-methylenecyclohexyl)methanol **363c**

$C_{17}H_{24}O_3$ (276.38), colorless oil; yield: 21% (72 mg isolated from **365c** (400 mg)). $R_f = 0.375$ (silica gel, petroleum ether: EtOAc (80:20)). 1H NMR (300 MHz, $CDCl_3$) δ 6.33 (m, 3H), 4.96 (s, 1H), 4.69 (s, 1H), 3.77 (s, 6H), 3.62-3.4 (AB, 2H), 3.10 (d, 1H), 2.50 (d, 1H), 2.25-2.07 (m, 2H), 1.68-1.39 (m, 6). HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{17}H_{24}NaO_3$: 299.1618; found 299.1612.

▪ (1-(3-methoxybenzyl)-2-methylenecyclohexyl)methanol **363d**

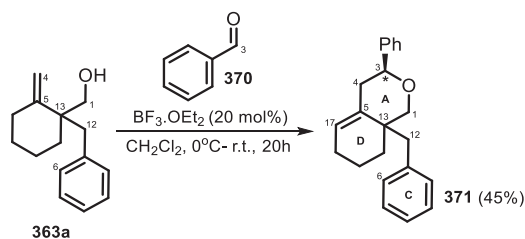
$C_{16}H_{22}O_2$ (246.35), colorless oil; yield: 69% (63 mg isolated from **365d** (107 mg)). $R_f = 0.275$ (silica gel, petroleum ether: EtOAc (80:20)). 1H NMR (400 MHz, $CDCl_3$) δ 7.14 – 7.01 (dd, $J = 8.2, 8.0$ Hz, 1H), 6.75 – 6.60 (m, 3H), 4.88 (d, $J = 1.2$ Hz, 1H), 4.59 (d, $J = 1.2$ Hz, 1H), 3.71 (s, 3H), 3.49 (d, $J = 14.3$ Hz, 1H), 3.34 (d, $J = 14.5$ Hz, 1H), 3.05 (d, $J = 13.1$ Hz, 1H), 2.46 (d, $J = 13.1$ Hz, 1H), 2.34 – 2.23 (m, 1H), 2.19 (m, 1H), 1.54 (m, 3H), 1.46 – 1.30 (m, 3H), 1.30 – 1.16 (Brd, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 151.1, 139.8, 128.6, 123.1, 116.5, 111.2, 109.9,

64.6, 55.1, 44.9, 40.1, 34.1, 33.6, 27.8, 21.8. **HRMS** (ESI): m/z $[M + Na]^+$ calcd for $C_{16}H_{22}NaO_2$: 269.1512; found 269.1509.

❖ Prins/Friedel-Crafts cyclization

General procedure: To a stirred solution of the chosen exo-olefinic alcohol (0.25 mmol) and aldehyde (0.25 mmol) in anhydrous dichloromethane (1.0 mL) was added $BF_3 \cdot OEt_2$ (0.05 mmol) at $0^\circ C$ under argon atmosphere. After the addition, the reaction mixture was stirred at room temperature for the specified time. The reaction mixture was then quenched with sat. $NaHCO_3(aq.)$ (3 mL) and extracted with ethyl acetate (20 mL, 10 mL \times 2). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate and concentrated. The crude product was purified by column chromatography, and the product was characterized and analyzed as stated below.^[53]

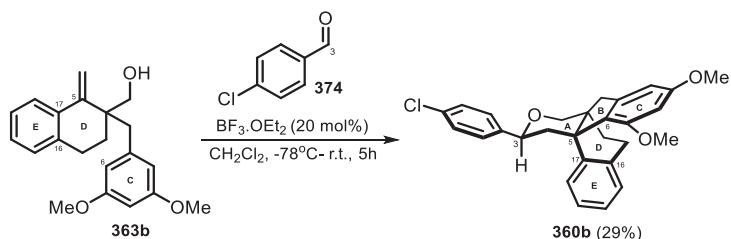
❖ First scenario



▪ (3*S*)-8a-benzyl-3-phenyl-3,4,6,7,8,8a-hexahydro-1*H*-isochromene **371**

$C_{22}H_{24}O$ (304.43), white solid; yield: 45% (63 mg isolated from **363a** (100 mg)). $R_f = 0.812$ (silica gel, petroleum ether: EtOAc (85:15)). 1H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.33 (m, 2H), 7.33 – 7.23 (m, 2H), 7.23 – 7.19 (m, 3H), 7.17 – 7.05 (m, 3H), 5.52 – 5.40 (dd, $J = 5.4, 1.7$ Hz, 1H), 4.35 – 4.20 (dd, $J = 11.7, 2.7$ Hz, 1H), 3.84 – 3.68 (d, $J = 12.4$ Hz, 1H), 3.15 (d, $J = 13.2$ Hz, 1H), 2.99 – 2.87 (d, $J = 13.2$ Hz, 1H), 2.78 – 2.64 (d, $J = 12.4$ Hz, 1H), 2.71 – 2.51 (m, 1H), 2.16 (dd, $J = 11.7, 2.7$ Hz, 1H), 2.01 – 1.79 (m, 2H), 1.66 – 1.32 (m, 3H), 0.88 – 0.64 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8, 138.9, 138.4, 131.0, 128.5, 128.0, 127.6, 126.1, 125.9, 122.6, 82.0, 75.6, 40.5, 39.3, 39.0, 27.8, 25.6, 17.9. **HRMS** (ESI): m/z $[M + Na]^+$ calcd for $C_{22}H_{24}NaO$: 327.1719; found 327.1721.

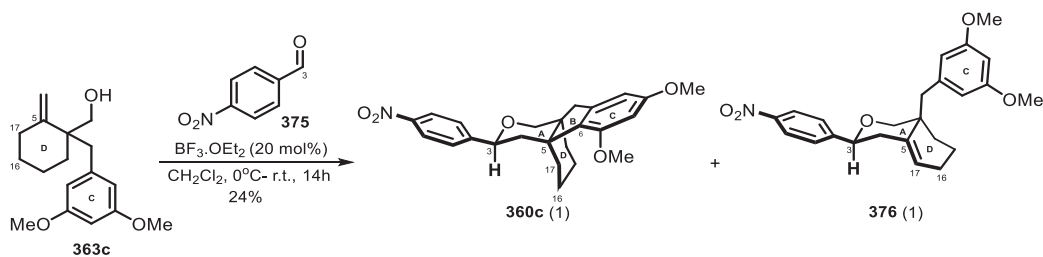
❖ **Second scenario**



- (6a*S*,11b*S*,13*S*)-13-(4-chlorophenyl)-9,11-dimethoxy-5,6-dihydro-7*H*-11b,6a-(ethanooxymethano)benzo[*c*]fluorene **360b**

$C_{28}H_{27}ClO_3$ (446.97), white solid; yield: 29% (10 mg isolated from **363b** (25 mg)). $R_f = 0.413$ (silica gel, petroleum ether: EtOAc (90:10)). 1H NMR (500 MHz, $CDCl_3$) δ 7.69 – 6.80 (m, 8H), 6.35 (d, $J = 1.9$ Hz, 1H), 6.27 (d, $J = 1.9$ Hz, 1H), 4.28 – 4.19 (dd, $J = 11.5, 1.7$ Hz, 1H), 3.92 (s, 3H), 3.70 (s, 3H), 3.64 – 3.57 (d, $J = 11.7$ Hz, 1H), 3.13 – 3.06 (dd, $J = 14.1, 1.8$ Hz, 1H), 3.05 – 2.96 (d, $J = 15.4$ Hz, 1H), 2.92 – 2.79 (dd, $J = 16.9, 6.3$ Hz, 1H), 2.60 – 2.45 (m, 1H), 2.03 – 1.93 (d, $J = 15.4$ Hz, 1H), 1.80 – 1.65 (m, 2H), 1.32 – 1.05 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.4, 157.9, 145.4, 144.2, 141.5, 132.9, 132.7, 128.8, 128.7, 128.3, 127.0, 126.5, 125.7, 125.3, 102.9, 97.5, 75.6, 55.4, 55.2, 53.3, 44.8, 40.9, 36.5, 26.3, 25.1. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{28}H_{27}ClNaO_3$: 469.1541; found 469.1541.

❖ **Third scenario**

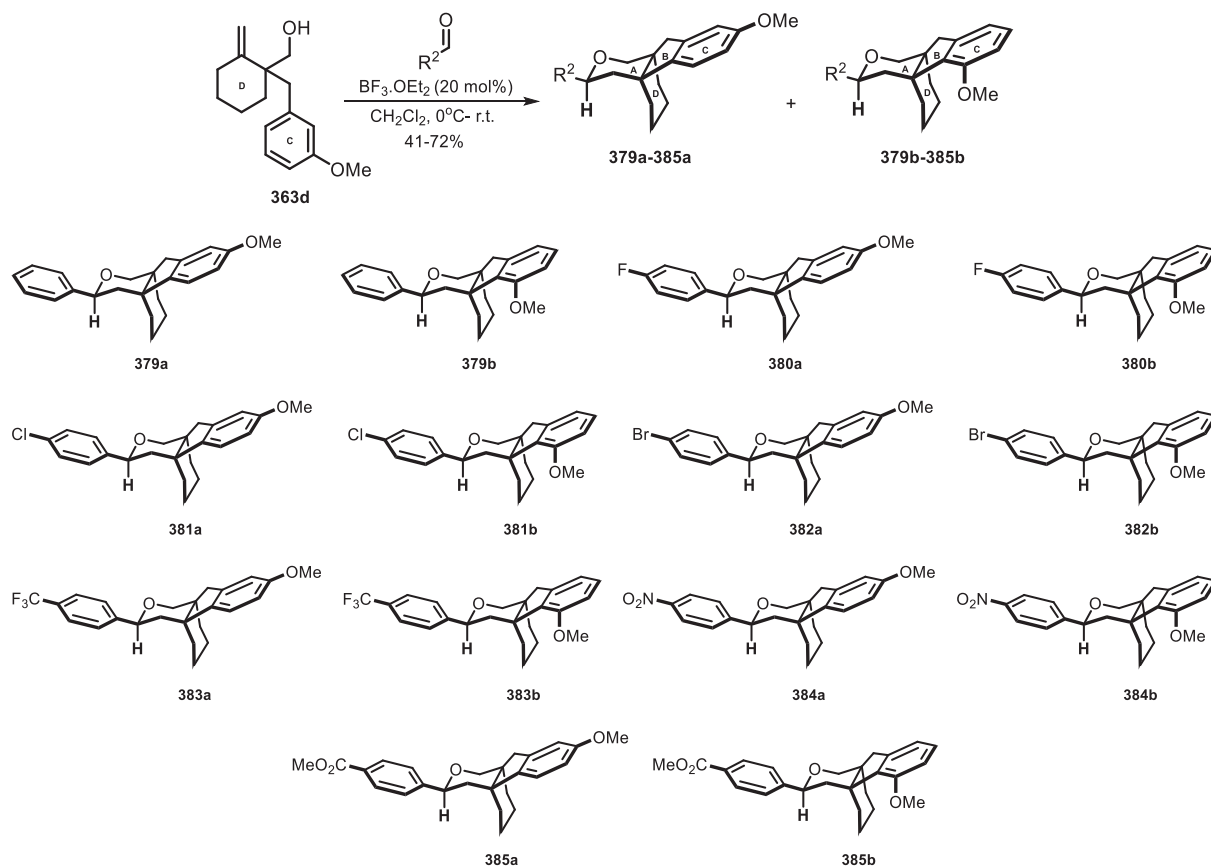


- (4a*S*,12*S*)-5,7-dimethoxy-12-(4-nitrophenyl)-1,2,3,4-tetrahydro-9*H*-4a,9a-(ethanooxymethano)fluorene **360c** + (3*S*)-8a-(3,5-dimethoxybenzyl)-3-(4-nitrophenyl)-3,4,6,7,8,8a-hexahydro-1*H*-isochromene **376**

$C_{24}H_{27}NO_5$ (409.48), yellow solid; yield: 24% (25 mg isolated from **363c** (71 mg)). $R_f = 0.500$ (silica gel, petroleum ether: EtOAc (85:15)). 1H NMR (300 MHz, $CDCl_3$) δ 8.24 (d, $J = 8.8$ Hz, 2H), 8.14 (d, $J = 8.8$ Hz, 2H), 7.64 – 7.57 (d, $J = 8.8$ Hz, 2H), 7.52 – 7.46 (d, $J = 8.8$ Hz, 2H), 6.43 (d, $J = 2.3$ Hz, 3H), 6.37 (t, $J = 2.3$ Hz, 1H), 6.26 (d, $J = 2.3$ Hz, 1H), 5.61 (dd, $J = 3.7, 1.8$ Hz,

1H), 4.65 (dd, $J = 11.9, 2.2$ Hz, 1H), 4.50 (dd, $J = 11.6, 3.0$ Hz, 1H), 3.98 (dd, $J = 15.4, 11.7$ Hz, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 3.73 (s, 3H), 3.43 (d, $J = 15.4$ Hz, 1H), 3.17 – 3.03 (m, 2H), 2.72 (dd, $J = 13.7, 10.3$ Hz, 2H), 2.64 – 2.37 (m, 1H), 2.37 – 2.24 (m, 2H), 1.96 – 1.81 (m, 3H), 1.78 – 1.12 (m, 16H). ^{13}C NMR (126 MHz, CDCl_3) δ 160.4, 160.1, 157.4, 150.6, 150.1, 147.2, 146.9, 144.2, 140.4, 137.8, 127.8, 126.4, 126.3, 126.1, 123.7, 123.5, 123.5, 123.4, 109.2, 102.7, 97.8, 97.0, 80.5, 75.7, 74.2, 69.6, 55.3, 55.2, 55.1, 48.2, 44.3, 43.6, 42.2, 40.3, 39.2, 39.2, 31.6, 27.9, 27.9, 25.5, 23.2, 22.6, 17.7. HRMS (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{24}\text{H}_{27}\text{NNaO}_5$: 432.1781; found 432.1779.

❖ Fourth scenario



- (4a*S*,9a*S*,12*S*)-7-methoxy-12-phenyl-1,2,3,4-tetrahydro-9H-4a,9a-(ethanooxymethano)fluorene **379a**

$\text{C}_{23}\text{H}_{26}\text{O}_2$ (334.46), colorless oil; $R_f = 0.350$ (silica gel, petroleum ether: EtOAc (95:5)). ^1H NMR (500 MHz, CDCl_3) δ 7.29 – 7.19 (m, 4H), 7.12 (m, 1H), 6.88 (d, $J = 8.2$ Hz, 1H), 6.76 (d, $J = 2.5$ Hz, 1H), 6.68 – 6.60 (dd, $J = 8.2, 2.5$ Hz, 1H), 4.49 – 4.40 (dd, $J = 11.3, 2.6$ Hz, 1H), 3.91 (d, $J =$

12.0, 1H), 3.77 – 3.72 (d, $J = 12.1$, 1H), 3.71 (s, 3H), 3.50 – 3.39 (d, $J = 15.1$ Hz, 1H), 2.23 (d, $J = 15.2$ Hz, 1H), 2.06 – 1.95 (m, 1H), 1.91 (d, $J = 14.1$ Hz, 1H), 1.60 – 1.39 (m, 3H), 1.38 – 1.07 (m, 5H). ^{13}C NMR (126 MHz, CDCl_3) δ 158.7, 143.0, 142.6, 142.4, 128.2, 127.3, 125.8, 121.9, 112.1, 111.6, 75.5, 70.1, 55.3, 46.4, 46.0, 44.3, 41.4, 31.4, 28.4, 22.6, 22.3. HRMS (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{23}\text{H}_{26}\text{NaO}_2$: 357.1825; found 357.1823.

▪ **380**

Yield: 68% (93 mg isolated from **363d** (96 mg)) (**380a/380b** (3:1)).

- (4a*S*,9a*S*,12*S*)-12-(4-fluorophenyl)-7-methoxy-1,2,3,4-tetrahydro-9H-4a,9a-(ethanooxymethano)fluorene **380a**

$\text{C}_{23}\text{H}_{25}\text{FO}_2$ (352.45), colorless oil; $R_f = 0.325$ (silica gel, Petroleum ether: EtOAc (95:5)). ^1H NMR (300 MHz, CDCl_3) δ 7.33 – 7.24 (m, 2H), 7.02 – 6.94 (m, 2H), 6.97 – 6.92 (d, $J = 8.1$ Hz, 1H), 6.85 (d, $J = 2.4$ Hz, 1H), 6.71 (dd, $J = 8.1, 2.4$ Hz, 1H), 4.51 (dd, $J = 10.4, 3.3$ Hz, 1H), 4.04 – 3.94 (d, $J = 12.1$ Hz, 1H), 3.85 – 3.76 (d, $J = 12.1$ Hz, 1H), 3.83 – 3.72 (s, 3H), 3.52 (d, $J = 15.4$ Hz, 1H), 2.31 (d, $J = 15.4$ Hz, 1H), 2.12 – 1.91 (m, 2H), 1.69 – 1.55 (m, 2H), 1.55 – 1.42 (m, 2H), 1.39 – 1.12 (m, 4H). ^{13}C NMR (75 MHz, CDCl_3) δ 163.6, 158.7, 142.9, 142.2, 138.5, 127.5, 127.4, 121.8, 115.1, 114.9, 112.1, 111.6, 74.8, 70.1, 55.3, 46.4, 46.0, 44.2, 41.3, 31.3, 28.3, 22.5, 22.3. ^{19}F NMR (282 MHz, CDCl_3) δ -115.39. HRMS (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{23}\text{H}_{25}\text{FNaO}_2$: 375.173079; found 375.173132.

- (4a*R*,9a*S*,12*S*)-12-(4-fluorophenyl)-5-methoxy-1,2,3,4-tetrahydro-9H-4a,9a-(ethanooxymethano)fluorene **380b**

$\text{C}_{23}\text{H}_{25}\text{FO}_2$ (352.45), pale yellow oil; $R_f = 0.463$ (silica gel, petroleum ether: EtOAc (95:5)). ^1H NMR (300 MHz, CDCl_3) δ 7.27 – 7.18 (m, 2H), 7.13 (dd, $J = 8.2, 7.5$ Hz, 1H), 6.92 – 6.84 (m, 2H), 6.79 (d, $J = 7.5$ Hz, 1H), 6.60 (d, $J = 8.2$ Hz, 1H), 4.56 (dd, $J = 11.8, 1.9$ Hz, 1H), 3.94 (d, $J = 12.3$ Hz, 1H), 3.76 – 3.70 (d, $J = 12.3$ Hz, 1H), 3.70 – 3.63 (s, 3H), 3.42 (d, $J = 14.8$ Hz, 1H), 2.25 (d, $J = 14.8$ Hz, 1H), 1.91 – 1.72 (m, 2H), 1.67 – 1.52 (m, 1H), 1.52 – 1.42 (m, 2H), 1.40 – 1.03 (m, 5H). ^{13}C NMR (101 MHz, CDCl_3) δ 163.2, 160.8, 156.8, 143.6, 138.7, 135.8, 127.6, 118.7, 115.0, 109.1, 74.4, 69.7, 55.1, 48.9, 43.8, 43.4, 41.7, 31.7, 27.9, 23.3, 22.6. ^{19}F NMR (282 MHz, CDCl_3) δ -115.58. HRMS (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{23}\text{H}_{25}\text{FNaO}_2$: 375.1731; found 375.1730.

▪ **381**

Yield: 69% (93 mg isolated from **363d** (90 mg)) (**381a**/**381b** (2.0:1)).

- (4a*S*,9a*S*,12*S*)-12-(4-chlorophenyl)-7-methoxy-1,2,3,4-tetrahydro-9H-4a,9a-(ethanooxymethano)fluorene **381a**

$C_{23}H_{25}ClO_2$ (368.90), white solid; $R_f = 0.375$ (silica gel, petroleum ether: EtOAc (95:5)). 1H NMR (300 MHz, $CDCl_3$) δ 7.17 (s, 4H), 6.88 (d, $J = 8.2$ Hz, 1H), 6.76 (d, $J = 2.3$ Hz, 1H), 6.62 (dd, $J = 8.2, 2.3$ Hz, 1H), 4.48 – 4.36 (dd, $J = 8.4, 5.0$ Hz, 1H), 3.92 – 3.85 (d, $J = 12.3$ Hz, 1H), 3.78 – 3.68 (d, $J = 12.3$ Hz, 1H), 3.75 – 3.64 (s, 3H), 3.47 – 3.35 (d, $J = 15.0$ Hz, 1H), 2.26 – 2.13 (d, $J = 15.0$ Hz, 1H), 2.01 – 1.83 (m, 2H), 1.58 – 1.45 (m, 1H), 1.45 – 1.35 (m, 2H), 1.32 – 1.02 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 142.9, 142.1, 141.2, 132.9, 128.3, 127.2, 121.8, 112.1, 111.6, 74.8, 70.0, 55.3, 46.4, 46.0, 44.2, 41.3, 31.3, 28.3, 22.5, 22.3. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{23}H_{25}ClNaO_2$: 391.1435; found 391.1438.

- (4a*R*,9a*S*,12*S*)-12-(4-chlorophenyl)-5-methoxy-1,2,3,4-tetrahydro-9H-4a,9a-(ethanooxymethano)fluorene **381b**

$C_{23}H_{25}ClO_2$ (368.90), pale yellow oil; $R_f = 0.450$ (silica gel, petroleum ether: EtOAc (95:5)). 1H NMR (300 MHz, $CDCl_3$) δ 7.26 (s, 4H), 7.12 (dd, $J = 8.2, 7.3$ Hz, 1H), 6.87 (d, $J = 7.3$ Hz, 1H), 6.68 (d, $J = 8.3$ Hz, 1H), 4.55 (dd, $J = 11.9, 2.2$ Hz, 1H), 4.01 (d, $J = 12.1$ Hz, 1H), 3.79 (d, $J = 12.1$ Hz, 1H), 3.76 (s, 3H), 3.54 – 3.43 (d, $J = 13.2$ Hz, 1H), 2.32 (d, $J = 13.2$ Hz, 1H), 1.99 – 1.79 (m, 2H), 1.70 – 1.59 (m, 1H), 1.59 – 1.48 (m, 2H), 1.43 – 1.15 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.8, 143.6, 141.5, 135.7, 132.8, 128.3, 127.6, 127.2, 118.7, 109.1, 74.3, 69.7, 55.1, 48.9, 43.8, 43.4, 41.7, 31.7, 27.9, 23.3, 22.6. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{23}H_{25}ClNaO_2$: 391.143528; found 391.143977.

▪ **382**

Yield: 57% (77 mg isolated from **363d** (80 mg)) (**382a**: **382b** (3.6:1)).

- (4a*S*,9a*S*,12*S*)-12-(4-bromophenyl)-7-methoxy-1,2,3,4-tetrahydro-9H-4a,9a-(ethanooxymethano)fluorene **382a**

$C_{23}H_{25}BrO_2$ (413.36), colorless oil; $R_f = 0.425$ (silica gel, Petroleum ether: EtOAc (90:10)). 1H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.27 (d, $J = 8.3$ Hz, 2H), 7.14 – 7.05 (d, $J = 8.3$ Hz, 2H), 6.91

– 6.84 (d, $J = 8.3$ Hz, 1H), 6.76 (d, $J = 2.3$ Hz, 1H), 6.62 (dd, $J = 8.3, 2.3$ Hz, 1H), 4.46 – 4.34 (dd, $J = 8.5, 5.5$ Hz, 1H), 3.95 – 3.85 (d, $J = 12.1$ Hz, 1H), 3.79 – 3.66 (d, $J = 12.1$ Hz, 1H), 3.72 – 3.63 (s, 3H), 3.46 – 3.33 (d, $J = 15.3$ Hz, 1H), 2.28 – 2.14 (d, $J = 15.3$ Hz, 1H), 2.03 – 1.81 (m, 2H), 1.62 – 1.45 (m, 2H), 1.41 (dd, $J = 11.9, 6.4$ Hz, 2H), 1.34 – 1.03 (m, 4H). ^{13}C NMR (101 MHz, CDCl_3) δ 158.7, 142.9, 142.1, 141.7, 131.3, 127.5, 121.8, 121.0, 112.1, 111.6, 74.8, 70.0, 55.3, 46.4, 45.9, 44.2, 41.3, 31.3, 28.3, 22.5, 22.3. HRMS (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{23}\text{H}_{25}\text{BrNaO}_2$: 435.0930; found 435.0927.

- (4a*R*,9a*S*,12*S*)-12-(4-bromophenyl)-5-methoxy-1,2,3,4-tetrahydro-9H-4a,9a-(ethanooxymethano)fluorene **382b**

$\text{C}_{23}\text{H}_{25}\text{BrO}_2$ (413.36), white solid; $R_f = 0.525$ (silica gel, petroleum ether: EtOAc (90:10)). ^1H NMR (300 MHz, CDCl_3) δ 7.36 – 7.28 (d, $J = 8.4$ Hz, 2H), 7.15 – 7.08 (d, $J = 8.4$ Hz, 2H), 7.05 (dd, $J = 8.3, 7.6$ Hz, 1H), 6.78 (d, $J = 7.6$ Hz, 1H), 6.64 – 6.55 (d, $J = 8.3$ Hz, 1H), 4.50 – 4.39 (dd, $J = 11.9, 2.0$ Hz, 1H), 3.98 – 3.89 (d, $J = 12.2$ Hz, 1H), 3.81 – 3.70 (d, $J = 12.2$ Hz, 1H), 3.68 – 3.62 (s, 3H), 3.39 (d, $J = 15.3$ Hz, 1H), 2.30 – 2.14 (d, $J = 15.3$ Hz, 1H), 1.80 (m, 1H), 1.65 – 1.38 (m, 2H), 1.37 – 1.04 (m, 7H). ^{13}C NMR (126 MHz, CDCl_3) δ 156.8, 143.6, 142.0, 135.7, 131.2, 127.6, 127.5, 120.9, 118.7, 109.1, 74.4, 69.6, 55.1, 48.9, 43.8, 43.4, 41.7, 31.7, 27.9, 23.3, 22.6. HRMS (ESI): m/z $[\text{M}]^+$ calcd for $\text{C}_{23}\text{H}_{25}\text{BrO}_2$: 412.1032; found 412.1024.

- **383**

Yield: 68% (59 mg isolated from **363d** (98 mg)) (**383a**/**383b** (3.1:1)).

- (4a*S*,9a*S*,12*S*)-7-methoxy-12-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydro-9H-4a,9a-(ethanooxymethano)fluorene **383a**

$\text{C}_{24}\text{H}_{25}\text{F}_3\text{O}_2$ (402.46), colorless oil; $R_f = 0.378$ (silica gel, Petroleum ether: EtOAc (95:5)). ^1H NMR (300 MHz, CDCl_3) δ 7.58 – 7.49 (d, $J = 8.2$ Hz, 2H), 7.47 – 7.39 (d, $J = 8.2$ Hz, 2H), 6.96 (d, $J = 8.2$ Hz, 1H), 6.85 (d, $J = 2.4$ Hz, 1H), 6.71 (dd, $J = 8.2, 2.4$ Hz, 1H), 4.58 (dd, $J = 8.8, 5.3$ Hz, 1H), 4.00 (d, $J = 12.1$ Hz, 1H), 3.84 (d, $J = 12.1$ Hz, 1H), 3.80 (s, 3H), 3.50 (d, $J = 15.3$ Hz, 1H), 2.31 (d, $J = 15.3$ Hz, 1H), 2.13 – 1.93 (m, 2H), 1.63 (m, 2H), 1.46 – 1.10 (m, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 158.8, 146.4, 142.9, 142.0, 126.2, 126.0, 125.2, 125.2, 121.9, 112.2, 111.7, 74.9, 70.1, 55.4, 46.4, 46.1, 44.1, 41.2, 31.4, 28.4, 22.6, 22.4. HRMS (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{24}\text{H}_{25}\text{F}_3\text{NaO}_2$: 425.1699; found 425.1706.

- (4aR,9aS,12S)-5-methoxy-12-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydro-9H-4a,9a-(ethanooxymethano)fluorene **383b**

$C_{24}H_{25}F_3O_2$ (402.46), yellow oil; $R_f = 0.600$ (silica gel, petroleum ether: EtOAc (90:5)). 1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, $J = 8.3$ Hz, 2H), 7.37 (d, $J = 8.3$ Hz, 2H), 7.05 (dd, $J = 8.2, 7.3$ Hz, 1H), 6.79 (d, $J = 7.3$ Hz, 1H), 6.61 (d, $J = 8.2$ Hz, 1H), 4.56 (dd, $J = 11.2, 1.6$ Hz, 1H), 3.95 (d, $J = 12.1$ Hz, 1H), 3.72 (d, $J = 12.1$ Hz, 1H), 3.69 (s, 3H), 3.42 (d, $J = 13.1$ Hz, 1H), 2.26 (d, $J = 13.1$ Hz, 1H), 1.90 – 1.76 (m, 2H), 1.60 (d, $J = 13.7$ Hz, 1H), 1.37 – 1.11 (m, 7H). ^{13}C NMR (101 MHz, C_6D_6) δ 156.8 146.7, 142.1, 141.9, 127.8, 126.5, 126.1, 125.4, 124.8, 118.7, 109.1, 74.6, 69.6, 55.1, 48.9, 43.8, 43.4, 41.7, 31.7, 27.9, 23.3, 22.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.44. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{24}H_{25}F_3NaO_2$: 425.1699; found 425.1695.

➤ **384**

Yield: 53% (65 mg isolated from **363d** (80 mg)) (**384a/384b** (3:1)).

- (4aS,9aS,12S)-7-methoxy-12-(4-nitrophenyl)-1,2,3,4-tetrahydro-9H-4a,9a-(ethanooxymethano)fluorene **384a**

$C_{23}H_{25}NO_4$ (379.46), white solid; $R_f = 0.388$ (silica gel, Petroleum ether: EtOAc (90:10)). 1H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, $J = 9.7$ Hz, 2H), 7.43 (d, $J = 9.7$ Hz, 2H), 6.97 (d, $J = 8.4$ Hz, 1H), 6.85 (d, $J = 2.3$ Hz, 1H), 6.71 (dd, $J = 8.4, 2.3$ Hz, 1H), 4.63 (dd, $J = 11.5, 2.9$ Hz, 1H), 3.97 – 3.84 (d, $J = 12.4$ Hz, 1H), 3.86 (d, $J = 12.4$ Hz, 1H), 3.70 (s, 3H), 3.46 – 3.36 (d, $J = 15.9$ Hz, 1H), 2.32 – 2.18 (d, $J = 15.9$ Hz, 1H), 2.07 – 1.86 (m, 2H), 1.53 (m, 1H), 1.47 – 1.27 (m, 3H), 1.23 – 1.03 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 150.2, 147.0, 142.8, 141.7, 126.4, 123.5, 121.9, 112.1, 111.7, 74.5, 69.9, 55.3, 46.4, 46.1, 44.1, 41.2, 31.2, 28.3, 22.5, 22.2. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{23}H_{25}NNaO_4$: 402.1676; found 402.1676.

- (4aR,9aS,12S)-5-methoxy-12-(4-nitrophenyl)-1,2,3,4-tetrahydro-9H-4a,9a-(ethanooxymethano)fluorene **384b**

$C_{23}H_{25}NO_4$ (379.46), yellow oil; $R_f = 0.428$ (silica gel, petroleum ether: EtOAc (90:10)). 1H NMR (500 MHz, $CDCl_3$) δ 8.10 – 8.02 (d, $J = 8.7$ Hz, 2H), 7.45 – 7.39 (d, $J = 8.7$ Hz, 2H), 7.06 (dd, $J = 8.3, 7.4$ Hz, 1H), 6.79 (d, $J = 7.4$ Hz, 1H), 6.62 (d, $J = 8.3$ Hz, 1H), 4.60 (dd, $J = 11.7, 1.9$ Hz, 1H), 3.94 (d, $J = 12.2$ Hz, 1H), 3.85 – 3.74 (d, $J = 12.2$ Hz, 1H), 3.74 – 3.66 (s, 3H), 3.44 – 3.34 (d, $J = 16.0$ Hz, 1H), 2.32 – 2.19 (d, $J = 16.0$ Hz, 1H), 1.88 – 1.79 (m, 2H), 1.58 (d, $J = 13.7$

Hz, 1H), 1.50 – 1.39 (m, 2H), 1.35 – 1.01 (m, 5H). ^{13}C NMR (126 MHz, CDCl_3) δ 156.8, 150.5, 147.0, 143.4, 135.3, 127.8, 126.4, 123.4, 118.7, 109.1, 74.1, 69.6, 55.1, 48.9, 43.9, 43.4, 41.6, 31.6, 27.9, 23.2, 22.6. HRMS (ESI): m/z $[\text{M}]^+$ calcd for $\text{C}_{23}\text{H}_{25}\text{NO}_4$: 379.1778; found 379.1777.

▪ **385**

Yield: 72% (104 mg isolated from **363d** (90 mg)) (**385a/385b** (2.3:1)).

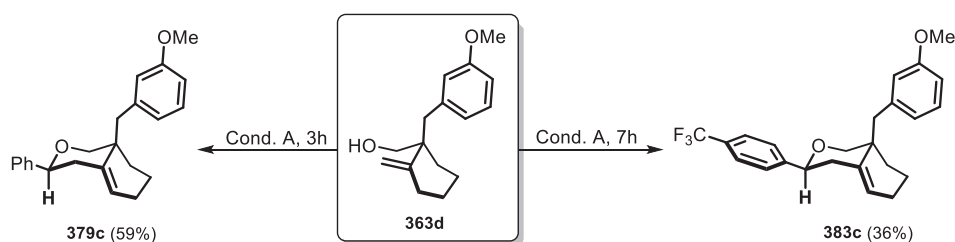
- Methyl 4-((4aS,9aS,12S)-7-methoxy-1,2,3,4-tetrahydro-9H-4a,9a-(ethanooxymethano)fluoren-12-yl)benzoate **385a**

$\text{C}_{25}\text{H}_{28}\text{O}_4$ (392.50), white solid; $R_f = 0.300$ (silica gel, petroleum ether: EtOAc (90:10)). ^1H NMR (300 MHz, CDCl_3) δ 7.96 (d, $J = 8.4$ Hz, 2H), 7.39 (d, $J = 8.3$ Hz, 2H), 6.96 (d, $J = 8.2$ Hz, 1H), 6.85 (d, $J = 2.4$ Hz, 1H), 6.71 (dd, $J = 8.2, 2.4$ Hz, 1H), 4.58 (dd, $J = 8.1, 5.9$ Hz, 1H), 3.99 (d, $J = 12.1$ Hz, 1H), 3.89 (s, 3H), 3.86 (d, $J = 12.1$ Hz, 1H), 3.78 (s, 3H), 3.51 (d, $J = 15.2$ Hz, 1H), 2.31 (d, $J = 15.2$ Hz, 1H), 2.13 – 1.93 (m, 2H), 1.62 (m, 1H), 1.56 – 1.48 (m, 1H), 1.46 – 1.32 (m, 3H), 1.32 – 1.16 (m, 3H). ^{13}C NMR (76 MHz, CDCl_3) δ 167.0, 158.7, 147.9, 142.9, 142.0, 129.6, 129.0, 125.6, 121.9, 112.1, 111.6, 75.1, 70.0, 55.3, 52.0, 46.4, 46.0, 44.2, 41.3, 31.3, 28.3, 22.5, 22.3. HRMS (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{25}\text{H}_{28}\text{NaO}_4$: 415.187980; found 415.187921.

- Methyl 4-((4aR,9aS,12S)-5-methoxy-1,2,3,4-tetrahydro-9H-4a,9a-(ethanooxymethano)fluoren-12-yl)benzoate **385b**

$\text{C}_{25}\text{H}_{28}\text{O}_4$ (392.50), pale yellow oil; $R_f = 0.370$ (silica gel, petroleum ether: EtOAc (90:10)). ^1H NMR (300 MHz, CDCl_3) δ 7.88 (d, $J = 8.5$ Hz, 2H), 7.35 – 7.29 (d, $J = 8.5$ Hz, 2H), 7.05 (dd, $J = 8.2, 7.4$ Hz, 1H), 6.79 (d, $J = 7.4$ Hz, 1H), 6.61 (d, $J = 8.2$ Hz, 1H), 4.56 (dd, $J = 12.0, 2.2$ Hz, 1H), 3.95 (d, $J = 12.1$ Hz, 1H), 3.81 (s, 3H), 3.72 (d, $J = 12.1$ Hz, 1H), 3.68 (s, 3H), 3.43 (d, $J = 13.2$ Hz, 1H), 2.26 (d, $J = 13.2$ Hz, 1H), 1.79 (m, 2H), 1.68 – 1.53 (m, 1H), 1.53 – 1.39 (m, 2H), 1.40 – 1.02 (m, 5H). ^{13}C NMR (126 MHz, CDCl_3) δ 167.0, 156.8, 148.2, 143.6, 135.6, 129.5, 128.9, 127.6, 125.6, 118.7, 109.1, 74.6, 69.6, 55.1, 52.0, 48.9, 43.8, 43.4, 41.7, 31.7, 27.9, 23.3, 22.6. HRMS (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{25}\text{H}_{28}\text{NaO}_4$: 415.187980; found 415.187767.

❖ Isolation of isochromenes **379c** and **383c**



(Cond. A: $\text{BF}_3 \cdot \text{OEt}_2$ (20 mol%), CH_2Cl_2 , 0°C - r.t.).

Procedure: “same as that of Prins/Friedel-Crafts cyclization”

➤ (3*S*)-8a-(3-methoxybenzyl)-3-phenyl-3,4,6,7,8,8a-hexahydro-1*H*-isochromene **379c**

$\text{C}_{23}\text{H}_{26}\text{O}_2$ (334.46), colorless oil; yield: 59% (50 mg isolated from **363d** (63 mg)). $R_f = 0.625$ (silica gel, petroleum ether: EtOAc (90:10)). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.52 – 7.18 (m, 6H), 6.90 (m, 1H), 6.86 – 6.83 (m, 1H), 6.79 (m, 1H), 5.58 (dd, $J = 3.7, 1.9$ Hz, 1H), 4.41 (dd, $J = 11.6, 2.9$ Hz, 1H), 3.90 (d, $J = 11.3$ Hz, 1H), 3.82 (s, 3H), 3.26 (d, $J = 13.3$ Hz, 1H), 3.07 (d, $J = 11.3$ Hz, 1H), 2.80 (d, $J = 13.3$ Hz, 1H), 2.71 (m, 1H), 2.29 (dd, $J = 14.1, 3.0$ Hz, 1H), 2.04 (m, 2H), 1.63 (m, 3H), 0.90 (m, 1H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 159.3, 142.8, 140.0, 138.8, 128.8, 128.4, 127.5, 125.8, 123.5, 122.6, 116.9, 111.1, 81.8, 75.7, 55.1, 40.5, 39.3, 39.0, 27.9, 25.5, 17.9. **HRMS** (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{23}\text{H}_{26}\text{NaO}_2$: 357.182501; found 357.182607.

▪ (3*S*,8a*S*)-8a-(3-methoxybenzyl)-3-(4-(trifluoromethyl)phenyl)-3,4,6,7,8,8a-hexahydro-1*H*-isochromene **383c**

$\text{C}_{24}\text{H}_{25}\text{F}_3\text{O}_2$ (402.46), pale yellow oil; yield: 36% (57 mg isolated from **363d** (98 mg)). $R_f = 0.538$ (silica gel, petroleum ether: EtOAc (95:5)). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.67 (d, $J = 8.4$ Hz, 2H), 7.63 – 7.56 (d, $J = 8.4$ Hz, 2H), 7.29 – 7.22 (dd, $J = 8.0, 7.39$ Hz, 1H), 6.91 (d, $J = 7.3$ Hz, 1H), 6.85 (d, $J = 2.5$ Hz, 1H), 6.82 (dd, $J = 8.0, 2.5$ Hz, 1H), 5.60 (m, 1H), 4.49 (dd, $J = 11.8, 2.3$ Hz, 1H), 3.92 (d, $J = 11.4$ Hz, 1H), 3.83 (s, 3H), 3.24 (d, $J = 13.7$ Hz, 1H), 3.09 (d, $J = 11.4$ Hz, 1H), 2.80 (d, $J = 13.7$ Hz, 1H), 2.74 – 2.58 (m, 1H), 2.33 (dd, $J = 14.0, 2.9$ Hz, 1H), 2.05 (m, 2H), 1.77 – 1.54 (m, 3H), 1.01 – 0.84 (m, 1H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 159.3, 146.7, 139.8, 138.2, 128.8, 125.9, 125.3, 125.3, 125.3, 123.4, 123.1, 116.9, 111.1, 81.0, 75.6, 55.1, 40.4, 39.2, 38.9, 27.8, 25.5, 17.8. $^{19}\text{F NMR}$ (471 MHz, CDCl_3) δ -62.4. **HRMS** (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{24}\text{H}_{25}\text{F}_3\text{NaO}_2$: 425.1699; found 425.1695.

Chapter 6

Part 1: Cordycol

❖ Alcohol protection of **420**

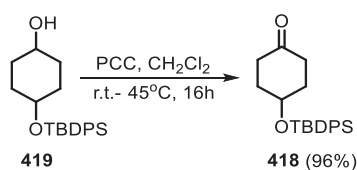


Procedure: To a solution of cis/trans mixture of 1,4-cyclohexanediol (6.85 g, 58.9 mmol) and imidazole (1.07 g, 15.7 mmol) in THF (189 mL) was added TBDPSCl (5.46 g, 19.6 mmol) at 0 °C. After stirring at ambient temperature for 20 hours, the resulting mixture was quenched with brine, extracted with EtOAc, dried over anhydrous MgSO₄ and concentrated in vacuo. The crude mixture was chromatographed on silica gel to give cis/trans mixture of **419**.

❖ 4-((Tert-butyldiphenylsilyl)oxy)cyclohexan-1-ol **419**

C₂₂H₃₀O₂Si (354.57), colorless oil; yield: 61% (4.28 g isolated from **420** (6.85 g)). *R_f isomer A* = 0.375, *R_f isomer B* = 0.313, (silica gel, petroleum ether: EtOAc (75:25)). ¹H NMR (300 MHz, CDCl₃) δ 7.64–7.69 (m, 4H), 7.33–7.45 (m, 6H), 3.62–3.88 (m, 2H), 1.14–1.95 (m, 9H), 1.05–1.07 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 135.7, 134.5, 129.5, 127.5, 70.7, 69.3, 32.3, 32.3, 27.02, 26.9, 19.19. *Spectroscopic data matches that reported in the literature.*^[54]

❖ Alcohol oxidation of **419**

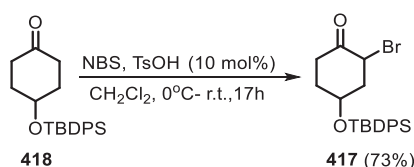


Procedure: To a stirred solution of **419** (1.15 g, 3.24 mmol) in dichloromethane (35 ml), PCC (1.05 g, 4.86 mmol) was added in one portion at room temperature. The reaction mixture was refluxed at 45 °C for one hour and then kept stirring at room temperature for 15 hours. At the end of the reaction, the obtained mixture was filtered over a Celite pad, and the filtrate was evaporated under reduced pressure to give a brown solid crude. The latter was further purified over silica gel to afford the title compound **418**.

➤ 4-((tert-butyldiphenylsilyl)oxy)cyclohexan-1-one **418**

$C_{22}H_{28}O_2Si$ (352.55), brown solid; yield: 96% (1.10 g isolated from **419** (1.15 g)). The ratio of the diastereoisomers is 2.4:1. $R_f = 0.713$ (silica gel, petroleum ether: EtOAc (93:7)). 1H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, $J = 7.5$ Hz, 4 H), 7.45 (t, $J = 7.5$ Hz, 2 H), 7.39 (t, $J = 7.5$ Hz, 4 H), 4.14–4.17 (m, 1 H), 2.70–2.80 (m, 2 H), 2.18–2.25 (m, 2 H), 1.92–1.98 (m, 2 H), 1.74–1.80 (m, 2 H), 1.10 (s, 9 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.5, 135.4, 133.7, 129.6, 127.5, 66.7, 36.7, 33.5, 26.7, 19.0. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{22}H_{28}NaO_2Si$: 375.1750; found 375.1744.^[55]

❖ α -Bromination of **418**

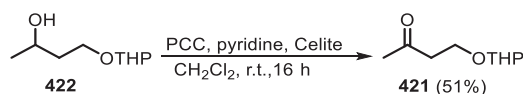


Procedure: A solution of cycloalkanones **418** (500 mg, 1.42 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a solution of *n*-bromosuccinimide (302 mg, 1.7 mmol) and *p*-TsOH (24 mg, 0.14 mmol) in CH_2Cl_2 (20 mL) at $0^\circ C$. The reaction mixture was then brought to reflux for 17 hours. After addition of H_2O (40 mL), the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2×30 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (30 mL) and brine (40 mL), dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. Finally, column chromatography on silica gel provided α -bromo cycloalkanone **417**.

➤ 2-Bromo-4-((tert-butyldiphenylsilyl)oxy)cyclohexan-1-one **417**

$C_{22}H_{27}BrO_2Si$ (431.45), pale orange oil; yield: 73% (450 mg isolated from **418** (500 mg)). The ratio of the diastereoisomers (A/B) is 2.4:1. R_f isomer A = 0.525, R_f isomer B = 0.375 (silica gel, petroleum ether: EtOAc (90:10)). Isomer A (major): 1H NMR (300 MHz, $CDCl_3$) δ 7.73 – 7.63 (m, 4H), 7.52 – 7.35 (m, 6H), 4.92 (m, 1H), 4.31 – 4.22 (m, 1H), 2.90 – 1.69 (m, 6H), 1.11 (s, 9H). Isomer A (minor): 1H NMR (300 MHz, $CDCl_3$) δ 7.73 – 7.63 (m, 4H), 7.52 – 7.35 (m, 6H), 4.40 (m, 1H), 4.07 (m, 1H), 2.90 – 1.69 (m, 6H), 1.07 (s, 9H). Both isomers (A+B): ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.0, 201.1, 135.8, 135.8, 135.7, 133.4, 133.4, 130.1, 130.1, 127.9, 127.9, 127.9, 127.8, 68.8, 67.5, 51.4, 50.4, 45.5, 45.4, 35.3, 35.2, 34.4, 34.1, 27.1, 27.0, 26.9, 19.3, 19.1. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{22}H_{27}BrNaO_2Si$: 453.0856; found 453.0861.

❖ **Alcohol oxidation of 422**

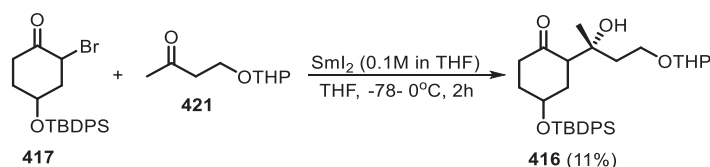


Procedure: Alcohol **422** (1 g, 5.74 mmol) in CH_2Cl_2 (10 mL) was added to a suspension of PCC (1.9 g, 8.78 mmol), pyridine (0.73 mL, 9.18 mmol), and Celite (4 g) in CH_2Cl_2 (30 mL) at room temperature and refluxed for 4 hours. After the usual workup, the crude product was chromatographed on SiO_2 and eluted with to give ketone **421**.^[59]

➤ 4-((Tetrahydro-2H-pyran-2-yl)oxy)butan-2-one **421**

$\text{C}_9\text{H}_{16}\text{O}_3$ (172.22), pale pink oil; yield: 51% (0.51 g isolated from **422** (1.00 g)). $R_f = 0.312$ (silica gel, petroleum ether: EtOAc (70:30)). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 4.55 (dd, $J = 4.5, 2.9$ Hz, 1H), 4.01 – 3.91 (m, 1H), 3.87 – 3.75 (m, 1H), 3.70 – 3.60 (m, 1H), 3.53 – 3.41 (m, 1H), 2.67 (td, $J = 6.2, 1.5$ Hz, 2H), 2.15 (s, 3H), 1.81 – 1.69 (m, 1H), 1.69 – 1.57 (m, 1H), 1.57 – 1.41 (m, 4H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 207.3, 99.2, 62.7, 62.4, 43.8, 30.7, 30.6, 25.5, 19.6. **HRMS** (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_9\text{H}_{16}\text{NaO}_3$: 195.0992; found 195.0990.^[57]

❖ **SmI_2 -promoted Reformatsky reaction between 417 and 421**



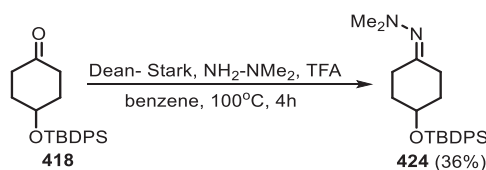
Procedure: A 250 ml teardrop-shaped flask equipped with a stir bar was charged with a 0.1M solution of diiodosamarium in tetrahydrofuran (20.5 ml, 2.05 mmol, 5 eq.) and cooled to -78°C . A solution of the α -haloketone **417** (0.41 mmol, 1 eq.) and the carbonyl electrophile **421** (0.41 mmol, 1 eq.) in 25 ml tetrahydrofuran was prepared. This solution was then added to the intensely blue solution of diiodosamarium over 25 minutes such that the solution ran down the side of the flask. The blue solution was stirred for an additional 1 h, maintaining a temperature of -78°C . The reaction was then exposed to air, and air was bubbled through the solution, warming to room temperature. After 5-10 minutes, the solution turned bright yellow and was immediately poured onto a mixture of saturated aqueous sodium thiosulfate, saturated aqueous sodium bicarbonate, brine, and diethyl ether. The layers were separated, and the aqueous layer was extracted thrice with

diethyl ether. The organic layers were combined, washed once with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting clear to slightly yellow oil was then purified by a classical column chromatography.^[60]

➤ 4-((tert-butyldiphenylsilyl)oxy)-2-((2R)-2-hydroxy-4-((tetrahydro-2H-pyran-2-yl)oxy)butan-2-yl)cyclohexan-1-one **416**

$C_{31}H_{44}O_5Si$ (524.77), colorless oil; yield: 11% (23 mg isolated from **417** (176 mg)). R_f isomer A = 0.375, R_f isomer B = 0.350, (silica gel, petroleum ether: EtOAc (75:25)). 1H NMR (300 MHz, $CDCl_3$) δ 7.69 – 7.50 (m, 4H), 7.45 – 7.21 (m, 6H), 4.55 – 4.38 (m, 1H), 4.22 – 4.11 (m, 1H), 4.10 – 3.65 (m, 2H), 3.45 (m, 2H), 3.20 – 3.03 (m, 1H), 2.98 – 2.76 (m, 1H), 2.74 – 2.57 (m, 1H), 2.23 – 1.40 (m, 10H), 1.36 (s, 6H), 1.12 – 0.93 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.8, 135.7, 135.7, 135.7, 134.8, 133.9, 129.8, 129.5, 127.7, 127.5, 94.6, 94.4, 66.9, 63.8, 62.9, 36.9, 33.7, 31.9, 30.7, 27.0, 27.0, 26.9, 26.9, 26.5, 25.4, 25.2, 20.2, 19.7, 19.3. HRMS (ESI): m/z [M + Na]⁺ calcd for $C_{31}H_{44}NaO_5Si$: 547.2850; found 547.2855.

❖ Preparation of dimethyl hydrazine **424**



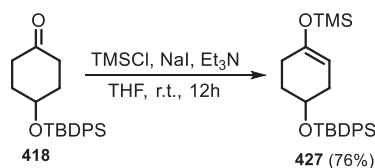
Procedure: The cycloalkanone **418** (1.10 g, 3.17 mmol) was dissolved in benzene (50 ml). *N,N*-dimethylhydrazine (0.31 g, 5.08 mmol) and trifluoroacetic acid (4 drops) were then added. The resulting mixture was heated to reflux for 4 hours using a Dean-Stark device. After completion, nearly all of the benzene was removed from the reaction mixture using the Dean-Stark equipment. The mixture was then diluted with diethyl ether (30 mL) and hydrolyzed with a saturated aqueous solution of $NaHCO_3$ (25 mL). The aqueous layer was extracted with diethyl ether (3 x 30 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under vacuum. The crude material was purified by distillation under reduced pressure to afford the title compound.^[61]

➤ 2-(4-((Tert-butyldiphenylsilyl)oxy)cyclohexylidene)-1,1-dimethylhydrazine **424**

$C_{24}H_{34}N_2OSi$ (394.63), pale yellow oil; yield: 36% (451 mg isolated from **418** (1.1 g)). R_f = 0.300 (silica gel, petroleum ether: EtOAc (75:25)). 1H NMR (300 MHz, $CDCl_3$) δ 7.68 (m, 4H), 7.47 –

7.32 (m, 6H), 4.01 (m, 1H), 2.84 – 2.61 (m, 2H), 2.61 – 2.47 (m, 2H), 2.43 (s, 6H), 2.29 – 2.04 (m, 2H), 1.96 (m, 1H), 1.87 – 1.47 (m, 1H), 1.09 (s, 9H). ^{13}C NMR (101 MHz, CDCl_3) δ 169.2, 135.7, 135.7, 129.8, 129.6, 127.7, 127.6, 68.6, 66.9, 47.5, 36.9, 34.6, 33.7, 33.7, 31.2, 27.0, 23.9, 19.2. HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{35}\text{N}_2\text{OSi}$: 395.2513; found 395.2505.

❖ Preparation of silyl enol ether **427**



Procedure: A RBF containing a mixture of ketone **418** (1.50 g, 4.25 mmol) and pre-dried sodium iodide (0.76 g, 5.10 mmol) was evacuated and filled with nitrogen three times, and dry THF (4 ml) was added, stirring for 5 min at room temperature. To the resulting solution, triethylamine (0.64 g, 6.38 mmol) was added, followed by chlorotrimethylsilane (0.65 ml, 5.10 mmol). The reaction mixture was then stirred for 12 hours at room temperature. The reaction was quenched with a mixture of ethyl acetate (50 mL) and saturated NH_4Cl (50 mL) at 0°C . The organic phase was separated, and the aqueous layer was extracted with ethyl acetate (2×30 mL). The combined organic fractions were washed with ice-water (50 mL) and saturated NH_4Cl (50 mL), and then dried over anhydrous MgSO_4 . The solvent was removed under reduced pressure and the residue was purified by column chromatography to give the desired product.^[62]

▪ Tert-butyldiphenyl((4-((trimethylsilyl)oxy)cyclohex-3-en-1-yl)oxy)silane **427**

$\text{C}_{25}\text{H}_{36}\text{O}_2\text{Si}_2$ (424.73), yellow oil; yield: 76% (1.32 g of isolated from **418** (1.50 g)). $R_f = 0.988$ (silica gel, petroleum ether: EtOAc (98:2)). ^1H NMR (300 MHz, CDCl_3) δ 7.75 – 7.64 (m, 4H), 7.48 – 7.33 (m, 6H), 4.67 (m, 1H), 3.96 (m, 1H), 2.30 – 2.06 (m, 3H), 1.98 (m, 1H), 1.74 (m, 2H), 1.08 (s, 9H), 0.18 (s, 9H). ^{13}C NMR (76 MHz, CDCl_3) δ 149.3, 135.4, 134.3, 134.2, 129.2, 129.1, 127.2, 127.1, 100.7, 67.4, 32.6, 30.8, 27.2, 26.6, 18.8, 0.0. HRMS (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{25}\text{H}_{36}\text{NaO}_2\text{Si}_2$: 447.2146; found 447.2143.

❖ **The Saegusa–Ito oxidation: preparation of enone 428**

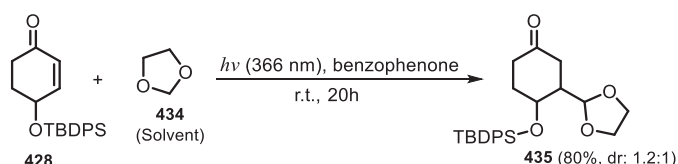


Procedure: To a clear solution of Pd(OAc)₂ (90 mg, 0.40 mmol) in 4 mL of acetonitrile, of 1-trimethylsilyloxy-1-cyclohexene **427** (164 mg, 0.40 mmol) was added with stirring under nitrogen at room temperature, and then the mixture was stirred for 16 hours. After classical extraction, the combined organic fractions were dried over anhydrous MgSO₄. The solvent was removed under reduced pressure and the residue was chromatographed to give the title compound.^[63]

➤ **4-((tert-butyl-diphenylsilyloxy)cyclohex-2-en-1-one 428**

C₂₂H₂₆O₂Si (350.53), yellow oil; yield: 86% (1.30 g isolated from **427** (1.84 g)). *R_f* = 0.163 (silica gel, petroleum ether: EtOAc (95:5)). ¹H NMR (300 MHz, CDCl₃) δ 7.72 – 7.64 (m, 4H), 7.42 (m, 6H), 6.79 (ddd, *J* = 10.2, 2.6, 1.1 Hz, 1H), 5.87 (dd, *J* = 10.2, 0.9 Hz, 1H), 4.56 – 4.43 (m, 1H), 2.50 (m, 1H), 2.27 – 2.00 (m, 3H), 1.09 (s, 9H). ¹³C NMR (76 MHz, CDCl₃) δ 198.9, 153.2, 135.7, 135.7, 133.4, 133.4, 130.0, 130.0, 128.7, 127.8, 127.8, 67.6, 35.3, 32.6, 26.8, 19.1. HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₂₂H₂₆NaO₂Si : 373.1594; found 373.1594.

❖ **The photoinduced Michael-type radical addition of 1,3-dioxolane 434 on 428**

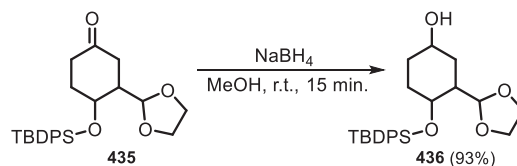


Procedure: A solution of unsaturated ketone **428** (200.0 mg, 0.57 mmol) and benzophenone (16 mg, 0.09 mmol) in 1,3-dioxolane **434** (46 mL) was poured into pyrex tubes and placed around a photochemical immersion well equipped with a cooling system. The resulting clear solution was then bubbled with argon for 10 minutes, and irradiation was carried out until complete disappearance of the starting material (TLC control). The solution was concentrated under vacuum and purified by flash-chromatography on silica to afford compound **435**.^[64]

▪ 4-((tert-butyldiphenylsilyl)oxy)-3-(1,3-dioxolan-2-yl)cyclohexan-1-one **435**

$C_{25}H_{32}O_4Si$ (424.61), colorless oil; yield: 80% (193 mg isolated from **428** (200 mg)). R_f isomer A = R_f isomer B = 0.688 (silica gel, petroleum ether: EtOAc (90:10)). Major isomer: 1H NMR (300 MHz, $CDCl_3$) δ 7.78 – 7.62 (m, 4H), 7.52 – 7.30 (m, 6H), 4.77 (d, J = 2.63 Hz, 1H), 4.15 (m, 1H), 4.01 – 3.63 (m, 4H), 2.74 – 1.75 (m, 6H), 1.71 – 1.52 (m, 1H), 1.09 (s, 9H). Minor isomer: 1H NMR (300 MHz, $CDCl_3$) δ 7.78 – 7.62 (m, 4H), 7.52 – 7.30 (m, 6H), 5.09 (d, J = 5.3 Hz, 1H), 4.48 – 4.34 (m, 1H), 4.01 – 3.63 (m, 4H), 2.74 – 1.75 (m, 6H), 1.71 – 1.52 (m, 1H), 1.10 (s, 9H). Both isomers: ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.6, 209.9, 135.9, 135.8, 135.7, 135.7, 135.7, 134.1, 133.9, 133.5, 133.4, 129.8, 129.8, 129.8, 127.7, 127.7, 127.6, 127.6, 103.5, 103.4, 68.3, 67.9, 65.1, 64.9, 64.8, 64.7, 47.4, 47.0, 37.7, 36.5, 36.4, 35.9, 31.4, 30.8, 27.1, 27.1, 27.0, 19.5, 19.3. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{25}H_{32}NaO_4Si$: 447.1962; found 447.1958.

❖ Ketone reduction of **435**



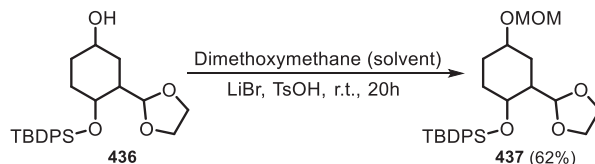
Procedure: $NaBH_4$ (29 mg, 0.75 mmol) was added in one portion to a solution of compound **435** (160 mg, 0.38 mmol) in methanol (5 ml). A vigorous gas evolution occurred and then stirring was continued for 15 minutes before the pH was adjusted to neutrality with diluted aqueous HCl. The mixture was extracted with diethyl ether (three times), then the combined organic extracts were dried over $MgSO_4$. Evaporation of the solvent gave a crude mixture, which was chromatographed on silica gel to give the desired product **436**.

▪ 4-((tert-butyldiphenylsilyl)oxy)-3-(1,3-dioxolan-2-yl)cyclohexan-1-ol **436**

$C_{25}H_{34}O_4Si$ (426.63), white solid; yield: 93% (150 mg isolated from **435** (160 mg)). R_f isomers = 0.225 (silica gel, petroleum ether: EtOAc (75:25)). All isomers: 1H NMR (300 MHz, $CDCl_3$) δ 7.80 – 7.56 (m, 9H), 7.50 – 7.28 (m, 14H), 5.28 (d, J = 2.1 Hz, 1H), 4.82 (d, J = 7.3 Hz, 1H), 4.31 – 4.19 (m, 1H), 3.99 – 3.50 (m, 13H), 2.15 – 1.17 (m, 19H), 1.06 (m, 23H). All isomers: ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.1, 136.1, 136.0, 135.9, 135.9, 135.8, 134.8, 134.6, 133.9, 133.8, 129.6, 129.6, 129.5, 129.5, 129.5, 129.4, 127.5, 127.5, 127.4, 127.4, 127.3, 104.3, 102.9, 72.0, 69.8, 69.2, 67.2, 65.2, 65.0, 64.9, 64.5, 64.4, 45.9, 45.8, 32.5, 32.3, 31.3, 30.5, 29.3, 27.2, 27.0, 27.0, 27.0,

19.6, 19.5, 19.4. **HRMS** (ESI): m/z $[M + Na]^+$ calcd for $C_{25}H_{34}NaO_4Si$: 449.2099; found 449.2095.

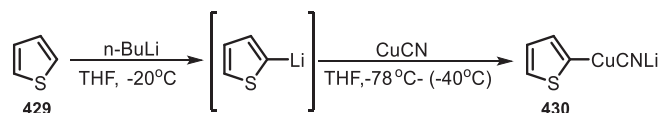
❖ **Alcohol protection of 436 using dimethoxymethane**



Procedure: To a stirred solution of alcohol **436** (125 mg, 0.29 mmol) in dimethoxymethane (2 mL) were added lithium bromide (10 mg, 0.12 mmol) and then *p*-toluenesulfonic acid (0.1 mg, 5.86×10^{-4} mmol). The resulting mixture was kept stirring at room temperature for 20 hours. The mixture was hydrolyzed with a saturated sodium chloride solution and extracted with diethyl ether. The organic layer was dried over sodium sulfate, evaporated, and purified by column chromatography on silica gel.^[65]

▪ ((2-(1,3-dioxolan-2-yl)-4-(methoxymethoxy)cyclohexyl)oxy)(tert-butyl)diphenylsilane **437** $C_{27}H_{38}O_5Si$ (470.68), white oil; yield: 62% (86 mg isolated from **436** (125 mg)). R_f isomers = 0.650 (silica gel, petroleum ether: EtOAc (80:20)). All isomers: 1H NMR (500 MHz, $CDCl_3$) δ 7.69 – 7.52 (m, 10H), 7.40 – 7.22 (m, 16H), 5.27 (d, $J = 2.3$ Hz, 1H), 4.71 (d, $J = 7.7$ Hz, 1H), 4.67 – 4.41 (m, 5H), 4.18 (d, $J = 2.6$ Hz, 1H), 3.84 – 3.66 (m, 10H), 3.62 – 3.52 (m, 1H), 3.50 – 3.36 (m, 2H), 3.30 (s, 3H), 3.22 (s, 3H), 2.03 – 1.08 (m, 19H), 1.06 – 0.87 (m, 25H). All isomers: ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.1, 136.0, 135.9, 135.9, 135.8, 135.8, 134.9, 134.6, 134.0, 133.8, 129.5, 129.5, 129.5, 129.4, 129.4, 127.5, 127.4, 127.4, 127.4, 127.3, 127.3, 127.3, 104.5, 102.8, 94.4, 94.3, 74.6, 74.2, 72.4, 67.1, 65.1, 65.0, 64.4, 64.4, 55.2, 55.1, 46.2, 46.2, 33.1, 30.8, 30.2, 28.4, 27.9, 27.2, 27.1, 27.0, 27.0, 26.9, 26.4, 19.6, 19.5. **HRMS** (ESI): m/z $[M + Na]^+$ calcd for $C_{27}H_{38}NaO_5Si$: 493.2112; found 493.2113.

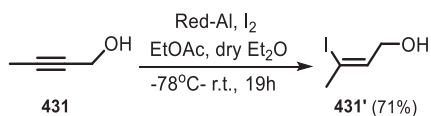
❖ **Preparation of a 0.1 M THF solution of 2-ThCu(CN)Li 430**



Procedure: Thiophene (10.2 mmol, 0.82 mL) is added to THF (10 mL) in a 20 mL 2-neck pear flask at $-78^\circ C$, followed by *n*-BuLi (10.0 mmol, 3.12 M, 3.18 mL). Stirring is continued at this

temperature for 15 minutes, then at -20°C for 30 minutes. The solution is transferred, *via* cannula, into a slurry of CuCN (10.0 mmol, 0.896 g) and THF (10 mL), with a wash of 10 mL of THF. Warming to -40°C gives a clear, light-tan solution which is diluted with THF (66 mL) and transferred, *via* cannula, to a dry storage vessel (100 ml Aldrich bottle) which is maintained under a positive argon atmosphere.^[66]

❖ Preparation of vinyl iodide **431'**

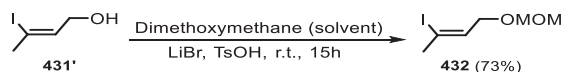


Procedure: A solution of Red-Al (9 ml, 31.50 mmol) was added dropwise over one hour to a solution of 2-butyne-1-ol **431** (1.7 ml, 22.7 mmol) in dry diethyl ether (35 ml) at 0°C under an inert atmosphere. The reaction mixture was allowed to warm slowly to r.t. and was stirred at ambient temperature overnight. After the starting material had been completely consumed (TLC monitoring), the mixture was cooled to 0°C and ethyl acetate was added dropwise. The mixture was then cooled to -78°C and a solution of I_2 (8.65 g, 34.1 mmol) in THF (25 ml) was added dropwise over 1.5 hours. After 30 minutes, the cooling bath was removed and stirring was continued at r.t. for 1 hour. The mixture was then poured into an ice-cold aqueous saturated solution of $\text{Na}_2\text{S}_2\text{O}_3$ and extracted with diethyl ether. The combined organic fractions were dried over Na_2SO_4 , filtered, concentrated and purified to give the title compound **431'**.^[67]

▪ 3-iodobut-2-en-1-ol **431'**

$\text{C}_4\text{H}_7\text{IO}$ (198.00), yellow oil; yield: 71% (3.2 g isolated from **431** (1.6 g)). $R_f = 0.375$ (silica gel, petroleum ether: EtOAc (80:20)). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 6.44–6.38 (m, 1H), 4.09 (t, $J = 6.0$ Hz, 2H), 2.45 (d, $J = 0.7$ Hz, 3H), 1.46 (brd, 1H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 139.8, 98.7, 60.1, 28.1. *The data are consistent with those reported in the literature.*^[68]

❖ Alcohol protection of **431'**



Procedure: To a stirred solution of alcohol **431'** (1.12g, 5.61mmol) in dimethoxymethane (7mL) were added lithium bromide (98mg, 1.12 mmol) and then *p*-toluenesulfonic acid (11mg, 5.61×10^{-2} mmol). The resulting mixture was kept stirring at room temperature for 15hours. The

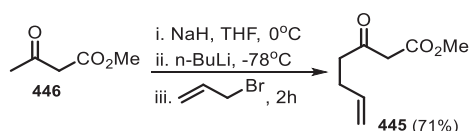
mixture was hydrolyzed with a saturated sodium chloride solution and extracted with diethyl ether. The organic layer was dried over sodium sulfate, evaporated, and purified by column chromatography on silica gel to afford the title compound **432**.^[65]

▪ 3-Iodo-1-(methoxymethoxy)but-2-ene **432**

C₆H₁₁IO₂ (242.06), orange oil; yield: 73% (0.95 g isolated from **431'** (1.11 g)). *R_f* = 0.363 (silica gel, petroleum ether: EtOAc (95.5:4.5)). ¹H NMR (300 MHz, CDCl₃) δ 5.74 (m, 1H), 4.65 (s, 2H), 4.10 (m, 2H), 3.39 (s, 3H), 2.55 (m, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 131.9, 102.7, 96.0, 71.8, 55.3, 33.7. *The data are consistent with those reported in the literature.*^[65]

Part 2: Idesolide monomer and analogues

❖ Allylation of methyl acetoacetate **446**

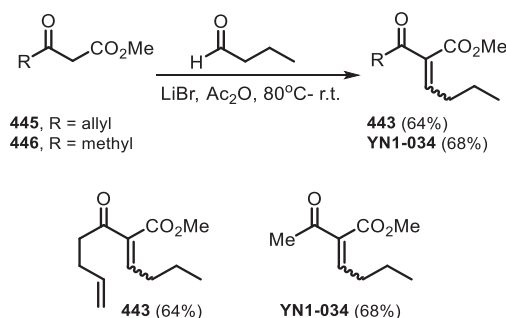


Procedure: To sodium hydride (10.33 mmol, 1.2 eq.) in THF (25 ml) under nitrogen stirred at 0°C, was added methyl acetoacetic (8.61 mmol, 1 eq.) dropwise. After 10 minutes, the temperature was lowered to -78°C, and n-BuLi (10.33 mmol, 4.5 ml, 2.5 M) was added to give a yellow solution. After 20 minutes, allyl bromide (10.33 mmol, 1.2 eq.) was added, and the solution was then allowed to warm to room temperature over 2-2.5 hours. The mixture was poured into a solution of ammonium chloride and extracted four times with diethyl ether. The organic phase was dried over MgSO₄ and the solvent was removed under reduced pressure. The residual was purified *via* column chromatography to afford the addressed compound.^[69]

▪ Methyl 3-oxohept-6-enoate **445**

C₈H₁₂O₃ (156.18), yellow oil; yield: 71% (1.9 g isolated from methyl acetoacetate **446** (1 g)). *R_f* = 0.425 (silica gel, petroleum ether: EtOAc (85:15)). ¹H NMR (300 MHz, CDCl₃) δ 5.79 (ddt, *J* = 16.7, 10.2, 6.5 Hz, 1H), 5.12 – 4.90 (m, 2H), 3.73 (s, 3H), 3.45 (s, 2H), 2.64 (t, *J* = 7.3 Hz, 2H), 2.34 (m, 2H). ¹³C NMR (75 MHz, CDCl₃) δ 201.8, 167.5, 136.5, 115.5, 52.3, 49.0, 42.0, 27.3. *Spectroscopic data matches that reported in the literature.*^[70]

❖ Knoevenagel condensation of **445/446** with butyraldehyde



Procedure: To a round-bottom flask, acetic anhydride (2 eq.), lithium bromide (30 mol%), and **444/446** (1 eq.) were added, stirred, and heated to 80°C for 0.5 hour. Butyraldehyde (3 eq.) was then added dropwise at room temperature. The resulting mixture was refluxed for one more hour before keeping it stirring at room temperature till the end of the reaction. After classical extraction, acetic anhydride was removed under reduced pressure and the crude residual was purified *via* column chromatography to afford the desired compound.^[71]

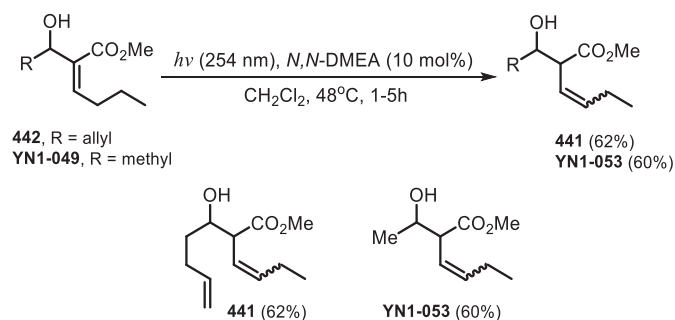
▪ Methyl 2-butyldiene-3-oxohept-6-enoate **443**

$\text{C}_{12}\text{H}_{18}\text{O}_3$ (210.27), yellow oil; yield: 64% (2.3 g of a mixture of E/Z isomers (A and B) isolated from **445** (2.7 g)). R_f isomer A = 0.625, R_f isomer B = 0.563, (silica gel, petroleum ether: EtOAc (85:15)). Major isomers: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 6.85 (t, $J = 7.7$ Hz, 1H), 5.91 – 5.70 (m, 1H), 5.11 – 4.90 (m, 2H), 3.82 (s, 3H), 2.72 (m, 2H), 2.42 – 2.22 (m, 4H), 1.52 (q, $J = 7.4$ Hz, 2H), 0.94 (t, $J = 7.4$ Hz, 3H). Minor isomer: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 6.85 (t, $J = 7.7$ Hz, 1H), 5.91 – 5.70 (m, 1H), 5.11 – 4.90 (m, 2H), 3.79 (s, 3H), 2.72 (m, 2H), 2.42 – 2.22 (m, 3H), 2.06 (m, 1H), 1.52 (m, 2H), 0.94 (t, $J = 7.4$ Hz, 3H). **HRMS** (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{12}\text{H}_{18}\text{NaO}_3$: 233.1148; found 233.1142.

▪ Methyl 2-acetylhex-2-enoate **YN1-034**

$\text{C}_9\text{H}_{14}\text{O}_3$ (170.21), yellow oil; yield: 68% (2.0 g isolated from methyl acetoacetate **446** (2.0 g)). The ratio of the obtained isomers A/B is 42:58. R_f isomer A = 0.385, R_f isomer B = 0.300, (silica gel, petroleum ether: EtOAc (90:10)). *Spectroscopic data matches that reported in the literature.*^[72]

❖ Photo-deconjugation reaction



Procedure: A solution of unsaturated ester **442** or **YN1-049** (1 eq.) and 2-dimethylaminoethanol (*N,N*-DMEA) (0.3 eq.) in dichloromethane (0.02M) was poured into a quartz tube and bubbled with argon for 10 minutes. The resulting clear solution was then placed in the Rayonet, and irradiation at 254 nm was carried out until the complete disappearance of the starting material (TLC control). The solution was concentrated under vacuum and purified by flash-chromatography on silica to afford compound **441** or **YN1-053**.

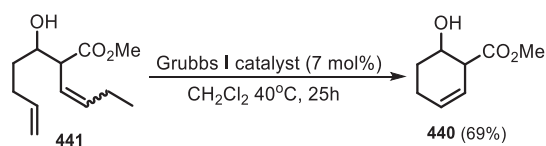
▪ Methyl 2-(but-1-en-1-yl)-3-hydroxyhept-6-enoate **441**

$\text{C}_{12}\text{H}_{20}\text{O}_3$ (212.29), pale yellow oil; yield: 62% (309 mg isolated from **442** (500 mg)). The ratio of the E/Z isomers is 66:34. R_f isomer A = 0.378, R_f isomer B = 0.275 (silica gel, petroleum ether: EtOAc (85:15)). Isomer A: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 5.93 – 5.60 (m, 2H), 5.51 (ddt, $J = 15.4, 7.6, 1.4$ Hz, 1H), 5.11 – 4.88 (m, 2H), 3.95 – 3.82 (m, 1H), 3.70 (m, 3H), 3.51 – 3.29 (s, 1H), 3.00 (dd, $J = 9.1, 4.7$ Hz, 1H), 2.75 – 1.91 (m, 4H), 1.87 – 1.10 (m, 2H), 1.07 – 0.81 (m, 3H). Isomer B: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 5.90 – 5.56 (m, 2H), 5.39 (ddt, $J = 15.4, 9.1, 1.6$ Hz, 1H), 5.11 – 4.87 (m, 2H), 3.81 (q, $J = 6.6, 5.1$ Hz, 1H), 3.70 (s, 3H), 3.05 (dd, $J = 9.1, 7.7$ Hz, 1H), 2.48 (brd, 1H), 2.32 – 1.90 (m, 4H), 1.73 – 1.27 (m, 2H), 1.06 – 0.90 (m, 3H). HRMS (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{12}\text{H}_{20}\text{NaO}_3$: 235.1305; found 235.1298.

▪ Methyl 2-(1-hydroxyethyl)hex-3-enoate **YN1-053**

$\text{C}_9\text{H}_{16}\text{O}_3$ (172.22), colorless oil; yield: 60% (70 mg isolated from **YN1-049** (116 mg)). $R_f = 0.523$ (silica gel, petroleum ether: EtOAc (70:30)). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 5.68 (dt, $J = 15.4, 6.3$ Hz, 1H), 5.38 (ddt, $J = 15.5, 9.2, 1.7$ Hz, 1H), 4.03-3.97 (m, 1H), 3.7 (s, 3H), 2.98 (dd, $J = 9.2, 8.6$ Hz, 1H), 2.51 (s, 1H), 2.10-2.00 (m, 2H), 1.17 (d, $J = 6.4$ Hz, 3H), 0.98 (t, $J = 7.5$ Hz, 3H); Spectroscopic data matches that reported in the literature.^[73]

❖ Ring-closing metathesis (RCM) of 441

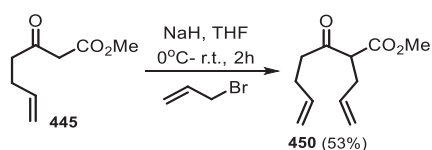


Procedure: Diene **441** (150 mg, 0.71 mmol) was dissolved in freshly distilled and degassed CH₂Cl₂ (100 mL) under an argon atmosphere. Ruthenium complex (Grubbs I catalyst) (40 mg, 7 mol%) was then added. After 25 hours of stirring the solution at reflux (40°C), the conversion was complete as indicated by TLC. Evaporation of the solvent gave a crude mixture, which was chromatographed on silica gel to give the desired product.^[74]

▪ Methyl 6-hydroxycyclohex-2-ene-1-carboxylate **440**

C₈H₁₂O₃ (156.18), pale brown oil; yield: 69% (76 mg isolated from **441** (150 mg)). **R_f isomer A** = 0.360, **R_f isomer B** = 0.313 (silica gel, petroleum ether: EtOAc (65:35)). Major isomer: ¹H NMR (300 MHz, CDCl₃) δ 5.92 – 5.77 (m, 1H), 5.74 – 5.56 (m, 1H), 4.18 (m, 1H), 3.72 (s, 3H), 3.36 – 3.22 (m, 1H), 2.98 (brd, 1H), 2.36 – 2.17 (m, 1H), 2.15 – 1.87 (m, 2H), 1.84 – 1.64 (m, 1H). Minor isomers: ¹H NMR (300 MHz, CDCl₃) δ 5.97 – 5.80 (m, 1H), 5.78 – 5.59 (m, 1H), 4.21 (m, 1H), 3.74 (s, 3H), 3.31 (m, 1H), 2.89 (brd, 1H), 2.37 – 0.97 (m, 4H). Both isomers: ¹³C NMR (101 MHz, CDCl₃) δ 173.5, 129.6, 121.5, 66.4, 51.9, 46.2, 27.7, 22.0. **HRMS** (ESI): *m/z* [M + Na]⁺ calcd for C₈H₁₂NaO₃: 179.0679; found 179.0681.

❖ Alkylation of 445

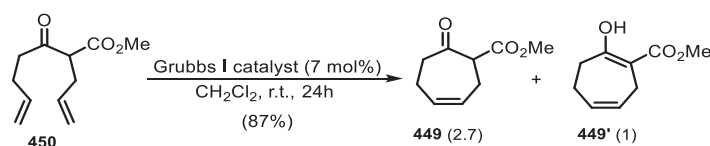


Procedure: “See the general procedure of α-alkylation in Chapter 2”.^[1]

▪ Methyl 2-allyl-3-oxohept-6-enoate **450**

C₁₁H₁₆O₃ (196.25), pale yellow oil; yield: 53% (1.67 g isolated from **445** (1 g)). **R_f** = 0.362 (silica gel, Petroleum ether: EtOAc (95:5)). ¹H NMR (300 MHz, CDCl₃) δ 5.74 (m,H), 5.19 – 4.85 (m, 4H), 3.73 (s, 3H), 3.55 (t, *J* = 7.4 Hz, 1H), 2.77 – 2.45 (m, 4H), 2.42 – 2.19 (m, 2H). *Spectroscopic data matches that reported in the literature.*^[75]

❖ Ring-closing metathesis of 450

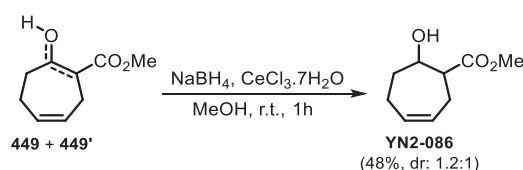


Procedure: Diene **450** (200 mg, 1.02 mmol) was dissolved in freshly distilled and degassed CH_2Cl_2 (80 mL) under an argon atmosphere. Ruthenium complex (Grubs I catalyst) (25.5 mg, 0.031 mmol, 3 mol%) was then added. After 24 hours of stirring the solution at room temperature, the conversion was complete as indicated by TLC. Evaporation of the solvent gave a crude mixture, which was chromatographed on silica gel to give the desired product.^[74]

- Methyl 7-oxocyclohept-3-ene-1-carboxylate **449** and methyl 2-hydroxycyclohepta-1,5-diene-1-carboxylate **449'**

$\text{C}_9\text{H}_{12}\text{O}_3$ (168.19), orange oil; yield: 87% (150 mg isolated from **450** (200 mg)). $R_f = 0.360$ (silica gel, Petroleum ether: EtOAc (85:15)). The ketone to enol ratio is 2.7:1. $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 12.55 (s, 1H), 5.88 – 5.71 (m, 5H), 5.71 – 5.62 (m, 1H), 5.58 (m, 1H), 3.81 (dd, $J = 10.7$, 3.8 Hz, 3H), 3.74 (s, 4H), 3.72 (s, 8H), 3.07 – 2.98 (m, 3H), 2.90 – 2.76 (m, 3H), 2.76 – 2.66 (m, 2H), 2.66 – 2.35 (m, 13H), 2.30 (m, 6H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 207.4, 177.1, 172.5, 170.2, 130.1, 128.8, 127.5, 127.0, 100.5, 57.6, 52.2, 51.5, 41.9, 32.0, 26.8, 24.7, 23.8, 22.4. **HRMS** (ESI): m/z [$\text{M} + \text{Na}^+$] calcd for $\text{C}_9\text{H}_{12}\text{NaO}_3$: 191.0681; found 191.0679.

❖ Ketone reduction of 449



Procedure: Compound **449** and its tautomer **449'** (470 mg, 2.8 mmol) and $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (1.561 g, 4.19 mmol) were dissolved in 50 ml of methanol. NaBH_4 (158 mg, 4.19 mmol) was then added in one portion with stirring. A vigorous gas evolution occurred and then stirring was continued for one hour before the pH was adjusted to neutrality with diluted aqueous HCl. The mixture was extracted with diethyl ether (three times), then the combined organic extracts were dried over

MgSO₄. Evaporation of the solvent gave a crude mixture, which was chromatographed on silica gel to give the desired product.^[76]

▪ methyl 7-hydroxycyclohept-3-ene-1-carboxylate **YN2-086**

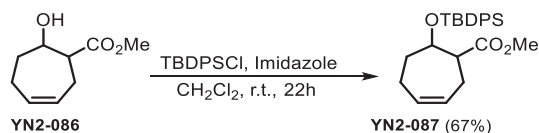
C₉H₁₄O₃ (170.21), colorless oil; yield: 48% (231 mg isolated from **449** and **449'** (470 mg)).

R_f (*first isomer*) = 0.373, **R_f** (*second isomer*) = 0.487 (silica gel, petroleum ether: EtOAc (65:35)).

The ratio of the two diastereoisomers is 1.2:1. **¹H NMR** (400 MHz, CDCl₃) δ 5.83 (dt, *J* = 11.8, 6.0 Hz, 1H), 5.78 – 5.68 (m, 1H), 4.19 (d, *J* = 3.7 Hz, 1H), 3.69 (s, 3H), 3.17 (d, *J* = 4.3 Hz, 1H), 2.74 (s, 2H), 2.44 – 2.28 (m, 1H), 2.12 (dd, *J* = 13.8, 7.9 Hz, 1H), 1.99 – 1.65 (m, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ 175.58, 133.30, 129.36, 129.35, 71.55, 51.81, 47.76, 32.44, 24.16, 22.15.

HRMS (ESI): *m/z* [M+ Na⁺] calcd for C₉H₁₄NaO₃ : 193.0830; found 193.0835.

❖ Alcohol protection of **YN2-086**



Procedure: Compound **YN2-086** (one of the separable diastereoisomers) (100 mg, 0.588 mmol) and Imidazole (6 mg, 0.088 mmol) were dissolved in 12 ml of dichloromethane. TBDPS-Cl (0.23 ml, 0.882 mmol) was then added dropwise at room temperature. After one day of stirring, the conversion was complete as indicated by TLC. The mixture was extracted with ethyl acetate (two times), then the combined organic extracts were dried over MgSO₄. Evaporation of the solvent gave a crude mixture, which was chromatographed on silica gel to give the desired product.

▪ Methyl 7-((tert-butyldiphenylsilyl)oxy)cyclohept-3-ene-1-carboxylate **YN2-087**

C₂₅H₃₂O₃Si (408.61), colorless oil; yield: 67% (160 mg isolated from **YN2-086** (100mg)). **R_f** = 0.475, (silica gel, Petroleum ether: EtOAc (95:5)). **¹H NMR** (400 MHz, CDCl₃) δ 7.78 – 7.55 (m, 4H), 7.39 (m, 6H), 5.76 (m, 2H), 4.60 (dd, *J* = 3.45, 7.04 Hz, 1H), 3.42 (s, 3H), 2.98 – 2.74 (m, 1H), 2.56 (m, 1H), 2.37 (m, 2H), 1.73 (m, 2H), 1.44 (m, 1H), 1.04 (s, 9H). **HRMS** (ESI): *m/z* [M+ Na⁺] calcd for C₂₅H₃₂NaO₃Si : 431.2013; found 431.2005.

❖ References

- [1] Y. Fukuyama, H. Yuasa, Y. Tono, K. Harada, M. Wada, Y. Asakawa, T. Hashimoto, *Tetrahedron* **2001**, *57*, 9299-9307.
- [2] P. Dowd, S. C. Choi, *Tetrahedron* **1989**, *45*, 77-90.
- [3] K. M. Peese, D. Y. Gin, *Org. Lett.* **2005**, *7*, 3323-3325.
- [4] J. Le Notre, D. van Mele, C. G. Frost, *Adv. Syn. Catal.* **2007**, *349*, 432-440.
- [5] S. Qin, T. Liu, Y. Luo, S. Jiang, G. Yang, *Org. Chem. Front.* **2019**, *6*, 732-735.
- [6] A. Tyszka-Gumkowska, J. Jurczak, *J. Org. Chem.* **2020**, *85*, 1308-1314.
- [7] R. A. Bunce, C. R. Harris, *J. Org. Chem.* **1992**, *57*, 6981-6985.
- [8] B. C. Ranu, K. Chattopadhyay, L. Adak, *Org. Lett.* **2007**, *9*, 4595-4598.
- [9] G. Fráter, *Helv. Chim. Acta* **1980**, *63*, 1383-1390.
- [10] A. G. Montalban, Y. A. Ma, S. Johannsen, S. Tandel, M. J. Martinelli, *Tetrahedron Lett.* **2015**, *56*, 378-381.
- [11] C. Fehr, J. Galindo, *Vol. 5442124*, Firmenich S. A., Switzerland, **1994**.
- [12] N. T. Tzvetkov, P. A. Waske, B. Neumann, H. G. Stammler, J. Mattay, *Tetrahedron Lett.* **2008**, *49*, 1710-1713.
- [13] a) X. L. Lu, M. Y. Lyu, X. S. Peng, H. N. C. Wong, *Angew. Chem.* **2018**, *130*, 11535-11538; b) L. H. P. Teixeira, E. J. Barreiro, C. A. M. Fraga, *Synth. Commun.* **1997**, *27*, 3241-3257.
- [14] O. Lahtigui, F. Emmetiere, W. Zhang, L. Jirno, S. Toledo-Roy, J. C. Hershberger, J. M. Macho, A. J. Grenning, *Angew. Chem. Int. Ed.* **2016**, *55*, 15792-15796.
- [15] A. Bacchi, M. Costa, N. Della Ca, B. Gabriele, G. Salerno, S. Cassoni, *J. Org. Chem.* **2005**, *70*, 4971-4979.
- [16] M. Blümel, R. D. Crocker, J. B. Harper, D. Enders, T. V. Nguyen, *Chem. Commun.* **2016**, *52*, 7958-7961.
- [17] M. Peifer, R. Berger, V. W. Shurtleff, J. C. Conrad, D. W. MacMillan, *J. Am. Chem. Soc.* **2014**, *136*, 5900-5903.
- [18] A. G. Griesbeck, M. Reckenthäler, *Beilstein J. Org. Chem.* **2014**, *10*, 1143-1150.
- [19] V. Maslak, Z. Tokic-Vujosevic, Z. Ferjancic, R. N. Saicic, *Tetrahedron Lett.* **2009**, *50*, 6709-6711.
- [20] a) K. Bica, P. Gaertner, *Eur. J. Org. Chem.* **2008**, *2008*, 3453-3456; b) V. Lecomte, C. Bolm, *Adv. Synth. Catal.* **2005**, *347*, 1666-1672; c) T. H. Chan, A. E. Schwerdtfeger, *J. Org. Chem.* **1991**, *56*, 3294-3298.
- [21] T. F. Yang, H. H. Chao, Y. H. Lu, C. J. Tsai, *Tetrahedron* **2003**, *59*, 8827-8831.
- [22] C. Fuganti, D. Joulain, F. Maggioni, L. Malpezzi, S. Serra, A. Vecchione, *Tetrahedron: Asymmetry* **2008**, *19*, 2425-2437.
- [23] H. Y. Lee, D. K. Moon, J. S. Bahn, *Tetrahedron Lett.* **2005**, *46*, 1455-1458.
- [24] L. Pehlivan, M. Jacolot, N. Coia, N. Monteiro, D. Bouyssi, G. Balme, *Tetrahedron Lett.* **2011**, *52*, 4716-4719.

- [25] a) R. E. Parker, N. S. Isaacs, *Chem. Rev.* **1959**, *59*, 737-799; b) G. A. Olah, P. S. Iyer, G. K. S. Prakash, *Synthesis* **1986**, *1986*, 513-531.
- [26] M. A. Hiebel, B. Pelotier, P. Goekjian, O. Piva, *Eur. J. Org. Chem.* **2008**, 713-720.
- [27] H. Thomanek, S. T. Schenk, E. Stein, K. H. Kogel, A. Schikora, W. Maison, *Org. Biomol. Chem.* **2013**, *11*, 6994-7003.
- [28] Z. Benfodda, F. Guillen, H. Arnion, A. Dahmani, H. Blancou, *Heteroat. Chem.* **2009**, *20*, 355-361.
- [29] L. Friedman, H. Shechter, *J. Org. Chem.* **1960**, *25*, 877-879.
- [30] F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless, V. V. Fokin, *J. Am. Chem. Soc.* **2005**, *127*, 210-216.
- [31] K. Nakashima, M. Imoto, T. Miki, *Heterocycles* **2002**, *56*, 85-89.
- [32] P. Pale, J. Chucho, *Eur. J. Org. Chem.* **2000**, 1019-1025.
- [33] S. Baskaran, I. Islam, M. Raghavan, S. Chandrasekaran, *Chem. Lett.* **1987**, *16*, 1175-1178.
- [34] A. B. Charette, A. Beauchemin, S. Francoeur, *J. Am. Chem. Soc.* **2001**, *123*, 8139-8140.
- [35] a) M. D'Auria, R. Racioppi, *Arkivoc* **2000**, *1*, 133-140; b) S. C. Freilich, K. S. Peters, *J. Am. Chem. Soc.* **1981**, *103*, 6255-6257; c) S. C. Freilich, K. S. Peters, *J. Am. Chem. Soc.* **1985**, *107*, 3819-3822.
- [36] S. Xie, D. Li, H. Huang, F. Zhang, Y. Chen, *J. Am. Chem. Soc.* **2019**, *141*, 16237-16242.
- [37] C. Richter, N. P. Ernsting, R. Mahrwald, *Synthesis* **2016**, *48*, 1217-1225.
- [38] D. A. Kambale, S. S. Thorat, M. S. Pratapure, R. G. Gonnade, R. Kontham, *Chem. Commun.* **2017**, 53, 6641-6644.
- [39] J. Fan, Z. Wang, *Chem. Commun.* **2008**, 5381-5383.
- [40] M. Liang, S. Zhang, J. Jia, C. H. Tung, J. Wang, Z. Xu, *Org. Lett.* **2017**, *19*, 2526-2529.
- [41] D. Sémeril, M. Cléran, A. J. Perez, C. Bruneau, P. H. Dixneuf, *J. Mol. Catal. A Chem.* **2002**, *190*, 9-25.
- [42] a) S. T. Diver, A. J. Giessert, *Chem. Rev.* **2004**, *104*, 1317-1382; b) A. Kinoshita, M. Mori, *J. Org. Chem.* **1996**, *61*, 8356-8357; c) C. S. Poulsen, R. Madsen, *Synthesis* **2003**, *1*, 1-18; d) H. Villar, M. Frings, C. Bolm, *Chem. Soc. Rev.* **2007**, *36*, 55-66; e) S. K. Chattopadhyay, S. Karmakar, T. Biswas, K. C. Majumdar, H. Rahaman, B. Roy, *Tetrahedron* **2007**, *63*, 3919-3952.
- [43] a) C. Amith, D. Ginsburg, *Tetrahedron* **1974**, *30*, 3415-3422; b) J. Kettenring, D. Ginsburg, *Tetrahedron* **1984**, *40*, 5269; c) M. Korat, D. Ginsburg, *Tetrahedron* **1973**, *29*, 2373-2381; d) T. Ibata, Y. Isogami, H. Tamura, *Chem. Lett.* **1988**, *17*, 1551-1554; e) I. Agmon, P. Ashkenazi, M. Kaftory, *Acta Cryst.* **1992**, *48*, 1479-1484; f) I. K. Korobitsyna, A. V. Khalikova, L. L. Rodina, N. P. Shusherina, *Chem. Heterocycl. Compd.* **1983**, *19*, 117-136.
- [44] a) M. V. Karkhelikar, R. R. Jha, Sridhar, P. R. Likhari, A. K. Verma, *Chem. Commun.* **2014**, *50*, 8526-8528; b) B. Dulla, S. K. Kolli, U. R. Chamakura, G. S. Deora, R. R. Raju, M. Pal, *Synth. Commun.* **2014**, *44*, 1466-1474.
- [45] a) R. Mancuso, S. Mehta, B. Gabriele, G. Salerno, W. S. Jenks, R. C. Larock, *J. Org. Chem.* **2010**, *75*, 897-901; b) V. Vijay, M. V. Karkhelikar, B. Sridhar, N. Mirzadeh, S. Bhargava, P. R. Likhari, *Org. Biomol. Chem.* **2016**, *14*, 288-295; c) T. Okitsu, A. Namura, S. Kondo, S. Tada, M. Yanagida, A. Wada, *Org. Chem. Front.* **2020**, *7*, 879-884.

- [46] M. Periasamy, N. Sanjeevakumar, P. O. Reddy, *Synthesis* **2012**, *44*, 3185-3190.
- [47] A. H. Aboo, E. L. Bennett, M. Deeprase, C. M. Robertson, J. A. Iggo, J. Xiao, *Chem. Commun.* **2018**, *54*, 11805-11808.
- [48] S. Avuluri, S. Bujaranipalli, S. Das, J. S. Yadav, *Tetrahedron Lett.* **2018**, *59*, 3547-3549.
- [49] T. Khomenko, A. Zakharenko, T. Odarchenko, H. J. Arabshahi, V. Sannikova, O. Zakharova, D. Korchagina, J. Reynisson, K. Volcho, N. Salakhutdinov, *Bioorg. Med. Chem.* **2016**, *24*, 5573-5581.
- [50] T. M. Khomenko, V. V. Zarubae, I. R. Orshanskaya, R. A. Kadyrova, V. A. Sannikova, D. V. Korchagina, K. P. Volcho, N. F. Salakhutdinov, *Bioorg. Med. Chem. Lett.* **2017**, *27*, 2920-2925.
- [51] S. A. Snyder, S. P. Breazzano, A. G. Ross, Y. Lin, A. L. Zografos, *J. Am. Chem. Soc.* **2009**, *131*, 1753-1765.
- [52] A. M. R. Smith, H. S. Rzepa, A. J. P. White, D. Billen, K. K. Hii, *J. Org. Chem.* **2010**, *75*, 3085-3096.
- [53] T. Kotipalli, D. R. Hou, *Org. Lett.* **2018**, *20*, 4787-4790.
- [54] a) Y. Nagao, M. Goto, M. Ochiai, *Chemistry Lett.* **1990**, *19*, 1507-1510; b) M. Uyanik, M. Akakura, K. Ishihara, *J. Am. Chem. Soc.* **2009**, *131*, 251-262.
- [55] M. Iinuma, K. Moriyama, H. Togo, *Eur. J. Org. Chem.* **2014**, *2014*, 772-780.
- [56] M. Prokopowicz, P. Młynarz, P. Kafarski, *Tetrahedron Lett.* **2009**, *50*, 7314-7317.
- [57] R. Yefidoff, A. Albeck, *Tetrahedron* **2004**, *60*, 8093-8102.
- [58] K. Rajkumari, I. B. Laskar, A. Kumari, B. Kalita, L. Rokhum, *React. Funct. Polym.* **2020**, *149*, 104519.
- [59] N. Watanabe, H. Kino, S. Watanabe, H. K. Ijuin, M. Yamada, M. Matsumoto, *Tetrahedron* **2012**, *68*, 6079-6087.
- [60] B. A. Sparling, R. M. Moslin, T. F. Jamison, *Organic Lett.* **2008**, *10*, 1291-1294.
- [61] F. d. r. Beltran, I. Fabre, I. Ciofini, L. Miesch, *Organic Lett.* **2017**, *19*, 5042-5045.
- [62] I. Khan, B. G. Reed-Berendt, R. L. Melen, L. C. Morrill, *Angew. Chem.* **2018**, *130*, 12536-12539.
- [63] Y. Ito, T. Hirao, T. Saegusa, *J. Org. Chem.* **1978**, *43*, 1011-1013.
- [64] Q. Glenadel, Y. Nassar, L. Raffier, S. Veys, O. Piva, *Tetrahedron* **2018**, *74*, 5367-5373.
- [65] D. Beruben, I. Marek, J. F. Normant, N. Platzner, *J. Org. Chem.* **1995**, *60*, 2488-2501.
- [66] B. H. Lipshutz, M. Koerner, D. A. Parker, *Tetrahedron Lett.* **1987**, *28*, 945-948.
- [67] C. Praveen, P. T. Perumal, *Chinese J. Catal.* **2016**, *37*, 288-299.
- [68] I. Paterson, E. A. Anderson, S. M. Dalby, J. H. Lim, P. Maltas, O. Loiseleur, J. Genovino, C. Moessner, *Org. Biomol. Chem.* **2012**, *10*, 5861-5872.
- [69] M. D. Keränen, K. Kot, C. Hollmann, P. Eilbracht, *Org. Biomol. Chem.* **2004**, *2*, 3379-3384.
- [70] a) D. F. Taber, P. B. Decker, M. D. Gaul, *J. Am. Chem. Soc.* **1987**, *109*, 7488-7494; b) T. Miyagi, S. Okada, N. Tada, M. Sugihara, N. Kagawa, T. Takabatake, M. Toyota, *Tetrahedron Lett.* **2019**, *60*, 1653-1657.
- [71] D. Prajapati, K. C. Lakhok, J. S. Sandhu, A. C. Ghosh, *J. Chem. Soc.* **1996**, 959-960.

- [72] R. Antonioletti, P. Bovicelli, S. Malancona, *Tetrahedron* **2002**, *58*, 589-596.
- [73] C. Tomassini, F. Di Sarra, B. Monti, L. Sancineto, L. Bagnoli, F. Marini, C. Santi, *Arkivoc* **2017**, *2*, 303-312.
- [74] S. Kinderman, J. van Maarseveen, H. Schoemaker, H. Hiemstra, F. Rutjes, *Organic Lett.* **2001**, *3*, 2045-2048.
- [75] M. A. Dombroski, S. A. Kates, B. B. Snider, *J. Am. Chem. Soc.* **1990**, *112*, 2759-2767.
- [76] D. I. Magee, S. Ratshonka, J. McConaghy, M. Hood, *Can. J. Chem.* **2012**, *90*, 450-463.

Photochimie et Réactions en Cascade: Accès aux Propellanes et aux Produits Naturels

Résumé

L'augmentation remarquable du nombre de nouveaux médicaments cibles peut se traduire directement par une demande de nouvelles méthodes pour construire rapidement de petites molécules très pures qui possèdent un niveau de complexité structurelle toujours croissant. Ces processus doivent également être plus efficaces, plus propres pour l'environnement et conduire à une plus grande diversité structurelle en peu de temps. Ces besoins ont conduit au développement de nouvelles stratégies, qui ont aidé à produire des composés à un rythme plus élevé que ce que l'on pensait possible auparavant. La photochimie ainsi que les réactions en cascade font partie de ces stratégies dans lesquelles elles sont très recherchées pour leur efficacité à construire un certain nombre de liaisons et de cycles et à augmenter la complexité moléculaire des produits qui en résultent. Cette thèse rapporte l'utilisation de la photochimie et des réactions en cascade pour la synthèse de structures complexes, telles que des propellanes et de certains produits naturels. Le chapitre 1 donne un aperçu de la conception et de la synthèse des α - (hydroxyméthyl) cycloalcanols et le chapitre 2 décrit l'utilisation de la photo-hydroxymethylation pour synthèse des éléments constitutifs du propellane. Les chapitres 3 à 5 concernent la synthèse de divers systèmes de cycles de propellane avec une architecture structurelle esthétiquement attrayante alors que, le dernier chapitre donne brièvement nos tentatives vers la synthèse totale de cordycol, le monomère de l'idesolide et d'un analogue.

Mots-clefs:

Photochimie – Réactions en cascade – Propellanes – Spirocycles – Synthèse totale – Cordycol – Lactones.

Equipe de Synthèse, Utilisation, Réactivité des Composés Organiques et OrganoFluorés (SURCOOF)

Université Claude Bernard Lyon 1

Institut de Chimie et de Biochimie Moléculaires et Supramoléculaires (ICBMS)

UMR CNRS 5246

Bâtiment Raulin, 2 Rue Victor Grignard, 69100 Villeurbanne Cedex