

Dissertation zur Erlangung des Doktorgrades  
der Fakultät für Chemie und Pharmazie der  
Ludwig-Maximilians-Universität München



---

CHIRAL POOL APPROACHES TO  
*LYCOPODIUM* ALKALOIDS, *ORCHIDACEAE* ALKALOIDS  
AND  
PHOTOSWITCHABLE CERAMIDES

---

Benjamin Matthew Williams

aus

Calgary, Canada

2018

**Erklärung:**

Diese Dissertation wurde im Sinne von §7 der Promotionsordnung vom 28. November 2011 von Herrn Prof. Dr. Dirk Trauner betreut.

**Eidesstattliche Versicherung:**

Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfe erarbeitet.

München, 16. Mai 2018

.....

Ben Williams

Dissertation eingereicht am: 27. März 2018  
Erstgutachter: Prof. Dr. Dirk Trauner  
Zweitgutachter: Dr. Dorian Didier  
Mündliche Prüfung am: 16. Mai 2018

*I don't like work – no man does –  
but I like what is in the work – the chance to find yourself.*

*Your own reality – for yourself not for others –  
what no other man can ever know.*

Joseph Conrad

To Anni and my Family





## ABSTRACT

The following dissertation presents a series of chiral pool approaches to amine-containing natural products and photoactive lipid analogues.

The first chapter summarizes the asymmetric total synthesis of lycopalhine A – a compact and stereochemically dense *Lycopodium* alkaloid – using L-glutamic acid as a starting point. The route features a diastereoselective Pauson–Khand reaction and an L-proline promoted 5-*endo*-trig Mannich cyclization. The successful synthesis allowed the characterization of a second co-eluting alkaloid, *epi*-lycopalhine A, and confirmed its interconversion with lycopalhine A through a retro-aldol/aldol equilibrium. A tentative path to palhinine D involving a reductive piperidine cyclization is afterwards presented.

An azomethine ylide [3 + 2]-cycloaddition strategy towards the bioactive *Orchidaceae* alkaloid (+)-dendrobine is described in the second chapter. A cyclization precursor was generated in seven steps from (*R*)-carvone through a convergent esterification and an unconventional high-pressure Ireland–Claisen rearrangement. The resulting aldehyde was employed in a decarboxylative azomethine ylide cycloaddition following condensation with *N*-methylglycine to yield 5-deoxymubironine C, which differs from the natural product mubironine C by the absence of a single hydroxyl group. Thwarted attempts to incorporate this final functional group include an  $\alpha$ -chlorination/lactonization sequence and an unplanned enal–ene reaction.

The final chapter describes the synthesis of two photoswitchable sphingoid bases (**aSph-1** and **-2**) from L-serine, and their coupling with alkyne-bearing fatty acids to generate clickable azobenzene-containing ceramide analogues (**caCer-3** and **caCer-4**). Together with fatty acid azobenzene (**FAAzo**)-based **caCer-1** and **caCer-2** developed by postdoctoral researcher Henry Toombs-Ruane, these molecules were evaluated as optically active substrates for sphingomyelin synthase (SMS2). **CaCers** were successfully incorporated into supported lipid bilayers (SLBs) and could alter the ordered/disordered domain ratio upon light irradiation. **CaCer-1**, **-2** and **-3** were competent substrates for SMS2 and conversion to their sphingomyelin analogues could be controlled in a light-dependent manner in both yeast membranes and HeLa cells.

---

## ACKNOWLEDGEMENTS

I would like to thank Professor Dirk Trauner for his liberal advice, often unrestrained enthusiasm and all-around good humor. Many of the findings contained in this thesis would remain fictions without his insight and encouragement. He has built an industrious and good-natured group in Munich, one which will no doubt lose none of its zeal on its move to New York City.

I reserve special thanks for all members of the UV lab. Three companions in particular – Daniel Terwilliger, Dr. Felix Hartrampf and David Konrad – have been with me since my first day of work, when they strong-armed me into joining the forlorn lab at the end of the hall. Four great years in the group have gone by in the blink of an eye with these friends and gifted chemists as constant company. Though Henry Toombs-Ruane, Ahmed Ali and Nils Winter all entered the UV lab at later dates, it feels like they always belonged here, or have never really left.

All other members of the Trauner group have contributed to this work in their own way. Dr. Nina Vrielink, Katherine Hüll and Nynke Veprek have been lively company while handling party planning and group organization. Dr. Pascal Ellerbrock, Dr. Nicolas Armanino, Dr. Julius Reyes and Dr. Bryan Matsuura have offered sound advice, proofread manuscripts and answered countless inane questions. Antonio Rizzo, Dr. Arunas Damijonaitis and Dr. Hong-Dong Hao have always been ready for a good discussion, chemistry-related or otherwise. All members of the Magauer group, trusted comrades-in-arms, are sorely missed. Dr. Klaus Speck expressly deserves my thanks for showing me how to perform high-pressure experiments.

I have received enormous help on each of the projects mentioned herein from four excellent interns. Fabio Raith assisted in the scale-up of lycopalhine A and in the alkyne homologation of an intermediate lactol. Moritz Bund helped to first explore the cross-metathesis route towards azobenzene-containing sphingosine analogues. Simon Schnell performed the synthesis of pyrrolidine tricycles and screened aza-Michael addition reactions in our bid at the palhinine D skeleton. Benni Bissinger was instrumental in ironing out wrinkles in the early stages of our asymmetric attempt toward dendrobine. They have each contributed significant synthetic effort to these projects and I wish them the best in their future careers.

Collaborators mentioned throughout this thesis deserve important recognition. Dr. James Frank directed much of the photoswitchable ceramide project and, more importantly, was a fellow Canadian when times were most German. Dr. Matthijs Kol and Prof. Joost Holthuis of the Universität Osnabrück devised and performed experiments in yeast membranes and living cells. Dr. Henri Franquelim and Prof. Petra Schwille of the Max Planck Institute of Biochemistry performed atomic force microscopy and fluorescent microscopy imaging experiments.

---

---

Little more can be said of the superb X-ray crystallography work performed by Dr. Peter Mayer than has already been mentioned in countless LMU theses. I am grateful to Dr. David Stephenson and Claudia Ober of the NMR department for  $^1\text{H}$  NMR and 2-D NMR spectroscopy as well as high-temperature NMR experiments.

I would like to thank each of the permanent staff for their involvement in the day-to-day operation of the group. Dr. Martin Sumser, Carrie Louis, Luis de la Osa de la Rosa and Mariia Palchyk have all done their best to keep the lab on its feet and in fighting shape. Heike Traub and Alex Grilc have likewise been irreplaceable when dealing with administrative affairs.

My brother Sam's and my sister-in-law Beta's bustling energy has kept me looking with impatience toward my own future. My parents have always given me everything they have to offer, whether times were good or less than so. My beautiful Annabelle is the single greatest sight imaginable to return home to, at least until we get a dog.

---

## PUBLICATIONS AND CONFERENCES

Portions of this thesis were published in peer-reviewed journals:

- ‘*Azomethine Ylide Cycloaddition Approach toward Dendrobine: Synthesis of 5-Deoxymubironine C*’ – B. M. Williams, D. Trauner, *J. Org. Chem.* **2018**, 83, 3061 – 3068.
- ‘*Expedient Synthesis of Lycopalhine A*’ – B. M. Williams, D. Trauner, *Angew. Chem. Int. Ed.* **2016**, 55, 3442 – 3445.

Portions of this thesis were presented at scientific conferences:

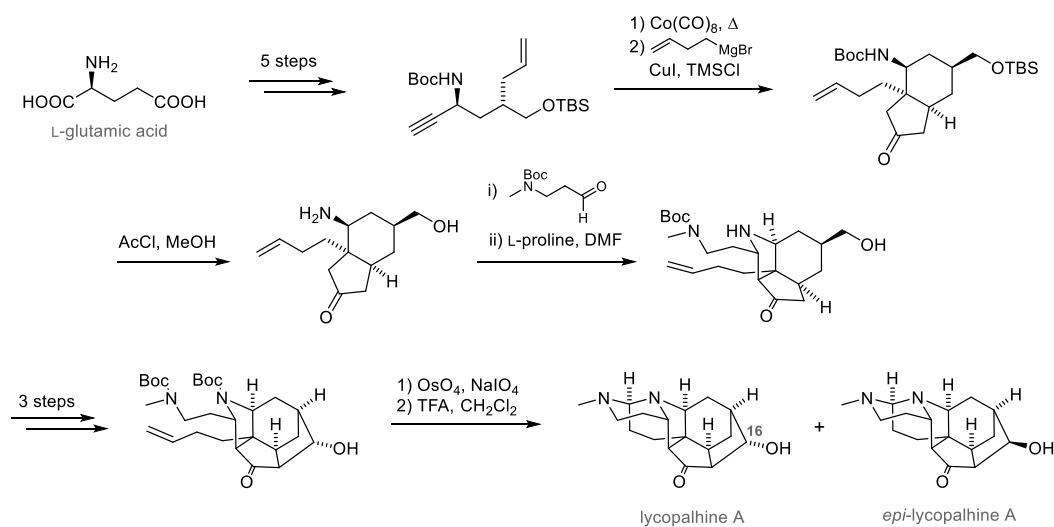
- ‘*Azomethine Ylide Cycloaddition Strategies toward Dendrobium Alkaloids*’ – Oral Presentation, 100<sup>th</sup> Canadian Chemistry Conference and Exhibition, Toronto, Canada, **2017**.
  - ‘*Concise Synthesis of Lycopalhine A and Efforts toward the Palhinine B Ring System*’ – Poster Presentation, 17th Tetrahedron Symposium, Sitges, Spain, **2016**.
  - ‘*Concise Synthesis of Lycopalhine A and Efforts toward the Palhinine B Ring System*’ – Poster Presentation, SFB 749 Symposium, Irsee, Germany, **2016**.
  - ‘*Enantiospecific Synthesis of the Hexacyclic Lycopodium Alkaloid Lycopalhine A*’ – Poster Presentation, Tokyo LMU Symposium, Munich, Germany, **2015**.
-

## SUMMARY

### Chapter I. Total Synthesis of (+)-Lycopalhine A

Lycopalhine A (**Scheme I**), isolated from *Palhinhaea cernua*, is one of the most heavily functionalized and stereochemically dense *Lycopodium* alkaloids described to date. Its compact frame contains nine stereogenic centers – eight of which are contiguous – as well as a fused piperidine/hexahydropyrimidine/pyrrolidine ring system.

We explored a short chiral pool synthesis of the molecule from inexpensive L-glutamic acid. The amino acid was elaborated to a linear enyne by a diastereoselective allylation and a chemoselective hydride reduction. This intermediate underwent a highly diastereoselective Pauson–Khand reaction followed by a conjugate addition to set the molecule's sole quaternary stereocenter and afford a key bicycle. To generate the heavily substituted pyrrolidine of the natural product, we developed a novel L-proline-mediated Mannich cyclization following condensation of an aminoketone with a  $\beta$ -amino aldehyde. The synthesis concluded with a biomimetic aldol reaction and a final oxidative olefin cleavage/aminal formation sequence to furnish the natural product.



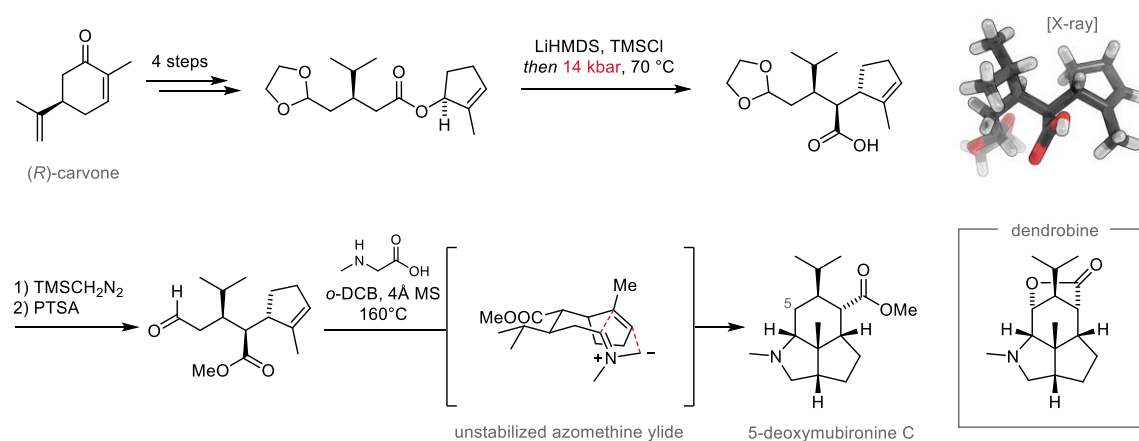
**Scheme I.** Total synthesis of (+)-lycopalhine A.

Following the synthesis of lycopalhine A, we observed a co-eluting side-product whose spectral data directly matched an impurity in the isolated natural product. Two-dimensional NMR analysis and deuterium exchange studies identified the minor product as the C16 epimer of lycopalhine A (*epi*-lycopalhine A) which is in equilibrium with the major diastereomer through a retro-aldol/aldol sequence. This marks the first synthesis of lycopalhine A in an efficient 14 steps from glutamic acid.

B. M. Williams, D. Trauner, *Angew. Chem. Int. Ed.* **2016**, *55*, 2191 – 2194.

## Chapter II. Azomethine Ylide Cycloaddition Strategy toward Dendrobine

Our early studies into the synthesis of lycopalline A explored an azomethine ylide cycloaddition route towards the molecule's crowded azatricyclo[6.2.1.0<sup>4,11</sup>]undecane core. Though ultimately unsuccessful, we recognized that such a strategy might be better suited for an efficient asymmetric synthesis of dendrobine, a highly caged alkaloid from *Dendrobium nobile* with convulsant and hypotensive properties. We believed the development of a general cycloaddition approach towards this tricyclic system could equally be applied to other complex *Orchidaceae* alkaloids such as mubironine C and dendrine.



**Scheme II.** Azomethine ylide cycloaddition approach to (–)-dendrobine.

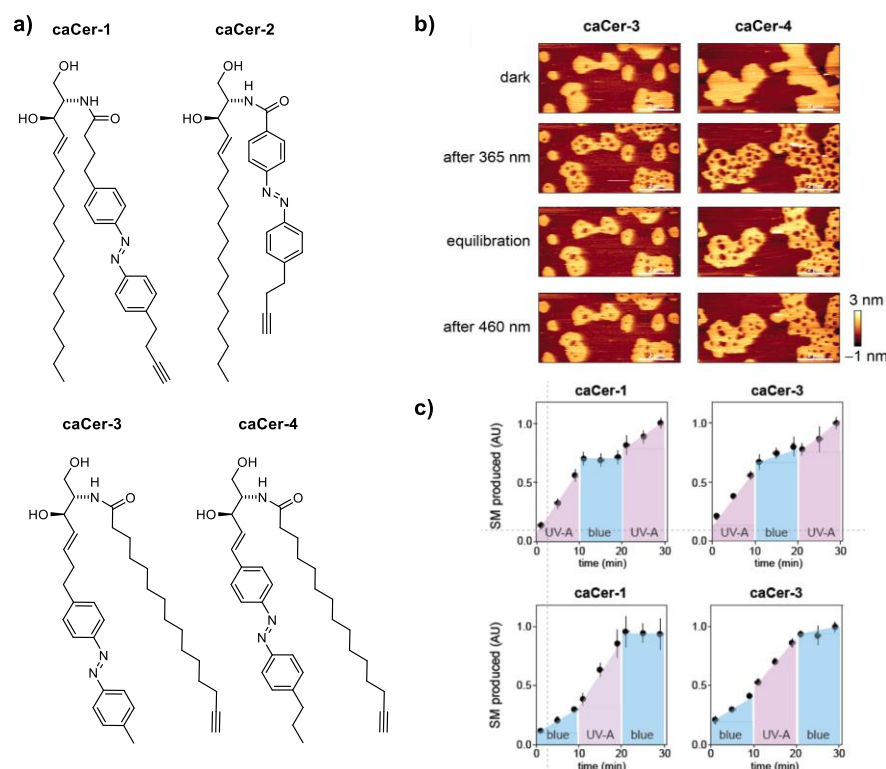
Our synthesis began with the construction of a chiral ester from (*R*)-carvone, which we intended to employ in an Ireland–Claisen reaction to set two contiguous stereocenters. As thermal conditions led to substantial decomposition of the starting material through ketene formation, we developed high-pressure conditions that suppressed alcohol extrusion while increasing reaction yield. Condensation of an ensuing aldehyde with sarcosine under dilute conditions and subsequent decarboxylation afforded an unstabilized azomethine ylide, which underwent a 1,3-dipolar cycloaddition to furnish the desired tricyclic system. We thereby obtained 5-deoxymubironine C – differing from the natural product mubironine C by only a single hydroxyl group – in eight steps from (*R*)-carvone. With the carbon skeleton of the natural product complete, we are currently engaged in selectively installing the final degree of oxidation at the C5 position.

B. M. Williams, D. Trauner, *J. Org. Chem.* **2018**, 83, 3061 – 3068.

### Chapter III. Synthesis of Photoswitchable Ceramides for Optical Control in Lipid Metabolism

The Trauner laboratory operates a wide-ranging program in photopharmacology, in which photoswitchable ligands are used to modulate biological systems with the spatiotemporal precision of light. Our laboratory has recently expanded this principle to the realm of lipids. In one recent instance, artificial ceramides with azobenzene-bearing fatty acid chains (**ACes**) were incorporated into supported lipid bilayers (SLBs) and used to optically control the structure of ordered and disordered lipid domains. Though these results allowed the modulation of artificial membranes with light, it was unclear whether these photoceramides could be incorporated into actual cellular membranes, or if they could act as competent and reversible substrates for sphingolipid metabolism.

To answer these questions, we developed a series of four azobenzene-bearing ceramides with added alkyne functionality, termed **clickable azo-ceramides (caCers 1-4, Figure I.a)**, for the study of lipid metabolism in living systems. **CaCer-1** and **caCer-2** featured the azobenzene and alkyne moieties on the fatty acid side chain, whereas **caCer-3** and **caCer-4** required incorporation of the azobenzene moiety directly into the backbone of the sphingoid base through a cross-metathesis strategy. In collaboration with the Schwille group at the Max Planck Institute of Biochemistry, we confirmed that **caCers-3** and **-4** also control membrane behavior in SLBs in a light-dependent manner (**Figure I.b**).



**Figure I.** a) Structures of **caCers**, b) AFM imaging indicates structures of **caCer**-incorporated SLBs are modulated with light, c) **caCers** in yeast membrane are transformed by SMS2 in a light-dependent fashion.

In partnership with the Holthuis group at the University of Osnabrück, **caCers** were investigated for their ability to act as substrates for sphingomyelin synthase (SMS), which converts ceramides to sphingomyelins through transfer of a phosphocholine headgroup to the primary alcohol. Initial studies in yeast membranes confirmed all **caCers** were converted into their SM analogues by SMS2, and UV-pretreated *cis*-**caCer-1**, in particular, showed markedly higher conversion than its *trans*-isomer. Indeed, SM analogue production could be alternately stimulated or inhibited by irradiating the **caCer**-incubated cells with UV or blue light, respectively (**Figure 1.c**). Importantly, this metabolism could be light-controlled in living cells: SMS2-V5 overexpressing HeLa cells were found to convert certain **caCers** to their SM analogues in a light-dependent manner. Overall, these findings represent the first photoswitchable enzyme substrates in lipid metabolism and open the possibility that lipid formation and signaling can be controlled with the precision of light.

---



**ABBREVIATIONS**

Ac	acetyl
acac	acetylacetonate
AD-mix	asymmetric dihydroxylation mix
AFM	atomic force microscopy
AIBN	azobisisobutyronitrile
AMPA	$\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ATR	attenuated total reflection
AU	arbitrary unit
9-BBN	9-borabicyclo(3.3.1)nonane
Bn	benzyl
Boc	<i>tert</i> -butyloxycarbonyl
BSA	bis(trimethylsilyl)acetamide
Bu	butyl
caCer	clickable azobenzene-containing ceramide analogues
CAM	cerium ammonium molybdate
CDI	carbonyldiimidazole
Cer	ceramide
CoA	coenzyme A
CSA	camphorsulfonic acid
DABCO	1,4-diazabicyclo[2.2.2]octane
DAG	diacylglyceride
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	<i>N,N'</i> -dicyclohexylcarbodiimide
DEAD	diethyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMF	dimethylformamide

---

---

DMSO	dimethyl sulfoxide
DMP	Dess-Martin periodinane
DOPC	1,2-O-dioleoyl-sn-glycero-3-O-phosphocholine
DTBMP	2,6-di- <i>tert</i> -butyl-4-methylpyridine
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EI	electron ionization
ESI	electrospray ionization
Et	ethyl
EV	empty vector
FA	fatty acid
GABA	$\gamma$ -aminobutyric acid
GCPR	G-protein-coupled receptor
HBTU	2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HG II	Hoveyda-Grubb's catalyst, second generation
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
HOBt	hydroxybenzotriazole
HRMS	high resolution mass spectrometry
IBX	2-iodoxybenzoic acid
IR	infrared
LAH	lithium aluminium hydride
L <sub>d</sub>	liquid-disordered
L <sub>o</sub>	liquid-ordered
LPA	lysophosphatidic acid
<i>m</i> CPBA	<i>meta</i> -chloroperoxybenzoic acid
Me	methyl
MOM	methoxymethyl
NBS	<i>N</i> -bromosuccinimide
NCS	<i>N</i> -chlorosuccinimide
NHC	N-heterocyclic carbene

---

---

NMDA	<i>N</i> -methyl-D-aspartic acid
NMO	<i>N</i> -methylnmorpholine <i>N</i> -oxide
NMP	<i>N</i> -methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
<i>o</i> -DCB	<i>ortho</i> -dichlorobenzene
ORTEP	Oak Ridge thermal ellipsoid plot
PC	phosphatidylcholine
PCC	pyridinium chlorochromate
PCL	photochromic ligand
PDC	pyridinium dichromate
PDP	bis(2-pyridylmethyl)]-2,2'-bipyrrolidine
Ph	phenyl
PIDA	phenyliodine(III) diacetate
PKC	protein kinase C
PKR	Pauson–Khand reaction
PPTS	pyridinium <i>p</i> -toluenesulfonate
Pr	propyl
PTL	photoswitchable tethered ligand
PTSA	<i>p</i> -toluenesulfonic acid monohydrate
R <sub>f</sub>	retardation factor
RT	room temperature
S1P	sphingosine-1-phosphate
S1PR	sphingosine-1-phosphate receptor
SLB	supported lipid bilayer
SM	sphingomyelin
SMS	sphingomyelin synthase
Sph	sphingosine
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide

---

TBS	<i>tert</i> -butyldimethylsilyl
TBTU	2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethylammonium tetrafluoroborate
TCBC	2,4,6-trichlorobenzoyl chloride
TES	triethylsilyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
TRPV	transient receptor potential cation channel vanilloid
UV	ultraviolet

---

**TABLE OF CONTENTS**

ABSTRACT .....	i
ACKNOWLEDGEMENTS .....	ii
PUBLICATIONS AND CONFERENCES .....	iv
SUMMARY .....	v
ABBREVIATIONS .....	ix
TABLE OF CONTENTS .....	ixiii

**CHAPTER I: TOTAL SYNTHESIS OF (+)-LYCOPALHINE A**

Introduction to Fawcettimine-Type <i>Lycopodium</i> Alkaloids.....	2
<i>Lycopodium</i> clubmosses.....	2
Classification and biosynthesis of <i>Lycopodium</i> alkaloids .....	3
Bioactivity of <i>Lycopodium</i> alkaloids.....	5
Synthetic approaches to fawcettimine-type alkaloids .....	6
Conjugate Addition Approaches .....	7
Pauson–Khand Approaches.....	11
Cycloaddition Approaches .....	14
Pinacol and Semi-Pinacol Rearrangement Approaches .....	18
Lycopalhine A .....	20
The Total Synthesis of Lycopalhine A .....	22
Synthetic efforts towards the Palhinine D ring system.....	27
X-ray crystal structures of compounds 10 and 17 .....	27
Efforts towards the skeleton of Palhinine D.....	27

**CHAPTER II: AZOMETHINE YLIDE CYCLOADDITION STRATEGY TOWARD DENDROBINE**

Introduction to Dendrobine.....	34
Dendrobine and the <i>Orchidaceae</i> alkaloids .....	34
Biosynthesis and Bioactivity of Dendrobine .....	35
Total syntheses of Dendrobine .....	37
Formal Syntheses of Dendrobine .....	44
Project goals .....	47

---

---

An Azomethine Ylide Cycloaddition Approach to Dendrobine.....	48
Unpublished Efforts toward <i>Orchidaceae</i> Alkaloids .....	57

**CHAPTER III: SYNTHESIS OF PHOTOSWITCHABLE CERAMIDES FOR OPTICAL  
CONTROL IN LIPID METABOLISM**

Introduction to the Photopharmacology of Lipids.....	60
Biological Roles of Lipids .....	60
Sphingolipids .....	62
Photopharmacology .....	64
Photolipids .....	66
Results and Discussion .....	68
Synthesis of Clickable Azobenzene-containing Ceramides.....	68
CaCers in Supported Lipid Bilayers (SLBs).....	72
Optical control of SM metabolism with caCers.....	73

**CHAPTER IV: EXPERIMENTAL INFORMATION**

General Experimental Details .....	80
Experimental Procedures for Chapter I .....	82
Experimental Procedures for Chapter II .....	107
Experimental Procedures for Chapter III .....	126

**CHAPTER V: APPENDIX**

<sup>1</sup> H NMR and <sup>13</sup> C NMR Spectra.....	146
<sup>1</sup> H NMR and <sup>13</sup> C NMR Spectra for Chapter I.....	146
<sup>1</sup> H NMR and <sup>13</sup> C NMR Spectra for Chapter II .....	177
<sup>1</sup> H NMR and <sup>13</sup> C NMR Spectra for Chapter III .....	199
Crystallographic Data .....	216
Crystallographic Data for Chapter I.....	216
Crystallographic Data for Chapter II .....	224
References.....	234

---

CHAPTER I:  
TOTAL SYNTHESIS OF (+)-LYCOPALHINE A

---

## 1.1. Introduction to Fawcettimine-Type *Lycopodium* Alkaloids

### 1.1.1. *Lycopodium* clubmosses

The *Lycopodium* (*sensu lato*) genus (family Lycopodiaceae) of clubmosses is a group of vascular plants characterized by their squat pine- or moss-like appearance, their small, narrow, uniform leaves and the distinct club-shaped strobili from which their name is derived (**Figure 1.1**).<sup>[1]</sup> They are geographically wide-spread and species can be found on most continents, ranging from the *Lycopodium clavatum* of Central Europe and South Africa, to the *Lycopodiella cernua* of the Hawaiian islands and Southern China and the *Diphasiastrum fawcettii* of Jamaica. The historical designation ‘*Lycopodium*’ was broad and encompassed many extant clubmosses. More recent taxonomy has subdivided the Lycopodiaceae family into four main genera – *Lycopodium*, *Lycopodiella*, *Diphasiastrum* and *Huperzia* – with *Huperzia* now often sorted into a separate Huperziaceae family.<sup>[2]</sup> In many instances, however, the term *Lycopodium* (*s.l.*) is still retained when referring in general terms to these clubmosses.<sup>[3]</sup>



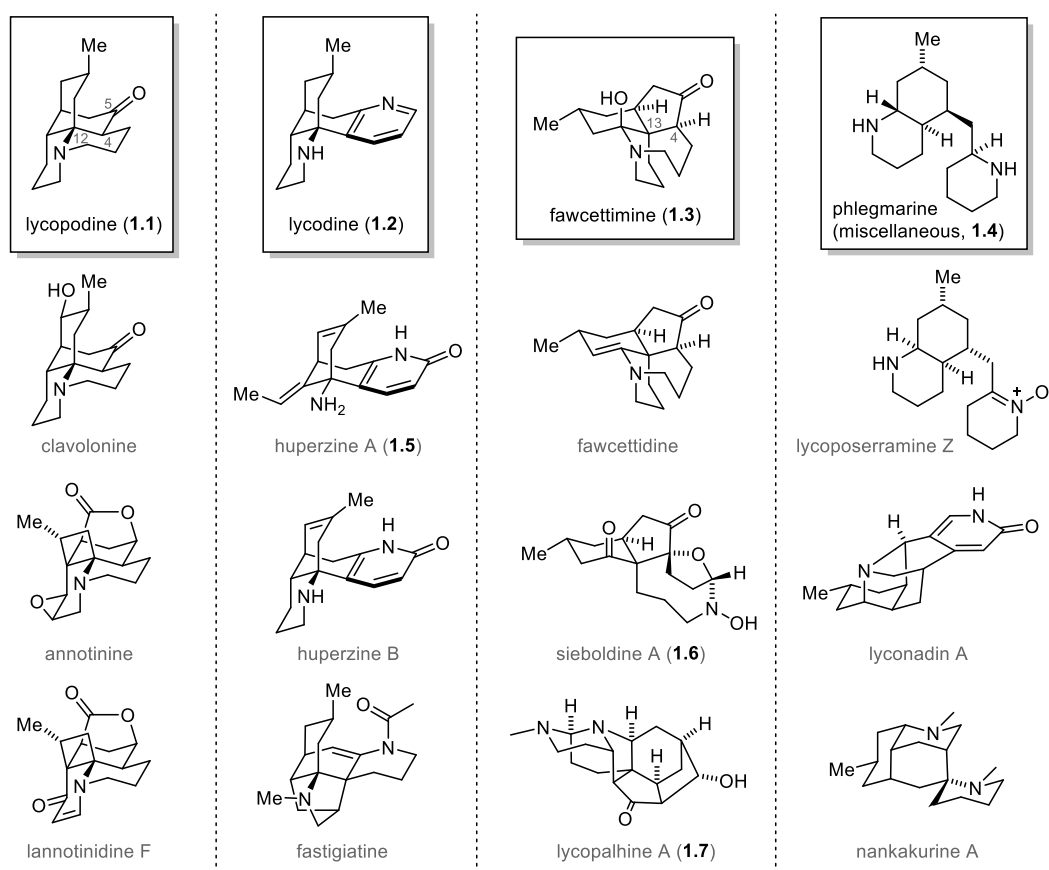
**Figure 1.1.** Photograph by Christian Fischer (left)<sup>[4]</sup> and Correvon’s illustration (middle) of the *Lycopodium clavatum*. Photograph by Jeferson Dutra (right)<sup>[5]</sup> of *Lycopodiella cernua* showcasing the club-shaped strobili.

Lycopods are ancient species that developed amongst terrestrial plants in the Devonian era some 380 million years ago.<sup>[6]</sup> On a more contemporary timescale, clubmosses have been used as remedies and medicines throughout human history and territory. The Blackfoot tribes of the Albertan plains used a decoction of *Lycopodium complanatum* for the treatment of lung and venereal disease;<sup>[7]</sup> Chinese medicinal practitioners since the Tang dynasty employed whole plant *Huperzia serrata* as the memory-enhancing remedy ‘Qian Ceng Ta’;<sup>[8]</sup> and the German polymath Hildegard von Bingen documented *Lycopodium clavatum* as a component for a medicinal tea treating a range of maladies.<sup>[3]</sup> Though interest in the medicinal properties of lycopods has largely subsided during modern times, the scientific community is still intrigued by their archaic nature and bioactive properties. For synthetic chemists and phytochemists, the source of interest in these plants is undoubtedly their high alkaloidal content. It was from *Lycopodium* clubmosses that the complex *Lycopodium* alkaloids were first isolated.



### 1.1.2. Classification and biosynthesis of *Lycopodium* alkaloids

The *Lycopodium* alkaloids are a group of highly diverse basic metabolites recognizable by their fused polycyclic systems and crowded stereochemistry. Since the discovery of lycopodine in 1881,<sup>[9]</sup> they have been a subject of extensive investigation by chemists and a number of reviews have since been written on their isolation, applications and syntheses.<sup>[2-3, 10-18]</sup> The *Lycopodium* alkaloids number over 300 members<sup>[18]</sup> and feature great structural diversity, making a global method of classification non-trivial. A system put forth by Ayers and Trifonov has been distinctly favoured by chemists in the 21<sup>st</sup> century.<sup>[13]</sup> Ayer's system sorts all alkaloids into four classes, each named after a representative parent molecule: lycopodine (**1.1**), lycodine (**1.2**), fawcettimine (**1.3**) and phlegmarine (**1.4**, also known as the miscellaneous class). The classes are displayed in **Figure 1.2** with notable examples.



**Figure 1.2.** The four classes of *Lycopodium* alkaloids and representative examples.

Lycopodine was the first *Lycopodium* alkaloid to be identified. Bödeker reported its extraction from *Lycopodium complanatum* in 1881<sup>[9]</sup> and its molecular formula was determined by Achmatowicz and Uzieblo in 1932.<sup>[19]</sup> Lycopodine-class molecules are characterized by their (generally) tetracyclic core of fused six-membered rings, their quinolizidine motifs, and a carbonyl or alcohol at the C5 position.<sup>[14]</sup> Their complexity and variety have made them early and popular targets of total synthesis.<sup>[20-29]</sup>

Lycodine was first isolated by Anet and Eves in 1958 from the *Lycopodium annotinum*<sup>[30]</sup> and its structure was elucidated by Ayer shortly afterward.<sup>[31]</sup> Lycodine-type alkaloids resemble the lycopodine class with the notable feature that the A-ring has been rearranged to form a pyridine, pyridone or similarly oxidized piperidine system. Many of the most studied biologically-active *Lycopodium* alkaloids fall into this class. The most notable, huperzine A (**1.5**),<sup>[32-33]</sup> acts as a potent acetylcholinesterase inhibitor and is often exhibited as a poster-child for *Lycopodium* bioactivity. It serves as a dietary supplement in America and is approved for therapeutic treatment in China.<sup>[14]</sup>

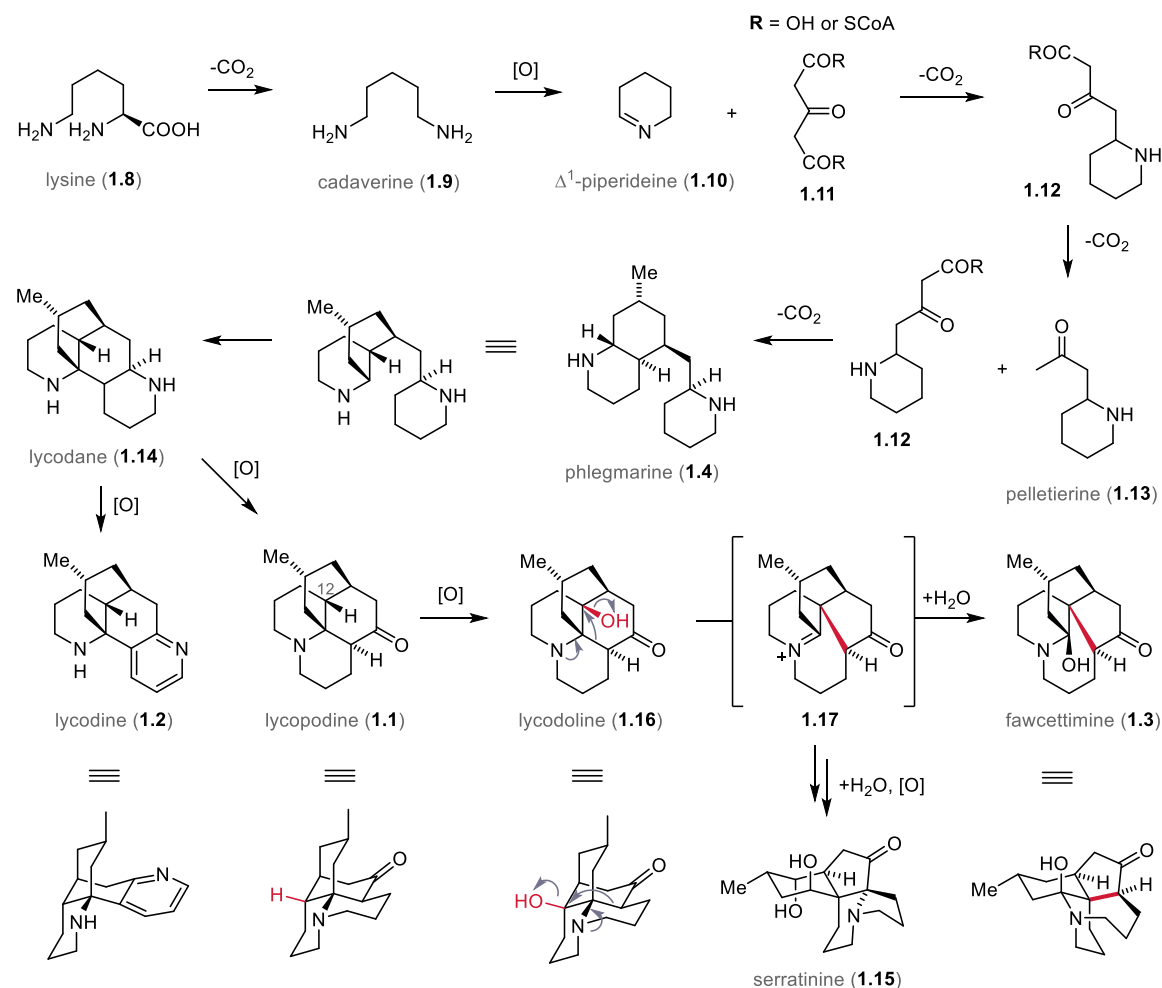
Fawcettimine-type alkaloids are the class with which this thesis is most concerned. Fawcettimine was isolated from the Jamaican clubmoss *Lycopodium fawcettii* by Burnell and colleagues and was initially referred to as base A.<sup>[34-35]</sup> Fawcettimine-class alkaloids are distinct in that the C4 atom is connected to the C12 atom rather than the C13 atom, resulting in a modified 5,6-bicyclic system and an azacyclononane ring. In addition, fawcettimine and many of its relatives exist either in a carbinolamine or keto-amine form, with the equilibrium generally favoring the closed carbinolamine.<sup>[36]</sup> This flexibility, together with subsequent biosynthetic oxidations, has made the fawcettimine class diverse and structurally convoluted.

The miscellaneous class is a repository for molecules that do not fit neatly into the aforementioned categories. Although phlegmarine<sup>[37]</sup> is often the representative example of the group, it has grown to include such unique skeletons as the nankakurines<sup>[38]</sup> and lyconadins.<sup>[39]</sup>

Biosynthetic studies into the origin of *Lycopodium* alkaloids have been hampered by the notorious difficulty of cultivating lycopods. Regardless, feeding experiments conducted by Spenser and colleagues with wild *Lycopodium tristachyum* using <sup>13</sup>C- and <sup>14</sup>C-labelled substrates have shed substantial light on the origin of these complex compounds.<sup>[40-49]</sup> The biosynthesis (**Scheme 1.1**) begins with the decarboxylation of lysine (**1.8**) to cadaverine (**1.9**), followed by oxidation to 5-aminopentanal and cyclization to  $\Delta^1$ -piperidine **1.10**.<sup>[50]</sup> Combination with acetonedicarboxylic acid<sup>[47]</sup> or its coenzyme A derivative (**1.11**) grants **1.112**, and decarboxylation then confers pelletierine **1.13**, an essential intermediate on the pathway to the *Lycopodium* alkaloids.<sup>[43]</sup> The formation of pelletierine is followed by an oxidative dimerization and decarboxylation process to afford the phlegmarine (**1.4**) skeleton. As only a single unit of labeled pelletierine was directly incorporated into lycodine during Spenser's studies, the second unit is hypothesized to originate from another molecule of **1.12**.<sup>[42, 49]</sup>

The phlegmarine backbone serves as the second key intermediate for the biogenesis of other *Lycopodium* alkaloids.<sup>[37]</sup> Oxidation and cyclization afford lycodane (**1.14**) – though it is possible the structure is directly formed from pelletierine heterodimerization<sup>[15]</sup> – and the tetracyclic core serves as the branching point for the remaining classes of alkaloids. Aromatization of the piperidine ring to a pyridine bestows lycodine **1.2** and its congeners, whereas oxidative

disconnection and recombination with the second nitrogen atom leads to lycodine **1.1**. Finally, a biogenetic origin of the fawcettimine class of alkaloids was proposed by Inubushi during his analysis of serratinine (**1.15**). The modified skeleton is thought to arise through an oxidative rearrangement of the lycodine system.<sup>[51]</sup> Oxidation at the C12 position gives lycodoline (**1.16**) and a pinacol-like rearrangement followed by hydration of iminium ion **1.17** produces the distinctive fawcettimine (**1.3**) ring system.

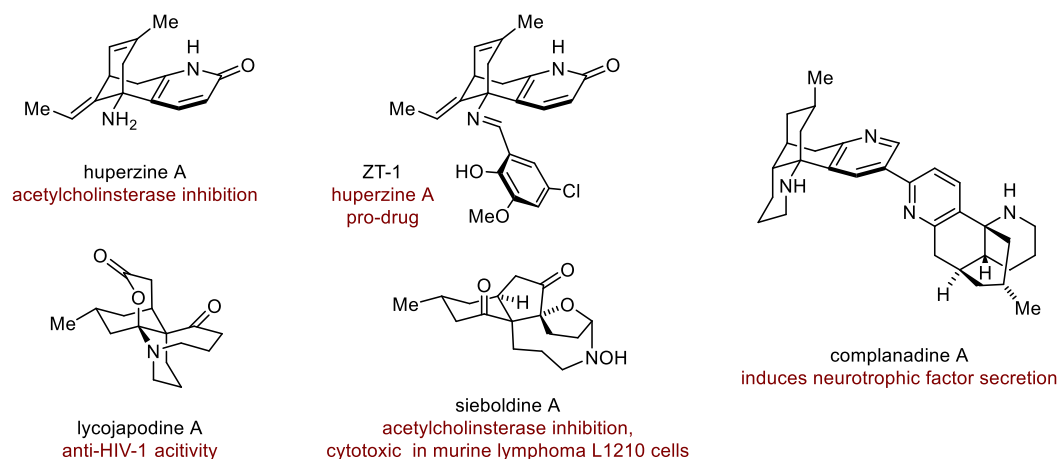


**Scheme 1.1.** Condensed biosynthesis of the *Lycopodium* alkaloids.

### 1.1.2. Bioactivity of *Lycopodium* alkaloids

Studies into the bioactivity of the *Lycopodium* alkaloids have largely focused on select members of the family (**Figure 1.3**). Huperzine A, isolated from the traditional Chinese medicine Qian Ceng Ta (whole plant *Huperzia serrata*), is by far the most researched bioactive *Lycopodium* alkaloid. As a potent and selective acetylcholinesterase inhibitor (IC<sub>50</sub> of 0.082  $\mu\text{M}$  in rat cortex)<sup>[52]</sup> it has been investigated for use in the treatment of Alzheimer's disease.<sup>[8]</sup> Interest in its efficacy, particularly in China, has led to the creation of derivatives and pro-drugs such as ZT-1. As the isolation of huperzine A was not patented, however, it is of limited interest to pharmaceutical companies in other countries.<sup>[8]</sup> Complanadine A, a dimeric lycodine-type

alkaloid, has also drawn some attention for its ability to induce neurotrophic factor secretion from 1321N1 cells.<sup>[53-54]</sup> The fawcettimine-type alkaloids contain few members that have demonstrated bioactivity of interest. Sieboldine A has displayed acetylcholinesterase inhibition comparable with huperzine A (electric eel, IC<sub>50</sub> of 1.6 μM) as well as modest cytotoxicity towards murine lymphoma L1210 cells (IC<sub>50</sub> of 5.1 μM).<sup>[55]</sup> Others, such as lycojapodine A, have demonstrated some anti-HIV activity.<sup>[56]</sup> Overall, however, the biological potential of the class remains largely unexplored.



**Figure 1.3.** Examples of bioactive *Lycopodium* alkaloids.

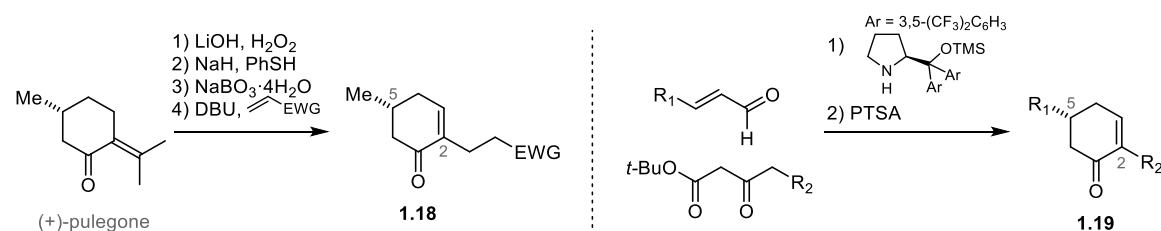
Regardless, the unmatched structures of *Lycopodium* alkaloids have proven a source of inspiration for the synthetic chemistry community. Many momentous accounts of lycopodine, lycodine and miscellaneous class alkaloid synthesis have been published. Acting within the constraints of this thesis, however, the following section will limit itself to the synthesis of fawcettimine class alkaloids, particularly those that exemplify historic and conceptual advances in the field.

### 1.1.3. Synthetic approaches to fawcettimine-type alkaloids

Despite the middling bioactivity of the class, fawcettimine-type alkaloids have been prized by synthetic chemists for their exceptional complexity and compact dimensions. The first synthesis of a fawcettimine-type alkaloid was that of serratinine by Inubushi in 1974,<sup>[57]</sup> followed in time by Inubushi's and Heathcock's seminal syntheses of fawcettimine proper. Though each subsequent synthesis has displayed its own unique tactics and eccentricities, a number of common strategies have emerged. They are divided here into four sections: conjugate addition approaches, Pauson–Khand reaction approaches, cycloaddition approaches and pinacol/semi-pinacol rearrangement approaches.

### 1.1.3.1. Conjugate Addition Approaches

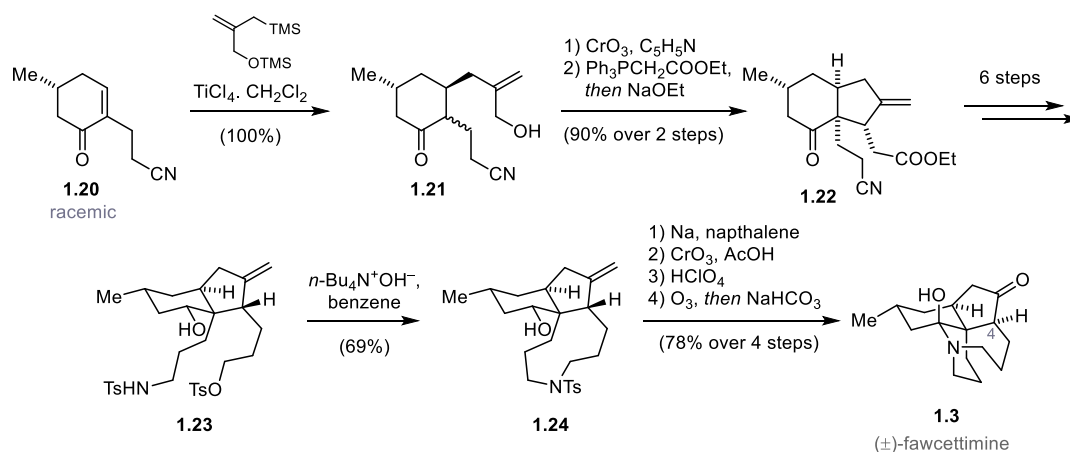
Due in part to the ready availability of cyclohexenone building blocks **1.18** and **1.19** – derived in enantioenriched form respectively from pulegone in a multi-step sequence<sup>[58-59]</sup> or from organocatalytic Robinson annulations<sup>[60]</sup> (**Scheme 1.2**) – conjugate addition approaches to fawcettimine-type alkaloids have consistently been favored by the synthetic community. The appeal of this strategy lies in the versatility and stereoselectivity of 1,4-addition early in the synthesis. The initial approach of the nucleophile is directed by the C5-substituent, and the subsequently generated enolate can be trapped by electrophiles or silylating agents to arrange the C2-position for ensuing C-C functionalization.



**Scheme 1.2.** Customary approaches to enantioenriched 2,4-substituted cyclohexenones.

#### Heathcock's synthesis of (±)-fawcettimine

One of the earliest syntheses of fawcettimine, preceded only by that of Inubushi in 1979 (see **Scheme 1.12** below), was conducted by the group of Heathcock in 1986 (**Scheme 1.3**).<sup>[36, 61]</sup> Though Inubushi's synthesis had confirmed the gross structure of the natural product, Heathcock's synthesis addressed questions concerning the stereochemistry of the C4 center and its bearing on carbinolamine formation. The synthesis began with racemic **1.20**, used in Heathcock's previous syntheses of lycodine<sup>[22]</sup> and employed here in a highly face-selective Hosomi-Sakurai reaction to afford **1.21** in quantitative yield. A chromium-mediated allylic oxidation and successive Horner–Wadsworth–Emmons olefination/intramolecular Michael addition constructed the bicyclo[4.3.0]nonane system **1.22** of the molecule.

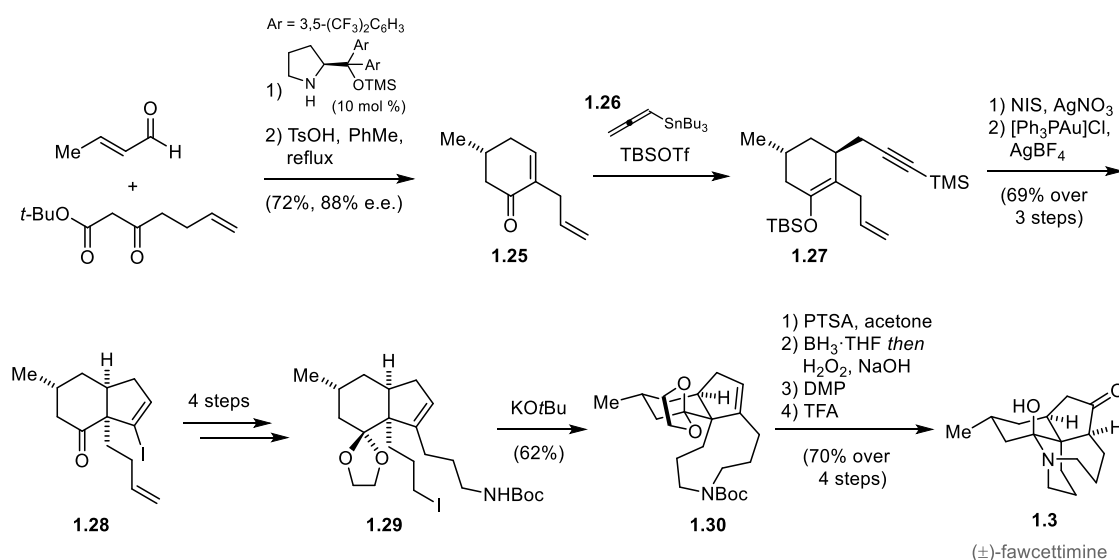


**Scheme 1.3.** Heathcock's racemic synthesis of fawcettimine.

An Arndt–Eistert homologation, reduction and tosylation sequence set the stage for the nine-membered ring formation – often a challenging aspect of fawcettimine-class alkaloid syntheses. Here, Heathcock used an  $S_N2$  displacement with a tosylamine **1.23** to form the azacyclononane **1.24**. Desulfonylation, oxidation to the ketone, and protection of the amine as the perchlorate salt was then followed by ozonolysis of the *exo*-methylene group. Treatment of the crude salt with sodium bicarbonate solution and standing in chloroform led to spontaneous epimerization of the C4 center and carbinolamine formation, concluding the synthesis of **1.3** in a concise fourteen steps. An X-ray crystal structure of the bromide salt of **1.3** then confirmed the configuration of the C4 position.

#### Toste's synthesis of (+)-fawcettimine

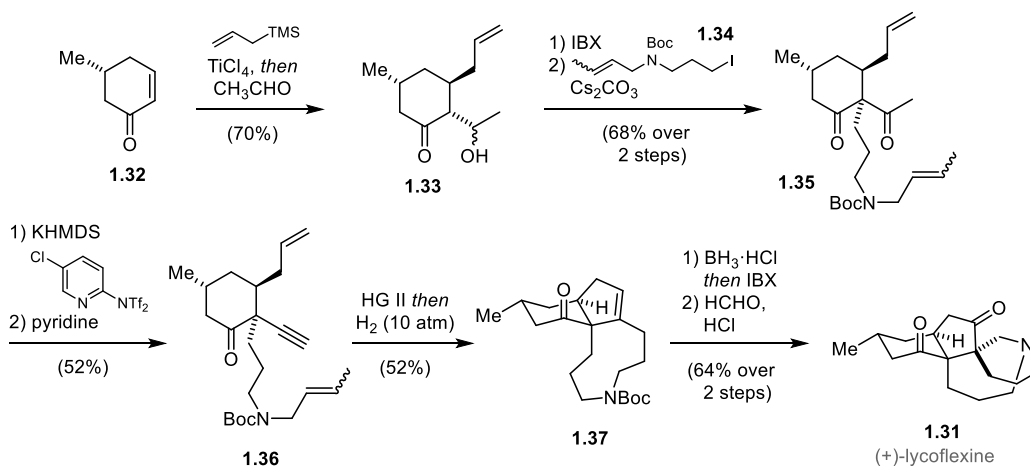
The earliest enantioselective synthesis of (+)-fawcettimine was conducted by the group of Toste in 2007 (Scheme 1.4).<sup>[62]</sup> As the first synthesis of this compound since Heathcock's effort 21 years earlier, it triggered renewed interest in the study of fawcettimine-group alkaloids during the ensuing decade. Toste first employed an organocatalytic cyclization originally developed by the Jørgensen group to build enantioenriched cyclohexenone **1.25**.<sup>[60]</sup> Conjugate addition of tin allene **1.26** using TMSOTf provided silyl enol ether **1.27**. A gold-catalyzed 5-*endo*-trig cyclization of the iodoacetylene, developed in the Toste laboratory,<sup>[63]</sup> then yielded bicyclo[4.3.0]nonenone **1.28**. Acetalization, Suzuki-Miyaura coupling and iodination yielded cyclization precursor **1.29** and carbamate alkylation mediated by KO $t$ Bu granted **1.30**. The synthesis culminated with a deacetalization, hydroboration/oxidation and acidic cyclization to afford the natural product and, by optical rotation and crystal structure analysis of its hydrobromide salt, established its absolute configuration.



**Scheme 1.4.** Toste's synthesis of (+)-fawcettimine by a gold(I)-catalyzed cyclization.

*Ramharter and Mulzer's synthesis of (+)-lycoflexine*

Ramharter and Mulzer's synthesis of lycoflexine (**1.31**) stands – in terms of step count – as one of the most efficient syntheses of fawcettimine-type alkaloids to date (**Scheme 1.5**). Beginning with **1.32**, Sakurai addition and trapping of the enolate with acetaldehyde provided alcohol **1.33**.<sup>[64]</sup> Oxidation and alkylation of the resulting  $\beta$ -diketone with iodide **1.34** furnished **1.35**, and formation and elimination of an enol triflate yielded alkyne **1.36**. A high-dilution one-pot ene-yne/ring-closing metathesis and chemoselective reduction of the disubstituted olefin using the same ruthenium catalyst formed the tricyclic carbon skeleton **1.37** of fawcettimine in a single transformation. Hydroboration and complementary iodoxybenzoic acid (IBX) oxidation followed by a Mannich cyclization with formaldehyde completed the synthesis of (+)-lycoflexine. When the hydroboration/oxidation product was treated with TMSCl in methanol, fawcettimine could be generated instead.<sup>[65]</sup>

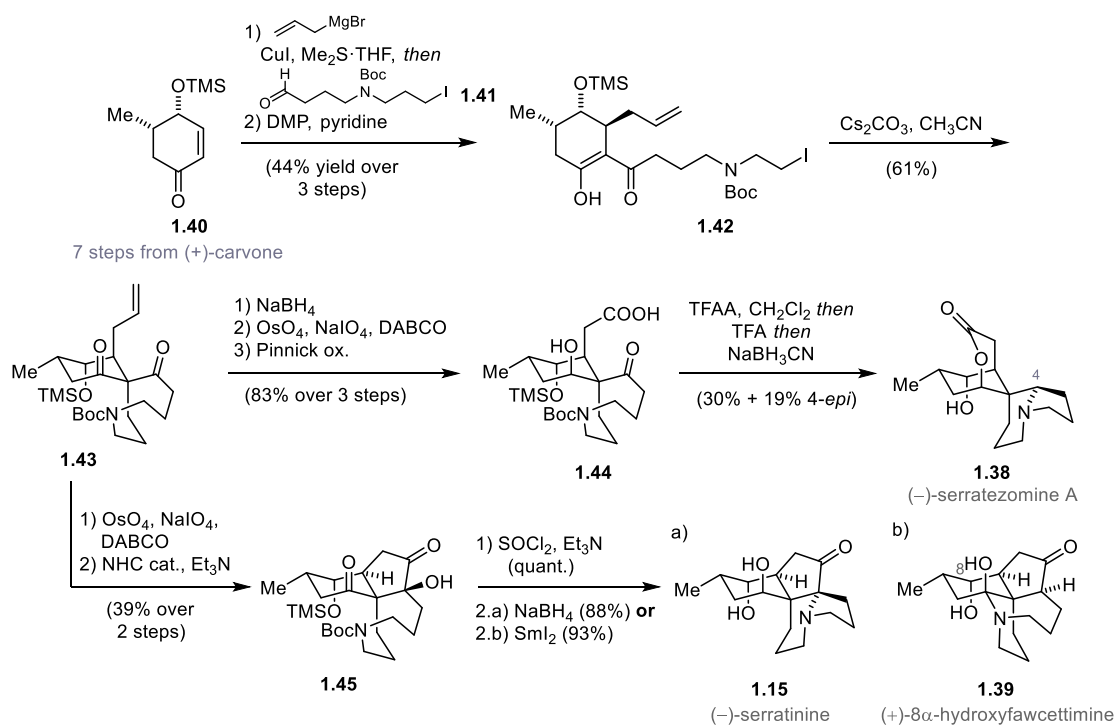


**Scheme 1.5.** Ramharter and Mulzer's concise synthesis of (+)-lycoflexine.

*Lei's synthesis of (-)-serratezomine A, (-)-serratinine and (+)-8 $\alpha$ -hydroxyfawcettimine*

The Lei laboratory has engaged in the synthesis of many fawcettimine-type alkaloids, with a particular emphasis on those with unusual degrees of oxidation that can be formed in short order through Michael addition approaches. A notable example (**Scheme 1.6**) is the syntheses of (-)-serratezomine A (**1.38**), (-)-serratinine (**1.15**) and (+)-8 $\alpha$ -hydroxyfawcettimine (**1.39**) (as well as (-)-lycoposerramine U, not shown here).<sup>[66]</sup> Building block **1.40** – possessing an extra  $\beta$ -hydroxy group at the C4-position relative to previously shown examples – was synthesised on multi-gram scale from (+)-carvone. Conjugate addition of allyl cuprate, trapping of the enolate with aldehyde **1.41** and oxidation of the aldol product afforded  $\beta$ -keto enol **1.42**. Intramolecular cyclization proceeded with limited O-alkylation (13%) to form the 9-membered ring of **1.43**, which constitutes the branching point of the divergent synthesis. Transformation of the terminal olefin to carboxylic acid **1.44** and a one-pot lactonization/deprotection/reductive amination sequence afforded both (-)-**1.38** and its C4-epimer. Conversely, **1.43** could be converted directly to an aldehyde and the cyclopentanone **1.45** formed by benzoin condensation with an NHC

precatalyst.<sup>[67]</sup> Intramolecular  $S_N2$  reaction and simultaneous silyl ether deprotection with thionyl chloride could be followed either by treatment with sodium borohydride or reductive cleavage with samarium diiodide to afford **1.15** and **1.39**, respectively.

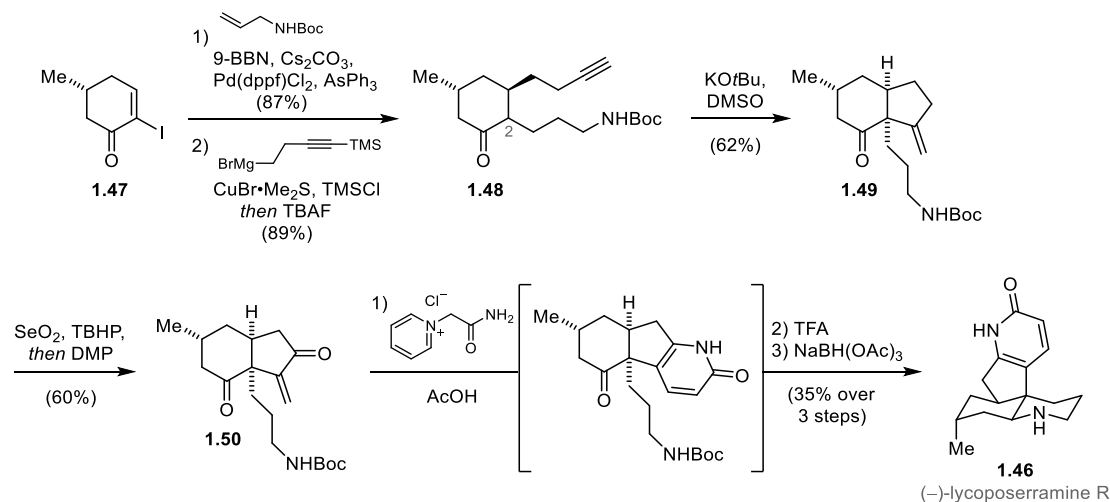


**Scheme 1.6.** Lei's divergent synthesis of (-)-serratezomine A, (-)-serratinine and (+)-8 $\alpha$ -hydroxyfawcettimine.

### Hartrampf and Trauner's synthesis of (-)-lycoposerramine R

Very recently, Hartrampf and Trauner accomplished a concise synthesis of the pyridone-containing alkaloid (-)-lycoposerramine R (**1.46**) using a conjugate addition strategy partnered with a powerful Conia-Ene-type reaction (**Scheme 1.7**).<sup>[68]</sup> Suzuki-Miyaura coupling with enantioenriched building block **1.47**<sup>[59-60]</sup> and conjugate addition of trimethylsilyl-3-butyryl magnesium bromide produced alkyne **1.48**. A novel base-mediated Conia-Ene-type cyclization allowed formation of the quaternary stereocenter of **1.49** without necessitating prior activation at the C2-position. Allylic oxidation with selenium dioxide and subsequent treatment with Dess-Martin periodinane gave enone **1.50**, which was then reacted with *N*-carbamoylmethylpyridinium chloride in a modified Kröhnke pyridine synthesis.<sup>[69]</sup> A final reductive amination provided the natural product in an efficient seven steps from **1.47**. A similar strategy was thereafter used to synthesize both lycoplamine A and carinatine A.<sup>[70]</sup>

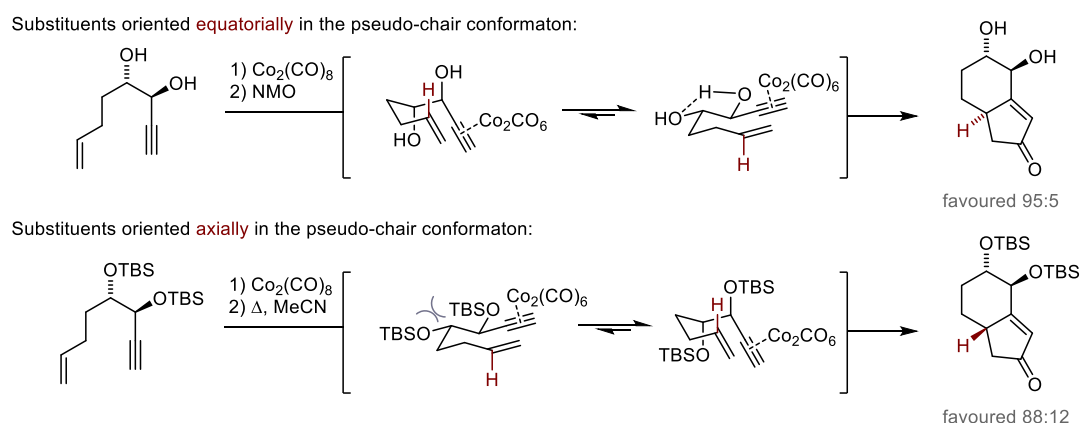




**Scheme 1.7.** Hartrampf and Trauner's synthesis of (-)-lycopserramine R by Conia-ene-type cyclization.

### 1.1.3.2. Pauson–Khand Approaches

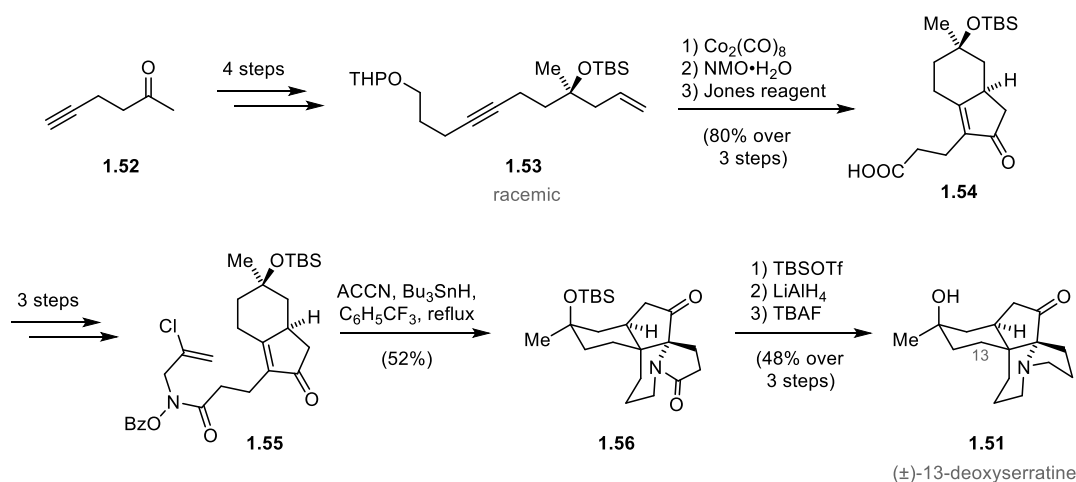
The Pauson–Khand reaction has proven to be of great value in the construction of hydroindanone cores of fawcettimine-type alkaloids, in part due to the exquisite diastereoselectivity of the reaction which can be finely tuned by the substitution pattern of its linear precursor. Prior to its use in natural product synthesis, Mukai and coworkers had comprehensively investigated the construction of bicyclo[4.3.0]nonenone systems by means of Pauson–Khand cyclizations.<sup>[71–72]</sup> An eventual conclusion of this work was that the diastereoselectivity of the reaction is dictated by a pseudo-chair-like conformation based on the substituents of the linear precursor (**Scheme 1.8**). Often, the substituents adopt pseudo-equatorial positions and the reacting olefin orients itself to minimize pseudo-diaxial interactions. Bulkier substituents in close proximity to each other, on the other hand, would adopt axial positions to minimize steric interactions. This same principle has been employed throughout fawcettimine-type alkaloid synthesis using Pauson–Khand reactions.



**Scheme 1.8.** Mukai's deductions on the diastereoselectivity of Pauson-Khand reactions to form bicyclo[4.3.0]nonenone systems.

*Cassayre and Zard's synthesis of (±)-13-deoxyserratine*

An early and particularly powerful use of the Pauson–Khand reaction in fawcettimine-type alkaloid synthesis was employed by Cassayre and Zard in the synthesis of 13-deoxyserratine (**1.51**).<sup>[73]</sup> Though **1.51** differs from the natural product serratine by a single hydroxyl group, its intriguing amidyl radical approach warrants inclusion in this section (**Scheme 1.9**). Allyl Grignard addition, silyl protection and alkyne alkylation from 5-hexyn-2-one **1.52** generated Pauson–Khand precursor **1.53**. The high diastereoselectivity of the ensuing Pauson–Khand reaction (93:7 in favor of **1.54**) is believed to be derived from the pseudo-equatorial orientation of the bulky silyl ether in the alkyne–Co<sub>2</sub>(CO)<sub>8</sub> complex, thus orienting the vinyl group with its internal proton downwards so as to minimize steric interactions. The synthesis continued with elaboration to allyl amide **1.55** as a precursor to an amidyl radical cascade initiated by homolytic cleavage of the *N*-O bond. Initial attempts at the reaction had demonstrated that an olefinic trap lacking a chloride substituent would lead to an unwanted 5-*exo*/5-*exo* cyclization cascade product. The vinyl chloride blocked this mode of reaction to give the desired 5-*exo*/6-*endo* cyclization product **1.56** and was easily removed in the same operation by the addition of a second equivalent of tin hydride to the reaction mixture. Final deprotection and reduction of the amide afforded **1.51** in a concise manner.

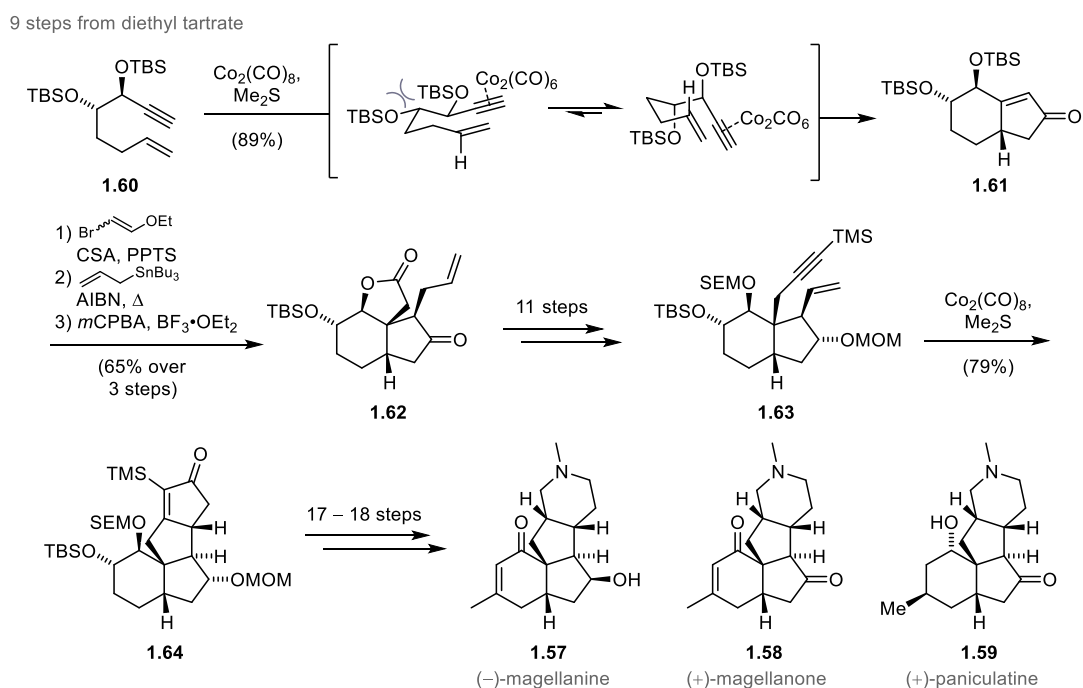


**Scheme 1.9.** Cassayre and Zard's synthesis of 13-deoxyserratine

*Mukai's synthesis of (–)-magellanine, (+)-magellanone and (+)-paniculatine*

Using the conclusions gleaned in their earlier studies on Pauson–Khand reactions, Mukai and colleagues conducted a unified synthesis of magellanine (**1.57**), magellanone (**1.58**) and paniculatine (**1.59**) (**Scheme 1.10**).<sup>[74]</sup> These three intriguing fawcettimine-type alkaloids were isolated from the *Lycopodium paniculatum* by Castillo and MacLean and feature a piperidine ring in a fused tetracyclic framework.<sup>[75–76]</sup> The authors first improve upon previous Pauson–Khand conditions with **1.60**<sup>[71]</sup> to afford **1.61** with good diastereoselectivity and yield. The quaternary stereocenter of the molecule is then constructed by means of a Ueno–Stork reaction and

simultaneous radical allylation to bestow **1.62**. Elaboration to alkyne **1.63** sets the stage for a second Pauson-Khand reaction to give cyclopentenone **1.64** with good selectivity. Construction of the piperidine ring using Overman's precedent<sup>[77]</sup> and extensive modification of functional groups then gave access to all three optically-active natural products. Mukai and colleagues have also employed Pauson-Khand reaction strategies in the synthesis of (+)-fawcettimine and (+)-lycoposerramine B,<sup>[78]</sup> and racemic fawcettidine, lycoflexine, and lycoposerramine Q.<sup>[79]</sup>

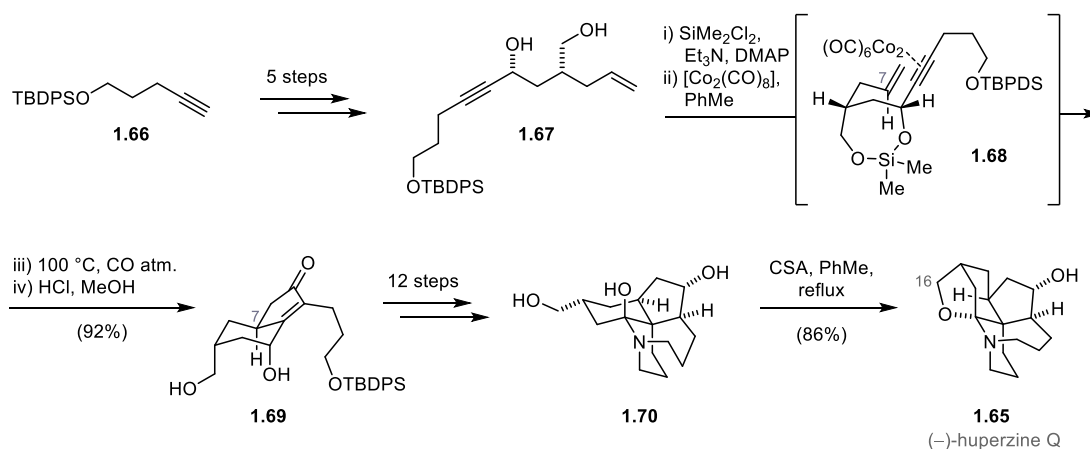


**Scheme 1.10.** Mukai's unified synthesis of (-)-magellanine, (+)-magellanone and (+)-paniculatine

#### Takayama's synthesis of (-)-huperzine Q

The group of Takayama has synthesized a number of fawcettimine-class alkaloids by Pauson-Khand strategies, including lycoposerramine C and phlegmariurine A.<sup>[16, 80]</sup> A particularly compelling illustration of the reaction's versatility is displayed in the group's synthesis of huperzine Q (**1.65**) (**Scheme 1.11**). The C16 methyl group of this alkaloid has been oxidized to bring about a ring-flipped spiroaminal ether, and the synthesis of Takayama uses this extra degree of oxidation to its advantage. A five-step sequence from **1.66** involving an asymmetric Noyori reduction and diastereoselective allylation affords chiral eneyne **1.67**. A Pauson-Khand reaction directly from **1.67** resulted in the incorrect stereochemistry at the C7 position due to the hydroxyl and hydroxymethylene substituents adopting pseudo-equatorial positions. However, pinning the hydroxy groups together with a silyl tether forced the substituents to adopt pseudo-axial positions during a subsequent PKR through intermediate **1.68** and conferred **1.69** with the desired stereochemistry at C7. The silylation/PKR/desilylation process could be performed in a single high-yielding one-pot procedure. Following conversion of **1.69** to the fawcettimine-like carbinolamine **1.70**, a high-temperature acid-catalyzed isomerization with anhydrous

(+)-camphorsulfonic acid then constructed the spiroaminal and completed the asymmetric synthesis of **1.65**.



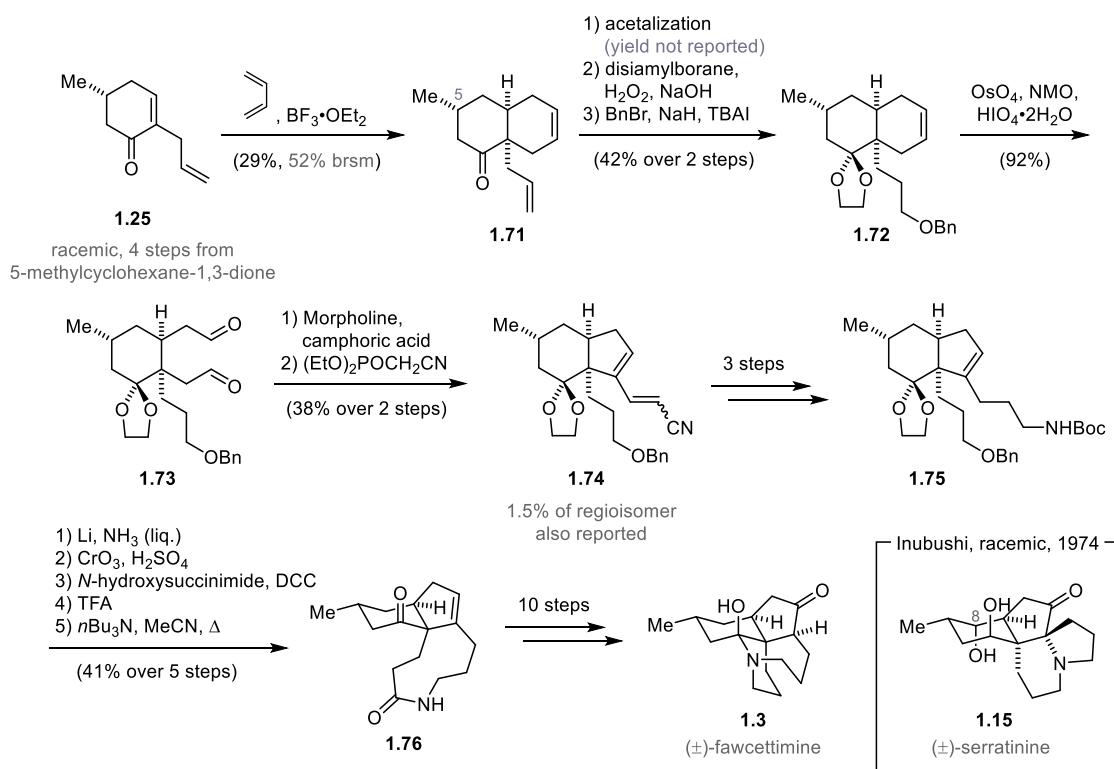
**Scheme 1.11.** Takayama's synthesis of (-)-huperzine Q using a silyl ether-tethered PKR precursor.

### 1.1.3.3. Cycloaddition Approaches

A number of groups have employed pericyclic reaction to great effect either by using relatively early-stage Diels–Alder reactions to access the carbocyclic fawcettimine core or by employing later-stage dipolar cycloadditions to form otherwise inaccessible heterocycles.

#### *Inubushi's synthesis of (±)-fawcettimine*

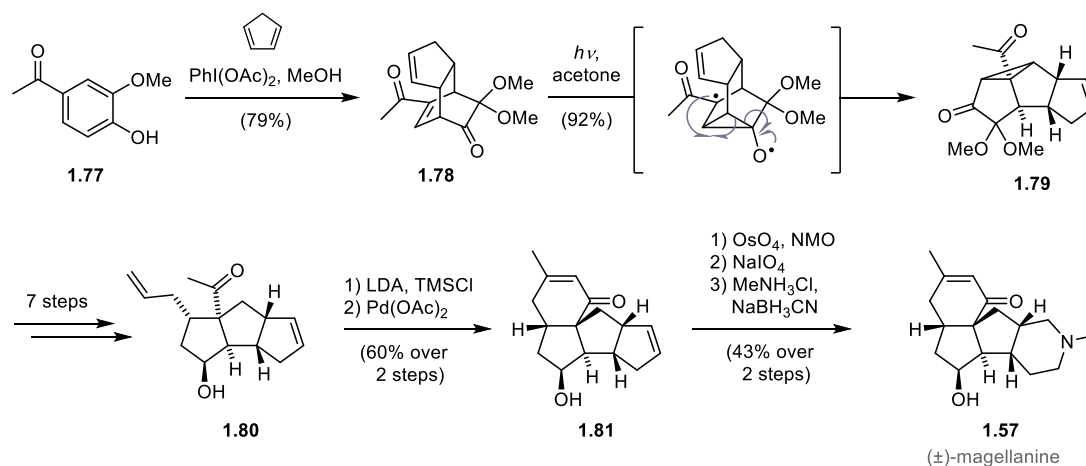
The first synthesis of fawcettimine was conducted racemically by the group of Inubushi in 1979 (**Scheme 1.12**),<sup>[81–83]</sup> this same group also performed the first synthesis of any fawcettimine-type alkaloid five years earlier when (±)-serratinine **1.15** was constructed through a Diels–Alder/aziridination strategy.<sup>[57]</sup> Before the advent of pulegone- or organocatalytic-based syntheses of cyclohexenone **1.25**, this building block had to be prepared racemically in a multi-step sequence from 5-methylcyclohexane-1,3-dione.<sup>[82]</sup> A Diels–Alder reaction with butadiene afforded *cis*-decalin **1.71** in modest yield with approach of the diene opposite the C5 methyl substituent. Acetalization, hydroboration/oxidation and benzyl protection to **1.72** were followed by oxidative cleavage of the *cis*-olefin to dialdehyde **1.73**. The regioselectivity of the subsequent aldol condensation proved difficult to direct and, after significant experimentation, the group found that a combination of morpholine and camphoric acid followed by Horner–Wadsworth–Emmons reaction gave conjugated nitrile **1.74**. After transformation of the nitrile to carbamate **1.75**, the problematic nine-membered ring of **1.76** was constructed through activation of an ensuing acid with *N*-hydroxysuccinimide, carbamate and acetal removal with TFA, and basic lactamization at elevated temperature and high dilution. An additional ten steps were required to reduce the lactone and install a second ketone by epoxidation of the olefin and Lewis acid-mediated opening to the enone. Alternatively, Inubushi synthesized 8-deoxyserratinine by opening the same epoxide in a transannular fashion with the pendant amine.



**Scheme 1.12.** Inubushi's synthesis of (±)-fawcettimine by a Diels–Alder/aldol condensation strategy.

#### Yen and Liao's synthesis of (±)-magellanine

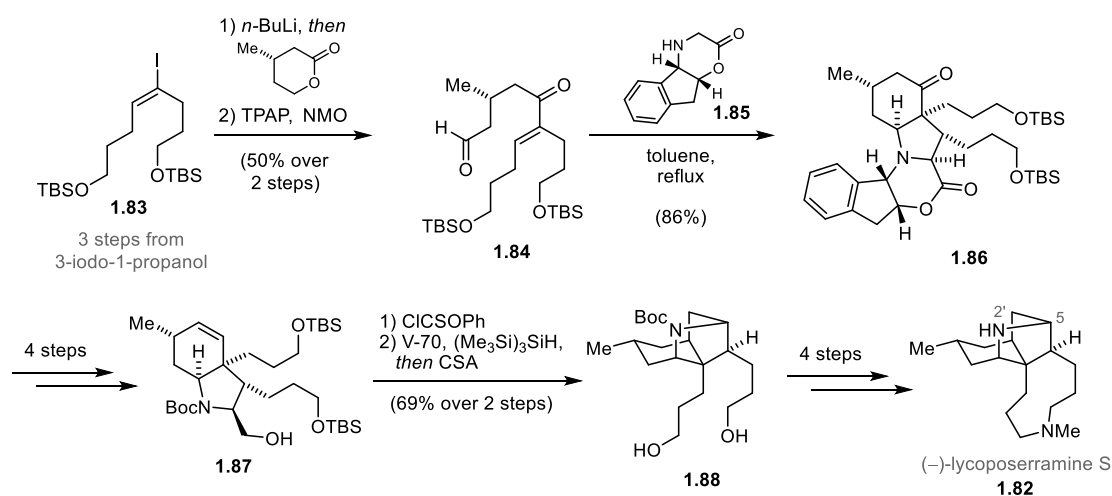
Yen and Liao's efficient synthesis of racemic magellanine (**1.57**) includes both cycloaddition and rearrangement key steps. The synthesis (**Scheme 1.13**) opens at a fast pace with a Diels–Alder reaction between cyclopentadiene and a masked *o*-benzoquinone generated from hypervalent iodine-mediated dearomatization of acetovanillone **1.77** to form **1.78**. The Diels–Alder was followed by a markedly high-yielding light-induced oxa-di- $\pi$ -methane rearrangement to form the triquinane skeleton **1.79**.<sup>[84]</sup> Many key contiguous stereocenters of magellanine, including the quaternary carbon, were thereby formed in only two steps from inexpensive starting materials. A series of transformations converted the tetracycle to ketone **1.80**. The silyl enol ether generated from **1.80** could then undergo cyclization to methylcyclopentenone **1.81** by means of a oxo- $\alpha$ -allylpalladium(II) complex.<sup>[85]</sup> A final oxidative cleavage to the dialdehyde and dual reductive amination then afforded **1.57** in a concise 14 steps and an efficient 9% overall yield.



**Scheme 1.13.** Yen and Liao's synthesis of (±)-magellanine by Diels-Alder/ di- $\pi$ -methane rearrangement.

#### Fukuyama's synthesis of (-)-lycoposerramine S

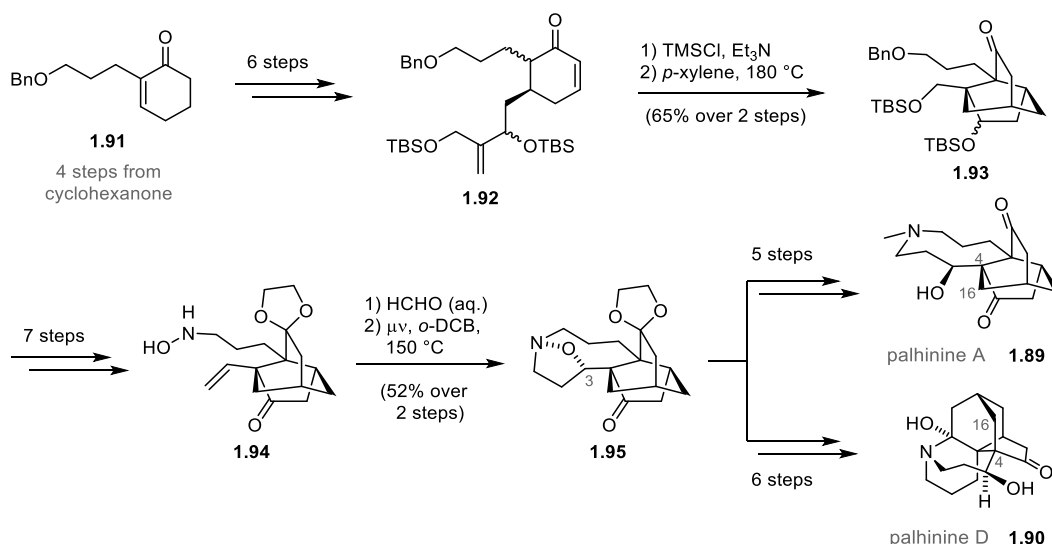
Lycoposerramine S (**1.82**) is an unusual fawcettimine-type alkaloid in that the incorporation of a second nitrogen atom and new N2'-C5 connectivity has resulted in a heavily-substituted pyrrolidine unit.<sup>[86]</sup> In 2008, the group of Fukuyama reported the first and only total synthesis of this natural product using an azomethine ylide cycloaddition strategy (**Scheme 1.14**).<sup>[87]</sup> Following anionic addition of iodide **1.83** to chiral lactone **1.84** and subsequent Ley oxidation, condensation with auxiliary-bound amino ester **1.85** resulted in a stabilized azomethine ylide. The morpholinone auxiliary directed the facial selectivity of the ensuing intramolecular 1,3-dipolar cycloaddition with the activated enone to set four stereocenters in a single transformation. Pyrrolidine **1.86** was converted to alcohol **1.87** by reductive cleavage of the auxiliary and selective elimination of a secondary alcohol. Thioester formation and a 5-*exo*-trig radical cyclization then granted the molecule's second carbocycle to form **1.88**. A short sequence involving simultaneous bismesylate displacement with 4-nitrobenzenesulfonamide and desulfonylation/methylation thereafter yielded lycoposerramine S.



**Scheme 1.14.** Fukuyama's synthesis of (-)-lycoposerramine S by azomethine ylide cycloaddition.

*Zhang's synthesis of (±)-palhinine A and (±)-palhinine D*

Important recent syntheses of fawcettimine-type alkaloids palhinine A (**1.89**) and D (**1.90**) were conducted by the group of Zhang (**Scheme 1.15**).<sup>[88]</sup> Both palhinines possess an additional degree of oxidation at the C16 position which has resulted in a C4-C16 bond and a bicyclo[2.2.2]octane system, granting these molecules architectures distinct from other *Lycopodium* alkaloids.<sup>[89-90]</sup> Zhang's synthesis began with the construction of cycloaddition precursor **1.92** from cyclohexenone **1.91**. The bicyclooctane core **1.93** of the molecule was generated by an intramolecular Diels–Alder between a derived silyl enol ether and the tethered olefin to form two contiguous quaternary stereocenters.<sup>[91]</sup> The group encountered great difficulty in forming the nine-membered ring ring of the target molecule; the dilemma was solved by an ingenious [3 + 2]-nitron cycloaddition from **1.94** to form azanonane **1.95** and simultaneously install the C3-hydroxyl group, albeit with inverted configuration compared to the targeted palhinines. Oxidation and protecting group manipulation was therefore all that was necessary to afford **1.89** and **1.90**.



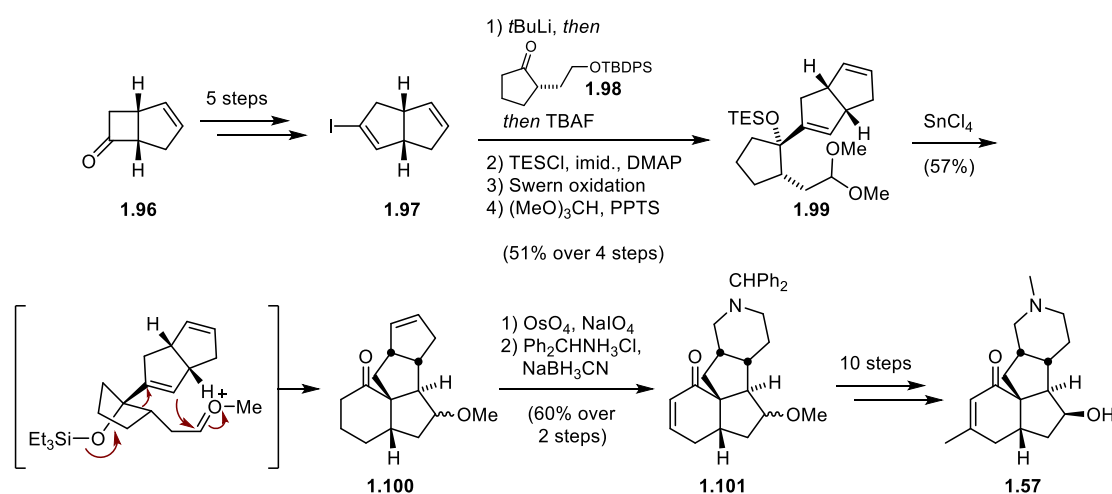
**Scheme 1.15.** Zhang's synthesis of (±)-palhinine A and (±)-palhinine D.

### 1.1.3.4. Pinacol and Semi-Pinacol Rearrangement Approaches

The final strategies discussed in this section are those featuring pinacol-type rearrangements. These syntheses generally involve the formation of the sole quaternary stereocenter of the fawcettimine-type system through reactions of this family.

#### Overman's synthesis of (–)-magellanine

The Overman group has employed complex pinacol and semi-pinacol rearrangements in the syntheses of many natural product, and the *Lycopodium* alkaloids are no exception. One of the earliest and most striking examples was adopted during the first synthesis of the megallanane alkaloids (**Scheme 1.16**).<sup>[77]</sup> Starting from bicyclo[3.2.0]heptenone **1.96**, a nucleophilic bithiol addition and ring expansion, reductive desulfuration and iodination granted bicyclo[3.3.0]octene **1.97**. Lithium/halogen exchange and addition to chiral ketone **1.98**, silylation, oxidation and acetal formation then bestowed diene **1.99**. Treatment with Lewis acid initiated the key Prins–pinacol-terminated cationic cascade proceeding along on the convex face of the bicyclooctene to form the lower three carbocycles of **1.100**. The characteristic piperidine ring of the alkaloid was made through Lemieux–Johnson cleavage of the cyclopentene ring and double reductive amination to **1.101**. Finally, incorporation of a methyl group yielded (–)-magellanine **1.57**. (+)-Magellanone (**1.58**) could be synthesized subsequently by oxidation of the alcohol.



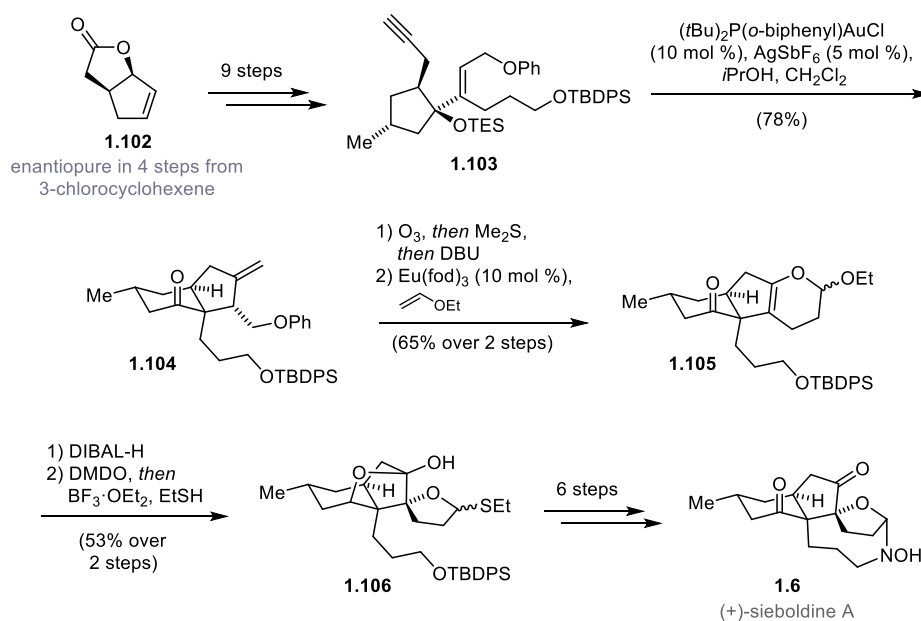
**Scheme 1.16.** Overman's synthesis of (–)-magellanine by a Prins–pinacol-terminated cationic cascade.

#### Overman's synthesis of (+)-sieboldine A

The natural product sieboldine A (**1.6**) is notable both for its potent ability to inhibit acetylcholinesterase inhibition – comparable to that of racemic huperzine A – as well as its uniquely oxidized azanonane system featuring an *N*-oxide-*N,O*-acetal.<sup>[55]</sup> The first enantioselective total synthesis of the molecule was conducted by the Overman laboratory (**Scheme 1.17**) using a semi-pinacol rearrangement-terminated gold(I)-promoted cyclization<sup>[92]</sup>



after exploring a series of pinacol-type rearrangements.<sup>[93]</sup> Enantiopure **1.102**<sup>[94]</sup> was transformed into eneyne **1.103** in preparation for the key cyclization. A pinacol-terminated cyclization cascade first investigated by Kirsch and coworkers<sup>[95]</sup> afforded hydroindanone system **1.104**. One-pot ozonolysis and elimination of phenol followed by Eu(III)-promoted cyclocondensation with ethyl vinyl ether to **1.105** provided the final required carbons. Reduction, face-selective oxidation of the enol ether and treatment with ethyl mercaptam under Lewis acidic conditions gave stable thioacetal **1.106**, which could be elaborated by incorporation of hydroxylamine into the final alkaloid **1.6**.

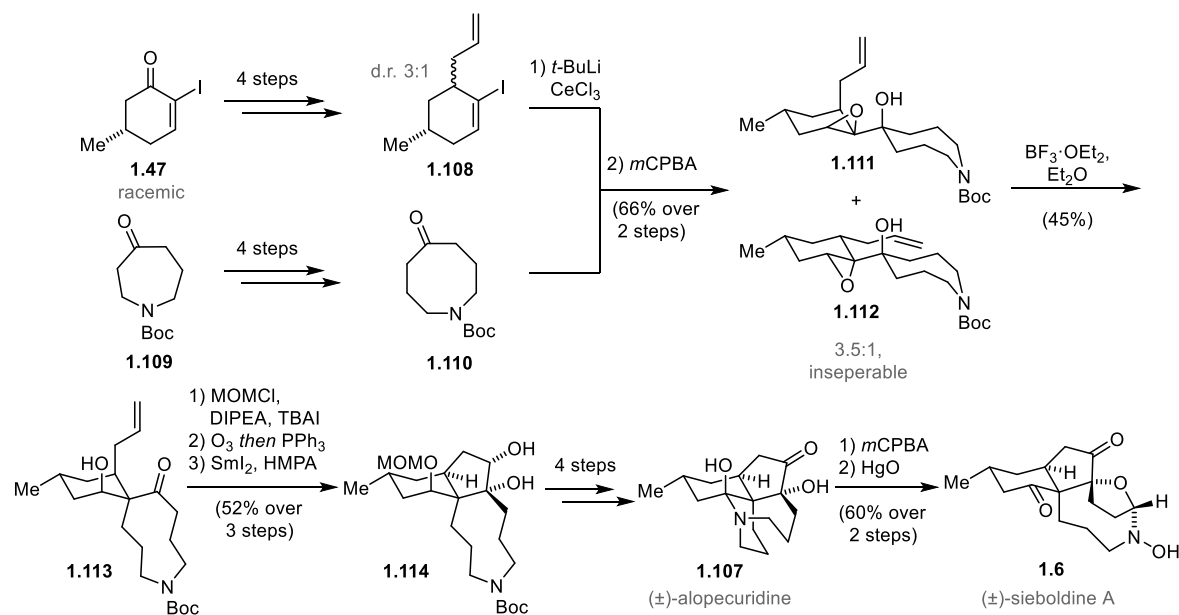


**Scheme 1.17.** Overman's synthesis of (+)-sieboldine A by a gold(I)-promoted cyclization.

#### Tu's synthesis of ( $\pm$ )-alopecuridine and ( $\pm$ )-sieboldine A

In contrast with Overman, Tu's synthesis of sieboldine A (**Scheme 1.18**) uses a biomimetic route to the alkaloid through a closely-related alkaloid, alopecuridine (**1.107**).<sup>[96]</sup> Tu likewise employed a semi-pinacol strategy in the construction of the molecule, but in this scenario used the transformation to expand the desired nine-membered ring rather than form the hydroindanone system. The convergent synthesis began with the construction of fragment **1.108** from racemic 2-iodocyclohexenone **1.47**. Addition of the cerium salt to ketone **1.110** (produced from commercially-available azepine **1.09**) and epoxidation of the tri-substituted olefin afforded the rearrangement precursor **1.111** and **1.112** as a mixture of diastereomers. The semi-pinacol rearrangement occurred cleanly to afford the azacyclonane **1.113**. Protection and ozonolysis of the terminal alkene followed by  $\text{SmI}_2$ -mediated pinacol coupling provided the final C-C bond, and **1.114** could be converted to alopecuridine **1.107** in few additional steps. The final transformation of **1.107** to **1.6**, based on the biosynthetic proposal of Kobayashi et al.,<sup>[55]</sup> involved a peroxide-

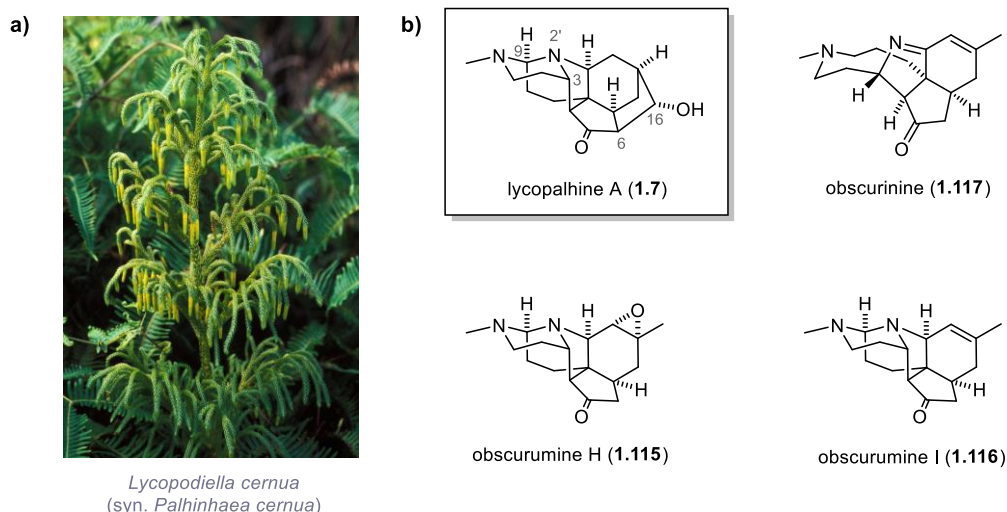
based oxidation of the amine to the *N*-oxide, a Polonovski-type elimination and further oxidation to the nitron. Nucleophilic trapping by the tertiary alcohol then yielded sieboldine A.



**Scheme 1.18.** Tu's synthesis of (±)-alopecuridine and (±)-sieboldine A using a semi-pinacol rearrangement.

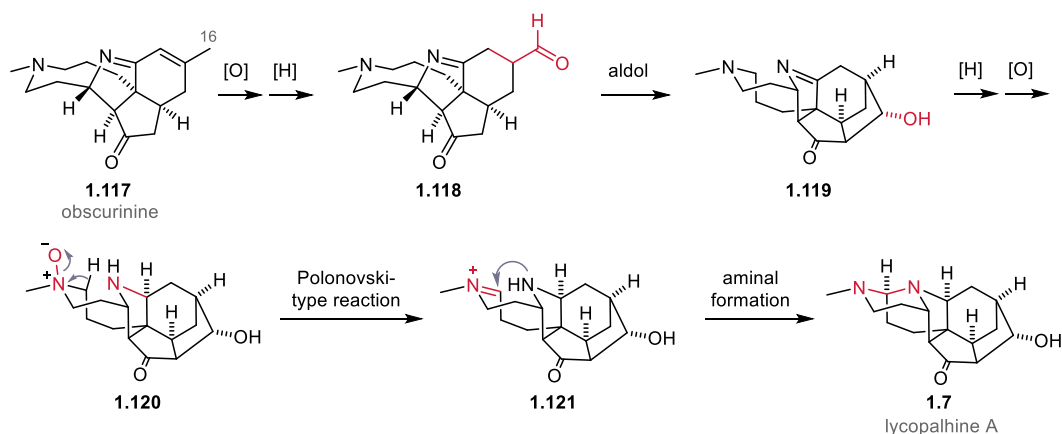
Many more synthetic methods have been and continue to be developed to perform ever-more concise routes to fawcettimine-type alkaloids. These syntheses, however, were particularly instructive in our strategy towards one such complex alkaloid, lycopalhine A.

**1.1.4. Lycopalhine A** In 2012, Zhao and coworkers reported the isolation of a highly oxidized fawcettimine class alkaloid, lycopalhine A (**1.7**, **Figure 1.4**), as a white gum from whole plant *Palhinhaea cernua* (syn. *Lycopodiella cernua*).<sup>[97]</sup> At the time of its discovery, lycopalhine A was the only known *Lycopodium* alkaloid with C9-N2' and C6-C16 connections, and was one of only a few to feature a C3-N2' bond. In early 2016, the group of Zhao reported the isolation of obscurumine H (**1.115**) and I (**1.116**), alkaloids which featured congruent C9-N2' linkages but lacked the extra C6-C16 bond.<sup>[98]</sup> Lycopalhine A demonstrated mild butyryl cholinesterase inhibition and no acetyl cholinesterase inhibition, but due to its unusual oxidation pattern and ring systems struck us as a considerable synthetic challenge.



**Figure 1.4.** a) Photograph of *Palhinhaea cernua* (syn. *Lycopodiella cernua*) by Henry Oppenheimer, reproduced here with his permission,<sup>[99]</sup> and b) lycopalhine A and closely related alkaloids.

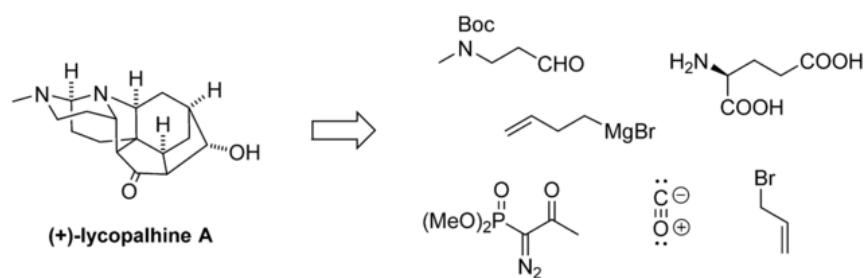
Lycopalhine A is hypothesized to be biogenetically derived from obscurinine (**1.117**) (**Scheme 1.19**) and the two compounds were isolated together from the whole plant extract. Zhao proposed that oxidation of C16 and reduction of the cyclohexenone leads to intermediate **1.118**. An aldol reaction then forges bicyclo[3.3.0]octanol **1.119**. Reduction of the imine and *N*-oxide formation yields **1.120** and a Polonovski-type oxidation to **1.121** with successive nucleophilic closure to the aminal gives **1.7**.



**Scheme 1.19.** Zhao's proposed biosynthesis of lycopalhine A from obscurinine

Due to its intricate, tightly-fused framework and its intriguing biosynthetic origin, we became interested in performing a concise synthesis of lycopalhine A. Our efforts to construct this complex fawcettimine-type base, as well as unpublished results towards similarly complex fawcettimine-type alkaloids, are contained within the next sections.

## 1.2. The Total Synthesis of Lycopalhine A



**Reprinted with permission from:**

B. M. Williams and D. Trauner

*Angew. Chem. Int. Ed.* **2016**, *55*, 2191 – 2194

**DOI:** 10.1002/anie.201509602

Copyright © 2017 Wiley Publishing

## Natural Product Synthesis

International Edition: DOI: 10.1002/anie.201509602  
German Edition: DOI: 10.1002/ange.201509602

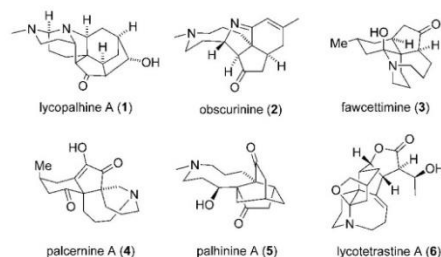
## Expedient Synthesis of (+)-Lycopalhine A

Benjamin M. Williams and Dirk Trauner\*

Dedicated to Prof. Dr. Johann Mulzer

**Abstract:** Two amino acids play a key role in the first total synthesis of lycopalhine A. L-glutamic acid serves as a convenient chiral starting material for the 13-step synthesis, and L-proline promotes an unusual 5-endo-trig Mannich cyclization that generates the central pyrrolidine ring of the *Lycopodium* alkaloid. The bicyclo[3.3.0]octanol moiety of the molecule is formed through an intramolecular aldol addition that may occur spontaneously in nature.

*Lycopodium* alkaloids continue to provide fascinating structures with which to probe the boundaries of synthetic chemistry.<sup>[1]</sup> The fawcettimine-type (3) alkaloids, in particular, have garnered significant attention due to their broad diversity and architectural complexity, and have inspired no small number of resourceful syntheses in the past decade.<sup>[2]</sup> In more recent years, the isolation of alkaloids with novel frameworks, such as lycopalhine A (1), palcermine A (4), palhinine A (5), and lycotetrastine A (6), has further broadened the synthetic appeal of this class of natural products (Figure 1).<sup>[3]</sup> Herein, we report our first studies into the



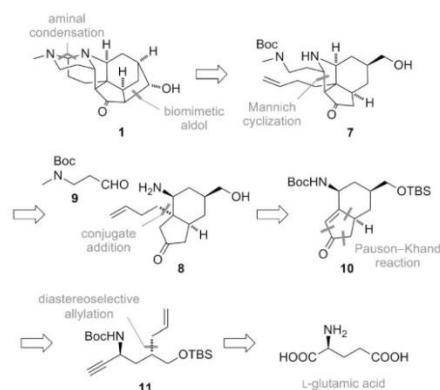
**Figure 1.** Fawcettimine-type alkaloids as an inspiration for synthetic chemists.

synthesis of *Lycopodium* alkaloids, culminating in a concise total synthesis of lycopalhine A.

Lycopalhine A was recently isolated from *Palhinhaea cernua*, together with its presumed biosynthetic progenitor

obscurinine (2).<sup>[4]</sup> The alkaloid features a complex hexacyclic ring system composed of one six-membered and two five-membered carbocycles, a piperidine and a hexahydropyrimidine heterocycle, and a densely substituted pyrrolidine core. The intricate skeleton contains nine stereogenic centers, eight of which are contiguous.

Our retrosynthetic analysis (Scheme 1) began with the disconnection of the most labile bonds, that is, the linchpin

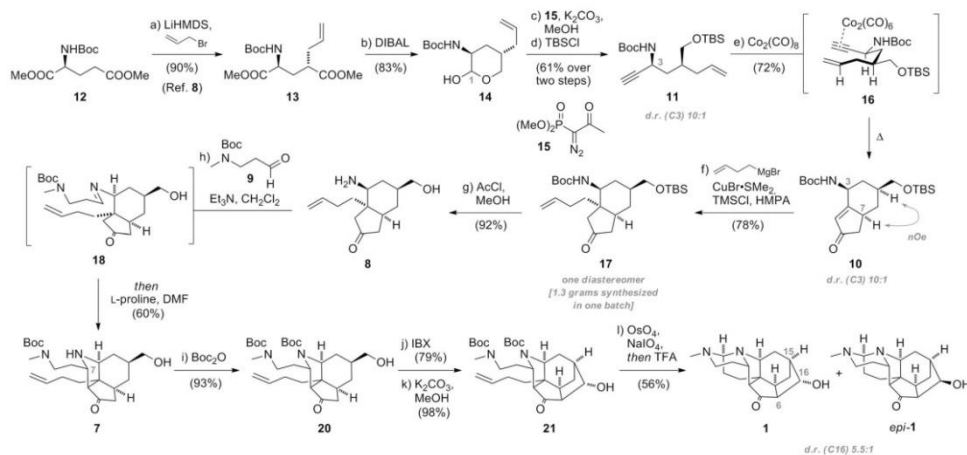


**Scheme 1.** Retrosynthetic analysis of lycopalhine A. Boc = *tert*-butyloxycarbonyl, TBS = *tert*-butyldimethylsilyl.

aminal, which could foreseeably arise through a late-stage condensation of two secondary amines and an aldehyde. We also assumed that the aldol moiety of the alkaloid, despite the strained nature of the bicyclo[3.3.0]octanol subsystem, could be generated with relative ease near the end of the synthesis by mimicking its potential biosynthetic formation. These considerations yielded pyrrolidine 7 as a logical precursor, wherein the requisite carbonyl groups are masked as a terminal alkene and a primary alcohol. We rationalized that the highly substituted pyrrolidine ring would best be attained through an intramolecular Mannich cyclization of aminoketone 8 with aldehyde 9. We were well aware that this transformation, in practice, would represent an audacious key step. Baldwin-disfavored<sup>[5]</sup> 5-*endo*-trig Mannich reactions occur in aza-Cope/Mannich cyclization cascades but are rarely triggered by condensation of an aminoketone with an enolizable aldehyde.<sup>[6]</sup> Amine 8 could be conferred by conjugate addition to cyclopentenone 10, formed in turn through a diastereoselective Pauson-Khand reaction from

[\*] B. M. Williams, Prof. Dr. D. Trauner  
Department of Chemistry, Ludwig-Maximilians-Universität München  
81377 Munich (Germany)  
E-mail: dirk.trauner@lmu.de

Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under <http://dx.doi.org/10.1002/anie.201509602>.



**Scheme 2.** Total synthesis of lycopalhine A. a) LiHMDS, THF,  $-78^{\circ}\text{C}$ , then allyl bromide; b) DIBAL (5.0 equiv), THF/PhMe,  $-78^{\circ}\text{C}$ ; c) dimethyl (1-diazo-2-oxopropyl)phosphonate **15**,  $\text{K}_2\text{CO}_3$ , MeOH,  $0^{\circ}\text{C}$   $\rightarrow$  RT; d) TBSCl, imidazole,  $\text{CH}_2\text{Cl}_2$ ,  $0^{\circ}\text{C}$   $\rightarrow$  RT; e)  $\text{Co}_2(\text{CO})_8$ , PhMe,  $70^{\circ}\text{C}$ ; f) 3-butenylmagnesium bromide (4.5 equiv),  $\text{CuBr}\cdot\text{SMe}_2$  (20 mol %), TMSCl, HMPA, THF,  $-78^{\circ}\text{C}$   $\rightarrow$   $-30^{\circ}\text{C}$ , then AcOH, RT; g) AcCl (10 equiv), MeOH,  $45^{\circ}\text{C}$ ; h) **9** (1.1 equiv),  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , then L-proline, DMF, RT; i)  $\text{Boc}_2\text{O}$ ,  $\text{CH}_2\text{Cl}_2$ , RT, 72 h; j) IBX, EtOAc,  $80^{\circ}\text{C}$ ; k)  $\text{K}_2\text{CO}_3$ , MeOH, RT. Boc = *tert*-butoxycarbonyl, DIBAL = diisobutylaluminum hydride, DMF = dimethylformamide, HMPA = hexamethylphosphoramide, IBX = 2-iodoxybenzoic acid, LiHMDS = lithium bis(trimethylsilyl)amide, TBS = *tert*-butyldimethylsilyl, TFA = trifluoroacetic acid, THF = tetrahydrofuran, TMS = trimethylsilyl.

propargylic carbamate **11**. This intermediate would ultimately be derived from L-glutamic acid.

Our actual synthesis of lycopalhine A, guided by these considerations, is presented in Scheme 2. To begin, dimethyl ester **12**, prepared from L-glutamic acid on a decagram scale in a one-pot procedure (see the Supporting Information),<sup>[7]</sup> was allylated with high *anti* diastereoselectivity in a procedure described by Hanessian and co-workers.<sup>[8]</sup> Chemoselective reduction of **13** by controlled addition of diisobutylaluminum hydride (DIBAL) afforded lactol **14** as a 1:1 mixture of diastereomers (C1). Alkynylation of **14** was complicated by the epimerization of the neighboring amine stereocenter under the basic conditions required to open the six-membered lactol. Optimized conditions using Ohira–Bestmann reagent **15**<sup>[9]</sup> and silyl protection of the resulting alcohol afforded alkyne **11** and its C3 epimer as an inseparable 10:1 mixture.<sup>[10]</sup> The ensuing Pauson–Khand reaction proceeded under thermal conditions and afforded enone **10** with the desired C7 stereoselectivity, confirmed by nuclear Overhauser effect (NOE) analysis, as a 10:1 mixture with the cyclized C3 epimer. The diastereoselectivity of related intramolecular Pauson–Khand reactions in the context of *Lycopodium* alkaloid synthesis has previously been explored by the groups of Zard,<sup>[11]</sup> Takayama,<sup>[20]</sup> and Mukai.<sup>[21]</sup> The authors propose that chair-like conformations of intermediate **16** translate to the desired configuration of the bicyclo-[4.3.0]nonenone.<sup>[12]</sup> TMSCl-promoted conjugate addition of butenylmagnesium bromide to the enone<sup>[13]</sup> and cleavage of the resulting silyl enol ether with acetic acid afforded **17**, featuring the sole quaternary stereocenter of the molecule, as a single diastereomer upon purification. The first six steps of

the synthesis were easily scalable and provided gram quantities of advanced intermediate **17**. Global deprotection with acetyl chloride in methanol then produced free aminoketone **8**.

The intramolecular 5-*endo*-trig Mannich cyclization proved to be a challenging transformation. Acidic conditions resulted mainly in self-condensation of the aldehyde. However, mixing amine **8** and aldehyde **9** with triethylamine followed by concentration under reduced pressure granted

**Table 1:** Conditions for the intramolecular Mannich cyclization.

Entry <sup>[a]</sup>	Additives (equiv)	Solvent	T [°C]	Yield <sup>[b]</sup> [%]
1	$\text{Yb}(\text{OTf})_3$ (1.0)	MeCN	0–RT	–
2	$\text{TiCl}_4$ (2.0) / $\text{Et}_3\text{N}$ (4.0)	$\text{CH}_2\text{Cl}_2$	$-30$ –RT	–
3	$\text{K}_2\text{CO}_3$ (3.0)	MeOH	RT	–
4 <sup>[c]</sup>	$\text{Et}_3\text{N}$ (3.0)	PhMe	RT–80	–
5	pyrrolidine (1.0)	DMF	RT	11
6	pyrrolidine (1.0) / AcOH (1.0)	DMF	RT	10
7	D-proline (1.0)	DMF	RT	20
8	L-proline (1.0)	DMF	RT	60
9 <sup>[d]</sup>	L-proline (0.5)	DMF	RT	39
10	L-phenylalanine (1.0)	MeCN	RT	30

[a] Reactions conducted under nitrogen atmosphere for 18–24 h.

[b] Yield of isolated product. [c] Reaction performed without preformation of imine by treatment with  $\text{Et}_3\text{N}$ .





the unstable crude imine **18**. Redissolving the imine in dimethylformamide (DMF) and exposure to pyrrolidine afforded **7** with the desired *S*-configured C7 stereochemistry in low yields, but with no trace of the undesired *R*-configured diastereomer **19** or 6-*endo*-trig regioisomers (Table 1, entry 5). A substantial increase in reaction yield was observed when using L-proline as the additive (entry 8). Although the reaction proceeded without preformation of the imine and with substoichiometric quantities of the amino acid (entry 9), lower yields led us to use a full equivalent of the additive. The reaction also proceeded in the presence of both D-proline (entry 7) and L-phenylalanine (entry 10), albeit in reduced yields. The tendency of primary and secondary, but not tertiary, amines to promote the reaction suggests a mechanism involving matched enamine catalysis rather than simple deprotonation of the ketone.

To complete the synthesis of lycopalhine A, the newly formed pyrrolidine was protected by using di-*tert*-butyl dicarbonate to yield dicarbamate **20** before oxidizing the remaining primary alcohol with 2-iodoxybenzoic acid (IBX). The potentially biomimetic intramolecular aldol reaction to form **21** occurred quickly and in excellent yield when using potassium carbonate in methanol.<sup>[14]</sup> The diastereoselectivity of the reaction likely reflects a thermodynamic preference of **21** for a  $\beta$ -hydroxyl group positioned on the concave face of the molecule, away from the congested inner ring system. A Lemieux–Johnson oxidative cleavage of the olefin followed by dual deprotection and acid-catalyzed amination afforded **1**.

The spectroscopic data and optical properties of our synthetic sample were identical in all respects to those reported for the natural product.<sup>[3a]</sup> Indeed, an inseparable side product (*epi*-**1**) purified together with lycopalhine A directly matched an uncharacterized impurity in the spectra of Zhao's isolated sample. Two-dimensional NMR spectroscopy of the mixture<sup>[15]</sup> identified the minor product as the C16 epimer of lycopalhine A, which likely exists in equilibrium with the major isomer through a retro-aldol/aldol-type mechanism. Deuterium exchange of the protons at C6 and C15 under basic conditions,<sup>[16]</sup> as well as the presence of epimers in both the isolated and synthetic samples, suggests that lycopalhine A exists as a thermodynamic mixture favoring the closed aldol product and lends further credibility to a spontaneous cyclization in its biosynthesis.

In summary, we have developed an expedient synthesis of the complex *Lycopodium* alkaloid lycopalhine A that relies on two readily available amino acids for its completion. L-glutamic acid provides an inexpensive chiral entry point that, to the best of our knowledge, has not been used previously in the synthesis of fawcettimine-type alkaloids. L-proline promotes a 5-*endo*-trig intramolecular Mannich cyclization with an  $\alpha$ -unsubstituted aldehyde under mild conditions. We anticipate that this organocatalytic approach and the scalable intermediates encountered in the course of this endeavor will prove valuable for future studies of complex *Lycopodium* alkaloids.

### Acknowledgements

We would like to acknowledge the Natural Sciences and Engineering Research Council of Canada and SFB 749 for financial support. We thank Fabio Raith for experimental assistance, and Felix Hartrampf and Nicolas Armanino for helpful discussions.

**Keywords:** aldol reaction · amino acids · *Lycopodium* alkaloids · Mannich reaction · total synthesis

**How to cite:** *Angew. Chem. Int. Ed.* **2016**, *55*, 2191–2194  
*Angew. Chem.* **2016**, *128*, 2231–2234

- [1] Recent reviews on the *Lycopodium* alkaloids: a) W. A. Ayer, *Nat. Prod. Rep.* **1991**, *8*, 455; b) W. A. Ayer, L. S. Trifonov in *The Alkaloids*, Vol. 45 (Eds.: G. A. Cordell, A. Brossi), Academic Press, New York, **1994**, p. 233; c) X. Ma, D. R. Gang, *Nat. Prod. Rep.* **2004**, *21*, 752; d) M. Kitajima, H. Takayama, *Top. Curr. Chem.* **2012**, *309*, 1; e) A. Nakayama, M. Kitajima, H. Takayama, *Synlett* **2012**, 23, 2014; f) P. Siengalewicz, J. Mulzer, U. Rinner in *The Alkaloids: Chemistry and Biology*, Vol. 72 (Ed.: H.-J. Knölker), Academic Press, New York, **2013**, p. 1; g) R. A. Murphy, R. Sarpong, *Chem. Eur. J.* **2014**, *20*, 42.
- [2] Selected recent syntheses of fawcettimine-type alkaloids: a) X. Linghu, J. J. Kennedy-Smith, F. D. Toste, *Angew. Chem. Int. Ed.* **2007**, *46*, 7671; *Angew. Chem.* **2007**, *119*, 7815; b) J. Ramharter, H. Weinstabl, J. Mulzer, *J. Am. Chem. Soc.* **2010**, *132*, 14338; c) V. Bisai, R. Sarpong, *Org. Lett.* **2010**, *12*, 2551; d) A. Nakayama, N. Kogure, M. Kitajima, H. Takayama, *Angew. Chem. Int. Ed.* **2011**, *50*, 8025; *Angew. Chem.* **2011**, *123*, 8175; e) N. Shimada, Y. Abe, S. Yokoshima, T. Fukuyama, *Angew. Chem. Int. Ed.* **2012**, *51*, 11824; *Angew. Chem.* **2012**, *124*, 11994; f) H. Li, X. Wang, X. Lei, *Angew. Chem. Int. Ed.* **2012**, *51*, 491; *Angew. Chem.* **2012**, *124*, 506; g) X.-M. Zhang, H. Shao, Y.-Q. Tu, F.-M. Zhang, S.-H. Wang, *J. Org. Chem.* **2012**, *77*, 8174; h) H. M. Ge, L.-D. Zhang, R. X. Tan, Z.-J. Yao, *J. Am. Chem. Soc.* **2012**, *134*, 12323; i) N. Itoh, T. Iwata, H. Sugihara, F. Inagaki, C. Mukai, *Chem. Eur. J.* **2013**, *19*, 8665; j) J. Zhang, J. Wu, B. Hong, W. Ai, X. Wang, H. Li, X. Lei, *Nat. Commun.* **2014**, *5*, 4614; k) B. Hong, H. Li, J. Wu, J. Zhang, X. Lei, *Angew. Chem. Int. Ed.* **2015**, *54*, 1011; *Angew. Chem.* **2015**, *127*, 1025.
- [3] Isolation: a) L.-B. Dong, J. Yang, J. He, H.-R. Luo, X.-D. Wu, X. Deng, L.-Y. Peng, X. Cheng, Q.-S. Zhao, *Chem. Commun.* **2012**, 48, 9038; b) F.-W. Zhao, Q.-Y. Sun, F.-M. Yang, J.-F. Luo, G.-W. Hu, F. Liu, Y.-H. Wang, C.-L. Long, *J. Braz. Chem. Soc.* **2012**, *23*, 349; c) F.-W. Zhao, Q.-Y. Sun, F.-M. Yang, G.-W. Hu, J.-F. Luo, G.-H. Tang, Y.-H. Wang, C.-L. Long, *Org. Lett.* **2010**, *12*, 3922; d) Y. Hirasawa, A. Astulla, M. Shiro, H. Morita, *Tetrahedron Lett.* **2011**, *52*, 4126.
- [4] T. Hu, R. F. Chandler, A. W. Hanson, *Tetrahedron Lett.* **1987**, *28*, 5993.
- [5] J. E. Baldwin, *J. Chem. Soc. Chem. Commun.* **1976**, 734.
- [6] Aza-Cope Mannich reactions: L. E. Overman, M.-A. Kakimoto, *J. Am. Chem. Soc.* **1979**, *101*, 1310; L. E. Overman, *Acc. Chem. Res.* **1992**, *25*, 352; 5-*endo*-trig Mannich cyclizations from condensations of aldehydes/ketones and primary amines: S. Suresh, M. Periasamy, *Tetrahedron Lett.* **2004**, *45*, 6291; Y. Shi, B. Yang, S. Cai, S. Gao, *Angew. Chem. Int. Ed.* **2014**, *53*, 9539; *Angew. Chem.* **2014**, *126*, 9693; 5-*endo*-trig Mannich cyclizations following Michael addition to iminoesters: R. Grigg, J. Kemp, J. F. Malone, *Tetrahedron* **1988**, *44*, 5361; A. Dehnel, J. M. Kanabus-Kaminska, G. Lavielle, *Can. J. Chem.* **1988**, *66*, 310; H. Y. Kim, E. O. Rooney, R. P. Meury, K. Oh, *Angew. Chem. Int. Ed.* **2013**, *52*, 8026; *Angew. Chem.* **2013**, *125*, 8184.
- [7] S. Yang et al., *J. Med. Chem.* **2006**, *49*, 4971.

- [8] S. Hanessian, R. Margarita, *Tetrahedron Lett.* **1998**, *39*, 5887.
- [9] S. Müller, B. Liepold, G. J. Roth, H. J. Bestmann, *Synlett* **1996**, 521.
- [10] Base/solvent combinations such as Cs<sub>2</sub>CO<sub>3</sub> in *i*PrOH or BnOH have been reported to hinder the epimerization of  $\alpha$ -stereocenters during Seyferth–Gilbert reactions: J. B. Brennehan, S. F. Martin, *Org. Lett.* **2004**, *6*, 1329. For our reaction, these conditions could not fully prevent isomerization.
- [11] J. Cassayre, F. Gagosz, S. Z. Zard, *Angew. Chem. Int. Ed.* **2002**, *41*, 1783; *Angew. Chem.* **2002**, *114*, 1861.
- [12] C. Mukai, J. S. Kim, H. Sonobe, M. Hanaoka, *J. Org. Chem.* **1999**, *64*, 6822.
- [13] S. Matsuzawa, Y. Horiguchi, E. Nakamura, I. Kuwajima, *Tetrahedron* **1989**, *45*, 349.
- [14] R. L. Funk, G. L. Bolton, *J. Org. Chem.* **1987**, *52*, 3173.
- [15] *Epi-1* was identified by using COSY, NOESY, HSQC, and HMBC correlations of the mixture along with changes in <sup>3</sup>J coupling constants. See the Supporting Information for details.
- [16] At the recommendation of a reviewer, deuterium exchange studies were performed with K<sub>2</sub>CO<sub>3</sub> and MeOD at ambient temperature. Exchange of protons at C6 and C15 after 2 hours was consistent with retro-aldol ring opening, epimerization of the aldehyde, and tautomerization of the enol, followed by ring closure. See the Supporting Information for details.

Received: October 13, 2015  
Published online: January 8, 2016



### 1.3. Synthetic efforts towards the Palhinine D ring system

#### 1.3.1. X-ray crystal structures of compounds **10** and **17**

Following the total synthesis of lycopalhine A and the publication of our results, the crystal structure of two key intermediates, **10** and **17** (Figure 1.5, numbering from *Angew. Chem. Int. Ed.* **2016**, *55*, 2191), were resolved by X-ray analysis. A sample of bicycle **17** had been left dissolved in diethyl ether and stored in the  $-35\text{ }^{\circ}\text{C}$  freezer for several months. Square crystals began to form and were collected for analysis. Compound **10** was submitted to identical conditions and a crystal structure of this compound was also analyzed. These crystal structures reinforce the relative stereochemistry of the intermediates and, by extension, the stereoselectivity of the PKR and conjugate addition reaction.

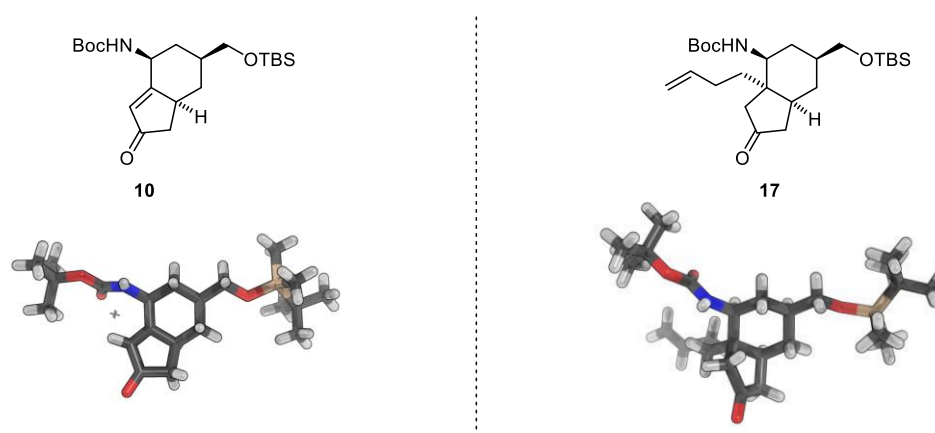
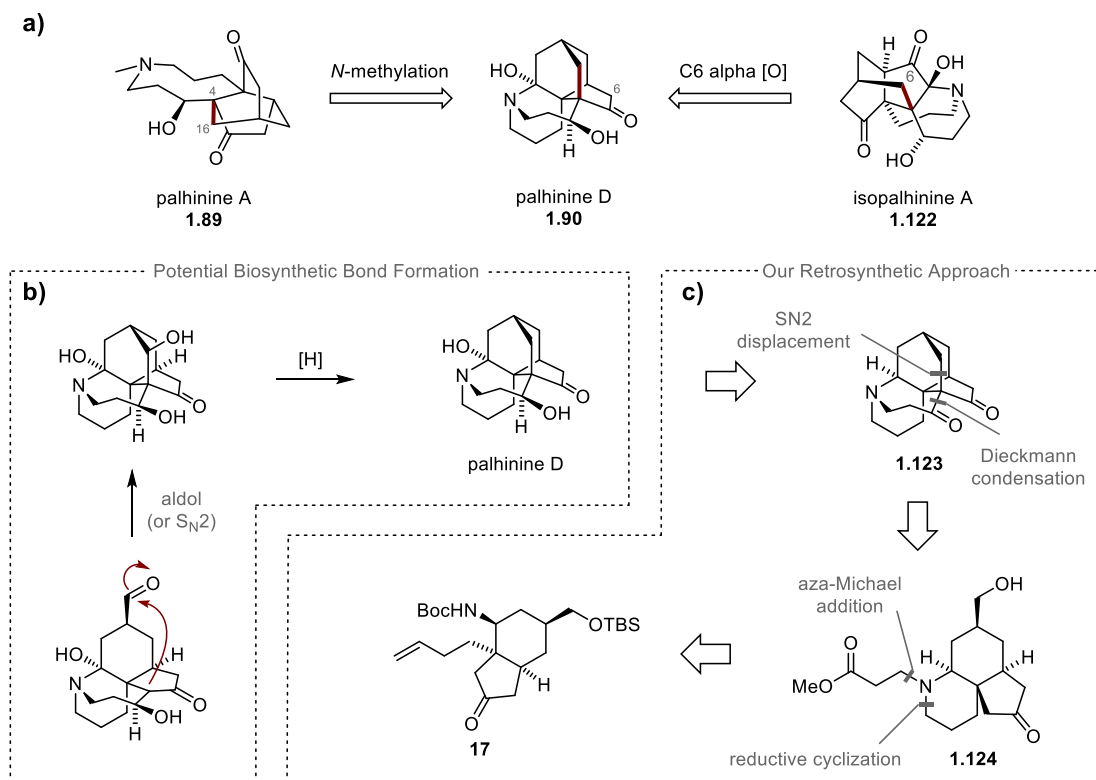


Figure 1.5. Molecular structures of compounds **10** and **17** as confirmed by X-ray crystallography.

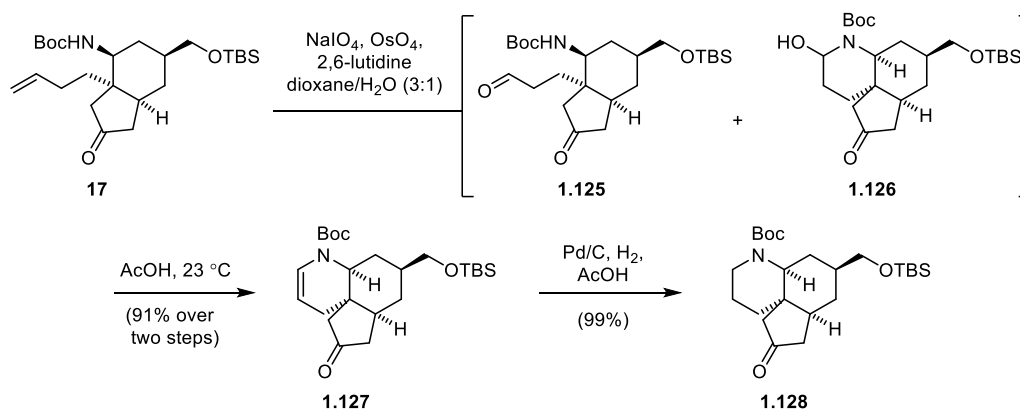
#### 1.3.2. Efforts towards the skeleton of Palhinine B

With the synthesis of lycopalhine A complete, we sought to apply our synthetic approach to other fawcettimine-type molecules possessing new connectivity at the C16 position. Of particular interest to our group was the palhinine subfamily of *Lycopodium* alkaloids. Palhinine A (**1.89**) and isopalhinine A (**1.122**) (Scheme 1.20) were recently isolated from the *Palhinhaea cernua* by the group of Zhao<sup>[89-90]</sup> and palhinine D (**1.90**, formerly palhinine B) was isolated by the group of Yu from the *Lycopodium japonicum*.<sup>[100]</sup> Their unique C4-C16 connectivity is believed to arise either from an intramolecular displacement (as proposed by Zhao) or an aldol reaction (as proposed by Yu) of a C16 oxidized precursor. Inspired by this biogenetic pathway, we believed a route from our previously synthesized bicycle **17** could deliver these complex skeletons in a concise synthesis. Nucleophilic displacement of a sulfonyl leaving group at C16 by a  $\beta$ -diketone, generated in turn from a Dieckmann condensation of **1.124**, would form the key bicyclo[2.2.2]octane system **1.123**. **1.124** could in turn be accessed from **17** by an aza-Michael reaction and a reductive amination.



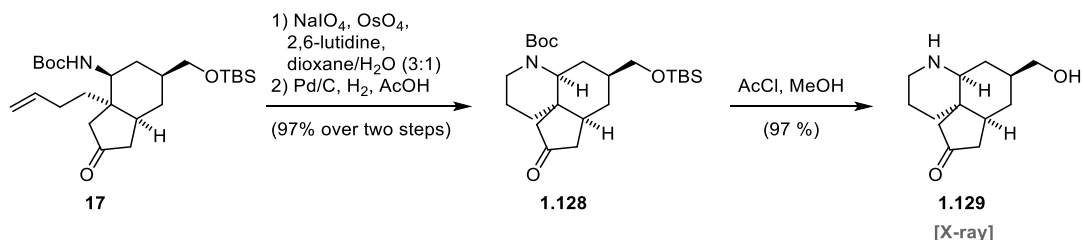
**Scheme 1.20.** a) Members of the palhinine subfamily, b) proposed biosynthetic formation of the C4-C16 bond, c) our retrosynthetic approach to the palhinine D skeleton.

The following work towards tricycle **1.124** was conducted with the assistance of M.Sc. intern Simon Schnell. Our synthesis began once more with bicycle **17** (**Scheme 1.21**). Lemieux-Johnson oxidative cleavage of the terminal olefin gave a 1:1 mixture of the open aldehyde **1.125** and the cyclized carbinolamine **1.126**. Treatment with acetic acid at ambient temperature promoted full cyclization to the lactamol and immediate dehydration to enamide **1.127**, which could be hydrogenated using standard conditions to tricycle **1.128**.



**Scheme 1.21.** Reductive cyclization to tricycle **1.128**.

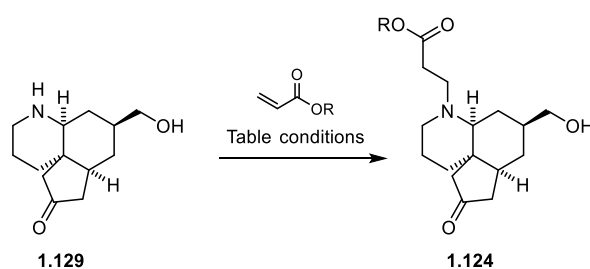
The entire sequence could be condensed in an efficient two-step protocol that afforded tricycle **1.128** in excellent yield (**Scheme 1.22**). Global deprotection of **1.128** to **1.129** was accomplished using acetyl chloride in methanol, and the structure of **1.129** was confirmed by X-ray analysis of the hydrochloride.



**Scheme 1.22.** Streamlined synthesis of **1.128** and deprotection to amine **1.129**.

A number of conditions for the aza-Michael addition of acrylates to **1.129** were investigated (**Table 1.1**). Though many conventional conditions were unable to grant the desired tertiary amine, excellent results were attained using DBU as a base in acetonitrile at higher temperatures.

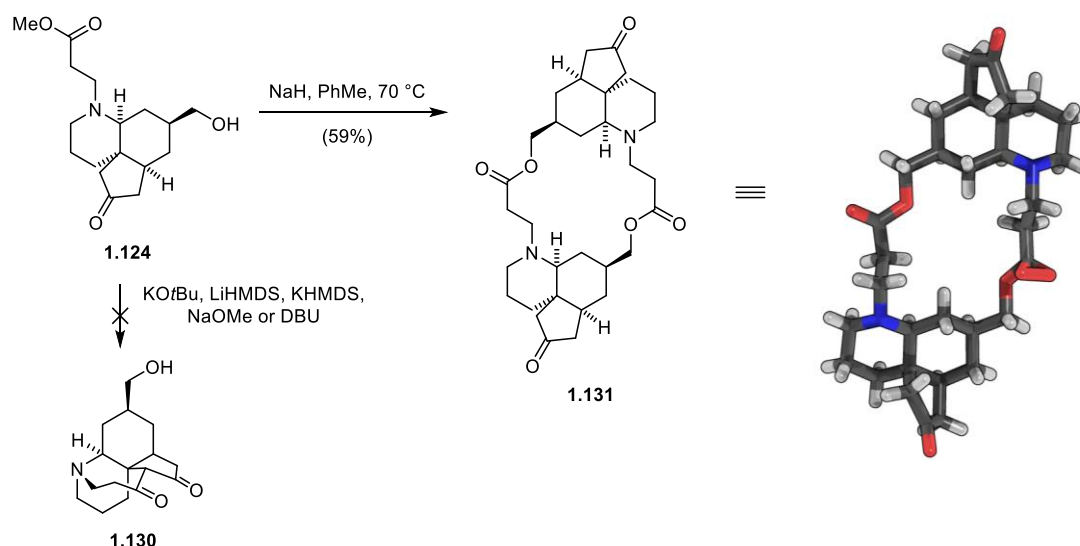
**Table 1.1.** Aza-Michael reaction conditions for the addition of acrylates to amine **1.124**.



Entry	Base	Solvent	T (°C)	R	Yield <sup>a</sup>
1	Et <sub>3</sub> N	THF	RT	Me	/
2	K <sub>2</sub> CO <sub>3</sub>	MeCN	82 °C	Me	/
3	KOtBu	THF	0 °C → RT	<i>t</i> Bu	/
4 <sup>b</sup>	DBU	MeCN	70 °C	Me	86%
5 <sup>c</sup>	DBU	MeCN	70 °C	Me	93%

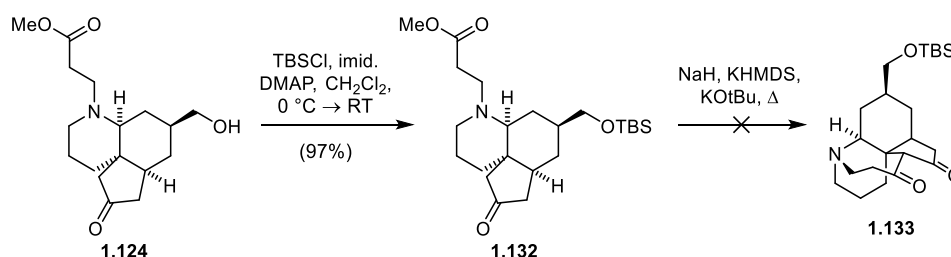
[a] Isolated yield. [b] 0.025 mmol scale. [c] 0.324 mmol scale.

With ester **1.124** in hand, we began exploring conditions for the Dieckmann condensation to tetracycle **1.130**. The use of bases such as KOtBu, NaOMe and LiHMDS led only to recovery of the starting material or decomposition. An excess of sodium hydride in toluene at elevated temperatures, conversely, gave rise to a new compound. Rather than granting the desired azaheptanone, however, these conditions had led to transesterification between the unprotected alcohol and the methyl ester, presumably through the alkoxide. Indeed, the structure of the crystalline solid according to X-ray analysis indicated that two units of tricycle had dimerized to form 18-membered lactone **1.131**.



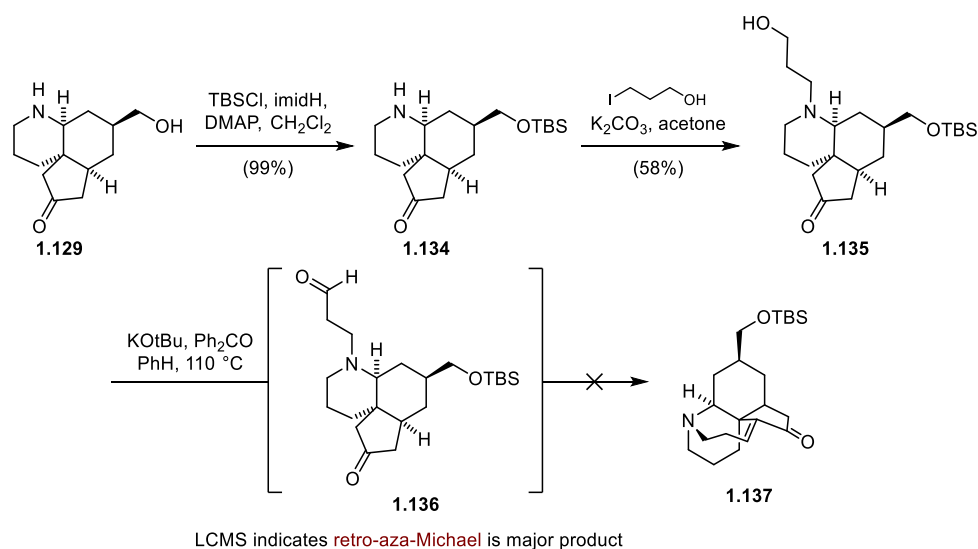
**Scheme 1.23.** Attempts at the Dieckmann condensation to **1.130** and lactonic homodimerization to **1.131**.

To avert this lactonization, **1.124** was protected as *tert*-butyldimethylsilyl ether **1.132** (**Scheme 1.24**). Resubmitting the reaction to the previous basic conditions yielded only starting material. In polar solvents such as methanol, gradual retro-*aza*-Michael reaction was observed.



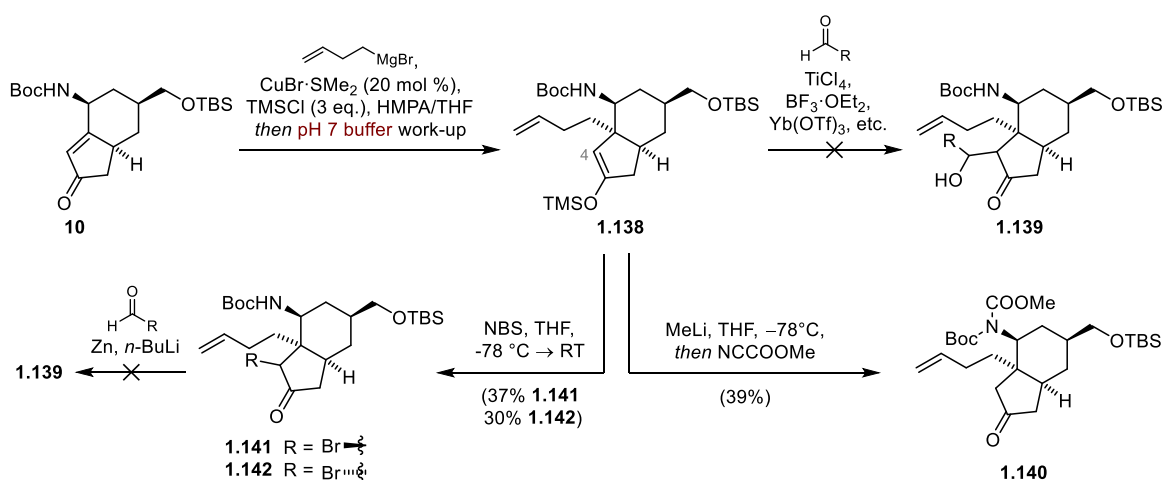
**Scheme 1.24.** Attempts at the Dieckmann condensation with TBS-protected alcohol **1.132**.

As it appeared that the cyclization required a more active electrophile, we opted to form the seven-membered ring through an intramolecular aldol reaction. The groups of Heathcock<sup>[101]</sup> and Carter<sup>[102]</sup> had previously used a one-pot Oppenauer oxidation/aldol condensation sequence to form the azahexene ring in syntheses of lycopodine, and we hypothesized the added reactivity of an aldehyde towards enolate addition might allow successful functionalization at C4. We synthesized **1.135** by TBS-protection and *N*-alkylation (**Scheme 1.25**). Unfortunately, the oxidation/aldol conditions led to decomposition of the material. HPLC-MS of the crude sample indicated formation of some retro-*aza*-Michael product, suggesting that the oxidation to **1.136** was successful but the cyclization to **1.137** did not proceed as planned.



**Scheme 1.25.** Attempted Oppenauer oxidation/aldol condensation to the seven-membered ring.

We returned to Pauson–Khand product **10** in a final attempt to functionalize the C4 position directly following conjugate addition to the enone. When the 1,4-addition of homoallylmagnesium bromide to **10** was worked up with pH 7 phosphate buffer rather than with acetic acid, crude silyl enol ether **1.138** could be isolated reasonably cleanly without the use silica gel chromatography (**Scheme 1.26**). However, Mukaiyama aldol reactions to **1.139** with this hindered enol were unsuccessful with a number of aldehydes and Lewis acids. Attempts to acylate the position directly by lithium-silyl exchange and treatment with Mander's reagent led instead to **1.140** through acylation of the *N*-acyl anion. The silyl enol ether could be successfully brominated to give a separable mixture of **1.141** and **1.142**, whose relative stereochemistry was determined by NOESY correlations. However, attempts to convert either diastereomer to **1.139** by Reformatsky reaction were also unsuccessful. As it was becoming clear that the formation of the seven-membered ring or C-C bond formation at the C4 position would require revising our strategy, we opted to focus our efforts on other projects.



**Scheme 1.26.** Attempts to alkylate or acylate the C4 position of **1.138**



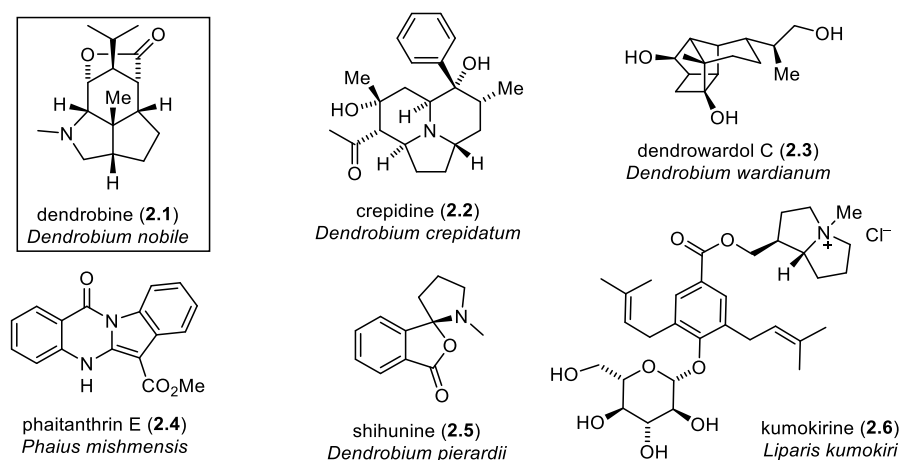
CHAPTER II:  
AZOMETHINE YLIDE CYCLOADDITION STRATEGY  
TOWARD DENDROBINE

---

## 2.1. Introduction to Dendrobine

### 2.1.1. Dendrobine and the *Orchidaceae* alkaloids

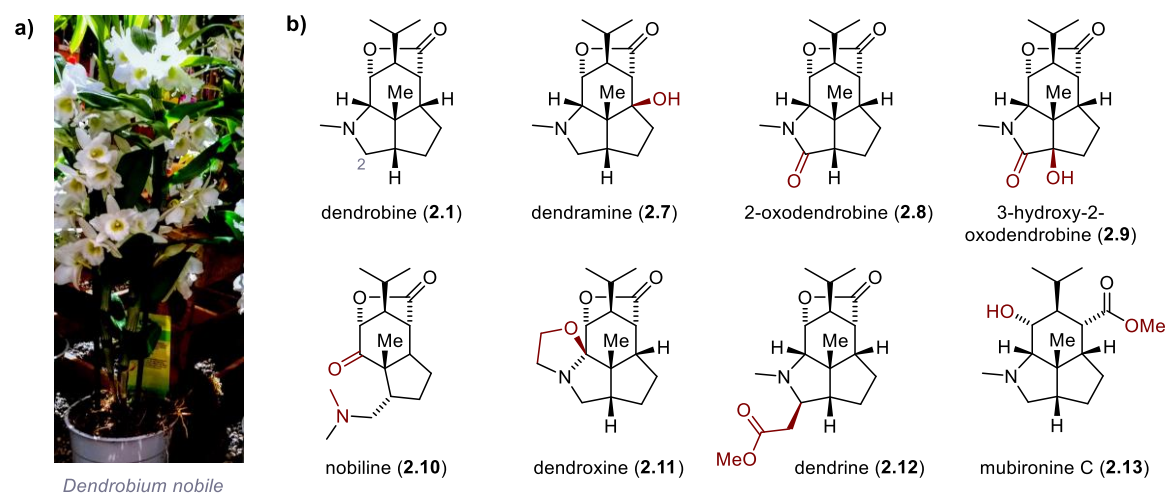
Alkaloids extracted from members of the *Orchidaceae* family are as varied and as elegant as the plants from which they originate. They include complex pyrrolidines, such as dendrobine (**2.1**); indolizidines, such as crepidine (**2.2**);<sup>[103]</sup> cyclobutanes, such as dendrowardol C (**2.3**);<sup>[104]</sup> quinazolinones, such as phaitanthrin E (**2.4**);<sup>[105]</sup> and intricate pyrrolizidines, such as kumokirine (**2.6**)<sup>[106]</sup> (**Figure 2.1**). Of these, dendrobine in particular has found itself a frequent participant in the labours of synthetic chemistry. A lactonic sesquiterpenoid base isolated from the orchid *Dendrobium nobile*, dendrobine has been the subject of 8 total syntheses, 5 formal syntheses, and innumerable attempts towards its deceptively simple core.



**Figure 2.1.** Alkaloids isolated from members of the *Orchidaceae* family.

Dendrobine was first isolated from the *Dendrobium nobile* (**Figure 2.2.a**) by Suzuki and coworkers in 1932, who initially reported the extraction of a base with chemical formula  $C_{16}H_{25}O_2N$  from the orchid-derived Chinese medicinal tonic ‘Chin-Shih-Hu’.<sup>[107-108]</sup> It was not until the substantial degradative and spectroscopic work of Inubushi in 1964, however, that the tetracyclic structure was correctly elucidated and the stereochemistry firmly established.<sup>[109-110]</sup> Although dendrobine is the most abundant and most commonly encountered of the sesquiterpenoid alkaloids isolated from the *D. nobile*, over 20 closely-related molecules with additional layers of oxidation have been identified in this plant and similar orchids.<sup>[111]</sup> Important examples include dendramine (**2.7**),<sup>[109]</sup> 2-oxodendrobine (**2.8**, mubironine A),<sup>[112]</sup> nobiline (**2.10**),<sup>[113]</sup> dendroxine (**2.11**),<sup>[114]</sup> dendrine (**2.12**)<sup>[115]</sup> and mubironine C<sup>[112]</sup> (**Figure 2.2.b**).



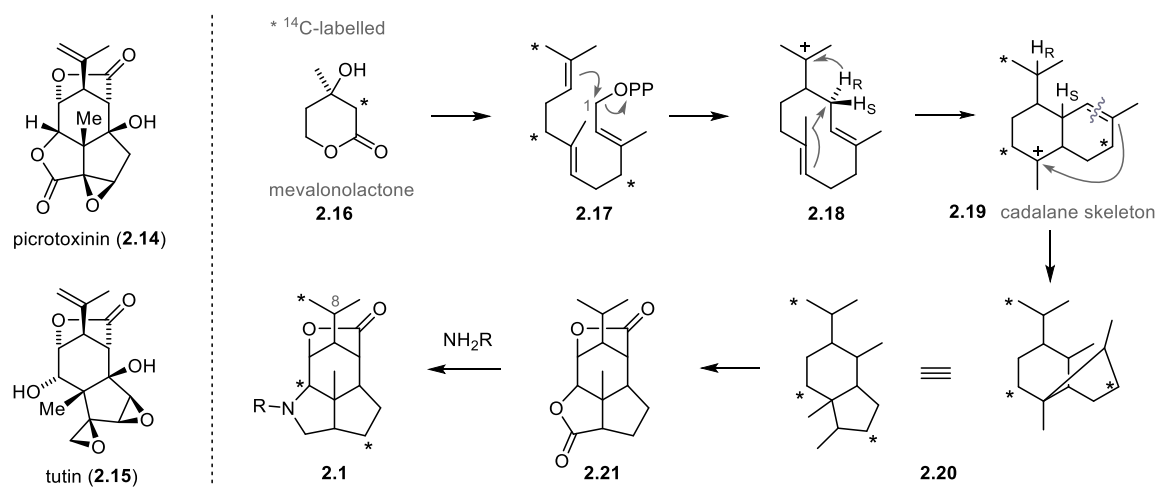


**Figure 2.2.** a) the *Dendrobium nobile* LINDL (photograph taken by the author at a local gardening store) and b) a selection of related alkaloids with additional oxidation or functionality (in red) relative to dendrobine.

A large portion of these alkaloids have been synthesized through partial synthesis from **2.1**, including nobiline, dendrine,<sup>[116]</sup> and 2-hydroxydendrobine. However, total syntheses of these molecules from commercially available starting materials remain infrequent, with a notable exception of Yamada's synthesis of 2-hydroxydendrobine and nobiline.<sup>[117]</sup>

### 2.1.2. Biosynthesis and Bioactivity of Dendrobine

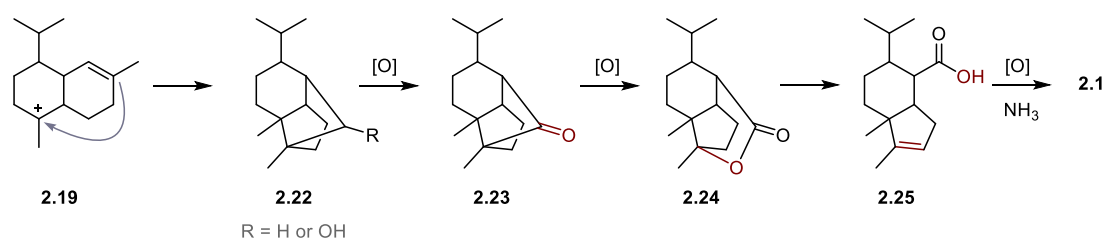
Dendrobine shares its biogenesis with the picrotoxane family of sesquiterpenes, of which picrotoxinin (**2.14**)<sup>[118]</sup> (Scheme 2.1), a potent non-competitive GABA<sub>A</sub> inhibitor,<sup>[119-120]</sup> and tutin (**2.15**),<sup>[121]</sup> a toxic glycine receptor antagonist,<sup>[122]</sup> are the most well-known members. The biosynthesis of the *Dendrobium* alkaloids (Scheme 2.1) has been illuminated by labelling studies performed by the laboratories of Yamazaki,<sup>[123]</sup> Edwards<sup>[124]</sup> and Jommi,<sup>[125-126]</sup> as well as by studies on tutin biogenesis by Biollaz, Arigoni<sup>[127]</sup> and Jommi.<sup>[128-129]</sup>



**Scheme 2.1.** Important picrotoxanes (left) and proposed biosynthesis of dendrobine (right).

Yamazaki first documented the incorporation of labelled mevalonic acid into dendrobine upon administration of 2-<sup>14</sup>C-sodium mevalonate to *Dendrobium nobile* stems,<sup>[123]</sup> thereby confirming that the biogenesis of the alkaloid follows the standard sesquiterpene pathway. According to Yamazaki's proposal, farnesyl pyrophosphate **2.17**, generated from mevalonolactone **2.16**, undergoes cationic cyclization to the cadalane skeleton **2.19** and subsequent rearrangement to the bicyclononane skeleton **2.20** of the picotoxanes. Oxidation to **2.21** and incorporation of ammonia or methylamine then provides dendrobine. These findings were further substantiated by Edwards' labelling studies using 4-<sup>14</sup>C-mevalonate.<sup>[124]</sup>

A closely related biogenetic hypothesis was put forth by Jommi, one reviewer of Edwards' manuscript, and more recently by Li et al.<sup>[130]</sup> based on isolated biosynthetic intermediates (**Scheme 2.2**). In this instance, cadalane skeleton **2.19** rearranges directly to copacamphane-like tricycle **2.22**. Baeyer–Villiger-type oxidation to **2.24** and lactone opening are then responsible for formation of bicyclononane **2.25**. As before, late-stage oxidation and incorporation of ammonia by a variety of enzymes, principally cytochrome P450s and aminotransferases, are posited to grant the highly oxidized core.<sup>[130]</sup>



**Scheme 2.2.** Alternate proposal for the biosynthesis of **2.1**.

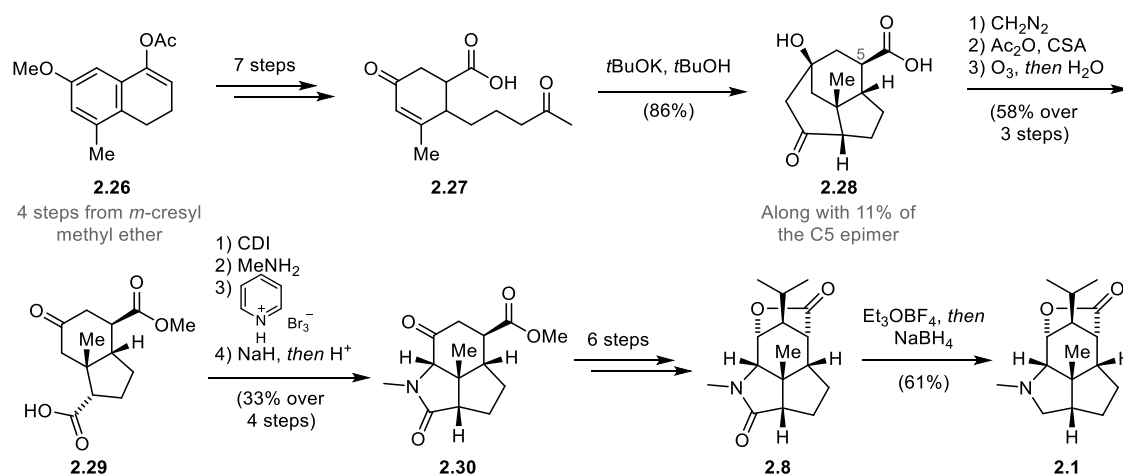
The picotoxane family is noted for its sophisticated bioactivity and dendrobine is no exception. The dried stems of the *Dendrobium nobile*, known in China as ‘Chin-Shi-Hu’ and in Japan as ‘Sekkuko,’ have been used as a medicinal tonic for hundreds of years.<sup>[131]</sup> In 1935, Chen and Chen conducted extensive pharmacological studies on dendrobine hydrochloride.<sup>[132-133]</sup> They found the alkaloid possessed moderate analgesic effects in frogs and mice lower than that of amidopyrine, produced moderate hyperglycemia in rabbits, diminished the cardiac activity of frogs, lowered the blood pressured of etherized cats, paralyzed rabbit intestines, contracted Guinea pig uteri, and produced death preceded by convulsions in frogs, mice and rabbits. In 1983, Yamada tested the neuropharmacological effects of dendrobine on isolated spinal cords of frogs.<sup>[134]</sup> Dendrobine blocked presynaptic inhibition and hyperpolarized dorsal and ventral roots in a manner reminiscent of strychnine. The alkaloid also displayed an antagonistic effect on  $\beta$ -alanine and taurine but, unlike picotoxinin, exhibited little inhibitory activity on glycine- and GABA-induced depolarizations. Recent research suggests dendrobine also possesses moderate antiviral activity against some strains of influenza A.<sup>[135]</sup>

### 2.1.3. Total syntheses of Dendrobine

The compact frame of dendrobine has often served as a showcase for new chemical methodologies or a demonstration of insightful retrosynthetic planning. As a result, there have been a great number of total and formal syntheses of dendrobine since Yamada<sup>[136]</sup> and Inubushi<sup>[137]</sup> independently synthesized the alkaloid in 1972. Herein is a summary of these works and their important features; attempted syntheses of dendrobine are not included.

#### *Yamada's synthesis of (±)-dendrobine*

The first synthesis of dendrobine by Yamada and colleagues derived the alkaloid's carbocyclic components from an aromatic precursor (**Scheme 2.3**).<sup>[136]</sup> The synthetic route began with acetylated dihydronaphthalenone **2.26**,<sup>[138]</sup> which was converted to diketoaacid **2.27** by ozonolysis, Wittig homologation and Birch reduction. A Michael reaction with concomitant aldol cyclization then yielded bicyclo[4.3.0]nonanol **2.28**. Methyl ester formation and ozonolysis of an acetate enol resulted in acid **2.29**, and the molecule's heterocycle was then generated by methylamide formation,  $\alpha$ -ketobromination with pyridinium tribromide, and anionic displacement to grant pyrrolidone **2.30**. Final installation of the isopropyl group, isomerization of the ester and reductive lactone formation resulted in the natural product (±)-oxodendrobine **2.8**, which could be converted to (±)-dendrobine using Borch's reduction.<sup>[139]</sup>

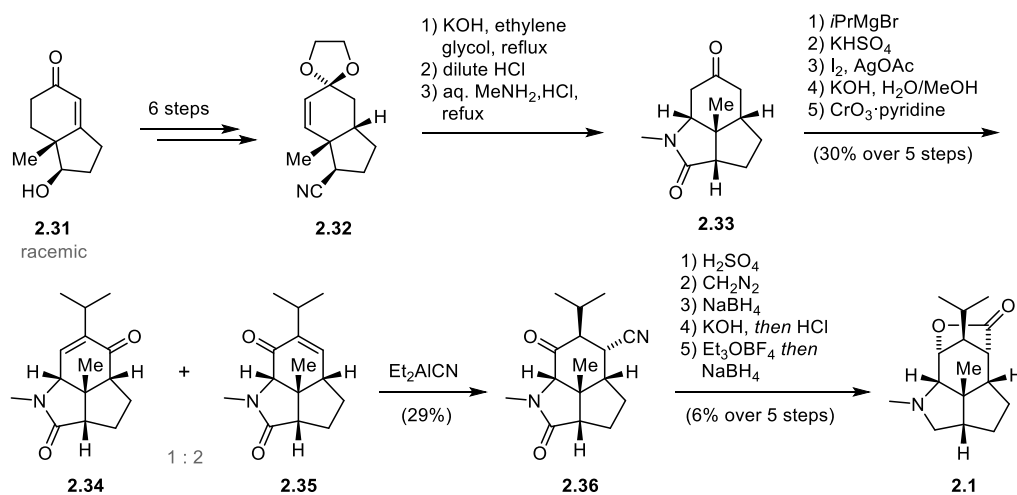


**Scheme 2.3.** Yamada's synthesis of (±)-dendrobine.

#### *Inubushi's synthesis of (±)-dendrobine*

The group of Inubushi reported a synthesis of (±)-dendrobine nearly simultaneously with Yamada's (**Scheme 2.4**).<sup>[137, 140]</sup> Opening with bicyclic enone **2.31**,<sup>[141]</sup> nitrile substitution with retention of stereochemistry, hydrogenation, bromination/elimination and acetalization bestowed ketal **2.32**. Hydrolysis of the nitrile, deacetalization/Michael addition, and refluxing in aqueous methylamine in the presence of acid yielded keto-lactam **2.33**, thus furnishing the tricyclic core of the alkaloid. The isopropyl group was installed through Grignard addition and elimination of the

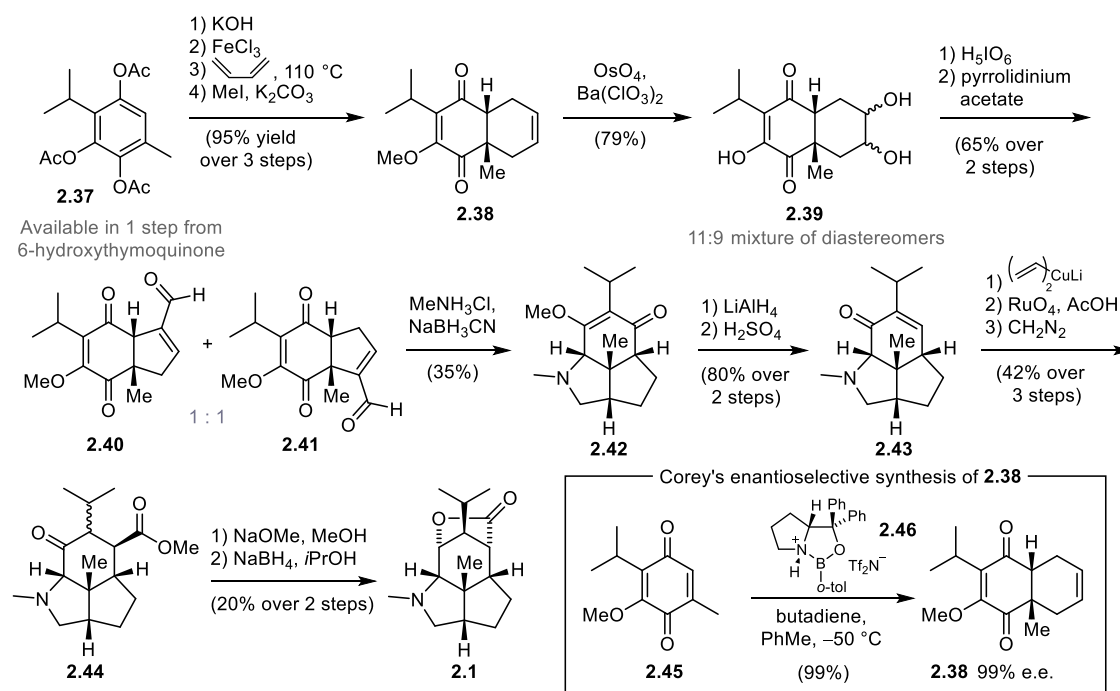
ensuing alcohol, and an allylic iodination/acetoxylation, saponification and oxidation sequence resulted in enone **2.35** together with its regioisomers **2.34**. The final carbon of the skeleton was then appended by hydrocyanation using diethylaluminum cyanide.<sup>[142]</sup> Though the reaction gave a mixture of diastereomers, the desired isomer **2.36** could be separated and taken forward for the remainder of the synthesis. A final series of operations resulted in nitrile hydrolysis, acid methylation, and ketone reduction to form the  $\gamma$ -lactone. Once more, reduction of an intermediate ethylimino ether by Borch's method granted ( $\pm$ )-**2.1**.



**Scheme 2.4.** Inubushi's synthesis of ( $\pm$ )-dendrobine.

*Kende's synthesis of (±)-dendrobine*

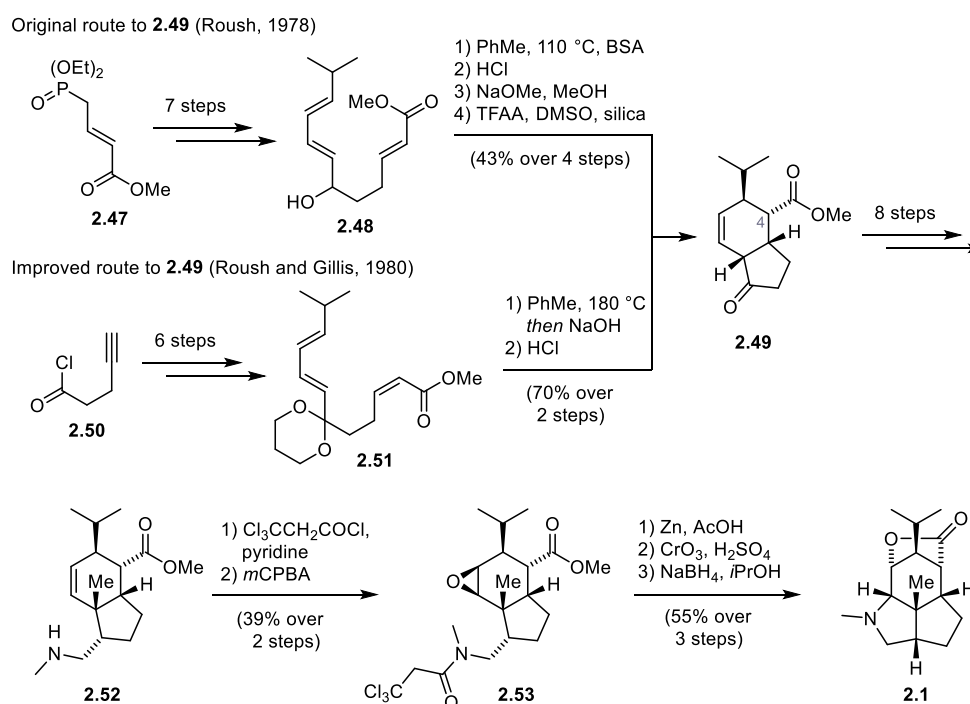
Following these initial two syntheses, Kende and colleagues developed a racemic synthesis of dendrobine using a Diels–Alder reaction to form the *cis*-substituted central bicyclic core of the sesquiterpenoid (**Scheme 2.5**).<sup>[143]</sup> Known triacetate **2.37**<sup>[144]</sup> was saponified and oxidized to the quinone, which underwent Diels–Alder cycloaddition with butadiene to form adduct **2.38** upon methylation. Osmium-catalyzed dihydroxylation then gave an unassigned mixture of isomers **2.39**. Oxidative cleavage of the diol and aldol condensation of the resultant dialdehyde afforded a separable mixture of regioisomers **2.40** and **2.41** in equal measures. The desired substrate **2.41** was submitted to double reductive amination to achieve the azaundecene system **2.42**. Reductive transposition of the unsaturated system resulted in enone **2.43**, which also served as the interception point for the formal syntheses of Mori, Padwa and Chen (see **Section 2.14** below). Subsequent conjugate addition of vinyl cuprate, ruthenium-based oxidative cleavage and methylation granted ester **2.44**, and partial isomerization with sodium methoxide followed by reductive ring-closure yielded (±)-dendrobine. In 2004, Corey and colleagues developed an enantioselective variation of the Diels–Alder reaction using chiral oxazaborolidinium **2.46** which conferred the adduct in excellent yield and enantiomeric excess, thus rendering Kende's synthesis theoretically asymmetric.<sup>[145]</sup>



**Scheme 2.5.** Kende's synthesis of (±)-dendrobine and Corey's enantioselective variant of the opening Diels–Alder reaction.

### Roush's synthesis of ( $\pm$ )-dendrobine

Between 1978 and 1980, Roush released four papers on an optimized Diels–Alder route to racemic dendrobine, a pathway that strategically resembled a contemporaneous synthesis of 8-*epi*-dendrobine by Borch.<sup>[146]</sup> The original synthesis of the alkaloid began with phosphonate **2.47** and the key Diels–Alder reaction was conducted after elaboration to triene **2.48**. Though the method successfully delivered the bicyclo[4.3.0]nonane system, it resulted in a mixture of four diastereomers and required basic epimerization of the C4 centre before oxidation to **2.49**. Following Roush's first synthesis of the alkaloid, Roush and Gillis revisited the route and optimized the Diels–Alder reaction with a shorter and higher yielding construction of the key bicycle from **2.50**. Cyclization of the resulting substrate **2.51** was surprisingly selective for the *exo* transition state, allowing for a more efficient route to **2.49**. The synthesis proceeded with  $\alpha$ -methylation to give the quaternary stereocentre, van Leusen reaction to convert the ketone to a nitrile, and reduction of the nitrile to amine **2.52**. Epoxidation of the olefin to **2.53** suffered from poor facial selectivity, but a concurrent deprotection and epoxide opening provided the pyrrolidine with the desired stereochemistry. Oxidation and reduction of the remaining alcohol to the correct face then afforded racemic **2.1**.

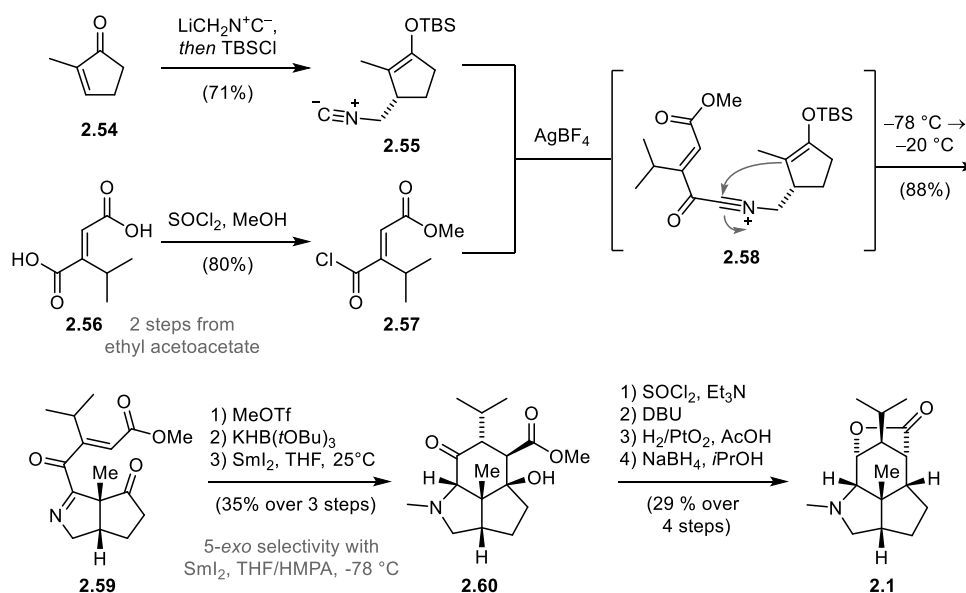


**Scheme 2.6.** Roush's Diels–Alder cycloaddition route to ( $\pm$ )-dendrobine.

### Livinghouse's synthesis of ( $\pm$ )-dendrobine

The shortest racemic synthesis of dendrobine - and the shortest synthesis overall to date - is that of the group of Livinghouse, who approached the molecule through a highly convergent route (**Scheme 2.7**).<sup>[147]</sup> 1,4-Addition of isocyanomethyl lithium to 2-methylcyclopentenone **2.54** and

trapping as the silyl enol ether gave isonitrile **2.55**. Chlorocarbonyl **2.57** was prepared in three steps from ethyl acetoacetate using a carefully controlled chloroacylation/methanolation protocol. Combination of the two units and addition to a solution of  $\text{AgBF}_4$  at low temperature formed transient acylnitrilium **2.58** which cyclized to pyrroline **2.59** upon gentle warming. *N*-Methylation and highly diastereoselective reduction with potassium tri-*tert*-butoxyborohydride afforded the pyrrolidine of dendrobine, and samarium-mediated free radical cyclization at higher temperatures overrode the kinetic preference for a 5-*exo* annulation to give the complete carbon skeleton (**2.60**) of dendrobine. The extraneous alcohol was eliminated and the resulting double bond isomerized into conjugation with both ester and ketone, whereupon stereoselective hydrogenation and known reduction of the ketone afforded racemic dendrobine.

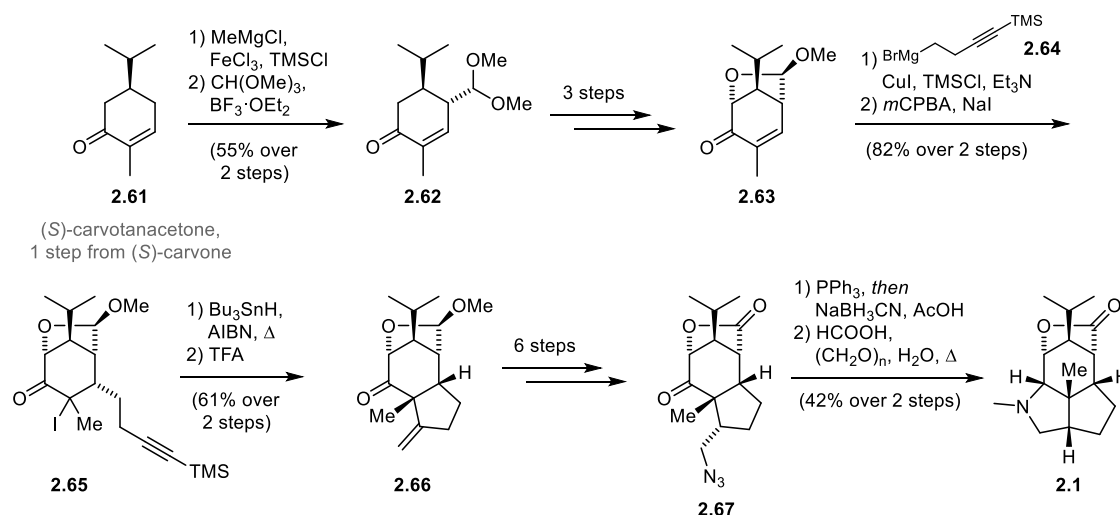


**Scheme 2.7.** Livinghouse's total synthesis of ( $\pm$ )-dendrobine by acylnitrilium ion cyclization and free radical annulation.

#### Sha's synthesis of (–)-dendrobine

The group of Sha reported the first enantioselective synthesis of natural (–)-dendrobine in 1997 by employing an impressive  $\alpha$ -carbonyl radical approach to the quaternary stereocenter of the molecule (**Scheme 2.8**).<sup>[148]</sup> (*S*)-Carvotanacetone **2.61**, available in one high-yielding step from (*S*)-carvone, was transformed to **2.62** by a Lewis acid-catalyzed aldol-type reaction with trimethyl orthoformate using the protocol of Takazawa et al.<sup>[149]</sup> Rubottom oxidation and acid-catalyzed cyclization led to methyl acetal **2.63**. Conjugate addition of alkynyl Grignard reagent **2.64** occurred exclusively from the  $\beta$ -face due to the imposed axial position of the bulky isopropyl group, and trapping as the silyl enol ether with  $\text{TMSCl}$  was followed by  $\alpha$ -iodination with *m*-chloroperbenzoic acid and sodium iodide to generate **2.65**. The  $\alpha$ -keto radical 5-*exo*-dig cyclization was then accomplished under standard radical conditions and removal of the trimethylsilyl vinylsilane with trifluoroacetic acid afforded tricycle **2.66**. Oxidation of the

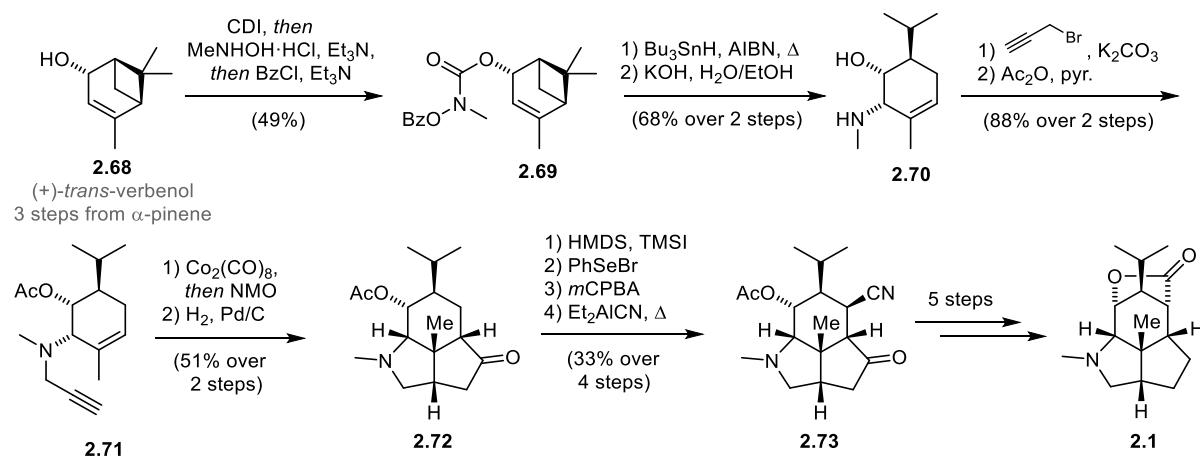
resulting system was achieved by elimination of an *m*CPBA-generated peroxyacetal to form the lactone, followed by  $\beta$ -face selective hydroboration/oxidation in which the ketone was also reduced, mesylation and azide displacement of the resulting alcohol, and regeneration of the ketone to finally yield azido alcohol **2.67**. The final pyrrolidine ring of the molecule was then formed by sequential Staudinger reaction, reduction of the engendered amine and *N*-methylation to accomplish the first asymmetric total synthesis of the *Orchidaceae* alkaloid.



**Scheme 2.8.** Sha's synthesis of (–)-dendrobine by  $\alpha$ -keto radical cyclization.

### Cassayre and Zard's synthesis of (–)-dendrobine

The synthesis of (–)-dendrobine by Cassayre and Zard is currently the shortest enantioselective total synthesis of the alkaloid (**Scheme 2.9**). (+)-*Trans*-verbenol **2.68**, available in three steps and 46% yield from  $\alpha$ -pinene, was transformed into *O*-benzoyl-*N*-hydroxycarbamate **2.69** in a one-pot procedure. An amidyl radical, generated from homolytic cleavage of the weak N–O bond, induced a radical cyclization/fragmentation cascade to furnish an oxazolidinone and an exocyclic isopropyl group. Hydrolysis of the oxazolidinone then afforded amino alcohol **2.70**.



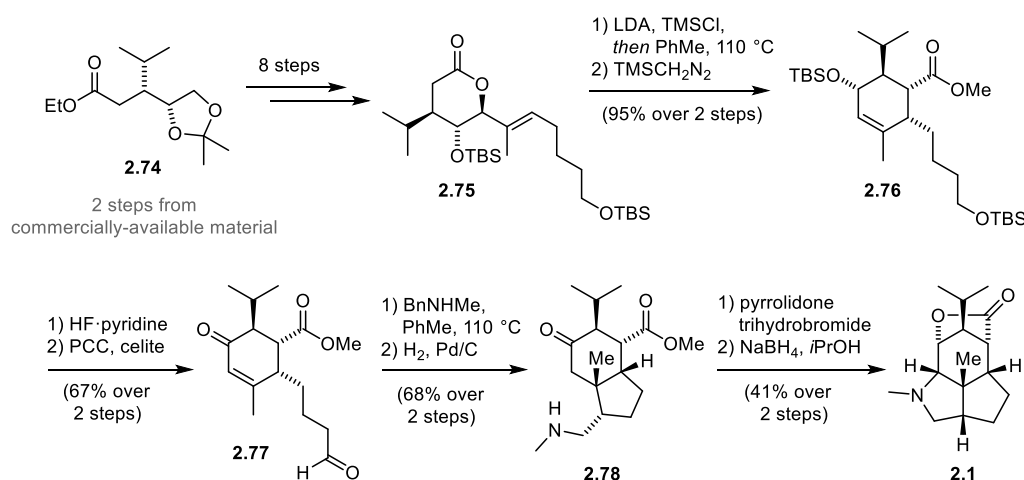
**Scheme 2.9.** Cassayre and Zard's synthesis of (–)-dendrobine by amidyl radical cyclization and PKR.



After attempts at a dichloroacetimide-based radical cyclization were thwarted,<sup>[150]</sup> the group instead proceeded with a Pauson–Khand strategy. Propargylation and acetylation yielded the desired precursor **2.71**. Treatment of the alkyne-Co<sub>2</sub>(CO)<sub>6</sub> complex with NMO affected the Pauson–Khand reaction and hydrogenation of the crude product granted tricycle **2.72**. Installation of the final carbon centre was carried out over four steps by ketone dehydrogenation through selenoxide elimination and hydrocyanation to give **2.73**. Subsequent erasure of the ketone, epimerization of the nitrile centre and acid-promoted cyclization/hydrolysis furnished **2.1** in a concise effort.

*Kreis and Carreira's total synthesis of (-)-dendrobine*

The most recent total synthesis of dendrobine was conducted asymmetrically by Kreis and Carreira in 2012 (**Scheme 2.10**). The starting diol **2.74** was generated from commercially-available ethyl (*R,E*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate by conjugate addition of 2-nitropropane and radical nitro group removal. Following expansion to lactone **2.75**, a high-yielding transannular Ireland–Claisen reaction formed the highly-substituted cyclohexane ring of dendrobine **2.76**. Double deprotection and oxidation of the primary and secondary alcohols yielded key precursor **2.77**. Addition of methylbenzylamine then induced enamine-Michael cyclization to form the second carbocycle, and in situ hydrogenation resulted in reductive incorporation of the pendant amine. The diastereoselectivity of the reduction is rationalized by concave protonation of the enamine following Michael addition and rapid reduction of the resulting iminium.  $\alpha$ -Bromination of ketone **2.78** with pyrrolidone hydrotribromide and displacement with the amine, reminiscent of Yamada's heterocycle formation (see **Scheme 2.3**), granted the pyrrolidine ring and the reduction/lactonization protocol developed by Kende then afforded **2.1**. The Carreira synthesis is currently the highest-yielding enantioselective total synthesis of dendrobine.



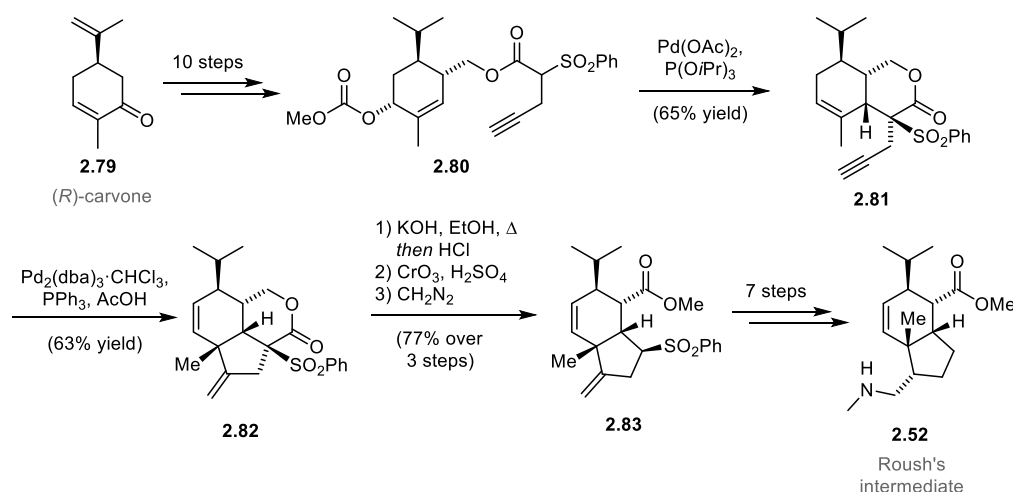
**Scheme 2.10.** Kreis and Carreira's synthesis of (-)-dendrobine by enamine-Michael addition.

### 2.1.4. Formal Syntheses of Dendrobine

A number of formal syntheses of dendrobine have been reported which intercept key intermediates of previous works, particularly those of Kende and Inubushi.

#### *Trost's formal synthesis of (-)-dendrobine*

The formal synthesis of (-)-dendrobine by Trost and colleagues in 1991 represents the first asymmetric pathway to the alkaloid (**Scheme 2.11**), courtesy of a chiral-pool approach from (*R*)-carvone **2.79**.<sup>[151]</sup> A multi-step derivatization of the carvone core afforded **2.80** and set the stage for a back-to-back palladium-catalyzed C-C bond formation. The first key step in the sequence was a Pd(0)-catalyzed allylic alkylation with a tethered sulfone ester, a reaction pioneered in part by the Trost group.<sup>[152]</sup> Interestingly, the allylic isomer of **2.80** – with the carbamate instead proximal and the olefin distal to the sulfone ester – was immune to the same reaction conditions, as was a derivative lacking the propargylic side-chain. The authors attribute the success of the reaction therefore to coordination between the alkyne tether and the palladium centre, which allows kinetic access of the catalyst to the olefin. The second reaction was a Pd(0)-catalyzed cycloisomerization to **2.82** which established the quaternary stereocenter of the molecule. After formation of these key carbon connections, saponification of the lactone and attendant decarboxylation was followed by oxidation and reaction with diazomethane to bicycle **2.83**. The final steps of the formal synthesis include hydroboration/oxidation of the olefin, epimerization of the resulting stereocenter by Swern oxidation/epimerization/reduction, erasure of the sulfone and finally displacement of a mesylate with methylamine to access Roush's intermediate **2.52**. As Roush's intermediate is five steps from dendrobine proper, the synthetic route is overall extensive but showcases exceptional resourcefulness and stereocontrol in its key steps.



**Scheme 2.11.** Trost's formal synthesis of (-)-dendrobine by dual Pd-catalyzed cyclizations.

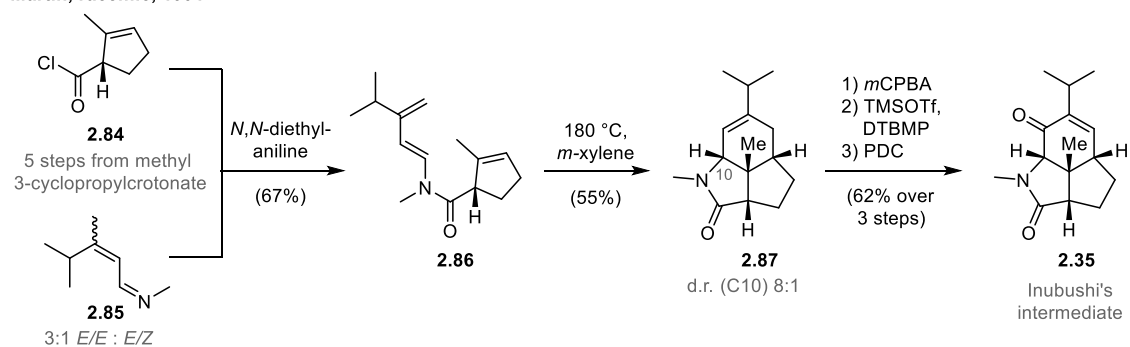
*Martin's, Mori's and Padwa's formal syntheses of dendrobine*

In the decade following Trost's efforts, a number of eminent formal syntheses of **2.1** were reported by several groups (**Scheme 2.12**). Publishing at the same time as Trost, Martin and Li presented a nicely convergent Diels–Alder strategy towards the molecule.<sup>[153-154]</sup> In contrast to the key Diels–Alder performed by Roush, Martin's pericyclic reaction was tethered through a more tenuous dienamine **2.86** formed by acylation of imine **2.85** with acyl chloride **2.84**. Optimization of the cycloaddition resulted in an 8:1 preference for the *endo* transition state and direct access to three stereocenters of aza[4.3.1.0]undecane core **2.87**. Intermediate **2.35** of Inubushi's synthesis could then be intercepted by simple epoxidation of the olefin, rearrangement to the allylic alcohol and oxidation to the enone.

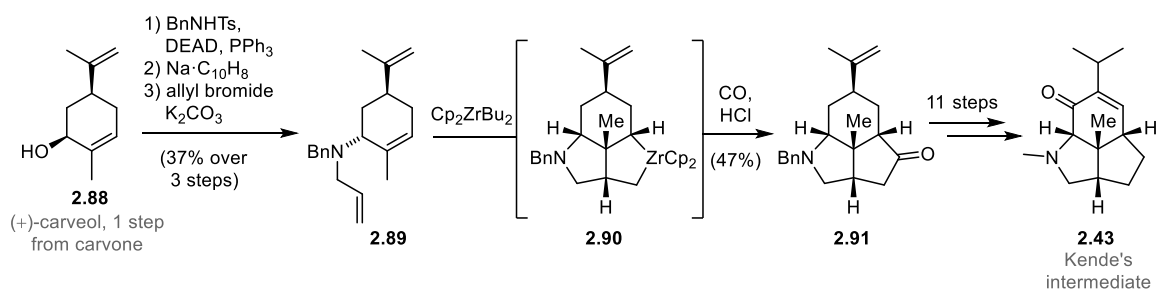
Mori and coworkers subsequently presented the second asymmetric path to (–)-dendrobine through a formal synthesis employing carveol as a starting material and a zirconium-mediated reductive cyclization as a key step.<sup>[155-156]</sup> As initial attempts at accessing chiral amine **2.89** from (–)-carveol through successive bromination/amination S<sub>N</sub>2 reactions resulted in almost complete racemization of the product, a Mitsunobu reaction between *N*-tosylbenzylamide and (+)-carveol **2.88** was employed in its stead. The zirconium-promoted diene cyclization was initiated by addition of Negishi reagent to **2.89** to give zirconocycle **2.90**, and subsequent stirring under carbon monoxide atmosphere and treatment with HCl successfully afforded tricycle **2.91**. This chiral pool approach therefore provided rapid access to the enantioenriched aza[4.3.1.0]undecane system. However, elaboration to Kende's intermediate **2.43** required an additional eleven steps of olefin isomerization and oxidative manipulations.

The group of Padwa reported a formal synthesis of the *Orchidaceae* alkaloid by means of an intramolecular amidofuran cycloaddition/rearrangement strategy.<sup>[157-159]</sup> The union of fragments **2.92** and **2.93**, generated expediently from ethyl dimethylacrylate and furfural<sup>[159]</sup> respectively, delivered amidofuran **2.94**. Intramolecular cycloaddition at 165 °C afforded tricyclic carbenamine **2.96** as an inconsequential 2:1 mixture of diastereomers, presumably through cycloadduct **2.95** and subsequent zwitterionic opening and 1,2-hydrogen shift. A series of functional group manipulations then conferred Kende's intermediate **2.43**.

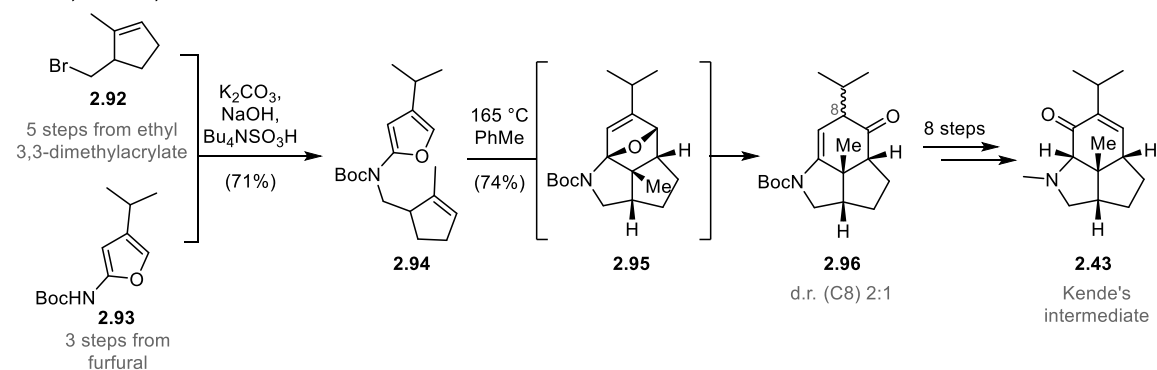
## Martin, racemic, 1991



## Mori, enantioselective, 1994



## Padwa, racemic, 2000

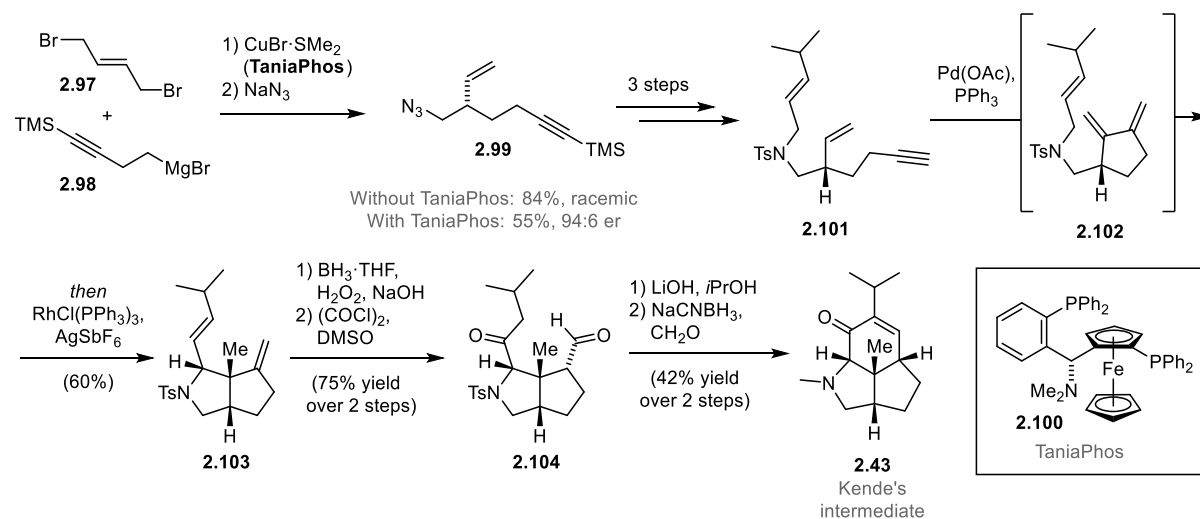


Scheme 2.12. Martin's, Mori's and Padwa's formal syntheses of dendrobine.

## Chen's formal synthesis of (±)-dendrobine

A final formal synthesis of dendrobine was accomplished very recently by Chen and colleagues and is conceptually different from its predecessors in that it uses a fully linear precursor to assemble the bicycloazaoctane system (Scheme 2.13).<sup>[160]</sup> The synthesis opened with a Cu(I)-catalyzed S<sub>N</sub>2' reaction between allyl bromide **2.97** and Grignard reagent **2.98**, followed by substitution of a bromide with sodium azide to furnish **2.99**. The S<sub>N</sub>2' reaction was conducted in a racemic fashion during the initial synthesis but could be rendered enantioselective by addition of the ferrocene ligand TaniaPhos (**2.100**).<sup>[161]</sup> The key step of the route hinged on sequential transition-metal-catalyzed cyclizations. A Pd-catalyzed enyne cycloisomerization generated triene **2.102**, which could be isolated or transformed immediately by addition of a Rh(I)-catalyst to initiate a highly diastereoselective diene-assisted C-H activation reaction.<sup>[162]</sup> This one pot procedure generated the bicyclic pyrrolidine **2.103** in good yield and as a single stereoisomer. An

impressively regioselective hydroboration/oxidation protocol to **2.104** followed by aldol condensation, tosyl elimination and reductive amination then provided Kende's intermediate **2.43** in 11 steps from commercial materials.

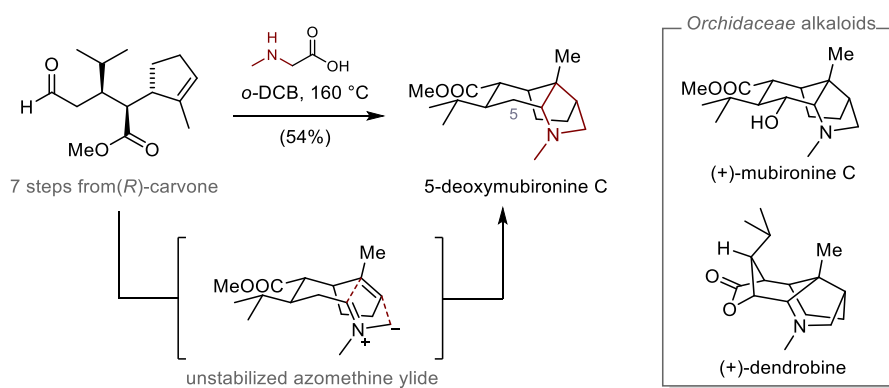


**Scheme 2.13.** Chen's formal synthesis of (±)-dendrobine through tandem Pd- and Rh-catalyzed cyclizations.

### 2.1.5. Project goals

As evidenced by these prior successes, dendrobine total synthesis is an exceptionally crowded field filled with many excellent methodologies and strategies. We too were drawn to the remarkable structure of dendrobine, largely due to the striking similarities between its azatricyclo[6.2.1.0<sup>4,11</sup>]undecane system and that of lycopalhine A (**1.7**). Importantly, we believed we could synthesize the molecule through an exceptionally efficient route that could be easily adapted to also afford mubironine C and dendrine. Outlined in the next section are our efforts towards the synthesis of this *Orchidaceae* alkaloid by means of an unstabilized azomethine ylide cycloaddition reaction.

## 2.2. Azomethine Ylide Cycloaddition Approach toward Dendrobine



Reprinted with permission from:

B. M. Williams and D. Trauner

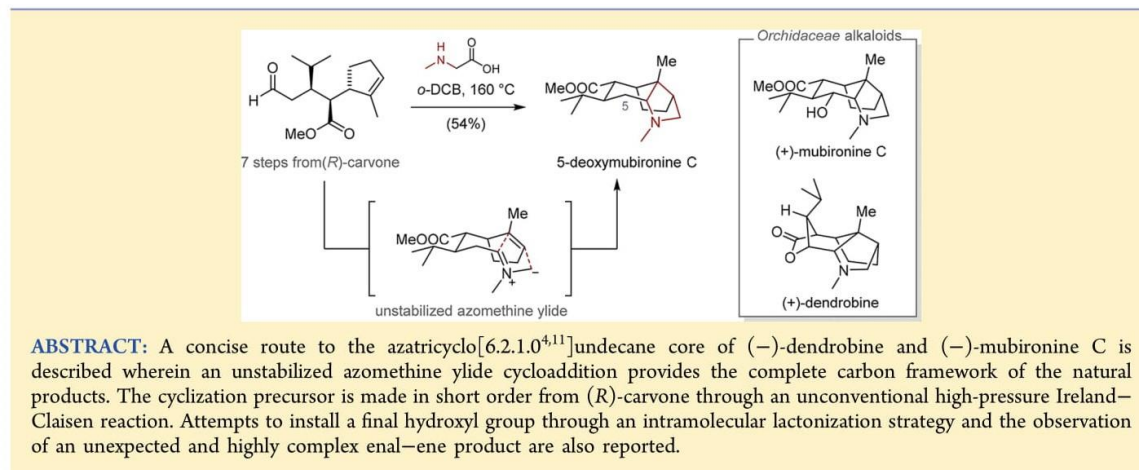
*J. Org. Chem.* **2018**, *83*, 3061 – 3068

DOI: 10.1021/acs.joc.8b00192

Copyright © 2018 American Chemical Society Publishing

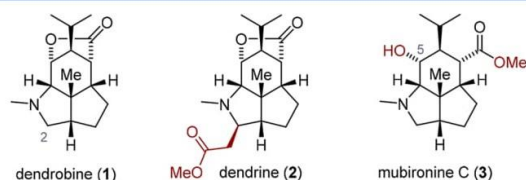
Azomethine Ylide Cycloaddition Approach toward Dendrobine:  
Synthesis of 5-Deoxymubirone CBenjamin M. Williams<sup>†</sup> and Dirk Trauner<sup>\*,†,‡,§</sup><sup>†</sup>Department of Chemistry Ludwig-Maximilians-Universität München Butenandtstrasse 5-13, 81377 München, Germany<sup>‡</sup>Department of Chemistry, New York University 100 Washington Square East, Room 712 New York, New York 10003, United States

Supporting Information



## INTRODUCTION

Dendrobine (**1**, Figure 1) is a sesquiterpenoid alkaloid isolated from the *Dendrobium nobile* and the major alkaloidal



**Figure 1.** Alkaloids isolated from the *Dendrobium nobile* (**1** and **2**) and *Dendrobium* Snowflake “Red Star” (**3**).

constituent of the Chinese folk medicine “Chin-Shih-Hu”.<sup>1–4</sup> The lactonic tetracycle exhibits analgesic, antipyretic, and convulsant activity<sup>5,6</sup> somewhat reminiscent of—though mechanistically unrelated to—picrotoxinin. A number of closely related congeners from similar orchid species have been identified which often differ in oxidation at the 2-position, as in dendrine (**2**),<sup>4</sup> or more rarely in methanolysis of the lactone, as in mubirone C (**3**).<sup>7</sup>

The broad bioactivity of **1**, its biogenetic kinship with the picrotoxanes, and its stereochemically crowded skeleton have made it the subject of numerous total<sup>8–15</sup> and formal<sup>16–20</sup> syntheses which have dissected the molecule in a variety of

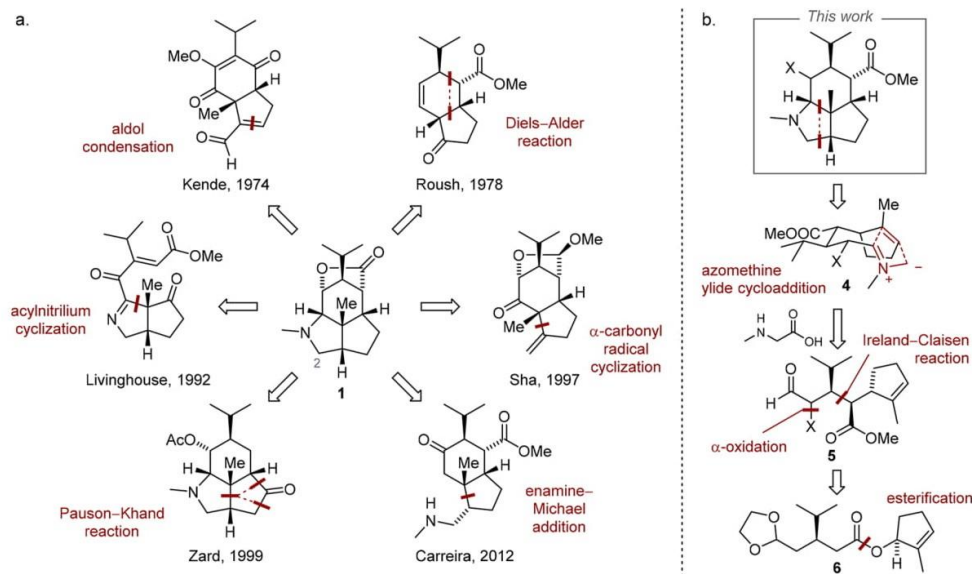
manners (Scheme 1a). Though thoughtful in strategy and inspiring in execution, many approaches require late-stage redox manipulation and/or incremental functional group interconversion. We initially sought a direct route to the molecule that would eliminate unnecessary reactions and constitute a path to synthetically underexplored Orchidaceae alkaloids. We report here the enantioselective synthesis of (–)-5-deoxymubirone C, which differs from the natural product mubirone C (**3**) by a single hydroxyl group, in eight operations from (*R*)-carvone. Notable transformations include a high-pressure Ireland–Claisen reaction and an intramolecular unstabilized azomethine ylide cycloaddition with an unactivated dipolarophile. An unusual ene reaction to form contiguous quaternary stereocenters is also reported.

Our retrosynthetic strategy (Scheme 1.b) centered on the disconnection of dendrobine’s pyrrolidine ring through an intramolecular 1,3-dipolar cycloaddition of an unstabilized azomethine ylide.<sup>21</sup> We posited that ylide **4** would be best formed by high temperature condensation/decarboxylation of sarcosine (*N*-methylglycine) or a related amino acid with  $\alpha$ -substituted aldehyde **5**.<sup>22</sup> As many dendrobine-like alkaloids vary in substitution at the 2-position, modifying the amino acid could thereby grant access to dendrine and other congeners. Though azomethine ylide cycloadditions between unstabilized

Received: January 22, 2018

Published: February 28, 2018

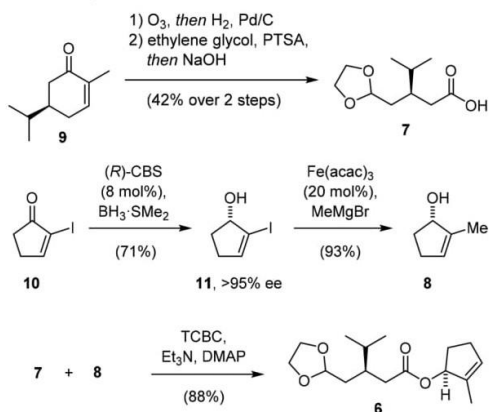


Scheme 1. (a) Key Intermediates in Previous Totals Syntheses of **1**. (b) Azomethine Ylide Strategy To Achieve the Azatricyclic Core

ylides and unactivated dipolarophiles are rare, we hoped the intramolecular nature of the reaction would overcome this reluctant reactivity.<sup>23</sup> We intended to use the wealth of new organocatalytic methodologies reported in the past 15 years to diastereoselectively functionalize the  $\alpha$ -position of the aldehyde. The contiguous stereocenters of **5** could be formed through an Ireland–Claisen rearrangement of ester **6**, which constitutes the union of two known and easily accessible fragments.

## RESULTS AND DISCUSSION

Our synthesis began with the construction of enantioenriched units **7** and **8** (Scheme 2). Acid **7** could be formed in two steps from (*R*)-carvotanacetone **9**<sup>24</sup> using a modified protocol by Deslongchamps et al. in which the monoterpene was treated with ozone and the resulting aldehyde acetalized to dioxolane

Scheme 2. Synthesis of Ester **6**<sup>a</sup>

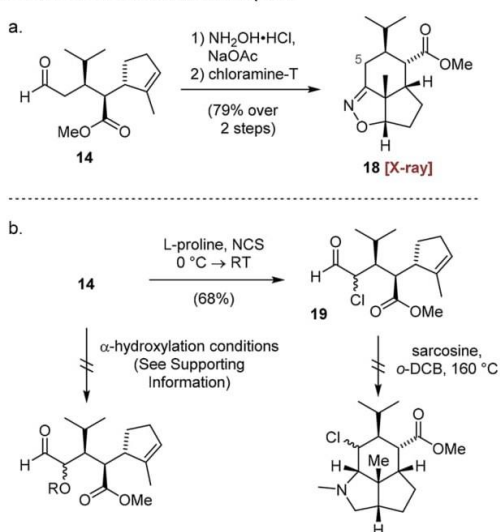
<sup>a</sup>TCBC = 1,3,5-trichlorobenzoyl chloride.

7.<sup>25</sup> Although the asymmetric reduction of commercially available 2-methyl-2-cyclopentenone directly to **8** is known,<sup>26</sup> difficulties were encountered with the high catalyst loadings required for good enantioselectivity (up to one full equivalent) and the volatility of the product. A more scalable route ensued from the Itsuno–Corey reduction of iodoenone **10** to grant **11** with excellent enantiomeric purity (>95% ee by Mosher ester analysis),<sup>27</sup> followed by iron-catalyzed cross-coupling with methylmagnesium bromide<sup>28</sup> to afford alcohol **8** in good yield. The best results for formation of **6** were attained using 1,3,5-trichlorobenzoyl chloride (TCBC), triethylamine, and a 1:1 molar ratio of reactants.

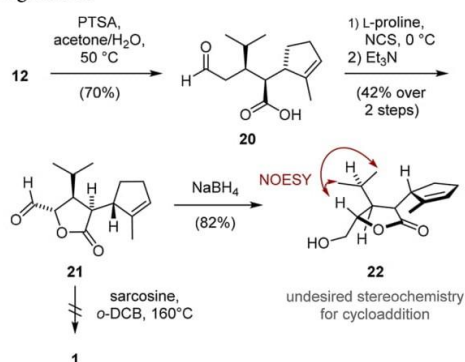
The Ireland–Claisen reaction of ester **6** proved to be challenging (Table 1). It quickly became apparent that conventional Ireland–Claisen conditions only afforded very low yields of product **12** (relative configuration confirmed by single-crystal X-ray diffraction) and its undesired diastereomer **13** (entry 1). Higher temperatures and hexamethyldisilamide bases resulted in increased conversion (entries 2 and 3), but yields were still disabligingly low due to extrusion of the cyclopentenol and ketene formation. When alternative silylating agents and additives failed to enhance the yield, we reasoned that ketene formation might be subdued through high-pressure conditions. Although high-pressure Claisen reactions are well-documented, we could only locate one instance of an Ireland–Claisen reaction conducted under high-pressure conditions in tandem with a Diels–Alder reaction, and the authors specify that these high-pressure conditions were chosen mainly to effect the Diels–Alder reaction.<sup>29</sup> Submitting the silyl ketene acetal to high pressure alone (11 kbar) resulted in trace conversion (entry 4). However, a combination of both elevated pressure and temperature proved highly effective and led to enhanced yield and good diastereoselectivity (entry 5). Upon scale-up, LiHMDS was determined to be the base of choice for the reaction (entries 6 and 7).





Scheme 4. (a) Synthesis of 18. (b) Attempts at Cyclization with Linear  $\alpha$ -Oxidized Aldehydes

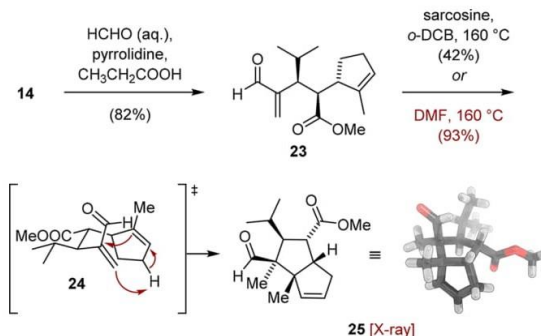
Scheme 5. Synthesis of Oxopentanolide 21 with Unfavorable Configuration



to acid aldehyde **20**, which was  $\alpha$ -chlorinated to yield an unstable chloride. The crude product was then treated with triethylamine to afford oxopentanolide **21** through an intramolecular  $S_N2$  reaction. However, reduction to alcohol **22** and 2D-NMR analysis of the product indicated that the aldehyde had immediately and fully epimerized to the convex face of the lactone. This rendered an intramolecular cycloaddition unlikely barring an epimerization of the stereocenter to the clearly disfavored face following ylide formation. Indeed, submitting **21** to our established conditions was ineffective as decomposition outcompeted epimerization.

Our second strategy was to equip aldehyde **14** with an  $\alpha$ -methylene group to block tautomerization during azomethine ylide formation and to proffer a synthetic handle following dipolar cycloaddition (Scheme 6). Enal **23** was first synthesized in good yield,<sup>38</sup> but submitting **23** to our model conditions unexpectedly resulted in the isolation of bicyclo[3.3.0]octene **25**. It was quickly determined that simply heating the precursor in DMF gave **25** in excellent yield. Based on the relative configuration of the system according to single-crystal X-ray

Scheme 6. Unexpected Ene Cyclization of Enal 23



diffraction, the bicycle likely arises from an ene reaction between the enal and the trisubstituted olefin through transition state **24**. The simplicity and efficiency of this reaction in creating contiguous quaternary stereocenters is noteworthy.

In summary, our initial efforts toward the synthesis of Orchidaceae alkaloids have resulted in a short, enantioselective synthesis of (–)-5-deoxymubironine **C** (**15**) through an unstabilized azomethine ylide cycloaddition. We have additionally demonstrated the effectiveness of high-pressure conditions in mediating a challenging Ireland–Claisen reaction and uncovered an exceptional enal–ene reaction to form a densely substituted bicyclo[3.3.0]octane system. As our current synthetic route supplies practical amounts of compound **15**, we are currently engaged in the oxidation of the C5 position via transition-metal-catalyzed C–H activation and enzymatic hydroxylation.

## EXPERIMENTAL SECTION

**General Experimental Details.** Unless otherwise stated, all reactions were performed with magnetic stirring under a positive pressure of nitrogen or argon gas. Oven-dried glassware (oven temperature of 100 °C) was further dried with a heat-gun at 650 °C under vacuum, followed by backfilling with inert gas, three times and fitted with rubber septa prior to use for moisture-sensitive reactions. Tetrahydrofuran (THF) and diethyl ether (Et<sub>2</sub>O) were distilled over sodium benzophenone under nitrogen atmosphere prior to use. Dichloromethane (CH<sub>2</sub>Cl<sub>2</sub>), triethylamine (Et<sub>3</sub>N), and chlorotrimethylsilane (TMSCl) were distilled over calcium hydride under a nitrogen atmosphere. *N,N*-Dimethylformamide (DMF), toluene (PhMe), and methanol (MeOH) were purchased from Acros Organics as “extra dry” reagents under inert gas atmosphere and stored over molecular sieves. Solvents used for extraction and flash column chromatography were purchased as technical grade and distilled under reduced pressure (ethyl acetate (EtOAc), pentane, Et<sub>2</sub>O) or purchased as HPLC grade (CH<sub>2</sub>Cl<sub>2</sub>, acetone, MeOH). All other solvents and reagents were used as received from commercial sources (Sigma-Aldrich, Tokyo Chemical Industry Co., Alfa Aesar, Acros Organics, Strem Chemicals). Reactions were monitored by thin-layer chromatography (TLC) using silica gel F254 precoated glass plates (Merck) and visualized by exposure to ultraviolet light ( $\lambda = 254$  nm) or by staining with aqueous potassium permanganate (KMnO<sub>4</sub>) or aqueous acidic ceric ammonium molybdate (IV) (CAM) solution. Flash column chromatography was performed using silica gel (60 E, 40–63  $\mu$ m, Merck) and a forced flow of eluent. High-pressure reactions were performed using a high-pressure apparatus (max 14 kbar, piston 25 mm) from Andreas Hofer Hochdrucktechnik GmbH equipped with a Julabo MA-4 heating circulator.

Proton (<sup>1</sup>H) and carbon (<sup>13</sup>C) nuclear magnetic resonance spectra were recorded on a Bruker Avance III HD 400 MHz spectrometer equipped with a CryoProbe, a Varian VXR400 S spectrometer, or a



Bruker AMX600 spectrometer. Proton chemical shifts are expressed in parts per million (ppm,  $\delta$  scale) and referenced to residual undeuterated solvent signals (CDCl<sub>3</sub>: 7.26 ppm). Carbon chemical shifts are expressed in parts per million (ppm,  $\delta$  scale) and referenced to the central carbon resonance of the solvent (CDCl<sub>3</sub>: 77.16 ppm). The reported data is represented as follows: chemical shift in parts per million (ppm,  $\delta$  scale) (multiplicity, coupling constants  $J$  in Hz, integration intensity). Abbreviations used for analysis of multiplets are as follows: s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (hexet), and m (multiplet). IR spectra were recorded on a PerkinElmer Spectrum BXII FTIR spectrometer equipped with an attenuated total reflection (ATR) measuring unit. IR data are recorded as frequency of absorption (wavenumber in cm<sup>-1</sup>) with bands described as weak (w), medium (m), strong (s), broad (br), and combinations thereof. Mass spectrometry (MS) experiments were performed at high resolution on a Thermo Finnigan MAT 95 (electron ionization [EI] double-focusing magnetic sector mass spectrometer) or on a Thermo Finnigan LTQ FT (electrospray ionization [ESI] linear ion trap-based Fourier transform ion cyclotron resonance mass spectrometer) instrument at the Ludwig-Maximilians-Universität mass spectrometry facility. Optical rotation values were measured on a Krüss P8000–P8100-T polarimeter equipped with a sodium lamp.

**Synthesis of (R)-3-((1,3-Dioxolan-2-yl)methyl)-4-methylpentanoic Acid (7).** Acid 7 was prepared using a modified procedure by Deslongchamps et al.<sup>25</sup> A stream of ozone was bubbled through a solution of (R)-carvotanacetone 9 (5.02 g, 33.0 mmol, 1.0 equiv) in EtOAc (90 mL) at -78 °C until a deep blue color persisted (approximately 25 min). Nitrogen was passed through the solution until the blue color dissipated, and the mixture was warmed to ambient temperature while nitrogen was bubbled through. The solution was then cooled to 0 °C, and palladium on charcoal (10% w/w, 70.2 mg, 65.9  $\mu$ mol, 0.2 mol %) was added. The vessel was purged with a hydrogen gas balloon for 5 min and then stirred under hydrogen atmosphere (balloon pressure) for 6 h at 0 °C. The mixture was filtered through Celite and concentrated to afford a crude yellow oil which was used without further purification.

The crude oil was dissolved in benzene (30 mL), and ethylene glycol (10.2 mL, 165 mmol, 5.0 equiv) and *p*-toluenesulfonic acid monohydrate (0.628 g, 3.30 mmol, 10 mol %) were added. The flask was equipped with a Dean–Stark trap and a reflux condenser, and the mixture was heated to reflux for 6 h. After the mixture was cooled to ambient temperature, benzene was removed under reduced pressure and 1 M NaOH (60 mL) was added. The biphasic mixture was stirred vigorously for 18 h. The aqueous layer was washed with Et<sub>2</sub>O (3  $\times$  100 mL), cooled to 0 °C, and acidified to pH 3 with 1 M HCl. The resulting cloudy layer was extracted with Et<sub>2</sub>O (3  $\times$  100 mL), and the combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (30% EtOAc in pentane) to afford acid 7 (2.78 g, 13.8 mmol, 42% over two steps) as a pale yellow oil. The <sup>1</sup>H NMR spectrum is in accordance with that previously reported in literature.<sup>25</sup> *R*<sub>f</sub>: 0.38 (30% EtOAc in pentane + 0.5% v/v acetic acid, stains with KMnO<sub>4</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  11.13 (br s, 1H), 4.90 (t,  $J$  = 4.8 Hz, 1H), 3.97 (m, 2H), 3.83 (m, 2H), 2.46 (dd,  $J$  = 15.8, 6.7 Hz, 1H), 2.35 (d,  $J$  = 15.8, 6.7 Hz, 1H), 2.05 (m,  $J$  = 8.7, 4.3, 2.2 Hz, 1H), 1.88–1.70 (m, 2H), 1.55 (ddd,  $J$  = 14.1, 8.7, 5.2 Hz, 1H), 0.89 (d,  $J$  = 6.0 Hz, 3H), 0.87 (d,  $J$  = 5.9 Hz, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  179.9, 104.1, 65.0, 64.7, 36.6, 36.3, 34.7, 30.5, 19.1, 18.7. IR (ATR):  $\tilde{\nu}$  = 3024 (br w), 2959 (m), 2877 (m), 1703 (s), 1466 (w), 1411 (m), 1389 (m), 1370 (m), 1280 (m), 1220 (m), 1132 (s), 1101 (m), 1042 (m), 944 (m), 825 (w). HRMS (ESI): calcd for C<sub>10</sub>H<sub>19</sub>O<sub>4</sub><sup>+</sup> [M + H<sup>+</sup>] 203.1278, found 203.1277. [ $\alpha$ ]<sub>D</sub><sup>20</sup> = -2.2 ( $c$  = 1.14, CHCl<sub>3</sub>).

**Synthesis of (S)-2-Methylcyclopent-2-enol (8).** Iodide 11 (7.02 g, 33.4 mmol, 1.0 equiv) was dissolved in THF (174 mL) and NMP (29.0 mL), and the resulting solution was cooled to 0 °C with an ice bath. Fe(acac)<sub>3</sub> (2.36 g, 6.69 mmol, 0.20 equiv) was added in one portion, and the bright orange suspension was stirred for 10 min. Methylmagnesium bromide (33.4 mL, 3 M in Et<sub>2</sub>O, 3.0 equiv) was

then added in a steady flow over the course of 5 min as a constant evolution of gas was observed. Following addition, the ice bath was removed and the dark brown mixture was stirred for 25 min at ambient temperature. Aqueous pH 7 phosphate buffer (100 mL) was carefully added to the mixture, and the aqueous phase was extracted with Et<sub>2</sub>O (3  $\times$  100 mL). The combined organic phases were washed with brine (80 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure (no lower than 200 mbar at 30 °C to prevent evaporation of product). The crude product was purified by flash column chromatography (30% Et<sub>2</sub>O in pentane) to afford cyclopentenone 8 (3.06 g, 31.2 mmol, 93%) as a pale yellow oil. Due to the volatile nature of the alcohol, diethyl ether (3.5 wt%) and THF (<2 wt%) are present in the product. The <sup>1</sup>H NMR spectrum is in accordance with that previously reported in literature.<sup>39</sup> <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  5.53 (m, 1H), 4.58 (m, 1H), 2.47–2.26 (m, 2H), 2.21 (m, 1H), 1.77 (m, 3H), 1.69 (ddt,  $J$  = 13.2, 8.8, 4.4 Hz, 1H), 1.39 (br s, 1H).

**Synthesis of (S)-2-Methylcyclopent-2-en-1-yl (R)-3-((1,3-Dioxolan-2-yl)methyl)-4-methylpentanoate (6).** Triethylamine (7.73 mL, 55.4 mmol, 2.0 equiv) and 2,4,6-trichlorobenzoyl chloride (5.20 mL, 33.3 mmol, 1.2 equiv) were added sequentially to a vigorously stirring solution of acid 7 (5.60 g, 27.7 mmol, 1.0 equiv) in THF (100 mL) at ambient temperature. The solution was stirred at ambient temperature for 1 h, where it became cloudy. Alcohol 8 (2.72 g, 27.7 mmol, 1.0 equiv) and DMAP (339 mg, 2.77 mmol, 0.10 equiv) in THF (20 mL) were then added to the suspension, and the flask was sealed with a Teflon cap and allowed to stir at ambient temperature for 17 h. Saturated aqueous ammonium chloride solution (80 mL) was added to the resulting bright yellow suspension, and the aqueous phase was extracted with EtOAc (3  $\times$  80 mL). The combined organic phases were washed with brine (80 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (7  $\rightarrow$  8% EtOAc in pentane) to afford ester 6 (6.88 g, 24.3 mmol, 88%) as a pale yellow oil. *R*<sub>f</sub>: 0.39 (10% EtOAc in pentane, stains with KMnO<sub>4</sub> and CAM). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  5.64 (s, 1H), 5.57 (m, 1H), 4.89 (t,  $J$  = 5.0 Hz, 1H), 3.95 (m, 2H), 3.82 (m, 2H), 2.48–2.18 (m, 5H), 2.06 (ddt,  $J$  = 8.6, 6.8, 4.6 Hz, 1H), 1.83–1.67 (m, 6H), 1.53 (ddd,  $J$  = 13.9, 8.5, 5.2 Hz, 1H), 0.87 (d,  $J$  = 6.9 Hz, 3H), 0.86 (d,  $J$  = 6.9 Hz, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  173.7, 138.2, 130.8, 104.2, 82.2, 64.9, 64.7, 36.9, 36.8, 34.9, 31.1, 30.5, 30.4, 19.1, 18.7, 13.9. IR (ATR):  $\tilde{\nu}$  = 2958 (m), 2876 (m), 1726 (s), 1457 (w), 1437 (m), 1412 (m), 1370 (m), 1334 (m), 1304 (m), 1210 (w), 1149 (s), 1103 (m), 1045 (m), 1024 (s), 979 (m), 955 (m), 920 (w), 834 (w), 712 (w). HRMS (EI): calcd for C<sub>16</sub>H<sub>26</sub>O<sub>4</sub> [M] 282.1818, found 282.1831. [ $\alpha$ ]<sub>D</sub><sup>20</sup> = -40.8 ( $c$  = 1.3, CHCl<sub>3</sub>).

**Synthesis of (2S,3S)-3-((1,3-Dioxolan-2-yl)methyl)-4-methyl-2-((S)-2-methylcyclopent-2-en-1-yl)pentanoic Acid (12).** Ester 6 (765 mg, 2.71 mmol, 1.0 equiv) in toluene (2.5 mL) was added dropwise to a solution of LiHMDS (3.53 mL, 1 M in THF, 1.3 equiv) in toluene (7 mL) at -78 °C. The pale orange mixture was stirred for 1 h at this temperature, whereupon freshly distilled TMSCl (516  $\mu$ L, 4.07 mmol, 1.5 equiv) was added dropwise. The mixture was stirred at -78 °C for 15 min and was then allowed to gradually warm to ambient temperature over 30 min. The resulting cloudy mixture was transferred to two 10 mL high-pressure containers (washing the original vessel with 3 mL PhMe), and the containers were subjected to 14 kbar of pressure at 70 °C for 21 h. Upon returning to ambient pressure and temperature, the contents of the containers were poured into saturated aqueous ammonium chloride solution (40 mL) and Et<sub>2</sub>O (40 mL). The aqueous layer was separated and further extracted with Et<sub>2</sub>O (2  $\times$  40 mL), and the combined organic layers were washed with brine (40 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (10  $\rightarrow$  15% EtOAc in pentane with added 0.5% v/v acetic acid) afforded acid 12 (578 mg, 2.05 mmol, 76%) and acid 13 (46.8 mg, 0.166 mmol, 6%) as pale yellow foams.

**12.** *R*<sub>f</sub>: 0.32 (25% EtOAc in pentane, stains with KMnO<sub>4</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  11.22 (bs, 1H), 5.39 (s, 1H), 4.97 (t,  $J$  = 4.9 Hz, 1H), 4.00 (m, 2H), 3.87 (m, 2H), 3.12 (q,  $J$  = 8.4 Hz, 1H), 2.41 (dd,  $J$



= 9.5, 4.9 Hz, 1H), 2.23–1.94 (m, 5H), 1.85 (ddd,  $J = 14.9, 10.1, 4.9$  Hz, 1H), 1.73 (dt,  $J = 14.5, 4.4$  Hz, 1H), 1.67 (s, 3H), 1.56 (dq,  $J = 12.4, 8.7$  Hz, 1H), 0.94 (d,  $J = 6.9$  Hz, 3H), 0.76 (d,  $J = 6.7$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  180.0, 142.6, 127.0, 104.5, 65.1, 64.8, 50.6, 46.9, 39.8, 30.8, 30.2, 30.1, 26.4, 23.5, 17.1, 16.1. IR (ATR):  $\tilde{\nu} = 3030$  (br w), 2956 (m), 2890 (m), 1699 (s), 1441 (w), 1413 (w), 1391 (w), 1370 (w), 1206 (m), 1140 (m), 1098 (m), 1041 (m), 968 (w), 943 (m), 839 (w), 799 (w). HRMS (ESI): calcd for  $\text{C}_{16}\text{H}_{25}\text{O}_4^- [\text{M} - \text{H}^+]$  281.1758, found 281.1761.  $[\alpha]_{\text{D}}^{20} = +5.2$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).

13.  $R_f$ : 0.21 (25% EtOAc in pentane, stains with  $\text{KMnO}_4$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.32 (s, 1H), 4.88 (t,  $J = 5.3$  Hz, 1H), 3.92 (m, 2H), 3.79 (m, 2H), 2.82 (m, 1H), 2.63 (dd,  $J = 10.1, 4.5$  Hz, 1H), 2.27–2.10 (m, 3H), 2.04–1.86 (m, 3H), 1.77 (dt,  $J = 14.9, 5.1$  Hz, 1H), 1.72 (s, 3H), 1.49 (dt,  $J = 14.9, 5.1$  Hz, 1H), 0.96 (d,  $J = 6.7$  Hz, 3H), 0.80 (d,  $J = 6.7$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  181.0, 140.4, 126.7, 104.5, 64.8, 64.7, 50.4, 48.7, 38.8, 33.5, 31.3, 27.7, 24.4, 20.9, 16.5, 15.1. IR (ATR):  $\tilde{\nu} = 3428$  (br w), 3039 (w), 2958 (m), 2876 (m), 1727 (s), 1464 (m), 1441 (m), 1389 (m), 1371 (m), 1207 (m), 1127 (s), 1089 (s), 1045 (s), 986 (m), 960 (s), 948 (s), 794 (m), 732 (m). HRMS (ESI): calcd for  $\text{C}_{16}\text{H}_{25}\text{O}_4^- [\text{M} - \text{H}^+]$  281.1758, found 281.1760.  $[\alpha]_{\text{D}}^{20} = +3.2$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).

**Synthesis of Methyl (2*S*,3*S*)-3-Isopropyl-2-((*S*)-2-methylcyclopent-2-en-1-yl)-5-oxopentanoate (14).** Trimethylsilyldiazomethane (1.32 mL, 2.0 M in hexanes, 1.2 equiv) was added dropwise to a solution of acid **12** (623 mg, 2.21 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (14.4 mL) and MeOH (1.6 mL) at 0 °C. The solution was allowed to warm to ambient temperature and stirred for 50 min, whereupon acetic acid (50  $\mu\text{L}$ ) was added to quench excess diazomethane and the solution was concentrated under reduced pressure to afford crude methyl ester. The oil was dissolved in acetone (18 mL) and  $\text{H}_2\text{O}$  (2.0 mL), and *p*-toluenesulfonic acid monohydrate (420 mg, 2.21 mmol, 1.0 equiv) was added. The flask was capped with a Teflon stopper and heated to 60 °C for 75 min, cooled to ambient temperature, and concentrated to ~4 mL total volume under reduced pressure. The sample was loaded directly onto a silica column and purified by flash column chromatography (8% Et<sub>2</sub>O in pentane) to afford aldehyde **14** (378 mg, 1.50 mmol, 68% over two steps) as a colorless oil.

$R_f$ : 0.36 (10% Et<sub>2</sub>O in pentane, stains with  $\text{KMnO}_4$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.74 (m, 1H), 5.32 (p,  $J = 2.0$  Hz, 1H), 3.62 (s, 3H), 2.90 (q,  $J = 7.9$  Hz, 1H), 2.58–2.45 (m, 2H), 2.42 (t,  $J = 6.9$  Hz, 1H), 2.32 (ddd,  $J = 16.3, 4.3, 1.8$  Hz, 1H), 2.14 (m, 2H), 2.02 (dtd,  $J = 12.5, 8.0, 4.2$  Hz, 1H), 1.85 (pd,  $J = 6.9, 2.5$  Hz, 1H), 1.73 (m, 1H), 1.60 (s, 3H), 0.85 (d,  $J = 6.9$  Hz, 3H), 0.70 (d,  $J = 6.9$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  202.3, 175.2, 141.5, 127.5, 51.4, 50.5, 47.8, 41.8, 37.7, 30.4, 29.0, 28.0, 22.6, 17.0, 15.9. IR (ATR):  $\tilde{\nu} = 3037$  (w), 2953 (m), 2720 (w), 1723 (s), 1456 (m), 1435 (m), 1371 (m), 1248 (m), 1230 (m), 1190 (m), 1161 (s), 1139 (m), 1105 (w), 1024 (m), 799 (w). HRMS (ESI): calcd for  $\text{C}_{15}\text{H}_{25}\text{O}_3 [\text{M} + \text{H}^+]$  253.1798, found 253.1805.  $[\alpha]_{\text{D}}^{20} = +31.8$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).

**Synthesis of Methyl (2*aS*,2*a'R*,4*aS*,5*S*,6*S*,7*aR*)-6-Isopropyl-1,2*a'*-dimethyldecahydro-1*H*-cyclopenta[*cd*]indole-5-carboxylate (15).** A 250 mL Schlenk flask was charged with a stir bar, 4 Å molecular sieves (freshly activated by heating to 650 °C at  $5 \times 10^{-2}$  mbar for 10 min, then backfilling with N<sub>2</sub> and repeating three times), sarcosine (393 mg, 4.41 mmol, 10.0 equiv), and *o*-dichlorobenzene (32 mL) and was submerged to the solvent line in a 160 °C oil bath. Aldehyde **14** (111 mg, 0.441 mmol, 1.0 equiv) in *o*-dichlorobenzene (6 mL) was added over the course of 2 h by means of a syringe pump. The suspension was stirred for an additional 4 h at 160 °C, then cooled to ambient temperature, filtered through cotton with Et<sub>2</sub>O (30 mL), and concentrated by rotary evaporator (heat bath set to 70 °C to remove *o*-dichlorobenzene following ether removal). Purification of the residue by column chromatography (2 → 4% MeOH/ $\text{CH}_2\text{Cl}_2$ ) afforded amine **15** as a pale yellow oil (74.1 mg, 0.265 mmol) in 54% yield.  $R_f$ : 0.26 (4% MeOH in  $\text{CH}_2\text{Cl}_2$ , stains with  $\text{KMnO}_4$  and CAM).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  3.63 (s, 3H), 2.71 (d,  $J = 9.2$  Hz, 1H), 2.58 (dd,  $J = 12.0, 5.5$  Hz, 1H), 2.31 (t,  $J = 8.6$  Hz, 1H), 2.09–1.97 (m, 6H), 1.90–1.62 (m, 5H), 1.54 (dd,  $J = 12.5, 6.4$  Hz, 1H), 1.23 (dt,  $J = 11.9, 6.2$  Hz, 1H), 1.16 (s, 3H), 1.15–1.06 (m, 1H), 0.92 (d,  $J = 6.9$  Hz, 3H), 0.74 (d,  $J = 6.9$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$

175.8, 73.0, 66.1, 51.2, 49.9, 49.4, 48.7, 47.0, 40.7, 33.9, 31.6, 30.4, 28.0, 26.4, 22.1, 21.5, 15.5. IR (ATR):  $\tilde{\nu} = 2948$  (s), 2867 (m), 2768 (m), 1737 (s), 1651 (w), 1455 (m), 1367 (w), 1344 (w), 1272 (w), 1245 (m), 1231 (w), 1207 (m), 1160 (s), 1141 (m), 1109 (m), 1044 (w), 1024 (w), 951 (w), 925 (w), 872 (w), 803 (w). HRMS (ESI): Calc. for  $\text{C}_{17}\text{H}_{30}\text{O}_2\text{N} [\text{M} + \text{H}^+]$  280.2271, found 280.2276.  $[\alpha]_{\text{D}}^{20} = -64.8$  ( $c = 0.50$ ,  $\text{CHCl}_3$ ).

**Synthesis of Methyl (3*S*,4*S*)-4-Isopropyl-1-methyl-3-((*S*)-2-methylcyclopent-2-en-1-yl)piperidin-2-one (16).** An oven-dried pressure tube was charged with aldehyde **14** (36.1 mg, 0.143 mmol, 1.0 equiv), sarcosine (127 mg, 1.43 mmol, 10.0 equiv), and *m*-xylene (1.4 mL). The tube was sealed with a Teflon cap, and the rapidly stirring suspension was heated at 150 °C for 75 min when gas evolution had ceased and all suspended sarcosine had been visibly consumed. The mixture was cooled to ambient temperature, additional sarcosine (127 mg, 1.43 mmol, 10.0 equiv) was added, and the tube was once more sealed and heated to 150 °C for 75 min. This process was repeated twice more for a total of 40 equiv of sarcosine. The mixture was then cooled to rt and concentrated under reduced pressure. Purification of the crude reaction mixture by column chromatography (first column: 2 → 4% MeOH/ $\text{CH}_2\text{Cl}_2$ , second column: 20 → 30% EtOAc/pent) afforded amine **15** as a pale yellow oil (9.3 mg, 0.033 mmol, 24%) and lactam **16** as a colorless oil (10.7 mg, 0.0455 mmol, 32% yield).  $R_f$ : 0.24 (30% EtOAc in pentane, stains with  $\text{KMnO}_4$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.48 (s, 1H), 3.27 (m, 2H), 2.86 (s, 3H), 2.70 (br s, 2H), 2.43 (m, 1H), 2.25–2.07 (m, 2H), 1.95–1.82 (m, 2H), 1.78–1.66 (m, 2H), 1.58 (s, 3H), 1.58–1.52 (m, 1H), 0.95 (d,  $J = 6.5$  Hz, 3H), 0.91 (d,  $J = 6.6$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  172.4, 141.3, 128.36, 48.9, 48.8, 46.0, 43.9, 35.2, 34.2, 30.7, 27.9, 22.1, 21.8, 20.4, 16.6. IR (ATR):  $\tilde{\nu} = 3036$  (w), 2954 (m), 2872 (m), 1736 (w), 1644 (s), 1502 (m), 1440 (m), 1399 (m), 1369 (w), 1342 (m), 1241 (m), 1110 (w), 1026 (w), 990 (w), 922 (w), 795 (w). HRMS (ESI): calcd for  $\text{C}_{15}\text{H}_{26}\text{ON} [\text{M} + \text{H}^+]$  236.2009, found 236.2011.  $[\alpha]_{\text{D}}^{20} = +112$  ( $c = 0.80$ ,  $\text{CHCl}_3$ ).

**Synthesis of Methyl (2*a'S*,4*S*,5*S*,5*aS*,7*aS*)-4-Isopropyl-2*a'*-methyl-2*a'*,3,4,5,5*a*,6,7,7*a*-octahydroindeno[7,1-*cd*]isoxazole-5-carboxylate (18).** Sodium acetate (256 mg, 3.48 mmol, 5.0 equiv) and hydroxylamine hydrochloride (194 mg, 2.79 mmol, 4.0 equiv) were added sequentially to a solution of aldehyde **14** (176 mg, 0.696 mmol, 1.0 equiv) in MeOH (12 mL) at ambient temperature. The mixture was stirred for 30 min at ambient temperature, where thin-layer chromatography analysis indicated complete conversion. The mixture was concentrated to ~2 mL using a stream of nitrogen gas and then partitioned between water (25 mL) and Et<sub>2</sub>O (25 mL). The aqueous layer was separated and further extracted with Et<sub>2</sub>O (2 × 25 mL), and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford crude oxime, which was used without further purification. The residue was dissolved in EtOH (10 mL), and silica gel (400 mg) and chloramine-T trihydrate (392 mg, 1.39 mmol, 2.0 equiv) were added sequentially at ambient temperature. The mixture was stirred for 45 min and additional silica gel (1.5 g) was added to the mixture. The suspension was concentrated to dryness and loaded onto silica gel column. Purification by flash column chromatography (30% Et<sub>2</sub>O in pentane) afforded isoxazoline **18** (147 mg, 0.553 mmol, 79%) as a white solid.  $R_f$ : 0.38 (30% Et<sub>2</sub>O in pentane, stains faintly with  $\text{KMnO}_4$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  4.52 (d,  $J = 6.1$  Hz, 1H), 3.67 (s, 3H), 2.80 (dd,  $J = 11.9, 4.6$  Hz, 1H), 2.54 (dd,  $J = 12.8, 4.0$  Hz, 1H), 2.24 (dt,  $J = 10.6, 5.6$  Hz, 1H), 2.07–1.86 (m, 3H), 1.76 (pd,  $J = 6.9, 2.6$  Hz, 1H), 1.70–1.54 (m, 2H), 1.48 (m, 1H), 1.36 (s, 3H), 0.94 (d,  $J = 6.9$  Hz, 3H), 0.85 (d,  $J = 6.9$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  174.4, 159.9, 90.3, 60.8, 51.8, 50.4, 44.6, 40.4, 35.0, 28.8, 26.3, 21.2, 20.4, 19.7, 15.6. IR (ATR):  $\tilde{\nu} = 2956$  (m), 2889 (w), 2845 (w), 1726 (s), 1453 (w), 1438 (m), 1374 (m), 1348 (m), 1334 (w), 1251 (w), 1205 (m), 1187 (w), 1162 (s), 1052 (w), 986 (m), 952 (w), 866 (w), 850 (m), 777 (w), 718 (w). HRMS (ESI): calcd for  $\text{C}_{15}\text{H}_{24}\text{O}_3\text{N} [\text{M} + \text{H}^+]$  266.1751, found 266.1751.  $[\alpha]_{\text{D}}^{20} = -54.0$  ( $c = 0.53$ ,  $\text{CHCl}_3$ ). Mp: 120–122 °C.

**Synthesis of Methyl (2*R*,3*S*)-4-Chloro-3-isopropyl-2-((*S*)-2-methylcyclopent-2-en-1-yl)-5-oxopentanoate (19).** *L*-Proline



(2.8 mg, 0.024 mmol, 30 mol %) was added to a solution of aldehyde **14** (20.2 mg, 0.0801 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (1.0 mL) at 0 °C. After the solution was stirred for 15 min, *N*-chlorosuccinimide (11.8 mg, 0.0881 mmol, 1.1 equiv) was added in one portion. The mixture was stirred for 1 h at 0 °C, allowed to warm to ambient temperature, and stirred for an additional 20 h. The mixture was diluted with pentane (15 mL), and the organic layer was washed with saturated aqueous ammonium chloride solution (10 mL), saturated aqueous sodium bicarbonate solution (10 mL), and brine (10 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (50%  $\text{CH}_2\text{Cl}_2$  in pentane) afforded chloride **19** (15.7 mg, 0.0547 mmol, 68%) as a colorless oil.  $^1\text{H}$  NMR analysis indicates a 1.1:1 mixture of diastereomers.

*R<sub>f</sub>*: 0.27 (6%  $\text{Et}_2\text{O}$  in pentane, stains with  $\text{KMnO}_4$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.60 (d,  $J = 1.5$  Hz, 1H), 9.54 (d,  $J = 3.2$  Hz, 1H), 5.44–5.37 (m, 2H), 4.68 (dd,  $J = 4.4, 1.5$  Hz, 1H), 4.38 (dd,  $J = 6.4, 3.2$  Hz, 1H), 3.67 (s, 6H), 3.03 (m, 1H), 2.91 (t,  $J = 6.6$  Hz, 1H), 2.83 (m, 1H), 2.74 (t,  $J = 6.5$  Hz, 1H), 2.65 (m, 1H), 2.51 (td,  $J = 6.4, 2.2$  Hz, 2H), 2.26–2.07 (m, 7H), 2.00 (m, 1H), 1.79 (m, 1H), 1.69 (s, 3H), 1.64 (s, 3H), 1.04 (d,  $J = 7.0$  Hz, 3H), 1.00 (d,  $J = 7.0$  Hz, 3H), 0.91 (d,  $J = 7.0$  Hz, 3H), 0.86 (d,  $J = 7.0$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  196.2, 195.6, 174.7, 174.1, 141.4, 141.4, 128.1, 128.1, 66.0, 65.1, 51.8, 51.7, 49.3, 48.5, 48.2, 47.7, 46.6, 46.6, 31.1, 30.5, 30.3, 29.4, 28.7, 27.9, 23.3, 22.4, 20.9, 17.4, 16.3, 16.1. IR (ATR):  $\tilde{\nu} = 2952$  (m), 2855 (w), 1732 (s), 1457 (m), 1435 (m), 1373 (m), 1192 (m), 1162 (s), 1051 (w), 1024 (w), 972 (w), 802 (w), 734 (w). HRMS (ESI): calcd for  $\text{C}_{14}\text{H}_{21}\text{O}_3$  [ $\text{M} + \text{H}^+$ ] 287.1409, found 287.1409.

**Synthesis of (2S,3S)-3-Isopropyl-2-((S)-2-methylcyclopent-2-en-1-yl)-5-oxopentanoic Acid (20).** *p*-Toluenesulfonic acid monohydrate (131 mg, 0.686 mmol, 1.0 equiv) was added to a solution of dioxolane **12** (194 mg, 0.686 mmol, 1.0 equiv) in acetone (12 mL) and  $\text{H}_2\text{O}$  (1.5 mL) at ambient temperature. The flask was sealed with a Teflon cap, heated to 50 °C for 4 h, cooled to ambient temperature, and concentrated to ~2 mL total volume under reduced pressure. The sample was loaded directly onto a silica column and purified by flash column chromatography (10% → 12% → 15% acetone in pentane) to afford aldehyde **20** (115 mg, 0.483 mmol, 70%) as a colorless oil. *R<sub>f</sub>*: 0.50 (20% acetone in pentane, stains with CAM).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.79 (t,  $J = 1.4$  Hz, 1H), 5.38 (s, 1H), 2.98 (m, 1H), 2.66 (ddd,  $J = 17.3, 6.8, 1.5$  Hz, 1H), 2.57 (tdd,  $J = 7.7, 6.8, 5.9, 2.6$  Hz, 1H), 2.48 (dd,  $J = 7.5, 6.4$  Hz, 1H), 2.39 (ddd,  $J = 17.3, 5.2, 1.8$  Hz, 1H), 2.20 (m, 2H), 2.09 (ddd,  $J = 12.4, 8.1, 3.8$  Hz, 1H), 1.95 (pd,  $J = 6.8, 2.6$  Hz, 1H), 1.81 (m, 1H), 1.69 (s, 3H), 0.91 (d,  $J = 6.8$  Hz, 3H), 0.80 (d,  $J = 6.8$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  202.3, 181.5, 141.3, 127.8, 50.3, 48.0, 41.7, 37.6, 30.5, 28.8, 28.3, 22.7, 17.1, 16.0. IR (ATR):  $\tilde{\nu} = 3020$  (br w), 3039 (w), 2959 (m), 2720 (w), 1723 (s), 1699 (s), 1442 (w), 1416 (w), 1391 (m), 1370 (m), 1250 (m), 1204 (m), 1135 (w), 1106 (w), 1024 (w), 928 (w), 800 (w). HRMS (ESI): calcd for  $\text{C}_{14}\text{H}_{21}\text{O}_3$  [ $\text{M} - \text{H}^+$ ] 237.1496, found 237.1498.  $[\alpha]_{\text{D}}^{20} = +29.0$  ( $c = 1.00, \text{CHCl}_3$ ).

**Synthesis of (2S,3S,4R)-3-Isopropyl-4-((S)-2-methylcyclopent-2-en-1-yl)-5-oxotetrahydrofuran-2-carbaldehyde (21).** *L*-Proline (7.2 mg, 0.038 mmol, 1.0 equiv) and *N*-chlorosuccinimide (10.1 mg, 0.0754 mmol, 1.2 equiv) were added simultaneously to a solution of aldehyde **20** (15.0 mg, 0.0628 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (1.0 mL) at 0 °C. The mixture was stirred for 50 min at 0 °C and then loaded onto a silica gel column and eluted with 10%  $\text{EtOAc}$  in pentane +1% v/v  $\text{AcOH}$ . The fractions containing the chloride were concentrated under reduced pressure. The oil was dissolved in  $\text{CH}_2\text{Cl}_2$  (1.0 mL), and  $\text{Et}_3\text{N}$  (13.1  $\mu\text{L}$ , 0.0942 mmol, 1.5 equiv) was added at ambient temperature. The mixture was stirred for 10 min, concentrated, and purified by flash column chromatography (30%  $\text{EtOAc}$  in pentane) to afford oxopentanolide **21** (6.2 mg, 26  $\mu\text{mol}$ , 42% over two steps) as a colorless oil. *R<sub>f</sub>*: 0.28 (30%  $\text{EtOAc}$  in pentane, stains with  $\text{KMnO}_4$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.79 (s, 1H), 5.46 (p,  $J = 1.8, 1.3$  Hz, 1H), 4.58 (d,  $J = 1.3$  Hz, 1H), 2.88 (m, 1H), 2.62 (ddd,  $J = 8.2, 3.1, 1.7$  Hz, 1H), 2.55 (t,  $J = 8.4$  Hz, 1H), 2.31–2.12 (m, 4H), 1.88 (s, 3H), 1.68 (m, 1H), 1.02 (d,  $J = 6.8$  Hz, 3H), 0.91 (d,  $J = 6.8$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  199.5,

176.8, 141.9, 128.1, 80.8, 47.1, 45.3, 44.3, 30.6, 30.5, 26.1, 22.0, 17.9, 17.1. IR (ATR):  $\tilde{\nu} = 3039$  (w), 2964 (m), 2858 (m), 1782 (s), 1737 (s), 1467 (w), 1444 (w), 1377 (w), 1351 (w), 1241 (w), 1176 (m), 1138 (m), 1118 (m), 1048 (m), 1024 (m), 934 (m), 884 (w), 804 (w), 658 (w). HRMS (ESI): calcd for  $\text{C}_{14}\text{H}_{21}\text{O}_3$  [ $\text{M} + \text{H}^+$ ] 237.1485, found 237.1485.  $[\alpha]_{\text{D}}^{20} = +44$  ( $c = 0.50, \text{CHCl}_3$ ).

**Synthesis of (3R,4S,5S)-5-(Hydroxymethyl)-4-isopropyl-3-((S)-2-methylcyclopent-2-en-1-yl)dihydrofuran-2(3H)-one (22).** Sodium borohydride (7.9 mg, 0.21 mmol, 2.0 equiv) was added to a solution of oxopentanolide **21** (25.0 mg, 0.106 mmol) in  $\text{MeOH}$  (2.0 mL) at 0 °C. After the solution was stirred for 30 min at this temperature, saturated aqueous ammonium chloride solution (3 mL) and  $\text{Et}_2\text{O}$  (3 mL) were added, and the biphasic mixture was stirred vigorously for 10 min. The aqueous phase was separated and further extracted with  $\text{Et}_2\text{O}$  ( $2 \times 3$  mL), and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (15 → 20 → 25%  $\text{EtOAc}$  in pentane) to afford hydroxypentanolide **22** (20.7 mg, 0.0877 mmol, 82%) as a colorless oil. *R<sub>f</sub>*: 0.32 (30%  $\text{EtOAc}$  in pentane, stains with  $\text{KMnO}_4$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.46 (s, 1H), 4.36 (dt,  $J = 5.8, 3.6$  Hz, 1H), 3.83 (dd,  $J = 12.2, 3.6$  Hz, 1H), 3.69 (dd,  $J = 12.3, 5.8$  Hz, 1H), 2.95 (t,  $J = 8.2$  Hz, 1H), 2.88 (m, 1H), 2.35–2.14 (m, 4H), 2.09 (pd,  $J = 6.8, 4.2$  Hz, 1H), 1.88 (s, 3H), 1.75 (m, 1H), 0.94 (d,  $J = 6.8$  Hz, 3H), 0.90 (d,  $J = 6.8$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  178.5, 141.9, 128.1, 79.4, 64.7, 45.9, 45.9, 44.8, 31.1, 30.5, 26.0, 22.1, 18.0, 17.1. IR (ATR):  $\tilde{\nu} = 3438$  (br m), 3038 (w), 2962 (s), 2875 (m), 1769 (s), 1466 (m), 1394 (m), 1376 (m), 1358 (m), 1240 (m), 1223 (m), 1176 (m), 1157 (m), 1063 (m), 1021 (m), 996 (m), 928 (w), 806 (w), 674 (w). HRMS (ESI): Calc. for  $\text{C}_{15}\text{H}_{23}\text{O}_5$  [ $\text{M} + \text{HCOO}^-$ ] 283.1551, found 283.1554.  $[\alpha]_{\text{D}}^{20} = +60.8$  ( $c = 1.0, \text{CHCl}_3$ ).

**Synthesis of Methyl (2R,3S)-4-Formyl-3-isopropyl-2-((S)-2-methylcyclopent-2-en-1-yl)pent-4-enoate (23).** Formaldehyde (37% in  $\text{H}_2\text{O}$ , 31.0  $\mu\text{L}$ , 0.415 mmol, 2.0 equiv), propionic acid (3.1  $\mu\text{L}$ , 42  $\mu\text{mol}$ , 0.2 equiv), and pyrrolidine (3.4  $\mu\text{L}$ , 42  $\mu\text{mol}$ , 0.2 equiv) were added sequentially to a solution of aldehyde **12** (52.3 mg, 0.207 mmol, 1.0 equiv) in *i*PrOH (2.0 mL) at ambient temperature. The flask was sealed with a Teflon cap, and the stirring mixture was heated to 45 °C for 6 h. Upon cooling to ambient temperature, the mixture was poured into  $\text{CH}_2\text{Cl}_2$  (10 mL) and saturated aqueous sodium bicarbonate (10 mL). The aqueous phase was separated and further extracted with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 10$  mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (5%  $\text{Et}_2\text{O}$  in pentane) to afford enal **23** (44.7 mg, 0.169 mmol, 82%) as a white solid. *R<sub>f</sub>*: 0.44 (10%  $\text{Et}_2\text{O}$  in pentane, stains with  $\text{KMnO}_4$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.51 (s, 1H), 6.22 (s, 1H), 6.20 (s, 1H), 5.31–5.24 (m, 1H), 3.65 (s, 3H), 3.37 (dd,  $J = 12.1, 4.3$  Hz, 1H), 2.97 (dd,  $J = 12.1, 2.6$  Hz, 1H), 2.58 (m, 1H), 2.17–1.97 (m, 3H), 1.92–1.81 (m, 2H), 1.69 (s, 3H), 0.74 (d,  $J = 6.9$  Hz, 3H), 0.70 (d,  $J = 6.9$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  194.7, 174.7, 148.3, 141.0, 136.9, 128.1, 52.1, 51.5, 48.9, 41.7, 30.8, 30.1, 29.7, 21.8, 16.9, 16.6. IR (ATR):  $\tilde{\nu} = 3036$  (w), 2958 (m), 2856 (m), 2700 (w), 1732 (s), 1693 (s), 1619 (w), 1435 (m), 1388 (m), 1370 (m), 1320 (w), 1227 (m), 1210 (m), 1190 (m), 1159 (s), 1092 (m), 1024 (w), 953 (m), 811 (w). HRMS (ESI): calcd for  $\text{C}_{16}\text{H}_{25}\text{O}_3$  [ $\text{M} + \text{H}^+$ ] 265.1798, found 265.1798.  $[\alpha]_{\text{D}}^{20} = +15$  ( $c = 1.0, \text{CHCl}_3$ ). Mp: 72–73 °C.

**Synthesis of Aldehyde Methyl (1R,2S,3S,3aS,6aS)-3-Formyl-2-isopropyl-3,3a-dimethyl-1,2,3,3a,6,6a-hexahydrofuran-2-ene-1-carboxylate (25).** A pressure tube was charged with enal **23** (40.1 mg, 0.152 mmol, 1.0 equiv) and DMF (5.0 mL), and the sealed vessel was heated to 160 °C for 4 h. Upon cooling to ambient temperature, the solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (8%  $\text{Et}_2\text{O}$  in pentane) to afford cyclopentanone **25** (37.5 mg, 0.142 mmol, 93%) as a white solid. *R<sub>f</sub>*: 0.30 (10%  $\text{Et}_2\text{O}$  in pentane, stains with  $\text{KMnO}_4$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.76 (s, 1H), 5.68 (dt,  $J = 5.6, 2.4$  Hz, 1H), 5.50 (ddd,  $J = 5.4, 2.4, 1.2$  Hz, 1H), 3.70 (s, 3H), 3.32 (t,  $J = 11.6$  Hz, 1H), 2.83 (dd,  $J = 11.6, 7.5$  Hz, 1H), 2.59 (dddd,  $J = 17.6, 7.5, 2.4, 1.2$  Hz,



1H), 2.14 (dd,  $J = 11.6, 6.9$  Hz, 1H), 2.03 (ddt,  $J = 17.6, 2.4, 1.2$  Hz, 1H), 1.59 (octet,  $J = 6.9$  Hz, 1H), 1.20 (s, 3H), 0.95 (s, 3H), 0.88 (d,  $J = 6.9$  Hz, 3H), 0.78 (d,  $J = 6.9$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  206.6, 175.0, 135.3, 130.3, 62.6, 61.9, 57.6, 51.7, 50.5, 47.7, 36.4, 28.4, 23.4, 21.2, 20.3, 16.3. IR (ATR):  $\tilde{\nu} = 3061$  (w), 2960 (m), 2901 (w), 2874 (w), 1722 (vs), 1454 (m), 1435 (m), 1383 (m), 1372 (m), 1341 (w), 1290 (w), 1207 (m), 1190 (s), 1174 (m), 1142 (m), 1123 (w), 1038 (w), 964 (m), 793 (w), 726 (m). HRMS (EI): calcd for  $\text{C}_{16}\text{H}_{24}\text{O}_3$  [M] 264.1725, found 264.1720.  $[\alpha]_{\text{D}}^{20} = -68.4$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ). Mp: 75–76 °C.

## ■ ASSOCIATED CONTENT

### ■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b00192.

$^1\text{H}$  and  $^{13}\text{C}$  spectra for all new compounds (PDF)

X-ray data for compounds 12, 18, and 25 (CIF)

## ■ AUTHOR INFORMATION

### Corresponding Author

\*E-mail: dirktrauner@nyu.edu.

### ORCID

Dirk Trauner: 0000-0002-6782-6056

### Notes

The authors declare no competing financial interest.

X-ray data for compounds 12 (CCDC 1817623), 18 (CCDC 1817624), and 25 (CCDC 1817621) are also available free from charge from the Cambridge Crystallographic Data Centre (<https://www.ccdc.cam.ac.uk/structures/>).

## ■ ACKNOWLEDGMENTS

Financial support from the Deutsche Forschungsgemeinschaft (SFB749) and a fellowship from the Natural Sciences and Engineering Research Council of Canada for B.M.W. are gratefully acknowledged. The authors would like to thank Benjamin Bissinger for experimental support, Dr. Peter Mayer for X-ray analysis, and Annabelle Hoegl, Dr. Felix Hartrampf, Daniel Terwilliger, and Dr. Julius Reyes for assistance during the preparation of this manuscript.

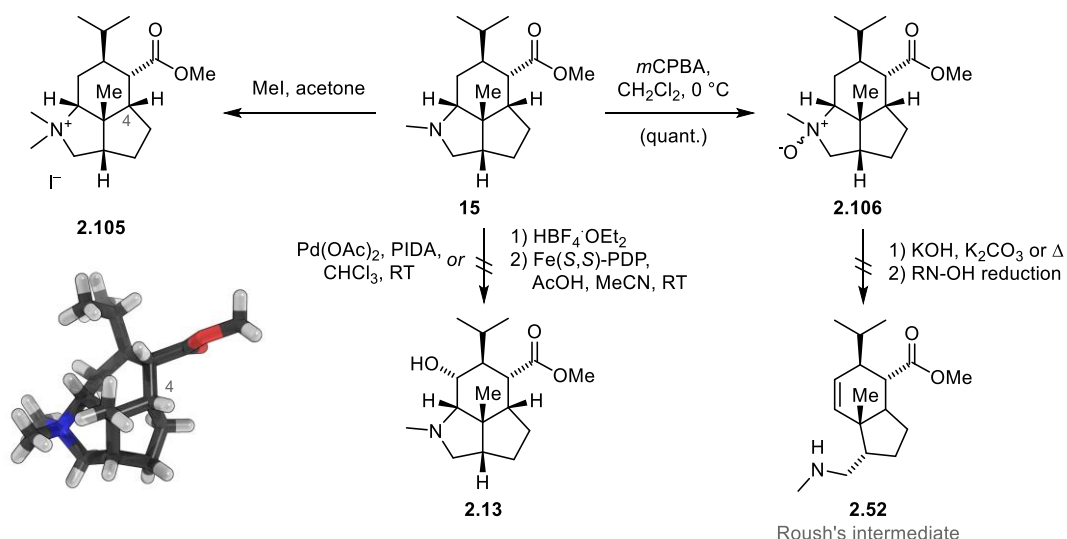
## ■ REFERENCES

- (1) Suzuki, H.; Keimatsu, I. *Yakugaku Zasshi* **1932**, *52*, 1049.
- (2) Suzuki, H.; Keimatsu, I.; Ito, K. *Yakugaku Zasshi* **1934**, *54*, 801.
- (3) Inubushi, Y.; Sasaki, Y.; Tsuda, Y.; Yasui, B.; Konita, T.; Matsumoto, J.; Katarao, E.; Nakano, J. *Tetrahedron* **1964**, *20*, 2007.
- (4) Inubushi, Y.; Nakano, J. *Tetrahedron Lett.* **1965**, *6*, 2723.
- (5) Chen, K. K.; Chen, A. L. *J. Biol. Chem.* **1935**, *111*, 653.
- (6) Chen, K. K.; Chen, A. L. *J. Pharmacol. Exp. Ther.* **1935**, *55*, 319.
- (7) Morita, H.; Fujiwara, M.; Yoshida, N.; Kobayashi, J. *Tetrahedron* **2000**, *56*, 5801.
- (8) Inubushi, Y.; Kikuchi, T.; Ibuka, T.; Tanaka, K.; Saji, I.; Tokane, K. *J. Chem. Soc., Chem. Commun.* **1972**, 1252.
- (9) Yamada, K.; Suzuki, M.; Hayakawa, Y.; Aoki, K.; Nakamura, H.; Nagase, H.; Hirata, Y. *J. Am. Chem. Soc.* **1972**, *94*, 8278.
- (10) Kende, A. S.; Bentley, T. J.; Mader, R. A.; Ridge, D. *J. Am. Chem. Soc.* **1974**, *96*, 4332.
- (11) Roush, W. R. *J. Am. Chem. Soc.* **1978**, *100*, 3599.
- (12) Lee, C. H.; Westling, M.; Livinghouse, T.; Williams, A. C. *J. Am. Chem. Soc.* **1992**, *114*, 4089.
- (13) Sha, C.-K.; Chiu, R.-T.; Yang, C.-F.; Yao, N.-T.; Tseng, W.-H.; Liao, F.-L.; Wang, S.-L. *J. Am. Chem. Soc.* **1997**, *119*, 4130.
- (14) Cassayre, J.; Zard, S. Z. *J. Am. Chem. Soc.* **1999**, *121*, 6072.
- (15) Kreis, L. M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3436.

- (16) Trost, B. M.; Tasker, A. S.; Ruther, G.; Brandes, A. *J. Am. Chem. Soc.* **1991**, *113*, 670.
- (17) Martin, S. F.; Li, W. *J. Org. Chem.* **1991**, *56*, 642.
- (18) Padwa, A.; Dimitroff, M.; Liu, B. *Org. Lett.* **2000**, *2*, 3233.
- (19) Uesaka, N.; Saitoh, F.; Mori, M.; Shibasaki, M.; Okamura, K.; Date, T. *J. Org. Chem.* **1994**, *59*, 5633.
- (20) Lee, Y.; Rochette, E. M.; Kim, J.; Chen, D. Y. K. *Angew. Chem., Int. Ed.* **2017**, *56*, 12250.
- (21) Smith, R.; Livinghouse, T. *J. Org. Chem.* **1983**, *48*, 1554.
- (22) Grigg, R.; Idle, J.; McMeekin, P.; Vipond, D. *J. Chem. Soc., Chem. Commun.* **1987**, 49.
- (23) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765.
- (24) Shipe, W. D.; Sorensen, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 7025.
- (25) Deslongchamps, P.; Bélanger, A.; Berney, D. J. F.; Borschberg, H.-J.; Brousseau, R.; Doutheau, A.; Durand, R.; Katayama, H.; Lapalme, R.; Leturc, D. M.; Liao, C.-C.; MacLachlan, F. N.; Maffrand, J.-P.; Marazza, F.; Martino, R.; Moreau, C.; Ruest, L.; Saint-Laurent, L.; Sainonge, R.; Soucy, P. *Can. J. Chem.* **1990**, *68*, 127.
- (26) Robertson, J.; Meo, P.; Dallimore, J. W. P.; Doyle, B. M.; Hoarau, C. *Org. Lett.* **2004**, *6*, 3861.
- (27) Chattopadhyay, A. K.; Ly, V. L.; Jakkepally, S.; Berger, G.; Hanessian, S. *Angew. Chem., Int. Ed.* **2016**, *55*, 2577.
- (28) Cahiez, G.; Avedissian, H. *Synthesis* **1998**, 1998, 1199.
- (29) Velker, J.; Roblin, J. P.; Neels, A.; Tesouro, A.; Stoeckli-Evans, H.; Klaerner, F.-G.; Gehrke, J.-S.; Neier, R. *Synlett* **1999**, 1999, 925.
- (30) Seidel, D. *Acc. Chem. Res.* **2015**, *48*, 317.
- (31) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808.
- (32) Kano, T.; Mii, H.; Maruoka, K. *J. Am. Chem. Soc.* **2009**, *131*, 3450.
- (33) Beshara, C. S.; Hall, A.; Jenkins, R. L.; Jones, T. C.; Parry, R. T.; Thomas, S. P.; Tomkinson, N. C. O. *Chem. Commun.* **2005**, 1478.
- (34) Beshara, C. S.; Hall, A.; Jenkins, R. L.; Jones, K. L.; Jones, T. C.; Killeen, N. M.; Taylor, P. H.; Thomas, S. P.; Tomkinson, N. C. O. *Org. Lett.* **2005**, *7*, 5729.
- (35) Vaismaa, M. J. P.; Yau, S. C.; Tomkinson, N. C. O. *Tetrahedron Lett.* **2009**, *50*, 3625.
- (36) Simonovich, S. P.; Van Humbeck, J. F.; MacMillan, D. W. C. *Chem. Sci.* **2012**, *3*, 58.
- (37) Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790.
- (38) Erkkilä, A.; Pihko, P. M. *J. Org. Chem.* **2006**, *71*, 2538.
- (39) Becker, N.; Carreira, E. M. *Org. Lett.* **2007**, *9*, 3857.

### 2.3. Unpublished Efforts toward *Orchidaceae* Alkaloids

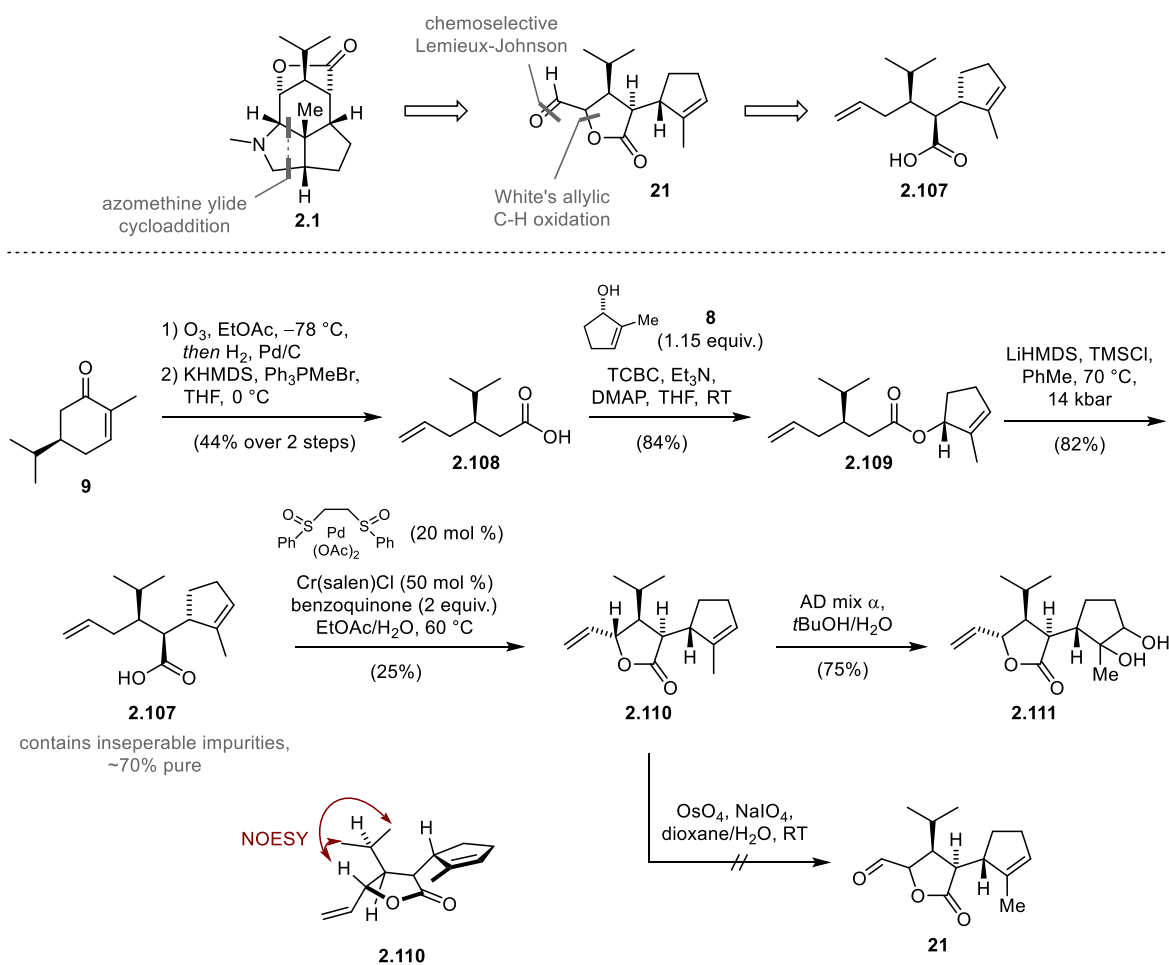
Additional research not described in the above publication is covered in the following section. Synthetic studies were performed with tricycle **15** (numbering from *J. Org. Chem.* **2018**, *83*, 3061) to firmly establish relative configuration as well as to attempt to intercept literature-known intermediates in a formal synthesis. First, reaction of **15** with methyl iodide yielded salt **2.105**, which could be crystallized out of a CH<sub>2</sub>Cl<sub>2</sub>/pentane mixture (**Scheme 2.14**). Single-crystal X-ray diffraction confirmed unequivocally that the desired configuration at the C4 stereocenter was formed during the [3+2]-cycloaddition. We then generated the *N*-oxide of **15** (**2.106**) using *m*CPBA and attempted to perform a Hoffman elimination/*N*-O reduction sequence to compound **2.52**. This would intercept an intermediate in Roush's work and thus constitute a formal synthesis of (–)-dendrobine. The Hoffman elimination, however, was unsuccessful in all attempted conditions and generally only resulted in auto-reduction back to the amine. Attempts to oxidize the C5-position by C-H activation to **2.13** using conditions by White<sup>[163]</sup> and Sanford<sup>[164]</sup> have thus far led to no reaction or complex mixtures of products.



**Scheme 2.14.** Formation of ammonium iodide **2.105**, attempts at C-H activation and Hoffman elimination.

Before we successfully generated compound **21** by  $\alpha$ -chlorination/lactonization, we had attempted an alternate route to this compound using an allylic C-H oxidation strategy from **2.107** (**Scheme 2.15**).<sup>[165-167]</sup> To this end, we began our synthesis anew from **9**. Following ozonolysis of the enone, the crude aldehyde/acid was treated with methyltriphenylphosphonium bromide and KHMDS to give olefin **2.108**. Esterification with **8** using previously established conditions afforded ester **2.109**. We submitted the ester to our optimized high-pressure Ireland–Claisen conditions. Though one major product was formed, it could not be cleanly separated from its diastereomer and certain undesired byproducts. Regardless, we assigned the major product as **2.109** by analogy with literature and our previous Ireland–Claisen product and carried it through the next reaction in hopes that the impurities could then be separated. White's bis-sulfoxide Pd-catalyst

conditions<sup>[165-167]</sup> were attempted for the lactonization and, after some initial screening, we found that using ethyl acetate as solvent at 60 °C led to the formation of lactone **2.110** in low yield. Unfortunately, it quickly became clear that Lemieux-Johnson protocols and other dihydroxylations selectively targeted the trisubstituted olefin rather than the terminal double-bond. NOESY correlations also indicated that the allyl stereocenter was the undesired configuration for intramolecular cycloaddition even if the oxidative cleavage were successful. It was at this point that we discovered the more robust  $\alpha$ -chlorination/lactonization pathway to **21** and abandoned this route.



**Scheme 2.15.** First-generation route to aldehyde **21** by allylic C-H activation.



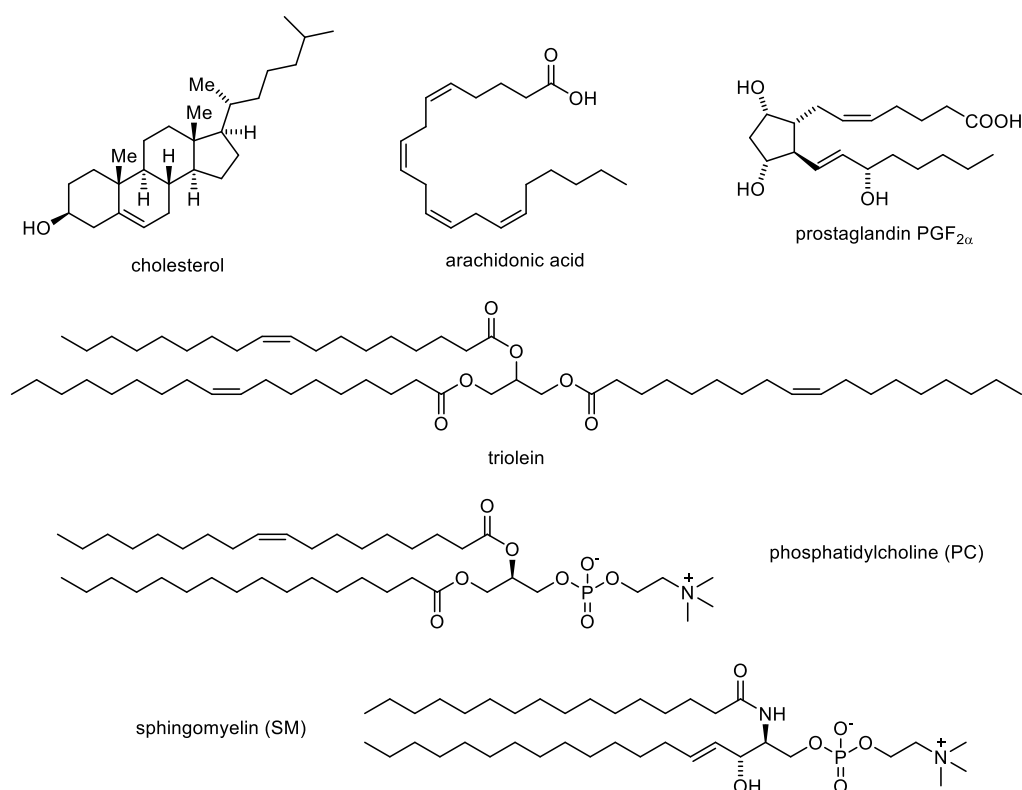
CHAPTER III:  
SYNTHESIS OF PHOTOSWITCHABLE CERAMIDES FOR  
OPTICAL CONTROL IN LIPID METABOLISM

---

### 3.1. Introduction to the Photopharmacology of Lipids

#### 3.1.1. Biological Roles of Lipids

Lipids are hydrophilic or amphipathic metabolites which constitute one of the major classes of biomolecules. They are essential for energy storage, cell signalling and membrane composition in eukaryotic organisms, which devote around 5% of their genetic code to their synthesis and metabolism.<sup>[168]</sup> A single cell can comprise over a thousand distinct lipid species,<sup>[168-169]</sup> ranging from rigid sterols such as cholesterol to dynamic glycerides such as triolein and zwitterionic membrane lipids such as phosphatidylcholine and sphingomyelin (**Figure 3.1**). Though they differ widely in form, they share a number of biological functions.



**Figure 3.1.** Select examples of lipids.

The first major role of lipids is the compartmentalization of the cell through membrane formation.<sup>[168, 170]</sup> The amphiphilic nature of membrane lipids promotes entropically-driven self-assembly into a lipid bilayer which separates the cell from its environment and certain organelles from the cytosol.<sup>[171]</sup> Eukaryotic membrane lipids are composed mainly of glycerophospholipids (largely phosphatidylcholine and phosphatidylethanolamine), sphingolipids (primarily sphingomyelin and glycosphingolipids) and sterols (cholesterol). Embedded membrane proteins also make up around 50% of bilayer mass, and its constitution is far from homogenous.<sup>[168, 172]</sup> Transmembrane composition varies from an outer exoplasmic leaflet rich in

phosphatidylcholine and sphingomyelin to a cytosolic leaflet heavy in aminophospholipids,<sup>[173]</sup> and can fluctuate depending on cell types and environmental conditions.

Laterally, the bilayer is partitioned into heterogeneous domains enriched in cholesterol and saturated sphingolipids. These ordered microdomains, called lipid rafts, are less than 200 nm in diameter<sup>[174]</sup> and play important parts in protein recruitment and transport, membrane trafficking and intracellular signalling.<sup>[175-176]</sup> Lipid rafts are believed to resemble the liquid ordered ( $L_o$ ) phase of model membrane systems,<sup>[177]</sup> which are significantly less fluid compared to the liquid disordered ( $L_d$ ) phase induced by unsaturated lipids in the rest of the plasma membrane.<sup>[176, 178]</sup> Though their nature and purpose are still under considerable scrutiny,<sup>[179]</sup> they likely play important roles in a number of signalling events such as insulin release,<sup>[180]</sup> neurotrophic factor and Ras signalling,<sup>[181]</sup> and neurotransmitter signalling.<sup>[179]</sup>

In addition to their role as structural components, lipids are vital signalling agents.<sup>[182]</sup> Studies in the 1930s first indicated that arachidonic acid metabolites, such as prostaglandins and leukotrienes, serve important functions in mediating inflammation and immune responses.<sup>[183-184]</sup> The importance of lipids in complex cell signalling pathways has since been cemented by the discovery that diacylglycerol regulates the action of protein kinase C (PKC)<sup>[185]</sup> and that lysophosphatidic acid (LPA) and other lysophospholipids act on cellular functions through specific families of GPCRs.<sup>[186]</sup> The study of bioactive lipids has accelerated in the past two decades due in part to advances in analytical techniques and a growing appreciation for lipid pharmacology. Sphingolipid signalling in particular has garnered attention due to the role of ceramides in apoptosis and the influence of sphingosine-1-phosphate in cell survival.<sup>[187]</sup>

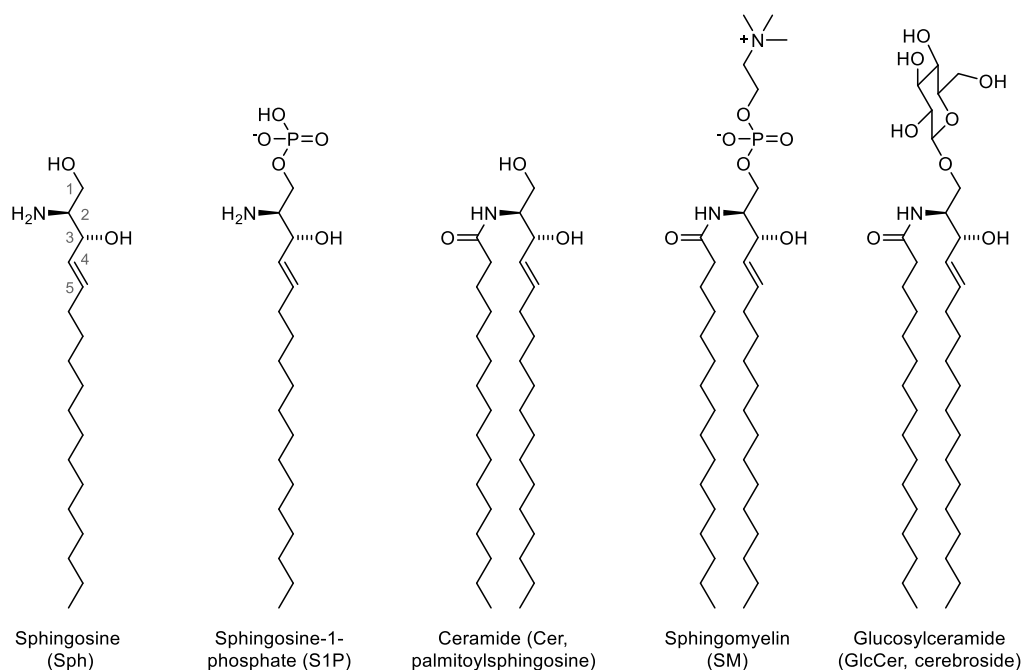
Beyond membrane composition and signalling, lipids serve as primary energy reserves for eukaryotic organisms. In mammals, triglycerides in adipose tissue are processed to long-chain fatty acids<sup>[188]</sup> which are transported to the mitochondrial matrix and, through  $\beta$ -oxidation, are transformed to acetyl-CoA and are fed into the citric acid cycle.<sup>[189-190]</sup> Lipids are also the primary insulators of cells, maintaining ion gradients and thus membrane potentials<sup>[191]</sup> and sheathing neuronal axons to speed the travel of electrical signals.<sup>[192]</sup>

The current interest of the Trauner group lies primarily with the signalling behaviour of membrane lipids, and this introduction will focus on one particular class known as sphingolipids.

### 3.1.2. Sphingolipids

Sphingolipids are a family of cell membrane lipids characterized by an aminodiol core with a hydrophobic tail – a sphingoid base – to which various fatty acids and polar head groups are appended. They were first described by Johann Thudichum in the 1870s and named after the mythical Sphinx for the enigma surrounding their behaviour and purpose.<sup>[193]</sup> They are found in great quantities in brain tissue and surrounding nerve cells.<sup>[194]</sup>

A number of important sphingolipids are presented in **Figure 3.2**. Sphingosine (Sph) was the first documented sphingolipid<sup>[187]</sup> and, though it constitutes the main sphingoid base on which other sphingolipids are contingent, its levels are kept relatively low in cells.<sup>[195]</sup> Phosphorylation at the primary alcohol gives sphingosine-1-phosphate (S1P), a carefully regulated and highly bioactive lipid.<sup>[196]</sup> Ceramides (Cers) are equipped with *N*-acyl fatty acid residues and are involved in cell proliferation and apoptosis. Sphingomyelin features a phosphocholine head group and is the most abundant sphingolipid in the plasma membrane.<sup>[197]</sup> Glycosphingolipids are carbohydrate-bearing ceramides; those with monosaccharides head groups are called cerebroside, while those with oligosaccharides containing a sialic acid residue are known as gangliosides.<sup>[198]</sup>

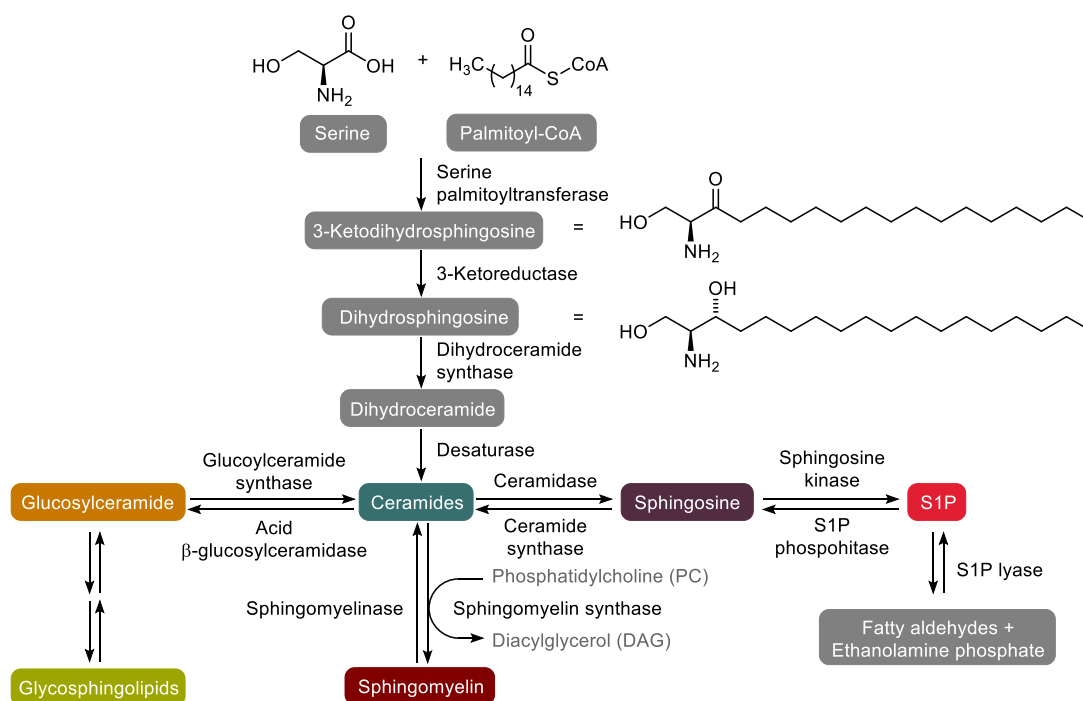


**Figure 3.2.** Important sphingolipids.

Many sphingolipids are crucial signalling molecules, and considerable scientific interest has been afforded to S1P and Cer. S1P binds to one of five G-protein coupled receptors (GPCRs), known as S1P receptors (S1PR1-5),<sup>[199]</sup> which mediate its cellular activity. S1P signalling often counteracts apoptosis<sup>[196]</sup> and regulates cell survival, immune cell trafficking<sup>[200]</sup> and inflammation.<sup>[201]</sup> The mechanism behind ceramide activity is less well-understood, but at least partially involves activation of protein phosphatases.<sup>[202]</sup> Ceramides promote apoptosis, cell

differentiation, cell-cycle arrest, and senescence.<sup>[203]</sup> The balance of pro-apoptotic Cer and pro-survival S1P constitutes a ‘sphingolipid rheostat’<sup>[203]</sup> of cell subsistence which is directed largely by the interconversion between Sph and S1P as well as Cer and ceramide-1-phosphate (C1P). Sphingolipid metabolism therefore plays a substantial part in regulating the cellular state.

Ceramides are the metabolic precursors of all known sphingolipids. Their biosynthesis (**Figure 3.3**) begins *de novo* from serine and palmitoyl-coenzyme A by a series of enzymatic transformations initiated by rate-limiting serine palmitoyltransferase.<sup>[202]</sup> Sphingosine itself is generated from ceramide by the action of a ceramidase, and sphingosine kinase in turn converts Sph to S1P. Sphingomyelin is derived by the transfer of the choline headgroup from phosphatidylcholine (PC) by sphingomyelin synthase (SMS). The only known exit from the metabolic cycle is by conversion of S1P to fatty aldehydes by a corresponding lyase.<sup>[202]</sup>



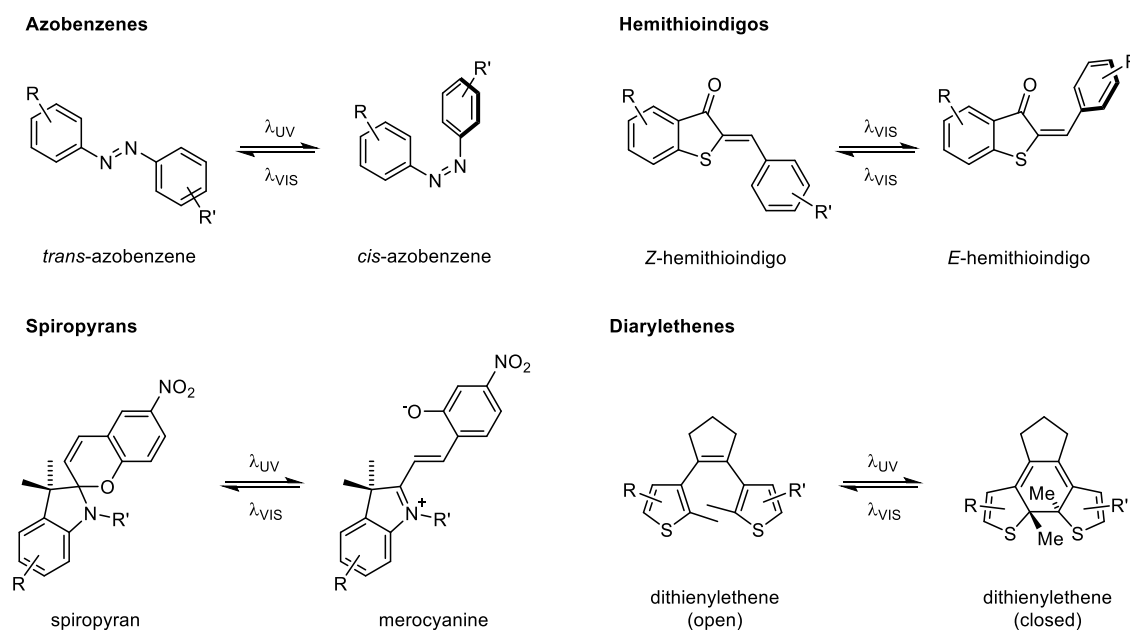
**Figure 3.3.** Overview of sphingolipid metabolism (adapted from Hannun and Obeid).<sup>[202]</sup>

Imbalances in sphingolipid signalling have been implicated in a number of important diseases, including autoimmune disorders, atherosclerosis, cancer and chronic inflammation.<sup>[195]</sup> As such, new tools for the study of their behaviour are highly desirable. The Trauner group has become interested in combining the activity of sphingolipids with our ongoing program in photopharmacology.

### 3.1.3. Photopharmacology

Pharmacology concerns itself with the effects of drugs on biological systems. While it is uncontested in its ability to produce life-saving therapeutics, classical pharmacology is generally diffusion-dependent and lacks mechanisms to control the timing and region of drug effect.<sup>[204]</sup> Photopharmacology, conversely, allows the regulation of biological function with the precision of light by means of embedded chromophores, called photoswitches, which isomerize upon irradiation.<sup>[205]</sup> By manipulating the shape and polarity of active pharmacophores, photoswitches grant optical control over a host of native biopolymers<sup>[205]</sup> and serve as valuable tools in basic research and targeted therapy.<sup>[206]</sup>

Photoswitches come in many forms, each with unique advantages when applied to biological systems (**Figure 3.4**). Hemithioindigos are robust and tunable units which toggle between *E* and *Z* in the visible range;<sup>[207-208]</sup> spiropyrans<sup>[209]</sup> undergo considerable changes in polarity upon irradiation;<sup>[210]</sup> and diarylethenes can isomerize tens of thousands of times without degrading.<sup>[211]</sup> Azobenzenes, however, are most often the switch of choice in photopharmacology<sup>[212]</sup> due to their ease of synthesis, practical isomerization, high photostationary states (the relative composition of isomers under irradiation) and resistance to photobleaching.<sup>[213]</sup> Standard azobenzenes switch from a planar *trans*-isomer to a plane-distorted *cis*-isomer upon irradiation with ultraviolet light ( $\pi - \pi^*$  transition), and undergo the reverse transformation with visible light ( $n - \pi^*$  transition) or by gradual thermal relaxation.

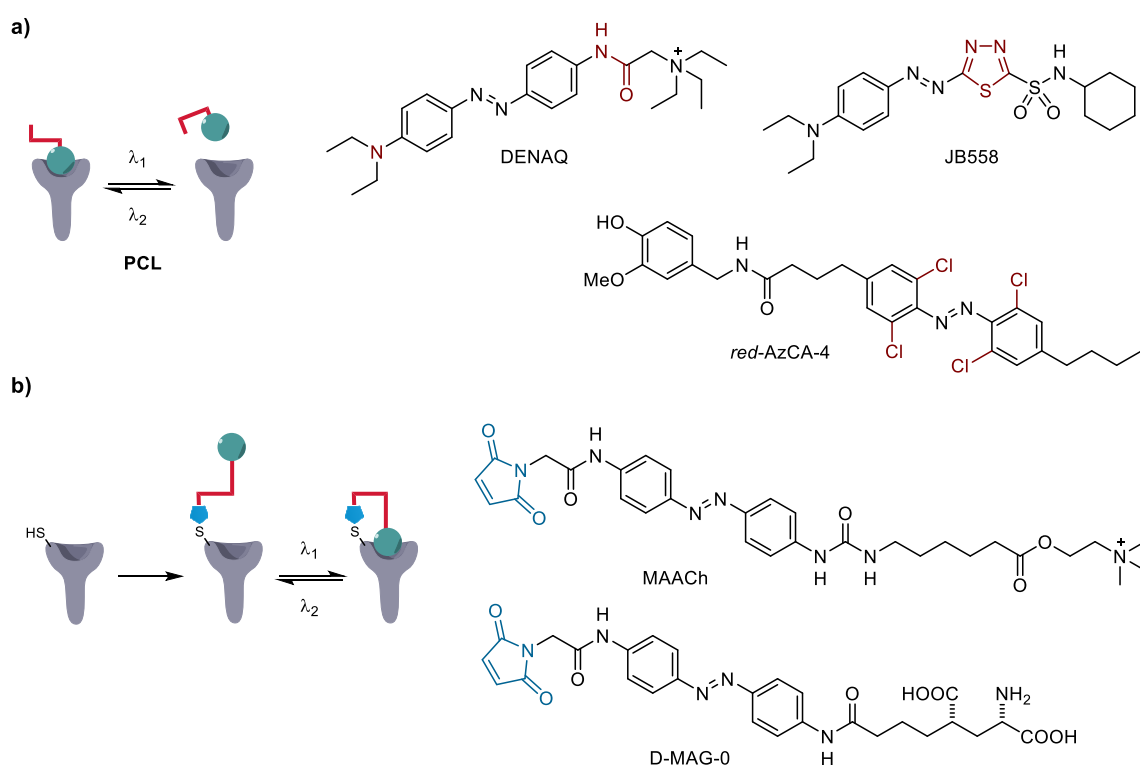


**Figure 3.4.** Generic photoswitches and their isomerizations upon irradiation.<sup>[213]</sup>

The switching wavelength and relaxation half-life of azobenzenes can be finely tuned by substituents and heteroatoms in the aromatic *azo* system. *Ortho*-electron donating groups, electronic “push-pull” systems and alternate aromates can all drive isomerization farther into the

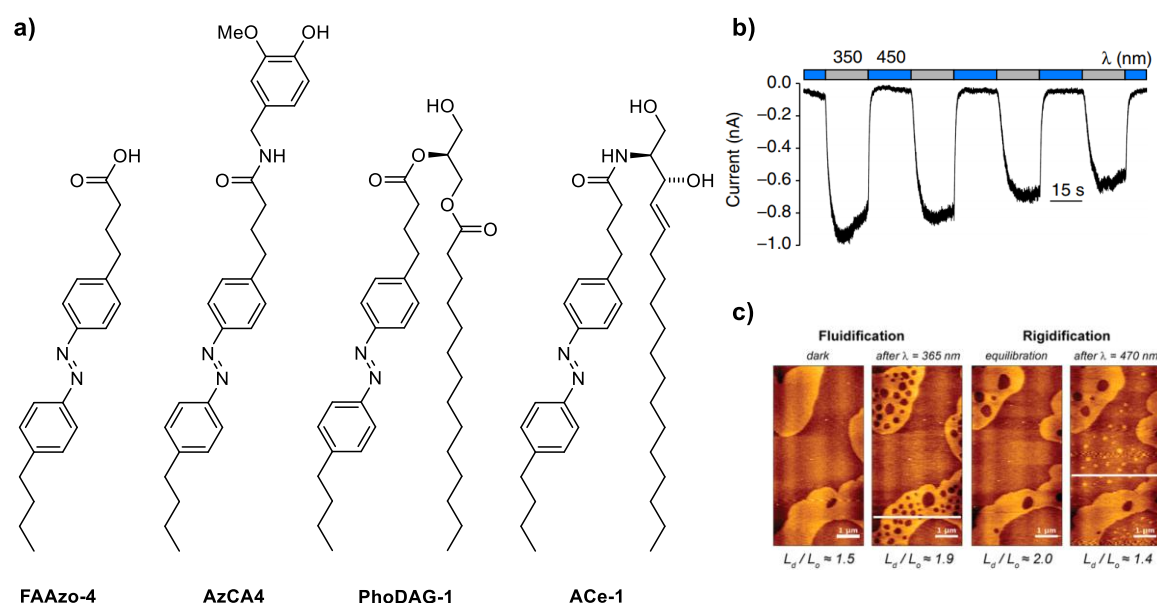
visible range (red-shifting), which is particularly desirable *in vivo* to maximize tissue penetration and reduce photodegradation.<sup>[206]</sup> In part due to this great versatility, azobenzene-bearing biomolecules have been used to regulate ionotropic glutamate,<sup>[214]</sup> NMDA<sup>[215]</sup> and AMPA<sup>[216]</sup> receptors, voltage-gated ion channels,<sup>[217]</sup> microtubule dynamics,<sup>[218]</sup> protein kinases<sup>[219]</sup> and many other targets.

Photopharmaceuticals can exert their influence through different mechanisms. Photoswitches that modulate activity while binding non-covalently to targets are identified as photochromic ligands (PCLs) (**Figure 3.5.a**). Others are instead tethered to the target protein, often through a genetically-engineered cysteine residue close to the binding pocket, and are branded as photoswitchable tethered ligands (PTLs) (**Figure 3.5.b**). Both benefit from the flexibility of azobenzene building blocks: PCLs remain compact and the wavelength of ligand activity transition can be red-shifted through methods described above (**Figure 3.5.a** features some examples), whereas the placement of azobenzenes in the PTL's tethers dictates ligand position and plasticity.



### 3.1.4. Photolipids

Prior work in photopharmacology has focused largely on the manipulation of receptors and ion channels; until recently, optical control of lipids has been limited to the assembly and disruption of artificial membranes.<sup>[220-222]</sup> Since 2014, the Trauner laboratory has been engaged in the optical control of lipid pathways through the use of azobenzene-bearing lipid analogues termed *photolipids*. The first examples of these were photoswitchable fatty acids (**FAAzos**, **Figure 3.6.a**), which were designed in part to reversibly mimic the *cis*-conformations of native FAs such as arachidonic acid.<sup>[223]</sup> Their initial incorporation into *azo*-capsaicin analogues (**AzCAs**) allowed for the modulation of TRPV1 channels in HEK cells by irradiation with UV-A and blue light (**Figure 3.6.b**).<sup>[223]</sup> **FAAzos** were also integrated into the diacylglycerol (DAG) scaffold to generate **phoDAGs**, allowing optical manipulation of protein kinase C.<sup>[219]</sup> The scope of photolipids was soon expanded to include light-induced control over lipid vesicles using azobenzene-containing phosphatidylcholine analogues (*azo*-**PCs**)<sup>[224]</sup> and cannabinoid receptors using photoswitchable  $\Delta^9$ -tetrahydrocannabinol (*azo*-**THCs**).<sup>[225]</sup>



**Figure 3.6.** a) Examples of photolipids developed in the Trauner laboratory, b) **AzCA-4** reversibly modulates TRPV1 in HEK293T cells by light in voltage clamp electrophysiology,<sup>[223]</sup> and c) **ACe-1** incorporated into SLBs enables fluidification and rigidity of artificial membranes by AFM analysis (reprinted with permission from *J. Am. Chem. Soc.* **2016**, *138*, 12981–12986. Copyright © 2018 American Chemical Society).

Recently, the Trauner laboratory has combined **FAAzos** with sphingoid bases to generate azobenzene-containing ceramide analogues (**ACes**, **Figure 3.6.a**).<sup>[178]</sup> These photocontrollable sphingolipid derivatives were integrated into raft-mimicking supported lipid bilayers (SLBs) and, using atomic force microscopy analysis (AFM), were found to modulate raft structure with



light.<sup>[178]</sup> Exposure to 365 nm light and conversion to the *cis*-isomer was found to induce fluidification and the formation of disordered ‘lakes’ in previously ordered phases, whereas return to the *trans*-isomer resulted in rigidification of the disordered phase (**Figure 3.6.c**).

Though these results confirmed that the ACes could successfully manipulate artificial membranes, it remained to be determined whether sphingolipid analogues could be taken up by cellular machinery and used to modulate lipid systems *in vivo*. The following section details our efforts to produce light-active ceramide derivatives whose behaviour can be evaluated in living systems. We were particularly interested in the metabolism of these ceramides to sphingomyelin by sphingomyelin synthase 2 (SMS2), which is a critical regulator of pro-apoptotic ceramide in the membrane.<sup>[226]</sup>

---

## 3.2. Results and Discussion

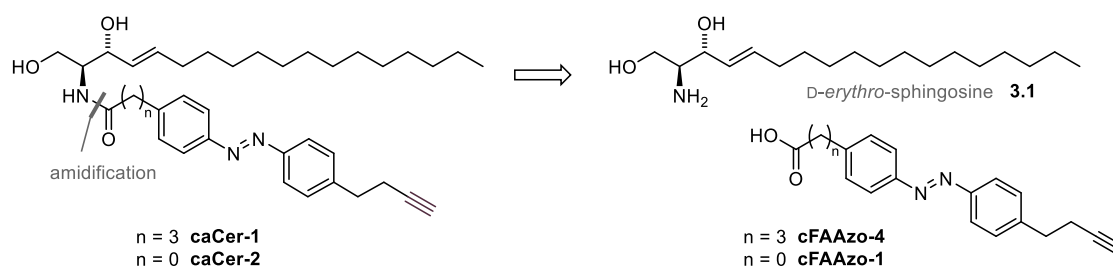
### 3.2.1. Project Contributions

The author conducted the synthesis of **caCer-3** and **caCer-4**, and UV/Vis analysis of all **caCers**. Dr. Henry Toombs-Ruane originally synthesized **caCer-1** and **caCer-2**. Dr. James Frank conceived experiments and performed atomic force microscopy and confocal fluorescence imaging in supported lipid bilayers with Dr. Henri Franquelin and Prof. Petra Schwille of the Max Planck Institute for Biochemistry. Dr. Matthijias Kol and Prof. Dr. Joost Holthuis of the Universität Osnabrück conceived experiments and performed studies in yeast membranes and HeLa cells.

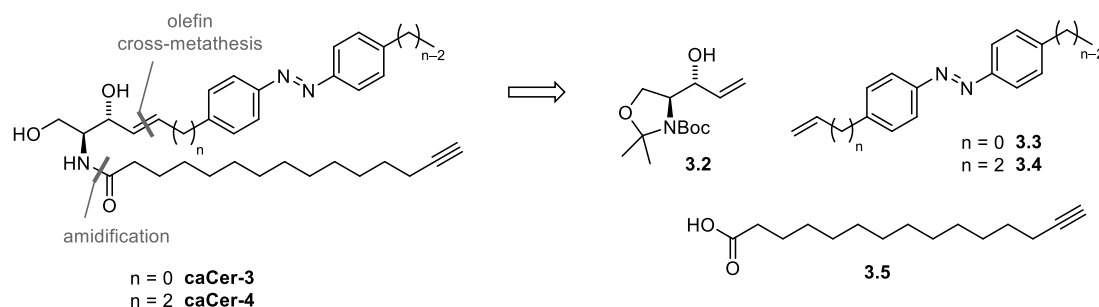
### 3.2.2. Synthesis of Clickable Azobenzene-containing Ceramides

We anticipated that optically-active sphingolipids prepared for metabolic studies would require three components: a sphingoid base for ligand compatibility with SMS, an azobenzene unit carefully positioned so as to modulate substrate binding and/or localization upon irradiation, and an alkyne handle for orthogonal conjugation to a fluorophore and subsequent analysis by chromatography. With these constraints in mind, we developed a series of four **clickable azobenzene ceramide analogues**, termed **caCers** (**Scheme 3.1**). The first two **caCers** (**caCer-1** and **-2**) possessed a photoswitch in fatty acid chains of varying length, similar to previously investigated **ACes** but with added alkyne groups at the FA terminus. These **caCers** could be generated by amide bond formation between **clickable fatty acid azobenzenes** (**cFAAzos**) and *D-erythro*-sphingosine (**3.1**).

**caCers with azobenzenes in the *N*-acyl fatty acid**



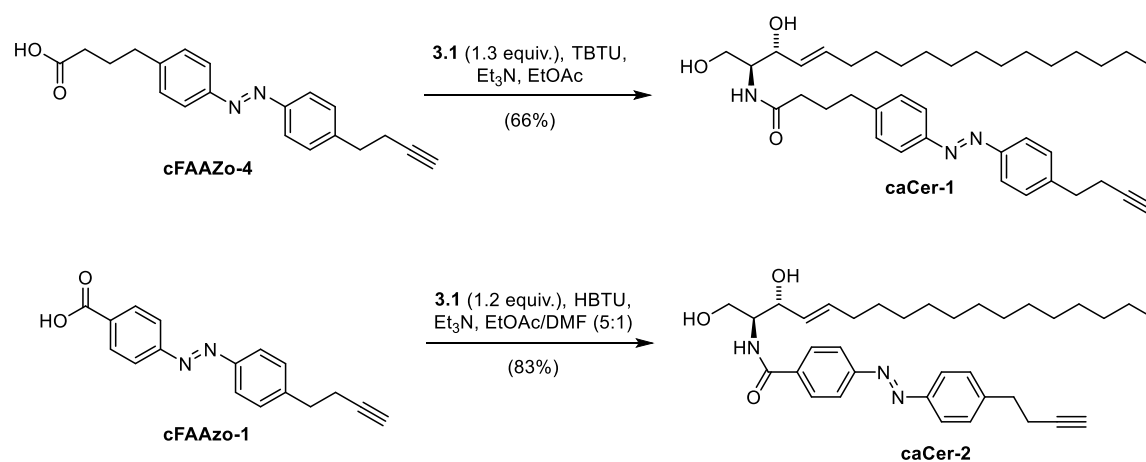
**caCers with azobenzenes in the sphingoid base**



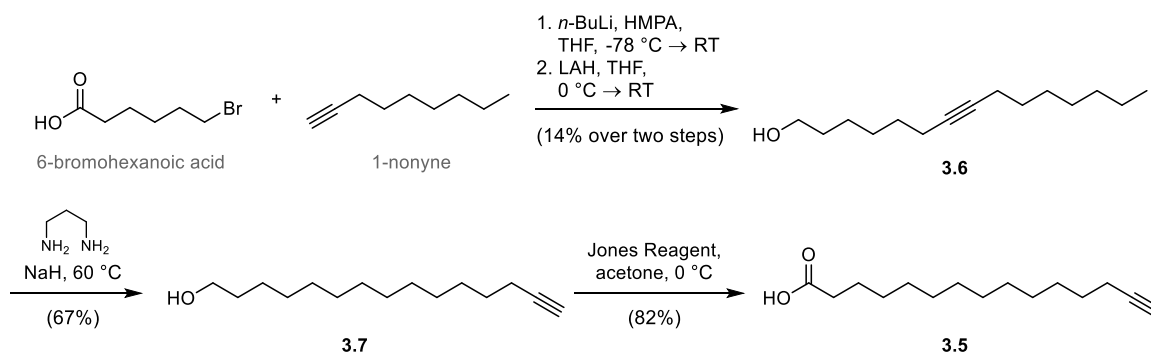
**Scheme 3.1.** Retrosynthesis of clickable azobenzene ceramide analogues (**caCers**).

Two additional **caCers** (**caCer-3** and **-4**) were designed with the azobenzene installed in the sphingoid base as a compliment to the **FAAZo**-derived **caCers**. After some unsuccessful efforts with a Horner-Wadsworth-Emmon-based route, we opted for a cross-metathesis strategy<sup>[227-228]</sup> between allylic alcohol **3.2** and photoswitchable olefins **3.3** and **3.4** to generate these **caCers**.

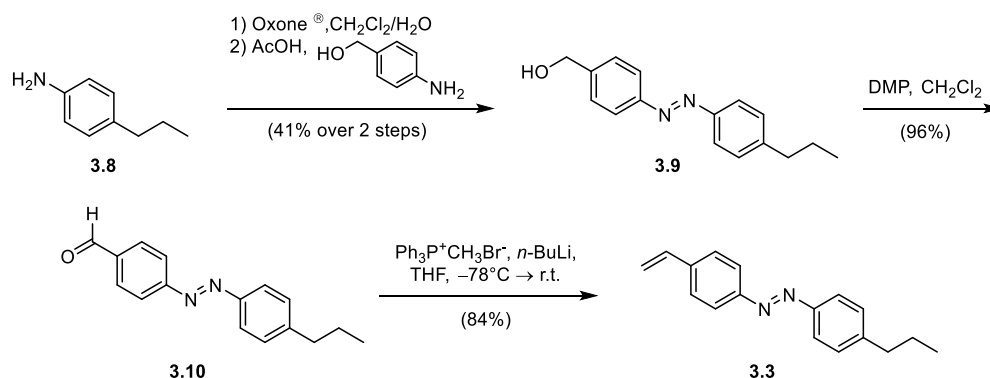
The initial synthesis of **caCers-1** and **-2** was accomplished by Henry Toombes-Ruane, a postdoctoral researcher in the Trauner group who constructed **cFAAZo-4** and **cFAAZo-1** and coupled them to *D-erythro*-sphingosine. The author of this thesis used a modified amide coupling reaction to generate additional material for biological testing and to collect final UV/Vis and characterization data for all compounds (**Scheme 3.2**).



The synthesis of **caCer-3** and **-4** required the incorporation of known 14-pentadecynoic acid (**3.5**)<sup>[229]</sup> to mimic the native fatty acids of ceramides. Though **3.5** is commercially available, its high cost led us to develop a short synthesis of the molecule (**Scheme 3.3**). Alkylation of non-1-yne with 6-bromohexanoic acid and reduction of the crude acid granted alcohol **3.6**. An alkyne-zipper reaction<sup>[230]</sup> afforded terminal alkyne **3.7**<sup>[231]</sup> and Jones oxidation<sup>[232]</sup> delivered **3.5**.

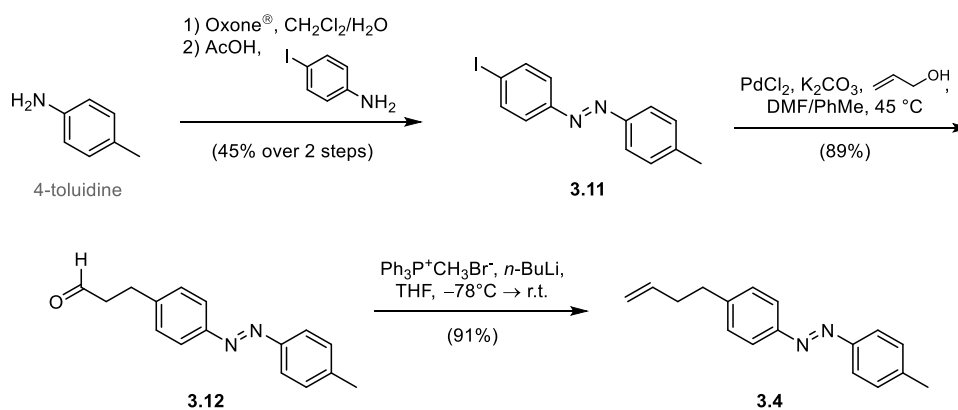


The synthesis of the corresponding sphingoid core was performed through an olefin cross-metathesis route using allylic alcohol **3.2** in a tactic previously employed by a number of groups.<sup>[227-228]</sup> The styrenal azobenzene **3.3** was first generated by oxidation of 4-propylaniline **3.8** to the nitrosobenzene and Mills reaction with 4-aminobenzyl alcohol to grant azobenzyl alcohol **3.9** (an attempted Mills reaction directly with 4-vinylaniline resulted instead in uncontrolled oxidation of the styrene).<sup>[233]</sup> Oxidation of the alcohol to aldehyde **3.10** and Wittig reaction with methyltriphenylphosphonium bromide delivered styrene **3.3**.



**Scheme 3.4.** Synthesis of 4-vinyl-4'-propylazobenzene **3.3**.

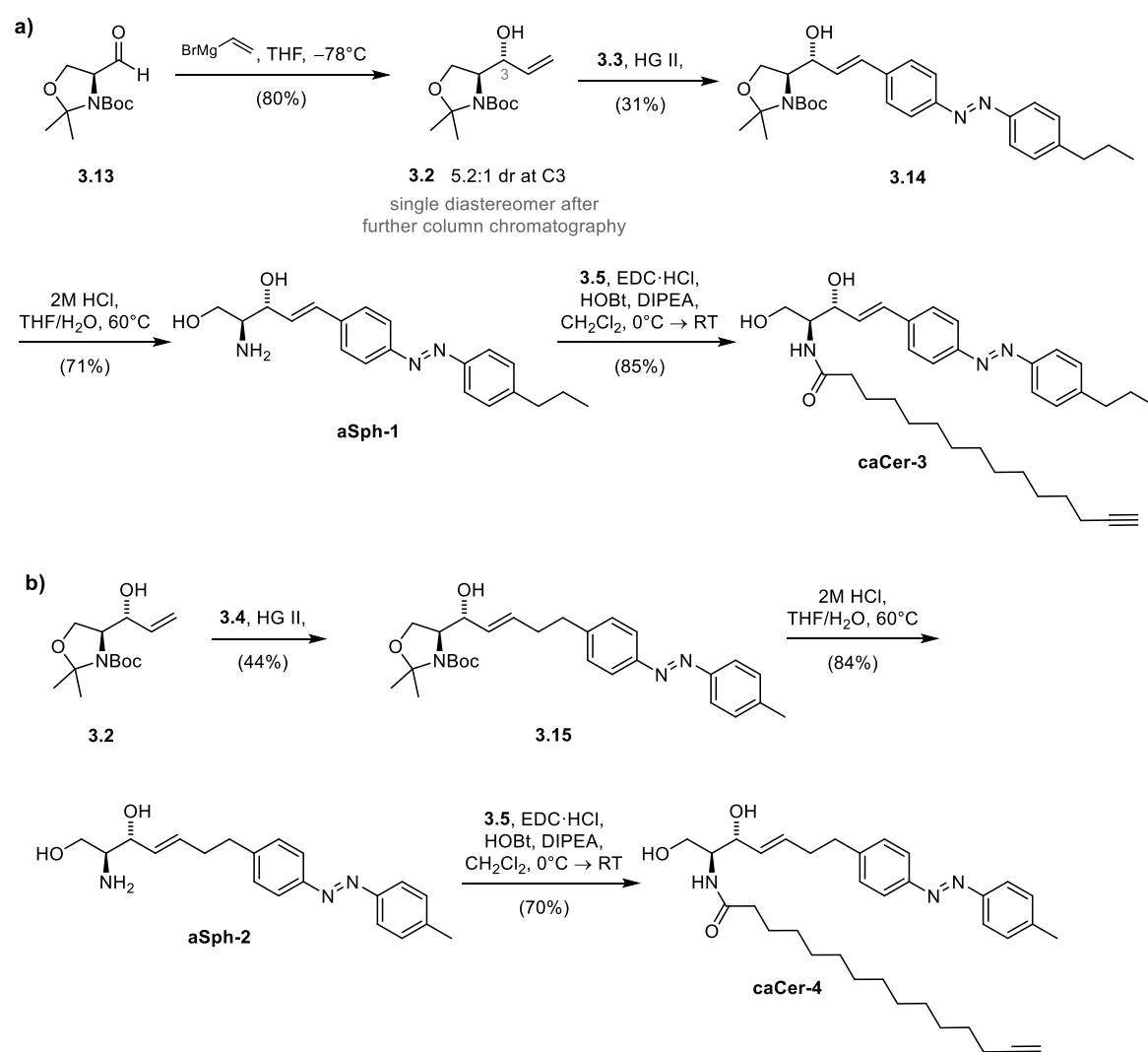
The second coupling partner (**3.4**) contained a two-carbon linker between the azobenzene and the terminal olefin and was synthesized in a similar fashion to the first. Known azobenzene **3.11**<sup>[234]</sup> was generated by Mills reaction between 4-nitrotoluene and 4-iodoaniline. Heck reaction with allyl alcohol<sup>[235]</sup> produced aldehyde **3.12** and Wittig reaction with methyltriphenylphosphonium bromide granted olefin **3.4** in good overall yield.



**Scheme 3.5.** Synthesis of 4-(but-3-enyl)-4'-methylazobenzene **3.4**.

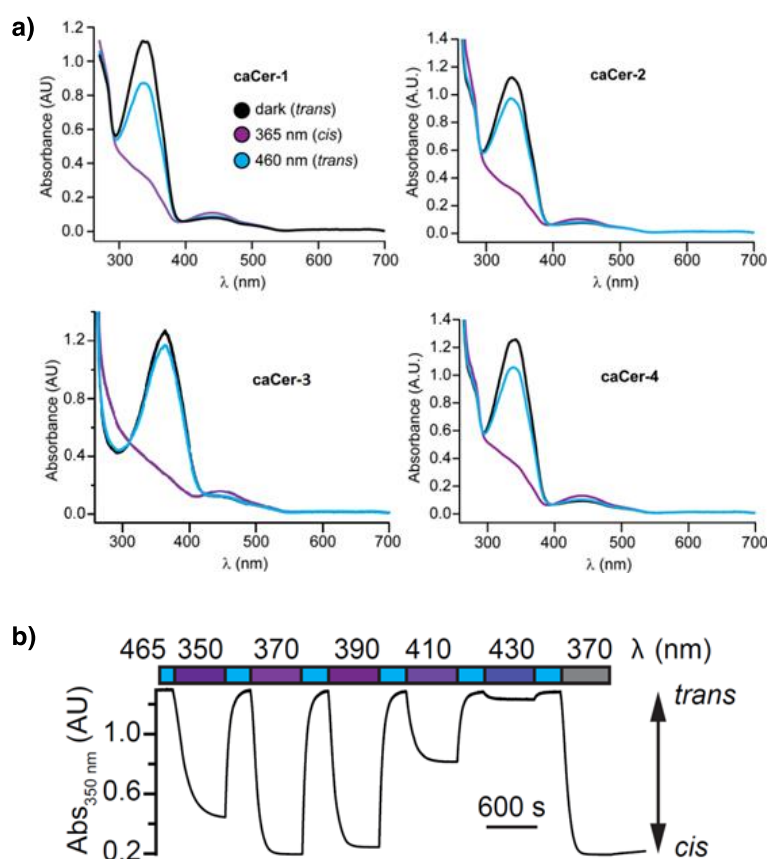
Allylic alcohol **3.2** was synthesized as previously described<sup>[236]</sup> by addition of vinylmagnesium bromide to aldehyde **3.13** (commonly referred to as Garner's aldehyde<sup>[237]</sup>) to give a 5.2:1 mixture of *erythro*/*threo* diastereomers (**Scheme 3.6.a**). During our first synthesis of the **caCers**, this mixture of diastereomers was carried forward in hopes that the *erythro* and *threo* diastereomers

could be separated at a later stage to give additional sphingolipid analogues for biological tests. Though **caCer-4** was successfully separated to its pure *erythro* isomer in this manner, we found it impossible to separate **caCer-3** completely – by HPLC and other methods – and a 7.2:1 mixture of *erythro* and *threo* diastereomers was therefore submitted for testing in supported lipid bilayers and biological systems. In a second synthesis, the 5.2:1 mixture of **3.2** was first carefully separated by column chromatography<sup>[236]</sup> and then taken through the same conditions to give **caCer-3** as the pure *erythro* diastereomer. The synthesis of **caCer-3** continued with the cross-metathesis of **3.2** and **3.3** using Hoveyda-Grubbs 2<sup>nd</sup> generation catalyst (HG II) to give *E*-alkene **3.14** in modest but acceptable yields. Simultaneous hydrolysis of the acetal and *tert*-butyl carbamate protecting groups granted azobenzene-containing sphingosine **aSph-1**, and amide coupling with acid **3.5** then yielded **caCer-3**. The analogous pathway using olefin **3.4** was conducted to afford **3.15**, **aSph-2** and **caCer-4** (Scheme 3.6.b).



**Scheme 3.6.** a) Synthesis of **caCer-3** and b) **caCer-4** through olefin cross-metathesis strategies.

UV/Vis spectroscopy (**Figure 3.7.a**) indicated that **caCers-1**, **-2** and **-4** behaved as standard dialkyl-substituted azobenzenes, with  $\lambda_{\text{max}}$  near 330 – 340 nm and a dark-adapted *trans* conformation that switched easily to *cis* with UV-A light (370 nm) and back to *trans* with blue light (460 nm). Styrenal **caCer-3**, conversely, was slightly red-shifted and exhibited a shift of  $\lambda_{\text{max}}$  to 380 nm. Kinetic experiments (**Figure 3.7b**) indicated that the optimal switching wavelength was still near 370 nm and **caCer-3** could therefore be photoisomerized during biological experiments using the same conditions as our other ceramide analogues.



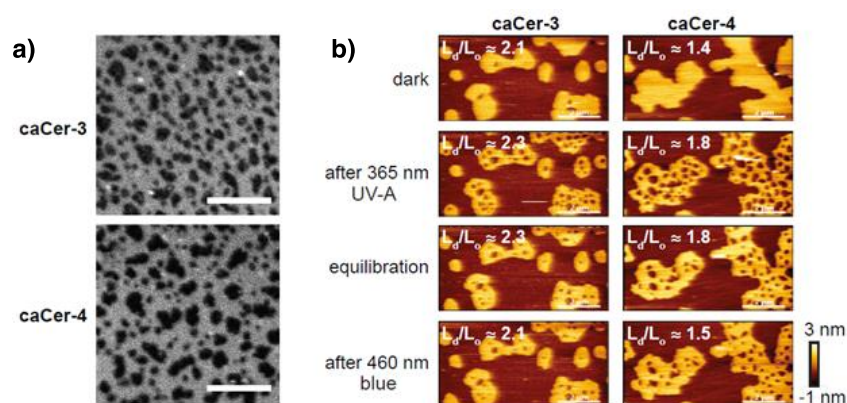
**Figure 3.7.** a) UV/Vis spectra of dark-adapted and illuminated (365 nm and 460 nm) **caCers** in DMSO (50  $\mu\text{L}$ ), and b) Kinetic studies of **caCer-3** conversion between *cis*- and *trans*-isomers at 20 nm wavelength increments.

### 3.2.3. CaCers in Supported Lipid Bilayers (SLBs)

Previous studies in the Trauner group demonstrated that ceramide derivatives with azobenzene-containing *N*-acyl groups (**ACes**, see **Section 3.1.5**) could optically regulate phase-separated lipid domains in supported lipid bilayers (SLBs). We assumed that **caCers-1** and **-2**, varying from these **ACes** only by the alkyne at the FA terminus, would behave similarly in artificial membranes. However, it remained to be established whether those analogues bearing the

azobenzene moiety in the sphingoid base, such as **caCers-3** and **-4**, could modulate bilayer structure in a light-dependent manner. To this end, SLBs were prepared containing a quaternary lipid mixture of 1,2-O-dioleoylglycero-3-O-phosphocholine (DOPC), cholesterol, SM (C-18) and dark-adapted *trans*-**caCer-3** or **caCer-4** at a molar ratio of 10:6.7:7:3 DOPC:cholesterol:SM:caCer, and were doped with 0.1 mol% ATTO-655-DOPE to distinguish liquid-ordered domains.

Confocal fluorescence imaging indicated that the bilayer segregated into darker, SM- and cholesterol-heavy liquid-ordered ( $L_o$ ) domains dispersed in a liquid-disordered ( $L_d$ ) phase. These findings were corroborated by atomic force microscopy (AFM) imaging, wherein the  $L_o$  domains rest a nanometer above the  $L_d$  phase. Switching the conformation of **caCers** from the *trans*- to *cis*-isomer upon exposure to 365 nm light resulted in the appearance of liquid-disordered “lakes” within the ordered domains, increasing the overall  $L_d/L_o$  area ratio. Irradiation with 460 nm light and conversion back to *trans*-azobenzene led to partial reversal of the fluidification. Overall, the results indicate that the *trans*-**caCers** are preferentially localized in the  $L_o$  domains, and upon isomerization to the *cis*-**caCers** interact better with the more dispersed lipids (such as DOPC) of the  $L_d$  phase. These findings were consistent with those observed for the **ACes** and established that **caCer-3** and **caCer-4** could likewise exert control over lipid membrane structure with light.



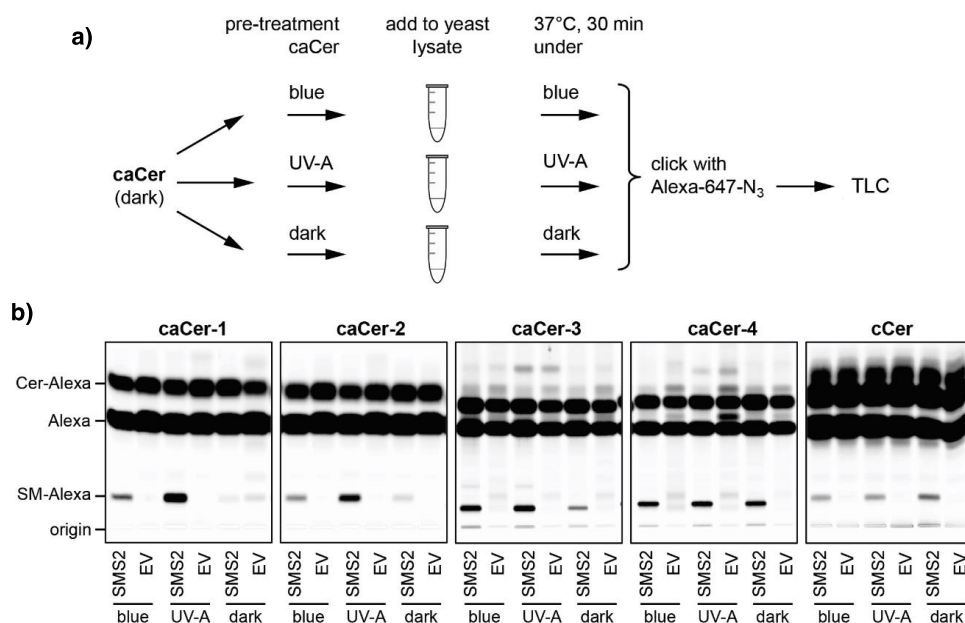
**Figure 3.8.** a) Confocal fluorescence microscopy of SLBs consisting of a quaternary mixture of DOPC:cholesterol:SM:caCer and b) Atomic force microscopy of SLBs prepared in identical fashion. Isomerization of **caCer-3** and **caCer-4** to *cis* with 365 nm light resulted in the appearance of fluidic ‘lakes’ inside the  $L_o$  domains and an increase in  $L_d/L_o$  area ratio. This effect was partially reversed on isomerization back to *trans* with 460 nm light (images courtesy of Dr. James Frank).

### 3.2.4. Optical control of SM metabolism with caCers

**CaCers** were next investigated for their ability to act as photocontrolled substrates for sphingomyelin synthase (SMS2 specifically). Experiments with yeast extract and HeLa cells were performed by collaborators Dr. Matthijs Kol and Prof. Dr. Joost Holthuis at the University of Osnabrück. The metabolic conversion of **caCers** to their SM analogues was first examined in

yeast cells using heterologously-expressed SMS2. The lysate of yeast cells transfected with either V5-tagged SMS2 or an empty vector (EV) was incubated with pre-irradiated *cis*- (365 nm) or *trans*- (dark-adapted or 470 nm) isomers of all four **caCers**. An additional ceramide **cCer**, generated by coupling acid **3.5** with *D-erythro*-sphingosine (performed by Dr. S. Korneev of the Universität Osnabrück) and thus lacking any azobenzene moiety, was used as a control. Conversion was monitored by lipid extraction, ligation to a fluorophore, thin layer chromatography (TLC) separation and fluorescence analysis. Alexa-647 was selected as the ligating agent as its absorbance spectrum did not overlap with the azobenzene.

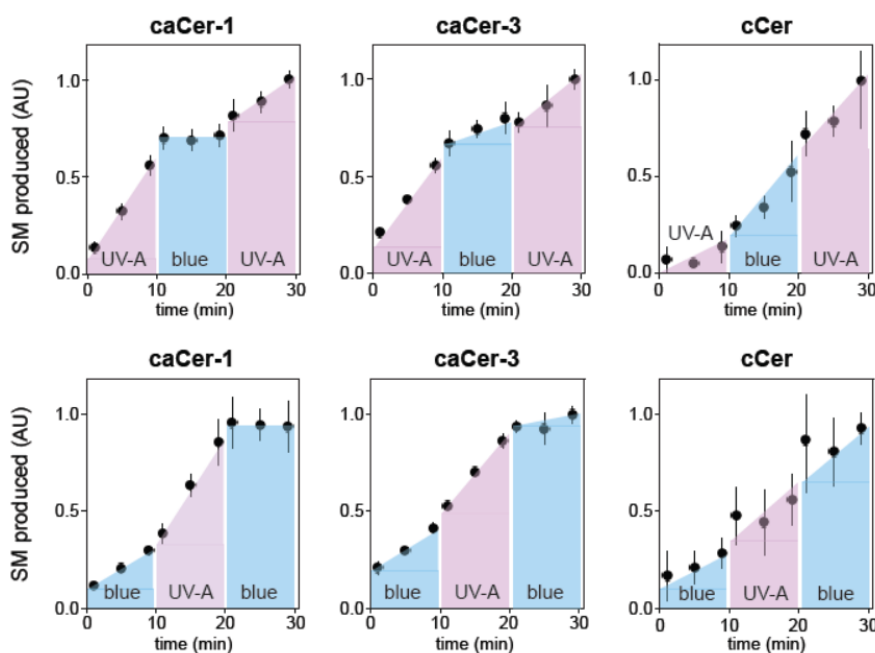
Assay results (Figure 3.9) indicated that all **caCers** and **cCer** were suitable substrates for SMS2 and were efficiently converted to their SM analogues. Importantly, *cis*-isomers of **caCer-1**, **caCer-2**, and, to a lesser extent, **caCer-3** were metabolized at a significantly higher rate than their *trans*-counterparts in both the dark-adapted and blue light-irradiated states. To confirm that these light-induced effects were due to the conformational changes of the substrates rather than different rates of incorporation of the pre-irradiated **caCers** into yeast membranes, SMS2 was expressed cell-free in the presence of liposomes already containing **caCer-1**. Consistent with our previous findings, dark-adapted **caCer-1** showed almost no conversion to SM during liposome-coupled translation of SMS2 mRNA, whereas irradiation with UV-A light inducing conformational change to the *cis*-isomer once more led to increased rates of SM metabolism.



**Figure 3.9.** **a)** Blue, UV-A or dark-adapted **caCers** were incubated with lysates of control or SMS2-expressing yeast cells for 30 min at 37°C and their metabolic conversion to SM was determined by TLC analysis of total lipid extracts click-reacted with Alexa-647, **b)** Lysates of control (EV) and SMS2-expressing yeast cells were incubated with **caCers** or **cCer**. Reaction samples were subjected to lipid extraction, click-reacted with Alexa-647 and analyzed by TLC (images courtesy of Dr. Matthijas Kol).



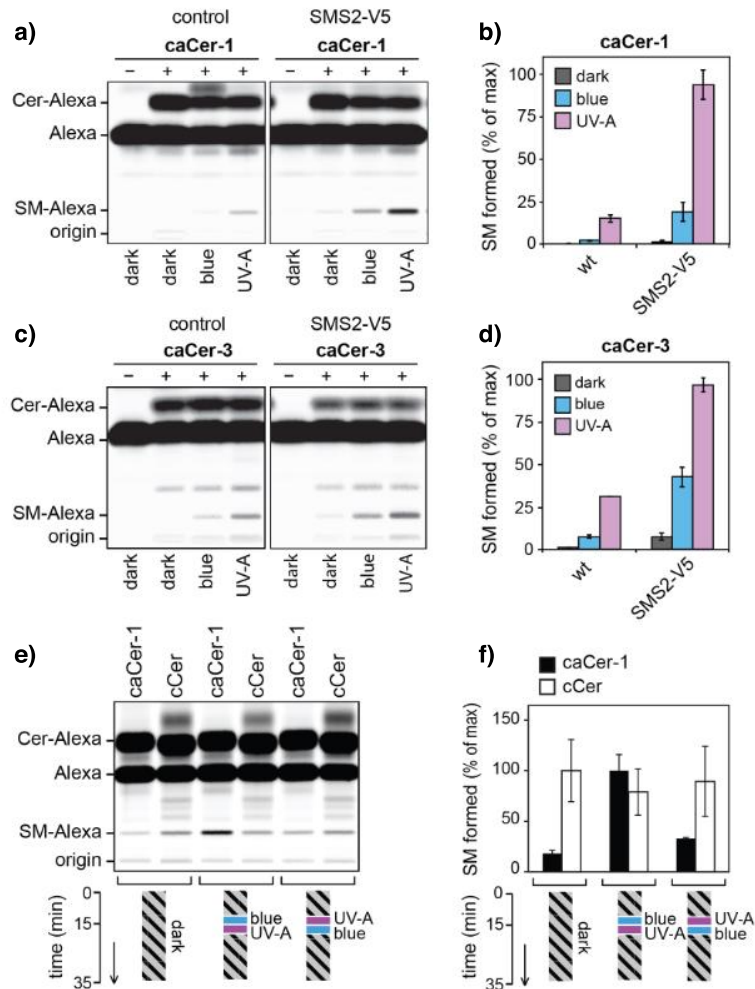
Light-based temporal control of **caCer** metabolism was also demonstrated through time-based illumination experiments. *Cis*- or *trans*-**caCer-1** and **caCer-3** were incubated in the lysate of SMS2-expressing yeast cells at 37 °C and **caCer** conformation was toggled every 10 minutes by alternately illuminating with UV-A or blue light. As illustrated in Figure 3.10, the rate of SMS2 metabolism of **caCer-1** was significantly enhanced during periods of UV-A illumination. Conversely, isomerization to the *trans*-isomer by exposure to blue light resulted in a near-arrest of conversion to SM. The same effects were present, though less pronounced, in **caCer-3**, whereas **cCer** metabolism was generally unaffected by irradiation.



**Figure 3.10.** **caCer** incubation with lysates of SMS2-expressing yeast cells at 37 °C under UV-A or blue illumination. After each 10 min period, **caCer** configuration was switched by illuminating the reactions with blue or UV-A light. Reaction samples were taken at the indicated time points, subjected to lipid extraction, click-reacted with Alexa-647 and analyzed by TLC. Presented are the relative amounts of SM formed (images courtesy of Dr. Matthijs Kol).

Having demonstrated optical control of sphingolipid metabolism in yeast cell membranes, we next investigated **caCer** behaviour in living cells. Pre-irradiated *cis*- or *trans*-isomers of **caCer-1** and **caCer-3** were added to SMS2-overexpressing HeLa cells and control cells and were incubated for 1 h at 37 °C. Conversion was again monitored by click reaction to Alexa-647 and TLC fluorescence analysis. Though all substrates showed improved conversion to SM analogues in SMS2-overexpressing cells compared to control (**Figure 3.11**), *cis*-**caCers** were once more metabolized at a far greater rate than *trans*-isomers in both cell lines. The difference in conversion between isomers was particularly prominent for **caCer-1**. Reversible optical control over SM metabolism was then evaluated by a second irradiation experiment. Dark-adapted *trans*-**caCer-1** was incubated in SMS2-overexpressing cells for 15 minutes before flash irradiation with UV-A

followed by blue light, or vice versa, and the incubation was continued in the dark for an additional 20 minutes before analysis. Irradiating with blue light followed by UV light resulted in increased conversion to SM, whereas the reverse resulted in conversion only slightly greater than the dark-adapted control, confirming that metabolism by SMS2 could be actively controlled by light-induced *cis/trans* isomerization in human cells.



**Figure 3.11.** Blue, UV-A or dark-adapted **a)** *caCer-1* or **c)** *caCer-3* was incubated with control or SMS2-V5-expressing HeLa cells for 1 h at 37°C. Metabolic conversion to SM was determined by TLC analysis of total lipid extracts click-reacted with Alexa-647. Quantitative analysis of SM formed from **b)** *caCer-1* or **d)** *caCer-3*. **e)** *caCer-1* or *cCer* were incubated with SMS2-V5-expressing HeLa cells at 37°C in the dark. After 15 min, cells were flash-illuminated by blue light followed by UV-A or vice versa and then incubated for another 20 min. Metabolic conversion of *caCer-1* or *cCer* to SM was determined by TLC analysis of total lipid extracts click-reacted with Alexa-647. **f)** Quantitative analysis of SM formed from *caCer-1* or *cCer*. All data shown are mean values  $\pm$  s.d. (n = 3) (images courtesy of Dr. Matthijs Kol).

Our results in both yeast membranes and human cells indicate that the *cis*-isomers of **caCer-1**, **caCer-2** and **caCer-3** are more readily converted to SM by SMS2 than the corresponding *trans*-isomers. It is possible that the conformational change of these ceramide analogues influences binding affinity for SMS2, and that *cis*-**caCers** are better suited for SMS binding despite possessing bent alkyl chains in comparison to the linear residues of native ceramides. However, SMS2 is a promiscuous enzyme and should tolerate a variety of substrates regardless of conformation.<sup>[238-239]</sup> An alternate explanation is that the isomerization of **caCers** alters their localization in cell membranes and thereby determines their interactions with SMS2. The *trans*-isomers tend to be closely packed and cluster in ordered phases, as demonstrated by our findings in SLBs (see **Figure 3.8.b**), whereas *cis*-**caCers** have disrupted packing and a preference for the liquid-disordered domains. This would suggest a lateral segregation between SMS and *trans*-**caCers** in native lipid membranes contributing to reduced metabolism of dark-adapted **caCers**.

Regardless, the development of the **caCers** series has illustrated that the biosynthesis of sphingolipids can be dynamically regulated by means of light. We have confidence that these chemical tools can soon be put to use to probe the fundamental role of ceramides in apoptosis and metabolic disorders.



CHAPTER IV:  
EXPERIMENTAL INFORMATION

---

## 4.1. General Experimental Details

Unless otherwise stated, all reactions were performed with magnetic stirring under a positive pressure of nitrogen or argon gas. Oven-dried glassware (oven temperature of 100 °C) was further dried with a heat-gun at 650 °C under vacuum, followed by back-filling with inert gas, three times and fitted with rubber septa prior to use for moisture-sensitive reactions.

**Solvents and Reagents:** Tetrahydrofuran (THF) and diethyl ether (Et<sub>2</sub>O) were distilled over sodium benzophenone under nitrogen atmosphere prior to use. Dichloromethane (CH<sub>2</sub>Cl<sub>2</sub>), triethylamine (Et<sub>3</sub>N) and chlorotrimethylsilane (TMSCl) were distilled over calcium hydride under a nitrogen atmosphere. *N,N*-dimethylformamide (DMF), toluene (PhMe) and methanol (MeOH) were purchased from Acros Organics as 'extra dry' reagents under inert gas atmosphere and stored over molecular sieves. Solvent used for extraction and flash column chromatography were purchased at technical grade and distilled under reduced pressure (ethyl acetate (EtOAc), pentane, Et<sub>2</sub>O) or purchased at HPLC grade (CH<sub>2</sub>Cl<sub>2</sub>, acetone, MeOH). Hexamethylphosphoramide (HMPA) and 1.0 M lithium bis(trimethylsilyl)amide (LiHMDS) in THF were purchased from Sigma Aldrich under inert gas atmosphere. Potassium carbonate was oven-dried (100 °C) for three days prior to use and cooled under nitrogen atmosphere. All other solvents and reagents were used as received from commercial sources (Sigma-Aldrich, Tokyo Chemical Industry Co., Alfa Aesar, Acros Organics, Strem Chemicals).

**Chromatography:** Reactions were monitored by thin-layer chromatography (TLC) using silica gel F254 pre-coated glass plates (*Merck*) and visualized by exposure to ultraviolet light ( $\lambda = 254$  nm) or by staining with aqueous potassium permanganate (KMnO<sub>4</sub>) or aqueous acidic ceric ammonium molybdate (IV) (CAM) solution. Flash column chromatography was performed using silica gel (60 Å, 40-63  $\mu$ m, *Merck*) and a forced flow of eluent.

**NMR Spectroscopy:** Proton (<sup>1</sup>H) and carbon (<sup>13</sup>C) nuclear magnetic resonance spectra were recorded on a Bruker Avance III HD 400 MHz spectrometer equipped with a CryoProbe™, a Varian VXR400 S spectrometer, a Bruker AMX600 spectrometer or a Bruker Avance III HD 800 MHz spectrometer. Proton chemical shifts are expressed in parts per million (ppm,  $\delta$  scale) and referenced to residual undeuterated solvent signals (CDCl<sub>3</sub>: 7.26 ppm, toluene-*d*<sup>8</sup>: 2.09 [pentet] ppm, pyridine-*d*<sup>5</sup>: 7.19 [t] ppm, CD<sub>3</sub>OD: 3.31 [pentet] ppm). Carbon chemical shifts are expressed in parts per million (ppm,  $\delta$  scale) and referenced to the central carbon resonance of the solvent (CDCl<sub>3</sub>: 77.2 ppm, toluene-*d*<sup>8</sup>: 137.9 ppm, pyridine-*d*<sup>5</sup>: 123.4 [t] ppm, CD<sub>3</sub>OD: 49.2 [heptet] ppm). The reported data is represented as follows: chemical shift in parts per million (ppm,  $\delta$  scale) (multiplicity, coupling constants *J* in Hz, integration intensity). Abbreviations used for analysis of multiplets are as follows: s (singlet), br s (broad singlet), d (doublet), t (triplet), q

(quartet), p (pentet), h (hextet), and m (multiplet). Variable temperature NMR spectroscopy was performed at the Ludwig-Maximilians-Universität NMR facility.

**FTIR Spectroscopy:** IR spectra were recorded on a PerkinElmer Spectrum BXII FTIR spectrometer equipped with an attenuated total reflection (ATR) measuring unit. IR data is recorded in frequency of absorption (wavenumber in  $\text{cm}^{-1}$ ) with bands described as weak (w), medium (m), strong (s), broad (br) and combinations thereof.

**Mass Spectrometry:** Mass spectrometry (MS) experiments were performed at high resolution on a Thermo Finnigan MAT 95 (electron ionization [EI] double-focusing magnetic sector mass spectrometer) or on a Thermo Finnigan LTQ FT (electrospray ionization [ESI] linear ion trap-based Fourier Transform Ion Cyclotron Resonance mass spectrometer) instrument at the Ludwig-Maximilians-Universität mass spectrometry facility.

**Optical Rotation:** Optical rotation values were measured on a PerkinElmer 411 polarimeter or a Krüss P8000-P8100-T polarimeter equipped with a sodium lamp.

**Melting Point:** Melting points were measured using a Stanford Research Systems MPA120 Automated Melting Point Apparatus in open capillaries and are uncorrected.

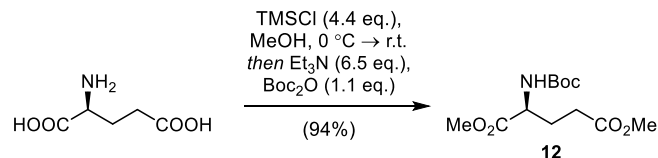
**High Pressure Experiments:** High-pressure reactions were performed using a high-pressure apparatus (max. 14 kbar, piston 25 mm) from *Andreas Hofer Hochdrucktechnik GmbH* equipped with a *Julabo* MA-4 heating circulator.

---

## 4.2. Experimental Procedures for Chapter I

The following section uses numbering from *Angew. Chem. Int. Ed.* **2016**, 55, 2191 – 2194.

### Synthesis of *N*-Boc-L-glutamic acid dimethyl ester (**12**)

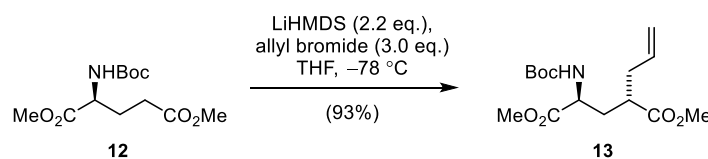


Following a procedure by Yang et al.,<sup>[240]</sup> L-glutamic acid (15.0 g, 102 mmol, 1.0 equiv.) was suspended in MeOH (250 mL) and the suspension was cooled to 0 °C. TMSCl (56.9 mL, 449 mmol, 4.4 equiv.) was added to the flask *via* drop funnel and the resulting clear solution was warmed to room temperature and stirred for 15 h. Et<sub>3</sub>N (92.4 mL, 663 mmol, 6.5 equiv.) was then added dropwise *via* syringe over the course of 1 h while an ice bath was used periodically to cool the warming solution. Following addition of base, di-*tert*-butyl dicarbonate (25.8 mL, 0.112 mol, 1.1 equiv.) was added *via* syringe and the cloudy white reaction mixture was stirred for 16 h, gradually turning clear and colorless. Solvent was removed under reduced pressure and the resulting white residue was taken up in Et<sub>2</sub>O (400 mL) and filtered through a pad of Celite<sup>®</sup>. The pad was washed with Et<sub>2</sub>O (800 mL) and the combined organic washings were concentrated under reduced pressure. The crude residue was purified by flash column chromatography (20% EtOAc in pentane) to afford *N*-Boc-L-glutamic acid dimethyl ester **12** (26.4 g, 95.9 mmol, 94%) as a colorless oil. The <sup>1</sup>H NMR spectrum is in agreement with that previously reported.<sup>[240]</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.10 (d, *J* = 8.2 Hz, 1H), 4.34 (q, *J* = 7.9 Hz, 1H), 3.75 (s, 3H), 3.68 (s, 3H), 2.50 – 2.31 (m, 2H), 2.19 (dq, *J* = 13.8, 6.5 Hz, 1H), 1.95 (dq, *J* = 13.8, 7.7 Hz, 1H), 1.44 (s, 9H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 173.30, 172.80, 155.45, 80.15, 52.95, 52.57, 51.94, 30.18, 28.41, 27.91.



**Synthesis of dimethyl (2*S*,4*S*)-2-allyl-4-((*tert*-butoxycarbonyl)amino)pentanedioate (**13**)**


Following a modified procedure by Hanessian et al.,<sup>[241]</sup> LiHMDS (1.0 M in THF, 59.2 mL, 2.2 equiv.) was added *via* cannula to a solution of *N*-Boc-L-glutamic acid dimethyl ester **12** (7.41 g, 26.9 mmol, 1.0 equiv.) in THF (100 mL) at  $-78\text{ }^\circ\text{C}$ . The reaction mixture was stirred at this temperature for 30 minutes, whereupon allyl bromide (6.83 mL, 80.7 mmol, 3.0 equiv.) was added and the pale yellow solution was stirred at  $-78\text{ }^\circ\text{C}$  for an additional 2 h. A saturated aqueous solution of  $\text{NH}_4\text{Cl}$  (50 mL) was then added and the reaction mixture was warmed to room temperature. The aqueous layer was separated and extracted with EtOAc ( $3 \times 120\text{ mL}$ ). The combined organic layers were rinsed with brine (50 mL), dried over anhydrous sodium sulfate ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (10 – 15% EtOAc in pentane) to afford allylated glutamic acid ester **13** (7.91 g, 25.1 mmol, 93%) as a pale yellow oil.

$R_f$ : 0.27 (15% EtOAc in pentane, stains with  $\text{KMnO}_4$ ).

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.70 (ddt,  $J = 17.2, 10.1, 7.0\text{ Hz}$ , 1H), 5.09 (dd, 17.2, 1.6 Hz, 1H), 5.06 (d, 10.1 Hz, 1H), 4.95 (d,  $J = 7.8\text{ Hz}$ , 1H), 4.35 (q,  $J = 7.8\text{ Hz}$ , 1H), 3.73 (s, 3H), 3.66 (s, 3H), 2.57 (quin,  $J = 7.0\text{ Hz}$ , 1H), 2.34 (m, 2H), 2.00 (t,  $J = 7.0\text{ Hz}$ , 2H), 1.43 (s, 9H).

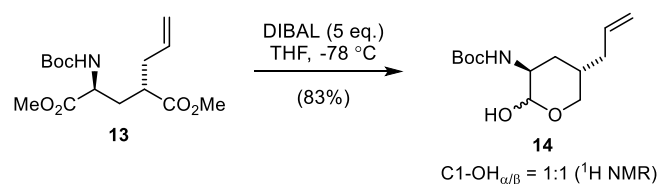
$^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  175.60, 172.94, 155.46, 134.47, 117.80, 80.16, 52.53, 52.22, 51.89, 41.96, 36.54, 33.81, 28.41.

HRMS (ESI<sup>+</sup>): Calc. for  $\text{C}_{15}\text{H}_{26}\text{NO}_6$  [ $\text{M} + \text{H}^+$ ]: 316.1755. Found: 316.1764.

IR (ATR):  $\tilde{\nu} = 3367$  (br w), 2979 (w), 2954 (w), 1734 (s), 1713 (s), 1512 (m), 1438 (m), 1367 (m), 1246 (m), 1161 (s), 1050 (w), 1026 (w), 995 (w), 919 (w), 857 (w), 780 (w).

$[\alpha]_D^{22} = +21.3^\circ$  ( $c = 1.2$ ,  $\text{CHCl}_3$ ).

### Synthesis of *tert*-butyl ((3*S*,5*S*)-5-allyl-2-hydroxytetrahydro-2*H*-pyran-3-yl)carbamate (**14**)



Allylated glutamic acid ester **13** (405 mg, 1.28 mmol, 1.0 equiv.) was dissolved in THF (12 mL) and the resulting solution was cooled to  $-78\text{ }^\circ\text{C}$ . DIBAL (1.0 M in PhMe, 5.78 mL, 5.78 mmol, 4.5 equiv.) was then slowly added to the solution along the walls of the vessel. The mixture was stirred at  $-78\text{ }^\circ\text{C}$  for 1 h where TLC analysis indicated some unreacted **13** remained. Additional DIBAL (0.64 mL, 0.5 equiv.) was added and the mixture was stirred at  $-78\text{ }^\circ\text{C}$  for 2 h before slow addition of MeOH (10 mL). The mixture was warmed to room temperature and poured into an Erlenmeyer containing a saturated aqueous solution of Rochelle's salt (20 mL). The resulting emulsion was stirred vigorously for 2 h until two clear and colorless phases formed. The aqueous phase was separated and extracted with Et<sub>2</sub>O ( $3 \times 30$  mL). The combined organic layers were then dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (20 – 30% EtOAc in pentane) to afford lactol **14** (274 mg, 1.06 mmol, 83%) as a colorless oil. <sup>1</sup>H NMR indicates a 1:1 mixture of diastereomers at C1.

**R<sub>f</sub>** : 0.70 (40% EtOAc in pentane, stains with KMnO<sub>4</sub>).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**  $\delta$  5.74 (m, 2H), 5.11 – 4.94 (m, 6H), 4.84 (br s, 2H), 3.98 (ddd,  $J = 11.5, 3.8, 1.1$  Hz, 1H), 3.87 (br s, 1H), 3.75 – 3.64 (m, 2H), 3.55 (dd,  $J = 10.8, 3.0$  Hz, 1H), 3.26 (dd,  $J = 11.5, 7.7$  Hz, 1H), 2.15 – 1.89 (m, 5H), 1.79 – 1.67 (m, 3H), 1.71 – 1.63 (m, 1H), 1.55 – 1.48 (m, 1H), 1.45 (s, 9H), 1.45 (s, 9H).

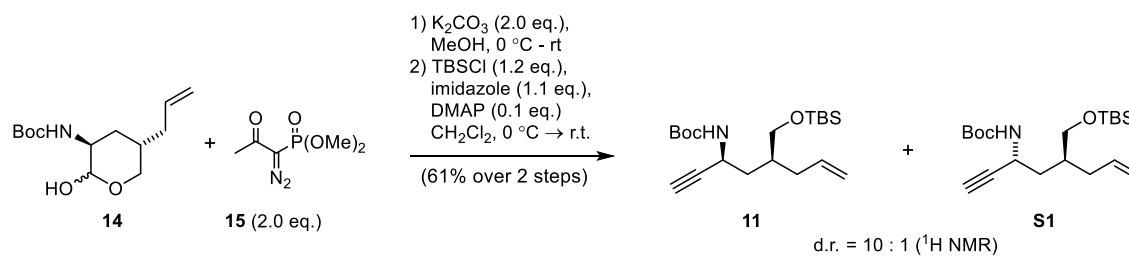
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)**  $\delta$  156.25, 155.86, 135.90, 135.62, 116.87, 116.85, 94.53, 94.34, 79.99, 67.37, 64.64, 48.47, 47.98, 36.66, 35.64, 32.33, 31.29, 30.99, 29.82, 28.47, 28.47, 27.98.

**HRMS (ESI<sup>+</sup>)**: Calc. for C<sub>13</sub>H<sub>23</sub>NO<sub>4</sub>Na<sup>+</sup> [ $M + \text{Na}^+$ ]: 280.1519. Found: 280.1518.

**IR (ATR)**:  $\tilde{\nu} = 3354$  (br s), 3077 (w), 2977 (m), 2932 (m), 1688 (s), 1641 (w), 1504 (s), 1448 (w), 1392 (m), 1366 (m), 1246 (m), 1169 (s), 1068 (s), 1014 (s), 915 (m), 881 (w), 778 (w).

$[\alpha]_D^{22} = -2.3^\circ$  ( $c = 2.0$ , CHCl<sub>3</sub>).

**Synthesis of *tert*-butyl ((3*S*,5*S*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)oct-7-en-1-yn-3-yl) carbamate (**11**)**



Potassium carbonate (5.96 g, 43.1 mmol, 2.0 equiv.) was added to a solution of dimethyl (1-diazo-2-oxopropyl)phosphonate **15** (8.83 g, 43.1 mmol, 2.0 equiv.) in MeOH (150 mL) at 0 °C and the bright yellow suspension was stirred at this temperature for 2 h. Lactol **14** (5.54 g, 21.5 mmol, 1.0 equiv.) in MeOH (25 mL) was then added dropwise *via* syringe. The mixture was gradually warmed to room temperature and stirred for 12 h. The reaction was diluted with  $\text{H}_2\text{O}$  (80 mL) and  $\text{Et}_2\text{O}$  (80 mL), and the aqueous phase was separated and further extracted with  $\text{Et}_2\text{O}$  (3  $\times$  50 mL). The combined organic layers were rinsed with brine (50 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (20 – 30% EtOAc in pentane) to afford a mixture of predominantly the alkyne product, along with some co-eluting unreacted **14** (~5 – 10%), as a colorless oil (4.31 g). The mixture was submitted directly to the next reaction.

Imidazole (1.27 g, 18.7 mmol, 1.1 equiv.) and DMAP (0.204 g, 1.67 mmol, 0.1 equiv.) were added sequentially to a solution of impure alkyne (4.31 g, assumed 16.7 mmol, 1.0 equiv.) in  $\text{CH}_2\text{Cl}_2$  (105 mL) at room temperature. The solution was cooled to 0 °C and TBSCl (3.07 g, 20.4 mmol, 1.2 equiv.) was added in a single portion. The resulting cloudy suspension was allowed to warm to room temperature and stirred for 4 h. A saturated aqueous solution of  $\text{NaHCO}_3$  (50 mL) was then added to the reaction mixture. The aqueous layer was separated and further extracted with  $\text{CH}_2\text{Cl}_2$  (50 mL) and the combined organic layers were rinsed with brine (50 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (3 – 4% EtOAc in pentane) to afford alkyne **11** (4.81 g, 13.1 mmol, 61% over two steps) as a pale yellow oil.  $^1\text{H}$  NMR indicates a 10:1 mixture of diastereomers with **S1**.

$R_f$  : 0.41 (4% EtOAc in pentane, stains with  $\text{KMnO}_4$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , major diastereomer)  $\delta$  5.73 (ddt,  $J$  = 18.4, 10.1, 7.0 Hz, 1H), 5.02 (d,  $J$  = 18.4 Hz, 1H), 5.01 (d,  $J$  = 10.1 Hz, 1H), 4.83 (d,  $J$  = 5.9 Hz, 1H), 4.42 (q,  $J$  = 6.8 Hz, 1H), 3.50 (m, 2H), 2.24 (s, 1H), 2.16 (dt,  $J$  = 13.4, 6.7 Hz, 1H), 2.03 (dt,  $J$  = 13.4, 6.7 Hz, 1H), 1.76 (dt,  $J$  = 12.2, 6.1 Hz, 1H), 1.68 (m, 1H), 1.60 (dt,  $J$  = 12.2, 6.4 Hz, 1H), 1.43 (s, 9H), 0.88 (s, 9H), 0.03 (s, 6H).

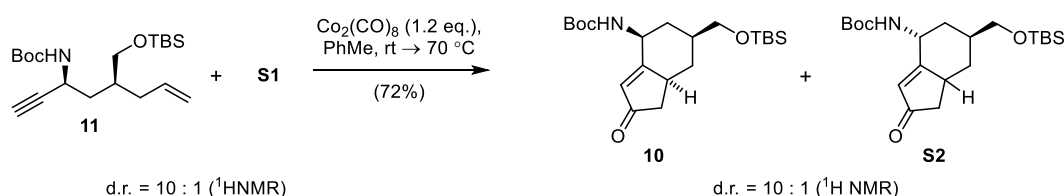
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , major diastereomer)  $\delta$  154.90, 136.55, 116.71, 84.19, 83.87, 79.83, 70.73, 64.83, 41.29, 37.44, 35.93, 28.47, 26.05, 18.39, -5.32.

HRMS ( $\text{ESI}^+$ ): Calc. for  $\text{C}_{20}\text{H}_{38}\text{NO}_3\text{Si}^+$  [ $\text{M} + \text{H}^+$ ]: 368.2616. Found: 368.2618.

IR (ATR):  $\tilde{\nu}$  = 3313 (w), 3077 (w), 2954 (m), 2929 (m), 2857 (m), 1704 (s), 1640 (w), 1496 (s), 1390 (w), 1366 (m), 1250 (s), 1168 (s), 1098 (m), 1004 (m), 912 (m), 833 (s), 774 (s).

$[\alpha]_D^{22} = -23.1^\circ$  ( $c = 1.7$ ,  $\text{CHCl}_3$ ).

**Synthesis of *tert*-butyl ((4*S*,6*S*,7*aS*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-oxo-2,4,5,6,7,7*a*-hexahydro-1*H*-inden-4-yl)carbamate (**10**)**



Cobalt carbonyl (2.44 g, 7.13 mmol, 1.2 equiv.) was added to a solution of alkyne **11** (2.18 g, 5.94 mmol, 1.0 equiv.) in degassed toluene (80 mL) at room temperature. The dark red solution was stirred for 1.5 h, whereupon thin layer chromatography analysis indicated complete conversion of starting material to the alkyne- $\text{Co}_2(\text{CO})_6$  complex. The mixture was heated to 70 °C for 15 h, then cooled to room temperature and filtered through a short pad of Celite.<sup>®</sup> The pad was washed with EtOAc (250 mL) and the combined solvent was concentrated under reduced pressure. The crude product was purified by flash column chromatography (15 – 30% EtOAc in pentane) to afford enone **10** (1.67 g, 4.28 mmol, 72%) as a clear, colorless oil.  $^1\text{H}$  NMR indicates a 10:1 mixture of diastereomers with **S2**.

$R_f$  : 0.23 (20% EtOAc in pentane, stains with  $\text{KMnO}_4$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , major diastereomer)  $\delta$  5.89 (s, 1H), 4.77 (br s, 1H), 4.44 (dt,  $J = 13.3, 6.8$  Hz, 1H), 3.45 (d,  $J = 5.7$  Hz, 2H), 2.81 (dt,  $J = 12.3, 6.6$  Hz, 1H), 2.64 (dd,  $J = 18.8, 6.6$  Hz, 1H), 2.25 – 2.10 (m, 2H, H-7a), 2.04 (d,  $J = 18.8$  Hz, 1H), 1.89 (m, 1H), 1.44 (s, 9H), 1.07 (q,  $J = 12.3$  Hz, 1H), 0.88 (m, 1H) 0.86 (s, 9H), 0.01 (s, 6H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , major diastereomer)  $\delta$  207.61, 184.28, 155.18, 125.25, 80.09, 66.81, 53.52, 51.32, 42.57, 40.22, 38.71, 36.97, 28.39, 25.97, 18.37, -5.38.

HRMS ( $\text{ESI}^+$ ): Calc. for  $\text{C}_{21}\text{H}_{38}\text{NO}_4\text{Si}^+$  [ $\text{M} + \text{H}^+$ ]: 396.25645. Found: 396.2564.



**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 5.78 (ddt, *J* = 17.1, 10.2, 6.6 Hz, 1H), 5.02 (d, *J* = 17.1 Hz, 1H), 4.93 (d, *J* = 10.2 Hz, 1H), 4.18 (d, *J* = 10.1 Hz, 1H), 3.92 (td, *J* = 10.1, 4.5 Hz, 1H), 3.45 (dd, *J* = 9.8, 5.2 Hz, 1H), 3.38 (dd, *J* = 9.8, 6.4 Hz, 1H), 2.55 (dd, *J* = 18.8, 7.3 Hz, 1H), 2.34 (d, *J* = 17.6 Hz, 1H), 2.29 (m, 2H), 2.03 (dq, *J* = 18.3, 5.8 Hz, 1H), 1.92 (d, *J* = 18.8 Hz, 1H), 1.86 (d, *J* = 12.5 Hz, 1H), 1.73 (d, *J* = 17.6 Hz, 1H), 1.73 (overlapping, 1H) 1.68 – 1.51 (m, 2H, H-4a), 1.43 (s, 9H), 1.30 (dt, *J* = 14.5, 11.9, 5.1 Hz, 1H), 1.06 (q, *J* = 12.5 Hz, 1H), 0.87 (s, 9H), 0.77 (q, *J* = 13.1 Hz, 1H), 0.02 (s, 6H).

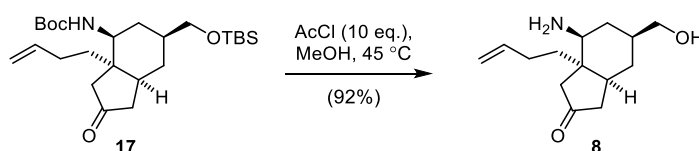
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)** δ 217.98, 155.55, 138.54, 114.88, 79.60, 67.46, 50.16, 46.10, 44.44, 43.29, 38.24, 36.63, 35.29, 33.16, 32.00, 28.48, 27.88, 26.08, 18.49, -5.25.

**HRMS (ESI<sup>+</sup>):** Calc. for C<sub>25</sub>H<sub>46</sub>NO<sub>4</sub>Si<sup>+</sup> [*M* + H<sup>+</sup>]: 452.3191. Found: 452.3191.

**IR (ATR):**  $\tilde{\nu}$  = 3348 (w), 2928 (m), 2856 (m), 1740 (s), 1711 (s), 1697 (s), 1518 (m), 1502 (m), 1462 (w), 1390 (m), 1365 (m), 1249 (s), 1172 (m), 1154 (m), 1109 (m), 1003 (m), 908 (m), 834 (s), 775 (s).

$[\alpha]_D^{22} = -53.7^\circ$  (*c* = 1.2, CHCl<sub>3</sub>).

**Synthesis of (3a*R*,4*S*,6*S*,7a*S*)-4-amino-3a-(but-3-en-1-yl)-6-(hydroxymethyl)octahydro-2*H*-inden-2-one (8)**



Acetyl chloride (539  $\mu$ L, 7.56 mmol, 10.0 equiv.) was added dropwise *via* syringe to a solution of carbamate **17** (342 mg, 0.756 mmol, 1.0 equiv.) in MeOH (10 mL) at room temperature. The pale pink reaction mixture was heated to 45 °C for 2 h, then cooled to room temperature and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (91.2:8:0.8 CH<sub>2</sub>Cl<sub>2</sub>/MeOH/aqueous NH<sub>3</sub> solution) to afford aminoketone **8** (165 mg, 0.696 mmol, 92%) as a yellow oil. **Note:** Neat **8** was prone to partial decomposition when left under strong vacuum for extended periods of time (>3 h).

**R<sub>f</sub>** : 0.39 (20% MeOH in CH<sub>2</sub>Cl<sub>2</sub>, stains with ninhydrin and KMnO<sub>4</sub>).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 5.78 (ddt, *J* = 16.7, 10.3, 6.4 Hz, 1H), 5.02 (d, *J* = 18.8 Hz, 1H), 4.95 (d, *J* = 10.3 Hz, 1H), 3.42 (d, *J* = 6.1 Hz, 2H), 2.97 (dd, *J* = 11.7, 4.4 Hz, 1H), 2.55 (dd, *J* = 18.8, 7.3 Hz, 1H), 2.39 (d, *J* = 18.3 Hz, 1H), 2.22 (dt, *J* = 12.8, 7.3 Hz, 1H), 2.07 (m, 2H), 1.89 (d,

$J = 18.8$  Hz, 1H), 1.78 (d,  $J = 18.3$  Hz, 1H), 1.76 (m, 1H), 1.74 (m, 1H), 1.72 (m, 1H) 1.59 (m, 1H), 1.38 (ddd,  $J = 15.6, 11.4, 5.2$  Hz, 1H), 1.05 (q,  $J = 12.2$  Hz, 1H), 0.79 (q,  $J = 12.8$  Hz, 1H).

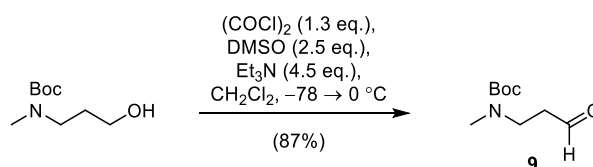
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  218.78, 138.34, 115.12, 67.64, 50.73, 46.99, 44.50, 43.34, 38.17, 36.50, 34.85, 33.72, 31.12, 27.84.

HRMS (ESI<sup>+</sup>): Calc. for  $\text{C}_{14}\text{H}_{24}\text{NO}_2^+$  [ $\text{M} + \text{H}^+$ ]: 238.1802. Found: 238.1801.

IR (ATR):  $\tilde{\nu} = 3352$  (br s), 2923 (s), 2857 (m), 2360 (m), 2340 (m), 1734 (s), 1640 (w), 1458 (m), 1406 (m), 1154 (m), 1060 (m), 912 (m), 670 (m).

$[\alpha]_D^{22} = -92.6^\circ$  ( $c = 0.7$ ,  $\text{CHCl}_3$ ).

### Synthesis of *N*-Boc-3-(methylamino)propanal (**9**)



Oxalyl chloride (1.61 mL [1.0 M in  $\text{CH}_2\text{Cl}_2$ ], 3.21 mmol, 1.3 equiv.) was added dropwise to a solution of DMSO (0.439 mL, 6.18 mmol, 2.5 equiv.) in  $\text{CH}_2\text{Cl}_2$  (15 mL) at  $-78^\circ\text{C}$  and the mixture was stirred at this temperature for 30 minutes. *N*-Boc-3-methylamino-1-propanol (463 mg, 2.47 mmol, 1.0 equiv.) in  $\text{CH}_2\text{Cl}_2$  (5 mL) was then added to the solution. The reaction mixture was stirred an additional 30 minutes at  $-78^\circ\text{C}$ , whereupon  $\text{Et}_3\text{N}$  (1.55 mL, 11.1 mmol, 4.5 equiv.) in  $\text{CH}_2\text{Cl}_2$  (5 mL) was added. The mixture was allowed to warm to room temperature and stirred for 16 h. The solution was then poured into brine (30 mL), and the aqueous layer was separated and further extracted with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 30$  mL). The combined organic layers were dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (30% EtOAc in pentane) to afford aldehyde **9** (401 mg, 2.14 mmol, 87%) as a colorless oil. *Note:*  $^1\text{H}$  NMR signals are broadened and some  $^{13}\text{C}$  NMR signals are doubled due to conformational isomerization of the Boc group.

$R_f$ : 0.35 (30% EtOAc in pentane, stains with  $\text{KMnO}_4$  and *p*-anisaldehyde solution).

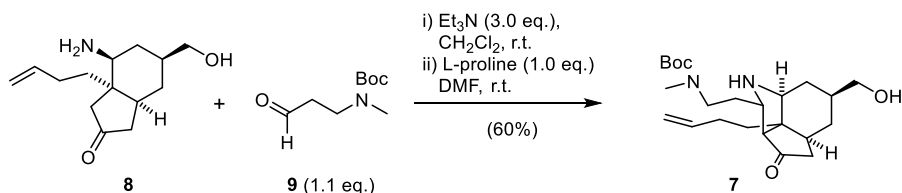
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.81 (br s, 1H), 3.54 (t,  $J = 6.4$  Hz, 2H), 2.87 (s, 3H), 2.68 (t,  $J = 6.4$  Hz, 2H), 1.45 (s, 9H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  201.28, 200.90, 155.75, 155.46, 80.01, 79.91, 42.85, 34.97, 34.65, 28.49.

HRMS (ESI<sup>+</sup>): Calc. for  $\text{C}_9\text{H}_{18}\text{NO}_3^+$  [ $\text{M} + \text{H}^+$ ]: 188.1281. Found: 188.1285.

**IR (ATR):**  $\tilde{\nu}$  = 2976 (w), 2933 (w), 2729 (w), 1722 (m), 1687 (s), 1481 (m), 1457 (w), 1391 (m), 1366 (m), 1321 (w), 1247 (w), 1218 (w), 1174 (m), 1146 (s), 1060 (m), 877 (m), 773 (m).

**Synthesis of *tert*-butyl (2-((2*S*,2*aR*,2*a1R*,4*aS*,6*S*,7*aS*)-2*a1*-(but-3-en-1-yl)-6-(hydroxymethyl)-3-oxodecahydro-1*H*-cyclopenta[*cd*]indol-2-yl)ethyl)(methyl)carbamate (**7**)**



Triethylamine (177  $\mu$ L, 1.27 mmol, 3.0 equiv.) was added to a solution of amine **8** (100 mg, 0.422 mmol, 1.0 equiv.) and aldehyde **9** (87.1 mg, 0.465 mmol, 1.1 equiv.) in  $\text{CH}_2\text{Cl}_2$  (6 mL) at room temperature. The mixture was stirred for 1.5 h, then concentrated under reduced pressure. The resulting residue was dissolved in DMF (5 mL) and L-proline (48.7 mg, 0.422 mmol, 1.0 equiv.) was added at room temperature. The reaction was stirred at room temperature for 18 h and then concentrated to afford a yellow residue. The crude product was purified by flash column chromatography (3 – 8% MeOH in  $\text{CH}_2\text{Cl}_2$ ) to afford pyrrolidine **7** (103 mg, 0.253 mmol, 60%) as a yellow oil.

**R<sub>f</sub>** : 0.60 (10% MeOH in  $\text{CH}_2\text{Cl}_2$ , stains with  $\text{KMnO}_4$ ).

**<sup>1</sup>H NMR (400 MHz,  $\text{CDCl}_3$ )**  $\delta$  5.80 (ddt,  $J$  = 17.1, 10.2, 6.3 Hz, 1H), 5.06 (d,  $J$  = 17.1 Hz, 1H), 5.00 (d,  $J$  = 10.2 Hz, 1H), 3.49 (m, 3H), 3.46 – 3.36 (m, 1H), 3.30 (q,  $J$  = 6.5 Hz, 1H), 3.12 (ddd,  $J$  = 14.2, 9.1, 5.2 Hz, 1H), 2.85 (s, 3H), 2.73 (dd,  $J$  = 17.7, 8.2 Hz, 1H), 2.32 (bs, 1H), 2.19 – 1.99 (m, 5H), 1.93 (m, 1H), 1.78 (m, 2H), 1.72 – 1.58 (m, 3H), 1.53 (m, 1H), 1.44 (s, 9H), 1.43 (overlapping, 1H).

**<sup>13</sup>C NMR (100 MHz,  $\text{CDCl}_3$ )**  $\delta$  218.24, 155.93, 137.84, 115.38, 79.75, 66.25, 62.40, 59.64, 57.61, 52.65, 46.57, 46.16, 39.10, 36.45, 34.74, 32.57, 29.86, 29.51, 29.26, 28.59, 28.12.

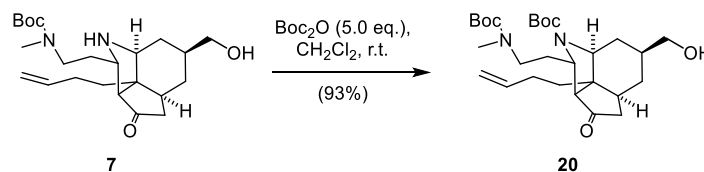
**HRMS (ESI<sup>+</sup>):** Calc. for  $\text{C}_{23}\text{H}_{39}\text{N}_2\text{O}_4^+$  [ $\text{M} + \text{H}^+$ ]: 407.2904. Found: 407.2906.

**IR (ATR):**  $\tilde{\nu}$  = 3305 (br m), 3076 (w), 2974 (w), 2923 (s), 2865 (m), 1733 (s), 1689 (s), 1641 (w), 1481 (m), 1451 (m), 1394 (m), 1365 (m), 1309 (w), 1251 (w), 1218 (w), 1154 (s), 1051 (m), 911 (m), 878 (m), 772 (m).

$[\alpha]_D^{22} = +4.2^\circ$  ( $c$  = 0.60,  $\text{CHCl}_3$ ).



**Synthesis of *tert*-butyl (2*S*,2*aR*,2*a1R*,4*aS*,6*S*,7*aS*)-2*a1*-(but-3-en-1-yl)-2-(2-((*tert*-butoxy carbonyl)(methyl)amino)ethyl)-6-(hydroxymethyl)-3-oxodecahydro-1*H*-cyclopenta[*cd*]indole-1-carboxylate (**20**)**



Di-*tert*-butyl dicarbonate (353  $\mu$ L, 1.48 mmol, 5.0 equiv.) was added to a solution of pyrrolidine **7** (120 mg, 0.296 mmol, 1.0 equiv.) in  $\text{CH}_2\text{Cl}_2$  (6 mL) at room temperature. The solution was stirred for 72 h, then concentrated under reduced pressure. The crude residue was purified by flash column chromatography (50% EtOAc in pentane) to afford dicarbamate **20** (140 mg, 0.276 mmol, 93%) as a colorless yellow oil.

$R_f$ : 0.34 (50% EtOAc in pentane, stains with  $\text{KMnO}_4$ )

$^1\text{H NMR}$  (400 MHz,  $d^8$ -toluene, 353 K)  $\delta$  5.70 (ddt,  $J = 16.8, 10.2, 6.5$  Hz, 1H), 5.03 (dt,  $J = 16.8, 1.3$  Hz, 1H), 4.95 (dq,  $J = 10.2, 1.3$  Hz, 1H), 3.94 (d,  $J = 9.7$  Hz, 1H), 3.52 (dd,  $J = 8.1, 4.2$  Hz, 1H), 3.36 (m, 1H), 3.17 (m, 2H), 3.10 (m, 1H), 2.76 (s, 3H), 2.40 (m, 1H), 2.26 (dd,  $J = 18.5, 10.2$  Hz, 1H), 1.96 (m, 2H), 1.87 (d,  $J = 18.5$  Hz, 1H), 1.83 – 1.76 (m, 2H, H-18a), 1.65 – 1.55 (m, 3H), 1.49 (m, 2H), 1.44 (s, 9H), 1.42 (s, 9H), 1.40 – 1.28 (m, 2H), 0.97 (dt,  $J = 14.6, 7.5$  Hz, 1H).

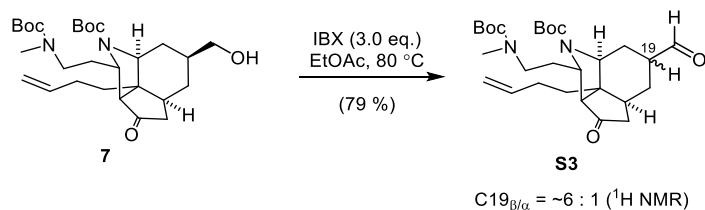
$^{13}\text{C NMR}$  (100 MHz,  $d^8$ -toluene, 333 K)  $\delta$  216.07, 155.72, 154.47, 138.77, 115.32, 79.79, 79.29, 68.20, 63.55, 59.93, 58.72, 52.42, 46.78, 45.92, 38.98, 36.33, 34.96, 34.31, 33.81, 29.93, 28.95, 28.95, 27.92, 25.21.

**HRMS (ESI<sup>+</sup>)**: Calc. for  $\text{C}_{28}\text{H}_{47}\text{N}_2\text{O}_6^+$  [ $\text{M} + \text{H}^+$ ]: 507.3429. Found: 507.3433.

**IR (ATR)**:  $\tilde{\nu} = 3455$  (br m), 2975 (m), 2928 (m), 2865 (m), 1739 (m), 1690 (s), 1479 (w), 1454 (w), 1392 (s), 1366 (m), 1316 (w), 1252 (w), 1219 (w), 1170 (s), 910 (w), 873 (w), 774 (w).

$[\alpha]_D^{22} = +40.3^\circ$  ( $c = 1.8, \text{CHCl}_3$ ).

**Synthesis of *tert*-butyl (2*S*,2*aR*,2*a1R*,4*aS*,7*aS*)-2*a1*-(but-3-en-1-yl)-2-(2-((*tert*-butoxycarbonyl)(methyl)amino)ethyl)-6-formyl-3-oxodecahydro-1*H*-cyclopenta[*cd*]indole-1-carboxylate (**S3**)**



2-Iodoxybenzoic acid (63.7 mg, 0.227 mmol, 3.0 equiv.) was added to a solution of alcohol **20** (38.4 mg, 0.0757 mmol, 1.0 equiv.) in EtOAc (4 mL) and the suspension was heated to 80 °C for 2 h. The mixture was then cooled to room temperature, filtered through a fritted glass filter and concentrated under reduced pressure. The crude product was purified by flash column chromatography (30% EtOAc in pentane) to afford aldehyde **S3** (30.2 mg, 0.0598 mmol, 79%) as a colorless oil.  $^1\text{H NMR}$  analysis ( $d^8$ -toluene, 353 K) indicated an inconsequential ~6:1 mixture of epimers at C19. *Note: S3 was prone to epimerization on silica and to degradation in  $\text{CHCl}_3$  and acetone.*

**R<sub>f</sub>** : 0.55 (40% EtOAc in pentane, stains with  $\text{KMnO}_4$ )

**$^1\text{H NMR}$  (400 MHz,  $d^8$ -toluene, 353 K, major diastereomer)**  $\delta$  9.31 (s, 1H), 5.70 (ddt,  $J = 17.1, 10.0, 6.4$  Hz, 1H), 5.04 (dd,  $J = 17.1, 1.7$  Hz, 1H), 4.98 (dd,  $J = 10.0, 1.7$  Hz, 1H), 3.89 (d,  $J = 10.1$  Hz, 1H), 3.51 (dd,  $J = 5.7$  Hz, 1H), 3.37 (ddd,  $J = 14.4, 10.3, 5.0$  Hz, 1H), 3.07 (ddd,  $J = 14.7, 9.8, 6.1$  Hz, 1H), 2.76 (s, 3H), 2.39 (br s, 1H), 2.19 (dd,  $J = 19.4, 10.5$  Hz, 1H), 1.93 (m, 4H), 1.69 (m, 2H), 1.58 (m, 2H), 1.45 (m, 11H), 1.43 (m, 10H), 1.35 (m, 1H), 1.20 (ddd,  $J = 13.8, 9.0, 4.4$  Hz, 1H) .

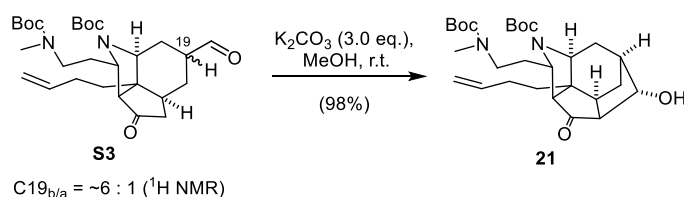
**$^{13}\text{C NMR}$  (100 MHz,  $d^8$ -toluene, 333 K, major diastereomer)**  $\delta$  215.45, 201.82, 155.70, 153.99, 138.56, 115.44, 80.04, 79.31, 62.38, 61.02, 59.34, 58.87, 52.30, 46.63, 44.86, 43.73, 41.81, 38.07, 35.52, 34.96, 29.72, 28.94, 28.88, 22.99.

**HRMS (ESI<sup>+</sup>)**: Calc. for  $\text{C}_{28}\text{H}_{45}\text{N}_2\text{O}_6^+$  [ $\text{M} + \text{H}^+$ ]: 505.3272. Found: 505.3272.

**IR (ATR)**: 2975 (w), 2930 (w), 1739 (m), 1690 (s), 1479 (w), 1455 (w), 1391 (m), 1366 (m), 1313 (w), 1255 (w), 1169 (m), 911 (w), 774 (w), 668 (w).

**$[\alpha]_D^{22}$**  = +99.6 ° (c = 0.17, PhMe).

**Synthesis of *tert*-butyl (2*S*,2*aR*,2*a1R*,4*aS*,6*S*,7*aS*,8*S*)-2*a1*-(but-3-en-1-yl)-2-(2-((*tert*-butoxy carbonyl)(methyl)amino)ethyl)-8-hydroxy-3-oxodecahydro-1*H*-4,6-methanocyclopenta[*cd*] indole-1-carboxylate (**21**)**



$\text{K}_2\text{CO}_3$  (24.3 mg, 0.176 mmol, 3.0 equiv.) was added to a solution of aldehyde **S3** (30.2 mg, 0.0598 mmol, 1.0 equiv.) in MeOH (1.5 mL) at room temperature. The pale yellow suspension was stirred for 20 minutes and then concentrated under reduced pressure. The residue was then partitioned between  $\text{H}_2\text{O}$  (5 mL) and  $\text{Et}_2\text{O}$  (5 mL) and the aqueous phase was further extracted with  $\text{Et}_2\text{O}$  ( $2 \times 10$  mL). The combined organic layers were dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (40% EtOAc in pentane) to afford alcohol **21** (29.6 mg, 0.0587 mmol, 98%) as a colorless oil.

$R_f$  : 0.28 (40% EtOAc in pentane, stains with  $\text{KMnO}_4$ )

$^1\text{H NMR}$  (400 MHz,  $d^8$ -toluene, 353 K)  $\delta$  5.71 (ddt,  $J = 17.1, 10.2, 6.5$  Hz, 1H), 5.05 (d,  $J = 17.1$  Hz, 1H), 4.94 (d,  $J = 10.2$  Hz, 1H), 3.96 (m, 1H), 3.69 (s, 1H), 3.49 (m, 1H), 3.34 (m, 1H), 3.07 (dt, 15.4, 7.7 Hz, 1H), 2.75 (s, 3H), 2.56 (br s, 1H), 2.40 (overlapping, 1H), 2.40 (d,  $J = 8.4$  Hz, 1H), 2.33 (dd,  $J = 8.4, 5.3$  Hz, 1H), 1.97 (m, 1H), 1.79-1.71 (m, 2H), 1.68 (ddd,  $J = 13.2, 11.6, 4.7$  Hz, 1H), 1.52 (ddd,  $J = 13.2, 8.7, 4.1$  Hz, 1H), 1.44 (s, 9H), 1.44 (overlapping, 2H), 1.39 (s, 9H), 1.30 (d,  $J = 11.8$  Hz, 1H), 1.30 (overlapping, 1H), 0.37 (dd,  $J = 15.8, 8.7$  Hz, 1H).

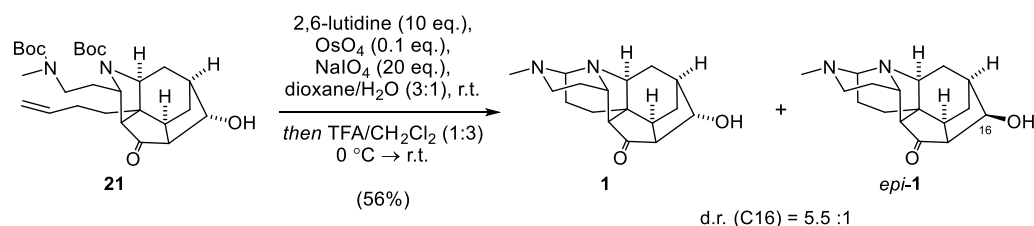
$^{13}\text{C NMR}$  (100 MHz,  $d^8$ -toluene, 333 K)  $\delta$  216.86, 155.80, 154.65, 138.83, 115.28, 85.00, 79.57, 79.29, 61.47, 59.22, 58.88, 54.66, 53.58, 47.24, 39.99, 39.86, 37.57, 34.79, 31.44, 30.60, 29.34, 28.96, 28.96, 28.03.

**HRMS (ESI $^+$ )**: Calc. for  $\text{C}_{28}\text{H}_{45}\text{N}_2\text{O}_6^+$  [ $\text{M} + \text{H}^+$ ]: 505.3272. Found: 505.3275.

**IR (ATR)**:  $\tilde{\nu} = 3446$  (br m), 2974 (m), 2932 (m), 1732 (m), 1690 (s), 1479 (w), 1454 (w), 1391 (s), 1366 (s), 1342 (w), 1316 (w), 1253 (w), 1212 (w), 1160 (s), 1088 (w), 1060 (w), 1028 (w), 995 (w), 911 (m), 871 (w), 773 (m), 731 (m).

$[\alpha]_D^{22} = +72.0^\circ$  ( $c = 0.40$ ,  $\text{CHCl}_3$ ).

### Synthesis of lycopalhine A (**2**) and *epi*-lycopalhine A



2,6-lutidine (14.3  $\mu$ L, 0.124 mmol, 5.0 equiv.), NaIO<sub>4</sub> (54.0 mg, 0.248 mmol, 10.0 equiv.), and OsO<sub>4</sub> (2.5% in *t*-BuOH, 30.8  $\mu$ L, 2.5  $\mu$ mol, 0.1 equiv.) were added sequentially to a solution of olefin **21** (12.5 mg, 0.025 mmol, 1.0 equiv.) in a 3:1 mixture of dioxane/H<sub>2</sub>O (1.2 mL) at room temperature. The mixture was stirred at room temperature for 2 h and the suspension was then diluted with CH<sub>2</sub>Cl<sub>2</sub> (4 mL) and Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (4 mL). The aqueous layer was further extracted with CH<sub>2</sub>Cl<sub>2</sub> (3  $\times$  5 mL) and the combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The resulting colorless residue was then dissolved in CH<sub>2</sub>Cl<sub>2</sub> (0.75 mL) and cooled to 0 °C, whereupon trifluoroacetic acid (0.25 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 1 h, then warmed to room temperature and stirred an additional 2 h. The solution was then diluted with CH<sub>2</sub>Cl<sub>2</sub> (4 mL) and the aqueous phase was adjusted to pH 10 by dropwise addition of saturated Na<sub>2</sub>CO<sub>3</sub> solution. The aqueous layer was separated and further extracted with CH<sub>2</sub>Cl<sub>2</sub> (2  $\times$  10 mL), and the combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (189:10:1 – 89:10:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH/aqueous NH<sub>3</sub> solution) to afford lycopalhine A (**1**) and *epi*-**1** (4.0 mg, 0.014 mmol, 56%) as a white gum. <sup>1</sup>H NMR analysis indicates a 5.5:1 mixture of diastereomers at C16.

**R<sub>f</sub>** : 0.33 (89:10:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH /aqueous NH<sub>3</sub> solution, stains with KMnO<sub>4</sub>)

**<sup>1</sup>H NMR (600 MHz, pyridine-*d*<sub>5</sub>, major diastereomer)**  $\delta$  6.81 (s, 1H), 4.29 (s, 1H), 3.65 (dd, *J* = 10.5, 6.7 Hz, 1H), 3.56 (ddd, *J* = 7.7, 5.8, 3.8 Hz, 1H), 3.05 (dd, *J* = 7.9, 2.3 Hz, 1H), 2.98 (ddd, *J* = 12.5, 9.8, 4.2 Hz, 1H), 2.57 (t, *J* = 10.1 Hz, 1H), 2.45 (s, 3H), 2.43 (m, 1H), 2.40 (m, 1H), 2.37 (ddd, *J* = 5.9, 2.4, 1.1 Hz, 1H), 2.34 (dt, *J* = 12.5, 5.5 Hz, 1H), 2.27 (m, 1H), 2.16 (dt, *J* = 11.6, 4.8 Hz, 1H), 2.07 (dt, *J* = 15.5, 9.8 Hz, 1H), 1.86 (td, *J* = 11.9, 7.1 Hz, 1H), 1.74 (m, 1H), 1.71 (m, 1H), 1.71 (m, 1H), 1.63 (m, 1H), 1.55 (dd, *J* = 12.4, 7.8 Hz, 1H), 0.93 (dd, *J* = 15.4, 10.3 Hz, 1H).

**<sup>13</sup>C NMR (150 MHz, pyridine-*d*<sub>5</sub>, major diastereomer)**  $\delta$  221.66, 85.63, 77.02, 65.56, 65.27, 63.46, 61.11, 54.34, 42.99, 42.85, 42.26, 41.36, 36.00, 27.94, 27.29, 25.46, 24.23.

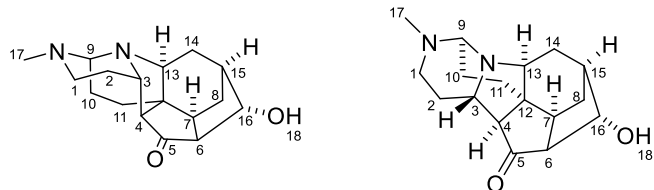
**<sup>13</sup>C NMR (150 MHz, pyridine-*d*<sub>5</sub>, minor diastereomer)**  $\delta$  219.17, 76.28, 75.55, 64.30, 62.13, 58.74, 58.21, 55.62, 43.82, 42.10, 41.05, 37.66, 36.69, 27.03, 23.53, 23.02, 22.84.

**HRMS (ESI<sup>+</sup>):** Calc. for C<sub>17</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub><sup>+</sup> [*M* + H<sup>+</sup>]: 289.1910. Found: 289.1911.

**IR (ATR):**  $\tilde{\nu}$  = 3370 (br s), 2930 (s), 1717 (s), 1454 (m), 1376 (w), 1300 (w), 1176 (m), 1098 (m), 1048 (m), 1027 (m), 854 (w), 711 (w), 644 (w).

$[\alpha]_D^{22} = +109^\circ$  (c = 0.15, CHCl<sub>3</sub>).

**Table 4.1.** Comparison of  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectral data and optical rotation between natural and synthetic lycopalhine A.<sup>[97]</sup>

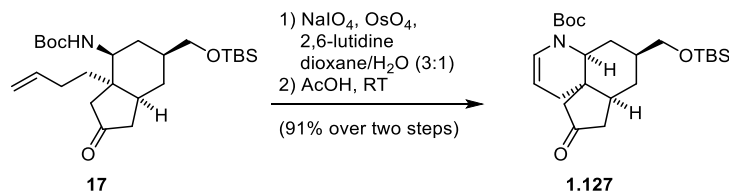


	$^1\text{H}$ NMR ( $\delta$ in ppm, $J$ in Hz)		$^{13}\text{C}$ NMR ( $\delta$ in ppm)	
	Natural (500 MHz) <sup>1</sup>	Synthetic (600 MHz)	Natural (125 MHz) <sup>1</sup>	Synthetic (150 MHz)
1a	2.98 (1H, ddd, 13.5, 10.5, 4.5)	2.98 (1H, ddd, 12.5, 9.8, 4.2)	43.06	42.99
1b	2.34 (1H, m)	2.34 (1H, dt, 12.5, 5.5)	-	-
2a	2.27 (1H, m)	2.27 (1H, m)	24.32	24.23
2b	1.74 (1H, m)	1.74 (1H, m)	-	-
3	3.56 (1H, m)	3.56 (1H, ddd, 7.7, 5.8, 3.8)	61.17	61.11
4	2.36 (1H, m)	2.37 (1H, ddd, 5.9, 2.4, 1.1)	63.57	63.46
5	-	-	221.56	221.66
6	3.05 (1H, d, 7.5)	3.05 (1H, dd, 7.9, 2.3)	65.58	65.56
7	2.43 (1H, m)	2.43 (1H, m)	42.31	42.26
8a	2.16 (1H, dt, 12.0, 4.5)	2.16 (1H, dt, 11.6, 4.8)	27.95	27.94
8b	1.70 (1H, overlap)	1.71 (1H, m)	-	-
9	3.64 (1H, dd, 10.5, 7.5)	3.65 (1H, dd, 10.5, 6.7)	77.12	77.02
10a	1.70 (1H, overlap)	1.71 (1H, m)	25.48	25.46
10b	1.63 (1H, m)	1.63 (1H, m)	-	-
11a	1.85 (1H, td, 12.0, 7.5)	1.86 (1H, td, 11.9, 7.1)	36.07	36.00
11b	1.55 (1H, dd, 12.0, 7.5)	1.55 (1H, dd, 12.4, 7.8)	-	-
12	-	-	54.38	54.34
13	2.56 (1H, t, 10.0)	2.57 (1H, t, 10.1)	65.35	65.27
14a	2.07 (1H, dt, 15.5, 10.0)	2.07 (1H, dt, 15.5, 9.8)	27.34	27.29
14b	0.92 (1H, dd, 15.5, 10.0)	0.93 (1H, dd, 15.4, 10.3)	-	-
15	2.40 (1H, m)	2.40 (1H, m)	41.41	41.36
16	4.29 (1H, br s)	4.29 (1H, s)	85.68	85.63
17	2.45 (3H, s)	2.45 (3H, s)	42.86	42.85
18	-	6.81 (1H, br s)	-	-

Natural (+)-lycopalhine A	Synthetic (+)-lycopalhine A
$[\alpha]_D^{15} = +89.1$ (c 0.17, $\text{CH}_3\text{OH}$ )	$[\alpha]_D^{22} = +109$ (c 0.15, $\text{CH}_3\text{OH}$ )

**Synthesis of *tert*-butyl (4*aR*,7*aS*,9*S*,10*aS*)-9-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-oxo-5,6,7,7*a*,8,9,10,10*a*-octahydrocyclopenta[*e*]quinoline-1(4*H*)-carboxylate (1.127)**



Olefin **17** (52.3 mg, 0.120 mmol, 1.0 equiv.) was dissolved in a 3:1 mixture of dioxane/H<sub>2</sub>O (2 mL) and the solution was cooled to 0 °C. 2,6-Lutidine (33.5 μL, 0.290 mmol, 2.5 equiv.), NaIO<sub>4</sub> (124 mg, 0.579 mmol, 5.0 equiv.) and OsO<sub>4</sub> (2.5% w/w in *t*BuOH, 72.0 μL, 5.80 μmol, 0.05 equiv.) were added sequentially to the reaction flask and the resulting white suspension was allowed to warm to ambient temperature and was stirred for 3.5 h. Saturated aqueous sodium thiosulfate solution (15 mL) was then added and the biphasic mixture was stirred for 25 minutes. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 20 mL) and the combined layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (10 → 20% EtOAc/pentane) to afford **1.125** and **1.12** together as colorless oils. The combined substrates were dissolved in AcOH (3 mL) and stirred at ambient temperature for 2 h, then concentrated under reduced pressure to afford enamine **1.127** as a colorless oil (47.6 mg, 0.109 mmol) in 91% yield.

**R<sub>f</sub>**: 0.56 (30% EtOAc in pentane, stains with KMnO<sub>4</sub>).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 6.77 (d, *J* = 8.3 Hz, 1H), 4.77 (ddd, *J* = 8.0, 5.3, 2.4 Hz, 1H), 3.57 (dd, *J* = 9.9, 4.6 Hz, 1H), 3.47 (dd, *J* = 11.8, 4.2 Hz, 1H), 3.40 (dd, *J* = 9.9, 6.9 Hz, 1H), 2.75 (m, 1H), 2.62 (dd, *J* = 18.6, 7.4 Hz, 1H), 2.35 (d, *J* = 18.6 Hz, 1H), 2.07 – 1.93 (m, 4H), 1.85 (m, 1H), 1.63 – 1.51 (m, 3H), 1.45 (s, 9H), 0.88 (s, 9H), 0.79 (m, 1H), 0.03 (s, 6H).

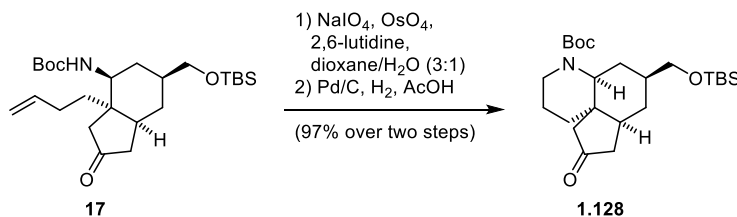
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)** δ 218.5, 153.3, 129.6, 103.7, 81.0, 68.1, 60.8, 45.2, 42.9, 42.6, 41.0, 38.7, 36.9, 33.6, 29.1, 28.5, 26.1, 18.5, -5.2.

**HRMS (ESI<sup>+</sup>)**: Calc. for C<sub>24</sub>H<sub>44</sub>O<sub>5</sub>NSi<sup>+</sup> [M + H<sub>3</sub>O<sup>+</sup>]: 454.2983. Found: 454.2988.

**IR (ATR)**:  $\tilde{\nu}$  = 2954 (m), 2928 (m), 2856 (m), 1742 (s), 1715 (s), 1657 (m), 1472 (w), 1391 (m), 1366 (m), 1339 (w), 1303 (m), 1269 (m), 1252 (s), 1165 (s), 1101 (s), 836 (s), 776 (m), 726 (w).

**[ $\alpha$ ]<sub>D</sub><sup>22</sup>** = -84° (c = 0.86, CHCl<sub>3</sub>).

**Synthesis of *tert*-butyl (4*aR*,7*aS*,9*S*,10*aS*)-9-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-oxodecahydrocyclopenta[*e*]quinoline-1(2*H*)-carboxylate (1.128)**



Olefin **17** (254 mg, 0.563 mmol, 1.0 equiv.) was dissolved in a 3:1 mixture of dioxane/H<sub>2</sub>O (8 mL) and the solution was cooled to 0 °C. 2,6-Lutidine (163 μL, 1.41 mmol, 2.5 equiv.), NaIO<sub>4</sub> (613 mg, 2.82 mmol, 5.0 equiv.) and OsO<sub>4</sub> (2.5% w/w in *t*BuOH, 350 μL, 0.0282 mmol, 0.05 equiv.) were added sequentially to the reaction flask and the resulting white suspension was allowed to warm to ambient temperature and was stirred for 2 h. Saturated aqueous sodium thiosulfate solution (10 mL) was then added and the biphasic mixture was stirred for 25 minutes. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 10 mL) and the combined layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude oil was dissolved in AcOH (8 mL) and stirred at ambient temperature for 20 minutes. Pd/C (10% w/w, 59.9 mg, 0.0563 mmol, 0.10 equiv.) was added and the suspension was stirred rapidly under H<sub>2</sub> atmosphere (balloon pressure) for 5 h. The sample was filtered over Celite<sup>®</sup> with EtOAc washing (50 mL) to remove catalyst and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash column chromatography (10 → 20% EtOAc/pentane) to afford **1.128** as a colorless oil (240 mg, 0.563 mmol) in 97% yield.

**R<sub>f</sub>**: 0.25 (10% EtOAc in pentane, stains with KMnO<sub>4</sub>).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 4.19 (d, *J* = 13.3 Hz, 1H), 3.48 (dd, *J* = 9.8, 6.5 Hz, 1H), 3.40 (dd, *J* = 9.8, 6.5 Hz, 1H), 3.06 (dd, *J* = 12.5, 3.7 Hz, 1H), 2.72 (td, *J* = 12.9, 3.3 Hz, 1H), 2.61 (d, *J* = 18.8 Hz, 1H), 2.54 (dd, *J* = 18.8, 7.6 Hz, 1H), 2.15 (q, *J* = 12.6 Hz, 1H), 2.06 – 1.87 (m, 4H), 1.86 – 1.72 (m, 2H), 1.70 – 1.47 (m, 3H), 1.42 (s, 9H), 1.40 (m, 1H), 0.88 (s, 9H), 0.76 (q, *J* = 12.6 Hz, 1H), 0.03 (s, 6H).

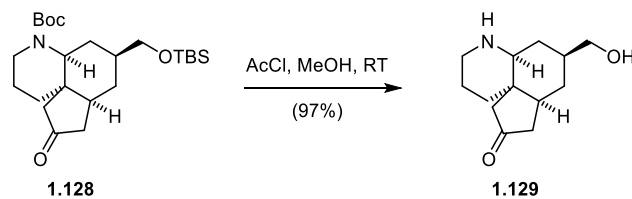
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)** δ 219.0, 155.0, 79.7, 68.0, 64.9, 49.4, 45.0, 44.1, 42.7, 40.4, 40.4, 37.6, 34.0, 30.9, 28.6, 26.1, 22.9, 18.5, -5.2, -5.2.

**HRMS (ESI<sup>+</sup>)**: Calc. for C<sub>24</sub>H<sub>44</sub>O<sub>4</sub>NSi<sup>+</sup> [M + H<sup>+</sup>]: 438.3034. Found: 438.3036.

**IR (ATR)**:  $\tilde{\nu}$  = 2928 (m), 2856 (m), 1741 (s), 1682 (s), 1464 (m), 1427 (m), 1390 (m), 1364 (m), 1250 (s), 1169 (s), 1155 (s), 1127 (m), 1097 (s), 1045 (m), 1007 (w), 836 (s), 775 (m), 667 (w).

**[ $\alpha$ ]<sub>D</sub><sup>22</sup>** = -90° (c = 0.43, CHCl<sub>3</sub>).



**Synthesis of (4a*R*,7a*S*,9*S*,10a*S*)-9-(hydroxymethyl)decahydrocyclopenta[*e*]quinolin-6(5*H*)-one (1.129)**

Acetyl chloride (392  $\mu\text{L}$ , 5.49 mmol, 10.0 equiv.) was added dropwise to a solution of carbamate **1.128** (240 mg, 0.549 mmol) in MeOH (10 mL) at ambient temperature. The mixture was then heated to 45  $^{\circ}\text{C}$  for 2 h 15 minutes, then cooled to ambient temperature and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (10% MeOH in  $\text{CH}_2\text{Cl}_2$  + 1% v/v aqueous  $\text{NH}_3$  solution) to afford amine **1.129** (119 mg, 0.535 mmol) in 97% yield.

**R<sub>f</sub>**: 0.18 (10% MeOH in  $\text{CH}_2\text{Cl}_2$  + 1% v/v aqueous  $\text{NH}_3$  solution, stains with  $\text{KMnO}_4$ ).

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )**  $\delta$  3.42 (m, 2H), 3.05 (m, 1H), 2.71 (td,  $J = 11.4, 5.0$  Hz, 1H), 2.58 – 2.37 (m, 4H), 2.30 (d,  $J = 18.9$  Hz, 1H), 2.16 (d,  $J = 18.9$  Hz, 1H), 1.95 – 1.82 (m, 2H), 1.77 – 1.56 (m, 6H), 1.27 (m, 1H), 1.11 (q,  $J = 12.2$  Hz, 1H), 0.78 (q,  $J = 13.3$  Hz, 1H).

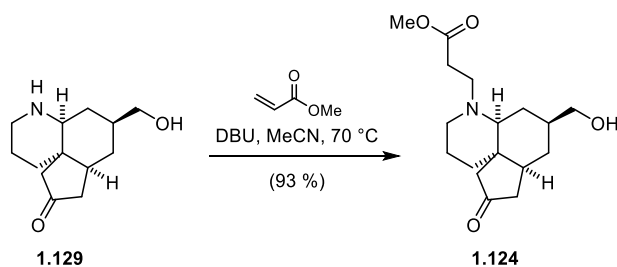
**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )**  $\delta$  219.2, 67.2, 62.4, 47.6, 43.9, 43.8, 41.2, 39.8, 38.6, 35.5, 33.4, 31.1, 23.0.

**HRMS (ESI<sup>+</sup>)**: Calc. for  $\text{C}_{13}\text{H}_{22}\text{O}_2\text{N}^+$  [ $\text{M} + \text{H}^+$ ]: 224.1645. Found: 224.1645.

**IR (ATR)**:  $\tilde{\nu} = 3282$  (br w), 2923 (m), 2854 (m), 1732 (s), 1459 (w), 1444 (w), 1407 (w), 1316 (w), 1157 (m), 1116 (w), 1067 (w), 1027 (w), 943 (w), 923 (w), 736 (m).

**$[\alpha]_D^{22}$**  =  $-123^{\circ}$  ( $c = 0.21$ ,  $\text{CHCl}_3$ ).

**Synthesis of methyl 3-((4aR,7aS,9S,10aS)-9-(hydroxymethyl)-6-oxodecahydrocyclopenta[e]quinolin-1(2H)-yl)propanoate (**1.124**)**



Methyl acrylate (88.1  $\mu\text{L}$ , 0.973 mmol, 3.0 equiv.) and DBU (145  $\mu\text{L}$ , 0.973 mmol, 3.0 equiv.) were added sequentially to a partially dissolved suspension of amine **1.129** (72.4 mg, 0.324 mmol, 1.0 equiv.) in acetonitrile (3.2 mL) at ambient temperature. The mixture was heated to 70  $^\circ\text{C}$  for 21 h, then cooled to ambient temperature and concentrated under reduced pressure. Purification by flash column chromatography (5% MeOH in  $\text{CH}_2\text{Cl}_2$ ) afforded aminoester **1.124** (93.2 mg, 0.301 mmol) in 93% yield.

**R<sub>f</sub>**: 0.26 (5% MeOH in  $\text{CH}_2\text{Cl}_2$ , stains with  $\text{KMnO}_4$ ).

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )**  $\delta$  3.62 (s, 3H), 3.45 (d,  $J = 6.1$  Hz, 2H), 2.96 (q,  $J = 6.7$  Hz, 1H), 2.85 (dd,  $J = 9.8, 2.4$ , 1H), 2.67 (ddd,  $J = 13.7, 8.3, 5.5$  Hz, 1H), 2.55 – 2.16 (m, 7H), 2.12 (d,  $J = 18.5$  Hz, 1H), 1.90 (m, 1H), 1.81 (d,  $J = 18.5$  Hz, 1H), 1.73 – 1.44 (m, 5H), 1.19 (m, 1H), 0.99 (q,  $J = 12.2$  Hz, 1H), 0.75 (q,  $J = 12.8$  Hz, 1H).

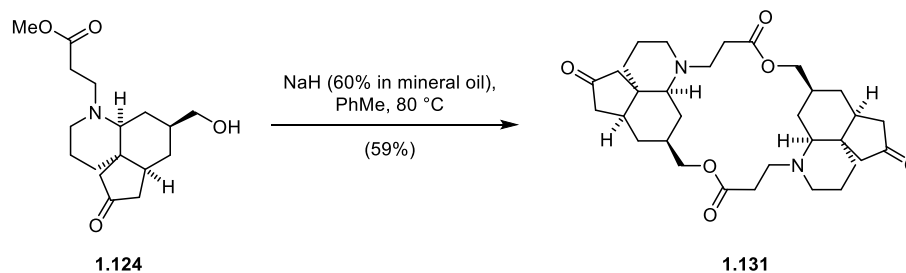
**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )**  $\delta$  219.5, 173.5, 67.6, 66.0, 53.6, 51.7, 47.8, 44.1, 44.0, 41.5, 41.0, 38.5, 35.7, 33.1, 30.8, 27.5, 21.7.

**HRMS (ESI<sup>+</sup>)**: Calc. for  $\text{C}_{17}\text{H}_{28}\text{O}_4\text{N}^+$  [ $\text{M} + \text{H}^+$ ]: 310.2013. Found: 310.2013.

**IR (ATR)**:  $\tilde{\nu} = 3450$  (br w), 2924 (m), 2854 (m), 1733 (s), 1440 (m), 1407 (w), 1376 (w), 1309 (w), 1292 (w), 1195 (m), 1161 (m), 1093 (w), 10248 (w), 1022 (w), 913 (w), 881 (w), 841 (w), 814 (w), 793 (w), 736 (w), 677 (w).

$[\alpha]_D^{20} = -59^\circ$  ( $c = 1.3$ ,  $\text{CHCl}_3$ ).

Synthesis of bis[3-((4a*R*,7a*S*,9*S*,10a*S*)-9-(hydroxymethyl)-6-oxodecahydrocyclopenta[*e*]quinolin-1(2*H*)-yl)propanoate] (**1.131**)



Sodium hydride (60% in mineral oil, 20.0 mg, 0.494 mmol, 10.0 equiv.) was added in one portion to a stirring solution of ketoester **1.124** in PhMe (2 mL) at ambient temperature. The cloudy mixture was stirred at ambient temperature for 20 minutes, then warmed to 80 °C for 2 h. Upon cooling once more to ambient temperature, saturated aqueous ammonium chloride solution (5 mL) was added and the product was extracted with EtOAc (3 × 5 mL). The combined layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (3 → 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to afford product **1.131** as a white solid (8.1 mg, 0.0292 mmol) in 59% yield.

**R<sub>f</sub>**: 0.43 (5% MeOH in CH<sub>2</sub>Cl<sub>2</sub>, stains with KMnO<sub>4</sub>).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 4.12 (dd, *J* = 10.6, 3.4 Hz, 1H), 3.66 (t, *J* = 10.6 Hz, 1H), 3.01 – 2.90 (m, 2H), 2.85 (m, 1H), 2.59 – 2.47 (m, 2H), 2.46 – 2.29 (m, 2H), 2.27 – 2.07 (m, 4H), 1.97 (q, *J* = 6.2 Hz, 1H), 1.86 (d, *J* = 18.5 Hz, 1H), 1.82 – 1.51 (m, 6H), 1.20 (m, 1H), 1.03 (q, *J* = 12.2 Hz, 1H), 0.79 (q, *J* = 13.0 Hz, 1H).

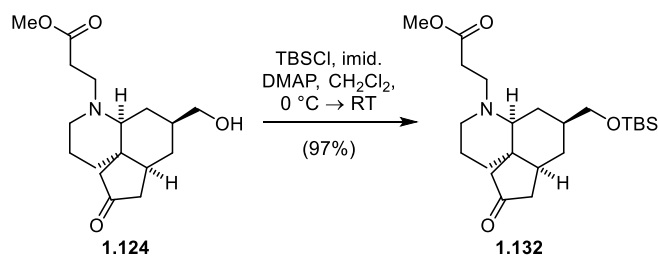
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)** δ 218.8, 172.6, 68.5, 65.2, 53.7, 49.3, 44.1, 44.1, 41.3, 41.0, 35.7, 35.6, 32.4, 29.2, 28.1, 22.1.

**HRMS (ESI<sup>+</sup>)**: Calc. for C<sub>32</sub>H<sub>47</sub>O<sub>6</sub>N<sub>2</sub><sup>+</sup> [M + H<sup>+</sup>]: 555.3429. Found: 555.3434.

**IR (ATR)**:  $\tilde{\nu}$  = 2925 (s), 2800 (w), 1735 (s), 1451 (m), 1406 (w), 1369 (m), 1309 (m), 1291 (m), 1188 (m), 1156 (m), 1097 (m), 1028 (m), 1007 (m), 987 (w), 968 (w), 914 (w), 881 (w), 732 (m).

**[ $\alpha$ ]<sub>D</sub><sup>20</sup>** = –139° (c = 0.76, CHCl<sub>3</sub>).

**Synthesis of methyl 3-((4a*R*,7a*S*,9*S*,10a*S*)-9-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-oxodecahydrocyclopenta[*e*]quinolin-1(2*H*)-*yl*)propanoate (**1.132**)**



Imidazole (10.0 mg, 0.147 mmol, 1.3 equiv.) and DMAP (2.8 mg, 0.023 mmol, 0.2 equiv.) were added sequentially to a solution of alcohol **1.124** (34.9 mg, 0.113 mmol, 1.0 equiv.) in CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) at ambient temperature. The solution was cooled to 0 °C and TBSCl (22.1 mg, 0.147 mmol, 1.3 equiv.) was added. The ice bath was removed and the cloudy mixture was stirred at ambient temperature for 4 h. Saturated aqueous ammonium chloride (6 mL) was added and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 10 mL). The combined layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Purification by flash column chromatography (3 → 4% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) afforded silyl ether **1.132** as a colorless oil (48.2 mg, 0.110 mmol) in 97% yield.

**R<sub>f</sub>**: 0.32 (4% MeOH in CH<sub>2</sub>Cl<sub>2</sub>, stains with KMnO<sub>4</sub>).

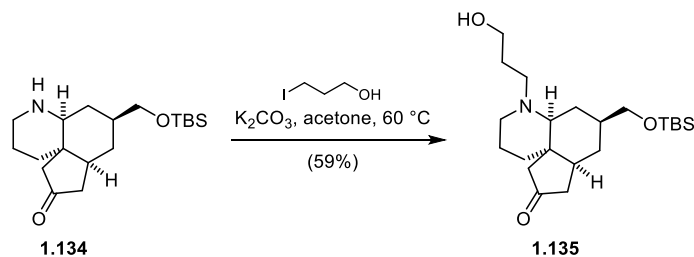
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 3.64 (s, 3H), 3.42 (d, *J* = 6.1 Hz, 2H), 2.97 (ddd, *J* = 13.8, 8.6, 6.6 Hz, 1H), 2.87 (m, 1H), 2.75 (ddd, *J* = 13.8, 8.6, 5.5 Hz, 1H), 2.51 (dd, *J* = 18.4, 6.9 Hz, 1H), 2.44 (m, 1H), 2.39 – 2.10 (m, 5H), 1.94 – 1.87 (m, 2H), 1.84 (d, *J* = 18.6 Hz, 1H), 1.73 – 1.46 (m, 5H), 1.19 (m, 1H), 0.97 (q, *J* = 13.1, 12.2 Hz, 1H), 0.86 (s, 9H), 0.73 (q, *J* = 12.7 Hz, 1H), 0.02 (s, 6H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)** δ 219.5, 173.3, 68.0, 66.1, 53.8, 51.7, 48.1, 44.2, 44.1, 41.6, 41.1, 38.8, 35.8, 33.3, 30.7, 27.6, 26.0, 22.0, 18.4, -5.2, -5.2.

**HRMS (ESI<sup>+</sup>)**: Calc. for C<sub>23</sub>H<sub>42</sub>NO<sub>4</sub>Si<sup>+</sup> [*M* + H<sup>+</sup>]: 424.2878. Found: 424.2874.

**IR (ATR)**:  $\tilde{\nu}$  = 2928 (m), 2855 (m), 1737 (s), 1462 (w), 1437 (w), 1408 (w), 1388 (w), 1250 (m), 1222 (w), 1195 (m), 1157 (m), 1157 (m), 1111 (s), 1094 (m), 1074 (m), 1006 (w), 939 (w), 914 (w), 836 (s), 776 (s), 668 (w).

**[ $\alpha$ ]<sub>D</sub><sup>20</sup>** = -43° (c = 1.00, CHCl<sub>3</sub>).

**Synthesis of (4a*R*,7a*S*,9*S*,10a*S*)-9-(((tert-butyldimethylsilyl)oxy)methyl)-1-(3-hydroxypropyl)decahydrocyclopenta[*e*]quinolin-6(5*H*)-one (1.135)**

$K_2CO_3$  (20.8 mg, 0.151 mmol, 2.1 equiv.) and 3-iodo-1-propanol (12.8  $\mu\text{L}$ , 0.108 mmol, 1.5 equiv.) were added to a solution of amine **1.134** (24.2 mg, 0.0717 mmol, 1.0 equiv.) in acetone (1.5 mL) at ambient temperature. The cloudy white mixture was heated to  $60\text{ }^\circ\text{C}$  and stirred for 3 h, then cooled to ambient temperature and concentrated. The crude residue was purified by flash column chromatography (3  $\rightarrow$  10% MeOH in  $\text{CH}_2\text{Cl}_2$ ) to afford product **1.135** as a white solid (16.6 mg, 0.0420 mmol) in 59% yield.

**R<sub>f</sub>**: 0.22 (5% MeOH in  $\text{CH}_2\text{Cl}_2$ , stains with  $\text{KMnO}_4$ ).

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )**  $\delta$  3.80 – 3.70 (m, 2H), 3.45 (d,  $J = 6.1$  Hz, 2H), 3.23 (d,  $J = 10.5$  Hz, 1H), 3.05 (ddd,  $J = 12.7, 8.1, 4.3$  Hz, 1H), 2.53 (dd,  $J = 18.5, 7.1$  Hz, 1H), 2.40 – 2.30 (m, 2H), 2.29 – 2.03 (m, 4H), 1.98 – 1.83 (m, 2H), 1.83 – 1.54 (m, 7H), 1.27 (m, 1H), 1.08 (q,  $J = 12.3$  Hz, 1H), 0.88 (s, 9H), 0.75 (q,  $J = 12.8$  Hz, 1H), 0.04 (s, 6H).

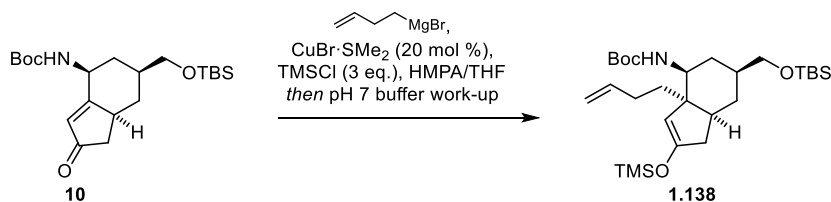
**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )**  $\delta$  218.4, 68.0, 67.9, 64.4, 54.6, 52.8, 44.0, 41.9, 40.8, 38.8, 35.6, 33.1, 28.3, 27.9, 26.1, 21.3, 18.5, -5.2, -5.2.

**HRMS (ESI<sup>+</sup>)**: Calc. for  $\text{C}_{22}\text{H}_{42}\text{O}_3\text{NSi}^+$  [ $\text{M} + \text{H}^+$ ]: 396.2929. Found: 396.2925.

**IR (ATR)**:  $\tilde{\nu} = 3406$  (br w), 2928 (m), 2855 (m), 1739 (s), 1471 (w), 1407 (w), 1388 (w), 1360 (w), 1251 (m), 1159 (m), 1111 (m), 1072 (m), 1006 (w), 836 (s), 776 (m), 668 (w).

$[\alpha]_D^{20} = -48^\circ$  ( $c = 1.1, \text{CHCl}_3$ ).

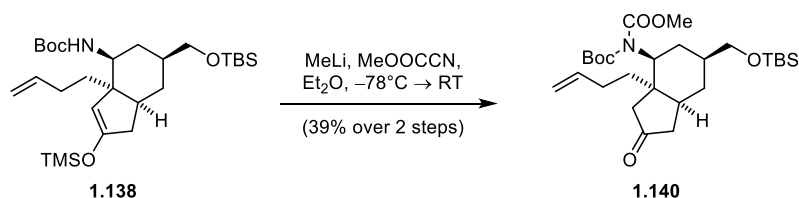
**Synthesis of tert-butyl ((3a*S*,4*S*,6*S*,7a*S*)-3a-(but-3-en-1-yl)-6-(((tert-butyl)dimethylsilyl)oxy)methyl)-2-((trimethylsilyl)oxy)-3a,4,5,6,7,7a-hexahydro-1*H*-inden-4-yl)carbamate (**1.138**)**



Freshly-prepared 3-butenylmagnesium bromide solution (131  $\mu\text{L}$ , 0.72 M in THF, 0.940 mmol, 4.5 equiv.) was added dropwise to a light brown suspension of  $\text{CuBr}\cdot\text{SMe}_2$  (8.6 mg, 0.042 mmol, 0.2 equiv.) in THF (3.2 mL) at  $-78^\circ\text{C}$ . The mixture was stirred at  $-78^\circ\text{C}$  for 1 h. HMPA (109  $\mu\text{L}$ , 0.626 mmol, 3.0 equiv.) was added and the mixture was stirred for 10 minutes.  $\text{TMSCl}$  (79.5  $\mu\text{L}$ , 0.626 mmol, 3.0 equiv.) and enone **10** (82.6 mg, 0.209 mmol, 1.0 equiv.) in THF (2.0 mL) were then added simultaneously. The resulting bright yellow reaction mixture was stirred for 2.5 h at  $-78^\circ\text{C}$  and 1 h at  $-40^\circ\text{C}$ . pH 7 Phosphate buffer (3 mL) was then added to the reaction mixture and the solution was allowed to warm to room temperature. The aqueous phase was extracted with pentane (50 mL) and the organic layer was rinsed numerous times with 10% w/w aqueous  $\text{LiCl}$  solution ( $7 \times 20$  mL mL) to remove HMPA. The pentane layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude silyl enol ether **1.138** was isolated as a colorless oil and was used directly in subsequent reactions without purification.

$^1\text{H NMR}$  (400 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  5.91 (m, 1H), 5.18 (d,  $J = 16.9$  Hz, 1H), 5.02 (d,  $J = 10.0$  Hz, 1H), 4.62 (d,  $J = 9.3$  Hz, 1H), 4.47 (s, 1H), 3.96 (td,  $J = 9.7, 3.4$  Hz, 1H), 3.33 – 3.20 (m, 2H), 2.62 (ddd,  $J = 15.6, 6.6, 2.1$  Hz, 1H), 2.44 (m, 1H), 2.25 – 2.04 (m, 2H), 1.88 – 1.61 (m, 4H), 1.60 – 1.38 (m, 12H), 1.12 (q,  $J = 11.3$  Hz, 1H), 0.98 (s, 9H), 0.13 (s, 9H), 0.06 (s, 6H).

**Synthesis of N-Boc-methyl ((3a*R*,4*S*,6*S*,7a*S*)-3a-(but-3-en-1-yl)-6-(((tert-butyl)dimethylsilyl)oxy)methyl)-2-oxooctahydro-1*H*-inden-4-yl)carbamate (**1.140**)**



The residue from the above reaction (assumed 0.713 mmol, 1.0 equiv.) was azeotroped twice with  $\text{PhMe}$ , dissolved in  $\text{Et}_2\text{O}$  (12 mL) and cooled to  $-78^\circ\text{C}$ .  $\text{MeLi}$  solution (1.6 M in  $\text{Et}_2\text{O}$ , 0.980 mL, 2.2 equiv.) was added dropwise to the flask and the mixture was stirred at  $-78^\circ\text{C}$  for 1 h,

warmed to  $-20\text{ }^{\circ}\text{C}$  for 20 minutes, then cooled to  $-78\text{ }^{\circ}\text{C}$  once more. HMPA (372  $\mu\text{L}$ , 2.14 mmol, 3.0 equiv.) and Mander's reagent (170  $\mu\text{L}$ , 2.14 mmol, 3.0 equiv.) were added sequentially and the reaction mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for 2.5 h. After allowing the mixture to warm gradually to ambient temperature, saturated aqueous ammonium chloride solution (10 mL) was added. The aqueous phase was extracted with  $\text{Et}_2\text{O}$  ( $3 \times 20\text{ mL}$ ) and the combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude residue was purified by flash column chromatography (2  $\rightarrow$  20  $\rightarrow$  30 %  $\text{Et}_2\text{O}$  in pentane) to afford product **1.140** as a bright yellow oil (142 mg, 0.278 mmol) in 39% yield over two steps.

**Rf** : 0.45 (20%  $\text{Et}_2\text{O}$  in pentane, stains with  $\text{KMnO}_4$ ).

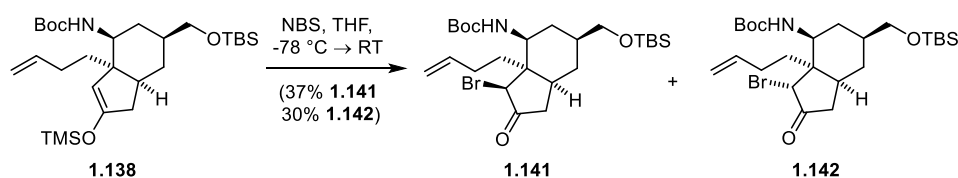
**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )**  $\delta$  5.72 (ddt,  $J = 16.8, 10.1, 6.4\text{ Hz}$ , 1H), 4.99 (dd,  $J = 17.1, 1.8\text{ Hz}$ , 1H), 4.91 (d,  $J = 10.2\text{ Hz}$ , 1H), 4.41 (dd,  $J = 12.6, 3.7\text{ Hz}$ , 1H), 3.73 (s, 3H), 3.49 – 3.34 (m, 2H), 2.67 (d,  $J = 18.1\text{ Hz}$ , 1H), 2.42 (dd,  $J = 18.1, 7.3\text{ Hz}$ , 1H), 2.33 – 2.17 (m, 2H), 2.05 – 1.53 (m, 8H), 1.45 (s, 9H), 1.23 (m, 1H), 0.93 – 0.74 (m, 10H), 0.00 (s, 6H).

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )**  $\delta$  219.0, 155.8, 153.6, 138.3, 114.8, 82.9, 67.6, 57.6, 53.6, 46.9, 45.2, 43.3, 39.7, 37.9, 34.8, 33.2, 29.8, 27.9, 27.7, 26.0, 18.5, -5.3, -5.3.

**HRMS (ESI $^-$ )**: Calc. for  $\text{C}_{27}\text{H}_{46}\text{O}_6\text{NSi}^-$  [ $\text{M} - \text{H}^+$ ]: 508.3100. Found: 508.3113.

**IR (ATR)**:  $\tilde{\nu} = 2953$  (w), 2930 (w), 2857 (w), 1741 (m), 1707 (s), 1641 (w), 1472 (w), 1462 (w), 1440 (m), 1392 (w), 1369 (m), 1332 (s), 1251 (m), 1221 (m), 1131 (s), 1113 (s), 1398 (s), 1006 (w), 972 (w), 911 (w), 835 (s), 814 (m), 775 (s), 734 (m), 668 (w).

**Synthesis of *tert*-butyl ((3*S*,3*aR*,4*S*,6*S*,7*aS*)-3-bromo-3*a*-(but-3-en-1-yl)-6-(((*tert*-butyldimethylsilyl)oxy) methyl)-2-oxooctahydro-1*H*-inden-4-yl)carbamate (**1.141**) and *tert*-butyl ((3*R*,3*aR*,4*S*,6*S*,7*aS*)-3-bromo-3*a*-(but-3-en-1-yl)-6-(((*tert*-butyldimethylsilyl)oxy) methyl)-2-oxooctahydro-1*H*-inden-4-yl)carbamate (**1.142**)**



Freshly recrystallized *N*-bromosuccinimide (7.6 mg, 0.0426 mmol, 1.2 equiv.) was added to a solution of silyl enol ether **1.138** (18.6 mg, 0.0355 mmol, 1.0 equiv.) in THF (1.0 mL) at  $-78\text{ }^{\circ}\text{C}$ . The solution was stirred for 1 h at  $-78\text{ }^{\circ}\text{C}$ , then was allowed to gradually warm to ambient temperature over 20 minutes. The sample was concentrated under reduced pressure and the crude residue was purified by flash column chromatography (5  $\rightarrow$  20%  $\text{Et}_2\text{O}$  in pentane) to afford

bromide **1.141** (6.9 mg, 0.0130 mmol, 37%) bromide and **1.142** (5.6 mg, 0.0106 mmol, 30%) as colorless oils.

Characterization data for bromide **1.141**:

**Rf** : 0.40 (15% Et<sub>2</sub>O in pentane, stains with KMnO<sub>4</sub>).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 5.75 (ddt, J = 17.0, 10.1, 6.5 Hz, 1H), 5.04 (d, J = 17.0 Hz, 1H), 4.99 – 4.85 (m, 2H), 4.10 (td, J = 12.2, 5.9 Hz, 1H), 3.89 (s, 1H), 3.49 (dd, J = 9.8, 4.5 Hz, 1H), 3.43 (dd, J = 9.8, 5.5 Hz, 1H), 2.65 (dd, J = 19.7, 8.2 Hz, 1H), 2.43 – 2.21 (m, 3H), 2.12 – 1.95 (m, 2H), 1.86 – 1.58 (m, 5H), 1.45 (s, 9H), 1.17 (m, 1H), 0.88 (s, 10H), 0.03 (s, 6H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)** δ 211.4, 155.9, 137.6, 115.6, 79.8, 77.2, 67.5, 52.9, 50.5, 49.1, 42.2, 38.4, 37.5, 37.1, 33.3, 32.8, 28.5, 26.1, 18.5, -5.2.

**HRMS (ESI<sup>+</sup>)**: Calc. for C<sub>25</sub>H<sub>45</sub>O<sub>4</sub>NBrSi<sup>+</sup> [M + H<sup>+</sup>]: 530.2296. Found: 530.2311.

**IR (ATR)**:  $\tilde{\nu}$  = 2928 (s), 2857 (m), 1751 (m), 1739 (s), 1496 (s), 1472 (m), 1391 (w), 1366 (m), 1252 (m), 1172 (m), 1110 (m), 1005 (w), 912 (w), 837 (s), 777 (m), 668 (w).

Characterization data for bromide **1.142**:

**Rf** : 0.21 (15% Et<sub>2</sub>O in pentane, stains with KMnO<sub>4</sub>).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 5.78 (ddt, J = 17.1, 10.1, 6.3 Hz, 1H), 5.12 (d, J = 10.1 Hz, 1H), 5.05 (d, J = 17.1 Hz, 1H), 4.96 (d, J = 10.1 Hz, 1H), 4.87 (s, 1H), 4.03 (m, 1H), 3.50 (dd, J = 9.9, 4.8 Hz, 1H), 3.40 (dd, J = 9.9, 6.2 Hz, 1H), 2.59 – 2.42 (m, 2H), 2.29 (m, 1H), 2.08 (d, J = 18.3 Hz, 1H), 2.04 – 1.86 (m, 3H), 1.87 – 1.66 (m, 2H), 1.44 (s, 9H), 1.20 (m, 1H), 1.12 – 0.92 (m, 2H), 0.87 (s, 9H), 0.02 (s, 6H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)** δ 209.2, 155.5, 137.9, 115.4, 79.6, 77.2, 67.2, 57.3, 50.4, 46.9, 40.9, 38.4, 35.6, 33.0, 31.4, 31.3, 28.5, 27.7, 26.1, 18.5, -5.2.

**HRMS (ESI)**: Calc. for C<sub>25</sub>H<sub>45</sub>O<sub>4</sub>NBrSi<sup>+</sup> [M + H<sup>+</sup>]: 530.2296. Found: 530.2308.

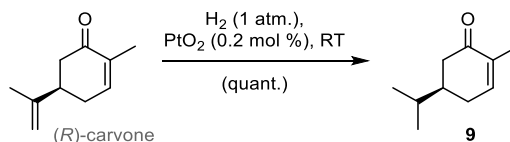
**IR (ATR)**:  $\tilde{\nu}$  = 3435 (w), 2928 (m), 2856 (m), 1757 (m), 1712 (s), 1642 (w), 1504 (m), 1472 (w), 1391 (w), 1366 (m), 1250 (m), 1173 (m), 1101 (m), 1006 (w), 912 (w), 836 (s), 812 (w), 776 (m), 668 (w).



### 4.3. Experimental Procedures for Chapter II

The following section uses numbering from *J. Org. Chem.* **2018**, 83, 3061 – 3068.

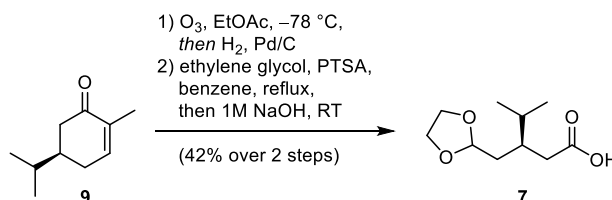
#### Synthesis of (*R*)-3-((1,3-dioxolan-2-yl)methyl)-4-methylpentanoic acid (**9**)



Platinum oxide (82.0 mg, 0.361 mmol, 0.16 mol %) was added to (*R*)-carvone (30.0 g, 230 mmol, 1.0 equiv.) and the mixture was stirred under a hydrogen atmosphere (balloon pressure) for 26 h at ambient temperature. Conversion was carefully monitored by  $^1\text{H}$  NMR to prevent overreduction. The mixture was passed through a short pad of silica to remove catalyst and the pad washed with  $\text{Et}_2\text{O}$  (500 mL). Concentration under reduced pressure afforded carvotanacetone **9** (30.3 g, 230 mmol) in quantitative yield. The  $^1\text{H}$  NMR spectrum is in accordance with that previously reported in literature.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.74 (d,  $J = 5.9$  Hz, 1H), 2.53 (dd,  $J = 15.8, 2.8$  Hz, 1H), 2.36 (dt,  $J = 17.7, 5.3$  Hz, 1H), 2.17 – 2.02 (m, 2H), 1.85 (m, 1H), 1.77 (s, 3H), 1.57 (h,  $J = 6.7$  Hz, 1H), 0.91 (d,  $J = 6.7$  Hz, 6H).

#### Synthesis of (*R*)-3-((1,3-dioxolan-2-yl)methyl)-4-methylpentanoic acid (**7**)



Acid **7** was prepared using a modified procedure by Deslongchamps et al.<sup>25</sup> A stream of ozone was bubbled through a solution of (*R*)-carvotanacetone **9** (5.02 g, 33.0 mmol, 1.0 equiv.) in  $\text{EtOAc}$  (90 mL) at  $-78$   $^\circ\text{C}$  until a deep blue color persisted (approximately 25 minutes). Nitrogen was passed through the solution until the blue color dissipated and the mixture was warmed to ambient temperature while nitrogen was bubbled through. The solution was then cooled to  $0$   $^\circ\text{C}$  and palladium on charcoal (10% w/w, 70.2 mg, 65.9  $\mu\text{mol}$ , 0.2 mol %) was added. The vessel was purged with a hydrogen gas balloon for 5 minutes and then stirred under hydrogen atmosphere (balloon pressure) for 6 h at  $0$   $^\circ\text{C}$ . The mixture was filtered through Celite and concentrated to afford a crude yellow oil which was used without further purification.

The crude oil was dissolved in benzene (30 mL), and ethylene glycol (10.2 mL, 165 mmol, 5.0 equiv.) and *p*-toluenesulfonic acid monohydrate (0.628 g, 3.30 mmol, 10 mol %) were added. The flask was equipped with a Dean-Stark trap and a reflux condenser and the mixture was heated to reflux for 6 h. After cooling to ambient temperature, benzene was removed under reduced pressure and 1 M NaOH (60 mL) was added. The biphasic mixture was stirred vigorously for 18 h. The aqueous layer was washed with Et<sub>2</sub>O (3 × 100 mL), then cooled to 0 °C and acidified to pH 3 with 1 M HCl. The resulting cloudy layer was extracted with Et<sub>2</sub>O (3 × 100 mL) and the combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (30% EtOAc in pentane) to afford acid **7** (2.78 g, 13.8 mmol, 42% over two steps) as a pale yellow oil. The <sup>1</sup>H NMR spectrum is in accordance with that previously reported in literature.

**R<sub>f</sub>**: 0.38 (30% EtOAc in pentane + 0.5% v/v acetic acid, stains with KMnO<sub>4</sub>).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 11.13 (br s, 1H), 4.90 (t, *J* = 4.8 Hz, 1H), 3.97 (m, 2H), 3.83 (m, 2H), 2.46 (dd, *J* = 15.8, 6.7 Hz, 1H), 2.35 (d, *J* = 15.8, 6.7 Hz, 1H), 2.05 (m, *J* = 8.7, 4.3, 2.2 Hz, 1H), 1.88 – 1.70 (m, 2H), 1.55 (ddd, *J* = 14.1, 8.7, 5.2 Hz, 1H), 0.89 (d, *J* = 6.0 Hz, 3H), 0.87 (d, *J* = 5.9 Hz, 3H).

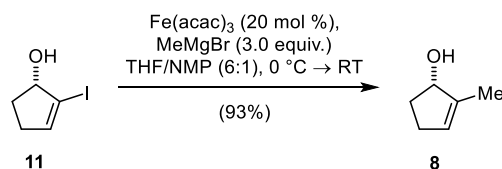
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)** δ 179.9, 104.1, 65.0, 64.7, 36.6, 36.3, 34.7, 30.5, 19.1, 18.7.

**IR (ATR)**:  $\tilde{\nu}$  = 3024 (br w), 2959 (m), 2877 (m), 1703 (s), 1466 (w), 1411 (m), 1389 (m), 1370 (m), 1280 (m), 1220 (m), 1132 (s), 1101 (m), 1042 (m), 944 (m), 825 (w).

**HRMS (ESI<sup>+</sup>)**: Calc. for C<sub>10</sub>H<sub>19</sub>O<sub>4</sub><sup>+</sup> [*M* + H<sup>+</sup>]: 203.1278. Found: 203.1277.

**[α]<sub>D</sub><sup>20</sup>** = -2.2° (c = 1.14, CHCl<sub>3</sub>).

### Synthesis of (*S*)-2-methylcyclopent-2-enol (**8**)

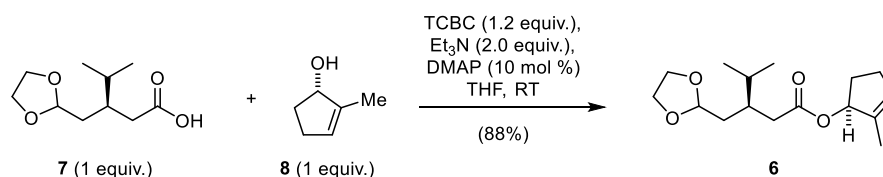


Iodide **11** (7.02 g, 33.4 mmol, 1.0 equiv.) was dissolved in THF (174 mL) and NMP (29.0 mL) and the resulting solution was cooled to 0 °C with an ice bath. Fe(acac)<sub>3</sub> (2.36 g, 6.69 mmol, 0.20 equiv.) was added in one portion and the bright orange suspension was stirred for 10 minutes. Methyl magnesium bromide (33.4 mL, 3 M in Et<sub>2</sub>O, 3.0 equiv.) was then added in a steady flow over the course of 5 mins as a constant evolution of gas was observed. Following addition, the ice bath was removed and the dark brown mixture was stirred for 25 minutes at ambient temperature.

Aqueous pH 7 phosphate buffer (100 mL) was carefully added to the mixture and the aqueous phase was extracted with Et<sub>2</sub>O (3 × 100 mL). The combined organic phases were washed with brine (80 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure (no lower than 200 mbar at 30 °C to prevent evaporation of product). The crude product was purified by flash column chromatography (30% Et<sub>2</sub>O in pentane) to afford cyclopentenone **8** (3.06 g, 31.2 mmol, 93%) as a pale yellow oil. Due to cautious evaporation of this volatile product, some solvent remains. Diethyl ether accounts for 3.5% of the sample by weight and THF accounts for < 2%. The <sup>1</sup>H NMR spectrum is in accordance with that previously reported in literature.<sup>[243]</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.53 (m, 1H), 4.58 (m, 1H), 2.47 – 2.26 (m, 2H), 2.21 (m, 1H), 1.77 (m, 3H), 1.69 (ddt, *J* = 13.2, 8.8, 4.4 Hz, 1H), 1.39 (br s, 1H).

**Synthesis of (S)-2-methylcyclopent-2-en-1-yl (R)-3-((1,3-dioxolan-2-yl)methyl)-4-methylpentanoate (6)**



Triethylamine (7.73 mL, 55.4 mmol, 2.0 equiv.) and 2,4,6-trichlorobenzoyl chloride (5.20 mL, 33.3 mmol, 1.2 equiv.) were added sequentially to a vigorously stirring solution of acid **7** (5.60 g, 27.7 mmol, 1.0 equiv.) in THF (100 mL) at ambient temperature. The solution was stirred at ambient temperature for 1 h, where it became cloudy. Alcohol **8** (2.72 g, 27.7 mmol, 1.0 equiv.) and DMAP (339 mg, 2.77 mmol, 0.10 equiv.) in THF (20 mL) were then added to the suspension and the flask was sealed with a Teflon cap and left to stir at ambient temperature for 17 h. Saturated aqueous ammonium chloride solution (80 mL) was added to the resulting bright yellow suspension and the aqueous phase was extracted with EtOAc (3 × 80 mL). The combined organic phases were washed with brine (80 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (7 → 8% EtOAc in pentane) to afford ester **6** (6.88 g, 24.3 mmol, 88%) as a pale yellow oil.

**R<sub>f</sub>**: 0.39 (10% EtOAc in pentane, stains with KMnO<sub>4</sub> and CAM).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.64 (s, 1H), 5.57 (m, 1H), 4.89 (t, *J* = 5.0 Hz, 1H), 3.95 (m, 2H), 3.82 (m, 2H), 2.48 – 2.18 (m, 5H), 2.06 (ddt, *J* = 8.6, 6.8, 4.6 Hz, 1H), 1.83 – 1.67 (m, 6H), 1.53 (ddd, *J* = 13.9, 8.5, 5.2 Hz, 1H), 0.87 (d, *J* = 6.9 Hz, 3H), 0.86 (d, *J* = 6.9 Hz, 3H).

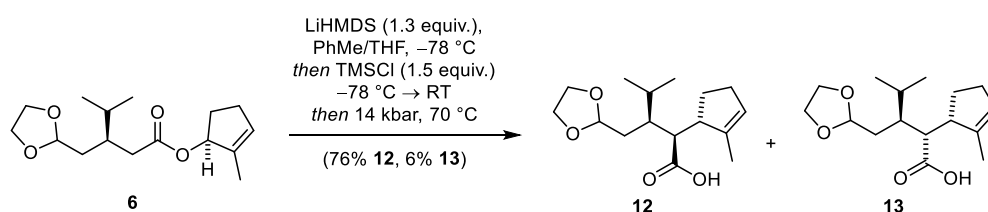
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  173.7, 138.2, 130.8, 104.2, 82.2, 64.9, 64.7, 36.9, 36.8, 34.9, 31.1, 30.5, 30.4, 19.1, 18.7, 13.9.

IR (ATR):  $\tilde{\nu}$  = 2958 (m), 2876 (m), 1726 (s), 1457 (w), 1437 (m), 1412 (m), 1370 (m), 1334 (m), 1304 (m), 1210 (w), 1149 (s), 1103 (m), 1045 (m), 1024 (s), 979 (m), 955 (m), 920 (w), 834 (w), 712 (w).

HRMS (EI): Calc. for  $\text{C}_{16}\text{H}_{26}\text{O}_4$  [M]: 282.1818. Found: 282.1831.

$[\alpha]_{\text{D}}^{20} = -40.8^\circ$  ( $c = 1.3$ ,  $\text{CHCl}_3$ ).

### Synthesis of (2*S*,3*S*)-3-((1,3-dioxolan-2-yl)methyl)-4-methyl-2-((*S*)-2-methylcyclopent-2-en-1-yl)pentanoic acid (**12**)



Ester **6** (765 mg, 2.71 mmol, 1.0 equiv.) in toluene (2.5 mL) was added dropwise to a solution of LiHMDS (3.53 mL, 1 M in THF, 1.3 equiv.) in toluene (7 mL) at  $-78^\circ\text{C}$ . The pale orange mixture was stirred for 1 h at this temperature, whereupon freshly distilled TMSCl (516  $\mu\text{L}$ , 4.07 mmol, 1.5 equiv.) was added dropwise. The mixture was stirred at  $-78^\circ\text{C}$  for 15 minutes and was then allowed to gradually warm to ambient temperature over 30 minutes. The resulting cloudy mixture was transferred to two 10 mL high pressure containers (washing the original vessel with 3 mL PhMe) and the containers were subjected to 14 kbar of pressure at  $70^\circ\text{C}$  for 21 h. Upon returning to ambient pressure and temperature, the contents of the containers were poured into saturated aqueous ammonium chloride solution (40 mL) and  $\text{Et}_2\text{O}$  (40 mL). The aqueous layer was separated and further extracted with  $\text{Et}_2\text{O}$  ( $2 \times 40$  mL) and the combined organic layers were washed with brine (40 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Purification by flash column chromatography (10  $\rightarrow$  15 % EtOAc in pentane with added 0.5% v/v acetic acid) afforded acid **12** (578 mg, 2.05 mmol, 76%) and acid **13** (46.8 mg, 0.166 mmol, 6%) as pale yellow foams.

Characterization data for acid **12**:

$R_f$ : 0.32 (25% EtOAc in pentane, stains with  $\text{KMnO}_4$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  11.22 (bs, 1H), 5.39 (s, 1H), 4.97 (t,  $J = 4.9$  Hz, 1H), 4.00 (m, 2H), 3.87 (m, 2H), 3.12 (q,  $J = 8.4$  Hz, 1H), 2.41 (dd,  $J = 9.5, 4.9$  Hz, 1H), 2.23 – 1.94 (m, 5H),

1.85 (ddd,  $J = 14.9, 10.1, 4.9$  Hz, 1H), 1.73 (dt,  $J = 14.5, 4.4$  Hz, 1H), 1.67 (s, 3H), 1.56 (dq,  $J = 12.4, 8.7$  Hz, 1H), 0.94 (d,  $J = 6.9$  Hz, 3H), 0.76 (d,  $J = 6.7$  Hz, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  180.0, 142.6, 127.0, 104.5, 65.1, 64.8, 50.6, 46.9, 39.8, 30.8, 30.2, 30.1, 26.4, 23.5, 17.1, 16.1.

IR (ATR):  $\tilde{\nu} = 3030$  (br w), 2956 (m), 2890 (m), 1699 (s), 1441 (w), 1413 (w), 1391 (w), 1370 (w), 1206 (m), 1140 (m), 1098 (m), 1041 (m), 968 (w), 943 (m), 839 (w), 799 (w).

HRMS (ESI<sup>-</sup>): Calc. for  $\text{C}_{16}\text{H}_{25}\text{O}_4^-$  [ $\text{M} - \text{H}^+$ ]: 281.1758. Found: 281.1761.

$[\alpha]_{\text{D}}^{20} = +5.2^\circ$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).

Characterization data for acid **13**:

Rf: 0.21 (25% EtOAc in pentane, stains with  $\text{KMnO}_4$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.32 (s, 1H), 4.88 (t,  $J = 5.3$  Hz, 1H), 3.92 (m, 2H), 3.79 (m, 2H), 2.82 (m, 1H), 2.63 (dd,  $J = 10.1, 4.5$  Hz, 1H), 2.27 – 2.10 (m, 3H), 2.04 – 1.86 (m, 3H), 1.77 (dt,  $J = 14.9, 5.1$  Hz, 1H), 1.72 (s, 3H), 1.49 (dt,  $J = 14.9, 5.1$  Hz, 1H), 0.96 (d,  $J = 6.7$  Hz, 3H), 0.80 (d,  $J = 6.7$  Hz, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  181.0, 140.4, 126.7, 104.5, 64.8, 64.7, 50.4, 48.7, 38.8, 33.5, 31.3, 27.7, 24.4, 20.9, 16.5, 15.1.

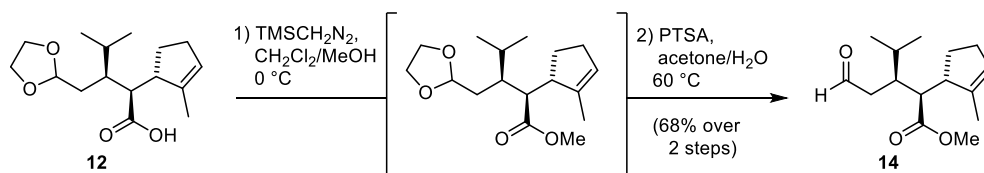
IR (ATR):  $\tilde{\nu} = 3428$  (br w), 3039 (w), 2958 (m), 2876 (m), 1727 (s), 1464 (m), 1441 (m), 1389 (m), 1371 (m), 1207 (m), 1127 (s), 1089 (s), 1045 (s), 986 (m), 960 (s), 948 (s), 794 (m), 732 (m).

HRMS (ESI): Calc. for  $\text{C}_{16}\text{H}_{25}\text{O}_4^-$  [ $\text{M} - \text{H}^+$ ]: 281.1758. Found: 281.1760.

$[\alpha]_{\text{D}}^{20} = +3.2^\circ$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).

---

**Synthesis of methyl (2*S*,3*S*)-3-isopropyl-2-((*S*)-2-methylcyclopent-2-en-1-yl)-5-oxopentanoate (**14**)**



Trimethylsilyldiazomethane (1.32 mL, 2.0 M in hexanes, 1.2 equiv.) was added dropwise to a solution of acid **12** (623 mg, 2.21 mmol, 1.0 equiv.) in CH<sub>2</sub>Cl<sub>2</sub> (14.4 mL) and MeOH (1.6 mL) at 0 °C. The solution was allowed to warm to ambient temperature and stirred for 50 minutes, whereupon acetic acid (50 μL) was added to quench excess diazomethane and the solution was concentrated under reduced pressure to afford crude methyl ester. The oil was dissolved in acetone (18 mL) and H<sub>2</sub>O (2.0 mL) and *p*-toluenesulfonic acid monohydrate (420 mg, 2.21 mmol, 1.0 equiv.) was added. The flask was capped with a Teflon stopper and heated to 60 °C for 75 minutes, then cooled to ambient temperature and concentrated to ~4 mL total volume under reduced pressure. The sample was loaded directly onto a silica column and purified by flash column chromatography (8% Et<sub>2</sub>O in pentane) to afford aldehyde **14** (378 mg, 1.50 mmol, 68% over two steps) as a colorless oil.

**R<sub>f</sub>**: 0.36 (10% Et<sub>2</sub>O in pentane, stains with KMnO<sub>4</sub>).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 9.74 (m, 1H), 5.32 (p, *J* = 2.0 Hz, 1H), 3.62 (s, 3H), 2.90 (q, *J* = 7.9 Hz, 1H), 2.58 – 2.45 (m, 2H), 2.42 (t, *J* = 6.9 Hz, 1H), 2.32 (ddd, *J* = 16.3, 4.3, 1.8 Hz, 1H), 2.14 (m, 2H), 2.02 (dtd, *J* = 12.5, 8.0, 4.2 Hz, 1H), 1.85 (pd, *J* = 6.9, 2.5 Hz, 1H), 1.73 (m, 1H), 1.60 (s, 3H), 0.85 (d, *J* = 6.9 Hz, 3H), 0.70 (d, *J* = 6.9 Hz, 3H).

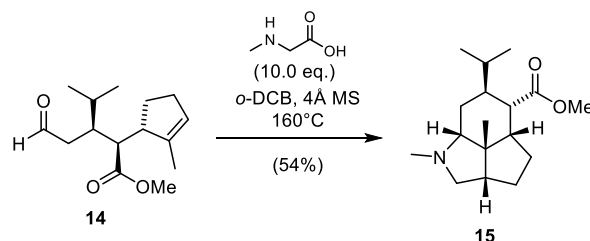
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)** δ 202.3, 175.2, 141.5, 127.5, 51.4, 50.5, 47.8, 41.8, 37.7, 30.4, 29.0, 28.0, 22.6, 17.0, 15.9.

**IR (ATR):**  $\tilde{\nu}$  = 3037 (w), 2953 (m), 2720 (w), 1723 (s), 1456 (m), 1435 (m), 1371 (m), 1248 (m), 1230 (m), 1190 (m), 1161 (s), 1139 (m), 1105 (w), 1024 (m), 799 (w).

**HRMS (ESI<sup>+</sup>):** Calc. for C<sub>15</sub>H<sub>25</sub>O<sub>3</sub><sup>+</sup> [M + H<sup>+</sup>]: 253.1798. Found: 253.1805.

**[α]<sub>D</sub><sup>20</sup>** = +31.8° (c = 1.0, CHCl<sub>3</sub>).

**Synthesis of methyl (2a*S*,2a<sup>1</sup>*R*,4a*S*,5*S*,6*S*,7a*R*)-6-isopropyl-1,2a<sup>1</sup>-dimethyldecahydro-1*H*-cyclopenta[*cd*]indole-5-carboxylate (**15**)**



A 250 mL Schlenk flask was charged with a stir bar, 4Å molecular sieves (freshly activated by heating to 650 °C at  $5 \times 10^{-2}$  mbar for 10 minutes, then backfilling with N<sub>2</sub> and repeating three times), sarcosine (393 mg, 4.41 mmol, 10.0 equiv.) and *o*-dichlorobenzene (32 mL) and was submerged to the solvent line in a 160 °C oil bath. Aldehyde **14** (111 mg, 0.441 mmol, 1.0 equiv.) in *o*-dichlorobenzene (6 mL) was added over the course of 2 hours by means of a syringe pump. The suspension was stirred for an additional 4 h at 160 °C, then cooled to ambient temperature, filtered through cotton with Et<sub>2</sub>O (30 mL) and concentrated by rotary evaporator (heat bath set to 70 °C to remove *o*-dichlorobenzene following ether removal). Purification of the residue by column chromatography (2 → 4% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) afforded amine **15** as a pale yellow oil (74.1 mg, 0.265 mmol) in 54% yield.

**R<sub>f</sub>**: 0.26 (4% MeOH in CH<sub>2</sub>Cl<sub>2</sub>, stains with KMnO<sub>4</sub> and CAM).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 3.63 (s, 3H), 2.71 (d, *J* = 9.2 Hz, 1H), 2.58 (dd, *J* = 12.0, 5.5 Hz, 1H), 2.31 (t, *J* = 8.6 Hz, 1H), 2.09 – 1.97 (m, 6H), 1.90 – 1.62 (m, 5H), 1.54 (dd, *J* = 12.5, 6.4 Hz, 1H), 1.23 (dt, *J* = 11.9, 6.2 Hz, 1H), 1.16 (s, 3H), 1.15 – 1.06 (m, 1H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.74 (d, *J* = 6.9 Hz, 3H).

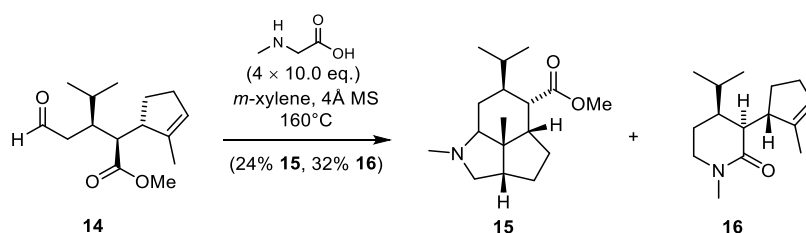
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)** δ 175.8, 73.0, 66.1, 51.2, 49.9, 49.4, 48.7, 47.0, 40.7, 33.9, 31.6, 30.4, 28.0, 26.4, 22.1, 21.5, 15.5.

**IR (ATR):**  $\tilde{\nu}$  = 2948 (s), 2867 (m), 2768 (m), 1737 (s), 1651 (w), 1455 (m), 1367 (w), 1344 (w), 1272 (w), 1245 (m), 1231 (w), 1207 (m), 1160 (s), 1141 (m), 1109 (m), 1044 (w), 1024 (w), 951 (w), 925 (w), 872 (w), 803 (w).

**HRMS (ESI<sup>+</sup>):** Calc. for C<sub>17</sub>H<sub>30</sub>O<sub>2</sub>N<sup>+</sup> [M + H<sup>+</sup>]:280.2271. Found: 280.2276.

**[α]<sub>D</sub><sup>20</sup>** = –64.8° (c = 0.50, CHCl<sub>3</sub>).

Synthesis of methyl (3*S*,4*S*)-4-isopropyl-1-methyl-3-((*S*)-2-methylcyclopent-2-en-1-yl)piperidin-2-one (**16**)



An oven-dried pressure tube was charged with aldehyde **14** (36.1 mg, 0.143 mmol, 1.0 equiv.), sarcosine (127 mg, 1.43 mmol, 10.0 equiv.), and *m*-xylene (1.4 mL). The tube was sealed with a Teflon cap and the rapidly stirring suspension was heated at 150 °C for 75 minutes when gas evolution had ceased and all suspended sarcosine had been visibly consumed. The mixture was cooled to ambient temperature, additional sarcosine (127 mg, 1.43 mmol, 10.0 equiv.) was added and the tube was once more sealed and heated to 150 °C for 75 minutes. This process was repeated twice more for a total of 40 equivalents of sarcosine. The mixture was then cooled to RT and concentrated under reduced pressure. Purification of the crude reaction mixture by column chromatography (first column: 2 → 4% MeOH/CH<sub>2</sub>Cl<sub>2</sub>, second column: 20 → 30% EtOAc/pent) afforded amine **15** as a pale yellow oil (9.3 mg, 0.033 mmol, 24%) and lactam **16** as a colorless oil (10.7 mg, 0.0455 mmol, 32% yield).

**R<sub>f</sub>**: 0.24 (30% EtOAc in pentane, stains with KMnO<sub>4</sub>).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 5.48 (s, 1H), 3.27 (m, 2H), 2.86 (s, 3H), 2.70 (br s, 2H), 2.43 (m, 1H), 2.25 – 2.07 (m, 2H), 1.95 – 1.82 (m, 2H), 1.78 – 1.66 (m, 2H), 1.58 (s, 3H), 1.58 – 1.52 (m, 1H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)** δ 172.4, 141.3, 128.36, 48.9, 48.8, 46.0, 43.9, 35.2, 34.2, 30.7, 27.9, 22.1, 21.8, 20.4, 16.6.

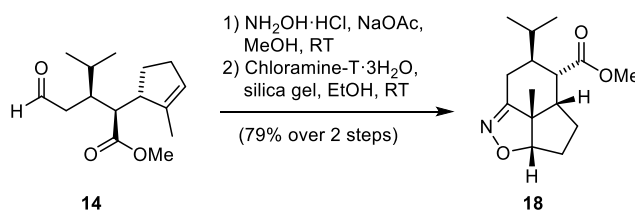
**IR (ATR):**  $\tilde{\nu}$  = 3036 (w), 2954 (m), 2872 (m), 1736 (w), 1644 (s), 1502 (m), 1440 (m), 1399 (m), 1369 (w), 1342 (m), 1241 (m), 1110 (w), 1026 (w), 990 (w), 922 (w), 795 (w).

**HRMS (ESI<sup>+</sup>):** Calc. for C<sub>15</sub>H<sub>26</sub>ON<sup>+</sup> [*M* + H<sup>+</sup>]: 236.2009. Found: 236.2011.

**[α]<sub>D</sub><sup>20</sup>** = +112° (c = 0.80, CHCl<sub>3</sub>).



**Synthesis of methyl (2a<sup>1</sup>S,4S,5S,5aS,7aS)-4-isopropyl-2a<sup>1</sup>-methyl-2a<sup>1</sup>,3,4,5,5a,6,7,7a-octahydro-indeno[7,1-cd]isoxazole-5-carboxylate (**18**)**



Sodium acetate (256 mg, 3.48 mmol, 5.0 equiv.) and hydroxylamine hydrochloride (194 mg, 2.79 mmol, 4.0 equiv.) were added sequentially to a solution of aldehyde **14** (176 mg, 0.696 mmol, 1.0 equiv.) in MeOH (12 mL) at ambient temperature. The mixture was stirred for 30 minutes at ambient temperature, where thin layer chromatography analysis indicated complete conversion. The mixture was concentrated to ~ 2 mL using a stream of nitrogen gas, then partitioned between water (25 mL) and Et<sub>2</sub>O (25 mL). The aqueous layer was separated and further extracted with Et<sub>2</sub>O (2 × 25 mL) and the combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford crude oxime, which was used without further purification. The residue was dissolved in EtOH (10 mL), and silica gel (400 mg) and chloramine-T trihydrate (392 mg, 1.39 mmol, 2.0 equiv.) were added sequentially at ambient temperature. The mixture was stirred for 45 minutes and additional silica gel (1.5 g) was added to the mixture. The suspension was concentrated to dryness and loaded onto an equilibrated silica gel column (30% Et<sub>2</sub>O in pentane). Purification by flash column chromatography (30% Et<sub>2</sub>O in pentane) afforded isoxazoline **18** (147 mg, 0.553 mmol, 79%) as a white solid.

**R<sub>f</sub>**: 0.38 (30% Et<sub>2</sub>O in pentane, stains faintly with KMnO<sub>4</sub>).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 4.52 (d, *J* = 6.1 Hz, 1H), 3.67 (s, 3H), 2.80 (dd, *J* = 11.9, 4.6 Hz, 1H), 2.54 (dd, *J* = 12.8, 4.0 Hz, 1H), 2.24 (dt, *J* = 10.6, 5.6 Hz, 1H), 2.07 – 1.86 (m, 3H), 1.76 (pd, *J* = 6.9, 2.6 Hz, 1H), 1.70 – 1.54 (m, 2H), 1.48 (m, 1H), 1.36 (s, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.85 (d, *J* = 6.9 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)** δ 174.4, 159.9, 90.3, 60.8, 51.8, 50.4, 44.6, 40.4, 35.0, 28.8, 26.3, 21.2, 20.4, 19.7, 15.6.

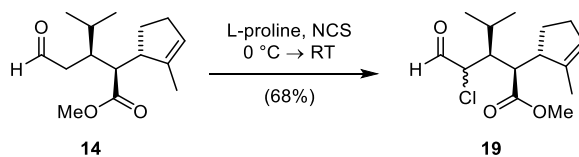
**IR (ATR):**  $\tilde{\nu}$  = 2956 (m), 2889 (w), 2845 (w), 1726 (s), 1453 (w), 1438 (m), 1374 (m), 1348 (m), 1334 (w), 1251 (w), 1205 (m), 1187 (w), 1162 (s), 1052 (w), 986 (m), 952 (w), 866 (w), 850 (m), 777 (w), 718 (w).

**HRMS (ESI<sup>+</sup>):** Calc. for C<sub>15</sub>H<sub>24</sub>O<sub>3</sub>N<sup>+</sup> [M + H<sup>+</sup>]: 266.1751. Found: 266.1751.

**[α]<sub>D</sub><sup>20</sup>** = −54.0° (c = 0.53, CHCl<sub>3</sub>).

**Melting Point:** 120 – 122 °C.

**Synthesis of methyl (2*R*,3*S*)-4-chloro-3-isopropyl-2-((*S*)-2-methylcyclopent-2-en-1-yl)-5-oxopentanoate (**19**)**



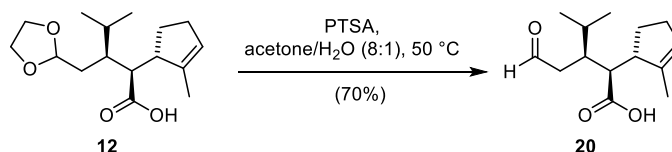
L-Proline (2.8 mg, 24  $\mu\text{mol}$ , 30 mol %) was added to a solution of aldehyde **14** (20.2 mg, 0.0801 mmol, 1.0 equiv.) in  $\text{CH}_2\text{Cl}_2$  (1.0 mL) at 0  $^\circ\text{C}$ . After stirring for 15 minutes, *N*-chlorosuccinimide (11.8 mg, 0.0881 mmol, 1.1 equiv.) was added in one portion. The mixture was stirred for 1 h at 0  $^\circ\text{C}$  and was allowed to warm to ambient temperature and stirred for an additional 20 h. The mixture was diluted with pentane (15 mL) and the organic layer was washed with saturated aqueous ammonium chloride solution (10 mL), saturated aqueous sodium bicarbonate solution (10 mL) and brine (10 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Purification by flash column chromatography (50%  $\text{CH}_2\text{Cl}_2$  in pentane) afforded chloride **19** (15.7 mg, 0.0547 mmol, 68%) as a colorless oil.  $^1\text{H}$  NMR analysis indicates a 1.1:1 mixture of diastereomers.

**R<sub>f</sub>**: 0.27 (6%  $\text{Et}_2\text{O}$  in pentane, stains with  $\text{KMnO}_4$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.60 (d,  $J = 1.5$  Hz, 1H), 9.54 (d,  $J = 3.2$  Hz, 1H), 5.44 – 5.37 (m, 2H), 4.68 (dd,  $J = 4.4, 1.5$  Hz, 1H), 4.38 (dd,  $J = 6.4, 3.2$  Hz, 1H), 3.67 (s, 6H), 3.03 (m, 1H), 2.91 (t,  $J = 6.6$  Hz, 1H), 2.83 (m, 1H), 2.74 (t,  $J = 6.5$  Hz, 1H), 2.65 (m, 1H), 2.51 (td,  $J = 6.4, 2.2$  Hz, 2H), 2.26 – 2.07 (m, 7H), 2.00 (m, 1H), 1.79 (m, 1H), 1.69 (s, 3H), 1.64 (s, 3H), 1.04 (d,  $J = 7.0$  Hz, 3H), 1.00 (d,  $J = 7.0$  Hz, 3H), 0.91 (d,  $J = 7.0$  Hz, 3H), 0.86 (d,  $J = 7.0$  Hz, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  196.2, 195.6, 174.7, 174.1, 141.4, 141.4, 128.1, 128.1, 66.0, 65.1, 51.8, 51.7, 49.3, 48.5, 48.2, 47.7, 46.6, 46.6, 31.1, 30.5, 30.3, 29.4, 28.7, 27.9, 23.3, 22.4, 20.9, 17.4, 16.3, 16.1. **IR (ATR)**:  $\tilde{\nu} = 2952$  (m), 2855 (w), 1732 (s), 1457 (m), 1435 (m), 1373 (m), 1192 (m), 1162 (s), 1051 (w), 1024 (w), 972 (w), 802 (w), 734 (w).

**HRMS (ESI<sup>+</sup>)**: Calc. for  $\text{C}_{15}\text{H}_{22}\text{O}_3\text{C}^+1$  [ $\text{M} + \text{H}^+$ ]: 287.1409. Found: 287.1409.

**Synthesis of (2*S*,3*S*)-3-isopropyl-2-((*S*)-2-methylcyclopent-2-en-1-yl)-5-oxopentanoic acid (20)**

*p*-Toluenesulfonic acid monohydrate (131 mg, 0.686 mmol, 1.0 equiv.) was added to a solution of dioxolane **12** (194 mg, 0.686 mmol, 1.0 equiv.) in acetone (12 mL) and H<sub>2</sub>O (1.5 mL) at ambient temperature. The flask was sealed with a Teflon cap and heated to 50 °C for 4 h, then cooled to ambient temperature and concentrated to ~2 mL total volume under reduced pressure. The sample was loaded directly onto a silica column and purified by flash column chromatography (10% → 12% → 15% acetone in pentane) to afford aldehyde **20** (115 mg, 0.483 mmol, 70%) as a colorless oil.

**R<sub>f</sub>**: 0.50 (20% acetone in pentane, stains with CAM).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 9.79 (t, *J* = 1.4 Hz, 1H), 5.38 (s, 1H), 2.98 (m, 1H), 2.66 (ddd, *J* = 17.3, 6.8, 1.5 Hz, 1H), 2.57 (tdd, *J* = 7.7, 6.8, 5.9, 2.6 Hz, 1H), 2.48 (dd, *J* = 7.5, 6.4 Hz, 1H), 2.39 (ddd, *J* = 17.3, 5.2, 1.8 Hz, 1H), 2.20 (m, 1H), 2.09 (dtd, *J* = 12.4, 8.1, 3.8 Hz, 1H), 1.95 (pd, *J* = 6.8, 2.6 Hz, 1H), 1.81 (m, 1H), 1.69 (s, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H).

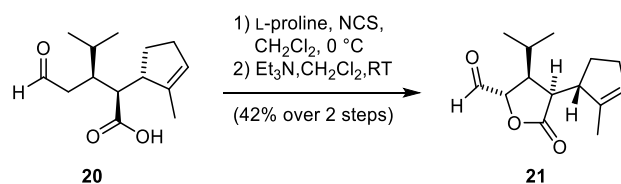
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)** δ 202.3, 181.5, 141.3, 127.8, 50.3, 48.0, 41.7, 37.6, 30.5, 28.8, 28.3, 22.7, 17.1, 16.0.

**IR (ATR):**  $\tilde{\nu}$  = 3020 (br w), 3039 (w), 2959 (m), 2720 (w), 1723 (s), 1699 (s), 1442 (w), 1416 (w), 1391 (m), 1370 (m), 1250 (m), 1204 (m), 1135 (w), 1106 (w), 1024(w), 928 (w), 800 (w).

**HRMS (ESI<sup>-</sup>):** Calc. for C<sub>14</sub>H<sub>21</sub>O<sub>3</sub><sup>-</sup> [M - H<sup>+</sup>]: 237.1496. Found: 237.1498.

**[α]<sub>D</sub><sup>20</sup>** = +29.0° (c = 1.00, CHCl<sub>3</sub>).

**Synthesis of (2*S*,3*S*,4*R*)-3-isopropyl-4-((*S*)-2-methylcyclopent-2-en-1-yl)-5-oxotetrahydrofuran-2-carbaldehyde (**21**)**



L-Proline (7.2 mg, 0.038 mmol, 1.0 equiv.) and *N*-chlorosuccinimide (10.1 mg, 0.0754 mmol, 1.2 equiv.) were added simultaneously to a solution of aldehyde **20** (15.0 mg, 0.0628 mmol, 1.0 equiv.) in  $\text{CH}_2\text{Cl}_2$  (1.0 mL) at 0 °C. The mixture was stirred for 50 minutes at 0 °C and then loaded onto a silica gel column and eluted with 10% EtOAc in pentane + 1% v/v AcOH. The fractions containing the chloride were concentrated under reduced pressure. The oil was dissolved in  $\text{CH}_2\text{Cl}_2$  (1.0 mL) and  $\text{Et}_3\text{N}$  (13.1  $\mu\text{L}$ , 0.0942 mmol, 1.5 equiv.) was added at ambient temperature. The mixture was stirred for 10 minutes, then concentrated and purified by flash column chromatography (30% EtOAc in pentane) to afford oxopentanolide **21** (6.2 mg, 26.3  $\mu\text{mol}$ , 42% over 2 steps) as a colorless oil.

**R<sub>f</sub>**: 0.28 (30% EtOAc in pentane, stains with  $\text{KMnO}_4$ ).

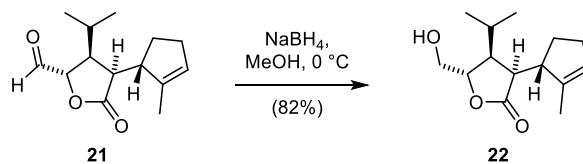
**<sup>1</sup>H NMR (400 MHz,  $\text{CDCl}_3$ )**  $\delta$  9.79 (s, 1H), 5.46 (p,  $J = 1.8, 1.3$  Hz, 1H), 4.58 (d,  $J = 1.3$  Hz, 1H), 2.88 (m, 1H), 2.62 (ddd,  $J = 8.2, 3.1, 1.7$  Hz, 1H), 2.55 (t,  $J = 8.4$  Hz, 1H), 2.31 – 2.12 (m, 4H), 1.88 (s, 3H), 1.68 (m, 1H), 1.02 (d,  $J = 6.8$  Hz, 3H), 0.91 (d,  $J = 6.8$  Hz, 3H).

**<sup>13</sup>C NMR (100 MHz,  $\text{CDCl}_3$ )**  $\delta$  199.5, 176.8, 141.9, 128.1, 80.8, 47.1, 45.3, 44.3, 30.6, 30.5, 26.1, 22.0, 17.9, 17.1.

**IR (ATR):**  $\tilde{\nu} = 3039$  (w), 2964 (m), 2858 (m), 1782 (s), 1737 (s), 1467 (w), 1444 (w), 1377 (w), 1351 (w), 1241 (w), 1176 (m), 1138 (m), 1118 (m), 1048 (m), 1024 (m), 934 (m), 884 (w), 804 (w), 658 (w).

**HRMS (ESI<sup>+</sup>):** Calc. for  $\text{C}_{14}\text{H}_{21}\text{O}_3^+$  [ $\text{M} + \text{H}^+$ ]: 237.1485. Found: 237.1485.

**$[\alpha]_{\text{D}}^{20} = +44^\circ$**  (c = 0.50,  $\text{CHCl}_3$ ).

**Synthesis of (3*R*,4*S*,5*S*)-5-(hydroxymethyl)-4-isopropyl-3-((*S*)-2-methylcyclopent-2-en-1-yl)dihydrofuran-2(3*H*)-one (**22**)**

Sodium borohydride (7.9 mg, 0.212 mmol, 2.0 equiv.) was added to a solution of oxopentanolide **21** (25.0 mg, 0.106 mmol) in MeOH (2.0 mL) at 0 °C. After stirring for 30 minutes at this temperature, saturated aqueous ammonium chloride solution (3 mL) and Et<sub>2</sub>O (3 mL) were added and the biphasic mixture was stirred vigorously for 10 minutes. The aqueous phase was separated and further extracted with Et<sub>2</sub>O (2 × 3 mL) and the combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (15 → 20 → 25% EtOAc in pentane) to afford hydroxypentanolide **22** (20.7 mg, 0.0877 mmol, 82%) as a colorless oil.

**R<sub>f</sub>**: 0.32 (30% EtOAc in pentane, stains with KMnO<sub>4</sub>).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 5.46 (s, 1H), 4.36 (dt, *J* = 5.8, 3.6 Hz, 1H), 3.83 (dd, *J* = 12.2, 3.6 Hz, 1H), 3.69 (dd, *J* = 12.3, 5.8 Hz, 1H), 2.95 (t, *J* = 8.2 Hz, 1H), 2.88 (m, 1H), 2.35 – 2.14 (m, 4H), 2.09 (pd, *J* = 6.8, 4.2 Hz, 1H), 1.88 (s, 3H), 1.75 (m, 1H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H).

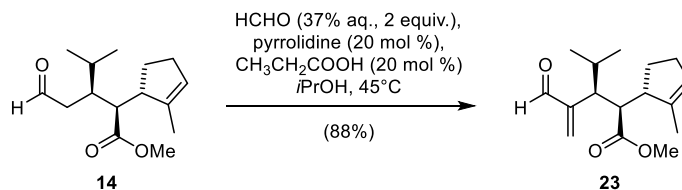
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)** δ 178.5, 141.9, 128.1, 79.4, 64.7, 45.9, 45.9, 44.8, 31.1, 30.5, 26.0, 22.1, 18.0, 17.1.

**IR (ATR):**  $\tilde{\nu}$  = 3438 (br m), 3038 (w), 2962 (s), 2875 (m), 1769 (s), 1466 (m), 1394 (m), 1376 (m), 1358 (m), 1240 (m), 1223 (m), 1176 (m), 1157 (m), 1063 (m), 1021 (m), 996 (m), 928 (w), 806 (w), 674 (w).

**HRMS (ESI<sup>-</sup>):** Calc. for C<sub>15</sub>H<sub>23</sub>O<sub>5</sub><sup>-</sup> [M + HCOO<sup>-</sup>]: 283.1551. Found: 283.1554.

**[ $\alpha$ ]<sub>D</sub><sup>20</sup>** = +60.8° (c = 1.0, CHCl<sub>3</sub>).

**Synthesis of methyl (2R,3S)-4-formyl-3-isopropyl-2-((S)-2-methylcyclopent-2-en-1-yl)pent-4-enoate (23)**



Formaldehyde (37% in H<sub>2</sub>O, 31.0  $\mu\text{L}$ , 0.415 mmol, 2.0 equiv.), propionic acid (3.1  $\mu\text{L}$ , 42  $\mu\text{mol}$ , 0.2 equiv.) and pyrrolidine (3.4  $\mu\text{L}$ , 42  $\mu\text{mol}$ , 0.2 equiv.) were added sequentially to a solution of aldehyde **12** (52.3 mg, 0.207 mmol, 1.0 equiv.) in *i*PrOH (2.0 mL) at ambient temperature. The flask was sealed with a Teflon cap and the stirring mixture was heated to 45  $^\circ\text{C}$  for 6 h. Upon cooling to ambient temperature, the mixture was poured into CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and saturated aqueous sodium bicarbonate (10 mL). The aqueous phase was separated and further extracted with CH<sub>2</sub>Cl<sub>2</sub> (2  $\times$  10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (5% Et<sub>2</sub>O in pentane) to afford enal **23** (44.7 mg, 0.169 mmol, 82%) as a white solid.

**R<sub>f</sub>**: 0.44 (10% Et<sub>2</sub>O in pentane, stains with KMnO<sub>4</sub>).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**  $\delta$  9.51 (s, 1H), 6.22 (s, 1H), 6.20 (s, 1H), 5.31 – 5.24 (m, 1H), 3.65 (s, 3H), 3.37 (dd, *J* = 12.1, 4.3 Hz, 1H), 2.97 (dd, *J* = 12.1, 2.6 Hz, 1H), 2.58 (m, 1H), 2.17 – 1.97 (m, 3H), 1.92 – 1.81 (m, 2H), 1.69 (s, 3H), 0.74 (d, *J* = 6.9 Hz, 3H), 0.70 (d, *J* = 6.9 Hz, 3H).

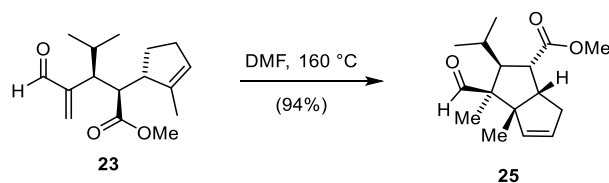
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)**  $\delta$  194.7, 174.7, 148.3, 141.0, 136.9, 128.1, 52.1, 51.5, 48.9, 41.7, 30.8, 30.1, 29.7, 21.8, 16.9, 16.6.

**IR (ATR):**  $\tilde{\nu}$  = 3036 (w), 2958 (m), 2856 (m), 2700 (w), 1732 (s), 1693 (s), 1619 (w), 1435 (m), 1388 (m), 1370 (m), 1320 (w), 1227 (m), 1210 (m), 1190 (m), 1159 (s), 1092 (m), 1024 (w), 953 (m), 811 (w).

**HRMS (ESI<sup>+</sup>):** Calc. for C<sub>16</sub>H<sub>25</sub>O<sub>3</sub><sup>+</sup> [M + H<sup>+</sup>]: 265.1798. Found: 265.1798.

**$[\alpha]_{\text{D}}^{20}$**  = +15 $^\circ$  (c = 1.0, CHCl<sub>3</sub>).

**Melting point:** 72 – 73  $^\circ\text{C}$ .

**Synthesis of aldehyde methyl (1*R*,2*S*,3*S*,3*aS*,6*aS*)-3-formyl-2-isopropyl-3,3*a*-dimethyl-1,2,3,3*a*,6,6*a*-hexahydropentalene-1-carboxylate (**25**)**

A pressure tube was charged with enal **23** (40.1 mg, 0.152 mmol, 1.0 equiv.) and DMF (5.0 mL) and the sealed vessel was heated to 160 °C for 4 h. Upon cooling to ambient temperature, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (8% Et<sub>2</sub>O in pentane) to afford cyclopentanone **25** (37.5 mg, 0.142 mmol, 93%) as a white solid.

**R<sub>f</sub>**: 0.30 (10% Et<sub>2</sub>O in pentane, stains with KMnO<sub>4</sub>).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 9.76 (s, 1H), 5.68 (dt, *J* = 5.6, 2.4 Hz, 1H), 5.50 (ddd, *J* = 5.4, 2.4, 1.2 Hz, 1H), 3.70 (s, 3H), 3.32 (t, *J* = 11.6 Hz, 1H), 2.83 (dd, *J* = 11.6, 7.5 Hz, 1H), 2.59 (dddd, *J* = 17.6, 7.5, 2.4, 1.2 Hz, 1H), 2.14 (dd, *J* = 11.6, 6.9 Hz, 1H), 2.03 (ddt, *J* = 17.6, 2.4, 1.2 Hz, 1H), 1.59 (octet, *J* = 6.9 Hz, 1H), 1.20 (s, 3H), 0.95 (s, 3H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.78 (d, *J* = 6.9 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)** δ 206.6, 175.0, 135.3, 130.3, 62.6, 61.9, 57.6, 51.7, 50.5, 47.7, 36.4, 28.4, 23.4, 21.2, 20.3, 16.3.

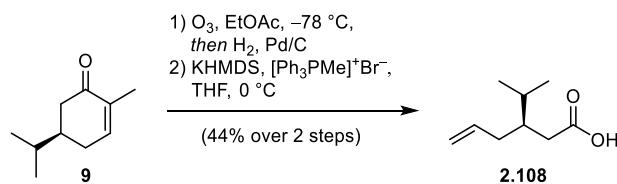
**IR (ATR):**  $\tilde{\nu}$  = 3061 (w), 2960 (m), 2901 (w), 2874 (w), 1722 (vs), 1454 (m), 1435 (m), 1383 (m), 1372 (m), 1341 (w), 1290 (w), 1207 (m), 1190 (s), 1174 (m), 1142 (m), 1123 (w), 1038 (w), 964 (m), 793 (w), 726 (m).

**HRMS (EI):** Calc. for C<sub>16</sub>H<sub>24</sub>O<sub>3</sub> [M]: 264.1725. Found: 264.1720.

**[ $\alpha$ ]<sub>D</sub><sup>20</sup>** = -68.4° (*c* = 1.0, CHCl<sub>3</sub>).

**Melting Point:** 75 – 76 °C.

### Synthesis of (*S*)-2-(2-isopropylpent-4-en-1-yl)-1,3-dioxolane (**2.108**)



A stream of ozone was bubbled through a solution of (*R*)-carvotanacetone **9** (3.01 g, 19.7 mmol, 1.0 equiv.) in EtOAc (60 mL) at  $-78\text{ }^\circ\text{C}$  until a deep blue color persisted (approximately 20 minutes). Nitrogen was passed through the solution until the blue color dissipated and the mixture was warmed to ambient temperature. The solution was then cooled to  $0\text{ }^\circ\text{C}$  and palladium on charcoal (10% w/w, 40.0 mg, 38.0  $\mu\text{mol}$ , 0.2 mol %) was added. The vessel was purged with a hydrogen gas balloon for 5 minutes and then stirred under hydrogen atmosphere (balloon pressure) for 6 h at  $0\text{ }^\circ\text{C}$ . The mixture was filtered through Celite and concentrated to afford a crude yellow oil of which a portion was used in the next procedure.

KHMDS (0.5 M in toluene, 12.8 mL, 2.0 equiv.) was added to a suspension of methyltriphenylphosphonium bromide (2.29g, 6.40 mmol, 2.0 equiv.) at  $0\text{ }^\circ\text{C}$ . The mixture was stirred at  $0\text{ }^\circ\text{C}$  for ten minutes, warmed to ambient temperature for twenty minutes, then cooled once more to  $0\text{ }^\circ\text{C}$ . A portion of crude oil (500 mg, 3.20 mmol [assumed], 1.0 equiv.) in THF (10 mL) was added dropwise to the mixture and the suspension was stirred at  $0\text{ }^\circ\text{C}$  for 1 h. 1 M HCl (30 mL) was added and the aqueous layer was extracted with  $\text{Et}_2\text{O}$  ( $4 \times 40\text{ mL}$ ). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (12  $\rightarrow$  17% EtOAc in pentane) to afford acid **2.108** (221 mg, 1.42 mmol, 44% over two steps) as a colorless oil.

**R<sub>f</sub>**: 018 – 0.35 (10% EtOAc in pentane, stains with  $\text{KMnO}_4$ ).

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )**  $\delta$  9.80 (br s, 1H), 5.75 (ddt,  $J = 17.2, 10.2, 7.0\text{ Hz}$ , 1H), 5.12 – 4.96 (m, 2H), 2.31 (dd,  $J = 15.5, 6.6$ , 1H), 2.24 (dd,  $J = 15.5, 6.6$ , 1H), 2.16 (dt,  $J = 13.1, 6.1$ , 1H), 1.98 (dt,  $J = 14.3, 7.7\text{ Hz}$ , 1H), 1.88 (h,  $J = 6.7\text{ Hz}$ , 2H), 1.76 (m, 1H), 0.88 (m, 6H)

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )**  $\delta$  180.3, 137.0, 116.8, 40.4, 35.6, 35.5, 29.8, 19.3, 18.9.

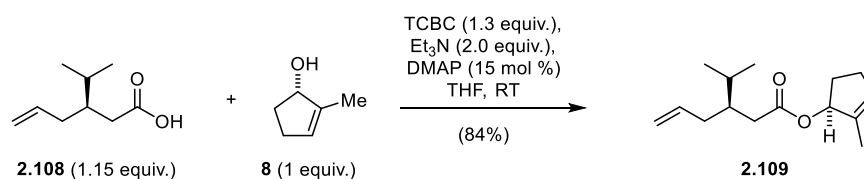
**IR (ATR)**:  $\tilde{\nu} = 3078$  (w), 2961 (m), 2930 (w), 1705 (s), 1641 (w), 1466 (w), 1412 (w), 1388 (w), 1370 (w), 1296 (w), 1228 (w), 1195 (w), 1120 (w), 995 (w), 913 (m).

**HRMS (ESI<sup>-</sup>)**: Calc. for  $\text{C}_9\text{H}_{15}\text{O}_4^-$  [ $\text{M} - \text{H}^+$ ]: 155.1078. Found: 155.1077.

**$[\alpha]_{\text{D}}^{20}$**  =  $+32.0^\circ$  ( $c = 1.00$ ,  $\text{CHCl}_3$ ).



### Synthesis of (*S*)-2-methylcyclopent-2-en-1-yl (*R*)-3-isopropylhex-5-enoate (**2.109**)



Triethylamine (545  $\mu$ L, 3.91 mmol, 2.0 equiv.) and 2,4,6-trichlorobenzoyl chloride (397  $\mu$ L, 2.54 mmol, 1.3 equiv.) were added sequentially to a vigorously stirring solution of acid **2.108** (351 g, 2.25 mmol, 1.15 equiv.) in THF (8 mL) at ambient temperature. The solution was stirred at ambient temperature for 1 h, where it became cloudy. Alcohol **8** (192 mg, 1.95 mmol, 1.0 equiv.) and DMAP (35.8 mg, 0.293 mmol, 0.10 equiv.) in THF (3 mL) were then added to the suspension and the flask was sealed with a Teflon cap and left to stir at ambient temperature for 16 h. Saturated aqueous ammonium chloride solution (10 mL) was added to the resulting bright yellow suspension and the aqueous phase was extracted with EtOAc ( $3 \times 10$  mL). The combined organic phases were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (1  $\rightarrow$  1.5% Et<sub>2</sub>O in pentane) to afford ester **2.109** (446 mg, 1.88 mmol, 84%) as a colorless oil.

**R<sub>f</sub>**: 0.52 (3% Et<sub>2</sub>O in pentane, stains with KMnO<sub>4</sub>).

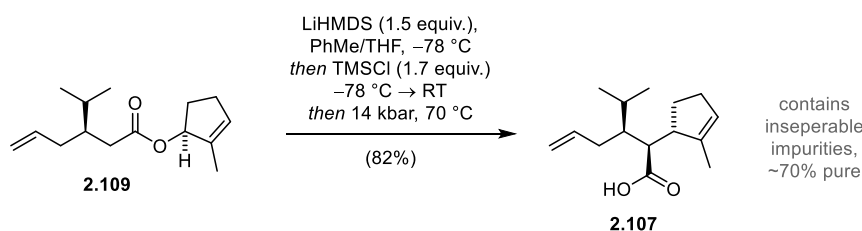
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**  $\delta$  5.74 (ddt,  $J = 17.2, 10.2, 7.0$  Hz, 1H), 5.65 (s, 1H), 5.57 (m, 1H), 5.06 – 4.96 (m, 2H), 2.52 – 2.17 (m, 5H), 2.14 (dt,  $J = 12.3, 5.7$  Hz, 1H), 2.02 – 1.85 (m, 2H), 1.81 – 1.64 (m, 5H), 0.93 – 0.82 (m, 6H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)**  $\delta$  174.1, 138.2, 137.3, 130.8, 116.4, 82.2, 40.6, 36.1, 35.7, 31.1, 30.4, 29.8, 19.4, 18.9, 14.0.

**IR (ATR):**  $\tilde{\nu} = 3077$  (w), 2960 (m), 2874 (w), 1728 (s), 1640 (w), 1439 (w), 1370 (2), 1335 (w), 1303 (2), 1253 (m), 1223 (m), 1167 (s), 1120 (m), 1024 (m), 975 (m), 911 (m), 831 (w).

**HRMS (EI):** Calc. for C<sub>15</sub>H<sub>24</sub>O<sub>2</sub> [M]: 236.1776. Found: 236.1772.

**$[\alpha]_D^{20}$**  =  $-24.0^\circ$  ( $c = 1.00$ , CHCl<sub>3</sub>).

**Synthesis of (*S*)-2-methylcyclopent-2-en-1-yl (*R*)-3-isopropylhex-5-enoate (**2.107**)**


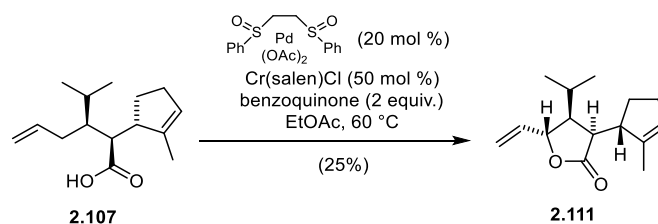
Ester **2.109** (300 g, 1.27 mmol, 1.0 equiv.) in PhMe (2 mL) was added to a solution of LiHMDS (1 M in THF, 1.90 mL, 1.90 mmol) at  $-78\text{ }^{\circ}\text{C}$ . The solution was stirred for 1 h at  $-78\text{ }^{\circ}\text{C}$ , whereupon TMSCl (271  $\mu\text{L}$ , 2.16 mmol, 1.7 equiv.) was added dropwise. The mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for 15 minutes and then allowed to warm gradually to ambient temperature over 30 minutes. The cloudy suspension was transferred to a  $\text{N}_2$ -purged high-pressure container and was submitted to 14 kbar of pressure at  $70\text{ }^{\circ}\text{C}$  for 24 h. Upon returning to ambient temperature and pressure, the mixture was poured into a saturated aqueous ammonium chloride solution (10 mL) and the aqueous phase was extracted with  $\text{Et}_2\text{O}$  ( $3 \times 10\text{ mL}$ ). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. Purification by flash column chromatography (10  $\rightarrow$  15% EtOAc in pentane) afforded acid **2.107** (246 mg, 1.04 mmol, 82%) as a pale yellow oil.  $^1\text{H}$  NMR analysis indicated that the product was obtained as a mixture, with the major product being ~70% pure.

**R<sub>f</sub>**: 0.27  $\rightarrow$  0.32 (10% EtOAc in pentane, stains with  $\text{KMnO}_4$ ).

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , major product)** 5.60 (ddt,  $J = 17.2, 10.2, 7.0\text{ Hz}$ , 1H), 5.22 (s, 1H), 4.94 (d,  $J = 17.1\text{ Hz}$ , 1H), 4.88 (d,  $J = 10.4\text{ Hz}$ , 1H), 2.91 (q,  $J = 8.6\text{ Hz}$ , 1H), 2.25 (dd,  $J = 8.5, 5.2\text{ Hz}$ , 1H), 2.10 – 1.80 (m, 6H), 1.63 (m, 1H), 1.52 (s, 3H), 1.41 (m, 1H), 0.80 (d,  $J = 7.1\text{ Hz}$ , 3H), 0.63 (d,  $J = 6.8\text{ Hz}$ , 3H).

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , major product)**  $\delta$  182.7, 142.3, 138.4, 127.1, 116.8, 49.6, 47.2, 44.0, 31.6, 30.3, 30.1, 27.3, 23.4, 17.4, 16.1.

**HRMS (ESI<sup>-</sup>)**: Calc. for  $\text{C}_{15}\text{H}_{23}\text{O}_2^-$  [ $\text{M} - \text{H}^+$ ]: 235.1704. Found: 235.1704.

**Synthesis of (*S*)-2-methylcyclopent-2-en-1-yl (*R*)-3-isopropylhex-5-enoate (**2.111**)**

A 10 mL round-bottom flask was charged with acid **2.107** (26.2 mg, 0.111 mmol, 1.0 equiv.), bis-sulfoxide-Pd(II) catalyst (11.1 mg, 0.0222 mmol, 0.2 equiv.), Cr(III)(salen)Cl (35.0 mg, 0.0554 mmol, 0.5 equiv.) and benzoquinone (24.0 mg, 0.222 mmol, 2.0 equiv.). EtOAc (1.1 mL) was added along the walls of the flask and the rapidly stirring solution was heated to 60 °C for 17 h. Upon cooling to ambient temperature, the mixture was diluted with Et<sub>2</sub>O (10 mL) and washed with saturated aqueous sodium metabisulfite solution (5 mL), saturated aqueous sodium thiosulfate solution (5 mL) and brine (10 mL). The ether layer was dried over anhydrous sodium sulfate, filtered and concentrated. Purification by flash column chromatography (6 → 8 → 10% Et<sub>2</sub>O in pentane) afforded lactone **2.111** (6.4 mg, 0.0273 mmol, 25%) as a colorless oil which solidified on standing.

**R<sub>f</sub>**: 0.48 (10% Et<sub>2</sub>O in pentane, stains with KMnO<sub>4</sub>).

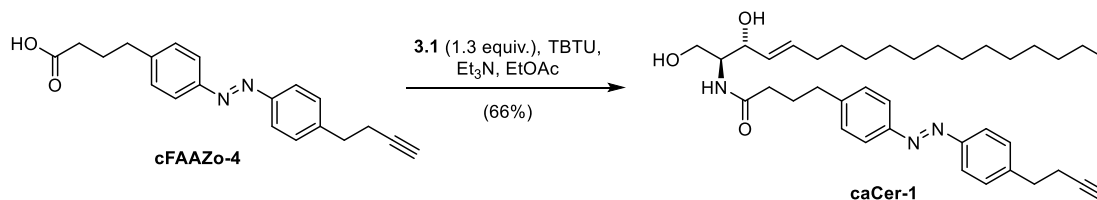
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 5.87 (ddd, J = 17.2, 10.6, 4.8 Hz, 1H), 5.45 (m, 1H), 5.35 (ddd, J = 17.1, 1.6, 1.1 Hz, 1H), 5.24 (ddd, J = 10.7, 1.6, 1.1 Hz, 1H), 4.78 (dq, J = 5.1, 1.8 Hz, 1H), 2.88 (m, 1H), 2.77 (t, J = 8.3 Hz, 1H), 2.31 – 2.16 (m, 4H), 2.10 (m, 1H), 1.89 (s, 3H), 1.70 (m, 1H), 0.99 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.9 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)** δ 178.0, 142.4, 136.0, 127.6, 116.4, 78.0, 50.1, 44.3, 44.2, 30.7, 30.6, 26.2, 22.1, 17.9, 17.2.

**HRMS (ES)**: Calc. for C<sub>15</sub>H<sub>23</sub>O<sub>2</sub> [M]: 234.1623. Found: 234.1620.

#### 4.4. Experimental Procedures for Chapter III

##### Synthesis of 4-(4-(4-(but-3-yn-1-yl)phenyl)diazenyl)phenyl)-N-((2*S*,3*R*,*E*)-1,3-dihydroxyoctadec-4-en-2-yl)butanamide (**caCer-1**)



To a stirred solution of **cFAAZo-4** (12.0 mg, 0.0371 mmol, 1.0 equiv.) in EtOAc (1.5 mL) was added TBTU (12.0 mg, 0.0374 mmol, 1.0 equiv.) at ambient temperature. After stirring for 1 h, D-erythro-sphingosine **3.1** (14.6 mg, 0.0487 mmol, 1.3 equiv.) was added to the solution, followed by Et<sub>3</sub>N (20.1  $\mu$ L, 0.150 mmol, 4.0 equiv.). The reaction was continued for 15 h, when progress was determined to be complete via TLC analysis. Aqueous saturated NaHCO<sub>3</sub> solution (3 mL) was added to the reaction mixture, and the aqueous layer was separated and further extracted with EtOAc (2  $\times$  5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (75  $\rightarrow$  85% EtOAc in hexanes) to afford **caCer-1** (14.8 mg, 0.0246, 66%) as an orange powder.

**R<sub>f</sub>**: 0.22 (80% EtOAc in hexane, stains with KMnO<sub>4</sub>).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz, 25 °C):  $\delta$  7.83 (t, *J* = 8.2 Hz, 4H), 7.34 (dd, *J* = 17.0, 8.5 Hz, 4H), 6.28 (d, *J* = 7.6 Hz, 1H), 5.81-5.75 (m, 1H), 5.55-5.49 (m, 1H), 4.30-4.28 (m, 1H), 3.97-3.89 (m, 2H), 3.68 (dd, *J* = 11.1, 3.2 Hz, 1H), 2.92 (t, *J* = 7.4 Hz, 2H), 2.74 (t, *J* = 7.5 Hz, 2H), 2.54 (td, *J* = 7.5, 2.6 Hz, 2H), 2.28-2.24 (m, 2H), 2.05-1.99 (m, 6H), 1.34-1.31 (m, 3H), 1.24 (s, 22H), 0.89-0.86 (m, 3H).

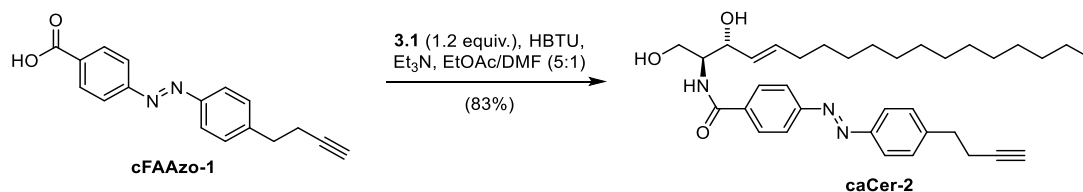
**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 101 MHz, 25 °C):  $\delta$  173.32, 151.47, 151.33, 144.87, 143.67, 134.42, 129.36, 129.31, 128.83, 123.03, 123.00, 83.53, 77.21, 74.79, 69.39, 62.50, 54.45, 35.89, 35.16, 34.77, 32.43, 32.06, 29.83, 29.80, 29.77, 29.63, 29.51, 29.37, 29.25, 27.00, 22.84, 20.52, 14.28.

**IR** (neat, ATR): 3294, 2919, 2850, 1646, 1603, 1547, 1498, 1466, 1417, 1378, 1302, 1271, 1223, 1201, 1154, 1102, 1056, 1025, 1013, 961, 920, 892, 850, 832, 720, 633, 571, 560.

**HRMS** (ESI<sup>+</sup>): Calc. for [C<sub>38</sub>H<sub>56</sub>N<sub>3</sub>O<sub>3</sub>]<sup>+</sup>: 602.4316, found: 602.4316 ([M+H]<sup>+</sup>).

**Melting point**: 103-105 °C.

**Synthesis of 4-(4-(but-3-yn-1-yl)phenyl)diazenyl-N-((2*S*,3*R*,*E*)-1,3-dihydroxyoctadec-4-en-2-yl)benzamide (caCer-2)**



To a stirred solution of **cFAAzo-1** (4.2 mg, 0.015 mmol, 1.0 equiv.) in EtOAc/DMF (5:1, 0.6 mL) was added HBTU (5.7 mg, 0.015 mmol, 1.0 equiv.) under an inert nitrogen atmosphere at ambient temperature. After 1 h, D-erythro-sphingosine **3.1** (5.4 mg, 0.018 mmol, 1.2 equiv.) was added, followed by Et<sub>3</sub>N (6.3 μL, 0.045 mmol, 3.0 equiv.). The reaction was continued for 6.5 h, when progress was determined to be complete via TLC analysis. The reaction was quenched by the addition of saturated NaHCO<sub>3</sub> solution (5 mL). The mixture was extracted with EtOAc (3 × 5 mL), and the combined organic layers were washed with brine (5 mL), dried with anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (60 → 75% EtOAc in pentane) to afford **caCer-2** as an orange powder (7.0 mg, 0.013 mmol, 83%).

**R<sub>f</sub>**: 0.43 (75% EtOAc in hexane, stains with KMnO<sub>4</sub>).

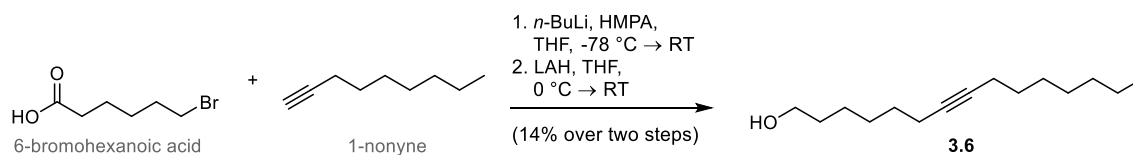
**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, 25 °C)**: δ 7.92 (d, J = 1.0 Hz, 4H), 7.88 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.12 (d, J = 7.6 Hz, 1H), 5.87-5.80 (m, 1H), 5.60 (dd, J = 15.4, 6.3 Hz, 1H), 4.47 (t, J = 4.7 Hz, 1H), 4.14-4.07 (m, 2H), 3.83 (dd, J = 11.2, 3.1 Hz, 1H), 2.93 (d, J = 14.8 Hz, 2H), 2.54 (td, J = 7.4, 2.6 Hz, 2H), 2.06 (dt, J = 11.0, 5.3 Hz, 2H), 2.01 (t, J = 4.1 Hz, 1H), 1.37-1.34 (m, 2H), 1.23 (s, 22H), 0.87 (t, J = 6.9 Hz, 3H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>, 101 MHz, 25 °C)**: δ 167.19, 154.59, 151.39, 144.62, 135.85, 134.71, 129.45, 128.88, 128.21, 123.39, 123.03, 83.43, 75.02, 69.48, 62.52, 54.88, 34.81, 32.46, 32.08, 29.84, 29.81, 29.76, 29.64, 29.52, 29.36, 29.27, 22.85, 20.47, 14.29.

**IR (neat, ATR)**: 3295, 2921, 2851, 1637, 1541, 1493, 1467, 1341, 1297, 1055, 1014, 964, 858.

**HRMS (ESI<sup>+</sup>)**: Calc. for [C<sub>35</sub>H<sub>50</sub>N<sub>3</sub>O<sub>3</sub>]<sup>+</sup>: 560.3847, found: 560.3851 ([M+H]<sup>+</sup>).

**Melting point**: 120 °C.

**Synthesis of pentadec-7-yn-1-ol (3.6)**

A solution of 1-nonyne (0.500 g, 4.03 mmol, 1.0 equiv.) in THF (30 mL) and HMPA (8 mL) was cooled to  $-78\text{ }^{\circ}\text{C}$  and treated with a solution of *n*-BuLi (2.48 M in hexanes, 3.41 mL, 8.45 mmol, 2.1 equiv.). The opaque, black solution was warmed to  $0\text{ }^{\circ}\text{C}$  and stirred for 1 h, then cooled once more to  $-78\text{ }^{\circ}\text{C}$  and 6-bromohexanoic acid (0.785 g, 4.03 mmol, 1.0 equiv.) in THF (6 mL) was added dropwise. The reaction mixture was allowed to warm to ambient temperature and stirred for 48 h, where the solution became clear and pale brown. Saturated aqueous ammonium chloride solution (25 mL) was then added to the solution and the aqueous layer was separated and extracted with EtOAc ( $3 \times 30\text{ mL}$ ). The combined organic layers were washed with distilled water ( $2 \times 20\text{ mL}$ ), saturated aqueous lithium chloride solution ( $2 \times 20\text{ mL}$ ) and brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The pale orange oil was used directly in the next procedure without purification.

The crude oil from the previous step was dissolved in THF (5 mL) and was added dropwise to a suspension of lithium aluminum hydride (229 mg, 6.05 mmol, 1.5 equiv.) cooled to  $0\text{ }^{\circ}\text{C}$  with an ice bath. The mixture was allowed to warm to room temperature and stirred for 1.5 h, where thin layer chromatography analysis indicated complete conversion. The mixture was cooled with an ice bath and carefully quenched with distilled water (5 mL) followed by 2 M aqueous sodium hydroxide solution (10 mL). The aqueous phase was extracted with Et<sub>2</sub>O ( $3 \times 30\text{ mL}$ ) and the combined organic layers were washed with saturated aqueous ammonium chloride (30 mL) and brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (15% EtOAc in pentane) to yield pentadec-7-yn-1-ol **3.6** (127 mg, 0.567 mmol, 14 % over two steps) as a colorless oil.

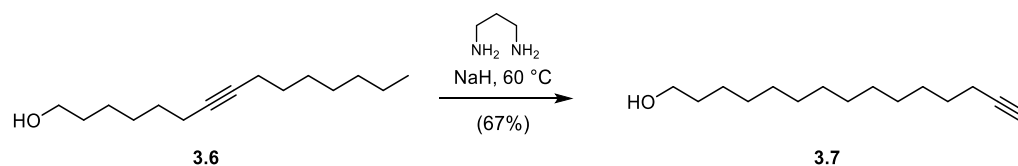
$R_f = 0.62$  (30% EtOAc in pentane, stains with CAM).

$^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz,  $25\text{ }^{\circ}\text{C}$ ):  $\delta$  3.64 (t,  $J = 6.6\text{ Hz}$ , 2H), 2.19 – 2.08 (m, 4H), 1.58 (pentet,  $J = 6.7\text{ Hz}$ , 2H), 1.53 – 1.18 (m, 17H), 0.88 (t,  $J = 6.8\text{ Hz}$ , 3H).

$^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz,  $25\text{ }^{\circ}\text{C}$ ):  $\delta$  80.55, 80.16, 63.14, 32.83, 31.93, 29.31, 29.21, 28.99, 28.99, 28.74, 25.43, 22.79, 18.90, 18.84, 14.26.

**IR** (neat, ATR): 3328, 2927, 2856, 1460, 1434, 1378, 1332, 1073, 1054, 1030, 724.

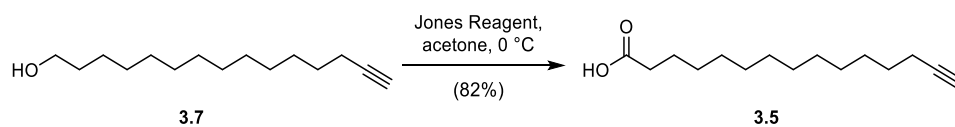
**MS** (FAB<sup>+</sup>): Calc. for  $[\text{C}_{16}\text{H}_{17}\text{N}_2\text{O}]^+$ : 225.4, found: 225.4 ( $[\text{M}+\text{H}]^+$ ).

**Synthesis of pentadec-14-yn-1-ol (3.7)**

Sodium hydride (60% in mineral oil, 149 mg, 3.74 mmol, 8.0 equiv.) was added in one portion to 1,3-diaminopropane (5 mL) at room temperature. The mixture was heated to 70 °C and stirred for 1h, where it became opaque and brown, then cooled to room temperature. Pentadec-7-yn-1-ol **3.6** (105 mg, 0.467 mmol, 1.0 equiv.) in 1,3-diaminopropane (2 mL) was added to the vessel and the mixture was heated to 60 °C and stirred for 19 h. The reaction mixture was allowed to cool to room temperature and diluted with Et<sub>2</sub>O (10 mL). Distilled water (10 mL) was then carefully added and the aqueous layer was separated and further extracted with Et<sub>2</sub>O (3 × 10 mL). The combined organic layers were washed with distilled water (10 mL), 1 M HCl (10 mL) and brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude residue was purified by flash column chromatography (15% EtOAc in pentane) to yield pentadec-14-yn-1-ol **3.7** (70.3 mg, 0.313 mmol, 67 %) as a white solid. The <sup>1</sup>H NMR spectrum is in agreement with that previously reported.<sup>[231]</sup>

$R_f = 0.44$  (20% EtOAc in pentane, stains with KMnO<sub>4</sub>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, 25 °C):  $\delta$  3.61 (t,  $J = 6.7$  Hz, 2H), 2.16 (td,  $J = 7.1, 2.7$  Hz, 2H), 1.92 (t,  $J = 2.7$  Hz, 1H), 1.59 – 1.46 (m, 5H), 1.40 – 1.22 (m, 18H).

**Synthesis of pentadec-14-ynoic acid (3.5)**

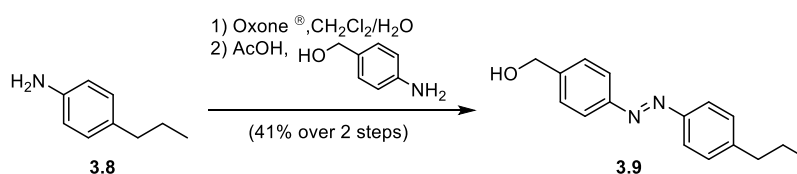
A chromic acid oxidizing solution was prepared according to literature.<sup>[232]</sup> Chromium trioxide (67.0 g, 670 mmol) was dissolved in distilled water (125 mL) and the solution was cooled to 0 °C. Concentrated sulfuric acid (58 mL) was added to the solution and the mixture was allowed to warm to room temperature. Distilled water was added to bring the total volume of the solution to 225 mL, making a ~3 M aqueous solution of chromic acid oxidizing solution. The chromic acid solution (0.149 mL, 0.446 mmol, 1.5 equiv.) was added dropwise to a solution of pentadec-14-yn-1-ol **3.7** (66.7 mg, 0.297 mmol, 1.0 equiv.) in acetone (2.0 mL) at 0 °C. The mixture was stirred for 2 h at 0 °C until TLC analysis indicated complete conversion. The solution was filtered through a pad of Celite<sup>®</sup> and the vessel and pad were washed with Et<sub>2</sub>O (50 mL). The filtrate was

washed with distilled water (20 mL) and brine (20 mL) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (10 → 30% EtOAc in pentane) to yield pentadec-14-ynoic acid **3.5** (58.1 mg, 0.244 mmol, 82 %) as a waxy white solid. The  $^1\text{H}$  NMR spectrum is in agreement with that previously reported.<sup>[229]</sup>

$R_f$  = 0.24 (20% EtOAc in pentane).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, 25 °C):  $\delta$  11.24 (broad s, 1H), 2.34 (t,  $J$  = 7.5 Hz, 2H), 2.18 (td,  $J$  = 7.1, 2.7 Hz, 2H), 1.94 (t,  $J$  = 2.6 Hz, 1H), 1.62 (q,  $J$  = 7.2 Hz, 2H), 1.52 (pentet,  $J$  = 7.2 Hz, 2H), 1.43 – 1.19 (m, 16H).

### Synthesis of 4-((4-propylphenyl)diazenyl)benzyl alcohol (**3.9**)



A solution of 4-propylaniline **3.8** (2.50 g, 18.5 mmol, 2.1 equiv.) in  $\text{CH}_2\text{Cl}_2$  (80 mL) was treated with Oxone<sup>®</sup> (22.7 g, 74.0 mmol, 8.5 equiv.) in distilled water (100 mL) at room temperature and the biphasic mixture was stirred vigorously at room temperature for 20 h. The aqueous phase was separated further extracted with  $\text{CH}_2\text{Cl}_2$  (2 × 60 mL). The combined organic phases washed with 1 M hydrochloric acid solution (75 mL), saturated aqueous sodium bicarbonate solution (75 mL) and brine (75 mL), then dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography ( $\text{CH}_2\text{Cl}_2$ ), and the collected green fractions were combined and concentrated to afford 4-propylnitrosobenzene as a clear green oil, which was taken directly to the next procedure.

The nitrosobenzene was redissolved in glacial acetic acid (75 mL) and 4-aminobenzyl alcohol (1.08 g, 8.74 mmol, 1.0 equiv.) in acetic acid (25 mL) was added to the solution at room temperature. The mixture was stirred vigorously for 72 h at room temperature, then concentrated under reduced pressure and azeotroped twice with toluene (50 mL). The crude orange solid was purified by flash column chromatography (20 → 25% EtOAc in pentane) to afford 4-((4-propylphenyl)diazenyl)benzyl alcohol **3.9** (911 mg, 3.58 mmol, 41% yield) as an orange solid.

$R_f$  = 0.43 (30% EtOAc in pentane).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, 25 °C):  $\delta$  7.90 (d,  $J$  = 8.4 Hz, 2H), 7.85 (d,  $J$  = 8.4 Hz, 2H), 7.50 (d,  $J$  = 8.4 Hz, 2H), 7.32 (d,  $J$  = 8.4 Hz, 2H), 4.77 (s, 2H), 2.67 (t,  $J$  = 7.5 Hz, 2H), 1.89 (broad s, 1H), 1.70 (pentet,  $J$  = 7.5 Hz, 2H), 0.97 (t,  $J$  = 7.5 Hz, 3H).



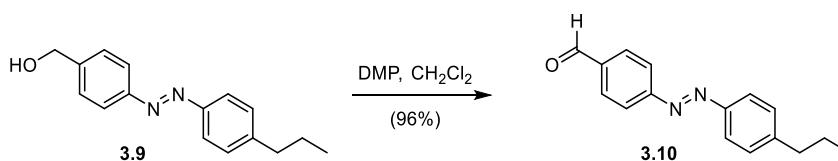
$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz, 25 °C):  $\delta$  152.32, 151.05, 146.49, 143.62, 129.31, 127.56, 123.07, 122.96, 65.03, 38.08, 24.55, 13.94.

IR (neat, ATR): 3332, 2958, 2930, 2869, 1661, 1585, 1499, 1449, 1417, 1340, 1303, 1222, 1026, 1010, 852, 832.

HRMS ( $\text{ESI}^+$ ): Calc. for  $[\text{C}_{16}\text{H}_{19}\text{N}_2\text{O}]^+$ : 255.1492, found: 255.1491 ( $[\text{M}+\text{H}]^+$ ).

Melting point: 138 °C.

### Synthesis of 4-((4-propylphenyl)diazenyl)benzaldehyde (**3.10**)



A solution of 4-((4-propylphenyl)diazenyl)benzyl alcohol **3.9** (302 mg, 1.19 mmol, 1.0 equiv.) in  $\text{CH}_2\text{Cl}_2$  (12 mL) was treated with Dess-Martin periodinane (655 mg, 1.55 mmol, 1.3 equiv.) at room temperature. The reaction mixture was left to stir for 45 minutes and a mixture of saturated aqueous sodium bicarbonate solution and saturated aqueous sodium thiosulfate solution (1:1, 20 mL) was added. The biphasic mixture was stirred for 30 minutes, then the aqueous phase was separated and extracted with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 20$  mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (3  $\rightarrow$  4% EtOAc in pentane) to afford 4-((4-propylphenyl)diazenyl)benzaldehyde **3.10** (282 mg, 1.12 mmol, 94%) as a red crystalline solid.

$R_f$  = 0.43 (30% EtOAc in pentane).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, 25 °C):  $\delta$  10.07 (s, 1H), 8.00 (s, 4H), 7.88 (d,  $J$  = 8.1 Hz, 2H), 7.32 (d,  $J$  = 8.1 Hz, 2H), 2.66 (t,  $J$  = 7.6 Hz, 2H), 1.69 (pentet,  $J$  = 7.5 Hz, 2H), 0.97 (t,  $J$  = 7.4 Hz, 3H).

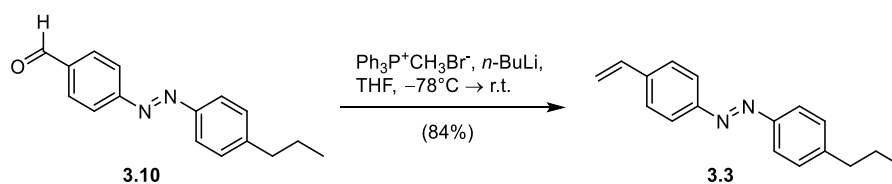
$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz, 25 °C):  $\delta$  191.64, 156.01, 150.91, 147.57, 137.24, 130.70, 129.34, 123.36, 123.25, 38.04, 24.40, 13.88.

IR (neat, ATR): 3023, 2956, 2929, 2845, 2739, 1696, 1597, 1581, 1498, 1460, 1416, 1378, 1316, 1304, 1289, 1197, 1183, 1148, 1129, 1112, 1090, 1003, 908, 847, 831, 811, 793, 75, 729, 663.

HRMS ( $\text{ESI}^+$ ): Calc. for  $[\text{C}_{16}\text{H}_{19}\text{N}_2\text{O}]^+$ : 253.1335, found: 253.1336 ( $[\text{M}+\text{H}]^+$ ).

Melting point: 107 °C.

### Synthesis of 1-(4-propylphenyl)-2-(4-vinylphenyl)diazene (**3.3**)



A suspension of methyltriphenylphosphonium bromide (439 mg, 1.23 mmol, 1.1 equiv.) in THF (12 mL) at  $0^\circ\text{C}$  was treated with a solution of  $n\text{-BuLi}$  (2.48 M in hexanes, 0.496 mL, 1.23 mmol, 1.1 equiv.). The resulting bright yellow suspension was stirred for 20 minutes at  $0^\circ\text{C}$  and a solution of 4-((4-propylphenyl)diazenyl)benzaldehyde **3.10** (282 mg, 1.12 mmol, 1.0 equiv.) in THF (5 mL) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 1 h. Saturated aqueous ammonium chloride solution (20 mL) was added and the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 20$  mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (dry loading with 1 g silica gel,  $0 \rightarrow 3\%$   $\text{Et}_2\text{O}$  in pentane) to yield 1-(4-propylphenyl)-2-(4-vinylphenyl)diazene **3.3** (237 mg, 0.946 mmol, 84%) as a crystalline orange solid.

$R_f = 0.43$  (30% EtOAc in pentane).

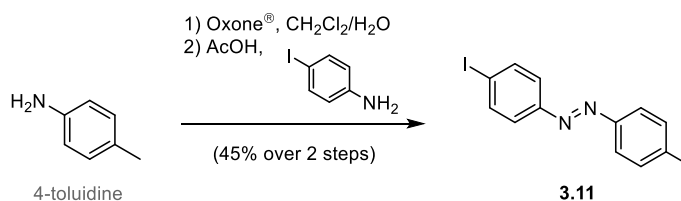
$^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz,  $25^\circ\text{C}$ ):  $\delta$  7.89 (d,  $J = 8.5$  Hz, 2H), 7.86 (d,  $J = 8.4$  Hz, 2H), 7.55 (d,  $J = 8.5$  Hz, 2H), 7.33 (d,  $J = 8.4$  Hz, 2H), 6.79 (dd,  $J = 17.6, 10.9$  Hz, 1H), 5.87 (d,  $J = 17.6$  Hz, 1H), 5.36 (d,  $J = 10.9$  Hz, 1H), 2.68 (t,  $J = 7.5$  Hz, 2H), 1.70 (hextet,  $J = 7.5$  Hz, 2H), 0.98 (t,  $J = 7.5$  Hz, 3H).

$^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz,  $25^\circ\text{C}$ ):  $\delta$  152.31, 151.17, 146.42, 140.00, 136.33, 129.30, 127.03, 123.21, 122.96, 115.55, 38.09, 24.56, 13.95.

**IR** (neat, ATR): 3045, 2958, 2929, 2870, 1626, 1598, 1497, 1454, 1414, 1402, 1303, 1287, 1226, 1155, 1109, 1011, 988, 908, 848, 802, 748.

**HRMS** ( $\text{ESI}^+$ ): Calc. for  $[\text{C}_{17}\text{H}_{19}\text{N}_2]^+$ : 251.1543, found: 251.1543 ( $[\text{M}+\text{H}]^+$ ).

**Melting point:**  $37^\circ\text{C}$ .

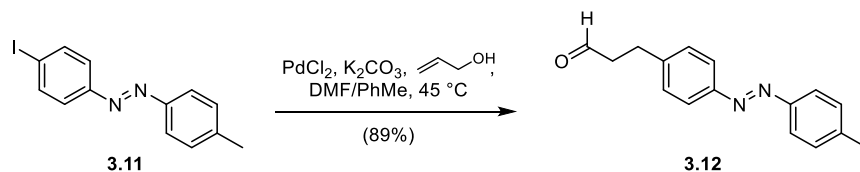
**Synthesis of 4-iodo-4'-methylazobenzene (3.11)**

4-Iodo-4'-methylazobenzene was synthesized following a modified procedure of Strueben *et al.*<sup>[234]</sup> A solution of *p*-toluidine (2.50 g, 24.3 mmol, 1.0 equiv.) in CH<sub>2</sub>Cl<sub>2</sub> (80 mL) was treated with Oxone<sup>®</sup> (29.8 g, 97.1 mmol, 4.1 equiv.) in distilled water (120 mL) at room temperature and the biphasic mixture was stirred vigorously at room temperature for 18 h. The aqueous phase was separated and further extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 50 mL). The combined organic phases were washed with 1 M hydrochloric acid solution (80 mL), saturated aqueous sodium bicarbonate solution (80 mL) and brine (80 mL), then dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>), and the collected green fractions were combined and concentrated to afford a clear green oil. The oil was redissolved in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and acetic acid (30 mL) and 4-iodoaniline (5.13 g, 23.4 mmol, 1.0 equiv.) was added to the solution. The mixture was stirred for 15 h at room temperature, during which an orange-yellow crystalline solid precipitated. The mixture was concentrated under reduced pressure, suspended in ice-cold ethanol (30 mL) and filtered. The recovered crystals were washed with ice-cold ethanol (30 mL) and dried to afford 4-iodo-4'-methylazobenzene **3.11** (3.35 g, 10.4 mmol, 45% yield) as an orange-yellow crystalline solid. The <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra are in agreement with those previously reported.<sup>[234]</sup>

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, 25 °C):** δ 7.85 (d, J = 8.5 Hz, 2H), 7.82 (d, J = 8.5 Hz, 2H), 7.64 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 8.5 Hz, 3H), 2.44 (s, 3H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz, 25 °C):** δ 152.13, 150.70, 142.17, 138.43, 129.96, 124.51, 123.12, 97.37, 21.72.

### Synthesis of 3-(4-(*p*-tolyl diazenyl)phenyl)propanal (**3.12**)



1-(4-Iodophenyl)-2-(*p*-tolyl)diazene **3.11** (3.34 g, 10.4 mmol, 1.0 equiv.) was suspended in DMF (12 mL) and toluene (12 mL) at room temperature and tetrabutylammonium chloride (2.89 g, 10.4 mmol, 1.0 equiv.), sodium bicarbonate (2.18 g, 26.0 mmol, 2.5 equiv.) and allyl alcohol (0.906 g, 15.6 mmol, 1.5 equiv.) were added sequentially to the stirring mixture. The orange suspension was stirred for 10 minutes at room temperature, whereupon PdCl<sub>2</sub> (0.369 mg, 2.08 mmol, 0.20 equiv.) was added to the flask. The bright red suspension was warmed to 45 °C and stirred for 2.5 h, then cooled back to room temperature and stirred for 48 h. The reaction mixture was then diluted with EtOAc (125 mL) and washed successively with 1 M aqueous hydrochloric acid solution (50 mL), distilled water (4 × 50 mL) and brine (50 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The crude residue was purified by flash column chromatography (6 → 10% EtOAc in pentane) to yield 3-(4-(*p*-tolyl diazenyl)phenyl)propanal **3.12** (2.28 g, 9.07 mmol, 87%) as a crystalline orange solid.

$R_f = 0.36$  (10% EtOAc in pentane).

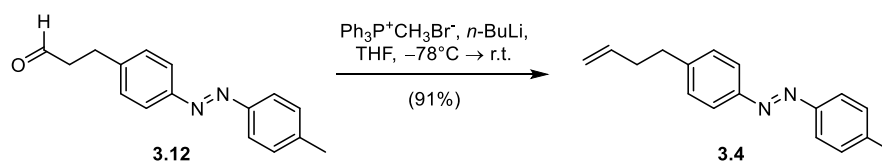
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, 25 °C): δ 9.82 (s, 1H), 7.85 (d, *J* = 7.5 Hz, 2H), 7.83 (d, *J* = 7.5 Hz, 2H), 7.33 (d, *J* = 7.5 Hz, 2H), 7.31 (d, *J* = 7.5 Hz, 2H), 3.02 (t, *J* = 7.5 Hz, 2H), 2.81 (t, *J* = 7.5 Hz, 2H), 2.43 (s, 1H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz, 25 °C): δ 201.18, 151.36, 150.78, 143.48, 141.52, 129.80, 129.06, 123.06, 122.85, 45.08, 27.97, 21.57.

IR (neat, ATR): 3022, 2921, 2832, 2730, 1716, 1600, 1497, 1448, 1416, 1390, 1356, 1302, 1221, 1210, 1153, 1111, 1061, 1038, 1011, 904, 843, 822, 728, 705, 682.

HRMS (ESI<sup>+</sup>): Calc. for [C<sub>16</sub>H<sub>17</sub>N<sub>2</sub>O]<sup>+</sup>: 253.1335, found: 253.1336 ([M+H]<sup>+</sup>).

Melting point: 78 °C.

**Synthesis of 1-(4-(but-3-en-1-yl)phenyl)-2-(*p*-tolyl)diazene (3.4)**

A suspension of methyltriphenylphosphonium bromide (3.87 g, 10.8 mmol, 1.2 equiv.) in THF (50 mL) at  $-78\text{ }^{\circ}\text{C}$  was treated with a solution of *n*-BuLi (2.48 M in hexanes, 4.37 mL, 10.8 mmol, 1.2 equiv.). The resulting bright yellow suspension was warmed to  $0\text{ }^{\circ}\text{C}$  for 20 minutes, then cooled once more to at  $-78\text{ }^{\circ}\text{C}$ . 3-(4-(*p*-Tolyldiazenyl)phenyl)propanal **3.12** (2.28 g, 9.02 mmol, 1.0 equiv.) in THF (10 mL) was added dropwise and the mixture was allowed to warm to room temperature and stirred for 15 h. Saturated aqueous ammonium chloride solution (60 mL) was added and the aqueous phase was separated and further extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 80 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (dry loading, 1 → 2% EtOAc in pentane) to yield 1-(4-(but-3-en-1-yl)phenyl)-2-(*p*-tolyl)diazene **3.4** (2.06 g, 8.22 mmol, 91%) as a crystalline orange solid.

$R_f = 0.30$  (2% EtOAc in pentane).

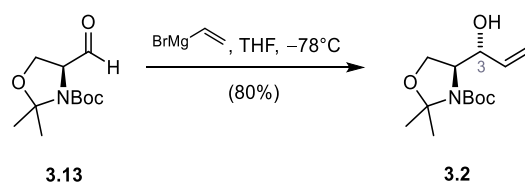
**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, 25 °C):**  $\delta$  7.78 (d,  $J = 8.2$  Hz, 2H), 7.76 (d,  $J = 7.5$  Hz, 2H), 7.25 (d,  $J = 8.2$  Hz, 2H), 7.23 (d,  $J = 7.5$  Hz, 2H), 5.80 (ddt,  $J = 16.9, 10.2, 6.6$  Hz, 1H), 4.99 (dd,  $J = 16.9, 1.7$  Hz, 1H), 4.94 (dd,  $J = 10.2, 1.7$  Hz, 1H), 2.72 (t,  $J = 7.5$  Hz, 2H), 2.36 (m, 5H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz, 25 °C):**  $\delta$  151.20, 150.92, 145.14, 141.35, 137.80, 129.82, 129.23, 122.88, 122.86, 115.38, 35.42, 35.37, 21.61.

**IR (neat, ATR):** 3074, 3054, 3024, 2977, 2922, 2857, 1640, 1601, 1580, 1497, 1440, 1415, 1302, 1224, 1209, 1155, 1105, 1012, 996, 950, 907, 837, 823, 708, 643.

**HRMS (ESI<sup>+</sup>):** Calc. for [C<sub>17</sub>H<sub>19</sub>N<sub>2</sub>]<sup>+</sup>: 251.1543, found: 251.1542 ([M+H]<sup>+</sup>).

**Melting point:** 57 °C.

**Synthesis of *N*-Boc-(*R*)-1-((*S*)-2,2-dimethyloxazolidin-4-yl)prop-2-en-1-ol (**3.2**)**


Vinyl magnesium bromide (1.0 M in THF, 22.7 mL, 22.7 mmol, 2.0 equiv.) was added over 30 minutes via drop funnel to a solution of (*S*)-1,1-dimethylethyl 4-formyl-2,2-dimethyloxazolidine-3-carboxylate **3.13** (2.61 g, 11.4 mmol, 1.0 equiv.) in THF (50 mL) at  $-78^\circ\text{C}$ . The reaction mixture was stirred for 2 h at  $-78^\circ\text{C}$  until TLC analysis indicated complete conversion, and saturated aqueous ammonium chloride solution (40 mL) was added at this temperature. After warming to room temperature, the aqueous layer was separated and extracted with EtOAc ( $3 \times 70$  mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The crude residue was purified by flash column chromatography (15% EtOAc in pentane) to afford **3.2** (2.33 g, 9.07 mmol, 80%) as a colorless oil. High-temperature  $^1\text{H}$  NMR analysis indicates a 5.2:1 *anti/syn* mixture of diastereomers at C3, consistent with previous literature results.<sup>[236]</sup> Further purification of the mixture by careful column chromatography (10% EtOAc in pentane) yielded the pure *anti* diastereomer.

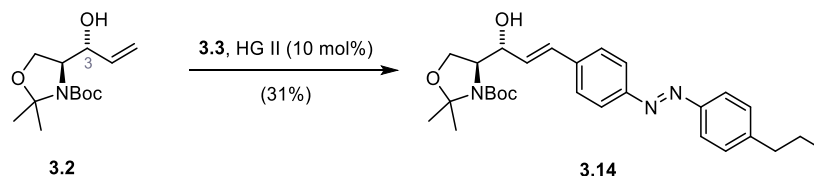
$R_f = 0.35$  (20% EtOAc in pentane).

$^1\text{H}$  NMR (toluene- $d_8$ , 400 MHz,  $90^\circ\text{C}$ ):  $\delta$  5.81 (ddd,  $J = 16.7, 10.5, 5.2$  Hz, 1H), 5.31 (dt,  $J = 16.7, 1.8$  Hz, 1H), 5.06 (d,  $J = 10.5$  Hz, 1H), 4.26 (broad s, 1H), 3.87 (m, 1H), 3.77 (m, 1H), 3.66 (dd,  $J = 9.0, 6.8$  Hz, 1H), 1.58 (s, 3H), 1.43 (s, 3H), 1.38 (s, 9H).

$^{13}\text{C}$  NMR (toluene- $d_8$ , 100 MHz,  $90^\circ\text{C}$ ):  $\delta$  153.39, 138.68, 115.44, 94.68, 80.27, 73.87, 64.81, 62.47, 28.49, 26.82, 24.43.

IR (neat, ATR): 3461, 2978, 2936, 2879, 1694, 1478, 1456, 1377, 1365, 1255, 1206, 1170, 1095, 1049, 989, 923, 848, 807, 767.

HRMS (ESI<sup>+</sup>): Calc. for  $[\text{C}_{13}\text{H}_{24}\text{NO}_4]^+$ : 258.1700, found: 258.1699 ( $[\text{M}+\text{H}]^+$ ).

**Synthesis of *N*-Boc-(*R,E*)-1-((*S*)-2,2-dimethyloxazolidin-4-yl)-3-((4-(4-propylphenyl)diazenyl)phenyl)prop-2-en-1-ol (**3.14**)**

Hoyveda-Grubbs 2<sup>nd</sup> generation catalyst (29.6 mg, 0.0472 mmol, 0.10 equiv.) was added to a solution of allyl alcohol **3.2** (121 mg, 0.472 mmol, 1.0 equiv.) and olefin **3.3** (236 mg, 0.944 mmol, 2.0 equiv.) in degassed CH<sub>2</sub>Cl<sub>2</sub> (6 mL) at room temperature. The deep red mixture was heated to 45 °C and stirred for 21 h. The mixture was cooled to temperature and, without concentrating, was loaded on an equilibrated silica gel column and purified by flash column chromatography (15 → 25% EtOAc in pentane). The combined fractions contained traces of remnant catalyst, and the product was purified a second time by flash column chromatography (15 → 25% EtOAc in pentane) to yield **3.14** (71.1 mg, 0.148 mmol, 31%) as a dark orange gum.

**R<sub>f</sub>** = 0.32 (20% EtOAc in pentane).

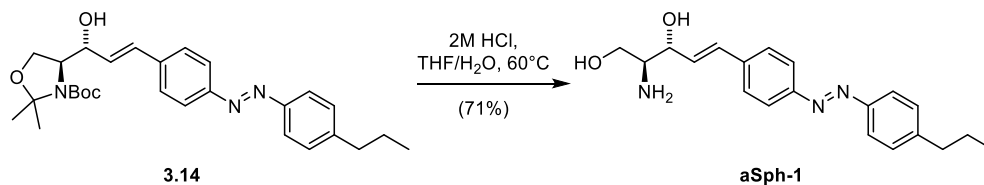
**<sup>1</sup>H NMR (toluene-*d*<sub>8</sub>, 400 MHz, 90 °C):** δ 7.90 (d, *J* = 8.3 Hz, 2H), 7.88 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 8.3 Hz, 2H), 6.68 (dd, *J* = 15.8, 1.5 Hz, 1H), 6.26 (dd, *J* = 15.8, 5.6 Hz, 1H), 4.37 (m, 1H), 3.98 (m, 1H), 3.81 (m, 1H), 3.70 (dd, *J* = 9.1, 6.7 Hz, 1H), 2.43 (t, *J* = 7.3, 2H), 1.56 (s, 3H), 1.52 (q, *J* = 7.3, 2H), 1.41 (s, 3H), 1.32 (s, 9H), 0.84 (t, *J* = 7.3 Hz, 3H).

**<sup>13</sup>C NMR (toluene-*d*<sub>8</sub>, 100 MHz, 90 °C):** δ 153.79, 152.91, 152.14, 146.11, 140.24, 131.86, 130.52, 129.35, 127.55, 123.72, 123.49, 94.78, 80.53, 74.33, 65.21, 62.93, 38.27, 28.46, 27.02, 24.51, 13.81.

**IR (neat, ATR):** 3426, 2976, 2933, 2873, 1693, 1600, 1497, 1477, 1455, 1389, 1376, 1366, 1255, 1205, 1156, 1100, 1068, 1050, 967, 921, 864, 847, 768, 733.

**HRMS (ESI<sup>+</sup>):** Calc. for [C<sub>28</sub>H<sub>38</sub>N<sub>3</sub>O<sub>4</sub>]<sup>+</sup>: 480.2857, found: 480.2860 ([M+H]<sup>+</sup>).

**Synthesis of (2*S*,3*R*,*E*)-2-amino-5-(4-((4-propylphenyl)diazenyl)phenyl) pent-4-ene-1,3-diol (aSph-1)**



Carbamate **3.14** (23.9 mg, 0.0498 mmol, 1.0 equiv.) was dissolved in THF (1.25 mL) and the solution was cooled to 0 °C with an ice bath. 2 M hydrochloric acid solution (0.50 mL) was added dropwise and the reaction mixture was heated to 60 °C. After stirring for 3 h, the solution was cooled to ambient temperature and saturated sodium carbonate solution (5 mL) was added. The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 10 mL) and the combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude orange solid was purified by flash column chromatography (5/94.5/0.5 → 10/89/1 MeOH/CH<sub>2</sub>Cl<sub>2</sub>/aqueous ammonium hydroxide solution) to afford **aSph-1** (13.1 mg, 0.0386 mmol, 77%) as an orange solid.

**R<sub>f</sub>** = 0.14 (40% acetone in toluene).

**<sup>1</sup>H NMR (methanol-d<sub>4</sub>, 400 MHz, 25 °C):** δ 7.77 (d, *J* = 8.6 Hz, 2H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.6 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 6.66 (d, *J* = 15.9 Hz, 1H), 6.38 (dd, *J* = 15.9, 6.8 Hz, 1H), 4.19 (t, *J* = 5.8 Hz, 1H), 3.65 (dd, *J* = 10.9, 4.6 Hz, 1H), 3.48 (dd, *J* = 10.9, 6.9 Hz, 1H), 2.85 (q, *J* = 5.7 Hz, 1H), 2.58 (d, *J* = 7.5 Hz, 2H), 1.60 (hextet, *J* = 7.4 Hz, 2H), 0.88 (t, *J* = 7.4 Hz, 3H).

**<sup>13</sup>C NMR (methanol-d<sub>4</sub>, 100 MHz, 25 °C):** δ 153.28, 152.36, 147.76, 141.00, 132.46, 132.26, 130.31, 128.38, 124.10, 123.82, 74.80, 64.24, 58.28, 38.89, 25.61, 14.10.

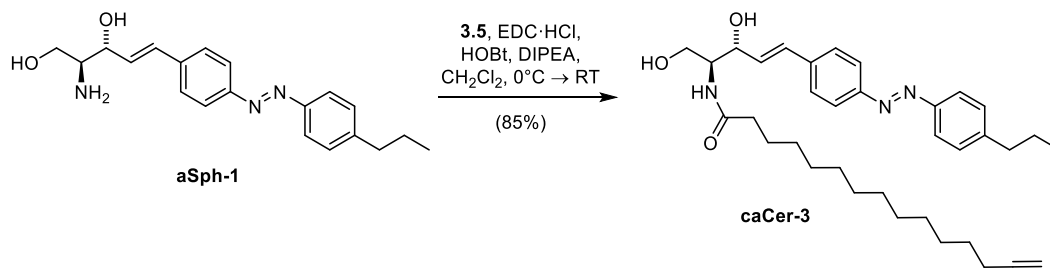
**IR (neat, ATR):** 3045, 2958, 2929, 2870, 1626, 1598, 1497, 1454, 1414, 1402, 1303, 1287, 1226, 1155, 1109, 1011, 988, 908, 848, 802, 748.

**HRMS (ESI<sup>+</sup>):** Calc. for [C<sub>20</sub>H<sub>26</sub>N<sub>3</sub>O<sub>2</sub>]<sup>+</sup>: 340.2020, found: 340.2020 ([M+H]<sup>+</sup>).

**Melting point:** 135 °C.



**Synthesis of *N*-((2*S*,3*R*,*E*)-1,3-dihydroxy-5-(4-((4-propylphenyl) diazenyl)phenyl)pent-4-en-2-yl)pentadec-14-ynamide (**caCer-3**)**



**ASp-1** (7.9 mg, 0.023 mmol, 1.0 equiv.) and pentadec-14-ynoic acid **3.5** (6.1 mg, 0.026 mmol, 1.1 equiv.) were dissolved in  $\text{CH}_2\text{Cl}_2$  (0.8 mL) and the solution was cooled to 0 °C with an ice bath. Diisopropylethylamine (12.2  $\mu\text{L}$ , 0.0698 mmol, 3.0 equiv.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (7.6 mg, 0.040 mmol, 1.7 equiv.) and 1-hydroxybenzotriazole hydrate (6.8 mg, 0.044 mmol, 1.9 equiv.) were added sequentially to the flask, and the mixture was allowed warm to room temperature and was stirred for 20 h. Saturated aqueous sodium bicarbonate solution (5 mL) was added. The aqueous layer was separated and extracted with  $\text{CH}_2\text{Cl}_2$  (3  $\times$  5 mL). The combined organic layers were washed with 1 M hydrochloric acid (5 mL) and brine (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (2  $\rightarrow$  4% MeOH in  $\text{CH}_2\text{Cl}_2$ ) to afford **caCer-3** (11.0 mg, 0.0197 mmol, 85%) as an orange solid.

**Note:** Due to initially proceeding with a mixture of epimers from compound **3.2**, our first synthesis of **caCer-3** produced a 7.3:1 mixture of *erythro*/*threo* ceramide by  $^1\text{H}$  NMR analysis and biological assays were conducted with this mixture. The procedures reported here are from a second synthesis conducted with anti-**3.2** to yield pure *erythro*-**caCer-3**.

$R_f$  = 0.36 (90% EtOAc in pentane).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, 25 °C):  $\delta$  7.86 (d,  $J$  = 8.5 Hz, 2H), 7.83 (d,  $J$  = 8.3 Hz, 2H), 7.50 (d,  $J$  = 8.5 Hz, 2H), 7.31 (d,  $J$  = 8.3 Hz, 2H), 6.77 (d,  $J$  = 16.1 Hz, 1H), 6.38 (dd,  $J$  = 16.1, 5.7 Hz, 1H), 6.37 (s, 1H), 4.59 (t,  $J$  = 4.0 Hz, 1H), 4.05 (m, 2H), 3.78 (m, 1H), 2.66 (t,  $J$  = 7.5 Hz, 2H), 2.24 (m, 2H), 2.16 (td,  $J$  = 7.1, 2.6 Hz, 2H), 1.94 (t,  $J$  = 2.6 Hz, 1H), 1.66 (m, 4H), 1.50 (pentet,  $J$  = 7.3 Hz, 2H) 1.41 – 1.15 (m, 18H), 0.97 (t,  $J$  = 7.3 Hz, 3H).

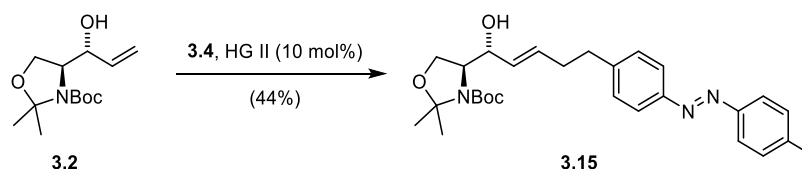
$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz, 25 °C):  $\delta$  174.30, 152.30, 151.11, 146.52, 138.71, 131.21, 130.19, 129.31, 127.38, 123.33, 122.99, 84.99, 74.62, 68.19, 62.52, 54.62, 38.09, 36.99, 29.74, 29.71, 29.64, 29.61, 29.52, 29.43, 29.25, 28.90, 28.62, 25.94, 24.55, 18.54, 13.95.

**IR (neat, ATR):** 3296, 2922, 2850, 1645, 1600, 1547, 1467, 1440, 1302, 1257, 1155, 1116, 1065, 1002, 964, 862, 825, 724, 696.

**HRMS (ESI<sup>+</sup>):** Calc. for [C<sub>35</sub>H<sub>50</sub>N<sub>3</sub>O<sub>3</sub>]<sup>+</sup>: 560.3847, found: 560.3862 ([M+H]<sup>+</sup>).

**Melting point:** 133 °C.

**Synthesis of *N*-Boc-(*R,E*)-1-((*S*)-2,2-dimethyloxazolidin-4-yl)-6-(4-(*p*-tolyl)diazenyl)phenyl)hex-2-en-1-ol (**3.15**)**



Hoyveda-Grubbs catalyst, 2<sup>nd</sup> generation (63.8 mg, 0.102 mmol, 0.10 equiv.) was added to a solution of allyl alcohol **3.2** (262 mg, 1.02 mmol, 1.0 equiv.) and 1-(4-(but-3-en-1-yl)phenyl)-2-(*p*-tolyl)diazene **3.4** (510 mg, 2.04 mmol, 2.0 equiv.) in degassed CH<sub>2</sub>Cl<sub>2</sub> (8 mL) at room temperature. The deep red mixture was heated to 45 °C and stirred for 16 h. The mixture was cooled to ambient temperature and, without concentrating, was loaded on an equilibrated silica gel column and purified by flash column chromatography (15 → 25% EtOAc in pentane). The combined fractions contained traces of remnant catalyst, and the product was purified a second time by flash column chromatography (15 → 25% EtOAc in pentane) to yield **3.15** (223 mg, 0.450 mmol, 44%) as an orange gum.

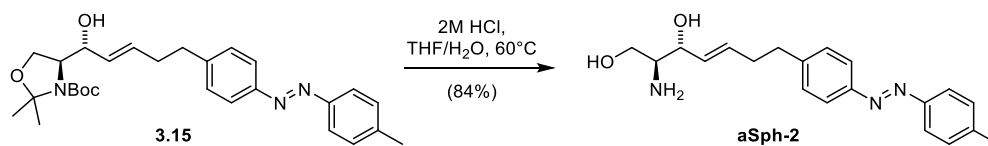
**R<sub>f</sub>** = 0.35 (20% EtOAc in pentane).

**<sup>1</sup>H NMR (toluene-*d*<sub>8</sub>, 400 MHz, 90 °C):** δ 7.89 (d, *J* = 8.1 Hz, 2H), 7.86 (d, *J* = 8.1 Hz, 2H), 7.08 (m, 4H), 5.72 (dt, *J* = 13.3, 6.5 Hz, 1H), 5.49 (dd, *J* = 15.4, 5.6 Hz, 1H), 5.06 (d, *J* = 10.5 Hz, 1H), 4.26 (broad s, 1H), 3.87 (m, 1H), 3.77 (m, 1H), 3.66 (dd, *J* = 9.0, 6.8 Hz, 1H), 2.15 (s, 3H), 1.58 (s, 3H), 1.43 (s, 3H), 1.38 (s, 9H).

**<sup>13</sup>C NMR (toluene-*d*<sub>8</sub>, 100 MHz, 90 °C)** 129.94, 129.37, 123.45, 123.38, 94.71, 80.24, 73.64, 64.92, 62.81, 35.99, 34.20, 28.60, 26.94, 24.55, 21.22.

**IR (neat, ATR):** 3448, 2978, 2933, 1694, 1602, 1498, 1478, 1454, 1388, 1376, 1365, 1255, 1206, 1156, 1101, 1067, 1014, 968, 912, 842, 768, 733.

**HRMS (ESI<sup>+</sup>):** Calc. for [C<sub>28</sub>H<sub>38</sub>N<sub>3</sub>O<sub>4</sub>]<sup>+</sup>: 480.2857, found: 480.2873 ([M+H]<sup>+</sup>).

**Synthesis of (2*S*,3*R*,*E*)-2-amino-7-(4-(*p*-tolylidiazenyl)phenyl)hept-4-ene-1,3-diol (aSph-2)**

2 M Hydrochloric acid solution (2 mL) was added dropwise to a solution of **3.15** (94.2 mg, 0.196 mmol, 1.0 equiv.) in THF (4 mL) at room temperature and the reaction mixture was heated to 60 °C for 3 h. The solution was then basified to pH 10 with 2 M sodium hydroxide solution (2.4 mL) and the aqueous mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude orange solid was purified by flash column chromatography (5/94.5/0.5 → 10/89/1 MeOH/CH<sub>2</sub>Cl<sub>2</sub>/aqueous 25% ammonium hydroxide solution) to afford **aSph-2** (55.5 mg, 0.164 mmol, 84%) as an orange solid.

**R<sub>f</sub>** = 0.14 (40% acetone in toluene).

**<sup>1</sup>H NMR (methanol-d<sub>4</sub>, 400 MHz, 25 °C):** δ 7.79 (d, J = 8.1 Hz, 2H), 7.76 (d, J = 7.9 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 7.9 Hz, 2H), 5.76 (dt, J = 15.4, 6.8 Hz, 1H), 5.47 (dd, J = 15.4, 6.8 Hz, 1H), 3.95 (t, J = 6.7 Hz, 1H), 3.59 (dd, J = 11.2, 4.1 Hz, 1H), 3.43 (dd, J = 11.2, 6.9 Hz, 1H), 2.80 (q, J = 6.8 Hz, 2H), 2.71 (q, J = 6.0 Hz, 1H), 2.45 (m, 2H), 2.40 (s, 3H).

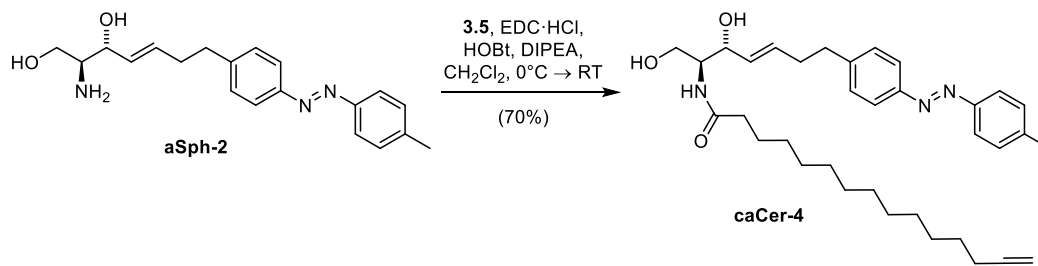
**<sup>13</sup>C NMR (methanol-d<sub>4</sub>, 100 MHz, 25 °C):** δ 152.39, 152.09, 146.59, 142.86, 133.97, 131.66, 130.80, 130.43, 123.77, 123.73, 74.42, 63.66, 57.95, 36.28, 35.05, 21.45.

**IR (neat, ATR):** 3345, 3286, 3024, 2922, 2855, 1601, 1581, 1497, 1451, 1416, 1302, 1154, 1050, 1034, 1012, 965, 849, 827, 712, 643, 617, 558.

**HRMS (ESI<sup>+</sup>):** Calc. for [C<sub>20</sub>H<sub>26</sub>N<sub>3</sub>O<sub>2</sub>]<sup>+</sup>: 340.2020, found: 340.2022 ([M+H]<sup>+</sup>).

**Melting point:** 141 °C.

**Synthesis of *N*-((2*S*,3*R*,*E*)-1,3-dihydroxy-7-(4-(*p*-tolyl diazenyl) phenyl)hept-4-en-2-yl)pentadec-14-ynamide (**caCer-4**)**



**aSph-2** (15.0 mg, 0.0442 mmol, 1.0 equiv.) and pentadec-14-ynoic acid **3.5** (10.5 mg, 0.0442 mmol, 1.0 equiv.) were dissolved in  $\text{CH}_2\text{Cl}_2$  (1.5 mL) and the solution was cooled to 0 °C with an ice bath. Diisopropylethylamine (23.1  $\mu\text{L}$ , 0.133 mmol, 3.0 equiv.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimidehydrochloride (12.7 mg, 0.0663 mmol, 1.5 equiv.) and 1-hydroxybenzotriazole hydrate (11.5 mg, 0.0751 mg, 1.7 equiv.) were added sequentially to the flask, and the mixture was allowed warm to room temperature and was stirred for 4 h. TLC analysis indicated some **aSph-2** remained, and the mixture was cooled to 0 °C and additional **3.5** (5.2 mg, 0.022 mmol, 0.5 equiv.), diisopropylethylamine (7.7  $\mu\text{L}$ , 0.044 mmol, 1.0 equiv.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimidehydrochloride (4.2 mg, 0.022 mmol, 0.5 equiv.) and 1-hydroxybenzotriazole hydrate (3.4 mg, 0.22 mmol, 0.5 equiv.) were added. The mixture was left to stir at room temperature for 17 h and saturated aqueous sodium bicarbonate solution (5 mL) was added. The aqueous layer was separated and extracted with  $\text{CH}_2\text{Cl}_2$  (3  $\times$  5 mL). The combined organic layers were washed with 1 M hydrochloric acid (5 mL) and brine (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (80% EtOAc in pentane) to afford **caCer-4** (17.2 mg, 0.0307 mmol, 70%) as an orange solid.

$R_f = 0.30$  (80% EtOAc in pentane).

$^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz, 25 °C):  $\delta$  7.82 (d,  $J = 8.4$  Hz, 2H), 7.80 (d,  $J = 8.4$  Hz, 2H), 7.31 (d,  $J = 8.4$  Hz, 2H), 7.29 (d,  $J = 8.4$  Hz, 2H), 6.20 (d,  $J = 7.6$  Hz, 1H), 5.79 (dt,  $J = 14.0, 6.5$  Hz, 1H), 5.52 (dd,  $J = 14.0, 6.2$  Hz, 1H), 4.28 (t,  $J = 5.0$  Hz, 1H), 3.85 (dq,  $J = 7.5, 3.7$  Hz, 1H), 3.79 (dd,  $J = 11.3, 3.9$  Hz, 1H), 3.61 (dd,  $J = 11.3, 3.5$  Hz, 1H), 2.79 (t,  $J = 7.5$  Hz, 2H), 2.46 (m, 2H), 2.43 (s, 3H), 2.18 (m, 4H), 1.94 (t,  $J = 2.6$  Hz, 1H), 1.61 (t,  $J = 7.3$  Hz, 2H), 1.50 (q,  $J = 7.3$  Hz, 2H), 1.43 – 1.33 (m, 2H), 1.30 – 1.22 (m, 16H).

$^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz, 25 °C):  $\delta$  174.14, 151.32, 150.86, 144.70, 141.56, 132.33, 130.28, 129.86, 129.30, 122.90, 122.89, 84.97, 74.45, 68.19, 62.41, 54.56, 36.92, 35.35, 33.83, 29.73, 29.71, 29.63, 29.51, 29.42, 29.25, 28.90, 28.62, 25.88, 21.65, 18.53.

**IR (neat, ATR):** 3294, 2920, 2850, 1643, 1603, 1542, 1467, 1377, 1279, 1156, 1104, 1049, 1014, 960, 895, 840, 722.

**HRMS (ESI<sup>+</sup>):** Calc. for [C<sub>35</sub>H<sub>50</sub>N<sub>3</sub>O<sub>3</sub>]<sup>+</sup>: 560.3847, found: 560.3851 ([M+H]<sup>+</sup>).

**Melting point:** 111 °C.

---

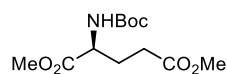
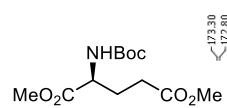
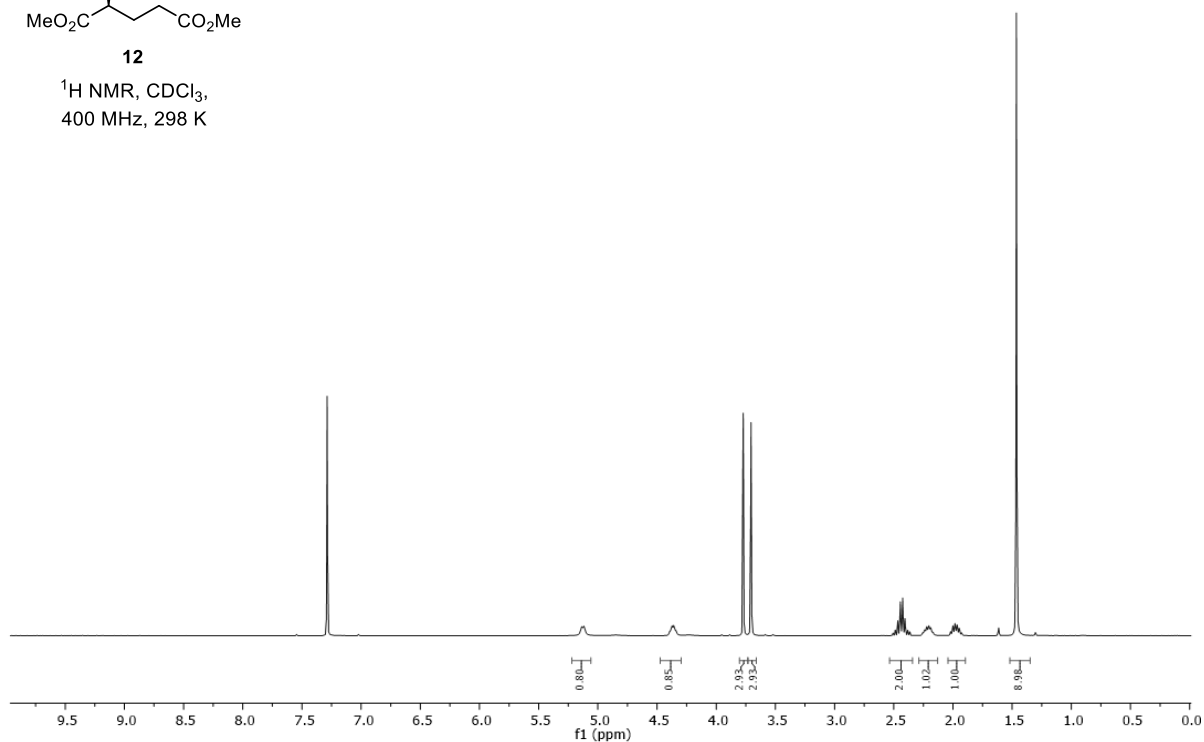
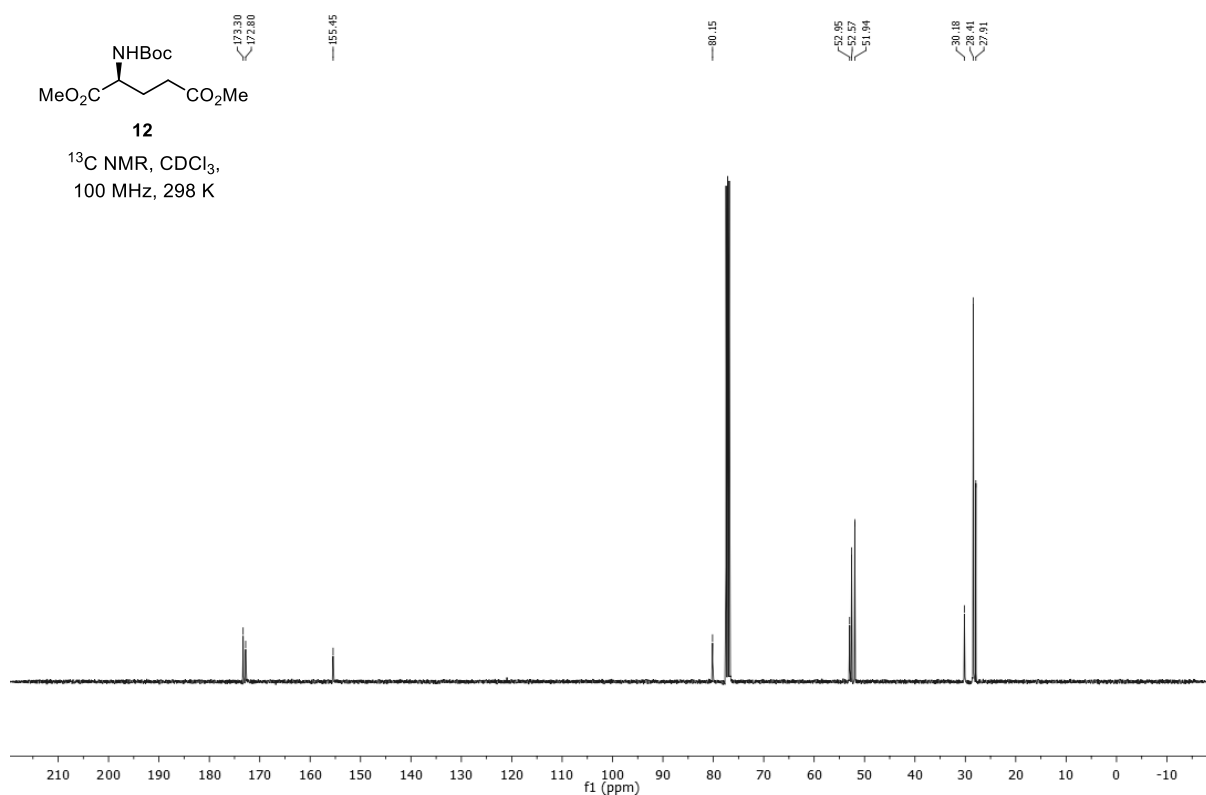


CHAPTER V:  
APPENDIX

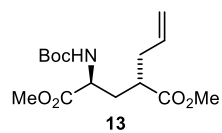
---

## 4.1. $^1\text{H}$ NMR and $^{13}\text{C}$ NMR Spectra

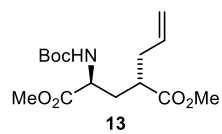
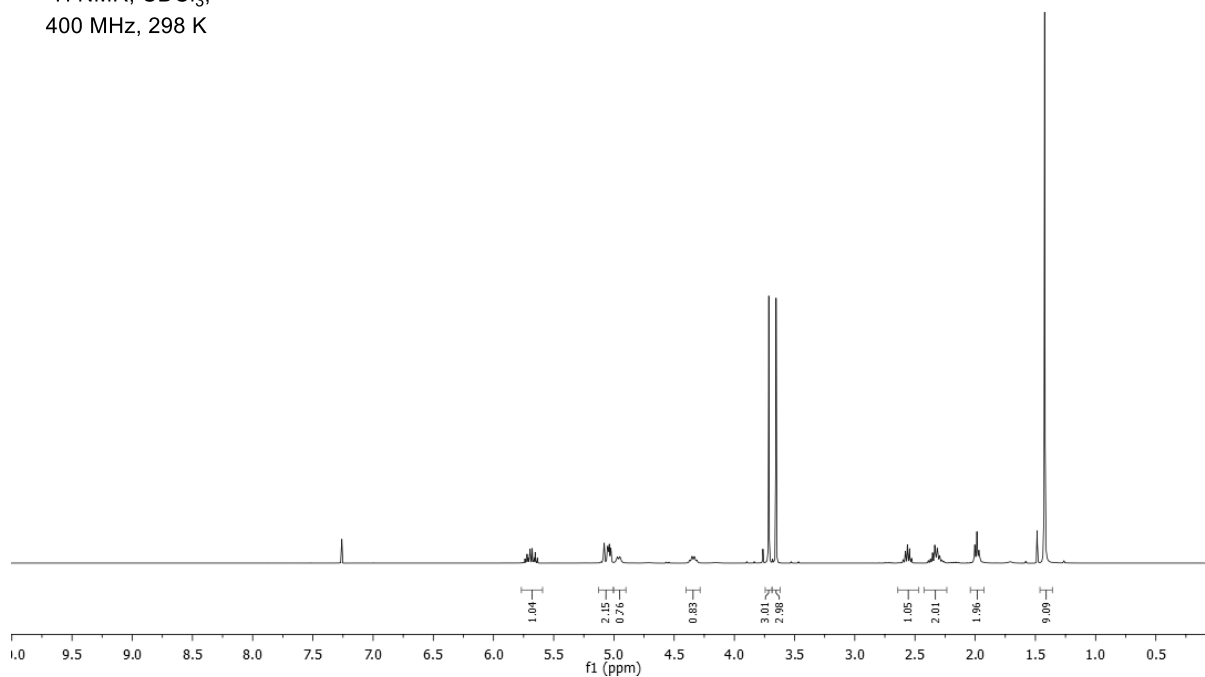
### 4.1.1. $^1\text{H}$ NMR and $^{13}\text{C}$ NMR Spectra for Chapter I

**12** $^1\text{H}$  NMR,  $\text{CDCl}_3$ ,  
400 MHz, 298 K**12** $^{13}\text{C}$  NMR,  $\text{CDCl}_3$ ,  
100 MHz, 298 K

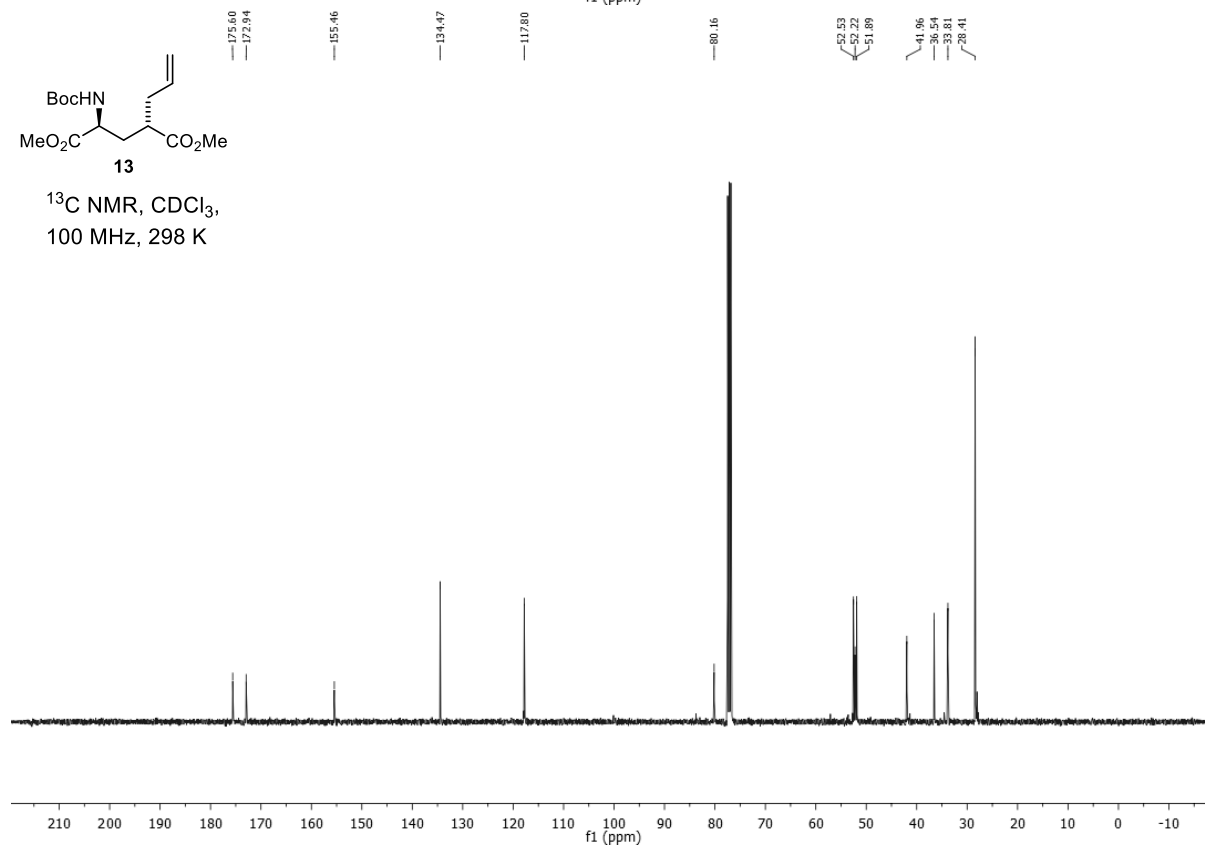


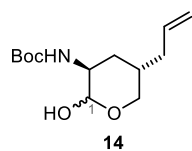


$^1\text{H}$  NMR,  $\text{CDCl}_3$ ,  
400 MHz, 298 K

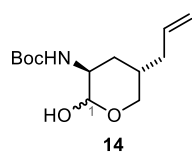
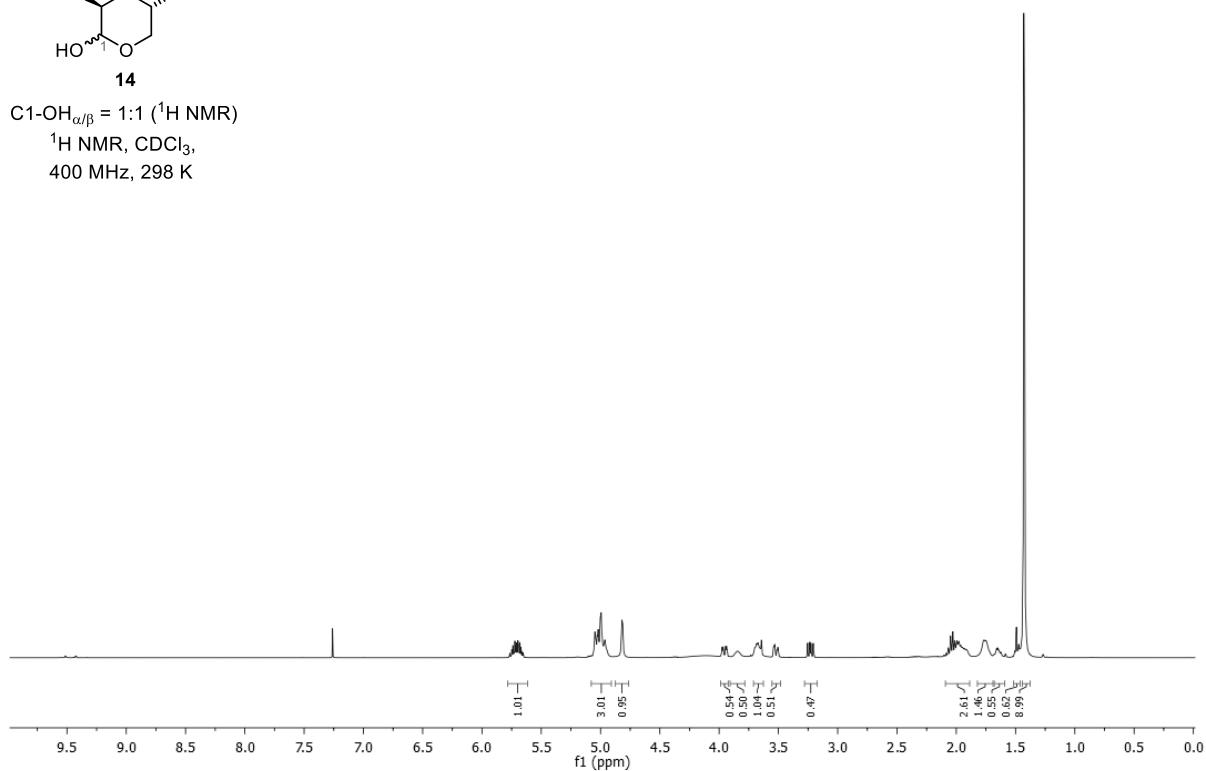


$^{13}\text{C}$  NMR,  $\text{CDCl}_3$ ,  
100 MHz, 298 K

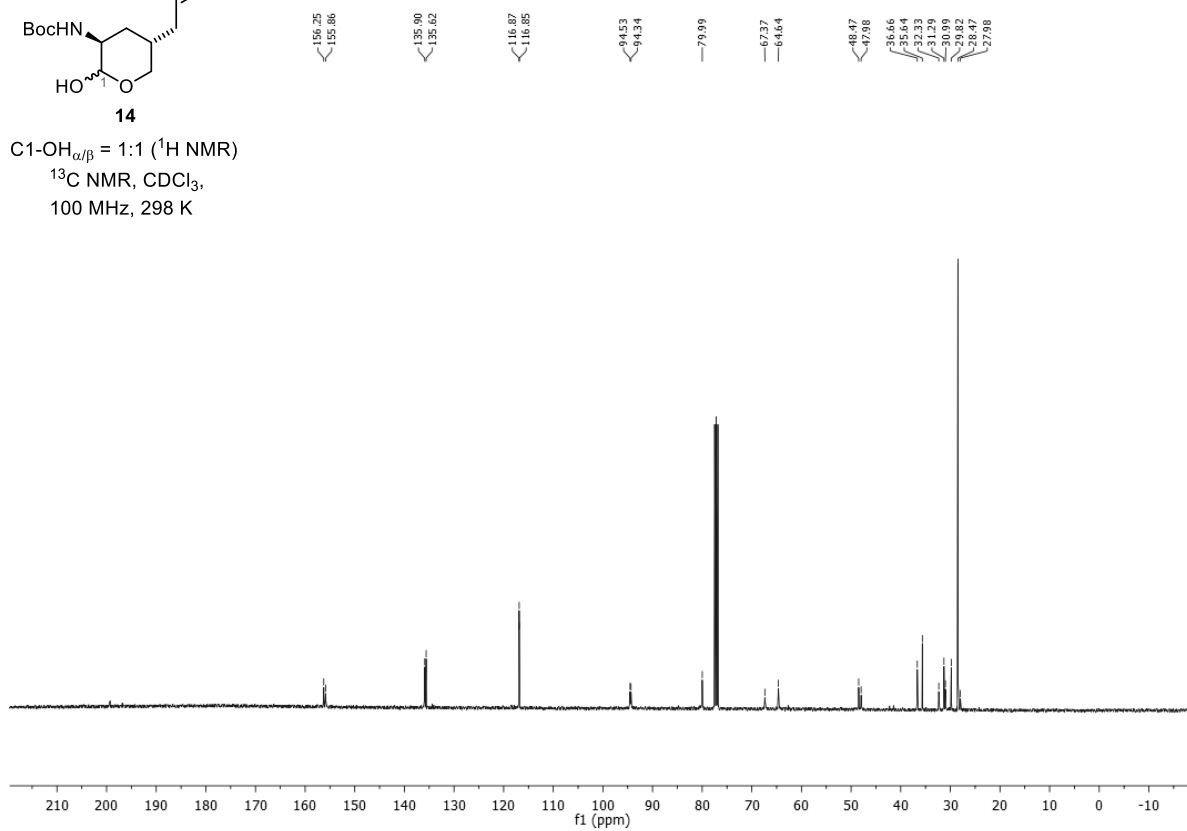


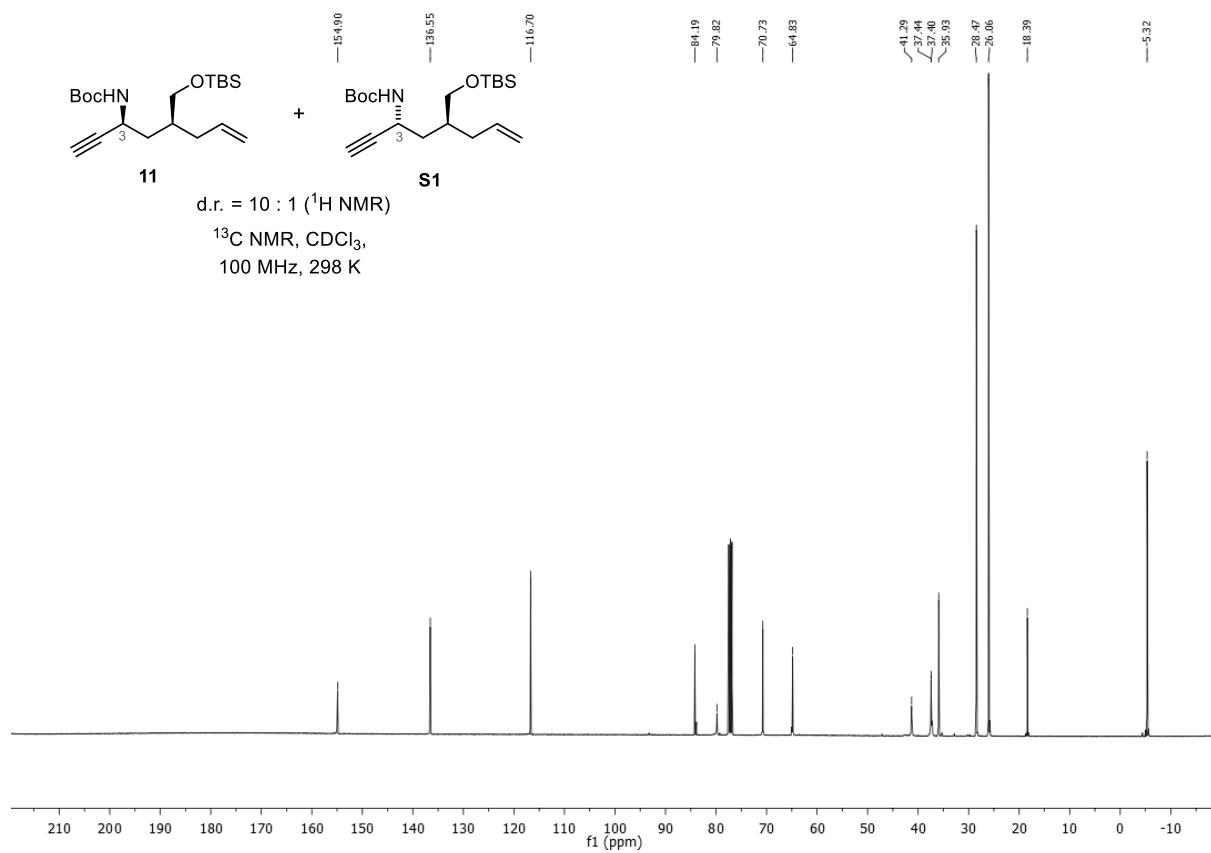
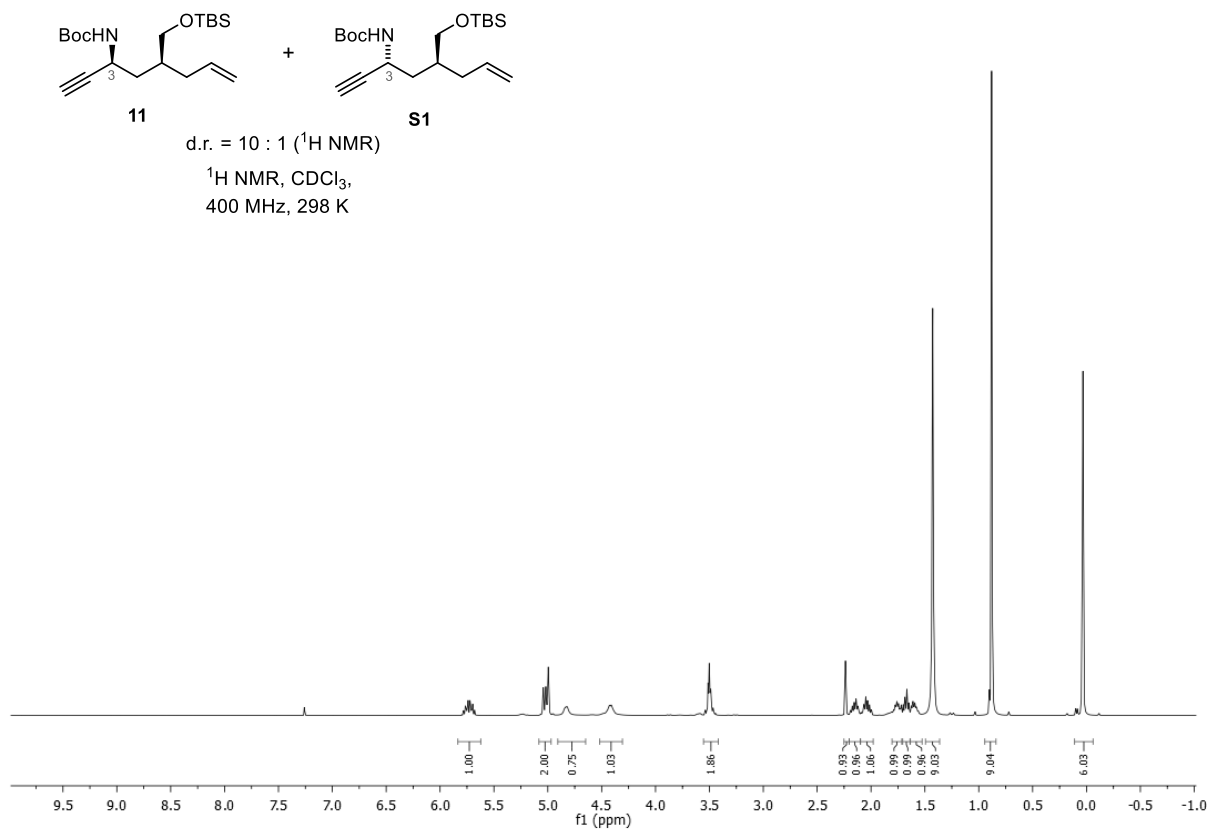


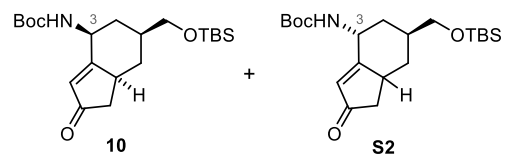
C1-OH<sub>α/β</sub> = 1:1 (<sup>1</sup>H NMR)  
<sup>1</sup>H NMR, CDCl<sub>3</sub>,  
 400 MHz, 298 K



C1-OH<sub>α/β</sub> = 1:1 (<sup>1</sup>H NMR)  
<sup>13</sup>C NMR, CDCl<sub>3</sub>,  
 100 MHz, 298 K

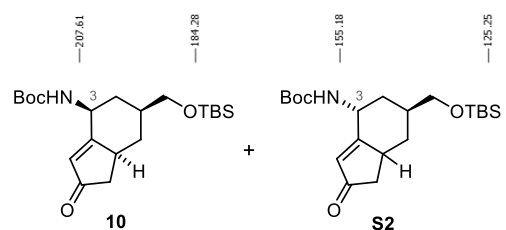
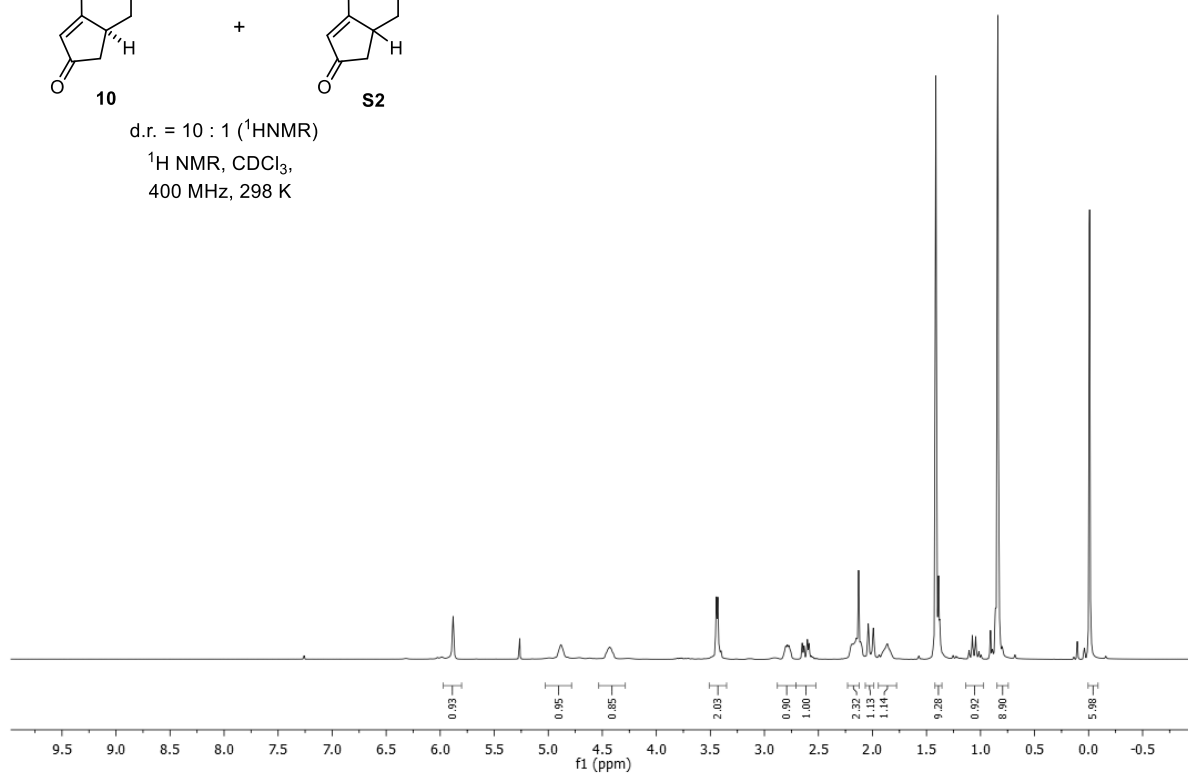






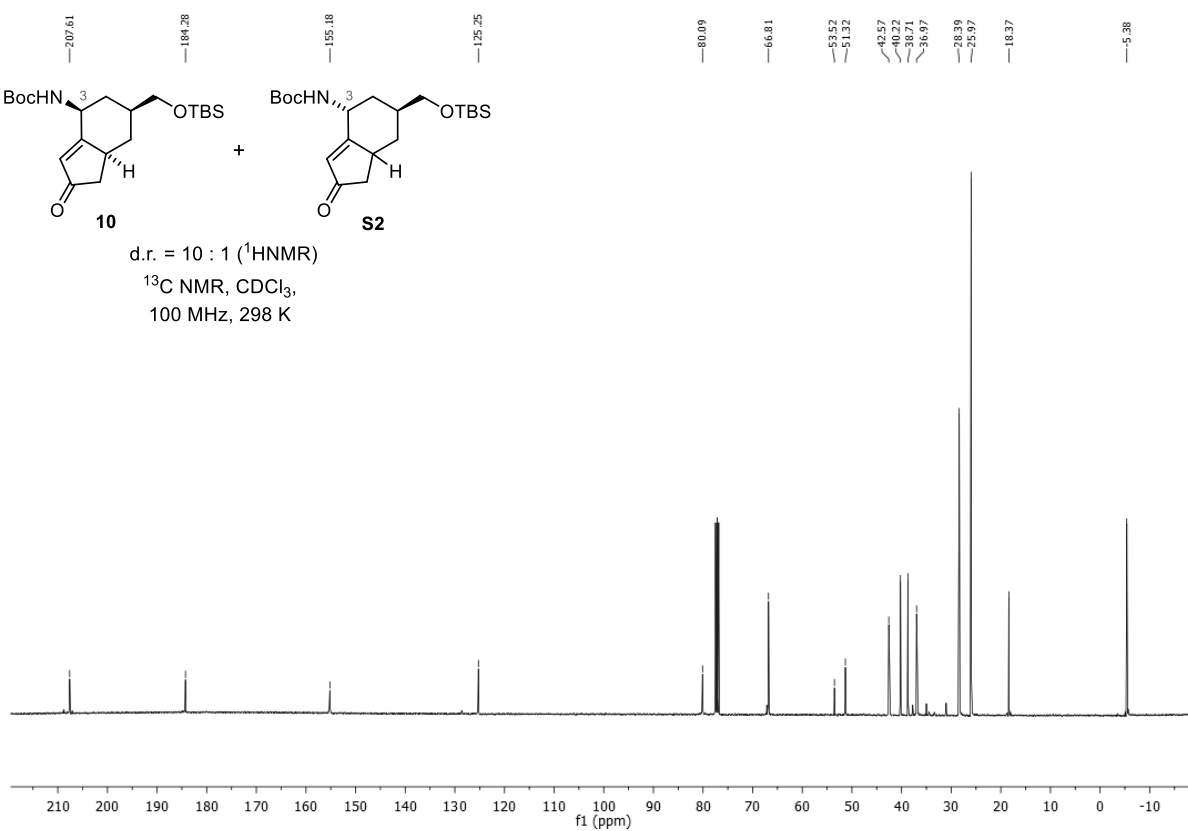
d.r. = 10 : 1 ( $^1\text{H NMR}$ )

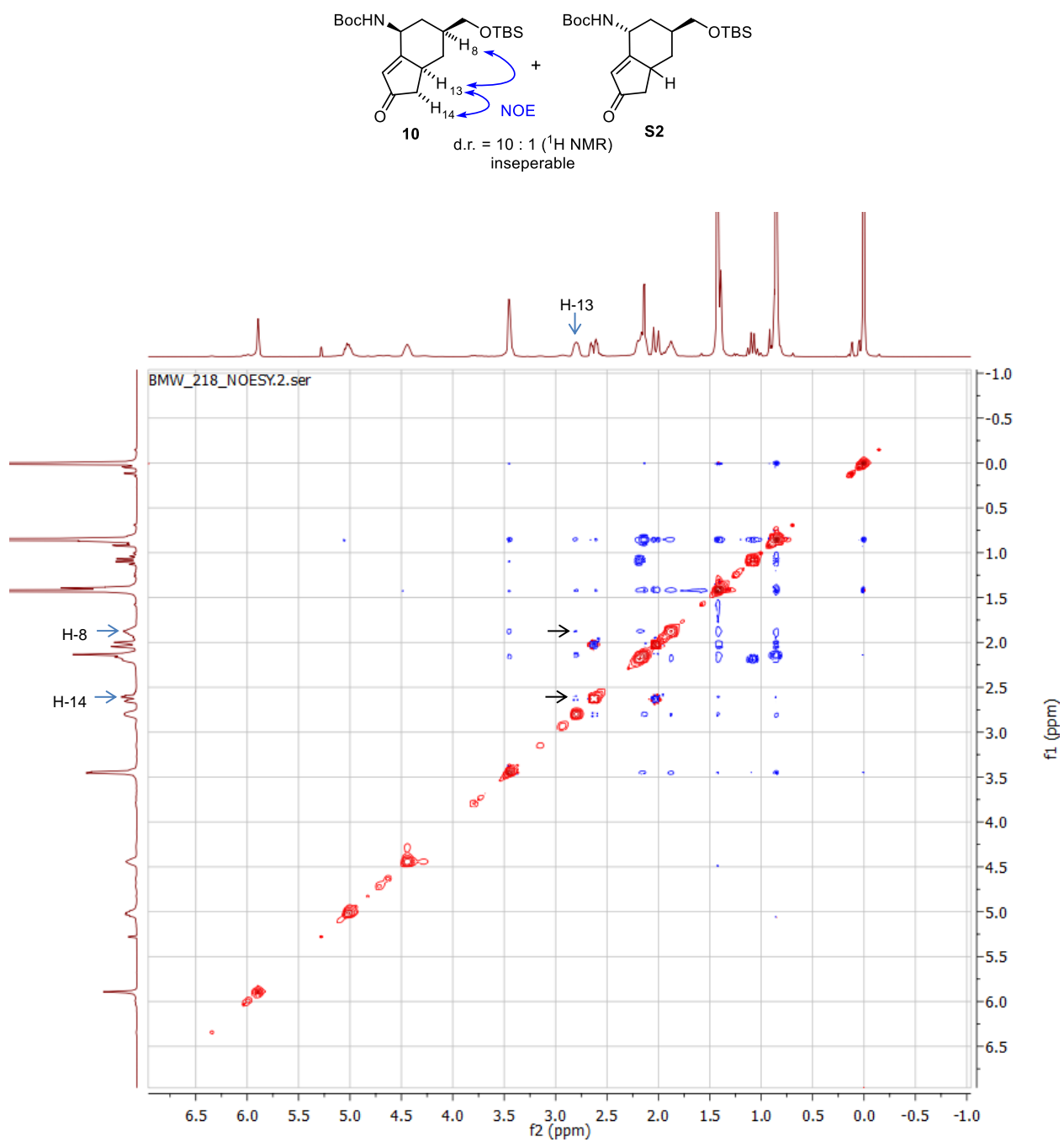
$^1\text{H NMR}$ ,  $\text{CDCl}_3$ ,  
400 MHz, 298 K

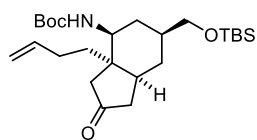


d.r. = 10 : 1 ( $^1\text{H NMR}$ )

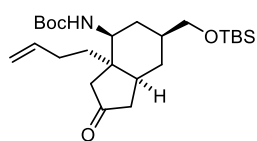
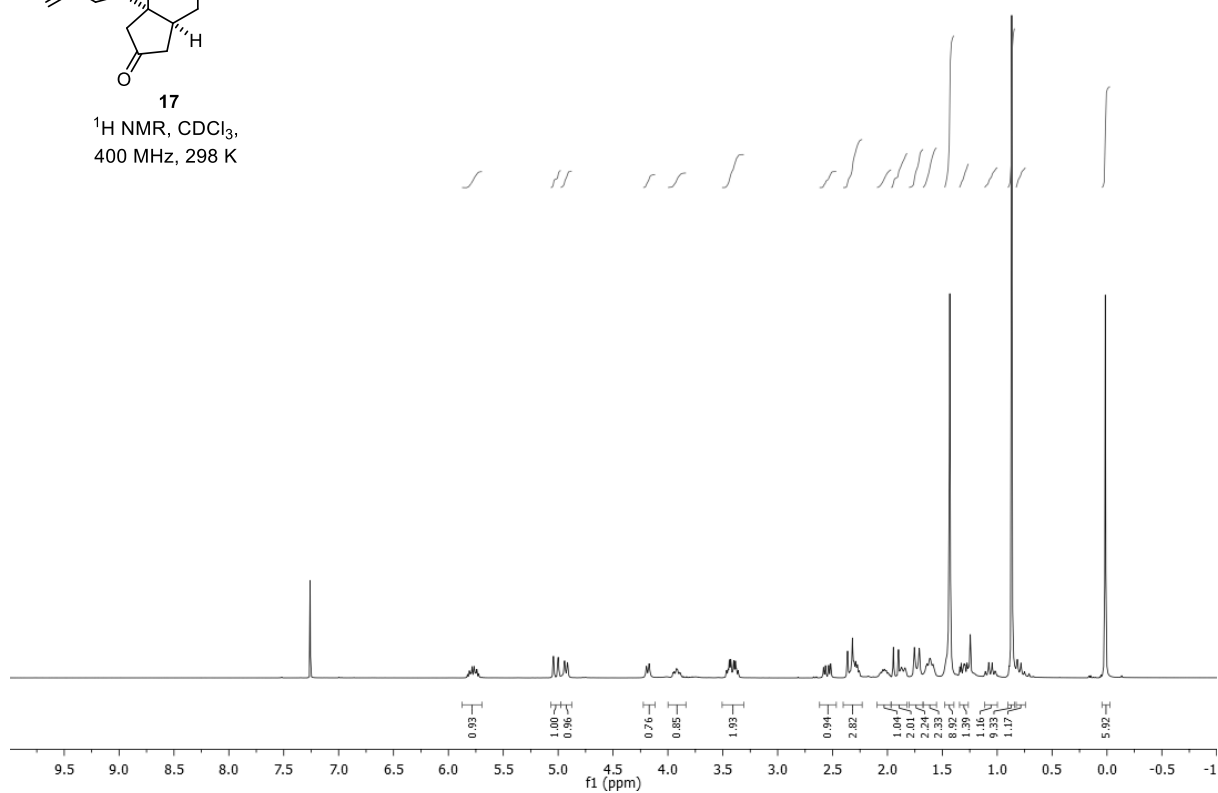
$^{13}\text{C NMR}$ ,  $\text{CDCl}_3$ ,  
100 MHz, 298 K



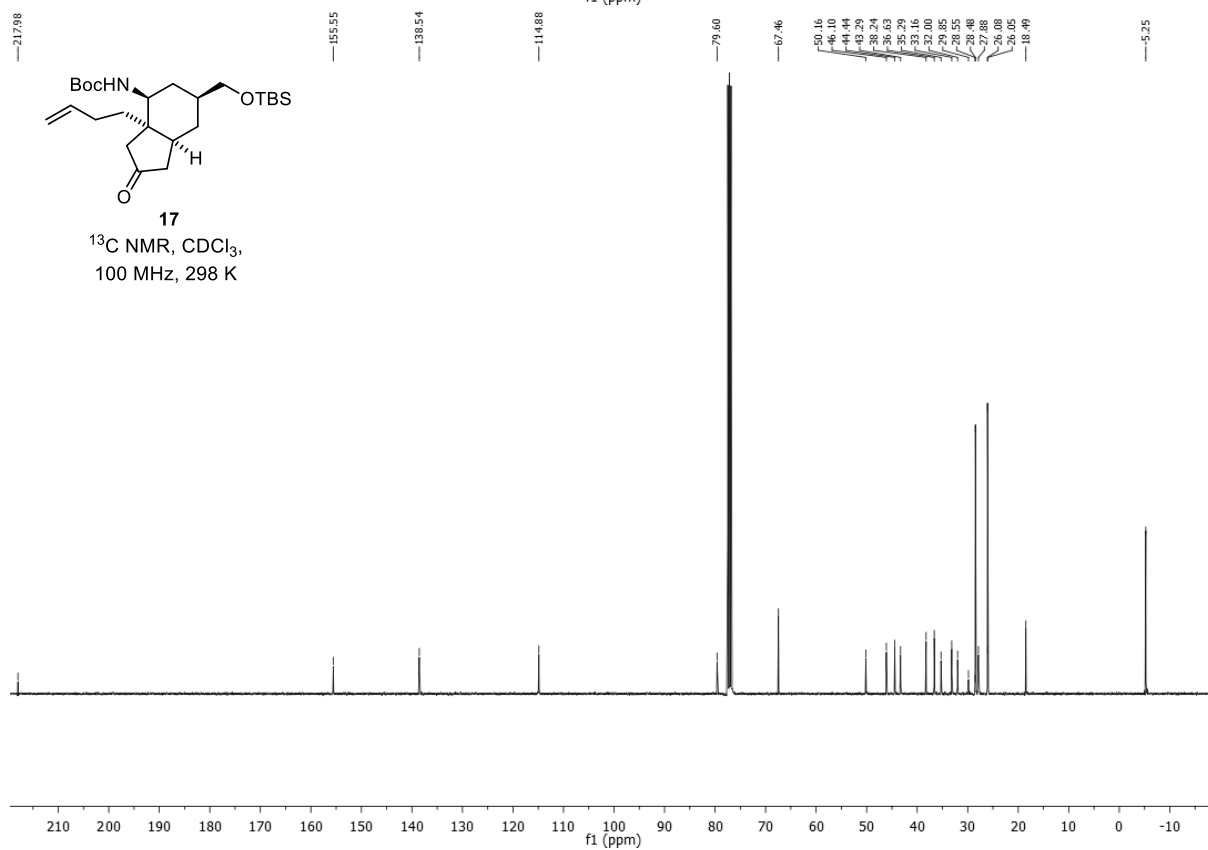
**Figure 5.1:** NOESY spectrum of **10** (CDCl<sub>3</sub>, 400 MHz).

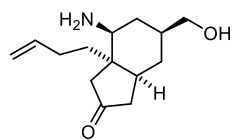
**17**

$^1\text{H NMR}$ ,  $\text{CDCl}_3$ ,  
400 MHz, 298 K

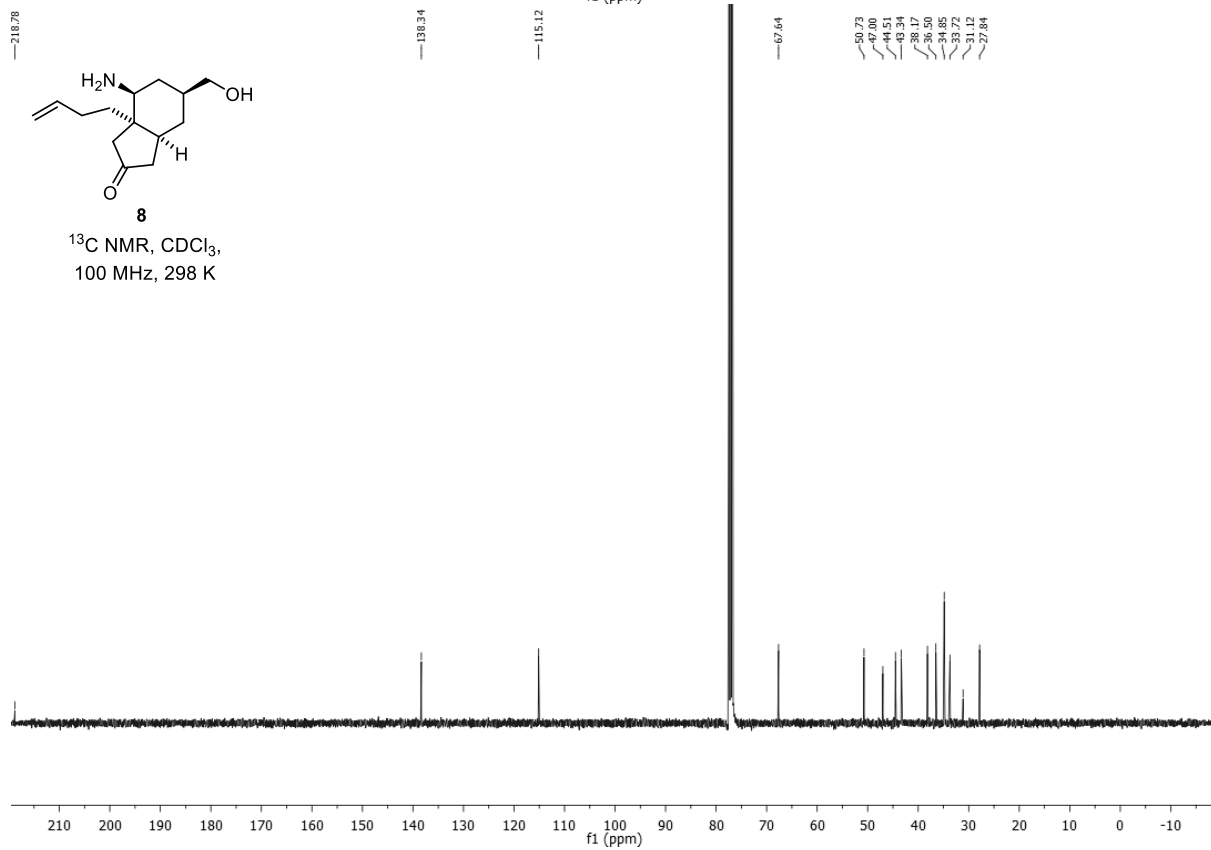
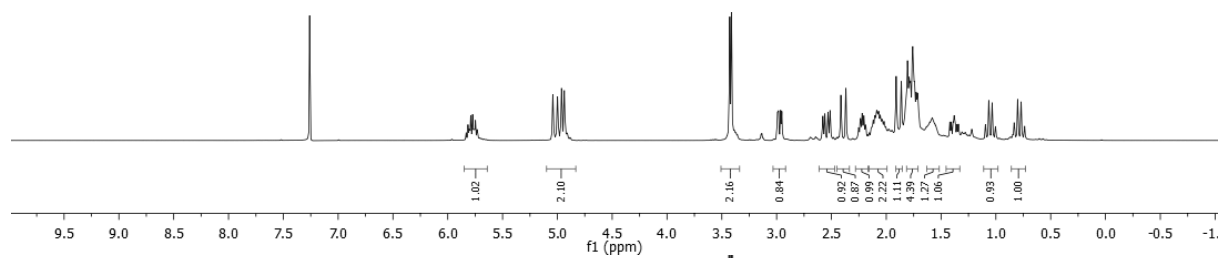
**17**

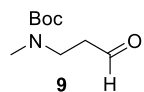
$^{13}\text{C NMR}$ ,  $\text{CDCl}_3$ ,  
100 MHz, 298 K



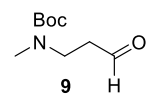
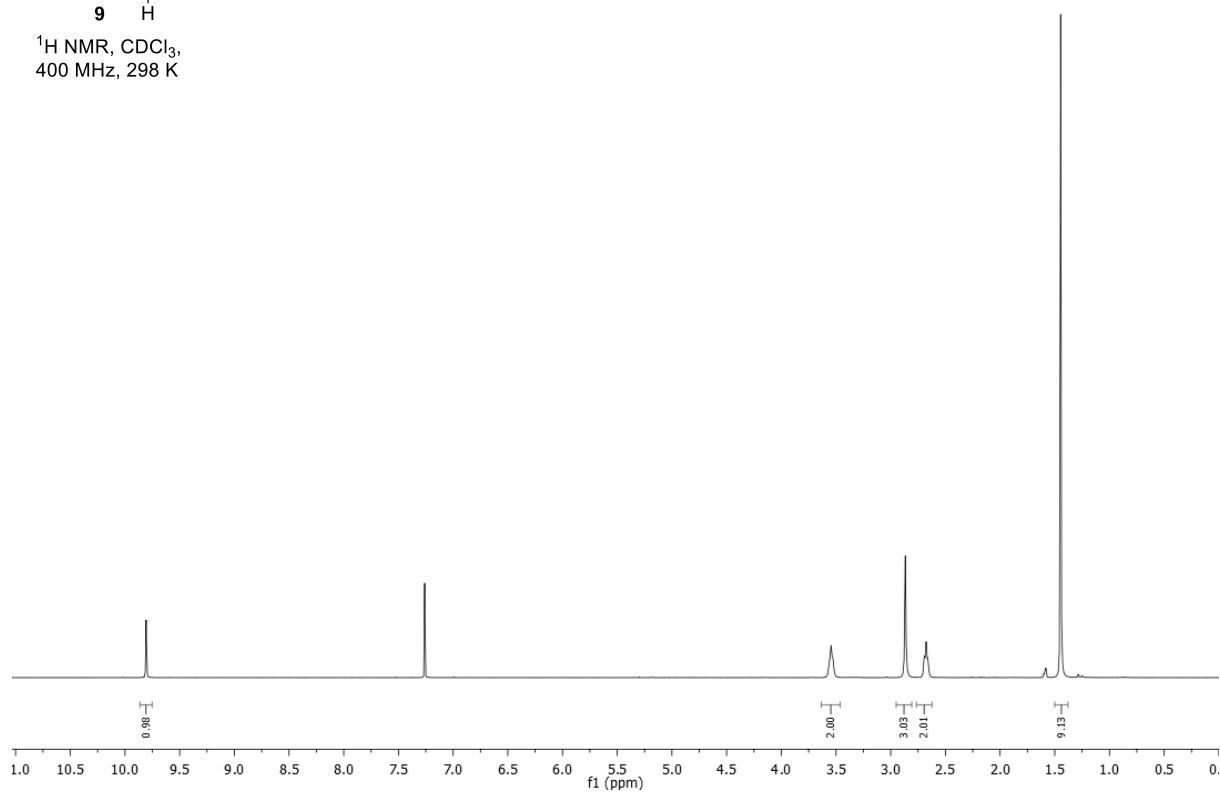
**8**

<sup>1</sup>H NMR, CDCl<sub>3</sub>,  
400 MHz, 298 K

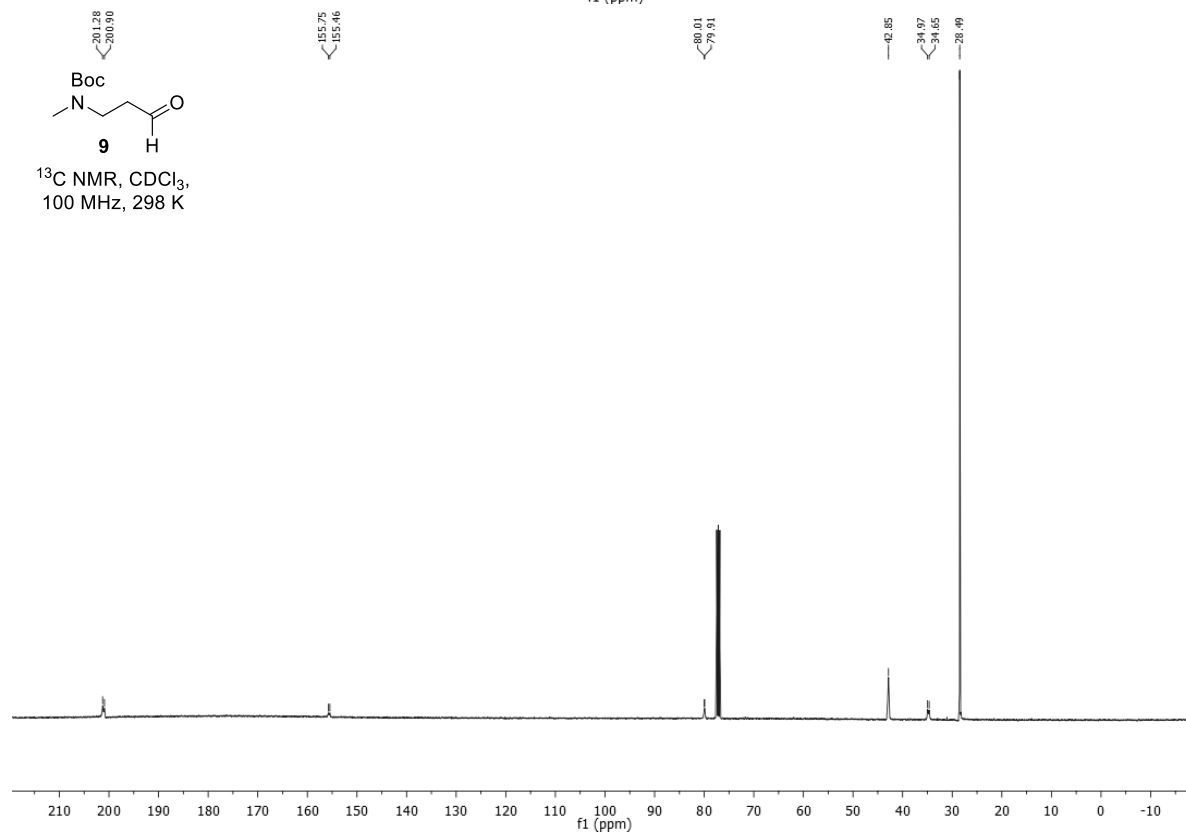




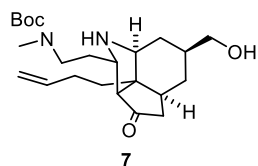
$^1\text{H}$  NMR,  $\text{CDCl}_3$ ,  
400 MHz, 298 K



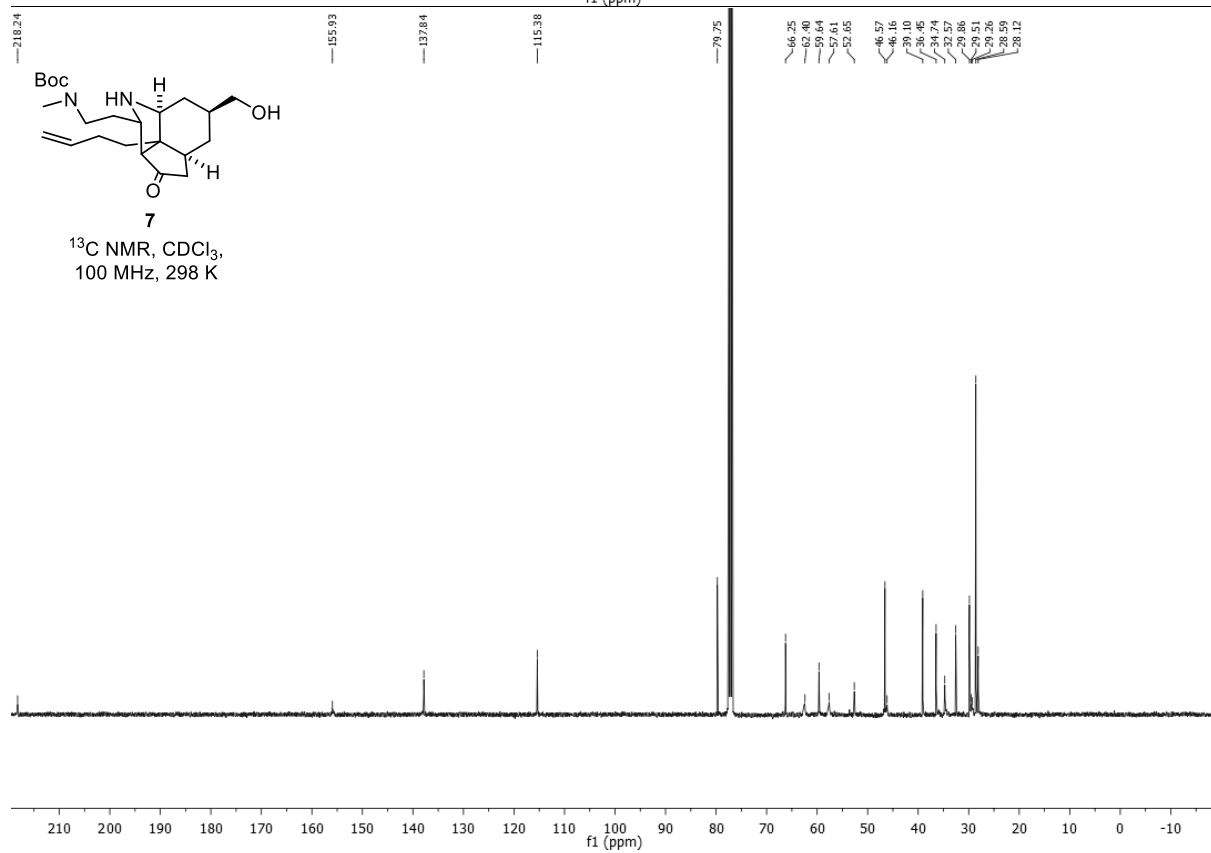
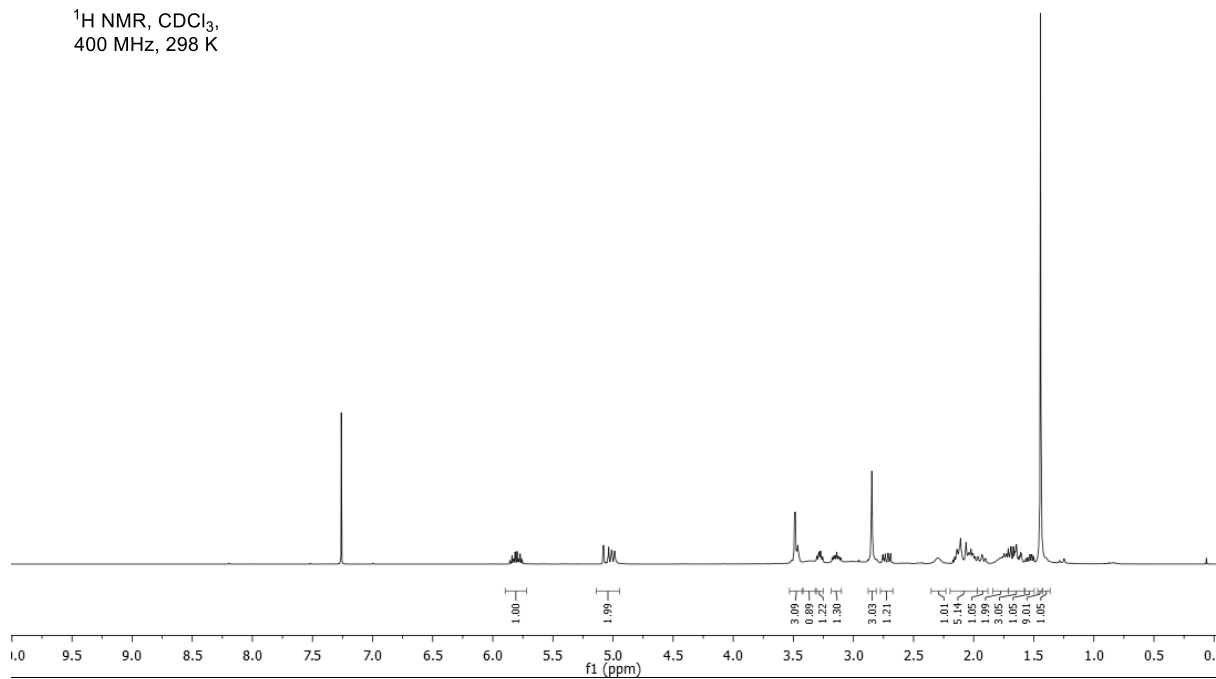
$^{13}\text{C}$  NMR,  $\text{CDCl}_3$ ,  
100 MHz, 298 K

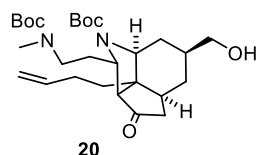




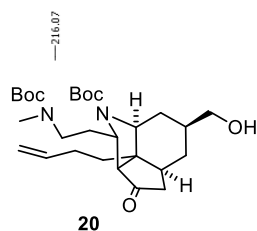
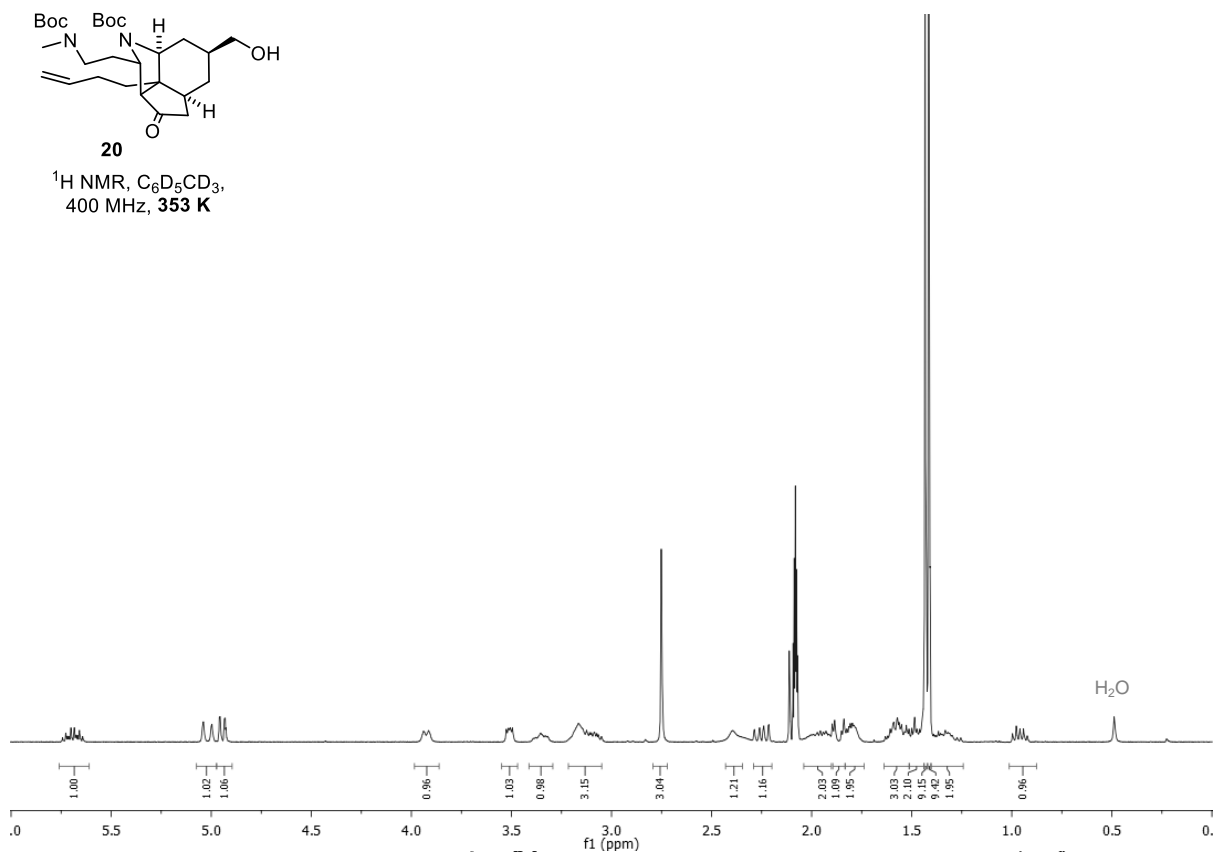


<sup>1</sup>H NMR, CDCl<sub>3</sub>,  
400 MHz, 298 K

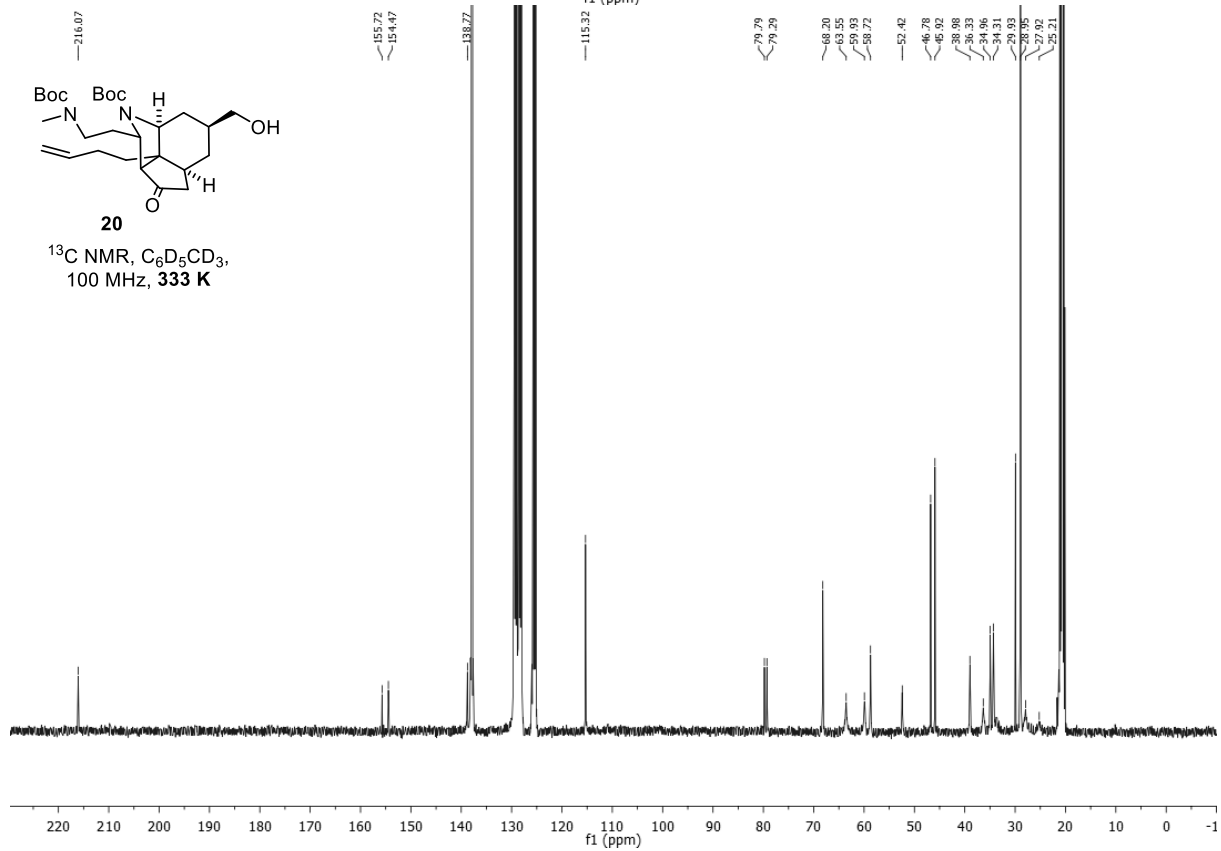


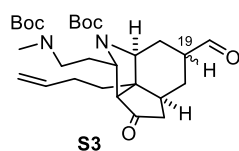


$^1\text{H}$  NMR,  $\text{C}_6\text{D}_5\text{CD}_3$ ,  
400 MHz, 353 K



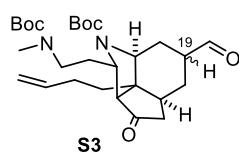
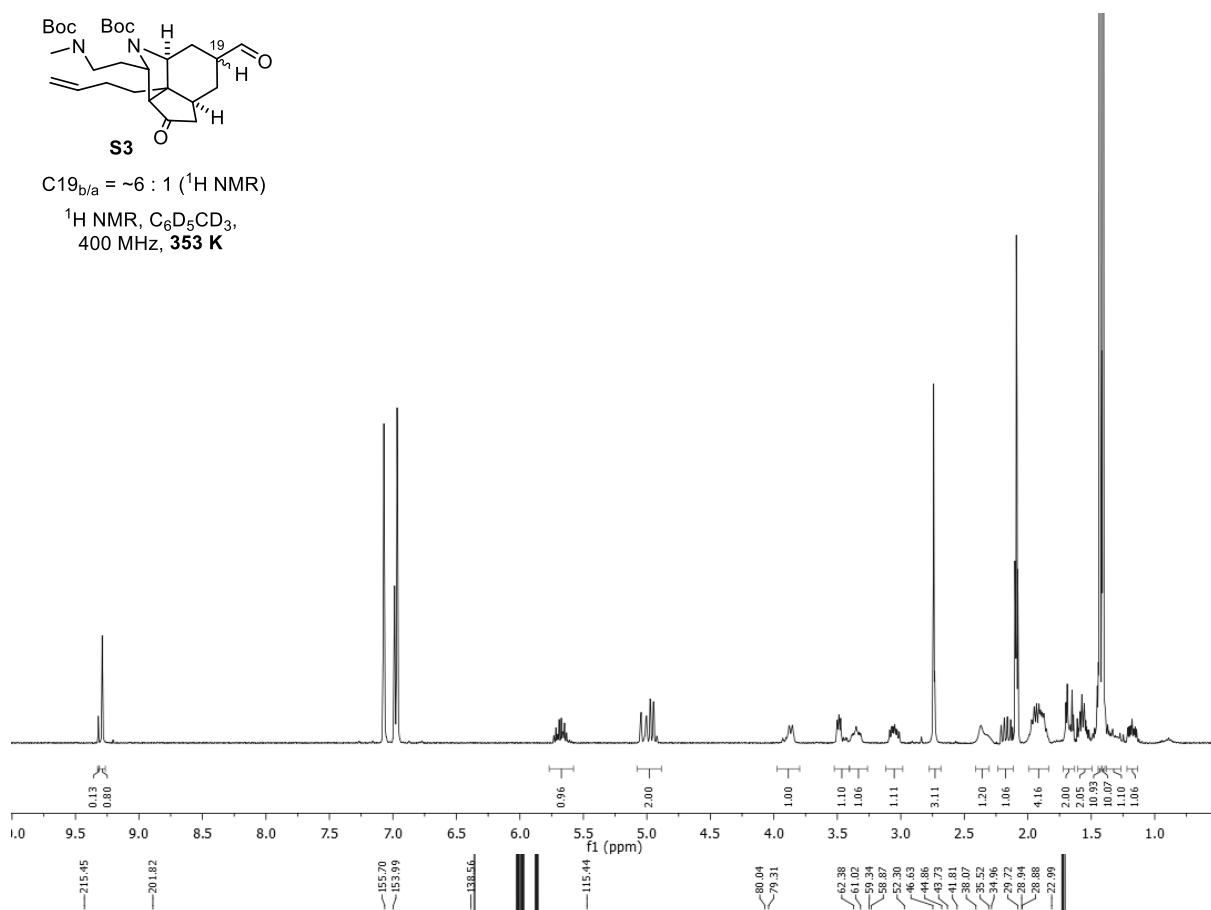
$^{13}\text{C}$  NMR,  $\text{C}_6\text{D}_5\text{CD}_3$ ,  
100 MHz, 333 K





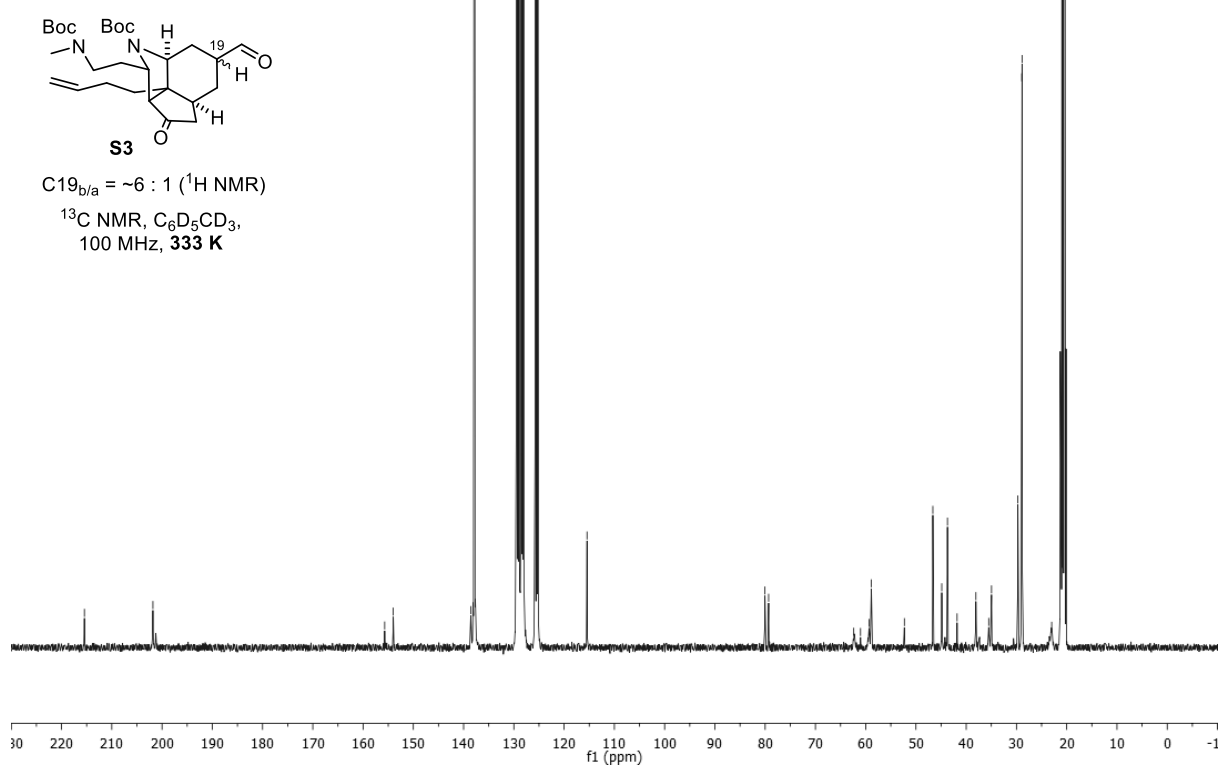
C19<sub>b/a</sub> = ~6 : 1 (<sup>1</sup>H NMR)

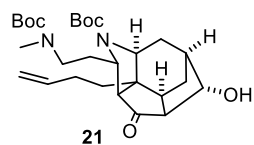
<sup>1</sup>H NMR, C<sub>6</sub>D<sub>5</sub>CD<sub>3</sub>,  
400 MHz, 353 K



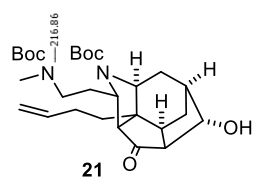
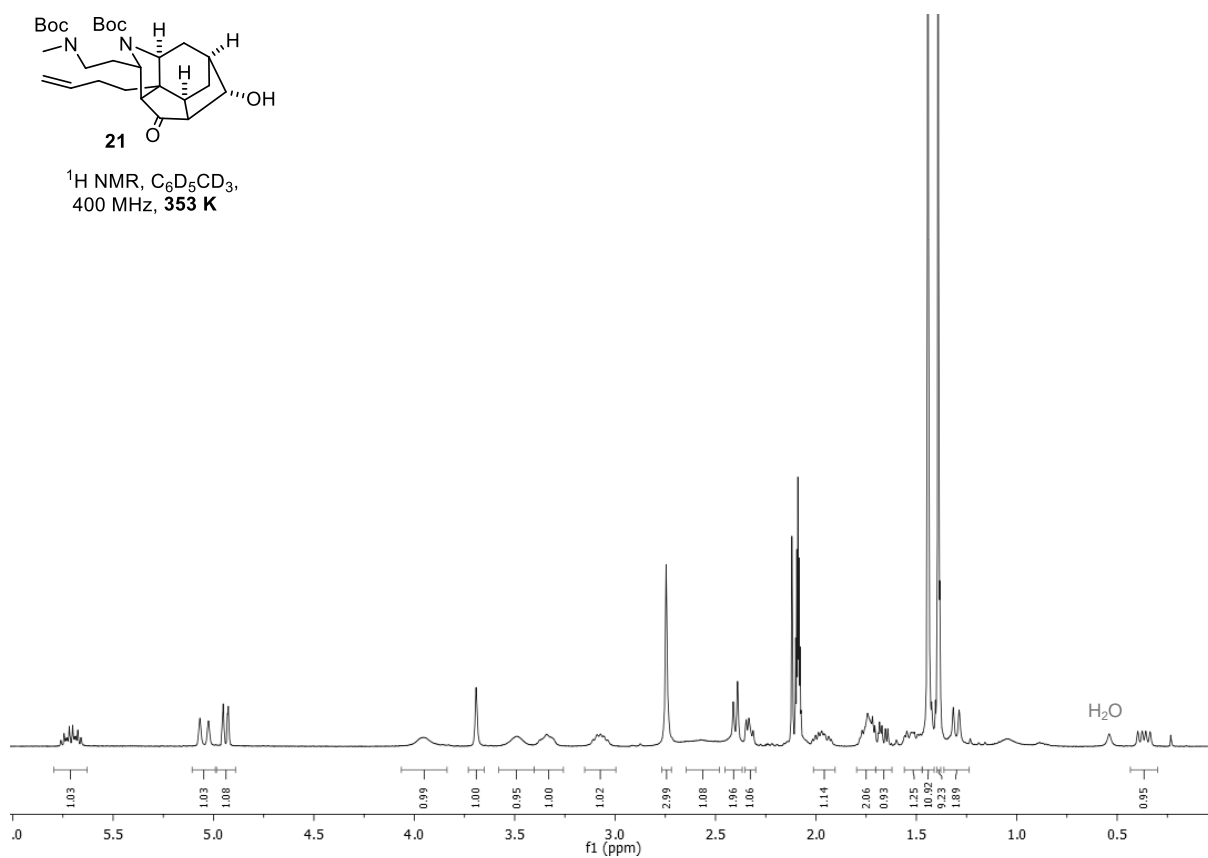
C19<sub>b/a</sub> = ~6 : 1 (<sup>1</sup>H NMR)

<sup>13</sup>C NMR, C<sub>6</sub>D<sub>5</sub>CD<sub>3</sub>,  
100 MHz, 333 K

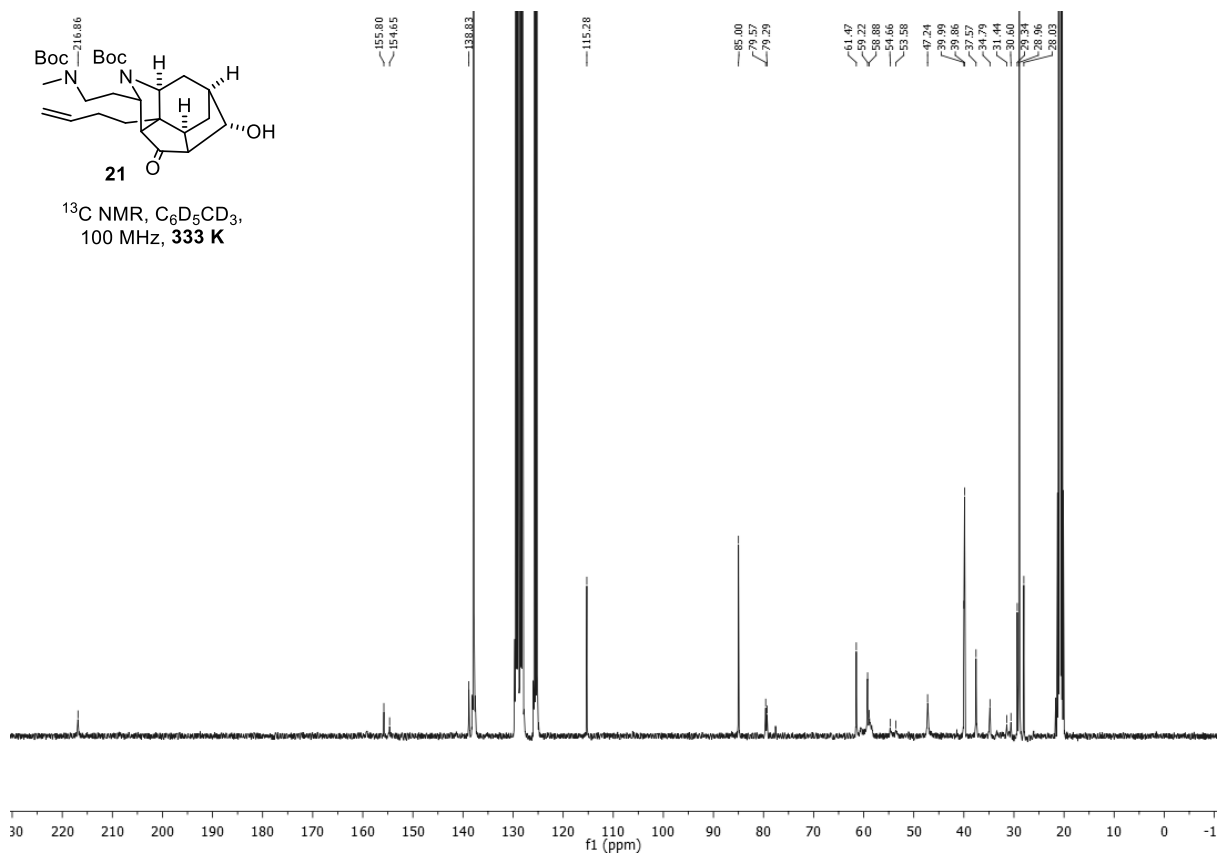


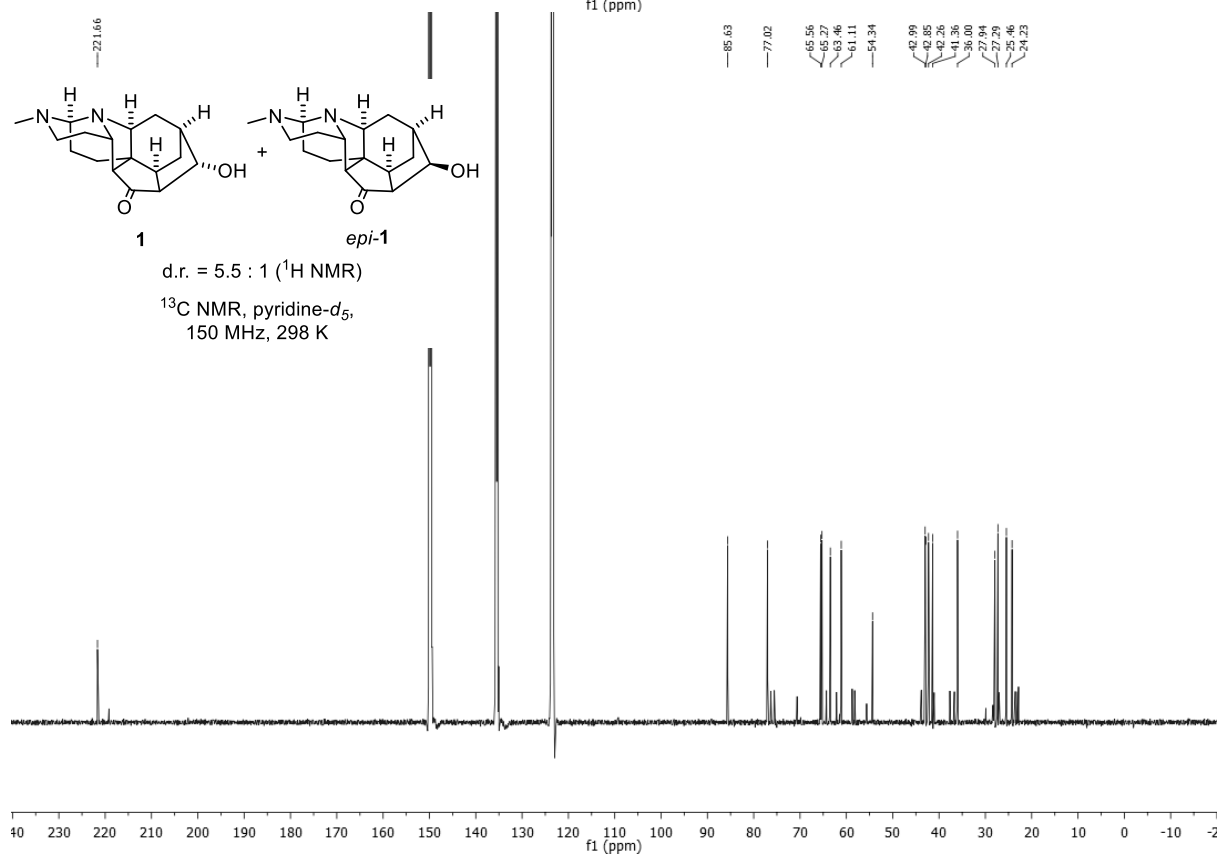
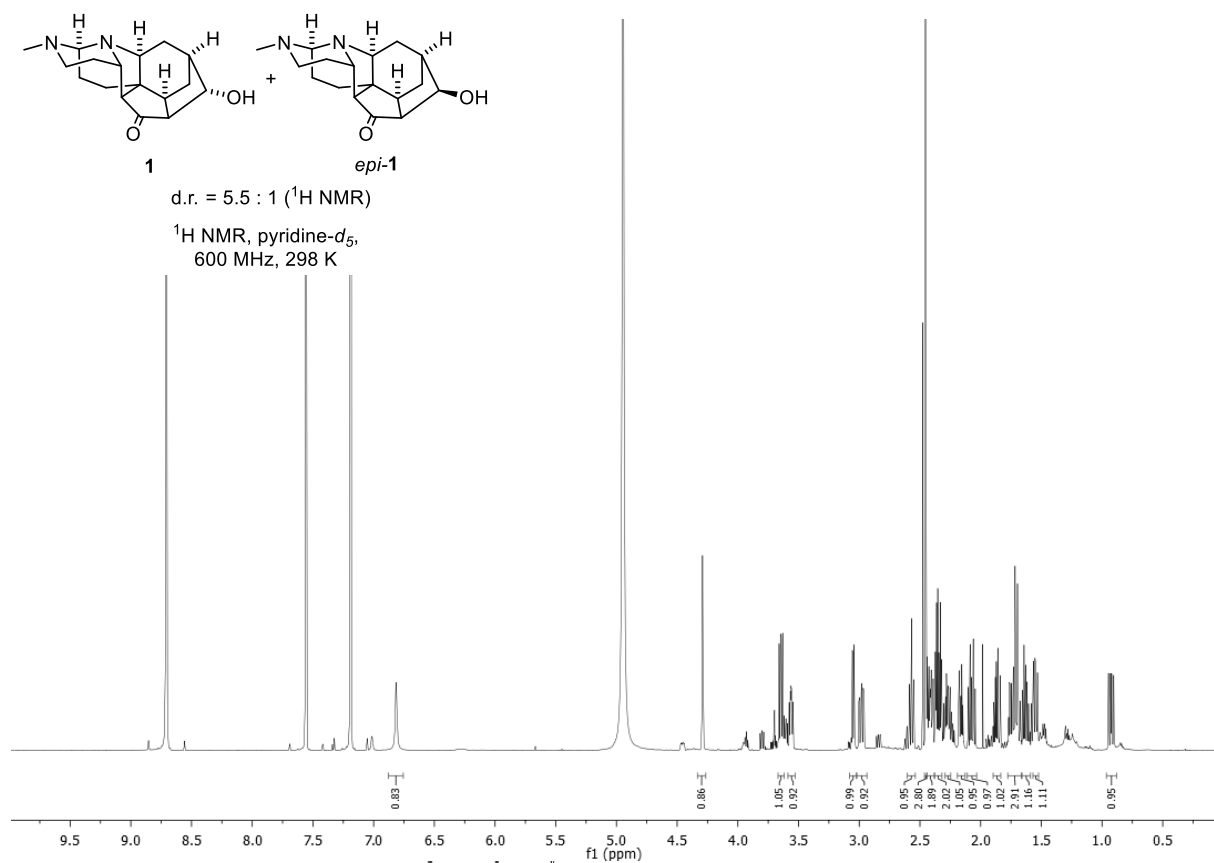


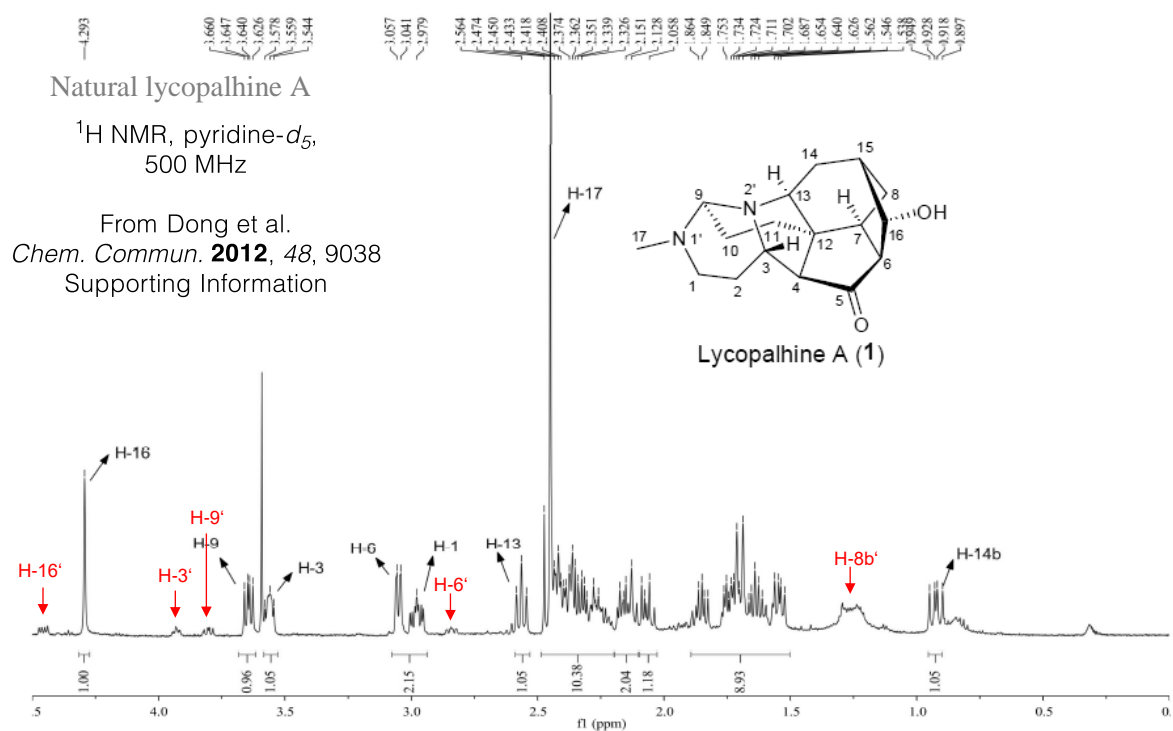
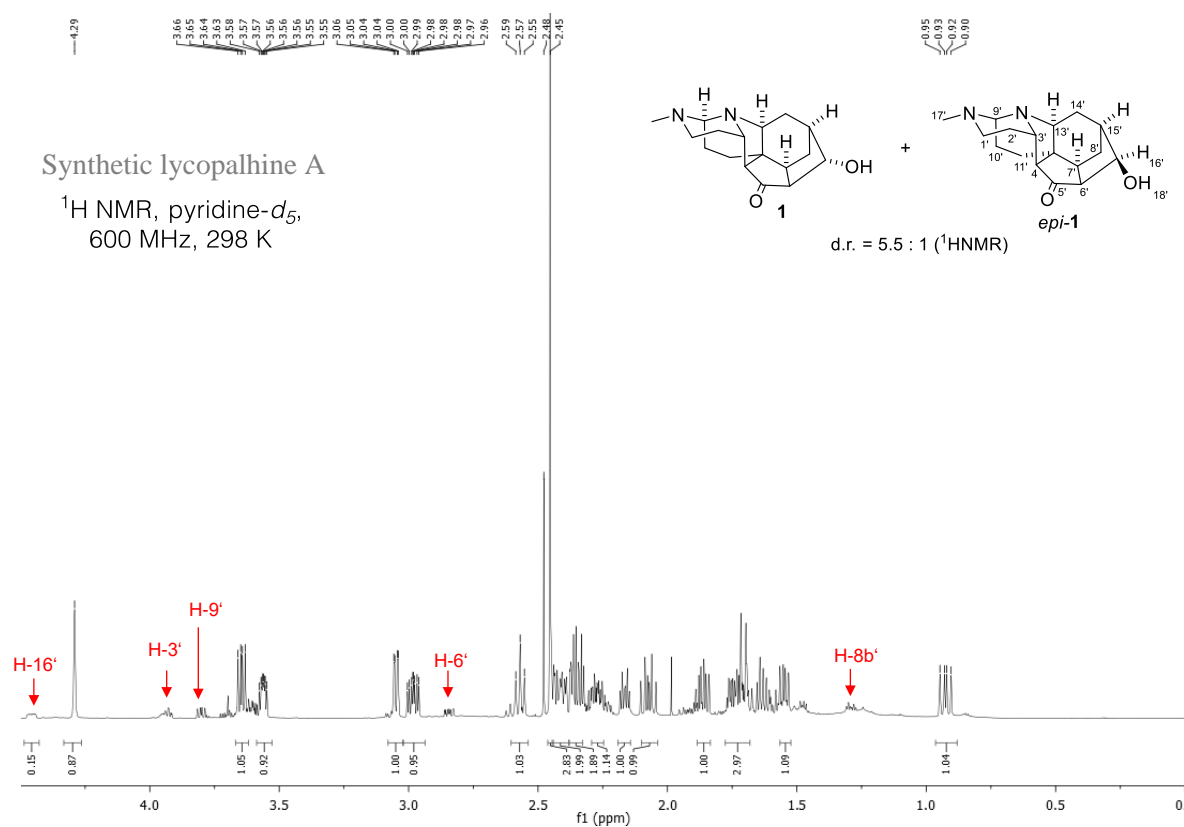
$^1\text{H NMR}$ ,  $\text{C}_6\text{D}_5\text{CD}_3$ ,  
400 MHz, 353 K

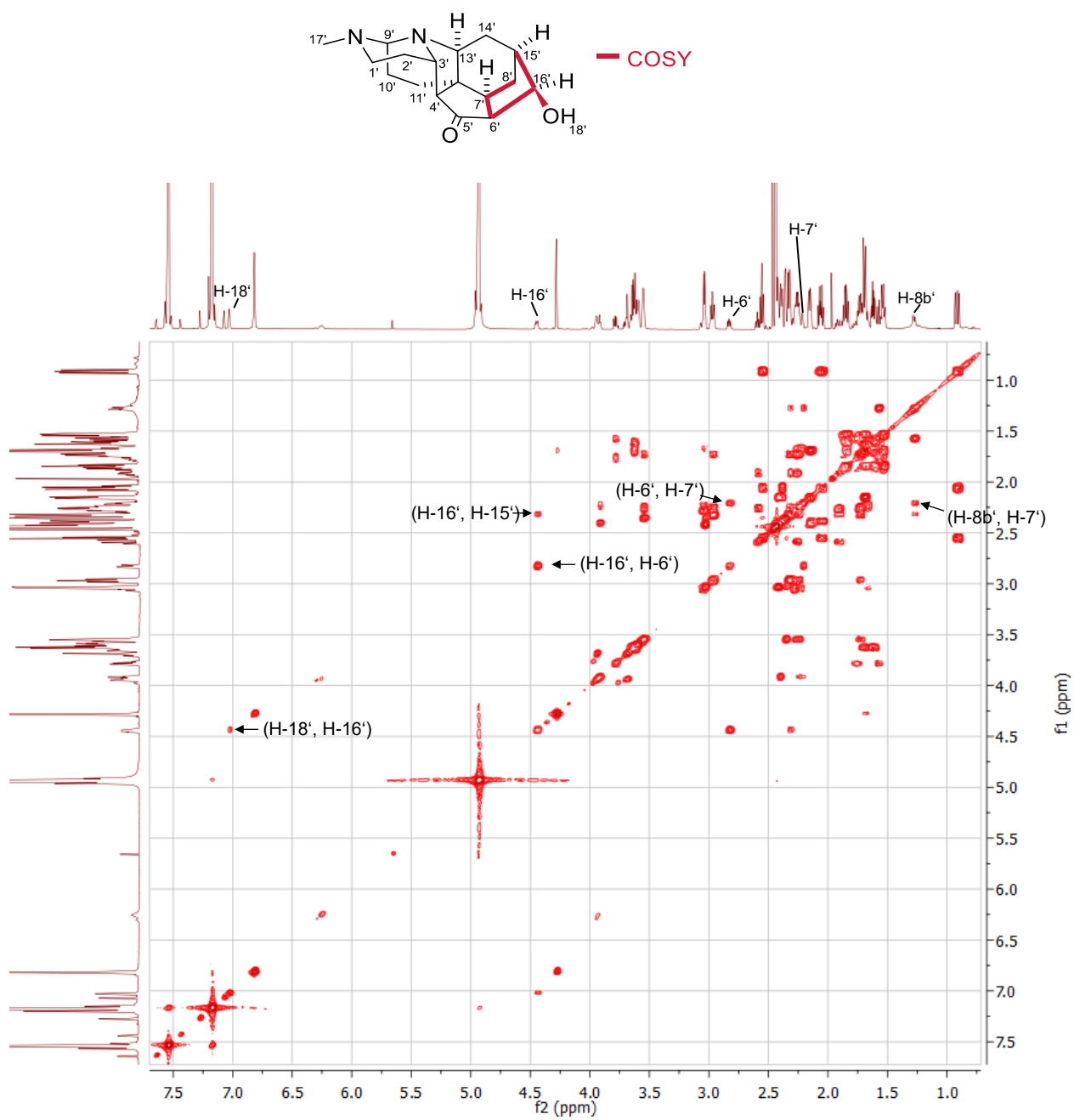


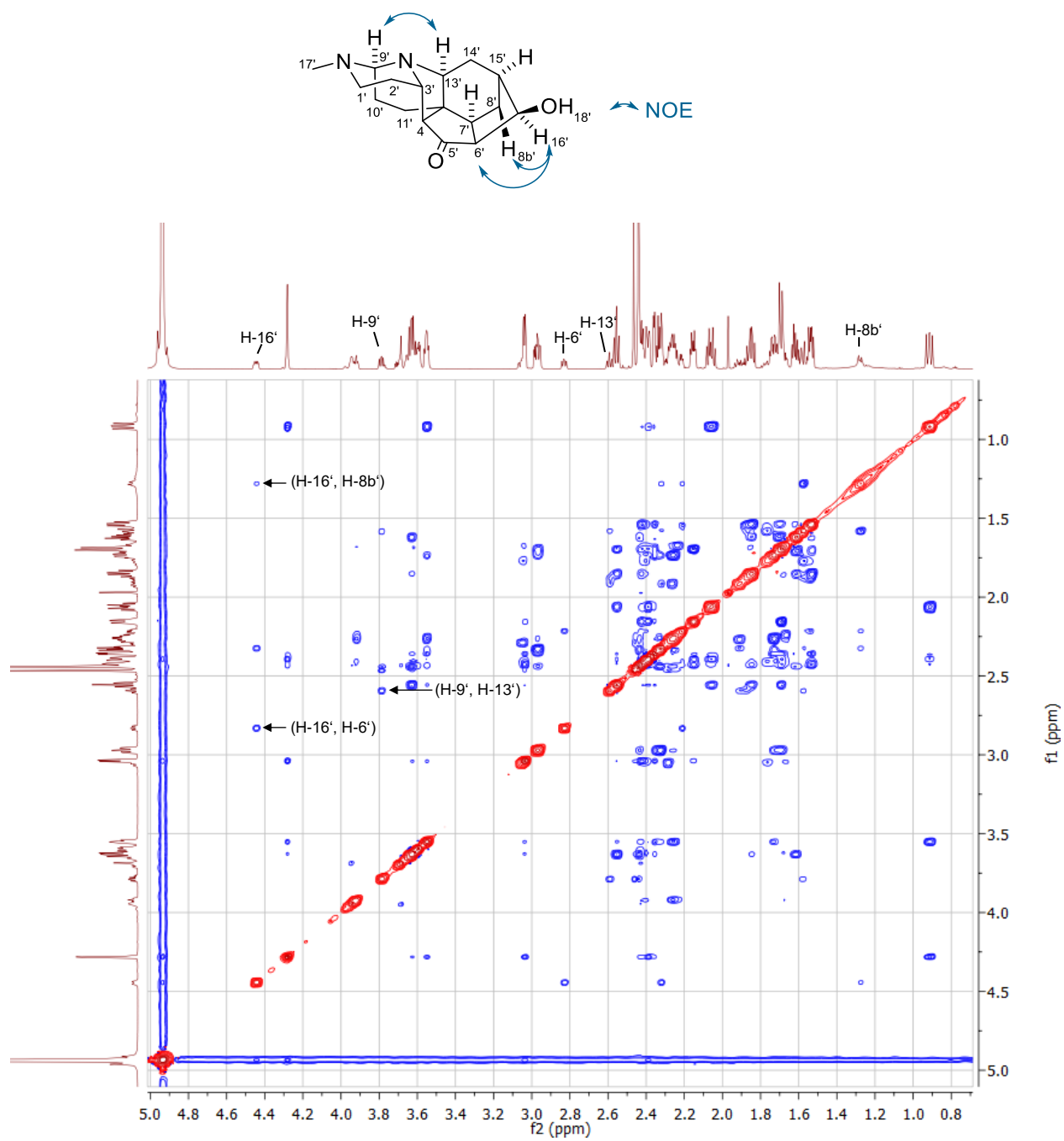
$^{13}\text{C NMR}$ ,  $\text{C}_6\text{D}_5\text{CD}_3$ ,  
100 MHz, 333 K



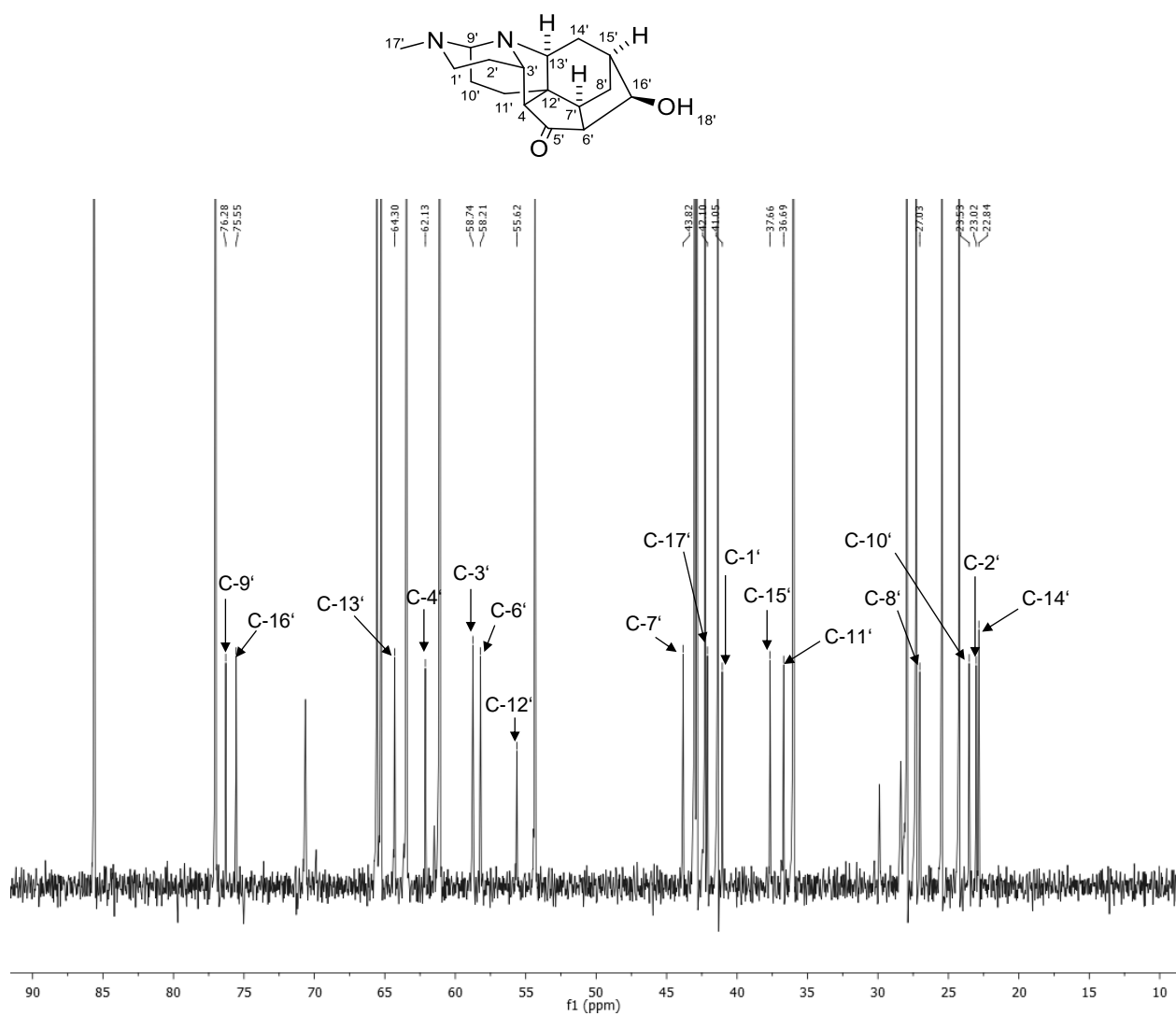


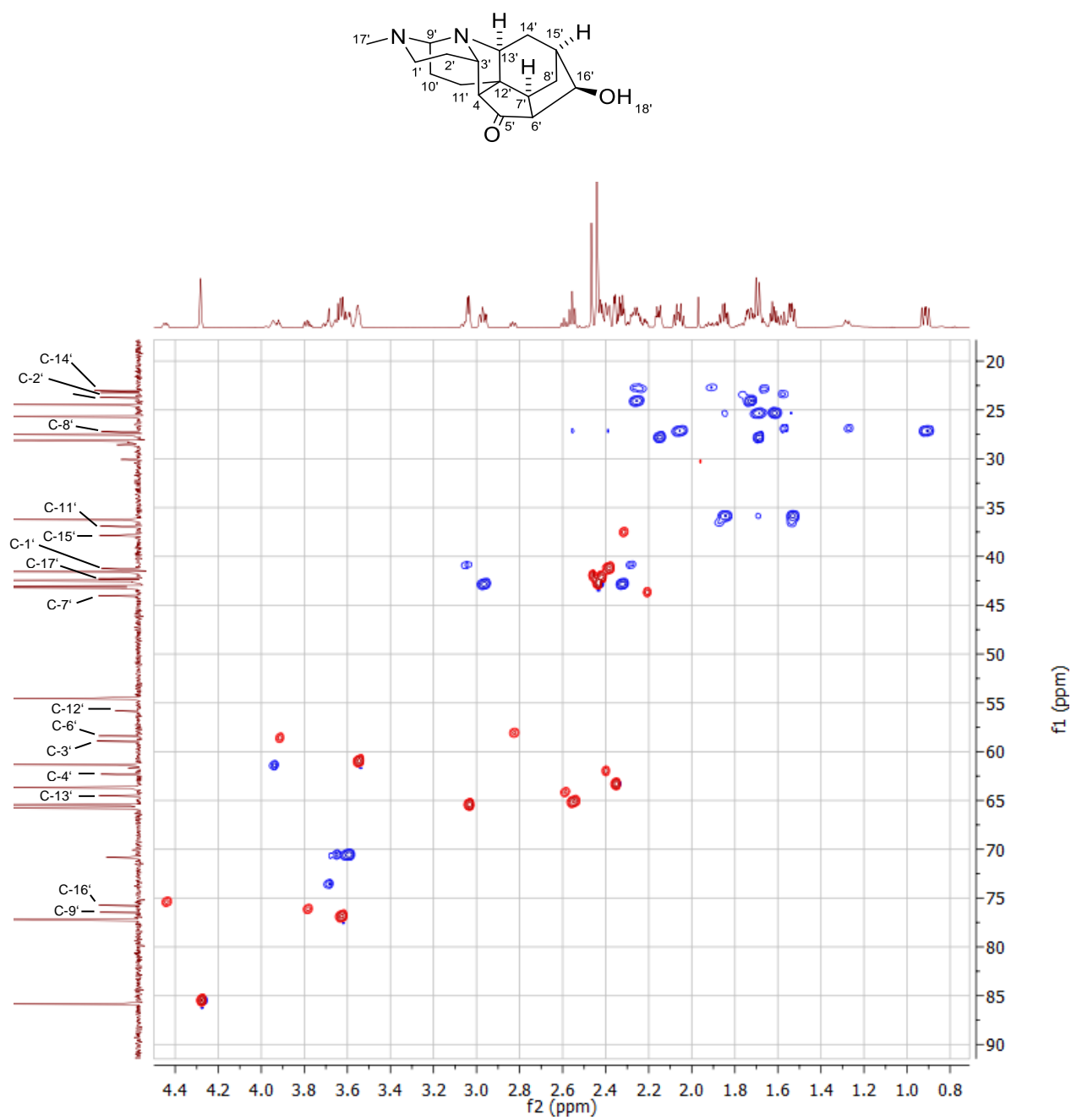
**<sup>1</sup>H NMR Comparison of Synthetic and Natural Lycopalhine A**

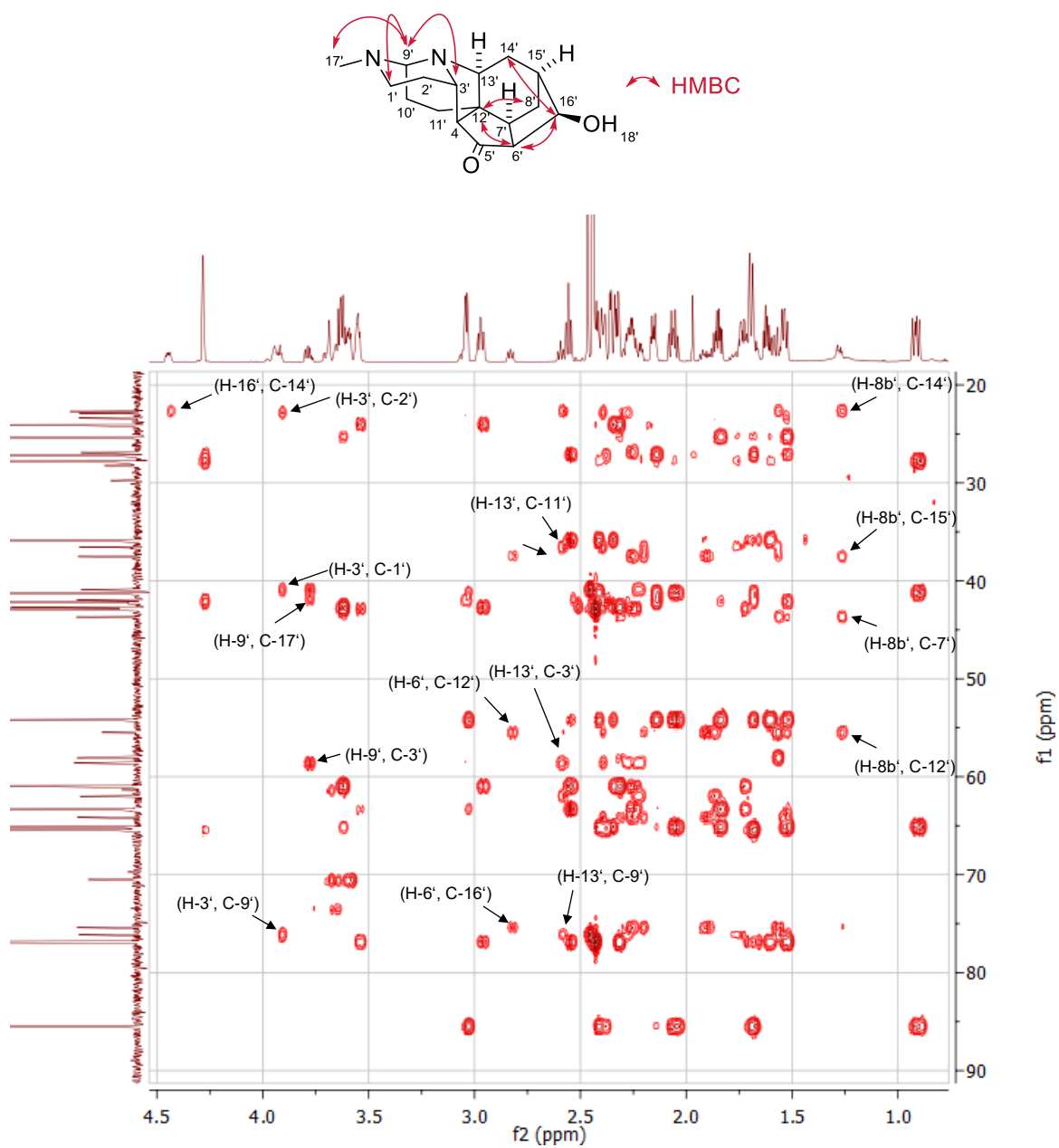
**Figure 5.2.** Key COSY correlations of *epi-1* (pyridine- $d_5$ , 800 MHz).

**Figure 5.3.** Key NOESY correlations of *epi-1* (pyridine- $d_5$ , 800 MHz).

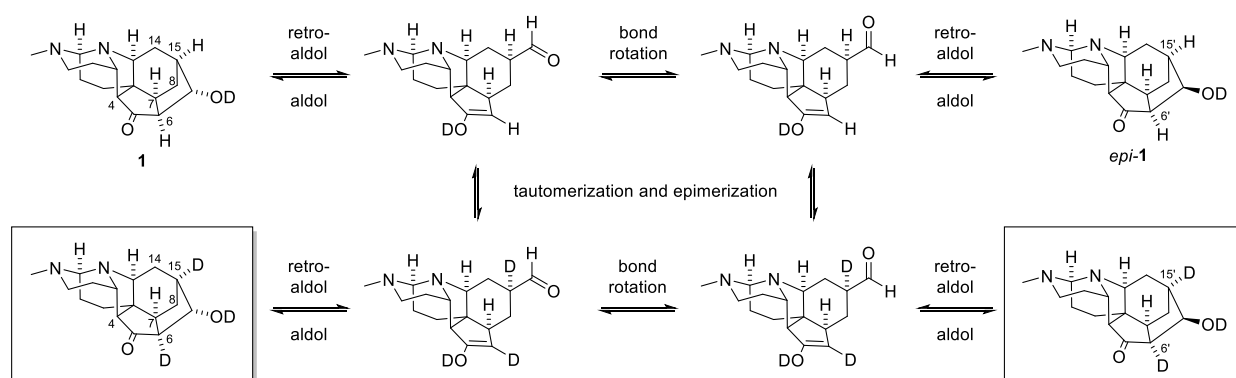


**Figure 5.4.**  $^{13}\text{C}$  NMR signal assignment of *epi-1* (pyridine- $d_5$ , 600 MHz).

**Figure 5.5.** HSQC correlations of *epi-1* (pyridine-*d*<sub>5</sub>, 800 MHz).

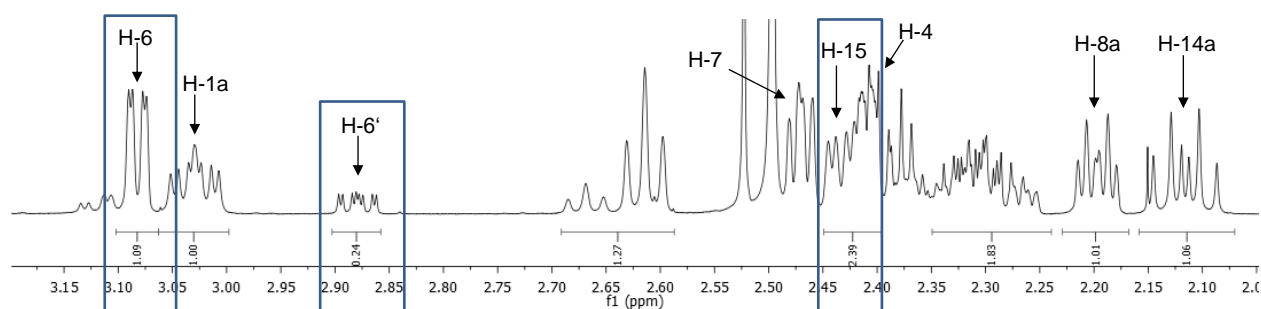
**Figure 5.6.** Key HMBC correlations of *epi-1* (pyridine- $d_5$ , 800 MHz).

## Deuterium exchange studies of lycopalhine A

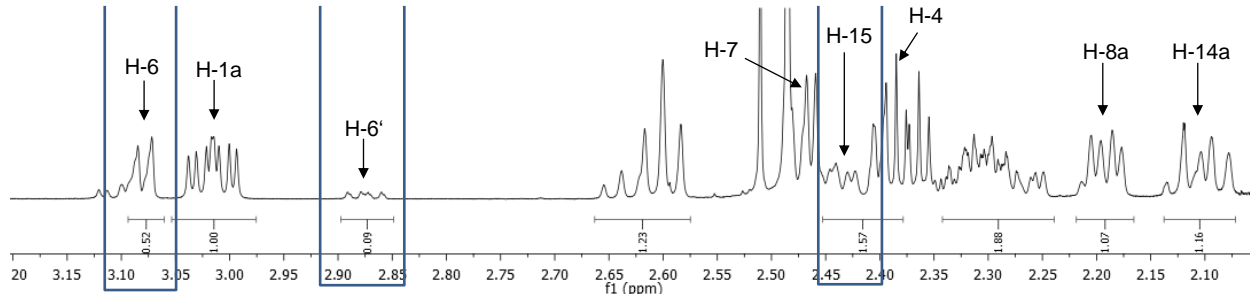


**Figure 5.7.** Deuterium exchange studies of lycopalhine A and *epi*-lycopalhine A

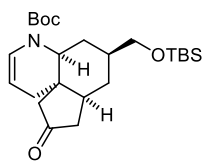
a. 1 and *epi*-1 (pyridine-*d*<sub>5</sub>, 600 MHz) before treatment with MeOD/K<sub>2</sub>CO<sub>3</sub>



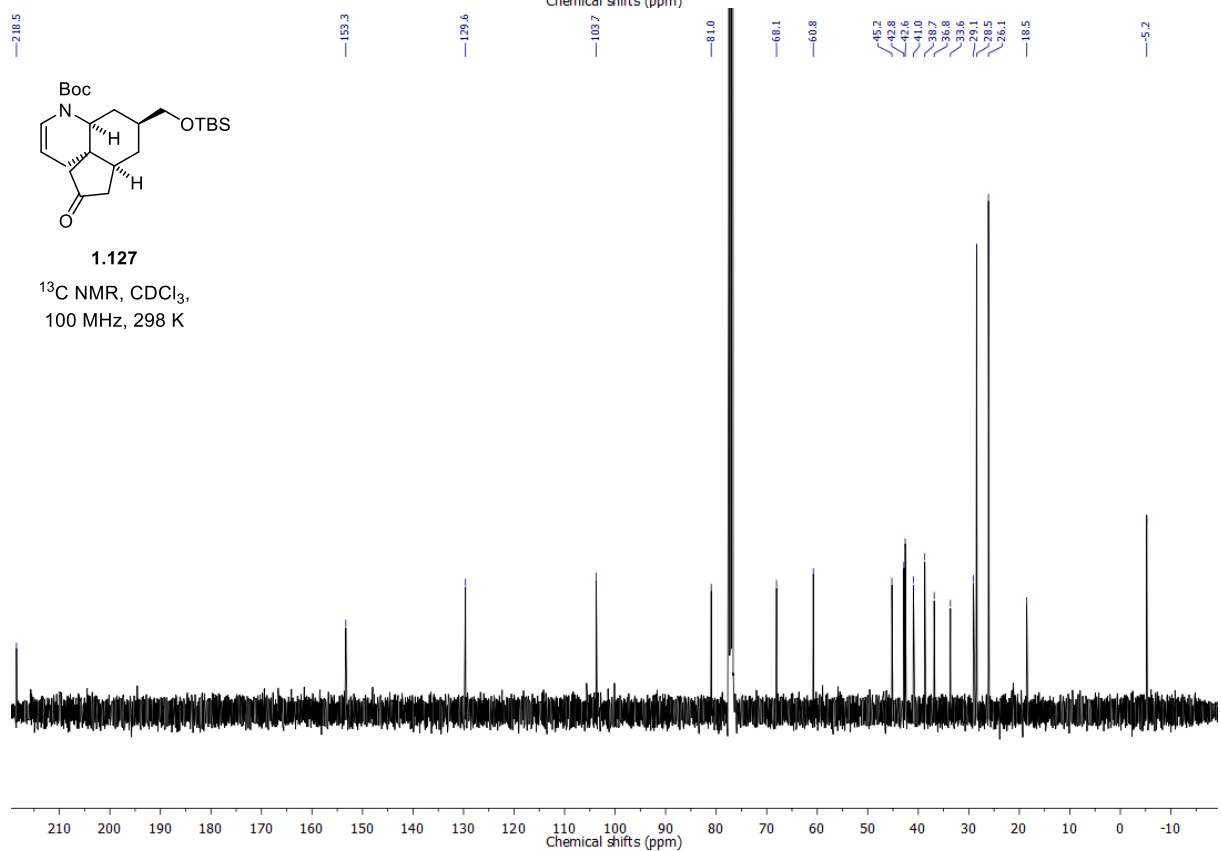
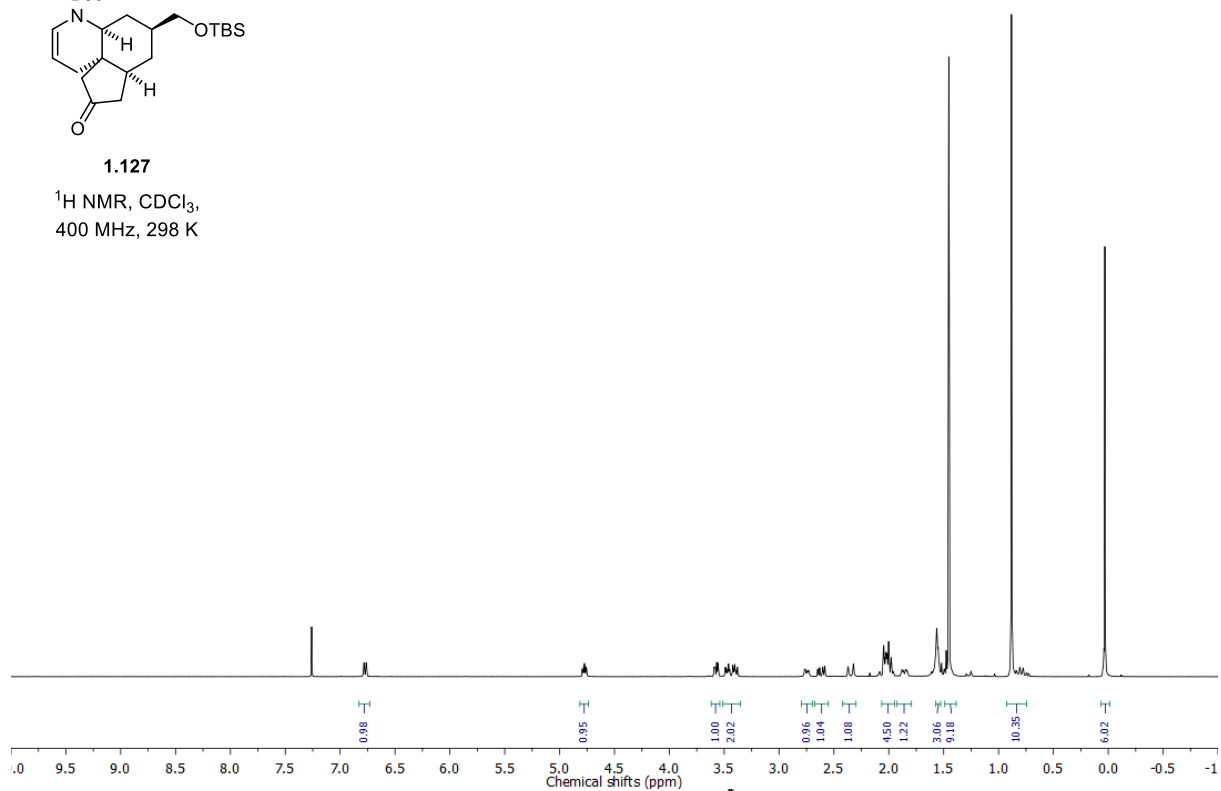
b. 1 and *epi*-1 (pyridine-*d*<sub>5</sub>, 600 MHz) after stirring in MeOD with K<sub>2</sub>CO<sub>3</sub> at ambient temperature for 2h

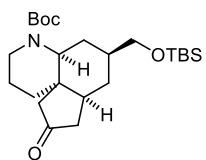


**Note:** No additional deuterium exchange was observed after stirring for >24 h in MeOD with K<sub>2</sub>CO<sub>3</sub> or after repeating the experiment over 3Å molecular sieves.

**1.127**

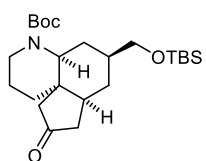
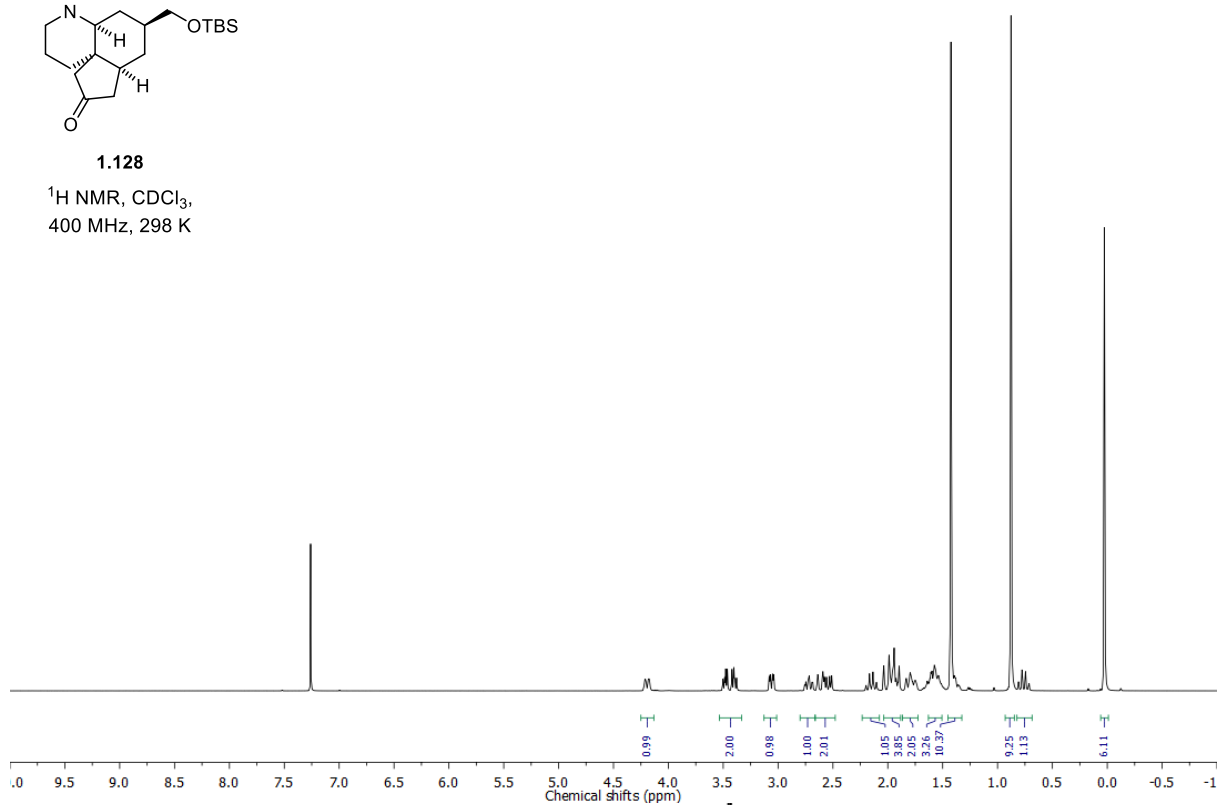
$^1\text{H}$  NMR,  $\text{CDCl}_3$ ,  
400 MHz, 298 K





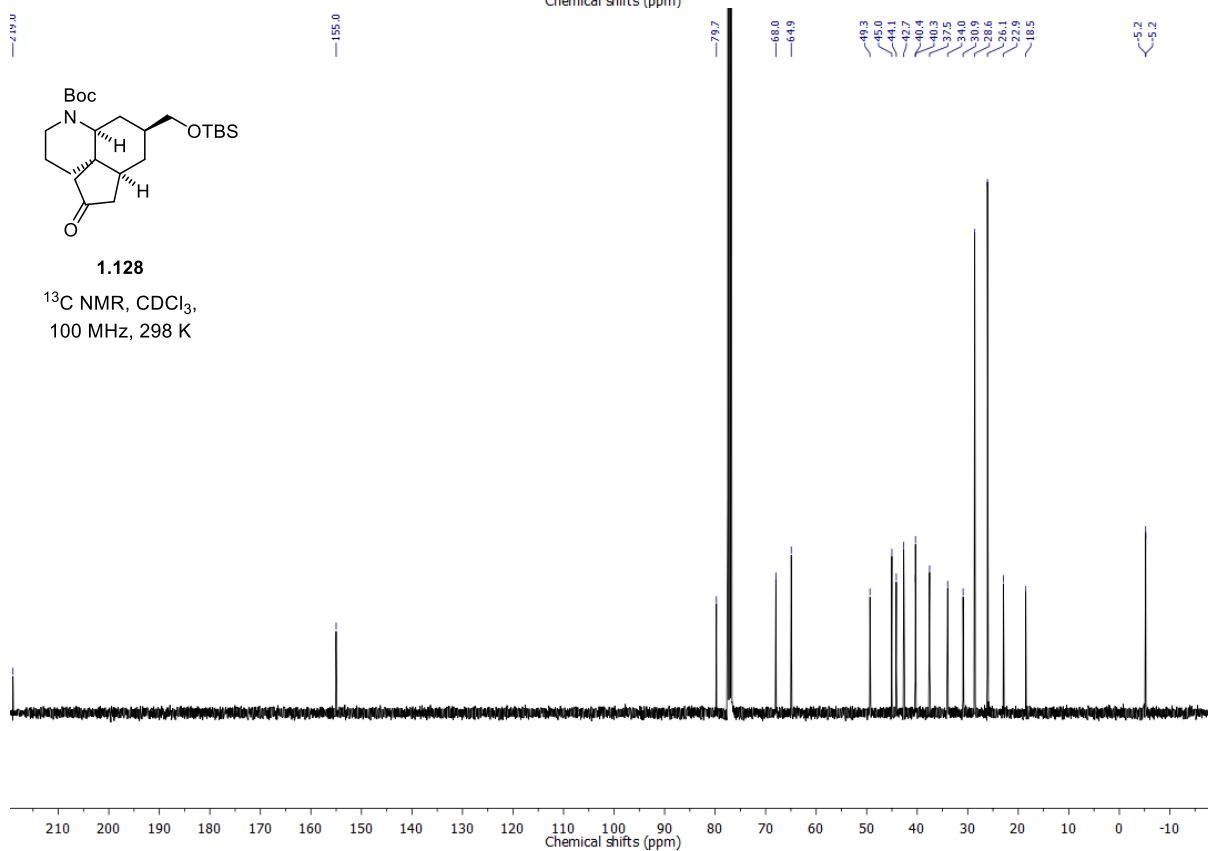
1.128

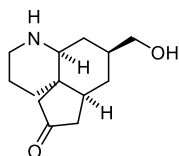
$^1\text{H}$  NMR,  $\text{CDCl}_3$ ,  
400 MHz, 298 K



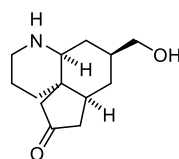
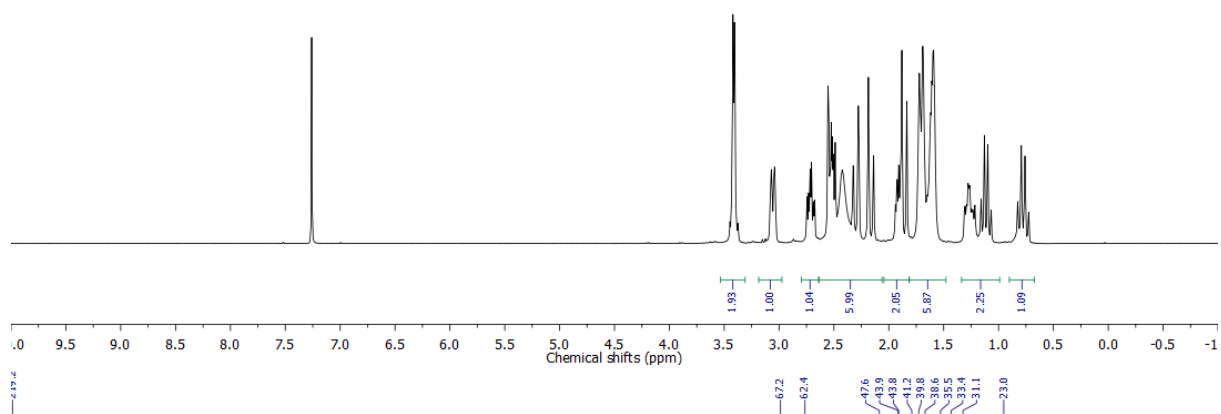
1.128

$^{13}\text{C}$  NMR,  $\text{CDCl}_3$ ,  
100 MHz, 298 K

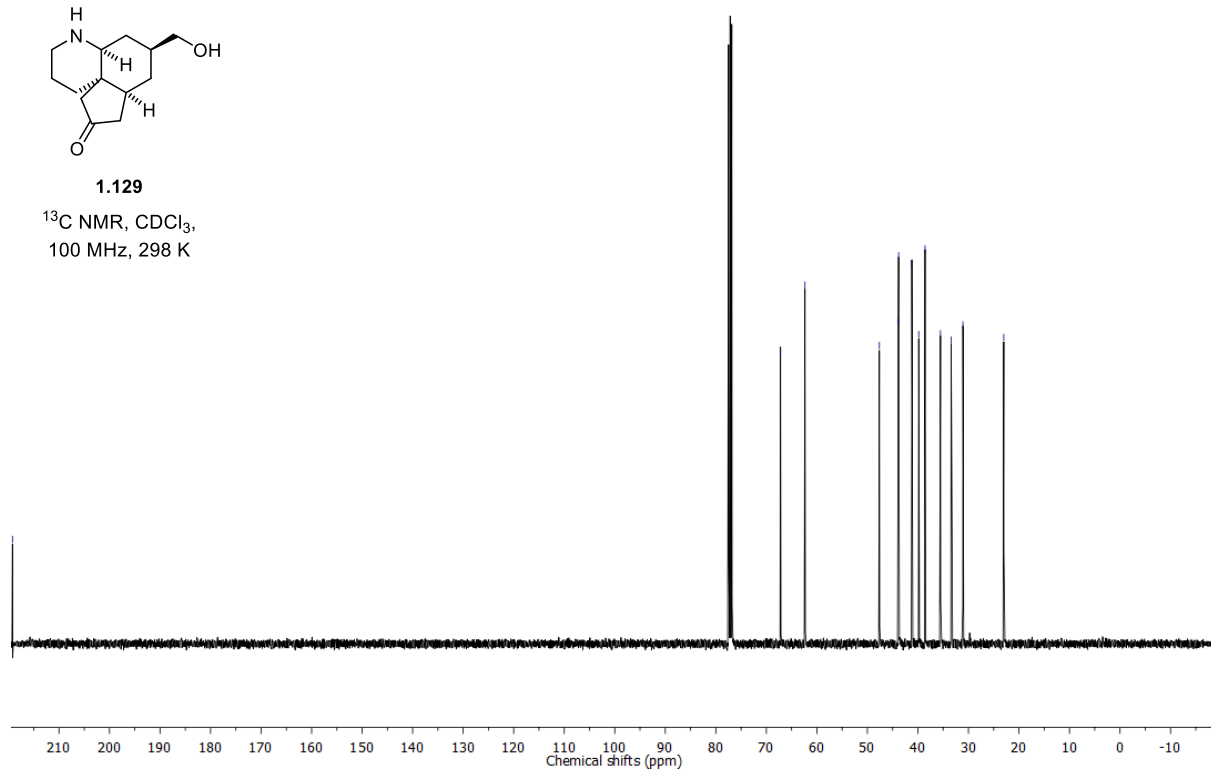


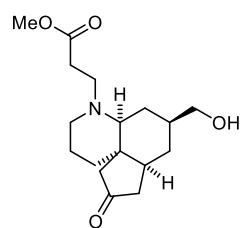
**1.129**

$^1\text{H}$  NMR,  $\text{CDCl}_3$ ,  
400 MHz, 298 K

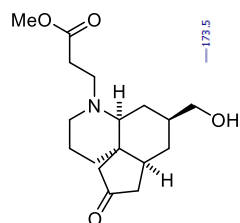
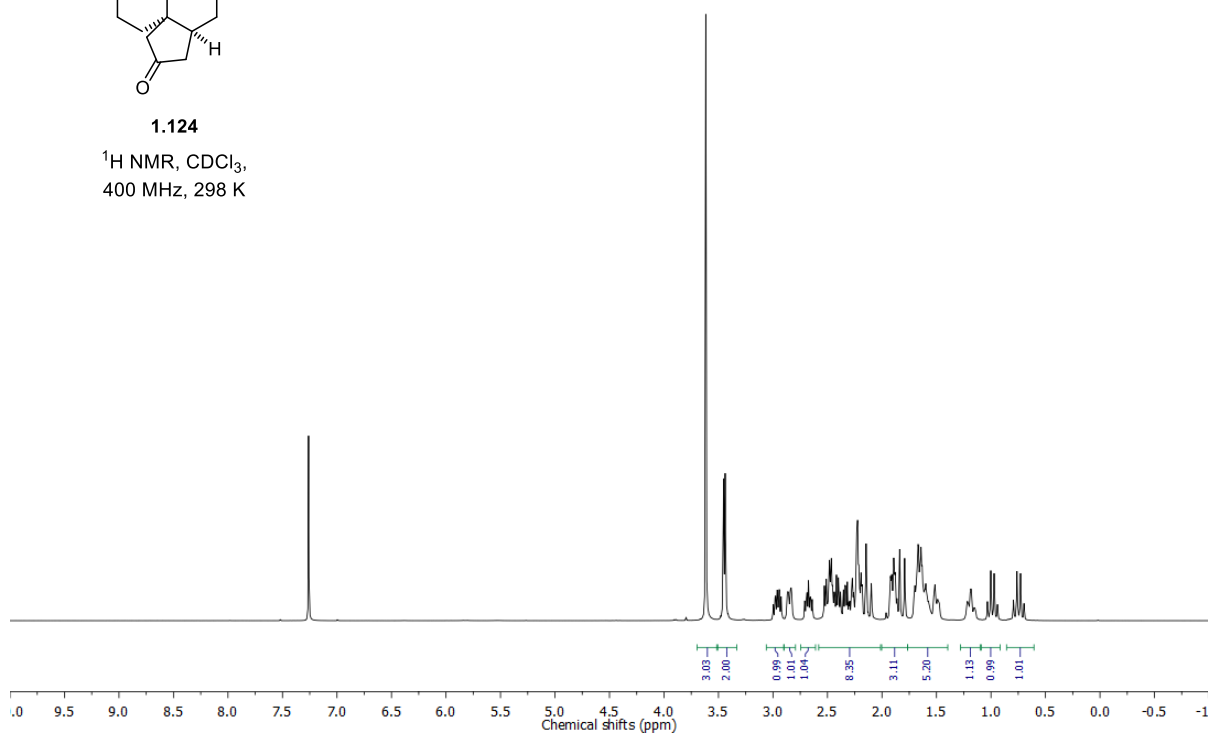
**1.129**

$^{13}\text{C}$  NMR,  $\text{CDCl}_3$ ,  
100 MHz, 298 K

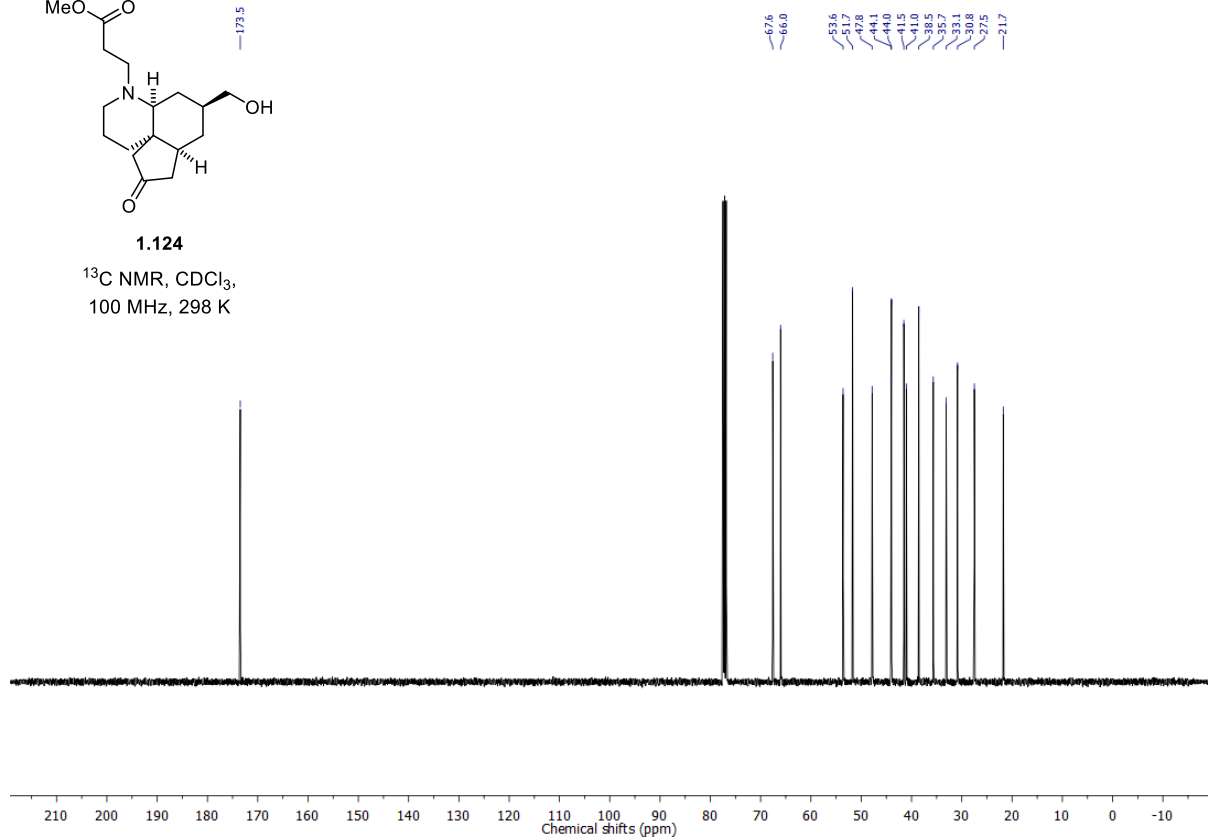


**1.124**

$^1\text{H}$  NMR,  $\text{CDCl}_3$ ,  
400 MHz, 298 K

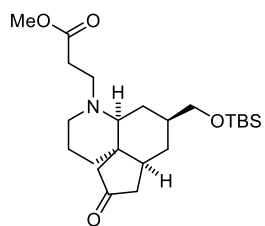
**1.124**

$^{13}\text{C}$  NMR,  $\text{CDCl}_3$ ,  
100 MHz, 298 K

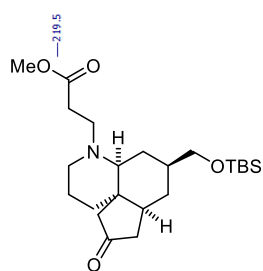
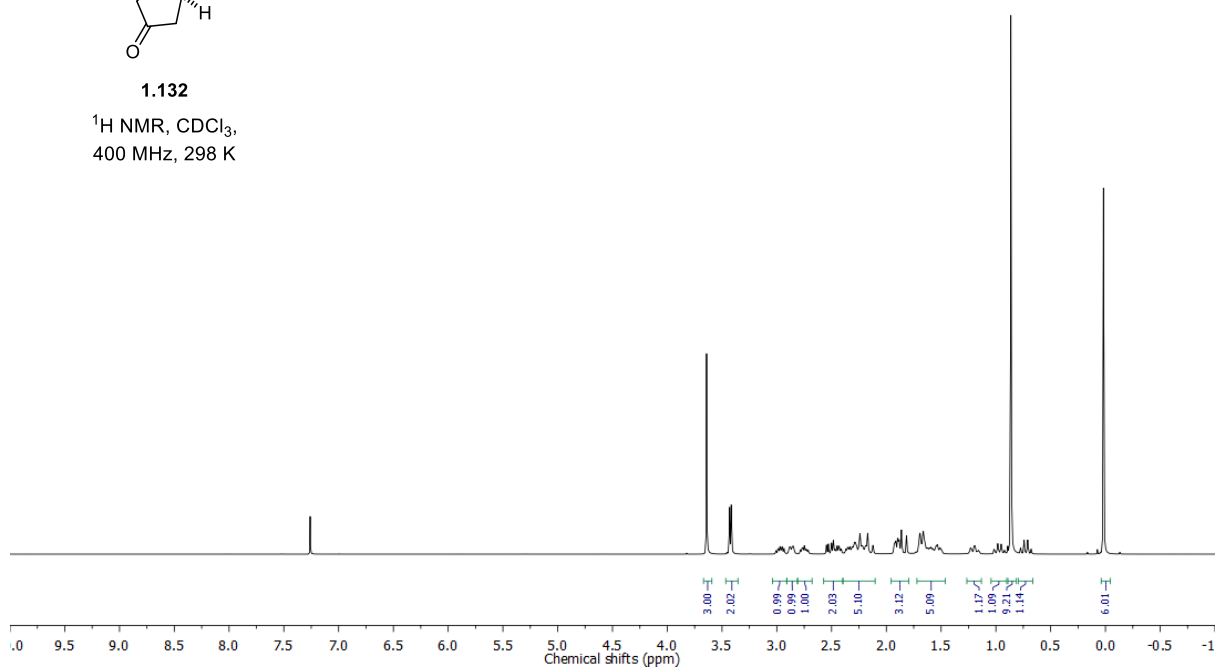




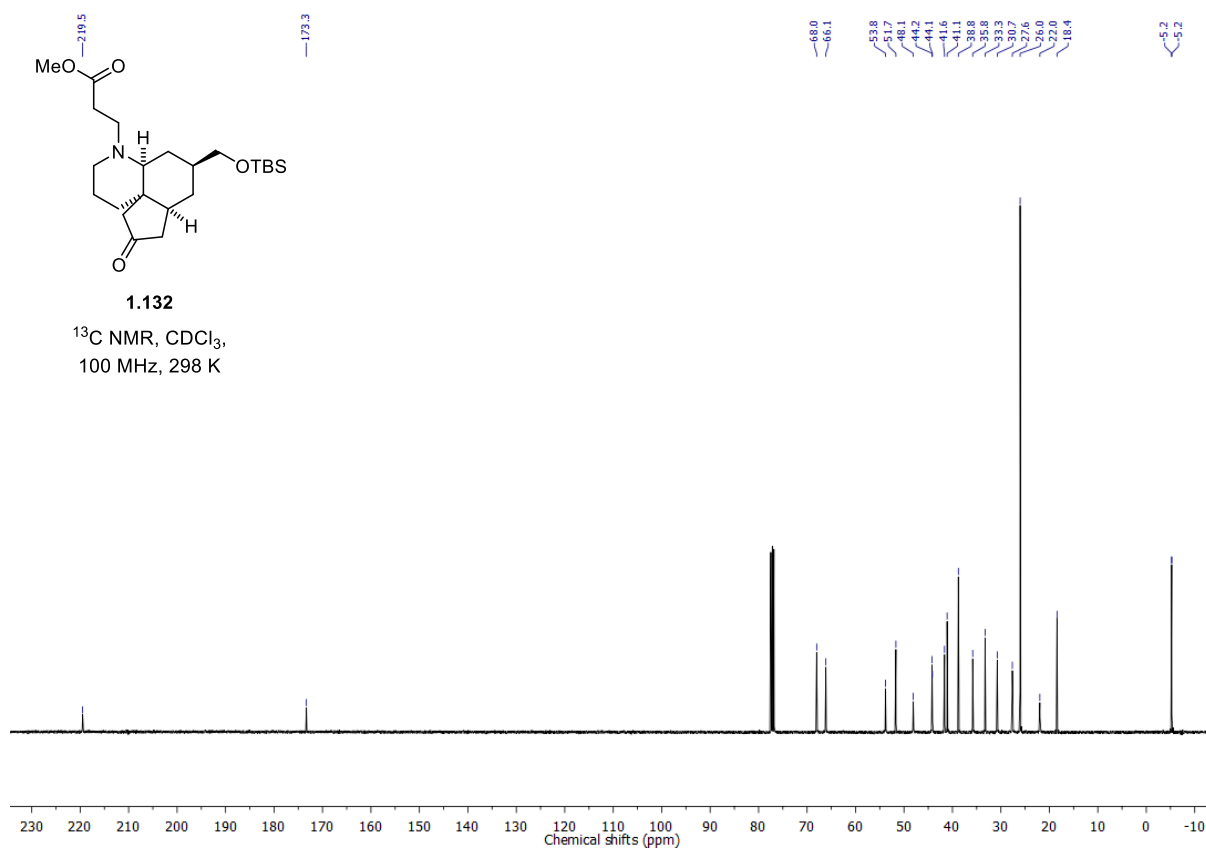


**1.132**

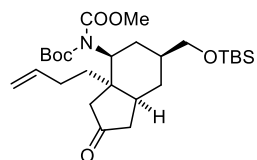
$^1\text{H NMR}$ ,  $\text{CDCl}_3$ ,  
400 MHz, 298 K

**1.132**

$^{13}\text{C NMR}$ ,  $\text{CDCl}_3$ ,  
100 MHz, 298 K

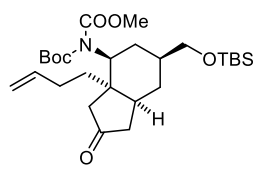
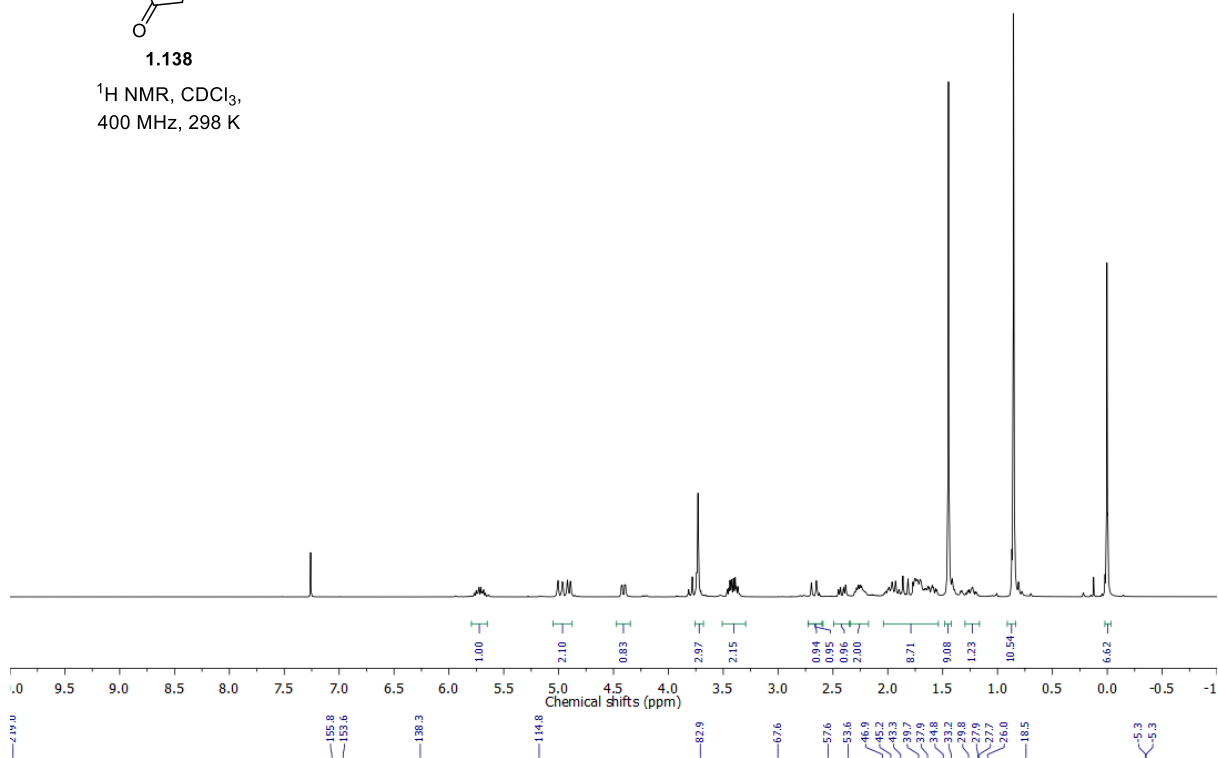






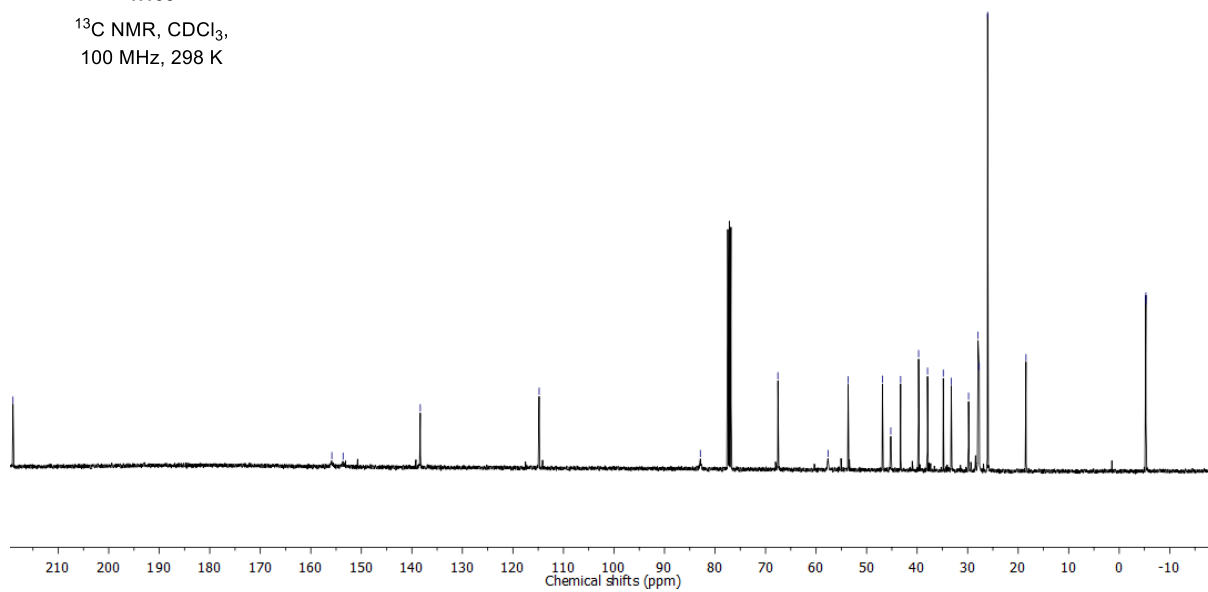
1.138

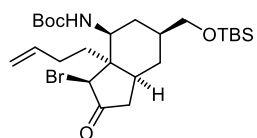
$^1\text{H}$  NMR,  $\text{CDCl}_3$ ,  
400 MHz, 298 K



1.138

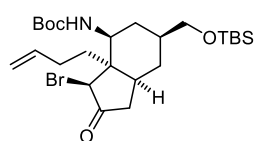
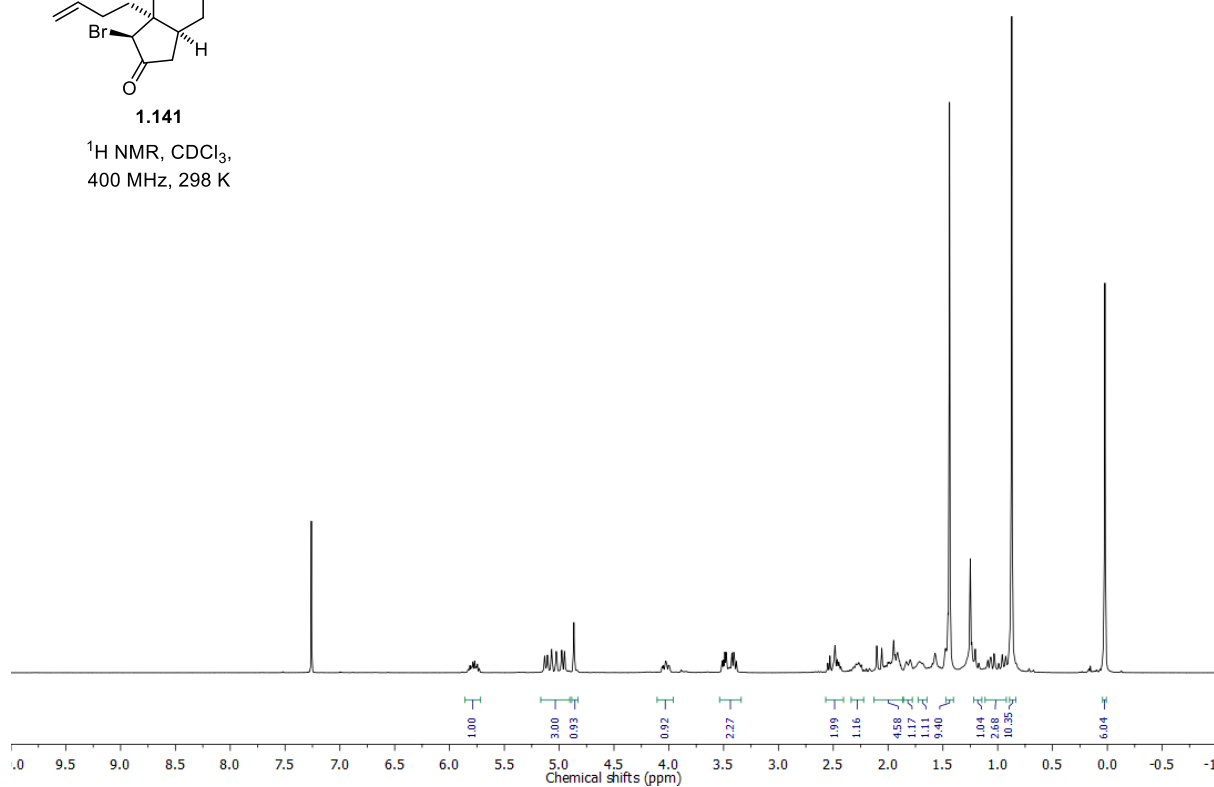
$^{13}\text{C}$  NMR,  $\text{CDCl}_3$ ,  
100 MHz, 298 K





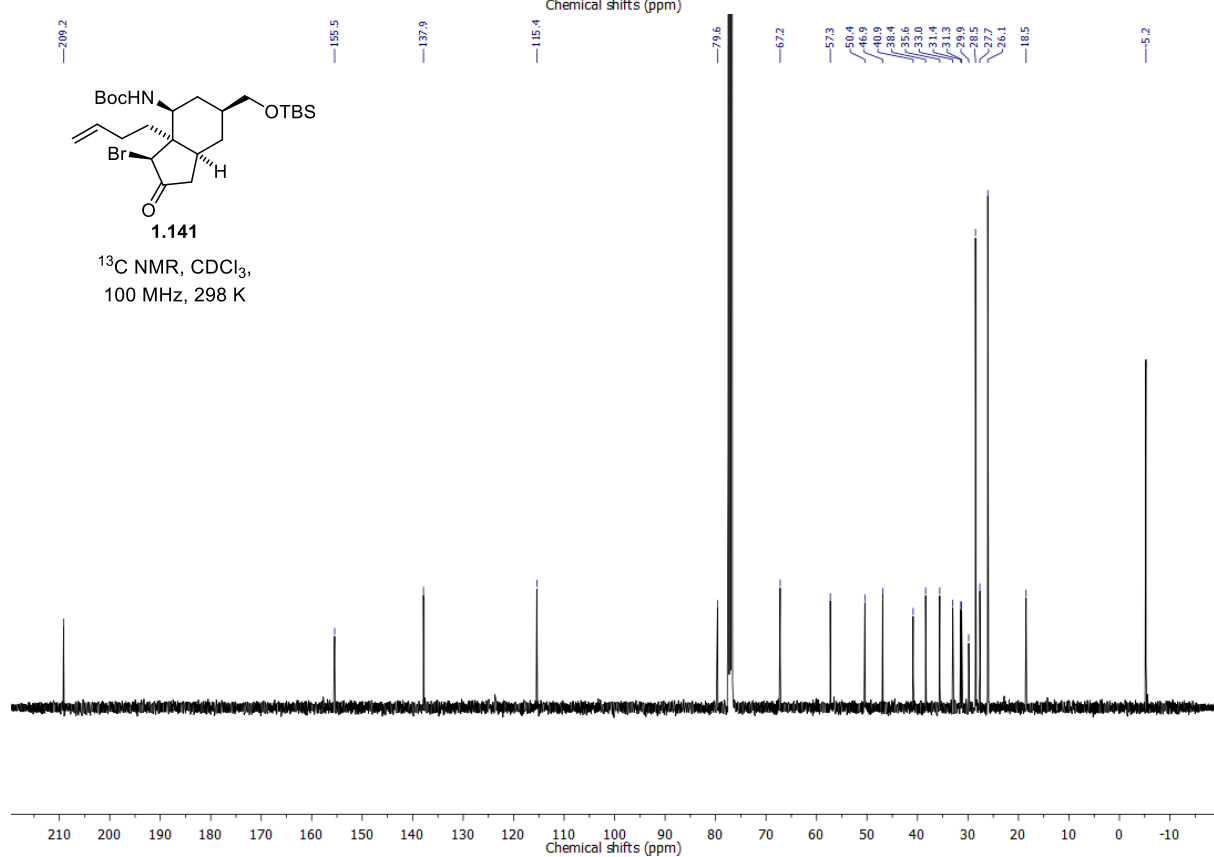
1.141

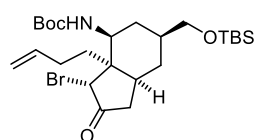
$^1\text{H}$  NMR,  $\text{CDCl}_3$ ,  
400 MHz, 298 K



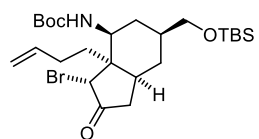
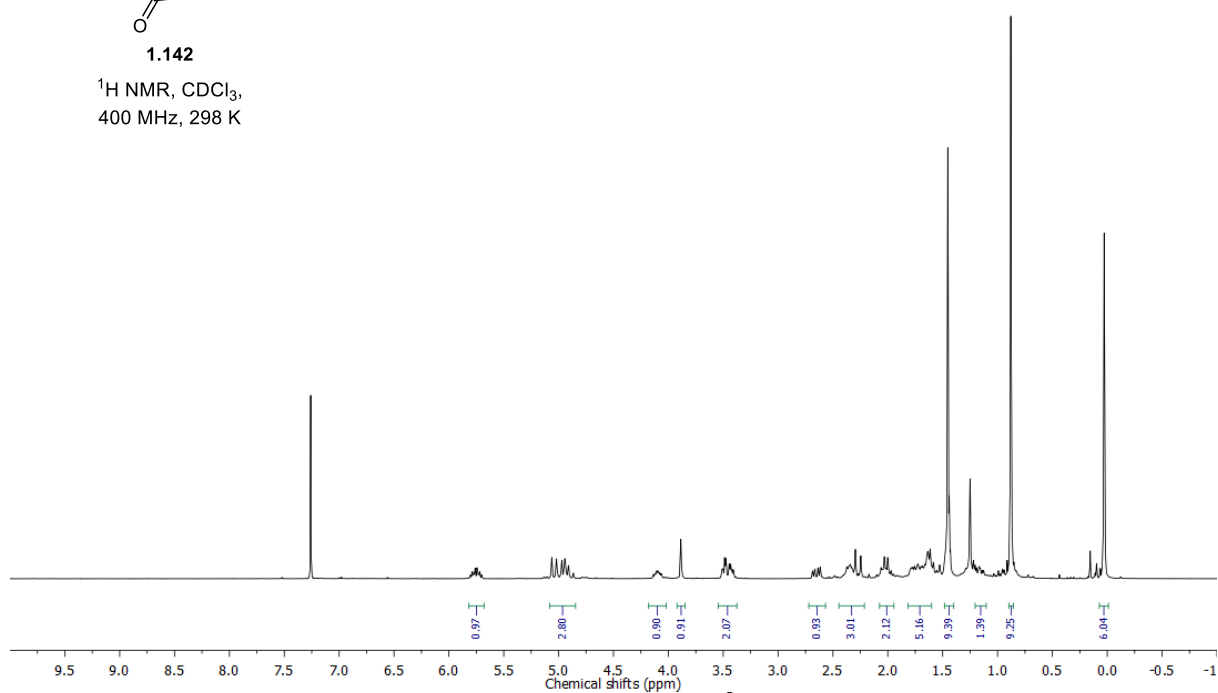
1.141

$^{13}\text{C}$  NMR,  $\text{CDCl}_3$ ,  
100 MHz, 298 K

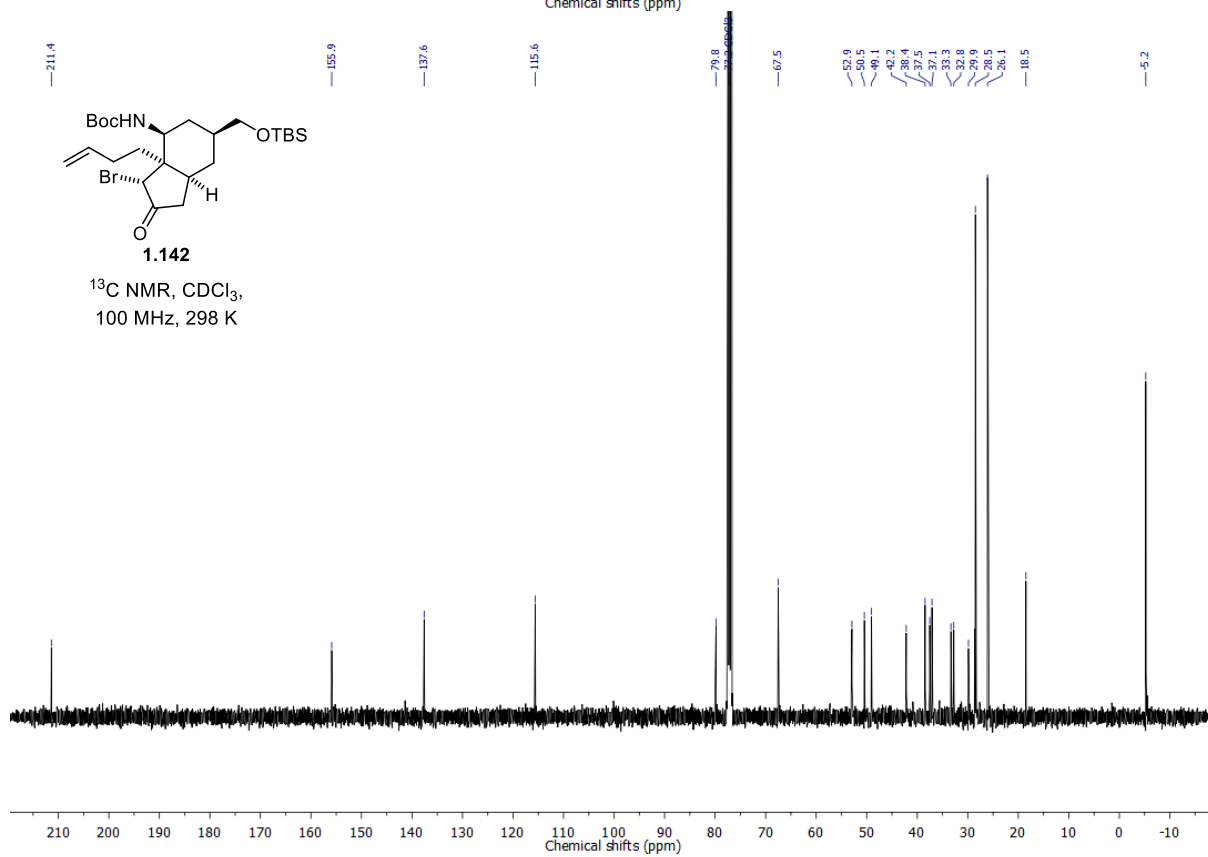


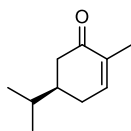
**1.142**

$^1\text{H}$  NMR,  $\text{CDCl}_3$ ,  
400 MHz, 298 K

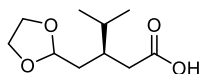
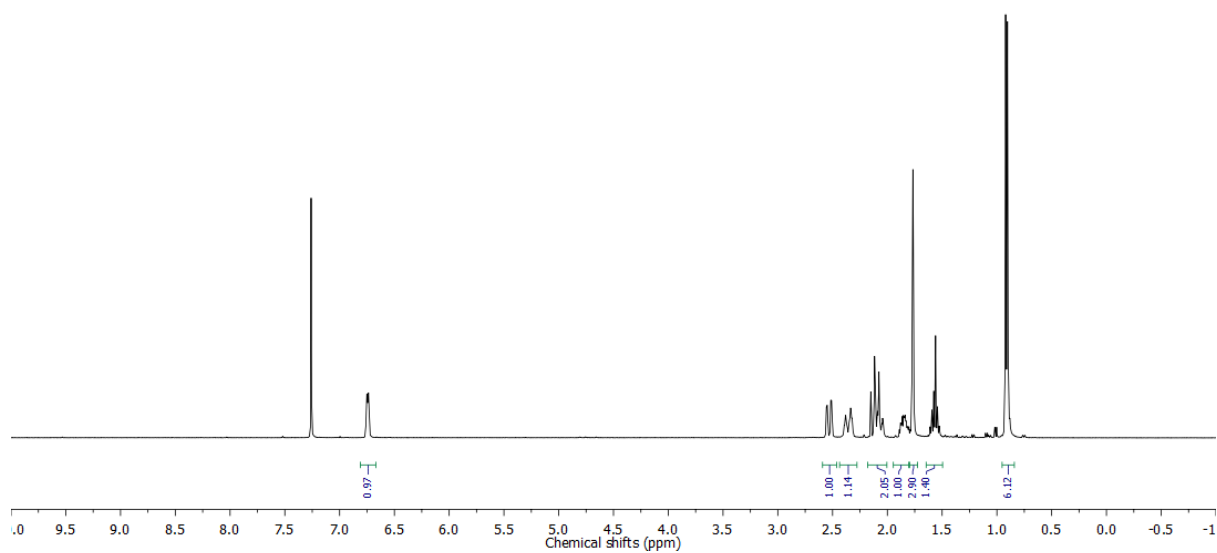
**1.142**

$^{13}\text{C}$  NMR,  $\text{CDCl}_3$ ,  
100 MHz, 298 K

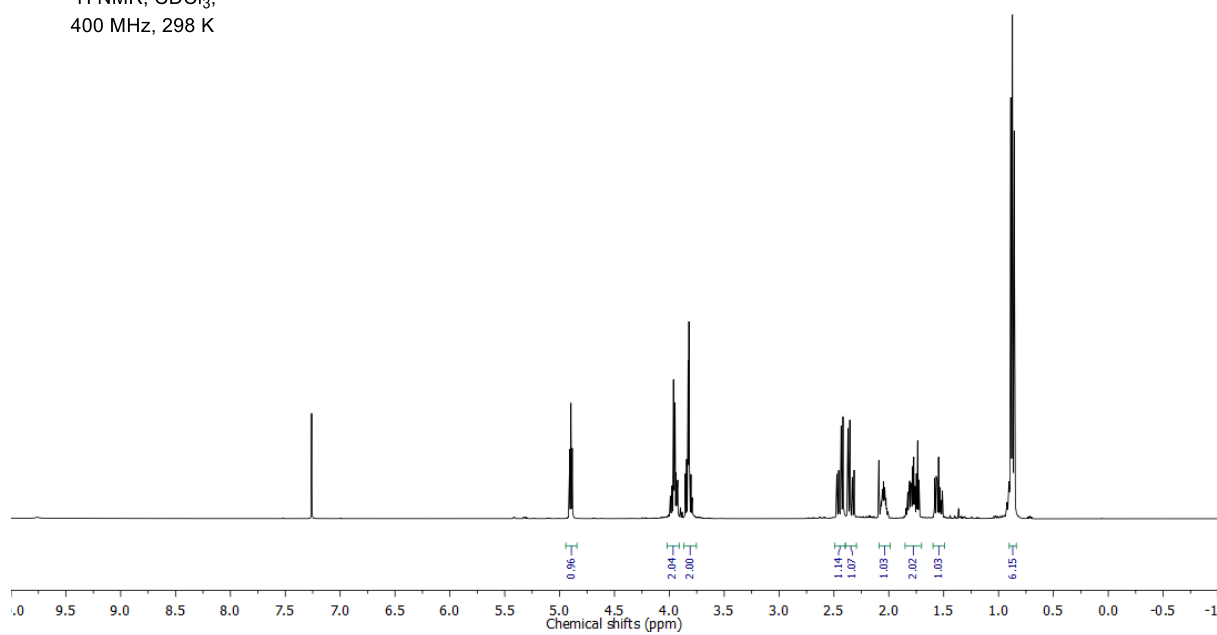


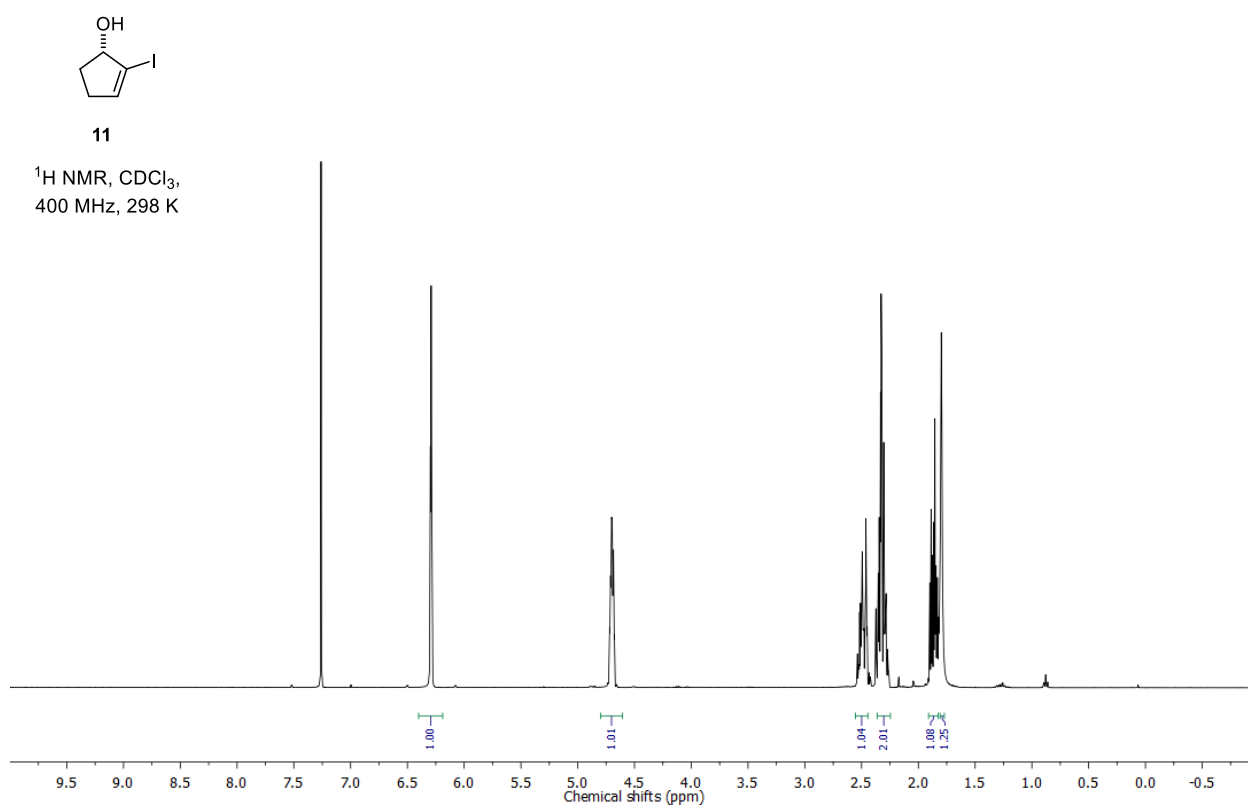
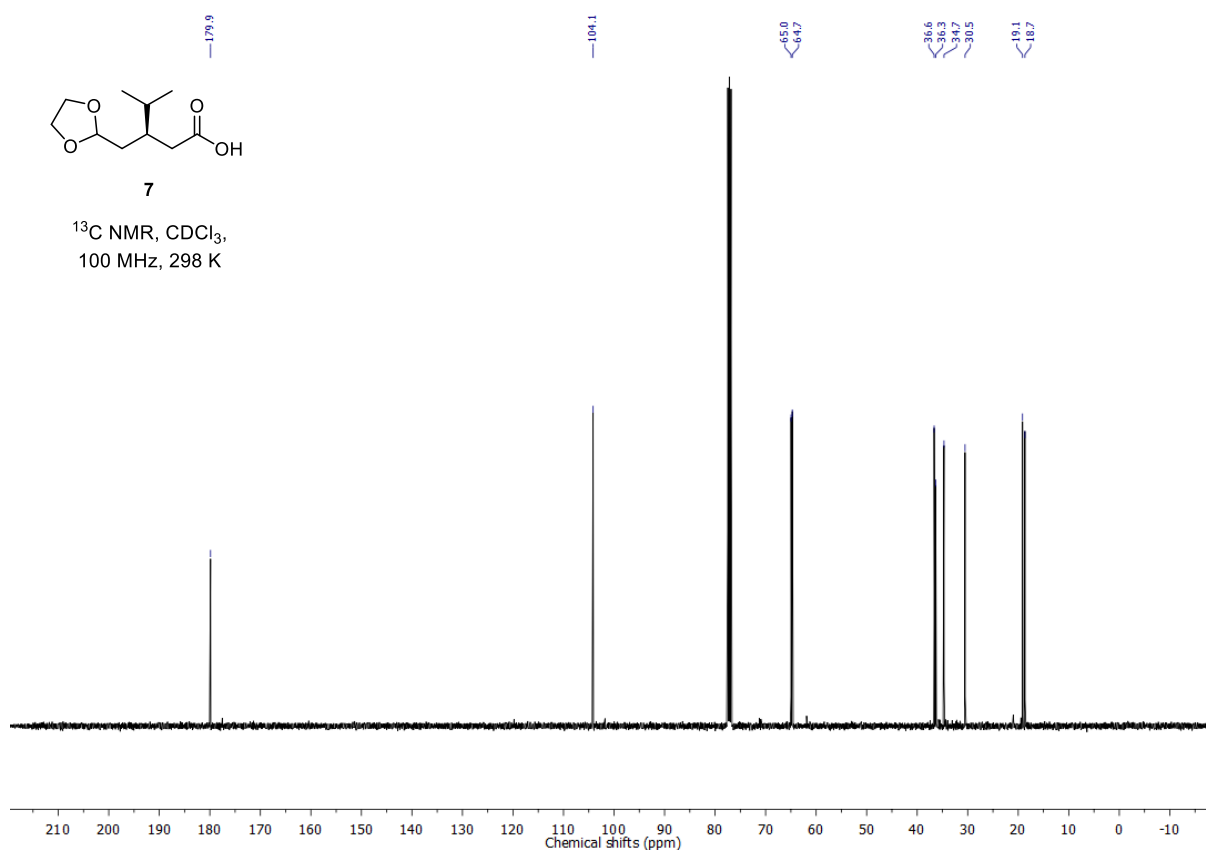
4.1.2.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR Spectra for Chapter II

9

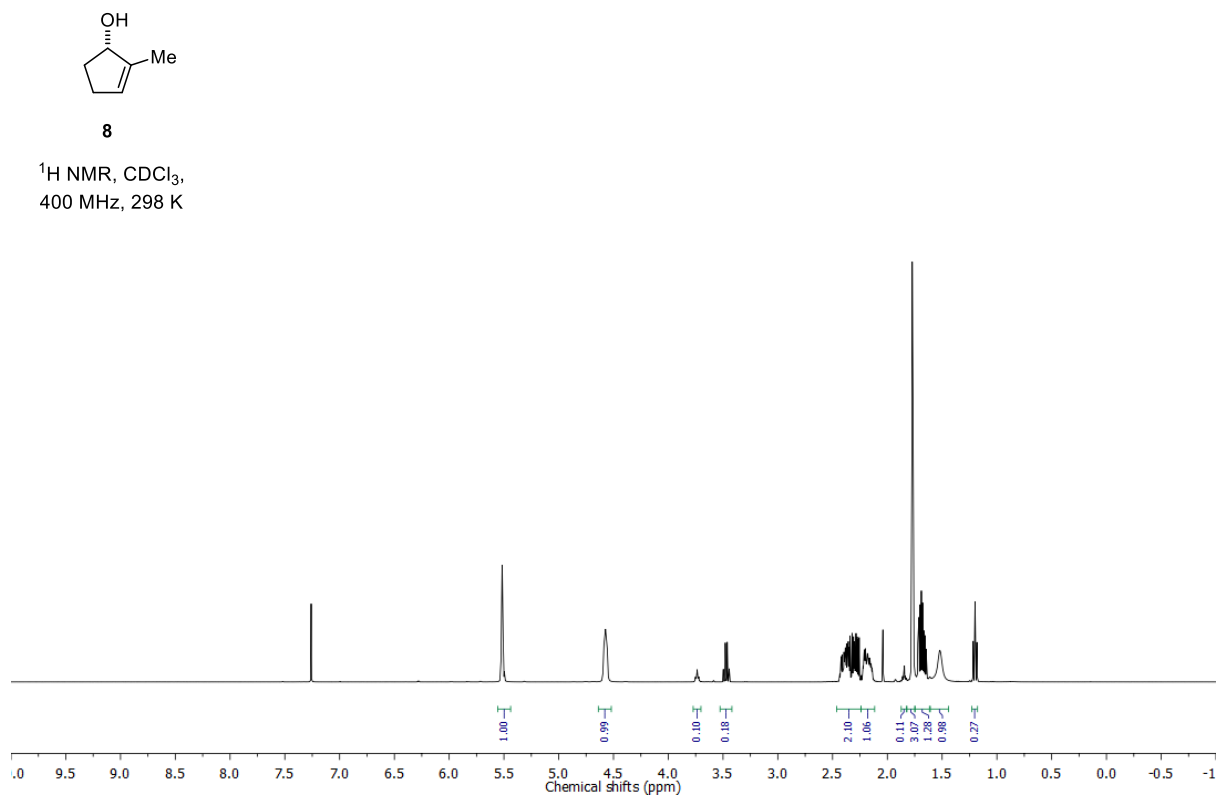
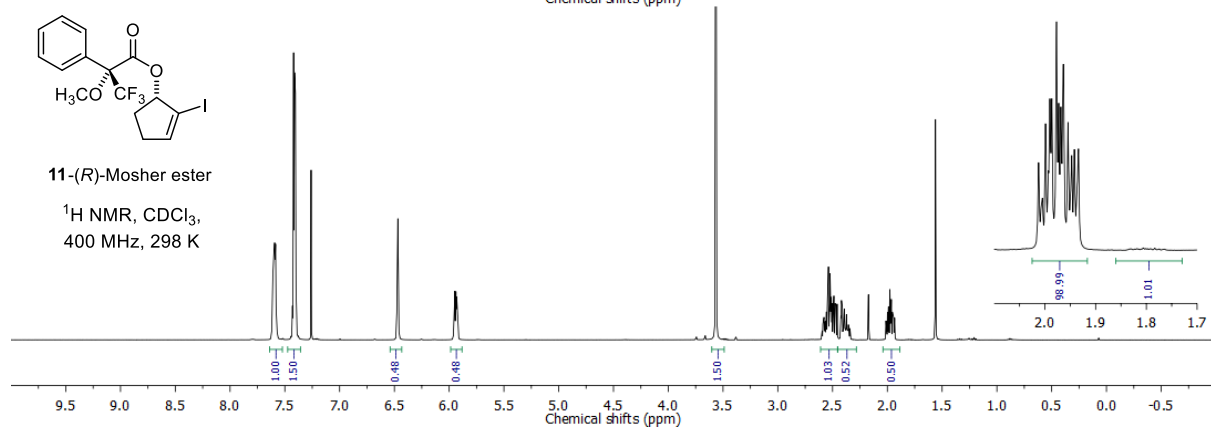
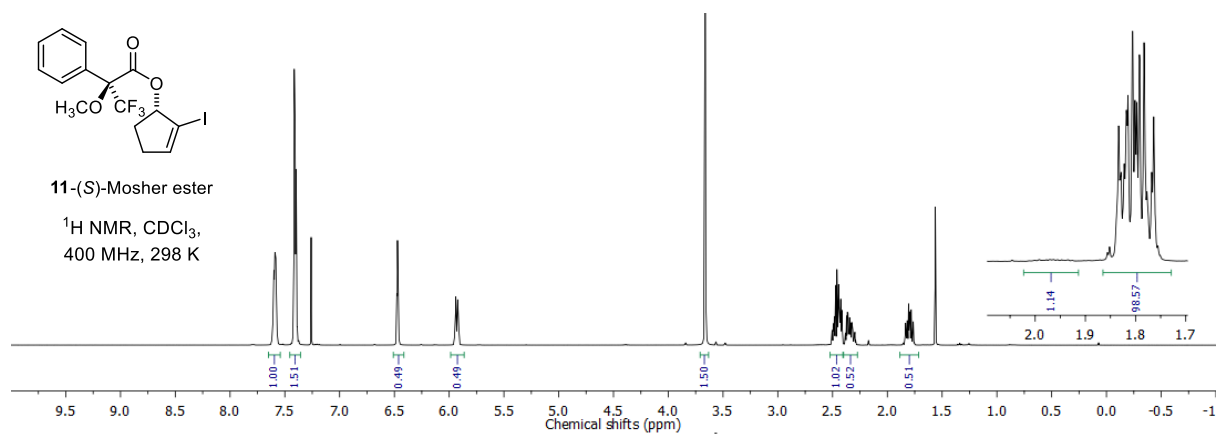
 $^1\text{H}$  NMR,  $\text{CDCl}_3$ ,  
400 MHz, 298 K

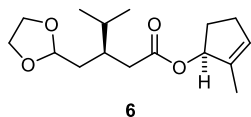
7

 $^1\text{H}$  NMR,  $\text{CDCl}_3$ ,  
400 MHz, 298 K

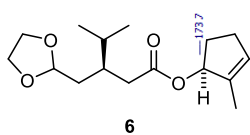
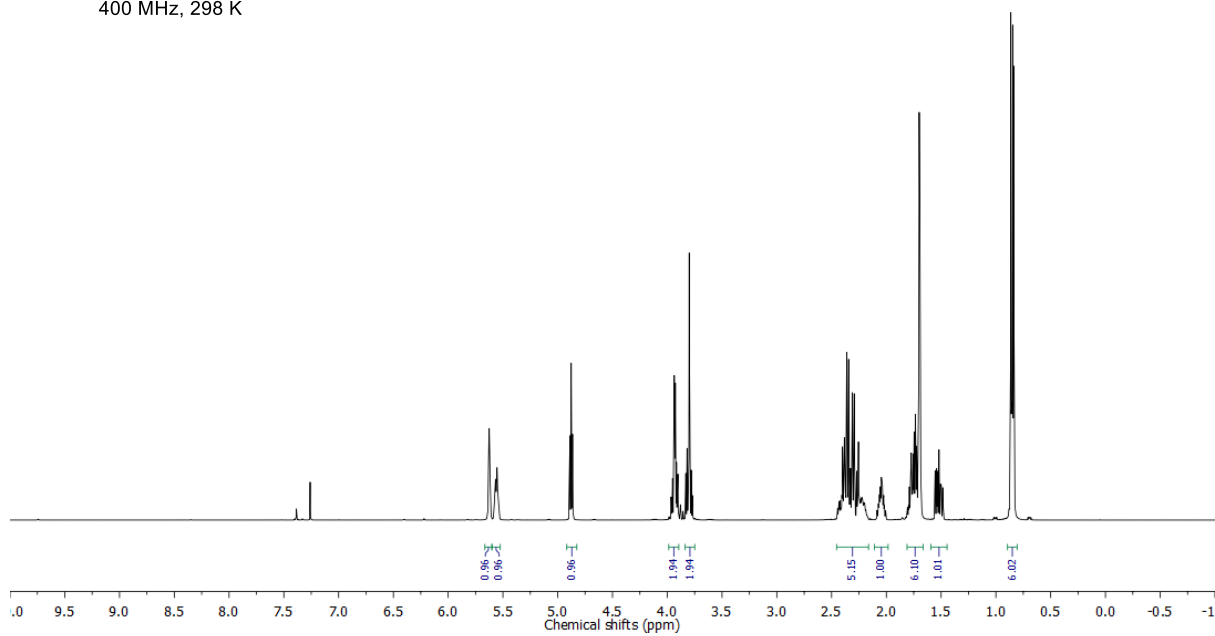




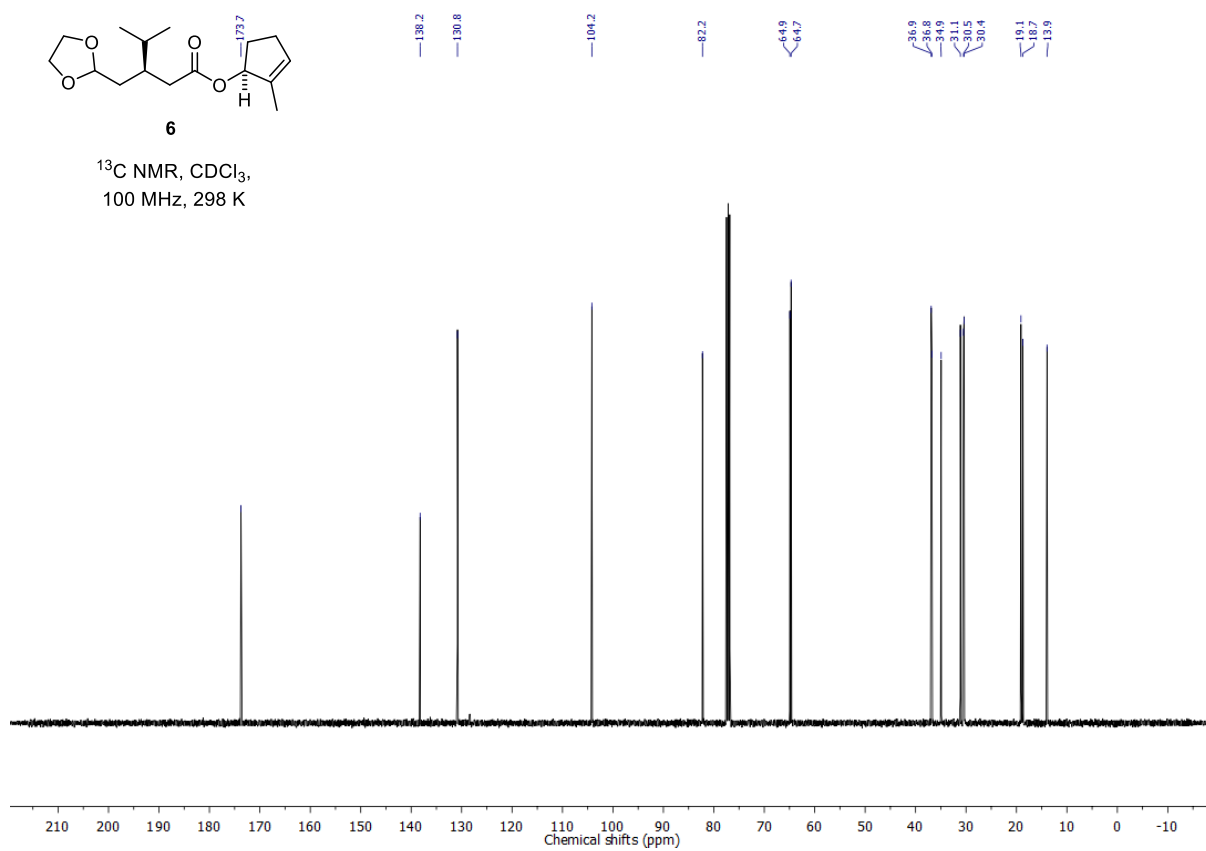


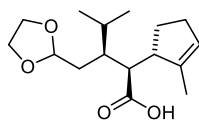


$^1\text{H}$  NMR,  $\text{CDCl}_3$ ,  
400 MHz, 298 K



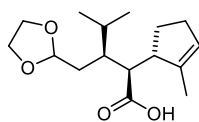
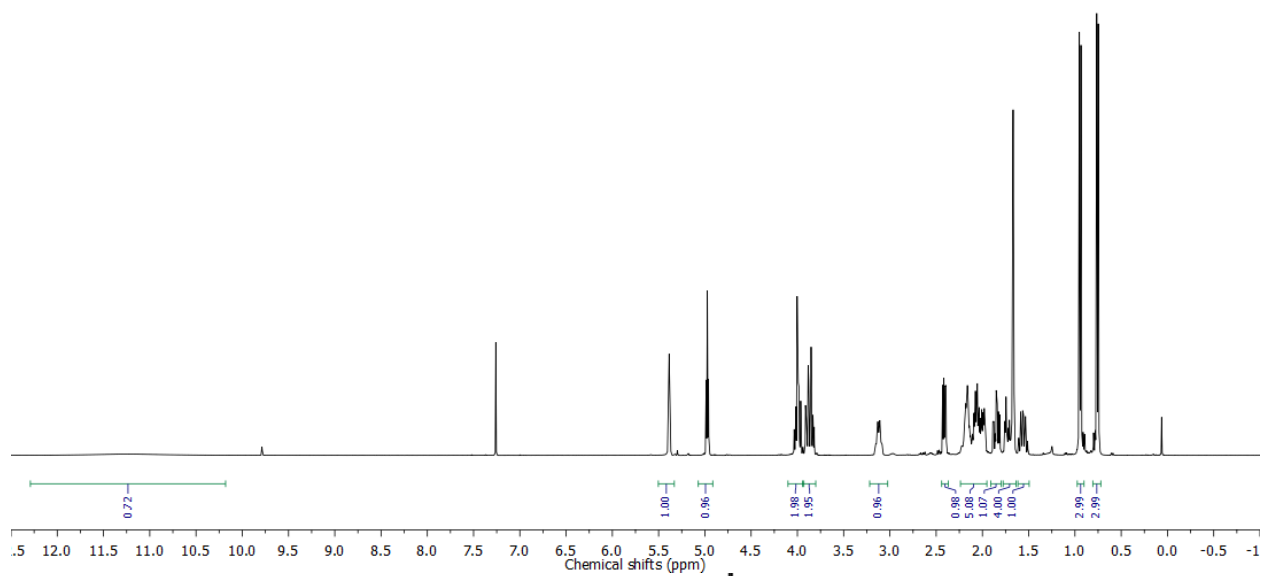
$^{13}\text{C}$  NMR,  $\text{CDCl}_3$ ,  
100 MHz, 298 K





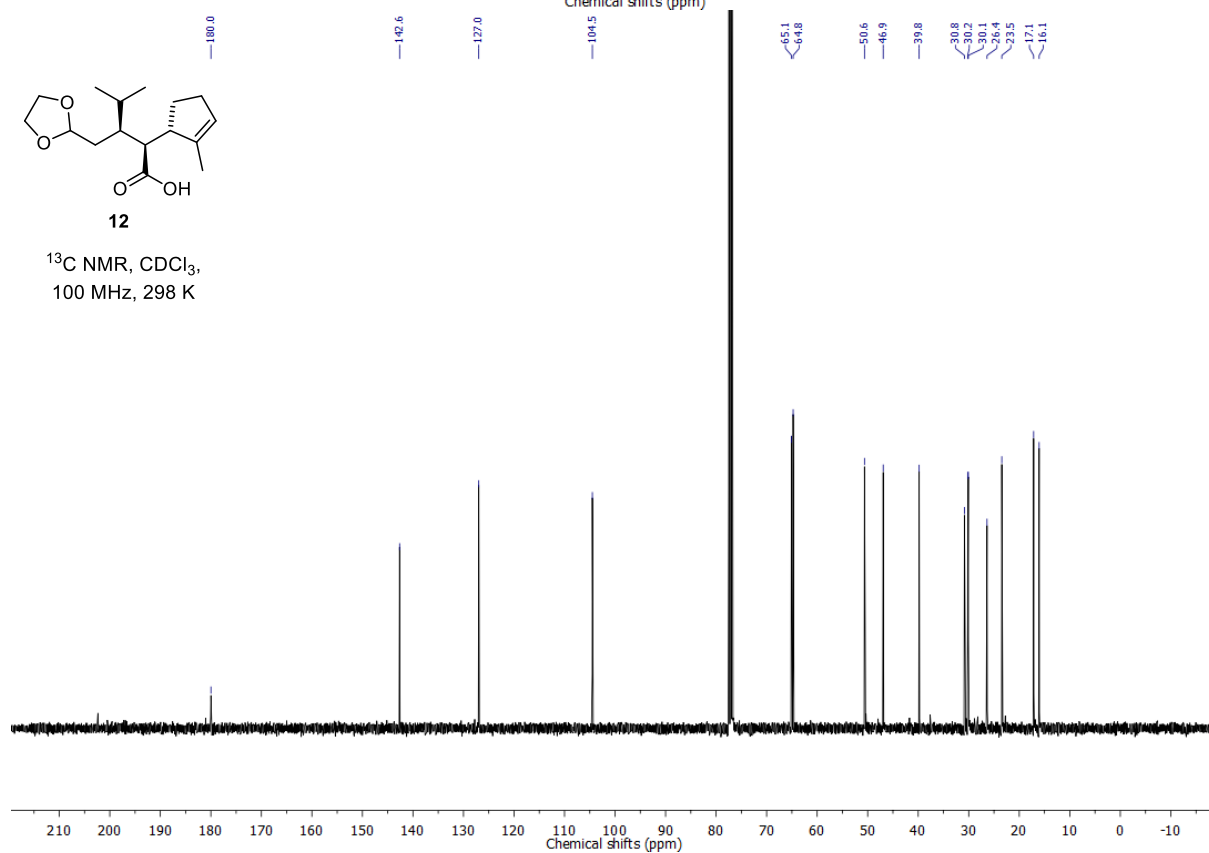
12

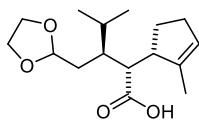
$^1\text{H}$  NMR,  $\text{CDCl}_3$ ,  
400 MHz, 298 K



12

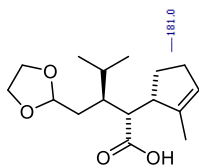
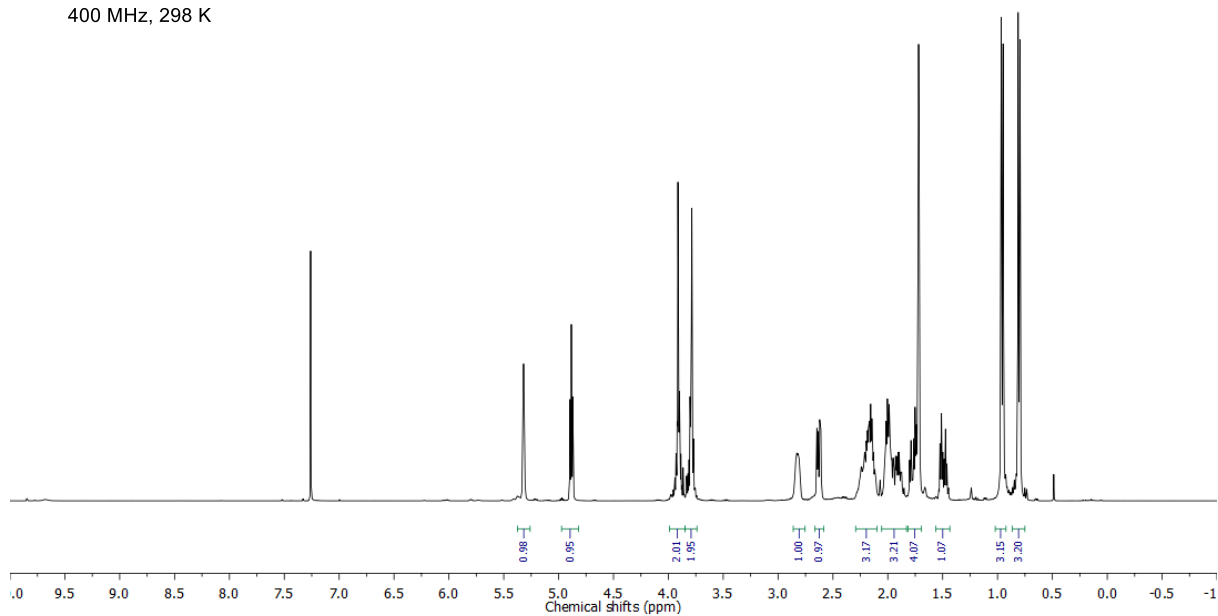
$^{13}\text{C}$  NMR,  $\text{CDCl}_3$ ,  
100 MHz, 298 K





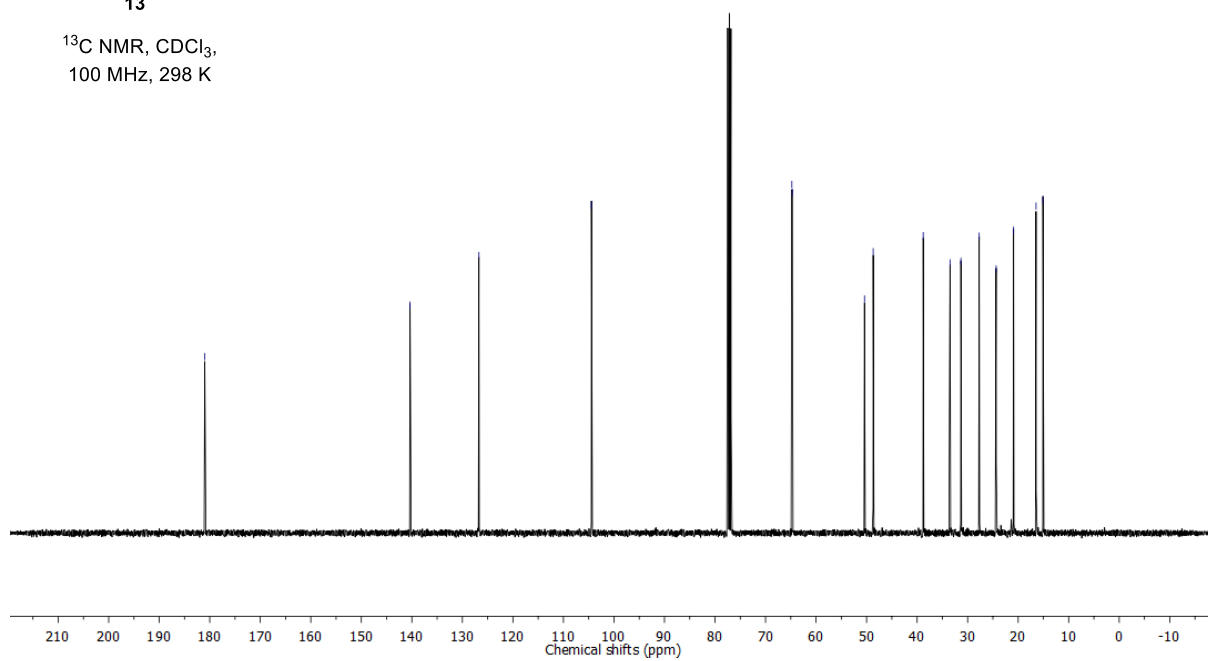
13

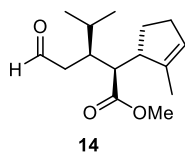
$^1\text{H}$  NMR,  $\text{CDCl}_3$ ,  
400 MHz, 298 K



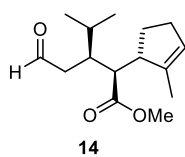
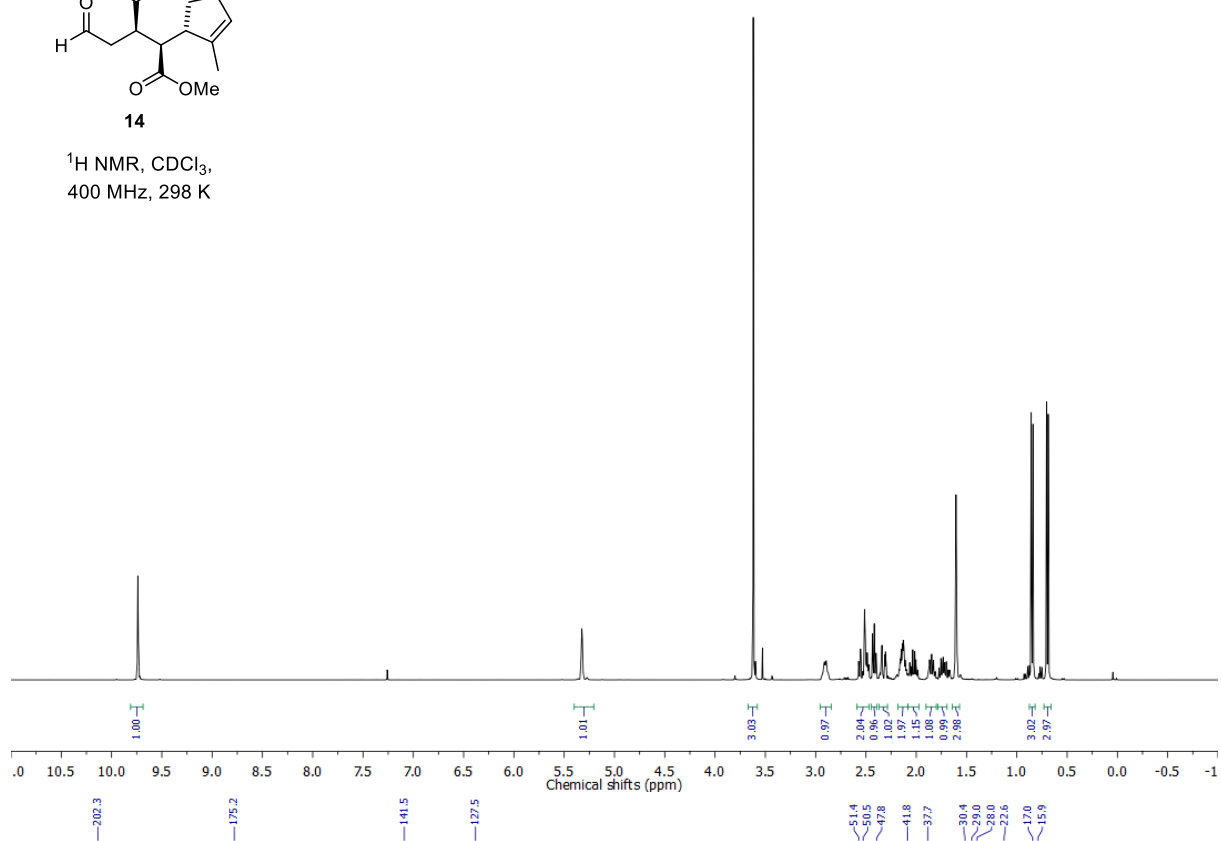
13

$^{13}\text{C}$  NMR,  $\text{CDCl}_3$ ,  
100 MHz, 298 K

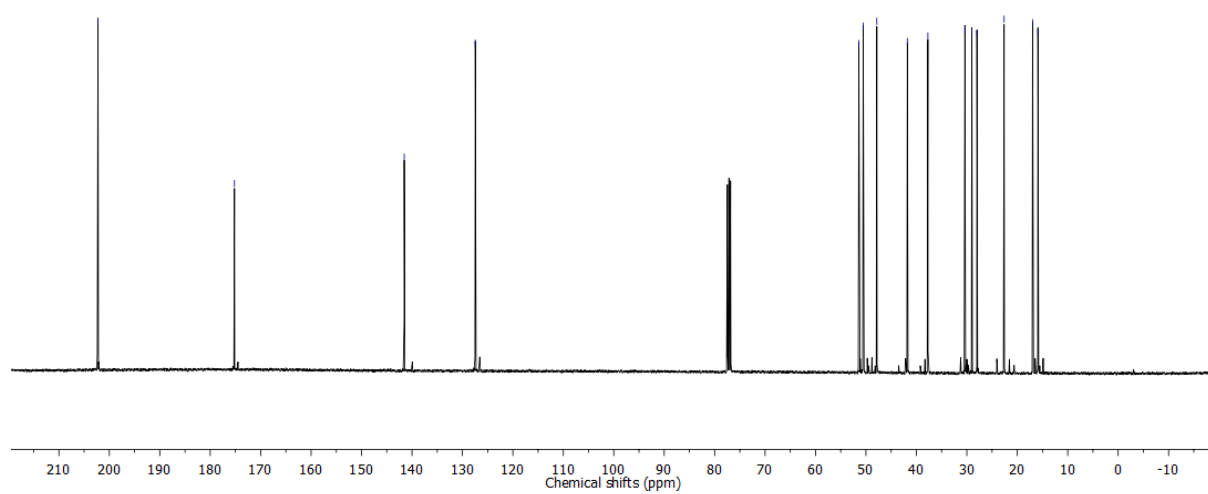


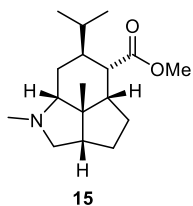
**14**

$^1\text{H}$  NMR,  $\text{CDCl}_3$ ,  
400 MHz, 298 K

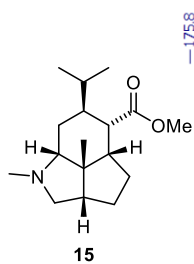
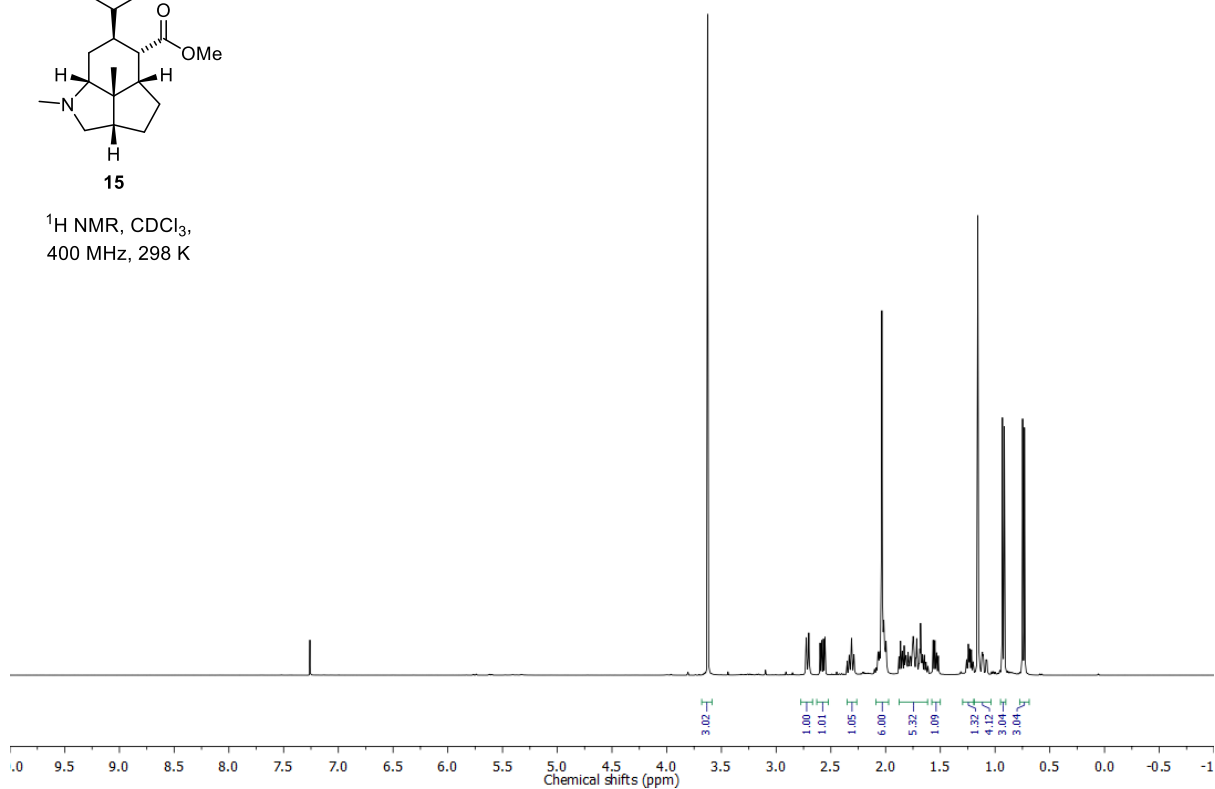
**14**

$^{13}\text{C}$  NMR,  $\text{CDCl}_3$ ,  
100 MHz, 298 K

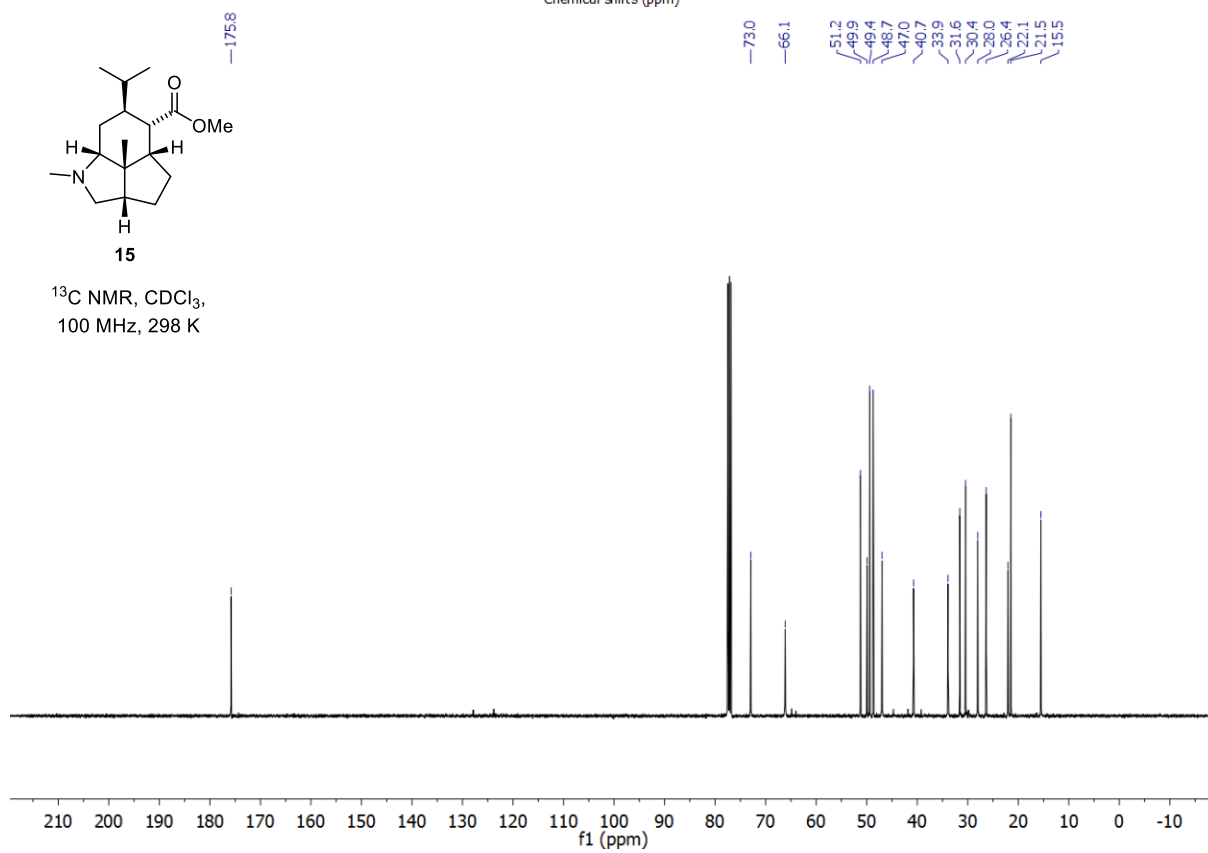


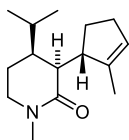


$^1\text{H NMR}$ ,  $\text{CDCl}_3$ ,  
400 MHz, 298 K

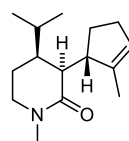
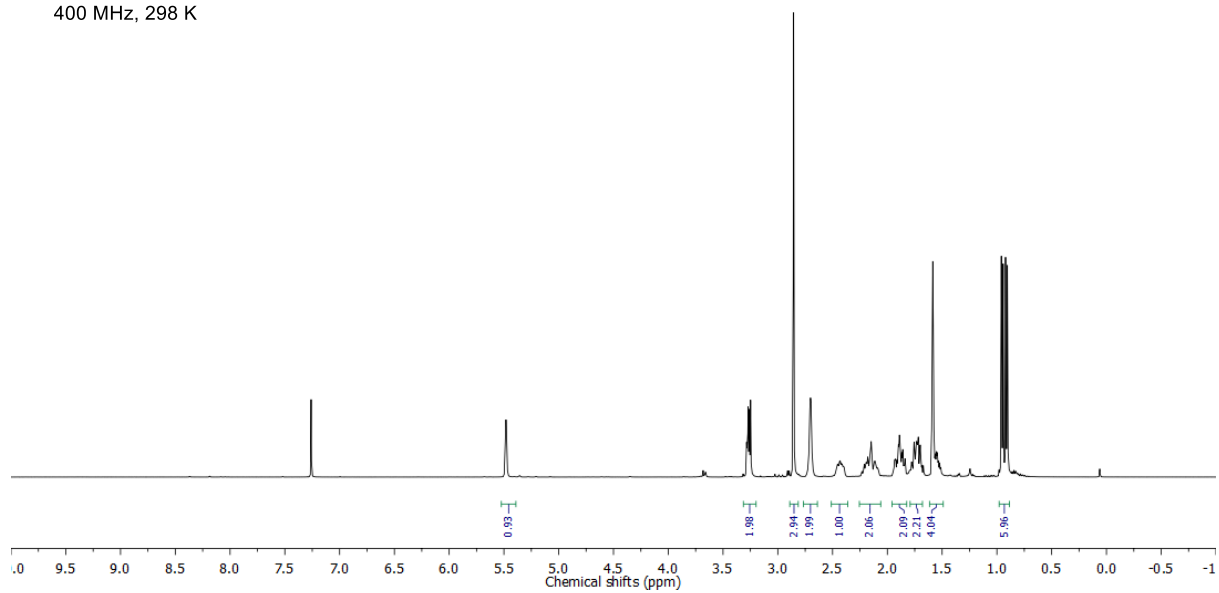


$^{13}\text{C NMR}$ ,  $\text{CDCl}_3$ ,  
100 MHz, 298 K

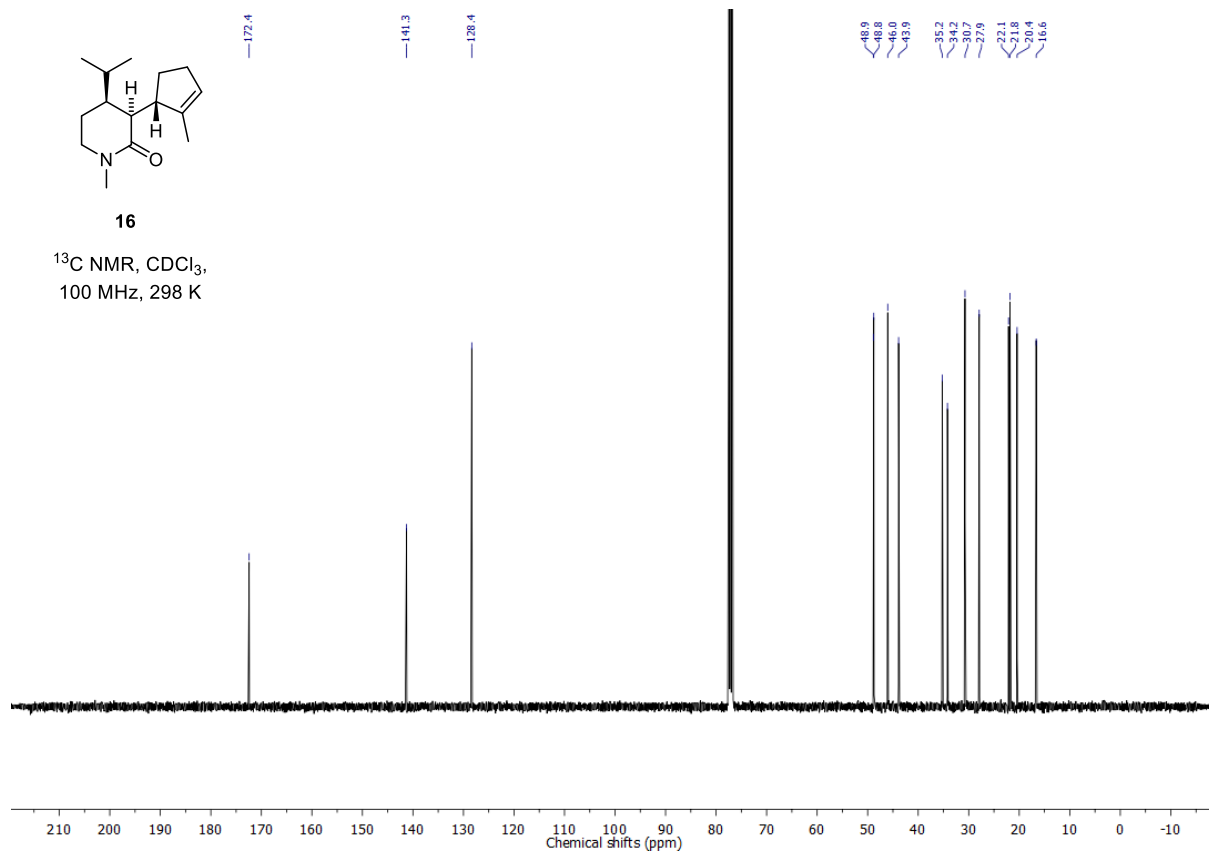


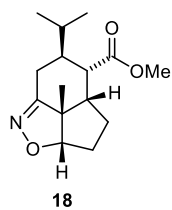
**16**

$^1\text{H}$  NMR,  $\text{CDCl}_3$ ,  
400 MHz, 298 K

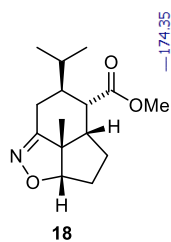
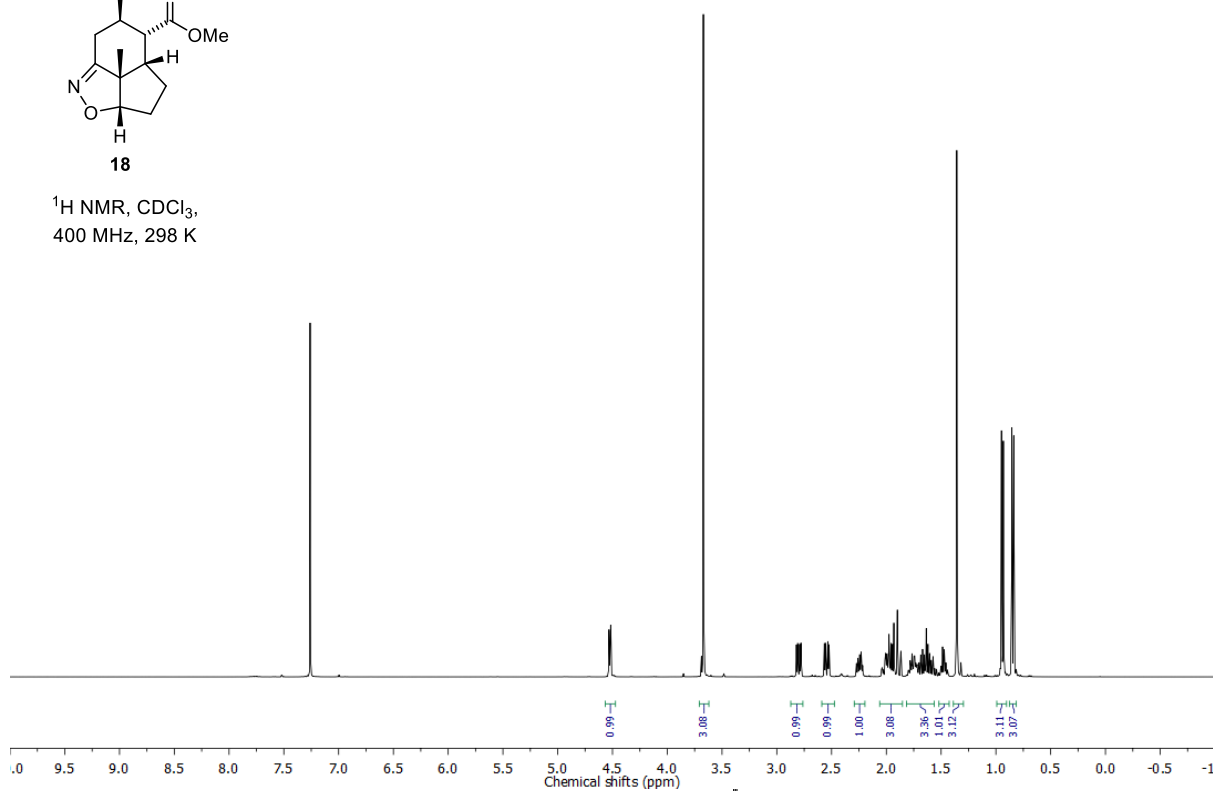
**16**

$^{13}\text{C}$  NMR,  $\text{CDCl}_3$ ,  
100 MHz, 298 K

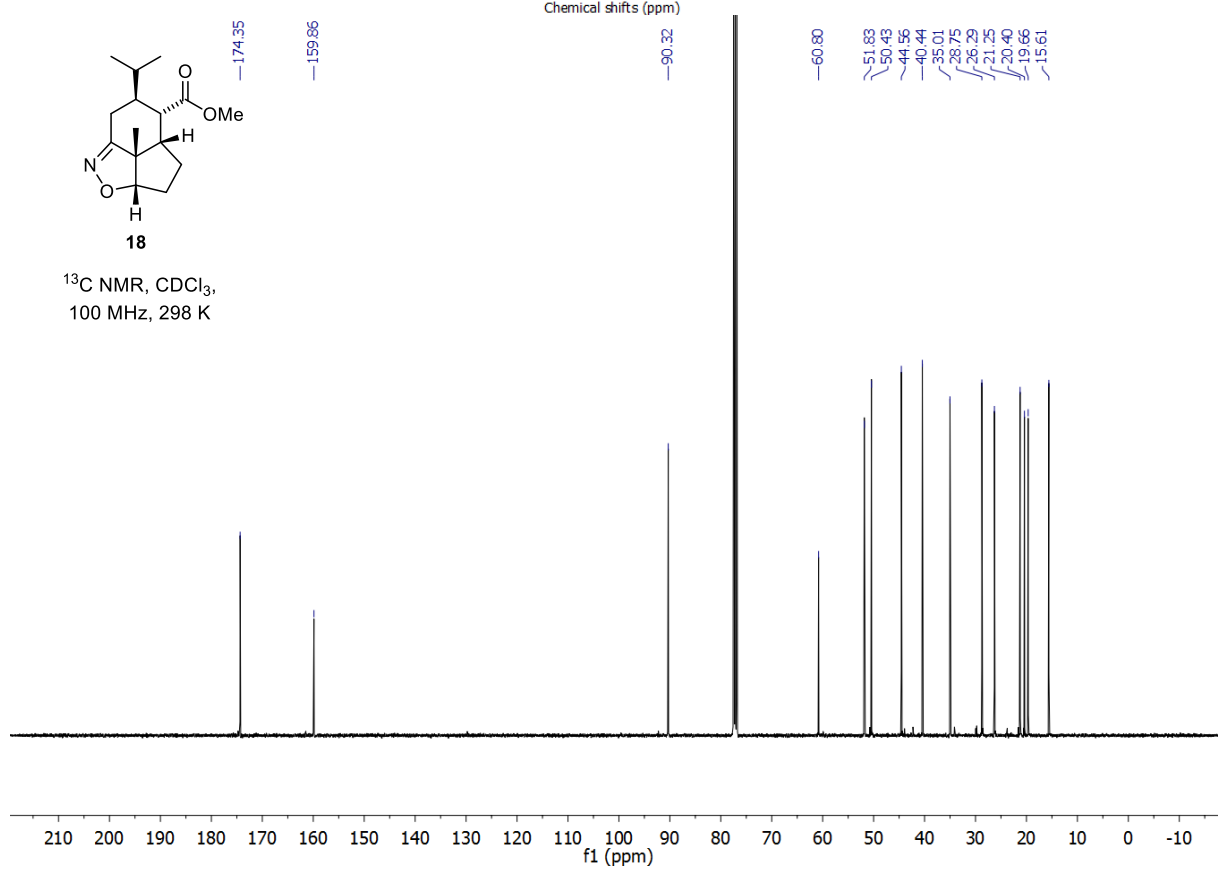




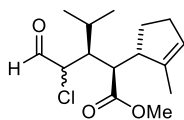
$^1\text{H}$  NMR,  $\text{CDCl}_3$ ,  
400 MHz, 298 K



$^{13}\text{C}$  NMR,  $\text{CDCl}_3$ ,  
100 MHz, 298 K

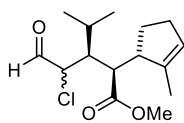
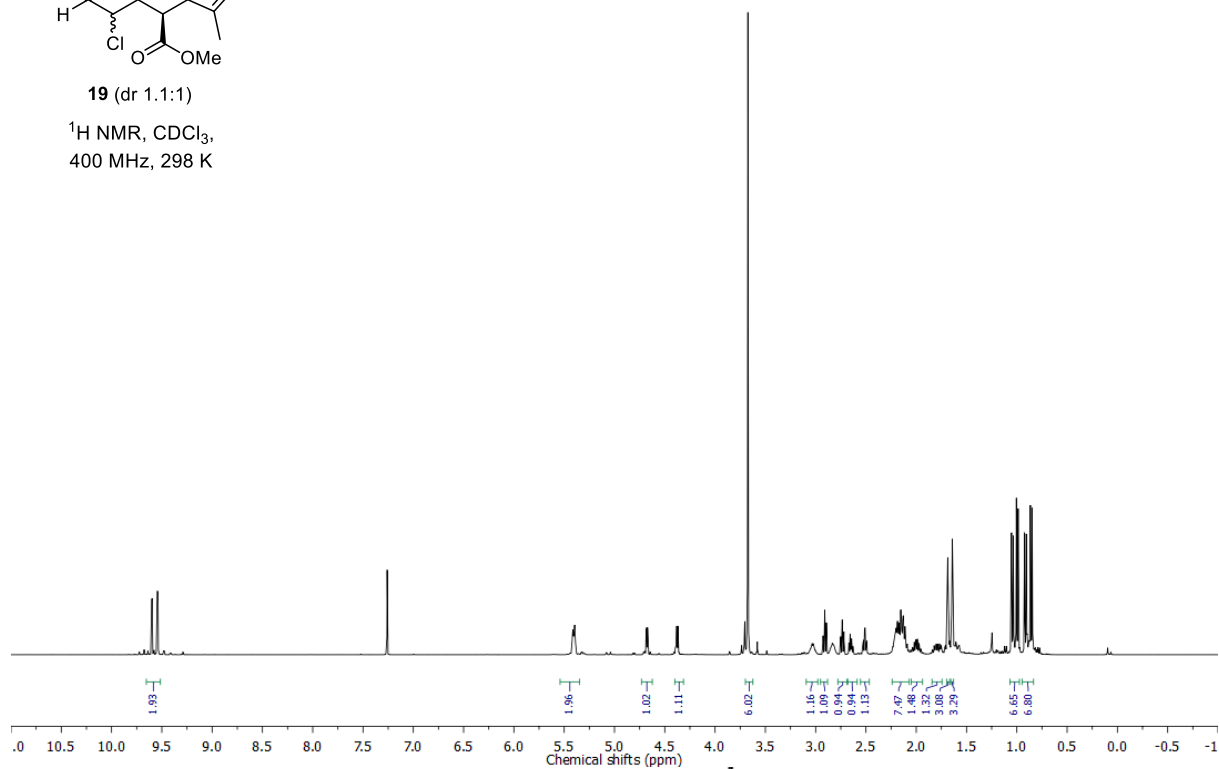






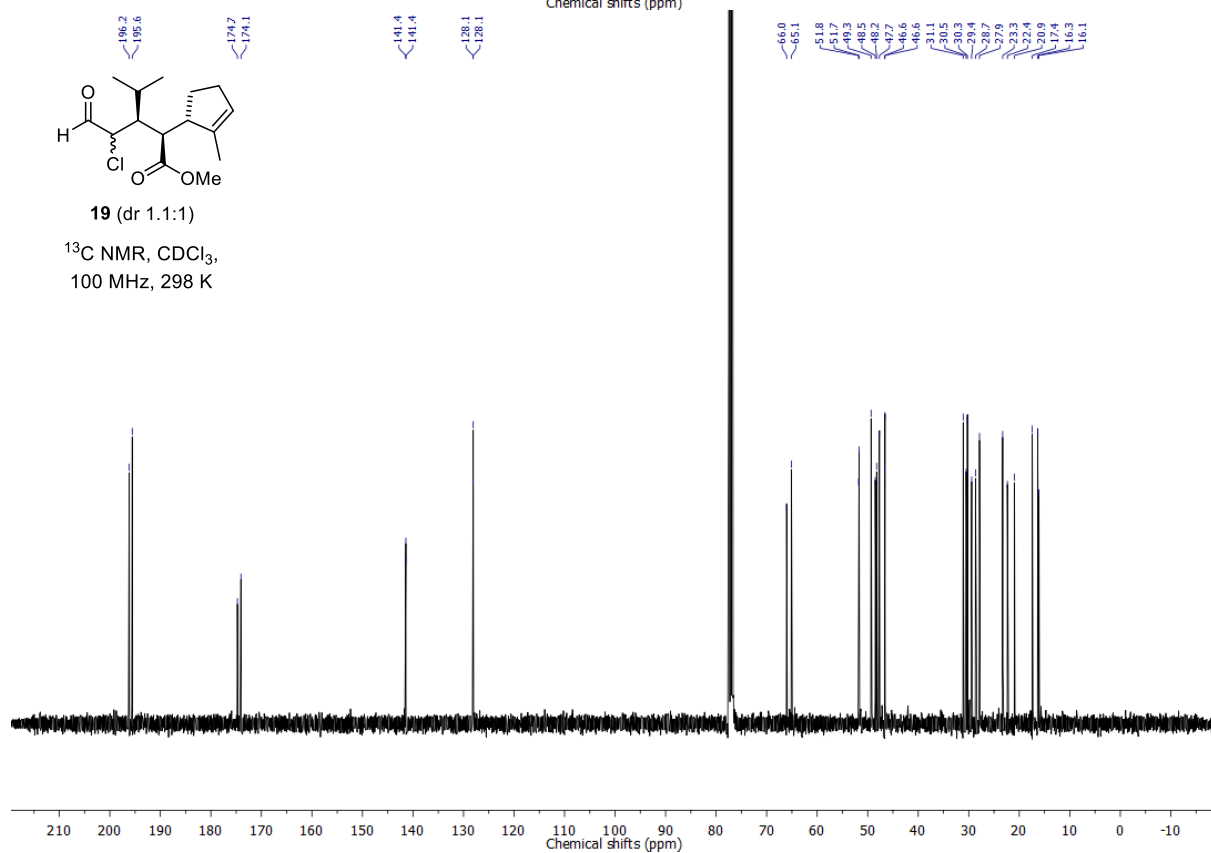
**19** (dr 1.1:1)

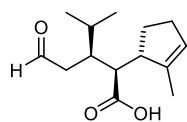
$^1\text{H}$  NMR,  $\text{CDCl}_3$ ,  
400 MHz, 298 K



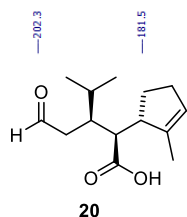
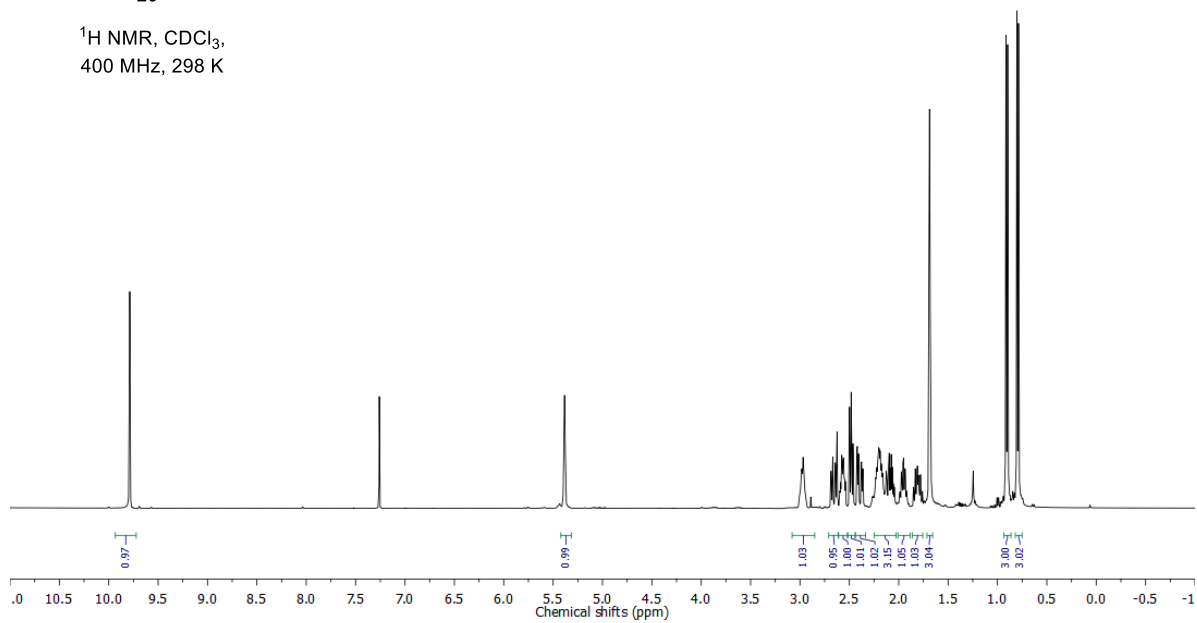
**19** (dr 1.1:1)

$^{13}\text{C}$  NMR,  $\text{CDCl}_3$ ,  
100 MHz, 298 K

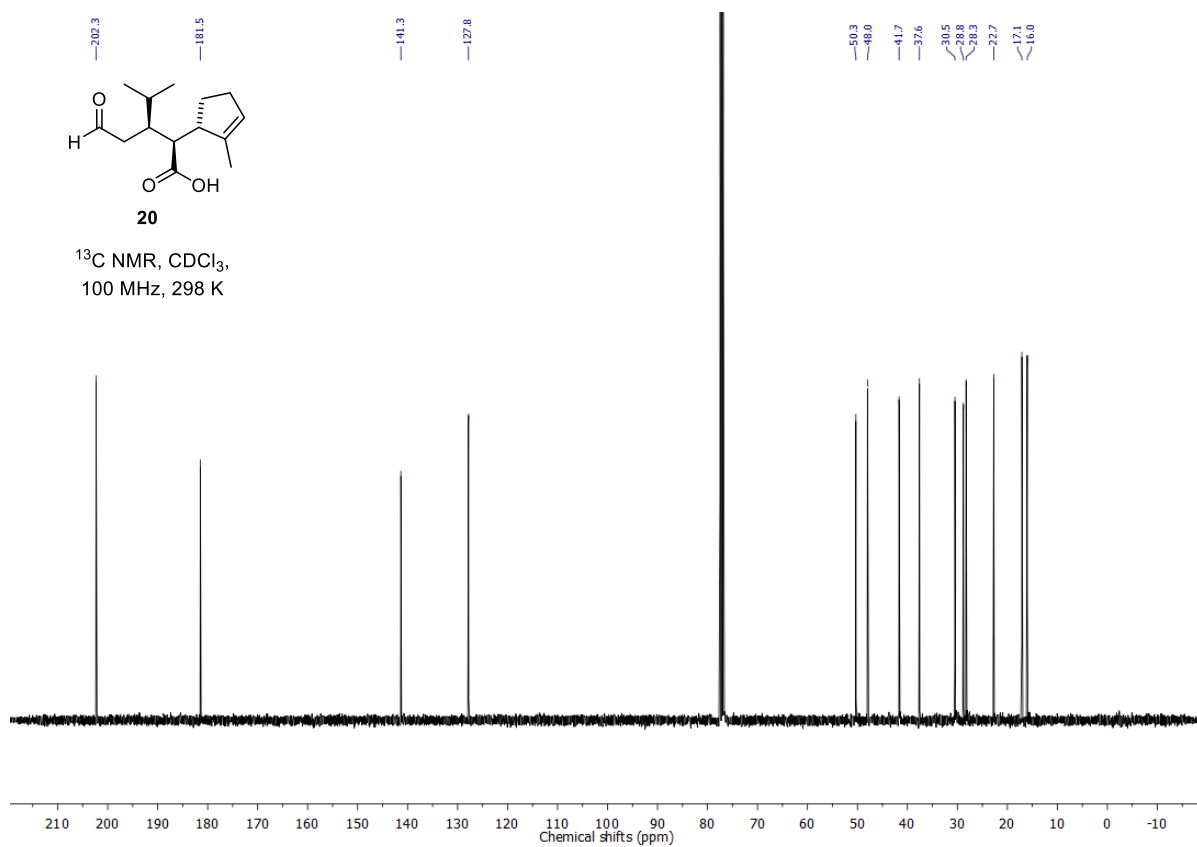


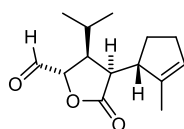
**20**

$^1\text{H}$  NMR,  $\text{CDCl}_3$ ,  
400 MHz, 298 K

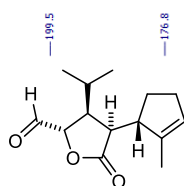
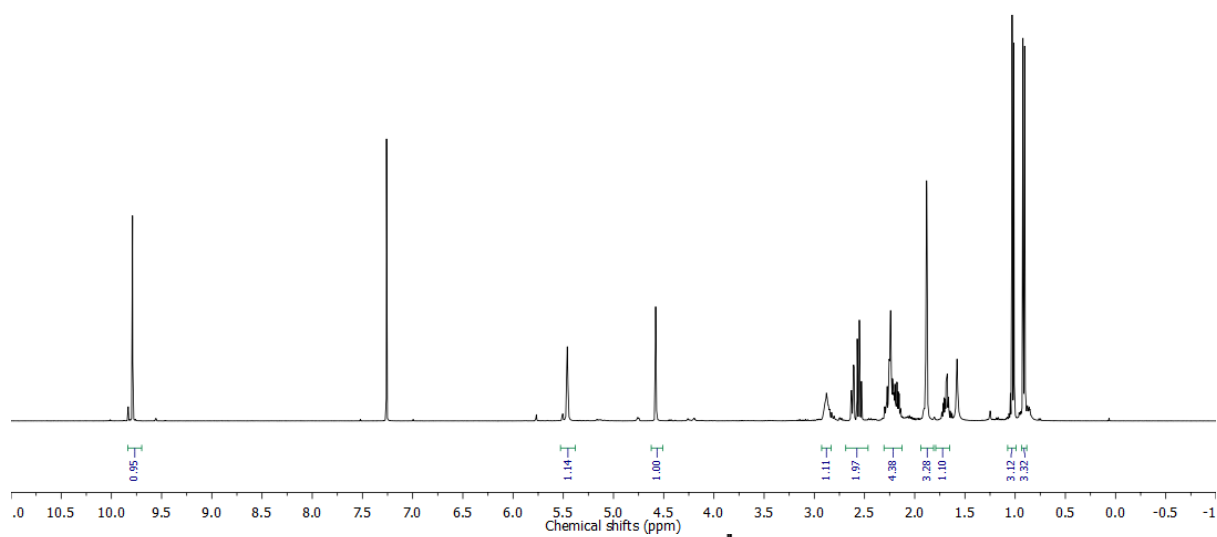
**20**

$^{13}\text{C}$  NMR,  $\text{CDCl}_3$ ,  
100 MHz, 298 K

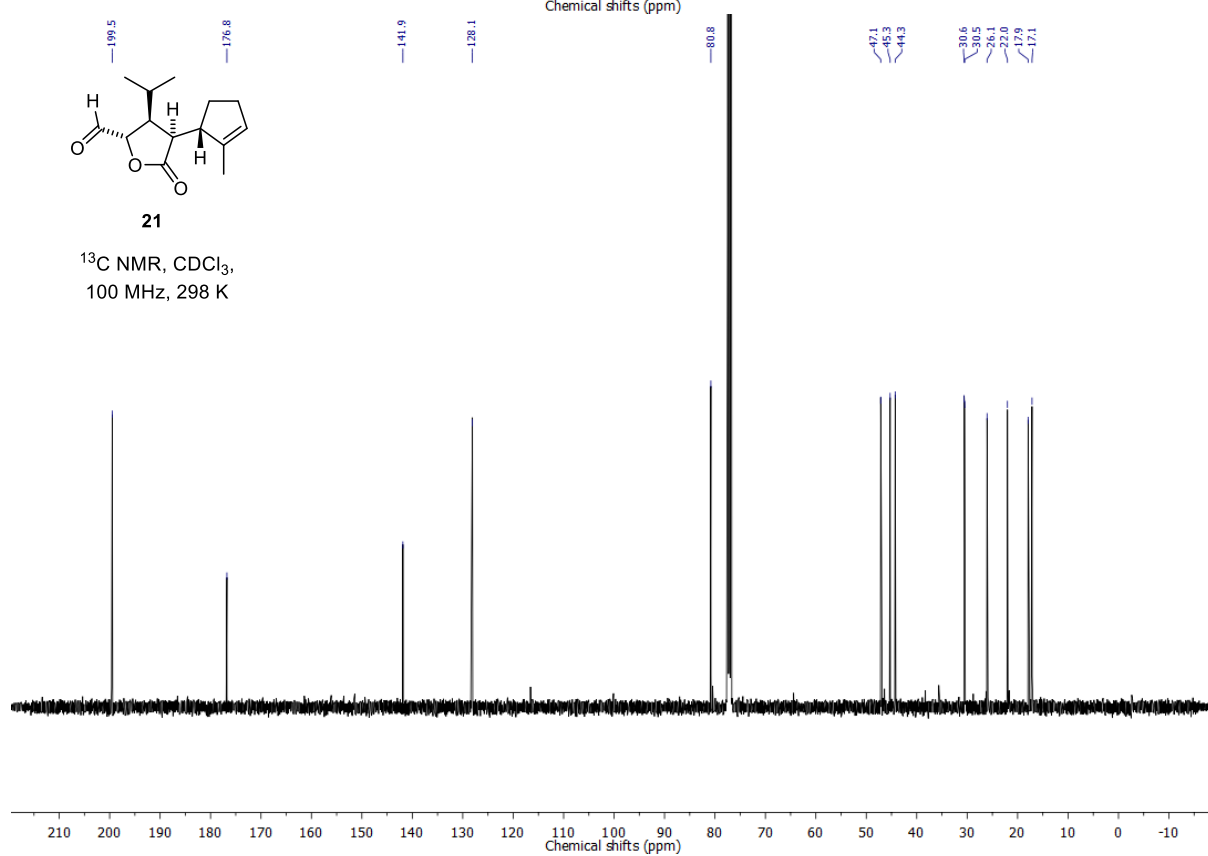


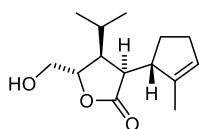
**21**

$^1\text{H}$  NMR,  $\text{CDCl}_3$ ,  
400 MHz, 298 K

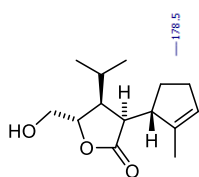
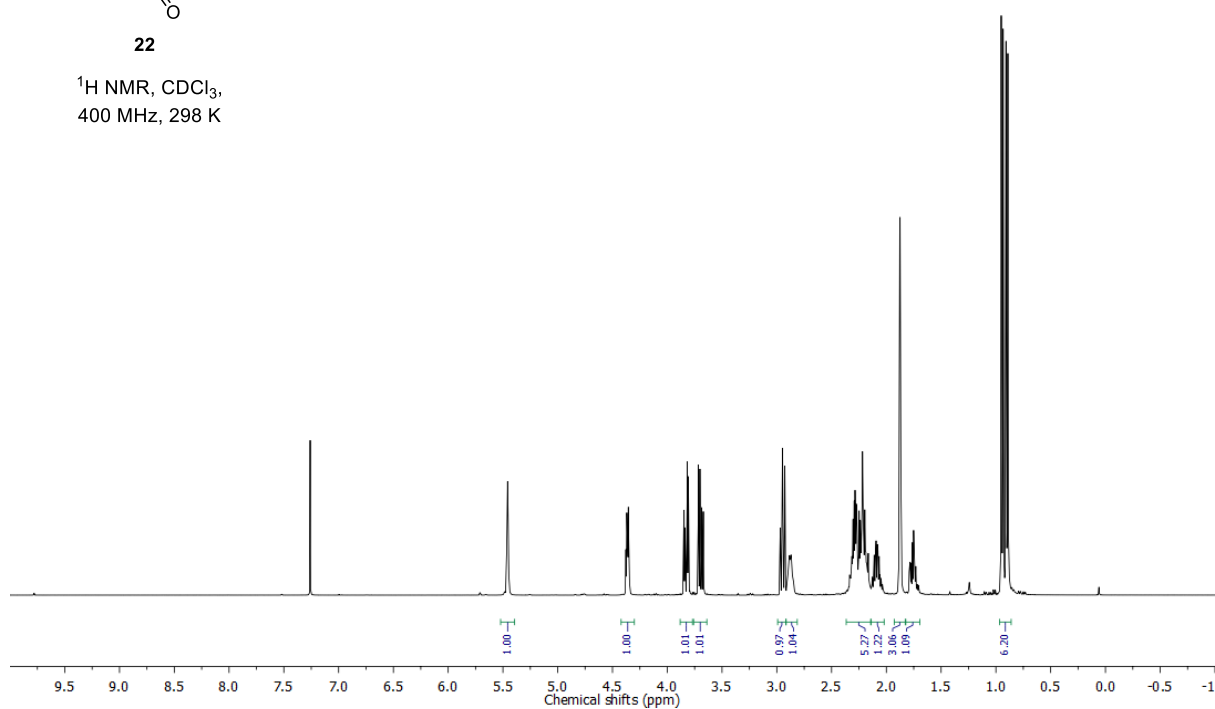
**21**

$^{13}\text{C}$  NMR,  $\text{CDCl}_3$ ,  
100 MHz, 298 K

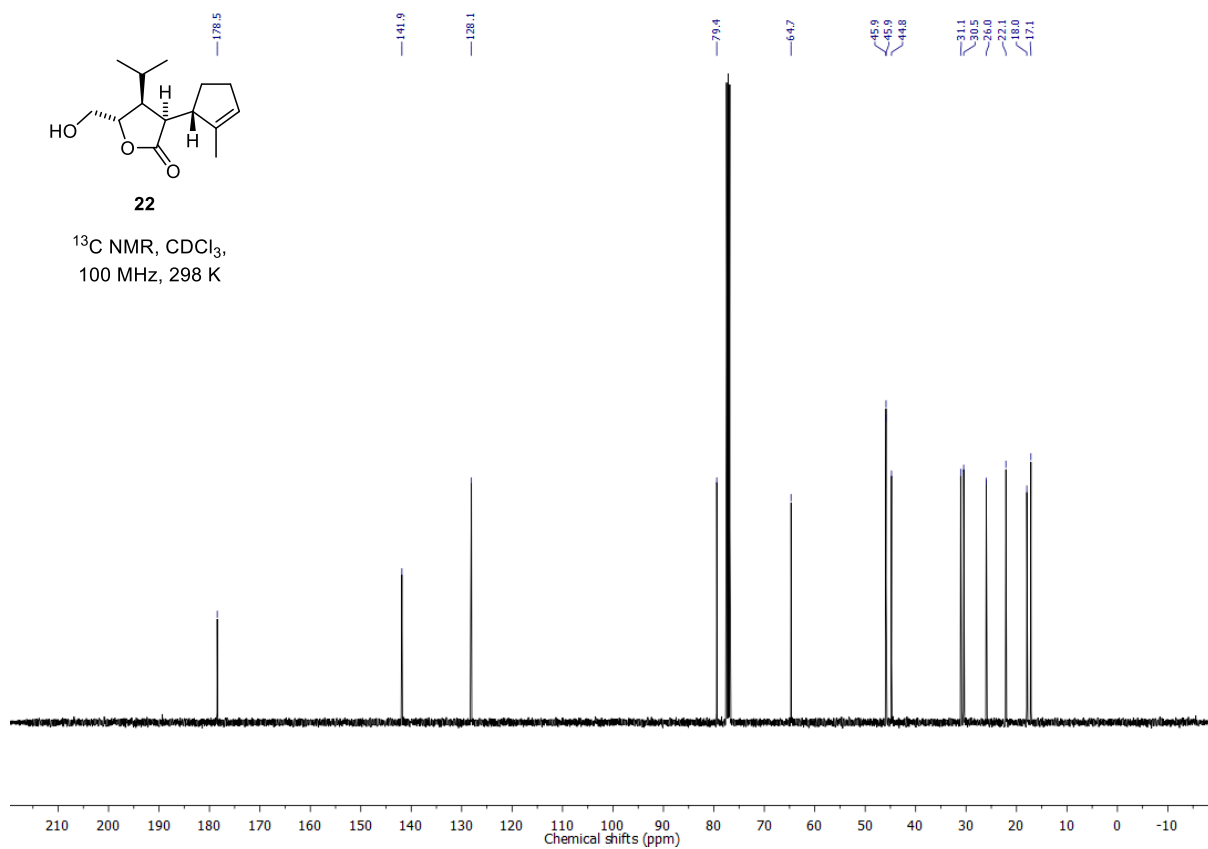


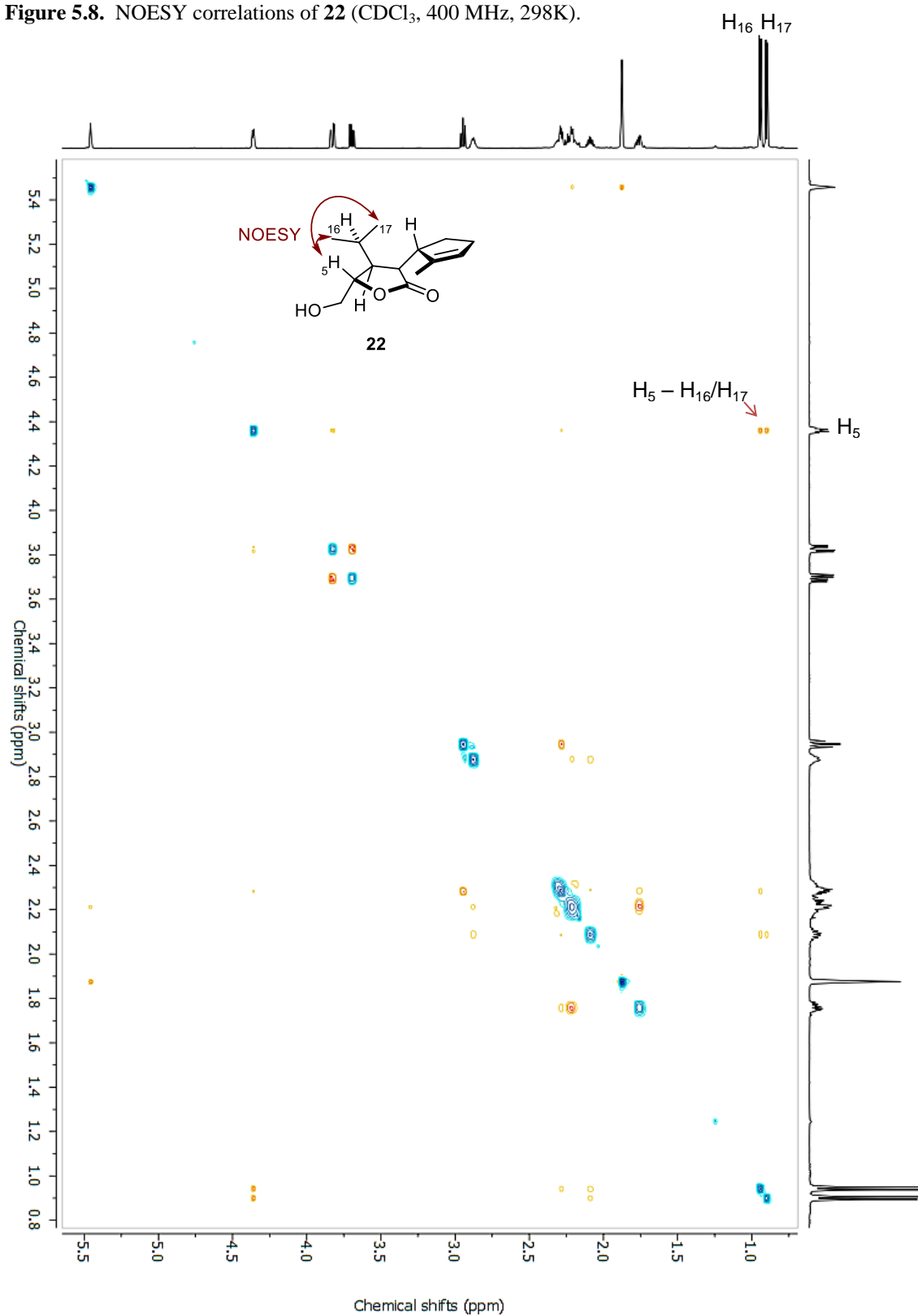
**22**

$^1\text{H}$  NMR,  $\text{CDCl}_3$ ,  
400 MHz, 298 K

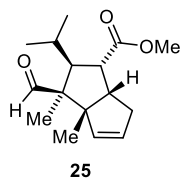
**22**

$^{13}\text{C}$  NMR,  $\text{CDCl}_3$ ,  
100 MHz, 298 K

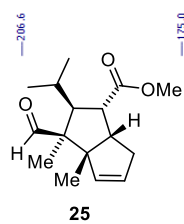
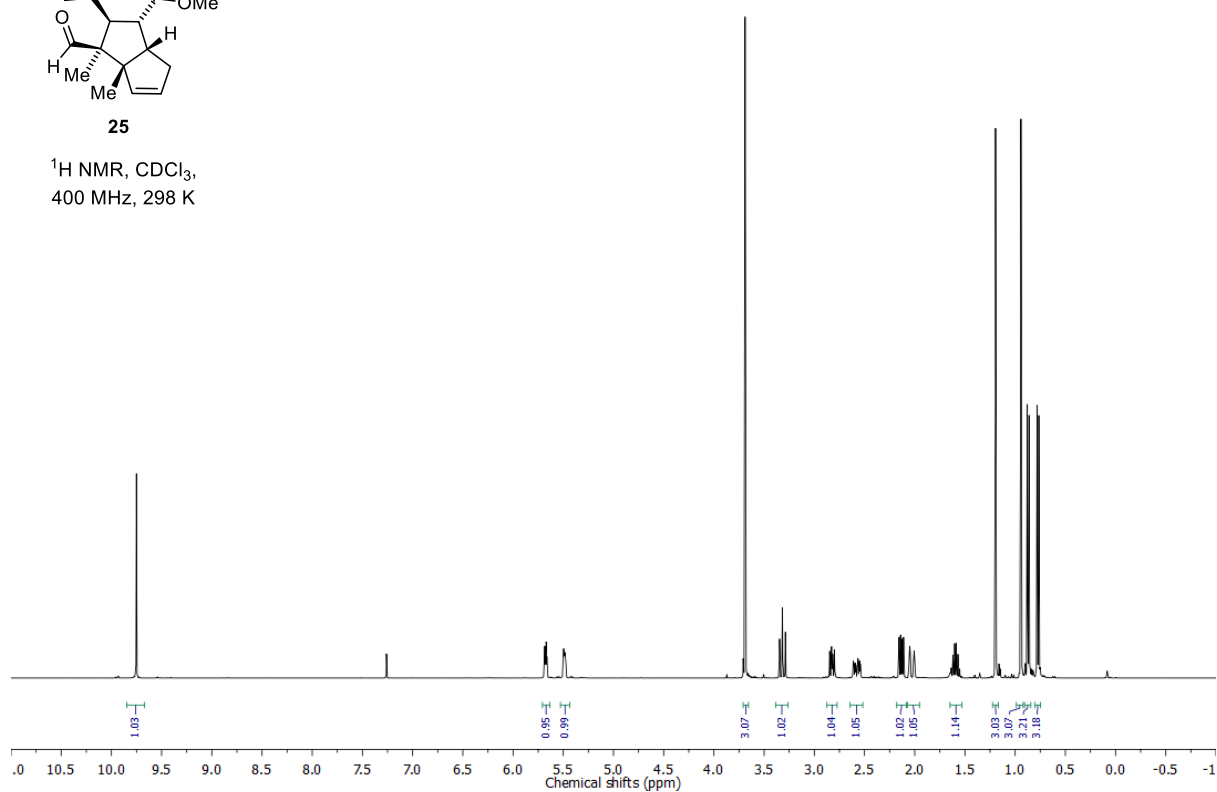


**Figure 5.8.** NOESY correlations of **22** (CDCl<sub>3</sub>, 400 MHz, 298K).

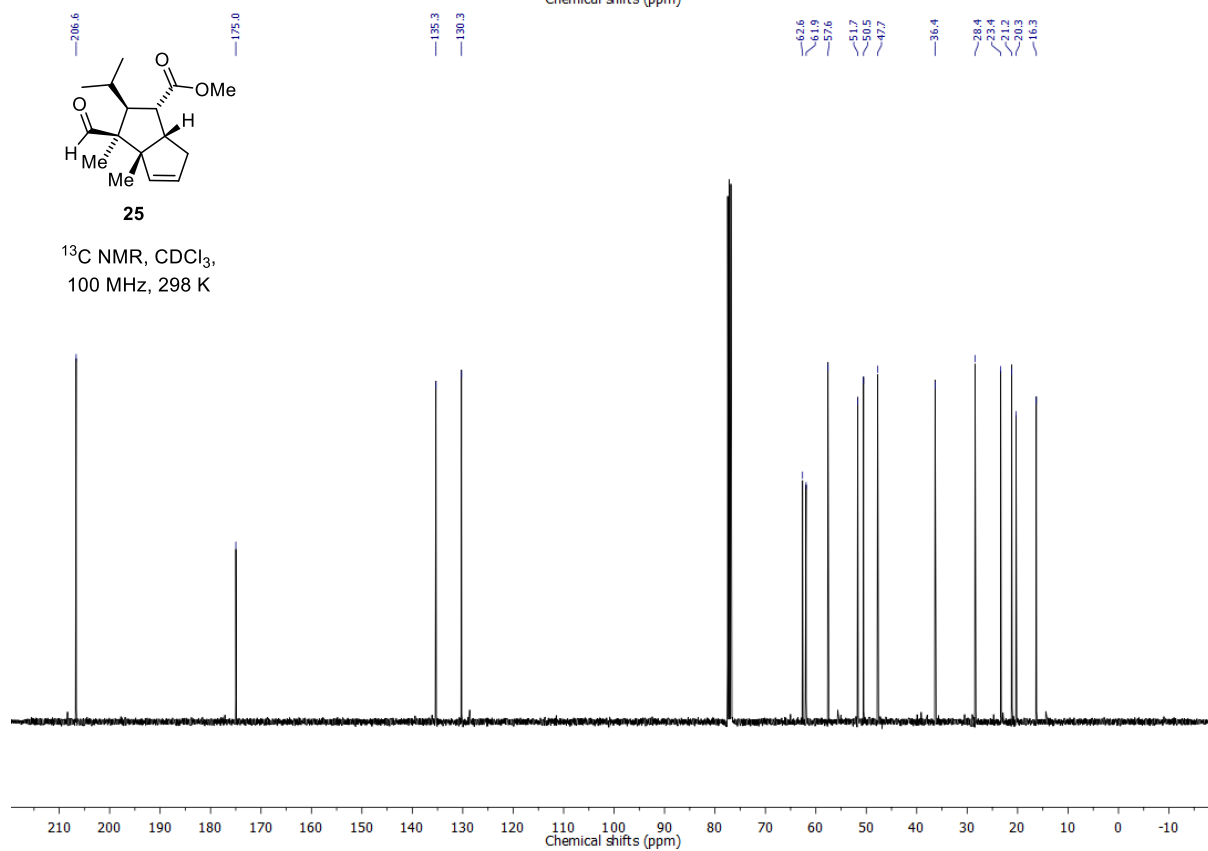


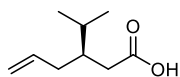


$^1\text{H}$  NMR,  $\text{CDCl}_3$ ,  
400 MHz, 298 K



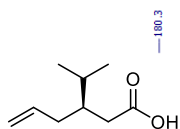
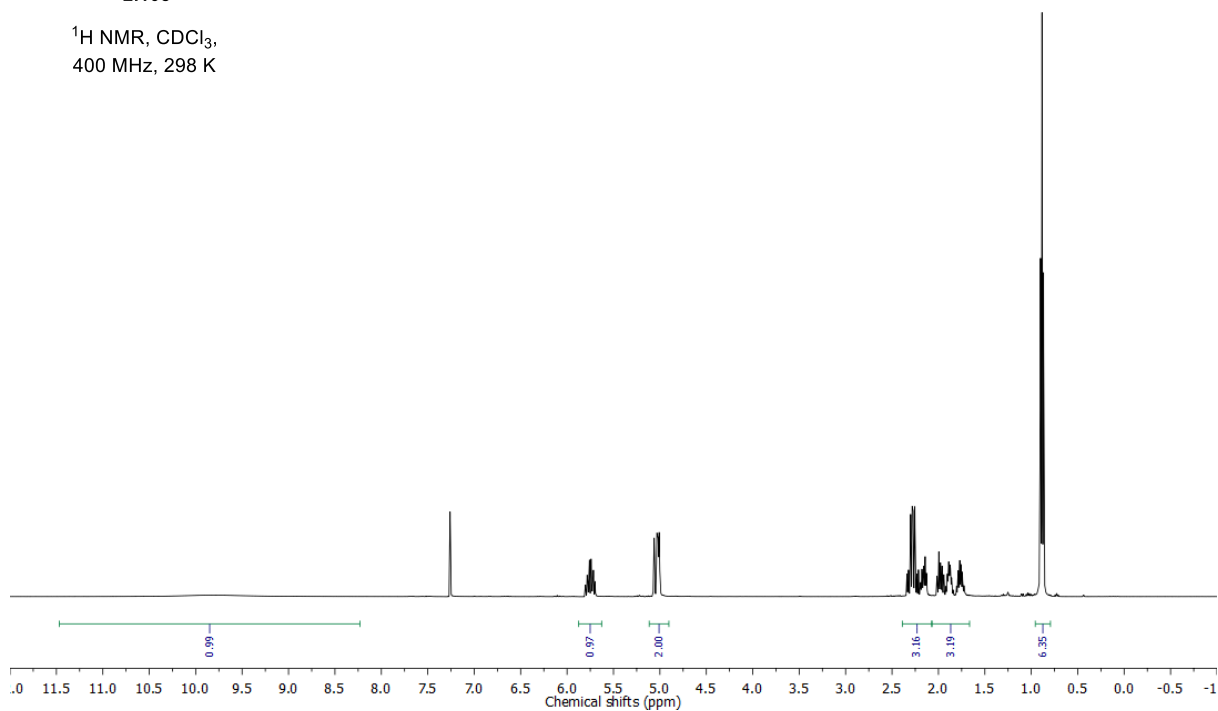
$^{13}\text{C}$  NMR,  $\text{CDCl}_3$ ,  
100 MHz, 298 K





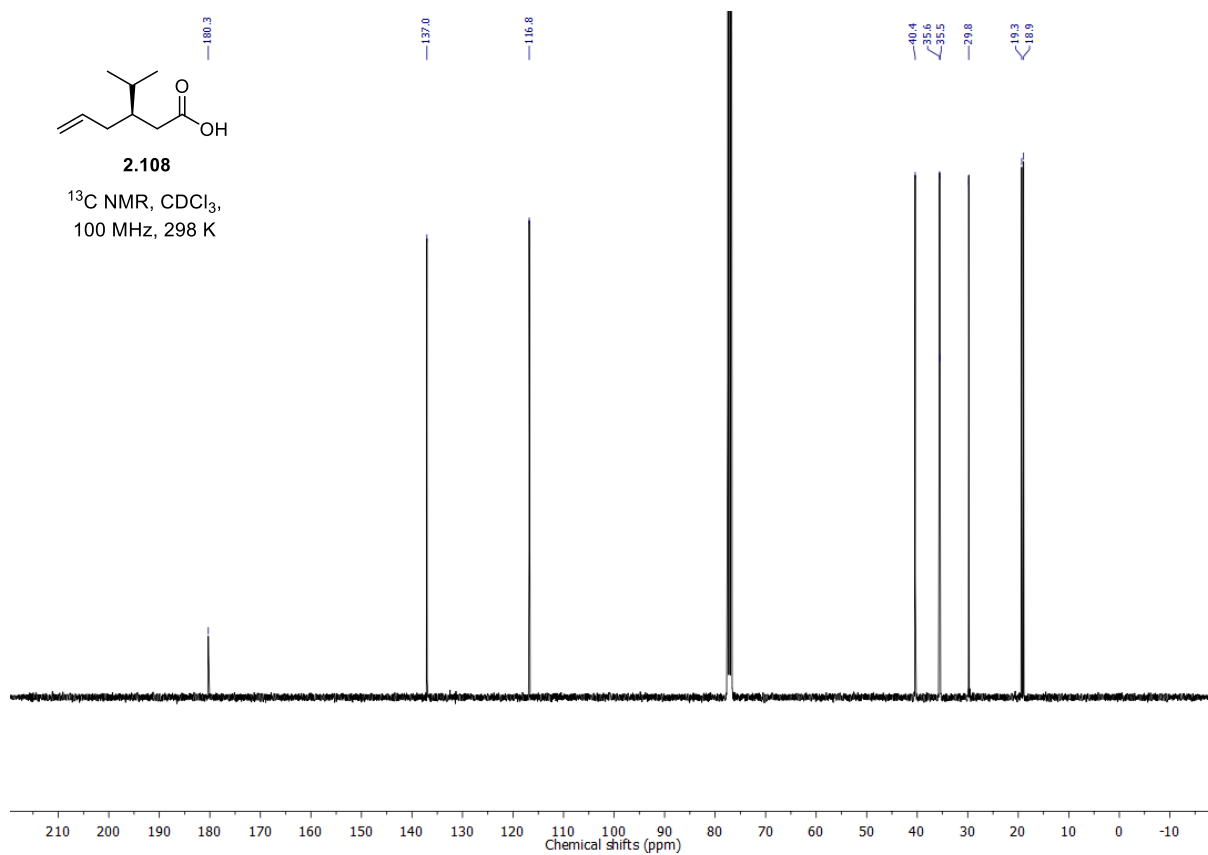
2.108

$^1\text{H}$  NMR,  $\text{CDCl}_3$ ,  
400 MHz, 298 K

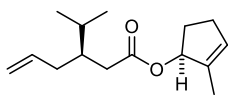


2.108

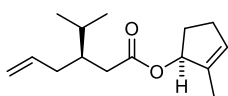
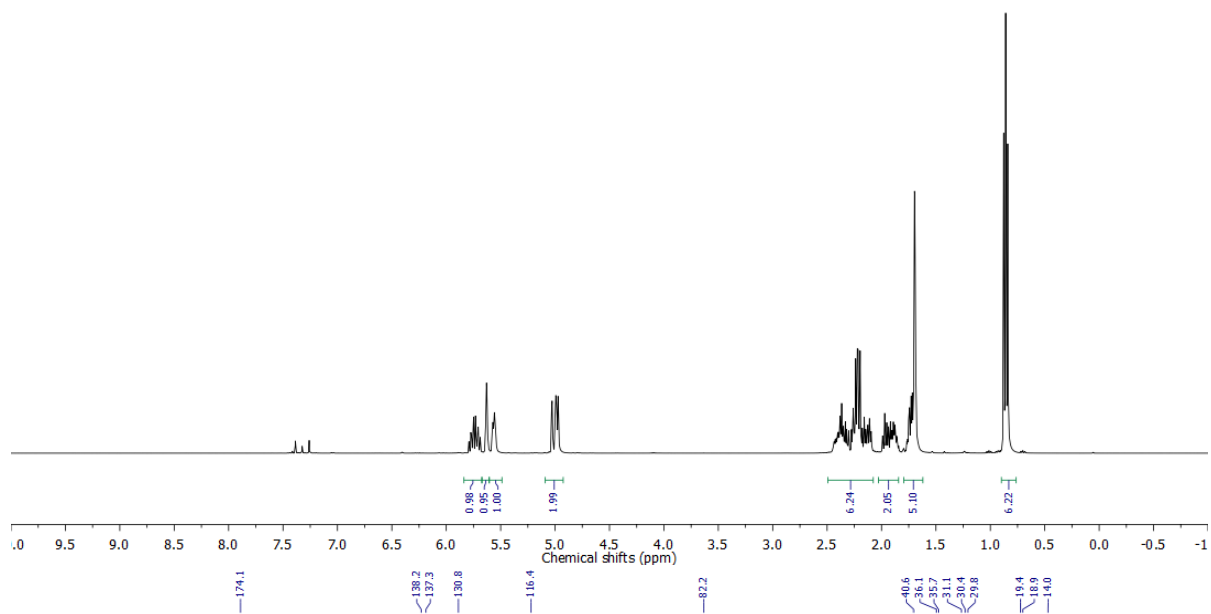
$^{13}\text{C}$  NMR,  $\text{CDCl}_3$ ,  
100 MHz, 298 K



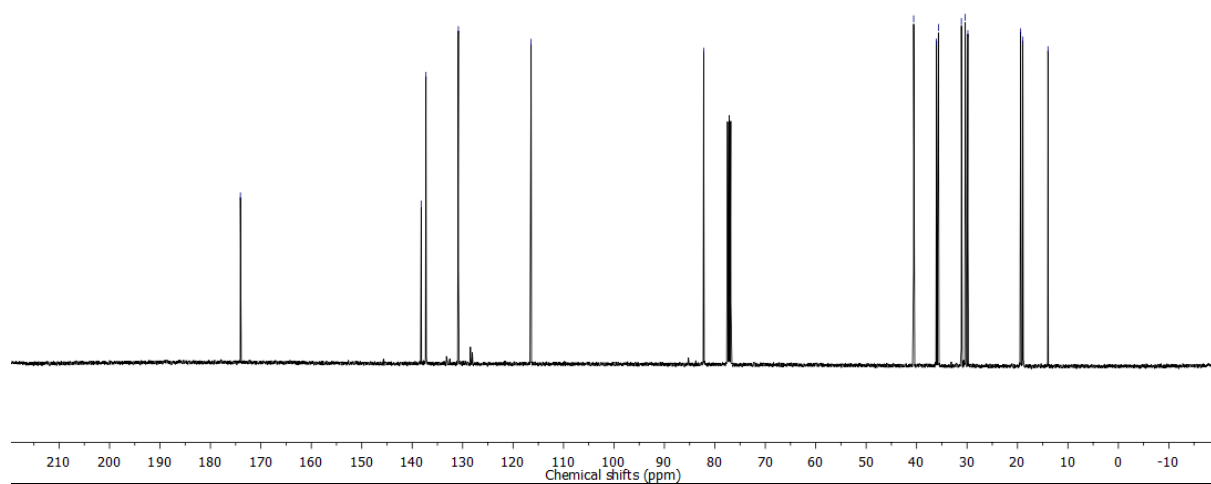


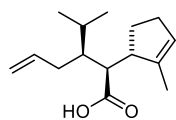
**2.109**

$^1\text{H}$  NMR,  $\text{CDCl}_3$ ,  
400 MHz, 298 K

**2.109**

$^{13}\text{C}$  NMR,  $\text{CDCl}_3$ ,  
100 MHz, 298 K

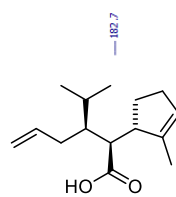
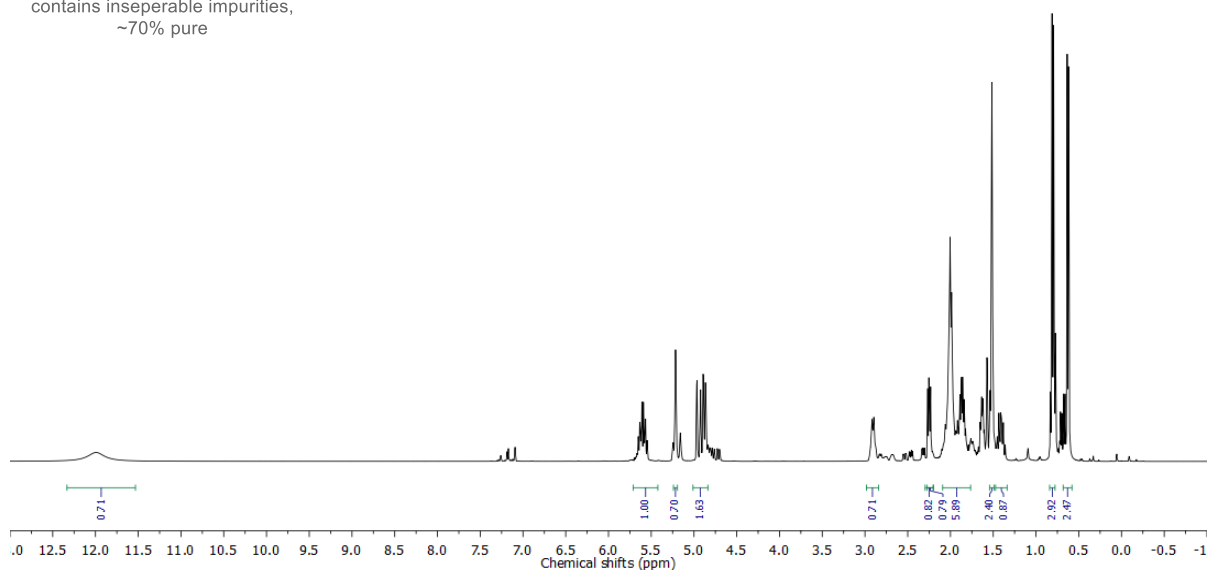




**2.107**

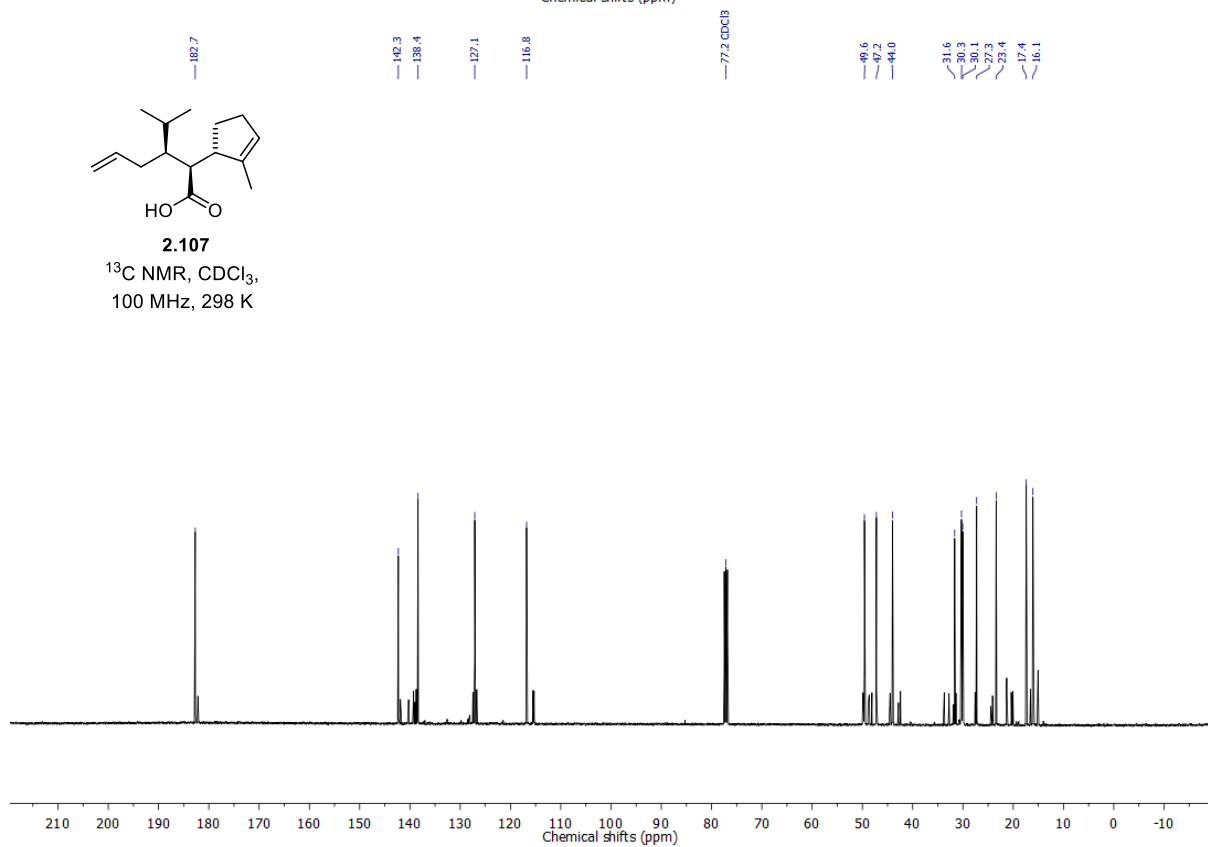
$^1\text{H NMR}$ ,  $\text{CDCl}_3$ ,  
400 MHz, 298 K

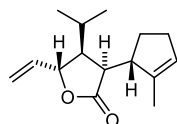
contains inseparable impurities,  
~70% pure



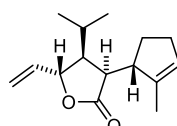
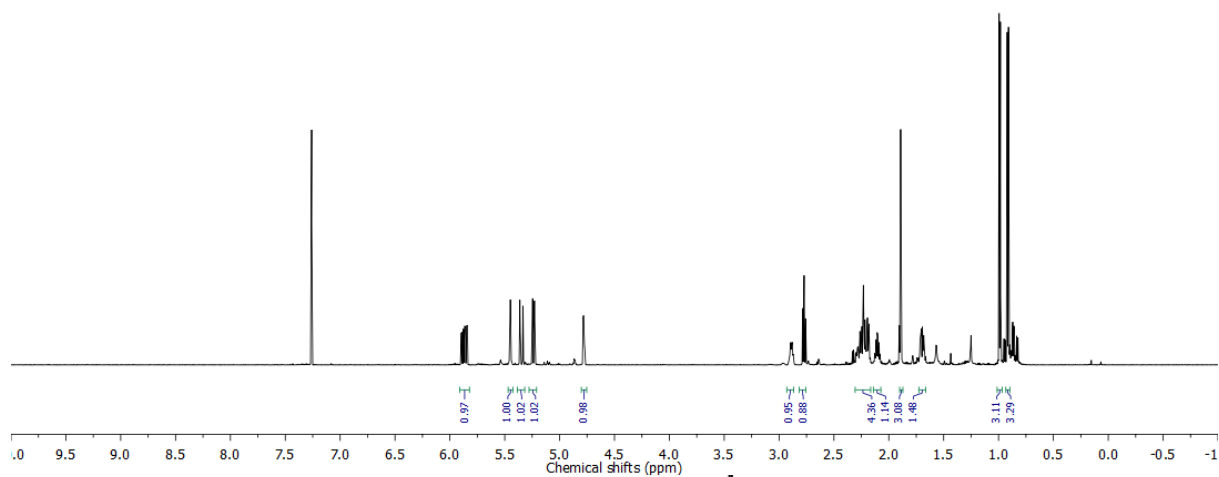
**2.107**

$^{13}\text{C NMR}$ ,  $\text{CDCl}_3$ ,  
100 MHz, 298 K

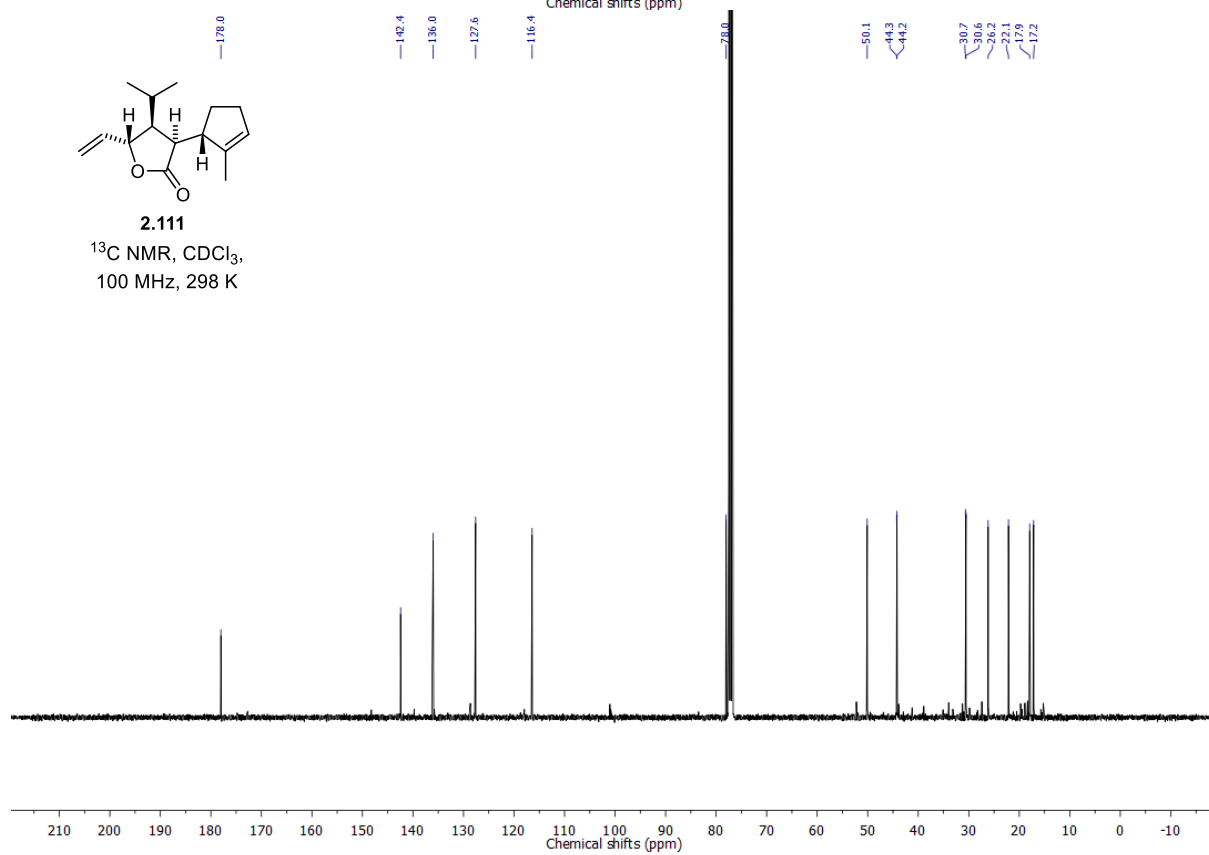


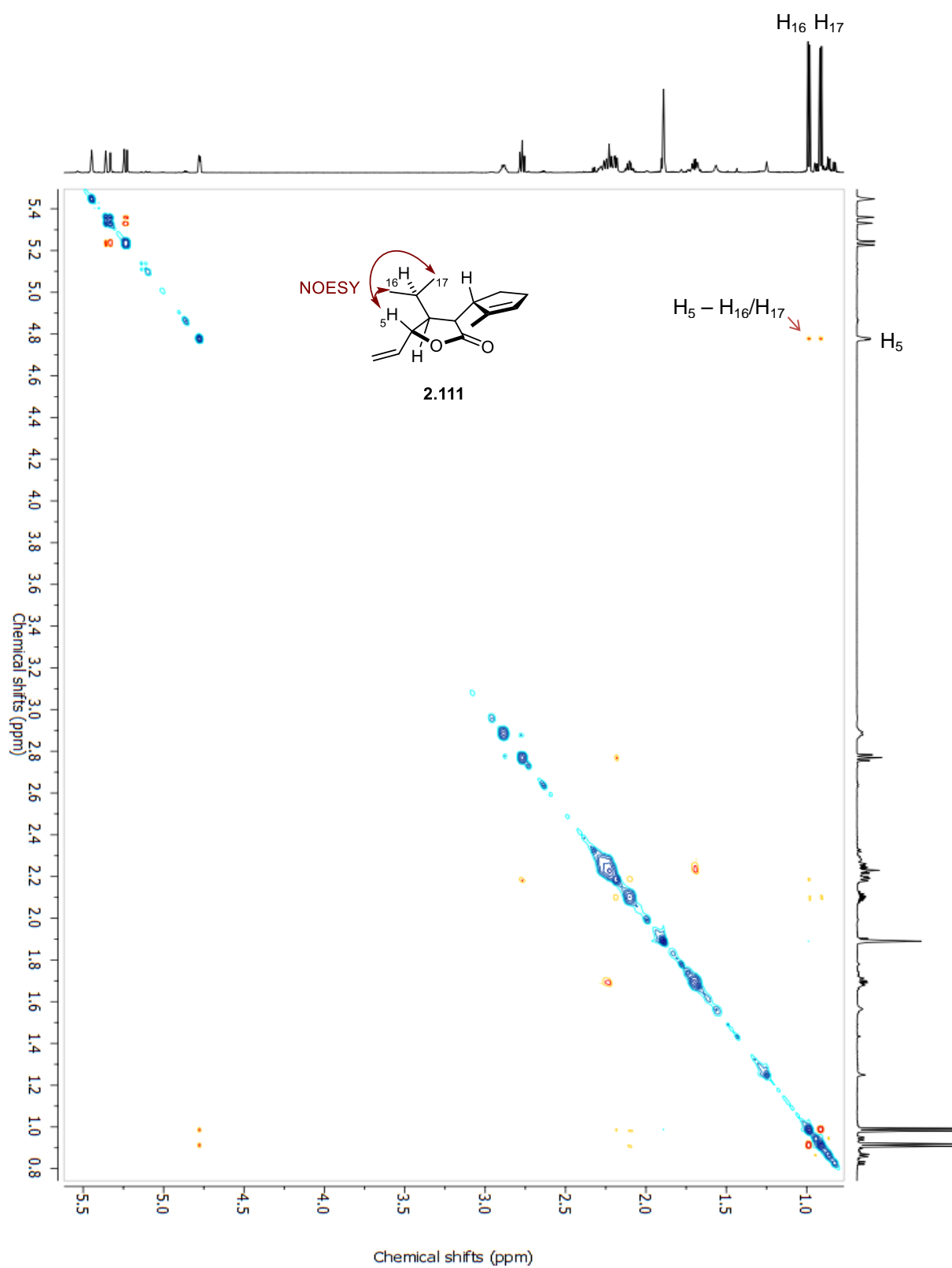
**2.111**

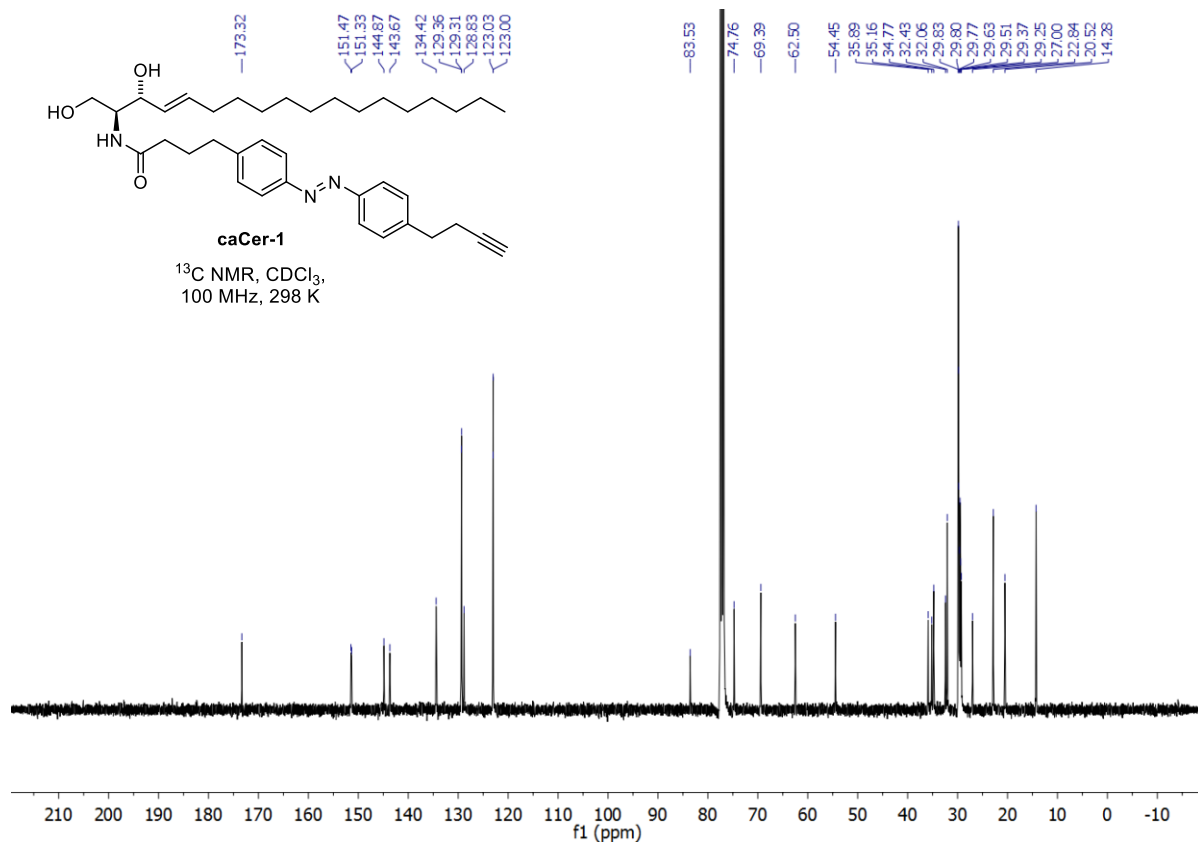
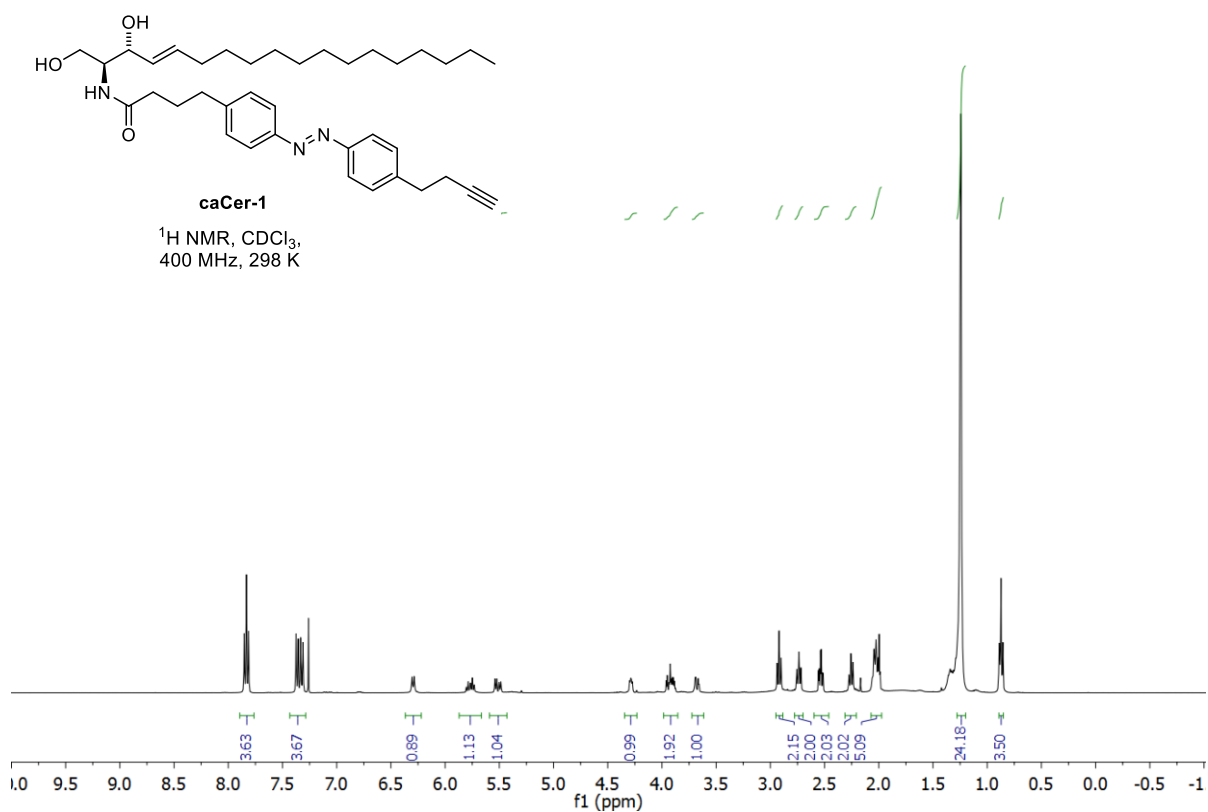
$^1\text{H}$  NMR,  $\text{CDCl}_3$ ,  
400 MHz, 298 K

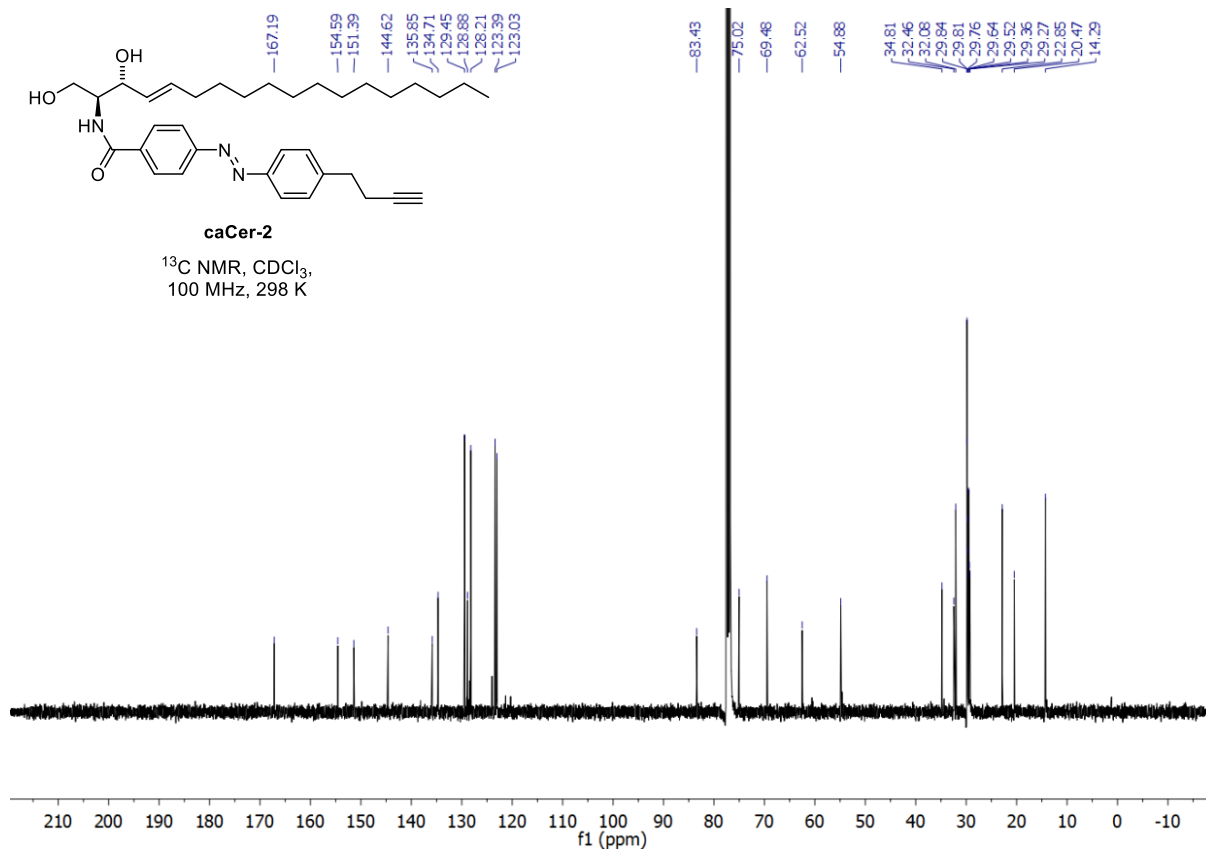
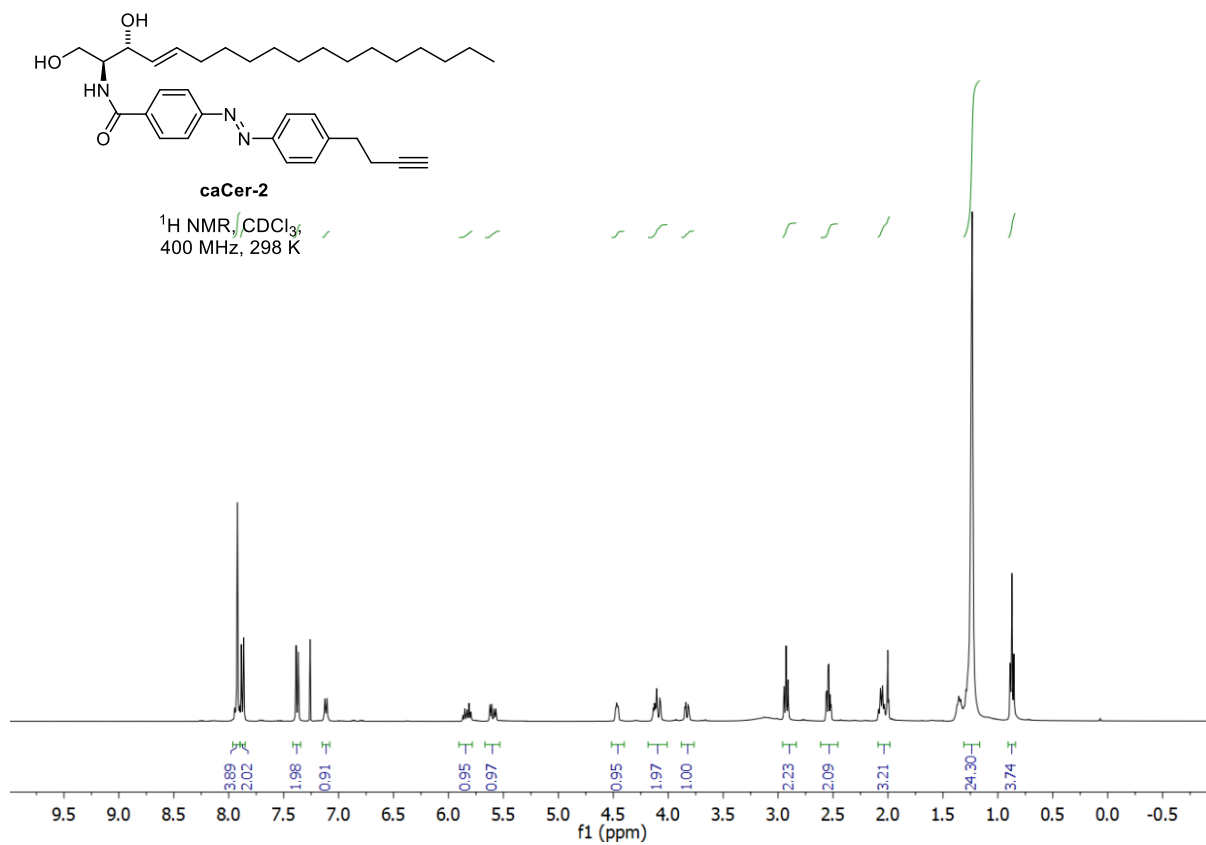
**2.111**

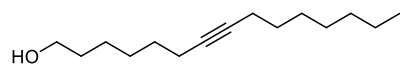
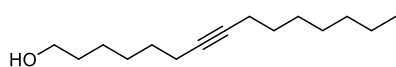
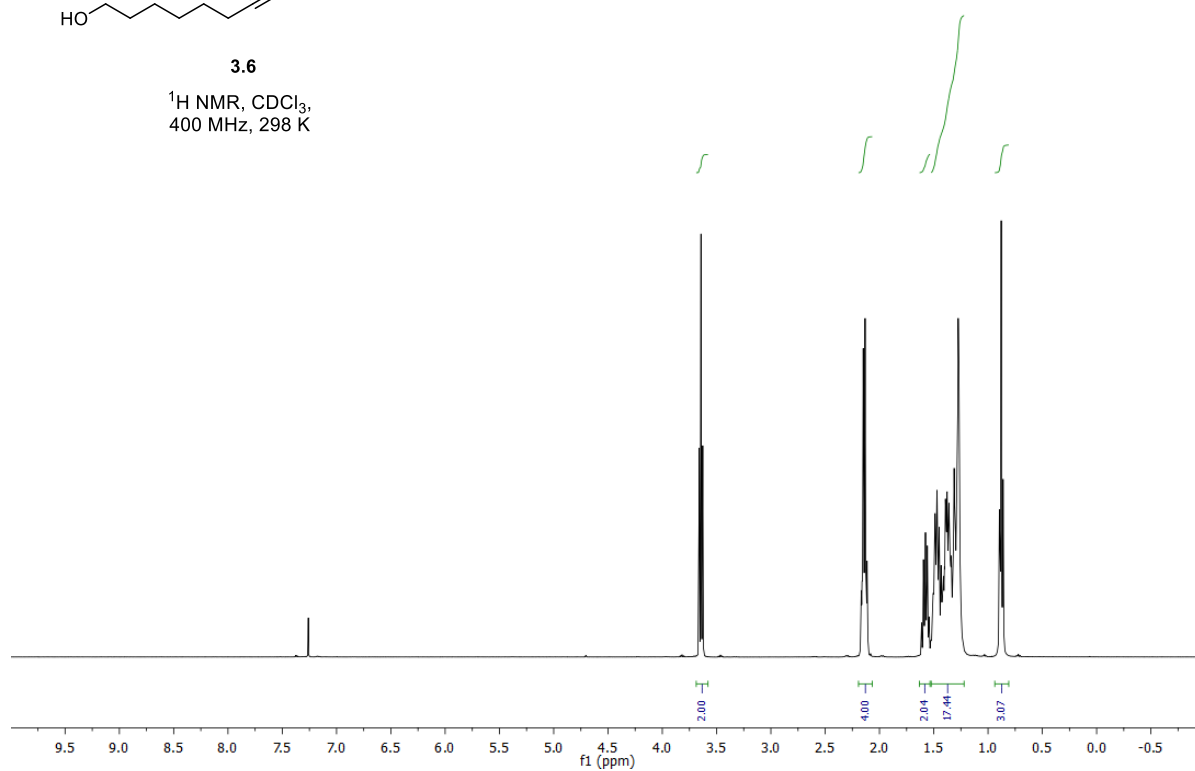
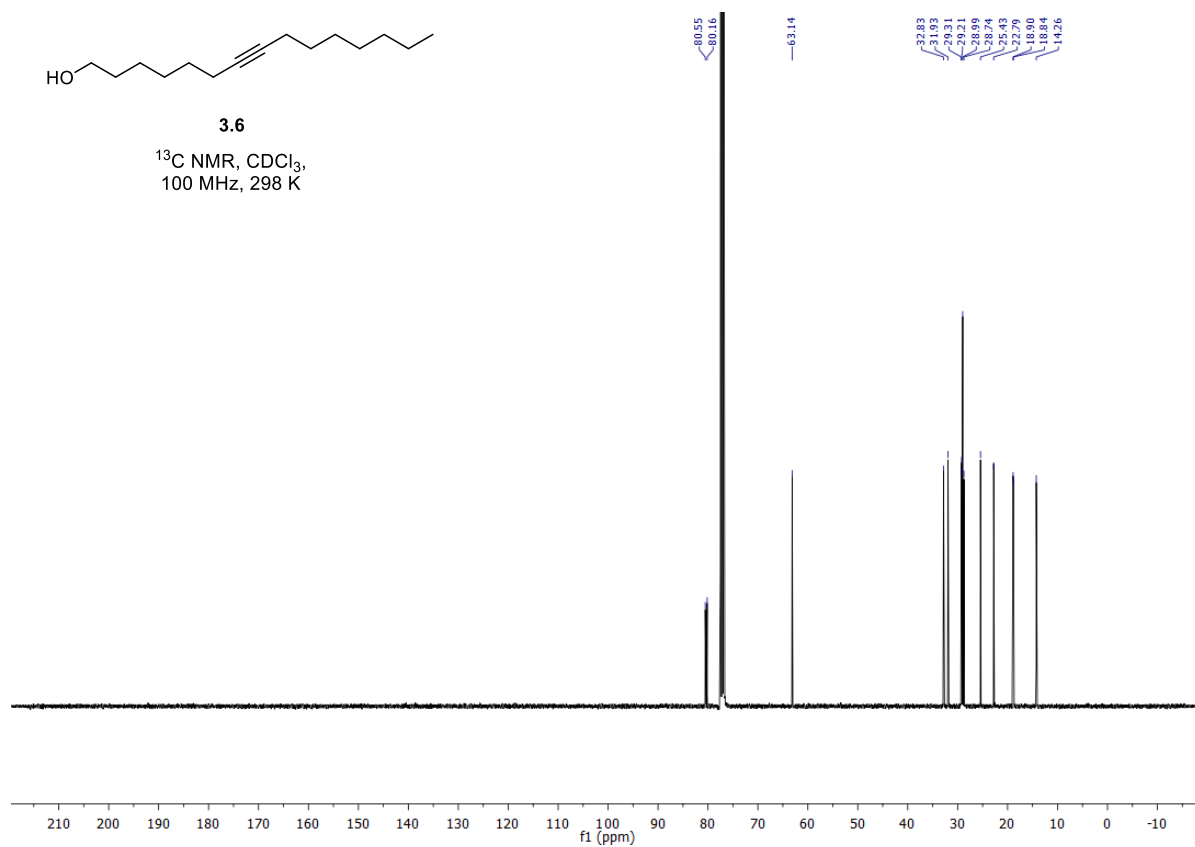
$^{13}\text{C}$  NMR,  $\text{CDCl}_3$ ,  
100 MHz, 298 K

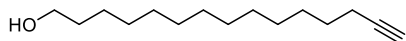


**Figure 5.9.** NOESY correlations of **2.111** (CDCl<sub>3</sub>, 400 MHz, 298K).

4.1.3.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR Spectra for Chapter III

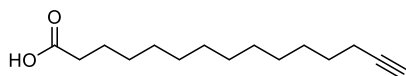
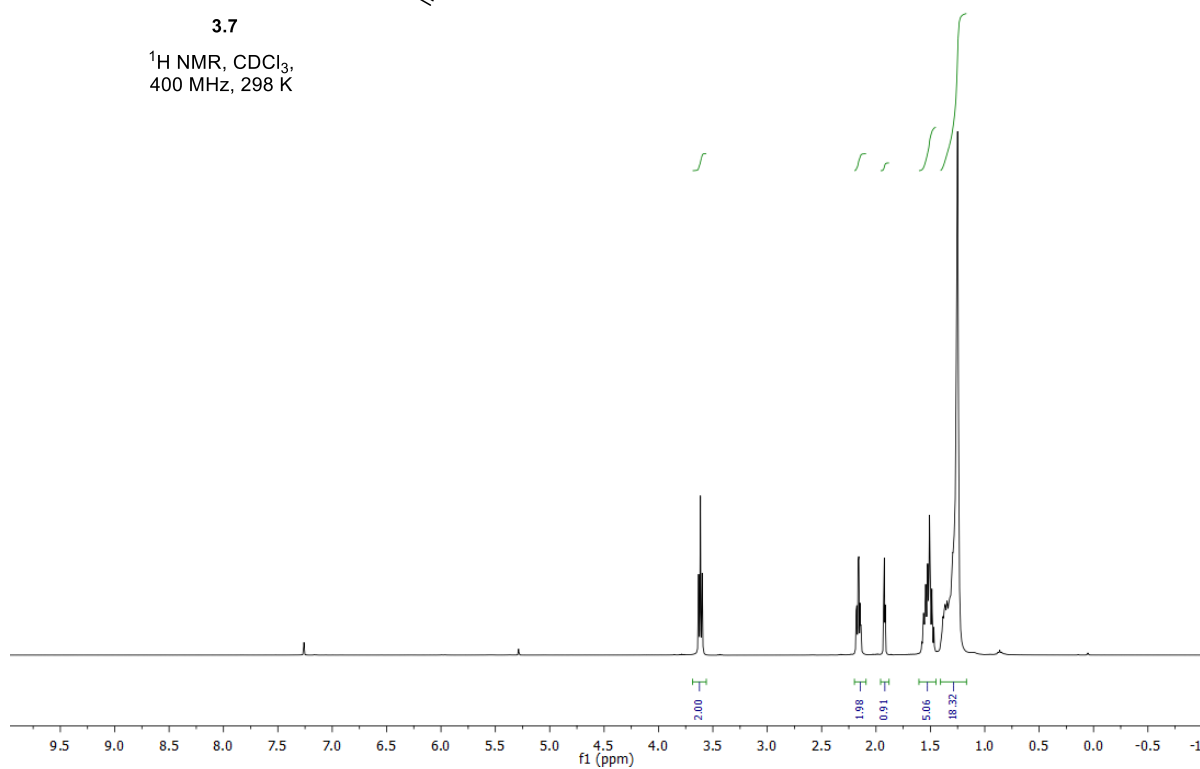


**3.6**<sup>1</sup>H NMR, CDCl<sub>3</sub>,  
400 MHz, 298 K**3.6**<sup>13</sup>C NMR, CDCl<sub>3</sub>,  
100 MHz, 298 K



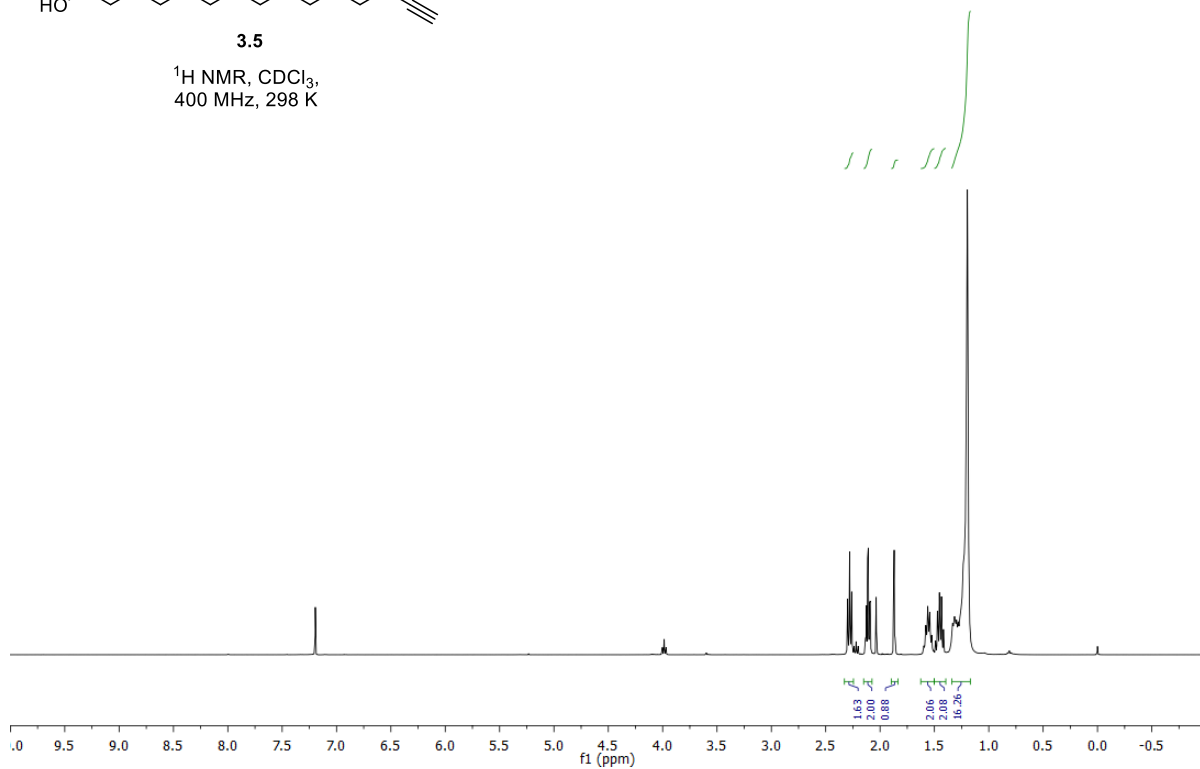
3.7

$^1\text{H}$  NMR,  $\text{CDCl}_3$ ,  
400 MHz, 298 K

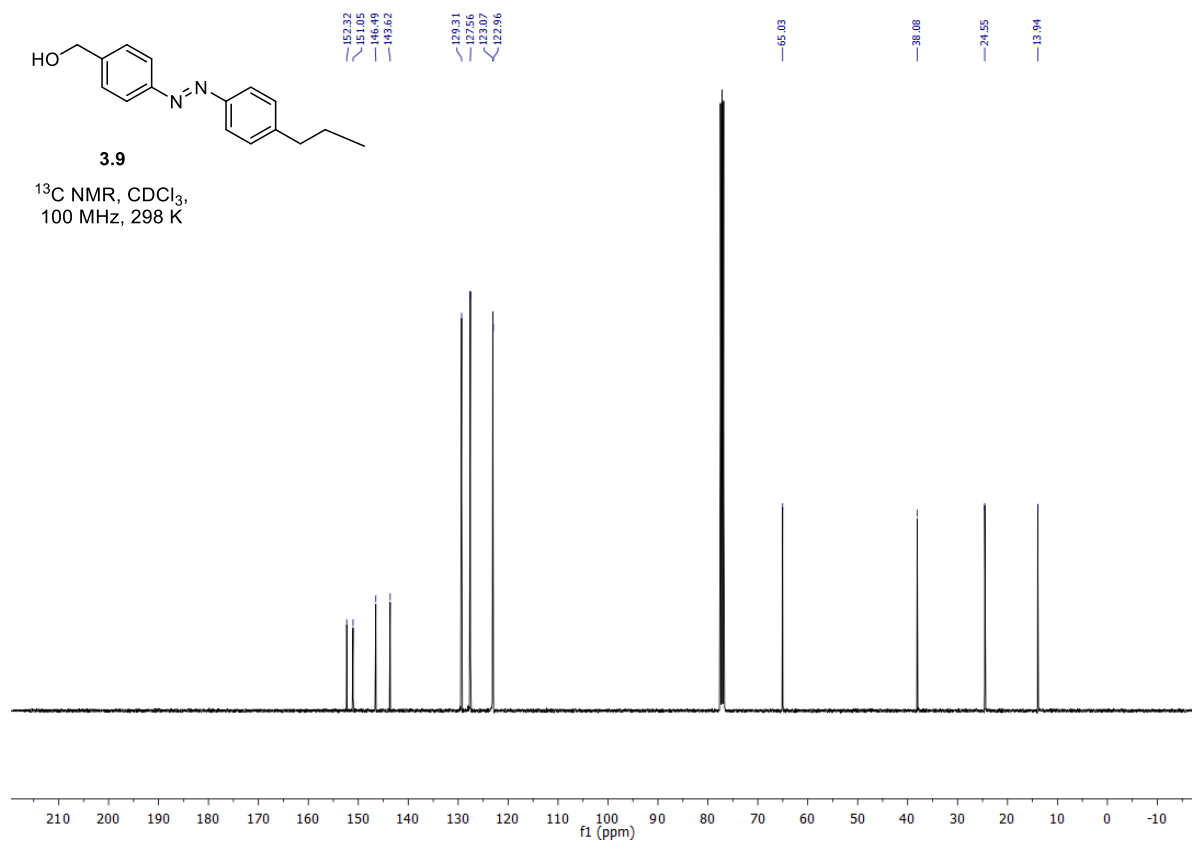
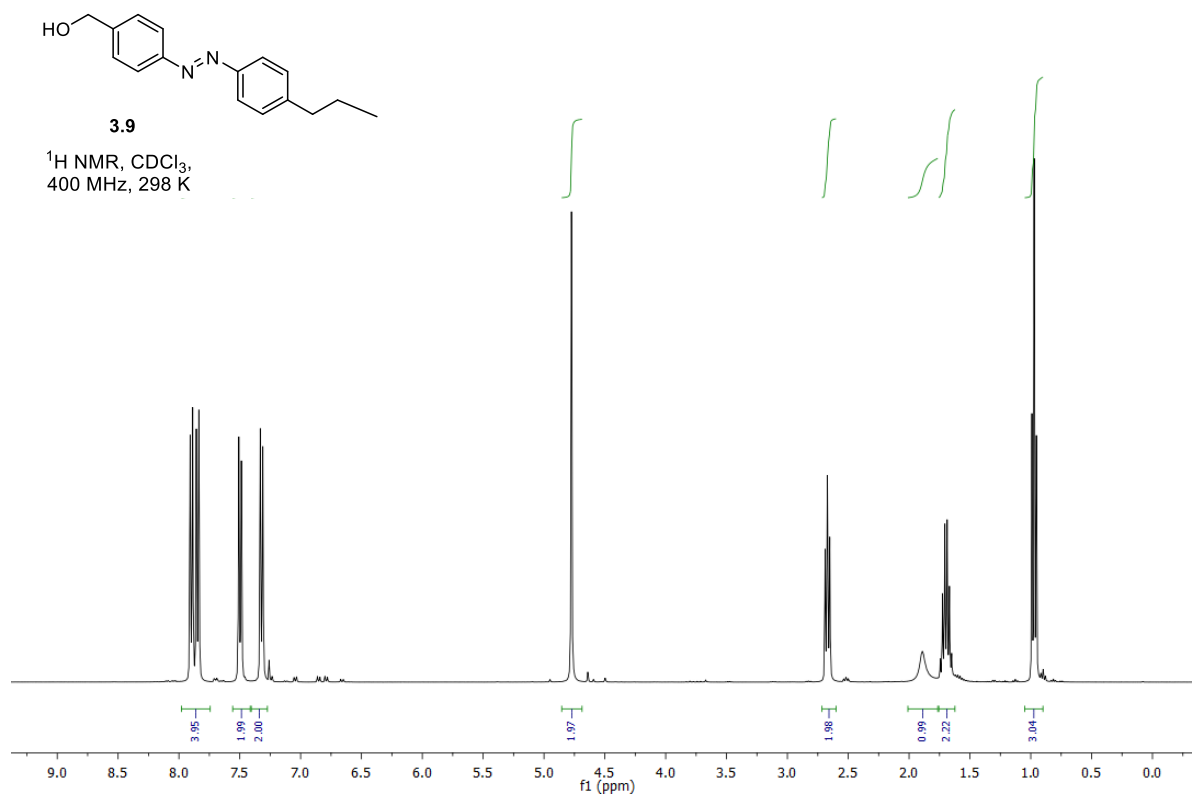


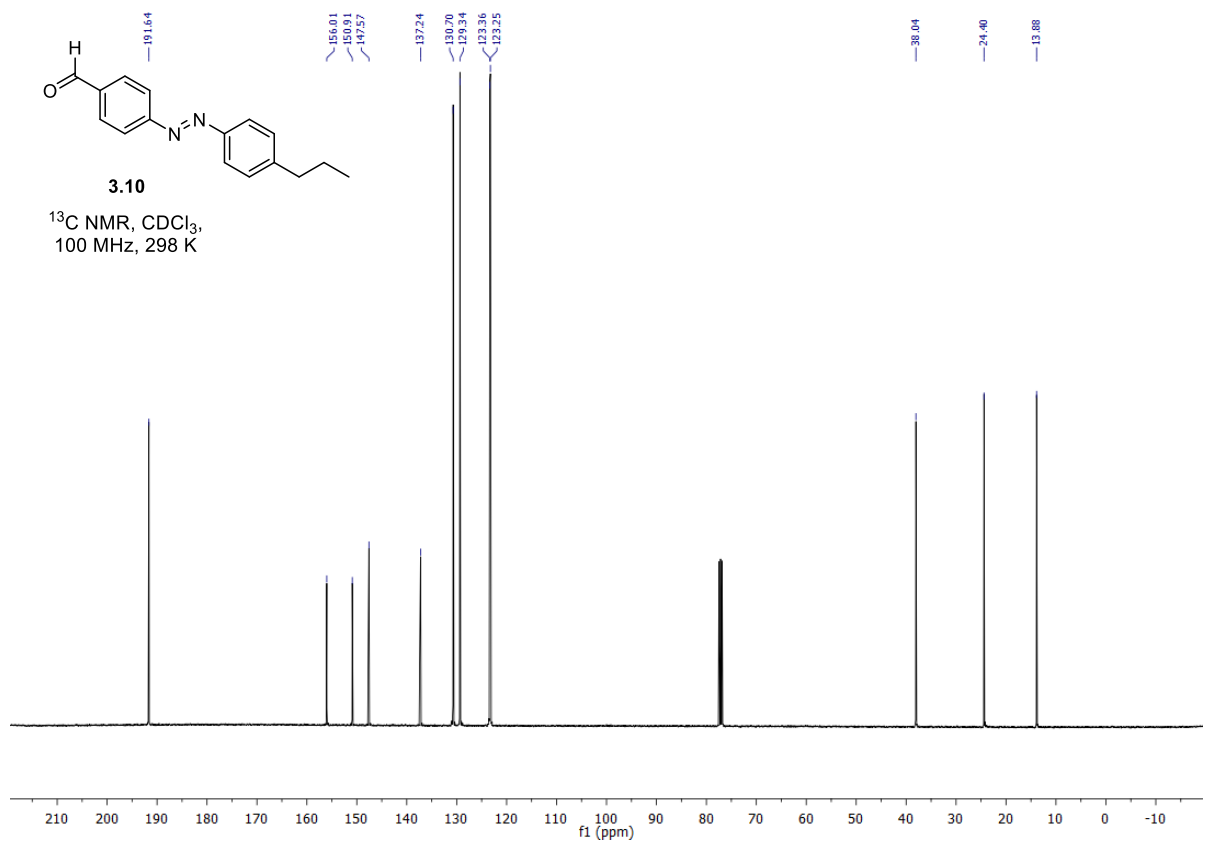
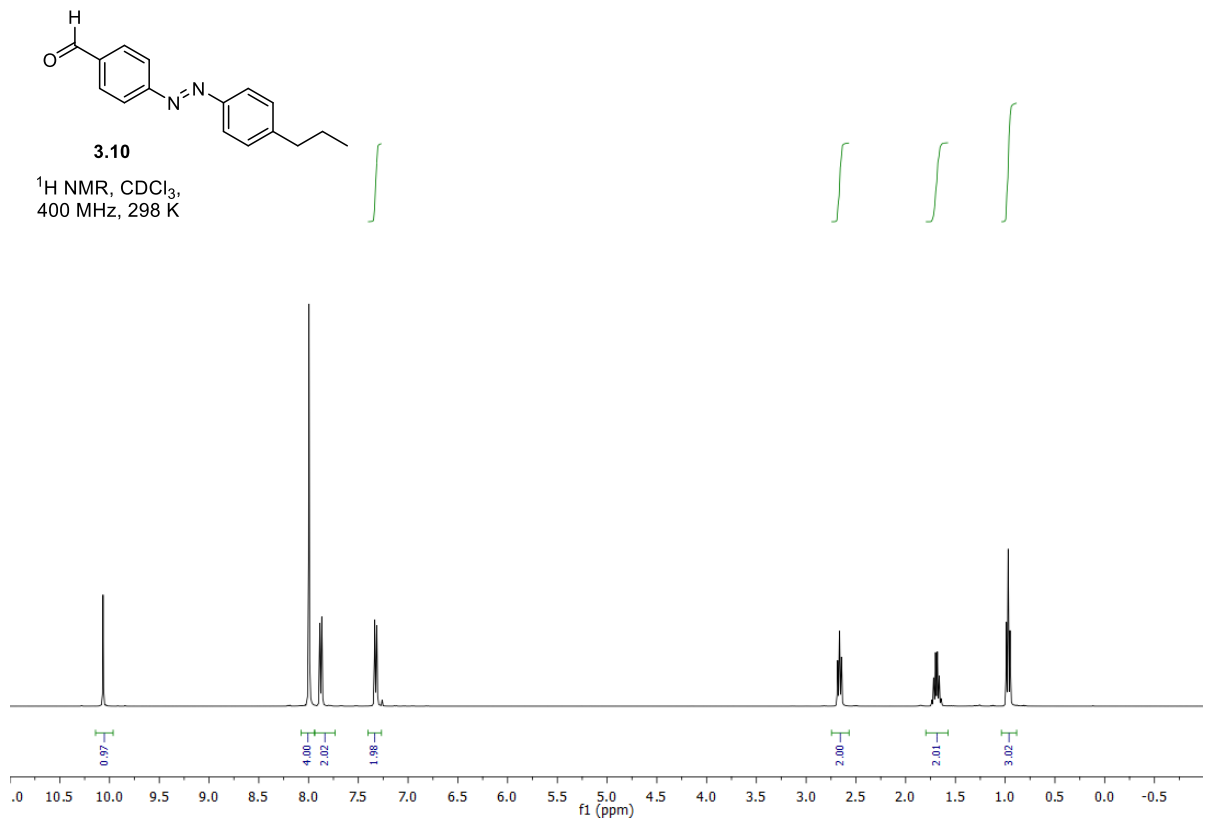
3.5

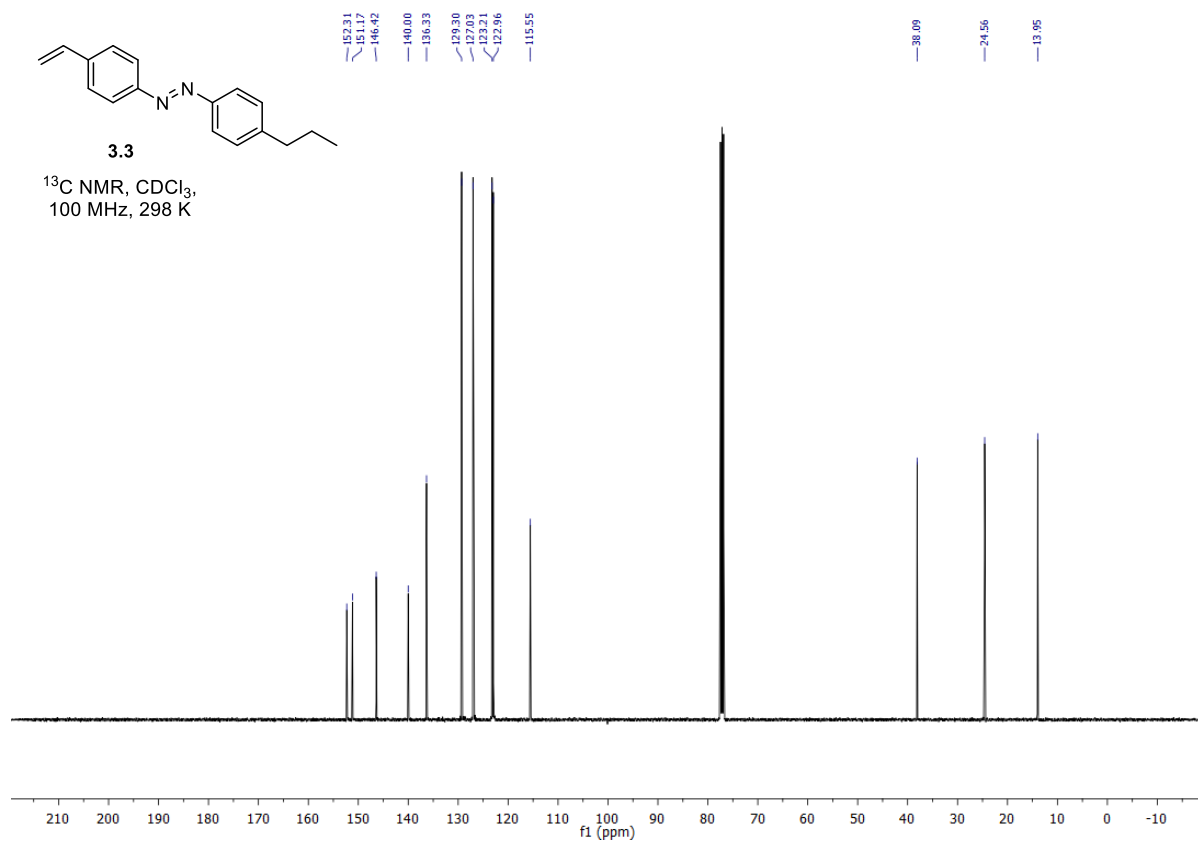
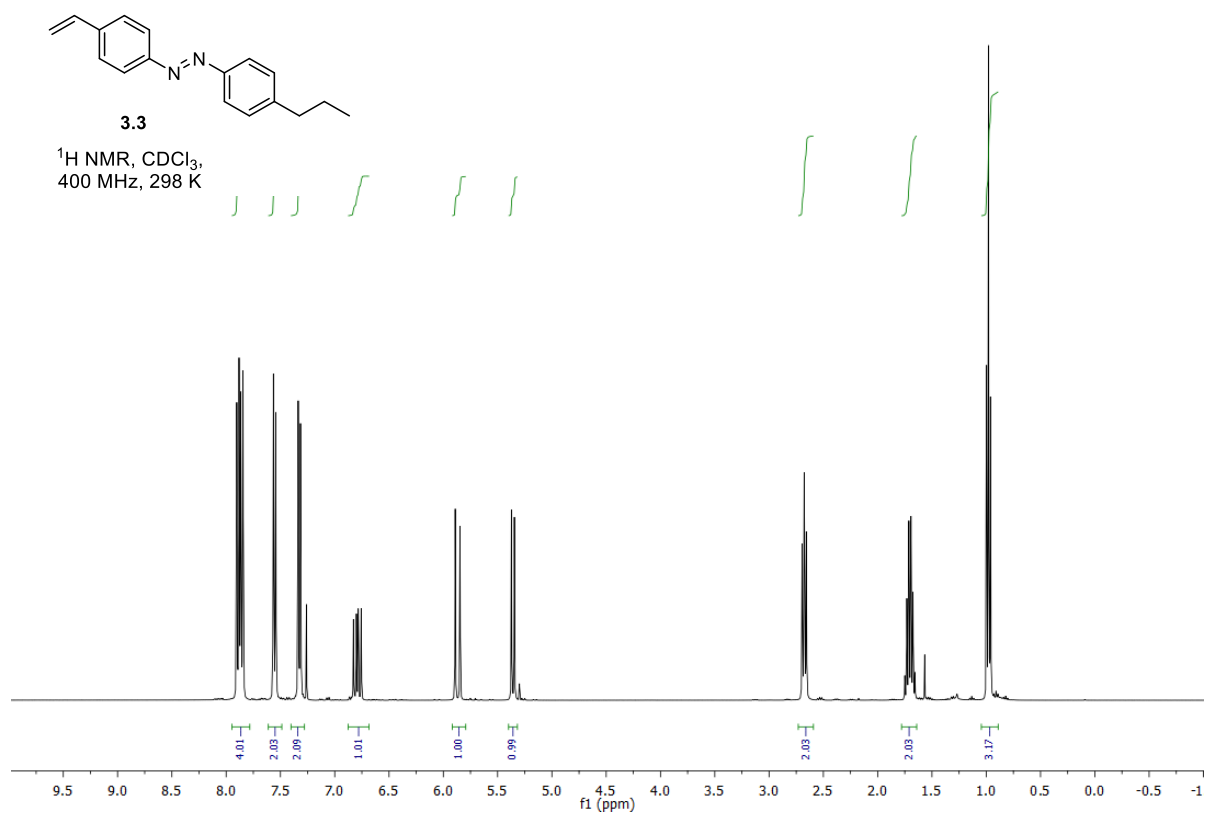
$^1\text{H}$  NMR,  $\text{CDCl}_3$ ,  
400 MHz, 298 K

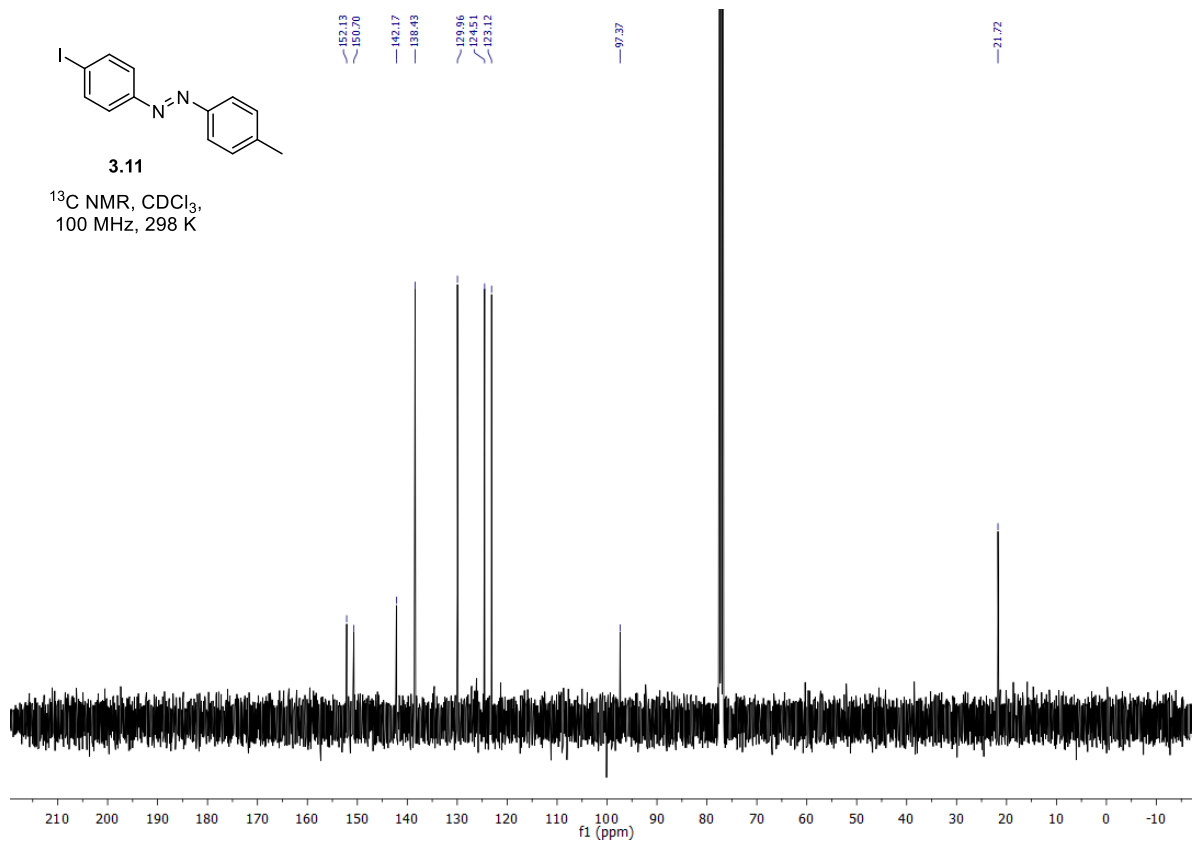
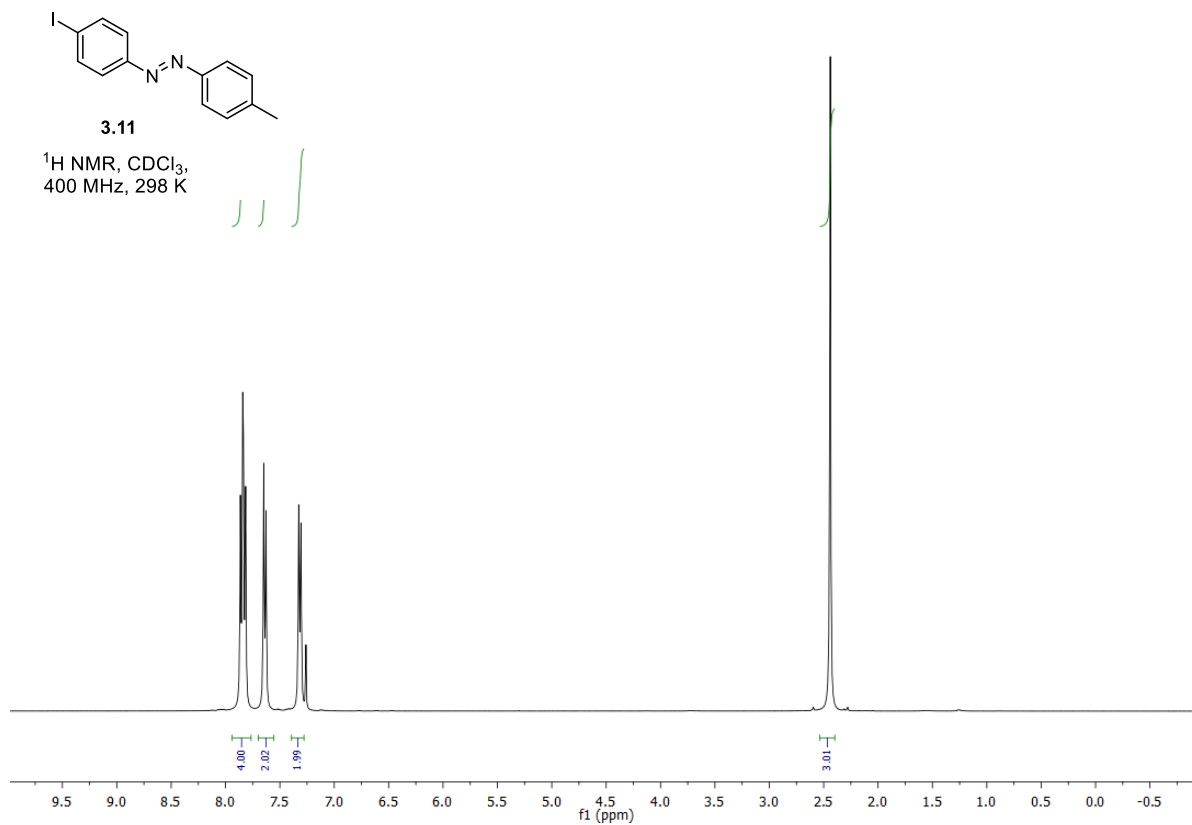


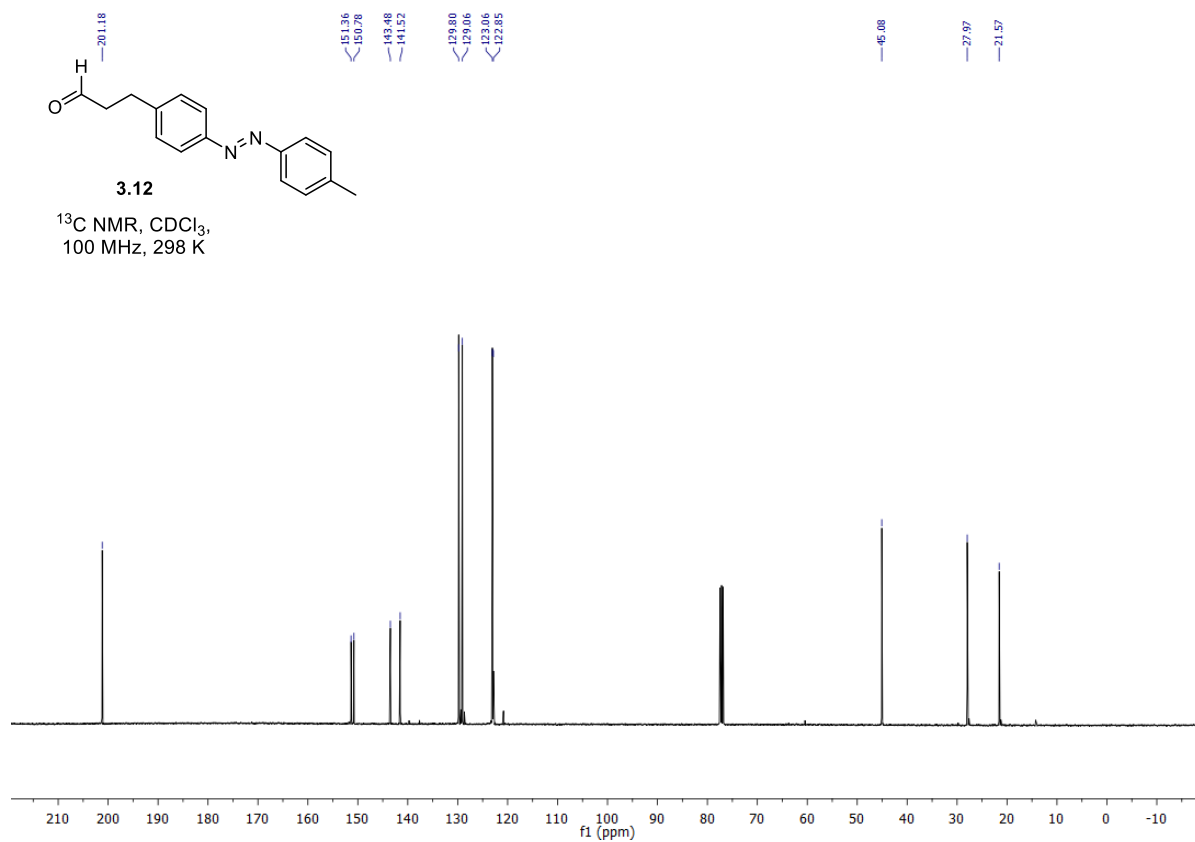
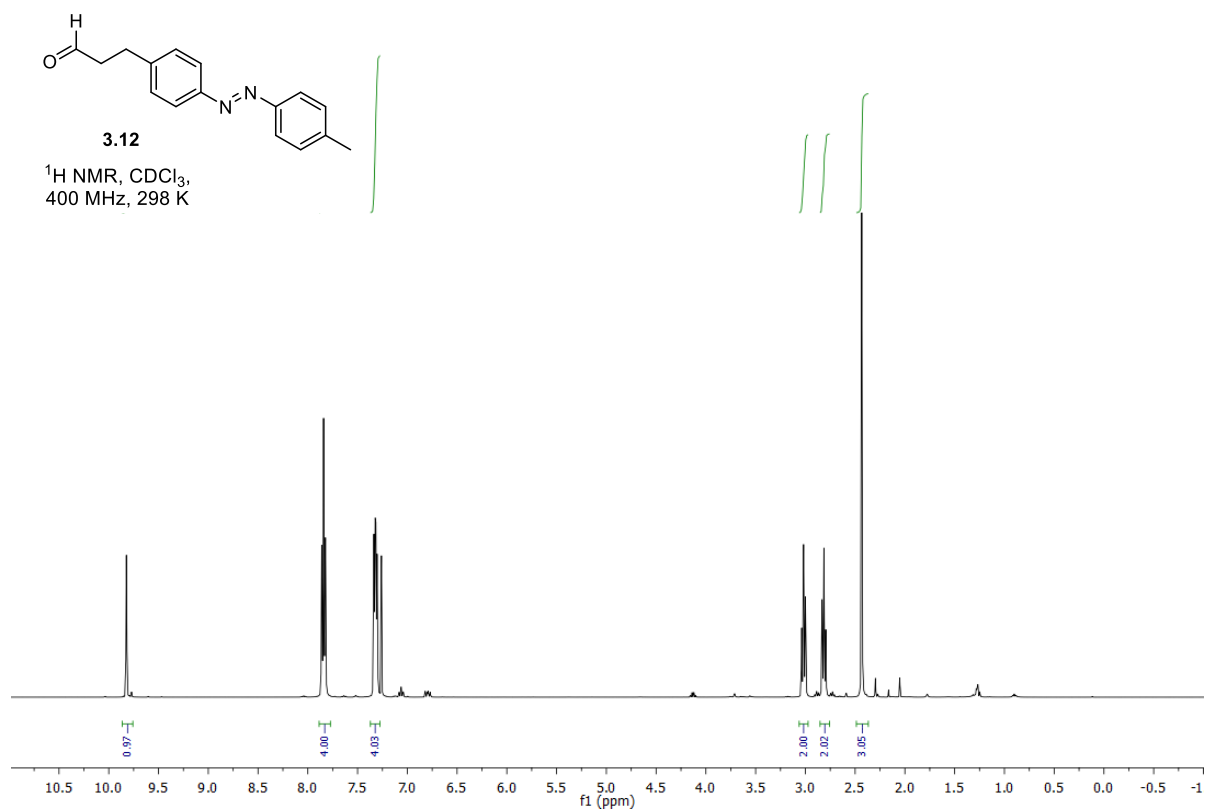


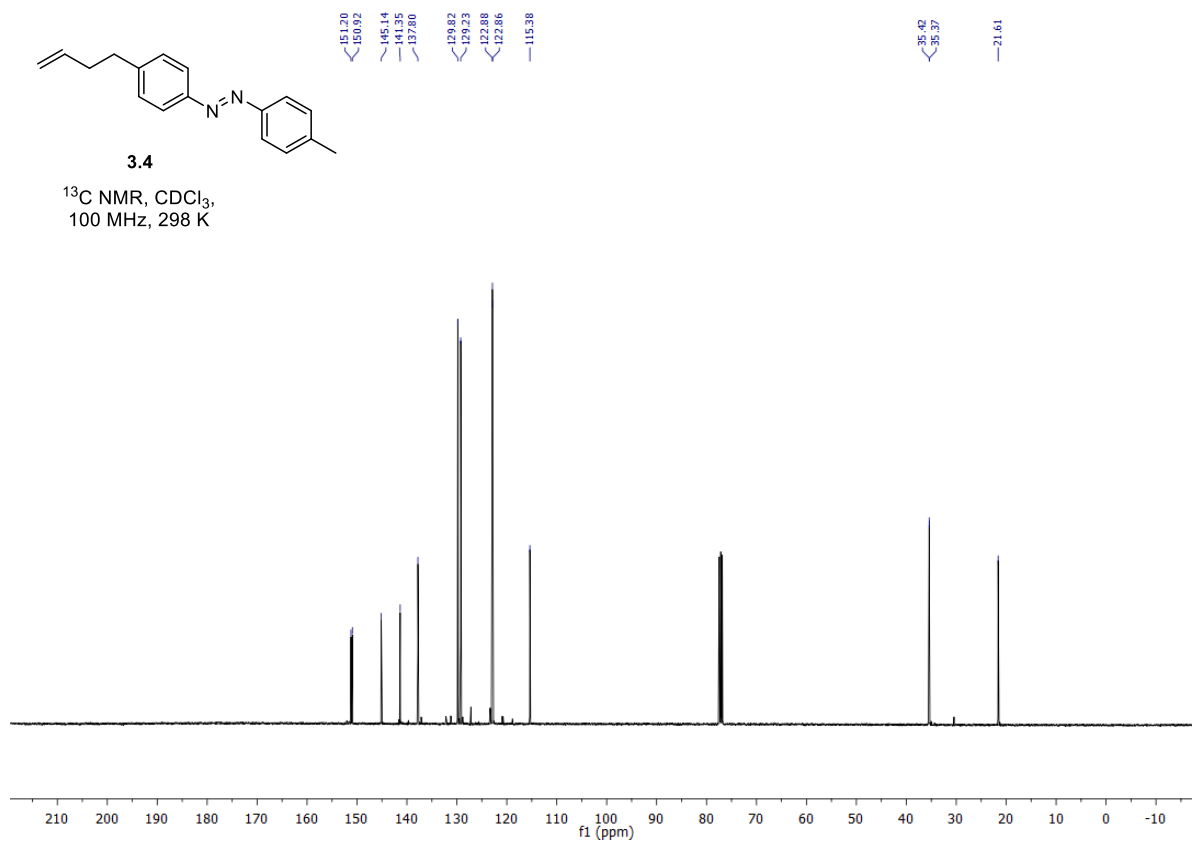
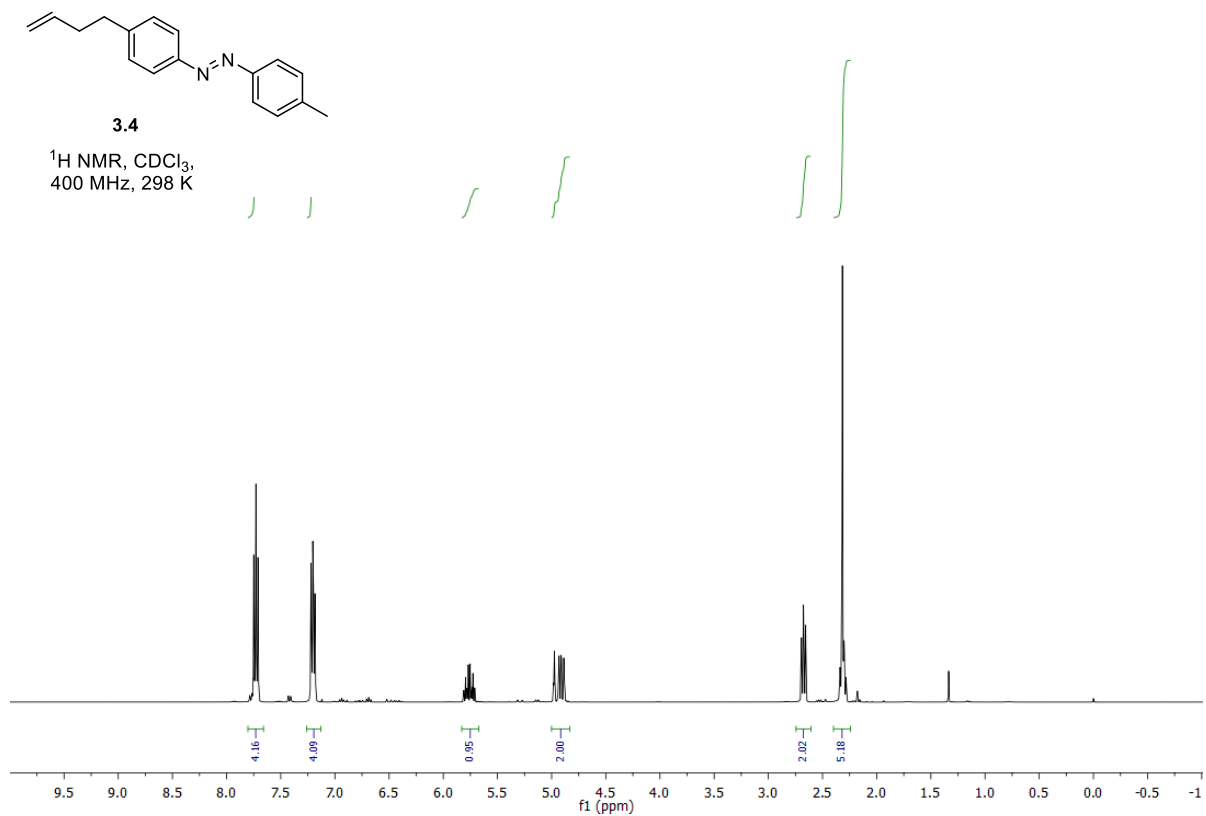


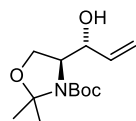




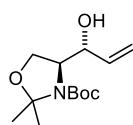
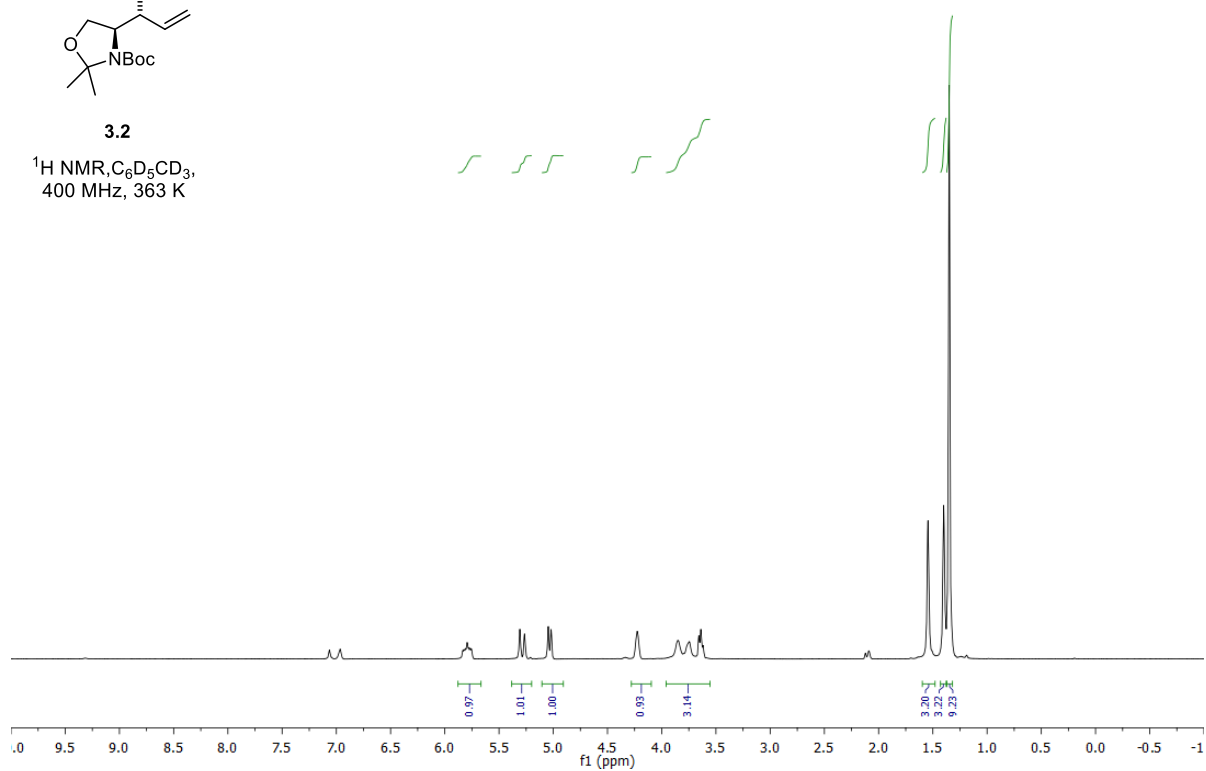




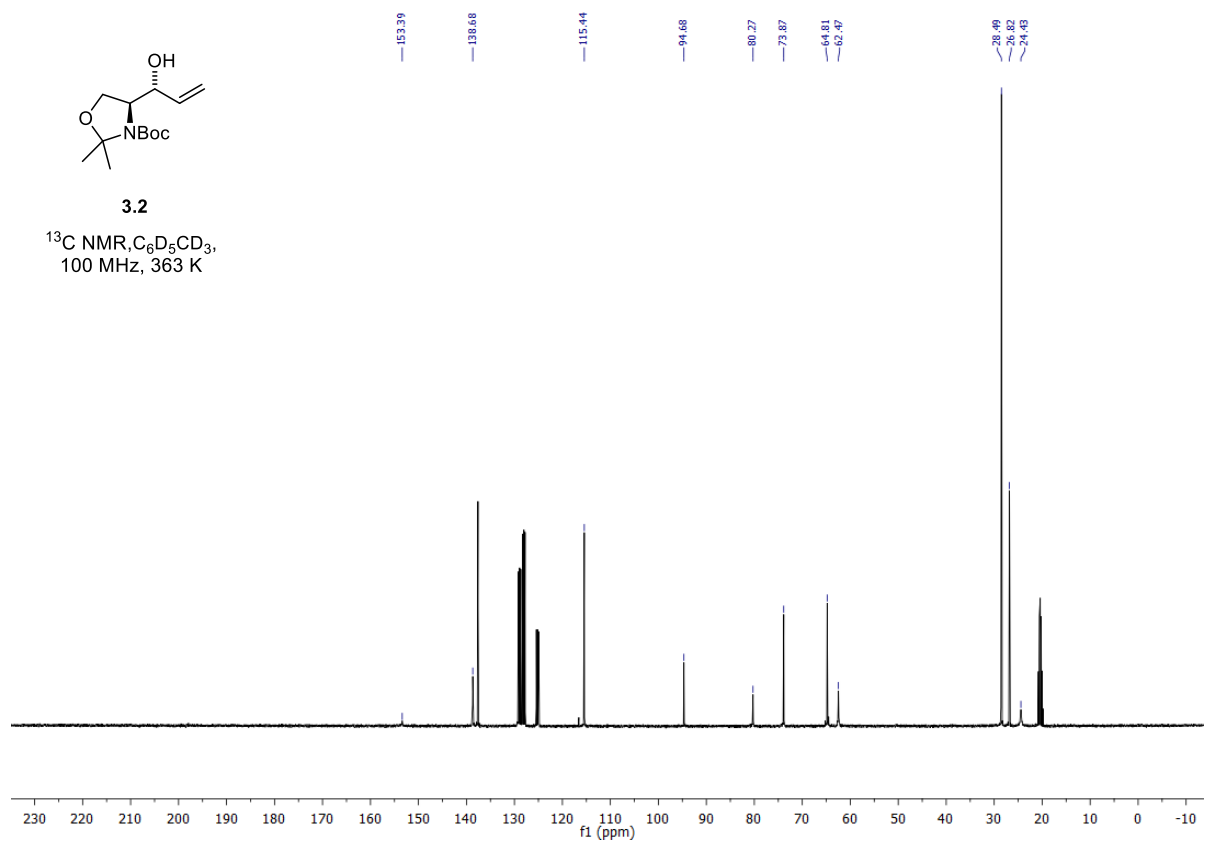


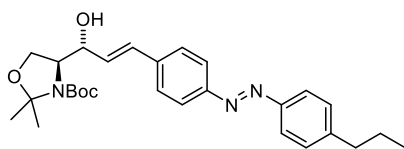
**3.2**

$^1\text{H}$  NMR,  $\text{C}_6\text{D}_5\text{CD}_3$ ,  
400 MHz, 363 K

**3.2**

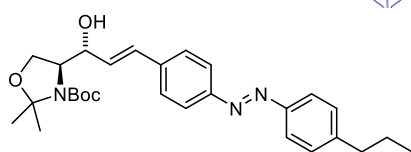
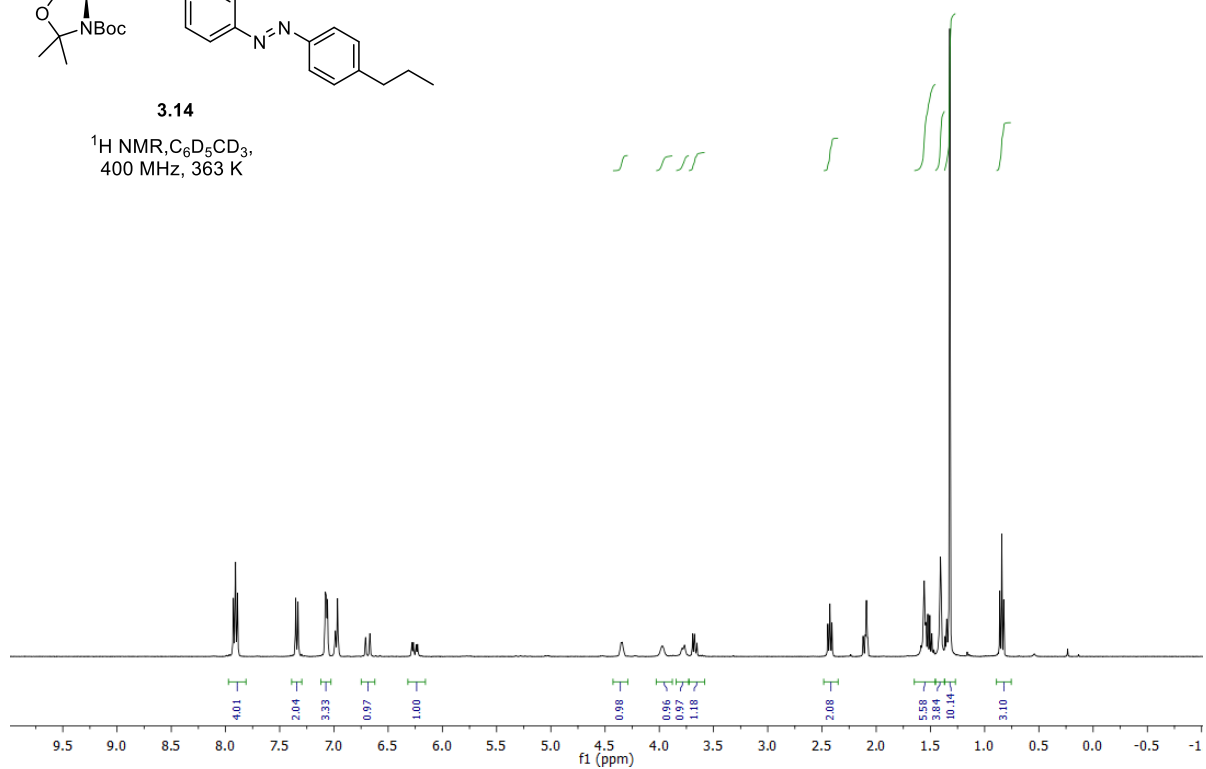
$^{13}\text{C}$  NMR,  $\text{C}_6\text{D}_5\text{CD}_3$ ,  
100 MHz, 363 K





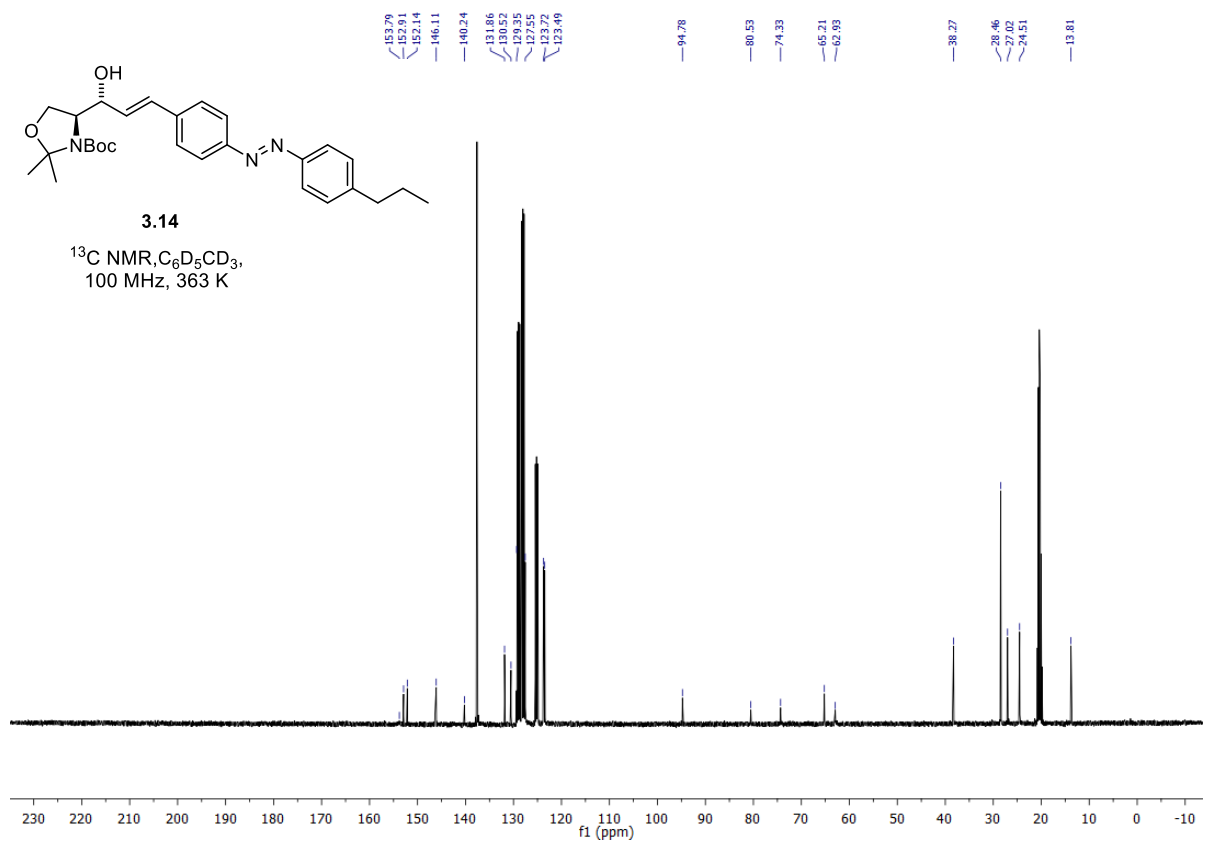
3.14

$^1\text{H NMR}$ ,  $\text{C}_6\text{D}_5\text{CD}_3$ ,  
400 MHz, 363 K

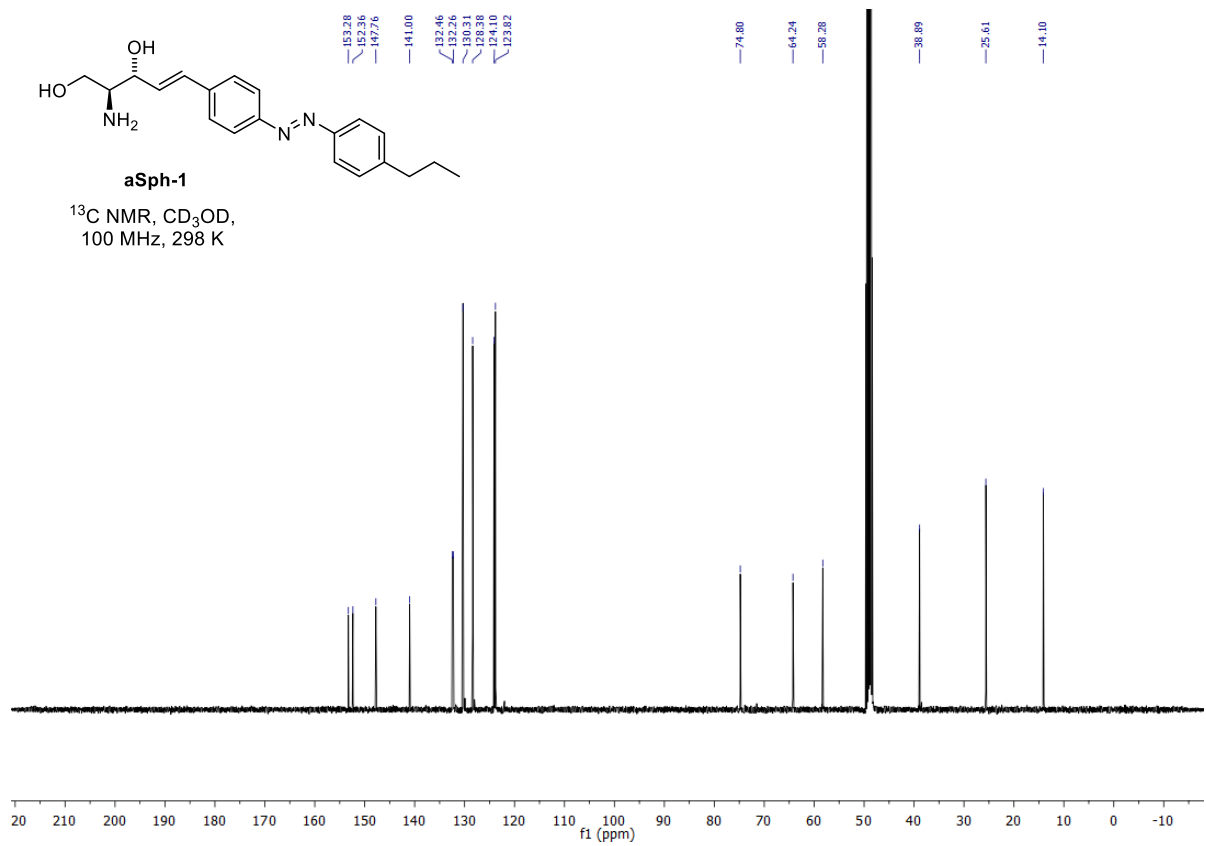
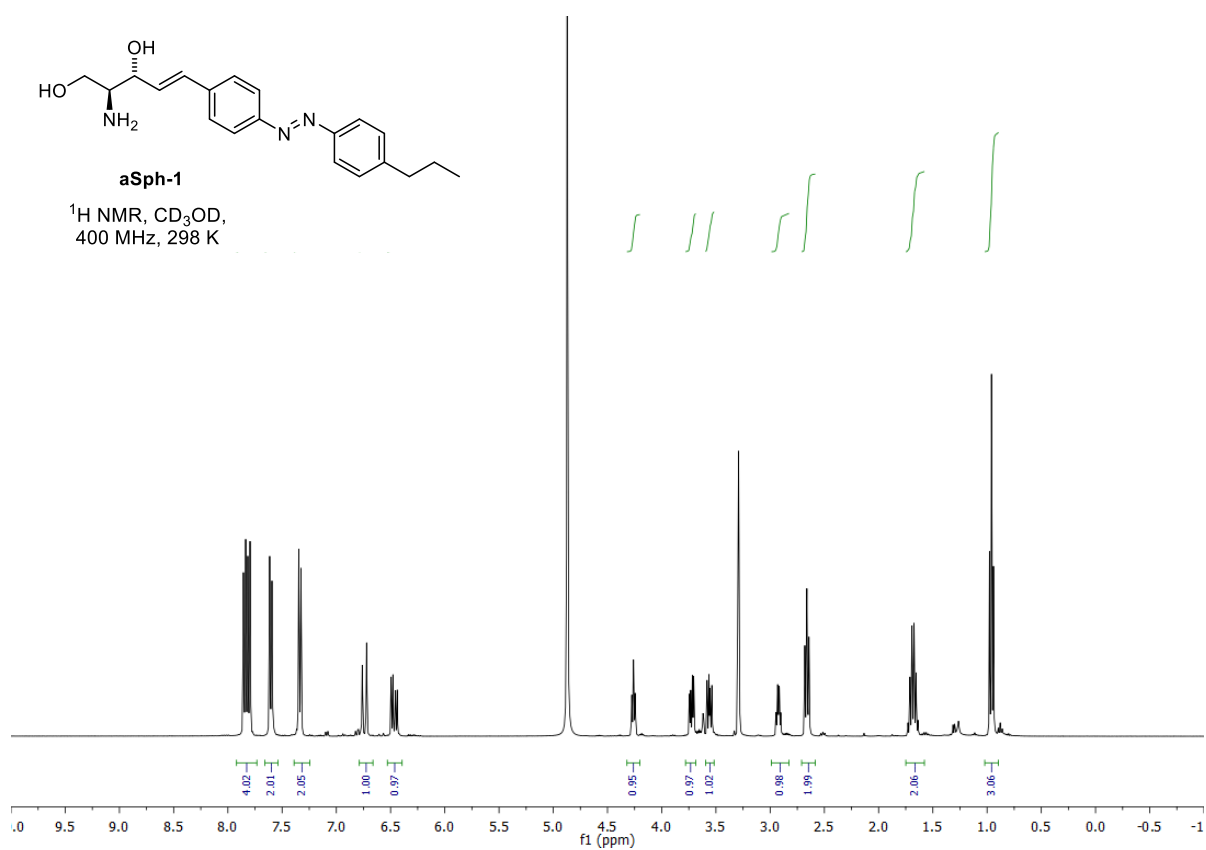


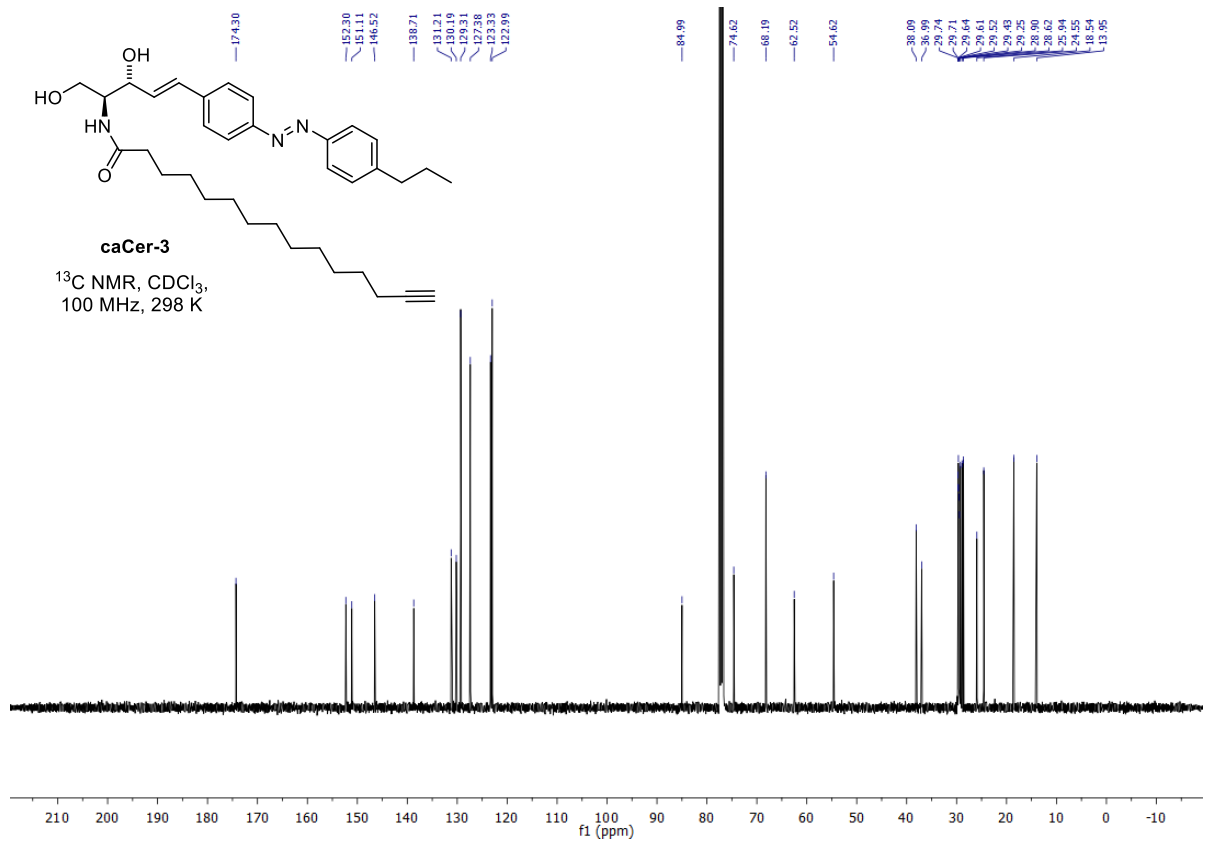
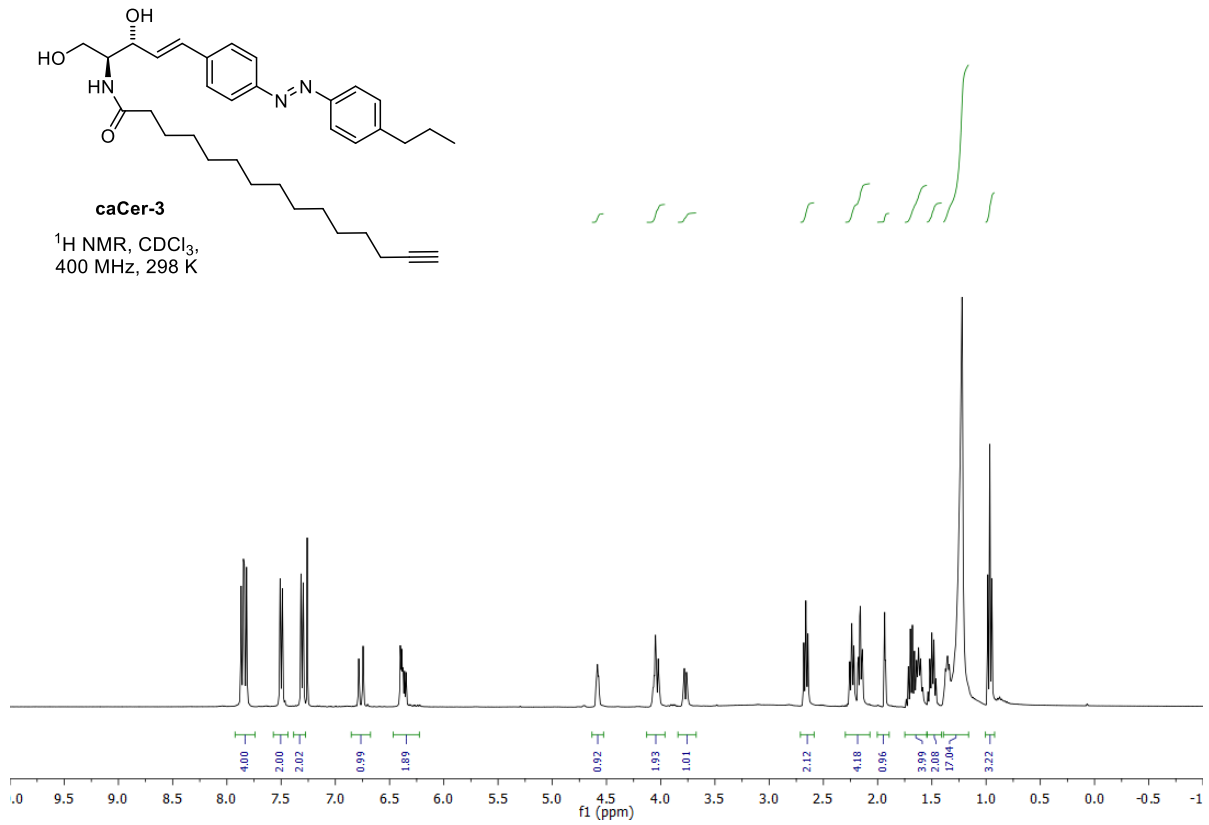
3.14

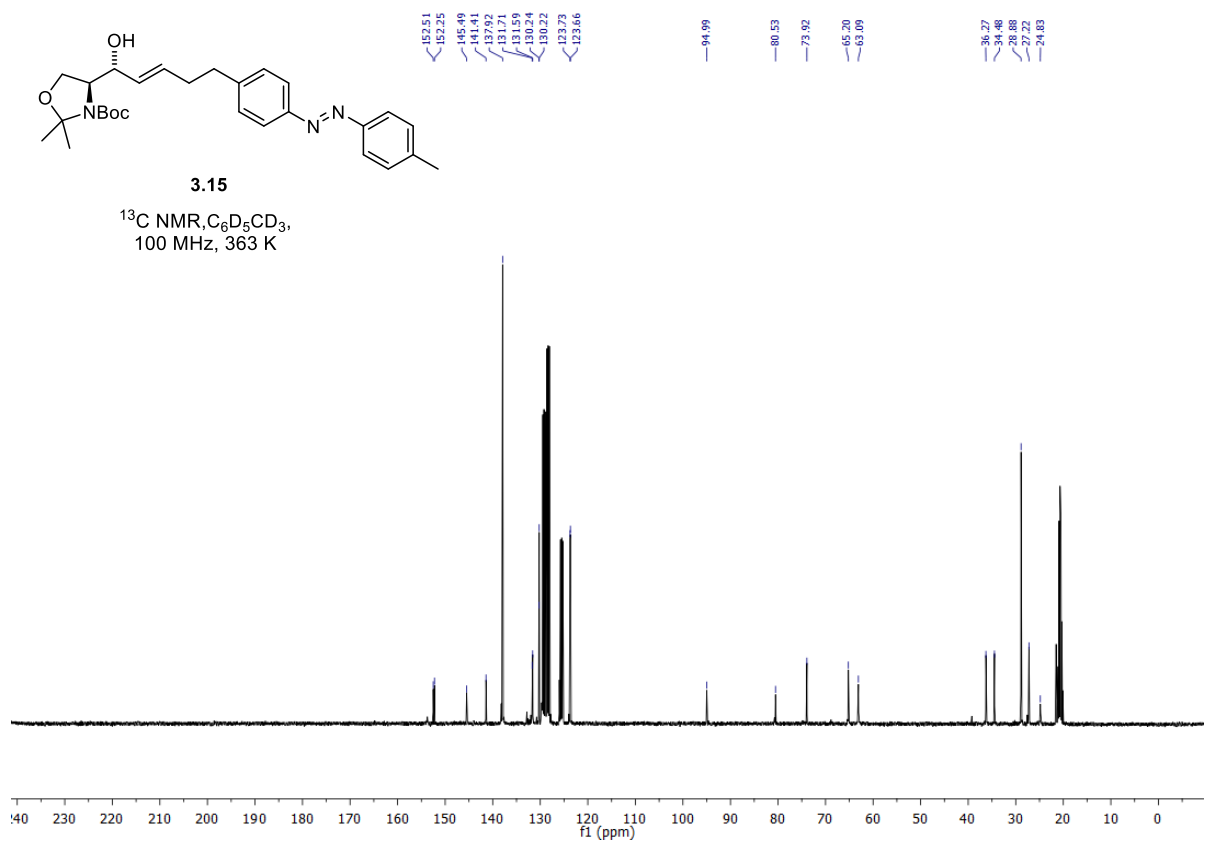
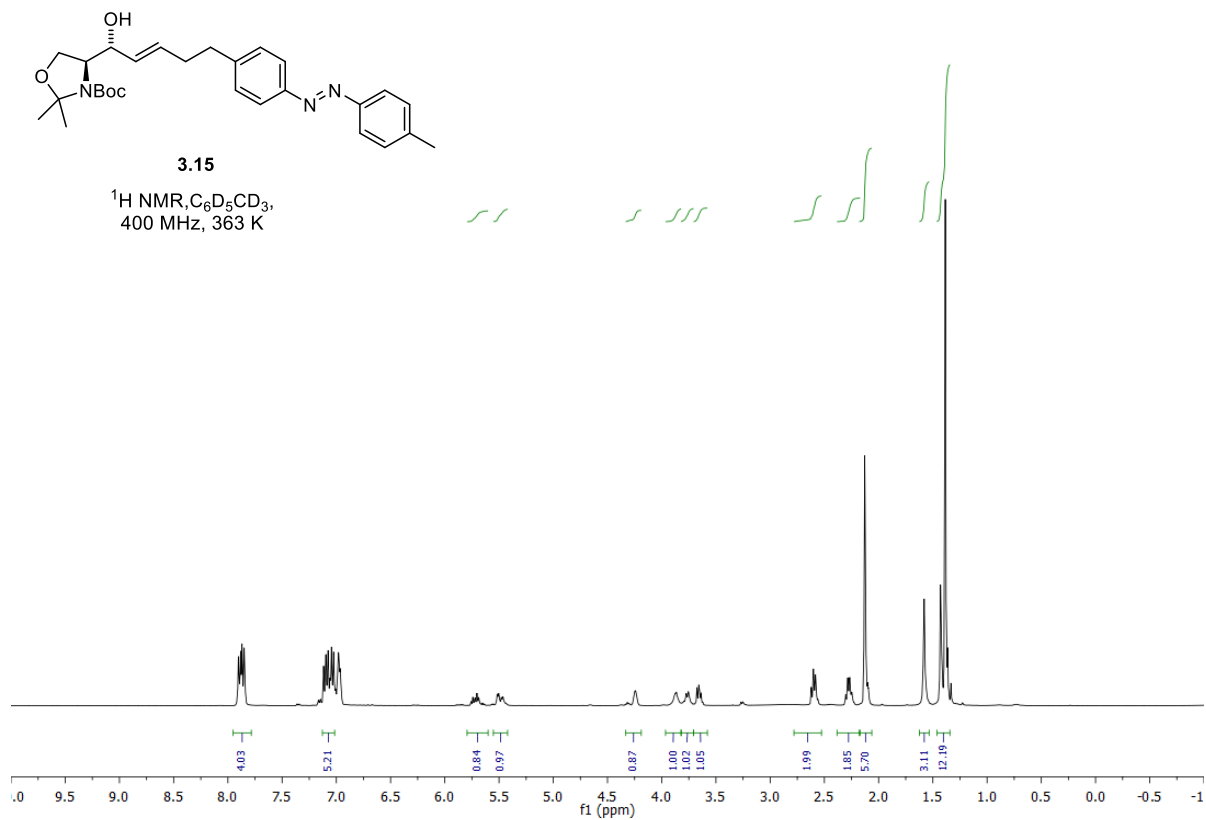
$^{13}\text{C NMR}$ ,  $\text{C}_6\text{D}_5\text{CD}_3$ ,  
100 MHz, 363 K

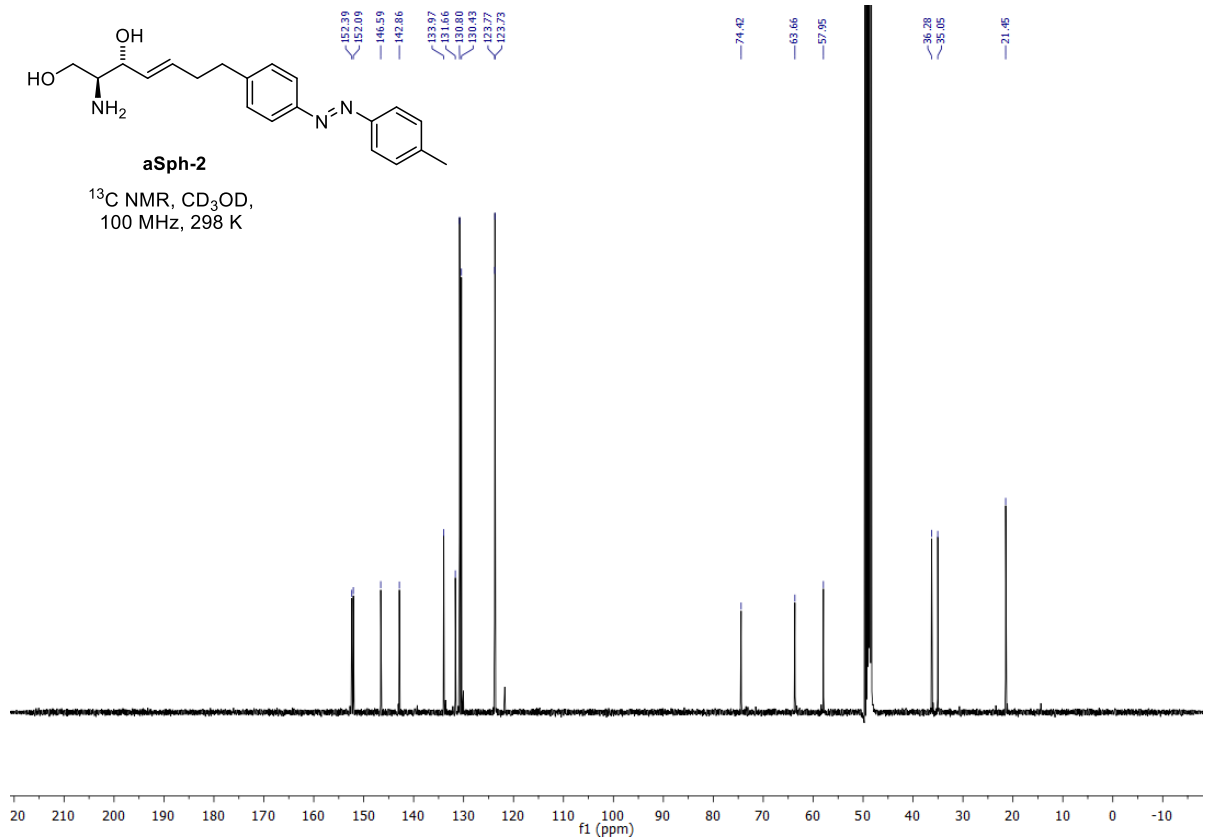
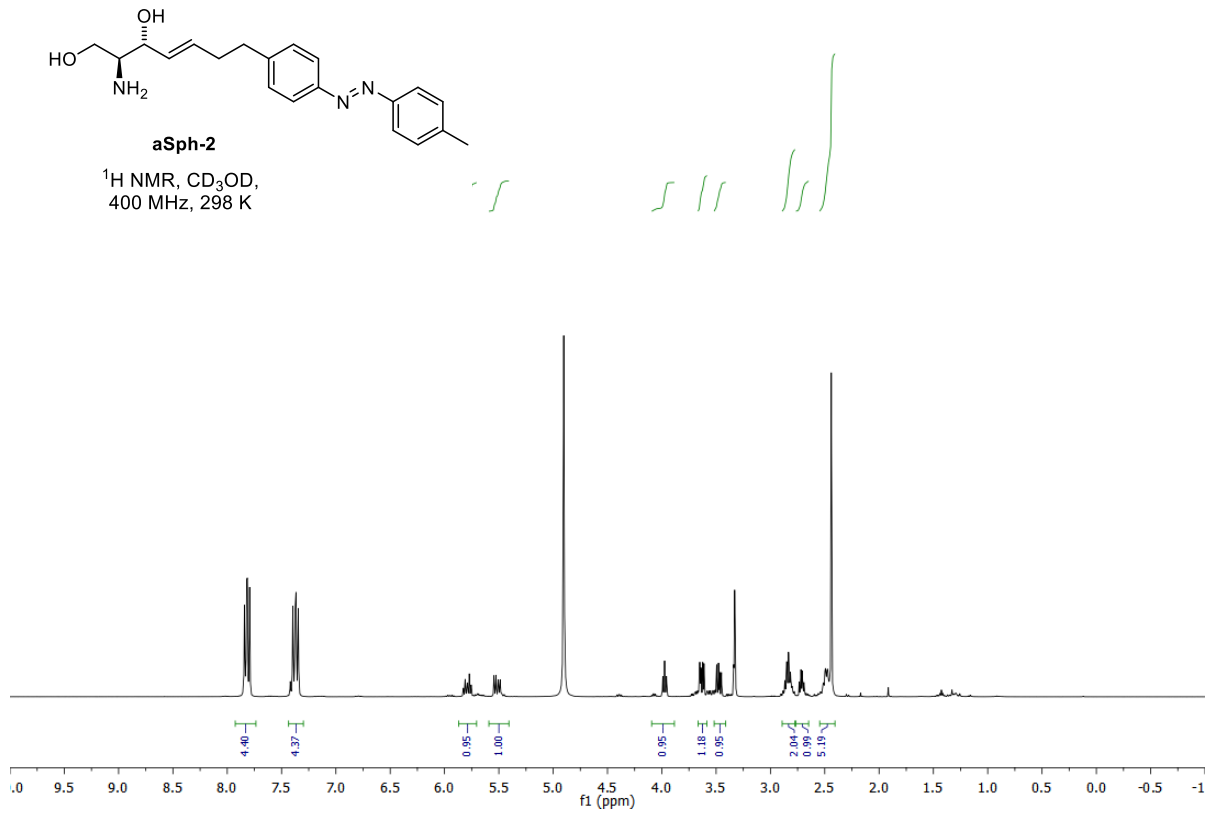


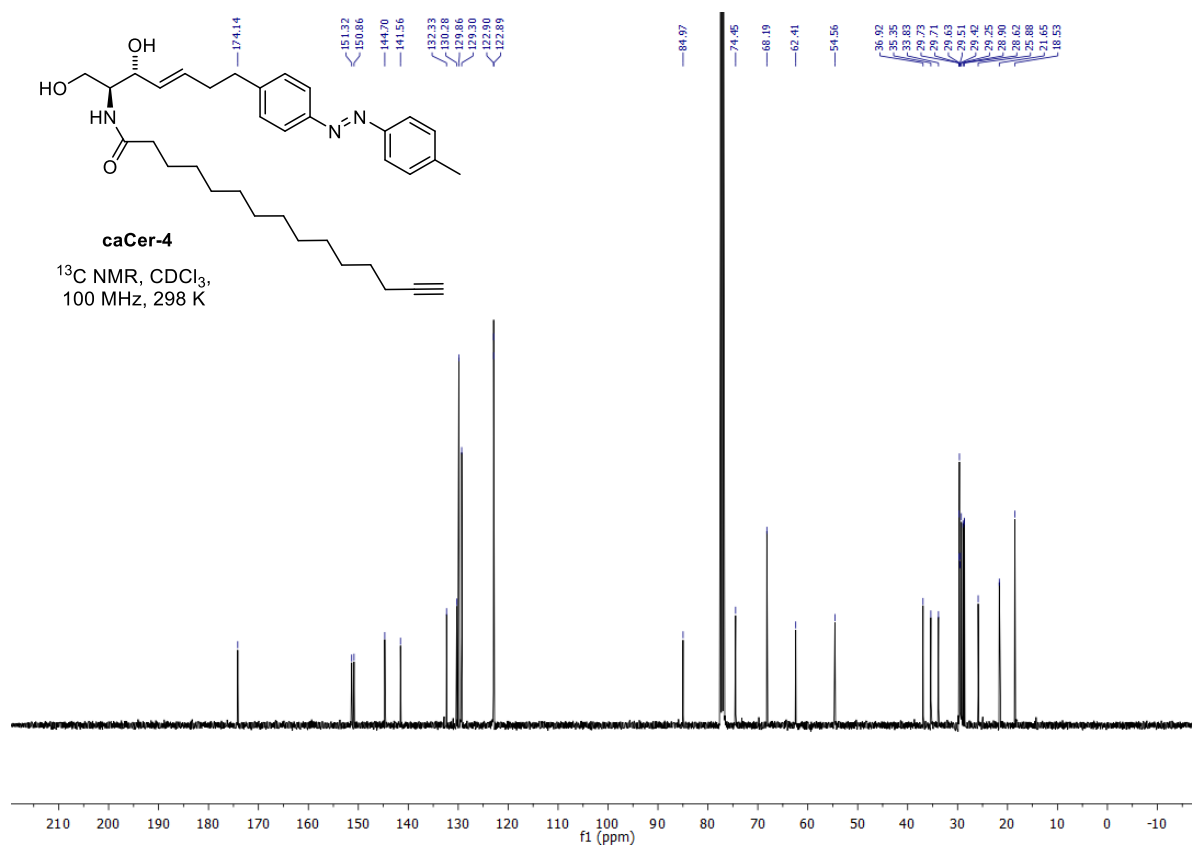
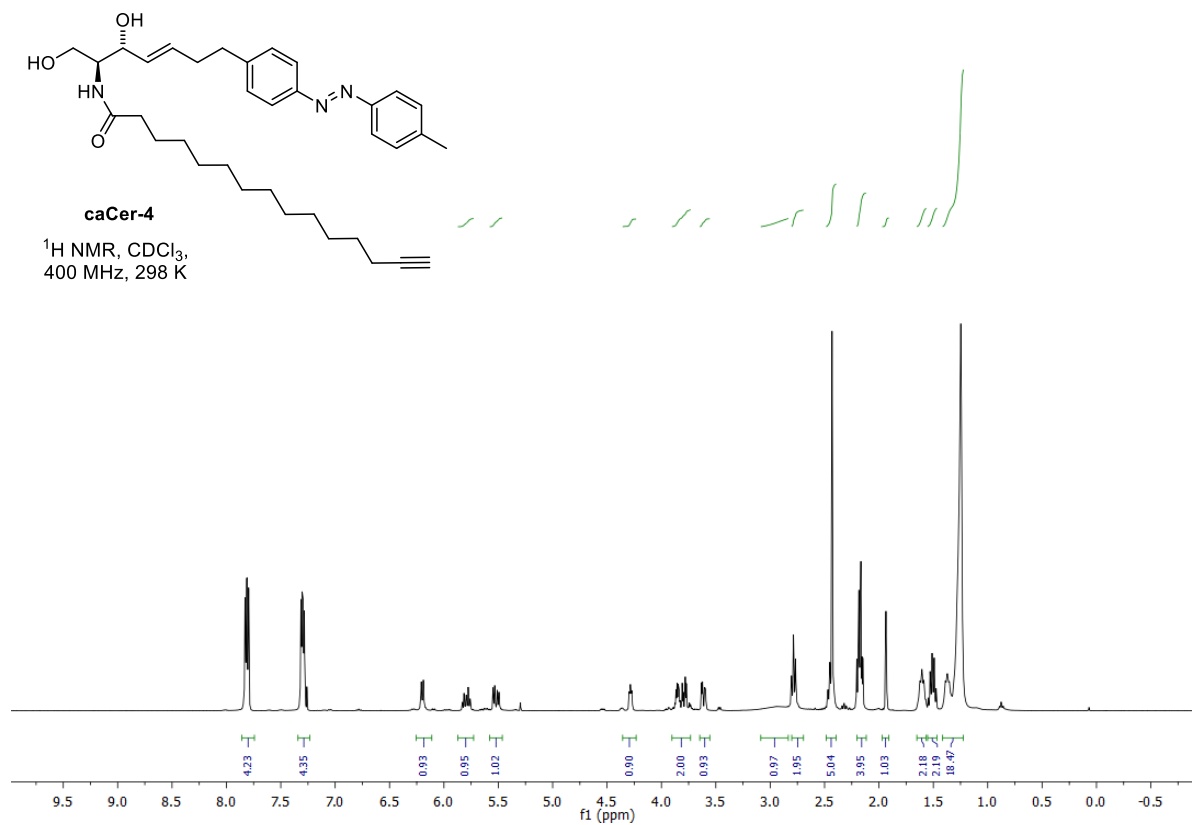








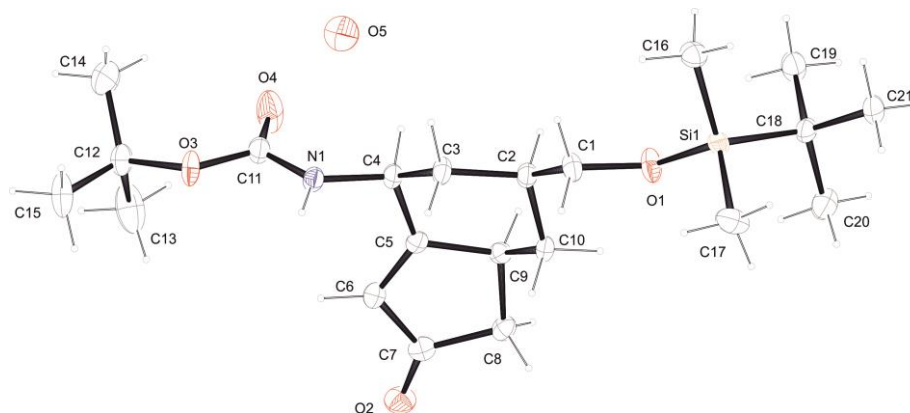




## 5.2. Crystallographic Data

### 5.2.1. Crystallographic Data for Chapter I

Crystallographic data for **10**



**Figure 5.10.** ORTEP projection of the molecular structure of **10** (50% probability ellipsoids).

Crystallized by dissolution in minimal Et<sub>2</sub>O and resting at -32 °C.

**Table 5.1.** Crystallographic data for **10**.

net formula	C <sub>21</sub> H <sub>37.50</sub> NO <sub>4.25</sub> Si
<i>M<sub>r</sub></i> /g mol <sup>-1</sup>	400.11
crystal size/mm	0.100 × 0.090 × 0.070
<i>T</i> /K	100.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	monoclinic
space group	'P 1 21 1'
<i>a</i> /Å	6.0492(4)
<i>b</i> /Å	11.3972(6)
<i>c</i> /Å	16.9316(10)
α/°	90
β/°	92.614(2)
γ/°	90
<i>V</i> /Å <sup>3</sup>	1166.12(12)
<i>Z</i>	2
calc. density/g cm <sup>-3</sup>	1.140
μ/mm <sup>-1</sup>	0.126
absorption correction	Multi-Scan
transmission factor range	0.8785–0.9705
refls. measured	7149

---

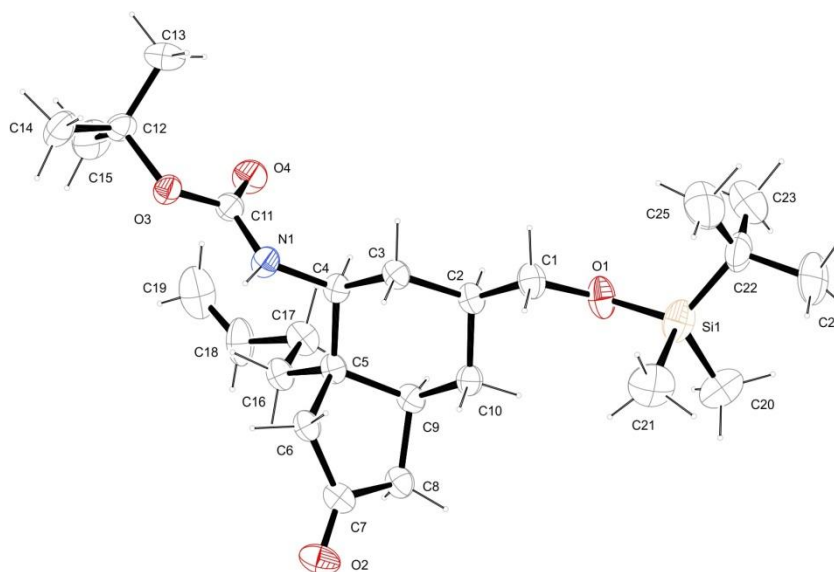
$R_{\text{int}}$	0.0281
mean $\sigma(I)/I$	0.0516
$\theta$ range	3.371–26.357
observed refls.	4044
$x, y$ (weighting scheme)	0.0278, 0.2427
hydrogen refinement	mixed
Flack parameter	0.03(8)
refls in refinement	4355
parameters	260
restraints	1
$R(F_{\text{obs}})$	0.0386
$R_w(F^2)$	0.0827
$S$	1.034
shift/error <sub>max</sub>	0.001
max electron density/e $\text{\AA}^{-3}$	0.252
min electron density/e $\text{\AA}^{-3}$	-0.169

---

H(C) constr, H(N) refall, H(O) not considered in refinement.

Formula:  $\text{C}_{21}\text{H}_{37}\text{NO}_4\text{Si} \cdot 0.25 \text{H}_2\text{O}$

---

*Crystallographic data for 17*

**Figure 5.11.** ORTEP projection of the molecular structure of **17** (50% probability ellipsoids).

Crystallized by dissolution in minimal Et<sub>2</sub>O and resting at –32 °C.

**Table 5.2.** Crystallographic data for **17**.

net formula	C <sub>25</sub> H <sub>45</sub> NO <sub>4</sub> Si
$M_r/g\ mol^{-1}$	451.71
crystal size/mm	0.563 × 0.473 × 0.374
$T/K$	173(2)
radiation	MoK $\alpha$
diffractometer	'Oxford XCalibur'
crystal system	tetragonal
space group	'P 43 21 2'
$a/\text{\AA}$	10.5065(3)
$b/\text{\AA}$	10.5065(3)
$c/\text{\AA}$	51.339(3)
$\alpha/^\circ$	90
$\beta/^\circ$	90
$\gamma/^\circ$	90
$V/\text{\AA}^3$	5667.1(4)
$Z$	8
calc. density/g cm <sup>-3</sup>	1.059
$\mu/\text{mm}^{-1}$	0.109
absorption correction	'multi-scan'
transmission factor range	0.75341–1.00000



---

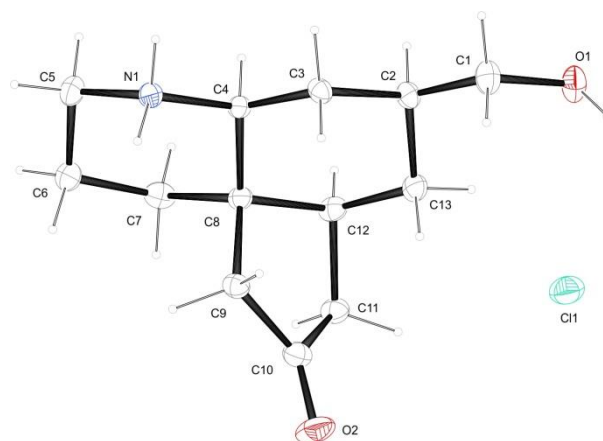
refls. measured	10498
$R_{\text{int}}$	0.0385
mean $\sigma(I)/I$	0.0553
$\theta$ range	4.337–25.022
observed refls.	3847
$x, y$ (weighting scheme)	0.0450, 0.3176
hydrogen refinement	Constr
Flack parameter	–0.06(9)
refls in refinement	4961
parameters	365
restraints	71
$R(F_{\text{obs}})$	0.0505
$R_w(F^2)$	0.1116
$S$	1.042
shift/error <sub>max</sub>	0.001
max electron density/e $\text{\AA}^{-3}$	0.128
min electron density/e $\text{\AA}^{-3}$	–0.174

---

C4 side-chain and *t*Bu/methyl groups bound to Si heavily disordered, split models applied; SIMU, ISOR, SAME restraints used to enhance the refinement quality. The figure shows the main parts of disordered groups only.

---

Crystallographic data for **1.129** (hydrochloride)



**Figure 5.12.** ORTEP projection of the molecular structure of **1.129** (hydrochloride, 50% probability ellipsoids).

Crystallized by slow evaporation of  $\text{CH}_2\text{Cl}_2$  solution.

**Table 5.3.** Crystallographic data for **1.129** (hydrochloride).

net formula	$\text{C}_{13}\text{H}_{22}\text{ClNO}_2$
$M_r/\text{g mol}^{-1}$	259.76
crystal size/mm	$0.286 \times 0.152 \times 0.138$
$T/\text{K}$	123(2)
radiation	MoK $\alpha$
diffractometer	'Oxford XCalibur'
crystal system	triclinic
space group	'P 1'
$a/\text{\AA}$	6.5578(8)
$b/\text{\AA}$	6.8576(6)
$c/\text{\AA}$	7.7584(9)
$\alpha/^\circ$	71.399(9)
$\beta/^\circ$	89.946(9)
$\gamma/^\circ$	79.903(9)
$V/\text{\AA}^3$	324.99(6)
$Z$	1
calc. density/ $\text{g cm}^{-3}$	1.327
$\mu/\text{mm}^{-1}$	0.285
absorption correction	'multi-scan'
transmission factor range	0.98377–1.00000
refls. measured	3605
$R_{\text{int}}$	0.0263

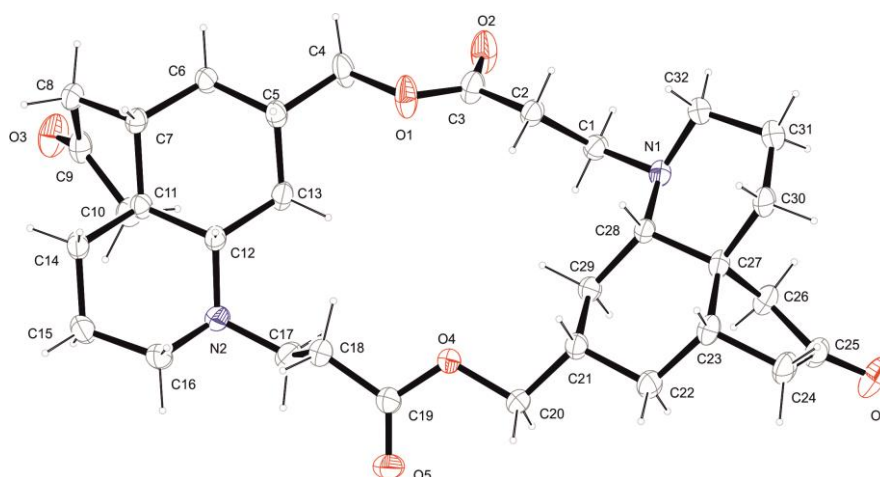
---

mean $\sigma(I)/I$	0.0487
$\theta$ range	4.329–25.346
observed refls.	2263
$x, y$ (weighting scheme)	0.0213, 0.0435
hydrogen refinement	Mixed
Flack parameter	0.04(4)
refls in refinement	2362
parameters	166
restraints	3
$R(F_{\text{obs}})$	0.0324
$R_w(F^2)$	0.0708
$S$	1.077
shift/error <sub>max</sub>	0.001
max electron density/e $\text{\AA}^{-3}$	0.186
min electron density/e $\text{\AA}^{-3}$	–0.164

---

C-H: constr, N-H and O-H: refall.

---

*Crystallographic data for 1.131*

**Figure 5.13.** ORTEP projection of the molecular structure of **1.131** (50% probability ellipsoids).

Crystallized by slow evaporation of Et<sub>2</sub>O solution.

**Table 5.4.** Crystallographic data for **1.131**.

net formula	C <sub>32</sub> H <sub>46</sub> N <sub>2</sub> O <sub>6</sub>
$M_r/g\ mol^{-1}$	554.71
crystal size/mm	0.100 × 0.060 × 0.040
$T/K$	173.(2)
radiation	MoK $\alpha$
diffractometer	'Bruker D8 Venture TXS'
crystal system	monoclinic
space group	'P 1 21 1'
$a/\text{\AA}$	8.0568(3)
$b/\text{\AA}$	16.5848(5)
$c/\text{\AA}$	11.2909(3)
$\alpha/^\circ$	90
$\beta/^\circ$	106.7530(10)
$\gamma/^\circ$	90
$V/\text{\AA}^3$	1444.66(8)
$Z$	2
calc. density/ $g\ cm^{-3}$	1.275
$\mu/mm^{-1}$	0.087
absorption correction	Multi-Scan
transmission factor range	0.9097–0.9705
refls. measured	18562
$R_{int}$	0.0331

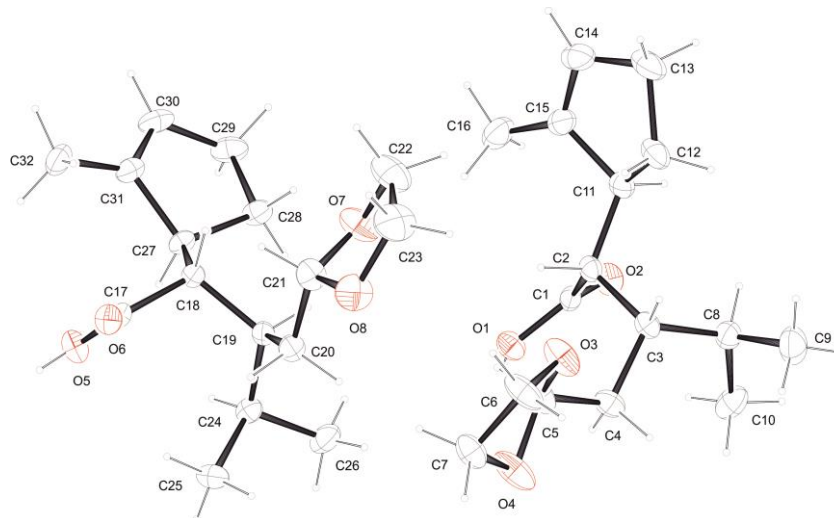
---

mean $\sigma(I)/I$	0.0528
$\theta$ range	3.607–30.492
observed refls.	7801
$x, y$ (weighting scheme)	0.0529, 0.2507
hydrogen refinement	constr
Flack parameter	0.0(4)
refls in refinement	8751
parameters	366
restraints	1
$R(F_{\text{obs}})$	0.0456
$R_w(F^2)$	0.1124
$S$	1.037
shift/error <sub>max</sub>	0.001
max electron density/e $\text{\AA}^{-3}$	0.286
min electron density/e $\text{\AA}^{-3}$	–0.283

---

## 5.2.2. Crystallographic Data for Chapter II

Crystallographic data for **12**



**Figure 5.14.** ORTEP projection of the molecular structure of **12** (50% probability ellipsoids).

**Table 5.5.** Crystallographic data for **12**.

net formula	$C_{16}H_{26}O_4$
$M_r/g\ mol^{-1}$	282.37
crystal size/mm	$0.100 \times 0.080 \times 0.050$
$T/K$	100.(2)
radiation	MoK $\alpha$
diffractometer	'Bruker D8 Venture TXS'
crystal system	orthorhombic
space group	'P 21 21 21'
$a/\text{\AA}$	10.3207(2)
$b/\text{\AA}$	13.0112(3)
$c/\text{\AA}$	24.0063(6)
$\alpha/^\circ$	90
$\beta/^\circ$	90
$\gamma/^\circ$	90
$V/\text{\AA}^3$	3223.68(13)
$Z$	8
calc. density/ $g\ cm^{-3}$	1.164
$\mu/mm^{-1}$	0.082
absorption correction	Multi-Scan
transmission factor range	0.9221–0.9705
refls. measured	19336

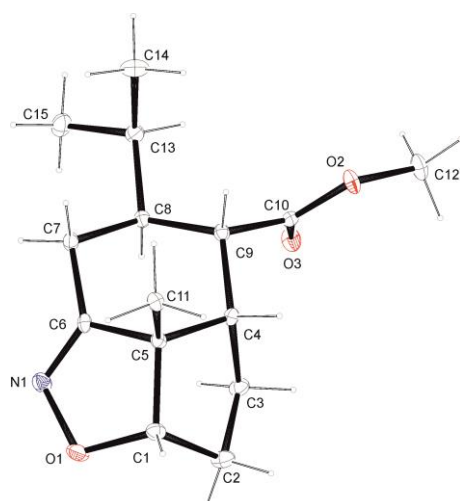
---

$R_{\text{int}}$	0.0268
mean $\sigma(I)/I$	0.0291
$\theta$ range	3.221–26.372
observed refls.	6102
$x, y$ (weighting scheme)	0.0562, 0.9609
hydrogen refinement	H(C) constr, H(O) refxyz
Flack parameter	0.1(3)
refls in refinement	6566
parameters	392
restraints	19
$R(F_{\text{obs}})$	0.0398
$R_w(F^2)$	0.1057
$S$	1.040
shift/error <sub>max</sub>	0.001
max electron density/e $\text{\AA}^{-3}$	0.441
min electron density/e $\text{\AA}^{-3}$	-0.278

---

Disorder handled by a split model.

---

Crystallographic data for **18**

**Figure 5.15.** ORTEP projection of the molecular structure of **18** (50% probability ellipsoids).

**Table 5.6.** Crystallographic data for **18**.

net formula	$C_{15}H_{23}NO_3$
$M_r/g\ mol^{-1}$	265.34
crystal size/mm	$0.080 \times 0.030 \times 0.030$
$T/K$	103.(2)
radiation	MoK $\alpha$
diffractometer	'Bruker D8 Venture TXS'
crystal system	monoclinic
space group	'C 1 2 1'
$a/\text{\AA}$	22.4524(8)
$b/\text{\AA}$	6.2502(2)
$c/\text{\AA}$	10.4159(4)
$\alpha/^\circ$	90
$\beta/^\circ$	102.2005(13)
$\gamma/^\circ$	90
$V/\text{\AA}^3$	1428.67(9)
$Z$	4
calc. density/ $g\ cm^{-3}$	1.234
$\mu/mm^{-1}$	0.085
absorption correction	Multi-Scan
transmission factor range	0.9298–0.9705
refls. measured	13065
$R_{int}$	0.0344
mean $\sigma(I)/I$	0.0258



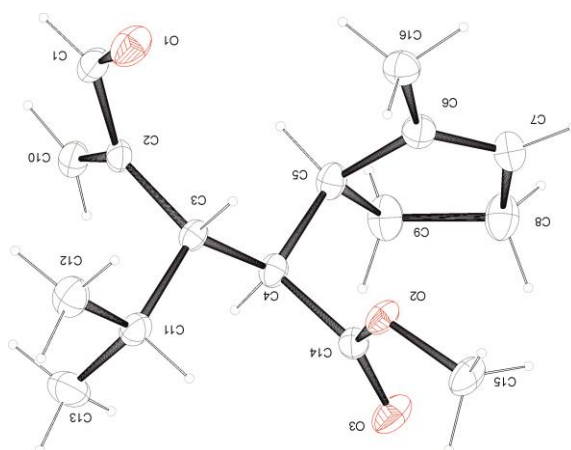
---

$\theta$ range	3.389–25.377
observed refls.	2473
$x, y$ (weighting scheme)	0.0299, 0.7409
hydrogen refinement	constr
Flack parameter	0.2(4)
refls in refinement	2594
parameters	176
restraints	1
$R(F_{\text{obs}})$	0.0307
$R_w(F^2)$	0.0714
$S$	1.082
shift/error <sub>max</sub>	0.001
max electron density/e $\text{\AA}^{-3}$	0.173
min electron density/e $\text{\AA}^{-3}$	-0.157

---

Correct structure derived from synthesis.

---

*Crystallographic data for 23*

**Figure 5.16.** ORTEP projection of the molecular structure of **23** (50% probability ellipsoids).

Crystallized by slow concentration of Et<sub>2</sub>O solution at ambient temperature.

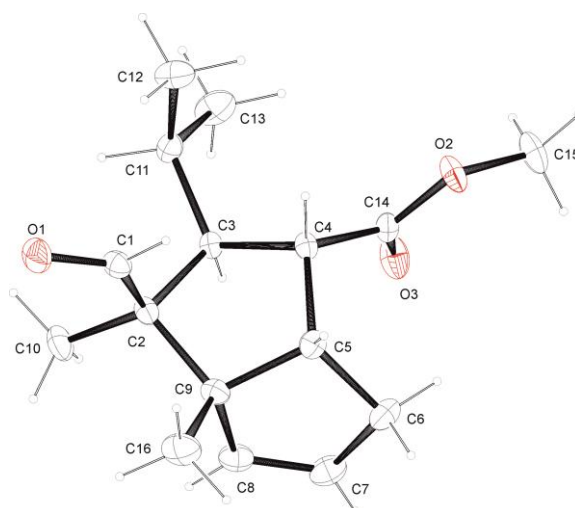
**Table 5.7.** Crystallographic data for **23**.

net formula	C <sub>16</sub> H <sub>24</sub> O <sub>3</sub>
Mr/g mol <sup>-1</sup>	264.35
crystal size/mm	0.100 × 0.080 × 0.070
T/K	103.(2)
radiation	MoK $\alpha$
diffractometer	'Bruker D8 Venture TXS'
crystal system	monoclinic
space group	'P 1 21 1'
a/Å	7.2928(4)
b/Å	11.7582(7)
c/Å	9.4213(5)
$\alpha$ /°	90
$\beta$ /°	112.645(2)
$\gamma$ /°	90
V/Å <sup>3</sup>	745.60(7)
Z	2
calc. density/g cm <sup>-3</sup>	1.177
$\mu$ /mm <sup>-1</sup>	0.080
absorption correction	Multi-Scan
transmission factor range	0.89–0.99
refls. measured	7557
R <sub>int</sub>	0.0243
mean $\sigma$ (I)/I	0.0322

---

$\theta$ range	3.465–26.358
observed refls.	2797
x, y (weighting scheme)	0.0281, 0.1653
hydrogen refinement	constr
Flack parameter	–0.3(4)
refls in refinement	3023
parameters	176
restraints	1
R(Fobs)	0.0332
Rw(F2)	0.0766
S	1.078
shift/errormax	0.001
max electron density/e $\text{\AA}^{-3}$	0.175
min electron density/e $\text{\AA}^{-3}$	–0.152

---

*Crystallographic data for 25*

**Figure 5.17.** ORTEP projection of the molecular structure of **25** (50% probability ellipsoids).

Crystallized by slow concentration of MeOH solution at ambient temperature.

**Table 5.8.** Crystallographic data for **25**.

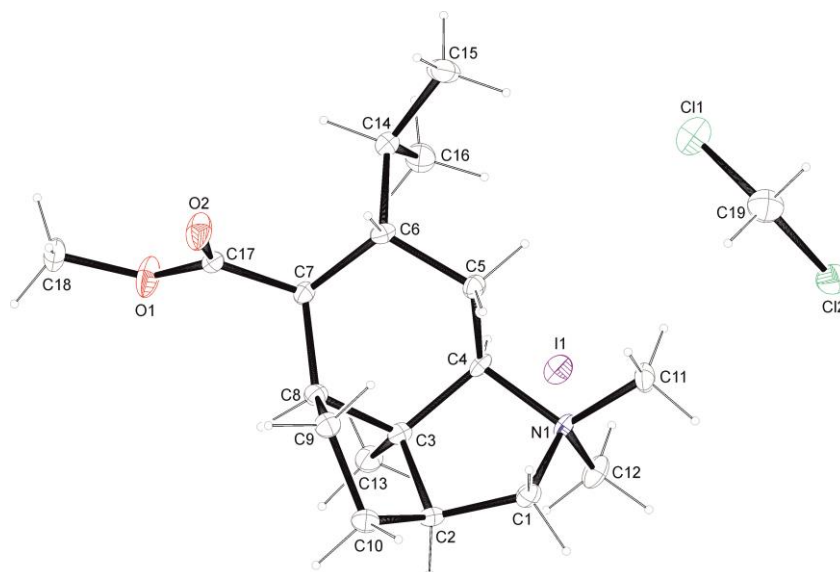
net formula	$C_{16}H_{24}O_3$
$M_r/g\ mol^{-1}$	264.35
crystal size/mm	$0.100 \times 0.090 \times 0.080$
$T/K$	103.(2)
radiation	MoK $\alpha$
diffractometer	'Bruker D8 Venture TXS'
crystal system	Monoclinic
space group	'P 1 21 1'
$a/\text{\AA}$	8.2370(2)
$b/\text{\AA}$	10.4144(3)
$c/\text{\AA}$	8.7895(3)
$\alpha/^\circ$	90
$\beta/^\circ$	102.9060(10)
$\gamma/^\circ$	90
$V/\text{\AA}^3$	734.95(4)
$Z$	2
calc. density/ $g\ cm^{-3}$	1.195
$\mu/mm^{-1}$	0.081
absorption correction	Multi-Scan
transmission factor range	0.91–0.99
refls. measured	8711
$R_{int}$	0.0210

---

mean $\sigma(I)/I$	0.0395
$\theta$ range	3.204–33.138
observed refls.	4926
$x, y$ (weighting scheme)	0.0555, 0.0556
hydrogen refinement	constr
Flack parameter	0.0(3)
refls in refinement	5437
parameters	177
restraints	1
$R(F_{\text{obs}})$	0.0397
$R_w(F^2)$	0.1032
$S$	1.069
shift/error <sub>max</sub>	0.001
max electron density/e $\text{\AA}^{-3}$	0.335
min electron density/e $\text{\AA}^{-3}$	–0.188

---

*Crystallographic data for 2.105*



**Figure 5.18.** ORTEP projection of the molecular structure of **2.105** (50% probability ellipsoids).

Crystallized from pentane/ $\text{CH}_2\text{Cl}_2$  at 4 °C.

**Table 5.9.** Crystallographic data for **2.105**.

net formula	$\text{C}_{19}\text{H}_{34}\text{Cl}_2\text{INO}_2$
$M_r/\text{g mol}^{-1}$	506.27
crystal size/mm	$0.100 \times 0.050 \times 0.020$
$T/\text{K}$	100.(2)
radiation	MoK $\alpha$
diffractometer	'Bruker D8 Venture TXS'
crystal system	orthorhombic
space group	'P 21 21 21'
$a/\text{\AA}$	7.5112(2)
$b/\text{\AA}$	10.2207(4)
$c/\text{\AA}$	28.8202(10)
$\alpha/^\circ$	90
$\beta/^\circ$	90
$\gamma/^\circ$	90
$V/\text{\AA}^3$	2212.52(13)
$Z$	4
calc. density/ $\text{g cm}^{-3}$	1.520
$\mu/\text{mm}^{-1}$	1.701
absorption correction	Multi-Scan
transmission factor range	0.89–0.97

---

refls. measured	23058
$R_{\text{int}}$	0.0314
mean $\sigma(I)/I$	0.0270
$\theta$ range	3.366–26.371
observed refls.	4349
$x, y$ (weighting scheme)	0.0241, 0.4564
hydrogen refinement	constr
Flack parameter	–0.032(8)
refls in refinement	4525
parameters	232
restraints	0
$R(F_{\text{obs}})$	0.0210
$R_w(F^2)$	0.0485
$S$	1.049
shift/error <sub>max</sub>	0.001
max electron density/e $\text{\AA}^{-3}$	0.364
min electron density/e $\text{\AA}^{-3}$	–0.416

---

## 5.2. References

- [1] B. Cobb, E. Farnsworth, C. Lowe, *A field guide to ferns and their related families : northeastern and central North America*, 2nd ed., Houghton Mifflin Co., Boston, **2005**.
  - [2] J. i. Kobayashi, H. Morita, in *The Alkaloids: Chemistry and Biology, Vol. 61* (Ed.: G. A. Cordell), Academic Press, **2005**, pp. 1-57.
  - [3] P. Siengalewicz, J. Mulzer, U. Rinner, in *The Alkaloids: Chemistry and Biology, Vol. 72* (Ed.: K. Hans-Joachim), Academic Press, **2013**, pp. 1-151.
  - [4] Copyright © 2010 by Christian Fischer. The photograph was obtained from the URL: <https://commons.wikimedia.org/wiki/File:LycopodiumClavatum.jpg> (active as of December 2017) and is licensed under the Creative Commons Attribution-Share Alike 2013.2010 Unported license (<https://creativecommons.org/licenses/by-sa/2013.2010/legalcode>). It is used here in its unmodified form.
  - [5] Copyright © 2017 by Jeferson Dutra. The photograph was obtained from the URL: [https://commons.wikimedia.org/wiki/File:Lycopodiella\\_cernua.jpg](https://commons.wikimedia.org/wiki/File:Lycopodiella_cernua.jpg) (active as of December 2017) and is licensed under the Creative Commons Attribution-Share Alike 2014.2010 International license (<https://creativecommons.org/licenses/by-sa/2014.2010/legalcode>). It is used here in its unmodified form.
  - [6] L. Margulis, M. J. Chapman, in *Kingdoms and Domains*, Academic Press, London, **2009**, pp. 411-462.
  - [7] A. Johnston, *Economic Botany* **1970**, *24*, 301-324.
  - [8] X. Ma, C. Tan, D. Zhu, D. R. Gang, P. Xiao, *J. Ethnopharmacol.* **2007**, *113*, 15-34.
  - [9] K. Bödeker, *Liebigs Ann. Chem.* **1881**, *208*, 363-367.
  - [10] D. B. MacLean, in *The Alkaloids: Chemistry and Physiology, Vol. 14* (Ed.: R. H. F. Manske), Academic Press, **1973**, pp. 347-405.
  - [11] D. B. Maclean, in *The Alkaloids: Chemistry and Pharmacology, Vol. 26* (Ed.: B. Arnold), Academic Press, **1985**, pp. 241-298.
  - [12] W. A. Ayer, *Nat. Prod. Rep.* **1991**, *8*, 455-463.
  - [13] W. A. Ayer, L. S. Trifonov, in *The Alkaloids: Chemistry and Pharmacology, Vol. 45* (Eds.: A. C. Geoffrey, B. Arnold), Academic Press, **1994**, pp. 233-266.
  - [14] X. Ma, D. R. Gang, *Nat. Prod. Rep.* **2004**, *21*, 752-772.
  - [15] M. Kitajima, H. Takayama, in *Alkaloid Synthesis* (Ed.: H.-J. Knölker), Springer Berlin Heidelberg, Berlin, Heidelberg, **2012**, pp. 1-31.
  - [16] A. Nakayama, M. Kitajima, H. Takayama, *Synlett* **2012**, *23*, 2014-2024.
  - [17] X. Wang, H. Li, X. Lei, *Synlett* **2013**, *24*, 1032-1043.
  - [18] R. A. Murphy, R. Sarpong, *Chem. Eur. J.* **2014**, *20*, 42-56.
  - [19] O. Achmatowicz, W. Uzieblo, *Rocz. Chem.* **1938**, *18*, 88-95.
-



- [20] W. A. Ayer, W. R. Bowman, T. C. Joseph, P. Smith, *J. Am. Chem. Soc.* **1968**, *90*, 1648-1650.
- [21] G. Stork, R. A. Kretchmer, R. H. Schlessinger, *J. Am. Chem. Soc.* **1968**, *90*, 1647-1648.
- [22] C. H. Heathcock, E. Kleinman, E. S. Binkley, *J. Am. Chem. Soc.* **1978**, *100*, 8036-8037.
- [23] C. H. Heathcock, E. F. Kleinman, E. S. Binkley, *J. Am. Chem. Soc.* **1982**, *104*, 1054-1068.
- [24] E. Wenkert, C. A. Broka, *J. Chem. Soc., Chem. Commun.* **1984**, 714-715.
- [25] G. A. Kraus, Y. S. Hon, *J. Am. Chem. Soc.* **1985**, *107*, 4341-4342.
- [26] P. A. Grieco, Y. Dai, *J. Am. Chem. Soc.* **1998**, *120*, 5128-5129.
- [27] H. Yang, R. G. Carter, *J. Org. Chem.* **2010**, *75*, 4929-4938.
- [28] H.-Y. Lin, R. Causey, G. E. Garcia, B. B. Snider, *J. Org. Chem.* **2012**, *77*, 7143-7156.
- [29] D. H. Ma, Z. L. Zhong, Z. M. Liu, M. J. Zhang, S. Y. Xu, D. Y. Xu, D. P. Song, X. G. Xie, X. G. She, *Org. Lett.* **2016**, *18*, 4328-4331.
- [30] F. A. L. Anet, C. R. Eves, *Can. J. Chem.* **1958**, *36*, 902-909.
- [31] W. A. Ayer, G. G. Iverach, *Can. J. Chem.* **1960**, *38*, 1823-1826.
- [32] X. C. Tang, P. De Sarno, K. Sugaya, E. Giacobini, *J. Neurosci. Res.* **1989**, *24*, 276-285.
- [33] J.-S. Liu, Y.-L. Zhu, C.-M. Yu, Y.-Z. Zhou, Y.-Y. Han, F.-W. Wu, B.-F. Qi, *Can. J. Chem.* **1986**, *64*, 837-839.
- [34] R. H. Burnell, *J. Chem. Soc.* **1959**, 3091-3093.
- [35] R. H. Burnell, C. G. Chin, B. S. Mootoo, D. R. Taylor, *Can. J. Chem.* **1963**, *41*, 3091-3094.
- [36] C. H. Heathcock, T. A. Blumenkopf, K. M. Smith, *J. Org. Chem.* **1989**, *54*, 1548-1562.
- [37] L. Nyembo, A. Goffin, C. Hootelé, J.-C. Braekman, *Can. J. Chem.* **1978**, *56*, 851-856.
- [38] Y. Hirasawa, H. Morita, J. i. Kobayashi, *Org. Lett.* **2004**, *6*, 3389-3391.
- [39] J. Kobayashi, Y. Hirasawa, N. Yoshida, H. Morita, *J. Org. Chem.* **2001**, *66*, 5901-5904.
- [40] T. Hemscheidt, I. D. Spenser, *J. Am. Chem. Soc.* **1992**, *114*, 5472-5473.
- [41] M. Castillo, R. N. Gupta, D. B. MacLean, I. D. Spenser, *Can. J. Chem.* **1970**, *48*, 1893-1903.
- [42] M. Castillo, R. N. Gupta, Y. K. Ho, D. B. MacLean, I. D. Spenser, *Can. J. Chem.* **1970**, *48*, 2911-2918.
- [43] J. C. Braekman, R. N. Gupta, D. B. MacLean, I. D. Spenser, *Can. J. Chem.* **1972**, *50*, 2591-2602.
- [44] W. D. Marshall, T. T. Nguyen, D. B. MacLean, I. D. Spenser, *Can. J. Chem.* **1975**, *53*, 41-50.
- [45] T. Hemscheidt, I. D. Spenser, *J. Am. Chem. Soc.* **1993**, *115*, 3020-3021.
- [46] T. Hemscheidt, I. D. Spenser, *J. Am. Chem. Soc.* **1990**, *112*, 6360-6363.
- [47] T. Hemscheidt, I. D. Spenser, *J. Am. Chem. Soc.* **1996**, *118*, 1799-1800.
-

- [48] R. N. Gupta, M. Castillo, D. B. MacLean, I. D. Spenser, J. T. Wrobel, *J. Am. Chem. Soc.* **1968**, *90*, 1360-1361.
- [49] M. Castillo, R. N. Gupta, Y. K. Ho, D. B. MacLean, I. D. Spenser, *J. Am. Chem. Soc.* **1970**, *92*, 1074-1075.
- [50] T. Hemscheidt, in *Biosynthesis: Aromatic Polyketides, Isoprenoids, Alkaloids* (Eds.: F. J. Leeper, J. C. Vederas), Springer Berlin Heidelberg, Berlin, Heidelberg, **2000**, pp. 175-206.
- [51] Y. Inubushi, H. Ishii, B. Yasui, T. Harayama, *Tetrahedron Lett.* **1966**, *7*, 1551-1559.
- [52] R. Wang, H. Yan, X.-c. Tang, *Acta Pharmacol. Sin.* **2006**, *27*, 1.
- [53] J. i. Kobayashi, Y. Hirasawa, N. Yoshida, H. Morita, *Tetrahedron Lett.* **2000**, *41*, 9069-9073.
- [54] H. Morita, K. i. Ishiuchi, A. Haganuma, T. Hoshino, Y. Obara, N. Nakahata, J. i. Kobayashi, *Tetrahedron* **2005**, *61*, 1955-1960.
- [55] Y. Hirasawa, H. Morita, M. Shiro, J. i. Kobayashi, *Org. Lett.* **2003**, *5*, 3991-3993.
- [56] J. He, X.-Q. Chen, M.-M. Li, Y. Zhao, G. Xu, X. Cheng, L.-Y. Peng, M.-J. Xie, Y.-T. Zheng, Y.-P. Wang, Q.-S. Zhao, *Org. Lett.* **2009**, *11*, 1397-1400.
- [57] T. Harayama, M. Ohtani, M. Oki, Y. Inubushi, *J. Chem. Soc., Chem. Commun.* **1974**, 827-828.
- [58] J. A. Kozak, G. R. Dake, *Angew. Chem. Int. Ed.* **2008**, *47*, 4221-4223.
- [59] D. Caine, K. Procter, R. A. Cassell, *J. Org. Chem.* **1984**, *49*, 2647-2648.
- [60] A. Carlone, M. Marigo, C. North, A. Landa, K. A. Jorgensen, *Chem. Commun.* **2006**, 4928-4930.
- [61] C. H. Heathcock, K. M. Smith, T. A. Blumenkopf, *J. Am. Chem. Soc.* **1986**, *108*, 5022-5024.
- [62] X. Linghu, J. J. Kennedy-Smith, F. D. Toste, *Angew Chem Int Edit* **2007**, *46*, 7671-7673.
- [63] S. T. Staben, J. J. Kennedy-Smith, D. Huang, B. K. Corkey, R. L. LaLonde, F. D. Toste, *Angew. Chem. Int. Ed.* **2006**, *45*, 5991-5994.
- [64] J. Ramharter, H. Weinstabl, J. Mulzer, *J. Am. Chem. Soc.* **2010**, *132*, 14338-14339.
- [65] J. Ramharter, Doctoral thesis, University of Vienna **2011**.
- [66] J. Zhang, J. Wu, B. Hong, W. Ai, X. Wang, H. Li, X. Lei, *Nat. Commun.* **2014**, *5*, 4614.
- [67] M. S. Kerr, J. Read de Alaniz, T. Rovis, *J. Org. Chem.* **2005**, *70*, 5725-5728.
- [68] F. W. W. Hartrampf, T. Furukawa, D. Trauner, *Angew Chem Int Edit* **2017**, *56*, 893-896.
- [69] Y. Besidsky, K. Luthman, A. Claesson, C. J. Fowler, I. Csoregh, U. Hacksell, *J. Chem. Soc. Perkin Trans. I* **1995**, 465-474.
- [70] F. W. W. Hartrampf, D. Trauner, *J Org Chem* **2017**, *82*, 8206-8212.
- [71] C. Mukai, J. S. Kim, H. Sonobe, M. Hanaoka, *J. Org. Chem.* **1999**, *64*, 6822-6832.
- [72] C. Mukai, J. S. Kim, M. Uchiyama, M. Hanaoka, *Tetrahedron Lett.* **1998**, *39*, 7909-7912.
-

- [73] J. Cassayre, F. Gagosz, S. Z. Zard, *Angew. Chem. Int. Ed.* **2002**, *41*, 1783-1785.
- [74] T. Kozaka, N. Miyakoshi, C. Mukai, *J. Org. Chem.* **2007**, *72*, 10147-10154.
- [75] M. Castillo, L. A. Loyola, G. Morales, I. Singh, C. Calvo, H. L. Rolland, D. B. MacLean, *Can. J. Chem.* **1976**, *54*, 2893-2899.
- [76] M. Castillo, G. Morales, L. A. Loyola, I. Singh, C. Calvo, H. L. Holland, D. B. MacLean, *Can. J. Chem.* **1976**, *54*, 2900-2908.
- [77] G. C. Hirst, T. O. Johnson, L. E. Overman, *J. Am. Chem. Soc.* **1993**, *115*, 2992-2993.
- [78] Y. Otsuka, F. Inagaki, C. Mukai, *J. Org. Chem.* **2010**, *75*, 3420-3426.
- [79] N. Itoh, T. Iwata, H. Sugihara, F. Inagaki, C. Mukai, *Chem. Eur. J.* **2013**, *19*, 8665-8672.
- [80] A. Nakayama, N. Kogure, M. Kitajima, H. Takayama, *Org. Lett.* **2009**, *11*, 5554-5557.
- [81] T. Harayama, M. Takatani, Y. Inubushi, *Tetrahedron Lett.* **1979**, *20*, 4307-4310.
- [82] T. Harayama, M. Takatani, Y. Inubushi, *Chem. Pharm. Bull.* **1979**, *27*, 726-730.
- [83] T. Harayama, M. Takatani, Y. Inubushi, *Chem. Pharm. Bull.* **1980**, *28*, 2394-2402.
- [84] C.-C. Liao, R. K. Peddinti, *Acc. Chem. Res.* **2002**, *35*, 856-866.
- [85] Y. Ito, H. Aoyama, T. Saegusa, *J. Am. Chem. Soc.* **1980**, *102*, 4519-4521.
- [86] H. Takayama, K. Katakawa, M. Kitajima, K. Yamaguchi, N. Aimi, *Tetrahedron Lett.* **2002**, *43*, 8307-8311.
- [87] N. Shimada, Y. Abe, S. Yokoshima, T. Fukuyama, *Angew. Chem. Int. Ed.* **2012**, *51*, 11824-11826.
- [88] F. X. Wang, J. Y. Du, H. B. Wang, P. L. Zhang, G. B. Zhang, K. Y. Yu, X. Z. Zhang, X. T. An, Y. X. Cao, C. A. Fan, *J. Am. Chem. Soc.* **2017**, 4282-4285.
- [89] F.-W. Zhao, Q.-Y. Sun, F.-M. Yang, G.-W. Hu, J.-F. Luo, G.-H. Tang, Y.-H. Wang, C.-L. Long, *Org. Lett.* **2010**, *12*, 3922-3925.
- [90] L.-B. Dong, X. Gao, F. Liu, J. He, X.-D. Wu, Y. Li, Q.-S. Zhao, *Org. Lett.* **2013**, *15*, 3570-3573.
- [91] G. B. Zhang, F. X. Wang, J. Y. Du, H. Qu, X. Y. Ma, M. X. Wei, C. T. Wang, Q. Li, C. A. Fan, *Org. Lett.* **2012**, *14*, 3696-3699.
- [92] S. M. Canham, D. J. France, L. E. Overman, *J. Am. Chem. Soc.* **2010**, *132*, 7876-7877.
- [93] S. M. Canham, D. J. France, L. E. Overman, *J. Org. Chem.* **2013**, *78*, 9-34.
- [94] M. Ernst, G. Helmchen, *Angew. Chem. Int. Ed.* **2002**, *41*, 4054-4056.
- [95] B. Baskar, H. J. Bae, S. E. An, J. Y. Cheong, Y. H. Rhee, A. Duschek, S. F. Kirsch, *Org. Lett.* **2008**, *10*, 2605-2607.
- [96] X.-M. Zhang, Y.-Q. Tu, F.-M. Zhang, H. Shao, X. Meng, *Angew. Chem. Int. Ed.* **2011**, *50*, 3916-3919.
- [97] L.-B. Dong, J. Yang, J. He, H.-R. Luo, X.-D. Wu, X. Deng, L.-Y. Peng, X. Cheng, Q.-S. Zhao, *Chem. Commun.* **2012**, *48*, 9038-9040.
-

- [98] W.-W. Jiang, Y.-C. Liu, Z.-J. Zhang, Y.-C. Liu, J. He, J. Su, X. Cheng, L.-Y. Peng, L.-D. Shao, X.-D. Wu, J.-H. Yang, Q.-S. Zhao, *Fitoterapia* **2016**, *109*, 155-161.
- [99] Copyright © 2010 by Hank L. Oppenheimer. The photograph was obtained from the URL: <https://commons.wikimedia.org/wiki/File:LycopodiumClavatum.jpg> (active as of December 2017) and is licensed under the Creative Commons Attribution-Share Alike 2013.2010 Unported license (<https://creativecommons.org/licenses/by-sa/2013.2010/legalcode>). It is used here in its unmodified form.
- [100] X.-J. Wang, L. Li, S.-S. Yu, S.-G. Ma, J. Qu, Y.-B. Liu, Y. Li, Y. Wang, W. Tang, *Fitoterapia* **2013**, *91*, 74-81.
- [101] C. H. Heathcock, E. Kleinman, E. S. Binkley, *J. Am. Chem. Soc.* **1978**, *100*, 8036-8037.
- [102] H. Yang, R. G. Carter, L. N. Zakharov, *J. Am. Chem. Soc.* **2008**, *130*, 9238-9239.
- [103] M. Elander, K. Leander, J. Rosenblom, E. Ruusa, *Acta Chem. Scand.* **1973**, *27*, 1907-1913.
- [104] W.-W. Fan, F.-Q. Xu, F.-W. Dong, X.-N. Li, Y. Li, Y.-Q. Liu, J. Zhou, J.-M. Hu, *Nat. Prod. Bioprospect.* **2013**, *3*, 89-92.
- [105] C.-W. Jao, W.-C. Lin, Y.-T. Wu, P.-L. Wu, *J. Nat. Prod.* **2008**, *71*, 1275-1279.
- [106] K. Nishikawa, M. Miyamura, Y. Hirata, *Tetrahedron Lett.* **1967**, *8*, 2597-2600.
- [107] H. Suzuki, I. Keimatsu, *J. Pharm. Soc. Japan* **1932**, *52*, 1049-1060.
- [108] H. Suzuki, I. Keimatsu, K. Ito, *J. Pharm. Soc. Japan* **1934**, *54*, 801-819.
- [109] Y. Inubushi, Y. Sasaki, Y. Tsuda, B. Yasui, T. Konita, J. Matsumoto, E. Katarao, J. Nakano, *Tetrahedron* **1964**, *20*, 2007-2023.
- [110] Y. Inubushi, Y. Sasaki, Y. Tsuda, J. Nakano, *Tetrahedron Lett.* **1965**, *6*, 1519-1523.
- [111] A. M. Pridgeon, P. J. Cribb, M. W. Chase, F. N. Rasmussen, *Genera Orchidacearum Volume 6: Epidendroideae*, OUP Oxford, **2014**.
- [112] H. Morita, M. Fujiwara, N. Yoshida, J. i. Kobayashi, *Tetrahedron* **2000**, *56*, 5801-5805.
- [113] S. Yamamura, Y. Hirata, *Tetrahedron Lett.* **1964**, *5*, 79-87.
- [114] T. Okamoto, M. Natsume, T. Onaka, F. Uchimarui, M. Shimizu, *Chem. Pharm. Bull.* **1966**, *14*, 672-675.
- [115] Y. Inubushi, J. Nakano, *Tetrahedron Lett.* **1965**, *6*, 2723-2728.
- [116] I. Granelli, K. Leander, *Acta Chem. Scand.* **1970**, *24*, 1108-1109.
- [117] S. Masaaki, Y. Kiyoyuki, H. Yoshimasa, *Chem. Lett.* **1975**, *4*, 611-614.
- [118] P. F. G. Boullay, *Ann. Chem. Phys.* **1811**, *80*, 209.
- [119] A. Takeuchi, N. Takeuchi, *The Journal of Physiology* **1969**, *205*, 377-391.
- [120] R. W. Olsen, *Proceedings of the National Academy of Sciences* **2006**, *103*, 6081-6082.
- [121] T. H. Easterfield, B. C. Aston, *Journal of the Chemical Society, Transactions* **1901**, *79*, 120-126.
-

- [122] J. Fuentealba, L. Guzmán, P. Manríquez-Navarro, C. Pérez, M. Silva, J. Becerra, L. G. Aguayo, *Eur. J. Pharmacol.* **2007**, *559*, 61-64.
- [123] M. Yamazaki, M. Matsuo, K. Arai, *Chem. Pharm. Bull.* **1966**, *14*, 1058-1059.
- [124] O. E. Edwards, J. L. Douglas, B. Mootoo, *Can. J. Chem.* **1970**, *48*, 2517-2524.
- [125] A. Corbella, P. Gariboldi, G. Jommi, M. Sisti, *J. Chem. Soc., Chem. Commun.* **1975**, 288-289.
- [126] A. Corbella, P. Gariboldi, G. Jommi, *J. Chem. Soc., Chem. Commun.* **1973**, 729-730.
- [127] M. Biollaz, D. Arigoni, *Journal of the Chemical Society D: Chemical Communications* **1969**, 633-634.
- [128] A. Corbella, P. Gariboldi, G. Jommi, C. Scolastico, *Journal of the Chemical Society D: Chemical Communications* **1969**, 634-635.
- [129] A. Corbella, P. Gariboldi, G. Jommi, *J. Chem. Soc., Chem. Commun.* **1972**, 600-600.
- [130] Q. Li, G. Ding, B. Li, S.-X. Guo, *Scientific Reports* **2017**, *7*, 316.
- [131] L. A. Porter, *Chem. Rev.* **1967**, *67*, 441-464.
- [132] K. K. Chen, A. L. Chen, *J. Biol. Chem.* **1935**, *111*, 653-658.
- [133] K. K. Chen, A. L. Chen, *J. Pharmacol. Exp. Ther.* **1935**, *55*, 319-325.
- [134] Y. Kudo, A. Tanaka, K. Yamada, *Br. J. Pharmacol.* **1983**, *78*, 709-715.
- [135] R. Li, T. Liu, M. Liu, F. Chen, S. Liu, J. Yang, *J. Agric. Food Chem.* **2017**, *65*, 3665-3674.
- [136] K. Yamada, M. Suzuki, Y. Hayakawa, K. Aoki, H. Nakamura, H. Nagase, Y. Hirata, *J. Am. Chem. Soc.* **1972**, *94*, 8278-8280.
- [137] Y. Inubushi, T. Kikuchi, T. Ibuka, K. Tanaka, I. Saji, K. Tokane, *J. Chem. Soc., Chem. Commun.* **1972**, 1252-1253.
- [138] L. Ruzicka, L. Sternbach, *Helv. Chim. Acta* **1940**, *23*, 355-363.
- [139] R. F. Borch, *Tetrahedron Lett.* **1968**, *9*, 61-65.
- [140] Y. Inubushi, T. Kikuchi, T. Ibuka, K. Tanaka, I. Saji, K. Tokane, *Chem. Pharm. Bull.* **1974**, *22*, 349-367.
- [141] C. B. C. Boyce, J. S. Whitehurst, *Journal of the Chemical Society (Resumed)* **1960**, 4547-4553.
- [142] W. Nagata, M. Yoshioka, *Tetrahedron Lett.* **1966**, *7*, 1913-1918.
- [143] A. S. Kende, T. J. Bentley, R. A. Mader, D. Ridge, *J. Am. Chem. Soc.* **1974**, *96*, 4332-4334.
- [144] *Proceedings of the Royal Society of London. Series A* **1933**, *143*, 177-191.
- [145] Q.-Y. Hu, G. Zhou, E. J. Corey, *J. Am. Chem. Soc.* **2004**, *126*, 13708-13713.
- [146] R. F. Borch, A. J. Evans, J. J. Wade, *J Am Chem Soc* **1977**, *99*, 1612-1619.
- [147] C. H. Lee, M. Westling, T. Livinghouse, A. C. Williams, *J. Am. Chem. Soc.* **1992**, *114*, 4089-4095.
-

- [148] C.-K. Sha, R.-T. Chiu, C.-F. Yang, N.-T. Yao, W.-H. Tseng, F.-L. Liao, S.-L. Wang, *J. Am. Chem. Soc.* **1997**, *119*, 4130-4135.
- [149] T. Osamu, T. Hiroshi, K. Kunio, H. Kazuo, *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1907-1911.
- [150] J. Cassayre, B. Quiclet-Sire, J.-B. Saunier, S. Z. Zard, *Tetrahedron* **1998**, *54*, 1029-1040.
- [151] B. M. Trost, A. S. Tasker, G. Ruther, A. Brandes, *J. Am. Chem. Soc.* **1991**, *113*, 670-672.
- [152] B. M. Trost, *Acc. Chem. Res.* **1980**, *13*, 385-393.
- [153] S. F. Martin, W. Li, *J. Org. Chem.* **1991**, *56*, 642-650.
- [154] S. F. Martin, W. Li, *J. Org. Chem.* **1989**, *54*, 265-268.
- [155] M. Mori, N. Uesaka, M. Shibasaki, *J. Org. Chem.* **1992**, *57*, 3519-3521.
- [156] N. Uesaka, F. Saitoh, M. Mori, M. Shibasaki, K. Okamura, T. Date, *J. Org. Chem.* **1994**, *59*, 5633-5642.
- [157] A. Padwa, M. Dimitroff, B. Liu, *Org. Lett.* **2000**, *2*, 3233-3235.
- [158] A. Padwa, M. A. Brodney, M. Dimitroff, B. Liu, T. Wu, *J. Org. Chem.* **2001**, *66*, 3119-3128.
- [159] A. Padwa, A. C. Flick, in *Adv. Heterocycl. Chem.*, Vol. 110 (Ed.: A. R. Katritzky), Academic Press, **2013**, pp. 1-41.
- [160] Y. Lee, E. M. Rochette, J. Kim, D. Y. K. Chen, *Angew. Chem. Int. Ed.* **2017**, *56*, 12250-12254.
- [161] F. Lopez, A. W. van Zijl, A. J. Minnaard, B. L. Feringa, *Chem. Commun.* **2006**, 409-411.
- [162] Q. Li, Z.-X. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 4542-4543.
- [163] J. M. Howell, K. Feng, J. R. Clark, L. J. Trzepakowski, M. C. White, *J. Am. Chem. Soc.* **2015**, *137*, 14590-14593.
- [164] L. V. Desai, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2004**, *126*, 9542-9543.
- [165] M. Bishop, J. Pietruszka, *Synlett* **2011**, *2011*, 2689-2692.
- [166] N. R. Gade, J. Iqbal, *Eur. J. Org. Chem.* **2014**, *2014*, 6558-6564.
- [167] P. E. Gormisky, M. C. White, *J. Am. Chem. Soc.* **2011**, *133*, 12584-12589.
- [168] G. van Meer, D. R. Voelker, G. W. Feigenson, *Nat. Rev. Mol. Cell Biol.* **2008**, *9*, 112.
- [169] M. Sud, E. Fahy, D. Cotter, A. Brown, E. A. Dennis, C. K. Glass, J. A. H. Merrill, R. C. Murphy, C. R. H. Raetz, D. W. Russell, S. Subramaniam, *Nucleic Acids Res.* **2007**, *35*, D527-D532.
- [170] J. Koolman, K.-H. Röhm, *Color atlas of biochemistry*, 3rd ed., Thieme, Stuttgart, **2013**.
- [171] T. Harayama, H. Riezman, *Nat. Rev. Mol. Cell Biol.* **2018**.
- [172] M. A. Kol, A. I. P. M. de Kroon, J. A. Killian, B. de Kruijff, *Biochemistry* **2004**, *43*, 2673-2681.
- [173] P. F. Devaux, R. Morris, *Traffic* **2004**, *5*, 241-246.
- [174] C. Eggeling, C. Ringemann, R. Medda, G. Schwarzmann, K. Sandhoff, S. Polyakova, V. N. Belov, B. Hein, C. von Middendorff, A. Schönle, S. W. Hell, *Nature* **2008**, *457*, 1159.
-

- [175] K. Simons, E. Ikonen, *Nature* **1997**, 387, 569.
- [176] K. A. Field, D. Holowka, B. Baird, *Proc. Natl. Acad. Sci. U. S. A.* **1995**, 92, 9201-9205.
- [177] L. J. Pike, *J. Lipid Res.* **2003**, 44, 655-667.
- [178] J. A. Frank, H. G. Franquelim, P. Schwille, D. Trauner, *J. Am. Chem. Soc.* **2016**, 138, 12981-12986.
- [179] J. A. Allen, R. A. Halverson-Tamboli, M. M. Rasenick, *Nat. Rev. Neurosci.* **2006**, 8, 128.
- [180] P. E. Bickel, *American Journal of Physiology-Endocrinology and Metabolism* **2002**, 282, E1-E10.
- [181] K. Simons, D. Toomre, *Nat. Rev. Mol. Cell Biol.* **2000**, 1, 31.
- [182] X. Wang, *Current Opinion in Plant Biology* **2004**, 7, 329-336.
- [183] C. N. Serhan, J. Savill, *Nat. Immunol.* **2005**, 6, 1191.
- [184] J. A. Salmon, G. A. Higgs, *British Medical Bulletin* **1987**, 43, 285-296.
- [185] Y. Nishizuka, *Science* **1992**, 258, 607-614.
- [186] D. Meyer zu Heringdorf, K. H. Jakobs, *Biochimica et Biophysica Acta (BBA) - Biomembranes* **2007**, 1768, 923-940.
- [187] Y. A. Hannun, L. M. Obeid, *Nat. Rev. Mol. Cell Biol.* **2008**, 9, 139.
- [188] D. R. Body, *Progress in Lipid Research* **1988**, 27, 39-60.
- [189] M. T. Nakamura, B. E. Yudell, J. J. Loor, *Progress in Lipid Research* **2014**, 53, 124-144.
- [190] H. Schulz, *Biochimica et Biophysica Acta (BBA) - Lipids and Lipid Metabolism* **1991**, 1081, 109-120.
- [191] C. Hammond, in *Cellular and Molecular Neurophysiology (Fourth edition)*, Academic Press, Boston, **2015**, pp. 39-54.
- [192] G. S. Tomassy, D. R. Berger, H.-H. Chen, N. Kasthuri, K. J. Hayworth, A. Vercelli, H. S. Seung, J. W. Lichtman, P. Arlotta, *Science* **2014**, 344, 319-324.
- [193] J. L. W. Thudichum, *A treatise on the chemical constitution of the brain*, Bailliere, Tindall and Cox, London, **1884**.
- [194] G. van Echten-Deckert, T. Herget, *Biochimica et Biophysica Acta (BBA) - Biomembranes* **2006**, 1758, 1978-1994.
- [195] T. Hla, Andrew J. Dannenberg, *Cell Metab.* **2012**, 16, 420-434.
- [196] M. Maceyka, K. B. Harikumar, S. Milstien, S. Spiegel, *Trends in Cell Biology* **2012**, 22, 50-60.
- [197] W. Stillwell, in *An Introduction to Biological Membranes (Second Edition)*, Elsevier, **2016**, pp. 331-347.
- [198] J. A. Shayman, P. D. Killen, in *Molecular and Genetic Basis of Renal Disease* (Ed.: M. R. Pollak), W.B. Saunders, Philadelphia, **2008**, pp. 195-199.
- [199] T. Sanchez, T. Hla, *J. Cell. Biochem.* **2004**, 92, 913-922.
- [200] T. Hla, *Seminars in Cell & Developmental Biology* **2004**, 15, 513-520.
-

- [201] S. E. Alvarez, K. B. Harikumar, N. C. Hait, J. Allegood, G. M. Strub, E. Y. Kim, M. Maceyka, H. Jiang, C. Luo, T. Kordula, S. Milstien, S. Spiegel, *Nature* **2010**, *465*, 1084.
- [202] Y. A. Hannun, L. M. Obeid, *Nat. Rev. Mol. Cell Biol.* **2017**.
- [203] M. P. Wymann, R. Schneiter, *Nat. Rev. Mol. Cell Biol.* **2008**, *9*, 162.
- [204] W. A. Velema, W. Szymanski, B. L. Feringa, *J. Am. Chem. Soc.* **2014**, *136*, 2178-2191.
- [205] J. Broichhagen, J. A. Frank, D. Trauner, *Acc. Chem. Res.* **2015**, *48*, 1947-1960.
- [206] M. Dong, A. Babalhavaeji, S. Samanta, A. A. Beharry, G. A. Woolley, *Acc. Chem. Res.* **2015**, *48*, 2662-2670.
- [207] Y. Takeo, S. Takahiro, T. Takashi, I. Kunihiro, *Bull. Chem. Soc. Jpn.* **1992**, *65*, 649-656.
- [208] S. Wiedbrauk, B. Maerz, E. Samoylova, A. Reiner, F. Trommer, P. Mayer, W. Zinth, H. Dube, *J. Am. Chem. Soc.* **2016**, *138*, 12219-12227.
- [209] G. Berkovic, V. Krongauz, V. Weiss, *Chem. Rev.* **2000**, *100*, 1741-1754.
- [210] M. Levitus, G. Glasser, D. Neher, P. F. Aramendía, *Chem. Phys. Lett.* **1997**, *277*, 118-124.
- [211] M. Irie, *Chem. Rev.* **2000**, *100*, 1685-1716.
- [212] A. A. Beharry, G. A. Woolley, *Chem. Soc. Rev.* **2011**, *40*, 4422-4437.
- [213] W. Szymański, J. M. Beierle, H. A. V. Kistemaker, W. A. Velema, B. L. Feringa, *Chem. Rev.* **2013**, *113*, 6114-6178.
- [214] M. Volgraf, P. Gorostiza, S. Szobota, M. R. Helix, E. Y. Isacoff, D. Trauner, *J. Am. Chem. Soc.* **2007**, *129*, 260-261.
- [215] L. Laprell, E. Repak, V. Franckevicius, F. Hartrampf, J. Terhag, M. Hollmann, M. Sumser, N. Rebola, D. A. DiGregorio, D. Trauner, *Nat. Commun.* **2015**, *6*, 8076.
- [216] M. Stein, S. J. Middendorp, V. Carta, E. Pejo, D. E. Raines, S. A. Forman, E. Sigel, D. Trauner, *Angew. Chem. Int. Ed.* **2012**, *51*, 10500-10504.
- [217] A. Mourot, T. Fehrentz, Y. Le Feuvre, C. M. Smith, C. Herold, D. Dalkara, F. Nagy, D. Trauner, R. H. Kramer, *Nat. Meth.* **2012**, *9*, 396.
- [218] M. Borowiak, W. Nahaboo, M. Reynders, K. Nekolla, P. Jalinot, J. Hasserodt, M. Rehberg, M. Delattre, S. Zahler, A. Vollmar, D. Trauner, O. Thorn-Seshold, *Cell*, *162*, 403-411.
- [219] J. A. Frank, D. A. Yushchenko, D. J. Hodson, N. Lipstein, J. Nagpal, G. A. Rutter, J.-S. Rhee, A. Gottschalk, N. Brose, C. Schultz, D. Trauner, *Nat. Chem. Biol.* **2016**, *12*, 755.
- [220] H. Fujiwara, Y. Yonezawa, *Nature* **1991**, *351*, 724.
- [221] X. Song, J. Perlstein, D. G. Whitten, *J. Am. Chem. Soc.* **1997**, *119*, 9144-9159.
- [222] K. Eggers, T. M. Fyles, P. J. Montoya-Pelaez, *J. Org. Chem.* **2001**, *66*, 2966-2977.
- [223] J. A. Frank, M. Moroni, R. Moshourab, M. Sumser, G. R. Lewin, D. Trauner, *Nat. Commun.* **2015**, *6*, 7118.
-



- [224] C. Pernpeintner, J. A. Frank, P. Urban, C. R. Roeske, S. D. Pritzl, D. Trauner, T. Lohmüller, *Langmuir* **2017**, *33*, 4083-4089.
- [225] M. V. Westphal, M. A. Schafroth, R. C. Sarott, M. A. Imhof, C. P. Bold, P. Leippe, A. Dhopeshwarkar, J. M. Grandner, V. Katritch, K. Mackie, D. Trauner, E. M. Carreira, J. A. Frank, *J. Am. Chem. Soc.* **2017**, *139*, 18206-18212.
- [226] F. G. Tafesse, K. Huitema, M. Hermansson, S. van der Poel, J. van den Dikkenberg, A. Uphoff, P. Somerharju, J. C. M. Holthuis, *J. Biol. Chem.* **2007**, *282*, 17537-17547.
- [227] C. Peters, A. Billich, M. Ghobrial, K. Högenauer, T. Ullrich, P. Nussbaumer, *J. Org. Chem.* **2007**, *72*, 1842-1845.
- [228] A. N. Rai, A. Basu, *Org. Lett.* **2004**, *6*, 2861-2863.
- [229] H. Seike, I. Ghosh, Y. Kishi, *Org. Lett.* **2006**, *8*, 3865-3868.
- [230] J. R. Falck, R. Kodela, R. Manne, K. R. Atcha, N. Puli, N. Dubasi, V. L. Manthathi, J. H. Capdevila, X.-Y. Yi, D. H. Goldman, C. Morisseau, B. D. Hammock, W. B. Campbell, *J. Med. Chem.* **2009**, *52*, 5069-5075.
- [231] W. Oppolzer, R. N. Radinov, E. El-Sayed, *J. Org. Chem.* **2001**, *66*, 4766-4770.
- [232] E. J. Eisenbraun, *Org. Synth.* **1965**, *45*, 28.
- [233] N. F. Hepfinger, C. E. Griffin, *Tetrahedron Lett.* **1963**, *4*, 1361-1364.
- [234] J. Strueben, P. J. Gates, A. Staubitz, *J. Org. Chem.* **2014**, *79*, 1719-1728.
- [235] A. J. Chalk, S. A. Magennis, *The Journal of Organic Chemistry* **1976**, *41*, 1206-1209.
- [236] I. Ojima, E. S. Vidal, *J. Org. Chem.* **1998**, *63*, 7999-8003.
- [237] P. Garner, *Tetrahedron Lett.* **1984**, *25*, 5855-5858.
- [238] P. Haberkant, F. Stein, D. Höglinger, M. J. Gerl, B. Brügger, P. P. Van Veldhoven, J. Krijgsveld, A.-C. Gavin, C. Schultz, *ACS Chem. Biol.* **2016**, *11*, 222-230.
- [239] K. Huitema, J. v. d. Dikkenberg, J. F. Brouwers, J. C. Holthuis, *The EMBO Journal* **2004**, *23*, 33-44.
- [240] S. Yang, S.-J. Chen, M.-F. Hsu, J.-D. Wu, C.-T. K. Tseng, Y.-F. Liu, H.-C. Chen, C.-W. Kuo, C.-S. Wu, L.-W. Chang, W.-C. Chen, S.-Y. Liao, T.-Y. Chang, H.-H. Hung, H.-L. Shr, C.-Y. Liu, Y.-A. Huang, L.-Y. Chang, J.-C. Hsu, C. J. Peters, A. H. J. Wang, M.-C. Hsu, *Journal of Medicinal Chemistry* **2006**, *49*, 4971-4980.
- [241] S. Hanessian, R. Margarita, *Tetrahedron Letters* **1998**, *39*, 5887-5890.
- [242] B. E. Love, E. G. Jones, *The Journal of Organic Chemistry* **1999**, *64*, 3755-3756.
- [243] N. Becker, E. M. Carreira, *Org. Lett.* **2007**, *9*, 3857-3858.
-