The Total Synthesis of Waihoensene and Studies Toward the Syntheses of Vallesamidine and Lyconadin C

Doctoral thesis for obtaining the academic degree

Doctor of Natural Science

(Dr. rer. nat.)

submitted by

Lisa-Catherine Rosenbaum

at the

Universität Konstanz

Faculty of Sciences

Department of Chemistry

Konstanz, 2022

Konstanzer Online-Publikations-System (KOPS)
URL: http://nbn-resolving.de/urn:nbn:de:bsz:352-2-r1hohn0b9dbk4

Date of the oral examination: 04 July 2022

1. Reviewer: Prof. Dr. Tanja Gaich

2. Reviewer: Prof. Dr. Rainer Winter

3. Reviewer: Prof. Dr. Andreas Marx

„Zwei Dinge sind zu unserer Arbeit nötig: Unermüdliche Ausdauer und die Bereitschaft, etwas, in das man viel Zeit und Arbeit gesteckt hat, wieder wegzuwerfen.“

Albert Einstein

Parts of this thesis have been presented at scientific conferences or have been published as scientific articles:

24. Tag der Organischen Chemie der Universität Stuttgart, Universität Stuttgart, 15.10.2021
Oral Presentation: “The Total Synthesis of Waihoensene”

L.-C. Rosenbaum*, M. Häfner*, T. Gaich, “Total Synthesis of the Diterpene Waihoensene”, *Angew. Chem. Int. Ed.* **2021**, *60*, 2939-2942.

Further publications not discussed in this thesis:

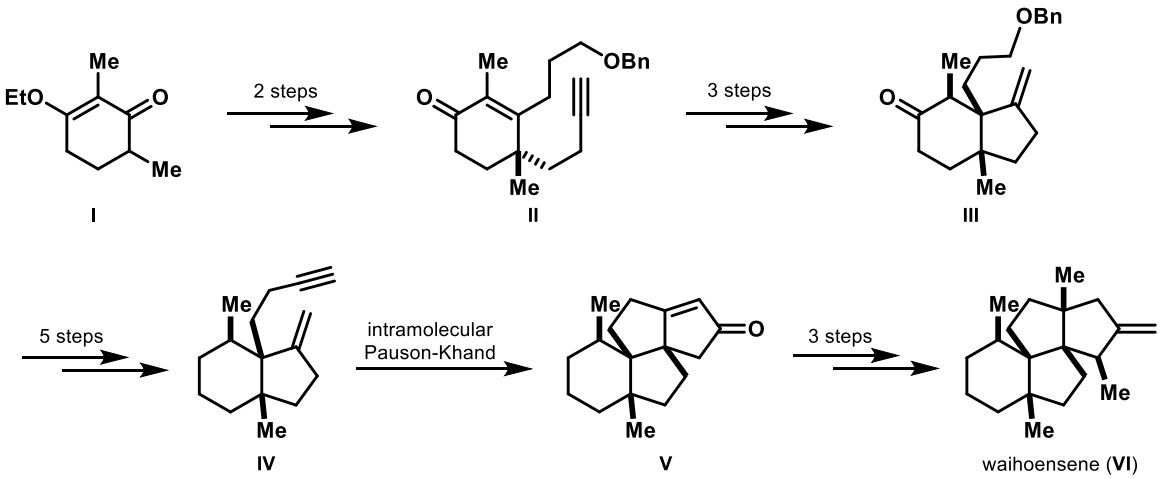
J. Opel*, **L.-C. Rosenbaum***, J. Brunner, A. Staiger, R. Zimmermanns, M. Kellermeier, T. Gaich, H. Cölfen, J.-M. García-Ruiz, “Light-switchable anchors on magnetized biomorphic microcarriers”, *J. Mater. Chem. B* **2020**, *8*, 4831-4835.

L. A. Casper, S. Oßwald, P. Anders, **L.-C. Rosenbaum**, R. F. Winter, “Extremely Electron-Poor Bis(diarylmethylium)-Substituted Ferrocenes and the First Peroxoferrocenophane”, *Z. Anorg. Allg. Chem.* **2020**, *646*, 712-725.

Abstract

I.

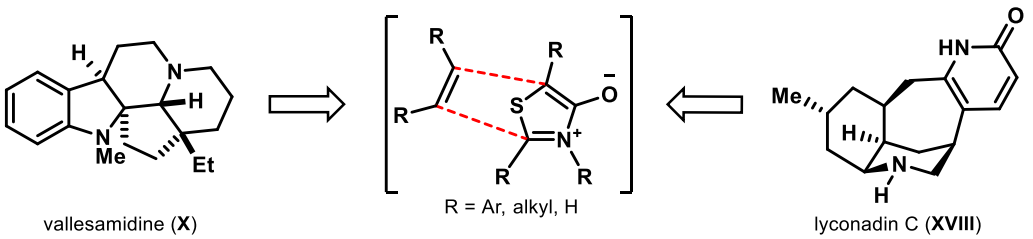
The total synthesis of waihoensene (**VI**) is described in the first part of this thesis. Herein the key reaction for construction of the unique carbon skeleton of the diterpene natural product is an intramolecular Pauson-Khand reaction. Several precedent attempts on the synthesis of a suitable cycloaddition precursor as well as a 14-step racemic total synthesis are discussed. Within this synthetic sequence, enone **II** was available in two steps from commercially available vinylogous ester **I** and allowed for stereoselective construction of the *cis*-hydrindane motif in **III** by use of a tin-mediated radical cyclization.



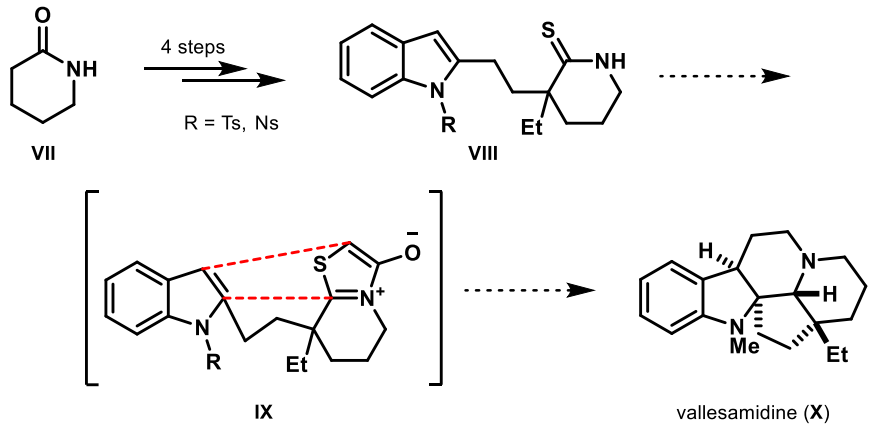
The fused tetracyclic carbon skeleton of waihoensene was delivered by an intramolecular Pauson-Khand reaction of cycloaddition precursor **IV** and converted to the hydrocarbon natural product in three further steps. In addition, the results of cooperative work with Dr. Maximilian Häfner on the enantioselective total synthesis of (+)-waihoensene are presented.

II.

Synthetic studies toward the total syntheses of the two alkaloid natural products vallesamidine (**X**) and lyconadin C (**XVIII**) are described in the second part of this thesis. In both cases, the intramolecular [3+2]-cycloaddition of a transient thioisomünchnone dipole was intended as key transformation for construction of the fused polycyclic skeleton of the natural product.

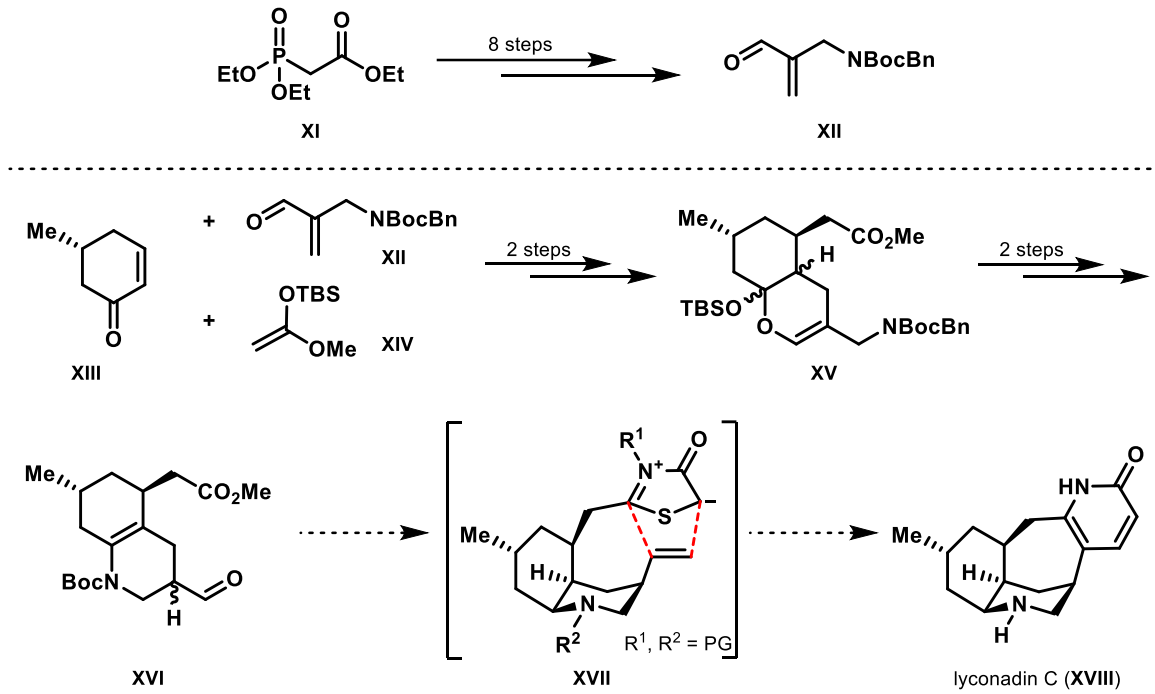


With regard to a potential synthetic access to the monoterpenoid trialkylindoline alkaloid vallesamidine (**X**), the short synthesis of two cycloaddition precursor thiolactams **VIII** from commercial 2-piperidone (**VII**) *via* different alkylation strategies and palladium(0)-mediated indole synthesis is presented. Furthermore, studies on the formation and planned cycloaddition of the corresponding intermediate thioisomünchnone dipoles **IX** are presented.



The synthetic efforts toward the *Lycopodium* alkaloid lyconadin C (**XVIII**) comprised the development of a sequence for preparation of a suitable Michael acceptor **XII**, which was accomplished in eight steps from commercially available triethylphosphono acetate (**XI**). Successful conjunction of the start building blocks **XIII**, **XII** and **XIV** afforded the bicyclic intermediate **XV**. Extensive studies on the accessibility of ene-carbamate **XVI** from **XV** were conducted and allowed for successful transformation in two steps.

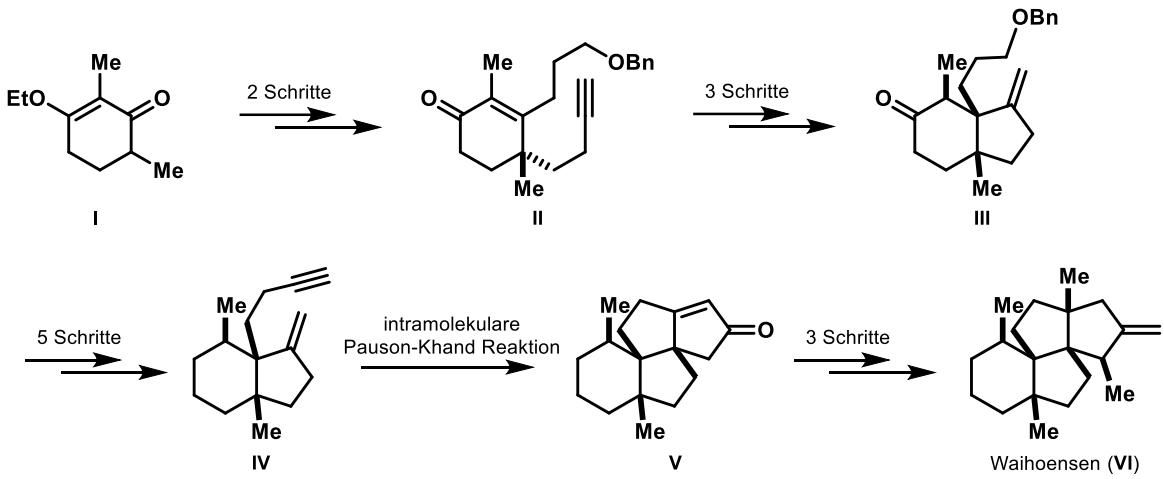
In addition, analysis of this intermediate and an outlook on further elaboration of the planned synthesis of lyconadin C (**XVIII**) *via* [3+2]-cycloaddition of thioisomünchnone **XVII** are given.



Zusammenfassung

I.

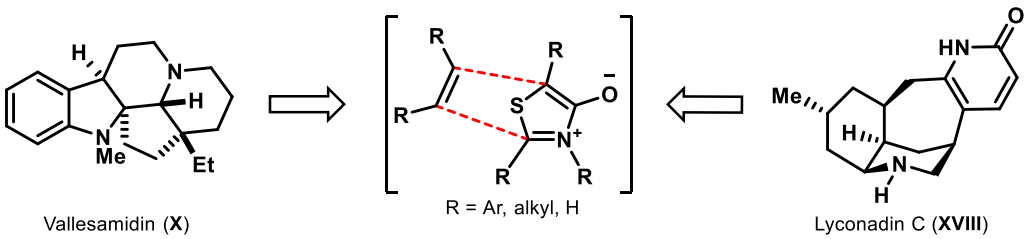
Der erste Teil dieser Arbeit präsentiert die Totalsynthese von Waihoensen (**VI**). Der Schlüsselschritt zum Aufbau des einzigartigen Kohlenstoffgerüsts des Diterpen-Naturstoffes ist eine intramolekulare Pauson-Khand Reaktion. Mehrere Ansätze zur Synthese einer geeigneten Vorläuferverbindung für diese Schlüsselreaktion sowie die erfolgreiche racemische Totalsynthese von Waihoensen (**VI**) in 14 Schritten werden vorgestellt und diskutiert. Enon **II** wurde dabei in zwei Schritten aus dem kommerziell erhältlichen vinylogen Ester **I** erhalten und ermöglichte überdies den stereoelektiven Aufbau des *cis*-Hydrindan Strukturmotivs in **III** über eine Zinn-vermittelte radikalische Ringschlussreaktion.



Das vollständige Molekülgerüst des Naturstoffes, welches aus vier kondensierten Kohlenstoffringen besteht, wurde in einer intramolekularen Pauson-Khand Reaktion aus der Cycloadditions-Vorläuferverbindung **IV** erzeugt und anschließend über drei weitere Schritte in den Kohlenwasserstoff Waihoensen (**VI**) überführt. Darüber hinaus werden die Ergebnisse einer gemeinschaftlichen Arbeit mit Dr. Maximilian Häfner zur enantio-selektiven Totalsynthese von (+)-Waihoensen präsentiert.

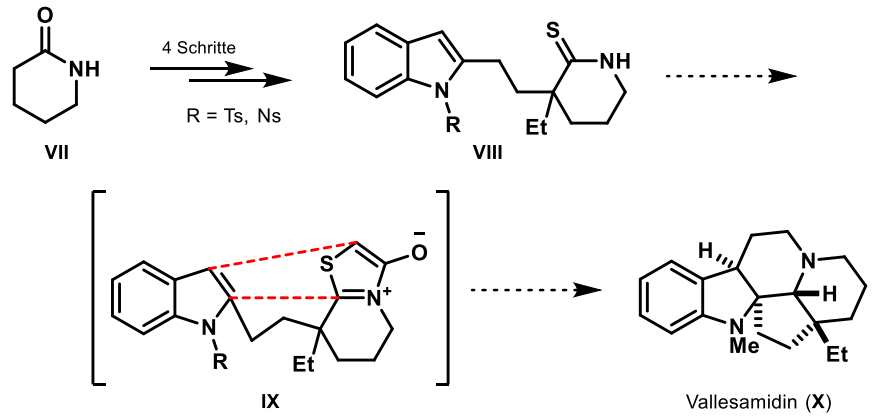
II.

Im zweiten Teil der Arbeit werden synthetische Studien zur versuchten Totalsynthese zweier Alkaloid-Naturstoffe, Vallesamidin (**X**) und Lyconadin C (**XVIII**), beschrieben. In beiden Fällen sollte das Gerüst aus mehreren fusionierten Ringen über die intramolekulare [3+2]-Cycloadditionsreaktion eines kurzlebigen Thioisomünchnon-Dipols aufgebaut werden.



Vallesamidin (**X**) R = Ar, alkyl, H Lyconadin C (**XVIII**)

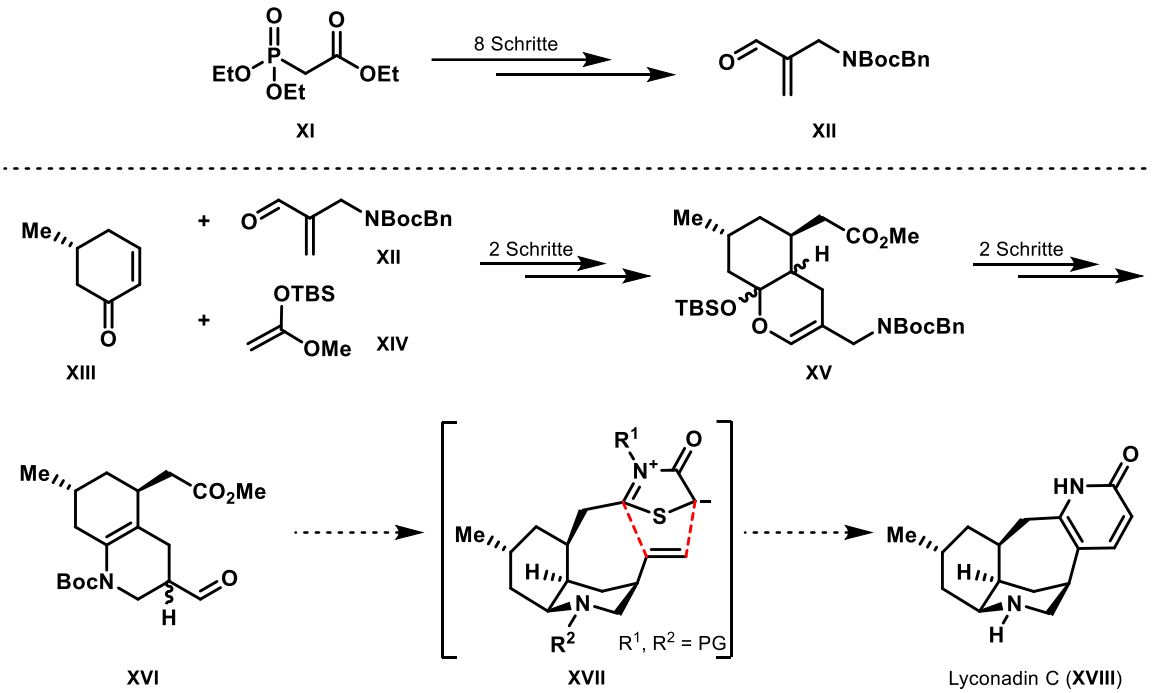
Hinsichtlich eines synthetischen Zugangs zu dem monoterpenoiden Trialkylindolin-Alkaloid Vallesamidin (**X**) wird die Synthese zweier möglicher Vorläuferverbindungen, Thiolactame **VIII**, ausgehend von kommerziell erhältlichem 2-Piperidon (**VII**) vorgestellt. Es werden verschiedene Alkylierungsstrategien sowie eine Palladium-katalysierte Indolsynthese thematisiert. Zudem wird die Bildung und geplante Cycloadditionsreaktion der jeweiligen intermediären Thioisomünchnon-Dipole **IX** untersucht und diskutiert.



VII **VIII** **IX** Vallesamidin (**X**)

Die synthetischen Arbeiten im Rahmen der geplanten Totalsynthese des *Lycopodium*-Alkaloids Lyconadin C (**XVIII**) beinhalteten unter anderem die Entwicklung einer Sequenz zur Herstellung eines geeigneten Michael-Akzeptors **XII**. Diese konnte ausgehend von kommerziell erhältlichem Triethylphosphonoacetat (**XI**) in acht Schritten realisiert werden. Die bicyclische Zwischenstufe **XV** wurde durch erfolgreiche Verknüpfung der Ausgangsverbindungen **XIII**, **XII** und **XIV** erhalten. Ausführliche Untersuchungen zur Umwandlung von **XV** in das gewünschte En-Carbamat **XVI** wurden durchgeführt und

erlaubten dessen Darstellung in zwei weiteren Schritten. Weiterhin wird die Analyse dieser Zwischenverbindung thematisiert, sowie ein Ausblick auf die weitere Ausarbeitung der geplanten synthetischen Sequenz über den Thioisomünchnon-Dipol **XVII** hin zu Lyconadin C (**XVIII**) gegeben.



List of Abbreviations

[α]	specific rotation
2D	two-dimensional
9-BBN	9-borabicyclo[3.3.1]nonane
ABSA	*p*-acetamidobenzenesulfonyl azide
Ac	acetyl
acac	acetylacetonate
ADP	adenosine diphosphate
AIBN	2,2'-azobis(2-methylpropionitrile)
APCI	atomic pressure chemical ionization
Ar	aryl
ATP	adenosine triphosphate
b.p.	boiling point
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
brsm	based on recovered starting material
calc.	calculated
CAR	collision activated reaction
cat.	catalytic
Cbz	benzyloxycarbonyl
CDI	carbonyldiimidazole
CDP-MEP	4-diphosphocytidyl-2-*C*-methyl-D-erythritol 2-phosphate
COSY	correlation spectroscopy
Cp	cyclopentadienyl
Cy	cyclohexyl
DAAA	decarboxylative asymmetric allylic alkylation
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimid
DCE	1,2-dichloroethane
DCM	methylene chloride

DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DFT	density functional theory
DiBAL-H	diisobutylaluminium hydride
DIPA	diisopropylamine
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMAPP	dimethylallyl pyrophosphate
DMF	*N,N*-dimethylformamide
DMP	Dess–Martin periodinane
DMPU	*N,N*'-dimethylpropyleneurea
DMSO	dimethylsulfoxide
DNPH	dinitrophenylhydrazine
DOXP	1-deoxy-D-xylulose-5-phosphate
dppf	1,1'-Bis(diphenylphosphino)ferrocene
DXR	1-deoxy-D-xylulose-5-phosphate reductoisomerase
DXS	1-deoxy-D-xylulose-5-phosphate synthase
e.g.	*exempli gratia*
EA	ethyl acetate
EDG	electron donating group
ee	enantiomeric excess
EI	electron ionisation
ESI	electrospray ionisation
Et	ethyl
et al.	*et alii*
EWG	electron withdrawing group
FGI	functional group interconversion
FGPP	farnesylgeranyl pyrophosphate
FPP	farnesyl pyrophosphate
GGPP	geranylgeranyl pyrophosphate
GPP	geranyl pyrophosphate
HAT	hydrogen atom transfer
HG II	second generation Hoveyda–Grubbs catalyst

HMBC	heteronuclear multiple bond correlation spectroscopy
HMBPP	(*E*)-4-hydroxy-3-methylbut-2-enyl pyrophosphate
HMG	hydroxy-3-methylglutaryl
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HR-MS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation spectroscopy
HWE-reaction	Horner-Wadsworth-Emmons reaction
hv	light irradiation
IBX	2-iodoxybenzoic acid
i.e.	*id est*
IPP	isopentenyl pyrophosphate
i-Pr	*iso*-propyl
IR	infrared spectroscopy
J	coupling constant
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium *N,N*-diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
LiICA	lithium cyclohexylisopropylamide
LiTMP	lithium 2,2,6,6-tetramethylpiperidide
m	*meta*
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MeOH	methanol
MEP	2*C*-methyl-D-erythritol-4-phosphate
MOM	methoxymethyl
Ms	methylsulfonyl
MVA	mevalonate
NADPH	nicotinamide adenine dinucleotide phosphate
NaHMDS	sodium bis(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
n-BuLi	*n*-butyllithium

NEt_3	triethylamine
NHS	*N*-hydroxysuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
Ns	nitrobenzenesulfonyl
Nu	nucleophile
o	*ortho*
OAc	acetate
p	*para*
PDC	pyridinium dichromate
PE	petroleum ether
PG	protecting group
Ph	phenyl
PhH	benzene
PhMe	toluene
PKR	Pauson-Khand reaction
PPTS	pyridinium *para*-toluenesulfonate
pyr	pyridine
quant.	quantitative
r.t.; RT	room temperature
R_F	retardation factor
t	time
T	temperature
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	tetra(*n*-butyl)ammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
TCDI	thiocarbonyldiimidazole
Tf	trifluoromethylsulfonyl

TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMANO	trimethylamine *N*-oxide
TMEDA	*N,N,N´,N´*-tetramethylethylenediamine
TMM	tetramethylenemethane
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Trt	trityl; triphenylmethyl
Ts	*p*-toluenesulfonyl
TTMSS	tris(trimethylsilyl)silane
UV-Vis	ultraviolet – visble (light)
δ	chemical shift

Table of Contents

Abstract VIII

Zusammenfassung XI

List of Abbreviations XIV

Table of Contents XIX

I. The Total Synthesis of Waihoensene 1

1. Introduction 2

1.1 Natural Products and Total Synthesis 2

1.2 Terpene Natural Products 3

1.2.1 Classification 4

1.2.2 Biosynthesis 5

1.2.3 Triquinane Natural Products 9

1.3 The Podocarp Diterpene (+)-Waihoensene 14

1.3.1 Isolation and Structural Characterization 14

1.3.2 Previous Total Syntheses and Synthetic Approaches toward Waihoensene 16

1.3.3 Preliminary Work in our Group 23

1.4 The Pauson-Khand [2+2+1]-Cycloaddition Reaction 25

1.4.1 Mechanistic Aspects 25

1.4.2 Scope and Limitations 28

1.4.3 Application in Total Synthesis 31

2. Results and Discussion 34

2.1 Approach A: Construction of the *cis*-Hydrindane Core Structure *via* Reductive Olefin Coupling 34

2.1.1 Retrosynthetic Analysis 34

2.1.2 Attempts toward the Synthesis of the cis-Hydrindane Core 35

2.2 Approach B: Construction of the *cis*-Hydrindane Core Structure *via* Intramolecular Sakurai Reaction 44

2.2.1 Retrosynthetic Analysis 44

2.2.2 Synthesis of the cis-Hydrindane Core *45*

2.2.3 Preparation of an 1,6-Enyne as Substrate for the intramolecular Pauson-Khand Reaction *50*

2.3 Approach C: The Total Synthesis of Waihoensene 60

2.3.1 Retrosynthetic Analysis *60*

2.3.2 Synthesis of the cis-Hydrindane by Intramolecular Radical Cyclization *60*

2.3.3 Synthesis of the Pauson-Khand Precursor *66*

2.3.4 The Intramolecular Pauson-Khand Reaction as Key Step *70*

2.3.5 Completion of the Total Synthesis *72*

2.4 The Asymmetric Total Synthesis of (+)-Waihoensene 76

2.4.1 Retrosynthetic Analysis *76*

2.4.2 Synthesis of a Chiral Intermediate by Use of the DAAA Reaction *77*

2.4.3 Completion of the Total Synthesis of (+)-Waihoensene *79*

3. Summary 81

II. Studies Toward the Total Syntheses of Vallesamidine and Lyconadin C 83

1. Introduction 84

1.1 Alkaloid Natural Products 84

1.1.1 Classification and Biosynthetic Origin *85*

1.2 The Monoterpenoid Dihydro-Indole Alkaloid Vallesamidine 87

1.2.1 Isolation, Structural Characterization and Proposed Biosynthesis *87*

1.2.2 Previous Total Syntheses and Formal Syntheses of Vallesamidine *91*

1.3 Lyconadin C – a *Lycopodium* Alkaloid 98

1.3.1 Isolation, Structural Characterization and Biosynthetic Origin of Lyconadin C *100*

1.3.2 Previous Total Syntheses of Lyconadin C *103*

1.4 [3+2]-Cycloaddition Reactions of Isomünchnone and Thioisomünchnone Dipoles 108

1.4.1 Selectivities in the [3+2]-Cycloaddition Reactions of Mesoionic Compounds *110*

1.4.2 Methods for the Preparation of Isomünchnones and Thioisomünchnones ... *111*

1.4.3 Scope and Limitations *115*

2. Results and Discussion 118
2.1 An Approach Toward the Synthesis of Vallesamidine 118
2.1.1 Retrosynthetic Analysis of Vallesamidine 118
2.1.2 Synthesis of a Suitably N-Protected Cycloaddition Precursor 119
2.1.3 Attempts on the [3+2]-Cycloaddition Reaction for Construction of the Vallesamidine Skeleton 123
2.2 An Approach Toward the Synthesis of Lyconadin C 129
2.2.1 Retrosynthetic Analysis of Lyconadin C 129
2.2.2 Synthesis of the Starting Building Blocks 130
2.2.3 Mukaiyama-Michael Addition and Attempted Functionalization in α-Position 134
2.2.4 Attempts Toward an Octahydroquinoline System 138
3. Summary and Outlook 147
III. Experimental Part 151
1. General Details 151
2. Analytical Methods 152
3. Experimental procedures 153
3.1 The Total Synthesis of Waihoensene 153
3.1.1 Approach A: Construction of the cis-Hydrindane Core Structure via Reductive Olefin Coupling 153
3.1.2 Approach B: Construction of the cis-Hydrindane Core Structure via Intramolecular Sakurai Reaction 160
3.1.3 Racemic and Asymmetric Total Synthesis of Waihoensene 174
3.1.4 NMR Spectra 194
3.1.5 X-Ray Crystallography 249
3.2 Studies Toward the Syntheses of Vallesamidine and Lyconadin C 251
3.2.1 An Approach Toward the Synthesis of Vallesamidine 251
3.2.2 An Approach Toward the Synthesis of Lyconadin C 259
3.2.3 NMR Spectra 270
List of Figures 298

List of Schemes 300
List of Tables 306
References 308
Danksagung 317

I. The Total Synthesis of Waihoensene

1. Introduction

1.1 Natural Products and Total Synthesis

In general, organic compounds derived from living organisms are referred to as natural products. Depending on their molecular structure and biological function, these compounds are classified into two sub-groups: primary and secondary metabolites. The primary metabolites comprise the fundamental building blocks of life, like amino acids, nucleic acids or carbohydrates and are essential for the development, growth and reproduction of the organism[1]. In nature, these molecules often occur in polymeric structures, *e.g.* proteins or polysaccharides. Historically, the term natural product was exclusively used for secondary metabolites. They occur with broad structural diversity and are not necessary for the cell life itself but offer numerous selection advantages for the producing organism. Alkaloids, polyketides, terpenoids as well as specialized carbohydrates and peptides function as part of the survival strategy of the producing organism and show a variety of physiological activities as biological weapons, hormones, metal transporting agents or agents for symbiosis[2]. The associated pharmacological potential has been used for the treatment of injuries and diseases for thousands of years. Between 1981 and 2014, about 65% of the newly approved drugs for cancer treatment were natural products or synthetic modifications thereof[3] demonstrating the importance of natural structure motifs for today's pharmaceutical industry. However, structural complexity and limited natural occurrence restrict the availability of many target molecules[4]. The strategies to circumvent this problem are semi-synthesis and total synthesis. Paclitaxel, known as Taxol® (**6**) (shown in *Figure 1*), represents probably the most popular example for semi-synthesis of an active substance. The polycyclic terpenoid from the taxane group shows cytostatic activity[5] and is used for treatment of various types of cancer. Due to its limited natural occurrence in the bark of *Taxus brevifolia*, alternative production processes were needed to meet the growing demand. Relatively large quantities of the related 10-deacetylbaccatin-III can be isolated from the European yew, *Taxus baccata*, and allow of short semi-synthetic access to paclitaxel[6]. Nowadays, plant cell fermentation affords paclitaxel on ton scale[7]. In contrast to the semi-synthetic approach, total synthesis constructs complex target molecules from simple building blocks by application of various synthetic methodologies. Starting in the late 1820s with Wöhler's synthesis of urea[8] (**1**),

total synthesis has developed over the years and allowed to synthesize myriads of compounds with increasingly complex molecular structures[9] (*Figure 1*).

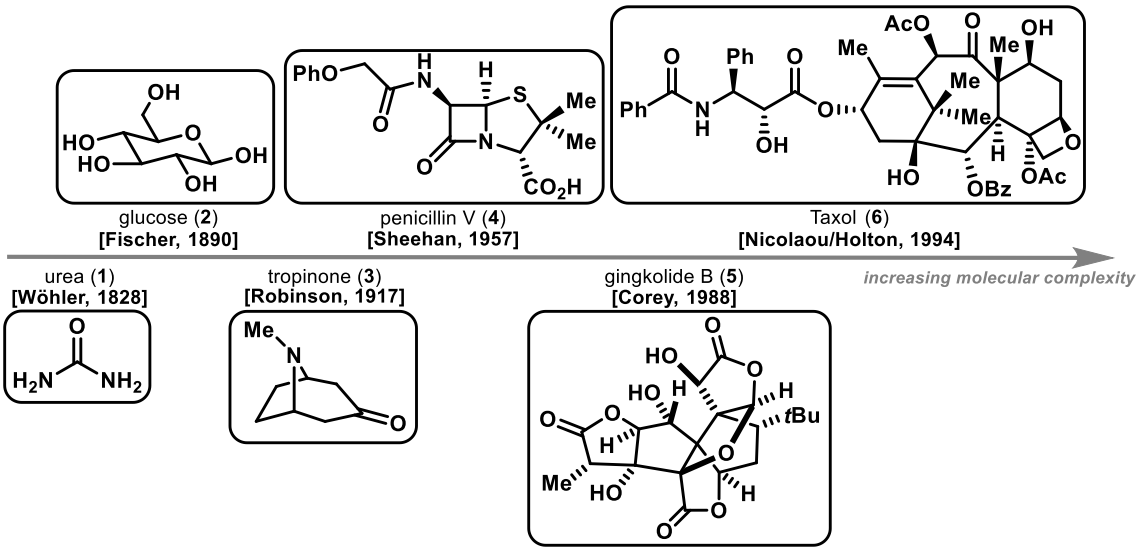


Figure 1: Chronological progress in total synthesis.

The synthetic methods used in total synthesis are not always suitable for pharmaceutical industry's large-scale production, but provide access to sufficient amounts of material needed for initial biological testing, molecular structure elucidation to validate hypothetical or proposed structures and the investigation of structure-activity relationships[4].

1.2 Terpene Natural Products

Originating from 'turpentine' (lat. *balsamum terebinthinae*), the term terpenes describes a natural product family that occurs in almost all known life forms, like plants, fungi, algae and sponges[10]. Turpentine itself is obtained from the resin of pine trees and contains significant amounts of hydrocarbons with repetitious C_5 carbon units as monomers. These hydrocarbons belong to the group of terpenes, which represent the largest group of natural products with wide structural diversity and more than 55,000 known members in 2007[11]. Although the biological function of most terpenes in plants is still unknown, their properties indicate protection of the producing organism against predatory or parasitic enemies as their main task[12]. Volatile mono-, sesqui- and diterpenes are part of the main defense mechanism in form of scents to repel herbivores and are released upon tissue damage. Additionally, enemies of the herbivores themselves are attracted. Less volatile members, who act as antifeedants, often feature a strongly bitter taste and toxicity[13] and in general, the complex plant defense mechanism is the result of an interaction of different types of

terpenes. Furthermore, the mimicry of pheromones aims to attract certain insects for pollination and thus, terpene natural products inevitably play a substantial role in the plant's reproduction cycle and are involved in mutualistic interactions among different organisms as well. Besides, insects and animals produce pheromones and growth factors by the metabolism of terpenes that were ingested with plant food. In the human body, multiple physiological functions of terpenes are known, *e.g.* in form of steroids as sexual hormones or vitamins[13]. In combination with their antibacterial, anti-inflammatory or antiviral activities, this provides a basis for the pharmacological application of terpene natural products.

1.2.1 Classification

The fundamental concept behind the immense structural variety found in terpene natural products is denoted by the 'isoprene rule'. Already in 1887, Otto Wallach[14] recognized the repetitious arrangement of isoprene units as core terpenoid structure. According to the number of linked isoprene units, the compounds are categorized into hemi- (C_5), mono- (C_{10}), sesqui- (C_{15}), di-(C_{20}), sester- (C_{25}), tri- (C_{30}), tetra- (C_{40}) and polyterpenes (more than eight isoprene units).

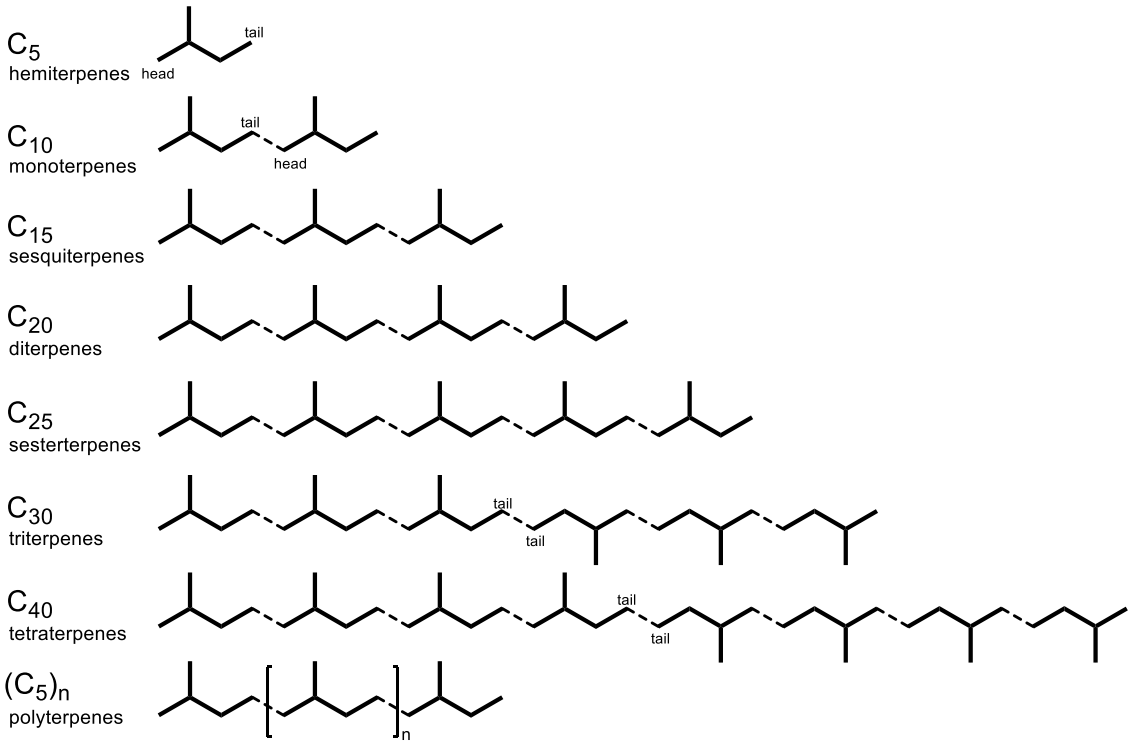


Figure 2: Classification of terpenes.

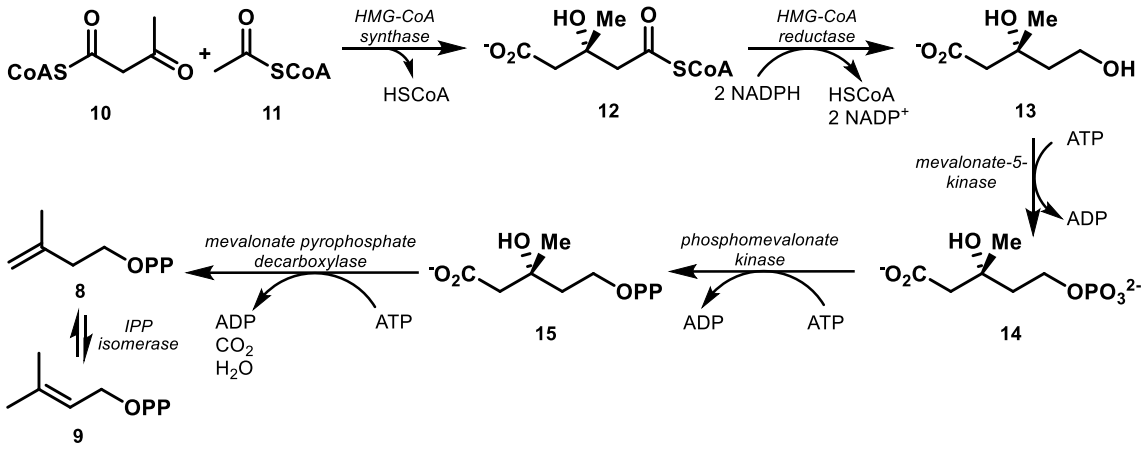
In general, the monomers are arranged 'head-to-tail' (*Figure 2*, see chapter 1.2.2 for details), but exceptions with 'tail-to-tail' linkage are also known, especially for tri- and tetraterpenes[13]. Ruzicka's extended biogenetic isoprene rule[15] allows for such deviations from the regular arrangement by rearrangement or degradation events during biosynthesis. The terms terpenoids and isoprenoids are recommended by the IUPAC to be used for isoprene polymers that chemically deviate from the isoprene rule, however, they are in general used interchangeably with the term terpenes.

1.2.2 Biosynthesis

isoprene (**7**) isopentenylpyrophosphate (IPP, **8**) γ,γ-dimethylallylpyrophosphate (DMAPP, **9**)

Figure 3: Isoprene and activated derivatives.

As indicated by Ruzicka's rule, all terpenes have their biogenetic origin in an activated isoprene building block, which is isopentenyl pyrophosphate (IPP, **8**) (*Figure 3*). This compound also exists in an isomeric form, *γ,γ*-dimethylallyl pyrophosphate (DMAPP, **9**), and biochemically originates from two different metabolic pathways: the mevalonate (MVA) pathway (*Scheme 1*) and the 2C-methyl-D-erythritol-4-phosphate (MEP) or 1-deoxy-D-xylulose-5-phosphate (DOXP) pathway (*Scheme 2*). The MVA pathway is common in almost all living organisms, namely most eukaryotes, archaea and some bacteria, and also takes place in the cytosol of plants[16].

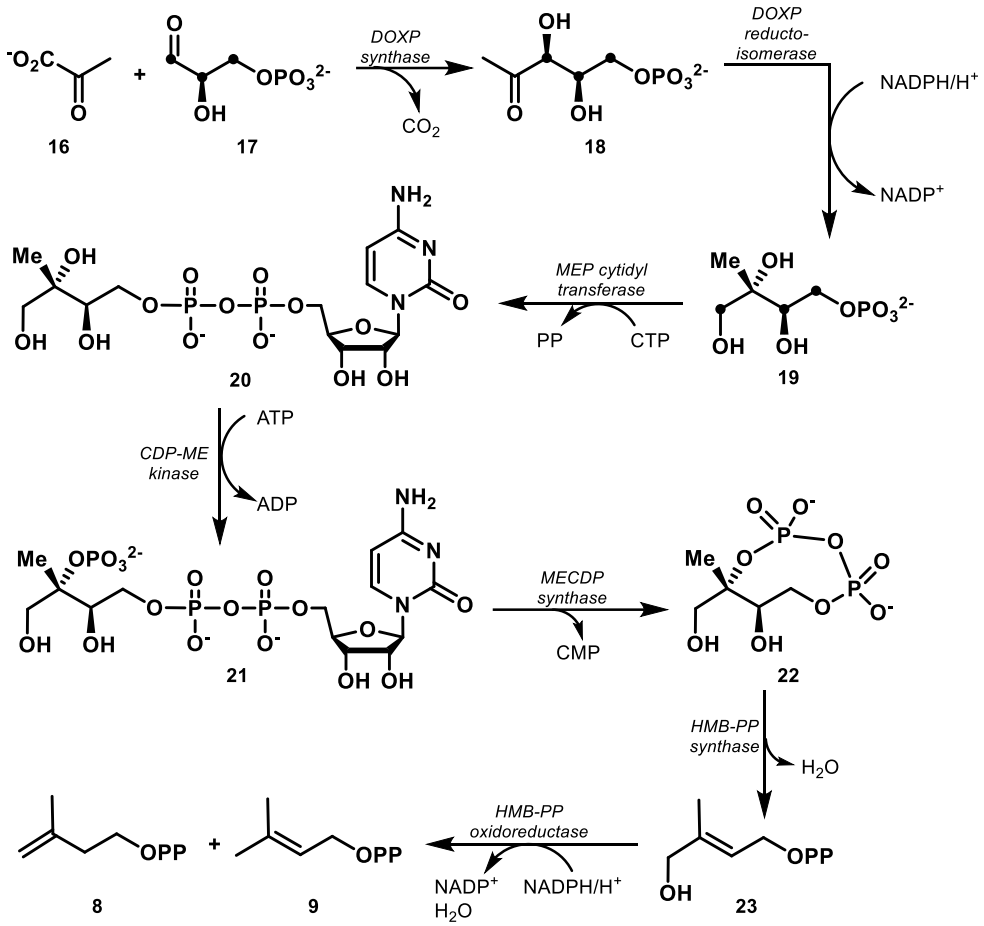


Scheme 1: Mevalonate pathway of IPP/DMAPP biosynthesis.

As depicted in *Scheme 1*, an initial aldol reaction of acetoacetyl-CoA (**10**) with a molecule of acetyl-CoA (**11**) yields β-hydroxy-β-methyl-glutaryl-CoA (HMG-CoA, **12**) and enzymatic

reduction of the latter with dihydronicotinamide adenine dinucleotide phosphate ($NADPH/H^+$) produces (*R*)-mevalonic acid (MVA, **13**). Stepwise phosphorylation to the corresponding diphosphate (**15**) by reaction with adenosine triphosphate (ATP) is followed by a decarboxylation/dehydration process and gives IPP (**8**). Isomerization to DMAPP (**9**) is catalyzed by the IPP isomerase.

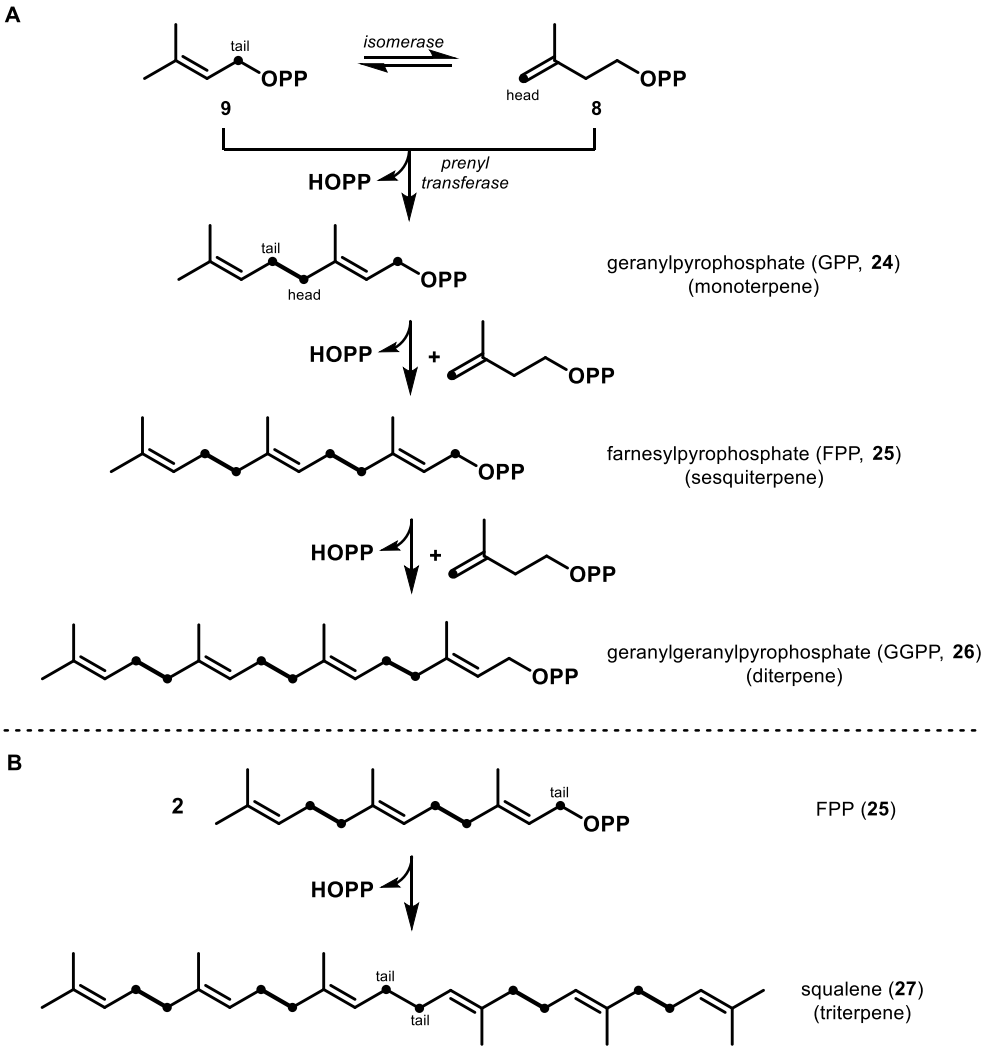
In some microorganisms and the plastids of plants and algae, IPP is produced by the alternative MEP/DOXP pathway that initiates from pyruvate (**16**) and glyceraldehyde-3-phosphate (**17**)[17] (shown in *Scheme 2*).



Scheme 2: MEP pathway of IPP/DMAPP biosynthesis.

The C_5-precursor of IPP, 1-deoxypentulose-5-phosphate (**18**), is produced in a condensation reaction catalyzed by the DOXP synthase. Activation of pyruvate (**16**) occurs by addition to the thiamine diphosphate cofactor and decarboxylation prior to the condensation. The DOXP reductoisomerase catalyzes the isomerization of 1-deoxypentulose-5-phosphate (**18**) to erythrose as well as the subsequent reduction to erythritol (**19**) with $NADPH/H^+$. 4-Diphosphocytidyl-2-C-methyl-D-erythritol-2-phosphate

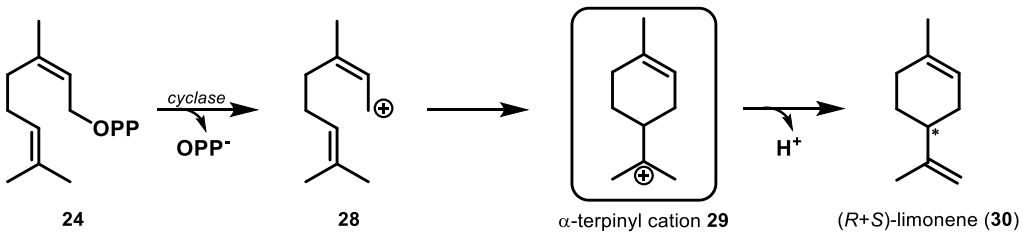
(CDP-MEP, **20**) is obtained by transfer of a cytidyl monophosphate to erythritol (**19**) and then phosphorylated in 2-position. Further cyclization to the corresponding cyclophosphate **22** and reduction under release of water give (*E*)-4-hydroxy-3-methylbut-2-enyl pyrophosphate (**23**), which is transformed to IPP (**8**) and DMAPP (**9**) with NADPH/H^+. This process is catalyzed by the HMB-PP oxidoreductase. In analogy to the MVA path, interconversion of IPP and DMAPP occurs by enzymatic catalysis. In every producing organism, the further terpene biosynthesis follows the same central route and is catalyzed by prenyltransferases (see *Scheme 3*).



Scheme 3: Terpene synthesis from IPP/DMAP **A** by head-to-tail or **B** by tail-to-tail linkage.

The basic principle of this process is the linear attachment of single IPP and DMAPP building blocks, generally by head-to-tail connection. The nucleophilic methylene group of IPP (denoted as head) reacts with the electrophilic allylic CH_2 group of DMAPP (denoted as tail) to form geranylpyrophosphate (GPP, **24**) as the simplest monoterpene (*Scheme 3* **A**).

Further attachment of an IPP molecule in head-to-tail fashion yields the sesquiterpene farnesylpyrophosphate (FPP, **25**). Higher homologues such as geranylgeranylpyrophosphate (GGPP, **26**) and farnesylgeranylpyrophosphate (FGPP) are produced by multiple repetitions of this sequence. In case of irregular tail-to-tail attachment of two molecules of FPP (**25**) the triterpene squalene (**27**) is formed (*Scheme 3* **B**) and the analogous linkage of two GGPP units produces the tetraterpene phytoene. Presumably, cyclizations to cyclic or polycyclic members occur by enzymatically induced dissociation of a pyrophosphate anion and reaction of the intermediate carbenium ion. The simplest example for the mentioned derivatization is shown in *Scheme 4* and describes formation of the monocyclic monoterpene limonene (**30**) from linear GPP (**24**) *via* the α-terpinyl cation **29**, which is suspected to be the key intermediate in many terpene cyclase reactions[13, 18].



Scheme 4: Terpene cyclase reaction of GPP to limonene *via* the α-terpinyl cation.

Although there is little evidence on the involvement of an intermediate carbenium ion species, this concept allows for rationalization of the evolution of a vast structural diversity within the terpene group. Alongside the mentioned cyclization, further enzymatic processes, like 1,2-hydride and 1,2-alkyl (Wagner-Meerwein) shifts or sigmatropic rearrangements, *e.g.* in form of the Cope rearrangement, are involved in these processes. Associated formation of diastereomeric and enantiomeric analogues is caused by the generation of new asymmetric carbon atoms[13].

1.2.3 Triquinane Natural Products

The polyquinane natural product family is a small subgroup among the terpenes, or more precisely, among sesqui-, di-, and sesterterpenes and steroids. The term quinane derives from 'quintet' (lat. *quintus*) which means five and refers to their common structure motif consisting of fused five-membered rings (*Figure 4*).

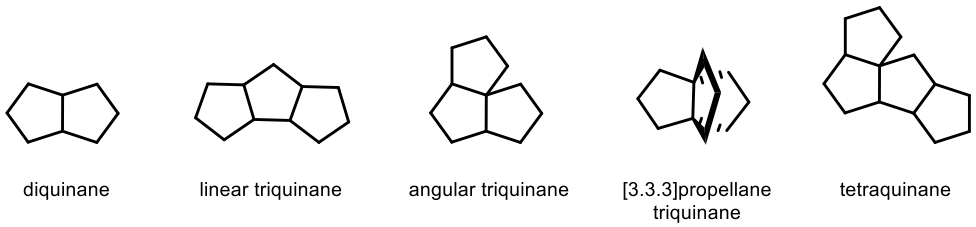


Figure 4: Common structure motifs of polyquinane natural products.

The first known representative, hirsutic acid C (**31**), was discovered already in 1947 by Heatley *et al*.[19], but its triquinane structure was not elucidated until 1966[20]. Since then, several hundred quinanes with up to four fused five-membered rings have been isolated from plant, marine and microbial sources. Depending on the number of rings, the compounds are categorized as di-, tri- or tetraquinanes and can be of linear, angular or propellane-type fusion (see *Figure 4*, *Figure 5*).

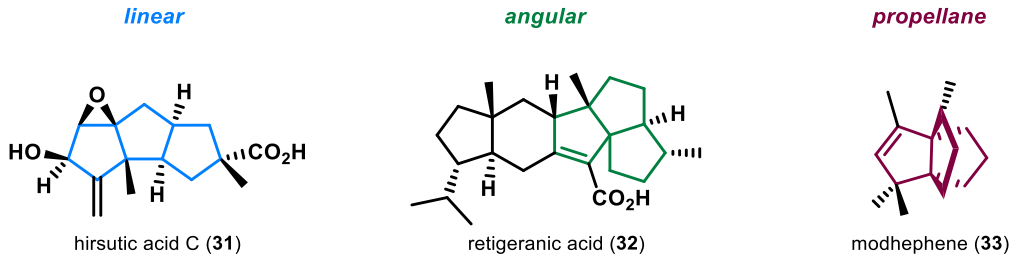


Figure 5: Exemplified compounds for the different classes of triquinane natural products.

As depicted in *Figure 6*, angular triquinanes occur in four skeletal types differing in the position of their substituents and the number of quaternary carbon centers: isocomanes, siliphinanes, pentalenanes and silphiperfolanes.

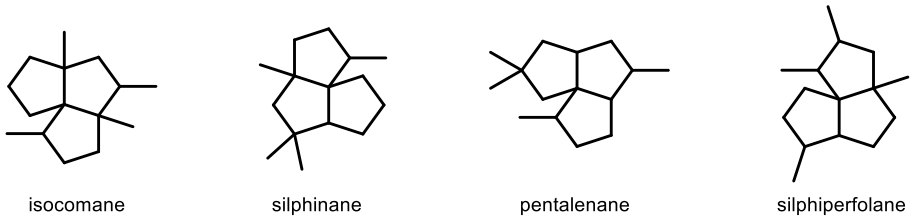
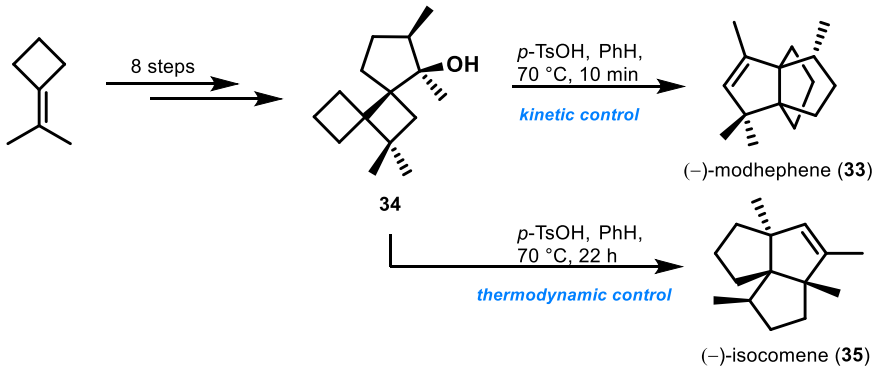


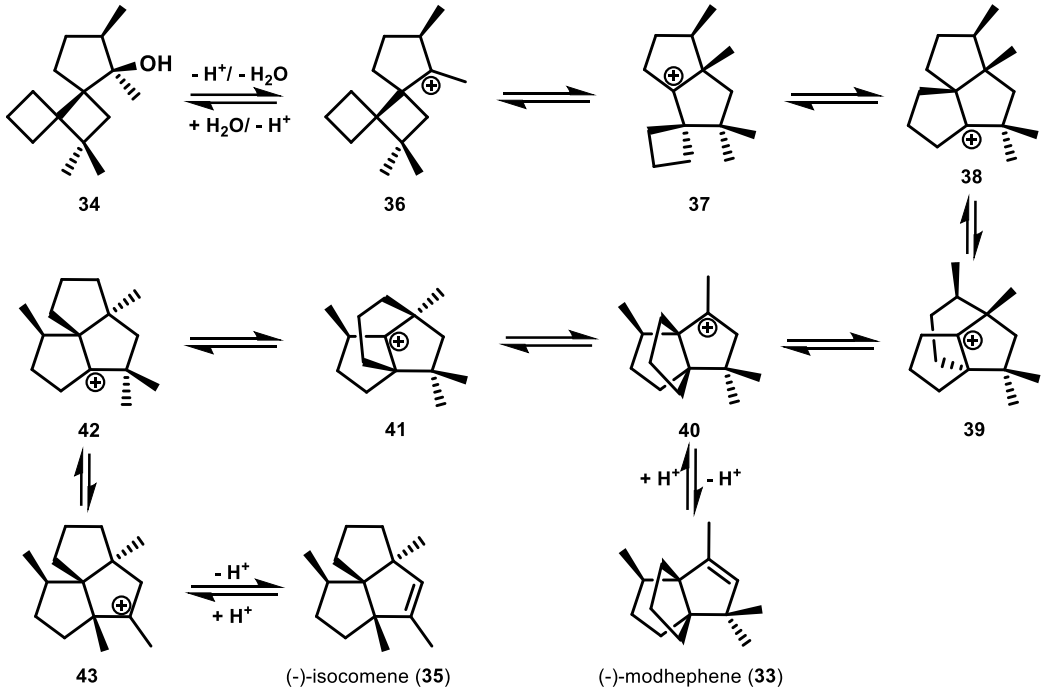
Figure 6: Skeletal types of angular triquinane natural products.

Comprising not only challenging structural complexity but also intriguing biological activities, natural products with a triquinane structure motif embody notable targets for synthetic chemists[21] and require for the development of new methods for their efficient synthesis. The strategic difficulty arises from the installation of several substituents under stereocontrol as well as stereoselective construction of the quaternary carbon atoms during the respective annulation reaction. Compared to the fusion of six-membered rings, additional strain energy is incorporated for the quinane analogues[22]. Several synthetic strategies have been applied in the syntheses of the angular triquinane structure motif, including ring expansion or contraction processes, photochemical approaches or rearrangement reactions[23]. The first known angular triquinane sesquiterpene α-isocomene (**35**) gained remarkable attention as a synthetic target[21], particularly due to its three contiguous quaternary carbon atoms. Fitjer *et al.*[24] attempted an acid-mediated, cationic rearrangement cascade of dispirane-based tertiary alcohol **34** (*Scheme 5*) and were able to access not only the isocomene motif but also the propellane (-)-modhephene (**33**) by consecutive 1,2-alkyl shifts.



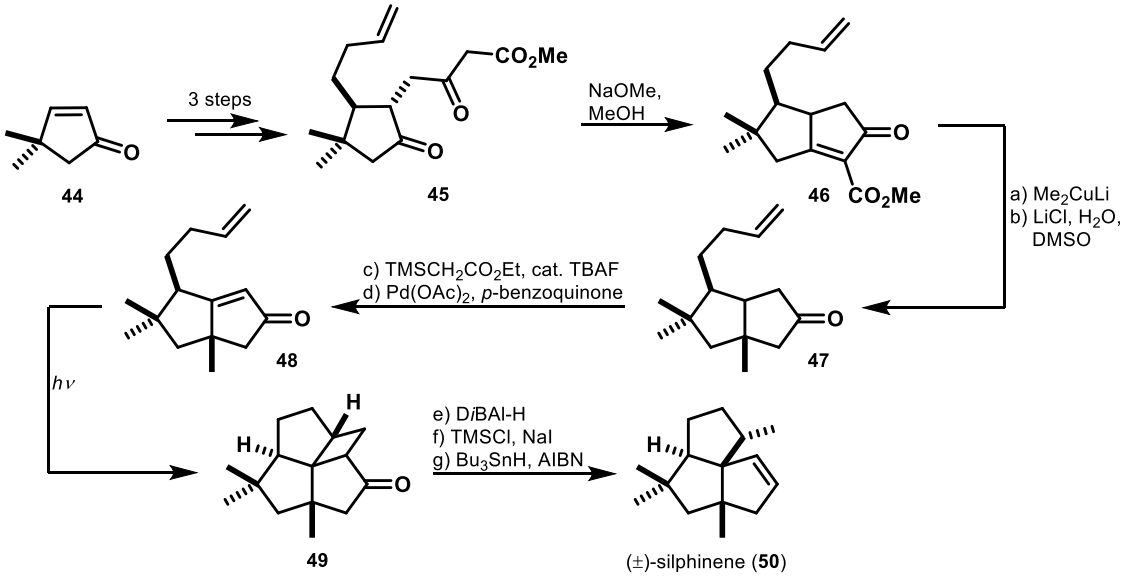
Scheme 5: Acid-mediated synthesis of (-)-modhephene (**33**) and (-)-isocomene (**35**) from propan-2-ylidenecyclobutane[24].

Both sesquiterpenes are known to coexist in *Isocoma Wrightii*[25] and presumably have the same biosynthetic origin comprising **40** as common precursor. As depicted in *Scheme* 6, acid-promoted conversion of **34** to the tertiary carbenium ion **36** was followed by a sequence of 1,2-shifts to release angle strain from the cyclobutanes. Further rearrangement of the intermediate angularly fused tricycle **38** produced key intermediate **40** which can either eliminate a proton to reversibly yield modhephene (**33**) as kinetic product of the sequence or form isocomene (**35**) as the thermodynamic product.



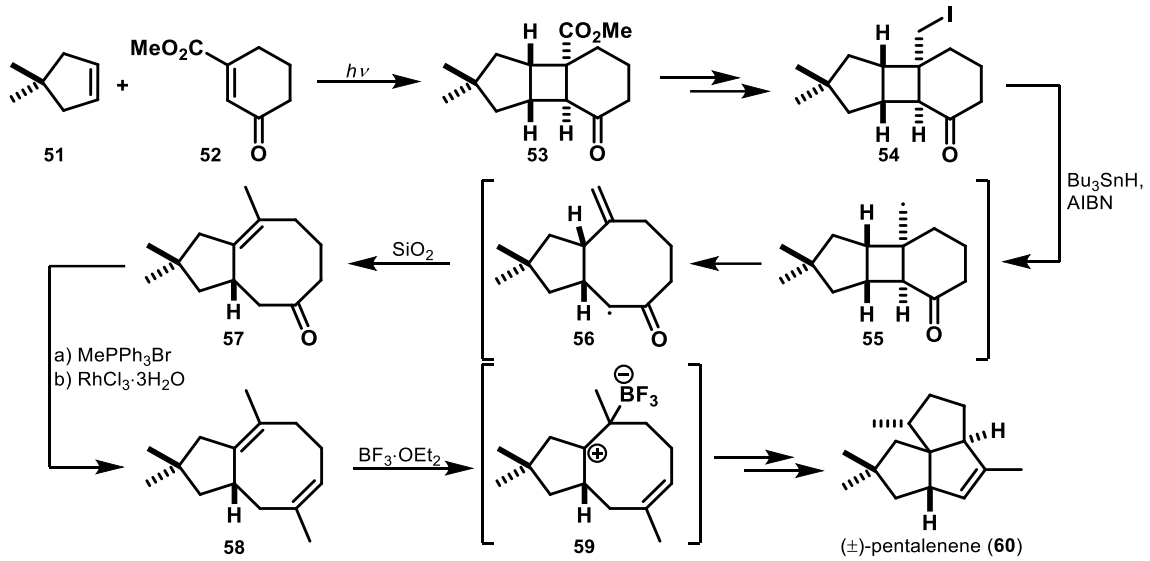
Scheme 6: Fitjer's acid-induced cationic rearrangement cascade of a dispirane-based tertiary alcohol to angular and propellane-type triquinanes[24].

An intramolecular photocycloaddition-cyclobutane fragmentation strategy was used by Crimmins *et al.* in the total synthesis of racemic silphinene (**50**)[26] (*Scheme 7*) and provided elegant access to the [4.5.5.5] fenestrane carbon skeleton. Intramolecular [2+2]-photocycloaddition of the enone in **48** with the terminal olefin afforded cyclobutane-fused angular triquinane **49**. Fragmentation of the four-membered ring and concomitant regioselective formation of the double bond were realized by radical tributyltin hydride reduction.



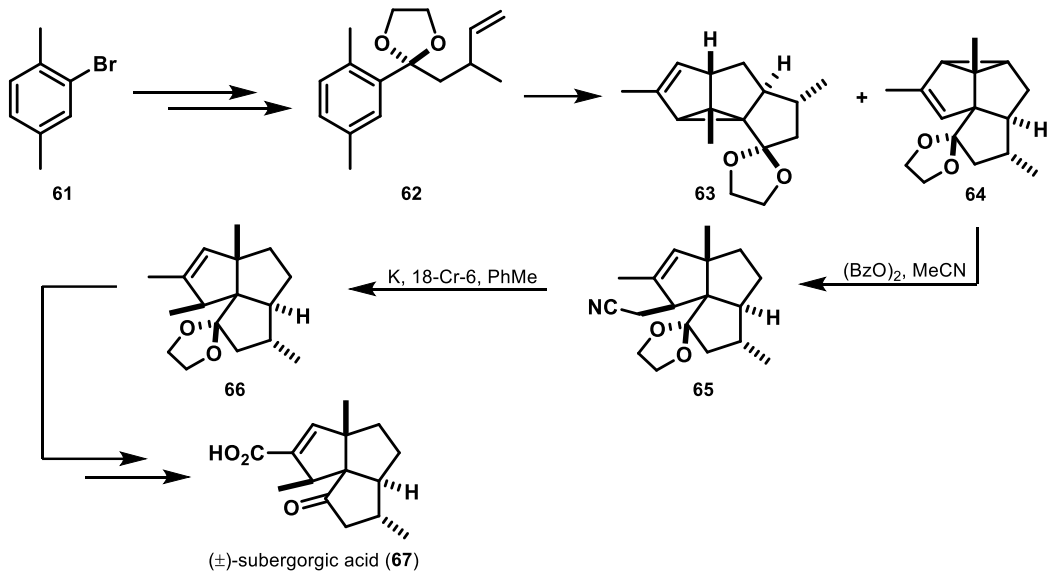
Scheme 7: Crimmins' synthesis of an angular triquinane by an intramolecular photocycloaddition-cyclobutane fragmentation strategy[26].

A similar, Grob-type radical fragmentation of a [2+2]-photoadduct was used by Lange *et al.*[27] in the formal synthesis of (±)-pentalenene (**60**) (*Scheme 8*). Upon treatment of iodide **54** with tributyltin hydride under radical conditions, a highly labile cyclobutylcarbinyl radical **55** was formed and immediately fragmented to a 5,7-bicyclic system **56** with a stabilized secondary radical. Treatment with silica gel afforded the known ketone **57**[28], which was converted into the corresponding cycloocta-1,5-diene **58** by Wittig methylenation and isomerization to the *endo*-olefin. Reaction with boron trifluoride etherate led to the desired stereospecific transannulation *via* carbenium ion intermediates and resulted in the formation of the triquinane pentalenene (**60**).



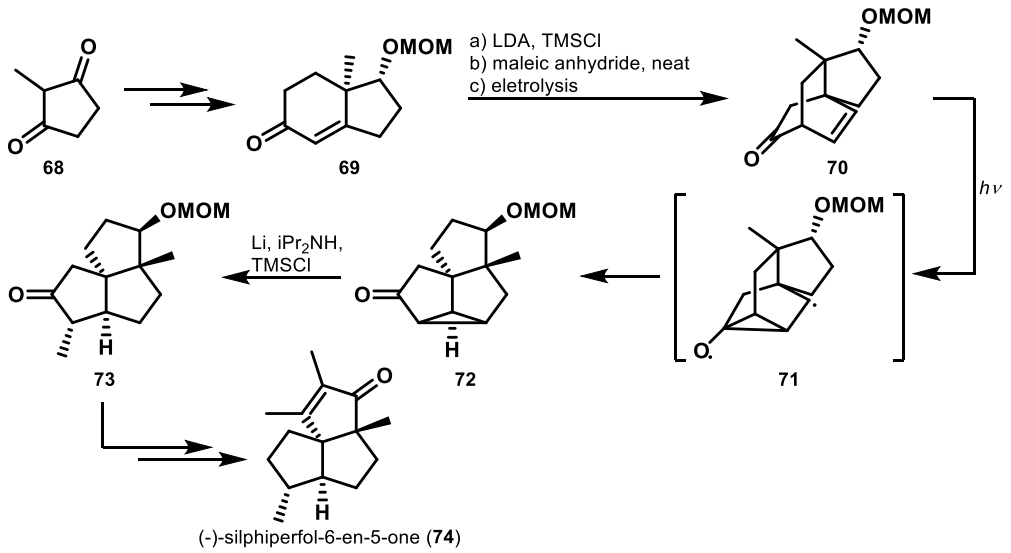
Scheme 8: Lange's pentalene synthesis via [2+2]-cycloaddition/ Grob fragmentation[27].

A totally different approach was chosen by Wender and deLong[29] for the total synthesis of (±)-subergorgic acid (**67**) (*Scheme 9*). The key transformation in their synthesis was an arene-alkene *meta*-photocycloaddition that constructs the triquinane motif in a single step from readily accessible precursors, albeit as a mixture of the undesired linear isomer **63** and the angular isomer **64**. This general finding for the *meta*-photocycloaddition process of such systems can be rationalized by a lack of regioselectivity for the recombination processes in the biradical intermediate and a slight energetic preference for the linear isomers[30]. A two-step sequence comprising the addition of a free radical obtained from acetonitrile to **64** and subsequent reductive decyanation reaction to the corresponding methylated compound **66** provided access to the complete carbon skeleton of subergorgic acid (**67**). The natural product was produced from **66** by application of a five-step allylic oxidation protocol.



Scheme 9: Wender's synthesis of subergorgic acid by arene-alkene *meta*-photocycloaddition[29].

Demuth and Hinsken[31] employed an interesting Diels-Alder/oxa-di-π-methane rearrangement sequence for construction of the silphiperfolane skeleton (*Scheme 10*). The precursor **70** for the photorearrangement was obtained by sequential intermolecular [4+2]-cycloaddition of the silyl enol ether of enone **69** with maleic anhydride as an acetylene equivalent, hydrolysis of the anhydride and electrochemical decarboxylation. Angular triquinane **72** was effectively produced by oxa-di-π-methane rearrangement under photoirradiation, and reductive cleavage of the cyclopropane afforded the carbon skeleton of silphiperfol-6-en-5-one (**74**).



Scheme 10: Demuth's synthesis of silphiperfolenone *via* a Diels-Alder/oxa-di-π-methane rearrangement sequence[31].

1.3 The Podocarp Diterpene (+)-Waihoensene

1.3.1 Isolation and Structural Characterization

The diterpene hydrocarbon (+)-waihoensene (**75**) (shown in *Figure 8*) was isolated by Weavers *et al.*[32] in 1997 from *Podocarpus totara varietas waihoensis*. Confined to the West Coast of New Zealand's South Island, this conifer is supposed to be closely related to *Podocarpus actufolius* and *Podocarpus totara* but constitutes an own species[33].

Figure 7: Podocarpus totara var. waihoensis. "In cultivation. Mar 2007", Photographer: Jeremy R. Rolfe, Licence: *CC BY.*[33b]

Samples of the tree contained waihoensene in up to 5% of the total amount of diterpenes, however, purification proved difficult due to the co-occurrence of several other diterpene hydrocarbons. The major impurities were identified as tricyclic hydrocarbons rimuene (**78**) and pimaradiene (**79**), both depicted in *Figure 8*. A pure sample of waihoensene (**75**) was obtained by a series of chromatographic purification steps including centrifugal chromatography on a silver nitrate impregnated silica plate and allowed for characterization of the tetracyclic structure of waihoensene. The new diterpene showed structural similarity to lauren-1-ene (**76**), which is still the only known natural product with a [5.5.5.7] carbon fenestrane ring system. Laurenene (**76**) itself accounts to noteworthy 35-50% of the total diterpenes isolated from *Podocarpus totara* and was originally isolated from *Dacrydium cupressinum* 18 years earlier by Corbett and Weavers[34]. Up to 1997, no laurenene-related natural products were known. The unique tetracyclic carbon framework of laurenene is characterized by a slight structural deformation at the central carbon atom, a feature that is caused by the central junction of four carbon rings. In fact, this was verified by single crystal structure analysis of synthesized 2-bromolauren-1-ene (**80**) showing

central bond angles in the range of 100° to 119°[32a]. The associated increasing strain manifests in a remarkable proneness towards structural rearrangement, which was indeed observed for treatment of laurenene (**76**) with various acids. One of the obtained rearrangement products was identified as **77** (*Figure 8*). This compound is a double bond position isomer of waihoensene (**75**) and suggests a common biosynthetic origin of the two diterpenes **75** and **76**. The hypothesis of waihoensene being a direct metabolite of laurenene was further substantiated by inevitable co-occurrence of the latter in all waihoensene-containing natural sources. Nevertheless, neither laurenene (**76**) nor its rearrangement product **77** could be converted into waihoensene (**75**) by chemical means yet. This seems logical considering that protonation of the *endo*-double bond in **77** would be required to occur from the sterically hindered *si*-face of the molecule and for this reason does not happen.

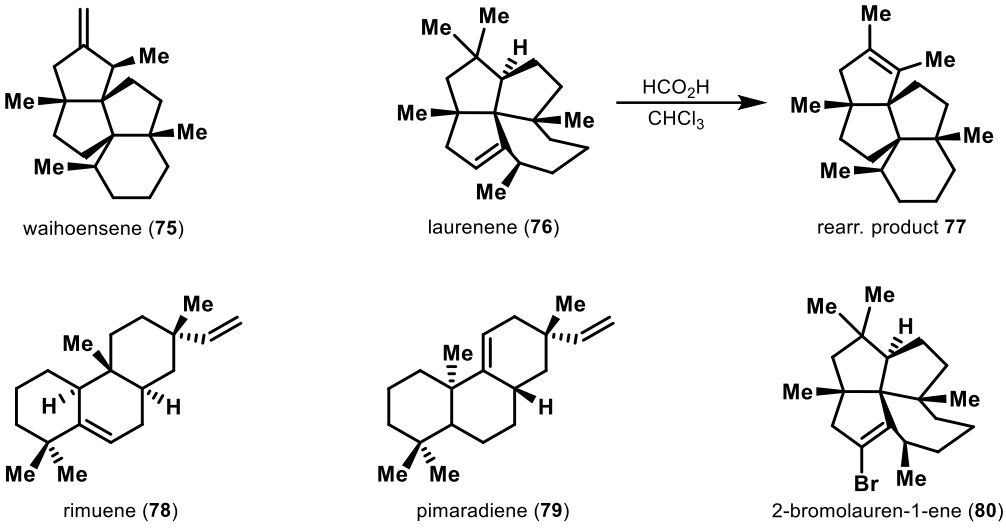


Figure 8: Diterpenes from *Podocarpus totara var. waihoensis*, laurenene rearrangement product **77** and 2-bromolauren-1-ene (**80**).

The tetracyclic skeleton of waihoensene (**75**) is unique among the hitherto known diterpenes and incorporates a silphiperfolane-type angular triquinane unit (highlighted in orange in *Figure 9*) and a thereto-annulated six-membered ring. All-*cis* junction of the rings and four contiguous quaternary carbon atoms (marked in green in *Figure 9*) result in a curved molecular shape and high steric congestion. Structure model calculations by Weavers suggested two low energy conformers that differ only in the conformation of the six-membered ring: the chair conformation with an axial methyl substituent or a twist boat, which is about 1.2 kcal/mol lower in energy compared to the chair conformation. However, ^{1}H NMR NOE difference experiments revealed the chair conformation to be the actual

structure in solution. A 1,1-disubstituted double bond constitutes the only functionality in the molecule (red in *Figure 9*). The hydrocarbon contains in total four *cis*-oriented methyl substituents, two of which are connected to quaternary carbon atoms.

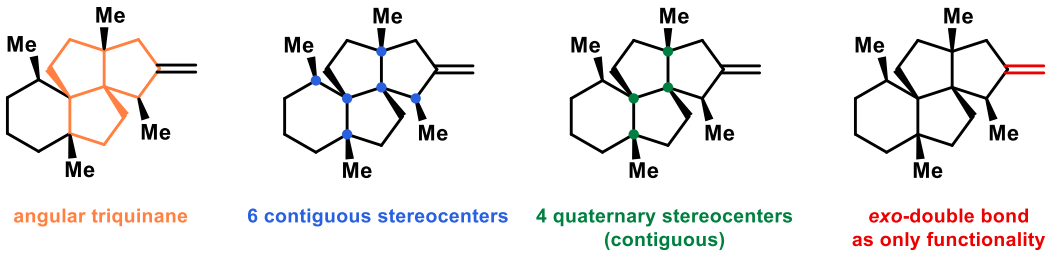
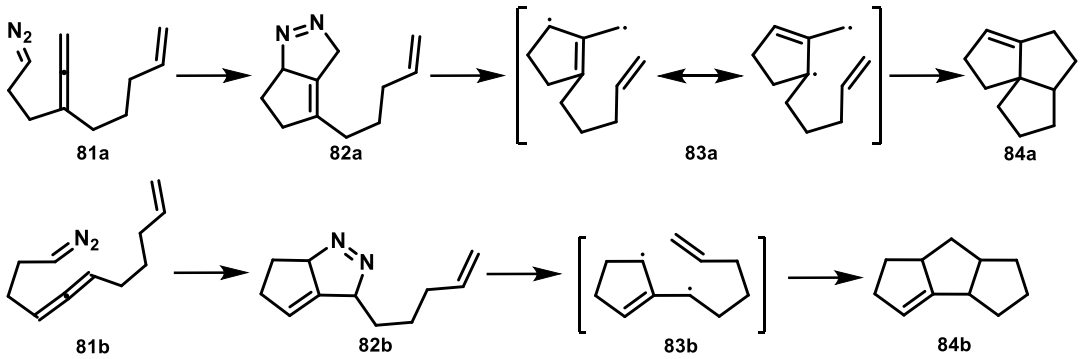


Figure 9: Structural features of waihoensene (**75**).

The relative stereochemistry of all six stereogenic centers (blue in *Figure 9*) in waihoensene could be determined by comparison of the obtained NMR spectra with the spectroscopic data of the laurenene rearrangement product and by additional ^{1}H NMR NOE experiments. The isolated compound showed dextrorotation but its absolute stereochemistry remained unknown by the time of the first asymmetric total synthesis[35] by Huang and Yang in 2020.

1.3.2 Previous Total Syntheses and Synthetic Approaches toward Waihoensene

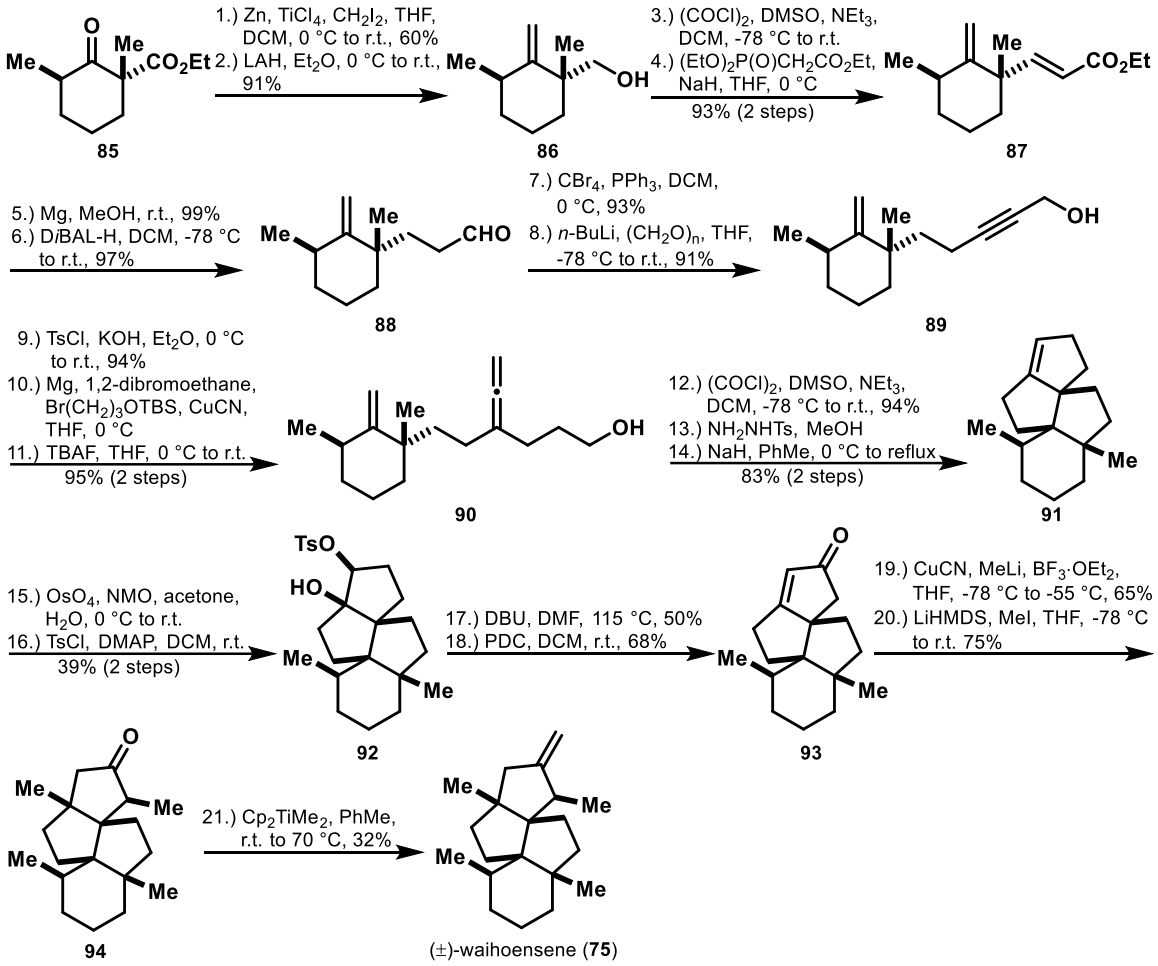
The unique and complex structure with multiple stereocenters and contiguous quaternary carbon atoms in combination with lacking functionalization of the molecule rendered waihoensene (**75**) an attractive and challenging target for synthetic chemists. The lack of traditional reactive functional groups and high steric congestion complicate an efficient synthetic access. In fact, 20 years passed by after the isolation before a first total synthesis was published by Lee *et al.*[36] in 2017. The application of their previously developed tandem cycloaddition strategy[37] *via* a trimethylenemethane (TMM) diyl intermediate allowed for elegant construction of the angular triquinane core structure of waihoensene.



Scheme 11: Lee's TMM-based tandem cycloaddition strategy for the synthesis of linear and angular triquinane systems[37].

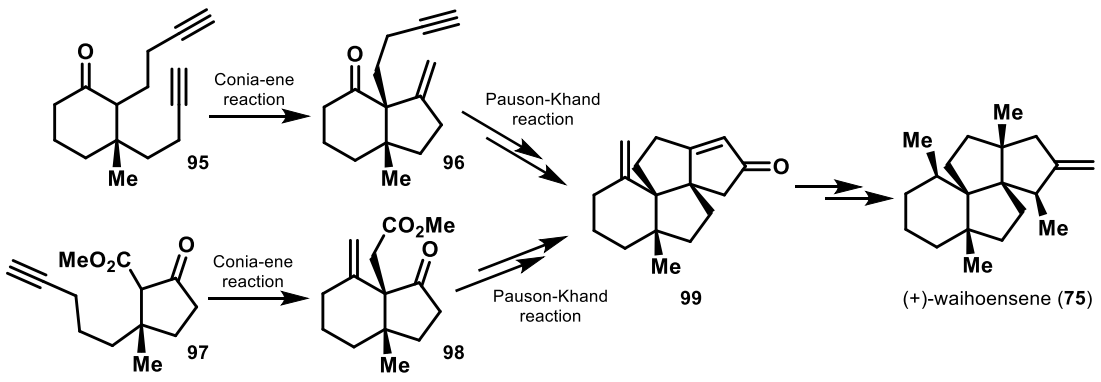
Depending on the substitution pattern on the allene moiety (see structures **81a/b** in *Scheme 11*), either angular **84a** or linear **84b** polyquinane systems are accessible. This methodology was also applied in the total synthesis of a few other polyquinane natural products[38]. In both of the above shown cases, efficient generation of the TMM diyls in **83a/b** could be realized by an intramolecular 1,3-dipolar cycloaddition reaction of a diazo compound with an allene followed by the loss of N_2 under thermal conditions. The second [3+2]-cycloaddition occurred by immediate intramolecular reaction of the highly reactive TMM diyl intermediates with the olefin and resulted in effective formation of the triquinane structure motif **84**.

The first step in Lee's total synthesis of tetracyclic (±)-waihoensene (**75**) (*Scheme 12*) was Takai-Lombardo olefination of literature-known ketoester **85**, which was followed by reduction of the ester functionality to the corresponding primary alcohol **86**. Two-carbon homologation was achieved in four steps and yielded aldehyde **88**. The propargylic alcohol functionality was introduced by use of the Corey-Fuchs alkyne synthesis with formaldehyde as trapping reagent for the acetylide ion. The alcohol in **89** was further converted into a leaving group and substituted in a copper-mediated S_N2' addition reaction with (3-((*tert*-butyldimethylsilyl)oxy)propyl) magnesium bromide. After *O*-silyl deprotection, alcohol **90** was oxidized to the aldehyde and further converted to the corresponding tosyl hydrazone. Treatment with sodium hydride provided an intermediate diazo allenyl compound, which reacted in the aforementioned [3+2]-cycloaddition cascade reaction to give the tetracyclic carbon skeleton of waihoensene. The desired compound **91** was formed as the major product but obtained in a 3.3:1 mixture with other stereo- and regioisomeric products. Separation of these isomers was not possible at this point. A four step allylic oxidation protocol was applied to access enone **93**, since direct Cr(VI)-mediated oxidation was unselective and gave the desired compound along with other oxidation products in low yield. The three steps containing endgame comprised stereospecific copper-mediated 1,4-addition and α-methylation as well as final olefination of the ketone **94** by Petasis reagent. Overall, Lee *et al.* obtained racemic waihoensene (**75**) by a 21-step sequence in an overall yield of 0.6%.



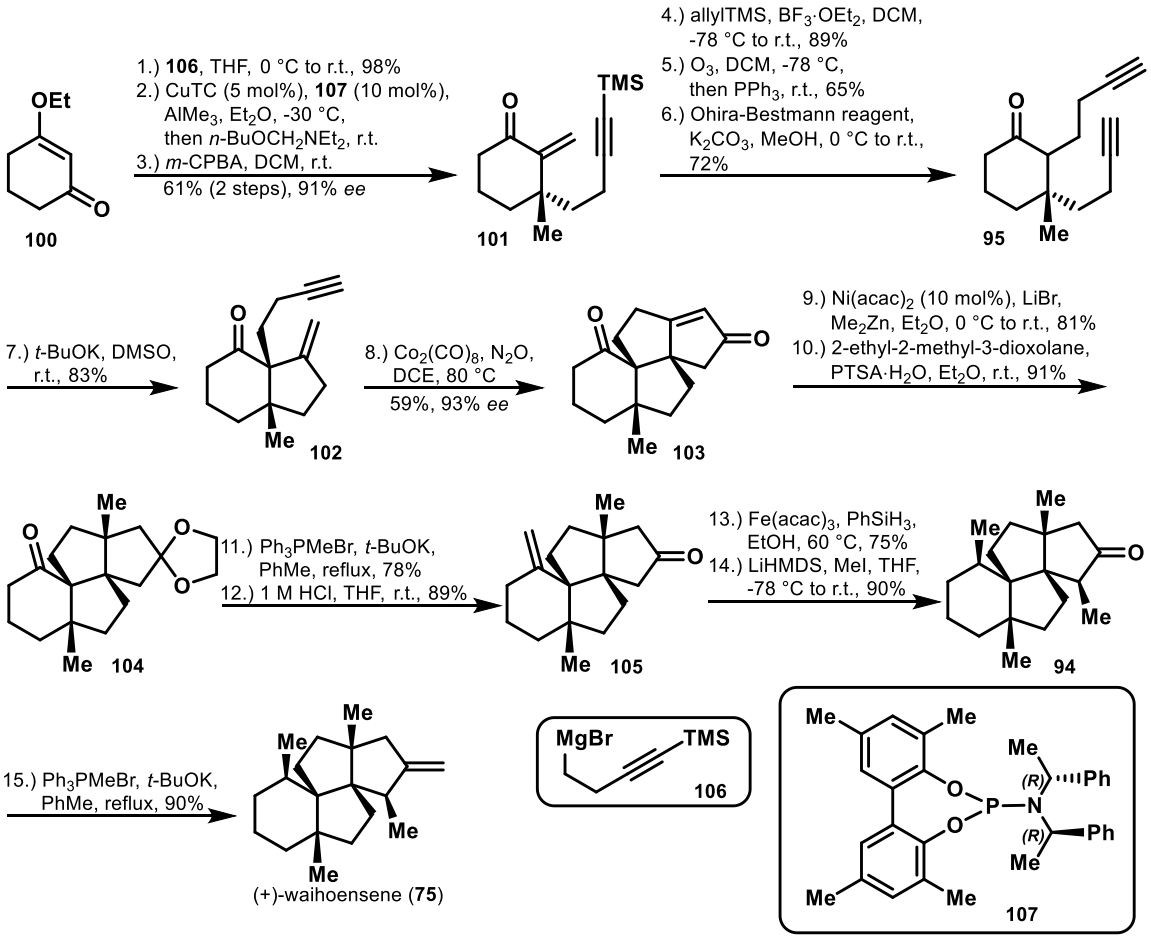
Scheme 12: Total synthesis of (±)-waihoensene (**75**) by Lee[36].

Lee's approach was the only synthetic access to waihoensene (**75**) for some time, before two rather similar asymmetric total syntheses were published in close succession by Huang and Yang[35] and the Snyder group[39] in 2020. Both approaches are based on a Pauson-Khand strategy for the construction of the tetracyclic skeleton of **75** and furthermore use a Conia-ene reaction to build up the *cis*-fused bicyclo[4.3.0]nonane system (*Scheme 13*).



Scheme 13: Synthetic strategy for the asymmetric total syntheses of (+)-waihoensene (**75**) by Huang & Yang[35] and Snyder[39].

The syntheses require 15 and 16 steps, respectively, and introduce chirality by use of a copper-catalyzed asymmetric conjugate addition. Huang and Yang's synthesis[35] (*Scheme* 14) commenced with the addition-elimination reaction of homopropargylic Grignard reagent **106** to commercially available vinylogous ester **100**, which generated an enone. This enone was subjected to the above-mentioned asymmetric 1,4-addition using chiral SimplePhos ligand **107**.

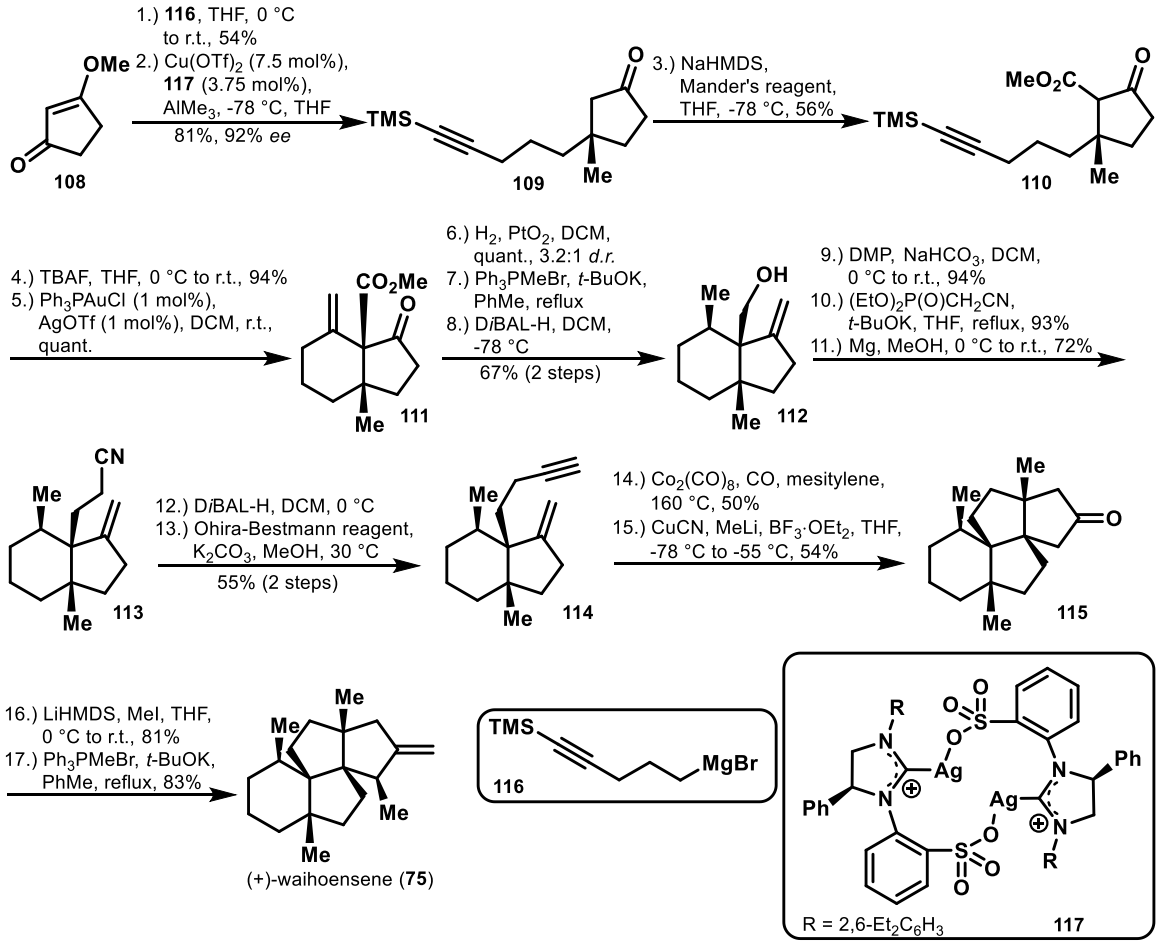


Scheme 14: Total synthesis of (+)-waihoensene (**75**) by Huang and Yang[35].

The enolate was trapped with an α-aminoether and further converted to the α,β-unsaturated ketone **101** by oxidation. The all-carbon stereocenter was obtained with an enantiomeric excess of 91%. Intermolecular Sakurai reaction with allyltrimethylsilane was followed by ozonolysis and conversion of the aldehyde to the terminal alkyne by treatment with Ohira-Bestmann reagent. Base-catalyzed Conia-ene type cyclization of **95** afforded the *cis*-fused hydrindane **102** as a single diastereomer and provided the precursor for the second key transformation in the reaction sequence, namely the Pauson-Khand reaction. For this, the use of dicobalt octacarbonyl in combination with nitrous oxide as

promoter was found to effectively mediate the ring annulation to the desired tetracyclic carbon framework of waihoensene. The missing quaternary stereocenter was constructed *via* a Ni-catalyzed conjugate addition to enone **103** and the resulting cyclopentanone was selectively acetalized in presence of the sterically encumbered cyclohexanone. Methylenation of the latter was followed by acetal deprotection and provided ketone **105**. Diastereoselective reduction of the *exo*-methylene to a methyl group was realized by proposed intramolecular iron(III)-catalyzed hydrogen atom transfer (HAT) and paved the way for the endgame of the synthesis consisting of α-methylation and Wittig olefination of the ketone.

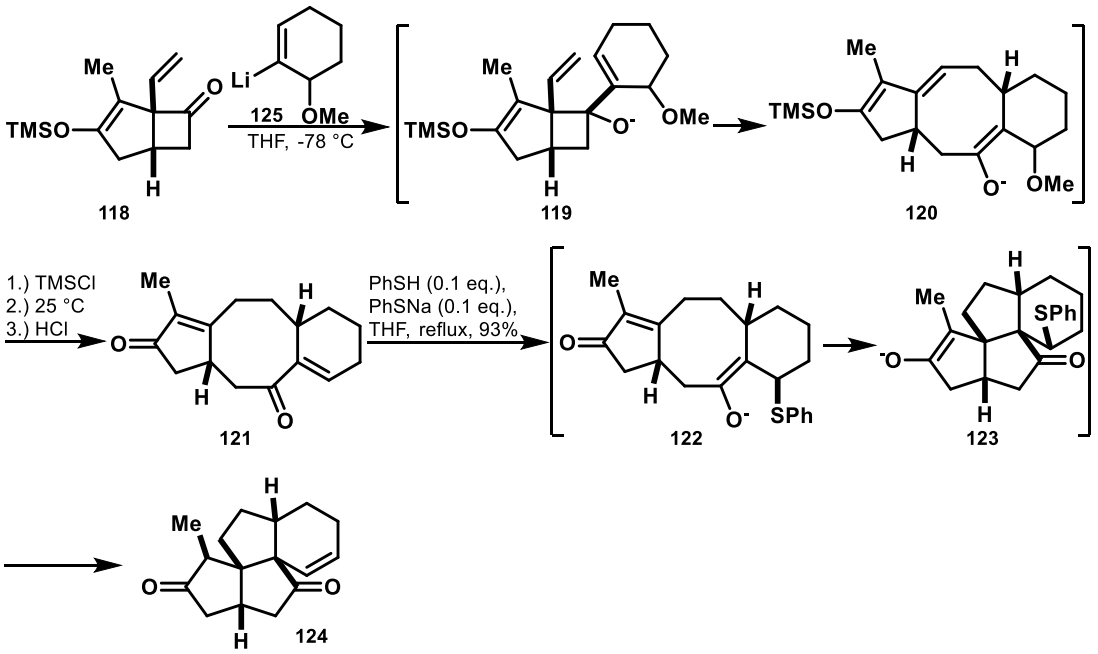
The synthetic route developed by Snyder *et al.*[39] (*Scheme 15*) used 3-methoxy-cyclopent-2-en-1-one (**108**) as the initial building block, yet the first two steps were virtually the same as in the Huang/Yang synthesis: Addition-elimination reaction with alkyl-Grignard **116** was followed by asymmetric conjugate addition for the construction of the first of six stereogenic carbon atoms.



Scheme 15: Total synthesis of (+)-waihoensene (**75**) by Snyder[39].

The latter was catalyzed by Hoveyda's chiral *N*-heterocyclic carbene complex **117** and furnished the β-disubstituted ketone **109** with high enantioselectivity (92% *ee*). *C*-acylation by use of Mander's reagent yielded β-ketoester **110**. After TBAF-mediated silyl deprotection of the alkyne, the *cis*-bicyclic core in **111** was established in a stereoselective gold(I)-catalyzed Conia-ene reaction. Hydrogenation of the *exo*-methylene unit by Adam's catalyst proceeded with preference for the desired all-*cis* product (3.2:1 *d.r.*). The ketone was olefinated and the remaining ester was transferred to the corresponding aldehyde in two steps and further converted to the required terminal alkyne substituent *via* nitrile **113**. The obtained enyne **114** was used as substrate for the desired Pauson-Khand reaction to install the triquinane core of waihoensene and was for that purpose treated with a slight excess amount of cobalt(0) carbonyl and heated in a CO atmosphere to 160 °C. The tetracyclic product was obtained in 50% yield and transformed to ketone **115** by copper(I)-mediated conjugate addition. The natural product **75** was obtained in analogy to the other total syntheses in two further steps.

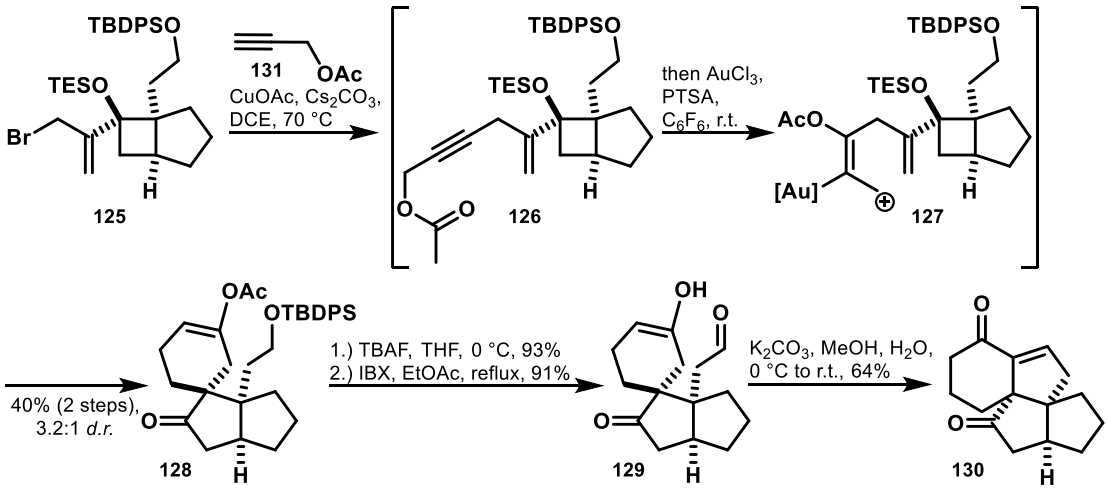
Furthermore, additional synthetic approaches toward the carbon skeleton of waihoensene (**75**) were reported in literature by two other research groups. Already in 1999, Moore and co-workers[40] published the synthesis of angular polyquinane ring systems by a tandem Michael addition sequence (*Scheme 16*).



Scheme 16: Synthetic approach toward the waihoensene carbon skeleton by Moore[40].

The tricyclic precursor **121** for their key cascade was readily prepared from squaric acid-derived bicyclo[3.2.0]heptenone **118** by addition of cyclic vinyllithium species **125**. After addition to the cyclobutenone carbonyl, immediate anionic oxy-Cope rearrangement of **119** resulted in ring annulation and expansion to the eight-membered ring. Subsequent elimination of methoxide from intermediate **120** and acidic hydrolysis led to a tricyclic dienone system. Remarkably efficient transformation of this precursor to the tetracyclic core of waihoensene was realized by dual Michael addition initiated by intermolecular conjugate addition of thiophenolate from the β-side of the molecule. This triggered a transannular ring closure followed by intramolecularly induced E2 elimination of thiophenol. The tetracyclic product **124** of the cascade exhibits the core structure of waihoensene (**75**) with its angular triquinane and the fused six-membered ring, albeit with only two instead of four quaternary carbon centers in place.

In 2020, another tandem reaction sequence leading to the waihoensene ring system was reported by Wang and Tu[41] (*Scheme 17*). Their approach comprised a Castro-Stephens coupling/acyloxy shift/cyclization/semipinacol rearrangement sequence of bicyclo[3.2.0]heptanol **125** and started with treatment of the latter with prop-2-yn-1-yl acetate (**131**) in the presence of copper(I) acetate and cesium carbonate.



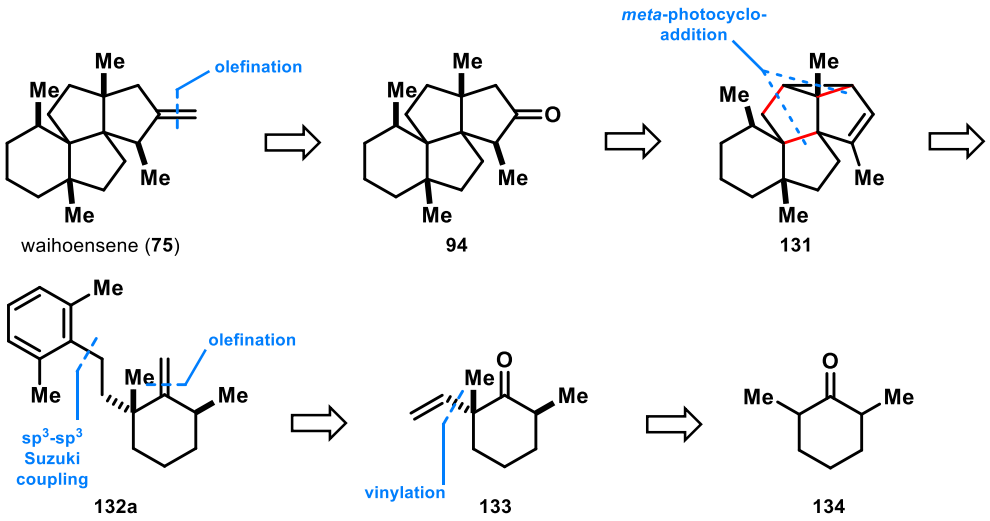
Scheme 17: Synthetic approach toward the waihoensene carbon skeleton by Wang and Tu[41].

Copper(I)-mediated Castro-Stephens coupling of the acetylide with the allylic bromide furnished the substrate **126** for the 1,3-acyl shift, which occurred upon addition of a gold catalyst. The intermediate cationic species **127** was trapped by a spontaneous intramolecular cyclization/semipinacol rearrangement to produce annulated

spirocyclo[4.5]decane **128** as a 3.2:1 mixture of diastereomers. Final intramolecular aldol condensation of **129** provided the angular triquinane motif present in waihoensene.

1.3.3 Preliminary Work in our Group

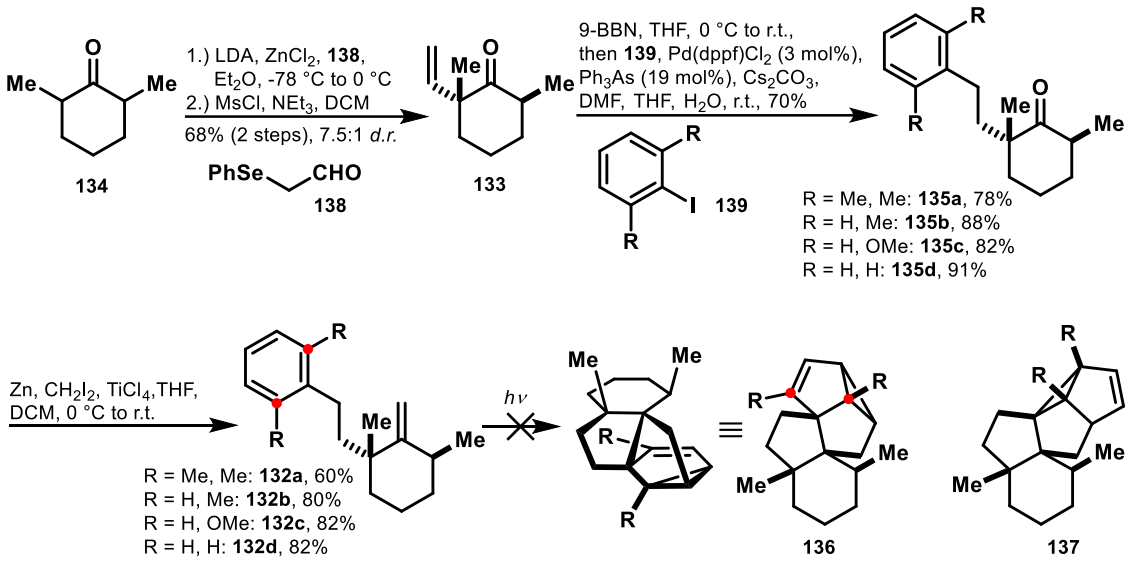
First attempts on a synthetic access toward the diterpene waihoensene were implemented by Dr. Maximilian Häfner during his master and PhD theses in our group[42]. The retrosynthetic analysis (*Scheme 18*) was remarkably short and incorporated application of a *meta*-photocycloaddition reaction as key step for the construction of the carbocyclic framework of waihoensene (**75**).



Scheme 18: Retrosynthetic approach toward waihoensene *via meta*-photocycloaddition.

Synthesis of photo precursor **132a** was realized in four steps from commercial 2,6-dimethylcyclohexanone (**134**) (*Scheme 19*). Diastereoselective aldol addition of the corresponding zinc enolate to phenylseleno aldehyde **138** was followed by elimination upon treatment of the selenoalcohol with methanesulfonyl chloride in the presence of triethylamine. The obtained α-vinylated ketone **133** was used as substrate in a sp^3-sp^3 Suzuki coupling reaction employing the conditions of Johnson and Braun[43], which prevent β-hydride elimination. The coupling with commercially available 2-iodo-1,3-dimethyl-benzene (**139a**) was efficiently accomplished and subsequent olefination of the ketone by use of Takai-Lombardo conditions provided the precursor for the *meta*-photocycloaddition. However, irradiation of compound **132a** in degassed pentane with a 125 W or 400 W medium pressure mercury lamp or with up to eight 18 W 254 nm lamps did not induce the desired photoreaction after different irradiation times (1 to 8 h). Since the methyl substituents on the aromatic moiety (marked in red in structures **132** and **136**, *Scheme 19*)

are not necessary for the photoreaction and might alternatively be introduced at a later stage of the synthesis, further irradiation precursors **132b-d** with less steric hindrance were synthesized accordingly to the developed method.

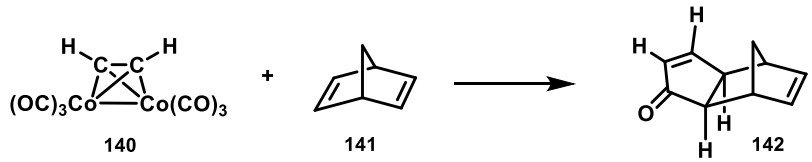


Scheme 19: Synthesis of photo precursors **132** and attempted *meta*-photocycloaddition.

Irradiation of **132b-d** under the same conditions as before did not induce the desired *meta*-photocycloaddition in all cases. Final DFT calculations on the lowest-energy conformation of **132a** revealed the two axially oriented methyl groups on the cyclohexane moiety to prevent the photoreaction from happening by shielding the *exo*-double bond, which is located in pseudo-equatorial position.

1.4 The Pauson-Khand [2+2+1]-Cycloaddition Reaction

Cobalt-mediated formal [2+2+1]-cycloaddition of an alkyne, alkene and carbon monoxide to give cyclopentenones was discovered and first reported by Pauson and Khand[44] in 1971 during their studies on the preparation and characterization of alkene and alkyne complexes derived from $Co_2(CO)_8$ (*Scheme 20*). Further investigations on this reaction were conducted by the Pauson group during the early 1970s and described in detail in 1973[45].



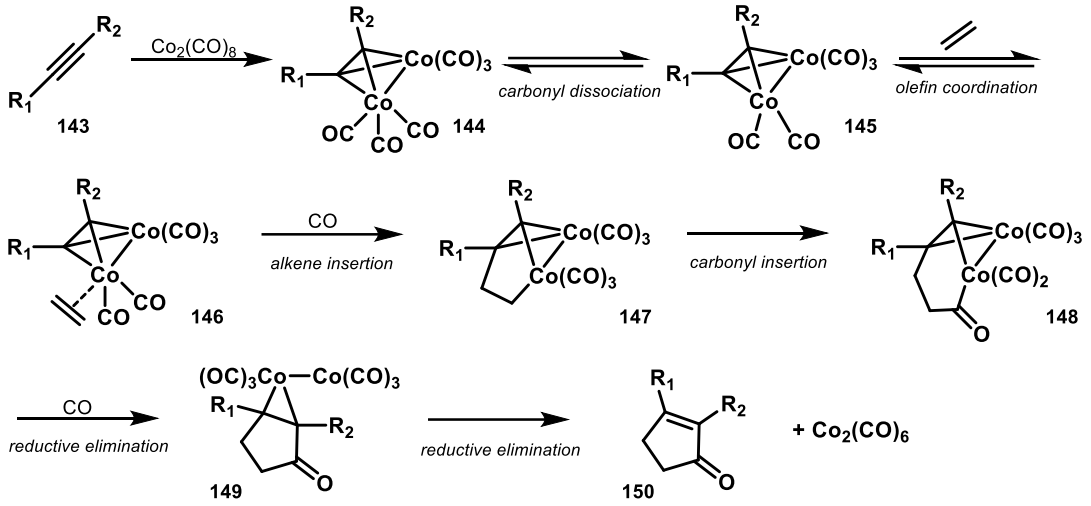
Scheme 20: First reported Pauson-Khand reaction[44].

Reaction of the cobalt complexes of type **140** of simple acetylenes with norbornadiene **141** or norbornene in an inert aromatic or nonaromatic hydrocarbon solvent at elevated temperatures was found to produce the corresponding enone products **142** in synthetically reasonable amounts (30 to 60%) and with significant regio- and stereoselectivity. Additionally, not only a stoichiometric but also a catalytic version of the reaction was described in these studies. Due to its high synthetic utility, various studies and reviews with regard to its scope, the control of regio- and stereoselectivity as well as optimization of the reaction conditions and the development of Pauson-Khand type reactions catalyzed by other transition metal complexes have been published since then[46].

1.4.1 Mechanistic Aspects

First attempts to explain the observed selectivities by mechanistic principles were made by Magnus and co-workers in 1985[47] based on their studies on the synthesis of bicyclo[3.3.0]octenones. However, since no intermediates were detected with the exception of the air-stable alkyne-dicobalthexacarbonyl complex **144** (*Scheme 21*), a mechanistic hypothesis referring to the relationship between stereo- and regiochemical outcome and acetylene substitution was formulated and rationalized by the minimization of steric interactions. Initially, formation of the alkyne-cobalt complex occurs by coordination of the alkyne **143** to binuclear dicobalt octacarbonyl and related substitution of one carbonyl ligand at each cobalt atom. Complexation of the alkene to one cobalt atom *via* a reversible dissociative mechanism comprising initial loss of a carbon monoxide ligand from **144** was proposed. Insertion of the alkene π-bond into one of the formal

carbon-cobalt bonds of the alkyne complex **146** would be irreversible and accompanied by re-coordination of a CO ligand.



Scheme 21: Proposed reaction mechanism of the cobalt-mediated Pauson-Khand by Magnus[47].

This process was assumed to be the rate- and product-determining step. In succession, a sequence of steps results in formation of the enone product commencing with migratory insertion of a cobalt-bound CO. The coordinatively unsaturated cobalt atom in **148** coordinates an additional CO molecule and concurrent reductive elimination of a $Co(CO)_3$ moiety produces the product as $Co_2(CO)_6$-complex **149**. Further reductive elimination liberates the enone **150** and concomitantly generates $Co_2(CO)_6$. Eight possible structures **146a-h** exist for the intermediate cobalt complex of a terminal alkyne and an unsymmetrically substituted olefin, as shown in *Figure 10*.

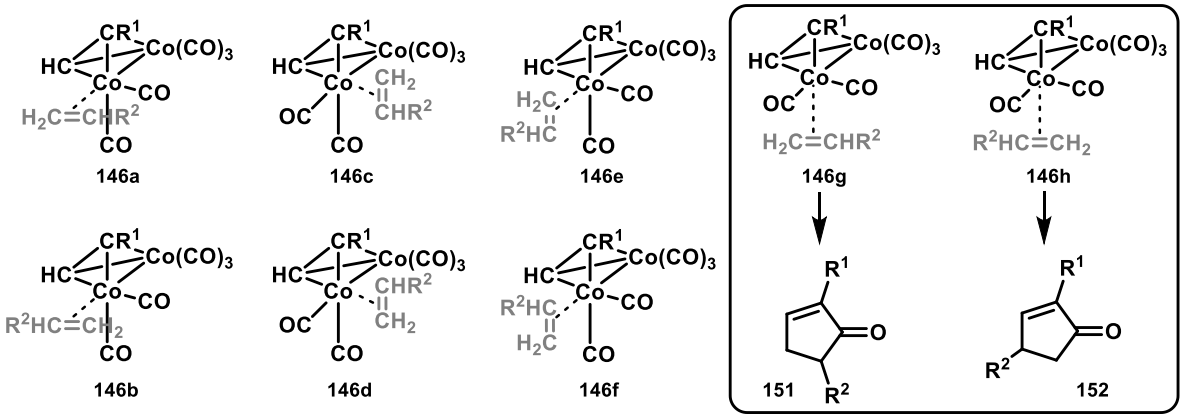
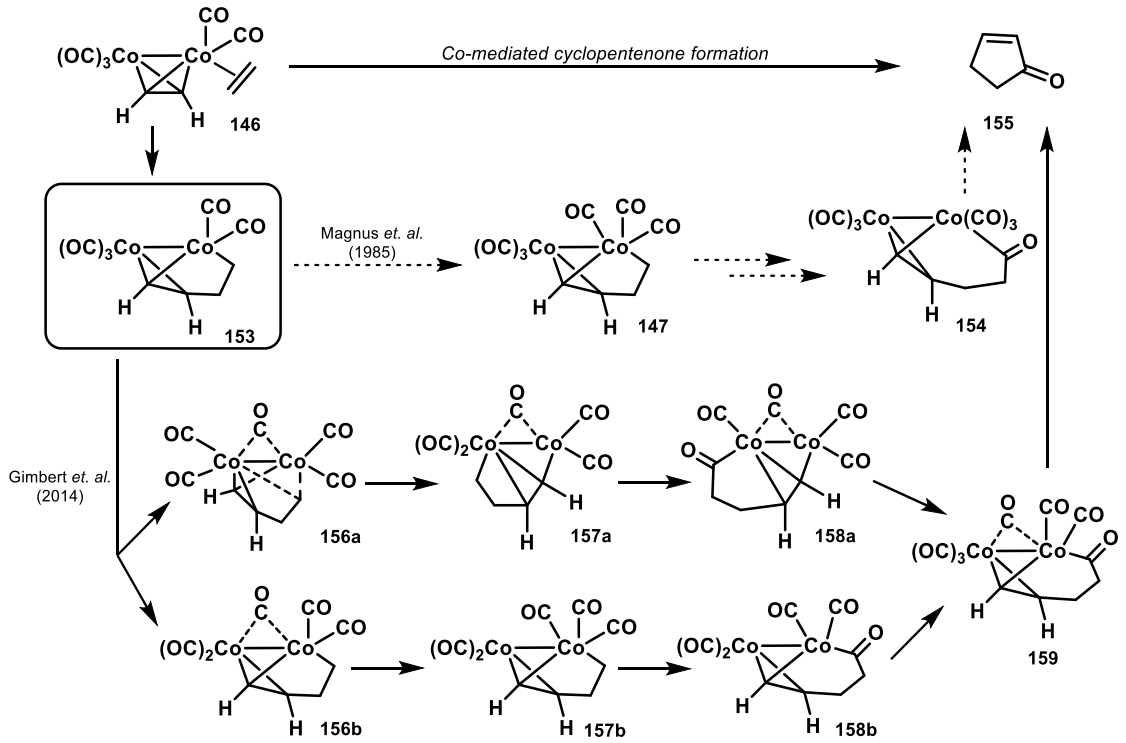


Figure 10: Structures for possible cobalt complexes of a terminal alkyne and an unsymmetric olefin and emergence of different enone products from favored intermediate complexes.

Complexation and insertion confine to the sterically less hindered site of the alkyne-cobalt complex, as it is the case in structures **146g** and **146h**, to prevent steric destabilization and

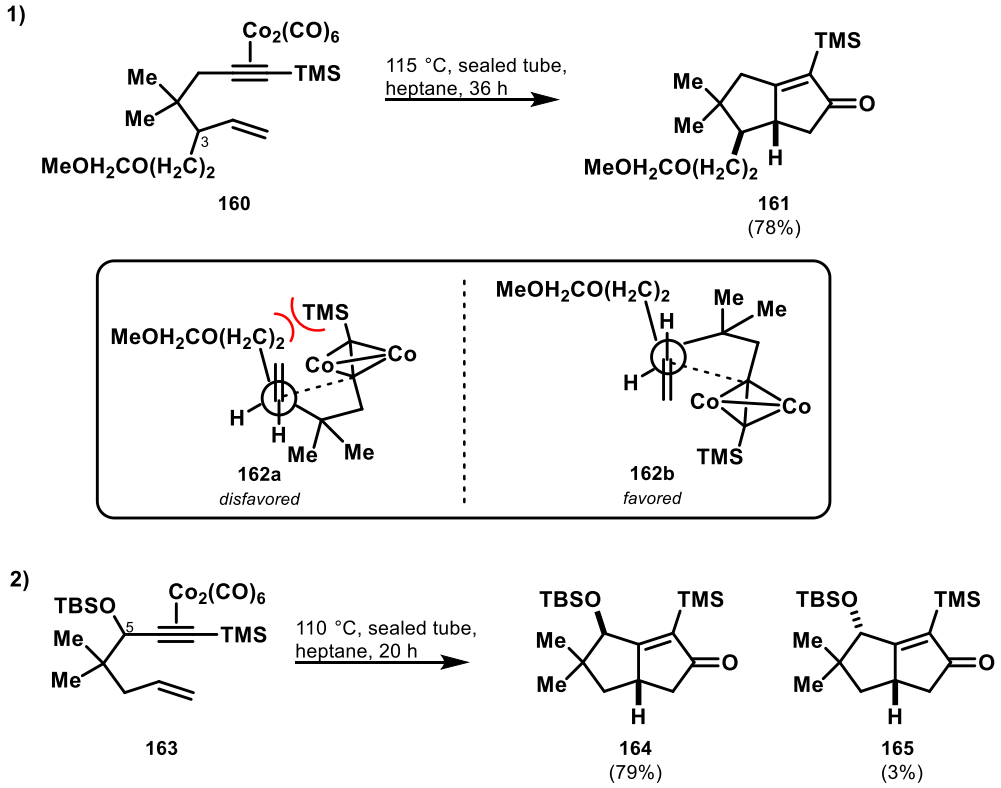
explain the observed regioselectivity in terms of alkyne incorporation. As a result, the larger substituent of the unsymmetrically substituted alkyne is located in 2-position of the final cyclopentenone (like in **151** and **152**), whereas rather unselective incorporation is observed for the olefin. In 2001, DFT calculations by Nakamura and Yamanaka[48] on a model Pauson-Khand reaction with ethylene and acetylene supported the mechanistic proposal of Magnus. However, collision activated reaction (CAR) experiments with ^{13}CO as the collision gas by Gimbert *et al.* in 2014[49] revealed the incorporated carbon monoxide to be retained in the complex throughout the whole process. Mass spectrometric analysis of the reaction and further theoretical calculations suggested alternative intramolecular pathways involving a transfer of CO from one cobalt to the other *via* bridging intermediates **156a/b** (*Scheme 22*). Kinetic simulations support this hypothesis and necessitate revision of the original mechanism.



Scheme 22: Proposed alternative mechanistic pathway of the cobalt-mediated Pauson-Khand reaction by Gimbert[49].

1.4.2 Scope and Limitations

The Pauson-Khand reaction is applicable to a variety of substrates and tolerates various functional groups, including ethers, alcohols, ketones, esters and tertiary amines or amides. Problems occur for allylic or propargylic functionalities and with further conjugated π-systems. In addition to the originally intermolecular Pauson-Khand reaction, an intramolecular version was also reported and applied in several total syntheses for the construction of complex carbon skeletons[46, 50]. Best results with regard to the yield are obtained in either case for strained cyclic alkenes, due to strain release induced by the cycloaddition reaction. An increasing degree of substitution at the olefin moiety is prejudicial to its reactivity in a Pauson-Khand reaction, since steric hindrance inhibits efficient coordination to the metal center and insertion into the metal-carbon bond. In these cases, alkyne trimerization or multicomponent cycloaddition reactions of the alkyne and CO were observed instead. A similar trend exists for alkynes, in which acetylene and simple, terminal alkynes give superior results compared to internal alkynes. For the intramolecular reaction of a sterically encumbered trisubstituted olefin, satisfactory yields were obtained only with terminal alkynes[50].

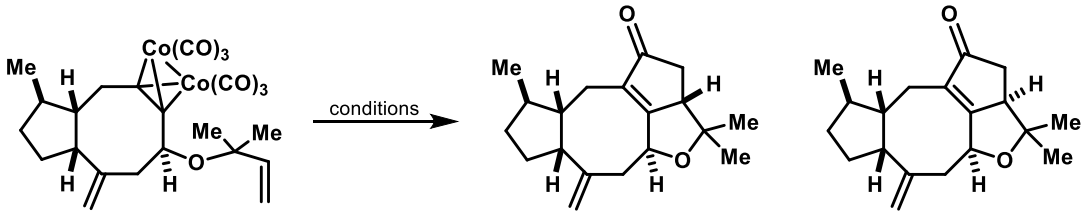


Scheme 23: Stereochemical effects of steric hindrance in the intramolecular Pauson-Khand reaction.

In general, substitution on the tether facilitates the intramolecular ring closure according to the Thorpe-Ingold effect and hence, it is frequently used to accelerate the reaction and improve the yields. In the course of the annulation, allylic (C3) or propargylic (C5) substituents preferentially position on the *exo*-face of the product (as depicted in *Scheme* 23) to escape from steric interactions on the *endo*-face. Bulky substitution on the alkyne terminus reinforces this effect.

Various strategies for the optimization of the Pauson-Khand reaction conditions are reported in literature[51]. Originally, rather forcing conditions (generally high temperatures or elevated pressure) were required to overcome the activation energy barrier for the ligand exchange at cobalt from CO to the olefin. The accelerating effect of so-called chemical promoters was first observed by Schreiber *et al*.[52] in 1990. The addition of *N*-methylmorpholine-*N*-oxide (NMO) was found to enable intramolecular Pauson-Khand reaction of multiple model substrates to occur at room temperature and with higher diastereoselectivity compared to the thermal reaction, as shown in *Table 1*.

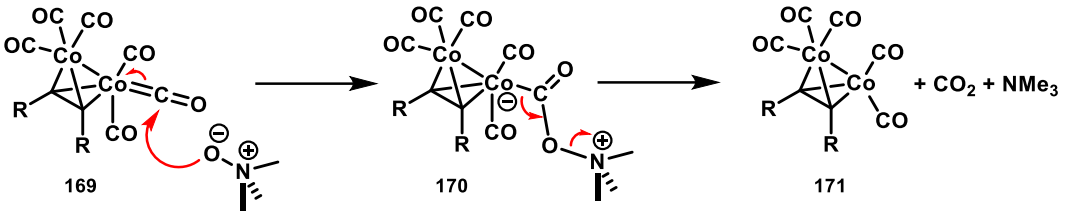
Table 1: Acceleration and altered stereoselectivity by use of chemical promoters in the Pauson-Khand reaction[52].



166 167 168

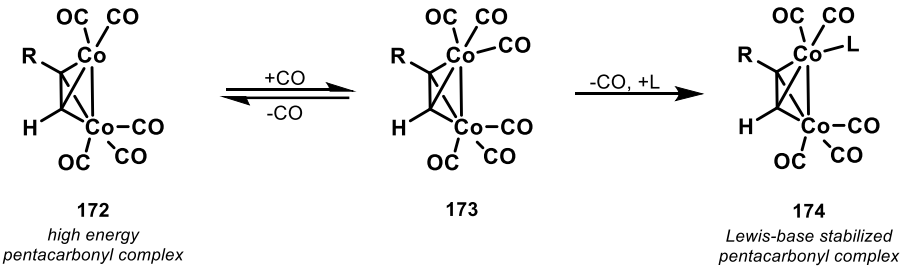
conditions	yield (%)	selectivity (167:168)
NMO, DCM, r.t.	68	11:1
MeCN, 82 °C	75	4:1
MeCN, ultrasound, 45 °C	45	3:1

Later, similar results were reported for several other *N*-oxides. The mechanistic pathway for *N*-oxide activation of metal carbonyls was suggested by Alper[53] and is outlined in *Scheme 24*. Initial oxidation of a CO ligand to CO_2 was proposed to generate an empty coordination site at the cobalt center and to render the dissociation step irreversible. Competing reaction of the coordinatively unsaturated complex **171** with either an excess of *N*-oxide, the emerging tertiary amine or direct coordination of the alkene was supposed.



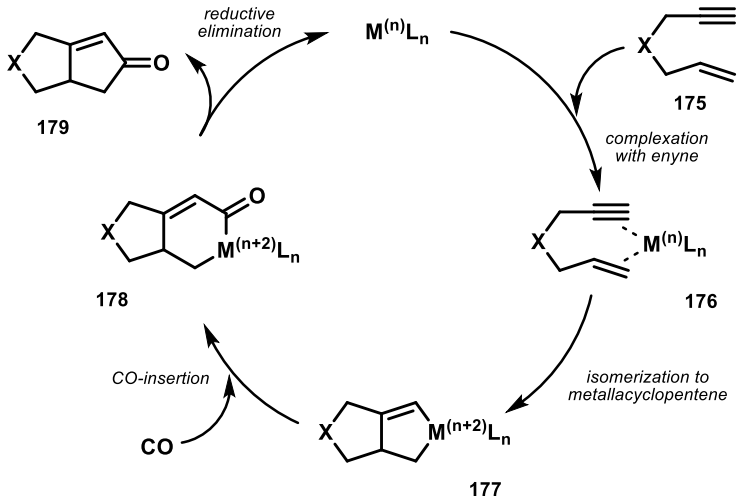
Scheme 24: Proposed mechanistic pathway for *N*-oxide activation of a $Co_2(CO)_6$-alkyne complex by Alper[53].

Increased reaction rates also occur upon addition of Lewis-basic co-solvents, *e.g.* DMSO or primary amines[54], which stabilize the coordinatively unsaturated metal center after CO dissociation and labilize further CO ligands in the Lewis-base substituted complex (*Scheme* 25).



Scheme 25: Stabilizing and destabilizing effects of CO or Lewis bases on the cobalt hexacarbonyl complex[46].

An accelerating effect is sometimes also achieved by reducing the partial CO pressure to favor the dissociation process[55], whereas an overpressure of CO results in decreased reaction rates[46]. Based on the original publication, several stoichiometric and catalytic Pauson-Khand reactions were conducted by use of other transition metal catalysts, *e.g.* titanium[56], ruthenium[57], nickel[58] or zirconium[59]. An intramolecular rhodium-catalyzed Pauson-Khand type reaction was published by the Narasaka group[60] and Jeong[61] in 1998.

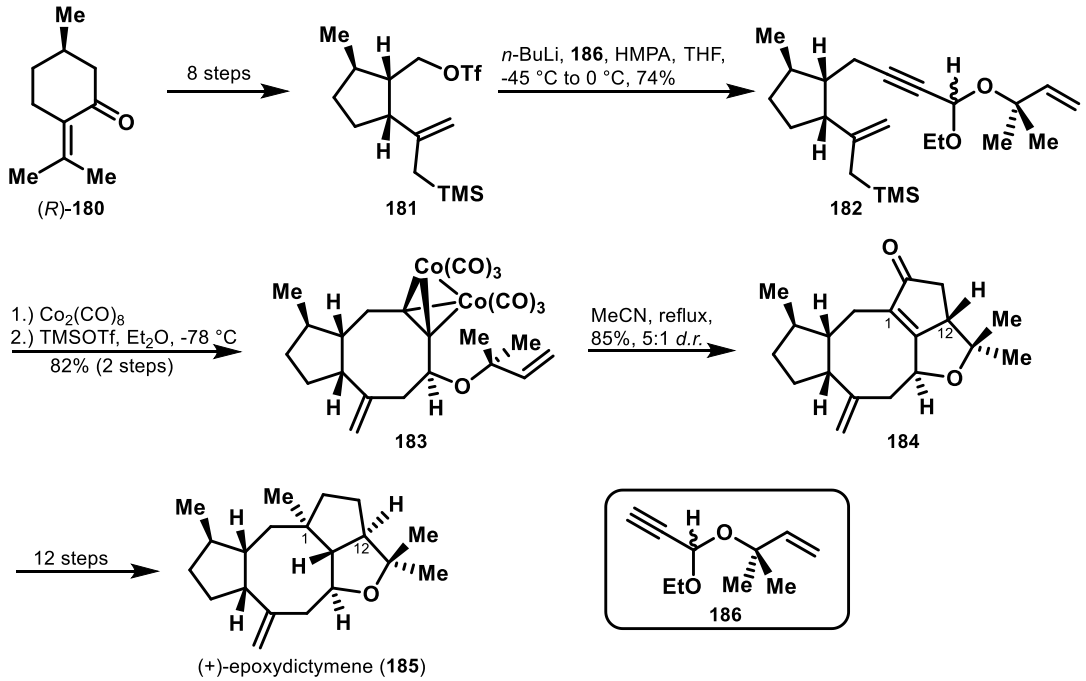


Scheme 26: Proposed mechanistic pathway for the rhodium(I)-catalyzed Pauson-Khand type reaction[62].

The reaction proceeds *via* a metallacyclopentene key intermediate **177**, as shown in *Scheme 26*. A smooth reaction process requires efficient catalyst binding to the enyne system to initiate the reaction - a capability that is promoted by π-acceptor ligands on the metal center[62]. This is contrasted to some extent by acceleration of the rate-determining oxidative isomerization from **176** to the metallacyclopentene **177** in the presence of electron-donating ligands. Systematic screening of a variety of rhodium catalysts revealed acceptor-ligand substituted complexes (or complexes with ligands that are *in situ* replaced by CO) as the catalysts of choice, *e.g.* $[RhCl(CO)_2]_2$ or $[RhCl(COD)_2]$[60a, 61].

1.4.3 Application in Total Synthesis

Since the Pauson-Khand reaction allows for the construction of highly functionalized polycyclic systems and asymmetric variants additionally enable the formation of multiple stereogenic centers in a single step, it has become a powerful tool for the total synthesis of complex natural products. An early example for synthetic application of the intramolecular Pauson-Khand reaction was the synthesis of (+)-epoxydictymene (**185**) by Schreiber[63] in 1994, shown in *Scheme 27*. Starting from (*R*)-pulegone (**180**), the precursor for the cobalt-mediated transformation, dienyne **182**, was obtained in nine steps.

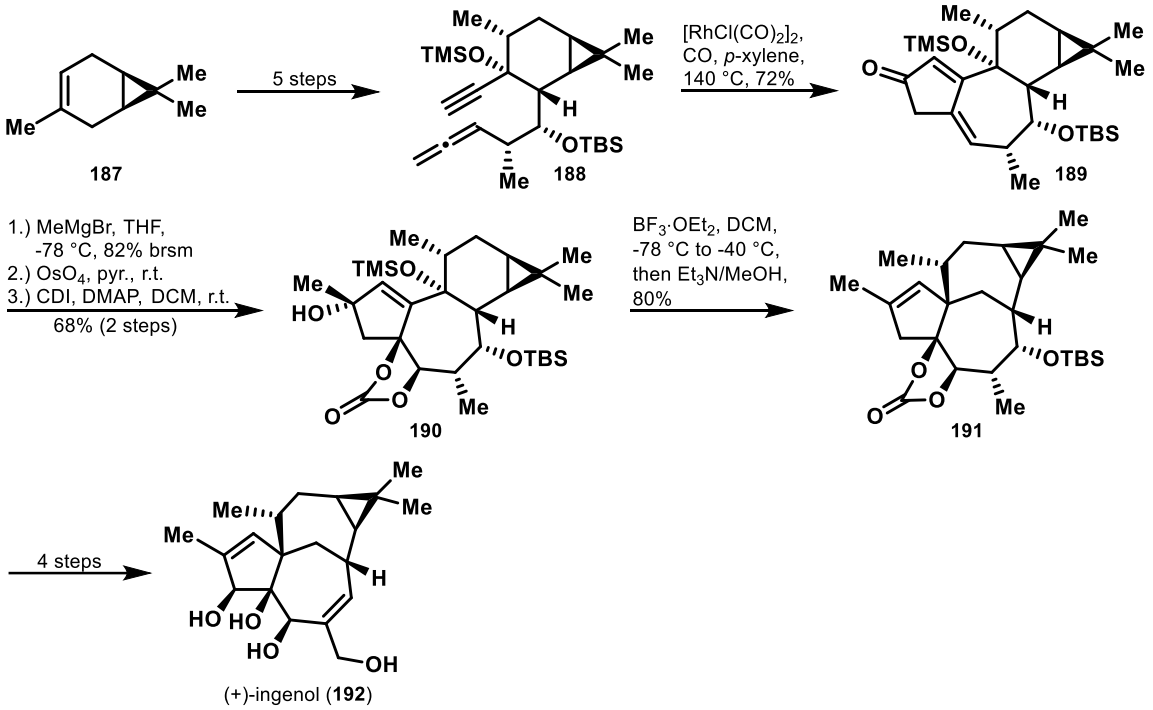


Scheme 27: Use of an intramolecular Pauson-Khand reaction for the total synthesis of (+)-epoxydictymene (**185**) by Schreiber[63].

Treatment with $Co_2(CO)_8$ yielded the corresponding Co-alkyne complex, which underwent intramolecular stereoselective Nicholas reaction to the 5,8-bicyclic system **183** under Lewis

acid catalysis. Subsequent heating in acetonitrile led to intramolecular Pauson-Khand reaction and construction of the tetracyclic skeleton of the natural product. Adjustment of the correct configuration at C12 and regioselective alkylation at C1 required additional 12 steps from PKR-product **184** and completed the total synthesis.

Application of a catalytic version of the Pauson-Khand reaction was reported by Baran and co-workers in the total synthesis of (+)-ingenol (**192**)[64]. Development of a synthetic access toward the diterpenoid attracted much attention due to the anticancer and anti-HIV activities of several semi-synthetic derivatives and concurrent insufficient availability from natural sources. An efficient 14-step total synthesis was designed by Baran using an intramolecular allenic Pauson-Khand reaction (*Scheme 28*).

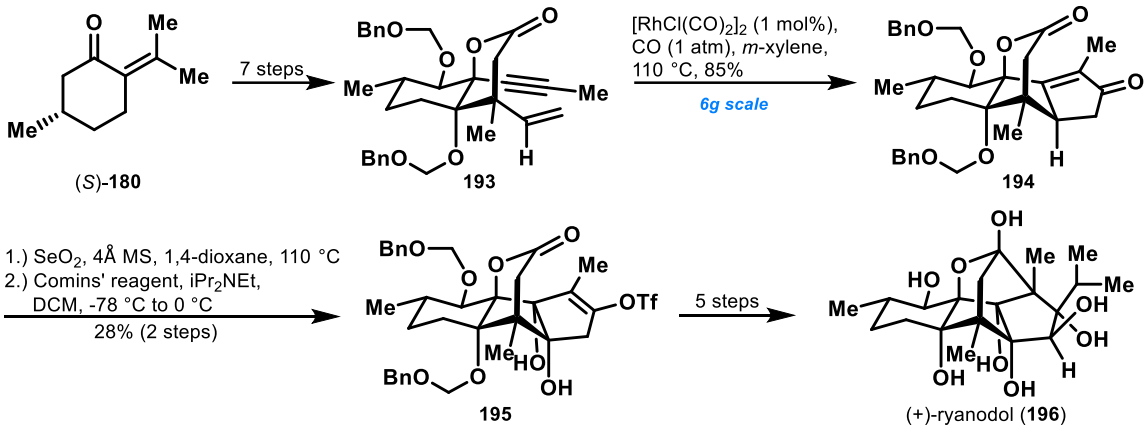


Scheme 28: Use of an allenic Pauson-Khand reaction for the total synthesis of (+)-ingenol (**192**) by Baran[64].

The precursor for this key reaction was obtained in a five-step sequence from (+)-3-carene (**187**). Silyl protection of the alcohol functionalities as well as a high dilution and the strict exclusion of water and air proved essential for the feasibility of the rhodium-mediated Pauson-Khand cyclization. The reaction was conducted under an atmosphere of carbon monoxide in refluxing *p*-xylene and produced the desired tricyclic product **189** in 72%. Subsequent 1,2-addition of methylmagnesium bromide, dihydroxylation and protection of the diol provided the precursor for a Lewis acid-catalyzed vinylogous pinacol rearrangement, which efficiently constructed the full ingenane skeleton

in **191**. The natural product (+)-ingenol (**192**) was obtained in four additional steps with an overall yield of 1.2%.

In 2016, Reisman and co-workers[65] published an elegant 15-step total synthesis of the structurally complex diterpenoid (+)-ryanodol (**196**). The sequence is outlined in *Scheme* 29. Starting from (*S*)-pulegone (**180**), the bicyclic enyne **193** with a lactone moiety was synthesized in a seven step sequence containing stereoselective 1,4-addition of a vinyl cuprate for efficient construction of the quaternary stereocenter.



Scheme 29: Use of an intramolecular Pauson-Khand reaction for the total synthesis of (+)-ryanodol (**196**) by Reisman[65].

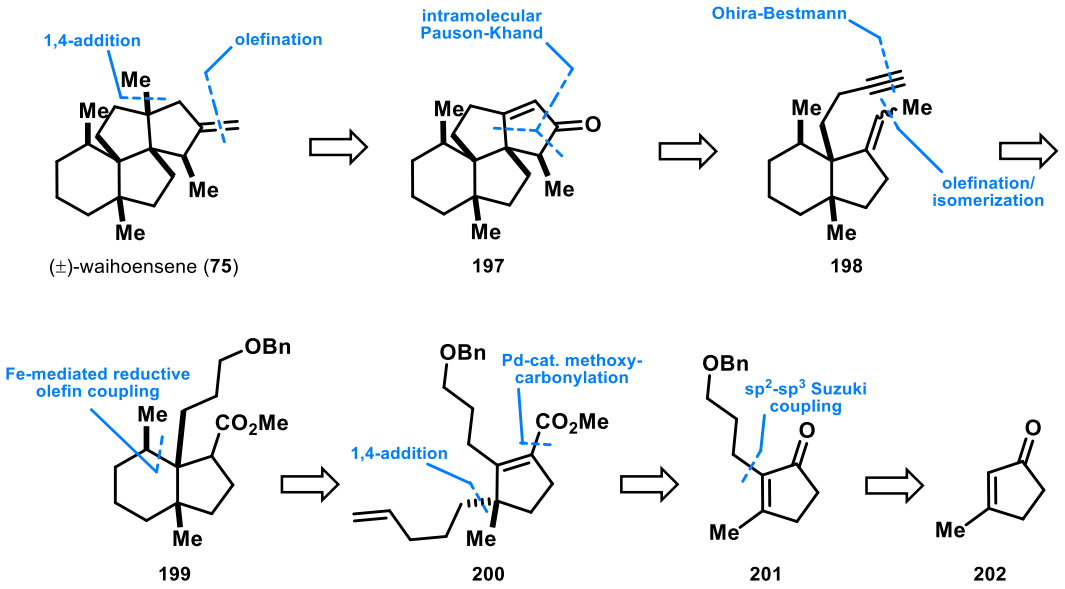
Treatment of this precursor compound with stoichiometric amounts of $Co_2(CO)_8$ produced the desired product only as a diastereomeric mixture, however, an alternative catalytic procedure with $[RhCl(CO)_2]_2$ under CO atmosphere provided the desired diastereomer as the only product in 85% yield. The scalability of the process to multi-gram scale demonstrates its versatility and robustness and emphasizes its relevance for the rapid construction of highly complex structures in natural product total synthesis.

2. Results and Discussion

2.1 Approach A: Construction of the *cis*-Hydrindane Core Structure *via* Reductive Olefin Coupling

2.1.1 Retrosynthetic Analysis

In the course of careful retrosynthetic analysis, an intramolecular Pauson-Khand reaction was chosen as the key reaction for construction of the angular triquinane core of waihoensene (**75**) from a bicyclic precursor. Since the Pauson-Khand reaction is capable of inducing high molecular complexity in a single step and does not require additional functional groups beside the enyne, an efficient potential access to the tetracyclic diterpene was designed (*Scheme 30*).



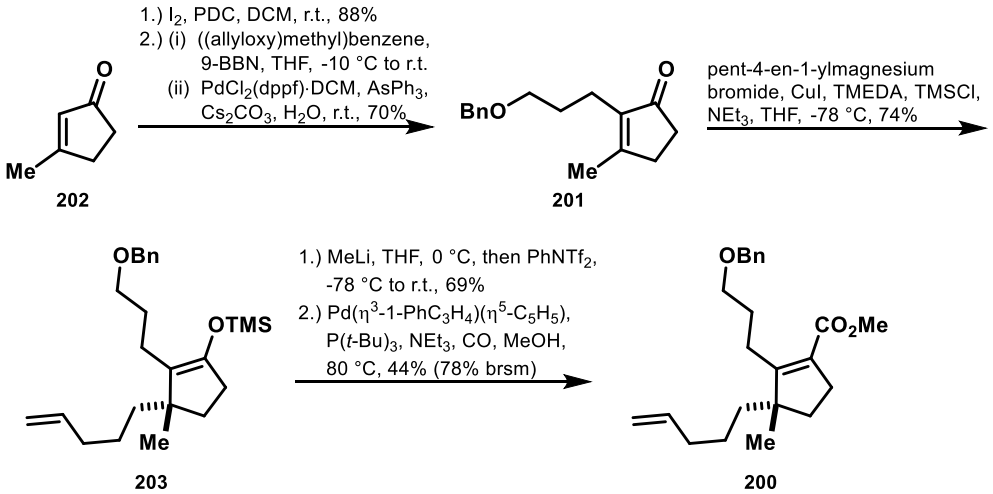
Scheme 30: Retrosynthetic approach A for the total synthesis of (±)-waihoensene (**75**).

Indeed, Hoshino *et al.*[66] have demonstrated the feasibility of angular triquinane synthesis by intramolecular Pauson-Khand reactions. The second key transformation within this first synthetic approach was a catalytic reductive olefin coupling by use of the method of Baran *et al.*[67], which should produce the bicyclic precursor for the Pauson-Khand reaction from substituted cyclopentene ester **200**. Starting in retrosynthetic direction, the target molecule **75** should arise from the product of a Pauson-Khand reaction by olefination of the ketone and preceding copper-mediated conjugate addition to enone **197**. As indicated, the angular triquinane in the tetracyclic enone is planned to be produced in an

intramolecular version of the Pauson-Khand reaction of bicyclic enyne **198**. The alkyne functionality should be introduced *via* the corresponding aldehyde by use of the Ohira-Bestmann reagent[68], while the trisubsituted olefin should be generated from the ester by a sequence of reduction to the aldehyde, olefination and isomerization of the double bond to the internal position. An iron-mediated intramolecular reductive olefin coupling should furnish the bicyclic core of compound **199**. This radical process was expected to entropically and sterically favor the formation of the desired all-*cis* product and should be realized by the application of conditions developed by Baran and co-workers[67, 69]. The substrate **200** for the cyclization could be obtained by Pd(0)-catalyzed methoxycarbonylation of the corresponding vinyl triflate, which in turn should be derived from copper-mediated conjugate addition of pent-4-en-1-ylmagnesium bromide to the enone moiety in **201**. Precedent functionalization in α-position of commercial 3-methylcyclopent-2-en-1-one (**202**) might be accomplished by a sp^2-sp^3 Suzuki coupling with 9-(3-(benzyloxy)propyl)-9-BBN.

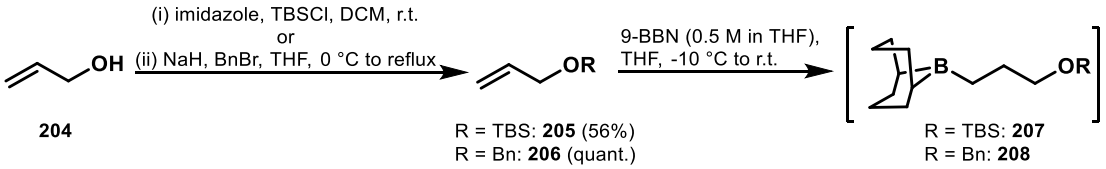
2.1.2 Attempts toward the Synthesis of the *cis*-Hydrindane Core

The precursor for the intramolecular reductive cyclization was successfully synthesized in five steps from 3-methylcyclopent-2-en-1-one (**202**) (*Scheme 31*). Alkylation in α-position was realized by application of a two-step protocol comprising iodination and palladium(0)-catalyzed sp^2-sp^3 Suzuki coupling. The iodination was performed according to a literature-known procedure for the formation of α-iodoenones by Nelis and co-workers[70].



Scheme 31: Synthetic access to cyclization precursor **200**.

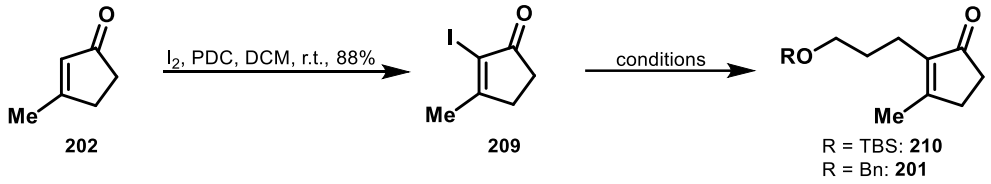
Suzuki coupling was chosen for further functionalization of the α-iodoenone, since organoboron compounds are generally easily accessible from the corresponding olefin by hydroboration and tolerate a variety of functional groups, *e.g.* ketones, esters and alcohols. Palladium(0)-catalyzed cross coupling of *B*-alkyl-9-borabicyclo[3.3.1]nonanes was described by Suzuki and Miyaura[71] and later applied by Johnson *et al*. for the synthesis of α-alkenones from iodoenones[43]. For this purpose, prop-2-en-1-ol (**204**) was protected as a silyl ether, and subjected to hydroboration conditions[43, 71] (*Scheme 32*).



Scheme 32: Synthesis of alkylboranes **207** and **208**.

However, low yields in the subsequent 1,4-addition step (see *Table 3*) revealed the benzyl ether **206** to be the superior substrate. The *in situ* generated organoborane was directly coupled to 2-iodo-3-methylcyclopent-2-en-1-one (**209**) under palladium catalysis (*Table* 2). As indicated by the findings of Suzuki and Johnson, β-hydride elimination from the alkylpalladium complex was effectively prevented by use of the $PdCl_2$(dppf) catalyst. Self-preparation of the catalyst[72] allowed for diminution of problems with the reproducibility of the coupling reaction.

Table 2: Optimization of the sp^2-sp^3 Suzuki coupling.



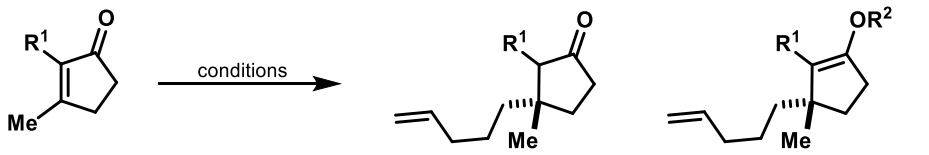
entry	conditions	organoborane (eq.)	result
1	$PdCl_2$(dppf), K_3PO_4, DMF, 70 °C	**207** (1.00)	20% **210**
2	$PdCl_2$(dppf), K_2CO_3, $AsPh_3$, DMF, 70 °C	**208** (2.00)	38% **201**
3	$PdCl_2$(dppf)·DCM[a)], K_2CO_3, DMF, 70 °C[b)]	**208** (2.50)	15% **201**
4	$PdCl_2$(dppf)·DCM[a)], K_2CO_3, DMF, 70 °C[c)]	**208** (3.00)	42% **201**
5	$PdCl_2$(dppf)·DCM[a)], Cs_2CO_3, $AsPh_3$, DMF, H_2O	**207** (1.30)	71% **210**
6	$PdCl_2$(dppf)·DCM[a)], Cs_2CO_3, $AsPh_3$, DMF, H_2O	**208** (1.50)	70% **201**

a) self-prepared by literature-known procedure[72]; b) 0.18 mmol scale; c) 2.14 mmol scale.

Johnson and Braun have already noticed cesium carbonate to be the base of choice, producing higher yields compared to the potassium bases used by Suzuki and Miyaura. Furthermore, Johnson reported increased yields with the addition of $AsPh_3$, due to a higher turnover rate and cleaner reaction. These observations are in accordance with the results shown in *Table 2*.

Copper-mediated conjugate addition of a pent-1-en-5-yl nucleophile to the enone was first attempted on 3-methylcyclopent-2-en-1-one **202** as a test substrate and later on the α-alkylated analogues (*Table 3*). Initially, a lower-order cyanocuprate RCu(CN)Li in combination with boron trifluoride etherate was chosen (entries 1-5). The necessity of carbonyl activation by a Lewis acid is caused by steric hindrance at the reacting carbon center of the enone. The use of a combination of cyanocuprate and trimethylsilyl chloride instead was not effective (entry 6). In addition, careful control of the reaction temperature was found to be crucial with regard to successful formation and stability of the organocuprate species. Reaction of the test enone **202** with the cyanocuprate generated from 5-bromopent-1-ene in presence of boron trifluoride etherate led to full consumption of the starting material and formation of desired **211** as the only product (entry 1).

Table 3: Optimization of the copper-catalyzed 1,4-addition.



R^1 = H: **202**
R^1 = $(CH_2)_3OBn$: **201**
R^1 = $(CH_2)_3OTBS$: **210**

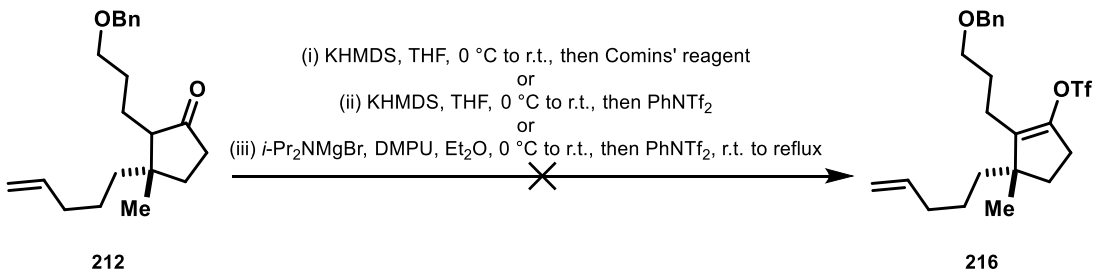
R^1 = H: **211**
R^1 = $(CH_2)_3OBn$: **212**
R^1 = $(CH_2)_3OTBS$: **213**

R^1 = H; R^2 = TMS: **214**
R^1 = H; R^2 = Tf: **215**
R_1 = $(CH_2)_3OBn$; R_2 = TMS: **203**

entry	conditions	result
1	5-bromopent-1-ene, *t*-BuLi, Et_2O, -78 °C, then CuCN, -50 °C; then $BF_3{\cdot}OEt_2$, **202**, Et_2O, -78 °C	full conversion after 30 mins, **211** as only product
2	5-bromopent-1-ene, *t*-BuLi, Et_2O, -78 °C, then CuCN, -50 °C; then $BF_3{\cdot}OEt_2$, **210**, Et_2O, -78 °C	16% **213** + decomposition
3	5-bromopent-1-ene, *t*-BuLi, Et_2O, -78 °C, then CuCN, -50 °C; then $BF_3{\cdot}OEt_2$, **201**, Et_2O, -78 °C	51% **212**
4	5-bromopent-1-ene, *t*-BuLi, Et_2O, -78 °C, then CuCN, -50 °C; then $BF_3{\cdot}OEt_2$, **201**, Et_2O, -78 °C, then Comins' reagent, -78 °C to r.t.	no **215** observed

entry	conditions	result
5	5-bromopent-1-ene, *t*-BuLi, Et_2O, -78 °C, then CuCN, -50 °C; then $BF_3{\cdot}OEt_2$, **201**, Et_2O, -78 °C, then DMPU, Comins' reagent, -78 °C to r.t.	no **215** observed
6	5-bromopent-1-ene, *t*-BuLi, Et_2O, -78 °C, then CuCN, -50 °C; then TMSCl, **201**, Et_2O, -78 °C	no reaction, recovered **201**
7	pent-4-en-1-ylmagnesium bromide, CuI, Et_2O, 0 °C, then NEt_3, TMSCl, TMEDA, -78 °C, then **202**, THF, -78 °C	55% **214**
8	pent-4-en-1-ylmagnesium bromide, CuI, Et_2O, 0 °C, then NEt_3, TMSCl, TMEDA, -78 °C, then **201**, THF, -78 °C	74% **203**

However, when the same conditions were applied to enone **210** the yield dropped significantly and no other defined compound than **213** could be isolated from the reaction mixture due to decomposition (entry 2). As mentioned above, a benzyl ether was used as alternative protecting group for the primary alcohol, and indeed, compound **201** could be transformed into addition product **212** with a yield of 51% (entry 3). The relative configuration of the adjacent stereocenters was not determined at this point, since envisaged conversion to the vinyl triflate would lead to formation of a sp^2-hybridized carbon atom in the next step anyway. However, all attempts for this transformation *via* consecutive deprotonation of ketone **212** with potassium hexamethyldisilazide or bromomagnesium diisopropylamide and addition of Comins' reagent or *N*-phenyl triflimide produced the desired vinyl triflate **216** only in trace amounts and led to reisolation of the starting material (*Scheme 33*).

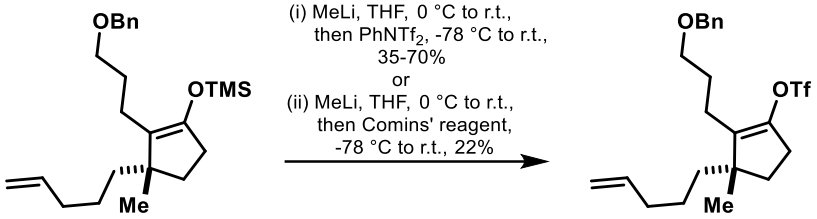


212 **216**

Scheme 33: Attempted triflation of ketone **212**.

Since alternative direct trapping of the intermediate enolate would allow for regioselective formation of the required vinyl triflate, Comins' reagent was added to the conjugate

addition reaction prior to the aqueous quench (entries 4 & 5). In neither case formation of the triflate was observed, which might be due to strong coordination of the enolate oxygen to boron. Application of a 1,4-addition protocol by Wright and Sperry[73] finally gave access to the respective trimethylsilyl enol ether in fair to good yields (entries 7 & 8). Subsequent conversion to the corresponding vinyl triflate was accomplished by regeneration of the enolate with methyllithium and further reaction with either Comins' reagent or *N*-phenyl triflimide. The reaction yield showed strong dependence on the quality of the triflating agent and varied from 22% for Comins' reagent to 35 to 70% for *N*-phenyl triflimide (*Scheme 34*).

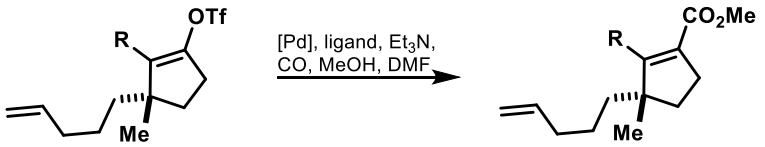


203 **216**

Scheme 34: Conversion of silylenol ether **203** to vinyl triflate **216**.

Unexpectedly, first attempts on palladium-catalyzed methoxycarbonylation of vinyl triflate **216** produced only trace amounts of the desired compound (*Table 4*, entry 1). To exclude problems with the palladium catalyst, a new batch of tetrakis (triphenyl-phosphine)-palladium(0) was prepared[74] and used for the reaction. As reaction monitoring by TLC did not show any conversion after two hours, the reaction was heated to 50 °C under a CO atmosphere. After two hours at this temperature, the desired methyl ester **200** could be isolated in 27% along with unreacted vinyl triflate **216** (entry 2). Prolongation of the reaction time under these conditions further increased the yield up to 36%, but also led to partial decomposition of the material (entry 4). In contrast, a control experiment using the identical conditions as in entry 1, but with the unsubstituted vinyl triflate analogue **215** as substrate, yielded the corresponding α,β-unsaturated methyl ester **217** in 87% after two hours and only trace amounts of the starting material were reisolated (entry 5). This indicated a drastically decelerated oxidative addition for the alkyl substituted derivative **216** and required for optimization of the catalytic system. *In situ* generated Pd(0) complexes from a Pd(II) precursor and bidentate biphosphine ligands have been reported in literature to efficiently catalyze alkoxycarbonylations[75].

Table 4: Catalyst screening for the methoxycarbonylation of vinyl triflates **215**/**216**.

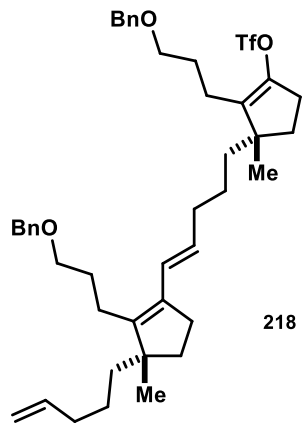


R = H: **215**
R = $(CH_2)_3OBn$: **216**

R = H: **217**
R = $(CH_2)_3OBn$: **200**

entry	substrate	catalyst (mol%)	ligand	T [°C]	t [h]	result
1	**216**	6% $Pd(PPh_3)_4$	-	r.t.	4	traces of **200**, recovered **216**
2	**216**	6% $Pd(PPh_3)_4$[a)]	-	r.t., then 50	2+2	27% **200**, recovered **216**
3	**216**	3% $Pd(OAc)_2$	dppp	60	18	2% **200**, 5% **218**, 67% **216**
4	**216**	6% $Pd(PPh_3)_4$[a)]	-	50	20	36% **200**, 40% **216**, decomposition observed
5	**215**	6% $Pd(PPh_3)_4$[a)]	-	r.t.	2	87% **217**
6	**216**	4% $Pd(\eta^3\text{-}PhC_3H_4)(\eta^5\text{-}C_5H_5)$[b)]	P(*t*-Bu)$_3$	80	24	38% **200**, recovered **216**
7	**216**	10% $Pd(\eta^3\text{-}PhC_3H_4)(\eta^5\text{-}C_5H_5)$[b)]	P(*t*-Bu)$_3$	80	24	44% **200**, 42% **216**

a) freshly prepared by literature-known procedure[74]; b) prepared by literature-known procedure[76].



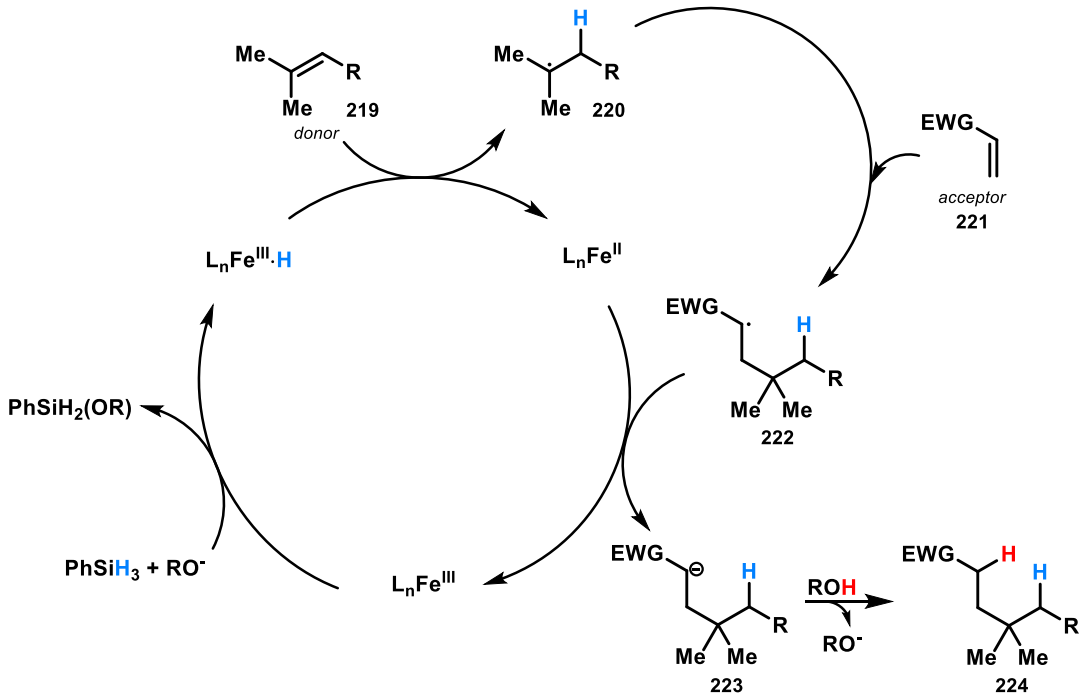
218

Figure 11: Side-product by intramolecular Heck coupling with the $Pd(OAc)_2$/dppp catalyst system.

The use of a 1,3-bis(diphenylphosphino)propane ligand instead of triphenylphosphine was reported to effect a significantly enhanced rate for the oxidative addition to palladium[77]. However, an alternative catalyst system consisting of palladium(II) acetate in combination with the dppp ligand did not prove to be suitable for the desired transformation (entry 3) and moreover, led to formation of the unexpected side-product **218** by intermolecular Heck coupling (*Figure 11*).

Baird and co-workers[76, 78] have described and applied Pd(η^3-1-PhC_3H_4)(η^5-C_5H_5) as effective catalyst precursor for a variety of cross-coupling reactions. The use of Pd(η^3-1-PhC_3H_4)(η^5-C_5H_5) in combination with P(*t*-Bu)$_3$ efficiently generates the desired palladium(0) species PdL_2 *in situ* and thus is very effective for many catalytic processes. Indeed, a cleaner reaction and a slightly increased yield were obtained by use of the above-mentioned catalyst system for methoxycarbonylation of **216** (entries 6 & 7), but full conversion was still not observed.

However, with compounds **200** and **217** in hands, intramolecular reductive olefin coupling for construction of the *cis*-hydrindane core was attempted. In 2014, Baran and co-workers[67, 69a] have reported inter- and intramolecular couplings of various unactivated olefins (donors, **219**) with electron-deficient olefins (acceptors, **221**) by use of an iron(III) catalyst and a silane reducing agent. As shown in the proposed mechanistic pathway in *Scheme 35*, the Mukaiyama-type olefin hydrofunctionalization is supposed to proceed *via* a nucleophilic radical intermediate **220** generated by a Fe(III)-hydride species.



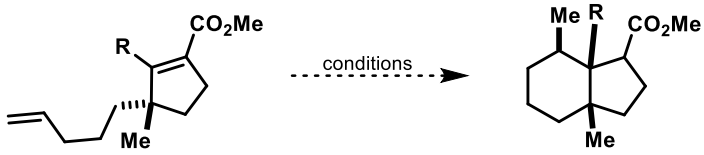
Scheme 35: Simplified proposed mechanistic pathway for the Fe(III)-mediated reductive olefin coupling developed by Baran and coworkers[67].

Furthermore, Baran demonstrated the reaction to be robust (insensitive to oxygen and moisture), easily scalable and capable of producing quaternary stereocenters.

In a first attempt, only partial decomposition was observed when subjecting test substrate **217** to the reported catalytic conditions. The reaction was stopped after four

hours and small quantities of unreacted starting material could be reisolated along with decomposed material (*Table 5*, entry 1). Degassing the solvents prior to use did not change the outcome (entry 2), but recrystallization of the iron catalyst from ethanol led to a drastic improvement: after 30 minutes under the same conditions the starting material was completely consumed (entry 3). The newly formed compounds were slightly less polar than the starting material and did not show any olefinic signals in the ^{1}H NMR spectra, but could not be further characterized as their separation was not possible by column chromatography or HPLC.

Table 5: Attempted intramolecular reductive olefin coupling.



R = H: **217**
R = $(CH_2)_3OBn$: **200**

R = H: **225**
R = $(CH_2)_3OBn$: **199**

entry	substrate	conditions	T [°C]	t [h]	result
1	**217**	$Fe(acac)_3$ (30 mol%), $PhSiH_3$ (1.50 eq.), EtOH/$(CH_2OH)_2$ (5:1)	60	4	partial decomposition, recovered **217**
2	**217**	$Fe(acac)_3$ (30 mol%), $PhSiH_3$ (1.50 eq.), EtOH/$(CH_2OH)_2$ (5:1)[b]	60	4	partial decomposition, recovered **217**
3	**217**	$Fe(acac)_3$[a] (30 mol%), $PhSiH_3$ (1.50 eq.), EtOH/$(CH_2OH)_2$ (5:1)	60	0.5	inseparable mixture of several compounds
4	**200**	$Fe(acac)_3$[a] (30 mol%), $PhSiH_3$ (1.50 + 1 eq.), EtOH/$(CH_2OH)_2$ (5:1)	60	4	decomposition
5	**200**	$Fe(acac)_3$[a] (5 mol%), $PhSiH_3$ (5 mol% + 1.50 eq.), styrene (5 mol%), THF/$(CH_2OH)_2$ (4:1)[b]	70	20	no reaction
6	**200**	$Fe(acac)_3$[a] (1.00 eq.), $PhSiH_3$ (2.50 eq.), EtOH	60	17	inseparable mixture of several compounds

a) recrystallized from EtOH prior to use; b) solvents degassed.

The reaction was repeated with the α-substituted analogue **200**, but no defined compound could be isolated from the reaction mixture (entry 4). Application of an improved second-generation set of conditions[69b], which comprised the addition of 5 mol% of styrene for catalyst activation, did not succeed for substrate **200** (entry 5). Stochiometric conditions gave a complex mixture of several compounds (entry 6), which were not separable at this point. Attempted conversion of the ester functionalities of these compounds to the corresponding secondary amides by treatment with methylamine hydrochloride and trimethylaluminum led to complete conversion of the starting mixture and formation of polar products. Subsequent purification by semi-preparative HPLC (gradient hexanes/EA 100:0 to 0:100 in 50 min) enabled separation and characterization of compound **226** from the mixture (*Figure 12*). An additional fraction contained an inseparable mixture of three compounds. Alternative reduction of the initial compound mixture by lithium aluminum hydride produced alcohol **227** alongside an inseparable complex mixture of several compounds (semi-preparative HPLC, gradient hexanes/EA 100:0 to 70:30 in 50 min). Further characterization of these compounds was not possible.

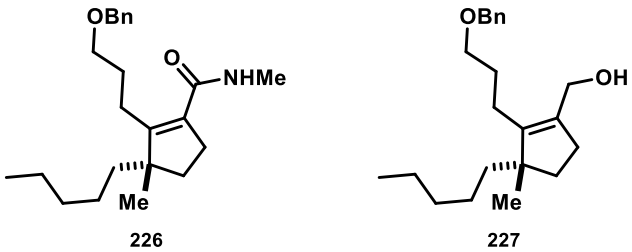


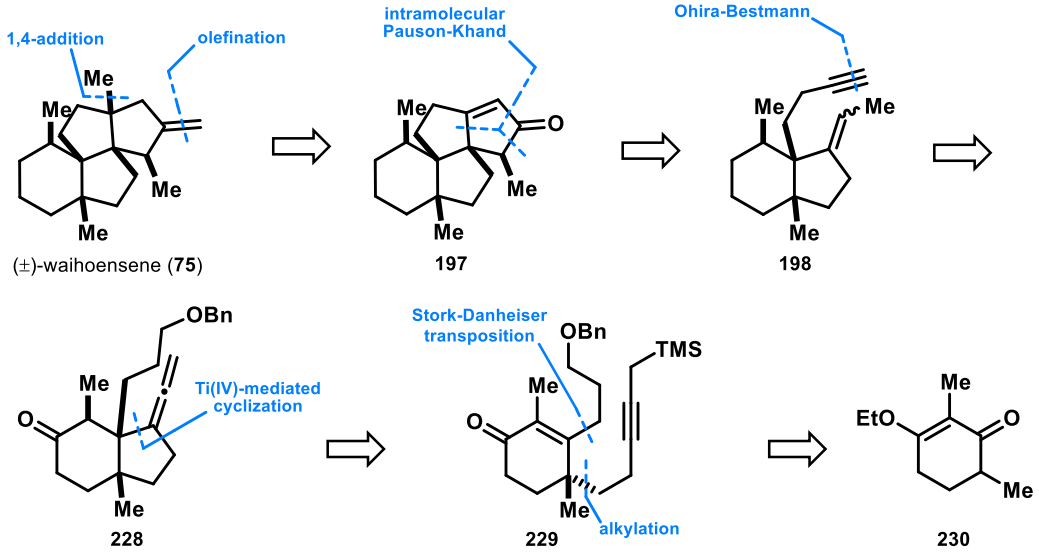
Figure 12: **226** and **227** by reduction of the terminal olefin under the reaction conditions.

The occurrence of **226** and **227** was rationalized by reduction of the starting olefin to the saturated alkyl analogue, which seemed reasonable with regard to the formation of an unstabilized secondary radical intermediate in a protic solvent. This competing side-reaction has also been observed by Baran and co-workers with some of their substrates[67, 69b].

2.2 Approach B: Construction of the *cis*-Hydrindane Core Structure *via* Intramolecular Sakurai Reaction

2.2.1 Retrosynthetic Analysis

Since intramolecular cyclization by reductive olefin-olefin coupling could not be successfully accomplished, an alternative strategy for the construction of the *cis*-hydrindane motif and modification of the synthetic approach toward waihoensene (**75**) were required. In analogy to the previous approach, the revised retrosynthesis (*Scheme 36*) comprised an intramolecular Pauson-Khand reaction of precursor **198** for construction of the angular triquinane motif and the endgame consisting of copper-mediated conjugate addition and ketone methylenation.



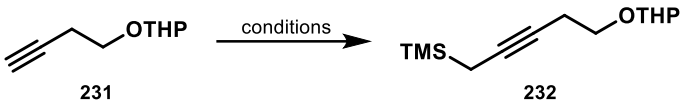
Scheme 36: Retrosynthetic approach B for the total synthesis of (±)-waihoensene (**75**).

As intended before, the alkyne in **198** would be provided by alkynylation reaction of the corresponding aldehyde with Ohira-Bestmann reagent. The bicyclic core was planned to be installed in a Ti(IV)-mediated intramolecular Sakurai reaction of propargylsilane **229**, which concurrently would lead to the formation of an allene functionality. This allene might subsequently be reduced to the trisubstituted olefin. A straightforward sequence of Stork-Danheiser transposition and alkylation of commercially available vinylogous ester **230** should deliver the precursor **229** for the cyclization reaction.

2.2.2 Synthesis of the *cis*-Hydrindane Core

The synthesis of cyclization precursor **229** commenced with alkylation of commercially available vinylogous ester **230**. A modified version of the general procedure for the alkylation of 3-ethoxycyclohexenones by Schinzer and co-workers[79] was used for the synthesis of compound **236** (see *Table 7*). Initial problems with the synthesis of the alkylating agent homopropargyl iodide **235** (depicted in *Scheme 37*) concerned not only the synthesis and THP deprotection of alcohol **232**, but also conversion of the latter into the iodide. After protection of the alcohol functionality of but-3-yn-1-ol (**233**) as THP ether, the terminal alkyne in **231** was deprotonated by reaction with *n*-butyllithium and alkylated by reaction with (iodomethyl)trimethylsilane. This sequence was initially reported by Aubé and Frank[80] but required minor modifications for the alkylation step. The tested conditions are shown in *Table 6*.

Table 6: Optimization of the alkylation of THP-protected 3-butin-1-ol **231**.

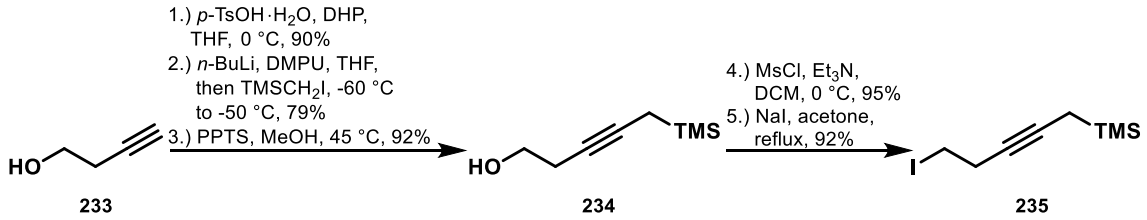


231 **232**

entry	conditions	t [min]	result
1	*n*-BuLi, DMPU, THF, -78 °C, then -60 °C, $TMSCH_2I$	10	recovered **231** + traces of **232**
2	*n*-BuLi, DMPU, THF, -78 °C, then -60 °C, $TMSCH_2I$	90	recovered **231** + traces of **232**
3	*n*-BuLi, DMPU, THF, -78 °C, then $TMSCH_2I$, -60 °C to r.t.	180	63% **232**
4	*n*-BuLi, DMPU, THF, -78 °C, then $TMSCH_2I$, -60 °C to r.t. (stepwise +10 °C/30 min)	300	70% **232**
5	*n*-BuLi, DMPU, THF, -78 °C, then $TMSCH_2OTf$, -60 °C to -10 °C	270	79% **232**
6	*n*-BuLi, DMPU, THF, -78 °C, then $TMSCH_2I$, -60 °C to r.t.	540	74% **232**
7	*n*-BuLi, DMPU, THF, -78 °C, then $TMSCH_2I$, -60 °C to -50 °C (overnight), then warm to r.t.	1440	79% **232**

The first experiments were carried out according to the literature procedure[80] but only traces of a new compound were observed on TLC after a reaction time of 10 minutes at -60 °C (*Table 6*, entry 1). Therefore, the reaction time and temperature program were altered (entries 2-4). Aubé used either trimethylsilylmethyl triflate or (iodomethyl)trimethylsilane for the alkylation and reported the triflate to give the better results with regard to the yield[80]. Both reagents were tested under adjusted conditions and found to give comparable yields of the desired compound **232** (entries 4 & 5), however, purification of the product turned out to be more efficient with the iodide. Furthermore, a prolonged reaction time at a temperature between -60 °C and -50 °C showed to be advantageous and enabled to increase the yield up to 79% (entry 7).

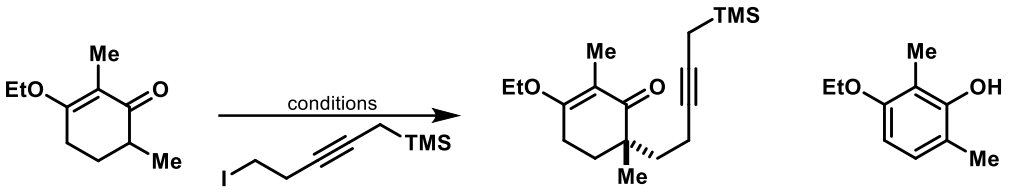
Aubé reported the subsequent THP deprotection to proceed with *p*-toluenesulfonic acid monohydrate in methanol at room temperature[80]. Due to problems with the reproducibility of this transformation, a modified procedure using pyridinium *p*-toluenesulfonate at elevated temperature was preferred (see *Scheme 37*).



Scheme 37: Optimized synthesis of homopropargyl iodide **235**.

However, bringing the reaction to completeness on decagram scale remained an unsolved problem and resulted in varying yields of 64 to 94%. Direct conversion of the alcohol **234** to the corresponding homopropargyl iodide **235** was attempted by Appel reaction using Garegg's conditions[81] but did not afford considerable amounts of the desired compound. Thus, an alternative two-step procedure *via* the mesylate was targeted and eventually, iodide **235** was obtained in five steps and with a good overall yield of 57% from commercial but-3-yn-1-ol (**233**). As mentioned beforehand, iodide **235** was used as alkylating agent in the alkylation reaction of vinylogous ester **230** (*Table 7*). Following the general procedure of Schinzer[79], the desired alkylation occurred only to a negligible extent and mainly unreacted starting material was recovered (entry 1). An alternative alkylation protocol by Abad[82] comprised an enhanced reaction temperature during enolate formation and produced significant amounts of the desired product **236** (entry 2).

Table 7: Optimization and scale-up of the alkylation of vinylogous ester **230**.



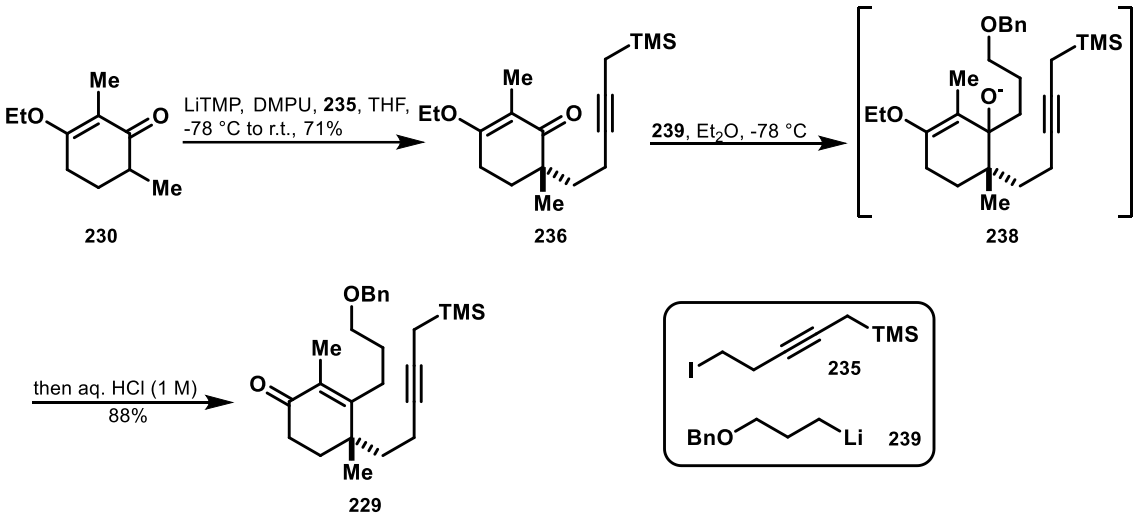
230 **235** **236** **237**

entry	conditions	result
1	LDA (1.20 eq.), THF (0.6 M), -78 °C, then DMPU (1.00 eq.), then **235** (1.05 eq.), -78 °C to r.t.	traces of **236**, recovered **230**
2	LDA (1.30 eq.), THF (0.3 M), -78 °C, then DMPU (1.60 eq.), -78 °C to r.t. to -78 °C, then **235** (1.50 eq.), -78 °C to r.t.	32% **236**, recovered **230**
3	LDA (1.20 eq.), THF (0.6 M), -78 °C, then -78 °C to r.t. to -78 °C, then DMPU (1.00 eq.), then **235** (2.00 eq.), -78 °C to r.t.	28% **236**, 68% **230**
4	DMPU (1.25 eq.), KHMDS (1.25 eq.), THF (0.3 M), -78 °C, then **235** (2.00 eq.), -78 °C to r.t.	no reaction
5	DMPU (1.25 eq.), LiHMDS (1.25 eq.), THF (0.5 M), -78 °C, then **235** (2.00 eq.), -78 °C to r.t.	2% **236**, recovered **230**
6	LiTMP (1.30 eq.), THF (0.3 M), -78 °C, then -78 °C to r.t. to -78 °C, then DMPU (1.60 eq.), then **235** (1.50 eq.), -78 °C to r.t.	39% **236**, traces of **237**
7	$LiNCy_2$ (1.20 eq.), PhMe (0.4 M), -78 °C, then -78 °C to r.t. to -78 °C, then **235** (1.00 eq.), -78 °C to r.t.	**237**, 2% **236**, recoveded **230**
8	LiTMP (1.30 eq.), THF (1 M), -78 °C, then -78 °C to r.t. to -78 °C, then DMPU (1.60 eq.), then **235** (2.00 eq.), -78 °C to r.t.[a)]	44% **236**, recovered **230**
9	LiTMP (1.30 eq.), THF (1 M), -78 °C, then -78 °C to r.t. to -78 °C, then DMPU (1.60 eq.), then **235** (2.00 eq.), -78 °C to r.t.[b)]	61% **236**
10	LiTMP (1.30 eq.), THF (1 M), -78 °C, then -78 °C to r.t. to -78 °C, then DMPU (1.60 eq.), then **235** (2.00 eq.), -78 °C to r.t.[c)]	71% **236**

a) 1.20 mmol scale; b) 12.1 mmol scale; c) 23.8 mmol scale.

This result served as a basis for further optimization of the reaction in the ensuing approaches. Application of the same temperature program to the conditions from entry 1 led to a similar result (entry 3). Other bases, like potassium bis(trimethylsilyl)amide, lithium bis(trimethylsilyl)amide or lithium dicyclohexylamide, produced only trace amounts of the desired alkylation product (entries 4, 5 & 7). Moreover, base-induced aromatization of compound **230** was observed as a side-reaction with lithium dicyclohexylamide and produced compound **237**. Lithium tetramethylpiperidide, on the other hand, afforded the desired product **236** in 39% in the first attempt (entry 6). Aromatization was also noticed under these conditions, albeit to a lower extent. A further increase of the concentration and the number of equivalents of the alkylating agent **235** as well as a scale-up of the reaction allowed for yields up to 71% (entries 8-10).

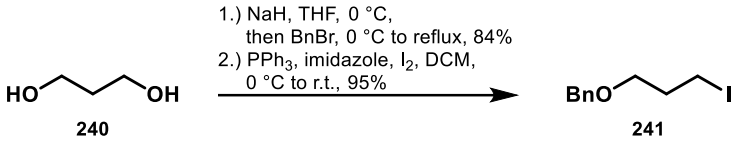
The experimental procedure for the ensuing transformation of vinylogous ester **236** to the cyclization precursor **229** by Stork-Danheiser addition-elimination reaction (*Scheme 38*) also required some optimization.



Scheme 38: Optimized alkylation of **230** and Stork-Danheiser transposition to enone **229**.

Benzylated 3-iodopropan-1-ol **241** was chosen as precursor for the organolithium nucleophile **239**, in which the primary alcohol functionality might be converted to the required homologated terminal alkyne later in the synthesis. A two-step sequence comprising mono-benzyl protection and Appel reaction of the unprotected alcohol furnished the desired alkyl iodide in very good yield from 1,3-propanol (**240**) (*Scheme 39*). *In situ* generation of the lithium nucleophile from **241** by lithium-halogen exchange with

t-butyllithium was monitored by TLC and careful addition of the vinylogous ester **236** to the reaction effectively prevented any side-reactions.



Scheme 39: Two-step synthesis of alkyl iodide **241** from 1,3-propanol.

Clean conversion of the intermediate tertiary alkoxide **238** (see *Scheme 38*) to the eliminated enone product **229** was achieved by an aqueous workup with 1 M hydrochloric acid. The choice of solvent for the subsequent extraction proved to play a crucial role with regard to the isolated yield of **229** and satisfactory results were only obtained for DCM extraction (80 to 90% yield), whereas other solvents, *e.g.* EA or Et_2O, led to a significantly reduced yield (<50%). Annulation of a five-membered ring to this enone was realized by application of the methodology of Schinzer and co-workers[79]. Treatment of a solution of enone **229** with titanium(IV) chloride at -78 °C in DCM caused an immediate deep red coloring of the reaction mixture and formation of an inseparable C7 diastereomeric mixture of the bicyclic product **228** (*Scheme 40*). Since higher temperatures resulted in concomitant Lewis acid-mediated benzyl deprotection, dropwise addition of the $TiCl_4$ solution as well as conscientious quenching prior to removal of the cooling bath were fundamental for successful implementation of the desired transformation.

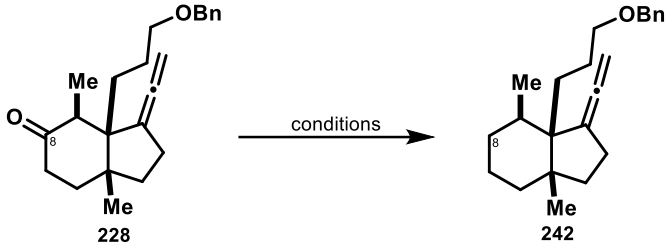
Scheme 40: Intramolecular Sakurai reaction by Lewis acid catalysis and subsequent epimerization to desired all-*cis* **228**.

Epimerization of the C7 methyl group in **228** to the desired thermodynamically favored all-*cis* configuration proceeded smoothly under basic conditions in methanol.

2.2.3 Preparation of an 1,6-Enyne as Substrate for the intramolecular Pauson-Khand Reaction

The ensuing deoxygenation of the C8 ketone functionality in **228** constituted an inevitable consequence of the retrosynthetic planning and was necessary due to the absence of any functional groups in the target molecule waihoensene (**75**). However, realization of the desired transformation caused considerable problems. Direct deoxygenation by use of a Wolff-Kishner reduction[83] produced the desired alkane **242** in only 25% along with a significant proportion of decomposed material due to the harsh reaction conditions (*Table* 8, entry 1).

Table 8: Screening of conditions for the deoxygenation of **228**.



228 **242**

entry	conditions	result
1	$N_2H_4 \cdot H_2O$ (65%, 8.00 eq.), KOH (9.00 eq.), diethylene glycol, 200 °C	25% **242**, decomposition
2	1.) $NaBH_4$ (1.00 eq.), MeOH, 0 °C to r.t., 85% 2.) TCDI (2.00 eq.), THF, reflux, 75% 3.) AIBN (10 mol%), $HSnBu_3$ (2.50 eq.), PhMe, reflux	no reaction, recovered carbothioate **243**
3	1.) NH_2NHTs (1.20 eq.), EtOH, 60 °C, 64%[a)] 2.) $NaBH_3CN$ (4.00 eq.), *p*-$TsOH \cdot H_2O$ (30 mol%), DMF/sulfolane (1:1), 110 °C	traces of **242**
4	1.) ethane-1,2-dithiol (4.00 eq.), $BF_3 \cdot OEt_2$ (2.70 eq.), AcOH, r.t. 2.) reductive desulfurization	isolation of **244** as only product from **1.)**
5	1.) NH_2NHTs (1.20 eq.), EtOH, 60 °C, 64%[a)] 2.) D*i*BAL-H (3.50 eq.), DCM, 0 °C to r.t.	13% **242**, recovered hydrazone **245**
6	1.) NH_2NHTs (1.20 eq.), EtOH, 60 °C, 64%[a)] 2.) $NaBH(OAc)_3$ (2.00 eq.), AcOH/MeCN (1:1), 0 °C to r.t.	recovered hydrazone **245**

entry	conditions	result
7	1.) NH_2NHTs (1.20 eq.), EtOH, 60 °C, 64%[a)] 2.) $NaBH_4$ (5.50 eq.), THF, r.t. to reflux	traces of **242**, recovered hydrazone **245**
8	1.) NH_2NHTs (1.20 eq.), EtOH, reflux, 68%[a)] 2.) catechol borane (1 M in THF, 2.40 eq.), DCM, 0 °C to r.t., then $NaOAc{\cdot}3H_2O$ (4.80 eq.), reflux	traces of **242**, recovered hydrazone **245**
9	1.) NH_2NHTs (1.20 eq.), EtOH, r.t., 60%[b)] 2.) catechol borane (1 M in THF, 2.40 eq.), DCM, 0 °C to r.t., then $NaOAc{\cdot}3H_2O$ (4.80 eq.), reflux	54% **242**
10	1.) NH_2NHTs (1.20 eq.), EtOH, 0 °C, 53%[c)] 2.) catechol borane (1 M in THF, 1.50 eq.), $CHCl_3$, -10 °C to r.t., then $NaOAc{\cdot}3H_2O$ (2.90 eq.), reflux	70% **242**
11	1.) NH_2NHTs (1.20 eq.), EtOH, 5-10 °C, 67% (77% brsm)[c)] 2.) catechol borane (1 M in THF, 1.50 eq.), $CHCl_3$, -10 °C to r.t., then $NaOAc{\cdot}3H_2O$ (2.90 eq.), reflux	66% **242**

a) hydrazone obtained as an inseparable mixture of stereoisomers; b) formation of desired hydrazone isomer favored (11:1); c) undesired isomer present in traces.

Conversion to the carbothioate *via* the corresponding alcohol succeeded, but subsequently attempted Barton McCombie deoxygenation[84] under radical conditions (entry 2) did not produce the desired product and led to reisolation of unreacted carbothioate **243** (see *Figure 13*). An interesting mild and selective deoxygenation protocol by Hutchins and co-workers[85] that is also applicable for hindered systems comprised *in situ* formation of an iminium ion intermediate. Therein, effective defunctionalization was achieved by selective reduction of the intermediate iminium ion of a hydrazone by sodium cyanoborohydride. In case of substrate **228**, only trace amounts of the desired deoxygenated product could be obtained under the described conditions (entry 3). An alternative method for the deoxygenation of ketones includes reductive desulfurization[86]. Initial treatment of carbonyl compound **228** with ethane-1,2-diol was intended to produce

the corresponding 1,2-dithiolane but afforded undesired **244** (*Figure 13*) as the only product in 55% yield (entry 4).

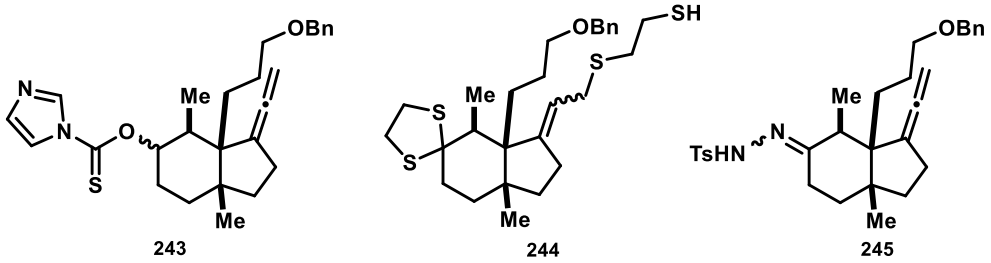


Figure 13: Observed side-products in course of the attempted deoxygenation of **228**.

The conversion of **228** with *p*-toluenesulfonyl hydrazide in ethanol proceeded rather smoothly and gave the desired tosylhydrazone compound **245** as a mixture of stereoisomers in fair yields. These isomers have not been further characterized but geometrical *E*/*Z*-isomerism of hydrazones is a known phenomenon[87].

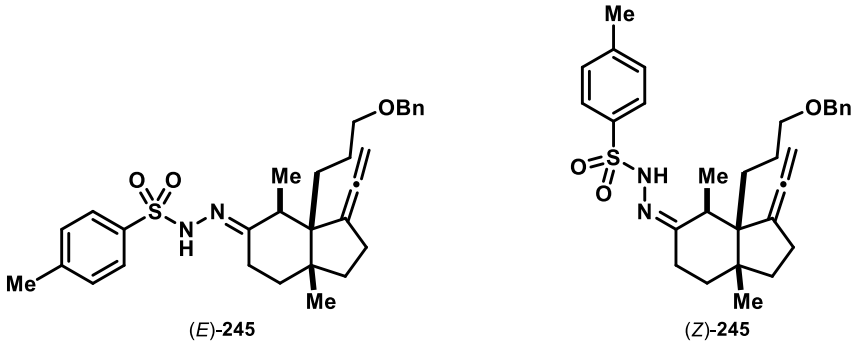
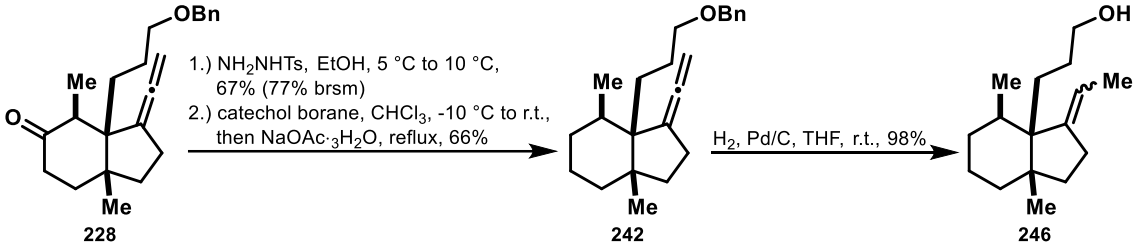


Figure 14: Proposed *E*/*Z*-isomerism of *p*-toluenesulfonyl hydrazone **245**.

Initially, all attempts to reduce these tosylhydrazones (shown in *Figure 14*) to the corresponding alkane compound proved unsatisfactory (entries 5-8). Efficient conversion of several tosylhydrazones to their methylene derivatives was reported by Kabalka and Baker[88] upon treatment with catechol borane and sodium acetate. Coincidentally, different reactivities of the isomers of hydrazone **245** toward the reduction with catechol borane were noticed. Considering the assumed *E*/*Z*-isomerism, this might be rationalized by differing steric hindrance for the particular isomers and thus, for the accessibility of the C-N double bond. Since separation of the isomers was not trivial, selective formation of one isomer was attempted and successfully implemented by reducing the reaction temperature during hydrazone formation (see entries 9-11). However, this was accompanied by a prolongation of the reaction time and incomplete conversion. Fortunately though, the obtained major stereoisomer (not further determined) could be efficiently reduced to the

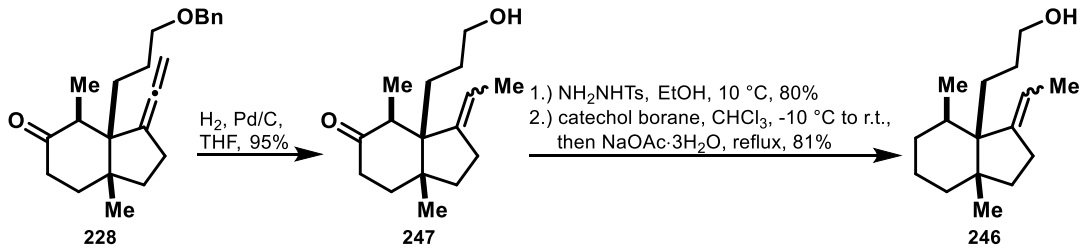
desired alkane analogue **242** by successive treatment with catechol borane and sodium acetate (entry 9) and the yield could be further increased by an enhanced reaction temperature during the elimination step (entries 10 & 11).

As outlined in *Scheme 41,* subsequent hydrogenation of the allene in **242** to the tertiary olefin and concurrent benzyl deprotection afforded compound **246** as an inseparable mixture of *E*/*Z*-isomers.



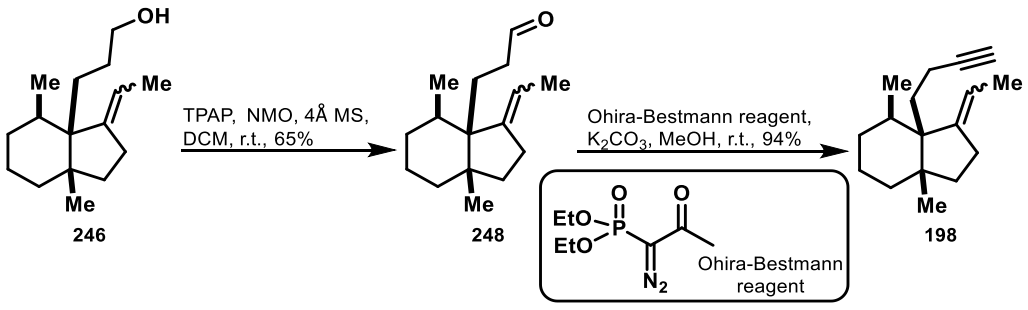
Scheme 41: Optimized synthetic sequence for the deoxygenation and hydrogenation of *cis*-hydrindane **228**.

Alternatively, a reversed course of reactions was implemented with the intention to further increase the yield (*Scheme 42*). For this purpose, bicyclic **228** was hydrogenated to **247** prior to the deoxygenation sequence and indeed, better results for both the tosylhydrazone formation and its subsequent reduction were obtained.



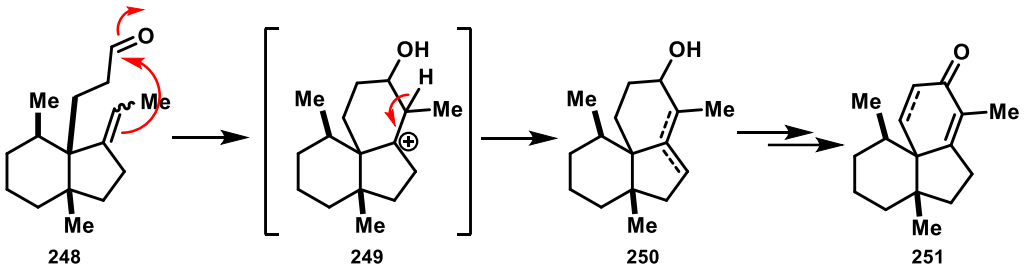
Scheme 42: Alternative, reversed sequence for the synthesis of **246** from *cis*-hydrindane **228**.

With alcohol **246** in hands, installation of the desired terminal alkyne was approached by oxidation to the corresponding aldehyde and Seyferth-Gilbert homologation using Ohira-Bestmann reagent (*Scheme 43*).



Scheme 43: Optimized synthetic sequence for the preparation of Pauson-Khand precursor enyne **198** from **246**.

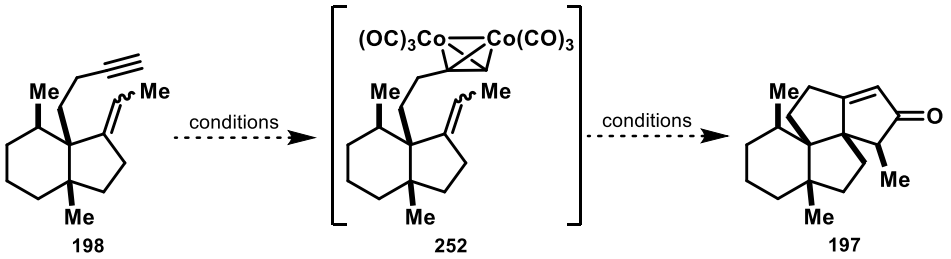
Treatment of alcohol **246** with Ley-Griffith reagent[89] led to full consumption of the starting material after one hour at room temperature, however, the desired aldehyde **248** could be isolated only in fair yields (50 to 65%). Concomitantly, formation of a second compound with similar polarity like the starting material was observed on TLC. This compound was not further characterized in the first instance, but could later be identified as the product of an unexpected intramolecular Prins cyclization (*Scheme 44*) that appears to occur during purification of the product on silica gel. Besides, slightly acidic oxidation conditions, *e.g.* IBX, also trigger this side-reaction and allow for further oxidation of the *in situ* formed (homo)allylic alcohol **250** to the corresponding enone or dienone system **251**.



Scheme 44: Proposed mechanism for the intramolecular Prins reaction of aldehyde **248** and formation of (di)enone **251**.

Selective formation of this carbon skeleton under adjusted conditions might be potentially interesting for the synthesis of taxane related compounds[90] and is currently under investigation in our group[91]. Meanwhile, the synthesis of Pauson-Khand precursor **198** was completed by reaction of aldehyde **248** with Ohira-Bestmann reagent (*Scheme* 43). Unfortunately, all attempts to realize the following intramolecular Pauson-Khand reaction failed (*Table 9*). Indeed, treatment of a diluted solution of enyne **198** in benzene with a slight excess of dicobalt octacarbonyl at room temperature led to consumption of the starting material and formation of the deep red and strongly apolar cobalt-alkyne complex **252**. This complex, however, could not be converted into the desired tetracyclic system **197** at elevated temperature (entry 1). Higher reaction temperature by use of toluene as the solvent and a prolongation of the reaction time did not change the outcome (entry 2). The addition of *N*-oxide promoters has been extensively investigated and reported in literature to drastically accelerate the PKR of several substrates[52, 54b, 92] by reduction of the activation barrier, but did not enable the desired transformation in case of substrate **198** (entries 3-5). A stepwise conversion by isolation of complex **252** failed as well as attempted oxidation of the latter by ceric ammonium nitrate to regenerate the alkyne **198**.

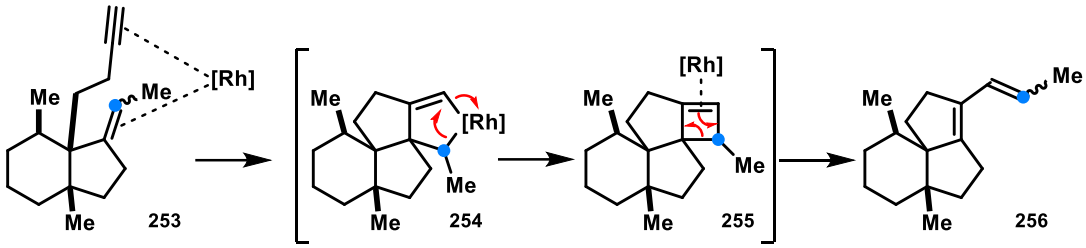
Table 9: Attempts on the intramolecular Pauson-Khand reaction of enyne **198**.



entry	conditions	additive	result
1	$Co_2(CO)_8$ (1.10 eq.), PhH (0.04 M), r.t., 1 h, sealed tube, then reflux, 17 h	-	no **197** observed
2	$Co_2(CO)_8$ (1.10 eq.), PhMe (0.04 M), r.t., 1 h, sealed tube, then reflux, 72 h	-	no **197** observed
3	$Co_2(CO)_8$ (1.20 eq.), DCM (6 mM), r.t., 15 h, sealed tube	NMO (6.00 eq.)[a)]	no **197** observed
4	$Co_2(CO)_8$ (1.10 eq.), DCM (0.02 M), r.t., 20 h, sealed tube	NMO (3.00 eq.)[b)]	no **197** observed
5	$Co_2(CO)_8$ (1.10 eq.), PhH (0.04 M), r.t., 1 h, sealed tube, then reflux, 17 h	TMANO (3.00 eq.)[c)]	no **197** observed
6	$[RhCl(CO)_2]_2$ (10 mol%), *p*-xylene (5 mM), reflux, 17 h	CO (1 atm)	no **197** observed
7	$[RhCl(CO)_2]_2$ (10 mol%), *p*-xylene (5 mM), reflux, 17 h	CO (5 atm)	no **197** observed

All used solvents were anhydrous and degassed by freeze-pump-thaw (3 cycles) prior to use; a) addition in one portion after 5 h; b) addition after 1.00 h, 1.50 h and 2.00 h in 1 eq. portions; c) addition in one portion prior to heating.

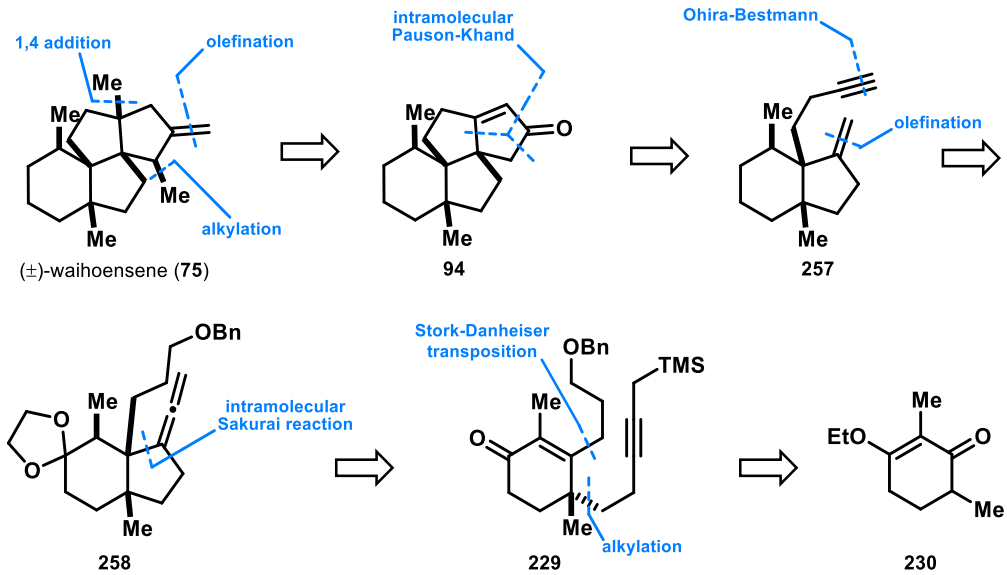
As it proceeds *via* a different mechanistic pathway (as described in chapter 1.4.2), an alternative rhodium(I)-catalyzed procedure was attempted. Interestingly, treatment of **198** with rhodium(I) carbonyl chloride in *p*-xylene at reflux and under an atmosphere of CO (entry 6) did not result in formation of the desired enone product but produced an apolar compound that showed strong UV activity on TLC. Although purification and characterization were difficult to realize due to its instability, it was possible to identify the compound as diene **256** (*Scheme 45*). The mechanistic genesis comprises an unusual skeletal reorganization of the 1,6-enyne, which has been reported in literature for various metal catalysts[93], including $[RhCl(CO)_2]_2$. Trost[94] observed a similar transformation upon treatment of 1,6- and 1,7-enynes with tetrakis(hydroxycarbonyl)palladacyclopentadiene ester and suggested an intermediate cyclobutene.



Scheme 45: Proposed mechanistic pathway for the formation of diene systems from 1,6-enynes by skeletal reorganization.

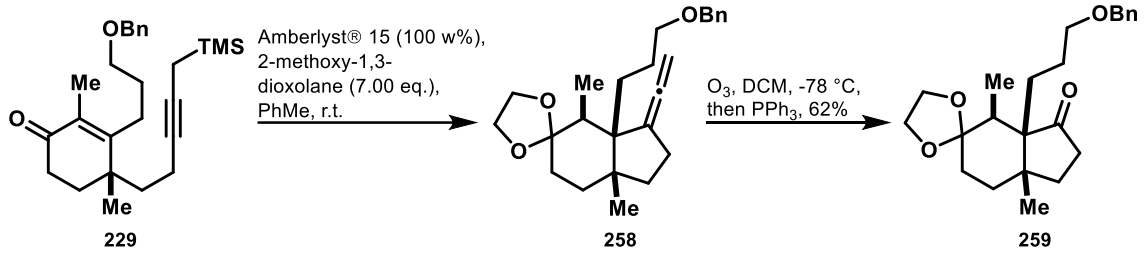
Later, other transition metal catalysts, *e.g.* $[RuCl_2(CO)_3]_2$, $PtCl_2$, $AuCl_3$, $[RhCl(CO)_2]_2$, were found to mediate the same skeletal reorganization[93, 95]. However, the actual mechanism is still not fully elucidated.

Even though elevated CO pressure is known to cause lower reaction rates for the Pauson-Khand reaction by prevention of metal-CO dissociation[46], the reaction was repeated under a slight overpressure of CO (5 atm). With regard to the above-described mechanism, premature reductive elimination of rhodium from the intermediate metallacyclopentene **254** should be avoided by preferential insertion of CO under elevated pressure. Unfortunately, the intended process could not be realized. As the Pauson-Khand reaction is known to be sensitive to steric hindrance from the olefin moiety[66, 96], the methyl substituent might account for the lacking reactivity and, upon reconsidering the retrosynthetic analysis, should be installed on a later stage in the sequence, as shown in *Scheme 46*. This would only require minor changes in the planned synthesis including ozonolysis of the allene moiety in **258** and olefination of the obtained carbonyl to the analogous *exo*-methylene derivative **257**.



Scheme 46: Revised retrosynthesis.

As the substrate **229** for the modified intramolecular Sakurai reaction was already known from the former approach, conversion to the ketalized *cis*-hydrindane system **258** could directly be approached. In contrast to the previous approach, cyclization of the propargylsilane **229** was conducted in the presence of methoxy dioxolane and Amberlyst® 15 as Brønstedt acid catalyst to deliver the corresponding ketal after a non-aqueous work-up (*Scheme 47*).

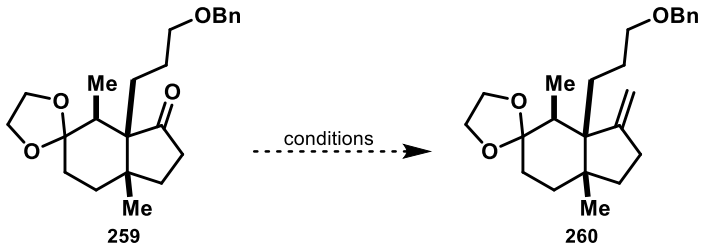


Scheme 47: Alternative intramolecular Sakurai cyclization and subsequent ozonolysis of the allene.

Protection of the carbonyl in **258** was required within this strategy to allow for efficient differentiation in the olefination step. In 1995, Schinzer and co-workers used a similar sequence of cyclization and ozonolysis for the total synthesis of β-pinguisene[97]. However, initial attempts by application of their reported conditions (*i.e.* trace amounts of Amberlyst® 15, 2.00 eq. 2-methoxy-1,3-dioxolane, 0.26 M in PhMe, r.t.) did not afford the desired hydrindane system **258**. No reaction was observed with increased amounts of acid (1.00 eq.) and ketalizing agent (10.0 eq.), and unreacted enone **229** was the only compound isolated from the reaction mixture. A control experiment with catalytic amounts of *p*-toluenesulfonic acid (30 mol%) and an excess of methoxy dioxolane (10.0 eq.) led to full consumption of the starting material within two hours and formation of the desired ketal **258**. However, the reaction was rather unclean and several spots were detected on TLC. To our delight, repetition with a freshly purchased batch of Amberlyst® 15 did indeed lead to formation of the desired product **258**, but in contrast to the reaction of Schinzer, an increased amount of resin equal in weight with the substrate was required to achieve full conversion. The obtained crude material was subjected to ozonolysis without further purification, since the ketal tended to hydrolyze on silica gel even in the presence of triethylamine. The ozonolysis proceeded with varying, but overall satisfactory yields and provided the desired cyclopentanone **259**. Different conditions were applied to realize methylenation of the carbonyl (*Table 10*). Wittig olefination conditions with methyltriphenylphosphonium bromide and different bases at different

temperatures (entries 1, 3 & 4) did not lead to any reaction and resulted in recovery of the starting material. Since steric hindrance was suspected to cause the lack of reactivity, Takai-Lombardo conditions[98] were applied. The titanium-mediated olefination is known to succeed even with sterically encumbered carbonyl substrates. However, no reaction was observed for substrate **259** (entries 2 & 6). In 2004, Yan *et. al.*[99] have developed an efficient methylenation methodology, especially for enolizable or sterically hindered ketones. This olefination is based on a $Mg/TiCl_4$-mediated dichloromethane activation and indeed produced 10% of the desired *exo*-methylene compound **260** after 24 h along with unreacted starting material **259** (entry 5), but a further increase of the yield was not possible. Other direct olefination conditions, like the use of Petasis reagent[100] or Horner-Wadsworth-Emmons reaction[101] with triethyl phosphonoacetate, failed (entries 7 & 8) and so did all the attempted two-step procedures (1,2-addition/ elimination) with different C1 nucleophiles (entries 9-11). As the *exo*-methylene substituted hydrindane system **260** did not seem to be efficiently accessible *via* the intramolecular Sakurai reaction route, the synthetic planning towards (±)-waihoensene (**75**) was revised again and a different strategy for construction of the bicyclic intermediate **257** was chosen.

Table 10: Attempts on the methylenation of ketone **259**.

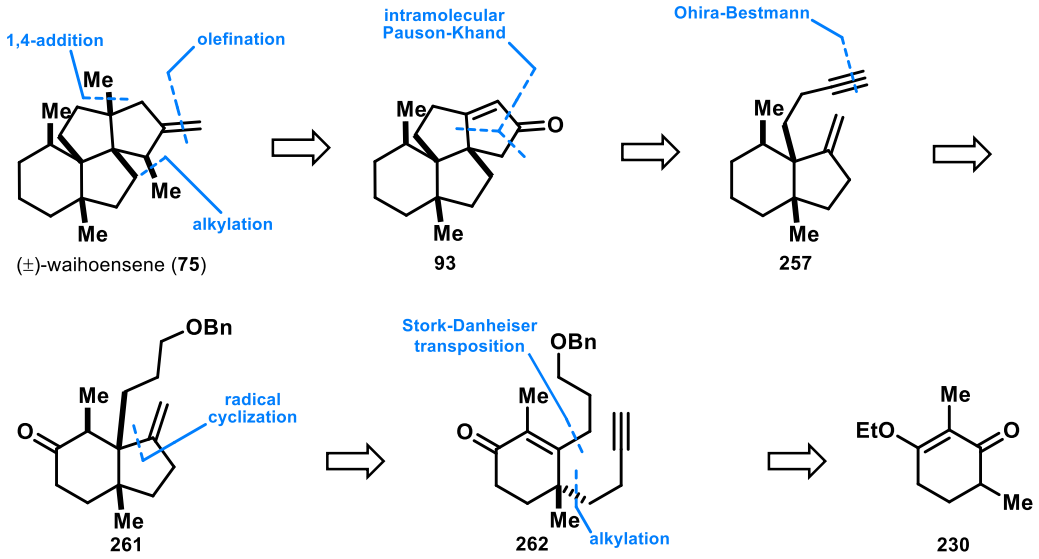


entry	conditions	result
1	NaHMDS (2 M in THF, 1.20 eq.), $MePPh_3Br$ (1.20 eq.), THF (0.15 M), 0 °C to r.t. to reflux	no reaction
2	Zn (13.5 eq.), CH_2I_2 (7.50 eq.), TiCl4 (1 M in DCM, 3.00 eq.), DCM/THF (1:3), r.t.	no reaction
3	$MePPh_3Br$ (2.00 eq.), *t*-BuOK (2.00 eq.), THF (0.1 M), r.t.	no reaction
4	$MePPh_3Br$ (1.30 eq.), *t*-BuOK (1.30 eq.), PhH (0.5 M), reflux	no reaction
5	Mg (10.0 eq.), $TiCl_4$ (1 M in DCM, 5.00 eq.), DCM/THF (3:1), 0 °C to 40 °C	10% **260**, recovered **259**
6	Zn (9.00 eq.), CH_2I_2 (3.00 eq.), $AlMe_3$ (2 M in PhMe, 0.60 eq.), THF (0.2 M), r.t.	no reaction
7	Petasis reagent (1 M in PhMe, 3.00 eq.),PhMe, 65 °C	no reaction
8	triethyl phosphonoacetate (5.00 eq.), NaH (60%, 5.00 eq.), THF (0.5 M), 0 °C to 50 °C	no reaction
9	1.) $TMSCH_2MgCl$ (1.1 M inTHF, 4.50 eq.), Et_2O (0.1 M), 0 °C to 35 °C 2.) Peterson olefination	no reaction in **1.)**
10	1.) MeLi (1.6 M in Et_2O, 1.50 eq. + 2.00 eq.), Et_2O (0.25 M), 0 °C to r.t. 2.) elimination	no reaction in **1.)**
11	1.) MeMgBr (1 M in THF, 10.0 eq.), THF (0.1 M), -65 °C to r.t. 2.) elimination	no reaction in **1.)**

2.3 Approach C: The Total Synthesis of Waihoensene

2.3.1 Retrosynthetic Analysis

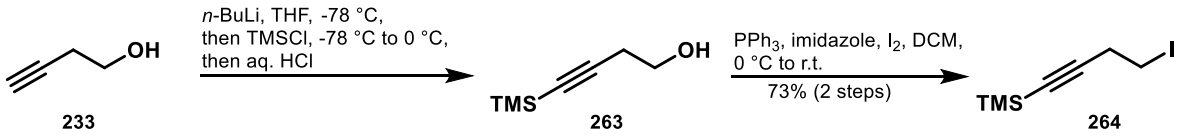
In analogy to the previous approach, the target molecule waihoensene (**75**) was planned to arise from the product **93** of an intramolecular Pauson-Khand reaction *via* a three-step endgame consisting of carbonyl olefination, copper-mediated conjugate addition and methylation in α-position (*Scheme 48*). The precursor **257** for the mentioned [2+2+1]-cycloaddition should feature an *exo*-methylene functionality, which might be generated from enone **262** in an intramolecular radical cyclization reaction with the terminal alkyne substituent. Sequential alkylation reaction and Stork-Danheiser transposition would give straightforward access to the appropriately substituted enone **262** from commercially available vinylogous ester **230**.



Scheme 48: Retrosynthetic analysis of approach C for the total synthesis of (±)-waihoensene (**75**).

2.3.2 Synthesis of the *cis*-Hydrindane by Intramolecular Radical Cyclization

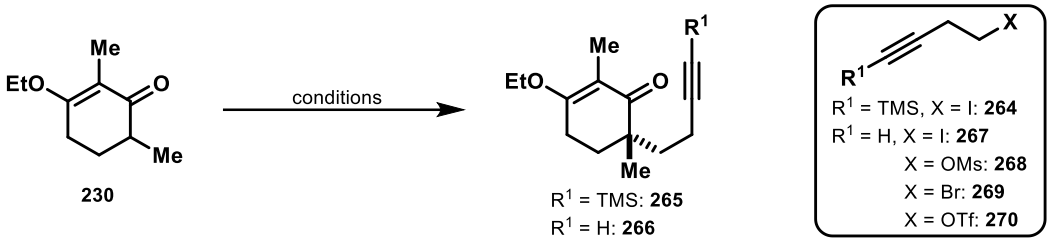
Trimethylsilyl-protected alkyne **264** was obtained in decagram scale according to a literature-known procedure[102] in two steps from commercially available 3-butyn-1-ol (**233**) (*Scheme 49*) and was used in the initial approach for the alkylation of vinylogous ester **230** (see *Table 11*).



Scheme 49: Synthetic access to alkylating agent **264**.

The same optimized conditions as previously for the alkylation with propargylsilane **235** (chapter 2.2.2) were applied. However, the best result for the alkylation with 2.00 equivalents of alkylating agent **264** was an isolated yield of 20% of the desired product **265** (*Table 11*, entry 1).

Table 11: Optimization of the alkylation of vinylogous ester **230**.



entry	conditions	alkylating agent	result
1	LiTMP (1.30 eq.), THF (1 M), DMPU (1.60 eq.),-78 °C to r.t.	**264** (2.00 eq.)	20% **265**, recovered **230**
2	LiTMP (1.30 eq.), THF (1 M), DMPU (1.60 eq.),-78 °C to r.t.	**264** (5.00 eq.)	30% **265**, recovered **230**
3	LiTMP (1.30 eq.), THF (1 M), DMPU (3.20 eq.),-78 °C to r.t.	**264** (5.00 eq.)	26% **265**, recovered **230**
4	LiTMP (1.30 eq.), THF (1 M), DMPU (1.60 eq.),-78 °C to r.t.	**267** (2.00 eq.)	56% **266**, recovered **230**
5	LDA (1.30 eq.), THF (1 M), DMPU (1.60 eq.),-78 °C to r.t.	**267** (2.00 eq.)	39% **266**, recovered **230**
6	LiTMP (1.30 eq.), THF (1 M), DMPU (1.60 eq.),-78 °C to r.t.	**268** (2.00 eq.)	15% **271**; traces of **266**, recovered **230**
7	LiTMP (1.30 eq.), THF (1 M), DMPU (1.60 eq.),-78 °C to r.t.	**269** (2.00 eq.)	formation of **271** + **266**, recovered **230**
8	LiTMP (1.30 eq.), THF (1 M), DMPU (1.60 eq.),-78 °C to r.t.[a)]	**270** (2.00 eq.)	74% **266**, formation of **272**
9	LiTMP (1.30 eq.), THF (1 M), DMPU (1.60 eq.),-78 °C to r.t.[b)]	**270** (2.00 eq.)	80% **266**

a) 3.48 mmol scale; b) 19.9 mmol scale.

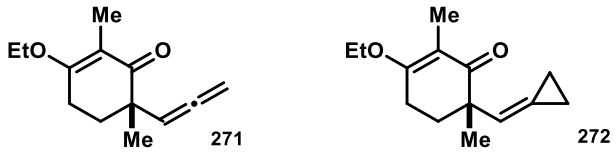
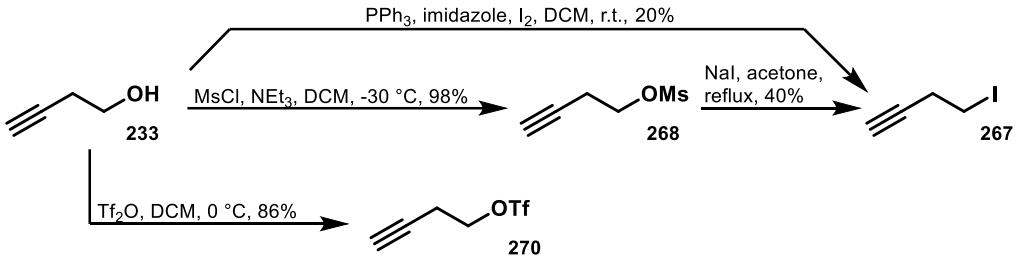


Figure 15: Observed side-products in the alkylation reaction of vinylogous ester **230**.

Increasing amounts of either iodide **264** (entry 2) or **264** and DMPU as polar additive (entry 3) entailed only slightly improved yields and in both cases unreacted starting material **230** was recovered. Since steric hindrance might have a negative impact on the generation of the quaternary carbon center during this reaction, other alkynes lacking the bulky TMS group were synthesized (compounds **267**, **268**, **270** in *Scheme 50*) or purchased (compound **269**) and tested as alternative alkylating agents (*Table 11*, entries 4-8).

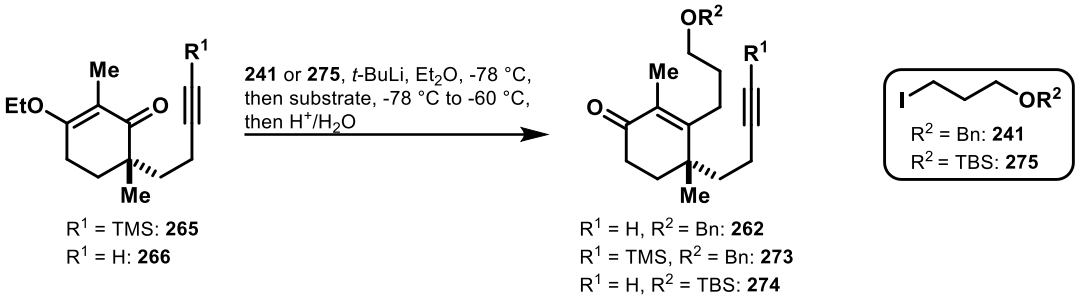


Scheme 50: Synthetic access to alkylating agents **267**, **268** and **270**.

Indeed, an improved yield of 56% was observed for the reaction with homopropargylic iodide **267** under otherwise identical conditions (entry 4). The use of lithium diisopropylamide instead of lithium tetramethylpiperidide as base did not prove to be advantageous with regard to the enolate formation and reactivity as the yield decreased (entry 5). However, an alternative for iodide **267** was desirable, since its preparation and handling caused problems: Both the direct synthesis from 3-butyn-1-ol (**233**) *via* Appel reaction and an alternative production using a Finkelstein reaction of the corresponding mesylate **268** (*Scheme 50*) provided the highly volatile and foul-smelling compound only in poor yields (20 to 40%). The use of mesylate **268** as alkylating agent resulted in the formation of allene **271** (*Figure 15*) as the major isolated product. Only trace amounts of the desired compound **266** were observed and the major part of the material was recovered as unreacted starting material **230** (entry 6). A similar result was obtained for the corresponding commercially available bromide **269** (entry 7). Eventually, a good yield of 74% **266** was obtained by using triflate **270** as the alkylating agent (entry 8) and an increased scale allowed for yields up to 80% (entry 9). Under these conditions, minor amounts of unexpected cyclopropylidene-substituted **272** were obtained as side-product. Nevertheless, with alkylation products **265** and **266** in hands, Stork-Danheiser transposition was approached. In analogy to the previous approach in

chapter 2.2.2, first attempts on this transformation were carried out with the TMS-protected substrate **265** using 2.00 eq. of lithium nucleophile (*Table 12*, entries 1-3).

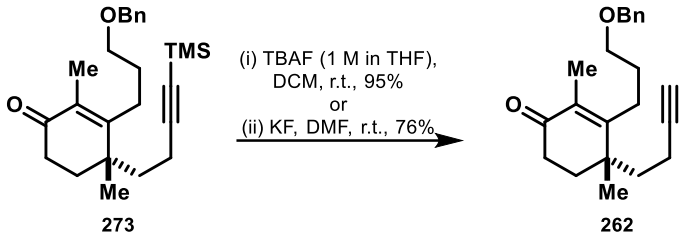
Table 12: Optimization of the Stork-Danheiser transposition for the synthesis of enones **262**/**273**/**274**.



entry	enone	iodide (eq.)	work-up	result
1	**265**	**241** (2.00)	NH_4Cl	86% **273**[a)]
2	**265**	**241** (2.00)	NH_4Cl	71% **273**[b)]
3	**265**	**241** (2.00)	NH_4Cl	61% **273**[c)]
4	**266**	**241** (3.00)	NH_4Cl	60% **262**
5	**266**	**275** (3.00)	NH_4Cl	13% **274**
6	**266**	**275** (3.00)	1 M HCl	32% **274**
7	**266**	**275** (3.00)	NH_4Cl	41% **274**[d)]
8	**266**	**275** (3.00)[e)]	NH_4Cl	decomposition
9	**266**	**241** (3.00)	2 M HCl	89% **262**

a) 1.93 mmol scale; b) 3.19 mmol scale; c) 8.78 mmol scale; d) warmed to -20 °C; e) solvents degassed, cooling bath removed for 30 min after addition of *t*-BuLi, then re-cooled to -78 °C.

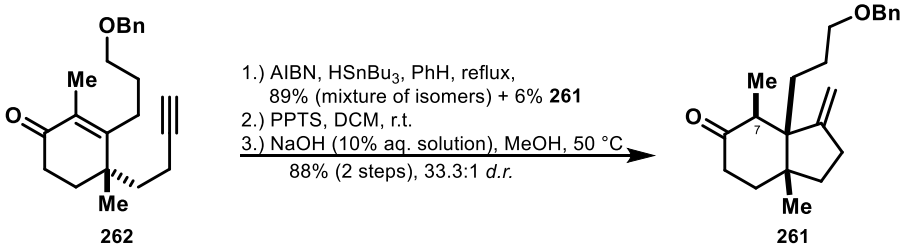
Good results were obtained, but increased reaction scales resulted in diminished yields (as indicated by entries 2 and 3), which might be rationalized by temperature sensitivity of the reaction during the nucleophilic addition step. Silyl-deprotection of **273** by use of potassium fluoride or tetrabutylammonium fluoride provided the substrate for the intramolecular radical cyclization (*Scheme 51*). Besides, the addition/elimination reaction was attempted with the alternative substrate **266** (*Table 12*, entries 4-9). As discussed earlier, this compound was readily accessible from **230** and in addition, would allow for a reduced overall step count, as the addition/elimination reaction would directly yield cyclization substrate **262**.



Scheme 51: Silyl deprotection of alkyne **273**.

The presence of the acidic terminal alkyne C-H required an increased amount of the organolithium reagent and 60% of the desired enone **262** could be isolated after aqueous work-up with a saturated ammonium chloride solution (entry 4). A TBS-protected alcohol functionality was expected to be advantageous with regard to a facile deprotection later in the synthesis, but the alternative use of silylated **275** proved unsatisfactory (entries 5-7). Taking account of similar experiences of Miller *et. al.*[103] during an analogous addition reaction of lithiated **275**, minor modifications of the experimental procedure during the lithium halogen exchange reaction were made (entry 8) but did not lead to the desired improvement. Moreover, an increasing degree of decomposition of the organolithium species was noticed and the desired enone **274** was not produced. Finally, the reaction with the benzylated derivative **241** and an aqueous workup with 2 M hydrochloric acid enabled a drastically improved yield (entry 9) and provided gram quantities of cyclization substrate **262**.

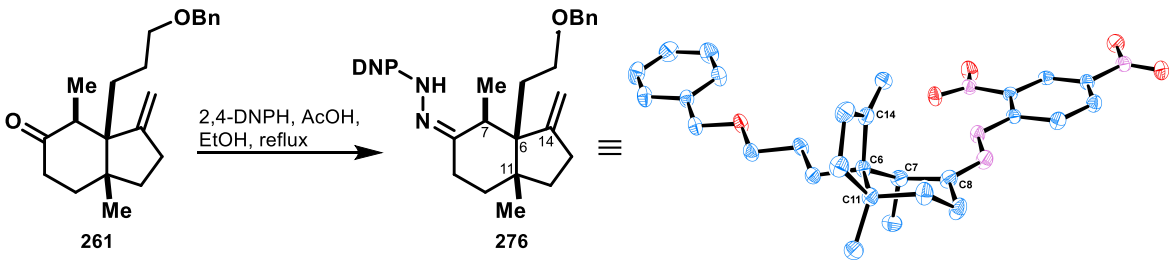
Inspired by a publication of Rajagopalan *et. al.*[104], synthesis of the *cis*-hydrindane core was approached by tin-mediated radical cyclization (*Scheme 52*). Initial attempts revealed the necessity of an excess of tributyltin hydride, *i.e.* 4.00 eq. at minimum, and addition of the latter and the radical initiator AIBN at regular intervals during the reaction in order to accomplish full conversion. In contrast to the work of Rajagopalan, protiodestannylation of the crude vinylstannane did not give satisfying results, which is caused by the excess of stannane from the preceding step.



Scheme 52: Optimized sequence of tin-mediated radical cyclization, protiodestannylation and epimerization.

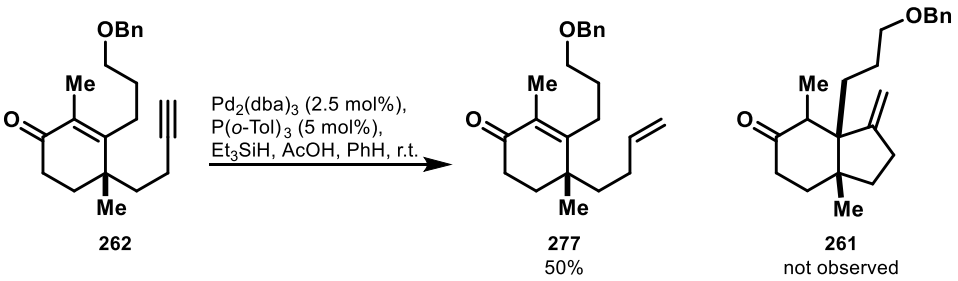
Thus, the intermediate vinylstannane was separated from other organotin residues by flash column purification prior to the treatment with pyridinium *p*-toluenesulfonate. Minor amounts of compound **261** were obtained after column chromatography due to partial destannylation on silica gel. The destannylated material was further subjected to base-mediated epimerization of the C7 stereocenter to give the desired bicyclic product in very good yield and a diastereomeric ratio of 33.3 to 1 in favor of the thermodynamically preferred all-*cis* configuration, as outlined in *Scheme 52*.

Conversion of the carbonyl into the 2,4-dinitrophenyl hydrazone (**276**)[105] (*Scheme 53*) and recrystallization from ethanol provided single crystals that were suitable for X-ray structure analysis and allowed for confirmation of the correct configuration at C7 and *cis*-fusion of the bicyclic system.



Scheme 53: Conversion of ketone **261** into the corresponding DNP hydrazone **276** and ORTEP of **276** with ellipsoid drawn at the 50% level and hydrogens omitted for clarity; only one stereoisomer shown.

Interestingly, an alternative direct approach by Trost[106] *via* palladium(0)-mediated reductive cyclization, which has previously been used with a similar system by Ding and co-workers[107], did not provide the hydrindane system **261**. Instead, terminal olefin **277** was obtained as the only product (*Scheme 54*).

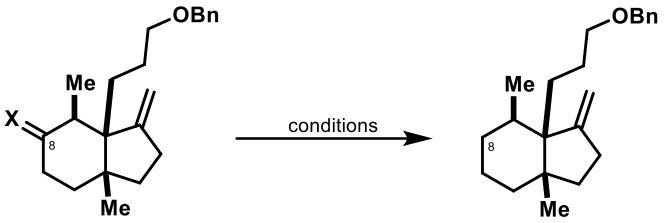


Scheme 54: Attempted palladium(0)-mediated reductive cyclization of enone **262**.

2.3.3 Synthesis of the Pauson-Khand Precursor

Based on the previous approach (see chapter 2.2.3), several methodologies were tested for the subsequent deoxygenation in C8 position of carbonyl compound **261** (*Table 13*) aiming to find the most efficient conditions for this substrate. Direct Wolff-Kishner reduction proved to be too harsh and provided the desired product in only 6% yield and in a mixture with traces of starting compound **261** and decomposed material (entry 1). Quantitative reduction of the ketone to the corresponding secondary alcohol **279** was realized by treatment with equimolar amounts of sodium borohydride in methanol. Application of conditions for an indium-mediated chemoselective reduction of secondary and tertiary alcohols[108] (entry 2) led to decomposition of the entire material, whereas conversion of **279** to the corresponding imidazole carbothioate by reaction with 1,1'-thiocarbonyldiimidazole and subsequent Barton-McCombie deoxygenation delivered 28% of the desired product (entry 3).

Table 13: Screening of conditions for the deoxygenation.



X = O: **261**
NNHTs: **278**
OH, H: **279**

280

entry	substrate	conditions	result
1	**261**	$N_2H_4 \cdot H_2O$ (65%, 3.00 eq.), KOH (4.50 eq.), triethylene glycol, 180 °C	6% **280** + traces of **261**, decomposition
2	**279**	$InCl_3$ (5 mol%), Ph_2SiClH (2.00 eq.), $(CH_2Cl)_2$, 80 °C	decomposition
3	**279**	1.) TCDI (2.00 eq.), THF, reflux, 93% 2.) AIBN (15 mol%), $HSnBu_3$ (3.50 eq.), PhH, reflux	28% **280**, 15% **281**, 54% **282**
4	**279**	1.) KHMDS (0.5 M in PhMe, 2.50 eq.), CS_2 (15.0 eq.), THF, -78 °C, then MeI (16.0 eq.), -78 °C to r.t., 80% 2.) AIBN (20 mol%), $HSnBu_3$ (2.00 eq.), PhH, reflux	51% **280**, formation of **281**

entry	substrate	conditions	result
5	**279**	1.) KHMDS (0.5 M in PhMe, 2.50 eq.), CS_2 (15.0 eq.), THF, -78 °C, then MeI (16.0 eq.), -78 °C to r.t., 80% 2.) AIBN (20 mol%), TTMSS (2.00 eq.), PhH, reflux	Complex mixture, no **280** observed
6	**278**	catechol borane (1 M in THF, 1.05 eq.), $CHCl_3$, -10 °C to r.t., 3 h, then $NaOAc{\cdot}3H_2O$ (2.50 eq.), reflux[a)]	50% **280**, 20% **278**
7	**278**	catechol borane (1 M in THF, 1.50 eq.), $CHCl_3$, -10 °C to r.t., 18 h, then $NaOAc{\cdot}3H_2O$ (2.90 eq.), reflux	50% **280**, 11% **278**
8	**278**	$NaBH_3CN$ (4.00 eq.), *p*-$TsOH{\cdot}H_2O$ (0.30 eq.), DMF/sulfolane (1:1), 110 °C	30% **280**, 22% **278**
9	**278**	D*i*BAL-H (3.50 eq.), DCM, 0 °C to r.t.	9% **280**, 33% **283**
10	**278**	catechol borane (1 M in THF, 1.50 eq.), $CHCl_3$, -10 °C to r.t., 17 h, then NaOH (10% aq., 2.90 eq.), reflux	45% **280**, no recovered **278**
11	**278**	$NaBH_3CN$ (1.40 eq.), $ZnCl_2$ (0.70 eq.), MeOH, 65 °C	31% **280**
12	**278**	catechol (2.00 eq.), $BH_3{\cdot}THF$ (1 M in THF, 2.00 eq.), THF, 0 °C to r.t., then **278**, $CHCl_3$, -10 °C to r.t., then $NaOAc{\cdot}3H_2O$ (3.50 eq.), reflux	traces of **280**
13	**278**	benzoic acid (4.00 eq.), $BH_3{\cdot}THF$ (2.00 eq.), $CHCl_3$, 0 °C, then **278**, $CHCl_3$, 0 °C, then $NaOAc{\cdot}3H_2O$ (2.70 eq.), reflux[b)]	65% **280**, 20% **278**
14	**278**	benzoic acid (4.00 eq.), $BH_3{\cdot}THF$ (2.00 eq.), $CHCl_3$, 0 °C, then **278**, $CHCl_3$, 0 °C, then $NaOAc{\cdot}3H_2O$ (4.80 eq.), reflux[c)]	44% **280**
15	**278**	catechol borane (1 M in THF, 2.00 eq.), $CHCl_3$, -10 °C to r.t., 3 h, then $NaOAc{\cdot}3H_2O$ (3.50 eq.), reflux[d)]	59% **280**

a) 0.40 mmol scale; b) 0.20 mmol scale; c) 1.01 mmol scale; d) 2.69 mmol scale. TCDI: 1,1'-thiocarbonyldiimidazole; TTMSS: tris(trimethylsilyl)silane.

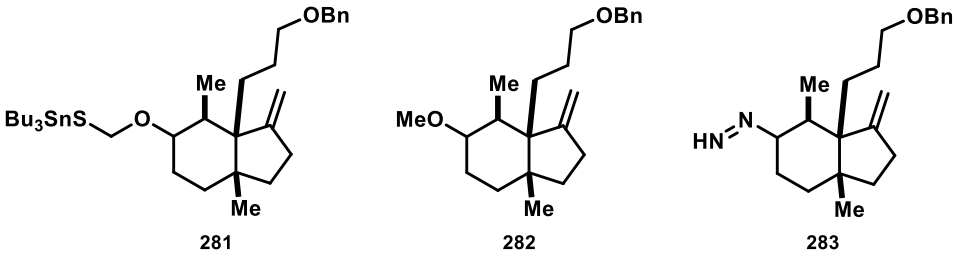
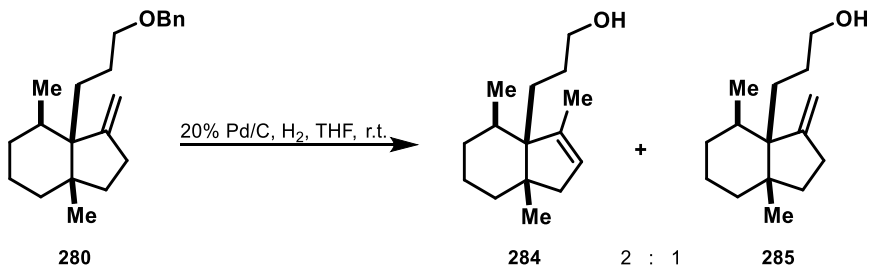


Figure 16: Observed side-products in the deoxygenation reaction.

Interestingly, two other compounds could be isolated from the reaction in entry 3, which were identified to be tributyl((alkoxymethyl)thio)stannane **281** and methoxy analogue **282** (*Figure 16*). Alternative radical deoxygenation of the xanthate provided 51% of the desired compound **280** (entry 4), however, formation of **281** was also observed under these conditions. Since formation of the above-mentioned side-products indicates favored reduction of the intermediate adduct radical over the desired fragmentation, an alternative efficient radical reducing agent, tris(trimethylsilyl)silane (TTMSS), was tested. In comparison to tributyltin hydride, TTMSS has a smaller rate constant for hydrogen abstraction by primary radicals[109], which might be advantageous with regard to the mentioned competing processes during Barton-McCombie deoxygenation. However, the intended improvement was not observed and instead, a complex mixture was obtained, in which the desired deoxygenated product **280** could not be identified (entry 5). Since a hydrazone-based method gave good results in the previous approach, the corresponding tosylhydrazone **278** was synthesized from ketone **261** by treatment with *p*-toluenesulfonyl hydrazide in ethanol. Fortunately, the yield of the hydrazone formation with substrate **261** could be increased to 94% by raising the reaction concentration to 4 M. In contrast to the deoxygenation in the previous approach (see chapter 2.2.3), no reactivity problems due to *E*/*Z*-isomerism of the hydrazone were observed with this substrate. An initial attempt for the defunctionalization of **278** with commercial catechol borane and sodium acetate hydrate yielded the desired compound **280** in 50% along with 20% unreacted starting material **278** (entry 6). A slightly increased amount of reducing agent in combination with a prolonged reduction time (entry 7) did not increase the yield of the desired product but led to a reduced amount of recovered starting material. Alternative mild reduction conditions with sodium cyanoborohydride in the presence of catalytic *p*-toluenesulfonic acid produced **280** in 30% (entry 8) and a similar result was obtained by use of the same reducing agent in combination with zinc(II) chloride[110] as the catalyst (entry 11).

Diisobutylaluminum hydride was also found to reduce hydrazone **278** to the corresponding hydrocarbon compound **280** to a small extent, but unexpected diazene **283** (*Figure 16*) was isolated as the major product from this reaction (entry 9). Since the reduction was performed at room temperature, the activation barrier for the nitrogen elimination process was probably not overcome and the intermediate diazene compound seemed stable enough to be isolated in small amounts. In consequence, further investigations on the reduction with catechol borane were conducted. Substitution of the sodium acetate base, which is required to induce the nitrogen elimination process, by sodium hydroxide (entry 10) gave similar results with regard to the product formation, but no starting material could be re-isolated. Reduction by *in situ* generated reducing borane from catechol and the borane-THF complex did not succeed (entry 11), whereas the reaction of freshly prepared bis(benzyloxy)borane seemed quite promising and delivered the desired product in 65% along with 20% of recovered starting material (entry 12). Unfortunately, the yield dropped significantly on lager scales (entry 13) for which reason the method of choice remained the reduction with commercial catechol borane (entry 14). The use of a slightly increased amount of borane (2.00 eq.) and sodium acetate (3.50 eq.) allowed for a satisfactory yield of about 60%, even on multigram scale.

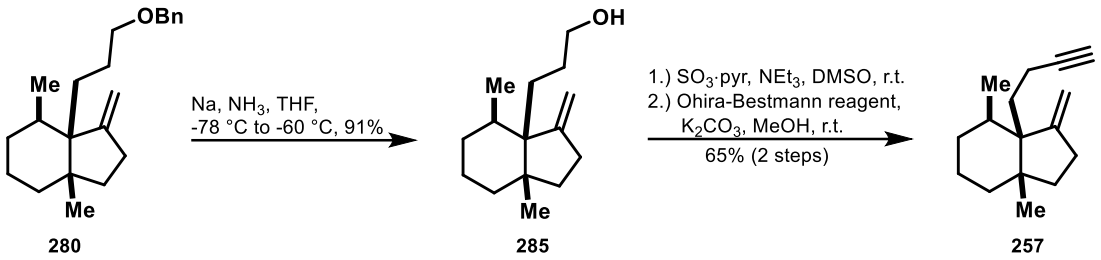
In contrast to the substrate in chapter 2.2.3, the ensuing benzyl deprotection of alcohol **280** was not as straightforward as expected and required further optimization. Application of hydrogenation conditions resulted in the formation of a polar spot on TLC. Upon further characterization, this turned out to be an inseparable 2:1 mixture of undesired, isomerized **284** and the desired alcohol **285** (*Scheme 55*) in favor of the undesired compound. This observation seemed reasonable with regard to the higher stability of *endo*-cyclic double bonds in simple hydrocarbon structures[111].



Scheme 55: Undesired isomerization to the *endo*-double bond upon hydrogenation of **280**.

Further attempts with Lewis acid led to decomposition (BCl_3, DCM, -78 °C) or clean isomerization to the *endo*-double bond without benzyl deprotection (BBr_3, DCM, 0 °C).

Finally, Birch conditions with sodium in liquid ammonia succeeded and selective cleavage of the *O*-benzyl bond and prevention of the unwanted double bond isomerization were observed. Minor optimization of the reaction temperature program and the amount of sodium metal were required to achieve full conversion and excellent yields (*Scheme 56*).



Scheme 56: Optimized sequence for the preparation of Pauson-Khand precursor enyne **257**.

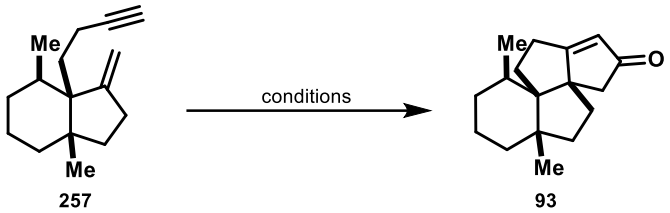
With regard to the previously observed acid-mediated Prins side-reaction in the course of the oxidation reaction (chapter 2.2.3), non-acidic conditions were aimed for the transformation of **285** to the aldehyde. Unexpectedly, formerly successful Ley oxidation provided the desired intermediate aldehyde only in trace amounts and in a complex mixture with other unidentified side-products. Alternative Parikh-Doering conditions, on the other hand, succeeded. However, some problems were experienced concerning reproducibility in terms of yield. Considering its proneness to undergo further intramolecular cyclization, the crude aldehyde was immediately used in the next reaction without further purification to prohibit any acid-induced loss of material during column chromatography. Ensuing treatment with Ohira-Bestmann reagent under basic conditions provided the enyne precursor **257** for the planned intramolecular Pauson-Khand reaction in a good yield of 65% over two steps.

2.3.4 The Intramolecular Pauson-Khand Reaction as Key Step

A first experiment on the key step of the synthetic sequence was carried out in anhydrous and degassed toluene with high dilution and a slight excess of dicobalt octacarbonyl (*Table* 14, entry 1). Formation of the intermediate cobalt-alkyne complex was indicated by appearance of an apolar, dark red spot on TLC and consumption of the starting material at room temperature. This cobalt complex was not isolated, but further converted by heating the reaction solution to 110 °C in a sealed tube. In contrast to the futile efforts with the ethylidene substrate (chapter 2.2.3), this intermediate indeed underwent the desired

cyclization and CO-insertion and delivered the tetracyclic core of waihoensene (**75**) in satisfactory 41%.

Table 14: Optimization of the intramolecular Pauson-Khand reaction of **257**.



257 93

entry	conditions	result
1	$Co_2(CO)_8$ (1.10 eq.), PhMe (0.035 M), r.t., 1 h, then 110 °C (sealed tube), 20 h	41% **93**
2	$Co_2(CO)_8$ (1.10 eq.), PhH (0.035 M), r.t., 1 h, then TMAO (3.00 eq.), 80 °C (sealed tube), 22 h	40% **93**
3	$Co_2(CO)_8$ (1.10 eq.), xylenes (0.035 M), r.t., 1 h, then 140 °C (sealed tube), 20-72 h	43-46% **93**
4	$Co_2(CO)_8$ (1.10 eq.), xylenes (0.035 M), r.t., 1 h, then 170 °C (sealed tube), 24 h	38% **93**

Minor modifications of the experimental procedure by addition of trimethylamine *N*-oxide as a promoter and a decreased reaction temperature (entry 2) did not significantly change the result. A slightly higher reaction temperature using xylenes as the reaction medium (entry 3) provided the desired product **93** in yields up to 46%, whereas a further increase of temperature (entry 4) resulted in diminished yields. Thermal decomposition processes presumably account for this trend. Single crystals of **93** suitable for X-ray structure analysis were obtained by spontaneous crystallization and enabled confirmation of the correct configuration (*Figure 17*).

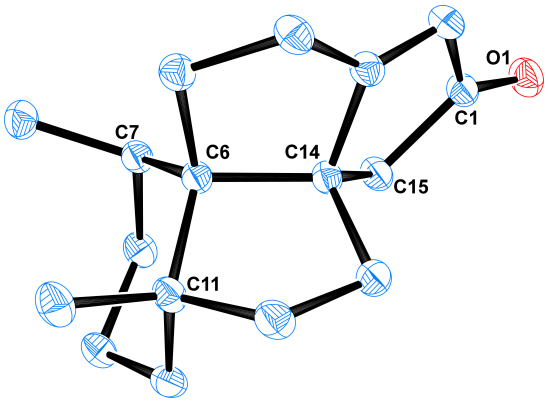
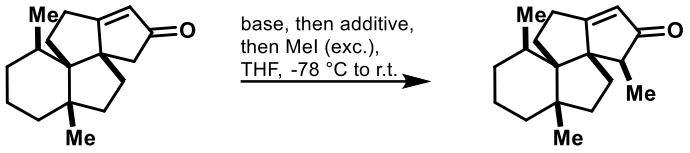


Figure 17: ORTEP of **93** with ellipsoid drawn at 50% level and hydrogen atoms omitted for clarity. Only one stereoisomer shown.

2.3.5 Completion of the Total Synthesis

With advanced intermediate **93** in hands, the endgame of the total synthesis was addressed. This endgame deviates from all previously reported syntheses[35-36, 39], which share a sequence consisting of sequential 1,4-addition to the enone, subsequent alkylation in α-position and final olefination of the carbonyl group. By contrast to these approaches, the herein reported synthesis generates the α-alkylated compound **197** by deprotonation with freshly prepared lithium diisopropylamide and treatment with methyl iodide in the presence of *N,N'*-dimethylpropyleneurea (*Table 15*).

Table 15: Screening of conditions for the α-methylation of **93**.

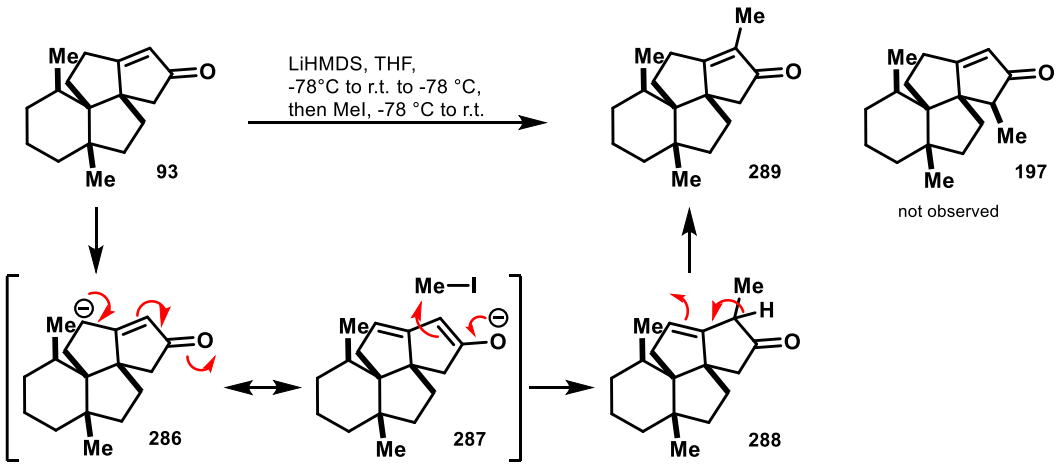


93 **197**

entry	base	additive	scale [mmol]	result
1	LDA	DMPU	0.21	34% **197** (68% brsm), 50% **93**
2	LDA[a)]	DMPU	0.10	49% **197** (73% brsm), 32% **93**
3	LDA	DMPU	0.82	29% **197**, 51% **93**
4	LiHMDS[b)]	-	0.08	**290** as only product (34%) + recovered **93**
5	LiTMP	DMPU	0.08	63% **197** (96% brsm), 36% **93**
6	LiTMP	DMPU	0.25	46% **197** (75% brsm), 34% **93**
7	LiTMP[a),c)]	DMPU	0.21	45% **197** (64% brsm), 29% **93**
8	LDA[a),d)]	HMPA[e)]	0.08	complex mixture of **93**, **289** and unidentified compound, formation of **197** not observed
9	LDA[a)]	HMPA	0.08	no reaction
10	LiICA[a)]	DMPU	0.08	61% **197** (94% brsm), 35% **93**
11	LiTMP[a)]	DMPU	0.12	62% **197**, 8% **93**

1.30 eq. of base were used (unless otherwise noted); in all cases: after addition of the starting material to the base at -78 °C, the reaction was allowed to warm to room temperature for an appropriate period to ensure complete deprotonation and was re-cooled before addition of the additive/methyl iodide; a) prepared on 10-fold scale for practical reasons, appropriate aliquot used for reaction; b) 5.00 eq.; c) 2.60 eq.; d) 1.10 eq., e) addition to base prior to addition of starting material.

However, the yield of this transformation was rather poor (entry 1) and the result turned out to depend not only on the choice of base and additive but also on the reaction scale. The yield noticeably increased when repeating the reaction on half the scale under otherwise identical conditions (entry 2), but further decreased on a larger scale (entry 3). Fortuitously, unreacted starting material **93** could be recovered in all cases and was re-subjected to the methylation conditions. Interestingly, the use of lithium bis(trimethylsilyl)amide for the deprotonation of **93** provided the unexpected compound **289** (*Scheme 57*), which was isolated in 34% as the only product alongside a minor amount of unreacted starting enone **93** (entry 4). Formation of this alternative product was rationalized by the competing formation of kinetic and thermodynamic enolates. In case of the weaker base lithium bis(trimethylsilyl)amide, deprotonation in *γ*-position of the enone was preferred over kinetic deprotonation in α-position, as outlined in *Scheme 57*.



Scheme 57: Proposed mechanism for the formation of **289** by methylation of the thermodynamic enolate of **93**.

A similar but rather unselective result was observed for the combination of lithium diisopropylamide and hexamethylphosphoramide when base and additive were mixed prior to the addition of the enone compound (entry 8). Unlike the aforementioned reaction, a mixture of enone **289**, unreacted starting material and an additional unidentified compound was obtained. Reverse order of addition (enone to base, then addition of hexamethylphosphoramide) led to no reaction at all (entry 9). The desired product **197** was observed in neither case and interestingly, compound **289** was never observed with any of the other base/additive combinations shown in *Table 15*. The alkylation reaction with lithium tetramethylpiperidide as the base in combination with

N,N'-dimethylpropyleneurea showed a similar trend as the reaction with lithium diisopropylamide did: Satisfactory results were obtained on small scale (entries 5 and 11), but a decreasing yield was observed upon scale-up (entry 6). The use of an excess of base (entry 7) did not change this tendency. Comparable results were obtained for lithium isopropylcyclohexylamide (entry 10). Aiming for the completion of the total synthesis, no further optimization of this reaction was essayed and sufficient amounts of enone **197** were produced from multiple reactions on 0.08 mmol scale. Recrystallization from hexanes provided single crystals of compound **197**, which allowed unambiguous confirmation of the correct stereochemistry of the new stereocenter by X-ray structure analysis (*Figure 18*).

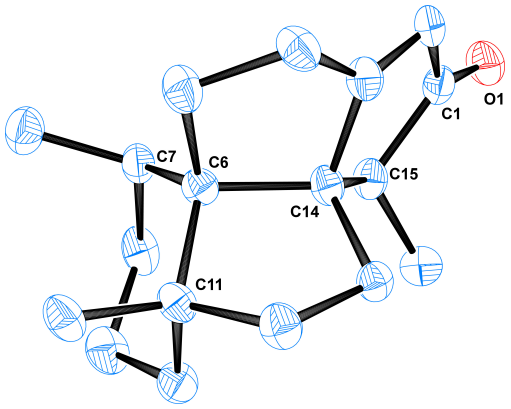
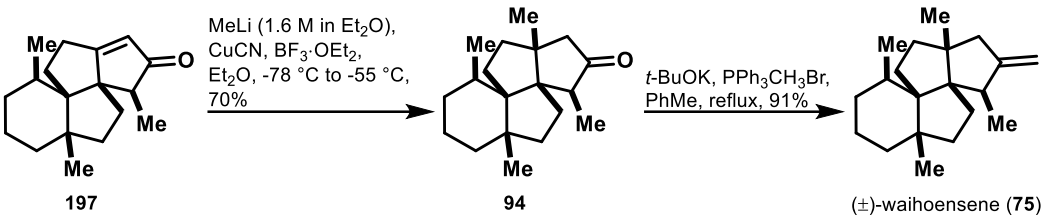


Figure 18: ORTEP of **197** with ellipsoid drawn at 50% level and hydrogens omitted for clarity. Only one stereoisomer shown.

An initial experiment on the subsequent copper(I)-mediated 1,4-addition using a slight excess of methyllithium (2.50 eq.) and copper(I) cyanide (2.75 eq.), to which a pre-cooled ether solution of the enone **197** and boron trifluoride etherate was added at -78 °C, generated the desired ketone **94** in 50% yield. Minor optimization included the use of an increased amount of cuprate (5.00 eq.), a reversed order of addition, *i.e.* dropwise addition of methyl cuprate to the enone/$BF_3{\cdot}OEt_2$ solution, and an increased reaction temperature (-55 °C). These modifications enabled an improved yield of 71% for the desired conjugate addition reaction (*Scheme 58)*. Considering the steric congestion of ketone **94** that caused Lee's issues with the final transformation to the hydrocarbon natural product **75**, olefination was attempted by the application of Takai-Lombardo conditions. In general, the low basicity of this system is suitable for enolizable substrates with α-chirality and, moreover, it was previously used in our group for successful methylenlation of sterically encumbered substrates (see chapter 1.3.3). In case of substrate **94**, the pre-formed CH_2I_2-Zn-$TiCl_4$ system showed moderate efficiency and the desired

hydrocarbon **75** was isolated from the reaction mixture only in trace amounts. By contrast, excellent yields were obtained by Wittig olefination with potassium *tert*-butoxide (*Scheme* 58). The combination of methyltriphenylphosphonium bromide and potassium base is known to be highly reactive, even with sterically hindered ketones[112].



Scheme 58: Optimized sequence for the synthesis of (±)-waihoensene (**75**) by 1,4-addition and Wittig olefination.

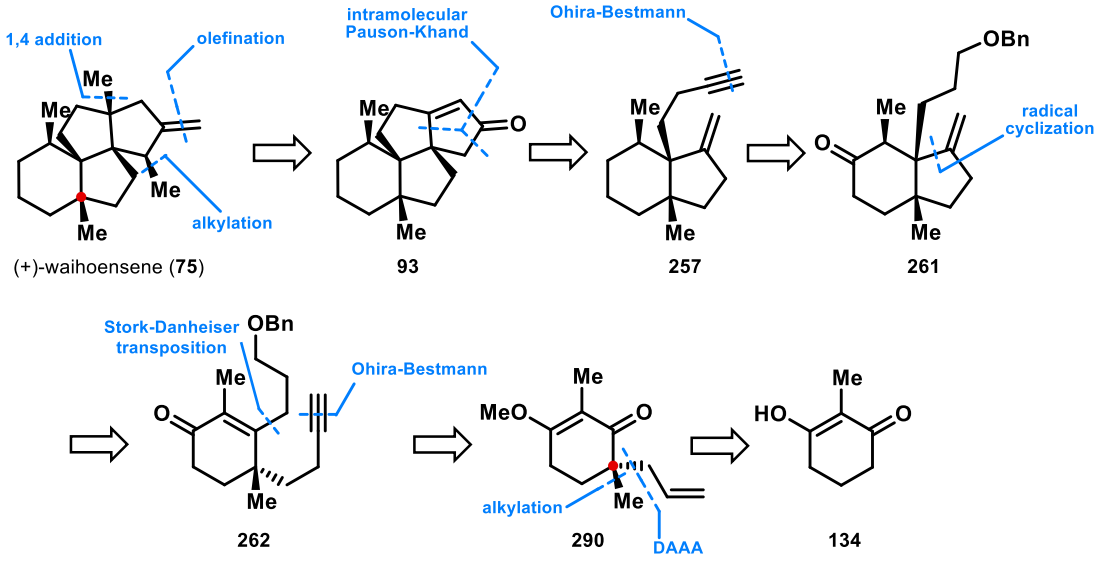
Despite the strongly basic conditions, the configuration at the α-stereocenter was preserved demonstrating its thermodynamic favorability. Several milligrams of the desired natural product waihoensene (**75**) in racemic form were obtained by a 14-step linear sequence with an overall yield of 3.7%. The obtained NMR spectroscopic data and high resolution mass matched the data of the isolated material (see experimental section). Furthermore, this approach represents the so far shortest route to (±)-waihoensene (**75**) and the major part of the above results were published in *Angewandte Chemie International Edition* **2021**, *60*, 2939-2942.

2.4 The Asymmetric Total Synthesis of (+)-Waihoensene

In addition to the successful implementation of a racemic total synthesis of waihoensene (**75**), an asymmetric access was approached in cooperation with Dr. Maximilian Häfner. The synthesis of chiral intermediate **262** (*Scheme 59*) was established in the context of his PhD thesis[42b] and completion of the asymmetric total synthesis was achieved by shared work in accordance with the racemic route. The following results were also part of the above-mentioned publication in *Angewandte Chemie*.

2.4.1 Retrosynthetic Analysis

The retrosynthetic approach toward (+)-waihoensene (*Scheme 59*) was consistent with the racemic synthetic route up to the common intermediate **262**. As distinguished from the approach shown in chapter 2.3, optically active **262** should be obtained from vinylogous ester **290** by sequential Stork-Danheiser transposition and a three-step homologation of the allyl substituent to the terminal alkyne. The α-quaternary stereocenter in **290** was planned to be installed by use of a methylation and palladium-catalyzed decarboxylative asymmetric allylic alkylation (DAAA) reaction leading back to commercial 2-methylcyclohexane-1,3-dione (**134**).



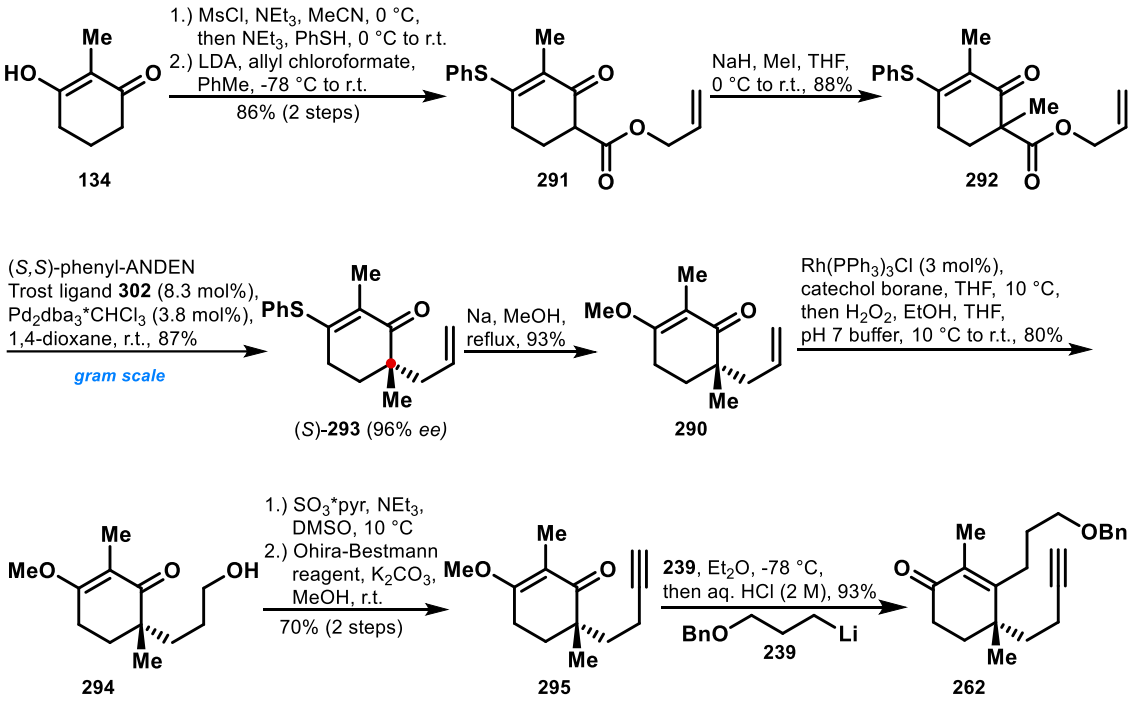
Scheme 59: Retrosynthetic analysis for the asymmetric total synthesis of (+)-waihoensene (**75**).

Since all the other reactions that generate a chiral carbon atom, *i.e.* intramolecular radical cyclization, intramolecular Pauson-Khand reaction, α-methylation and 1,4-cuprate addition, would proceed under substrate control, this first stereocenter should serve as a chiral relay throughout the planned synthetic sequence.

2.4.2 Synthesis of a Chiral Intermediate by Use of the DAAA Reaction

The following studies were mainly conducted by Dr. Maximilian Häfner in the course of his PhD project and hence, the results will not be discussed in detail but a short summary is given here. For the corresponding detailed report as well as experimental procedures see the mentioned thesis[42b] and publication[113].

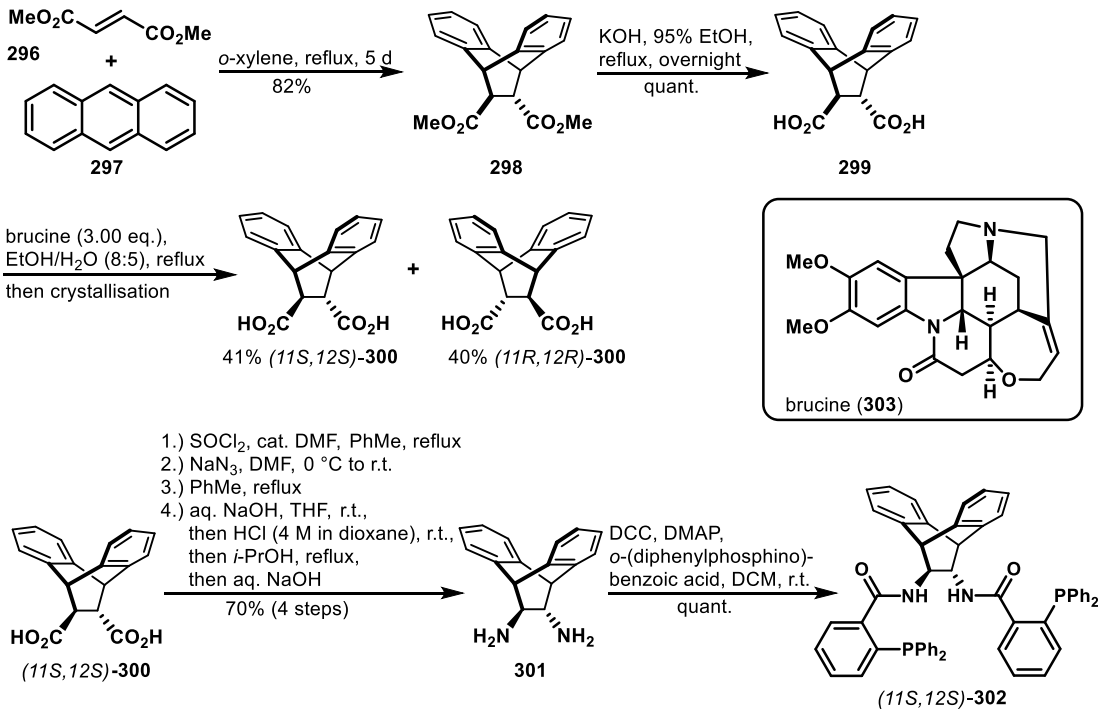
The precursor **292** for the planned DAAA was synthesized in three steps from **134** (*Scheme* 60). Conversion to the vinylogous thioester and subsequent acylation in α-position proceeded smoothly according to the procedure reported by Stoltz *et al.*[114]. On the contrary, ensuing α-quaternization by methylation required some optimization of literature-known procedures[114-115] regarding the amount of methyl iodide and the reaction time. Finally, the desired β-ketoester **292** was obtained in satisfactory yields and in gram quantities.



Scheme 60: Synthetic sequence for the synthesis of chiral intermediate **262**.

The use of a vinylogous thioester in this sequence is due to the poorer orbital overlap of carbon and sulfur, which results in a higher reactivity of the β-ketoester in the decarboxylative alkylation step compared to the *O*-analogue. This effect was previously described by Trost and co-workers[115].

Heading toward the planned DAAA reaction, the phenyl-ANDEN Trost ligand **302** was prepared from dimethyl fumarate (**296**) and anthracene (**297**) by application of literature-known procedures[116], as outlined in *Scheme 61*. Diels-Alder reaction and subsequent saponification of the methyl ester provided the corresponding diacid **299**, which was subjected to chiral resolution by the aid of brucine (**303**)[117]. This procedure allows, in principle, the preparation of both enantiomers of the ligand, as the (11*S*,12*S*)-salt is obtained in crystalline form, whereas the (11*R*,12*R*)-salt remains in solution. However, aiming for the synthesis of (+)-waihoensene, only the (11*S*,12*S*)-isomer was further converted to the ligand. A slightly modified version of Trost's four-step sequence[116b] included purification *via* the bishydrochloride and furnished the desired diamine **301** on gram scale. The final amidation proceeded without any problems and afforded the desired phenyl-ANDEN Trost ligand (11*S*,12*S*)-**302** in gram quantities and with a high enantiomeric excess of 96%.



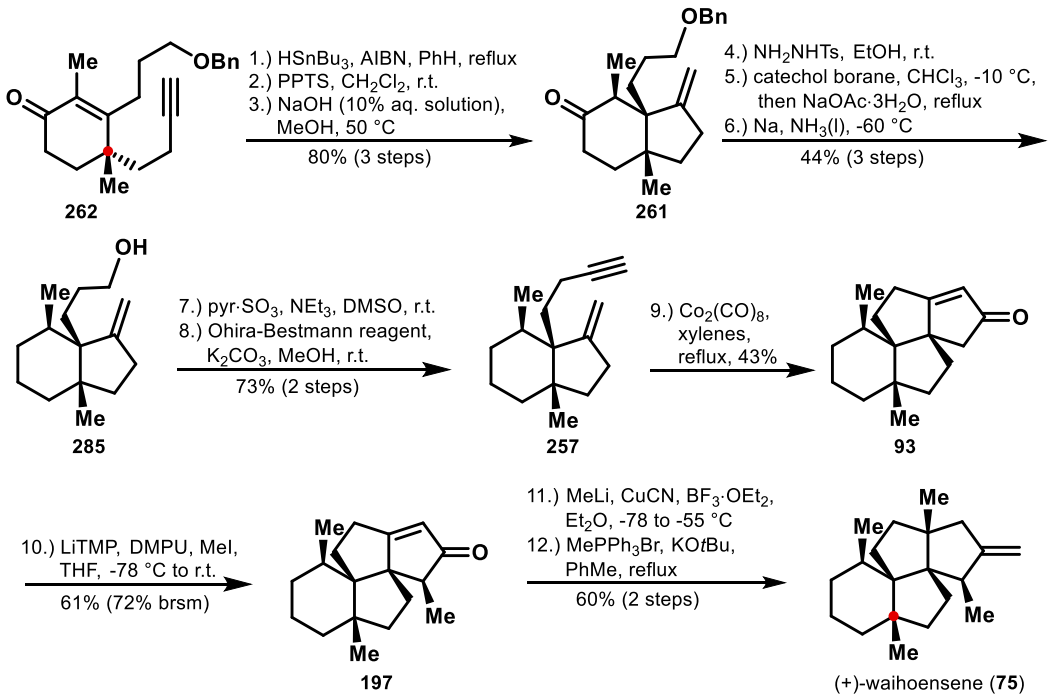
Scheme 61: Optimized synthesis of the phenyl-ANDEN Trost ligand (*11S,12S*)-**302**.

Initially observed low yields for the DAAA were overcome by the use of self-prepared tris-(dibenzylideneaceton)-dipalladium(0) chloroform adduct[118] and adjusted ligand and catalyst loadings. These modifications allowed for a scale-up of the reaction onto gram scale and very good yields with an excellent enantiomeric excess of around 96%, as stated in *Scheme 60*. Having optically active **293** in hands, the vinylogous thioester was

transesterified to the corresponding vinylogous methyl ester according to Trost's procedure[115]. As attempted aldehyde-selective Wacker oxidation[119] did not succeed, homologation of the allyl substituent to the alkyne in **295** was realized in good yield by a sequence comprising rhodium-mediated hydroboration[120] of the olefin, oxidation under non-acidic Parikh-Doering conditions and final alkynylation with Ohira-Bestmann reagent. In analogy to the racemic synthesis (see chapter 2.3.2), treatment of **295** with lithiated **239** produced the desired enone **262** in a Stork-Danheiser addition/elimination reaction. Key intermediate **262** was obtained in optically active form with an enantiomeric excess of 96% and in gram quantitites with a total yield of 32% over nine steps.

2.4.3 Completion of the Total Synthesis of (+)-Waihoensene

With the established access to optically active compound **262**, the following completion of the asymmetric total synthesis of (+)-waihoensene (**75**) was conducted as shared work and in analogy to the racemic route. The herein obtained yields were in accordance with the yields of the racemic synthesis for all steps (see chapter 2.3). Tin-mediated intramolecular cyclization, followed by protiodestannylation and epimerization provided the all-*cis* hydrindane system **261** in good yield (*Scheme 62*).



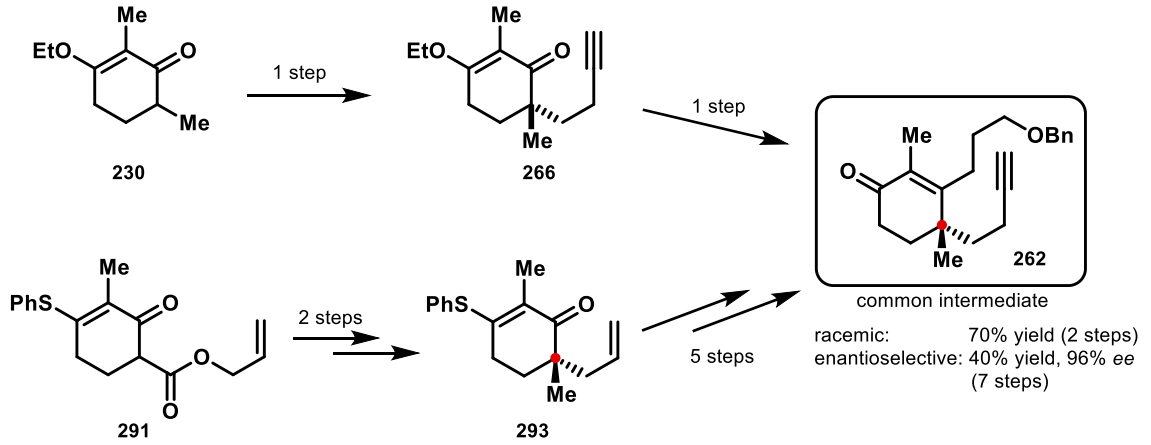
Scheme 62: Completion of the asymmetric total synthesis of (+)-waihoensene (**75**) in analogy to the racemic synthesis.

Formation of the new stereocenters in the cyclization step was efficiently guided by the quaternary stereocenter in **262**. The obtained bicyclic compound **261** was

O-defunctionalized and further subjected to Birch conditions to liberate the primary alcohol **285**. Oxidation and Ohira-Bestmann alkynylation furnished chiral precursor **257** for the key transformation of the synthetic sequence, *i.e.* the intramolecular Pauson-Khand reaction. Once again, the existing stereocenters directed formation of the new quaternary stereocenter to give the tetracyclic product **93** as the only diastereomer in 43% yield. The three-step endgame of the total synthesis comprised α-methylation, cuprate 1,4-addition and final Wittig olefination and delivered the desired diterpene (+)-waihoensene (**75**) as a colorless oil. The measured optical rotation factor $[\alpha]_D^{23}$: +42.4 (c 0.18, $CHCl_3$) is in accordance with the value reported for the isolated material $[\alpha]_D^{22}$: +43.9 (c 0.09, $CHCl_3$)[32a]. In total, 19 steps were required for this asymmetric version of the total synthesis of (+)-waihoensene furnishing the natural product in an overall yield of 1.5% from commercially available vinylogous thioester **291**.

3. Summary

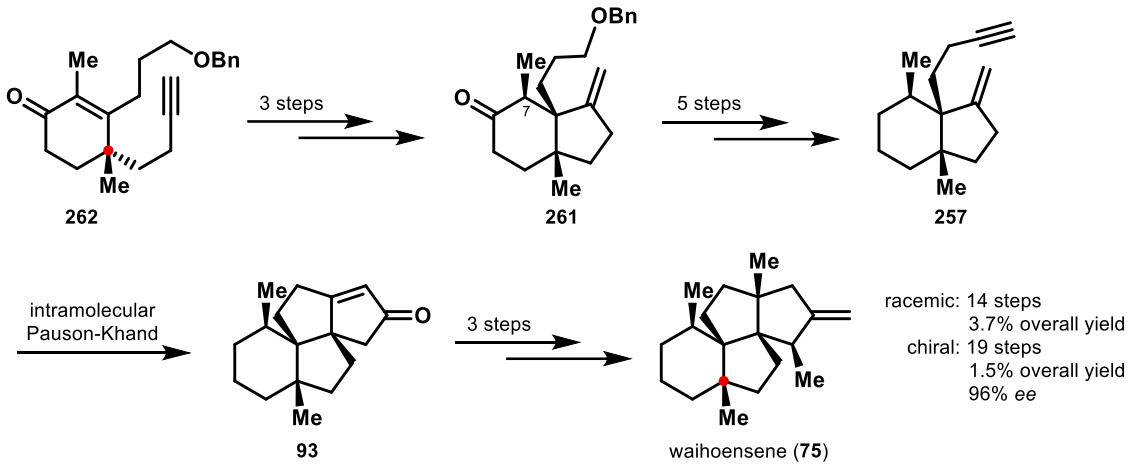
Multiple synthetic approaches as well as a successful racemic total synthesis of the natural product waihoensene (**75**) were discussed in the first part of this thesis. In addition, the results of cooperative work with Dr. Maximilian Häfner on the asymmetric total synthesis of (+)-waihoensene were described. A common intermediate **262** of the racemic and enantioselective route enabled a synthetically convergent access to the achiral and the chiral natural product, as outlined in *Scheme 63*.



Scheme 63: Synthetic access to the common intermediate **262** of racemic and enantioselective route.

In the course of the racemic approach, a sequence of two steps was developed to access enone **262** from commercially available vinylogous ester **230** in 70% yield. The same intermediate was obtained in chiral form in seven steps and in 40% overall yield. An excellent enantiomeric excess of 96% was achieved by application of a palladium(0)-catalyzed decarboxylative asymmetric allylic alkylation reaction, which was used to construct the first of six stereogenic carbon atoms of the natural product (+)-waihoensene (**75**). From enone **262** onward, both the racemic and the enantioselective total synthesis were consistent (figured in *Scheme 64*) and continued with a tin-mediated intramolecular radical cyclization reaction for the construction of the *cis*-hydrindane core **261**. Substrate control caused preferential formation of the desired all-*cis* isomer and subsequent base treatment allowed for epimerization at C7 of the minor stereoisomer. The relative stereochemistry was confirmed by single crystal X-ray analysis of the corresponding dinitrophenyl hydrazone. Deoxygenation *via* a two-step protocol, subsequent benzyl deprotection under mild Birch conditions and oxidation of the primary alcohol to the corresponding aldehyde were followed by Seyferth-Gilbert homologation

with Ohira-Bestmann reagent and furnished the precursor for the intramolecular Pauson-Khand reaction.



Scheme 64: Completion of racemic and enantioselective total synthesis of waihoensene (**75**).

The key transformation of the synthetic sequence was also constrained by substrate control and stereoselectively produced the desired tetracyclic enone **93**. This transformation occurred with a yield of around 45%, which is doubtless satisfactory with respect to the complexity of the produced structure. The endgame comprised methylation of the kinetic enolate, copper-mediated conjugate addition and final Wittig olefination and provided the desired diterpene natural products (±)-waihoensene and (+)-waihoensene, respectively. The racemic sequence numbers 14 steps in total and constitutes the so far shortest synthetic access to (±)-waihoensene from commercial starting materials. The enantioselective synthesis requires 19 steps and delivers (+)-waihoensene with high enantiomeric excess and overall 1.5% yield.

II. Studies Toward the Total Syntheses of Vallesamidine and Lyconadin C

1. Introduction

1.1 Alkaloid Natural Products

Featuring a variety of biological and physiological activities, alkaloid natural products have been used for therapeutic purposes since ancient times, *e.g.* in form of alkaloid-containing plants[121]. The term alkaloid derives from Arabic '*al qualja*' ('plant ashes') and Greek '*-oides'* ('like') and attributes to the compounds' resemblance to alkaline substances. It was established by the German pharmacist C. F. W. Meißner in 1819[122] in the course of his studies on the seeds of *Schoenocaulon officinale* and the therein contained veratrine. The latter is a mixture of several substances and later, one of its major constituents was identified to be veratridine (**305**)[123] (shown in *Figure 19*). In general, the name alkaloids refers to a class of secondary metabolites comprising nitrogen-containing organic compounds that often exhibit complex heterocyclic structures and diverse biological activities.

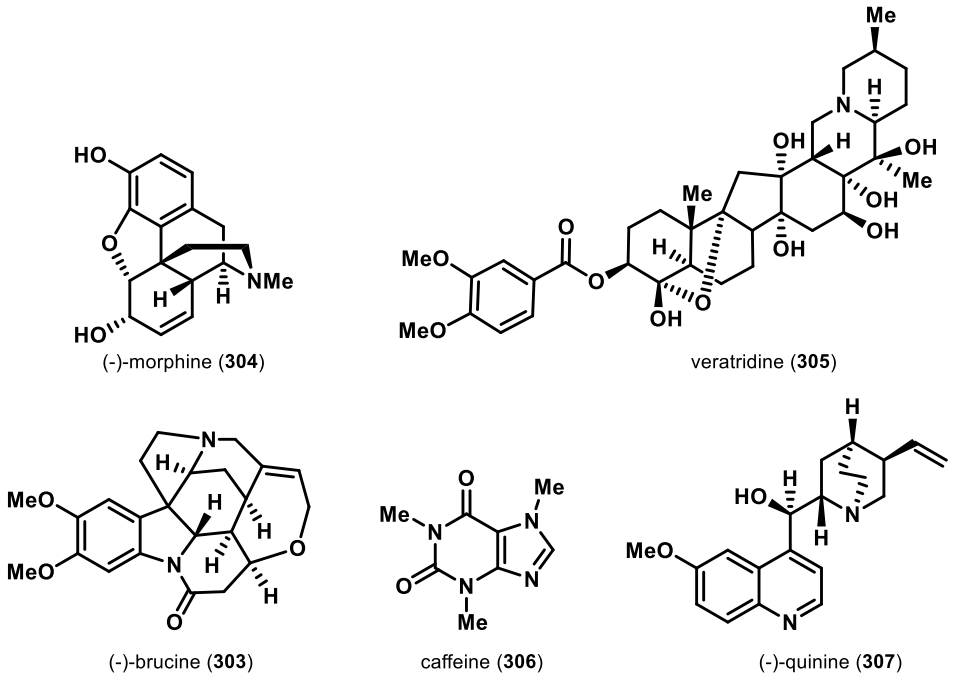


Figure 19: Structure of morphine (**304**), veratridine (**305**) and some exemplary alkaloids isolated by Pelletier and Caventou[121].

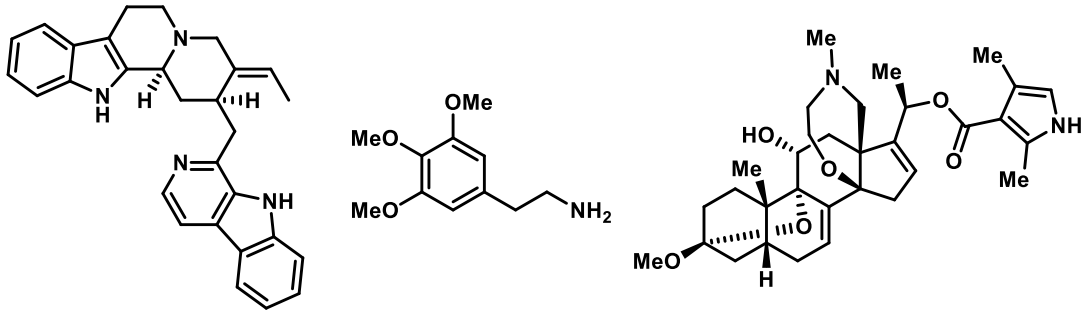
Already in 1805, Sertürner has reported the discovery and isolation of morphine (**304**) and also noticed its alkali-like behavior[121]. Although Sertürner recognized the relationship to L-tyrosine, the correct structure of morphine (**304**) was elucidated not earlier than about 120 years later by Gulland and Robinson in 1923[124]. Following the example of Sertürner,

Pelletier and Caventou were able to isolate a number of further alkaloid natural products[121] between 1817 and 1821, *e.g.* brucine (**303**), caffeine (**306**) and quinine (**307**). However, these substances were only obtained in impure form as mixtures together with other alkaloid compounds and their exact structures could not been determined at this point[121]. Since these early studies, the field of alkaloid natural products has gained remarkable scientific interest, not only from pharmacists and biologists but also from chemists with regard to a potential synthetic access and the development of new drugs. With over 21,000 plant-derived members known today[125], the group of alkaloids is remarkably smaller than the non-nitrogen-containing class of natural products and in contrast to the latter, the number of newly discovered compounds per year rather decreased between 2000 and 2009[126]. Alkaloid natural products are present in about a quarter of the higher plants but also occur in other plants like algae and mosses as well as in bacteria, fungi and marine organisms[125]. The nitrogen-containing substances naturally exist in form of acid salts, quaternary amine salts and tertiary *N*-oxides, or they occur in form of esters or amides or attached to sugar molecules. Mainly functioning as part of the chemical defense mechanism of the producing organism against herbivores and predators, they participate in various biological processes and exhibit activity on different cellular levels. Many representatives show more than one biological function and provide interesting lead structures for drug development[4, 127]. Even though plant-derived alkaloids constitute only 16% of the total number of known natural products, they account for roughly half of all pharmaceutically and biologically significant natural products, as stated by Cordell[128]. This is even more remarkable regarding the fact that approximately 75% of the known alkaloids have not been subjected to any biological assay yet. Cordell attributes this outstanding potential to their vast structural diversity. Besides, progressive pharmacological research eventuates in a rising number of non-natural alkaloids that are structurally altered derivatives or analogues.

1.1.1 Classification and Biosynthetic Origin

In general, alkaloid natural products are secondary metabolism molecules with vastly different structures and properties, which makes it difficult to establish a generally valid definition or classification of these compounds by means of bioactivity or structure. Nevertheless, consideration of their biosynthetic origin allows for classification into three

structural groups: the true alkaloids, the protoalkaloids and the pseudoalkaloids[129]. The former two directly derive from amino acids, their precursors or postcursors, whereas amination and transamination reactions are involved in the formation process of the third group, *i.e.* the pseudoalkaloids. The highly bioactive true alkaloids feature a nitrogen-heterocyclic ring and comprise the group of indole alkaloids amongst others. Their common biosynthetic precursors are various amino acids, like L-ornithine, L-lysine, L-phenylalanine, L-tyrosine, L-tryptophan or L-histidine. An example of this group of alkaloids is usambarensine (**308**) (*Figure 20*), which shows strong anti-malarial activity and inhibits the growth of leukemia cells[130]. In contrast to this first group, the nitrogen atom is not part of a heterocycle within the protoalkaloids but still originates from an amino acid, like L-tyrosine or L-tryptophan. This minor group of alkaloids exhibits rather simple structural motifs, as illustrated in *Figure 20* by its psychedelic representative mescaline (**309**). As stated above, members of the third structural group of plant-derived alkaloids, the pseudoalkaloids, do not directly originate from aminoacids and but their synthesis involves late-stage transamination processes for the introduction of nitrogen atoms to their structure. Steroidal or terpenoid alkaloids belong to this group, for example the highly poisonous alkaloid batrachotoxin (**310**).



usambarensine (**308**) mescaline (**309**) (-)-batrachotoxin (**310**)

Figure 20: Structural examples for true alkaloids, protoalkaloids and pseudoalkaloids.

In general, all naturally occurring alkaloids originate from one of the four basic building blocks of secondary metabolism[129], namely acetyl CoA, shikimic acid, mevalonic acid and 1-deoxyxylulose-5-phosphate. Additionally, the Krebs cycle provides L-ornithine and L-lysine as further building blocks. The key building blocks and their origin, the derived amino acids as well as potential transformations within alkaloid synthesis are schematically depicted in *Figure 21*.

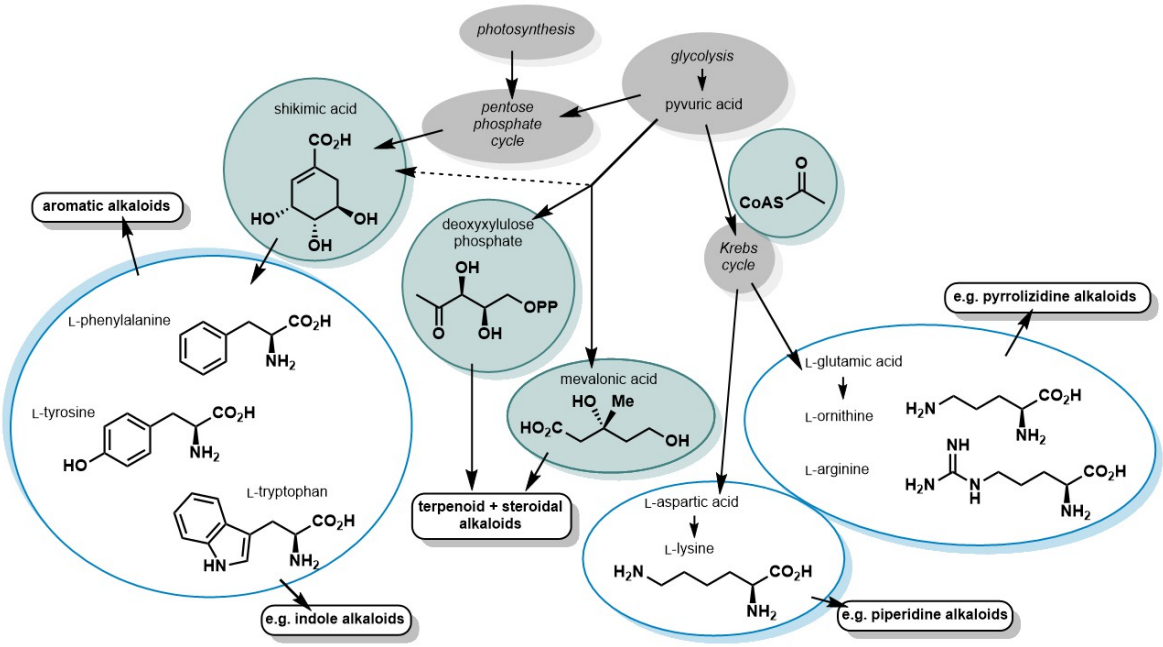


Figure 21: Secondary metabolism building blocks and amino acids in alkaloid biosynthesis.

1.2 The Monoterpenoid Dihydro-Indole Alkaloid Vallesamidine

1.2.1 Isolation, Structural Characterization and Proposed Biosynthesis

Figure 22: Vallesia glabra (Cav.) Link observed in Mexico by Jose Luis Leon de la Luz (licensed under *http://creativecommons.org/licenses/by-nc/4.0/*)[132b]

In 1965, Djerassi *et al.*[131] isolated the structurally novel alkaloid vallesamidine (**311**) (*Figure 23*) along with 27 other known and unknown indole and dihydro-indole alkaloids from *Vallesia dichotoma* RUIZ *et* PAV. This *Vallesia* species, native to tropical America, occurs in form of small shrubs and is a member of the *Apocynaceae* family[132]. Vallesamidine's bioactivity has not been investigated yet but is presumed to resemble other *Apocynaceae*'s, which have been widely used in traditional medicine for centuries and esteemed for their antioxidant, antimicrobial, anti-inflammatory and cytotoxic activities[133]. In the course of the initial studies, the actual structure of **311** could not be elucidated due to the very limited amount of material. Initial speculations on the new compound being a stereoisomer of

N-methylaspidospermidine (**313**) were disproven by comparison of the obtained spectral data with those of known (**313**) and synthesized 19-*epi*-*N*-methylaspidospermidine (**314**).

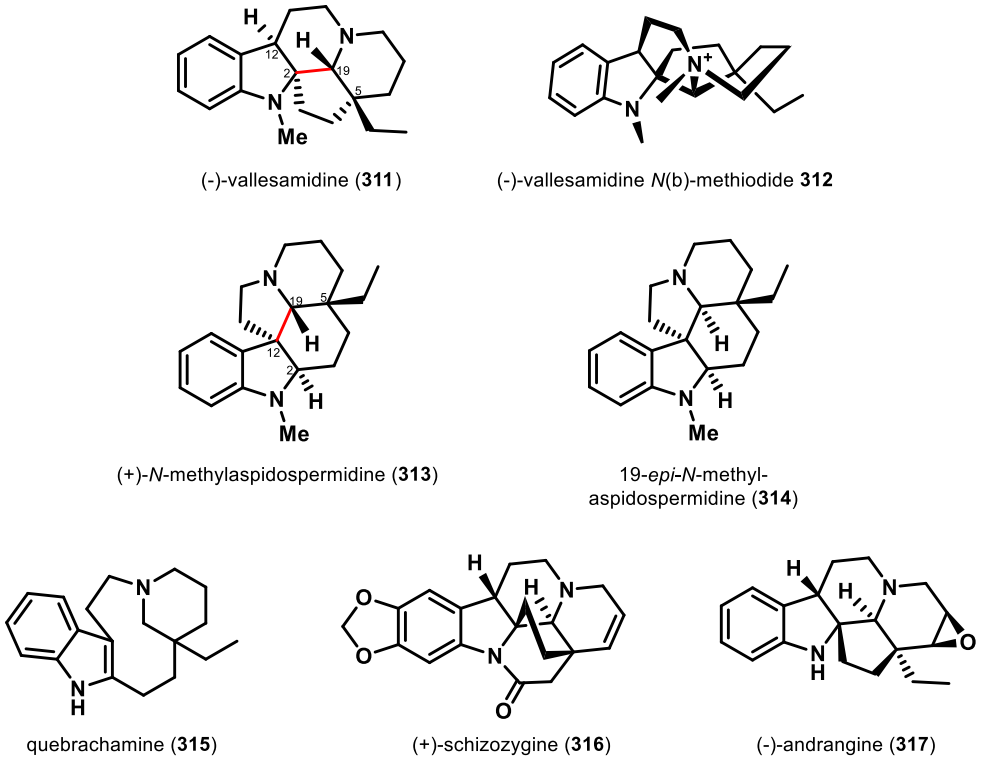
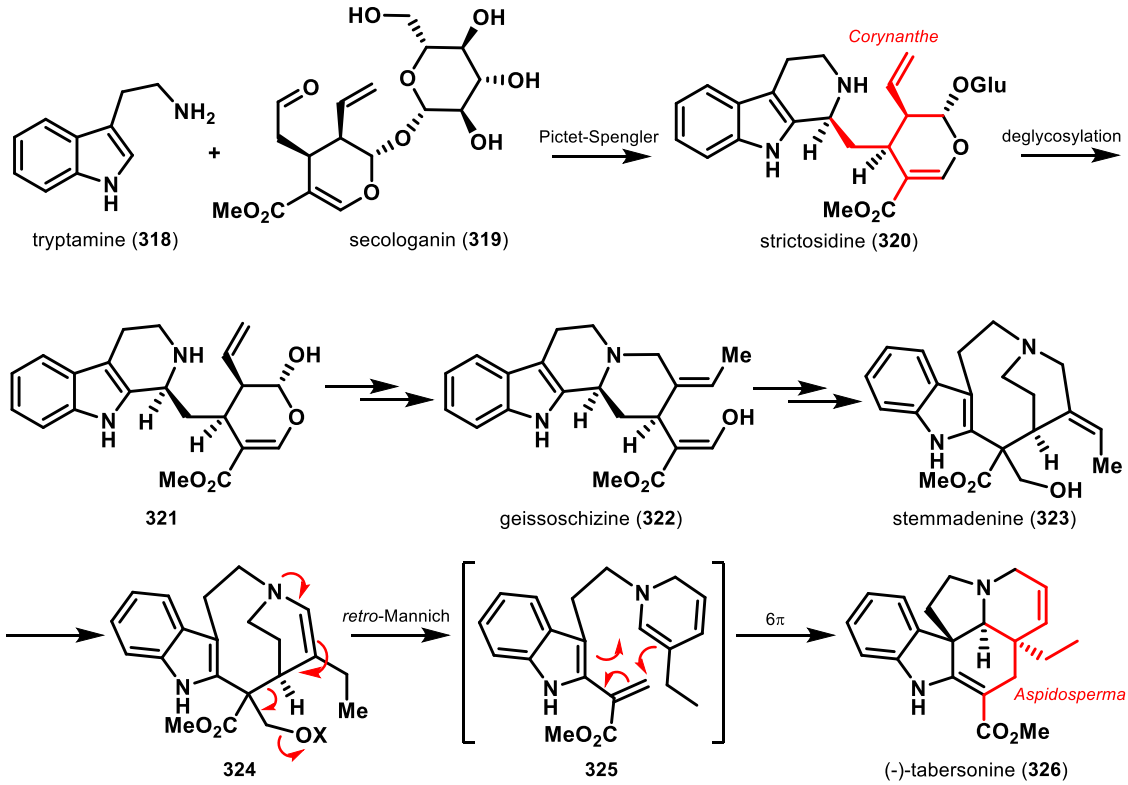


Figure 23: Molecular structure of (-)-vallesamidine (**311**) and related compounds.

Mass spectroscopic data and X-ray diffraction analysis of single crystals of vallesamidine *N*(b)-methiodide **312** (see *Figure 23* for three-dimensional projection) allowed at first for determination of the sum formula ($C_{20}H_{28}N_2$) and later elucidation of the molecular structure and absolute configuration[134]. This revealed the new alkaloid's structural relation to the aspidospermin skeleton but also the deviating attachment of C19 to C2 instead of C12 of the indolenin core (highlighted in red in structures **311** and **313** in *Figure* 23). Furthermore, vallesamidine (**311**) exhibits the same absolute configuration as all co-occuring *Aspidosperma* alkaloids in *Vallesia dichotoma* and is suspected to have a related biosynthetic origin comprising an intramolecular cyclization of quebrachamine (**315**)-like intermediates[134-135]. Although the actual biosynthetic route to vallesamidine (**311**) is not known, it can be exemplified by the proposed biosynthesis of *Aspidosperma* alkaloid tabersonine (**326**) (depicted in *Scheme 65*). The synthesis of strictosidine (**320**), which constitutes the common precursor for all terpenoid indole alkaloids, comprises enzyme-catalyzed Pictet-Spengler reaction of tryptamine (**318**, derived from tryptophan) and secologanin (**319**). Deglycosylation is followed by

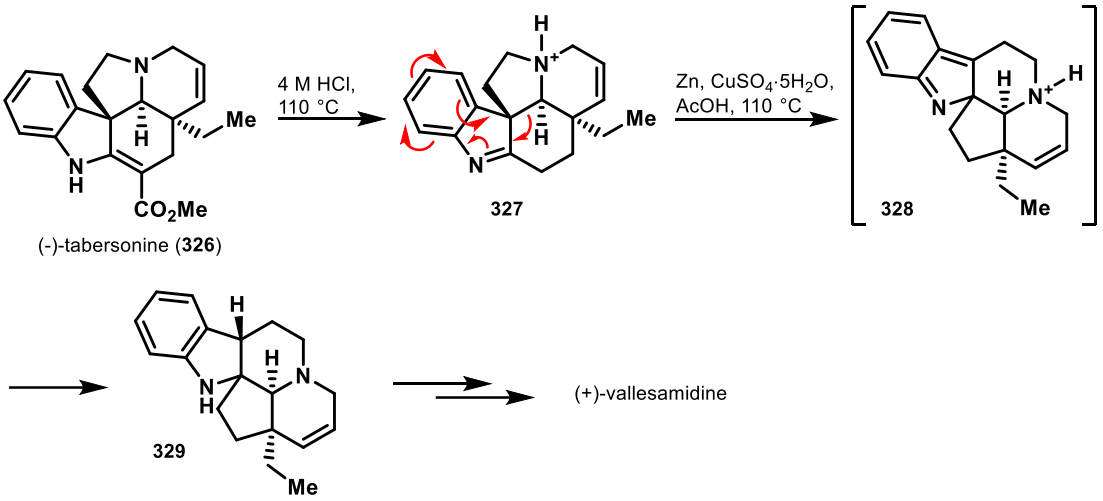
transformation to geissoschizine (**322**) and further transformation of the latter to stemmadenine (**323**).



Scheme 65: Proposed biosynthesis of the monoterpenoid indole alkaloid tabersonine (**326**).

Both intermediates have been isolated from *Vinca rosea* and characterized[136] and gave, in combination with additional labelling experiments[137], undeniable proof to the hypothesized conversion of the *Corynanthe*-type C10 unit of strictosidine (**320**) (marked in red in *Scheme 65*) to the rearranged skeleton of *Aspidosperma* and *Iboga* alkaloids. Isomerization of the *exo*-double bond in **323** to the *endo*-position enables dehydration of the primary alcohol functionality and concurrent C-C bond cleavage by reverse Mannich-type reaction resulting in the formation of labile intermediate **325**. Eventual production of the alkaloid tabersonine (**326**) was proposed to occur *via* an electrocyclic mechanism[138]. A plausible route from the *Aspidosperma* skeleton to the vallesamidine structure was suggested by the observations of Le Men *et al.*[139] upon their semi-synthesis of (+)-vallesamidine. As shown in *Scheme 66*, treatment of decarboxylated derivative **327** with zinc and copper(II) sulfate in acetic acid with heating triggered a reductive rearrangement and produced the indoline carbon skeleton of vallesamidine. So far, the same skeletal structure was detected only in one other compound, which is (-)-andrangine (**317**) (*Figure 23*), and thus, vallesamidine (**311**) cannot be attributed to a

particular class of alkaloids. A similar structure motif is also present in the *Schizozygia* alkaloids, *e.g.* (+)-schizozygine (**316**). Formally, vallesamidine (**311**) corresponds to a fully reduced member of this substance group, however, these compounds show a reverse absolute configuration[140] (*Figure 23*), implying a divergent biogenetic origin.



Scheme 66: Le Men's semi-synthesis of vallesamidine from tabersonine[139].

Its unique structure with a 2,2,3-trialkylindoline skeleton (blue in *Figure 24*) renders vallesamidine (**311**) an unsual indole alkaloid and an attractive target for synthetic chemists. The pentacyclic compound contains a decahydroquinolizine motif (rings C and D, red in *Figure 24*) fused to the indoline A/B-ring system and four contiguously arranged stereogenic centers (green in *Figure 24*). As mentioned above, the absolute stereochemistry of these stereocenters was determined by X-ray structure analysis of the corresponding *N*(b)-methiodide **312** and found to be identical to the absolute configuration at respective asymmetric C5 and C19 of co-isolated (+)-*N*-methylaspidospermidine (**313**). In addition, the crystal structure (see *Figure 23* for projection) revealed a curved shape of the annulated C/D/E-ring system and boat conformation of the D ring.

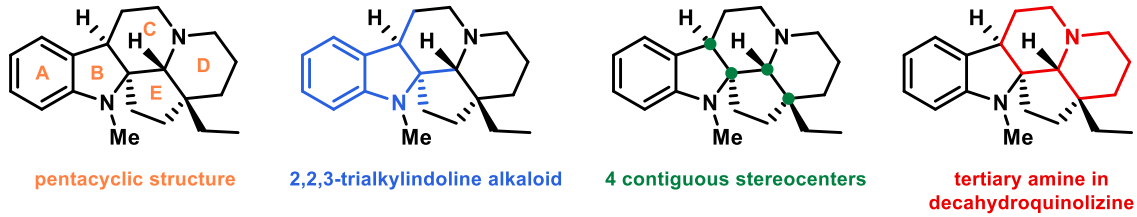
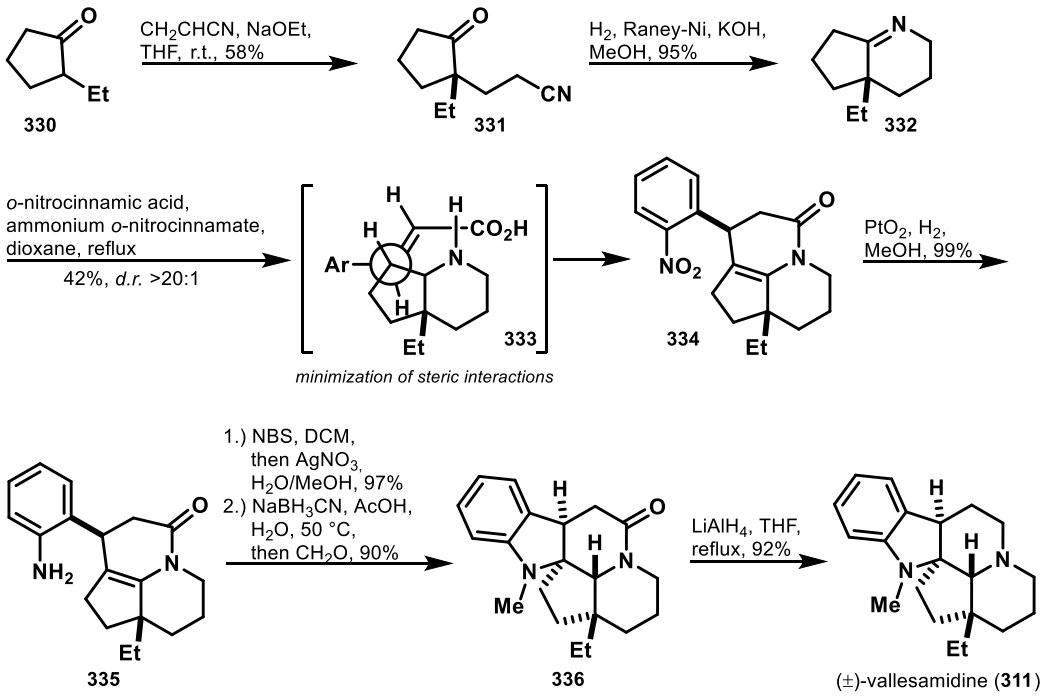


Figure 24: Structural features of vallesamidine (**311**).

1.2.2 Previous Total Syntheses and Formal Syntheses of Vallesamidine

The initial studies on a semi-synthetic access to vallesamidine (**311**) were carried out by Le Men *et al*.[139] in 1971 and have already been presented in the previous chapter (see chapter 1.2.1). However, a total synthesis of this structurally unique monoterpenoid alkaloid had not been published for a period of almost 25 years after its isolation. In 1989, the first and remarkably short total synthesis of racemic vallesamidine was reported by Heathcock[141] (*Scheme 67*).

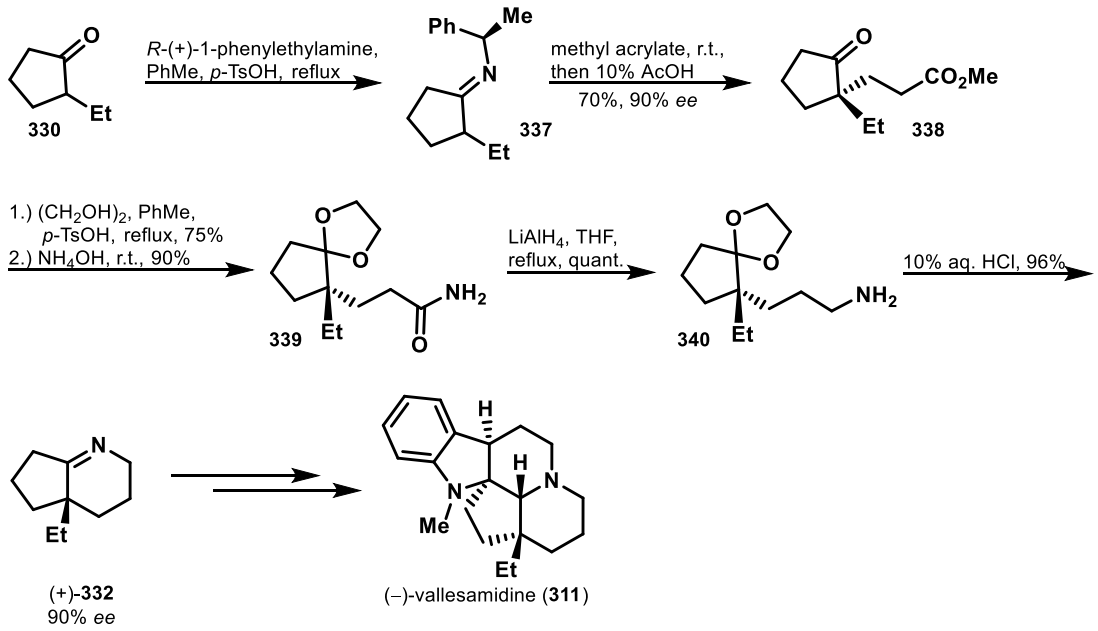


Scheme 67: Total synthesis of (±)-vallesamidine (**311**) by Heathcock[141].

The linear sequence required only seven steps starting from commercial 2-ethylcyclopentanone (**330**) and furnished the pentacyclic alkaloid **311** in an overall yield of 19%. Michael addition of the thermodynamic enolate of **330** to acrylonitrile and subsequent reductive hydrogenation induced cyclization to the imine compound **332**, which was further converted in a proposed Michael addition/lactamization sequence of its enamine tautomer with *o*-nitrocinnamic acid. The observed stereoselectivity was rationalized by a minimization of steric interactions in the corresponding transition state **333** and produced tricyclic lactam **334**. Formation of the indoline core was accomplished by reductive hydrogenation to the aniline, NBS-mediated cyclization and hydrolysis of the bromo lactam to the hydroxy analogue. Reduction to the lactam and methylation of the indoline nitrogen was followed by lithium aluminum hydride reduction

of the lactam in **336** to the tertiary amine and provided the natural product vallesamidine (**311**) in racemic form.

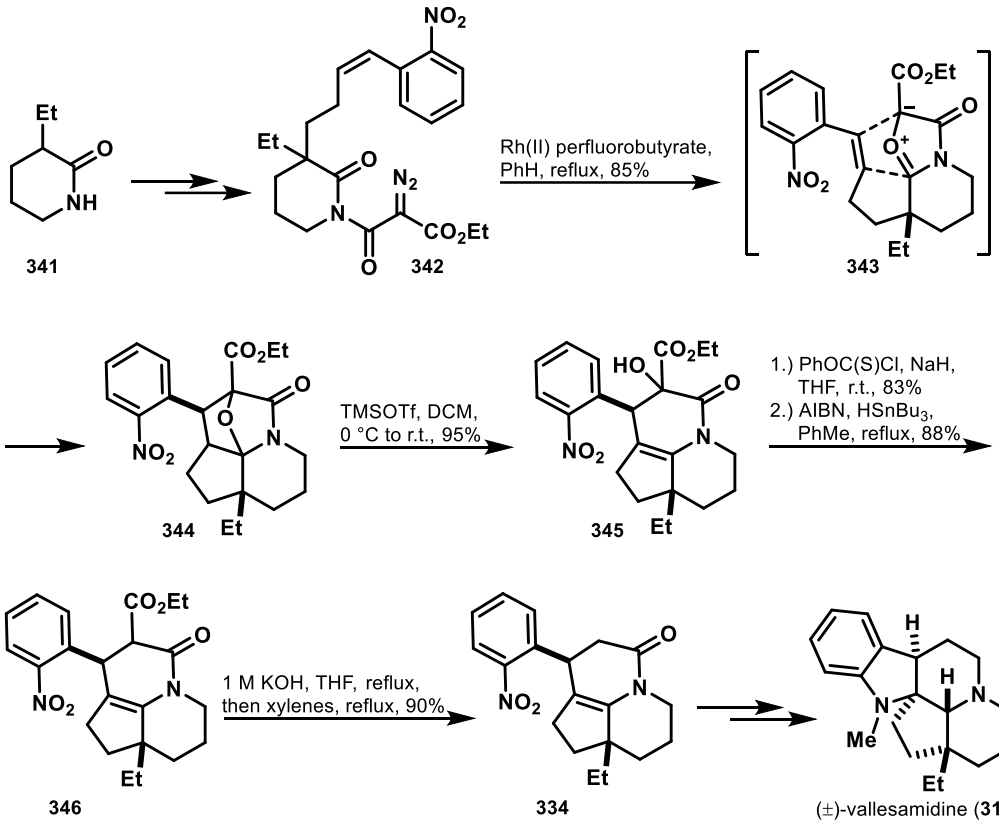
Four years later, in 1993, Bergter *et al.*[142] published an asymmetric access to (-)-vallesamidine (*Scheme 68*) *via* Heathcock's intermediate imine **332**.



Scheme 68: Formal asymmetric synthesis of (-)-vallesamidine (**311**) by Bergter[142].

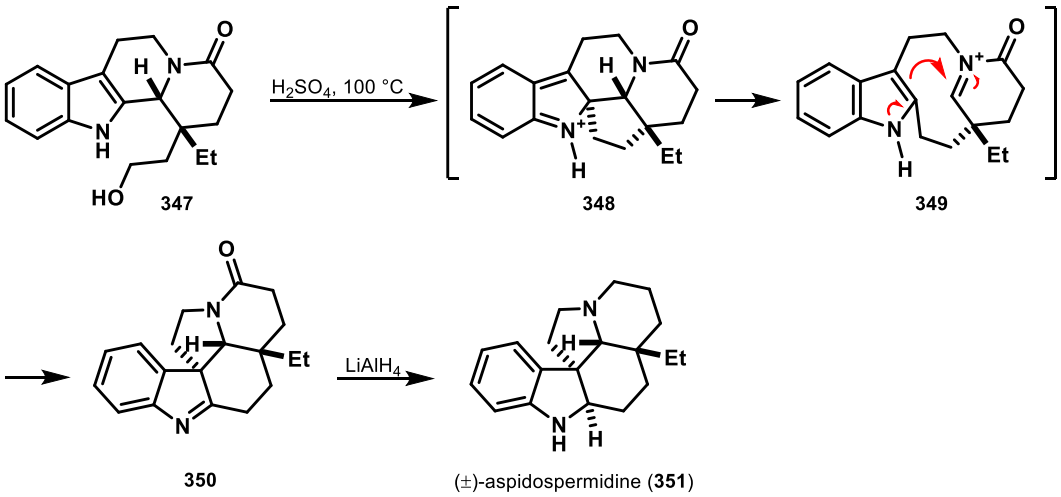
Starting from the same building block 2-ethylcyclopentanone (**330**), chirality was introduced by asymmetric alkylation of chiral imine **337** with methyl acrylate and gave **338** in 70% yield and with 90% *ee*. The ester in **338** was further converted to the amine *via* the amide **339** and subsequent acid-mediated cyclization produced Heathcock's imine **332** in enantioenriched form.

Application of an intramolecular cycloaddition of a mesoionic betaine for construction of the trialkylindoline structure of vallesamidine was approached by Padwa and co-workers[143] and is depicted in *Scheme 69*. Diazo-containing cycloaddition precursor **342** was efficiently synthesized from 3-ethyl-2-piperidone (**341**) and treated with rhodium(II) perfluorobutyrate to induce formation of an intermediate isomünchnone dipole **343**, which corresponds to a cyclic carbonyl ylide. Smooth [3+2]-cycloaddition of the 1,3-dipole to the styrene double bond furnished desired **344** as a single diastereomer in 85% yield. Heathcock's intermediate tricyclic lactam **334** was obtained in high yield after sequential Lewis acid-mediated cleavage of the *N,O*-acetal, Barton-McCombie deoxygenation and saponification/decarboxylation of the ester functionality.



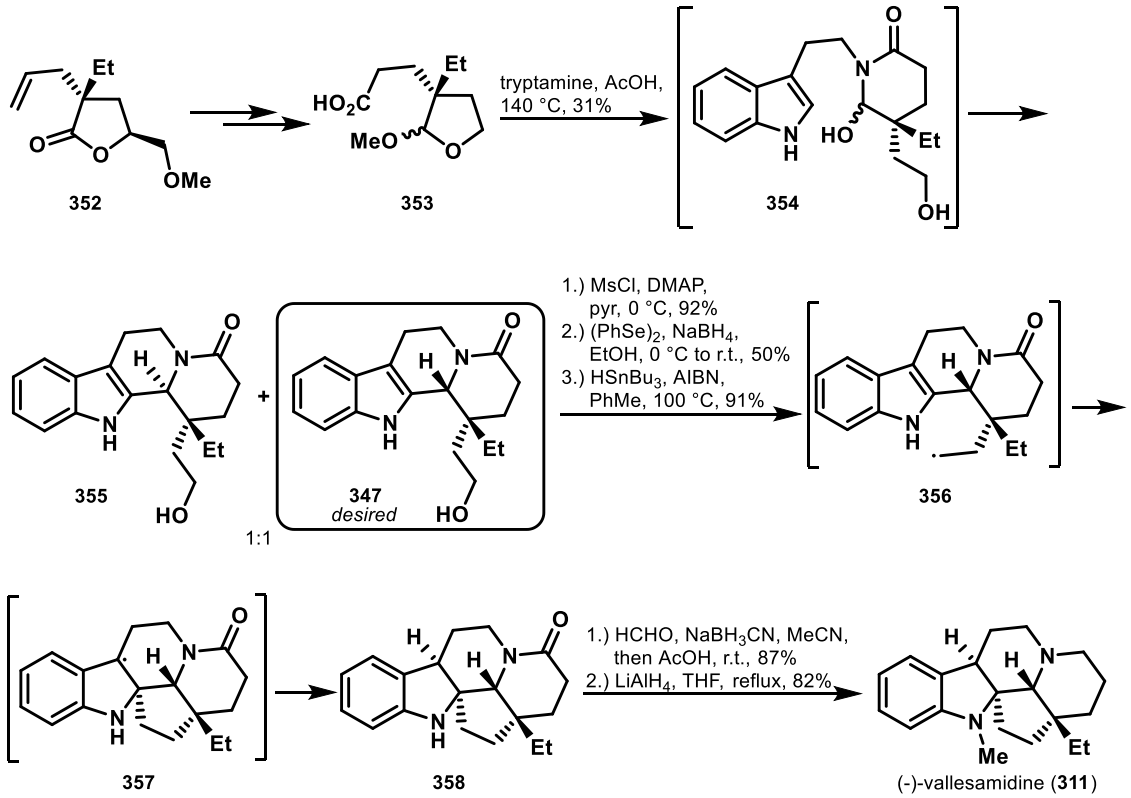
Scheme 69: Intramolecular cycloaddition of a mesoionic betaine in the formal synthesis of (±)-vallesamidine (**311**) by Padwa[143].

An alternative potential intramolecular indoline C2 alkylation was already discussed by Heathcock[141] with regard to an earlier report by Harley-Mason and Kaplan in 1967[144]. In the course of their studies on the total synthesis of aspidospermidine (**351**), treatment of hydroxyl lactam **347** with sulfuric acid led to the formation of the aspidospermidine skeleton (*Scheme 70*).



Scheme 70: Synthetic access to aspidospermidine (**351**) by skeletal rearrangement *via* quebrachamine-type intermediate **349**[144].

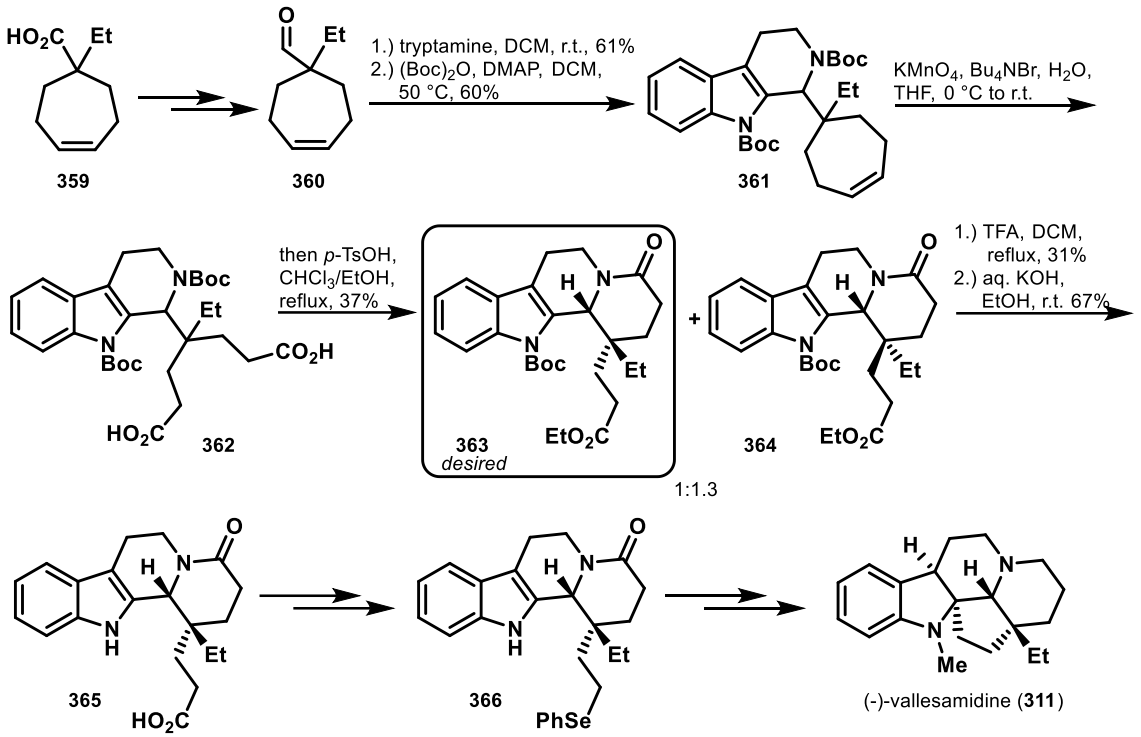
According to Heathcock, presumptive formation of cation **348**, fragmentation to a quebrachamine-like intermediate **349** and attack of the indole, preferably at the C3 position, would rationalize the observed skeletal rearrangement. This behavior was supposed to prohibit the desired alkylation at C2 *via* cationic intermediates. Accordingly, Okada[145] reported an intramolecular cyclization of an alkyl selenide *via* radical intermediate **356** for the installation of the pentacyclic alkaloid carbon skeleton (*Scheme* 71).



Scheme 71: Okada's radical approach toward (-)-vallesamidine (**311**)[145].

Readily available **352** was converted to key building block carboxylic acid **353** in seven steps. Subsequent Pictet-Spengler reaction with tryptamine *via* intermediate hydroxyl lactam **354** gave the desired compound **347** in a 1:1 diastereomeric mixture with corresponding **355**. Conversion of the alcohol of the desired isomer to the selenide and treatment with tributyltin hydride in the presence of a radical initiator induced a radical cyclization to the indole and thus, enabled indole C2 alkylation by circumvention of a cationic intermediate. Final transformation of cyclization product **358** to the natural product **311** was carried out in analogy to Heathcock's synthesis (see *Scheme 67*).

Similar to Okada's approach, Ho[146] achieved the formal total synthesis of (-)-vallesamidine (**311**) by use of a radical cyclization (*Scheme 72*).

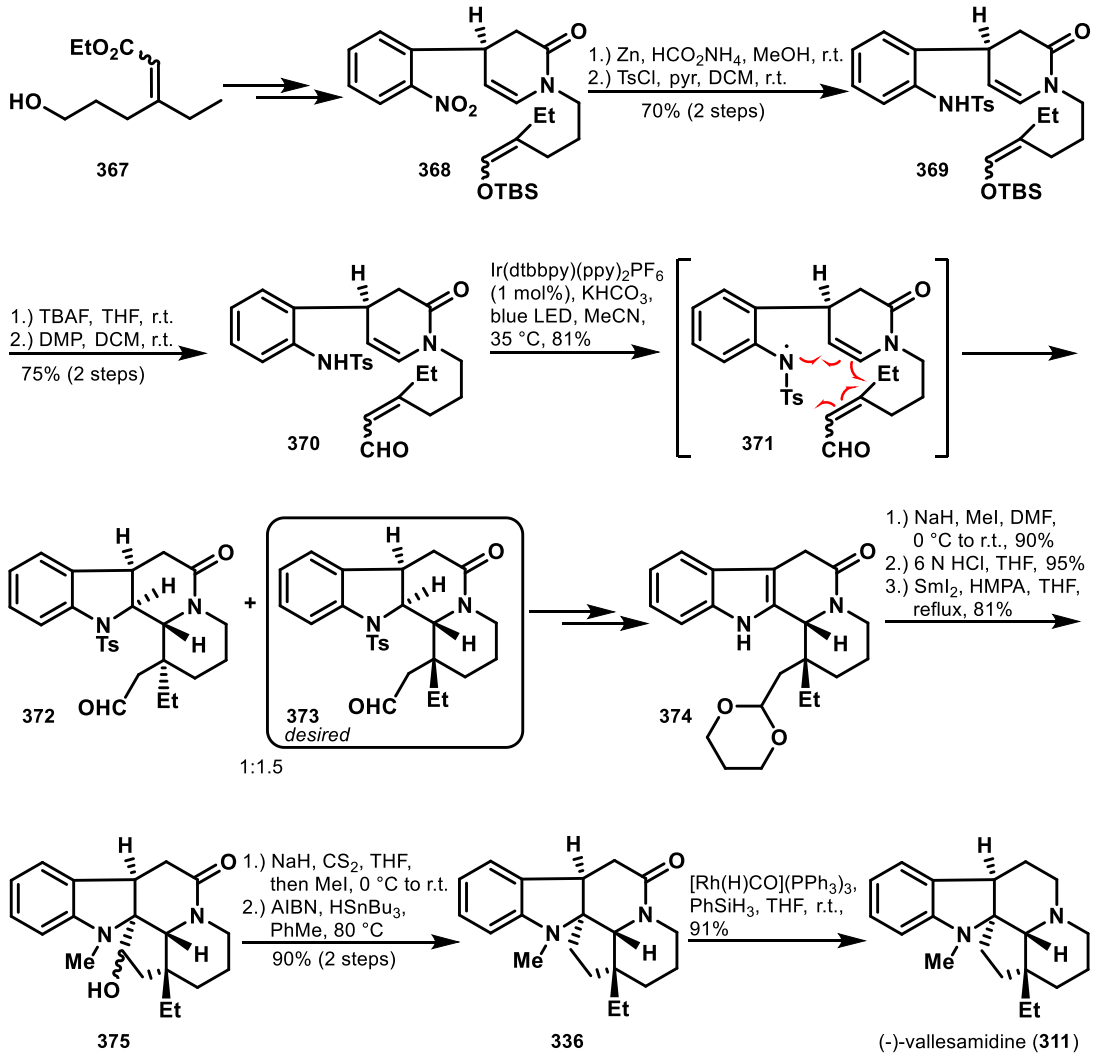


Scheme 72: Asymmetric formal synthesis of vallesamidine (**311**) by Ho[146].

Starting from cyclohept-4-ene-1-carboxylic acid (**359**), the corresponding aldehyde **360** was condensed to tryptamine in a Pictet-Spengler reaction and after Boc-protection of both nitrogens, oxidative cleavage of the cycloheptene in **361** produced diacid **362**. Esterification and concurrent Boc-deprotection of the non-indolic nitrogen resulted in formation of a 1:1.3 diastereomeric mixture of tetracyclic **363** and **364** by lactamization. As the initially attempted direct cyclization by radical Barton decarboxylation of the Boc-protected analogue of compound **365** failed, the acid was further converted to known selenide **366**, which is a known intermediate from Okada's route and allowed for successful completion of the synthesis of vallesamidine (**311**).

Roughly 10 years later, in 2017, Qin[147] reported the total synthesis of (-)-vallesamidine (**311**) by means of a photocatalytic radical cascade that enabled collective syntheses of several monoterpenoid indole alkaloids (*Scheme 73*). Cyclization precursor **370** was treated with an iridium photocatalyst and exposed to blue LED. This generated a nitrogen-based radical **371** and triggered an *exo*-5-*trig*/*exo*-6-*trig* cyclization cascade to tetracyclic **372** and **373** in a 1:1.5 ratio. The desired stereoisomer **373** was further converted to the acetal and deprotection of the indoline enabled oxidation to the indole. Methylation of the indole nitrogen and deprotection of the acetal provided the substrate for a second radical process, which was samarium(II) iodide-mediated cyclization

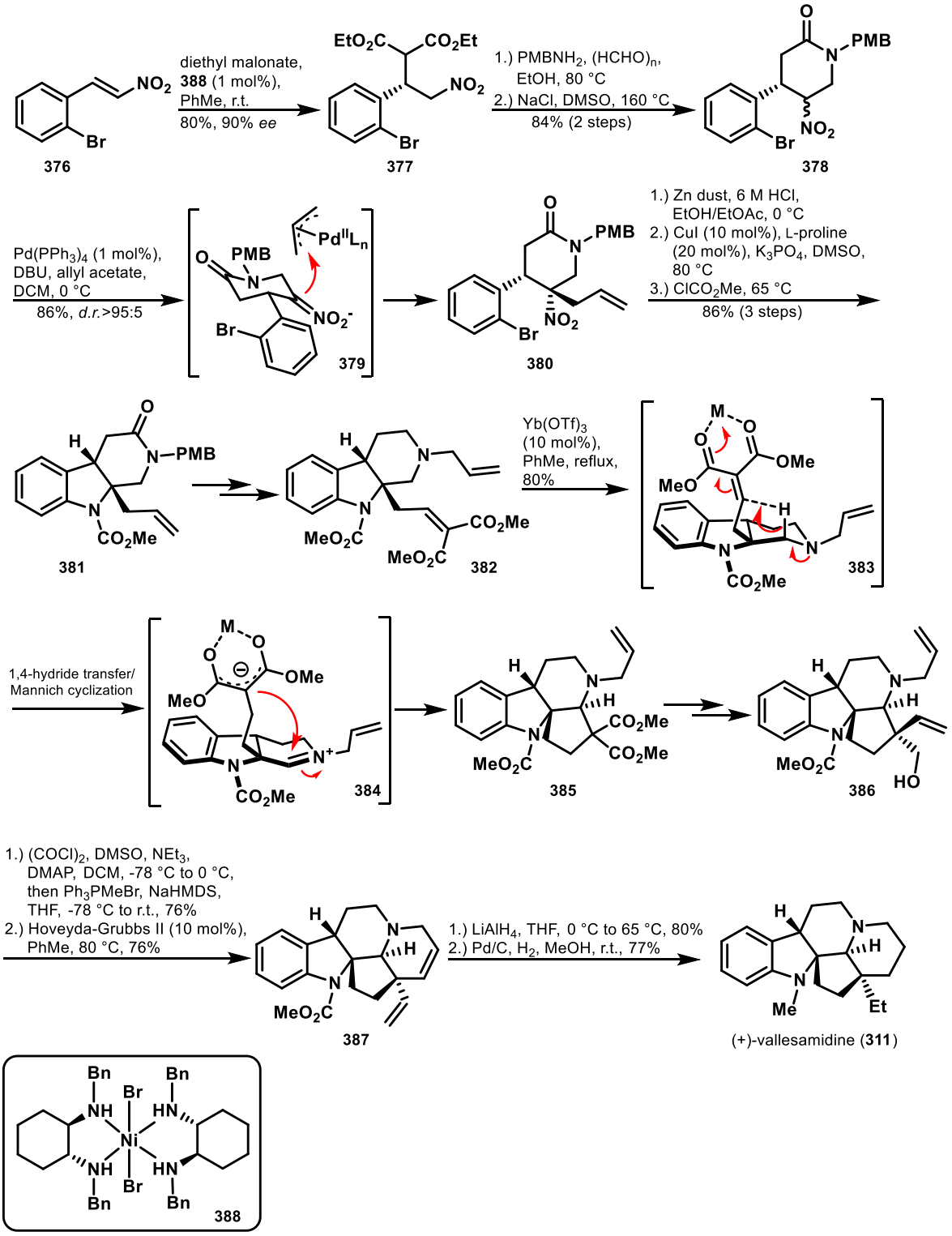
to the indole **375**. This step proceeded in analogy to Okada's radical cyclization (see *Scheme* 71) and yielded the pentacyclic structure motif of vallesamidine. Barton-McCombie deoxygenation furnished known intermediate **336**, which was converted to the natural product by rhodium(I)-catalyzed lactam reduction.



Scheme 73: Qin's total synthesis of (-)-vallesamidine (**311**)[147].

Lately, Anderson[148] published the total synthesis of non-natural (+)-vallesamidine (**311**) by use of a 1,4-hydride transfer/Mannich cyclization strategy (shown in *Scheme 74*). Initial nickel(II)-catalyzed asymmetric Michael addition of diethyl malonate to 2-bromonitrostyrene (**376**) afforded compound **377** in good yield and with 90% *ee*. A nitro-Mannich/lactamization cascade was followed by stereoselective Tsuji-Trost allylation and gave allylated **380**. Sequential reduction of the nitro group, intramolecular copper(I)-catalyzed C-N coupling and protection of the nitrogen provided indoline **381**, which was further transformed to substrate **382** for Lewis acid-mediated hydride

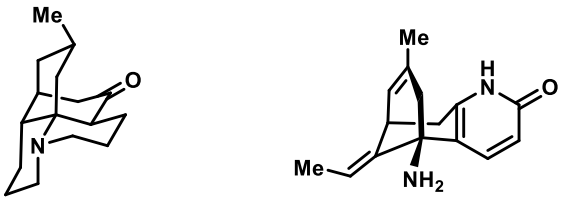
transfer/cyclization reaction. The desired process selectively furnished the desired tetracycle **385** in 80% yield and, after a number of functional group interconversions, allowed for construction of the missing six-membered ring by olefin metathesis. A reductive endgame provided (+)-vallesamidine (**311**).



Scheme 74: Anderson's total synthesis of (+)-vallesamidine (**311**)[148].

1.3 Lyconadin C – a *Lycopodium* Alkaloid

The *Lycopodium* family is one of the largest among alkaloid natural products[149]. More than 500 species of the *Lycopodium* genus are known, comprising the *Lycopodicaceae* and *Huperziaceae* families, but only about 10% of them have been studied yet[150]. These species occur in form of fern-like mosses in moderate or tropical climatic zones and were found to contain a variety of quinolizine-, pyridine- or α-piperidone-type alkaloids. Roughly 200 natural products have been isolated so far, in which unique structural architectures and remarkable biological activities were discovered. In Chinese folk medicine, plants of the *Huperziaceae* and *Lycopodiaceae* families have been used for centuries for the treatment of diseases related to the cardiovascular and neuromuscular systems[150].



(-)-lycopodine (**389**) huperzine A (**390**)

Figure 25: Structures of *Lycopodium* alkaloids lycopodine (**389**) and huperzine A (**390**).

The first known member of the *Lycopodium* alkaloid family, lycopodine (**389**) (*Figure 25*), was isolated from *Lycopodium complanatum* in 1881 by Bödeker[151]. Extensive studies of Manske and Marion[152] in the 1940s included isolation of 35 alkaloids from *Lycopodium* club mosses and marked the beginning of an increasing interest in these compounds that reached its peak between 1986 and 1990. This was due to the isolation of huperzine A (**390**), a lycodine-type alkaloid, and the discovery of its efficient acetylcholinesterase inhibition[153]. A potential application for the treatment of neurodegenerative diseases, *e.g.* Alzheimer's disease, Parkinson's disease or multiple sclerosis, also motivated the investigation of other tricyclic *Lycopodium* alkaloids as possible lead structures for the development of new drugs[154]. In consequence, these compounds were of great scientific interest and a multitude of studies on their isolation, molecular structures, biogenesis and possible synthetic accesses were conducted[150, 155].

Categorization of this abundance of compounds was approached by Ayer and Trifonov[156] on basis of structural similarities. According to this classification, *Lycopodium* alkaloids can be divided into four groups with a prototype alkaloid as lead substance (depicted in *Figure* 26): the lycopodine group, the lycodine group, the fawcettimine group and the

miscellaneous group. The latter comprises alkaloids belonging to none of the other groups and thus, shows a broad variety of structural motifs. Sometimes this group is denoted as the phlegmarine group, referring to the common biosynthetic phlegmarine (**391**)-type precursor.

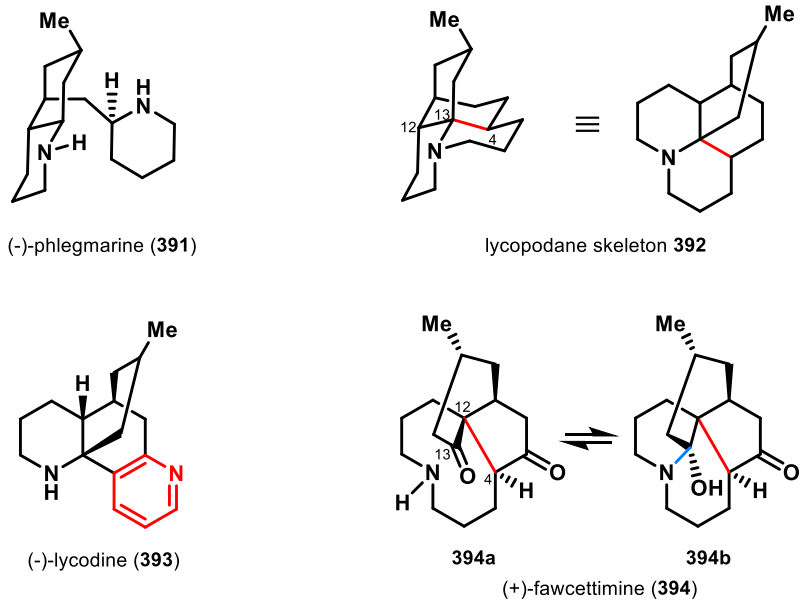


Figure 26: Classification of the *Lycopodium* alkaloids according to Ayer amd Trifonov[156a].

Compounds of the lycopodine group share the tetracyclic $C_{16}N$ lycopodane skeleton **392**, which is exemplified by (-)-lycopodine (**389**) (*Figure 25*). A characteristic feature is the connection between C4 and C13 (highlighted in red in structure **392** in *Figure 26*). The lycodine group members exhibit a dinitrogenous $C_{16}N_2$ skeleton with a fused, sometimes reduced pyridine ring or an α-pyridone (red in structure **393** in *Figure 26*). The lead compound of this group is (-)-lycodine (**393**). The remaining fawcettimine group, represented by its eponymous congener (+)-fawcettimine (**394**), has a five-membered ring constricted by a C4-C12 connection (red in structures **394a/b** in *Figure 26*). A peculiarity among these compounds is an additional structural subdivision with regard to the possible existence of a C13-N bond (blue in structure **394b** in *Figure 26*). This is due to tautomerism of lead compound fawcettimine (**394**) between its keto amine form **394a** and the corresponding carbinolamine form **394b**.

1.3.1 Isolation, Structural Characterization and Biosynthetic Origin of Lyconadin C

Isolation of the structurally unique tetracyclic *Lycopodium* alkaloid lyconadin C (**397**) was described by Kobayashi[157] in 2011. Aqueous alcoholic extraction of samples of the club moss *Lycopodium complanatum* endemic to Nayoro, Hokkaido, and ensuing chromatographic purification yielded three unknown alkaloid substances, which were assigned as lyconadin C (**397**) and F (**398**) and the hemiaminal of lyconadin F **399** (see *Figure 28*).

Figure 27: Diphasiastrum complanatum – photographed by Bernd Haynold, (licenced under *https://creativecommons.org/licenses/by-sa/3.0/)*[157b]

These compounds showed no structural relationship with any of the other known *Lycopodium* alkaloids, except for lyconadin A (**395**) and B (**396**) (see *Figure 28*), and thus, are assigned to the miscellaneous group of alkaloids. The $C_{16}N_2$ *Lycopodium* alkaloid lyconadin C (**397**) was obtained as a colorless amorphous solid corresponding to its TFA salt and in a remarkably low yield of 0.00002% after reverse phase HPLC purification with a MeOH/H_2O/TFA eluent. The very limited amount of material impeded structure elucidation and thus, only a gross structure was proposed by Kobayashi based on the obtained spectral data. By the aid of 2D NMR experiments, the relative stereochemistry could be determined, however, the absolute configuration remained unknown and was proposed to correspond to the configurations of structurally similar lyconadins A, B and F. This assumption was afterwards confirmed by the first asymmetric total synthesis by Fukuyama[158] in 2013. The free base was determined to cause dextrorotation, whereas the corresponding TFA salt is levorotatory[158-159], which accords with the data from the isolation paper.

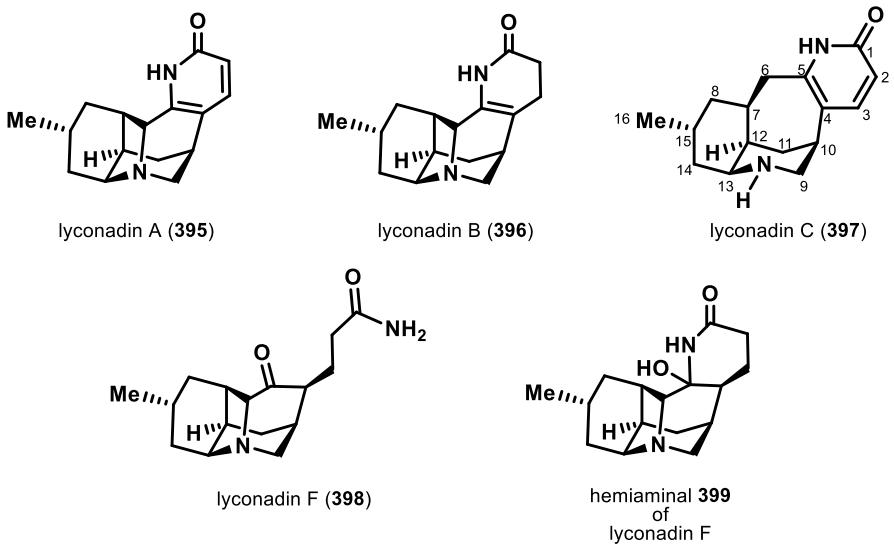
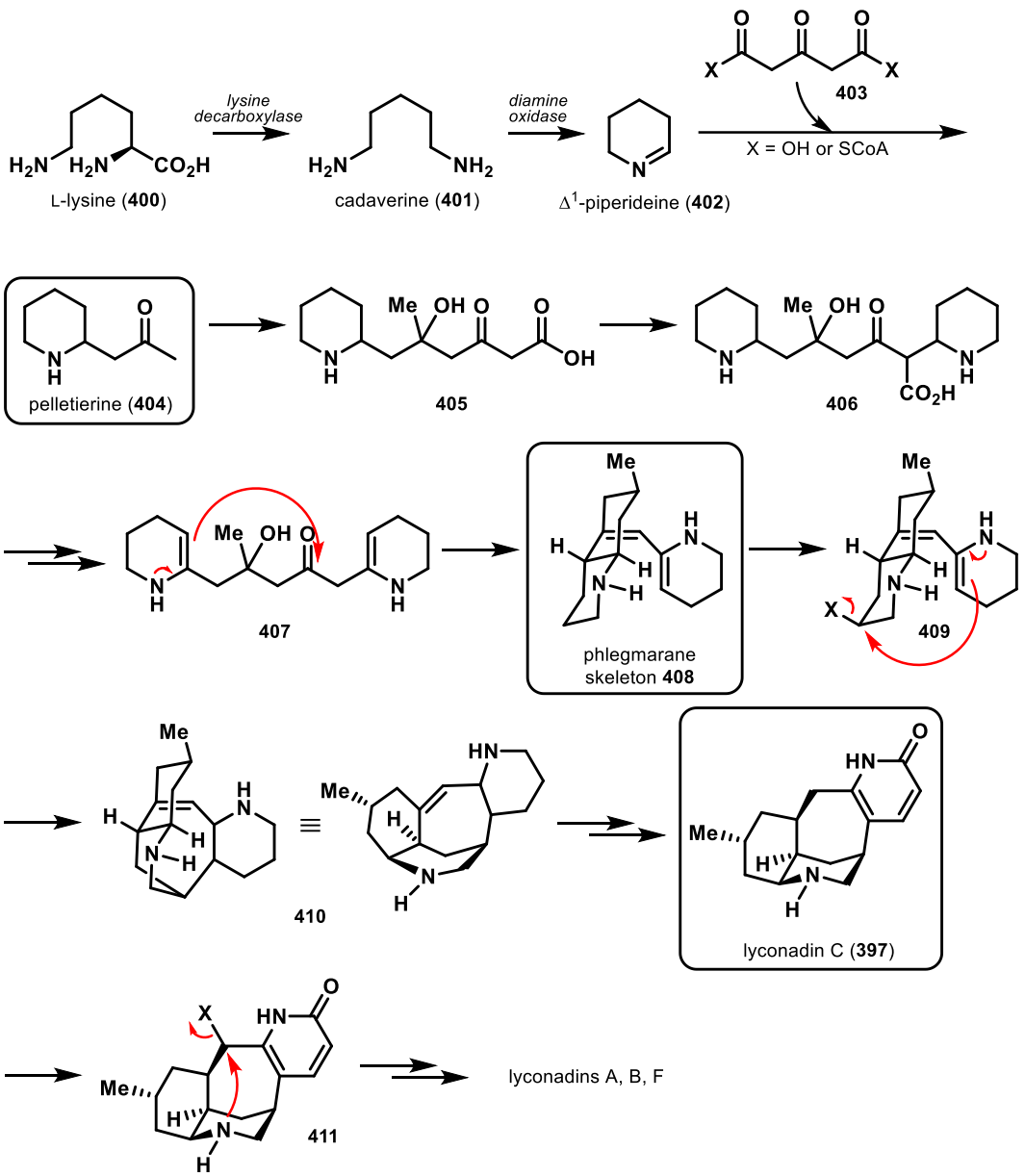


Figure 28: Structures of *Lycopodium* alkaloids isolated from *L. complanatum* by Kobayashi and lyconadin A (**395**) and B (**396**).

Due to recognition of the structural analogies to the other lyconadin alkaloids, a common biosynthetic pathway was hypothesized[157a]. However, investigation of the actual biogenesis could not be accomplished since cultivation of *Lycopodium* club mosses or their plant tissue proved difficult[160]. Although only a few involved enzymes have been identified yet, the knowledge obtained from isotope-labelled feeding studies of *Lycopodium* species by Spenser *et al.*[161] allowed for the formulation of an approximate biogenetic path (shown in *Scheme 75*)[150, 155a, 157a]. In general, all *Lycopodium* alkaloids are supposed to arise from the amino acid L-lysine (**400**). Decarboxylation, presumably catalyzed by lysine decarboxylase, results in the formation of the diamine cadaverine (**401**). Oxidation and condensation *via* intermediate 5-aminopentanal gives Δ^1-piperideine (**402**). The enzyme involved in this transformation is probably diamine oxidase. In the subsequent step, the imine reacts with acetonedicarboxylic acid or its bis-CoA analogue (compound **403**), which originates from two molecules of malonyl-CoA. This enzyme-mediated process includes decarboxylation and furnishes pelletierine (**404**), which is denoted as a key intermediate in the biosynthesis of all *Lycopodium* alkaloids. According to studies of Braekman, two acetate units are incorporated into the molecule prior to the addition of another lysine-derived fragment[162]. Compounds **405** and **406** constitute hypothetical intermediates on the way to cyclization precursor **407**. Intramolecular cyclization by an enamine aldol reaction produces the phlegmarane skeleton **408** and thus, marks a central point for structural diversity of all classes of *Lycopodium* alkaloids.



Scheme 75: Proposed biogenesis of lyconadins A, B, C and F.

In case of the lyconadin alkaloids, functionalization of the piperidine, as indicated by substitutent X in **409**, leads to a further cyclization and installation of the fused tetracyclic core **410**. This structure already corresponds to the lyconadin C skeleton, whereas formation of an additional C6-N bond *via* intermediate **411** would provide related lyconadins A, B and F. Due to a very limited amount of isolated material, the biological and pharmacological activities of lyconadin C (**397**) have not been studied yet, but are supposed to resemble to those of lyconadins A and B. These compounds show anticancer activities[163] and are known to have a favorable effect on the emergence of nerve growth factors[164]. They are thus considered to have a potential application in the treatment of neurodegenerative diseases[149]. Not only a prospective pharmaceutical application but

also the synthetic challenge in view of its structural complexity rendered the lyconadin alkaloids an interesting target for total synthesis. Structurally, the tetracyclic alkaloid **397** is characterized by a *cis*-decahydroquinoline core and an α-pyridione (rings A/B and D, highlighted in blue in *Figure 29*), both connected *via* a fused cycloheptene ring (ring C, red in *Figure 29*). Sophisticated 2D NMR investigation revealed the cyclohexane and the piperidine to both exist in chair conformation. The methyl group (C16) was assigned to the equatorial position. Overall five stereogenic centers (green in *Figure 29*) and the bridging annulation implicate the unique, curved molecular shape of lyconadin C.

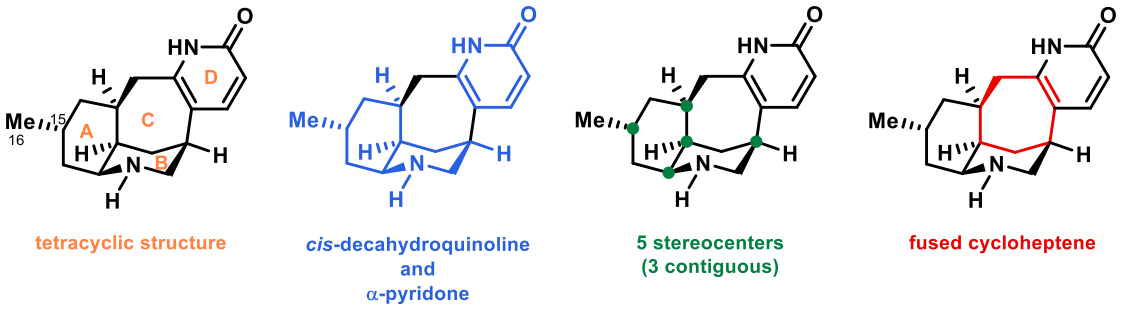
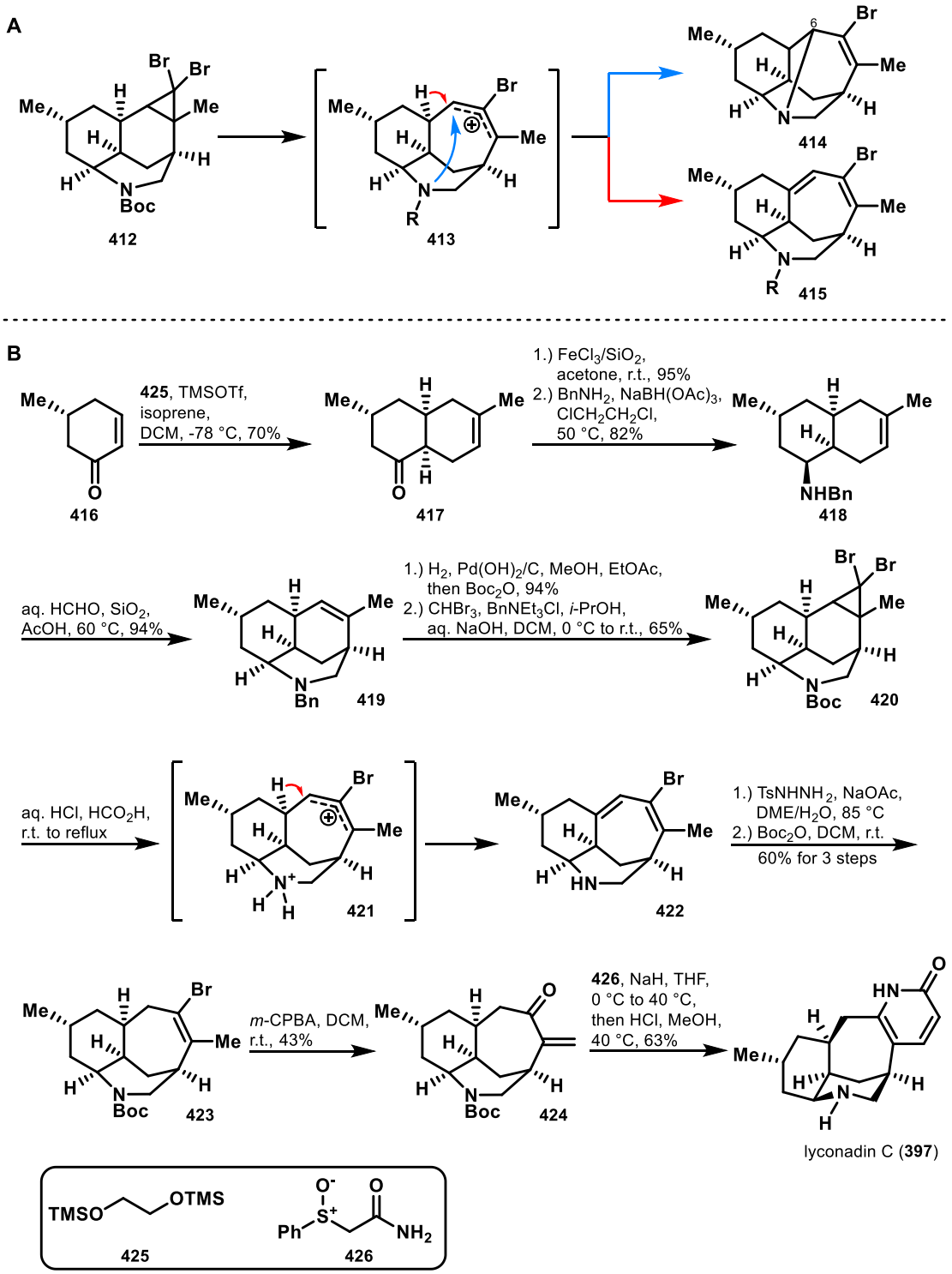


Figure 29: Structural features of lyconadin C.

1.3.2 Previous Total Syntheses of Lyconadin C

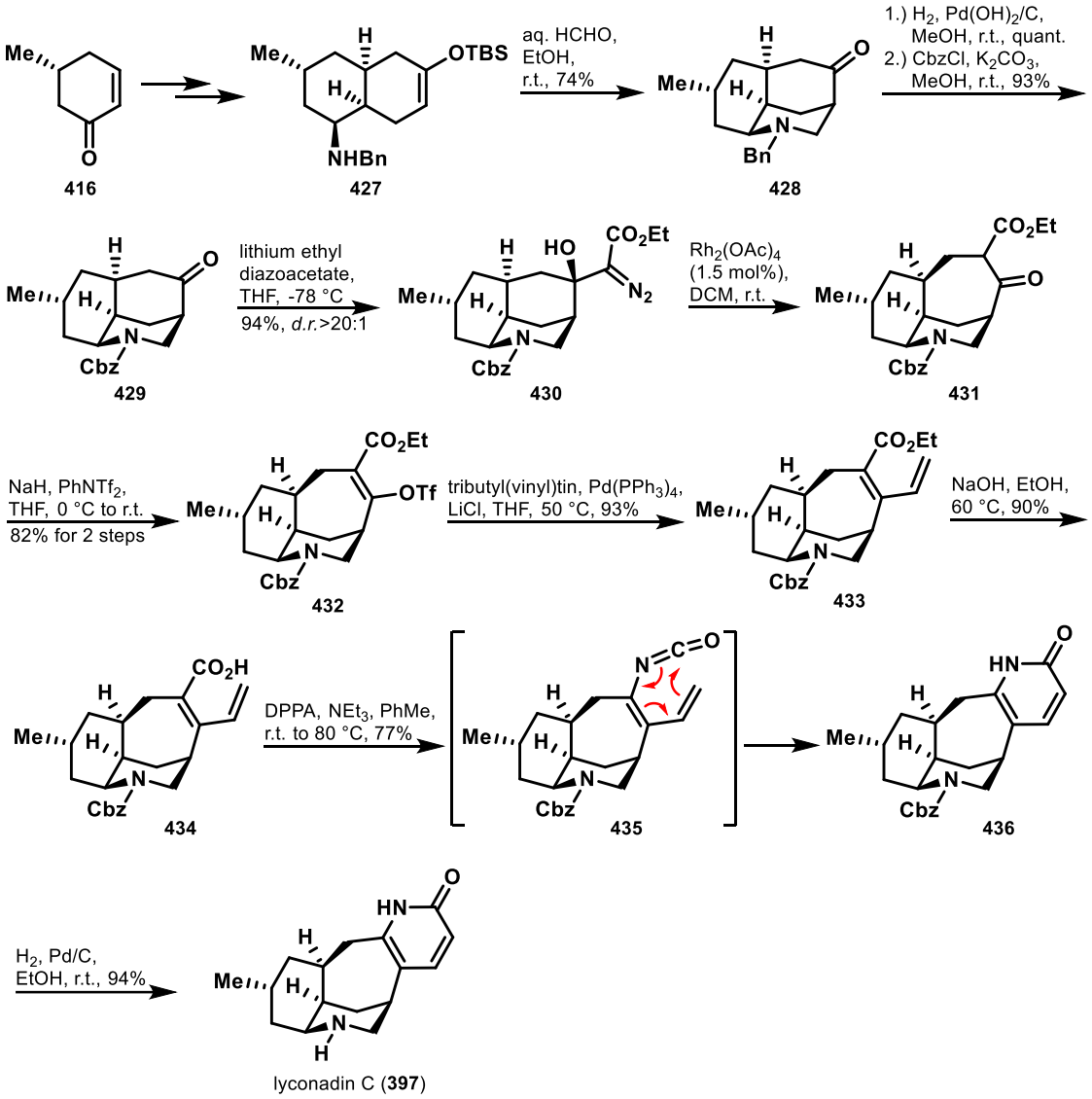
Already two years after its isolation, the first total synthesis of lyconadin C (**397**) in asymmetric form was published by Fukuyama *et al.*[158]. Application of an adjusted *cis*-decalin ring expansion strategy[165] (depicted in *Scheme 76* **A**) allowed for a collective and rather short synthetic access to lyconadins A (**395**), B (**396**) and C (**397**). Electrocyclic ring opening of a dibromocyclopropane **412** generated an intermediate allylic cation **413**, which could be either transformed to the tri- or the tetracyclic product (**415** and **414**). The tetracyclic product **414** with an additional C6-N bond corresponds to the core structure found in lyconadins A and B, while lyconadin C lacks this connection. By variation of the nitrogen protective group within the ring expansion step, selective transformation to the desired framework was successfully accomplished. The enantioselective synthesis (see *Scheme 76* **B**) started with construction of the *cis*-decalin system **417** by intermolecular Diels-Alder reaction of readily available (*R*)-5-methyl-cyclohex-2-en-1-one (**416**) and isoprene. Reductive amination was followed by an *aza*-Prins reaction and furnished tricycle **419**. Dibromocyclopropanation of its Boc-protected analogue gave the substrate **420** for the ring expansion, which occurred ensuing to *in situ* Boc-deprotection and quaternization upon treatment with formic acid and hydrochloric acid. This efficiently prevented nucleophilic

attack of the nitrogen to the intermediate carbon cation in **421** and elimination of a proton was preferred and generated diene system **422**. Diimide reduction of the less hindered olefin and final installation of the α-pyridone provided the desired target molecule lyconadin C (**397**) in an overall yield of 5.1%.



Scheme 76: **A** *Cis*-decalin ring expansion strategy and possible interceptions of the allylic cation; **B** Total synthesis of lyconadin C (**397**) by Fukuyama[158].

In the same year, Waters[159] reported a 12-step enantioselective total synthesis of lyconadin C *via* a Curtius rearrangement/6π-electrocyclization cascade (shown in *Scheme* 77). Analogously to Fukuyama's synthesis (see *Scheme 76* **B**), *cis*-decalin system **427** was synthesized by an intermolecular Diels-Alder reaction and subsequent reductive amination. Mannich-type cyclization afforded tricyclic compound **428**.

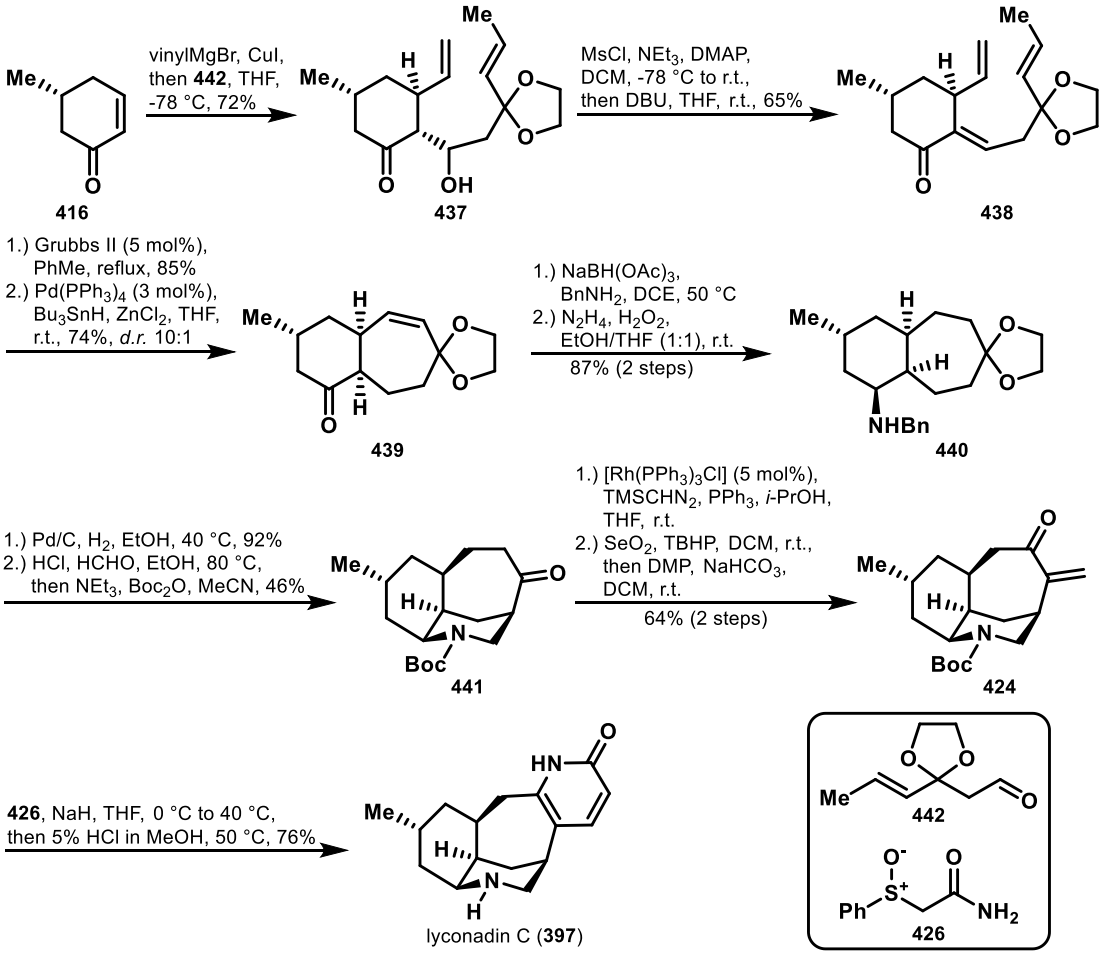


Scheme 77: Total synthesis of lyconadin C (**397**) by Waters[159].

The amine was converted to the carbamate **429** and reaction of the carbonyl with lithiated ethyl diazoacetate delivered the precursor **430** for rhodium(II)-catalyzed Tiffeneau-Demjanov ring expansion to β-keto ester **431**. A sequence of enolate triflation, palladium(0)-catalyzed Stille cross coupling and base-mediated saponification of the ethyl ester produced the precursor **434** for the planned annulation of the α-pyridone moiety. Curtius rearrangement of an intermediate acyl azide to the highly reactive dienyl

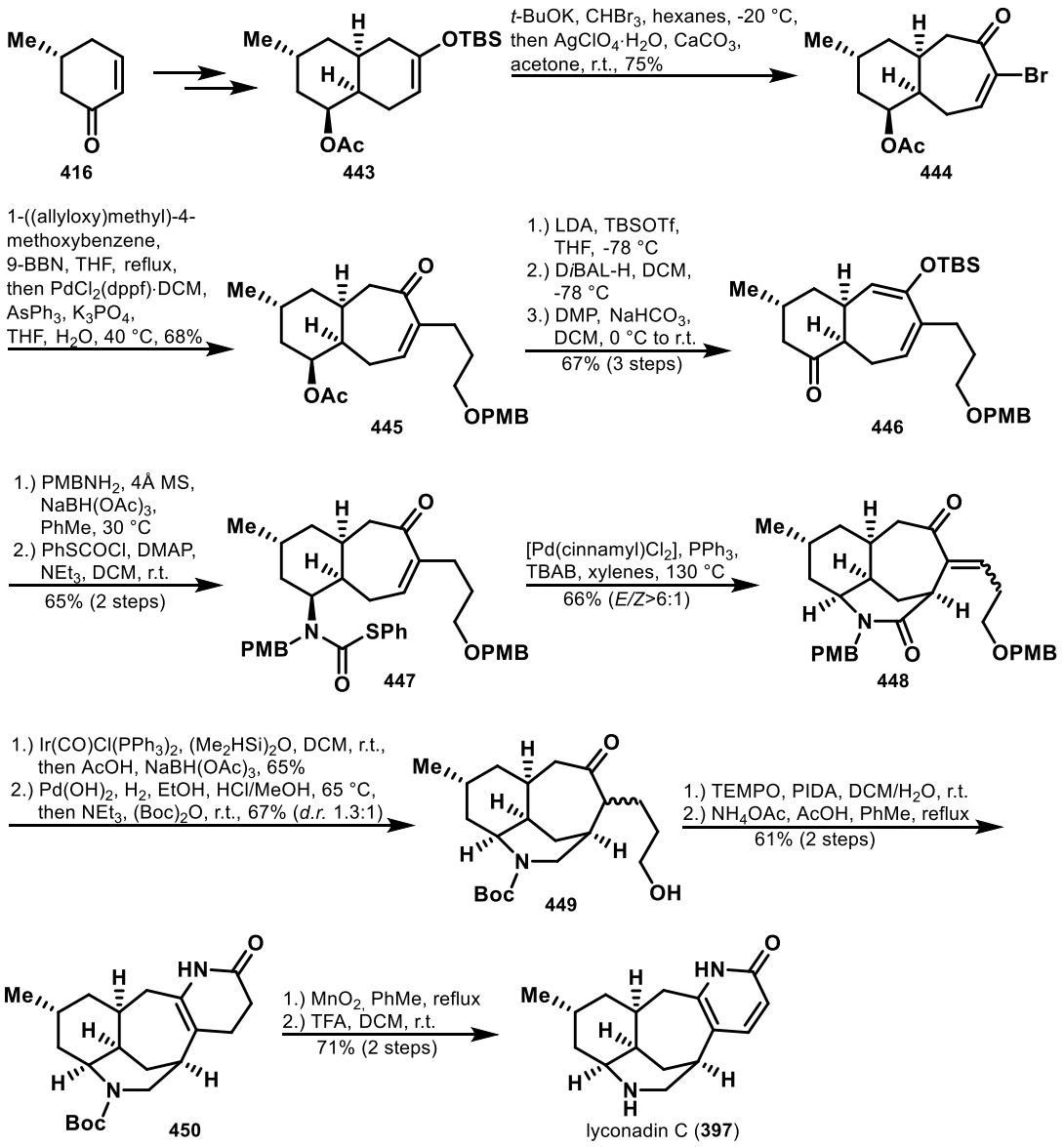
isocyanate **435** was followed by spontaneous 6π-electrocyclization to the desired fused pyridone **436**. The natural product **397** was obtained by reductive Cbz-deprotection.

A different strategy for the construction of the 6,7-fused ring system was chosen by Dai[166] in his total synthesis of lyconadin C in 2014 (depicted in *Scheme 78*). Starting from known enone **416**, a tandem 1,4-addition/α-functionalization sequence and dehydration gave compound **437**, which was cyclized to the 6,7-fused bicycle by ring-closing metathesis of **438**. 1,4-reduction preferentially furnished *cis*-fused **439** in a diastereomeric ratio of 10:1. The ketone was converted to the secondary amine by reductive amination and subsequent diimine reduction of the olefin yielded **440**. Reductive cleavage of the *N*-benzyl group delivered the primary amine which was reacted in a ketal removal/Mannich reaction sequence. Fused tricyclic compound **441** was obtained from Boc-protection of the intermediate secondary amine. Methylenation and allylic oxidation finally provided enone **424**, which was Fukuyama's late-stage intermediate and substrate for the α-pyridone annulation.



Scheme 78: Total synthesis of lyconadin C (**397**) by Dai[166].

Lately, in 2020, Yang[167] and co-workers published a divergent synthetic strategy using a palladium-catalyzed Heck-type coupling, which allowed for collective syntheses of seven *Lycopodium* alkaloids including lyconadin C (**397**) (see *Scheme 79*).



Scheme 79: Total synthesis of lyconadin C (**397**) by Yang[167].

Synthesis of the bicyclic Heck reaction precursor **447** was accomplished by an intermolecular Diels-Alder sequence similar to the approaches shown above. Ring enlargement to generate the 6,7-ring system was realized by ring opening of a dibromocyclopropane to α-bromo enone **444**. Suzuki-Miyaura coupling was followed by a five-step sequence to install the *S*-phenyl thiocarbamate and furnished the precursor **447** for the intramolecular Heck-type reaction. Palladium(0)-catalyzed ring closure produced the common tricyclic core of the target natural products and allowed for divergent

syntheses of the latter. In case of the total synthesis of lyconadin C (**397**), iridium(I)-mediated amide reduction was followed by deprotection of the obtained amine and the primary alcohol functionality and subsequent formation of the carbamate **449**. Annulation of the α-pyridone succeeded in three steps comprising oxidation of the alcohol to the carboxylic acid, cyclocondensation with ammonium acetate under acidic conditions and further oxidation of the intermediate dihydropyridone **450** by manganese(IV) oxide. Boc-deprotection upon treatment with trifluoroacetic acid finally delivered the natural product lyconadin C (**397**) in a total yield of 1.7% over 17 steps.

1.4 [3+2]-Cycloaddition Reactions of Isomünchnone and Thioisomünchnone Dipoles

The [3+2]-cycloaddition of 1,3-dipoles with suitable dipolarophiles constitutes a valuable tool in organic synthesis for the construction of complex polycyclic systems, especially with heterocyclic moieties[168]. The fundamental concept behind these reactions was described by Huisgen[169] in the 1960s. Since then, a variety of 1,3-dipoles has been reported to undergo cycloaddition reactions with a dipolarophile, usually with high regio- and stereoselectivities[170].

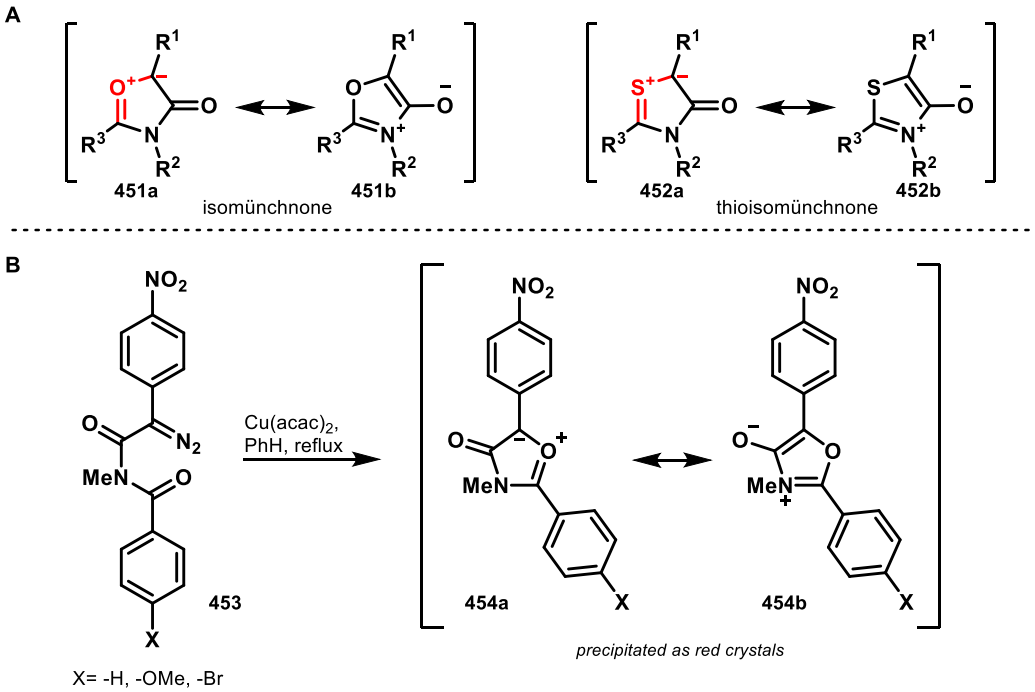
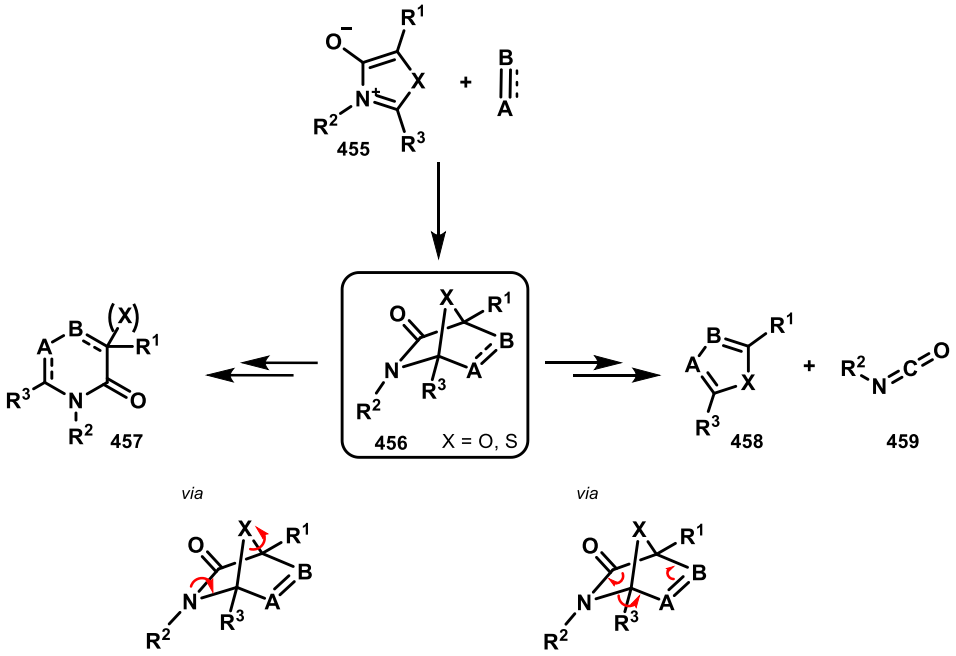


Figure 30: **A** Possible resonance structures of mesoionic isomünchnones and thioisomünchnones; **B** Isomünchnone derivative by Ibata and Hamaguchi: dipolar aromatic resonance structure causes high stability[171].

Not only simple 1,3-dipoles but also masked analogues were applied in such reactions. These compounds are assigned as mesoionic species and thus, generally consist of

five-membered heterocyclic rings that are described by several resonance hybrid structures (see *Figure 30* **A** for exemplary isomünchnones **451** and thioiso-münchnones **452**). The isomünchnone dipole corresponds to a cyclic carbonyl ylide dipole (highlighted in red in structure **451a**) stabilized by the adjacent nitrogen atom[172]. A highly stable derivative of this substance class with additional aromatic substituents as stabilizing moieties was prepared and isolated by Ibata and Hamaguchi[171] in 1974 (see *Figure 30* **B**). Application of these dipoles in a [3+2]-cycloaddition provides potential access to different heterocyclic structure motifs from the same cycloadduct. As outlined in *Scheme* 80, α-pyridones or lactams of structure **457** are obtained by cleavage of the *N,O*-acetal/oxygen-bridged motif in the intermediate cycloadduct **456**, while furans **458** are accessible *via* cycloreversion and concomitant extrusion of isocyanic acid or the respective isocyanate **459**[173]. In analogy, masked thiocarbonyl ylides in form of thioisomünchnone dipoles provide access to six-membered ring α-pyridones or lactams by desulfurization of the primary cycloadduct[174]. Five-membered heterocycles in form of thiophenes are produced by a [4+2]-cycloreversion process. The latter readily occurs if R^1 is an aromatic substituent[175], whereas formation of a pyridone is rather favorized upon reaction with acetylenic dipolarophiles and in R^2,R^3-ring annulated systems[172, 174, 176].



Scheme 80: Potential transformations of the cycloadduct obtained from the [3+2]-cycloaddition of an isomünchnone dipole and a dipolarophile AB.

1.4.1 Selectivities in the [3+2]-Cycloaddition Reactions of Mesoionic Compounds

In general, the concerted reaction proceeds under kinetic control and preferentially proceeds *via* the energetically slightly lower *exo*-transition states[177] (see *Figure 31* for possible transition states and products). In contrast to the related [4+2]-Diels Alder cycloadditions, no equilibration processes were observed in the course of 1,3-dipolar cycloadditions of isomünchnone dipoles and thus, an irreversible process is assumed.

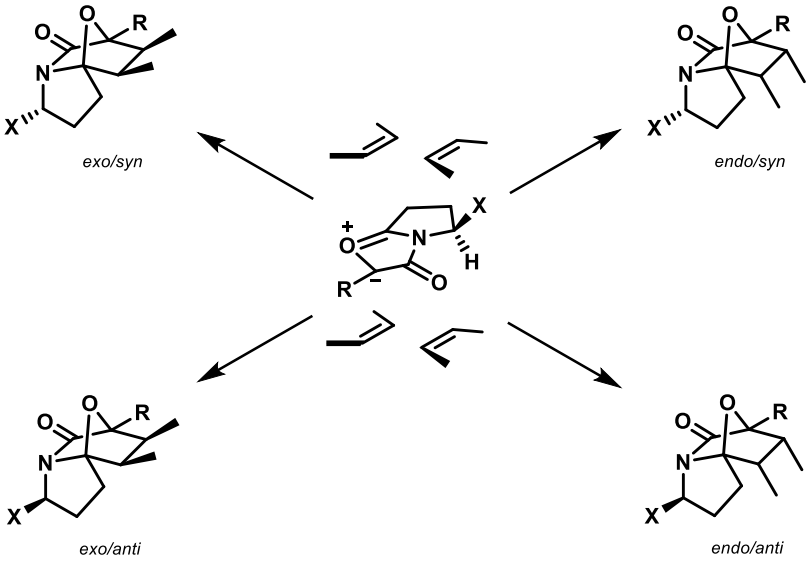


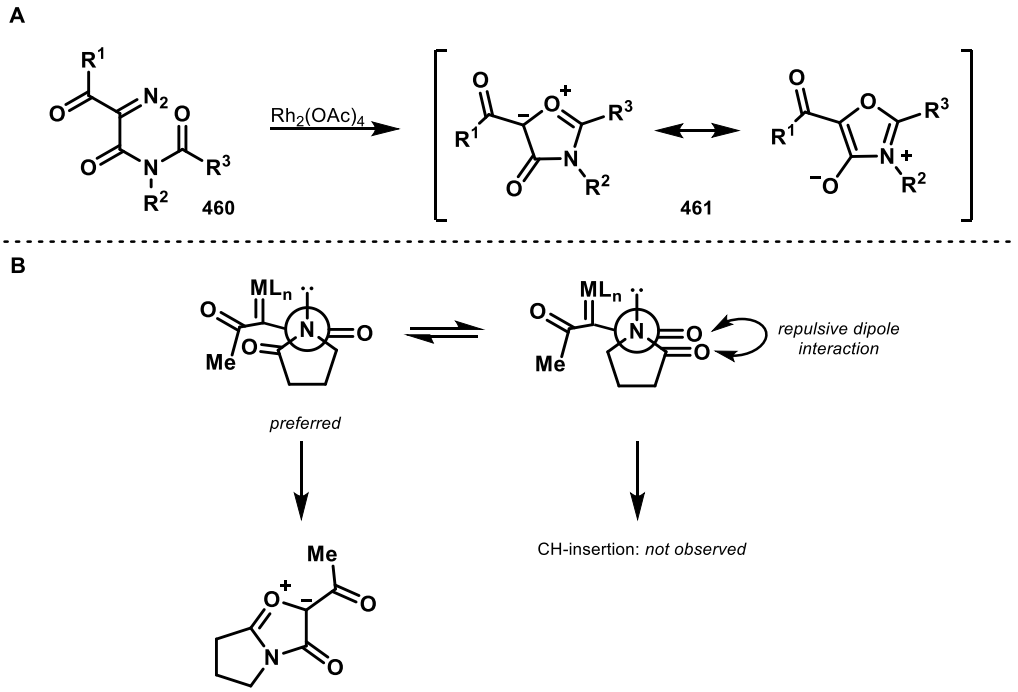
Figure 31: Possible transition states and products from a [3+2] cycloaddition of an isomünchnone dipole with a symmetric dipolarophile.

The inherent e*xo*-selectivity in intermolecular [3+2]-cycloadditions is enhanced by substituents in any position of the dipole and furthermore, significant π-facial selectivity can be induced by sterically relevant substituents at adjacent stereocenters[177], *e.g.* substituent X in the example in *Figure 31*. The regioselectivity observed for the cycloaddition reaction to unsymmetrical dipolarophiles was rationalized by frontier molecular orbital theory[178], *i.e.* consideration of the stabilization in the transition states by maximized overlap of the molecular orbitals. Depending on the subsitutents, which influence the energies of 1,3-dipole and dipolarophile frontier orbitals and thus their relative disposition, the reaction is either guided by interaction of the dipole HOMO with the dipolarophile LUMO or the dipole reacts *via* its LUMO with the dipolarophile HOMO[179]. In case of the frequently used acetyl or ester substitution at the 1,3-dipole, energetically lowered molecular orbitals are the result of the electron-withdrawing properties of the additional functionalities. Concomitant affection of the relative orbital coefficients at the reactive centers of the dipole is negligible[177]. Intramolecular versions of the

[3+2]-cycloaddition of mesoionic isomünchnones and thioisomünchnones have been extensively investigated by Padwa and co-workers[180] and were, in general, found to exhibit complete stereospecifity leading to the *endo*-cycloadducts. These observations proved reasonable with regard to the lower strain energies compared to the energies of the *exo*-isomers.

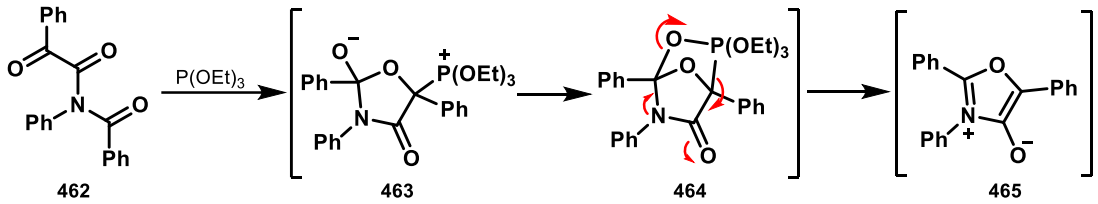
1.4.2 Methods for the Preparation of Isomünchnones and Thioisomünchnones

Different strategies for the preparation of isomünchnone and thioisomünchnone dipoles are available in the literature[170]. All methods comprise efficient preparation from amide or thioamide starting materials. In addition to the copper-mediated conversion of a diazo precursor, as reported by Ibata and Hamaguchi[171] (see *Figure 30* **B**), rhodium(II)-mediated transformation of diazo imide precursors **460** to isomünchnone dipoles **461** was described by Maier[181] and Padwa[182] (see *Scheme 81* **A**). Conformational preferences of the intermediate rhodium carbene species originate from repulsive dipole interactions, as shown in *Scheme 81* **B**, and inevitably entail formation of the mesoionic carbonyl ylide instead of competitive CH-insertion. Accessibility of the diazo precursor compounds was established by use of aceto- or malonylacylation of the respective amides and subsequent diazo-transfer[170].



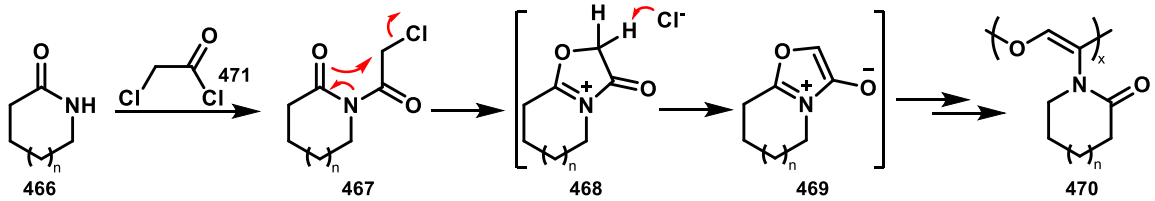
Scheme 81: **A** Rhodium(II)-mediated generations of isomünchnone dipoles from diazo imides, as reported by Maier[181] and Padwa[182]; **B** Selective 1,3-dipole formation due to rhodium carbenoid conformation.

Dipole generation by reaction of an imide with triethyl phosphite was reported by Freeman[183] and is outlined in *Scheme 82*. Nucleophilic attack of the phosphite at the reactive ketone in **462** induced cyclization and upon elimination of triethyl phosphate, an isomünchnone dipole **465** was released.



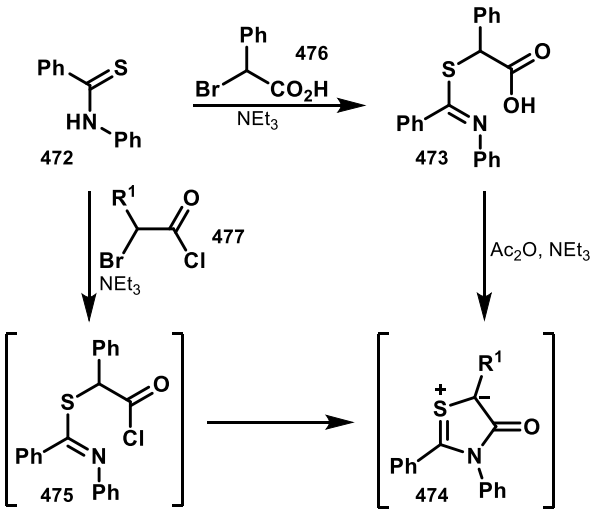
Scheme 82: Formation of an isomünchnone by reaction of an imide with triethyl phosphite, as reported by Freeman[183].

A different pathway of isomünchnone dipole formation was observed by Mathias *et al.*[184] in the course of polymerization of 1-(2-chloroacetyl)lactams **467** to poly(oxyvinylene)-lactams **470** (*Scheme 83*).



Scheme 83: Generation of isomünchnone dipoles by reaction of amides with chloroacetylchloride and polymerization to poly(oxyvinylene)lactams.

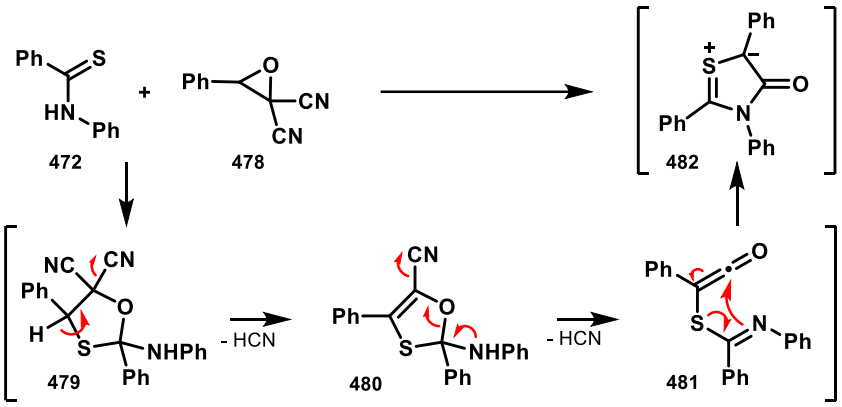
1-(2-Chloroacetyl)lactams **467** were prepared from the corresponding lactams **466** by reaction with chloroacetyl chloride (**471**) and further transformed into an intermediate 1,3-dipole species **469** at elevated temperatures. Polymerization was proposed to occurr by reaction of **469** with the transient species **468**[184b].



Scheme 84: Stepwise formation of an isomünchnone dipole from a thioamide *via* an intermediate thioimidate.

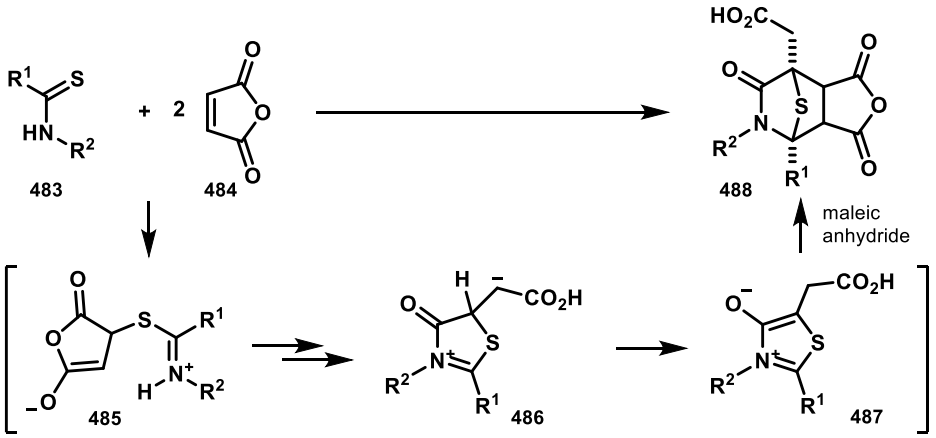
Besides, numerous similar strategies have been applied for the preparation of isomeric thioisomünchnones from thioamides. Potts *et al.* described the conversion of thioamides to the corresponding thioimidate species with either an α-halo acetic acid **476**[172] or a 1,2-dielectrophile in form of an α-haloacetyl chloride **477**[175](*Scheme 84*). In case of carboxylic acid thioimidate **473**, further conversion to the thioisomünchnone was achieved by treatment with acetic anhydride and triethylamine, whereas the transient thioimidate compound **475** immediately cyclized to **474** in the presence of triethylamine.

Alternative reaction of thioamide **472** with *gem*-dicyano epoxide **478** afforded thioisomünchnone **482**, as displayed in *Scheme 85*. Proposed epoxide opening and concomitant cyclization to intermediate **479** preceded double elimination of hydrogen cyanide[185]. Subsequent cyclization of ketene species **481** produced the mesoionic compound **482**.



Scheme 85: Generation of a thioisomünchnone dipole by reaction of a thioamide and a *gem*-dicyano epoxide.

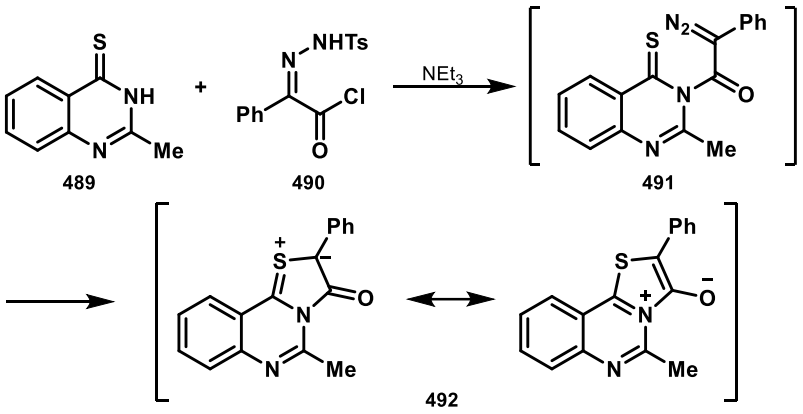
Reaction of acetic acid-substituted thioisomünchnone derivatives **487** was reported by Takido and Itabashi upon treatment of thioamides with an excess of maleic anhydride[186].



Scheme 86: In situ generation of a thioisomünchnone dipole from a thioamide and maleic anhydride and its [3+2]-cycloaddition.

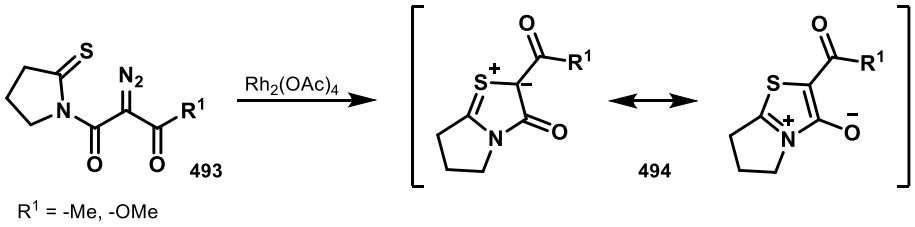
The proposed mechanistic pathway for the one-step synthesis of trione **488** is depicted in *Scheme* 86. The intermediate thioisomünchnone emerged from initial conjugate addition of a thioamide **483** to the conjugated system of maleic anhydride (**484**) and ensuing rearrangement to the dihydrothiazolium species **486**. Further [3+2]-cycloaddition with an excess of the maleic anhydride dipolarophile provided cycloadduct **488**.

The generation of mesoionic compounds *via* an intermediate carbenoid by use of Zimmerman's reagent (**490**)[187] was reported by Potts[188]. The proposed reaction path is shown in *Scheme 87*.



Scheme 87: Use of Zimmerman's reagent (**490**) for the generation of a thioisomünchnone dipole.

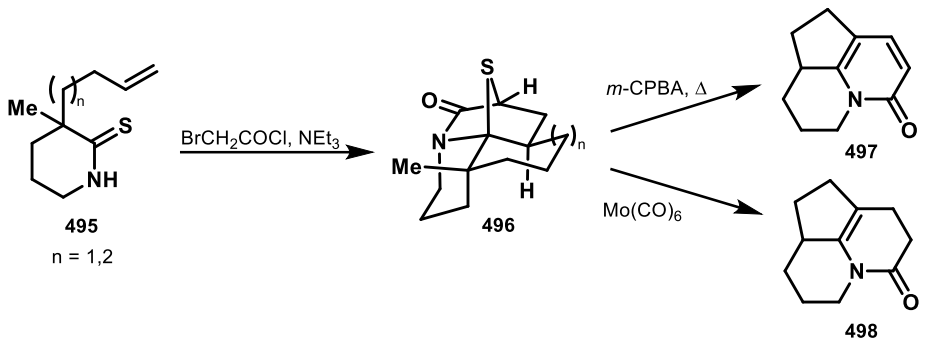
Initial *N*-acylation of a thioamide produced a diazo amide **491**, which delivered a reactive carbene in the further course of the reaction. This latter transient species immediately underwent cyclization with the thiocarbonyl moiety - a process that is in analogy to the previously described rhodium(II)-mediated reaction of diazo imides (see *Scheme* 81). Accordingly, effective generation of thioisomünchnone dipoles was also documented by metal-catalyzed conversion of diazo precursors **493**[189] (*Scheme 88*).



Scheme 88: Formation of thioisomünchnone dipoles from diazo thioamide precursors by Rh(II) catalysis.

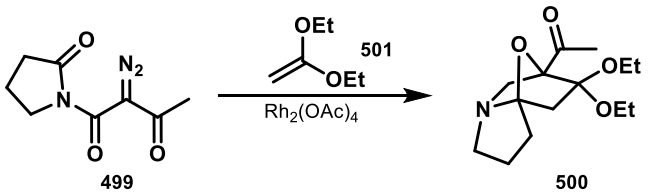
1.4.3 Scope and Limitations

Bimolecular cycloaddition reactions of thioisomünchnone dipoles to electron-deficient dipolarophiles, *e.g.* maleic anhydride, dimethyl maleate and *N*-phenylmaleimide, were reported on several occasions[180a]. Initially, substitution at the dipole was limited to stabilizing aromatic moieties and cycloaddition reactions with electron-rich dipolarophiles or simple olefins could not be accomplished[172, 175, 190]. Over the course of time, further investigations on transient, alkyl-substituted thioisomünchnone derivatives and intramolecular versions of the [3+2]-cycloadditions were conducted. Padwa reported intramolecular *endo*-cycloaddition of a tethered olefin to an *in situ* generated thioisomünchnone dipole by reaction of a thiolactam **495** with bromoacetyl chloride in the presence of triethylamine[180a] (*Scheme 89*). The obtained cycloadduct **496** was further modified by desulfurization: Oxidative treatment with *m*-chloroperbenzoic acid[191] furnished α-pyridone **497**, whereas molybdenum hexacarbonyl[192] reduced the sulfide to the corresponding enamide **498**.



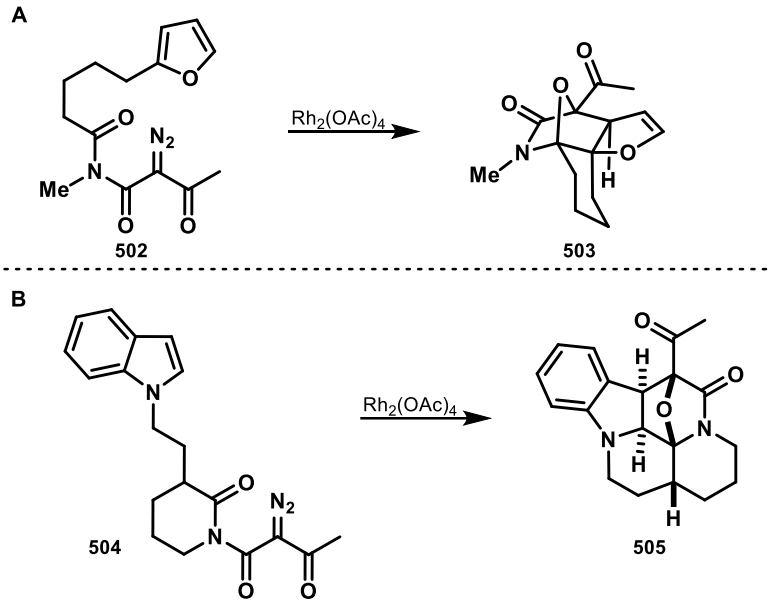
Scheme 89: Intramolecular [3+2]-cycloaddition for generation of fused heterocyclic systems.

The same group accomplished and reported the first example of an intermolecular [3+2]-cycloaddition of an isomünchnone dipole with an electron-rich dipolarophile[193] (*Scheme 90*). Diazo imide precursor **499** was treated with diethyl ketene acetal (**501**) in the presence of rhodium(II) and smoothly underwent the desired cycloaddition reaction.



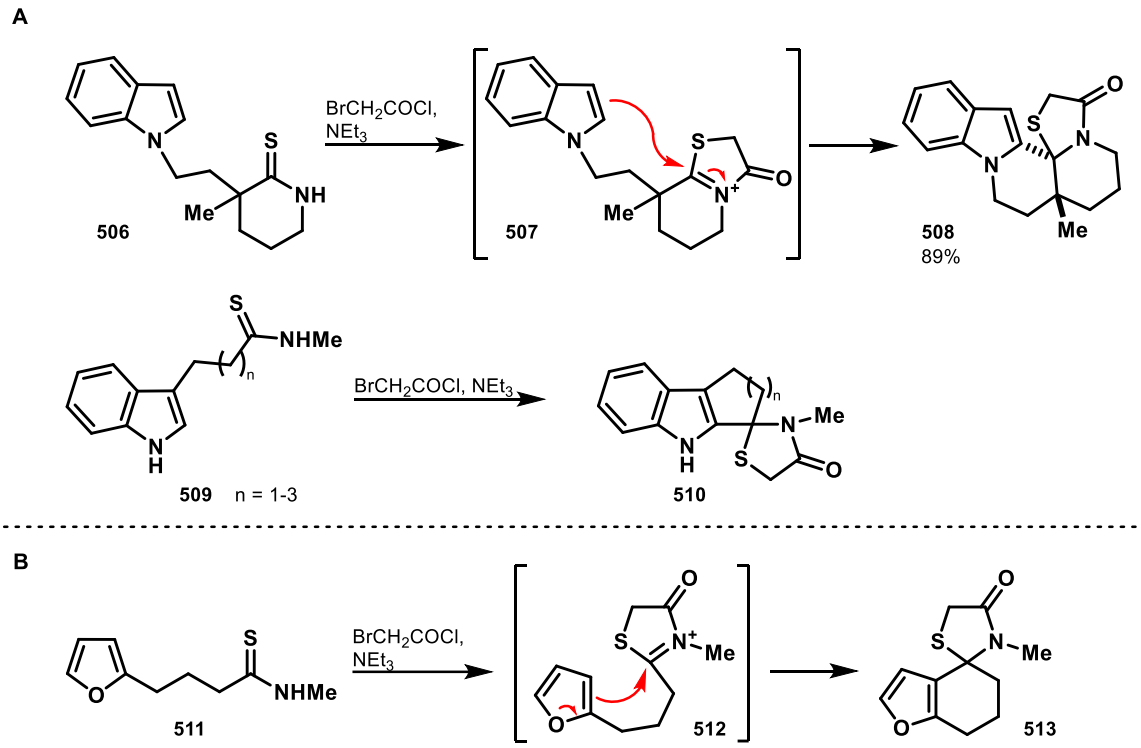
Scheme 90: First example of a bimolecular [3+2]-cycloaddition of an isomünchnone dipole to an electron-rich dipolarophile[193].

Furthermore, successful intramolecular [3+2]-cycloadditions of transient isomünchnone dipoles to heteroaromatic π-bonds was described[180b, 194]. Examples are shown in *Scheme* 91 and illustrate the remarkable potential of this transformation regarding the generation of complex polyheterocyclic molecular structures in a single step.



Scheme 91: Examples for the [3+2]-cycloaddition of isomünchnone dipoles to heteroaromatic π-bonds: **A** Intramolecular addition to a furan π-bond; **B** Intramolecular addition to an indole π-bond.

Similar efforts were made on the analogous reaction of thioisomünchnone dipoles with heteroaromatic olefins as dipolarophiles but proved unsuccessful[180a]. Hypothesized formation of highly reactive *N*-acyl iminium ion intermediates (*e.g.* **507** and **512** in *Scheme* 92) in the course of stepwise thioisomünchnone formation with bromoacetyl chloride would allow for an alternative reaction pathway. Due to the nucleophilic character of the heteroaromatic dipolarophile, *e.g.* an indolyl π-bond (*Scheme 92* **A**) or a furan (*Scheme 92* **B**), premature cyclization was suspected to effectively prevent dipole formation and thus, the expected cycloadducts were formed in neither case. Instead, functionalization of the heterocycle in either 2- or 3-position by intramolecular nucleophilic attack to the transient cationic species was observed.



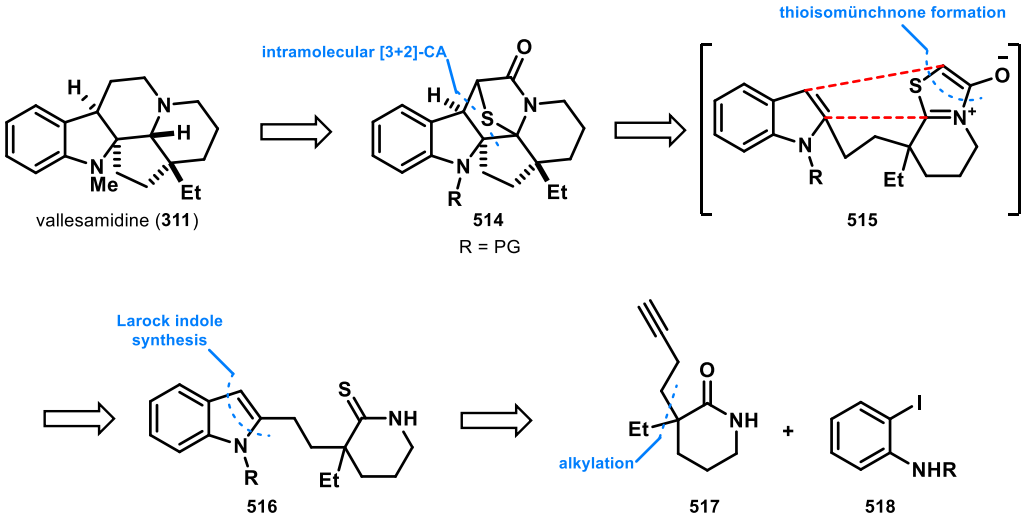
Scheme 92: Prevention of thioisomünchnone formation by nucleophilic attack of electron-rich heteroaromatic dipolarophiles to the intermediate *N*-acyl iminium ions.

2. Results and Discussion

2.1 An Approach Toward the Synthesis of Vallesamidine

2.1.1 Retrosynthetic Analysis of Vallesamidine

The retrosynthetic considerations on the pentacyclic vallesamidine skeleton included application of an intramolecular [3+2]-cycloaddition reaction. The fused 2,2,3-trialkylindoline motif in **311** might be accessible *via* cycloaddition reaction of a mesoionic moiety, functioning as a 1,3-dipole, with the indolyl π-bond as dipolarophile. Since a competing nucleophilic addition was reported to occur for electron-rich heteroaromatic dipolarophiles[180a] (see chapter 1.4.3), electron-withdrawing protective groups on the indole nitrogen were expected to prevent this undesired process and thus, formation of the dipole and ensuing [3+2]-cyclopaddition might be favored. As depicted in *Scheme 93*, the planned racemic approach would commence with methylation of the indole nitrogen and several functional group interconversions, including lactam reduction and desulfurization, to obtain the target compound vallesamidine (**311**) from cycloadduct **514**.



Scheme 93: Retrosynthetic analysis of vallesamidine (**311**).

The mentioned intramolecular [3+2]-cycloaddition should furnish **514** in a single step from thiolactam **516** and a suitable C2-building block, *e.g.* bromoacetyl chloride. An *in situ* generated thioisomünchnone 1,3-dipole might undergo the desired cycloaddition reaction with the heteroaromatic dipolarophile and concurrently produce the unique carbon skeleton of vallesamidine (**311**). The precursor **516** for this key transformation should originate from two readily available building blocks lactam **517** and aniline **518** by

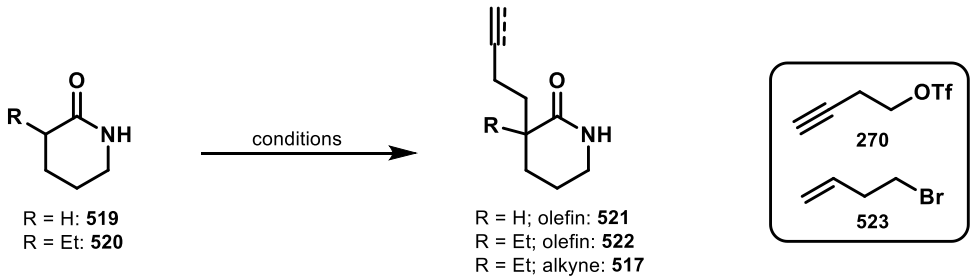
palladium(0)-catalyzed Larock indole synthesis[195]. Lactam **517** is a literature-known compound and obtained by alkylation from commercial 2-piperidone. A successful implementation of this synthetic strategy would allow for a remarkably short access to the pentacyclic natural product vallesamidine (**311**). In addition, potential enantioselective lactam alkylation[196] would allow for an asymmetric version of the total synthesis since this first stereogenic center would serve as a chiral relay throughout the whole synthetic sequence.

2.1.2 Synthesis of a Suitably *N*-Protected Cycloaddition Precursor

Synthesis of the substrate for the planned indole formation was attempted *via* different strategies. Since alkylation with homopropargyl triflate **270** would allow for short and straightforward access to the desired building block **517**, initial experiments focused on this method instead of a literature-known 4-step sequence[197] with 4-bromo-1-butene (**523**). *C*-alkylation of commercial 2-piperidone (**519**) with a slight excess of iodoethane was carried out according to a procedure of Stoltz[196] and provided desired 3-ethylpiperidin-2-one (**520**) in very good yield. Application of formerly optimized alkylation conditions with triflate **270** and LiTMP/DMPU (see chapter 2.3.2) produced the desired compound **517** only in trace amounts and predominantly led to reisolation of unreacted starting material (*Table 16*, entry 1). Since *n*-butyllithium seemed to be the base of choice for lactam alkylation[196-197], the reaction was repeated in analogy to the preceding ethylation of **519**. The desired compound **517** could be isolated from the reaction in 20% yield, however, incomplete conversion after 24 hours led to concomitant reisolation of starting material (entry 2). Increased amounts of base and alkylating agent improved the conversion, but problems during purification of compound **517** only allowed for yields around 30% (entry 3). An altogether high polarity of both starting lactam **520** and product **517** resulted in a strongly decelerated elution during column chromatography on silica gel with 100% ethyl acetate eluent. Alternative use of a dichloromethane/methanol eluent led to no significant improvement and, moreover, the separation of minor impurities was not feasible with this system. Attempted recrystallization from different solvents, *e.g.* toluene, EA, hexanes or mixtures of these, also proved unsatisfactory. Hence, further optimization of the alkylation process was approached aiming for a cleaner reaction and complete conversion. Since the combination of *n*-butyllithium and DMPU did not lead to

the expected improvement (entry 4), the alkylation strategy was changed and the alternative literature-known sequence of Padwa *et al.*[197] was applied. Herein, the desired alkyne functionality was introduced *via* bromination and double elimination from the terminal olefin.

Table 16: C-alkylation of lactams **519**/**520**.



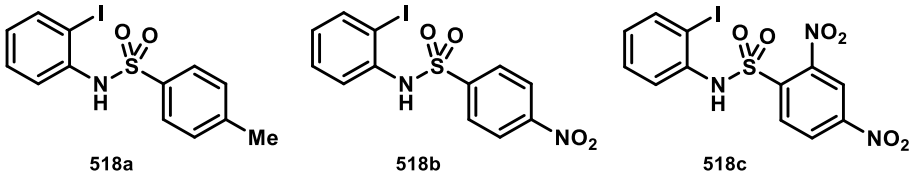
entry	substrate	conditions	result
1	**520**	LiTMP (2.30 eq.), DMPU (2.60 eq.), **270** (2.00 eq.), THF, -78 °C to r.t.	traces of **517** + recovered **520**
2	**520**	*n*-BuLi (2.01 eq.), **270** (1.50 eq.), THF, -78 °C to r.t.	20% **517** + recovered **520**
3	**520**	*n*-BuLi (2.10 eq.), **270** (2.00 eq.), THF, -78 °C to r.t.	30% (isolated) **517** + 35% **520**
4	**520**	*n*-BuLi (2.10 eq.), DMPU (1.50 eq.), **270** (1.50 eq.), THF, -78 °C to r.t.	26% **517**, 61% **520**
5	**520**	*n*-BuLi (2.20 eq.), **523** (1.10 eq.), THF, -78 °C to r.t.	39% **522**[a)]
6	**519**	*n*-BuLi (2.20 eq.), **523** (1.10 eq.), THF, -78 °C to r.t.	79% **521**[a)]
7	**519**	1.) *n*-BuLi (2.20 eq.), **523** (1.10 eq.), THF, -78 °C to r.t. 2.) *n*-BuLi (2.20 eq.), EtI (1.10 eq.), THF, -78 °C to r.t. 3.) Br_2 (1.00 eq.), DCM, r.t. 4.) LDA (7.00 eq.), THF, -78 °C to r.t.	**517**: 28% for 4 steps[a)]

a) performed by B.Sc. Kevin Kappes as part of his bachelor thesis.

Alkylation of **520** with 4-bromo-1-butene (**523**) furnished the desired lactam **522** in rather poor yields (entry 5), whereas the analogous reaction of 2-piperidone (**519**) delivered monosubstituted **521** in good to very good yields (entry 6). Consequently, alkylation of **519**

with **523** was followed by carbon quaternization with iodoethane and the resulting compound **522** was further converted to the corresponding alkyne **517** by the mentioned bromination/elimination sequence (entry 7). Incomplete conversion, especially for the second alkylation step with iodoethane, and separation problems during column chromatography remained unsolved problems. The overall yield for this alkylation protocol was determined to be 28% (4 steps).

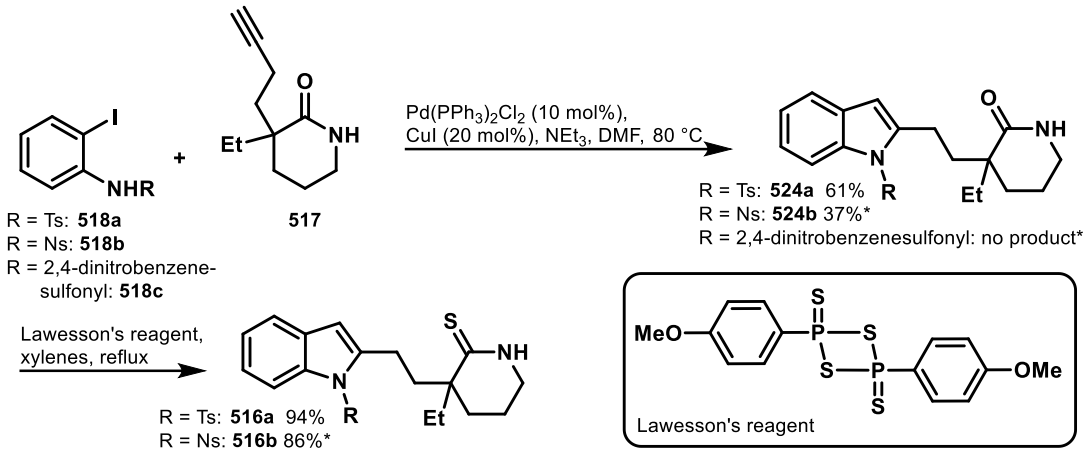
With alkyne **517** in hands, the indole synthesis was approached. As previously alluded, the electronic properties of the indolyl π-bond were suspected to play a crucial role regarding its behavior as potential dipolarophile in the planned [3+2]-cycloaddition. Hence, electron-withdrawing protective groups on the indole nitrogen atom were supposed to have an advantageous effect on the relevant reactivity. Three sulfonamides with increasingly electron-deficient character (*Figure 32*) were chosen for this purpose and synthesized from commercial 2-iodoaniline in one step each (see experimental section 3.2.1).



518a 518b 518c

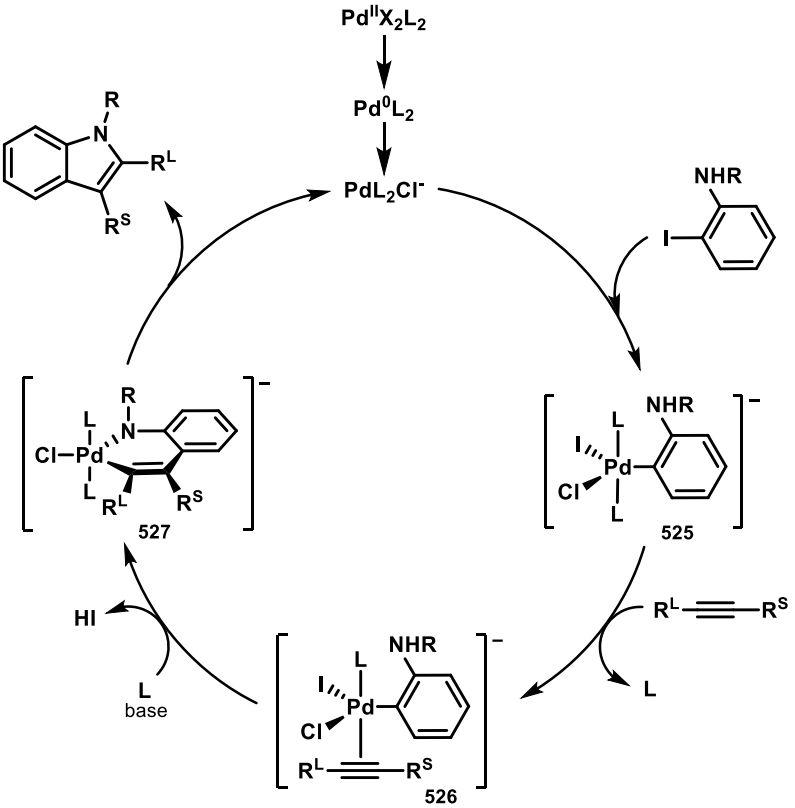
Figure 32: Iodoanilides with electron-withdrawing protective groups.

The aspired palladium(0)-catalyzed indole synthesis was based upon former work of Larock[195], who described the annulation of internal alkynes for the synthesis of 2,3-disubstituted indoles under palladium catalysis. Already in 1988, Yamanaka and co-workers[198] had reported a similar protocol for the synthesis of 2-substituted 1-methylsulfonylindoles from *N*-(2-halophenyl)methanesulfonamides with terminal alkynes. An initial experiment with *N*-(2-iodophenyl)-4-methylbenzenesulfonamide (**518a**), a slight excess of alkyne **517**, 5 mol% of bis(triphenylphosphine)palladium chloride catalyst and 8 mol% of copper(I) iodide as co-catalyst produced the desired heteroaromatic product **524a** in 32% (*Scheme 94*). No other defined compound was isolated from the reaction. An ensuing attempt with an increased amount of catalyst and co-catalyst (10 and 20%, respectively) and an excess amount of sulfonamide delivered the desired indole **524a** in 61%. The analogous reaction with **518b** furnished corresponding indole **524b** in 37%, whereas no formation of a heteroaromatic compound was observed with **518c**.



Scheme 94: Indole synthesis and thiolactam formation.
*performed by B.Sc. Kevin Kappes as part of his bachelor thesis.

Instead, decomposition of the starting materials was observed under the reaction conditions. With regard to the proposed mechanistic pathway[195] (*Scheme 95*), these findings might be caused by a strongly reduced ability of the sulfonamide nitrogen to displace a halide ligand at the palladium center in the intermediate complex **526**. This was rationalized by the highly electron-deficient dinitrobenzenesulfonyl substituent in **518c**.



Scheme 95: Proposed mechanistic pathway for the palladium-catalyzed Larock indole synthesis[195].

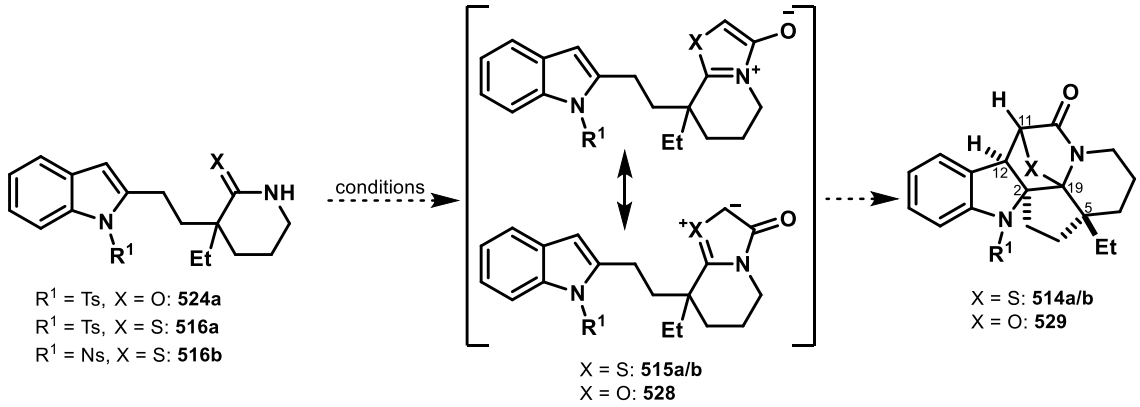
Successfully synthesized indoles **524a** and **524b** were further transformed to the corresponding thiolactams **516a** and **516b** by reaction with Lawesson's

reagent [199] (*Scheme 94*). In the course of these synthetic studies, the reaction proved to be strongly dependent from the quality of the thiation reagent. Initial attempts with an old batch of Lawesson's reagent delivered the desired thiolactams only in poor yields (< 40%) along with recovered starting material. Recrystallization of the reagent from toluene prior to use could improve the yield, but virtually full conversion still required an excess of reagent and heating to reflux for several hours. Since the reagent tends to decompose upon prolonged heating[200], addition of small amounts at regular intervals proved favorable with regard to an optimum yield. However, further storage of the recrystallized reagent under ambient conditions led to a declining reactivity und thus, the transformation of lactams **524a**/**524b** to thiolactams **516a**/**516b** suffered from fluctuating reproducibility. The use of a newly purchased batch of Lawesson's reagent improved the yield to above 90%. With sufficient amounts of material the planned key [3+2]-cycloaddition reaction was attempted.

2.1.3 Attempts on the [3+2]-Cycloaddition Reaction for Construction of the Vallesamidine Skeleton

Simple *in situ* preparation of thioisomünchnone dipoles was reported *via* reaction of a thioamide with bromoacetyl chloride in the presence of triethylamine[175] (see chapter 1.4.2). With regard to previously described competitive nucleophilic indole addition to an intermediate *N*-acyl iminium ion, electron-withdrawing groups, *i.e. p*-toluenesulfonyl and *p*-nitrobenzenesulfonyl groups, were chosen for protection of the indole nitrogen and expected to prevent nucleophilic attack of the indole. The initial experiments were carried out in analogy to the reported procedures[180a] and thiolactam **516a** was treated with bromoacetyl bromide in xylenes or dichloromethane at room temperature before triethylamine was added (entries 1 & 2, *Table 17*). The polarity of the obtained compound was very similar to that of the starting thiolactam **516a** and thus, reaction monitoring by TLC proved unsatisfactory. On the contrary, APCI TLC mass spectrometric analysis revealed consumption of the starting material within short time and formation of a new compound with the molecular mass of desired **514a**.

Table 17: Attempts on the planned intramolecular [3+2]-cycloaddition reaction of precursors **516**/**524**.



entry	substrate	conditions	result
1	**516a**	bromoacetyl bromide (1.20 eq.), xylenes, r.t., then NEt_3 (1.40 eq.)	**531a** as only product
2	**516a**	bromoacetyl bromide (1.20 eq.), DCM, r.t., then NEt_3 (1.40 eq.)	95% **531a**
3	**516a**	NEt_3 (2.00 eq.), DCM, r.t., then bromoacetyl chloride (1.20 eq.)	**531a**
4	**516a**	NEt_3 (2.00 eq.), DCM, -40 °C, then bromoacetyl chloride (1.20 eq.)	**531a**
5	**524a**	NEt_3 (2.00 eq.), DCM, r.t., then bromoacetyl chloride (1.20 eq.)	recovered **524a**
6	**524a**	NEt_3 (2.00 eq.), xylene, r.t., then bromoacetyl chloride (1.20 eq.), 60 °C	recovered **524a**
7	**516a**	NEt_3 (excess), bromoacetyl chloride (1.20 eq.), neat, r.t.	recovered **516a**
8	**516a**	NEt_3 (50.0 eq.), bromoacetyl chloride (1.20 eq.), DCM, r.t.	recovered **516a**
9	**516b**	NEt_3 (2.00 eq.), DCM, r.t., then bromoacetyl chloride (1.20 eq.)	70% **531b**[a)]

a) performed by B.Sc. Kevin Kappes as part of his bachelor thesis.

After evaporation of the solvent and purification of the crude material by column chromatography on silica gel, the obtained compound was further analyzed by 2D NMR spectroscopic experiments. For the desired cycloadduct **514a**, two characteristic CH signals were expected for the hydrogen atoms at the benzylic C12 position and the adjacent C11 carbon (see structure **514**). Indeed, the ^{1}H NMR spectrum showed two coupling signals at

3.78 ppm and 3.65 ppm, respectively, but the large coupling constant of $J = 15.6$ *Hz* indicated rather diastereotopic geminal $^{2}J_{HH}$ coupling than a vicinal $^{3}J_{HH}$ coupling. This assumption was confirmed by a HSQC NMR experiment, which revealed the two coupling protons to be connected to the same carbon atom (see *Figure 33*, labelled signals).

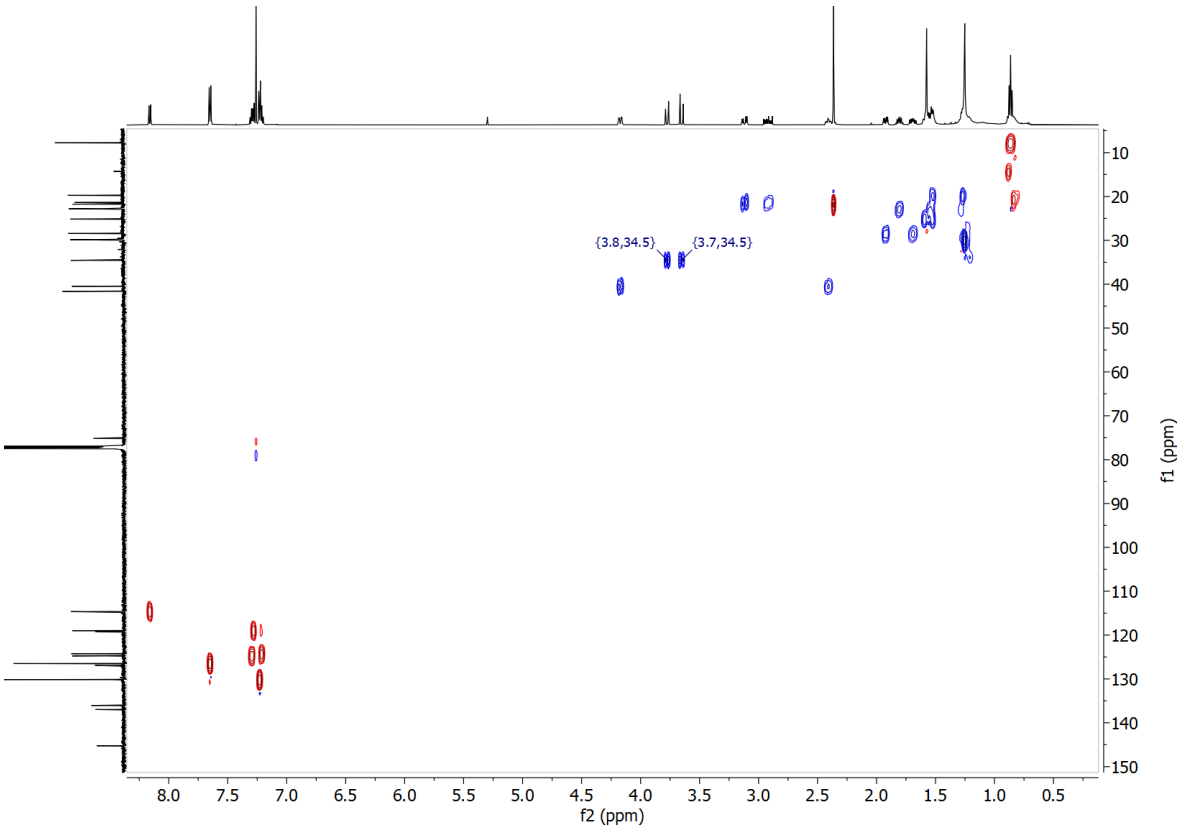
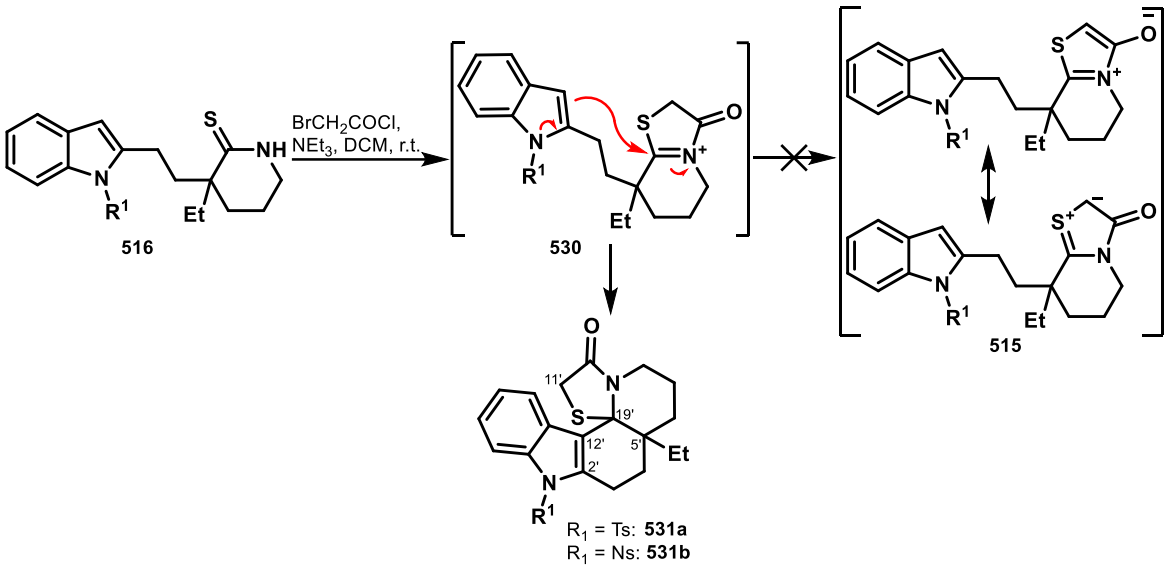


Figure 33: HSQC NMR spectrum of the new compound from the reaction of thiolactam **516a** with bromoacetyl bromide and triethylamine.

Further analysis by the aid of HMBC NMR data allowed for structure determination and identification of the obtained compound as pentacyclic **531a** (shown in *Scheme 96*). The mentioned CH_2 group could unambiguously be assigned to C11' (see structure **531** in *Scheme 96*). Determination of the relative stereochemistry of **531a** was not performed at this point. In summary, these results led to the conclusion that intramolecular nucleophilic addition of the indole to an intermediate *N*-acyl iminium ion **530** was fast and still highly preferred over formation of the desired thioisomünchnone dipole **515**. With regard to the previous reports of Padwa on the attempted thioisomünchnone [3+2]-cycloaddition to heteroaromatic dipolarophiles (see chapter 1.4.3), this seemed reasonable but was unexpected due to the modified electronic situation.

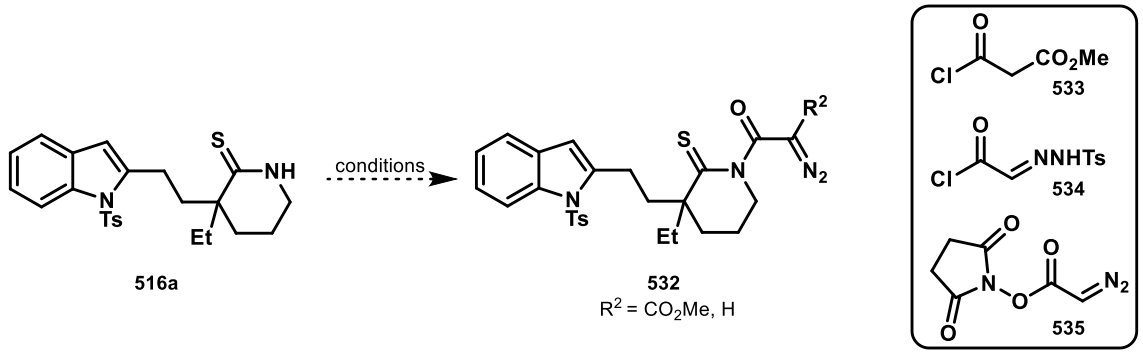


Scheme 96: Proposed alternative pathway to the observed products by reaction of thiolactams **516** with bromoacetyl bromide.

Further attempts to alter the reaction pathway by changing the order of reagent addition (*Table 17* ,entry 3) or conducting the reaction at a lower temperature did not succeed and clean intramolecular indole addition was observed even at -40 °C (entry 4). The use of an excess of base (entries 7 & 8) did not either lead to the formation of the desired pentacycle **515a** but rather caused decomposition of the acid chloride and recovery of unreacted starting material. Since successful cycloaddition of an isomünchnone dipole to an indolyl π-bond has previously been reported[180b, 194], precursor lactam **524a** was used as an alternative substrate in the analogous reaction with bromoacetyl chloride and triethylamine (entry 5). Unexpectedly, no reaction was observed after one hour at room temperature and the same result was obtained after 4.5 h at 60 °C in xylenes (entry 6). Furthermore, *p*-nitrobenzenesulfonyl-protected indolyl thiolactam **516b** was treated with base and acid chloride in analogy to the previous experiments (entry 9). Despite the increased electron-deficient character of the sulfonamide, nucleophilic indole addition to the *N*-acyl iminum ion and formation of **531b** as the only product was observed for this substrate. In consequence, circumvention of the highly reactive cationic intermediate was considered and an alternative method for dipole formation was sought. Rhodium(II)-mediated carbene generation from diazo amide precursors is a commonly used method for the *in situ* isomünchnone formation in [3+2]-cycloadditions[180b, 193-194] and additionally, a few examples for an analogous reaction of diazo thioamides have been

reported[189, 201]. Therefore, preparation of a diazo thioamide precursor **532** was targeted and different reagents were tested for *N*-acylation, as shown in *Table 18*.

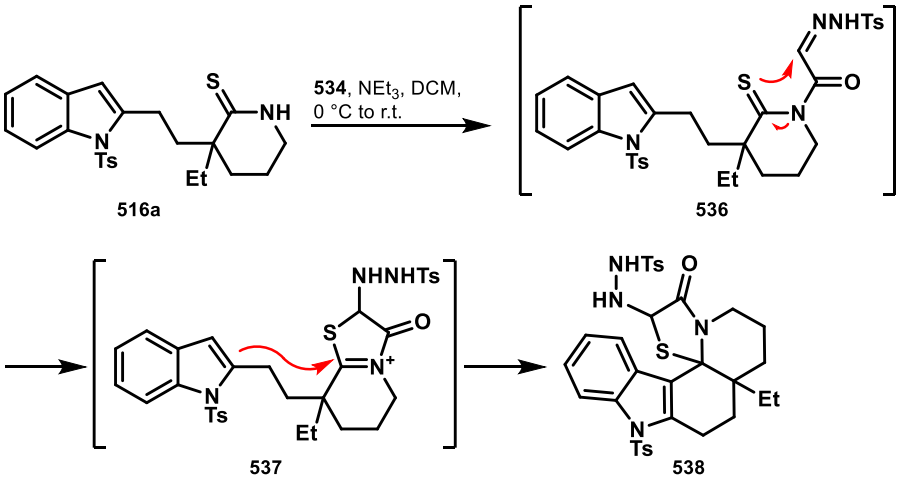
Table 18: Attempts on the synthesis of a diazo precursor for thioisomünchnone generation.



entry	conditions	result
1	1.) NEt_3 (3.00 eq.), DCM, r.t., then **533** (1.10 eq.) 2.) diazo transfer	no reaction, recovered **516a**
2	**534** (1.00 eq.), DCM, 0 °C, then DBU (2.00 eq.), 0 °C to r.t.	no reaction, recovered **516a**
3	**534** (1.03 eq.), DCM, 0 °C, then addition of **516a** and NEt_3 (1.03 eq.) in DCM, 0 °C to r.t., then 0 °C, NEt_3 (1.15 eq.)	**538** as only product
4	NEt_3 (1.25 eq.), DCM, 0 °C, then **535** (1.00 eq.), 0 °C to r.t.	no reaction, recovered **516a**
5	NEt_3 (3.00 eq.), DCM, r.t, then **535** (1.50 eq.)	no reaction, recovered **516a**

A first attempt comprised *N*-acylation with methyl (chloroformyl)acetate (**533**) and subsequent α-diazotization, which would furnish a diazo thioamide with an additional ester functionality. An accelerating effect on the formation of the 1,3-dipole with an additional electron-withdrawing substituent was supposed to be responsible for improved yields[170]. This was rationalized by an enhanced electrophilicity of the intermediate rhodium carbenoid and in consequence, diminution of undesired side-reactions in the course of dipole formation. Unexpectedly though, no reaction was observed when treating thioamide **516a** with the acid chloride in the presence of triethylamine (entry 1). The reason for the lacking reactivity of the thioamide toward methyl (chloroformyl)acetate could not be identified at this point but a similar result was obtained with 2-(2-tosylhydrazono)acetyl chloride (**534**) and DBU as the base (entry 2).

Reagent **534** lacks the potentially advantageous ester functionality but resembles to the aforementioned Zimmerman's reagent[187] and is commonly used for the preparation of diazo acetamides[202]. Application of alternative conditions with **534** and triethylamine as the base provided unexpected tosylhydrazide **538** (*Scheme 97*) as the only product (entry 3) and again demonstrated the proneness of the system to undergo an intramolecular cyclization by nucleophilic attack of the indole 3-position.

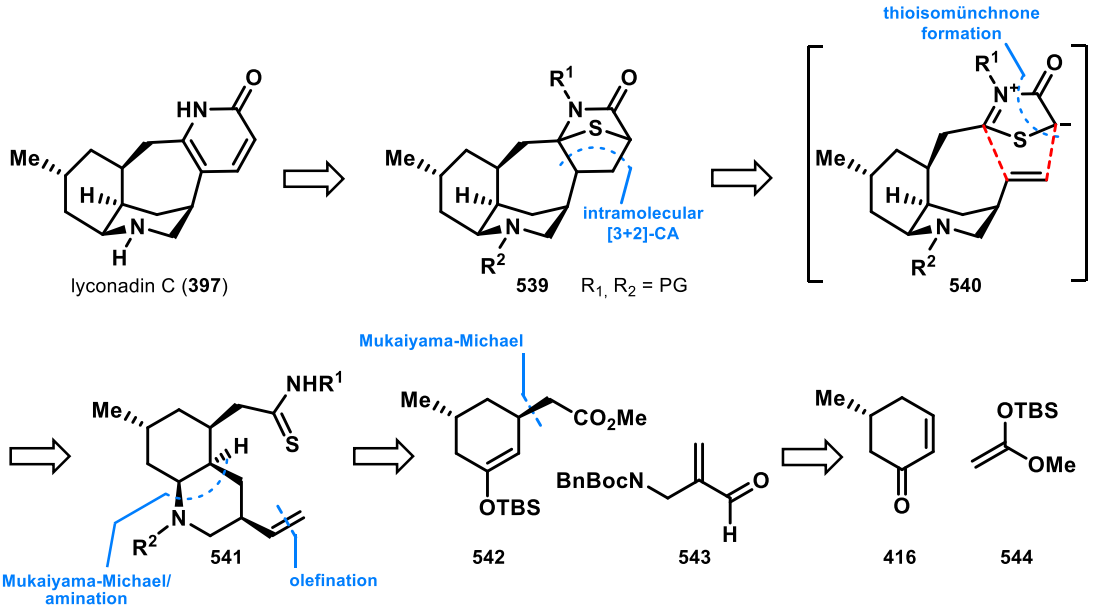


Scheme 97: Unexpected product from reaction of thioamide **516a** with 2-(2-tosylhydrazono)acetyl chloride and proposed mechanistic pathway.

NHS-derived activated ester **535** was described as an alternative acylating reagent by Wulff and was applied for substrate **516a**, but again only unreacted starting material was recovered and no reaction occurred at 0 °C and at room temperature (entries 4 & 5). The observed lacking reactivity of thioamide **516a** toward almost all of the tested acylating reagents was rather unexpected and without any apparent reason. Furthermore, the results from the acylation with 2-(2-tosylhydrazono)acetyl chloride (**534**) indicate again formation of an electrophilic iminium ion intermediate (as depicted in *Scheme 97*). Thus, further efforts should focus on an alternative preparation of a suitable dipole precursor to enable investigation of the planned intramolecular [3+2]-cycloaddition to the heteroaromatic indolyl π-bond.

2.2 An Approach Toward the Synthesis of Lyconadin C

2.2.1 Retrosynthetic Analysis of Lyconadin C

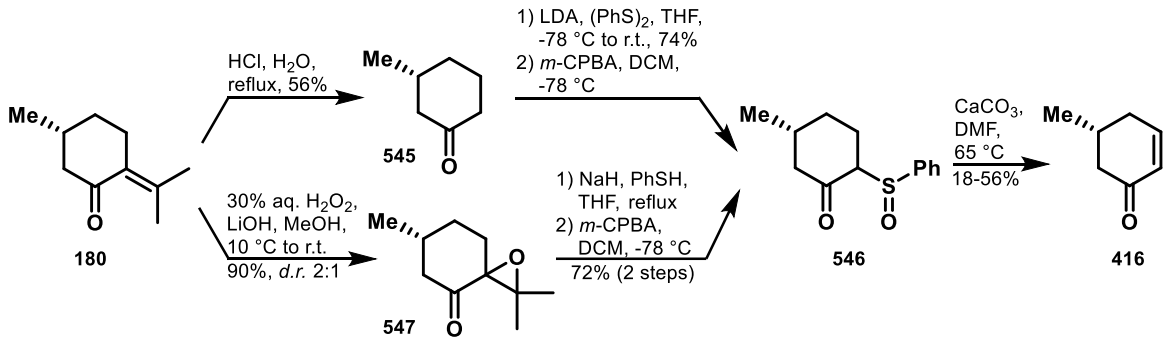


Scheme 98: Retrosynthetic analysis of lyconadin C (**397**).

The key transformation in the planned asymmetric total synthesis of lyconadin C (**397**) was thought to be an intramolecular [3+2]-cycloaddition of a thioisomünchnone dipole. In contrast to the previously presented approach toward vallesamidine (see chapter 2.1.1), a simple terminal olefin was chosen as dipolarophile in this approach. The full skeleton of the target natural product lyconadin C might directly be obtained from bicyclic precursor **541** by the mentioned cyclization reaction of an intermediate thioisomünchnone dipole **540** (*Scheme 98*). A method for conversion of the initial cycloadduct to a corresponding α-pyridone was first reported by Kato[191] and should deliver the natural product **397** from compound **539**. The bicyclic structure of cycloaddition precursor **541** was intended to arise from a formal Mukaiyama-Michael addition/reductive amination sequence from **542**. This would also include methylenation of an aldehyde functionality for generation of the dipolarophile double bond. Initial Mukaiyama-Michael reaction of ketene methyl TBS acetal (**544**) to known (*R*)-5-methyl-cyclohex-2-en-1-one (**416**) should deliver the TBS enol ether substrate **542** for the planned sequence.

2.2.2 Synthesis of the Starting Building Blocks

Chiral enone **416** has been used as starting material in numerous asymmetric syntheses of natural products[158-159, 166-167, 203] and can be obtained from natural (*R*)-pulegone (**180**) by literature-known procedures[203b, 204]. However, satisfactory literature reproduction proved to be rather difficult due to incomplete conversions and the volatility of the target compound. Two different strategies were approached, as depicted in *Scheme 99*.

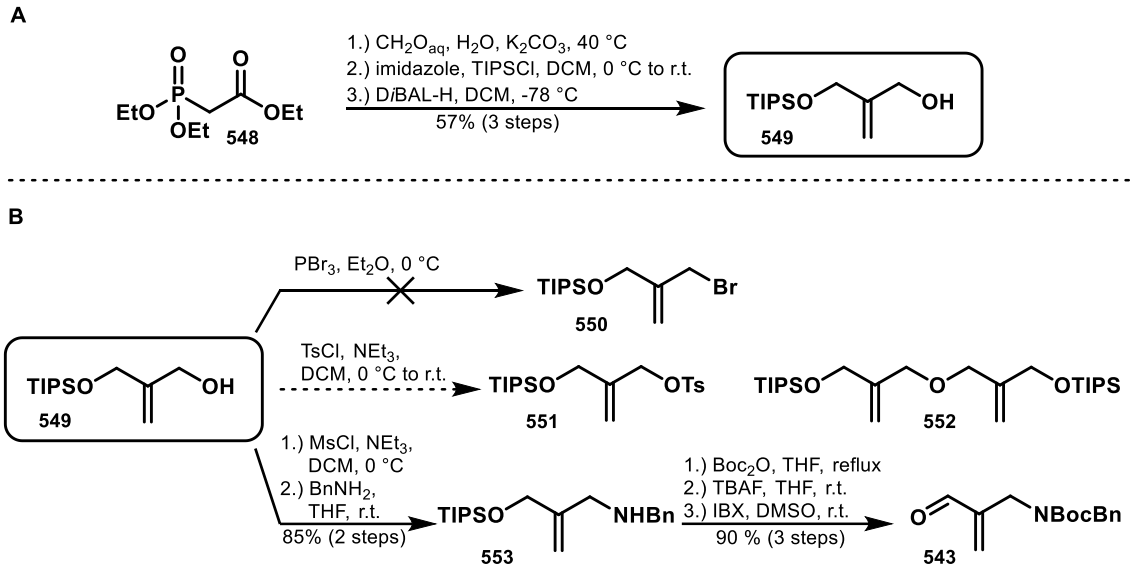


Scheme 99: Different strategies for the synthesis of (*R*)-5-methyl-cyclohex-2-en-1-one (**416**).

Acid-mediated retroaldolization in aqueous media under continuous removal of the forming acetone delivered (*R*)-3-methylcyclohexanone (**545**) in fair yield (see upper pathway in *Scheme 99*). Sulfenylation was performed according to the report of Oppolzer[203b] by sequential treatment with lithium diisopropylamide and diphenyldisulfide. However, in contrast to Oppolzer, regioselective enolate formation was not achieved and thus, the desired sulfide was obtained as an inseparable mixture of three compounds. A similar observation was reported by Caine and co-workers, who described formation of 3-methyl-2-cyclohexenone as a byproduct from this reaction sequence[204a]. Nevertheless, the obtained mixture was further subjected to oxidation by *m*-chlorperbenzoic acid and subsequently heated in the presence of calcium carbonate to induce sulfoxide elimination and generation of enone **416**. Formation of several nonpolar compounds was observed on TLC during the elimination reaction, which impeded efficient purification of the desired compound. As a result, the rather volatile product was obtained in varying yields and purity. The main impurity was classified as a sulfur-containing compound but was not further characterized. An alternative sequence for the preparation of sulfoxide **546** was described by Caine[204a] and comprised the epoxidation of (*R*)-pulegone (**180**) by Scheffer-Weitz reaction[205] (see lower pathway in *Scheme 99*). The epoxidation has been described first by Reusch and Johnson[204c] and was further optimized by Mutti and co-workers[204b]. The reaction of **180** with hydrogen peroxide in the presence

of lithium hydroxide furnished a 2:1 diastereomeric mixture of pulegone epoxide **547**. Subsequent epoxide opening with thiophenoxide triggered a retroaldol reaction under elimination of acetone and generation of the intermediate sulfide, which was oxidized to the corresponding sulfoxide **546** by treatment with *m*-chlorperbenzoic acid. Up to this stage of the sequence, all reactions proceeded with good to very good yields and delivered the desired sulfoxide as a single regioisomer in gram quantities. However, as noticed earlier, the sulfoxide elimination process proceeded rather sluggishly and furnished the desired enone **416** in a maximum isolated yield of 56%.

In parallel, the synthesis of a suitable Michael acceptor was attempted from TIPS-protected 2-methylenepropane-1,3-diol **549**, which was prepared in three steps from commercial triethyl phosphonoacetate (**548**)[206] (as depicted in *Scheme 100* **A**). Transformation of the unprotected allylic alcohol functionality into a leaving group required some optimization (as indicated in *Scheme 100* **B**).

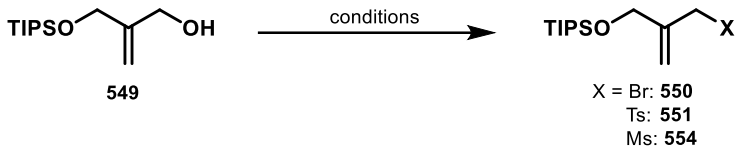


Scheme 100: **A** Preparation of bisallylic alcohol **549** from triethyl phosphonoacetate; **B** Attempts on the further conversion of **549** to a suitable Michael acceptor.

Initially attempted conversion to the corresponding allylic bromide **550** by treatment with phosphorus tribromide resulted in decomposition of the starting alcohol **549** (see *Table 19*, entry 1). A first experiment for alternative formation of the respective *p*-toluenesulfonate comprised treatment of **549** with *p*-toluenesulfonyl chloride in the presence of triethylamine at room temperature and delivered the desired compound **551** as the only product in 20% isolated yield (entry 2). However, no product formation was observed upon scale-up of the reaction and dimer **552** (see *Scheme 100* **B**) was exclusively

produced (entry 3). Repeating the reaction at 0 °C enabled isolation of 51% of the desired compound **551** alongside with 16% of **552** (entry 4). Minimization of this unwanted side-reaction could be realized by an increased dilution of the reaction and allowed to further increase the yield of **551** to 65% (entry 5). However, in all cases, efficient purification of the product by column chromatography was difficult to achieve.

Table 19: Attempts on the conversion of the allylic alcohol functionality in **549** into a leaving group.

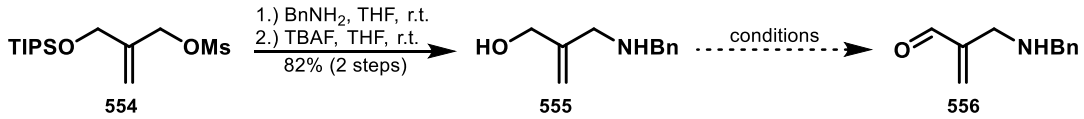


entry	conditions	scale [mmol]	c [M]	result
1	PBr_3 (0.35 eq.), Et_2O, 0 °C	0.28	0.13	decomposition, partially recovered **549**
2	TsCl (2.00 eq.), NEt_3 (3.00 eq.), DCM, 0 °C to r.t.	0.04	0.20	20% **551** (only product)
3	TsCl (2.00 eq.), NEt_3 (3.00 eq.), DCM, 0 °C to r.t.	0.82	0.20	no **551** obtained, **552** as only product
4	TsCl (2.00 eq.), NEt_3 (3.00 eq.), DCM, 0 °C	0.41	0.20	16% **552** + 51% **551**
5	TsCl (2.00 eq.), NEt_3 (3.00 eq.), DCM, 0 °C	0.82	0.08	65% **551** + traces of **552**
6	MsCl (1.30 eq.), NEt_3 (1.40 eq.), DCM, 0 °C	0.82	0.50	87% **554**
7	MsCl (1.30 eq.), NEt_3 (1.40 eq.), DCM, 0 °C	4.09	0.50	83% **554** + traces of corresponding dimer

Alternative mesylation with methanesulfonyl chloride and triethylamine furnished the desired methanesulfonate **554** in 87% yield (entry 6) and furthermore, proved to proceed with comparable success on larger scale (entry 7). It is noteworthy that the desired product **554** has a similar polarity as the starting material **549** and thus, both compounds show an identical R_F-value on TLC. Since mass spectroscopic analysis of both the starting material and product proved to be hampered by a strong tendency to fragment, monitoring of the reaction progress was not possible and thus, a standard reaction time of four to five

hours was established. With both the tosylate **551** and the mesylate **554** in hands, further conversion to a suitable Michael acceptor was targeted. Base-mediated reaction of **551** or **554** with a slight excess of sodium hydride (1.30 eq.) and benzyl amine (1.05 eq.) in DMF at room temperature gave the desired secondary amine in 45 to 55%. Incomplete conversion on one hand and the basicity of the secondary amine on the other hand accounted for these unsatisfactory results. Facile protonation of the secondary amine caused good water solubility and the result was a significant loss of material during aqueous workup. Treatment of a THF solution of **554** with a large excess of benzyl amine (10.0 eq.) showed to be superior, as this procedure did not require an aqueous extraction and delivered **553** in 98% (as shown in *Scheme 100* **B**). Fluoride-mediated silyl deprotection of the allylic alcohol produced the substrate **555** for the planned oxidation to the α,β-unsaturated system **556** in very good yield without further optimization needed. Application of mild oxidation conditions using manganese(IV) dioxide did not furnish the desired product but resulted in complete decomposition of the material (see *Table 20*, entry 1). The same result was observed upon treatment with IBX (entry 2), the use of Parikh-Doering conditions (entry 3) and attempted Corey-Kim oxidation[207] (entry 4), which strongly indicated instability of acrolein derivative **556**.

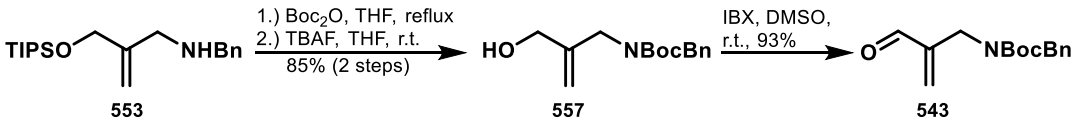
Table 20: Attempted pathway to Michael acceptor **556**.



554 555 556

entry	conditions	result
1	MnO_2 (10.0 eq.), DCM, r.t.	decomposition
2	IBX (2.50 eq.), DMSO, r.t.	decomposition
3	SO_3·pyr (4.00 eq.), NEt_3 (8.00 eq.), DMSO, r.t.	decomposition
4	NCS (5.00 eq.), SMe_2 (25.0 eq.), NEt_3 (17.0 eq.), DCM, -78 °C to -40 °C	decomposition

Since the secondary amine was suspected to cause these findings, its precedent conversion to the corresponding carbamate was pursued. Therefore, TIPS-protected **553** was reacted with di-*tert*-butyl dicarbonate in THF and subsequently subjected to silyl-deprotection conditions to produce allylic alcohol **557** (*Scheme 101*).

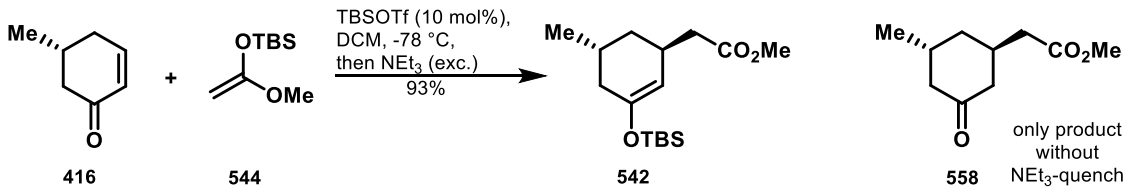


Scheme 101: Conversion of **553** to Michael acceptor **543** in three steps.

When this compound was treated with manganese(IV) dioxide, the corresponding aldehyde **543** was indeed formed, but completeness of the reaction was only achieved by use of a huge excess of oxidizing agent (20.0-30.0 eq.) and after long reaction times (> 24 h). However, alternative IBX oxidation was found to be complete after 30 minutes and delivered the desired Michael acceptor **543** in excellent yield.

2.2.3 Mukaiyama-Michael Addition and Attempted Functionalization in α-Position

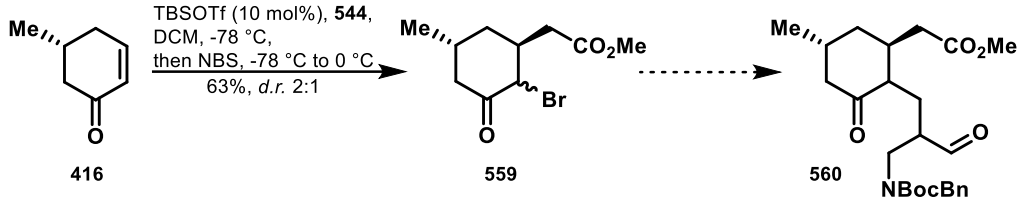
Aiming for the preparation of silylenol ether **542**, (*R*)-5-methyl-cyclohex-2-en-1-one (**416**) was treated with ketene methyl TBS acetal (**544**) in the presence of catalytic TBS triflate at 0 °C. Reaction monitoring by TLC revealed formation of a non-polar compound and full consumption of the starting enone after one hour. However, in the course of an aqueous workup with sodium bicarbonate and DCM extraction, the non-polar compound appeared to be quantitatively transformed into a polar substance, which was identified as the ketone **558** (see *Scheme 102*).



Scheme 102: Mukaiyama-Michael addition of **544** to enone **416**.

The use of equimolar amounts of TBS triflate did not allow for isolation of the observed intermediate non-polar species. Coincidentally, when the reaction was repeated at -78 °C and quenched with aqueous sodium bicarbonate at this temperature, trace amounts of this rather instable compound could be isolated alongside ketone **558**. This enabled structural characterization and identification of the non-polar intermediate as the desired silylenol ether **542**. Unexpectedly, repeated experiments using the same conditions at -78 °C did not provide the desired compound at all. Fortuitously, the addition of an excess of anhydrous triethylamine at -78 °C prior to the aqueous workup efficiently prevented hydrolysis of the desired enol ether **542** and allowed for its isolation in excellent yields (see *Scheme* 102). The substrate for the second planned Mukaiyama-Michael addition reaction was obtained

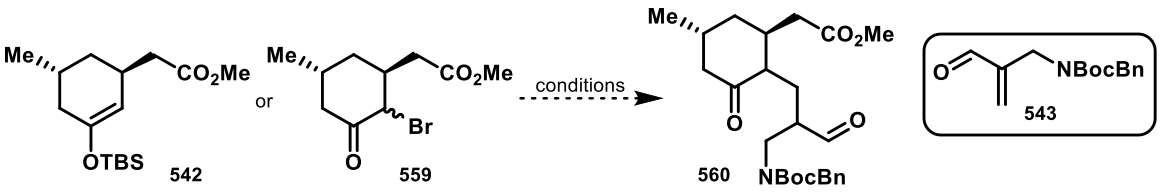
as a single diastereomer and proved stable upon column chromatography on silica gel. This second conjugate addition should enable α-alkylation.



Scheme 103: Attempted alternative functionalization strategy of enone **416** *via* α-bromo ketone **559**.

Because of initial problems with the isolation of **542**, an alternative strategy toward functionalization in α-position has been considered. This approach is outlined in *Scheme* 103 and comprised trapping of the intermediate enolate in form of an α-bromo ketone. Therefore, the Mukaiyama-aldol reaction of **416** and **544** was conducted with catalytic amounts of TBS triflate at -78 °C and monitored by TLC. Upon full consumption of the starting enone, *N*-bromosuccinimide was added and induced formation of a 2:1 diastereomeric mixture of bromide **559**. With silylenol ether **542** and bromide **559** in hands, further functionalization in α-position was approached (see *Table 21*). Reformatsky-type reaction of the α-bromo ketone was attempted according to the procedure reported by Watt *et al.*[208]. Since no conversion was observed at room temperature, the reaction mixture was heated to reflux. The crude ^{1}H NMR spectrum after four hours indeed proved consumption of both starting materials, but the obtained compound did not show any aldehyde signals nor signals for the cyclohexane moiety and thus, was not further characterized (entry 1). Alternative conditions for effective aldol reactions of α-halo ketones were described by Nozaki[209] using activated zinc in form of the zinc-silver couple in combination with an aluminum-based Lewis acid, in this case diethylaluminum chloride. When bromo ketone **559** was subjected to the according conditions, only decomposition of the starting materials was observed (entry 4). Concurrent attempts with the silylenol ether **542** turned out to be more promising. Treatment of this compound with a solution of aldehyde **543** and titanium(IV) chloride led to decomposition of the enol ether but not the aldehyde (entry 2). Although these conditions were reported to effectively induce Michael reactions[210], no other defined compound than **543** could be isolated from the reaction. Application of the formerly successful Mukaiyama-Michael addition protocol (see *Scheme 102*) to substrate **542** gave a similar result as aldehyde **543** was recovered alongside known ketone **558** (entry 3).

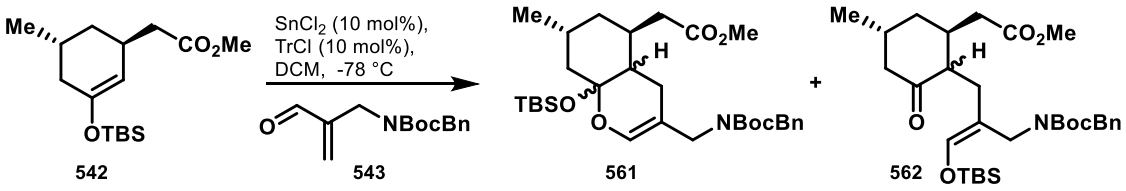
Table 21: Screening of conditions for the planned α-functionalization.



entry	substrate	conditions	result
1	**559**	Zn dust (1.5 eq.), **543** (4.00 eq.), DMSO/PhH (1:10), r.t., then reflux	unidentified compound
2	**542**	$TiCl_4$ (1 M in DCM, 1.00 eq.), **543** (1.50 eq.), DCM, -78 °C	decomposition of **542**, recovered **543**
3	**542**	TBSOTf (10 mol%), **543** (1.00 eq.), DCM, -78 °C to r.t.	**558** + recovered **543**
4	**559**	Zn/Ag (1.50 eq.), Et_2AlCl (1 M in hexane, 1.10 eq.), **543** (1.10 eq.), THF, -20 °C to -10 °C	decomposition
5	**542**	$Zn(OTf)_2$ (3 mol%), **543** (1.50 eq.), DCM, 0 °C to r.t.	**558** + recovered **543**
6	**542**	$SnCl_2$ (5 mol%), TrCl (5 mol%), **543** (0.90 eq.), DCM, -78 °C to r.t.	recovered **543** + traces of **561**
7	**542**	$SnCl_2$ (10 mol%), TrCl (10 mol%), **543** (0.90 eq.), DCM, -78 °C	recovered **543** + 50% **561**
8	**542**	$SnCl_2$ (10 mol%), TrCl (10 mol%), **543** (0.45 eq.), DCM, -78 °C	60% **561**
9	**542**	$SnCl_2$ (10 mol%), TrCl (10 mol%), **543** (0.67 eq.), DCM, -78 °C[a)]	73% **561** + recovered **542**, **543** + traces of **562**
10	**542**	$SnCl_2$ (10 mol%), TrCl (10 mol%), **543** (0.67 eq.), DCM, -78 °C[b)]	92% **561** + traces of **562**
11	**542**	$SnCl_2$ (10 mol%), TrCl (10 mol%), **543** (0.77 eq.), DCM, -78 °C[c)]	38% **561** + 25% **562**+ **558**
12	**542**	$SnCl_2$ (10 mol%), TrCl (10 mol%), **543** (0.77 eq.), DCM, -78 °C[c)]	52% **561**
13	**542**	$SnCl_2$ (10 mol%), TrCl (10 mol%), **543** (0.67 eq.), DCM, -78 °C[b)]	67% **561** + **562**

a) 0.29 mmol scale (ref. to aldehyde **543**); b) 0.58 mmol scale (**543**); c) 1.09 mmol scale (**543**).

Zinc(II)-catalyzed Michael addition of silylenol ethers was described earlier[211] but was not successful for the desired transformation of **542** and again furnished the hydrolyzed enol ether, *i.e.* ketone **558**, and recovered aldehyde **543** (entry 5). Finally, treatment of TBS enol ether **542** with aldehyde **543** in the presence of a pre-generated trityl cation catalyst[212] produced minor amounts of a new compound (entry 6). In the ^{1}H NMR spectrum, this new compound did not show any signal corresponding to an aldehyde CH functionality, which would exist in the expected product **560**. Moreover, signals of a sp^2 CH group and a TBS functionality were identified. Extensive 2D NMR spectroscopic analysis allowed to assign the unknown compound to the structure of bicyclic **561** (see *Scheme 104*). The compound was obtained as a single diastereomer but determination of the configuration of the two adjacent stereocenters at the ring fusion was not possible since the NMR spectroscopic data was not unequivocal and no crystal structure could be obtained. Thus, the actual conformation of the fused dihydropyran moiety remained unknown.



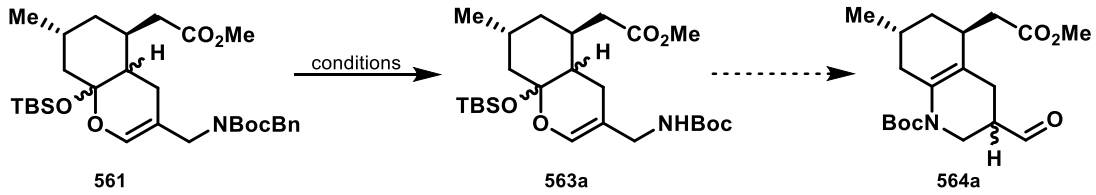
Scheme 104: Mukaiyama-Michael/acetalization cascade reaction of silylenol ether **542** with α,β-unsaturated aldehyde **543** to **561** and acyclic Michael adduct **562**.

An increased amount of catalyst in the conjugate addition reaction led to an improved result but unreacted aldehyde **543** was still recovered (*Table 21*, entry 7). The use of increased amounts of silylenol ether **542** provided compound **561** in 60-73% (entries 8 & 9), but the reaction was still accompanied by incomplete conversion of the starting materials. In addition, decreased yields and increasing formation of a second similar product was observed upon scale-up of the reaction and resulted in generally varying yields (entries 9-13). Structure elucidation of this side-product proved difficult due to NMR signal broadening, which was presumably caused by the existence of rotational isomers of the carbamate. Nevertheless, the compound could be identified as the corresponding acyclic Michael adduct **562**. The formation of this additional product could be slightly reduced but not entirely prevented by careful addition of aldehyde and enolether to the catalyst solution (entry 12). However, since both compounds **561** and **562** might be converted to the desired octa- or decahydroquinoline motif, no further optimization was attempted at this point.

2.2.4 Attempts Toward an Octahydroquinoline System

Since the reactivity and behavior of a nitrogen atom is strongly affected by its substituents, a divergent protecting group strategy was pursued for the intended transformation of the hexahydrochromenol motif in **561** to the octahydroquinoline **564**. Benzyl deprotection would deliver the secondary carbamate **563a**, which was expected to show a diminished nucleophilicity but also a reduced basicity compared to the benzyl substituted analogue **563b**. Both **563a** and **563b** might be possible substrates for the above-mentioned ring opening/annulation cascade to compounds **564a**/**564b**. The desired *N*-debenzylation was attempted using reductive conditions (see *Table 22*). Treatment of **561** with hydrogen gas in THF under ambient conditions and in the presence of palladium on carbon provided a mixture of unreacted starting material, desired secondary carbamate **563a** and a third, structurally similar compound (*Table 22*, entry 1).

Table 22: Tested conditions for *N*-benzyl deprotection of **561**.



entry	conditions	result
1	H_2, Pd/C, THF, r.t., 23 h	38% **563a**, 10% **561**, 26% **565**
2	H_2, Pd/C, MeOH, r.t., 6 h	**566**
3	H_2, Pd/C, THF, r.t., 4 h	49% **563a**, 10% **561**, traces of **565**
4	Na (13.0 eq.), NH_3(l), THF, -78 °C to -60 °C	complex mixture, traces of **563a**
5	H_2, $Pd(OH)_2$, THF, r.t., 6 h	73% **563a**, traces of **561**

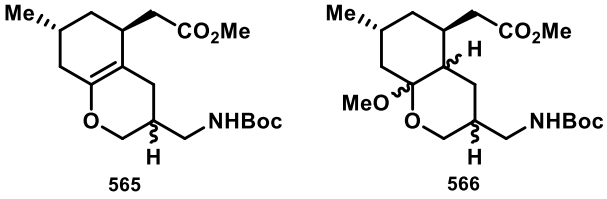
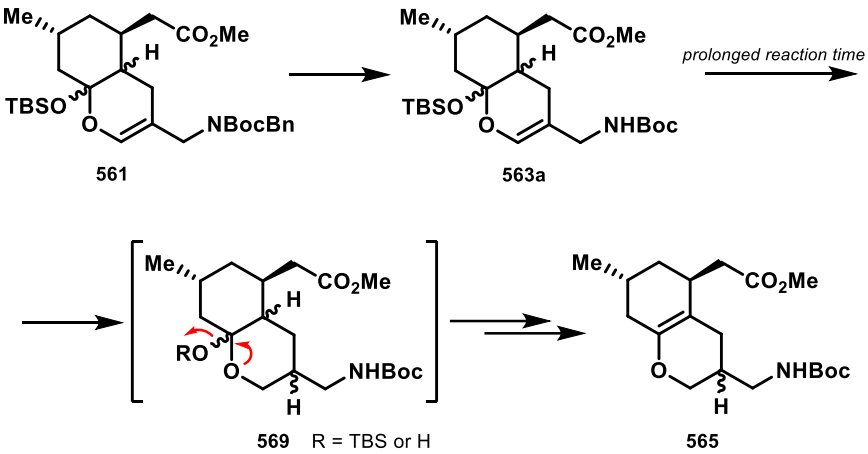


Figure 34: Observed side-products from the attempted *N*-debenzylation.

This side-product was identified as hexahydrochromene **565** (see *Figure 34*) by 2D NMR spectroscopic analysis and mass spectrometry. When the same reaction was interrupted after four hours (entry 3), only trace amounts of **565** were observed and the yield of the desired carbamate **563a** had increased to 49%, compared to 38% after 23 hours. The proposed mechanistic pathway for the formation of **565** is shown in *Scheme 105*.

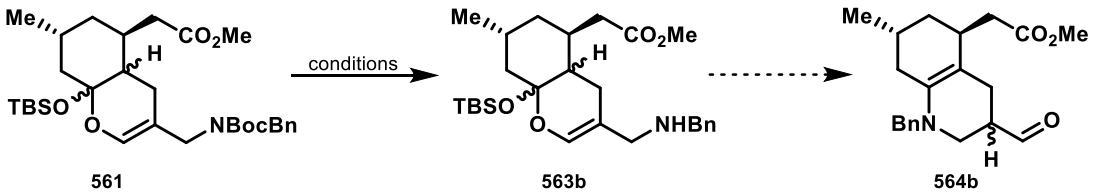


Scheme 105: Rationalization of the emergence of hexahydrochromene **565** from the hydrogenation of **561**.

Surprisingly, the content of recovered starting material was detected to be the same for both experiments. These findings led to the following hypothetical conclucions: 1.) The binding affinity of debenzylated **563a** to the palladium catalyst is significantly higher than the affinity of the starting material **561** and thus **563a** impedes full conversion of **561** by 'catalyst poisoning'. This strong adsorption might also explain the observed loss of a significant amount of material in the course of this reaction. 2.) The unexpected hydrogenation of the trisubstituted double bond could be enabled by strong adsorption of **563a** to the catalyst and prolonged reaction times. 3.) Reduction to the intermediate octahydrochromenol **569** entails an enhanced electron density at the heterocyclic oxygen and thus, might induce elimination to the vinyl ether, as proposed in *Scheme 105*. Since no other compounds could be isolated from the reaction, it remains unknown whether the elimination occurrs from the TBS acetal or the hemiacetal form of **569**, but indeed, lability of TBS ethers under palladium/carbon-catalyzed hydrogenation conditions has previously been described in the literature[213]. Alternatively attempted hydrogenation in methanol furnished compound **566** as the major product (*Table 22*, entry 2), which is in accordance with the above conclusions. The application of Birch conditions produced a complex mixture of several compounds, in which only trace amounts of the desired product **563a**

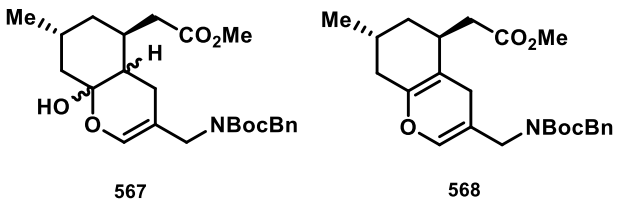
could be identified (entry 4). Eventually, Pearlman's catalyst[214] proved superior for the desired *N*-debenzylation providing the desired secondary carbamate **563a** in 73% yield (entry 5). As mentioned above, cleavage of the Boc protecting group from substrate **561** was targeted in parallel. For this purpose, several conditions were tested and the results are shown in *Table 23*.

Table 23: Screening of conditions for *N*-Boc deprotection of **561**.



561 563b 564b

entry	conditions	result
1	TFA (5.00 eq.), DCM, r.t., 1 h	decomposition
2	TFA (5.00 eq.), DCM, r.t., 30 min	**567** or **568** (proposed)
3	TFA (1.00 eq. + 1.00 eq. + 1.00 eq.), DCM, r.t.	decomposition
4	TFA (1.50 eq.), DCM, r.t.	**567** or **568** (proposed)
5	TFA (5.00 eq.), DCM, r.t., then AcOH (5.00 eq.), PhMe, reflux	decomposition
6	$BF_3{\cdot}OEt_2$ (5.00 eq.), 4 Å MS, DCM, 0 °C	decomposition
7	37% HCl (5.00 eq.), PhMe, 65 °C	**567** or **568** (proposed)
8	$SnCl_4$ (1 M in DCM, 5.00 eq.), ethyl acetate, r.t.	decomposition
9	neat, 185 °C	recovered **561**
10	$ZnBr_2$ (2.00 eq.), DCM, r.t.	81% **563b**



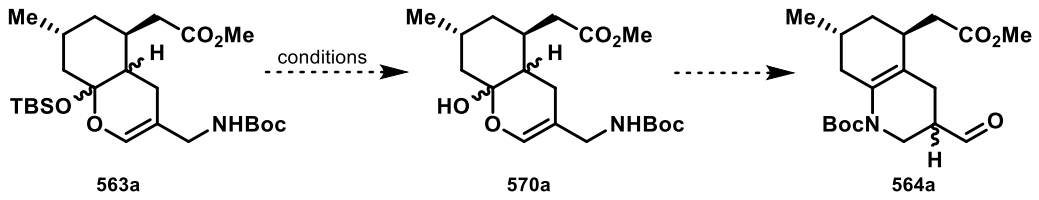
567 568

Figure 35: Proposed side-products from the attempted Boc-deprotection of **561**.

In a first experiment, **561** was treated with trifluoroacetic acid at room temperature (entry 1). TLC indicated the formation of several compounds with higher polarity and after one hour, full conversion of the starting material was observed. The crude

^{1}H NMR spectrum of the reaction showed traces of an aldehyde compound, but the majority of the material was decomposed. Generation of an aldehyde functionality might be rationalized by direct rearrangement of the intermediate *N*-deprotected compound **563b** to the octahydroquinoline **564**. Thus, the reaction was repeated but interrupted after 30 minutes (entry 2). Indeed, a defined product was obtained, which showed no signals for the TBS group but for the Boc substituent. Unambiguous structure determination was not possible since only a very limited amount of material was obtained, however, two proposed alternative structures (compounds **567** and **568**) are shown in *Figure 35*. With regard to the apparent instability of this intermediate compound under the acidic reaction conditions, purposive *N*-Boc deprotection was attempted by monitored addition of trifluoroacetic acid aliquots but did not succeed (entry 3). By use of 1.50 equivalents of acid, the same proposed intermediate compound **567** or **568** was obtained as the only product (entry 4). Alternative sequential treatment of **561** with trifluoroacetic acid and with acetic acid at elevated temperature though resulted in decomposition (entry 5). Further attempts on a stepwise conversion and thus selective Boc cleavage included boron trifluoride diethyl etherate (entry 6) and tin(IV) chloride (entry 8), but decomposition was observed for both reactions. The use of aqueous hydrochloric acid at elevated temperature again produced the previously proposed intermediate compound **567** or **568** (entry 7), whereas thermal treatment of neat **561** did not cause any reaction but led to reisolation of unreacted starting material (entry 9). Fortuitously, selective removal of the Boc protecting group from **561** could finally be accomplished in 81% yield by the use of zinc(II) bromide (entry 10), in analogy to the reports of Wermutha and co-workers[215]. Having both the secondary carbamate **563a** and the benzyl-substituted derivative **563b** in hands, selective TBS removal and intramolecular amination by rearrangement were addressed. The tested conditions for **563a** are listed in *Table 24*. No reaction was observed upon treatment of **563a** with pyridinium *p*-toluenesulfonate at room temperature, whereas decomposition of the starting material occurred under the same conditions in refluxing toluene (entries 1 & 2). Attempted reaction with tetrabutylammonium fluoride furnished an inseparable mixture of three compounds that exhibited neither a TBS group nor an olefin nor an aldehyde (entry 3). Thus, these compounds were not subjected to further structural characterization.

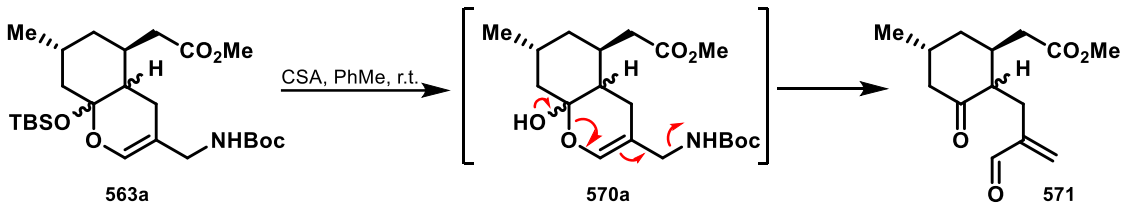
Table 24: Attempts on TBS-deprotection and intramolecular amination of carbamate **563a**.



563a **570a** **564a**

entry	conditions	result
1	PPTS (1.00 eq.), DCM, r.t., then 3x co-evaporation under reduced pressure with PhH	no reaction
2	PPTS (1.00 eq.), PhMe, reflux	decomposition
3	TBAF (1 M in THF, 1.00 eq.), THF, r.t.	inseparable mixture
4	*p*-TsOH·H_2O (1.00 eq.), PhMe, reflux, 15 min	decomposition, traces of **564a**
5	*p*-TsOH·H_2O (1.00 eq.), PhMe, 80 °C, 50 min	16% **564a** (*d.r.* 1:1)
6	*p*-TsOH·H_2O (20 mol%), PhMe, 80 °C, 1 h	traces of **564a**
7	*p*-TsOH·H_2O (1.00 eq.), PhMe, r.t., 18 h	decomposition
8	AcOH/H_2O/THF (3:1:1), 80 °C	decomposition
9	HF·pyr (70% in pyr, 20.0 eq.), pyridine (13.0 eq.), THF, 0 °C to r.t.	no reaction
10	NH_4F (14.0 – 150 eq.), MeOH, 60 °C	no reaction
11	BF_3·OEt_2 (10.0 eq.), $CHCl_3$, 0 °C to r.t.	decomposition
12	CSA (1.00 eq.), PhMe, r.t.	**564a** in varying yields: traces to 42% (*d.r.* 1:1), **571**, decomposition
13	CSA (20 mol%), PhMe, r.t.	decomposition, traces of **564a**, **571**
14	CSA (1.00 eq.), DCM, 0 °C	28% **564a**, decomposition
15	CSA (1.00 eq.), DCM, -78 °C to -10 °C	no reaction
16	CSA (20 mol%), DCM, 0 °C	recovered **563a**, traces of **564a**
17	TASF (1.05 eq.), DMF, r.t.	decomposition
18	TASF (2.50 eq.), H_2O (5.00 eq.), DMF, r.t.	inseparable mixture, no **564a**

Treatment with *p*-toluenesulfonic acid in refluxing toluene led to decomposition of the major part of the material (entry 4), in conformity with the results from the reaction with pyridinium *p*-toluenesulfonate. However, also traces of the desired ene-carbamate **564a** were identified. A decreased temperature and concurrent prolongation of the reaction time resulted in reduced decomposition and furnished 16% of the desired compound **564a** as a 1:1 diastereomeric mixture (entry 5). Considering the significant proportion of decomposed material, a catalytic version was approached but delivered only trace amounts of **564a** (entry 6). Further attempts at room temperature did not succeed either (entry 7). Acetic acid in a water/THF mixture as well as boron trifluoride diethyl etherate seemed too harsh and induced decomposition of the entire material (entries 8 & 11), whereas no reaction was observed with hydrogen fluoride pyridine complex or an excess of ammonium fluoride (entries 9 & 10). First experiments with camphorsulfonic acid provided promising results. When carbamate **563a** was treated with an equimolar amount of the acid in toluene at room temperature a 1:1 diastereomeric mixture of the desired ene-carbamate **564a** could be isolated in 42% yield (entry 12). On the other hand, the rest of the material had decomposed and upon multiple repetitions of the reaction under identical conditions, the product compound was obtained in yields varying from < 10% up to 40%. In addition, formation of an unexpected side-product **571** by elimination (see *Scheme 106*) hampered efficient purification of **564a** and caused impure product fractions.



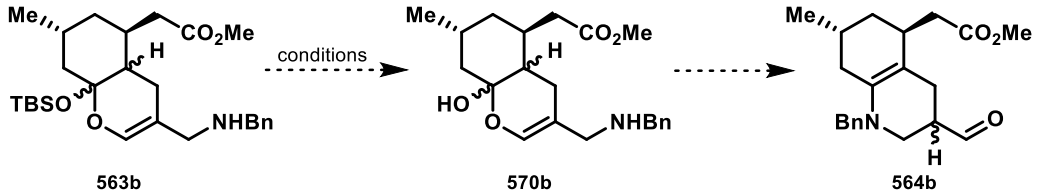
Scheme 106: Proposed mechanism leading to formation of the observed side-product **571** in the reaction of **563a** with camphorsulfonic acid.

Furthermore, a general sensitivity of desired **564a** to various conditions was assumed to cause further decomposition during workup and/or column chromatography. Reducing the equivalents of acid resulted in diminished product emergence and similar observations were made for lower reaction temperatures (entries 13-16).

The TASF reagent was reported in literature as a mild alternative for selective deprotection of silyl protecting groups and was successfully used for a range of acid- and base-sensitive

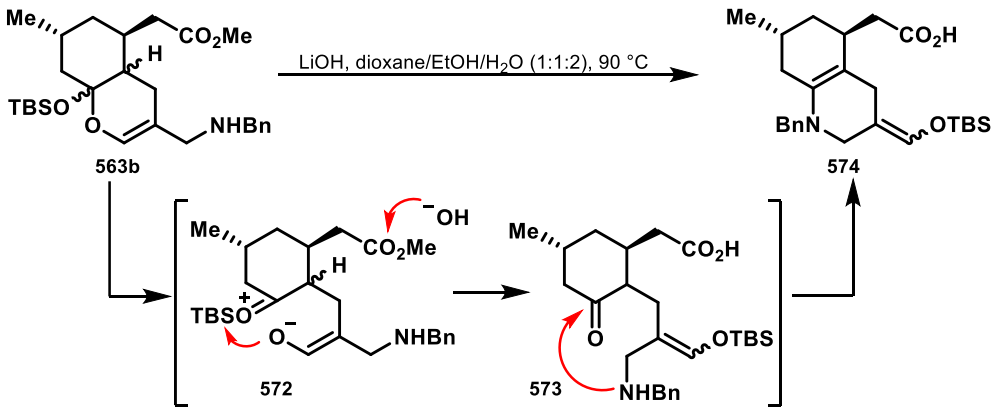
substrates[216]. However, only decomposition was observed when carbamate **563a** was treated with this desilylating agent in DMF (entry 17). A further moderating effect on the reagent's basicity by the addition of water was reported in the context of a sensitive hemiketal[217] and could indeed prevent the beforehand observed decomposition. Unfortunately, formation of the desired compound **564a** was not observed either (entry 18). Thus, further synthetic efforts focused on the benzyl-substituted substrate **563b**, but this substrate proved to decompose under almost all applied reaction conditions, as depicted in *Table 25*.

Table 25: Attempts on TBS-deprotection and intramolecular amination of secondary amine **563b**.



entry	conditions	result
1	CSA (1.00 eq.), PhMe, 80 °C	decomposition
2	TBAF (1 M in THF, 1.00 eq.), THF, r.t.	decomposition
3	TBAF (1 M in THF, 3.10 eq.), 4 Å MS, THF, r.t.	decomposition
4	TBAF (1 M in THF, 5.00 eq.), NH_4F (5.00 eq.), THF, r.t.	decomposition
5	NH_4F (150 eq.), MeOH, 60 °C	no reaction
6	HF·pyr (70% in pyr, 20.0 eq.), pyridine (13.0 eq.), THF, 0 °C	no reaction
7	*p*-TsOH·H_2O (1.00 eq.), PhMe, 80 °C	decomposition
8	AcOH/H_2O/THF (3:1:1), 80 °C	decomposition
9	TFA/H_2O (9:1), DCM, r.t.	decomposition
10	CsF (10.0 eq.), MeCN/H_2O (9:1), r.t.	no reaction
11	LiOH (5.00 eq.), dioxane/EtOH/H_2O (1:1:2), 90 °C	**574**
12	TASF (1.05 eq.), DMF, r.t.	decomposition
13	TASF (2.50 eq.), H_2O (5.00 eq.), DMF, r.t.	decomposition

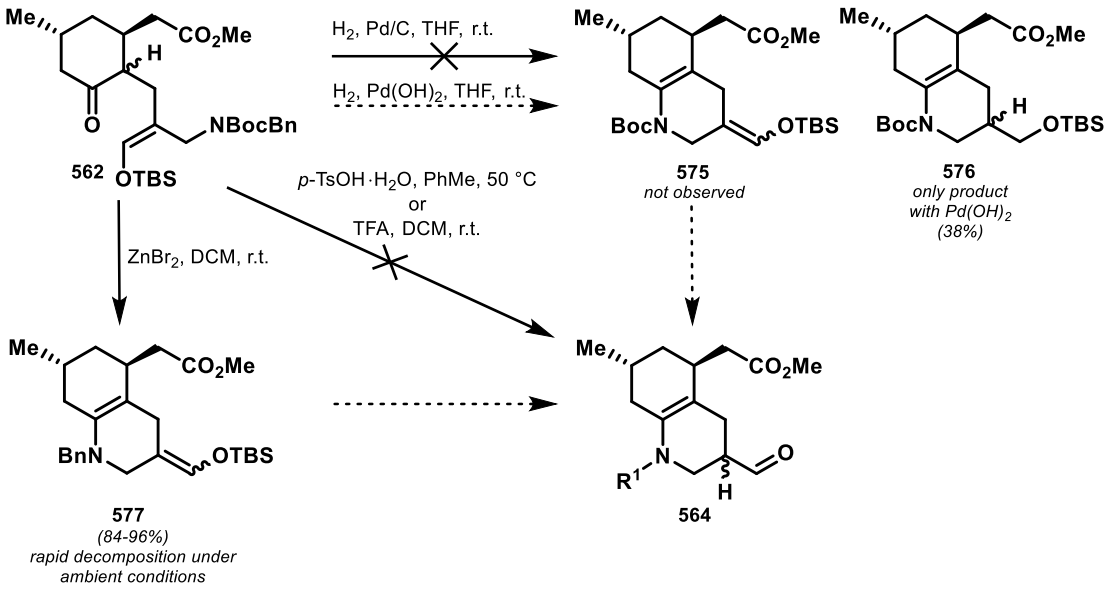
In conformity with the carbamate substrate **563a**, no reaction of **563b** was observed with hydrogen fluoride pyridine complex or ammonium fluoride (entries 5 & 6) and unreacted starting material could be recovered. This was also found for the reaction with cesium fluoride (entry 10) and with aqueous acetic acid (entry 8). With all other acidic conditions, including camphorsulfonic acid (entry 1) and *p*-toluenesulfonic acid (entry 7), only decomposed material was obtained. Analysis of these results and consideration of the basicity of the tertiary amine in **563b** led to the conclusion that non-acidic conditions might be favorable for the desired transformation, but all attempts with rather basic tetrabutylammonium fluoride (entries 2-4) or mild TASF reagent (entries 12 & 13) led to decomposition as well. The only conditions inducing clean conversion of the starting material to a defined product were found to be heating of **563b** to 90 °C in a mixture of 1,4-dioxane, ethanol and water in the presence of an excess of lithium hydroxide (entry 11). In the course of this reaction, the methyl ester was hydrolized to the corresponding carboxylic acid as indicated by the ^{1}H NMR spectrum of the crude compound. Furthermore, presumed acetal cleavage and concomitant intramolecular transfer of the TBS group caused ring opening of the heterocycle and formation of a silylenol ether (see *Scheme 107*). In succession, cyclization of intermediate **573** to the octahydroquinoline motif occurred by intramolecular amination and furnished compound **574** as the only product.



Scheme 107: Proposed mechanism for conversion of benzyl-protected **563b** to enamine **574** under basic conditions.

A similar compound was obtained from the reaction of the acyclic Michael adduct **562** (depicted in *Scheme 108*). As previously stated (chapter 2.2.3), further conversion of this former side-product was also tested. Therefore, cleavage of the respective protecting group was attempted in analogy to the cyclic substrate. Since

hydrogenation reaction with palladium on carbon produced the same side-product **565** (see *Figure 34*) as for the cyclic substrate and no desired product at all, alternative debenzylation conditions with Pearlman's catalyst were applied. Hydrogenolysis with palladium(II) hydroxide in THF had previously succeeded for benzyl deprotection of the cyclic substrate **561** but did not afford the desired compound **575**. Instead, slow conversion and decomposition were accompanied by the formation of compound **576** as the only product.



Scheme 108: Attempted conversion of the acyclic Michael adduct **562** to the octahydroquinoline motif.

Additionally, treatment of the same substrate **562** with trifluoroacetic acid was performed aiming for Boc deprotection and potential concomitant hydrolysis of the silylenol ether. Repeated experiments resulted only in decomposition of the material and the same result was obtained by use of *p*-toluenesulfonic acid. Hence, a stepwise process to **564** was addressed. Cleavage of the carbamate in **562** was successfully accomplished by use of zinc(II) bromide and indeed, the desired intramolecular amination occurred and generated bicyclic enamine **577**. Reaction monitoring by TLC revealed a clean reaction and the product was obtained in high yields of 84 to 96%. Compound **577** resembled previously observed **574** but unfortunately exhibited a significant instability under ambient conditions and decomposed not only in solution during NMR spectroscopic analysis but also upon storage in pure form at 5-8 °C. Since no effective conditions for the transformation to **564** were found, fundamental revision of the synthetic strategy might be advisable.

3. Summary and Outlook

Two synthetic approaches toward the total syntheses of vallesamidine (**311**) and lyconadin C (**397**) were discussed in the second part of this thesis. Both planned sequences contained a key [3+2]-cycloaddition reaction of a thioisomünchnone dipole for construction of the target molecules' fused ring systems (*Figure 36*).

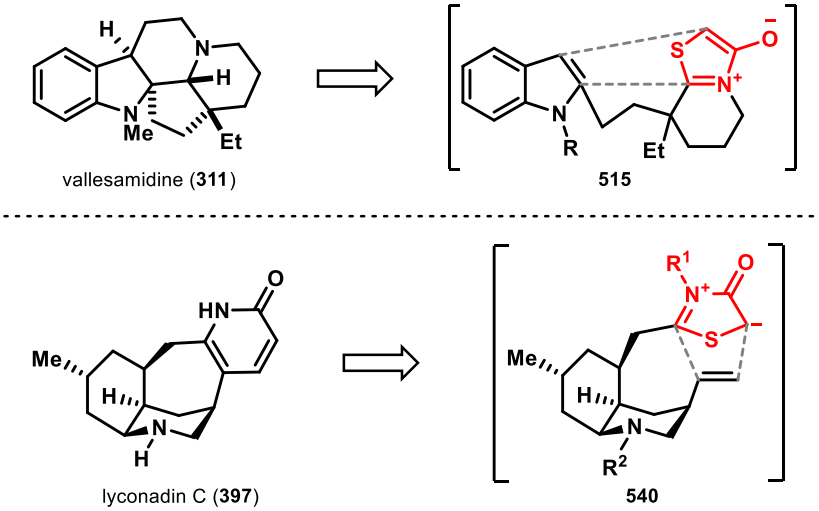
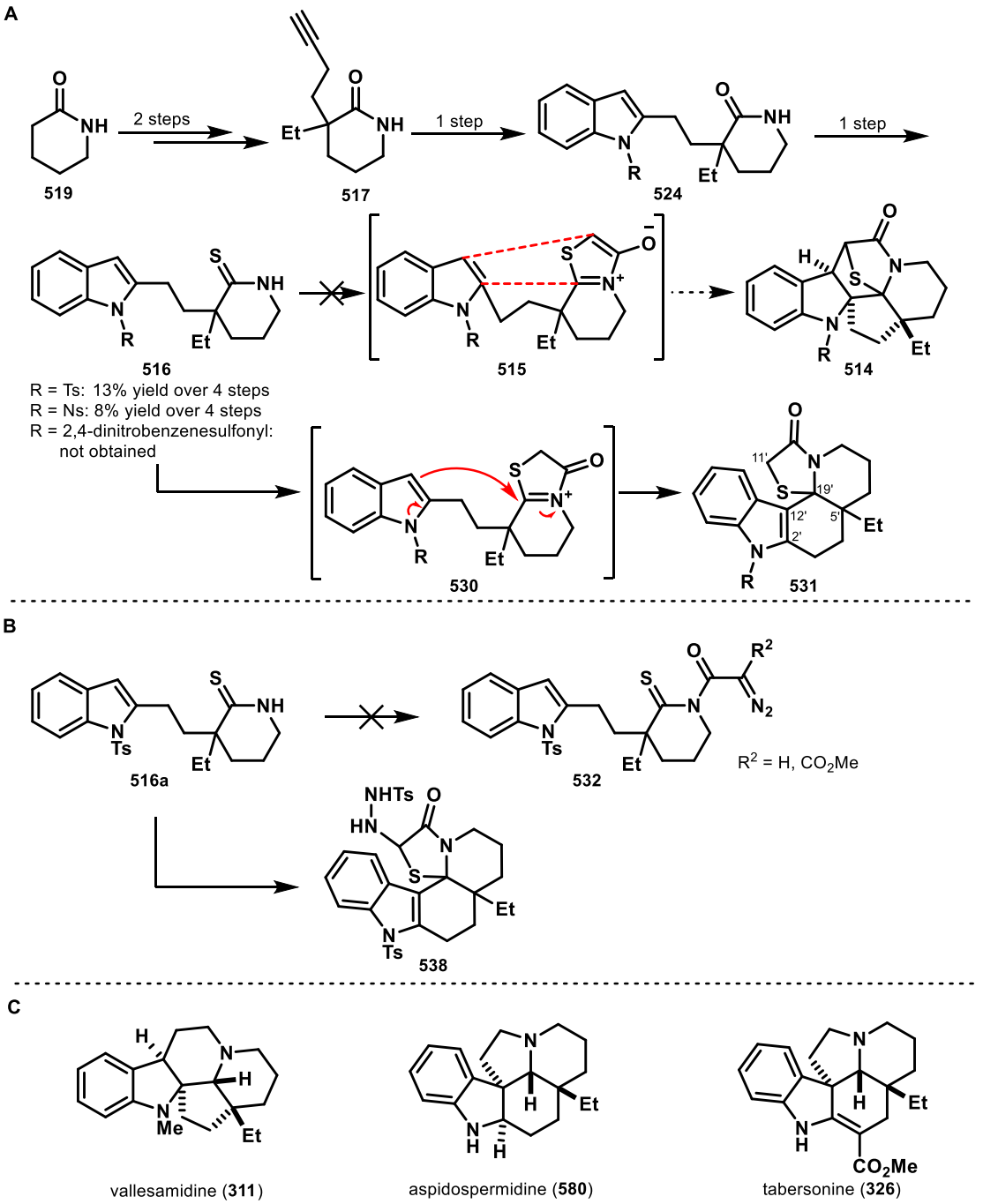


Figure 36: Planned key [3+2]-cycloaddition reactions of respective thioisomünchnone dipoles for the total syntheses of vallesamidine (**311**) and lyconadin C (**397**).

The fused pentacyclic core of indoline alkaloid vallesamidine (**311**) was envisioned to emerge from intramolecular [3+2]-cycloaddition of the thioisomünchnone moiety to the indolyl π-bond in intermediate **515**. Similarly, ring annulation by [3+2]-cycloaddition of the thioisomünchnone dipole to the terminal olefin in **540** was planned to generate the tetracyclic carbon framework of lyconadin C (**397**).

Synthesis of thiolactam cycloaddition precursors **516a** and **516b** with electron-withdrawing *N*-protecting groups was successfully accomplished in four steps with an overall yield of 13% and 8%, respectively (see *Scheme 109* **A**). A two-step sequence from 2-piperidone (**519**) to literature-known alkyne **517** was established and produced **517** in 26% yield from **519**. A four-steps containing sequence was reported in literature to give the same compound in 59%[197], but the best result upon reproducing this sequence was only 28% over four steps and thus, comparable to the herein developed 2-step sequence. Further conversion of this building block with different 2-iodoanilides **518a/b/c** in a Larock-type indole synthesis succeeded for the *N*-*p*-toluenesulfonyl and the

N-2-nitrobenzenesulfonyl derivatives **518a** and **518b** but did not provide the desired product in case of the 2,4-dinitrobenzenesulfonamide **518c**.

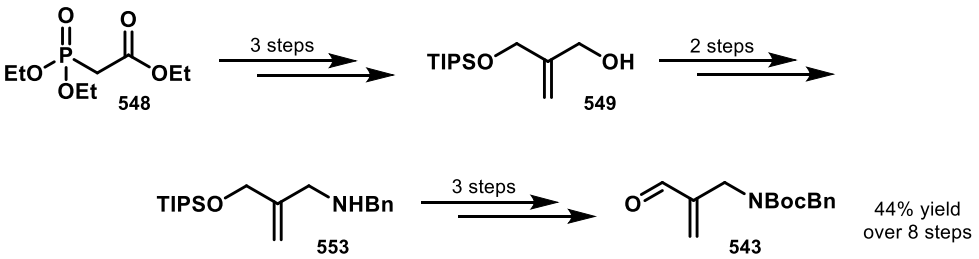


Scheme 109: **A** Synthetic access to cycloaddition precursors **516** and planned vs. observed reactivity; **B** Unsuccessful attempt toward diazo thioamide precursor **532**; **C** Vallesamidine (**311**) and related *Aspidosperma* alkaloids **580**, **326**.

Reaction with Lawesson's reagent furnished cycloaddition precursor thiolactams **516**. Formation of the desired thioisomünchnone dipole **515** could not be accomplished and instead, nucleophilic addition of the indole to an intermediate *N*-acyl iminium ion **530** led to formation of **531**. A similar reactivity was previously described in literature[180a] and

could not be altered by an electron-withdrawing character of the indole *N*-protecting group. Moreover, preparation of a diazo thioamide precursor **532** for alternative rhodium(II)-mediated dipole formation failed because of lacking reactivity of thioamide **516a** toward the tested acylating reagents or the occurrence of undesired cyclization by nucleophilic indole addition (*Scheme 109* **B**). These unexpected results prohibited effective investigation of potential alternative dipole formation from a diazo precursor and again require reconsideration of the synthetic planning in terms of effective dipole generation. The obtained structure motifs **531** and **538** with the undesired connection between C12' and C19' resembles to the carbon skeleton of the related *Aspidosperma* alkaloids (see *Scheme 109* **C** for exemplary compounds). Hence, this efficient pathway could potentially be used in future synthetic studies to access the aspidospermin skeleton by C11'-C12' bond formation. Moreover, with regard to the reports of Le Men[139], further cationic rearrangement of this structure motif might eventually allow to access the vallesamidine skeleton.

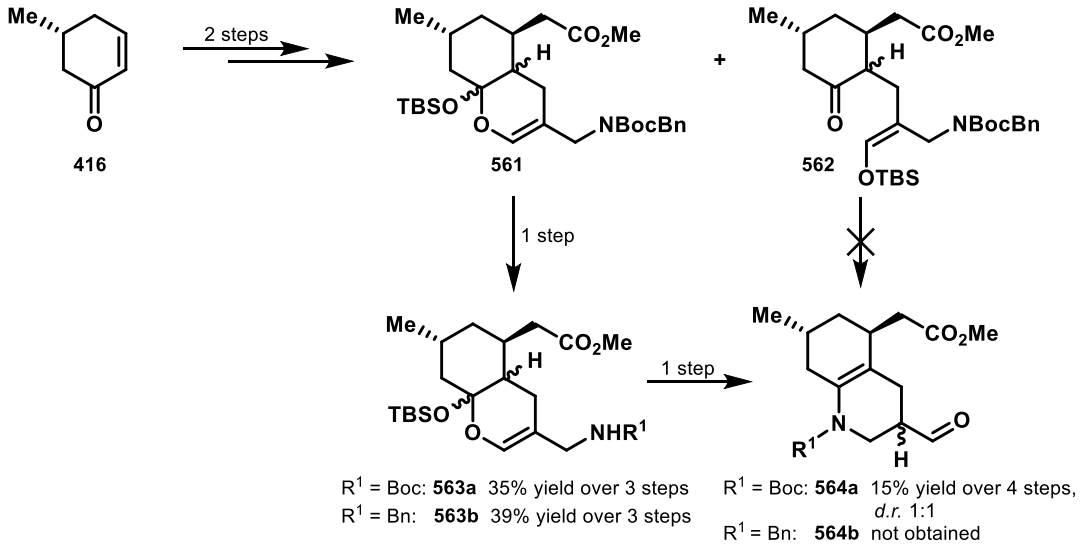
The synthetic approach toward lyconadin C (**397**) comprised the development of a synthetic sequence for preparation of a suitable Michael acceptor. After optimization of the protecting group strategy, acrolein derivative **543** was successfully obtained from triethyl phosphonoacetate (**548**) in eight steps and with an overall yield of 44% (see *Scheme 110*).



Scheme 110: Synthetic access to acrolein derivative **543** from commercial triethyl phosphonoacetate (**548**).

Attachment of this building block to the cyclic starting compound **416** (*Scheme 111*) was accomplished in the course of a two-step functionalization by sequential Mukayiama-Michael addition reactions. Both obtained products **561** and **562** were attempted to be further converted to the desired octahydroquinoline motif **564** by use of a diverse protecting group strategy, which succeeded for cyclic substrate **561** but not its acyclic derivative **562**. The Boc protected ene-carbamate **564a** was obtained as a

1:1 diastereomeric mixture in four steps from starting enone **416** and with an overall yield of 15%. Attempted analogous conversion of the benzyl-substituted derivative **563b** to **564b** did not succeed and decomposition was observed under almost all tested conditions.



Scheme 111: Synthetic access to the octahydroquinoline structure motif.

The preparation of sufficient amounts of material for elaboration of further experiments toward a cycloaddition precursor with an incorporated thioisomünchnone dipole was impeded by the inherent instability of ene-carbamate **564a**, and thus could not be accomplished. These results reveal the necessity to revise the synthetic strategy to effectively access the desired cycloaddition precursor *via* alternative intermediates.

III. Experimental Part

1. General Details

All moisture and oxygen sensitive reactions were performed in flame-dried glassware under a slight nitrogen overpressure. All reactions were stirred magnetically. Sensitive solutions, solvents or reagents were transferred *via* cannula or syringe. Evaporations were conducted under reduced pressure at temperatures less than 40°C, unless otherwise noted. Further dryings of the residues were accomplished using a high vacuum pump. Reactions were monitored by thin-layer chromatography (TLC) or NMR of the crude mixture. TLC was carried out on pre-coated silica gel aluminum plates impregnated with a fluorescent indicator (Merck 60-F254) to monitor all reactions. The detection of spots was performed by using a UV (254nm) lamp followed by visualization with an iodine-, vanillin- or $KMnO_4$-based TLC stain. Flash column chromatography was performed on silica gel (40-63 µm, 240-400 mesh, Merck). All solvents were purchased as the highest available grade from Merck, Acros-Organics or Fisher-Chemicals. Ethyl acetate, hexanes and dichloromethane for column chromatography were distilled and used without further purification. All other reagents were used as received from Merck, Acros-Organics, ABCR, Alfa Aesar, TCI, Fluorochem or Fisher-Chemicals unless otherwise noted. Triethylamine (NEt_3) and diisoproylamine (DIPA) were distilled under nitrogen from calcium hydride prior to use. All other dry solvents were purchased from Acros-Organics as “extra dry” reagents over molecular sieves and used as received.

$Pd(PPh_3)_4$[74], $PdCl_2(dppf)\cdot DCM$[72], $Pd(\eta^3\text{-}PhC_3H_4)(\eta^5\text{-}C_5H_5)$[76] and Ohira-Bestmann reagent[68] were prepared according to literature-known procedures.

2. Analytical Methods

All NMR spectra were measured on a Bruker Avance III 400, Avance III 600 or JEOL RESONANCE ECZ 400S. Chemical shifts are given in ppm and referenced to the solvent residual peaks (Chloroform-D ^{1}H δ = 7.26 ppm, ^{13}C δ = 77.00 ppm; Benzene-D_6 ^{1}H δ = 7.16 ppm, ^{13}C δ = 128.06 ppm; DMSO-D_6 ^{1}H δ = 2.50 ppm, ^{13}C δ = 39.5 ppm). Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constant *J*, integration. In case of combined multiplicities, the multiplicity with the larger coupling constant is stated first.

High resolution mass spectra were measured on an LTQ Orbitrap Velos spectrometer from Thermo Fisher Scientific (Velos Pro) with or without loop-mode injection from a Waters (RP18) HPLC system or a Micromass LCT spectrometer *via* loop-mode injection from a Waters (Alliance 2695) HPLC system. Ionization was achieved by ESI, modes of ionization, calculated and found mass are given.

IR spectra were measured on a PerkinElmer Spectrum 100 FT-IR spectrometer. Data are given in frequency of absorption in wavenumber [cm^{-1}]. Samples were prepared as neat film.

Optical rotation was measured on a Jasco P-2000 polarimeter using the sodium D line (589nm). Concentration (in g/100 mL) and solvent are denoted.

Chiral HPLC analysis was performed on an Agilent 1100 series HPLC-System with a Chiral PAK AD column.

X-ray diffraction analysis of single crystals was performed at 100K on a STOE IPDS-II diffractometer equipped with a graphite-monochromated radiation source (λ = 0.71073Å) and an image plate detection system. A crystal mounted on a fine glass fiber with silicon grease was employed.

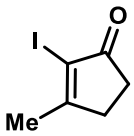
Melting points of crystalline materials were determined in open capillaries with a Krüss Melting-Point Meter KSP1 and are uncorrected.

3. Experimental procedures

3.1 The Total Synthesis of Waihoensene

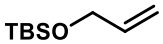
3.1.1 Approach A: Construction of the *cis*-Hydrindane Core Structure *via* Reductive Olefin Coupling

2-iodo-3-methylcyclopent-2-en-1-one (209)[218]



Iodine (15.5 g, 61.2 mmol, 1.50 eq.) and PDC (4.59 g, 12.2 mmol, 0.30 eq.) were added to a solution of 3-methylcyclopent-2-en-1-one (4 mL, 40.8 mmol, 1.00 eq.) in DCM (270 mL, 0.15 M) and the reaction was stirred at room temperature for 48 hours under light exclusion. The mixture was filtered over Celite and consecutively washed with 1 M HCl, saturated $Na_2S_2O_3$ and brine. The solution was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Pure 2-iodo-3-methylcyclopent-2-en-1-one (**209**) (7.94 g, 35.8 mmol) was obtained in 88% yield by gradient column chromatography on silica gel (10:1, then 3:1 hexanes/EA). The obtained spectroscopic data were consistent with those reported in literature. **^{1}H-NMR** (400 MHz, Chloroform-*D*): δ [ppm] = 2.77 – 2.74 (m, 2H), 2.59 – 2.56 (m, 2H), 2.22 (s, 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*): δ [ppm] = 203.7, 179.9, 102.8, 35.9, 34.4, 33.3, 22.2.

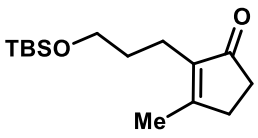
(allyloxy)(*tert*-butyl)dimethylsilane (205)[219]



Allylalcohol (3.4 mL, 50.0 mmol, 1.00 eq.) was dissolved in DCM (100 mL, 0.50 M) and the solution was cooled in a water bath. Imidazole (3.91 g, 57.5 mmol, 1.15 eq.) and TBSCl (8.67 g, 57.5 mmol, 1.15 eq.) were added sequentially. The resulting mixture was stirred at room temperature for 4 h. Saturated aqueous NH_4Cl was added and the phases were separated. The aqueous phase was extracted with DCM and the combined organic phases were dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (20:1 hexanes/EA) to give **205** as a colorless liquid (4.80 g, 27.8 mmol, 56%). The obtained spectroscopic data were consistent with those reported in literature. **^{1}H-NMR** (400 MHz, Chloroform-*D*): δ [ppm] = 5.92 (ddt, *J* = 17.1, 10.4, 4.6 Hz, 1H), 5.27 (dq, *J* = 17.1, 1.9 Hz, 1H), 5.08 (dq, *J* = 10.4, 1.8 Hz, 1H), 4.18 (dt, *J* = 4.6, 1.8 Hz, 2H), 0.92 (s, 9H),

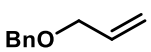
0.07 (s, 6H); **^{13}C-NMR** (101 MHz, Chloroform-*D*): δ [ppm] = 137.7, 114.1, 64.3, 26.1, 18.6, -5.1.

2-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-3-methylcyclopent-2-en-1-one (210)



In a flame-dried Schlenk tube, allylic alcohol **205** (505 mg, 2.93 mmol, 1.30 eq.) was degassed *via* freeze-pump-thaw (3 cycles). 9-BBN (0.5 M solution in THF, 5.9 mL, 2.93 mmol, 1.30 eq.) was added dropwise at 0 °C over a period of 15 minutes. The resulting suspension was stirred and warmed to room temperature overnight. In a separate Schlenk tube, α-iodoenone **209** (500 mg, 2.25 mmol, 1.00 eq.), K_3PO_4 (573 g, 2.70 mmol, 1.20 eq.), $PdCl_2$(dppf)·DCM (37.0 mg, 0.05 mmol, 0.02 eq.) and water (0.4 mL, 22.5 mmol, 10.0 eq.) were suspended in DMF (9.4 mL, 0.24 M), and the mixture was degassed *via* freeze-pump-thaw. Under vigorous stirring, the pre-formed borane was added dropwise. The reaction was heated to 50 °C for 7.5 h. After cooling to room temperature, water was added and the mixture was extracted with Et_2O. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (10:1 hexanes/EA). **210** was obtained in 71% yield (429 mg, 1.60 mmol). **R_F** = 0.36 (7:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*): δ [ppm] = 3.57 (t, *J* = 6.3 Hz, 2H), 2.52 – 2.44 (m, 2H), 2.38 – 2.31 (m, 2H), 2.27 – 2.19 (m, 2H), 2.05 (s, 3H), 1.65 – 1.53 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H); **^{13}C-NMR** (101 MHz, Chloroform-*D*): δ [ppm] = 209.8, 170.6, 140.4, 62.7, 34.5, 31.7, 31.4, 26.1, 19.4, 18.4, 17.3, -5.1; **IR** (film) ν 2932, 2855, 2346, 1696, 1650, 1441, 1386, 1256, 1177, 1098, 837, 777 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{15}H_{29}O_2Si^+$ $[M+H]^+$: 269.1931; found: 269.1922.

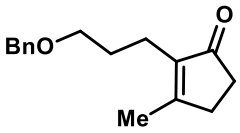
((allyloxy)methyl)benzene (206)[220]



NaH (60% dispersion in mineral oil, 2.60 g, 65.0 mmol, 1.30 eq.) was suspended in anhydrous THF (10 mL) and cooled to 0 °C. Allylalcohol (6.8 mL, 100 mmol, 2.00 eq.) was dissolved in THF (15 mL) and added dropwise. The reaction mixture was stirred for 1 h at 0 °C before benzyl bromide (5.9 mL, 50.0 mmol, 1.00 eq.) was added dropwise. After complete addition, the cooling bath was removed and the reaction was allowed to warm to room temperature. The reaction was heated to reflux for 1 h. Saturated NH_4Cl was added and the mixture was extracted with DCM. The combined organic phases

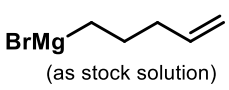
were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude material was purified by column chromatography on silica gel (20:1 hexanes/EA) and the desired benzyl alcohol **206** was obtained in quantitative yield (7.39 g, 49.9 mmol). The obtained spectroscopic data were consistent with those reported in literature. **^{1}H-NMR** (400 MHz, Chloroform-*D*): δ [ppm] = 7.39 – 7.26 (m, 5H), 5.97 (ddt, *J* = 17.2, 10.3, 5.6 Hz, 1H), 5.36 – 5.18 (m, 2H), 4.53 (s, 2H), 4.04 (dt, *J* = 5.6, 1.4 Hz, 2H), 1.57 (s, OH).; **^{13}C-NMR** (101 MHz, Chloroform-*D*): δ [ppm] = 138.5, 134.9, 128.5, 127.9, 127.7, 117.3, 72.3, 71.3.

2-(3-(benzyloxy)propyl)-3-methylcyclopent-2-en-1-one (201)



In a flame-dried Schlenk tube, ((allyloxy)methyl)benzene (**206**) (1.00 g, 6.76 mmol, 1.50 eq.) was dissolved in anhydrous THF (6 mL, 1.10 M), and the resulting solution was degassed *via* freeze-pump-thaw (3 cycles). 9-BBN (0.47 M solution in THF, 14.5 mL, 6.76 mmol, 1.50 eq.) was added dropwise at -10 °C over a period of 15 minutes. The resulting suspension was warmed to room temperature and stirred for 4 hours. The amount of solvent was reduced by 50% *in vacuo.* In a separate Schlenk tube, α-iodoenone **209** (1.00 g, 4.50 mmol, 1.00 eq.), Cs_2CO_3 (2.64 g, 8.10 mmol, 1.80 eq.), $PdCl_2$(dppf)·DCM (0.11 g, 0.14 mmol, 0.03 eq.) and Ph_3As (0.14 g, 0.45 mmol, 0.10 eq.) were suspended in DMF (15 mL, 0.30 M), and the mixture was degassed *via* freeze-pump-thaw. Under vigorous stirring, water (1 mL, 54.0 mmol, 12.0 eq.) and the pre-formed borane were added dropwise. An exothermic reaction was observed and the color of the mixture turned darker. After 1.5 hours at room temperature, saturated NH_4Cl was added and the mixture was extracted with Et_2O. After removal of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel (7:1 hexanes/EA). The desired product **201** was obtained in 70% yield (0.76 g, 3.11 mmol). **R_F** = 0.16 (7:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*): δ [ppm] = 7.37 – 7.26 (m, 5H), 4.48 (s, 2H), 3.43 (t, *J* = 6.3 Hz, 2H), 2.50 – 2.46 (m, 2H), 2.36 – 2.33 (m, 2H), 2.28 (dd, *J* = 8.3, 6.7 Hz, 2H), 2.04 (s, 3H), 1.75 – 1.68 (m, 2H); **^{13}C-NMR** (101 MHz, Chloroform-*D*): δ [ppm] = 209.8, 170.8, 140.1, 138.7, 128.5, 127.8, 127.6, 73.0, 69.9, 34.5, 31.7, 28.3, 19.8, 17.3; **IR** (film) ν 2916, 2855, 1693, 1645, 1496, 1441, 1385, 1353, 1305, 1198, 1177, 1097, 1028, 985, 946, 857, 815, 735, 697 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{16}H_{21}O_2^+$ $[M+H]^+$: 245.1536; found: 245.1530.

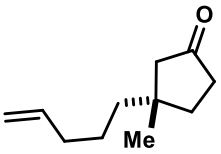
pent-4-en-1-ylmagnesium bromide (580) stock solution



(as stock solution)

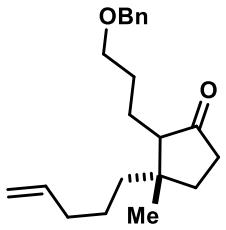
In a 250 mL flame-dried three-necked round bottom flask, magnesium turnings (2.43 g, 100 mmol, 2.00 eq.) were covered with anhydrous Et_2O. The reaction was initiated by the addition of 0.5 mL 5-bromopent-1-ene and heating with a heatgun. Remaining 5-bromopent-1-ene (4.6 mL, 50.0 mmol in total, 1.00 eq.) was dissolved in Et_2O (100 mL, 0.50 M) and added dropwise to the refluxing reaction mixture. After complete addition, the reaction was heated to reflux for 2 h. The concentration of Grignard reagent **580** was determined by titration[221] with (-)-menthol and 1,10-phenanthroline to be 0.47 M. Storage at 4 °C under N_2.

3-methyl-3-(pent-4-en-1-yl)cyclopentan-1-one (211)



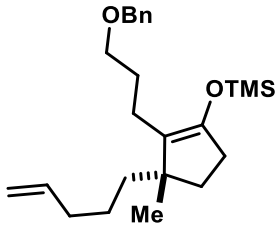
A solution of *t*-BuLi (1.9 M solution in pentane, 1.4 mL, 2.60 mmol, 5.00 eq.) was cooled to -78 °C and 5-bromopent-1-ene (194 mg, 1.30 mmol, 2.50 eq.) in Et_2O (7.6 mL, 0.17 M) was added dropwise. The resulting solution was stirred for 30 min before CuCN (128 mg, 1.43 mmol, 2.75 eq.) was added in one portion. The flask was transferred into a -55 °C cooling bath for 5 min (until dissolution of the solid) and then re-cooled to -78 °C. In a separate flask, enone **202** (50 mg, 0.52 mmol, 1.00 eq.) was dissolved in Et_2O (4 mL, 0.13 M) and cooled to -78 °C. $BF_3{\cdot}OEt_2$ (0.17 mL, 1.30 mmol, 2.50 eq.) was added and the pre-cooled mixture was added dropwise to the cuprate solution. After 30 min the reaction was quenched by the addition of aqueous saturated $NaHCO_3$ and warmed to room temperature. The mixture was extracted with Et_2O and the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (10:1 hexanes/EA). $\mathbf{R_F}$ = 0.68 (5:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*): δ [ppm] = 5.80 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.01 (dq, *J* = 17.1, 1.6 Hz, 1H), 4.96 (ddt, *J* = 10.2, 2.2, 1.2 Hz, 1H), 2.32 – 2.24 (m, 2H), 2.11 – 1.97 (m, 4H), 1.85 – 1.71 (m, 2H), 1.51 – 1.28 (m, 4H), 1.05 (s, 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*): δ [ppm] = 220.2, 138.7, 114.9, 52.4, 41.4, 39.6, 36.9, 35.4, 34.4, 25.2, 24.2; **IR** (film) ν 2932, 1739, 1641, 1461, 1405, 1380, 1257, 1166, 993, 909 cm^{-1}.

2-(3-(benzyloxy)propyl)-3-methyl-3-(pent-4-en-1-yl)cyclopentan-1-one (212)



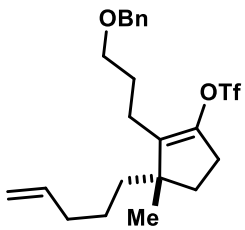
In a flame-dried Schlenk tube, a solution of *t*-BuLi (1.9 M solution in pentane, 1.1 mL, 2.04 mmol, 5.00 eq.) was cooled to -78 °C and 5-bromopent-1-ene (152 mg, 1.02 mmol, 2.50 eq.) in Et_2O (6 mL, 0.17 M) was added dropwise. The resulting solution was stirred for 30 min before CuCN (100 mg, 1.12 mmol, 2.75 eq.) was added in one portion. The flask was transferred into a -55 °C cooling bath for 5 min (until dissolution of the solid) and then re-cooled to -78 °C. In a separate flask, enone **201** (100 mg, 0.41 mmol, 1.00 eq.) was dissolved in Et_2O (3.2 mL, 0.13 M) and cooled to -78 °C. $BF_3{\cdot}OEt_2$ (0.13 mL, 1.02 mmol, 2.50 eq.) was added and the pre-cooled mixture was added dropwise to the cuprate solution. After 30 min the reaction was quenched by the addition of aqueous saturated $NaHCO_3$ and warmed to room temperature. The mixture was extracted with Et_2O and the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (10:1 hexanes/EA). The desired ketone **212** was obtained as a 0.67:1 mixture of diastereomers in 51% yield (65.0 mg, 0.21 mmol). **R_F** = 0.30 (10:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*): δ [ppm] = 7.37 – 7.26 (m, 5H), 5.88 – 5.71 (m, 1H), 5.06 – 4.92 (m, 2H), 4.51 (s, 2H), 3.55 – 3.43 (m, 2H), 2.33 – 2.20 (m, 1H), 2.19 – 2.06 (m, 2H), 2.05 – 1.88 (m, 3H), 1.86 – 1.79 (m, 1H), 1.75 – 1.69 (m, 1H), 1.69 – 1.63 (m, 1H), 1.61 – 1.45 (m, 3H), 1.44 – 1.28 (m, 4H), 1.27 – 1.13 (m, 1H), 1.10 (s, 1.2H), 0.79 (s, 1.8H); **^{13}C-NMR** (101 MHz, Chloroform-*D*): δ [ppm] = 220.7, 220.7, 138.8, 138.8, 138.7, 128.5, 127.8, 127.63, 114.90, 114.83, 72.98, 70.56, 70.45, 61.04, 59.13, 42.44, 42.19, 41.06, 35.12, 35.08, 34.5, 34.5, 33.6, 32.7, 31.7, 28.8, 28.6, 26.0, 23.8, 23.6, 21.4, 21.1, 19.7; **IR** (film) ν 2932, 2858, 1735, 1640, 1454, 1411, 1361, 1204, 1099, 1028, 992, 909, 734, 697 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{21}H_{31}O_2^+$ $[M+H]^+$: 315.2319; found: 315.2310.

((2-(3-(benzyloxy)propyl)-3-methyl-3-(pent-4-en-1-yl)cyclopent-1-en-1-yl)oxy)trimethyl-silane (203)



Pent-4-en-1-ylmagnesium bromide (**580**) (0.47 M in Et_2O, 13 mL, 6.27 mmol, 2.00 eq.) was cooled to 0 °C, and CuI (180 mg, 0.94 mmol, 0.30 eq.) was added in one portion. The mixture was stirred for 20 minutes at 0 °C, and was then cooled to -78 °C. A mixture of NEt_3 (2.1 mL, 15.4 mmol, 4.90 eq.) and TMSCl (2 mL, 16.0 mmol, 5.10 eq.), and TMEDA (0.6 mL, 4.08 mmol, 1.30 eq.) were added sequentially, and the resulting mixture was stirred for 20 minutes. Enone **201** (766 mg, 3.14 mmol, 1.00 eq.) in THF (2.1 mL, 1.50 M) was added dropwise, and the color of the reaction mixture turned yellow. After five hours at -78 °C, the cooling bath was removed, and the reaction was quenched by the addition of ice-cold saturated NH_4Cl. The mixture was extracted with ethyl acetate, and the combined organic layers were washed with saturated $NaHCO_3$ and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (15:1 hexanes/EA). Silylenol ether **203** was obtained as colorless oil in 74% yield (895 mg, 2.31 mmol). $\mathbf{R_F}$ = 0.55 (20:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*): δ [ppm] = 7.37 – 7.26 (m, 5H), 5.86 – 5.75 (m, 1H), 5.05 – 4.88 (m, 2H), 4.51 (s, 2H), 3.48 (t, J = 6.7 Hz, 2H), 2.29 – 2.15 (m, 2H), 2.08 – 1.93 (m, 3H), 1.92 – 1.82 (m, 1H), 1.74 (dddd, *J* = 13.9, 12.7, 8.3, 6.3 Hz, 3H), 1.50 (dddd, *J* = 12.7, 8.7, 6.5, 0.7 Hz, 1H), 1.37 – 1.20 (m, 4H), 0.99 (s, 3H), 0.17 (s, 9H).; **^{13}C-NMR** (101 MHz, Chloroform-*D*): δ [ppm] = 147.0, 139.4, 139.0, 128.5, 127.7, 127.5, 123.0, 114.3, 72.8, 71.2, 46.5, 40.5, 34.7, 34.0, 32.0, 29.2, 27.5, 24.3, 20.6, 0.8; **IR** (film) ν 2950, 2851, 1675, 1641, 1455, 1317, 1251, 1205, 1099, 1001, 908, 841, 734, 696 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{24}H_{39}O_2Si^+$ $[M+H]^+$: 387.2714; found: 387.2710.

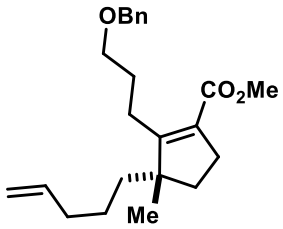
2-(3-(benzyloxy)propyl)-3-methyl-3-(pent-4-en-1-yl)cyclopent-1-en-1-yl trifluoromethane-sulfonate (216)



Silylenol ether **203** (150 mg, 0.39 mmol, 1.00 eq.) was dissolved in THF (0.3 mL) and cooled to 0 °C. MeLi (1.6 M in Et_2O, 0.5 mL, 0.85 mmol, 2.20 eq.) was added dropwise, and the reaction was warmed to room temperature and stirred for 3 h. The reaction was cooled to -78 °C and bis(trifluoromethanesulfonyl)aniline (304 mg, 0.85 mmol, 2.20 eq.) in

THF (0.7 mL) was added dropwise. The mixture was warmed to room temperature overnight and stirred for 24 hours. Water was added and the mixture was extracted with Et_2O. The combined organic phases were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel (100:1 hexanes/EA). Vinyl triflate **216** was obtained as a colorless oil in 69% yield (120 mg, 0.27 mmol). $\mathbf{R_F}$ = 0.57 (20:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*): δ [ppm] = 7.38 – 7.27 (m, 5H), 5.79 (ddt, *J* = 16.9, 10.1, 6.6 Hz, 1H), 5.07 – 4.91 (m, 2H), 4.51 (s, 2H), 3.49 (t, *J* = 6.3 Hz, 2H), 2.55 (t, *J* = 7.4 Hz, 2H), 2.24 – 2.12 (m, 1H), 2.10 – 1.98 (m, 3H), 1.89 (dt, *J* = 12.7, 7.2 Hz, 1H), 1.79 (dq, *J* = 7.9, 6.4 Hz, 2H), 1.68 (dt, *J* = 12.8, 7.4 Hz, 1H), 1.44 – 1.32 (m, 3H), 1.31 – 1.18 (m, 2H), 1.08 (s, 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*): δ [ppm] = 143.2, 138.7, 138.7, 137.9, 128.5, 127.7, 127.7, 114.9, 73.0, 70.3, 47.0, 39.7, 34.3, 33.6, 29.1, 28.6, 26.5, 23.8, 20.9; **^{19}F-NMR** (377 MHz, Chloroform-*D*): δ [ppm] = -74.42; **IR** (film) ν 2934, 2865, 1691, 1642, 1455, 1416, 1249, 1205, 1139, 1028, 988, 936, 911, 829, 734, 696 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{22}H_{30}F_3O_4S^+$ $[M+H]^+$: 447.1811; found: 447.1812.

methyl 2-(3-(benzyloxy)propyl)-3-methyl-3-(pent-4-en-1-yl)cyclopent-1-ene-1-carboxylate (200)

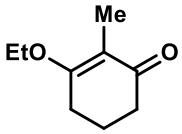


Vinyl triflate **216** (45.0 mg, 101 µmol, 1.00 eq.), Et_3N (40.0 µL, 303 µmol, 3.00 eq.), MeOH (0.5 mL, 0.2 M) and DMF (1.0 mL, 0.1 M) were mixed in a Schenk flask. P(*t*-Bu)$_3$ (4.9 µL, 20.0 µmol, 0.20 eq.) and Pd(η^3-1-PhC_3H_4)(η^5-C_5H_5) (3.00 mg, 10.0 µmol, 0.10 eq.) were added and CO gas was bubbled through the solution for 5 minutes. The flask was sealed with a rubber septum and a CO-balloon was set up. The reaction was heated to 80 °C for 24 hours. After cooling to room temperature, water was added and the mixture was extracted with Et_2O. The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (40:1 hexanes/EA). The desired α,β-unsaturated methyl ester **200** was obtained in 44% yield (78% brsm, 16.0 mg, 45.0 µmol). $\mathbf{R_F}$ = 0.23 (20:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*): δ [ppm] = 7.39 – 7.26 (m, 5H), 5.78 (ddt, *J* = 16.9, 10.1, 6.7 Hz, 1H), 5.03 – 4.90 (m, 2H), 4.53 (s, 2H), 3.70 (s, 3H), 3.54 (t, J = 6.4 Hz, 2H), 2.56 – 2.43 (m, 3H), 2.29 (td, *J* = 11.6, 5.7 Hz,

1H), 2.06 – 1.96 (m, 2H), 1.88 – 1.68 (m, 3H), 1.59 – 1.51 (m, 1H), 1.46 – 1.31 (m, 3H), 1.30 – 1.16 (m, 1H), 1.05 (s, 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*): δ [ppm] = 166.7, 165.9, 138.9, 138.9, 128.5, 127.8, 127.6, 127.1, 114.7, 72.9, 71.1, 52.8, 51.1, 39.1, 35.0, 34.5, 30.7, 30.0, 25.3, 24.2, 24.0; **IR** (film) ν 2933, 2860, 1709, 1635, 1455, 1433, 1362, 1309, 1264, 1213, 1100, 1028, 998, 909, 733, 697 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{23}H_{33}O_3^+$ [M+H]$^+$: 357.2424; found: 357.2420.

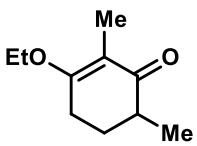
3.1.2 Approach B: Construction of the *cis*-Hydrindane Core Structure *via* Intramolecular Sakurai Reaction

3-ethoxy-2-methylcyclohex-2-en-1-one (581)[222]



In a 500 mL flask with a Dean-Stark trap, 2-methylcyclohexane-1,3-dione (10.0 g, 79.3 mmol, 1.00 eq.) was dissolved in a mixture of ethanol (100 mL, 1.71 mol, 22.0 eq.) and toluene (180 mL). *p*-TsOH (0.30 g, 1.59 mmol, 0.02 eq.) was added, and the resulting mixture was heated to reflux. The water/ethanol/toluene azeotrope was distilled from the reaction and additional 100 mL of an ethanol/toluene mixture (1:2) were added each after 1, 4 and 6 h. After 8 h, the solvent was removed *in vacuo*. The remaining solid was recrystallized from hexane to give the desired vinylogous ester **581** as pale yellow crystals in 96% yield (11.7 g, 75.9 mmol). The obtained spectroscopic data were consistent with those reported in literature. **m.p.** 58 °C; **^{1}H-NMR** (400 MHz, Chloroform-*D*): δ [ppm] = 4.05 (q, *J* = 7.0 Hz, 2H), 2.55 – 2.52 (m, 2H), 2.35 – 2.30 (m, 2H), 1.96 (p, *J* = 6.3 Hz, 2H), 1.69 (t, *J* = 1.6 Hz, 3H), 1.34 (t, *J* = 7.0 Hz, 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*): δ [ppm] = 199.0, 171.5 115.3, 63.6, 36.5, 25.5, 21.2, 15.5, 7.6.

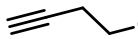
3-ethoxy-2,6-dimethylcyclohex-2-en-1-one (230)



In a flame-dried 250 mL Schlenk flask, DIPA (12 mL, 88.2 mmol, 1.20 eq.) was dissolved in THF (37 mL) and *n*-BuLi (2.5 M solution in hexanes, 32 mL, 80.9 mmol, 1.10 eq.) was added dropwise at -20 °C. The mixture was stirred for 15 mins at this temperature and then cooled to -78 °C. Vinylogous ester **581** (11.3 g, 73.5 mmol, 1.00 eq.) in THF (93 mL) was added, and the reaction was stirred for 1 h before DMPU (8 mL, 66.2 mmol, 0.90 eq.) was added. After 20 min, methyl

iodide (4.8 mL, 77.2 mmol, 1.05 eq.) was added and the reaction was stirred for 2 h at -78 °C, and was then allowed to warm to room temperature in the cooling bath overnight. The reaction was quenched by the addition of ice-cold water, and the mixture was extracted with Et_2O. The combined organic phases were washed with brine and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave a pale yellow solid, which was recrystallized from hexane. Yield 80% (9.81 g, 58.3 mmol). The obtained spectroscopic data were consistent with those reported in literature[223]. **m.p.** 47 °C; **^{1}H-NMR** (400 MHz, Chloroform-*D*): *δ* [ppm] = 4.12 – 3.98 (m, 2H), 2.67 – 2.58 (m, 1H), 2.56 – 2.46 (m, 1H), 2.32 – 2.21 (m, 1H), 2.06 (dq, *J* = 13.1, 4.9 Hz, 1H), 1.70 (t, *J* = 1.6 Hz, 3H), 1.72 – 1.62 (m, 1H), 1.34 (t, *J* = 7.0 Hz, 3H), 1.14 (d, *J* = 6.8 Hz, 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*): *δ* [ppm] = 201.4, 170.3, 114.5, 63.4, 39.6, 29.1, 24.7, 15.8, 15.5, 7.9.

2-(but-3-yn-1-yloxy)tetrahydro-2H-pyran (231)[80]



3-Butyn-1-ol (5.4 mL, 71.3 mmol, 1.00 eq.) and *p*-TsOH·H_2O (0.68 g, 3.57 mmol, 0.05 eq.) were dissolved in THF (25 mL) and the resulting mixture was cooled in an ice bath. 3,4-Dihydropyran (7.8 mL, 85.6 mmol, 1.20 eq.) was added dropwise and the reaction was stirred at 0 °C for 60 mins. Saturated $NaHCO_3$ was added and the mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (10:1 hexanes/EA) to give the desired product **231** in 90% yield (9.87 g, 64.0 mmol). The obtained spectroscopic data were consistent with those reported in literature. **R_F** = 0.75 (5:1 hexanes/EA); **^{1}H-NMR** (800 MHz, Chloroform-*D*): δ [ppm] = 4.62 (t, *J* = 3.7 Hz, 1H), 3.86 (ddd, *J* = 11.3, 8.5, 2.9 Hz, 1H), 3.81 (dt, *J* = 9.8, 7.0 Hz, 1H), 3.54 (dt, *J* = 9.8, 7.1 Hz, 1H), 3.51 – 3.46 (m, 1H), 2.47 (td, *J* = 7.0, 2.7 Hz, 2H), 1.95 (t, *J* = 2.7 Hz, 1H), 1.84 – 1.76 (m, 1H), 1.69 (ddt, *J* = 13.2, 9.8, 3.4 Hz, 1H), 1.62 – 1.53 (m, 2H), 1.52 – 1.48 (m, 2H); **^{13}C-NMR** (201 MHz, Chloroform-*D*): *δ* [ppm] = 98.8, 81.5, 69.3, 65.6, 62.3, 30.6, 25.5, 20.0, 19.5.

trimethyl(5-((tetrahydro-2H-pyran-2-yl)oxy)pent-2-yn-1-yl)silane (232)[80]

Alkyne **231** (20.0 g, 0.13 mol, 1.00 eq.) was dissolved in THF (430 mL) and the solution was cooled to -78 °C. DMPU (42 mL, 0.35 mol, 2.70 eq.) and *n*-BuLi (67 mL, 0.17 mol, 1.30 eq.) were added sequentially. The reaction was stirred for

15 mins and was then warmed to -60 °C. $TMSCH_2I$ (25 mL, 0.17 mol, 1.30 eq.) was added dropwise and the mixture was kept between -60 and -50 °C for 14 h. The reaction was allowed to warm to room temperature and was quenched by the addition of water. The mixture was extracted with Et_2O, the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and compound **232** was obtained as a colorless liquid by distillation under reduced pressure (10-2 mbar, 65-82 °C) and flash column chromatography on silica gel (30:1 hexanes/EA). Yield 79% (24.6 g, 0.10 mmol). The obtained spectroscopic data were consistent with those reported in literature. $\mathbf{R_F}$ = 0.37 (20:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*): δ [ppm] = 4.68 – 4.60 (m, 1H), 3.88 (ddd, J = 11.3, 8.3, 3.5 Hz, 1H), 3.81 – 3.73 (m, 1H), 3.50 (dt, J = 9.6, 7.3 Hz, 2H), 2.45 (tt, J = 7.3, 2.7 Hz, 2H), 1.88 – 1.76 (m, 1H), 1.76 – 1.65 (m, 1H), 1.65 – 1.47 (m, 4H), 1.42 (t, J = 2.7 Hz, 2H), 0.08 (s, 9H); **^{13}C-NMR** (101 MHz, Chloroform-*D*): *δ* [ppm] = 98.9, 78.7, 75.5, 66.8, 62.3, 30.8, 25.6, 20.6, 19.6, 7.1, -2.0.

5-(trimethylsilyl)pent-3-yn-1-ol (234)

Alkyne **232** (3.24 g, 13.5 mmol, 1.00 eq.) and pyridinium *p*-toluenesulfonate (1.36 g, 5.40 mmol, 0.40 eq.) were dissolved in MeOH (17 mL) and the reaction was heated to 45 °C for 4 h. The mixture was concentrated under reduced pressure and Et_2O was added. The organic phase was washed with brine, dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude alcohol was purified by column chromatography on silica gel (10:1 hexanes/EA). 5-(Trimethylsilyl)pent-3-yn-1-ol (**234**) was obtained as a colorless oil in 92% yield (1.94 g, 12.4 mmol). The obtained spectroscopic data were consistent with those reported in literature[80]. $\mathbf{R_F}$ = 0.30 (5:1 hexanes/EA); brownish with vanillin stain; **^{1}H-NMR** (500 MHz, Chloroform-*D*): δ [ppm] = 3.66 (t, *J* = 6.2 Hz, 2H), 2.43 (ddd, *J* = 8.9, 6.2, 2.7 Hz, 2H), 1.73 (bs, 1H), 1.45 (t, *J* = 2.7 Hz, 2H), 0.10 (s, 9H); **^{13}C-NMR** (126 MHz, Chloroform-*D*): *δ* [ppm] = 80.4, 75.0, 61.8, 23.5, 7.1, -2.0.

5-(trimethylsilyl)pent-3-yn-1-yl methanesulfonate (582)[224]

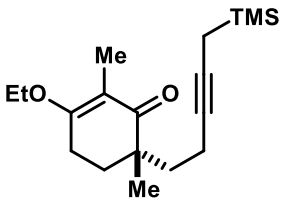
Alcohol **234** (4.00 g, 25.6 mmol, 1.00 eq.) was dissolved in DCM (85 mL) and cooled to 0 °C. MsCl (3 mL, 38.4 mmol, 1.5 eq.) and NEt_3 (5.3 mL, 38.4 mmol, 1.5 eq.) were added sequentially and the reaction mixture was stirred for 6 h at 0 °C. Saturated NH_4Cl was added, and the mixture was allowed to warm to room

temperature and was extracted with DCM. The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (5:1 hexanes/EA) to give the desired mesylated alcohol **582** as a colorless oil (5.68 g, 24.3 mmol, 95%). The obtained spectroscopic data were consistent with those reported in literature. $\mathbf{R_F}$ = 0.30 (5:1 hexanes/EA); red with vanillin stain; **^{1}H-NMR** (400 MHz, Chloroform-*D*): δ [ppm] = 4.25 (t, *J* = 7.0 Hz, 2H), 3.03 (s, 3H), 2.62 (tt, *J* = 7.0, 2.7 Hz, 2), 1.42 (t, *J* = 2.7 Hz, 2H), 0.09 (s, 9H); **^{13}C-NMR** (126 MHz, Chloroform-*D*): *δ* [ppm] = 80.8, 72.7, 68.3, 37.8, 20.4, 7.0, -2.0.

(5-iodopent-2-yn-1-yl)trimethylsilane (235)[224]

Mesylate **582** (5.68 g, 24.3 mmol, 1.00 eq) was dissolved in acetone (121 mL) and sodium iodide (7.27 g, 48.5 g, 2.00 eq.) was added in one portion. The mixture was heated to reflux for 6 h and cooled to room temperature. Water was added and the mixture was extracted with hexanes. The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude iodide was subjected to column chromatography on silica gel (20:1 hexanes/EA) to yield a colorless oil (5.92 g, 22.2 mmol, 92%). The obtained spectroscopic data were consistent with those reported in literature. *Can be stored at -20 °C for short period, decomposition at 8 °C observed!* $\mathbf{R_F}$ = 0.50 (100% hexanes); **^{1}H-NMR** (400 MHz, Chloroform-*D*): δ [ppm] = 3.23 (t, *J* = 7.3 Hz, 2H), 2.76 (tt, *J* = 7.2, 2.6 Hz, 2H), 1.44 (t, *J* = 2.7 Hz, 2H), 0.13 (s, 9H); **^{13}C-NMR** (101 MHz, Chloroform-*D*): *δ* [ppm] = 80.3, 77.6, 24.5, 7.2, 3.6, -1.9.

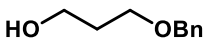
3-ethoxy-2,6-dimethyl-6-(5-(trimethylsilyl)pent-3-yn-1-yl)cyclohex-2-en-1-one (236)



A solution of TMP (5.6 mL, 33.3 mmol, 1.40 eq.) in THF (12 mL) was cooled to 0 °C and *n*-BuLi (2.5 M solution in hexanes, 12.4 mL, 30.9 mmol, 1.30 eq.) was added dropwise. The mixture was stirred for 30 mins at 0 °C and was then cooled to -78 °C. Vinylogous ester **230** (4.00 g, 23.8 mmol, 1.0 eq.) in THF (12 mL) was added dropwise, the reaction was stirred for 30 mins at this temperature and was then removed from the cooling bath for 10 minutes. The reaction was re-cooled to -78 °C and DMPU (4.6 mL, 38.1 mmol, 1.6 eq.)

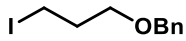
was added. After 10 mins, iodide **235** (12.7 g, 47.6 mmol, 2.00 eq.) was added and the reaction was allowed to warm to room temperature in the cooling bath overnight. The reaction was quenched by addition of aqueous saturated NH_4Cl and the phases were separated. The aqueous layer was extracted with Et_2O and the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (15:1 hexanes/EA) to give the desired alkylated product **236** as a pale yellow oil in 71% yield (5.17 g, 16.9 mmol). $\mathbf{R_F}$ = 0.20 (15:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*) δ [ppm] = 4.05 (q, *J* = 7.0 Hz, 2H), 2.65 – 2.47 (m, 2H), 2.22 – 1.99 (m, 2H), 1.93 (dt, *J* = 12.9, 6.1 Hz, 1H), 1.78 – 1.65 (m, 3H), 1.67 (s, 3H), 1.39 (t, *J* = 2.3 Hz, 2H), 1.34 (t, *J* = 6.6 Hz, 3H), 1.05 (s, 3H), 0.07 (s, 9H).**^{13}C-NMR** (101 MHz, Chloroform-*D*) δ = 202.6, 169.1, 113.5, 79.0, 63.3, 42.5, 37.0, 32.0, 22.4, 22.4, 15.5, 14.4, 8.1, 7.1, -1.9; **IR** (film) ν 2920, 2236, 1709, 1453, 1379, 1250, 1095, 1044, 844, 759, 699 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{18}H_{31}O_2Si^+$ $[M+H]^+$: 307.2088; found:307.2082.

3-(benzyloxy)propan-1-ol (583)[225]



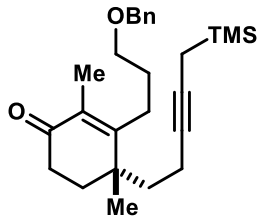
NaH (60% dispersion in mineral oil, 4.40 g, 0.11 mol, 1.10 eq.) was suspended in anhydrous THF (150 mL) and cooled to 0 °C. Propane-1,3-diol (14.5 mL, 0.20 mol, 2.00 eq.) in THF (50 mL) was added dropwise, and the reaction was kept for 1 h at 0 °C. Benzyl bromide (12 mL, 0.10 mol, 1.00 eq.) was added dropwise. The reaction was warmed to room temperature and heated to reflux for 90 min. The reaction was quenched by the addition of aqueous saturated NH_4Cl and the mixture was extracted with DCM. The organic phase was washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude ether was purified by distillation under reduced pressure (77-82 °C, 10^{-2} mbar). Yield 84% (14.0 g, 84.2 mmol). The obtained spectroscopic data were consistent with those reported in literature. **^{1}H-NMR** (400 MHz, Chloroform-*D*): *δ* [ppm] = 7.38 – 7.27 (m, 5H), 4.53 (s, 2H), 3.79 (t, *J* = 5.7 Hz, 2H), 3.67 (t, *J* = 5.7 Hz, 2H), 2.19 (bs, 1H), 1.88 (p, *J* = 5.7 Hz, 2H); **^{13}C-NMR** (101 MHz, Chloroform-*D*): δ [ppm] = 138.2, 128.6, 127.9, 127.8, 73.4, 69.6, 62.1, 32.3.

((3-iodopropoxy)methyl)benzene (241)[225]



3-(Benzyloxy)propan-1-ol (**583**) (6.22 g, 37.4 mmol, 1.00 eq.) was dissolved in DCM (125 mL) and cooled to 0 °C. PPh_3 (10.3 g, 39.3 mmol, 1.05 eq.) and imidazole (2.82 g, 41.4 mmol, 1.10 eq.) were added sequentially. Iodine (11.9 g, 46.8 mmol, 1.25 eq.) was added portionwise and the resulting reaction mixture was stirred for 24 h at room temperature under the exclusion of light. The reaction was quenched by the addition of saturated $Na_2S_2O_3$ and the phases were separated. The aqueous phase was extracted with DCM and the combined organic layers were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was subjected to flash chromatography on silica gel (20:1 hexanes/EA). Pure alkyl iodide **241** was obtained as a pale yellow liquid (9.80 g, 35.5 mmol, 95% yield). The obtained spectroscopic data were consistent with those reported in literature. **^{1}H-NMR** (400 MHz, Chloroform-*D*): *δ* [ppm] = 7.40 – 7.27 (m, 5H), 4.53 (s, 2H), 3.55 (t, *J* = 5.8 Hz, 2H), 3.31 (t, *J* = 6.8 Hz, 2H), 2.10 (p, *J* = 6.3, 5.8 Hz, 2H); **^{13}C-NMR** (101 MHz, Chloroform-*D*): δ [ppm] = 138.4, 128.6, 127.8, 73.3, 69.8, 33.7, 3.6.

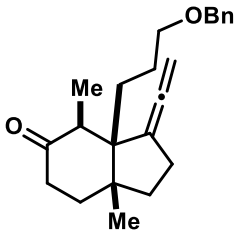
3-(3-(benzyloxy)propyl)-2,4-dimethyl-4-(5-(trimethylsilyl)pent-3-yn-1-yl)cyclohex-2-en-1-one (229)



In a flame-dried Schlenk flask, *t*-BuLi (1.9 M solution in pentane, 6.9 mL, 13.1 mmol, 4.00 eq.) was cooled to -78 °C and iodide **235** (1.80 g, 6.52 mmol, 2.00 eq.) in Et_2O (15 mL) was added over a period of 30 min. The reaction was stirred for 30 min at this temperature before a solution of vinylogous ester **236** (1.00 g, 3.26 mmol, 1.00 eq.) in Et_2O (6.5 mL) was added dropwise. The reaction mixture was allowed to warm to -65 °C over 4 h. TLC indicated complete consumption of the starting material and the reaction was quenched by the addition of 1 M HCl and warmed to room temperature. The mixture was extracted with DCM, and the combined organic layers where washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (10:1 hexanes/EA). The desired enone **229** was obtained as pale yellow oil in 88% yield (1.18 g, 2.87 mmol). **R_F** = 0.47 (5:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*) δ [ppm] = 7.39 – 7.26 (m, 5H), 4.53 (s, 2H), 3.52 (t, *J* = 6.2 Hz, 2H), 2.47 – 2.39 (m, 2H), 2.38 – 2.22 (m, 2H), 2.21 –

2.10 (m, 1H), 2.09 – 1.99 (m, 1H), 1.95 (ddd, *J* = 13.2, 7.4, 5.6 Hz, 1H), 1.82 – 1.63 (m, 5H), 1.79 (s, 3H), 1.40 (t, *J* = 2.7 Hz, 2H), 1.15 (s, 3H), 0.08 (s, 9H); **^{13}C-NMR** (101 MHz, Chloroform-*D*) δ [ppm] = 199.0, 164.0, 138.6, 132.2, 128.6, 127.7, 127.7, 78.4, 78.2, 73.1, 70.4, 39.5, 38.6, 34.1, 33.1, 29.3, 27.6, 24.5, 14.6, 11.9, 7.1, 0.2, -1.9; **IR** (film) ν 2956, 1704, 1661, 1603, 1454, 1378, 1358, 1248, 1203, 1169, 1099, 1073, 1027, 842, 745, 697 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{26}H_{39}O_2Si^+$ $[M+H]^+$: 411.2714; found:411.2707.

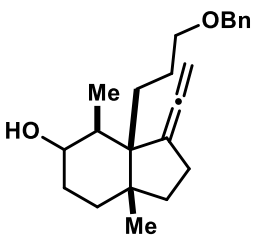
3a-(3-(benzyloxy)propyl)-4,7a-dimethyl-3-vinylideneoctahydro-5*H*-inden-5-one (228)



In a flame-dried Schlenk tube, enone **229** (5.04 g, 12.28 mmol, 1.00 eq.) was dissolved in DCM (51 mL) and cooled to -78 °C. With dropwise addition of $TiCl_4$ (1 M solution in DCM, 21.5 mL, 21.5 mmol, 1.75 eq.) the color of the reaction mixture changed to dark red. After complete addition, the reaction was stirred for 30 mins at -78 °C and was quenched at this temperature by the addition of water. The mixture was warmed to room temperature and DCM and aqueous potassium sodium tartrate solution were added. The slurry was vigorously stirred for 30 mins. The phases were separated and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was subjected to base-catalyzed epimerization. Crude **228** was dissolved in MeOH (123 mL) and aqueous NaOH (5% in H_2O, 14 mL, 18.4 mmol, 1.50 eq.) was added. The mixture was heated to 50 °C for 2.5 h. After cooling to room temperature, MeOH was removed under reduced pressure and aqueous NH_4Cl was added. The product was extracted with DCM and the organic phase was washed with brine and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (5:1 hexanes/EA) to give the desired all-*cis* bicyclic product as a pale yellow oil (3.70 g, 10.9 mmol, 89% over 2 steps). $\mathbf{R_F}$ = 0.36 (5:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*) δ [ppm] = 7.37 – 7.26 (m, 5H), 4.77 (t, *J* = 4.4 Hz, 2H), 4.48 (s, 2H), 3.40 (qt, *J* = 9.3, 6.3 Hz, 2H), 2.57 – 2.45 (m, 4H), 2.33 (dddd, *J* = 14.6, 8.6, 6.0, 1.4 Hz, 1H), 1.94 – 1.86 (m, 2H), 1.80 (ddd, *J* = 14.2, 8.6, 5.8 Hz, 1H), 1.65 – 1.55 (m, 2H), 1.54 – 1.39 (m, 3H), 1.14 (s, 3H), 1.09 (d, *J* = 7.2 Hz, 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*) δ [ppm] = 214.1, 204.1, 138.8, 128.5, 127.7, 127.6, 110.1, 78.4, 72.9, 71.0, 55.6, 47.6, 44.4, 36.0, 35.9, 35.9, 28.0, 25.4, 24.3, 23.1, 11.6; **IR** (film) ν 2956, 2871, 1957, 1705, 1496, 1454, 1373, 1330,

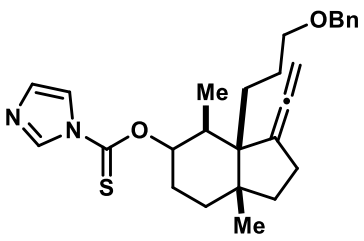
1274, 1203, 1167, 1098, 1027, 1008, 907, 844, 735, 697 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{23}H_{31}O_2^+$ $[M+H]^+$: 339.2319; found: 339.2312.

3a-(3-(benzyloxy)propyl)-4,7a-dimethyl-3-vinylideneoctahydro-1*H*-inden-5-ol (584)



A solution of ketone **228** (100 mg, 0.30 mmol, 1.00 eq.) in MeOH (1.5 mL, 0.20 M) was cooled to 0 °C and $NaBH_4$ (12.0 mg, 0.30 mmol, 1.00 eq.) was added. The reaction was stirred for 10 mins at 0 °C and was then warmed to room temperature. As TLC indicated complete conversion of the starting material (~2 h), water was added and the mixture was extracted with Et_2O. The organic phase was washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was subjected to column chromatography to give alcohol **584** in 85% yield (85.0 mg, 0.25 mmol). *Note: The alcohol was obtained as a single diastereomer. The configuration of the stereocenter was not determined.* $\mathbf{R_F}$ = 0.19 (5:1 hexanes/EA); **^{1}H-NMR** (600 MHz, Chloroform-*D*) δ [ppm] = 7.36 – 7.27 (m, 5H), 4.77 (dt, *J* = 9.2, 4.5 Hz, 1H), 4.69 (dt, *J* = 9.3, 4.5 Hz, 1H), 4.51 (s, 2H), 3.88 (dt, *J* = 11.8, 4.4 Hz, 1H), 3.47 (tt, *J* = 6.6, 3.6 Hz, 2H), 2.41 (dp, *J* = 8.1, 3.8 Hz, 2H), 2.09 (td, *J* = 7.4, 5.0 Hz, 1H), 1.73 (td, *J* = 12.8, 4.5 Hz, 1H), 1.65 – 1.54 (m, 4H), 1.52 – 1.47 (m, 3H), 1.31 – 1.25 (m, 2H), 1.19 (td, *J* = 12.9, 4.3 Hz, 1H), 1.04 (s, 3H), 0.96 (d, *J* = 7.3 Hz, 3H); **^{13}C-NMR** (151 MHz, Chloroform-*D*) δ [ppm] = 202.9, 138.7, 128.4, 127.6, 127.5, 108.3, 77.3, 72.8, 71.1, 70.1, 53.0, 43.7, 37.3, 35.9, 35.8, 29.0, 26.2, 25.2, 23.2, 21.5, 7.7; **IR** (film) ν 3388, 2937, 2871, 1957, 1704, 1454, 1361, 1263, 1204, 1097, 1017, 948, 912, 877, 842, 734, 697 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{23}H_{33}O_2^+$ $[M+H]^+$:341.2475; found: 341.2478.

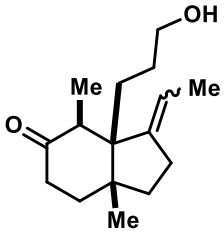
***O*-(3a-(3-(benzyloxy)propyl)-4,7a-dimethyl-3-vinylideneoctahydro-1*H*-inden-5-yl) 1*H*-imidazole-1-carbothioate (585)**



1,1'-Thiocarbonyldiimidazole (89.0 mg, 0.50 mmol, 2.00 eq.) was added to a solution of alcohol **584** (85.0 mg, 0.25 mmol, 1.00 eq.) in THF (0.8 mL, 0.3 M) and the mixture was heated to reflux for 2 h. After cooling to room temperature, water was added and the mixture was extracted with DCM. The combined organic phases were washed with 0.1 M HCl, $NaHCO_3$ and brine and dried over

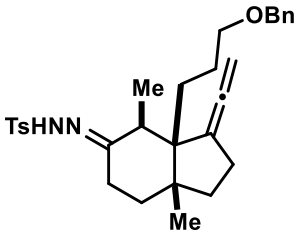
$MgSO_4$. The solvent was removed and the crude product was purified by column chromatography on silica gel (5:1 hexanes/EA). Yield 75% (84 mg, 0.19 mmol). **R_F** = 0.19 (5:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*) δ [ppm] = 8.33 (t, *J* = 1.1 Hz, 1H), 7.62 (t, *J* = 1.5 Hz, 1H), 7.38 – 7.26 (m, 5H), 7.02 (dd, *J* = 1.7, 0.9 Hz, 1H), 5.82 (dt, *J* = 11.5, 5.0 Hz, 1H), 4.96 (dt, *J* = 9.2, 4.5 Hz, 1H), 4.76 (dt, *J* = 9.3, 4.5 Hz, 1H), 4.50 (s, 2H), 3.47 (qt, *J* = 9.3, 6.4 Hz, 2H), 2.55 – 2.42 (m, 2H), 2.43 – 2.37 (m, 1H), 1.92 – 1.81 (m, 2H), 1.81 – 1.70 (m, 2H), 1.70 – 1.62 (m, 2H), 1.60 – 1.53 (m, 1H), 1.52 – 1.43 (m, 1H), 1.42 – 1.31 (m, 2H), 1.29 – 1.22 (m, 2H), 1.11 (d, *J* = 7.3 Hz, 3H), 1.11 (s, 3H); **^{13}C-NMR** (126 MHz, Chloroform-*D*) δ [ppm] = 203.0, 183.5, 138.8, 136.9, 130.7, 128.5, 127.7, 127.6, 118.0, 107.6, 84.0, 78.9, 72.9, 70.9, 53.5, 43.8, 37.3, 35.1, 33.4, 29.0, 25.2, 23.3, 22.3, 21.5, 9.7; **IR** (film) ν 2946, 2874, 1957, 1703, 1531, 1463, 1383, 1357, 1333, 1280, 1230, 1094, 1041, 976, 909, 844, 729, 697, 656 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{27}H_{35}N_2O_2S^+$ $[M+H]^+$: 451.2414; found: 451.2413.

3-ethylidene-3a-(3-hydroxypropyl)-4,7a-dimethyloctahydro-5*H*-inden-5-one (247)



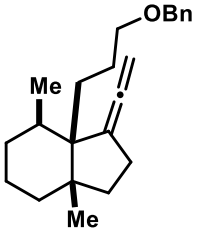
Allene **228** (200 mg, 0.59 mmol, 1.00 eq.) was dissolved in THF (12 mL, 0.05 M) and Pd/C (10% Pd, 126 mg, 0.12 mmol, 0.20 eq.) was added and a H_2-balloon was set up. The reaction was flushed with H_2 and stirred for 1 h at room temperature under an H_2-atmosphere. TLC indicated complete conversion of the starting material and the mixture was filtered over a pad of Celite. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (3:1 hexanes/EA). The desired compound **247** was obtained as a colorless oil in 95% yield (140 mg, 0.56 mmol). *Note: The desired compound was obtained as an inseparable mixture of stereoisomers. Only signals of the major isomer are assigned.* **R_F** = 0.31 (2:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*) δ [ppm] = 5.45 – 5.33 (m, 1H), 3.58 (t, *J* = 6.4 Hz, 2H), 2.83 (qd, *J* = 7.1, 1.2 Hz, 1H), 2.49 – 2.29 (m, 4H), 1.89 – 1.73 (m, 4H), 1.72 – 1.68 (m, 3H), 1.67 – 1.61 (m, 1H), 1.60 – 1.51 (m, 2H), 1.50 – 1.44 (m, 1H), 1.44 – 1.36 (m, 1H), 1.11 (d, *J* = 7.1 Hz, 3H), 1.11 (s, 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*) δ [ppm] = 215.3, 146.3, 119.1, 63.9, 58.1, 47.7, 45.7, 36.3, 36.2, 35.5, 30.8, 28.3, 27.5, 24.2, 14.5, 11.9; **IR** (film) ν 3419, 2940, 2875, 1703, 1448, 1373, 1321, 1262, 1153, 1053, 1012, 945, 886, 802, 734 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{16}H_{27}O_2^+$ $[M+H]^+$: 251.2006; found: 251.2004.

_N'_-(3a-(3-(benzyloxy)propyl)-4,7a-dimethyl-3-vinylideneoctahydro-5_H_-inden-5-ylidene)-4-methylbenzenesulfonohydrazide (245)



Ketone **228** (3.70 g, 10.9 mmol, 1.00 eq.) was dissolved in EtOH (5.5 mL, 2 M) and cooled to 5 °C. *p*-Toluenesulfonyl hydrazide (2.44 g, 13.1 mmol, 1.20 eq.) was added in one portion and the reaction was kept between 5 and 10 °C for 20 h. The mixture was concentrated and the crude product **245** was purified by column chromatography on silica gel (3:1 hexanes/EA). Yield 67% (77% brsm, 3.70 g, 7.30 mmol). *Note: Formation of two isomeric hydrazones observed. The slightly less polar isomer was separated and discarded as it does not show any reaction with catechol borane and cannot be converted into the reactive isomer. This unreactive isomer is the major product at reaction temperatures >10 °C.* $\mathbf{R_F}$ = 0.26 (3:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*) δ [ppm] = 7.86 – 7.80 (m, 2H), 7.37 – 7.26 (m, 7H), 4.56 (dt, *J* = 9.1, 4.4 Hz, 1H), 4.47 (s, 2H), 4.31 (dt, *J* = 9.2, 4.3 Hz, 1H), 3.40 – 3.30 (m, 2H), 2.57 (q, *J* = 7.3 Hz, 1H), 2.39 (s, 3H), 2.38 – 2.31 (m, 2H), 2.31 – 2.26 (m, 1H), 2.25 – 2.16 (m, 1H), 1.65 – 1.55 (m, 3H), 1.54 – 1.46 (m, 3H), 1.46 – 1.39 (m, 2H), 1.37 – 1.19 (m, 2H), 1.07 (s, 3H), 1.06 (d, *J* = 7.4 Hz, 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*) δ [ppm] = 204.2, 143.9, 138.8, 135.8, 129.5, 128.5, 128.4, 127.7, 127.6, 108.6, 78.2, 72.8, 71.0, 53.3, 44.4, 41.1, 36.9, 35.1, 28.3, 25.5, 24.0, 22.4, 21.7, 20.9, 14.7; **IR** (film) ν 3216, 2936, 2860, 1957, 1711, 1598, 1496, 1453, 1331, 1157, 1093, 1002, 926, 846, 813, 734, 698, 667 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{30}H_{39}N_2O_3S^+$ $[M+H]^+$: 507.2676; found: 507.2676.

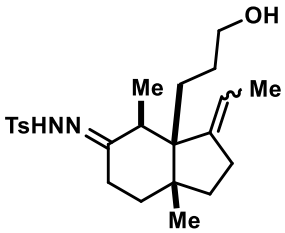
7a-(3-(benzyloxy)propyl)-3a,7-dimethyl-1-vinylideneoctahydro-1_H_-indene (242)



Hydrazone **245** (3.70 g, 7.30 mmol, 1.00 eq.) was dissolved in $CHCl_3$ (15 mL, 0.5 M), cooled to -10 °C and catecholborane (1 M solution in THF, 11 mL, 11.0 mmol, 1.50 eq.) was added dropwise. The reaction was stirred for 20 mins at -10 °C and then warmed to room temperature. After 2 h, $NaOAc{\cdot}3H_2O$ (2.88 g, 21.2 mmol, 2.90 eq.) was added carefully (gas evolution!) and the resulting slurry was heated to reflux for 1 h. Water was added and the mixture was extracted with DCM. The combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification *via* column chromatography on silica gel (40:1 hexanes/EA) yielded

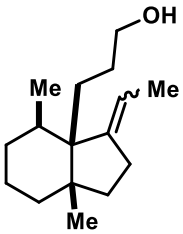
the desired compound **242** as a colorless oil in 66% yield (1.56 g, 4.80 mmol). $\mathbf{R_F}$ = 0.24 (40:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*) δ [ppm] = 7.37 – 7.27 (m, 5H), 4.68 (ddt, *J* = 18.2, 9.1, 4.5 Hz, 2H), 4.51 (s, 2H), 3.44 (td, *J* = 6.6, 2.1 Hz, 2H), 2.43 (dq, *J* = 9.4, 4.3 Hz, 2H), 1.96 – 1.80 (m, 1H), 1.64 – 1.54 (m, 5H), 1.51 – 1.33 (m, 4H), 1.31 – 1.22 (m, 3H), 1.02 (s, 3H), 0.99 (d, *J* = 7.2 Hz, 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*) δ [ppm] = 203.7, 138.9, 128.5, 127.8, 127.6, 109.6, 76.8, 72.9, 71.6, 51.9, 44.6, 37.3, 36.8, 30.2, 28.5, 25.7, 24.3, 22.6, 18.3, 16.0, 1.2; **IR** (film) ν 2931, 2864, 1957, 1721, 1495, 1454, 1360, 1273, 1203, 1100, 1028, 981, 911, 878, 839, 732, 712, 696 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{23}H_{33}O^+$ [M+H]$^+$: 325.2526; found: 325.2521.

_N_′-(3-ethylidene-3a-(3-hydroxypropyl)-4,7a-dimethyloctahydro-5_H_-inden-5-ylidene)-4-methylbenzenesulfonohydrazide (586)



Ketone **247** (51.0 mg, 0.20 mmol, 1.00 eq.) was dissolved in anhydrous EtOH (0.11 mL) and cooled to 10 °C. *p*-Toluenesulfonyl hydrazide (46.0 mg, 0.24 mmol, 1.20 eq.) was added in one portion and the resulting mixture was stirred for 24 h at 10 °C and then stored at -25 °C overnight. The solvent was removed under reduced pressure and the residue was subjected to column chromatography on silica gel (2:1 hexanes/EA) to give the desired hydrazone **586** as a mixture of isomers (68.0 mg, 0.16 mmol, 80%). *Note: Only signals of the major isomer are assigned.* $\mathbf{R_F}$ = 0.36 (1:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*) δ [ppm] = 7.86 – 7.77 (m, 2H), 7.38 – 7.27 (m, 2H), 5.18 (qt, *J* = 7.5, 2.1 Hz, 1H), 3.58 – 3.46 (m, 2H), 2.89 (q, *J* = 7.3 Hz, 1H), 2.43 (s, 3H), 2.32 – 2.16 (m, 4H), 1.61 – 1.49 (m, 5H), 1.49 – 1.39 (m, 7H), 1.07 (d, *J* = 7.2 Hz, 3H), 1.04 (s, 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*) δ [ppm] = 165.2, 146.0, 143.9, 135.7, 129.5, 128.3, 119.1, 63.9, 55.2, 45.7, 41.7, 37.1, 35.3, 31.5, 28.7, 28.2, 24.3, 21.8, 21.7, 14.8, 14.3; **IR** (film) ν 3219, 2941, 2875, 2249, 1599, 1448, 1384, 1330, 1186, 1162, 1093, 1051, 997, 908, 812, 728, 706, 668 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{23}H_{35}N_2O_3S^+$ [M+H]$^+$: 419.2363; found: 419.2351.

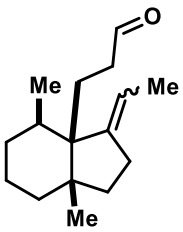
3-(3-ethylidene-4,7a-dimethyloctahydro-3a*H*-inden-3a-yl)propan-1-ol (246)



Method A: Compound **242** (1.56 g, 4.80 mmol, 1.00 eq.) was dissolved in THF (95 mL, 0.05 M) under N_2. Palladium on carbon (10% Pd, 1.02 g, 0.96 mmol, 0.20 eq.) was added and a H_2-balloon was set up. The reaction was stirred for 2 h at room temperature under an H_2-atmosphere. The balloon was removed and the mixture was filtered over Celite. The solvent was removed under reduced pressure and crude **246** was purified by flash column chromatography on silica gel (7:1 hexanes/EA). Yield 98% (1.12 g, 4.72 mmol).

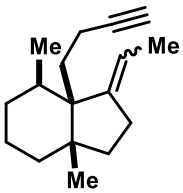
Method B: In a flame-dried Schlenk tube, hydrazone **586** (68.0 mg, 0.16 mmol, 1.00 eq.) was dissolved in anhydrous $CHCl_3$ (0.3 mL) and cooled to -10 °C. A solution of catechol borane (1 M in THF, 0.4 mL, 0.41 mmol, 2.50 eq.) was added dropwise and the reaction was stirred for 30 mins at -10 °C and then for 2 h at room temperature. $NaOAc{\cdot}3H_2O$ (87.0 mg, 0.64 mmol, 3.90 eq.) was added in one portion and the resulting slurry was heated to reflux for 1 h. After cooling to room temperature, water was added and the mixture was extracted with DCM. The combined organic phases were washed with brine and dried over $MgSO_4$ and the solvent was removed under reduced pressure. Column chromatography on silica gel (7:1 hexanes/EA) gave the desired deoxygenated bicycle **246** as a colorless oil (31.0 mg, 0.13 mmol, 81%). $\mathbf{R_F}$ = 0.06 (20:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*) δ [ppm] = 5.34 (qt, *J* = 7.4, 2.1 Hz, 1H), 3.66 – 3.55 (m, 2H), 2.45 – 2.30 (m, 3H), 1.67 (dt, *J* = 7.5, 2.0 Hz, 3H), 1.64 – 1.53 (m, 4H), 1.48 – 1.39 (m, 3H), 1.38 – 1.25 (m, 6H), 1.24 – 1.17 (m, 1H), 1.01 (s, 3H), 0.99 (d, *J* = 7.3 Hz, 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*) δ [ppm] = 146.9, 116.8, 64.4, 53.9, 45.8, 36.6, 36.4, 30.9, 30.5, 30.3, 28.1, 27.6, 23.8, 18.3, 16.1, 14.4; **IR** (film) ν 3301, 2929, 2869, 1457, 1384, 1219, 1170, 1133, 1056, 980, 946, 927, 839, 787, 761 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{16}H_{29}O^+[M+H]^+$: 237.2213; found: 237.2208.

3-(3-ethylidene-4,7a-dimethyloctahydro-3a*H*-inden-3a-yl)propanal (248)



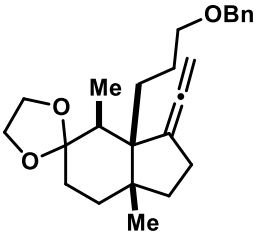
Alcohol **246** (1.00 g, 4.72 mmol, 1.00 eq.) was dissolved in anhydrous DCM (42 mL, 0.11 M) and NMO (743 mg, 6.35 mmol, 1.35 eq.) and powdered 4 Å molecular sieves (2.12 g, 450 mg/mmol) were added. The resulting mixture was stirred for 10 min before TPAP (74.0 mg, 0.21 mmol, 0.04 eq.) was added. The reaction progress was monitored by TLC and upon consumption of the starting material (~4.5 h), DCM was added and the mixture was filtered over Celite. The solvent was removed under reduced pressure and the crude product was used in the next step without further purification. *Note: Intramolecular Prins cyclization of the desired product observed even under slightly acidic conditions, e.g. during IBX oxidation.* $\mathbf{R_F}$ = 0.45 (10:1 hexanes/EA).

7a-(but-3-yn-1-yl)-1-ethylidene-3a,7-dimethyloctahydro-1*H*-indene (198)



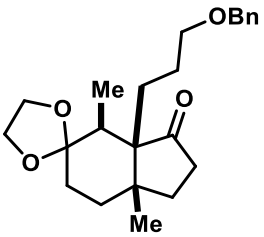
Aldehyde **248** (670 mg, 2.86 mmol, 1.00 eq.) was dissolved in MeOH (11.5 mL, 0.25 M), and K_2CO_3 (791 mg, 5.72 mmol, 2.00 eq.) and Ohira-Bestmann reagent (824 mg, 4.29 mmol, 1.50 eq.) were added sequentially. The reaction was stirred for 3 h at room temperature before aqueous $NaHCO_3$ was added. The aqueous phase was extracted with Et_2O and the combined organic layers were washed with brine and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude alkyne which was purified by column chromatography on silica gel (100% hexanes). Pure alkyne **198** (659 mg, 2.86 mmol) was obtained as a colorless liquid in 91% yield. $\mathbf{R_F}$ = 0.44 (100% hexanes); **^{1}H-NMR** (400 MHz, Chloroform-*D*) δ [ppm] = 5.38 (qt, *J* = 7.5, 2.1 Hz, 1H), 2.43 – 2.25 (m, 3H), 2.25 – 2.17 (m, 2H), 1.94 (t, *J* = 2.6 Hz, 1H), 1.93 – 1.86 (m, 1H), 1.65 (dt, *J* = 7.5, 2.0 Hz, 3H), 1.62 – 1.55 (m, 2H), 1.42 – 1.34 (m, 3H), 1.33 – 1.14 (m, 4H), 1.00 (s, 3H), 0.99 (d, *J* =7.2 Hz, 3 H); **^{13}C-NMR** (101 MHz, Chloroform-*D*) δ [ppm] = 146.0, 117.5, 86.3, 67.7, 54.1, 45.9, 36.3, 36.0, 30.8, 30.2, 25.1, 24.0, 18.5, 16.2, 14.6, 14.5, 14.3, 12.2; **IR** (film) ν 3313, 2916, 2849, 1461, 1384, 978, 729 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{17}H_{27}^+$ $[M+H]^+$: 231.2107; found: 231.2104.

3a-(3-(benzyloxy)propyl)-4,7a-dimethyl-3-vinylideneoctahydrospiro[indene-5,2'-[1,3] dioxolane] (258)



Propargyl silane **229** (420 mg, 1.02 mmol, 1.00 eq.) was dissolved in toluene (3.4 mL, 0.3 M) and Amberlyst® 15 (420 mg, 100 w%) and 2-methoxy-1,3-dioxolane (0.7 mL, 7.16 mmol, 7.00 eq.) were added sequentially. The reaction was stirred for 15 h at room temperature, diluted with Et_2O and filtered. The solvents were removed under reduced pressure and the desired compound was obtained as a colorless oil and used in the next step without further purification. $\mathbf{R_F}$ = 0.63 (5:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*) δ [ppm] = 7.36 – 7.26 (m, 5H), 4.74 – 4.62 (m, 2H), 4.50 (s, 2H), 3.98 – 3.88 (m, 2H), 3.88 – 3.79 (m, 2H), 3.49 – 3.36 (m, 2H), 2.60 – 2.38 (m, 2H), 1.96 (qd, *J* = 7.2, 1.1 Hz, 1H), 1.85 – 1.71 (m, 2H), 1.69 – 1.58 (m, 4H), 1.54 – 1.38 (m, 3H), 1.37 – 1.28 (m, 1H), 1.02 (s, 3H), 0.98 (d, *J* = 7.2 Hz, 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*) δ [ppm] = 204.9, 139.0, 128.5, 127.7, 127.6, 111.4, 109.0, 77.4, 72.8, 71.7, 64.6, 64.3, 53.9, 44.7, 36.1, 32.9, 29.0, 28.6, 26.0, 24.7, 11.1; **IR** (film) ν 3393, 2952, 2878, 1956, 1717, 1453, 1356, 1314, 1275, 1176, 1096, 1028, 949, 913, 841, 731, 697 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{25}H_{35}O_3^+$ $[M+H]^+$: 383.2581; found: 383.2574.

3a-(3-(benzyloxy)propyl)-4,7a-dimethylhexahydrospiro[indene-5,2'-[1,3]dioxolan]-3(2*H*)-one (259)

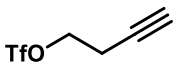


In a three-necked flask with gas inlet tube and bubble counter, a solution of crude allene **258** (50.0 mg, 0.13 mmol, 1.00 eq.) in DCM (13 mL, 0.01 M) was cooled to -78 °C. O_3 gas was bubbled through the solution until a blue color persisted (~2 min). After removal of excess O_3 by bubbling O_2 through the solution, PPh_3 (68.0 mg, 0.26 mmol, 2.00 eq.) was added and the mixture was allowed to warm to room temperature. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (5:1 hexanes/EA + 1% NEt_3). Ketone **259** was obtained in 62% yield (30 mg, 0.08 mmol). $\mathbf{R_F}$ = 0.22 (5:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*) δ [ppm] = 7.37 – 7.27 (m, 5H), 4.47 (s, 2H), 3.98 – 3.76 (m, 4H), 3.40 (qt, *J* = 9.4, 6.2 Hz, 2H), 2.48 – 2.33 (m, 1H), 2.30 – 2.14 (m, 2H), 1.97 – 1.78 (m, 2H), 1.77 – 1.60 (m, 2H), 1.59 – 1.32 (m, 5H), 1.30 – 1.20 (m, 1H), 1.15 (s, 3H),

1.00 (d, *J* = 7.4 Hz, 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*) δ [ppm] = 219.1, 138.8, 128.5, 127.6, 127.6, 110.8, 72.8, 70.7, 64.3, 62.9, 56.9, 41.3, 34.9, 34.9, 34.0, 33.4, 27.0, 26.7, 23.5, 22.9, 11.5; **IR** (film) ν 2958, 2883, 1731, 1454, 1409, 1362, 1315, 1263, 1181, 1091, 1027, 1005, 972, 947, 913, 897, 803, 734, 697 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{23}H_{33}O_4^+$ $[M+H]^+$: 373.2373; found: 373.2371.

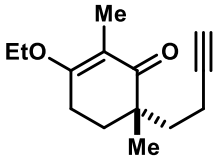
3.1.3 Racemic and Asymmetric Total Synthesis of Waihoensene

but-3-yn-1-yl trifluoromethanesulfonate (270)



Triflic anhydride (16.8 mL, 0.10 mol, 1.00 eq.) was dissolved in DCM (65 mL) and cooled to 0 °C. A mixture of but-3-yn-1-ol (7.6 mL, 0.10 mol, 1.00 eq.) and pyridine (8.1 mL, 0.10 mol, 1.00 eq.) in DCM (60 mL) was added dropwise and the resulting mixture was stirred for 2 h at 0 °C. Water was added and the phases were separated. The aqueous phase was extracted with DCM and the combined organic phases were washed with water and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by distillation (63 °C, 30 mbar) to give triflate **270** as a colorless liquid (17.3 g, 85.6 mmol, 86% yield). The obtained spectroscopic data were consistent with those reported in literature.[226] **^{1}H-NMR** (400 MHz, Chloroform-*D*): *δ* [ppm] = 4.58 (t, *J* = 6.8 Hz, 2H), 2.74 (td, *J* = 6.8, 2.6 Hz, 2H), 2.12 (t, *J* = 2.6 Hz, 1H); **^{13}C-NMR** (101 MHz, Chloroform-*D*): δ [ppm] = 118.7 (q, *J* = 319.6 Hz), 77.0, 73.66, 72.0, 20.0; **^{19}F-NMR** (377 MHz, Chloroform-*D*): *δ* [ppm] = -74.49.

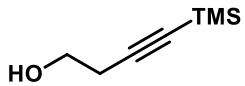
6-(but-3-yn-1-yl)-3-ethoxy-2,6-dimethylcyclohex-2-en-1-one (266)



2,2,6,6-Tetramethylpiperidine (4.7 mL, 27.8 mmol, 1.40 eq.) was dissolved in THF (7 mL) and cooled to 0 °C. *n*-BuLi (2.5 M solution in hexanes, 10 mL, 25.8 mmol, 1.30 eq.) was added dropwise and the resulting mixture was stirred for 15 mins. The reaction was cooled to -78 °C and a solution of 3-ethoxy-2,6-dimethylcyclohex-2-en-1-one (**230**) (3.34 g, 19.9 mmol, 1.00 eq.) in THF (13 mL) was added. After 30 mins, the reaction was removed from the cooling bath, stirred at room temperature for 10 mins and was then re-cooled to -78 °C. DMPU (4 mL, 31.8 mmol, 1.60 eq.) was added and the reaction was stirred for 40 mins. Triflate **15** (8.03 g, 39.7 mmol, 2.0 eq.) was added, and the reaction mixture was allowed

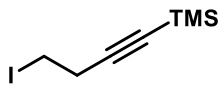
to warm to room temperature in the cooling bath overnight. The reaction was quenched by the addition of aqueous saturated NH_4Cl and the mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography on silica gel (10:1 hexanes/EA) gave a pale yellow solid (3.48 g, 15.8 mmol, 80% yield). $\mathbf{R_F}$ = 0.30 (7:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*): δ [ppm] = 4.06 (q, *J* = 7.0 Hz, 2H), 2.66 – 2.49 (m, 2H), 2.23 – 2.05 (m, 2H), 1.98 – 1.91 (m, 1H), 1.92 (t, *J* = 2.7 Hz, 1H), 1.85 – 1.69 (m, 3H), 1.68 (t, *J* = 1.6 Hz, 3H), 1.35 (t, *J* = 7.0 Hz, 3H), 1.07 (s, 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*): δ [ppm] = 202.2, 169.2, 113.4, 85.0, 68.3, 63.3, 42.4, 36.2, 32.1, 22.4, 22.3, 15.5, 13.9, 8.0; **IR** (film) ν 3237, 2933, 1630, 1601, 1444, 1379, 1359, 1307, 1245, 1220, 1151, 1118, 1097, 1040, 1010, 889, 857, 763, 702, 674 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{14}H_{21}O_2^+$ $[M+H]^+$: 221.1536; found: 221.1532.

4-(trimethylsilyl)but-3-yn-1-ol (263)[102]



n-BuLi (2.5 M solution in hexanes, 44 mL, 110 mmol, 2.20 eq.) was added dropwise to a solution of but-3-yn-1-ol (3.8 mL, 50.0 mmol, 1.00 eq.) in THF (115 mL, 0.44 M) at -78 °C. The mixture was stirred for 2 h at this temperature before TMSCl (16 mL, 125 mmol, 2.5 eq.) was added. The reaction was allowed to warm to 0 °C over a period of 1 h and was quenched by the addition of water. The phases were separated and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with 1 M HCl, $NaHCO_3$ and brine and dried over $MgSO_4$. The solvent was removed and the crude material was directly used in the next step without further purification.

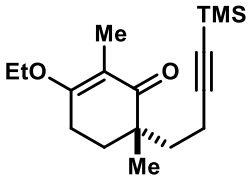
(4-iodobut-1-yn-1-yl)trimethylsilane (264)[102]



Crude **263** was dissolved in DCM (115 mL, 0.44 M) and cooled to 0 °C. PPh_3 (19.7 g, 75.0 mmol, 1.50 eq.) and imidazole (6.47 g, 95.0 mmol, 1.90 eq.) were added sequentially. Iodine (15.2 g, 60.0 mmol, 1.20 eq.) was added portionwise and after complete addition, the reaction mixture was warmed to room temperature and stirred for 15 h. A saturated aqueous solution of $Na_2S_2O_3$ was added and the phases were separated. The aqueous phase was extracted with hexanes and the combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent was

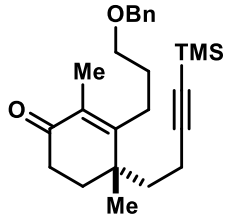
removed under reduced pressure. The residue was subjected to column chromatography on silica gel (100% hexanes) to give the desired iodide **264** as a pale yellow oil in 73% yield (9.23 g, 36.6 mmol). The obtained spectroscopic data were consistent with those reported in literature. $\mathbf{R_F}$ = 0.48 (100% hexanes); **^{1}H-NMR** (400 MHz, Chloroform-*D*): *δ* [ppm] = 3.22 (t, *J* = 7.5 Hz, 2H), 2.79 (t, *J* = 7.5 Hz, 2H), 0.16 (s, 9H); **^{13}C-NMR** (101 MHz, Chloroform-*D*): δ [ppm] = 105.2, 87.0, 25.2, 1.1, 0.1.

3-ethoxy-2,6-dimethyl-6-(4-(trimethylsilyl)but-3-yn-1-yl)cyclohex-2-en-1-one (265)



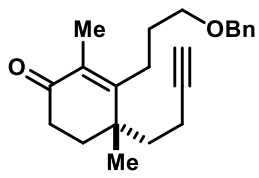
2,2,6,6-Tetramethylpiperidine (1.5 mL, 8.96 mmol, 1.40 eq.) in THF (3 mL) was cooled to 0 °C and *n*-BuLi (2.5 M solution in hexanes, 3.3 mL, 8.32 mmol, 1.30 eq.) was added dropwise. The reaction mixture was stirred for 30 mins and was then cooled to -78 °C. 3-Ethoxy-2,6-dimethylcyclohex-2-en-1-one (**230**) (1.08 g, 6.40 mmol, 1.00 eq.) was dissolved in THF (3.4 mL) and added to the reaction. After 30 mins at -78 °C, the cooling bath was removed for 10 mins. The reaction was re-cooled to -78 °C and DMPU (1.3 mL, 10.2 mmol, 1.60 eq.) was added. After further 10 mins, iodide **264** (8.10 g, 32.1 mmol, 5.00 eq.) was added and the reaction was allowed to warm to room temperature overnight. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl and extracted with Et_2O. The organic phase was washed with brine and dried over $MgSO_4$ and the residue was purified by column chromatography on silica gel (10:1 hexanes/EA). The desired compound was obtained in 30% yield (565 mg, 1.93 mmol). $\mathbf{R_F}$ = 0.41 (10:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*) δ [ppm] = 4.05 (q, *J* = 7.0 Hz, 2H), 2.68 – 2.47 (m, 2H), 2.28 – 2.07 (m, 2H), 1.94 (dt, *J* = 13.5, 5.9 Hz, 1H), 1.82 – 1.70 (m, 3H), 1.67 (dt, *J* = 1.5, 1.0 Hz, 3H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.06 (s, 3H), 0.13 (s, 9H); **^{13}C-NMR** (101 MHz, Chloroform-*D*) δ [ppm] = 202.3, 169.2, 113.4, 107.9, 84.4, 63.3, 42.5, 36.1, 32.0, 22.4, 22.3, 15.5, 15.3, 8.1, 0.3; **IR** (film) ν 2959, 2932, 2174, 1616, 1448, 1377, 1353, 1301, 1247, 1218, 1118, 1025, 1003, 980, 932, 838, 758, 698, 671 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{17}H_{29}O_2Si^+$ $[M+H]^+$: 293.1931; found: 293.1926.

3-(3-(benzyloxy)propyl)-2,4-dimethyl-4-(4-(trimethylsilyl)but-3-yn-1-yl)cyclohex-2-en-1-one (273)



A solution of *t*-BuLi (1.9 M in pentane, 4.1 mL, 7.72 mmol, 4.00 eq.) was cooled to -78 °C and alkyl iodide **241** (1.07 g, 3.86 mmol, 2.00 eq.) in Et_2O (8.8 mL) was added dropwise. After 1 h, TLC indicated complete conversion of the starting material and a solution of vinylogous ester **265** (565 mg, 1.93 mmol, 1.00 eq.) in Et_2O (3.9 mL) was added. The reaction mixture was stirred for 1 h at -78 °C, was then warmed to -60 °C over a period of 1 h and quenched by the addition of a saturated aqueous solution of NH_4Cl. The phases were separated and the aqueous phase was extracted with DCM. The combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography to yield the desired enone in 86% (659 mg, 1.66 mmol). $\mathbf{R_F}$ = 0.20 (7:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*) δ [ppm] = 7.40 – 7.27 (m, 5H), 4.53 (s, 2H), 3.52 (t, *J* = 6.1 Hz, 2H), 2.46 – 2.40 (m, 2H), 2.39 – 2.30 (m, 1H), 2.30 – 2.18 (m, 2H), 2.18 – 2.08 (m, 1H), 1.96 (ddd, *J* = 13.0, 7.3, 5.3 Hz, 1H), 1.87 – 1.64 (m, 5H), 1.79 (s, 3H), 1.15 (s, 3H), 0.14 (s, 9H); **^{13}C-NMR** (101 MHz, Chloroform-*D*) δ [ppm] = 198.9, 163.7, 138.6, 132.4, 128.6, 127.8, 127.7, 107.0, 85.1, 73.1, 70.4, 39.4, 37.5, 34.1, 33.0, 29.3, 27.7, 24.5, 15.5, 11.9, 0.2; **IR** (film) ν 2957, 2864, 2174, 1663, 1605, 1454, 1377, 1358, 1336, 1249, 1201, 1100, 1027, 1004, 839, 756, 697, 667 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{25}H_{37}O_2Si^+$ $[M+H]^+$: 397.2557; found: 397.2557.

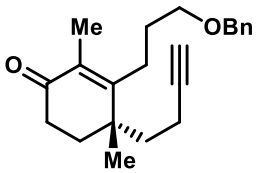
3-(3-(benzyloxy)propyl)-4-(but-3-yn-1-yl)-2,4-dimethylcyclohex-2-en-1-one (262)



Method A: Enone **273** (344 mg, 0.87 mmol, 1.00 eq.) was dissolved in DCM (2.2 mL, 0.4 M) and a solution of TBAF (1 M in THF, 1.1 mL, 1.09 mmol, 1.25 eq.) was added dropwise. The reaction was stirred for 1 h at room temperature. A saturated aqueous solution of NH_4Cl was added and the mixture was extracted with Et_2O. The organic phase was washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (5:1 hexanes/EA) to give the desilylated alkyne in 95% yield (270 mg, 0.83 mmol).

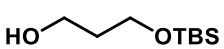
Method B: In a flame-dried Schlenk flask, *t*-BuLi (1.9 M in pentane, 20 mL, 37.4 mmol, 6.00 eq.) was cooled to -78 °C and a solution of ((3-iodopropoxy)methyl)-benzene (**241**) (5.17 g, 18.7 mmol, 3.00 eq.) in Et_2O (43 mL) was added dropwise. After 1 h, a solution of vinylogous ester **266** (1.37 g, 6.24 mmol, 1.00 eq.) in Et_2O (13 mL) was added. The reaction mixture was stirred for 2 h at -78 °C and was then allowed to warm to -60 °C. Consumption of the starting material was checked by TLC (approx. 2 h at -60 °C) and the reaction was quenched by the addition of 2 M HCl. The mixture was extracted with DCM, the combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by gradient column chromatography on silica gel (20:1, then 7:1 hexanes/EA). Yield 89% (1.81 g, 5.58 mmol). $\mathbf{R_F}$ = 0.19 (7:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*): δ [ppm] = 7.38 – 7.26 (m, 5H), 4.53 (s, 2H), 3.52 (t, *J* = 6.2 Hz, 2H), 2.45 – 2.40 (m, 2H), 2.39 – 2.23 (m, 2H), 2.22 – 2.14 (m, 1H), 2.12 – 2.03 (m, 1H), 1.96 (t, *J* = 2.7 Hz, 1H), 1.94 – 1.81 (m, 2H), 1.79 (s, 3H), 1.78 – 1.65 (m, 4H), 1.16 (s, 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*): δ [ppm] = 198.6, 163.4, 138.5, 132.4, 128.5, 127.7, 127.6, 84.2, 73.0, 70.3, 68.8, 39.3, 37.7, 33.9, 33.0, 29.3, 27.5, 24.3, 14.0, 11.9; **IR** (film) ν 3289, 2938, 2861, 1661, 1605, 1454, 1357, 1336, 1199, 1099, 1027, 736, 698 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{22}H_{29}O_2^+$ $[M+H]^+$: 325.2162; found: 325.2155.

(*R*)-3-(3-(benzyloxy)propyl)-4-(but-3-yn-1-yl)-2,4-dimethylcyclohex-2-en-1-one ((+)-262)



The compound was obtained from compound **295**[42b, 113] by the procedure described above. Analytical data matched with the racemic sample. **$[\alpha]_D^{23}$:** +4.0 (c 1.86, $CHCl_3$).

3-((*tert*-butyldimethylsilyl)oxy)propan-1-ol (587)[227]



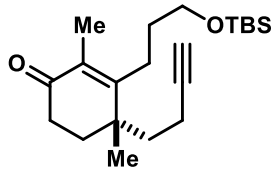
A suspension of NaH (60% dispersion in mineral oil, 2.00 g, 50.0 mmol, 1.00 eq.) in THF (50 mL) was cooled to 0 °C and propane-1,3-diol (3.6 mL, 50.0 mmol, 1.00 eq.) in THF (25 mL) was added dropwise. The cooling bath was removed and the mixture was stirred for 1 h at room temperature. A solution of TBSCl (7.54 g, 50.0 mmol, 1.00 eq.) in THF (25 mL) was added dropwise and the reaction was stirred for 1 h before a saturated aqueous solution of $NaHCO_3$ was added. The phases were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with

brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was subjected to flash column chromatography on silica gel (4:1 hexanes/EA) to give **587** in 87% yield (8.30 g, 43.6 mmol). The obtained spectroscopic data were consistent with those reported in literature. $\mathbf{R_F}$ = 0.60 (2:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*): δ [ppm] = 3.86 – 3.76 (m, 4H), 2.65 – 2.58 (m, 1H), 1.78 (pd, *J* = 5.6, 1.0 Hz, 2H), 0.93 – 0.86 (m, 9H), 0.07 (s, 3H), 0.07 (s, 3H).

tert-butyl(3-iodopropoxy)dimethylsilane (275)[227]

Imidazole (8.91 g, 131 mmol, 3.00 eq.) and PPh_3 (12.6 g, 48.0 mmol, 1.10 eq.) were dissolved in DCM (100 mL) and the solution was cooled in an ice bath. Iodine (12.2 g, 48.0 mmol, 1.10 eq.) was added in small portions and the resulting mixture was stirred for 10 mins at the same temperature before a solution of alcohol **587** (8.30 g, 43.6 mmol, 1.00 eq.) in DCM (50 mL) was added dropwise. The ice bath was removed and the reaction was stirred for 15 h under the exclusion of light. A saturated aqueous solution of $Na_2S_2O_3$ was added and the mixture was extracted with DCM. The organic phase was dried over $MgSO_4$, the solvent was removed under reduced pressure and the residue was repeatedly washed with hexanes. The hexane phases were combined and the solvent was evaporated under reduced pressure. The crude product was subjected to column chromatography on silica gel (50:1 hexanes/EA to 20:1). Yield 59% (7.68 g, 25.6 mmol). The obtained spectroscopic data were consistent with those reported in literature. **^{1}H-NMR** (400 MHz, Chloroform-*D*): δ [ppm] = 3.67 (t, *J* = 5.7 Hz, 2H), 3.28 (t, *J* = 6.7 Hz, 2H), 1.99 (tt, *J* = 6.6, 5.7, 2H), 0.90 (s, 9H), 0.07 (s, 6H).

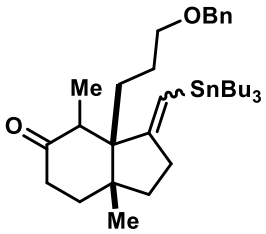
4-(but-3-yn-1-yl)-3-(3-((tert-butyldimethylsilyl)oxy)propyl)-2,4-dimethylcyclohex-2-en-1-one (274)



In a flame-dried Schlenk flask, *t*-BuLi (1.9 M in pentane, 1 mL, 1.82 mmol, 8.00 eq.) was cooled to -78 °C and a solution of *tert*-butyl(3-iodopropoxy) dimethylsilane (**275**) (273 mg, 0.91 mmol, 4.00 eq.) in Et_2O (2.1 mL) was added dropwise. After 1 h, a solution of vinylogous ester **266** (50.0 mg, 0.23 mmol, 1.00 eq.) in Et_2O (0.5 mL) was added. The reaction mixture was stirred for 2 h at -78 °C and was then allowed to warm to -20 °C. Consumption of the starting material was checked by TLC (approx. 30 mins at -20 °C) and

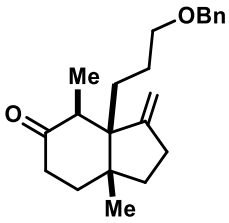
the reaction was quenched by the addition of NH_4Cl. The mixture was extracted with DCM, the combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (100% hexanes, then 10:1 hexanes/EA). Yield 41% (32 mg, 0.09 mmol). $\mathbf{R_F}$ = 0.46 (5:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*): δ [ppm] = 3.64 (t, *J* = 5.9 Hz, 2H), 2.42 (dd, *J* = 8.3, 6.0 Hz, 2H), 2.32 (td, *J* = 12.6, 12.0, 6.1 Hz, 1H), 2.24 (dd, *J* = 11.4, 5.6 Hz, 1H), 2.20 – 2.13 (m, 1H), 2.12 – 2.01 (m, 1H), 1.95 (t, *J* = 2.6 Hz, 1H), 1.93 – 1.79 (m, 2H), 1.77 (s, 3H), 1.76 – 1.56 (m, 4H), 1.15 (s, 3H), 0.89 (s, 9H), 0.05 (s, 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*): δ [ppm] = 198.8, 163.8, 132.4, 84.3, 68.8, 63.1, 39.4, 37.8, 34.0, 33.1, 32.2, 27.3, 26.1, 24.4, 18.4, 14.1, 11.8, -5.2; **IR** (film) ν 3266, 2928, 2857, 1647, 1603, 1470, 1379, 1358, 1337, 1245, 1198, 1102, 1081, 1013, 982, 963, 860, 770, 723, 692, 670 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{21}H_{37}O_2Si^+$ $[M+H]^+$: 349.2557; found: 349.2554.

3a-(3-(benzyloxy)propyl)-4,7a-dimethyl-3-((tributylstannyl)methylene)octahydro-5*H*-inden-5-one (588)



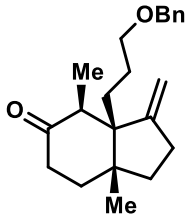
In a 500 mL round-bottom flask with reflux condenser, enone **262** (6.81 g, 21.0 mmol, 1.00 eq.) was dissolved in anhydrous benzene (350 mL). $HSnBu_3$ (11 mL, 42.0 mmol, 2.00 eq.) and AIBN (0.17 g, 1.05 mmol, 0.05 eq.) were added, and the mixture was heated to reflux for 4 h. $HSnBu_3$ (5.5 mL, 21.0 mmol, 1.00 eq.) and AIBN (0.17 g, 1.05 mmol, 0.05 eq.) were added, and the reaction was heated for further 4 h at which point a third portion of $HSnBu_3$ (1.00 eq.) and AIBN (0.05 eq.) was added. The solution was heated for 14 h as TLC indicated consumption of the starting material. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (10:1 hexanes/EA) to remove excess stannane, and the obtained mixture of isomers (11.5 g, 18.7 mmol, 89% yield) was directly used for protiodestannylation. $\mathbf{R_F}$ = 0.48 (7:1 hexanes/EA). Additional 0.47 g (1.4 mmol, 6%) of the corresponding destannylated olefin **261** were obtained due to partial protiodestannylation on silica gel.

3a-(3-(benzyloxy)propyl)-4,7a-dimethyl-3-methyleneoctahydro-5*H*-inden-5-one (261)



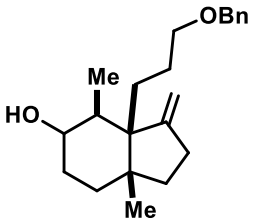
Vinyl stannane **588** (11.5 g, 18.7 mmol, 1.00 eq.) and PPTS (9.40 g, 37.4 mmol, 2.00 eq.) were dissolved in DCM (260 mL, 0.07 M) and the reaction was stirred at room temperature for 16 h. Water was added, the phases were separated and the aqueous phase was extracted with EA. The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a mixture of diastereomers (*d.r.* 5.6:1), which was subjected to base-catalyzed epimerization. The crude product was dissolved in MeOH (300 mL) and aqueous NaOH solution (10%, 20 mL, 56.1 mmol, 3.0 eq.) was added. The mixture was heated to 50 °C for 3 h and subsequently cooled to room temperature. The solvent was removed under reduced pressure and saturated NH_4Cl was added. The mixture was extracted with DCM, the organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (10:1 hexanes/EA) to give a colorless oil. Yield 88% (33.3:1 d.r., 5.39 g, 16.5 mmol). $\mathbf{R_F}$ = 0.29 (7:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*): δ [ppm] = 7.37 – 7.24 (m, 5H), 4.94 (t, *J* = 2.2 Hz, 1H), 4.73 (t, *J* = 2.2 Hz, 1H), 4.48 (s, 2H), 3.46 – 3.35 (m, 2H), 2.53 – 2.31 (m, 5H), 1.91 – 1.76 (m, 3H), 1.57 – 1.35 (m, 5H), 1.10 (s, 3H), 1.08 (d, *J* = 7.1 Hz, 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*): δ [ppm] = 214.5, 156.5, 138.8, 128.5, 127.7, 127.6, 108.4, 72.9, 71.1, 56.1, 46.4, 44.1, 36.1, 36.0, 34.5, 28.0, 27.0, 24.2, 23.3, 11.2; **IR** (film) ν 2952, 2861, 1707, 1647, 1496, 1454, 1373, 1327, 1205, 1156, 1100, 1028, 1007, 946, 885, 821, 734, 697 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{22}H_{31}O_2^+$ $[M+H]^+$: 327.2319; found: 327.2315.

(3a*R*,4*S*,7a*R*)-3a-(3-(benzyloxy)propyl)-4,7a-dimethyl-3-methyleneoctahydro-5*H*-inden-5-one ((+)-261)



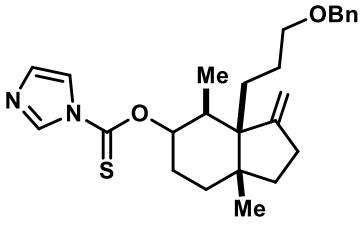
The compound was obtained by the same procedure as for the racemic route. Analytical data matched with the racemic sample. **$[\alpha]_D^{23}$:** +4.0 (c 1.86, $CHCl_3$).

3a-(3-(benzyloxy)propyl)-4,7a-dimethyl-3-methyleneoctahydro-1*H*-inden-5-ol (279)



Ketone **261** (1.00 g, 3.06 mmol, 1.00 eq.) was dissolved in MeOH (15 mL, 0.2 M) and cooled to 0 °C. $NaBH_4$ (116 mg, 3.06 mmol, 1.00 eq.) was added in one portion and the resulting mixture was stirred at 0 °C for 20 mins and then warmed to room temperature. The reaction progress was monitored by TLC and the reaction was quenched by the addition of water (~2 h). The mixture was extracted with DCM, the combined organic phases were dried over $MgSO_4$ and the solvent was removed. The crude material was purified by column chromatography on silica gel (5:1 hexanes/EA) to give pure alcohol **279** as a colorless solid in quantitative yield (1.00 g, 3.06 mmol). *Note: The alcohol was obtained as a single diastereomer. The stereochemistry of the new stereocenter was not determined.* **R_F** = 0.17 (5:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*) δ [ppm] = 7.38 – 7.26 (m, 5H), 4.96 (t, *J* = 2.1 Hz, 1H), 4.75 (t, *J* = 2.5 Hz, 1H), 4.50 (s, 2H), 3.96 (ddd, *J* = 11.8, 5.0, 4.1 Hz, 1H), 3.45 (t, *J* = 6.6 Hz, 2H), 2.39 – 2.29 (m, 2H), 2.22 – 2.12 (m, 1H), 1.71 – 1.59 (m, 2H), 1.59 – 1.50 (m, 2H), 1.50 – 1.34 (m, 4H), 1.27 – 1.15 (m, 2H), 1.06 (s, 3H), 0.99 (d, *J* = 7.3 Hz, 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*) δ [ppm] = 155.2, 138.8, 128.5, 127.7, 127.6, 106.6, 73.0, 72.8, 71.2, 69.5, 53.3, 44.7, 43.8, 36.2, 35.9, 35.6, 28.4, 28.0, 27.5, 26.6, 23.1, 21.9, 7.7; **IR** (film) ν 3258, 2934, 2868, 1646, 1454, 1365, 1204, 1090, 1053, 1023, 993, 944, 899, 879, 734, 697 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{22}H_{33}O_2^+$ $[M+H]^+$: 329.2475; found: 329.2471.

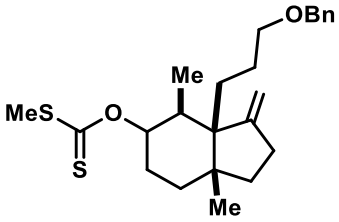
***O*-(3a-(3-(benzyloxy)propyl)-4,7a-dimethyl-3-methyleneoctahydro-1*H*-inden-5-yl) 1*H*-imidazole-1-carbothioate (589)**



1,1'-Thiocarbonyldiimidazole (53.0 mg, 0.30 mmol, 2.00 eq.) was added to a solution of alcohol **279** (50.0 mg, 0.15 mmol, 1.00 eq.) in THF (0.5 mL, 0.3 M) and the resulting mixture was heated to reflux for 2.5 h. Water was added to the reaction and the mixture was extracted with DCM. The combined organic phases were washed with 0.1 M HCl, $NaHCO_3$ and brine and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was subjected to column chromatography on silica gel (5:1 hexanes/EA). Compound **589** was obtained in 93% yield (61 mg, 0.14 mmol). **R_F** = 0.17 (5:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*) δ [ppm] = 8.33 (t, *J* = 1.1 Hz,

1H), 7.63 (dd, *J* = 1.3 Hz, 1H), 7.39 – 7.26 (m, 5H), 7.03 (dd, *J* = 1.7, 0.9 Hz, 1H), 5.76 (ddd, *J* = 12.2, 5.2, 4.3 Hz, 1H), 5.06 (dt, *J* = 6.5, 2.3 Hz, 2H), 4.49 (s, 2H), 3.50 – 3.38 (m, 2H), 2.63 (p, *J* = 6.9 Hz, 1H), 2.39 (tq, *J* = 7.0, 2.2 Hz, 2H), 1.95 (dtd, *J* = 13.9, 12.3, 3.7 Hz, 1H), 1.82 – 1.71 (m, 1H), 1.71 – 1.59 (m, 2H), 1.59 – 1.46 (m, 3H), 1.45 – 1.32 (m, 2H), 1.32 – 1.22 (m, 2H), 1.13 (s, 3H), 1.07 (d, *J* = 7.3 Hz, 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*) δ [ppm] = 183.3, 153.9, 138.8, 136.9, 130.8, 128.5, 127.7, 127.6, 118.0, 107.8, 83.9, 72.9, 71.0, 53.8, 43.7, 36.3, 35.3, 32.0, 27.8, 27.3, 23.1, 22.8, 21.7, 9.3; **IR** (film) ν 2942, 2874, 1647, 1530, 1463, 1383, 1359, 1334, 1280, 1231, 1094, 1040, 974, 918, 889, 824, 734, 696, 656 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{26}H_{35}N_2O_2S^+$ [M+H]$^+$: 439.2414; found: 439.2401.

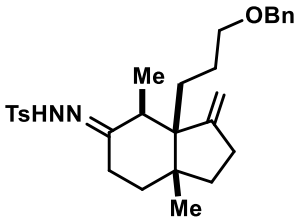
_O_-(3a-(3-(benzyloxy)propyl)-4,7a-dimethyl-3-methyleneoctahydro-1_H_-inden-5-yl) _S_-methyl carbonodithioate (590)



A solution of alcohol **279** (250 mg, 0.76 mmol, 1.00 eq.) in THF (15 mL, 0.05 M) was cooled to -78 °C and CS_2 (0.7 mL, 11.4 mmol, 15.0 eq.) and KHMDS (0.5 M in toluene, 3.8 mL, 1.90 mmol, 2.50 eq.) were added sequentially. The resulting mixture was stirred for 30 mins at -78 °C and for further 10 mins at room temperature. The reaction was re-cooled to -78 °C and MeI (0.76 mL, 12.2 mmol, 16.0 eq.) was added dropwise. After 20 mins at -78 °C, the cooling bath was removed and the reaction was stirred for 15 mins at room temperature. A saturated aqueous solution of $NaHCO_3$ was added and the mixture was extracted with Et_2O. The organic phase was washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude material was purified by column chromatography on silica gel (40:1 hexanes/EA) to give pure **590** as a pale yellow solid in quantitative yield (335 mg, 0.76 mmol). **R_F** = 0.36 (20:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*) δ [ppm] = 7.37 – 7.26 (m, 5H), 5.79 (ddd, *J* = 12.2, 5.2, 4.3 Hz, 1H), 5.03 (dt, *J* = 12.4, 2.3 Hz, 2H), 4.48 (s, 2H), 3.43 (tt, *J* = 6.4, 3.1 Hz, 2H), 2.65 – 2.57 (m, 1H), 2.54 (s, 3H), 2.36 (tq, *J* = 7.2, 2.2 Hz, 2H), 1.90 (dtd, *J* = 14.0, 12.3, 3.6 Hz, 1H), 1.73 – 1.66 (m, 2H), 1.65 – 1.55 (m, 1H), 1.54 – 1.48 (m, 2H), 1.48 – 1.37 (m, 1H), 1.32 (dt, *J* = 13.9, 3.6 Hz, 1H), 1.25 (ddd, *J* = 12.7, 7.2, 5.0 Hz, 1H), 1.11 (s, 3H), 1.10 – 1.02 (m, 1H), 1.02 (d, *J* = 7.2 Hz, 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*) δ [ppm] = 214.8, 154.0, 138.9, 128.5, 127.7, 127.6, 107.7, 83.6, 72.8, 71.1, 53.8, 43.7, 36.4, 35.4, 31.9, 27.8, 27.3, 23.1, 22.9, 21.7, 18.9, 9.1; **IR** (film) ν 2956, 2923, 2847, 1645, 1453,

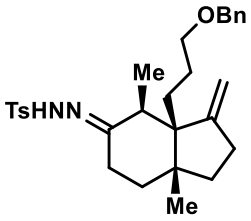
1408, 1362, 1307, 1256, 1223, 1198, 1177, 1125, 1075, 1056, 1044, 991, 942, 930, 907, 735, 696 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{24}H_{35}O_2S_2^+$ $[M+H]^+$: 419.2073; found: 419.2071.

_N'_-(3a-(3-(benzyloxy)propyl)-4,7a-dimethyl-3-methyleneoctahydro-5H-inden-5-ylidene)-4-methylbenzenesulfonohydrazide (278)



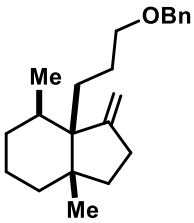
Ketone **261** (5.39 g, 16.5 mmol, 1.00 eq.) was dissolved in anhydrous EtOH (4.2 mL, 4 M) and cooled to 0 °C. *p*-Toluenesulfonyl hydrazide (4.61g, 24.8 mmol, 1.50 eq.) was added in one portion, and the reaction was allowed to warm to room temperature. After stirring for 24 h, the solvent was removed and the crude hydrazone was purified by column chromatography on silica gel (5:1 hexanes/EA). Hydrazone **278** was obtained as a colorless foam in 94% yield (7.67 g, 15.5 mmol). *Note: The hydrazone was obtained as mixture of isomers, which have not been further characterized. Only NMR signals for the major isomer are assigned.* $\mathbf{R_F}$ = 0.15 (5:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*): δ [ppm] = 8.02 (bs, NH), 7.83 (d, *J* = 8.3 Hz, 2H) , 7.34-7.27 (m, 7H), 4.60 (m, 1H), 4.46 (s, 2H), 4.43 (m, 1H), 3.40-3.31 (m, 2H), 2.57 (q, *J* = 7.2 Hz, 1H), 2.40 (s, 3H), 2.32-2.14 (m, 4H), 1.56-1.46 (m, 2H), 1.41-1.34 (m, 4H), 1.23-1.18 (m, 1H), 1.07 (s, 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*): δ [ppm] = 164.4, 155.2, 145.6, 138.8, 137.5, 130.1, 128.5, 127.7, 127.7, 123.8, 116.5, 109.2, 73.0, 71.0, 54.0, 44.2, 40.5, 35.4, 35.3, 28.1, 26.9, 24.0, 22.4, 21.3, 14.9; **IR** (film) v 3218, 2940, 2875, 1647, 1599, 1496, 1453, 1384, 1332, 1185, 1163, 1093, 997, 925, 885, 813, 735, 697, 667 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{29}H_{39}N_2O_3S^+$ $[M+H]^+$: 495.2676; found: 495.2672.

_N'_-((3a*R*,4*S*,7a*R*)-3a-(3-(benzyloxy)propyl)-4,7a-dimethyl-3-methyleneoctahydro-5*H*-inden-5-ylidene)-4-methylbenzenesulfonohydrazide ((+)-278)



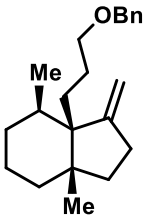
The compound was obtained by the same procedure as for the racemic route. Analytical data matched with the racemic sample. **$[\alpha]_D^{22}$:** +35.6 (c 1.83, $CHCl_3$).

7a-(3-(benzyloxy)propyl)-3a,7-dimethyl-1-methyleneoctahydro-1*H*-indene (280)



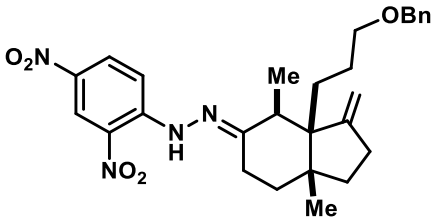
In a flame-dried Schlenk tube, hydrazone **278** (7.67 g, 15.5 mmol, 1.00 eq.) was dissolved in anhydrous $CHCl_3$ (31 mL, 0.5 M) and the solution was cooled to -10 °C. Catechol borane (1 M solution in THF, 31 mL, 31.0 mmol, 2.00 eq.) was added dropwise, and the reaction was stirred for 40 mins at -10 °C and then warmed to room temperature. After 3 h, $NaOAc{\cdot}3H_2O$ (7.38 g, 27.9 mmol, 3.50 eq.) was added in one portion, and the resulting slurry was heated to reflux for 90 mins. Water was added, and the mixture was extracted with DCM. The combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent was removed *in vacuo*. The residue was subjected to column chromatography on silica gel (80:1 hexanes/EA), and the desired defunctionalized bicycle **280** was obtained as colorless oil in 62% yield (2.98 g, 9.54 mmol). $\mathbf{R_F}$ = 0.24 (20:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*): δ [ppm] = 7.37 – 7.25 (m, 5H), 4.92 (td, *J* = 2.1, 0.9 Hz, 1H), 4.66 (td, *J* = 2.5, 0.9 Hz, 1H), 4.50 (s, 2H), 3.43 (t, *J* = 6.6 Hz, 2H), 2.36 (tq, *J* = 7.7, 2.3 Hz, 2H), 1.92 – 1.83 (m, 1H), 1.72 – 1.55 (m, 3H), 1.54 – 1.29 (m, 6H), 1.29 – 1.15 (m, 3H), 1.02 (s, 3H), 1.00 (d, *J* = 7.3 Hz, 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*): δ [ppm] = 156.8, 138.9, 128.5, 127.8, 127.6, 106.3, 72.9, 71.7, 51.8, 44.5, 36.7, 35.9, 29.9, 29.7, 28.3, 27.2, 24.2, 23.0, 18.5, 15.9; **IR** (film) ν 2934, 2863, 1646, 1496, 1454, 1360, 1204, 1099, 1028, 878, 733, 696 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{22}H_{33}O^+$ $[M+H]^+$: 313.2526; found: 313.2519; calculated for $C_{15}H_{25}^+$ $[M-OBn]^+$: 205.1951; found: 205.1948.

(3a*S*,7*R*,7a*R*)-7a-(3-(benzyloxy)propyl)-3a,7-dimethyl-1-methyleneoctahydro-1*H*-indene ((-)-280)



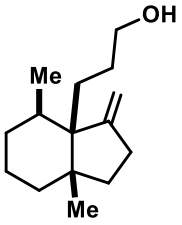
Compound **(-)-280** was obtained by the same procedure as for the racemic route. The analytical data matched with the racemic sample. $\mathbf{[\alpha]_D^{22}}$: -9.8 (c 1.18, $CHCl_3$).

1-(3a-(3-(benzyloxy)propyl)-4,7a-dimethyl-3-methyleneoctahydro-5*H*-inden-5-ylidene)-2-(2,4-nitrophenyl)hydrazine (276)



Ketone **261** (0.25 g, 0.77 mmol, 1.00 eq.) was dissolved in anhydrous EtOH (8 mL, 0.1 M) and 2,4-dinitrophenylhydrazine (70%, 0.21 g, 0.73 mmol, 0.95 eq.) and 6 drops of AcOH (96%) were added. The orange solution was heated to reflux for 24 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (7:1 hexanes/EA) to give hydrazone **276** as a mixture of isomers. Recrystallization from EtOH gave orange crystals, which were suitable for X-Ray single-crystal structure analysis. *Note: NMR of the isomeric mixture, only signals for the major isomer are assigned.* $\mathbf{R_F}$ = 0.34 (7:1 hexanes/EA); **m.p.** 128 °C (major isomer), 158 °C (minor isomer); **^{1}H-NMR** (400 MHz, Chloroform-*D*): δ [ppm] = 11.17 (s, 1H), 9.11 (d, *J* = 2.6 Hz, 1H), 8.27 (ddd, *J* = 9.9, 3.0 Hz, 1H), 7.93 (d, *J* = 9.6 Hz, 1H), 7.37 – 7.27 (m, 6H), 4.98 (t, *J* = 2.0 Hz, 1H), 4.82 (t, *J* = 2.0 Hz, 1H), 4.50 (s, 2H), 3.50 – 3.42 (m, 2H), 2.84 (q, *J* = 7.3 Hz, 1H), 2.54 – 2.43 (m, 2H), 2.42 – 2.31 (m, 2H), 1.72 – 1.47 (m, 7H), 1.38 – 1.31 (m, 1H), 1.27 (d, *J* = 7.3 Hz, 3H), 1.19 (s, 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*): δ [ppm] = 164.4, 155.2, 145.6, 138.8, 137.5, 130.1, 128.5, 127.7, 127.7, 123.8, 116.5, 109.2, 73.0, 71.0, 54.0, 44.2, 40.5, 35.4, 35.3, 28.1, 26.9, 24.0, 22.4, 21.3, 14.9; **IR** (film) ν 3306, 2946, 1618, 1593, 1517, 1502, 1452, 1422, 1336, 1308, 1217, 1124, 1072, 919, 875, 833, 740, 695 cm^{-1}; **HRMS** (ESI) calculated for $C_{28}H_{35}N_4O_5^+$ $[M+H]^+$: 507.2602; found: 507.2590.

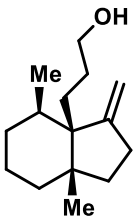
3-(4,7a-dimethyl-3-methyleneoctahydro-3a*H*-inden-3a-yl)propan-1-ol (285)



A three-necked round bottom flask was equipped with a gas inlet tube and a bubble counter, and the flask was cooled to -78 °C under N_2. About 30 mL of ammonia were condensed and sodium metal (2.19 g, 95.4 mmol, 10.0 eq.) was added portionwise. The dark blue mixture was stirred for 40 mins at -78 °C. A solution of benzyl ether **280** (2.98 g. 9.54 mmol, 1.00 eq.) in THF (12 mL) was added, and the reaction was warmed to -60 °C and kept at this temperature for 18 h. The mixture was re-cooled to -78 °C and solid NH_4Cl (10.2 g, 190 mmol, 20.0 eq.) was added. Ammonia was evaporated by slowly warming the reaction to room temperature. Aqueous saturated NH_4Cl and EA were added to the residue and the

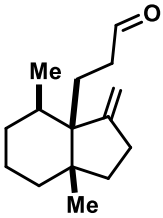
phases were separated. The aqueous phase was extracted with EA and the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (7:1 hexanes/EA) to give a pale yellow solid. Yield 91% (1.92 g, 8.65 mmol). **R_F** = 0.27 (5:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*): δ [ppm] = 4.93 (t, *J* = 2.2 Hz, 1H), 4.66 (t, *J* = 2.2 Hz, 1H), 3.60 (t, *J* = 6.4 Hz, 2H), 2.40 – 2.33 (m, 2H), 1.93 – 1.82 (m, 1H), 1.72 – 1.13 (m, 13H), 1.03 (s, 3H), 1.00 (d, *J* = 7.2 Hz, 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*): δ [ppm] = 156.8, 106.3, 64.2, 51.8, 44.5, 36.8, 35.9, 29.9, 29.7, 28.3, 27.4, 26.9, 22.9, 18.5, 15.8; **IR** (film) ν 3311, 2932, 2866, 1646, 1459, 1384, 1055, 1009, 981, 950, 877, 745 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{15}H_{27}O^+$ $[M+H]^+$: 223.2056; found: 223.2054; calculated for $C_{15}H_{25}^+$ $[M-OH]^+$: 205.1951; found: 205.1949.

3-((3a*R*,4*R*,7a*S*)-4,7a-dimethyl-3-methyleneoctahydro-3a*H*-inden-3a-yl)propan-1-ol ((-)-285)



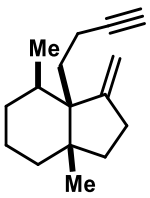
The compound was obtained by the same procedure as for the racemic route. Analytical data matched with the racemic sample. **$[\alpha]_D^{22}$:** -7.3 (c 1.83, $CHCl_3$).

3-(4,7a-dimethyl-3-methyleneoctahydro-3a*H*-inden-3a-yl)propanal (591)



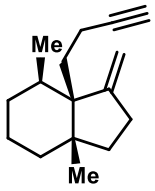
Alcohol **285** (1.92 g, 8.65 mmol, 1.00 eq.) was dissolved in DMSO (22 mL) and cooled in a water bath. NEt_3 (9.6 mL, 69.2 mmol, 8.00 eq.) and SO_3·pyr (5.50 g, 34.6 mmol, 4.00 eq.) in DMSO (21 mL) were added sequentially and the mixture was stirred for 20 h at room temperature. Water was added and the mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude aldehyde was directly used in the next step without further purification. **R_F** = 0.40 (10:1 hexanes/EA).

7a-(but-3-yn-1-yl)-3a,7-dimethyl-1-methyleneoctahydro-1*H*-indene (257)



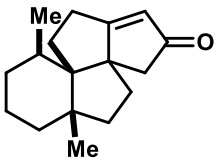
K_2CO_3 (2.39 g, 17.3 mmol, 2.00 eq.) and Ohira-Bestmann reagent (2.49 g, 13.0 mmol, 1.50 eq.) were added sequentially to the crude aldehyde **591** in MeOH (35 mL, 0.25 M). The reaction mixture was stirred at room temperature for 2.5 h. Saturated $NaHCO_3$ was added and the mixture was extracted with pentane. The combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (100% pentane) to give the desired enyne **257** as a colorless liquid (1.22 g, 5.62 mmol, 65% o2s). $\mathbf{R_F}$ = 0.48 (pentane); **^{1}H-NMR** (400 MHz, Chloroform-*D*): δ [ppm] = 4.96 (td, *J* = 2.2, 0.7 Hz, 1H), 4.64 (t, *J* = 2.2 Hz, 1H), 2.41 – 2.34 (m, 2H), 2.19 – 2.00 (m, 2H), 1.93 (t, *J* = 2.7 Hz, 1H), 1.87 – 1.77 (m, 2H), 1.67 – 1.62 (m, 1H), 1.57 – 1.48 (m, 2H), 1.44 – 1.28 (m, 4H), 1.25 – 1.17 (m, 2H), 1.06 (s, 3H), 1.03 (d, *J* = 7.3 Hz, 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*): δ [ppm] = 155.8, 106.8, 86.0, 67.8, 51.9, 44.4, 36.9, 36.0, 30.2, 29.5, 29.2, 28.2, 22.6, 18.1, 15.8, 13.2; **IR** (film) ν 3312, 2936, 2118, 1646, 1459, 1448, 1385, 1239, 1059, 979, 883, 750 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{16}H_{25}^+$ $[M+H]^+$: 217.1951; found: 217.1946.

(3a*S*,7*R*,7a*R*)-7a-(but-3-yn-1-yl)-3a,7-dimethyl-1-methyleneoctahydro-1*H*-indene ((-)-257)



Compound **(-)-257** was obtained by the same procedure as for the racemic route. Analytical data matched with the racemic sample. **$[\alpha]_D^{22}$:** -19.2 (c 1.62, $CHCl_3$).

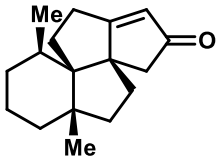
5a,9-dimethyl-5,5a,6,7,8,9,10,11-octahydro-4*H*-pentaleno[6a,1-c]inden-2(3*H*)-one (93)



Enyne **257** (407 mg, 1.88 mmol, 1.00 eq.) was dissolved in anhydrous xylene (54 mL) and the solution was degassed *via* freeze-pump-thaw (3 cycles). $Co_2(CO)_8$ (709 mg, 2.07 mmol, 1.10 eq.) was added and the reaction was stirred for 2 h at room temperature, and then heated in a sealed tube to 140 °C for 21 h. The mixture was filtered over Celite with ethyl acetate, and the solvents were removed under reduced pressure. The residue was purified by column chromatography on silica gel (10:1 hexanes/EA) to give desired enone **93** as a colorless

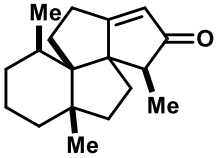
solid in 46% yield (211 mg, 0.86 mmol). Spontaneous crystallization of the compound gave colorless crystals, which were suitable for X-ray single-crystal structure analysis. R_F = 0.19 (10:1 hexanes/EA); **m.p.** 56 °C; **^{1}H-NMR** (600 MHz, Chloroform-*D*): δ [ppm] = 5.63 (t, *J* = 1.5 Hz, 1H), 2.73 (d, *J* = 17.0 Hz, 1H), 2.55 (m, 2H), 2.29 (d, *J* = 17.0 Hz, 1H), 2.21 (ddd, *J* = 14.0, 8.7, 5.4 Hz, 1H), 1.84 (dt, *J* = 13.6, 8.4 Hz, 1H), 1.75 – 1.66 (m, 2H), 1.65 – 1.51 (m, 4H), 1.46 – 1.34 (m, 5H), 1.15 (s, 3H), 0.97 (d, *J* = 7.1 Hz, 3H); **^{13}C-NMR** (151 MHz, Chloroform-*D*): δ [ppm] = 211.8, 194.9, 120.3, 64.6, 56.8, 50.6, 45.4, 41.5, 38.8, 37.7, 33.5, 33.0, 30.4, 28.1, 24.8, 17.7, 17.0; **IR** (film) ν 2916, 2864, 1695, 1630, 1457, 1408, 1379, 1295, 1244, 1196, 1169, 988, 913, 839, 808, 746, 681 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{17}H_{25}O^+$ $[M+H]^+$: 245.1900; found: 245.1893.

(3a*S*,5a*S*,9*R*,9a*S*)-5a,9-dimethyl-5,5a,6,7,8,9,10,11-octahydro-4*H*-pentaleno[6a,1-*c*]inden-2(3*H*)-one ((-)-93)



Compound **(-)-93** was obtained by the same procedure as for the racemic route. Analytical data matched with the racemic sample. **$[\alpha]_D^{22}$:** -42.4 (c 1.11, $CHCl_3$).

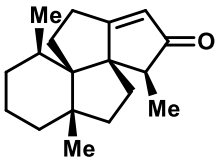
3,5a,9-trimethyl-5,5a,6,7,8,9,10,11-octahydro-4*H*-pentaleno[6a,1-c]inden-2(3*H*)-one (197)



In a flame-dried Schlenk tube, TMP (20 µL, 0.11 mmol, 1.40 eq.) was dissolved in THF (30 µL) and cooled to -20 °C. *n*-BuLi (2.5 M solution in hexanes, 40 µL, 0.10 mmol, 1.30 eq.) was added dropwise, and the resulting solution was stirred at -20 °C for 15 mins and then cooled to -78 °C. Enone **93** (20 mg, 0.08 mmol, 1.00 eq.) in THF (70 µL) was added and the reaction was stirred for 30 mins. The flask was removed from the cooling bath for 10 mins and then re-cooled to -78 °C. DMPU (20 µL, 0.13 mmol, 1.60 eq.) was added and the mixture was stirred for 20 mins before MeI (20 µL, 0.32 mmol, 4.00 eq.) was added. The reaction was allowed to warm to room temperature in the cooling bath overnight and quenched by the addition of saturated NH_4Cl. The mixture was extracted with Et_2O and the combined organic phases were washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography on silica gel (10:1 hexanes/EA) gave the

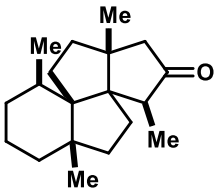
desired methylated compound as a colorless solid in 63% yield (13 mg, 0.05 mmol) along with 7 mg (0.03 mmol, 36%) of recovered starting material. Combined yield 96%. Recrystallization of the methylated compound from hexanes gave colorless needle-shaped crystals, which were suitable for X-ray single-crystal structure analysis. **R_F** = 0.23 (10:1 hexanes/EA); **m.p.** 81 °C; **^{1}H-NMR** (400 MHz, Chloroform-*D*): *δ* [ppm] = 5.67 (br s, 1H), 2.56 – 2.46 (m, 3H), 2.26 (ddd, *J* = 13.9, 9.0, 3.7 Hz, 1H), 1.98 (ddd, *J* = 13.9, 9.6, 8.0 Hz, 1H), 1.67 – 1.55 (m, 5H), 1.48 – 1.35 (m, 4H), 1.33 – 1.29 (m, 1H), 1.27 (d, *J* = 7.2 Hz, 3H), 1.26 – 1.22 (m, 1H), 1.17 (s, 3H), 0.98 (d, *J* = 7.1 Hz, 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*): *δ* [ppm] = 213.2, 193.4, 119.3, 67.3, 57.6, 49.0, 45.0, 41.6, 37.0, 34.4, 33.7, 31.7, 30.0, 28.5, 24.9, 17.5, 16.8, 12.3; **IR** (film) ν 2937, 2853, 1687, 1635, 1456, 1384, 1370, 1302, 1248, 1200, 1124, 1046, 1011, 866, 787, 744, 686, 664 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{18}H_{27}O^+$ $[M+H]^+$: 259.2058; found: 259.2048.

(3*S*,3a*S*,5a*S*,9*R*,9a*S*)-3,5a,9-trimethyl-5,5a,6,7,8,9,10,11-octahydro-4*H*-pentaleno[6a,1-*c*]inden-2(3*H*)-one ((-)-197)



Compound **(-)-197** was obtained by the same procedure as for the racemic route. Analytical data matched with the racemic sample. **$[\alpha]_D^{22}$:** -62.7 (c 0.52, $CHCl_3$).

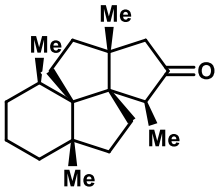
3,5a,9,11a-tetramethyldecahydro-4*H*-pentaleno[6a,1-c]inden-2(3*H*)-one (94)



In a flame-dried Schlenk tube, CuCN (82 mg, 0.91 mmol, 5.00 eq.) was suspended in Et_2O (1 mL) and cooled to -78 °C. MeLi (1.6 M solution in Et_2O, 1.2 mL, 1.82 mmol, 10.0 eq.) was added dropwise and the mixture was stirred for 5 mins at -78 °C and for further 5 mins at room temperature. The colorless solution was re-cooled to -78 °C. In a separate Schlenk tube, enone **23** (47 mg, 0.18 mmol, 1.00 eq.) was dissolved in Et_2O (0.5 mL) and cooled to -78 °C. $BF_3{\cdot}OEt_2$ (60 µL, 0.46 mmol, 2.50 eq.) was added dropwise followed by the cuprate solution. The reaction mixture was warmed to -55 °C and stirred for 3 h at this temperature. Saturated NH_4Cl solution was added and the mixture was warmed to room temperature. The phases were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on

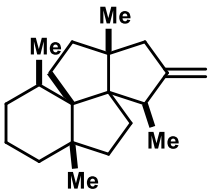
silica gel (80:1 hexanes/EA) to give ketone **94** as a coloress solid in 70% yield (35 mg, 0.13 mmol). $\mathbf{R_F}$ = 0.25 (20:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*): δ [ppm] = 2.52 (q, *J* = 8.3, 7.7 Hz, 1H), 2.29 (dd, *J* = 19.3, 1.4 Hz, 1H), 2.21 (d, *J* = 19.3 Hz, 1H), 1.74 – 1.40 (m, 11H), 1.33 – 1.27 (m, 3H), 1.15 – 1.02 (m, 1H), 1.14 (s, 3H), 1.11 (d, *J* = 7.8 Hz, 3H), 1.06 (s, 3H), 0.80 (d, *J* = 6.7 Hz, 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*): δ [ppm] = 224.1, 66.1, 60.6, 52.5, 50.1, 49.1, 45.0, 42.4, 41.5, 34.6, 33.2, 29.0, 28.6, 25.7, 24.8, 19.8, 17.8, 15.6; **IR** (film) ν 2972, 2926, 2864, 1726, 1456, 1400, 1384, 1229, 1195, 1171, 1141, 1011, 963, 858, 796, 714, 667 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{19}H_{31}O^+$ $[M+H]^+$: 275.2369; found: 275.2361.

(3*S*,3a*S*,5a*S*,9*R*,9a*S*,11a*R*)-3,5a,9,11a-tetramethyldecahydro-4*H*-pentaleno [6a,1-*c*]inden-2(3*H*)-one ((+)-94)



Compound **(+)-94** was obtained by the same procedure as for the racemic route. Analytical data matched with the racemic sample. **$[\alpha]_D^{22}$:** +5.8 (c 1.68, $CHCl_3$).

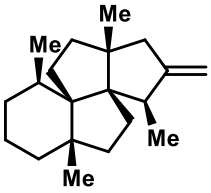
(±)-waihoensene (75)



A suspension of KO*t*Bu (81 mg, 0.72 mmol, 9.00 eq.) in anhydrous toluene (2 mL) was heated to 110 °C until a clear solution formed. Methyltriphenylphosphonium bromide (286 mg, 0.80 mmol, 10.0 eq.) was added in one portion and the bright yellow mixture was heated to 110 °C for 60 mins. A solution of ketone **94** (22 mg, 0.08 mmol, 1.00 eq.) in toluene (0.7 mL) was added and the reaction was heated for further 90 mins. The reaction was cooled to room temperature and water was added. The aqueous phase was extracted with Et_2O and the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (100% pentane) to give (±)-waihoensene as a colorless oil in 83% yield (18 mg, 0.07 mmol). $\mathbf{R_F}$ = 0.86 (pentane); **^{1}H-NMR** (400 MHz, Chloroform-*D*): δ [ppm] = 4.69 (q, *J* = 1.9 Hz, 2H), 2.71 (q, *J* = 7.3 Hz, 1H), 2.24 – 2.20 (m, 2H), 1.79 (pd, *J* = 7.0, 3.5 Hz, 1H), 1.64 (td, *J* = 13.6, 6.7 Hz, 1H), 1.62 – 1.59 (m, 1H), 1.59 – 1.57 (m, 1H), 1.56 – 1.54 (m, 2H), 1.53 – 1.50 (m, 1H), 1.50 – 1.44 (m, 1H), 1.44 – 1.40 (m,

1H), 1.40 – 1.31 (m, 2H), 1.31 – 1.27 (m, 1H), 1.27 – 1.24 (m, 1H), 1.19 – 1.14 (m, 1H), 1.14 – 1.10 (m, 1H), 1.04 (d, *J* = 7.3 Hz, 3H), 1.02 (s, 3H), 1.02 (s, 3H), 0.91 (d, *J* = 6.9 Hz, 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*): *δ* [ppm] = 159.8, 103.1, 68.4, 60.5, 52.6, 48.2, 44.8, 44.0, 42.1, 41.0, 36.1, 32.0, 30.6, 30.4, 28.8, 25.5, 25.1, 20.0, 19.3, 17.6; **IR** (film) ν 2924, 2866, 1656, 1458, 1375, 1263, 975, 874 cm^{-1}; **HRMS** (EI) calculated for $C_{20}H_{32}^{+}$ $[M]^{+}$: 272.2504; found: 272.2501.

(+)-waihoensene ((+)-75)

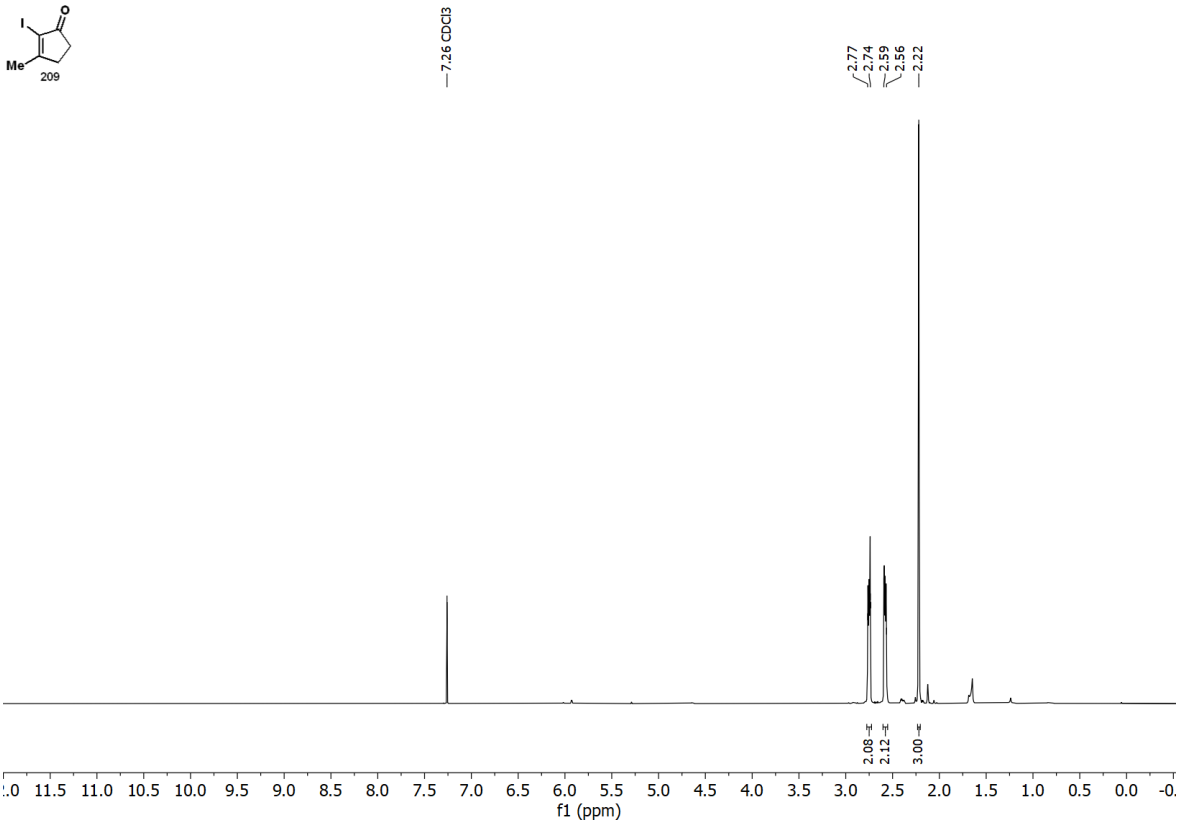


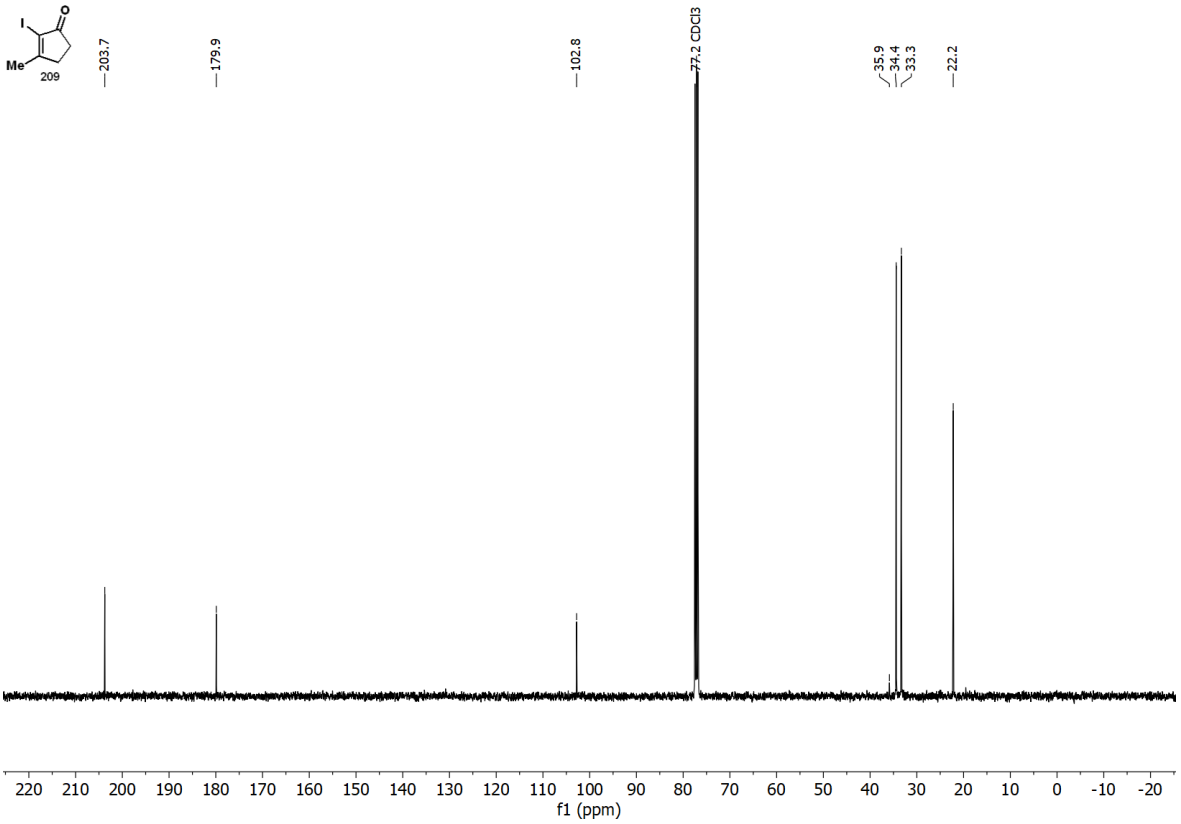
(+)-waihoensene (**75**) was obtained by the same procedure as for the racemic route. Analytical data matched with the racemic sample. **$[\alpha]_D^{23}$:** +42.4 (c 0.18, $CHCl_3$); Lit.: **$[\alpha]_D^{22}$** = +43.9 ° (c 0.09, $CHCl_3$) [5]

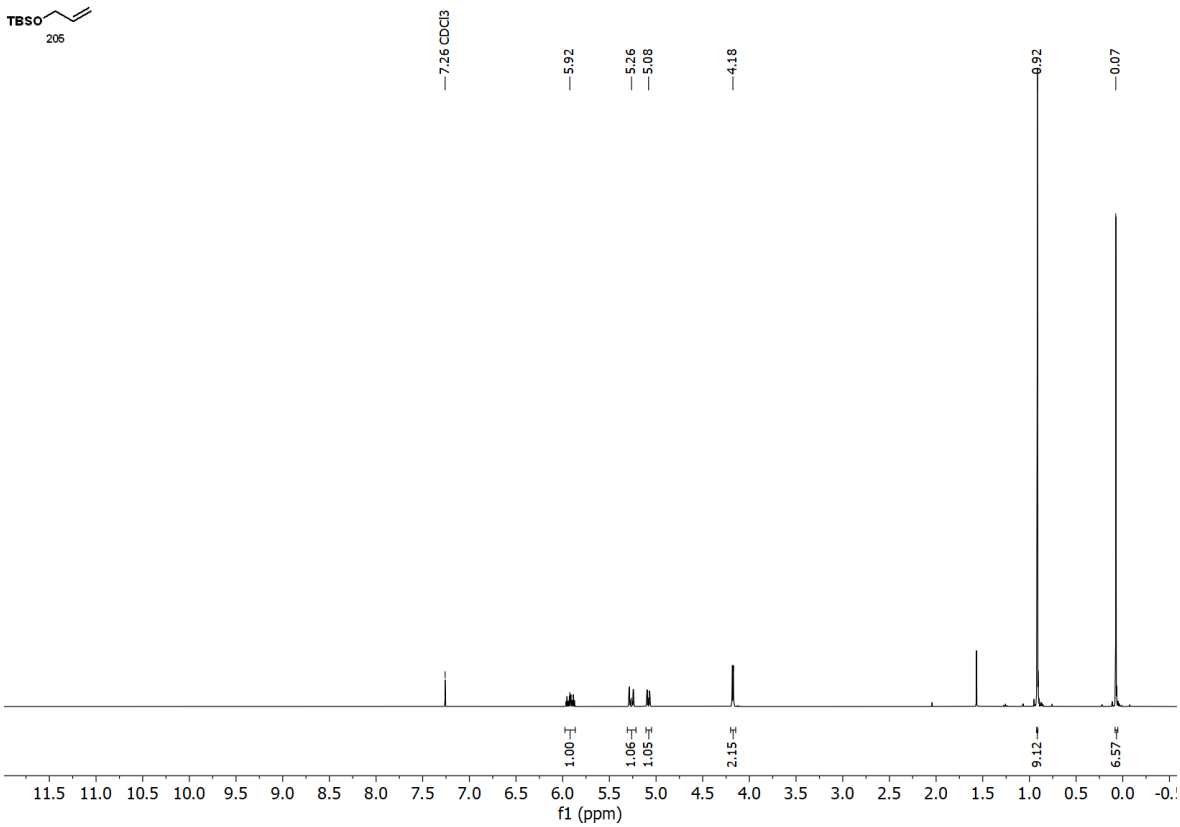
Comparison of NMR data of synthetic waihoensene (**75**) with literature [5]

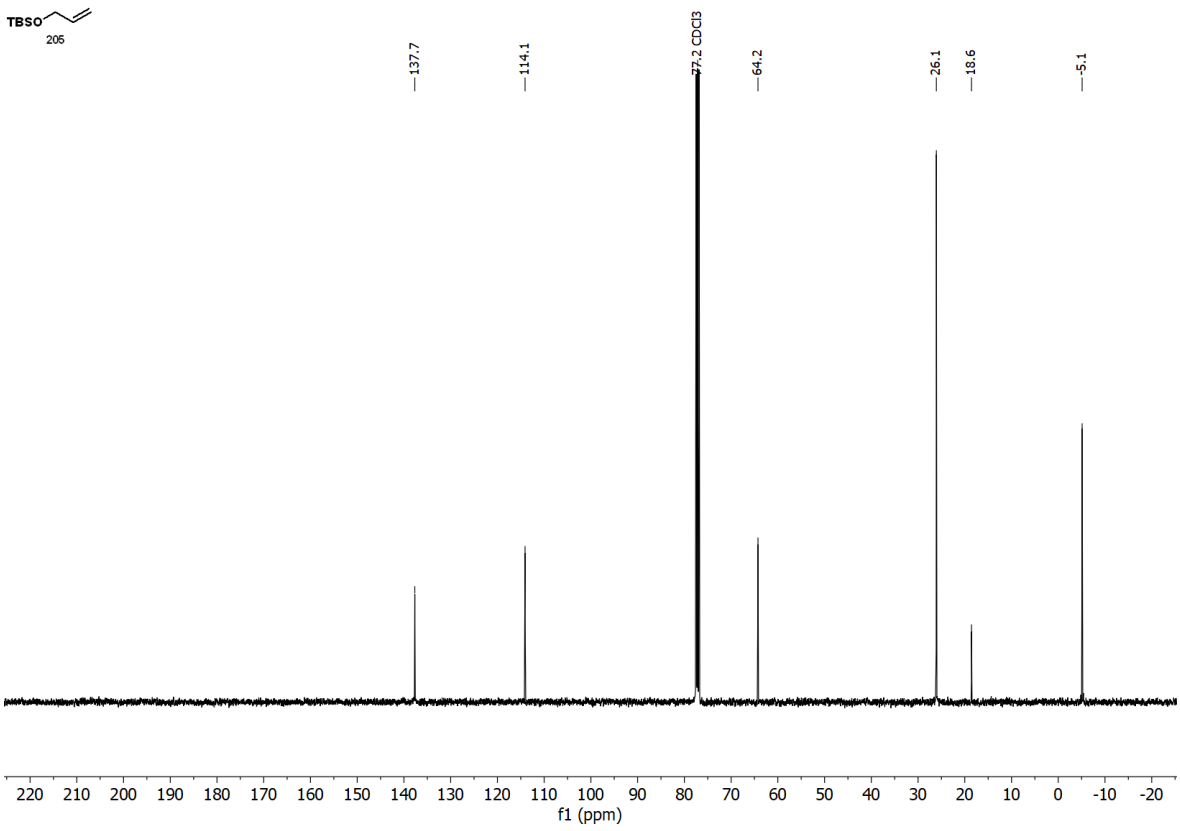
^{1}H-NMR		^{13}C-NMR	
isolated	synthetic	Isolated	synthetic
0.89 (d, *J* = 7 Hz, 3H)	0.91 (d, *J* = 6.9 Hz, 3H)	17.61	17.6
0.99 (s, 3H)	1.02 (s, 3H)	19.23	19.3
1.00 (s, 3H)	1.02 (s, 3H)	19.90	20.0
1.02 (d, *J* = 7 Hz, 3H)	1.04 (d, *J* = 7.3 Hz, 3H)	25.06	25.1
1.12 (m, 1H)	1.14 – 1.10 (m, 1H)	25.42	25.5
1.15 (m, 1H)	1.19 – 1.14 (m, 1H)	28.75	28.8
1.25 (m, 1H)	1.27 – 1.24 (m, 1H)	30.35	30.4
1.27 (m, 1H)	1.31 – 1.27 (m, 1H)	30.55	30.6
1.36 (m, 2H)	1.40 – 1.31 (m, 2H)	31.93	32.0
1.42 (m, 1H)	1.44 – 1.40 (m, 1H)	36.03	36.1
1.43 (m, 1H)	1.50 – 1.44 (m, 1H)	40.98	41.0
1.50 (m, 1H)	1.53 – 1.50 (m, 1H)	42.07	42.1
1.54 (m, 2H)	1.56 – 1.54 (m, 2H)	43.92	44.0
1.55 (m, 1H)	1.59 – 1.57 (m, 1H)	44.76	44.8
1.56 (m, 1H)	1.62 – 1.59 (m, 1H)	48.12	48.2
1.64 (m, 1H)	1.64 (td, *J* = 13.6, 6.7 Hz, 1H)	52.58	52.6
1.79 (m, 1H)	1.79 (pd, *J* = 7.0, 3.5 Hz, 1H)	60.50	60.5
2.20 (bs, *J* = 1 Hz, 2H)	2.24 – 2.20 (m, 2H)	68.35	68.4
2.69 (q, *J* = 7 Hz, 1H)	2.71 (q, *J* = 7.3 Hz, 1H)	102.96	103.1
4.69 (q, *J* = 2 Hz, 2H)	4.69 (q, *J* = 1.9 Hz, 2H)	159.70	159.8

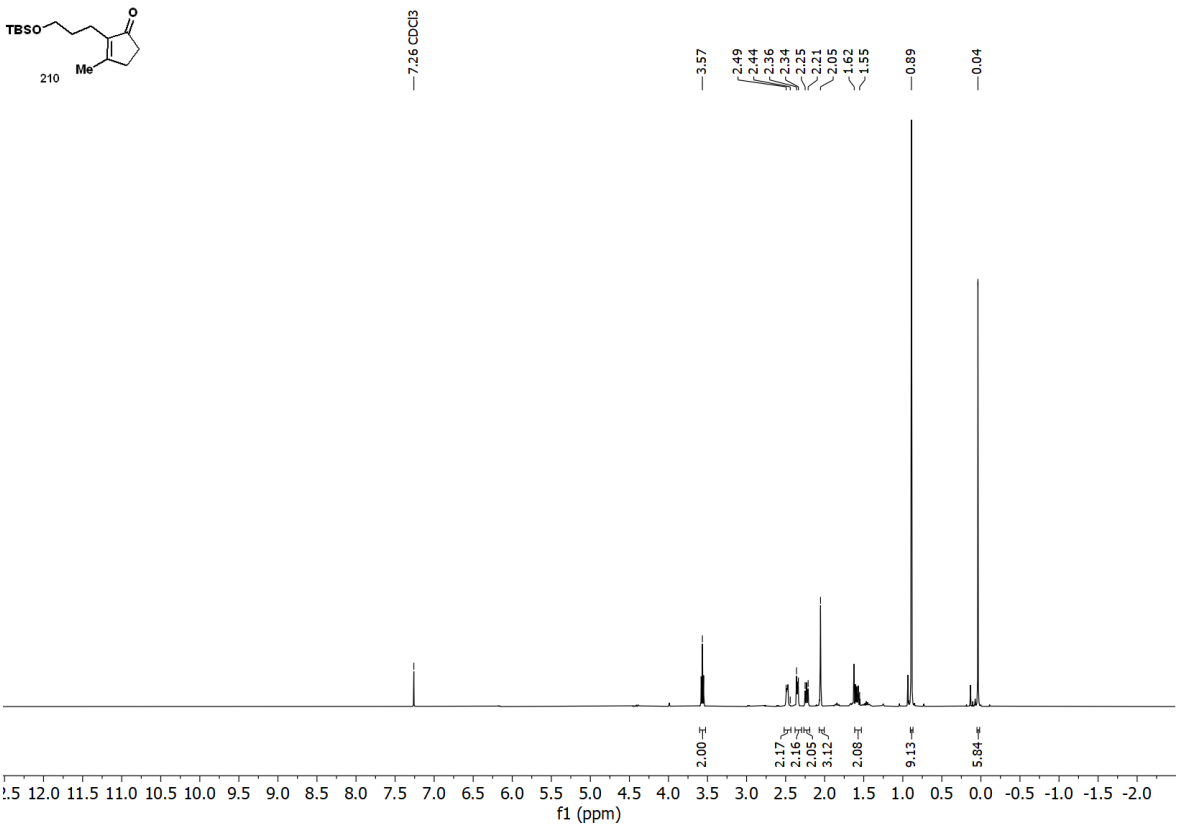
3.1.4 NMR Spectra

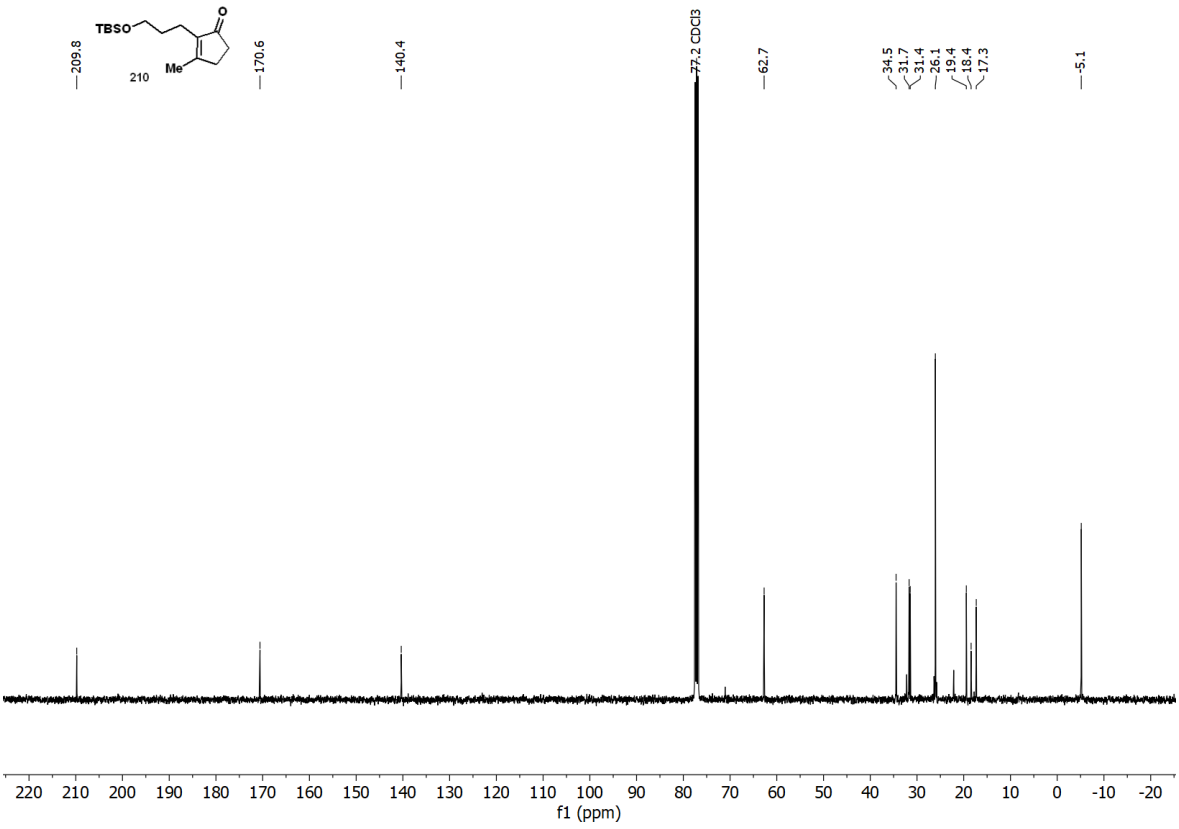


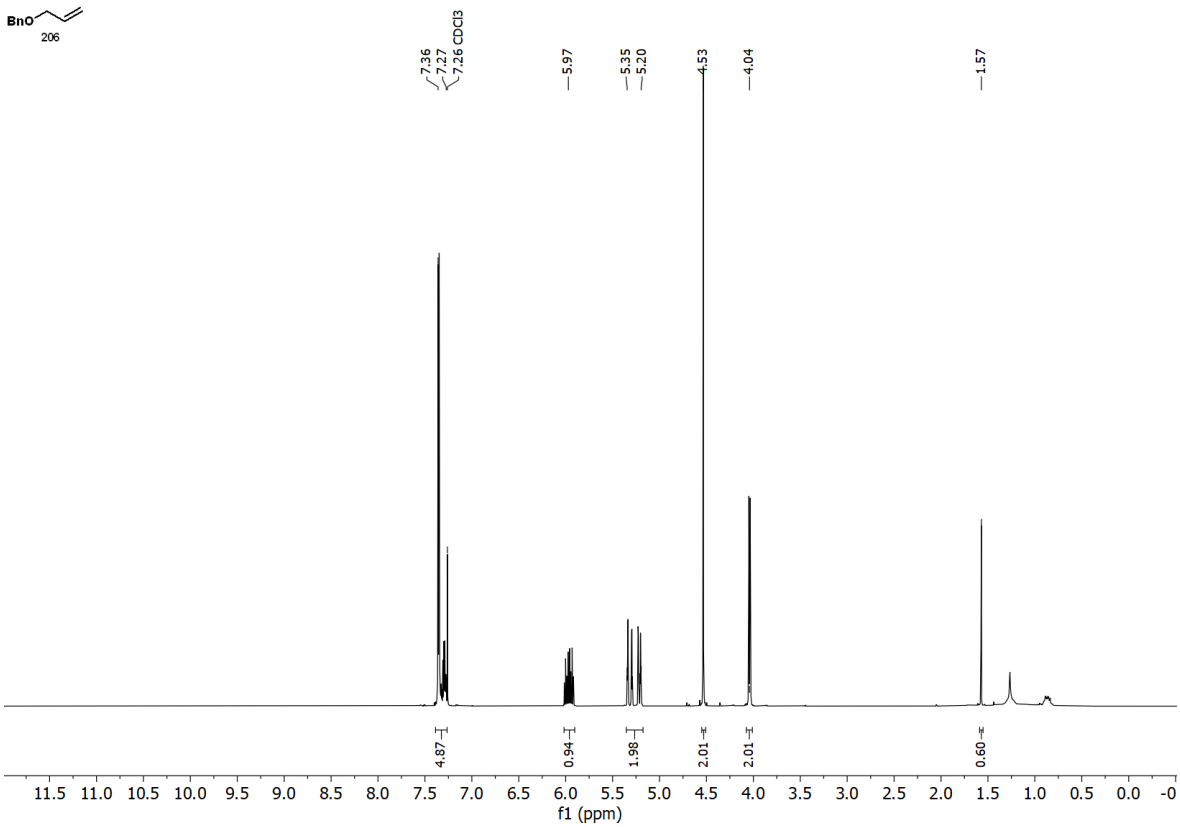


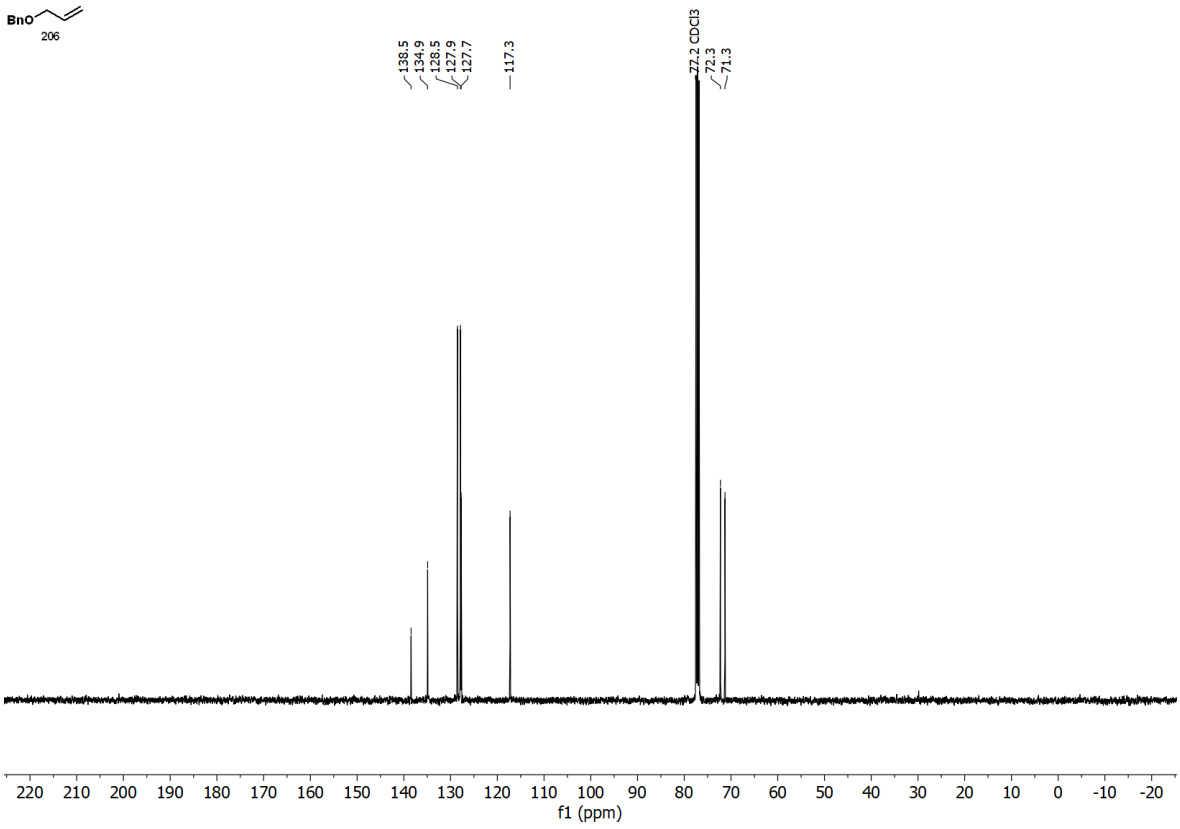

TBSO
205
7.26 CDCl3
5.92
5.26
5.08
4.18
0.92
0.07
1.00
1.06
1.05
2.15
9.12
6.57
f1 (ppm)

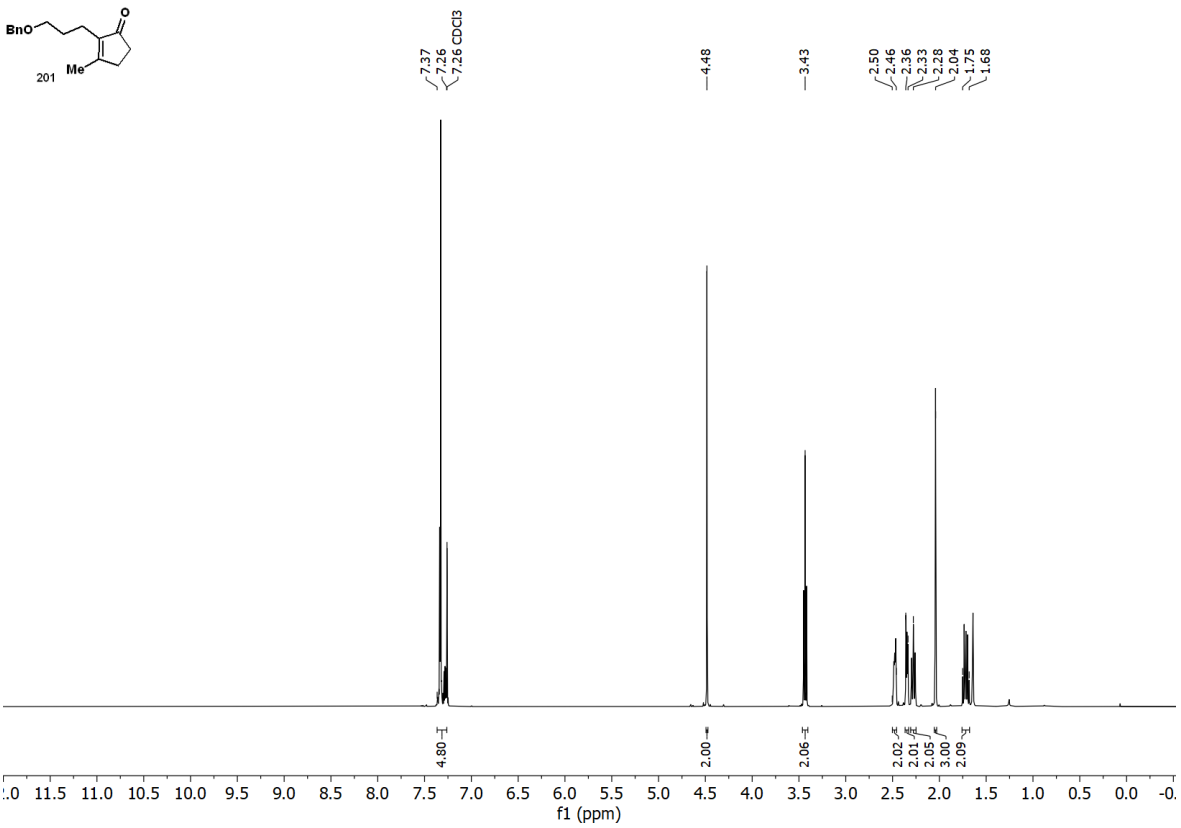

TBSO
205
137.7
114.1
77.2 CDCl3
64.2
26.1
18.6
-5.1
f1 (ppm)

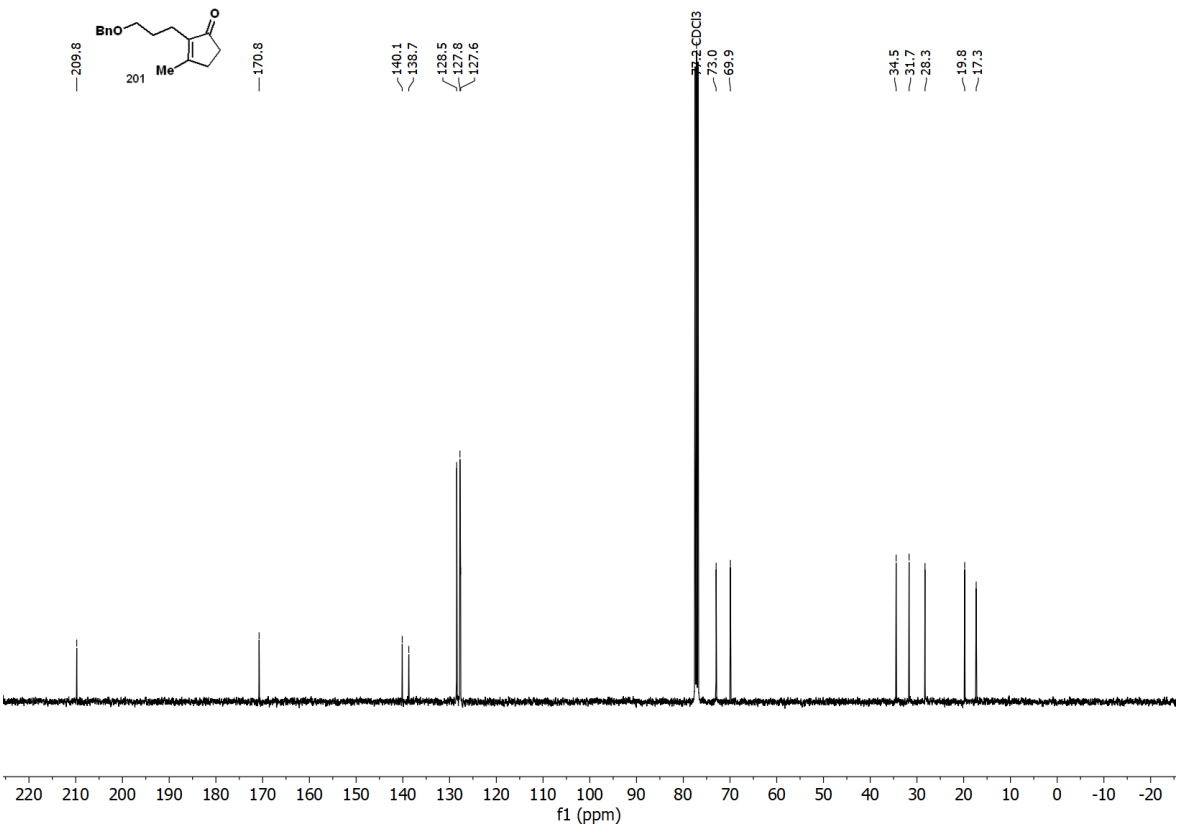

TBSO
O
Me
210
7.26 CDCl3
3.57
2.49
2.44
2.36
2.34
2.25
2.21
2.05
1.62
1.55
0.89
0.04
2.00
2.17
2.16
2.05
3.12
2.08
9.13
5.84
f1 (ppm)

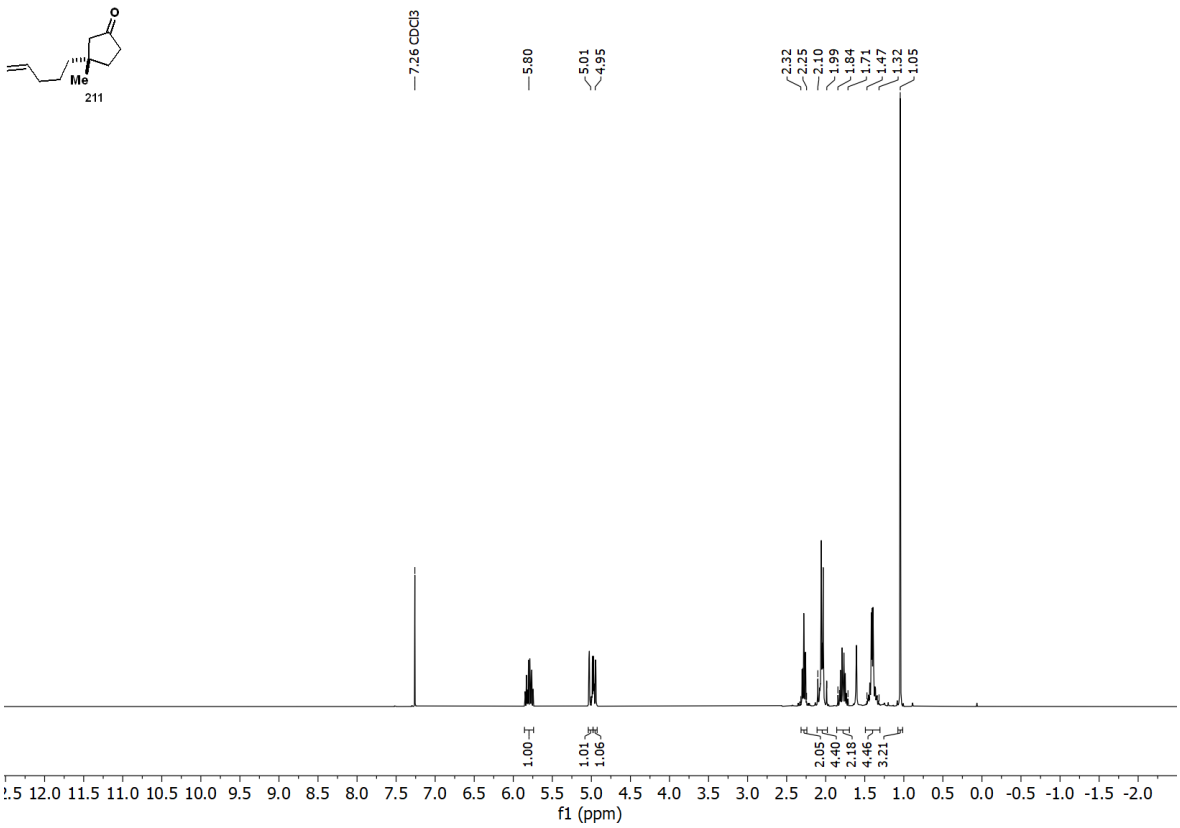

TBSO
O
Me
210
209.8
170.6
140.4
77.2 CDCl3
62.7
34.5
31.7
31.4
26.1
19.4
18.4
17.3
-5.1
f1 (ppm)

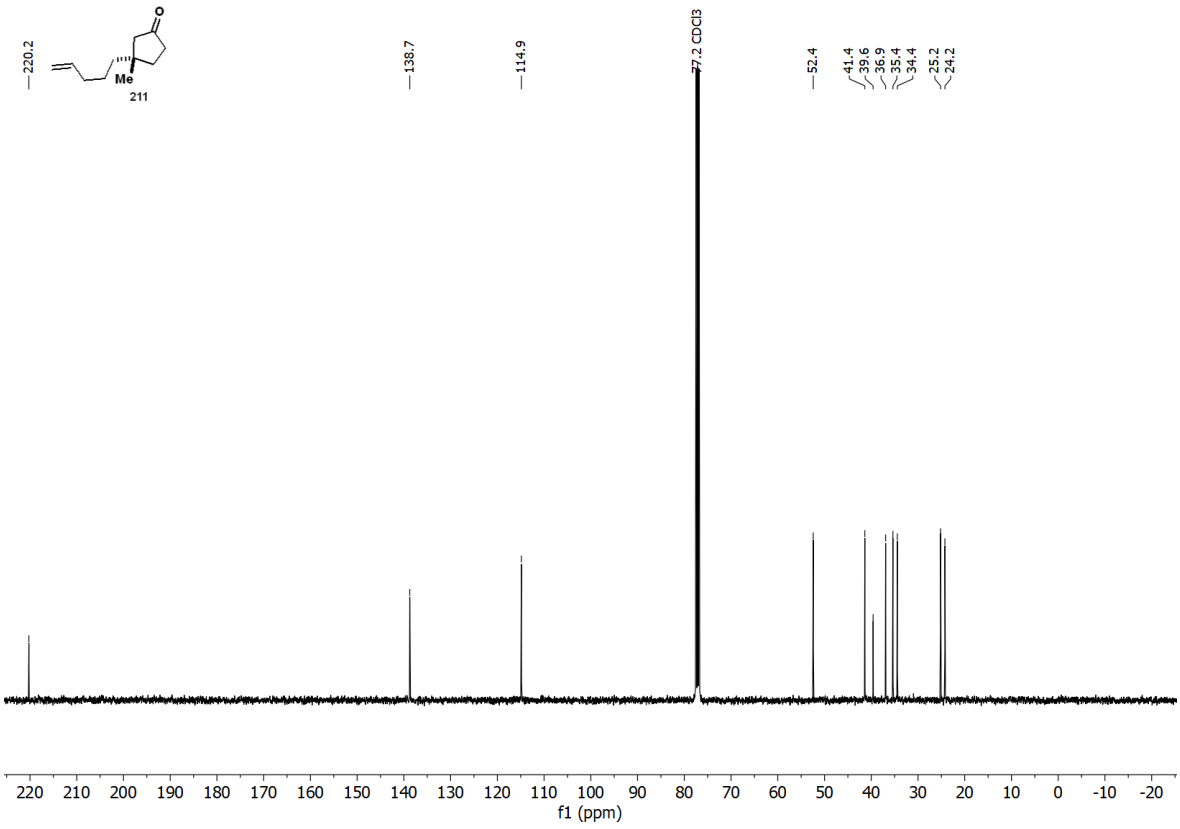

BnO
206
7.36
7.27
7.26 CDCl3
5.97
5.35
5.20
4.53
4.04
1.57
4.87
0.94
1.98
2.01
2.01
0.60
f1 (ppm)

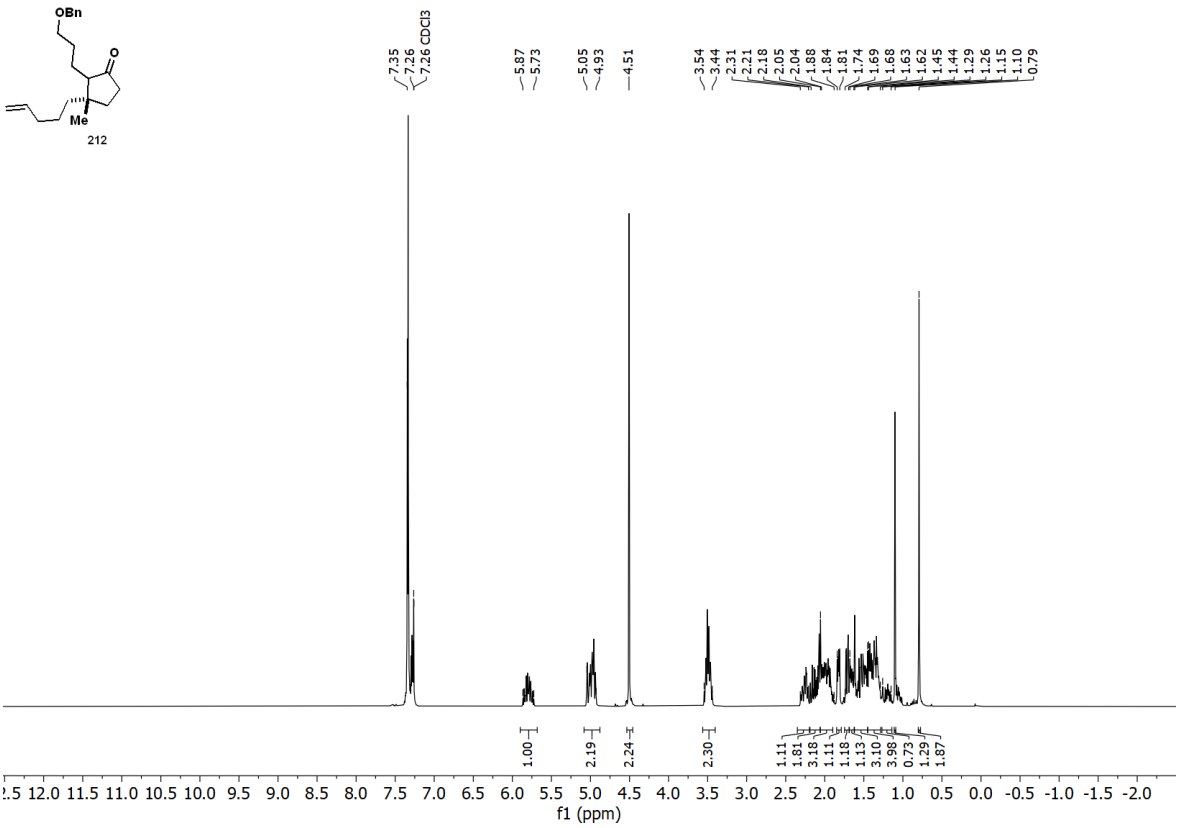

BnO
206
138.5
134.9
128.5
127.9
127.7
117.3
77.2 CDCl3
72.3
71.3
f1 (ppm)

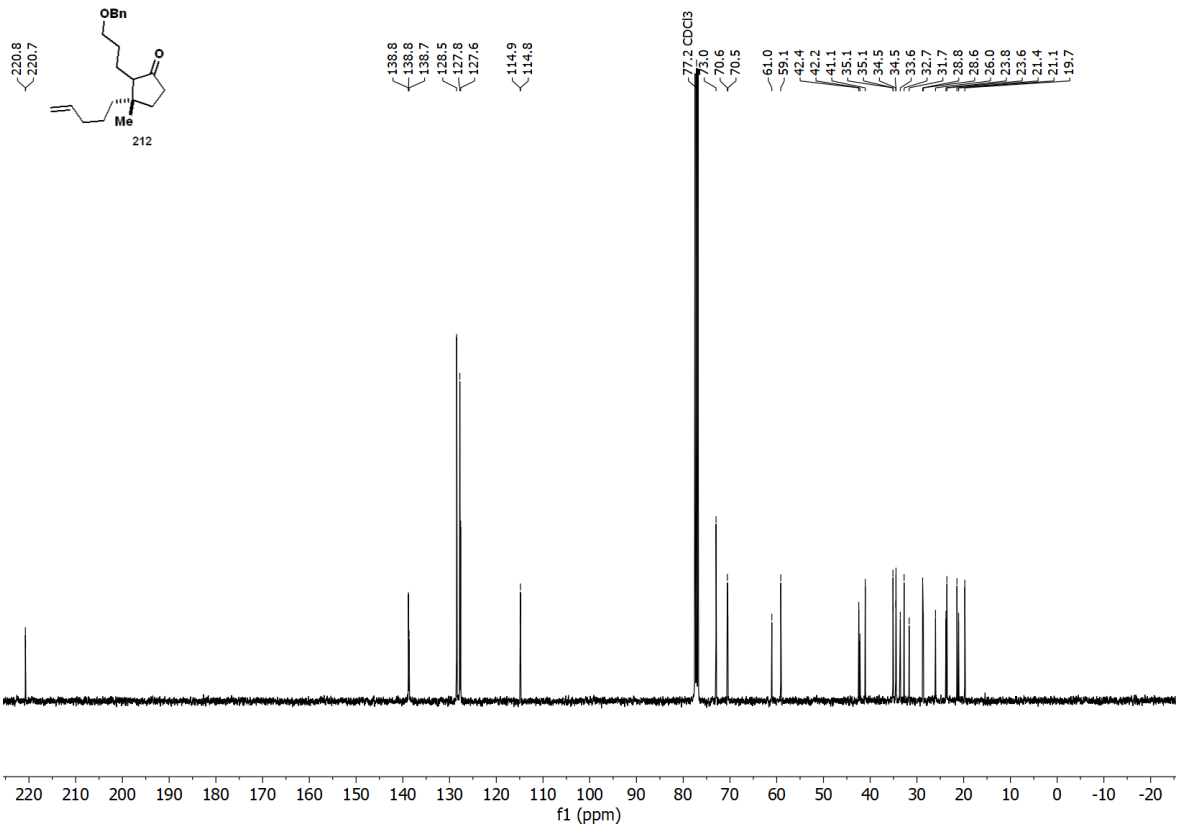

BnO
O
Me
201
7.37
7.26
7.26 CDCl3
4.48
3.43
2.50
2.46
2.36
2.33
2.28
2.04
1.75
1.68
4.80
2.00
2.06
2.02
2.01
2.05
3.00
2.09
f1 (ppm)

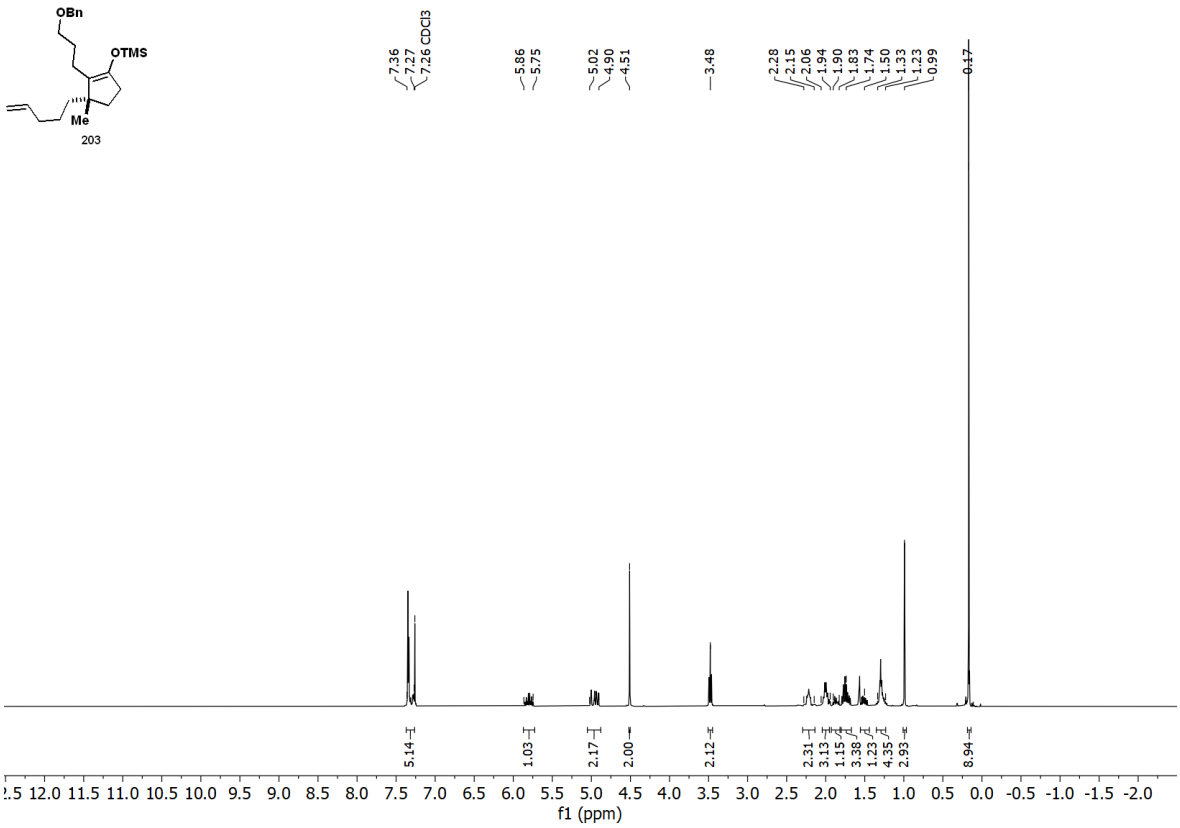

BnO
O
Me
201
209.8
170.8
140.1
138.7
128.5
127.8
127.6
77.2 CDCl3
73.0
69.9
34.5
31.7
28.3
19.8
17.3
f1 (ppm)

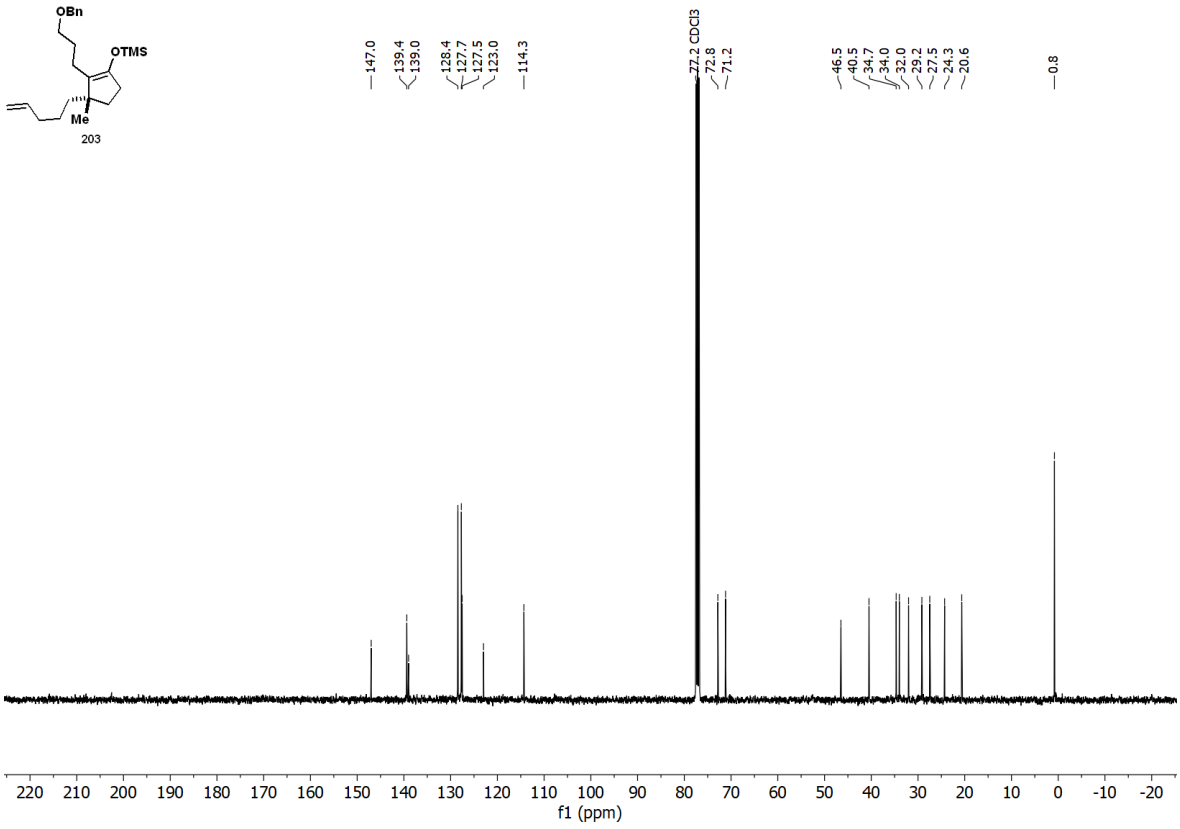

O
Me
211
7.26 CDCl3
5.80
5.01
4.95
2.32
2.25
2.10
1.99
1.84
1.71
1.47
1.32
1.05
1.00
1.01
1.06
2.05
4.40
2.18
4.46
3.21
f1 (ppm)

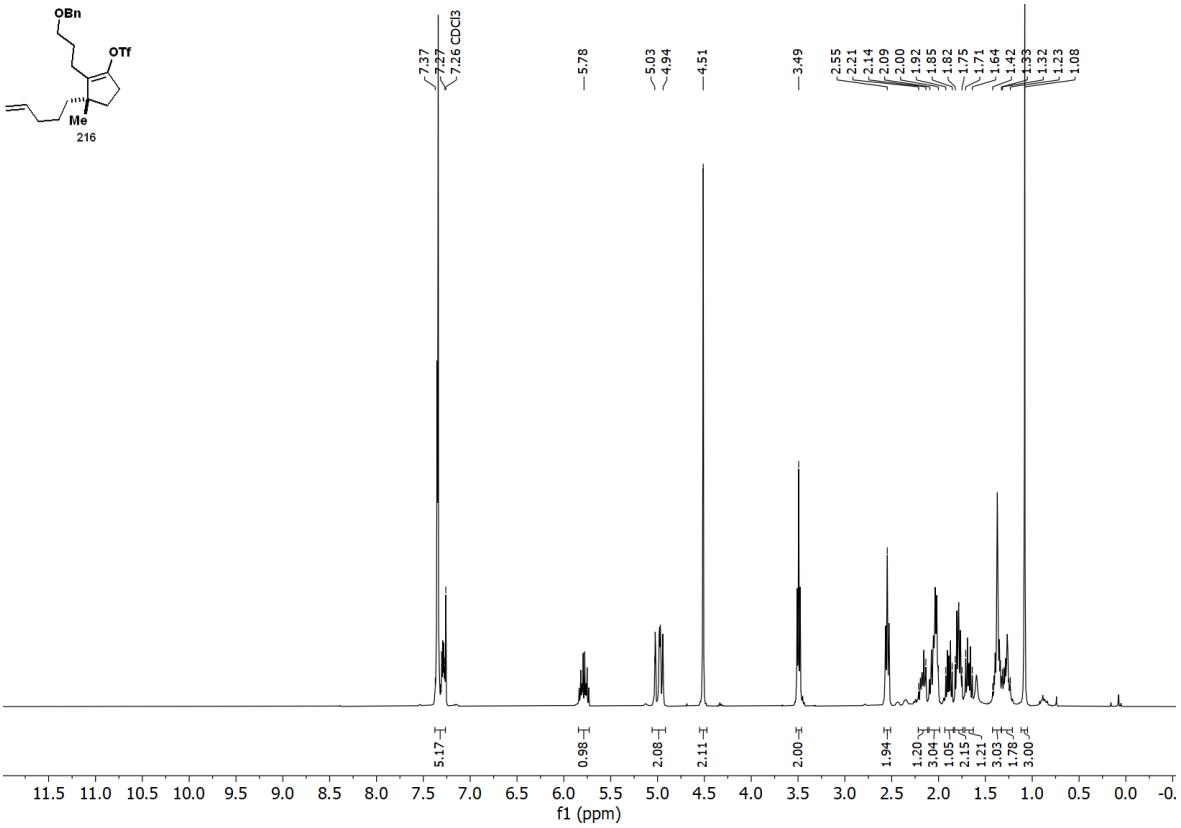

O
Me
211
220.2
138.7
114.9
77.2 CDCl3
52.4
41.4
39.6
36.9
35.4
34.4
25.2
24.2
f1 (ppm)

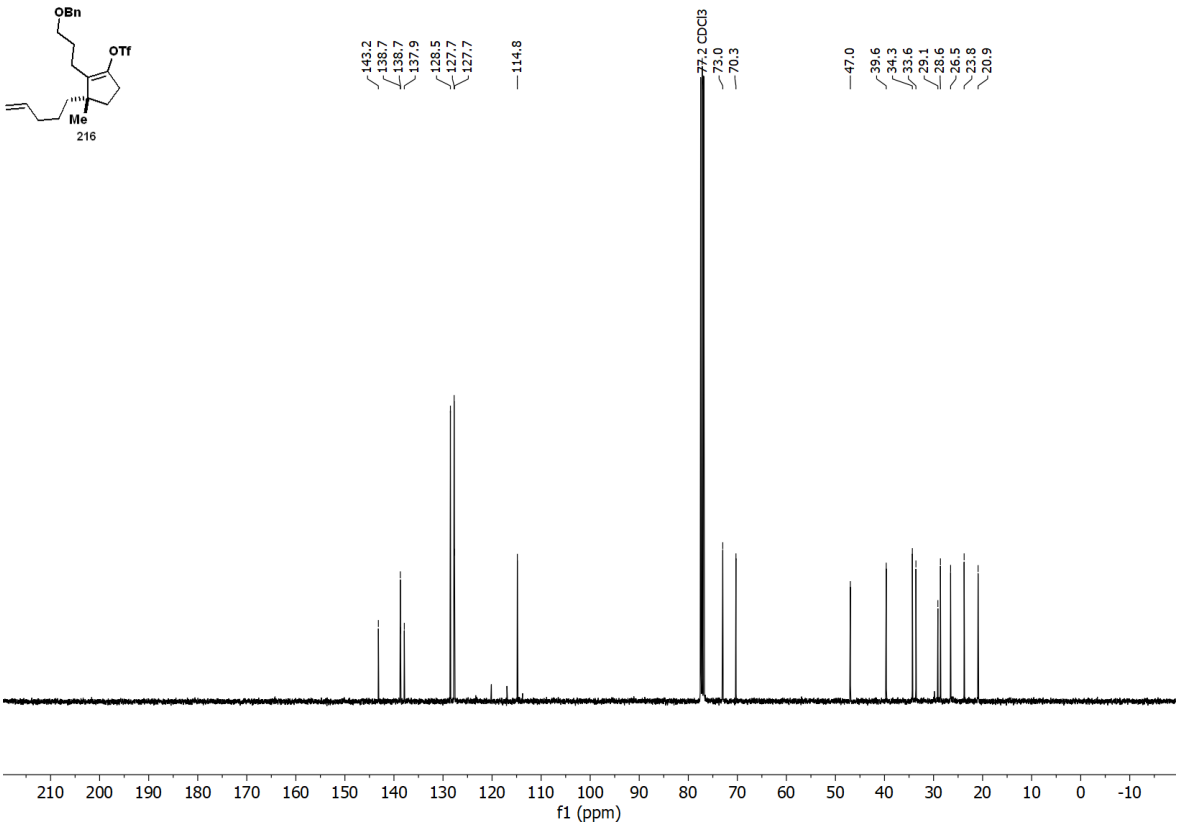

OBn
O
Me
212
7.35
7.26
7.26 CDCl3
5.87
5.73
5.05
4.93
4.51
3.54
3.44
2.31
2.21
2.18
2.05
2.04
1.88
1.84
1.81
1.74
1.69
1.68
1.63
1.62
1.45
1.44
1.29
1.26
1.15
1.10
0.79
1.00
2.19
2.24
2.30
1.11
1.81
3.18
1.11
1.18
1.13
3.10
3.98
0.73
1.29
1.87
f1 (ppm)

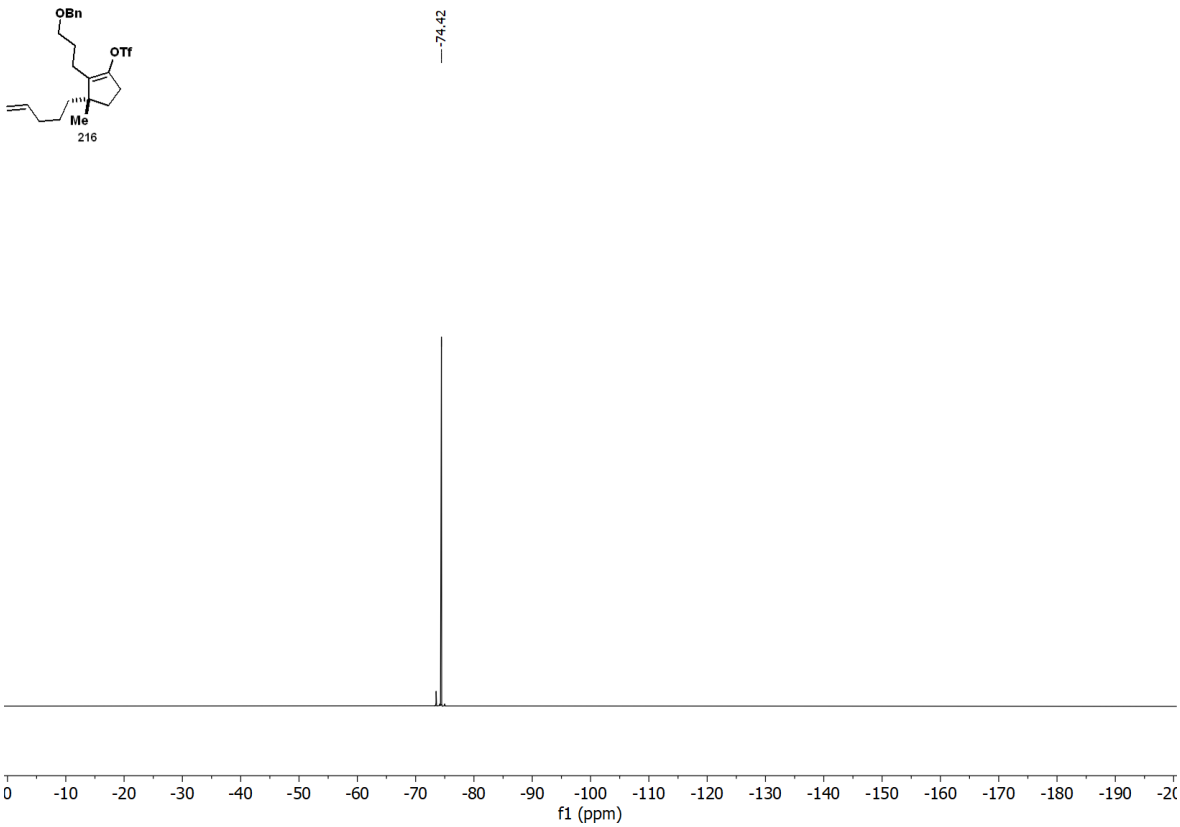

OBn
O
Me
212
220.8
220.7
138.8
138.8
138.7
128.5
127.8
127.6
114.9
114.8
77.2 CDCl3
73.0
70.6
70.5
61.0
59.1
42.4
42.2
41.1
35.1
35.1
34.5
34.5
33.6
32.7
31.7
28.8
28.6
26.0
23.8
23.6
21.4
21.1
19.7
f1 (ppm)

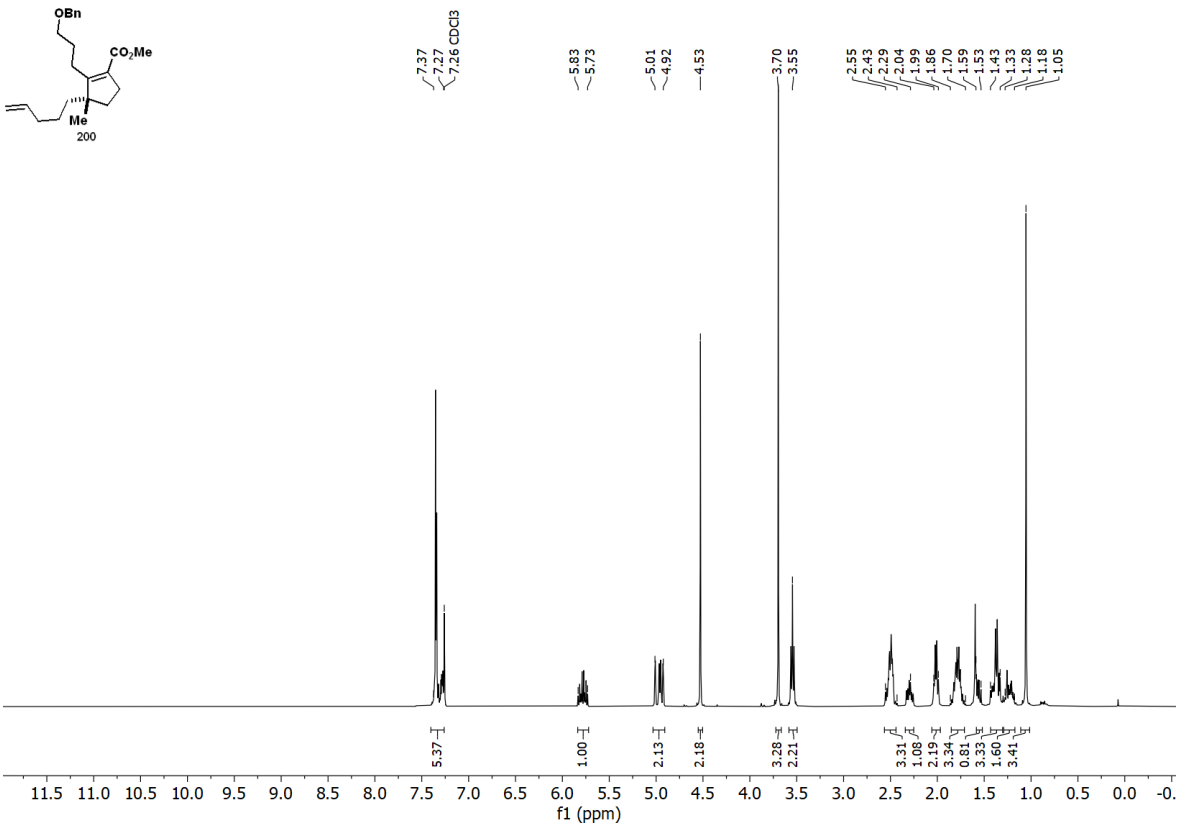

OBn
OTMS
Me
203
7.36
7.27
7.26 CDCl3
5.86
5.75
5.02
4.90
4.51
3.48
2.28
2.15
2.06
1.94
1.90
1.83
1.74
1.50
1.33
1.23
0.99
0.17
5.14
1.03
2.17
2.00
2.12
2.31
3.13
1.15
3.38
1.23
4.35
2.93
8.94
f1 (ppm)

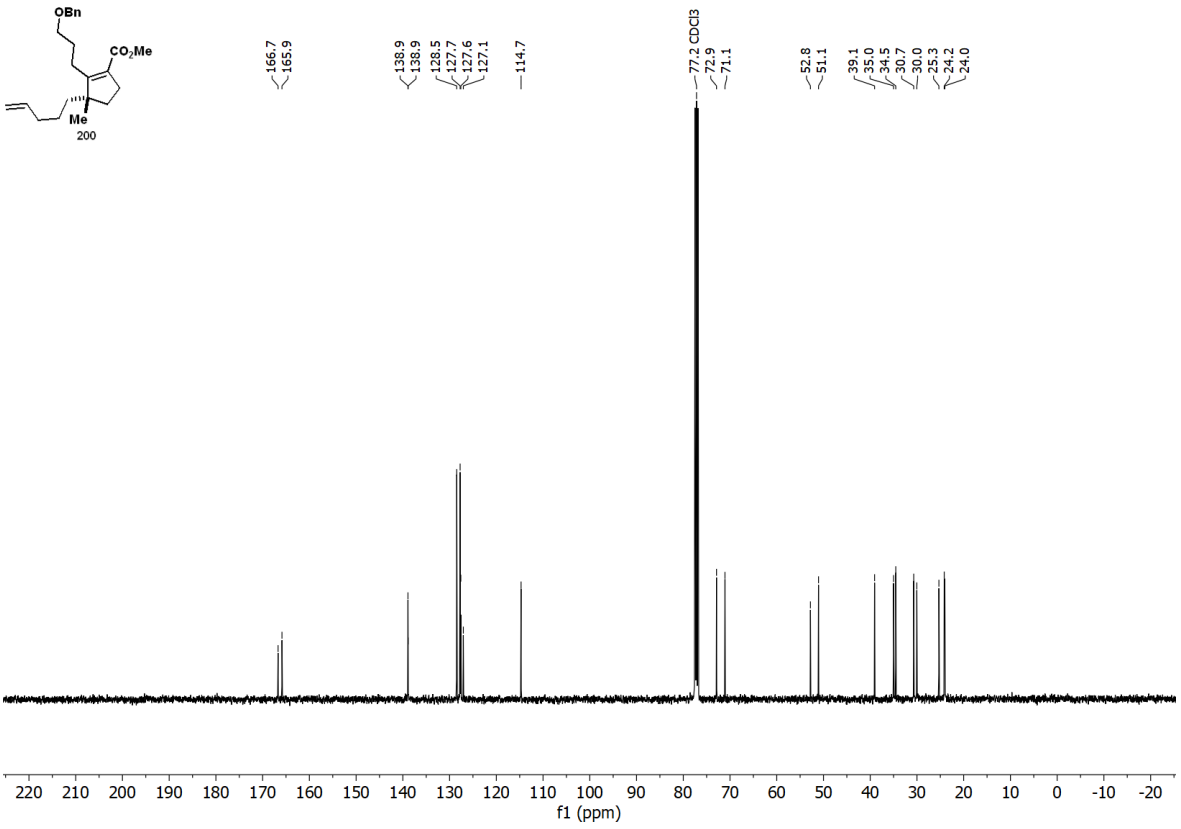

OBn
OTMS
Me
203
147.0
139.4
139.0
128.4
127.7
127.5
123.0
114.3
77.2 CDCl3
72.8
71.2
46.5
40.5
34.7
34.0
32.0
29.2
27.5
24.3
20.6
0.8
f1 (ppm)


OBn
OTf
Me
216
7.37
7.27
7.26 CDCl3
5.78
5.03
4.94
4.51
3.49
2.55
2.21
2.14
2.09
2.00
1.92
1.85
1.82
1.75
1.71
1.64
1.42
1.33
1.32
1.23
1.08
5.17
0.98
2.08
2.11
2.00
1.94
1.20
3.04
1.05
2.15
1.21
3.03
1.78
3.00
f1 (ppm)

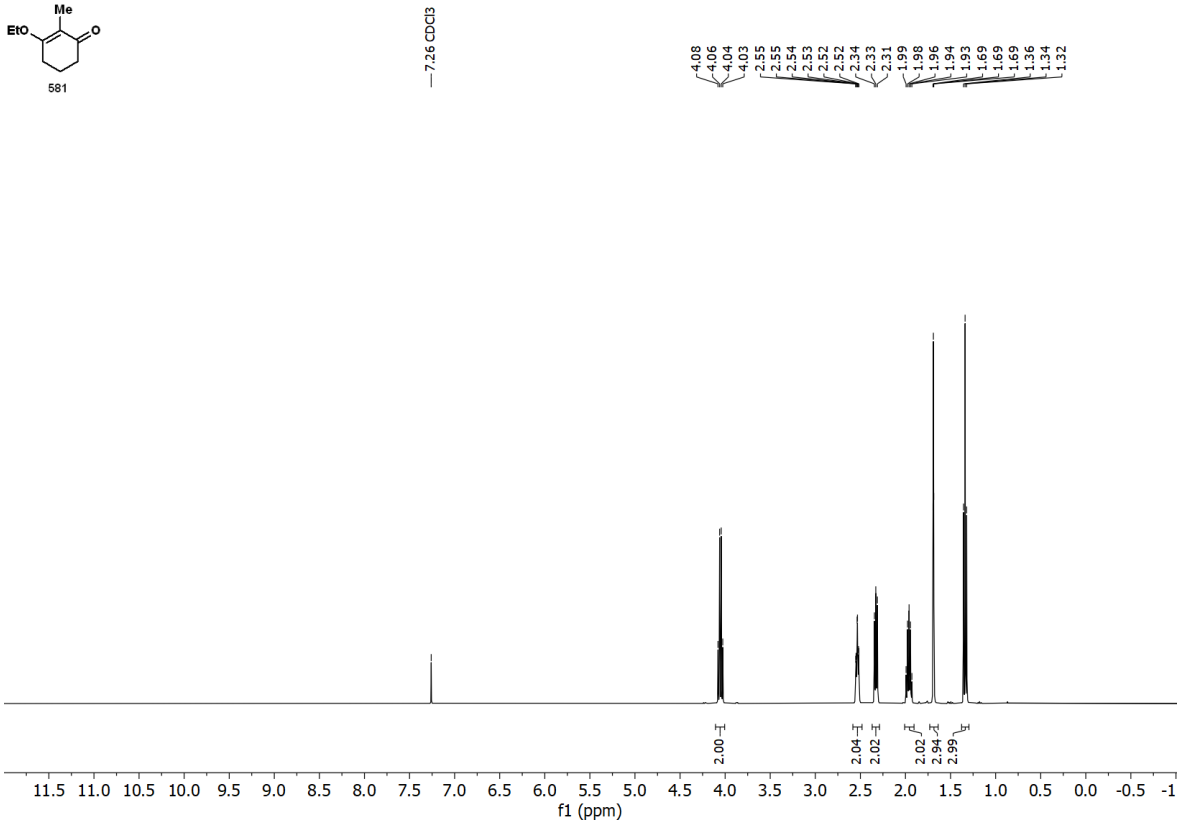

OBn
OTf
Me
216
143.2
138.7
138.7
137.9
128.5
127.7
127.7
114.8
77.2 CDCl3
73.0
70.3
47.0
39.6
34.3
33.6
29.1
28.6
26.5
23.8
20.9
f1 (ppm)

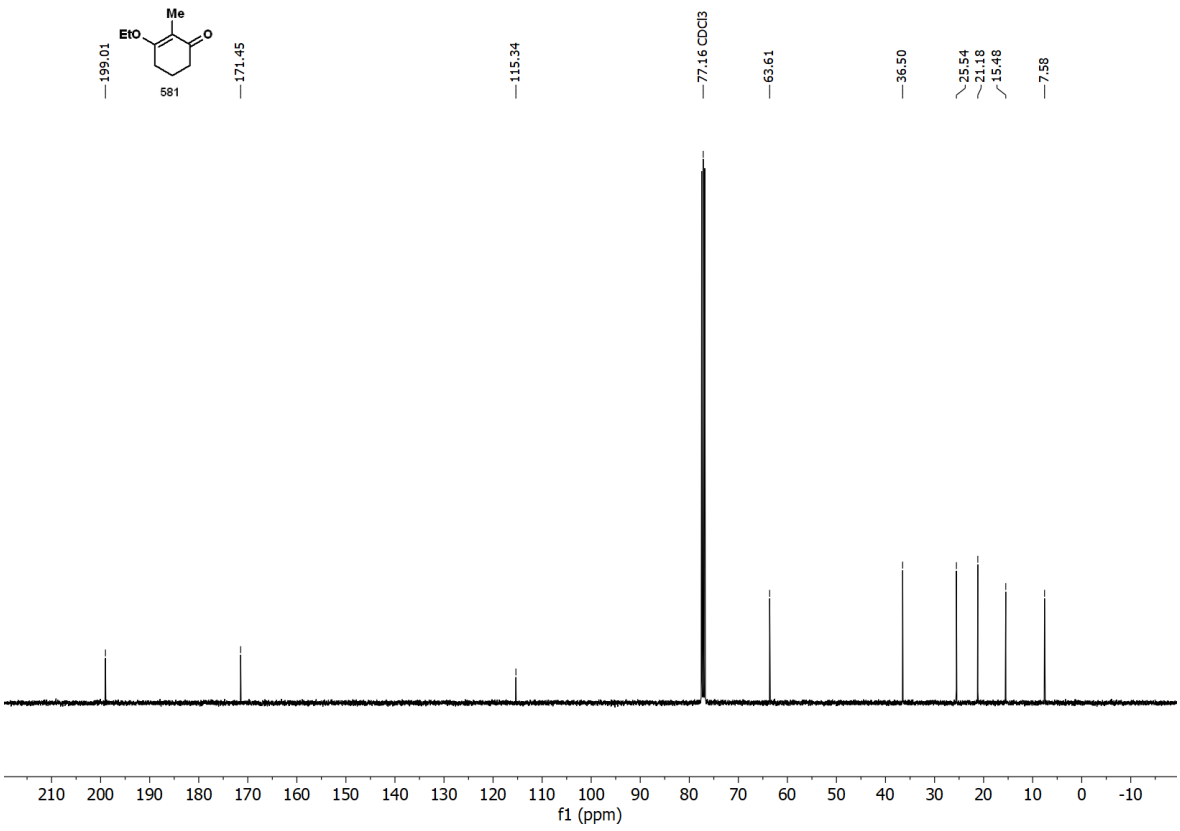

OBn
OTf
Me
216
-74.42
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

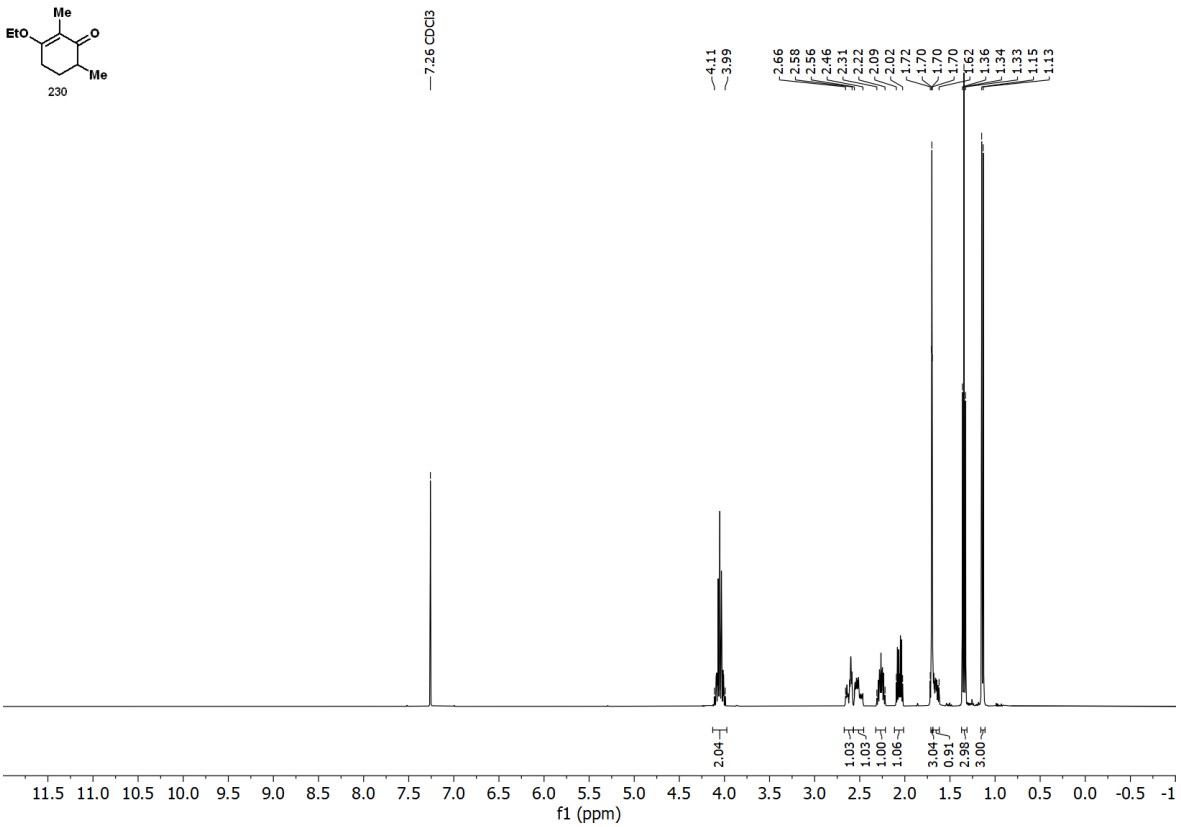

OBn
CO2Me
Me
200
7.37
7.27
7.26 CDCl3
5.83
5.73
5.01
4.92
4.53
3.70
3.55
2.55
2.43
2.29
2.04
1.99
1.86
1.70
1.59
1.53
1.43
1.33
1.28
1.18
1.05
5.37
1.00
2.13
2.18
3.28
2.21
3.31
1.08
2.19
3.34
0.81
3.33
1.60
3.41
f1 (ppm)

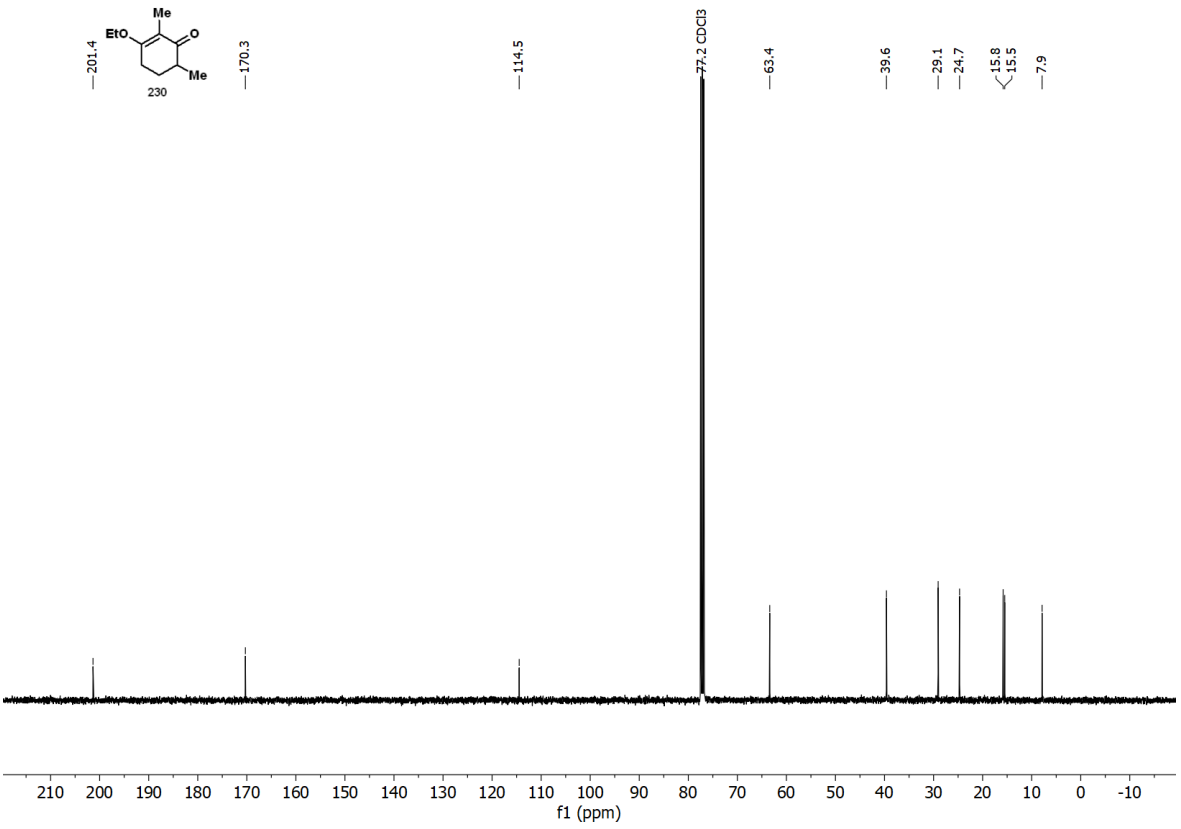

OBn
CO2Me
Me
200
166.7
165.9
138.9
138.9
128.5
127.7
127.6
127.1
114.7
77.2 CDCl3
72.9
71.1
52.8
51.1
39.1
35.0
34.5
30.7
30.0
25.3
24.2
24.0
f1 (ppm)

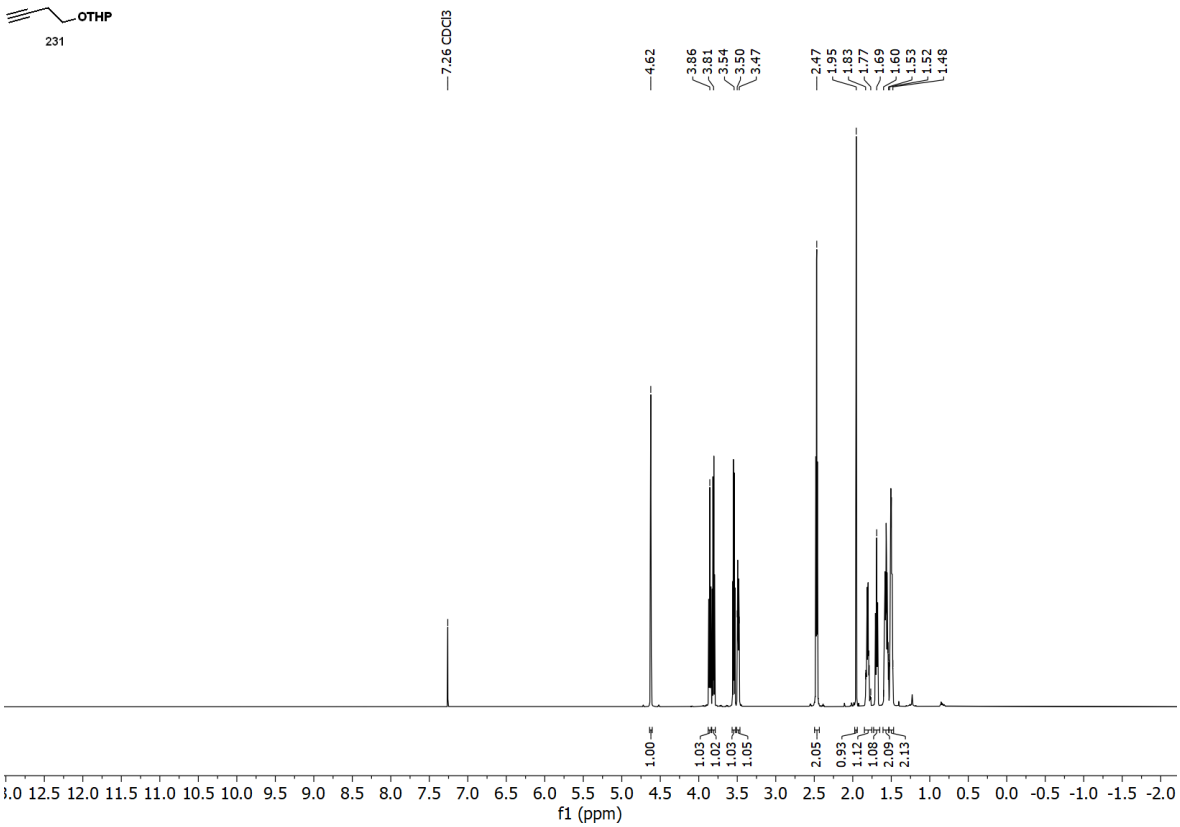
Me
EtO
O
581

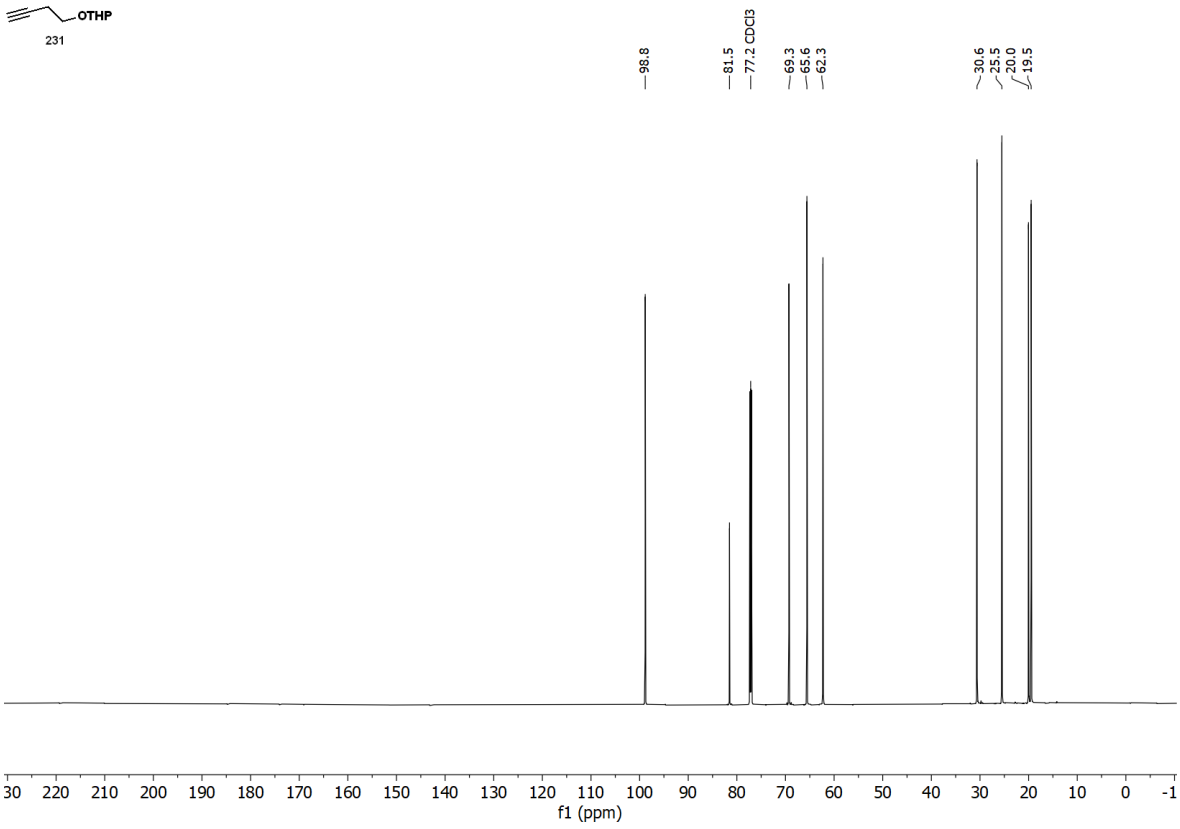

7.26 CDCl3
4.08
4.06
4.04
4.03
2.55
2.55
2.54
2.53
2.52
2.52
2.34
2.33
2.31
1.99
1.98
1.96
1.94
1.93
1.69
1.69
1.69
1.36
1.34
1.32
2.00
2.04
2.02
2.02
2.94
2.99
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

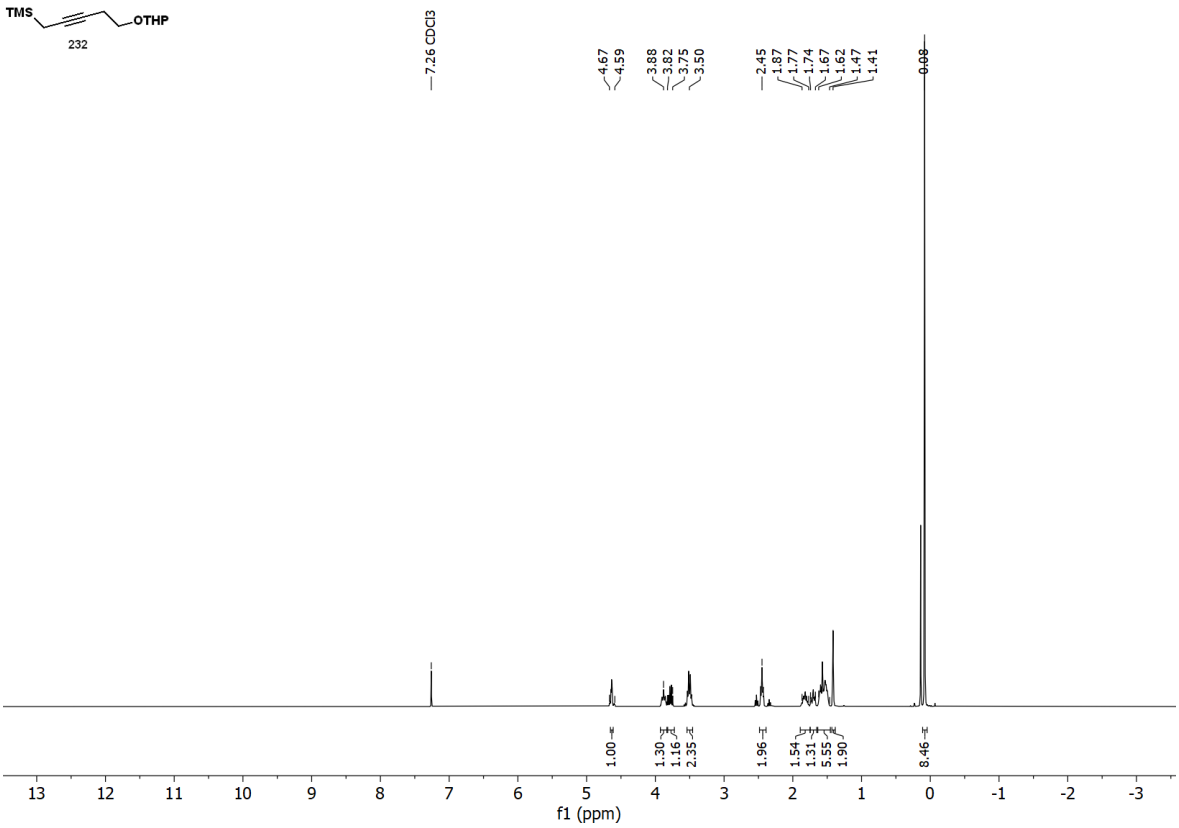

Me
EtO
O
581
199.01
171.45
115.34
77.16 CDCl3
63.61
36.50
25.54
21.18
15.48
7.58
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

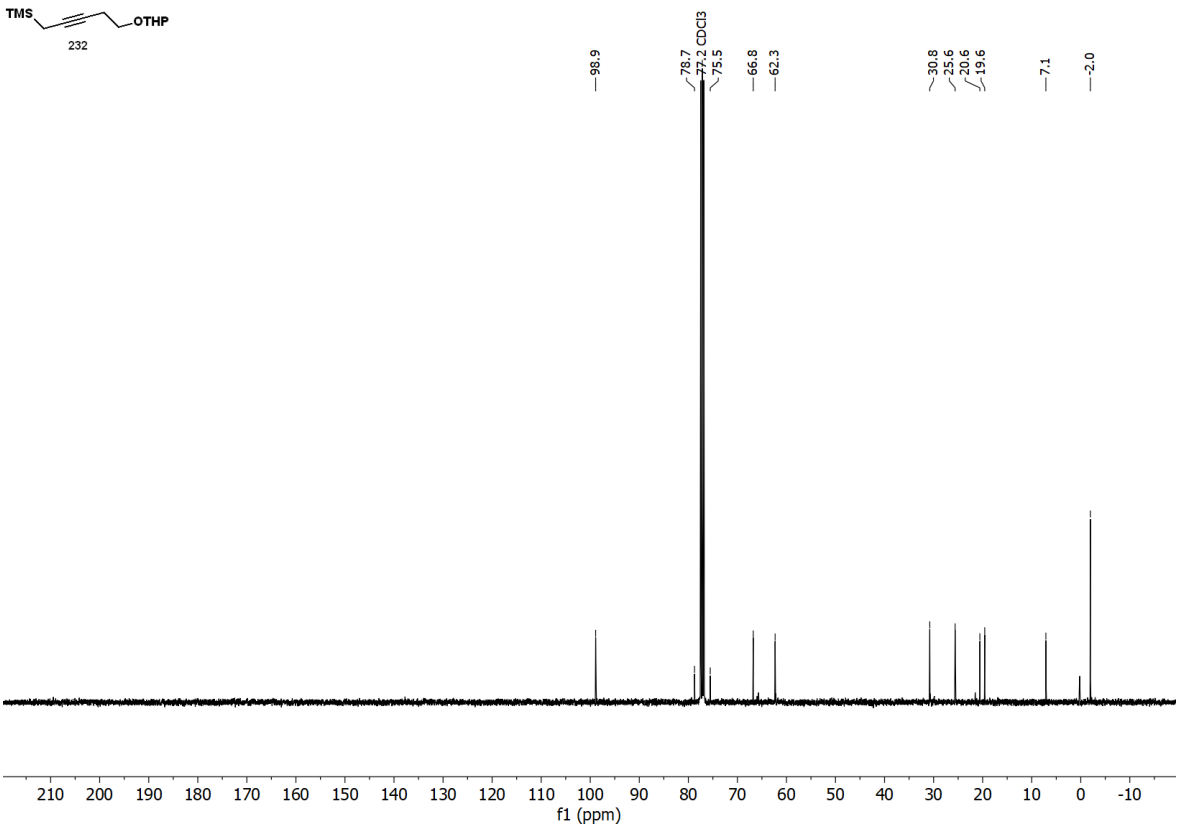

Me
EtO
O
Me
230
7.26 CDCl3
4.11
3.99
2.66
2.58
2.56
2.46
2.31
2.22
2.09
2.02
1.72
1.70
1.70
1.70
1.62
1.36
1.34
1.33
1.15
1.13
2.04
1.03
1.03
1.00
1.06
3.04
0.91
2.98
3.00
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

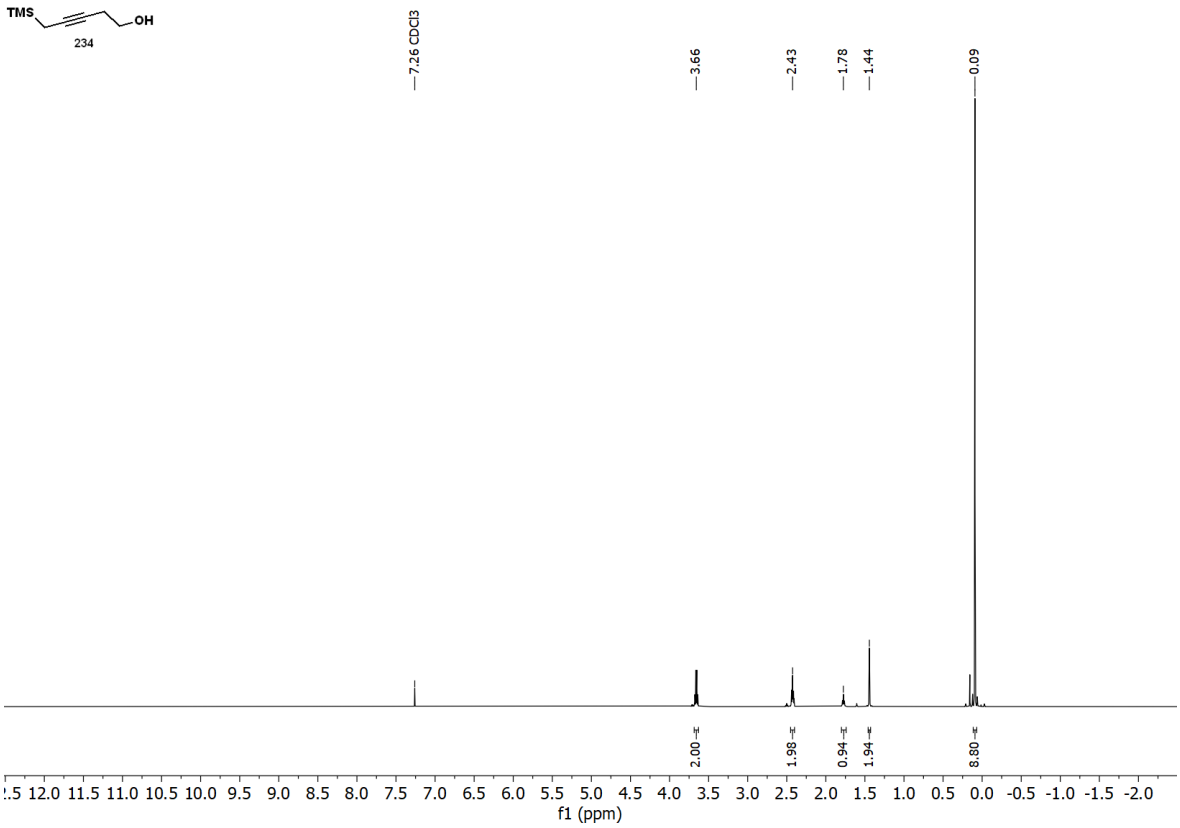

Me
EtO
O
Me
230
201.4
170.3
114.5
77.2 CDCl3
63.4
39.6
29.1
24.7
15.8
15.5
7.9
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

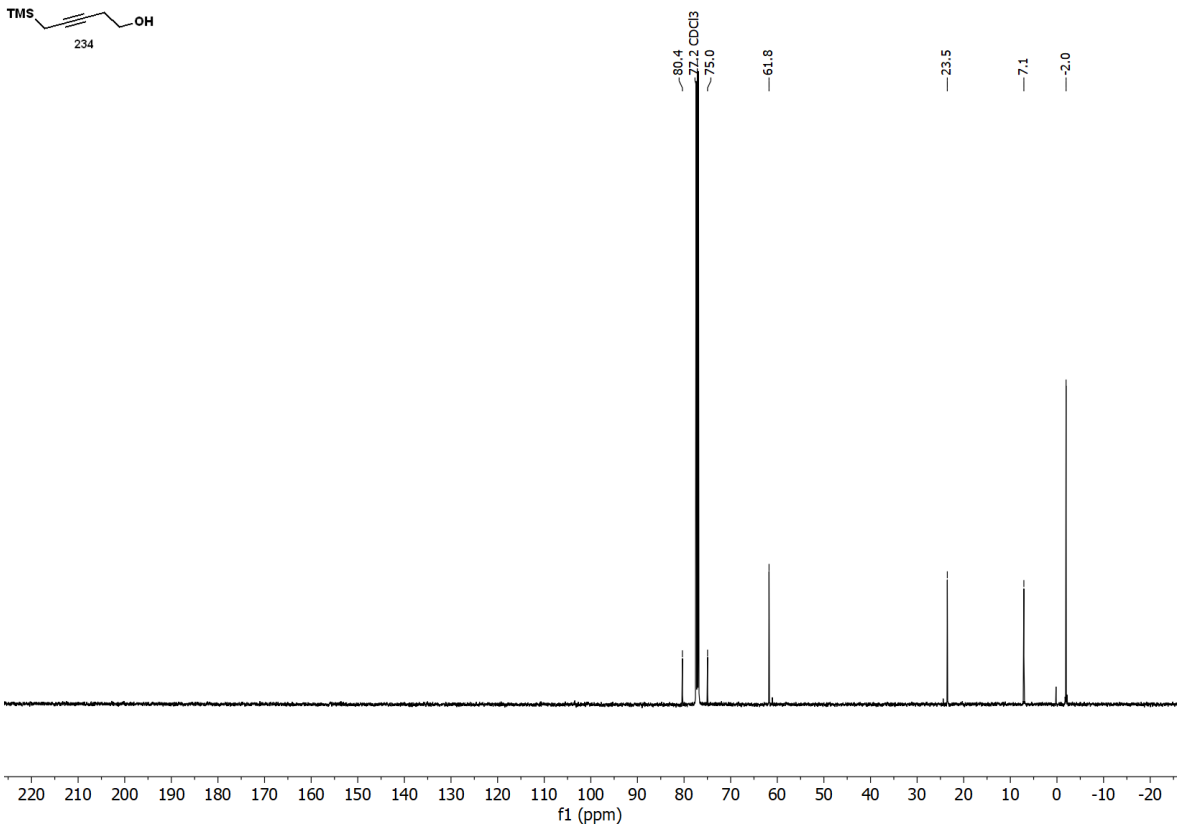

OTHP
231
7.26 CDCl3
4.62
3.86
3.81
3.54
3.50
3.47
2.47
1.95
1.83
1.77
1.69
1.60
1.53
1.52
1.48
1.00
1.03
1.02
1.03
1.05
2.05
0.93
1.12
1.08
2.09
2.13
f1 (ppm)

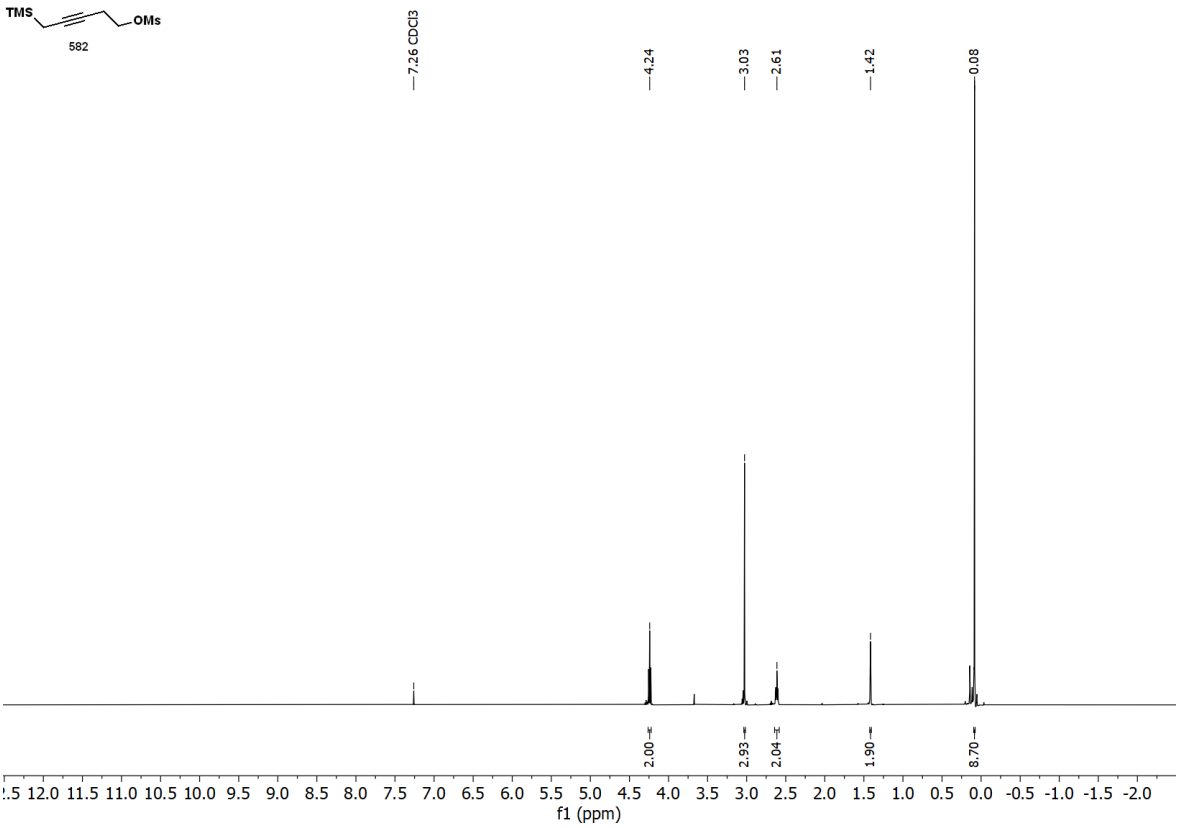

OTHP
231
98.8
81.5
77.2 CDCl3
69.3
65.6
62.3
30.6
25.5
20.0
19.5
f1 (ppm)

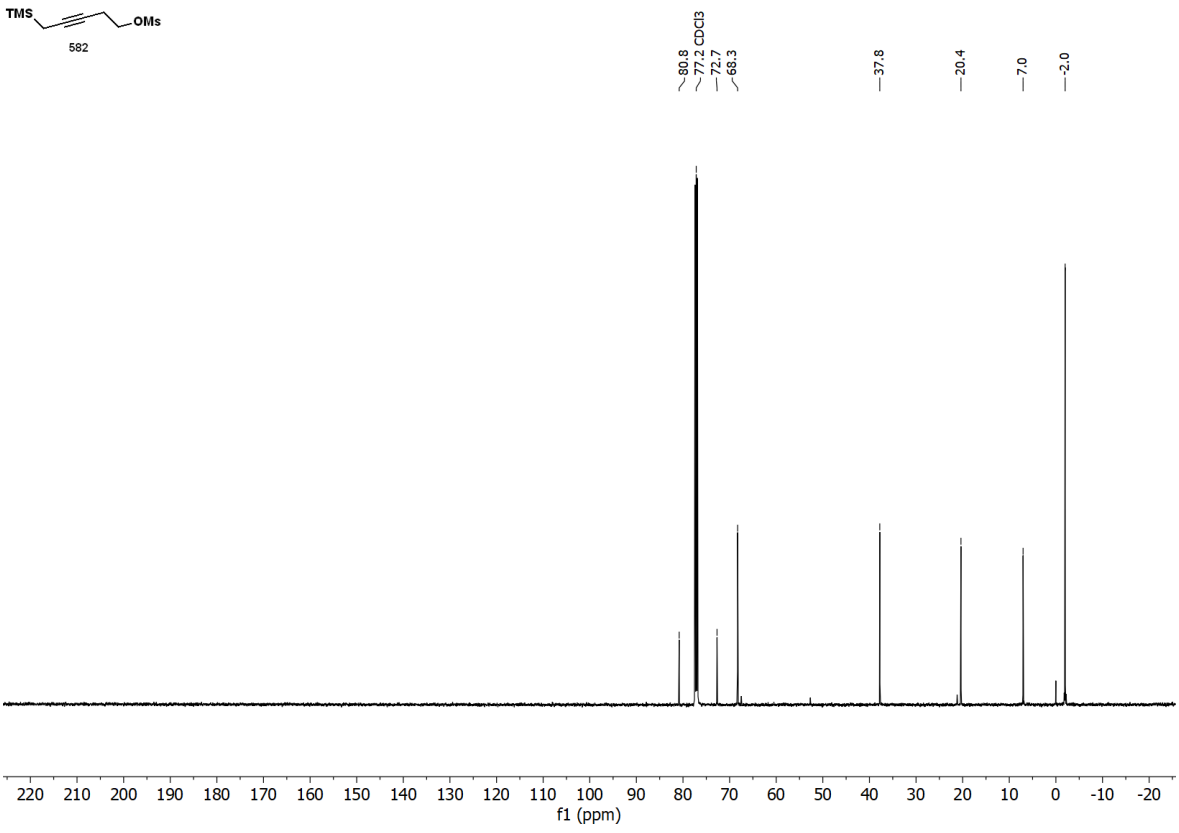

TMS
OTHP
232
7.26 CDCl3
4.67
4.59
3.88
3.82
3.75
3.50
2.45
1.87
1.77
1.74
1.67
1.62
1.47
1.41
0.08
1.00
1.30
1.16
2.35
1.96
1.54
1.31
5.55
1.90
8.46
f1 (ppm)

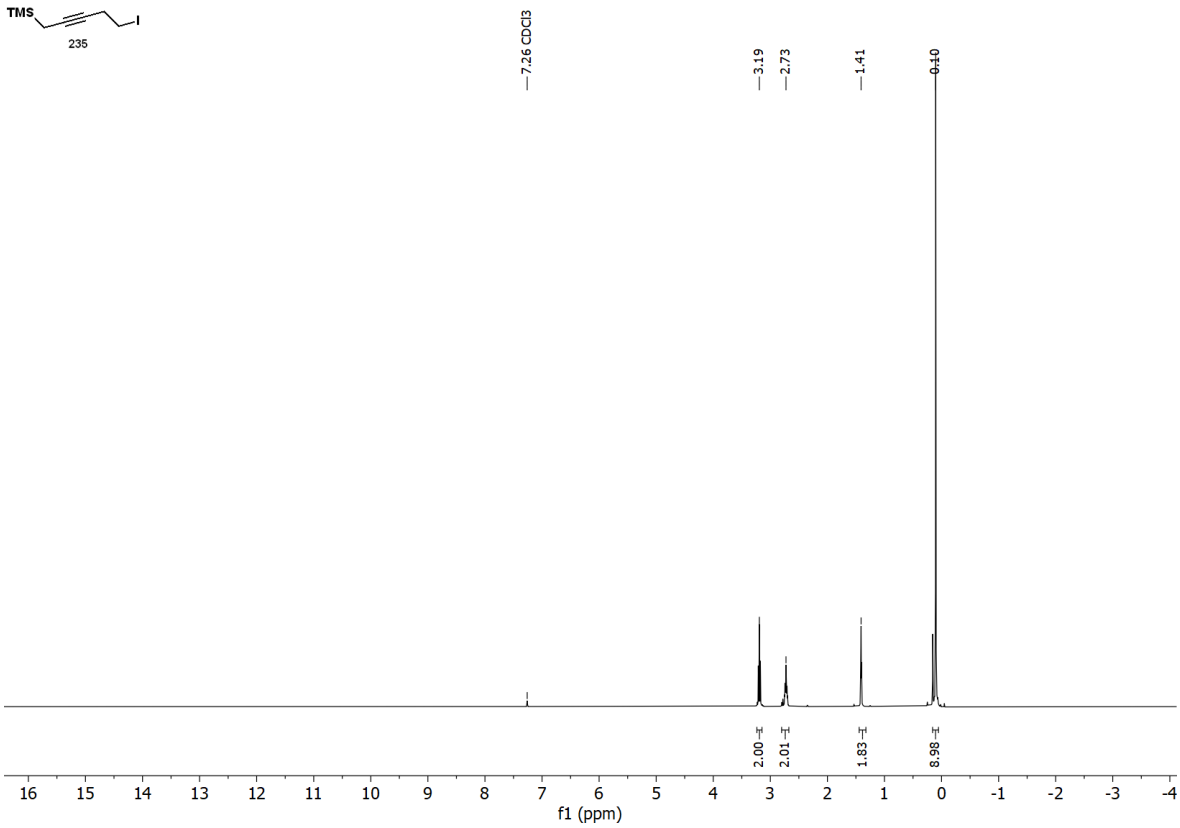

TMS
OTHP
232
98.9
78.7
77.2 CDCl3
75.5
66.8
62.3
30.8
25.6
20.6
19.6
7.1
-2.0
f1 (ppm)

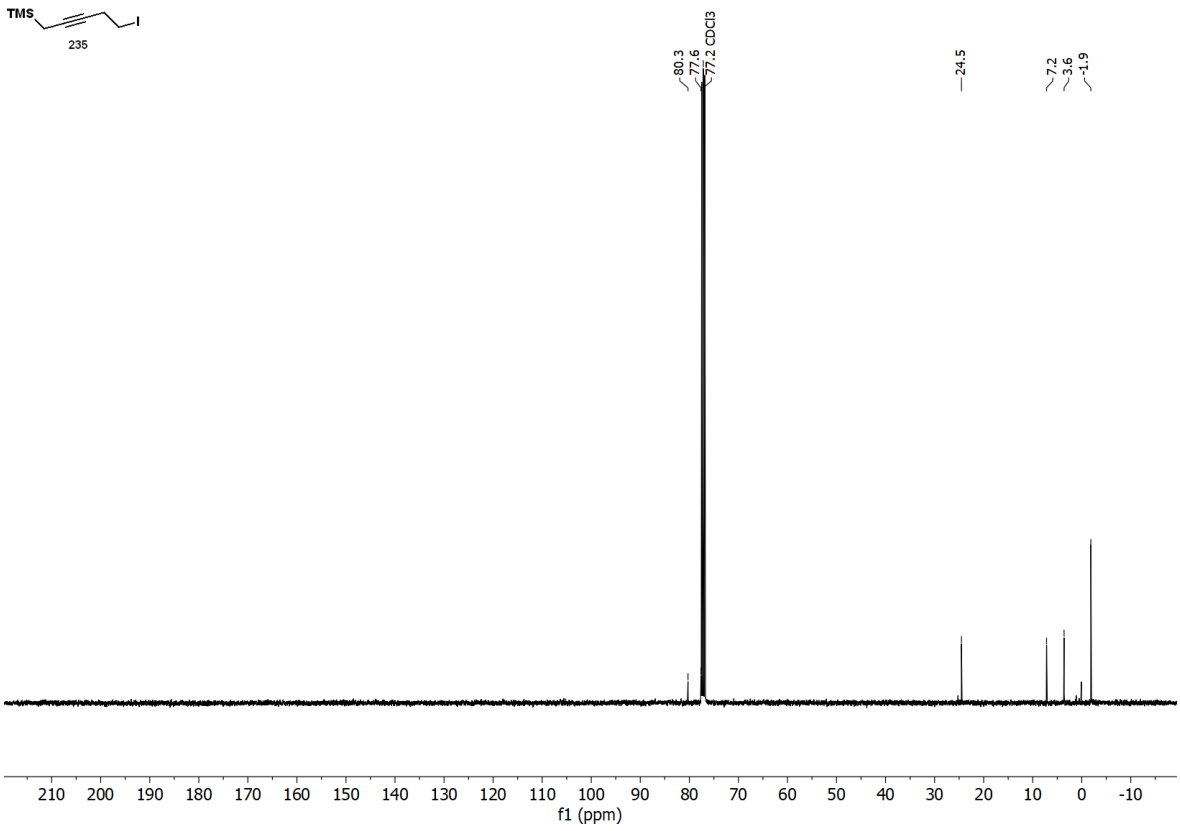

TMS
OH
234
7.26 CDCl3
3.66
2.43
1.78
1.44
0.09
2.00
1.98
0.94
1.94
8.80
f1 (ppm)

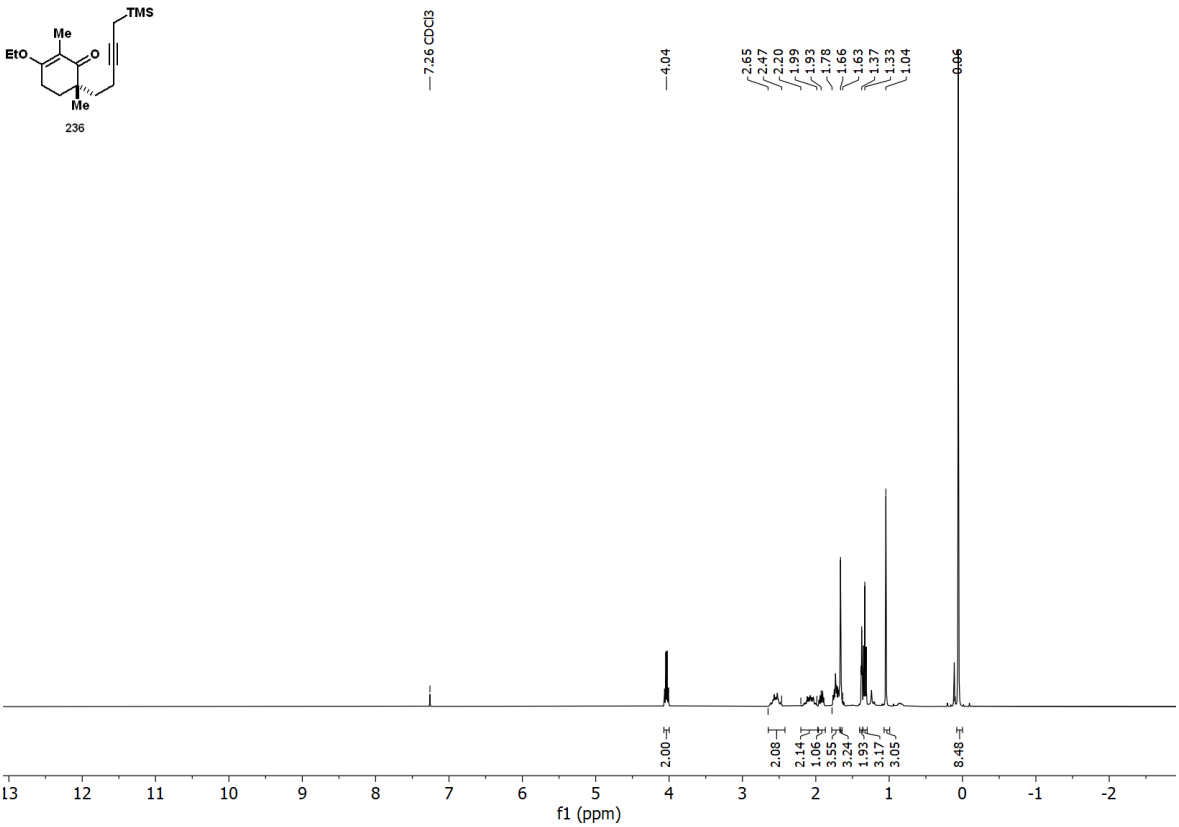

TMS
OH
234
80.4
77.2 CDCl3
75.0
61.8
23.5
7.1
-2.0
f1 (ppm)

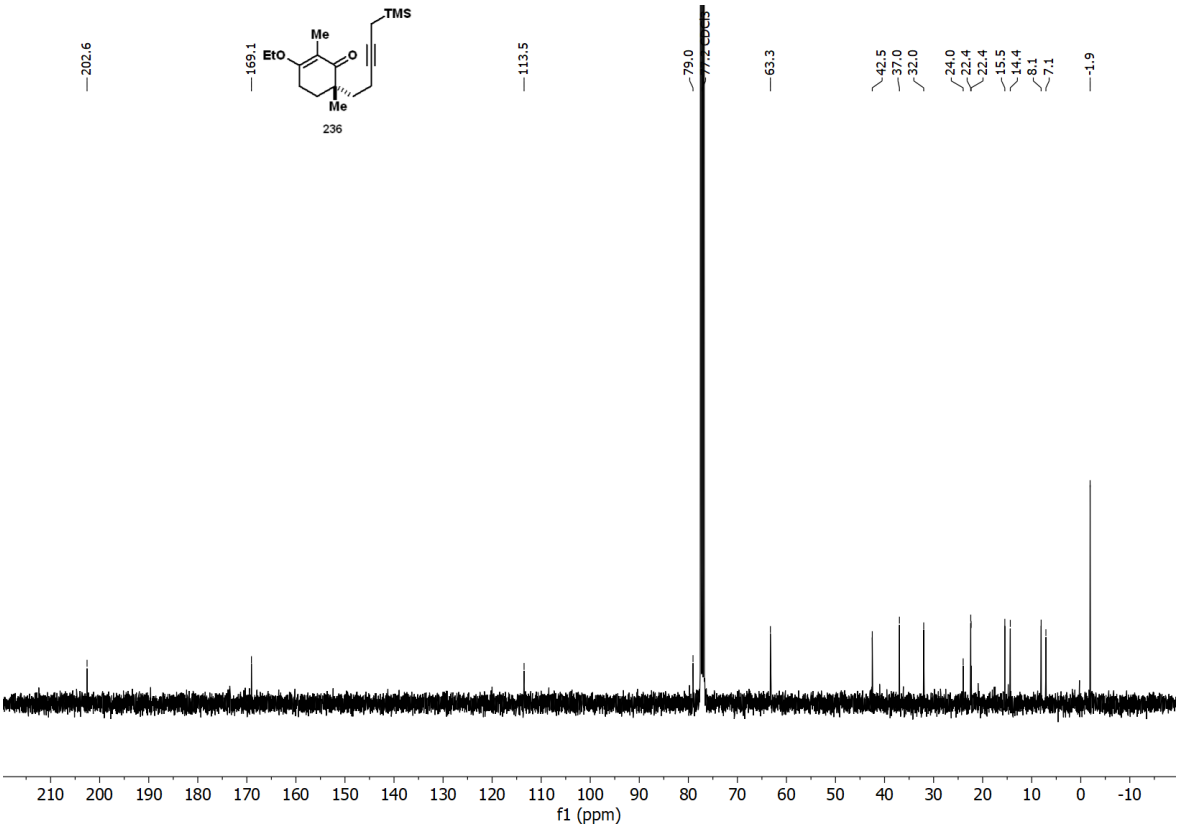

TMS
OMs
582
7.26 CDCl3
4.24
3.03
2.61
1.42
0.08
2.00
2.93
2.04
1.90
8.70
f1 (ppm)

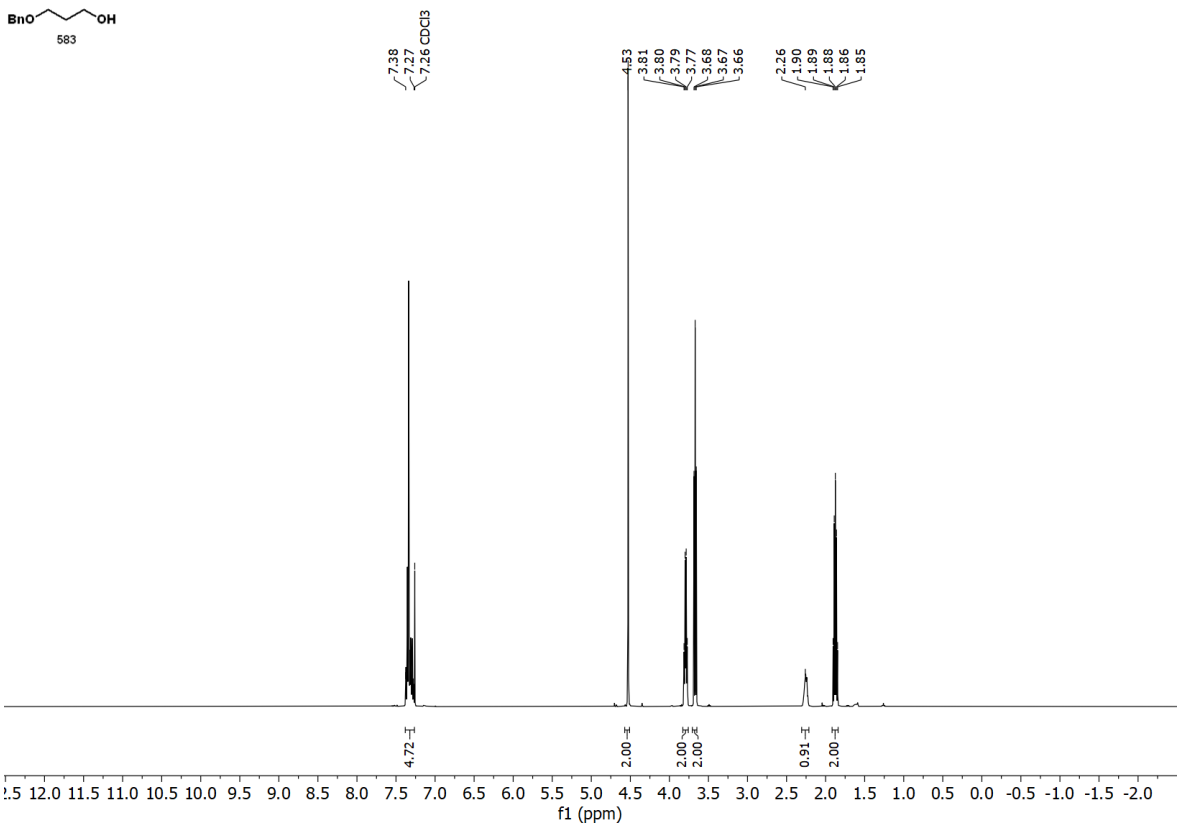

TMS
OMs
582
80.8
77.2 CDCl3
72.7
68.3
37.8
20.4
7.0
-2.0
f1 (ppm)

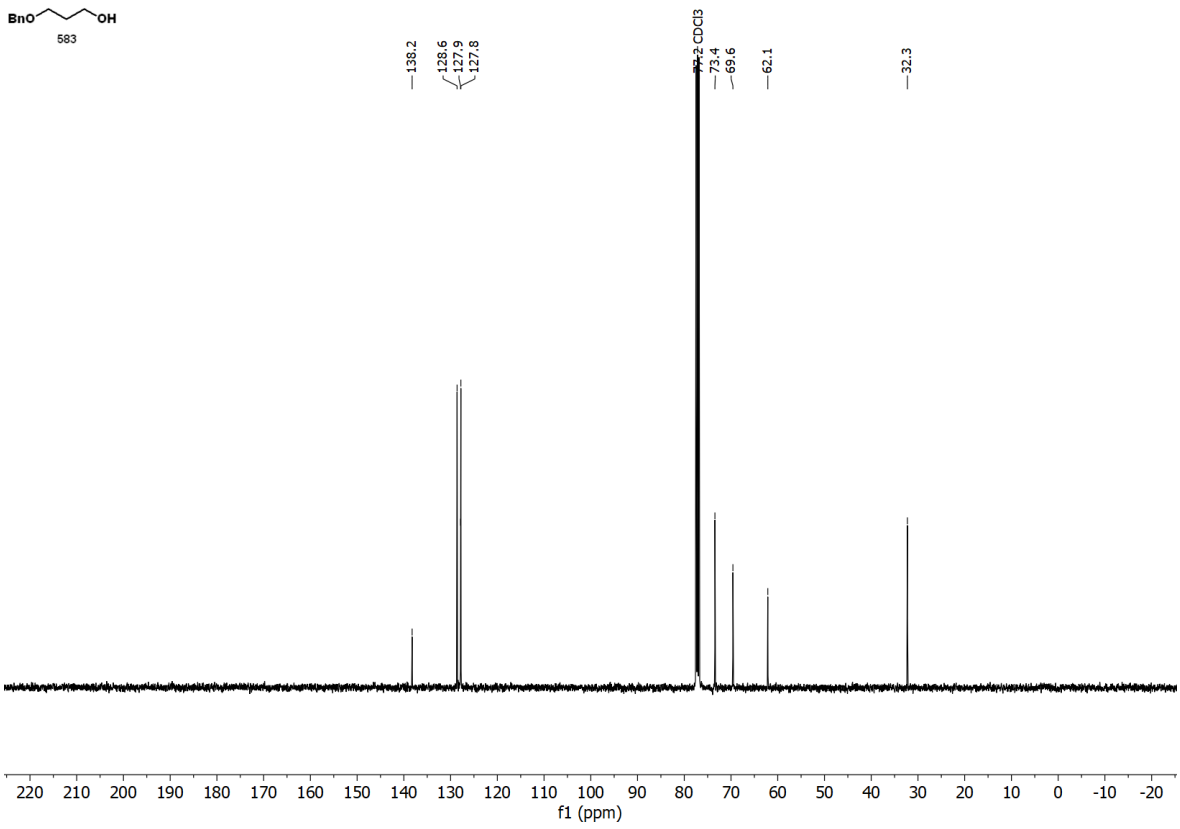

TMS
I
235
7.26 CDCl3
3.19
2.73
1.41
0.10
2.00
2.01
1.83
8.98
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 -4
f1 (ppm)

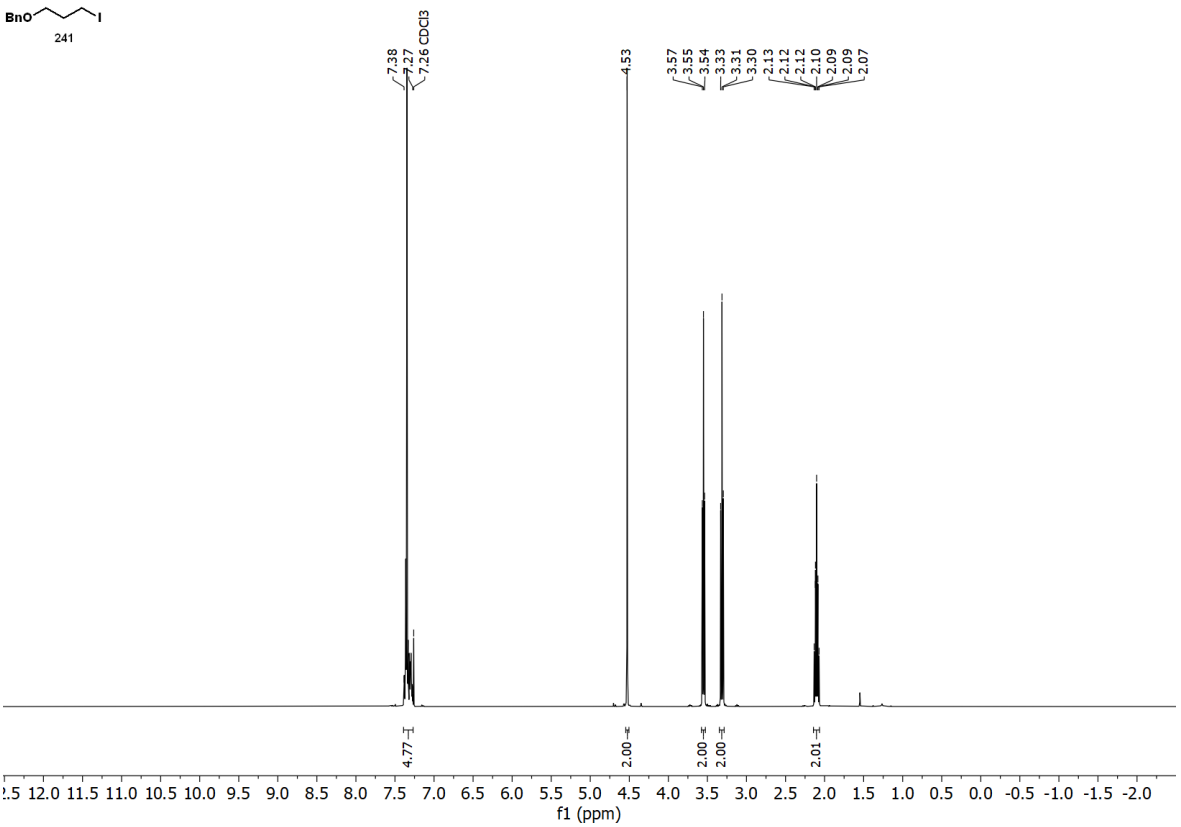

TMS
I
235
80.3
77.6
77.2 CDCl3
24.5
7.2
3.6
-1.9
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

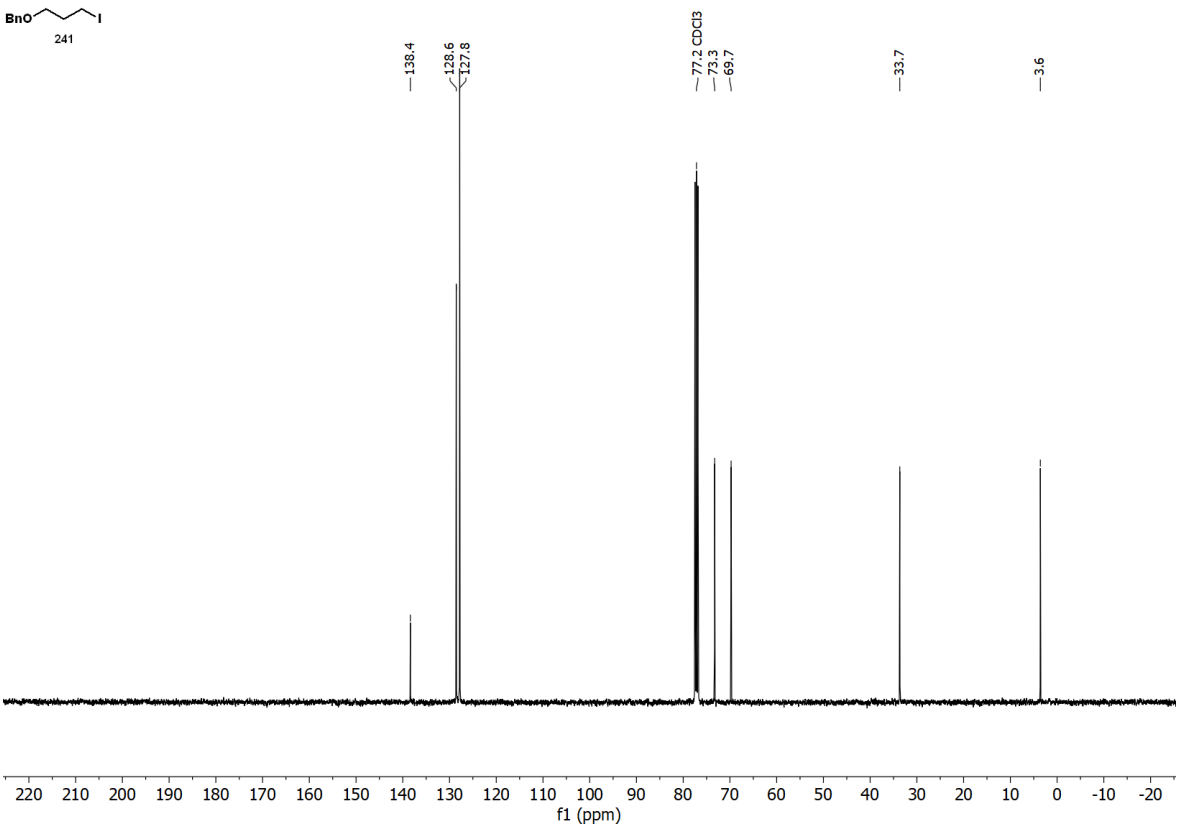

TMS
Me
EtO
O
Me
236
7.26 CDCl3
4.04
2.65
2.47
2.20
1.99
1.93
1.78
1.66
1.63
1.37
1.33
1.04
0.06
2.00
2.08
2.14
1.06
3.55
3.24
1.93
3.17
3.05
8.48
f1 (ppm)

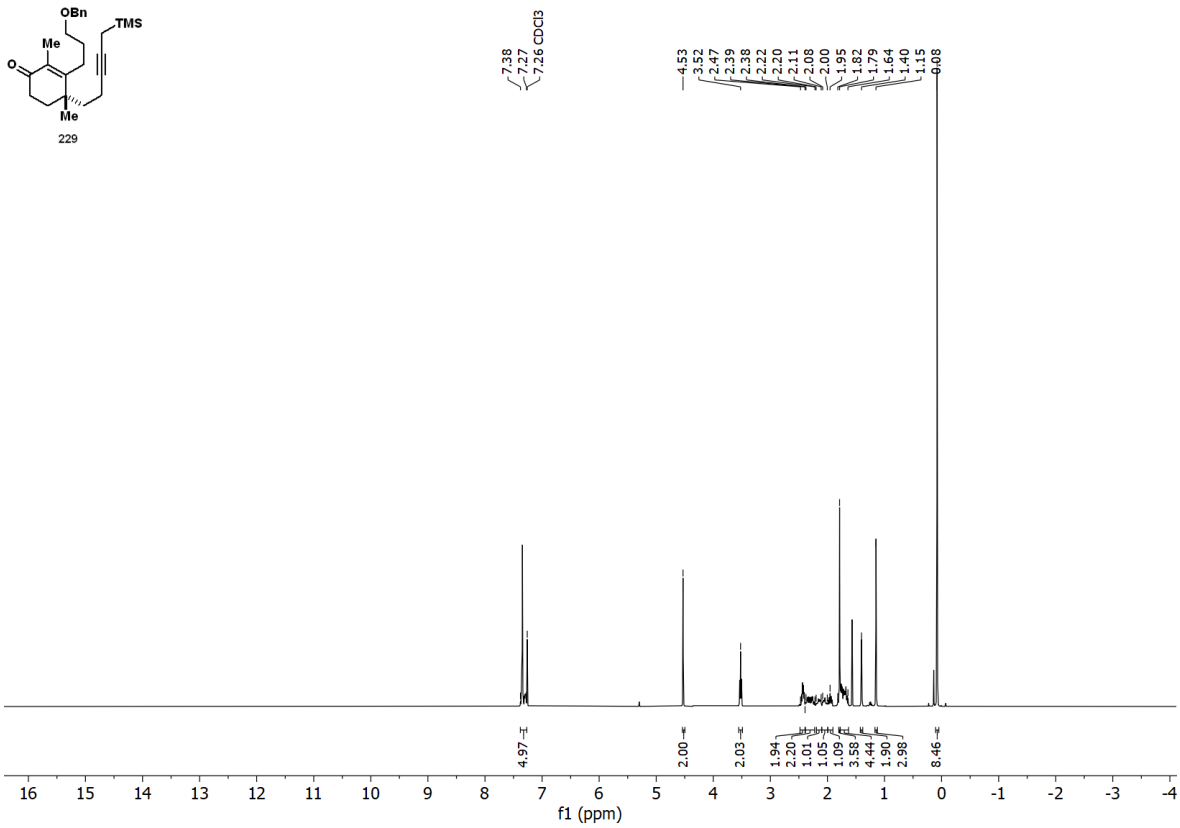

TMS
Me
EtO
O
Me
236
202.6
169.1
113.5
79.0
77.2 CDCl3
63.3
42.5
37.0
32.0
24.0
22.4
22.4
15.5
14.4
8.1
7.1
-1.9
f1 (ppm)

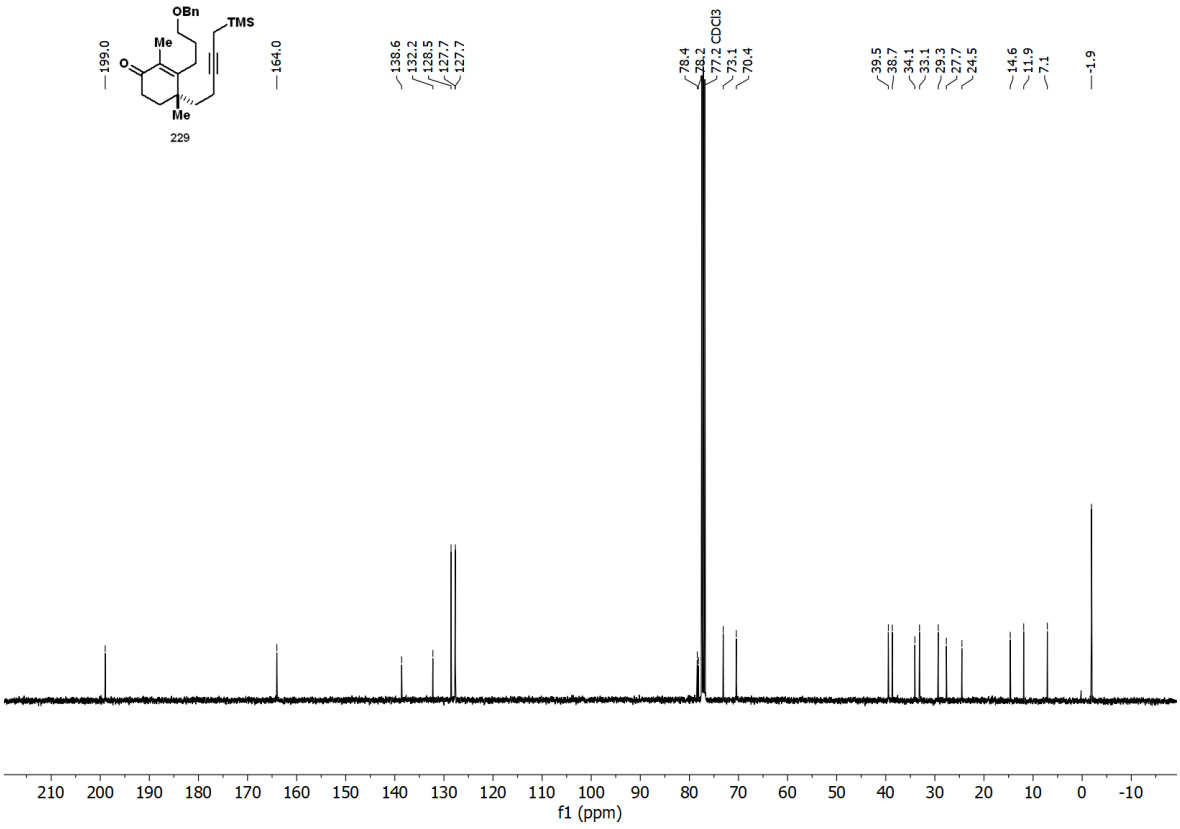

BnO
OH
583
7.38
7.27
7.26 CDCl3
4.53
3.81
3.80
3.79
3.77
3.68
3.67
3.66
2.26
1.90
1.89
1.88
1.86
1.85
4.72
2.00
2.00
2.00
0.91
2.00
f1 (ppm)

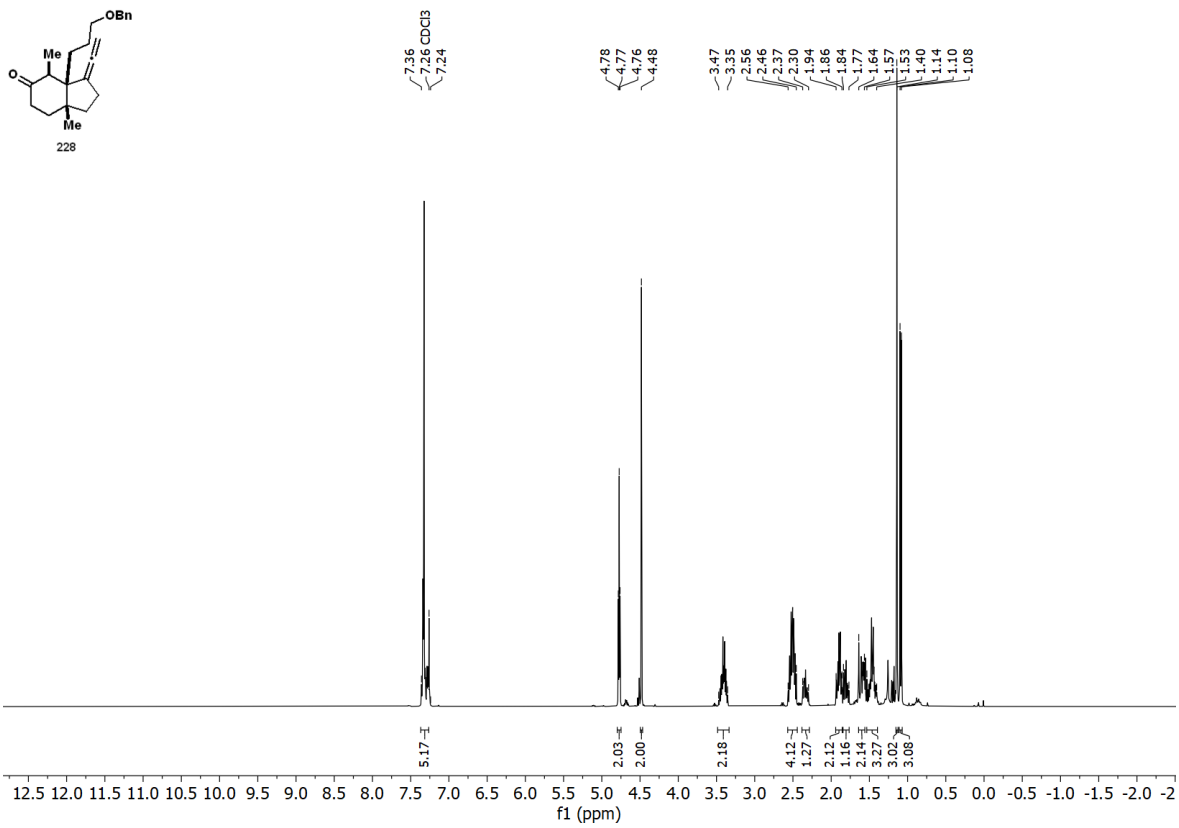

BnO
OH
583
138.2
128.6
127.9
127.8
77.2 CDCl3
73.4
69.6
62.1
32.3
f1 (ppm)

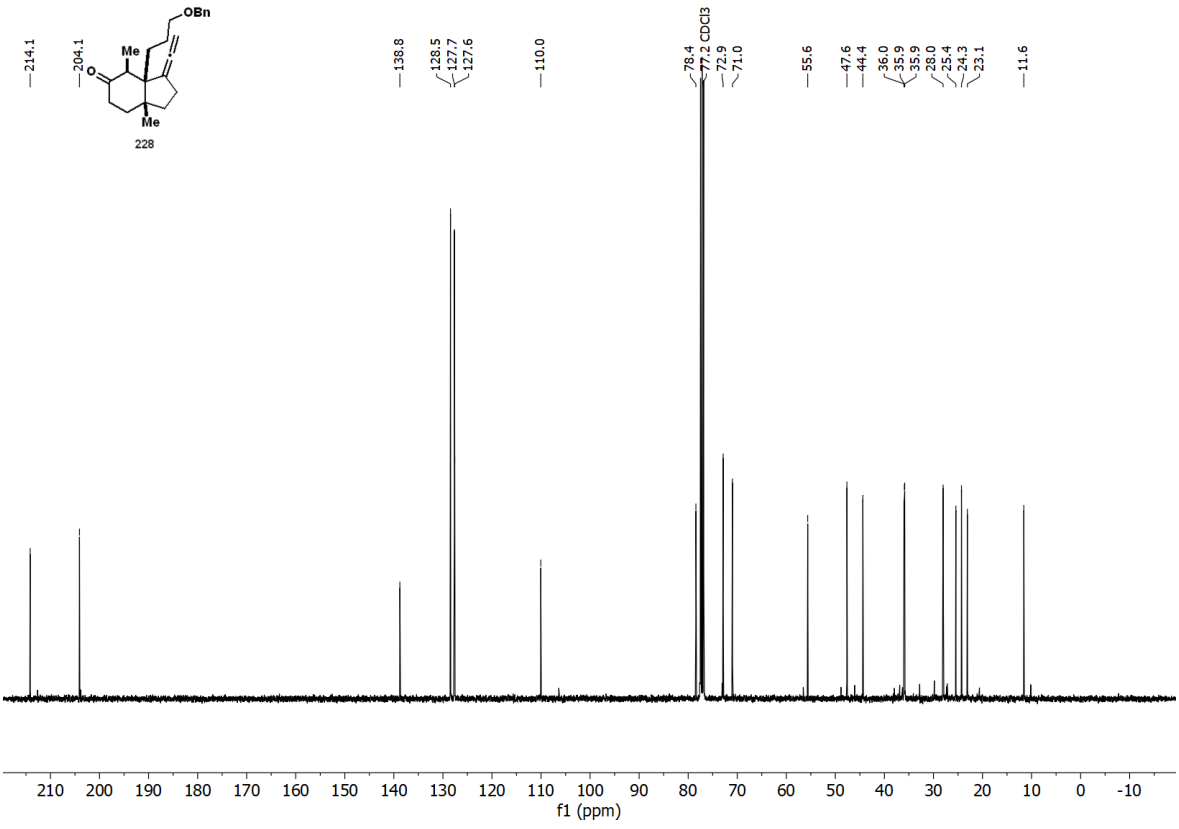

BnO
I
241
7.38
7.27
7.26 CDCl3
4.53
3.57
3.55
3.54
3.33
3.31
3.30
2.13
2.12
2.12
2.10
2.09
2.09
2.07
4.77
2.00
2.00
2.00
2.01
f1 (ppm)

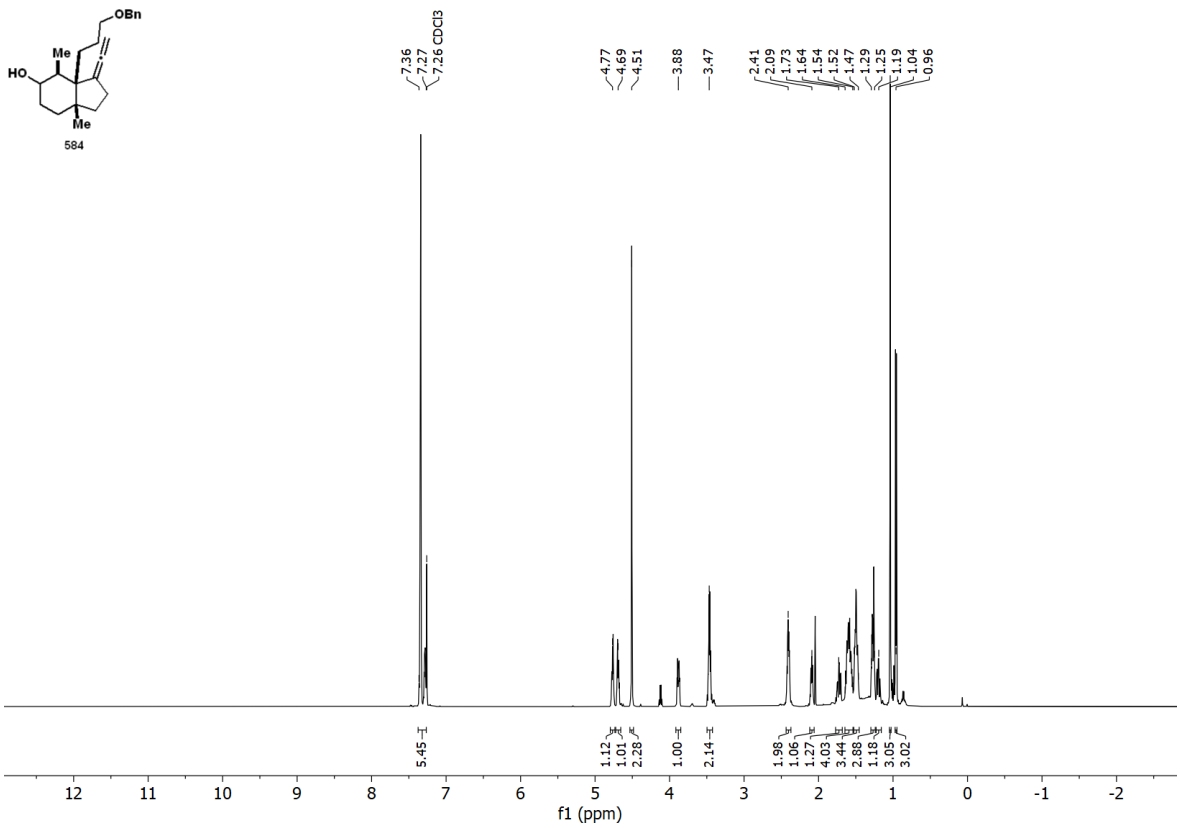

BnO
I
241
138.4
128.6
127.8
77.2 CDCl3
73.3
69.7
33.7
3.6
f1 (ppm)

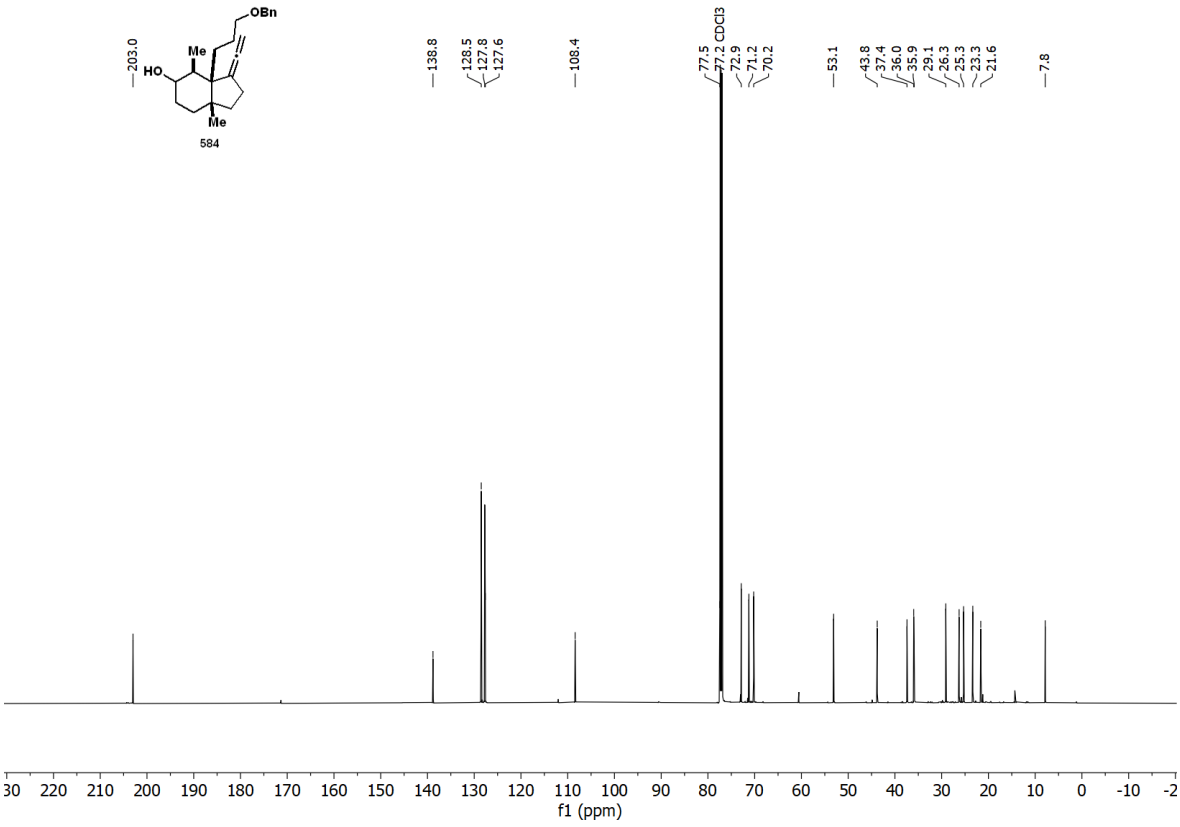

OBn
TMS
Me
O
Me
229
7.38
7.27
7.26 CDCl3
4.53
3.52
2.47
2.39
2.38
2.22
2.20
2.11
2.08
2.00
1.95
1.82
1.79
1.64
1.40
1.15
0.08
4.97
2.00
2.03
1.94
2.20
1.01
1.05
1.09
3.58
4.44
1.90
2.98
8.46
f1 (ppm)

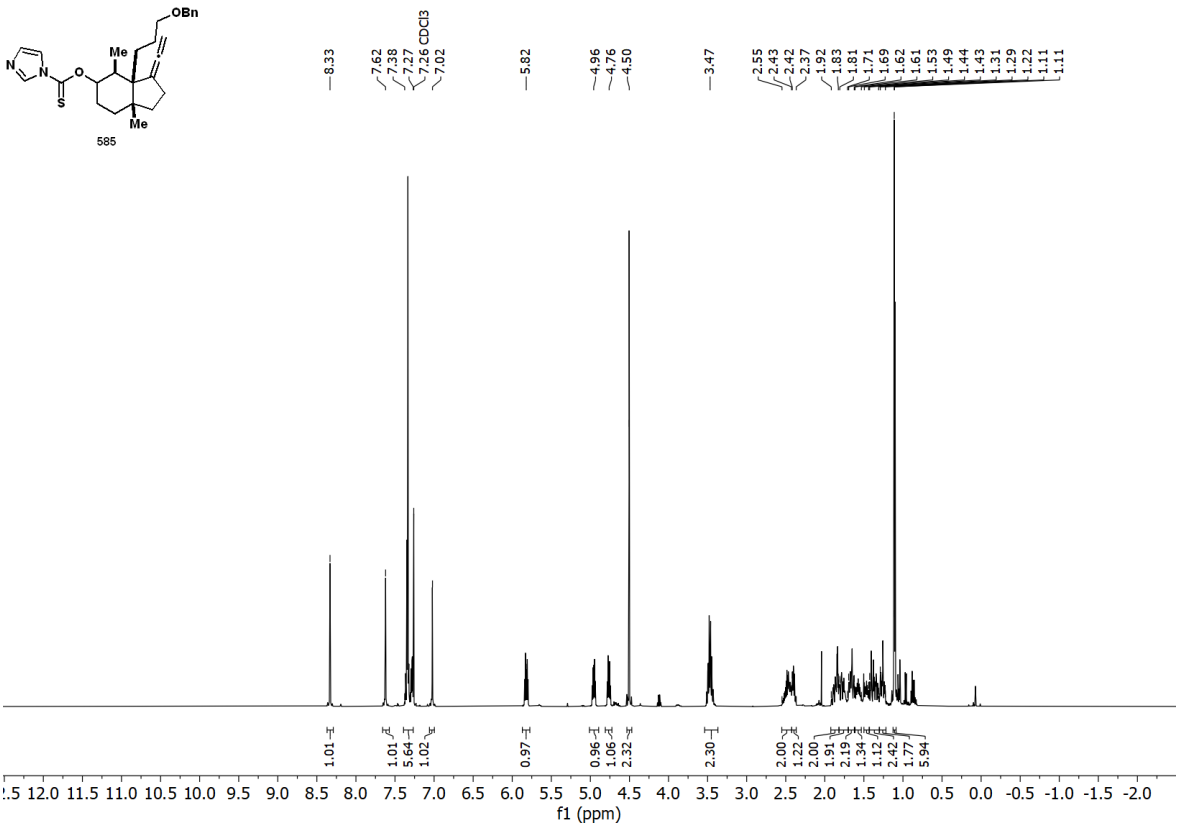

OBn
TMS
Me
O
Me
229
199.0
164.0
138.6
132.2
128.5
127.7
127.7
78.4
78.2
77.2 CDCl3
73.1
70.4
39.5
38.7
34.1
33.1
29.3
27.7
24.5
14.6
11.9
7.1
-1.9
f1 (ppm)

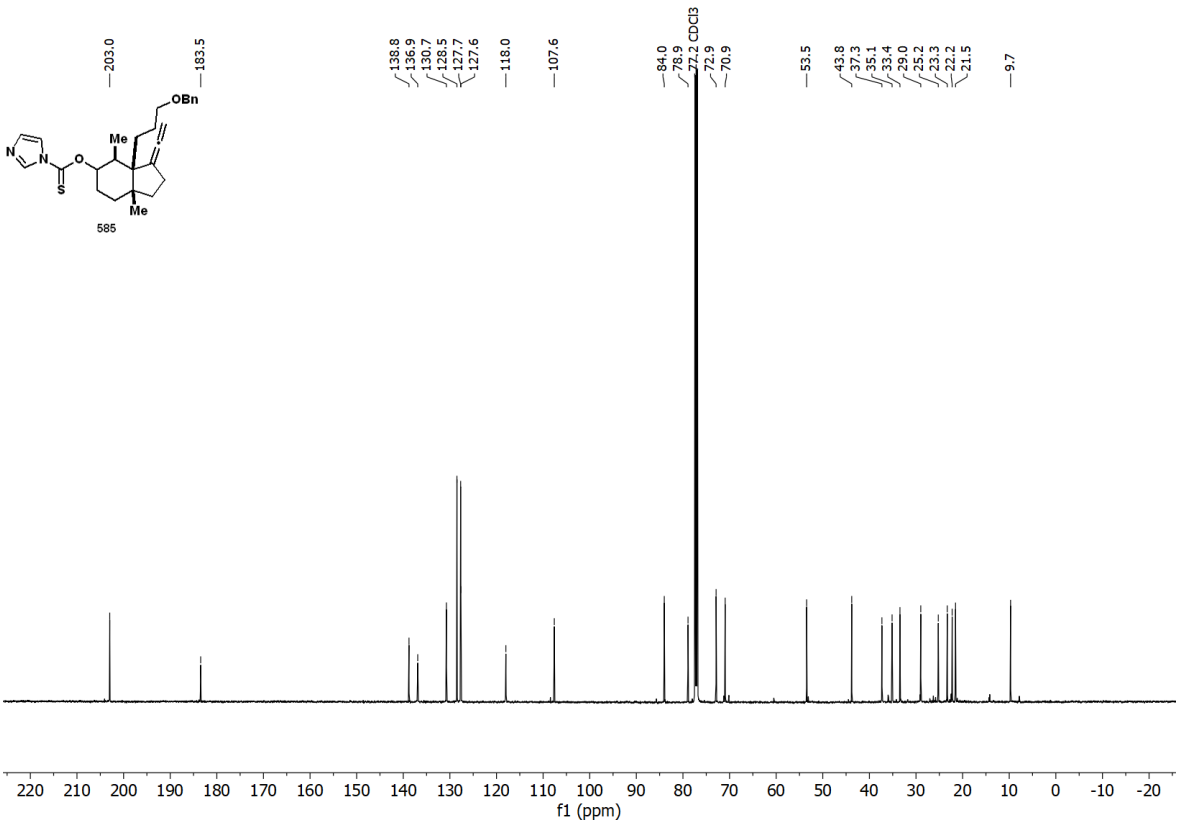

OBn
Me
O
Me
228
7.36
7.26 CDCl3
7.24
4.78
4.77
4.76
4.48
3.47
3.35
2.56
2.46
2.37
2.30
1.94
1.86
1.84
1.77
1.64
1.57
1.53
1.40
1.14
1.10
1.08
5.17
2.03
2.00
2.18
4.12
1.27
2.12
1.16
2.14
3.27
3.02
3.08
f1 (ppm)

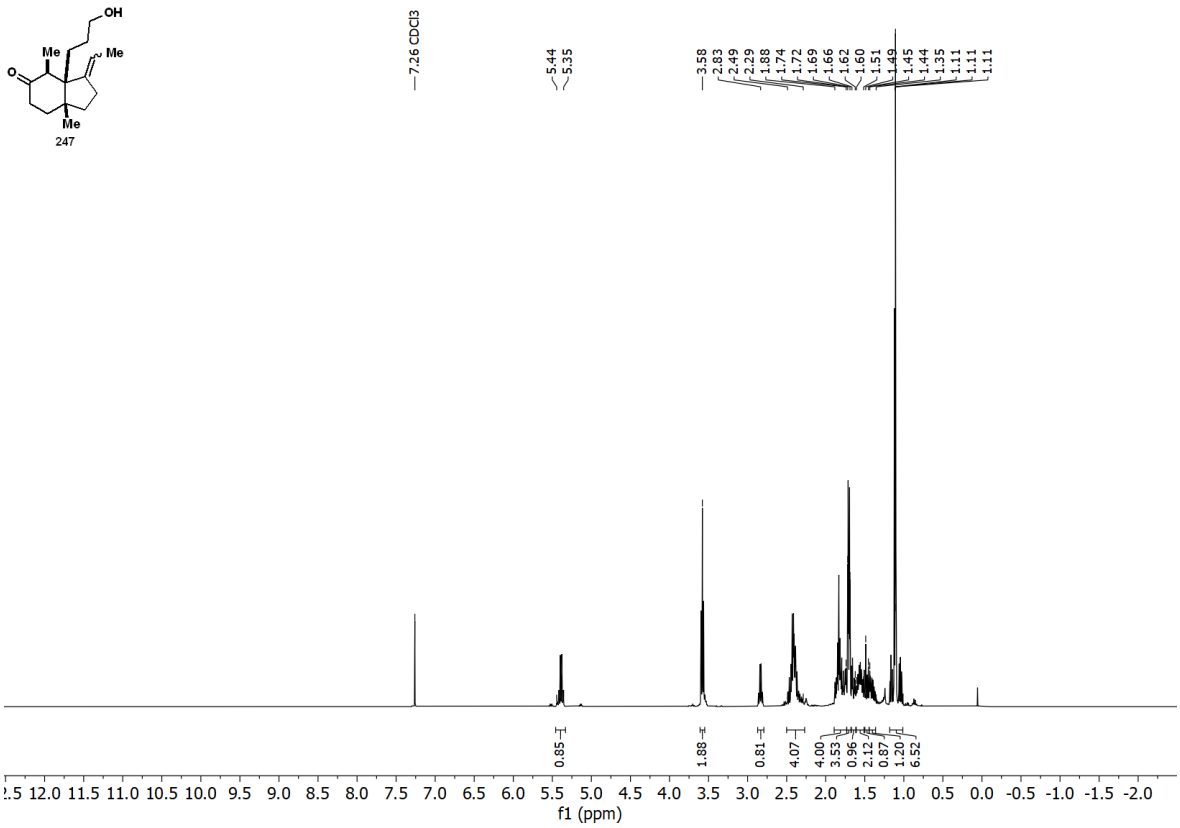

OBn
Me
O
Me
228
214.1
204.1
138.8
128.5
127.7
127.6
110.0
78.4
77.2 CDCl3
72.9
71.0
55.6
47.6
44.4
36.0
35.9
35.9
28.0
25.4
24.3
23.1
11.6
f1 (ppm)

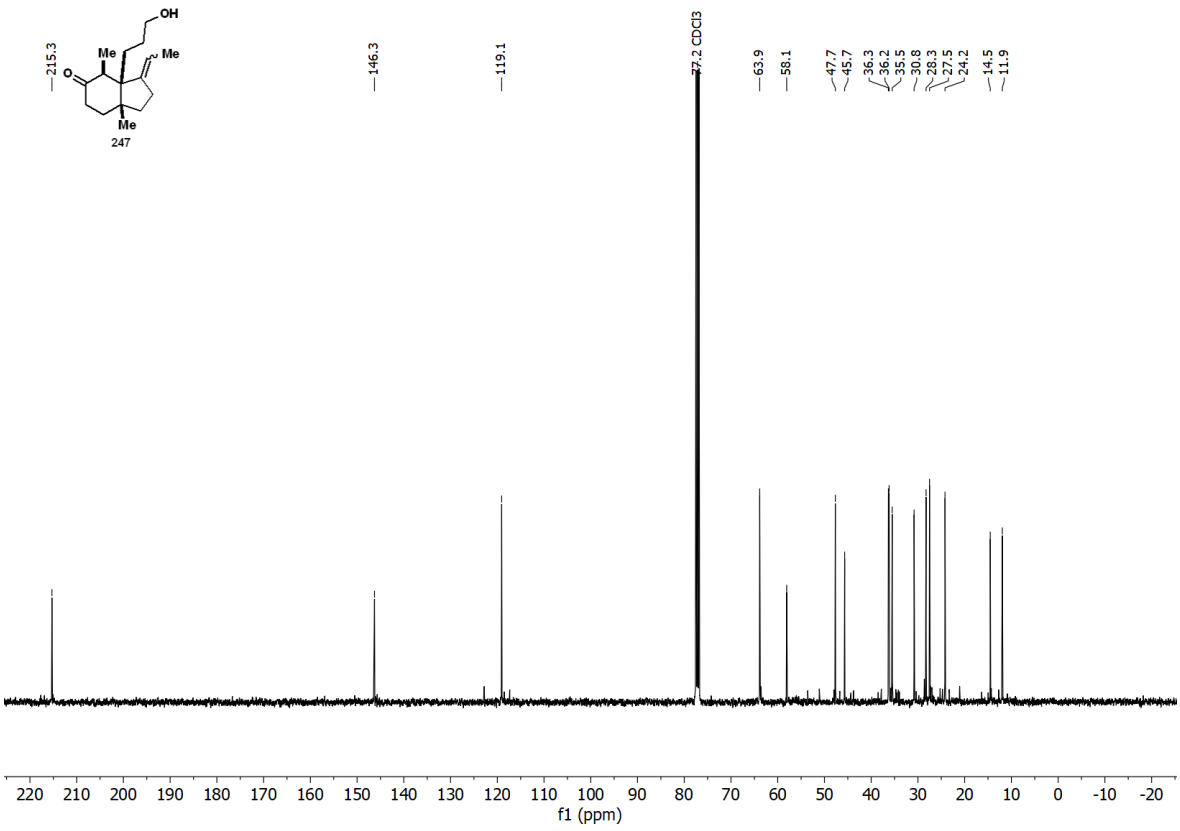

OBn
Me
HO
Me
584
7.36
7.27
7.26 CDCl3
4.77
4.69
4.51
3.88
3.47
2.41
2.09
1.73
1.64
1.54
1.52
1.47
1.29
1.25
1.19
1.04
0.96
5.45
1.12
1.01
2.28
1.00
2.14
1.98
1.06
1.27
4.03
3.44
2.88
1.18
3.05
3.02
f1 (ppm)

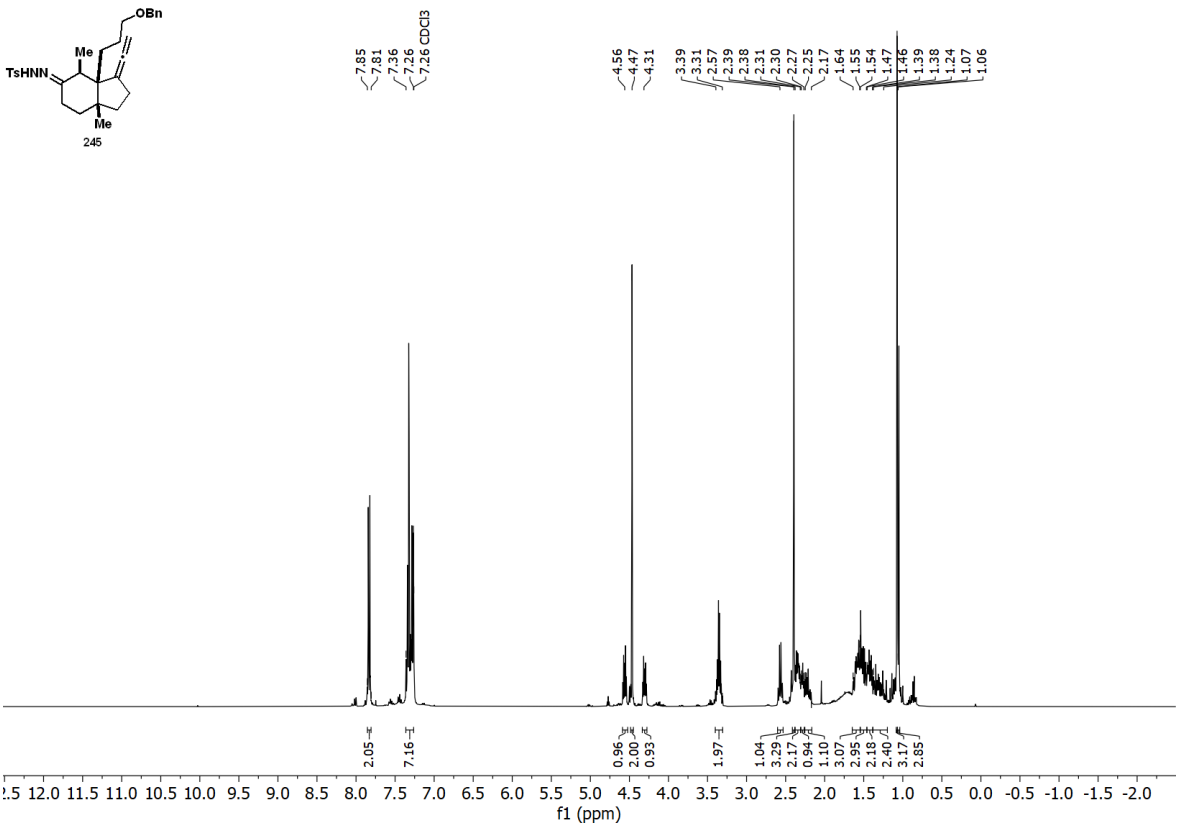

OBn
Me
HO
Me
584
203.0
138.8
128.5
127.8
127.6
108.4
77.5
77.2 CDCl3
72.9
71.2
70.2
53.1
43.8
37.4
36.0
35.9
29.1
26.3
25.3
23.3
21.6
7.8
f1 (ppm)

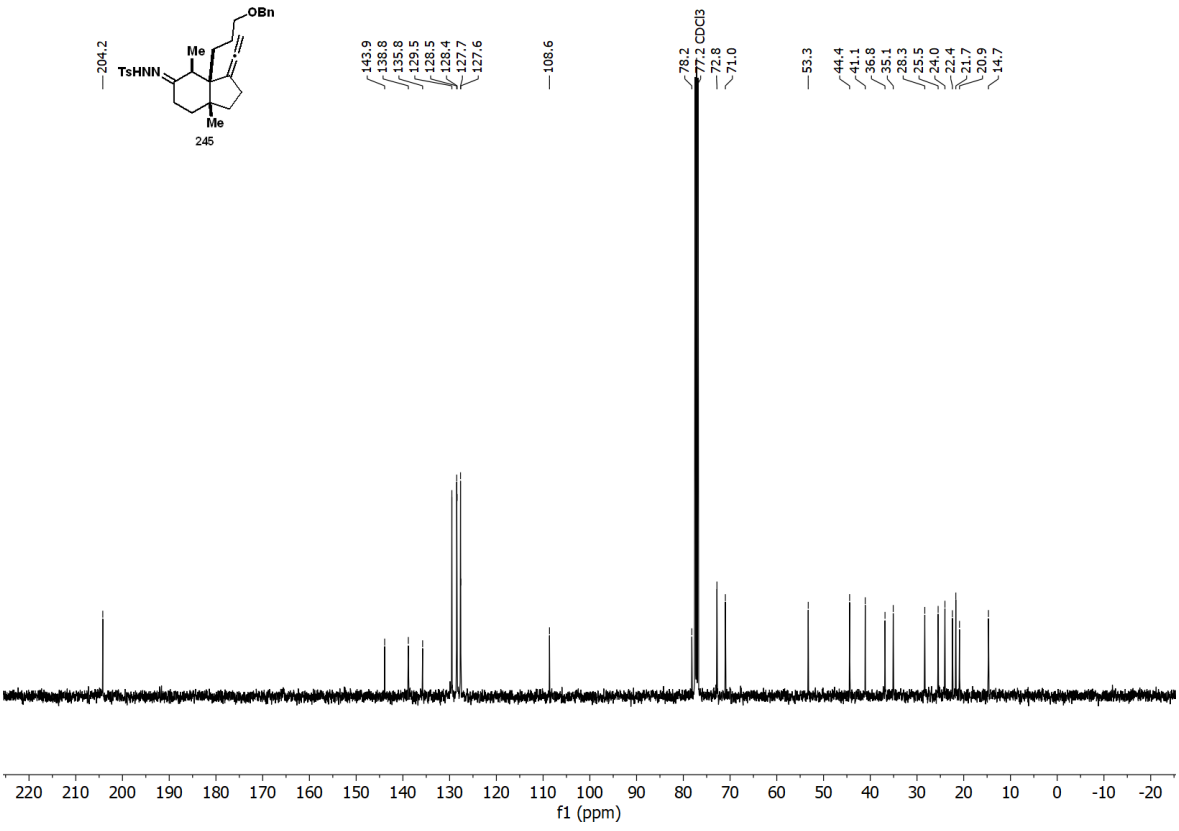

OBn
Me
Me
585
8.33
7.62
7.38
7.27
7.26 CDCl3
7.02
5.82
4.96
4.76
4.50
3.47
2.55
2.43
2.42
2.37
1.92
1.83
1.81
1.71
1.69
1.62
1.61
1.53
1.49
1.44
1.43
1.31
1.29
1.22
1.11
1.11
1.01
1.01
5.64
1.02
0.97
0.96
1.06
2.32
2.30
2.00
1.22
2.00
1.91
2.19
1.34
1.12
2.42
1.77
5.94
f1 (ppm)

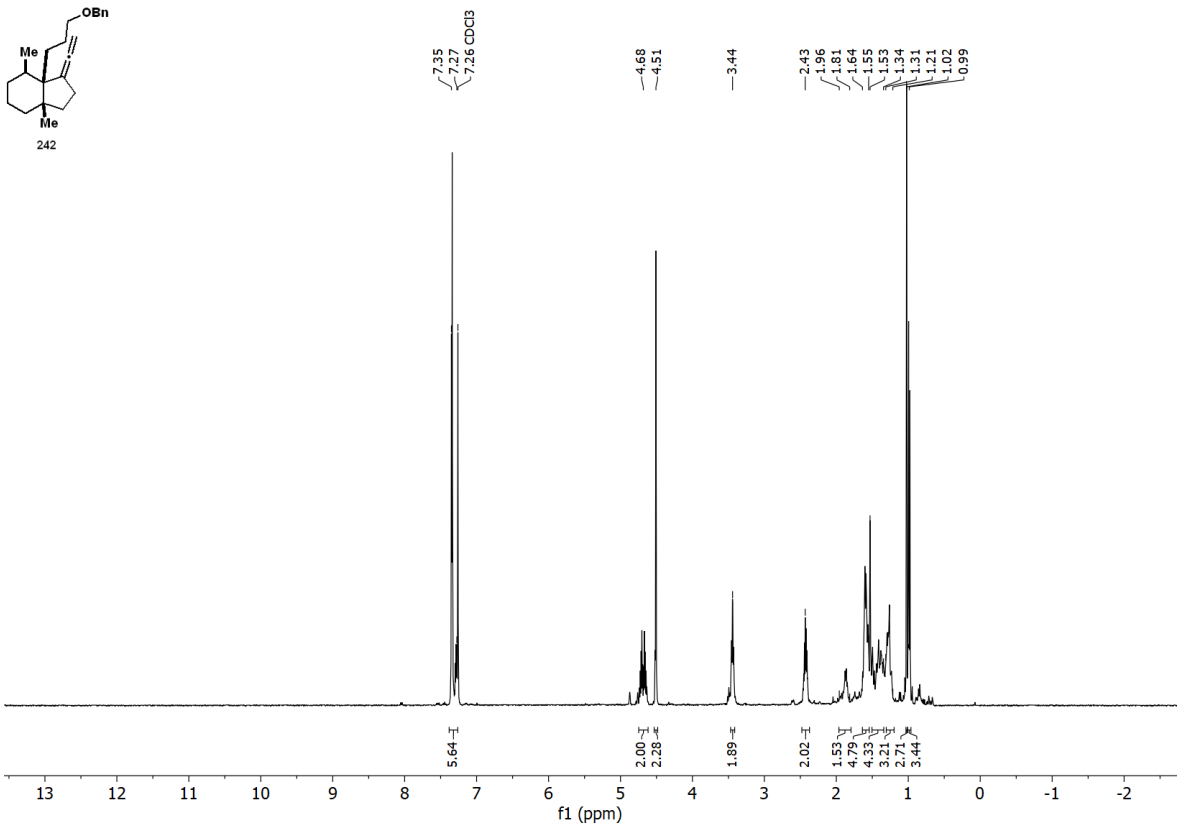

OBn
Me
Me
585
203.0
183.5
138.8
136.9
130.7
128.5
127.7
127.6
118.0
107.6
84.0
78.9
77.2 CDCl3
72.9
70.9
53.5
43.8
37.3
35.1
33.4
29.0
25.2
23.3
22.2
21.5
9.7
f1 (ppm)

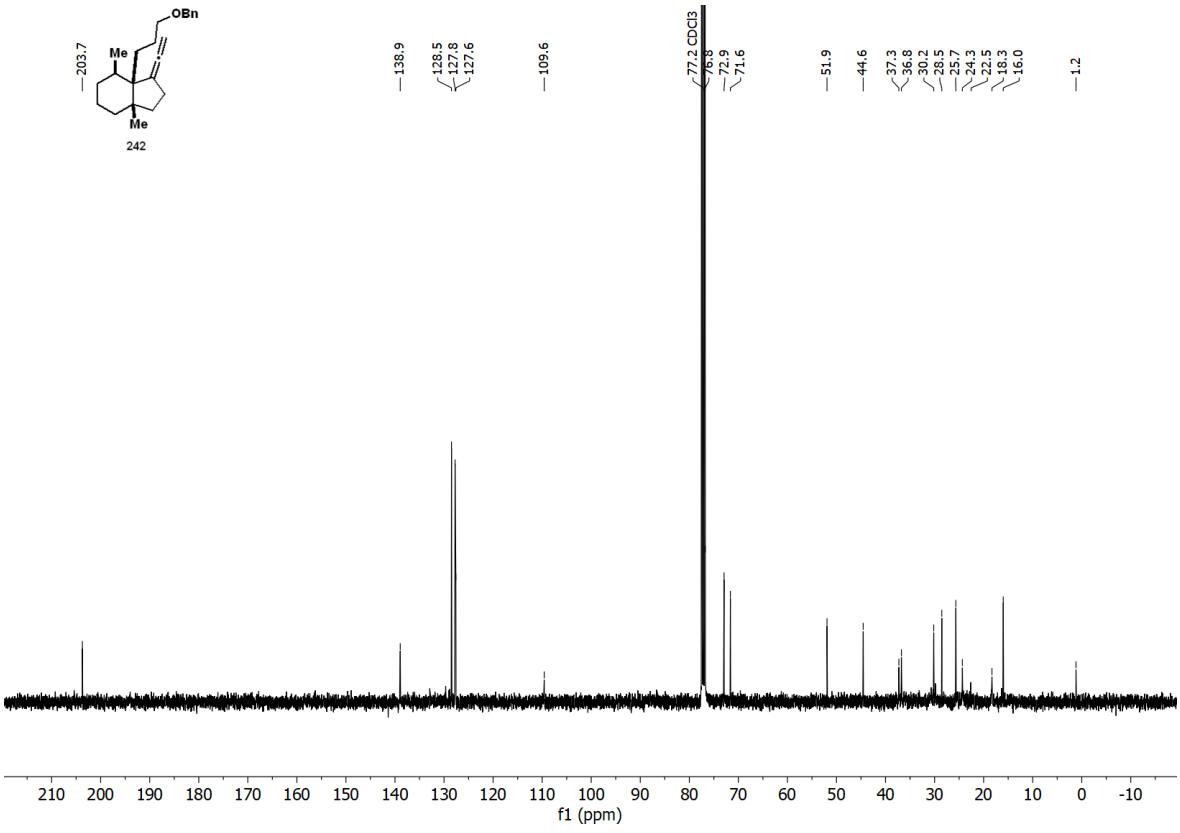

OH
Me
Me
O
Me
247
7.26 CDCl3
5.44
5.35
3.58
2.83
2.49
2.29
1.88
1.74
1.72
1.69
1.66
1.62
1.60
1.51
1.49
1.45
1.44
1.35
1.11
1.11
1.11
0.85
1.88
0.81
4.07
4.00
3.53
0.96
2.12
0.87
1.20
6.52
f1 (ppm)

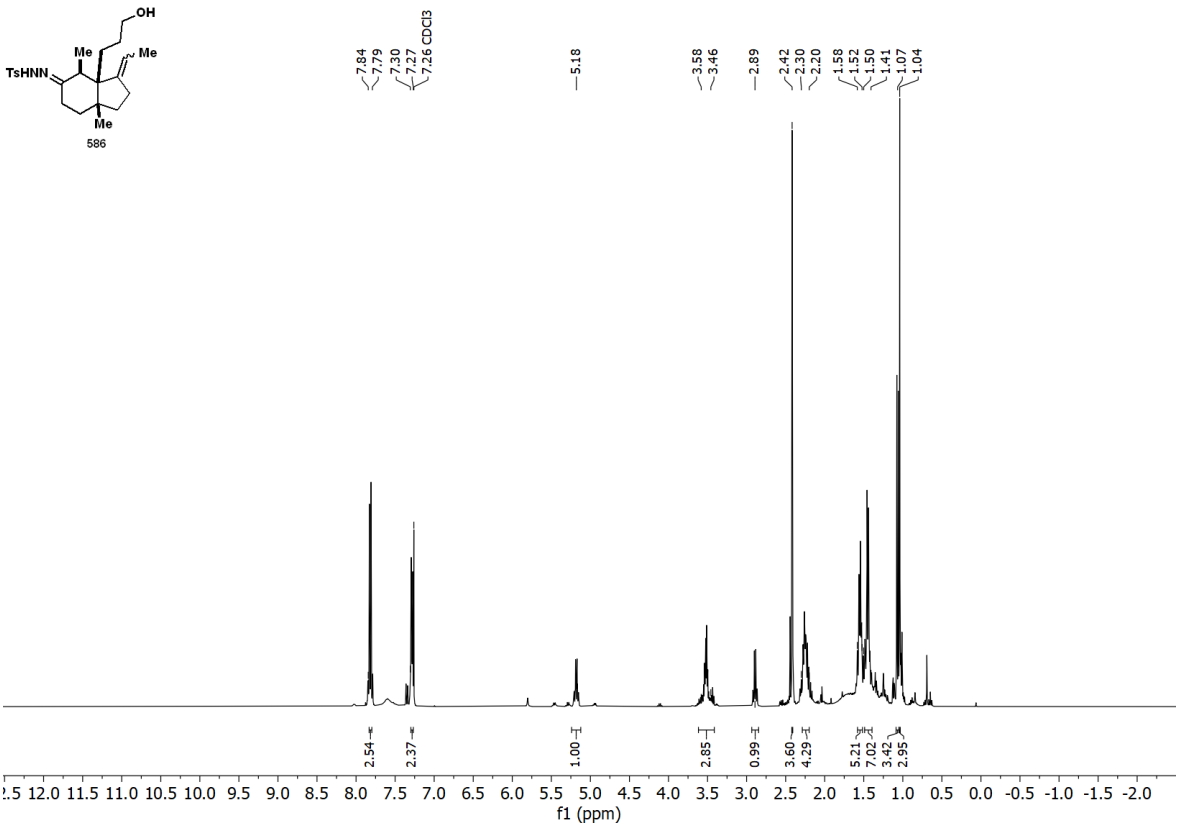

OH
Me
Me
O
Me
247
215.3
146.3
119.1
77.2 CDCl3
63.9
58.1
47.7
45.7
36.3
36.2
35.5
30.8
28.3
27.5
24.2
14.5
11.9
f1 (ppm)

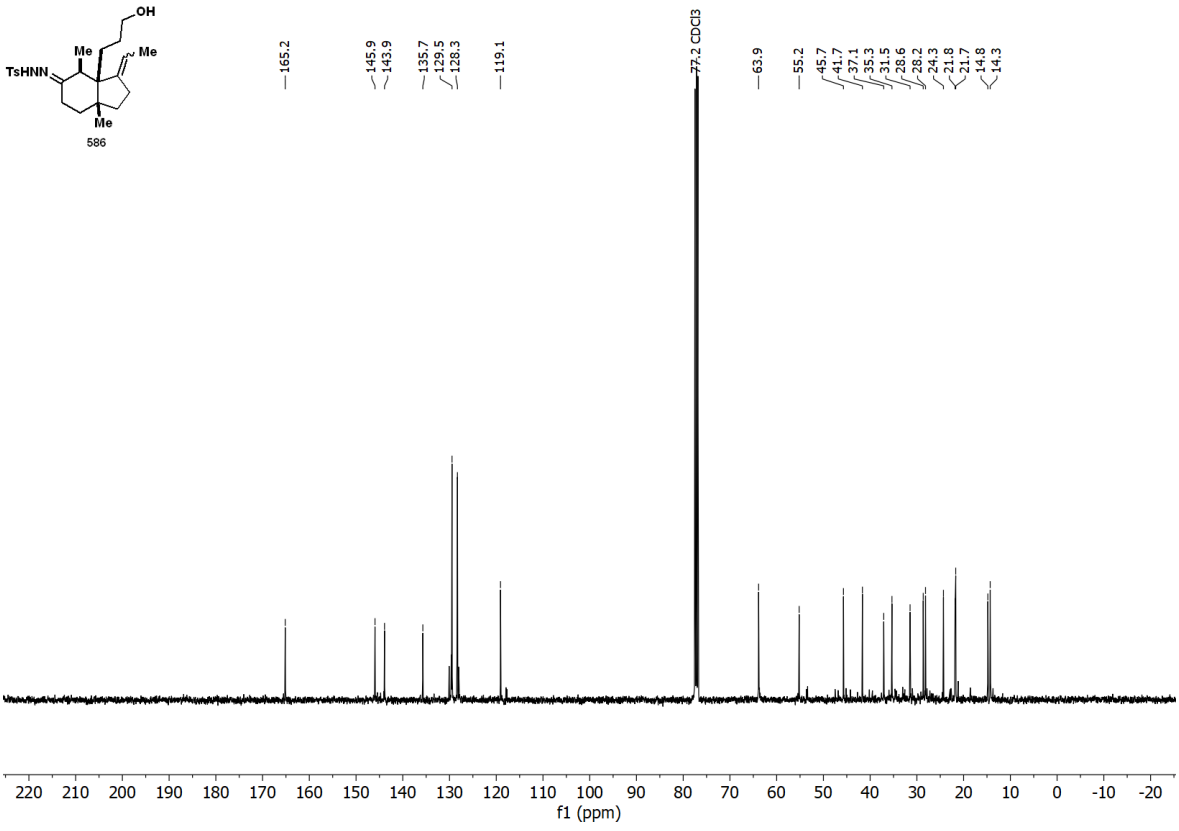

OBn
Me
TsHNN
Me
245
7.85
7.81
7.36
7.26
7.26 CDCl3
4.56
4.47
4.31
3.39
3.31
2.57
2.39
2.38
2.31
2.30
2.27
2.25
2.17
1.64
1.55
1.54
1.47
1.46
1.39
1.38
1.24
1.07
1.06
2.05
7.16
0.96
2.00
0.93
1.97
1.04
3.29
2.17
0.94
1.10
3.07
2.95
2.18
2.40
3.17
2.85
f1 (ppm)

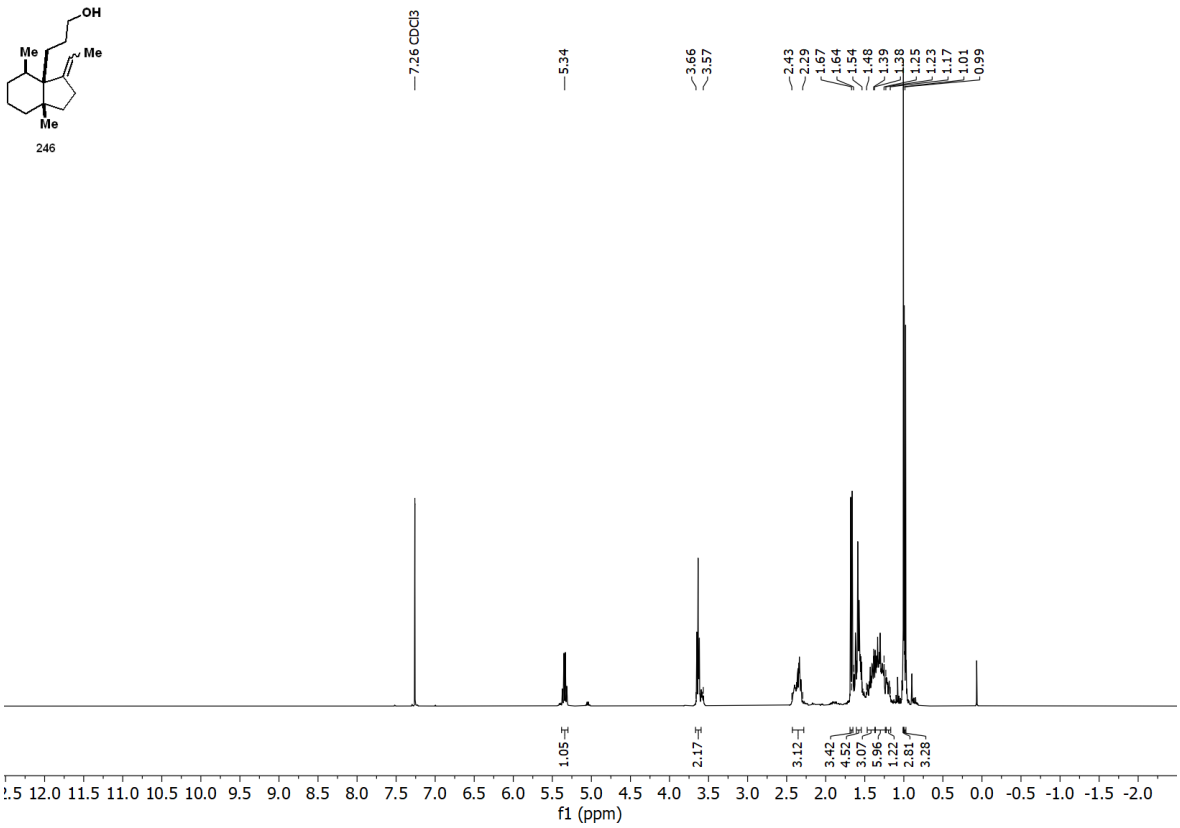

OBn
Me
TsHNN
Me
245
204.2
143.9
138.8
135.8
129.5
128.5
128.4
127.7
127.6
108.6
78.2
77.2 CDCl3
72.8
71.0
53.3
44.4
41.1
36.8
35.1
28.3
25.5
24.0
22.4
21.7
20.9
14.7
f1 (ppm)

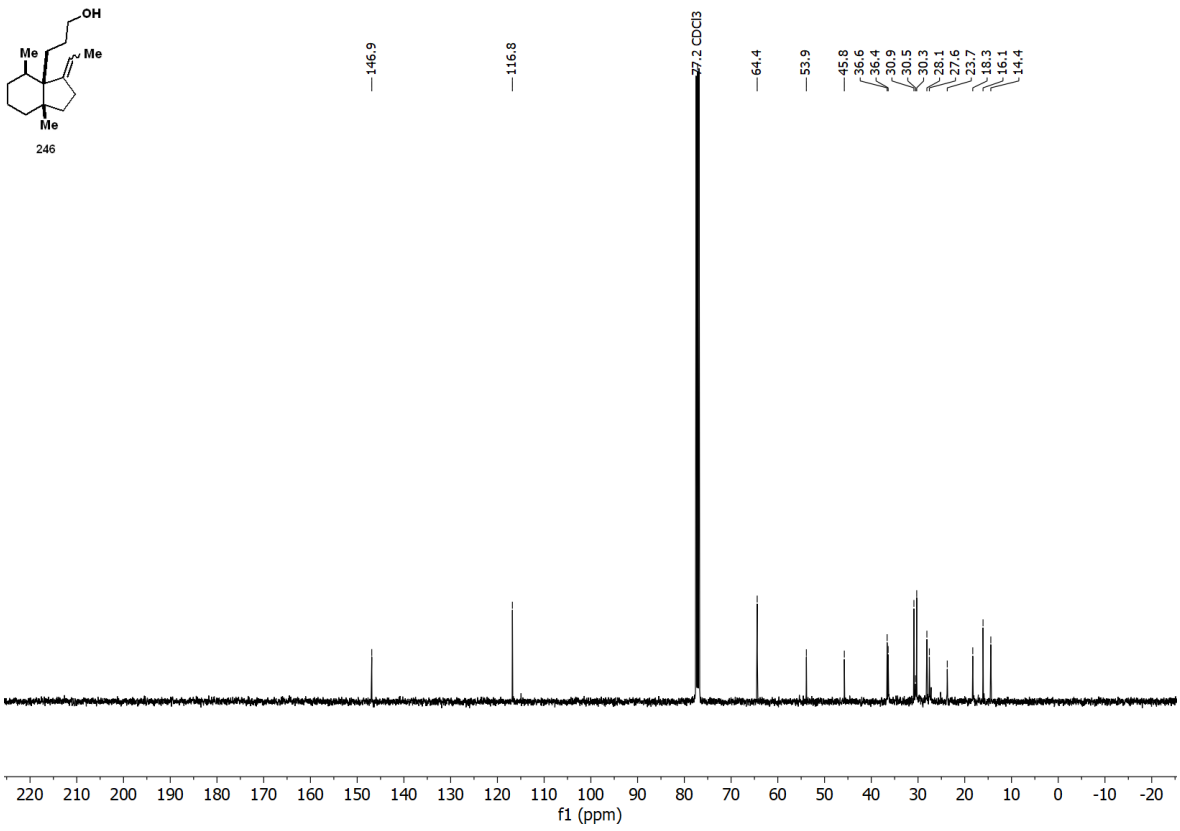

OBn
Me
Me
242
7.35
7.27
7.26 CDCl3
4.68
4.51
3.44
2.43
1.96
1.81
1.64
1.55
1.53
1.34
1.31
1.21
1.02
0.99
5.64
2.00
2.28
1.89
2.02
1.53
4.79
4.33
3.21
2.71
3.44
f1 (ppm)

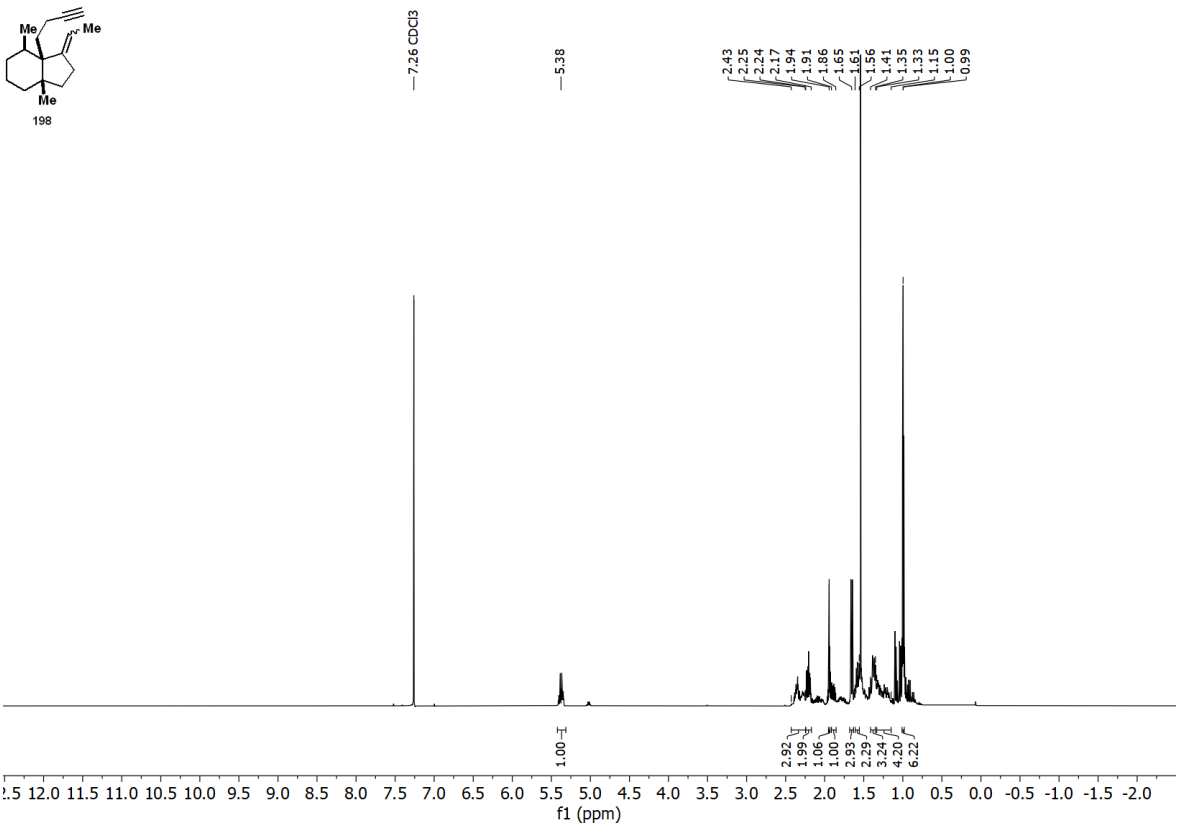

OBn
Me
Me
242
203.7
138.9
128.5
127.8
127.6
109.6
77.2 CDCl3
76.8
72.9
71.6
51.9
44.6
37.3
36.8
30.2
28.5
25.7
24.3
22.5
18.3
16.0
1.2
f1 (ppm)

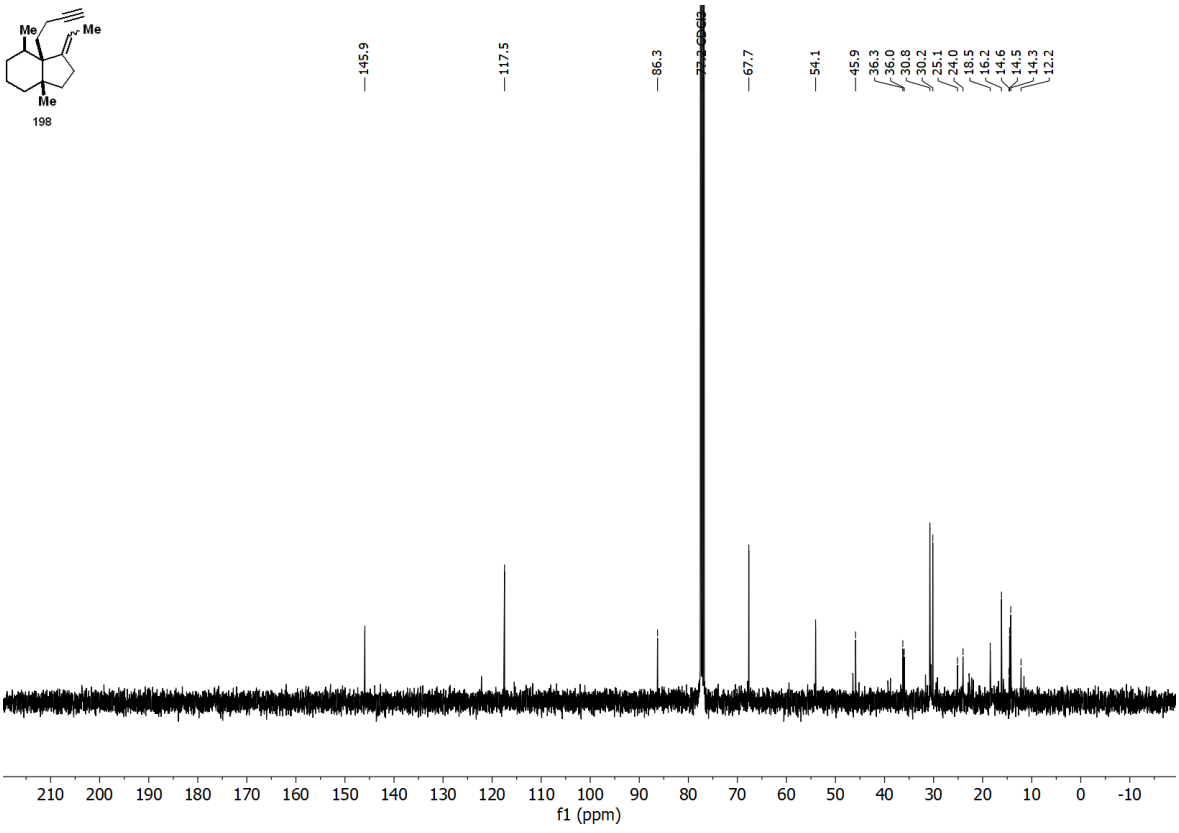

OH
Me
Me
TsHNN
Me
586
7.84
7.79
7.30
7.27
7.26 CDCl3
5.18
3.58
3.46
2.89
2.42
2.30
2.20
1.58
1.52
1.50
1.41
1.07
1.04
2.54
2.37
1.00
2.85
0.99
3.60
4.29
5.21
7.02
3.42
2.95
f1 (ppm)

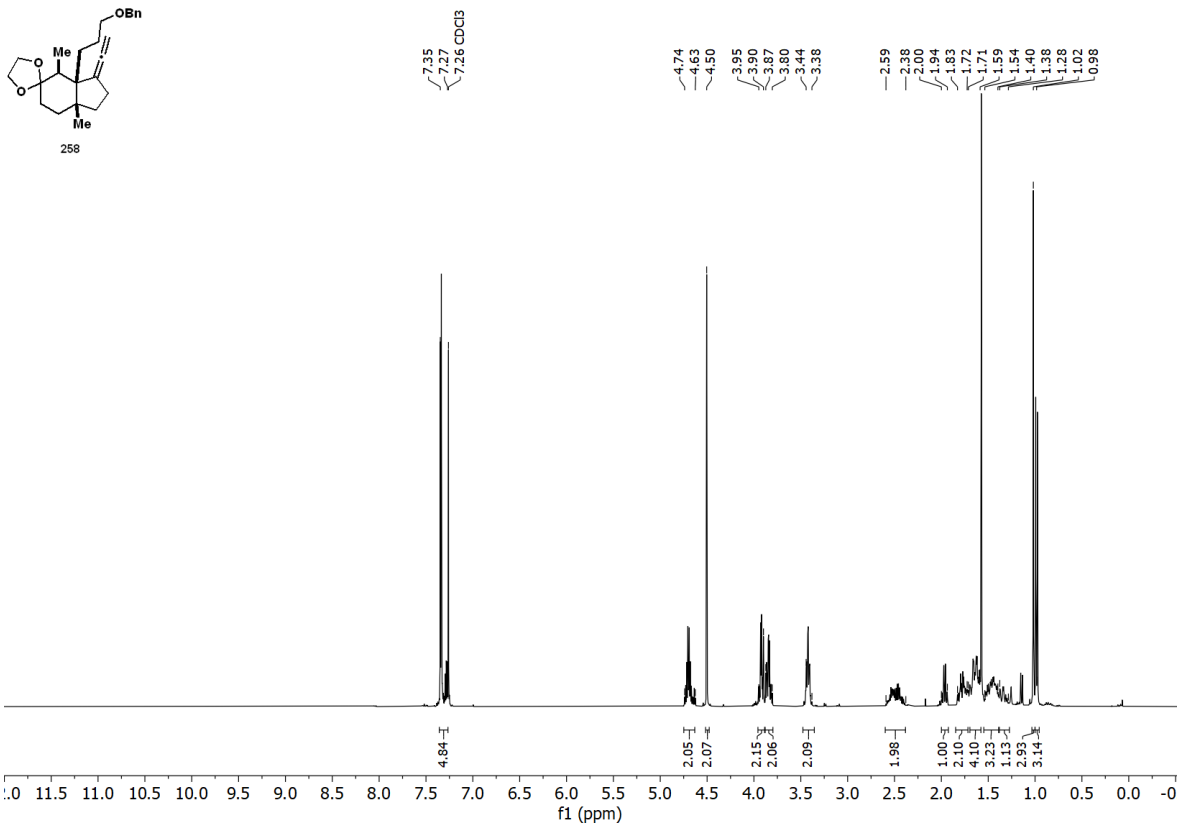

OH
Me
Me
TsHNN
Me
586
165.2
145.9
143.9
135.7
129.5
128.3
119.1
77.2 CDCl3
63.9
55.2
45.7
41.7
37.1
35.3
31.5
28.6
28.2
24.3
21.8
21.7
14.8
14.3
f1 (ppm)

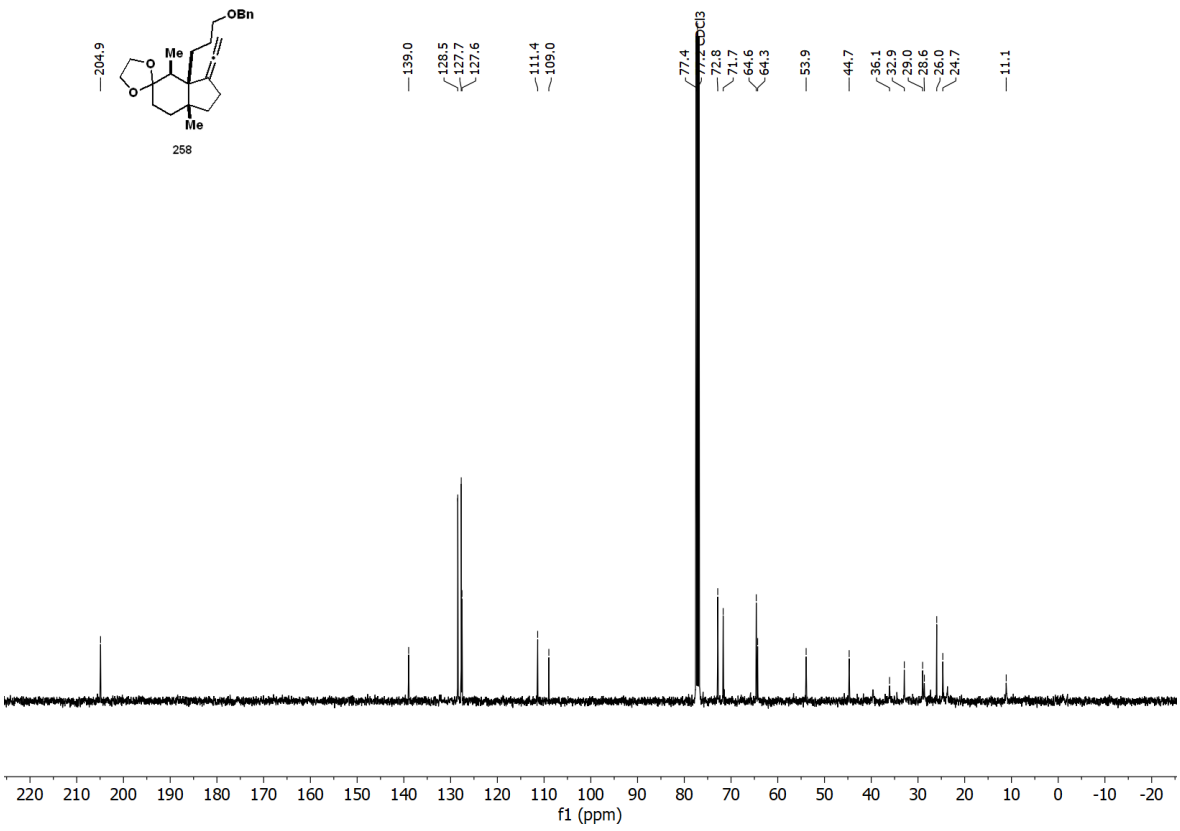

OH
Me
Me
Me
246
7.26 CDCl3
5.34
3.66
3.57
2.43
2.29
1.67
1.64
1.54
1.48
1.39
1.38
1.25
1.23
1.17
1.01
0.99
1.05
2.17
3.12
3.42
4.52
3.07
5.96
1.22
2.81
3.28
f1 (ppm)

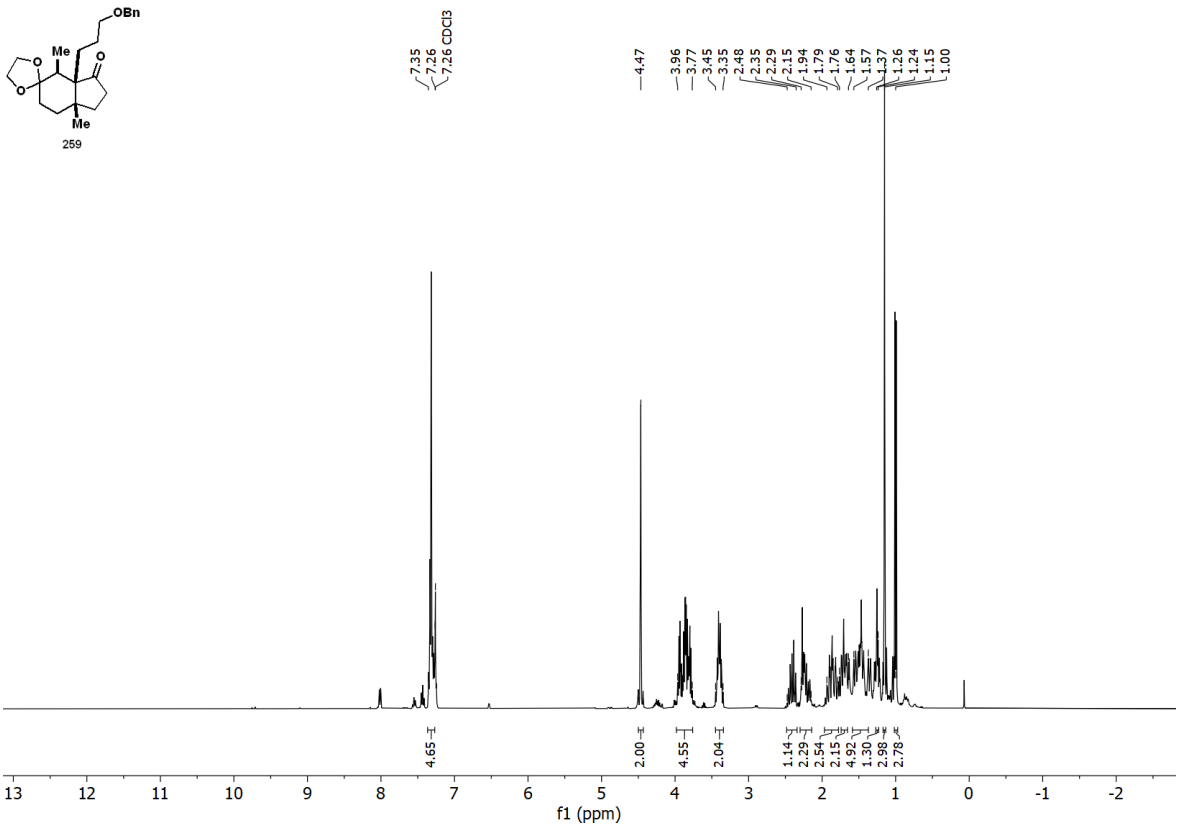

OH
Me
Me
Me
246
146.9
116.8
77.2 CDCl3
64.4
53.9
45.8
36.6
36.4
30.9
30.5
30.3
28.1
27.6
23.7
18.3
16.1
14.4
f1 (ppm)

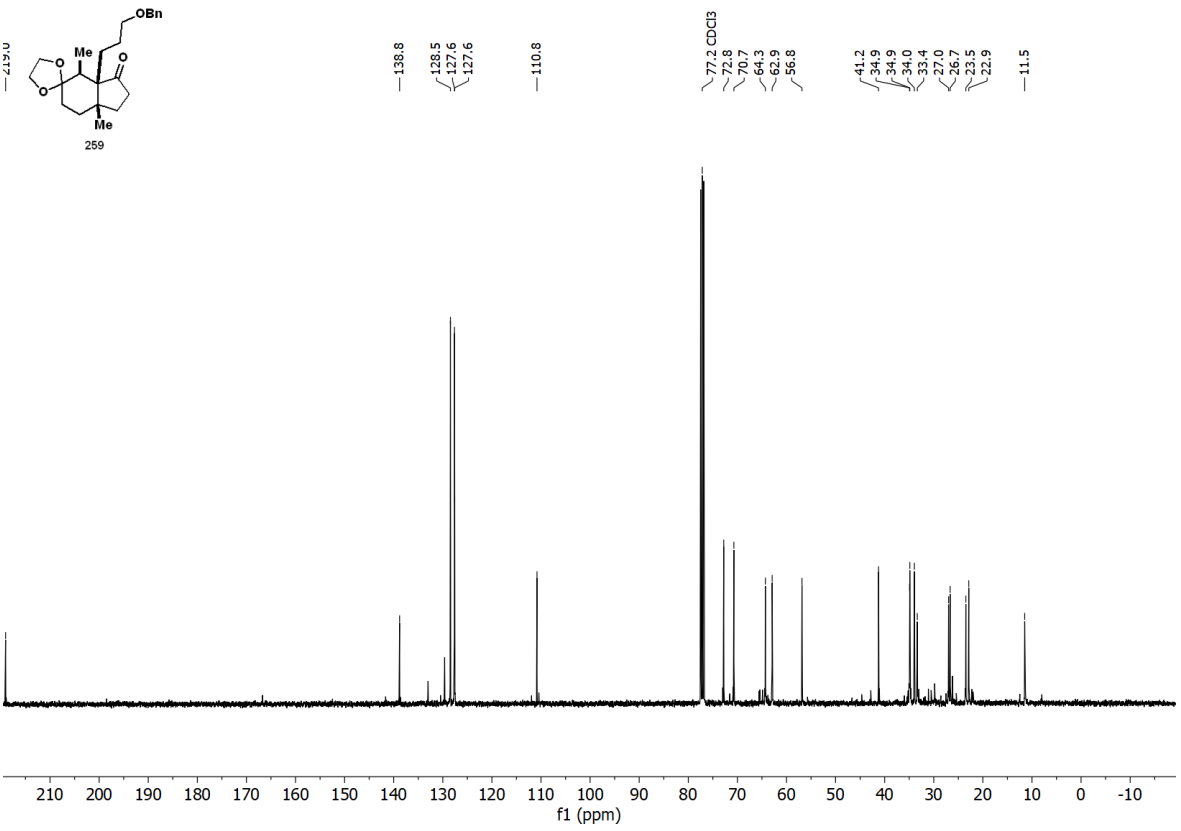

Me
Me
Me
198
7.26 CDCl3
5.38
2.43
2.25
2.24
2.17
1.94
1.91
1.86
1.65
1.61
1.56
1.41
1.35
1.33
1.15
1.00
0.99
1.00
2.92
1.99
1.06
1.00
2.93
2.29
3.24
4.20
6.22
f1 (ppm)

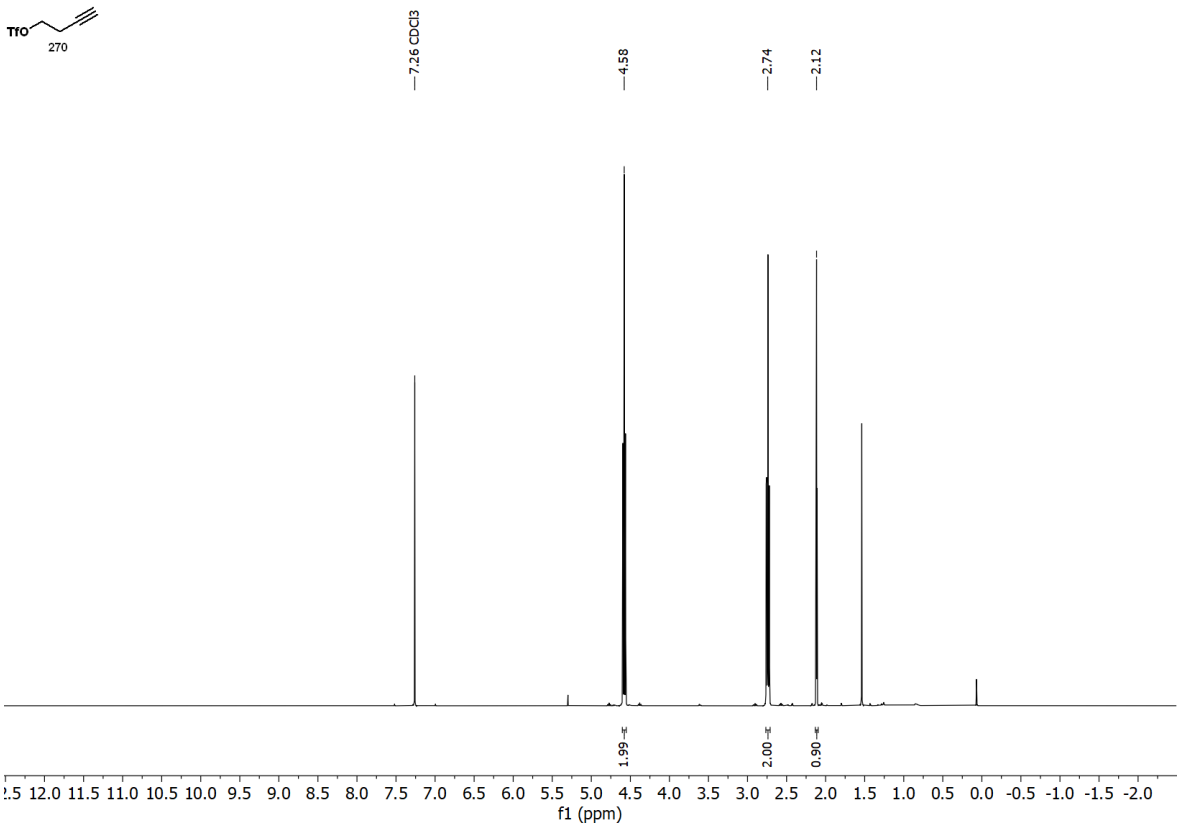

Me
Me
Me
198
145.9
117.5
86.3
77.3 CDCl3
67.7
54.1
45.9
36.3
36.0
30.8
30.2
25.1
24.0
18.5
16.2
14.6
14.5
14.3
12.2
f1 (ppm)

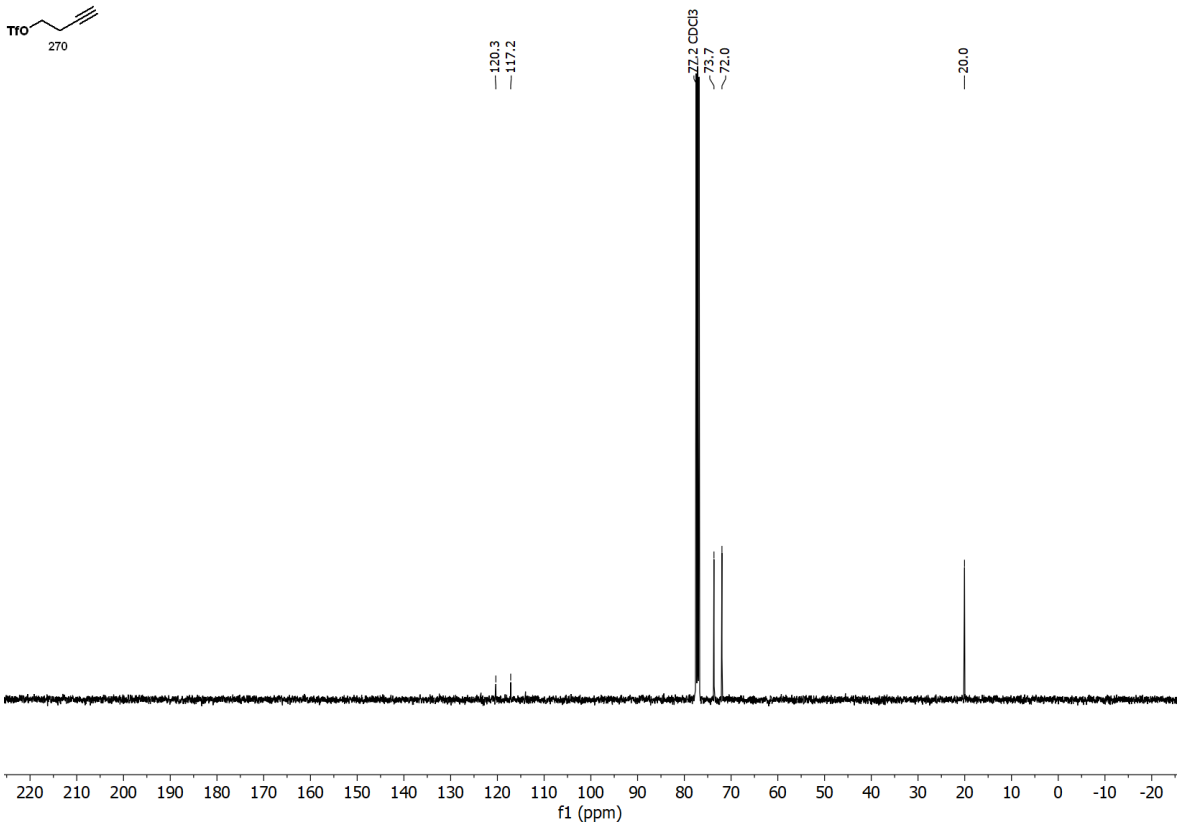

OBn
Me
Me
O
O
258
7.35
7.27
7.26 CDCl3
4.74
4.63
4.50
3.95
3.90
3.87
3.80
3.44
3.38
2.59
2.38
2.00
1.94
1.83
1.72
1.71
1.59
1.54
1.40
1.38
1.28
1.02
0.98
4.84
2.05
2.07
2.15
2.06
2.09
1.98
1.00
2.10
4.10
3.23
1.13
2.93
3.14
f1 (ppm)

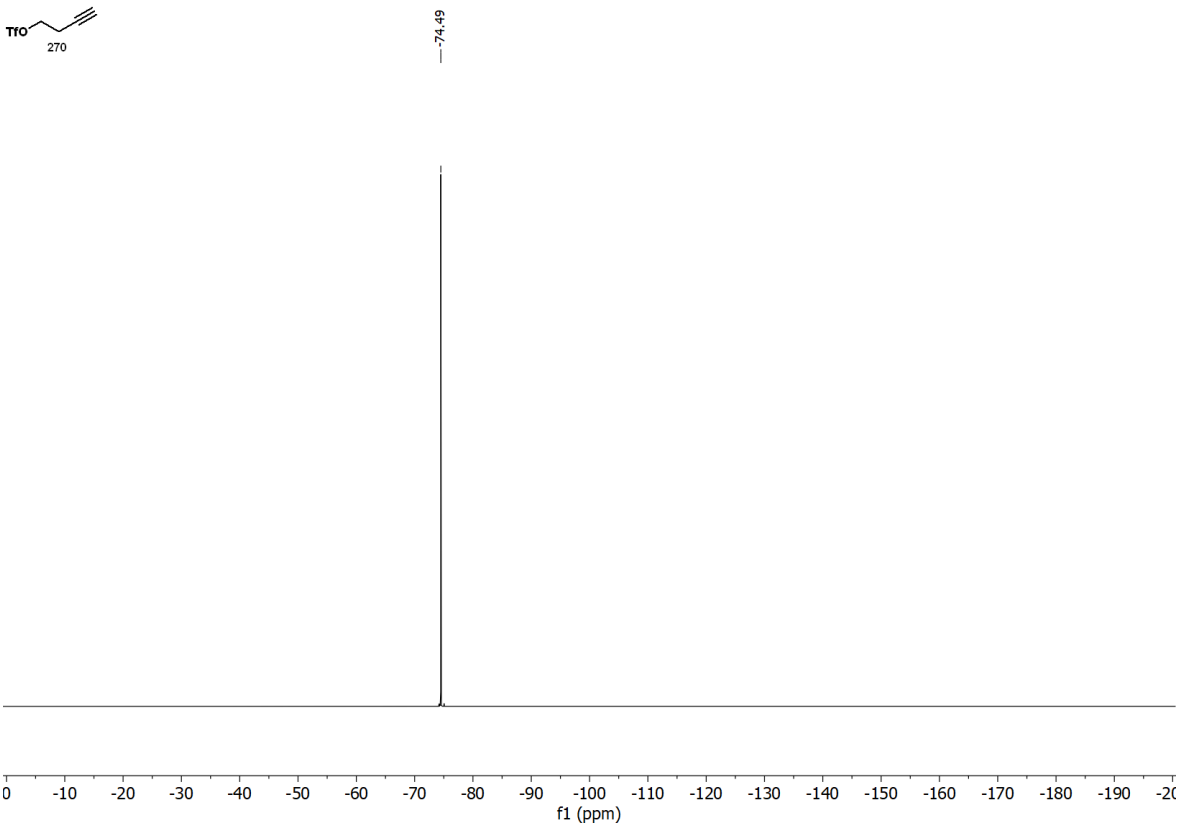

OBn
Me
Me
O
O
258
204.9
139.0
128.5
127.7
127.6
111.4
109.0
77.4
77.2 CDCl3
72.8
71.7
64.6
64.3
53.9
44.7
36.1
32.9
29.0
28.6
26.0
24.7
11.1
f1 (ppm)

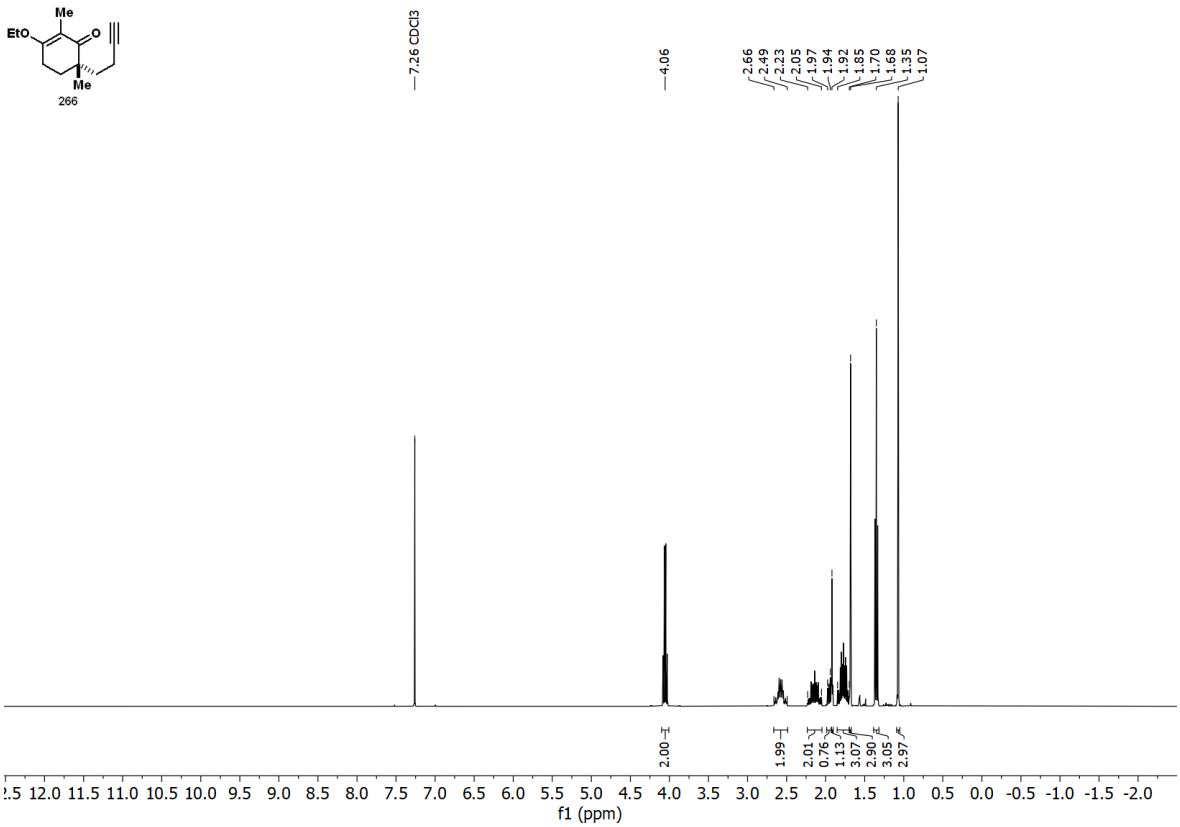

OBn
Me
O
O
Me
259
7.35
7.26
7.26 CDCl3
4.47
3.96
3.77
3.45
3.35
2.48
2.35
2.29
2.15
1.94
1.79
1.76
1.64
1.57
1.37
1.26
1.24
1.15
1.00
4.65
2.00
4.55
2.04
1.14
2.29
2.54
2.15
4.92
1.30
2.98
2.78
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2
f1 (ppm)

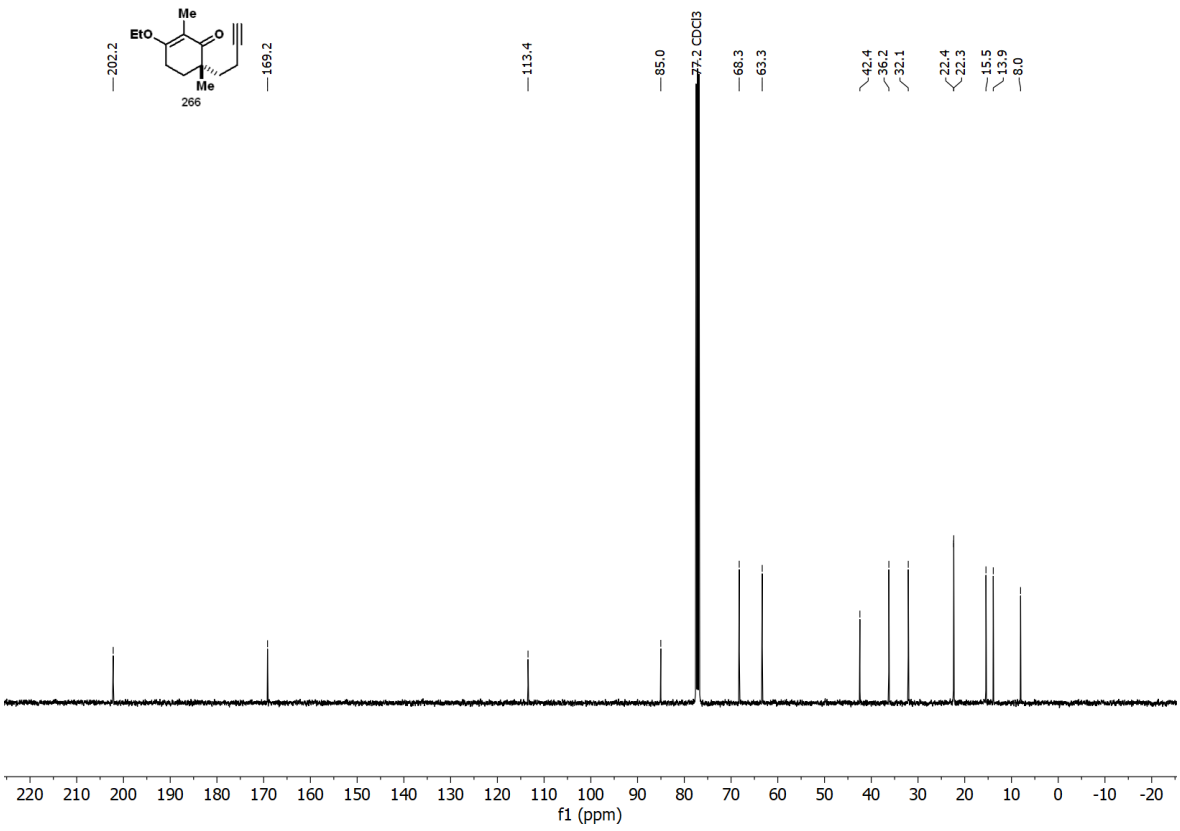

OBn
Me
O
O
Me
259
138.8
128.5
127.6
127.6
110.8
77.2 CDCl3
72.8
70.7
64.3
62.9
56.8
41.2
34.9
34.9
34.0
33.4
27.0
26.7
23.5
22.9
11.5
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

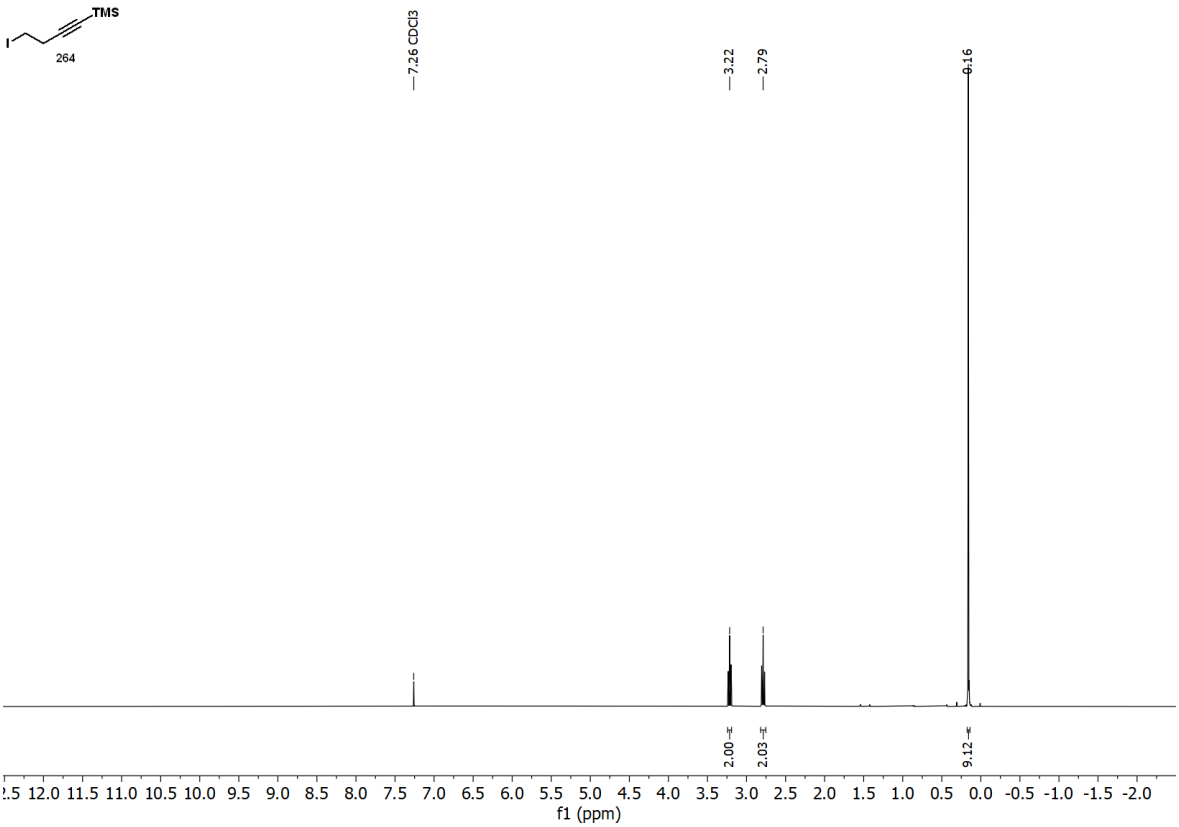

TfO
270
7.26 CDCl3
4.58
2.74
2.12
1.99
2.00
0.90
f1 (ppm)

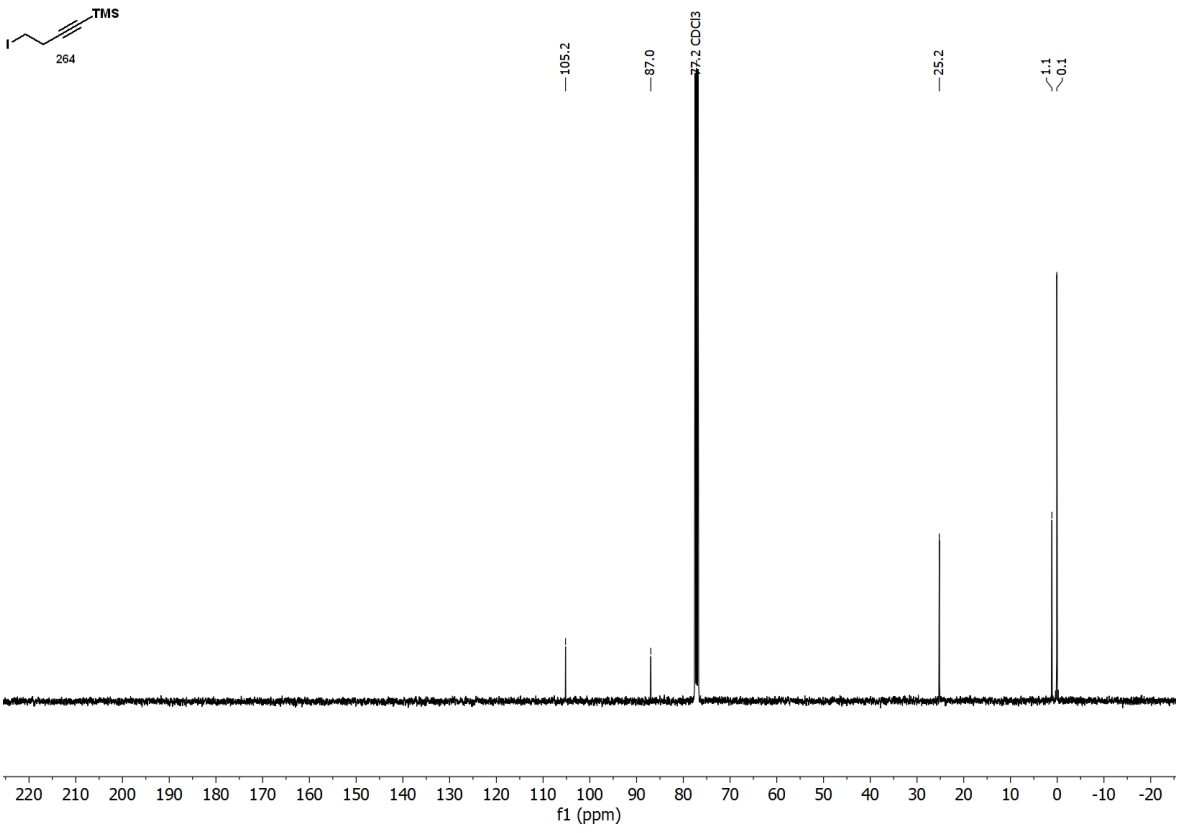

TfO
270
120.3
117.2
77.2 CDCl3
73.7
72.0
20.0
f1 (ppm)

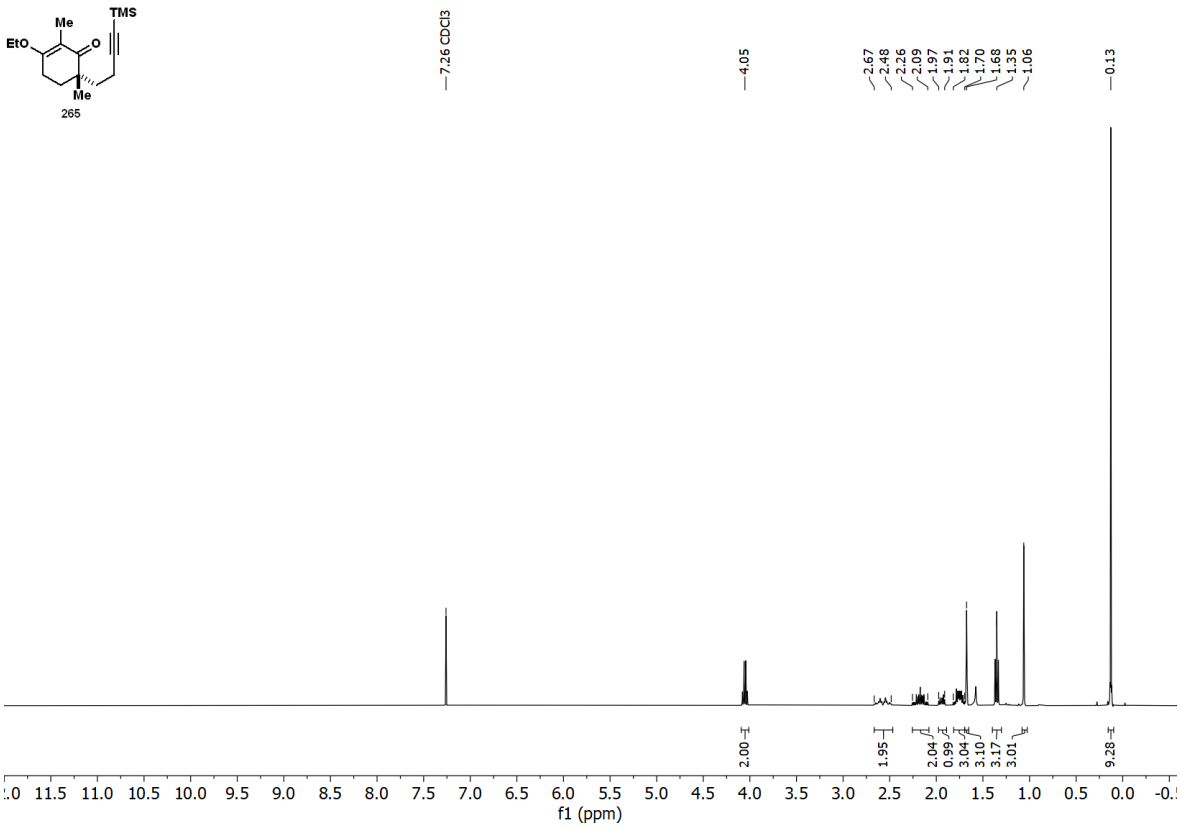

TfO
270
-74.49
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

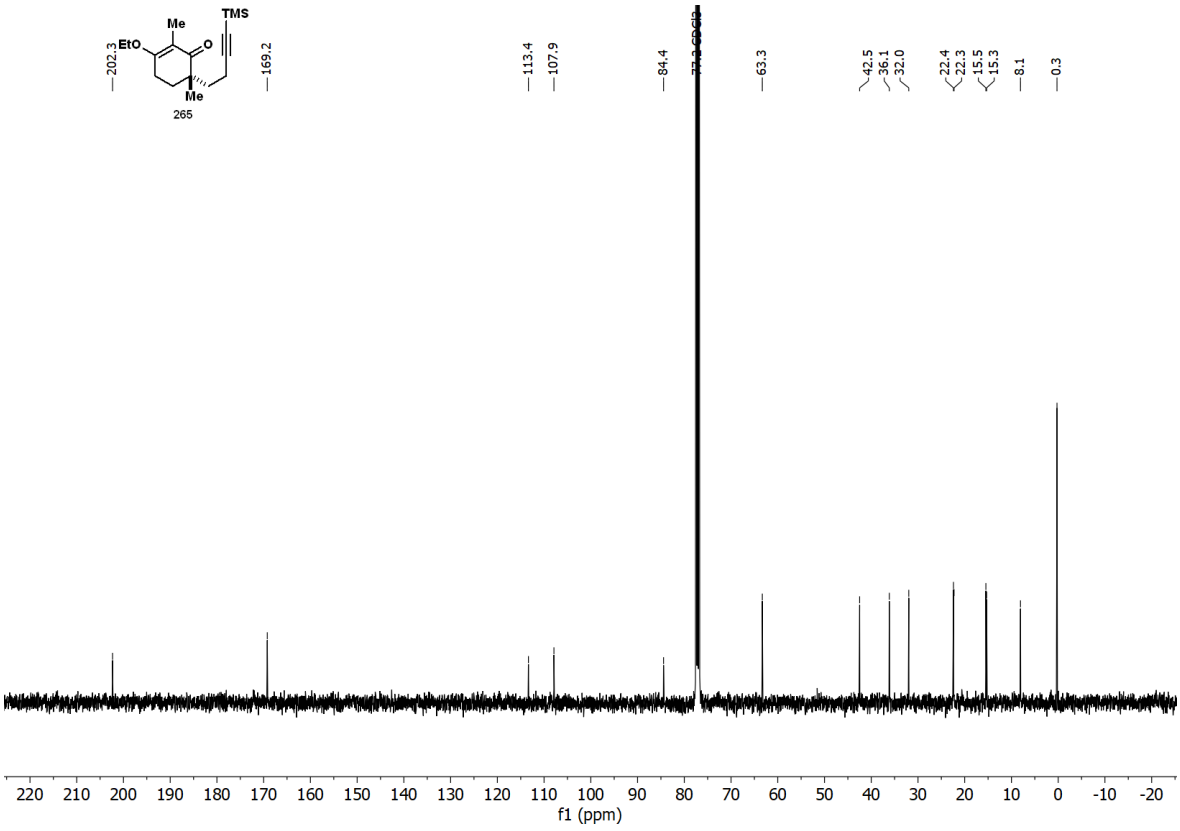

Me
EtO
O
Me
266
7.26 CDCl3
4.06
2.66
2.49
2.23
2.05
1.97
1.94
1.92
1.85
1.70
1.68
1.35
1.07
2.00
1.99
2.01
0.76
1.13
3.07
2.90
3.05
2.97
f1 (ppm)

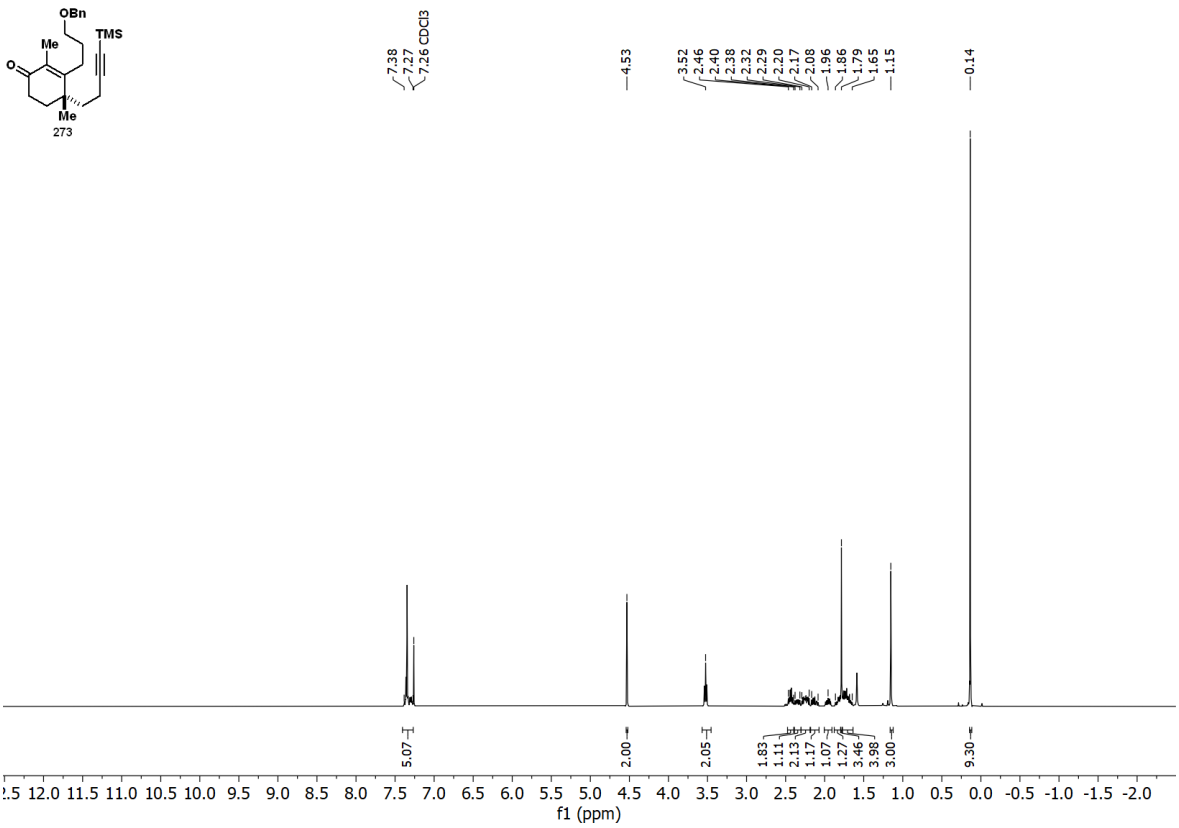

Me
EtO
O
Me
266
202.2
169.2
113.4
85.0
77.2 CDCl3
68.3
63.3
42.4
36.2
32.1
22.4
22.3
15.5
13.9
8.0
f1 (ppm)

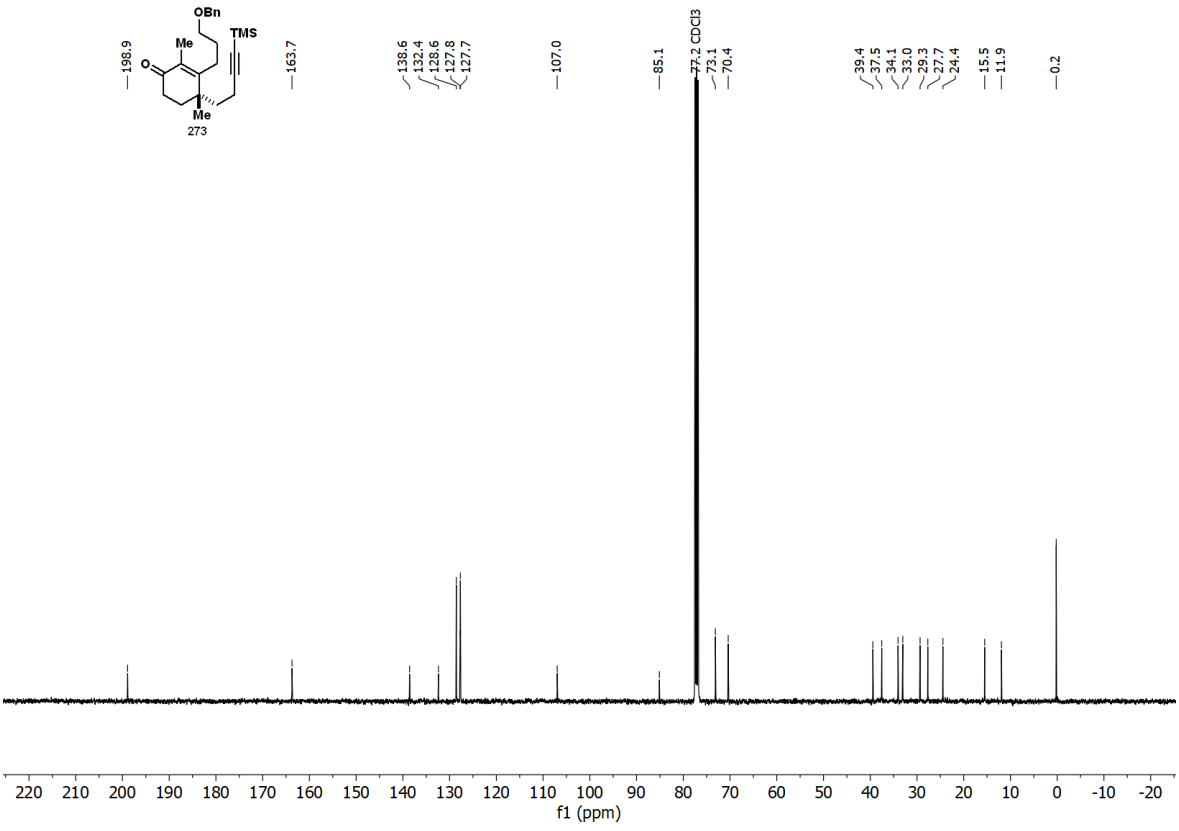

TMS
264
7.26 CDCl3
3.22
2.79
0.16
2.00
2.03
9.12
f1 (ppm)

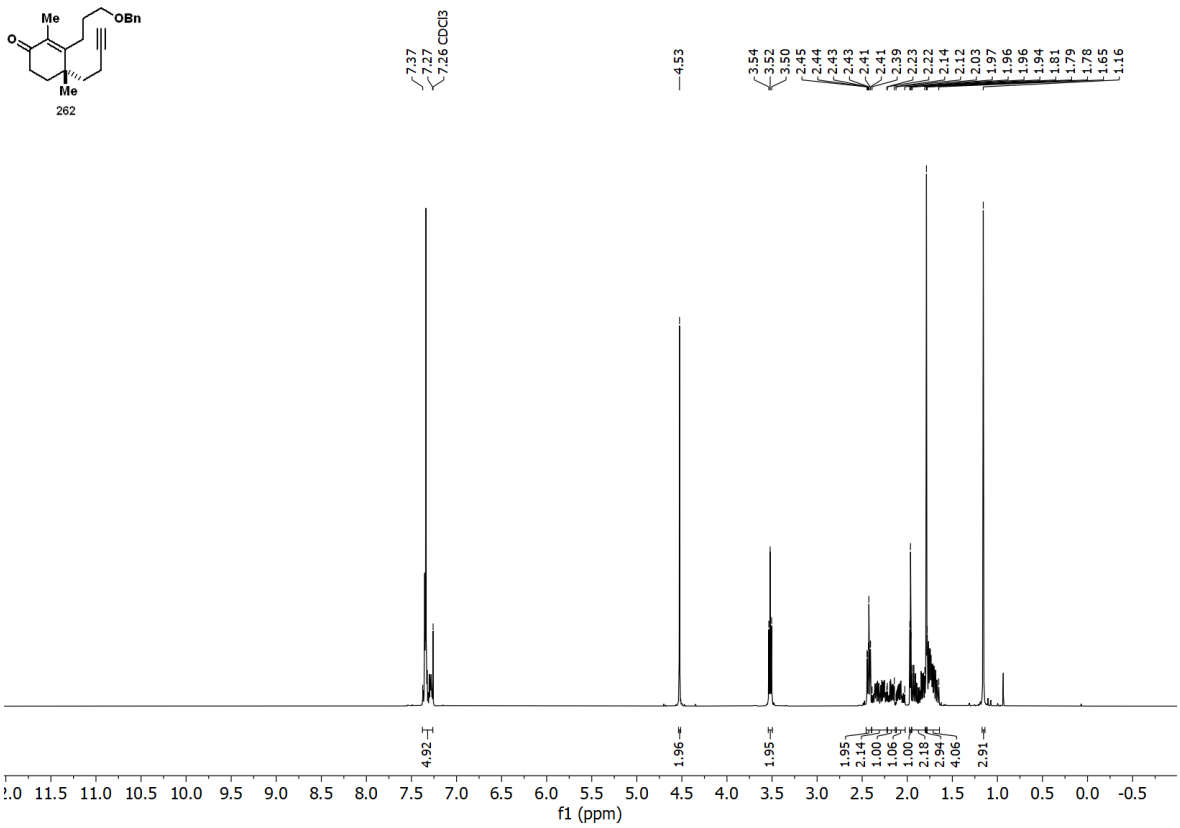

TMS
264
105.2
87.0
77.2 CDCl3
25.2
1.1
0.1
f1 (ppm)

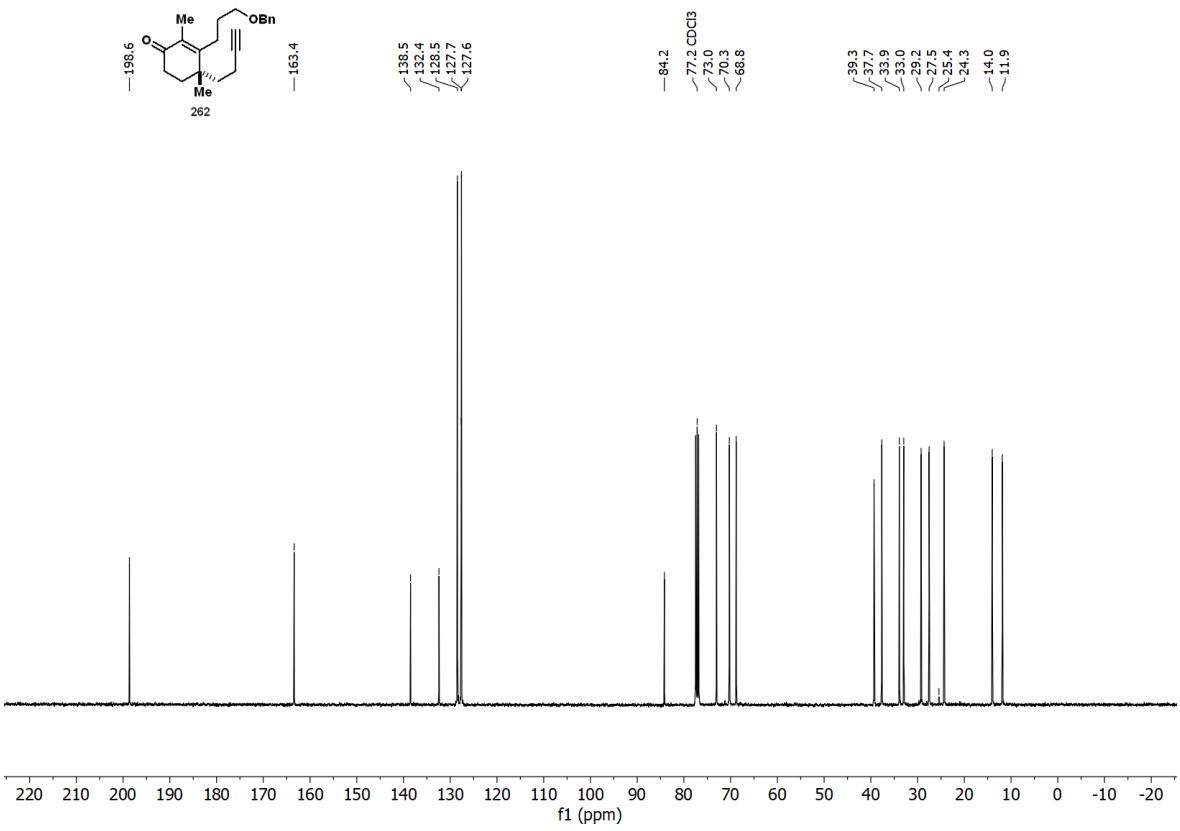

Me
TMS
EtO
O
Me
265
7.26 CDCl3
4.05
2.67
2.48
2.26
2.09
1.97
1.91
1.82
1.70
1.68
1.35
1.06
0.13
2.00
1.95
2.04
0.99
3.04
3.10
3.17
3.01
9.28
f1 (ppm)

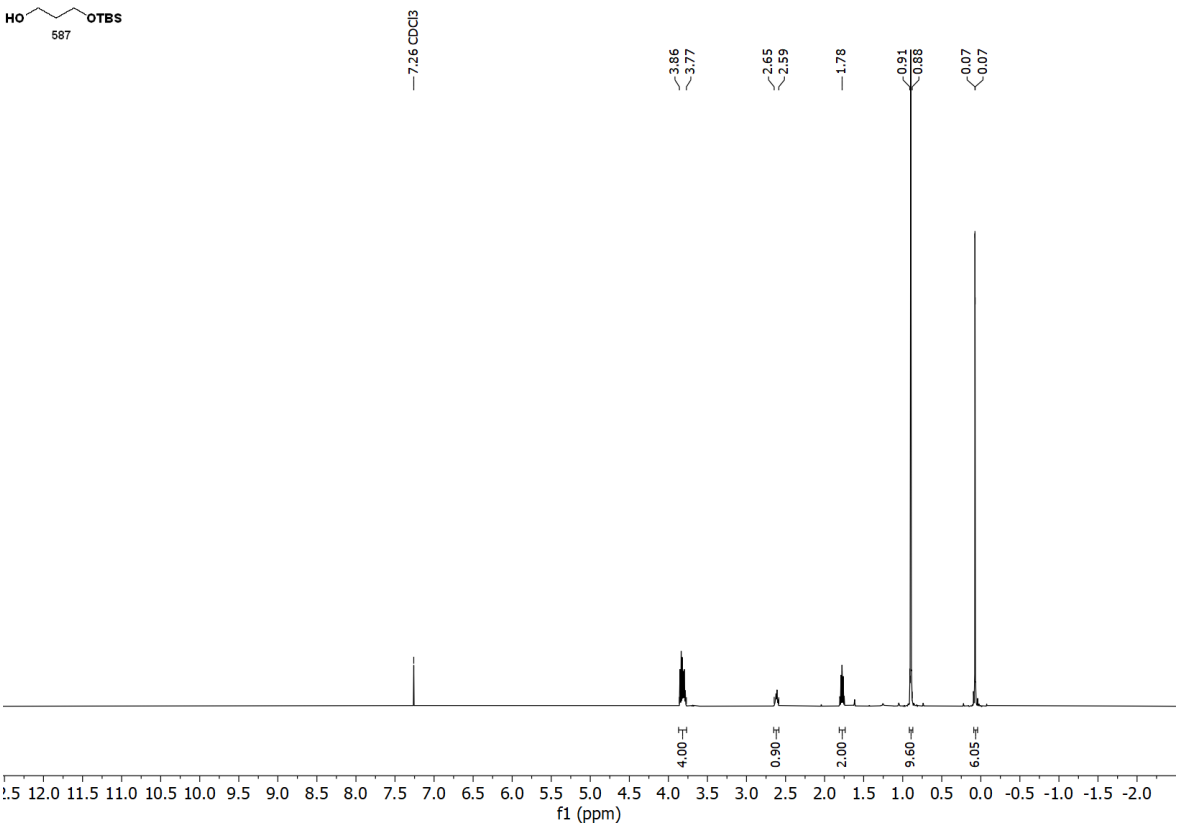

Me
TMS
EtO
O
Me
265
202.3
169.2
113.4
107.9
84.4
77.3 CDCl3
63.3
42.5
36.1
32.0
22.4
22.3
15.5
15.3
8.1
0.3
f1 (ppm)

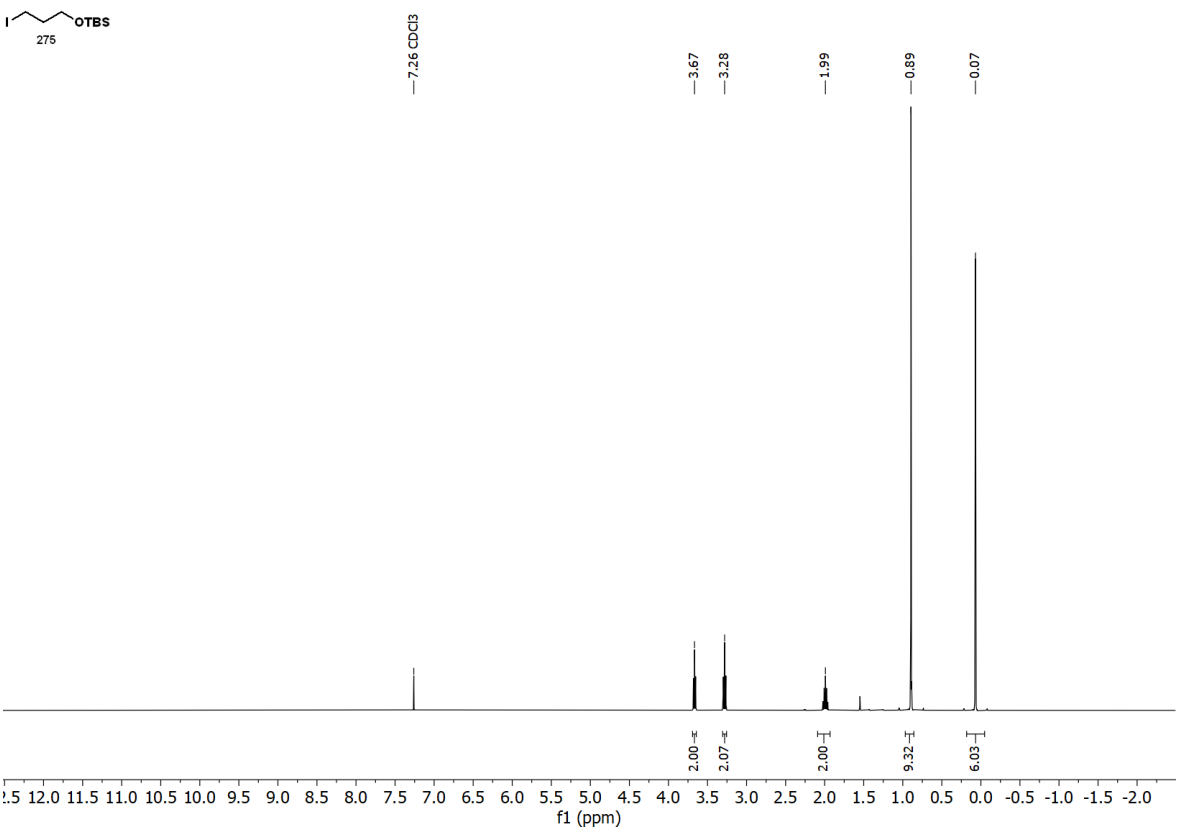

OBn
TMS
Me
Me
273
7.38
7.27
7.26 CDCl3
4.53
3.52
2.46
2.40
2.38
2.32
2.29
2.20
2.17
2.08
1.96
1.86
1.79
1.65
1.15
0.14
5.07
2.00
2.05
1.83
1.11
2.13
1.17
1.07
1.27
3.46
3.98
3.00
9.30
f1 (ppm)

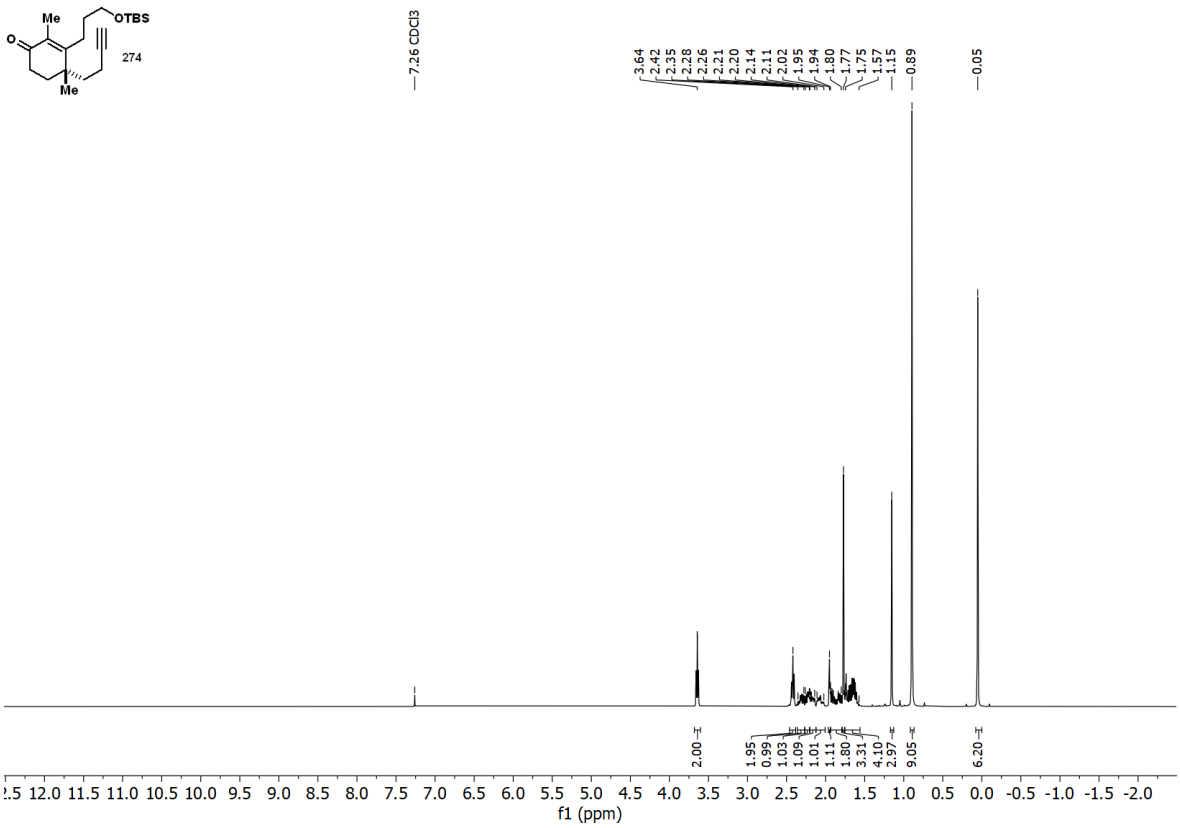

OBn
TMS
Me
Me
273
198.9
163.7
138.6
132.4
128.6
127.8
127.7
107.0
85.1
77.2 CDCl3
73.1
70.4
39.4
37.5
34.1
33.0
29.3
27.7
24.4
15.5
11.9
0.2
f1 (ppm)

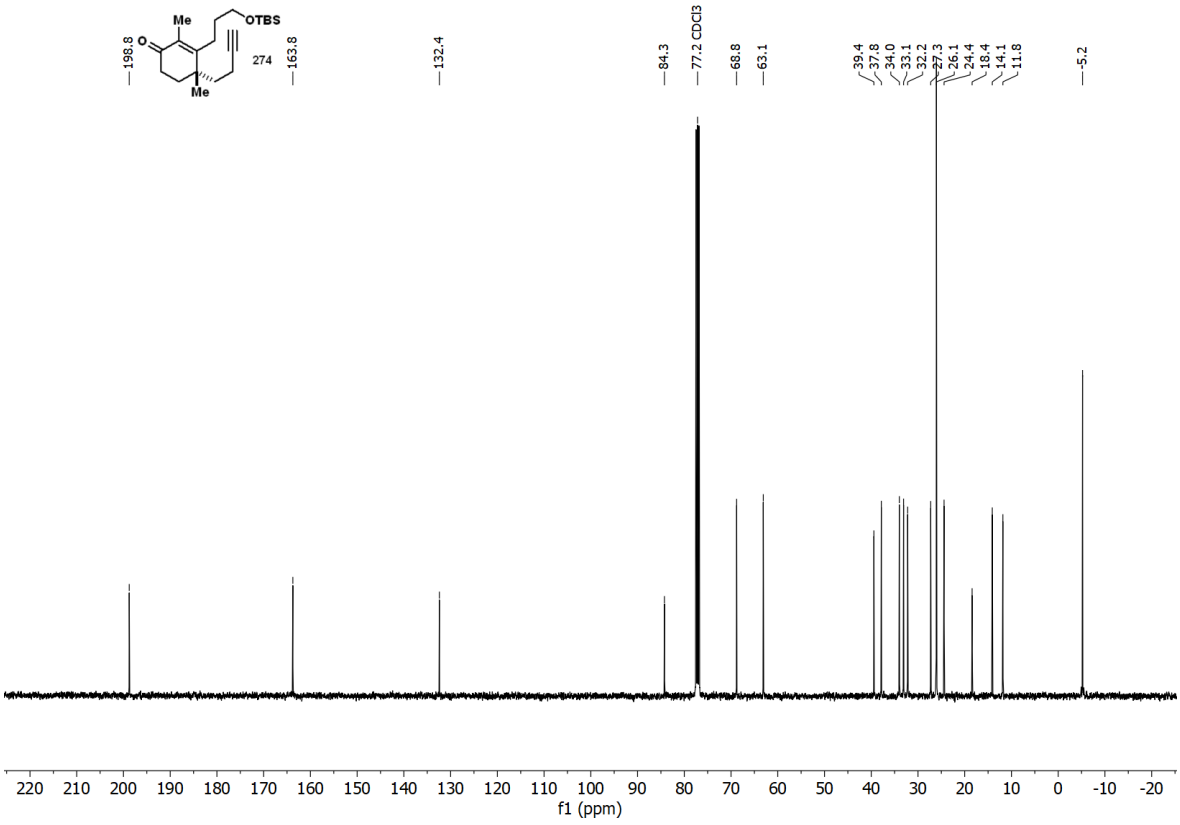

Me
OBn
Me
262
7.37
7.27
7.26 CDCl3
4.53
3.54
3.52
3.50
2.45
2.44
2.43
2.43
2.41
2.41
2.39
2.23
2.22
2.14
2.12
2.03
1.97
1.96
1.96
1.94
1.81
1.79
1.78
1.65
1.16
4.92
1.96
1.95
1.95
2.14
1.00
1.06
1.00
2.18
2.94
4.06
2.91
f1 (ppm)

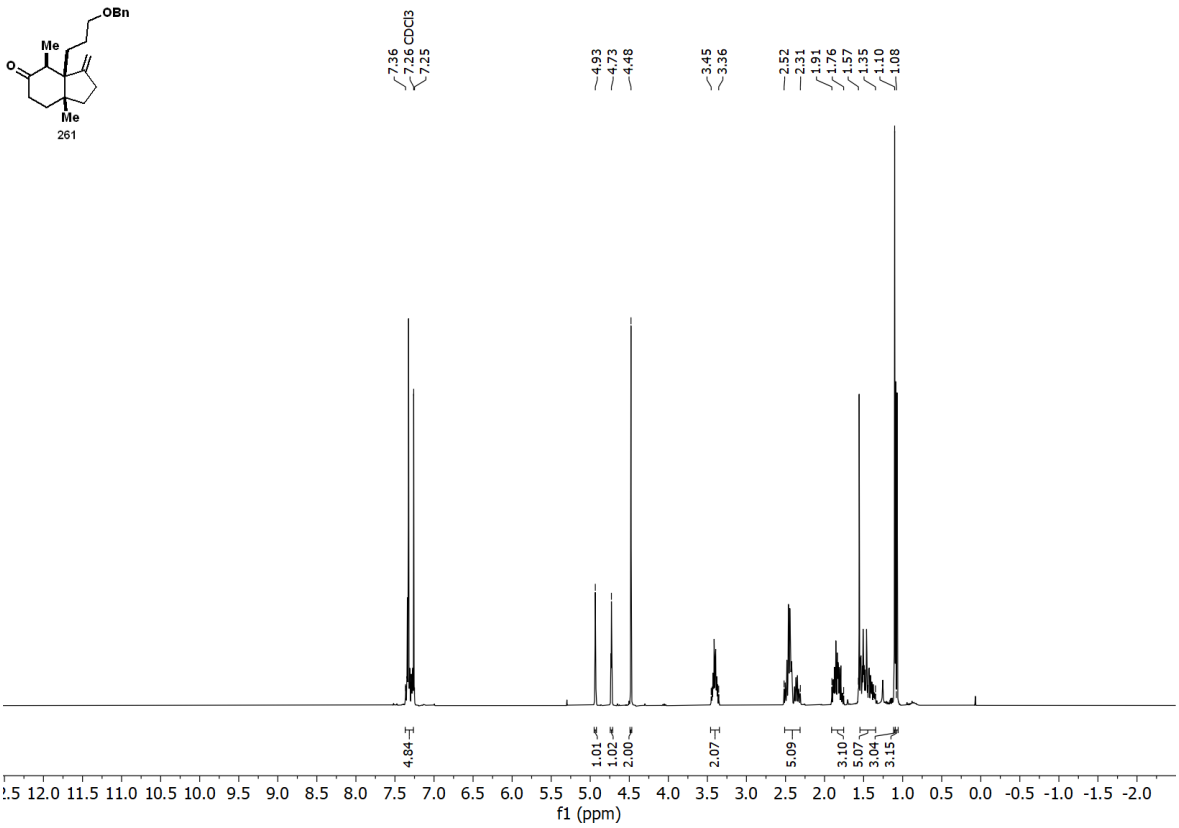

Me
OBn
Me
262
198.6
163.4
138.5
132.4
128.5
127.7
127.6
84.2
77.2 CDCl3
73.0
70.3
68.8
39.3
37.7
33.9
33.0
29.2
27.5
25.4
24.3
14.0
11.9
f1 (ppm)

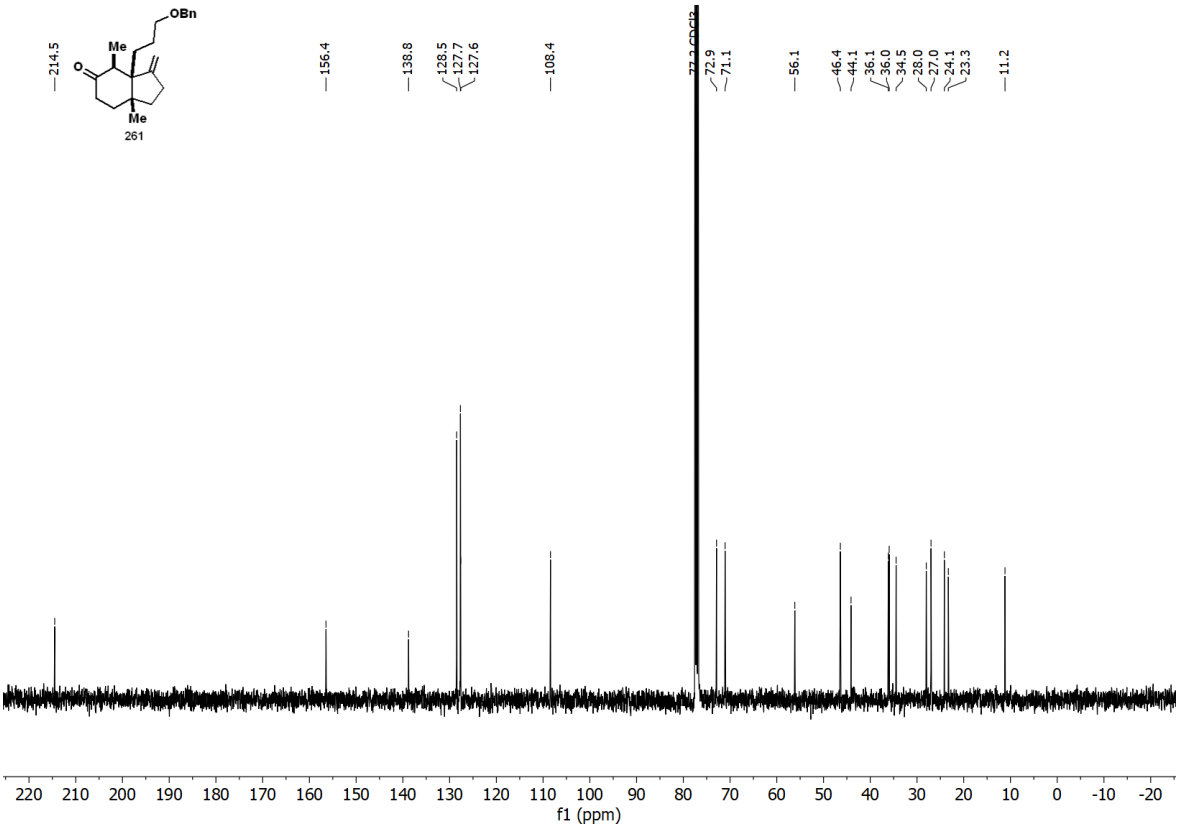

HO
OTBS
587
7.26 CDCl3
3.86
3.77
2.65
2.59
1.78
0.91
0.88
0.07
0.07
4.00
0.90
2.00
9.60
6.05
f1 (ppm)

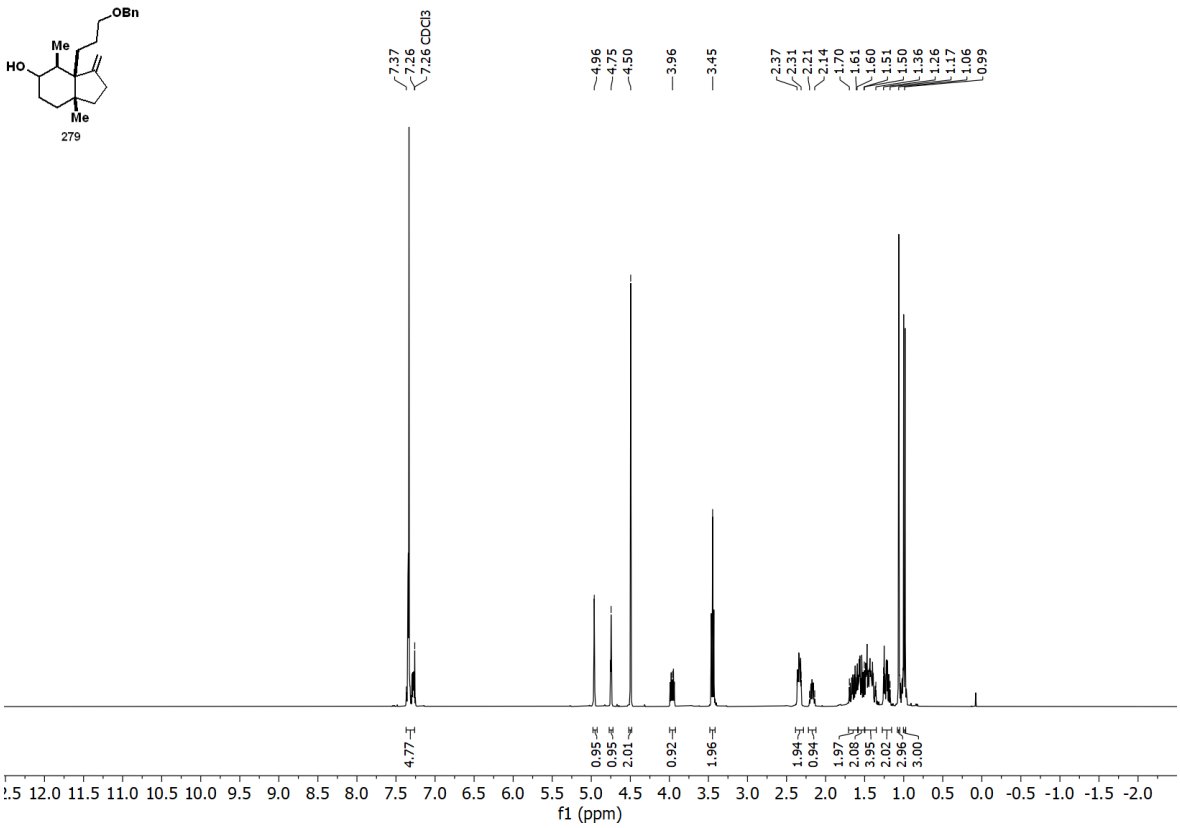

OTBS
275
7.26 CDCl3
3.67
3.28
1.99
0.89
0.07
2.00
2.07
2.00
9.32
6.03
f1 (ppm)

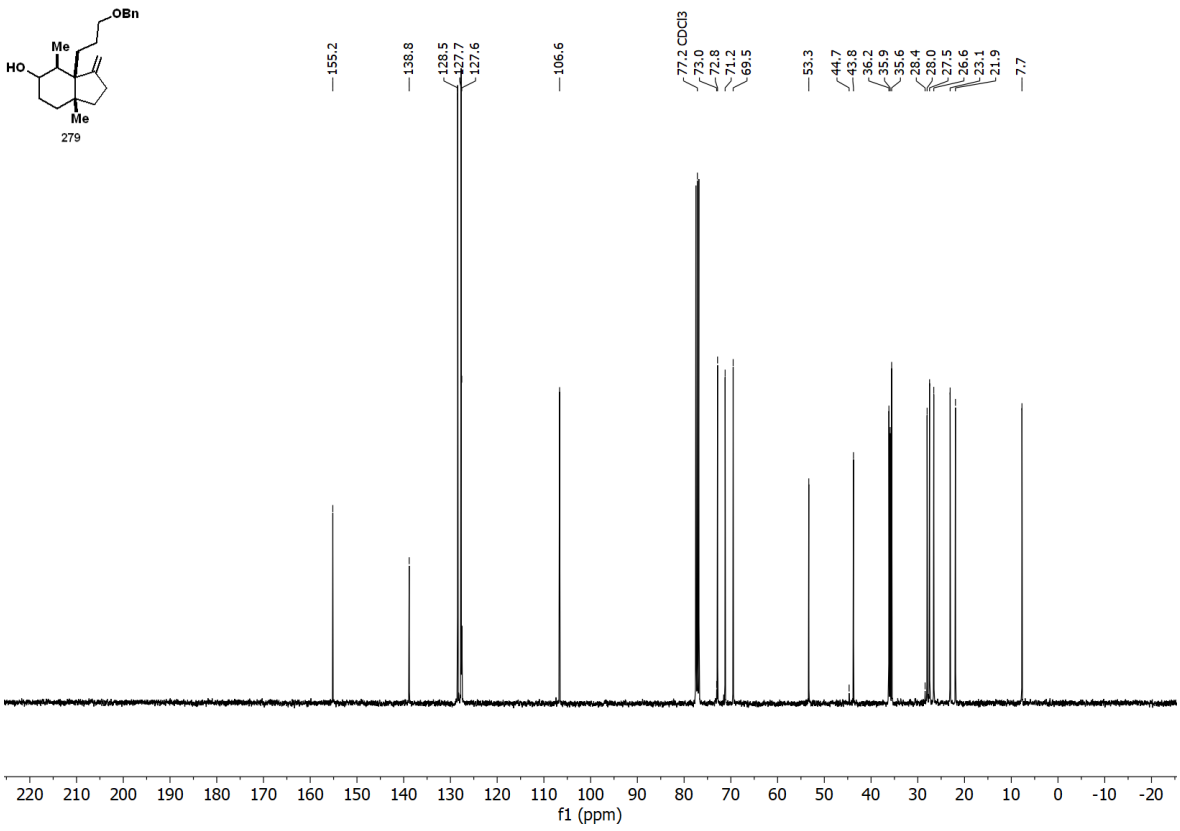

Me
OTBS
O
274
Me
7.26 CDCl3
3.64
2.42
2.35
2.28
2.26
2.21
2.20
2.14
2.11
2.02
1.95
1.94
1.80
1.77
1.75
1.57
1.15
0.89
0.05
2.00
1.95
0.99
1.03
1.09
1.01
1.11
1.80
3.31
4.10
2.97
9.05
6.20
f1 (ppm)

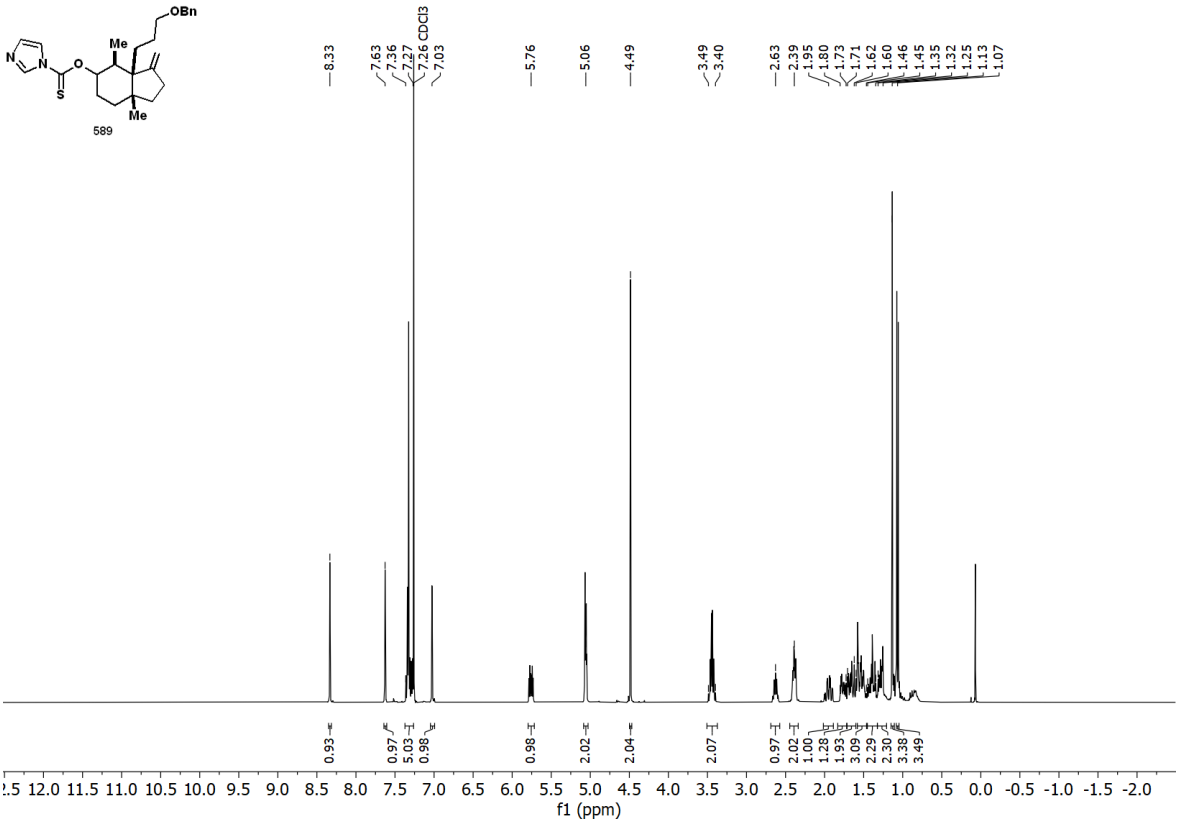

Me
OTBS
O
274
Me
198.8
163.8
132.4
84.3
77.2 CDCl3
68.8
63.1
39.4
37.8
34.0
33.1
32.2
27.3
26.1
24.4
18.4
14.1
11.8
-5.2
f1 (ppm)

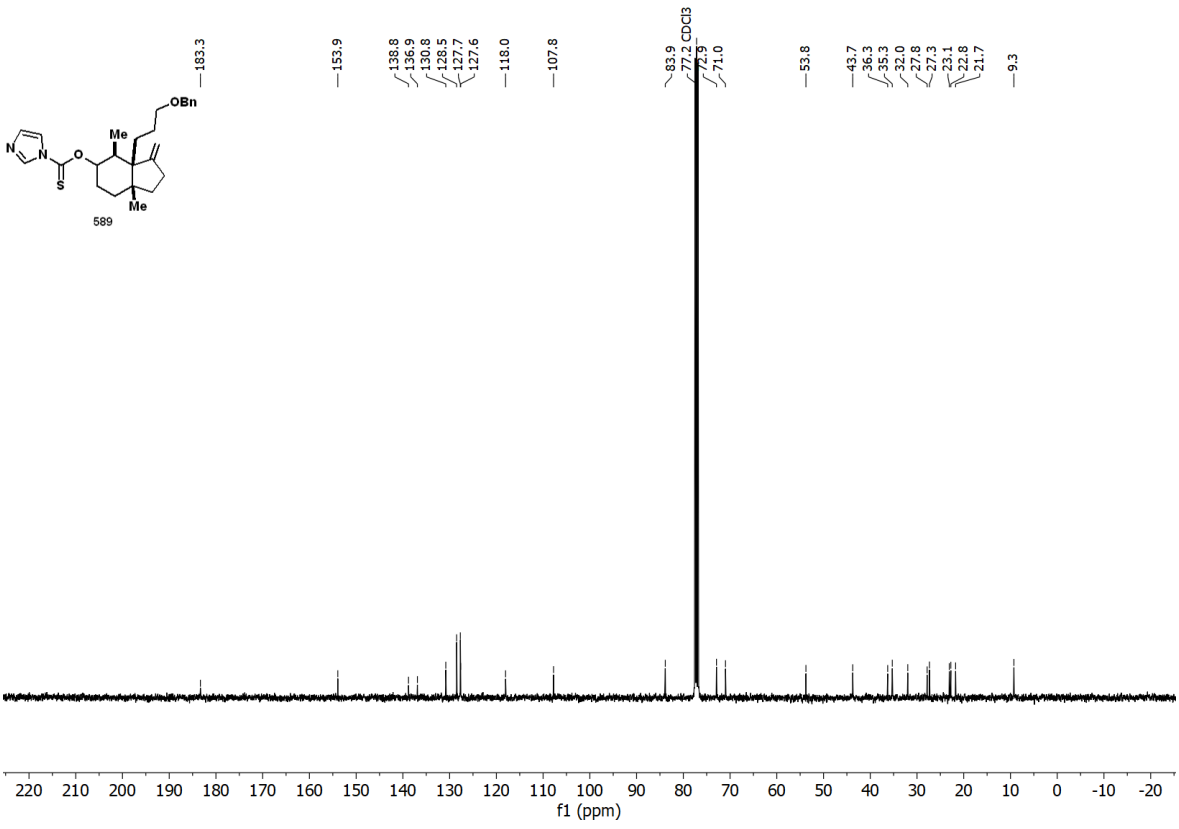

OBn
Me
O
Me
261
7.36
7.26 CDCl3
7.25
4.93
4.73
4.48
3.45
3.36
2.52
2.31
1.91
1.76
1.57
1.35
1.10
1.08
4.84
1.01
1.02
2.00
2.07
5.09
3.10
5.07
3.04
3.15
f1 (ppm)

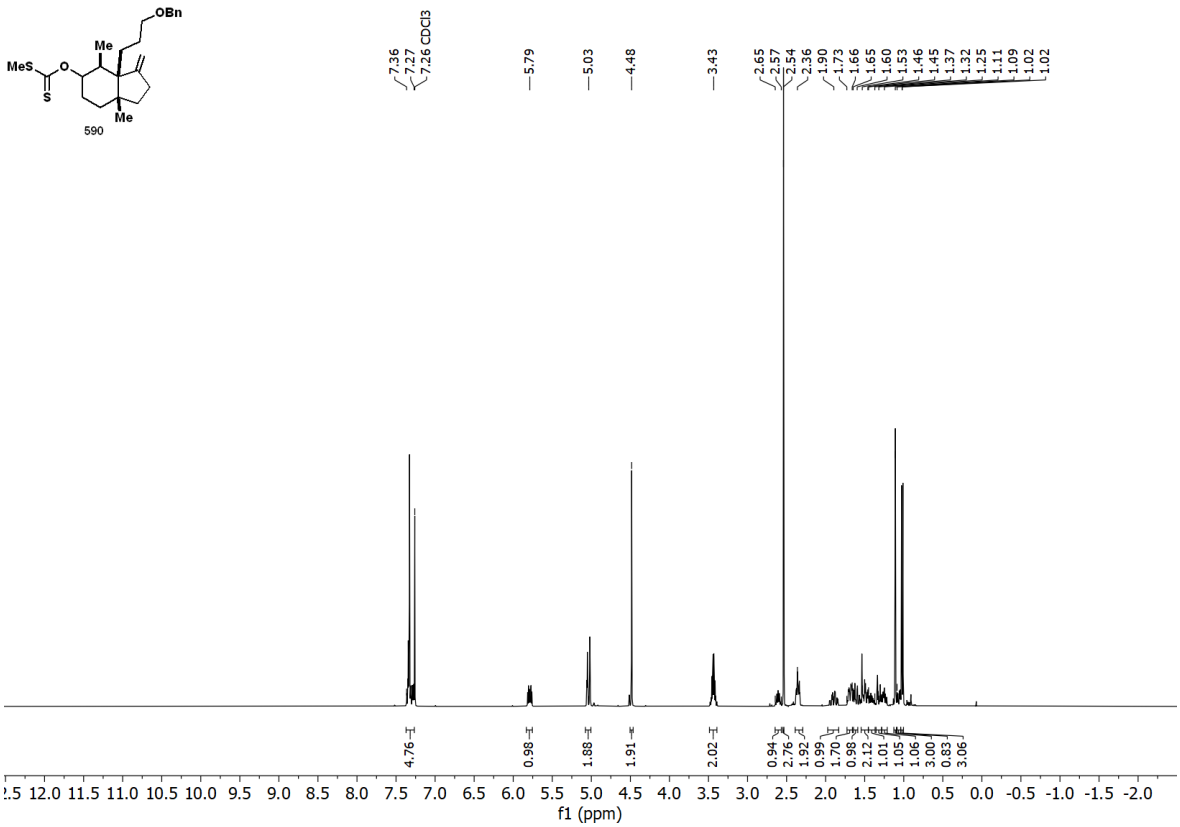

OBn
Me
O
Me
261
214.5
156.4
138.8
128.5
127.7
127.6
108.4
77.3 CDCl3
72.9
71.1
56.1
46.4
44.1
36.1
36.0
34.5
28.0
27.0
24.1
23.3
11.2
f1 (ppm)

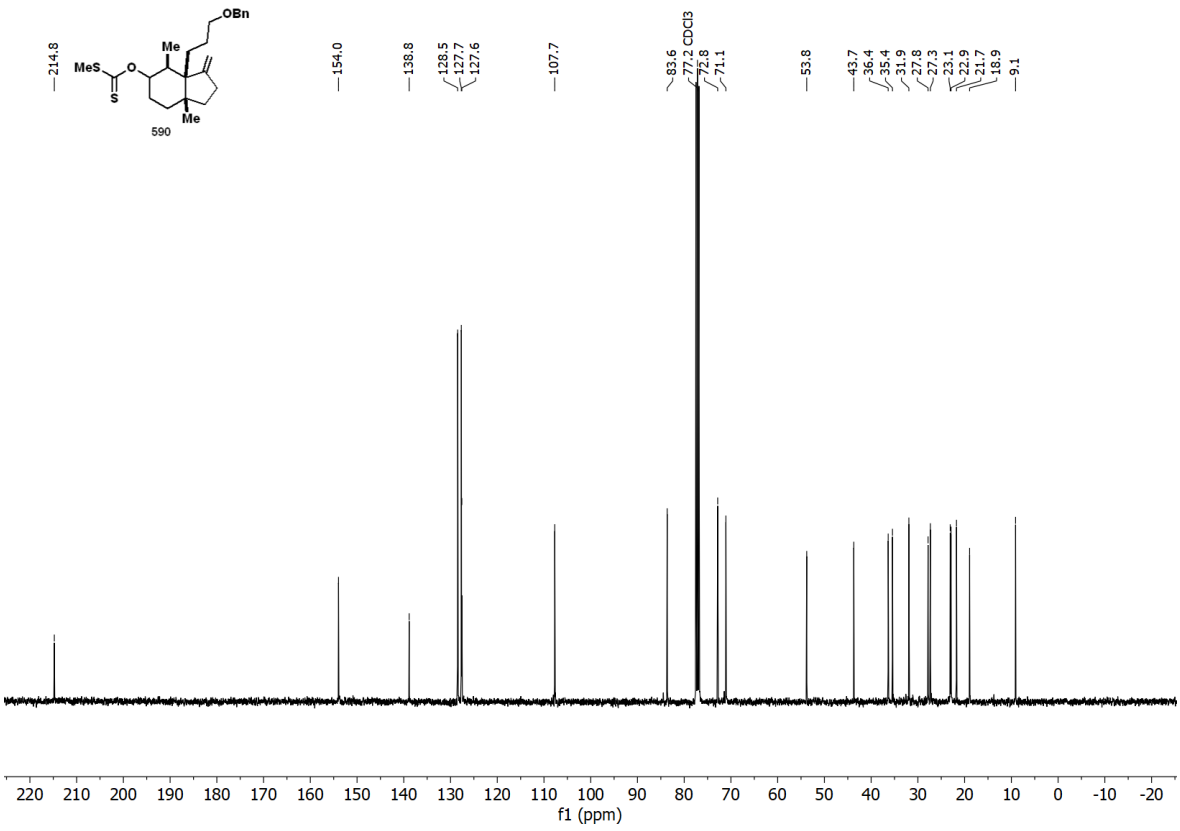

OBn
Me
HO
Me
279
7.37
7.26
7.26 CDCl3
4.96
4.75
4.50
3.96
3.45
2.37
2.31
2.21
2.14
1.70
1.61
1.60
1.51
1.50
1.36
1.26
1.17
1.06
0.99
4.77
0.95
0.95
2.01
0.92
1.96
1.94
0.94
1.97
2.08
3.95
2.02
2.96
3.00
f1 (ppm)

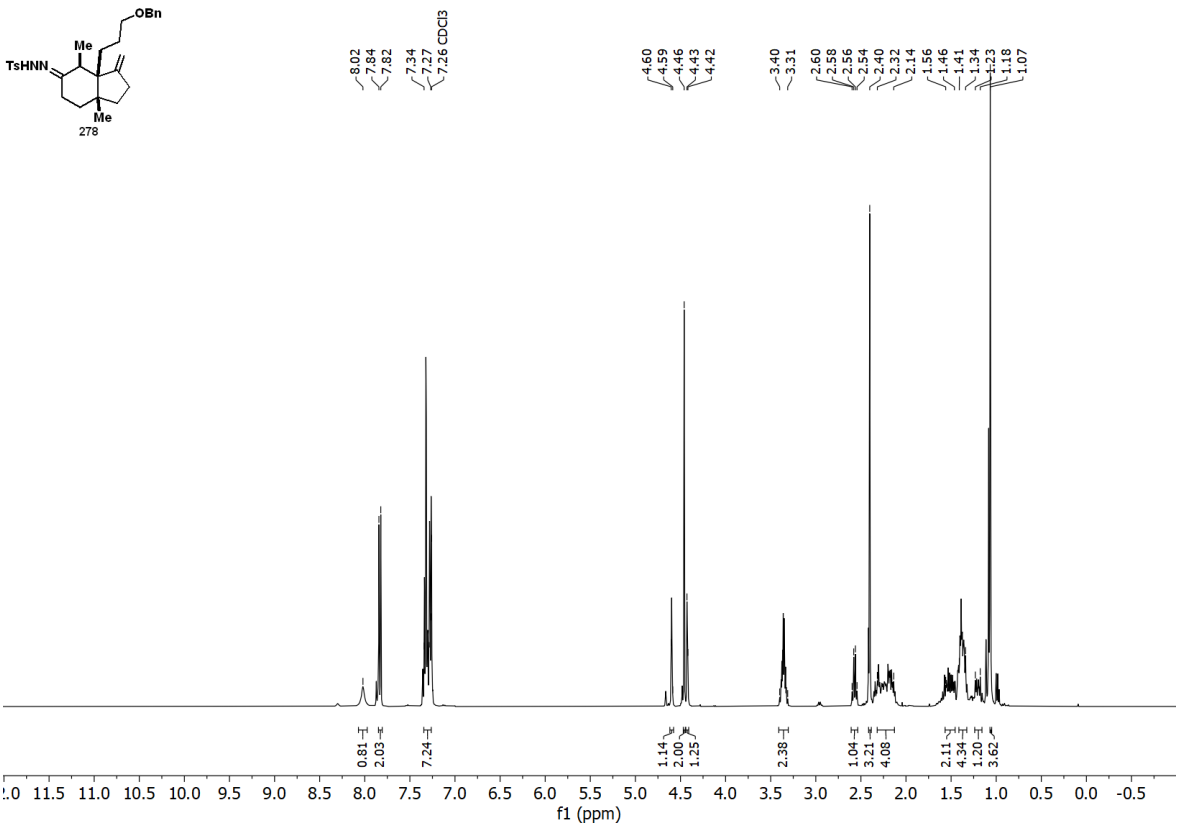

OBn
Me
HO
Me
279
155.2
138.8
128.5
127.7
127.6
106.6
77.2 CDCl3
73.0
72.8
71.2
69.5
53.3
44.7
43.8
36.2
35.9
35.6
28.4
28.0
27.5
26.6
23.1
21.9
7.7
f1 (ppm)

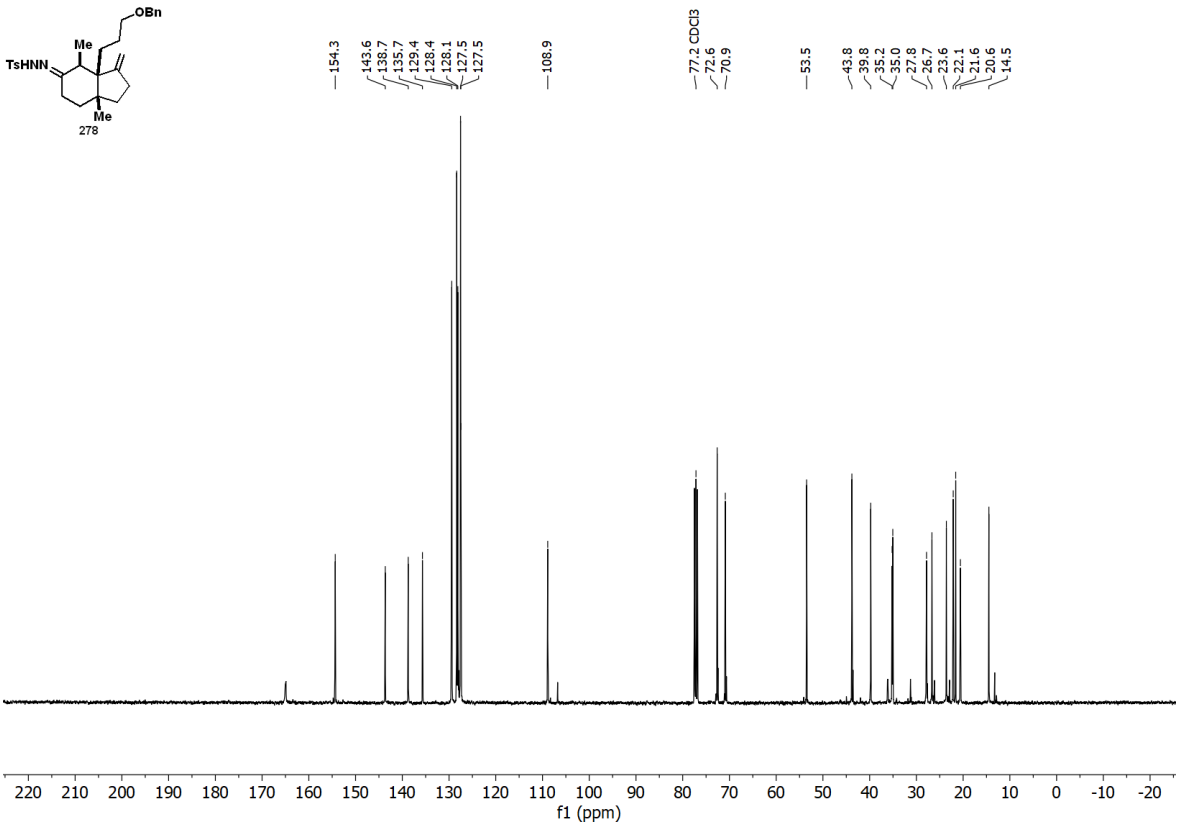

OBn
Me
Me
N
O
S
589
8.33
7.63
7.36
7.27
7.26 CDCl3
7.03
5.76
5.06
4.49
3.49
3.40
2.63
2.39
1.95
1.80
1.73
1.71
1.62
1.60
1.46
1.45
1.35
1.32
1.25
1.13
1.07
0.93
0.97
5.03
0.98
0.98
2.02
2.04
2.07
0.97
2.02
1.00
1.28
1.93
3.09
2.29
2.30
3.38
3.49
f1 (ppm)

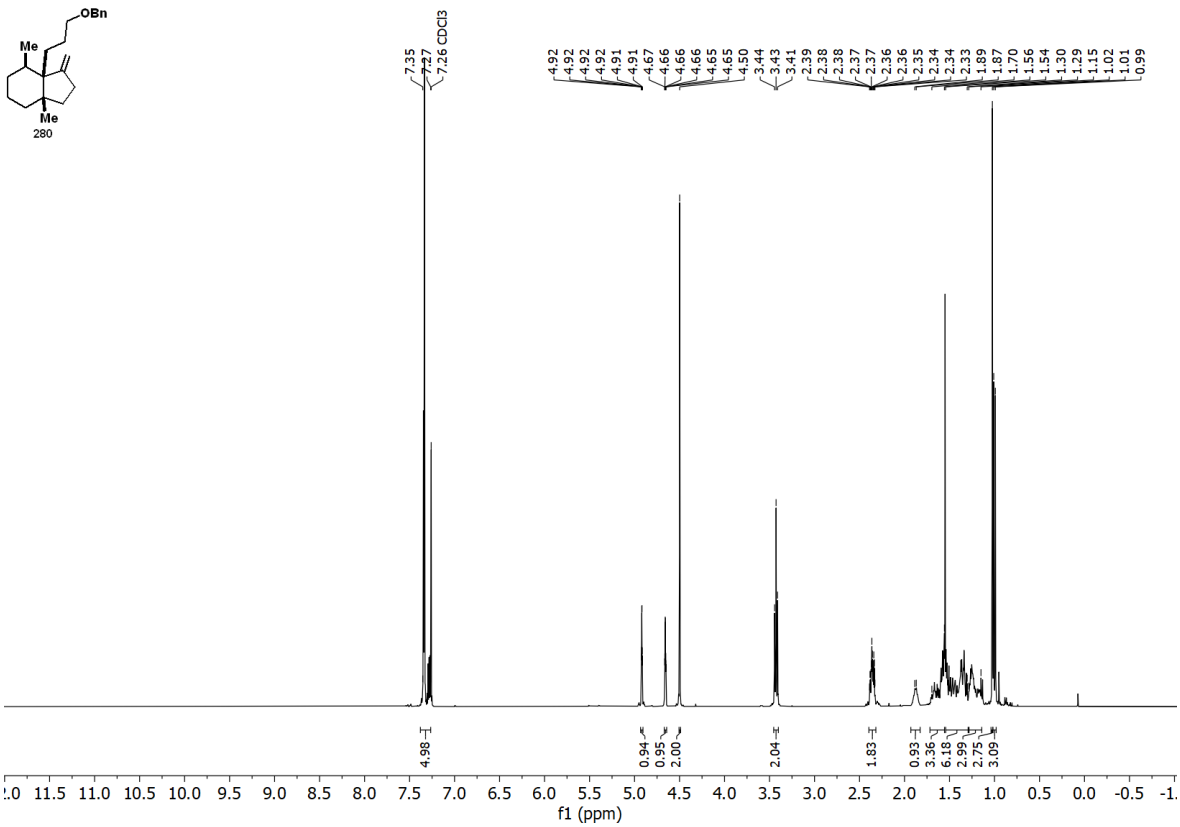

OBn
Me
Me
N
O
S
589
183.3
153.9
138.8
136.9
130.8
128.5
127.7
127.6
118.0
107.8
83.9
77.2 CDCl3
72.9
71.0
53.8
43.7
36.3
35.3
32.0
27.8
27.3
23.1
22.8
21.7
9.3
f1 (ppm)

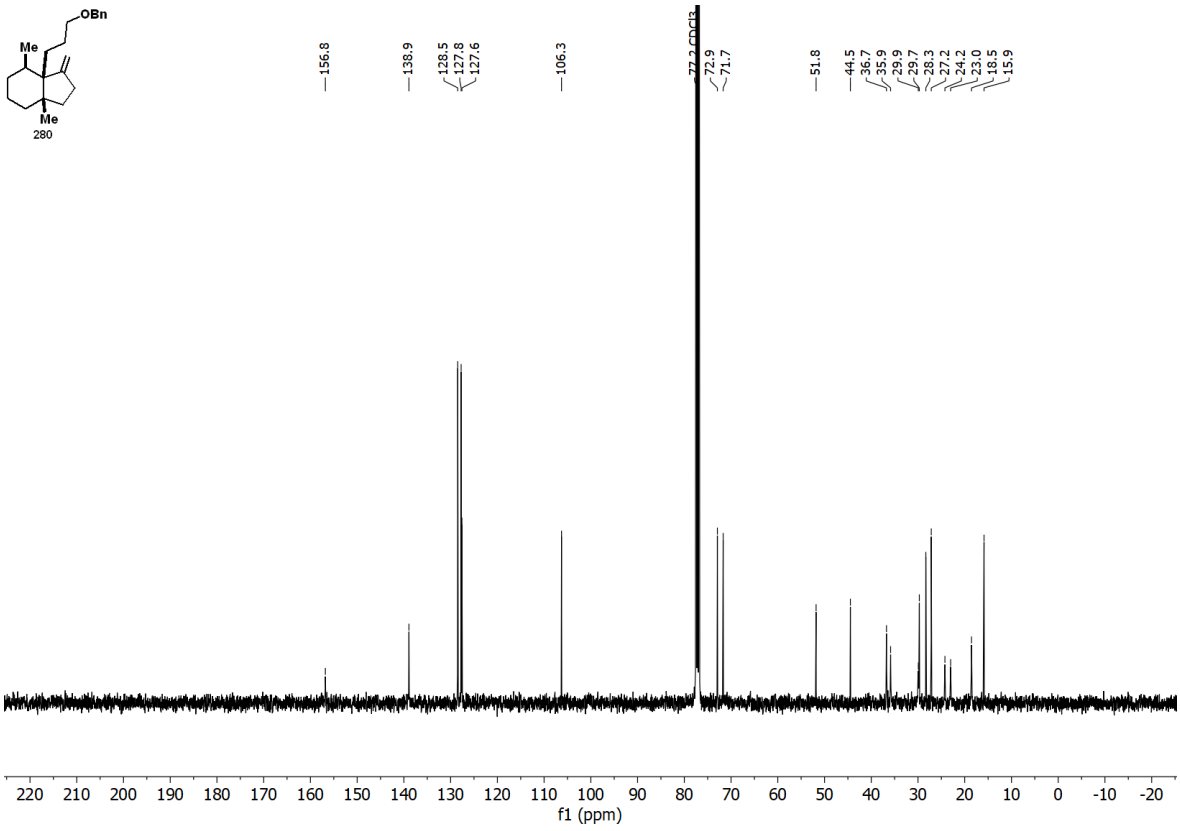

OBn
Me
MeS
O
S
Me
590
7.36
7.27
7.26 CDCl3
5.79
5.03
4.48
3.43
2.65
2.57
2.54
2.36
1.90
1.73
1.66
1.65
1.60
1.53
1.46
1.45
1.37
1.32
1.25
1.11
1.09
1.02
1.02
4.76
0.98
1.88
1.91
2.02
0.94
2.76
1.92
0.99
1.70
0.98
2.12
1.01
1.05
1.06
3.00
0.83
3.06
f1 (ppm)

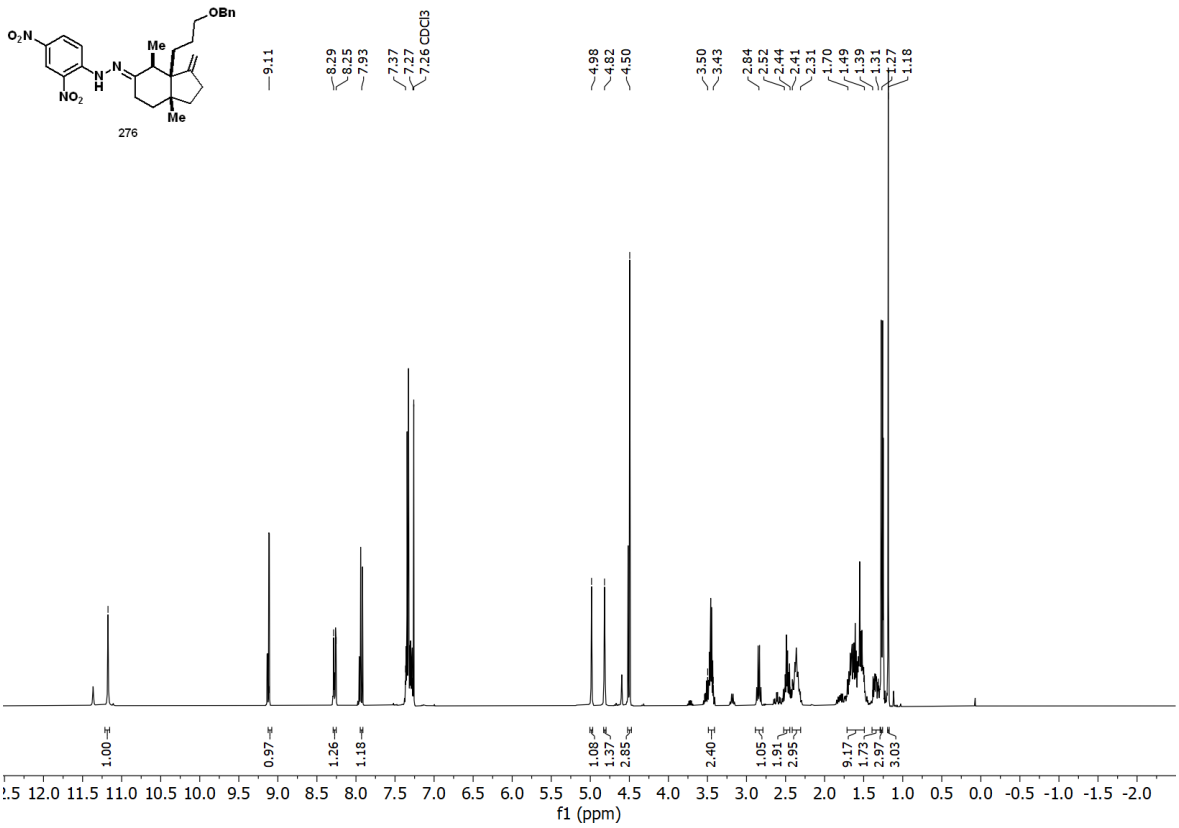

OBn
Me
MeS
O
S
Me
590
214.8
154.0
138.8
128.5
127.7
127.6
107.7
83.6
77.2 CDCl3
72.8
71.1
53.8
43.7
36.4
35.4
31.9
27.8
27.3
23.1
22.9
21.7
18.9
9.1
f1 (ppm)

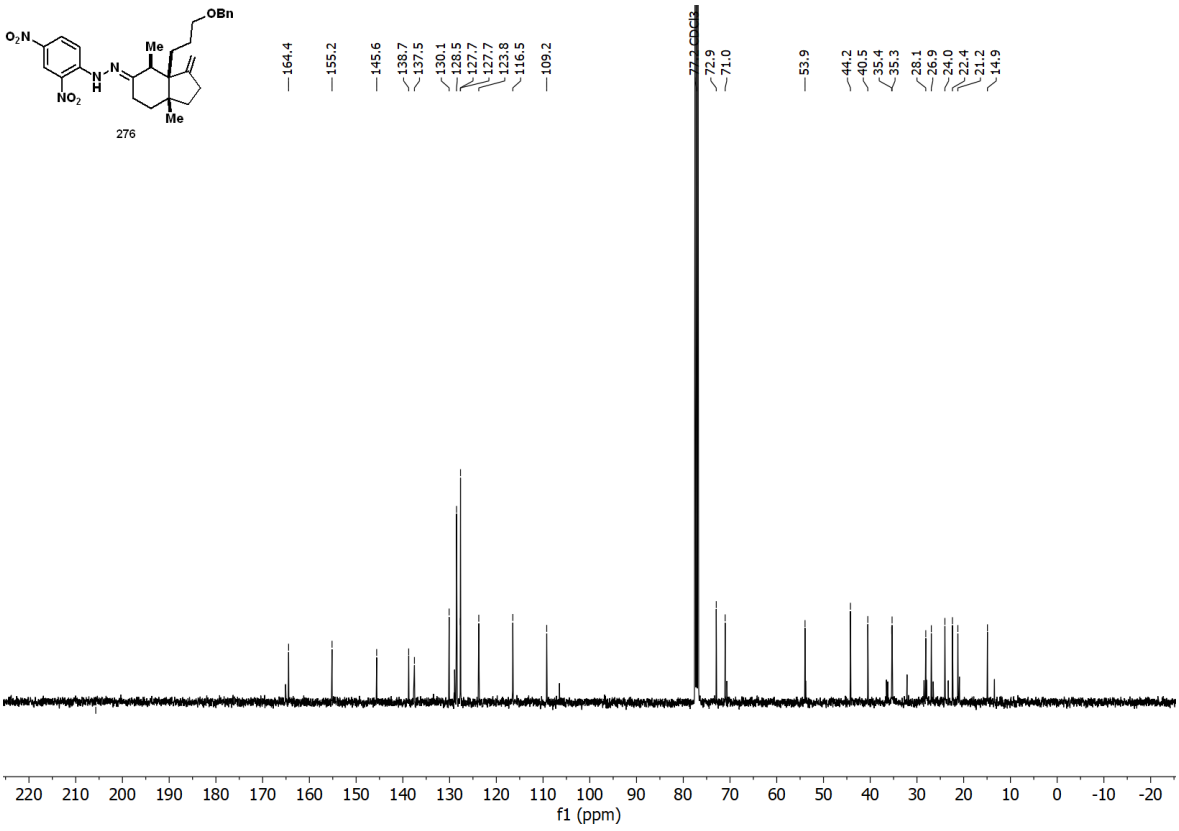

OBn
Me
TsHNN
Me
278
8.02
7.84
7.82
7.34
7.27
7.26 CDCl3
4.60
4.59
4.46
4.43
4.42
3.40
3.31
2.60
2.58
2.56
2.54
2.40
2.32
2.14
1.56
1.46
1.41
1.34
1.23
1.18
1.07
0.81
2.03
7.24
1.14
2.00
1.25
2.38
1.04
3.21
4.08
2.11
4.34
1.20
3.62
f1 (ppm)

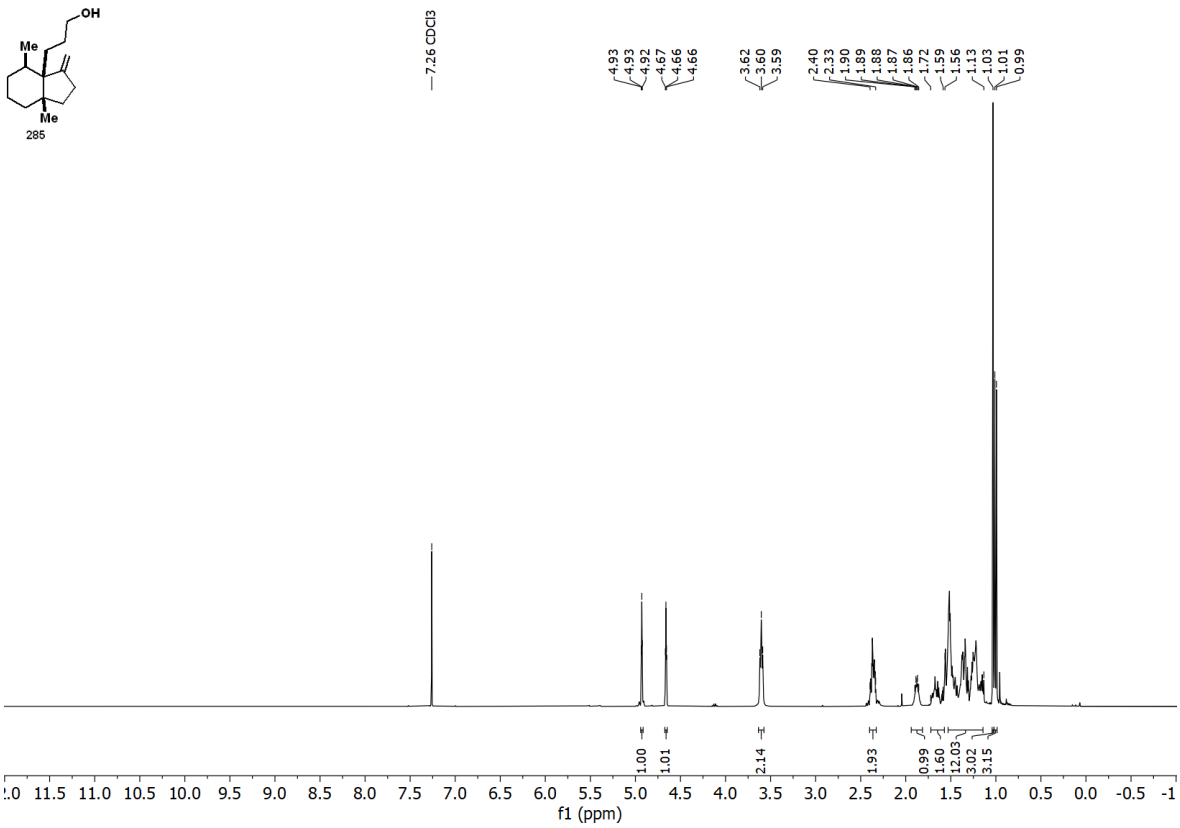

OBn
Me
TsHNN
Me
278
154.3
143.6
138.7
135.7
129.4
128.4
128.1
127.5
127.5
108.9
77.2 CDCl3
72.6
70.9
53.5
43.8
39.8
35.2
35.0
27.8
26.7
23.6
22.1
21.6
20.6
14.5
f1 (ppm)

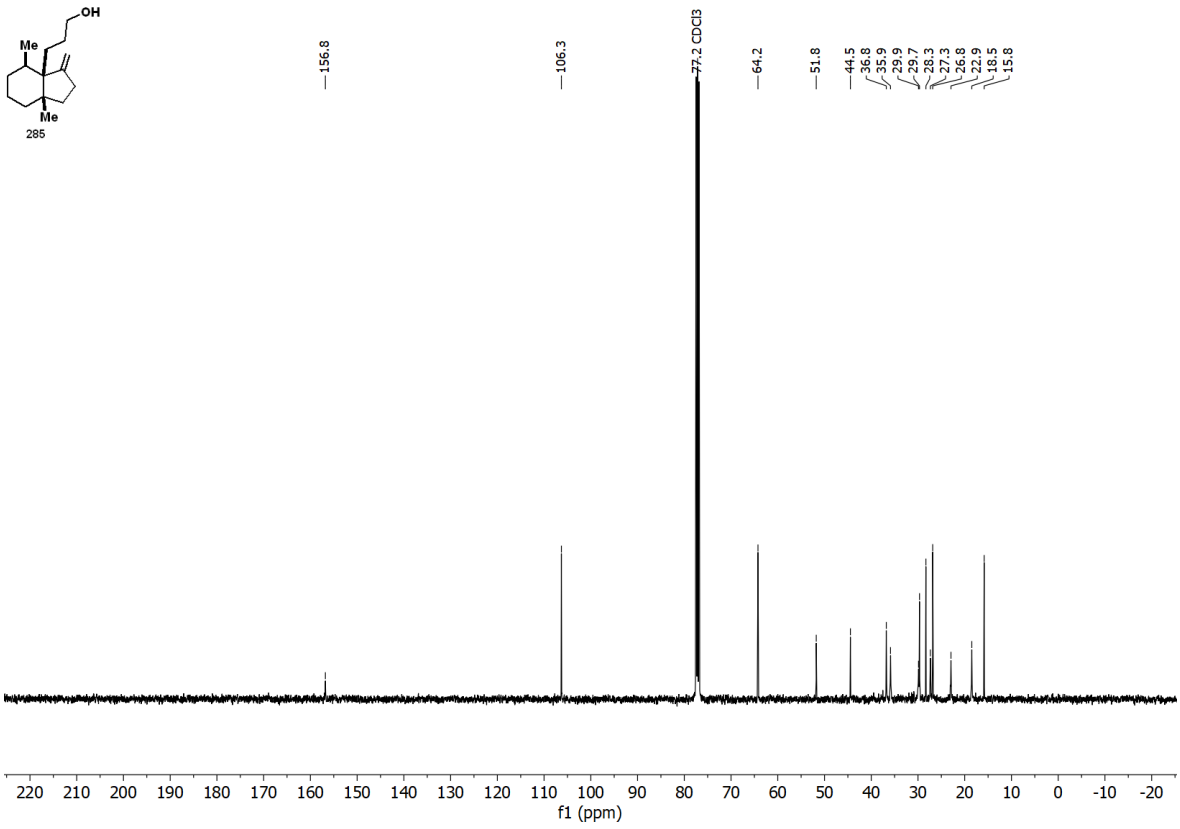

OBn
Me
Me
280
7.35
7.27
7.26 CDCl3
4.92
4.92
4.92
4.92
4.91
4.91
4.67
4.66
4.66
4.66
4.65
4.65
4.50
3.44
3.43
3.41
2.39
2.38
2.38
2.37
2.37
2.36
2.36
2.35
2.34
2.34
2.33
1.89
1.87
1.70
1.56
1.54
1.30
1.29
1.15
1.02
1.01
0.99
4.98
0.94
0.95
2.00
2.04
1.83
0.93
3.36
6.18
2.99
2.75
3.09
f1 (ppm)

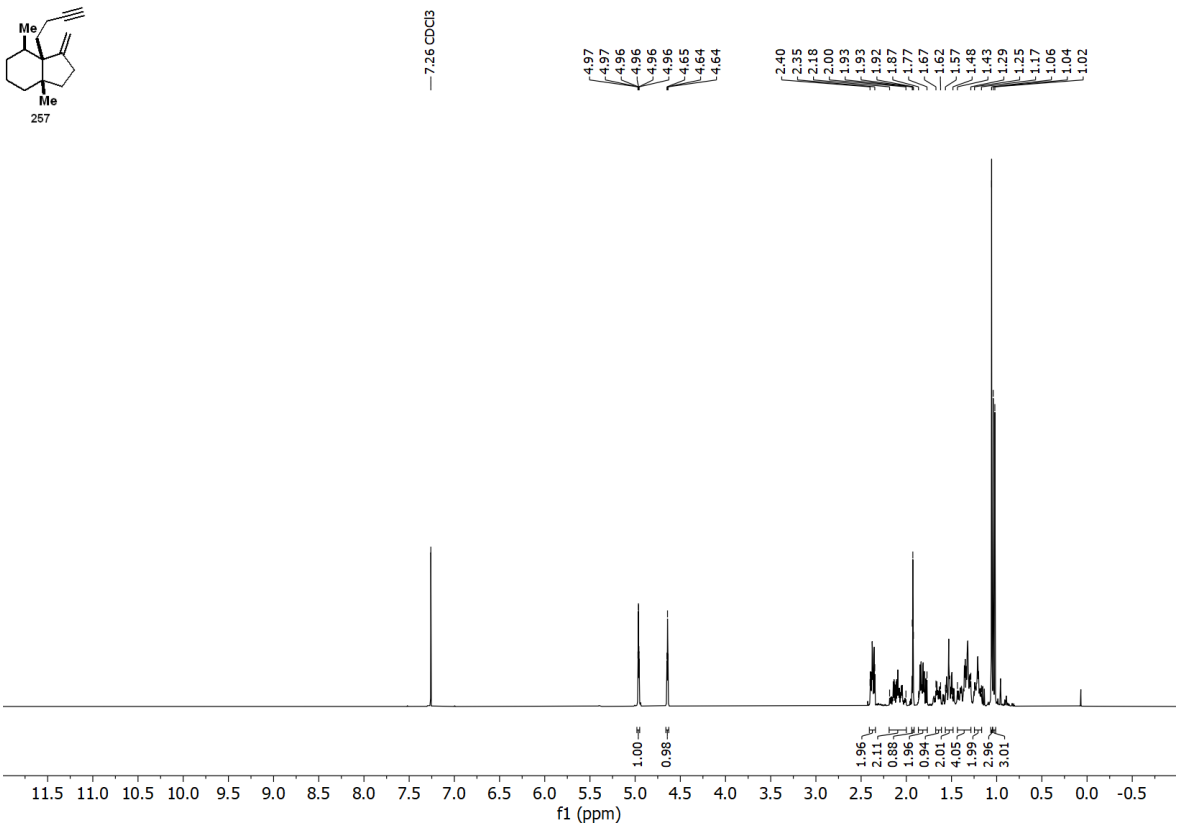

OBn
Me
Me
280
156.8
138.9
128.5
127.8
127.6
106.3
77.2 CDCl3
72.9
71.7
51.8
44.5
36.7
35.9
29.9
29.7
28.3
27.2
24.2
23.0
18.5
15.9
f1 (ppm)

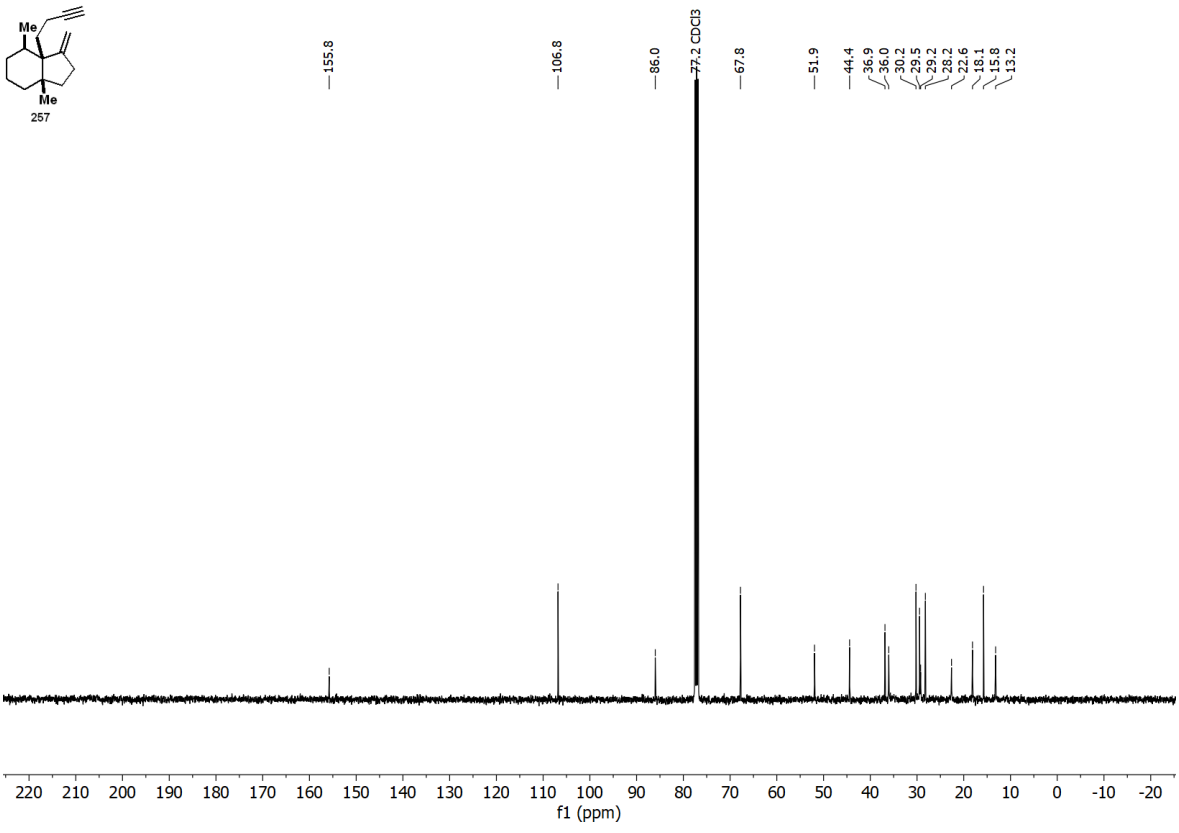

276
9.11
8.29
8.25
7.93
7.37
7.27
7.26 CDCl3
4.98
4.82
4.50
3.50
3.43
2.84
2.52
2.44
2.41
2.31
1.70
1.49
1.39
1.31
1.27
1.18
1.00
0.97
1.26
1.18
1.08
1.37
2.85
2.40
1.05
1.91
2.95
9.17
1.73
2.97
3.03
f1 (ppm)

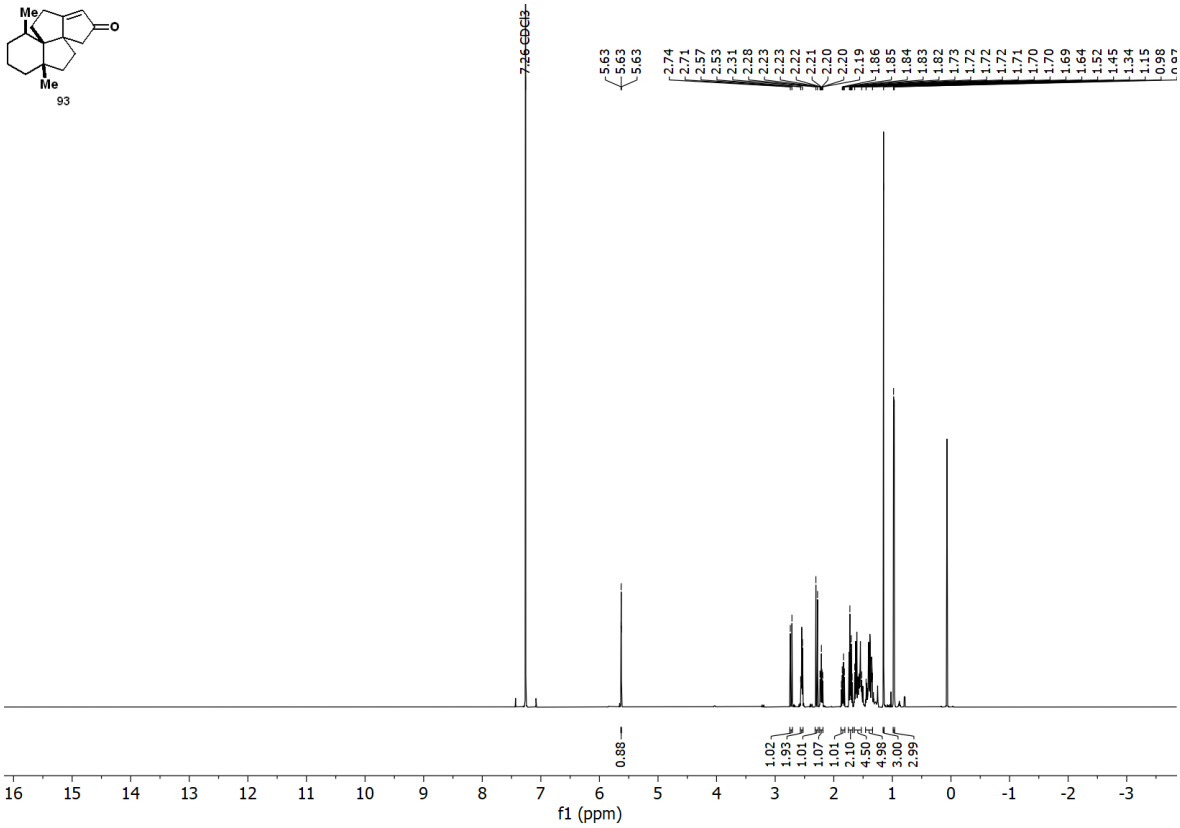

276
164.4
155.2
145.6
138.7
137.5
130.1
128.5
127.7
127.7
123.8
116.5
109.2
77.3 CDCl3
72.9
71.0
53.9
44.2
40.5
35.4
35.3
28.1
26.9
24.0
22.4
21.2
14.9
f1 (ppm)

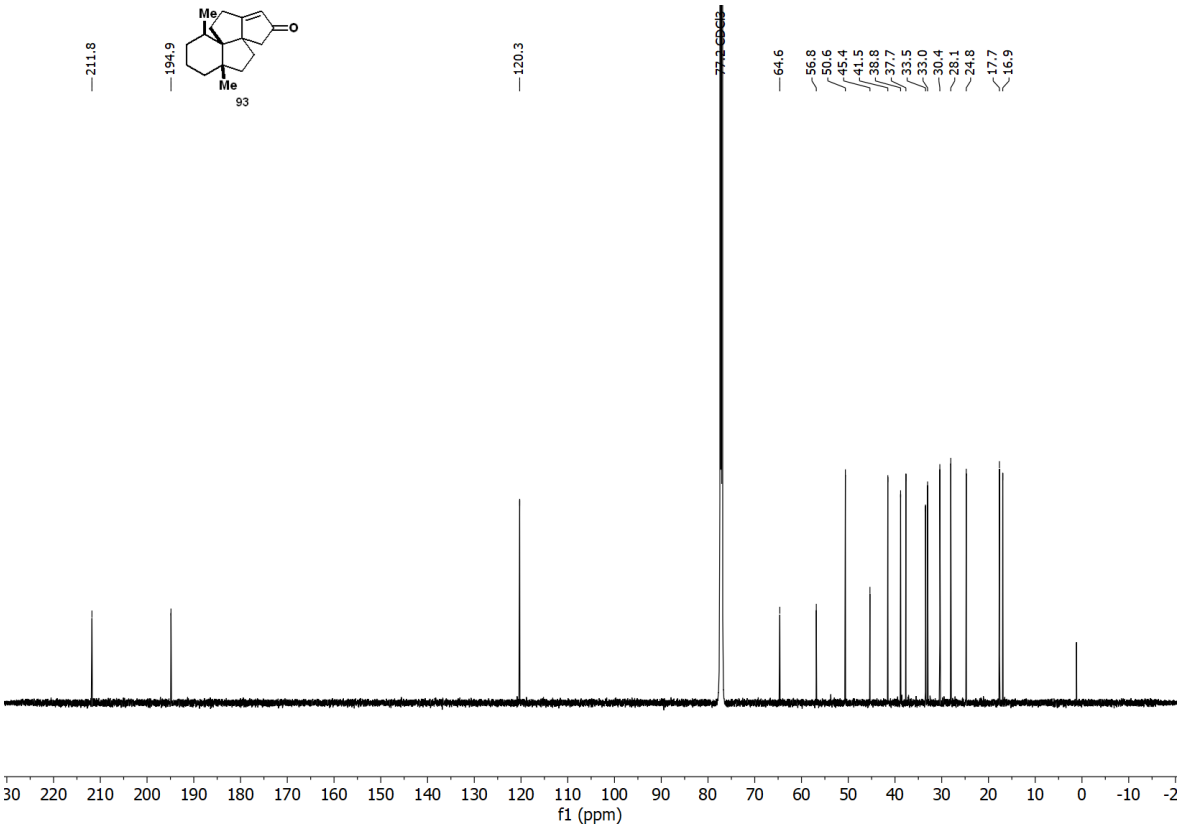

OH
Me
Me
285
7.26 CDCl3
4.93
4.93
4.92
4.67
4.66
4.66
3.62
3.60
3.59
2.40
2.33
1.90
1.89
1.88
1.87
1.86
1.72
1.59
1.56
1.13
1.03
1.01
0.99
1.00
1.01
2.14
1.93
0.99
1.60
12.03
3.02
3.15
f1 (ppm)

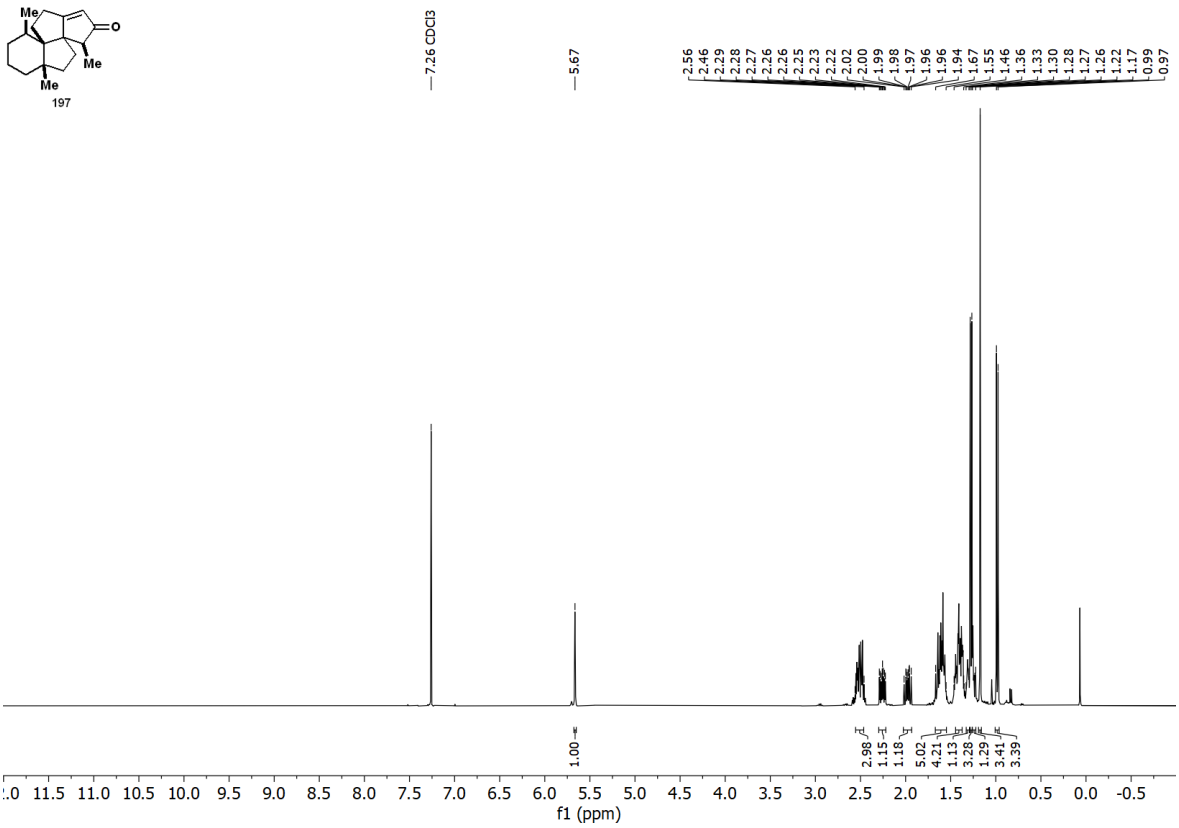

OH
Me
Me
285
156.8
106.3
77.2 CDCl3
64.2
51.8
44.5
36.8
35.9
29.9
29.7
28.3
27.3
26.8
22.9
18.5
15.8
f1 (ppm)

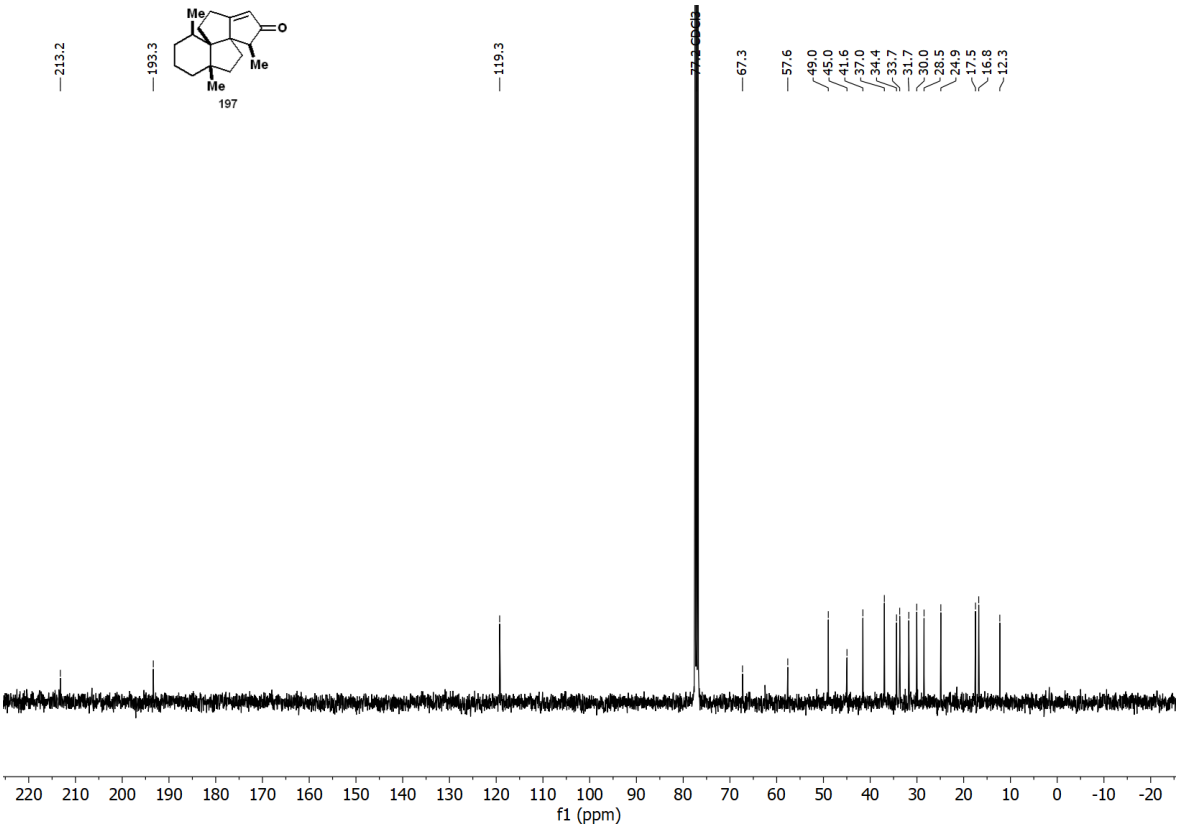

Me
Me
257
7.26 CDCl3
4.97
4.97
4.96
4.96
4.96
4.65
4.64
4.64
2.40
2.35
2.18
2.00
1.93
1.93
1.92
1.87
1.77
1.67
1.62
1.57
1.48
1.43
1.29
1.25
1.17
1.06
1.04
1.02
1.00
0.98
1.96
2.11
0.88
1.96
0.94
2.01
4.05
1.99
2.96
3.01
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


Me
Me
257
155.8
106.8
86.0
77.2 CDCl3
67.8
51.9
44.4
36.9
36.0
30.2
29.5
29.2
28.2
22.6
18.1
15.8
13.2
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

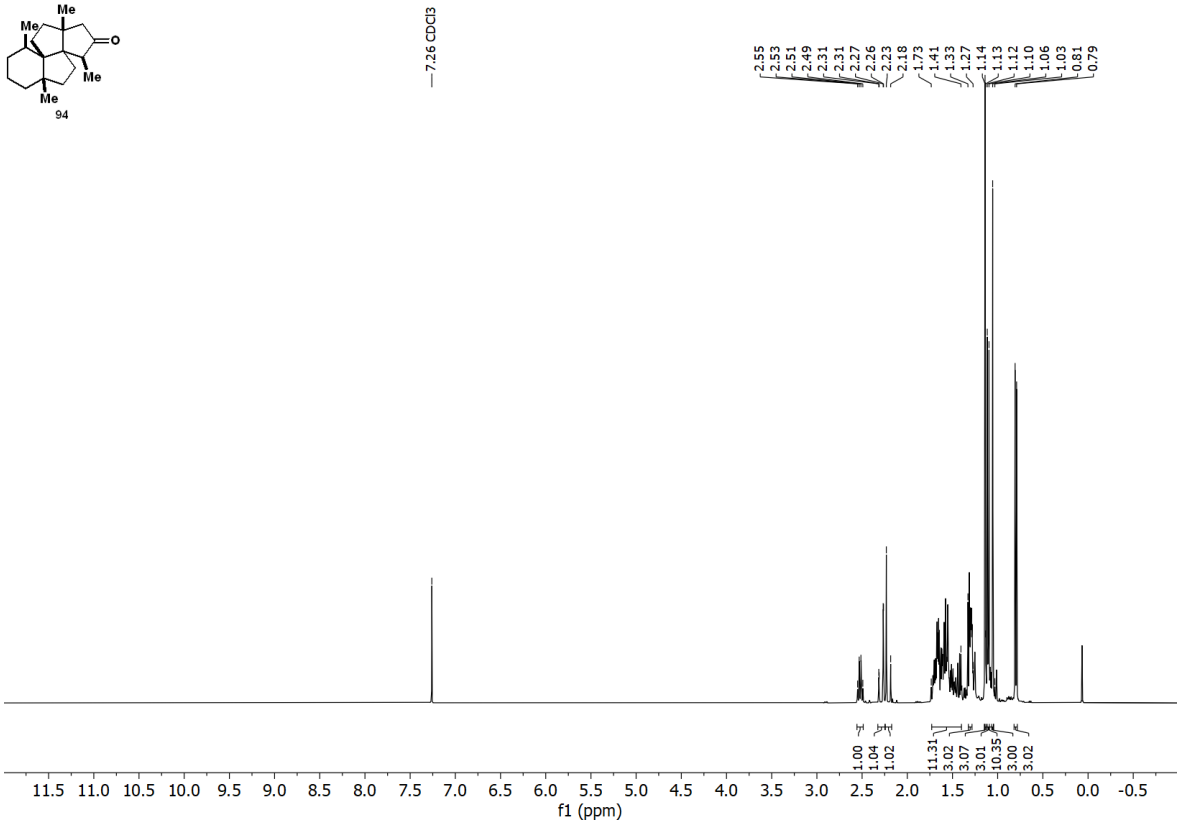

Me
O
Me
93
7.26 CDCl3
5.63
5.63
5.63
2.74
2.71
2.57
2.53
2.31
2.28
2.23
2.23
2.22
2.21
2.20
2.20
2.19
1.86
1.85
1.84
1.83
1.82
1.73
1.72
1.72
1.72
1.71
1.70
1.70
1.69
1.64
1.52
1.45
1.34
1.15
0.98
0.88
1.02
1.93
1.01
1.07
1.01
2.10
4.50
4.98
3.00
2.99
f1 (ppm)


211.8
194.9
Me
O
Me
93
120.3
77.3 CDCl3
64.6
56.8
50.6
45.4
41.5
38.8
37.7
33.5
33.0
30.4
28.1
24.8
17.7
16.9
f1 (ppm)

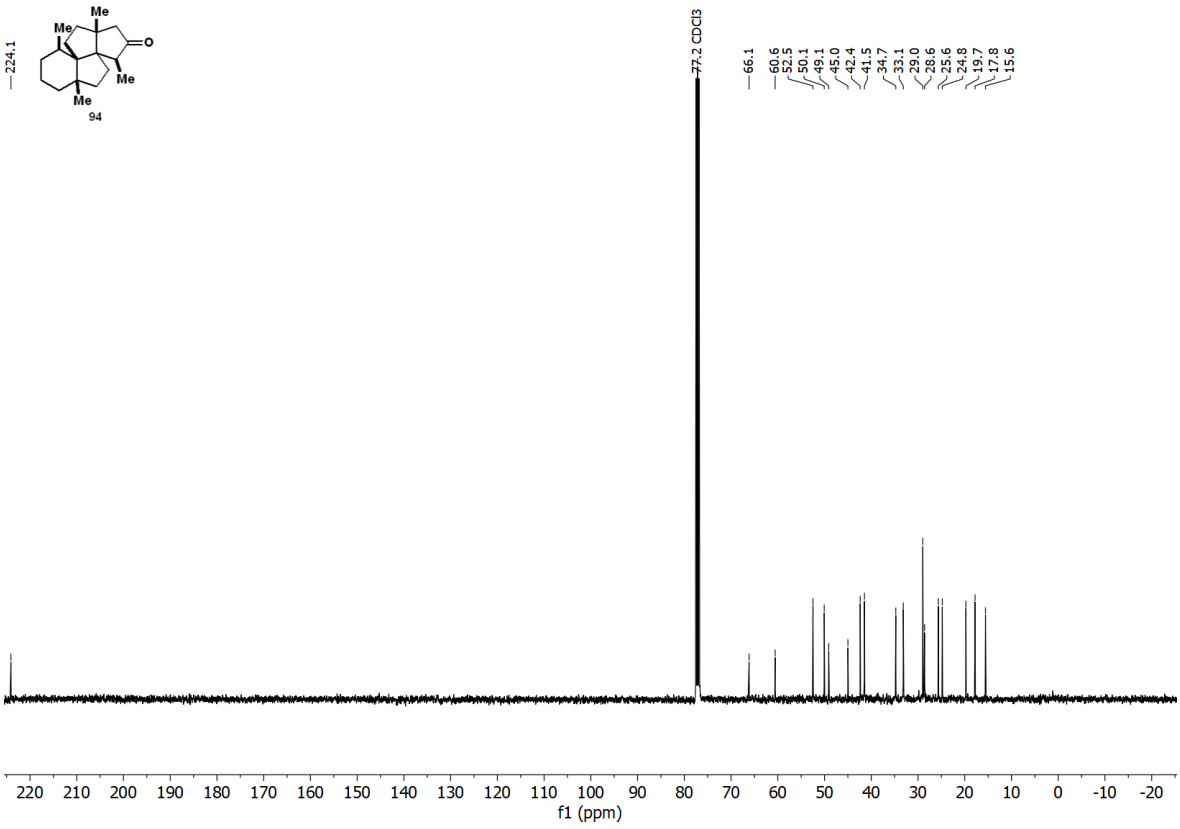

Me
O
Me
Me
197
7.26 CDCl3
5.67
2.56
2.46
2.29
2.28
2.27
2.26
2.26
2.25
2.23
2.22
2.02
2.00
1.99
1.98
1.97
1.96
1.96
1.94
1.67
1.55
1.46
1.36
1.33
1.30
1.28
1.27
1.26
1.22
1.17
0.99
0.97
1.00
2.98
1.15
1.18
5.02
4.21
1.13
3.28
1.29
3.41
3.39
f1 (ppm)


213.2
193.3
Me
O
Me
Me
197
119.3
77.3 CDCl3
67.3
57.6
49.0
45.0
41.6
37.0
34.4
33.7
31.7
30.0
28.5
24.9
17.5
16.8
12.3
f1 (ppm)

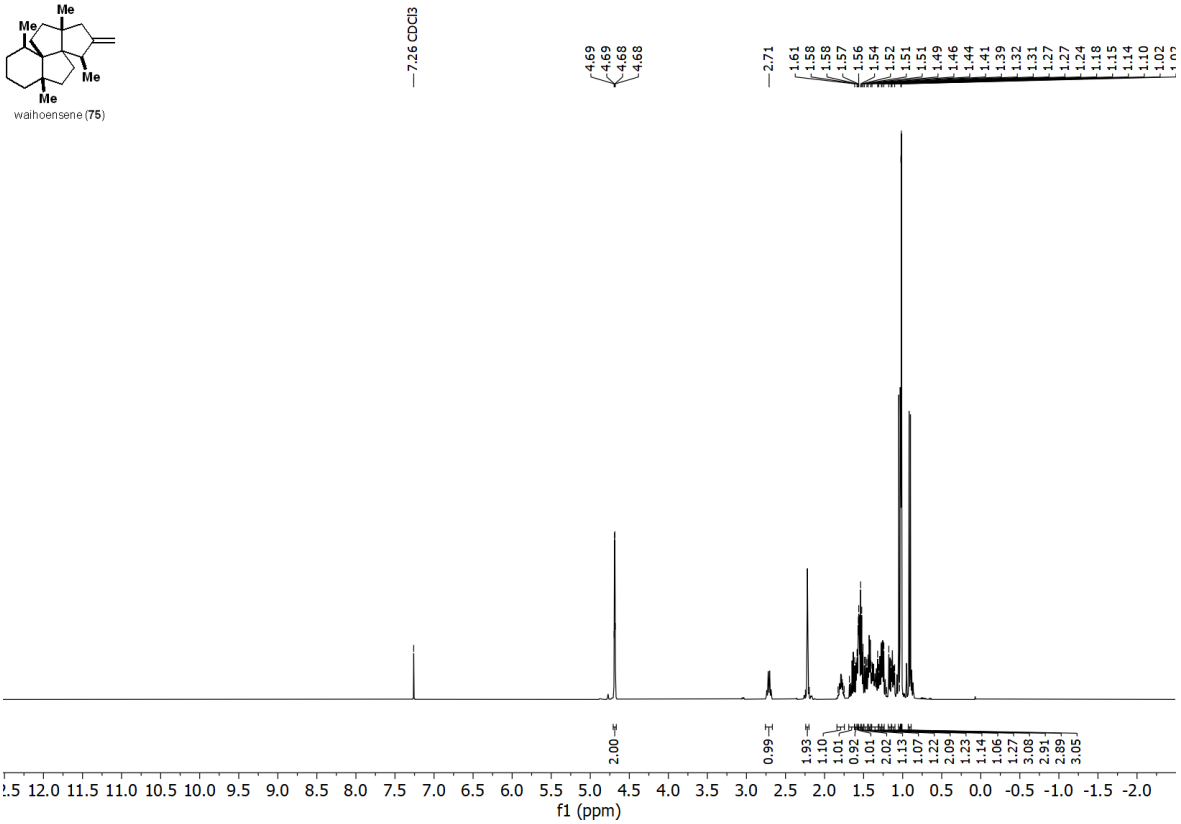
Me
Me
O
Me
Me
94


7.26 CDCl3
2.55
2.53
2.51
2.49
2.31
2.31
2.27
2.26
2.23
2.18
1.73
1.41
1.33
1.27
1.14
1.13
1.12
1.10
1.06
1.03
0.81
0.79
1.00
1.04
1.02
11.31
3.02
3.07
3.01
10.35
3.00
3.02
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

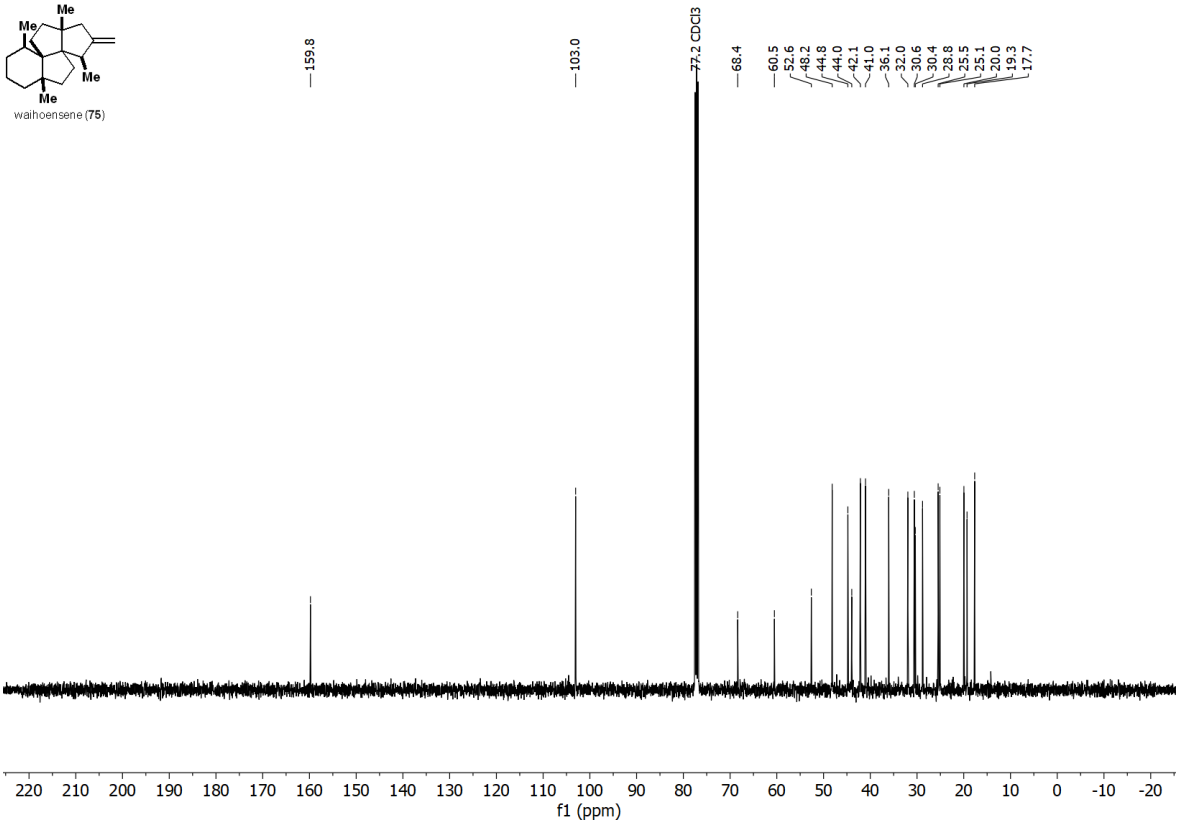
224.1
Me
Me
O
Me
Me
Me
94


77.2 CDCl3
66.1
60.6
52.5
50.1
49.1
45.0
42.4
41.5
34.7
33.1
29.0
28.6
25.6
24.8
19.7
17.8
15.6
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

waihoensene (**75**)



waihoensene (**75**)



3.1.5 X-Ray Crystallography

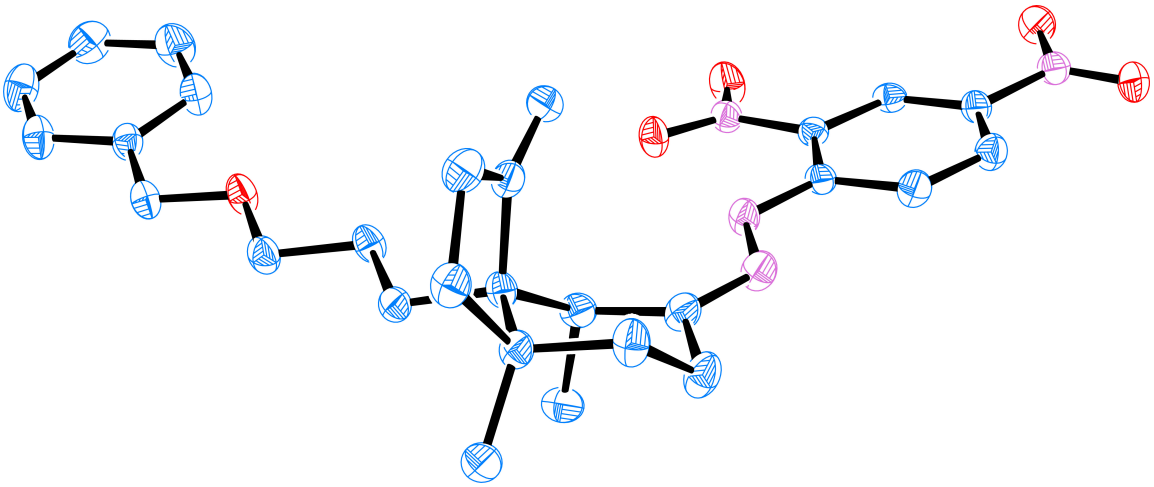


Figure S1. ORTEP of **276** with ellipsoid drawn at the 50% level and hydrogens omitted for clarity; only one stereoisomer shown. CCDC 2016640 contains the supplementary crystallographic data.

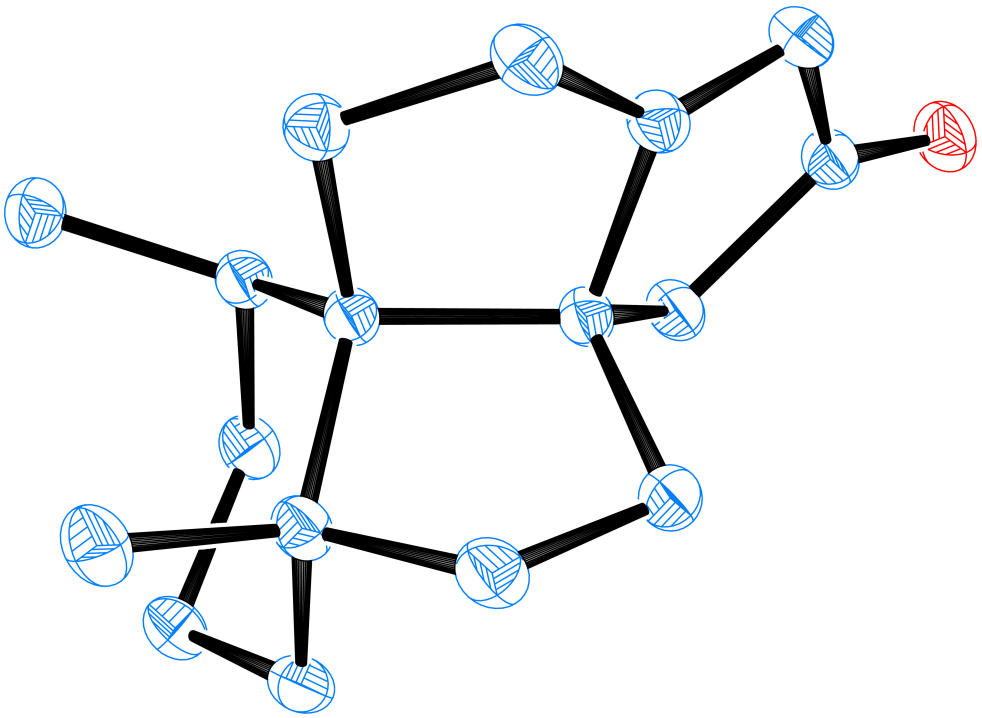


Figure 2. ORTEP of **93** with ellipsoid drawn at the 50% level and hydrogens omitted for clarity; only one stereoisomer shown. CCDC 2016641 contains the supplementary crystallographic data.

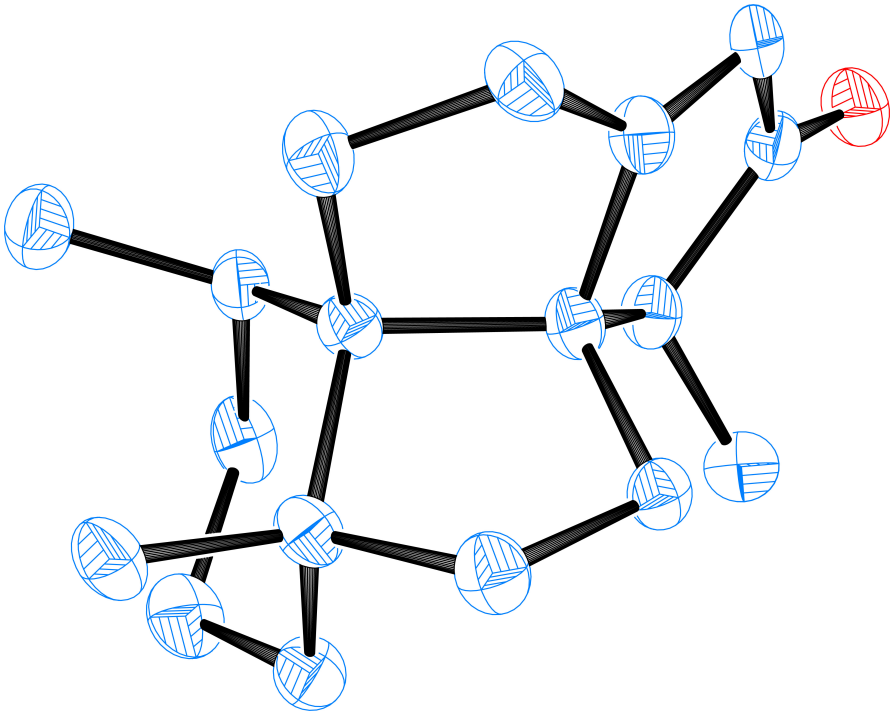
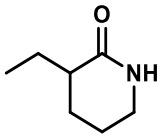


Figure 3. ORTEP of **197** with ellipsoid drawn at the 50% level and hydrogens omitted for clarity; only one stereoisomer shown. CCDC 2016642 contains the supplementary crystallographic data.

3.2 Studies Toward the Syntheses of Vallesamidine and Lyconadin C

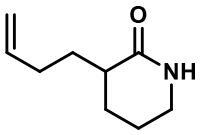
3.2.1 An Approach Toward the Synthesis of Vallesamidine

3-ethylpiperidin-2-one (520)[196]



In a flame-dried Schlenk flask, 2-piperidone (**519**) (7.00 g, 70.6 mmol, 1.00 eq.) was dissolved in THF (150 mL, 0.45 M) and the solution was cooled to -78 °C. *n*-BuLi (2.5 M in hexanes, 57 mL, 142 mmol, 2.01 eq.) was added dropwise and the reaction was warmed to 0 °C and stirred for 1 h. Iodoethane (8.5 mL, 106 mmol, 1.50 eq.) was added dropwise and the mixture was kept for 45 min at this temperature. The reaction was quenched by the addition of saturated NH_4Cl solution and extracted with DCM. The combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was subjected to column chromatography on silica gel (100% EA). The desired compound was obtained as a colorless solid in 86% yield (7.76 g, 61.0 mmol). The obtained spectroscopic data were consistent with those reported in literature. $\mathbf{R_F}$ = 0.24 (100% EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*) δ [ppm] = 6.30 (bs, 1H), 3.35 – 3.20 (m, 2H), 2.20 (tdd, *J* = 9.0, 6.1, 4.1 Hz, 1H), 1.99 – 1.88 (m, 2H), 1.88 – 1.80 (m, 1H), 1.77 – 1.62 (m, 1H), 1.62 – 1.45 (m, 2H), 0.94 (t, *J* = 7.5 Hz, 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*) δ [ppm] = 175.2, 42.6, 42.5, 25.6, 24.5, 21.5, 11.5.

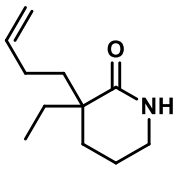
3-(but-3-en-1-yl)piperidin-2-one (521)[228]



In a flame-dried Schlenk flask, *n*-BuLi (2.5 M solution in hexanes, 18 mL, 44.4 mmol, 2.20 eq.) was added to a solution of 2-piperidone (**519**) (2.00 g, 20.2 mmol, 1.00 eq.) in THF (68 mL, 0.3 M) at -78 °C. The reaction was warmed to 0 °C, stirred for 1 h at this temperature and re-cooled to -78 °C. 4-Bromo-1-butene (2.3 mL, 22.2 mmol, 1.10 eq.) was added dropwise and after complete addition, the cooling bath was removed and the mixture was warmed to room temperature and stirred overnight. The reaction was quenched by the addition of aqueous saturated NH_4Cl and the mixture was extracted with EA. The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was subjected to column chromatography on silica gel (30:1 DCM/MeOH) to give **521** as a colorless solid in 79% yield (2.43 g, 15.9 mmol). The obtained spectroscopic data were

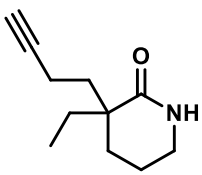
consistent with those reported in literature[229]. **^{1}H-NMR** (400 MHz, Chloroform-*D*) δ [ppm] = 5.87 (bs, 1H), 5.82 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.08 – 4.93 (m, 2H), 3.36 – 3.22 (m, 2H), 2.29 (tdd, *J* = 9.4, 6.0, 4.0 Hz, 1H), 2.24 – 2.13 (m, 1H), 2.12 – 2.02 (m, 2H), 2.01 – 1.92 (m, 1H), 1.92 – 1.82 (m, 1H), 1.78 – 1.63 (m, 1H), 1.60 – 1.46 (m, 2H); **^{13}C-NMR** (101 MHz, Chloroform-*D*) δ [ppm] = 174.9, 138.4, 115.1, 42.6, 40.6, 31.3, 30.8, 26.2, 21.6.

3-(but-3-en-1-yl)-3-ethylpiperidin-2-one (522)[229]



3-(But-3-en-1-yl)piperidin-2-one (**521**) (2.32 g, 15.2 mmol, 1.00 eq.) was dissolved in THF and the solution was cooled to -78 °C. *n*-BuLi (2.5 M solution in hexanes, 13 mL, 33.4 mmol, 2.20 eq.) was added dropwise and the resulting mixture was transferred to an ice-bath and stirred for 1 h. The reaction was cooled to -78 °C and iodoethane (1.3 mL, 16.7 mmol, 1.10 eq.) was added dropwise. The reaction was allowed to warm to room temperature overnight and was then quenched by aqueous saturated NH_4Cl. The mixture was extracted with EA and the organic phase was dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by gradient column chromatography (70:1 DCM/MeOH, then 10:1 DCM/MeOH) to give the desired alkylated compound in 64% (1.76 g, 9.73 mmol). The obtained spectroscopic data were consistent with those reported in literature. **^{1}H-NMR** (400 MHz, Chloroform-*D*) δ [ppm] = 5.90 – 5.67 (m, 1H), 5.87 (bs, 1H), 5.06 – 4.88 (m, 2H), 3.27 (tdd, *J* = 6.1, 2.4, 1.2 Hz, 2H), 2.17 – 1.96 (m, 2H), 1.84 – 1.66 (m, 6H), 1.59 – 1.46 (m, 2H), 0.89 (tt, *J* = 7.5, 0.8 Hz, 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*) δ [ppm] = 177.1, 139.0, 114.5, 44.8, 42.9, 37.6, 31.2, 29.3, 28.9, 20.1, 8.8.

3-(but-3-yn-1-yl)-3-ethylpiperidin-2-one (517)



Method A: In a flame-dried Schlenk flask, n-BuLi (2.5 M solution in hexanes, 6.6 mL, 16.5 mmol, 2.10 eq.) was added dropwise to a solution of lactam **520** (1.00 g, 7.86 mmol, 1.00 eq.) in THF (18 mL, 0.45 M) at -78 °C. The mixture was warmed to 0 °C for 2 h and re-cooled to -78 °C. Homopropargyl triflate **270** (3.20 g, 15.7 mmol, 2.00 eq.) was added and the reaction was stirred and warmed to room temperature overnight. An aqueous saturated solution of NH_4Cl was added and the mixture was extracted with EA. The combined organic phases were washed

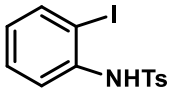
with brine and dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification of the residue by column chromatography on silica gel (100% EA) furnished the desired compound as a pale yellow solid in 30% (392 mg, 2.19 mmol).

Method B: Bromine (0.7 mL, 13.0 mmol, 1.00 eq.) was added dropwise to a solution of **522** (2.15 g, 11.9 mmol, 1.00 eq.) in DCM (50 mL, 0.24 M) and the resulting mixture was stirred for 1 h at room temperature. The solvent was removed under reduced pressure and the crude dibromide was used in the subsequent elimination reaction without purification. In a flame-dried Schlenk flask, diisopropylamine (12 mL, 82.9 mmol, 7.00 eq.) was dissolved in THF (75 mL) and cooled in an ice-bath. *n*-BuLi (2.5 M solution in hexanes, 33 mL, 82.9 mmol, 7.00 eq.) was added dropwise and after 1 h at 0 °C, the mixture was cooled to -78 °C. A solution of the dibromide in THF (25 mL) was added and the reaction was stirred and warmed to room temperature overnight. After quench with aqueous saturated NH_4Cl, the mixture was extracted with EA and the organic phase was dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude alkyne was purified by column chromatography on silica gel (20:1 DCM/MeOH) to give the pure product as a pale yellow solid in 80% (1.69 g, 9.42 mmol). The obtained spectroscopic data were consistent with those reported in literature[229]. **R_F** = 0.48 (100% EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*) δ [ppm] = 6.04 – 5.82 (m, 1H), 3.27 (tt, *J* = 6.2, 1.8 Hz, 2H), 2.24 (ddt, *J* = 9.1, 7.1, 2.9 Hz, 2H), 1.97 – 1.89 (m, 2H), 1.83 – 1.65 (m, 6H), 1.59 – 1.47 (m, 1H), 0.88 (td, *J* = 7.5, 0.9 Hz, 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*) δ [ppm] = 176.4, 84.8, 68.3, 44.6, 42.8, 37.0, 30.7, 29.3, 19.8, 14.1, 8.6.

General procedure for the preparation of sulfonamide substrates 518a-c

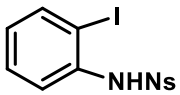
2-Iodoaniline (1.00 eq.) was dissolved in anhydrous DCM (0.5 M) and pyridine (1.00 eq.) and the respective sulfonylchloride (1.00 eq.) were added sequentially. The resulting mixture was stirred at room temperature until TLC indicated full conversion of the starting material. 1 M HCl was added and the mixture was extracted with DCM. The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The tosyl-protected anilide was purified by recrystallization from EtOH/hexanes. The nitro-substituted derivatives were subjected to column chromatography on silica gel (10:1 hexanes/EA to 2:1 hexanes/EA).

***N*-(2-iodophenyl)-4-methylbenzenesulfonamide (518a)**



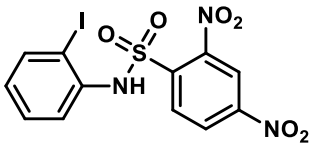
The obtained spectroscopic data were consistent with those reported in literature[230]. **^{1}H-NMR** (400 MHz, Chloroform-*D*) δ [ppm] = 7.68 – 7.60 (m, 4H), 7.33 – 7.28 (m, 1H), 7.23 – 7.19 (m, 2H), 6.82 (ddd, *J* = 8.0, 7.4, 1.5 Hz, 1H), 6.79 (bs, 1H), 2.38 (s, 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*) δ [ppm] = 144.4, 139.3, 137.7, 136.1, 129.8, 129.7, 127.6, 127.0, 122.6, 92.4, 21.7.

***N*-(2-iodophenyl)-4-nitrobenzensulfonamide (518b)**



The obtained spectroscopic data were consistent with those reported in literature[231]. **^{1}H-NMR** (400 MHz, Chloroform-*D*) δ [ppm] = 8.29 – 8.24 (m, 2H), 7.93 – 7.87 (m, 2H), 7.69 (ddd, *J* = 13.5, 8.1, 1.5 Hz, 2H), 7.41 – 7.36 (m, 1H), 6.93 (ddd, *J* = 8.0, 7.4, 1.6 Hz, 1H), 6.82 (bs, 1H); **^{13}C-NMR** (101 MHz, Chloroform-*D*) δ [ppm] = 150.6, 144.6, 139.5, 136.5, 130.0, 128.9, 128.3, 124.4, 124.2, 93.5.

***N*-(2-iodophenyl)-2,4-dinitrobenzenesulfonamide (518c)**

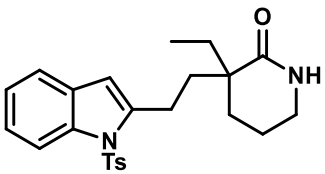


R_F = 0.13 (7:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*) δ [ppm] = 8.72 (d, *J* = 2.2 Hz, 1H), 8.45 (dd, *J* = 8.6, 2.3 Hz, 1H), 8.06 (d, *J* = 8.7 Hz, 1H), 7.74 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.65 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.41 (ddd, *J* = 8.1, 7.4, 1.5 Hz, 1H), 6.99 (ddd, *J* = 8.0, 7.4, 1.6 Hz, 1H); **^{13}C-NMR** (101 MHz, Chloroform-*D*) δ [ppm] = 150.3, 148.4, 139.9, 139.0, 136.6, 132.6, 129.8, 129.0, 127.3, 126.6, 121.1, 93.6; **IR** (film) ν 2938, 1655, 1598, 1525, 1452, 1349, 1172, 1091, 1005, 903, 814, 738, 670 cm^{-1}.

General procedure for the Larock-type indole synthesis

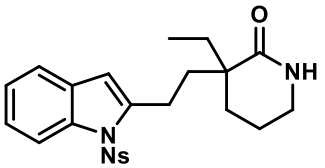
In a flame-dried Schlenk tube, the alkyne **517** (77.0 mg, 0.43 mmol, 1.00 eq.), CuI (16.0 mg, 86.0 µmol, 0.20 eq.), $Pd(PPh_3)_2Cl_2$ (30.0 mg, 43.0 µmol, 0.10 eq.) and the respective sulfonamide (1.29 mmol, 3.00 eq.) were dissolved in DMF (4.3 mL, 0.1 M) and NEt_3 (0.9 mL, 6.45 mmol, 15.0 eq.) was added. The reaction mixture was heated to 80 °C (oil bath) for 2-22 h. After cooling to room temperature, the solution was diluted with EA and concentrated on a rotary evaporator at 50 °C. The residue was subjected to column chromatography on silica gel.

3-ethyl-3-(2-(1-tosyl-1*H*-indol-2-yl)ethyl)piperidin-2-one (524a)



Column chromatography on silica gel with 100% hexanes, then 4:1 EA/hexanes. The desired indole was obtained as a colorless foam in 61% yield (111 mg, 0.26 mmol). $\mathbf{R_F}$ = 0.45 (1:4 hexanes/EA); **^{1}H-NMR** (500 MHz, Chloroform-*D*$_3$) δ [ppm] = 8.13 (dq, *J* = 8.3, 0.9 Hz, 1H), 7.61 – 7.57 (m, 2H), 7.40 – 7.36 (m, 1H), 7.25 – 7.14 (m, 4H), 6.41 (q, *J* = 1.0 Hz, 1H), 6.02 (d, *J* = 7.9 Hz, 1H), 3.32 (tdd, *J* = 8.5, 7.2, 6.1, 4.0 Hz, 2H), 3.11 (dddd, *J* = 15.6, 12.4, 4.5, 1.1 Hz, 1H), 2.98 (dddd, *J* = 15.5, 12.4, 4.6, 1.1 Hz, 1H), 2.31 (s, 3H), 2.13 – 2.03 (m, 1H), 1.96 (td, *J* = 12.7, 4.5 Hz, 1H), 1.89 – 1.78 (m, 5H), 1.61 (dq, *J* = 13.7, 7.5 Hz, 1H), 0.93 (t, *J* = 7.5 Hz, 3H); **^{13}C-NMR** (126 MHz, Chloroform-*D*) δ [ppm] = 176.8, 144.8, 142.5, 137.3, 136.2, 130.0, 129.9, 126.4, 123.9, 123.6, 120.3, 114.9, 109.2, 44.9, 42.9, 37.8, 31.0, 29.4, 24.3, 21.6, 19.9, 8.8; **IR** (film) ν 3197, 2941, 2871, 1652, 1596, 1490, 1451, 1363, 1304, 1248, 1222, 1188, 1170, 1145, 1119, 1090, 1048, 1016, 914, 811, 746, 705, 681, 662 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{24}H_{29}N_2O_3S^+$ $[M+H]^+$: 425.1893; found: 425.1895.

3-ethyl-3-(2-(1-((4-nitrophenyl)sulfonyl)-1*H*-indol-2-yl)ethyl)piperidin-2-one (524b)

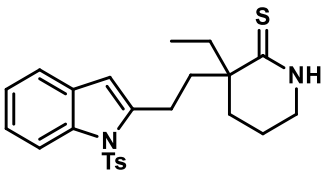


Column chromatography on silica gel with 1:1 hexanes/EA, then 4:1 EA/hexanes. Yield 37%. $\mathbf{R_F}$ = 0.55 (1:5 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*) δ [ppm] = 8.25 – 8.20 (m, 2H), 8.10 (ddt, *J* = 8.3, 1.4, 0.8 Hz, 1H), 7.91 – 7.86 (m, 2H), 7.40 (ddd, *J* = 7.3, 1.6, 0.7 Hz, 1H), 7.30 – 7.20 (m, 2H), 6.47 (q, *J* = 1.0 Hz, 1H), 5.71 (bs, 1H), 3.34 (dq, *J* = 8.1, 2.6 Hz, 2H), 3.12 (dddd, *J* = 15.7, 12.1, 4.8, 1.1 Hz, 1H), 3.00 (dddd, *J* = 15.7, 12.2, 4.8, 1.1 Hz, 1H), 2.01 (dddd, *J* = 38.4, 13.2, 12.1, 4.7 Hz, 2H), 1.89 – 1.75 (m, 5H), 1.69 – 1.60 (m, 1H), 0.94 (t, *J* = 7.5 Hz, 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*) δ [ppm] = 176.5, 150.7, 144.0, 142.4, 137.1, 130.3, 127.8, 124.7, 124.6, 124.5, 120.8, 114.9, 110.7, 44.9, 42.9, 37.7, 30.9, 29.7, 24.6, 19.9, 8.7; **IR** (film) ν 3090, 1526, 1455, 1350, 1317, 1317, 1226, 1180, 1145, 1092, 1056, 899, 856, 724, 681 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{23}H_{26}N_3O_5S^+$ $[M+H]^+$: 456.1588; found: 456.1592.

General procedure for the preparation of thiolactams

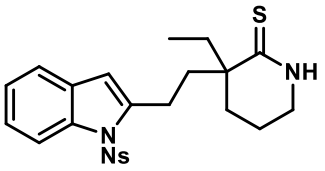
Lawesson's reagent (240 mg, 0.59 mmol, 0.50 eq.) was added in one portion to a solution of the lactam (1.18 mmol, 1.00 eq.) in anhydrous xylene (4.2 mL, 0.28 M). The mixture was heated to 120 °C and the reaction progress was monitored by TLC. After complete consumption of the starting material (~5 h, strongly depending on quality of Lawesson's reagent; if still starting material left, addition of further 0.3 eq. Lawesson's reagent is required to finish the reaction) the reaction was cooled to room temperature and the solvent was removed *in vacuo*. The crude product was purified by column chromatography on silica gel.

3-ethyl-3-(2-(1-tosyl-1*H*-indol-2-yl)ethyl)piperidine-2-thione (516a)



Column chromatography with 2:1 hexanes/EA gave the desired thiolactam **516a** as a colorless foam in 94% yield (488 mg, 1.11 mmol). $\mathbf{R_F}$ = 0.33 (2:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*) δ [ppm] = 8.84 (bs, 1H), 8.12 (dq, *J* = 8.3, 0.9 Hz, 1H), 7.64 – 7.57 (m, 2H), 7.38 (ddd, *J* = 7.5, 1.6, 0.7 Hz, 1H), 7.25 – 7.13 (m, 4H), 6.45 (q, *J* = 1.1 Hz, 1H), 3.42 – 3.27 (m, 2H), 3.17 – 3.01 (m, 2H), 2.38 (ddd, *J* = 13.1, 11.4, 5.3 Hz, 1H), 2.30 (s, 3H), 2.13 – 1.98 (m, 2H), 1.98 – 1.80 (m, 4H), 1.82 – 1.70 (m, 1H), 0.95 (t, *J* = 7.4 Hz, 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*) δ [ppm] = 210.9, 144.8, 142.3, 137.2, 136.1, 130.1, 129.9, 126.4, 123.9, 123.6, 120.3, 114.9, 109.1, 48.8, 45.5, 41.2, 35.4, 27.7, 24.3, 21.6, 19.7, 8.8; **IR** (film) ν 3143, 2932, 1593, 1566, 1451, 1363, 1316, 1301, 1201, 1169, 1145, 1088, 1052, 933, 911, 875, 856, 817, 799, 748, 705, 677, 666 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{24}H_{29}N_2O_2S_2^+$ $[M+H]^+$: 441.1665; found: 441.1663.

3-ethyl-3-(2-(1-((4-nitrophenyl)sulfonyl)-1*H*-indol-2-yl)ethyl)piperidine-2-thione (516b)

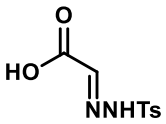


Thiolactam **516b** was obtained by the above procedure as a yellow foam in 86% yield. Column chromatography on silica gel (5:1 hexanes/EA).

$\mathbf{R_F}$ = 0.33 (3:1 hexanes/EA); **^{1}H-NMR** (500 MHz, Chloroform-*D*) δ [ppm] = 8.32 (bs, 1H), 8.26 – 8.19 (m, 2H), 8.09 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.93 – 7.86 (m, 2H), 7.43 – 7.36 (m, 1H), 7.31 – 7.19 (m, 2H), 6.50 (q, *J* = 1.1 Hz, 1H), 3.39 (dddd, *J* = 16.3, 13.1, 7.2, 2.9 Hz, 2H), 3.16 – 3.04 (m, 2H), 2.47 – 2.36 (m, 1H), 2.10 – 1.98 (m, 2H), 1.99 – 1.92 (m, 2H), 1.91 – 1.85 (m, 2H),

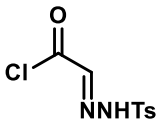
1.85 – 1.78 (m, 1H), 0.97 (t, *J* = 7.4 Hz, 3H); **^{13}C-NMR** (126 MHz, Chloroform-*D*) δ [ppm] = 211.2, 150.7, 143.9, 142.1, 137.1, 130.3, 127.9, 124.6, 124.5, 120.8, 114.9, 110.5, 48.9, 45.7, 40.7, 35.5, 27.8, 24.6, 19.7, 8.7; **IR** (film) ν 2941, 1606, 1529, 1451, 1347, 1175, 1145, 1120, 1088, 1053, 1008, 909, 854, 818, 738, 682 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{23}H_{26}N_3O_4S_2^+$ $[M+H]^+$: 472.1359; found: 472.1350.

2-(2-tosylhydrazineylidene)acetic acid (592)[232]



A mixture of glyoxylic acid hydrate (9.20 g, 100 mmol, 1.00 eq.) and water (100 mL, 1 M) was warmed to 40 °C and NH_2NHTs (18.6 g, 100 mmol, 1.00 eq.) in aqueous HCl (2.5 M, 50 mL, 125 mmol) was added. The resulting slurry was stirred vigorously and heated to 60 - 70 °C for 3 h. After cooling to room temperature, the solid was filtered by use of a Büchner funnel, washed with cold H_2O and dried under air. The crude product was dissolved in boiling EA and hexanes were added until a persistent turbidity occurred. The mixture was kept in a freezer overnight, the precipitate was filtered and washed with ice-cold hexanes/EA (2:1) and dried *in vacuo*. The mother liquor was concentrated to give a second crop of product. Combined yield 70% (16.9 g, 70 mmol). The obtained spectroscopic data were consistent with those reported in literature. **^{1}H-NMR** (400 MHz, DMSO-D_6) δ [ppm] = 12.27 (bs, 1H), 7.75 – 7.67 (m, 2H), 7.49 – 7.38 (m, 2H), 7.19 (s, 1H), 2.39 (s, 3H).

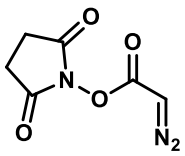
2-(2-tosylhydrazineylidene)acetyl chloride (534)[202]



Freshly distilled thionylchloride (10 mL, 140 mmol, 2.00 eq.) was added dropwise to a suspension of **592** (16.9 g, 70.0 mmol, 1.00 eq.) in anhydrous benzene (85 mL, 0.8 M). The mixture was stirred at room temperature for 15 min and then heated to reflux until gas evolution ceased (~1.5 h). After cooling to room temperature, the mixture was filtered unter N_2 and the solvent was removed *in vacuo*. The residue was suspended in warm, anhydrous benzene (15 mL, 40-50 °C) and filtered quickly over a Büchner funnel. The solid was washed with cold benzene (2x 10 mL) and re-dissolved in hot benzene (30 mL). 30 mL hexanes were added and the mixture was cooled in an ice-bath. The precipitate was filtered and dried under vacuum. Acid chloride **534** was obtained as a pale yellow solid in 61% (11.0 g, 42.3 mmol). The obtained spectroscopic data were consistent with those reported in literature. **^{1}H-NMR** (400 MHz, Chloroform-*D*)

δ [ppm] = 9.37 (bs, 1H), 7.91 – 7.82 (m, 2H), 7.42 – 7.34 (m, 2H), 7.24 (d, *J* = 0.9 Hz, 1H), 2.46 (s, 3H).

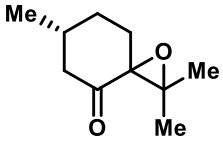
2,5-dioxopyrrolidin-1-yl-2-diazoacetate (535)[202]



A mixture of *N*-hydroxysuccinimide (2.43 g, 21.1 mmol, 1.10 eq.) and Na_2CO_3 (3.05 g, 28.8 mmol, 1.50 eq.) in DCM (28 mL) was cooled to 0 °C and a solution of **534** (5.00 g, 19.2 mmol, 1.00 eq.) in DCM (38 mL) was added over a period of 2 h. The resulting mixture was stirred at this temperature for 1 h, was then allowed to warm to room temperature and stirred for 3 h. The solid was filtered, washed with EA and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (3:1 Et_2O/hexanes to 10:1 to 100% Et_2O). Yield 61% (2.15 g, 11.7 mmol). The obtained spectroscopic data were consistent with those reported in literature. **^{1}H-NMR** (400 MHz, Chloroform-*D*) δ [ppm] = 5.12 (bs, 1H), 2.83 (s, 4H).

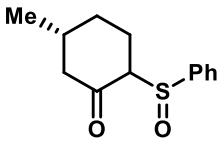
3.2.2 An Approach Toward the Synthesis of Lyconadin C

(*6R*)-2,2,6-trimethyl-1-oxaspiro[2.5]octan-4-one (547)[204c]



(*R*)-Pulegone (**180**) (5.00 g, 33.0 mmol, 1.00 eq.) was dissolved in MeOH (27 mL, 1.22 M) and 30% aq. H_2O_2 (3.9 mL, 50.0 mmol, 1.50 eq.) was added. The mixture was cooled in a water/ice bath to 10 °C and an aqueous solution of LiOH (0.17 g in 1.7 mL H_2O, 7.00 mmol, 0.20 eq.) was added dropwise while the temperature was kept below 15 °C. After complete addition, the cooling bath was removed and the reaction was stirred at room temperature for 4 h and reaction progress was monitored by TLC. Upon completion, brine was added and the mixture was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (10:1 hexanes/EA) to give the desired epoxide **547** as a 2:1 mixture of diastereomers in 90% yield (5.00 g, 29.7 mmol). The obtained spectroscopic data were consistent with those reported in literature[233]. *Note: The peaks with * are due to the minor stereoisomer.* **^{1}H-NMR** (400 MHz, Chloroform-*D*) δ [ppm] = 2.61* (dt, *J* = 13.5, 3.1 Hz, 1/3H), 2.42 (qt, *J* = 2.5, 1.6 Hz, 2H), 2.19 (ddd, *J* = 13.9, 12.2, 4.5 Hz, 2/3H), 2.08 – 1.72 (m, 4H), 1.43 (s, 3H), 1.22 and 1.21* (each s, in total 3H), 1.08* and 1.06 (each d, *J* = 6.0 and 6.9 Hz, in total 3H).

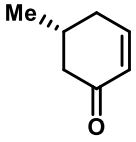
(5*R*)-5-methyl-2-(phenylsulfinyl)cyclohexan-1-one (546)[204a]



NaH (60% in paraffin, 3.45 g, 86.2 mmol, 2.00 eq.) was suspended in anhydrous THF (150 mL) and cooled to 0 °C. Thiophenol (8.8 mL, 86.2 mmol, 2.00 eq.) was added dropwise. After complete addition the ice bath was removed and the mixture was stirred for 30 mins at room temperature. Pulegon oxides **547** (7.25 g, 43.1 mmol, 1.00 eq.) in THF (250 mL) were added dropwise. The reaction was heated to reflux for 24 h and cooled to room temperature. A saturated aqueous solution of NH_4Cl was added and the mixture was extracted with Et_2O. The combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure to give the crude sulfide as a yellow oil which was dissolved in DCM (250 mL). The solution was cooled to -78 °C and *m*-CPBA (10.1 g, 45.3 mmol, 1.05 eq.) in DCM (450 mL) was added dropwise. The mixture was stirred for 3 h at -78 °C and monitored by TLC. Further 0.2 eq. *m*-CPBA (1.93 g, 8.60 mmol) were added to

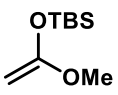
complete the reaction. Aqueous $Na_2S_2O_3$ was added and the mixture was allowed to warm to room temperature and extracted with DCM. The combined organic layers were washed with $NaHCO_3$ and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude sulfoxide was subjected to column chromatography on silica gel (1:1 hexanes/EA). Yield 72% over 2 steps (7.30 g, 30.9 mmol). *Note: The obtained mixture of sulfoxide diastereomers was used in the next step without further characterization.*

(*R*)-5-methylcyclohex-2-en-1-one (416)



Sulfoxide **546** (7.30 g, 30.9 mmol, 1.00 eq.) was dissolved in DMF (220 mL, 0.14 M) and $CaCO_3$ (3.00 g, 29.7 mmol, 1.00 eq.) was added. The mixture was heated to 80 °C for 27 h (monitored by TLC), cooled to room temperature and filtered over Celite. Water was added and the mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was subjected to repeated column chromatography on silica gel (9:1 pentane/Et_2O) to give the desired enone **416** as a pale yellow liquid (1.92 g, 17.4 mmol, 56%). The obtained spectroscopic data were consistent with those reported in literature[203b]. **$[\alpha]_D^{20}$**: -85.6 (c 1.10, $CHCl_3$); **^{1}H-NMR** (500 MHz, Chloroform-*D*) δ [ppm] = 6.96 (ddd, *J* = 10.1, 5.5, 2.7 Hz, 1H), 6.01 (ddt, *J* = 10.0, 2.6, 1.1 Hz, 1H), 2.52 – 2.45 (m, 1H), 2.45 – 2.37 (m, 1H), 2.29 – 2.16 (m, 1H), 2.16 – 2.08 (m, 1H), 2.09 – 1.99 (m, 1H), 1.07 (d, *J* = 6.4 Hz, 3H);**^{13}C-NMR** (126 MHz, Chloroform-*D*) δ [ppm] = 200.2, 150.0, 129.8, 46.4, 34.2, 30.5, 21.3.

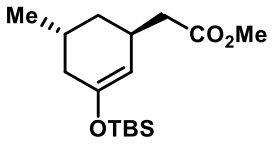
***tert*-butyl((1-methoxyvinyl)oxy)dimethylsilane (544)**[234]



A solution of diisopropylamine (5 mL, 36.0 mmol, 1.20 eq.) in THF (75 mL) was cooled in an ice-bath and *n*-BuLi (2.5 M solution in hexanes, 13 mL, 33.0 mmol, 1.10 eq.) was added dropwise. The resulting mixture was stirred for 20 min at 0 °C, before it was cooled to -78 °C. Methyl acetate (2.4 mL, 30.0 mmol, 1.00 eq.) was added over 10 mins and the mixture was stirred for 30 mins. DMPU (6 mL, 51.0 mmol, 1.70 eq.) and a solution of TBSCl (5.00 g, 33.0 mmol, 1.20 eq.) in THF (8 mL) were added sequentially. After stirring at -78 °C for 1 h, the reaction was allowed to warm to room temperature over a period of 1 h and was then quenched by the addition of water. The mixture was extracted with pentane and the organic phase was washed with brine, dried over $MgSO_4$ and the

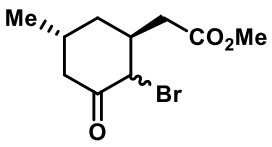
solvent was removed under reduced pressure. Pure *tert*-butyl((1-methoxyvinyl)oxy)-dimethylsilane (**544**) (5.31 g, 28.2 mmol, 94%) was distilled at 71-73 °C (31 mbar). The obtained spectroscopic data were consistent with those reported in literature. **^{1}H-NMR** (400 MHz, Chloroform-*D*) δ [ppm] = 3.54 (s, 3H), 3.23 (d, *J* = 2.6 Hz, 1H), 3.10 (d, *J* = 2.6 Hz, 1H), 0.93 (s, 9H), 0.17 (s, 6H); **^{13}C-NMR** (101 MHz, Chloroform-*D*) δ [ppm] = 162.5, 60.2, 55.2, 25.7, 18.2, -4.6.

methyl-2-((1*S*,5*R*)-((*tert*-butyldimethylsilyl)oxy)-5-methylcyclohex-2-en-1-yl)acetate (542)



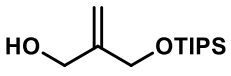
(*R*)-5-Methylcyclohex-2-en-1-one (**416**) (300 mg, 2.72 mmol, 1.00 eq.) was dissolved in anhydrous DCM (27 mL) and the resulting solution was cooled to -78 °C. TBSOTf (49 µL, 0.27 mmol, 0.01 eq.) in DCM (2.7 mL) was added and after 10 mins **544** (768 mg, 4.08 mmol, 1.50 eq.) was added dropwise. The reaction was stirred for 2 h at -78 °C before anhydrous NEt_3 (3.8 mL, 27.2 mmol, 10.0 eq.) was added. A saturated aqueous solution of $NaHCO_3$ was added and the phases were separated. The aqueous phase was extracted with DCM and the combined organic layers were dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel. The desired silyl enol ether **542** was obtained as a single diastereomer in 93% (754 mg, 2.53 mmol). **R_F** = 0.71 (10:1 hexanes/EA); **$[\alpha]_D^{21}$:** +64.5 (c 1.00, $CHCl_3$); **^{1}H-NMR** (400 MHz, Chloroform-*D*) δ [ppm] = 4.80 (dt, *J* = 4.4, 1.3 Hz, 1H), 3.67 (s, 3H), 2.77 – 2.67 (m, 1H), 2.36 – 2.24 (m, 2H), 2.11 – 2.00 (m, 1H), 1.94 – 1.81 (m, 1H), 1.66 (ddt, *J* = 16.8, 8.3, 1.9 Hz, 1H), 1.37 (dd, *J* = 8.2, 5.2 Hz, 2H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.91 (s, 9H), 0.12 (d, *J* = 1.7 Hz, 6H); **^{13}C-NMR** (101 MHz, Chloroform-*D*) δ [ppm] = 173.5, 151.2, 106.9, 51.5, 41.1, 38.1, 35.4, 30.3, 25.8, 25.4, 21.2, 18.2, -4.2, -4.3; **IR** (film) ν 2954, 2929, 2858, 1740, 1667, 1436, 1361, 1251, 1194, 1072, 1023, 1006, 970, 907, 870, 833, 777, 675 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{16}H_{31}O_3Si^+$ $[M+H]^+$: 299.2037; found: 299.2034.

methyl 2-((1*S*,5*R*)-2-bromo-5-methyl-3-oxocyclohexyl)acetate (559)



(*R*)-5-Methylcyclohex-2-en-1-one (**416**) (100 mg, 0.91 mmol, 1.00 eq.) was dissolved in anhydrous DCM (9 mL) and the resulting solution was cooled to -78 °C. TBSOTf (16 µL, 0.09 mmol, 0.01 eq.) in DCM (0.9 mL) was added and after 10 mins, ketene acetal **544** (256 mg, 1.36 mmol, 1.50 eq.) was added dropwise. The reaction was stirred at -78 °C until TLC indicated complete conversion of the starting material (~2 h). NBS (194 mg, 1.09 mmol, 1.20 eq.) was added in one portion and the resulting mixture was stirred for 2 h at -78 °C and for 30 mins at 0 °C. Water was added and the mixture was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude bromo ketone was subjected to column chromatography on silica gel (10:1 hexanes/EA) and the pure product was obtained as an inseparable 2:1 mixture of diastereomers (152 mg, 0.58 mmol, 63%). *Note: The peaks with * belong to the major stereoisomer.* $\mathbf{R_F}$ = 0.50 (2:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*) δ [ppm] = 4.48 (dt, J = 3.7, 1.2 Hz, 1/3H), 4.25* (dt, *J* = 5.2, 1.2 Hz, 2/3H), 3.69 (s, 3H), 3.19 (dd, *J* = 14.1, 6.0 Hz, 1/3H), 2.83 – 2.75 (m, 1H), 2.78 – 2.70* (m, 2/3H), 2.68 – 2.57 (m, 2/3H), 2.55 – 2.39* (m, 4/3H), 2.39 – 2.30 (m, 1H), 2.19 – 2.09 (m, 1H), 2.08 – 1.93 (m, 1H), 1.72 – 1.65* (m, 2/3H), 1.56 – 1.47 (m, 1/3H), 1.04* and 1.00 (each d, *J* = 6.5 and 7.1 Hz, in total 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*) δ [ppm] = 203.3*, 203.2, 172.0, 171.7*, 58.6, 55.0*, 52.1*, 52.0, 44.8*, 43.1, 40.2*, 37.6*, 37.4, 35.2, 33.8*, 33.1, 29.5*, 29.3, 21.3*, 19.9; **IR** (film) ν 2956, 2928, 1734, 1437, 1372, 1247, 1221, 1173, 1095, 1018, 882, 706 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{10}H_{16}BrO_3^+$ $[M+H]^+$: 263.0277; found: 263.0276.

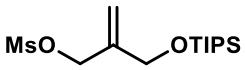
2-(((triisopropylsilyl)oxy)methyl)prop-2-en-1-ol (549)[235]



D*i*BAL-H (1 M solution in hexane, 44 mL, 43.6 mmol, 2.50 eq.) was added dropwise to a solution of ethyl 2-(((triisopropylsilyl)oxy)-methyl)acrylate[235] (5.00 g, 17.5 mmol, 1.00 eq.) in DCM (35 mL, 0.5 M) at -78 °C. The resulting mixture was stirred at this temperature for 4 h and was then added to an aqueous potassium sodium tartrate solution with vigorous stirring. After 30 mins, the phases were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine and dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica

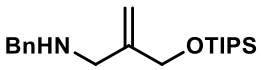
gel (7:1 hexanes/EA). Yield 80% (3.43 g, 14.0 mmol). The obtained spectroscopic data were consistent with those reported in literature. $\mathbf{R_F}$ = 0.52 (3:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*) δ [ppm] = 5.14 – 5.11 (m, 1H), 5.08 (h, *J* = 1.2 Hz, 1H), 4.34 (t, *J* = 1.4 Hz, 2H), 4.20 (d, *J* = 4.2 Hz, 2H), 2.05 – 1.98 (m, 1H), 1.19 – 1.02 (m, 21H); **^{13}C-NMR** (101 MHz, Chloroform-*D*) δ [ppm] = 147.6, 111.2, 65.7, 65.1, 18.1, 12.1; **IR** (film) ν 3330, 2943, 2892, 2866, 1660, 1463, 1384, 1247, 1118, 1090, 1060, 1014, 996, 907, 881, 804, 680, 659 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{13}H_{29}O_2Si^+$ $[M+H]^+$: 245.1931; found: 245.1925.

2-(((triisopropylsilyl)oxy)methyl)allyl methanesulfonate (554)



Bisallylic alcohol **549** (3.43 g, 14.0 mmol, 1.00 eq.) was dissolved in DCM (47 mL, 0.3 M) and cooled to 0 °C. NEt_3 (2.7 mL, 19.6 mmol, 1.40 eq.) and MsCl (1.4 mL, 18.2 mmol, 1.30 eq.) were added sequentially and the resulting mixture was stirred for 4.5 h at 0 °C. An aqueous saturated solution of NH_4Cl was added and the phases were separated. The aqueous layer was extracted with DCM and the combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (20:1 hexanes/EA, then 10:1) to give the desired mesylate **554** as colorless oil in 85% (3.82 g, 11.9 mmol). $\mathbf{R_F}$ = 0.52 (3:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*) δ [ppm] = 5.39 (q, *J* = 1.6 Hz, 1H), 5.29 (h, *J* = 1.2 Hz, 1H), 4.76 (d, *J* = 1.0 Hz, 2H), 4.29 (t, *J* = 1.5 Hz, 2H), 3.02 (s, 3H), 1.23 – 0.94 (m, 21H);**^{13}C-NMR** (101 MHz, Chloroform-*D*) δ [ppm] = 141.8, 115.8, 70.3, 63.7, 38.0, 18.1, 12.1; **IR** (film) ν 2943, 2866, 1463, 1354, 1248, 1175, 1121, 1092, 1068, 996, 967, 923, 881, 805, 756, 681, 660 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{14}H_{31}O_4SSi^+$ $[M+H]^+$: 323.1707; found: 323.1701.

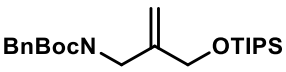
***N*-benzyl-2-(((triisopropylsilyl)oxy)methyl)prop-2-en-1-amine (553)**



Mesylate **554** (2.77 g, 8.60 mmol, 1.00 eq.) was dissolved in THF (29 mL, 0.3 M) and benzylamine (9.4 mL, 86.0 mmol, 10.0 eq.) was added. The reaction mixture was stirred for 15 h at room temperature before the solvent was removed under reduced pressure. Column chromatography on silica gel (56:4:1 DCM/MeOH/25% NH_3) gave amine **553** in quantitative yield (2.86 g, 8.60 mmol). $\mathbf{R_F}$ = 0.32 (3:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*) δ [ppm] = 7.35 – 7.22 (m, 5H), 5.19 (tq, *J* = 1.7, 0.9 Hz, 1H), 5.03 (m, 1H), 4.27 (t, *J* = 1.6 Hz, 2H), 3.77 (s,

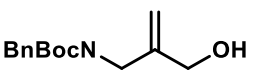
2H), 3.28 (d, J = 0.9 Hz, 2H), 1.15 – 1.03 (m, 21H); **^{13}C-NMR** (101 MHz, Chloroform-*D*) δ [ppm] = 147.0, 140.6, 128.5, 128.3, 127.0, 110.2, 65.5, 53.4, 51.6, 18.2, 12.2; **IR** (film) ν 2942, 2865, 1657, 1495, 1454, 1383, 1248, 1102, 1067, 1028, 1013, 995, 905, 805, 736, 697 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{20}H_{36}NOSi^+$ $[M+H]^+$: 334.2561; found: 334.2551.

tert-butyl benzyl(2-(((triisopropylsilyl)oxy)methyl)allyl)carbamate (591)



The secondary amine **553** (2.86 g, 8.60 mmol, 1.00 eq.) was dissolved in THF (62 mL, 0.14 M), Boc_2O (2.08 g, 9.53 mmol, 1.10 eq.) was added and the resulting solution was stirred and heated to reflux for 3 h. The solvent was removed under reduced pressure and the residue was subjected to column chromatography on silica gel (20:1 hexanes/EA). Pure carbamate **591** was obtained in 93% (3.49 g, 8.04 mmol). *Note: The compound exhibits conformational isomerism, presumably due to the formation of isomeric carbamates. NMR spectra were measured at 283 K, at which signal sets for both rotamers in a 1:1 ratio were obtained. All signals are given, further assignment was not executed.* **R_F** = 0.50 (7:1 hexanes/EA); **^{1}H-NMR** (600 MHz, Benzene-*D_6*) δ [ppm] = 7.33 – 7.00 (m, 5H), 5.47 (s, 1/2H), 5.37 (s, 1/2H), 4.95 – 4.91 (m, 1H), 4.57 (s, 1H), 4.35 (s, 1H), 4.28 (s, 1H), 4.14 (s, 1H), 3.99 (s, 1H), 3.76 (s, 1H), 1.49 (s, 9/2H), 1.41 (s, 9/2H), 1.10 (s, 21H); **^{13}C-NMR** (151 MHz, Benzene-*D_6*) δ [ppm] = 155.6, 155.4, 144.7, 144.4, 138.6, 138.5, 138.5, 138.5, 128.5, 128.0, 127.9, 127.7, 127.6, 110.7, 109.9, 79.1, 79.1, 64.3, 64.1, 49.0, 48.9, 47.9, 28.0, 26.8, 17.9, 11.9; **IR** (film) ν 2942, 2866, 1695, 1454, 1409, 1365, 1239, 1164, 1115, 1068, 1014, 970, 881, 808, 767, 733, 699, 681, 659 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{25}H_{44}NO_3Si^+$ $[M+H]^+$: 434.3085; found: 434.3075; calculated for $C_{20}H_{36}NOSi^+$ $[M\text{-}Boc+2H]^+$: 334.2561; found: 334.2551.

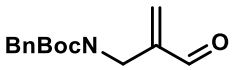
tert-butyl benzyl(2-(hydroxymethyl)allyl)carbamate (557)



TBAF (1 M solution in THF, 16 mL, 16.08, 2.00 eq.) was added dropwise to a solution of silylated **591** (3.49 g, 8.04 mmol, 1.00 eq.) in THF (20 mL, 0.4 M). The reaction was stirred at room temperature for 1 h. 1 M NH_4OH was added and the mixture was extracted with EA. The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Column chromatography on silica gel (5:1 hexanes/EA) gave the deprotected alcohol **557** as a colorless oil in 91% (2.03 g, 7.33 mmol). *Note: The compound exhibits conformational isomerism, presumably due to*

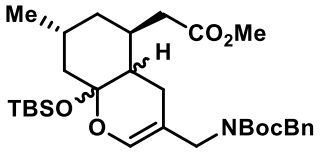
the formation of isomeric carbamates. NMR spectra were measured at 283 K. Signals for the major isomer at this temperature are given. **R_F** = 0.50 (1:1 hexanes/EA); **^{1}H-NMR** (600 MHz, Benzene-D_6) δ [ppm] = 7.16 – 7.03 (m, 5H), 4.93 (s, 1H), 4.63 (s, 1H), 4.12 (s, 1H), 4.06 (s, 1H), 3.87 (s, 1H), 1.33 (s, 9H); **^{13}C-NMR** (151 MHz, Benzene-D_6) δ [ppm] = 156.9, 145.6, 138.3, 128.8, 128.4, 127.5, 113.5, 80.4, 63.7, 49.6, 48.4, 28.2; **IR** (film) ν 3429, 2977, 2927, 1669, 1496, 1454, 1412, 1366, 1243, 1160, 1117, 1065, 1029, 968, 905, 878, 814, 767, 734, 698 cm^{-1}; **HRMS** (ESI) m/z calculated for calculated for $C_{11}H_{16}NO^+$ $[M\text{-}Boc+2H]^+$: 178.1226; found: 178.1225.

tert-butyl benzyl(2-formylallyl)carbamate (543)



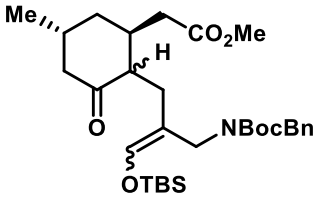
Allylalcohol **557** (2.03 g, 7.33 mmol, 1.00 eq.) was dissolved in DMSO (37 mL, 0.2 M), cooled in a water bath and IBX (5.13 g, 18.3 mmol, 2.50 eq.) was added in one portion. The resulting mixture was stirred for 30 mins at room temperature. Water was added and the mixture was extracted with Et_2O. The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the remaining crude aldehyde was purified by column chromatography on silica gel (5:1 hexanes/EA). Aldehyde **543** was obtained as colorless oil in 93% (1.89 g, 6.84 mmol). **R_F** = 0.50 (2:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*) δ [ppm] = 9.60 (s, 1H), 7.37 – 7.17 (m, 5H), 6.26 (d, *J* = 39.8 Hz, 1H), 6.10 (d, *J* = 8.0 Hz, 1H), 4.44 (d, *J* = 12.9 Hz, 2H), 4.05 (s, 1H), 3.97 (s, 1H), 1.46 (s, 9H); **^{13}C-NMR** (101 MHz, Chloroform-*D*) δ [ppm] = 193.9, 138.1, 134.7, 133.7, 128.7, 128.1, 127.5, 80.4, 51.4, 50.3, 44.3, 28.5; **IR** (film) ν 2977, 2934, 1687, 1496, 1453, 1409, 1366, 1243, 1159, 1122, 1076, 1029, 956, 882, 856, 768, 740, 698 cm^{-1}; **HRMS** (ESI) m/z calculated for calculated for $C_{11}H_{14}NO^+$ $[M\text{-}Boc+2H]^+$: 176.1070; found: 176.1068.

methyl 2-((5*S*,7*R*)-3-((benzyl(*tert*-butoxycarbonyl)amino)methyl)-8a-((*tert*-butyldimethylsilyl)-oxy)7-methyl-4a,5,6,7,8,8a-hexahydro-4*H*-chromen-5-yl) acetate (561)



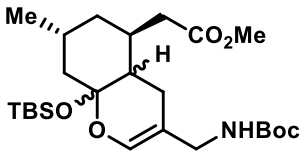
Freshly dried $SnCl_2$ (21.0 mg, 0.11 mmol, 0.10 eq.) was suspended in anhydrous DCM (1.5 mL) and TrCl (31.0 mg, 0.11 mmol, 0.10 eq.) was added. The bright yellow mixture was stirred for 30 mins at room temperature and was then cooled to -78 °C. A solution of TBS-enol ether **542** (423 mg, 1.42 mmol, 1.30 eq.) and aldehyde **543** (300 mg, 1.09 mmol, 1.00 eq.) in DCM (3.5 mL) was added dropwise over a period of 45 mins. The reaction was stirred for 16 h at -78 °C and was quenched by the addition of saturated aqueous $NaHCO_3$. The phases were separated and the aqueous layer was extracted with DCM. The combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was subjected to column chromatography on silica gel (20:1 hexanes/EA) to give bicyclic **561** as a colorless oil in 52% (325 mg, 0.57 mmol). *Note: Acyclic **562** obtained as side-product. Ratio seems to depend on reaction temperature. Bicyclic compound **561** obtained as a single diastereomer, determination of stereochemistry by NMR spectroscopic analysis not possible.* $\mathbf{R_F}$ = 0.40 (7:1 hexanes/EA); **^{1}H-NMR** (500 MHz, Chloroform-*D*) δ [ppm] = 7.41 – 7.17 (m, 5H), 6.05 (s, 1H), 4.53 – 4.25 (m, 2H), 3.82 – 3.45 (m, 2H), 3.66 (s, 3H), 2.57 (dd, *J* = 15.6, 5.0 Hz, 1H), 2.43 – 2.30 (m, 1H), 2.10 (td, *J* = 12.0, 10.9, 5.9 Hz, 2H), 1.98 (q, *J* = 6.3 Hz, 1H), 1.94 – 1.88 (m, 1H), 1.65 – 1.60 (m, 1H), 1.58 (d, *J* = 10.5 Hz, 2H), 1.55 – 1.42 (m, 9H), 1.38 (q, *J* = 6.7 Hz, 2H), 0.96 (d, *J* = 7.0 Hz, 3H), 0.87 (s, 9H), 0.13 (s, 3H), 0.08 (s, 3H); **^{13}C-NMR** (126 MHz, Chloroform-*D*) δ [ppm] = 173.9, 156.2, 147.0, 138.5, 129.0, 128.6, 128.1, 127.8, 127.4, 127.2, 100.1, 79.9, 51.5, 48.2, 42.6, 42.1, 39.2, 35.3, 28.6, 26.5, 26.1, 21.1, 18.2, -2.3, -2.9; **IR** (film) ν 2928, 2856, 1739, 1693, 1454, 1415, 1388, 1365, 1245, 1146, 1118, 1068, 1023, 983, 908, 879, 835, 802, 777, 732, 698, 674 cm^{-1}; **HRMS** (ESI) m/z calculated for calculated for $C_{32}H_{51}NNaO_6Si^+$ $[M+Na]^+$: 596.3378; found: 596.3375.

methyl 2-((1*S*,5*R*)-2-(2-((benzyl(*tert*-butoxycarbonyl)amino)methyl)-3-((*tert*-butyldimethylsilyl)oxy)allyl)-5-methyl-3-oxocyclohexyl)acetate (562)



Note: This compound was obtained as an inseparable mixture of diastereomers. Conformational isomerism is supposed in addition. All signals are given. **R_F** = 0.32 (5:1 hexanes/EA); **^{1}H-NMR** (500 MHz, Chloroform-*D*) δ [ppm] = 7.33 – 7.17 (m, 5H), 6.39 – 6.07 (m, 1H), 4.47 – 4.17 (m, 2H), 4.12 – 3.88 (m, 2H), 3.66 (s, 3H), 2.55 – 2.42 (m, 2H), 2.41 – 2.20 (m, 4H), 2.17 – 1.97 (m, 3H), 1.55 – 1.38 (m, 9H), 1.03 – 0.95 (m, 3H), 0.81 (s, 9H), 0.08 (s, 3H); **^{13}C-NMR** (151 MHz, Chloroform-*D*) δ [ppm] = 213.2, 212.9, 173.0, 172.5, 156.2, 156.1, 140.0, 139.8, 138.7, 138.5, 128.7, 128.3, 128.2, 127.8, 127.5, 126.9, 114.1, 113.4, 80.2, 79.7, 52.7, 52.6, 51.7, 48.6, 48.0, 47.3, 46.9, 40.6, 38.6, 38.3, 36.9, 35.7, 34.3, 32.9, 31.1, 30.3, 30.3, 29.8, 29.8, 29.6, 28.6, 28.5, 25.7, 22.4, 21.5, 18.3, -5.3, -5.3; **HRMS** (ESI) m/z calculated for calculated for $C_{32}H_{52}NO_6Si^+$ $[M+H]^+$: 574.3558; found: 574.3556.

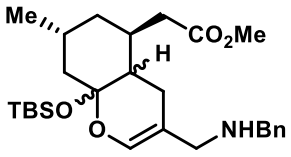
methyl 2-((5*S*,7*R*)-3-(((*tert*-butoxycarbonyl)amino)methyl)-8a-((*tert*-butyldimethylsilyl) oxy)-7-methyl-4a,5,6,7,8,8a-hexahydro-4*H*-chromen-5-yl) acetate (563a)



In a Schlenk flask under N_2, the bis-protected amine **561** (200 mg, 0.35 mmol, 1.00 eq.) was dissolved in THF (12 mL, 0.03 M) and $Pd(OH)_2$ (250 mg, 0.35 mmol, 1.00 eq.) was added. The flask was equipped with a rubber septum and H_2-balloon and the reaction was stirred for 6 h. The mixture was filtered over Celite and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (10:1 hexanes/EA) to give **563a** in 73% yield (124 mg, 0.26 mmol). **R_F** = 0.26 (7:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*) δ [ppm] = 6.18 – 6.14 (m, 1H), 4.53 (s, 1H), 3.67 (s, 3H), 3.65 – 3.48 (m, 2H), 2.54 (dd, J = 15.8, 5.7 Hz, 1H), 2.31 (dd, *J* = 15.8, 7.7 Hz, 1H), 2.23 – 2.15 (m, 1H), 2.11 (dt, *J* = 7.6, 5.2 Hz, 1H), 2.02 – 1.95 (m, 1H), 1.89 (dd, *J* = 17.2, 5.9 Hz, 1H), 1.61 (qd, *J* = 7.0, 6.4, 4.7 Hz, 3H), 1.44 (s, 9H), 1.41 – 1.34 (m, 2H), 0.96 (d, *J* = 7.1 Hz, 3H), 0.85 (s, 9H), 0.12 (s, 3H), 0.06 (s, 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*) δ [ppm] = 174.2, 156.2, 137.8, 108.1, 99.7, 79.2, 51.6, 42.9, 42.7, 39.3, 36.2, 31.6, 28.6, 26.7, 26.0, 23.7, 20.9, 18.2, -2.4, -3.1; **IR** (film) ν 3381, 2952, 2928, 2856, 1716, 1505, 1460, 1436, 1389, 1365, 1247, 1165, 1148,

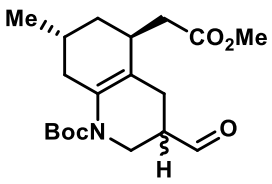
1097, 1069, 1019, 984, 938, 907, 868, 835, 802, 777, 742, 673 cm^{-1}; **HRMS** (ESI) m/z calculated for calculated for $C_{25}H_{45}NNaO_6Si^+$ $[M+Na]^+$: 506.2908; found: 506.2901.

methyl 2-((5*S*,7*R*)-3-((benzylamino)methyl)-8a-((*tert*-butyldimethylsilyl)oxy)-7-methyl-4a,5,6,7,8,8a-hexahydro-4*H*-chromen-5-yl)acetate (563b)



Anhydrous $ZnBr_2$ (118 mg, 0.52 mmol, 2.00 eq.) was added to a solution of the bis-protected amine **561** (150 mg, 0.26 mmol, 1.00 eq.) in DCM (2.6 mL, 0.1 M) at room temperature. The resulting mixture was stirred for 6 h and quenched by the addition of 1 M NH_4OH. The phases were separated and the aqueous layer was extracted with EA. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was subjected to column chromatography on silica gel (200:4:1 DCM/MeOH/25% NH_3). The desired secondary amine **563b** was obtained in 81% yield (100 mg, 0.21 mmol). $\mathbf{R_F}$ = 0.26 (20:1 DCM/MeOH); **^{1}H-NMR** (400 MHz, Chloroform-*D*) δ [ppm] = 7.34 – 7.21 (m, 5H), 6.18 – 6.14 (m, 1H), 3.73 (d, *J* = 3.0 Hz, 2H), 3.62 (s, 3H), 3.12 – 3.07 (m, 2H), 2.62 (dd, *J* = 15.6, 5.3 Hz, 1H), 2.37 (dd, *J* = 15.6, 8.7 Hz, 1H), 2.20 (ddd, *J* = 17.2, 6.1, 1.4 Hz, 1H), 2.16 – 2.09 (m, 1H), 2.09 – 2.02 (m, 1H), 1.98 (td, *J* = 7.0, 4.9 Hz, 1H), 1.66 (q, *J* = 6.5 Hz, 1H), 1.59 (d, *J* = 6.1 Hz, 2H), 1.51 – 1.43 (m, 1H), 1.42 – 1.33 (m, 2H), 0.96 (d, *J* = 7.0 Hz, 3H), 0.87 (s, 9H), 0.13 (s, 3H), 0.07 (s, 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*) δ [ppm] = 174.1, 140.7, 137.4, 128.5, 128.2, 127.0, 109.1, 100.0, 53.0, 51.5, 51.2, 42.7, 42.4, 39.3, 35.6, 32.5, 26.6, 26.5, 26.1, 24.7, 21.1, 18.3, -2.3, -2.9; **IR** (film) ν 2951, 2928, 2856, 1737, 1677, 1455, 1436, 1360, 1250, 1164, 1147, 1095, 1068, 1022, 984, 908, 879, 835, 803, 777, 733, 697 cm^{-1}; **HRMS** (ESI) m/z calculated for calculated for $C_{27}H_{44}NO_4Si^+$ $[M+H]^+$: 474.3034; found: 474.3016.

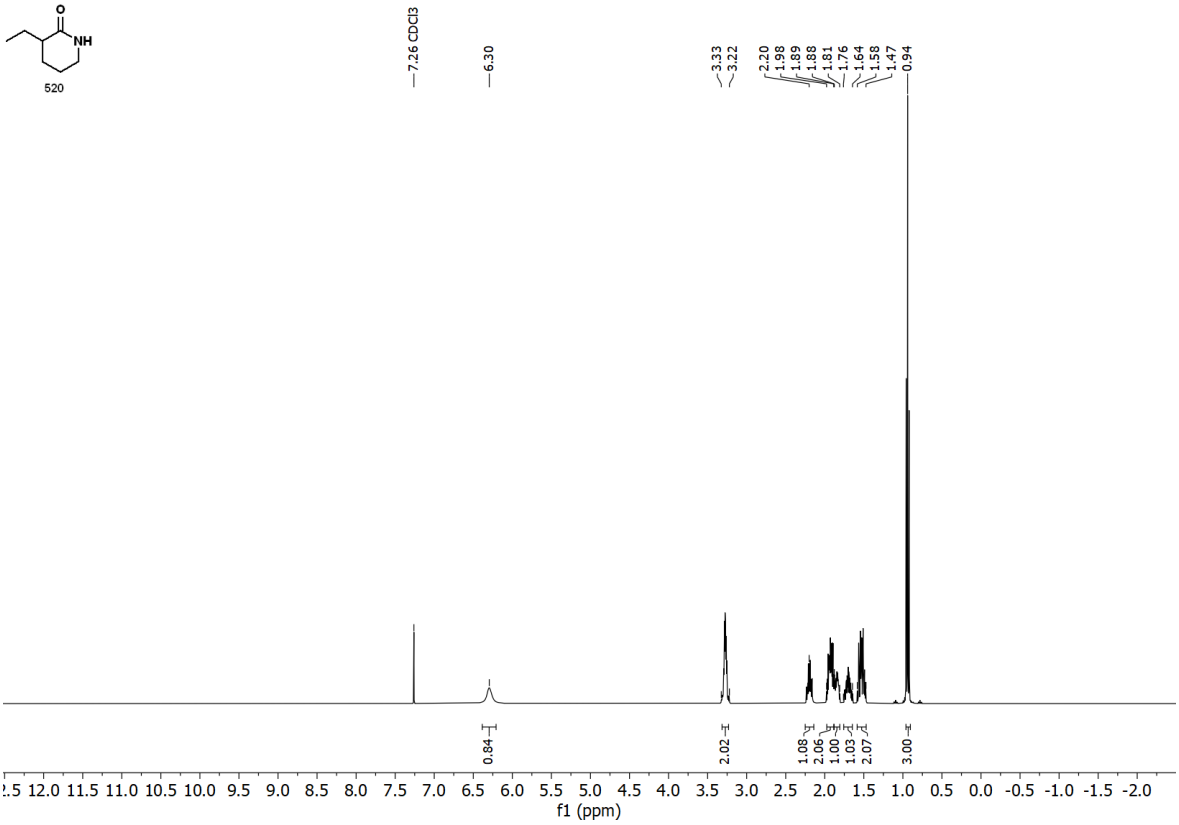
***tert*-butyl (5*S*,7*R*)-3-formyl-5-(2-methoxy-2-oxoethyl)-7-methyl-3,4,5,6,7,8-hexahydroquinoline-1(2*H*)-carboxylate (564a)**

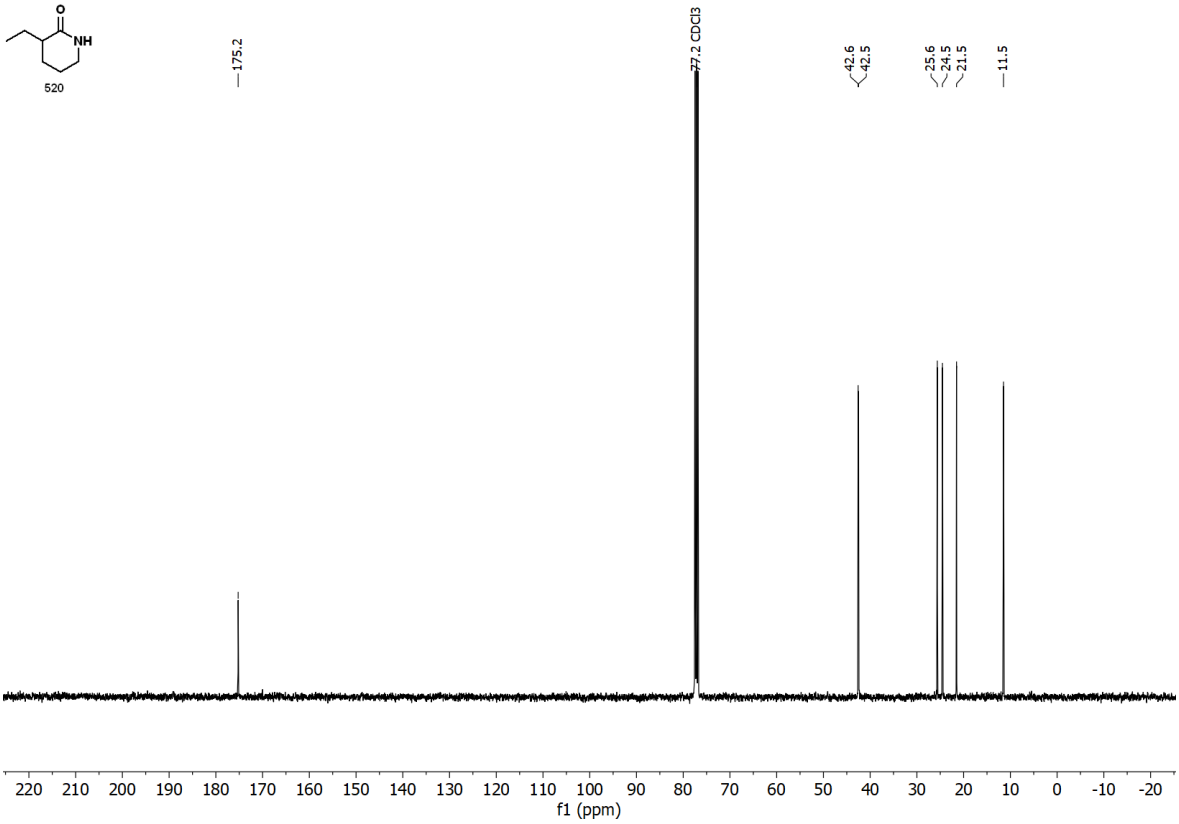


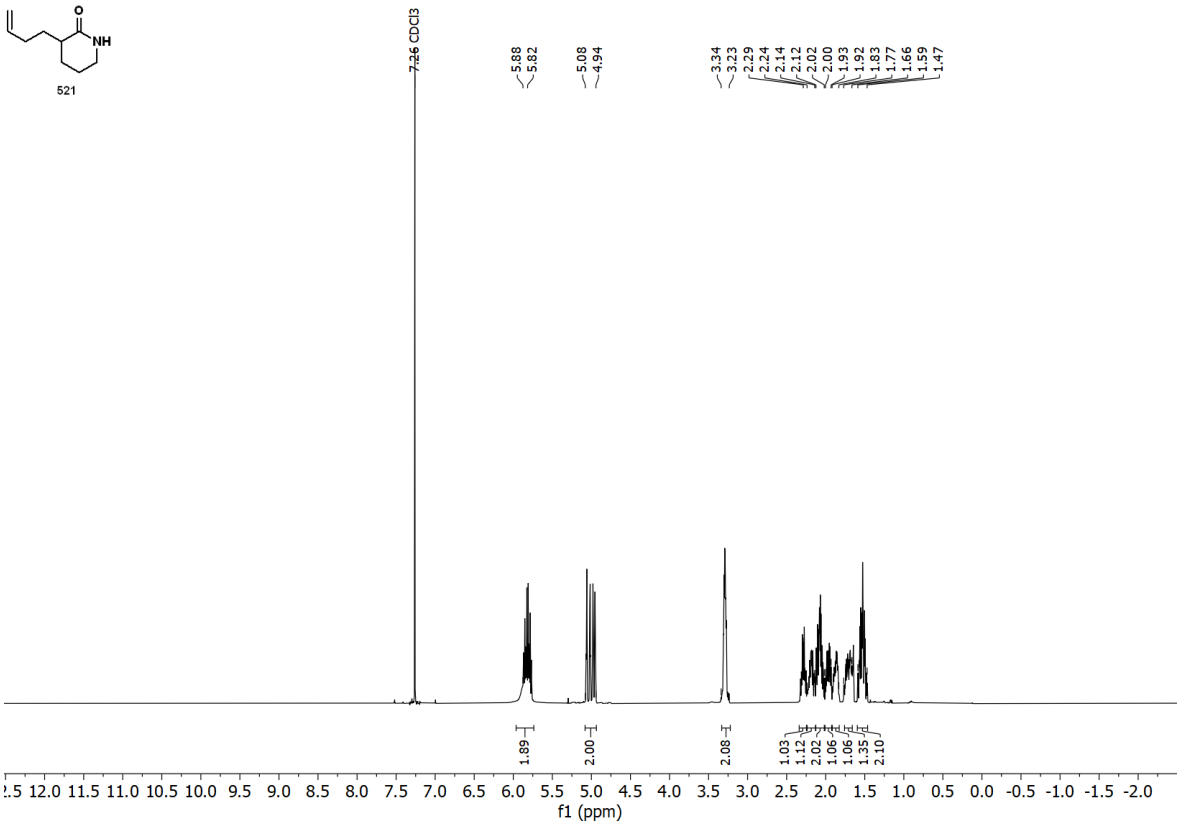
Carbamate **563a** (10.0 mg, 21.0 µmol, 1.00 eq.) was dissolved in toluene (0.4 mL, 0.05 M) and camphorsulfonic acid (5.00 mg, 21.0 µmol, 1.00 eq.) was added. The mixture was stirred at room temperature for 2 h and the solvent was removed under reduced pressure. The residue was subjected to flash column chromatography on silica gel

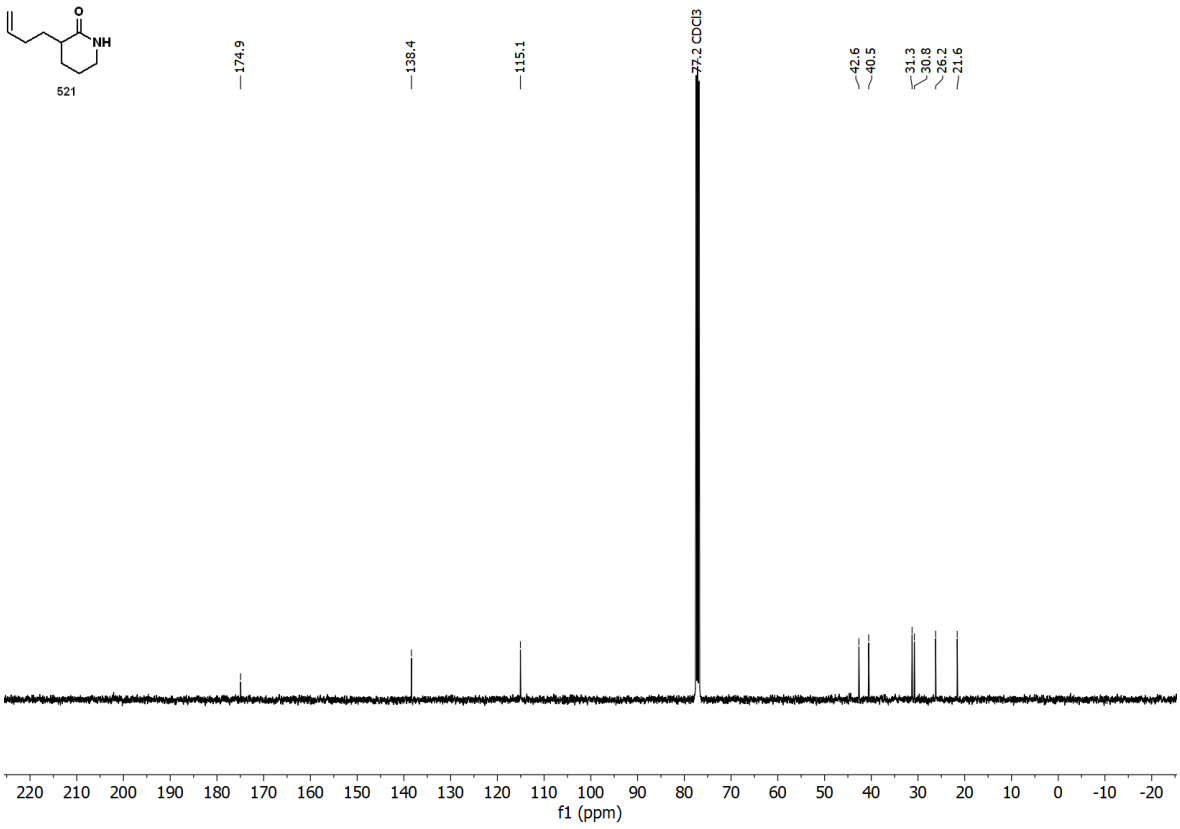
(7:1 hexanes/EA) to give the desired aldehyde. *Note: Product obtained as ~1:1 mixture of stereoisomers. Varying yields. The product tends to decompose under ambient conditions.* **R_F** = 0.39 (2:1 hexanes/EA); **^{1}H-NMR** (400 MHz, Chloroform-*D*) δ [ppm] = 9.72 and 9.69 (d each, *J* = 0.9 Hz, in total 1H), 3.96 (dd, *J* = 12.8, 3.9 Hz, 1/2H), 3.85 (dd, *J* = 12.9, 6.2 Hz, 1/2H), 3.69 (s, 3H), 3.64 (ddd, *J* = 12.9, 4.0, 0.8 Hz, 1/2H), 3.43 (ddd, *J* = 12.8, 7.8, 0.8 Hz, 1/2H), 2.85 – 2.75 (m, 1H), 2.64 – 2.57 (m, 3/2H), 2.54 (dd, *J* = 15.1, 3.8 Hz, 1/2H), 2.50 – 2.38 (m, 3/2H), 2.34 – 2.23 (m, 2H), 2.15 – 1.95 (m, 3/2H), 1.83 – 1.70 (m, 1H), 1.56 – 1.49 (m, 1H), 1.47 and 1.46 (s each, in total 9H), 1.45 – 1.35 (m, 1H), 0.95 and 0.94 (d, *J* = 4.5 and 4.1 Hz, in total 3H); **^{13}C-NMR** (101 MHz, Chloroform-*D*) δ [ppm] = 201.5, 201.3, 173.7, 173.5, 153.8, 153.7, 134.6, 134.4, 119.8, 119.8, 81.2, 81.1, 51.8, 47.6, 47.5, 43.7, 43.6, 38.9, 38.7, 37.7, 37.5, 35.9, 35.9, 35.8, 35.7, 28.5, 25.7, 25.5, 24.9, 24.8, 21.7, 21.6; **IR** (film) ν 2927, 1730, 1693, 1455, 1435, 1381, 1364, 1282, 1254, 1152, 1014, 966, 908, 869, 767, 732 cm^{-1}; **HRMS** (ESI) m/z calculated for calculated for $C_{19}H_{30}NO_5^+$ $[M+H]^+$: 352.2118; found: 352.2116.

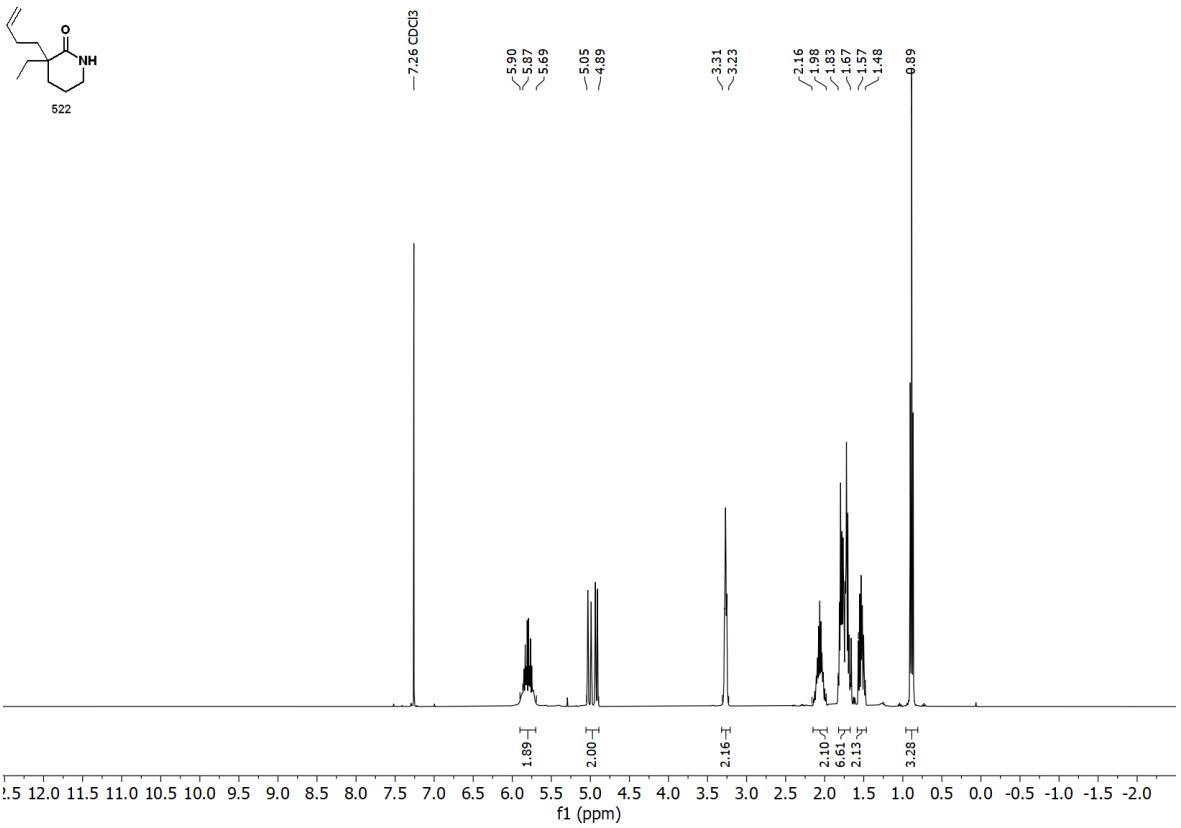
3.2.3 NMR Spectra

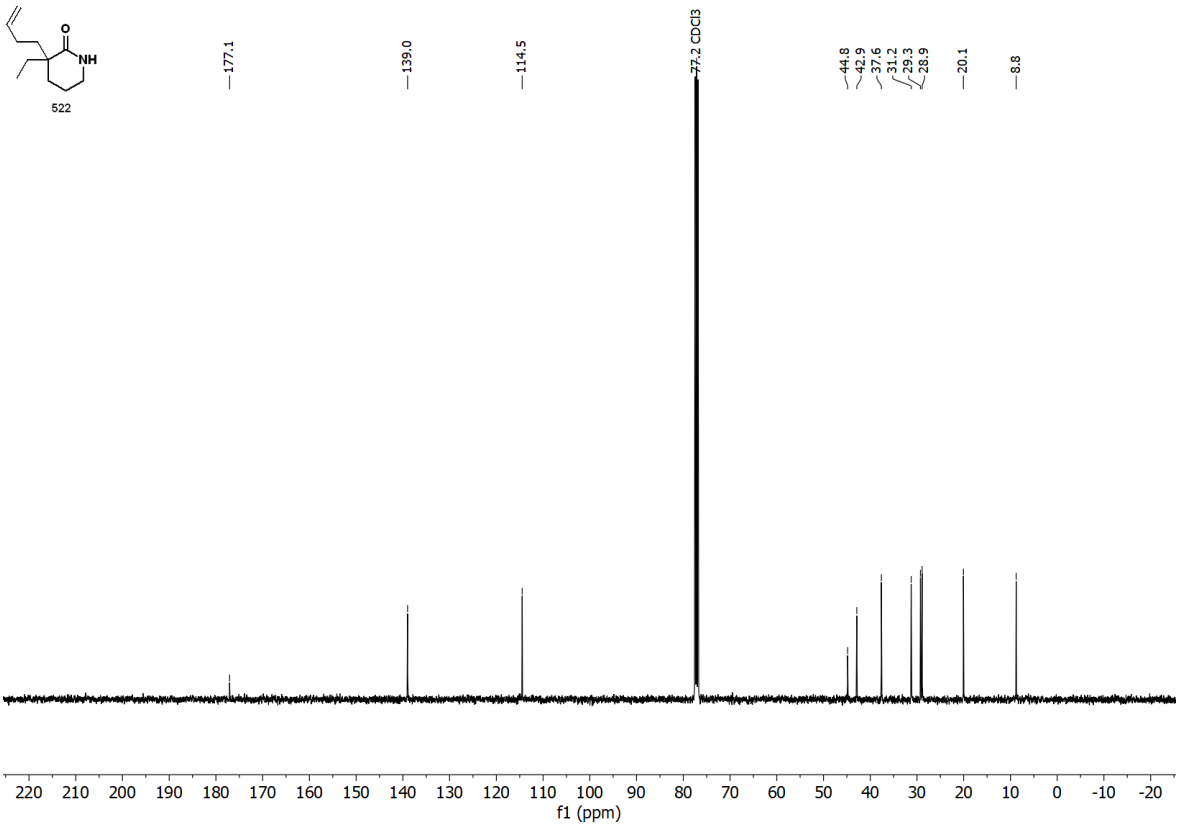


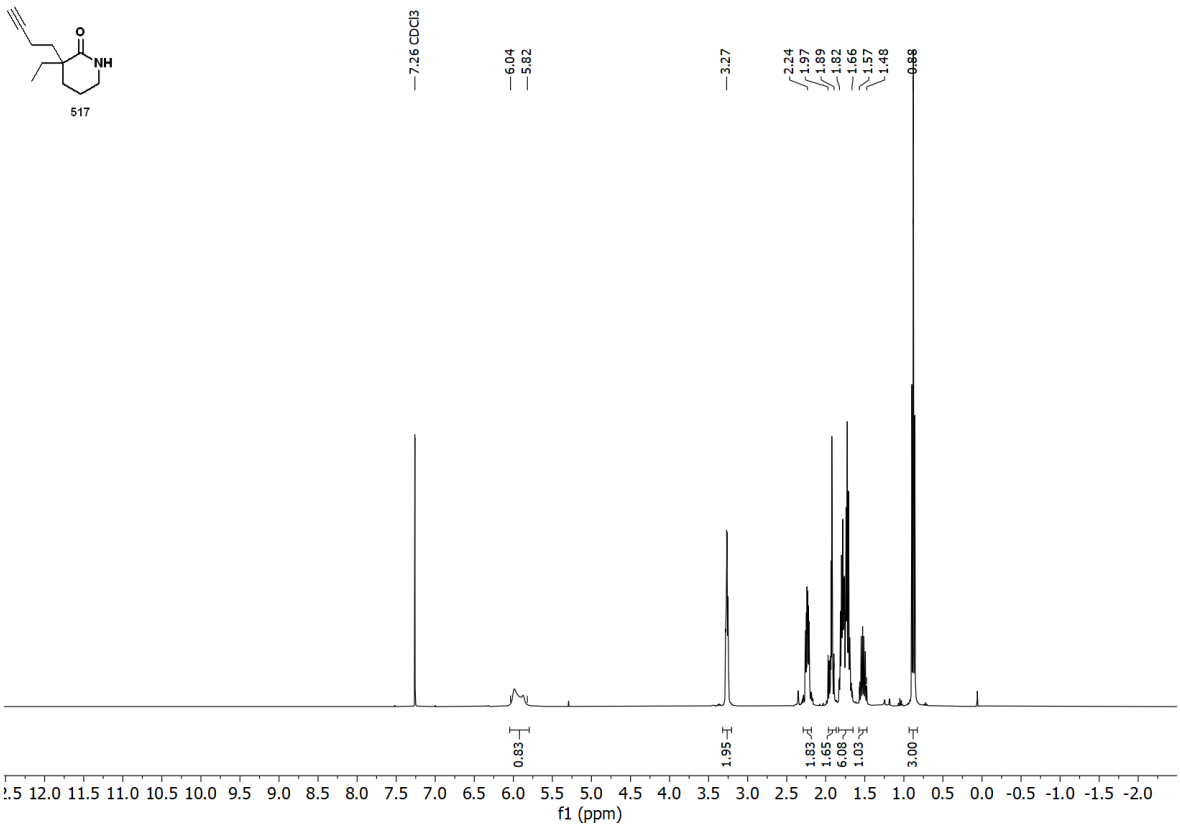


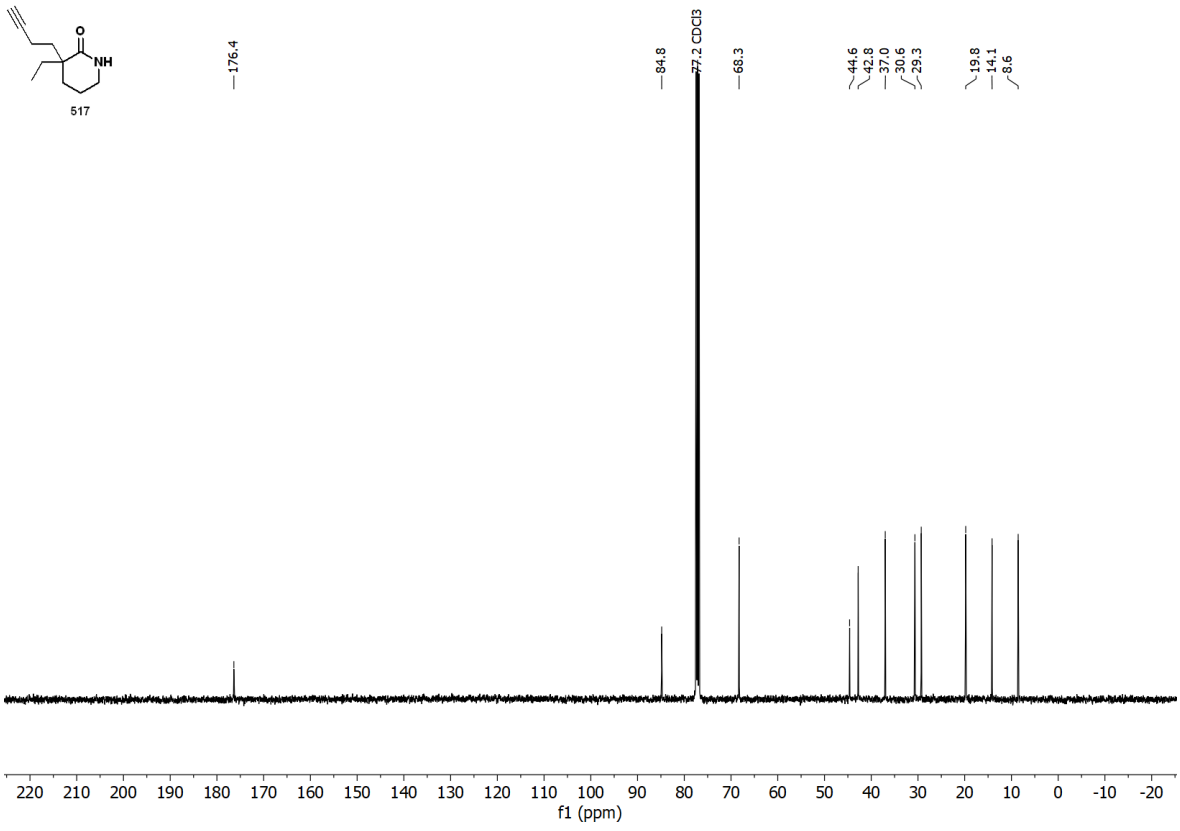

521
7.26 CDCl3
5.88
5.82
5.08
4.94
3.34
3.23
2.29
2.24
2.14
2.12
2.02
2.00
1.93
1.92
1.83
1.77
1.66
1.59
1.47
1.89
2.00
2.08
1.03
1.12
2.02
1.06
1.06
1.35
2.10
f1 (ppm)

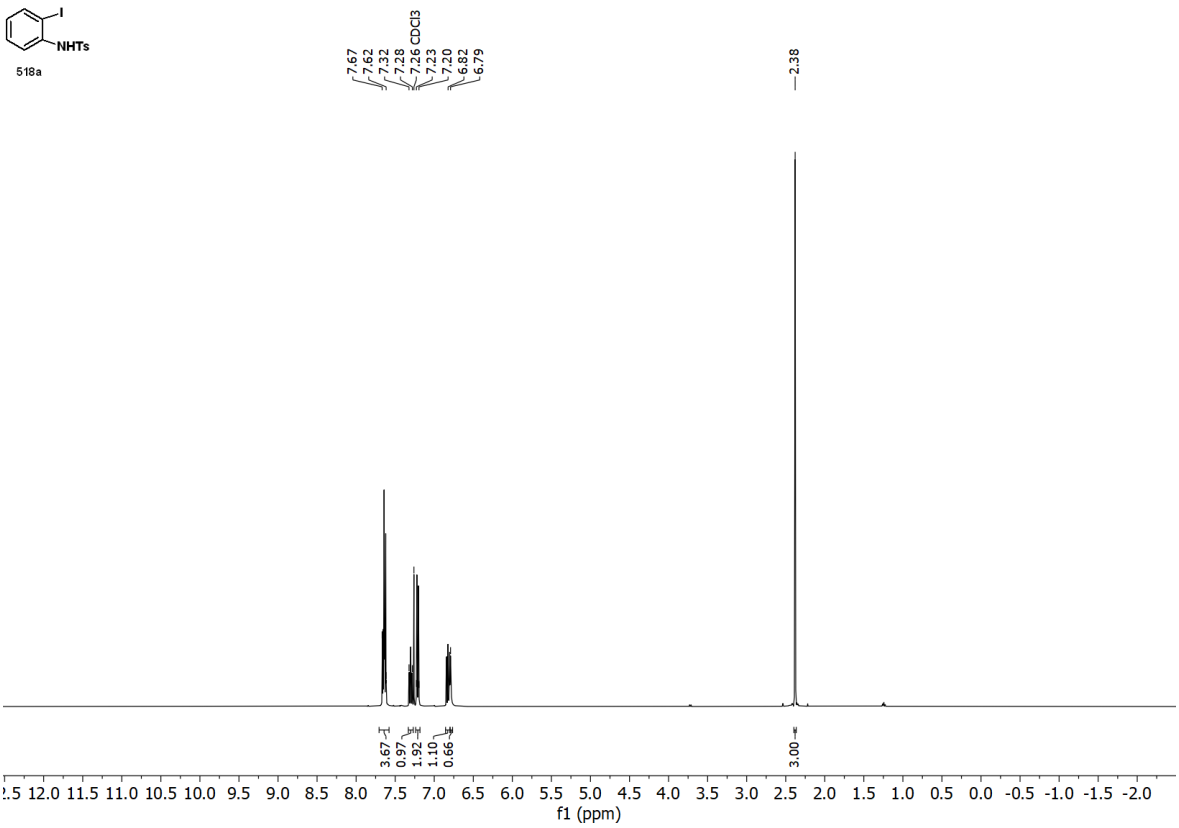

521
174.9
138.4
115.1
77.2 CDCl3
42.6
40.5
31.3
30.8
26.2
21.6
f1 (ppm)

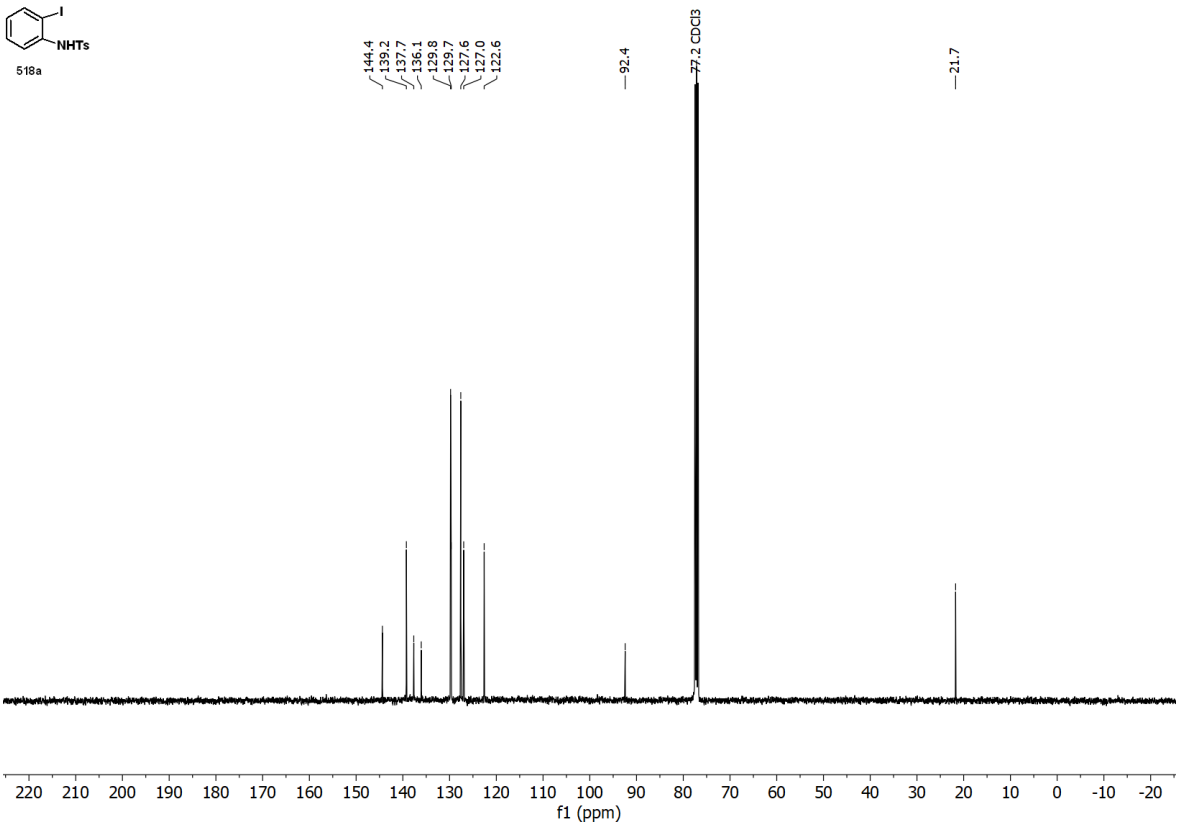

522
7.26 CDCl3
5.90
5.87
5.69
5.05
4.89
3.31
3.23
2.16
1.98
1.83
1.67
1.57
1.48
0.89
1.89
2.00
2.16
2.10
6.61
2.13
3.28
f1 (ppm)

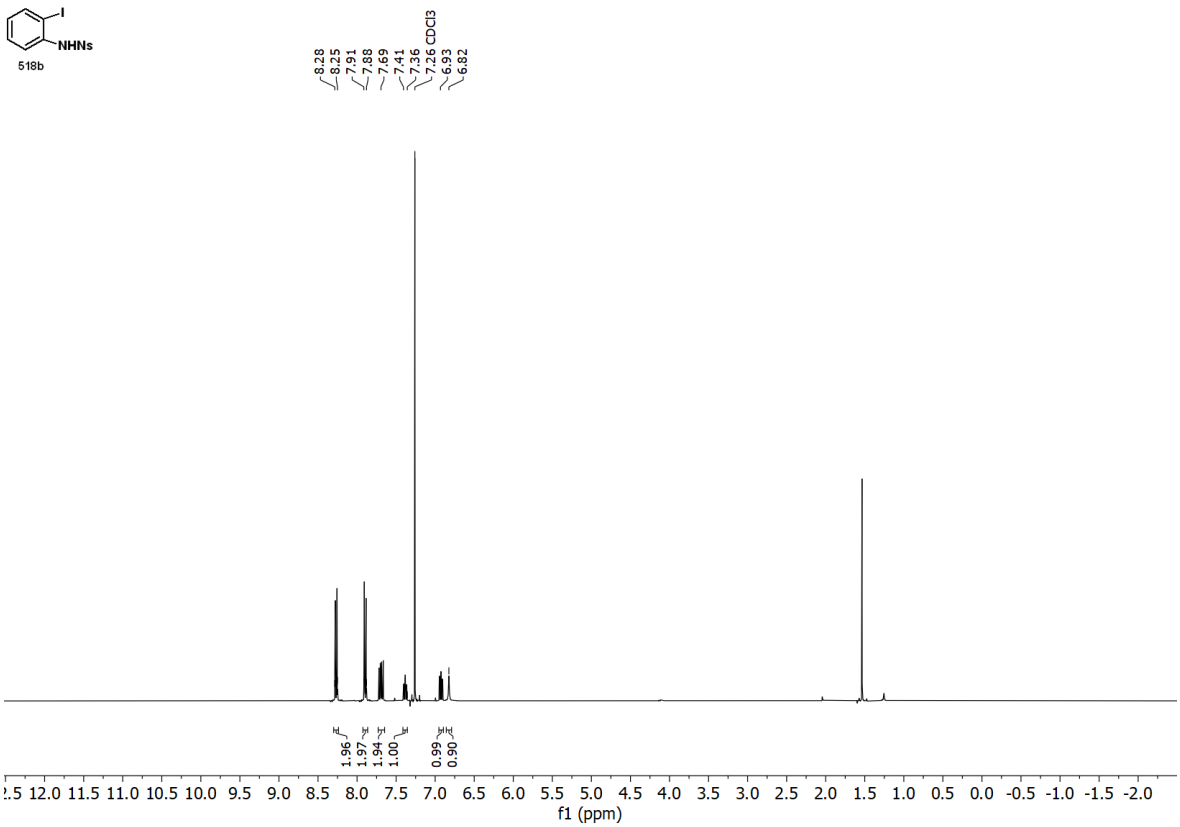

522
177.1
139.0
114.5
77.2 CDCl3
44.8
42.9
37.6
31.2
29.3
28.9
20.1
8.8
f1 (ppm)

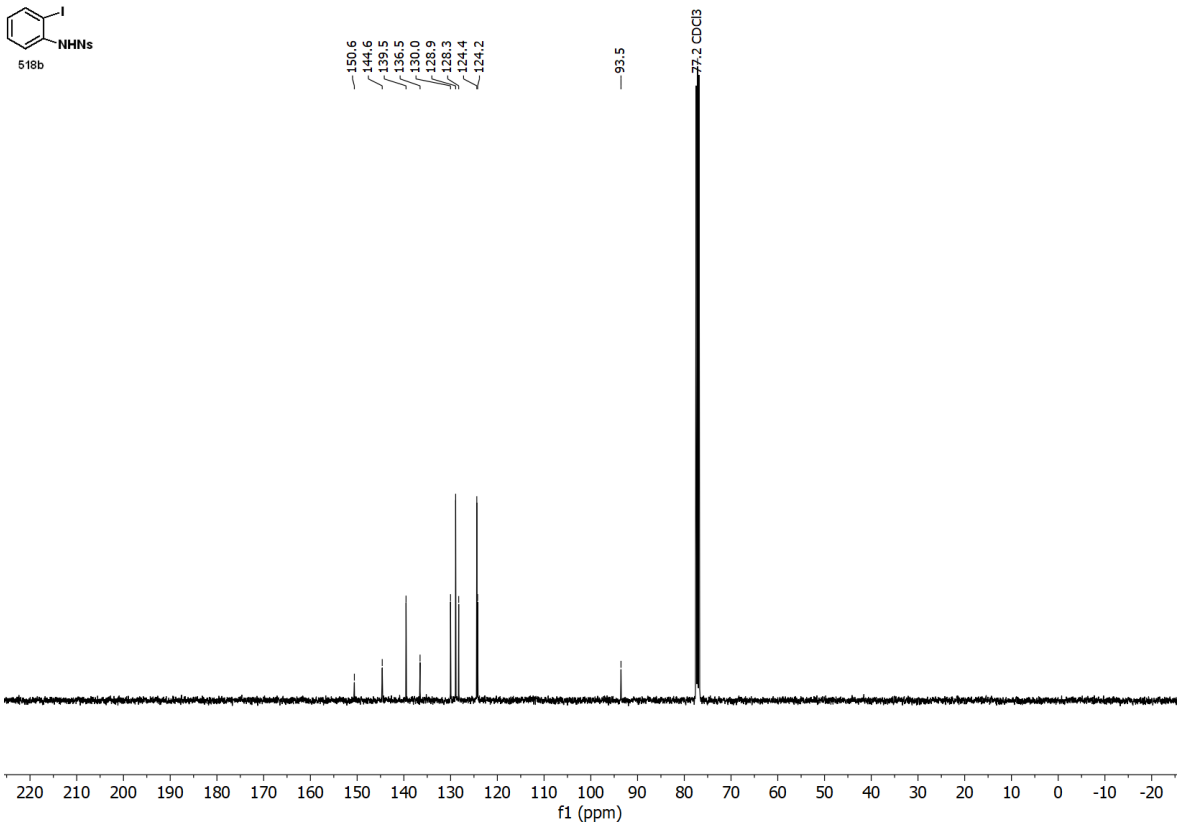

517
7.26 CDCl3
6.04
5.82
3.27
2.24
1.97
1.89
1.82
1.66
1.57
1.48
0.88
0.83
1.95
1.83
1.65
6.08
1.03
3.00
f1 (ppm)

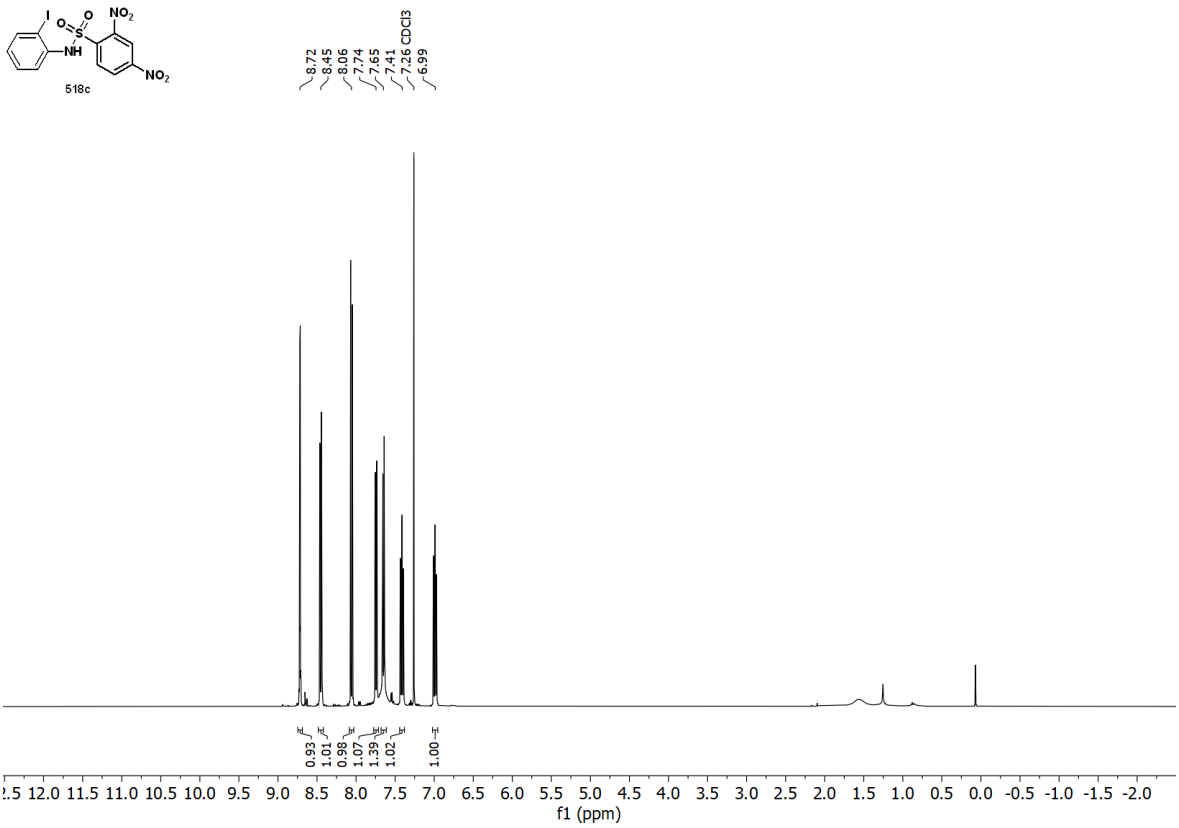

517
176.4
84.8
77.2 CDCl3
68.3
44.6
42.8
37.0
30.6
29.3
19.8
14.1
8.6
f1 (ppm)

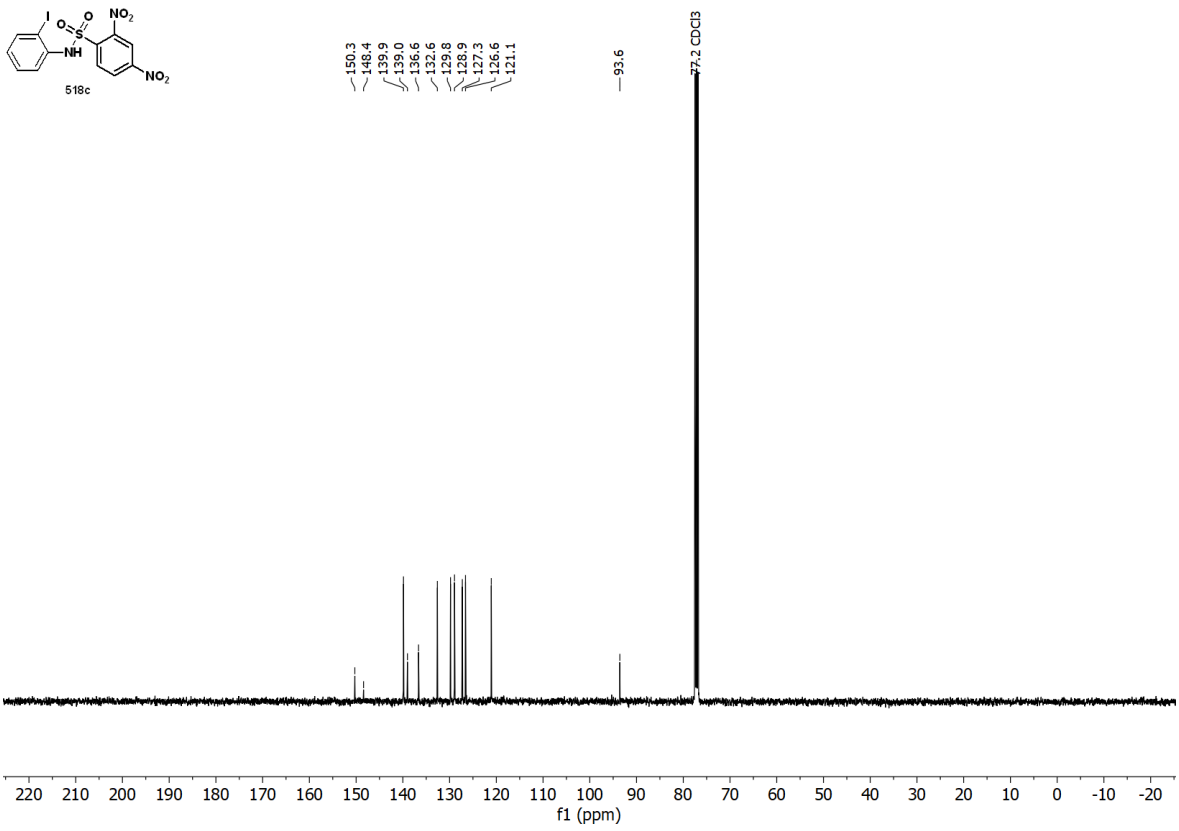

I
NHTs
518a
7.67
7.62
7.32
7.28
7.26 CDCl3
7.23
7.20
6.82
6.79
2.38
3.67
0.97
1.92
1.10
0.66
3.00
f1 (ppm)

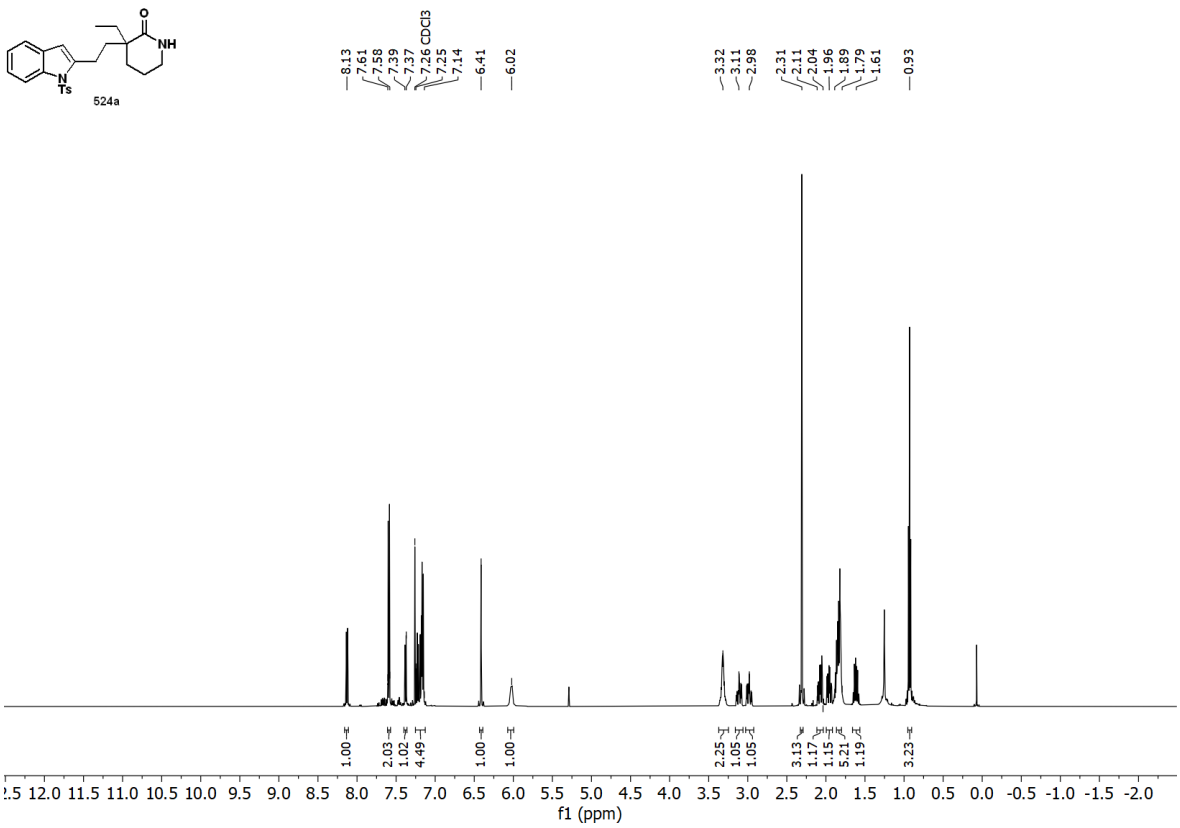

I
NHTs
518a
144.4
139.2
137.7
136.1
129.8
129.7
127.6
127.0
122.6
92.4
77.2 CDCl3
21.7
f1 (ppm)

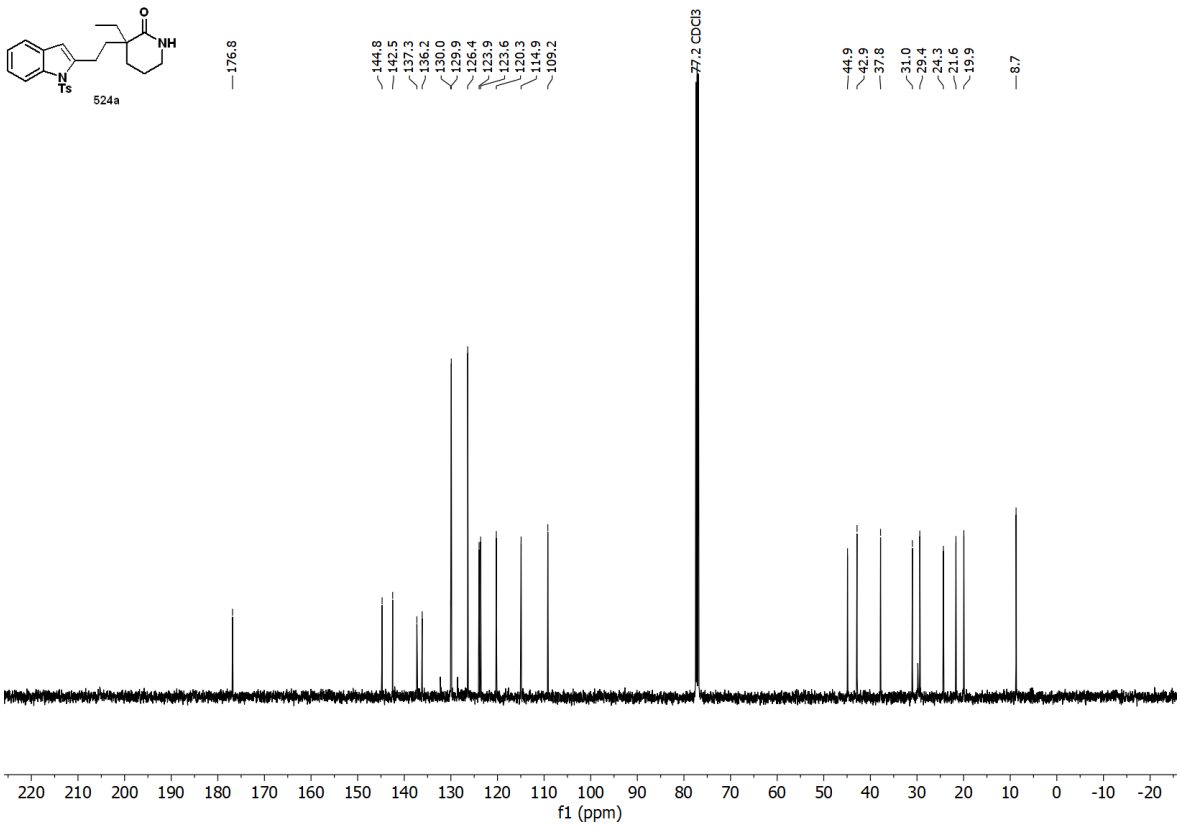

I
NHNs
518b
8.28
8.25
7.91
7.88
7.69
7.41
7.36
7.26 CDCl3
6.93
6.82
1.96
1.97
1.94
1.00
0.99
0.90
f1 (ppm)

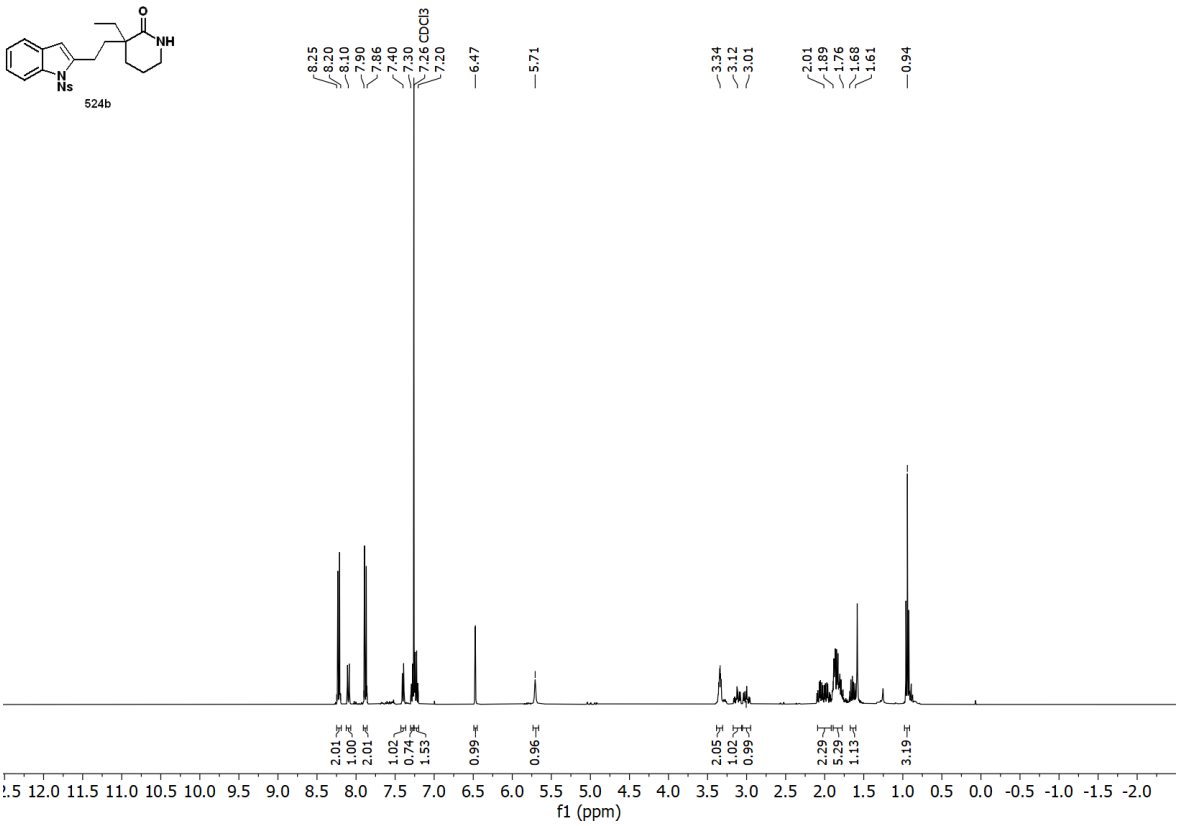

I
NHNs
518b
150.6
144.6
139.5
136.5
130.0
128.9
128.3
124.4
124.2
93.5
77.2 CDCl3
f1 (ppm)

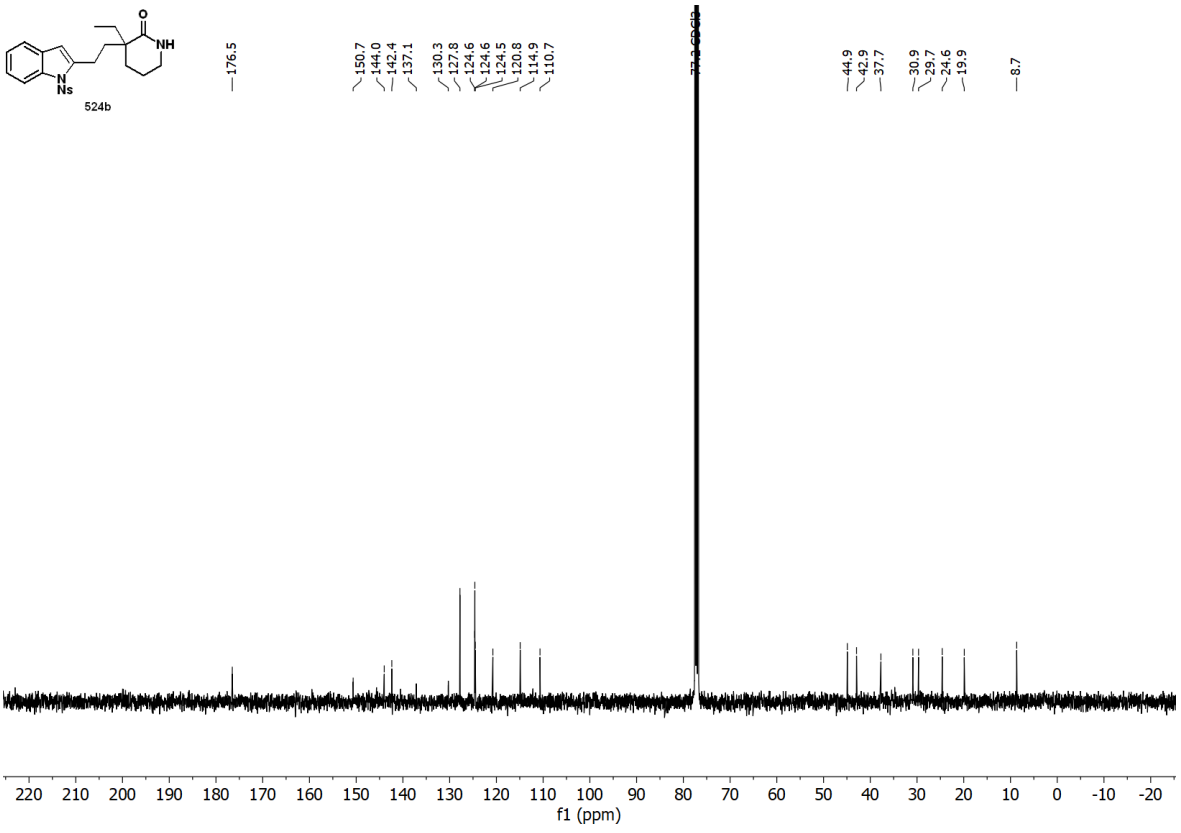

518c
8.72
8.45
8.06
7.74
7.65
7.41
7.26 CDCl3
6.99
0.93
1.01
0.98
1.07
1.39
1.02
1.00
f1 (ppm)

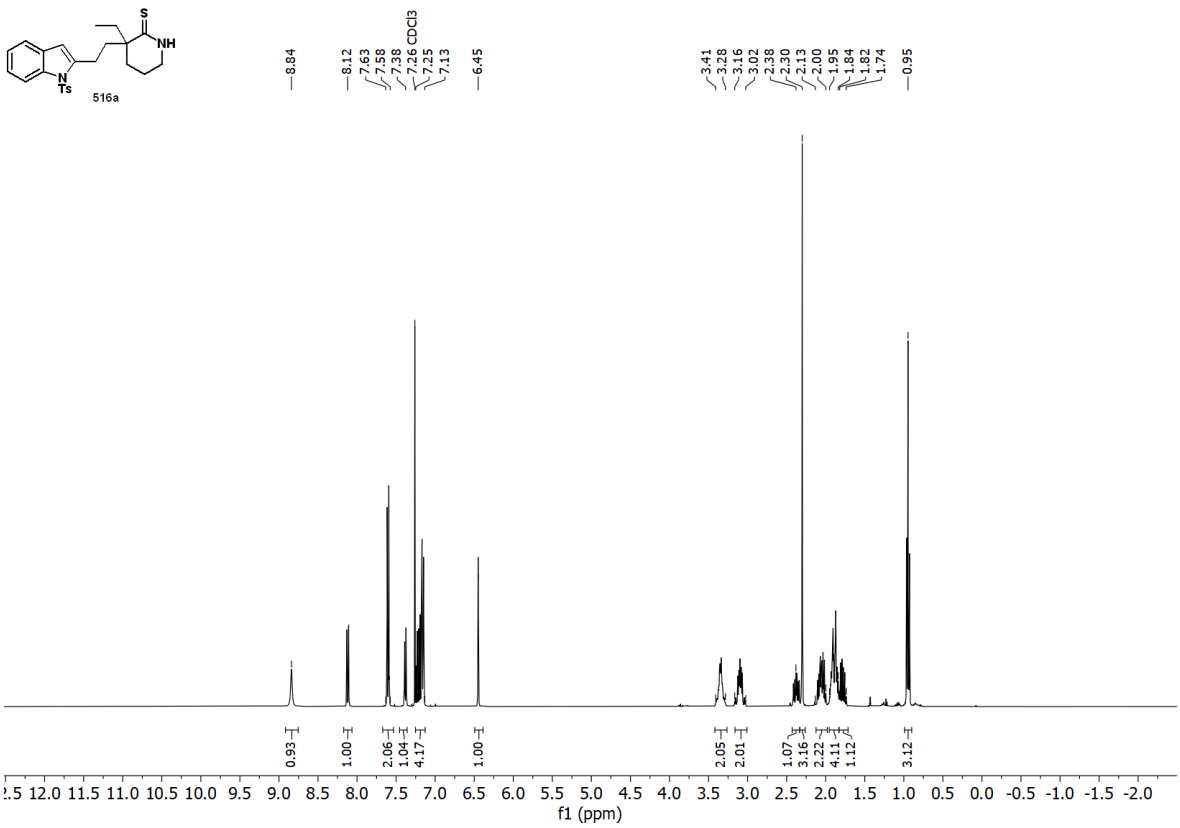

518c
150.3
148.4
139.9
139.0
136.6
132.6
129.8
128.9
127.3
126.6
121.1
93.6
77.2 CDCl3
f1 (ppm)

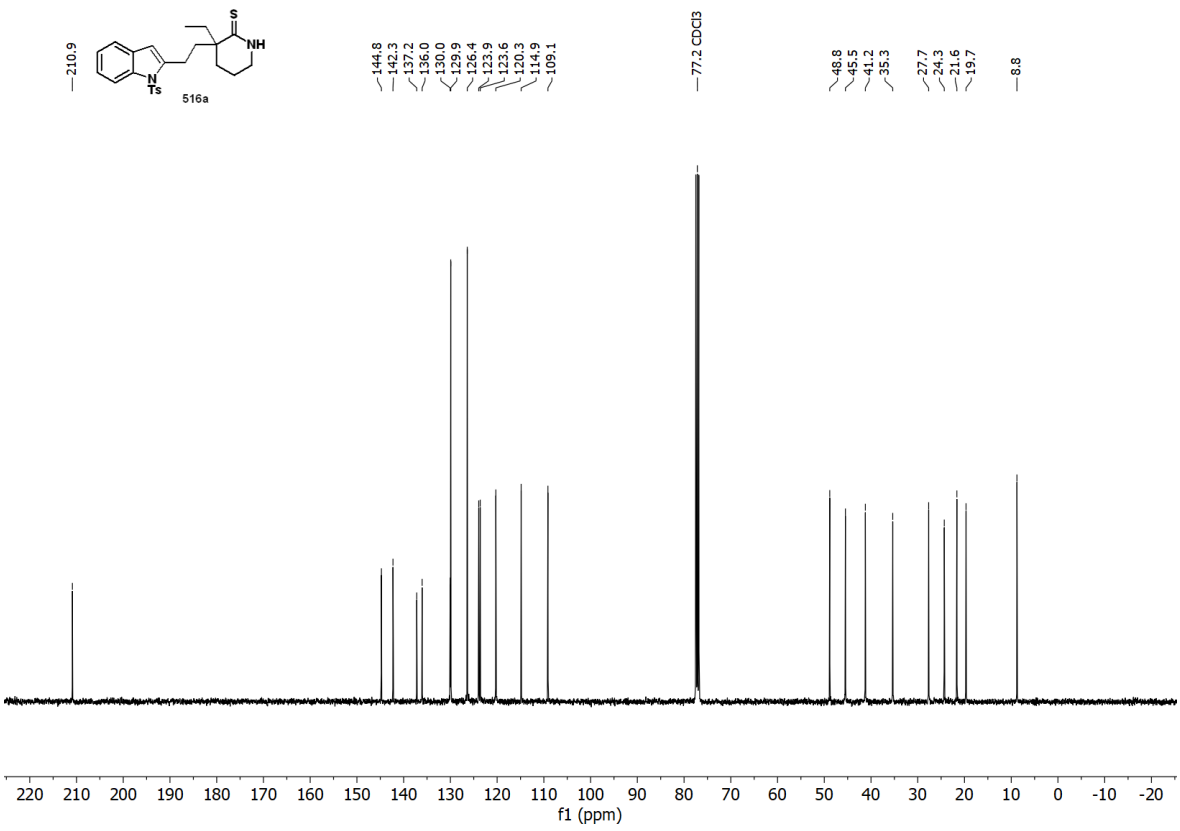

524a
8.13
7.61
7.58
7.39
7.37
7.26 CDCl3
7.25
7.14
6.41
6.02
3.32
3.11
2.98
2.31
2.11
2.04
1.96
1.89
1.79
1.61
0.93
1.00
2.03
1.02
4.49
1.00
1.00
2.25
1.05
1.05
3.13
1.17
1.15
5.21
1.19
3.23
f1 (ppm)

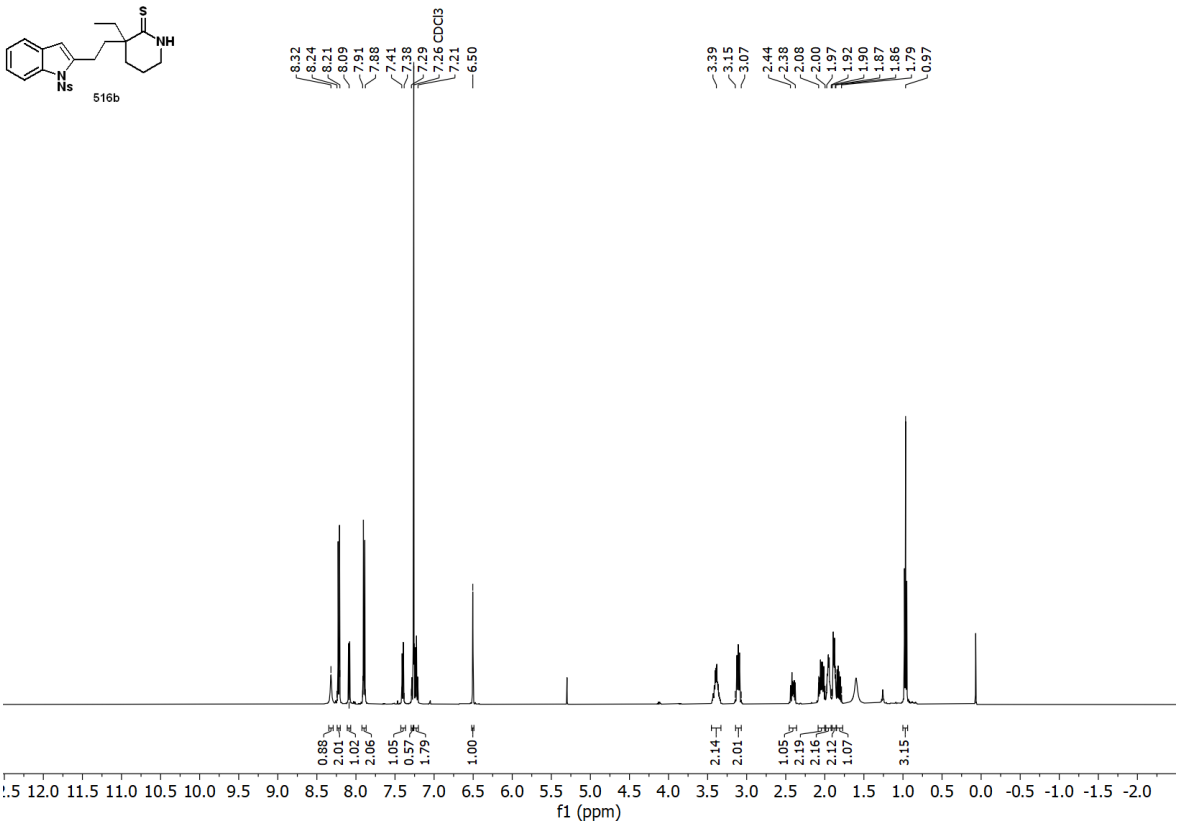

524a
176.8
144.8
142.5
137.3
136.2
130.0
129.9
126.4
123.9
123.6
120.3
114.9
109.2
77.2 CDCl3
44.9
42.9
37.8
31.0
29.4
24.3
21.6
19.9
8.7
f1 (ppm)

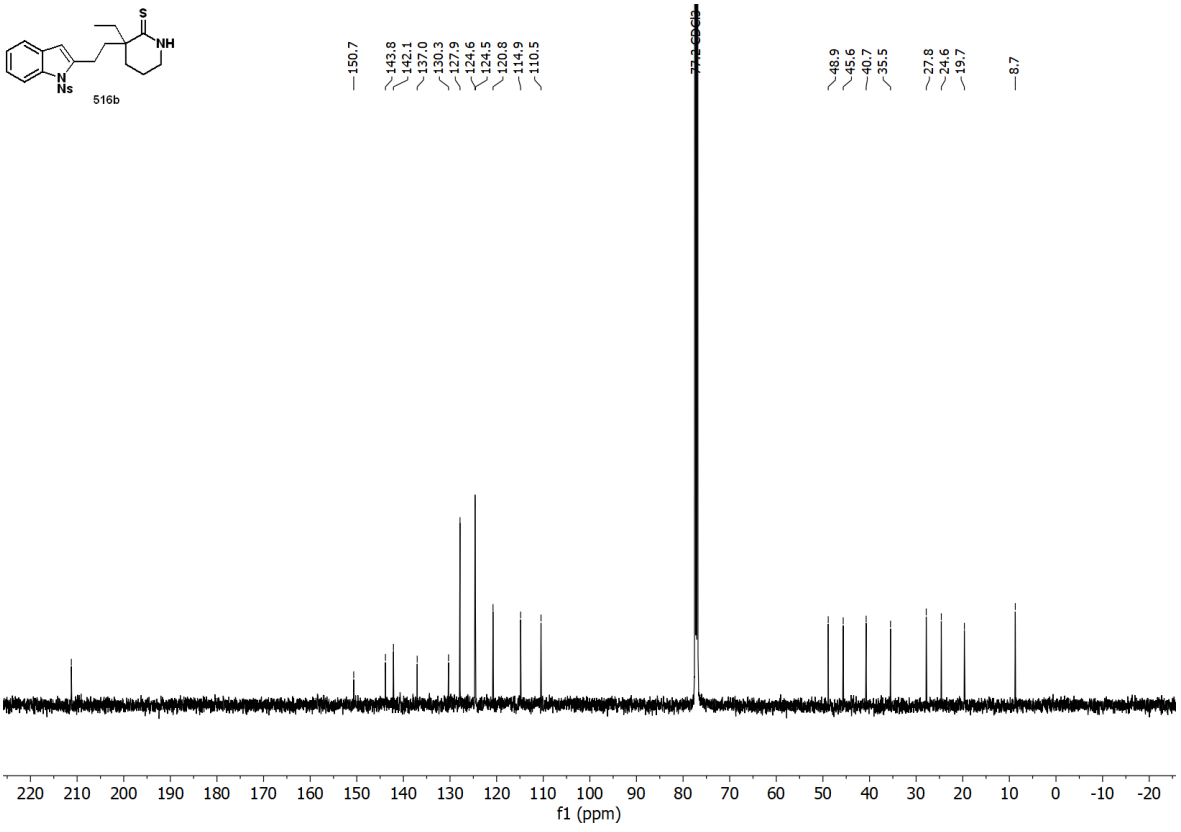

524b
8.25
8.20
8.10
7.90
7.86
7.40
7.30
7.26 CDCl3
7.20
6.47
5.71
3.34
3.12
3.01
2.01
1.89
1.76
1.68
1.61
0.94
2.01
1.00
2.01
1.02
0.74
1.53
0.99
0.96
2.05
1.02
0.99
2.29
5.29
1.13
3.19
f1 (ppm)

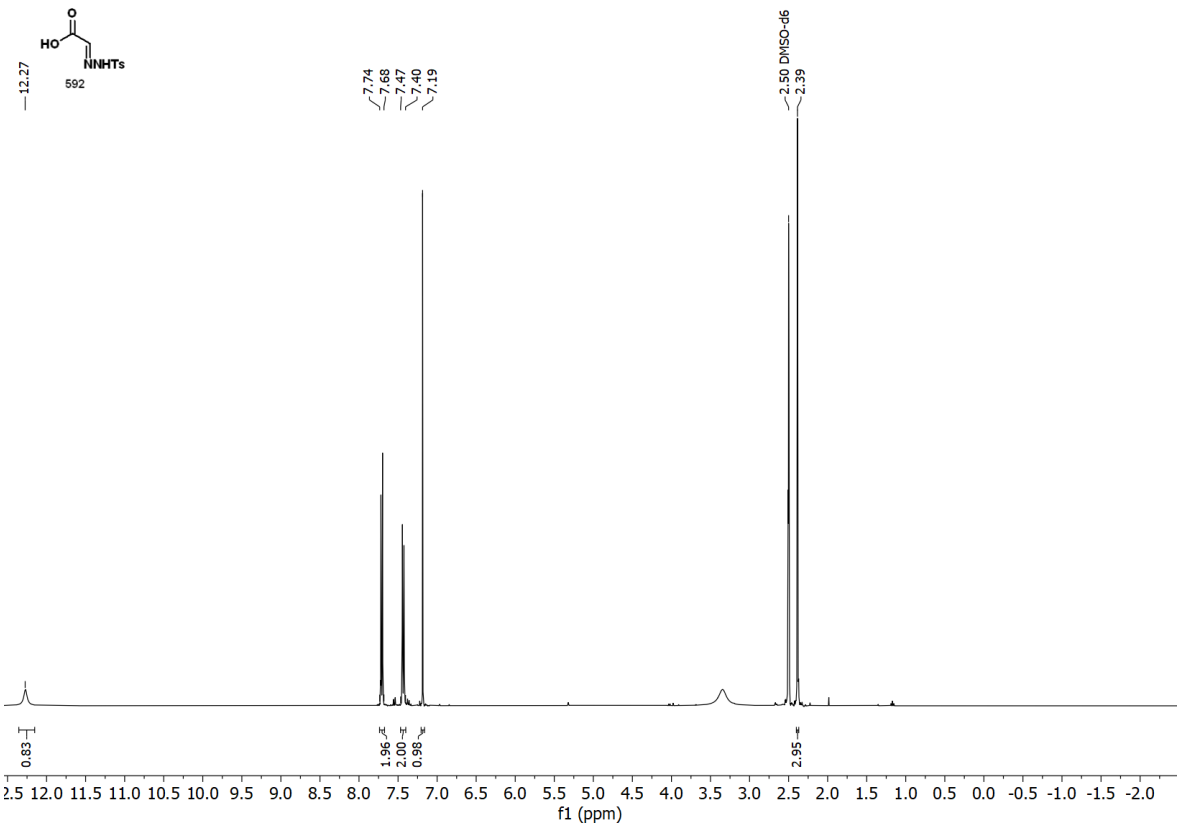

524b
176.5
150.7
144.0
142.4
137.1
130.3
127.8
124.6
124.6
124.5
120.8
114.9
110.7
77.3 CDCl3
44.9
42.9
37.7
30.9
29.7
24.6
19.9
8.7
f1 (ppm)

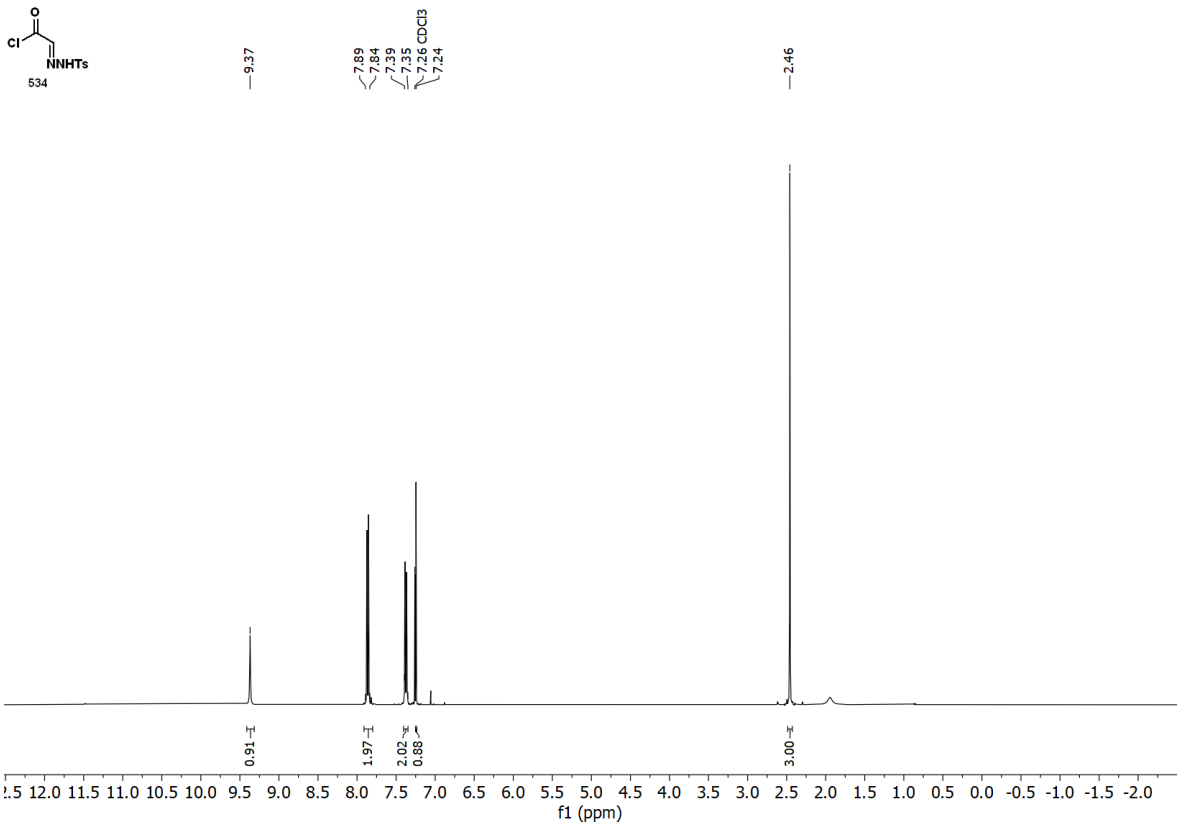

S
NH
N
Ts
516a
8.84
8.12
7.63
7.58
7.38
7.26 CDCl3
7.25
7.13
6.45
3.41
3.28
3.16
3.02
2.38
2.30
2.13
2.00
1.95
1.84
1.82
1.74
0.95
0.93
1.00
2.06
1.04
4.17
1.00
2.05
2.01
1.07
3.16
2.22
4.11
1.12
3.12
f1 (ppm)

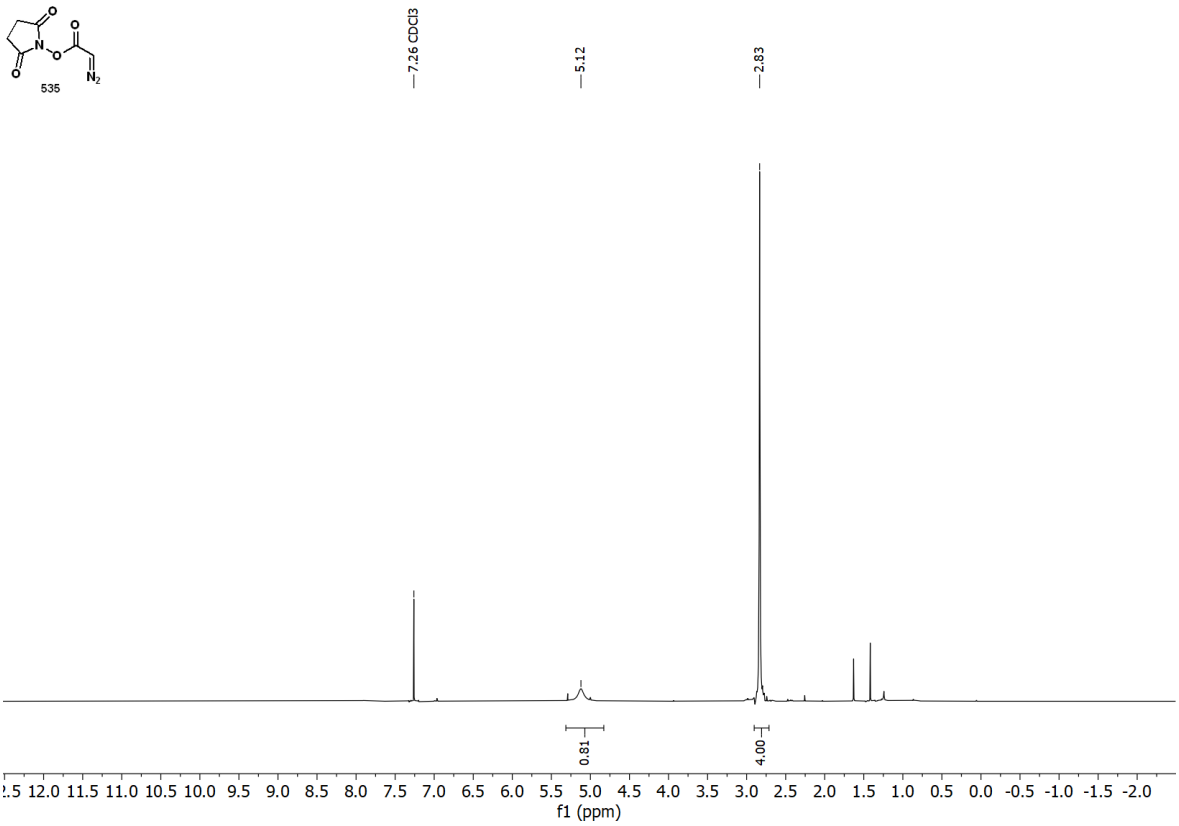

S
NH
N
Ts
516a
210.9
144.8
142.3
137.2
136.0
130.0
129.9
126.4
123.9
123.6
120.3
114.9
109.1
77.2 CDCl3
48.8
45.5
41.2
35.3
27.7
24.3
21.6
19.7
8.8
f1 (ppm)

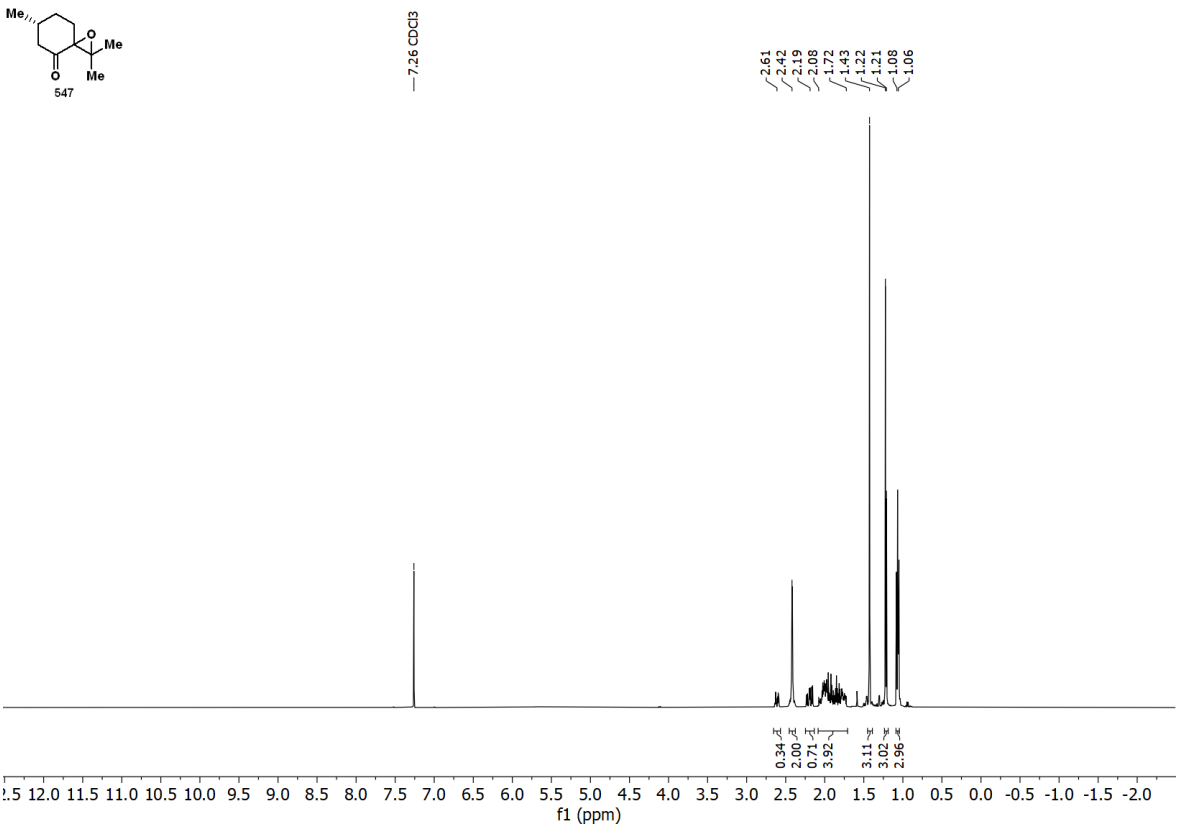

S
NH
N
Ns
516b
8.32
8.24
8.21
8.09
7.91
7.88
7.41
7.38
7.29
7.26 CDCl3
7.21
6.50
3.39
3.15
3.07
2.44
2.38
2.08
2.00
1.97
1.92
1.90
1.87
1.86
1.79
0.97
0.88
2.01
1.02
2.06
1.05
0.57
1.79
1.00
2.14
2.01
1.05
2.19
2.16
2.12
1.07
3.15
f1 (ppm)

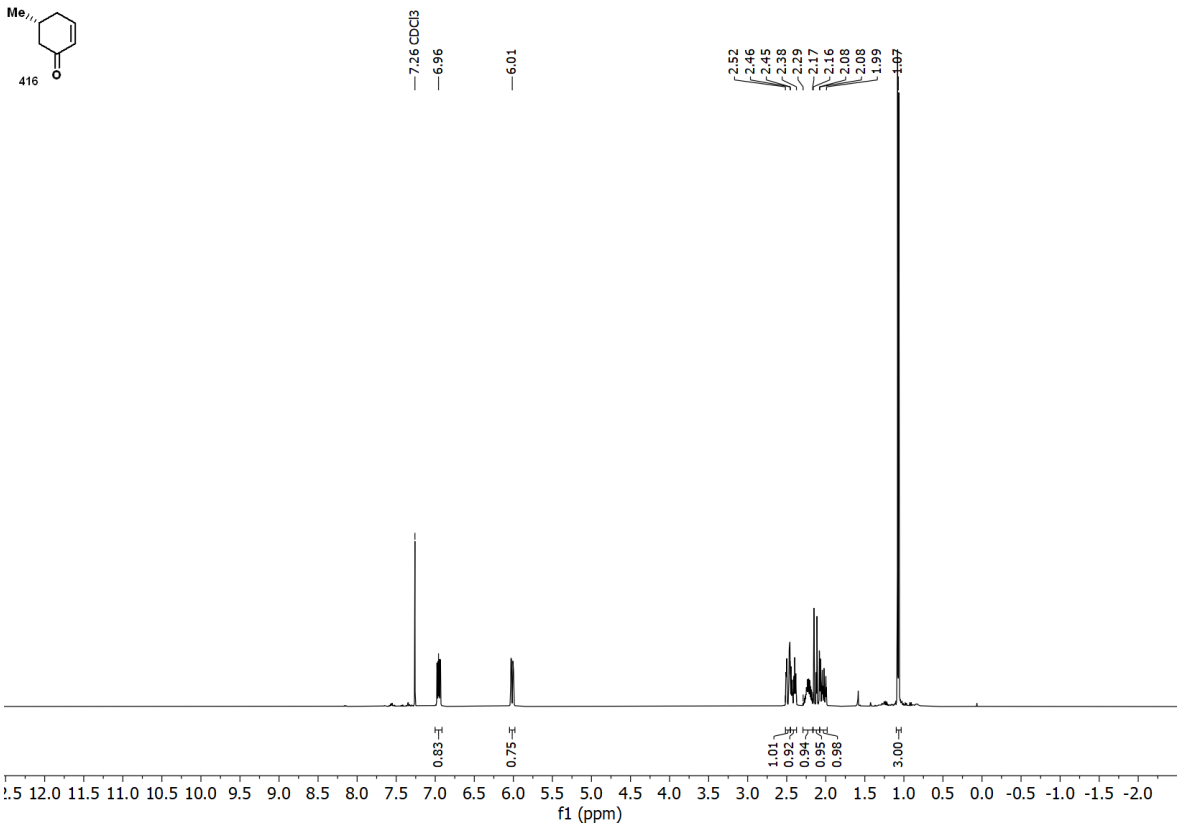

S
NH
N
Ns
516b
150.7
143.8
142.1
137.0
130.3
127.9
124.6
124.5
120.8
114.9
110.5
48.9
45.6
40.7
35.5
27.8
24.6
19.7
8.7
f1 (ppm)

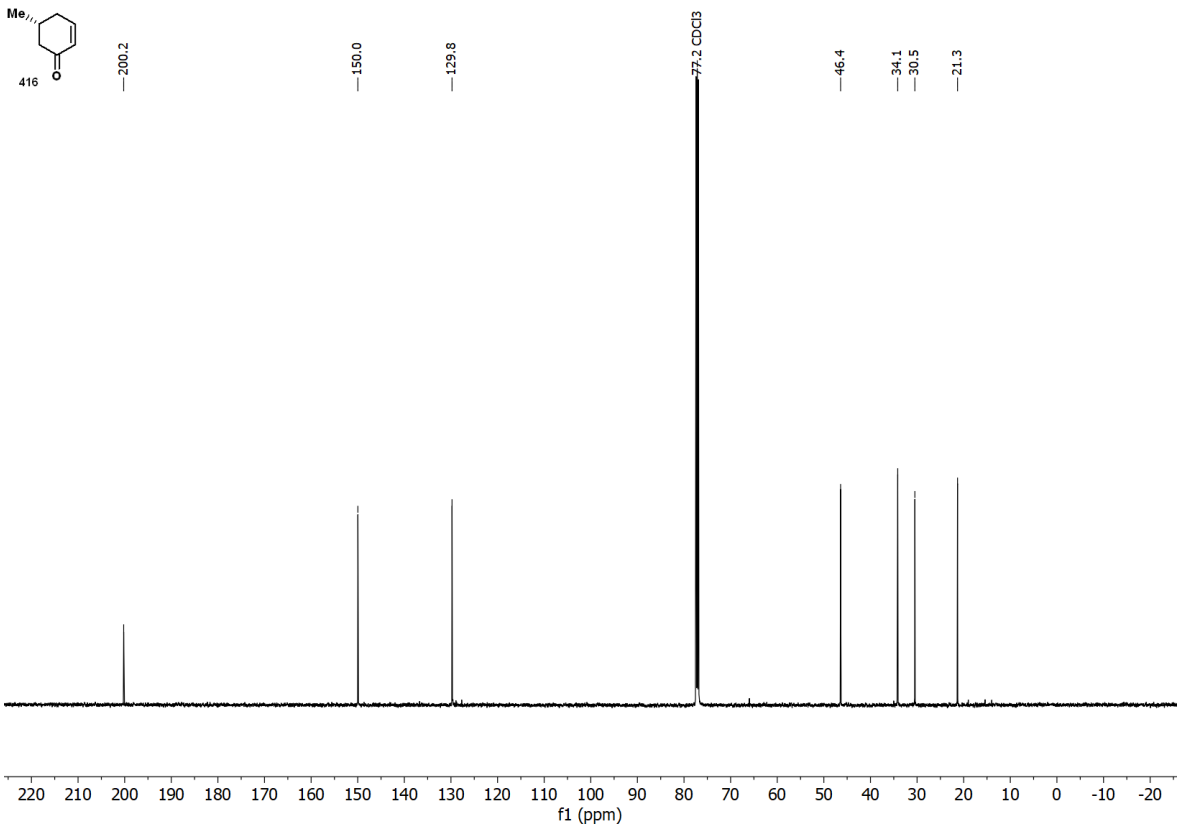

HO
O
NNHTs
592
12.27
7.74
7.68
7.47
7.40
7.19
2.50 DMSO-d6
2.39
0.83
1.96
2.00
0.98
2.95
f1 (ppm)

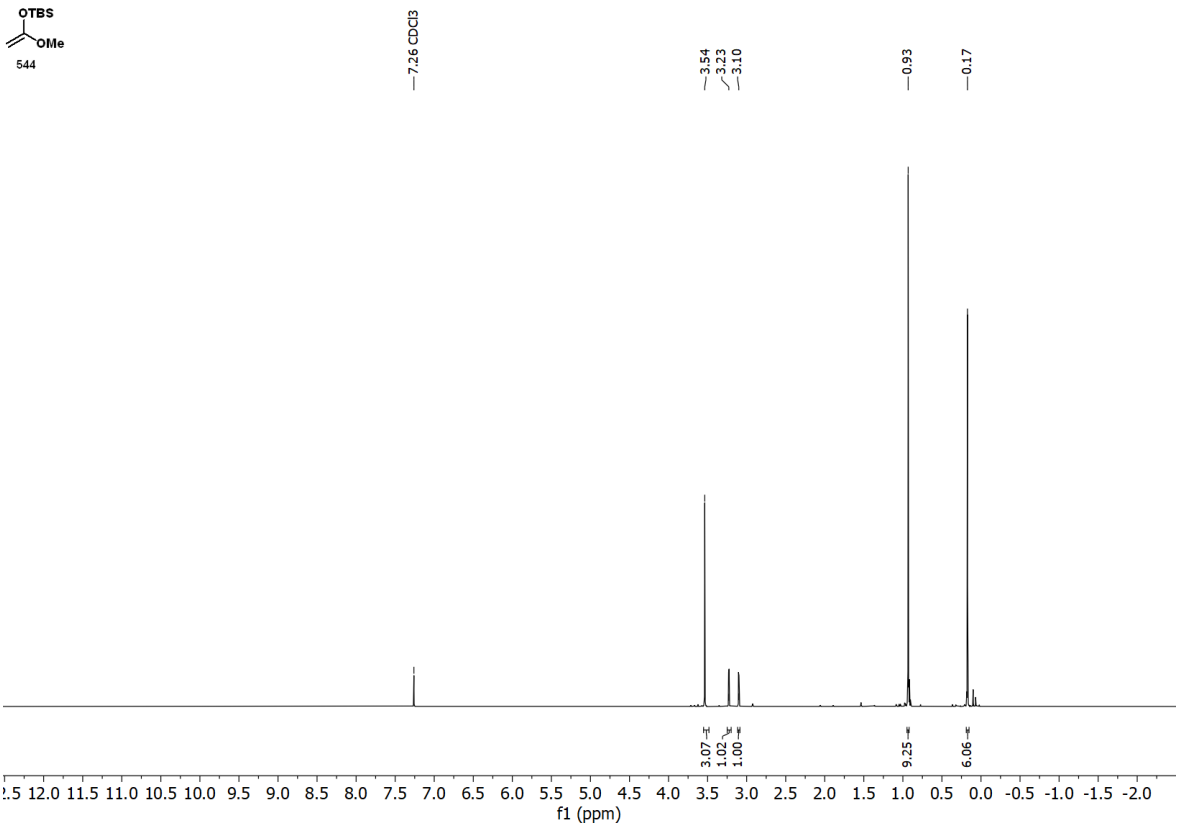

Cl
O
NNHTs
534
9.37
7.89
7.84
7.39
7.35
7.26 CDCl3
7.24
2.46
0.91
1.97
2.02
0.88
3.00
f1 (ppm)

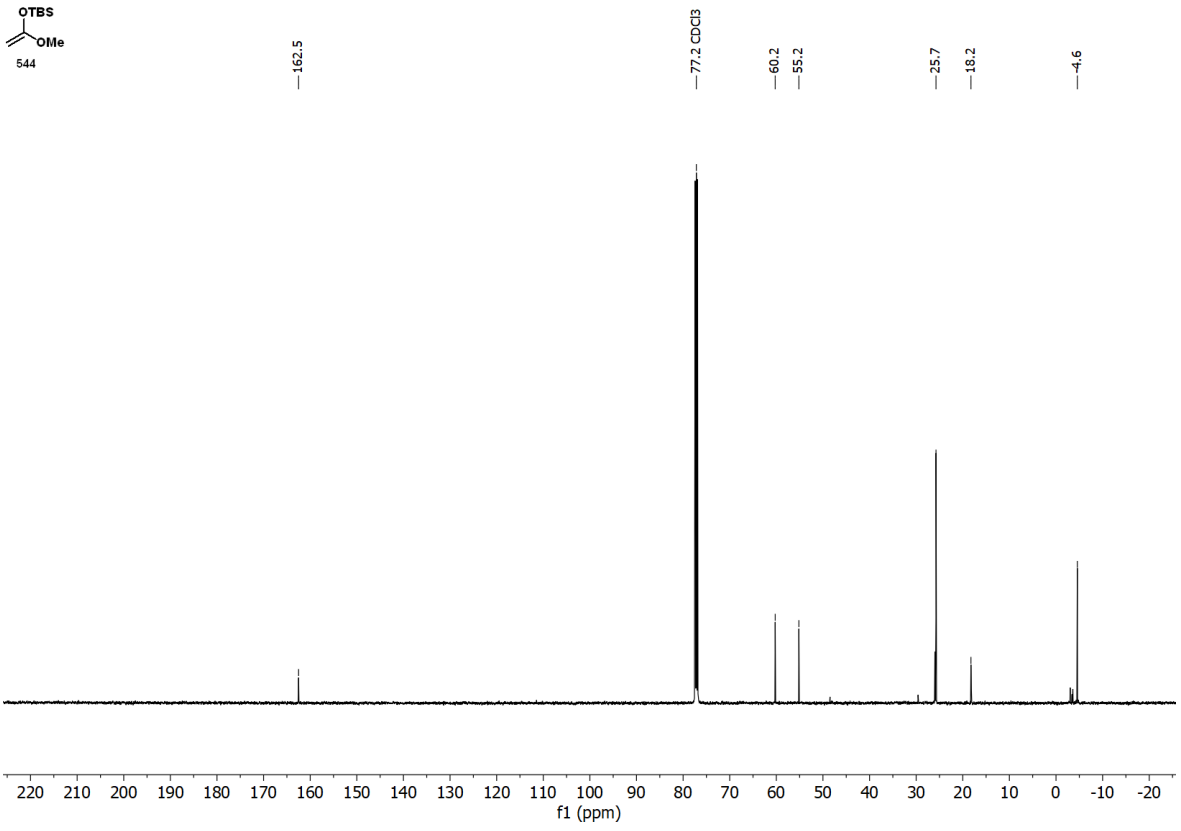

535
7.26 CDCl3
5.12
2.83
0.81
4.00
f1 (ppm)

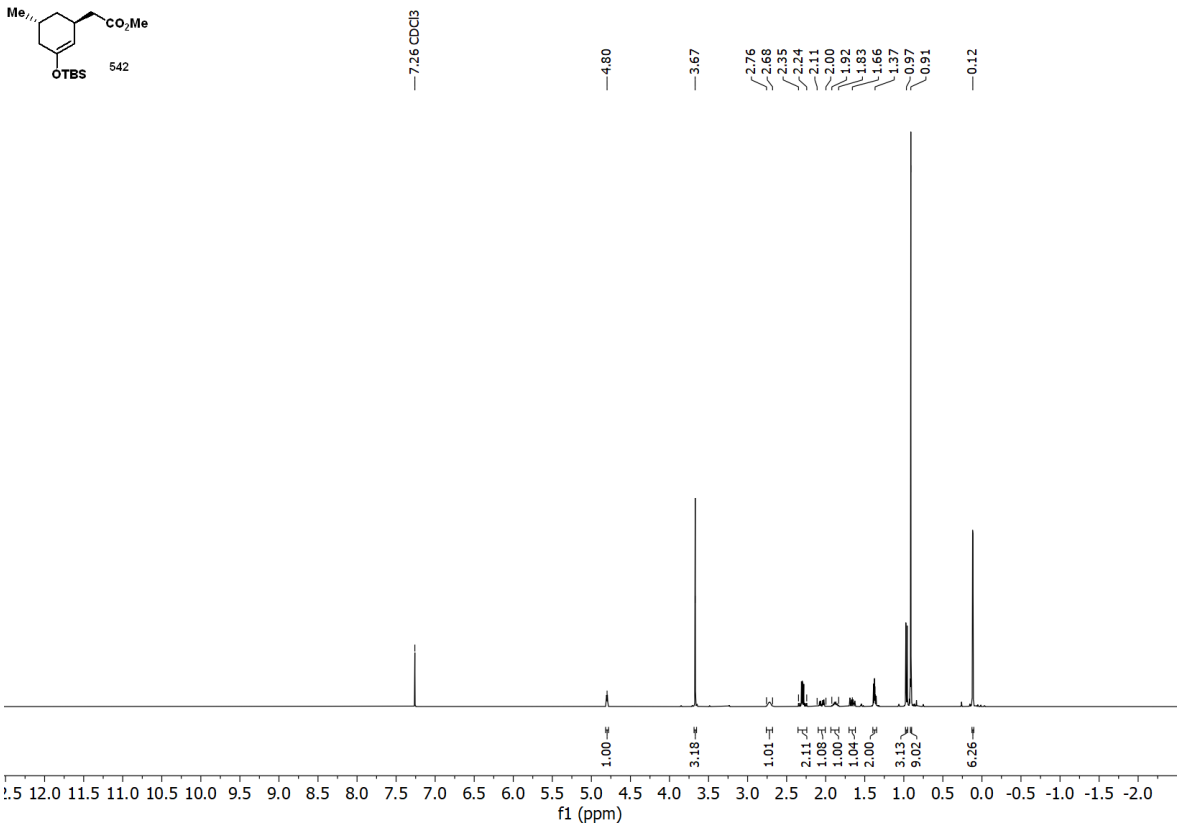

Me
Me
Me
547
7.26 CDCl3
2.61
2.42
2.19
2.08
1.72
1.43
1.22
1.21
1.08
1.06
0.34
2.00
0.71
3.92
3.11
3.02
2.96
f1 (ppm)

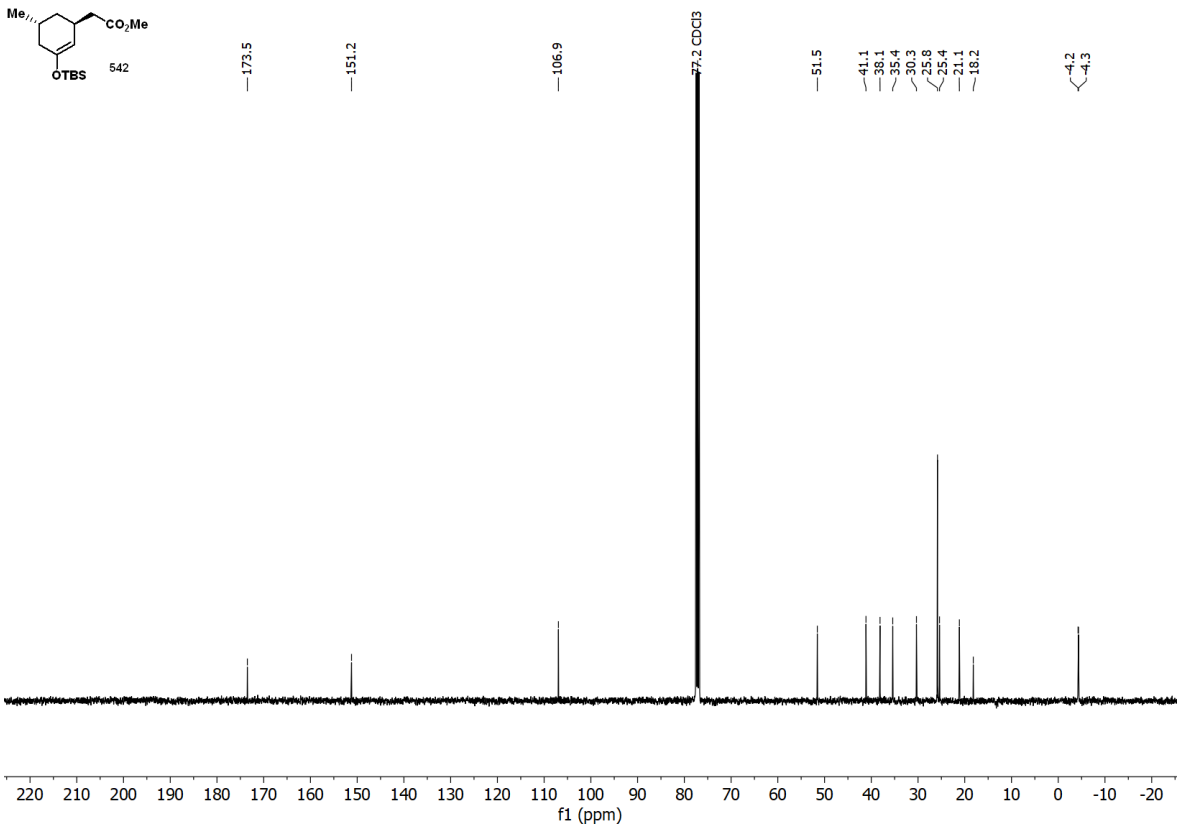

Me
416
7.26 CDCl3
6.96
6.01
2.52
2.46
2.45
2.38
2.29
2.17
2.16
2.08
2.08
1.99
1.07
0.83
0.75
1.01
0.92
0.94
0.95
0.98
3.00
f1 (ppm)

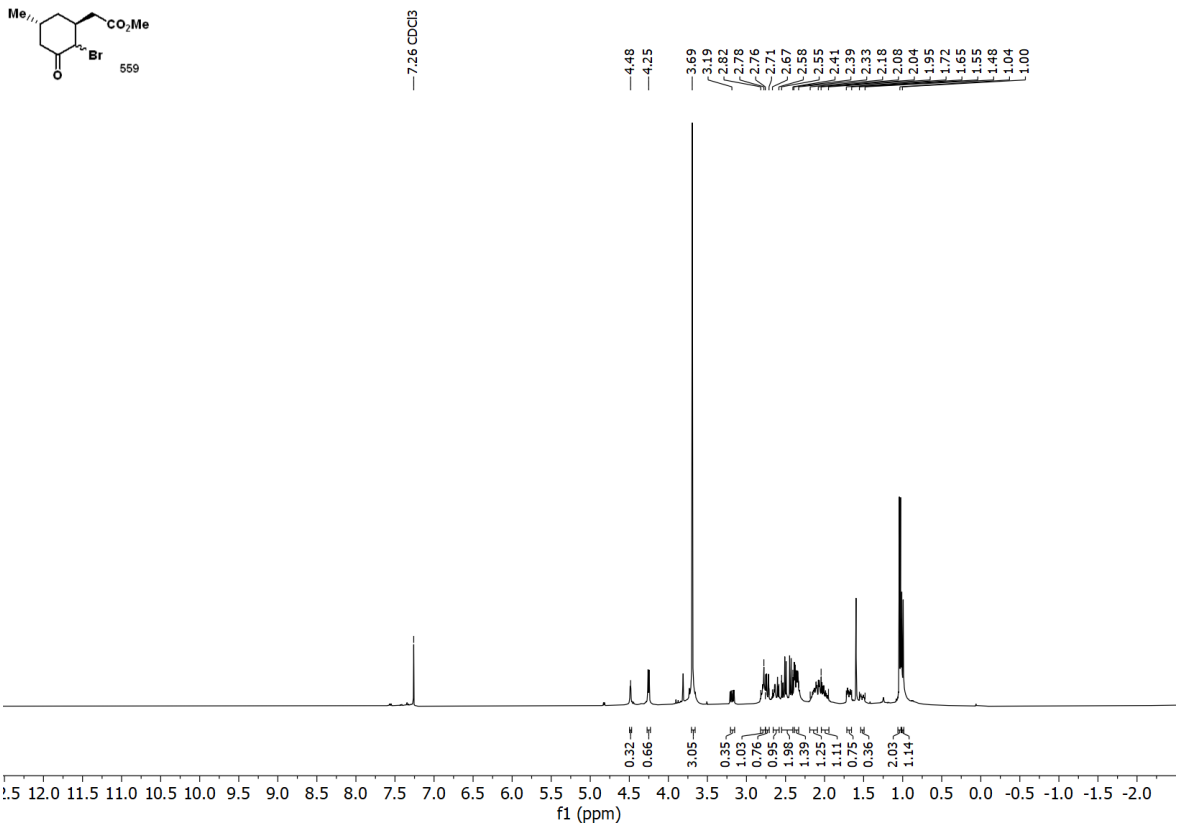

Me
416
200.2
150.0
129.8
77.2 CDCl3
46.4
34.1
30.5
21.3
f1 (ppm)

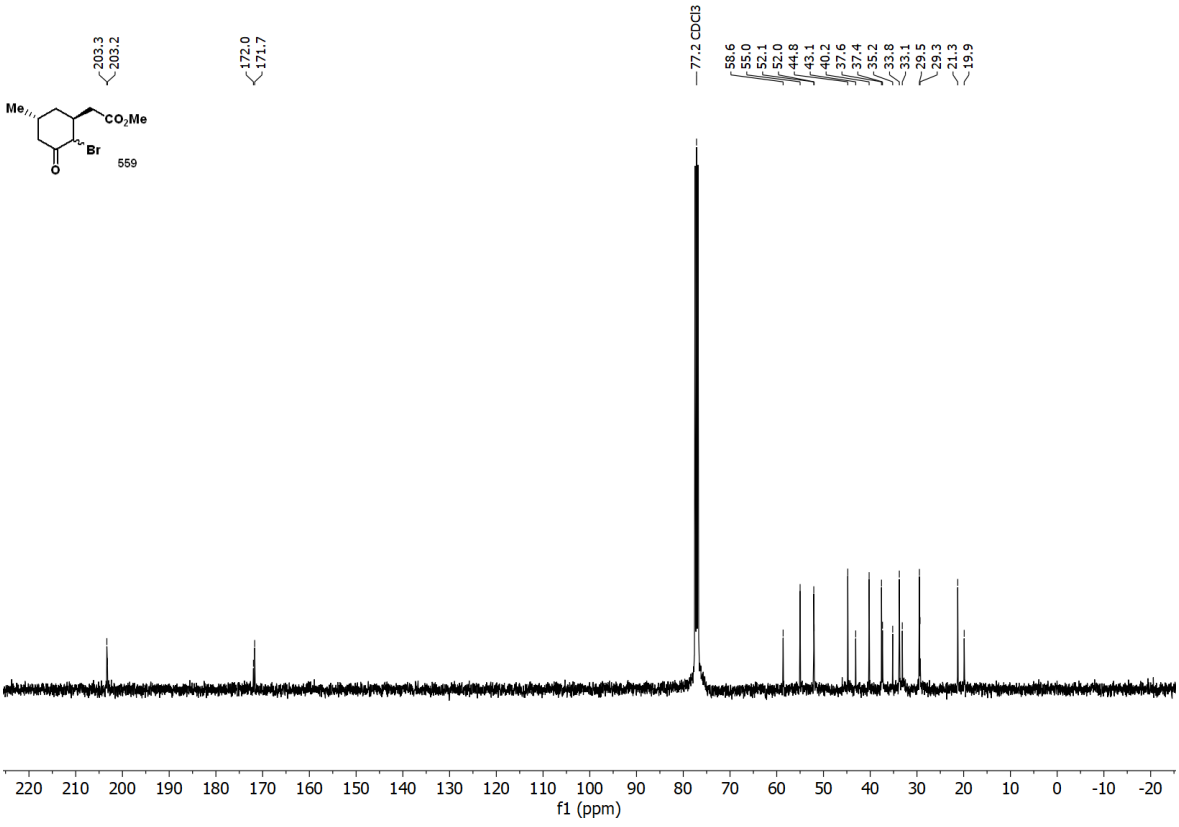

OTBS
OMe
544
7.26 CDCl3
3.54
3.23
3.10
0.93
0.17
3.07
1.02
1.00
9.25
6.06
f1 (ppm)

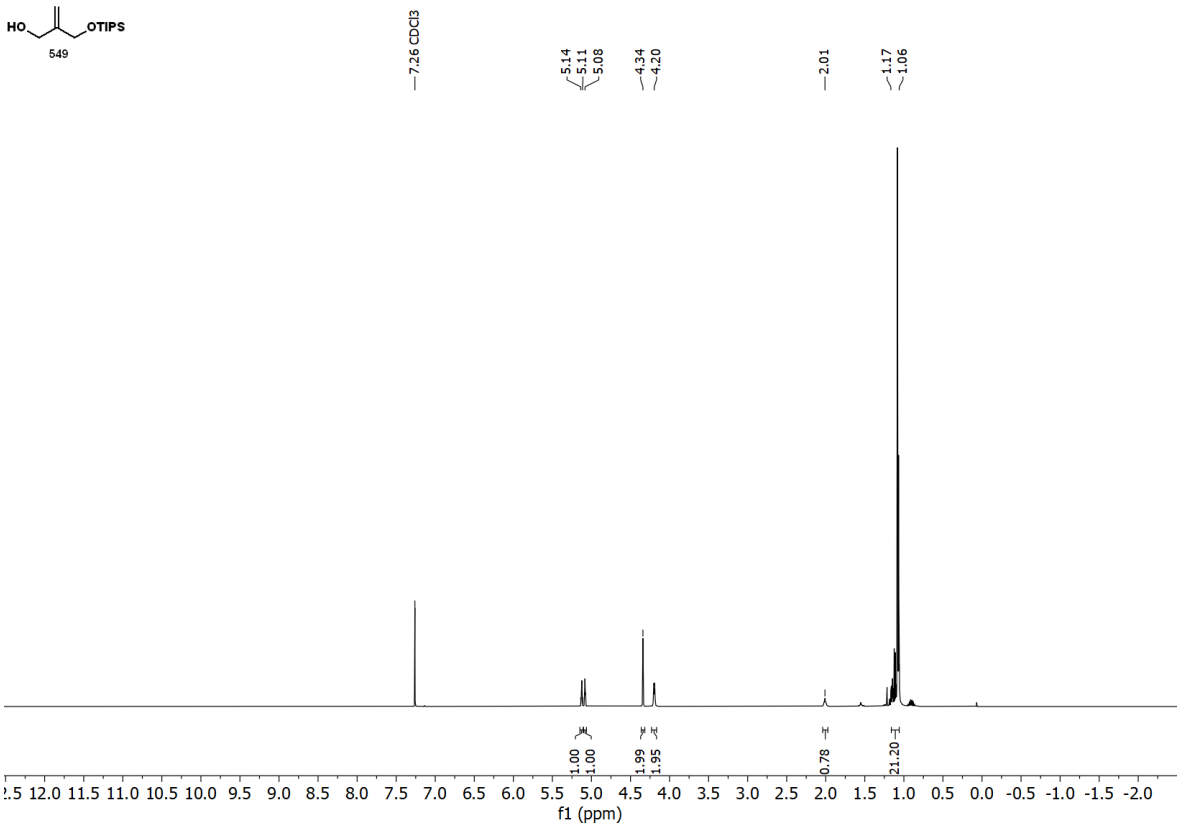

OTBS
OMe
544
162.5
77.2 CDCl3
60.2
55.2
25.7
18.2
-4.6
f1 (ppm)

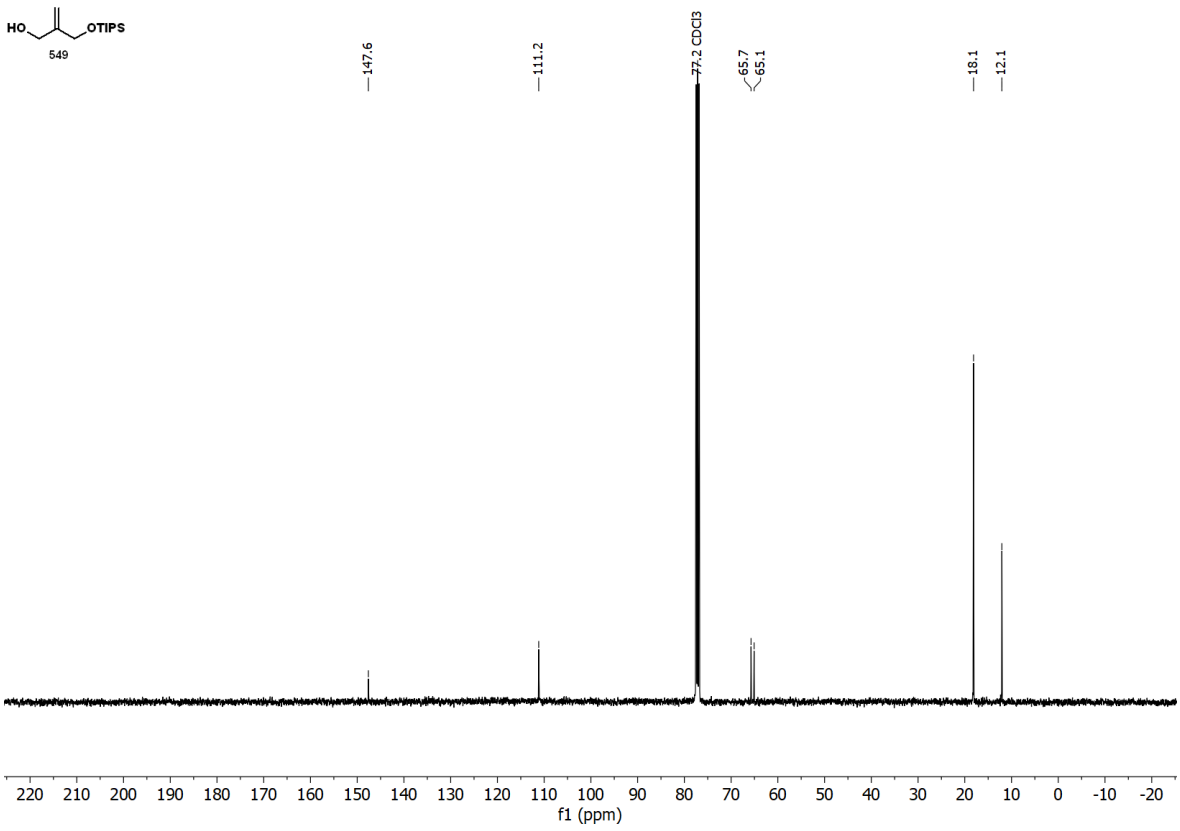

Me
CO2Me
OTBS
542
7.26 CDCl3
4.80
3.67
2.76
2.68
2.35
2.24
2.11
2.00
1.92
1.83
1.66
1.37
0.97
0.91
0.12
1.00
3.18
1.01
2.11
1.08
1.00
1.04
2.00
3.13
9.02
6.26
f1 (ppm)

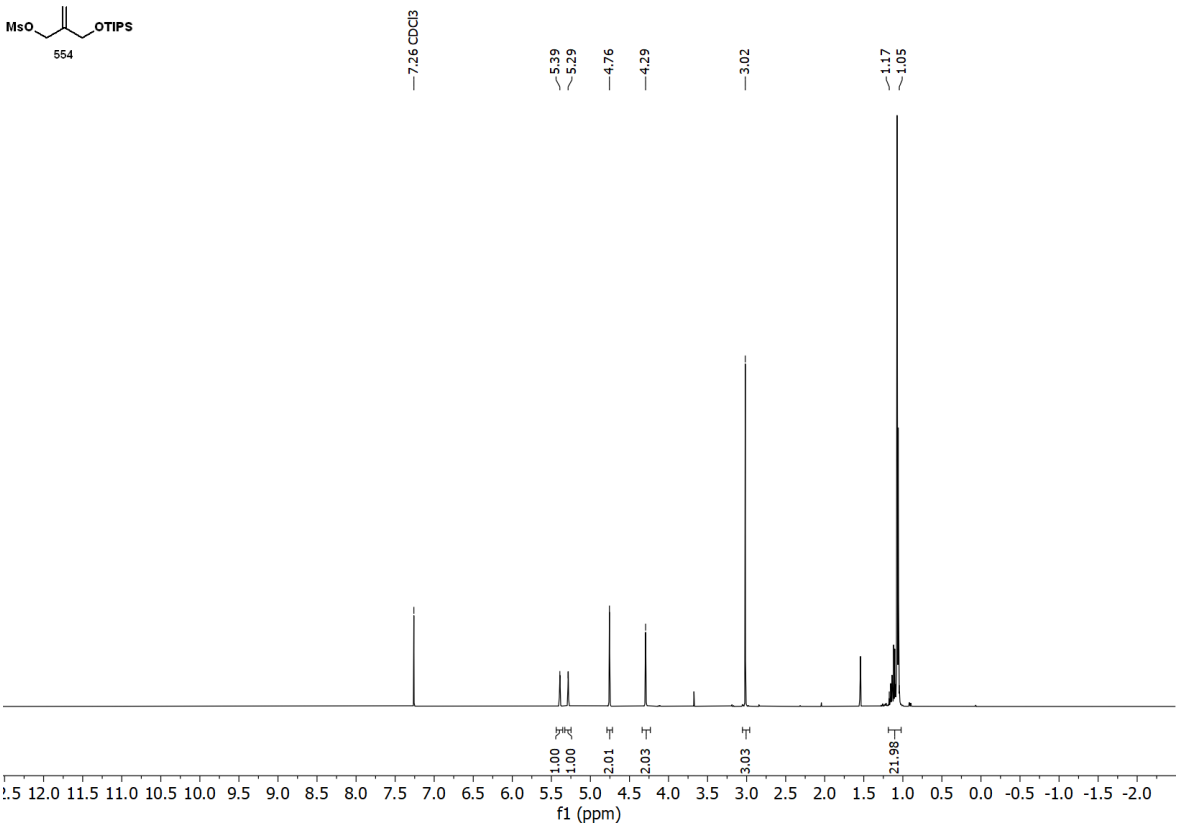

Me
CO2Me
OTBS
542
173.5
151.2
106.9
77.2 CDCl3
51.5
41.1
38.1
35.4
30.3
25.8
25.4
21.1
18.2
-4.2
-4.3
f1 (ppm)

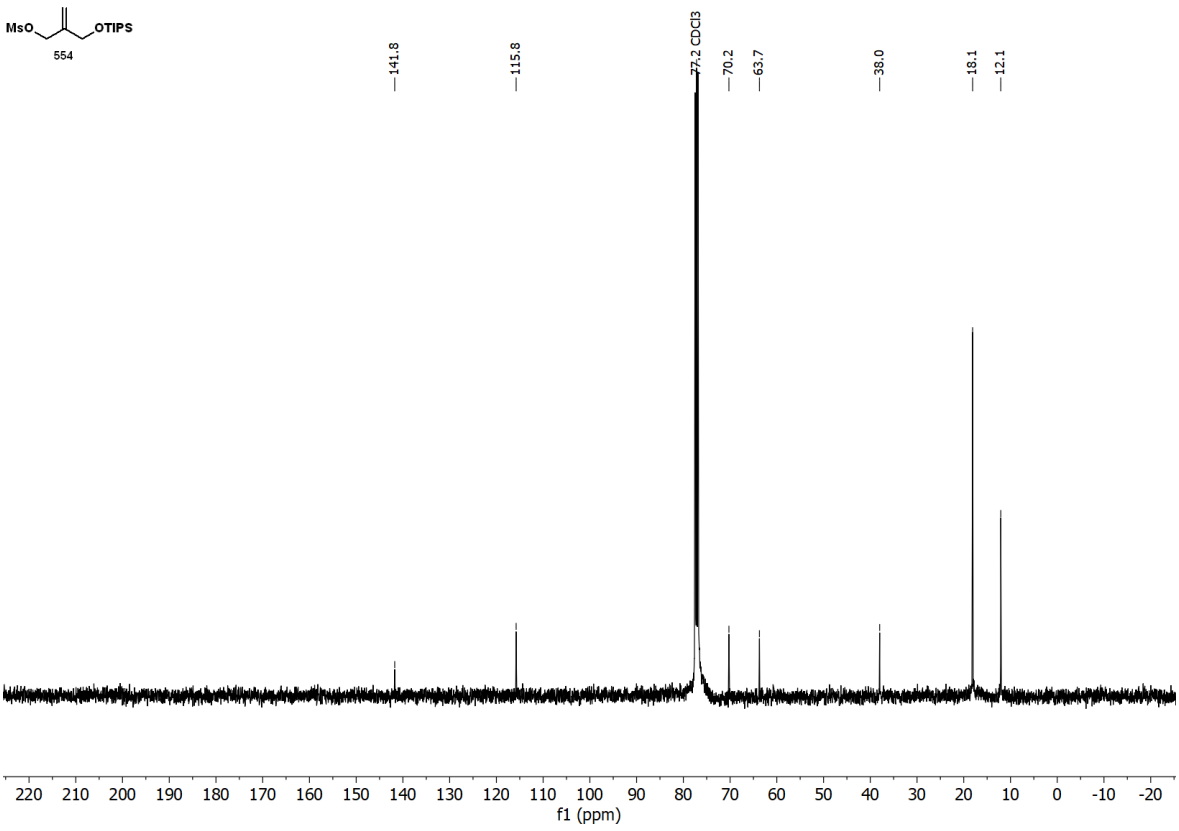

Me
CO2Me
Br
O
559
7.26 CDCl3
4.48
4.25
3.69
3.19
2.82
2.78
2.76
2.71
2.67
2.58
2.55
2.41
2.39
2.33
2.18
2.08
2.04
1.95
1.72
1.65
1.55
1.48
1.04
1.00
0.32
0.66
3.05
0.35
1.03
0.76
0.95
1.98
1.39
1.25
1.11
0.75
0.36
2.03
1.14
f1 (ppm)

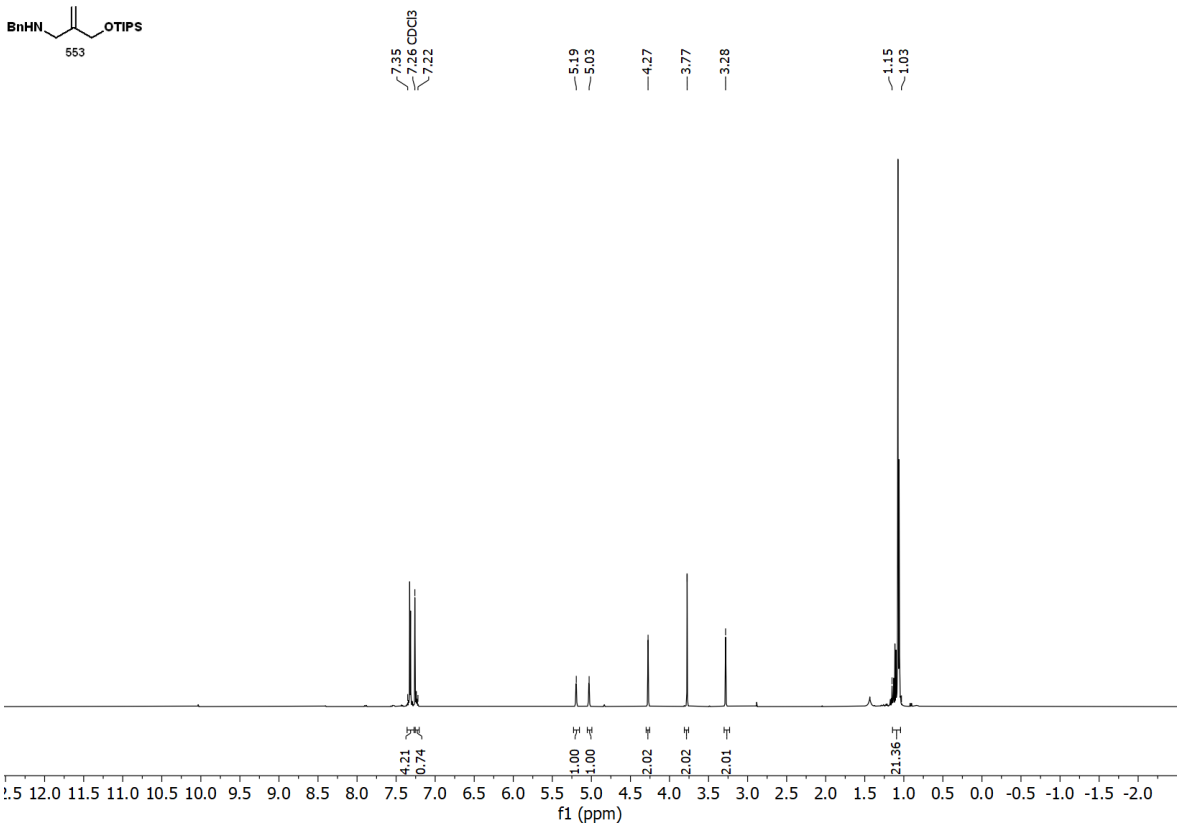

203.3
203.2
172.0
171.7
77.2 CDCl3
58.6
55.0
52.1
52.0
44.8
43.1
40.2
37.6
37.4
35.2
33.8
33.1
29.5
29.3
21.3
19.9
Me
CO2Me
Br
O
559
f1 (ppm)

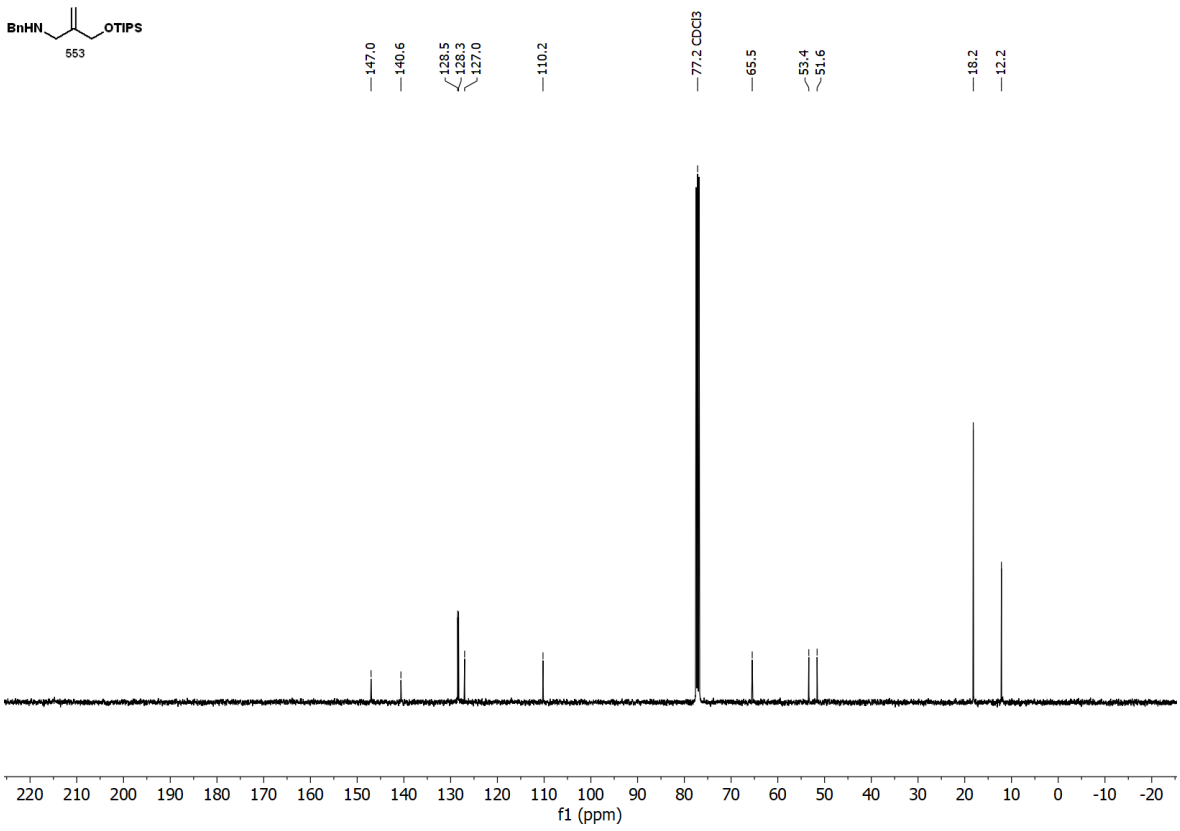

HO
OTIPS
549
7.26 CDCl3
5.14
5.11
5.08
4.34
4.20
2.01
1.17
1.06
1.00
1.00
1.99
1.95
0.78
21.20
f1 (ppm)

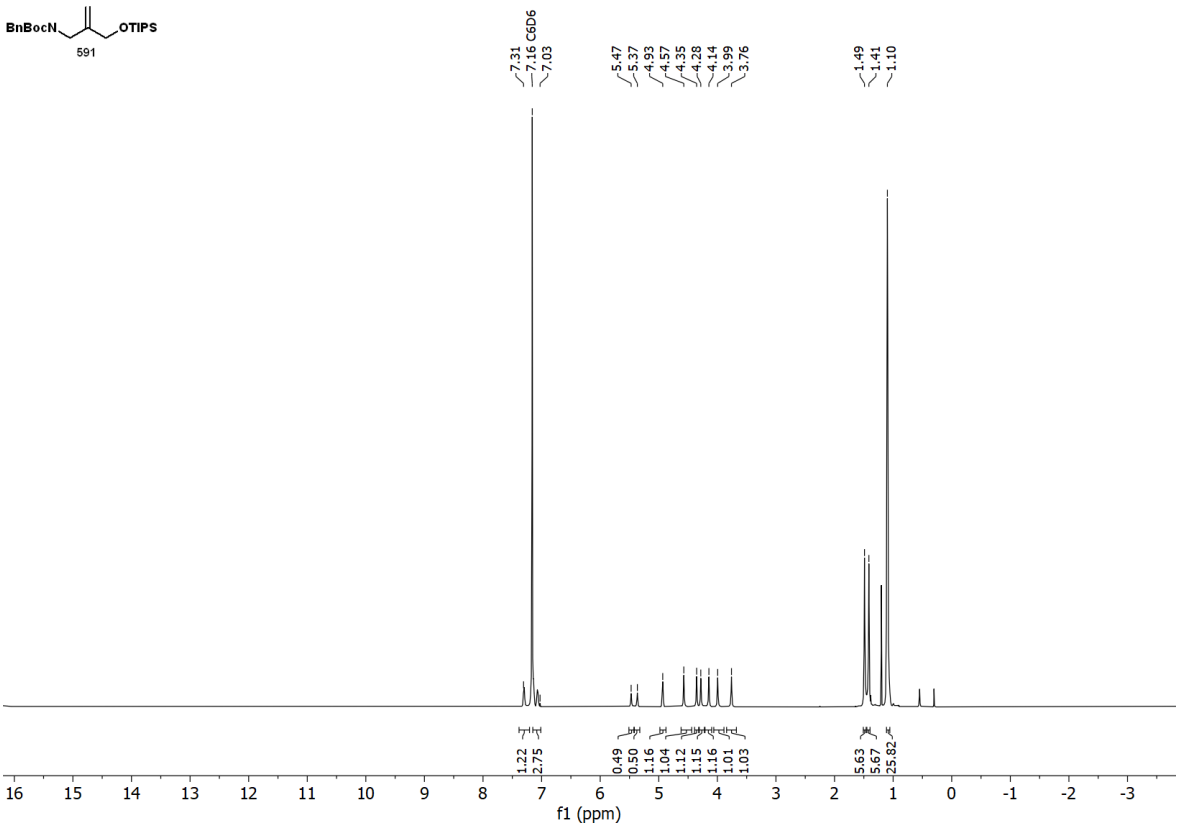

HO
OTIPS
549
147.6
111.2
77.2 CDCl3
65.7
65.1
18.1
12.1
f1 (ppm)

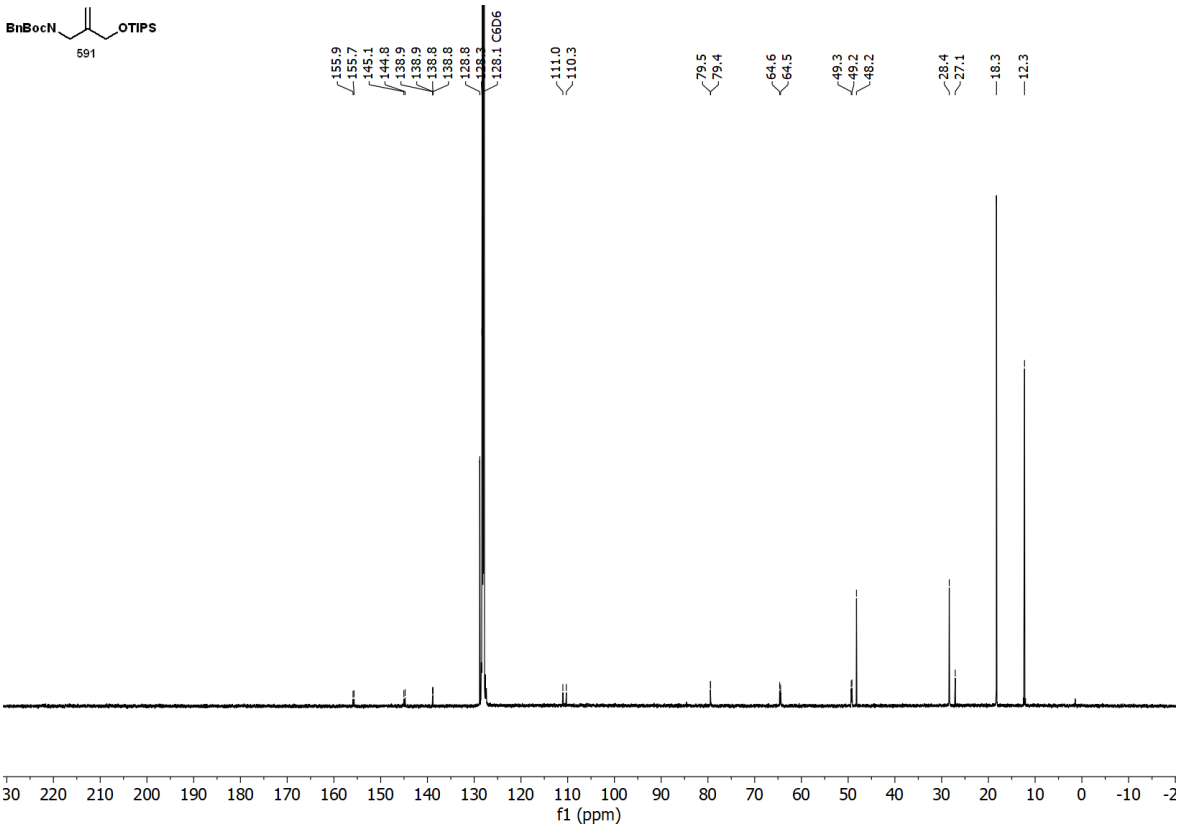

MsO
OTIPS
554
7.26 CDCl3
5.39
5.29
4.76
4.29
3.02
1.17
1.05
1.00
1.00
2.01
2.03
3.03
21.98
f1 (ppm)

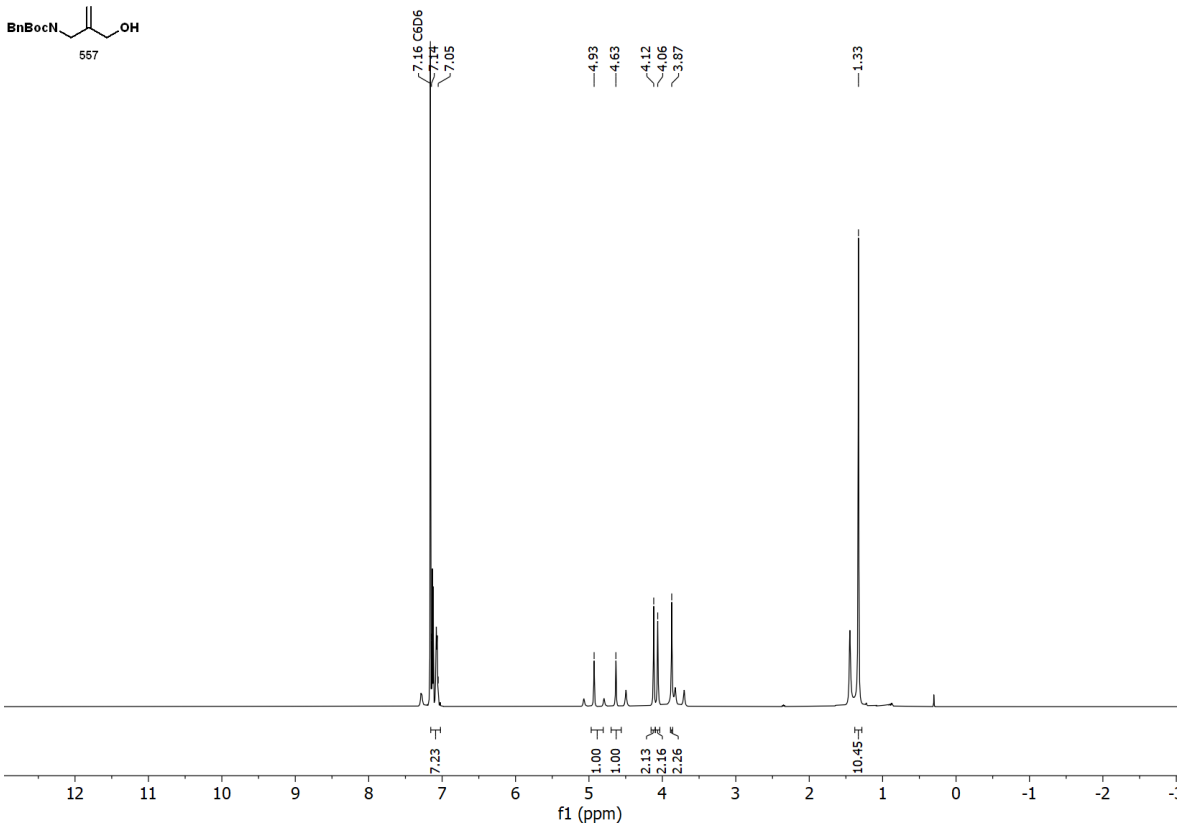

MsO
OTIPS
554
141.8
115.8
77.2 CDCl3
70.2
63.7
38.0
18.1
12.1
f1 (ppm)

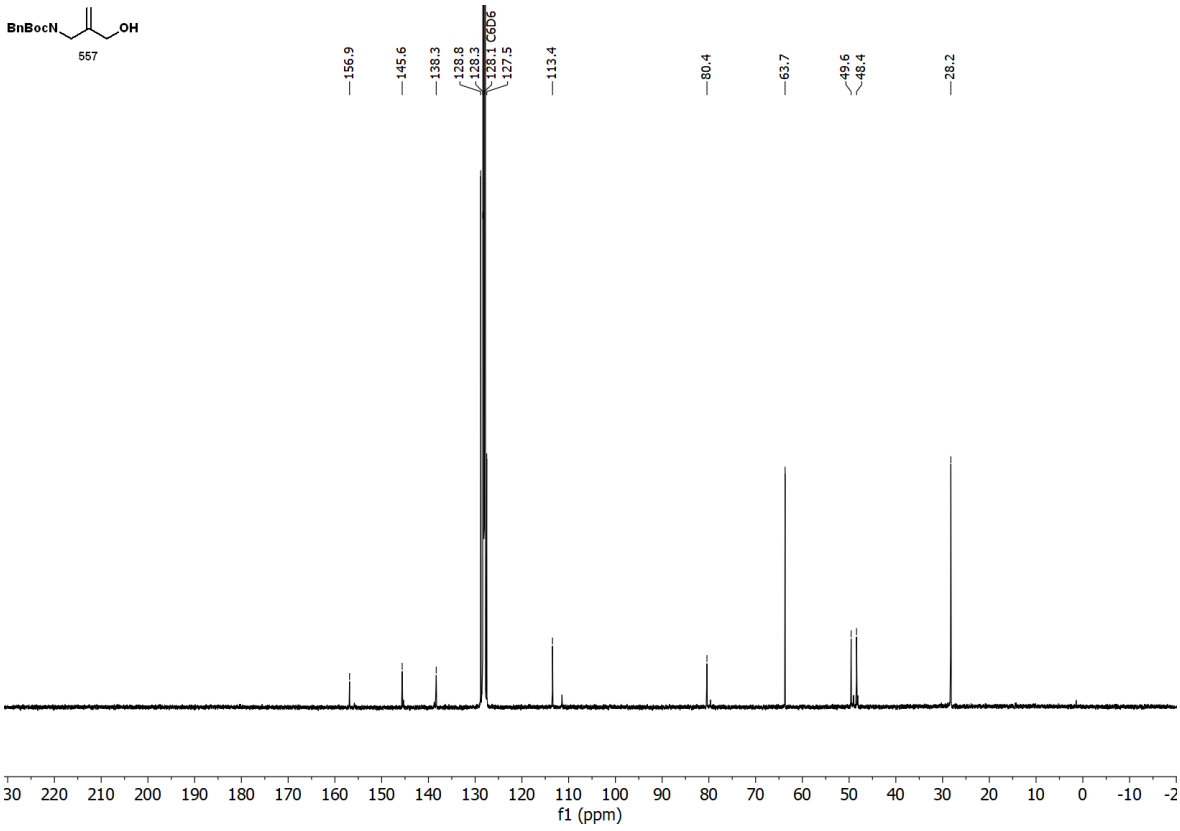

BnHN
OTIPS
553
7.35
7.26 CDCl3
7.22
5.19
5.03
4.27
3.77
3.28
1.15
1.03
4.21
0.74
1.00
1.00
2.02
2.02
2.01
21.36
f1 (ppm)

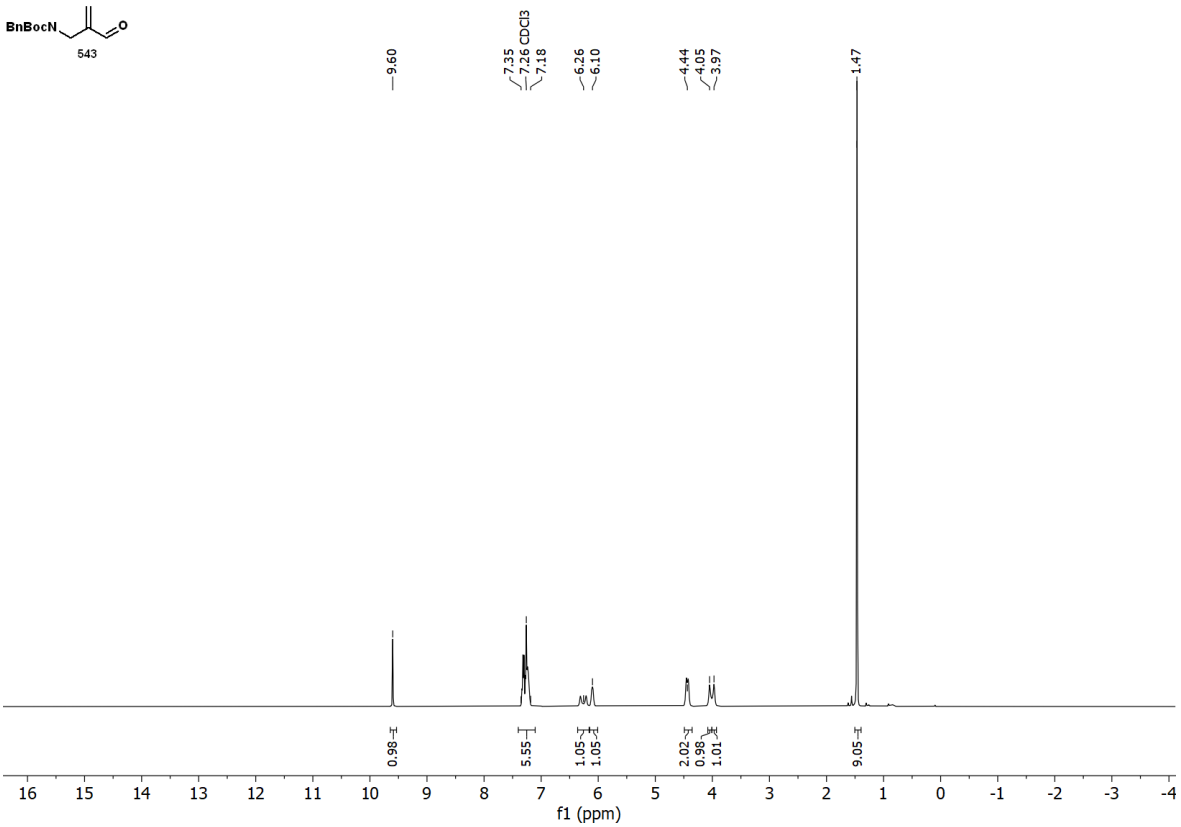

BnHN
OTIPS
553
147.0
140.6
128.5
128.3
127.0
110.2
77.2 CDCl3
65.5
53.4
51.6
18.2
12.2
f1 (ppm)

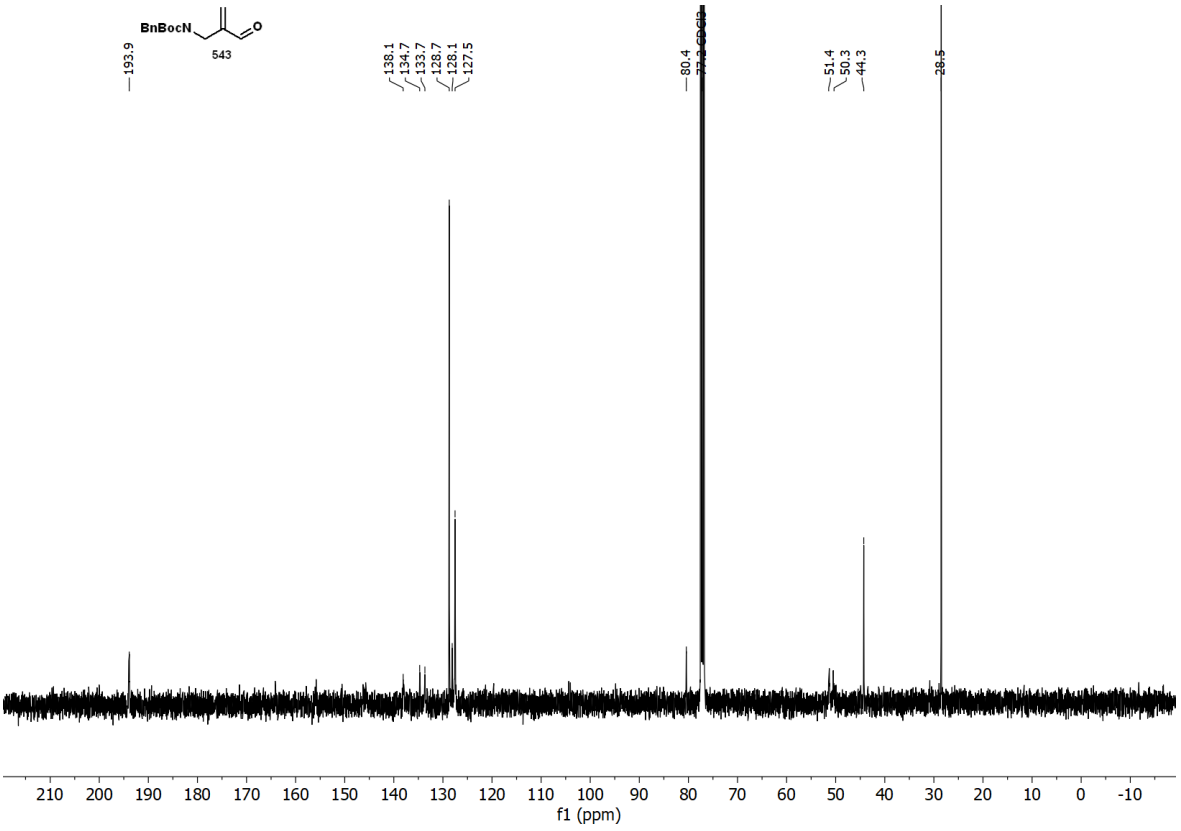

BnBocN
OTIPS
591
7.31
7.16 C6D6
7.03
5.47
5.37
4.93
4.57
4.35
4.28
4.14
3.99
3.76
1.49
1.41
1.10
1.22
2.75
0.49
0.50
1.16
1.04
1.12
1.15
1.16
1.01
1.03
5.63
5.67
25.82
f1 (ppm)

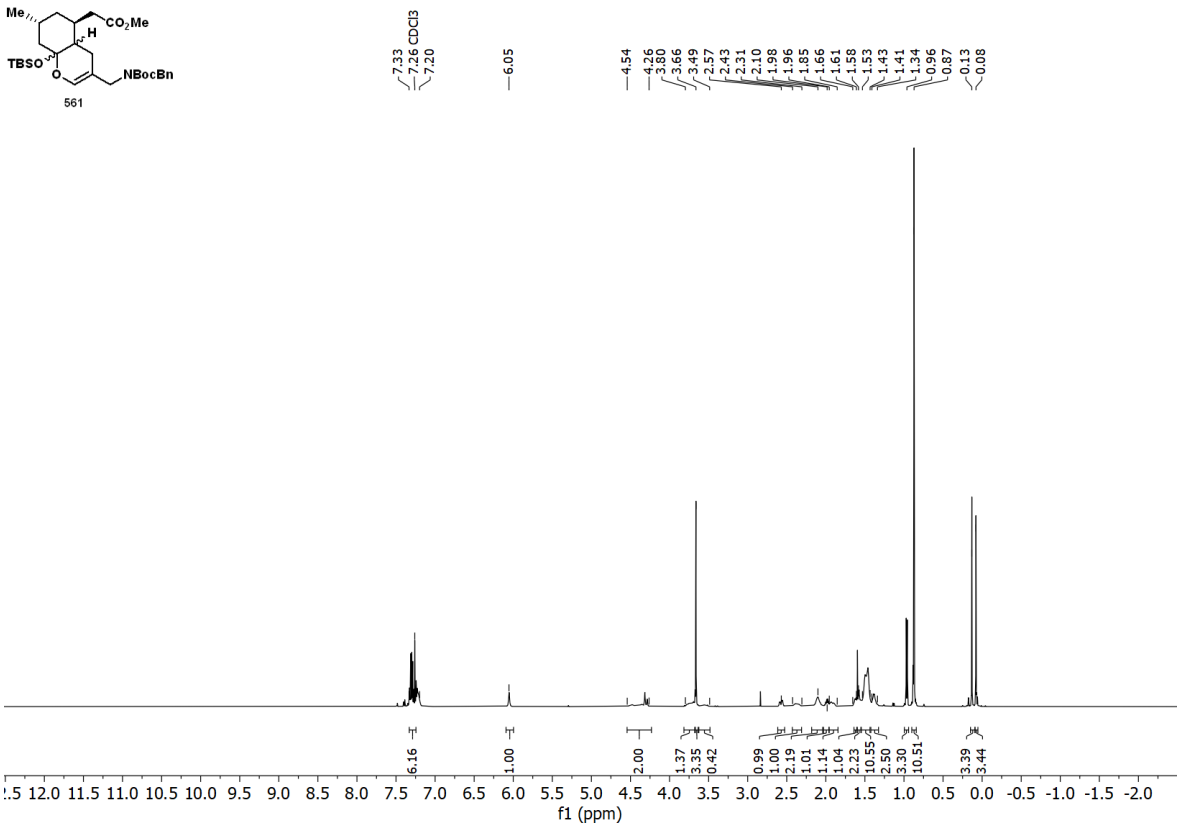

BnBocN
OTIPS
591
155.9
155.7
145.1
144.8
138.9
138.9
138.8
138.8
128.8
128.3
128.1 C6D6
111.0
110.3
79.5
79.4
64.6
64.5
49.3
49.2
48.2
28.4
27.1
18.3
12.3
f1 (ppm)

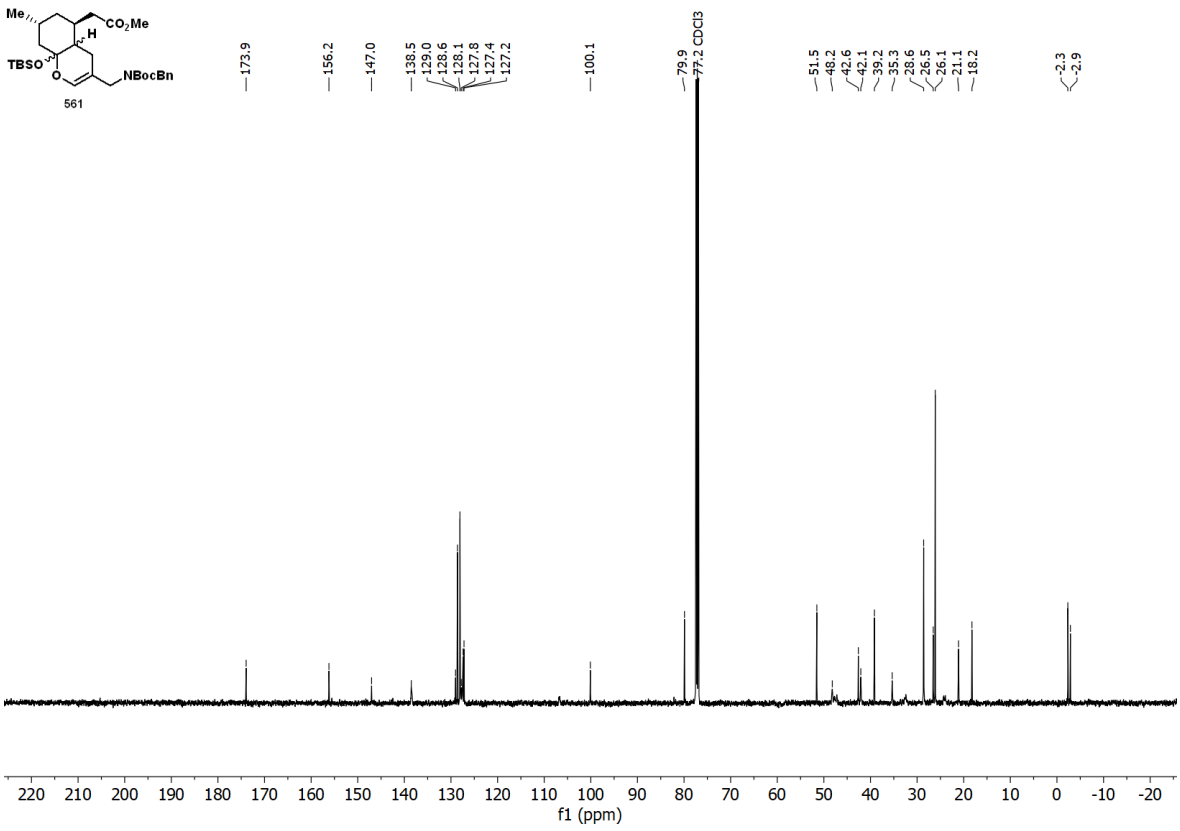

BnBocN
OH
557
7.16 C6D6
7.14
7.05
4.93
4.63
4.12
4.06
3.87
1.33
7.23
1.00
1.00
2.13
2.16
2.26
10.45
f1 (ppm)

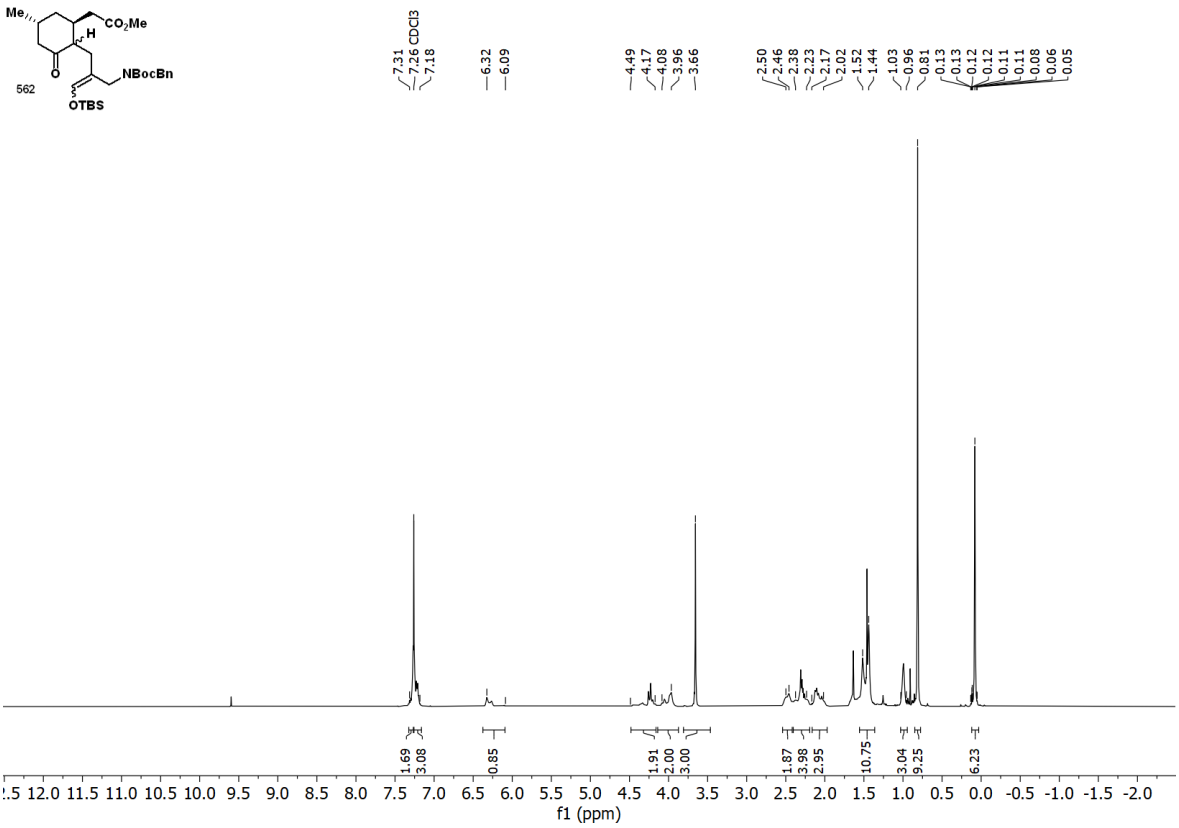

BnBocN
OH
557
156.9
145.6
138.3
128.8
128.3
128.1 C6D6
127.5
113.4
80.4
63.7
49.6
48.4
28.2
f1 (ppm)

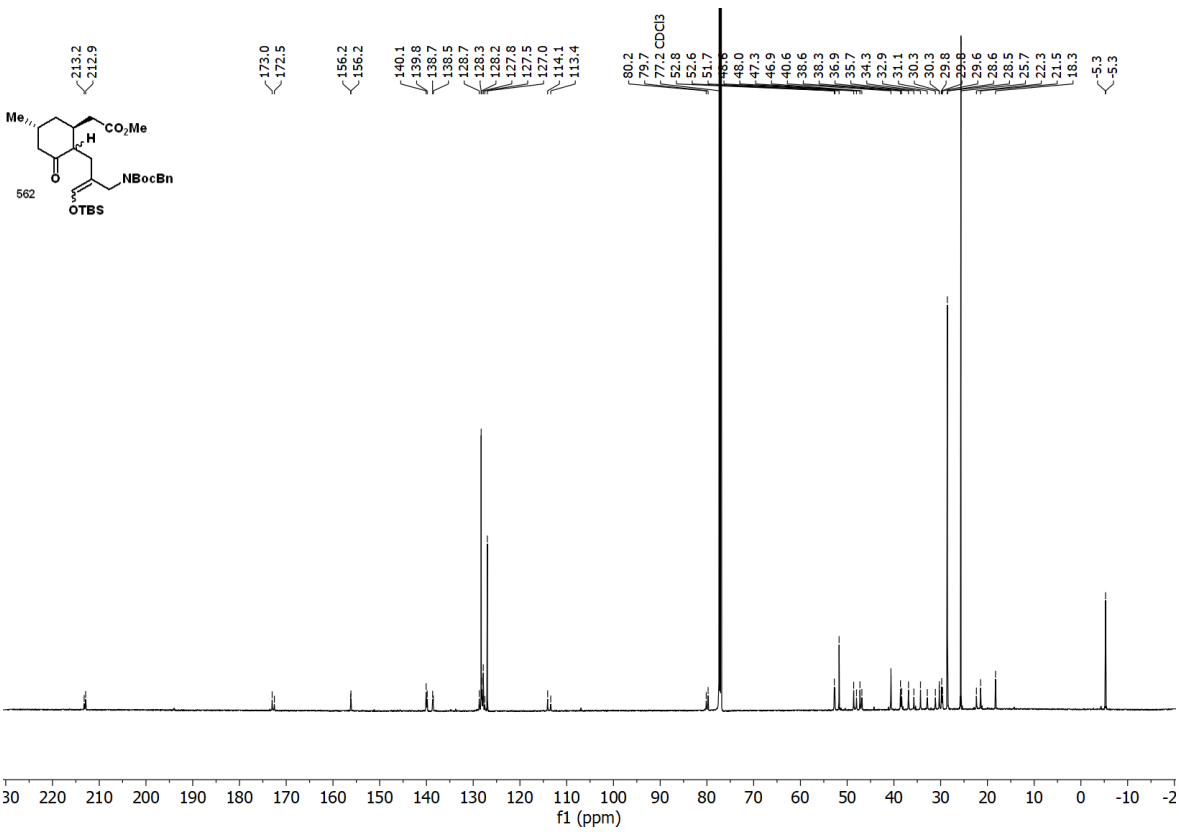

BnBocN
543
9.60
7.35
7.26 CDCl3
7.18
6.26
6.10
4.44
4.05
3.97
1.47
0.98
5.55
1.05
1.05
2.02
0.98
1.01
9.05
f1 (ppm)

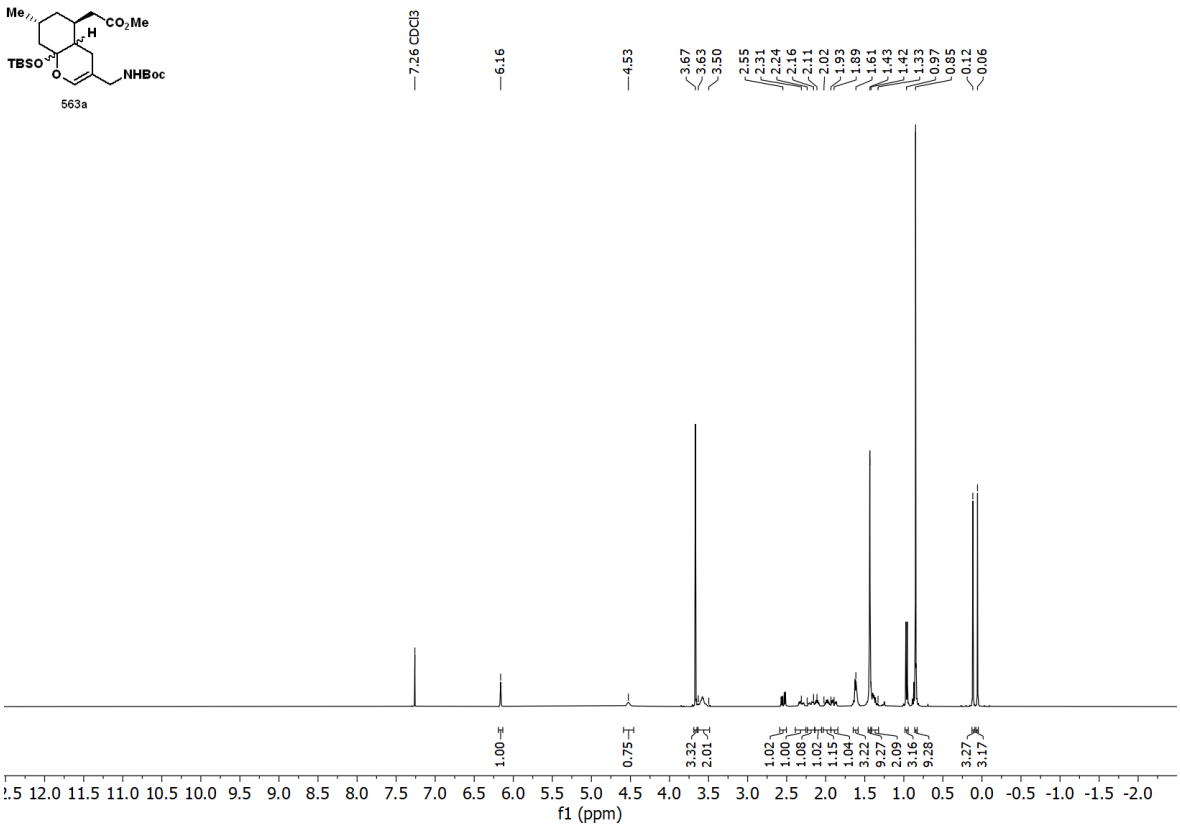

BnBocN
543
193.9
138.1
134.7
133.7
128.7
128.1
127.5
80.4
77.3 CDCl3
51.4
50.3
44.3
28.5
f1 (ppm)

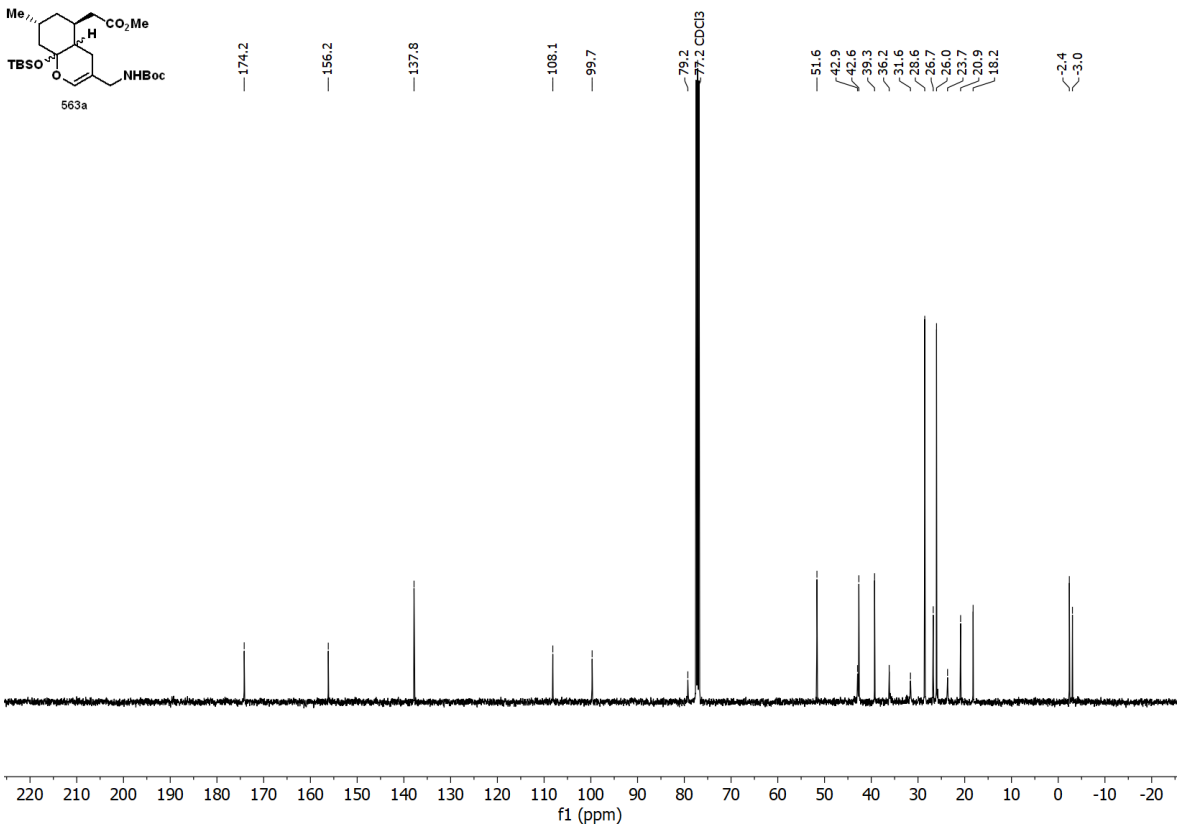

Me
CO2Me
H
TBSO
O
NBocBn
561
7.33
7.26 CDCl3
7.20
6.05
4.54
4.26
3.80
3.66
3.49
2.57
2.43
2.31
2.10
1.98
1.96
1.85
1.66
1.61
1.58
1.53
1.43
1.41
1.34
0.96
0.87
0.13
0.08
6.16
1.00
2.00
1.37
3.35
0.42
0.99
1.00
2.19
1.01
1.14
1.04
2.23
10.55
2.50
3.30
10.51
3.39
3.44
f1 (ppm)


Me
CO2Me
H
TBSO
O
NBocBn
561
173.9
156.2
147.0
138.5
129.0
128.6
128.1
127.8
127.4
127.2
100.1
79.9
77.2 CDCl3
51.5
48.2
42.6
42.1
39.2
35.3
28.6
26.5
26.1
21.1
18.2
-2.3
-2.9
f1 (ppm)


Me
CO2Me
H
O
NBocBn
562
OTBS
7.31
7.26 CDCl3
7.18
6.32
6.09
4.49
4.17
4.08
3.96
3.66
2.50
2.46
2.38
2.23
2.17
2.02
1.52
1.44
1.03
0.96
0.81
0.13
0.13
0.12
0.12
0.11
0.08
0.06
0.05
1.69
3.08
0.85
1.91
2.00
3.00
1.87
3.98
2.95
10.75
3.04
9.25
6.23
f1 (ppm)

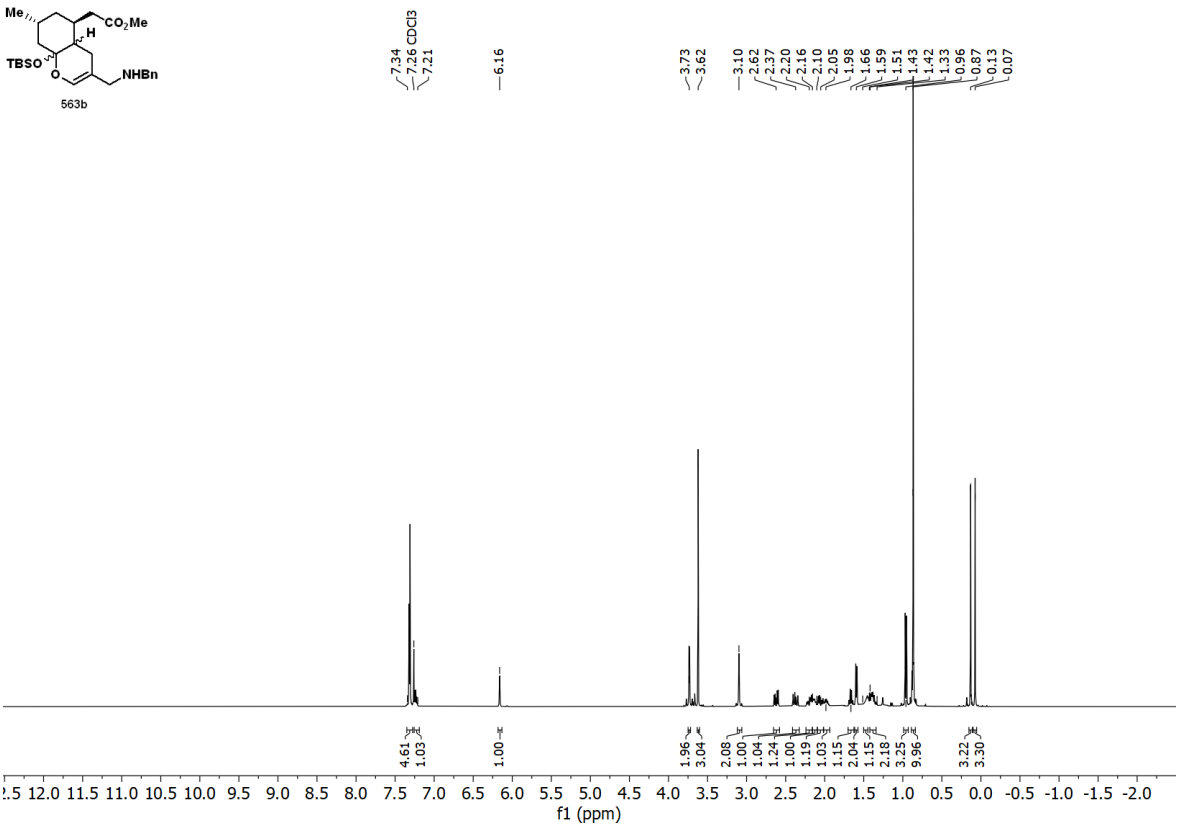

213.2
212.9
173.0
172.5
156.2
156.2
140.1
139.8
138.7
138.5
128.7
128.3
128.2
127.8
127.5
127.0
114.1
113.4
80.2
79.7
77.2 CDCl3
52.8
52.6
51.7
48.6
48.0
47.3
46.9
40.6
38.6
38.3
36.9
35.7
34.3
32.9
31.1
30.3
30.3
29.8
29.6
29.6
28.6
28.5
25.7
22.3
21.5
18.3
-5.3
-5.3
Me
CO2Me
H
O
NBocBn
562
OTBS
f1 (ppm)


Me
CO2Me
H
TBSO
O
NHBoc
563a
7.26 CDCl3
6.16
4.53
3.67
3.63
3.50
2.55
2.31
2.24
2.16
2.11
2.02
1.93
1.89
1.61
1.43
1.42
1.33
0.97
0.85
0.12
0.06
1.00
0.75
3.32
2.01
1.02
1.00
1.08
1.02
1.15
1.04
3.22
9.27
2.09
3.16
9.28
3.27
3.17
f1 (ppm)


Me
CO2Me
H
TBSO
O
NHBoc
563a
174.2
156.2
137.8
108.1
99.7
79.2
77.2 CDCl3
51.6
42.9
42.6
39.3
36.2
31.6
28.6
26.7
26.0
23.7
20.9
18.2
-2.4
-3.0
f1 (ppm)

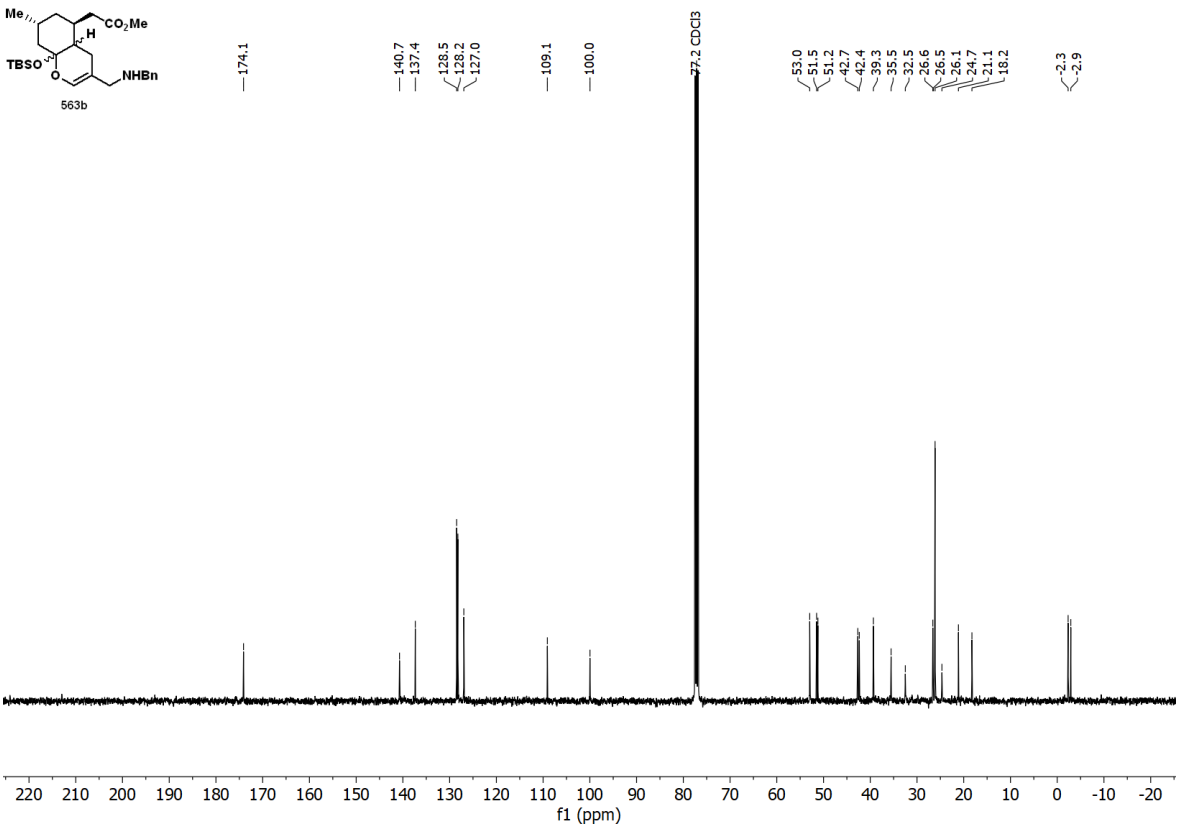
Me
CO2Me
H
TBSO
O
NHBn

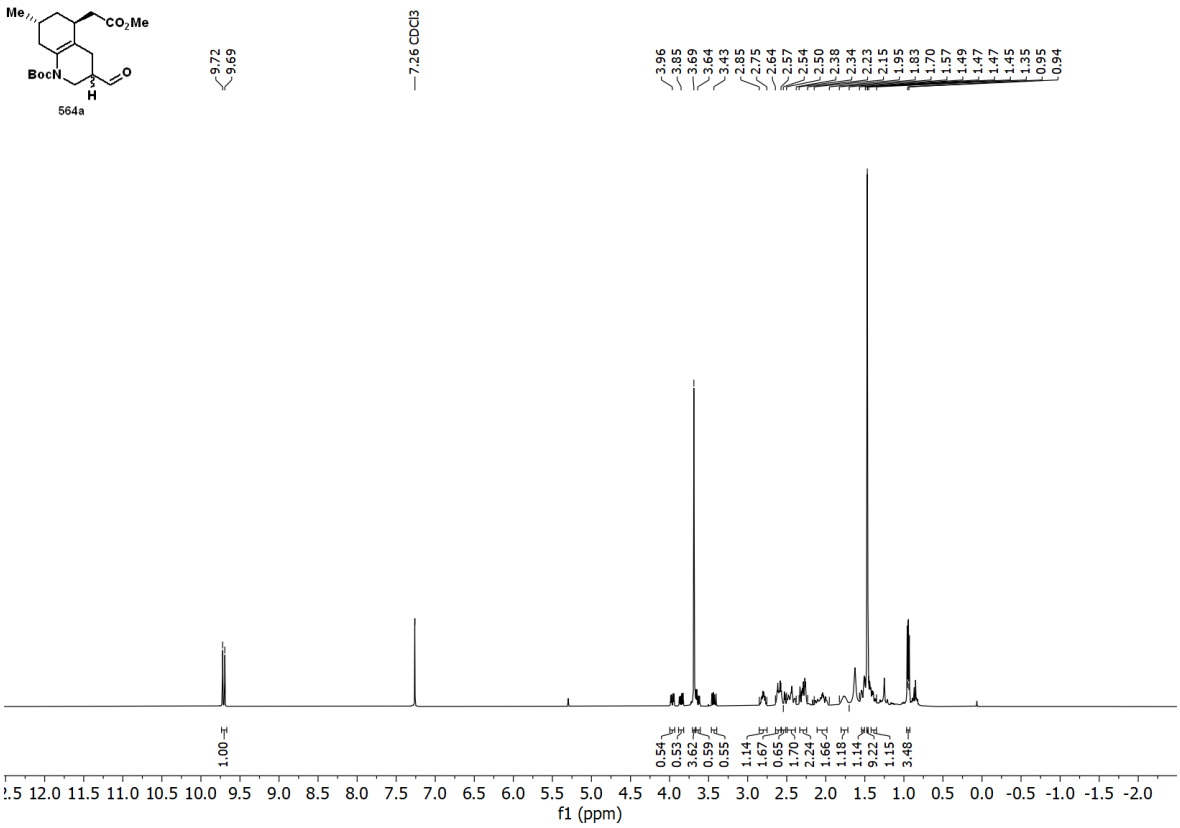
563b

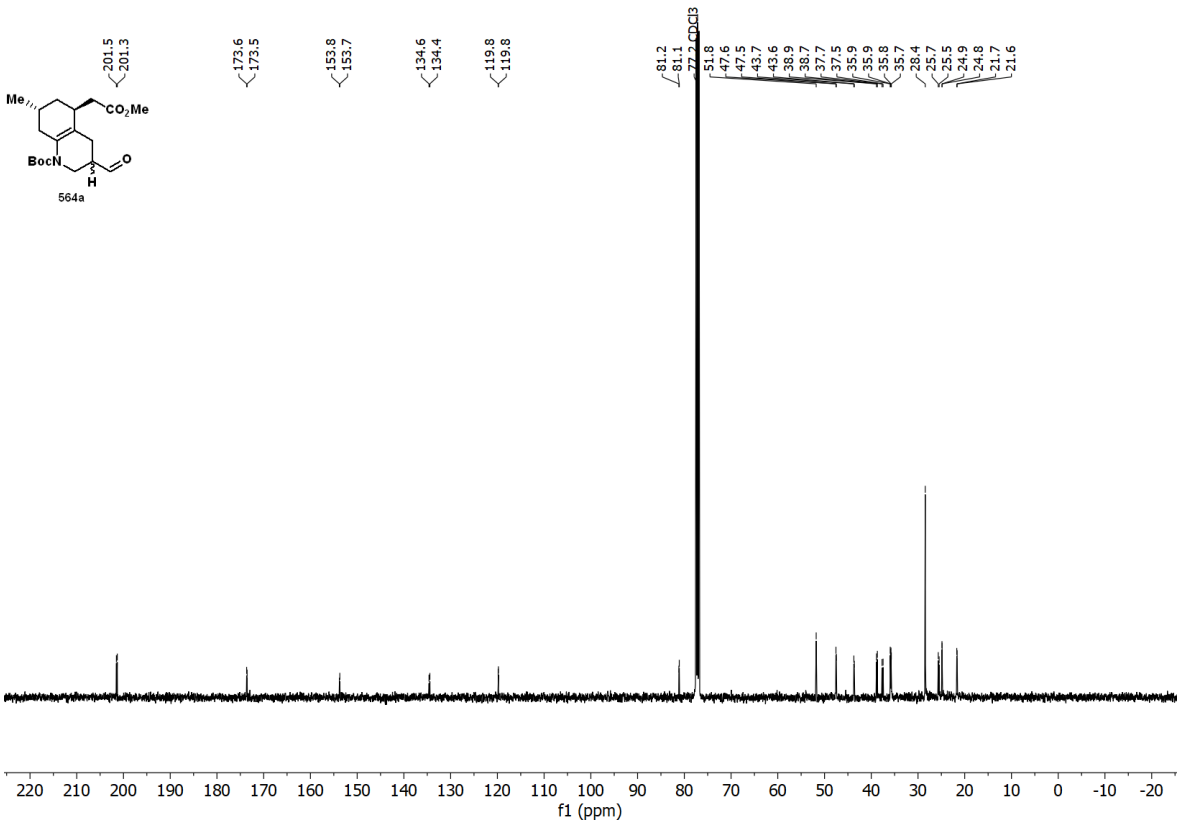

7.34
7.26 CDCl3
7.21
6.16
3.73
3.62
3.10
2.62
2.37
2.20
2.16
2.10
2.05
1.98
1.66
1.59
1.51
1.43
1.42
1.33
0.96
0.87
0.13
0.07
4.61
1.03
1.00
1.96
3.04
2.08
1.00
1.04
1.24
1.00
1.19
1.03
1.15
2.04
1.15
2.18
3.25
9.96
3.22
3.30
f1 (ppm)

Me
CO2Me
H
TBSO
O
NHBn

563b


174.1
140.7
137.4
128.5
128.2
127.0
109.1
100.0
77.2 CDCl3
53.0
51.5
51.2
42.7
42.4
39.3
35.5
32.5
26.6
26.5
26.1
24.7
21.1
18.2
-2.3
-2.9
f1 (ppm)


Me
CO2Me
BocN
O
H
564a
9.72
9.69
7.26 CDCl3
3.96
3.85
3.69
3.64
3.43
2.85
2.75
2.64
2.57
2.54
2.50
2.38
2.34
2.23
2.15
1.95
1.83
1.70
1.57
1.49
1.47
1.47
1.45
1.35
0.95
0.94
1.00
0.54
0.53
3.62
0.59
0.55
1.14
1.67
0.65
1.70
2.24
1.66
1.18
1.14
9.22
1.15
3.48
f1 (ppm)


201.5
201.3
173.6
173.5
153.8
153.7
134.6
134.4
119.8
119.8
81.2
81.1
77.2 CDCl3
51.8
47.6
47.5
43.7
43.6
38.9
38.7
37.7
37.5
35.9
35.9
35.8
35.7
28.4
25.7
25.5
24.9
24.8
21.7
21.6
Me
CO2Me
BocN
O
H
564a
f1 (ppm)

List of Figures

Figure 1: Chronological progress in total synthesis. 3
Figure 2: Classification of terpenes. 4
Figure 3: Isoprene and activated derivatives. 5
Figure 4: Common structure motifs of polyquinane natural products. 9
Figure 5: Exemplified compounds for the different classes of triquinane natural products.9
Figure 6: Skeletal types of angular triquinane natural products. 9
Figure 7: Podocarpus totara var. waihoensis. "In cultivation. Mar 2007", Photographer: Jeremy R. Rolfe, Licence: CC BY.[33b] 14
Figure 8: Diterpenes from Podocarpus totara var. waihoensis, laurenene rearrangement product **77** and 2-bromolauren-1-ene (**80**). 15
Figure 9: Structural features of waihoensene (**75**). 16
Figure 10: Structures for possible cobalt complexes of a terminal alkyne and an unsymmetric olefin and emergence of different enone products from favored intermediate complexes. 26
Figure 11: Side-product by intra- 40
Figure 12: **226** and **227** by reduction of the terminal olefin under the reaction conditions. 43
Figure 13: Observed side-products in course of the attempted deoxygenation of **228**. ... 52
Figure 14: Proposed E/Z-isomerism of p-toluenesulfonyl hydrazone **245**. 52
Figure 15: Observed side-products in the alkylation reaction of vinylogous ester **230**. 61
Figure 16: Observed side-products in the deoxygenation reaction. 68
Figure 17: ORTEP plot of **93** with ellipsoid drawn at 50% level and hydrogen atoms omitted for clarity. Only one stereoisomer shown. 71
Figure 18: ORTEP plot of **197** with ellipsoid drawn at 50% level and hydrogens omitted for clarity. 74
Figure 19: Structure of morphine (**304**), veratridine (**305**) and some exemplary alkaloids isolated by Pelletier and Caventou[121]. 84
Figure 20: Structural examples for true alkaloids, protoalkaloids and pseudoalkaloids. ... 86
Figure 21: Secondary metabolism building blocks and amino acids in alkaloid biosynthesis. 87

Figure 22: Vallesia glabra (Cav.) Link observed in Mexico by Jose Luis Leon de la Luz (licensed under http://creativecommons.org/licenses/by-nc/4.0/)[128b] 87
Figure 23: Molecular structure of (-)-vallesamidine (**311**) and related compounds..... 88
Figure 24: Structural features of vallesamidine (**311**). 90
Figure 25: Structures of Lycopodium alkaloids lycopodine (**389**) and huperzine A (**390**). . 98
Figure 26: Classification of the Lycopodium alkaloids according to Ayer amd Trifonov[156a]. 99
Figure 27: Diphasiastrum complanatum – photographed by Bernd Haynold, ... 100
Figure 28: Structures of Lycopodium alkaloids isolated from L. complanatum by Kobayashi and lyconadin A (**395**) and B (**396**). 101
Figure 29: Structural features of lyconadin C. 103
Figure 30: **A** Possible resonance structures of mesoionic isomünchnones and thioisomünchnones; **B** Isomünchnone derivative by Ibata and Hamaguchi: dipolar aromatic resonance structure causes high stability[171]. 108
Figure 31: Possible transition states and products from a [3+2] cycloaddition of an isomünchnone dipole with a symmetric dipolarophile. 110
Figure 32: Iodoanilides with electron-withdrawing protective groups. 121
Figure 33: HSQC NMR spectrum of the new compound from the reaction of thiolactam **516a** with bromoacetyl bromide and triethylamine. 125
Figure 34: Observed side-products from the attempted N-debenzylation. 138
Figure 35: Proposed side-products from the attempted Boc-deprotection of **561**. 140
Figure 36: Planned key [3+2]-cycloaddition reactions of respective thioisomünchnone dipoles for the total syntheses of vallesamidine (**311**) and lyconadin C (**397**). 147

List of Schemes

Scheme 1: Mevalonate pathway of IPP/DMAPP biosynthesis. 5
Scheme 2: MEP pathway of IPP/DMAPP biosynthesis. 6
Scheme 3: Terpene synthesis from IPP/DMAP **A** by head-to-tail or **B** by tail-to-tail linkage. 7
Scheme 4: Terpene cyclase reaction of GPP to limonene via the α-terpinyl cation. 8
Scheme 5: Acid-mediated synthesis of (-)-modhephene (**33**) and (-)-isocomene (**35**) from propan-2-ylidenecyclobutane[24]. 10
Scheme 6: Fitjer's acid-induced cationic rearrangement cascade of a dispirane-based tertiary alcohol to angular and propellane-type triquinanes[24]. 11
Scheme 7: Crimmins' synthesis of an angular triquinane by an intramolecular photocycloaddition-cyclobutane fragmentation strategy[26]. 11
Scheme 8: Lange's pentalene synthesis via [2+2]-cycloaddition/ Grob fragmentation[27]. 12
Scheme 9: Wender's synthesis of subergorgic acid by arene-alkene meta-photocycloaddition[29]. 13
Scheme 10: Demuth's synthesis of silphiperfolenone via a Diels-Alder/oxa-di-π-methane rearrangement sequence[31]. 13
Scheme 11: Lee's TMM-based tandem cycloaddition strategy for the synthesis of linear and angular triquinane systems[37]. 16
Scheme 12: Total synthesis of (±)-waihoensene (**75**) by Lee[36]. 18
Scheme 13: Synthetic strategy for the asymmetric total syntheses of (+)-waihoensene (**75**) by Huang & Yang[35] and Snyder[39]. 18
Scheme 14: Total synthesis of (+)-waihoensene (**75**) by Huang and Yang[35]. 19
Scheme 15: Total synthesis of (+)-waihoensene (**75**) by Snyder[39]. 20
Scheme 16: Synthetic approach toward the waihoensene carbon skeleton by Moore[40]. 21
Scheme 17: Synthetic approach toward the waihoensene carbon skeleton by Wang and Tu[41]. 22
Scheme 18: Retrosynthetic approach toward waihoensene via meta-photocycloaddition. 23
Scheme 19: Synthesis of photo precursors **132** and attempted meta-photocycloaddition. 24

Scheme 20: First reported Pauson-Khand reaction[44]. 25
Scheme 21: Proposed reaction mechanism of the cobalt-mediated Pauson-Khand by Magnus[47]. 26
Scheme 22: Proposed alternative mechanistic pathway of the cobalt-mediated Pauson-Khand reaction by Gimbert[49]. 27
Scheme 23: Stereochemical effects of steric hindrance in the intramolecular Pauson-Khand reaction. 28
Scheme 24: Proposed mechanistic pathway for N-oxide activation of a $Co_2(CO)_6$-alkyne complex by Alper[53]. 30
Scheme 25: Stabilizing and destabilizing effects of CO or Lewis bases on the cobalt hexacarbonyl complex[46]. 30
Scheme 26: Proposed mechanistic pathway for the rhodium(I)-catalyzed Pauson-Khand type reaction[62]. 30
Scheme 27: Use of an intramolecular Pauson-Khand reaction for the total synthesis of (+)-epoxydictymene (**185**) by Schreiber[63]. 31
Scheme 28: Use of an allenic Pauson-Khand reaction for the total synthesis of (+)-ingenol (**192**) by Baran[64]. 32
Scheme 29: Use of an intramolecular Pauson-Khand reaction for the total synthesis of (+)-ryanodol (**196**) by Reisman[65]. 33
Scheme 30: Retrosynthetic approach A for the total synthesis of (±)-waihoensene (**75**). . 34
Scheme 31: Synthetic access to cyclization precursor **200**. 35
Scheme 32: Synthesis of alkylboranes **207** and **208**. 36
Scheme 33: Attempted triflation of ketone **212**. 38
Scheme 34: Conversion of silylenol ether **203** to vinyl triflate **216**. 39
Scheme 35: Simplified proposed mechanistic pathway for the Fe(III)-mediated reductive olefin coupling developed by Baran and coworkers[67]. 41
Scheme 36: Retrosynthetic approach B for the total synthesis of (±)-waihoensene (**75**). . 44
Scheme 37: Optimized synthesis of homopropargyl iodide **235**. 46
Scheme 38: Optimized alkylation of **230** and Stork-Danheiser transposition to enone **229**. 48
Scheme 39: Two-step synthesis of alkyl iodide **241** from 1,3-propanol. 49

Scheme 40: Intramolecular Sakurai reaction by Lewis acid catalysis and subsequent epimerization to desired all-cis **228**. 49
Scheme 41: Optimized synthetic sequence for the deoxygenation and hydrogenation of cis-hydrindane **228**. 53
Scheme 42: Alternative, reversed sequence for the synthesis of **246** from cis-hydrindane **228**. 53
Scheme 43: Optimized synthetic sequence for the preparation of Pauson-Khand precursor enyne **198** from **246**. 53
Scheme 44: Proposed mechanism for the intramolecular Prins reaction of aldehyde **248** and formation of (di)enone **251**. 54
Scheme 45: Proposed mechanistic pathway for the formation of diene systems from 1,6-enynes by skeletal reorganization. 56
Scheme 46: Revised retrosynthesis. 56
Scheme 47: Alternative intramolecular Sakurai cyclization and subsequent ozonolysis of the allene. 57
Scheme 48: Retrosynthetic analysis of approach C for the total synthesis of (±)-waihoensene (**75**). 60
Scheme 49: Synthetic access to alkylating agent **264**. 60
Scheme 50: Synthetic access to alkylating agents **267**, **268** and **270**. 62
Scheme 51: Silyl deprotection of alkyne **273**. 64
Scheme 52: Optimized sequence of tin-mediated radical cyclization, protiodestannylation and epimerization. 64
Scheme 53: Conversion of ketone **261** into the corresponding DNP hydrazone **276** and ORTEP of **276** with ellipsoid drawn at the 50% level and hydrogens omitted for clarity; only one stereoisomer shown. 65
Scheme 54: Attempted palladium(0)-mediated reductive cyclization of enone **262**. 65
Scheme 55: Undesired isomerization to the endo-double bond upon hydrogenation of **280**. 69
Scheme 56: Optimized sequence for the preparation of Pauson-Khand precursor enyne **257**. 70
Scheme 57: Proposed mechanism for the formation of **289** by methylation of the thermodynamic enolate of **93**. 73

Scheme 58: Optimized sequence for the synthesis of (±)-waihoensene (**75**) by 1,4-addition and Wittig olefination. 75
Scheme 59: Retrosynthetic analysis for the asymmetric total synthesis of (+)-waihoensene (**75**). 76
Scheme 60: Synthetic sequence for the synthesis of chiral intermediate **262**. 77
Scheme 61: Optimized synthesis of the phenyl-ANDEN Trost ligand (11S,12S)-**302**. 78
Scheme 62: Completion of the asymmetric total synthesis of (+)-waihoensene (**75**) in analogy to the racemic synthesis. 79
Scheme 63: Synthetic access to the common intermediate **262** of racemic and enantioselective route. 81
Scheme 64: Completion of racemic and enantioselective total synthesis of waihoensene (**75**). 82
Scheme 65: Proposed biosynthesis of the monoterpenoid indole alkaloid tabersonine (**326**). 89
Scheme 66: Le Men's semi-synthesis of vallesamidine from tabersonine[139]. 90
Scheme 67: Total synthesis of (±)-vallesamidine (**311**) by Heathcock[141]. 91
Scheme 68: Formal asymmetric synthesis of (-)-vallesamidine (**311**) by Bergter[142]. 92
Scheme 69: Intramolecular cycloaddition of a mesoionic betaine in the formal synthesis of (±)-vallesamidine (**311**) by Padwa[143]. 93
Scheme 70: Synthetic access to aspidospermidine (**351**) by skeletal rearrangement via quebrachamine-type intermediate **349**[144]. 93
Scheme 71: Okada's radical approach toward (-)-vallesamidine (**311**)[145]. 94
Scheme 72: Asymmetric formal synthesis of vallesamidine (**311**) by Ho[146]. 95
Scheme 73: Qin's total synthesis of (-)-vallesamidine (**311**)[147]. 96
Scheme 74: Anderson's total synthesis of (+)-vallesamidine (**311**)[148]. 97
Scheme 75: Proposed biogenesis of lyconadins A, B, C and F. 102
Scheme 76: **A** Cis-decalin ring expansion strategy and possible interceptions of the allylic cation; **B** Total synthesis of lyconadin C (**397**) by Fukuyama[158]. 104
Scheme 77: Total synthesis of lyconadin C (**397**) by Waters[159]. 105
Scheme 78: Total synthesis of lyconadin C (**397**) by Dai[166]. 106
Scheme 79: Total synthesis of lyconadin C (**397**) by Yang[167]. 107

Scheme 80: Potential transformations of the cycloadduct obtained from the [3+2]-cycloaddition of an isomünchnone dipole and a dipolarophile AB. 109
Scheme 81: **A** Rhodium(II)-mediated generations of isomünchnone dipoles from diazo imides, as reported by Maier[181] and Padwa[182]; **B** Selective 1,3-dipole formation due to rhodium carbenoid conformation. 111
Scheme 82: Formation of an isomünchnone by reaction of an imide with triethyl phosphite, as reported by Freeman[183]. 112
Scheme 83: Generation of isomünchnone dipoles by reaction of amides with chloroacetylchloride and polymerization to poly(oxyvinylene)lactams. 112
Scheme 84: Stepwise formation of an isomünchnone dipole from a thioamide via an intermediate thioimidate. 112
Scheme 85: Generation of a thioisomünchnone dipole by reaction of a thioamide and a gem-dicyano epoxide. 113
Scheme 86: In situ generation of a thioisomünchnone dipole from a thioamide and maleic anhydride and its [3+2]-cycloaddition. 113
Scheme 87: Use of Zimmerman's reagent (**490**) for the generation of a thioisomünchnone dipole. 114
Scheme 88: Formation of thioisomünchnone dipoles from diazo thioamide precursors by Rh(II) catalysis. 114
Scheme 89: Intramolecular [3+2]-cycloaddition for generation of fused heterocyclic systems. 115
Scheme 90: First example of a bimolecular [3+2]-cycloaddition of an isomünchnone dipole to an electron-rich dipolarophile[193]. 115
Scheme 91: Examples for the [3+2]-cycloaddition of isomünchnone dipoles to heteroaromatic π-bonds: **A** Intramolecular addition to a furan π-bond; **B** Intramolecular addition to an indole π-bond. 116
Scheme 92: Prevention of thioisomünchnone formation by nucleophilic attack of electron-rich heteroaromatic dipolarophiles to the intermediate N-acyl iminium ions. . 117
Scheme 93: Retrosynthetic analysis of vallesamidine (**311**). 118
Scheme 94: Indole synthesis and thiolactam formation. 122
Scheme 95: Proposed mechanistic pathway for the palladium-catalyzed Larock indole synthesis[195]. 122

Scheme 96: Proposed alternative pathway to the observed products by reaction of thiolactams **516** with bromoacetyl bromide. 126
Scheme 97: Unexpected product from reaction of thioamide **516a** with 2-(2-tosylhydrazono)acetyl chloride and proposed mechanistic pathway. 128
Scheme 98: Retrosynthetic analysis of lyconadin C (**397**). 129
Scheme 99: Different strategies for the synthesis of (R)-5-methyl-cyclohex-2-en-1-one (**416**). 130
Scheme 100: **A** Preparation of bisallylic alcohol **549** from triethyl phosphonoacetate; .. 131
Scheme 101: Conversion of **553** to Michael acceptor **543** in three steps. 134
Scheme 102: Mukaiyama-Michael addition of **544** to enone **416**. 134
Scheme 103: Attempted alternative functionalization strategy of enone **416** via α-bromo ketone **559**. 135
Scheme 104: Mukaiyama-Michael/acetalization cascade reaction of silylenol ether **542** with α,β-unsaturated aldehyde **543** to **561** and acyclic Michael adduct **562**. 137
Scheme 105: Rationalization of the emergence of hexahydrochromene **565** from the hydrogenation of **561**. 139
Scheme 106: Proposed mechanism leading to formation of the observed side-product **571** in the reaction of **563a** with camphorsulfonic acid. 143
Scheme 107: Proposed mechanism for conversion of benzyl-protected **563b** to enamine **574** under basic conditions. 145
Scheme 108: Attempted conversion of the acyclic Michael adduct **562** to the octahydroquinoline motif. 146
Scheme 109: **A** Synthetic access to cycloaddition precursors **516** and planned vs. observed reactivity; **B** Unsuccessful attempt toward diazo thioamide precursor **532**; **C** Vallesamidine (**311**) and related Aspidosperma alkaloids **580**, **326**. 148
Scheme 110: Synthetic access to acrolein derivative **543** from commercial triethyl phosphonoacetate (**548**). 149
Scheme 111: Synthetic access to the octahydroquinoline structure motif. 150

List of Tables

Table 1: Acceleration and altered stereoselectivity by use of chemical promoters in the Pauson-Khand reaction[52]. 29
Table 2: Optimization of the sp^2-sp^3 Suzuki coupling. 36
Table 3: Optimization of the copper-catalyzed 1,4-addition. 37
Table 4: Catalyst screening for the methoxycarbonylation of vinyl triflates **215**/**216**. 40
Table 5: Attempted intramolecular reductive olefin coupling. 42
Table 6: Optimization of the alkylation of THP-protected 3-butin-1-ol **231**. 45
Table 7: Optimization and scale-up of the alkylation of vinylogous ester **230**. 47
Table 8: Screening of conditions for the deoxygenation of **228**. 50
Table 9: Attempts on the intramolecular Pauson-Khand reaction of enyne **198**. 55
Table 10: Attempts on the methylenation of ketone **259**. 59
Table 11: Optimization of the alkylation of vinylogous ester **230**. 61
Table 12: Optimization of the Stork-Danheiser transposition for the synthesis of enones **262**/**273**/**274**. 63
Table 13: Screening of conditions for the deoxygenation. 66
Table 14: Optimization of the intramolecular Pauson-Khand reaction of **257**. 71
Table 15: Screening of conditions for the α-methylation of **93**. 72
Table 16: C-alkylation of lactams **519**/**520**. 120
Table 17: Attempts on the planned intramolecular [3+2]-cycloaddition reaction of precursors **516**/**524**. 124
Table 18: Attempts on the synthesis of a diazo precursor for thioisomünchnone generation. 127
Table 19: Attempts on the conversion of the allylic alcohol functionality in **549** into a leaving group. 132
Table 20: Attempted pathway to Michael acceptor **556**. 133
Table 21: Screening of conditions for the planned α-functionalization. 136
Table 22: Tested conditions for N-benzyl deprotection of **561**. 138
Table 23: Screening of conditions for N-Boc deprotection of **561**. 140
Table 24: Attempts on TBS-deprotection and intramolecular amination of carbamate **563a**. 142

Table 25: Attempts on TBS-deprotection and intramolecular amination of secondary amine **563b**. 144

References

[1] J. R. Hanson, in *Natural Products: The Secondary Metabolites, Vol. 17* (Ed.: J. R. Hanson), The Royal Society of Chemistry, **2003**, pp. 1-34.

[2] a) A. L. Demain, A. Fang, in *History of Modern Biotechnology I* (Ed.: A. Fiechter), Springer Berlin Heidelberg, Berlin, Heidelberg, **2000**, pp. 1-39; b) R. A. Maplestone, M. J. Stone, D. H. Williams, *Gene* **1992**, *115*, 151-157.

[3] D. J. Newman, G. M. Cragg, *J. Nat. Prod.* **2020**, *83*, 770-803.

[4] W. H. Li Jesse, C. Vederas John, *Science* **2009**, *325*, 161-165.

[5] M. C. Wani, H. L. Taylor, M. E. Wall, P. Coggon, A. T. McPhail, *J. Am. Chem. Soc.* **1971**, *93*, 2325-2327.

[6] R. A. Holton, EP0400971A2, *Method for Preparation of Taxol*, **1990**.

[7] Bringi, Kadkade, Prince, Roach, US7264951B1, *Enhanced Production of Taxol and Taxanes by Cell Cultures of Taxus Species*, **2007**.

[8] F. Wöhler, *Ann. Phys.* **1828**, *88*, 253-256.

[9] K. C. Nicolaou, D. Vourloumis, N. Winssinger, P. S. Baran, *Angew. Chem. Int. Ed.* **2000**, *39*, 44-122.

[10] R. Croteau, T. M. Kutchan, N. G. Lewis, in *Biochemistry and Molecular Biology of Plants* (Eds.: B. Buchanan, W. Gruissem, R. Jones), American Society of Plant Physiologists, Rockville, **2000**, pp. 1250-1319.

[11] T. J. Maimone, P. S. Baran, *Nat. Chem. Biol.* **2007**, *3*, 396-407.

[12] J. Gershenzon, N. Dudareva, *Nat. Chem. Biol.* **2007**, *3*, 408-414.

[13] E. Breitmaier, *Terpenes: Flavors, Fragrances, Pharmaca, Pheromones*, Wiley, **2006**.

[14] a) O. Wallach, *Justus Liebigs Ann. Chem.* **1887**, *238*, 78-89; b) O. Wallach, *Justus Liebigs Ann. Chem.* **1914**, *403*, 73-105.

[15] a) L. Ruzicka, *Experientia* **1953**, *9*, 357-367; b) L. Ruzicka, *Proc. Chem. Soc.* **1959**, 341-376.

[16] a) H. M. Miziorko, *Arch. Biochem. Biophys.* **2011**, *505*, 131-143; b) A. Böttger, U. Vothknecht, C. Bolle, A. Wolf, in *Lessons on Caffeine, Cannabis & Co: Plant-derived Drugs and their Interaction with Human Receptors*, Springer International Publishing, Cham, **2018**, pp. 153-170; c) E. González-Burgos, M. P. Gómez-Serranillos, *Curr Med Chem* **2012**, *19*, 5319-5341.

[17] M. Rohmer, *Lipids* **2008**, *43*, 1095-1107.

[18] D. J. McGarvey, R. Croteau, *The Plant Cell* **1995**, *7*, 1015-1026.

[19] N. G. Heatley, M. A. Jennings, H. W. Florey, *Br. J. Exp. Pathol.* **1947**, *28*, 35-46.

[20] a) F. W. Comer, F. McCapra, I. H. Qureshi, A. I. Scott, *Tetrahedron* **1967**, *23*, 4761-4768; b) F. W. Comer, F. McCapra, I. H. Qureshi, J. Trotter, A. I. Scott, *Chem. Commun. (London)* **1965**, 310-311; c) F. W. Comer, J. Trotter, *J. Chem. Soc. B* **1966**, 11-18.

[21] G. Mehta, A. Srikrishna, *Chem. Rev.* **1997**, *97*, 671-720.

[22] L. A. Paquette, A. M. Doherty, in *Polyquinane Chemistry: Syntheses and Reactions*, Springer, Berlin, Heidelberg, **1987**, p. 1.

[23] L. A. Paquette, A. M. Doherty, in *Polyquinane Chemistry. Reactivity and Structure Concepts in Organic Chemistry., Vol. 26*, Springer, Berlin, Heidelberg, **1987**, pp. 169-208.

[24] L. Fitjer, A. Kanschik, M. Majewski, *Tetrahedron Lett.* **1988**, *29*, 5525-5528.

[25] L. H. Zalkow, R. N. Harris, D. Van Derveer, *J. Chem. Soc., Chem. Commun.* **1978**, 420-421.

[26] a) M. T. Crimmins, S. W. Mascarella, *J. Am. Chem. Soc.* **1986**, *108*, 3435-3438; b) M. T. Crimmins, S. W. Mascarella, L. D. Bredon, *Tetrahedron Lett.* **1985**, *26*, 997-1000.
[27] a) G. L. Lange, C. Gottardo, *Tetrahedron Lett.* **1990**, *31*, 5985-5988; b) G. L. Lange, C. Gottardo, *J. Org. Chem.* **1995**, *60*, 2183-2187.
[28] G. Pattenden, S. J. Teague, *Tetrahedron Lett.* **1984**, *25*, 3021-3024.
[29] a. P. A. Wender, M. A. deLong, *Tetrahedron Lett.* **1990**, *31*, 5429-5432.
[30] U. Streit, C. G. Bochet, *Beilstein J. Org. Chem.* **2011**, *7*, 525-542.
[31] a) M. Demuth, W. Hinsken, *Angew. Chem. Int. Ed.* **1985**, *24*, 973-975; b) M. Demuth, W. Hinsken, *Helv. Chim. Acta* **1988**, *71*, 569-576.
[32] a) D. B. Clarke, S. F. R. Hinkley, R. T. Weavers, *Tetrahedron Lett.* **1997**, *38*, 4297-4300; b) A. F. O. Chin, D. B. Clarke, S. F. R. Hinkley, N. B. Perry, R. T. Weavers, *Aust. J. Chem.* **2001**, *54*, 205-211.
[33] a) P. Wardle, *N. Z. J. Bot.* **1972**, *10*, 195-201; b) P. J. d. Lange (2022): *Podocarpus totara var. waihoensis Fact Sheet (content continuously updated).* New Zealand Plant Conservation Network. https://www.nzpcn.org.nz/flora/species/podocarpus-totara-var-waihoensis/ (19.01.2022).
[34] R. E. Corbett, D. R. Lauren, R. T. Weavers, *J. Chem. Soc., Perkin Trans. 1* **1979**, 1774-1790.
[35] Y. Qu, Z. Wang, Z. Zhang, W. Zhang, J. Huang, Z. Yang, *J. Am. Chem. Soc.* **2020**, *142*, 6511-6515.
[36] H. Lee, T. Kang, H.-Y. Lee, *Angew. Chem. Int. Ed.* **2017**, *56*, 8254-8257.
[37] T. Kang, W.-Y. Kim, Y. Yoon, B. G. Kim, H.-Y. Lee, *J. Am. Chem. Soc.* **2011**, *133*, 18050-18053.
[38] a) S. Geum, H.-Y. Lee, *Org. Lett.* **2014**, *16*, 2466-2469; b) T. Kang, S. B. Song, W.-Y. Kim, B. G. Kim, H.-Y. Lee, *J. Am. Chem. Soc.* **2014**, *136*, 10274-10276; c) Y.-J. Kim, Y. Yoon, H.-Y. Lee, *Tetrahedron* **2013**, *69*, 7810-7816; d) S.-S. Lee, W.-Y. Kim, H.-Y. Lee, *Chem. Asian J.* **2012**, *7*, 2450-2456.
[39] C. Peng, P. Arya, Z. Zhou, S. A. Snyder, *Angew. Chem. Int. Ed.* **2020**, *59*, 13521-13525.
[40] J.-K. Ergüden, H. W. Moore, *Org. Lett.* **1999**, *1*, 375-378.
[41] Y. Zhang, T.-L. Zheng, F. Cheng, K.-L. Dai, K. Zhang, A.-J. Ma, F.-M. Zhang, X.-M. Zhang, S.-H. Wang, Y.-Q. Tu, *Chem. Sci.* **2020**, *11*, 3878-3884.
[42] a) M. Häfner, Master thesis, University of Konstanz (Konstanz), **2016**; b) M. Häfner, PhD thesis, University of Konstanz (Konstanz), **2021**.
[43] C. R. Johnson, M. P. Braun, *J. Am. Chem. Soc.* **1993**, *115*, 11014-11015.
[44] I. U. Khand, G. R. Knox, P. L. Pauson, W. E. Watts, *J. Chem. Soc. D* **1971**, 36a-36a.
[45] a) I. U. Khand, G. R. Knox, P. L. Pauson, W. E. Watts, *J. Chem. Soc., Perkin Trans. 1* **1973**, 975-977; b) I. U. Khand, G. R. Knox, P. L. Pauson, W. E. Watts, M. I. Foreman, *J. Chem. Soc., Perkin Trans. 1* **1973**, 977-981.
[46] R. R. Torres, *The Pauson-Khand Reaction: Scope, Variations and Applications*, Wiley, **2012**.
[47] a) P. Magnus, C. Exon, P. Albaugh-Robertson, *Tetrahedron* **1985**, *41*, 5861-5869; b) P. Magnus, L. M. Principe, *Tetrahedron Lett.* **1985**, *26*, 4851-4854.
[48] M. Yamanaka, E. Nakamura, *J. Am. Chem. Soc.* **2001**, *123*, 1703-1708.
[49] D. Lesage, A. Milet, A. Memboeuf, J. Blu, A. E. Greene, J.-C. Tabet, Y. Gimbert, *Angew. Chem. Int. Ed.* **2014**, *53*, 1939-1942.
[50] N. E. Schore, in *Organic Reactions, Vol. 40* (Ed.: L. A. Paquette), John Wiley & Sons Inc. , **1991**, pp. 1-90.
[51] O. Geis, H.-G. Schmalz, *Angew. Chem. Int. Ed.* **1998**, *37*, 911-914.

[52] S. Shambayani, W. E. Crowe, S. L. Schreiber, *Tetrahedron Lett.* **1990**, *31*, 5289-5292.
[53] H. Alper, J. T. Edward, *Can. J. Chem.* **1970**, *48*, 1543-1549.
[54] a) T. Sugihara, M. Yamada, H. Ban, M. Yamaguchi, C. Kaneko, *Angew. Chem. Int. Ed.* **1997**, *36*, 2801-2804; b) Y. K. Chung, B. Y. Lee, N. Jeong, M. Hudecek, P. L. Pauson, *Organometallics* **1993**, *12*, 220-223.
[55] H.-W. Lee, F.-Y. Kwong, *Eur. J. Org. Chem.* **2010**, *2010*, 789-811.
[56] a) F. A. Hicks, S. L. Buchwald, *J. Am. Chem. Soc.* **1996**, *118*, 11688-11689; b) F. A. Hicks, N. M. Kablaoui, S. L. Buchwald, *J. Am. Chem. Soc.* **1996**, *118*, 9450-9451.
[57] a) T. Kondo, N. Suzuki, T. Okada, T.-a. Mitsudo, *J. Am. Chem. Soc.* **1997**, *119*, 6187-6188; b) T. Morimoto, N. Chatani, Y. Fukumoto, S. Murai, *J. Org. Chem.* **1997**, *62*, 3762-3765.
[58] a) M. Zhang, S. L. Buchwald, *J. Org. Chem.* **1996**, *61*, 4498-4499; b) K. Tamao, K. Kobayashi, Y. Ito, *J. Am. Chem. Soc.* **1988**, *110*, 1286-1288; c) K. Tamao, K. Kobayashi, Y. Ito, *Synlett* **1992**, *1992*, 539-546.
[59] a) E. Negishi, S. J. Holmes, J. M. Tour, J. A. Miller, F. E. Cederbaum, D. R. Swanson, T. Takahashi, *J. Am. Chem. Soc.* **1989**, *111*, 3336-3346; b) E.-i. Negishi, F. E. Cederbaum, T. Takahashi, *Tetrahedron Lett.* **1986**, *27*, 2829-2832.
[60] a) T. Kobayashi, Y. Koga, K. Narasaka, *J. Organomet. Chem.* **2001**, *624*, 73-87; b) K. Yuji, K. Toshitake, N. Koichi, *Chem. Lett.* **1998**, *27*, 249-250.
[61] N. Jeong, S. Lee, B. K. Sung, *Organometallics* **1998**, *17*, 3642-3644.
[62] N. Jeong, in *Modern Rhodium-Catalyzed Organic Reactions*, **2005**, pp. 215-240.
[63] T. F. Jamison, S. Shambayati, W. E. Crowe, S. L. Schreiber, *J. Am. Chem. Soc.* **1994**, *116*, 5505-5506.
[64] L. Jørgensen, S. J. McKerrall, C. A. Kuttruff, F. Ungeheuer, J. Felding, P. S. Baran, *Science* **2013**, *341*, 878-882.
[65] K. V. Chuang, C. Xu, S. E. Reisman, *Science* **2016**, *353*, 912-915.
[66] a) M. Ishizaki, K. Iwahara, K. Kyoumura, O. Hoshino, *Synlett* **1999**, *1999*, 587-589; b) M. Ishizaki, K. Iwahara, Y. Niimi, H. Satoh, O. Hoshino, *Tetrahedron* **2001**, *57*, 2729-2738.
[67] J. C. Lo, Y. Yabe, P. S. Baran, *J. Am. Chem. Soc.* **2014**, *136*, 1304-1307.
[68] J. Pietruszka, A. Witt, *Synthesis* **2006**, *2006*, 4266-4268.
[69] a) J. C. Lo, J. Gui, Y. Yabe, C.-M. Pan, P. S. Baran, *Nature* **2014**, *516*, 343; b) J. C. Lo, D. Kim, C.-M. Pan, J. T. Edwards, Y. Yabe, J. Gui, T. Qin, S. Gutiérrez, J. Giacoboni, M. W. Smith, P. L. Holland, P. S. Baran, *J. Am. Chem. Soc.* **2017**, *139*, 2484-2503.
[70] P. Bovonsombat, G. J. Angara, E. Mc Nelis, *Tetrahedron Lett.* **1994**, *35*, 6787-6790.
[71] N. Miyaura, T. Ishiyama, H. Sasaki, M. Ishikawa, M. Sato, A. Suzuki, *J. Am. Chem. Soc.* **1989**, *111*, 314-321.
[72] B. Corain, B. Longato, G. Favero, D. Ajò, G. Pilloni, U. Russo, F. R. Kreissl, *Inorg. Chim. Acta* **1989**, *157*, 259-266.
[73] J. B. Sperry, D. L. Wright, *Tetrahedron* **2006**, *62*, 6551-6557.
[74] M. Ranger, D. Rondeau, M. Leclerc, *Macromolecules* **1997**, *30*, 7686-7691.
[75] C. F. J. Barnard, *Organometallics* **2008**, *27*, 5402-5422.
[76] A. W. Fraser, J. E. Besaw, L. E. Hull, M. C. Baird, *Organometallics* **2012**, *31*, 2470-2475.
[77] G. P. Roth, J. A. Thomas, *Tetrahedron Lett.* **1992**, *33*, 1959-1962.
[78] a) D. M. Norton, E. A. Mitchell, N. R. Botros, P. G. Jessop, M. C. Baird, *J. Org. Chem.* **2009**, *74*, 6674-6680; b) A. W. Fraser, B. E. Jaksic, R. Batcup, C. D. Sarsons, M.

Woolman, M. C. Baird, *Organometallics* **2013**, *32*, 9-11; c) S. Borjian, D. M. E. Tom, M. C. Baird, *Organometallics* **2014**, *33*, 3928-3935.
[79] D. Schinzer, G. Dettmer, M. Ruppelt, S. Solyom, J. Steffen, *J. Org. Chem.* **1988**, *53*, 3823-3828.
[80] K. E. Frank, J. Aubé, *J. Org. Chem.* **2000**, *65*, 655-666.
[81] P. J. Garegg, B. Samuelsson, *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866-2869.
[82] A. Abad, C. Agulló, M. Arnó, A. C. Cuñat, B. Meseguer, R. J. Zaragozá, *J. Org. Chem.* **1998**, *63*, 5100-5106.
[83] L. Wolff, *Justus Liebigs Ann. Chem.* **1912**, *394*, 86-108.
[84] D. H. R. Barton, S. W. McCombie, *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574-1585.
[85] R. O. Hutchins, C. A. Milewski, B. E. Maryanoff, *J. Am. Chem. Soc.* **1973**, *95*, 3662-3668.
[86] a) B. Bredenkötter, U. Flörke, D. Kuck, *Chem. Eur. J.* **2001**, *7*, 3387-3400; b) J. R. Hwu, J. M. Wetzel, *J. Org. Chem.* **1992**, *57*, 922-928; c) C. G. Gutierrez, R. A. Stringham, T. Nitasaka, K. G. Glasscock, *J. Org. Chem.* **1980**, *45*, 3393-3395.
[87] G. J. Karabatsos, C. E. Osborne, *Tetrahedron* **1968**, *24*, 3361-3368.
[88] G. W. Kabalka, J. D. Baker, *J. Org. Chem.* **1975**, *40*, 1834-1835.
[89] S. V. Ley, J. Norman, W. P. Griffith, S. P. Marsden, *Synthesis* **1994**, *1994*, 639-666.
[90] a) N. A. Barton, B. J. Marsh, W. Lewis, N. Narraidoo, G. B. Seymour, R. Fray, C. J. Hayes, *Chem. Sci.* **2016**, *7*, 3102-3107; b) S. Edgar, K. Zhou, K. Qiao, J. R. King, J. H. Simpson, G. Stephanopoulos, *ACS Chem. Biol.* **2016**, *11*, 460-469; c) B. W. Biggs, J. E. Rouck, A. Kambalyal, W. Arnold, C. G. Lim, M. De Mey, M. O'Neil-Johnson, C. M. Starks, A. Das, P. K. Ajikumar, *ACS Chem. Biol.* **2016**, *11*, 1445-1451.
[91] a) C. Feldmann, Master thesis, University of Konstanz (Konstanz), **2021**; b) L. Emmes, Unpublished results, University of Konstanz.
[92] N. Jeong, Y. K. Chung, B. Y. Lee, S. H. Lee, S.-E. Yoo, *Synlett* **1991**, *1991*, 204-206.
[93] N. Chatani, T. Morimoto, T. Muto, S. Murai, *J. Am. Chem. Soc.* **1994**, *116*, 6049-6050.
[94] B. M. Trost, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **1993**, *32*, 1085-1087.
[95] a) N. Chatani, N. Furukawa, H. Sakurai, S. Murai, *Organometallics* **1996**, *15*, 901-903; b) N. Chatani, H. Inoue, T. Kotsuma, S. Murai, *J. Am. Chem. Soc.* **2002**, *124*, 10294-10295; c) N. Chatani, H. Inoue, T. Morimoto, T. Muto, S. Murai, *J. Org. Chem.* **2001**, *66*, 4433-4436.
[96] a) J. D. Ricker, L. M. Geary, *Top. Catal.* **2017**, *60*, 609-619; b) A. C. Regan, in *Comprehensive Organic Functional Group Transformations* (Eds.: A. R. Katritzky, O. Meth-Cohn, C. W. Rees), Elsevier Science, Oxford, **1995**, pp. 501-551.
[97] D. Schinzer, K. Ringe, P. G. Jones, D. Döring, *Tetrahedron Lett.* **1995**, *36*, 4051-4054.
[98] a) L. Lombardo, *Tetrahedron Lett.* **1982**, *23*, 4293-4296; b) J.-i. Hibino, T. Okazoe, K. Takai, H. Nozaki, *Tetrahedron Lett.* **1985**, *26*, 5579-5580.
[99] T.-H. Yan, C.-C. Tsai, C.-T. Chien, C.-C. Cho, P.-C. Huang, *Org. Lett.* **2004**, *6*, 4961-4963.
[100] N. A. Petasis, E. I. Bzowej, *J. Am. Chem. Soc.* **1990**, *112*, 6392-6394.
[101] W. S. Wadsworth, W. D. Emmons, *J. Am. Chem. Soc.* **1961**, *83*, 1733-1738.
[102] A. M. Haydl, B. Breit, *Chem. Eur. J.* **2017**, *23*, 541-545.
[103] T. J. K. Findley, D. Sucunza, L. C. Miller, D. T. Davies, D. J. Procter, *Chem. Eur. J.* **2008**, *14*, 6862-6865.
[104] S. Janardhanam, P. Shanmugam, K. Rajagopalan, *J. Org. Chem.* **1993**, *58*, 7782-7788.
[105] D. J. Dibble, J. W. Ziller, K. A. Woerpel, *J. Org. Chem.* **2011**, *76*, 7706-7719.
[106] B. M. Trost, F. Rise, *J. Am. Chem. Soc.* **1987**, *109*, 3161-3163.

[107] C. He, C. Zhu, Z. Dai, C.-C. Tseng, H. Ding, *Angew. Chem. Int. Ed.* **2013**, *52*, 13256-13260.
[108] M. Yasuda, Y. Onishi, M. Ueba, T. Miyai, A. Baba, *J. Org. Chem.* **2001**, *66*, 7741-7744.
[109] C. Chatgilialoglu, C. Ferreri, Y. Landais, V. I. Timokhin, *Chem. Rev.* **2018**, *118*, 6516-6572.
[110] S. Kim, C. H. Oh, J. S. Ko, K. H. Ahn, Y. J. Kim, *J. Org. Chem.* **1985**, *50*, 1927-1932.
[111] H. C. Brown, J. H. Brewster, H. Shechter, *J. Am. Chem. Soc.* **1954**, *76*, 467-474.
[112] L. Fitjer, U. Quabeck, *Synth. Commun.* **1985**, *15*, 855-864.
[113] L.-C. Rosenbaum, M. Häfner, T. Gaich, *Angew. Chem. Int. Ed.* **2021**, *60*, 2939-2942.
[114] K. V. Petrova, J. T. Mohr, B. M. Stoltz, *Org. Lett.* **2009**, *11*, 293-295.
[115] B. M. Trost, R. N. Bream, J. Xu, *Angew. Chem. Int. Ed.* **2006**, *45*, 3109-3112.
[116] a) W. E. Bachmann, L. B. Scott, *J. Am. Chem. Soc.* **1948**, *70*, 1458-1461; b) B. M. Trost, D. L. Van Vranken, C. Bingel, *J. Am. Chem. Soc.* **1992**, *114*, 9327-9343.
[117] M. Passarello, S. Abbate, G. Longhi, S. Lepri, R. Ruzziconi, V. P. Nicu, *J. Phys. Chem. A* **2014**, *118*, 4339-4350.
[118] T. Ukai, H. Kawazura, Y. Ishii, J. J. Bonnet, J. A. Ibers, *J. Organomet. Chem.* **1974**, *65*, 253-266.
[119] a) K. E. Kim, J. Li, R. H. Grubbs, B. M. Stoltz, *J. Am. Chem. Soc.* **2016**, *138*, 13179-13182; b) X.-S. Ning, M.-M. Wang, C.-Z. Yao, X.-M. Chen, Y.-B. Kang, *Org. Lett.* **2016**, *18*, 2700-2703.
[120] D. A. Evans, G. C. Fu, A. H. Hoveyda, *J. Am. Chem. Soc.* **1992**, *114*, 6671-6679.
[121] Seneca, in *Alkaloids - Secrets of Life* (Ed.: T. Aniszewski), Elsevier, Amsterdam, **2007**, pp. 1-59.
[122] C. F. W. Meißner, *Journal für Chemie und Physik* **1819**, *25*, 379-381.
[123] S. M. Kupchan, D. Lavie, C. V. Deliwala, B. Y. A. Andoh, *J. Am. Chem. Soc.* **1953**, *75*, 5519-5524.
[124] J. M. Gulland, R. Robinson, *J. Chem. Soc., Trans.* **1923**, *123*, 980-998.
[125] M. Wink, in *The Alkaloids: Chemistry and Biology, Vol. 64* (Ed.: G. A. Cordell), Academic Press, **2007**, pp. 1-47.
[126] M. C. Leal, C. Madeira, C. A. Brandão, J. Puga, R. Calado, *Molecules* **2012**, *17*, 9842-9854.
[127] S. Qiu, H. Sun, A.-H. Zhang, H.-Y. Xu, G.-L. Yan, Y. Han, X.-J. Wang, *Chin. J. Nat. Med.* **2014**, *12*, 401-406.
[128] G. A. Cordell, M. L. Quinn-Beattie, N. R. Farnsworth, *Phytother. Res.* **2001**, *15*, 183-205.
[129] Seneca, in *Alkaloids - Secrets of Life* (Ed.: T. Aniszewski), Elsevier, Amsterdam, **2007**, pp. 61-139.
[130] L. Dassonneville, N. Wattez, C. Mahieu, P. Colson, C. Houssier, M. Frederich, M. Tits, L. Angenot, C. Bailly, *Anticancer Res.* **1999**, *19*, 5245-5250.
[131] A. Walser, C. Djerassi, *Helv. Chim. Acta* **1965**, *48*, 391-404.
[132] a) M. Zèches, K. Mesbah, B. Richard, C. Moretti, J. M. Nuzillard, L. L. Men-Olivier, *Planta Med.* **1995**, *61*, 89-91; b) J. L. L. d. l. Luz (2021): *Vallesia glabra (Cav.) Link* https://www.inaturalist.org/photos/113516848 (21.01.2022).
[133] a) B. S. Bhadane, M. P. Patil, V. L. Maheshwari, R. H. Patil, *Phytother. Res.* **2018**, *32*, 1181-1210; b) E. W. C. Chan, S. K. Wong, H. T. Chan, *J. Integr. Med.* **2016**, *14*, 269-284.
[134] S. H. Brown, C. Djerassi, P. G. Simpson, *J. Am. Chem. Soc.* **1968**, *90*, 2445-2446.

[135] a) E. Wenkert, *J. Am. Chem. Soc.* **1962**, *84*, 98-102; b) J. P. Kutney, E. Piers, *J. Am. Chem. Soc.* **1964**, *86*, 953-955; c) A. Camerman, N. Camerman, J. P. Kutney, E. Piers, J. Trotter, *Tetrahedron Lett.* **1965**, *6*, 637-642; d) W. Klyne, R. J. Swan, B. W. Bycroft, D. Schumann, H. Schmid, *Helv. Chim. Acta* **1965**, *48*, 443-452; e) C. Djerassi, A. A. P. G. Archer, T. George, B. Gilbert, L. D. Antonaccio, *Tetrahedron* **1961**, *16*, 212-223.
[136] a) A. A. Qureshi, A. I. Scott, *Chem. Commun. (London)* **1968**, 948-950; b) A. R. Battersby, E. S. Hall, *J. Chem. Soc. D* **1969**, 793-794; c) A. I. Scott, P. C. Cherry, A. A. Qureshi, *J. Am. Chem. Soc.* **1969**, *91*, 4932-4933.
[137] A. R. Battersby, A. R. Burnett, E. S. Hall, P. G. Parsons, *Chem. Commun. (London)* **1968**, 1582-1583.
[138] A. A. Qureshi, A. I. Scott, *Chem. Commun. (London)* **1968**, 945-946.
[139] J. Lévy, P. Maupérin, M. D. de Maindreville, J. Le Men, *Tetrahedron Lett.* **1971**, *12*, 1003-1006.
[140] J. E. Saxton, in *The Alkaloids: Volume 6, Vol. 6* (Ed.: M. F. Grundon), The Royal Society of Chemistry, **1976**, pp. 189-251.
[141] C. H. Heathcock, M. H. Norman, D. A. Dickman, *J. Org. Chem.* **1990**, *55*, 798-811.
[142] P. R. R. Costa, R. N. Castro, F. M. C. Farias, O. A. C. Antunes, L. Bergter, *Tetrahedron: Asymmetry* **1993**, *4*, 1499-1500.
[143] A. Padwa, S. R. Harring, M. A. Semones, *J. Org. Chem.* **1998**, *63*, 44-54.
[144] J. Harley-Mason, M. Kaplan, *Chem. Commun. (London)* **1967**, 915-916.
[145] a) H. Tanino, K. Fukuishi, M. Ushiyama, K. Okada, *Tetrahedron* **2004**, *60*, 3273-3282; b) H. Tanino, K. Fukuishi, M. Ushiyama, K. Okada, *Tetrahedron Lett.* **2002**, *43*, 2385-2388.
[146] T.-L. Ho, C.-K. Chen, *Helv. Chim. Acta* **2006**, *89*, 249-257.
[147] X. Wang, D. Xia, W. Qin, R. Zhou, X. Zhou, Q. Zhou, W. Liu, X. Dai, H. Wang, S. Wang, L. Tan, D. Zhang, H. Song, X.-Y. Liu, Y. Qin, *Chem* **2017**, *2*, 803-816.
[148] X. Zhang, J. C. Anderson, *Angew. Chem. Int. Ed.* **2019**, *58*, 18040-18045.
[149] Y. Yang, M. Dai, *Synlett* **2014**, *25*, 2093-2098.
[150] X. Ma, D. R. Gang, *Nat. Prod. Rep.* **2004**, *21*, 752-772.
[151] K. Bödeker, *Justus Liebigs Ann. Chem.* **1881**, *208*, 363-367.
[152] a) L. Marion, R. H. F. Manske, *Can. J. Res.* **1942**, *20b*, 153-156; b) L. Marion, R. H. F. Manske, *Can. J. Res.* **1944**, *22b*, 1-4; c) R. H. Manske, L. Marion, *J. Am. Chem. Soc.* **1947**, *69*, 2126-2129; d) L. Marion, R. H. Manske, *Can. J. Res.* **1948**, *26*, 1; e) R. H. Manske, L. Marion, *Can. J. Res.* **1946**, *24*, 57-62; f) L. Marion, R. H. Manske, *Can. J. Res.* **1946**, *24*, 63-65.
[153] a) 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; b) L. Jiasen, Y. Chaomei, Z. Youzuo, H. Yanyi, Q. Baofeng, Z. Yuanlong, *Acta Chim. Sin.* **1986**, *44*, 1035-1040; c) X.-C. Tang, P. De Sarno, K. Sugaya, E. Giacobini, *J. Neurosci. Res.* **1989**, *24*, 276-285; d) X. C. Tang, Y. Han, X. P. Chen, X. D. Zhu, *Acta Pharmacol. Sin.* **1986**, *7*, 507-511; e) Y. Q. Liang, X. C. Tang, *Neurosci. Lett.* **2004**, *361*, 56-59; f) M. K. M. Tun, S. B. Herzon, *J. Exp. Pharmacol.* **2012**, *4*, 113-123.
[154] R. M. Wilson, S. J. Danishefsky, *Acc. Chem. Res.* **2006**, *39*, 539-549.
[155] a) J. i. Kobayashi, H. Morita, in *The Alkaloids: Chemistry and Biology, Vol. 61* (Ed.: G. A. Cordell), Academic Press, **2005**, pp. 1-57; b) Y. Hirasawa, J. Kobayashi, H. Morita, *Heterocycles* **2009**, *77*, 679-729.

[156] a) W. A. Ayer, L. S. Trifonov, in *The Alkaloids: Chemistry and Pharmacology, Vol. 45* (Eds.: G. A. Cordell, A. Brossi), Academic Press, **1994**, pp. 233-266; b) W. A. Ayer, *Nat. Prod. Rep.* **1991**, *8*, 455-463.
[157] a) K. i. Ishiuchi, T. Kubota, H. Ishiyama, S. Hayashi, T. Shibata, J. i. Kobayashi, *Tetrahedron Lett.* **2011**, *52*, 289-292; b) B. Haynold (2007): *Diphasiastrum complanatum* https://commons.wikimedia.org/w/index.php?curid=3231733 (26.01.2022).
[158] T. Nishimura, A. K. Unni, S. Yokoshima, T. Fukuyama, *J. Am. Chem. Soc.* **2013**, *135*, 3243-3247.
[159] X. Cheng, S. P. Waters, *Org. Lett.* **2013**, *15*, 4226-4229.
[160] P. Siengalewicz, J. Mulzer, U. Rinner, in *The Alkaloids: Chemistry and Biology, Vol. 72* (Ed.: H.-J. Knölker), Academic Press, **2013**, pp. 1-151.
[161] a) R. N. Gupta, M. Castillo, D. B. MacLean, I. D. Spenser, J. T. Wrobel, *J. Am. Chem. Soc.* **1968**, *90*, 1360-1361; b) M. Castillo, R. N. Gupta, D. B. MacLean, I. D. Spenser, *Can. J. Chem.* **1970**, *48*, 1893-1903; c) M. Castillo, R. N. Gupta, Y. K. Ho, D. B. MacLean, I. D. Spenser, *Can. J. Chem.* **1970**, *48*, 2911-2918.
[162] a) D. B. Maclean, in *The Alkaloids: Chemistry and Pharmacology, Vol. 26* (Ed.: A. Brossi), Academic Press, **1985**, pp. 241-298; b) L. Nyembo, A. Goffin, C. Hootelé, J.-C. Braekman, *Can. J. Chem.* **1978**, *56*, 851-856.
[163] J. i. Kobayashi, Y. Hirasawa, N. Yoshida, H. Morita, *J. Org. Chem.* **2001**, *66*, 5901-5904.
[164] K. i. Ishiuchi, T. Kubota, T. Hoshino, Y. Obara, N. Nakahata, J. i. Kobayashi, *Biorg. Med. Chem.* **2006**, *14*, 5995-6000.
[165] T. Nishimura, A. K. Unni, S. Yokoshima, T. Fukuyama, *J. Am. Chem. Soc.* **2011**, *133*, 418-419.
[166] Y. Yang, C. W. Haskins, W. Zhang, P. L. Low, M. Dai, *Angew. Chem. Int. Ed.* **2014**, *53*, 3922-3925.
[167] J. Zhang, Y. Yan, R. Hu, T. Li, W.-J. Bai, Y. Yang, *Angew. Chem. Int. Ed.* **2020**, *59*, 2860-2866.
[168] a) A. Padwa, W. H. Pearson, *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products, Volume 59*, Wiley, **2003**; b) M. Breugst, H.-U. Reissig, *Angew. Chem. Int. Ed.* **2020**, *59*, 12293-12307; c) W. Oppolzer, *Angew. Chem. Int. Ed.* **1977**, *16*, 10-23.
[169] a) R. Huisgen, *Angew. Chem. Int. Ed.* **1963**, *2*, 565-598; b) R. Huisgen, *Proc. Chem. Soc.* **1961**, 357-396.
[170] M. H. Osterhout, W. R. Nadler, A. Padwa, *Synthesis* **1994**, 123-141.
[171] M. Hamaguchi, T. Ibata, *Tetrahedron Lett.* **1974**, *15*, 4475-4476.
[172] K. T. Potts, E. Houghton, U. P. Singh, *J. Org. Chem.* **1974**, *39*, 3627-3631.
[173] a) K. T. Potts, J. Marshall, *J. Chem. Soc., Chem. Commun.* **1972**, 1000-1000; b) K. T. Potts, J. L. Marshall, *J. Org. Chem.* **1979**, *44*, 626-628.
[174] K. T. Potts, J. Baum, E. Houghton, *J. Org. Chem.* **1974**, *39*, 3631-3641.
[175] K. T. Potts, S. J. Chen, J. Kane, J. L. Marshall, *J. Org. Chem.* **1977**, *42*, 1633-1638.
[176] D. L. Hertzog, W. R. Nadler, Z. J. Zhang, A. Padwa, *Tetrahedron Lett.* **1992**, *33*, 5877-5880.
[177] A. Padwa, M. Prein, *J. Org. Chem.* **1997**, *62*, 6842-6854.
[178] K. N. Houk, J. Sims, C. R. Watts, L. J. Luskus, *J. Am. Chem. Soc.* **1973**, *95*, 7301-7315.
[179] R. Sustmann, *Tetrahedron Lett.* **1971**, *12*, 2717-2720.

[180] a) A. Padwa, S. R. Harring, D. L. Hertzog, W. R. Nadler, *Synthesis* **1994**, 993-1004; b) D. L. Hertzog, D. J. Austin, W. R. Nadler, A. Padwa, *Tetrahedron Lett.* **1992**, *33*, 4731-4734.
[181] M. E. Maier, K. Evertz, *Tetrahedron Lett.* **1988**, *29*, 1677-1680.
[182] A. Padwa, D. L. Hertzog, R. L. Chinn, *Tetrahedron Lett.* **1989**, *30*, 4077-4080.
[183] M. J. Haddadin, A. M. Kattan, J. P. Freeman, *J. Org. Chem.* **1982**, *47*, 723-725.
[184] a) L. J. Mathias, D. R. Moore, *J. Am. Chem. Soc.* **1985**, *107*, 5817-5818; b) D. R. Moore, L. J. Mathias, *Macromolecules* **1986**, *19*, 1530-1536.
[185] a) M. Baudy, A. Robert, *J. Chem. Soc., Chem. Commun.* **1976**, 23-24; b) M. Baudy, A. Robert, A. Foucaud, *J. Org. Chem.* **1978**, *43*, 3732-3736.
[186] T. Takido, K. Itabashi, *Synthesis* **1985**, *1985*, 430-432.
[187] H. E. Zimmerman, R. A. Bunce, *J. Org. Chem.* **1982**, *47*, 3377-3396.
[188] K. T. Potts, P. Murphy, *J. Chem. Soc., Chem. Commun.* **1984**, 1348-1349.
[189] A. Padwa, F. R. Kinder, W. R. Nadler, L. Zhi, *Heterocycles* **1993**, *35*, 367-383.
[190] a) K. T. Potts, J. Baum, S. K. Datta, E. Houghton, *J. Org. Chem.* **1976**, *41*, 813-818; b) K. T. Potts, J. Baum, E. Houghton, *J. Org. Chem.* **1976**, *41*, 818-824.
[191] H. Matsukubo, H. Kato, *J. Chem. Soc., Perkin Trans. 1* **1976**, 2565-2569.
[192] H. Alper, C. Blais, *J. Chem. Soc., Chem. Commun.* **1980**, 169-170.
[193] A. Padwa, D. L. Hertzog, *Tetrahedron* **1993**, *49*, 2589-2600.
[194] A. Padwa, D. L. Hertzog, W. R. Nadler, *J. Org. Chem.* **1994**, *59*, 7072-7084.
[195] R. C. Larock, E. K. Yum, M. D. Refvik, *J. Org. Chem.* **1998**, *63*, 7652-7662.
[196] X. Xing, N. R. O'Connor, B. M. Stoltz, *Angew. Chem. Int. Ed.* **2015**, *54*, 11186-11190.
[197] A. Padwa, A. C. Flick, H. I. Lee, *Org. Lett.* **2005**, *7*, 2925-2928.
[198] T. Sakamoto, Y. Kondo, S. Iwashita, T. Nagano, H. Yamanaka, *Chem. Pharm. Bull.* **1988**, *36*, 1305-1308.
[199] I. Thomsen, K. Clausen, S. Scheibye, S.-O. Lawesson, *Org. Synth.* **1984**, *62*, 158.
[200] J. Voss, J. Voss, (**2006**), *2,4-Bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-Disulfide*, *Encyclopedia of Reagents for Organic Synthesis*.
[201] A. Padwa, F. R. Kinder, L. Zhi, *Synlett* **1991**, *1991*, 287-288.
[202] A. K. Gupta, X. Yin, M. Mukherjee, A. A. Desai, A. Mohammadlou, K. Jurewicz, W. D. Wulff, *Angew. Chem. Int. Ed.* **2019**, *58*, 3361-3367.
[203] a) J. A. Kozak, G. R. Dake, *Angew. Chem. Int. Ed.* **2008**, *47*, 4221-4223; b) W. Oppolzer, M. Petrzilka, *Helv. Chim. Acta* **1978**, *61*, 2755-2762.
[204] a) D. Caine, K. Procter, R. A. Cassell, *J. Org. Chem.* **1984**, *49*, 2647-2648; b) S. Mutti, C. Daubié, F. Decalogne, R. Fournier, P. Rossi, *Tetrahedron Lett.* **1996**, *37*, 3125-3128; c) W. Reusch, C. K. Johnson, *J. Org. Chem.* **1963**, *28*, 2557-2560; d) H. Rupe, E. Kambli, *Justus Liebigs Ann. Chem.* **1927**, *459*, 195-217; e) E. J. Eisenbraun, S. M. McElvain, *J. Am. Chem. Soc.* **1955**, *77*, 3383-3384.
[205] E. Weitz, A. Scheffer, *Ber. Dtsch. Chem. Ges. (A & B)* **1921**, *54*, 2327-2344.
[206] J. Villieras, M. Rambaud, *Org. Synth.* **1988**, *66*, 220.
[207] E. J. Corey, C. U. Kim, *J. Am. Chem. Soc.* **1972**, *94*, 7586-7587.
[208] T. A. Spencer, R. W. Britton, D. S. Watt, *J. Am. Chem. Soc.* **1967**, *89*, 5727-5729.
[209] K. Maruoka, S. Hashimoto, Y. Kitagawa, H. Yamamoto, H. Nozaki, *J. Am. Chem. Soc.* **1977**, *99*, 7705-7707.
[210] N. Koichi, S. Kenso, M. Teruaki, *Chem. Lett.* **1974**, *3*, 1223-1224.
[211] K. R. Rohit, S. M. Ujwaldev, K. K. Krishnan, G. Anilkumar, *Asian J. Org. Chem.* **2018**, *7*, 85-102.
[212] T. Mukaiyama, S. Kobayashi, *J. Organomet. Chem.* **1990**, *382*, 39-52.

[213] a) K. Hattori, H. Sajiki, K. Hirota, *Tetrahedron Lett.* **2000**, *41*, 5711-5714; b) K. Hattori, H. Sajiki, K. Hirota, *Tetrahedron* **2001**, *57*, 2109-2114.
[214] a) W. M. Pearlman, *Tetrahedron Lett.* **1967**, *8*, 1663-1664; b) R. C. Bernotas, R. V. Cube, *Synth. Commun.* **1990**, *20*, 1209-1212; c) K. Yoshida, S. Nakajima, T. Wakamatsu, Y. Ban, M. Shibasaki, *Heterocycles* **1988**, *27*, 1167-1168.
[215] S. C. Nigama, A. Mann, M. Taddei, C.-G. Wermutha, *Synth. Commun.* **1989**, *19*, 3139-3142.
[216] K. A. Scheidt, H. Chen, B. C. Follows, S. R. Chemler, D. S. Coffey, W. R. Roush, *J. Org. Chem.* **1998**, *63*, 6436-6437.
[217] K. A. Scheidt, T. D. Bannister, A. Tasaka, M. D. Wendt, B. M. Savall, G. J. Fegley, W. R. Roush, *J. Am. Chem. Soc.* **2002**, *124*, 6981-6990.
[218] A. Richter, C. Hedberg, H. Waldmann, *J. Org. Chem.* **2011**, *76*, 6694-6702.
[219] T. T. A. Gene W. Wong, Clark R. Landis, *Org. Synth.* **2012**, *89*, 243-254.
[220] A. Pollex, M. Hiersemann, *Org. Lett.* **2005**, *7*, 5705-5708.
[221] S. C. Watson, J. F. Eastham, *J. Organomet. Chem.* **1967**, *9*, 165-168.
[222] M. D. Corporation, WO 2004/087630 A1 *Process for producing cyclohexanone long-chain alcohols*, **2004**.
[223] M. Norio, S. Yoshitaka, H. Shoji, S. Akira, *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2029-2031.
[224] H. Hiemstra, W. J. Klaver, W. Nico Speckamp, *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 299-306.
[225] G. Barbe, M. St-Onge, A. B. Charette, *Org. Lett.* **2008**, *10*, 5497-5499.
[226] M. Čížková, D. Šaman, D. Koval, V. Kašička, B. Klepetářová, I. Císařová, F. Teplý, *Eur. J. Org. Chem.* **2014**, *2014*, 5681-5685.
[227] T. Hu, J. V. Schaus, K. Lam, M. G. Palfreyman, M. Wuonola, G. Gustafson, J. S. Panek, *J. Org. Chem.* **1998**, *63*, 2401-2406.
[228] K. T. Potts, T. Rochanapruk, A. Padwa, S. J. Coats, L. Hadjiarapoglou, *J. Org. Chem.* **1995**, *60*, 3795-3805.
[229] D. R. Bobeck, H. I. Lee, A. C. Flick, A. Padwa, *J. Org. Chem.* **2009**, *74*, 7389-7402.
[230] F.-T. Luo, R.-T. Wang, *Heterocycles* **1991**, *32*, 2365 - 2372.
[231] J.-Y. Ong, X. Q. Ng, S. Lu, Y. Zhao, *Org. Lett.* **2020**, *22*, 6447-6451.
[232] H. Lei, J. Atkinson, *J. Org. Chem.* **2000**, *65*, 2560-2567.
[233] D. Oguro, N. Mori, H. Takikawa, H. Watanabe, *Tetrahedron* **2018**, *74*, 5745-5751.
[234] A. G. Wenzel, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 12964-12965.
[235] M. Sickert, H. Weinstabl, B. Peters, X. Hou, M. Lautens, *Angew. Chem. Int. Ed.* **2014**, *53*, 5147-5151.

Danksagung

Zunächst ein herzliches Dankeschön an Frau Prof. Tanja Gaich. Vielen Dank für die Aufnahme in deine Arbeitsgruppe und die Möglichkeit auf den beiden Projekten zu arbeiten. Ich danke dir für eine tolle Zeit und dafür, dass du jederzeit ein offenes Ohr für Probleme hast und uns gleichzeitig den Freiraum lässt, unsere eigenen Ideen umzusetzen. Ich konnte unglaublich viel lernen in den vergangenen viereinhalb Jahren. Dafür vielen Dank!

Ebenfalls vielen lieben Dank an Herrn Prof. Rainer Winter als Zweitbetreuer meiner Doktorarbeit und für die Übernahme der Zweitgutachtens. Dankeschön auch an Herrn Prof. Marx für die Übernahme des Drittgutachtens. Herrn Prof. Valentin Wittmann danke ich herzlich für die Übernahme des Prüfungsvorsitzes.

Ich danke der gesamten Arbeitsgruppe für eine angenehme Arbeitsatmosphäre und viele gemeinsame Erlebnisse. Danke vor allem an die Hannoveraner und die erste Generation der Konstanzer Gaichis – ihr habt mich schon für meine Masterarbeit herzlich in die Gruppe aufgenommen und ich konnte unglaublich viel von euch lernen. Ich erinnere mich echt gerne an die schöne Zeit mit euch, seien es produktive und weniger produktive Gespräche im Labor, Kaffeepausen in der Akademie oder feuchtfröhliche Abende bei der Resi.
Auch ein großes Dankeschön an die neuere Generation der AG. Vor allem danke an die L6-Crew *alias* AG Mattheus, denn ohne euch wäre der Corona-Alltag wesentlich schwerer zu ertragen gewesen. Danke für viele erheiternde Mittagspausen und das ein oder andere wohlverdiente Feierabendbier. An dieser Stelle auch ein zusätzlicher Dank an Lena und Till für‘s Korrekturlesen dieser Arbeit.

Vielen Dank auch an alle, die auf meinen Projekten mitgearbeitet haben, sei es Form einer Bachelor- oder Masterarbeit oder als HiWi. Danke an Philipp, Philipp und Philipp, sowie an Chrissy und Kevin für die gute Zusammenarbeit mit euch.

Weiterhin danke ich allen Festangestellten der AG. Danke Thomas für deine Hilfsbereitschaft bei allen möglichen Fragen und Problemen, für deinen gigantischen Vorrat an irgendwelchen Laborgeräten oder Chemikalien und auch für lustige Abende beim

AG-Retreat. Einen großen Dank auch an Malin, für deine Hilfe mit den Analytikgeräten oder bei sonstigen Problemen und danke vor allem für viele, viele Messungen an der HRMS. Danke an Angelika für deine ständige Hilfsbereitschaft, für das ein oder andere wohltuende Schwätzle zwischendurch und für ein bisschen Heimatgefühl von dr‘ Alb. Vielen Dank auch an Milena für deine Unterstützung bei allen organisatorischen Angelegenheiten.

Ein großer Dank geht auch an Anke Friemel und Ulrich Haunz vom NMR-Center für unzählige Messungen, eure ständige Hilfsbereitschaft und die Fähigkeit, aus jeder vermeintlich hoffnungslosen Probe noch ein gutes Spektrum rauszuholen.
Auch dem Team vom Chemikalienlager möchte ich danken - ein Besuch bei euch ist auf jeden Fall immer mit guter Laune verbunden. Vielen lieben Dank dafür.

Ein besonderer Dank gilt meinen Freunden, vor allem der Mittwoch-Baraction und den Fantastischen, aber auch meinen Abi-Mädels von Zuhause. Danke, dass wir die letzten Jahre gemeinsam erlebt haben! Ohne euch hätte ich das alles sicherlich nicht durchgehalten.

Meiner Familie, besonders meinen Eltern, danke ich für den ständigen Rückhalt während der letzten Jahre. Danke, dass ihr mir ermöglicht habt, meinen Weg zu gehen und mich auch in schwierigen Situationen unterstützt habt. Danke, dass ihr für mich da seid!

Mein letzter und größter Dank geht an Max. Danke, dass wir das alles irgendwie geschafft haben und auch die schwierigen Zeiten überstanden haben. Danke, dass wir immer über alles reden können. Danke, dass du alle meine Launen erträgst und vor allem danke dafür, dass du mich immer wieder dazu motivierst mein Bestes zu geben.