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A Unified Approach toward Astellatol, Nitiol and YW 3548

Vorgelegt von

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-Meiner Familie-

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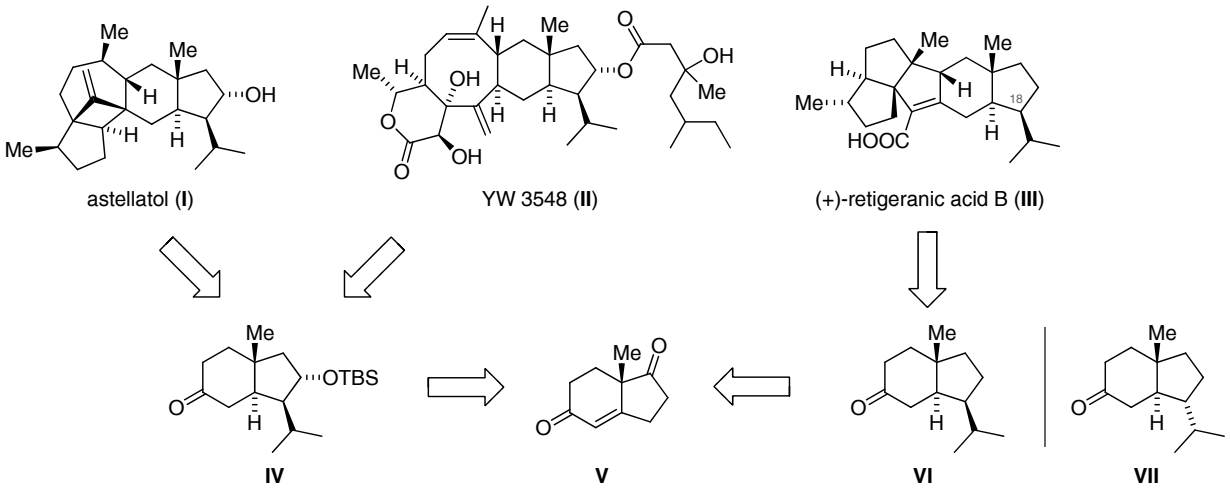
'Synthetic Studies toward Astellatol', D. T. Hog, P. Mayer, D. Trauner, ORCHEM 2012, Weimar, Germany, 24.09.2012 – 26.09.2012.

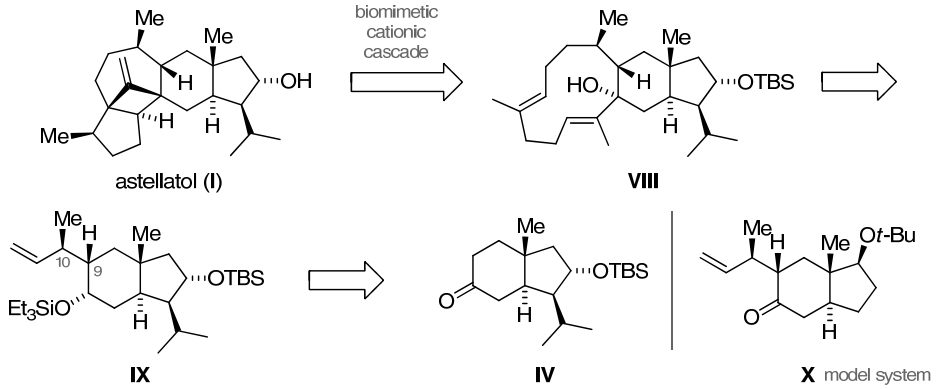
ABSTRACT

Among the large family of terpenoid natural products, sesterterpenoids form a small subclass. Nevertheless, due to the diversity of cyclization modes and oxidation processes in biosynthesis, a broad range of unique structures has been isolated within the last 50 years. Not surprisingly, these structurally intriguing frameworks have captured the attention of synthetic chemists, resulting is several elegant approaches (Chapter 1). One small family of sesterterpenoids represented by astellatol (**I**), YW 3548 (**II**), and retigeranic acid B (**III**, Scheme A) comprises a *trans*-hydrindane portion that is substituted with an angular methyl group and an *iso*-propyl residue. Although the daunting carbon backbones of the 15 members of this subclass and their interesting biological properties render these natural products attractive targets for total synthesis, only few reports have been reported in the literature. In total, only four successful total syntheses of retigeranic acid A, the C-18 epimer of retigeranic acid B (**III**), and six approaches toward this family of sesterterpenoids have been published.



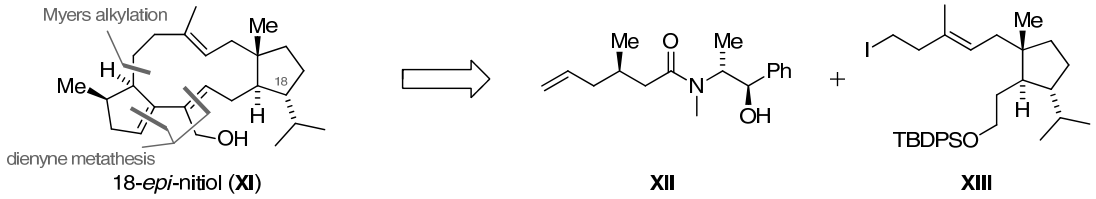
Scheme A Divergent synthesis of three building blocks suitable for *trans*-hydrindane *iso*-propyl sesterterpenoids.

In the course of this Ph.D. thesis, we envisioned accessing the structurally unique architectures of *trans*-hydrindane *iso*-propyl sesterterpenoids in order to evaluate their biological properties, gain insight into their biogenesis and confirm their relative and absolute configuration. Moreover, we aimed to access a total of eight natural products by a divergent approach utilizing the two versatile building blocks **IV** and **VI**. Chapter 2 describes our successful efforts in developing a practical and scalable route to the *trans*-hydrindanes **IV** and **VI**, starting from enantiopure diketone **V**. In these investigations, the focus was laid on the diastereoselective installation of the sterically congested *trans*-hydrindane portion. Moreover, we disclose the surprising outcome of a seemingly straight-forward hydrogenation. This result culminated in an efficient synthesis of a third versatile building block **VII**, which was an important intermediate in Corey's and Hudlicky's total syntheses of retigeranic acid A.



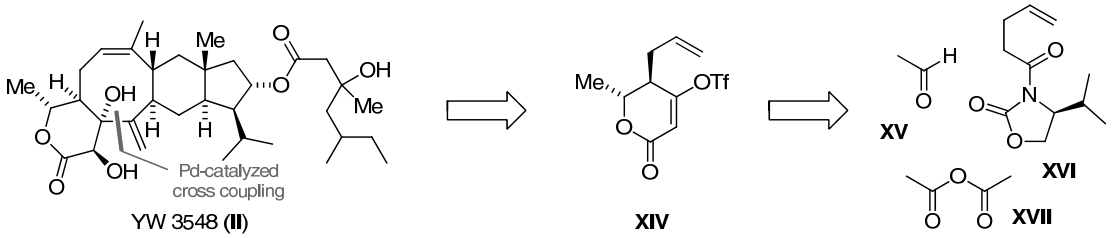
Scheme B Retrosynthetic analysis of astellatol (**I**): key intermediates and model system **X**.

In chapter 3, our current progress toward the total synthesis of the unique pentacarbocyclic backbone of astellatol (**I**) is described. We envisaged constructing this unique pentacarbocyclic architecture **I** by a biomimetic cationic cascade from tricycle **VIII** (Scheme B). The first part of this chapter details our strategy for installing the C-9 and C-10 stereogenic centers in alkene **IX** starting from building block **IV**. In addition, we also report our progress toward the synthesis of the strained 11-membered ring following three different routes, carried out on a model system **X**. Ultimately, preliminary results of a strategy to prepare the carbon framework of astellatol (**I**) *via* a [2+2]-cycloaddition are presented.



Scheme C Retrosynthetic analysis of 18-*epi*-nitiol (**XI**).

Chapter 4 features the synthetic program directed toward a synthesis of nitiol and its C-18 epimer **XI**. We envisaged accessing tricycle **XI** *via* a dienyne metathesis, the precursor of which should be merged from two building blocks **XII** and **XIII** by a Myers alkylation (Scheme C). This chapter describes a successful preparation of western portion **XII** and our progress toward the eastern fragment **XIII**, starting from *trans*-hydrindane building block **VII**.



Scheme D Progress toward YW 3548 (**II**): efficient enantioselective synthesis of enol triflate **XXI**.

Finally, chapter 5 outlines our progress *en route* to the potent GPI anchor inhibitor YW 3548 (**II**). Thereby, an asymmetric synthesis of a suitable western fragment enol triflate **XIV** was focused on, starting from simple building blocks **XV**, **XVI** and **XVII** (Scheme D). In addition, the ability of enol triflate **XIV** to engage in Pd-catalyzed cross coupling reactions is disclosed.

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LIST OF ABBREVIATIONS

9-BBN	9-borabicyclo[3.3.1]nonane
Ac	acetyl
ADDP	1,1'-(azodicarbonyl)dipiperidine
ADP	adenosine triphosphate
AIBN	azobisisobutyronitrile
Ar	undefined aryl substituent
ATP	adenosine triphosphate
ATR	attenuated total reflection (IR)
BAIB	bis(acetoxy)iodobenzene
Bn	benzyl
br	broad (NMR spectroscopy, IR spectroscopy)
BSTFA	*N*,*O*-bis(trimethylsilyl)trifluoroacetamide
Bu	butyl
catBH	catecholborane
CCDC	Cambridge Crystallographic Data Centre
Cp	cyclopentadienyl
COSY	homonuclear correlation spectroscopy
CSA	camphorsulfonic acid
d	dublet (NMR spectroscopy)
DABCO	1,4-diazabicyclo[2.2.2]octane
DCE	1,2-dichloroethane
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-4,5-dicyano-1,3-benzoquinone
DIBAL-H	diisobutylaluminum hydride
DIPA	diisopropylamine
DIPEA	diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMAPP	dimethylallyl pyrophosphate
DMF	dimethylformamide

DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
dppf	1,1´-bis(diphenylphosphino)ferrocene
d.r.	diastereomeric ratio
EDCI	*N*-(3-dimethylaminopropyl)-*N´*-ethylcarbodiimide hydrochloride
ee	enantiomeric excess
EI	electron impact ionization (mass spectrometry)
eq.	equivalent(s)
ESWHP	Eder-Sauer-Wiechert-Hajos-Parrish
Et	ethyl
ESI	electron spray ionization (mass spectrometry)
FAB	fast atom bombardment (mass spectrometry)
FCC	flash column chromatography
FVP	flash vacuum pyrolysis
g	gram(s)
GPI	glycosylphosphatidylinositol
h	hour(s)
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HIV	human immunodeficiency virus
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple bond coherence
HPLC	high-performance liquid chromatography
HSQC	heteronuclear single quantum coherence
HWE	Horner-Wodswarth-Emmons
Hz	Hertz (frequency)
i	*iso* (isomer)
IBX	2-iodoxybenzoic acid
IL-2	interleukin-2
Im	imidazole
ino	inositol
Ipc	isopinocampheoyl
IPP	isopentenyl pyrophosphate

IR	infrared
IUPAC	International Union of Pure and Applied Chemistry
KHMDS	potassium hexamethyldisilazide
K-Selectride®	potassium tri-*sec*-butylborohydride
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
L_n	ligand(s)
L-Selectride®	lithium tri-*sec*-butylborohydride
m	medium (IR spectroscopy)
m	multiplet (NMR spectroscopy)
m_C	centrosymmetric multiplet (NMR spectroscopy)
man	mannose
*m*CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MIC	minimal inhibition concentration
min	minute(s)
mL	milliliter
MMC	methoxymagnesium methyl carboxylate
mmol	millimole
MOM	methoxymethyl
MoOPH	oxodiperoxymolybdenum(pyridine)(hexamethylphosphoramide)
MPO	4-methoxyl pyridine *N*-oxide
mRNA	messenger RNA
MS	mass spectrometry
MsCl	methanesulfonyl chloride
MVA	mevalonic acid
MVK	methylvinylketone
NADPH	nicotinamide adenine dinucleotide phosphate hydrogen
NBS	*N*-bromosuccinimide
NHK	Nozaki-Hiyama-Kishi
NIS	*N*-iodosuccinimide
NMO	*N*-morpholine *N*-oxide
NMR	nuclear magnetic resonance

NOESY	nuclear Overhauser effect correlation spectroscopy
p	*para* (isomer)
PCC	pyridinium chlorochromate
Ph	phenyl
$PhNTf_2$	*N*-phenyl(bistrifluoromethanesulfonimide)
pin	pinacol
Piv	pivaloyl
PMB	*para*-methoxybenzyl
PMBTCA	*para*-methoxybenzyl-2,2,2-trichloroacetamide
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
PTAB	phenyltrimethylammonium tribromide
*p*TsOH	*para*-toluenesulfonic acid
q	quartet (NMR spectroscopy)
R	undefined substituent
RCM	ring closing metathesis
R_f	retardation factor
ROESY	rotating-frame nuclear Overhauser effect correlation spectroscopy
rt	room temperature
s	strong (IR spectroscopy)
s	singlet (NMR spectroscopy)
SEM	2-(trimethylsilyl)ethoxymethyl
sia	siamyl
s.m.	starting material
Super-Hydride®	lithium triethylborohydride
T	temperature
t	time
t-	(*tert*-) tertiary (isomer)
t	triplet (NMR spectroscopy)
TBACl	tetrabutylammonium chloride
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride

TBAI	tetrabutylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf_2O	trifluoromethanesulfonic anhydride
THF	tetrahydrofurane
THP	tetrahydropyranyl
Thx	thexyl
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylendiamine
TMS	trimethylsilyl
TPP	thiamine pyrophosphate
tol	toluidine
w	weak (IR spectroscopy)
wt%	weight percent

TABLE OF CONTENTS

EXPERIMENTAL SECTION

APPENDICES

THEORETICAL SECTION

1 INTRODUCTION

1.1 Terpenoids: Biosynthetic Origin and Inspiration for Chemists

With over 35.000 members,[1] terpenoids* constitute the largest class of natural products and their physical and biological properties have been exploited by mankind throughout history. In the modern world, these small molecules have found a variety of applications ranging from odors for perfumery and cosmetic products to therapeutic agents.[2] While low-molecular weight molecules like citronellol (**2**) or menthol (**3**) are utilized in industry as fragrances,[3] several terpenoid natural products are used for the treatment of human diseases,[4] exemplified by the antimalarial compound artemisinin (**4**)[5] and the anticancer drug paclitaxel (**5**, Figure 1.1).[6]

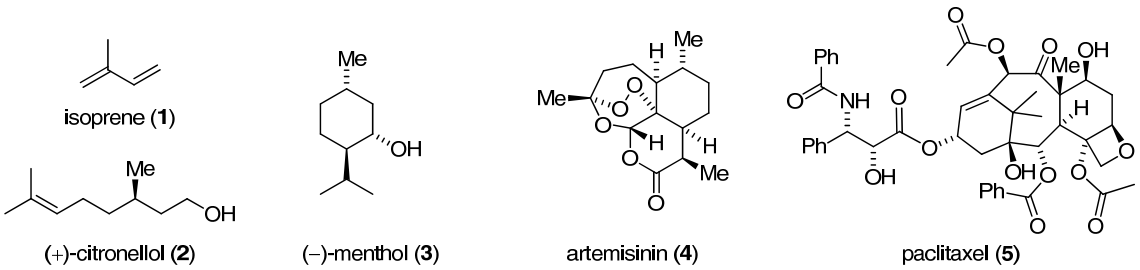
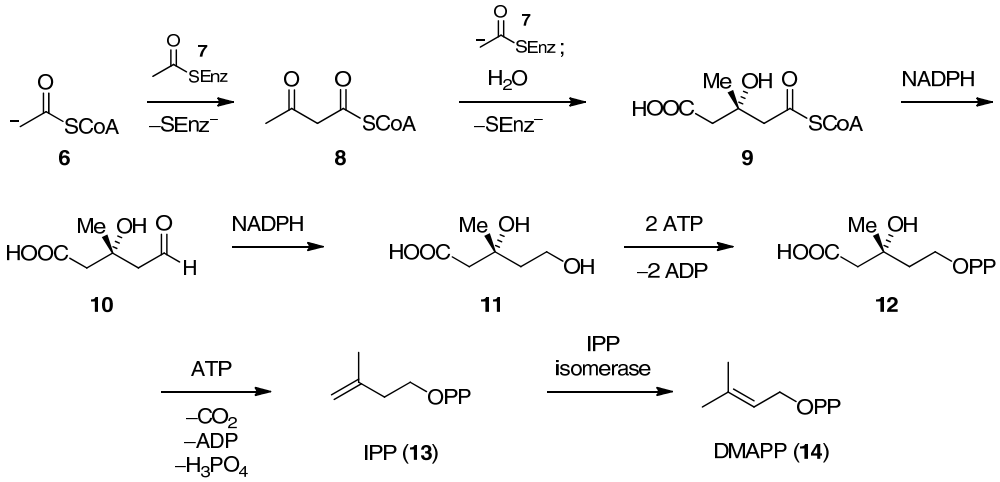


Figure 1.1 Molecular structures of isoprene (**1**), terpenoid odorants and terpenoid therapeutics for treating human diseases.

Not surprisingly, the importance of these natural products has evoked a myriad of studies to gain insight into their biosynthesis, biological properties and function in Nature.[7] Early examples of these investigations were described in the pioneering works of Wallach[8] and Ruzicka,[9] who formulated the 'isoprene rule' stating that all terpenoids arise from a varying number of a fundamental C_5 building block, isoprene (**1**). Upon further investigations propelled by the impressive contributions of Bloch[10] and Lynen,[11] it was established that isoprene (**1**) itself is not involved in the biogenesis of terpenoids. Instead, Nature employs two activated forms of isoprene (**1**) as key building blocks, namely isopentenyl pyrophosphate (IPP, **13**) and dimethylallyl pyrophosphate (DMAPP, **14**). Both compounds **13** and **14** in turn arise from two different pathways.[12] In the mevalonate pathway,[13] mevalonic acid (MVA, **11**) is the key intermediate for the production of IPP (**13**) and DMAPP (**14**). In the process, a Claisen condensation of the enolate of acetyl-SCoA (**6**) with an enzyme-bound acetyl group (**7**) initially forms diketone **8** (Scheme 1.1) that in turn undergoes a stereospecific aldol reaction of the enolate derived from an enzyme-bound acetyl group (**7**). After hydrolysis of the attached enzyme, the thioester functionality of the thus generated acid 3-hydroxy-3-methylglutaryl-CoA (**9**) gets reduced to an aldehyde in mevaldic acid (**10**) by NADPH.

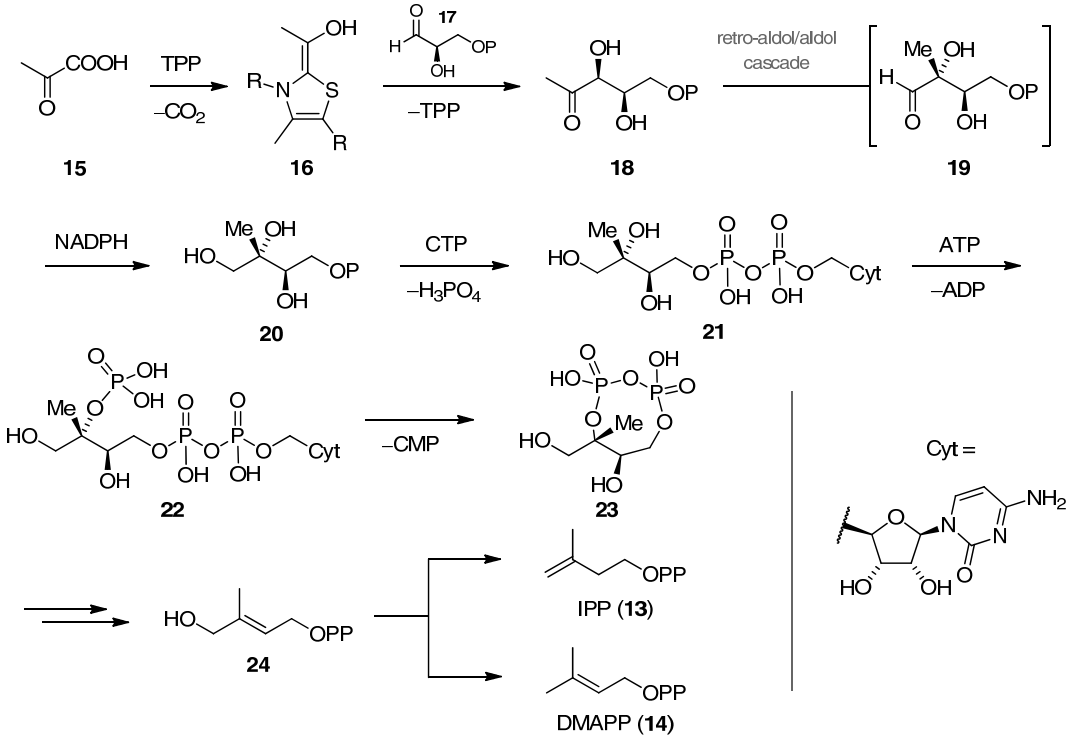
* According to IUPAC, the term 'terpenes' comprises all pure hydrocarbons in this class of natural products, whereas 'terpenoids' refers to further functionalized molecules, which are *e.g.* oxygenated. However, both terms are often used as synonyms. In this Ph.D. thesis only the term terpenoid(s) will be employed.



Scheme 1.1 Formation of IPP (**13**) and DMAPP (**14**) *via* the mevalonate pathway.

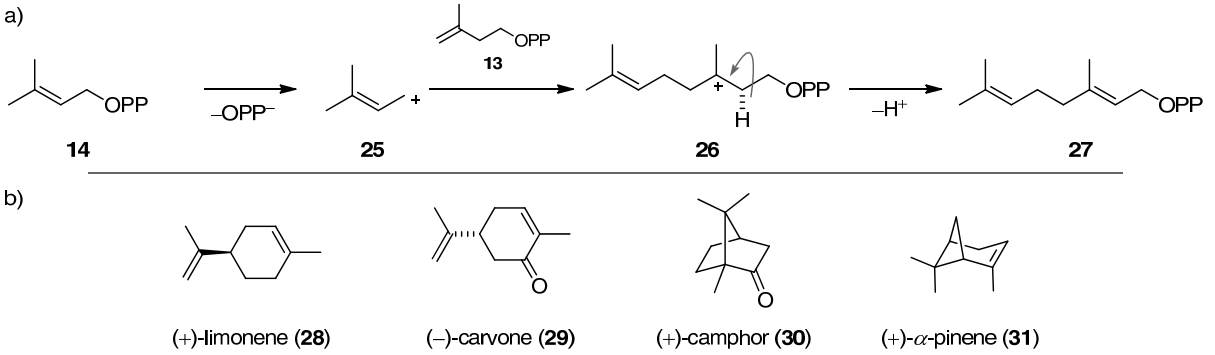
Another NADPH mediated reduction leads to the formation of MVA (**11**), which is then transformed into IPP (**13**) commencing with the sequential phosphorylation of the primary alcohol to generate pyrophosphate **12**. In the following enzyme mediated transformation, an adenosine triphosphate (ATP) assisted decarboxylation/elimination reaction ultimately furnishes IPP (**13**) that is transformed into DMAPP (**14**) by IPP isomerase *via* a stereospecific allylic isomerisation reaction removing the *pro-R* proton.

The second, non-mevalonate pathway, also known as methylerythritol phosphate (MEP) pathway, involves intermediates from the glycolytic biosynthesis.[14] Reaction of pyruvic acid (**15**) with thiamin pyrophosphate (TPP) provides enamine **16** with loss of CO_2. Subsequently, the latter intermediate **16** nucleophilically attacks glyceraldehyde 3-phosphate (**17**) leading to the deoxy-xylulose derivative **18** (Scheme 1.2).



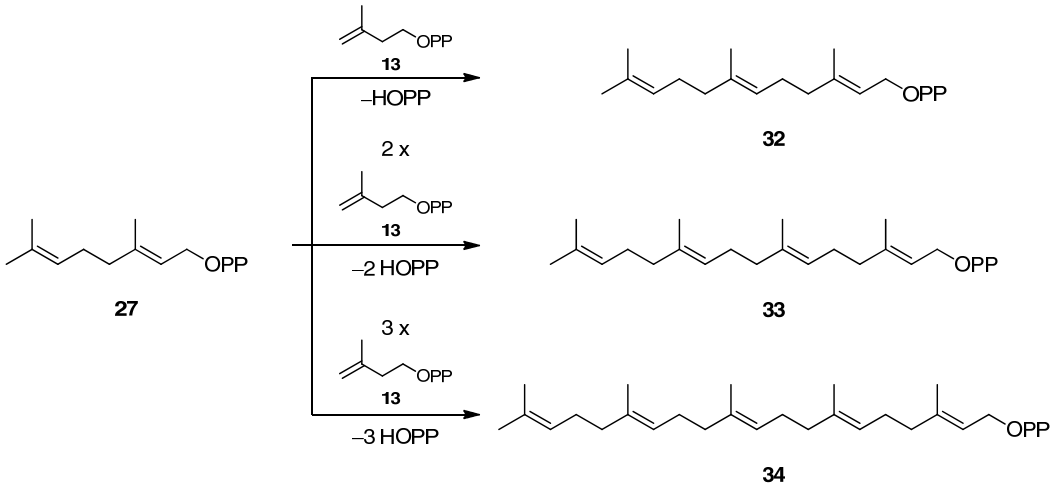
Scheme 1.2 Biosynthetic formation of IPP (**13**) and DMAPP (**14**) *via* the MEP pathway.

This β-hydroxy ketone **18** undergoes a retro-aldol/aldol cascade in the presence of a reductoisomerase to form aldehyde **19**, which is reduced to MEP (**20**) by NADPH in the same sequence. In the following transformations, the C-1 alcohol of the C_5 compound **20** reacts with cytidine triphosphate (CTP) to form cytidine diphosphate (CDP) derivative **21**. After phosphorylation of the tertiary alcohol, the resulting intermediate **22** produces cyclic phosphate **23** *via* an intramolecular hydrolysis that concomitantly releases cytidine monophosphate (CMP). Whereas these steps are well understood, the following processes still require investigations to clarify the mechanisms. However, it has been shown that the cyclic phosphate **23** is enzymatically transformed to primary alcohol **24**, which is converted into both IPP (**13**) and DMAPP (**14**) by reductive processes, with a 5:1 to 4:1 preference for IPP (**13**).[12]



Scheme 1.3 (*a*) Biosynthetic formation of geranyl pyrophosphate (**27**), the biosynthetic origin for all monoterpenoids. (*b*) Molecular structures of the mono- and bicarbocyclic monoterpenoids.

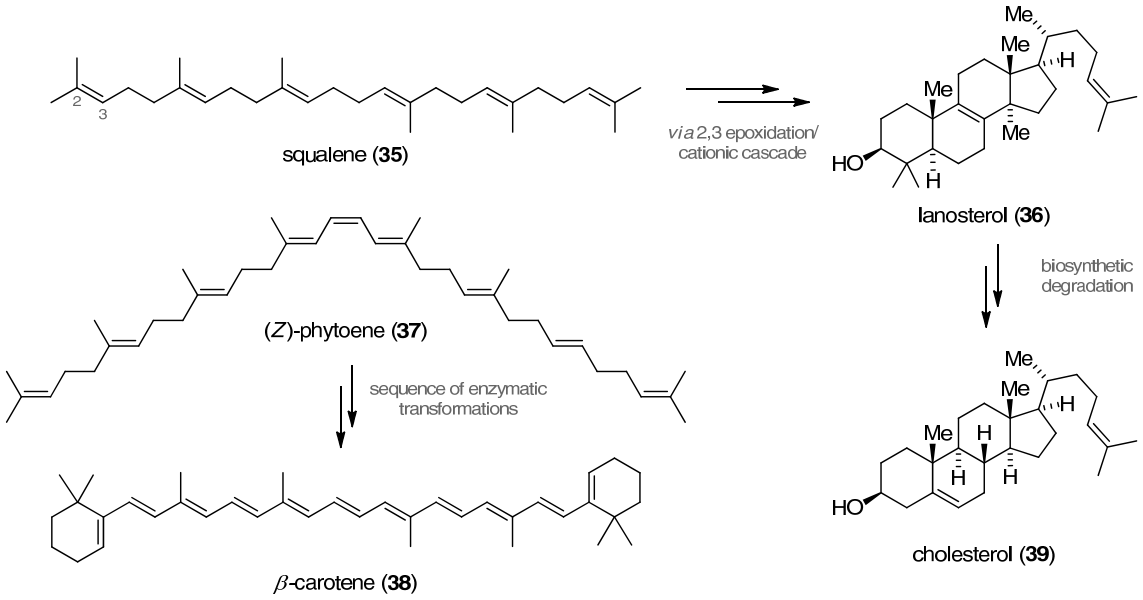
In the course of the biogenesis of complex molecules, DMAPP (**14**) forms allylic cation **25**, which is nucleophilically attacked by IPP (**13**, Scheme 1.3).[12] Subsequent stereospecific loss of the *pro-R* proton from the intermediate tertiary carbocation **26** generates geranyl pyrophosphate (**27**). This C_{10} building block **27** is the basis of the formation of monoterpenoids *via* cationic cascades in the presence of terpenecyclases and subsequent oxidations, forming *e.g.* monocarbocyclic compounds like limonene (**28**) and carvone (**29**) or bicycles like camphor (**30**) and α-pinene (**31**).[15]



Scheme 1.4 Biosynthetic production of farnesyl pyrophosphate (**32**), geranylgeranyl pyrophosphate (**33**) and geranylfarnesyl pyrophosphate (**34**), the precursors for sesquiterpenoids, diterpenoids and sesterterpenoids, respectively.

Following the same mechanism, another C_5 chain elongation of geranyl pyrophosphate (**27**) with IPP (**13**) produces farnesyl pyrophosphate (**32**), while two elongations give rise to geranylgeranyl pyrophosphate (**33**, Scheme 1.4). Analogously to the biosynthesis of monoterpenoids, these two building blocks provide the basis of the generation of sesquiterpenoids and diterpenoids,[16] respectively. A fourth chain elongation with IPP (**13**) results in the formation of the C_{25} building block geranylfarnesyl pyrophosphate (**34**) that is the biosynthetic precursor for all members of the sesterterpenoid subclass (*cf.* Chapter 1.2).

In contrast to the previously discussed C_{10}–C_{25} terpenoids, the precursor for triterpenoids is not formed *via* an IPP (**13**) homologation, but by a complex dimerization process of two molecules of farnesyl pyrophosphate (**32**) leading to squalene (**35**, Scheme 1.5).[12] Further transformations, *e.g.* a selective epoxidation to 2,3-oxidosqualene (not shown), then set the stage for cationic epoxide opening cascades, resulting in the formation of penta- and tetracarbocyclic triterpenoids such as lanosterol (**36**). The latter compound **36** and other structurally related triterpenoids serve as precursors for steroids, *i.e.* cholesterol (**39**), through biosynthetic degradation under the loss of carbon atoms. Thus, from a more general perspective, steroids are classified as *nor*-triterpenoids.



Scheme 1.5 Molecular structures of squalene (**35**) and (*Z*)-phytoene (**37**): biosynthetic precursors for tri- and tetraterpenoids like lanosterol (**36**), cholesterol (**39**) and *β*-carotene (**38**).

Analogously to triterpenoids, tetraterpenoids are usually generated from C_2 symmetric compounds like (*Z*)-phytoene (**37**), which in turn are formed through dimerization processes from geranylgeranyl pyrophosphate (**34**). The structural diversity of this subclass of terpenoids is mainly limited to the carotenoids[17] such as *β*-carotene (**38**) that play an important role in photosynthesis and in the vision process, and show anti-oxidant properties. Apart from these 'classical' subgroups, higher terpenoids and meroterpenoids are produced in Nature.[12] While the first subclass is rather rare, meroterpenoids are abundant and comprise, in addition to terpenoidal parts, structural elements in the carbon skeleton, which are derived from other sources, *e.g.* the acetate or the shikimate pathways.

From a synthetic point of view, the structural diversity of terpenoids, exhibiting a plethora of unique and intriguing architectures, combined with their broad range of biological activities has attracted synthetic chemists since the inception of organic chemistry.[18] Whereas a major goal of these efforts was certainly the production of substantial amounts of material for the evaluation of biological and/or therapeutic properties due to the small quantities being isolated, these programs have expanded the knowledge of chemical synthesis in the broadest sense. This is based on the fact that the pursued avenues often went hand in hand with the discovery of unknown reactivity (*e.g.* the Wagner-Meerwein rearrangement),[19] the development of new synthetic methodologies, their application in complex settings and mechanistic studies. In addition, important chemical principles such as retrosynthetic[20] and conformational[21] analysis were applied in early studies toward terpenoids.

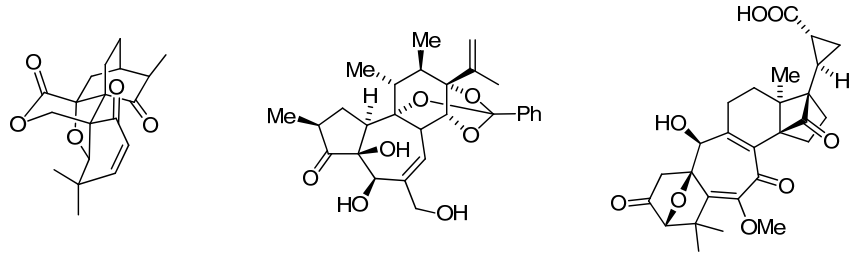


Figure 1.2 Molecular structures of selected bioactive terpenoids, recently accessed by total synthesis.

Historically, the total synthesis of terpenoids dates back to the early 1900's, at which time Komppa succeeded in the first industrial preparation of camphor (**30**).[22] In the further evolution of synthesis, the bioactivity of steroids and their application as drugs initiated extensive explorations towards an artificial production, accompanied by the discovery and application of synthetic transformations. For instance, these investigations involved an early example of a Diels-Alder reaction in a total synthesis by Woodward[23] and pioneering reports on (enantioselective) organocatalysis in the synthesis of Wieland-Miescher-ketone[24] and the Eder-Sauer-Wiechert-Hajos-Parrish ketone (*cf.* Chapter 2).[25] With the advent of modern analytical methods and a continuously expanding repertoire of synthetic tools, terpenoids of increasingly complexity were accessed over the last decades,[26] exemplified by the total syntheses of maoecrystal V (**40**, Yang, 2010),[27] yuanhuapin analog **41** (Wender, 2011),[28] and solanoeclepin A (**42**, Tanino, 2011).[29] Whereas the molecules depicted in Figure 1.2 are formed *via* diterpenoid or triterpenoid pathways, the subclass of sesterterpenoids with its C_{25} backbone also provides a high diversity of unique structures and determined biological profiles, rendering them attractive targets for total synthesis. Further information on this beautiful class of natural products will be provided in the next subchapter, thereby focusing on synthetic strategies and interesting key steps *en route* to complex molecules.

1.2 Sesterterpenoids: Challenging Targets for Total Synthesis

Among the terpenoid family, sesterterpenoids form a small subclass with 965 isolated members[30a] that have been isolated from a variety of organisms, including fungi, lichens, plants, and marine sources such as sponges.[30–33] Their name is derived from the Latin word *sester*, meaning 'two and a half', which was also incorporated into *sestertius*, an ancient Roman coin. *Sester* is thus referring to the old nomenclature that terpenoids are assembled from C_{10} units. As discussed, the biosynthetic origin is based on IPP (**13**) and DMAPP (**14**) which generate the pentaprenyl C_{25} building block farnesylgeranyl pyrophosphate (**34**).[12] Subsequent cyclization *via* cationic intermediates, hydride- and methyl-shifts, late-stage oxidations and eventually loss of carbon atoms lead to a variety of structural architectures. This process will be discussed for the biosynthesis of astellatol (**103**, Chapter 3.1) in detail. Due to the broad range of structural features, a further classification into linear, mono-, di-, tri-, tetra- and pentacarbocyclic sesterterpenoids is common. In addition, three major subclasses have been found within the diversity of carbon backbones that were named as ophiobolins, cheilantanes and scalaranes, respectively (Figure 1.3).

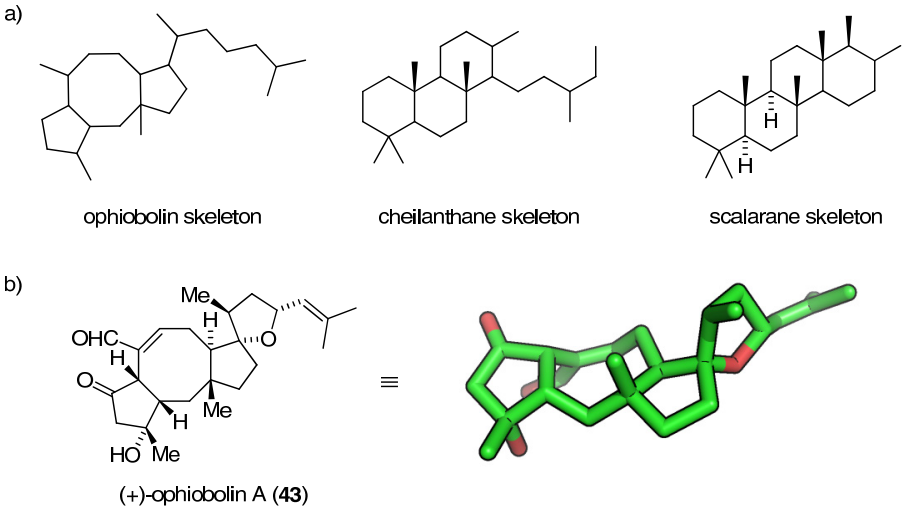


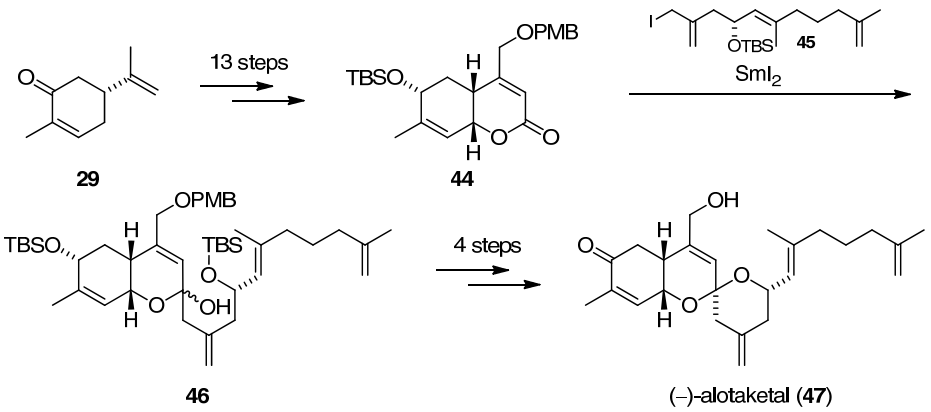
Figure 1.3 (*a*) Carbon scaffolds of the sesterterpenoid families named ophiobolins, cheilanthanes and scalaranes. (*b*) Molecular and X-ray structure of (+)-ophiobolin A (**43**, hydrogen atoms omitted for clarity).

One member of the ophiobolins called (+)-ophiobolin A (**43**) was the first sesterterpenoid to be isolated in 1958 as a toxic agent to rice seedlings[34] and its structure was deduced from NMR studies and a X-ray structure analysis of a bromo-methoxy derivative (not shown).[35] Quite recently, the X-ray structure of the 'free' (+)-ophiobolin A (**43**) was reported too.[36] In the following decades, more than 20 members of the tricarbocyclic ophiobolin family have been isolated, most of them exhibiting biological activities as inhibitors against fungi and bacteria as well as cytotoxins against cancer cells.[37] Another subclass of tricarbocyclic sesterterpenoids, the cheilanthanes, comprises about 50 members that have been mostly isolated during the 1990's from marine sources. Their occurrence, their broad range of biological activities and successful syntheses have been reviewed recently.[38] A

structurally related sesterterpenoid subclass is called the scalaranes. In contrast to the cheilathanes, these natural products bear an additional ring and thus contain a tetracarbocyclic carbon backbone. Similarly however, most scalarane compounds have been found in marine sources like sponges and reveal a promising spectrum of potential applications due to observed anti-feedant properties or strong cytotoxicity.[39]

Despite the beautiful and often intriguing architectures of sesterterpenoids, the number of total syntheses remains in the dozens, many of those accessing cheilanthanes and scalaranes by semi-synthetic approaches (*cf.* Scheme 1.14).[40] In the following text, a few examples of successfully prepared sesterterpenoids will be given, focusing on key steps to access complex molecules. This summary will be ordered by the numbering of carbocycles, while total syntheses of and approaches toward *trans*-hydrindane *iso*-propyl sesterterpenoid will be discussed in Chapter 1.3 in more detail.

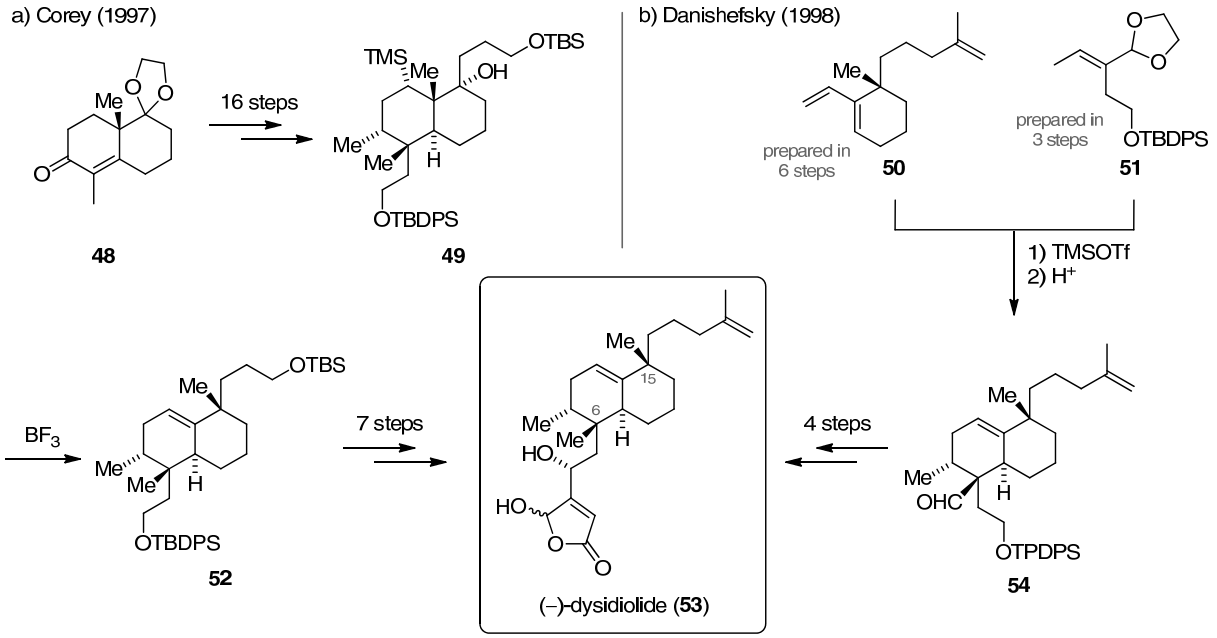
In 2009, the monocarbocyclic sesterterpenoid (–)-alotaketal (**47**)[41] was found to be a potent activator of the cAMP cell signaling, which is essential for a diverse range of cellular processes. Thus, new modulators such as (–)-alotaketal (**47**) or its derivatives might be used in treating heart failure, cancer, and neurodegenerative diseases.[42] In 2012, Yang and co-workers disclosed the first enantioselective route to (–)-alotaketal (**47**) (Scheme 1.6).[43]



Scheme 1.6 Yang's enantioselective synthesis of the cAMP signaling agonist (–)-alotaketal (**47**) *via* a SmI_2 mediated intramolecular Barbier-type ketalization.

Their strategy hinged on a SmI_2-mediated coupling between two fragments **44** and **45**, whereby the former compound **44** was accessed *ex*-chiral pool starting from (*R*)-carvone (**29**). Contrarily, the sole stereogenic center within allyl iodide **45** originated from a Nagao-Fujita aldol reaction, which is based on an Evans-type auxiliary. With both fragments in hand, the envisaged coupling efficiently delivered intermediate **46** as mixture of hemiacetal epimers. This key compound was then transformed to (–)-alotaketal (**47**) *via* desilylation, spiroketalization, oxidation and PMB deprotection. Later that year, the group of Dalby reported a second synthesis of (–)-alotaketal (**47**).[44] Their strategy was based on the same disconnection and similar building blocks, but preparing the fragment analogous to bicycle **44** by an alternative route. Both reports paved the way for further evaluation of biological properties of (–)-alotaketal A (**47**) and for the preparation of synthetic congeners.

In contrast to (−)-alotaketal A (**47**), the sesterterpenoid (−)-dysidiolide (**53**, Scheme 1.7) exhibits an additional carbocycle and this bicarbocyclic sesterterpenoid **53** has been a popular target at the turn of the millennium.[45] On the one hand, this was due to the fact that its octahydronaphthaline structure comprises two quaternary stereocenters and a bicyclic system, the large substituents of which interestingly adopt sterically disfavored pseudo-axial positions as proven by X-ray crystallography. On the other hand, (−)-dysidiolide (**53**) has been shown to inhibit growth of A-549 human lung carcinoma and P388 leukemia cell lines, thus making it a potential anti-cancer agent.[46] The resulting synthetic endeavors culminated in numerous approaches and successful total syntheses.[40] The key step of the routes of Corey[47] and Danishefsky[48] are presented in Scheme 1.7.



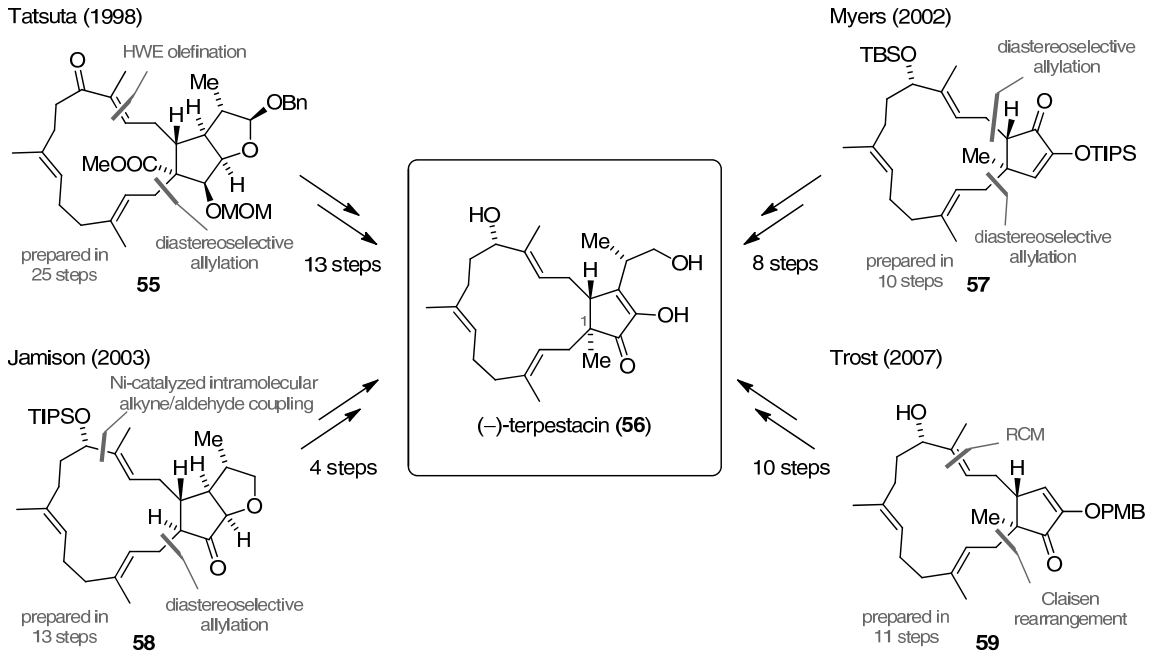
Scheme 1.7 (*a*) Corey's divergent enantioselective route to (−)-dysidiolide (**53**) featuring a bioinspired 1,2-Me shift. (*b*) Danishefsky's convergent racemic synthesis of dysidiolide (**53**) demonstrating the power of the Diels-Alder reaction.

In his enantioselective synthesis, Corey utilized a bioinspired key step to install the quaternary stereogenic center at C-15.[47] To this end, bicycle **49** was prepared in a lengthy sequence, starting from Wieland-Miescher ketone analog **48**. Noteworthy, they introduced the correct relative configuration at C-6 *via* an enone reduction under Birch conditions with subsequent trapping of the formed enolate with allyl bromide. The intermediate **49** was then treated with gaseous BF_3, resulting in the formation of a tertiary carbocation and triggering a 1,2-methyl shift (not shown). The newly generated tertiary carbocation, stabilized by a β-silyl effect underwent an ensuing regioselective elimination to afford intermediate **52**. With the cyclic framework installed, (−)-dysidiolide (**53**) was finally prepared by a series of standard transformation, including a Rose-Bengal mediated oxidation of a furan to the butenolide moiety. Contrarily to this linear approach, Danishefsky and co-workers envisaged a more convergent, yet racemic synthesis.[48] Thereby, they impressively demonstrated the synthetic power of the Diels-Alder reaction to install quaternary stereogenic centers.[49] At first, the team quickly built up two reaction partners, dienophile **51** and diene **50**, the quaternary center of

which was installed by an alkylation. Upon exposure to TMSOTf at low temperatures, the reaction partners smoothly underwent a Gassmann Diels-Alder reaction, furnishing the bicarbocyclic system **54** after acetal cleavage with all stereogenic centers set. This compound was then easily transformed to the desired target **53**.

At around the same time, several research groups embarked on the total synthesis of another bicarbocyclic sesterterpenoid named (–)-terpestacin (**56**), an inhibitor of the formation of multinuclear cell bodies, which are part of the pathology of an HIV infection.[50] In contrast to both previously discussed natural products, almost all 25 carbon atoms are embedded in the two carbocycles, one of which is 15-membered. Attracted by those features, six research groups reported successful approaches toward terpestacin (**56**) and four key intermediates with the respective strategic disconnections on closing the 15-membered ring and installing the quaternary stereogenic center at C-1 are depicted in Scheme 1.8.

The first asymmetric synthesis of (–)-terpestacin (**56**) has been accomplished by the group of Tatsuta in 1998.[51] In their strategy, they utilized the conformational bias of a tricyclic system, directing an allylation with a farnesly derived allylic chloride to install the requisite relative configuration at C-1 (not shown). Further transformations set the stage for the key intramolecular HWE reaction, which formed macrocycle **55**. Additional functional group manipulations finally gave rise to (–)-terpestacin (**56**).



Scheme 1.8 Intermediates in the total syntheses of terpestacin (**56**) by the groups of Matsuda, Myers, Jamison and Trost, including comparison of key C–C bond forming reactions.

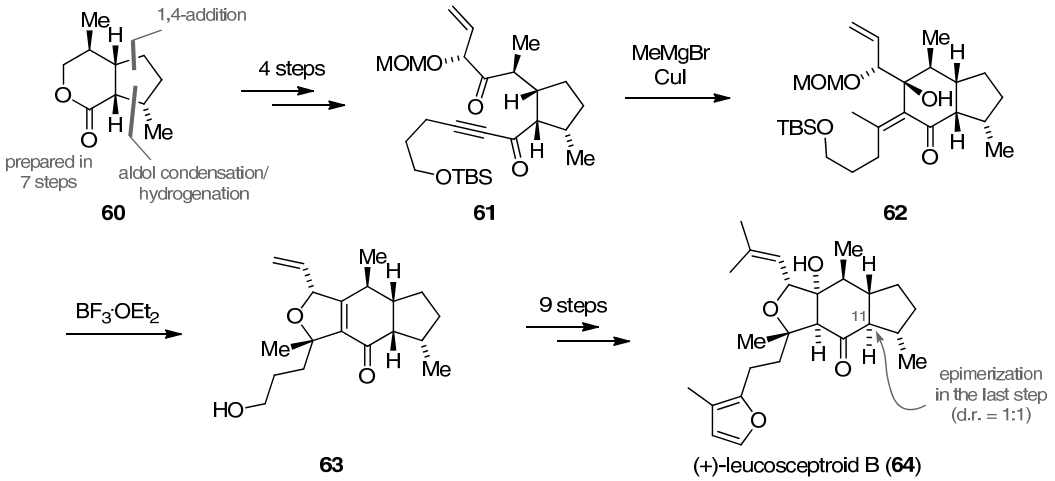
In 2002, the group of Myers at Harvard University reported a more concise synthesis of (–)-terpestacin (**56**)[52] that was based on three diastereoselective allylation reactions. Initially, the group diastereoselectively prepared a cyclopentanone moiety *via* an alkylation protocol developed in the same laboratories (not shown). The conformational bias of the cyclic system then allowed for both

the stereocontrolled installation of the C-1 stereocenter as well as ring-closure in the presence of Masamune's base $LiN(SiMe_2Ph)_2$ to form bicycle **57** in an efficient manner.

Similarly, in 2003 the group of Jamison constructed the macrocycle of (–)-terpestacin (**56**) *via* an allylation, but setting the quaternary stereogenic center in terpestacin (**56**) last.[53] Previously they had chosen to prepare the precursor **58** by a Ni-catalyzed intramolecular coupling of an alkyne and a farnesyl derived aldehyde. In the following, an allylation closed the 15-membered ring and ketone **58** underwent a regio- and diastereoselective methylation with NaH to generate the requisite configuration at C-1. Interestingly, this transformation only occurred in the presence of H_2O, which prompted the authors to attribute this *in situ* effect to the production of finely dispersed NaOH.

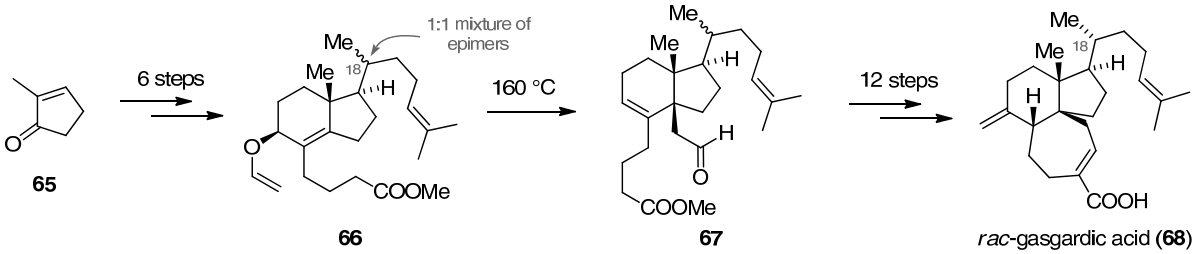
Yet another possibility to close the 15-membered macrocycle was presented by Trost and co-workers in 2007.[54] At first, a sequence consisting of a Pd-catalyzed asymmetric alkylation and a subsequent Claisen rearrangement installed the stereogenic quaternary center at C-1 (not shown). Thereafter, a series of transformation gave rise to a pentaene, setting the stage for the envisaged key step: a ring-closing metathesis (RCM). In the event, subjection of the substrate to Grubbs 2nd generation metathesis catalyst closed the macrocycle **59** in moderate yield, but high (*E*)-selectivity. Further reaction conditions, including another AAA/Claisen sequence then furnished (–)-terpestacin (**56**). Since this report, the groups of Tius[55] and Qui[56] also disclosed a racemic and an enantioselective total synthesis, in 2007 and 2012 respectively. Similarly to the approach of Matsuda, both groups constructed the macrocycle *via* an intramolecular HWE reaction, whereas the C-1 quaternary stereogenic center was installed by enolate allylation chemistry (not shown).

From 2010 on, a new family of sesterterpenoids called leucosceptroids has been isolated from the small tree *Leucosceptrum canum*, representing a rare example of sesterterpenoids from higher plant origin.[57] The 15 members of this subclass, represented by (+)-leucosceptroid B (**64**), have been found to possess anti-feedant and anti-fungal properties, prompting the authors to name this family 'harbor defense sesterterpenoids'.



Scheme 1.9 Liu's asymmetric total synthesis of (+)-leucosceptroid B (**64**) *via* a Michael addition/aldol sequence and a tandem Lewis acid mediated deprotection/dihydrofuran formation.

Already one year later, in 2011, Horne and co-workers published a Diels-Alder approach to furnish the tricyclic skeleton of the leucosceptroids (not shown),[58] and in 2013, the group of Liu succeeded in the first enantioselective synthesis of (+)-leucosceptroid B (**64**, Scheme 1.9).[59] Utilizing a seven-step sequence consisting of a Michael addition, ozonolysis, aldol condensation and diastereoselective hydrogenation, they quickly built up bicyclic lactone **60**, which was further elaborated to enyne **61** by standard transformations. Thereafter, the authors beautifully orchestrated two consecutive key steps to construct the tricarbocyclic backbone. First, a Michael-addition/aldol sequence with a methyl cuprate derived from MeMgBr and CuCN preferentially gave rise to (*Z*)-configured alkene (**62**, d.r. = 3.6:1). This was followed by a MOM deprotection in the presence of $BF_3 \cdot Et_2O$ with concomitant formation of the dihydrofuran moiety and desilylation, furnishing tricycle **63**. Finally, a nine-step sequence afforded (+)-leucosceptroid B (**64**). It is worth noting that the authors installed the stereochemistry at C-11 in the last step *via* epimerization leading to an approximately 1:1 mixture of (+)-leucosceptroid B (**64**) and its β-epimer (not shown).

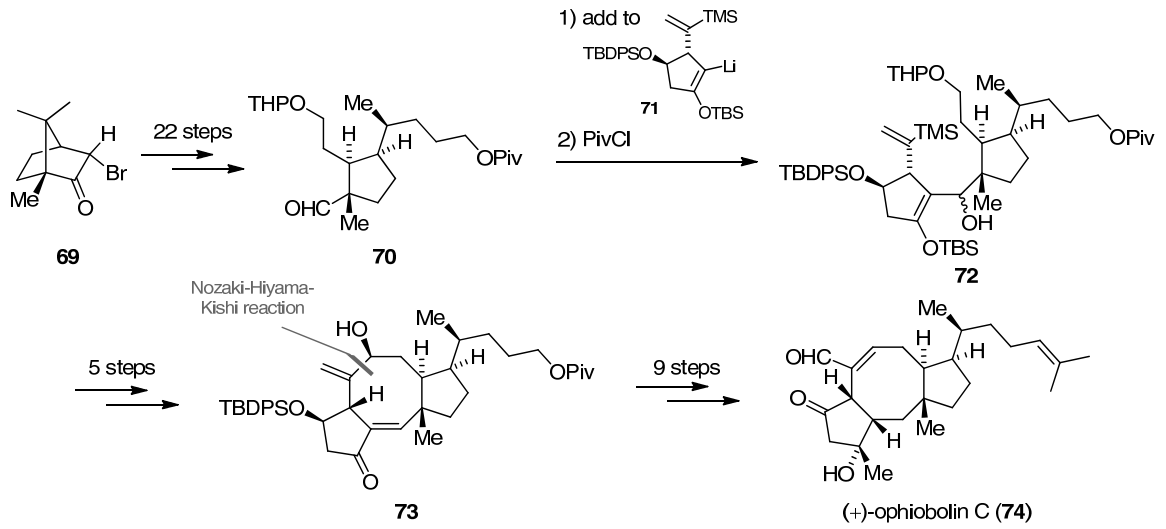


Scheme 1.10 Boeckman's racemic synthesis of gascardic acid (**68**) featuring a highly diastereoselective Claisen rearrangement to install the second adjacent quaternary stereocenter.

Around 30 years earlier, in 1979, the group of Boeckman published the first synthesis of a structurally complex sesterterpenoid[60] named gascardic acid (**68**). This tricarbocyclic compound **68** had been isolated already in 1960[61a] and despite further careful investigations,[61b] the relative stereochemistry was not clarified. Boeckman *et al.* commenced their synthesis with cyclopentenone **65**, which was transformed to vinyl allyl ether **66** (obtained as a mixture of diastereomers at C-18), featuring a three-component coupling (cuprate addition, enolate Michael addition, aldol condensation) as the key element (Scheme 1.10). Subjecting this compound **66** to elevated temperatures triggered a Claisen rearrangement to diastereoselectively set the quaternary stereoecenter in aldehyde **67**. This example impressively demonstrated the power of intramolecular sigmatropic reactions to install stereocenters in sterically encumbered settings.[62] Further transformations including the separation of the diastereomers at C-18 provided Boeckman *et al.* with gascardic acid (**68**), which could now be assigned based on comparison of NMR spectroscopic data.[60a,63]

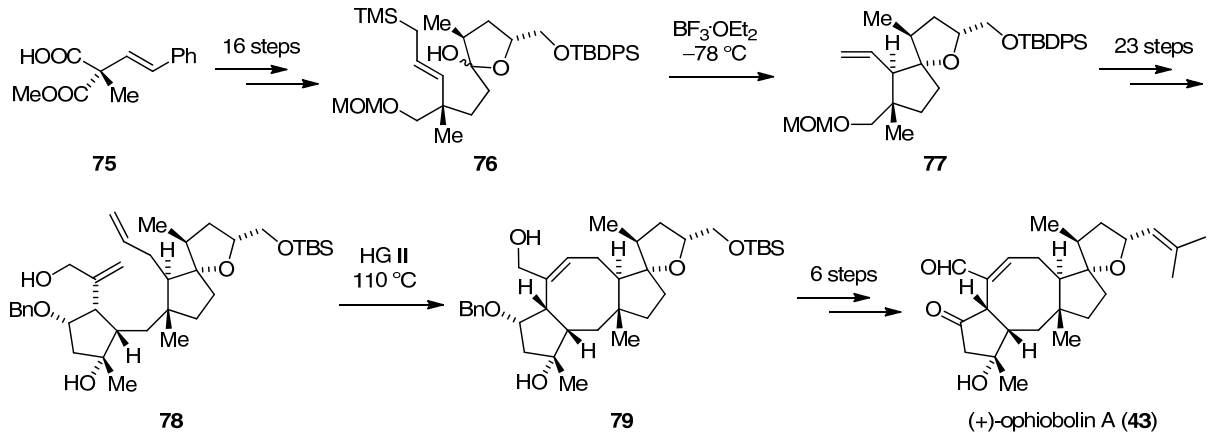
As pointed out earlier, the family of the ophiobolins constitutes a larger subfamily of sesterterpenoid natural products. Not surprisingly, several research groups were attracted by their structural and biological profiles and these studies culminated in numerous publications.[64] As most of this work was carried out in the *pre*-metathesis era, the ophiobolins and related terpenoids provided an inspiration to study the synthesis of eight-membered rings.[65,66] Despite the enormous synthetic efforts undertaken,

only the groups of Kishi in 1989[67] and Nakada in 2011[68] succeeded in total syntheses of (+)-ophiobolin C (**74**)[69] and (+)-ophiobolin A (**43**),[35] respectively.



Scheme 1.11 Kishi's enantioselective route to (+)-ophiobolin C (**74**) constructing the central eight-membered ring *via* a Nozaki-Hiyama-Kishi reaction.

As depicted in Scheme 1.11, Kishi addressed the problem of establishing the central eight-membered ring by a Nozaki-Hiyama-Kishi (NHK) reaction, a $CrCl_2$ and $NiCl_2$ mediated coupling between an aldehyde and a vinyl iodide.[67] Starting from camphor derivative **69**, they therefore prepared aldehyde **70**, which in turn was reacted with vinyl lithium **71**. After reinstallation of the pivaloate, the resulting alcohol **72** was successfully carried on to the desired [5-8-5]-tricarbocyclic ring system found in allylic alcohol **73**, constructing the allylic C–C bond *via* the aforementioned methodology. Ultimately, standard functional group interconversion provided access to (+)-ophiobolin C (**74**).

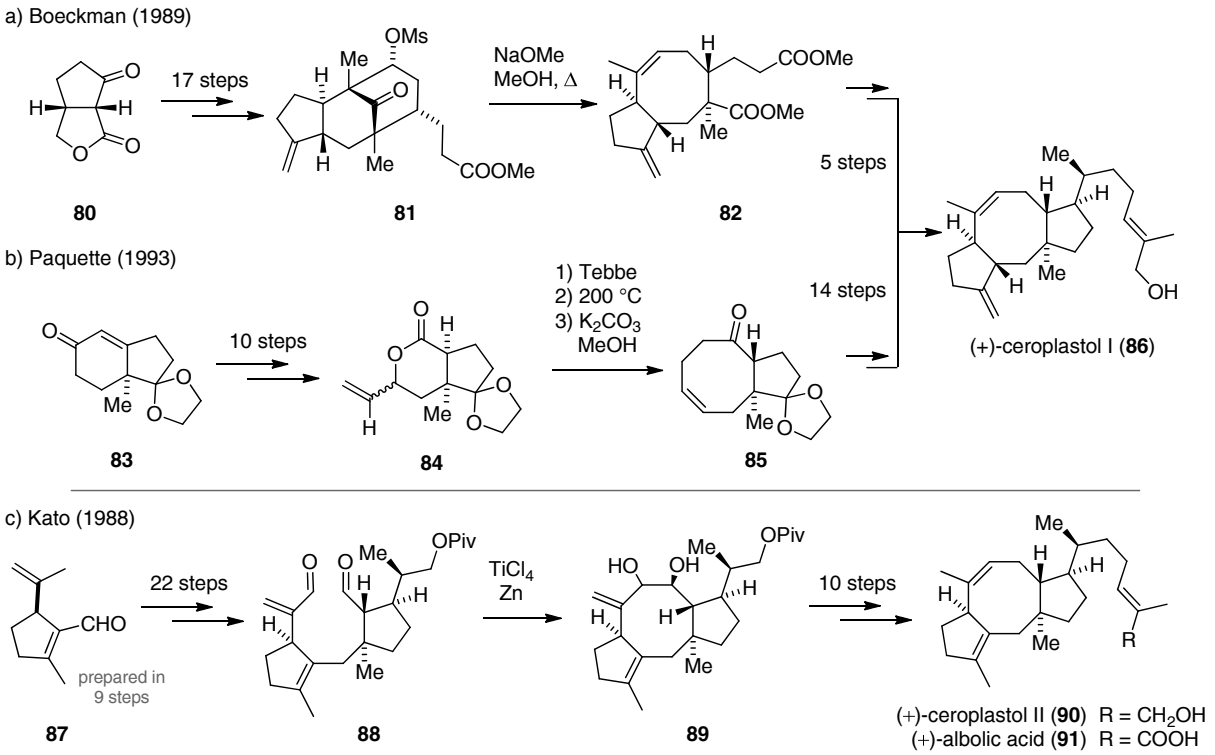


Scheme 1.12 Nakada's enantioselective synthesis of (+)-ophiobolin A (**43**) closing the central eight-membered ring by a ring-closing metathesis reaction.

In contrast to Kishi's synthesis, the group of Nakada exploited a more recent synthetic tool in constructing the eight-membered ring of (+)-ophiobolin A (**43**), namely a RCM reaction.[68] In order to prepare a feasible precursor, they converted acid **75** in a 16-step sequence to hemiacetal **76**, which underwent an intramolecular Sakurai type allylation to effectively form the two adjacent stereocenters

in spiro compound **77** (Scheme 1.12). This intermediate **77** was further elaborated to diene **78** over a series of transformations, involving several protecting group manipulations as the RCM reaction proved to be sensitive to the steric environment at the reacting sites.[68b] Subjecting diene **78** to the 2nd generation Hoveyda-Grubbs catalyst (HGII) in refluxing toluene closed the macrocycle in diol **79**, and an additional six-step protocol provided, at long last, (+)-ophiobolin A (**43**), more than 50 years after its isolation.

The structurally related natural products (+)-ceroplastol I (**86**),[70] (+)-ceroplastol II (**90**)[71] and albolic acid (**91**)[72] have also been accessed by the groups of Boeckman,[73] Paquette[74] and Kato.[75] Analogously to the ophiobolins, the central feature of these total syntheses was the construction of the eight-membered ring (Scheme 1.13). The synthesis of Boeckman and co-workers commenced with racemic bicycle **80**, which was further functionalized to ketone **81** bearing the requisite relative stereochemistry for a key Grob fragmentation.[73] As envisaged, subjection of tricycle **81** to NaOMe in refluxing MeOH triggered the formation of the eight-membered ring in diester **82** and subsequent manipulations afforded ceroplastol I (**86**).

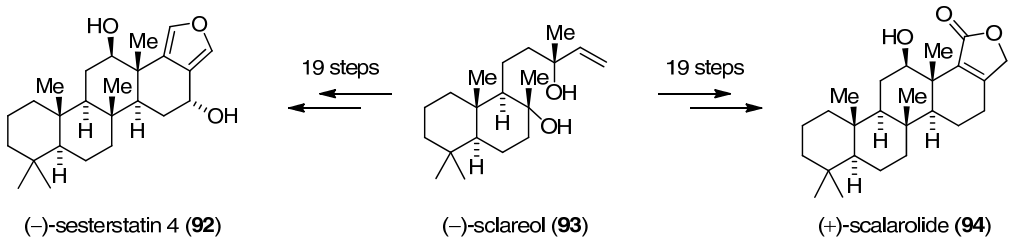


Scheme 1.13 Successful approaches toward the ceroplastins: (*a*) Boeckman's racemic synthesis of ceroplastol I (**86**). (*b*) Paquette's asymmetric synthesis of (+)-ceroplastol I (**86**). (*c*) Kato's enantioselective synthesis of (+)-ceroplastol II (**90**) and (+)-albolic acid (**91**).

In an alternative line of investigations, Paquette's group utilized a Claisen rearrangement to conduct a ring-expansion *en route* to the eight-membered ring.[74] To this end, they elaborated the enantiopure Eder-Sauer-Wiechert-Hajos-Parrish analog **83** to lactone **84**, the carbonyl functionality of which was methylenated by treatment with Tebbe's reagent. The resulting allyl vinyl ether rearranged at elevated temperatures and a following epimerization furnished the essential *trans*-ring junction in ketone **85**.

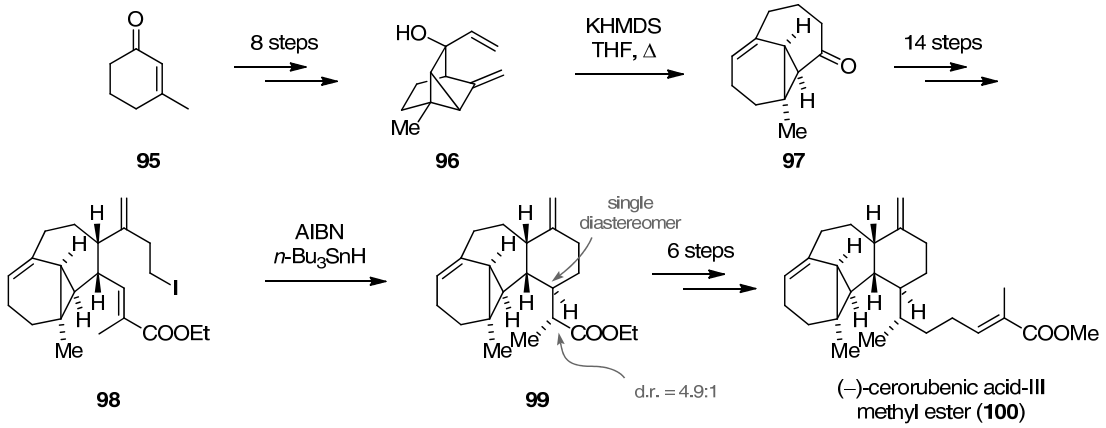
Ultimately, further transformations including a 1,3-carbonyl transposition and a Michael addition/annulation protocol afforded the optically active natural product (+)-ceroplastol I (**86**).

Another methodology to construct the [5-8-5]-tricarbocyclic architecture of the ceroplastins was presented by Kato and co-workers, which culminated in total syntheses of (+)-ceroplastol II (**90**) and (+)-albolic acid (**91**).[75] In the course of their synthetic studies, Kato *et al.* synthesized enantiopure enal **87** *via* an optical resolution. It should be noted that the authors employed the other enantiomer in the preparation of intermediate **88**, thus making the resolution process not wasteful. In the ensuing key step, bisaldehyde **88** was exposed to a lower valent Ti species (prepared *in situ* from $TiCl_4$ and Zn) resulting in a pinacol coupling and closing the eight-membered ring. With the carbon backbone in hand, the remaining protocol produced both sesterterpenoids *via* a diversification in the last step: saponification of an ethyl ester with NaOH gave rise to (+)-albolic acid (**91**), whereas reduction with $LiAlH_4$ furnished (+)-ceroplastol II (**90**).



Scheme 1.14 Molecular structures of the scalarane sesterterpenoids (–)-sesterstatin 4 (**92**) and (+)-scalarolide (**94**), both being semi-synthetically prepared starting from (–)-sclareol (**93**) in the 2010's.

The last subclass concerning the synthesis of sesterterpenoids being discussed in this section are the tetracarbocyclic members. Whereas such compounds in general are rare, one big family are the scalaranes (*vide supra*). Showing interesting biological properties, several of these members including (–)-sesterstatin 4 (**92**)[76] and (+)-scalarolide (**94**)[77] have been synthesized over the last years, often *via* a semi-synthetic route starting from the inexpensive chiral building bock (–)-sclareol (**93**, Scheme 1.14).[78,79]



Scheme 1.15 Paquette's asymmetric route to (–)-cerorubenic acid-III methyl ester (**100**) featuring an anionic oxy-Cope rearrangement and a free-radical cyclization to construct the tetracarbocyclic core.

In contrast to the scalaranes, cerorubenic acid-III methyl ester (**100**),[80] another tetracarbocyclic sesterterpenoid addressed by the group of Paquette, consists of an unique [8.4.1.0.0]pentadecane skeleton. After extensive efforts spanning over one decade,[81] the group finally disclosed the successful preparation of this daunting structure in 1998.[82] In these studies, they took advantage of two key steps: an anionic oxy-Cope rearrangement and a diastereoselective free-radical cyclization. Starting from enone **95**, Paquette and co-workers prepared allylic alcohol **96** in several steps, three being an optical resolution and thus rendering their approach enantioselective (Scheme 1.15). In the following, the aforementioned anionic oxy-Cope rearrangement took place when heating diene **96** with KHMDS in THF to reflux. The resulting ketone **97** already contained the bridgehead double bond and the cyclopropyl moiety found within the natural product **100**. Notably, these moieties stayed intact throughout the whole synthesis, which eventually provided homo allylic iodide **98**. This precursor for the second key step was then subjected to reductive radical conditions (Bu_3SnH, AIBN), resulting in a 6-*exo*-trig-cyclization to give tetracycle **99** with a good diastereoselectivity (d.r. = 4.9:1) at the side chain's stereogenic center. With all stereogenic centers correctly set and the carbon backbone installed, simple chain elongation finally provided (–)-cerorubenic acid III methyl ester (**100**), constituting its first and sole preparation.[82]

The total syntheses discussed in this chapter showcase how sesterterpenoid natural products have inspired organic chemists. Based on structurally unique architectures, a broad array of chemical tools, ranging from classical rearrangements to modern transition metal catalysis, has been employed to access the target molecules and provide the foundation for biological evaluation and derivatization.[40] Whereas this chapter detailed the properties of sesterterpenoids in general and gave a brief overview on synthetic progress toward this group of natural products, the next chapter will focus on a specific subclass, possessing a *trans*-hydrindane *iso*-propyl moiety.

1.3 *trans*-Hydrindane *iso*-Propyl Sesterterpenoids: Introduction to the Subclass and Previous Synthetic Efforts

Within the class of sesterterpenoids,[30] a limited number of compounds has been isolated that comprise a *trans*-hydrindane moiety with an angular methyl group. Moreover, these natural products feature an *iso*-propyl or an isopropenyl group at C-3 (IUPAC numbering), a substituent which either resides in a *trans*-relationship to the angular methyl group or in a *cis*-fashion (Figure 1.4). Additionally, differences have been found concerning the skeletal order, namely the connectivity to further carbon atoms on the six-membered ring. Whilst the *trans*-hydrindane portion in type B is fused at the C-4 and C-5 (IUPAC numbering) position often generating a third carbocycle, the carbon backbone of type A is connected to further carbon atoms at C-5 and C-6.

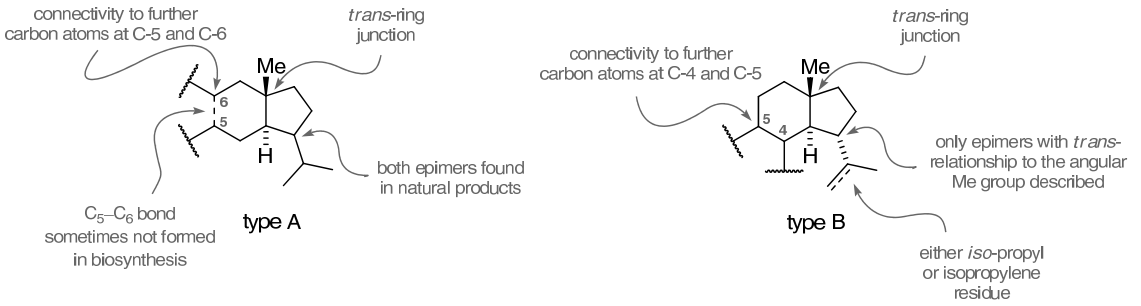


Figure 1.4 Classification of the carbon skeleton of *trans*-hydrindane *iso*-propyl sesterterpenoids into type A and type B, depending on their connectivity at the six-membered ring.

In the following text, the 15 known members of this subclass will be introduced. It should be noted that some members are drawn as their unnatural enantiomers to facilitate comparison with the enantiomeric series in which the synthetic work of these Ph.D. studies was carried out (*cf.* Chapters 2–5). Furthermore, if no sign (dextrorotary or levorotary) of the optical rotation is given, the absolute configuration of the natural product has not been assigned to the best of our knowledge.

The oldest member of the *trans*-hydrindane *iso*-propyl sesterterpenoids is named (–)-retigeranic acid A (**101**), which was isolated for the first time in 1965 and bears a triquinane motif in addition to the *trans*-hydrindane portion (Figure 1.5, depicted as its unnatural isomer).[83] It took seven years until, in 1972, its structure was finally elucidated[84] and in 1974 confirmed by X-ray crystallography as its *p*-bromophenyl amide derivative (Figure 1.5b).[85] During efforts to synthesize this intriguing structure, it was found by HPLC analysis that the crystallized structure refers only to the minor component of the isolated material.

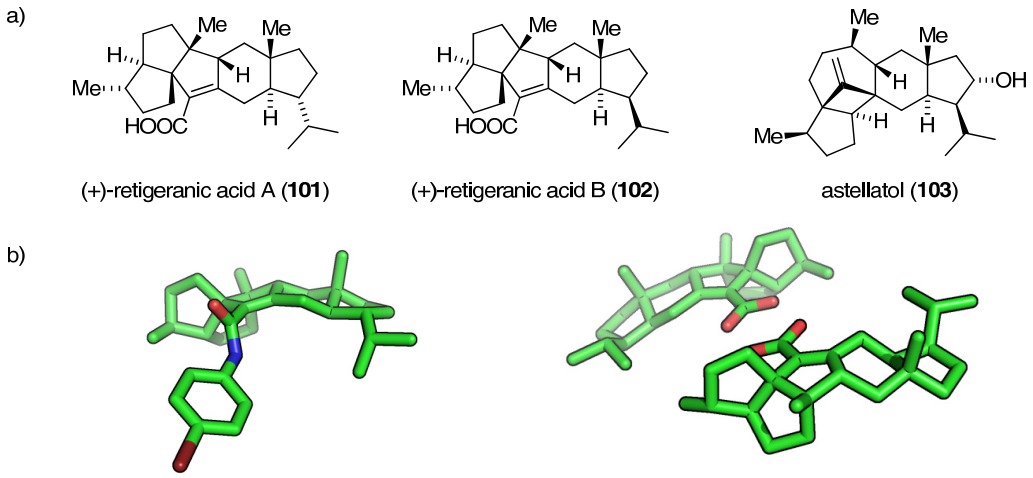


Figure 1.5 (*a*) Molecular structures of the type A *trans*-hydrindane *iso*-propyl sesterterpenoids (+)-retigeranic acid A (**101**), (+)-retigeranic acid B (**102**) and astellatol (**103**). (*b*) X-ray structures of the *p*-bromophenyl amide derivative of retigeranic acid A (**101**) and the dimer of retigeranic acid B (**102**, hydrogen atoms omitted for clarity).

The obtained spectroscopic data suggested the major compound being epimeric to (–)-retigeranic acid A (**101**) and the synthetic endeavors by the groups of Corey,[86] Paquette,[87] Wender[88] and Hudlicky[89] (*vide infra*) excluded some potential diastereomers.[90,91] Subsequent X-ray analysis

unraveled the structure of (–)-retigeranic acid B (**102**) as the α-epimer at the *iso*-propyl residue (Figure 1.5a, depicted as its unnatural enantiomer).[92] In addition, it is noteworthy that retigeranic acid A (**101**) is unique amongst type A *trans*-hydrindane *iso*-propyl sesterterpenoids, as it is the only member featuring a *trans*-relationship between the *iso*-propyl residue and the angular methyl group in the hydrindane portion. Similarly to the retigeranic acids, the unparalleled pentacarbocyclic structure of astellatol (**103**), established by extensive NMR studies in the late 1980's, exhibits only one oxygenated site, namely an alcohol functionality at the five-membered ring of the *trans*-hydrindane portion (Figure 1.5a).[93] As astellatol (**103**) has been one major target within our synthetic efforts, its isolation and structural features as well as the proposed biosynthesis will be detailed in Chapter 3.1.

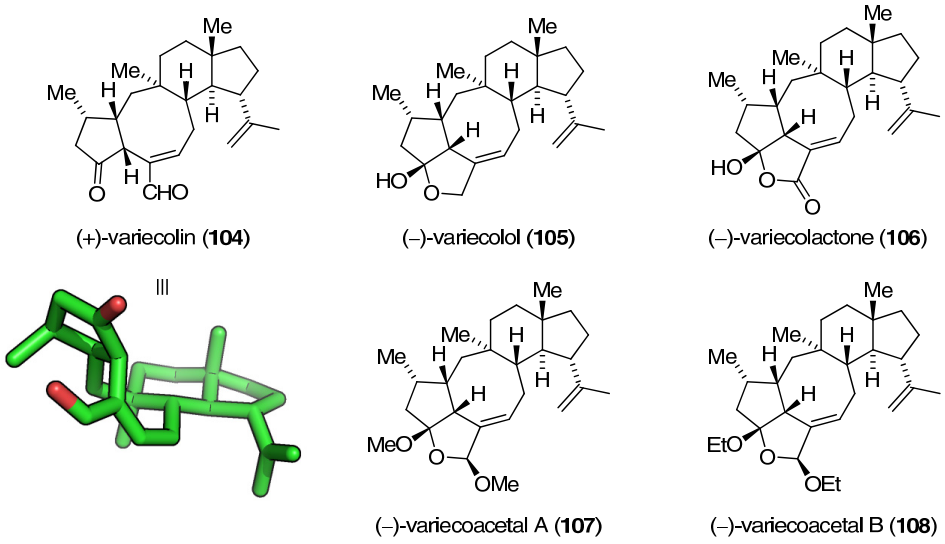


Figure 1.6 Molecular structures of type B *trans*-hydrindane *iso*-propyl sesterterpenoids (+)-variecolin (**104**), (–)-variecolol (**105**), (–)-variecolactone (**106**), (–)-variecoacetal A (**107**) and (–)-variecoacetal B (**108**) and X-ray structure of (+)-variecolin (**104**, hydrogen atoms omitted for clarity).

Contrarily to astellatol's (**103**) type A skeleton, the natural product (–)-variecolin (**104**, depicted as its unnatural enantiomer), isolated in 1991 from *aspergillus variecolor*, is a type B *trans*-hydrindane *iso*-propyl sesterterpenoid and (–)-variecolin (**104**) has been evaluated as an angiotensin II receptor binding inhibitor (Figure 1.6).[94,95] Its isolation has been accompanied by the congeners (–)-variecolol (**105**),[96] (–)-variecolactone (**106**),[96] (–)-variecoacetal A (**107**)[97] and (–)-variecoacetal B (**108**),[97] all possessing immunsuppresive activities and stemming from the same cyclization mode as (–)-variecolin (**104**), but from different oxidations mechanisms in biosynthesis.

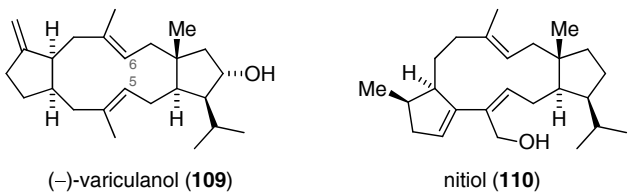


Figure 1.7 Molecular structures of the type A *trans*-hydrindane *iso*-propyl sesterterpenoids variculanol (**109**) and nitiol (**110**), lacking the C_5–C_6 bond formation (IUPAC numbering for hydrindanes) during biosynthesis.

In 1991, the Merck laboratories in Basel isolated a different type of carbon backbone from the same cultures of *apergillus variecolor* and named the compound based after its origin (–)-variculanol (**109**, Figure 1.7).[98] However, this sesterterpenoid differed from the rest of the variecolin family in two aspects. Firstly, its skeleton rather resembles a type A *trans*-hydrindane *iso*-propyl sesterterpenoid, and, secondly, the six-membered ring of the *trans*-hydrindane has not been closed during biogenesis of variculanol (**109**) and thus no *trans*-hydrindane portion is present. Due to the structural similarity however, we still classify variculanol (**109**) as a type A *trans*-hydrindane *iso*-propyl sesterterpenoid. The only other member within this whole subclass lacking such a C–C bond formation is the tricarbocyclic compound nitiol (**110**), which has been isolated by the group of Kawahara in 1999.[99] Further details on this natural product **110** will be provided in Chapter 4.1.

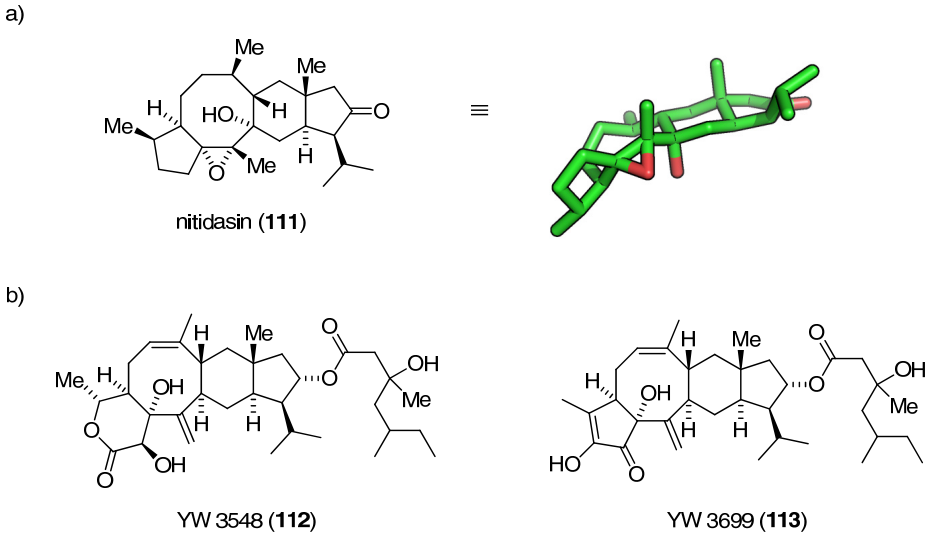


Figure 1.8 (*a*) Molecular and X-ray structure (hydrogen atoms omitted for clarity) of nitidasin (**111**). (*b*) Molecular structures of the GPI anchor inhibitors YW 3548 (**112**) and YW 3699 (**113**).

Already two years before, in 1997, Kawahara and co-workers had identified another *trans*-hydrindane *iso*-propyl sesterterpenoid, nitidasin (**111**), and verified its structure by NMR studies and X-ray crystallography (Figure 1.8a).[100] Although nitidasin (**111**) was isolated from plants used in Peruvian folk medicine ('Hercampuri'), the authors did not evaluate its biological activities. At around the same time, Wang and co-workers reported the intriguing structure of YW 3548 (**112**, Figure 1.8b). In the course of these studies, the authors elucidated the relative configuration of the tetracyclic backbone, while the relative stereochemistry at the heptanoate side chain could not be assigned.[101] Yang *et al.* additionally investigated the biological properties and found that YW 3548 (**112**) is a selective inhibitor of GPI anchoring biosynthesis in mammalian cells. These properties have also been evaluated for YW 3699 (**113**).[102] Further discussion on the biological background combined with a structural analysis can be found in Chapter 5.1.

In the last decade, the structures of two more sesterterpenoids with the *trans*-hydrindane *iso*-propyl motif have been disclosed, one being the tricarbocyclic compound alborosin (**114**), which has been isolated by Kawahara and co-workers from *gentinella alborosin* in 2000 (Figure 1.9).[103] Although the

relative configuration of four stereogenic centers could not be assigned based on 2D NMR studies, it is reasonable to suggest that alborosin (**114**) is a degradation product of nitidasin (**111**) by an oxidative cleavage, and thus the missing stereoinformation might match those of the tetracarbocyclic natural product **111**.

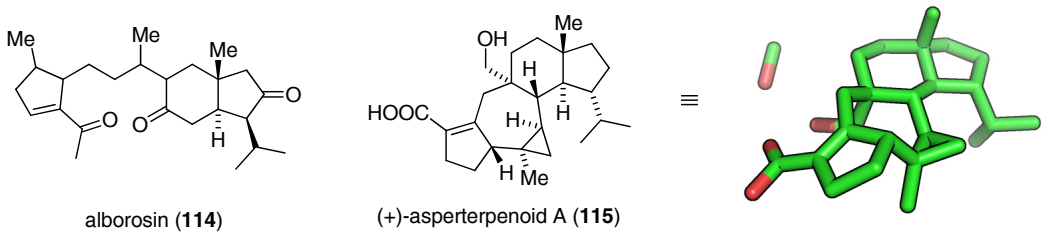
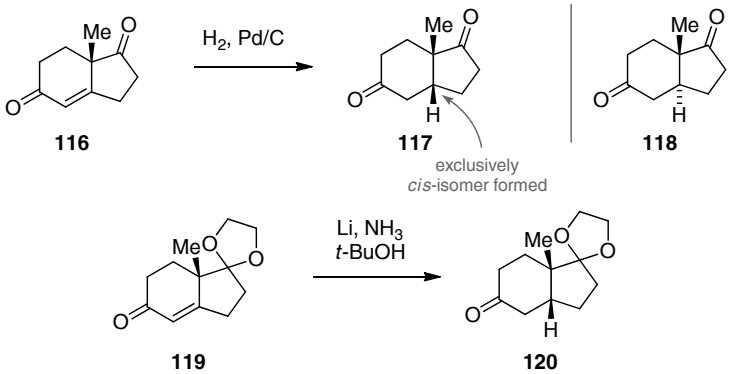


Figure 1.9 Molecular structure of the sesterterpenoids alborosin (**114**) and (+)-asperterpenoid A (**115**) and the X-ray structure of asperterpenoid A (co-crystallized with MeOH, hydrogen atoms omitted for clarity).

Very recently, in February 2013, She *et al.* discovered a new type B skeleton while establishing the pentacarbocyclic structure of asperterpenoid A (**115**) by NMR techniques and X-ray crystallography (Figure 1.9).[104] The backbone of asperterpenoid A (**115**), isolated from *aspergillus* sp. 16-5c, is closely related to the one found in variecolin (**104**), comprising a [7.1.0]cyclooctane moiety instead of a regular cyclooctene ring and a different oxidation pattern. In addition to its daunting structural features, the authors determined a strong inhibitory activity against *mycobacterium tuberculosis* protein tyrosine phosphatase B. This enzyme facilitates host infections and thus inhibitors as asperterpenoid A (**115**) might emerge as potential drugs for the treatment of pulmonary tuberculosis.

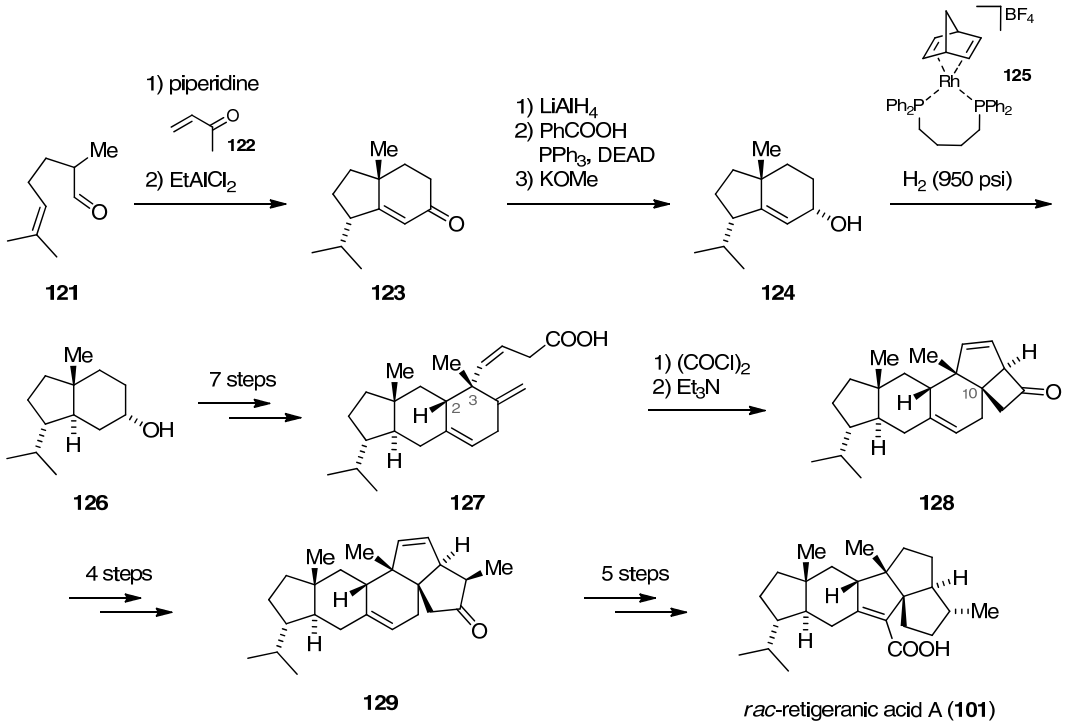
From a chemist's perspective, the above presented natural products represent highly attractive targets for synthetic programs due to their structurally intriguing ring systems and their associated biological properties. Although most isolations date back more than one decade, a literature survey surprisingly revealed that only retigeranic acid A (**101**) has been successfully accessed by total synthesis. In addition, very few approaches toward the variecolin family, nitiol (**110**) and YW 3699 (**113**) have been described over the years.[40]



Scheme 1.16 The challenge in installing a *trans*-hydrindane moiety exemplified on reductions of the diketone **116** and its monoketal derivative **119**.

The small number of endeavors might be explained by three major challenges associated with *trans*-hydrindane *iso*-propyl sesterterpenoids. On the one hand, it is a well-known problem to install a *trans*-ring junction in a hydrindane portion.[105] This is due to thermodynamic reasons, which usually favor the less strained *cis*-ring junction, exemplified by the hydrogenation of the Hajos-Parrish-Eder-Sauer-Wiechert ketone (**116**, Scheme 1.16). Based on simple steric factors, one would assume that the angular methyl group shields the top face of the bicycle and thus directs the hydrogenation to occur from the bottom face to yield *trans*-fused ring system **118**. However, only the *cis*-isomer **117** is formed under standard hydrogenation conditions.[106] Under classical thermodynamic conditions *e.g.* dissolving metal reduction, the same results were obtained when employing ketal protected derivative **119** to form exclusively *cis*-isomer **120**.[106] The second problem, in particular related to the type A *trans*-hydrindane *iso*-propyl sesterterpenoids, is the sterically encumbered situation at the five-membered ring, resulting in disfavored steric interactions between the angular methyl group and the *iso*-propyl substituent. If one solves these two problems, the last remaining hurdle is the appropriate construction of the fully substituted ring systems with several stereogenic centers and challenging oxidation patterns. Some groups have surmounted these challenges and their findings will be presented in the following text ordered by the time of appearance in the literature.[40]

In 1985, the group of Corey at Harvard University succeeded in the first total synthesis of a *trans*-hydrindane *iso*-propyl sesterterpenoid, namely retigeranic acid A (**101**, Scheme 1.17).[86] The approach initiated with the preparation of the *trans*-hydrindane portion starting from racemic melonal (**121**), which underwent a Robinson annulation with MVK (**122**) providing a cyclohexenone (not shown).

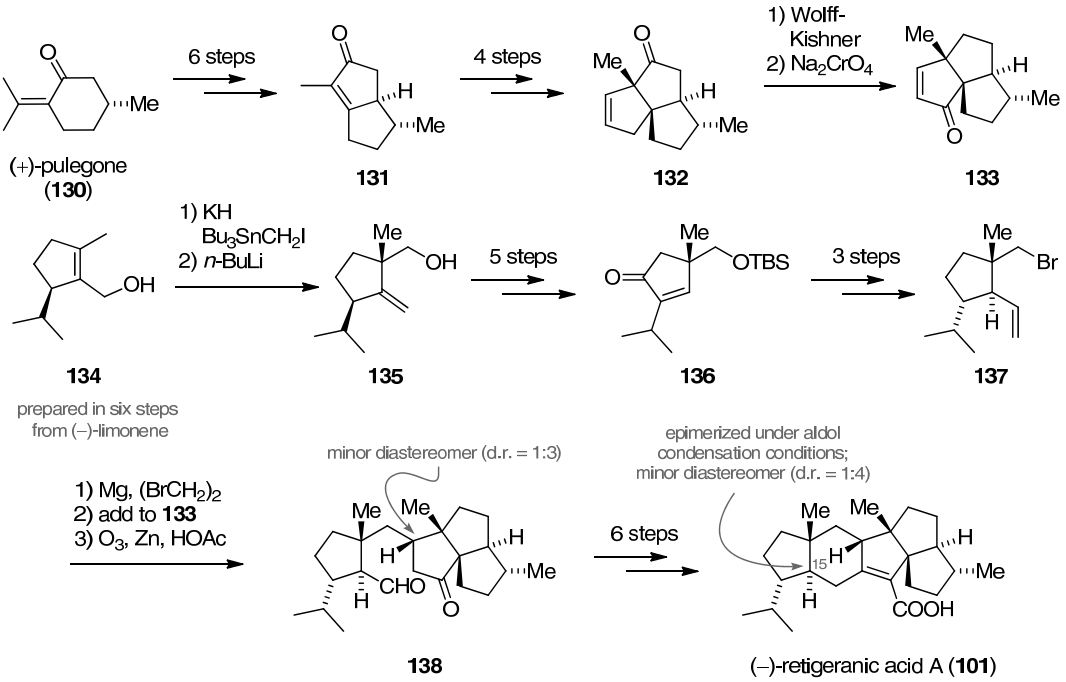


Scheme 1.17 Corey's racemic synthesis of retigeranic acid A (**101**) installing the *trans*-hydrindane *iso*-propyl portion by a Lewis acid-mediated conjugate addition of an electron-rich alkene and a substrate-directed hydrogenation.

Upon exposure to Et_2AlCl, the Lewis acid triggered a Prins-type cyclization followed by two stereospecific 1,2-hydride shifts to generate indenone **123** that comprised the correct *trans*-relationship between the angular methyl group and the *iso*-propyl moiety. The next task to be solved was the installation of the *trans*-ring junction. As pointed out earlier, a direct hydrogenation of the double bond would rather produce the undesired *cis*-isomer (not shown). Thus, Corey and co-workers resorted to a substrate directed hydrogenation employing cationic Rh-catalyst **125**.[86b] In order to execute this transformation, the ketone functionality within enone **123** was stereoselectively reduced and a subsequent Mitsunobu inversion/saponification protocol furnished the requisite alcohol **124**, setting the stage for the envisaged hydrogenation. The desired transformation took place in the presence of catalyst **125** and elevated pressure of H_2 (66 bar) to furnish *trans*-hydrindane **126**. Thereafter, a series of transformations, including a Diels-Alder reaction to diastereoselectively install the C-2 and C-3 stereogenic centers, provided acid **127**. Sequential treatment of intermediate **127** with $(COCl)_2$ and Et_3N generated an alkene-ketene intermediate, which cleanly underwent an intermolecular [2+2]-cycloaddition to install the third quaternary stereogenic center at C-10 in cyclobutanone **128**. A ring expansion of the four-membered ring *via* a thio-pinacol rearrangement then yielded cyclopentanone **129**, the α-methyl group of which was epimerized to the desired relative configuration. After a chemoselective hydrogenation of the less substituted double bond and deoxygenation of the carbonyl moiety, dihydroxylation of the remaining alkene was followed by Criegee-oxidation with $Pb(OAc)_4$, aldol condensation in the presence of Al_2O_3 and Pinnick oxidation to finally furnish retigeranic acid A (**101**).

At around the same time, Paquette and co-workers embarked on an enantioselective synthesis of (−)-retigeranic acid A (**101**) and they published their convergent approach in 1987.[87] The triquinane portion present in retigeranic acid A (**101**) was prepared starting from (+)-pulegone (**130**), which was transformed to diquinane **131** in a multistep sequence, including a Favorskii rearrangement to induce a ring contraction (Scheme 1.18). This was followed by a diastereoselective cuprate addition/aldol reaction protocol, and the thus installed alcohol was dehydrated *via* a Chugaev elimination generating the alkene in triquinane **132**. After further functional group manipulations (Wolff-Kishner reduction, allylic oxidation), the group accessed enone **133**, having a Michael-acceptor for the envisioned fragment union.[87c] For the preparation of the second building block, Paquette *et al.* once more turned to the chiral pool, starting from (−)-limonene (**28**), which was elaborated to allylic alcohol **134** following a known protocol. An ensuing Wittig-Still rearrangement installed a *cis*-relationship between the angular methyl group and the *iso*-propyl substituent in alkene **135**. Since the relative configuration of retigeranic acid B (**102**) was unknown at that time, Paquette unmasked the ketone functionality by ozonolysis and erased the stereoinformation at the *iso*-propyl moiety while installing a double bond that facilitated an allylic oxidation, giving rise to enone **136**. Next, the authors prepared alkyl bromide **137** *via* a diastereoselective Michael addition with vinyl cuprate, Wolff-Kishner

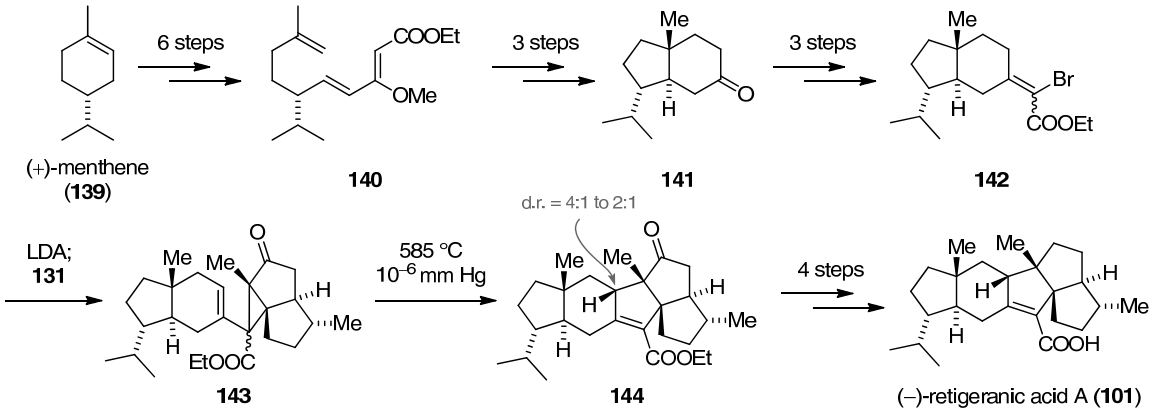
reduction with concomitant silyl ether cleavage and subsequent bromination, only being effective under Mitsunobu-type reaction conditions.



Scheme 1.18 Paquette's enantioselective *ex*-chiral pool synthesis of (–)-retigeranic acid A (**101**) featuring a late-stage aldol-condensation to install the *trans*-hydrindane moiety.

The intermediate **137** incorporated the correct stereochemistry of all stereogenic centers at the five-membered ring of the *trans*-hydrindane moiety and underwent exclusive 1,4-addition to the sterically congested enone **133** upon generation of the corresponding Grignard species. However, a drawback of this convergent approach was the poor selectivity observed in this step, providing the desired product **138** as the minor diastereomer (d.r. = 1:3) after ozonolysis. Unfortunately, the subsequent installation of the *trans*-hydrindane moiety by an intramolecular aldol condensation did not add to the overall efficiency of the synthesis as it required forcing conditions (piperidine, HOAc, 100 °C, not shown) and resulted in an epimerization at C-15, providing the *trans*-ring junction as minor diastereomer (d.r. = 1:4). This result once more emphasized the challenges associated with the preparation of *trans*-hydrindanes. At last, a five-step sequence gave rise to (–)-retigeranic acid A (**101**), constituting its first enantioselective synthesis.

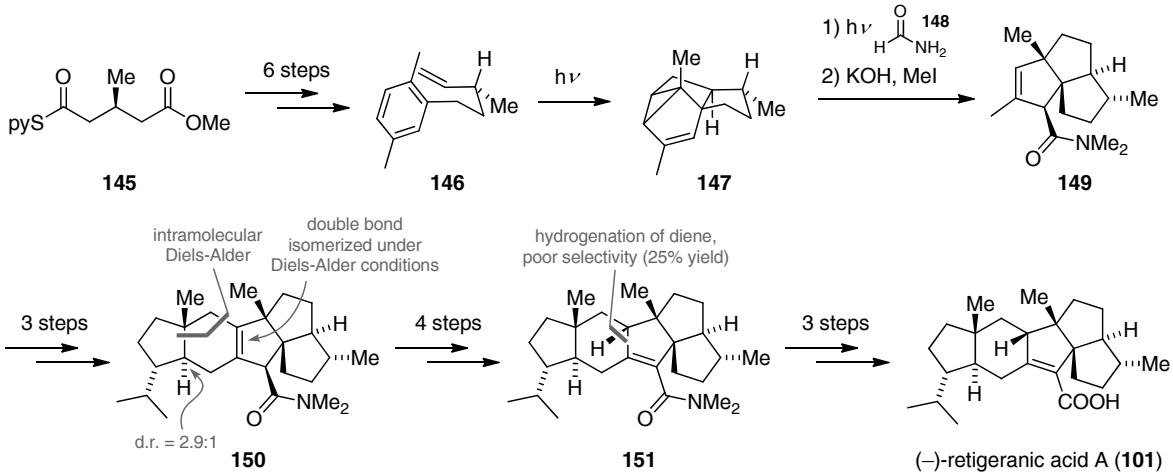
Only one year later, in 1988, the group of Hudlicky published a very elegant convergent and enantioselective route toward (–)-retigeranic acid A (**101**).[88] They converted (+)-menthene (**139**) to triene **140** in several steps, which then underwent an intramolecular inverse electron demand Diels-Alder reaction (Scheme 1.19). After enol ether cleavage and Krapcho decarboxylation, *trans*-hydrindanone **141** was obtained that has already been an intermediate in Corey's synthesis, albeit in racemic form.[86] Thereafter, a straight-forward homologation/dibromination/monodebromination sequence furnished vinyl bromide **142**, the corresponding vinylogous enolate of which underwent a clean fragment coupling with diquinane **131** prepared in analogy to Paquette's approach.[87]



Scheme 1.19 Hudlicky's convergent synthesis of (–)-retigeranic acid A (**101**) installing the *trans*-hydrindane *iso*-propyl moiety *via* an intramolecular Diels-Alder reaction.

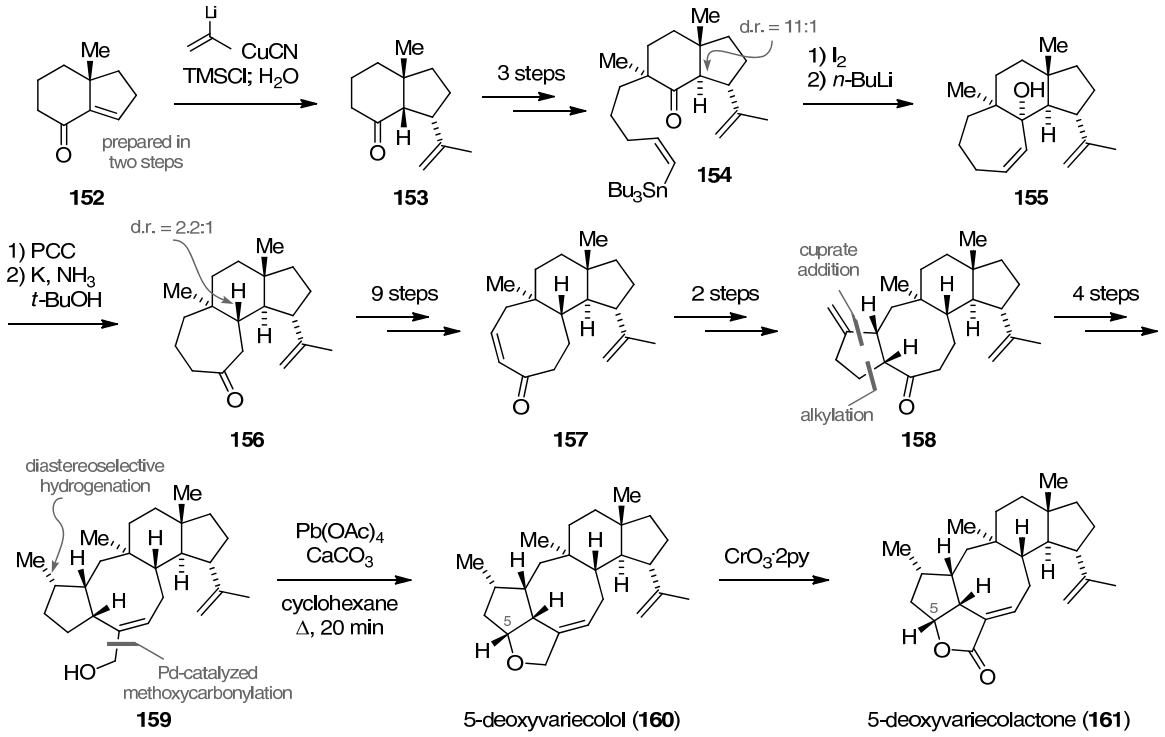
With the resulting intermediate **143** in hand, the stage was set for the key step of their synthesis: a vinylcyclopropane rearrangement. Thus, subjecting intermediate **143** to flash vacuum pyrolysis conditions (FVP, 585 °C, 10^{-6} mm Hg) triggered the desired rearrangement and formed the pentacarbocyclic compound **144** in high yield and moderate diastereoselectivity (4:1 to 2:1 depending on the isomer used). With all stereogenic centers set and the complete carbon skeleton in place, Hudlicky *et al.* readily accessed (–)-retigeranic acid A (**101**) by sequential reduction, Barton-McCombie deoxygenation and saponification in a longest linear sequence of 19 steps.

In 1990, Wender and co-workers at Stanford University described another approach to (–)-retigeranic acid A (**101**),[89] taking advantage of a photochemical arene-alkene meta cycloaddition. For this purpose, six steps were required to convert compound **145** (prepared enantioselectively by enzymatic resolution) to alkene **146** (Scheme 1.20). The envisaged photoreaction proceeded efficiently to furnish the desired tetracycle **147**, albeit as the minor isomer (1:2). However, it should be noted that this transformation rapidly built up structural complexity and the unwanted isomer could be recycled, thus raising the overall yield and providing grams of material.



Scheme 1.20 Wender's enantioselective synthesis of (–)-retigeranic acid A (**101**) *via* a photochemical arene-alkene cycloaddition and a late-stage intramolecular Diels-Alder reaction to generate the *trans*-hydrindane portion.

Exposure of intermediate **147** to an acyl radical prepared photochemically from formamide (**148**) resulted in opening of the cyclopropane moiety and the installation of a triquinane system with appropriate functional groups, leading to alkene **149** after *N*-methylation. A three-step sequence including an allylic oxidation gave rise to a triene (not shown), which underwent a thermal Diels-Alder reaction (250 °C, 22 h). This protocol installed the *trans*-hydrindane portion as the major isomer **150** along with two isomers (8.6:3:1, *cis*-hydrindane, one double bond regioisomer with *cis*-hydrindane formed) in a moderate overall yield of 64%. As direct double-bond isomerization attempts remained unfruitful, Wender's group had to utilize an indirect methodology to install a diene moiety (not shown), which was subsequently hydrogenated under high pressure to yield amide **151**. Unfortunately, this transformation remained unselective despite enormous efforts and provided the desired diastereomer in a poor yield of 25%, thus being detrimental for the overall efficiency of the synthesis. Ultimately, a stepwise adjustment of the oxidation state furnished (−)-retigeranic acid (**101**), constituting its fourth and thus far last preparation. Since then, no reports on progress toward the retigeranic acids have been published. In addition, Wender's synthesis constituted the last successful total synthesis of any member of the *trans*-hydrindane *iso*-propyl sesterterpenoids. However, some synthetic studies toward this subclass of sesterterpenoids appeared in literature and these synthetic strategies will be detailed in the following.

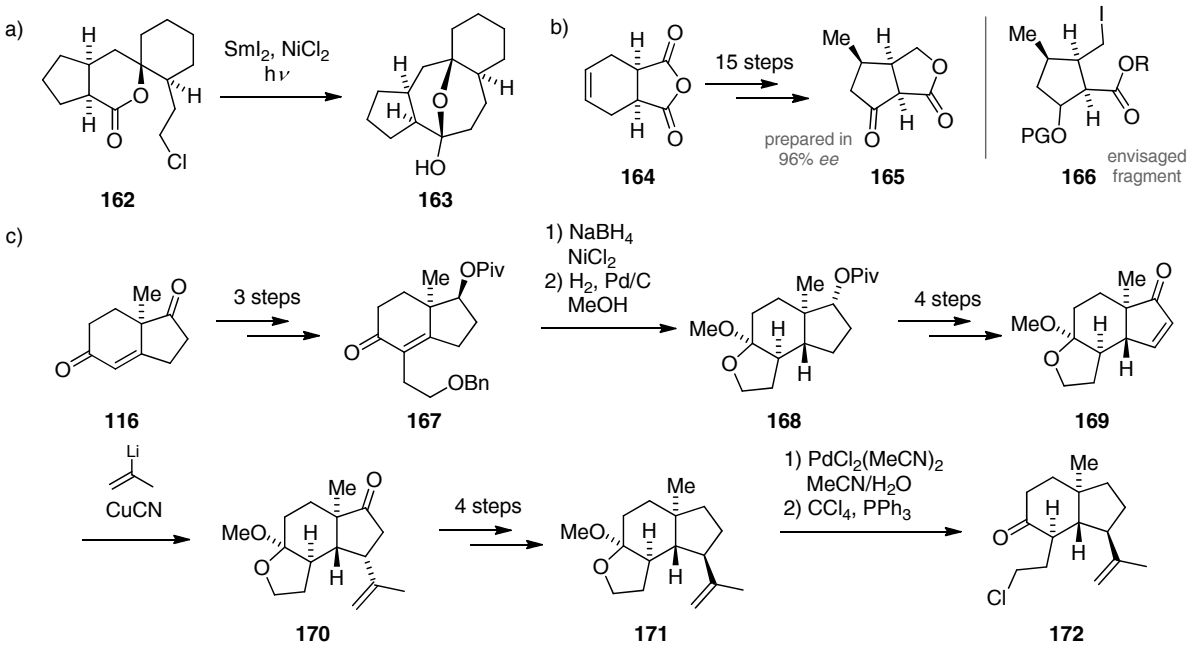


Scheme 1.21 Pier's racemic synthesis of 5-deoxyvariecolol (**160**) and 5-deoxyvariecolactone (**161**) *via* sequential ring annulation protocols, a late-stage C–H activation and an interesting epimerization to install the *trans*-hydrindane portion.

In 1997, Piers and co-workers reported their synthetic efforts toward a racemic synthesis of variecolin (**104**)[107] and more advanced studies were provided by the Ph.D. thesis of S. D. Walker in 2002. This work was also carried in the Piers laboratories and resulted in the preparation of

5-deoxyvariecolol (**160**) and 5-deoxyvariecolactone (**161**, Scheme 1.21).[108] Utilizing a cuprate addition/aldol condensation annulation protocol, they prepared bicycle (**152**) that in turn was exposed to an isopropylene cuprate in the presence of TMSCl, diastereoselectively affording *cis*-hydrindane **153** in high yield. Interestingly, a NaOMe promoted epimerization provided the corresponding *trans*-fused bicycle in good selectivity (d.r. = 11:1, not shown), which was further elaborated to vinyl stannane **154** by a sequential double alkylation, installing a second quaternary stereogenic center. In the following, iododestannylation gave rise to a vinyl iodide that upon exposure to *n*-BuLi underwent a ring closure under Barbier conditions to yield tricycle **155**. A subsequent Dauben oxidation set the stage for a Birch SET reduction, favoring the requisite *trans*-junction within ketone **156** in moderate selectivity (d.r. = 2.2:1). Unfortunately, several steps were required to effect a 1,2-oxygen transposition, an oxidative ring-expansion and an unsaturation to prepare the eight-membered ring within enone **157**, providing the substrate for a final annulation to yield tetracycle **158**. All tasks remaining were to complete the preparation of the variecolin family's common carbon skeleton by a one-carbon homologation and an ensuing adjustment of oxidation states. To this end, ketone **158** was converted to the corresponding enol triflate (not shown), which cleanly allowed for a Pd-catalyzed methoxy-carbonylation. Following reduction and a chemo- and diastereoselective hydrogenation of the exomethylene group in the presence of Pt/Al_2O_3, the group accessed allylic alcohol **159**. The authors utilized this functional handle to effect a $Pb(OAc)_4$ mediated C–H activation, resulting in the formation of 5-deoxyvariecolol (**160**) that was further oxidized to 5-deoxyvariecolactone (**161**). Unluckily, material constraints prevented further investigations on the C-5 oxidation to access the corresponding natural products within Walker's Ph.D. thesis, and no additional progress by the group of Piers has been published since then.

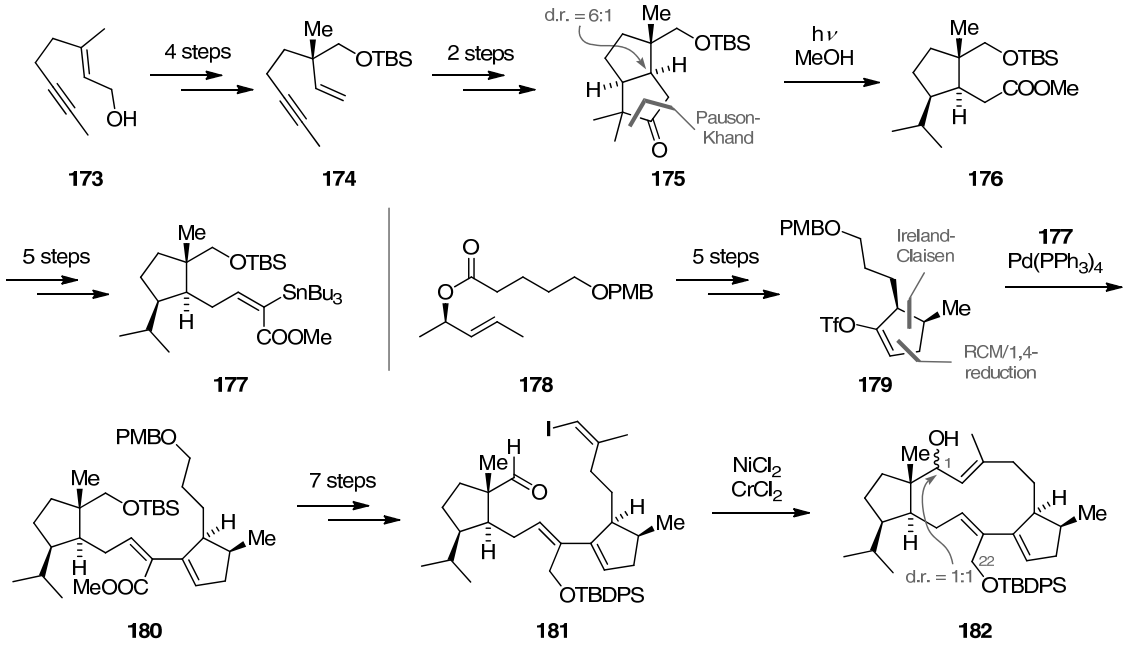
At around the same time, in 2001, the laboratories of Molander disclosed an alternative approach toward the tetracyclic architecture of the variecolin family.[109] Initially, Molander and co-workers developed a route to the central eight-membered ring, hinging on a SmI_2 promoted intramolecular cyclization of a primary chloride to a lactone. The group demonstrated the feasibility of the envisaged key step by subjecting chloride **162** to SmI_2 and $NiCl_2$ under photochemical reaction conditions and isolating tetracycle **163**, hemiacetal moiety of which might be further elaborated (Scheme 1.22). In light of the obtained results, the authors were poised to explore this chemistry on a real system. To this end, they prepared enantiopure lactone **165** in a lengthy sequence, starting from commercially available racemic anhydride **164** and benefiting from an enzyme catalyzed desymmetrization. However, the following conversion to coupling partner **166** has not yet been accomplished. The synthesis of the second coupling partner commenced from enantiopure diketone **116**, which was transformed into enone **167**, being the substrate for the installation of the crucial *trans*-hydrindane pattern. In the event, exposure of bicycle **167** to $NaBH_4$ in the presence of $NiCl_2$ allowed for the preparation of the desired *trans*-ring junction, furnishing tricycle **168** in a modest yield of 52% after hydrogenolysis of the benzyl ether and concomitant ketal formation.



Scheme 1.22 Molander's progress toward an enantioselective synthesis of (+)-variecolin (**104**): (*a*) Demonstration of the envisaged key step in a model system. (*b*) Prepared intermediate **165** *en route* to the alkyl iodide fragment **166**. (*c*) Asymmetric preparation of *trans*-hydrindane **172** installing the *trans*-junction by a $NiCl_2$-mediated reduction.

Thereafter, protecting group- and redox-manipulations delivered the α,β-unsaturated ketone **169**, which in turn was exposed to isopropenyl cuprate. This protocol gave rise to a single diastereomer **170** that exhibits a *cis*-relationship between the angular methyl group and the newly installed substituent. After a Wolff-Kishner reduction, the undesired outcome of this reaction was easily corrected by an ozonolysis/epimerization/Wittig olefination sequence furnishing the thermodynamically more stable β-isomer **171**. Finally, Molander *et al.* completed the synthesis of the second coupling partner **172** by two more steps, namely a Pd-catalyzed cleavage of the acetal and an ensuing Appel reaction to install the alkyl chloride. Although the authors refer to further investigations in their outlook, no reports toward a synthesis of alkyl iodide **166** and results on the fragment coupling have been published to date.

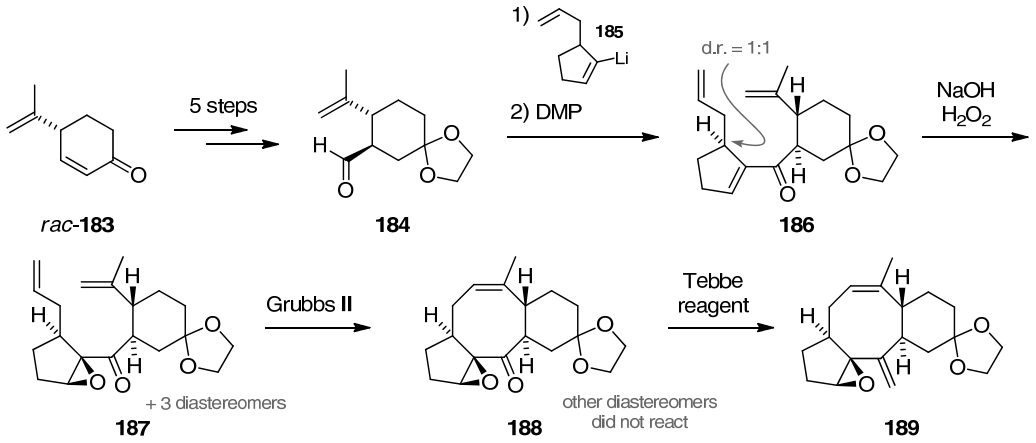
Also in 2001, a first report of Dake *et al.* toward a total synthesis of nitiol (**110**) appeared in literature, followed by a full paper five years later.[110] The authors stated that "it is well established that reactions generating *trans*-hydrindanes bearing pendant methyl and *iso*-propyl groups almost exclusively result in a *trans*-relationship between the methyl and the *iso*-propyl groups". Thus, Dake opted to use the conformational bias of a [3.3.0]cyclooctane system to diastereoselectively install this stereochemical setting. To this end, they enantioselectively prepared enyne **174** starting from geraniol-derived alcohol **173** *via* a Sharpless enantioselective epoxidation, TBS protection, a Lewis acid promoted silyloxy-epoxide rearrangement and standard Wittig olefination (Scheme 1.23). Subsequently, a Pauson-Khand reaction furnished a bicycle as the major diastereomer (d.r. = 6:1, not shown), the enone system of which was in turn reduced with L-Selectride®. The resulting lithium enolate was then intercepted with MeI giving rise to ketone **175**, the precursor for the key Norrish fragmentation.[110a]



Scheme 1.23 Dake's enantioselective approach toward nitiol (**112**) preparing two 1,22-dihydroxynitianes and installing the *cis*-relationship between the methyl and the *iso*-propyl group on the five-membered ring by a Norrish fragmentation.

As envisaged, exposure of ketone **175** to photochemical reaction conditions installed the desired *cis*-relationship between the methyl and the *iso*-propyl group in cyclopentane **176** and the ester functionality was further manipulated to access vinyl stannane **177**. The preparation of a second fragment, enol triflate **179**, commenced with allylic ester **178** that was subsequently transformed to a cyclopentenone by a highly diastereoselective Ireland-Claisen rearrangement and a RCM (not shown). The authors noted that the steps of this sequence needed careful optimization to avoid epimerization of the carbonyl's α-stereocenter, as the *cis*-relationship of the two adjacent substituents is thermodynamically disfavored due to steric reasons. At last, a 1,4-reduction affected by L-Selectride® and trapping of the generated enolate with $PhNTf_2$ provided access to vinyl triflate **179**. Next, both coupling partners **177** and **179** were merged by a Stille cross-coupling furnishing diene **180**. This compound **180** served as a common intermediate for the exploration of several routes in order to close the macrocycle, the only effective one being a NHK reaction. Thereby, Dake *et al.* transformed diene **180** to aldehyde **181** that upon exposure to standard NHK conditions yielded allylic alcohol **182** as a 1:1 mixture of diastereomers at C-1 (nitiol numbering). Unfortunately, all attempts to deoxygenate the obtained products **182** failed and thus no total synthesis of nitiol (**110**) has been accomplished so far.[110b]

Apart from the previously discussed examples, only one more report dealing with an approach to a *trans*-hydrindane *iso*-propyl sesterterpenoids has been published. More precisely, Tori and co-workers pursued a RCM strategy to close the central eight-membered ring of YW 3699 (**113**) in 2009.[111] Along these lines, enone **183** was converted to aldehyde **184** in a six-step sequence, bearing the correct *trans*-substitution of the six-membered ring (Scheme 1.24).



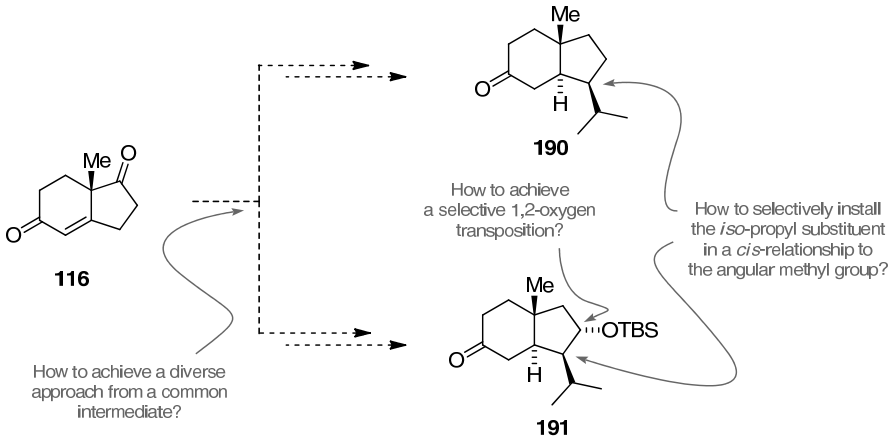
Scheme 1.24 Tori's racemic approach to YW 3699 (**113**) closing the central eight-membered ring *via* a RCM.

The latter compound **184** was then reacted with racemic vinyl lithium species **185** that has been prepared by a Shapiro reaction from the corresponding trisylhydrazone and *t*-BuLi. A subsequent Dess-Martin periodinane (DMP) oxidation furnished both epimers of ketone **186**, which served as a substrate for a nucleophilic epoxidation under Scheffer-Weitz conditions leading to a set of four diastereomers **187** in total (only one shown). Subjecting all obtained isomers independently to RCM reaction conditions (Grubbs II in refluxing CH_2Cl_2), Tori *et al.* found that only the depicted isomer **187** participated in an efficient ring closure in high yield to construct the trisubstituted alkene in ketone **188**. Fortunately, this isomer **188** comprised the desired relative stereochemistry of all methines at the ring junctures and subsequent exposure to the Tebbe reagent cleanly afforded tricycle **189**. However, these model studies have not yet addressed the installation of the *trans*-hydrindane system found within YW 3699 (**113**). As discussed, this portion represents a significant challenge for synthetic chemists due to the *cis*-relationship between the methyl group and the *iso*-propyl residue and the unusual oxidation pattern. Since this publication and despite their inspiring beautiful structures and interesting biological properties, no further reports on the class of *trans*-hydrindane *iso*-propyl sesterterpenoids have appeared in the literature.

1.4 Project Objectives

As discussed in the previous section, little synthetic endeavors on *trans*-hydrindane *iso*-propyl sesterterpenoids have been published over the last decades.[40] This is especially true for those members, the *iso*-propyl substituent of which resides in a *cis*-relationship to the angular methyl group in the *trans*-hydrindane moiety providing a challenging task to synthetic chemists: solely the reports by Dake toward a synthesis of nitiol (**110**) included such an achievement. However, one has to mention that this target **110** did not require the installation of a full *trans*-hydrindane motif due to the missing C_5–C_6 bond formation in biogenesis.[110] Inspired by the beauty and complexity of the structural architectures presented in Chapter 1.3 and attracted by the fascinating biological profile of

the type A *trans*-hydrindane *iso*-propyl sesterterpenoids, this Ph.D. thesis was aimed at exploring a divergent[112] and concise synthetic route to this subclass of terpenoid natural products.

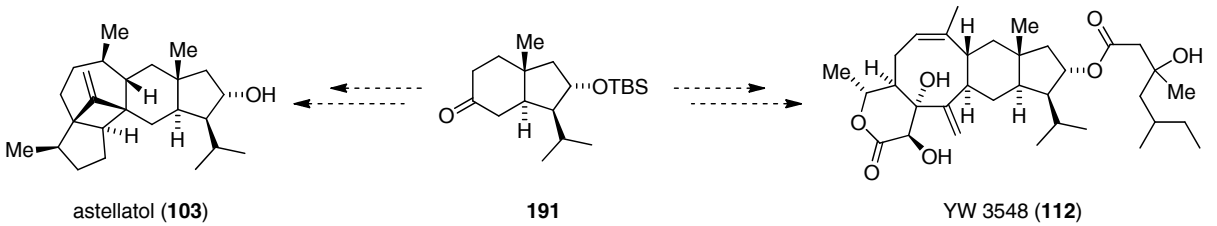


Scheme 1.25 The first major goal of this Ph.D. project: an enantioselective synthesis of two intermediates **190** and **191** *en route* to type A *trans*-hydrindane *iso*-propyl sesterterpenoids.

More precisely, we aimed in the first place for the development of an enantioselective route to two versatile *trans*-hydrindane building blocks **190** and **191**, resembling precursors for synthetic programs directed toward syntheses of type A *trans*-hydrindane *iso*-propyl sesterterpenoids (Scheme 1.25). In spite of the complexity of the target natural products, we further sought to access these building blocks **190** and **191** by a robust route applicable on multigram scale from a common intermediate, hence taking advantage of a diverse approach. Ideally, we opted for a reaction sequence starting from diketone **116**[25] that is readily available in either enantiomeric series on large scale and has been employed previously in total syntheses.[113] As the conversion of diketone **116** into a *trans*-hydrindane system has been explored by a few research groups,[105] one formidable challenge in the preparation of building blocks **190** and **191** relies on a diastereoselective installation of the *iso*-propyl substituent, residing in a *cis*-relationship to the angular methyl group. If such an introduction was accomplished, it would essentially constitute the first entry for a total synthesis of any type A *trans*-hydrindane sesterterpenoid with this relative configuration. A second significant task concerning *trans*-hydrindane **191** is the selective installation of the alcohol functionality at the five-membered ring, formally going along with a 1,2-oxygen transposition.

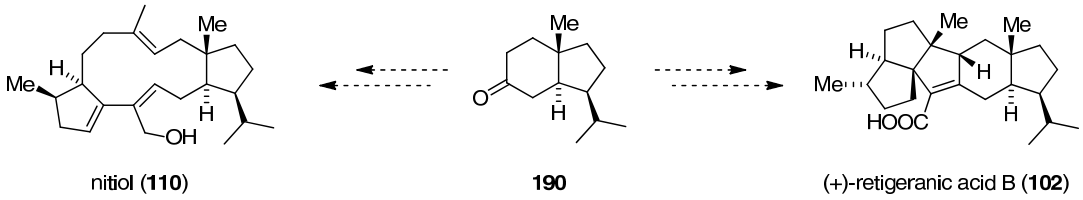
Having successfully established a practical synthesis of the two intermediates **190** and **191**, we would aim in second place at launching a total synthesis program, allowing a collective preparation of several type A *trans*-hydrindane *iso*-propyl sesterterpenoids (Scheme 1.26). On the one hand, we became particularly fascinated by the unique pentacarbocyclic architecture found within astellatol (**103**),[93] comprising four-, five, six- and seven-membered rings and a total of ten stereogenic centers. Thereby, a total synthesis would allow for the elucidation of the absolute configuration and for a verification of the reported structure, which has been only assigned based on extensive NMR studies to date. In addition, the biological properties of this beautiful structure **103** have not been explored yet. Thus, a

viable route would pave the way for investigations concerning the function of astellatol (**103**) in Nature.



Scheme 1.26 Molecular structures of the sesterterpenoids astellatol (**103**) and YW 3548 (**112**), potentially accessible by total synthesis from the bisoxygenated *trans*-hydrindane building block **191**.

On the other hand, we were interested in the GPI anchor inhibitors YW 3548 (**112**) and YW 3699 (**113**) due to their fascinating biological profile (*cf.* Chapter 5.1) and their intriguing structural features.[101,102] Analogously to astellatol (**101**), the absolute configuration as well as the relative stereochemistry at the heptanoate side chain has not been determined and thus their structures remain unconfirmed. In addition, synthetic intermediates could provide a valuable starting point for testing their biological activities and further derivatization of the natural products could initiate SAR studies.



Scheme 1.27 Molecular structures of the sesterterpenoids nitiol (**110**) and (+)-retigeranic acid B (**102**), potentially accessible by total synthesis from the monooxygenated *trans*-hydrindane building block **190**.

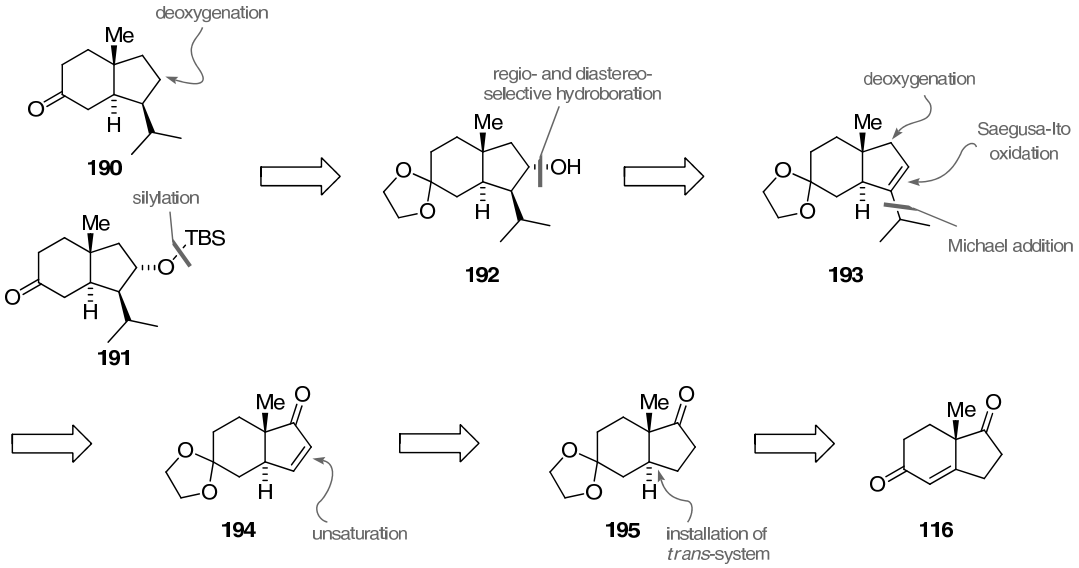
As we were aware of the fact that the installation of the correct oxygenation pattern at the five-membered ring within bicycle **191** might be plagued by selectivity problems, preventing a practical preparation on large scale, we aimed additionally for synthetic studies toward nitiol (**110**, Scheme 1.27).[99] Even more, a successful route toward the monooxygenated bicycle **190** would also allow to revisit the retigeranic acids, particularly in order to develop a first route toward retigeranic acid B (**102**).[92]

From a general synthetic perspective, efforts toward this class of natural products would stand as an excellent framework upon which to develop and apply state-of-the-art synthetic methods and examine their feasibility in a congested steric environment. Moreover, we envisaged implementing a bioinspired key step,[114] *i.e.* a cascade reaction[115] which rapidly builds up structural complexity in order to access the unique architectures presented above. Such a strategy has become a signature of the Trauner laboratories as evidenced by recently published reports,[116] and would allow to gain information on the potential biogenesis of the target molecules.

2 A UNIFIED APPROACH TOWARD *TRANS*-HYDRINDANE *ISO*-PROPYL SESTERTERPENOIDS

2.1 Retrosynthetic Analysis

As described in the previous chapter, the first major aim of this Ph.D. thesis consisted in the establishment of a robust route to two building blocks **190** and **191** which could be employed for the synthesis of type A *trans*-hydrindane *iso*-propyl sesterterpenoids. In our initial retrosynthetic proposal, we envisioned accessing building block **190** from alcohol **192** by a deoxygenation, *e.g.* following the Barton-McCombie protocol,[117] and subsequent liberation of the ketone functionality (Scheme 2.1). Alcohol **192** could also be seen as a retrosynthetic precursor for the bisoxgenated building block **191** by a two-step protection/deprotection sequence. The order of these transformations could easily be inverted in case the envisaged TBS protecting group would not resist the acidic conditions required for an acetal cleavage. Thus, alcohol **192** would represent the branching point toward both building blocks **190** and **191**.



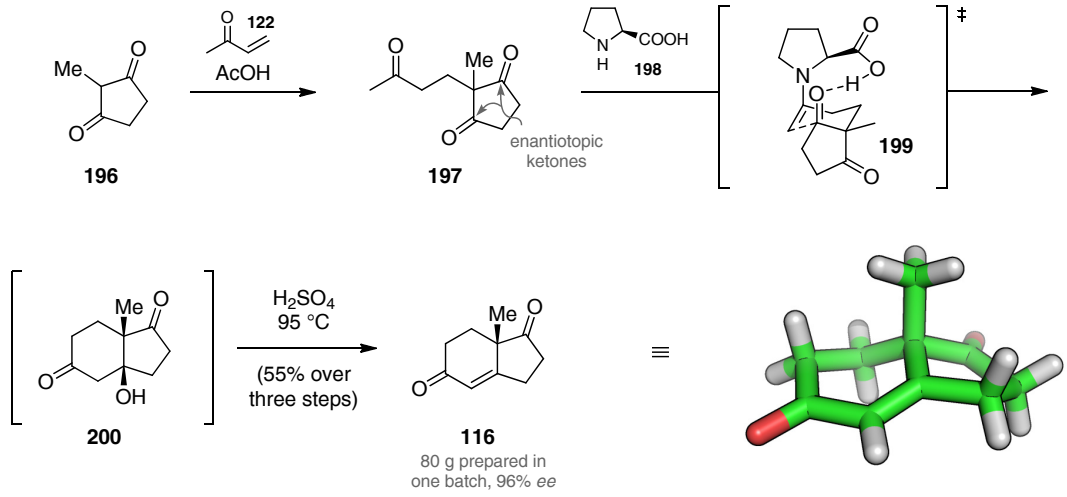
Scheme 2.1 Initial retrosynthetic analysis of the two *trans*-hydrindane *iso*-propyl building blocks **190** and **191**.

The key intermediate **192** could arise from an electronically controlled regioselective hydroboration/oxidation protocol leading to alkene **193** as a logical precursor In addition, we assumed that the angular methyl group in bicycle **193** would prevent the initial hydroboration to occur from the top face, thus efficiently setting two stereogenic centers in one single reaction. The latter compound **193** could be traced back to enone **194** by a Michael addition, Saegusa-Ito oxidation[118] and deoxygenation.[119] In analogy to the discussed hydroboration, the 1,4-addition was thought to proceed preferentially from the bottom face due to the shielding effect of the methyl group, thus providing the undesired stereochemistry and requiring a subsequent reoxidation to invert the stereochemistry (*vide*

infra). A direct trapping of the Cu enolate resulting from the Michael addition, with TMSCl was envisaged, which would directly provide the silyl enol ether necessary for a Saegusa-Ito oxidation.[120] Further retrosynthetic simplification would give ketone **195**, which should be readily available from ESWHP ketone (**116**)[25] according to literature precedence.

2.2 Preparation of the ESWHP-Ketone and Installation of the *trans*-Ring Junction†

With the envisaged retrosynthesis in mind (*cf.* Chapter 2.1), we first set out to prepare ESWHP ketone (**116**) on large scale following the procedure described by Hajos and Parrish.[121] To this end, commercially available diketone **196** was submitted to acidic reaction conditions (catalytic amount of AcOH) in the presence of MVK (**122**) on a 100 g scale, triggering a Michael-addition to yield triketone **197**, which was used in the next step without further purification (Scheme 2.2). Subsequently, an aldol cyclization catalyzed by L-proline (**198**) discriminated the two enantiotopic carbonyl functionalities on the six-membered ring within triketone **197** and provided bicycle **200** in approximately 90% *ee*.[121]



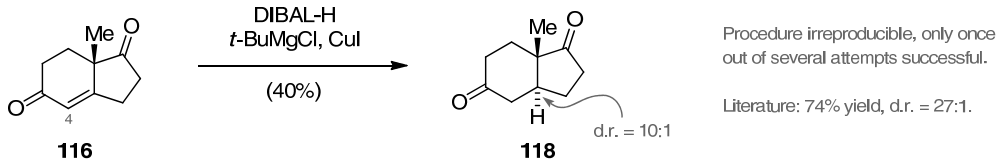
Scheme 2.2 Large scale preparation of diketone **116** utilizing an enantioselective organocatalytic protocol.

As pointed out before (*cf.* Chapter 1.1), this reaction is an early example of enantioselective organocatalysis that involves the formation of an enamine. More precisely, the reaction presumably proceeds *via* the Houk-List transition state **199**[122], in which an intramolecular activation by the carboxylic acid differentiates the two carbonyl functionalities. Having successfully introduced asymmetry, enantioenriched bicycle **200** was then dehydrated in the same reaction vessel by treatment with H_2SO_4 at elevated temperature to furnish the desired diketone **116**. The obtained crude

† Part of the experimental work on large scale was carried out in collaboration with Sebastian Rappenglück, Thomas M. Wildenhof, Martin Rossa and Florian Weinzierl as part of their Bachelor's Theses (S. R., M. R.) and undergraduate research stays (T. M. W., F. W.) in the Trauner laboratories.

product **116** was purified by sequential extraction, flash column chromatography and finally recrystallization to increase the enantiomeric excess. The procedure allowed the preparation of 80 g of the desired diketone **116** in a single batch and provided hydrindenone **116** in 96% *ee* and with an overall yield of 55% over three steps. Moreover, the X-ray crystal structure of diketone **116** was elucidated for the first time.[123] It should be noted that both enantiomers of diketone **116** are readily available following this strategy, depending solely on the chiral information of the catalyst **198** employed. Since the absolute configuration of the major targets astellatol (**103**), nitiol (**110**) and YW 3548 (**112**) has not been established, we used the less expensive L-proline (**198**) for our synthetic studies.

Next, our attention was shifted to the installation of the *trans*-ring junction. As discussed previously (*cf*. Chapter 1.3), such a transformation presents a significant challenge and only a handful of protocols have been explored. This is especially true for enone precursors like diketone **116** lacking a substituent at the 4-position (IUPAC numbering) and bearing an angular substituent.[105] Initially, we envisioned to follow a report by Daniewski and co-workers,[124] who developed a direct installation of the *trans*-junction by exposure of diketone **116** to a bulky CuH species formed *in situ* from a mixture of CuI, *t*-BuMgCl and DIBAL-H. In addition, the use of HMPA as a highly polar solvent to break metal clusters is required to provide *trans*-hydrindane **118** in good yield and high diastereoselectivity (d.r. = 27:1).

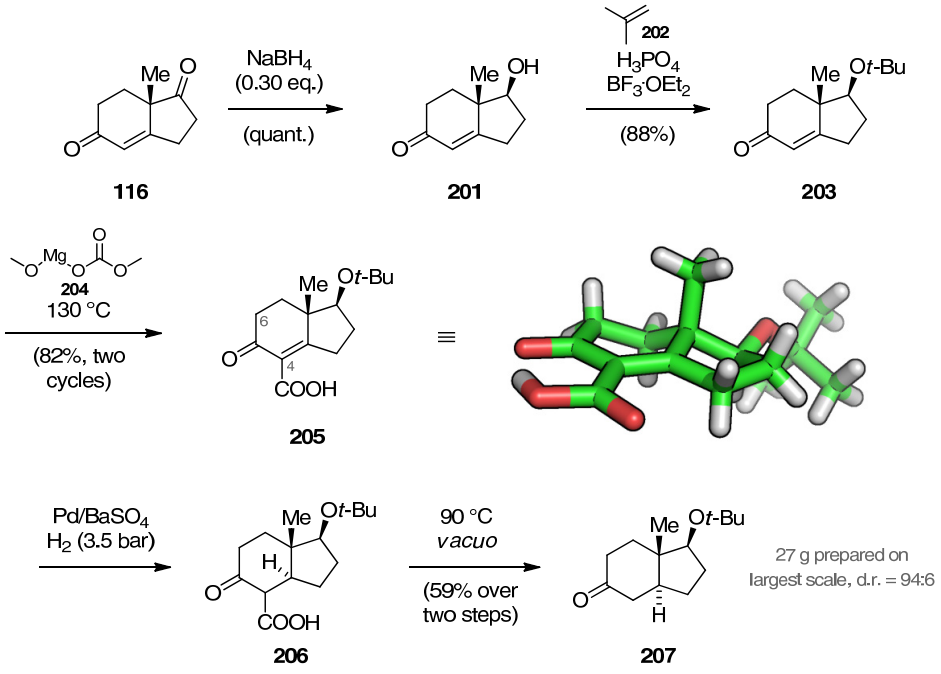


Scheme 2.3 Irreproducible diastereoselective reduction of diketone **116** following Daniewski's protocol.

Although this protocol has been utilized a few times in the literature on scaled up to 1 g,[125] the procedure was barely reproducible in our hands and led to the desired *trans*-hydrindane **118** in 40% yield and 10:1 d.r. despite several attempts (Scheme 2.3). In the other cases, the reaction furnished the *cis*-fused bicycle and alcohol side-products. Facing these selectivity issues and being aware that the opening steps of the envisioned total synthesis had to be applicable on large scale,[126] we focused on a five-step protocol to install the *trans*-ring junction. This procedure was originally reported on multi-gram scale by an industry research group headed by Hajos and Parrish in 1975[127] and has been adapted by the groups of Danishefsky,[128] Nicolaou,[129] Sörensen[130] and recently by Myers[131] during their synthetic programs on the total syntheses of paclitaxel (**5**) and the cortistatin family, respectively.

The protocol commenced with a chemoselective reduction of the less electron-rich carbonyl in diketone **116** *via* the slow addition of $NaBH_4$ (0.30 eq.) to a solution of diketone **116** in EtOH at −18 °C (Scheme 2.4).[132] Noteworthy, the steric shielding of the angular methyl group induced a substrate controlled diastereoselectivity providing exclusively bicycle **201** in quantitative yield. The alcohol functionality in enone **201** was then protected as its *t*-Bu ether by exposure to

isobutylene (**202**) in the presence of H_3PO_4 and $BF_3 \cdot OEt_2$ to obtain indenone **203**. In their seminal work,[133] Hajos and Parrish observed that the choice of a sterically demanding protecting group such as *t*-Bu is crucial to increase the *trans*-selectivity in the hydrogenation step (*vide supra*). Even more important is the installation of a substituent at the 4-position for the successful construction of the *trans*-ring junction, although the reasons for that observation are not completely understood. As no substituent at this position is required in our synthesis, the introduced residue has to be easily removable after the desired hydrogenation. Again, it was the industry research group headed by Hajos and Parrish, who found a solution for this problem.[126,133] More precisely, they developed an efficient protocol for the installation of an acid functionality. In these studies, they observed that the use of methoxymagnesium methyl carboxylate (MMC, **204**), essentially a magnesium methoxide with a built-in source of CO_2, resulted in a superior regioselectivity (C-4 vs. C-6) compared to other reagent combinations (*e.g.* NaH/CO_2).[126] The authors attributed this finding to "the enhanced stability of the resultant magnesium chelates produced (relative to the analogous sodium chelates[…])", which reduces the reversibility of the carboxylation process.



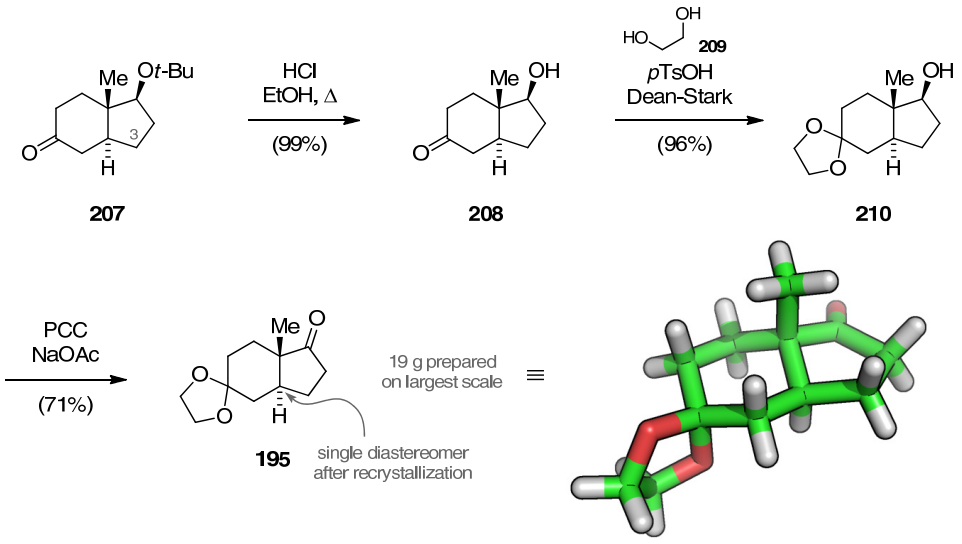
Scheme 2.4 Large scale installation of the *trans*-hydrindane pattern in ketone **207** following a known five-step protocol and X-ray structure of acid **205**.

In practice, exposure of indenone **203** to MMC (**204**) in DMF at 130 °C provided the desired acid **205** in 66% yield along with its C-6 regioisomer (not shown), which spontaneously decarboxylated during acidic work up (Scheme 2.4). After separation, the thus reisolated starting material **203** was again subjected to the carboxylation conditions furnishing acid **205** in an overall yield of 82% after a second cycle on a 57 g scale. In addition, the structure of acid **205** was determined by X-ray crystallography.[123] It exhibits an intramolecular hydrogen bonding of the acidic proton with the adjacent carbonyl functionality. More interestingly, no situation is visible, which might explain the higher selectivity for the installation of the *trans*-ring junction compared to diketone **116** based on a

preferred reaction face. With large amounts of acid **205** prepared, the crucial hydrogenation was carried out in the presence of catalytic amounts of $Pd/BaSO_4$ under elevated pressure of H_2 (3.5 bar),[134] affording *β*-keto acid **206**. This intermediate **206** was immediately subjected to a heat- and *vacuo*-mediated decarboxylation[126] to furnish *trans*-hydrindane **207** in 59% yield over the two steps. On the largest scale, 27 g of building block **207** were prepared that was contaminated with approximately 6% of its *cis*-isomer. In addition to the investigations presented in this chapter, ketone **207** served as starting point for model studies toward a total synthesis of astellatol (**103**, *cf.* Chapter 3). Having successfully completed the installation of the *trans*-hydrindane backbone, the focus was now turned to the incorporation of the *iso*-propyl moiety.

2.3 Diastereoselective Installation of the *iso*-Propyl Moiety

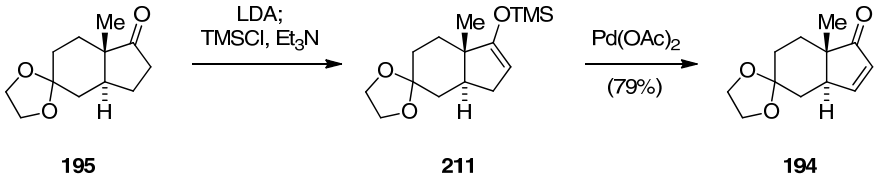
Considering the retrosynthetic analysis, we opted to install the *iso*-propyl moiety at C-3 (IUPAC numbering) of the *trans*-hydrindane portion *via* a cuprate 1,4-addition. For this purpose, we had to adjust the oxidation states and manipulate protecting groups, commencing with the cleavage of the *t*-Bu ether by exposure of *trans*-hydrindane **207** to 6N aqueous HCl in refluxing EtOH (Scheme 2.5).[135] Notably, these harsh reaction conditions cleanly led to the formation of alcohol **208** in almost quantitative yield and did not provoke any rearrangement by the formation of carbocationic intermediates.



Scheme 2.5 Synthesis of *trans*-hydrindanone **195** *via* redox and protecting-group manipulations and verification of the *trans*-hydrindane pattern by X-ray crystal analysis of ketone **195**.

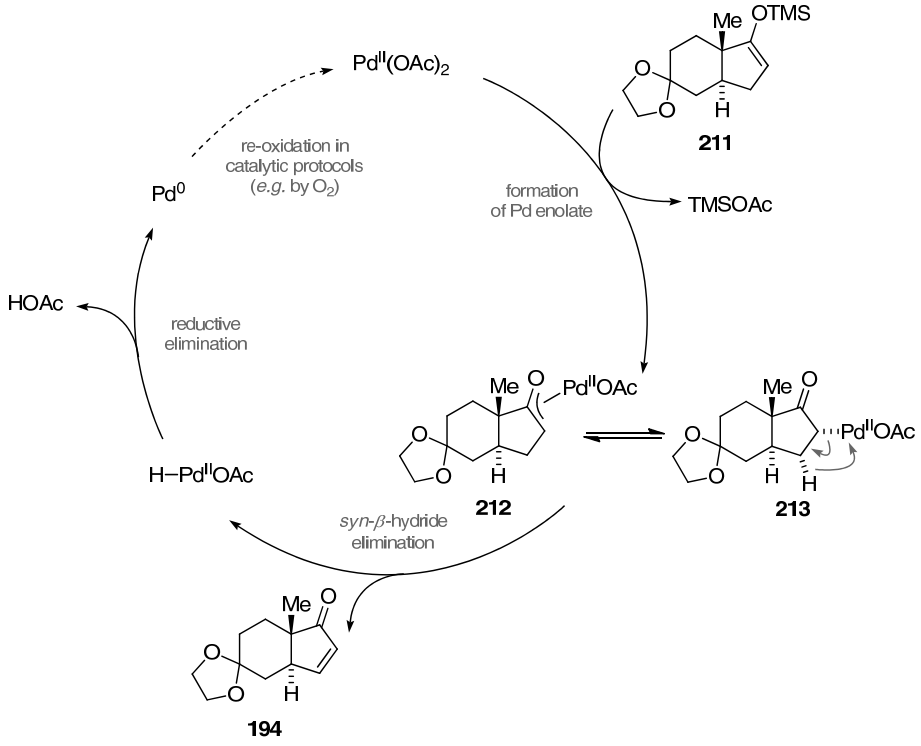
Subsequently, the free carbonyl within ketone **208** was protected as its 1,3-dioxalane by treatment with ethylene glycol (**209**) in the presence of catalytic amounts of *p*TsOH and utilizing a Dean-Stark apparatus. The obtained alcohol **210** was next oxidized to the corresponding ketone **195** using PCC under buffered reaction conditions. It turned out that the latter compound **195** was highly crystalline

and a final recrystallization from hexanes not only allowed for the removal of any traces of the undesired *cis*-isomer (*vide supra*), but also for a verification of the desired *trans*-hydrindane pattern by X-ray crystallography.[123] Overall, this reaction sequence was six steps longer compared to the direct reduction following Daniewski's protocol (*cf.* Chapter 2.2) and an ensuing regioselective protection.[136] However, the developed route is very robust, scalable and provided on the largest batch 19 g of ketone **195** in an overall yield of 29% for eight steps starting from diketone **116**.



Scheme 2.6 Preparation of enone **194** *via* Saegusa-Ito oxidation on 1 g scale.

With a significant amounts of bicycle **195** prepared, the attention was now turned to the installation of a α,β-unsaturated ketone in order to prepare a substrate for the envisaged Michael addition. A literature survey revealed that a Saegusa-Ito oxidation[118] is the method of choice for such transformations in *trans*-hydrindane systems. We thus decided to investigate this reaction first. Hence, ketone **195** was converted to the corresponding TMS silyl enol ether **211** by sequential exposure to LDA and TMSCl/Et_3N. This intermediate **211** was carefully isolated by aqueous work up and used without chromatographic purification for the next step. Thereby, treatment with 1.1 equivalents of $Pd(OAc)_2$ at 40 °C resulted in the formation of metallic palladium, indicating the successful oxidation of ketone **195**. Indeed, after careful flash column chromatography, the desired product **194** was obtained in 79% yield along with recovered starting material **195** on a 1 g scale (Scheme 2.6).

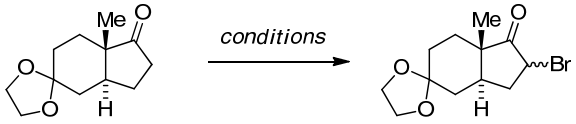


Scheme 2.7 Mechanism of the (catalytic) Saegusa-Ito oxidation.

Mechanistically,[137] treatment of intermediate **211** with stoichiometric amounts of $Pd(OAc)_2$ results in the cleavage of the Si–O bond and the formation of a Pd^{II} enolate, which can be either described as its η^3-complex **212** or as η^1-complex **213** (Scheme 2.7). The latter intermediate **213** then undergoes a β-hydride elimination to liberate the desired product **194** and an H–Pd^{II} species that collapses immediately to form Pd^0, usually observed as a palladium mirror on the flask. Over the years, several methods have been developed in order to reoxidize Pd^0 to Pd^{II} utilizing terminal oxidants as *e.g.* O_2, benzoquinone or allyl methyl carbonate and thus rendering the process catalytic in Pd^{II}.[138] However, one has to state that these protocols still show room for improvement, as in most cases a stoichiometric use of $Pd(OAc)_2$ is favored due to superior yields.[139] Since 'classical' Saegusa-Ito oxidation show high costs on large scale, we explored other procedures including catalytic protocols of the Saegusa-Ito oxidation to install the requisite enone **194** prior to up-scale.

These investigations‡ commenced with attempts to effect an α-bromination on ketone **195** giving rise to compound **214**. This intermediate **214** could be later elaborated to the enone system in tricycle **194** by exposure to basic conditions,[140] constituting a cheap alternative on large scale. In order to avoid cleavage of the dioxolane moiety by strongly acidic reaction conditions utilizing Br_2, we employed $PhMe_3NBr_3$ (PTAB) as a substitute.

Table 2.1 Studies toward the synthesis of α-bromo ketone **214**: variation of reaction conditions.[a]



195 **214**

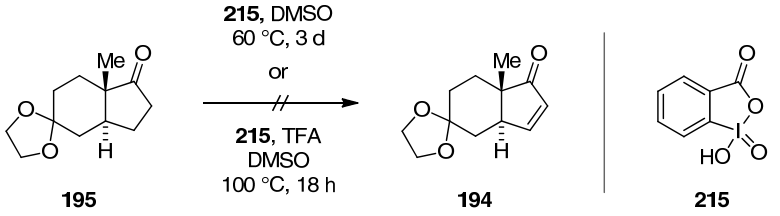
Entry	Source of Br^+	Promoter	Solvent	T [°C]	*t* [h]	Observation
1	$PhNMe_3Br_3$	HOAc	THF	0 to rt	4	decomposition
2	NBS	NH_4OAc	Et_2O	rt	10	s.m.
3	NBS	Amberlyst-15	EtOAc	rt	4	monobromination/ acetal cleavage
4	NBS	KMMDS	THF	–78 to rt	20	little conversion/ mainly s.m.

(*a*) All reactions were carried out on 200 μmol scale of ketone **195**. rt = room temperature, s.m. = starting material.

However, reaction of ketone **195** with this source of Br^+ in the presence of catalytic amounts HOAc[141] resulted in decomposition (Table 2.1, Entry 1). We next examined NBS as a potential other mild source of Br^+. While subjecting ketone **195** to acidic conditions with NH_4OAc as reported by Tanemura and co-workers[142] did not lead to conversion (TLC analysis, Entry 2), the use of Amberlyst-15[143] resulted in full conversion and the isolation of a new compound (Entry 3). Subsequent ^1H NMR analysis showed a successful monobromination as indicated by the specific

‡ These investigations were carried out in collaboration with Florian Weinzierl as part of his undergraduate research stay in the Trauner laboratories.

signals around 4.7 ppm (two diastereomers). However, these reaction conditions also caused the cleavage of the dioxolane moiety in ketone **195**. Therefore, the nature of the isolated diastereomeric mixture as well as the bromination site-selectivity was not further investigated and anionic conditions were tested. To this end, ketone **195** was converted to the corresponding potassium enolate by treatment with KHMDS at low temperature and then reacted with NBS while allowing the reaction mixture to warm to room temperature (Entry 4). Although this procedure has been described in literature on a related system by Rawal and co-workers,[144] no conversion was observed.

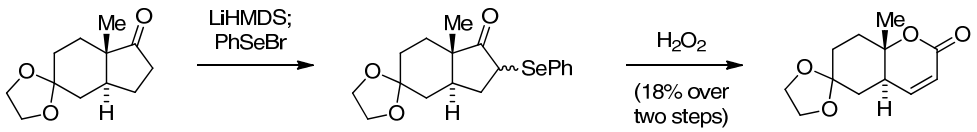


195 **194** **215**

Scheme 2.8 Unsuccessful attempts to synthesize enone **194** by the Nicolaou-Baran method utilizing IBX (**215**).

Since attempts toward selective α-bromination proved unsuccessful, the attention was next turned to the Nicolaou-Baran method for unsaturation of ketones.[145] Thus, ketone **195** was treated with IBX (**215**) in DMSO, a highly polar solvent which is necessary due to the poor solubility of oxidant **215** in most common organic solvents. Unfortunately, neither reaction at 60 °C for three days nor with catalytic amounts of TFA[146] at 100 °C for 18 h resulted in any conversion (Scheme 2.8). It should be noted that in further efforts the IBX·MPO complex could be explored, which has been reported to show superior reactivity compared to IBX (**215**) in the oxidation of silyl enol ethers to the corresponding enones.[147]

Another frequently used method to oxidize a cyclic ketone to the corresponding enone involves an α-selenylation followed by oxidation to the selenoxide, triggering an intramolecular *syn*-elimination to furnish the alkene moiety. To this end, ketone **195** was initially deprotonated with LiHMDS and the thus generated Li-enolate was reacted with PhSeBr to form ketone **216** as an undetermined mixture of diastereomers (Scheme 2.9).

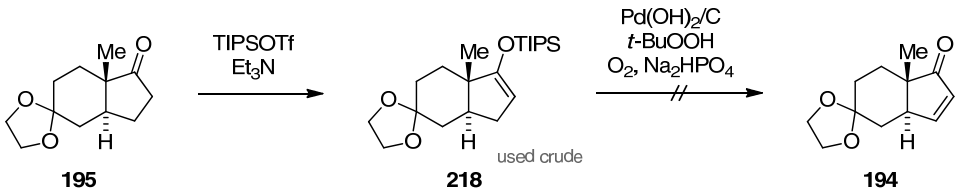


195 **216** **217**

Scheme 2.9 Unexpected Baeyer-Villiger oxidation generating bicyclic lactone **217** during attempts to install a cyclopentenone pattern *via* a selenoxide elimination.

Without further purification, the oxidation/elimination step was next examined. Whereas the use of $NaIO_4$ as oxidant did not result in any conversion, utilizing excess H_2O_2 according to a procedure by Shair and co-workers[148] prompted the formation of a new UV-active product as indicated by TLC analysis. Following purification, examination of NMR spectroscopic and mass spectrometric data of the new compound **217** revealed that the desired unsaturated system was successfully installed in a

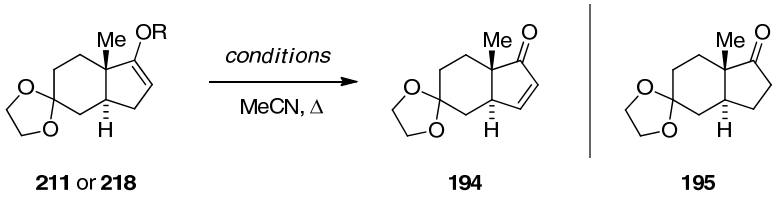
poor yield of 18%. Unfortunately, the reaction conditions concomitantly led to a Baeyer-Villiger oxidation forming bicyclic lactone **217**, presumably due to the release of ring strain.[149] Further attempts to avoid this side reaction employing exactly one equivalent of H_2O_2 resulted in poor conversion and the detection of traces of the desired enone **194** as indicated by TLC analysis.



Scheme 2.10 Toward unsaturation of ketone **195**: exploration of a protocol developed by Corey and co-workers.

The focus was then centered on Pd-mediated enone formations. Thereby, a publication by Corey and co-workers captured our attention. They reported the formation of cyclic enones from the corresponding TIPS enol ethers in the presence of Pearlman's catalyst ($Pd(OH)_2/C$) and Na_2HPO_4 and utilizing excess *t*-BuOOH under O_2 atmosphere as terminal oxidants.[150] Thus, TIPS enol ether **218** was prepared by treatment of ketone **195** with TIPSOTf and Et_3N at 0 °C as indicated by ^{1}H NMR spectroscopy (Scheme 2.10). Subsequently, the crude silyl enol ether **218** was submitted to the reaction conditions developed by Corey. Although the reaction was performed for a prolonged time of four days and with a excess of reagents, no formation of the desired product **194** could be detected.

Table 2.2 Toward a catalytic Saegusa-Ito oxidation: variation of reaction conditions.[a]

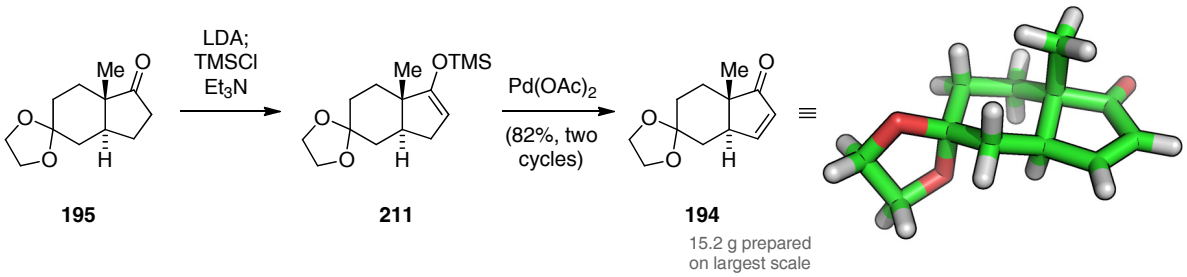


Entry	R	$Pd(OAc)_2$ [mol-%]	Equivalents of allyl methyl carbonate	*t* [h]	Observation
1	TIPS	40	9.45	144	13% **194** isolated
2[b]	TMS	10	1.35	1	**195**:**194** = 2:1
3[b]	TMS	40	1.35	1	**195**:**194** = 3:1

(*a*) All reactions were carried out on 0.2 mmol scale in MeCN (2 mL), preparing the corresponding silyl enol ether immediately prior to use. (*b*) The ratio was determined by ^{1}H NMR spectroscopy after filtering the reaction mixture over silica (eluting with hexanes:EtOAc = 1:1).

Finally, we returned to Saegusa-Ito conditions and investigated catalytic protocols employing commercially available allyl methyl carbonate as a stoichiometric oxidant. As the reactivity and the stability of the employed silyl enol ether plays a crucial role, we first tested the TIPS enol ether **218** due to its previously observed enhanced stability compared to TMS enol ether **211**. However, a prolonged reaction time and a final total amount of 40 mol-% $Pd(OAc)_2$ resulted in a low yield of 13% (Table 2.2, Entry 1). Changing the silyl group for a less sterically demanding TMS enol ether **211**, and using 10 mol-% $Pd(OAc)_2$ resulted in a 2:1 ratio of ketone **195** and **194** as indicated by ^{1}H NMR

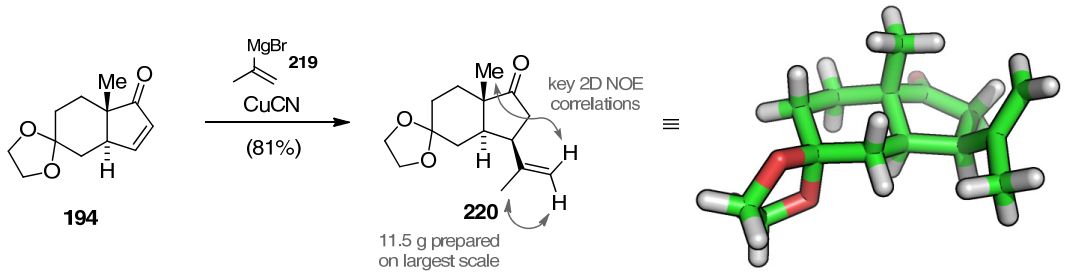
spectroscopy of baseline separated signals for the angular methyl groups (Entry 2). Unexpectedly, this first promising ratio dropped to 3:1 while employing 40 mol-% catalyst loading (Entry 3).



Scheme 2.11 Preparation of enone **194** *via* Saegusa-Ito oxidation on large scale and its X-ray structure.

Due to the unsuccessful results, we abandoned these investigations at this stage in order to further explore the retrosynthetic proposal. In future experiments, however, additional protocols for the synthesis of enone **194** should be examined.[138,147,151] Thus, we finally returned to 'classical' Saegusa-Ito conditions for the preparation of enone **194** on larger scale. While increasing the amount of employed substrate **195** to 6 g, the yield decreased form 79% to 69%. However, resubjection of the isolated starting material to the reaction conditions raised the overall conversion from ketone **195** to Michael acceptor **194**, providing 15.2 g of enone **194** in 82% yield on the largest scale after the combination of different reaction batches (Scheme 2.11). In addition to the previously employed standard analytical methods such as NMR spectroscopy and mass spectrometry, the structure of bicycle **194** was now also resolved by X-ray diffraction of a single crystal.[123]

The next task ahead was the investigation of a cuprate addition in order to install the desired *iso*-propyl substituent. Based on a literature precedent by Molander and co-workers[109] and due to the enhanced reactivity of vinyl cuprates, we decided to explore the Michael addition of an isopropenyl residue first. To this end, a higher order cyano cuprate was prepared by slow addition of 4.5 equivalents of isopropenylmagnesium bromide (**219**) to 2.25 equivalents CuCN at 0 °C. After an additional 30 min, the mixture was cooled to −78 °C and enone **194** was added resulting in the formation of alkene **220** as a single diastereomer in a good yield of 81% (Scheme 2.12).



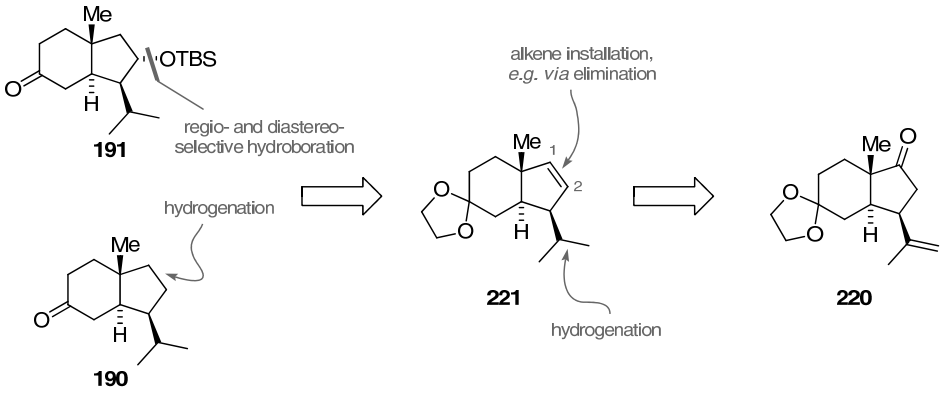
Scheme 2.12 Diastereoselective installation of an isopropylene substituent *via* a cuprate addition.

Surprisingly, 2D NOE NMR spectroscopy indicated that this addition occurred from the top face, *i.e.* *syn* to the angular methyl group, which was assumed to shield this side. This stereochemical outcome

was unexpected based on inspecting molecular models and the X-ray structure of enone **194** and was later on unambiguously confirmed by X-ray crystallography.[123] To our delight, this result matched the *iso*-propyl's relative stereochemistry found in our major synthetic targets astellatol (**103**), nitiol (**110**) and YW 3548 (**112**). As experiments with an *iso*-propyl cuprate gave only unsatisfactory results in our hands (not shown), we scaled up the installation of the isopropylene unit. Due to the experienced sensitivity of this cuprate addition, the reaction was conducted on not more than 1.5 g of ketone **194** in a single reaction vessel. A combined flash column chromatography of several reaction batches provided around 11.5 g of ketone **220** on the largest scale. To the best of our knowledge, only two examples with similar diastereoselective outcome in *trans*-hydrindenones have been reported by the groups of Molander[109] and Bull[152] in their efforts toward (+)-variecolin (**104**, *cf.* Chapter 1.3) and on an estrone derivative (not shown), respectively. Since our results rendered a second unsaturation in order to install the desired stereochemistry of the *iso*-propyl substituent redundant (*cf.* Chapter 2.1), we revisited our retrosynthetic analysis and shifted the attention directly to the syntheses of building blocks **190** and **191**.

2.4 *En Route* to Building Blocks for *trans*-Hydrindane *iso*-Propyl Sesterterpenoids

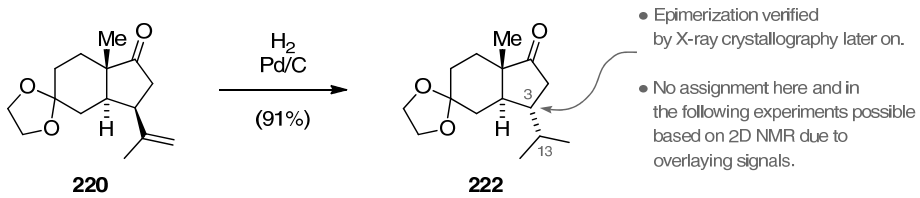
Given the successful and unexpected diastereoselective installation of an isopropylene residue, the retrosynthetic analysis was revised. We now envisioned accessing bisoxgenated building block **191** *via* a three-step sequence featuring a diastereo- and regioselective hydroboration as a key element and thus tracing ketone **191** back to alkene **221** (Scheme 2.13).



Scheme 2.13 Revised retrosynthetic analysis of the *trans*-hydrindane *iso*-propyl building blocks **190** and **191**.

Whereas the diastereoselective outcome of the crucial hydroboration was not considered a problem based on the steric bias induced by both the angular methyl and the *iso*-propyl moiety, the regioselectivity could be problematic since both alkene carbons atoms in compound **221** are monosubstituted. However, the different steric environment at C-1 (being neopentylic) and C-2 (possessing an adjacent trisubstituted carbon atom) could suffice to discriminate the rates of

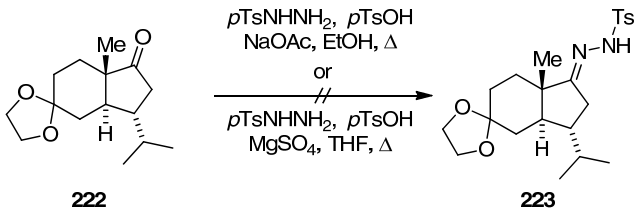
hydroboration in favor of the desired regioisomeric outcome. In addition, a careful choice of the hydroboration agent might enhance the regioselectivity to provide a practical entry into this series of type A *trans*-hydrindane *iso*-propyl sesterterpenoids. On the other hand, monooxygenated building block **190** could as well arise from alkene **221** *via* a hydrogenation/deprotection protocol, thus rendering the latter compound **221** the new branching point. Dioxolane **221** could in turn be prepared from ketone **220** by sequential hydrogenation and alkene installation, *e.g. via* an E2 elimination of the corresponding mesylate or a Shapiro reaction.[153]



220 **222**

Scheme 2.14 Reduction of alkene **220** under standard hydrogenation conditions.

Following this retrosynthesic plan, the first step was readily accomplished by submitting alkene **220** to standard hydrogenation conditions (Pd/C, H_2) furnishing ketone **222** in 91% yield after purification by recrystallization (Scheme 2.14). It should be noted that we verified the unexpected epimerization at C-3 observed in this reaction by X-ray crystallography later on (*cf.* Chapter 2.5). Within the experiments discussed in this section, no assignment of the relative stereochemistry at C-3 was possible based on 2D NOE NMR spectroscopy due to overlaying signals in the ^{1}H NMR spectra. Moreover, we were not aware at this stage of any literature example describing an almost complete epimerization or racemization of an adjacent stereogenic center under hydrogenation conditions. It was thus assumed that the relative stereochemistry in ketone **222** matched the one established in alkene **220** (*vide infra*). It should be emphasized, however, that the transformations tested on this system provided helpful information for the further synthesis with the desired stereochemistry at C-3 (*cf.* Chapter 2.6).



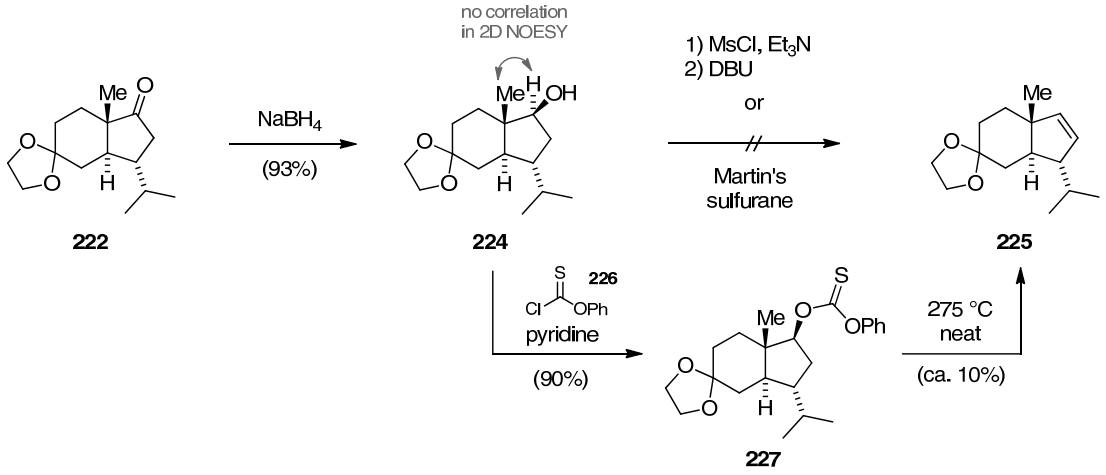
222 **223**

Scheme 2.15 Attempts to convert ketone **222** to tosylhydrazone **223**.

Having prepared substantial amount of ketone **222**, the installation of an alkene moiety following different strategies was next explored. Initially, we aimed for a two-step Shapiro protocol and we thus subjected ketone **222** to hydrazone formation conditions with *p*TsNHNH$_2$.[154] However, neither reaction in refluxing EtOH with a *p*TsOH/NaOAc buffer nor in boiling THF in the presence of *p*TsOH and $MgSO_4$ effected the desired formation of hydrazone **223** (Scheme 2.15). These findings were attributed to the neopentylic nature and steric encumbrance of the carbonyl functionality. In addition,

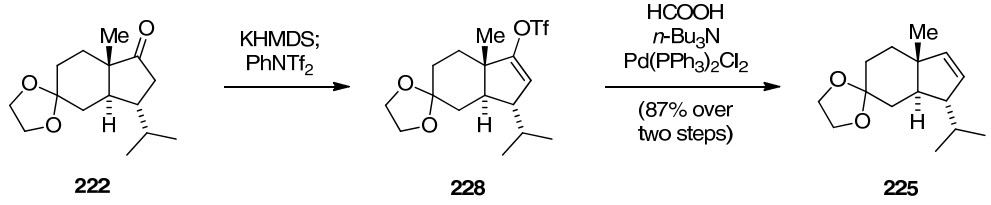
the use of strong aqueous acids such as H_2SO_4 or HCl known to accelerate the desired reaction was avoided due to the acid sensitivity of the dioxolane moiety within ketone **220**.

In an alternative approach, ketone **222** was cleanly reduced to alcohol **224** by treatment with $NaBH_4$ and the relative configuration of the newly installed stereogenic center was established by NOESY experiments (Scheme 2.16). Subsequently, dehydration attempts utilizing either Martin's sulfurane[155] or sequential mesylation and E2 elimination in the presence of DBU were explored. These protocols remained unfruitful since no formation of alkene **225** was observed.



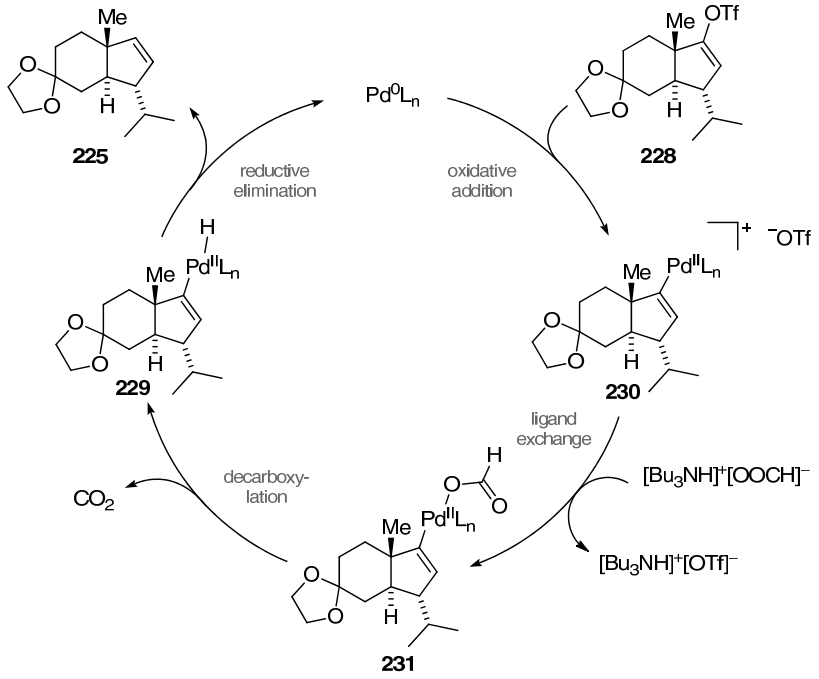
Scheme 2.16 *En route* to alkene **221**: dehydration attempts and first successful synthesis *via* Chugaev elimination.

Next, we resorted to a *syn*-elimination protocol involving a protocol pioneered by Chugaev.[156] For this purpose, reaction of alcohol **224** with chlorothionocarbonate **226** in the presence of pyridine[157] afforded tricycle **227** in 90% yield (Scheme 2.16). Initial experiments in a melting point apparatus (neat in a tubule, 230 °C) resulted in conversion of intermediate **227** to a new compound as indicated by TLC analysis. We thus explored this reaction on a larger scale heating neat compound **227** to 275 °C in a Kugelrohr apparatus according to a literature precedent by Trost and co-workers.[158] Fortunately, the desired product **225** was directly distilled out of the reaction mixture in poor yield and its structure was subsequently verified by NMR spectroscopy and mass analysis. A further optimization of the reaction conditions conducting the transformation in a high boiling point solvent such as Ph_2O or in 1,2-dichlorobenzene under microwave-conditions[159] was not investigated since a more convenient synthesis of alkene **225** was accomplished *via* another strategy (Scheme 2.17).



Scheme 2.17 Efficient two-step protocol for the synthesis of alkene **221**.

Therein, exposure of ketone **220** to KHMDS at low temperature generated the corresponding potassium enolate, which in turn was trapped with $PhNTf_2$ furnishing enol triflate **228**. This latter compound **228** was directly subjected to reductive coupling conditions employing *n*-Bu_3N, formic acid and catalytic amounts of $Pd(PPh_3)_2Cl_2$.[160] This protocol led to the clean formation of alkene **225** in a high yield of 87% over the two steps. Notably, the use of volatile solvents such as Et_2O and *n*-pentane was necessary during the work up and purification process presumably due to the apolar nature and the previously observed low boiling point of alkene **225**.



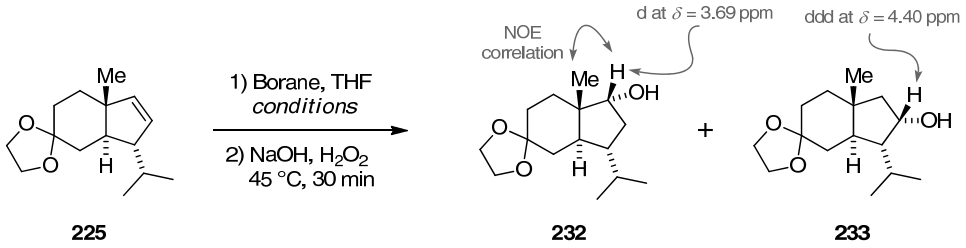
Scheme 2.18 Catalytic cycle of the Pd-catalyzed reductive detriflation.

Mechanistically,[161] this reaction proceeds *via* a standard Pd-catalyzed cross-coupling mechanism. The catalytic cycle commences with an oxidative addition of the *in situ* formed Pd^0 species into the alkenyl triflate bond of tricycle **228** forming Pd^{II} complex **230**, which in turn undergoes a ligand exchange with the *in situ* formed ammonium formate (Scheme 2.18). This intermediate **231** presumably falls apart instantly under extrusion of CO_2 generating H–Pd^{II} complex **229** by a process which formally constitutes a β-hydride elimination. The catalytic cycle is terminated by a reductive elimination, liberating the desired product **225** and regenerating the catalytically active Pd^0 species.

Having established an efficient access to alkene **225**, the attention was next focused on the envisioned hydroboration.[162] To this end, alkene **225** was subjected to different hydroboration agents (Table 2.3), followed by oxidative work up and determination of the regioisomeric ratio between alcohols **232** and **233** in the ^{1}H NMR spectra of the crude reaction mixture. The ratio was determined by integration of the characteristic signals at the newly formed stereogenic center (d at δ = 3.69 ppm for alcohol **232**, ddd at δ = 4.40 ppm for alcohol **233**). These investigation commenced with the exposure of alkene **225** to excess BH_3·THF complex at 0 °C. Upon slowly warming the reaction temperature to room temperature and performing an oxidative work up, decomposition of the starting alkene **225** was

observed (Table 2.3, Entry 1). Next, the amount of BH_3·THF complex was reduced to equimolar stoichiometry, which surprisingly cleaved the acetal moiety instead of performing the desired hydroboration as observed by ^{1}H NMR spectroscopy (Entry 2). This observation was attributed to the Lewis acidity of the hydroboration agent and similar findings have been reported previously.[163]

Table 2.3 Toward a regioselective hydroboration of alkene **225**: variation of reaction conditions.[a]



225 **232** **233**

Entry	Borane (equiv.)	*T* [°C]	*t* [h]	Ratio 232:233[b] (yield)	Observation
1	BH_3·THF (5.0)	0 to rt	0.5	-	decomposition
2	BH_3·THF (1.0)	0 to rt	0.5	-	acetal cleaved
3	BH_3·SMe_2 (1.1)	0 to rt	1	2:1 (90%)	-
4	BH_3·SMe_2 (1.2)	0	4	1.7:1	incomplete conversion
5	BACH-EI (**234**, 1.2)	0	5	1.7:1	incomplete conversion
6	$ThxBH_2$ (**235**, 2.0)[c]	0 to rt	2	1.7:1	-
7	$(sia)_2BH$ (**236**, 2.0)[c]	0 to 66	16	-	s.m.
8	9-BBN (**237**, 2.0)[d]	66	16	-	s.m.
9[e]	9-BBN (**237**, 3.0)[d]	180	6	-	decomposition
10	$Rh(PPh)_3Cl$ (0.05) catBH (**238**, 2.0)	0 to 66	16	-	s.m.
11[f]	BH_3·SMe_2 (1.25)	0 to rt		1:1 (76%)	-

(*a*) All reactions were carried out on 10 mg scale in THF (20mM), unless otherwise stated. (*b*) The ratio was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. (*c*) The hydroboration agent was prepared immediately prior to use from the corresponding alkene and BH_3·SMe_2 complex. (*d*) A solution of 9-BBN (**237**) in the appropriate solvent was freshly prepared from 9-BBN dimer. (*e*) The reaction was conducted in toluene in a pressure tube. (*f*) The reaction was carried out on 200 mg scale. s.m. = starting material.

Thus, we resorted to the BH_3·SMe_2 complex, featuring enhanced stability and therefore less Lewis acidic properties. Indeed, the reaction proceeded smoothly and furnished a 2:1 mixture of regioisomeric alcohols **232** and **233** in a combined yield of 90% (Entry 3). Unexpectedly, this ratio was in favor of the undesired isomer **232**. Upon separation by flash column chromatography, both isomers **232** and **233** were characterized. By comparison with its epimer **224** obtained by reduction with $NaBH_4$, alcohol **232** revealed different physical properties (NMR data, R_f value). In addition a NOESY correlation between the proton at C-1 and the angular methyl group confirmed that the hydroboration occurred from the bottom face. Further variation of the reaction temperature and utilizing the BACH-EI complex (**234**, Figure 2.1) did not alter the regioisomeric ratio dramatically,

enhancing it slightly to 1.7:1 with incomplete conversion (Table 2.3, Entries 4, 5). Thus, more bulky hydroboration agents such as $ThxBH_2$ (**235**), $(sia)_2BH$ (**236**) or 9-BBN (**237**) were examined. However, these reagents either did not influence the selectivity (Entry 6), resulted in no conversion (Entries 7, 8) or led to decomposition (Entry 9). Besides, a Rh-catalyzed hydroboration utilizing Wilkinson's catalyst and catecholborane (**238**), which has been reported to invert the regioselectivity obtained under standard hydroboration conditions in some cases,[164,165] was explored. This protocol was unsuccessful since again only starting material was observed (Entry 10).

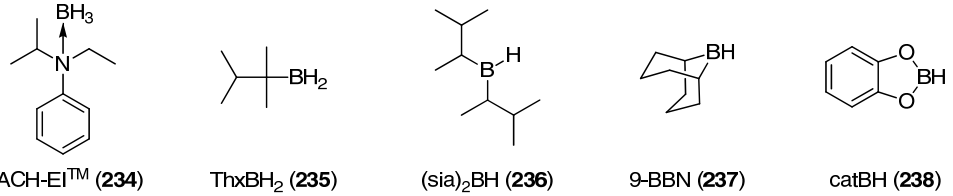
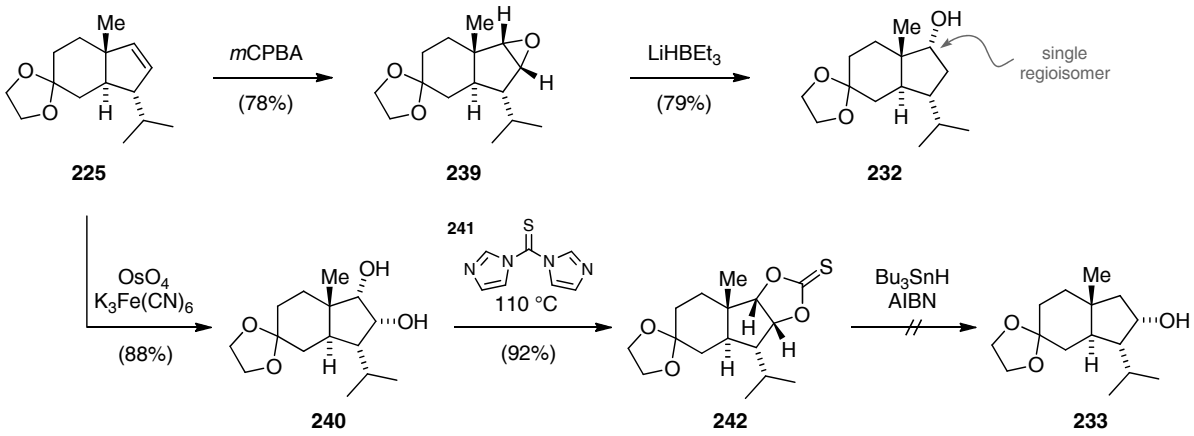


Figure 2.1 Molecular structures of the employed hydroboration agents BACH-EI™ (**234**), thexylborane (**235**), disiamylborane (**236**), 9-BBN (**237**) and catecholborane (**238**).

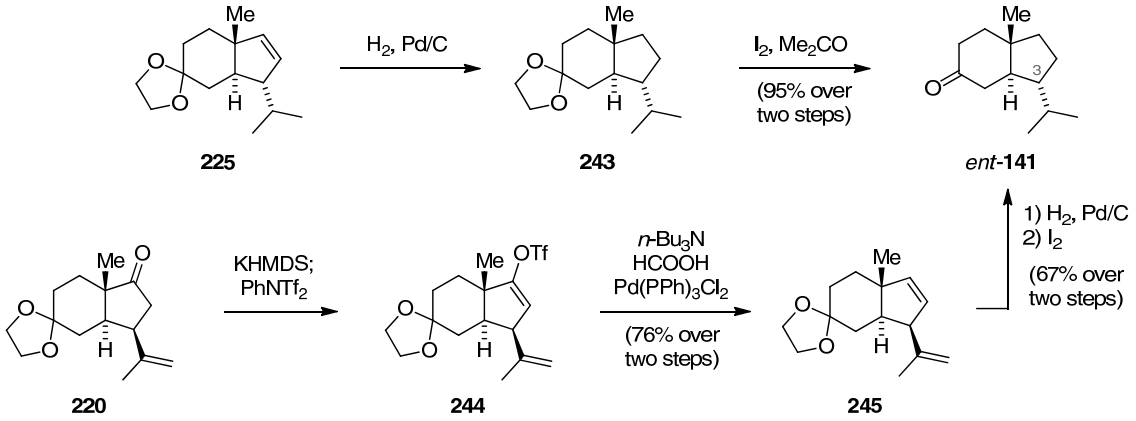
Ultimately, the most convenient procedure with $BH_3 \cdot SMe_2$ complex was scaled to 200 mg of alkene **225** and, interestingly, both alcohols **232** and **233** were obtained in an approximate 1:1 mixture in a combined yield of 76% (Table 2.3, Entry 11). As pointed out previously, separation of the isomers by flash column chromatography was facile and would potentially allow to increase the overall efficiency of this process by recycling the undesired isomer **232** *via* an oxidation/alkene installation sequence. Nevertheless, a higher yielding and more straight-forward route to compound **233** would be beneficial to provide multi-gram quantities for our total synthesis program. We therefore examined alternative protocols in that regard. To this end, alkene **225** was initially reacted with *m*CPBA to yield epoxide **239** as a single diastereomer (Scheme 2.19). This intermediate **239** was subsequently subjected to different hydride reagents in order to effect a regioselective epoxide opening. Unfortunately, treatment with $LiAlH_4$ (THF, reflux) or Super-Hydride® (THF, 0 °C to rt) resulted in a clean reaction generating selectively the undesired regioisomeric alcohol **232**, the spectroscopic data of which matched the ones obtained previously *via* hydroboration.



Scheme 2.19 Further attempts to install the desired oxidation pattern at the cyclopentane moiety *via* hydride epoxide opening or a radical-mediated regioselective reduction.

In another attempt to install the desired oxidation pattern at the cyclopentene moiety, alkene **225** smoothly underwent dihydroxylation in the presence of OsO_4 and $K_3Fe(CN)_6$ as terminal oxidant yielding diol **240** (Scheme 2.18). This compound **240** was in turn exposed to thiocarbonyldiimidazole **241** at elevated temperature to yield thiocarbonate **242**. When submitting the intermediate **242** to reductive radical conditions (Bu_3SnH, AIBN) to initiate a regioselective reduction,[166] no reaction took place in our hands.

Having all these results in mind, we decided to focus on the preparation of the deoxygenated bicyclic building block **190**, applicable for studies toward nitiol (**110**) or retigeranic acid B (**102**). Hence, submission of alkene **225** to hydrogenation conditions (Pd/C, H_2) eventually furnished saturated *trans*-hydrindane **243** (Scheme 2.20). The use of *n*-pentane as a rather unusual solvent was owed to the observed volatility of substrate **225** and the thus assumed similar physical properties of bicycle **243**.



Scheme 2.20 Two protocols for the synthesis of the *trans*-hydrindane building block *ent*-**141**.

Subsequently, the carbonyl functionality was unmasked by treatment with catalytic amounts of iodine in acetone[167] to furnish ketone *ent*-**141**. It should be noted that the overall reaction step count could be reduced by one step when converting ketone **220** to diene **245** *via* enol triflate **244** following the protocol established previously. Again, hydrogenation of diene **245** employing Pd/C as catalyst smoothly afforded the fully saturated bicycle **245**, which in turn was elaborated to ketone *ent*-**141** on a 1.0 g scale, albeit in a lower yield compared to the first route. Having successfully established a robust route toward the monooxygenated *trans*-hydrindane building block *ent*-**141**, we were still confident at this time that the *iso*-propyl residue at C-3 was α-configured. Since the enantiomer of ketone *ent*-**141** had been previously prepared,[168] we were now interested in comparing our analytical data with the one reported in the literature. Particularly, we were curious to explore how the relative configuration at C-3 would change the spectroscopic properties of the two diastereomers. These investigations and the surprising outcome of an X-ray single crystal analysis will be described in the next subchapter.

2.5 Evolution of Hydrogenation Catalysts as a Diversification Tool

As pointed out before, the successful enantioselective synthesis of ketone *ent*-**141** enabled a comparison to the analytical data of *trans*-hydrindane **141**. Surprisingly, a literature survey revealed that only the optical rotation of this compound **141** had been published.[168] This was in contrast to the fact that ketone **141** has been prepared several times and was an important intermediate in the synthesis of retigeranic acid A (**101**) by Hudlicky[86] and Corey.[88] The former research group reported the optical rotation of enantiopure ketone **141** prepared from menthene (**139**) (*cf.* Chapter 1.3) with a levorotary value of −10.0 (*c* 0.07, $CDCl_3$, Figure 2.2).

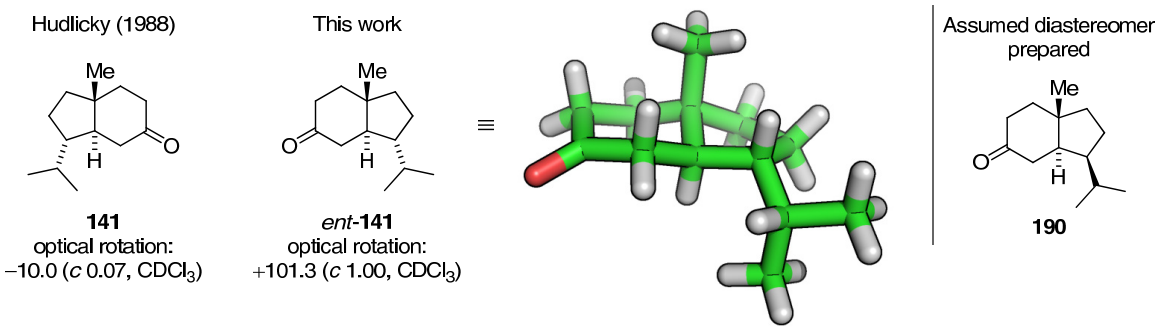


Figure 2.2 Comparison of specific optical rotation for enantiomeric ketones **141** and *ent*-**141** and X-ray structure of ketone *ent*-**141**.

Having this data in mind, we initially set out to measure the optical rotation of the prepared bicycle *ent*-**141** that was still assumed to be its diastereomer **190** (Figure 2.2). Since our synthetic studies were conducted in the enantiomeric series relative to Hudlicky's report,[88] we unsurprisingly determined a dextrorotary specific rotation with a value of +101.3 (*c* 1.00, $CDCl_3$). Based on the discrepancy of the absolute values, we were confident to have prepared ketone **190**. On the other hand, we realized that our value differed from the one reported by Hudlicky solely by a factor of 10, which could easily arise from mistyping or miscalculating. Due to this observation, we opted to prove our assumed structure **190** unambiguously by growing crystals suitable for X-ray diffraction. To our surprise, the X-ray analysis of our prepared compound revealed that the *iso*-propyl moiety within ketone *ent*-**141** resided in a *trans*-relationship to the angular methyl group,[123] thus matching the structure reported by Hudlicky.[88] It remained unclear however at which stage of the reaction sequence the observed epimerization occurred.

In light of this unexpected stereochemistry, several previously observed results could now be rationalized based on steric arguments. With respect to the hydroboration of alkene **225**, the relative configuration at C-3 created a sterically more demanding situation at C-2. Moreover, the steric setting induced a preference to locate the boron atom at the less crowded C-1 carbon (Figure 2.3), ultimately leading to alcohol **232** as the major regioisomer (*cf.* Table 2.3).

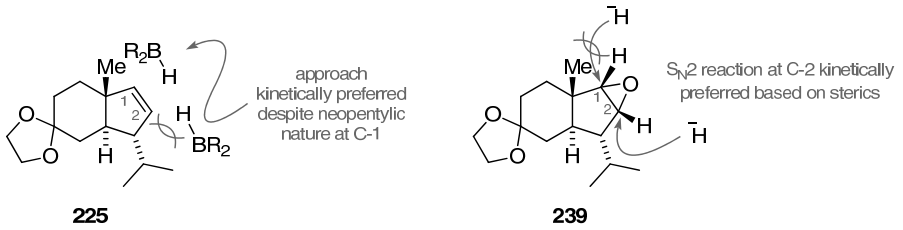
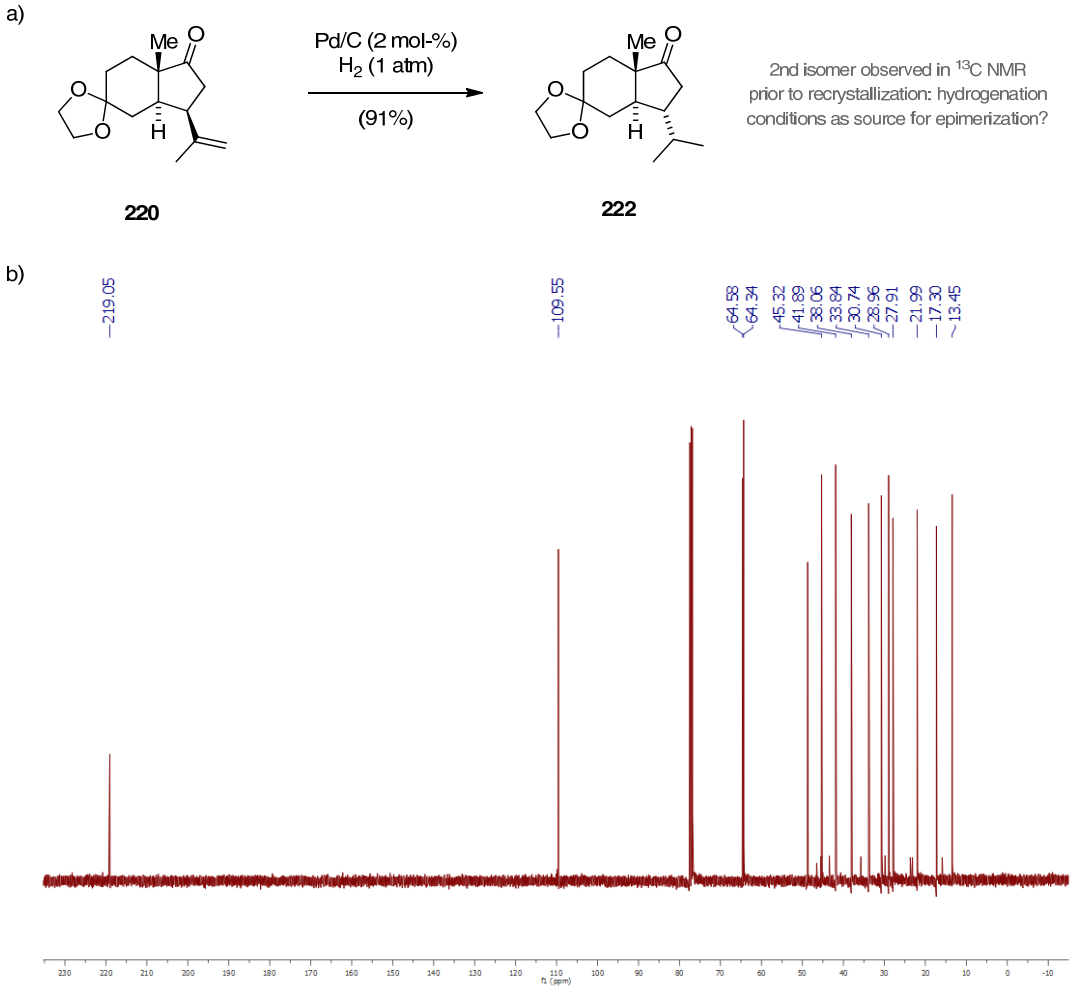


Figure 2.3 Retrospective rationalization of previously observed selectivity with reactions of alkene **225** and epoxide **239** based on the now established steric environment.

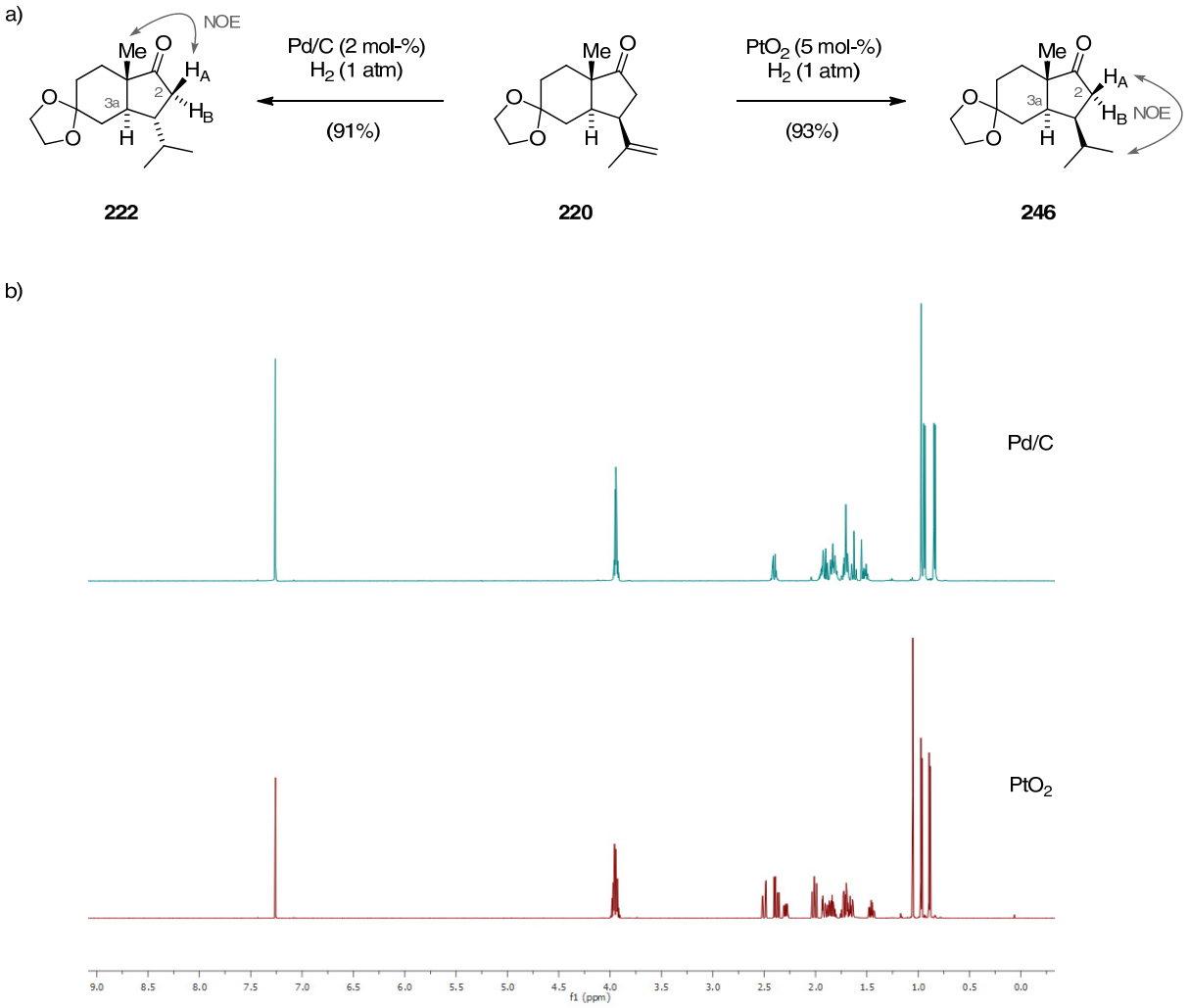
Despite the relative stereochemistry of the *iso*-propyl moiety, this addition as well as the epoxidation and the dihydroxylation (*cf.* Scheme 2.19) were notably still highly diastereoselective and only controlled by the angular methyl group shielding the top face. Additionally, the outcome of the regioselective opening of epoxide **239** could be explained as this reaction occurs *via* a S_N2 mechanism, *i.e.* a back-side attack at C-2 that is more easily accessible from the top face than C-1.

Overall, the surprising X-ray structure of ketone *ent*-**141** prompted us to thoroughly check the proceeded route in order to discover the reaction conditions that led to this unexpected and undesired epimerization. Starting from the unambiguously assigned structure of ketone **220**, we reexamined our synthetic procedures and meticulously analyzed the spectroscopic data.



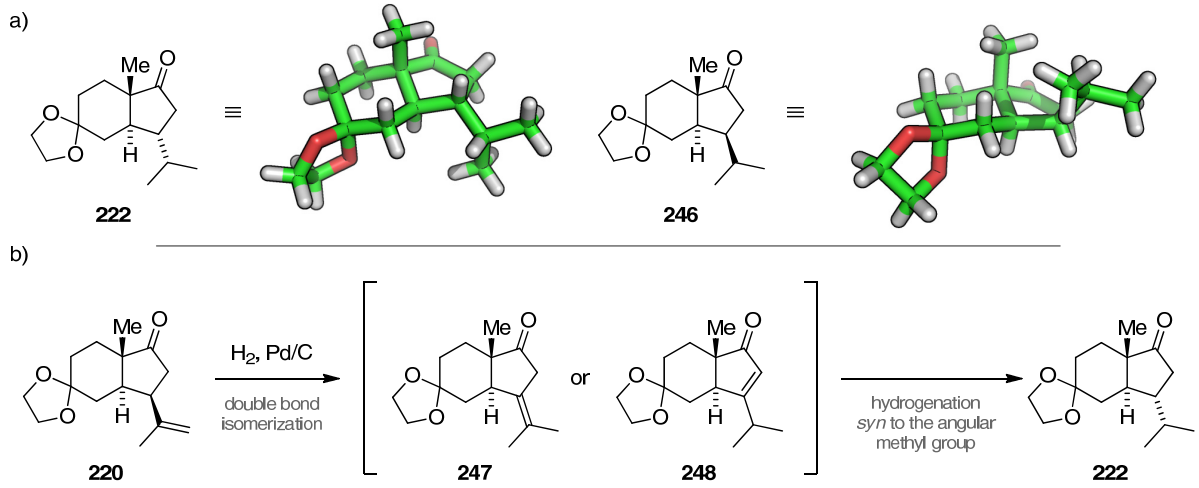
Scheme 2.21 (*a*) Hydrogenation of ketone **220** in the presence of Pd/C required a recrystallization to obtain pure ketone **222**. (*b*) Observation of small amounts of a second diastereomer in the ^{13}C NMR spectrum prior to purification.

Thereby, it was possible to identify the hydrogenation step as a potential origin for this isomerization since a second set of signals observed in the ^{13}C NMR spectra captured our attention (Scheme 2.21). This impurity or, seen from the retrospect, potential diastereomer was conveniently removed in the original procedure by recrystallization yielding ketone **222** in 91% yield. A thorough literature survey revealed that transition metal catalyzed hydrogenations sometimes lead to double bond isomerization prior to reduction.[169] Although often unnoticed in substrates where the isomerized product is subsequently reduced without any consequences, this process holds the potential to result in epimerization or racemization. Consequently, the choice of the hydrogenation catalyst was revisited and Pd/C was replaced with Adam's catalyst (PtO_2), which has been used for the hydrogenation of isopropylene residues in complex environments.[170] Notably, conducting the reaction in MeOH resulted in partial reduction of the carbonyl functionality in ketone **220**. This undesired side reaction was bypassed when submitting ketone **220** to Adam's catalyst in EtOH under an atmosphere of hydrogen. Following this protocol, the reaction resulted in a clean conversion to a product identical to the one observed with Pd/C as catalyst by TLC analysis.



Scheme 2.22 (*a*) Changing the catalyst from Pd/C to PtO_2 resulted in the formation of a new compound. (*b*) Comparison of ^1H NMR spectra for the hydrogenation of ketone **220** in the presence of Pd/C (top) and PtO_2 (bottom).

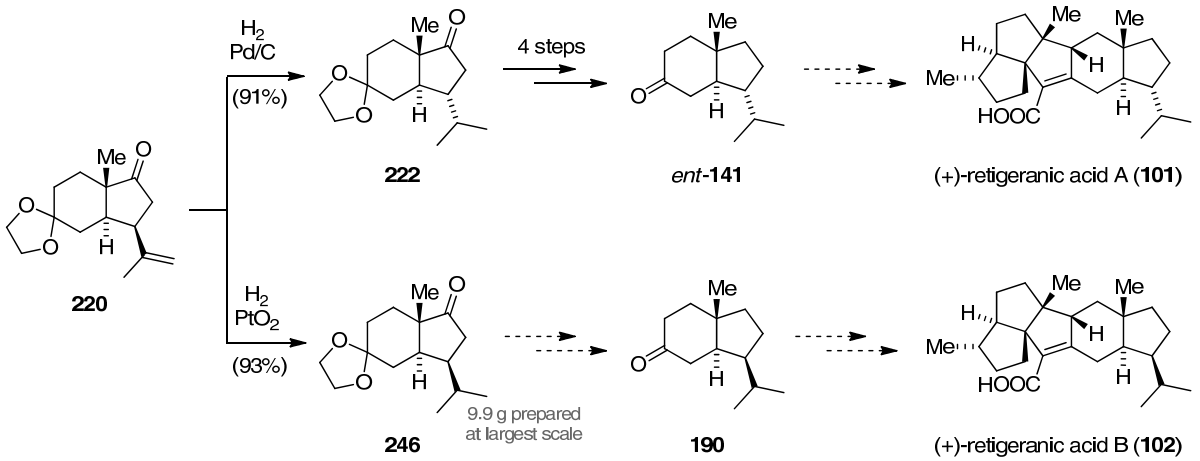
The compound was isolated in 93% yield and an ensuing NMR analysis revealed the formation of a diastereomer **246** comprising distinctly different NMR properties compared to ketone **222**. This is exemplified with protons at C-2 and C-3a (IUPAC numbering). For ketone **222**, a signal for 2-H_A at $\delta = 2.40$ ppm is visible and the diastereotopic proton 2-H_B was part of a multiplet at $\delta = 1.98–1.87$ ppm. In contrast, the corresponding protons for ketone **246** are centered at $\delta = 2.48$ ppm for 2-H_A and at $\delta = 2.37$ ppm for 2-H_B, respectively (Scheme 2.22). This significant downfield shift was also observed for the methine at C-3a. Its signal was determined as part of a multiplet at $\delta = 1.86–1.76$ ppm for ketone **222**, while a clean ddd at $\delta = 2.28$ ppm was observed in the case of diastereomer **246**. Moreover, the analysis of the ^{13}C NMR spectra revealed the carbon signals for ketone **246** match those of the 'impurity' observed during the preparation of hydrogenation product **222**. While these observations already indicated the successful synthesis of the desired ketone **246**, an unambiguous proof of these assumptions was worth striving for.



Scheme 2.23 (*a*) X-ray structures of hydrogenation products **222** and **246**. (*b*) Proposed mechanism for the observed epimerization during hydrogenation of ketone **220** with Pd/C.

To this end, attempts to crystallize both epimers **222** and **246** finally culminated in the elucidation of their structures by X-ray crystallography as depicted in Scheme 2.23.[123] Mechanistically, it is assumed that the use of Pd/C results in a double bond isomerization furnishing either tetrasubstituted alkene **247** or enone **248**, which might both be instantly reduced with H_2 (Scheme 2.23). It was shown that the presence of H_2 played a crucial role since a blank experiment employing solely the catalyst Pd/C under N_2 atmosphere did not result in any conversion. Interestingly, the hydrogenation of the isomerized alkene then occurred *syn* to the angular methyl group in analogy to the previously observed Michael reaction (*cf.* Chapter 2.3). One might argue that this reaction pathway is favorable as it provides the presumably more thermodynamically stable ketone **222**, avoiding unfavored interactions between the angular methyl group and the *iso*-propyl substituent. Ultimately, it should be stated that this outcome can be exploited in a useful way for synthetic studies to both retigeranic acids A (**102**) and B (**103**, Scheme 2.24). While the preparation of ketone *ent*-**141** was already accomplished (*cf.*

Chapter 2.4), a successful synthesis of its epimeric congener **190** would provide the basis to construct the pentacyclic architecture **103**.

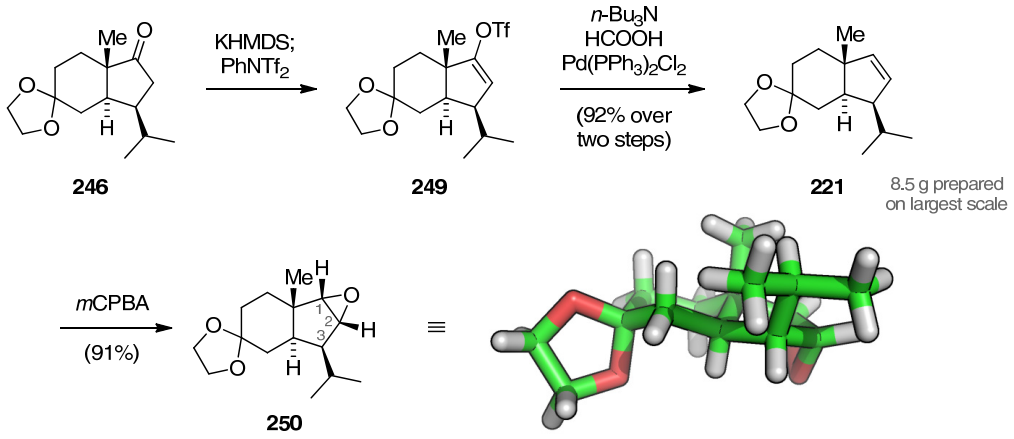


Scheme 2.24 Hydrogenation catalysts as a diversification tool for synthetic programs toward retigeranic acids A (**101**) and B (**102**).

Thus, these observations represent a handle for diversification in these total syntheses since simply changing the catalyst can provide both products **222** and **246** in high yield and selectivity. This is underlined by the fact that the hydrogenation with PtO_2 was easily scalable, furnishing a total of 9.9 g of ketone **246** in 93% yield on the largest scale. With substantial amount of ketone **246** prepared, further transformations *en route* to the key building blocks **190** and **191** were then tackled.

2.6 Synthesis of Two Versatile Building Blocks for Type A *trans*-Hydrindane *iso*-Propyl Sesterterpenoids

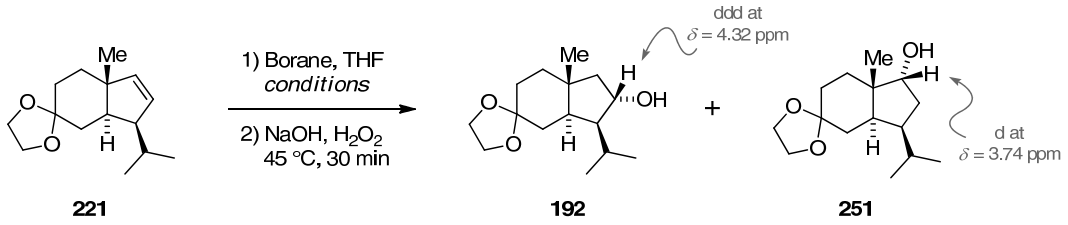
Having unambiguously assigned the point of epimerization, we embarked on the synthesis of building blocks **191** and **190**. At first, ketone **246** was converted to the corresponding enol triflate **249** by sequential exposure to KHMDS and $PhNTf_2$ (Scheme 2.25). This intermediate **249** then smoothly underwent the Pd-catalyzed reductive detriflation,[160] yielding alkene **221** in an excellent yield of 92% over the two steps. The reaction was conducted on up to 3 g of ketone **221** and on the largest scale, 8.5 g of alkene **221** have been prepared. In analogy to the hydrogenation products **222** and **246**, alkenes **225** and **221** showed remarkably different properties in NMR spectroscopy, indicating the successful preparation of alkene **221** without any unexpected epimerization at C-3 (IUPAC numbering). Alkene **221** was then treated with *m*CPBA to yield epoxide **250** with a fully substituted cyclopentane moiety. The structure of tetracycle **250** was established by X-ray crystallography,[123] confirming once more the correct relative stereochemistry at C-3. Interestingly, subjecting epoxide **250** to a hydride donor such as Super-Hydride® did not result in any conversion, even when conducting the reaction at 140 °C in boiling Bu_2O. These observations clearly underlined that the trajectory for an S_N2 displacement was now blocked at both C-1 and C-2 by geometric constraints.



Scheme 2.25 Successful large scale preparation of alkene **221** and verification of the C-3 relative stereochemistry by X-ray diffraction of epoxide **250**.

Next, a screening of alkene hydroboration conditions was carried out. Initially, a slight excess of $BH_3 \cdot SMe_2$ complex was employed and the reaction was allowed to warm from 0 °C to room temperature (Table 2.4 Entry 1).

Table 2.4 Hydroboration of alkene **221**: variation of reaction conditions.[a]

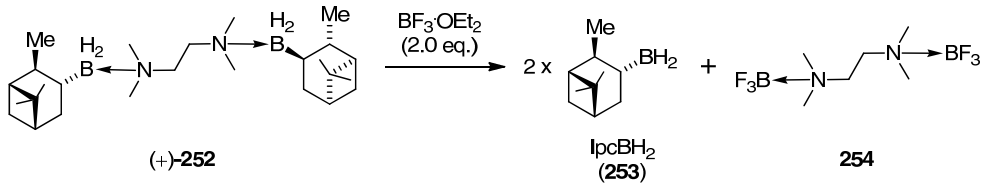


Entry	Borane (equiv.)	*T* [°C]	*t* [h]	Ratio 192:251[b]	Observation/ Remarks
1	$BH_3 \cdot SMe_2$ (1.3)	0 to rt	0.5	2.7:1	-
2	$BH_3 \cdot SMe_2$ (1.3)	rt	0.5	2.6:1	-
3	$BH_3 \cdot SMe_2$ (1.3)	rt	2	2.0:1	slow addition of BH_3 in 2 h at 0 °C
4	$BH_3 \cdot SMe_2$ (1.3)	0 to rt	0.5	2.7:1	0.2M in alkene **221**
5	$BH_3 \cdot SMe_2$ (1.6)	0 to rt	1	2.1:1	-
6	$BH_3 \cdot SMe_2$ (0.7)	0 to rt	1	2.9:1	-
7	9-BBN (**237**, 5.0)	0 to 66	15	-	s.m.
8	$ThxBH_2$ (**235**, 1.6)[c]	0 to rt	1	-	acetal cleaved[d]
9	$(sia)_2BH$ (**236**, 2.5)[c]	0 to rt	1	-	acetal cleaved[d]

(*a*) All reactions were carried out on 10 mg scale in THF (*c* 0.03M) unless otherwise stated. (*b*) The ratio was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. (*c*) The hydroboration agent was prepared immediately prior to use. (*d*) Observed by ^{1}H NMR spectroscopy of the crude reaction mixture. rt = room temperature, s.m. = starting material.

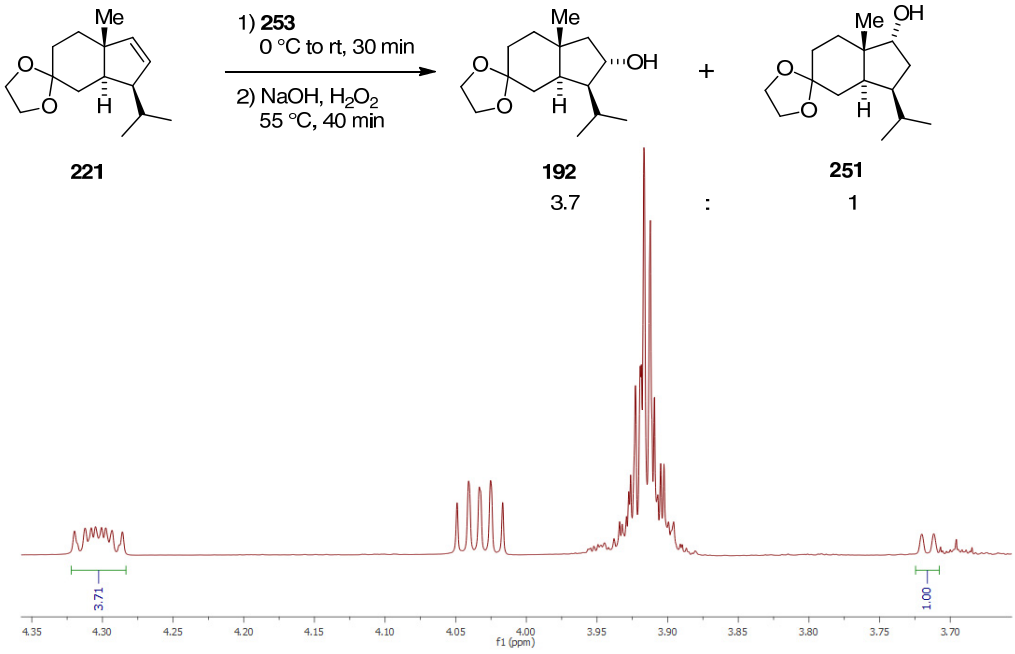
After oxidative work up, this procedure delivered a 2.7:1 mixture of regioisomeric alcohols **192** and **251** as assigned by ^{1}H NMR spectroscopy (ddd at δ = 4.32 ppm for alcohol **192**, d at δ = 3.74 ppm

for regioisomer **251**, *cf.* Figure 2.4) in favor of the desired product **192**. Thereafter, parameters such as temperature (Table 2.4, Entries 2, 3), addition rate (Entry 3), concentration (Entry 4) and equivalents of hydroboration agent (Entries 5, 6) were varied, but did not result in a significant improvement of the regioselectivity. Thus, the more bulky boron reagents $ThxBH_2$ (**235**), $(sia)_2BH$ (**236**) and 9-BBN (**237**) were tested. Unfortunately, they all remained unsuccessful and either led to acetal cleavage (Entries 8, 9) or no conversion of the starting material (Entry 7). It is worth noting that the amount of equivalents of hydroboration agent exceeds a profound effect on the regioselectivity of the reaction. Whereas the best result was obtained by quick addition of a substoichiometric amount (0.7 equivalents) of $BH_3 \cdot SMe_2$, the ratio dropped to 2.1:1 by employing 1.6 equivalents. Potentially, this observation could be rationalized by the *in situ* formation of a chiral hydroboration agent RBH_2.



Scheme 2.26 Preparation of the chiral hydroboration agent $IpcBH_2$ (**253**).

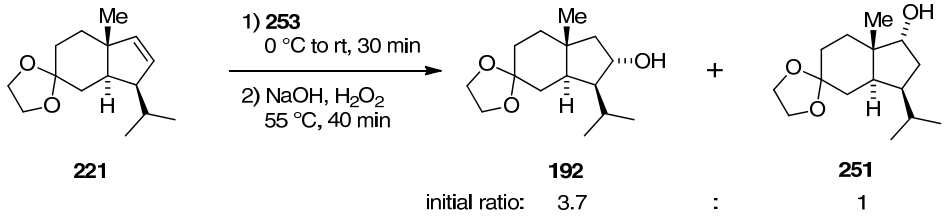
Consequently, a pinene-derived chiral hydroboration agent developed by Brown and co-workers[171] was examined. Hence, commercially available (*S*)-Alpine-Boramine™ (**252**) was treated with $BF_3 \cdot OEt_2$ to liberate the free chiral compound **253** along with the precipitated $BF_3 \cdot TMEDA$ complex (**254**), which was conveniently removed by filtration (Scheme 2.26).[171] The resulting solution of enantiopure borane **253** was immediately used in the subsequent hydroboration with alkene **221**. To our delight, ^1H NMR spectroscopy of the crude reaction mixture after oxidative work up revealed an improved regiomeric ratio of 3.7:1 (Scheme 2.27).



Scheme 2.27 ^1H NMR of the crude reaction mixture from the hydroboration of alkene **221** with $IpcBH_2$ (**253**).

In contrast to the hydroboration of alkene **225**, alcohols **192** and **251** were hardly separable, but careful flash column chromatography allowed for an enhancement of the ratio to 5.5:1 with a 84% yield on a 550 mg scale (Table 2.5, Entry 1).

Table 2.5 Hydroboration of alkene **221** with the chiral borane **253**.[a]

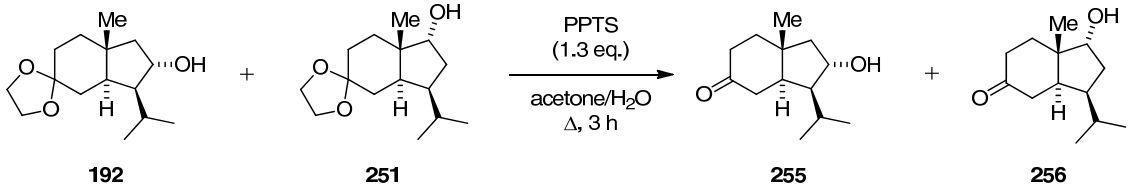


Entry	Scale [g]	Equiv. 253	Yield after FCC [%]	Ratio 192:251 After FCC[b]
1	0.55	1.5	84	5.5:1
2	3.20	1.2	73	6.6:1
3	3.80	1.2	67	12.4:1

(*a*) The initial ratio of hydroboration remained unchanged. For further details on the reaction conditions see the experimental section. (*b*) The ratio was determined by ^{1}H NMR spectroscopy. FCC = flash column chromatography.

During scale-up with 16.1 and 13.6 mmol of alkene **221**, this result was even further improved and delivered alcohol **192** in a ratio of 12.4:1 and 6.6:1, respectively (Table 2.5, Entries 2, 3) yielding a total amount of 5.20 g on the largest scale. Besides, the reaction with the enantiomeric borane *ent*-**253**, generated from (*R*)-Alpine Boramine^{TM}, was tested and gave an approximately 1:1 mixture of regioisomers **192** and **251** (not shown). Therefore, the reaction of alkene **225** with borane **253** constituted a matched case of double diastereoselection.

Table 2.6 Conversion of dioxolanes **192** and **251** to ketones **255** and **256**.

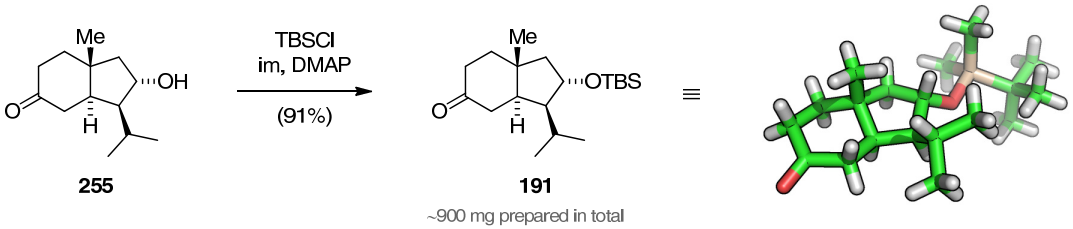


Entry	Scale [mg]	Ratio 192:251	Yield after FCC [%]	Ratio 255:256[a]
1	495	5.5:1	75	12:1
2	2660	12.4:1	82	>95:5

(*a*) The ratio was determined by ^{1}H NMR spectroscopy. For details on reaction conditions see the experimental section. FCC = flash column chromatography.

Having synthesized substantial amounts of dioxolane **192**, the next task was a deprotection/protection sequence. Hence, the diastereomeric mixture of alcohols **192** and **251** was subjected to acidic conditions employing PPTS in an acetone/water mixture[172] to liberate the carbonyl functionality within ketones **255** and **256**. Gratifyingly, a slightly easier separation by flash column chromatography

was feasible at this stage, allowing for an improvement of the regioisomeric ratio from 5.5:1 to 12:1 with a yield of 75% on a 495 mg scale (Table 2.6, Entry 1). On a 2.66 g scale, an initial 12.4:1 mixture was converted to pure alcohol **255** (>95:5) in 82% yield (Entry 2). The major amount of material has not been employed for further studies and has been stored in case another protecting group would prove necessary.

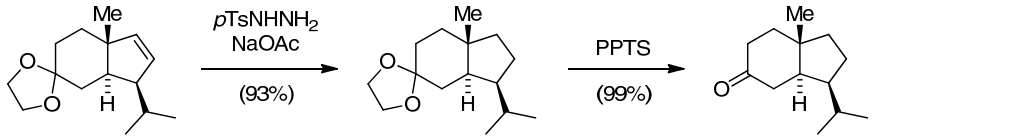


255 **191**

~900 mg prepared in total

Scheme 2.28 Synthesis and X-ray structure of *trans*-hydrindane *iso*-propyl building block **191**.

With ketone **255** in hand, a suitable protecting group needed to be installed in order to further transform the cylcohexanone core. For this purpose, a TBS silyl ether was chosen and alcohol **255** was submitted to standard silylation conditions. This protocol furnished the pure ketone **191** in 91% yield (Scheme 2.28) and, overall, approximately 900 mg of this bicycle **191** have been prepared to date. The structure of this versatile *trans*-hydrindane building block **191** was unambiguously proven by X-ray diffraction.[123] It should be noted that an inverted order of the protecting group manipulations was inconvenient as the secondary TBS ether did not resist the acidic conditions required for the deprotection of the dioxolane moiety (not shown).



221 **257** **190**

optical rotation:
+11.2 (*c* 0.25, CH_2Cl_2)

Scheme 2.29 Successful preparation of building block **190** exploiting a diimide reduction of alkene **221**.

Having successfully accomplished the synthesis of the first envisaged building block **191**, the attention was now focused on the deoxygenated analog **190**. Thus, alkene **221** was subjected to hydrogenation conditions and, in analogy to the hydrogenation of ketone **220** (*cf.* Chapter 2.5), the use of Pd/C as a catalyst resulted in epimerization. The outcome was less pronounced in this case and gave rise to a 1:2 ratio of the two diastereomers **243** and **257** as indicated by ^{1}H NMR spectroscopy. More interestingly, the hydrogenation in the presence of PtO_2 also occurred with partial epimerization in the same ratio as with Pd/C. This contrasts the previous experiences on the transformation of alkene **220** to ketone **246**. We thus resorted to a non-metal mediated reduction protocol. Hence, alkene **221** was treated with *p*TsNHNH$_2$ and NaOAc at 80 °C,[173] generating diimide *in situ* and resulting in a clean reaction to afford dioxolane **257** (Scheme 2.29). Ultimately, the carbonyl functionality was unmasked by treatment with PPTS to yield building block **190**, which exhibited distinctly different properties in

comparison with its diastereomeric counterpart *ent*-**141** regarding NMR spectroscopy and optical rotation.

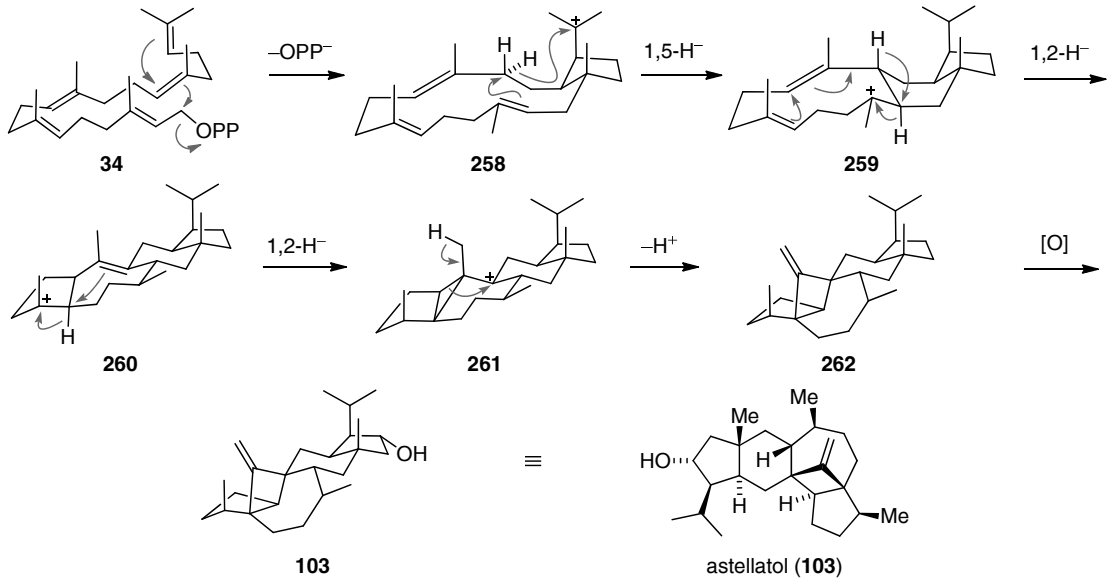
2.7 Conclusion

In conclusion, this chapter detailed the evolution of the synthesis of three building blocks (*ent*-**141**, **190** and **191**) starting from enantiomerically pure diketone **116**. The developed route featured several highly diastereoselective transformations and showcased the diversification of two building blocks **220** and **221**, thus constituting a unified approach. Moreover, the observed epimerization during hydrogenation of ketone **220** emphasized the importance of meticulous analysis of intermediates, even with seemingly straightforward reactions. Ultimately, it should be noted that the strategy was, as envisaged, robust and easily scalable to multigram quantities. These findings provided the basement for synthetic studies toward all type A *trans*-hydrindane *iso*-propyl sesterterpenoids, for which little progress has been reported previously. The details concerning our efforts toward the enantioselective syntheses of astellatol (**103**), nitiol (**110**) and YW3548 (**112**) will be presented in the next chapters of this Ph.D. thesis.

3 SYNTHETIC STUDIES TOWARD ASTELLATOL

3.1 Astellatol: Isolation and Background

The sesterterpenoid astellatol (**103**) was isolated in 1989 by Simpson and Sadler from *aspergillus variecolor (syn A. stellatus)*.[93] Its unique architecture was elucidated by extensive applications of a variety of NMR techniques,[174] establishing astellatol (**103**) as a member of the rare class of pentacarbocyclic sesterterpenoids. More precisely, the carbon backbone comprises four-, five-, six- and seven-membered rings and features a total of ten stereogenic centers, three of which are all-carbon substituted. In addition to the previously introduced sterically encumbered *trans*-hydrindane portion, astellatol (**103**) possesses an exocyclic methylene moiety attached to a four-membered ring. Remarkably, only a single oxygenated site was established, thus rendering astellatol (**103**) a challenging target for total synthesis. Although astellatol (**103**) has been found by Simpson during the course of structural and biosynthetic studies on xanthone pigments, the authors did not examine the biological properties of this daunting natural product. Thus, a total synthesis of astellatol (**103**) would not only allow one to unambiguously confirm its relative and absolute configuration, but would also provide the basis to investigate its biological function in Nature.



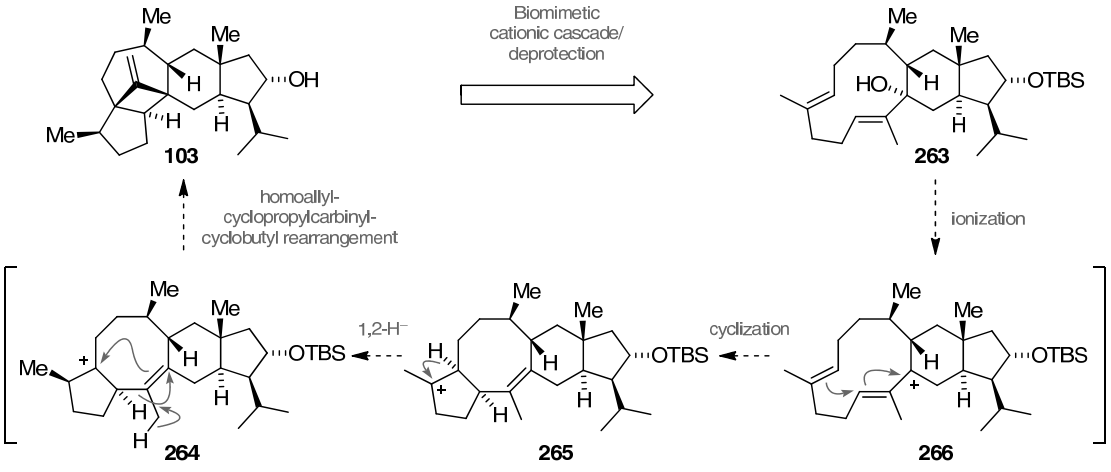
Scheme 3.1 Proposed biosynthesis of astellatol (**103**) from pyrophosphate **34** put forward by Simpson.[175]

Beside elucidating the structural features of astellatol (**103**), Simpson also put forth a biosynthetic proposal some years later.[175] Within this report, he supported his hypothesis by ^{13}C labeled acetate feeding experiments, which indicates an origin along the lines of classical terpenoid biogenesis, thus commencing from an initial folding of geranylfarnesyl pyrophosphate (**34**, Scheme 3.1).[12] In the presence of the terpenecyclase, pentaene **34** undergoes the first C–C bond formation with generation of a carbocation to form bicycle **258**, setting the *cis*-relationship between angular methyl group and the

iso-propyl residue. In the following, a 1,5-hydride shift is accompanied by the generation of the *trans*-hydrindane portion, eventually leading to tertiary carbocation **259**. This intermediate **259** is now prone to undergo a series of two stereospecific 1,2-hydride shifts, the result of which is the relative configuration of the two stereogenic centers at C-9 and C-10 (astellatol numbering). The thus constructed homoallylic carbocation **260** is further driven to the thermodynamic minimum by a homoallyl-cyclopropylcarbinyl-cyclobutyl rearrangement, generating the intriguing ring system in pentacarbocyclic intermediate **261** *via* a ring-expansion of cyclopropane **262**. Ultimately, a site-selective enzymatic oxidation furnishes the natural product **103**.

3.2 Retrosynthetic Analysis

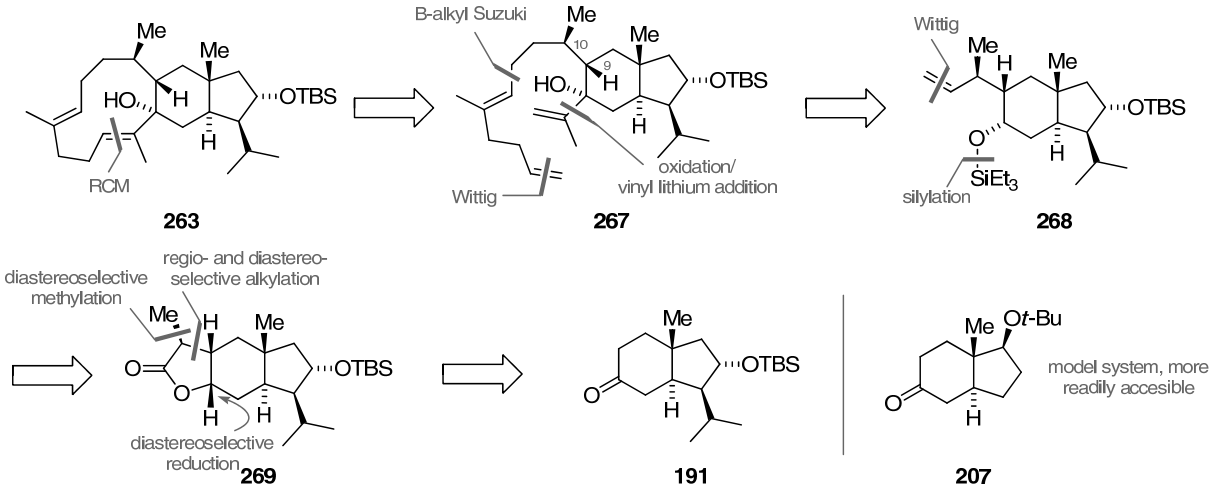
Retrosynthetically, we envisaged to access astellatol (**103**) *via* a bioinspired cationic cascade from allylic alcohol **263** according to the biosynthetic proposal of Simpson (Scheme 3.2).[175] In the forward sense, treatment of alcohol **263** with a Lewis or a Brønsted acid would form the stabilized tertiary carbocation **266**, which could then trigger a ring closure to form tetracycle **265**. In order to access the natural product by a stereospecific 1,2-hydride shift to form homoallylic cation **264**, this cyclization should result in the diastereomer **265**. Finally, carbocation **264** could next engage in the aforementioned homoallyl-cyclopropylcarbinyl-cyclobutyl rearrangement[176] to furnish the natural product **103** after subsequent deprotection.



Scheme 3.2 Proposed retrosynthesis of astellatol (**103**) *via* a biomimetic cationic cascade.

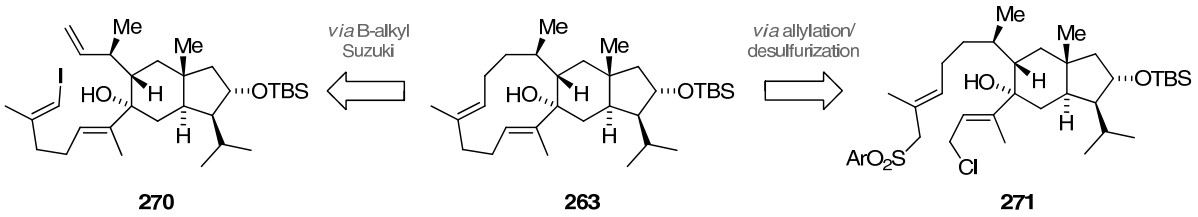
Domino transformations of this kind are highly challenging to realize in the laboratory without the help of an enzymatic environment, given the number of possible reaction pathways and side products. However, we assumed that the conformational bias associated with the already installed *trans*-hydrindane portion might influence the outcome of the cascade in favor of the formation of astellatol (**101**). It should be stressed that this novel cationic cascade would explore the boundaries of biomimetic synthesis,[114] rapidly build up complexity and provide insight into the biogenesis of astellatol (**103**).

One major challenge concerning this envisaged route was the construction of the highly strained 11-membered ring in tricycle **263** comprising two (*E*)-configured trisubstituted alkenes. Although these moieties have been found in natural products such as the dolabellane terpenoids, only a few successful routes toward their synthesis have been described in literature.[177,178] In this first retrosynthetic proposal, we aimed at closing the macrocycle by a ring-closing metathesis (RCM) from allylic alcohol **267**, a moiety which is known to engage in RCM reactions (Scheme 3.3).[179,180] The latter intermediate **267** in turn could arise from alkene **268** by a sequential B-alkyl Suzuki coupling[181,182] and a vinyl lithium addition.



Scheme 3.3 Retrosynthetic analysis of tricycle **263** by a RCM.

Further retrosynthetic dissection *via* a lactol-Wittig reaction would give lactone **269**, which already features the desired *cis*-relationship between the C-9 methine and the C-10 methyl group (astellatol numbering). The installation of this relative stereochemistry might be otherwise difficult to address at a later stage of the synthesis. We further envisaged installing the C-10 stereogenic center by the conformational bias ('open-book effect') of a tricyclic compound. To this end, tricycle **269** should be formed by a series of diastereo- and regioselective transformations, finally tracing astellatol (**103**) back to our previously synthesized building block **191**. Although we had prepared larger amounts of *trans*-hydrindane building block **191** and the associated route was practical, we decided to base our investigations on the more easily accessible model system **207**. This ketone **207** differs from bicycle **191** only in the substitution pattern at the five-membered ring and we thus reasoned that both compounds would behave similarly in reactions at the cyclohexanone moiety. Moreover, reports on the mild and functional group tolerant cleavage of the *t*-butyl ether have been published,[183] which might allow for the installation of the required portion of astellatol (**103**) at a later stage of the synthesis following the chemistry established previously (*cf.* Chapter 2).

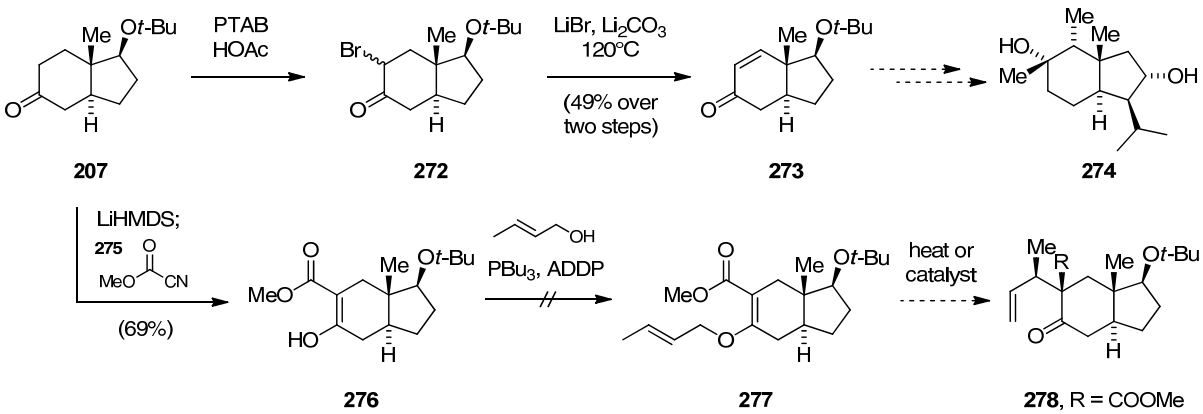


Scheme 3.4 Alternative strategies to construct tricycle **263**, the precursor for the envisaged biomimetic cascade.

In addition to this RCM strategy, we also envisioned closing the 11-membered rings by means of other methodologies. In particular, we thought that we could construct the macrocycle by an intramolecular B-alkyl Suzuki coupling from vinyl iodide **270** (Scheme 3.4). Alternatively, we aimed at examining an intramolecular allylation of allylic sulfone **271**, the sulfur moiety of which could be later reductively cleaved. Notably, both cyclization precursors **270** and **271** should also be accessible from alkene **268**, thus rendering this compound **268** a key intermediate in our efforts toward astellatol (**103**). A more detailed retrosynthetic analysis of these approaches will be given at the relevant sections (*cf.* Chapters 3.5, 3.6).

3.3 Installation of the Stereogenic Centers at C-9 and C-10

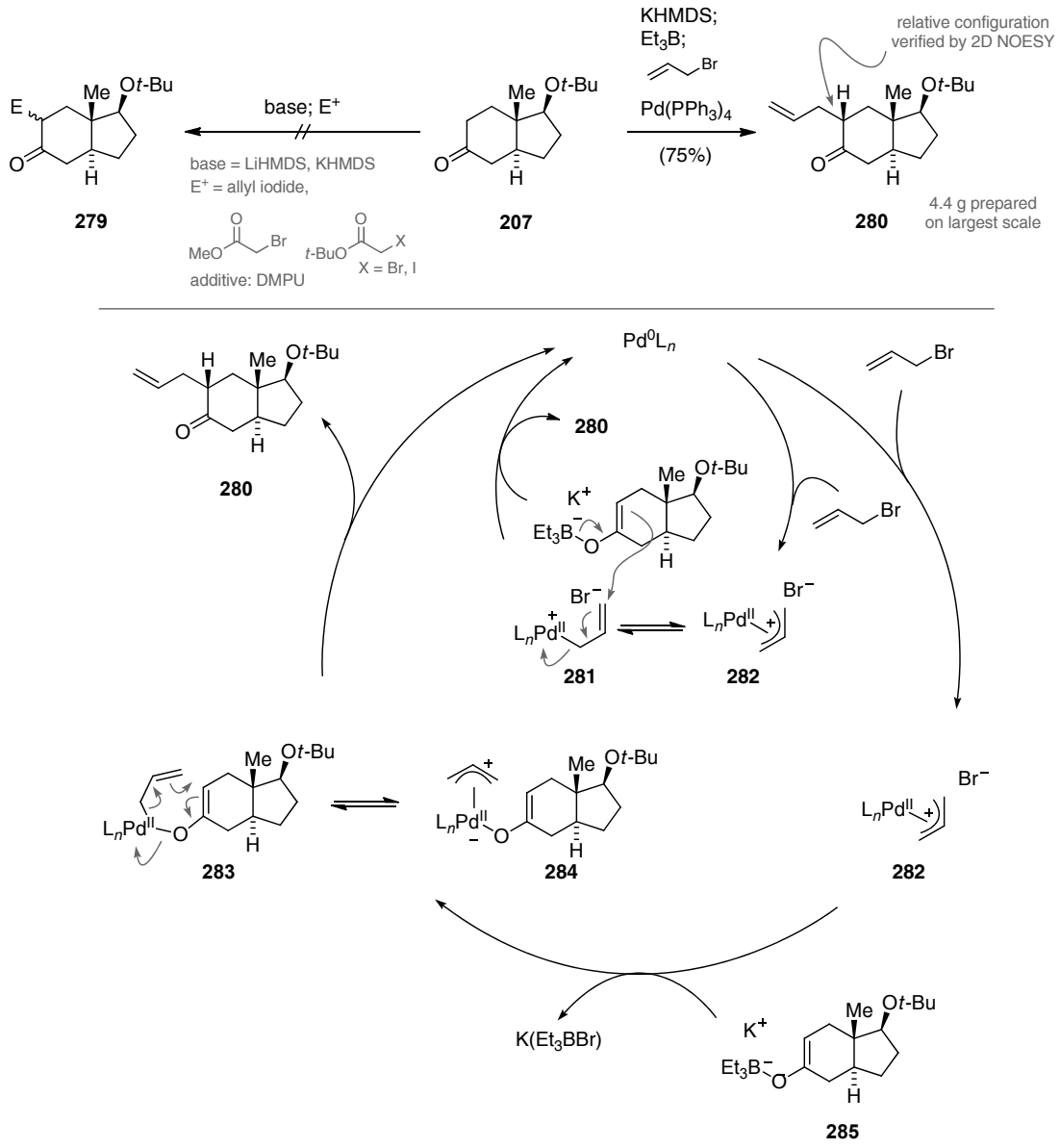
In light of the retrosynthesis presented above, we embarked on a total synthesis program toward astellatol (**103**). Thereby, the installation of the two adjacent stereogenic centers at C-9 and C-10 was initially center stage. As pointed out before, these investigations were conducted utilizing enantiomerically pure ketone **207** as a model substrate.



Scheme 3.5 Proof of site-selective reactivity of ketone **207**: preparation of enone **273** and bicycle **276**.

In order to establish the desired regioselectivity in reactions involving the carbonyl functionality in ketone **207**, we initially carried out two simple transformations (Scheme 3.5). On the one hand, ketone **207** was treated with phenyltrimethylammonium tribromide (PTAB) in the presence of catalytic amounts of HOAc[141] to generate a diastereomeric mixture of α-bromo carbonyl compound **272**. This compound was further elaborated to enone **273** by exposure to LiBr and

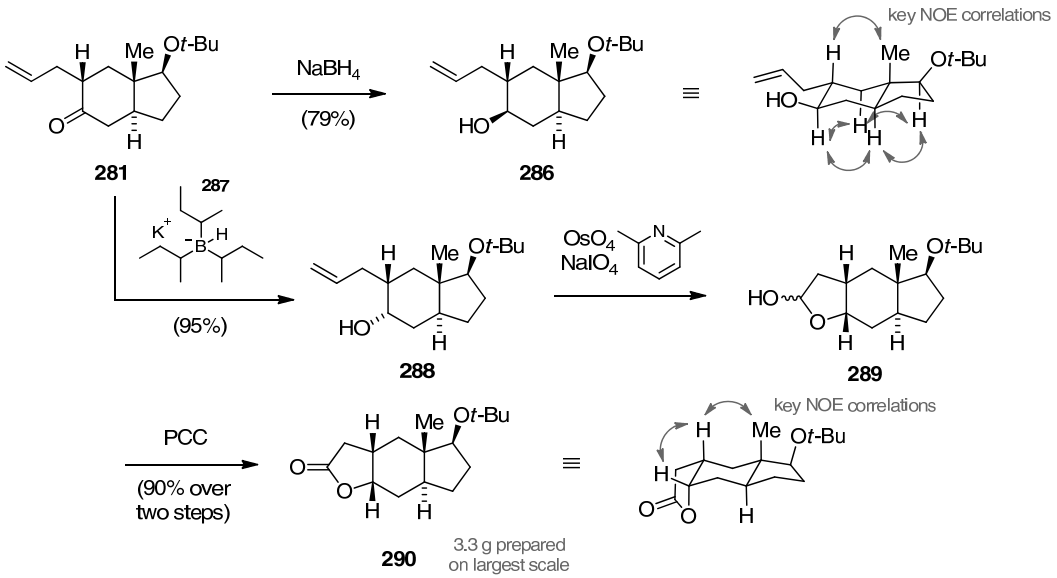
Li_2CO_3[140] at 120 °C in 49% yield over the two steps as the sole product. Notably, *trans*-hydrindenone **273** might at some point serve as an intermediate for synthetic studies toward the structurally related sesquiterpenoid 8,10-dihydroseiricardine A (**274**).[184] On the other hand, we conducted a regioselective methoxy-carbonylation by sequential treatment with LDA and Mander's reagent (**275**)[185] and the structure of the single product, *β*-keto ester **276**, was elucidated by 2D NMR analysis. Furthermore, we investigated the conversion of compound **276** to vinyl allyl ether **277** following a protocol reported by Jacobsen and co-workers.[186] However, a brief screen of reaction conditions employing 1,1'-(azodicarbonyl)dipiperidine (ADDP) did not result in any conversion. We were particularly interested in this transformation since the latter intermediate **277** could serve as a precursor for a Claisen rearrangement.[62] Potentially, such a process could install the C-9 and C-10 stereogenic centers in intermediate **278** by a stereospecific reaction *via* a chair-like six-membered transition state.



Scheme 3.6 Attempts to functionalize hydrindanone **207** *via* alkylation or allylation: diastereo- and regioselective synthesis of ketone **280** by Pd-catalysis and two proposed catalytic cycles.

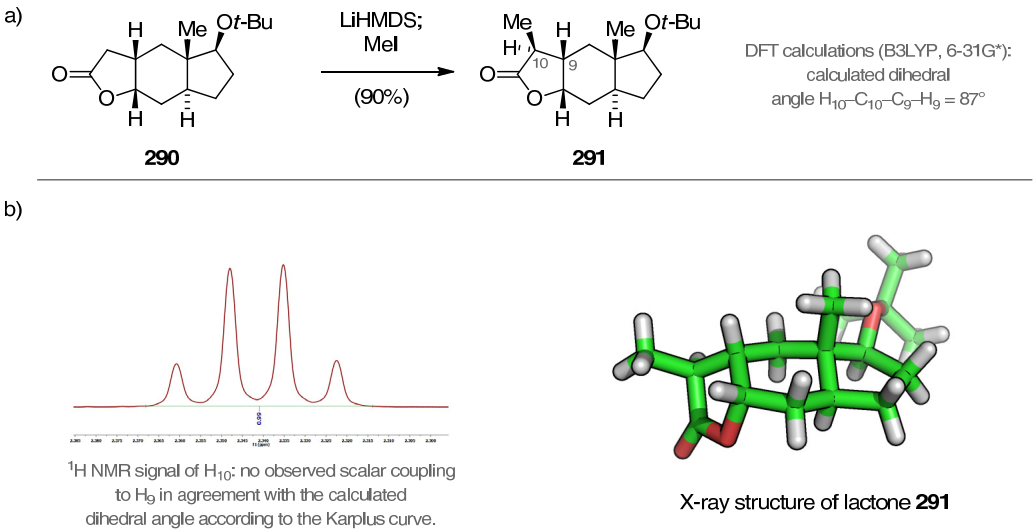
Since a proof for the desired regioselectivity in transformations of ketone **207** had been achieved, we next focused on alkylation/allylation protocols utilizing different electrophiles such as allyl iodide or α-halo acetic acid derivatives (Scheme 3.6). Unfortunately, ketone **207** was resistant to all the attempts to form product **279** resulting in no or very poor conversion. These observations were in accordance with previous reports by Collins[187] as well as by Covey and co-workers[134,188] in their efforts to construct rearranged steroid ring systems. Fortunately, Covey found in these investigations that indenone **207** can be "alkylated regio- and diastereoselectively at C-6 (IUPAC numbering) with allylic electrophiles *via* potassium enoxyborates in the presence of catalytic amounts of a palladium complex".[187] This methodology had been developed earlier by Negishi and co-workers and was shown to be general for a broad range of ketones.[189] Encouraged by this report, we set out to reproduce these results in our hands. Eventually, generation of the potassium enolate of ketone **207** by exposure to KHMDS at room temperature was followed by sequential addition of Et_3B and a mixture of allyl bromide and catalytic amounts of $Pd(PPh_3)_4$ at −78 °C. Upon warming to room temperature for 3 h and subsequent aqueous work up, the desired product **280** was isolated in 75% yield on a 5 g scale. The relative configuration of the newly installed stereogenic center was verified by 2D NOESY experiments. Noteworthy, it turned out that the success of this reaction was highly dependent on the quality of the Et_3B solution employed since reliable results were only obtained by preparing a solution of Et_3B immediately prior to use from neat Et_3B and thoroughly degassed THF. While the mechanism of this reaction has been not illuminated thus far, a plausible catalytic cycle commences by the formation of Pd^{II} π-allyl complex **282** from allyl bromide and the active Pd^0 species. In the following, this intermediate **282** might undergo a transmetallation with potassium enoxyborate **285** generated previously. The resulting Pd-enolate could be described as η^1,η^3-complex **283** or the bis-η^1-complex **284**. The latter intermediate **284** was recently proposed by Morken and co-workers in a Pd-catalyzed allyl-allyl cross coupling of allylic boronates[190] and was proven *in silico* to be the active species for the enantioselective decarboxylative Tsuji allylation by Stoltz and Goodard.[191] Intermediate **284** could undergo a reductive 3,3'-elimination to furnish the desired product **280** and regenerate Pd^0. Alternatively, one could formulate a direct S_N2-type substitution of the enoxy boronate **285** on the η^1-bound complex **281**. Such a mechanism would presumably rather involve an outer-sphere nucleophilic attack as found for Pd-catalyzed allylations with stabilized enolates in the pioneering work of Helmchen.[192]

Having prepared substantial amounts of allylated hydrindane **280**, we examined a reduction of the ketone moiety. In the event, we found a reversal of diastereoselectivity depending on the reducing reagent employed (Scheme 3.7). Whereas exposure of ketone **280** to $NaBH_4$ at 0 °C delivered alcohol **286** in 79% yield, treatment of intermediate **280** with the bulky hydride donor K-Selectride® (**287**)[193] exclusively led to an equatorial attack to furnish α-diastereomer **288** in high yield. The structure of alcohol **286** was elucidated based on 2D NOESY experiments and careful analysis of coupling constants.



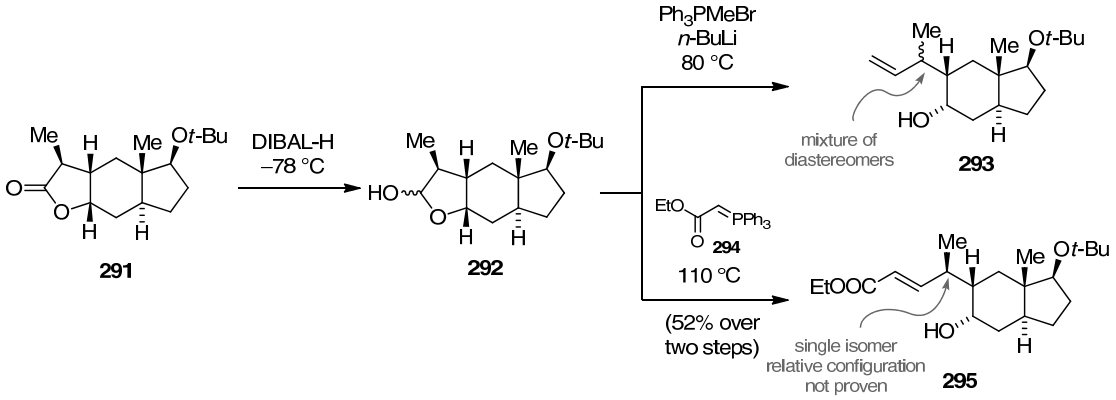
Scheme 3.7 Reagent controlled reduction of ketone **280** and preparation of lactone **290**.

In order to install the envisioned γ-lactone moiety, we subsequently sought to covert alkene **288** to the corresponding aldehyde by ozonolysis in a CH_2Cl_2/ROH solvent mixture. Unfortunately, under these reaction conditions, the intermediately generated lactol **289** was quantitatively converted to the corresponding acetals by reaction with the protic co-solvents EtOH or MeOH (not shown). As carrying out an ozonolysis in CH_2Cl_2 resulted with multiple unidentified side products, we next submitted alkene **288** to a Lemieux-Johnson oxidation employing a catalytic amount of OsO_4 in the presence of $NaIO_4$ and 2,6-lutidine and using 1,4-dioxane and H_2O as a solvent mixture.[194] These reaction conditions, essentially a dihydroxylation followed by diol cleavage in one pot, efficiently provided a diastereomeric mixture of lactol **289**, which was oxidized to the corresponding lactone **290** by treatment with PCC. Overall, this two-step protocol gave tricycle **290** in an excellent yield of 90% on a 3.6 g scale and the three-dimensional architecture was verified by key NOE correlations as shown in Scheme 3.7.



Scheme 3.8 (*a*) Diastereoselective synthesis of lactone **291** benefiting from the conformational bias of substrate **290**. (*b*) Structure elucidation of tricycle **291** by coupling constant analysis and X-ray diffraction.

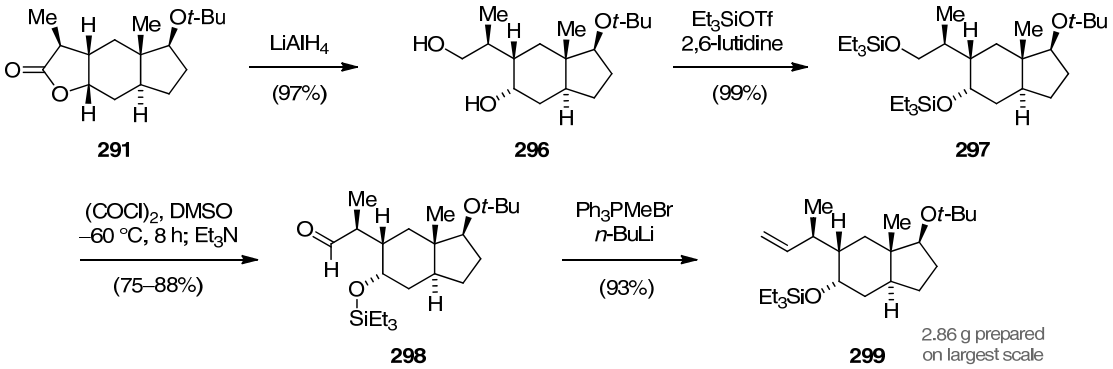
Next, the installation of the C-10 methyl residue was explored. For this purpose, deprotonation of lactone **290** with LiHMDS generated the lithium enolate, which in turn was intercepted with excess MeI.[195] As expected from the cyclic conformational bias of the substrate **290**, tricycle **291** was obtained as a single diastereomer in good yield. The desired stereochemical outcome of this reaction was initially elucidated by careful analysis of coupling constants. As shown in Scheme 3.8, the C-10 methine proton was observed as a quartet, originating from coupling with the three protons of the newly installed methyl residue. This observation indicated a dihedral angle $H_{10}–C_{10}–C_9–H_9$ of around 90°, resulting in a small coupling constant close to 0 Hz according to the Karplus curve.[196] DFT calculations performed by Dr. R. Webster in the Trauner Group revealed an dihedral angle of 87° for lactone **291**, which was in agreement with the observed spectroscopic data. Later on, we additionally established the structure of tricycle **291** unambiguously by X-ray crystallography.



Scheme 3.9 Attempts to effect a Wittig reaction on lactol **292**: synthesis of unsaturated ester **295**.

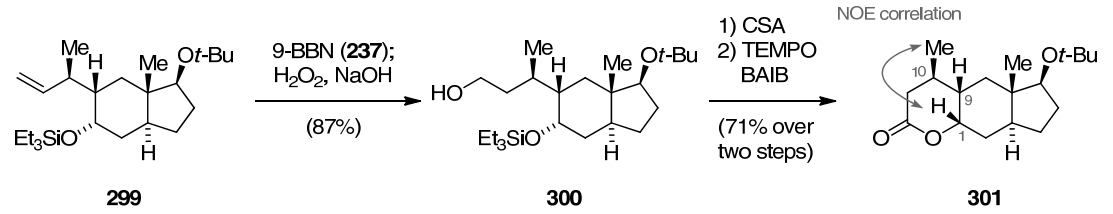
As outlined in our retrosynthetic analysis (*cf.* Chapter 3.2), the focus was now turned to the installation of an alkene moiety. To this end, we initially reduced lactone **291** to the corresponding lactol **292** by treatment with DIBAL-H at low temperature (Scheme 3.9). Thereafter, we envisioned to transform this intermediate **292** into secondary alcohol **293** by exposure to standard Wittig methylenation conditions, a process well precedent in literature.[197] In our hands however, this reaction proceeded only at elevated temperatures and provided alcohol **293** in traces as a mixture of diastereomers as indicated by ^{1}H NMR spectroscopy. In contrast, reaction with ylene **294** yielded a single diastereomer **295**, albeit in moderate yield even at prolonged reaction times (40 h) and 110 °C. Its relative stereochemistry at C-10 could not be assigned unambiguously.

With these results in mind, we decided to pursue another strategy and synthesized diol **296** by treatment with $LiAlH_4$ in excellent yield (Scheme 3.10). In order to avoid an orthogonal protecting group strategy to distinguish the two free alcohol functionalities present in bicycle **296**, we exploited the potential of Swern oxidation conditions to convert primary TES ethers directly to aldehydes.[198] To this end, we accessed intermediate **297** by double silylation of diol **296** with Et_3SiOTf and investigated the subsequent Swern oxidation.



Scheme 3.10 Synthesis of building block **299** *via* deprotective Swern oxidation.

We found that a careful control of the external temperature not exceeding −60 °C and prolonged reaction times (7–8 h) were crucial for a success of the reaction since otherwise lower yields and/or the bisoxidized carbonyl compound were observed (not shown). Under the optimized reaction conditions, aldehyde **298** was obtained in 88% yield on a 1.48 g scale as a single diastereomer, not indicating any epimerization at the α-stereogenic center by NMR spectroscopy. While scaling to 5.31 g of bissilyl ether **297**, the yield decreased (75%) and remaining starting material **297** was recovered (8%). Therefore, the reaction times should be further extended in future experiments on this or any larger scale. Ultimately, a Wittig methylenation converted aldehyde **298** to alkene **299** in a high yield of 93%. On the largest scale, 2.86 g of this valuable intermediate **299** have been prepared, which served as the branching point for several routes toward constructing the strained 11-membered ring (*cf.* Chapters 3.4–3.7).

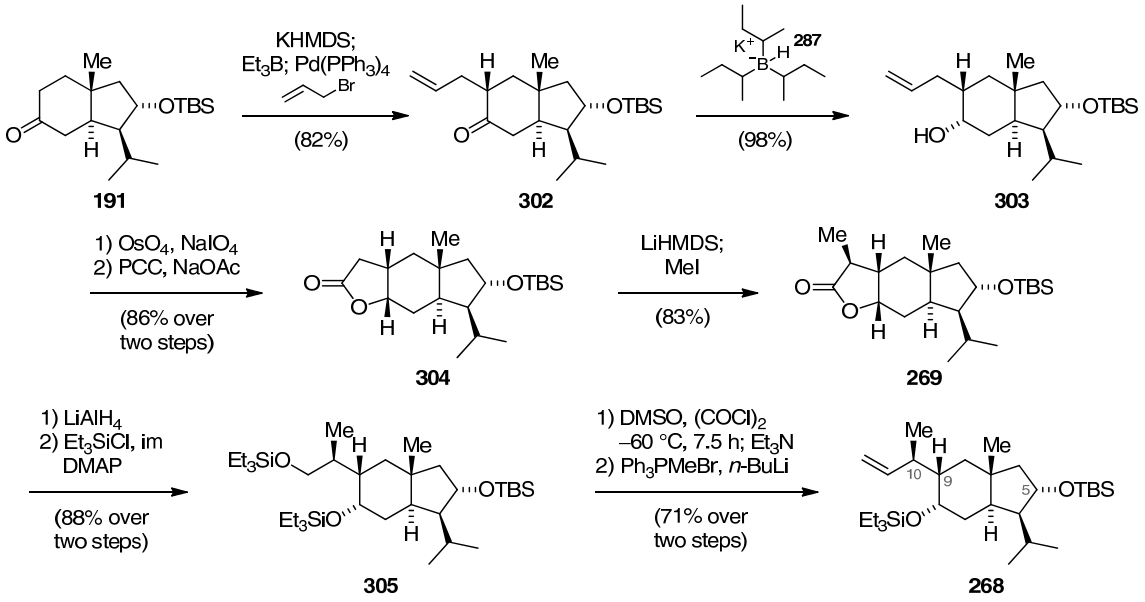


Scheme 3.11 Conversion of alkene **299** to tricyclic lactone **301**.

In order to provide additional proof for the relative stereochemistry at C-10, the alkene moiety present in *trans*-hydrindane **299** was subjected to hydroboration conditions with 9-BBN (**237**) and subsequent oxidative work up gave rise to primary alcohol **300** (Scheme 3.11). Upon CSA mediated silyl ether cleavage, the resulting diol (not shown) was further elaborated to lactone **301** by a TEMPO/BAIB oxidation.[199] Unfortunately, the proton signals at C-9 and C-10 (astellatol numbering) possess the same shifts in the ^{1}H NMR spectrum in $CDCl_3$, but a NOE correlation between the C-10 methyl group and the C-1 methine indicated that no epimerization took place during $LiAlH_4$ reduction, Swern oxidation and Wittig olefination.

Having established an efficient and scalable route to alkene **299**, we set out to adapt the reaction conditions to *trans*-hydrindane building block **191** with the correct substitution pattern on the five-membered ring in place. Thus, we submitted ketone **191** to the allylation conditions established

previously and isolated the desired product **302** in 82% yield as a single diastereomer (Scheme 3.12). Subsequently, exposure of ketone **302** to K-Selectride® (**287**) gave rise to secondary alcohol **303**, which in turn set the stage for the Lemieux-Johnson oxidation. After some optimization, this reaction proceeded smoothly and we accomplished the synthesis of tricycle **304** after PCC oxidation in 86% yield over the two steps.

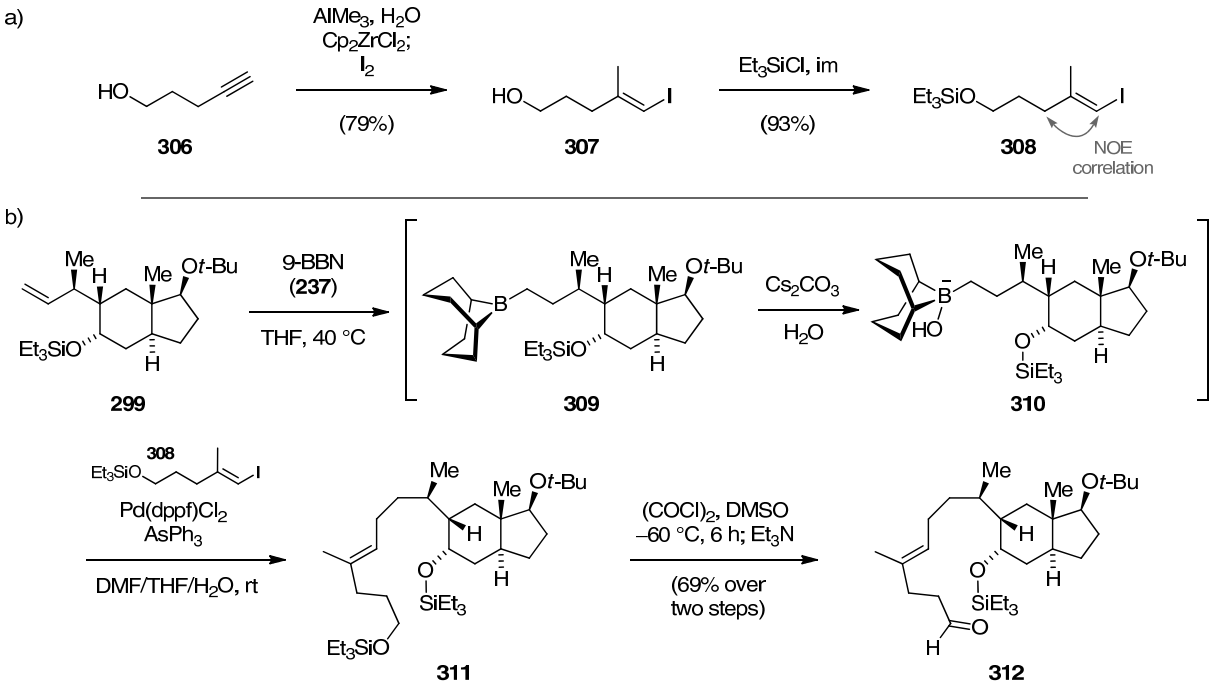


Scheme 3.12 Application of reaction conditions from the model studies: synthesis of building block **268**.

Compared to the model system, the subsequent diastereoselective methylation required a slightly higher reaction temperature of –40 °C in order to achieve full conversion, leading cleanly to the formation of lactone **269** in 83% yield (Scheme 3.12). In analogy to the preparation of alkene **299**, this intermediate **269** was next reduced with $LiAlH_4$ and the generated corresponding diol (not shown) was immediately used in the following reaction. This was due to the acid sensitivity of the diol that became apparent by partial cleavage of the secondary TBS ether *e.g.* in the NMR solvent $CDCl_3$ despite previous neutralization by filtering over basic alumina. Nevertheless, subsequent silylation with Et_3SiCl gave access to bicycle **305** in 88% yield over the two steps. At last, deprotective Swern oxidation and Wittig methylenation completed the preparation of alkene **268** on a largest scale of 80 mg. In initial experiments, we already found that a selective cleavage of the TES ether in bicycle **268** under acidic conditions (*e.g.* CSA or PPTS in CH_2Cl_2/MeOH) will require careful control of the reaction times to avoid a concomitant cleavage of the sterically more demanding TBS ether (not shown). In future experiments, a thorough screening of reagents and reaction conditions should be investigated since both secondary alcohols need to be distinguished by orthogonal protecting groups in the further course of the synthetic studies toward astellatol (**103**). Alternatively, a more robust protecting group such as TBDPS, TIPS, SEM or MOM at the C-5 hydroxyl group (astellatol numbering) should be introduced before conducting the reaction sequence presented in this chapter. With the correct relative stereochemistry at C-9 and C-10 installed, the preparation of the strained 11-membered ring for the envisioned biomimetic cationic cascade was now focused on.

3.4 Toward Constructing the Macrocycle: The Metathesis Approach

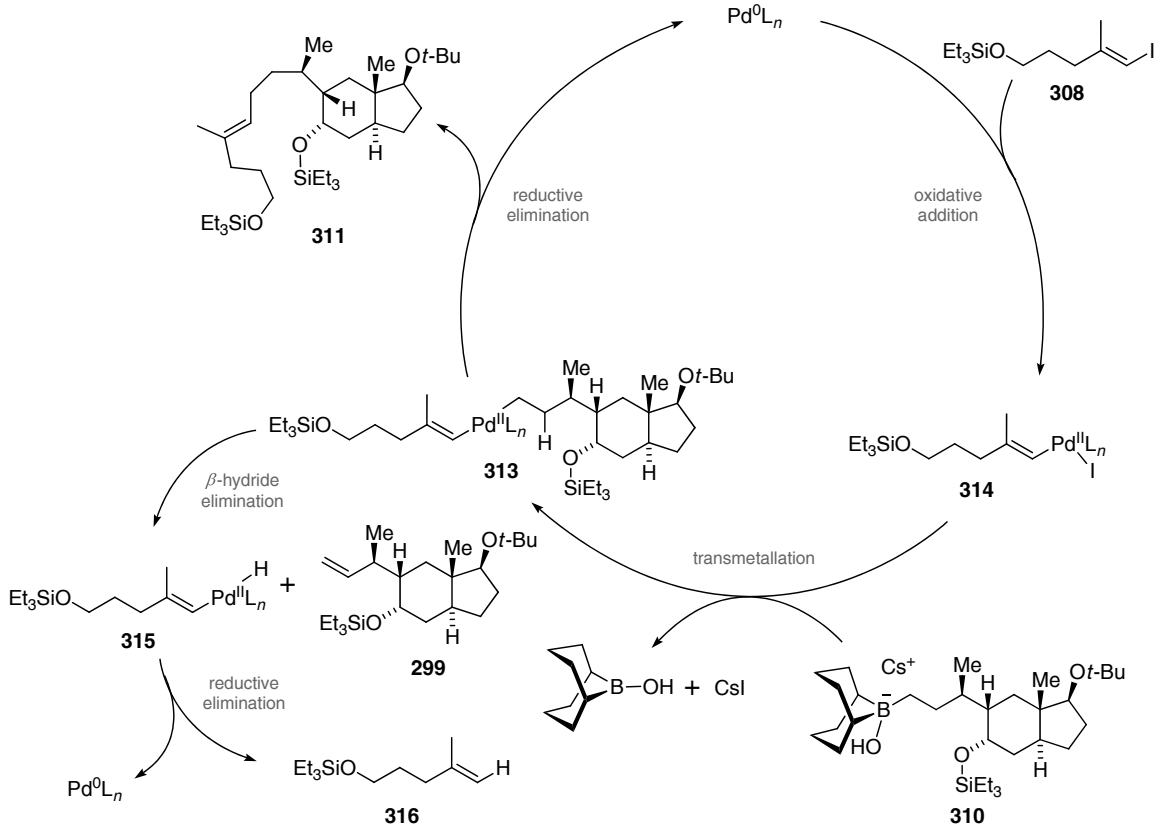
As pointed out earlier, our studies toward the construction of the 11-membered macrocycle were carried out on a model system (*cf.* Chapter 3.2). Since we had prepared substantial quantities of alkene **299**, our route toward the precursor for a RCM macrocyclization commenced with the synthesis of an appropriate vinyl iodide for a Pd-catalyzed B-alkyl Suzuki coupling.[181] To this end, commercially available alkyne **306** was subjected to Negishi carboalumination conditions following a protocol by Floreancig and co-workers (Scheme 3.12).[200] Thereby, alkyne **306** was reacted with $AlMe_3$ in the presence of catalytic amounts of Cp_2ZrCl_2 and 1.0 equivalent of H_2O, both being known to facilitate the desired transformation.[201,202] Following *syn*-selective carboalumination, the intermediate organoaluminum species (not shown) was next intercepted with I_2 to yield vinyl iodide **307** under retention of the alkene geometry. Subsequently, silylation of the free alcohol under standard reaction conditions gave rise to coupling partner **308**, the (*E*)-configuration of which was verified by NOE spectroscopy.



Scheme 3.13 (*a*) Two-step synthesis of vinyl iodide **308** by a Negishi carbalumination strategy. (*b*) Fragment coupling of alkene **299** and vinyl iodide **308** *via* a B-alkyl Suzuki coupling and synthesis of aldehyde **312**.

With both reaction partners in hand, efforts toward the fragment coupling were undertaken (Scheme 3.13). As a guide we considered the previous studies on the hydroboration of alkene **299** with 9-BBN (**237**). It was established that this reaction occurs best while heating the unsaturated intermediate **299** with hydroboration agent **237** to 40 °C for 3 h (*cf.* Chapter 3.3). Using these conditions, we generated the corresponding alkyl-boron species **309**, which was subsequently treated with aqueous Cs_2CO_3 solution to form the corresponding boronate **310**. This intermediate was then combined with vinyl iodide **308** in the presence of catalytic amounts of $Pd(dppf)Cl_2$ and $AsPh_3$ as

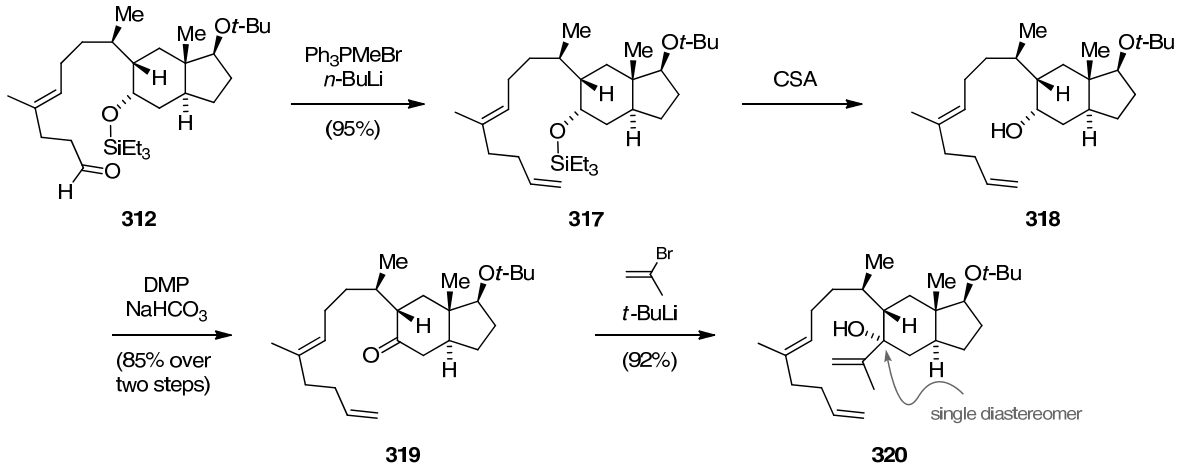
an additional ligand in a THF/DMF/H_2O mixture.[203] The desired coupling occurred smoothly and provided trisubstituted alkene **311**, which could not be entirely purified at this stage. Nevertheless, bissilyl ether **311** was submitted to the previously established deprotective Swern oxidation conditions (*cf.* Chapter 3.3) furnishing aldehyde **312** in a good yield of 69% over the two steps. This sequence demonstrated the robustness and generality of B-alkyl Suzuki couplings, which has led to widespread applications in organic synthesis,[181] *e.g.* evidenced by the large scale synthesis of discodermolide performed at Novartis.[204]



Scheme 3.14 Catalytic cycle of for the Pd-catalyzed B-alkyl Suzuki coupling.

Mechanistically,[181] this reaction proceeds *via* a standard catalytic cycle of a Pd-mediated cross coupling and commences with the oxidative addition of Pd^0 into the C–I bond of alkene **308** to furnish Pd^{II}-complex **314** (Scheme 3.14). An ensuing transmetallation with the previously generated boronate **310** delivers intermediate **313** and sets the stage for a final reductive elimination to afford the coupled product **311** under regeneration of the catalytically active Pd^0 species. The ligand dppf was employed in this process due to its large bite angle since this ligand scaffold has previously been shown to suppress β-hydride eliminations in cross coupling reactions.[205] Additionally, ligands with larger bite angles have proven to accelerate reductive eliminations. The choice of the ligand thus allows for the Pd-catalyzed coupling of aliphatic organometallic reagents, which is usually complicated by competing hydride elimination processes. This mechanistic route would first result in the formation of alkene **299** and H–Pd^{II} species **315** that in turn would instantly regenerate catalytically active Pd^0 and the protodeiodinated coupling partner **316**. Moreover, the use of $AsPh_3$ as

an additive has been shown to provide cleaner reactions at higher turnover rates by Johnson[206] and is since then frequently used in B-alkyl Suzuki couplings.

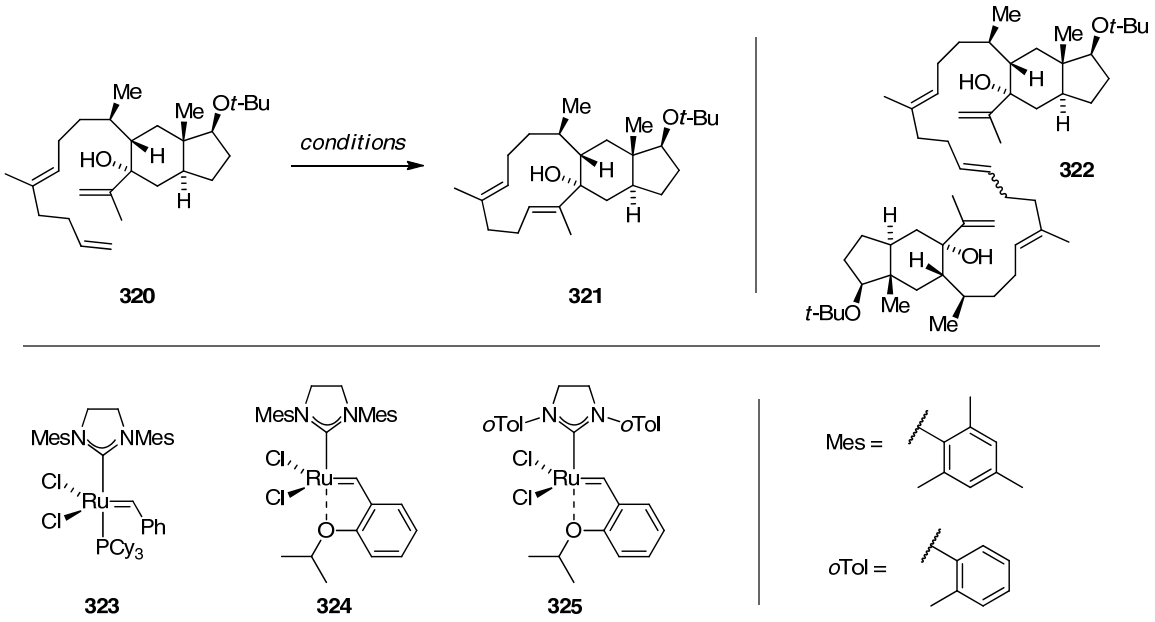


Scheme 3.15 Efficient preparation of RCM precursor **320**.

In order to complete the synthesis of the model RCM precursor **320**, the aldehyde functionality in bicycle **312** was converted to an alkene *via* a Wittig reaction giving rise to diene **317** in high yield (Scheme 3.15). Next, the silyl ether within *trans*-hydrindane **317** was cleaved and the resulting secondary alcohol **318** was oxidized with Dess-Martin periodinane (DMP)[207,208] under buffered reaction conditions. By this two-step sequence, ketone **319** was efficiently accessed in 85% yield. All remaining was the installation of an isopropylene moiety that was realized by addition of a vinyl lithium species generated *in situ* from 2-bromopropene and *t*-BuLi at −78 °C. The desired transformation was surprisingly high yielding (92%) given the steric encumbrance at the carbonyl functionality, and furnished tertiary alcohol **320** as single diastereomer. The relative configuration at the newly formed stereogenic center could not be assigned unambiguously at this stage, but we assumed an equatorial attack due to the shielding effect of the adjacent substituent, blocking an axial attack from the *si*-face. It should be noted that the relative configuration was inconsequential for the further synthesis as the tertiary alcohol would serve as the precursor for the generation of a carbocation to trigger the envisaged cationic cascade (*cf.* Chapter 3.2).

Next, we embarked on the investigation of the key RCM metathesis. Although, the power of this synthetic tool has been increasing over the years, there is only little precedence reported for the preparation of 11-membered rings.[209] This fact is especially true for the synthesis of trisubstituted alkenes, thus underlining the challenges associated with the envisaged ring closure. Following a report by Fujii and co-workers,[210] we initially tested the use of Grubbs 2nd generation catalyst (**323**) in refluxing CH_2Cl_2 (Table 3.1, Entry 1). This and the following reactions were performed at high dilution (0.004M) to disfavor intermolecular reactions. These conditions led to the formation of a new product, which was not the desired tricycle **321**, but rather the homocoupled dimer **322** as an undetermined mixture of the (*E*)- and (*Z*)-isomers.

Table 3.1 Toward a RCM macrocyclization: variation of reaction conditions.[a]



Entry	Catalyst [mol-%]	Solvent	*T* [°C]	*t* [h]	Observation
1	**323** (20)	CH_2Cl_2	40	6	Dimer **322**
2[b]	**323** (30)	benzene	81	16	Dimer **322**
3[b]	**324** (10)	DCE	83	19	Dimer **322**
4[b,c]	**323** (20)	PhMe	110	24	s.m.
5[b]	**323** (30)	PhMe	110	72	Dimer **322**
6[b]	**325** (40)	benzene	81	40	Dimer **322**

(*a*) All reactions were carried out on 5 mg scale in degassed solvents (3 x freeze-pump-thaw). (*b*) The substrate was added to a refluxing solution of the employed catalyst (0.2 mM) within 2–4 h using a syringe-pump. (*c*) The reaction was carried out with *para*-benzoquinone (30 mol-%) as additive. s.m. = starting material.

This product **322** was indentified by ESI mass spectrometry and ^{1}H NMR and HSQC spectroscopy. The ^{1}H NMR spectrum clearly showed the consumption of the terminal alkene by the disappearance of the respective ^{1}H NMR signals (ddt at δ = 5.81 ppm and centrosymmetric multiplets at δ = 5.01 and 4.94 ppm). At the same time, a new signal at δ = 5.39 and 5.34 ppm for the (*E*)- and (*Z*)-isomer appeared. In addition, the characteristic signals for the isopropylene moiety at δ = 5.09 and 4.88 ppm remained unchanged. (Figure 3.1). We assumed that this outcome might be attributed to a high activation barrier for the formation of the strained macrocycle and thus changed the solvent to the higher boiling benzene (Table 3.1, Entry 2). Furthermore, the dilution was increased by slowly adding a solution of substrate **320** to catalyst **323**. However, this procedure did not provide any new reaction product as indicated by ^{1}H NMR spectroscopy.

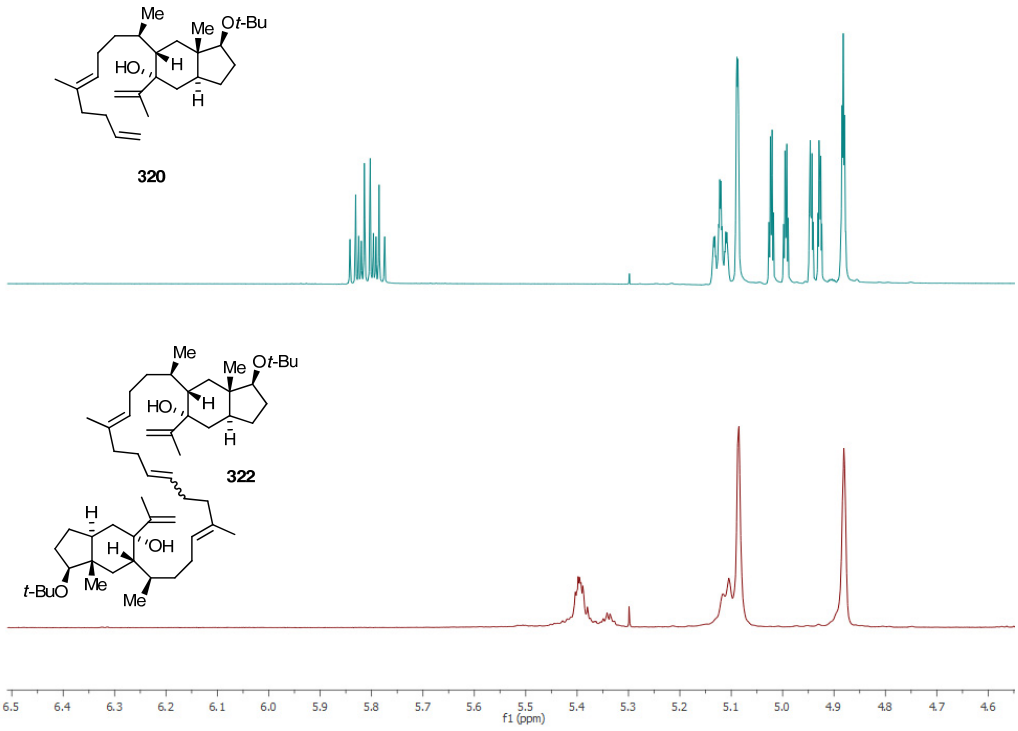


Figure 3.1 Comparison of ^{1}H NMR spectra (both recorded at 600 MHz in $CDCl_3$) of substrate **320** and obtained homocoupled dimer **322**.

We next examined the use of the Grubbs-Hoveyda 2nd generation catalyst (**324**) in refluxing 1,2-dichloroethane (DCE), a solvent that has been shown to avoid decomposition of the catalyst at elevated temperatures (Table 3.1, Entry 3).[211] While following this protocol, we could again only observe the homocoupled dimer **322** and we therefore resorted to toluene as an ever higher boiling solvent. In this experiment, we used catalyst **323** and added *p*-benzoquinone to the reaction mixture, which has been shown to suppress Ru-catalyzed alkene isomerisation processes.[212] Interestingly, these reaction conditions resulted mainly in the reisolation of starting material **320**, even when using 20 mol-% catalyst loading and prolonged reaction times (Entry 4). Next, we repeated the experiment without the additive and after 72 h, only the formation of dimer **322** was observed (Entry 5). In an additional experiment, we examined the reactivity of the Stewart-Grubbs catalyst **325**. This Ru-complex **325** was developed for sterically demanding substrates and has been efficiently utilized for the cross metathesis of hindered allylic alcohols[213] and the construction of tri- and even tetrasubstituted alkenes by RCM.[214] Unfortunately, exposure of substrate **320** to catalyst **325** again resulted in the formation of dimer **322** (Entry 6) and we thus focused on other strategies to assemble the strained 11-membered ring in the following.

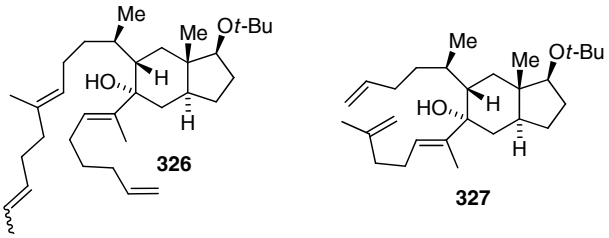
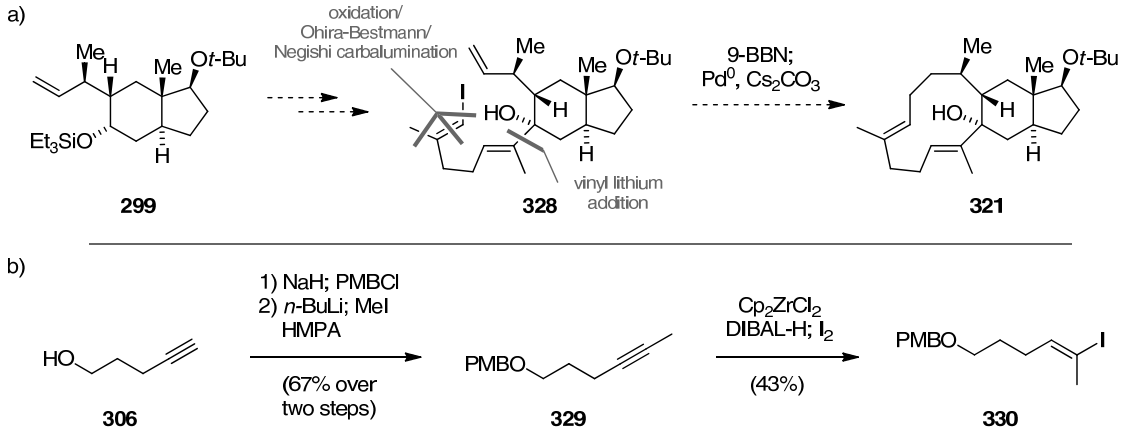


Figure 3.2 Potential substrates for future RCM strategies.

Ultimately, it should be stated that is worth revisiting the RCM strategy and examine other catalysts such as the Mo-based ones reported by Schrock and co-workers.[215] In addition, one reason for the so far unsuccessful attempts could be the encumbered reaction site at the isopropylene residue since metathesis reaction are often highly sensitive to the steric environment. Thus, one possibility for further investigations following this strategy could involve a relay metathesis, first introduced by Hoye[216] and recently applied several times for the construction of ring systems in natural product synthesis.[217] Such a process would involve the synthesis of tetraene **326** (Figure 3.2). Alternatively, one could envisage relocating the reaction sites for the RCM with triene **327**, in which the terminal alkene and the isopropylene moiety are embedded in a sterically less demanding setting.

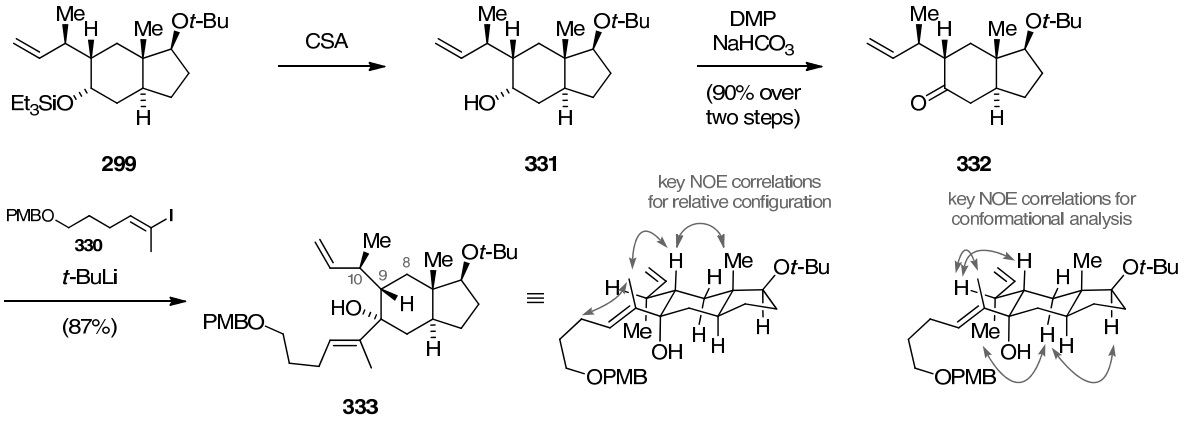
3.5 Toward Constructing the Macrocycle: The B-Alkyl Suzuki Approach

In addition to the RCM approach described in the previous chapter, three further strategies toward the total synthesis of astellatol (**103**) were investigated in the course of this Ph.D. thesis, all starting from the versatile building block **299**. One of these routes involved an intramolecular B-alkyl Suzuki coupling of alkene **328** to close the 11-membered macrocycle in tricycle **321** for the envisioned bioinspired cationic cascade (Scheme 3.16). As discussed, the B-alkyl Suzuki reaction is frequently employed in organic synthesis[181] and it has been utilized by several research groups to access strained medium-sized rings.[218]



Scheme 3.16 (*a*) Envisaged route toward tricycle **321** *via* a B-alkyl Suzuki macrocyclization. (*b*) Three-step synthesis of vinyl iodide **330**.

From a retrosynthetic point of view, we envisaged to accomplish the synthesis of cyclization precursor **328** *via* addition of a vinyl lithium species to a ketone and a subsequent elaboration of a primary alcohol functionality to vinyl iodide **328** by a Negishi carboalumination. Thus, this strategy would allow for the stereospecific installation of the double bond geometries found in triene **328**. In order to access the desired substrate **328**, we initially prepared a C_6-building block following a procedure by Zakarian and co-workers as outlined in Scheme 3.16.[219] The sequence commenced with the protection of the alcohol functionality in alkyne **306** as its PMB ether (not shown). Generation of the resulting alkynyl lithium species by exposure to *n*-BuLi was followed by reaction with excess MeI to afford alkyne **329**. Notably, this reaction required the addition of HMPA to proceed in completion. Otherwise, a mixture of starting material and the desired product **329** was obtained, which was inseparable by flash column chromatography. Next, alkyne **329** was subjected to hydrozirconation conditions, which are known to result in good regioselectivity for methyl substituted internal alkynes. To this end, treatment of intermediate **329** with Schwartz's reagent $Cp_2Zr(Cl)H$[220] generated *in situ* from Cp_2ZrCl_2 and DIBAL-H and subsequent stereospecific iododezirconation afforded vinyl iodide **330** as an approximately 10:1 mixture of regioisomers as determined by ^1H NMR spectroscopy. Careful flash column chromatography allowed for the isolation of pure fragment **330**, albeit in a modest yield of 43%.

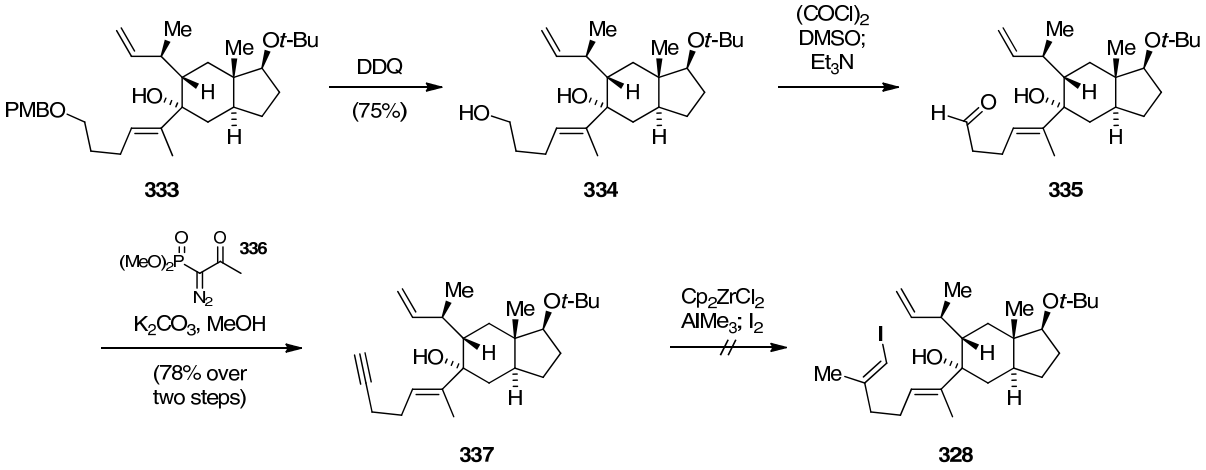


Scheme 3.17 Synthesis of tertiary alcohol **333** and its preferred conformation based on NOE spectroscopy and coupling constant analysis.

With vinyl iodide **330** in hand, we next deprotected the silylated secondary alcohol functionality in bicycle **299** under acidic conditions and the resulting alcohol **331** was oxidized by DMP[207] to provide ketone **332** in 90% yield over the two steps (Scheme 3.17). Thereafter, both fragments were coupled. To this end, a halogen-lithium exchange of vinyl iodide **330** with *t*-BuLi provided the corresponding organo lithium species, which cleanly reacted with ketone **332** at −78 °C to afford allylic alcohol **333** as a single diastereomer. The outcome of this reaction was verified by key NOE correlations as shown in Scheme 3.17. Moreover, careful analysis of the spectroscopic data revealed the preferred conformation of the stereogenic center at C-10. Based on the lacking NOE signal between 10-H and 9–H, both groups could potentially point into opposite directions. This assumption was further

supported by the scalar coupling of the C-9 methine (ddd at δ = 1.86 ppm with J = 12.7, 3.7 and 2.3 Hz). While the first two values could be identified to an axial-axial coupling and an axial-equatorial coupling within the six-membered ring (to 8-H), the remaining coupling constant of J = 2.3 Hz accounts for the coupling of 10-H. Thus, this value indicates a dihedral angle of around 67° according to the Karplus curve.[221] Consequently, this observation suggested that a rotation around the C_9–C_{10} bond would be required for an efficient ring closure, thus constituting an important factor for the activation barrier.

Having combined the two fragments, we next focused on the transformation of the PMB ether in *trans*-hydrindane **333** to an alkyne moiety, the precursor for the installation of the required vinyl iodide. For this purpose, the PMB ether was cleaved under oxidative reaction conditions using DDQ and the resulting diol **334** was smoothly oxidized under Swern conditions[222] to furnish aldehyde **335** (Scheme 3.18). In contrast to this protocol, the latter transformation occurred only at elevated temperature and in the presence of a large excess of oxidation agent when using DMP.

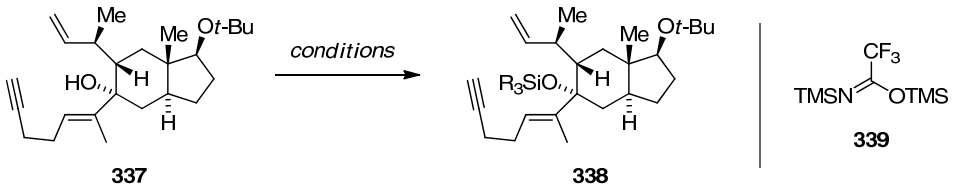


Scheme 3.18 Three-step sequence from PMB ether **333** to alkyne **337** and attempted Negishi carbalumination.

Next, the crude intermediate **335** was homologated using the Ohira-Bestmann reagent (**336**)[223] that generates the Gilbert-Seyferth reagent[224] *in situ* by a retro aldol reaction of β-keto phosphonate **335** with KOMe. This three-step sequence efficiently provided access to alkyne **337**, which in turn was subjected to Negishi carboalumination conditions. Unfortunately, consecutive exposure of alkyne **337** to $Cp_2ZrCl_2/AlMe_3$ and I_2 led to decomposition of the starting material, although there has been literature precedence for the exploitation of this methodology in complex settings.[225] Due to this observation, we resorted to an alternative four-step protocol for the preparation of the requisite vinyl iodide **328**, which involved a regioselective Pd-catalyzed silylstannylation of the terminal alkyne moiety present in tertiary alcohol **337**. This methodology was first reported by Chenard at DuPont[226] and has been successfully applied in natural product synthesis.[227] In addition, the research group of RajanBabu has expanded the scope of this catalytic procedure,[228] thereby demonstrating that free alcohol functionalities poison the catalyst and thus lower the efficiency of the process. Therefore, we initially set out to silylate alcohol **337**. As we were aware of the fact that the alkyne moiety is prone to

be deprotonated, we avoided the use of strong bases such as KHMDS, LDA or *n*-BuLi and examined other protocols as presented in Table 3.2.

Table 3.2 Attempted silylation of alcohol **337**: variation of reaction conditions.[a]

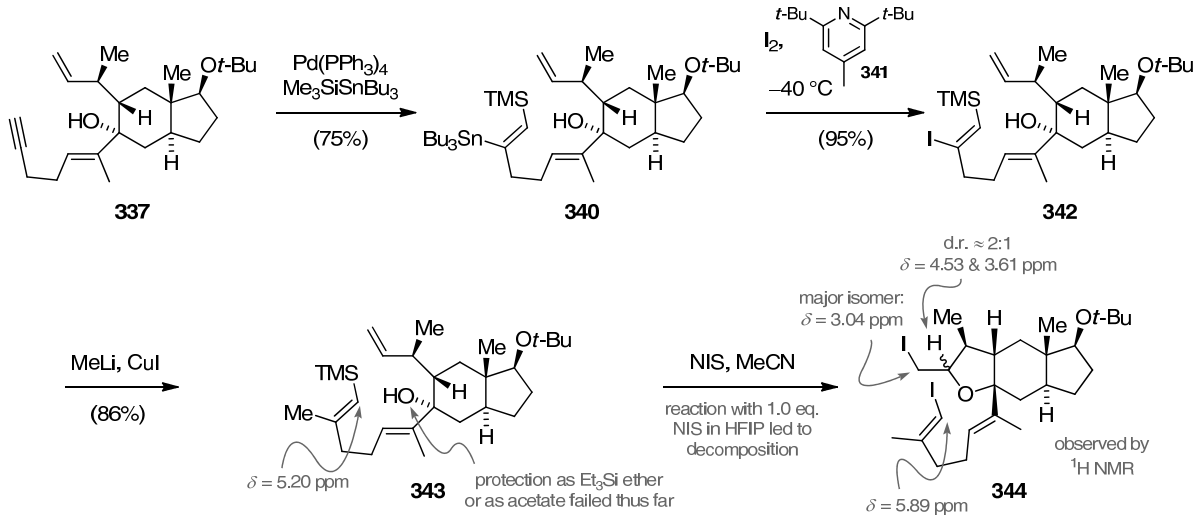


337 **338** **339**

Entry	Silylation Agent	Base/additive	Solvent	*T* [°C]	*t* [h]	Observation
1	TMSOTf	2,6-lutidine	CH_2Cl_2	0 to 40	5	s.m.
2	Et_3SiCl	DMAP	pyridine	90	20	s.m.
3	**339**	-	DMF	rt	16	s.m.

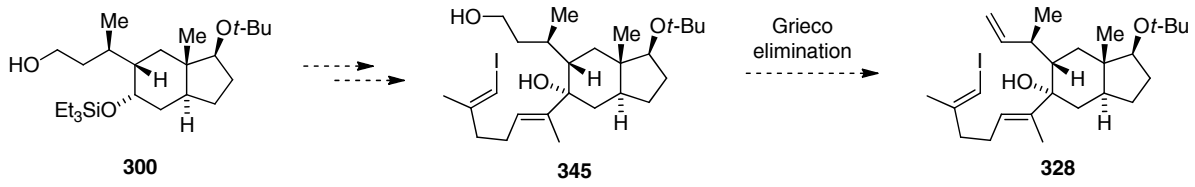
(*a*) All reactions were carried out on 5 mg scale with excess silylation agent (3–10 eq.). s.m. = starting material, rt = room temperature.

However, neither using TMSOTf/2,6-lutidine in boiling CH_2Cl_2 (Table 3.2, Entry 1)[229] nor Et_3SiCl/DMAP in pyridine[230] at 90 °C (Entry 2) effected the desired transformation to a silyl ether **338**. As even subjection of alcohol **337** to the highly reactive silylation agent BSTFA (**339**) in DMF[231] resulted in reisolation of starting material (Entry 3), we reasoned that the alcohol functionality in alkyne **337** might be sterically so inaccessible that it would not thwart the Pd-catalysis. Thus, we exposed alkyne **337** to a catalytic amount of $Pd(PPh_3)_4$ and excess $Me_3SiSnBu_3$ in refluxing THF following a procedure by Williams (Scheme 3.19).[232] Gratifyingly, these conditions resulted in the formation of vinyl stannane **340** as a single regioisomer in 75% yield and we verified the diastereoselective outcome by HMBC and NOE spectroscopy. It should be mentioned that the reasons for this selectivity have not been clarified in the literature to date to the best of our knowledge.



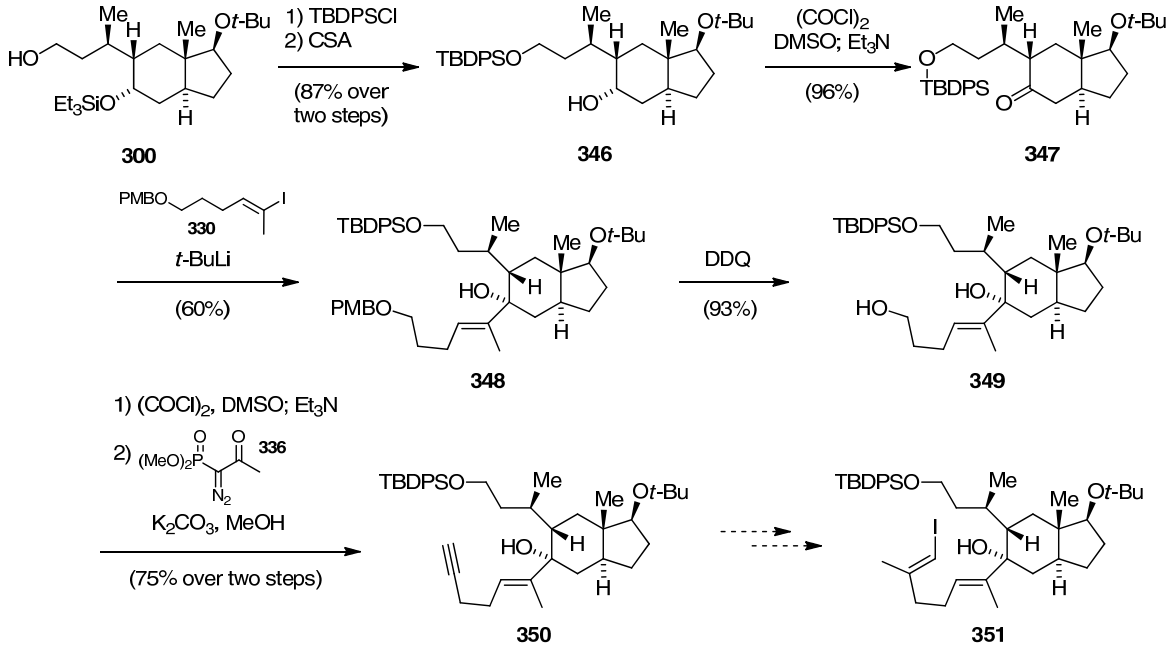
Scheme 3.19 Toward the installation of a vinyl iodide: synthesis of vinyl silane **343** *via* regioselective silylstannylation.

With the addition product **340** in hand, we embarked on the installation of the trisubstituted alkene moiety. To this end, intermediate **340** engaged in a chemoselective iododestannylation by treatment with 1.0 equivalent of I_2 at −40 °C in the presence of the bulky pyridine derivative **341**[232] to furnish vinyl iodide **342** in high yield. A subsequent cuprate coupling afforded vinyl silane **343**, at which point we established the (*E*)-double bond geometry by NOESY experiments once more. Notably, triene **343** contained all carbon atoms required for the construction of the pentacyclic backbone of astellatol (**103**), only missing the correct substitution pattern at the cyclopentane portion. The iododesilylation of vinyl silane **343** remained to be studied in order to access macrocyclization precursor **328**. Hence, we treated vinyl silane **343** with excess NIS (≈ 2.5 equivalents) in MeCN[232] and observed the formation of a new product. Upon isolation, ^{1}H NMR spectroscopy revealed that the iododesilylation took place as indicated by a downfield shift of the vinyl proton from δ = 5.20 ppm to δ = 5.89 ppm. Unfortunately, the reaction conditions presumably also caused an iodoetherification as proton signals at δ = 4.53 and 3.61 ppm were observed, which could belong to protons attached to a heteroatom. In addition, the characteristic protons signals for a terminal vinyl group disappeared and we thus tentatively assigned the structure of the new compound as tricycle **344**. While the use of excess NIS in MeCN is usually required for the iododesilylation to secure retention of the double bond geometry,[233] Zakarian has shown that the use of 1,1,1,3,3,3-hexafluoro-2-pronanol (HFIP) as solvent allows to lower the amount of NIS to stoichiometric quantities.[234] Unfortunately, this protocol resulted in decomposition of vinyl silane **343** in our hands. In light of the observation of side product **344**, we rationalized that a protection of the alcohol functionality might avoid the intramolecular cyclization, but the examined conditions (KHMDS, Et_3SiCl or Ac_2O, py, 90 °C) did not meet with success. Due to material constraints, no further investigations could be undertaken at this stage. Thus, this strategy should be reexamined with larger quantities of vinyl silane **343** in order to perform at thorough screening for the protection of the alcohol functionality and to test other iododesilylation conditions.



Scheme 3.20 Revised strategy to vinyl iodide **328** involving a late-stage alkene installation.

An alternative solution for the above presented problem of the undesired etherification could be a late-stage installation of the terminal alkene in cyclization precursor **328**. This aim could be achieved by a Grieco elimination[235] from the corresponding primary alcohol **345** (Scheme 3.20) since protocols for this transformation in the presence of a sensitive vinyl iodide moiety are known.[236] Bicycle **345** in turn should be accessible from previously prepared alcohol **300** based on our earlier explorations (*vide supra*).

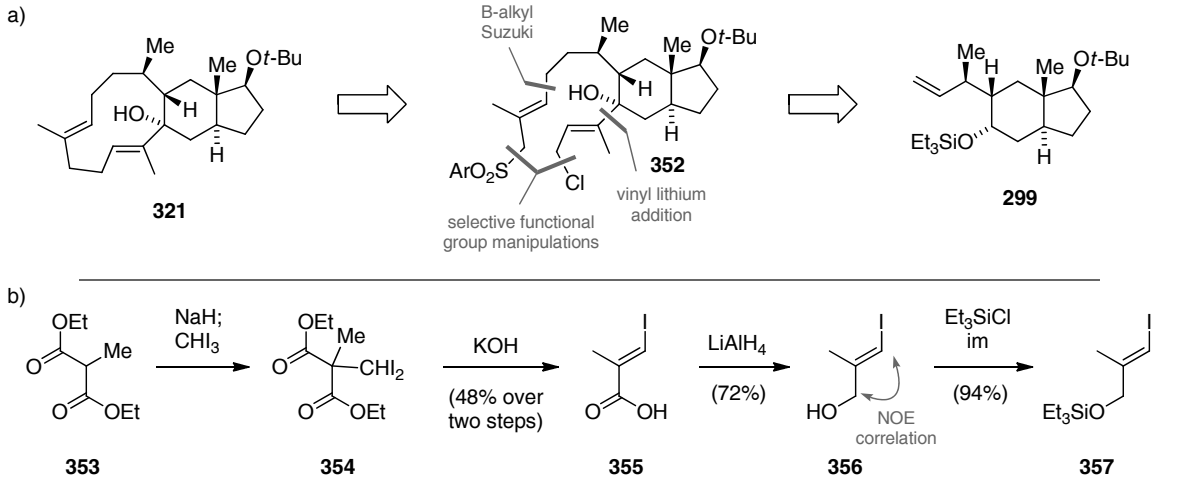


Scheme 3.21 Progress toward the preparation of vinyl iodide **351**: a seven-step synthesis of alkyne **350**.

In order to examine this route, alcohol **300** (*cf.* Chapter 3.3) was converted to its TBDPS ether (not shown) and a chemoselective desilylation under acidic conditions provided secondary alcohol **346** in 87% yield (Scheme 3.21). Following Swern oxidation[222] to afford ketone **347**, the two fragments **347** and **330** were coupled as previously established. Thus, exposure of *trans*-hydrindane **347** to an organo lithium species generated from vinyl iodide **330** furnished allylic alcohol **348** in a moderate yield of 60%. Next, cleavage of the PMB ether with DDQ provided access to diol **349**, which in turn was elaborated to alkyne **350** by sequential Swern oxidation[222] and Ohira-Bestmann homologation.[223] The following steps toward vinyl iodide **351** and cyclization precursor **328** have not yet been explored and should be addressed in future efforts.

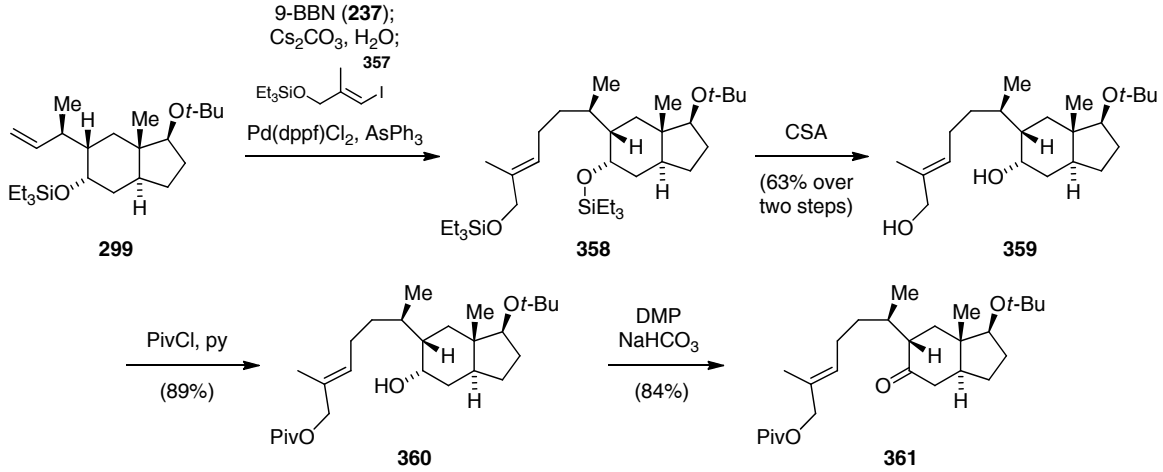
3.6 Toward Constructing the Macrocycle: The Allylation Approach

In parallel to the two approaches detailed in the previous subchapters, we explored a third strategy to close the strained 11-membered macrocycle in alcohol **321**. This route hinged on an intramolecular allylation of sulfone **352** and a subsequent desulfurization based on a report by Yamada,[237] who successfully accessed dolabellane marine diterpenoids[177] with this strategy (Scheme 3.22). Allyl sulfone **352** should again arise from alkene **299** by sequential B-alkyl Suzuki coupling, vinyl lithium addition to a cyclohexanone moiety and selective manipulation of functional groups. For this purpose, we first prepared an appropriate vinyl iodide fragment **357** suitable for the installation of a trisubstituted alkene by B-alkyl Suzuki coupling. The synthesis started from malonate **353**, which was alkylated with iodoform to yield diester **354** on multigram scale according to a procedure by Menche and co-workers (Scheme 3.22).[238]



Scheme 3.22 (*a*) Envisaged strategy to close the strained 11-membered ring *via* an intramolecular allylation. (*b*) Synthesis of vinyl iodide **357** starting from malonate **353**.

This intermediate **354** underwent then saponification with concomitant decarboxylative elimination in the presence of KOH in a refluxing 3:1 mixture of EtOH and H_2O. An ensuing reduction of the resulting carboxylic acid **355** with $LiAlH_4$ gave rise to vinyl iodide **356** with (*E*)-alkene geometry, which was verified by NOE spectroscopy and matched the data reported by Menche.[238] Ultimately, a silylation provided a convenient access to silyl ether **357** in four steps.

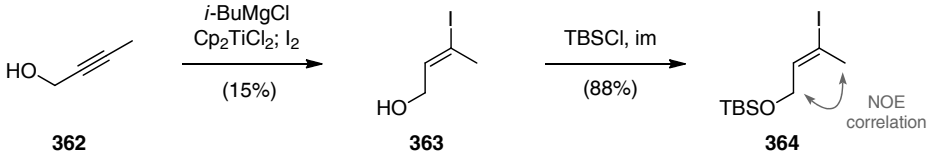


Scheme 3.23 Fragment union of alkene **299** and vinyl iodide **357** and synthesis of ketone **361**.

Having prepared substantial quantities of vinyl iodide **357**, the Pd-catalyzed coupling with the boron species derived from alkene **299** and 9-BBN (**237**) was explored. This reaction occurred smoothly and delivered *trans*-hydrindane **358** that in turn was globally desilylated to provide diol **359** in 63% overall yield (Scheme 3.23). A protection of the primary alcohol as its pivalate **360** differentiated between the two alcohol functionalities and the remaining secondary alcohol was next oxidized with DMP[207] accomplishing the synthesis of ketone **361**.

In the following investigations, the preparation of a second vinyl iodide building block was center stage. For this purpose, we took advantage of a protocol originally developed by Sato[239] and recently applied by Paterson and co-workers.[240] Therein, alkyne **362** was exposed to *i*-BuMgCl in the presence

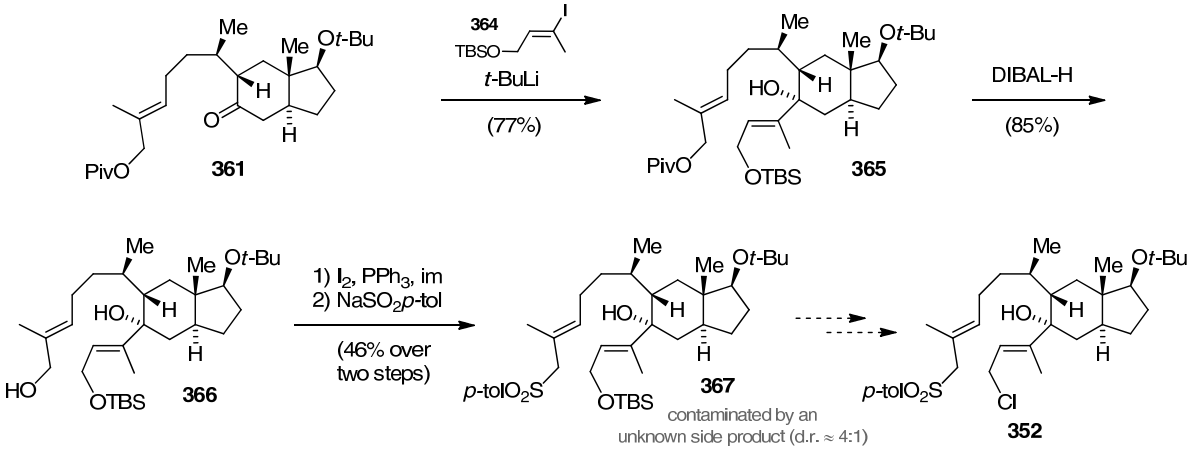
of Cp_2TiCl_2 to trigger a hydrotitanation. After complete conversion, the resulting organometallic species was reacted with I_2 to give the desired vinyl iodide **363**, albeit in a poor yield of 15% (literature:[240] 49%, Scheme 3.24).



Scheme 3.24 Two-step synthesis of vinyl iodide **364**.

This disappointing outcome was attributed to the addition of solid I_2, which was barely soluble in the reaction mixture. In future experiments, one should thus resort to the addition of I_2 in solution and conceivably add HMPA as reported by Gibbs.[241] Nevertheless, we obtained sufficient amounts of alcohol **363** and a final silylation completed the synthesis of vinyl iodide **364**, the structure of which was verified by 2D NOE experiments.

Next, the two fragments **361** and **364** were combined in analogy to the previous approaches. Hence, treatment of vinyl iodide **364** with *t*-BuLi generated an organo lithium species *in situ*, which in turn was slowly added to ketone **361** to form tertiary alcohol **365** in high yield and as a single diastereomer (Scheme 3.25). The relative configuration of the new introduced stereogenic center was assigned based on the previous results (*cf.* Chapter 3.5). Noteworthy, the pivalate remained intact despite using excess of the vinyl lithium species. Furthermore, product **365** already contained all carbon atoms necessary for the model studies toward astellatol (**103**). Having successfully installed the second side chain, we cleaved the pivaloyl ester in alcohol **365** with excess DIBAL-H at −78 °C, which furnished diol **366** in good yield. While we pursued a step-wise procedure in these initial experiments, a direct cleavage of the protecting group could be accomplished by adding excess MeLi or EtMgBr to the reaction mixture after complete conversion. Such a protocol has been utilized recently by Carreira and co-workers[242] and would reduce the overall step count.



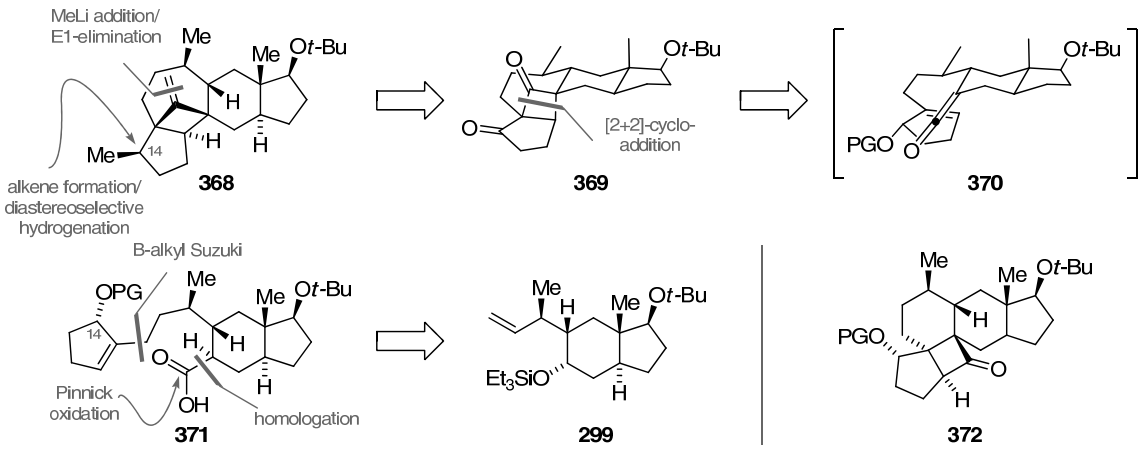
Scheme 3.25 Progress toward the synthesis of cyclization precursor **352**.

The latest transformation examined to date was the conversion of allylic alcohol **366** to a toluenesulfone species. Thereby, treatment of intermediate **366** with I_2 in the presence of PPh_3 and

imidazole yielded an allylic iodide (not shown) which was substituted with $NaSO_2p$-tol in DMF.[232] The desired compound **367** was obtained in 46% yield and characterized by NMR spectroscopy and mass spectrometry. However, the reaction was accompanied by the formation of an inseparable unidentified side product (d.r. ≈ 4:1). We reasoned that this observation might be attributed to the ability of I_2 to isomerize double bonds. Thus, further protocols for the installation should be investigated in future, including a consecutive tosylation/iodination/substitution procedure. Alternatively, the use of PBu_3/PhSSPh in pyridine should be examined since this reagent combination has been shown to convert allylic alcohols into the corresponding sulfides,[237] the oxidation state of which could then be adjusted by selective oxidation to the sulfone. If this transformation is successfully optimized, the desilylation and conversion to an allylic chloride **352** are yet to be investigated in order to set the stage for the investigation of the envisaged ring closure.

3.7 An Alternative Approach: Toward a Ketene-Alkene Cycloaddition

While the strategies discussed in the earlier chapters toward a total synthesis of astellatol (**103**) focused on assembling the pentacarbocyclic architecture by a bioinspired cationic cascade, we also developed an additional route hinging on an intramolecular [2+2]-cycloaddition to construct the cyclobutane moiety (Scheme 3.26).[243,244]

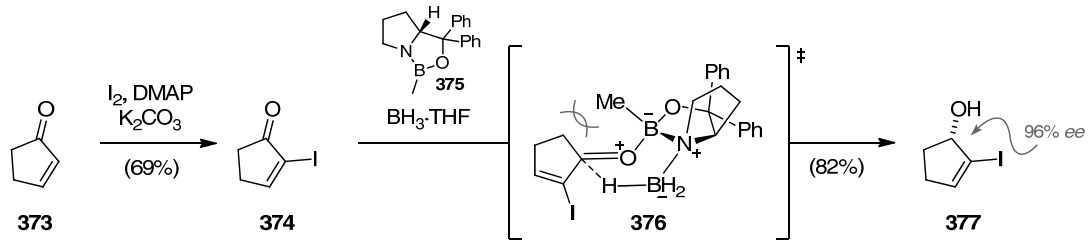


Scheme 3.26 Retrosynthetic strategy toward construction of the pentacyclic architecture **368** *via* an intramolecular cycloaddition and potential isomer **372** arising from this approach.

From a retrosynthetic point of view, the pentacyclic structure **368** was traced back to cyclobutanone **369** by the sequential interconversion of two carbonyl functionalities including a substrate controlled diastereoselective hydrogenation. This intermediate **369** in turn should arise from ketene **370** *via* the aforementioned cycloaddition strategy. We were aware of the fact that this reaction might be accompanied by the formation of another pentacyclic backbone **372**, which also is a highly strained ring system. Independently of which isomer might arise, this transformation would build up structural complexity, set two all-carbon stereogenic centers in one single operation and was thus

worth being examined in our eyes. Beside the potential exploitation of Lewis acid catalysis,[245] we were interested how the relative confirmation of the allylic stereogenic center at C-14 (astellatol numbering) and a variation of the associated alcohol protecting group could influence the selectivity of this reaction. As starting point, we envisioned utilizing the α-epimer at C-14 to direct an approach of the ketene moiety from the top. The precursor **370** should be generated *in situ* from the corresponding acid chloride (not shown) that should arise from carboxylic acid **371**. Following a one carbon homologation, further retrosynthetic simplification would dissect intermediate **371** to alkene **299** and an appropriate vinyl iodide *via* a B-alkyl Suzuki coupling.[181]

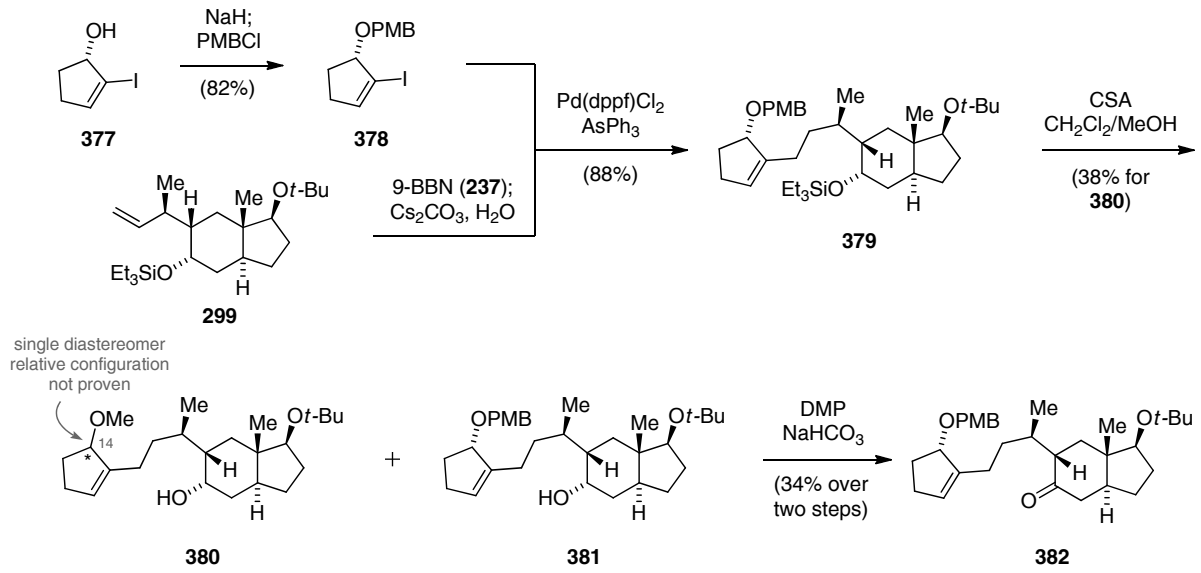
In practice, we commenced with the synthesis of a suitable coupling partner by transferring cyclopentenone **373** to the corresponding α-iodo enone **374** under standard reaction conditions (I_2, K_2CO_3, DMAP, Scheme 3.27),[246] setting the stage for an enantioselective Corey-Itsuno reduction.[247,248] For this purpose, ketone **374** was exposed to the oxazaborolidine catalyst **375** and $BH_3 \cdot THF$ complex following a procedure developed by Uskokovic[249] to furnish allylic alcohol **377** in 82% yield and 96% *ee* on multigram scale.[250]



Scheme 3.27 Enantioselective synthesis of vinyl iodide **377** *via* a Corey-Itsuno reduction.

Mechanistically, this reaction proceeds *via* the boat like transition state **376**, in which the larger substituent of the prochiral ketone, *i.e.* the iodoalkene fragment, adopts a position to minimize the disfavored steric interactions with the catalyst as depicted. Such a conformation results in a preferential intramolecular delivery of the hydride form the *re*-face and forms the desired product **377**. Moreover, it has been shown that the catalyst **375** differentiates the two substituents with extraordinary selectivity in cyclic α-halo enones.[248]

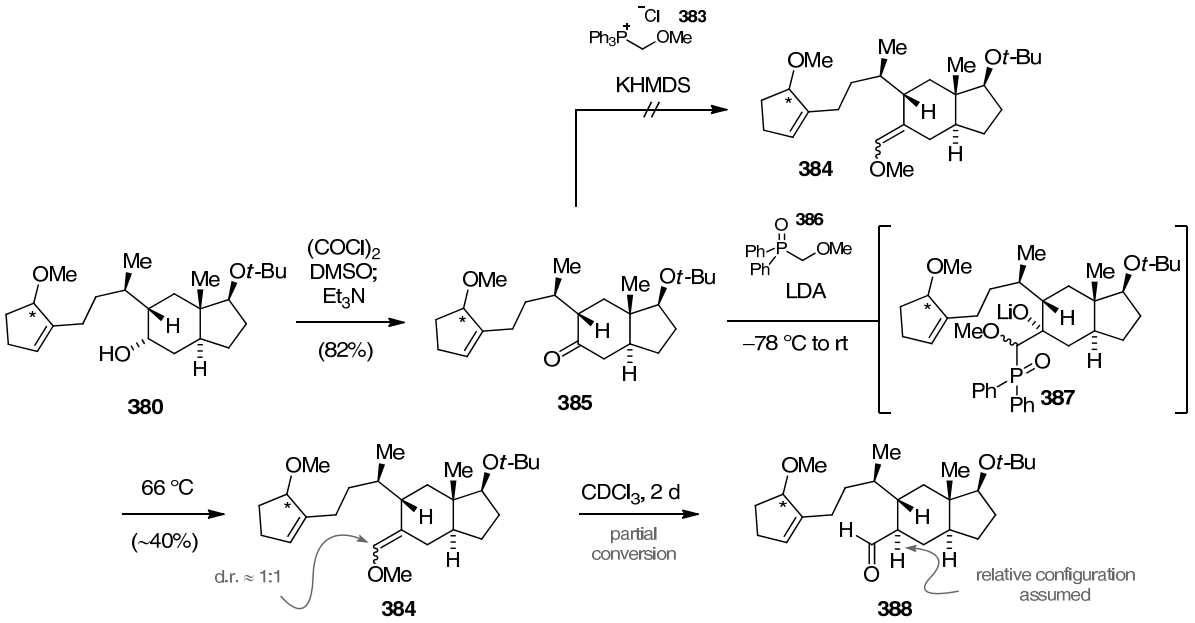
In subsequent experiments, the alcohol functionality of vinyl iodide **377** was protected as its PMB ether under basic conditions (NaH, PMBCl, Scheme 3.28). Interestingly, the obtained optical rotation of alkene **378** (+2.2, *c* 1.00, $CHCl_3$) differed dramatically from the one reported by Paquette and co-workers for *ent*-**378** (+37.0, *c* 1.08 $CHCl_3$),[251] but an alternative preparation under acidic conditions (PMBTCA, CSA) gave the exact same value. Thus, we were confident that no epimerization occurred and submitted cyclopentenol **378** to the B-alkyl Suzuki reaction conditions employed previously. To our delight, a sole product **379** was obtained in 88% yield, indicating that enantiomerically pure vinyl iodide **378** had been employed. Next, the silyl ether in *trans*-hydrindane **379** was cleaved under acidic conditions (CSA, CH_2Cl_2/MeOH) that we had frequently used before (*vide supra*). These conditions were chosen since the 'real' system would necessitate a differentiation between a secondary TES ether and a secondary TBS ether (*cf.* Chapter 3.3).



Scheme 3.28 Synthesis of ketone **382** *via* B-alkyl Suzuki coupling and observation of a transetherification.

While this reaction occurred smoothly on a 20 mg scale, we observed two products **380** and **381** in an approximately 1:1 ratio when utilizing 710 mg of substrate **379** (Scheme 3.28). Thereby, the more polar product **381** was identified as the desired secondary alcohol. Interestingly, the reaction conditions also effected a concomitant conversion of the PMB protecting group to a methyl ether **380** as established by NMR spectroscopy and mass spectrometry. The latter product **380** was obtained as a single diastereomer, but its relative configuration at C-14 (astellatol numbering) was not assignable based on 2D NMR experiments. Therefore, no hints on the mechanistic nature of this unexpected transetherification, presumably involving a S_N2-substitution, were gained. In the future, one should examine other desilylation agents such as TBAF or HF·pyridine. Due to these not unexpected difficulties, ketone **382** was isolated after oxidation of alcohol **381** with DMP[207] in a disappointingly low yield of 34% over the two steps.

In addition, we converted side product **380** to cyclohexanone **385** under Swern conditions[222] and utilized this intermediate for initial experiments toward a homologation (Scheme 3.29). For this purpose, two reaction conditions have been examined so far. Whereas exposure of ketone **385** to the Kluge-Wittig ylide derived from phosphonium chloride **383** did not result in any conversion to enol ether **384**,[252] the more nucleophilic lithium salt of phosphine oxide **386**[253] reacted with ketone **385** to some extent. Due to incomplete conversion, the temperature was raised to 66 °C triggering an elimination of the addition product **387** to enol ether **384** in the same reaction pot. Usually, this transformation is accomplished in a separate reaction by exposure to a strong base such as NaH.[254] However, no complete conversion of ketone **385** was observed. The intermediate approximate 1:1 mixture of enol isomers **384** could not be characterized properly to date due to the fact that the sample decomposed during the recording of NMR spectra. Presumably, aldehyde **388** was formed by traces of acid present in $CDCl_3$ as indicated by characteristic signals observed in the ^1H and the ^{13}C NMR spectra at $\delta = 9.48$ (d, $^3J = 4.6$ Hz) ppm and $\delta = 205.7$ ppm, respectively.



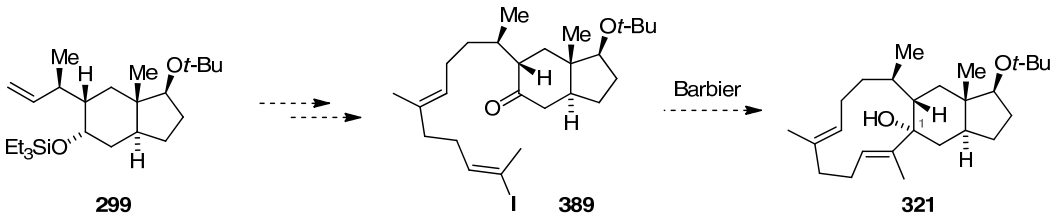
Scheme 3.29 Efforts toward a homologation: reaction of ketone **385** with the lithium salt of phosphine oxide **386**.

With these observations in mind, we are optimistic that the desired homologation of ketone **385** to aldehyde **388** can be optimized in near future. Moreover, the developed protocols could be adopted for ketone **380** to provide sufficient quantities of the corresponding homologated aldehyde (not shown). If this reaction sequence proves successful, a subsequent Pinnick oxidation[255] should then give rise to acid **371** and provide the basis to investigate the key intramolecular [2+2]-cycloaddition. Due to the observed acid sensitivity of the PMB ether however, it might be necessary to install a more robust protecting group such as MOM, SEM, TIPS or TBDPS.

3.8 Conclusion and Future Directions

In summary, this chapter detailed our current progress toward a total synthesis of the pentacarbocyclic sesterterpenoid astellatol (**103**). Therein, we succeeded in the synthesis of the bicyclic building block **268**, which comprises the correct relative configuration of astellatol (**103**) at six stereogenic centers. The preparation of alkene **268** was accomplished by a series of diastereoselective operations, mainly originating from substrate control. In the course of these ventures, we established the installation of the C-9 and C-10 stereogenic centers in model studies and accessed *trans*-hydrindane **299** on multigram scale. This intermediate **299** in turn provided the basis for the examination of four different strategies to assemble the carbon backbone assigned for the natural product **103**. Whereas the major portion of experiments was dedicated to the installation of a strained 11-membered macrocycle in order to pursue a bioinspired route *via* a cationic cascade (*cf.* Chapter 3.4–3.6), the last strategy focused on a more 'traditional' route, namely a [2+2]-cycloaddition to construct the cyclobutane moiety within astellatol (**103**, *cf.* Chapter 3.7). Despite enormous efforts however, these approaches did not yet meet with success or the precursors for the key cyclizations

have not been accessed to date. Therefore, these strategies will be further investigated in our on-going synthetic program *en route* to the total synthesis of type A *trans*-hydrindane *iso*-propyl sesterterpenoids.



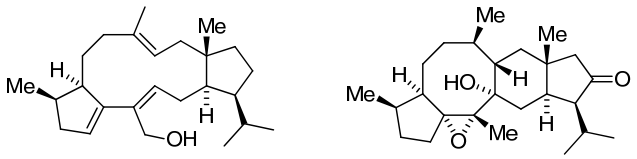
Scheme 3.30 Alternative strategy to access the precursor for a biomimetic cationic cascade under Barbier conditions.

In our studies toward the macrocycle, we encountered problems concerning the tertiary allylic alcohol at C-1. Thus, an alternative route toward the 11-membered ring in tricycle **321** could involve the late-stage installation of this moiety. To this end, one could prepare vinyl iodide **389** along the lines of the previously explorations, involving a B-alkyl Suzuki coupling of alkene **299** (Scheme 3.30). This intermediate **389** could then be transformed the macrocycle in tricycle **321** under Barbier conditions employing *e.g.* Zn.[256] Moreover, one could think of a plethora of methodologies, *e.g.* a Nozaki-Hiyama-Kishi coupling,[257] to construct this strained ring by other retrosynthetic disconnections, thus proving an array of opportunities for future experiments.

4 SYNTHETIC STUDIES TOWARD NITIOL

4.1 Nitiol: Isolation and Background

In 1999, the group of Kawahara reported the novel structure of a sesterterpenoid named nitiol (**110**, Figure 4.1). This natural product **110** was extracted from 'Hercampuri' (*Gentianella nitida*),[99] which is used in Peruvian folk medicine as a remedy for hepatitis and in the treatment of obesity. Based on extensive NMR spectroscopic investigations, the authors assigned the tricarbocyclic architecture comprising two five-membered rings and a central 12-membered macrocycle. Moreover, careful analysis of NOE spectra allowed for the elucidation of the relative configuration of all fives stereogenic centers and the double bond geometry of the three alkenes present in nitiol (**110**). In analogy to astellatol (**103**) and the retigeranic acids, nitiol (**110**) only contains one oxygenated site, thus requiring careful retrosynthetic planning of functional group interconversions.



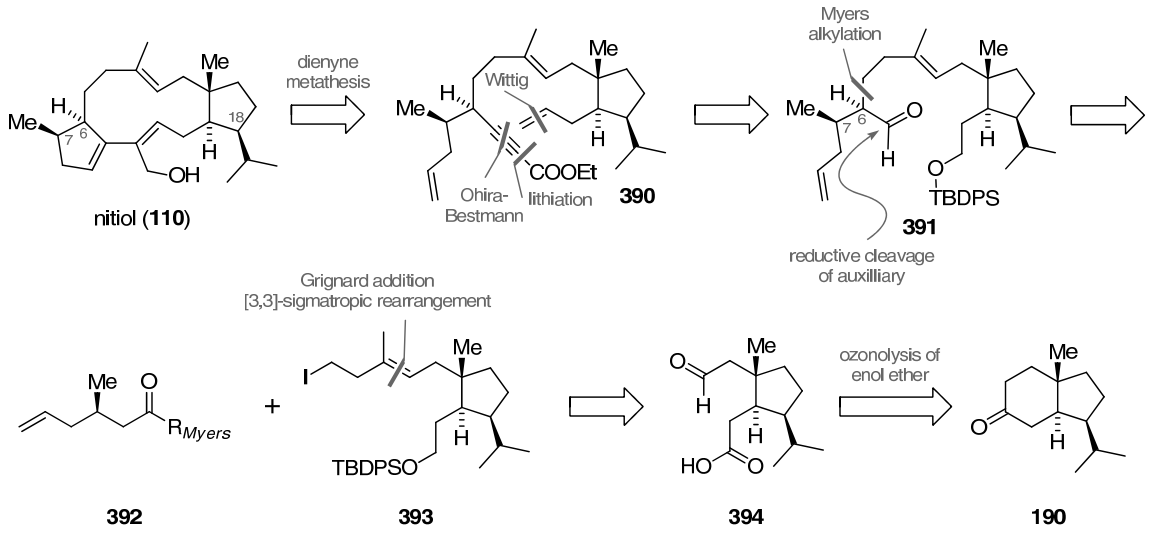
nitiol (**110**) nitidasin (**111**)

Figure 4.1 Molecular structures of the sesterterpenoids nitiol (**110**) and nitidasin (**111**), both isolated from 'Hercampuri', a Peruvian folk medicine

Nitiol (**110**) was found during efforts to identify new low-molecular lipophilic probes in order to study intracellular signal transduction mechanisms in human cells. Thus, Kawahara *et al.* determined the effect of nitiol (**110**) on the gene expression of interleukin-2 (IL-2).[258] This polypeptide regulates the activity of white blood cells and is necessary for the growth and proliferation of T-cells, which are produced during an immune response. Additionally, the application of synthetic IL-2 has been approved as an immunotherapy for the treatment of renal cell cancer and malignant melanoma. Within their tests, Kawahara and co-workers found that nitiol (**110**) enhanced the IL-2 mRNA level in Jurkat cells by a factor of three, whereas its structural analog nitidasin (**111**),[100] isolated as well from *Gentianella nitida*, remained ineffective. In conclusion, the authors stated that the structure of nitiol (**112**), distinctly differing from other known IL-2 gene expression modulators, might serve as a new tool to gain further insights into signal transduction pathways, ultimately leading to the transcriptional control of the IL-2 gene.

4.2 Retrosynthetic Analysis

From a retrosynthetic perspective, we envisioned to access nitiol (**110**) *via* a dienyne metathesis and a subsequent reduction from precursor **390** (Scheme 4.1). On the one hand, this strategy would avoid the difficulty to carry out a late-stage deoxygenation of a carbonyl or an alcohol functionality, which might be very problematic as experienced by Dake and co-workers (*cf.* Chapter 1.3).[110b] On the other hand, this route would also elegantly construct two rings in one single operation and constitute a rare example of macrocycle formation *via* dienyne metathesis.[259,260] Dienyne **390** could arise from aldehyde **391** by sequential standard functional group manipulation. This intermediate **391** could in turn stem from homoallylic iodide **393** and ephedrine derivative **392** *via* a Myers alkylation followed by reductive removal of the auxiliary.[261] Myers' protocol is widely used in organic synthesis and allows for the diastereoselective installation of various alkyl substituents, even on sterically hindered substrates. Within the proposed synthesis, this transformation would thus generate the desired *cis*-relationship between the two substituents at C-6 and C-7 (nitiol numbering).

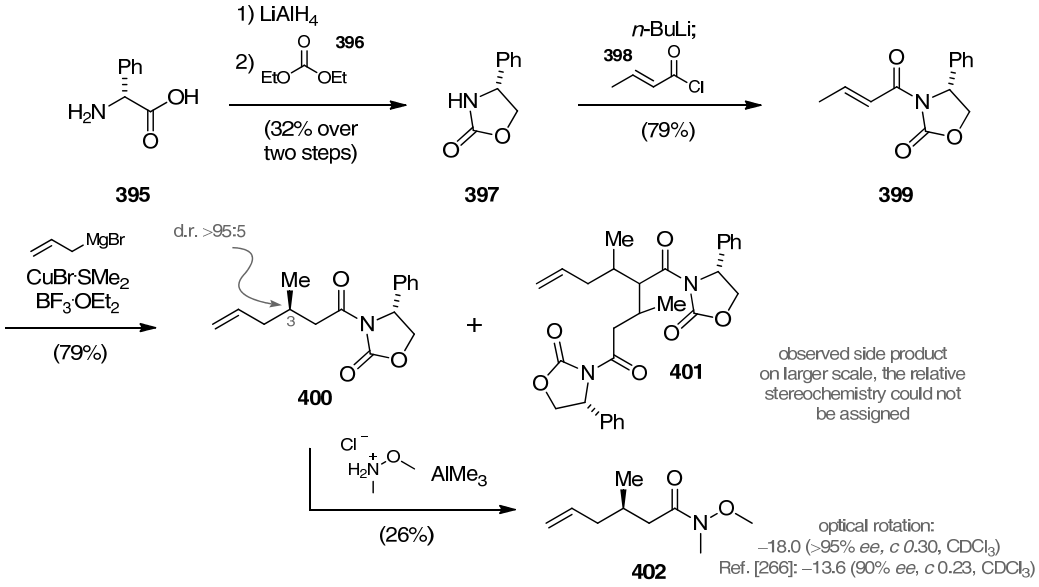


Scheme 4.1 Retrosynthetic analysis of nitiol (**110**) featuring a dienyne metathesis as key step.

Whereas the western fragment **392** should be accessible from the corresponding acid, the eastern portion **393** could be prepared starting from dicarbonyl compound **394**. This pathway could be realized by a multistep sequence involving a vinyl Grignard addition and a subsequent [3,3]-sigmatropic rearrangement according to the Johnson-Claisen protocol to selectively install the trisubstituted alkene present in cyclopentane **393**. It should be noted that such an approach would require the dissection of one carbon atom. Alternatively, other classical olefination strategies such as a Horner-Wadsworth-Emmons reaction might also be considered. Further retrosynthetic simplification, in particular ozonolysis of a silyl enol ether, should ultimately trace nitiol (**110**) back to building block **190**, the synthesis of which has already been accomplished previously (*cf.* Chapter 2).

4.3 Synthesis of the Western Fragment[§]

Our studies toward nitiol (**110**) commenced with the synthesis of the western fragment **392**. The first task at hand was to install the requisite absolute configuration of the stereogenic center at C-3 (IUPAC numbering) in a selective fashion. A literature survey revealed that the corresponding acid has been synthesized in its enantiomeric form *via* a ketene-aldehyde cycloaddition approach (not shown).[262] Since this strategy required the multistep synthesis of a chiral ligand, we resorted to a classical route employing a diastereoselective cuprate addition to crotyl amide derivative **399** as described by Williams and co-workers.[263] Therein, the chiral auxiliary (readily prepared from cheap commercially available starting materials) induces a high degree of diastereoselectivity in order to install the desired absolute configuration at C-3.

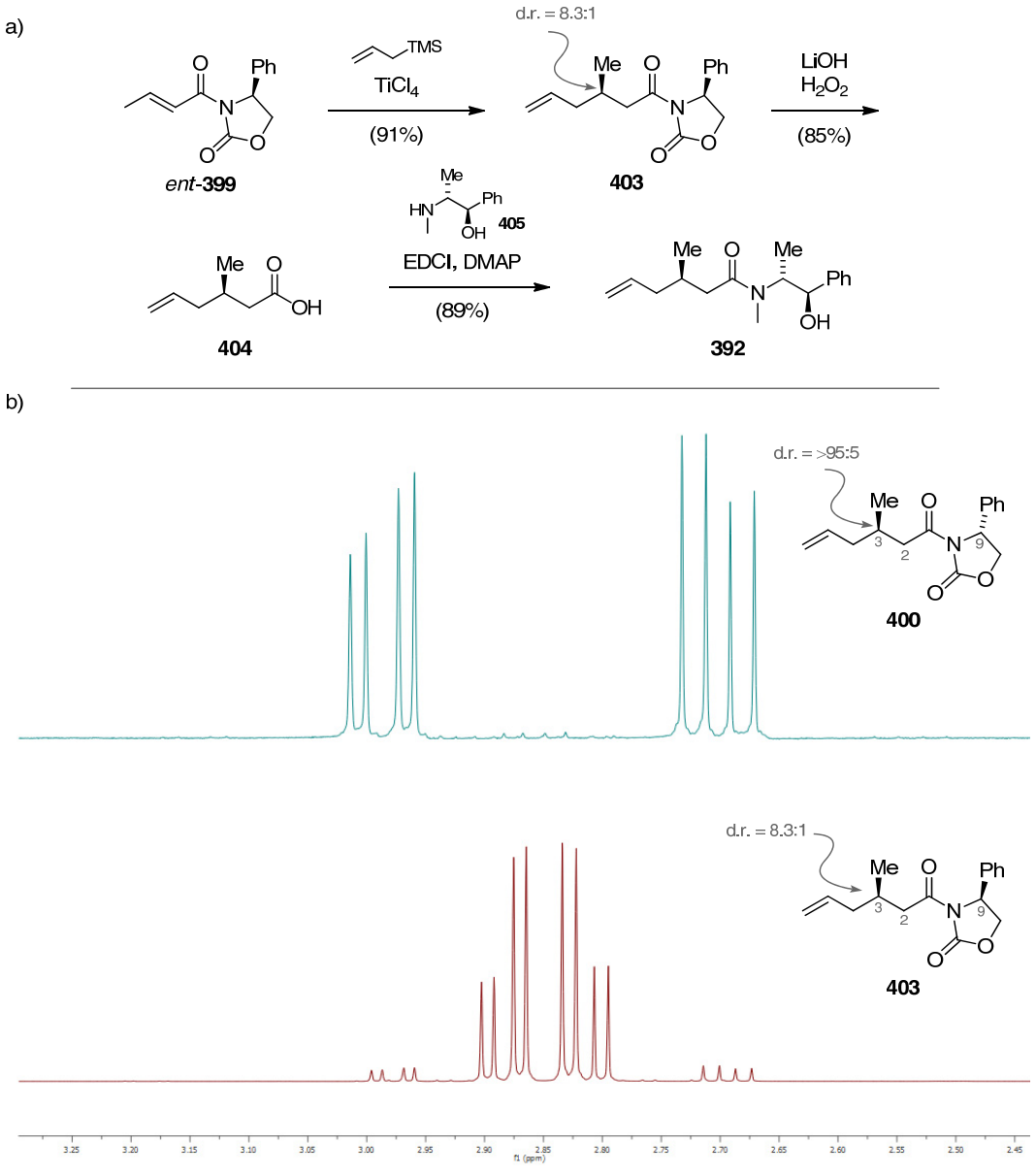


Scheme 4.2 Diastereoselective installation of the stereogenic center at C-3.

Along these lines, we prepared oxazolidinone **397** from amino acid **395** in a two-step protocol (Scheme 4.2).[264] Subsequently, treatment of auxiliary **397** with *n*-BuLi followed by addition of crotyl chloride (**398**) furnished α,β-unsaturated compound **399**, the substrate for the aforementioned 1,4-addition.[265] Eventually, exposure of the intermediate **399** to a Yamamoto organocopper(I) species generated *in situ* from equimolar amounts of allylmagnesium bromide, $BF_3 \cdot Et_2O$ and $CuBr \cdot SMe_2$ yielded the addition product **400** in 79% yield on a 100 mg scale. Moreover, the chiral auxiliary induced a high diastereoselectivity of >95:5 as determined by ^1H NMR spectroscopy. Unfortunately, the yield of this reaction dropped dramatically upon scale up (400 mg – 3.0 g). Apart from recovered starting material, one side product **401**, arising from two consecutive Michael additions, was isolated. This product was characterized by mass spectrometry and NMR spectroscopy albeit without establishing the relative configuration of the newly installed stereogenic centers. Mechanistically, the

[§] The experimental part of this subchapter was conducted in collaboration with Thomas M. Wildenhof as part of his undergraduate research stay in the Trauner laboratories.

diastereoselective outcome of the initial allyl cuprate addition is not completely understood and Williams and co-workers concluded: "stereocontrol […] is complicated by the availability of several activated conformers, by the nature of the Lewis acid, and by the structure and mechanism associated with the organocopper species itself".[263] Unfortunately, we were not able to obtain crystals suitable for X-ray diffraction and we thus converted **400** (obtained from the cuprate addition) to the corresponding Weinreb amide **402** (>95% *ee*). This compound **402** was literature known (90% *ee*, obtained *via* Sakurai reaction conditions, *vide infra*) and our analytical data including optical rotation agreed in all respects to the ones previously reported.[266]



Scheme 4.3 (*a*) Preparation of the western fragment **392** *via* Sakurai allylation. (*b*) ^{1}H NMR spectra (both in $CDCl_3$ at 400 MHz) of the diasterotopic protons at C-2: proof of inverse outcome by changing cuprate for Sakurai conditions.[267]

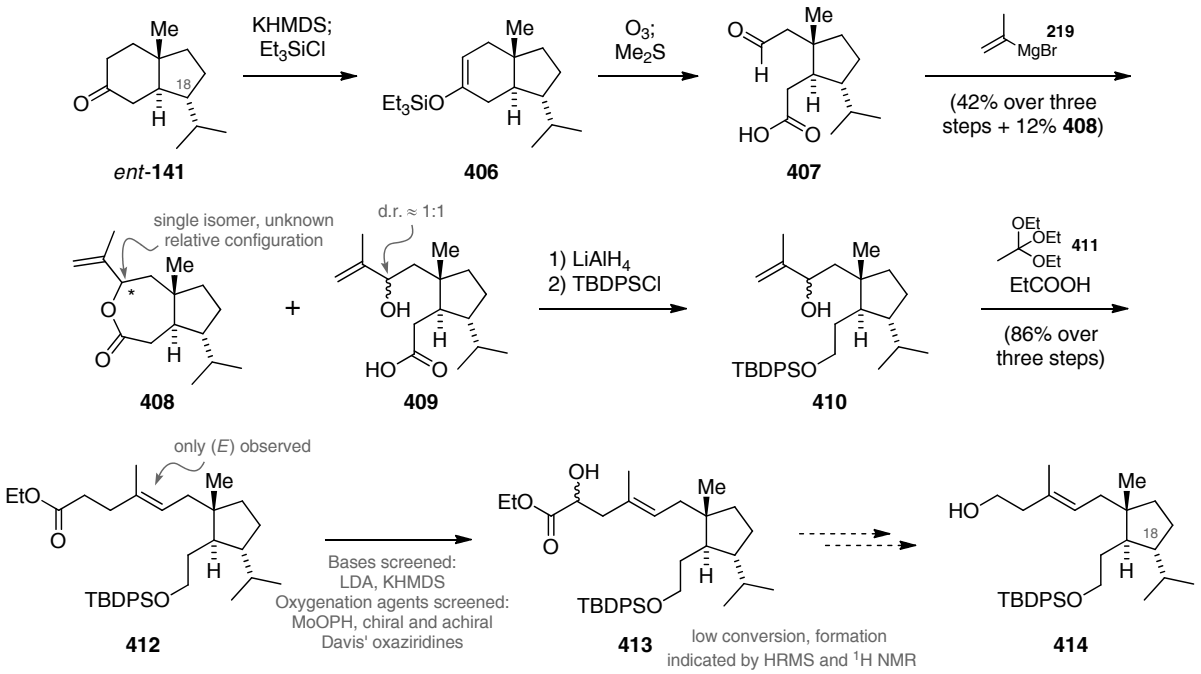
Since the cuprate route was impractical on larger scale, we resorted to a different approach. This was based on the fact that Williams and co-workers had discovered a counterintuitive reversal in selectivity of the 1,4-addition by simply changing from an organocopper addition to a Sakurai allylation.[267]

Eventually, treatment of the optical antipode *ent*-**399** (obtained in analogy to the previously described protocol) with $TiCl_4$ and allyltrimethylsilane smoothly delivered adduct **403** in 91% yield on a 700 mg scale following a modified procedure from Takayama (Scheme 4.3).[266] The reversed diastereoselectivity could be easily observed by comparison of the chemical shifts of the diasterotopic protons at C-2 as depicted in Scheme 4.3b. Whereas the signals of diastereotopic protons at C-2 for the (3*R*,9*R*)-diastereomer **400** were centered at δ = 2.98 ppm and δ = 2.69 ppm, the corresponding signals for (3*R*,9*S*)-diastereomer **403** were observed at δ = 2.89 ppm and δ = 2.82 ppm, respectively. One small drawback of this more convenient procedure was the lower diastereoselectivity, which provided alkene **403** in a d.r. of 8.3:1. Nevertheless, the Evans auxiliary in amide **403** was readily cleaved upon exposure to LiOOH generated *in situ*[268] to furnish acid (**404**). The determined optical rotation of acid **404** (+1.6, *c* 0.53, $CHCl_3$),matched the absolute values of –0.71 (*c* 1.13, $CHCl_3$) and –2.8 (*c* 1.00, $CHCl_3$) for its antipode *ent*-**404** reported by Chang[269] and Nevado,[262] respectively. Once more, this finding confirmed the desired (*R*)-configuration at C-3. In order to finish the synthesis of western fragment **392**, the incorporation of the pseudoephedrine auxiliary **405** was then attempted. This task was readily accomplished by treatment of acid **404** with EDCI and DMAP in the presence of Et_3N affording amide **392** in 89% yield.[270] With the first substrate **392** for the fragment coupling in hand, we next focused on the synthesis of alkyl iodide **393**.

4.4 Progress toward the Eastern Fragment

According to our retrosynthetic analysis, (*cf.* Chapter 4.2), we opted to access alkyl iodide **393** starting from ketone **190**. Since we had prepared larger quantities of its diastereomeric counterpart *ent*-**141**, we carried out our preliminary investigations with the α-series, which would ultimately provide access to the C-18 epimer of nitiol (**110**). Based on our previous experiences with the regioselective deprotonation of ketone **207** (*cf.* Chapter 3.3), *trans*-hydrindane building block *ent*-**141** was exposed to KHMDS at −78 °C and the resulting potassium enolate was intercepted with Et_3SiCl to furnish silyl enol ether **406** (Scheme 4.4). Following aqueous work up, this intermediate **406** was instantly subjected to ozonolysis reaction conditions.[271] Upon treatment with Me_2S, labile keto acid **407** was obtained and was used immediately for the next transformation. Thus, aldehyde **407** was reacted with excess isopropenylmagnesium bromide (**219**)[272] to provide allylic alcohol **409** as an inconsequential 1:1 mixture of diastereomers in 42% yield over three steps. The isolation of the desired product **409** was accompanied by the formation of ε-lactone **408**, presumably generated upon acidic work up with 2N HCl. Notably, bicycle **408** was obtained as a single diastereomer in 12% yield, but its relative configuration could not be assigned. In future experiments, the formation of side product **408** could be bypassed by carrying out the work up under less acidic conditions using aqueous NH_4Cl. As seco

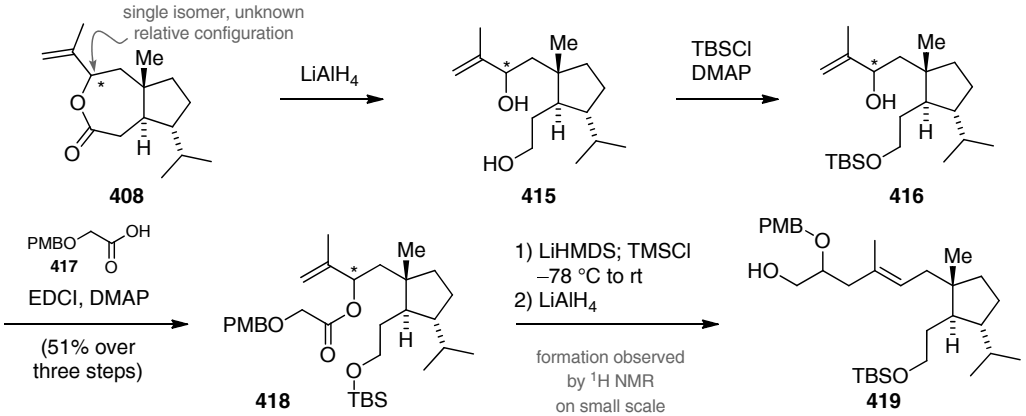
acid **409** proved to be somewhat unstable, it was instantly reduced to the corresponding diol (not shown) by treatment with $LiAlH_4$.



Scheme 4.4 Toward the synthesis of an appropriate eastern fragment.

Next, a monosilylation of the primary alcohol was accomplished with TBDPSCl to furnish allylic alcohol **410**,[273] setting the stage for the Johnson variant of the Claisen rearrangement (Scheme 4.4).[62] To this end, alcohol **410** was dissolved in orthoester **411** and the mixture was heated to 130 °C in the presence of catalytic amounts of propionic acid.[274] This procedure resulted in the formation of ester **412** in an excellent yield of 86% over three steps. Moreover, a single alken isomer was obtained, the desired *(E)*-configuration of which was verified by 2D NOE NMR experiments. With ester **412** in hand, the next task was to shorten the chain by one carbon atom that we initially envisaged to prepare the alcohol **414** *via* a diol cleavage and $NaBH_4$ reduction. For this purpose, we aimed at preparing alcohol **413** by an α-oxygenation of the ester functionality, which would provide the requisite diol upon $LiAlH_4$ reduction. Unfortunately, variation of bases (LDA, KHMDS), oxygenation agents (MoOPh,[275] chiral and achiral Davis' oxaziridine[276]) and reaction temperatures resulted in poor conversion and isolation of only small quantities of the desired product **413** as indicated by mass spectrometry and ^1H NMR spectroscopy.

With this in mind, we decided to alter our retrosynthesis and install the oxygenation pattern necessary for a diol cleavage at the stage of the [3,3]-sigmatropic rearrangement. To this end, we opted for a variant of the Claisen rearrangement introduced by Kallmerten and Burke[277] and thus treated lactone **408** with $LiAlH_4$ to obtain diol **415**, now as a single diastereomer (Scheme 4.5).

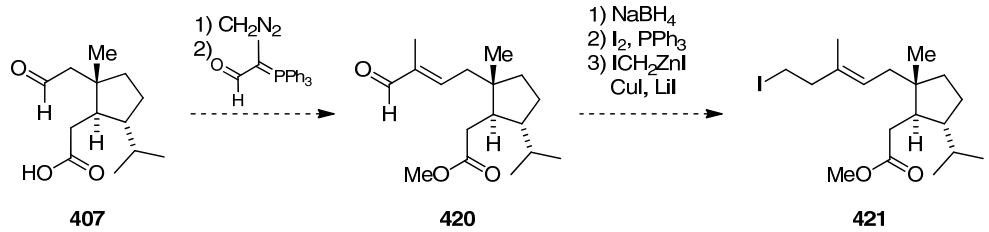


Scheme 4.5 Potential access to alcohol **419** *via* a Kallmerten-Burke rearrangement.

Since we had encountered difficulties in purifying the regioselective silylation product when using TBDPSCl due to hardly separable silanol byproducts, diol **415** was monosilylated with TBSCl.[278] Next, the resulting allylic alcohol **416** was acetylated with acetic acid derivative **417**[279] to access ester **418**, the precursor for the aforementioned rearrangement, in a yield of 51% over the three steps. In an initial experiment on small scale, the corresponding TMS silyl enol ether generated by sequential treatment with LiHMDS and TMSCl triggered the desired [3,3]-sigmatropic rearrangement upon warming to room temperature.[280] A subsequent $LiAlH_4$ reduction formed alcohol **419** as indicated by ^{1}H NMR analysis.

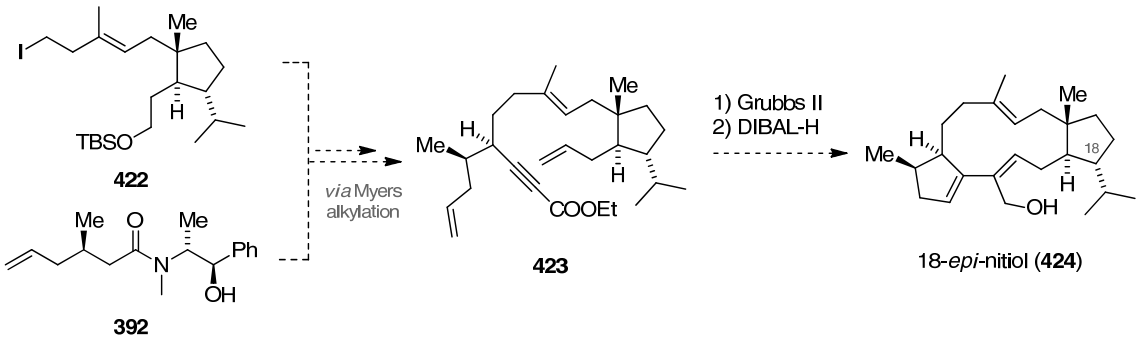
4.5 Conclusion and Future Directions

In summary, first attempts toward the envisaged total synthesis of nitiol (**110**) have been investigated. Thereby, we accomplished the synthesis of western fragment **392** based on literature precedence starting from oxazolidinones **397** and *ent*-**397** (*cf.* Chapter 4.3). It turned out that an approach involving a cuprate addition resulted in almost complete diastereoselective control, whereas Sakurai conditions utilizing the enantiomeric chiral auxiliary were more convenient for a preparation on larger scale. We also explored the synthesis of eastern fragment **422** commencing with ketone *ent*-**141** (*cf.* Chapter 4.4). This route featured a regioselective cleavage of the cyclohexanone moiety by sequential enol ether formation and ozonolysis. Despite the unstable nature of some intermediates, we installed the trisubstituted alkene in **412** *via* a Johnson-Claisen rearrangement. As our attempts to shorten the side chain in ester **412** were met with little success so far, we embarked on another strategy starting from lactone **408** (a side product from the previous investigations) that involved a Kallmerten-Burke rearrangement. A first promising result indicating the formation of primary alcohol **419** was obtained on small scale. In the future, this experiment should be repeated on a larger scale and the subsequent transformations toward the alkyl iodide **422** should be examined. Alternatively, one could examine a Hunsdiecker reaction[281] to convert the corresponding acid of ester **418** directly to alkyl iodide **393**.



Scheme 4.6 Proposed alternative strategy to generate alkyl iodide **421** involving a Wittig olefination.

Additionally, a second strategy toward alternative fragment **421** could be tested as outlined in Scheme 4.6. Thereby, an initial esterification of acid **407** would be followed by a Wittig olefination to access keto ester **420**, which in turn could be elaborated to the corresponding allyl iodide (not shown) by a chemoselective reduction and an Appel reaction. Finally, a one carbon extension developed by Knochel and co-workers[282] would furnish iodide **421**.



Scheme 4.7 Proposed fragment combination and the key dienyne metathesis toward 18-*epi*-nitiol (**424**).

With both portions **392** and **422** (or **421**) in hand, a Myers alkyation combining these two fragments should be feasible. Additional reactions, including the key dienyne metathesis of intermediate **423**, along the lines of the presented retrosynthetic analysis (*cf.* Chapter 4.2) could furnish 18-*epi*-nitiol (**424**, Scheme 4.7). If this protocol proves to be efficient, it should be readily transferrable to building block **190** and allow for a synthesis of the naturally occurring nitiol (**110**).

5 SYNTHETIC STUDIES TOWARD YW 3548

5.1 YW 3548: Isolation and Background

The sesterterpenoid YW 3548 (**112**) was isolated from the fungal strain *Paecilomyces inflatus* by Wang *et al.* in 1998 and its relative configuration was established by thorough analysis of NMR spectroscopic data, including ^{1}H, ^{13}C, DQ-COSY, ROESY, HSQC and HMBC experiments (Figure 5.1a).[101] Structurally, YW 3548 (**112**) exhibits a unique tricarbocyclic sesterterpenoid δ-lactone architecture featuring a total of ten stereogenic centers, one of which is all-carbon substituted. Moreover, this type A *trans*-hydrindane *iso*-propyl sesterterpenoid **112** comprises the sterically enbumbered *trans*-hydrindane portion fused to an eight-membered ring bearing both an exomethylene group and an embedded trisubstituted alkene moiety. Furthermore, this intriguing carbon backbone, YW 3548 (**112**) is regioselectively acylated by a heptanoate side chain with two further stereogenic centers. The relative configuration at this site as well as the absolute configuration of YW 3548 (**112**) was not evaluated and its structure remains thus unconfirmed.

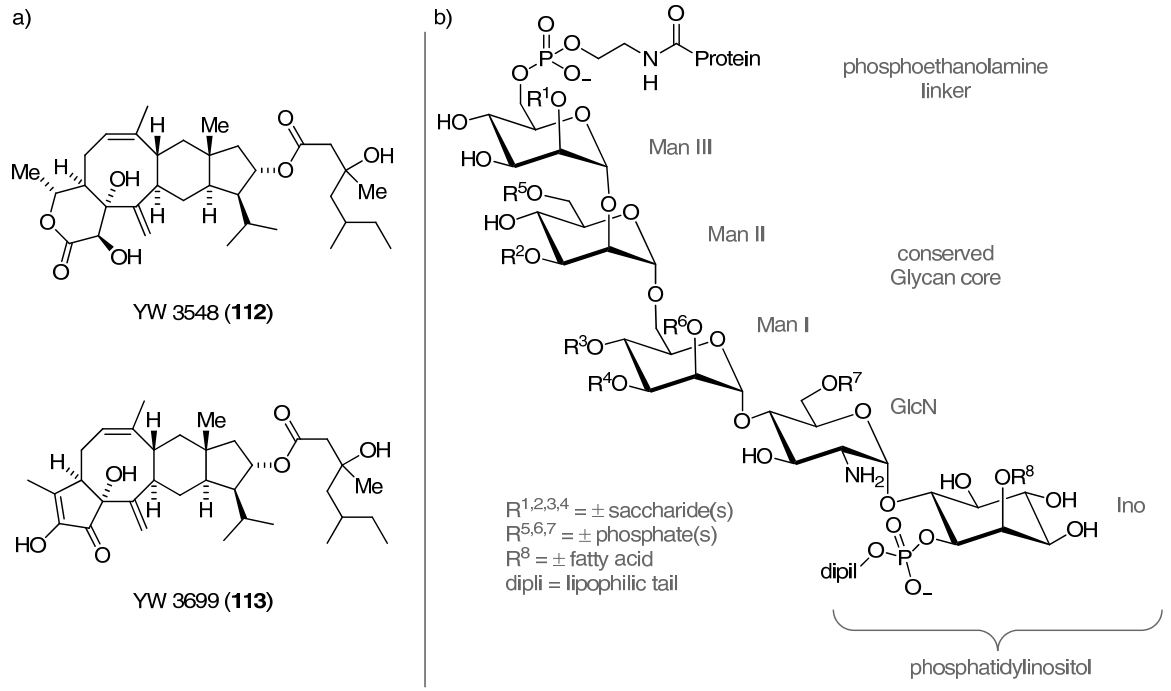


Figure 5.1 (*a*) Molecular structures of the GPI anchor inhibitors YW 3548 (**112**) and YW 3699 (**113**). (*b*) Conserved GPI core structure and possible modifications, adapted from reference [288].

The research team at Novartis Pharma Inc. discovered YW 3548 (**112**) while seeking for novel inhibitors of gycosylphosphatidylinositiol (GPI) anchoring, a biological process which has been discovered almost three decades ago.[283,284] From a biological point of view, the authors determined YW 3548 (**112**) and its analog YW 3699 (**113**)[102] to selectively inhibit GPI-anchor synthesis *in vitro* by yeast mircosomes with a *minimal inhibiton concentration (MIC)* of 3.4 nM and 3.5 mM,

respectively.[285] Among eukaryotes, GPI-anchoring covalently binds proteins to the extracellular space of the cell membrane.[286] More specifically, the C-terminus of the protein is connected *via* ethanolamine to a glycan, which in turn is linked to the 6-position of the *myo*-inositol ring of phosphatidylinositol (PI, Figure 5.1b). Ultimately, two fatty acid units on the PI moiety anchor the protein to the cell membrane. Once the protein is attached to the extracellular surface of the membrane, it often plays a crucial role as receptor or co-receptor for ligands that modulate signal transduction.[286] Although the process of GPI anchoring is common to mammals and protozoa, sharing an identical glycan core, different biosynthetic pathways have been reported over the years.[286] In addition, it was established that protozoa tend to express a significantly higher density of GPI-anchored protein than eukaryotes, playing an important role in determining survival and infectiveness of the parasite. This is exemplified on *Trypanosoma Brunei*, the parasite causing the African sleeping sickness: it expresses a cell-surface coat of a GPI-anchored glycoprotein, which acts on the one hand as a barrier against macromolecules from the host immune system and on the other hand enables the evasion of specific immune attacks through antigenetic variation.[287] Thus, selective inhibitors of GPI-anchoring in protozoa could act as potential drugs against these parasites.

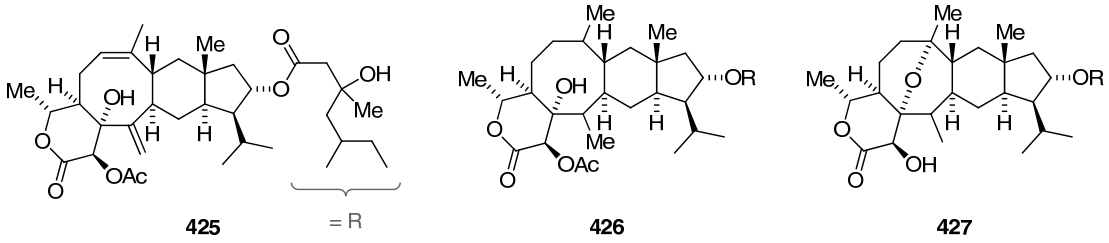
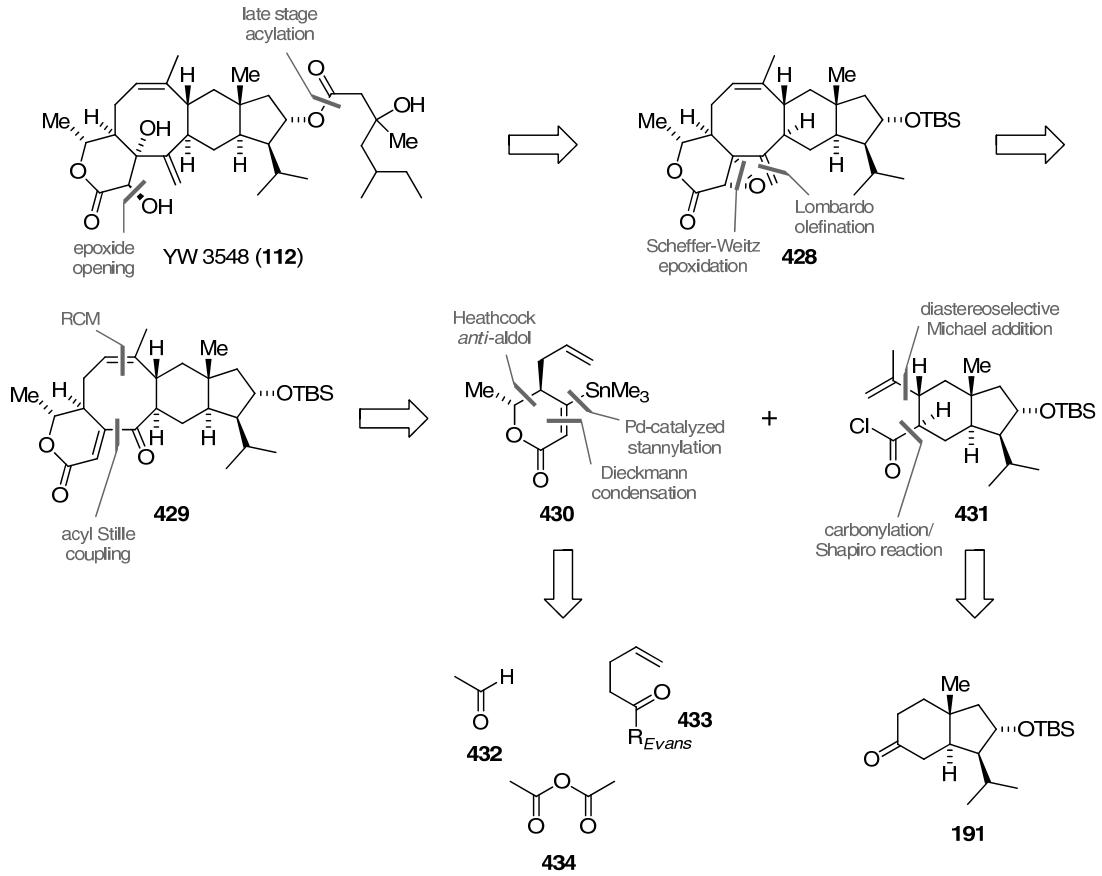


Figure 5.2 Artificial analogues of YW 3548 (**112**) exhibiting less activity in inhibition of GPI anchor biosynthesis.

Based on initial SAR studies, Wang and co-workers revealed that the δ-lactone moiety and the double bonds within YW 3548 (**112**) were necessary for its activity. Indeed, chemically prepared analogues **425**, **426** and **427** (Figure 5.2) caused a loss of activity, represented by *MIC* of 3.2, 1.7 and 17 μM, respectively.[101,285] The authors further speculated on the mode of inhibition and finally stated that YW 3548 (**112**) blocks the addition of the third mannose unit to the GPI backbone. Additionally, it eventually prevents the incorporation of [^{3}H]*myo*-inositol into proteins and thus the transport of GPI-anchored proteins to the Golgi, resulting in toxicity. These effects have been proven for mammalian cells as well as for yeast, whereas YW 3548 (**112**) remained ineffective for protozoa. Nevertheless, the novel structure of YW 3548 (**112**), synthetic precursors and related analogues could provide a basis to gain further insights into the mechanism of inhibition and might provide hints toward lead structures for selective inhibition of the protozoa pathway. In addition, the synthetic efforts could contribute to expand the knowledge about the function of the GPIs, which is, as opposed to the biological significance, still hardly explored and a current topic of interest in chemical biology.[288] These interesting biological activity and the unique tetracyclic backbone of YW 3548 (**112**) prompted us to develop a convergent retrosynthetic analysis.

5.2 Retrosynthetic Analysis

From a retrosynthetic point of view, we envisioned installing the heptanoate side chain of YW 3548 (**112**) by means of a late-stage acylation (Scheme 5.1). The diol moiety in the lactone portion could arise from a Lewis or Brønsted acid-mediated epoxide opening,[289] providing tetracycle **428** as a synthetic precursor that in turn could be prepared from ketone **429** by sequential nucleophilic epoxidation and a chemoselective Lombardo olefination.[290] Further dissection by an acyl-Stille coupling[291] and a challenging RCM[180] to close the central eight-membered ring with a trisubstituted double bond would lead back to western fragment **430** and eastern portion **431** as key building blocks. Notably, such a RCM strategy has been explored by the group of Tori in their model studies toward YW 3699 (**113**) (*cf.* Chapter 1.3).[111]



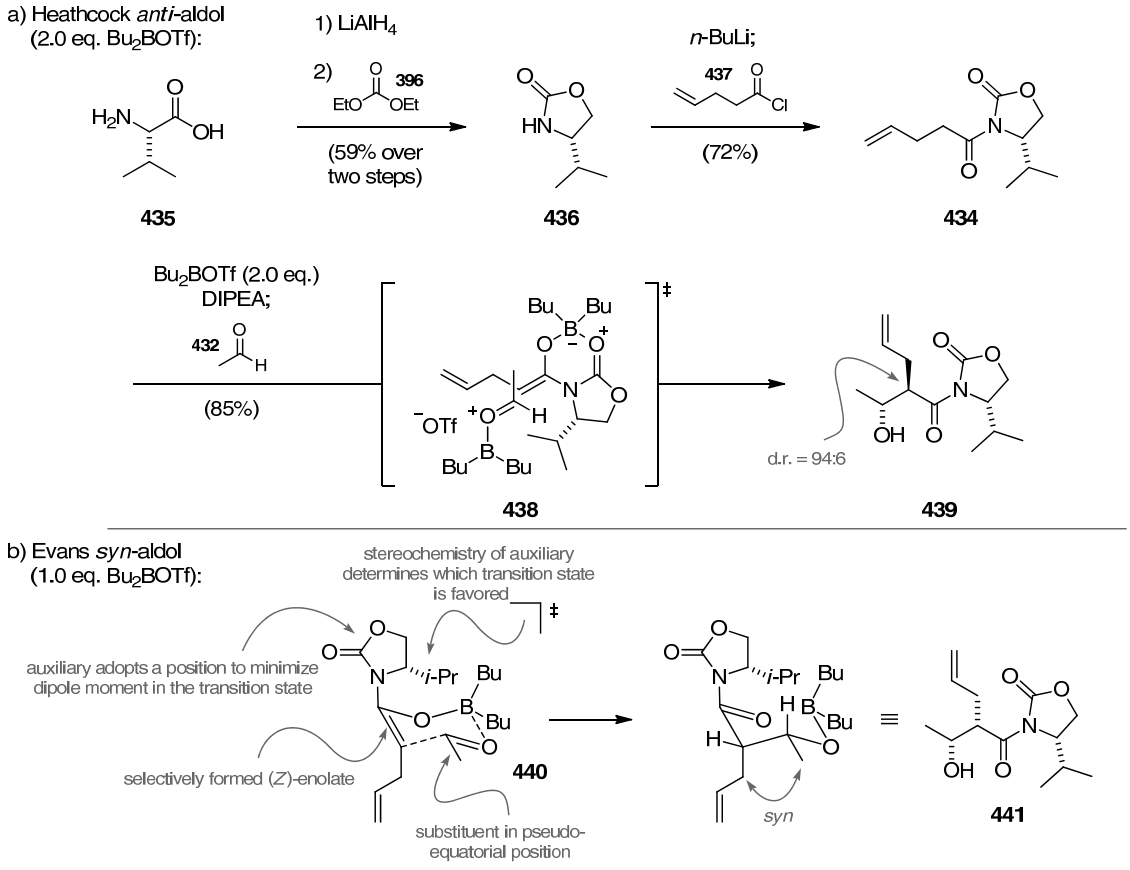
Scheme 5.1 Convergent retrosynthetic analysis for YW 3548 (**112**) *via* an acyl-Stille coupling and a RCM to close the central eight-membered ring.

Further retrosynthetic simplification would trace western fragment **430** back to three simple building blocks: acetaldehyde (**432**), acetic anhydride (**433**) and a 5-pentenoic acid derivative **434** containing an Evans-auxiliary. The envisaged route would proceed *via* a Heathcock *anti*-aldol reaction[292] followed by acetylation and Dieckmann condensation.[293] A final Pd-catalyzed stannylation would then furnish vinyl stannane **430**. On the other hand, eastern fragment **431** should be accessible starting from the previously synthesized building block **191** *via* a Pd-catalyzed carbonylation[294] or a Shapiro

reaction[153] and an ensuing diastereoselective cuprate addition. Alternatively, the installation of the isopropylene moiety might be achieved following Koga's protocol utilizing a *tert*-leucine derived directing group (not shown), which allows for the selective 1,4-addition of Grignard reagents.[295] Concerning the configuration of the aldehyde functionality, we assumed that this residue would adapt the desired thermodynamically more favored feasible by a base-promoted epimerization. A final Pinnick oxidation[255]/acid chloride formation protocol would then provide access to the envisaged key fragment **431**. Along these lines, we embarked on the total synthesis of YW 3548 (**112**), thereby mainly focusing on developing a convenient access to western fragment **430**.

5.3 Progress toward the Western Fragment**

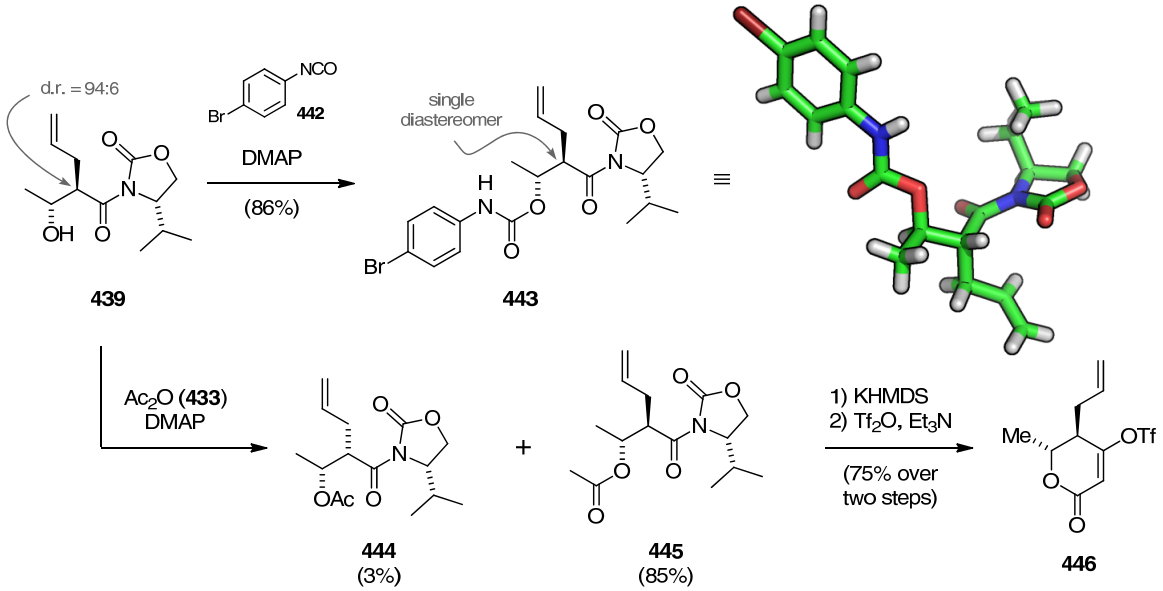
Based on the retrosynthetic analysis, our synthesis commenced with the large scale preparation of L-valine (**435**) derived Evans-auxiliary **436** by sequential $LiAlH_4$ reduction and carbamate formation with diethyl carbonate (**396**) following literature procedures (Scheme 5.2).[296]



Scheme 5.2 (*a*) Synthesis of alcohol **439** *via* the Heathcock modification of the Evans-aldol reaction proceeding through an open transition state **438**. (*b*) The logic of the *syn*-Evans aldol chemistry, which would lead to alcohol **441**.

** The experimental work of this subchapter was performed together with Sebastian Rappenglück as part of his Bachelor's Thesis in the Trauner laboratories.

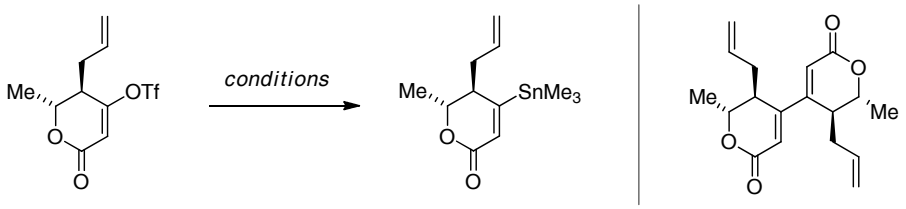
The lithium species generated by treatment of carbamate **436** with *n*-BuLi was then reacted with commercially available acid chloride **437** to furnish oxazolidinone **434**,[297] the precursor for a Heathcock *anti*-aldol reaction.[292] To this end, compound **434** was treated with two equivalents of Bu_2BOTf[298] in the presence of DIPEA to give rise to the corresponding (*Z*)-enolate (not shown). This intermediate was in turn further reacted with acetaldehyde (**432**) at −78 °C and careful work up (quenching with tartaric acid at −78 °C) afforded the desired *anti*-aldol product **439** in good yield (85%) and high diastereoselectivity (d.r. = 94:6) on a reasonable 1.5 g scale. However, the resulting alcohols **439** and **441** were inseparable by flash column chromatography at this stage. Mechanistically, this reaction proceeds *via* an open transition state **438**. Therein, the stereoselectivity solely originates from the minimization of the steric interactions between the alkyl residue of the aldehyde (*i.e.* a methyl group) and the auxiliary (Scheme 5.2a).[292] Thus, a reaction with acetaldehyde (**432**) is extremely challenging as the transition state **438** has to discriminate between a proton and a methyl group, which itself is not highly sterically demanding. Furthermore, the absolute configuration of the chiral auxiliary enforces an exclusive *si*-face attack, thus conferring a high level of induced diastereoselectivity. In contrast, a standard Evans-aldol reaction employing one equivalent of Bu_2BOTf involves a closed Zimmermann-Traxler transition state **440** that results in the selective formation of the *syn*-isomer **441** (Scheme 5.2b). This is due to four factors: (*a*) selective formation of the (*Z*)-enolate, (*b*) the aldehyde residue R adopts a pseudo-equatorial position, (*c*) the *iso*-propyl moiety induces diastereoselectivity by residing in a position which minimizes steric interactions with the chair transition state, (*d*) the overall dipole moment of the transition state is minimized.[299] Considering these arguments, it is remarkable that the simple use of one additional equivalent Bu_2BOTf allows for a reversal of the diastereoselectivity in Heathcock's modification.



Scheme 5.3 Synthesis of vinyl triflate **446** *via* a Dieckmann-type cyclization and verification of the desired outcome of the *anti*-aldol reaction by X-ray crystallography of carbamate **443**.

Since a verification of the outcome of the Heathcock *anti*-aldol reaction was worth striving for, a sample of the mixture was reacted with *p*-bromophenyl isocyanate **442** using Steglich's catalyst DMAP (Scheme 5.3).[300] Gratifyingly, the resulting carbamates could be separated by flash column chromatography and the major isomer **443** was isolated in 86% yield (minor isomer was not characterized). Moreover, the structure and the absolute configuration of the desired *anti*-aldol derivative **443** were unambiguously verified by X-ray crystallography. With this result in mind, we turned our attention to the envisaged acetylation, which occurred smoothly by treatment of alcohols **439** and **441** with acetic anhydride (**433**) in the presence of DMAP. Fortunately, the generated acetates **444** and **445** were also easily separated by flash column chromatography, furnishing the desired isomer **445** in 85% yield. Next, acetate **445** was exposed to excess KHMDS at −78 °C to trigger an Dieckmann condensation while liberating the free auxiliary **436** (not shown).[293b] As the purification of this intermediate was surprisingly difficult, the crude reaction mixture was subsequently reacted with triflic anhydride in the presence of Et_3N[301] to furnish enol triflate **446** in a good yield of 75% over the two steps. With enol triflate **446** in hand, the stage was set for the investigation of a Pd-catalyzed triflate-Sn exchange. To this end, different reaction conditions were examined (Table 5.1), among which was a catalytic system that was recently successfully applied in the Trauner laboratories.[302]

Table 5.1 Toward a triflate-Sn exchange: variation of the reaction conditions.[a]



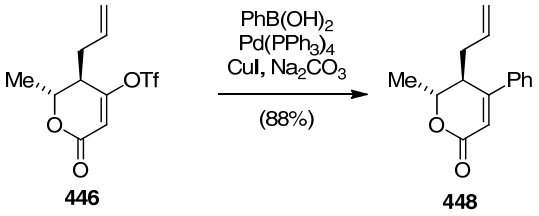
446 **430** **447**

Entry	Catalyst (eq.)	eq. of Me_6Sn_2	Additive (eq.)	Solvent	*T* [°C]	*t* [h]	Observation
1	$Pd(PPh_3)_4$ (0.1)	1.5	LiCl (6.0)	THF	60	16	decomp.
2	$Pd(PPh_3)_4$ (0.2)	2.0	CuI (0.4)	DMF	rt	1.2	decomp.
3	$Pd(PPh_3)_4$ (0.2)	1.5	-	DMF	rt	2.5	decomp.
4	$Pd(PPh_3)_4$ (0.1)	1.5	-	benzene	80		decomp.
5	Pd_2dba_3 (0.17)	1.5	CuI (0.3)	DMF	rt	1	**447** (72%)

(*a*) All reactions were carried out on 10–30 mg scale. eq. = equivalents, decomp. = decomposition, rt = room temperature.

Unfortunately, submitting enol triflate **446** to coupling conditions with Me_6Sn_2 in the presence of catalytic amounts of $Pd(PPh_3)_4$ and excess LiCl resulted only in decomposition, and no desired product formation was observed by ^1H NMR spectroscopy (Table 5.1, Entry 1). Similarly, when exchanging LiCl with CuI (Entry 2) or using no additive (Entry 3) and switching to DMF as a solvent, only decomposition was detected. The same observation was made when utilizing benzene as a solvent at

elevated temperature (Entry 4). As these results were not fruitful, we opted for an alternative source of Pd^0. Therefore, we exchanged $Pd(PPh_3)_4$ with Pd_2dba_3. When reacting enol triflate **446** with Me_6Sn_2 in the presence of this catalyst and CuI at room temperature,[302] a new product was detected, the structure of which was subsequently elucidated by NMR spectroscopy and mass spectrometry (Entry 5). Interestingly, these investigations revealed the new compound to be the homocoupled dimer **447** instead of the desired stannane **430**. It is assumed that the initially formed vinyl stannane **430** instantly reacts with remaining triflate **430** to form the observed product **447**.

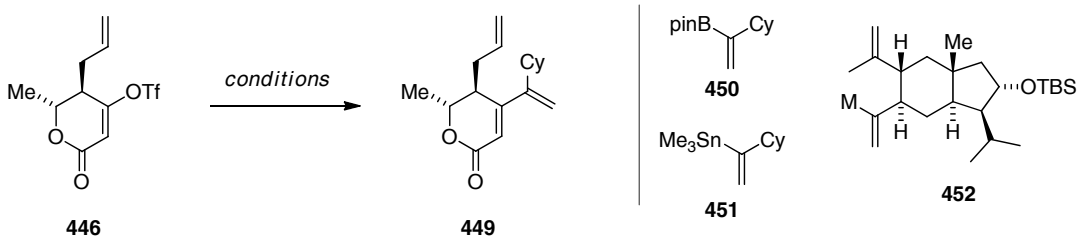


446 **448**

Scheme 5.4 Proof for the capability of triflate **446** to undergo Pd-catalyzed couplings: synthesis of lactone **448**.

In light of this finding, we decided to explore a direct coupling of enol triflate **446** with organometallic reagents rather than converting triflate **446** to stannane **430**. In order to provide a proof of principle, we conducted an initial Suzuki-coupling with phenylboronic acid in the presence of $Pd(PPh_3)_4$ and CuI in benzene/EtOH.[303] The expected reaction occurred smoothly and furnished the coupled product **448** in a high yield of 88% (Scheme 5.4).

Table 5.2 Toward a Pd-catalyzed cross coupling: variation of the reaction conditions



446 **449**

Entry	Coupling Partner	Pd[b]	Additive	Base[c]	Solvent	*T* [°C]	*t* [h]	Observation
1	**450**	$Pd(PPh_3)_4$	TBAB[d]	Na_2CO_3	benzene	80	16	decomp.
2	**450**	$Pd(dppf)Cl_2$	TBAB[d]	K_3PO_4	MeCN	81	1.2	decomp.
3	**450**	$Pd(PPh_3)_4$	TBAB[e]	K_3PO_4	Dioxane/H_2O	reflux	2.5	decomp.
4	**451**	$Pd(PPh_3)_4$	CuI, CsF[f]	-	DMF	50	1.3	decomp.
5	**451**	Pd_2dba_3	CuI[f]	-	DMF	50	3.3	decomp.

(*a*) All reactions were carried out on 10–25 mg scale. (*b*) 0.1 eq. for entries 1–3, 0.15 eq. for entries 4, 5. (*c*) 6.9 eq. for entry 1, 3.0 eq. for entries 2, 3. (*d*) 0.14 eq. (*e*) 0.28 eq. (*f*) 0.25 eq. CuI, 2.0 eq. CsF. eq. = equivalents, decomp. = decomposition, rt = room temperature.

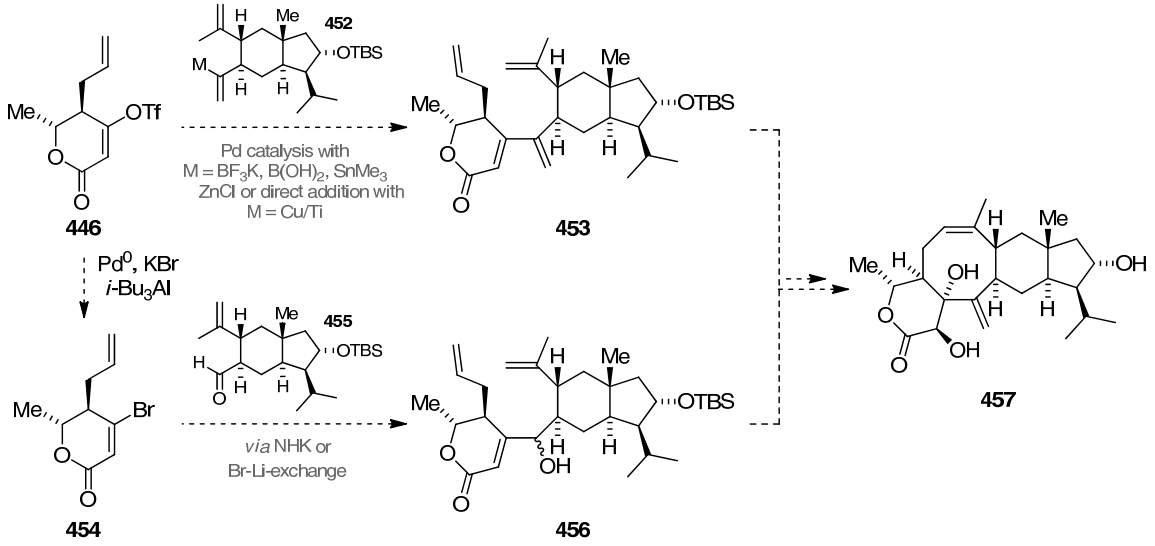
Encouraged by the capability of enol triflate **346** to engage in Pd-catalyzed cross coupling reactions, we prepared literature known boron-pinacol ester **450**[304] and vinyl stannane **451**[305] (syntheses not shown), both representing an alternative eastern fragment **452**. Next, their reactivity in a Suzuki or a Stille coupling with enol triflate **446** was explored to obtain intermediate **449**. For this purpose, we

initially altered the solvents as well as the source of Pd^0 using boron species **450** as coupling partner (Table 5.2, Entries 1–3).[306] However, solely decomposition of the starting material was observed. Unfortunately, submission of enol triflate **446** to reaction conditions for a Stille coupling with stannane **451** also resulted in decomposition of the substrate (Entries 4, 5).[307]

5.4 Conclusion and Future Directions

This chapter detailed our preliminary studies directed toward the synthesis of the potent GPI anchor inhibitor YW 3548 (**112**), focusing on the preparation of a suitable western fragment. Within these endeavors, we enantioselectively constructed enol triflate **446** in a concise five-step sequence starting from Evans auxiliary **436** (*cf*. Chapter 5.3). In addition, we conducted initial experiments on the ability of enol triflate **446** to undergo Pd-catalyzed coupling reactions. Although the preparation of the corresponding vinyl stannane **430** has not been accomplished yet, we were pleased to find that enol triflate **446** engaged smoothly in a Suzuki coupling with phenylboronic acid.

Since initial investigations to install an exomethylene moiety with organometallic reagents *via* Suzuki or Stille coupling remained unsuccessful,[308] a thorough screening with variation of temperature, solvent, base, Pd-sources and ligands should be performed in future to accomplish a synthesis of intermediate **453** (Scheme 5.5). In addition, other reaction partners such as boronic acids,[309] BF_3K[310] salts or organozinc species[311] should be explored. It should be noted that side reactions such as an intramolecular Heck reaction might occur when using 'real' coupling partner **452**. In this case, an alternative strategy could be investigated that involves a direct addition of a cuprate species[312] or an organotitanium reagent[313] to enol triflate **446**. However, such a protocol could be accompanied by a C–C bond fragmentation/ring opening of cyclic vinylogous acyl triflate **446** as described by Dudley for the addition of Grignard and organolithium nucleophiles.[301,314]

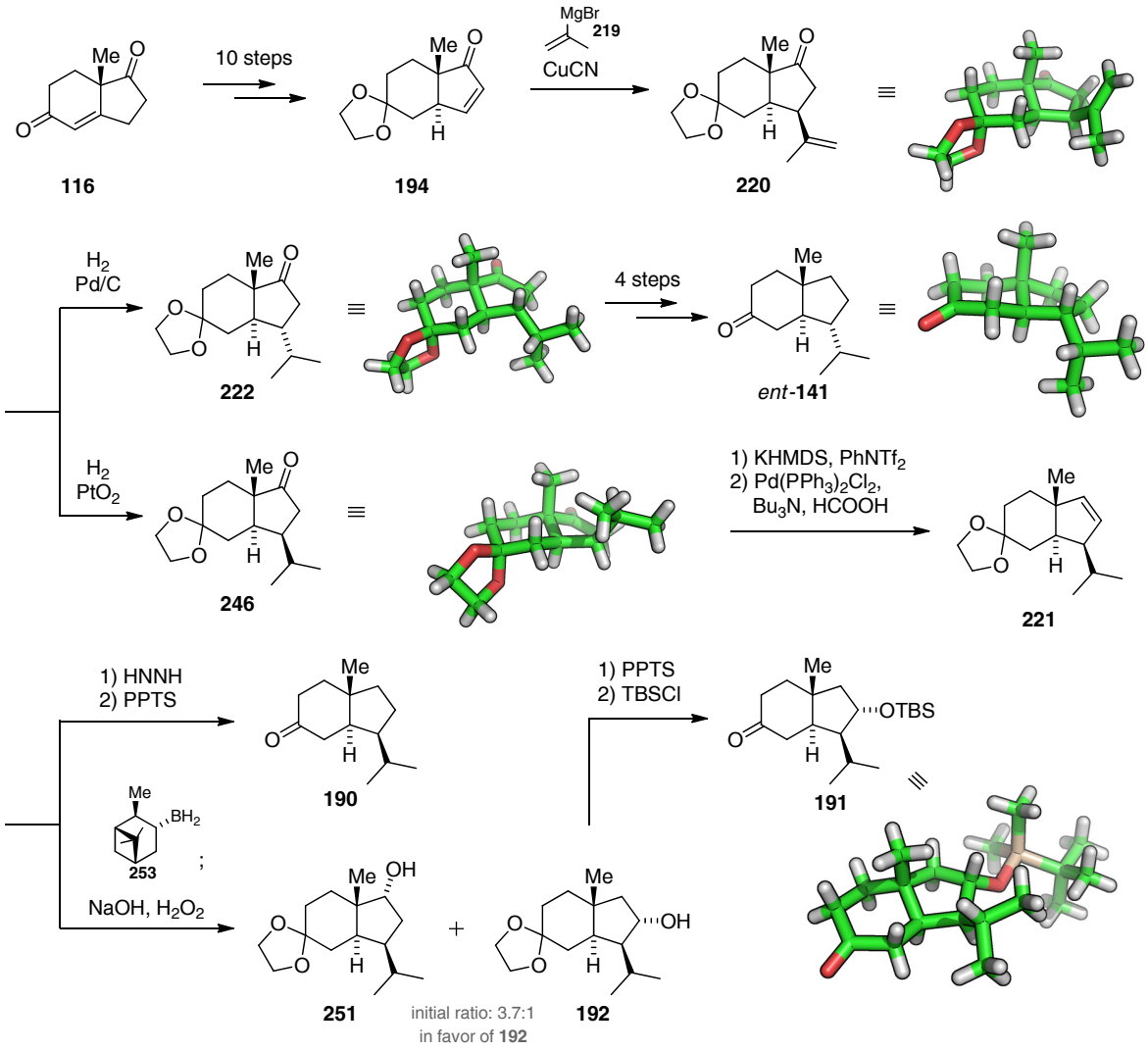


Scheme 5.5 Potential strategies for the combination of fragments *en route* to the tetracyclic backbone **457** of YW 3548 (**112**).

Alternatively, one could explore a NHK coupling[257] of vinyl triflate **446** with aldehyde **455** to form secondary alcohol **456**. However, the synthesis of this or the related eastern fragment **452** has not been examined to date. Along the lines of the NHK reaction, it might be worth to investigate the transformation of vinyl triflate **446** into the corresponding vinyl bromide **454** following a recently published procedure.[315,316] Such strategy would not only represent the preparation of another coupling partner for Pd-catalysis, but would also pave the way for a strategy hinging on a nucleophilic attack of the corresponding lithium species on aldehyde **455**. Overall, enol triflate **446** seems to be a valuable and readily accessible intermediate offering multiple possibilities for further investigations. If the task of fragment combination can be solved, the next challenge would be the closure of the central eight-membered ring by RCM. Ultimately, the endgame proposed in the retrosynthetic analysis should culminate in the first preparation of the tetracyclic backbone **457** of YW 3548 (**112**).

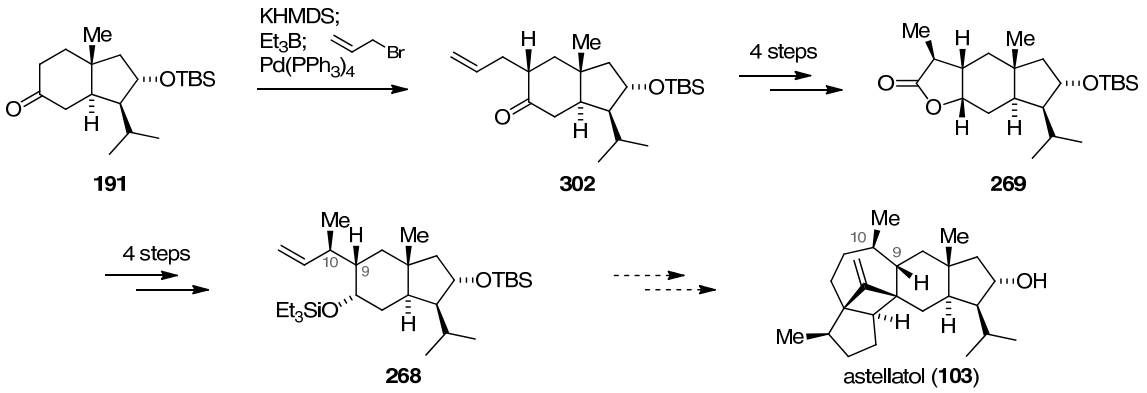
6 SUMMARY

In summary, this Ph.D. thesis detailed our progress toward the total synthesis of the type A *trans*-hydrindane *iso*-propyl sesterterpenoids astellatol (**103**), nitiol (**110**) and YW 3548 (**112**). Our program commenced with the evolution of an enantioselective route to three versatile building blocks suitable for synthetic studies toward these and structurally related natural products. Starting form enantiomerically pure diketone **116**, we prepared enone **194** in a multistep sequence on decagram scale, which in turn underwent a counterintuitive, but diastereoselective cuprate addition to furnish alkene **220** as the sole diastereomer (Scheme 6.1). Interestingly, the relative configuration at the newly introduced stereogenic center matched the one found in our target molecules. This result constituted a major achievement since it allowed for the selective installation of a *cis*-relationship between the angular methyl group and the isopropylene residue on a *trans*-hydrindane portion, a configuration which is otherwise difficult to address.



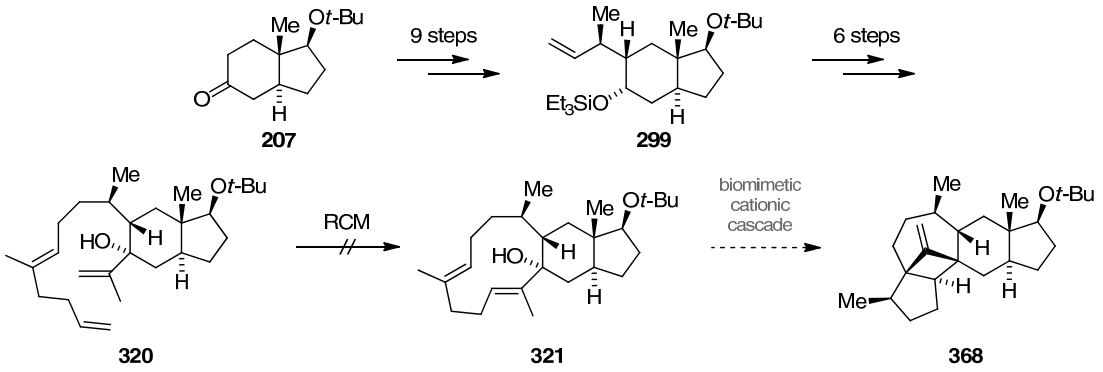
Scheme 6.1 Divergent asymmetric synthesis of versatile building blocks *ent*-**141**, **190** and **191** suitable for type A *trans*-hydrindane *iso*-propyl sesterterpenoids, and X-ray structures of important intermediates.

In the following investigations, we serendipitously discovered a highly selective diversification of ketone **220** utilizing hydrogenation conditions (Scheme 6.1). Whereas the use of Pd/C as a catalyst resulted in an almost complete inversion of the stereochemistry at the former allylic stereogenic center furnishing bicycle **222** in 91% yield, subjection of alkene **220** to PtO_2 under an atmosphere of hydrogen exclusively afforded the desired *β*-isomer **246** in 93% yield. Notably, we exploited this rare observation of an alkene isomerization under hydrogenation conditions in useful ways. On the one hand, we prepared ketone *ent*-**141** in a four-step reaction sequence starting from *a*-epimer **222**. On the other hand, ketone **246** was converted to alkene **221** *via* a highly efficient Pd-catalyzed hydrodetriflation. A subsequent straight-forward two-step protocol then provided building block **190**. Whereas ketone *ent*-**141** has been an intermediate in Corey's and Hudlicky's total syntheses of the pentacarbocyclic architecture of retigeranic acid A (**101**), its diastereomeric counterpart **190** could serve as the starting point for the first preparation of retigeranic acid B (**102**). Efforts toward this synthesis are currently under investigation by Florian M. E. Huber, a graduate student in the Trauner laboratories. Furthermore, these studies enabled us to access a third *trans*-hydrindane building block **191**, which contains an oxidized site in the cyclopentane moiety by diversification of alkene **221**. An extensive screening of hydroboration conditions revealed that the use of the chiral borane **253** gave the best results in respect to the regioselectivity. With this protocol, alcohols **192** and **251** were obtained in a synthetically useful ratio of 3.7:1 in favor of the desired product **192**. The reaction as well constituted a matched case of double diastereoselection. Upon careful flash column chromatography in the subsequent steps, we succeeded in the isolation of pure ketone **191**. Overall, this developed first-generation route was as envisaged robust and scalable and allowed for the preparation of multigram quantities of versatile intermediates **190** and **191** albeit requiring a total of 19 and 20 steps, respectively. Since ^{1}H and 2D NMR analysis was often thwarted by overlaying signals, our studies heavily relied on X-ray crystal structure analysis for unambiguous structure elucidation. Moreover, the observed stereochemical surprises emphasize a meticulous analysis of products, even with seemingly straight-forward reactions.



Scheme 6.2 Progress toward astellatol (**103**): installation of the stereogenic centers at C-9 and C-10 in alkene **268** by a series of diastereoselective operations starting from building block **191**.

After the successful preparation of building blocks *ent*-**141**, **190** and **191**, we launched further studies toward type A *trans*-hydrindane *iso*-propyl sesterterpenoids. The major portion of these investigations was focused on intermediates *en route* to the unique pentacarbocyclic structure of astellatol (**103**). To this end, we initially opted to secure a reliable route for the installation of two adjacent stereogenic centers at C-9 and C-10 (astellatol numbering) and decided to take advantage of the conformational bias of a tricyclic system. As ketone **191** proved to be complicated to alkylate at C-9 under standard conditions, we resorted to a Pd-catalyzed allylation of the corresponding boron enolate to yield ketone **302** (Scheme 6.2). Further reactions including two highly diastereoselective transformations, a reagent-controlled reduction and a substrate controlled methylation, gave lactone **269** as single diastereomer that in turn was elaborated to alkene **268** in several steps. The key feature of this protocol was a chemoselective deprotective Swern oxidation, requiring a careful optimization of reaction conditions regarding temperature and time. Notably, at this stage the final fragment **268** incorporated the correct relative configuration at six out of ten stereogenic centers found in astellatol (**103**).

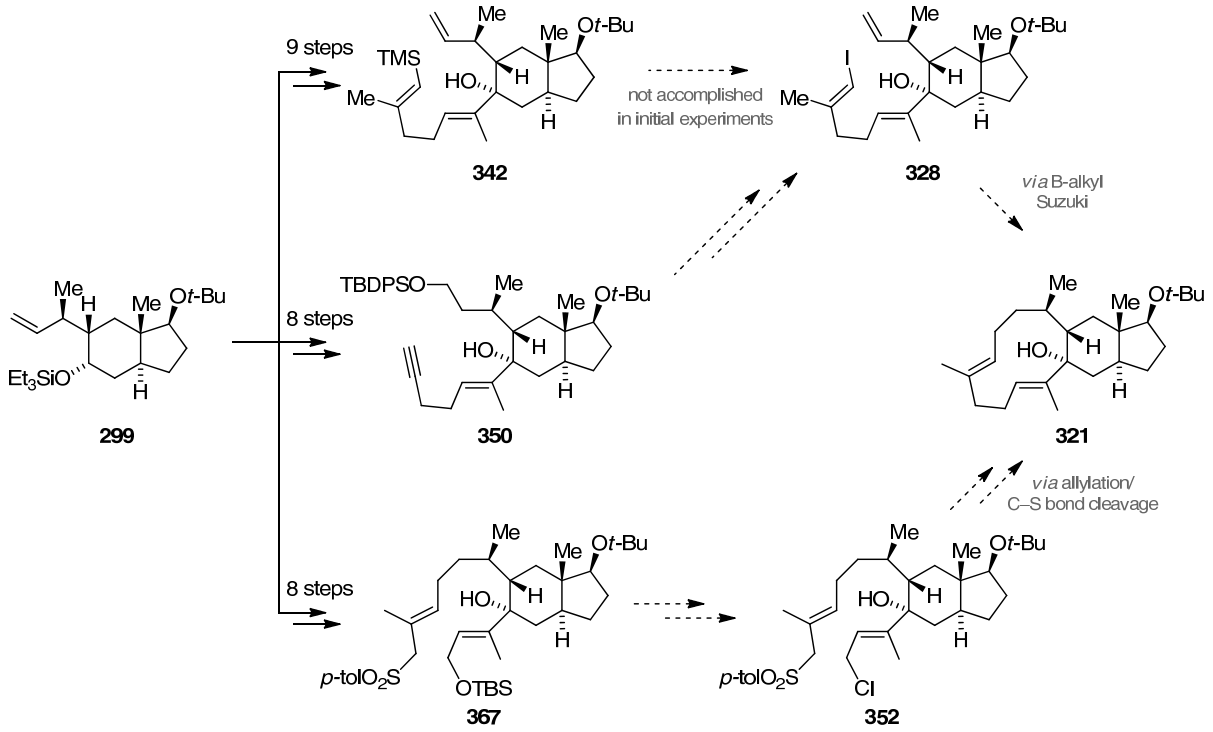


Scheme 6.3 First generation approach *en route* to tricycle **328**: attempted RCM of triene **320**.

As this reaction sequence had been previously established on a more easily accessible model system **207**, we performed further studies toward the synthesis of astellatol (**103**) utilizing alkene **299** as the branching point. This intermediate **299** was synthesized on multigram scale and four strategies to assemble the pentacyclic carbon skeleton of astellatol (**103**) were examined in the course of this Ph.D. thesis. Three of these routes hinged on the preparation of a strained 11-membered macrocycle **321**, the precursor for an envisaged biomimetic cationic cascade to prepare pentacycle **368** (Scheme 6.3). In our first approach, we elaborated alkene **299** in several synthetic operations to triene **320** featuring a B-alkyl Suzuki coupling and a second deprotective Swern oxidation as key elements. Unfortunately, the investigated RCM reaction conditions have not yet effected a ring closure to macrocycle **321** but rather furnished the homodimer, arising from cross metathesis at the more easily accessible terminal vinyl moiety (*cf.* Chapter 3.4).

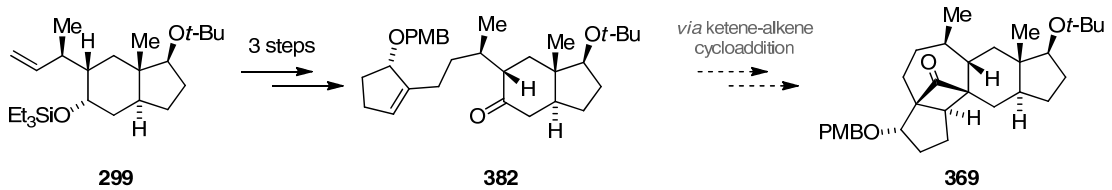
In a second route, alkene **299** was converted to vinyl silane **342** in a multistep sequence involving a regioselective Pd-catalyzed silylstannylation and a diastereoselective vinyl lithium addition as key transformations (Scheme 6.4). While investigating the required iododesilylation to prepare vinyl iodide **328**, the precursor for a B-alkyl Suzuki macrocyclization, an undesired iodoetherification took

place (*cf.* Chapter 3.5). Initial experiments to circumvent this side reaction have failed so far, and this strategy thus will be studied more thoroughly in future experiments. In addition, we designed an approach involving a late-stage alkene installation and already prepared alkyne **350**, which needs to be elaborated to vinyl iodide **328**.



Scheme 6.4 Progress toward constructing the macrocycle in key substrate **321**: successful synthesis of advanced intermediates and future milestones for the B-alkyl Suzuki and the allylation approach, respectively.

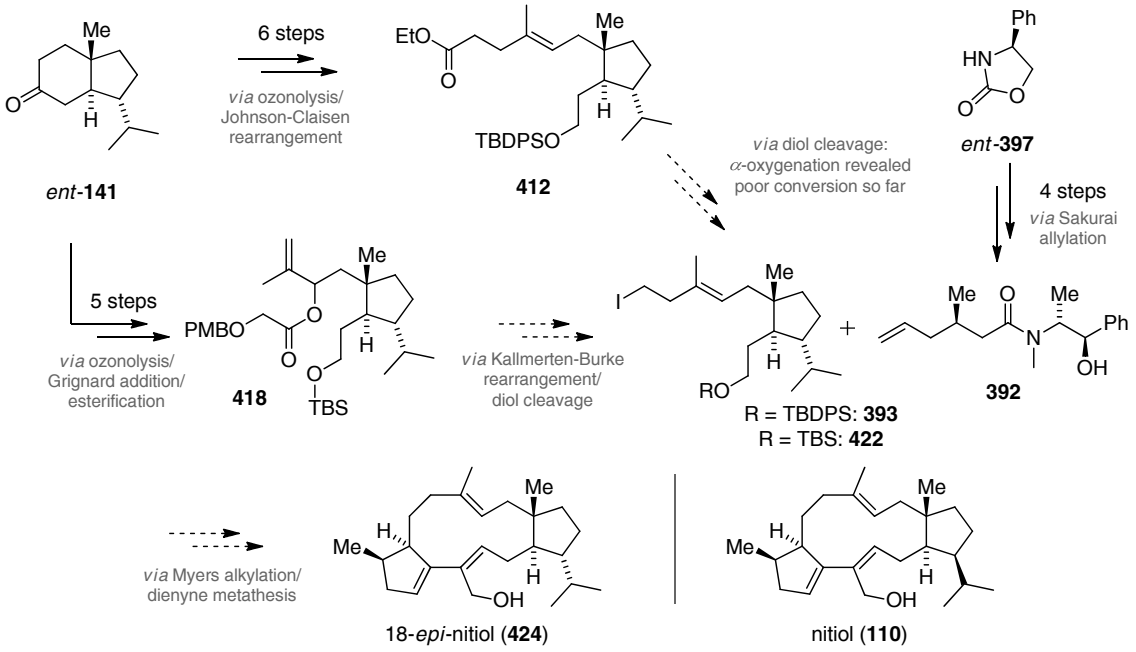
In contrast to the two earlier routes which rely on modern transition metal catalysis to close the 11-membered ring, a third strategy was based on an intramolecular allylation of sulfone **352**. To this end, alkene **299** was elaborated to alcohol **367** by sequential B-alkyl Suzuki coupling, vinyl lithium addition and selective functional group manipulations (Scheme 6.4). The remaining two steps for the synthesis of allyl chloride **352** have not been examined in the course of this Ph.D. thesis and will be explored in near future. Notably, the prepared intermediates **320**, **342** and **352** and contain all 22 carbon atoms necessary for the construction of tricycle **321**.



Scheme 6.5 Progress toward the assembly of pentacycle **369** *via* a thermal [2+2]-cycloaddition: synthesis of ketone **382**.

As an alternative to the highly challenging preparation of astellatol (**103**) *via* a bioinspired cationic cascade starting from tricycle **321**, we embarked on efforts toward the installation of the carbon backbone by an intramolecular [2+2]-cycloadditon. In these studies, alkene **299** served again as the starting point and was elaborated to ketone **382** utilizing a B-alkyl Suzuki coupling (Scheme 6.5). In

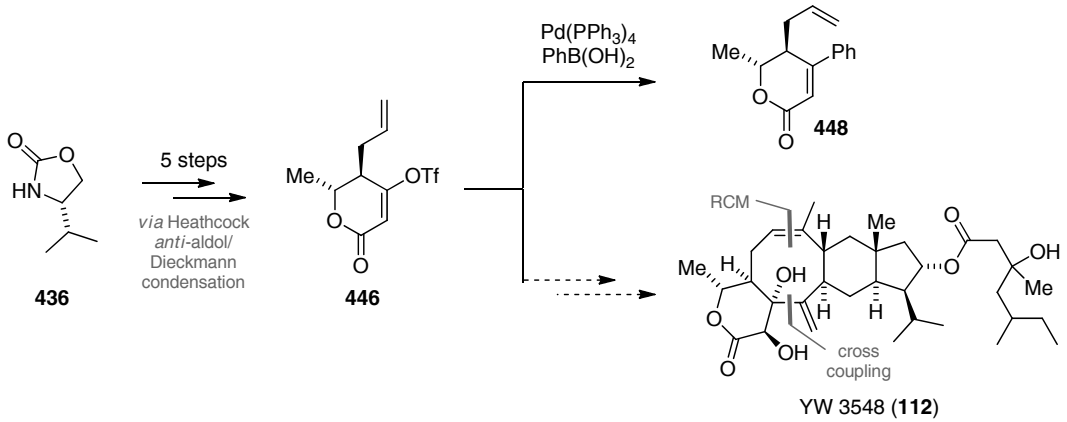
initial experiments on an analog bearing a methyl instead of the PMB ether, we partially succeeded in homologating the ketone functionality to an aldehyde (*cf.* Chapter 3.7). Thus, we are optimistic that the reaction conditions can be optimized soon. If this task is realized, the developed protocols need to be tested on ketone **382** in order to prepare the substrate for the envisaged key ketene-alkene cycloaddition to construct pentacycle **369**.



Scheme 6.6 *En route* to 18-*epi*-nitiol (**424**): successful synthesis of western fragment **392** and progress toward the preparation of alkyl iodides **393** and **422**.

Beside these extensive studies toward astellatol (**103**), we investigated the total synthesis of the tricyclic sesterterpenoid nitiol (**110**). Since the surprising stereochemical outcome of the hydrogenation of ketone **220** in the presence of Pd/C was only established at a later stage, substantial amounts of ketone *ent*-**141** were still left. This material was employed for model studies toward the C-18 epimer **424** of nitiol (**110**). In our initial approach toward a suitable eastern fragment **393** or **422**, we accomplished the synthesis of ester **412** starting from ketone *ent*-**141** in several steps that included an ozonolysis of a regioselectively generated silyl enol ether and a Claisen-Johnson rearrangement to install the trisubstituted alkene (Scheme 6.6). As attempts to shorten the side chain by one carbon atom met with little success, we prepared ester **418** in a second-generation route. This compound **418** constitutes a precursor for a Kallmerten-Burke rearrangement and has the additional oxygen functionality already in place to later conduct a diol cleavage. In preliminary studies, we already observed the desired product originating from the desired sigmatropic rearrangement. Thus future explorations should address experiments along the lines of this promising result. In addition, we succeeded in the synthesis of the western fragment **392**, comprising a pseudoephedrine auxiliary for the envisaged fragment union by a Myers alkylation. The preparation of amide **392** commenced with diastereoselective 1,4-additions under cuprate or Sakurai conditions, which interestingly required the use of enantiomeric Evans-auxiliaries **397** (*cf.* Chapter 4.3). In the course of these studies, the Sakurai

reaction turned out to be more convenient on larger scale albeit less diastereoselective. Ultimately, simple saponification of the chiral auxiliary and an EDCI mediated coupling with pseudoephedrine gave the desired fragment **392**.



Scheme 6.7 *En route* to YW 3548 (**112**): enantioselective five-step synthesis of enol triflate **446**, obtained coupling product **448** and key disconnections for the construction of the central eight-membered ring.

The last part of this Ph.D. thesis discussed the studies toward a δ-lactone **446**, which might serve as a valuable intermediate for the total synthesis of the structurally intriguing GPI anchor inhibitor YW 3548 (**112**). We exploited the Heathcock *anti*-aldol protocol to establish two adjacent stereocenters with high diastereoselectivity. In this reaction, the *syn*-selectivity of a standard Evans aldol reaction is inverted by adding a second equivalent of Bu_2BOTf. Further synthetic operations including a Dieckmann condensation to close the six-membered ring with concomitant cleavage of the amide auxiliary **436** furnished enol triflate **446** (Scheme 6.7). While attempts to convert this compound **446** to the corresponding vinyl stannane have not been successful yet, we demonstrated the ability of enol triflate **446** to engage in Pd-catalyzed cross coupling reactions by preparing alkene **448**. In future directions, a thorough screening of reaction conditions such as ligands, solvents, temperatures and the careful choice of a suitable coupling partner will be required in order to construct the tetracyclic architecture of YW 3548 (**112**).

Overall, the pursued strategies presented in this Ph.D. thesis constituted significant progress toward the first total synthesis of any type A *trans*-hydrindane *iso*-propyl sesterterpenoid, exhibiting a sterically encumbered *trans*-hydrindane portion with an *iso*-propyl moiety residing in a *cis*-relationship with the angular methyl group. The developed robust and scalable route to various versatile building blocks provided a basis for further efforts toward these structurally intriguing natural products that are currently under investigation in the Trauner laboratories. Thus, these challenging architectures will certainly continue to inspire and train a new generation of synthetic chemists, which will hopefully access one of these sesterterpenoids in the near future.

EXPERIMENTAL SECTION

1 GENERAL WORKING METHODS

All reactions were magnetically stirred and carried out under a positive pressure of inert-gas (N_2 or argon) utilizing standard Schlenk-techniques. Glassware was dried in an oven at 120 °C and repeatedly at 650 °C *in vacuo* prior to use. Liquid reagents and solvents were added by syringes or oven-dried stainless steel cannulas through rubber septa. Solids were added under inert gas counter flow or were dissolved in appropriate solvents. Low temperature reactions were carried out in a Dewar vessel using a cryo cooler or filled with a cooling agent: acetone/dry ice (–78 °C), acetonitrile/liquid N_2 (–40 °C), NaCl/ice (–20 °C) or ice/water (0 °C). Reaction temperatures above room temperature were conducted in a heated oil bath. High pressure reactions were conducted in a miniclave steel apparatus from *BÜCHI AG*. Drying of organic extracts over $MgSO_4$ or Na_2SO_4 implicates a subsequent removal of the drying agent by filtration and rinsing of the filter cake with an appropriate solvent. Yields refer to isolated homogeneous and spectroscopically pure materials.

Solvents and reagents

Tetrahydrofurane (THF) and diethyl ether (Et_2O) were distilled under N_2 atmosphere from Na/benzophenone as drying agent prior to use. Triethylamine (Et_3N), diisopropylamine (DIPA) and Hünig's base (DIPEA) were distilled under N_2 atmosphere from CaH_2 as drying agent prior to use. Further dry solvents such as dichloromethane (CH_2Cl_2), *N*,*N*-dimethylformamide (DMF), acetonitrile (MeCN), acetone, methanol (MeOH), benzene and toluene were purchased as 'Extra Dry over Molecular Sieves' from *Acros Organics* and were used as received. Hexamethylphosphoramide (HMPA) was distilled from CaH_2 *in vacuo* and stored over molecular sieves under an atmosphere of N_2. Solvents for extraction, crystallization and flash column chromatography were purchased in technical grade and distilled under reduced pressure prior to use. (*S*)-Alpine-Boramine™, (*R*)-Alpine-Boramine™, 9-BBN dimmer and CBS catalyst **375** were purchased from *Sigma-Aldrich* and stored in a UNIlab glove-box from *MBRAUN*. Methyl vinyl ketone (MVK, **122**) was purchased in technical grade (90%) and distilled immediately prior to use. Allyl bromide was distilled prior to use and stored under an atmosphere of N_2. Et_3B was purchased neat and appropriate solutions in degassed THF (freeze-pump-thaw method) were freshly prepared immediately prior to use. The following reagents were prepared according to literature procedures: Evans auxiliaries **397**,[264] *ent*-**397**[264] and **436**,[296] oxazolidinone **403**,[266] vinyl iodide **307**,[200] PMB ether **329**,[219] Ohira-Bestmann reagent (**336**),[317] vinyl iodide **356**,[238] vinyl iodide **363**,[240] vinyl iodide **377**,[249] pinacol borate **450**,[304] vinyl stannane **451**,[305] DMP,[208] Bu_2BOTf,[298] MoOPH.[275] All other reagents and solvents were purchased from chemical suppliers (*Sigma-Aldrich*, *Acros Organics*, *Alfa Aesar*, *Merck*, *Strem*, *ABCR*, *TCI Europe*) and were used as received.

Chromatography

Reactions and chromatography fractions were monitored by qualitative thin-layer chromatography (TLC) on silica gel F_{254} TLC plates from *Merck KGaA*. Analytes on the glass plates were visualized by irradiation with UV-light and/or by immersion of the TLC plate in an appropriate staining solution followed by heating with a hot-air gun (350 °C). The following staining solutions were applied:

- *p*-anisaldehyde staining solution (3.7 mL *p*-anisaldehyde, 5.0 mL concentrated aqueous H_2SO_4, 1.5 mL glacial AcOH, 135 mL EtOH).
- CAM staining solution (5.0 g, $Ce(SO_4)_2$, 25 g $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, 50 mL concentrated aqueous H_2SO_4, 450 mL H_2O).
- $KMnO_4$ staining solution (3.0 g $KMnO_4$, 20 g K_2CO_3, 5.0 mL aqueous 5% NaOH, 300 mL H_2O).
- DNP staining solution (12 g 2,4-dinitrophenylhydrazine, 60 mL concentrated aqueous H_2SO_4, 200 mL EtOH, 80 mL H_2O).

Flash column chromatography was performed on Geduran® Si60 (40–63 μm) silica gel from *Merck KGaA*. All fractions containing a desired substrate were combined and solvents were removed under reduced pressure followed by drying *in high vacuo* (10^{-2} mbar).

NMR spectroscopy

NMR spectra were recorded by the analytic section of the Department of Chemistry of the *Ludwig-Maximilians-Universität München* using *Bruker* AXR300, *Varian* VXR400 S and *Bruker* AMX600 spectrometers operating at 300 MHz, 400 MHz and 600 MHz for proton nuclei (75 MHz, 100 MHz, 150 MHz for carbon nuclei). $CDCl_3$, CD_2Cl_2 and C_6D_6 were purchased from Sigma-Aldrich and Euriso-top. The ^{1}H NMR shifts are reported in ppm related to the chemical shift of TMS. ^{1}H NMR shifts were calibrated to residual solvent resonances: $CDCl_3$ (7.26 ppm), CD_2Cl_2 (5.32 ppm) C_6D_6 (7.16 ppm). ^{13}C NMR shifts were calibrated to the center of the multiplet signal of the residual solvent resonance: $CDCl_3$ (77.16 ppm), CD_2Cl_2 (54.00 ppm), C_6D_6 (128.37 ppm).

^{1}H NMR spectroscopic data are reported as follows: Chemical shift in ppm (multiplicity, coupling constants *J*, integration intensity). The multiplicities are abbreviated with s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and m_C (centrosymmetric multiplet). In case of combined multiplicities, the multiplicity with the larger coupling constant is stated first. Except for multiplets, the chemical shift of all signals, as well for centrosymmetric multiplets, is reported as the center of the resonance range. Additionally to recording ^{1}H and ^{13}C NMR spectra, 2D NMR techniques such as homonuclear correlation spectroscopy (COSY), heteronuclear single quantum coherence (HSQC), heteronuclear multiple bond coherence (HMBC), nuclear Overhauser enhancement correlation spectroscopy (NOESY) were used to assign signals. Thereby, the numbering of the carbon skeleton does not correspond to the IUPAC nomenclature. If two signals could not be

assigned unambiguously by these methods, the assigned carbon atoms are marked as '*', '**', etc. and the assignment is interchangeable. Coupling constants ${}^{n}J_{A/B}$ between protons A and B across *n* bonds are reported in Hz, if an assignment of the two coupling partners was possible. Otherwise, coupling constants are given as *J* in Hz. Diastereotopic protons were named as H_A and H_B with H_A corresponding to the more downfield-shifted signal. All NMR spectra were analyzed using the program *MestRe NOVA 5.2.0* from *Mestrelab Research S. L.*

Mass spectrometry

All mass spectra were measured by the analytic section of the Department of Chemistry of the *Ludwig-Maximilians-Universität München*. Mass spectra were recorded on the following spectrometers (ionization mode in brackets): MAT 95 (EI) and MAT 90 (ESI) from *Thermo Finnigan GmbH* or JMS-700 (FAB) from *Jeol Ltd.* Mass spectra were recorded in high-resolution and the only characteristic molecule fragments or molecule ion peaks are indicated for each analyte. The method used is reported at the relevant section of the experimental part.

IR spectroscopy

IR spectra were recorded on a *PerkinElmer* Spectrum BX II FT-IR system. All substances were dissolved in CH_2Cl_2 and directly applied on the ATR unit. The measured wave numbers are reported in cm^{-1} and the band intensities are described with br (broad), s (strong), m (medium) and w (weak).

Melting points

Melting points were measured on a B-540 melting point apparatus from *BÜCHI Labortechnik AG* and are uncorrected.

Optical rotation

Optical rotation values were recorded on a polarimeter P8000-T from *A. Krüss Optronic GmbH* or on a *PerkinElmer* 241 polarimeter. The specific rotation is calculated as follows:

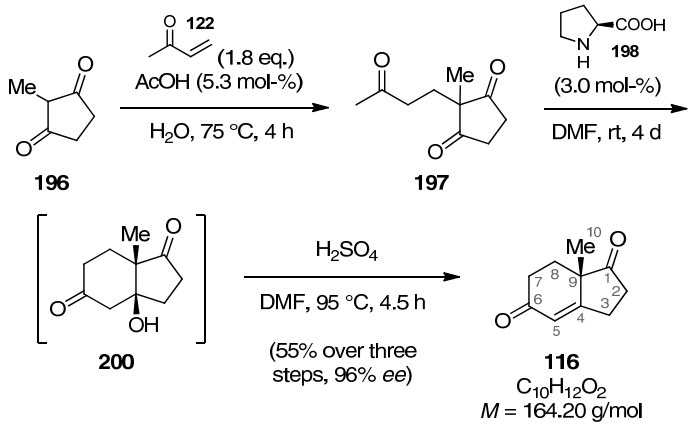
$$[\alpha]_{\lambda}^{\vartheta} = \frac{[\alpha] \cdot 100}{c \cdot d}$$

The wave length λ is reported in nm and the measuring temperature ϑ in °C. α resembles the recorded optical rotation at the apparatus, *c* the concentration of the analyte in 10 mg/mL and *d* the length of the cuvette in dm. Thus, the specific rotation is given in $10^{-1} \cdot deg \cdot cm^2 \cdot g^{-1}$. Usage of the sodium D line (λ = 589 nm) is indicated by D instead of the wavelength in nm. The respective concentration as well as the solvent is denoted in the analytical part of the experimental description.

2 EXPERIMENTAL PROCEDURES

2.1 Experimental Procedures for Chapter 2: 'A Unified Approach toward *trans*-Hydrindane *iso*-Propyl Sesterterpenoids'

Synthesis of the ESWHP Ketone (116)



To a suspension of diketone **196** (100 g, 890 mmol, 1.0 eq.) in H_2O (220 mL) was added methylvinylketone (**122**, 130 mL, 1.59 mol, 1.8 eq.) followed by AcOH (2.70 mL, 47.0 mmol, 5.3 mol-%). The reaction apparatus was shielded from light and the mixture was heated to 75 °C for 4 h. The reaction was allowed to cool to room temperature and the product was extracted with CH_2Cl_2 (1 x 500 mL, 2 x 100 mL). The combined organic layers were washed with saturated aqueous NaCl (1 x 300 mL, 1 x 200 mL) and the combined aqueous layers were re-extracted with CH_2Cl_2 (2 x 150 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure to afford crude triketone **197** (147 g, 808 mmol, 91%) as a light-orange oil, which was used without further purification.

A light-protected suspension of (*S*)-proline (**198**, 2.80 g, 24.3 mmol, 3.0 mol-%) in DMF (607 mL) was degassed four times (evacuated and backfilled with N_2) and stirred at 16 °C for 1 h. Then, a solution of crude triketone **197** (147 g, 808 mmol, 1.0 eq.) in DMF (200 mL + 2 x 25 mL rinse) was added and the mixture was degassed four times. After slowly warming to room temperature and stirring for an additional four days at ambient temperature, the reaction was judged to be complete by TLC and the mixture, containing crude bicycle **200**, was used in the next step without further purification.

Initially, a solution of H_2SO_4 in DMF was prepared by dropwise addition of concentrated H_2SO_4 (6.36 mL) to DMF (116 mL) at –21 °C.

The above prepared mixture of crude bicycle **200** in DMF was heated to 95 °C. When the external temperature reached 75 to 80 °C, an aliquot of the H_2SO_4 solution (58 mL) was added. After stirring for 1 h at 95 °C, another aliquot of the H_2SO_4 solution (23 mL) was added and the mixture was stirred

for an additional 3.5 h at this temperature, before being allowed to cool to room temperature. The solvent was removed under reduced pressure and the resulting residual dark brown oil was dissolved in CH_2Cl_2 (1.1 L). The organic layer was washed with NaCl-saturated H_2SO_4 (1M, 2 x 500 mL), NaCl-saturated aqueous saturated $NaHCO_3$ (2 x 500 mL) and with saturated aqueous NaCl (500 mL). Each aqueous layer was extracted with the same fraction of CH_2Cl_2 (2 x 500 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residual brown oil was dissolved in EtOAc and the solution was filtered over dry silica. The product containing fractions were combined and the solvent was removed under reduced pressure to obtain a brownish solid. Such material was subjected to bulb-to-bulb distillation (210 °C, 0.4 mbar) giving a pale yellow solid. Finally, recrystallization (Et_2O/hexanes) afforded diketone **116** (80 g, 488 mmol, 55% over three steps, 96% *ee*) as colorless crystals, which were suitable for X-ray analysis.

R_f = 0.30 (hexanes:EtOAc = 1:1).

Melting point = 63.0–64.0 °C (Et_2O/hexanes).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.93 (m_C, 1H, 5-H), 2.93 (m_C, 1H, 3-H_A), 2.82–2.67 (m, 2H, 2-H_A, 3-H_B), 2.56–2.33 (m, 3H, 2-H_B, 7-H), 2.07 (ddd, $^2J_{8A/8B}$ = 13.5 Hz, $^3J_{8A/7}$ = 5.1, 2.2 Hz, 1H, 8-H_A), 1.82 (ddd, $^2J_{8B/8A} = {}^3J_{8B/7}$ = 13.7 Hz, $^3J_{8B/7}$ = 5.6 Hz, 1H, 8-H_B), 1.29 (s, 3H, 10-H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 216.6 (C-1), 198.2 (C-6), 169.8 (C-4), 123.9 (C-5), 48.8 (C-9), 36.0 (C-2), 33.0 (C-7), 29.3 (C-8), 26.9 (C-3), 20.7 (C-10) ppm.

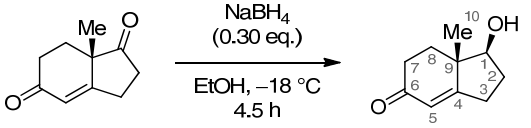
EI-MS for $C_{10}H_{12}O_2^+$ [M^+]: calcd. 164.0832
found 164.0831.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 2932 (w), 2871 (w), 1745 (s), 1667 (s), 1448 (w), 1348 (w), 1232 (w), 1148 (w), 1060 (w), 866 (w).

$[\alpha]_D^{20}$ = +332.0 (*c* 1.00, toluene).

The analytical data matched those reported previously.[121]

Synthesis of Alcohol 201



116 **201**

$C_{10}H_{14}O_2$

M = 166.22 g/mol

Due to the limited capacities of Dewar vessels, two experiments were set up in parallel: To a solution of diketone **116** (25.4 g, 155 mmol, 1.0 eq.) in EtOH (400 mL) at −18 °C was added dropwise a solution of $NaBH_4$ (1.76 g, 46.6 mmol, 0.30 eq.) in EtOH (275 mL) within 3.5 h (dropping funnel) and the mixture was stirred for an additional 1 h at this temperature. Then, the reaction was quenched by slow addition of aqueous HCl (2M) until the pH was adjusted to approximately 6. Both experiments (50.5 g of diketone **116** in total) were combined and the solvent was evaporated under reduced pressure. The resulting residue was partitioned between EtOAc (500 mL) and saturated aqueous NaCl (125 mL) and the aqueous layer was extracted with EtOAc (3 x 125 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were evaporated under reduced pressure. The thus obtained crude product was purified by flash column chromatography (silica, CH_2Cl_2:MeOH = 93:7) to yield title compound **201** (51.2 g, 308 mmol, quant.) as a pale yellow wax.

R_f = 0.23 (CH_2Cl_2:MeOH = 93:7).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.76 (m_C, 1H, 5-H), 3.83 (dd, $^3J_{1/2}$ = 10.3, 7.6 Hz, 1H, 1-H), 2.69 (m_C, 1H, 3-H_A), 2.57–2.31 (m, 4H, 3-H_B, 7-H, *O*H), 2.18–2.05 (m, 2H, 2-H_A, 8-H_A), 1.88–1.70 (m, 2H, 2-H_B, 8-H_B), 1.13 (s, 3H, 10-H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.5 (C-6), 175.5 (C-4), 123.5 (C-5), 80.7 (C-1), 45.3 (C-9), 34.2 (C-8), 33.4 (C-7), 29.2 (C-2), 26.6 (C-3), 15.2 (C-10) ppm.

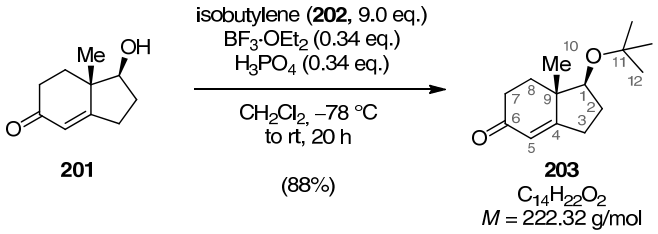
EI-MS for $C_{10}H_{14}O_2^+$ [M^+]: calcd. 166.0988
found 166.0980.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 3400 (br s), 2967 (m), 2867 (w), 1643 (s), 1417 (w), 1349 (m), 1322 (w), 1201 (m), 1086 (m), 1074 (m), 1034 (w), 956 (w).

$[\alpha]_D^{20}$ = +78.6 (*c* 1.00, CH_2Cl_2).

The analytical data matched those reported previously.[127,132]

Synthesis of Enone 203



To a solution of alcohol **201** (40.7 g, 245 mmol, 1.0 eq.) in CH_2Cl_2 (400 mL) at −78 °C was added isobutylene (**202**, approximately 200 mL, 2.23 mol, 9.0 eq.) and H_3PO_4 (100%, 4.50 mL, 0.34 eq.) followed by $BF_3{\cdot}OEt_2$ (10.3 mL, 83.5 mmol, 0.34 eq.). The reaction was stirred for 2 h at −78 °C and was then allowed to warm to room temperature. After stirring for an additional 18 h at room temperature, the reaction was quenched by addition of aqueous NH_4OH (2M, 400 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 350 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 3:1 to 2:1) to yield enone **203** (47.8 g, 215 mmol, 88%) as a colorless solid.

R_f = 0.51 (hexanes:EtOAc = 3:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.74 (m_C, 1H, 5-H), 3.55 (dd, $^3J_{1/2}$ = 9.8, 7.3 Hz, 1H, 1-H), 2.67 (m_C, 1H, 3-H_A), 2.49 (ddd, J = 17.7, 14.3, 5.2 Hz, 1H, 7-H_A), 2.41–2.28 (m, 2H, 3-H_B, 7-H_B), 2.05–1.90 (m, 2H, 2-H_A, 8-H_A), 1.85–1.64 (m, 2H, 2-H_B, 8-H_B), 1.16 (s, 9H, 12-H), 1.09 (s, 3H, 10-H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.5 (C-6), 175.6 (C-4), 123.0 (C-5), 79.8 (C-1), 73.2 (C-11), 44.9 (C-9), 34.5 (C-8), 33.6 (C-7), 29.7 (C-2), 28.8 (C-12), 27.0 (C-3), 15.8 (C-10) ppm.

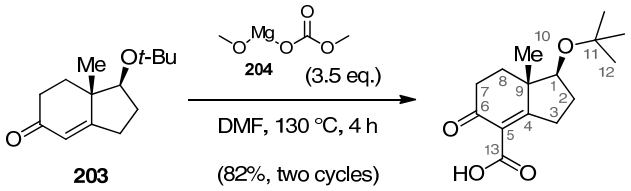
EI-MS for $C_{14}H_{23}O_2^+$ [$(M+H)^+$]: calcd. 223.1685
found 223.1693.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 2973 (m), 2936 (w), 1671 (s), 1464 (w), 1419 (w), 1390 (w), 1364 (w), 1218 (m), 1199 (m), 1092 (m), 1028 (w), 1005 (w), 956 (w), 891 (w).

$[\alpha]_D^{20}$ = +49.9 (c 1.00, $CHCl_3$).

The analytical data matched those reported previously.[127]

Synthesis of Carboxylic Acid 205



To a solution of indenone **203** (56.9 g, 256 mmol, 1.0 eq.) in DMF (560 mL) was added MMC (**204**, 450 mL of a 2M solution in DMF, 900 mmol, 3.5 eq.) and the mixture was degassed (N_2 bubbling) for 30 min. Then, the reaction vessel was placed in an oil bath (pre-heated to 130 °C) and the mixture was stirred for 4 h at 130 °C (*Caution: initially vigorous gas evolution*). The mixture was allowed to cool to room temperature and then further cooled to 0 °C before slowly adding aqueous HCl (2N) until the solution solidified. Thereafter, Et_2O (500 mL) was added followed by concentrated aqueous HCl until the pH was adjusted to 2–3 and two homogenous layers were formed (*Caution: slow addition of HCl is necessary due to gas evolution*). The phases were separated and the aqueous layer was extracted with Et_2O (4 x 600 mL, 1 x 400 mL). The combined organic layers were splitted into two equivolumetric parts and each aliquot was washed with 10% aqueous NaCl (300 mL acidified with HCl to pH = 2–3). The aqueous layers were re-extracted with Et_2O (2 x 300 mL) and the combined organic layers were dried over $MgSO_4$. Having evaporated the solvents under reduced pressure, the crude product was recrystallized from hexanes at –78 °C to yield acid **205** (35.4 g, 133 mmol, 52%).
The mother liquor was concentrated and subjected to flash column chromatography (silica, hexanes:EtOAC:HOAc = 8:1:0.045 to 8:1:0.09 to 4:1:0.09 to yield additional acid **205** (9.27 g, 34.8 mmol, 14%) along with recovered starting material **203** (16.6 g, 74.8 mmol, 29%), which was subjected to another cycle as described above.
Overall, indenone **203** (56.9 g, 256 mmol) was converted to acid **205** (55.7 g, 209 mmol) in 82% yield.

Crystals suitable for X-ray analysis were obtained by slow evaporation of a solution of acid **205** in hexanes.

R_f = 0.18 (hexanes:EtOAc = 4:1, 1% HOAc).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.65 (dd, $^3J_{1/2}$ = 10.3, 7.1 Hz, 1H, 1-H), 3.34–3.08 (m, 2H, 3-H), 2.77 (ddd, $^2J_{7A/7B}$ = 18.8 Hz, $^3J_{7A/8}$ = 14.1, 5.7 Hz, 1H, 7-H_A), 2.62 (ddd, $^2J_{7B/7A}$ = 18.9 Hz, $^3J_{7B/8}$ = 5.6, 2.0 Hz, 1H, 7-H_B), 2.11–1.98 (m, 2H, 2-H_A, 8-H_A), 1.93–1.73 (m, 2H, 2-H_B, 8-H_B), 1.17 (s, 12H, 10-H, 12-H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.9 (C-6), 196.3 (C-13), 164.3 (C-4), 120.5 (C-5), 78.9 (C-1), 73.6 (C-11), 48.4 (C-9), 33.6 (C-7), 32.0 (C-8), 31.5 (C-3), 30.1 (C-2), 28.7 (C-12), 16.4 (C-10) ppm.

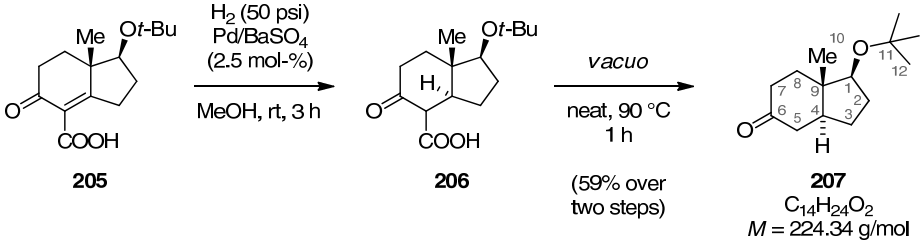
ESI-MS for $C_{15}H_{21}O_4^-$ [$(M-H)^-$]: calcd. 265.1445
found 265.1441.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 2979 (m), 2943 (w), 1737 (s), 1630 (s), 1390 (m), 1352 (m), 1284 (w), 1264 (w), 1193 (m), 1103 (m), 1031 (w), 1020 (w), 941 (w).

$[\alpha]_D^{20}$ = +30.2 (*c* 1.00, CH_2Cl_2).

The analytical data matched those reported previously.[127,134]

Synthesis of Ketone 207



To a solution of carboxylic acid **205** (25.3 g, 94.8 mmol, 1.0 eq.) in MeOH (200 mL) was added $Pd/BaSO_4$ (5% Pd, 5.10 g, 2.41 mmol, 2.5 mol-%) and the mixture was purged with H_2 (50 psi) for 3 h in a pressure reactor. The H_2 pressure was released and the mixture was filtered over a pad of Celite® (washings with MeOH). The solvent was removed under reduced pressure to yield β-keto acid **206** as colorless foam which was used without further purification.

The flask containing crude β-keto acid **206** was evacuated under high pressure and was subsequently heated to 90 °C (pre-heated oil bath) with stirring, resulting in gas evolution. The mixture was stirred for 1 h and was then cooled to room temperature. The crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 16:1) to give *trans*-hydrindane **207** as a colorless solid, which was contaminated by ca. 6% of the *cis*-product.

Purification by flash column chromatography was carried out on the crude product of several reaction batches. Overall, keto-acid **205** (54.1 g, 203 mmol) was converted to *trans*-hydrindane **207** (26.8 g, 120 mmol) in 59% yield.

R_f = 0.21 (hexanes:EtOAc = 16:1).

Melting point = 37.3–38.3 °C (hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.45 (dd, $^3J_{1/2}$ = 9.1, 7.7 Hz, 1H, 1-H), 2.40 (ddd, J = 16.3, 12.8. 7.0 Hz, 1H, 7-H_A), 2.34–2.25 (m, 3H, 5-H, 7-H_B), 2.04–1.90 (m, 2H, 2-H_A, 8-H_A), 1.77–1.66 (m, 1H, 4-H),1.64–1.53 (m, 2H, 2-H_B, 3-H_A), 1.46–1.34 (m, 2H, 3-H_B, 8-H_B), 1.13 (s, 9H, 12-H), 0.96 (s, 3H, 10-H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.3 (C-6), 79.5 (C-1), 72.7 (C-11), 44.8 (C-4), 43.1 (C-5), 42.2 (C-9), 37.5 (C-7), 35.4 (C-8), 31.9 (C-2), 28.8 (C-12), 25.9 (C-3), 10.3 (C-10) ppm.

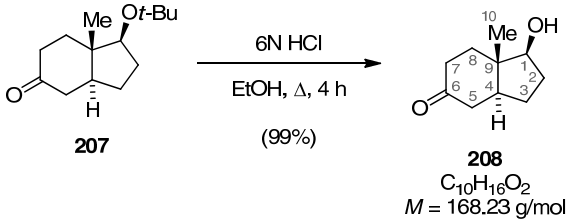
EI-MS for $C_{14}H_{25}O_2^+$ [$(M+H)^+$]: calcd. 225.1850
found 225.1845.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 2971 (s), 2874 (m), 1711 (s), 1464 (w), 1418 (w), 1362 (m), 1252 (w), 1193 (s), 1123 (m), 1104 (w), 1060 (s), 901 (w).

$[\alpha]_D^{20}$ = +79.0 (*c* 1.00, CH_2Cl_2).

The analytical data matched those reported previously.[127,134]

Synthesis of Alcohol 208



To a solution of *trans*-hydrindane **207** (30.4 g, 136 mmol, 1.0 eq.) in EtOH (310 mL) was added aqueous HCl (6N, 44 mL) and the reaction mixture was heated to reflux for 4 h. After cooling to 0 °C, the pH was adjusted to 7 by adding solid Na_2CO_3 and the solvent was evaporated under reduced pressure. The residue was diluted with CH_2Cl_2 (800 mL) and H_2O (200 mL) was added. The organic layer was separated, washed with saturated aqueous NaCl (200 mL) and dried over Na_2SO_4. The solvents were removed under reduced pressure and the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 1:1) to yield the title compound **208** (22.6 g, 134 mmol, 99%) as a colorless oil.

R_f = 0.16 (hexanes:EtOAc = 2:1).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.74 (dd, $^3J_{1/2}$ = 9.1, 8.2 Hz, 1H, 1-H), 2.74–2.19 (m, 4H, 5-H, 7-H), 2.19–2.09 (m, 1H, 2-H_A), 2.00 (m_C, 1H, 8-H_A), 1.86 (br s, 1H, *O*H), 1.76 (m_C, 1H, 4-H), 1.69–1.34 (m, 4H, 2-H_B, 3-H, 8-H_B), 0.98 (s, 3H, 10-H) ppm.

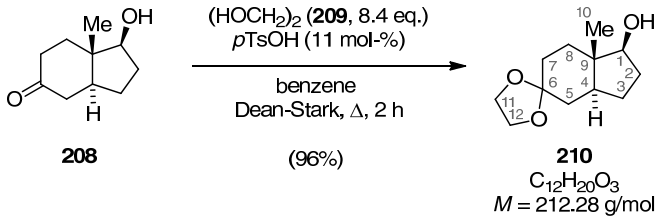
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 211.7 (C-6), 80.4 (C-1), 44.8 (C-4), 43.0 (C-5), 42.5 (C-9), 37.3 (C-7), 34.8 (C-8), 31.2 (C-2), 25.4 (C-3), 9.9 (C-10) ppm.

EI-MS for $C_{10}H_{16}O_2^+$ [M^+]: calcd. 168.1150
found 168.1147.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 3420 (br m), 2951 (m), 2872 (m), 1702 (s), 1466 (w), 1417 (w), 1317 (m), 1200 (w), 1124 (m), 1044 (s), 998 (w).

$[\alpha]_D^{20}$ = +75.6 (*c* 1.00, CH_2Cl_2).

Synthesis of Dioxolane 210



208 **210**
$C_{12}H_{20}O_3$
M = 212.28 g/mol

To a solution of alcohol **208** (22.6 g, 135 mmol, 1.0 eq.) and ethylene glycol (**209**, 63.0 mL, 1.13 mol, 8.4 eq.) in benzene (500 mL) was added *p*-toluenesulfonic acid (2.50 g, 14.5 mmol, 11 mol-%) and the suspension was heated to reflux for 2 h using a Dean-Stark trap to remove the liberated water. The mixture was allowed to cool to room temperature and the reaction was quenched by adding saturated aqueous $NaHCO_3$ (400 mL). After phase separation, the aqueous layer was extracted with EtOAc (3 x 400 mL) and the combined organic layers were washed with saturated aqueous NaCl (300 mL), dried over Na_2SO_4 and the solvents were removed under reduced pressure. The obtained crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 3:2) to yield alcohol **210** (27.5 g, 130 mmol, 96%) as a pale yellow oil.

R_f = 0.45 (hexanes:EtOAc = 1:1).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.00–3.84 (m, 4H, 11-H, 12-H), 3.71 (dd, $^3J_{1/2}$ = 8.8, 7.9 Hz, 1H, 1-H), 2.18–2.06 (m, 1H, 2-H_A), 1.79–1.42 (m, 9H, 2-H_B, 3-H_A, 4-H, 5-H, 7-H, 8-H_A, *O*H), 1.39–1.22 (m, 2H, 3-H_B, 8-H_B), 0.81 (s, 3H, 10-H) ppm.

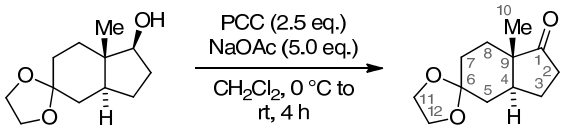
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 110.1 (C-6), 81.1 (C-1), 64.4 (C-11)*, 64.3 (C-12)*, 42.6 (C-9), 42.5 (C-4), 35.8 (C-5)**, 33.7 (C-8), 31.2 (C-7)**, 31.1 (C-2), 25.1 (C-3), 9.7 (C-10) ppm.

EI-MS for $C_{12}H_{20}O_3^+$ [M^+]: calcd. 212.1412
found 212.1405.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 3420 (br m), 2949 (s), 2874 (s), 1469 (w), 1446 (w), 1349 (m), 1192 (m), 1117 (s), 1074 (s), 1043 (s), 944 (s), 894 (s), 858 (s).

$[\alpha]_D^{20}$ = +18.8 (*c* 1.00, CH_2Cl_2).

Synthesis of Ketone 195



210 (71%) **195**
$C_{12}H_{18}O_3$
M = 210.27 g/mol

To a suspension of pyridinium chlorochromate (68.0 g, 320 mmol, 2.5 eq.) and NaOAc (52.0 g, 640 mmol, 5.0 eq.) in CH_2Cl_2 (700 mL) at 0 °C was added dropwise a solution of alcohol **210** (27.2 g, 128 mmol, 1.0 eq.) in CH_2Cl_2 (150 mL). The mixture was allowed to warm to room temperature and stirred for an additional 4 h. After filtering over a plug of silica (eluted with hexanes:EtOAc = 1:2) and evaporation of the solvents under reduced pressure, the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 5:1) to yield ketone **195** (22.1 g, 106 mmol, 80%) as a colorless solid, being contaminated by the *cis*-isomer from the previous reactions. Further purification by recrystallization from hexanes yielded pure *trans*-hydrindane **195** (19.0 g, 90.4 mmol, 71%) as a colorless crystalline solid.

Crystals suitable for X-ray analysis were obtained by recrystallization from *n*-pentane.

R_f = 0.61 (hexanes:EtOAc = 1:1).

Melting point = 76.0–77.0 °C (hexanes).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.94 (m_C, 4H, 11-H, 12-H), 2.45 (ddd, $^2J_{2A/2B}$ = 19.3 Hz, $^3J_{2A/3B}$ = 8.8 Hz, $^3J_{2A/3A}$ = 1.1 Hz, 1H, 2-H_A), 2.14 (ddd, $^2J_{2B/2A}$ = 19.2 Hz, $^3J_{2B/3A}$ = $^3J_{2B/3B}$ = 9.2 Hz, 1H, 2-H_B), 2.01 (dddd, $^3J_{4/5}$ = 18.9 Hz, $^3J_{4/3B}$ = 13.0 Hz, $^3J_{4/3A}$ = 5.8 Hz, $^3J_{4/5}$ = 3.8 Hz, 1H, 4-H), 1.86 (dddd,

$^2J_{3A/3B}$ = 12.4 Hz, $^3J_{3A/2B}$ = 8.9 Hz, $^3J_{3A/4}$ = 5.8 Hz, $^3J_{3A/2A}$ = 1.1 Hz, 1H, 3-H_A), 1.79–1.69 (m, 5H, 5-H, 7-H, 8-H_A), 1.62 (dddd, $^2J_{3B/3A}$ = $^3J_{3B/4}$ = 12.7 Hz, $^3J_{3B/2A}$ = $^3J_{3/2B}$ = 9.0 Hz, 1H, 3-H_B), 1.49 (m_C, 1H, 8-H_B), 0.93 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 219.7 (C-1), 109.6 (C-6), 64.6 (C-11)*, 64.4 (C-12)*, 47.1 (C-9), 42.8 (C-4), 36.2 (C-2), 35.6 (C-5), 30.9 (C-7), 28.7 (C-8), 23.7 (C-3), 12.3 (C-10) ppm.

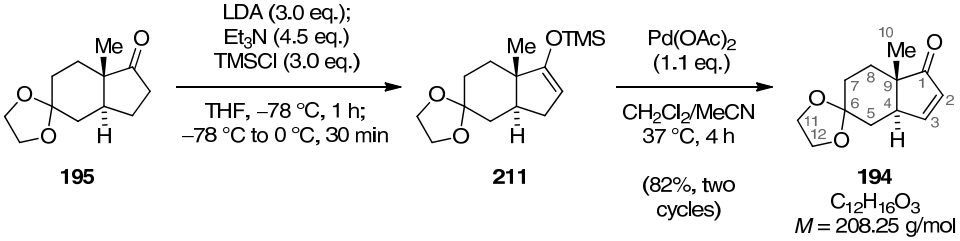
EI-MS for $C_{12}H_{18}O_3^+$ [M^+]: calcd. 210.1256
found 212.1249.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 2924 (w), 1730 (s), 1412 (w), 1350 (w), 1118 (s), 1066 (s), 1036 (s), 938 (s).

$[\alpha]_D^{20}$ = +83.6 (*c* 1.00, CH_2Cl_2).

This compound has been prepared by an alternative route, having identical physical properties.[125c,d]

Synthesis of Enone 194



To a solution of diisopropylamine (12.0 mL, 86.0 mmol, 3.0 eq.) in THF (120 mL) at −78 °C was added *n*-BuLi (34.0 mL of a 2.5M solution in hexanes, 86.0 mmol, 3.0 eq.). The yellowish solution was stirred for 10 min at −78 °C and an additional 15 min at 0 °C before being cooled to −78 °C. Then, a solution of ketone **195** (6.00 g, 28.6 mmol, 1.0 eq.) in THF (30 mL) was added within 15 min. After stirring for 45 min at −78 °C, Et_3N (18.0 mL, 129 mmol, 4.5 eq.) was added followed by TMSCl (14.6 mL, 114 mmol, 4.0 eq.). The solution was stirred for 30 min at −78 °C and was then allowed to warm to 0 °C. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (50 mL) and the mixture was diluted with *n*-pentane (100 mL). The phases were separated and the aqueous layer was extracted with *n*-pentane (3 x 50 mL). The combined organic layers were washed with saturated aqueous NaCl (50 mL) and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure (water bath temperature: 35 °C) yielded crude silyl enol ether **211** which was used without further purification.

To a solution of crude silyl enol ether **211** in CH_2Cl_2 (100 mL) and MeCN (34 mL) was added $Pd(OAc)_2$ (7.67 g, 31.5 mmol, 1.1 eq.) in one portion and the solution was stirred at 37 °C for 4 h. The

mixture was filtered over a plug of silica (eluted with hexanes:EtOAc = 1:1) and the solvents were evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 7:1 to 5:1 to 4:1 to 2:1) to yield α,β-unsaturated ketone **194** (4.10 g, 19.7 mmol, 69%) as a colorless crystalline solid along with recovered starting material **195** (1.30 g, 6.20 mmol, 22%).
A second cycle of the above described reaction and additional reaction batches resulted in an overall transformation from ketone **195** (18.8 g, 89.5 mmol) to enone **194** (15.2 g, 73.1 mmol) in 82% yield.

Crystals suitable for X-ray analysis were obtained by recrystallization from hexanes.

R_f = 0.50 (hexanes:EtOAc = 1:1).

Melting point = 127.5–129.5 °C (hexanes/EtOAc).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.38 (dd, $^3J_{3/2}$ = 5.9 Hz, $^3J_{3/4}$ = 1.8 Hz, 1H, 3-H), 6.03 (dd, $^3J_{2/3}$ = 5.9 Hz, $^4J_{2/4}$ = 3.2 Hz, 1H, 2-H), 4.00–3.92 (m, 4H, 11-H, 12-H), 3.04 (m_C, 1H, 4-H), 1.96–1.86 (m, 3H, 5-H, 7-H_A), 1.82–1.74 (m, 2H, 7-H_B, 8-H_A), 1.69 (ddd, $^2J_{8B/8A}$ = 13.2 Hz, $^3J_{8B/7A}$ = $^3J_{8B/7B}$ = 4.8 Hz, 1H, 8-H_B), 1.13 (s, 3H, 10-H) ppm.

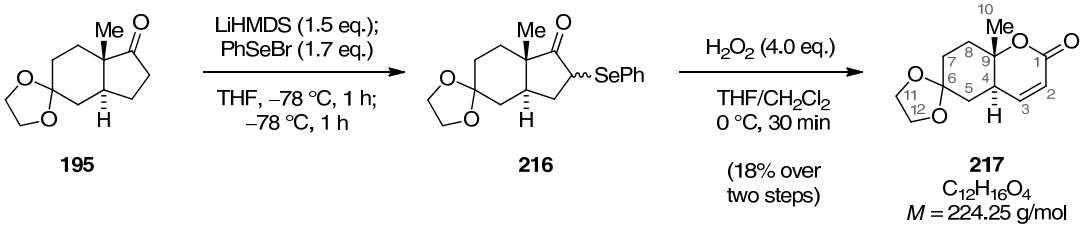
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 211.7 (C-1), 160.6 (C-3), 132.0 (C-2), 109.7 (C-6), 64.8 (C-11)*, 64.3 (C-12)*, 50.7 (C-9), 48.1 (C-4), 33.6 (C-5), 31.7 (C-7), 26.8 (C-8), 19.4 (C-10) ppm.

EI-MS for $C_{12}H_{16}O_3^+$ [M^+]: calcd. 208.1099
found 208.1097.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 2963 (w), 2934 (w), 1699 (s), 1466 (w), 1237 (w), 1180 (w), 1134 (w), 1092 (s), 1066 (w), 949 (w).

$[\alpha]_D^{20}$ = –67.2 (*c* 1.00, CH_2Cl_2).

Synthesis of Lactone 217



195 **216** **217**
$C_{12}H_{16}O_4$
M = 224.25 g/mol

To a solution of ketone **195** (43.0 mg, 200 μmol, 1.0 eq.) in THF (2 mL) at −78 °C was slowly added LiHMDS (300 μL of a 1.0M solution in THF, 300 μmol, 1.5 eq.) and the mixture was stirred for 1 h at this temperature. Then, a solution of PhSeBr (80.0 mg, 340 μmol, 1.7 eq.) in THF (1 mL) was added dropwise and the mixture was stirred for an additional 1 h at −78 °C prior to be quenched by addition of saturated aqueous NH_4Cl (4 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with saturated aqueous NaCl (10 mL) and dried over $MgSO_4$. Evaporation of the solvents under reduced pressure yielded ketone **216** as a mixture of diastereomers, which was used without further purification.

To a solution of ketone **216** (assumed 200 μmol) in THF/CH_2Cl_2 (1:1, 2 mL) at 0 °C was slowly added H_2O_2 (900 μL of a 30 wt% solution in H_2O, 800 μmol, 4.0 eq.) and the mixture was stirred at this temperature for 30 min. The reaction was quenched by addition of saturated aqueous $Na_2S_2O_3$ (2 mL) and the biphasic mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 2:1 to 1:1) to yield lactone **217** (8.0 mg, 36 μmol, 18%) as a colorless solid.

R_f = 0.16 (hexanes:EtOAc = 2:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 6.51 (dd, $^3J_{3/2}$ = 9.7 Hz, $^3J_{3/4}$ = 2.1 Hz, 1H, 3-H), 6.02 (dd, $^3J_{2/3}$ = 9.6 Hz, $^4J_{2/4}$ = 3.2 Hz, 1H, 2-H), 4.02–3.93 (m, 4H, 11-H, 12-H), 3.04 (m_C, 1H, 4-H), 2.05 (m_C, 1H, 8-H_A), 1.93–1.86 (m, 2H, 5-H_A, 7-H_A), 1.83 (m_C, 1H, 7-H_B), 1.70 (ddd, J = 14.2, 14.2, 4.8 Hz, 1H, 8-H_B), 1.64 (dd, J = 14.0, 13.4 Hz, 1H, 5-H_B), 1.39 (s, 3H, 10-H) ppm.

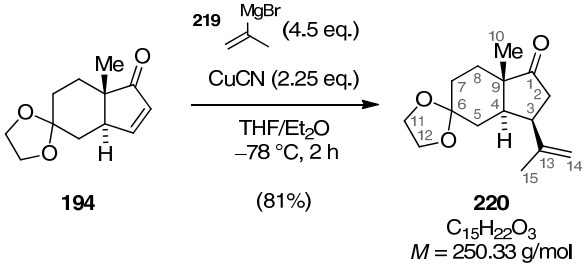
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 164.1 (C-1), 148.1 (C-3), 121.7 (C-2), 108.0 (C-6), 82.6 (C-9), 64.9 (C-11)*, 64.6 (C-12)*, 39.9 (C-4), 36.4 (C-5), 35.7 (C-8), 32.1 (C-7), 17.0 (C-10) ppm.

EI-MS for $C_{12}H_{16}O_4^+$ [M^+]: calcd. 224.1043
found 224.1051.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 2954 (br w), 1718 (s), 1381 (w), 1259 (w), 1159 (w), 1117 (s), 1090 (m), 1057 (m), 1004 (w), 982 (w), 817 (w).

$[\alpha]_D^{20}$ = +15.0 (*c* 0.17, CH_2Cl_2).

Synthesis of Ketone 220



To a suspension of CuCN (1.45 g, 16.2 mmol, 2.25 eq.) in Et_2O (48 mL) at 0 °C was added isopropylenemagnesium bromide (**219**, 65.0 mL of a 0.5M solution in THF, 32.4 mmol, 4.5 eq.) within 15 min. The resulting mixture was stirred for 30 min at this temperature and subsequently cooled to –78 °C. Then, a solution of enone **194** (1.50 g, 7.20 mmol, 1.0 eq.) in THF (15 mL) was added slowly and, after stirring for an additional 2 h at –78 °C, the reaction was quenched by addition of saturated aqueous NH_4Cl (40 mL). The mixture was allowed to warm to room temperature, diluted with Et_2O (100 mL) and filtered over a pad of Celite® (washings with Et_2O). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 40 mL). The combined organic layers were washed with saturated aqueous NaCl (50 mL), dried over $MgSO_4$ and the solvents were evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 7:1 to 5:1) to yield alkene **220** as a colorless solid.

Flash column chromatography was carried out to purify the combined crude products of several reactions which were carried out as described above. In overall, use of substrate **194** (11.9 g, 57.2 mmol) resulted in the formation of the desired product **220** (11.5 g, 46.0 mmol) in 81% yield.

Crystals suitable for X-ray analysis were grown by slow evaporation of a solution of ketone **220** in *n*-pentane at –25 °C.

R_f = 0.43 (hexanes:EtOAc = 3:1).

Melting point = 69.0–70.5 °C (hexanes/EtOAc).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 4.97 (s, 1H, 14-H_A), 4.83 (s, 1H, 14-H_B), 4.03–3.89 (m, 4H, 11-H, 12-H), 2.86 (m_C, 1H, 3-H), 2.77 (dd, $^2J_{2A/2B}$ = 19.7 Hz, $^3J_{2A/3}$ = 1.8 Hz, 1H, 2-H_A), 2.49 (dd, $^2J_{2B/2A}$ =

19.5 Hz, $^3J_{2B/3}$ = 9.2 Hz, 1H, 2-H_B), 2.41–2.34 (m, 1H, 4-H), 1.99–1.91 (m, 2H, 5-H), 1.81 (s, 3H, 15-H), 1.75 (ddd, $^2J_{7A/7B}$ = $^3J_{7A/8B}$ = 13.8 Hz, $^3J_{7A/8A}$ = 4.8 Hz, 1H, 7-H_A), 1.68 (m_C, 1H, 7-H_B), 1.63 (ddd, $^2J_{8A/8B}$ = 13.1 Hz, $^3J_{8A/7A}$ = 4.6 Hz, $^3J_{8A/7B}$ = 2.6 Hz, 1H, 8-H_A), 1.43 (ddd, $^2J_{8B/8A}$ = $^3J_{8B/7A}$ = 13.5 Hz, $^3J_{8B/7B}$ = 3.9 Hz, 1H, 8-H_B), 1.04 (s, 3H, 10-H) ppm.

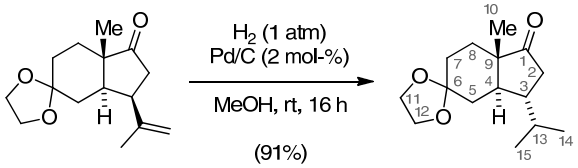
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 220.6 (C-1), 146.1 (C-13), 112.3 (C-14), 109.8 (C-6), 64.7 (C-11),* 64.4 (C-12)*, 47.1 (C-9), 45.8 (C-4), 42.2 (C-2), 41.9 (C-3), 35.7 (C-5), 30.9 (2C, C-7, C-8), 24.9 (C-15), 15.3 (C-10) ppm.

EI-MS for $C_{15}H_{22}O_3^+$ [M^+]: calcd. 250.1569
found 250.1565.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 2954 (m), 2879 (m), 1737 (s), 1440 (w), 1350 (w), 1291 (w), 1135 (m), 1095 (s), 1053 (s), 942 (w), 894 (w).

$[\alpha]_D^{20}$ = +30.6 (*c* 1.00, CH_2Cl_2).

Synthesis of Ketone 222



220 **222**
$C_{15}H_{24}O_3$
M = 252.35 g/mol

To a solution of alkene **220** (250 mg, 1.00 mmol, 1.0 eq.) in MeOH (10 mL) was added Pd/C (10% Pd, 20 mg, 19 μmol, 1.9 mol-%) and the solution was stirred under an atmosphere of H_2 (double layer balloon, 1 atm) for 16 h. The reaction mixture was filtered over a pad of Celite® (washings with EtOAc) and the solvents were evaporated under reduced pressure. The resulting crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 4:1) to yield the title compound **222** (240 mg, 952 μmol) as a colorless solid, which was contaminated by a small impurity (<5% by NMR). Recrystallization from *n*-pentane provided pure ketone **222** (230 mg, 913 μmol, 91%).

Crystals suitable for X-ray analysis were grown by slow evaporation of a solution of ketone **222** in Et_2O/*n*-pentane.

R_f = 0.54 (hexanes:EtOAc = 3:1).

Melting point = 88–90 °C (hexanes/EtOAc).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.94 (m_C, 4H, 11-H, 12-H), 2.40 (m_C, 1H, 2-H_A), 1.98–1.87 (m, 2H, 2-H_B, 3-H), 1.86–1.76 (m, 3H, 4-H, 5-H_A, 13-H), 1.75–1.66 (m, 3H, 7-H, 8-H_A), 1.62 (m_C, 1H, 5-H_B), 1.54–1.45 (m, 1H, 8-H_B), 0.97 (s, 3H, 10-H), 0.94 (d, $^3J_{15/13}$ = 6.8 Hz, 3H, 15-H)*, 0.84 (d, $^3J_{14/13}$ = 6.9 Hz, 3H, 14-H)* ppm.

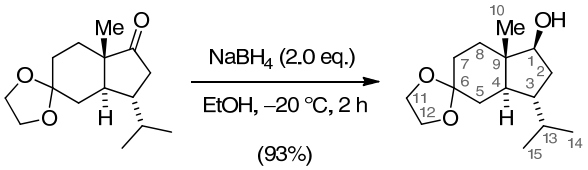
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 219.0 (C-1), 109.6 (C-6), 64.6 (C-11)*, 64.4 (C-12)*, 48.8 (C-9), 45.4 (C-4), 42.0 (C-3), 38.1 (C-2), 33.9 (C-5), 30.8 (C-7), 29.0 (C-8), 28.0 (C-13), 22.0 (C-14)**, 17.4 (C-15)**, 13.5 (C-10) ppm.

FAB-MS for $C_{15}H_{25}O_3^+$ [$(M+H)^+$]: calcd. 253.1798
found 253.1793.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 2960 (m), 2875 (m), 1737 (s), 1466 (w), 1389 (w), 1351 (w), 1231 (w), 1141 (m), 1122 (m), 1046 (m), 975 (w), 938 (m), 902 (w), 858 (w).

$[\alpha]_D^{20}$ = +65.0 (*c* 1.00, CH_2Cl_2).

Synthesis of Alcohol 224



222 **224**
$C_{15}H_{26}O_3$
M = 254.37 g/mol

To a solution of ketone **222** (100 mg, 398 µmol, 1.0 eq.) in EtOH (10 mL) at –20 °C was added a solution of $NaBH_4$ (30 mg, 0.80 mmol, 2.0 eq.) in EtOH (3 mL) within 1 h. The solution was stirred for an additional 2 h at this temperature and was then allowed to warm to room temperature. The reaction was quenched by addition of saturated aqueous NH_4Cl (5 mL) and the solvent was evaporated under reduced pressure. The residue was dissolved in EtOAc (30 mL) and the organic layer was sequentially washed with H_2O (5 mL) and saturated aqueous NaCl (5 mL). The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 4:1 to 2:1) to yield alcohol **224** (93 mg, 0.37 mmol, 93%) as a colorless solid.

The stereochemistry at C-1 was established by 2D NOESY spectroscopy, indicating no correlation between the signals at C-1 (δ = 3.66–3.59 ppm) and at C-10 (δ = 0.85 ppm). This is in contrast to the observation for its C-1 diastereomeric counterpart (*vide infra*).

R_f = 0.20 (hexanes:EtOAc = 3:1).

Melting point = 117.0–118.5 °C (hexanes/EtOAc).

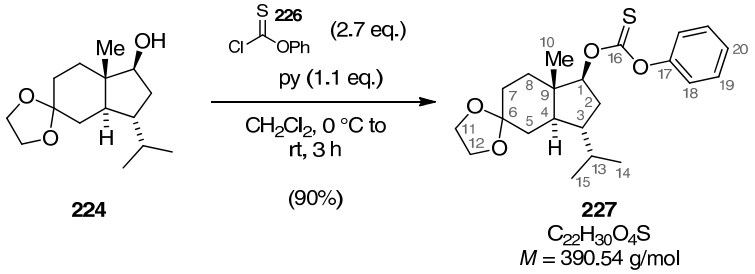
^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.96–3.89 (m, 4H), 3.66–3.59 (m, 1H), 1.89–1.81 (m, 1H), 1.76–1.66 (m, 3H), 1.66–1.57 (m, 3H), 1.55–1.46 (m, 3H), 1.40 (br s, 1H, *O*H), 1.35–1.28 (m, 1H), 0.87 (d, *J* = 6.7 Hz, 3H), 0.85 (s, 3H), 0.81 (d, *J* = 6.8 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 110.1 (C_q), 80.2 (CH), 64.4 (CH_2), 64.3 (CH_2), 45.1 (CH), 43.9 (CH), 43.8 (C_q), 34.8 (CH_2), 34.2 (CH_2), 34.0 (CH_2), 31.2 (CH_2), 29.4 (CH), 22.0 (CH_3), 18.2 (CH_3), 10.9 (CH_3) ppm.

FAB-MS for $C_{15}H_{27}O_3^+$ [$(M+H)^+$]: calcd. 255.1955
found 255.1954.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 3260 (br m), 2950 (s), 2872 (m), 1466 (w), 1387 (w), 1301 (w), 1196 (w), 1122 (m), 1091 (m), 1076 (m), 1050 (m), 942 (m).

Synthesis of Thionocarbonate 227



To a solution of alcohol **224** (25 mg, 0.10 mmol, 1.0 eq.) in CH_2Cl_2 (2 mL) at 0 °C was sequentially added pyridine (20 µL, 0.11 mmol, 1.1 eq.) and phenyl chlorothionocarbonate (**226**, 21 µL, 0.27 mmol, 2.7 eq.). The resulting yellow solution was allowed to warm up to room temperature and was stirred for 3 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (5 mL) and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with H_2O (5 mL), saturated aqueous $NaHCO_3$ (5 mL) and saturated aqueous NaCl (5 mL), and were dried over Na_2SO_4. After removal of the solvents under reduced pressure, the crude product was

purified by flash column chromatography (silica, hexanes:EtOAc = 19:1) to yield thionocarbonate **227** (35 mg, 90 μmol, 90%) as a pale yellow solid.

R_f = 0.13 (hexanes:EtOAc = 16:1).

Melting point = 116.0–118.0 °C (hexanes/EtOAc).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.40 (m_C, 2H), 7.28 (m_C, 1H), 7.10 (m_C, 2H), 5.09 (dd, J = 9.3, 7.0 Hz, 1H), 4.00–3.87 (m, 4H), 2.27–2.17 (m, 1H) 1.79–1.60 (m, 8H), 1.56–1.51 (m, 2H), 0.97 (s, 3H), 0.90 (d, J = 6.8 Hz, 3H), 0.86 (d, J = 6.7 Hz, 3H) ppm.

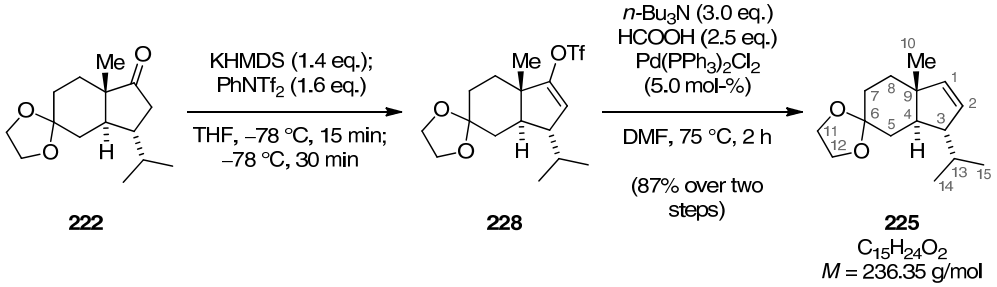
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 195.1 (C_q), 153.6 (C_q), 129.6 (CH), 126.6 (CH), 122.1 (CH), 109.7 (C_q), 91.0 (CH), 64.5 (CH_2), 64.3 (CH_2), 44.6 (CH), 44.0 (CH), 43.9 (C_q), 34.4 (CH_2), 34.2 (CH_2), 31.0 (CH_2), 30.4 (CH_2), 29.2 (CH), 21.9 (CH_3), 18.0 (CH_3), 12.3 (CH_3) ppm.

FAB-MS for $C_{22}H_{31}O_4S^+$ [$(M+H)^+$]: calcd. 391.1938
found 391.1935.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 2955 (m), 2927 (m), 1491 (w), 1308 (m), 1296 (m), 1276 (m), 1201 (s), 1093 (w), 1018 (w), 945 (w), 884 (w), 770 (w), 689 (w).

$[\alpha]_D^{20}$ = +42.2 (c 0.50, CH_2Cl_2).

Synthesis of Alkene 225



222 **228** **225**
$C_{15}H_{24}O_2$
M = 236.35 g/mol

To a solution of ketone **222** (380 mg, 1.51 mmol 1.0 eq.) in THF (25 mL) at –78 °C was added dropwise KHMDS (4.83 mL of a 0.5M solution in toluene, 2.41 mmol, 1.6 eq.) and the resulting slightly yellow solution was stirred for 15 min. After adding $PhNTf_2$ (755 mg, 2.11 mmol, 1.4 eq.) in one portion, the reaction mixture was stirred for an additional 30 min at this temperature. The reaction was quenched by addition of saturated aqueous NH_4Cl (10 mL) and the mixture was allowed to warm to room temperature. The layers were separated and the aqueous phase was extracted with

Et_2O (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and the solvents were removed under reduced pressure to yield crude enol triflate **228**.

The obtained crude enol triflate **228** (assumed 1.51 mmol) was dissolved in DMF (10 mL) and *n*-Bu_3N (1.07 mL, 838 mg, 4.53 mmol, 3.0 eq.), HCOOH (140 µL, 173 mg, 3.78 mmol, 2.5 eq.) and $Pd(PPh_3)_2Cl_2$ (53 mg, 80 µmol, 5.0 mol-%) were sequentially added. The yellow suspension was placed in an oil-bath (pre-heated to 75 °C) forming a clear solution which turned dark red. After stirring for an additional 2 h at 75 °C, the mixture was allowed to cool to room temperature and the reaction was quenched by adding H_2O (10 mL). Following extraction with Et_2O (5 x 15 mL), the combined organic layers were washed with 10% aqueous NaCl (3 x 15 mL) and dried over Na_2SO_4. The solvents were evaporated under reduced pressure (600 mbar) and the crude product was purified by flash column chromatography (silica, *n*-pentane:Et_2O = 49:1 to 19:1) to yield alkene **225** (310 mg, 1.31 mmol, 87%) as a colorless oil.

R_f = 0.52 (hexanes:EtOAc = 7:1).

^{1}H NMR (CD_2Cl_2, 400 MHz): δ = 5.85 (dd, $^3J_{1/2}$ = 5.8 Hz, $^4J_{1/3}$ = 2.5 Hz, 1H, 1-H), 5.66 (dd, $^3J_{2/1}$ = 5.8 Hz, $^3J_{2/3}$ = 1.5 Hz, 1H, 2-H), 3.96–3.86 (m, 4H, 11-H, 12-H), 2.20 (m_C, 1H, 3-H), 1.83–1.59 (m, 7H, 4-H, 5-H, 7-H, 8-H_A, 13-H), 1.56–1.47 (m, 1H, 8-H_B), 0.98 (d, $^3J_{14/13}$ = 6.9 Hz, 3H, 14-H)*, 0.86 (d, J = 0.5 Hz, 3H, 10-H), 0.84 (d, $^3J_{15/13}$ = 6.8 Hz, 3H, 15-H)* ppm.

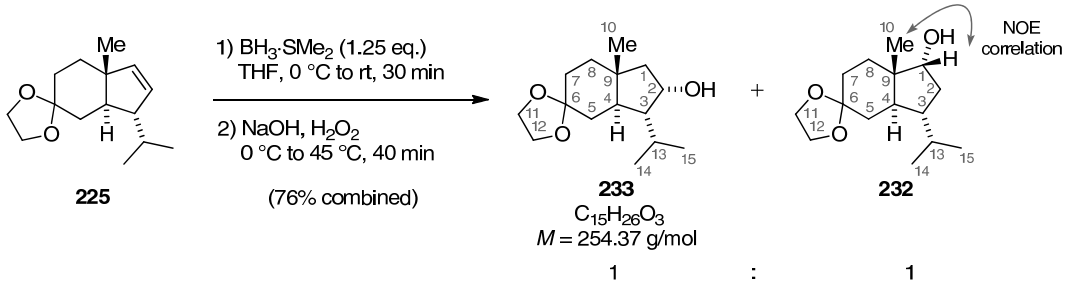
^{13}C NMR (CD_2Cl_2, 100 MHz): δ = 142.7 (C-1), 132.9 (C-2), 110.7 (C-6), 64.8 (C-11)*, 64.6 (C-12)*, 52.2 (C-3), 49.4 (C-4), 46.5 (C-9), 34.1 (2C, C-5, C-8), 32.2 (C-7), 28.8 (C-13), 22.3 (C-14)**, 19.4 (C-15)**, 16.8 (C-10) ppm.

EI-MS for $C_{15}H_{24}O_2^+$ [M^+]: calcd. 236.1771
found 236.1778.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 3043 (w), 2945 (s), 2872 (s), 1465 (w), 1432 (w), 1350 (w), 1294 (w), 1255 (w), 1167 (w), 1119 (m), 1082 (s), 1054 (m), 954 (m), 883 (w), 730 (w).

$[\alpha]_D^{20}$ = +85.8 (*c* 1.00, CH_2Cl_2).

Synthesis of Alcohols 232 and 233



To a solution of alkene **225** (200 mg, 850 µmol, 1.0 eq.) in THF (20 mL) at 0 °C was added dropwise $BH_3 \cdot SMe_2$ complex (530 µL of a 2.0M solution in THF, 1.06 mmol, 1.25 eq.) and the mixture was stirred for an additional 30 min at room temperature before being cooled to 0 °C. Subsequently, aqueous NaOH (3N, 7.5 mL) and H_2O_2 (30 wt%, 7.5 mL) were added and the biphasic mixture was heated to 45 °C for 30 min. The mixture was cooled to room temperature and the reaction was quenched by addition of saturated aqueous NH_4Cl (15 mL). The aqueous phase was extracted with EtOAc (3 x 30 mL) and the combined organic layers were dried over Na_2SO_4. After evaporation of the solvents under reduced pressure, the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 7:1 to 4:1) to yield alcohol **232** (85 mg, 0.33 mmol, 39%) as a colorless solid along with its regioisomer **233** (80 mg, 0.31 mmol, 37%) as a colorless oil.

Analytical data for regioisomer **233**:

R_f = 0.50 (hexanes:EtOAc = 2:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 4.40 (ddd, $^3J_{2/1A} = {}^3J_{2/3}$ = 7.4 Hz, $^3J_{2/1B}$ = 5.5 Hz, 1H, 2-H), 3.99–3.88 (m, 4H, 11-H, 12-H), 2.11 (dd, $^2J_{1A/1B}$ = 12.9 Hz, $^3J_{1A/2}$ = 7.3 Hz, 1H, 1-H_A), 1.90 (m_C, 1H, 13-H), 1.86–1.80 (m, 2H, 4-H, 7-H_A) 1.76–1.69 (m, 1H, 5-H_A), 1.64–1.59 (m, 2H, 5-H_B, 8-H_A) 1.51–1.43 (m, 3H, 3-H, 7-H_B, 8-H_B), 1.32 (br s, 1H, *O*H), 1.14 (dd, $^2J_{1B/1A}$ = 13.0 Hz, $^3J_{1B/2}$ = 5.6 Hz, 1H, 1-H_B), 1.04–0.93 (m, 6H, 14-H, 15-H), 0.81 (s, 3H, 10-H) ppm.

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 110.1 (C-6), 74.1 (C-2), 64.4 (C-11)*, 64.3 (C-12)*, 51.0 (C-1), 50.6 (C-3), 46.0 (C-4), 38.8 (C-9), 36.4 (C-8), 35.8 (C-7), 31.3 (C-5), 27.0 (C-13), 23.0 (C-14)**, 21.5 (C-15)**, 18.7 (C-10) ppm.

FAB-MS for $C_{15}H_{27}O_3^+$ [$(M+H)^+$]: calcd. 255.1960
found 255.1969.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 3484 (m), 2954 (s), 2974 (s), 1465 (w), 1441 (w), 1386 (w), 1367 (w), 1354 (w), 1306 (w), 1267 (w), 1244 (w), 1136 (w), 1082 (m), 1040 (w), 893 (w), 819 (w).

$[\alpha]_D^{20}$ = +42.6 (*c* 0.65, CH_2Cl_2).

Analytical data for regioisomer **232**:

R_f = 0.40 (hexanes:EtOAc = 2:1).

Melting point = 76.4–77.4 °C (hexanes/EtOAc).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 4.01–3.86 (m, 4H, 11-H, 12-H), 3.69 (m_C, 1H, 1-H), 2.23 (ddd, $^3J_{2A/2B}$ = 15.1 Hz, $^3J_{2A/3}$ = 10.1 Hz, $^3J_{2A/1}$ = 5.9 Hz, 1H, 2-H_A), 1.86 (ddd, *J* = 13.3, 11.6 Hz, 3.5 Hz, 1H, 4-H), 1.83–1.73 (m, 3H, 5-H_A, 7-H_A, 8-H_A), 1.72–1.64 (m, 2H, 5-H_B, 13-H), 1.53 (dddd, $^3J_{3/13}$ = 16.8 Hz, $^3J_{3/2A}$ = 10.1 Hz, $^3J_{3/2B}$ = 6.7 Hz, $^3J_{3/4}$ = 5.2 Hz, 1H, 3-H), 1.47 (dd, $^2J_{7B/7A}$ = $^3J_{7B/6A}$ = 13.0 Hz, 1H, 7-H_B), 1.38–1.34 (m, 1H, 8-H_B), 1.27 (dd, $^2J_{2B/2A}$ = 15.3 Hz, $^3J_{2B/3}$ = 6.8 Hz, 1H, 2-H_B), 1.23 (br s, 1H, *O*H), 0.90 (d, $^3J_{14/13}$ = 6.9 Hz, 3H, 14-H)*, 0.85 (d, $^3J_{15/13}$ = 6.7 Hz, 3H, 15-H)*, 0.77 (s, 3H, 10-H) ppm.

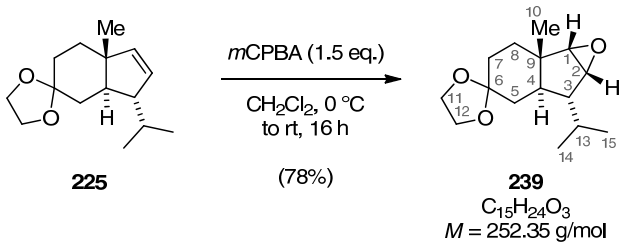
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 110.0 (C-6), 78.0 (C-1), 64.4 (C-11)*, 64.3 (C-12)*, 45.8 (C-9), 45.5 (C-3), 42.6 (C-4), 36.2 (C-2), 34.9 (C-7), 30.9 (C-5), 29.5 (C-13), 28.7 (C-8), 22.1 (C-14)**, 18.4 (C-15)**, 17.0 (C-10) ppm.

FAB-MS for $C_{15}H_{27}O_3^+$ [$(M+H)^+$]: calcd. 255.1960
found 255.1963.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 3490 (br m), 2952 (s), 2871 (s), 1464 (w), 1440 (w), 1387 (w), 1353 (w), 1301 (w), 1265 (w), 1189 (w), 1129 (m), 1136 (m) 1081 (s), 1039 (m), 1018 (w), 973 (m), 894 (w), 820 (w).

$[\alpha]_D^{20}$ = +17.4 (*c* 0.65, CH_2Cl_2).

Synthesis of Epoxide 239



225 **239**
$C_{15}H_{24}O_3$
M = 252.35 g/mol

To a solution of alkene **225** (18 mg, 76 µmol, 1.0 eq.) in CH_2Cl_2 (2 mL) at 0 °C was added *m*CPBA (20 mg, 0.11 mmol, 1.5 eq.) in one portion and the resulting colorless solution was stirred in the melting ice bath for 16 h. After diluting with CH_2Cl_2 (5 mL), washing with saturated aqueous K_2CO_3 (3 mL) and phase separation, the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and the solvents were evaporated under reduced pressure. The thus obtained crude product was purified by flash column chromatography (silica, *n*-pentane:Et_2O = 16:1 to 9:1) to yield epoxide **239** (15 mg, 59 µmol, 78%) as a colorless solid.

R_f = 0.25 (hexanes:EtOAc = 7:1).

Melting point = 60.0–61.0 °C (pentane/Et_2O).

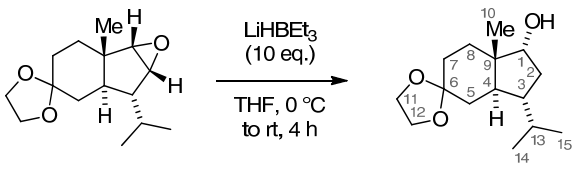
^{1}H NMR (CD_2Cl_2, 400 MHz): δ = 3.97–3.80 (m, 4H, 11-H, 12-H), 3.29 (dd, $^3J_{2/1}$ = 3.0 Hz, $^3J_{2/3}$ = 1.1 Hz, 1H, 2-H), 3.00 (dd, $^3J_{1/2}$ = 3.1 Hz, ^4J = 0.8 Hz, 1H, 1-H), 1.81–1.70 (m, 2H, 7-H_A, 13-H), 1.68–1.58 (m, 3H, 5-H_A, 7-H_B, 8-H_A), 1.53–1.41 (m, 3H, 4-H, 5-H_B, 8-H_B), 1.36 (m_C, 1H, 3-H), 1.05 (d, $^3J_{14/13}$ = 7.0 Hz, 3H, 14-H)*, 0.98 (d, $^3J_{15/13}$ = 6.9 Hz, 3H, 15-H)*, 0.82 (s, 3H, 10-H) ppm.

^{13}C NMR (CD_2Cl_2, 100 MHz): δ = 110.2 (C-6), 64.9 (C-11)*, 64.7 (C-12)*, 59.8 (C-1), 55.6 (C-2), 47.0 (C-3), 41.6 (C-9), 38.4 (C-4), 33.6 (C-5), 31.8 (C-7), 30.6 (C-8), 27.9 (C-13), 22.8 (C-14)**, 20.1 (C-15)**, 15.4 (C-10) ppm.

FAB-MS for $C_{15}H_{25}O_3^+$ [$(M+H)^+$]: calcd. 253.1804
found 253.1824.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 2953 (s), 2932 (m), 2879 (m), 1464 (m), 1385 (m), 1342 (w), 1299 (w), 1255 (w), 1172 (m), 1125 (m), 1087 (s), 1075 (s), 1034 (w), 994 (w), 943 (m), 869 (s), 805 (w), 676 (w).

Synthesis of Alcohol 232 by Reductive Epoxide Opening



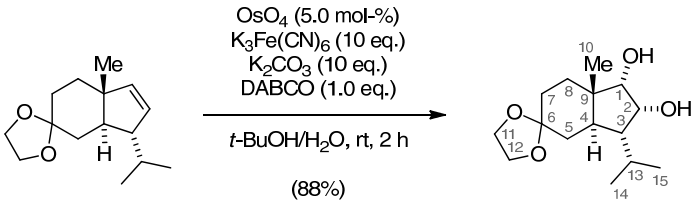
239 **232**
$C_{15}H_{26}O_3$
M = 254.37 g/mol

To a solution of epoxide **239** (5.0 mg, 20 µmol, 1.0 eq.) in THF (2 mL) at 0 °C was added $LiHBEt_3$ (200 µL of a 1.0M solution in THF, 200 µmol, 10 eq.). The resulting colorless solution was allowed to warm to room temperature and stirred for 4 h before the reaction was quenched by slow

addition of saturated aqueous NH_4Cl (2 mL) at 0 °C. After phase separation the aqueous layer was extracted with EtOAc (3 x 3 mL) and the combined organic layers were washed with brine (2 mL) and dried over $MgSO_4$. Having evaporated the solvent under reduced pressure, the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 3:1) to yield the title compound **232** (4.0 mg, 16 µmol, 79%) as a colorless solid.

The analytical data matched those obtained previously.

Synthesis of Diol 240



225 **240**
$C_{15}H_{26}O_4$
M = 270.35 g/mol

To a stirred biphasic mixture of alkene **225** (10 mg, 42 µmol, 1.0 eq.) in *t*-BuOH/H_2O (1:1, 2.5 mL) was sequentially added $K_3Fe(CN)_6$ (138 mg, 420 µmol, 10 eq.), K_2CO_3 (58 mg, 420 µmol, 10.0 eq.), DABCO (5.2 mg, 42 µmol, 1.0 eq.) and OsO_4 (30 µL of a 2.5 wt% solution in *t*-BuOH, 2.1 µmol, 5.0 mol-%). The resulting yellow reaction mixture was stirred for 2 h before being quenched by addition of solid Na_2SO_3 (40 mg). The mixture was stirred for an additional 45 min, filtered over a plug of Celite® and diluted with H_2O (3 mL). After extraction with EtOAc (3 x 5 mL), the combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 2:1) to yield diol **240** (10 mg, 37 µmol, 88%) as a colorless solid.

R_f = 0.26 (hexanes:EtOAc = 2:1).

Melting point = 91.0–92.5 °C (hexanes/EtOAc).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.42 (ddd, $^3J_{2/3}$ = 8.6 Hz, $^3J_{2/OH}$ = 8.0 Hz, $^3J_{2/1}$ = 5.3 Hz, 1H, 2-H), 3.99–3.89 (m, 4H, 11-H, 12-H), 3.64 (dd, $^3J_{1/2}$ = 5.4 Hz, $^3J_{1/OH}$ = 4.0 Hz, 1H, 1-H), 2.51 (d, $^3J_{OH/2}$ = 7.9 Hz, 1H, *O*H), 2.46 (d, $^3J_{OH/1}$ = 4.0 Hz, 1H, *O*H), 2.04 (ddd, $^3J_{4/3}$ = $^3J_{4/5B}$ = 12.8 Hz, $^3J_{4/5A}$ = 3.3 Hz, 1H, 4-H), 1.92–1.84 (m, 3H, 5-H_A, 8-H_A, 13-H), 1.76 (ddd, J = 13.4, 13.4, 4.4 Hz, 1H, 7-H_A), 1.68 (m_C, 1H, 7-H_B), 1.52 (ddd, $^3J_{3/4}$ = 12.3 Hz, $^3J_{3/2}$ = 8.6 Hz, $^3J_{3/13}$ = 6.4 Hz, 1H, 3-H), 1.48 (dd, $^2J_{5B/5A}$ = $^3J_{5B/4}$ = 13.1 Hz, 1H, 5-H_B), 1.41 (m_C, 1H, 8-H_B), 1.00 (d, $^3J_{14/13}$ = 6.9 Hz, 3H, 14-H)*, 0.98 (d, $^3J_{15/13}$ = 6.9 Hz, 3H, 15-H)*, 0.79 (s, 3H, 10-H) ppm.

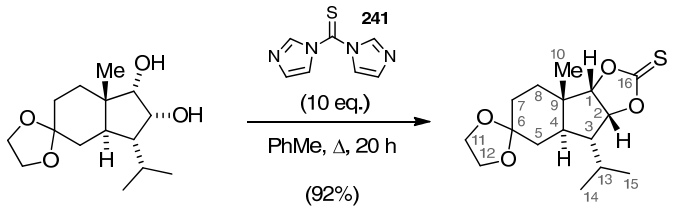
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 109.8 (C-6), 77.8 (C-1), 73.5 (C-2), 64.4 (C-11)*, 64.3 (C-12)*, 49.2 (C-3), 42.9 (C-9), 41.9 (C-4), 35.8 (C-5), 30.6 (C-7), 29.3 (C-8), 27.3 (C-13), 23.3 (C-14)**, 21.4 (C-15)**, 16.9 (C-10) ppm.

ESI-MS for $C_{15}H_{25}O_4^-$ [$(M-H)^-$]: calcd. 269.1758
found 269.1758.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 3412 (br s), 2951 (s), 2872 (s), 1464 (w), 1434 (w), 1382 (w), 1356 (w), 1306 (w), 1269 (w), 1184 (w), 1118 (m), 1081 (s), 1045 (m), 970 (w).

$[\alpha]_D^{20}$ = +24.4 (*c* 0.50, CH_2Cl_2).

Synthesis of Thionocarbonate 242



To a solution of diol **240** (14 mg, 56 µmol, 1.0 eq.) in toluene (5 mL) was added 1,1'-thiocarbonyldiimidazole (**241**, 98 mg, 0.54 mmol, 10 eq.) and the resulting yellow solution was heated to reflux for 20 h. After cooling to room temperature, the solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 4:1) to yield thiocarbonate **242** (16 mg, 51 µmol, 92%) as an off-white solid.

R_f = 0.42 (hexanes:EtOAc = 2:1).

Melting point = 174.0–175.5 °C (hexanes/EtOAc).

^{1}H NMR (C_6D_6, 400 MHz): δ = 4.35 (dd, $^3J_{2/1} = {}^3J_{2/3}$ = 6.1 Hz, 1H, 2-H), 3.81 (d, $^3J_{1/2}$ = 6.2 Hz, 1H, 1-H), 3.57–3.35 (m, 4H, 11-H, 12-H), 2.07–1.93 (m, 2H, 4-H, 8-H_A), 1.79 (dd, $^2J_{5A/5B}$ = 13.1 Hz, $^3J_{5A/4}$ = 3.2 Hz, 1H, 5-H_A), 1.70 (m_C, 1H, 13-H), 1.62–1.52 (m, 2H, 7-H), 1.37 (dd, $^2J_{5B/5A} = {}^3J_{5B/4}$ = 13.0 Hz, 1H, 5-H_B) 1.19 (m_C, 1H, 8-H_B), 1.03 (ddd, ^3J = 13.1, 7.1, 6.0 Hz, 1H, 3-H), 0.94 (d, $^3J_{14/13}$ = 6.9 Hz, 3H, 14-H)*, 0.89 (d, $^3J_{15/13}$ = 7.0 Hz, 3H, 15-H)*, 0.19 (s, 3H, 10-H) ppm.

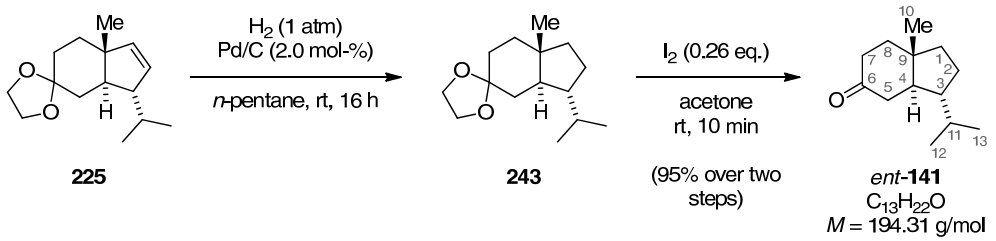
^{13}C NMR (C_6D_6, 100 MHz): δ = 191.7 (C-16), 108.7 (C-6), 90.2 (C-1), 87.8 (C-2), 64.5 (C-11)*, 64.3 (C-12)*, 50.7 (C-3), 33.0 (C-9), 41.9 (C-4), 35.1 (C-5), 30.5 (C-7), 29.3 (C-8), 27.1 (C-13), 21.2 (C-14)**, 21.1 (C-15)**, 15.9 (C-10) ppm.

ESI-MS for $C_{15}H_{24}O_4ClS^-$ [$(M+Cl)^-$]: calcd. 347.1089
found 347.1088.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 2959 (w), 2876 (w), 1465 (w), 1435 (w), 1349 (m), 1280 (s), 1173 (m), 1137 (w), 1117 (w), 1085 (m), 1009 (m), 976 (m), 913 (w), 889 (w), 829 (w).

$[\alpha]_D^{20}$ = +63.4 (*c* 0.50, CH_2Cl_2).

Synthesis of Ketone *ent*-141



To a solution of alkene **225** (300 mg, 1.27 mmol, 1.0 eq.) in *n*-pentane (15 mL) was added Pd/C (10% Pd, 33 mg, 25 μmol, 2.0 mol-%) and the resulting suspension was stirred under an atmosphere of H_2 (balloon, 1 atm) for 16 h. The reaction mixture was filtered over a pad of Celite® (washings with Et_2O) and the solvents were carefully removed under reduced pressure. The thus obtained colorless oil, ketal **243**, was used without further purification.

To a solution of crude ketal **243** (assumed 1.27 mmol) in acetone (15 mL) was added I_2 (86 mg, 0.34 mmol, 26 mol-%) in one portion. The solution was stirred for 10 min at room temperature and the reaction was quenched by addition of aqueous $Na_2S_2O_3$ (5 wt%, 10 mL). The mixture was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were dried over $MgSO_4$. After evaporation of the solvents under reduced pressure, the crude product was purified by flash column chromatography (silica, *n*-pentane:Et_2O = 24:1 to 19:1) to yield ketone *ent*-**141** (234 mg, 1.21 mmol, 95%) as a colorless solid.

Crystals suitable for X-ray analysis were grown from a solution of ketone **141** in *n*-pentane at –25 °C.

R_f = 0.55 (hexanes:EtOAc = 7:1).

Melting point = 64.5–66.0 °C (CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.44–2.36 (m, 2H, 5-H_A, 7-H_A), 2.31 (dddd, J = 16.5, 5.7, 1.8, 1.8 Hz, 1H, 7-H_B), 2.15 (m_C, 1H, 5-H_B), 1.90–1.79 (m, 2H, 2-H_A, 8-H_A), 1.67–1.58 (m, 2H, 3-H, 11-H), 1.57–1.44 (m, 4H, 1-H_A, 2-H_B, 4-H, 8-H_B), 1.21–1.14 (m, 1H, 1-H_B), 0.99 (s, 3H, 10-H), 0.87 (d, $^3J_{12/11}$ = 6.6 Hz, 3H, 12-H)*, 0.79 (d, $^3J_{13/11}$ = 6.7 Hz, 3H, 13-H)* ppm.

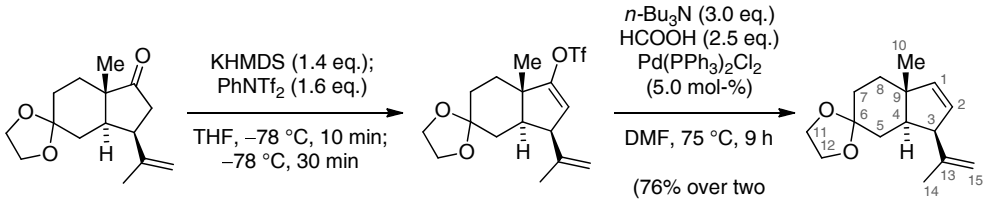
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 212.2 (C-6), 50.2 (C-4), 47.2 (C-3), 42.8 (C-5), 41.3 (C-9), 38.3 (C-1), 37.9 (C-7), 37.2 (C-8), 29.4 (C-11), 25.1 (C-2), 21.9 (C-12)*, 18.1 (C-13)*, 17.3 (C-10) ppm.

EI-MS for $C_{13}H_{22}O^+$ [M^+]: calcd. 199.1665
found 199.1661.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 2950 (s), 2870 (s), 1703 (s), 1465 (w), 1412 (w), 1387 (w), 1278 (w), 1240 (w), 1228 (w), 1214 (w), 1140 (w), 1079 (w), 738 (w).

$[\alpha]_D^{20}$ = +92.8 (*c* 0.50, CH_2Cl_2), $[\alpha]_D^{20}$ = +101.3 (*c* 1.00, $CDCl_3$).

Synthesis of Diene 245



220 **244** **245**
$C_{15}H_{22}O_2$
M = 234.33 g/mol

To a solution of ketone **220** (1.36 g, 5.44 mmol, 1.0 eq.) in THF (75 mL) at –78 °C was added dropwise KHMDS (17.4 mL of a 0.5M solution in toluene, 8.70 mmol, 1.6 eq.). After 10 min $PhNTf_2$ (2.72 g, 7.62 mmol, 1.4 eq.) was added in one portion and the mixture was stirred for 30 min at –78 °C. The reaction was quenched by addition of saturated aqueous NH_4Cl (20 mL) and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined organic layers were dried over Na_2SO_4. The solvents were removed under reduced pressure (water bath temperature: 35 °C) to give enol triflate **244** as a yellowish oil which was used without further purification.

To a solution of crude enol triflate **244** (assumed 5.44 mmol) in DMF (30 mL) was added *n*-Bu_3N (3.87 mL, 16.3 mmol, 3.0 eq.), HCOOH (513 µL, 13.6 mmol, 2.5 eq.) and $Pd(PPh_3)_2Cl_2$ (190 mg, 270 µmol, 5.0 mol-%) and the reaction mixture was heated to 75 °C for 9 h. The reaction was quenched by addition of H_2O (20 mL) and the mixture was extracted with

Et_2O (4 x 50 mL). The combined organic layers were washed with 10% aqueous NaCl (3 x 40 mL), dried over Na_2SO_4 and the solvents were removed under reduced pressure. The crude product was purified by flash column chromatography (silica, *n*-pentane:Et_2O = 99:1 to 19:1) to yield diene **245** (980 mg, 4.15 mmol, 76% over two steps) as a colorless liquid.

R_f = 0.66 (hexanes:EtOAc = 7:1).

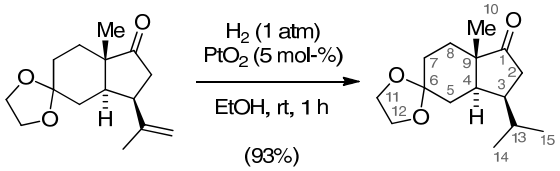
^{1}H NMR (CD_2Cl_2, 400 MHz): δ = 5.95 (m_C, 1H, 1-H), 5.77 (dd, $^3J_{2/1}$ = 5.8 Hz, $^3J_{2/3}$ = 2.8 Hz, 1H, 2-H), 4.81–4.78 (m, 1H, 15-H_A), 4.70–4.65 (m, 1H, 15-H_B), 3.99–3.85 (m, 4H, 11-H, 12-H), 3.01 (m_C, 1H, 3-H), 2.23 (ddd, ^3J = 14.4, 8.5, 2.8 Hz, 1H, 4-H), 1.92 (m_C, 1H, 5-H_A), 1.81 (ddd, $^2J_{7A/7B}$ = $^3J_{7A/8B}$ = 13.8 Hz, $^3J_{7A/8A}$ = 5.3 Hz, 1H, 7-H_A), 1.80–1.73 (m, 4H, 5-H_B, 14-H), 1.64 (m_C, 1H, 7-H_B), 1.56 (ddd, $^2J_{8A/8B}$ = 12.6 Hz, $^3J_{8A/7A}$ = 5.3 Hz, $^3J_{8A/7B}$ = 2.3 Hz, 1H, 8-H_A), 1.44 (m_C 1H, 8-H_B), 0.93 (d, ^4J = 0.6 Hz, 3H, 10-H) ppm.

^{13}C NMR (CD_2Cl_2, 100 MHz): δ =147.5 (C-13), 142.8 (C-1), 132.9 (C-2), 112.3 (C-15), 110.7 (C-6), 65.0 (C-11)*, 64.7 (C-12)*, 53.1 (C-3), 48.8 (C-4), 46.8 (C-9), 34.5 (C-5), 35.1 (C-8), 32.5 (C-7), 24.4 (C-14), 18.9 (C-10) ppm.

FAB-MS for $C_{15}H_{23}O_2^+$ [$(M+H)^+$]: calcd. 235.1693
found 235.1692.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 3041 (w), 2951 (s), 2877 (s), 1440 (w), 1348 (m), 1287 (w), 1247 (w), 1184 (m), 1102 (m), 1054 (m), 974 (w), 946 (w), 892 (w), 749 (w).

Synthesis of Ketone 246



220 **246**
$C_{15}H_{24}O_3$
M = 252.35 g/mol

To a solution of ketone **220** (3.98 g, 15.9 mmol, 1.0 eq.) in EtOH (300 mL) was added PtO_2 (181 mg, 800 µmol, 5.0 mol-%) and the resulting suspension was purged with H_2 (balloon, 1 atm) for 60 min. The mixture was filtered over a pad of Celite® (washings with Et_2O) and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 5:1) to yield ketone **246** as colorless solid.

Flash column chromatography was carried out to purify the combined crude of several reactions which were carried out as described above. Thus, use of substrate (10.7 g, 42.3 mmol) resulted in the formation of the desired product **246** (9.90 g, 39.3 mmol) in 93% yield.

Crystals suitable for X-ray analysis were grown by slow evaporation of a solution of ketone **246** in Et_2O/*n*-pentane.

R_f = 0.46 (hexanes:EtOAc = 3:1).

Melting point = 65.5–67.0 °C (CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 4.00–3.87 (m, 4H, 11-H, 12-H), 2.48 (dd, $^2J_{2A/2B}$ = 19.7 Hz, $^3J_{2A/3}$ = 2.4 Hz, 1H, 2-H_A), 2.37 (dd, $^2J_{2B/2A}$ = 19.7 Hz, $^3J_{2B/3}$ = 8.9 Hz, 1H, 2-H_B), 2.28 (ddd, $^3J_{4/5A}$ = 13.8 Hz, $^3J_{4/3}$ = 7.2 Hz, $^3J_{4/5B}$ = 3.2 Hz, 1H, 4-H), 2.00 (dd, $^3J_{5A/4}$ = 13.7 Hz, $^2J_{5A/5B}$ = 12.8 Hz, 1H, 5-H_A), 1.91 (ddd, $^2J_{5B/5A}$ = 12.7 Hz, $^3J_{5B/4}$ = 3.2 Hz, $^4J_{5B/7}$ = 2.2 Hz, 1H, 5-H_B), 1.89–1.79 (m, 2H, 3-H, 13-H), 1.74–1.62 (m, 3H, 7-H, 8-H_A), 1.44 (ddd, *J* = 13.3, 13.3, 4.8 Hz, 1H, 8-H_B), 1.04 (s, 3H, 10-H), 0.96 (d, $^3J_{14/13}$ = 6.0 Hz, 3H, 14-H)*, 0.87 (d, $^3J_{15/13}$ = 6.1 Hz, 3H, 15-H)* ppm.

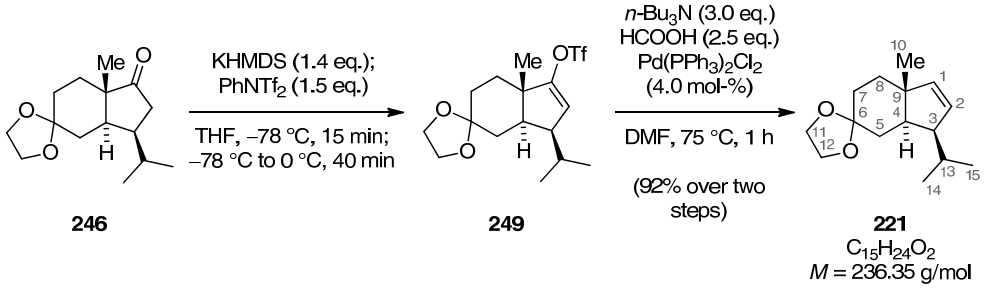
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 220.7 (C-1), 109.9 (C-6), 64.6 (C-11)*, 64.4 (C-12)*, 46.5 (C-9), 45.5 (C-4), 43.5 (C-3), 41.9 (C-2), 35.8 (C-5), 30.7 (C-7), 30.6 (C-8), 29.9 (C-13), 23.7 (C-14)*, 23.2 (C-15)*, 15.9 (C-10) ppm.

EI-MS for $C_{15}H_{24}O_3^+$ [M^+]: calcd. 252.1720
found 252.1722.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 2954 (s), 2879 (s), 1740 (s), 1472 (w), 1406 (w), 1382 (w), 1346 (w), 1306 (w), 1290 (w), 1263 (w), 1231 (w), 1172 (w), 1139 (m), 1113 (m), 1102 (m), 1086 (s), 1045 (s), 1010 (w), 970 (w), 942 (m), 921 (w), 885 (w), 861 (w).

$[\alpha]_D^{20}$ = +56.6 (*c* 1.00, CH_2Cl_2).

Synthesis of Alkene 221



246 **249** **221**

$C_{15}H_{24}O_2$

M = 236.35 g/mol

To a solution of ketone **246** (3.00 g, 11.9 mmol 1.0 eq.) in THF (120 mL) at −78 °C was added dropwise KHMDS (33.4 mL of a 0.5M solution in toluene, 16.7 mmol, 1.4 eq.) and the resulting slightly yellow solution was stirred for 15 min. After adding $PhNTf_2$ (6.37 g, 17.9 mmol, 1.5 eq.) in one portion the reaction mixture was stirred an additional 10 min at −78 °C. The reaction was allowed to warm to 0 °C and stirred for an additional 30 min at this temperature before being quenched by addition of saturated aqueous NH_4Cl (40 mL). The aqueous phase was extracted with Et_2O (3 x 40 mL) and the combined organic layers were washed with saturated aqueous NaCl (30 mL). The organic layer was dried over $MgSO_4$ and the solvents were removed under reduced pressure to obtain crude enol triflate **249**.

The crude enol triflate **249** (assumed 11.9 mmol) was dissolved in DMF (30 mL) and *n*-Bu_3N (8.47 mL, 6.60 g, 35.7 mmol, 3.0 eq.), HCOOH (1.12 mL, 1.37 g, 29.8 mmol, 2.5 eq.) and $Pd(PPh_3)_2Cl_2$ (334 mg, 476 µmol, 4.0 mol-%) were sequentially added. The yellow suspension was placed in a pre-heated oil bath at 75 °C and stirred for 1 h forming a clear solution which turned dark red. After cooling to room temperature, the reaction was quenched by adding H_2O (30 mL). The mixture was filtered over a plug of Celite® (washings with Et_2O) and the aqueous layer was extracted with Et_2O (5 x 40 mL). The combined organic layers were washed with 10% aqueous NaCl (3 x 75 mL) and dried over $MgSO_4$. Having evaporated the volatiles under reduced pressure (600 mbar) the crude product was purified by flash column chromatography (silica, *n*-pentane:Et_2O = 49:1 to 19:1) to yield alkene **221** (2.57 g, 10.9 mmol, 92% over two steps) as a colorless oil. Due to volatility of title compound **221**, evaporation of the solvents was carried out at min. 600 mbar.

R_f = 0.68 (hexanes:EtOAc = 7:1).

^{1}H NMR (CD_2Cl_2, 400 MHz): δ = 5.86 (m_C, 1H, 1-H), 5.81 (dd, $^3J_{2/1}$ = 5.9 Hz, $^3J_{2/3}$ = 2.8 Hz, 1H, 2-H), 3.94–3.88 (m, 4H, 11-H, 12-H), 2.15 (ddd, ^3J = 12.6, 7.6, 4.4 Hz, 1H, 4-H), 2.06 (dddd, $^3J_{3/13}$ = 9.9 Hz, $^3J_{3/4}$ = 7.6 Hz, $^3J_{3/2}$ = 2.8 Hz, $^4J_{3/1}$ = 1.4 Hz, 1H, 3-H), 1.90–1.84 (m, 2H, 5-H_A, 5-H_B), 1.79 (dd, $^2J_{7A/7B}$ = 13.8 Hz, $^3J_{7A/8A}$ = 5.1 Hz, 1H, 7-H_A), 1.72 (dtt, $^3J_{13/3}$ = 9.8 Hz, $^3J_{13/14}$ = $^3J_{13/15}$ = 6.6 Hz, 1H, 13-H), 1.64 (m_C, 1H, 7-H_B), 1.56 (ddd, $^2J_{8A/8B}$ = 12.5 Hz, $^3J_{8A/7A}$ = 5.2 Hz, $^3J_{8A/7B}$ = 2.4 Hz, 1H, 8-H_A), 1.45 (m_C, 1H, 8-H_B), 1.00 (d, J = 0.6 Hz, 3H, 10-H), 0.91 (d, $^3J_{14/13}$ = 6.5 Hz, 3H, 14-H)*, 0.85 (d, $^3J_{15/13}$ = 6.7 Hz, 3H, 15-H)* ppm.

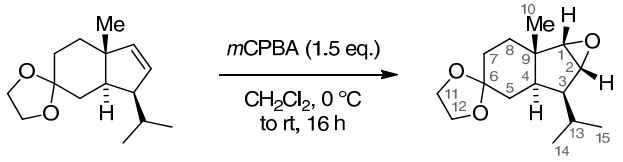
^{13}C NMR (CD_2Cl_2, 100 MHz): δ = 142.2 (C-1), 134.5 (C-2), 110.8 (C-6), 64.9 (C-11)*, 64.7 (C-12)*, 54.8 (C-3), 48.8 (C-4), 46.2 (C-9), 35.4 (2C, C-5, C-8), 32.6 (C-7), 30.3 (C-13), 23.9 (C-14)**, 22.6 (C-15)**, 21.5 (C-10) ppm.

EI-MS for $C_{15}H_{24}O_2^+$ [M^+]: calcd. 236.1771
found 236.1758.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 3045 (w), 2952 (s), 2932 (s), 2868 (s), 1465 (w), 1348 (w), 1291 (w), 1249 (w), 1185 (w), 1108 (w), 1085 (m), 1052 (w), 973 (w), 942 (w), 879 (w), 818 (w), 741 (w).

$[\alpha]_D^{20}$ = –75.8 (*c* 1.00, CH_2Cl_2).

Synthesis of Epoxide 250



221 **250**
$C_{15}H_{24}O_3$
M = 252.35 g/mol

To solution of alkene **221** (30 mg, 0.13 mmol, 1.0 eq.) in CH_2Cl_2 (4 mL) at 0 °C was added *m*CPBA (33 mg, 0.19 mmol, 1.5 eq.) in one portion and the solution was stirred in the melting ice bath for 16 h. The reaction was quenched by addition of saturated aqueous K_2CO_3 (3 mL) and the mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were removed under reduced pressure. The crude product was purified by flash column chromatography (silica, *n*-pentane:Et_2O = 19:1 to 7:1) to yield epoxide **250** (29 mg, 0.12 mmol, 91%) as a colorless solid.

Crystals suitable for X-ray analysis were obtained by slow evaporation of a solution of **250** in Et_2O/*n*-pentane.

R_f = 0.35 (hexanes:EtOAc = 7:1).

Melting point = 69.0–71.0 °C (CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.97–3.88 (m, 4H, 11-H, 12-H), 3.40 (m_C, 1H, 2-H), 3.16 (m_C, 1H, 1-H), 1.94 (ddd, *J* = 14.2, 7.3, 3.4 Hz, 1H, 4-H), 1.81 (m_C, 1H, 5-H_A), 1.80–1.71 (m, 3H, 3-H, 5-H_B,

7-H_A), 1.71–1.61 (m, 3H, 7-H_B, 8-H_A, 13-H), 1.49 (ddd, $^2J_{8B/8A}$ = 11.9 Hz, $^3J_{8B/7}$ = 4.5, 2.0 Hz, 1H, 8-H_B), 0.98 (d, $^3J_{15/13}$ = 6.6 Hz, 3H, 15-H)*, 0.97 (s, 3H, 10-H), 0.90 (d, $^3J_{14/13}$ = 6.4 Hz, 3H, 14-H)* ppm.

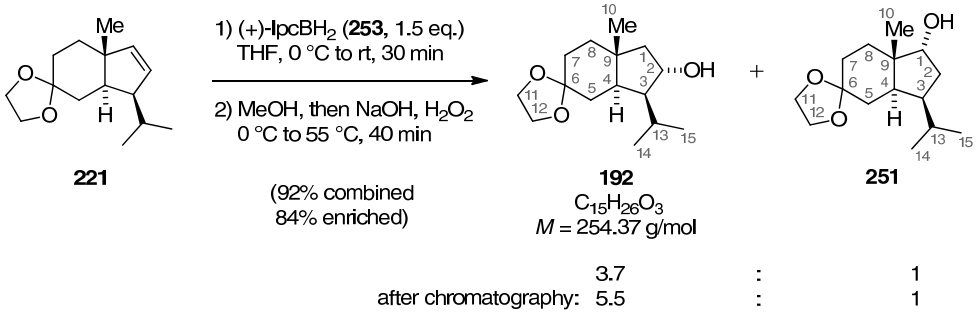
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 110.1 (C-1), 64.6 (C-11)*, 64.3 (C-12)*, 62.7 (C-1), 57.7 (C-2), 47.6 (C-3), 40-7 (C-9), 40.1 (C-4), 33.9 (C-5), 31.7 (C-8), 31.5 (C-7), 27.2 (C-13), 24.2 (C-14)**, 21.8 (C-15)**, 17.4 (C-10) ppm.

EI-MS for $C_{15}H_{25}O_3^+$ [$(M+H)^+$]: calcd. 253.1798
found 253.1787.

IR (ATR): $\tilde{\upsilon}$/ cm^{-1} = 2956 (s), 2873 (s), 1468 (w), 1388 (w), 1354 (w), 1293 (w), 1252 (w), 1179 (w), 1115 (w), 1087 (m), 1060 (w), 949 (w), 848 (w).

$[\alpha]_D^{20}$ = –33.5 (*c* 0.20, CH_2Cl_2).

Synthesis of Alcohols 192 and 251



To a solution of (*S*)-Alpine-Boramine™ (**252**, 1.26 g, 3.02 mmol, 1.3 eq.) in THF (4.8 mL) was added $BF_3{\cdot}OEt_2$ (744 µL, 6.04 mmol, 2.6 eq.) and the mixture was stirred at room temperature for 2 h forming a white precipitate. The mixture was filtered using a syringe filter and the resulting solution of enantiopure $IpcBH_2$ (**253**) was used directly. The concentration was considered to be ca. 1M.[171]

To a solution of alkene **221** (550 mg, 2.33 mmol, 1.0 eq.) in THF (60 mL) at 0 °C was added dropwise (+)-$IpcBH_2$ (**253**, 3.5 mL of a ca. 1M solution in THF, 3.5 mmol, 1.5 eq.). The mixture was allowed to warm to room temperature and stirred an additional 30 min, at which time thin layer chromatography indicated complete consumption of the starting material. The mixture was cooled to 0 °C and MeOH (500 µL) was added followed by aqueous NaOH (3N, 10 mL) and aqueous H_2O_2 (30%, 10 mL). After heating the biphasic mixture to 55 °C for 40 min, the mixture was allowed to cool to room temperature and saturated aqueous NH_4Cl (20 mL) was added. The phases were separated and the aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic layers were washed

with saturated aqueous NaCl (2 x 40 mL), which in turn were re-extracted with Et_2O (2 x 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 2:1) to yield the regioisomers **192** and **251** (3.7:1, 549 mg, 2.16 mmol, 92%) as a colorless oil. Further purification by flash column chromatography (silica, hexanes:EtOAc = 4:1) yielded alcohols **17** and **18** (502 mg, 1.98 mmol, 84%) in an enhanced ratio of 5.5:1.
On larger scale, 3.8 g (16.1 mmol) and 3.2 g (13.6 mmol) of alkene **221**, respectively, the initial ratio of hydroboration remained unchanged. Careful flash column chromatography, however, gave alcohols **192** and **251** (2.70 g, 10.6 mmol, 67% and 2.50 g, 9.84 mmol, 73%) in lower yield but in enhanced ratios of 12.4:1 and 6.6:1, respectively.

An analytical sample of regioisomer **192** was obtained by repeated flash column chromatography. The analytical data of alcohol **251** was obtained from a sample which was contaminated by ca. 14% of alcohol **192** as assigned by ^{1}H NMR spectroscopy.

Analytical data for alcohol **192**:

R_f = 0.34 (hexanes:EtOAc = 2:1, stains green with anisaldehyde).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 4.32 (ddd, $^3J_{2/1B}$ = 8.6 Hz, $^3J_{2/1A}$ = 7.2 Hz, $^3J_{2/3}$ = 4.4 Hz, 1H, 2-H), 3.98–3.90 (m, 4H, 11-H, 12-H), 2.25 (ddd, ^3J = 14.1, 10.5, 3.3 Hz, 1H, 4-H), 2.01 (dd, $^2J_{1A/1B}$ = 11.6 Hz, $^3J_{1A/2}$ = 7.1 Hz, 1H, 1-H_A), 1.85 (m_C, 1H, 5-H_A), 1.73–1.62 (m, 3H, 5-H_B, 7-H_A, 13-H), 1.58 (m_C, 1H, 7-H_B), 1.54 (ddd, J = 12.8, 4.7, 2.5 Hz, 1H, 8-H_A), 1.48 (ddd, $^3J_{3/4}$ = $^3J_{3/13}$ = 10.4 Hz, $^3J_{3/2}$ = 4.3 Hz, 1H, 3-H), 1.42 (m_C, 1H, 8-H_B), 1.37 (br s, 1H, *O*H), 1.22 (m_C, 1H, 1-H_B), 1.00 (d, $^3J_{14/13}$ = 6.6 Hz, 3H, 14-H)*, 0.94 (d, $^3J_{15/13}$ = 6.6 Hz, 3H, 15-H)*, 0.87 (s, 3H, 10-H) ppm.

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 110.4 (C-6), 77.9 (C-2), 64.5 (C-11)*, 64.4 (C-12)*, 57.2 (C-3), 50.1 (C-1), 46.9 (C-4), 41.2 (C-9), 36.9 (C-8), 34.8 (C-5), 30.8 (C-7), 29.9 (C-13), 24.1 (C-15)**, 22.0 (C-14)**, 19.1 (C-10) ppm.

EI-MS for $C_{15}H_{26}O_3^+$ [M^+]: calcd. 254.1876
found 254.1879.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 3418 (br s), 2950 (s), 2876 (s), 1457 (w), 1388 (w), 1354 (w), 1289 (w), 1255 (w), 1193 (w), 1111 (m), 1095 (m), 1035 (m), 994 (w), 946 (w), 874 (w).

$[\alpha]_D^{20}$ = –1.3 (*c* 1.00, CH_2Cl_2).

Analytical data for alcohol **251**:

R_f = 0.31 (hexanes:EtOAc = 2:1, stains violet with anisaldehyde).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.99–3.92 (m, 4H, 11-H, 12-H), 3.74 (d, $^3J_{1/2A}$ = 5.1 Hz, 1H, 1-H), 2.37 (ddd, ^3J = 14.3, 9.8, 3.5 Hz, 1H, 4-H), 2.00 (m_C, 1H, 2-H_A), 1.93 (m_C, 1H, 5-H_A), 1.85 (m_C, 1H, 3-H), 1.82–1.71 (m, 4H, 2-H_B, 5-H_B, 7-H_A, 8-H_A), 1.69–1.64 (m, 1H, 7-H_B), 1.63–1.58 (m, 1H, 13-H), 1.36–1.27 (m, 2H, 8-H_A, *O*H), 0.90 (d, $^3J_{14/13}$ = 6.4 Hz, 3H, 14-H)*, 0.84 (s, 3H, 10-H), 0.82 (d, $^3J_{15/13}$ = 6.6 Hz, 3H, 15-H)* ppm.

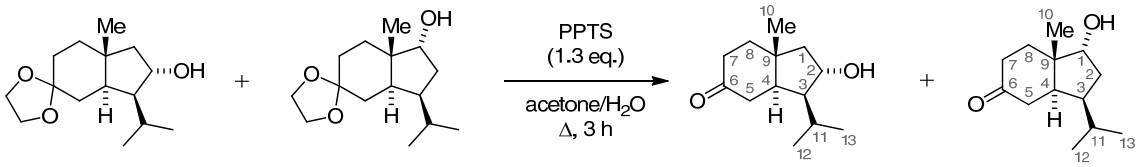
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 110.4 (C-6), 79.0 (C-1), 64.5 (C-11)*, 64.4 (C-12)*, 45.6 (C-9), 44.9 (C-3), 42.4 (C-4), 38.5 (C-2), 34.9 (C-5), 30.8 (C-7), 30.7 (C-13), 29.6 (C-8), 24.1 (C-14)**, 22.3 (C-15)**, 18.3 (C-10) ppm.

EI-MS for $C_{15}H_{26}O_3^+$ [M^+]: calcd. 236.1876
found 236.1869.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 3446 (br s), 2954 (s), 2872 (s), 1461 (w), 1386 (w), 1353 (w), 1291 (w), 1257 (w), 1190 (w), 1112 (w), 1086 (m), 1057 (w), 1036 (w), 976 (w), 948 (w), 884 (w).

$[\alpha]_D^{20}$ = –46.0 (*c* 0.50, CH_2Cl_2).

Synthesis of Ketones 255 and 256



192 + **251** → (89% combined, 75% enriched) → **255** $C_{13}H_{22}O_2$, *M* = 210.31 g/mol + **256**

	5.5	:	1
after chromatography:	12	:	1

To a solution of alcohols **192** and **251** (5.5:1, 495 mg, 1.95 mmol, 1.0 eq.) in acetone/H_2O (10:1, 44 mL) was added PPTS (635 mg, 2.53 mmol, 1.3 eq.) and the mixture was heated to reflux for 3 h. The reaction was allowed to cool to room temperature and the pH was adjusted to 7–8 by adding solid $NaHCO_3$. The mixture was subsequently freed of acetone and the residue was diluted with Et_2O (80 mL). The organic layer was consecutively washed with saturated aqueous $NaHCO_3$ (2 x 20 mL), aqueous HCl (1N, 2 x 20 mL) and saturated aqueous $NaHCO_3$ (20 mL). The combined

$NaHCO_3$ layers and the combined HCl layers were separately re-extracted with Et_2O (2 x 20 mL) and the combined organic layers were dried over $MgSO_4$. The solvents were removed under reduced pressure and the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 4:1 to 2:1) to yield ketones **255** and **256** (12:1, 307 mg, 1.46 mmol, 75%) as a colorless solid.
On a larger scale, reaction of a 12.4:1 mixture of alcohols **192** and **251** (2.66 g, 10.5 mmol) provided pure ketone **255** (1.81 g, 8.62 mmol) in 82% yield.

Analytical samples of both regioisomers **255** and **256** were obtained by repeated flash column chromatography. Ketone **256** was obtained as viscous colorless oil.

Analytical data for ketone **255**:

R_f = 0.22 (hexanes:EtOAc = 2:1, stains yellow-green with anisaldehyde).

Melting point = 52.5–54.5 °C (hexanes/EtOAc).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 4.42 (ddd, $^3J_{2/1A}$ = 9.4 Hz, $^3J_{2/1B}$ = 7.0 Hz, $^3J_{2/3}$ = 4.9 Hz, 1H, 2-H), 2.58 (ddd, J = 14.3, 3.4, 1.7 Hz, 1H, 5-H_A), 2.44–2.30 (m, 4H, 4-H, 5-H_B, 7-H), 2.10 (dd, $^2J_{1A/1B}$ = 11.7 Hz, $^3J_{1A/2}$ = 7.0 Hz, 1H, 1-H_A), 1.84 (ddd, J = 13.0, 7.1, 2.1 Hz, 1H, 8-H_A), 1.73–1.67 (m, 1H, 11-H), 1.62–1.55 (m, 3H, 3-H, 8-H_B, *O*H), 1.31 (dd, $^2J_{1B/1A}$ = 11.7 Hz, ^3J = 9.3 Hz, 1H, 1-H_B), 1.04 (d, $^3J_{13/11}$ = 6.6 Hz, 3H, 13-H)*, 1.04 (s, 3H, 10-H), 0.94 (d, $^3J_{12/11}$ = 6.4 Hz, 3H, 12-H)* ppm.

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 212.0 (C-6), 77.7 (C-2), 56.6 (C-3), 49.4 (C-1), 48.6 (C-4), 41.6 (C-5), 40.9 (C-9), 37.7 (C-8), 37.2 (C-7), 29.2 (C-11), 24.2 (C-12)*, 21.7 (C-13)*, 19.1 (C-10) ppm.

EI-MS for $C_{13}H_{22}O_2^+$ [M^+]: calcd. 210.1614
found 210.1613.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 3406 (br s), 2955 (s), 2932 (s), 2871 (m), 1703 (s), 1462 (w), 1420 (w), 1388 (w), 1228 (w), 1170 (w), 1149 (w), 1129 (w), 1101 (w), 1034 (m), 999 (w), 973 (w), 818 (w), 741 (w).

$[\alpha]_D^{20}$ = +72.0 (*c* 0.125, CH_2Cl_2).

Analytical data for ketone **256**:

R_f = 0.28 (hexanes:EtOAc = 2:1, stains violet with anisaldehyde).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.84 (d, $^3J_{1/2A}$ = 4.8 Hz, 1H, 1-H), 2.63 (m_C, 1H, 5-H_A), 2.54–2.36 (m, 4H, 4-H, 5-H_B, 7-H), 2.06 (ddd, $^2J_{2A/2B}$ = 14.7 Hz, $^3J_{2A/3}$ = 7.3 Hz, $^3J_{2A/1}$ = 4.7 Hz, 1H, 2-H_A), 2.04–1.98 (m, 1H, 8-H_A), 1.98–1.92 (m, 1H, 3-H), 1.83 (dd, $^2J_{2B/2A}$ = 14.8 Hz, $^3J_{2B/3}$ = 8.9 Hz, 1H, 2-H_B), 1.64 (m_C, 1H, 11-H), 1.59 (ddd, J = 12.7, 7.1, 2.4 Hz, 1H, 8-H_B), 1.41 (br s, 1H, *O*H), 1.00 (d, J = 0.6 Hz, 3H, 10-H), 0.90 (d, ^3J = 6.6 Hz, 3H, 12-H)*, 0.86 (d, ^3J = 6.6 Hz, 3H, 13-H)* ppm.

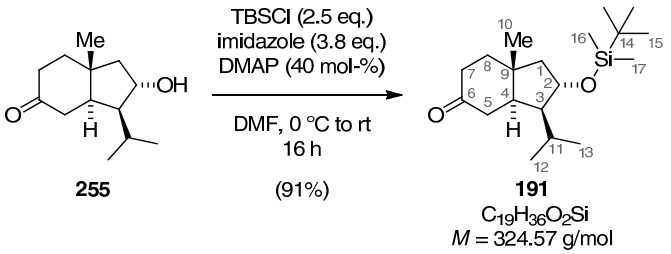
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 212.6 (C-6), 78.4 (C-1), 45.5 (C-9), 44.6 (C-3), 44.2 (C-4), 41.5 (C-5), 38.8 (C-2), 37.1 (C-7), 30.1 (C-11), 30.0 (C-8), 24.1 (C-12)*, 22.0 (C-13)*, 18.4 (C-10) ppm.

EI-MS for $C_{13}H_{22}O_2^+$ [M^+]: calcd. 210.1614
found 210.1614.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 3434 (br s), 2957 (s), 2894 (s), 2874 (s), 1698 (s), 1466 (w), 1424 (w), 1386 (w), 1368 (w), 1343 (w), 1309 (w), 1266 (w), 1234 (w), 1171 (w), 1144 (w), 1127 (w), 1031 (m), 954 (w).

$[\alpha]_D^{20}$ = –9.2 (*c* 0.50, CH_2Cl_2).

Synthesis of *trans*-Hydrindane Building Block 191



255 **191**

$C_{19}H_{36}O_2Si$

M = 324.57 g/mol

To a solution of alcohols **255** and **256** (12:1, 100 mg, 480 µmol, 1.0 eq.) in DMF (6 mL) at 0 °C was sequentially added imidazole (122 mg, 1.80 mmol, 3.8 eq.), DMAP (23 mg, 0.19 mmol, 40 mol-%) and TBSCl (181 mg, 1.20 mmol, 2.5 eq.). The mixture was allowed to warm to room temperature and stirred for 16 h. The reaction was quenched by addition of H_2O (15 mL) and the biphasic mixture was extracted with Et_2O (3 x 25 mL). The combined organic layers were washed with 10% aqueous NaCl (3 x 15 mL) and the combined aqueous layers were re-extracted with Et_2O (2 x 15 mL). The

combined organic layers were dried over $MgSO_4$ and the solvents were evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica, hexanes: EtOAc = 70:1 to 50:1 to 30:1) to yield ketone **191** (141 mg, 434 μmol, 91%) as a colorless solid and as single isomer.

Crystals suitable for X-ray analysis were obtained by recrystallization from MeOH.

R_f = 0.15 (hexanes:EtOAc = 30:1).

Melting point = 49.5–51.0 °C (hexanes/EtOAc).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 4.36 (ddd, $^3J_{2/1B}$ = 8.8 Hz, $^3J_{2/1A}$ = 6.9 Hz, $^3J_{2/3}$ = 4.2 Hz, 1H, 2-H), 2.56 (ddd, $^2J_{5A/5B}$ = 14.7 Hz, J = 3.6, 1.7 Hz, 1H, 5-H_A), 2.43–2.36 (m, 2H, 5-H_B, 7-H_A), 2.35–2.28 (m, 2H, 4-H, 7-H_B), 1.98 (dd, $^2J_{1A/1B}$ = 11.8 Hz, $^3J_{1A/2}$ = 6.9 Hz, 1H, 1-H_A), 1.81 (ddd, $^2J_{8A/8B}$ = 12.9 Hz, $^3J_{8A/7B}$ = 7.1 Hz, $^3J_{8A/7A}$ = 2.0 Hz, 1H, 8-H_A), 1.71–1.63 (m, 2H, 3-H, 11-H), 1.58 (m_C, 1H, 8-H_B), 1.27 (dd, $^2J_{1B/1A}$ = 11.7 Hz, $^3J_{1B/2}$ = 8.8 Hz, 1H, 1-H_B), 1.03 (s, 3H, 10-H), 0.98 (d, $^3J_{13/11}$ = 6.2 Hz, 3H, 13-H)*, 0.91 (d, $^3J_{12/11}$ = 6.0 Hz, 3H, 12-H)*, 0.87 (s, 9H, 15-H), 0.06 (s, 3H, 16-H)**, 0.04 (s, 3H, 17-H)** ppm.

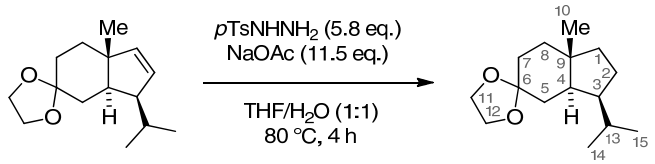
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 212.3 (C-6), 77.8 (C-2), 56.5 (C-3), 50.2 (C-1), 48.1 (C-4), 41.6 (C-5), 40.9 (C-9), 38.0 (C-8), 37.3 (C-7), 29.2 (C-11), 26.0 (C-15), 24.4 (C-12)*, 21.9 (C-13)*, 19.2 (C-10), 18.0 (C-14), –3.5 (C-16)**, –4.7 (C-17)** ppm.

EI-MS for $C_{18}H_{33}O_2Si^+$ [$(M–Me)^+$]: calcd. 309.2244
found 309.2226.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 2956 (s), 2929 (s), 2899 (s), 2857 (s), 1711 (s), 1472 (w), 1462 (w), 1420 (w), 1388 (w), 1254 (m), 1106 (m), 1073 (m), 1006 (w), 941 (w), 887 (w), 851 (w), 836 (m), 774 (m).

$[\alpha]_D^{20}$ = +59.7 (c 0.33, CH_2Cl_2).

Synthesis of Dioxolane 257



To a solution of alkene **221** (140 mg, 590 µmol, 1.0 eq.) and NaOAc (556 mg, 6.80 mmol, 11.5 eq.) in THF/H_2O (1:1, 18 mL) was added *p*-toluenesulfonyl hydrazide (631 mg, 3.39 mmol, 5.8 eq.) in one portion. The mixture was heated to 80 °C for 4 h and was then allowed to cool to room temperature. The reaction was quenched by addition of saturated aqueous K_2CO_3 (2 mL), the organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were evaporated under reduced pressure. The resulting residue was suspended in *n*-pentane/Et_2O (1:1, 5 mL) and purified by flash column chromatography (silica, *n*-pentane:Et_2O = 19:1 to 9:1) to yield saturated compound **257** (130 mg, 546 µmol, 93%) as a colorless oil.

R_f = 0.37 (hexanes:EtOAc = 16:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 4.02–3.88 (m, 4H), 1.91–1.78 (m, 3H), 1.77–1.67 (m, 3H), 1.64–1.53 (m, 4H), 1.47 (dd, *J* = 11.8, 7.6 Hz, 1H), 1.32 (m_C, 1H), 1.13 (m_C, 1H), 0.89 (d, *J* = 6.3 Hz, 3H), 0.86 (br s, 3H), 0.82 (d, *J* = 6.6 Hz, 3H) ppm.

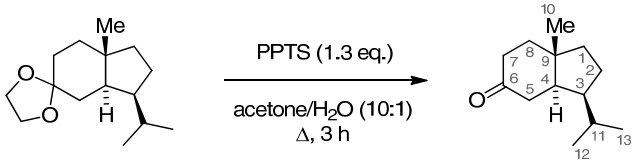
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 110.9, 64.4, 64.3, 48.4, 46.7, 41.0, 40.3, 37.2, 35.4, 31.3 (2C), 28.7, 24.1, 22.4, 17.9 ppm.

EI-MS for $C_{15}H_{26}O_2^+$ [M^+]: calcd. 238.1927
found 238.1927.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 2950 (s), 2873 (s), 1464 (w), 1386 (w), 1356 (w), 1289 (w), 1256 (w), 1190 (m), 1115 (m), 1096 (s), 1057 (w), 947 (m), 882 (w), 718 (w), 668 (w).

$[\alpha]_D^{20}$ = –24.8 (*c* 0.25, CH_2Cl_2).

Synthesis of Building Block 190



257 **190**
$C_{13}H_{22}O$
M = 194.31 g/mol

To a solution of dioxolane **257** (100 mg, 0.420 mmol, 1.0 eq.) in acetone/H_2O (9:1, 10 mL) was added PPTS (137 mg, 0.546 mmol, 1.3 eq.) and the reaction mixture was heated to reflux for 3 h. The mixture was allowed to cool to room temperature and the pH value was adjusted to 7–8 by the addition of solid $NaHCO_3$. Having freed the mixture of acetone, the residue was diluted with Et_2O (10 mL). The organic layer was separated and sequentially washed with saturated aqueous $NaHCO_3$ (3 mL), HCl (2N, 2 x 3 mL) and saturated aqueous $NaHCO_3$ (2 x 3 mL). The organic layer was dried over $MgSO_4$ and the solvents were removed under reduced pressure. The crude product was purified by flash column chromatography (silica, *n*-pentane:Et_2O = 20:1 to 9:1) to yield ketone **190** (80 mg, 0.41 mmol, 99%) as a colorless oil.

R_f = 0.29 (hexanes:EtOAc = 16:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.58 (ddd, $^2J_{5A/5B}$ = 15.0 Hz, $^3J_{5A/4}$ = 4.1 Hz, $^4J_{5A/7B}$ = 1.8 Hz, 1H, 5-H_A), 2.47–2.40 (m, 2H, 5-H_B, 7-H_A), 2.31 (dddd, $^2J_{7B/7A}$ = 16.3 Hz, $^3J_{7B/8B}$ = 5.7 Hz, $^3J_{7B/8A}$ = $^4J_{7B/5A}$ = 1.8 Hz, 1H, 7-H_B), 1.97–1.88 (m, 2H, 2-H_A, 4-H), 1.86 (ddd, $^2J_{8A/8B}$ = 12.9 Hz, $^3J_{8A/7A}$ = 7.3 Hz, $^3J_{8A/7B}$ = 1.9 Hz, 1H, 8-H_A), 1.81–1.68 (m, 2H, 2-H_B, 3-H) 1.65–1.57 (m, 2H, 1-H_A, 11-H), 1.49 (ddd, $^2J_{8B/8A}$ = $^3J_{8B/7A}$ = 13.0 Hz, $^3J_{8B/7B}$ = 5.8 Hz, 1H, 8-H_B), 1.19 (ddd, $^2J_{1B/1A}$ = $^3J_{1B/2}$ = 11.8 Hz, $^3J_{1B/2}$ = 8.4 Hz, 1H, 1-H_B), 1.04 (s, 3H, 10-H), 0.88 (d, $^3J_{12/11}$ = 6.4 Hz, 3H, 12-H)*, 0.86 (d, $^3J_{13/11}$ = 6.4 Hz, 3H, 13-H)* ppm.

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 213.2 (C-6), 50.2 (C-4), 46.5 (C-3), 42.3 (C-5), 41.1 (C-9), 39.9 (C-1), 37.8 (C-8), 37.6 (C-7), 30.6 (C-11), 29.3 (C-2), 24.1 (C-12)*, 22.1 (C-13)*, 17.8 (C-10) ppm.

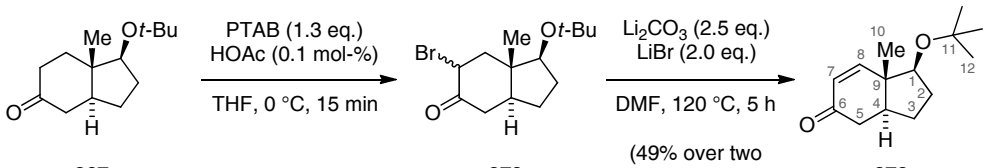
EI-MS for $C_{13}H_{22}O^+$ [M^+]: calcd. 194.1665
found 194.1674.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 2954 (s), 2868 (s), 1711 (s), 1464 (w), 1420 (w), 1386 (w), 1289 (w), 1214 (w), 1146 (w), 1045 (w), 921 (w), 816 (w).

$[\alpha]_D^{20}$ = +11.2 (*c* 0.25, CH_2Cl_2).

2.2 Experimental Procedures for Chapter 3: 'Synthetic Studies toward Astellatol'

Synthesis of Enone 273



207 **272** **273**

$C_{14}H_{22}O_2$
M = 222.32 g/mol

To a solution of ketone **207** (200 mg, 893 μmol, 1.0 eq.) in THF (44 mL) at 0 °C was added PTAB (441 mg, 1.16 mmol, 1.3 eq.) in one portion followed by HOAc (0.66 mL of a 1 vol-% solution in THF, 0.12 nmol, 0.13 mol-%) and the mixture was stirred for 15 min at this temperature. The reaction was quenched by addition of saturated aqueous $Na_2S_2O_3$ (15 mL), the phases were separated and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with saturated aqueous NaCl (20 mL) and were dried over $MgSO_4$. Having evaporated the solvents under reduced pressure, the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 16:1 to 14:1 to 9:1) to yield brominated compound **272** (223 mg, 738 μmol, 78%, R_f = 0.67, hexanes:EtOAc = 3:1) as a mixture of diastereomers.

To a solution of *α*-bromo ketone **272** (150 mg, 500 μmol, 1.0 eq.) in DMF (6 mL) was added LiBr (87 mg, 1.0 mmol, 2.0 eq.) and Li_2CO_3 (109 mg, 1.50 mmol, 2.5 eq.) and the resulting suspension was heated to 120 °C for 5 h. The mixture was allowed to cool to room temperature and the reaction was quenched by addition of saturated aqueous NH_4Cl (10 mL). The mixture was extracted with Et_2O (4 x 10 mL) and the combined organic layers were washed with 10% aqueous NaCl (3 x 10 mL). Having dried the combined organic layers over $MgSO_4$, the solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 20:1 to 16:1) to yield enone **273** (70 mg, 315 μmol, 63%, 49% over two steps) as a colorless oil.

R_f = 0.15 (hexanes:EtOAc = 16:1).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.12 (dd, $^3J_{8/7}$ = 9.8 Hz, *J* = 0.7 Hz, 1H, 8-H), 5.84 (dd, $^3J_{7/8}$ = 9.7 Hz, $^4J_{7/5A}$ = 0.6 Hz, 1H, 7-H), 3.70–3.64 (m, 1H, 1-H), 2.44 (ddd, $^2J_{5A/5B}$ = 17.4 Hz, $^3J_{5A/4}$ = 5.2 Hz, $^4J_{5A/7}$ = 0.7 Hz, 1H, 5-H_A), 2.36 (dd, $^2J_{5B/5A}$ = 17.4 Hz, $^3J_{5B/4}$ = 13.4 Hz, 1H, 5-H_B), 2.07–1.93 (m, 2H,

2-H_A, 4-H), 1.70–1.61 (m, 1H, 3-H_A), 1.60–1.46 (m, 2H, 2-H_B, 3-H_B), 1.17 (s, 9H, 12-H), 0.93 (s, 3H, 10-H).

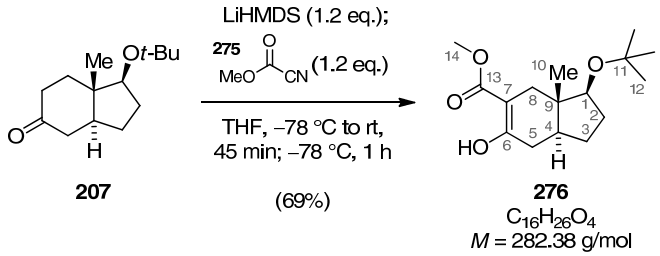
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 200.9 (C-6), 157.3 (C-8), 128.6 (C-7), 75.6 (C-1), 72.9 (C-11), 45.4 (C-9), 41.8 (C-4), 39.4 (C-5), 30.9 (C-2), 28.8 (C-12), 25.5 (C-3), 12.7 (C-10) ppm.

EI-MS for $C_{10}H_{14}O_2^+$ [$(M-C_3H_8)^+$]: calcd. 166.0988
found 166.0984.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 2973 (s), 2906 (m), 2878 (m), 1676 (s), 1474 (w), 1364 (w), 1239 (w), 1194 (m), 1122 (w), 1105 (w), 1070 (m), 902 (w), 780 (w).

$[\alpha]_D^{20}$ = +30.4 (*c* 0.50, CH_2Cl_2).

Synthesis of β-Keto Ester 276



To a solution of ketone **207** (100 mg, 450 μmol, 1.0 eq.) in THF (4.5 mL) at −78 °C was added dropwise LiHMDS (0.54 mL of a 1.0M solution in THF, 0.54 mmol, 1.2 eq.). The mixture was allowed to warm to room temperature and was stirred for an additional 45 min before being cooled to −78 °C. Then, Mander's reagent (**275**, 43 μL, 0.43 mmol, 1.2 eq.) was added dropwise and the mixture was stirred an additional 1 h at −78 °C. The reaction was diluted with Et_2O (5 mL) and poured onto H_2O (5 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The combined organic layers were washed with saturated aqueous NaCl (5 mL), dried over Na_2SO_4 and the solvents were evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 40:1) to yield β-keto ester **276** (88 mg, 0.31 mmol, 69%) as a colorless oil.

R_f = 0.55 (hexanes:EtOAc = 16:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 12.30 (s, 1H, *O*H), 3.75 (s, 3H, 14-H), 3.53 (m_C, 1H, 1-H), 2.35–2.29 (m, 2H, 5-H_A, 8-H_A), 2.11 (m_C, 1H, 5-H_B), 1.94 (m_C, 1H, 2-H_A), 1.88 (m_C, 1H, 8-H_B), 1.69–1.48 (m, 3H, 2-H_B, 3-H_A, 4-H), 1.36 (m_C, 1H, 3-H_B), 1.17 (s, 9H, 12-H), 0.72 (s, 3H, 10-H) ppm.

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 173.8 (C-13), 172.3 (C-6), 97.0 (C-7), 80.2 (C-1), 72.6 (C-11), 51.6 (C-14), 41.7 (C-9), 40.0 (C-4), 35.1 (C-8), 32.3 (C-5), 31.6 (C-2), 28.9 (C-12), 25.8 (C-2), 10.7 (C-10) ppm.

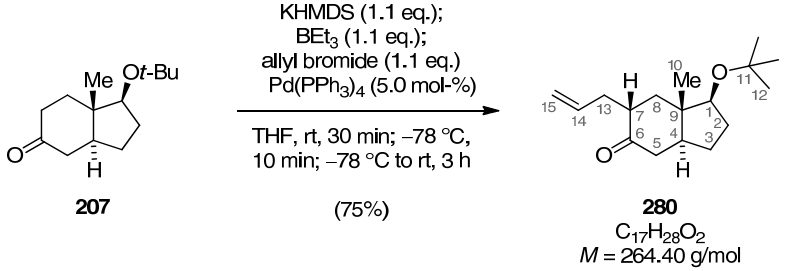
EI-MS for $C_{16}H_{26}O_4^+$ [M^+]: calcd. 282.1826
found 282.1836.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 2972 (s), 1654 (s), 1608 (m), 1442 (m), 1383 (w), 1362 (m), 1269 (s), 1232 (w), 1210 (s), 1117 (w), 1092 (w), 1062 (w).

$[\alpha]_D^{20}$ = +103.6 (*c* 0.50, CH_2Cl_2).

This compound has been prepared by an alternative procedure having identical physical properties.[134]

Synthesis of Ketone 280



To a solution of ketone **207** (5.00 g, 22.3 mmol, 1.0 eq.) in THF (200 mL) at room temperature was added dropwise KHMDS (50 mL of a 0.5M solution in toluene, 25.0 mmol, 1.1 eq.) and the resulting solution was stirred for 30 min. Then, the mixture was cooled to –78 °C and Et_3B (25.0 mL of a freshly prepared 1.0M solution in THF, 25.0 mmol, 1.1 eq.) was added dropwise. After stirring an additional 10 min, a solution of $Pd(PPh_3)_4$ (1.28 g, 1.15 mmol, 5.0 mol-%) and allyl bromide (2.20 mL, 25.0 mmol, 1.1 eq.) in THF (20 mL) was slowly added. The cold bath was removed and the mixture was allowed to warm to room temperature, and was stirred for 3 h. The reaction was quenched by careful addition of 2N HCl (30 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL) and dried over $NaSO_4$. The solvents were removed under reduced

pressure and the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 40:1 to 30:1) to yield ketone **280** (4.40 g, 16.7 mmol, 75%) as a colorless oil.

R_f = 0.73 (hexanes:EtOAc = 7:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 5.76 (m_C, 1H, 14-H), 5.04–4.96 (m, 2H, 15-H), 3.44 (dd, $^3J_{1/2}$ = 8.9, 7.6 Hz, 1H, 1-H), 2.56 (m_C, 1H, 13-H_A), 2.41 (m_C, 1H, 7-H), 2.37–2.28 (m, 2H, 5-H), 2.06 (dd, $^2J_{8A/8B}$ = 12.8 Hz, $^3J_{8A/7}$ = 6.3 Hz, 1H, 8-H_A), 2.02–1.94 (m, 2H, 2-H_A, 13-H_B), 1.69–1.62 (m, 1H, 4-H), 1.62–1.53 (m, 2H, 2-H_B, 3-H_A), 1.46–1.38 (m, 1H, 3-H_B), 1.13 (s, 9H, 12-H), 1.08 (dd, $^2J_{8B/8A}$ = $^3J_{8B/7}$ = 12.8 Hz, 1H, 8-H_B), 1.01 (s, 3H, 10-H) ppm.

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 212.1 (C-6), 136.8 (C-14), 116.3 (C-15), 79.5 (C-1), 72.7 (C-11), 45.8 (C-4), 45.3 (C-7), 43.1 (C-5), 42.8 (C-9), 42.3 (C-8), 34.1 (C-13), 32.0 (C-2), 28.8 (C-12), 25.9 (C-3), 11.3 (C-10) ppm.

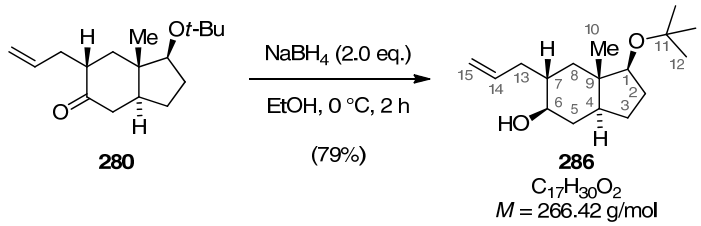
EI-MS for $C_{17}H_{28}O_2^+$ [M^+]: calcd. 264.2084
found 264.2082.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 3076 (w), 2973 (s), 2876 (m), 1708 (s), 1463 (w), 1390 (w), 1361 (m), 1252 (w), 1192 (m), 1114 (m), 1061 (m), 1027 (w), 999 (w), 903 (w).

$[\alpha]_D^{20}$ = +56.3 (*c* 1.00, CH_2Cl_2).

The analytical data matched those reported previously.[188]

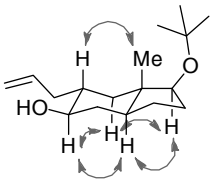
Synthesis of Alcohol 286



To a solution of ketone **280** (26 mg, 0.10 mmol, 1.0 eq.) in EtOH (2 mL) at 0 °C was added $NaBH_4$ (7.7 mg, 0.20 mmol, 2.0 eq.) in one portion and the mixture was stirred for an additional 2 h. The reaction was quenched by careful addition of HCl (2N, few drops) and the pH was adjusted to 7–8 by addition of solid $NaHCO_3$. The solvent was evaporated under reduced pressure and the residue was dissolved in EtOAc (10 mL). The organic layer was washed with saturated aqueous NH_4Cl (5 mL) and

the aqueous layer was re-extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with saturated aqueous NaCl (2 x 5 mL), dried over $MgSO_4$ and the solvents were evaporated under reduced pressure. The residue was purified by flash column chromatography (silica, hexanes:EtOAc = 20:1 to 10:1) to yield alcohol **286** (21 mg, 79 μmol, 79%) as a colorless wax.

The stereochemistry of the newly formed stereogenic center was assigned by 2D NOESY experiments showing the proximity of protons as depicted beside.



R_f = 0.43 (hexanes:EtOAc = 4:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 5.86 (dddd, $^3J_{14/15A}$ =17.3 Hz, $^3J_{14/15B}$ = 10.2 Hz, $^3J_{14/13A}$ = $^3J_{14/13B}$ = 7.2 Hz, 1H, 14-H), 5.06 (m_C, 1H, 15-H_A), 5.01 (m_C, 1H, 15-H_B), 3.35 (dd, $^3J_{1/2}$ = 8.9, 7.4 Hz, 1H, 1-H), 3.27 (ddd, $^3J_{6/7}$ = $^3J_{6/5B}$ = 10.3 Hz, $^3J_{6/5A}$ = 5.0 Hz, 1H, 6-H), 2.41 (m_C, 1H, 13-H_A), 2.01–1.95 (m, 1H, 13-H_B), 1.94–1.86 (m, 1H, 2-H_A), 1.80 (ddd, *J* = 12.0, 5.0, 3.0 Hz, 1H, 5-H_A), 1.75 (dd, $^2J_{8A/8B}$ = 13.0 Hz, $^3J_{8A/7}$ = 4.3 Hz, 1H, 8-H_A), 1.72–1.59 (m, 2H, 7-H, *O*H), 1.59–1.41 (m, 2H, 2-H_B, 3-H_A), 1.40–1.29 (m, 2H, 3-H_B, 5-H_B), 1.29–1.22 (m, 1H, 4-H), 1.12 (s, 9H, 12-H), 0.77 (s, 3H, 10-H), 0.73 (dd, $^2J_{8B/8A}$ = $^3J_{8B/7}$ = 12.9 Hz, 1H, 8-H_B) ppm.

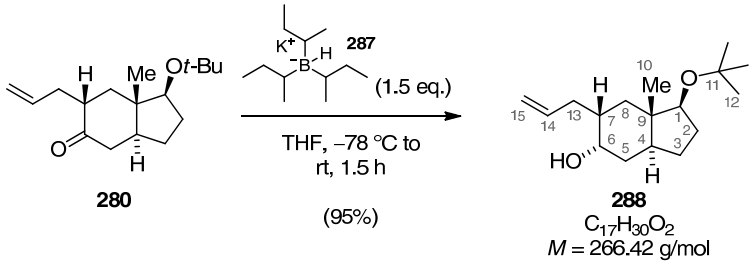
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 137.8 (C-14), 116.3 (C-15), 80.5 (C-1), 76.2 (C-6), 72.5 (C-11), 43.4 (C-4), 43.0 (C-9), 41.5 (C-8), 40.4 (C-7), 38.5 (C-13), 35.0 (C-5), 31.8 (C-2), 29.0 (C-12), 25.5 (C-3), 11.9 (C-10) ppm.

EI-MS for $C_{17}H_{30}O_2^+$ [M^+]:	calcd.	266.2240
	found	266.2237.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 3218 (br m), 3078 (w), 2973 (s), 2927 (s), 2910 (s), 2874 (m), 1465 (w), 1393 (w), 1361 (w), 1256 (w), 1198 (w), 1126 (w), 1070 (w), 1038 (w), 907 (w).

$[\alpha]_D^{20}$ = +0.4 (*c* 0.50, CH_2Cl_2).

Synthesis of Alcohol 288



To a solution of ketone **280** (2.70 g, 10.2 mmol, 1.0 eq.) in THF (100 mL) at –78 °C was added dropwise K-Selectride® (**287**, 15.4 mL of a 1.0M solution in THF, 15.4 mmol, 1.5 eq.). Upon complete addition, the cold bath was removed and the solution was stirred an additional 1.5 h at room temperature. The mixture was cooled to 0 °C, and MeOH (18 mL) was carefully added to quench excess hydride source. Subsequently, aqueous NaOH (3N, 36 mL) and H_2O_2 (30% in H_2O, 27 mL) were added and the biphasic mixture was stirred an additional 3 h at room temperature. The mixture was diluted with saturated aqueous NH_4Cl (30 mL) and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with saturated aqueous NaCl (2 x 50 mL), dried over $MgSO_4$ and the solvents were removed under reduced pressure. The crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 20:1 to 15:1) to yield alcohol **288** (2.61 g, 9.81 mmol, 95%) as a colorless oil.

The stereochemistry was assigned as depicted above since this compound was the minor product in the reduction with $NaBH_4$. In addition, the small coupling constants (ca. 2.5 Hz) for the newly formed methine proton indicated no axial-axial coupling.

R_f = 0.18 (hexanes:EtOAc = 10:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 5.84 (m_C, 1H, 14-H), 5.06 (m_C, 1H, 15-H_A), 5.01 (m_C, 1H, 15-H_B), 3.92 (m_C, 1H, 6-H), 3.45 (dd, $^3J_{1/2}$ = 8.8, 7.5 Hz, 1H, 1-H), 2.20–2.13 (m, 1H, 13-H_A), 2.06–2.00 (m, 1H, 13-H_B), 1.95–1.87 (m, 1H, 2-H_A), 1.74–1.63 (m, 3H, 4-H, 5-H_A, 7-H), 1.56–1.40 (m, 4H, 2-H_B, 3-H_A, 5-H_B, 8-H_A), 1.34–1.22 (m, 2H, 3-H_B, *O*H), 1.13 (s, 9H, 12-H), 1.09 (dd, $^2J_{8B/8A}$ = $^3J_{8B/7}$ = 12.6 Hz, 1H, 8-H_B), 0.73 (s, 3H, 10-H) ppm.

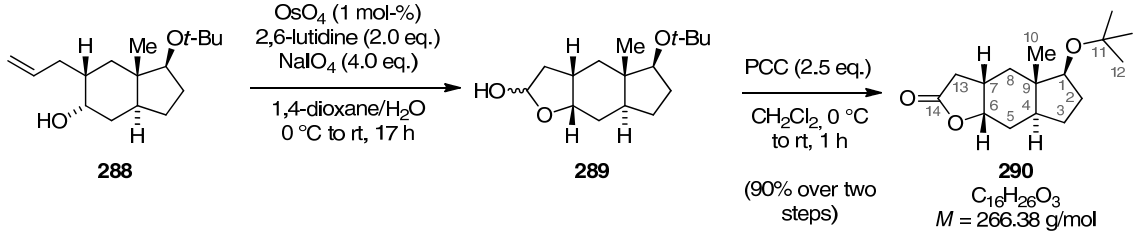
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 137.7 (C-14), 115.9 (C-15), 80.6 (C-1), 72.4 (C-11), 69.0 (C-6), 43.0 (C-9), 38.6 (C-8), 37.7 (C-13)*, 37.5 (C-7)*, 37.4 (C-4)*, 33.6 (C-5), 31.4 (C-2), 28.9 (C-12), 25.6 (C-3), 10.9 (C-10) ppm.

EI-MS for $C_{17}H_{30}O_2^+$ [M^+]: calcd. 266.2240
found 266.2234.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 3408 (br m), 2973 (s), 2929 (s), 1462 (w), 1389 (w), 1361 (m), 1256 (m), 1196 (s), 1128 (m), 1066 (s), 1029 (m), 1006 (m), 908 (m), 864 (w), 803 (w).

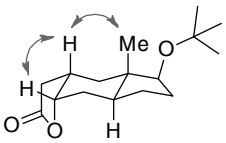
$[\alpha]_D^{20}$ = +46.4 (*c* 0.25, CH_2Cl_2).

Synthesis of Lactone 290



To a solution of alkene **288** (3.59 g, 13.5 mmol, 1.0 eq.) in 1,4-dioxane/H_2O (3:1, 200 mL) at 0 °C was sequentially added 2,6-lutidine (3.14 mL, 27.0 mmol, 2.0 eq.) and OsO_4 (838 µL of a 4 wt% solution in H_2O, 135 µmol, 1.0 mol-%). Then, $NaIO_4$ (11.6 g, 54.0 mmol, 4.0 eq.) was added in portions and the mixture was allowed to warm to room temperature. After stirring for an additional 17 h, the reaction was diluted with H_2O (150 mL) and the mixture was extracted with CH_2Cl_2 (4 x 200 mL). The combined organic layers were washed with saturated aqueous NaCl (100 mL) and dried over Na_2SO_4. The solvents were removed under reduced pressure to yield crude intermediate lactol **289** as a mixture of epimers (R_f = 0.2, hexanes:EtOAc = 4:1), which was used without further purification.
To a suspension of PCC (7.30 g, 33.8 mmol, 2.5 eq.) in CH_2Cl_2 (200 mL) at 0 °C was added dropwise a solution of crude lactol **289** (assumed 13.5 mmol, 1.0 eq.) in CH_2Cl_2 (40 mL + 5 mL rinse). The resulting mixture was allowed to warm to room temperature and was stirred for an additional 1 h before being directly applied to flash column chromatography (silica, hexanes:EtOAc = 3:1). The solvent of the product containing fractions was evaporated under reduced pressure and the residue was purified by flash column chromatography (silica, hexanes:EtOAc = 8:1) to yield lactone **290** (3.23 g, 12.1 mmol, 90% over two steps) as a colorless solid.

The stereochemistry of the tricyclic system was assigned according to the key NOESY correlations as indicated beside.



R_f = 0.38 (hexanes:EtOAc = 4:1).

Melting point = 118.5–121.0 °C (CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 4.56 (m_C, 1H, 6-H), 3.39 (dd, $^3J_{1/2}$ = 8.8, 8.0 Hz, 1H, 1-H), 2.73 (dd, $^2J_{13A/13B}$ = 16.8 Hz, $^3J_{13A/7}$ = 7.0 Hz, 1H, 13-H_A), 2.51 (m_C, 1H, 7-H), 2.20 (d, $^2J_{13B/13A}$ = 16.9 Hz, 1H,

13-H_B), 2.12 (m_C, 1H, 5-H_A), 1.92 (m_C, 1H, 2-H_A), 1.81 (dd, $^2J_{8A/8B}$ = 13.1 Hz, $^3J_{8A/7}$ = 6.4 Hz, 1H, 8-H_A), 1.63–1.43 (m, 4H, 2-H_B, 3-H_A, 4-H, 5-H_B), 1.31 (m_C, 1H, 3-H_B), 1.12 (s, 9H, 12-H), 0.91 (m_C, 1H, 8-H_B), 0.73 (s, 3H, 10-H) ppm.

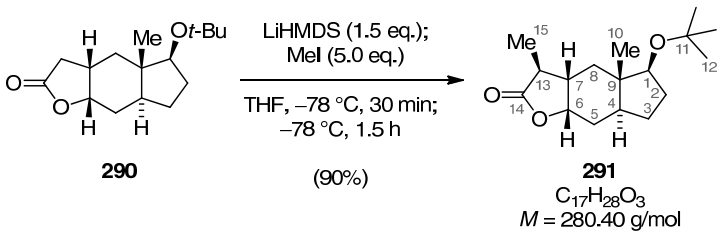
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 177.4 (C-14), 80.2 (C-6), 80.1 (C-1), 72.6 (C-11), 41.1 (C-9), 39.6 (C-8), 38.4 (C-13), 37.0 (C-4), 33.1 (C-7), 30.8 (C-2), 28.9 (C-12), 28.5 (C-5), 25.3 (C-3), 10.4 (C-10) ppm.

EI-MS for $C_{16}H_{26}O_3^+$ [M^+]: calcd. 266.1876
found 266.1881.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 2971 (s), 2932 (m), 2874 (m), 1779 (s), 1462 (w), 1389 (w), 1361 (w), 1215 (w), 1196 (m), 1179 (m), 1155 (m), 1124 (w), 1062 (m), 1043 (w), 1028 (w), 1000 (w), 968 (w), 911 (w).

$[\alpha]_D^{20}$ = +12.4 (*c* 1.00, CH_2Cl_2).

Synthesis of Lactone 291



290 **291**
$C_{17}H_{28}O_3$
M = 280.40 g/mol

To a solution of lactone **290** (3.23 g, 12.1 mmol, 1.0 eq.) in THF (180 mL) at –78 °C was added dropwise LiHMDS (18.2 mL of a 1.0M solution in THF, 18.2 mmol, 1.5 eq.) and the resulting mixture was stirred for 45 min at this temperature before adding MeI (3.80 mL, 60.5 mmol, 5.0 eq.) dropwise. After stirring the mixture for an additional 90 min, the reaction was quenched by addition of HCl (2N, 40 mL). The mixture was allowed to warm to room temperature and was diluted with half-saturated aqueous NH_4Cl (100 mL). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organic layers were sequentially washed with saturated aqueous $NaHCO_3$ (70 mL) and saturated aqueous NaCl (70 mL), and dried over Na_2SO_4. The solvents were evaporated under reduced pressure and the crude product was purified by flash column chromatography (short plug of silica, hexanes:EtOAc = 8:1). Further purification by flash column chromatography (silica, hexanes:EtOAc = 14:1 to 10:1 to 7:1) yielded lactone **291** (3.06 g, 10.9 mmol, 90%) as a colorless solid and as single diastereomer.

Crystals suitable for X-ray analysis were obtained by cooling a saturated solution of lactone **291** in hexanes/EtOAc to –25 °C.

R_f = 0.62 (hexanes:EtOAc = 4:1).

Melting point = 152.0–154.0 °C (CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 4.72–4.69 (m, 1H, 6-H), 3.37 (dd, $^3J_{1/2}$ = 8.7, 8.0 Hz, 1H, 1-H), 2.34 (q, $^3J_{13/15}$ = 7.6 Hz, 1H, 13-H), 2.17–2.09 (m, 2H, 5-H_A, 7-H), 1.91 (m_C, 1H, 2-H_A), 1.84 (dd, $^2J_{8A/8B}$ = 13.1 Hz, $^2J_{8A/7}$ = 6.5 Hz, 1H, 8-H_A), 1.61–1.41 (m, 4H, 2-H_B, 3-H_A, 4-H, 5-H_B), 1.33–1.25 (m, 1H, 3-H_B), 1.30 (d, $^3J_{15/13}$ = 7.7 Hz, 3H, 15-H), 1.11 (s, 9H, 12-H), 0.88 (m_C, 1H, 8-H_B), 0.70 (s, 3H, 10-H) ppm.

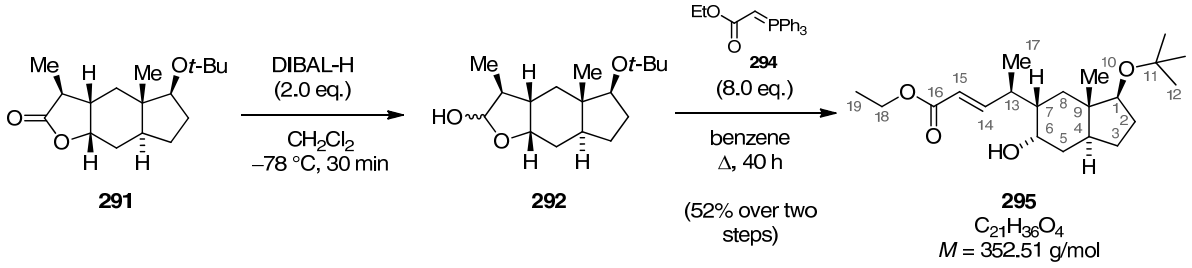
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 180.5 (C-14), 80.1 (C-1), 77.9 (C-6), 72.5 (C-11), 45.0 (C-13), 42.0 (C-9), 40.0 (C-7)*, 39.9 (C-8)*, 37.1 (C-4), 30.8 (C-2), 28.9 (C-12), 28.5 (C-5), 25.3 (C-3), 15.0 (C-15), 10.3 (C-10) ppm.

EI-MS for $C_{13}H_{20}O_3^+$ [$(M–C_3H_8)^+$]: calcd. 224.1407
found 224.1413.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 2973 (s), 2938 (s), 2904 (m), 2874 (m), 1757 (s), 1464 (w), 1362 (w), 1213 (m), 1200 (m), 1183 (m), 1132 (w), 1111 (w), 1083 (w), 1064 (w), 1023 (w), 974 (w), 941 (w).

$[\alpha]_D^{20}$ = –2.6 (*c* 1.00, CH_2Cl_2).

Synthesis of Alcohol 295



To a solution of lactone **291** (82 mg, 0.29 mmol, 1.0 eq.) in CH_2Cl_2 (6 mL) at –78 °C was added dropwise DIBAL-H (0.58 mL of a 1.0M solution in CH_2Cl_2, 0.58 mmol, 2.0 eq.) and the mixture was stirred for 30 min at this temperature. Then, EtOAc (1 mL) was added to quench excess hydride source followed by half-saturated aqueous Rochelle salt (10 mL). The mixture was allowed to warm to

room temperature and was stirred vigorously for an additional 1 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was filtered over a pad of silica (hexanes:EtOAc = 6:1) to yield lactol **292** as a mixture of epimers, which was used without further purification.

To a solution of lactol **292** (20 mg, 71 μmol, 1.0 eq.) in benzene (6 mL) was added ylid **294** (148 mg, 0.43 mmol, 6.0 eq.) and the mixture was heated to reflux for 24 h. As TLC indicated remaining starting material, more reagent **294** (49 mg, 0.14 mmol, 2.0 eq.) was added and the mixture was heated to reflux for an additional 16 h. The mixture was allowed to cool to room temperature and the reaction was quenched by addition of saturated aqueous NH_4Cl (5 mL). After phase separation, the aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organic layers were dried over $MgSO_4$. The solvents were removed under reduced pressure and the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 10:1 to 7:1) to yield ester **295** (14 mg, 37 μmol, 52% over two steps) as a highly viscous colorless oil.

R_f = 0.47 (hexanes:EtOAc = 4:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 6.94 (dd, $^3J_{14/15}$ = 15.6 Hz, $^3J_{14/13}$ = 9.5 Hz, 1H, 14-H), 5.87 (dd, $^3J_{15/14}$ = 15.6 Hz, $^4J_{15/13}$ = 0.8 Hz, 1H, 15-H), 4.19 (q, $^3J_{18/19}$ = 7.2 Hz, 2H, 18-H), 3.90 (m_C, 1H, 6-H), 3.46 (dd, $^3J_{1/2}$ = 8.9, 7.7 Hz, 1H, 1-H), 2.39 (m_C, 1H, 13-H), 1.95–1.88 (m, 1H, 2-H_A), 1.74–1.65 (m, 2H, 4-H, 8-H_A), 1.60 (m_C, 1H, 5-H_A), 1.53–1.40 (m, 4H, 2-H_B, 3-H_A, 5-H_B, 7-H), 1.34–1.23 (m, 1H, 3-H_B), 1.29 (t, $^3J_{19/18}$ = 7.1 Hz, 3H, 19-H), 1.14 (s, 9H, 12-H), 1.10–1.02 (m, 1H, 8-H_B), 1.05 (d, $^3J_{17/13}$ = 6.8 Hz, 3H, 17-H), 0.71 (s, 3H, 10-H) ppm.

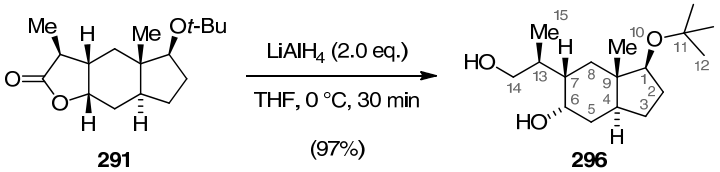
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 167.0 (C-16), 154.2 (C-14), 120.4 (C-15), 80.7 (C-1), 72.4 (C-11), 68.1 (C-6), 60.4 (C-18), 42.8 (C-9), 42.7 (C-7), 38.7 (C-13), 37.4 (C-4), 35.9 (C-8), 34.0 (C-5), 31.3 (C-2), 28.9 (C-12), 25.6 (C-3), 18.2 (C-17), 14.4 (C-19), 11.0 (C-11) ppm.

EI-MS for $C_{21}H_{36}O_4^+$ [M^+]: calcd. 352.2608
found 352.2624.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 3480 (br w), 2973 (s), 2935 (s), 2874 (m), 1718 (m), 1463 (w), 1362 (w), 1262 (w), 1225 (w), 1195 (w), 1125 (w), 1063 (w).

$[\alpha]_D^{20}$ = +51.2 (*c* 0.25, CH_2Cl_2).

Synthesis of Diol 296



291 **296**

$C_{17}H_{32}O_3$

M = 284.43 g/mol

To a suspension of $LiAlH_4$ (806 mg, 21.2 mmol, 2.0 eq.) in THF (60 mL) at 0 °C was added a solution of lactone **291** (3.06 g, 10.9 mmol, 1.0 eq.) in THF (30 mL + 10 mL rinse) *via* cannula within 20 min and the mixture was stirred for an additional 15 min at this temperature. Then, half-saturated aqueous Rochelle salt (100 mL) was added and the biphasic mixture was vigorously stirred for 1 h at room temperature. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with saturated aqueous NaCl (80 mL) and dried over $MgSO_4$. The crude product was purified by flash column chromatography (silica, CH_2Cl_2:MeOH = 100:2.5) to yield diol **296** (2.99 g, 10.6 mmol, 97%) as a colorless solid.

R_f = 0.24 (CH_2Cl_2:MeOH = 100:5).

Melting point = 128.5–130.0 °C (CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 4.11 (m_C, 1H, 6-H), 3.68 (dd, $^2J_{14A/14B}$ = 10.7 Hz, $^3J_{14A/13}$ = 2.8 Hz, 1H, 14-H_A), 3.58 (dd, $^2J_{14B/14A}$ = 10.8 Hz, $^3J_{14B/13}$ = 6.1 Hz, 1H, 14-H_B), 3.47 (dd, $^3J_{1/2}$ = 8.8, 7.4 Hz, 1H, 1-H), 3.08 (br s, 2H, *O*H), 1.94–1.87 (m, 1H, 2-H_A), 1.76–1.63 (m, 3H, 4-H, 5-H_A, 13-H), 1.56–1.39 (m, 5H, 2-H_B, 3-H_A, 5-H_B, 7-H, 8-H_A), 1.32–1.22 (m, 2H, 3-H_B, 8-H_B), 1.13 (s, 9H, 12-H), 1.00 (d, $^3J_{15/13}$ = 7.2 Hz, 3H, 15-H), 0.72 (s, 3H, 10-H) ppm.

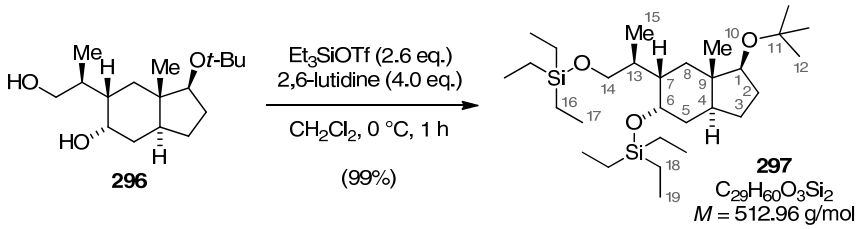
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 80.8 (C-1), 72.4 (C-11), 66.9 (C-6), 65.8 (C-14), 43.1 (C-9), 42.2 (C-7), 38.2 (C-13), 37.6 (C-4), 37.5 (C-8), 33.6 (C-5), 31.4 (C-2), 28.9 (C-12), 25.6 (C-3), 16.3 (C-15), 11.0 (C-10) ppm.

EI-MS for $C_{17}H_{32}O_3^+$ [M^+]: calcd. 284.2346
found 284.2342.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 3298 (br s), 2971 (s), 2929 (s), 2874 (s), 1462 (w), 1387 (w), 1360 (m), 1253 (w), 1196 (m), 1114 (w), 1062 (m), 1009 (m), 972 (w), 937 (w), 902 (w).

$[\alpha]_D^{20}$ = +38.0 (*c* 0.50, CH_2Cl_2).

Synthesis of *trans*-Hydrindane 297



To a solution of diol **296** (2.97 g, 10.5 mmol, 1.0 eq.) and 2,6-lutidine (4.90 mL, 42.1 mmol, 4.0 eq.) in CH_2Cl_2 (100 mL) at 0 °C was added dropwise Et_3SiOTf (6.20 mL, 27.4 mmol, 2.6 eq.) and the mixture was stirred for 1 h at this temperature. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (60 mL), the phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with saturated aqueous NaCl (50 mL) and dried over $MgSO_4$. The crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 100:1 to 60:1 to 40:1) to yield the title compound **297** (5.34 g, 10.4 mmol, 99%) as a colorless oil.

R_f = 0.23 (hexanes:EtOAc = 30:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 4.00 (m_C, 1H, 6-H), 3.52 (dd, $^2J_{14A/14B}$ = 9.5 Hz, $^3J_{14A/13}$ = 5.0 Hz, 1H, 14-H_A), 3.45 (dd, $^2J_{14B/14A}$ = 9.6 Hz, $^3J_{14B/13}$ = 6.1 Hz, 1H, 14-H_B), 3.42 (dd, $^3J_{1/2}$ = 8.9, 7.4 Hz, 1H, 1-H), 1.95–1.84 (m, 1H, 2-H_A), 1.77–1.65 (m, 2H, 4-H, 13-H), 1.56–1.51 (m, 2H, 5-H_A, 7-H), 1.50–1.32 (m, 4H, 2-H_B, 3-H_A, 5-H_B, 8-H_A), 1.25 (m_C, 1H, 3-H_B), 1.14 (s, 9H, 12-H), 1.12 (m_C, 1H, 8-H_B), 0.99–0.94 (m, 18H, 17-H, 19-H), 0.89 (d, $^3J_{15/13}$ = 6.9 Hz, 3H, 15-H), 0.70 (s, 3H, 10-H), 0.63–0.54 (m, 12H, 16-H, 18-H) ppm.

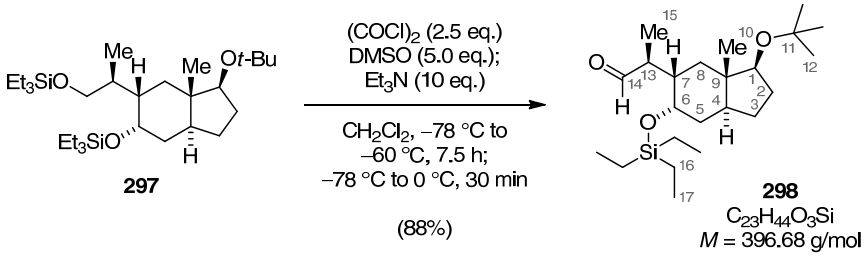
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 81.0 (C-1), 72.3 (C-11), 70.5 (C-6), 66.5 (C-14), 42.7 (C-9), 38.7 (C-7), 37.4 (2C, C-4, C-13), 35.0 (C-8), 34.7 (C-5), 31.5 (C-2), 29.0 (C-12), 25.6 (C-3), 15.1 (C-15), 11.1 (C-10), 7.2 (C-17)*, 7.0 (C-19)*, 5.5 (C-16)**, 4.6 (C-18)** ppm.

EI-MS for $C_{29}H_{60}O_3Si_2^+$ [M^+]: calcd. 512.4076
found 512.4076.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 2954 (s), 2911 (s), 2987 (s), 1459 (w), 1414 (w), 1387 (w), 1361 (w), 1238 (w), 1196 (w), 1062 (m), 1015 (m), 976 (w), 725 (m).

$[\alpha]_D^{20}$ = +24.2 (*c* 1.00, CH_2Cl_2).

Synthesis of Aldehyde 298



To a solution of DMSO (1.02 mL, 14.5 mmol, 5.0 eq.) in CH_2Cl_2 (30 mL) at −78 °C was slowly added $(COCl)_2$ (3.61 mL of a 2.0M solution in CH_2Cl_2, 7.22 mmol, 2.5 eq.) and the mixture was stirred for 15 min at this temperature. Then, a solution of bissilyl ether **297** (1.48 g, 2.89 mmol, 1.0 eq.) in CH_2Cl_2 (7 mL) was added within 30 min using a syringe pump. The reaction was allowed to warm to –60 °C and was stirred for 7 h at –65 to –60 °C (cryocooler). The mixture was cooled to −78 °C and Et_3N (3.95 mL, 28.4 mmol, 9.8 eq.) was added dropwise. The mixture was stirred for an additional 10 min at this temperature and was allowed to warm slowly to 0 °C forming a white precipitate. After stirring an additional 15 min at 0 °C, the reaction was quenched by adding H_2O (20 mL) and the biphasic mixture was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were washed with saturated aqueous NaCl (30 mL), dried over $MgSO_4$ and the solvents were removed under reduced pressure. Purification by flash column chromatography (silica, hexanes:EtOAc = 60:1 to 30:1) yielded aldehyde **298** (992 mg, 2.53 mmol, 88%) as a colorless oil.
On a larger scale (5.31 g, 10.4 mmol of bissilyl ether **297**), aldehyde **298** (3.10 g, 7.82 mmol) was isolated in 75% yield along with recovered starting material **297** (430 mg, 840 μmol, 8%).

R_f = 0.31 (hexanes:EtOAc = 30:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 9.74 (d, $^3J_{14/13}$ = 1.7 Hz, 1H, 14-H), 4.04 (m_C, 1H, 6-H), 3.44 (dd, $^3J_{1/2}$ = 9.0, 7.4 Hz, 1H, 1-H), 2.40 (qdd, $^3J_{13/7}$ = $^3J_{13/15}$ = 7.2 Hz, $^3J_{13/14}$ = 1.7 Hz, 1H, 13-H), 1.96–1.86 (m, 2H, 2-H_A, 7-H), 1.73 (dddd, ^3J = 13.0, 13.0, 7.0, 3.3 Hz, 1H, 4-H), 1.60 (ddd, $^2J_{5A/5B}$ = 13.7 Hz, $^3J_{5A/4}$ = $^3J_{5A/6}$ = 3.2 Hz, 1H, 5-H_A), 1.53–1.40 (m, 4H, 2-H_A, 3-H_A, 5-H_B, 8-H_A), 1.35 (dd, $^2J_{8B/8A}$ = $^3J_{8B/7}$ = 12.6 Hz, 1H, 8-H_B), 1.31–1.23 (m, 1H, 3-H_B), 1.14 (s, 9H, 12-H), 1.07 (d, $^3J_{15/13}$ = 7.1 Hz, 3H, 15-H), 0.94 (t, $^3J_{17/16}$ = 8.0 Hz, 9H, 17-H), 0.74 (s, 3H, 10-H), 0.58 (q, $^3J_{16/17}$ = 8.0 Hz, 6H, 16-H) ppm.

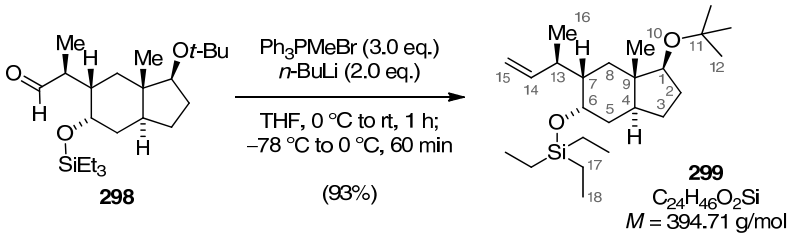
^{13}C NMR ($CDCl_3$, 150 MHz): δ= 205.2 (C-14), 80.8 (C-1), 72.4 (C-11), 68.7 (C-6), 48.3 (C-13), 42.9 (C-9), 40.3 (C-7), 37.2 (C-4), 36.2 (C-8), 33.9 (C-5), 31.4 (C-2), 29.0 (C-12), 25.5 (C-3), 12.2 (C-15), 10.9 (C-10), 7.1 (C-17), 5.3 (C-16) ppm.

EI-MS for $C_{23}H_{44}O_3Si^+$ [M^+]: calcd. 396.3054
found 396.3065.

IR (ATR): $\tilde{\nu}/cm^{-1}$ = 2955 (s), 2876 (s), 1722 (s), 1461 (w), 1414 (w), 1389 (w), 1362 (w), 1238 (w), 1195 (m), 1126 (w), 1086 (s), 1045 (s), 1005 (m), 973 (w), 945 (w), 919 (w), 726 (m).

$[\alpha]_D^{20}$ = +63.6 (*c* 0.50, CH_2Cl_2).

Synthesis of Alkene 299



To a suspension of methyltriphenylphosphonium bromide (8.33 g, 23.3 mmol, 3.0 eq.) in THF (120 mL) at 0 °C was slowly added *n*-BuLi (6.20 mL of a 2.5M solution in hexanes, 15.6 mmol, 2.0 eq.). The mixture was allowed to warm to room temperature, stirred for an additional 1 h and was subsequently cooled to –78 °C. Then, a solution of aldehyde **298** (3.08 g, 7.78 mmol, 1.0 eq.) in THF (12 mL + 5 mL rinse) was added within 15 min (syringe pump). The cold bath was removed and replaced by an ice/water bath. The mixture was stirred for 60 min at 0 °C and the reaction was quenched by addition of saturated aqueous NH_4Cl (50 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 70 mL). The combined organic layers were washed with saturated aqueous NaCl (50 mL) and dried over $MgSO_4$. Having evaporated the solvents under reduced pressure, the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 100:1 to 60:1) to afford alkene **299** (2.86 g, 7.26 mmol, 93%) as a colorless oil.

R_f = 0.21 (hexanes:EtOAc = 60:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 5.77 (ddd, $^3J_{14/15A}$ = 17.3 Hz, $^3J_{14/15B}$ = 10.3 Hz, $^3J_{14/13}$ = 8.2 Hz, 1H, 14-H), 4.97 (ddd, $^3J_{15A/14}$ = 17.3 Hz, $^2J_{15A/15B}$ = 2.1 Hz, $^4J_{15A/13}$ = 1.0 Hz, 1H, 15-H_A), 4.93 (ddd, $^3J_{15B/14}$ = 10.4 Hz, $^2J_{15B/14A}$ = 2.1 Hz, $^4J_{15B/13}$ = 0.5 Hz, 1H, 15-H_B), 4.00 (m_C, 1H, 6-H), 3.43 (dd, $^3J_{1/2}$ = 8.9, 7.4 Hz, 1H, 1-H), 2.22 (m_C, 1H, 13-H), 1.91 (m_C, 1H, 2-H_A), 1.74 (dddd, *J* = 12.9, 12.9, 7.0, 3.4 Hz, 1H, 4-H), 1.58–1.52 (m, 2H, 5-H_A, 8-H_A), 1.48–1.34 (m, 3H, 2-H_B, 3-H_A, 5-H_B), 1.29–1.21 (m, 2H, 3-H_B, 7-H), 1.15 (s, 9H, 12-H), 1.07 (dd, $^2J_{8B/8A}$ = $^3J_{8B/7}$ = 12.4 Hz, 1H, 8-H_B), 0.96 (t, $^3J_{18/17}$ = 7.9 Hz, 9H, 18-H), 0.95 (d, $^3J_{16/13}$ = 6.9 Hz, 3H, 16-H), 0.70 (s, 3H, 10-H), 0.62–0.54 (m, 6H, 17-H) ppm.

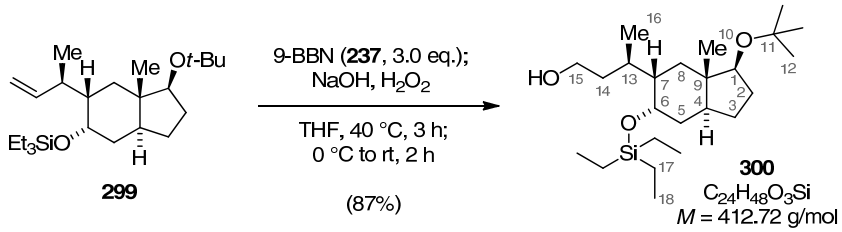
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 145.1 (C-14), 113.0 (C-13), 80.9 (C-1), 72.3 (C-11), 69.4 (C-6), 43.6 (C-7), 42.8 (C-9), 39.0 (C-13), 37.3 (C-4), 35.6 (C-8), 34.4 (C-5), 31.6 (C-2), 29.0 (C-12), 25.5 (C-3), 18.7 (C-16), 11.2 (C-10), 7.3 (C-18), 5.6 (C-17) ppm.

EI-MS for $C_{24}H_{46}O_2Si^+$ [M^+]: calcd. 394.3262
found 394.3262.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 3087 (w), 2972 (s), 2955 (s), 2911 (s), 2876 (s), 1460 (m), 1415 (w), 1361 (w), 1237 (w), 1196 (m), 1128 (w), 1060 (m), 1045 (m), 1106 (m), 974 (w), 909 (m), 796 (w), 724 (m).

$[\alpha]_D^{20}$ = +37.6 (*c* 0.50, CH_2Cl_2).

Synthesis of Alcohol 300



To a solution of alkene **299** (394 mg, 1.00 mol, 1.0 eq.) in THF (12 mL) was added 9-BBN (**237**, 4.00 mL of a 0.5M solution in THF, 2.00 mmol, 2.0 eq.) and the mixture was heated to 40 °C for 3.5 h. The mixture was cooled to 0 °C and MeOH (2 mL), aqueous NaOH (3N, 4 mL) and aqueous H_2O_2 (30 wt%, 4 mL) were consecutively added. The mixture was stirred at 40 °C for 1 h and for an additional 1 h at room temperature, and H_2O (10 mL) was added. The mixture was extracted with Et_2O (3 x 25 mL) and the combined organic layers were washed with saturated aqueous NaCl (2 x 20 mL). The NaCl layers were re-extracted with Et_2O (2 x 10 mL) and the combined organic layers were dried over $MgSO_4$. The solvents were evaporated under reduced pressure and the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 9:1) to yield alcohol **300** (357 mg, 867 μmol, 87%) as a colorless oil.

R_f = 0.17 (hexanes:EtOAc = 7:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 4.07 (m_C, 1H, 6-H), 3.71 (ddd, $^2J_{15A/15B}$ = 10.4 Hz, $^3J_{15A/14}$ = 8.5, 5.5 Hz, 1H, 15-H_A), 3.64 (ddd, $^2J_{15B/15A}$ = 10.3 Hz, $^3J_{15B/14}$ = 8.2, 6.8 Hz, 1H, 15-H_B), 3.42 (dd, $^3J_{1/2}$ = 8.8, 7.5 Hz, 1H, 1-H), 1.94–1.87 (m, 1H, 2-H_A), 1.80–1.70 (m, 2H, 4-H, 14-H_A), 1.67–1.61 (m, 1H, 13-H), 1.59–1.54 (m, 1H, 5-H_A), 1.49 (dd, $^2J_{8A/8B}$ = 12.3 Hz, $^3J_{8A/7}$ = 3.5 Hz, 1H, 8-H_A), 1.47–1.35 (m, 4H, 2-H_B, 3-H_A, 5-H_B, 13-H), 1.30–1.23 (m, 2H, 3-H_B, 7-H), 1.16–1.08 (m, 1H, 8-H_B), 1.14 (s, 9H,

12-H), 0.96 (t, $^3J_{18/17}$ = 8.0 Hz, 9H, 18-H), 0.88 (d, $^3J_{16/15}$ = 6.8 Hz, 3H, 16-H), 0.69 (s, 3H, 10-H), 0.64–0.55 (m, 6H, 17-H) ppm.

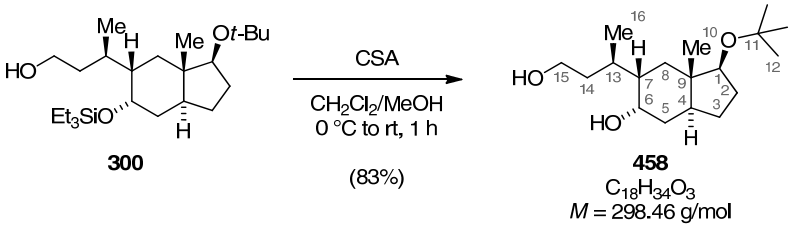
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 81.0 (C-1). 72.3 (C-11), 70.0 (C-6), 61.7 (C-15), 42.7 (2C, C-7, C-9), 38.3 (C-14), 37.4 (C-4), 35.2 (C-8), 34.6 (C-5), 31.6 (C-2), 31.4 (C-13), 29.0 (C-12), 25.5 (C-3), 17.4 (C-16), 11.1 (C-10), 7.2 (C-18), 5.5 (C-17) ppm.

EI-MS for $C_{24}H_{48}O_3Si^+$ [M^+]: calcd. 412.3367
found 412.3359.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 3355 (br m), 2955 (s), 2876 (s), 1461 (w), 1379 (w), 1362 (w), 1196 (w), 1130 (w), 1062 (m), 1009 (w), 977 (w), 797 (w), 741 (w).

$[\alpha]_D^{20}$ = +20.0 (*c* 0.33, CH_2Cl_2).

Synthesis of Diol 458



To a solution of silyl ether **300** (14 mg, 39 µmol, 1.0 eq.) in CH_2Cl_2/MeOH (7:1, 1.6 mL) at 0 °C was added (1*R*)-(–)-camphorsulfonic acid (spatula tip). The mixture was allowed to warm to room temperature and was stirred for 1 h before being diluted with CH_2Cl_2 (5 mL) and quenched by addition of saturated aqueous $NaHCO_3$ (5 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were evaporated under reduced pressure. The obtained crude product was purified by flash column chromatography (silica, CH_2Cl_2:MeOH = 100:2.5) to yield diol **458** (9 mg, 32 µmol, 83%) as a viscous colorless oil.

R_f = 0.24 (CH_2Cl_2:MeOH = 100:5).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 4.15 (m_C, 1H, 6-H), 3.76 (ddd, $^2J_{15A/15B}$ = 10.2 Hz, $^3J_{15A/14}$ = 6.4, 4.3 Hz, 1H, 15-H_A), 3.64 (ddd, $^2J_{15B/15A}$ = 10.1 Hz, $^3J_{15B/14}$ = 9.2, 5.4 Hz, 1H, 15-H_B), 3.44 (dd, $^3J_{1/2}$ = 8.8, 7.5 Hz, 1H, 1-H), 2.06–1.82 (m, 4H, 2-H_A, 14-H_A, *O*H), 1.70–1.57 (m, 4H, 4-H, 5-H_A, 8-H_A, 13-H), 1.55–1.41 (m, 3H, 2-H_B, 3-H_A, 5-H_B), 1.34–1.23 (m, 3H, 3-H_B, 7-H, 14-H_B), 1.13 (s, 9H,

12-H), 1.02 (dd, $^2J_{8B/8A} = {}^3J_{8B/7}$ = 12.9 Hz, 1H, 8-H_B), 0.94 (d, $^3J_{16/13}$ = 6.8 Hz, 3H, 16-H), 0.70 (s, 3H, 10-H) ppm.

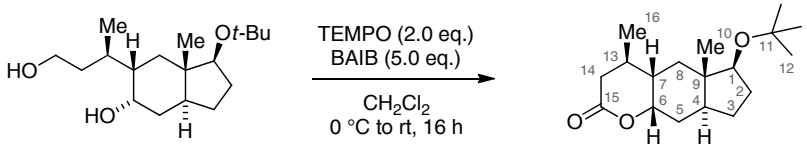
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 80.8 (C-1), 72.4 (C-11), 67.6 (C-6), 61.6 (C-15), 42.8 (C-9), 42.5 (C-7), 37.5 (C-4), 37.1 (C-14), 36.4 (C-8), 33.8 (C-5), 31.4 (C-2), 31.2 (C-13), 28.9 (C-12), 25.6 (C-3), 18.6 (C-16), 11.0 (C-10) ppm.

EI-MS for $C_{18}H_{34}O_3^+$ [M^+]: calcd. 298.2502
found 298.2509.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 3350 (br s), 2972 (s), 2931 (s), 2873 (s), 1462 (w), 1388 (w), 1361 (m), 1197 (m), 1130 (w), 1062 (m), 1028 (w), 1008 (w), 976 (w), 903 (w).

$[\alpha]_D^{20}$ = +40.8 (*c* 0.33, CH_2Cl_2).

Synthesis of Lactone 301



To a solution of diol **458** (6.0 mg, 20 µmol, 1.0 eq.) and BAIB (32 mg, 0.10 mmol, 5.0 eq.) in CH_2Cl_2 (1.5 mL) at 0 °C was added TEMPO (1 mg, 4 µmol, 0.2 eq.). The mixture was allowed to warm to room temperature and stirred for 2 h. Then, additional TEMPO (9.0 mg, 36 µmol, 1.8 eq.) was added and the mixture was stirred for 14 h. The reaction was diluted with CH_2Cl_2 (10 mL) and was quenched by addition of saturated aqueous Na_2SO_3 (3 mL). After phase separation, the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (5 mL) and saturated aqueous NaCl (5 mL), and were dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 7:1) to yield lactone **301** (5.0 mg, 17 µmol, 85%) as a colorless solid.

R_f = 0.18 (Hexanes:EtOAc = 7:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 4.50 (ddd, $^3J_{6/5A} = {}^3J_{6/5B} = {}^3J_{6/7}$ = 3.0 Hz, 1H, 6-H), 3.42 (dd, $^3J_{1/2A}$ = 8.8 Hz, $^3J_{1/2B}$ = 7.7 Hz, 1H, 1-H), 2.53 (dd, $^2J_{14A/14B}$ = 15.8 Hz, $^3J_{14A/13}$ = 6.2 Hz, 1H, 14-H_A) 2.18 (dd,

$^2J_{14B/14A}$ = 15.8 Hz, $^3J_{14B/13}$ = 9.6 Hz, 1H, 14-H_B), 1.95 (ddd, $^2J_{5A/5B}$ = 14.1 Hz, $^3J_{5A/4}$ = $^3J_{5A/6}$ = 3.0 Hz, 1H, 5-H_A), 1.91 (dddd, *J* = 13.5, 9.2, 9.2, 6.3 Hz, 1H, 2-H_A), 1.72–1.63 (m, 3H, 4-H, 7-H, 13-H), 1.62 (dd, $^2J_{8A/8B}$ = 12.8 Hz, $^3J_{8A/7}$ = 4.8 Hz, 1H, 8-H_A), 1.58 (m_C, 1H, 5-H_B), 1.55–1.49 (m, 1H, 3-H_A), 1.47–1.40 (m, 1H, 2-H_B), 1.28 (m_C, 1H, 3-H_B) 1.14 (d, $^3J_{16/13}$ = 6.9 Hz, 3H, 16-H), 1.12 (s, 9H, 12-H), 1.08 (dd, $^2J_{8B/8A}$ = $^3J_{8B/7}$ = 12.8 Hz, 1H, 8-H_B), 0.75 (s, 3H, 10-H) ppm.

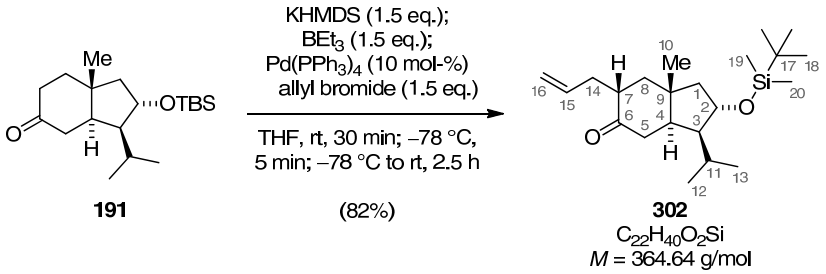
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 173.7 (C-15), 80.3 (C-1), 75.4 (C-6), 72.5 (C-11), 42.7 (C-9), 40.2 (C-8), 37.7 (C-7)*, 37.5 (C-4), 35.8 (C-14), 32.0 (C-13)*, 31.1 (C-2), 30.3 (C-5), 28.9 (C-12), 25.3 (C-3), 22.1 (C-16), 10.7 (C-10) ppm.

EI-MS for $C_{18}H_{30}O_3^+$ [M^+]:	calcd.	294.2189
	found	294.2177.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2971 (s), 2931 (s), 2873 (m), 1745 (s), 1461 (w), 1362 (w), 1308 (w), 1280 (w), 1251 (m), 1196 (m), 1165 (w), 1123 (w), 1064 (m), 1004 (w), 902 (w).

$[\alpha]_D^{20}$ = –7.2 (*c* 0.25, CH_2Cl_2).

Synthesis of Ketone 302



To a solution of ketone **191** (380 mg, 1.17 mmol, 1.0 eq.) in degassed THF (12 mL) at room temperature was added KHMDS (3.5 mL of a 0.5M solution in toluene, 1.75 mmol, 1.5 eq.) and the resulting yellow solution was stirred for 30 min before being cooled to –78 °C. Then, Et_3B (3.50 mL of a freshly prepared 0.5M solution in THF, 1.75 mmol, 1.5 eq.) was added dropwise and the mixture was stirred for 5 min. After slowly adding a solution of $Pd(PPh_3)_4$ (135 mg, 117 μmol, 10 mol-%) and allyl bromide (151 μL, 1.75 mmol, 1.5 eq.) in degassed THF (4 mL), the cold bath was removed and the mixture was stirred for 2.5 h at room temperature. The reaction was quenched by addition of saturated aqueous NH_4Cl (20 mL) and diluted with Et_2O (20 mL). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with saturated aqueous NaCl (30 mL) and dried over $MgSO_4$. The solvents were evaporated under reduced

pressure and the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 60:1) to yield ketone **302** (350 mg, 961 μmol, 82%) as a colorless oil.

R_f = 0.38 (hexanes:EtOAc = 16:1)

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 5.73 (m_C, 1H, 15-H), 5.03–4.97 (m, 2H, 16-H), 4.36 (ddd, $^3J_{2/1B}$ = 8.6 Hz, $^3J_{2/1A}$ = 7.0 Hz, $^3J_{2/3}$ = 4.2 Hz, 1H, 2-H), 2.58 (dd, $^2J_{5A/5B}$ = 13.8 Hz, $^3J_{5A/4}$ = 3.8 Hz, 1H, 5-H_A), 2.57–2.53 (m, 1H, 14-H_A), 2.45–2.36 (m, 2H, 5-H_B, 7-H), 2.23 (ddd, $^3J_{4/5B}$ = 15.2 Hz, $^3J_{4/3}$ = 9.9 Hz, $^3J_{4/5A}$ = 3.8 Hz, 1H, 4-H), 2.04–1.96 (m, 1H, 14-H_B), 1.97 (dd, $^2J_{1A/1B}$ = 11.5 Hz, $^3J_{1A/2}$ = 7.0 Hz, 1H, 1-H_A), 1.93 (dd, $^2J_{8A/8B}$ = 12.8 Hz, $^3J_{8A/7}$ = 6.3 Hz, 1H, 8-H_A), 1.71–1.64 (m, 1H, 13-H), 1.62 (ddd, $^3J_{3/4}$ = $^3J_{3/11}$ = 9.9 Hz, $^3J_{3/2}$ = 4.2 Hz, 1H, 3-H), 1.28–1.21 (m, 2H, 1-H_B, 8-H_B), 1.07 (s, 3H, 10-H), 0.97 (d, $^3J_{13/11}$ = 6.4 Hz, 3H, 13-H)*, 0.90 (d, $^3J_{12/11}$ = 6.2 Hz, 3H, 12-H)*, 0.86 (s, 9H, 18-H), 0.05 (s, 3H, 20-H)**, 0.03 (s, 3H, 19-H)** ppm.

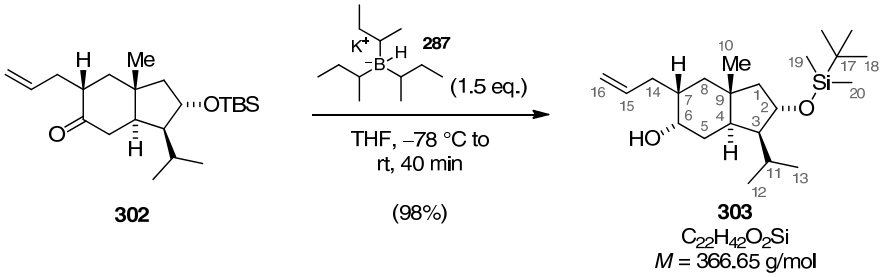
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 212.1 (C-6), 136.7 (C-15), 116.5 (C-16), 77.9 (C-2), 56.9 (C-3), 50.3 (C-1), 49.3 (C-4), 45.2 (C-7), 45.0 (C-8), 42.0 (C-5)*, 41.7 (C-9)*, 34.0 (C-14), 29.3 (C-11), 26.0 (C-18), 24.3 (C-12)**, 22.0 (C-13)**, 20.1 (C-10), 17.9 (C-17), –3.5 (C-19)***, –4.7 (C-20)*** ppm.

EI-MS for $C_{22}H_{40}O_2Si^+$ [M^+]: calcd. 364.2792
found 364.2808.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 3077 (w), 2956 (s), 2928 (s), 2856 (s), 1708 (s), 1471 (w), 1462 (w), 1388 (w), 1255 (w), 1108 (w), 1072 (m), 836 (m), 774 (w).

$[\alpha]_D^{20}$ = +30.4 (*c* 0.50, CH_2Cl_2).

Synthesis of Alcohol 303



To a solution of ketone **302** (326 mg, 896 μmol, 1.0 eq.) in THF (12 mL) at –78 °C was added dropwise K-Selectride® (**287**, 1.35 mL of a 1.0M solution in THF, 1.35 mmol, 1.5 eq.). The mixture

was stirred for 10 min at this temperature and an additional 30 min at room temperature. The mixture was cooled to 0 °C and MeOH (1.6 mL) was added followed by NaOH (3N, 3.2 mL) and H_2O_2 (30% in H_2O, 2.4 mL). The mixture was stirred at room temperature for 1 h and the reaction was diluted with saturated aqueous NH_4Cl (10 mL). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with saturated aqueous NaCl (2 x 15 mL) and dried over $MgSO_4$. The solvents were evaporated under reduced pressure and the crude product was purified by flash column chromatography (silica, *n*-pentane:Et_2O = 12:1 to 9:1) to yield alcohol **303** (323 mg, 883 μmol, 98%) as a highly viscous colorless oil.

R_f = 0.13 (hexanes:EtOAc = 16:1)

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 5.81 (ddt, $^3J_{15/16A}$ = 17.1 Hz, $^3J_{15/16B}$ = 10.3 Hz, $^3J_{15/14}$ = 7.3 Hz, 1H, 15-H), 5.05 (m_C, 1H, 16-H_A), 5.00 (m_C, 1H, 16-H_B), 4.26 (ddd, $^3J_{2/1B}$ = 8.3 Hz, $^3J_{2/1A}$ = 7.1 Hz, $^3J_{2/3}$ = 3.9 Hz, 1H, 2-H), 3.96 (ddd, $^3J_{6/5A}$ = $^3J_{6/5B}$ = $^3J_{6/7}$ = 2.9 Hz, 1H, 6-H), 2.30 (ddd, $^3J_{4/5B}$ = 14.0 Hz, $^3J_{4/3}$ = 10.0 Hz, $^3J_{4/5A}$ = 3.1 Hz, 1H, 4-H), 2.16 (m_C, 1H, 14-H_A), 1.99 (m_C, 1H, 1-H_B), 1.92 (ddd, $^2J_{5A/5B}$ = 13.5 Hz, $^3J_{5A/4}$ = $^3J_{5A/6}$ = 3.2 Hz, 1H, 5-H_A), 1.87 (dd, $^2J_{1A/1B}$ = 11.5 Hz, $^3J_{1A/2}$ = 7.0 Hz, 1H, 1-H_A), 1.69–1.58 (m, 3H, 5-H_B, 7-H, 11-H), 1.56 (ddd, $^3J_{3/4}$ = $^3J_{3/11}$ = 10.1 Hz, $^3J_{3/2}$ = 3.8 Hz, 1H, 3-H), 1.42 (br s, 1H, *O*H), 1.36 (dd, $^2J_{8A/8B}$ = 12.8 Hz, $^3J_{8A/7}$ = 3.9 Hz, 1H, 8-H_A) 1.28 (dd, $^2J_{8B/8A}$ = $^3J_{8B/7}$ = 12.8 Hz, 1H, 8-H_B), 1.22 (dd, $^2J_{1B/1A}$ = 11.6 Hz, $^3J_{1B/2}$ = 8.4 Hz, 1H, 1-H_B), 0.94 (d, $^3J_{13/11}$ = 6.5 Hz, 3H, 13-H)*, 0.92 (d, $^3J_{12/11}$ = 6.2 Hz, 3H, 12-H)*, 0.86 (s, 9H, 18-H), 0.81 (s, 3H, 10-H), 0.04 (s, 3H, 19-H)**, 0.02 (s, 3H, 20-H)** ppm.

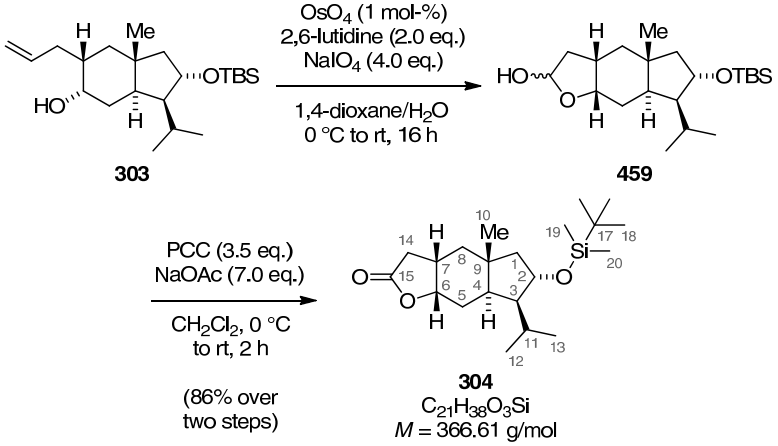
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 137.6 (C-15), 116.0 (C-16), 77.5 (C-2), 69.4 (C-6), 56.9 (C-3), 51.6 (C-1), 42.2 (C-9), 41.8 (C-4), 41.5 (C-8), 37.4 (C-14), 36.7 (C-7), 32.5 (C-5), 30.0 (C-11), 26.0 (C-18), 24.4 (C-12)*, 22.2 (C-13)*, 20.0 (C-10), 18.0 (C-17), –3.5 (C-20)**, –4.7 (C-19)** ppm.

EI-MS for $C_{22}H_{42}O_2Si^+$ [M^+]: calcd. 366.2949
found 366.2947.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 3387 (br w), 3076 (w), 2955 (s), 2928 (s), 2856 (s), 1471 (w), 1462 (w), 1387 (w), 1367 (w), 1254 (m), 1108 (w), 1070 (m), 1016 (w), 911 (w), 889 (w), 859 (w), 835 (m), 773 (w).

$[\alpha]_D^{20}$ = +34.5 (*c* 0.33, CH_2Cl_2).

Synthesis of Lactone 304



To a solution of alkene **303** (155 mg, 420 µmol, 1.0 eq.) and 2,6-lutidine (100 µL, 0.85 mmol, 2.0 eq.) in 1,4-dioxane/H_2O (3:1, 12 mL) at 0 °C was sequentially added OsO_4 (27 µL of a 4 wt% solution in H_2O, 4.2 µmol, 1.0 mol-%) and $NaIO_4$ (364 mg, 1.70 mmol, 4.0 eq.). The mixture was allowed to warm to room temperature and was stirred for 16 h forming a white suspension. The mixture was partitioned between H_2O (15 mL) and CH_2Cl_2 (30 mL) and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were washed with saturated aqueous NaCl (20 mL), and dried over $MgSO_4$. The solvents were evaporated under reduced pressure to yield crude lactol **459** which was used in the next step without further purification.

To a suspension of PCC (316 mg, 1.47 mmol, 3.5 eq.) and NaOAc (244 mg, 2.94 mmol, 7.0 eq.) in CH_2Cl_2 (10 mL) at 0 °C was added a solution of crude lactol **459** (assumed 0.42 mmol, 1.0 eq.) in CH_2Cl_2 (3 mL). The mixture was allowed to warm to room temperature and stirred for 3 h before being directly applied to flash column chromatography (silica, hexanes:EtOAc = 3:1). The title compound **304** (133 mg, 363 µmol, 86% over two steps) was obtained as a highly viscous colorless oil.

*Note: intermediate lactol **459** and lactone **304** are co-polar on TLC.*

R_f = 0.30 (hexanes:EtOAc = 4:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 4.60 (m_C, 1H, 6-H), 4.24 (ddd, $^3J_{2/1B}$ = 8.8 Hz, $^3J_{2/1A}$ = 7.0 Hz, $^3J_{2/3}$ = 4.2 Hz, 1H, 2-H), 2.70 (dd, $^2J_{14A/14B}$ = 16.8 Hz, $^3J_{14A/7}$ = 7.1 Hz, 1H, 14-H_A), 2.47 (m_C, 1H, 7-H), 2.32 (m, 1H, 5-H_A), 2.16 (d, $^2J_{14B/14A}$ = 16.9 Hz, 1H, 14-H_B), 2.15–2.10 (m, 1H, 4-H), 1.85 (dd, $^2J_{1A/1B}$ = 11.6 Hz, $^3J_{1A/2}$ = 7.0 Hz, 1H, 1-H_A), 1.74 (ddd, $^2J_{5B/5A}$ = $^3J_{5B/4}$ = 14.5 Hz, $^3J_{5B/6}$ = 3.8 Hz, 1H, 5-H_B), 1.67 (dd, $^2J_{8A/8B}$ =13.2 Hz, $^3J_{8A/7}$ = 6.4 Hz, 1H, 8-H_A), 1.65–1.59 (m, 2H, 3-H, 13-H), 1.21 (dd, $^2J_{1B/1A}$ = 11.6 Hz, $^3J_{1B/2}$ = 8.8 Hz, 1H, 1-H_B), 1.11 (dd, $^2J_{8B/8A}$ = $^3J_{8B/7}$ = 12.6 Hz, 1H, 8-H_B), 0.96 (d, $^3J_{12/11}$ = 6.4 Hz, 3H, 12-H)*, 0.95 (d, $^3J_{13/11}$ = 6.0 Hz, 3H, 13-H)*, 0.86 (s, 9H, 17-H), 0.81 (s, 3H, 10-H), 0.04 (s, 3H, 18-H)**, 0.02 (s, 3H, 19-H)** ppm.

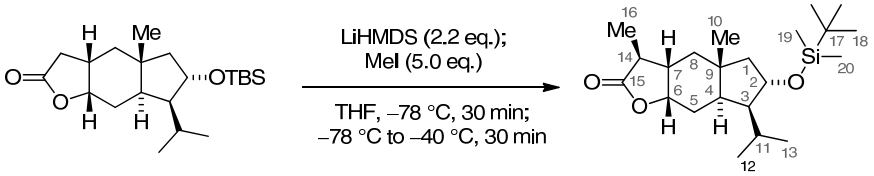
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 177.1 (C-15), 80.1 (C-6), 76.7 (C-2), 55.8 (C-3), 50.6 (C-1), 42.4 (C-8), 41.1 (C-4), 40.5 (C-9), 38.3 (C-14), 32.3 (C-7), 29.4 (C-11), 26.5 (C-5), 26.0 (C-17), 24.5 (C-13)*, 22.0 (C-12)*. 19.3 (C-10), 17.9 (C-16), –3.5 (C-19)**, –4.7 (C-18)** ppm.

EI-MS for $C_{21}H_{37}O_3Si^+$ [$(M-H)^+$]: calcd. 365.2506
found 365.2502.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2954 (s), 2938 (s), 2898 (s), 2855 (s), 1775 (s), 1389 (w), 1285 (w), 1253 (w), 1191 (m), 1154 (m), 1096 (m), 1070 (m), 976 (w), 940 (m), 905 (w), 882 (w), 835 (m), 773 (m).

$[\alpha]_D^{20}$ = –8.8 (*c* 0.50, CH_2Cl_2).

Synthesis of Lactone 269



304 **269**
$C_{22}H_{40}O_3Si$
M = 380.64 g/mol

To a solution of lactone **304** (100 mg, 273 µmol, 1.0 eq.) in THF (11 mL) at –78 °C was added dropwise LiHMDS (600 µL of a 1.0M solution in THF, 600 mmol, 2.2 eq.) and the resulting mixture was stirred for 30 min. Then, MeI (84 mL, 1.35 mmol, 5.0 eq.) was added and the mixture was allowed to warm to –40 °C (MeCN/liquid N_2 bath). After stirring an additional 30 min at this temperature, the reaction was quenched by addition of half-saturated aqueous NH_4Cl (10 mL). The biphasic mixture was allowed to warm to room temperature, the phases were separated and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with saturated aqueous NaCl (10 mL) and dried over $MgSO_4$. The solvents were evaporated under reduced pressure and the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 12:1) to yield lactone **269** (86 mg, 0.23 mmol, 83%) as a highly viscous colorless oil.

R_f = 0.20 (hexanes:EtOAc = 10:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 4.73 (m_C, 1H, 6-H), 4.22 (ddd, $^3J_{2/1B}$ = 8.9 Hz, $^3J_{2/1A}$ = 7.0 Hz, $^3J_{2/3}$ = 4.2 Hz, 1H, 2-H), 2.32 (m_C, 1H, 5-H_A), 2.29 (q, $^3J_{14/16}$ = 7.6 Hz, 1H, 14-H), 2.14–2.06 (m, 2H, 4-H, 7-H), 1.83 (dd, $^2J_{1A/1B}$ = 11.6 Hz, $^3J_{1A/2}$ = 6.9 Hz, 1H, 1-H_A), 1.74–1.67 (m, 2H, 5-H_B, 8-H_A), 1.65–1.58 (m, 2H, 3-H, 11-H), 1.28 (d, $^3J_{16/14}$ = 7.7 Hz, 3H, 16-H), 1.19 (dd, $^2J_{1B/1A}$ = 11.6 Hz, $^3J_{1B/2}$ =

9.0 Hz, 1H, 1-H_B), 1.08 (dd, $^2J_{8B/8A} = {}^3J_{8B/7}$ = 12.9 Hz, 1H, 8-H_B), 0.94 (m_C, 6H, 12-H, 13-H), 0.84 (s, 9H, 18-H), 0.78 (s, 3H, 10-H), 0.03 (s, 3H, 20-H)*, 0.01 (s, 3H, 19-H)* ppm.

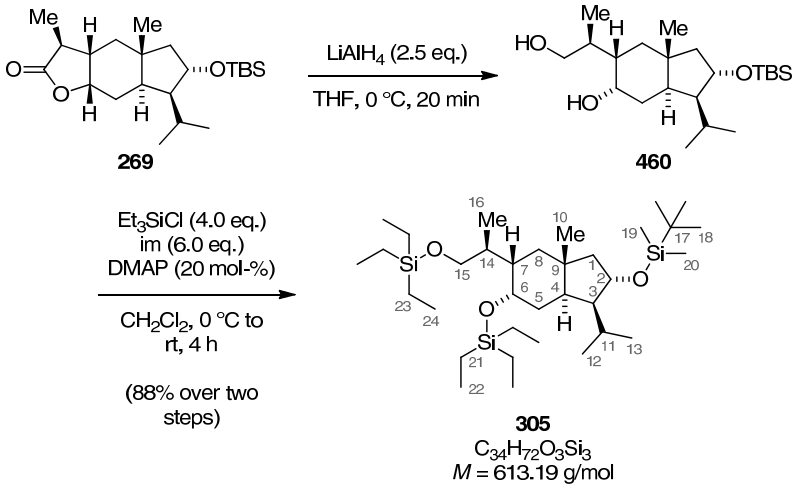
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 180.2 (C-15), 77.9 (C-6), 76.7 (C-2), 55.8 (C-3), 50.6 (C-1), 44.9 (C-14), 42.8 (C-8), 41.1 (C-4), 40.5 (C-9), 39.2 (C-7), 29.4 (C-11), 26.4 (C-5), 26.0 (C-18), 24.5 (C-12)*, 22.0 (C-13)*, 19.2 (C-10), 17.9 (C-17), 14.9 (C-16), –3.4 (C-19)**, –4.7 (C-20)** ppm.

EI-MS for $C_{22}H_{39}O_3Si^+$ [$(M–H)^+$]: calcd. 379.2663
found 379.2673.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 2955 (s), 2931 (s), 2900 (s), 2855 (s), 1772 (s), 1389 (w), 1255 (w), 1190 (m), 1109 (w), 1076 (m), 1008 (w), 941 (w), 836 (m), 773 (m).

$[\alpha]_D^{20}$ = –13.8 (*c* 0.33, CH_2Cl_2).

Synthesis of *trans*-Hydrindane 305



To a suspension of $LiAlH_4$ (15 mg, 0.40 mmol, 2.5 eq.) in THF (5 mL) at 0 °C was added dropwise a solution of lactone **269** (60 mg, 0.16 mmol, 1.0 eq.) in THF (3 mL) and the mixture was stirred for 20 min. The reaction was quenched by careful addition of half-saturated aqueous Rochelle salt (10 mL) and the biphasic mixture was stirred vigorously at room temperature for 30 min. The mixture was diluted with Et_2O (10 mL) and the phases were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organic layers were washed with saturated aqueous NaCl (10 mL), and dried over Na_2SO_4. Having evaporated the solvents under reduced pressure, the crude product was purified by short flash column chromatography (silica, CH_2Cl_2:MeOH = 100:2.5) to yield diol **460** (R_f = 0.17, CH_2Cl_2:MeOH = 95:5), which was immediately used in the next reaction.

To a solution of diol **460** (assumed 0.16 mmol, 1.0 eq.) in CH_2Cl_2 (8 mL) at 0 °C was sequentially added imidazole (64.5 mg, 0.95 mmol, 6.0 eq.), DMAP (7 mg, 63 μmol, 20 mol-%) and Et_3SiCl (106 μL, 632 μmol, 4.0 eq.). The mixture was allowed to warm to room temperature and stirred for 4 h at which point the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (7 mL). The mixture was diluted with CH_2Cl_2 (10 mL) and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 7 mL) and the combined organic layers were washed with saturated aqueous NaCl (10 mL), and dried over Na_2SO_4. Having evaporated the solvent under reduced pressure, the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 100:1) to yield the title compound **305** (85 mg, 0.14 mmol, 88% over two steps) as a colorless oil.

R_f = 0.31 (hexanes:EtOAc = 60:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 4.25 (ddd, $^3J_{2/1B}$ = 8.6 Hz, $^3J_{2/1A}$ = 7.0 Hz, $^3J_{2/3}$ = 4.3 Hz, 1H, 2-H), 4.06 (m_C, 1H, 6-H), 3.48 (dd, $^2J_{15A/15B}$ = 9.7 Hz, $^3J_{15A/14}$ = 5.2 Hz, 1H, 15-H_A), 3.44 (dd, $^2J_{15B/15A}$ = 9.7 Hz, $^3J_{15/14}$ = 6.0 Hz, 1H, 15-H_B), 2.38 (ddd, $^3J_{4/5B}$ = 13.6 Hz, $^3J_{4/3}$ = 10.6 Hz, $^3J_{4/5A}$ = 3.0 Hz, 1H, 4-H), 1.84 (dd, $^2J_{1A/1B}$ = 11.4 Hz, $^3J_{1A/2}$ = 7.0 Hz, 1H, 1-H_A), 1.81 (ddd, $^2J_{5A/5B}$ = 13.5 Hz, $^3J_{5A/4}$ = $^3J_{5A/6}$ = 3.2 Hz, 1H, 5-H_A), 1.67 (m_C, 1H, 14-H), 1.63–1.56 (m, 1H, 11-H), 1.56–1.50 (m, 2H, 5-H_B, 7-H), 1.48 (ddd, $^3J_{3/4}$ = $^3J_{3/11}$ = 10.3 Hz, $^3J_{3/2}$ = 4.2 Hz, 1H, 3-H), 1.34 (dd, $^2J_{8A/8B}$ = $^3J_{8A/7}$ = 12.5 Hz, 1H, 8-H_A), 1.27 (dd, $^2J_{8B/8A}$= 12.3 Hz, $^3J_{8B/7}$ = 4.0 Hz, 1H, 8-H_B), 1.23 (dd, $^2J_{1B/1A}$ = 11.4 Hz, $^3J_{1B/2}$ = 8.7 Hz, 1H, 1-H_B), 0.99–0.92 (m, 18H, 22-H, 24-H), 0.93 (d, $^3J_{12/11}$ = 6.8 Hz, 3H, 12-H)*, 0.91 (d, $^3J_{13/11}$ = 6.4 Hz, 3H, 13-H)*, 0.87 (s, 9H, 18-H), 0.86 (d, $^3J_{16/14}$ = 6.9 Hz, 3H, 16-H), 0.78 (s, 3H, 10-H), 0.64–0.54 (m, 12H, 21-H, 23-H), 0.05 (s, 3H, 19-H)**, 0.04 (s, 3H, 20-H)** ppm.

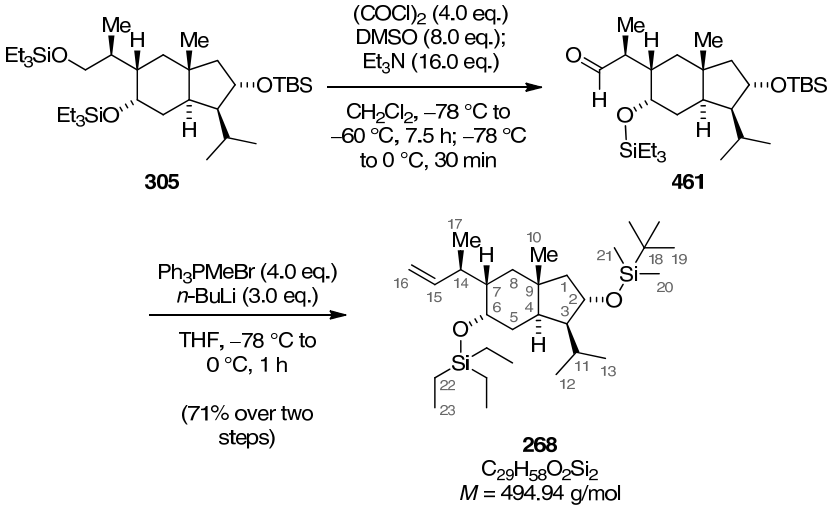
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 77.8 (C-2), 70.8 (C-6), 66.3 (C15), 56.8 (C-3), 51.8 (C-1), 41.9 (C-9), 41.4 (C-4), 38.0 (C-8), 37.9 (C-7), 37.3 (C-14), 33.4 (C-5), 30.1 (C-11), 26.1 (C-18), 24.3 (C-13)*, 22.3 (C-12)*, 20.2 (C-10), 18.0 (C-17), 15.0 (C-16), 7.2 (C-22)**, 7.0 (C-24)**, 5.5 (C-21)***, 4.6 (C-23)***, –3.4 (C-20)****, –4.6 (C-19)**** ppm.

EI-MS for $C_{34}H_{72}O_3Si_3^+$ [M^+]: calcd. 612.4784
found 612.4770.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 2954 (s), 2935 (s), 2909 (s), 2875 (s), 1461 (w), 1414 (w), 1386 (w), 1367 (w), 1255 (w), 1070 (m), 1046 (w), 1006 (w), 887 (w), 836 (w), 741 (w).

$[\alpha]_D^{20}$ = +22.4 (*c* 0.33, CH_2Cl_2).

Synthesis of Alkene 268



To a solution of DMSO (73 µL, 1.0 mmol, 8.0 eq.) in CH_2Cl_2 (5 mL) at −78 °C was added dropwise $(COCl)_2$ (260 µL of a 2.0M solution in CH_2Cl_2, 520 µmol, 4.0 eq.) and the mixture was stirred for 15 min at this temperature. Then, a solution of silyl ether **305** (80 mg, 0.13 mmol, 1.0 eq.) in CH_2Cl_2 (1.5 mL) was added over 30 min (syringe pump). The mixture was allowed to warm to −60 °C and was stirred for 7 h at −65 to −60 °C (cryo cooler). The reaction was then cooled to −78 °C and Et_3N (0.29 mL, 2.1 mmol, 16.0 eq.) was added dropwise. The cold bath was replaced by an ice/water bath and the mixture was stirred for 30 min at 0 °C before the reaction was quenched by addition of H_2O (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with saturated aqueous NaCl (10 mL) and dried over $MgSO_4$. Having evaporated the solvents under reduced pressure, the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 80:1 to 60:1) to yield aldehyde **461** (57 mg, R_f = 0.16, hexanes:EtOAc = 30:1) as a pale yellow oil, which was immediately used in the next step.

To a suspension of Ph_3PMeBr (184 mg, 517 µmol, 4.0 eq.) in THF (5 mL) at 0 °C was added dropwise *n*-BuLi (138 µL of a 2.5M solution in hexanes, 345 µmol, 3.0 eq.) and the mixture was allowed to warm to room temperature. The mixture was stirred for 1 h and was subsequently cooled to −78 °C. Then, a solution of aldehyde **461** (57 mg, 0.15 mmol, 1.0 eq.) in THF (1.5 mL) was added slowly. The cold bath was replaced by an ice/water bath and the mixture was stirred for 1 h at 0 °C. The reaction was quenched by addition of saturated aqueous NH_4Cl/H_2O (1:1, 5 mL) and the biphasic mixture was extracted with Et_2O (3 x 8 mL). The combined organic layers were washed with saturated aqueous NaCl (5 mL) and were dried over $MgSO_4$. Having evaporated the solvents under reduced pressure, the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 1:0 to 100:1) to yield alkene **268** (45 mg, 91 µmol, 71% over two steps) as a colorless oil.

R_f = 0.63 (hexanes:EtOAc = 60:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 5.75 (ddd, $^3J_{15/16A}$ = 17.1 Hz, $^3J_{15/16B}$ = 10.3 Hz, $^3J_{15/14}$ = 8.2 Hz, 1H, 15-H), 4.97 (ddd, $^3J_{16A/15}$ = 17.2 Hz, $^2J_{16A/16B}$ = 2.1 Hz, $^4J_{16A/14}$ = 1.0 Hz, 1H, 16-H_A), 4.92 (ddd, $^3J_{16B/15}$ = 10.3 Hz, $^2J_{16B/16A}$ = 2.0 Hz, $^4J_{16B/14}$ = 0.6 Hz, 1H, 16-H_B), 4.24 (ddd, $^3J_{2/1B}$ = 8.4 Hz, $^3J_{2/1A}$ = 7.0 Hz, $^3J_{2/3}$ = 4.1 Hz, 1H, 2-H), 4.06 (m_C, 1H, 6-H), 2.39 (ddd, $^3J_{4/5B}$ = 13.6 Hz, $^3J_{4/3}$ = 10.6 Hz, $^3J_{4/5A}$ = 3.0 Hz, 1H, 4-H), 2.20 (m_C, 1H, 14-H), 1.85 (dd, $^2J_{1A/1B}$ = 11.1 Hz, $^3J_{1A/2}$ = 7.0 Hz, 1H, 1-H_A), 1.83 (m_C, 1H, 5-H_A), 1.62–1.55 (m, 1H, 11-H), 1.53–1.44 (m, 2H, 3-H, 5-H_B), 1.37 (dd, $^2J_{8A/8B}$ = 11.9 Hz, $^3J_{8A/7}$ = 3.5 Hz, 1H, 8-H_A), 1.30 (dd, $^2J_{8B/8A}$ = $^2J_{8B/7}$ = 12.1 Hz, 1H, 8-H_B), 1.27–1.20 (m, 2H, 1-H_B, 7-H), 0.97 (t, $^3J_{23/22}$ = 7.9 Hz, 9H, 23-H), 0.94 (d, $^3J_{12/11}$ = 6.6 Hz, 3H, 12-H)*, 0.91 (d, $^3J_{17/14}$ = 6.8 Hz, 3H, 17-H), 0.90 (d, $^3J_{13/11}$ = 6.3 Hz, 3H, 13-H)*, 0.87 (s, 9H, 19-H), 0.78 (s, 3H, 10-H), 0.65–0.55 (m, 6H, 22-H), 0.05 (s, 3H, 20-H)**, 0.04 (s, 3H, 21-H)* ppm.

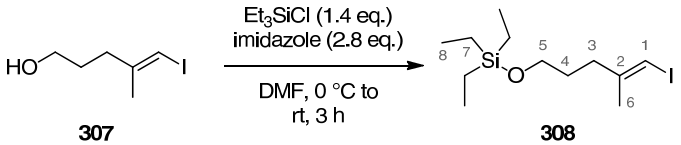
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 144.9 (C-15), 113.0 (C-14), 77.8 (C-2), 69.9 (C-6), 56.8 (C-3), 51.7 (C-1), 42.9 (C-7), 42.0 (C-9), 41.3 (C-4), 38.9 (C-14), 38.7 (C-8), 33.2 (C-5), 30.1 (C-11), 26.1 (C-19), 24.3 (C-13)*, 22.3 (C-12)*, 20.3 (C-10), 18.5 (C-17), 18.0 (C-18), 7.3 (C-23), 5.6 (C-22), –3.4 (C-21)**, –4.6 (C-20)** ppm.

EI-MS for $C_{25}H_{49}O_2Si_2^+$ [(M–*t*-Bu)$^+$]: calcd. 437.3266
found 437.3277.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 3077 (w), 2955 (s), 2932 (s), 2875 (s), 1461 (w), 1414 (w), 1387 (w), 1368 (w), 1255 (w), 1070 (m), 1044 (m), 1005 (w), 911 (w), 835 (m), 773 (w).

$[\alpha]_D^{20}$ = +27.3 (*c* 0.33, CH_2Cl_2).

Synthesis of Vinyl Iodide 308



307 **308**
$C_{12}H_{25}IOSi$
M = 340.32 g/mol

To a solution of alcohol **307**[200] (910 mg, 4.02 mmol, 1.0 eq.) in DMF (9 mL) at 0 °C was sequentially added imidazole (765 mg, 11.2 mmol, 2.8 eq.) and Et_3SiCl (944 µL, 5.64 mmol, 1.4 eq.). The mixture was allowed to warm to room temperature and was stirred for 3 h. The reaction was diluted with *n*-pentane (25 mL) and was then quenched by addition of H_2O (10 mL). The organic layer was separated and the aqueous layer was extracted with *n*-pentane (3 x 15 mL). The combined organic layers were washed with 10% aqueous NaCl (2 x 10 mL) and dried over $MgSO_4$. The solvents were evaporated

under reduced pressure and the crude product was purified by flash column chromatography (silica, hexanes:Et_2O = 50:1) to yield vinyl iodide **308** (1.27 g, 3.74 mmol, 93%) as a colorless liquid.

R_f = 0.33 (hexanes:Et_2O = 50:1).

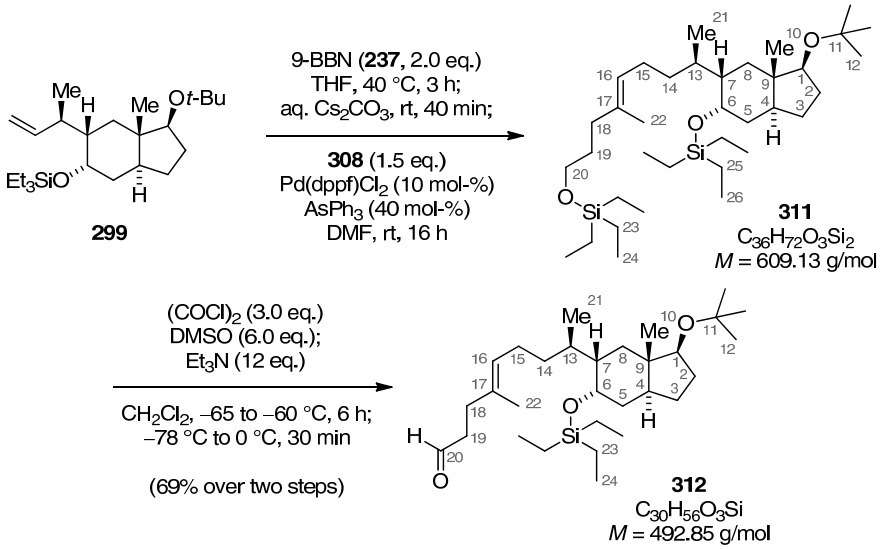
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.86 (dq, $^4J_{1/3} = {}^4J_{1/6}$ = 1.1 Hz, 1H, 1-H), 3.59 (t, $^3J_{5/4}$ = 6.4 Hz, 2H, 5-H), 2.27 (m_C, 2H, 3-H), 1.84 (d, $^4J_{6/1}$ = 1.1 Hz, 3H, 6-H), 1.71–1.62 (m, 2H, 4-H), 1.00–0.92 (m, 9H, 8-H), 0.65–0.54 (m, 6H, 7-H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 147.9 (C-2), 74.8 (C-1), 62.1 (C-5), 36.0 (C-3), 31.0 (C-4), 24.1 (C-6), 6.9 (C-8), 4.6 (C-7) ppm.

EI-MS for $C_{12}H_{25}OISi^+$ [M^+]: calcd. 340.0714
found 340.0716.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 2953 (s), 2912 (s), 2876 (s), 1458 (w), 1414 (w), 1378 (w), 1268 (w), 1239 (w), 1142 (w), 1103 (s), 1007 (m), 959 (w), 770 (w), 743 (m).

Synthesis of Aldehyde 312



To a solution of alkene **299** (394 mg, 1.00 mmol, 1.0 eq.) in THF (6 mL) was added 9-BBN (**237**, 4.00 mL of a 0.5M solution in THF, 2.00 mmol, 2.0 eq.) and the reaction was heated to 40 °C for 3 h. The reaction was allowed to cool to room temperature and degassed aqueous Cs_2CO_3 (3N, 1.16 mL, 3.48 mmol, 3.5 eq.) was added. The mixture was vigorously stirred for 40 min and then degassed (N_2 bubbling for 5 min). Next, a solution of vinyl iodide **308** (510 mg, 1.50 mmol, 1.5 eq.) and $AsPh_3$ (122 mg, 400 μmol, 40 mol-%) in degassed DMF (10 mL) was added followed by addition of

$Pd(dppf)Cl_2$ (complex with CH_2Cl_2, 81 mg, 0.10 mmol, 10 mol-%). The mixture was stirred for 16 h at room temperature, diluted with Et_2O (20 mL), and was subsequently quenched by addition of H_2O (10 mL). The phases were separated and the aqueous layer was extracted with Et_2O (4 x 20 mL). The combined organic layers were washed with 10% aqueous NaCl (3 x 15 mL), which in turn were re-extracted with Et_2O (2 x 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were evaporated under reduced pressure. The obtained crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 1:0 to 100:1) to yield the desired coupling product **311** (564 mg, 930 μmol, 93%), which was immediately used in the next step.

To a solution of DMSO (390 μL, 5.54 mmol, 6.0 eq.) in CH_2Cl_2 (10 mL) at −78 °C was added dropwise $(COCl)_2$ (1.39 mL of a 2.0M solution in CH_2Cl_2, 2.77 mmol, 3.0 eq.) and the mixture was stirred for 15 min at this temperature. Then, a solution of bissilyl ether **311** (564 mg, ~930 μmol, 1.0 eq.) in CH_2Cl_2 (3 mL + 1 mL rinse) was added within 30 min (syringe pump). The mixture was allowed to warm to −65 °C and was stirred between −65 and −60 °C (cryo cooler) for 6 h. The reaction was cooled to −78 °C and Et_3N (1.50 mL, 11.1 mmol, 12 eq.) was added. The mixture was stirred for an additional 10 min at this temperature, was allowed to warm to 0 °C and stirred for an additional 15 min. The reaction was quenched by addition of H_2O (10 mL) and the biphasic mixture was diluted with CH_2Cl_2 (20 mL). After phase separation, the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were washed with saturated aqueous NaCl (20 mL). The organic layer was dried over $MgSO_4$ and the solvents were removed under reduced pressure. The crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 40:1 to 30:1) to yield aldehyde **312** (340 mg, 691 μmol, 69% over two steps) as a colorless oil.

Analytical data for bissilyl ether **311**:

R_f = 0.23 (hexanes:EtOAc = 30:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 5.13 (br t, $^3J_{16/15}$ = 7.1 Hz, 1H, 16-H), 4.05 (m_C, 1H, 6-H), 3.58 (t, $^3J_{20/19}$ = 6.9 Hz, 2H, 20-H), 3.42 (dd, $^3J_{1/2}$ = 8.6, 7.7 Hz, 1H, 1-H), 2.08–1.95 (m_C, 1H, 15-H_A), 2.00 (m_C, 2H, 18-H), 1.94–1.84 (m, 2H, 2-H_A, 15-H_B), 1.77–1.70 (m, 1H, 4-H), 1.66–1.61 (m, 2H, 19-H), 1.60 (s, 3H, 22-H), 1.56–1.36 (m, 7H, 2-H_B, 3-H_A, 5-H, 8-H_A, 13-H, 14-H_A), 1.28–1.21 (m, 2H, 3-H_B, 7-H), 1.16–1.05 (m, 1H, 14-H_B), 1.14 (s, 9H, 12-H), 1.08 (dd, $^2J_{8B/8A}$ = $^3J_{8B/7}$ = 12.3 Hz, 1H, 8-H_B), 1.00–0.91 (m, 18H, 24-H, 26-H), 0.86 (d, $^3J_{21/13}$ = 6.8 Hz, 3H, 21-H), 0.69 (s, 3H, 10-H), 0.64–0.54 (m, 12H, 23-H, 25-H) ppm.

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 134.2 (C-17), 125.2 (C-16), 81.0 (C-1), 72.3 (C-11), 70.0 (C-6), 62.8 (C-20), 42.7 (C-9), 42.6 (C-7), 37.4 (C-4), 36.0 (C-18), 35.4 (C-8), 35.3 (C-14), 34.7 (C-5),

34.0 (C-13), 31.6 (C-2), 31.4 (C-19), 29.0 (C-12), 25.6 (C-3)*, 25.5 (C-15)*, 17.2 (C-21), 16.1 (C-22), 11.1 (C-10), 7.2 (C-24)**, 7.0 (C-26)**, 5.5 (C-23)***, 4.6 (C-25)*** ppm.

EI-MS for $C_{36}H_{72}O_3Si_2^+$ [M^+]: calcd. 608.5015
found 608.5014.

Analytical data for aldehyde **312**:

R_f = 0.10 (hexanes:EtOAc = 30:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 9.76 (t, $^3J_{20/19}$ = 2.0 Hz, 1H, 20-H), 5.16 (m_C, 1H, 16-H), 4.04 (m_C, 1H, 6-H), 3.42 (dd, $^3J_{1/2}$ = 8.8, 7.5 Hz, 1H, 1-H), 2.53–2.49 (m, 2H, 19-H), 2.31 (m_C, 2H, 18-H), 2.07–1.99 (m, 1H, 15-H_A), 1.94–1.83 (m, 2H, 2-H_A, 15-H_B), 1.73 (dddd, J = 13.0, 13.0, 7.0, 3.3 Hz, 1H, 4-H), 1.62 (s, 3H, 22-H), 1.57–1.34 (m, 7H, 2-H_B, 3-H_A, 5-H, 8-H_A, 13-H, 14-H_A), 1.29–1.21 (m, 2H, 3-H_B, 7-H), 1.18–1.03 (m, 2H, 8-H_B, 14-H_B), 1.14 (s, 9H, 12-H), 0.99–0.91 (m, 9H, 24-H), 0.85 (d, $^3J_{21/13}$ = 6.7 Hz, 3H, 21-H), 0.69 (s, 3H, 10-H), 0.62–0.55 (m, 6H, 23-H) ppm.

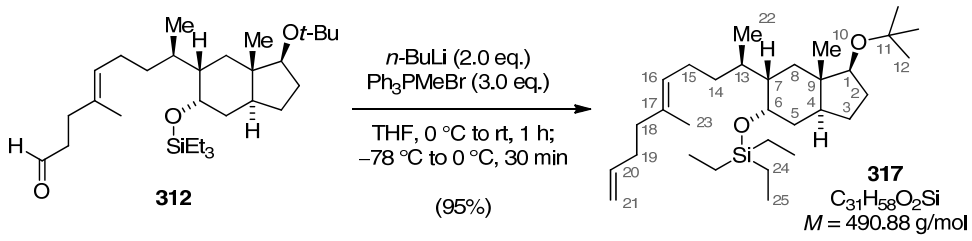
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 202.8 (C-20), 132.5 (C-17), 126.4 (C-16), 81.0 (C-1), 72.3 (C-11), 69.9 (C-6), 42.7 (C-9), 42.6 (C-7), 42.4 (C-14), 37.4 (C-4), 35.4 (C-8), 35.2 (C-14), 34.7 (C-5), 34.0 (C-13), 32.1 (C-18), 31.6 (C-2), 29.0 (C-12), 25.6 (C-15), 25.5 (C-3), 17.2 (C-21), 16.2 (C-22), 11.1 (C-10), 7.2 (C-24), 5.5 (C-23) ppm.

EI-MS for $C_{30}H_{56}O_3Si^+$ [M^+]: calcd. 492.3993
found 492.3992.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 2954 (s), 2912 (s), 2987 (s), 2712 (w), 1729 (m), 1460 (w), 1288 (w), 1362 (w), 1237 (w), 1196 (w), 1129 (w), 1063 (m), 1009 (w), 797 (w), 741 (w).

$[\alpha]_D^{20}$ = +42.8 (c 0.25, CH_2Cl_2).

Synthesis of Diene 317



To a suspension of Ph_3PMeBr (717 mg, 2.01 mmol, 3.0 eq.) in THF (12 mL) at 0 °C was added *n*-BuLi (540 µL of a 2.5M solution in hexanes, 1.34 mmol, 2.0 eq.). The resulting mixture was allowed to warm to room temperature and was stirred for 1 h at this temperature before being cooled to –78 °C. Then, a solution of aldehyde **312** (330 mg, 670 µmol, 1.0 eq.) in THF (2 mL) was added dropwise. The cold bath was replaced by an ice/water bath and the mixture was stirred for 30 min at 0 °C. The reaction mixture was diluted with Et_2O (10 mL) and quenched by addition of saturated aqueous NH_4Cl (10 mL). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with saturated aqueous NaCl (20 mL), dried over $MgSO_4$ and the solvents were removed under reduced pressure. Purification of the crude product by flash column chromatography (silica, hexanes:EtOAc = 100:1 to 60:1) yielded diene **317** (313 mg, 639 µmol, 95%) as a colorless oil.

R_f = 0.48 (Hexanes:EtOAc = 30:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 5.81 (ddt, $^3J_{20/21A}$ = 17.1 Hz, $^3J_{20/21B}$ = 10.2 Hz, $^3J_{20/19}$ = 6.5 Hz, 1H, 20-H), 5.14 (m_C, 1H, 16-H), 5.01 (m_C, 1H, 21-H_A), 4.93 (m_C, 1H, 21-H_B), 4.05 (m_C, 1H, 6-H), 3.42 (m_C, 1H, 1-H), 2.18–2.12 (m, 2H, 19-H), 2.09–1.99 (m, 3H, 15-H_A, 18-H), 1.94–1.85 (m, 2H, 2-H_A, 15-H_B), 1.73 (dddd, *J* = 13.0, 13.0, 7.1, 3.3 Hz, 1H, 4-H), 1.61 (s, 3H, 23-H), 1.57–1.36 (m, 7H, 2-H_B, 3-H_A, 5-H, 8-H_A, 13-H, 14-H_A), 1.29–1.21 (m, 2H, 3-H_B, 7-H), 1.17–1.05 (m, 2H, 8-H_B, 14-H_B), 1.15 (s, 9H, 12-H), 0.99–0.93 (m, 9H, 25-H), 0.86 (d, $^3J_{22/13}$ = 6.8 Hz, 3H, 22-H), 0.69 (s, 3H, 10-H), 0.63–0.53 (m, 6H, 24-H) ppm.

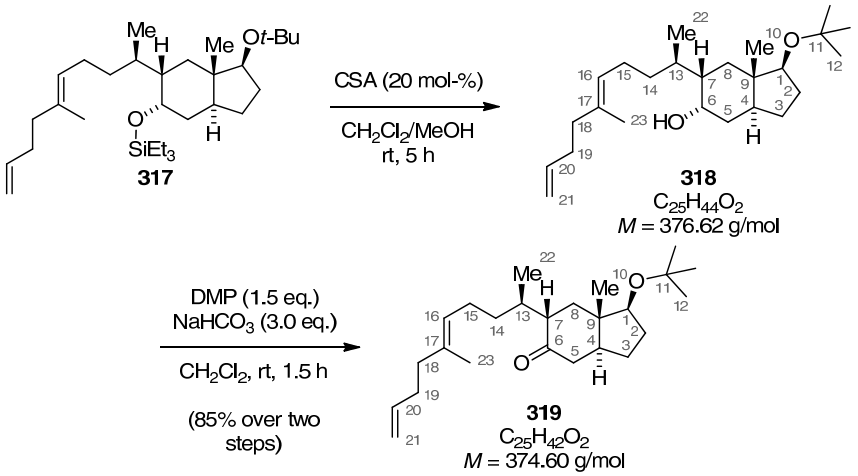
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 139.0 (C-20), 134.0 (C-17), 125.5 (C-16), 114.3 (C-21), 81.0 (C-1), 72.3 (C-11), 69.9 (C-6), 42.7 (C-9), 42.5 (C-7), 39.3 (C-18), 37.4 (C-4), 35.4 (2C, C-8, C-14), 34.7 (C-5), 34.0 (C-13), 32.6 (C-19), 31.6 (C-2), 29.0 (C-12), 25.5 (2C, C-3, C-15), 17.2 (C-22), 16.1 (C-23), 11.1 (C-10), 7.2 (C-25), 5.5 (C-24) ppm.

EI-MS for $C_{31}H_{58}O_2Si^+$ [M^+]: calcd. 490.4201
found 490.4199.

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3078 (w), 2954 (s), 2932 (s), 2913 (s), 2876 (s), 1460 (w), 1414 (w), 1379 (w), 1361 (w), 1237 (w), 1063 (m), 1046 (m), 1007 (w), 977 (w), 910 (w), 797 (w), 741 (w).

$[\alpha]_D^{20}$ = +32.4 (*c* 0.50, CH_2Cl_2).

Synthesis of Ketone 319



To a solution of silyl ether **317** (313 mg, 638 μmol, 1.0 eq.) in CH_2Cl_2/MeOH (7:1, 4.8 mL) was added (1*R*)-(−)-camphorsulfonic acid (30 mg, 0.13 mmol, 20 mol-%) and the mixture was stirred for 5 h at room temperature. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (10 mL) and the biphasic mixture was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with saturated aqueous NaCl (10 mL) and dried over $MgSO_4$. The solvents were removed under reduced pressure to yield crude alcohol **318** as pale yellow oil which was used without further purification in the next step.

To a suspension of crude alcohol **318** (assumed 638 μmol, 1.0 eq.) and $NaHCO_3$ (161 mg, 1.92 mmol, 3.0 eq.) in CH_2Cl_2 (6 mL) was added DMP (407 mg, 960 μmol, 1.5 eq.) and the mixture was stirred for 1.5 h at room temperature. The reaction was quenched by addition of saturated aqueous $NaHCO_3$/saturated aqueous $Na_2S_2O_3/H_2O$ (1:1:1, 10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with saturated aqueous NaCl (10 mL) and dried over $MgSO_4$. After evaporation of the solvents under reduced pressure, the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 40:1 to 30:1) to yield ketone **319** (202 mg, 540 μmol, 85% over two steps) as a colorless oil.

R_f = 0.39 (Hexanes:EtOAc = 10:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 5.80 (ddt, $^3J_{20/21A}$ = 17.1 Hz, $^3J_{20/21B}$ = 10.2 Hz, $^3J_{20/19}$ = 6.6 Hz, 1H, 20-H), 5.14 (m_C, 1H, 16-H), 5.00 (m_C, 1H, 21-H_A), 4.93 (m_C, 1H, 21-H_B), 3.47 (dd, $^3J_{1/2}$ = 8.9, 7.7 Hz, 1H, 1-H), 2.36–2.29 (m, 2H, 5-H_A, 7-H), 2.29–2.21 (m, 2H, 5-H_B, 13-H), 2.18–2.10 (m, 2H, 19-H), 2.07–2.03 (m, 2H, 18-H), 2.02–1.91 (m, 3H, 2-H_A, 15-H), 1.87 (dd, $^2J_{8A/8B}$ = 12.6 Hz, $^3J_{8A/7}$ = 6.4 Hz, 1H, 8-H_A), 1.68–1.54 (m, 3H, 2-H_B, 3-H_A, 4-H), 1.59 (s, 3H, 23-H), 1.43–1.35 (m, 1H, 3-H_B), 1.27–1.13 (m, 3H, 8-H_B, 14-H), 1.15 (s, 9H, 12-H), 0.97 (s, 3H, 10-H), 0.76 (d, $^3J_{22/13}$ = 6.7 Hz, 3H, 22-H) ppm.

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 212.5 (C-6), 138.9 (C-20), 134.7 (C-17), 124.8 (C-16), 114.4 (C-21), 80.0 (C-1), 72.7 (C-11), 49.3 (C-7), 44.6 (C-4), 43.3 (C-5), 42.2 (C-9), 39.2 (C-18), 35.5 (C-8), 34.9 (C-14), 32.5 (C-19), 31.9 (C-2), 30.7 (C-13), 28.9 (C-12), 26.1 (C-15), 25.9 (C-3), 16.1 (C-22)*, 16.0 (C-23)*, 11.2 (C-10) ppm.

EI-MS for $C_{25}H_{42}O_2^+$ [M^+]: calcd. 374.3179
found 374.3178.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 3076 (w), 2972 (s), 2931 (s), 2876 (s), 1706 (s), 1461 (w), 1388 (w), 1362 (w), 1252 (w), 1192 (m), 1120 (w), 1062 (m), 903 (w).

$[\alpha]_D^{20}$ = +7.8 (*c* 0.50, CH_2Cl_2).

An analytical sample of alcohol **318** was obtained by flash column chromatography (silica, hexanes:EtOAc = 16:1) as a colorless oil:

R_f = 0.16 (Hexanes:EtOAc = 16:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 5.80 (ddt, $^3J_{20/21A}$ = 16.9 Hz, $^3J_{20/21B}$ = 10.3 Hz, $^3J_{20/19}$ = 6.6 Hz, 1H, 20-H), 5.14 (m_C, 1H, 16-H), 5.00 (m_C, 1H, 21-H_A), 4.93 (m_C, 1H, 21-H_B), 4.10 (m_C, 1H, 6-H), 3.44 (dd, $^3J_{1/2}$ = 8.9, 7.4 Hz, 1H, 1-H), 2.18–2.12 (m, 2H, 19-H), 2.09–2.01 (m, 3H, 15-H_A, 18-H), 1.98–1.88 (m, 2H, 2-H_A, 15-H_B), 1.70–1.62 (m, 3H, 4-H, 5-H_A, 8-H_A), 1.60 (br s, 3H, 23-H), 1.59–1.55 (m, 1H, 14-H_A), 1.52–1.41 (m, 4H, 2-H_B, 3-H_A, 5-H_B, 13-H), 1.37–1.31 (m, 1H, 7-H), 1.30–1.24 (m, 1H, 3-H_B), 1.23–1.15 (m, 2H, 14-H_B, *O*H), 1.14 (s, 9H, 12-H), 1.02 (dd, $^2J_{8B/8A}$ = $^3J_{8B/7}$ = 12.9 Hz, 1H, 8-H_B), 0.92 (d, $^3J_{22/13}$ = 6.6 Hz, 3H, 22-H), 0.71 (s, 3H, 10-H) ppm.

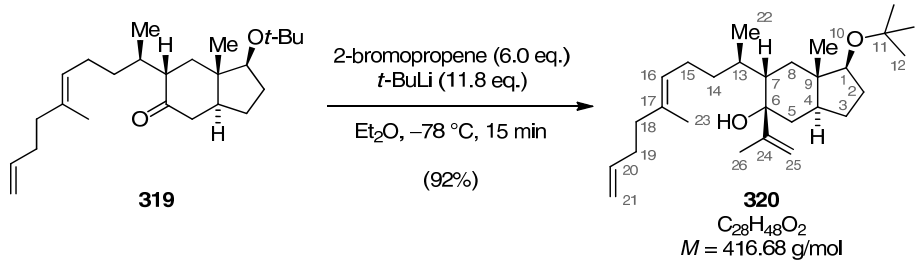
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 138.9 (C-20), 134.7 (C-17), 125.2 (C-16), 114.4 (C-21), 80.8 (C-1), 72.4 (C-11), 68.4 (C-6), 42.8 (C-9), 42.0 (C-7), 39.2 (C-18), 37.6 (C-4), 36.0 (C-8), 35.6 (C-14), 34.0 (C-5), 33.8 (C-13), 32.5 (C-19), 31.4 (C-2), 28.9 (C-12), 25.6 (C-3), 25.3 (C-15), 17.7 (C-22), 16.2 (C-23), 11.0 (C-10) ppm.

EI-MS for $C_{25}H_{44}O_2^+$ [M^+]: calcd. 376.3336
found 376.3328.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 3432 (br s), 3078 (w), 2973 (s), 2929 (s), 2913 (s), 2873 (s), 1461 (w), 1378 (w), 1361 (m), 1254 (w), 1197 (m), 1063 (m), 1046 (m), 1004 (w), 907 (w), 880 (w), 861 (w).

$[\alpha]_D^{20}$ = +27.6 (*c* 0.50, CH_2Cl_2).

Synthesis of Alcohol 320



In a Schlenk-tube was added *t*-BuLi (1.86 mL of a 1.7M solution in pentane, 3.16 mmol, 11.8 eq.) to Et_2O (8 mL) at −78 °C followed by dropwise addition of 2-bromopropene (142 µL, 1.60 mmol, 6.0 eq.). The resulting mixture was allowed to warm to 0 °C and was stirred for 30 min before being cooled to −78 °C. Then, a solution of ketone **319** (100 mg, 267 µmol, 1.0 eq.) in Et_2O (2 mL) was added dropwise and the mixture was stirred for an additional 15 min. The reaction was quenched by addition of saturated aqueous NH_4Cl (10 mL) at −78 °C and the mixture was allowed to warm to room temperature. The phases were separated and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with saturated aqueous NaCl (15 mL) and dried over $MgSO_4$. The solvents were evaporated under reduced pressure and the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 50:1) to yield alcohol **320** (102 mg, 245 µmol, 92%) as a colorless oil and single diastereomer.

R_f = 0.13 (Hexanes:EtOAc = 30:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 5.81 (ddt, $^3J_{20/21A}$ = 17.0 Hz, $^3J_{20/21B}$ = 10.1 Hz, $^3J_{20/19}$ = 6.7 Hz, 1H, 20-H), 5.14 (m_C, 1H, 16-H), 5.09 (m_C, 1H, 25-H_A), 5.01 (m_C, 1H, 21-H_A), 4.94 (m_C, 1H, 21-H_B), 4.88 (m_C, 1H, 25-H_B), 3.51 (dd, $^3J_{1/2}$ = 9.0, 7.3 Hz, 1H, 1-H), 2.17–2.13 (m, 2H, 19-H), 2.07–2.03 (m, 2H, 18-H), 1.96–1.89 (m, 3H, 2-H_A, 15-H), 1.80–1.72 (m, 2H, 4-H, 7-H), 1.76 (br s, 3H, 26-H), 1.65 (m_C, 1H, 13-H), 1.59 (s, 3H, 23-H), 1.55 (br s, 1H, *O*H), 1.50–1.42 (m, 3H, 2-H_B, 3-H_A, 8-H_A), 1.31–1.17 (m, 6H, 3-H_B, 5-H, 8-H_B, 14-H), 1.15 (s, 9H, 12-H), 0.86 (d, $^3J_{22/13}$ = 6.8 Hz, 3H, 22-H), 0.76 (s, 3H, 10-H) ppm.

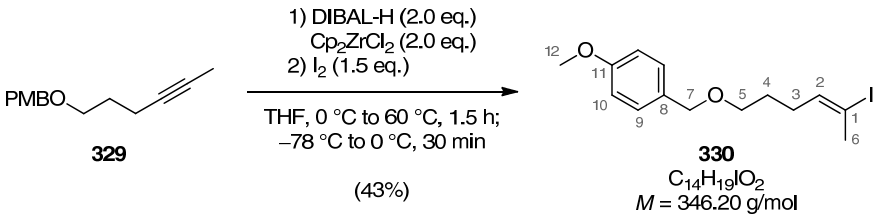
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 151.7 (C-24), 138.9 (C-20), 134.7 (C-17), 125.0 (C-16), 114.4 (C-21), 109.9 (C-25), 80.9 (C-1), 80.1 (C-6), 72.4 (C-11), 42.6 (C-9), 40.7 (C-7), 39.3 (C-4)*, 39.2 (C-18)*, 39.1 (C-5)*, 38.0 (C-14), 32.9 (C-8), 32.6 (C-19), 31.5 (C-2), 31.2 (C-13), 29.0 (C-12), 26.1 (C-15), 25.8 (C-3), 19.8 (C-26), 16.6 (C-22), 16.1 (C-23), 11.1 (C-10) ppm.

EI-MS for $C_{28}H_{48}O_2^+$ [M^+]: calcd. 416.3649
found 416.3642.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 3598 (br w), 3077 (w), 2973 (s), 2954 (s), 2932 (s), 2875 (s), 1401 (w), 1388 (w), 1362 (w), 1254 (w), 1198 (m), 1125 (w), 1095 (w), 1063 (m), 991 (w), 903 (w).

$[\alpha]_D^{20}$ = +26.4 (*c* 0.25, CH_2Cl_2).

Synthesis of Vinyl Iodide 330



To a solution of Cp_2ZrCl_2 (5.85 g, 20.0 mmol, 2.0 eq.) in THF (50 mL) at 0 °C was added DIBAL-H (20.0 mL of a 1.0M solution in toluene, 20.0 mmol, 2.0 eq.) within 1 h forming a white suspension. After stirring an additional 1.5 h at this temperature, a solution of alkyne **329**[219] (2.19 g, 10.0 mmol, 1.0 eq.) in THF (10 + 2 mL rinse) was added and the resulting mixture was heated to 50 °C for 1.5 h at which point TLC analysis showed complete consumption of the starting material. The mixture was cooled to −78 °C and a solution of I_2 (3.81 g, 15.0 mmol, 1.5 eq.) in THF (20 mL) was slowly added. The cold bath was exchanged with an ice/water bath and the solution was stirred for an additional 30 min at 0 °C. The reaction was quenched by addition of saturated aqueous $Na_2S_2O_3$ (30 mL) and the mixture was diluted with half-saturated aqueous Rochelle salt (100 mL). After stirring vigorously at room temperature for 2.5 h, the layers were separated and the aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with saturated aqueous NaCl (100 mL) and dried over $MgSO_4$. Having evaporated the solvents under reduced pressure, the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 30:1) to yield vinyl iodide **330** (2.08 g, 6.01 mmol, 60%) as a pale yellow liquid and as a 10:1 mixture of regioisomers as determined by ^{1}H NMR spectroscopy. Further careful flash column chromatography (silica, hexanes:EtOAc = 60:1) yielded vinyl iodide **330** (1.48 g, 4.28 mmol, 43%) as a light yellow oil.

R_f = 0.47 (Hexanes:EtOAc = 7:1).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.29–7.22 (m, 2H, 9-H), 6.91–6.84 (m, 2H, 10-H), 6.14 (tq, $^3J_{2/3}$ = 7.6 Hz, $^4J_{2/6}$ = 1.6 Hz, 1H, 2-H), 4.42 (s, 2H, 7-H), 3.81 (s, 3H, 12-H), 3.42 (t, $^3J_{5/4}$ = 6.2 Hz, 2H, 5-H), 2.37–2.35 (m, 3H, 6-H), 2.12 (m_C, 2H, 3-H), 1.70–1.62 (m, 2H, 4-H) ppm.

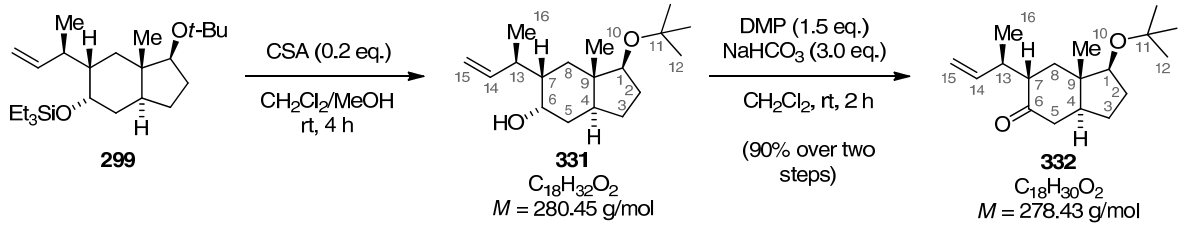
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 159.3 (C-8), 140.7 (C-2), 130.7 (C-11), 129.4 (C-9), 113.9 (C-10), 94.2 (C-1), 72.8 (C-7), 69.0 (C-5), 55.4 (C-12), 29.0 (C-4), 27.6 (C-6), 27.4 (C-3) ppm.

EI-MS for $C_{14}H_{19}IO_2^+$ [M^+]: calcd. 346.0424
found 346.0427.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 2934 (m), 2854 (m), 1586 (w), 1512 (s), 1463 (w), 1363 (w), 1302 (w), 1245 (s), 1098 (s), 1036 (m), 820 (w).

The analytical data matched those reported previously.[219]

Synthesis of Ketone 332



To a solution of silyl ether **299** (300 mg, 761 µmol, 1.0 eq.) in CH_2Cl_2/MeOH (7:1, 8 mL) was added (1*R*)-(–)-camphorsulfonic acid (35 mg, 0.15 mmol, 20 mol-%) and the mixture was stirred for 4 h at room temperature. The reaction was diluted with CH_2Cl_2 (5 mL) and quenched by addition of saturated aqueous $NaHCO_3$ (5 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with saturated aqueous NaCl (5 mL) and dried over $MgSO_4$. The solvents were evaporated under reduced pressure to yield crude alcohol **331** which was used without further purification.

To a suspension of crude alcohol **331** (assumed 761 µmol, 1.0 eq.) and $NaHCO_3$ (192 mg, 2.28 mmol, 3.0 eq.) in CH_2Cl_2 at room temperature was added DMP (483 mg, 1.14 mmol, 1.5 eq.). The mixture was stirred for 2 h and the reaction was quenched by addition of saturated aqueous $NaHCO_3$/saturated aqueous $Na_2S_2O_3$/H_2O (1:1:1, 8 mL). After extracting the mixture with CH_2Cl_2 (3 x 15 mL), the combined organic layers were washed with saturated aqueous NaCl (10 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 40:1) to yield ketone **332** (191 mg, 687 µmol, 90% over two steps) as a colorless oil.

R_f = 0.47 (Hexanes:EtOAc = 10:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 5.82 (m_C, 1H, 14-H), 5.02–4.96 (m, 2H, 15-H), 3.46 (dd, $^3J_{1/2}$ = 8.9, 7.8 Hz, 1H, 1-H), 2.87 (m_C, 1H, 13-H), 2.42 (ddd, $^3J_{7/8B}$ = 12.9 Hz, $^3J_{7/8A}$ = 6.3 Hz, $^3J_{7/13}$ = 3.5 Hz, 1H, 7-H), 2.34–2.25 (m, 2H, 5-H), 2.02–1.94 (m, 1H, 2-H_A), 1.88 (dd, $^2J_{8A/8B}$ = 12.8 Hz, $^3J_{8A/7}$ = 6.3 Hz, 1H, 8-H_A), 1.65 (m_C, 1H, 4-H), 1.61–1.54 (m, 2H, 2-H_B, 3-H_A), 1.43–1.36 (m, 1H, 3-H_B), 1.21 (dd, $^2J_{8B/8A}$ = $^3J_{8B/7}$ = 12.8 Hz, 1H, 8-H_B), 1.14 (s, 9H, 12-H), 0.97 (s, 3H, 10-H), 0.95 (d, $^3J_{16/13}$ = 6.9 Hz, 3H, 16-H) ppm.

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 211.6 (C-6), 142.7 (C-14), 113.8 (C-15), 79.9 (C-1), 72.7 (C-11), 49.9 (C-7), 45.0 (C-4), 43.4 (C-5), 42.4 (C-9), 36.8 (C-8), 35.7 (C-13), 31.9 (C-2), 28.8 (C-12), 25.9 (C-3), 15.2 (C-16), 11.2 (C-10) ppm.

EI-MS for $C_{18}H_{30}O_2^+$ [M^+]: calcd. 278.2240
found 278.2241.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 3073 (w), 2972 (s), 2874 (m), 1706 (s), 1461 (w), 1389 (w), 1362 (m), 1251 (w), 1192 (m), 1122 (w), 1061 (m), 1001 (w), 901 (w).

$[\alpha]_D^{20}$ = +43.1 (*c* 1.00, CH_2Cl_2).

An analytical sample of alcohol **331** was obtained by flash column chromatography (silica, hexanes:EtOAc = 30:1) as a colorless wax:

R_f = 0.31 (Hexanes:EtOAc = 10:1).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.82 (ddd, $^3J_{14/15A}$ = 17.1 Hz, $^3J_{14/15B}$ = 10.2 Hz, $^3J_{14/13}$ = 9.1 Hz, 1H, 14-H), 5.07 (ddd, $^3J_{15A/14}$ = 17.1 Hz, $^2J_{15A/15B}$ = 2.0 Hz, $^4J_{15A/13}$ = 0.8 Hz, 1H, 15-H_A), 4.98 (dd, $^3J_{15B/14}$ = 10.2 Hz, $^2J_{15B/15A}$ = 1.9 Hz, 1H, 15-H_B), 3.98 (br s, 1H, 6-H), 3.45 (dd, $^3J_{1/2}$ = 8.9, 7.7 Hz, 1H, 1-H), 2.12 (m_C, 1H, 13-H), 1.98–1.84 (m, 1H, 2-H_A), 1.76–1.59 (m, 3H, 4-H, 5-H_A, 8-H_A), 1.55–1.23 (m, 5H, 2-H_B, 3-H, 5-H_B, 7-H), 1.14 (s, 9H, 12-H), 1.07 (m_C, 1H, 8-H_B), 1.02 (d, $^3J_{16/13}$ = 6.6 Hz, 3H, 16-H), 0.71 (s, 3H, 10-H) ppm.

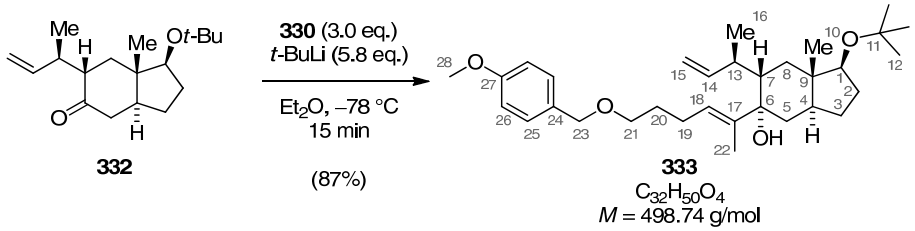
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 144.5 (C-14), 113.5 (C-15), 80.7 (C-1), 72.4 (C-11), 68.0 (C-6), 42.8 (2C, C-7, C-9), 40.8 (C-13), 37.6 (C-4), 36.3 (C-8), 33.3 (C-5), 31.4 (C-2), 28.9 (C-12), 25.6 (C-3), 19.1 (C-16), 11.0 (C-10) ppm.

EI-MS for $C_{18}H_{32}O_2^+$ [M^+]: calcd. 280.2397
found 280.2389.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 3428 (br s), 3312 (br s), 3073 (w), 2973 (s), 2934 (s), 2902 (s), 1460 (w), 1389 (w), 1361 (w), 1198 (w), 1168 (w), 1127 (w), 1071 (w), 1002 (w), 906 (w).

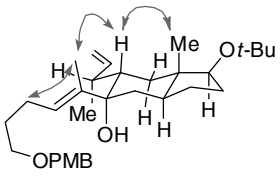
$[\alpha]_D^{20}$ = +50.4 (*c* 0.5, CH_2Cl_2).

Synthesis of Alcohol 333



To a solution of vinyl iodide **330** (546 mg, 1.57 mmol, 3.0 eq.) in Et_2O (15 mL) at –78 °C was added dropwise *t*-BuLi (1.79 mL of a 1.7M solution in pentane, 3.04 mmol, 5.8 eq.) and the mixture was stirred for 30 min at this temperature. Then, a solution of ketone **332** (145 mg, 520 μmol, 1.0 eq.) in Et_2O (3 mL + 1 mL rinse) was added dropwise. After 15 min, the reaction was quenched by addition of saturated aqueous NH_4Cl (10 mL). The mixture was allowed to warm to room temperature and was diluted with H_2O (10 mL) and Et_2O (20 mL). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with saturated aqueous NaCl (30 mL) and dried over $MgSO_4$. Having evaporated the solvents under reduced pressure, the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 24:1) to yield title compound **333** (226 mg, 453 μmol, 87%) as a highly viscous colorless oil.

The relative stereochemistry at C-6 was established by key NOE correlations as depicted aside.



R_f = 0.15 (hexanes:EtOAc = 10:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.27–7.24 (m, 2H, 25-H), 6.87 (m_C, 2H, 26-H), 5.78 (ddd, $^3J_{14/15A}$ = 16.7 Hz, $^3J_{14/15B}$ = 10.9 Hz, $^3J_{14/13}$ = 6.9 Hz, 1H, 14-H), 5.57 (m_C, 1H, 18-H), 4.91–4.84 (m, 2H, 15-H), 4.42 (m_C, 2H, 23-H), 3.80 (s, 3H, 28-H), 3.50 (dd, $^3J_{1/2}$ = 9.1, 7.4 Hz, 1H, 1-H), 3.44 (t, $^3J_{21/20}$ = 6.5 Hz, 2H, 21-H), 2.28 (m_C, 1H, 13-H), 2.14 (m_C, 2H, 19-H), 1.95–1.89 (m, 1H, 2-H_A), 1.86 (ddd, $^3J_{7/8B}$ = 12.7 Hz, $^3J_{7/8A}$ = 3.7 Hz, $^3J_{7/13}$ = 2.3 Hz, 1H, 7-H), 1.78–1.64 (m, 4H, 4-H, 5-H_A, 20-H), 1.61 (s, 3H, 22-H), 1.49 (dd, $^2J_{8A/8B}$ = 12.4 Hz, $^3J_{8A/7}$ = 3.7 Hz, 1H, 8-H_A), 1.48–1.42 (m, 2H, 2-H_B,

3-H_A), 1.30–1.22 (m, 2H, 3-H_B, 8-H_B), 1.17–1.09 (m, 1H, 5-H_B), 1.15 (s, 9H, 12-H), 0.95 (d, $^3J_{16/13}$ = 6.8 Hz, 3H, 16-H), 0.74 (s, 3H, 10-H) ppm.

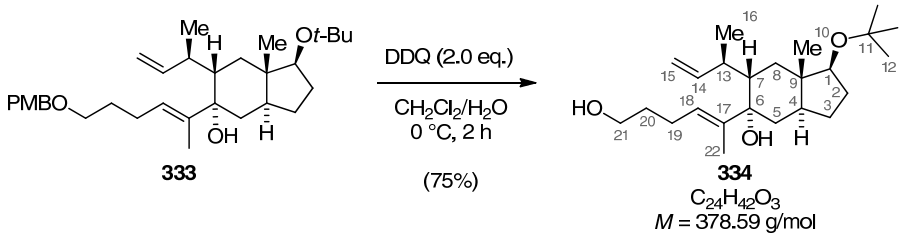
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 159.3 (C-27), 145.5 (C-14), 141.4 (C-17), 130.9 (C-24), 129.4 (C-25), 122.9 (C-18), 113.9 (C-26), 112.0 (C-15), 80.9 (C-1), 79.7 (C-6), 72.8 (C-23), 72.4 (C-11), 69.7 (C-21), 55.4 (C-28), 42.6 (C-9), 40.2 (C-7), 39.3 (C-4), 39.2 (C-5), 36.5 (C-13), 33.9 (C-8), 31.5 (C-2), 29.9 (C-20), 28.9 (C-12), 25.7 (C-3), 24.7 (C-19), 15.0 (C-16), 13.7 (C-22), 10.9 (C-10) ppm.

ESI-MS for $C_{32}H_{49}O_4^-$ [$(M–H)^-$]: calcd. 497.3636
found 497.3633.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 3484 (br w), 3074 (w), 2971 (s), 2954 (s), 2869 (m), 1634 (w), 1587 (w), 1513 (m), 1388 (w), 1362 (m), 1248 (m), 1196 (w), 1097 (m), 1061 (m), 1048 (m), 905 (w), 821 (w).

$[\alpha]_D^{20}$ = +23.4 (*c* 0.50, CH_2Cl_2).

Synthesis of Diol 334



To a solution of PMB ether **333** (175 mg, 351 µmol, 1.0 eq.) in CH_2Cl_2/H_2O (10:1, 22 mL) at 0 °C was added DDQ (159 mg, 708 µmol, 2.0 eq.) in one portion and the biphasic mixture was stirred vigorously for 2 h. The mixture was filtered over a pad of Celite® (washings with CH_2Cl_2) and the resulting solution was sequentially washed with saturated aqueous $NaHCO_3$ (3 x 25 mL), H_2O (20 mL) and saturated aqueous NaCl (20 mL), and dried over $MgSO_4$. The solvents were evaporated under reduced pressure and the crude product was purified by flash column chromatography (silica, CH_2Cl_2:MeOH = 100:1) to yield diol **334** (99 mg, 262 µmol, 75%) as a pale yellow oil.

R_f = 0.19 (hexanes:EtOAc = 4:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 5.79 (ddd, $^3J_{14/15A}$ = 16.7 Hz, $^3J_{14/15B}$ = 10.7 Hz, $^3J_{14/13}$ = 7.0 Hz, 1H, 14-H), 5.61 (m_C, 1H, 18-H), 4.91–4.85 (m, 2H, 15-H), 3.67 (t, $^3J_{21/20}$ = 6.5 Hz, 2H, 21-H), 3.50 (dd, $^3J_{1/2}$ = 9.1, 7.4 Hz, 1H, 1-H), 2.28 (m_C, 1H, 13-H), 2.15 (m_C, 2H, 19-H), 1.95–1.89 (m, 1H, 2-H_A),

1.87 (ddd, ^3J = 12.8, 3.7, 2.3 Hz, 1H, 7-H), 1.78–1.70 (m, 2H, 4-H, 5-H_A), 1.70–1.64 (m, 2H, 20-H), 1.63 (s, 3H, 22-H), 1.52–1.39 (m, 5H, 2-H_B, 3-H_A, 8-H_A, *O*H), 1.30–1.22 (m, 2H, 3-H_B, 8-H_B), 1.17–1.10 (m, 1H, 5-H_B), 1.15 (s, 9H, 12-H), 0.96 (d, $^3J_{16/13}$ = 7.0 Hz, 3H, 16-H), 0.74 (s, 3H, 10-H) ppm.

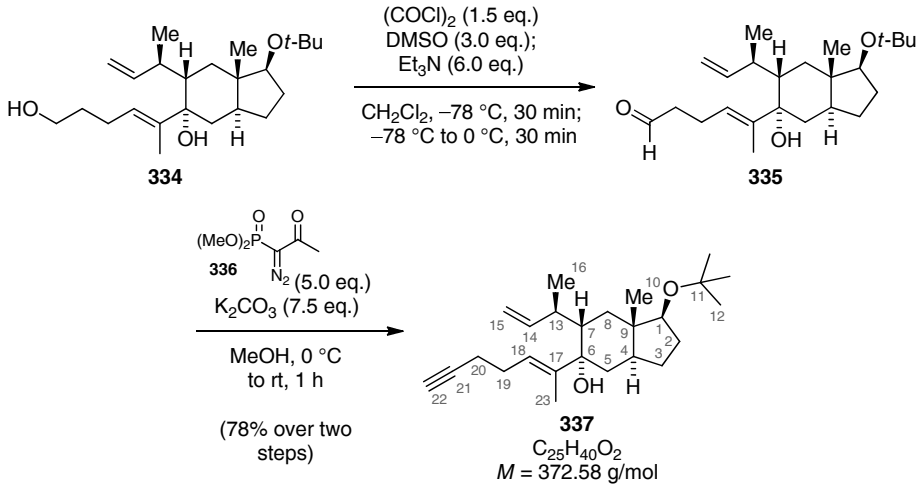
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 145.4 (C-14), 141.6 (C-17), 122.7 (C-18), 112.1 (C-15), 80.9 (C-1), 79.7 (C-6), 72.4 (C-11), 62.9 (C-21), 42.6 (C-9), 40.2 (C-7), 39.3 (C-4), 39.2 (C-5), 36.6 (C-13), 34.0 (C-8), 32.8 (C-20), 31.5 (C-2), 28.9 (C-12), 25.7 (C-3), 24.4 (C-19), 15.1 (C-16), 13.7 (C-22), 10.9 (C-10) ppm.

ESI-MS for $C_{24}H_{42}O_3^+$ [M^+]: calcd. 378.3128
found 378.3121.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 3416 (br m), 3074 (w), 2972 (s), 2954 (s), 2946 (s), 2872 (s), 1461 (w), 1388 (w), 1362 (m), 1254 (w), 1196 (m), 1129 (w), 1096 (w), 1061 (m), 905 (w).

$[\alpha]_D^{20}$ = +34.7 (*c* 0.15, CH_2Cl_2).

Synthesis of Alkyne 337



To a solution of DMSO (55 µL, 0.78 mmol, 3.0 eq.) in CH_2Cl_2 (5 mL) at –78 °C was added dropwise $(COCl)_2$ (195 µL of a 2.0M solution in CH_2Cl_2, 390 µmol, 1.5 eq.) and the mixture was stirred for 30 min. Then, a solution of diol **334** (99 mg, 0.26 mmol, 1.0 eq.) in CH_2Cl_2 (2 mL) was added slowly and the reaction was stirred for an additional 30 min at –78 °C. After addition of Et_3N (220 µL, 1.56 mmol, 6.0 eq.), the cold bath was replaced by an ice/water bath and the mixture was stirred for 30 min. The reaction was partitioned between H_2O (10 mL) and CH_2Cl_2 (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with

saturated aqueous NaCl (15 mL) and dried over $MgSO_4$. The solvents were removed under reduced pressure and the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 7:1) to yield aldehyde **335**, which was immediately used in the next step.

To a solution of aldehyde **335** (assumed 0.26 mmol, 1.0 eq.) in MeOH (7 mL) at 0 °C was consecutively added K_2CO_3 (259 mg, 1.88 mmol, 7.5 eq.) and a solution of Ohira-Bestmann reagent (**336**, 243 mg, 1.25 mmol, 5.0 eq.) in MeOH (2 mL). The mixture was allowed to warm to room temperature and stirred for 1 h. The reaction was diluted with H_2O (15 mL) and the mixture was extracted with Et_2O (5 x 10 mL). The combined organic layers were washed with saturated aqueous NaCl (10 mL) and dried over $MgSO_4$. The solvents were removed under reduced pressure and the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 40:1) to yield alkyne **337** (75 mg, 0.20 mmol, 78% over two steps) as a colorless oil.

R_f = 0.13 (hexanes:EtOAc = 30:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 5.79 (ddd, $^3J_{14/15A}$ = 17.6 Hz, $^3J_{14/15B}$ = 9.8 Hz, $^3J_{14/13}$ = 7.0 Hz, 1H, 14-H), 5.63 (m_C, 1H, 18-H), 4.91–4.85 (m, 2H, 15-H), 3.50 (dd, $^3J_{1/2}$ = 9.2, 7.4 Hz, 1H, 1-H), 2.36–2.22 (m, 5H, 13-H, 19-H, 20-H), 1.95–1.84 (m, 1H, 2-H_A), 1.93 (t, $^4J_{22/20}$ = 2.5 Hz, 1H, 22-H), 1.87 (ddd, ^3J = 12.7, 3.8, 2.3 Hz, 1H, 7-H), 1.78–1.70 (m, 2H, 4-H, 5-H_A), 1.65 (s, 3H, 23-H), 1.56 (br s, 1H, *O*H), 1.50 (dd, $^2J_{8A/8B}$ = 12.6 Hz, $^3J_{8A/7}$ = 3.9 Hz, 1H, 8-H_A), 1.48–1.41 (m, 2H, 2-H_B, 3-H_A), 1.32–1.19 (m, 2H, 3-H_B, 8-H_B), 1.18–1.10 (m, 1H, 5-H_B), 1.15 (s, 9H, 12-H), 0.96 (d, $^3J_{16/13}$ = 7.1 Hz, 3H, 16-H), 0.74 (s, 3H, 10-H) ppm.

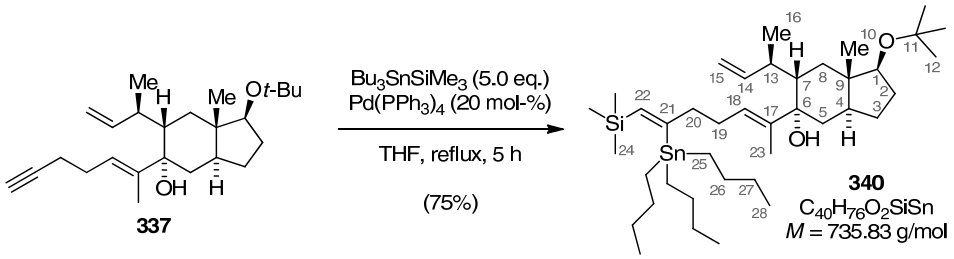
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 145.5 (C-14), 142.6 (C-17), 121.6 (C-18), 112.1 (C-15), 84.5 (C-21), 80.9 (C-1), 79.8 (C-6), 72.4 (C-11), 68.4 (C-22), 42.6 (C-9), 40.2 (C-7), 39.3 (C-4), 39.1 (C-5), 36.5 (C-13), 34.0 (C-8), 31.5 (C-2), 28.9 (C-12), 27.3 (C-19), 25.7 (C-3), 18.9 (C-20), 16.1 (C-16), 13.8 (C-23), 10.9 (C-10) ppm.

EI-MS for $C_{25}H_{39}O_2^+$ [$(M–H)^+$]: calcd. 371.2945
found 371.2943.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 3545 (br w), 3309 (m), 3076 (w), 2971 (s), 2871 (s), 1462 (w), 1388 (w), 1361 (m), 1253 (w), 1196 (m), 1127 (w), 1095 (w), 1061 (m), 995 (w), 904 (w).

$[\alpha]_D^{20}$ = +41.7 (*c* 0.33, CH_2Cl_2).

Synthesis of Vinyl Stannane 340



To a solution of alkyne **337** (52 mg, 0.14 mmol, 1.0 eq.) in THF (5 mL) was added trimethyl(tri-*n*-butylstannyl)silane (244 µL, 700 µmol, 5.0 eq.) and $Pd(PPh_3)_4$ (32 mg, 28 µmol, 20 mol-%). The yellow solution was heated to reflux for 5 h changing its color to dark brown. The reaction mixture was allowed to cool to room temperature and was diluted with hexanes (15 mL). The mixture was filtered over a pad of silica (washings with Et_2O) and the solvents were removed under reduced pressure. The thus obtained orange crude oil was purified by flash column chromatography (silica, hexanes:EtOAc = 1:0 to 80:1) to yield stannane **340** (77 mg, 105 µmol, 75%) as a colorless oil.

R_f = 0.18 (hexanes:EtOAc = 30:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 6.37 (br s, 1H, 22-H), 5.79 (m_C, 1H, 14-H), 5.55 (m_C, 1H, 18-H), 4.91–4.85 (m, 2H, 15-H), 3.50 (dd, $^3J_{1/2}$ = 9.0, 7.3 Hz, 1H, 1-H), 2.38–2.24 (m 3H, 13-H, 20-H), 2.11–2.02 (m, 2H, 19-H), 1.95–1.89 (m, 1H, 2-H_A), 1.87 (m_C, 1H, 7-H), 1.79–1.69 (m, 2H, 4-H, 5-H_A), 1.63 (s, 3H, 23-H), 1.54–1.41 (m, 9H, 2-H_B, 3-H_A, 8-H_A, 26-H), 1.32 (m_C, 6H, 27-H), 1.28–1.22, (m, 2H, 3-H_B, 8-H_B), 1.18–1.12 (m, 1H, 5-H_B), 1.15 (s, 9H, 12-H), 1.01–0.83 (m, 18H, 16-H, 25-H, 28-H), 0.74 (s, 3H, 10-H), 0.09 (s, 9H, 24-H) ppm.

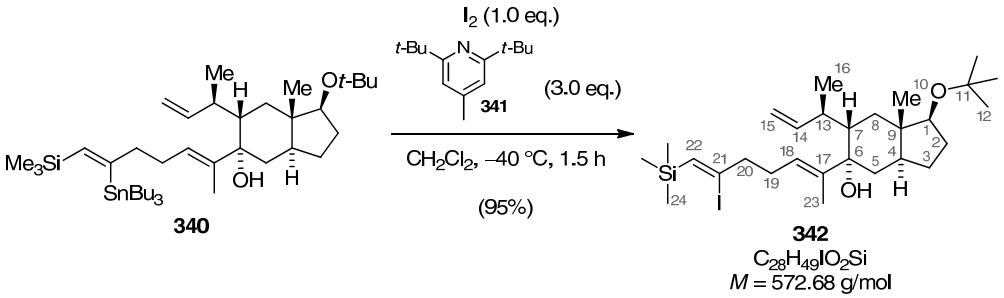
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 165.2 (C-21), 145.6 (C-14), 143.7 (C-22), 141.0 (C-17), 122.8 (C-18), 112.0 (C-15), 80.9 (C-1), 79.7 (C-6), 72.4 (C-11), 47.2 (C-20), 42.6 (C-9), 40.3 (C-7), 39.3 (2C, C-4, C-5), 36.6 (C-13), 34.1 (C-8), 31.5 (C-2), 29.4 (C-26), 28.9 (C-12), 28.6 (C-19), 27.7 (C-27), 25.7 (C-3), 16.1 (C-16), 13.8 (2C, C-23, C-28), 11.4 (C-25), 10.9 (C-10), 0.4 (C-24) ppm.

ESI-MS for $C_{40}H_{76}O_2SiSnCl^-$ [$(M+Cl)^-$]: calcd. 771.4331
found 771.4325.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 3599 (br w), 3071 (w), 2953 (s), 2929 (s), 2871 (s), 2855 (m), 1463 (w), 1375 (w), 1361 (w), 1246 (w), 1196 (w), 1128 (w), 1063 (w), 905 (w), 861 (w), 835 (w).

$[\alpha]_D^{20}$ = +11.4 (*c* 0.33, CH_2Cl_2).

Synthesis of Vinyl Iodide 342



To a solution of stannane **340** (74 mg, 0.10 mmol, 1.0 eq.) in CH_2Cl_2 (6 mL) at –40 °C was added 2,6-di-*tert*-butyl-4-methylpyridine (**341**, 62 mg, 0.30 mmol, 3.0 eq.) followed by I_2 (26 mg, 0.10 mmol, 1.0 eq.). The yellow mixture was stirred at this temperature for 1.5 h and the reaction was then quenched by addition of saturated aqueous $Na_2S_2O_3$ (7 mL). The mixture was diluted with H_2O (7 mL) and CH_2Cl_2 (10 mL), and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were dried over Na_2SO_4. The solvents were evaporated under reduced pressure and the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 80:1 to 60:1) to yield vinyl iodide **342** (55 mg, 95 µmol, 95%) as a colorless oil.

R_f = 0.09 (hexanes:EtOAc = 30:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 6.33 (t, $^4J_{22/20}$ = 1.0 Hz, 1H, 22-H), 5.79 (m_C, 1H, 14-H), 5.55 (m_C, 1H, 18-H), 4.91–4.86 (m, 2H, 15-H), 3.50 (dd, $^3J_{1/2}$= 8.9, 7.4 Hz, 1H, 1-H), 2.61 (m_C, 2H, 20-H), 2.33–2.23 (m, 3H, 13-H, 19-H), 1.95–1.90 (m, 1H, 2-H_A), 1.87 (m_C, 1H, 7-H), 1.76–1.70 (m, 2H, 4-H, 5-H_A), 1.66 (s, 3H, 23-H), 1.50 (dd, $^2J_{8A/8B}$ = 12.7 Hz, $^3J_{8A/7}$ = 3.7 Hz, 1H, 8-H_A), 1.48–1.41 (m, 2H, 2-H_B, 3-H_A), 1.32–1.21 (m, 2H, 3-H_B, 8-H_B), 1.17–1.11 (m, 1H, 5-H_B), 1.15 (s, 9H, 12-H), 0.96 (d, $^3J_{16/13}$ = 6.9 Hz, 3H, 16-H), 0.74 (s, 3H, 10-H), 0.18 (s, 9H, 24-H) ppm.

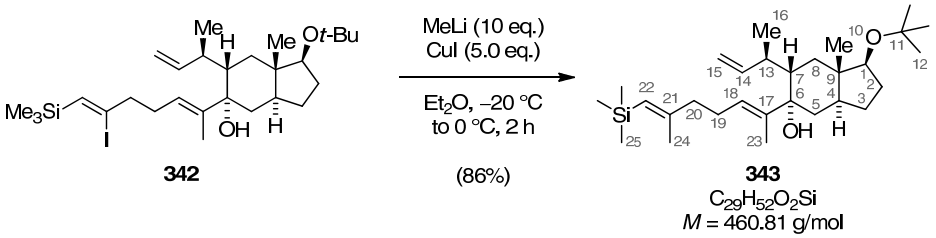
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 145.4 (C-14), 142.4 (C-17), 137.4 (C-22), 122.8 (C-21), 121.2 (C-18), 112.1 (C-15), 80.9 (C-1), 79.8 (C-6), 72.4 (C-11), 50.9 (C-20), 42.6 (C-9), 40.3 (C-7), 39.4 (C-4)*, 39.3 (C-5)*, 36.5 (C-13), 34.0 (C-8), 31.4 (C-2), 28.9 (C-12), 28.0 (C-19), 25.7 (C-3), 16.1 (C-16), 13.9 (C-23), 10.9 (C-10), –1.0 (C-24) ppm.

ESI-MS for $C_{28}H_{48}IOSi^+$ [$(M–OH)^+$]: calcd. 555.2514
found 555.2510.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 3560 (br w), 3072 (w), 2972 (s), 2955 (s), 2873 (m), 1595 (m), 1461 (w), 1388 (w), 1361 (w), 1248 (m), 1196 (m), 1127(w), 1062 (w), 905 (w), 863 (w), 841 (m).

$[\alpha]_D^{20}$ = +32.0 (*c* 0.25, CH_2Cl_2).

Synthesis of Vinyl Silane 343



342 **343**
$C_{29}H_{52}O_2Si$
M = 460.81 g/mol

To a suspension of CuI (87 mg, 0.45 mmol, 5.0 eq.) in Et_2O (5 mL) at –20 °C was added dropwise MeLi (0.57 mL of a 1.6M solution in Et_2O, 0.91 mmol, 10 eq.) and the resulting pale yellow solution was stirred for an additional 15 min. Then, a solution of vinyl iodide **342** (52 mg, 91 μmol, 1.0 eq.) in Et_2O (1.5 mL) was added dropwise and the reaction mixture was allowed to slowly warm to 0 °C. After stirring for an additional 60 min at 0 °C, the reaction was quenched by addition of saturated aqueous NH_4Cl (5 mL) and the biphasic mixture was filtered over a pad of Celite® (washings with Et_2O). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with saturated aqueous NaCl (10 mL) and dried over $MgSO_4$. The solvents were evaporated under reduced pressure and the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 70:1 to 60:1) to yield vinyl silane **343** (36 mg, 78 μmol, 86%) as a colorless oil.

The C-21/C-22 double bond geometry has been verified to be (*E*) by 2D NOESY experiments, indicating a proximity between 24-H and 25-H.

R_f = 0.18 (hexanes:EtOAc = 30:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 5.79 (m_C, 1H, 14-H), 5.55 (m_C, 1H, 18-H), 5.20 (m_C, 1H, 22-H), 4.91–4.84 (m, 2H, 15-H), 3.50 (dd, $^3J_{1/2}$ = 9.0, 7.4 Hz, 1H, 1-H), 2.31–2.26 (m, 1H, 13-H), 2.26–2.09 (m, 4H, 19-H, 20-H), 1.95–1.85 (m, 1H, 2-H_A), 1.87 (ddd, $^3J_{7/8B}$ = 12.8 Hz, $^3J_{7/8A}$ = 3.6 Hz, $^3J_{7/13}$ = 2.3 Hz, 1H, 7-H), 1.78 (d, $^4J_{24/22}$ = 0.8 Hz, 3H, 24-H), 1.77–1.69 (m, 2H, 4-H, 5-H_A), 1.63 (s, 3H, 23-H), 1.49 (dd, $^2J_{8A/8B}$ = 12.6 Hz, $^3J_{8A/7}$ = 3.8 Hz, 1H, 8-H_A), 1.48–1.41 (m, 2H, 2-H_B, 3-H_A), 1.30–1.22 (m, 1H, 3-H_B), 1.24 (dd, $^2J_{8B/8A}$ = $^3J_{8B/7}$ = 12.7 Hz, 1H, 8-H_B), 1.18–1.11 (m, 1H, 5-H_B), 1.15 (s, 9H, 12-H), 0.96 (d, $^3J_{16/13}$ = 6.9 Hz, 3H, 16-H), 0.74 (s, 3H, 10-H), 0.09 (s, 9H, 25-H) ppm.

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 154.9 (C-21), 145.4 (C-14), 140.9 (C-17), 123.1 (C-22), 122.8 (C-18), 111.8 (C-15), 80.7 (C-1), 79.5 (C-6), 72.3 (C-11), 42.4 (C-9), 42.2 (C-20), 40.1 (C-7),

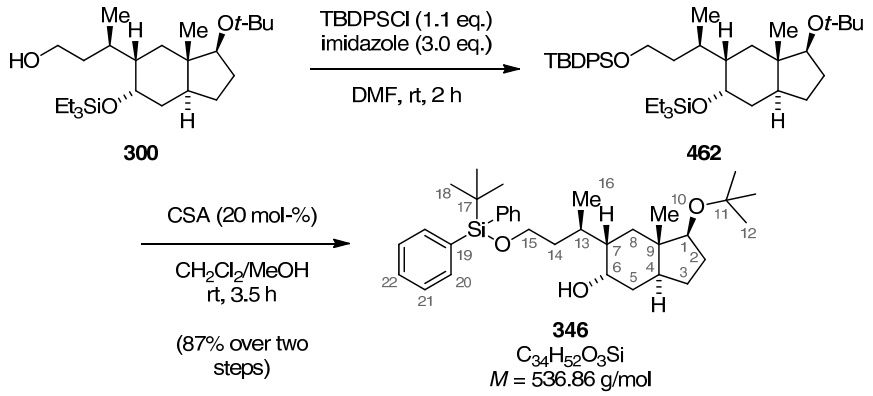
39.1 (2C, C-4, C-5), 36.3 (C-13), 33.8 (C-8), 31.3 (C-2), 28.7 (C-12), 26.4 (C-19), 25.5 (C-3), 21.6 (C-24), 15.9 (C-16), 13.5 (C-23), 10-7 (C-10), 0.1 (C-25) ppm.

ESI-MS for $C_{30}H_{53}O_4Si^-$ [$(M+HCOO)^-$]: calcd. 505.3719
found 505.3719.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 3598 (br w), 3073 (w), 2972 (s), 2955 (s), 2876 (m), 1618 (w), 1461 (w), 1376 (w), 1362 (w), 1248 (m), 1197 (m), 1128 (w), 1062 (w), 906 (w), 866 (w), 838 (m).

$[\alpha]_D^{20}$ = +28.4 (*c* 0.25, CH_2Cl_2).

Synthesis of Alcohol 346



To a solution of alcohol **300** (330 mg, 801 µmol, 1.0 eq.) in DMF (8 mL) was sequentially added imidazole (163 mg, 2.40 mmol, 3.0 eq.) and TBDPSCl (239 µL, 921 µmol, 1.1 eq.), and the mixture was stirred for 2 h at room temperature. The reaction was quenched by addition of H_2O (8 mL) and the mixture was extracted with Et_2O (4 x 15 mL). The combined organic layers were washed with 10% aqueous NaCl (3 x 8 mL) and subsequently dried over $MgSO_4$. Having evaporated the solvents under reduced pressure, the crude product was subjected to a short flash column chromatography (silica, hexanes:EtOAc = 60:1) to yield bissilyl ether **462** (R_f = 0.37, hexanes:EtOAc = 16:1) as a colorless oil, which was directly used in the next step.

To a solution of crude bissilyl ether **462** (assumed 801 µmol, 1.0 eq.) in CH_2Cl_2/MeOH (7:1, 12 mL) was added (1*R*)-(–)-camphorsulfonic acid (35 mg, 0.15 mmol, 20 mol-%) and the mixture was stirred for 3.5 h at room temperature. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (8 mL) and the mixture was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with saturated aqueous NaCl (10 mL) and dried over $MgSO_4$. Having evaporated the solvents under reduced pressure, the crude product was purified by flash column chromatography (silica, *n*-pentane:Et_2O = 8:1) to yield silyl ether **346** (345 mg, 644 µmol, 87% over two steps) as a colorless honey.

R_f = 0.30 (hexanes:EtOAc = 7:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.69–7.65 (m, 4H, 20-H)*, 7.44–7.40 (m, 2H, 22-H), 7.40–7.37 (m, 4H, 21-H)*, 4.05 (m_C, 1H, 6-H), 3.76–3.70 (m, 1H, 15-H_A), 3.69–3.64 (m, 1H, 15-H_B), 3.45 (m_C, 1H, 1-H), 1.93–1.84 (m, 2H, 2-H_A, 14-H_A), 1.73–1.58 (m, 4H, 4-H, 5-H_A, 8-H_A, 13-H), 1.51–1.40 (m, 4H, 2-H_B, 3-H_A, 5-H_B, *O*H), 1.34–1.23 (m, 3H, 3-H_B, 7-H, 14-H_B), 1.14 (s, 9H, 12-H), 1.05 (s, 9H, 18-H), 1.04–0.99 (m, 1H, 8-H_B), 0.85 (d, $^3J_{16/13}$ = 6.8 Hz, 3H, 16-H), 0.68 (s, 3H, 10-H) ppm.

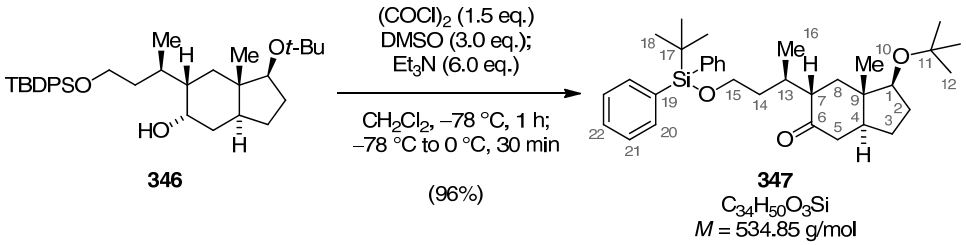
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 135.8 (C-20)*, 134.0 (C-19), 129.7 (C-22), 127.8 (C-21)*, 80.8 (C-1), 72.4 (C-11), 67.9 (C-6), 62.5 (C-15), 42.8 (C-9), 42.1 (C-7), 37.5 (C-4), 37.1 (C-14), 36.2 (C-8), 33.7 (C-5), 31.5 (C-2), 3.1 (C-13), 28.9 (C-12), 27.1 (C-18), 25.6 (C-3), 19.3 (C-17), 18.2 (C-16), 11.0 (C-10) ppm.

ESI-MS for $C_{34}H_{53}O_3Si^+$ [$(M+H)^+$]: calcd. 537.3758
found 537.3761.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 3480 (br w), 3071 (w), 2981 (s), 2932 (s), 1472 (w), 1428 (w), 1389 (w), 1361 (w), 1197 (w), 1112 (m), 1086 (m), 1063 (m), 702 (m).

$[\alpha]_D^{20}$ = +22.8 (*c* 0.50, CH_2Cl_2).

Synthesis of Ketone 347



To a solution of DMSO (120 µL, 1.68 mmol, 3.0 eq.) in CH_2Cl_2 (15 mL) at –78 °C was added $(COCl)_2$ (420 µL of a 2.0M solution in CH_2Cl_2, 840 µmol, 1.5 eq.) within 5 min and the mixture was stirred for 15 min. Then, a solution of alcohol **346** (300 mg, 560 µmol, 1.0 eq.) in CH_2Cl_2 (3 mL) was added slowly and the mixture was stirred for an additional 45 min prior to adding Et_3N (470 µL, 3.36 mmol, 6.0 eq.). The cold bath was replaced with an ice/water bath and the mixture was stirred at 0 °C for 30 min. The reaction was quenched by addition of H_2O (20 mL) and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were washed with saturated aqueous NaCl (15 mL), and were dried over $MgSO_4$. Having evaporated the

solvents under reduced pressure, the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 16:1) to yield ketone **347** as a colorless oil.
Purification was carried out combined with a smaller reaction batch. Overall, alcohol **346** (320 mg, 596 μmol) was converted to ketone **347** (305 mg, 571 μmol) in 96% yield.

R_f = 0.47 (hexanes:EtOAc = 7:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.69–7.63 (m, 4H, 20-H)*, 7.43–7.40 (m, 2H, 22-H), 7.40–7.35 (m, 4H, 21-H)*, 3.69–3.62 (m, 2H, 15-H), 3.45 (m_C, 1H, 1-H), 2.40 (m_C, 1H, 13-H), 2.01–1.95 (m, 3H, 5-H, 7-H), 2.01–1.95 (m, 1H, 2-H_A), 1.82 (dd, $^2J_{8A/8B}$ = 12.4 Hz, $^3J_{8A/7}$ = 6.4 Hz, 1H, 8-H_A), 1.67–1.52 (m, 3H, 2-H_B, 3-H_A, 4-H), 1.51–1.47 (m, 2H, 14-H), 1.40–1.36 (m, 1H, 3-H_B), 1.20–1.14 (m, 1H, 8-H_B), 1.15 (s, 9H, 12-H), 1.04 (s, 9H, 18-H), 0.89 (s, 3H, 10-H), 0.76 (d, $^3J_{16/13}$ = 6.8 Hz, 3H, 16-H) ppm.

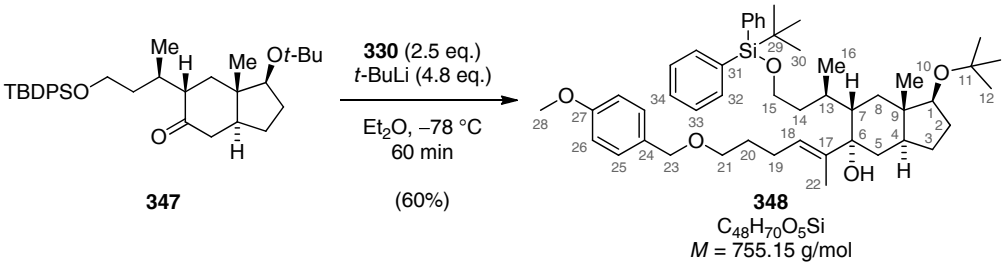
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 212.1 (C-6), 135.7 (C-20)*, 134.1 (C-19), 129.7 (C-22), 127.7 (C-21)*, 80.0 (C-1), 72.7 (C-11), 62.5 (C-15), 49.2 (C-7), 44.7 (C-4), 43.2 (C-5), 42.3 (C-9), 37.2 (C-14), 35.8 (C-8), 31.8 (C-2), 28.9 (C-12), 27.8 (C-13), 27.1 (C-18), 25.9 (C-3), 19.3 (C-17), 16.4 (C-16), 11.2 (C-10) ppm.

EI-MS for $C_{33}H_{47}O_3Si^+$ [$(M–Me)^+$]: calcd. 519.3289
found 519.3283.

IR (ATR): $\tilde{\nu}/cm^{-1}$ = 3072 (w), 2960 (s), 2931 (s), 2859 (s), 1705 (s), 1472 (m), 1428 (m), 1389 (w), 1362 (m), 1253 (w), 1192 (m), 1109 (s), 1061 (s), 899 (w), 738 (w), 701 (s).

$[\alpha]_D^{20}$ = +14.4 (*c* 1.00, CH_2Cl_2).

Synthesis of Alcohol 348



To a solution of vinyl iodide **330** (494 mg, 2.74 mmol, 2.5 eq.) in Et_2O (15 mL) at –78 °C was added *t*-BuLi (1.61 mL of a 1.7M solution in pentane, 1.43 mmol, 4.8 eq.) and the resulting solution was

stirred for 30 min at this temperature. Then, a solution of ketone **347** (305 mg, 571 μmol, 1.0 eq.) in Et_2O (4 mL) was added dropwise and the mixture was stirred for 60 min prior to quenching the reaction by addition of saturated aqueous NH_4Cl (10 mL). The mixture was allowed to warm to room temperature and was diluted with H_2O (10 mL) and Et_2O (15 mL). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 12:1 to 7:1) to yield alcohol **348** (260 mg, 345 μmol, 60%) as a colorless oil and single isomer.

R_f = 0.29 (hexanes:EtOAc = 7:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.67–7.63 (m, 4H, 32-H)*, 7.42–7.38 (m, 2H, 34-H), 7.38–7.34 (m, 4H, 33-H)*, 7.24 (m_C, 2H, 25-H), 6.86 (m_C, 2H, 26-H), 5.54 (m_C, 1H, 18-H), 4.40 (m_C, 2H, 23-H), 3.79 (s, 3H, 28-H), 3.65–3.58 (m, 2H, 15-H), 3.49 (dd, $^3J_{1/2}$ = 9.0, 7.4 Hz, 1H, 1-H), 3.40 (t, $^3J_{21/20}$ = 6.5 Hz, 2H, 21-H), 2.14–2.02 (m, 2H, 19-H), 1.95–1.88 (m, 1H, 2-H_A), 1.83–1.77 (m, 1H, 13-H), 1.76–1.59 (m, 5H, 4-H, 5-H_A, 7-H, 20-H), 1.55 (s, 3H, 22-H), 1.51–1.36 (m, 5H, 2-H_B, 3-H_A, 8-H_A, 14-H), 1.30–1.20 (m, 2H, 3-H_B, 8-H_B), 1.15 (s, 9H, 12-H), 1.09–1.01 (m, 1H, 5-H_B), 1.03 (s, 9H, 30-H), 0.77 (d, $^3J_{16/13}$ = 6.9 Hz, 3H, 16-H), 0.71 (s, 3H, 10-H) ppm.

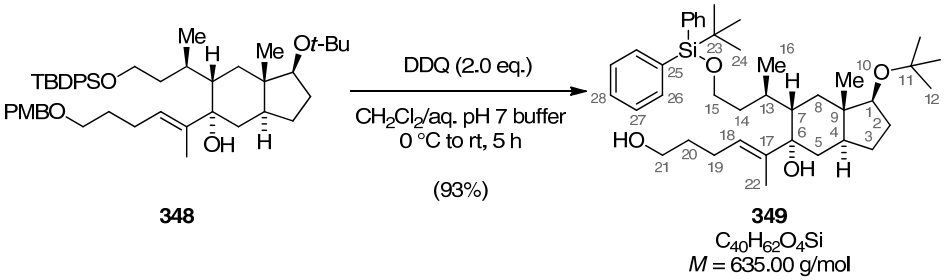
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 159.2 (C-27), 141.3 (C-17), 135.7 (C-32)*, 134.2 (C-31), 130.9 (C-24), 129.7 (C-34), 129.4 (C-25), 127.7 (C-33)*, 122.6 (C-18), 113.9 (C-26), 80.9 (C-1), 80.1 (C-6), 72.7 (C-23), 72.4 (C-11), 69.8 (C-21), 62.4 (C-15), 55.4 (C-28), 42.6 (C-9), 40.6 (C-14), 40.4 (C-7), 39.3 (C-4), 39.1 (C-5), 33.0 (C-8), 31.5 (C-2), 29.9 (C-20), 28.9 (C-12), 27.8 (C-13), 27.0 (C-30), 25.8 (C-3), 24.7 (C-19), 19.3 (C-29), 16.4 (C-16), 13.6 (C-22), 11.0 (C-10) ppm.

ESI-MS for $C_{48}H_{74}O_5NSi^+$ [$(M+NH_4)^+$]: calcd. 772.5331
found 772.5330.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 3481 (br w), 3071 (w), 2933 (s), 2858 (s), 1513 (w), 1302 (w), 1248 (m), 1196 (w), 1111 (m), 1093 (m), 1063 (w), 823 (w), 703 (w).

$[\alpha]_D^{20}$ = +16.8 (*c* 0.33, CH_2Cl_2).

Synthesis of Diol 349



348 **349**

$C_{40}H_{62}O_4Si$

M = 635.00 g/mol

To a solution of PMB ether **348** (260 mg, 345 μmol, 1.0 eq.) in CH_2Cl_2 (24 mL) and aqueous pH 7 buffer (3 mL) at 0 °C was added DDQ (157 mg, 690 μmol, 2.0 eq.) in one portion. The biphasic mixture was allowed to warm to room temperature and was stirred for an additional 5 h prior to filtering over a pad of Celite® (washings with CH_2Cl_2, ca. 50 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (3 x 20 mL) and the combined aqueous layers were re-extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with H_2O (20 mL) and saturated aqueous NaCl (20 mL), and were dried over $MgSO_4$. Having evaporated the solvents under reduced pressure, the crude product was purified by flash column chromatography (silica, CH_2Cl_2:MeOH = 50:1) to yield diol **349** (204 mg, 321 μmol, 93%) as a colorless foam.

R_f = 0.39 (hexanes:EtOAc = 7:3).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.66–7.62 (m, 4H, 26-H)*, 7.43–7.38 (m, 2H, 28-H), 7.38–7.34 (m, 4H, 27-H)*, 5.56 (m_C, 1H, 18-H), 3.65–3.55 (m, 4H, 15-H, 21-H), 3.48 (dd, $^3J_{1/2}$ = 9.0, 7.3 Hz, 1H, 1-H), 2.12–2.00 (m, 2H, 19-H), 1.93–1.87 (m, 1H, 2-H_A), 1.83–1.77 (m, 1H, 13-H), 1.76–1.69 (m, 2H, 4-H, 5-H_A) 1.66 (m_C, 1H, 7-H) 1.59 (m_C, 2H, 20-H), 1.56 (s, 3H, 22-H), 1.51–1.35 (m, 5H, 2-H_B, 3-H_A, 8-H_A, 14-H), 1.29–1.19 (m, 3H, 3-H_B, 8-H_B, *O*H), 1.14 (s, 9H, 12-H), 1.10–1.07 (m, 1H, 5-H_B), 1.03 (s, 9H, 30-H), 0.77 (d, $^3J_{16/13}$ = 6.9 Hz, 3H, 16-H), 0.71 (s, 3H, 10-H) ppm.

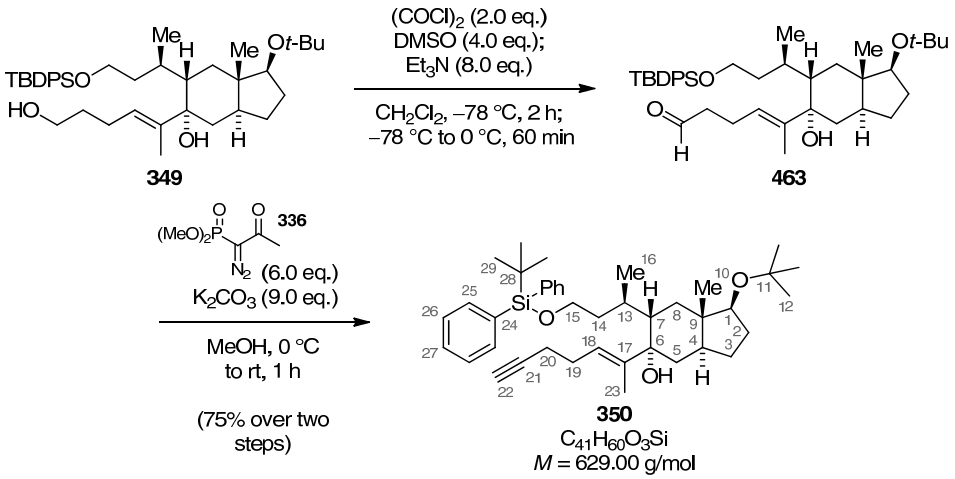
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 141.5 (C-17), 136.7 (C-26)*, 134.2 (C-25), 129.7 (C-28), 122.7 (C-27)*, 122.4 (C-18), 80.9 (C-1), 80.1 (C-6), 72.4 (C-11), 62.8 (C-21), 62.4 (C-15), 42.6 (C-9), 40.6 (C-14), 40.5 (C-7), 39.3 (C-4), 39.1 (C-5), 33.0 (C-8), 32.8 (C-20), 31.5 (C-2), 28.9 (C-12), 27.8 (C-13), 27.0 (C-24), 25.8 (C-3), 24.3 (C-19), 19.3 (C-23), 16.4 (C-16), 13.6 (C-22), 11.0 (C-10) ppm.

ESI-MS for $C_{40}H_{62}O_4NaSi^+$ [$(M+Na)^+$]: calcd. 657.4310
found 657.4307.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 3433 (br m), 3071 (w), 2932 (s), 2859 (s), 1472 (w), 1428 (w), 1389 (w), 1362 (w), 1196 (w), 1112 (m), 1092 (m), 1062 (w), 901 (w), 824 (w).

$[\alpha]_D^{20}$ = +9.2 (*c* 0.50, CH_2Cl_2).

Synthesis of Alkyne 350



To a solution of DMSO (87 µL, 1.2 mmol, 4.0 eq.) in CH_2Cl_2 (7 mL) at –78 °C was added dropwise $(COCl)_2$ (310 µL of a 2.0M solution in CH_2Cl_2, 620 µmol, 2.0 eq.) and the mixture was stirred for 20 min. Then, a solution of diol **349** (195 mg, 308 µmol, 1.0 eq.) in CH_2Cl_2 (3 mL) was added within 5 min and the reaction was stirred for an additional 2 h at –78 °C. After addition of Et_3N (343 µL, 2.46 mmol, 8.0 eq.), the cold bath was replaced by an ice/water bath and the mixture was stirred for 60 min. The reaction mixture was partitioned between H_2O (10 mL) and CH_2Cl_2 (15 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with saturated aqueous NaCl (20 mL) and dried over $MgSO_4$. The solvents were removed under reduced pressure and the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 5:1) to yield aldehyde **463** (176 mg, 278 µmol, 91%, R_f = 0.48, hexanes:EtOAc = 4:1) as a light yellow oil, which was immediately used in the next step.

To a solution of aldehyde **463** (176 mg, 278 µmol, 1.0 eq.) in MeOH (7 mL) at 0 °C was sequentially added K_2CO_3 (345 mg, 2.50 mmol, 9.0 eq.) and a solution of Ohira-Bestmann reagent (**336**, 320 mg, 1.67 mmol, 6.0 eq.) in MeOH (3 mL). The mixture was allowed to warm to room temperature and was stirred for 4 h prior to being diluted with H_2O (10 mL). The biphasic mixture was extracted with Et_2O (5 x 20 mL) and the combined organic layers were washed with saturated aqueous NaCl (15 mL), and dried over $MgSO_4$. The solvents were removed under reduced pressure and the crude product was purified by flash column chromatography (silica, *n*-pentane:Et_2O = 16:1 to 12:1) to yield alkyne **350** (141 mg, 230 µmol, 75% over two steps) as a colorless oil.

R_f = 0.53 (hexanes:EtOAc = 7:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.67–7.63 (m, 4H, 26-H)*, 7.44–7.40 (m, 2H, 27-H), 7.40–7.35 (m, 4H, 25-H)*, 5.60 (m_C, 1H, 18-H), 3.65–3.56 (m, 2H, 15-H), 3.49 (m_C, 1H, 1-H), 2.29–2.15 (m, 4H, 19-H, 20-H), 1.95–1.89 (m, 1H, 2-H_A), 1.87 (t, $^4J_{22/20}$ = 2.4 Hz, 1H, 22-H), 1.82 (m_C, 1H, 13-H), 1.77–1.69 (m, 2H, 4-H, 5-H_A), 1.67 (m_C, 1H, 7-H), 1.58 (s, 3H, 23-H), 1.50–1.38 (m, 5H, 2-H_B, 3-H_A, 8-H_A, 14-H), 1.33–1.19 (m, 2H, 3-H_B, 8-H_B), 1.15 (s, 9H, 12-H), 1.11 (m_C, 1H, 5-H_B), 1.04 (s, 9H, 29-H), 0.78 (d, $^3J_{16/13}$ = 7.0 Hz, 3H, 16-H), 0.72 (s, 3H, 10-H) ppm.

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 142.5 (C-17), 135.7 (C-25)*, 134.2 (C-24), 129.7 (C-27), 127.7 (C-26)*, 121.3 (C-18), 84.5 (C-21), 80.9 (C-1), 80.1 (C-6), 72.4 (C-11), 68.4 (C-22), 62.4 (C-15), 42.6 (C-9), 40.6 (C-14), 40.4 (C-7), 39.3 (C-4), 39.1 (C-5), 33.0 (C-8), 31.5 (C-2), 28.9 (C-12), 27.8 (C-13), 27.3 (C-19), 27.0 (C-29), 25.8 (C-3), 19.3 (C-28), 19.0 (C-20), 16.4 (C-16), 13.7 (C-23), 11.0 (C-10) ppm.

ESI-MS for $C_{42}H_{61}O_5Si^-$ [(M+HCOO)$^-$]: calcd. 673.4294
found 673.4304.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 3311 (w), 3072 (w), 2957 (s), 2931 (s), 2857 (m), 1472 (w), 1428 (w), 1389 (w), 1362 (w), 1259 (w), 1196 (w), 1111 (m), 1063 (w), 738 (w), 702 (w).

$[\alpha]_D^{20}$ = +7.0 (*c* 0.25, CH_2Cl_2).

Synthesis of Vinyl Iodide 357

356 (94%) **357**
$C_{10}H_{21}IOSi$
M = 312.26 g/mol

To a solution of vinyl iodide **356**[238] (700 mg, 3.53 mmol, 1.0 eq.) in DMF (7 mL) was added imidazole (626 mg, 9.20 mmol, 2.6 eq.) and Et_3SiCl (770 µL, 4.60 mmol, 1.3 eq.). The mixture was stirred for 2 h at room temperature before the reaction was quenched by addition of H_2O (7 mL). The mixture was diluted with *n*-pentane (15 mL), the phases were separated and the aqueous layer was extracted with *n*-pentane (3 x 15 mL). The combined organic layers were washed with 10% aqueous NaCl (2 x 10 mL) and dried over $MgSO_4$. Having evaporated the solvents under reduced pressure, the crude product was purified by flash column chromatography (silica, *n*-pentane:Et_2O = 1:0 to 30:1) to yield vinyl iodide **357** (1.04 g, 3.33 mmol, 94%) as a colorless liquid.

R_f = 0.47 (hexanes:EtOAc = 30:1).

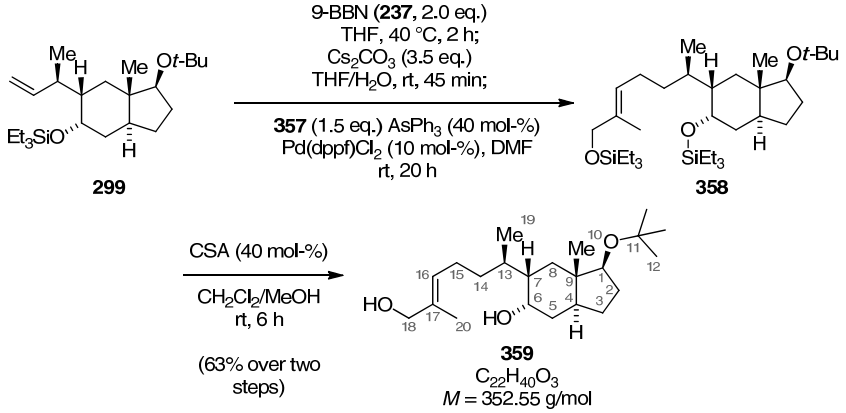
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.24–6.21 (m, 1H, 1-H), 4.11 (m_C, 2H, 3-H), 1.79 (m_C, 3H, 4-H), 1.00–0.93 (m, 9H, 6-H), 0.66–0.56 (m, 6H, 5-H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 146.9 (C-2), 76.2 (C-1), 66.9 (C-3), 21.3 (C-4), 6.9 (C-6), 4.6 (C-5) ppm.

EI-MS for $C_{10}H_{21}IOSi^+$ [M^+]: calcd. 312.0401
found 312.0406.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 2955 (s), 2910 (s), 2876 (s), 1458 (w), 1413 (w), 1377 (w), 1280 (w), 1250 (w), 1143 (w), 1106 (m), 1007 (w), 815 (w), 744 (w).

Synthesis of Diol 359



To a solution of alkene **299** (624 mg, 1.58 mmol, 1.0 eq.) in THF (9.5 mL) was added 9-BBN (**237**, 6.35 mL of a 0.5M solution in THF, 3.16 mmol, 2.0 eq.) and the resulting mixture was stirred at 40 °C for 3 h. The solution was cooled to 0 °C and degassed aqueous Cs_2CO_3 (3N, 1.9 mL, 5.53 mmol, 3.5 eq.) was added. The mixture was stirred vigorously for 45 min at room temperature and a solution of vinyl iodide **357** (740 mg, 2.37 mmol, 1.5 eq.) and $AsPh_3$ (193 mg, 632 μmol, 40 mol-%) in degassed DMF (15.8 mL) was added. The mixture was degassed (N_2 bubbling for 5 min) and Pd(dppf)Cl_2 (complex with CH_2Cl_2, 128 mg, 158 μmol, 10 mol-%) was added. The reaction mixture was stirred for 20 h at room temperature and was then diluted with H_2O (20 mL) and Et_2O (20 mL). The layers were separated and the aqueous layer was extracted with Et_2O (4 x 20 mL). The combined organic layers were washed with 10% aqueous NaCl (3 x 20 mL) and the aqueous layers were re-extracted with Et_2O (2 x 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 100:1 to 60:1) to yield bissilyl ether **358** (R_f = 0.2,

hexanes:EtOAc = 30:1, 700 mg, ~1.21 mmol, ~77%) as a yellow liquid, which was contaminated by some impurities and used without further purification in the next step.

To a solution of crude bissilyl ether **358** (700 mg, 1.21 mmol, 1.0 eq.) in CH_2Cl_2/MeOH (5:1, 24 mL) was added (1*R*)-(−)-camphorsulfonic acid (112 mg, 480 μmol, 40 mol-%) and the solution was stirred for 6 h at room temperature. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (15 mL) and the aqueous layer was extracted with CH_2Cl_2 (4 x 15 mL). The combined organic layers were washed with saturated aqueous NaCl (20 mL) and dried over $MgSO_4$. Having evaporated the solvents under reduced pressure, the crude product was purified by flash column chromatography (silica, CH_2Cl_2:MeOH = 100:1 to 50:1) to yield diol **359** (350 mg, 994 μmol, 63% over two steps) as a pale yellow highly viscous oil.

R_f = 0.19 (hexanes:EtOAc = 7:3).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 5.42 (m_C, 1H, 16-H), 4.09 (m_C, 1H, 6-H), 3.99 (s, 2H, 18-H), 3.44 (dd, $^3J_{1/2}$ = 8.8, 7.5 Hz, 1H, 1-H), 2.15–2.05 (m, 1H, 15-H_A), 2.04–1.96 (m, 1H, 15-H_B), 1.95–1.85 (m, 1H, 2-H_A), 1.70–1.56 (m, 4H, 4-H, 5-H_A, 8-H_A, 14-H_A), 1.67 (s, 3H, 20-H), 1.54–1.30 (m, 7H, 2-H_B, 3-H_A, 7-H, 13-H, 14-H_B, *O*H), 1.30–1.18 (m, 2H, 3-H_B, 5-H_B), 1.13 (s, 9H, 12-H), 1.02 (dd, $^2J_{8A/8B}$ = $^3J_{8A/7}$ = 12.7 Hz, 1H, 8-H_A), 0.92 (d, $^3J_{19/13}$ = 6.7 Hz, 3H, 19-H), 0.71 (s, 3H, 10-H) ppm.

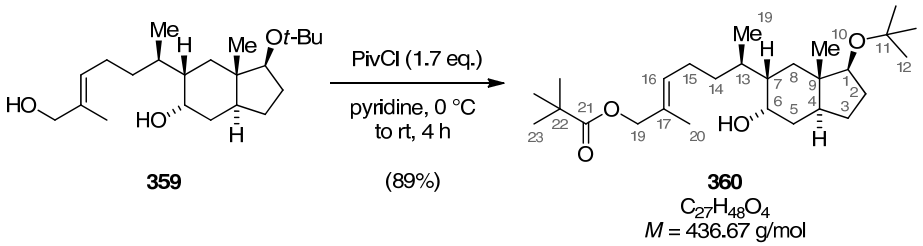
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 134.9 (C-17), 126.8 (C-16), 80.8 (C-1), 72.4 (C-11), 69.2 (C-18), 68.3 (C-6), 42.8 (C-9), 42.0 (C-7), 37.6 (C-4), 36.0 (C-8), 34.3 (C-5), 34.1 (C-14), 33.7 (C-13), 31.4 (C-2), 28.9 (C-12), 25.6 (C-3), 25.1 (C-15), 17.6 (C-19), 13.9 (C-20), 11.0 (C-10) ppm.

EI-MS for $C_{22}H_{38}O_2^+$ [$(M-H_2O)^+$]: calcd. 334.2866
found 334.2875.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 3360 (br s), 2973 (s), 2930 (s), 2871 (s), 1461 (w), 1388 (w), 1361 (w), 1197 (w), 1128 (w), 1063 (w), 1007 (w).

$[\alpha]_D^{20}$ = +33.9 (*c* 0.50, CH_2Cl_2).

Synthesis of Alcohol 360



359 (89%) **360**

$C_{27}H_{48}O_4$

M = 436.67 g/mol

To a solution of diol **359** (358 mg, 1.02 mmol, 1.0 eq.) in pyridine (10 mL) at 0 °C was added PivCl (213 µL, 1.73 mmol, 1.7 eq.). The mixture was allowed to warm to room temperature and was stirred for 4 h prior to being diluted with CH_2Cl_2 (60 mL). The solution was washed with HCl (2N, 2 x 25 mL) and the combined aqueous layers were re-extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were washed with saturated aqueous NaCl (20 mL) and dried over $MgSO_4$. After evaporation of the solvents under reduced pressure, purification of the crude product by flash column chromatography (silica, hexanes:EtOAc = 10:1) afforded alcohol **360** (394 mg, 904 µmol, 89%) as a colorless oil.

R_f = 0.19 (hexanes:EtOAc = 10:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 5.44 (m_C, 1H, 16-H), 4.44 (s, 2H, 18-H), 4.08 (m_C, 1H, 6-H), 3.44 (m_C, 1H, 1-H), 2.15–2.07 (m, 1H, 15-H_A), 2.04–1.96 (m, 1H, 15-H_B), 1.95–1.87 (m, 1H, 2-H_A), 1.72–1.56 (m, 4H, 4-H, 5-H_A, 8-H_A, 14-H_A), 1.64 (s, 3H, 20-H), 1.55–1.36 (m, 4H, 2-H_B, 3-H_A, 13-H, 14-H_B*), 1.36–1.32 (m, 1H, 7-H), 1.32–1.18 (m, 2H, 3-H_B, 5-H_B*), 1.21 (s, 9H, 23-H), 1.14 (s, 9H, 12-H), 1.03 (dd, $^2J_{8A/8B} = {}^3J_{8A/7}$ = 12.7 Hz, 1H, 8-H_A), 0.92 (d, $^3J_{19/13}$ = 6.7 Hz, 3H, 19-H), 0.71 (s, 3H, 10-H) ppm.

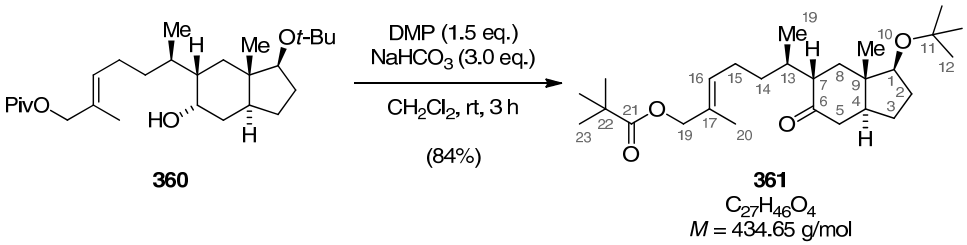
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 178.6 (C-21), 130.3 (C-17), 129.5 (C-16), 80.8 (C-1), 72.4 (C-11), 70.2 (C-18), 68.3 (C-6), 42.9 (C-9), 42.0 (C-7), 39.0 (C-22), 37.5 (C-4), 35.9 (C-8), 34.2 (C-5)*, 34.1 (C-14)*, 33.8 (C-13), 31.4 (C-2), 28.9 (C-12), 27.4 (C-23), 25.6 (C-3), 25.2 (C-15), 17.6 (C-19), 14.0 (C-20), 11.0 (C-10) ppm.

ESI-MS for $C_{27}H_{48}O_4Na^+$ [$(M+Na)^+$]: calcd. 459.3445
found 459.3444.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 3520 (br w), 2972 (s), 2933 (s), 2873 (m), 1730 (m), 1480 (w), 1461 (w), 1388 (w), 1362 (w), 1284 (w), 1197 (w), 1156 (m), 1063 (w).

$[\alpha]_D^{20}$ = +27.0 (c 1.00, CH_2Cl_2).

Synthesis of Ketone 361



360 **361**

$C_{27}H_{46}O_4$

M = 434.65 g/mol

To a suspension of alcohol **360** (390 mg, 894 µmol, 1.0 eq.) and $NaHCO_3$ (225 mg, 2.68 mmol, 3.0 eq.) in CH_2Cl_2 (15 mL) was added DMP (568 mg, 1.34 mmol, 1.5 eq.) in one portion. The resulting mixture was stirred for 3 h at room temperature prior to quenching the reaction by addition of saturated aqueous $NaHCO_3$/saturated aqueous $Na_2S_2O_3/H_2O$ (1:1:1, 10 mL). The biphasic mixture was stirred vigorously at room temperature until two clear layers were obtained. The mixture was then diluted with CH_2Cl_2 (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with saturated aqueous NaCl (20 mL) and were dried over $MgSO_4$. Having evaporated the solvents under reduced pressure, the crude product was purified by flash column chromatography (silica, *n*-pentane:Et_2O = 8:1 to 4:1) to yield ketone **361** (326 mg, 751 µmol, 84%) as a colorless oil.

R_f = 0.19 (hexanes:EtOAc = 10:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 5.44 (m_C, 1H, 16-H), 4.44 (s, 2H, 18-H), 3.47 (dd, $^3J_{1/2}$ = 9.0, 7.7 Hz, 1H, 1-H), 2.37–2.19 (m, 4H, 5-H, 7-H, 13-H), 2.08–1.94 (m, 3H, 2-H_A, 15-H), 1.87 (dd, $^2J_{8A/8B}$ = 12.6 Hz, $^3J_{8A/7}$ = 6.5 Hz, 1H, 8-H_A), 1.68–1.50 (m, 3H, 2-H_B, 3-H_A, 4-H), 1.63 (s, 3H, 20-H), 1.43–1.35 (m, 1H, 3-H_B), 1.26 (m_C, 2H, 14-H), 1.22–1.16 (m, 1H, 8-H_B), 1.21 (s, 9H, 23-H), 1.15 (s, 9H, 12-H), 0.97 (s, 3H, 10-H), 0.79 (d, $^3J_{19/13}$ = 6.8 Hz, 3H, 19-H) ppm.

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 212.4 (C-6), 178.5 (C-21), 130.5 (C-17), 129.0 (C-16), 80.0 (C-1), 72.7 (C-11), 70.1 (C-18), 49.4 (C-7), 44.6 (C-4), 43.2 (C-5), 42.3 (C-9), 39.0 (C-22), 35.7 (C-8), 34.4 (C-14), 31.9 (C-2), 30.8 (C-13), 28.9 (C-12), 27.5 (C-23), 26.0 (C-15)*, 25.9 (C-3)*, 16.0 (C-14), 13.9 (C-20), 11.2 (C-10) ppm.

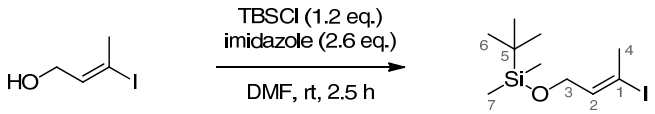
ESI-MS for $C_{27}H_{46}O_4Na^+$ [$(M+Na)^+$]: calcd. 457.3288

found 457.3287.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 2970 (s), 2933 (s), 2872 (s), 1727 (s), 1705 (s), 1479 (w), 1460 (w), 1389 (w), 1362 (m), 1282 (m), 1192 (m), 1151 (s), 1061 (m), 1031 (w), 901 (w).

$[\alpha]_D^{20}$ = +6.0 (*c* 0.50, CH_2Cl_2).

Synthesis of Vinyl Iodide 364



363 (88%) **364**
$C_{10}H_{21}IOSi$
M = 312.26 g/mol

To a solution of alcohol **363**[240] (297 mg, 1.50 mmol, 1.0 eq.) in DMF (3 mL) was consecutively added imidazole (265 mg, 3.90 mmol, 2.6 eq.) and TBSCl (271 mg, 1.80 mmol, 1.2 eq.), and the mixture was stirred for 2.5 h at room temperature. The reaction was quenched by addition of H_2O (7 mL) and the mixture was diluted with *n*-pentane (15 mL). The phases were separated and the aqueous layer was extracted with *n*-pentane (3 x 10 mL). The combined organic layers were washed with 10% aqueous NaCl (2 x 7 mL) and dried over $MgSO_4$. Having evaporated the solvents under reduced pressure, the crude product was purified by flash column chromatography (silica, *n*-pentane:Et_2O = 1:0 to 30:1) to yield vinyl iodide **364** (413 mg, 1.32 mmol, 88%) as a pale yellow liquid.

The double bond configuration was verified to be (*E*) by 2D NOESY experiments indicating a proximity between 3-H and 4-H.

R_f = 0.43 (hexanes:EtOAc = 30:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 6.29 (tq, $^3J_{2/3}$ = 6.5 Hz, $^4J_{2/4}$ = 1.4 Hz, 1H, 2-H), 4.12 (d, $^3J_{3/2}$ = 6.4 Hz, 2H, 3-H), 2.41 (br s, 3H, 4-H), 0.90 (s, 9H, 6-H), 0.07 (s, 6H, 7-H) ppm.

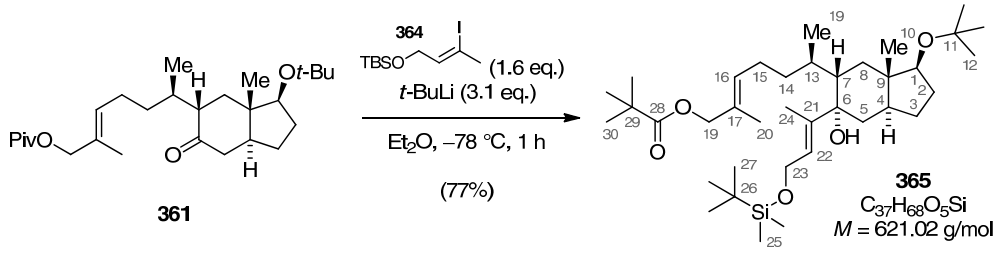
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 140.8 (C-2), 96.1 (C-1), 60.8 (C-3), 28.2 (C-4), 26.0 (C-6), 18.5 (C-5), –5.1 (C-7) ppm.

EI-MS for $C_{10}H_{21}IOSi^+$ [M^+]:	calcd.	312.0401
	found	312.0382.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 2954 (s), 2929 (s), 2885 (m), 2857 (s), 1472 (w), 1463 (w), 1380 (w), 1256 (m), 1089 (s), 1042 (m), 836 (s), 776 (m).

The analytical data matched those reported previously.[241]

Synthesis of Alcohol 365



To a solution of vinyl iodide **364** (350 mg, 1.12 mmol, 1.6 eq.) in Et_2O (7 mL) at −78 °C was slowly added *t*-BuLi (1.27 mL of a 1.7M solution in pentane, 2.16 mmol, 3.1 eq.) and the mixture was stirred for 30 min at this temperature. The thus obtained solution of the corresponding vinyl lithium species was added dropwise *via* cannula to a solution of ketone **361** (318 mg, 696 μmol, 1.0 eq.) in Et_2O (14 mL) at −78 °C. The mixture was stirred for an additional 2 h and the reaction was quenched by addition of half-saturated aqueous NH_4Cl (25 mL). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 25 mL). The combined organic layers were washed with saturated aqueous NaCl (15 mL) and dried over $MgSO_4$. Having evaporated the solvents under reduced pressure, the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 30:1) to yield tertiary alcohol **365** (330 mg, 539 μmol, 77%) as a colorless oil and single isomer.

R_f = 0.14 (hexanes:EtOAc = 16:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 5.73 (m_C, 1H, 22-H), 5.41 (m_C, 1H, 16-H), 4.43 (s, 2H, 18-H), 4.27 (m_C, 2H, 23-H), 3.50 (dd, $^3J_{1/2}$ = 9.0, 7.5 Hz, 1H, 1-H), 1.99–1.88 (m, 3H, 2-H_A, 15-H), 1.79–1.71 (m, 3H, 4-H, 5-H_A, 7-H), 1.68–1.53 (m, 1H, 13-H), 1.62 (s, 3H, 20-H), 1.60 (s, 3H, 24-H), 1.50–1.41 (m, 3H, 2-H_B, 3-H_B, 8-H_A), 1.31–1.18 (m, 4H, 3-H_B, 8-H_B, 14-H), 1.21 (s, 9H, 30-H), 1.18–1.10 (m, 1H, 5-H_B), 1.15 (s, 9H, 12-H), 1.09 (br s, 1H *O*H), 0.91 (s, 9H, 27-H), 0.85 (d, $^3J_{19/13}$ = 6.9 Hz, 3H, 19-H), 0.75 (s, 3H, 10-H), 0.08 (s, 6H, 25-H) ppm.

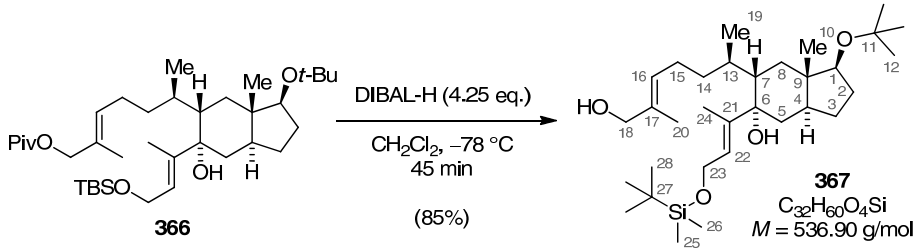
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 178.5 (C-28), 141.6 (C-21), 130.3 (C-17), 129.4 (C-16), 124.1 (C-22), 80.9 (C-1), 79.9 (C-6), 72.4 (C-11), 70.2 (C-18), 60.9 (C-23), 42.6 (C-9), 39.8 (C-7), 39.2 (C-29)*, 39.0 (C-4)*, 38.8 (C-5), 37.4, (C-14), 32.9 (C-8), 31.5 (2C, C-2, C-13), 28.9 (C-12), 27.4 (C-30), 26.2 (C-27), 26.1 (C-15), 25.8 (C-3), 18.5 (C-26), 16.7, (C-19), 13.9 (C-20), 13.8 (C-24), 11.1 (C-10), –4.9 (C-25) ppm.

ESI-MS for $C_{37}H_{72}O_5NSi^+$ [$(M+NH_4)^+$]: calcd. 638.5174
found 638.5173.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 3529 (br w), 2956 (s), 2932 (s), 2878 (m), 1730 (m), 1462 (w), 1388 (w), 1283 (w), 1254 (w), 1196 (w), 1155 (m), 1062 (m), 836 (w).

$[\alpha]_D^{20}$ = +19.8 (*c* 0.50, CH_2Cl_2).

Synthesis of Diol 366



To a solution of pivalate **365** (330 mg, 531 μmol, 1.0 eq.) in CH_2Cl_2 (25 mL) at –78 °C was slowly added DIBAL-H (1.86 mL of a 1.0M solution in toluene, 1.86 mmol, 3.5 eq.) and the resulting mixture was stirred for 30 min. Due to incomplete conversion, another aliquot of DIBAL-H (400 μL of a 1.0M solution in toluene, 400 μmol, 0.75 eq.) was added and the mixture was stirred for an additional 15 min. The reaction was quenched by addition of half-saturated aqueous Rochelle salt (25 mL) and the biphasic mixture was vigorously stirred at room temperature for 2 h. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 20 mL). The combined organic layers were washed with saturated aqueous NaCl (20 mL) and were dried over $MgSO_4$, Having evaporated the solvents under reduced pressure, the crude product was purified by flash column chromatography (silica, *n*-pentane:Et_2O = 4:1) to yield diol **366** (241 mg, 449 μmol, 85%) as a colorless oil.

R_f = 0.42 (hexanes:EtOAc = 4:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 5.72 (m_C, 1H, 22-H), 5.37 (m_C, 1H, 16-H), 4.27 (m_C, 2H, 23-H), 3.98 (m_C, 2H, 18-H), 3.50 (dd, $^3J_{1/2}$ = 9.0, 7.4 Hz, 1H, 1-H), 1.98–1.89 (m, 3H, 2-H_A, 15-H), 1.79–1.70 (m, 3H, 4-H, 5-H_A, 7-H), 1.65 (s, 3H, 20-H), 1.64–1.59 (m, 1H, 13-H), 1.60 (s, 3H, 24-H), 1.50–1.41 (m, 4H, 2-H_B, 3-H_B, 8-H_A *O*H), 1.32–1.17 (m, 5H, 3-H_B, 8-H_B, 14-H, *O*H), 1.17–1.10 (m, 1H, 5-H_B), 1.15 (s, 9H, 12-H), 0.91 (s, 9H, 28-H), 0.85 (d, $^3J_{19/13}$ = 6.8 Hz, 3H, 19-H), 0.75 (s, 3H, 10-H), 0.08(2) (s, 3H, 25-H)*, 0.08(0) (s, 3H, 26-H)* ppm.

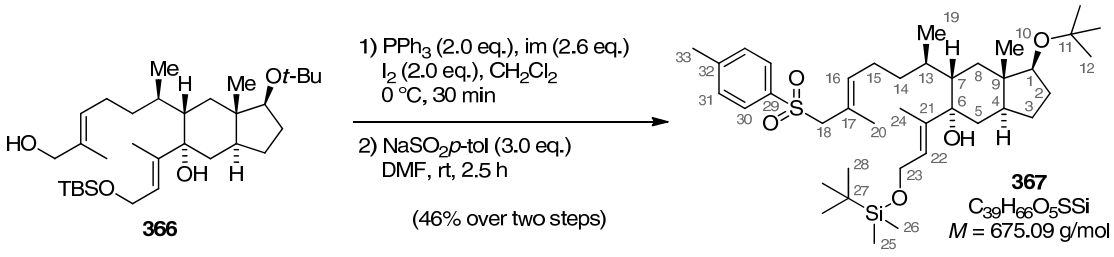
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 141.7 (C-21), 134.8 (C-17), 126.5 (C-16), 124.0 (C-22), 80.9 (C-1), 79.9 (C-6), 72.4 (C-11), 69.1 (C-18), 61.0 (C-23), 42.6 (C-9), 39.8 (C-7), 39.2 (C-4), 38.8 (C-5), 37.6 (C-14), 32.9 (C-8), 31.5 (C-2), 31.2 (C-13), 28.9 (C-12), 26.2 (C-28), 25.8 (2C, C-3, C-15), 18.6 (C-27), 16.7 (C-19), 13.8 (2C, C-20, C-24), 11.0 (C-10), –4.8 (C-25)*, –4.9 (C-26)* ppm.

ESI-MS for $C_{32}H_{60}O_4NaSi^+$ [$(M+Na)^+$]: calcd. 559.4153
found 559.4152.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 3410 (br m), 2954 (s), 2931 (s), 2858 (s), 1472 (w), 1463 (w), 1388 (w), 1362 (w), 1255 (w), 1196 (w), 1062 (m), 836 (w) 776 (w).

$[\alpha]_D^{20}$ = +18.4 (*c* 0.50, CH_2Cl_2).

Synthesis of Sulfone 367



To a solution of diol **366** (14 mg, 26 µmol, 1.0 eq.) in CH_2Cl_2 at 0 °C was sequentially added imidazole (4.6 mg, 68 µmol, 2.6 eq.), PPh_3 (14 mg, 52 µmol, 2.0 eq.) and I_2 (13 mg, 52 µmol, 2.0 eq.) and the reaction was stirred for 30 min. The mixture was diluted with *n*-pentane (10 mL) and filtered over a short plug of silica (eluted with *n*-pentane:Et_2O = 4:1). The product containing fractions were carefully evaporated under reduced pressure (water bath temperature: 30 °C) to yield an intermediate allylic iodide (R_f = 0.68, hexanes:EtOAc = 7:1) which was used without further purification.

To a solution of crude allylic iodide (assumed 26 µmol, 1.0 eq.) in DMF (2 mL) was added $NaSO_2p$-tol (14 mg, 78 µmol, 3.0 eq.) in one portion and the mixture was stirred for 2.5 h in the dark. The reaction was quenched by addition of H_2O (3 mL) and the biphasic mixture was extracted with Et_2O (4 x 5 mL). The combined organic layers were washed with 10% aqueous NaCl (3 x 3 mL) and dried over $MgSO_4$. The solvents were removed under reduced pressure and the crude product was purified by flash column chromatography (silica, *n*-pentane:Et_2O = 7:1 to 5:1) to yield allylic sulfone **367** (8 mg, 12 µmol, 46% over two steps) as a colorless oil.

The product was contaminated by ca. 25% of an unknown impurity. Based on the ^{13}C NMR spectrum, this compound is presumably a diastereomer, the structure of which needs to be elucidated in future experiments.

R_f = 0.53 (hexanes:EtOAc = 4:1).

^{1}H NMR ($CDCl_3$, 600 MHz, major isomer quoted): δ = 7.72 (m_C, 2H), 7.33 (m_C, 2H), 5.71 (m_C, 1H) 5.09 (m_C, 1H), 4.26 (m_C, 2H), 3.76 (s, 2H), 3.50 (dd, J = 9.0, 7.4 Hz, 1H), 2.45 (s, 3H), 1.99–1.80 (m, 3H), 1.78–1.64 (m, 6H), 1.63–1.33 (m, 7H), 1.29–1.22 (m, 2H), 1.18–1.08 (m, 1H), 1.16 (s, 9H), 1.06 (br s, 1H), 1.03–0.97 (m, 2H), 0.90 (s, 9H), 0.80 (d, J = 6.8 Hz, 3H), 0.75 (s, 3H), 0.07 (s, 6H) ppm.

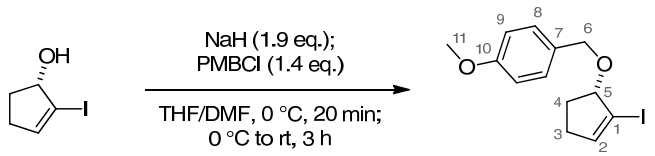
^{13}C NMR ($CDCl_3$, 150 MHz, major isomer quoted): δ = 144.5 (C_q), 141.5 (C_q), 136.5 (CH), 135.7 (C_q), 129.6 (CH), 128.7 (CH), 124.1 (CH), 123.3 (C_q), 80.9 (CH), 79.8 (C_q), 72.5 (C_q), 66.5 (CH_2), 60.9 (CH_2), 42.6 (C_q), 39.8 (CH), 39.1 (CH), 38.8 (CH_2), 37.0 (CH_2), 32.9 (CH_2), 31.6 (CH_2)*, 31.5 (CH)*, 29.0 (CH_3), 26.9 (CH_2), 26.2 (CH_3), 25.8 (CH_2), 21.8 (CH_3), 18.5 (C_q), 16.8 (CH_3), 16.6 (CH_3), 13.8 (CH_3), 11.1 (CH_3), –4.8(5) (CH_3), –4.9(0) (CH_3) ppm.

ESI-MS for $C_{39}H_{70}O_5NSSi^+$ [$(M+NH_4)^+$]: calcd. 692.4738
found 692.4733.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 3518 (br w), 2951 (s), 2857 (m), 1463 (w), 1361 (w), 1315 (w), 1256 (w), 1197 (w), 1132 (w), 1088 (w), 1062 (w), 835 (w).

Since the product had been obtained as a mixture of isomers, the specific optical rotation was not determined.

Synthesis of Vinyl Iodide 378



377 **378**
$C_{13}H_{15}IO_2$
M = 330.16 g/mol

To a solution of vinyl iodide **377**[249] (630 mg, 3.00 mmol, 1.0 eq.) in THF/DMF (2:1, 12 mL) at 0 °C was added NaH (60% in mineral oil, 228 mg, 5.70 mmol, 1.9 eq.) in one portion and the resulting suspension was stirred for 20 min at this temperature. Then, PMBCl (560 µL, 4.13 mmol, 1.4 eq.) was slowly added and the mixture was allowed to warm to room temperature. After stirring for an additional 3 h, the reaction was carefully quenched with saturated aqueous NH_4Cl (15 mL) and the biphasic mixture was stirred for 30 min prior to diluting with H_2O (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic layers were sequentially washed with saturated aqueous $CuSO_4$ (10 mL), saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous NaCl (10 mL), and dried over $MgSO_4$. After evaporation of the solvents under

reduced pressure, the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 20:1) to yield vinyl iodide **378** (810 mg, 2.46 mmol, 82%) as a colorless oil.

R_f = 0.58 (hexanes:EtOAc = 4:1).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.34 (m_C, 2H, 8-H), 6.89 (m_C, 2H, 9-H), 6.35 (m_C, 1H, 2-H), 4.58–4.49 (m, 3H, 5-H, 6-H), 3.81 (s, 3H, 11-H), 2.54–2.43 (m, 1H, 3-H_A), 2.34–2.10 (m, 2H, 3-H_B, 4-H_A), 2.00–1.89 (m, 1H, 4-H_B) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 159.4 (C-10), 143.7 (C-2), 130.6 (C-7), 129.6 (C-8), 113.8 (C-9), 96.7 (C-1), 88.2 (C-5), 70.5 (C-6), 55.4 (C-11), 33.1 (C-3), 29.1 (C-4) ppm.

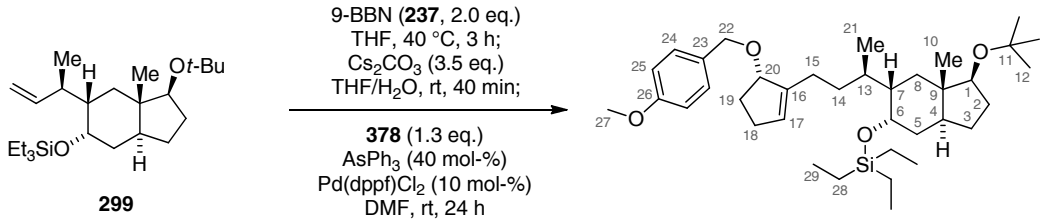
EI-MS for $C_{13}H_{15}IO_2^+$ [M^+]: calcd. 330.0111
found 330.0113.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 2998 (w), 2934 (m), 2848 (m), 1612 (m), 1586 (w), 1512 (s), 1463 (w), 1339 (w), 1302 (w), 1245 (s), 1172 (m), 1158 (w), 1075 (m), 1034 (s), 922 (w), 889 (w), 821 (m).

$[\alpha]_D^{20}$ = +2.2 (*c* 1.00, $CHCl_3$).

The analytical data matched those reported previously.[251]

Synthesis of PMB Ether 379



379
$C_{37}H_{62}O_4Si$
M = 598.97 g/mol

To a solution of alkene **299** (600 mg, 1.50 mmol, 1.0 eq.) in THF (9 mL) was added 9-BBN (**237**, 6.00 mL of 0.5M solution in THF, 3.00 mmol, 2.0 eq.) and the resulting solution was heated to 40 °C for 3 h. The mixture was cooled to 0 °C and degassed aqueous Cs_2CO_3 (3N, 1.75 mL, 5.25 mmol, 3.5 eq.) was added. The reaction was stirred vigorously at room temperature for 40 min prior to adding a solution of vinyl iodide **378** (643 mg, 1.95 mmol, 1.3 eq.) and $AsPh_3$ (184 mg, 600 μmol, 40 mol-%) in degassed DMF (15 mL). The reaction mixture was degassed (N_2 bubbling) and Pd(dppf)Cl_2

(complex with CH_2Cl_2, 122 mg, 150 μmol, 10 mol-%) was added in one portion. The mixture was stirred for 24 h, at which time the reaction was partitioned between H_2O (20 mL) and Et_2O (30 mL). The aqueous layer was extracted with Et_2O (3 x 30 mL), the combined organic layers were washed with 10% aqueous NaCl (2 x 30 mL) and saturated aqueous NaCl (30 mL), and dried over $MgSO_4$. Having evaporated the solvents under reduced pressure, the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 50:1) to yield silyl ether **379** (793 mg, 1.32 mmol, 88%) as a colorless oil.

R_f = 0.34 (hexanes:EtOAc = 16:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.28 (m_C, 2H, 24-H), 6.87 (m_C, 2H, 25-H), 5.56 (m_C, 1H, 17-H), 4.50 (d, $^2J_{22A/22B}$ = 11.3 Hz, 1H, 22-H_A), 4.48 (m_C, 1H, 20-H), 4.38 (d, $^2J_{22B/22A}$ = 11.3 Hz, 1H, 22-H_B), 4.02 (m_C, 1H, 6-H), 3.80 (s, 3H, 27-H), 3.42 (dd, $^3J_{1/2}$ = 8.9, 7.5 Hz, 1H, 1-H), 2.45–2.39 (m, 1H, 18-H_A), 2.23–2.17 (m, 1H, 18-H_B), 2.17–2.04 (m, 3H, 15-H, 19-H_A), 1.94–1.83 (m, 2H, 2-H_A, 19-H_B), 1.73 (m_C, 1H, 4-H), 1.60–1.47 (m, 4H, 5-H_A, 8-H_A, 13-H, 14-H_A), 1.47–1.35 (m, 3H, 2-H_B, 3-H_A, 5-H_B), 1.32–1.21 (m, 3H, 3-H_B, 7-H, 14-H_B), 1.15 (s, 9H, 12-H), 1.10 (dd, $^2J_{8B/8A}$ = $^3J_{8B/7}$ = 12.5 Hz, 1H, 8-H_B), 0.95 (t, $^3J_{29/28}$ = 8.0 Hz, 9H, 29-H), 0.87 (d, $^3J_{21/13}$ = 6.8 Hz, 3H, 21-H), 0.69 (s, 3H, 10-H), 0.62–0.52 (m, 6H, 28-H) ppm.

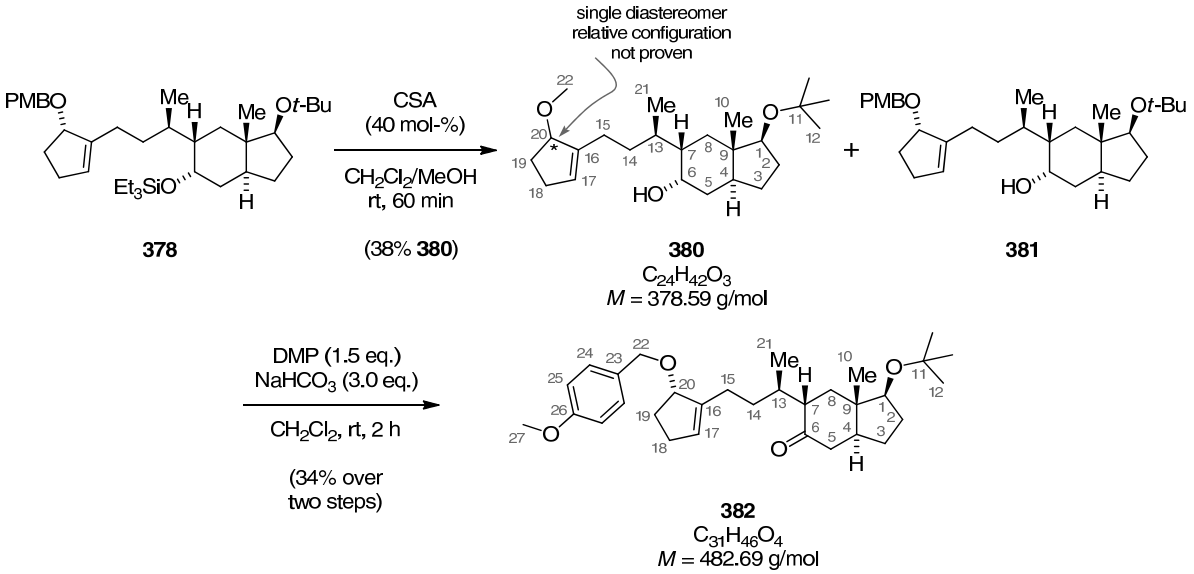
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 159.2 (C-26), 145.4 (C-16), 131.4 (C-23), 129.3 (C-24), 127.4 (C-17), 113.8 (C-25), 85.0 (C-20), 81.0 (C-1), 72.3 (C-11), 70.0 (2C, C-6, C-22), 55.4 (C-27), 42.7 (C-9), 42.5 (C-7), 37.4 (C-4), 35.4 (C-8), 34.7 (C-5), 34.2 (C-13), 33.3 (C-14), 31.6 (C-2), 30.3 (C-18), 30.0 (C-19), 29.0 (C-12), 25.9 (C-15), 25.5 (C-3), 17.2 (C-21), 11.1 (C-10), 7.2 (C-29), 5.5 (C-28) ppm.

ESI-MS for $C_{37}H_{62}O_4NaSi^+$ [$(M+Na)^+$]: calcd. 621.4310
found 621.4314.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 2952 (s), 2933 (s), 2911 (s), 2874 (s), 1612 (w), 1513 (m), 1462 (w), 1361 (w), 1247 (m), 1195 (w), 1062 (m), 1042 (m), 976 (w), 798 (w), 741 (w)

$[\alpha]_D^{20}$ = +36.6 (*c* 0.50, CH_2Cl_2).

Synthesis of Ketone 382 and Methyl Ether 380



378 (38% **380**) **380** **381**

$C_{24}H_{42}O_3$
M = 378.59 g/mol

382
$C_{31}H_{46}O_4$
M = 482.69 g/mol

To a solution of silyl ether **378** (710 mg, 1.18 mmol, 1.0 eq.) in CH_2Cl_2/MeOH (3:1, 20 mL) was added (1*R*)-(−)-camphorsulfonic acid (110 mg, 470 µmol, 40 mol-%) in one portion and the mixture was stirred for 1 h prior to being partitioned between saturated aqueous $NaHCO_3$ (20 mL) and CH_2Cl_2 (20 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with saturated aqueous NaCl (20 mL) and were dried over $MgSO_4$. Having evaporated the solvents under reduced pressure, the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 8:1) to yield methyl ether **380** (172 mg, 454 µmol, 38%) along with PMB ether **381** (R_f = 0.43, hexanes:EtOAc = 4:1, 264 mg, 540 µmol, 46%), which was immediately used in the next step.

To a suspension of crude alcohol **381** (264 mg, 540 µmol, 1.0 eq.) and $NaHCO_3$ (136 mg, 1.62 mmol, 3.0 eq.) in CH_2Cl_2 (10 mL) was added DMP (343 mg, 810 µmol, 1.5 eq.) in one portion and the mixture was stirred for 2 h at room temperature. The reaction was quenched by addition of saturated aqueous $Na_2S_2O_3$/saturated aqueous $NaHCO_3$/H_2O (1:1:1, 10 mL) and the biphasic mixture was stirred vigorously for 30 min. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with saturated aqueous NaCl (10 mL), dried over $MgSO_4$ and the solvents were evaporated under reduced pressure. Purification by flash column chromatography (silica, pentane:Et_2O = 5:1) yielded ketone **382** (195 mg, 405 µmol, 34% over two steps) as a colorless oil.

R_f = 0.59 (hexanes:EtOAc = 4:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.26 (m_C, 2H, 24-H), 6.87 (m_C, 2H, 25-H), 5.58 (m_C, 1H, 17-H), 4.51 (d, $^2J_{22A/22B}$ = 11.3 Hz, 1H, 22-H_A), 4.46 (m_C, 1H, 20-H), 4.36 (d, $^2J_{22B/22A}$ = 11.5 Hz, 1H, 22-H_B), 3.80 (s, 3H, 27-H), 3.45 (dd, $^3J_{1/2}$ = 8.9, 7.8 Hz, 1H, 1-H), 2.42 (m_C, 1H, 18-H_A), 2.34–2.28 (m, 2H,

5-H_A, 7-H), 2.28–2.05 (m, 6H, 5-H_B, 13-H, 15-H, 18-H_B, 19-H_A), 2.02–1.95 (m, 1H, 2-H_A), 1.89–1.81 (m, 2H, 8-H_A, 19-H_B), 1.67–1.53 (m, 3H, 2-H_B, 3-H_A, 4-H), 1.44–1.32 (m, 3H, 3-H_B, 14-H), 1.22–1.12 (m, 1H, 8-H_B), 1.15 (s, 9H, 12-H), 0.96 (s, 3H, 10-H), 0.79 (d, $^3J_{21/13}$ = 6.8 Hz, 3H, 21-H) ppm.

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 212.5 (C-6), 159.2 (C-26), 144.6 (C-16), 131.3 (C-23), 129.3 (C-24), 127.9 (C-17), 113.9 (C-25), 85.1 (C-20), 80.0 (C-1), 72.7 (C-11), 70.2 (C-22), 55.4 (C-27), 49.6 (C-7), 44.7 (C-4), 43.3 (C-5), 42.3 (C-9), 35.8 (C-8), 32.6 (C-14), 31.9 (C-2), 31.0 (C-13), 30.3 (C-18), 30.0 (C-19), 28.9 (C-12), 26.6 (C-15), 25.9 (C-3), 16.0 (C-21), 11.2 (C-10) ppm.

ESI-MS for $C_{31}H_{46}O_4Na^+$ [$(M+Na)^+$]: calcd. 505.3288
found 505.3287.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 2970 (s), 2931 (s), 2854 (m), 1704 (m), 1612 (s), 1513 (m), 1462 (w), 1361 (w), 1301 (w), 1248 (m), 1192 (w), 1062 (m), 1038 (w), 820 (w).

$[\alpha]_D^{20}$ = +15.6 (*c* 0.50, CH_2Cl_2).

Methyl ether **380** was obtained as colorless oil and as a single diastereomer. The relative configuration at C-20 could not be assigned by 2D NMR spectroscopy.

R_f = 0.48 (hexanes:EtOAc = 4:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 5.59 (m_C, 1H, 17-H), 4.27 (m_C, 1H, 20-H), 4.08 (ddd, $^3J_{6/5A}$ = $^3J_{6/5B}$ = $^3J_{6/7}$ = 2.8 Hz, 1H, 6-H), 3.45 (dd, $^3J_{1/2}$ = 8.8, 7.4 Hz, 1H, 1-H), 3.30 (s, 3H, 22-H), 2.44–2.37 (m, 1H, 18-H_A), 2.28–2.14 (m, 3H, 15-H, 18-H_B), 2.13–2.07 (m, 1H, 19-H_A), 1.97–1.85 (m, 2H, 2-H_A, 14-H_A), 1.80 (m_C, 1H, 19-H_B), 1.73–1.60 (m, 3H, 4-H, 5-H_A, 8-H_A), 1.53–1.38 (m, 4H, 2-H_B, 3-H_A, 5-H_B, 13-H), 1.32–1.21 (m, 2H, 3-H_B, 7-H), 1.19–1.07 (m, 1H, 14-H_B), 1.13 (s, 9H, 12-H), 1.00 (m_C, 1H, 8-H_B), 0.89 (d, $^3J_{21/13}$ = 6.7 Hz, 3H, 21-H), 0.70 (s, 3H, 10-H) ppm.

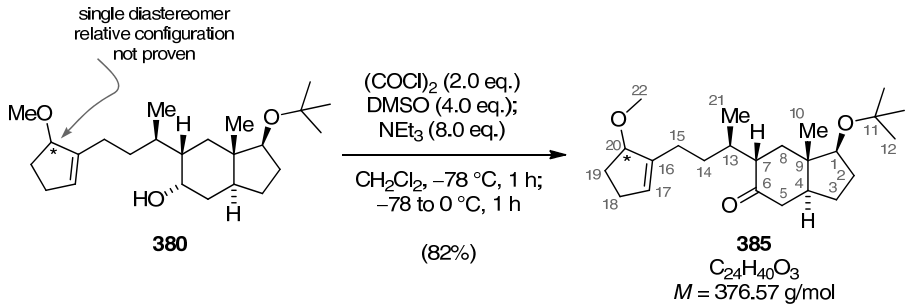
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 143.4 (C-16), 129.9 (C-17), 89.1 (C-20), 80.9 (C-1), 72.3 (C-11), 67.2 (C-6), 56.3 (C-22), 42.8 (C-9), 42.4 (C-7), 37.5 (C-4), 36.4 (C-8), 33.5 (C-5), 32.4 (C-13), 31.7 (C-14), 31.5 (C-2), 30.1 (C-18), 29.7 (C-19), 28.9 (C-12), 26.8 (C-15), 25.6 (C-3), 17.2 (C-21), 11.0 (C-10) ppm.

EI-MS for $C_{24}H_{42}O_3^+$ [M^+]: calcd. 378.3128
found 378.3120.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 3462 (br m), 2971 (s), 2929 (s), 2870 (s), 1461 (w), 1387 (w), 1361 (m), 1253 (w), 1196 (m), 1127 (w), 1062 (m), 1025 (w), 1008 (w).

$[\alpha]_D^{20}$ = +32.6 (*c* 0.50, CH_2Cl_2).

Synthesis of Ketone 385



To a solution of DMSO (97.0 µL, 1.38 mmol, 4.0 eq.) in CH_2Cl_2 (5 mL) at −78 °C was added dropwise $(COCl)_2$ (344 µL of a 2.0M solution in CH_2Cl_2, 688 µmol, 2.0 eq.) and the mixture was stirred for 30 min prior to adding slowly a solution of alcohol **380** (130 mg, 344 µmol, 1.0 eq.) in CH_2Cl_2 (1 mL). The reaction was stirred for an additional 1 h at −78 °C and Et_3N (380 µL, 2.75 mmol, 8.0 eq.) was added in one portion. The cold bath was replaced by an ice/water bath and the mixture was stirred for 1 h at 0 °C. The reaction was partitioned between H_2O (5 mL) and CH_2Cl_2 (5 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL), and the combined organic layers were washed with saturated aqueous NaCl (5 mL) and dried over $MgSO_4$. Having evaporated the solvents under reduced pressure, the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 8:1) to yield ketone **385** (106 mg, 281 µmol, 82%) as a colorless oil.

R_f = 0.59 (hexanes:EtOAc = 4:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 5.56 (m_C, 1H, 17-H), 4.30 (m_C, 1H, 20-H), 3.47 (m_C, 1H, 1-H), 3.30 (s, 3H, 22-H), 2.43–2.34 (m, 2H, 7-H 18-H_A), 2.31 (dd, $^2J_{5A/5B}$ = 14.9 Hz, $^3J_{5A/4}$ = 4.9 Hz, 1H, 5-H_A), 2.29–2.07 (m, 5H, 5-H_B, 13-H, 15-H_A, 18-H_B, 19-H_A), 2.04–1.95 (m, 2H, 2-H_A, 15-H_B), 1.88 (dd, $^2J_{8A/8B}$ = 12.8 Hz, $^3J_{8A/7}$ = 6.3 Hz, 1H, 8-H_A), 1.78 (m_C, 1H, 19-H_B), 1.68–1.54 (m, 3H, 2-H_B, 3-H_A, 4-H), 1.45–1.32 (m, 3H, 3-H_B, 14-H), 1.19 (m_C, 1H, 8-H_B), 1.15 (s, 9H, 12-H), 0.97 (s, 3H, 10-H), 0.89 (d, $^3J_{21/13}$ = 6.6 Hz, 3H, 21-H) ppm.

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 212.5 (C-6), 144.5 (C-16), 127.7 (C-17), 87.3 (C-20), 80.0 (C-1), 72.7 (C-11), 55.9 (C-22), 49.0 (C-7), 44.6 (C-4), 43.3 (C-5), 42.2 (C-9), 35.4 (C-8), 32.6 (C-14), 31.9 (C-2), 30.9 (C-13), 30.2 (C-18), 29.3 (C-19), 28.9 (C-12), 26.5 (C-15), 25.9 (C-3), 16.2 (C-21), 11.2 (C-10) ppm.

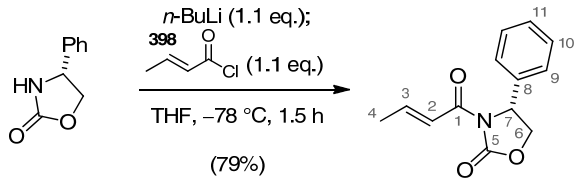
EI-MS for $C_{24}H_{40}O_3^+$ [M^+]: calcd. 376.2972
found 376.2971.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 3376 (br w), 2969 (s), 2931 (s), 2873 (m), 1704 (s), 1461 (w), 1388 (w), 1361 (m), 1251 (w), 1192 (m), 1103 (w), 1061 (m), 1026 (w).

$[\alpha]_D^{20}$ = +1.6 (*c* 0.50, CH_2Cl_2).

2.3 Experimental Procedures for Chapter 4: 'Synthetic Studies toward Nitiol'

Synthesis of Oxazolidinone 399



397 **399**
$C_{13}H_{13}NO_3$
M = 231.25 g/mol

To a solution of Evans auxiliary **397**[264] (4.71 g, 28.9 mmol, 1.0 eq.) in THF (120 mL) at –78 °C was added dropwise *n*-BuLi (12.7 mL of a 2.5M solution in hexanes, 31.8 mmol, 1.1 eq.) and the mixture was stirred for 30 min at this temperature before adding dropwise a solution of crotonyl chloride (**398**, 3.04 mL, 31.8 mmol, 1.1 eq.) in THF (10 mL). The mixture was stirred for an additional 60 min at –78 °C and was allowed to warm to 0 °C. The reaction was quenched by addition of saturated aqueous NH_4Cl (15 mL) and the mixture was freed of THF under reduced pressure. The resulting suspension was partitioned between Et_2O (100 mL) and H_2O (30 mL) and the layers were separated. The aqueous phase was extracted with Et_2O (30 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 x 30 mL) and saturated aqueous NaCl (30 mL). Having dried the organic layer over Na_2SO_4 and evaporated the solvents under reduced pressure, the crude product was purified by flash column chromatography (hexanes:EtOAc = 5:1 to 1:1) to yield oxazolidinone **399** (5.16 g, 22.3 mmol, 78%) as a pale yellow solid.

R_f = 0.50 (hexanes:EtOAc = 7:3).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.41–7.24 (m, 6H, 2-H, 9-H, 10-H, 11-H), 7.09 (dq, $^3J_{2/3}$ = 15.3 Hz, $^3J_{3/4}$ = 6.8 Hz, 1H, 3-H), 5.48 (dd, $^3J_{7/6A}$ = 8.7 Hz, $^3J_{7/6B}$ = 3.8 Hz, 1H, 7-H), 4.69 (dd, $^2J_{6A/6B}$ = $^3J_{6A/6B}$ = 8.8 Hz, 1H, 6-H_A), 4.27 (dd, $^2J_{6B/6A}$ = 8.9 Hz, $^3J_{6B/7}$ = 3.9 Hz, 1H, 6-H_B), 1.93 (dd, $^3J_{4/3}$ = 6.9 Hz, $^4J_{4/2}$ = 1.6 Hz, 3H, 4-H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 164.4 (C-1), 153.8 (C-5), 147.4 (C-3), 139.2 (C-8), 129.3 (C-10), 128.7 (C-11), 126.1 (C-9), 121.8 (C-2), 70.1 (C-7), 57.8 (C-6), 18.6 (C-4) ppm.

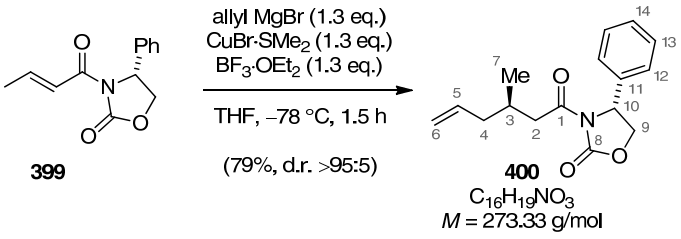
ESI-MS for $C_{13}H_{13}NNaO_3^+$ [$(M+Na)^+$]: calcd. 254.0788
found 254.0788.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 3034 (w), 2977 (w), 1774 (s), 1618 (w), 1495 (w), 1338 (m), 1234 (m), 1197 (m), 1126 (w), 1024 (w), 968 (w), 924 (w), 830 (w), 762 (w).

$[\alpha]_D^{20}$ = –113.6 (*c* 1.00, $CHCl_3$).

The analytical data matched those reported previously.[265]

Synthesis of Michael Adduct 400



To a slurry of $CuBr{\cdot}SMe_2$ (115 mg, 560 µmol, 1.3 eq.) in THF (5 mL) at –40 °C was added allylmagnesium bromide (560 µL mL of a 1.0M solution in Et_2O, 560 µmol, 1.3 eq.) within 10 min. The solution was stirred for an additional 30 min at this temperature before being cooled to –78 °C. To the resulting black reaction mixture was sequentially added $BF_3{\cdot}OEt_2$ (70 µL, mmol, 1.3 eq.) and a solution of oxazolidinone **399** (100 mg, 430 µmol, 1.0 eq.) in THF (2 mL). The mixture was stirred for an additional 90 min and the reaction was quenched by addition of saturated aqueous NH_4Cl (5 mL). The biphasic mixture was diluted with Et_2O (5 mL), filtered over a pad of Celite® and the layers were separated. The aqueous layer was extracted with Et_2O (4 x 5 mL) and the combined organic layers were dried over $MgSO_4$. The solvents were removed under reduced pressure and the crude product

was purified by flash column chromatography (hexanes:EtOAc = 5:1) to yield oxazolidinone **400** (93 mg, 0.34 mmol, 79%, d.r. > 95:5) as a colorless solid.

R_f = 0.29 (hexanes:EtOAc = 4:1).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.43–7.26 (m, 5H, 12-H, 13-H, 14-H), 5.72 (m_C, 1H, 5-H), 5.43 (dd, $^3J_{10/9A}$ = 8.8 Hz, $^3J_{10/9B}$ = 3.8 Hz, 1H, 10-H), 5.01–4.93 (m, 2H, 6-H), 4.68 (dd, $^2J_{9A/9B}$ = $^3J_{9A/10}$ = 8.8 Hz, 1H, 9-H_A), 4.27 (dd, $^2J_{9B/9A}$ = 8.9 Hz, $^3J_{9B/10}$ = 3.8 Hz, 1H, 10-H_B), 2.99 (dd, $^2J_{2A/2B}$ = 16.5 Hz, $^3J_{2A/3}$ = 5.9 Hz, 1H, 2-H_A), 2.71 (dd, $^2J_{2B/2A}$ = 16.4 Hz, $^3J_{2B/3}$ = 8.2 Hz, 1H, 2-H_B), 2.16–1.93 (m, 3H, 3-H, 4-H), 0.88 (d, $^3J_{7/3}$ = 6.6 Hz, 3H, 7-H) ppm.

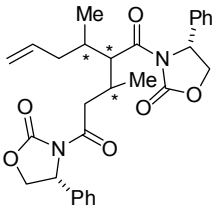
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 172.3 (C-1), 153.8 (C-8), 139.3 (C-11), 136.6 (C-5), 129.3 (C-13), 128.8 (C-14), 126.1 (C-12), 116.7 (C-6), 70.0 (C-10), 57.7 (C-9), 42.0 (C-2), 41.1 (C-4), 29.4 (C-3), 19.6 (C-7) ppm.

ESI-MS for $C_{16}H_{19}NNaO_3^+$ [$(M+Na)^+$]: calcd. 296.1257
found 296.1255.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 2962 (w), 2917 (w), 1778 (s), 1703 (m), 1495 (w), 1458 (w), 1384 (m), 1322 (m), 1196 (m), 1044 (w), 1001 (w), 916 (w), 762 (w), 710 (w).

$[\alpha]_D^{20}$ = –59.6 (*c* 0.50, $CHCl_3$), lit. for *ent*-**400**, $[\alpha]_D^{20}$ = +53.8 (*c* 2.12, $CHCl_3$).[263]

On a larger scale, the yield dropped dramatically. Beside recovered starting material, side product **401** was isolated in 10% yield as colorless foam, which was contaminated by some minor impurities. The relative stereochemistry of this single diastereomer could not be determined.



401
$C_{29}H_{32}N_2O_6$
M = 504.57 g/mol

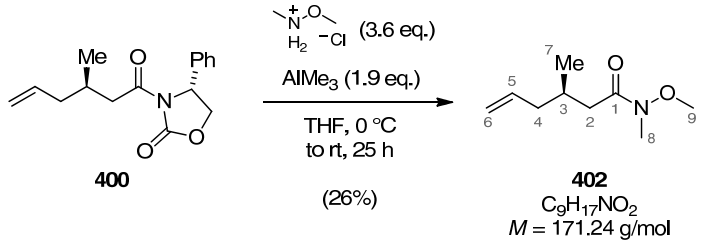
R_f = 0.09 (hexanes:EtOAc = 4:1).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.40–7.27 (m, 8H), 7.25–7.20 (m, 2H), 5.75 (m_C, 1H), 5.43 (dd, *J* = 8.6, 3.3 Hz, 1H), 5.32 (dd, *J* = 8.7, 3.8 Hz, 1H), 5.05–4.96 (m, 2H), 4.61 (m_C, 2H), 4.22 (dd, *J* = 8.9, 3.2 Hz, 1H), 4.20 (dd, *J* = 8.9, 3.9 Hz, 1H), 4.09 (t, *J* = 7.5 Hz, 1H), 2.81 (dd, *J* = 17.7, 10.3 Hz, 1H), 2.71 (dd, *J* = 17.8, 3.0 Hz, 1H), 2.49–2.41 (m, 1H), 2.33–2.25 (m, 1H), 2.01–1.94 (m, 1H), 1.91–1.83 (m, 1H), 0.92 (d, *J* = 6.3 Hz, 3H), 0.75 (d, *J* = 6.4 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 174.7 (C_q), 171.8 (C_q) 153.7 (C_q), 153.5 (C_q), 139.5 (C_q), 139.2 (C_q), 136.5 (CH), 129.2 (2C, CH), 128.7 (2C, CH), 126.3 (CH), 125.9 (CH), 116.6 (CH_2), 69.9 (CH_2), 69.5 (CH_2), 58.0 (CH), 57.7 (CH), 50.1 (CH), 38.9 (CH_2), 38.6 (CH_2), 33.1 (CH), 29.8 (CH), 17.8 (CH_3), 15.6 (CH_3) ppm.

ESI-MS for $C_{29}H_{33}N_2O_6^+$ [$(M+H)^+$]: calcd. 505.2339
found 505.2334.

Synthesis of Weinreb Amide 402



400 **402**
$C_9H_{17}NO_2$
M = 171.24 g/mol

To a suspension of (MeO)NHMe·HCl (92 mg, 0.94 mmol, 3.6 eq.) in THF (2.5 mL) at 0 °C was slowly added $AlMe_3$ (245 µL of a 2.0M solution in toluene, 490 µmol, 1.9 eq.) and the mixture was stirred for 1 h at room temperature. After cooling to 0 °C, a solution of oxazolidinone **400** (72 mg, 0.26 mmol, 1.0 eq.) in THF (2 mL) was added and the mixture was stirred for 30 min at 0 °C and an additional 16 h at room temperature. The reaction was quenched by addition of saturated aqueous Rochelle salt (4 mL) and the mixture was diluted with H_2O (2 mL) and CH_2Cl_2 (4 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were evaporated under reduced pressure. Purification of the obtained crude product by flash column chromatography (silica, hexanes:EtOAc = 4:1) yielded the desired Weinreb amide **402** (12 mg, 70 mmol, 26%) as a volatile colorless liquid.

R_f = 0.19 (hexanes:EtOAc = 4:1).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.78 (m_C, 1H, 5-H), 5.05–4.99 (m, 2H, 6-H), 3.67 (s, 3H, 9-H), 3.18 (s, 3H, 8-H), 2.42 (dd, $^2J_{2A/2B}$ = 15.0 Hz, $^3J_{2/3}$ = 5.4 Hz, 1H, 2-H_A), 2.28–2.05 (m, 3H, 2-H_B, 3-H, 4-H_A), 2.04–1.95 (m, 1H, 4-H_B), 0.95 (d, $^3J_{7/3}$ = 6.4 Hz, 3H, 7-H) ppm.

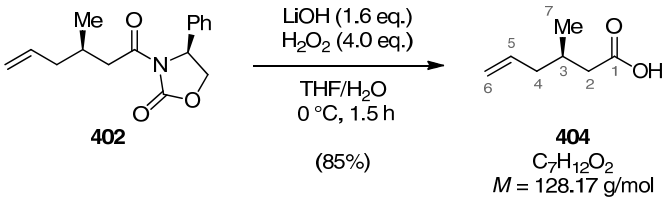
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 137.0 (C-5), 116.4 (C-6), 61.3 (C-9), 41.4 (C-4), 38.5 (C-2), 32.3 (br, C-8), 29.7 (C-3), 20.0 (C-7) ppm (C1 obscured).

FAB-MS for $C_9H_{18}NO_2^+$ [$(M+H)^+$]: calcd. 172.1338
found 172.1333.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 3093 (w), 2928 (w), 2873 (w), 1524 (s), 1481 (w), 1349 (s), 1266 (m), 1202 (w), 1041 (m), 919 (w), 893 (w).

$[\alpha]_D^{20} = -18.0$ (*c* 0.30, $CHCl_3$), Lit.: $[\alpha]_D^{20} = -13.1$ (*c* 0.23, $CHCl_3$).[266]

Synthesis of Carboxylic Acid 404



To a solution of oxazolidinone **403**[266] (400 mg, 1.46 mmol, 1.0 eq.) in THF/H_2O (4:1, 8 mL) at 0 °C was consecutively added H_2O_2 (30% in H_2O, 660 µL, 5.84 mmol, 4.0 eq.) and a solution of LiOH (56.0 mg, 2.34 mmol, 1.6 eq.) in H_2O (4 mL). The mixture was stirred for an additional 90 min at 0 °C before quenching the reaction by adding a solution of Na_2SO_3 (736 mg, 5.84 mmol, 4.0 eq.) in H_2O (6 mL). Most of the THF was removed under reduced pressure (water bath temperature: 30 °C) and the resulting basic phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were removed under reduced pressure to yield recovered Evans auxiliary.

The pH of the aqueous phase was adjusted at 0 °C to pH = 1 by addition of HCl (2N). The aqueous phase was extracted with CH_2Cl_2 (4 x 10 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was carefully removed under reduced pressure (water bath temperature: 30 °C) to yield acid **404** (159 mg, 1.24 mmol, 85%) as a colorless liquid judged to be pure by ^{1}H NMR spectroscopy.

R_f = 0.23 (hexanes:EtOAc = 10:1, 1% AcOH).

^{1}H NMR (CD_2Cl_2, 400 MHz): δ = 5.79 (m_C, 1H, 5-H), 5.06–5.00 (m, 2H, 6-H), 2.39 (dd, $^2J_{2A/2B}$ = 15.1 Hz, $^3J_{2A/3}$ = 5.3 Hz, 1H, 2-H_A), 2.18–2.00 (m, 4H, 2-H_B, 3-H, 4-H), 0.98 (d, $^3J_{7/3}$ = 6.6 Hz, 3H, 7-H) ppm.

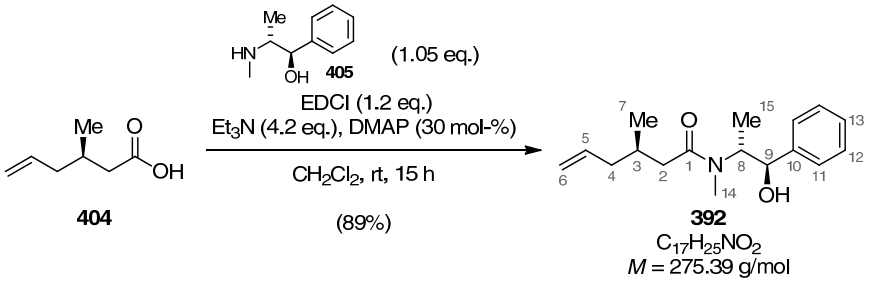
^{13}C NMR (CD_2Cl_2, 100 MHz): δ = 179.8 (C-1), 137.0 (C-5), 117.0 (C-6), 41.4 (C-4), 41.2 (C-2), 30.5 (C-3), 19.8 (C-7) ppm.

ESI-MS for $C_{14}H_{23}O_4^-$ [$(2M–H)^-$]: calcd. 255.1602
found 255.1610.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 3079 (w), 2962 (w), 1703 (s), 1642 (m), 1541 (w), 1411 (m), 1380 (w), 1284 (w), 1196 (m), 1032 (w), 995 (w), 913 (w).

$[\alpha]_D^{20}$ = +1.6 (*c* 0.53, $CHCl_3$), lit. for *ent*-**404**: $[\alpha]_D^{20}$ = –0.71 (*c* 1.13, $CHCl_3$),[269] –2.8 (*c* 1.00, $CHCl_3$).[262]

Synthesis of Western Fragment 392*



To a solution of acid **404** (100 mg, 780 µmol, 1.0 eq.), EDCI (180 mg, 940 µmol, 1.2 eq.), Et_3N (390 µL, 2.81 mmol, 4.2 eq.) and DMAP (20 mg, 0.160 mmol, 30 mol-%) in CH_2Cl_2 (7 mL) was added (1*R*,2*R*)-pseudoephedrine (**405**, 135 mg, 820 µmol, 1.05 eq.) and the mixture was stirred for 15 h at room temperature. The mixture was quenched by addition of saturated aqueous NH_4Cl (5 mL) and the aqueous phase was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were washed with saturated aqueous NaCl (5 mL), dried over Na_2SO_4 and the solvents were removed under reduced pressure. The crude product was purified by flash column chromatography (silica, CH_2Cl_2:MeOH = 97:3) to yield amide **392** (190 mg, 691 µmol, 89%) as a highly viscous colorless oil.

R_f = 0.23 (hexanes:EtOAc = 1:1).

^{1}H NMR ($CDCl_3$, 300 MHz, 3.6:1 mixture of rotamers, asterix denotes minor rotamer): δ = 7.41–7.22 (m, 5H, 11-H, 12-H, 13-H), 5.86–5.69 (m, 1H, 5-H), 5.10–4.93 (m, 2H, 6-H), 4.64–4.52 (m, 1H, 8-H), 4.51–4.38 (m, 1H, 9-H), 4.07–3.96 (m, 1H, 9-H)*, 2.91 (s, 3H, 14-H)*, 2.81 (s, 3H, 14-H), 2.49–1.87 (m, 5H, 2-H, 3-H, 4-H), 1.11 (d, $^3J_{15/8}$ = 7.1 Hz, 3H, 15-H), 0.98 (d, $^3J_{15/8}$ = 6.8 Hz, 3H, 15-H)*, 0.95 (d, $^3J_{7/3}$ = 5.8 Hz, 3H, 7-H)*, 0.94 (d, $^3J_{7/3}$ = 6.0 Hz, 3H, 7-H) ppm.

* The analytical data was obtained from a sample assumed to be >90% *ee* pure. This assumption is based on the fact that acid **404** had been prepared utilizing highly diastereomerically enriched oxazolidinone **400**.

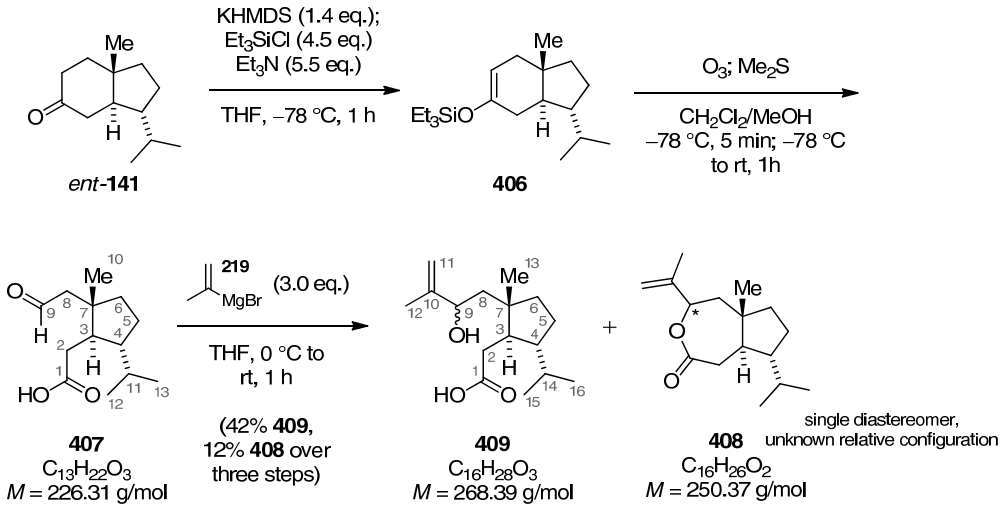
^{13}C NMR ($CDCl_3$, 75 MHz, asterix denotes minor rotamer): δ = 175.0 (C-1), 173.7 (C-1)*, 142.7 (C-10), 141.3 (C-10)*, 137.2 (C-5)*, 136.9 (C-5), 128.9 (C-11)*, 128.6 (C-13)*, 128.5 (C-11), 127.8 (C-13), 127.1 (C-12)*, 126.5 (C-12), 116.5 (C-6), 116.3 (C-6)*, 76.7 (C-9), 75.7 (C-9)*, 58.5 (C-8), 58.1 (C-8)*, 41.5 (C-4)*, 41.3 (C-4), 40.8 (C-2), 40.3 (C-2)*, 33.4 (C-14), 30.2 (C-3)*, 30.1 (C-3), 26.9 (C-14)*, 20.1 (C-7)*, 19.9 (C-7), 15.5 (C-15)*, 14.7 (C-15) ppm.

ESI-MS for $C_{17}H_{26}NO_2^+$ [$(M+H)^+$]: calcd. 276.1958
found 276.1956.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 3376 (br m), 3065 (w), 2972 (m), 2930 (m), 1617 (s), 1454 (m), 1405 (m), 1377 (w), 1260 (w), 1200 (w), 1111 (w), 1052 (w), 912 (w), 701 (w).

$[\alpha]_D^{20}$ = –96.8 (*c* 0.50, $CHCl_3$).

Synthesis of Acid 409 and Lactone 408



To a solution of ketone *ent*-**141** (500 mg, 2.57 mmol, 1.0 eq.) in THF (25 mL) at –78 °C was added dropwise KHMDS (7.20 mL of a 0.5M solution in toluene, 3.60 mmol, 1.4 eq.) and the mixture was stirred for 30 min at this temperature. Then Et_3N (1.79 mL, 12.9 mmol, 4.0 eq.) and Et_3SiCl (1.94 mL, 11.6 mmol, 4.5 eq.) were added dropwise and the reaction was stirred for an additional 30 min. The reaction was quenched by addition of saturated aqueous NH_4Cl (10 mL) and the mixture was diluted with *n*-pentane (50 mL). The mixture was allowed to warm to room temperature and the phases were separated. The aqueous layer was extracted with *n*-pentane (2 x 20 mL) and the combined organic layers were dried over Na_2SO_4. The solvents were removed under reduced pressure (water bath temperature: 30 °C) to yield silylenol ether **406** as a colorless oil, which was used without further purification.

Through a solution of crude enol ether **406** in MeOH (15 mL) and CH_2Cl_2 (15 mL) at −78 °C was bubbled O_3 until the solution turned blue. After bubbling N_2 through the solution for 10 min, Me_2S (5.6 mL, 77.1 mmol, 30 eq.) was added and the mixture was allowed to warm to room temperature within 1 h. The solution was stirred for an additional 1 h at this temperature before the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (silica, CH_2Cl_2:MeOH = 10:1) to yield labile acid **407** (594 mg, quantitative) as a pale yellow oil, which was immediately used in the next step.

To a solution of aldehyde **407** (assumed 2.57 mmol, 1.0 eq.) in THF (30 mL) at 0 °C was slowly added isopropenylmagnesium bromide (**219**, 15.0 mL of a 0.5M in THF, 7.50 mmol, 3.0 eq.). The mixture was stirred an additional 10 min at this temperature and then for 1 h at room temperature. The mixture was quenched by addition of saturated aqueous NH_4Cl (15 mL) and the aqueous phase was acidified with HCl (2N). The biphasic mixture was extracted with Et_2O (3 x 30 mL) and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvents under reduced pressure and purification of the crude product by flash column chromatography (hexanes:EtOAc = 5:1, 1% AcOH) yielded labile seco acid **409** (290 mg, 1.08 mmol, 42% over three steps) as an inseparable, approximately 1:1 mixture of diastereomers, which was immediately used in the next step.

Additionally, lactone **408** (80 mg, 0.32 mmol, 12% over three steps) was isolated as a single diastereoisomer, the relative configuration of which was not be determined. This compound was contaminated by Et_3SiOH and was characterized by ^{1}H NMR, ^{13}C NMR and low resolution mass spectrometry.

Analytical data for acid **407**:

R_f = 0.39 (CH_2Cl_2:MeOH = 10:1).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.81 (dd, $^3J_{9/8A}$ = 3.2 Hz, $^3J_{9/8B}$ = 2.6 Hz, 1H, 9-H), 2.46 (dd, $^2J_{8A/8B}$ = 14.9 Hz, $^3J_{8A/9}$ = 3.2 Hz, 1H, 8-H_A), 2.39–2.25 (m, 3H, 2-H, 8-H_B), 1.94 (m_C, 1H, 3-H) 1.74–1.54 (m, 5H, 4-H, 5-H_A, 6-H, 11-H), 1.49–1.41 (m, 1H, 5-H_B), 0.98 (s, 3H, 10-H), 0.91 (d, $^3J_{12/11}$ = 6.8 Hz, 3H, 12-H)*, 0.82 (d, $^3J_{13/11}$ = 6.6 Hz, 3H, 13-H)* ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 203.3 (C-9), 179.4 (C-1), 54.8 (C-8), 49.6 (C-4), 47.6 (C-3), 43.6 (C-7), 38.4 (C-6), 35.1 (C-2), 29.3 (C-11), 23.2 (C-5), 22.5 (C-12)*, 21.0 (C-10), 16.8 (C-13)* ppm.

ESI-MS for $C_{26}H_{43}O_6^-$ [(2M–H)$^-$]: calcd. 451.3065
found 451.3064.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 2951 (s), 2870 (m), 1703 (s), 1467 (w), 1412 (w), 1387 (w), 1367 (w), 1301 (w), 1278 (w), 1240 (w), 1141 (w), 1079 (w).

Analytical data for allylic alcohol **409**:

R_f = 0.49 (CH_2Cl_2:MeOH = 10:1).

^{1}H NMR ($CDCl_3$, 600 MHz, both diastereomers quoted): δ = 4.95 (m_C, 0.5H, 11-H_A), 4.94 (m_C, 0.5H, 11-H_A), 4.78 (m_C, 0.5H, 11-H_B), 4.77 (m_C, 0.5H, 11-H)$_B$, 4.23 (d, J = 8.5 Hz, 0.5H, 9-H), 4.22 (d, J = 4.22 Hz, 0.5H, 9-H), 2.42 (dd, $^2J_{2A/2B}$ = 15.5 Hz, $^3J_{2A/3}$ = 6.3 Hz, 0.5H, 2-H_A), 2.40 (dd, $^2J_{2A/2B}$ = 15.3 Hz, $^3J_{2A/3}$ = 5.7 Hz, 0.5H, 2-H_A), 2.18 (dd, $^2J_{2B/2A}$ = 15.2 Hz, $^3J_{2B/3}$ = 7.0 Hz, 0.5H, 2-H_B), 2.17 (dd, $^2J_{2B/2A}$ = 15.4 Hz, $^3J_{2B/3}$ = 6.8 Hz, 0.5H, 2-H_B), 1.97 (m_C, 0.5H, 3-H), 1.90 (m_C, 0.5H, 3-H), 1.73 (s, 3H, 12-H), 1.72–1.55 (m, 5H, 4-H, 5-H_A, 6-H_A, 8-H_A, 14-H), 1.54–1.33 (m, 4H, 5-H_B, 6-H_B, 8-H_B, *O*H), 0.94 (s, 1.5H, 13-H), 0.96 (d, $^3J_{15/14}$ = 6.7 Hz, 3H, 15-H)*, 0.86 (s, 1.5H, 13-H), 0.82 (d, $^3J_{16/14}$ = 6.4 Hz, 1.5H, 16-H)*, 0.81 (d, $^3J_{16/14}$ = 6.5 Hz, 1.5H, 16-H)* ppm.

^{13}C NMR ($CDCl_3$, 150 MHz, both diastereomers quoted): δ = 179.6 (C-1), 179.3 (C-1), 149.2 (C-10), 149.1 (C-10), 110.5 (C-11), 110.3 (C-11), 74.2 (C-9), 73.4 (C-9), 50.8 (C-4), 50.1 (C-4), 47.3 (C-3), 47.1 (C-8), 46.4 (C-3), 45.9 (C-8), 44.3 (C-7), 44.2 (C-7), 39.0 (C-6), 38.2 (C-6), 35.8 (C-2), 35.6 (C-2), 29.5 (C-14), 29.2 (C-14), 23.1 (C-5), 22.9 (C-5), 22.6 (2C, C-15)*, 21.3 (C-13), 20.9 (C-13), 18.0 (C-12), 17.8 (C-12), 16.8 (C-16)*, 16.5 (C-16)* ppm.

ESI-MS for $C_{16}H_{27}O_3^-$ [$(M–H)^-$]: calcd. 267.1966
found 267.1970.

IR (ATR): $\tilde{\upsilon}/\ cm^{-1}$ = 3401 (br w), 2957 (s), 2929 (s), 2876 (m), 1708 (s), 1454 (w), 1438 (w), 1388 (w), 1235 (w), 1015 (w).

Since this compound had been obtained as a mixture of diastereomers, the specific optical rotation was not determined.

Analytical data for lactone **408**:

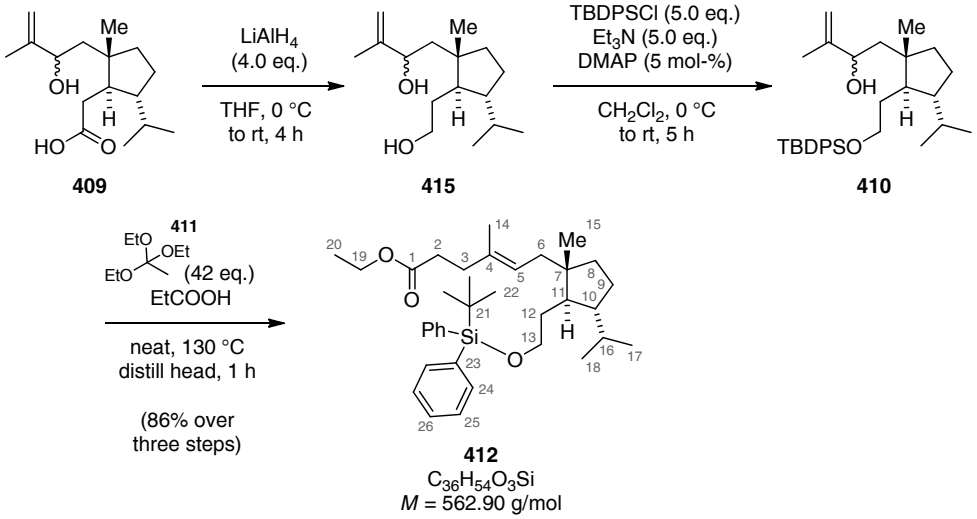
R_f = 0.14 (hexanes:EtOAc = 16:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 5.01 (m_C, 1H), 4.86 (m_C, 1H), 4.27 (d, J = 10.3 Hz, 1H), 2.57–2.47 (m, 2H), 1.83–1.59 (m, 5H), 1.79 (s, 3H), 1.58–1.54 (m, 1H), 1.49–1.40 (m, 2H), 1.27–1.20 (m, 1H), 0.99 (s, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.81 (d, J = 7.2 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 174.8, 144.0, 112.6, 79.5, 46.8, 46.7, 46.0, 42.9, 40.0, 33.2, 28.5, 22.3, 22.1, 18.2, 18.1, 16.8 ppm.

LRESI-MS for $C_{16}H_{27}O_2^+$ [$(M+H)^+$]: calcd. 251.4
found 251.3.

Synthesis of Ester 412



To solution of seco acid **409** (220 mg, 820 μmol, 1.0 eq.) in THF (10 mL) at 0 °C was added $LiAlH_4$ (3.30 mL of a 1.0M solution in THF, 3.30 mmol, 4.0 eq.) dropwise. The mixture was allowed to warm to room temperature and stirred for 4 h before being quenched by addition of NaOH (3M, 2 mL). The mixture was diluted with Et_2O (20 mL) and water (5 mL) and filtered over a pad of Celite® (washings with Et_2O). The aqueous phase was extracted with Et_2O (2 x 10 mL) and the combined organic layers were dried over $MgSO_4$. The solvents were evaporated under reduced pressure and the crude product was purified by flash column chromatography (hexanes:EtOAc = 2:1) to yield diol **415** (195 mg, 768 μmol, 96%) as a mixture of diastereomers, which was immediately used in the next step.

To a solution of diol **415** (165 mg, 650 μmol, 1.0 eq.) in CH_2Cl_2 (10 mL) at 0 °C was added subsequently Et_3N (498 μL, 3.58 mmol, 5.0 eq.), TBDPSCl (850 μL, 3.25 mmol, 5.0 eq.) and DMAP (4.3 mg, 30 μmol, 5.0 mol-%). The mixture was allowed to warm to room temperature and stirred for an additional 5 h. The mixture was diluted with CH_2Cl_2 (10 mL) and the reaction was quenched by addition of saturated aqueous NH_4Cl (10 mL). The aqueous layer was extracted with

CH_2Cl_2 (3 x 15 mL) and the combined organic layers were washed with saturated aqueous NaCl (20 mL) and dried over $MgSO_4$. The solvents were evaporated under reduced pressure and the crude product was purified by flash column chromatography (hexanes:EtOAc = 24:1) to yield alcohol **410** as mixture of diastereomers. Due to silanol impurities, this material was directly used in the next step.

The crude alcohol **410** (assumed 650 μmol, 1.0 eq.) was dissolved in triethyl orthoacetate (**411**, 5 mL, 27.3 mmol, 42 eq.) and one drop of propionic acid was added. The mixture was heated to 130 °C for 1 h, distilling off generated EtOH. The reaction was allowed to cool to room temperature and excess orthoacetate **411** was removed under reduced pressure. The residue was dissolved in Et_2O (50 mL) and was sequentially washed with saturated aqueous $NaHCO_3$ (2 x 10 mL) and saturated aqueous NaCl (10 mL). The organic layer was dried over $MgSO_4$, the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (hexanes:EtOAc = 39:1) to yield ester **412** (330 mg, 587 μmol, 86% over three steps) as a highly viscous colorless oil.

The configuration of the double bond was determined to be (*E*) by 2D NOESY NMR spectroscopy showing the proximity of 3-H and 5-H.

R_f = 0.48 (hexanes:EtOAc = 7:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.69–7.65 (m, 4H, 25-H)*, 7.43–7.35 (m, 6H, 24-H*, 26-H), 5.19 (m_C, 1H, 5-H), 4.11 (q, $^3J_{19/20}$ = 7.1 Hz, 2H, 19-H), 3.66 (dd, $^3J_{13/12A}$ = $^3J_{13/12B}$ = 7.3 Hz, 2H, 13-H), 2.40–2.33 (m, 2H, 2-H), 2.32–2.26 (m, 2H, 3-H), 2.02 (dd, $^2J_{6A/6B}$ = 14.3 Hz, $^3J_{6A/5}$ = 8.2 Hz, 1H, 6-H_A), 1.76 (dd, $^2J_{6B/6A}$ = 14.2 Hz, $^3J_{6B/5}$ = 7.0 Hz, 1H, 6-H_B), 1.70–1.63 (m, 1H, 12-H_A), 1.61–1.56 (m, 1H, 16-H), 1.54 (s, 3H, 14-H), 1.53–1.40 (m, 3H, 9-H_A, 10-H, 12-H_B), 1.36–1.22 (m, 4H, 8-H, 9-H_B, 11-H), 1.24 (t, $^3J_{20/19}$ = 7.1 Hz, 3H, 20-H), 1.05 (s, 9H, 22-H), 0.82 (d, $^3J_{17/16}$ = 7.0 Hz, 3H, 18-H)**, 0.72 (d, $^3J_{18/16}$ = 6.8 Hz, 3H, 16-H)**, 0.69 (s, 3H, 15-H) ppm.

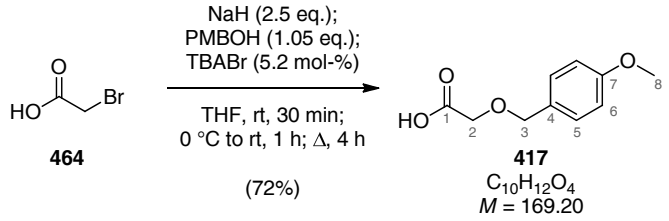
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 173.7 (C-1), 135.7 (C-25)*, 134.4 (C-4), 132.2 (C-23), 129.6 (C-26), 127.7 (C-24)*, 122.8 (C-5), 64.8 (C-13), 60.4 (C-19), 50.8 (C-10), 46.5 (C-11), 45.5 (C-7), 39.9 (C-6), 38.6 (C-8), 35.2 (C-3), 34.3 (C-12), 33.6 (C-2), 29.8 (C-16), 27.1 (C-22), 22.9 (C-17)**, 22.8 (C-9), 20.7 (C-15), 19.3 (C-21), 16.4 (C-18)**, 16.3 (C-14), 14.4 (C-20) ppm.

ESI-MS for $C_{36}H_{58}O_3NSi^+$ [$(M+NH_4)^+$]: calcd. 580.4180
found 580.4179.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 3072 (w), 3051 (w), 2957 (s), 2932 (s), 2860 (s), 1737 (s), 1472 (w), 1464 (w), 1428 (w), 1386 (w), 1368 (w), 1300 (w), 1254 (w), 1177 (w), 1560 (w), 1112 (m), 1093 (m), 941 (w) 823 (w), 702 (m), 614 (w).

$[\alpha]_D^{20}$ = –0.8 (*c* 0.50, CH_2Cl_2).

Synthesis of Carboxylic Acid 417



To a suspension of NaH (60 wt% in mineral oil, 5.73 g, 144 mmol, 2.5 eq.) in THF (75 mL) was carefully added bromoacetic acid (**464**, 7.90 g, 57.4 mmol, 1.0 eq.) and the mixture was stirred at room temperature until H_2 evolution had ceased. After cooling to 0 °C, a solution of PMBOH (7.10 mL, 58.0 mmol, 1.05 eq.) in THF (150 mL) was carefully added *via* cannula. The mixture was allowed to warm to room temperature and stirred for an additional 1 h at this temperature before adding Bu_4NBr (1.00 g, 3.00 mmol, 5.2 mol-%) and heating the suspension to reflux for 4 h. The reaction was cooled to 0 °C and EtOH (20 mL) was carefully added. The white precipitate was filtered off and dissolved in H_2O (50 mL). This solution was acidified with aqueous HCl (2N, 20 mL) to pH = 1 precipitating a colorless solid. The aqueous phase was extracted with Et_2O (3 x 50 mL) and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvent under reduced pressure yielded carboxylic acid **417** (8.10 g, 41.3 mmol, 72%) as a colorless solid.

R_f = 0.31 (hexanes:EtOAc = 1:1, 1% AcOH).

Melting point = 53.5–55.0 °C (Et_2O).

^{1}H NMR ($CDCl_3$, 300 MHz): δ= 10.86 (brs, 1H, *O*H), 7.29 (m_C, 2H, 5-H), 6.89 (m_C, 2H, 6-H), 4.58 (s, 2H, 3-H), 4.11 (s, 2H, 2-H), 3.81 (s, 3H, 8-H) ppm.

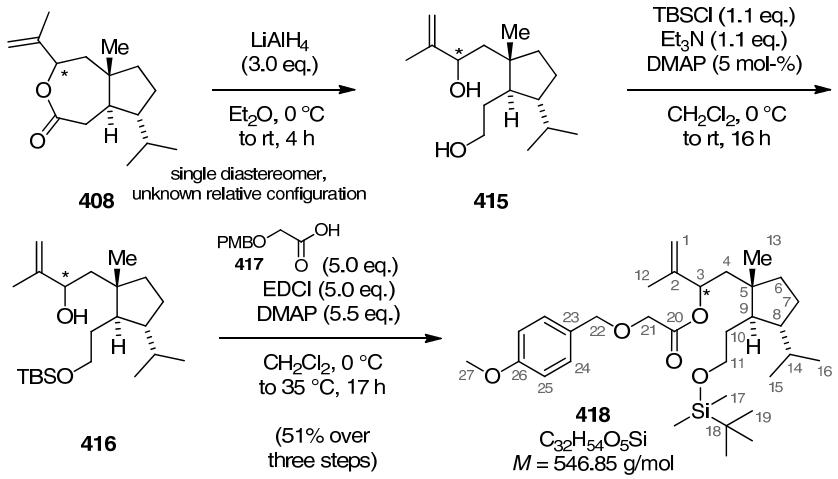
^{13}C NMR ($CDCl_3$, 75 MHz): δ= 175.5 (C-1), 159.8 (C-7), 130.0 (C-5), 128.8 (C-4), 114.1 (C-6), 73.2 (C-3), 66.4 (C-2), 55.4 (C-8) ppm.

ESI-MS for $C_{10}H_{11}O_4^-$ [$(M–H)^-$]: calcd. 195.0663
found 195.0669.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 3125 (br m), 2960 (m), 2840 (w), 1756 (s), 1724 (s), 1611 (m), 1583 (w), 1511 (s), 1461 (m), 1429 (m), 1374 (w), 1301 (w), 1249 (s), 1214 (m), 1174 (s), 1094 (m), 1026 (m), 999 (m), 952 (m), 933 (w), 903 (w), 816 (s), 758 (w).

The analytical data matched those reported previously.[279]

Synthesis of Ester 418



To a solution of lactone **408** (50 mg, 0.20 mmol, 1.0 eq.) in Et_2O (4 mL) at 0 °C was added $LiAlH_4$ (23 mg, 0.60 mmol, 3.0 eq.) in one portion and the mixture was stirred at room temperature for 4 h. The reaction was quenched at 0 °C by carefully adding half-saturated aqueous Rochelle salt (4 mL) and the biphasic mixture was stirred vigorously for 1 h at room temperature. The phases were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were evaporated under reduced pressure. The crude product was purified by a short flash column chromatography (silica, hexanes:EtOAc = 2:1 to 1:1) to yield diol **415** (37 mg, 0.15 mmol, 73%, R_f = 0.18, CH_2Cl_2:MeOH = 100:5) as a colorless solid, which was used without further characterization.

To a solution of diol **415** (30 mg, 0.12 mmol, 1.0 eq.) in CH_2Cl_2 (2 mL) at 0 °C was added Et_3N (18 µL, 0.13 mmol, 1.1 eq.), TBSCl (20 mg, 0.13 mmol, 1.1 eq.) and DMAP (spatula tip). The mixture was allowed to warm to room temperature and was stirred an additional 16 h prior to being diluted with CH_2Cl_2 (10 mL). The reaction was quenched by addition of saturated aqueous NH_4Cl (5 mL) and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic layers were dried over Na_2SO_4. The solvents were evaporated under reduced pressure and the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 16:1) to yield allylic alcohol **416** (34 mg, 92 µmol, 78%, R_f = 0.12, hexanes:EtOAc = 30:1) as a highly viscous colorless oil, which was used in the next step without further characterization.

To a solution of allylic alcohol **416** (30 mg, 82 μmol, 1.0 eq.), carboxylic acid **417** (80 mg, 0.41 mmol, 5.0 eq.) and DMAP (55 mg, 0.45 mmol, 5.50 eq.) in CH_2Cl_2 (5 mL) at 0 °C was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (78 mg, 0.41 mmol, 5.0 eq.). The mixture was allowed to warm to room temperature and stirred for an additional 30 min before being stirred at 35 °C for 16 h. The reaction was cooled to room temperature, diluted with CH_2Cl_2 (5 mL) and quenched by addition of H_2O (5 mL). The organic phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic layers were sequentially washed with saturated aqueous $NaHCO_3$ (4 mL) and saturated aqueous NH_4Cl (4 mL), and dried over $MgSO_4$. Having evaporated the solvents under reduced pressure, the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 20:1) to yield ester **418** (40 mg, 73 μmol, 90%) as a colorless oil.
*Note: the intermediate allylic alcohol **416** and ester **418** are co-polar on TLC.*

R_f = 0.12 (hexanes:EtOAc = 30:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.29 (m_C, 2H, 24-H), 6.88 (m_C, 2H, 25-H), 5.37 (dd, $^3J_{3/4A}$ = 8.4 Hz, $^3J_{3/4B}$ = 3.0 Hz, 1H, 3-H), 4.95 (br s, 1H, 1-H_A), 4.83 (m_C, 1H, 1-H_B), 4.56 (s, 2H, 22-H), 4.03 (s, 2H, 21-H), 3.80 (s, 3H, 27-H), 3.64 (ddd,$^2J_{11A/11B}$ = 9.8 Hz, $^3J_{11A/10B}$ = 8.4 Hz, $^3J_{11A/10A}$ = 5.4 Hz, 1H, 11-H_A), 3.58 (ddd, $^2J_{11B/11A}$ = 9.9 Hz, $^3J_{11B/10A}$ = 8.1 Hz, $^3J_{11B/10B}$ = 6.9 Hz, 1H, 11-H_B), 1.89 (dd, $^2J_{4A/4B}$ = 14.9 Hz, $^3J_{4A/3}$ = 8.5 Hz, 1H, 4-H_A), 1.72 (s, 3H, 12-H), 1.70 (m_C, 1H, 14-H), 1.64–1.59 (m, 2H, 8-H, 10-H_A), 1.57–1.48 (m, 2H, 6-H_A, 7-H_A), 1.45–1.40 (m, 2H, 4-H_B, 10-H_B), 1.48–1.33 (m, 1H, 7-H_B), 1.31–1.26 (m, 2H, 6-H_B, 9-H), 0.91–0.87 (m, 3H, 15-H)*, 0.89 (s, 9H, 19-H), 0.81 (s, 3H, 13-H), 0.77 (d, $^3J_{16/15}$ = 6.9 Hz, 3H, 16-H)*, 0.04 (s, 6H, 17-H) ppm.

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 169.8 (C-20), 159.6 (C-26), 144.6 (C-2), 129.9 (C-24), 129.5 (C-23), 114.0 (C-25), 112.4 (C-1), 76.6 (C-3), 73.0 (C-22), 67.2 (C-21), 62.9 (C-11), 55.4 (C-27), 50.1 (C-8), 48.0 (C-9), 45.0 (C-4), 44.3 (C-5), 38.8 (C-6), 34.2 (C-10), 29.7 (C-14), 26.1 (C-19), 22.8 (2C, C-7, C-15*), 20.4 (C-13), 18.5 (C-18), 18.3 (C-12), 16.3 (C-16)*, –5.1 (C-17) ppm.

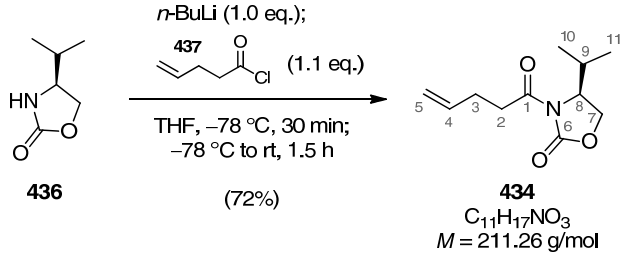
ESI-MS for $C_{32}H_{58}NO_5Si^+$ [$(M+NH_4)^+$]: calcd. 564.4079
found 564.4078.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 2954 (s), 2959 (m), 1755 (m), 1613 (w), 1514 (m), 1463 (w), 1386 (w), 1250 (m), 1197 (w), 1108 (m), 1039 (w), 940 (w), 835 (w), 775 (w).

$[\alpha]_D^{20}$ = +4.0 (*c* 0.50, CH_2Cl_2).

2.4 Experimental Procedures for Chapter 5: 'Synthetic Studies toward YW 3548'

Synthesis of Oxazolidinone 434



To a solution of Evans auxiliary **436**[296] (1.58 g, 12.2 mmol, 1.0 eq.) in THF (30 mL) at –78 °C was added *n*-BuLi (5.60 mL of a 2.4M solution in hexanes, 13.4 mmol, 1.0 eq.) and the mixture was stirred for 30 min. Then, a solution of 4-pentenoyl chloride (**437**, 1.50 mL, 13.6 mmol, 1.1 eq.) in THF (1.5 mL) was added dropwise and the reaction mixture was stirred for 30 min at –78 °C prior to removing the cold bath. After stirring for an additional 30 min at room temperature, the reaction was quenched by addition of saturated aqueous NH_4Cl (15 mL) and the aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were removed under reduced pressure. The crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 7:1) to yield oxazolidinone **434** (1.87 g, 8.83 mmol, 72%) as a colorless oil.

R_f = 0.34 (hexanes:EtOAc = 4:1).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.85 (ddt, $^3J_{4/5A}$ = 16.9 Hz, $^3J_{4/5B}$ = 10.2 Hz, $^3J_{4/3}$ = 6.6 Hz, 1H, 4-H), 5.07 (ddt, $^3J_{5A/4}$ = 17.1 Hz, $^2J_{5A/5B}$ = $^4J_{5A/3}$ = 1.6 Hz, 1H, 5-H_A), 5.00 (ddt, $^3J_{5B/4}$ = 10.3 Hz, $^2J_{5B/5A}$ = $^4J_{5B/3}$ = 1.4 Hz, 1H, 5-H_B), 4.43 (m_C, 1H, 8-H), 4.26 (dd, $^2J_{7A/7B}$ = 9.2 Hz, $^3J_{7A/8}$ = 8.1 Hz, 1H, 7-H_A), 4.19 (dd, $^2J_{7B/7A}$ = 9.2 Hz, $^3J_{7B/8}$ = 3.4 Hz, 1H, 7-H_B), 3.10 (ddd, $^2J_{2A/2B}$ = 17.0 Hz, $^3J_{2A/3}$ = 7.8 Hz, $^3J_{2A/3}$ = 7.0 Hz, 1H, 2-H_A), 2.97 (ddd, $^2J_{2B/2A}$ = 17.1 Hz, $^3J_{2B/3}$ = 7.5, 7.5 Hz, 1H, 2-H_B), 2.49–2.28 (m, 3H, 3-H, 11-H), 0.90 (d, $^3J_{10/9}$ = 7.0 Hz, 3H, 10-H)*, 0.86 (d, $^3J_{11/9}$ = 6.9 Hz, 3H, 11-H)* ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 172.6 (C-1), 154.2 (C-6), 136.8 (C-4), 115.8 (C-5), 63.5 (C-7), 58.5 (C-8), 34.9 (C-2), 28.5 (2C, C-3, C-9), 18.1 (C-10)*, 14.8 (C-11)* ppm.

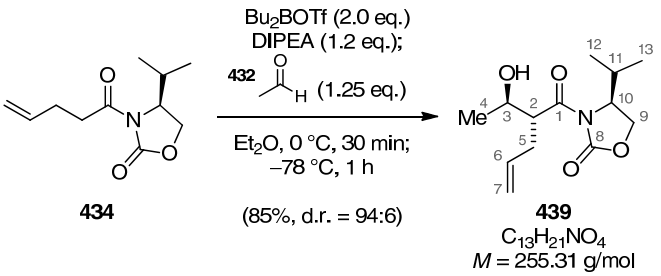
EI-MS for $C_{11}H_{17}NO_3^+$ [M^+]:	calcd.	211.1203
	found	211.1201.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 3079 (w), 2965 (w), 2877 (w), 1776 (s), 1706 (s), 1641 (w), 1487 (w), 1439 (w), 1389 (s), 1302 (m), 1204 (s), 1061 (m), 916 (w).

$[\alpha]_D^{20}$ = +50.2 (*c* 1.00, $CHCl_3$).

The analytical data matched those reported previously.[297]

Synthesis of Aldol Product 439



To a solution of oxazolidinone **434** (1.45 g, 6.85 mmol, 1.0 eq.) in Et_2O (20 mL) at 0 °C was consecutively added Bu_2BOTf (3.32 mL, 13.7 mmol, 2.0 eq.) and DIPEA (1.40 mL, 8.09 mmol, 1.2 eq.). The resulting suspension was stirred for an additional 30 min at 0 °C and then cooled to −78 °C before adding a solution of acetaldehyde (**432**, 482 µL, 8.56 mmol, 1.25 eq.) in Et_2O (6.8 mL) within 10 min. The reaction mixture was stirred for an additional 1 h at −78 °C and was then quenched by addition of tartaric acid (5.13 g, 34.0 mmol, 5.0 eq.). The mixture was allowed to warm to room temperature and stirred for 2 h at this temperature, forming a dark brown solution. The acid was filtered off, the filter cake was rinsed with Et_2O (30 mL) and the organic layer was washed with H_2O (30 mL). The aqueous phase was extracted with Et_2O (2 x 40 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 x 80 mL). The aqueous phases were re-extracted with Et_2O (3 x 80 mL) and the combined organic layers were washed with saturated aqueous NaCl (100 mL). The volume of the Et_2O phase was reduced to ca. 180 mL, before the solution was cooled to 0 °C and a mixture of MeOH/H_2O_2 (3:1, 35 mL) was added dropwise. The biphasic mixture was stirred for 1 h at room temperature changing its color from orange to yellow. The mixture was diluted with Et_2O (100 mL) and the organic phase was washed with saturated aqueous $NaHCO_3$ (75 mL) and saturated aqueous NaCl (75 mL). Having dried the organic layer over Na_2SO_4 and having evaporated the solvent under reduced pressure, the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 5:1 to 4:1 to 3:1) to yield alcohol **439** (1.48 g, 5.8 mmol, 85%, d.r. = 94:6) as an inseparable mixture of diastereomers as a colorless oil.

The diastereomeric ratio was determined by ^1H NMR spectroscopy by integration of the baseline separated doublet signals of 4-H at 1.29 ppm (major) and 1.22 ppm (minor).

R_f = 0.29 (hexanes:EtOAc = 3:1).

^{1}H NMR ($CDCl_3$, 600 MHz, only major isomer quoted): δ = 5.75 (m_C, 1H, 6-H), 5.06 (ddt, $^3J_{7A/6}$ = 17.1 Hz, $^2J_{7A/7B}$ = $^4J_{7A/5}$ = 1.6 Hz, 1H, 7-H_A), 5.00 (m_C, 1H, 7-H_B), 4.42 (ddd, $^3J_{10/9A}$ = 7.9 Hz, $^3J_{10/11}$ = 3.9 Hz, $^3J_{10/9B}$ = 3.0 Hz, 1H, 10-H), 4.23 (dd, $^2J_{9A/9B}$ = 9.0 Hz, $^3J_{9A/10}$ = 7.8 Hz, 1H, 9-H_A), 4.20 (dd, $^2J_{9B/9A}$ = 9.0 Hz, $^3J_{9B/10}$ = 3.0 Hz, 1H, 9-H_B), 4.02 (ddd, $^3J_{2/3}$ = 9.0 Hz, $^3J_{2/5A}$ = 6.0 Hz, $^3J_{2/5B}$ = 5.6 Hz, 1H, 2-H), 3.93 (ddq, $^3J_{3/2}$ = $^3J_{3/OH}$ = 8.9 Hz, $^3J_{3/4}$ = 6.3 Hz, 1H, 3-H), 2.60 (d, $^3J_{OH/3}$ = 9.1 Hz, 1H, *O*H), 2.54–2.26 (m, 3H, 5-H, 11-H), 1.27 (d, $^3J_{4/3}$ = 6.4 Hz, 3H, 4-H), 0.92 (d, $^3J_{12/11}$ = 7.1 Hz, 3H, 12-H)*, 0.88 (d, $^3J_{13/11}$ = 7.0 Hz, 3H, 13-H)* ppm.

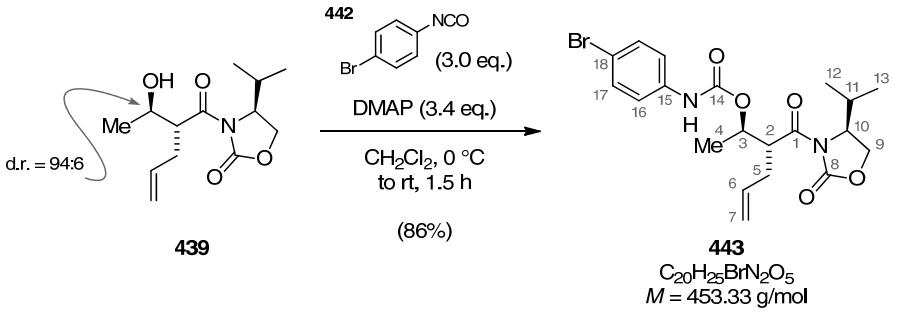
^{13}C NMR ($CDCl_3$, 75 MHz, only major isomer quoted): δ = 175.5 (C-1), 154.4 (C-8), 135.1 (C-6), 117.4 (C-3), 69.4 (C-3), 63.5 (C-9), 59.0 (C-10), 49.5 (C-2), 33.8 (C-5), 28.7 (C-11), 21.8 (C-4), 18.1 (C-12)*, 14.8 (C-13)* ppm.

EI-MS for $C_{13}H_{21}NO_4^+$ [M^+]: calcd. 255.1465
found 255.1455.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 3508 (br s), 3078 (w), 2967 (m), 2932 (m), 2876 (w), 1776 (s), 1696 (m), 1641 (w), 1489 (w), 1439 (w), 1385 (m), 1300 (w), 1202 (m), 1119 (w), 1057 (w).

$[\alpha]_D^{20}$ = +61.2 (*c* 1.00, d.r. = 94:6, CH_2Cl_2).

Synthesis of Carbamate 443



To a solution of alcohol **439** (d.r. = 94:6, 28 mg, 0.11 mmol, 1.0 eq.) in CH_2Cl_2 (3 mL) at 0 °C was added DMAP (28 mg, 0.35 mmol, 3.4 eq.) and 4-bromophenyl isocyanate (**442**, 65 mg, 0.33 mmol, 3.0 eq.). The thus formed yellow solution was allowed to warm to room temperature and stirred for 1.5 h precipitating a white solid. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (5 mL) and the mixture was extracted with Et_2O (2 x 15 mL). The combined organic layers were washed with saturated aqueous NaCl (10 mL) and dried over Na_2SO_4. After evaporation of the solvents under reduced pressure, the crude product was purified by flash column

chromatography (silica, hexanes:EtOAc = 7:1 to 5:1) to yield carbamate **443** (43 mg, 95 μmol, 86%) as a colorless solid. The minor diastereomer was separable by flash column chromatography, but not isolated.

Crystals suitable for X-ray analysis were obtained by slow evaporation of a solution of carbamate **443** in Et_2O/*n*-pentane (1:1).

R_f = 0.36 (hexanes:EtOAc = 3:1).

Melting point = 106.0–108.0 °C (hexanes/EtOAc).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.41–7.37 (m, 2H, 17-H), 7.29–7.23 (m, 2H, 16-H), 6.65 (br s, 1H, *N*H), 5.75 (m_C, 1H, 6-H), 5.22 (m_C, 1H, 3-H), 5.07 (dd, $^3J_{7A/6}$ = 17.1 Hz, $^4J_{7A/5}$ = 1.3 Hz, 1H, 7-H_A), 5.03 (d, $^3J_{7B/6}$ = 10.1 Hz, 1H, 7-H_B), 4.44 (m_C, 1H, 10-H), 4.37 (m_C, 1H, 2-H), 4.23 (dd, $^2J_{9A/9B}$ = 9.0 Hz, $^3J_{9A/10}$ = 8.3 Hz, 1H, 9-H_A), 4.18 (dd, $^2J_{9B/9A}$ = 9.1 Hz, $^3J_{9B/10}$ = 3.0 Hz, 1H, 9-H_B), 2.45–2.28 (m, 3H, 5-H, 11-H), 1.29 (d, $^3J_{4/3}$ = 6.5 Hz, 3H, 4-H), 0.87 (d, $^3J_{12/11}$ = 7.2 Hz, 3H, 12-H)*, 0.84 (d, $^3J_{13/11}$ = 7.0 Hz, 3H, 13-H)* ppm.

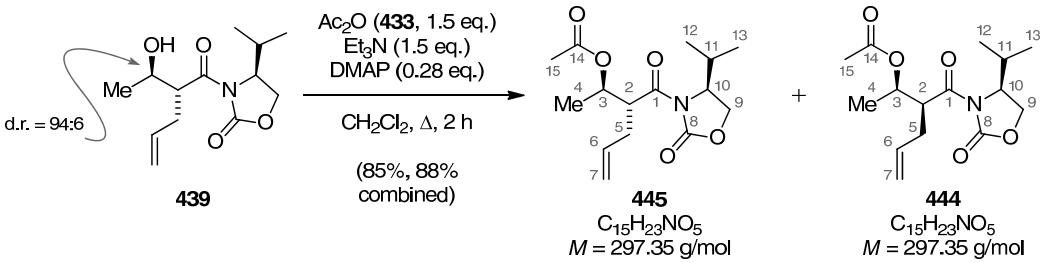
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 173.2 (C-1), 154.0 (C-8), 152.3 (C-14), 137.1 (C-15) 134.2 (C-6), 132.1 (C-17), 120.2 (C-16), 118.0 (C-7), 116.0 (C-18), 72.8 (C-3), 63.4 (C-9), 58.9 (C-10), 47.4 (C-2), 33.5 (C-5), 28.7, (C-11), 18.2 (C-4), 18.1 (C-12)*, 14.8 (C-13)* ppm.

ESI-MS for $C_{20}H_{25}BrN_2NaO_5^+$ [$(M+Na)^+$]: calcd. 475.0839
found 475.0838.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 3334 (br w), 3077 (w), 2965 (w), 2875 (w), 1775 (s), 1702 (s), 1593 (m), 1527 (s), 1489 (m), 1396 (s), 1386 (s), 1305 (m), 1219 (s), 1118 (w), 1099 (w), 1073 (m), 1055 (m), 1007 (w), 977 (w), 922 (w), 825 (w), 767 (w), 707 (w).

$[\alpha]_D^{20}$ = +38.8 (*c* 1.00, CH_2Cl_2).

Synthesis of Acetates 444 and 445



To a solution of alcohol **439** (d.r. = 94:6, 950 mg, 3.72 mmol, 1.0 eq.) in CH_2Cl_2 (35 mL) was added Et_3N (780 µL, 5.62 mmol, 1.5 eq.), DMAP (129 mg, 1.06 mmol, 28 mol-%) and Ac_2O (**433**, 560 µL, 5.50 mmol, 1.5 eq.). The resulting solution was heated to reflux for 2 h and, after cooling to room temperature, the mixture was diluted with CH_2Cl_2 (35 mL). The organic phase was washed with 1N HCl (30 mL), saturated aqueous $NaHCO_3$ (40 mL) and saturated aqueous NaCl (50 mL). Having dried the organic layer over Na_2SO_4 and evaporated the solvent under reduced pressure, the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 5:1) to yield acetate **445** (940 mg, 3.16 mmol, 85%) as a colorless solid along with the *syn*-diastereomer **444** (30 mg, 0.10 mmol, 3%) from the previous reaction as a colorless oil.

Analytical data for *anti*-diastereomer **445**:

R_f = 0.30 (hexanes:EtOAc = 3:1).

Melting point = 65.0–67.0 °C (hexanes/EtOAc).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 5.78–5.70 (m, 1H, 6-H), 5.17 (dq, $^3J_{3/2}$ = 8.5 Hz, $^3J_{3/4}$ = 6.3 Hz, 1H, 3-H), 5.05 (ddt, $^3J_{7A/6}$ = 17.1 Hz, $^2J_{7A/7B}$ = $^4J_{7A/5}$ = 1.6 Hz, 1H, 7-H_A), 5.01 (m_C, 1H, 7-H_B), 4.43 (ddd, $^3J_{10/9A}$ = 8.2 Hz, $^3J_{10/11}$ = 4.0 Hz, $^3J_{10/9B}$ = 3.2 Hz, 1H, 10-H), 4.31 (dt, $^3J_{2/3}$ = 8.5 Hz, $^3J_{2/5}$ = 5.6 Hz, 1H, 2-H), 4.22 (dd, $^2J_{9A/9B}$ = 9.1 Hz, $^3J_{9A/10}$ = 8.2 Hz, 1H, 9-H_A), 4.18 (dd, $^2J_{9B/9A}$ = 9.2 Hz, $^3J_{9B/10}$ = 3.2 Hz, 1H, 9-H_B), 2.40–2.27 (m, 3H, 5-H, 11-H), 1.96 (s, 3H, 15-H), 1.29 (d, $^3J_{4/3}$ = 6.3 Hz, 3H, 4-H), 0.90 (d, $^3J_{12/11}$ = 7.1 Hz, 3H, 12-H)*, 0.88 (d, $^3J_{13/11}$ = 7.0 Hz, 3H, 13-H)* ppm.

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 173.2 (C-1), 170.0 (C-14), 153.9 (C-8), 134.2 (C-6), 117.9 (C-7), 71.7 (C-3), 63.3 (C-9), 58.7 (C-10), 47.3 (C-2), 33.4 (C-5), 28.7 (C-11), 21.2 (C-15), 18.1 (C-12)*, 17.6 (C-4), 14.9 (C-13)* ppm.

FAB-MS for $C_{15}H_{24}NO_5^+$ [$(M+H)^+$]: calcd. 298.1649
found 298.1653.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 3274 (br w), 2975 (w), 1776 (s), 1733 (s), 1697 (s), 1386 (s), 1372 (s), 1300 (m), 1231 (s), 1201 (s), 1120 (m), 1098 (m), 1056 (m), 978 (w), 950 (w), 927 (w).

$[\alpha]_D^{20}$ = +54.0 (*c* 1.00, CH_2Cl_2).

Analytical data for *syn*-diastereomer **444**:

R_f = 0.38 (hexanes:EtOAc = 3:1).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.73 (m_C, 1H, 6-H), 5.26 (m_C, 1H, 3-H), 5.11–4.95 (m, 2H, 7-H), 4.44 (m_C, 1H, 10-H), 4.28–4.14 (m, 3H, 2-H, 9-H), 2.56–2.44 (m, 1H, 5-H_A), 2.39–2.24 (m, 2H, 5-H_B, 11-H), 2.00 (s, 3H, 14-H), 1.27 (d, $^3J_{4/3}$ = 6.3 Hz, 3H, 4-H), 0.91 (d, $^3J_{12/11}$ = 7.1 Hz, 3H, 12-H)*, 0.90 (d, $^3J_{13/11}$ = 7.0 Hz, 3H, 13-H)* ppm.

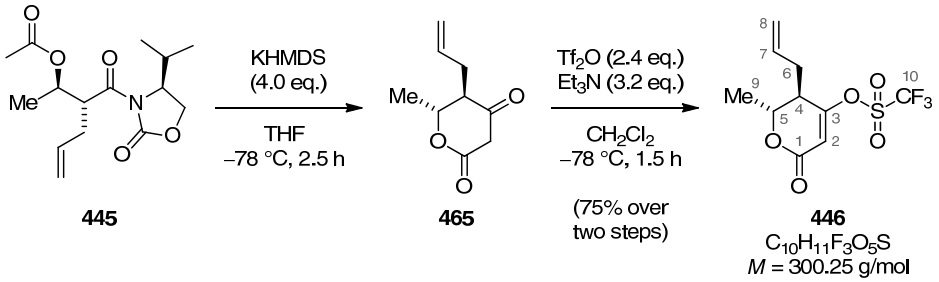
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 172.7 (C-1), 170.2 (C-14), 154.0 (C-8), 135.2 (C-6), 117.3 (C-7), 70.6 (C-3), 63.3 (C-9), 58.7 (C-10), 46.8 (C-2), 31.9 (C-5), 28.5 (C-11), 21.2 (C-15), 18.1 (C-12)*, 17.7 (C-4), 14.6 (C-13)* ppm.

FAB-MS for $C_{15}H_{24}NO_5^+$ [$(M+H)^+$]: calcd. 298.1649
found 298.1666.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 3080 (w), 2967 (m), 1777 (s), 1739 (s), 1697 (m), 1387 (m), 1371 (m), 1301 (w), 1236 (s), 1203 (m), 1122 (w), 1098 (w), 1058 (w), 1020 (w).

$[\alpha]_D^{20}$ = +41.4 (*c* 1.00, CH_2Cl_2).

Synthesis of Enol Triflate 446



To a solution of acetate **445** (750 mg, 2.52 mmol, 1.0 eq.) in THF (40 mL) at –78 °C was added dropwise KHMDS (20.0 mL of a 0.5M solution in toluene, 10.0 mmol, 4.0 eq.) and the pale yellow solution was stirred for 2.5 h at –78 °C prior to quenching the reaction by addition of MeOH/saturated

aqueous NH_4Cl/H_2O (1:1:1, 40 mL). After warming to room temperature, the pH was adjusted to 2–3 by adding 1N HCl and the biphasic mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and evaporation of the solvents under reduced pressure yielded crude ketone **465** as an orange oil, which was used without further purification.

The crude oil **465** (assumed 2.52 mmol, 1.0 eq.) was redissolved in CH_2Cl_2 (13 mL) and the solution was cooled to −78 °C. Then Et_3N (1.10 mL, 7.94 mmol, 3.2 eq.) and Tf_2O (6.00 mL of a 1.0M solution in CH_2Cl_2, 6.00 mmol, 2.4 eq.) were sequentially added and the solution was stirred for an additional 90 min at this temperature. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (25mL) and the mixture was allowed to warm to room temperature before being extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were removed under reduced pressure. The crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 7:1) to yield enol triflate **446** (566 mg, 1.89 mmol, 75% over two steps) as a pale yellow oil

R_f = 0.32 (hexanes:EtOAc = 9:1).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.08 (s, 1H, 2-H), 5.72 (dddd, $^3J_{7/8B}$ = 17.1 Hz, $^3J_{7/8A}$ = 10.3 Hz, $^3J_{7/6}$ = 7.5, 6.7 Hz, 1H, 7-H), 5.22 (m_C, 1H, 8-H_A), 5.19 (ddt, $^3J_{8B/7}$ = 16.9 Hz, $^2J_{8B/8A}$ = $^4J_{8B/6}$ = 1.4 Hz, 1H, 8-H_B), 4.65 (qd, $^3J_{4/9}$ = 6.7 Hz, $^3J_{4/5}$ = 3.2 Hz, 1H, 4-H), 2.57 (ddd, $^3J_{5/6A}$ = 7.6 Hz, $^3J_{5/6B}$ = 4.8 Hz, $^3J_{5/4}$ = 3.2 Hz, 1H, 5-H), 2.55–2.41 (m, 2H, 6-H), 1.47 (d, $^3J_{9/4}$ = 6.6 Hz, 1H, 9-H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 163.6 (C-1), 161.9 (C-3), 131.9 (C-7), 120.4 (C-8), 118.4 (q, $^1J_{10/F}$ = 321 Hz, C-10), 109.7 (q, $^5J_{2/F}$ = 0.8 Hz, C-2), 75.8 (C-5), 42.8 (C-4), 34.5 (C-6), 19.8 (C-9) ppm.

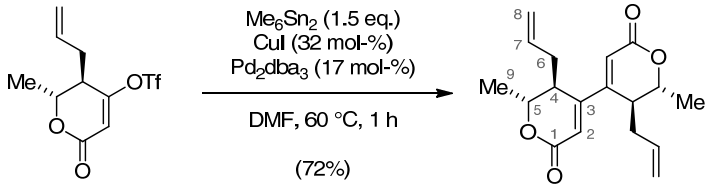
^{19}F NMR ($CDCl_3$, 377 MHz): δ = –73.2 ppm.

FAB-MS for $C_{10}H_{12}F_3O_5S^+$ [$(M+H)^+$]:	calcd.	301.0352
	found	301.0345.

IR (ATR): $\tilde{\upsilon}/cm^{-1}$ = 3085 (w), 2987 (w), 1730 (s), 1659 (w), 1429 (s), 1366 (w), 1305 (m), 1246 (m), 1213 (s), 1136 (s), 1078 (m), 1042 (w), 980 (w), 916 (w), 884 (m), 797 (w), 762 (w).

$[\alpha]_D^{20}$ = +95.0 (*c* 1.00, CH_2Cl_2).

Synthesis of Dimer 447



446

447
$C_{18}H_{22}O_4$
M = 302.26 g/mol

To a degassed solution of enol triflate **446** (30 mg, 0.10 mmol, 1.0 eq.) and Me_6Sn_2 (47 mg, 0.15 mmol, 1.5 eq.) in DMF (2.5 mL) was added CuI (6.0 mg, 32 μmol, 32 mol-%) followed by Pd_2dba_3 (16 mg, 17 μmol, 17 mol-%) and the resulting suspension was stirred at 60 °C for 1 h. After cooling to room temperature, the reaction was quenched by addition of H_2O (3 mL) and the mixture was extracted with Et_2O (3 x 7 mL). The combined organic layers were washed with 10% aqueous NaCl (2 x 10 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 5:1 to 3:1) to yield dimer **447** (11 mg, 36 μmol, 72%) as a colorless amorphous solid.

R_f = 0.12 (hexanes:EtOAc = 3:1).

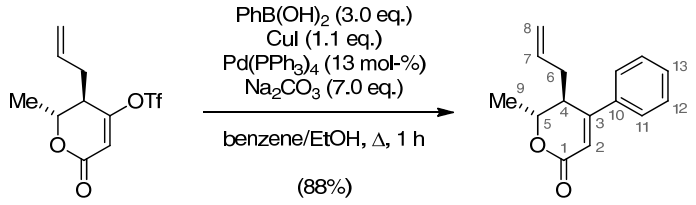
^{1}H NMR ($CDCl_3$, 600 MHz): δ = 6.24 (s, 2H, 2-H), 5.75 (m_C, 2H, 7-H), 5.20 (m_C, 2H, 8-H_A), 5.16 (m_C, 2H, 8-H_B), 4.84 (m_C, 2H, 5-H), 2.53 (m_C, 2H, 4-H), 2.34–2.24 (m, 4H, 6-H), 1.39 (d, $^3J_{9/5}$ = 6.8 Hz, 6H, 9-H) ppm.

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 162.6 (C-1), 151.6 (C-3), 133.5 (C-7), 119.8 (C-2)*, 119.4 (C-8)*, 75.7 (C-5), 38.8 (C-4), 36.9 (C-6), 20.0 (C-9) ppm.

FAB-MS for $C_{18}H_{23}O_4^+$ [$(M+H)^+$]:	calcd.	303.1591
	found	303.1577.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 3078 (w), 2979 (w), 1704 (s), 1437 (w), 1380 (w), 1350 (w), 1224 (m), 1135 (w), 1039 (m), 994 (w), 917 (w), 885 (w).

Synthesis of Lactone 448



To a suspension of enol triflate **446** (24 mg, 80 µmol, 1.0 eq.), $Pd(PPh_3)_4$ (12 mg, 10 µmol, 0.13 eq.), CuI (8.8 mg, 88 µmol, 1.1 eq.) and Na_2CO_3 (59 mg, 0.56 mmol, 7.0 eq.) in degassed benzene (5 mL) was added a solution of phenylboronic acid (29 mg, 0.24 mmol, 3.0 eq.) in EtOH (1.5 mL) and the reaction mixture was heated to reflux for 1 h changing its color from pale yellow to deep red. The mixture was allowed to cool to room temperature and quenched by addition of saturated aqueous $NaHCO_3$ (4 mL). The mixture was diluted with EtOAc (5 mL) and the organic layer was washed with H_2O (2 x 10 mL) and saturated aqueous $NaHCO_3$ (3 x 10 mL). The combined aqueous phases were re-extracted with EtOAc (2 x 10 mL) and the combined organic layers were washed with saturated aqueous NaCl (30 mL). After drying the organic layer over $MgSO_4$ and evaporation of the solvent under reduced pressure, the crude product was purified by flash column chromatography (silica, hexanes:EtOAc = 1:0 to 9:1) to yield lactone **448** (16 mg, 70 µmol, 88%) as a highly viscous colorless oil.

R_f = 0.42 (hexanes:EtOAc = 3:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.54–7.50 (m, 2H, 11-H), 7.48–7.43 (m, 3H, 12-H, 13-H), 6.31 (s, 1H, 2-H), 5.74 (m_C, 1H, 8-H), 5.14–5.09 (m, 2H, 9-H), 4.83 (qd, $^3J_{5/6}$ = 6.8 Hz, $^3J_{5/4}$ = 1.1 Hz, 1H, 5-H), 2.78 (m_C 1H, 4-H), 2.34 (m_C, 2H, 7-H), 1.47 (d, $^3J_{6/5}$ = 6.7 Hz, 3H, 6-H) ppm.

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 164.0 (C-1), 156.9 (C-3), 136.2 (C-10), 134.4 (C-8), 130.7 (C-13), 129.3 (C-12), 126.5 (C-11), 118.8 (C-9), 114.8 (C-2), 75.5 (C-5), 41.9 (C-4), 36.7 (C-7), 20.0 (C-6) ppm.

EI-MS for $C_{14}H_{16}O^+$ [$(M–CO)^+$]: calcd. 200.1196
found 200.1191.

IR (ATR): $\tilde{\upsilon}$/cm^{-1} = 3077 (w), 2979 (w), 1707 (s), 1640 (w), 1618 (w), 1446 (w), 1363 (m), 1258 (w), 1225 (m), 1135 (w), 1043 (m), 996 (w), 961 (w), 920 (w), 874 (m), 771 (m).

$[\alpha]_D^{20}$ = +241.6 (*c* 0.25, CH_2Cl_2).

APPENDICES

A1 X-RAY CRYSTALLOGRAPHIC DATA

The data collections were performed on an Oxford Diffraction Xcalibur diffractometer or on a Nonius KappaCCD diffractometer at 100K or 173 K using MoKα-radiation (λ = 0.71073 Å, graphite monochromator). The CrysAlisPro software (version 1.171.33.41)[318] was applied for the integration, scaling and multi-scan absorption correction of the data. The structures were solved by direct methods with SIR97[319] and refined by least-squares methods against $F2$ with SHELXL-97.[320] All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed in ideal geometry riding on their parent atoms. More details are provided in tables A1.1–A1.12 at the different sections.

A1.1 Diketone 116

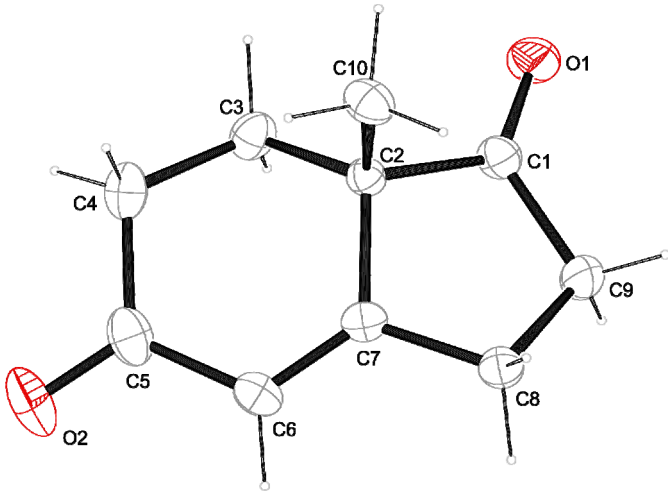
CCDC 934941 contains the supplementary crystallographic data for diketone **116**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table A1.1 Crystallographic Data for Diketone **116**.

net formula	$C_{10}H_{12}O_2$
M_r/g mol^{-1}	164.201
crystal size/mm	0.43 × 0.37 × 0.28
T/K	100(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	orthorhombic
space group	$P2_12_12_1$
a/Å	7.3464(3)
b/Å	10.3828(4)
c/Å	11.4263(4)
α/°	90
β/°	90
γ/°	90
V/Å^3	871.56(5)
Z	4
calc. density/g cm^{-3}	1.25139(7)
μ/mm^{-1}	0.086
absorption correction	'multi-scan'
transmission factor range	0.99380–1.00000
refls. measured	6290
R_{int}	0.0282
mean σ(I)/I	0.0327
θ range	4.31–28.28
observed refls.	1942
x, y (weighting scheme)	0.0370, 0.1077
hydrogen refinement	constr
Flack parameter	–0.4(13)
refls in refinement	2149
parameters	110
restraints	0

$R(F_{obs})$	0.0350
$R_w(F^2)$	0.0834
S	1.056
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.184
min electron density/e Å^{-3}	–0.126

Flack test meaningless (Mo radiation, no anomalous scatterer), correct structure derived from synthesis.



A1.2 Acid 205

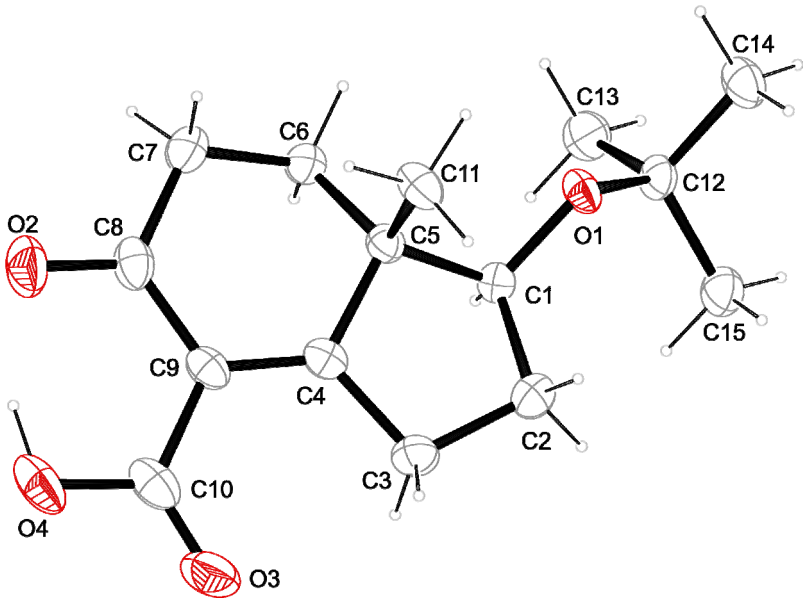
CCDC 934940 contains the supplementary crystallographic data for acid **205**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table A1.2 Crystallographic data for acid **205**.

net formula	$C_{15}H_{22}O_4$
M_r/g mol^{-1}	266.333
crystal size/mm	0.25 × 0.17 × 0.12
T/K	100(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	orthorhombic
space group	$P2_12_12_1$
a/Å	6.3678(7)
b/Å	9.2177(8)
c/Å	24.664(3)
α/°	90
β/°	90
γ/°	90
V/Å^3	1447.7(3)
Z	4
calc. density/g cm^{-3}	1.2220(3)
μ/mm^{-1}	0.087
absorption correction	'multi-scan'
transmission factor range	0.98476–1.00000
refls. measured	7632

R_{int}	0.0350
mean σ(I)/I	0.0423
θ range	4.23–25.34
observed refls.	2316
x, y (weighting scheme)	0.0262, 0.3919
hydrogen refinement	mixed
Flack parameter	0.0(12)
refls in refinement	2641
parameters	180
restraints	0
$R(F_{obs})$	0.0389
$R_w(F^2)$	0.0832
S	1.022
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.152
min electron density/e Å^{-3}	−0.159

Flack test meaningless (no anomalous scatterer, Mo radiation), correct structure derived from synthesis. C-bound H: constr, O-bound H: refall.



A1.3 Ketone 195

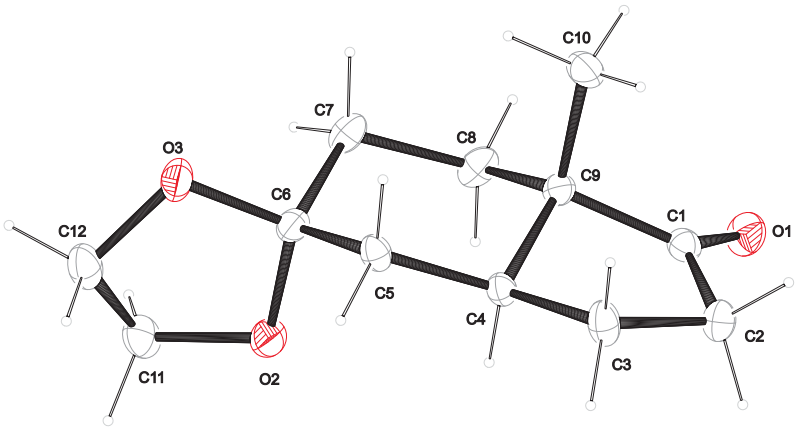
CCDC 865613 contains the supplementary crystallographic data for ketone **195**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table A1.3 Crystallographic data for ketone **195**

net formula	$C_{12}H_{18}O_3$
M_r/g mol^{-1}	210.270
crystal size/mm	0.31 × 0.28 × 0.12
T/K	173(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'

crystal system	orthorhombic
space group	$P2_12_12_1$
a/Å	9.2588(5)
b/Å	9.4467(5)
c/Å	12.5446(7)
α/°	90
β/°	90
γ/°	90
V/Å^3	1097.21(10)
Z	4
calc. density/g cm^{-3}	1.27292(12)
μ/mm^{-1}	0.090
absorption correction	'multi-scan'
transmission factor range	0.89301–1.00000
refls. measured	8113
R_{int}	0.0310
mean σ(I)/I	0.0270
θ range	4.31–26.33
observed refls.	1051
x, y (weighting scheme)	0.0500, 0
hydrogen refinement	Constr
Flack parameter	–3.1(15)
refls in refinement	1301
parameters	137
restraints	0
$R(F_{obs})$	0.0320
$R_w(F^2)$	0.0784
S	0.969
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.166
min electron density/e Å^{-3}	–0.136

Flack parameter meaningless. 933 Friedel pairs merged.



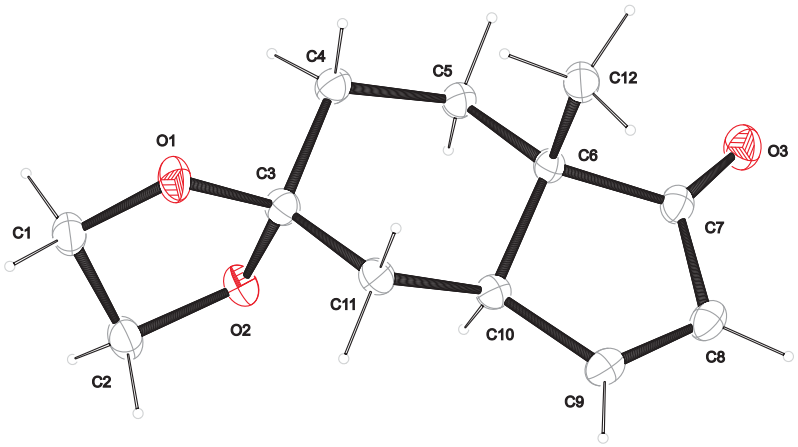
A1.4 Enone 194

CCDC 865618 contains the supplementary crystallographic data for enone **194**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table A1.4 Crystallographic data for enone **194**

net formula	$C_{12}H_{16}O_3$
M_r/g mol^{-1}	208.254
crystal size/mm	0.49 × 0.16 × 0.03
T/K	173(2)
Radiation	MoKα
diffractometer	'KappaCCD'
crystal system	monoclinic
space group	$P2_1$
a/Å	6.4233(5)
b/Å	9.7999(7)
c/Å	8.5116(7)
α/°	90
β/°	100.147(4)
γ/°	90
V/Å^3	527.41(7)
Z	2
calc. density/g cm^{-3}	1.31138(17)
μ/mm^{-1}	0.093
absorption correction	none
refls. measured	3526
R_{int}	0.0515
mean σ(I)/I	0.0365
θ range	3.84–25.32
observed refls.	874
x, y (weighting scheme)	0.0496, 0.0788
hydrogen refinement	constr
Flack parameter	–1.7(19)
refls in refinement	1016
parameters	137
restraints	1
$R(F_{obs})$	0.0379
$R_w(F^2)$	0.0953
S	1.081
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.166
min electron density/e Å^{-3}	–0.185

Flack parameter meaningless, absolute structure deduced from synthesis, 845 Friedel pairs merged.



A1.5 Ketone 220

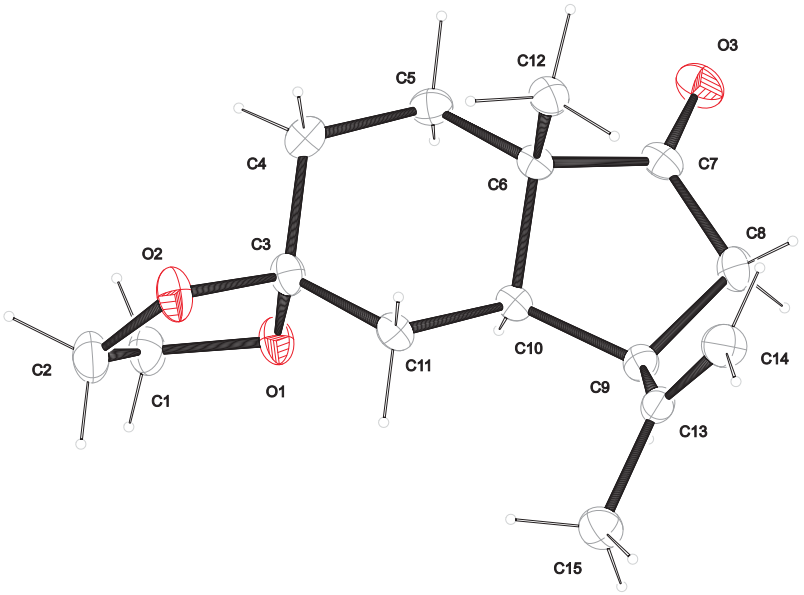
CCDC 865615 contains the supplementary crystallographic data for ketone **220**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table A1.5 Crystallographic data for ketone **220**.

net formula	$C_{15}H_{22}O_3$
M_r/g mol^{-1}	250.333
crystal size/mm	0.29 × 0.17 × 0.07
T/K	173(2)
Radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	monoclinic
space group	$P2_1$
a/Å	9.6490(5)
b/Å	5.8746(3)
c/Å	12.3783(7)
α/°	90
β/°	107.487(6)
γ/°	90
V/Å^3	669.22(6)
Z	2
calc. density/g cm^{-3}	1.24233(11)
μ/mm^{-1}	0.085
absorption correction	'multi-scan'
transmission factor range	0.96533–1.00000
refls. measured	4829
R_{int}	0.0299
mean σ(I)/I	0.0419
θ range	4.20–26.33
observed refls.	1167
x, y (weighting scheme)	0.0412, 0
hydrogen refinement	constr
Flack parameter	–2.5(13)
refls in refinement	1488
parameters	165
restraints	1
$R(F_{obs})$	0.0344

$R_w(F^2)$	0.0732
S	0.926
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.169
min electron density/e Å^{-3}	−0.118

Flack parameter meaningless. 741 Friedel pairs merged. Absolute structure deduced from synthesis.



A1.6 Ketone *ent*-141

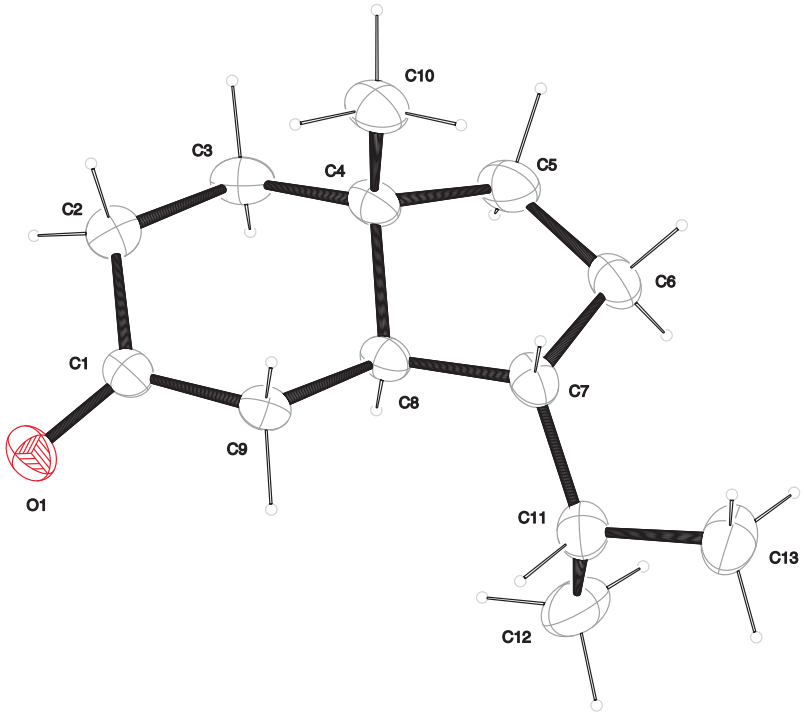
CCDC 865614 contains the supplementary crystallographic data for ketone *ent*-**141**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table A1.6 Crystallographic data for ketone *ent*-**141**.

net formula	$C_{13}H_{22}O$
M_r/g mol^{-1}	194.313
crystal size/mm	0.15 × 0.14 × 0.04
T/K	173(2)
Radiation	MoKα
Diffractometer	'KappaCCD'
crystal system	monoclinic
space group	$P2_1$
a/Å	7.2906(10)
b/Å	6.4842(11)
c/Å	13.310(2)
α/°	90
β/°	104.680(10)
γ/°	90
V/Å^3	608.67(17)
Z	2
calc. density/g cm^{-3}	1.0602(3)
μ/mm^{-1}	0.064
absorption correction	none

refls. Measured	2730
R_{int}	0.0901
mean σ(*I*)/*I*	0.0727
θ range	3.63–23.63
observed refls.	715
x, y (weighting scheme)	0.0964, 0.0251
hydrogen refinement	constr
Flack parameter	−1(5)
refls in refinement	974
Parameters	130
Restraints	1
$R(F_{obs})$	0.0686
$R_w(F^2)$	0.1868
S	1.180
shift/error$_{max}$	0.001
max electron density/e Å^3	0.190
min electron density/e Å^3	−0.185

Flack parameter meaningless, 589 Friedel pairs merged. Investigated crystal had poor scattering strength leading to reduced resolution.



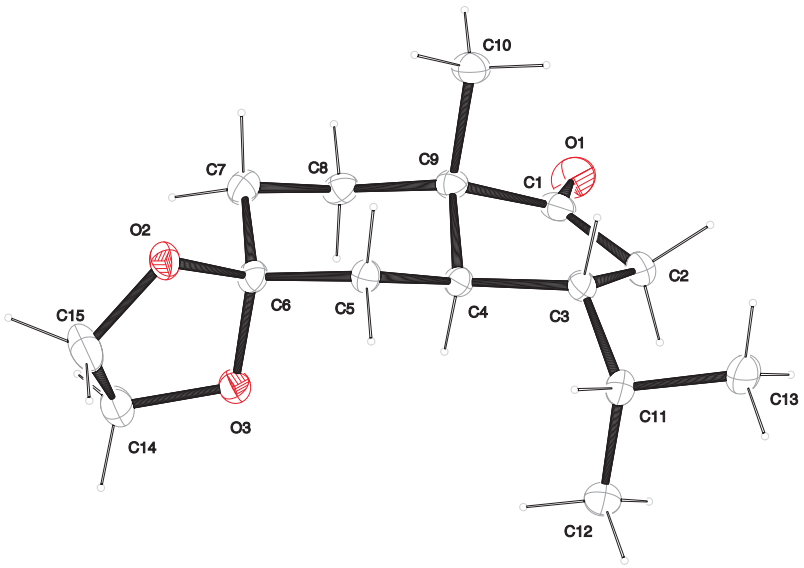
A1.7 Ketone 222

CCDC 865619 contains the supplementary crystallographic data for ketone **222**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table A1.7 Crystallographic data for ketone **222**.

net formula	$C_{15}H_{24}O_3$
M_r/g mol^{-1}	252.349
crystal size/mm	0.23 × 0.20 × 0.11
T/K	173(2)
Radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	Orthorhombic
space group	$P2_12_12_1$
a/Å	5.8846(4)
b/Å	9.0415(5)
c/Å	26.2051(14)
α/°	90
β/°	90
γ/°	90
V/Å^3	1394.26(14)
Z	4
calc. density/g cm^{-3}	1.20219(12)
μ/mm^{-1}	0.082
absorption correction	'multi-scan'
transmission factor range	0.98145–1.00000
refls. Measured	5778
R_{int}	0.0359
mean σ(I)/I	0.0470
θ range	4.20–26.24
observed refls.	1215
x, y (weighting scheme)	0.0388, 0
hydrogen refinement	constr
Flack parameter	1.5(14)
refls in refinement	1665
Parameters	166
Restraints	0
$R(F_{obs})$	0.0361
$R_w(F^2)$	0.0738
S	0.894
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.177
min electron density/e Å^{-3}	–0.124

Flack Parameter meaningless, 1256 Friedel pairs merged. Absolute structure derived from synthesis.



A1.8 Ketone 246

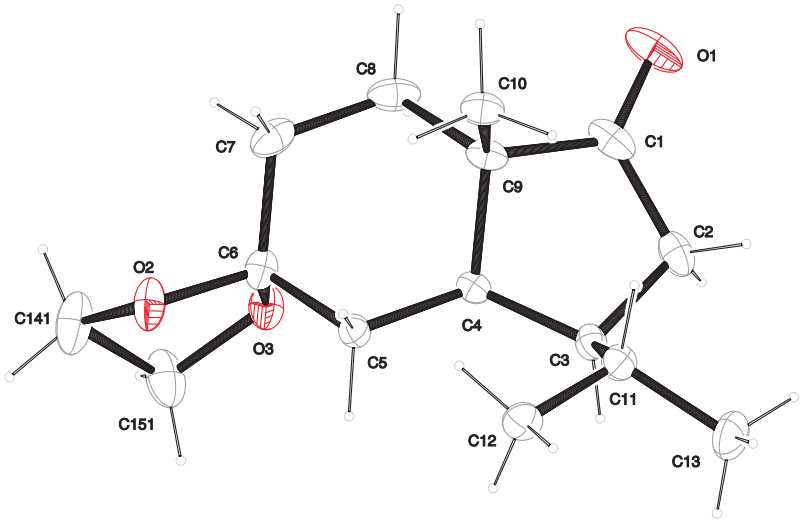
CCDC 865616 contains the supplementary crystallographic data for ketone **246**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table A1.8 Crystallographic data for ketone **246**.

net formula	$C_{15}H_{24}O_3$
M_r/g mol^{-1}	252.349
crystal size/mm	0.26 × 0.11 × 0.06
T/K	173(2)
Radiation	MoKα
Diffractometer	'KappaCCD'
crystal system	monoclinic
space group	$P2_1$
a/Å	10.0211(5)
b/Å	5.8555(2)
c/Å	11.9154(6)
α/°	90
β/°	93.215(2)
γ/°	90
V/Å^3	698.08(5)
Z	2
calc. density/g cm^{-3}	1.20056(9)
μ/mm^{-1}	0.082
absorption correction	None
refls. Measured	4457
R_{int}	0.0240
mean σ(I)/I	0.0351
θ range	3.89–25.31
observed refls.	2167
x, y (weighting scheme)	0.0396, 0.1213
hydrogen refinement	Constr
Flack parameter	0.7(12)
refls in refinement	2417

Parameters	185
Restraints	2
$R(F_{obs})$	0.0392
$R_w(F^2)$	0.0970
S	1.148
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.143
min electron density/e Å^{-3}	−0.152

Flack test results meaningless, no anomalous scatterer in structure. C14 and C15 are disordered, split model applied, sof ratio 0.58/0.42. Only the main part of the disordered group C14/C15 is shown is the figure:



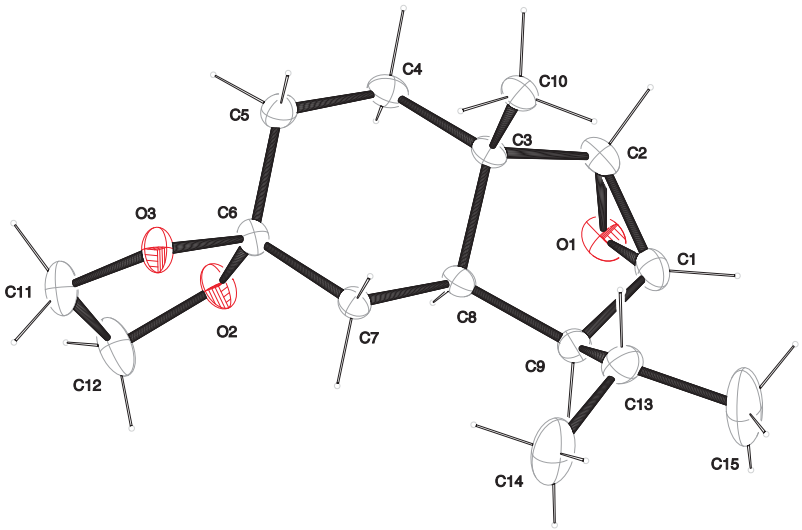
A1.9 Epoxide 250

CCDC 934938 contains the supplementary crystallographic data for epoxide **250**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table A1.9 Crystallographic data for epoxide **250**.

net formula	$C_{15}H_{24}O_3$
M_r/g mol^{-1}	252.349
crystal size/mm	0.33 × 0.09 × 0.07
T/K	173(2)
radiation	MoKα
diffractometer	'KappaCCD'
crystal system	orthorhombic
space group	$P2_12_12_1$
a/Å	5.88880(10)
b/Å	14.6273(4)
c/Å	16.5099(4)
α/°	90
β/°	90
γ/°	90
V/Å^3	1422.12(6)

Z	4
calc. density/g cm^{-3}	1.17864(5)
μ/mm^{-1}	0.080
absorption correction	None
refls. Measured	9872
R_{int}	0.0312
mean σ(I)/I	0.0265
θ range	3.72–26.00
observed refls.	2449
x, y (weighting scheme)	0.0613, 0.3685
hydrogen refinement	constr
Flack parameter	–0.2(13)
refls in refinement	2785
parameters	166
restraints	0
$R(F_{obs})$	0.0450
$R_w(F^2)$	0.1169
S	1.047
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.368
min electron density/e Å^{-3}	–0.258



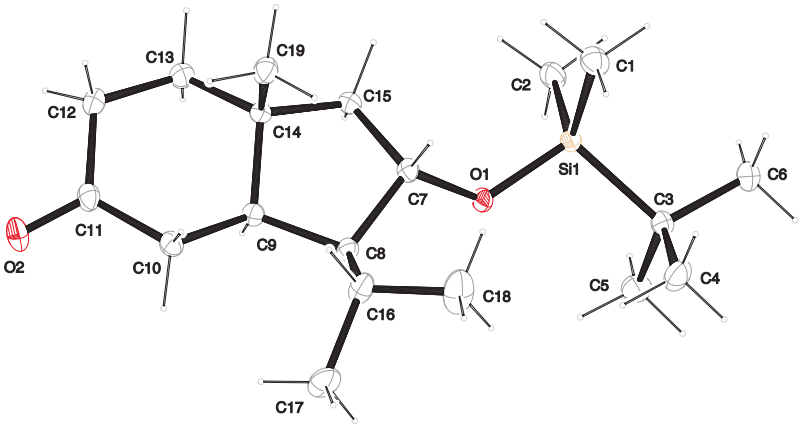
A1.10 Ketone 191

CCDC 865617 contains the supplementary crystallographic data for ketone **191**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table A1.10 Crystallographic data for ketone **191**.

net formula	$C_{19}H_{36}O_2Si$
M_r/g mol^{-1}	324.573
crystal size/mm	0.31 × 0.29 × 0.15
T/K	173(2)
Radiation	MoKα
Diffractometer	'Oxford XCalibur'

crystal system	orthorhombic
space group	$P2_12_12_1$
a/Å	6.1373(2)
b/Å	10.5263(4)
c/Å	30.6532(13)
α/°	90
β/°	90
γ/°	90
V/Å^3	1980.29(13)
Z	4
calc. density/g cm^{-3}	1.08868(7)
μ /mm^{-1}	0.124
absorption correction	'multi-scan'
transmission factor range	0.93992–1.00000
refls. Measured	15263
R_{int}	0.0421
mean σ(I)/I	0.0564
θ range	4.25–26.35
observed refls.	3138
x, y (weighting scheme)	0.0376, 0
hydrogen refinement	constr
Flack parameter	0.00(11)
refls in refinement	3991
parameters	207
restraints	0
$R(F_{obs})$	0.0344
$R_w(F^2)$	0.0720
S	0.920
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.200
min electron density/e Å^{-3}	–0.170



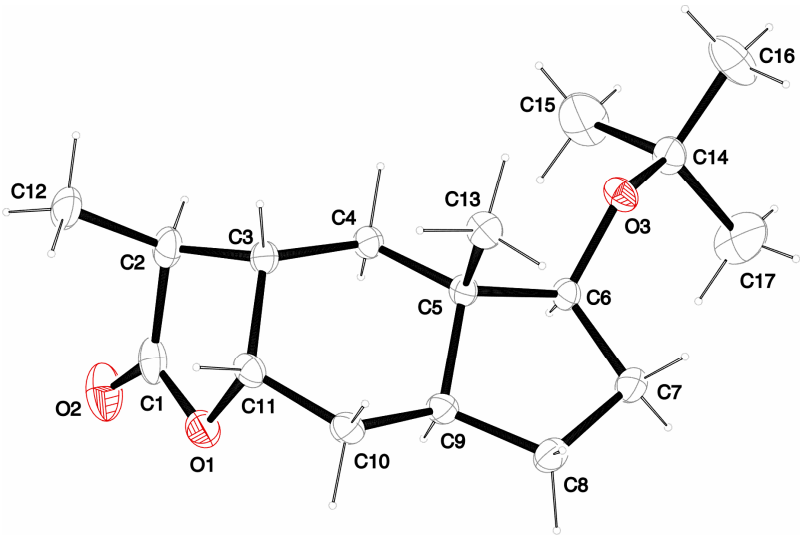
A1.11 Lactone 291

CCDC 934939 contains the supplementary crystallographic data for lactone **291**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table A.11 Crystallographic data for lactone **291**.

net formula	$C_{17}H_{28}O_3$
M_r/g mol^{-1}	280.402
crystal size/mm	0.33 × 0.20 × 0.15
T/K	173(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	orthorhombic
space group	$P2_12_12_1$
a/Å	9.1321(9)
b/Å	11.8589(12)
c/Å	15.1809(15)
α/°	90
β/°	90
γ/°	90
V/Å^3	1644.0(3)
Z	4
calc. density/g cm^{-3}	1.1329(2)
μ/mm^{-1}	0.076
absorption correction	'multi-scan'
transmission factor range	0.75017–1.00000
refls. Measured	5560
R_{int}	0.0337
mean σ(I)/I	0.0342
θ range	4.31–26.10
observed refls.	1655
x, y (weighting scheme)	0.0545, 0.1445
hydrogen refinement	Constr
Flack parameter	–1.1(15)
refls in refinement	1869
Parameters	186
Restraints	0
$R(F_{obs})$	0.0400
$R_w(F^2)$	0.1031
S	1.060
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.167
min electron density/e Å^{-3}	–0.199

Flack parameter meaningless, 1386 Friedel pairs merged, correct structure deduced from synthesis.



A1.12 Carbamate 443

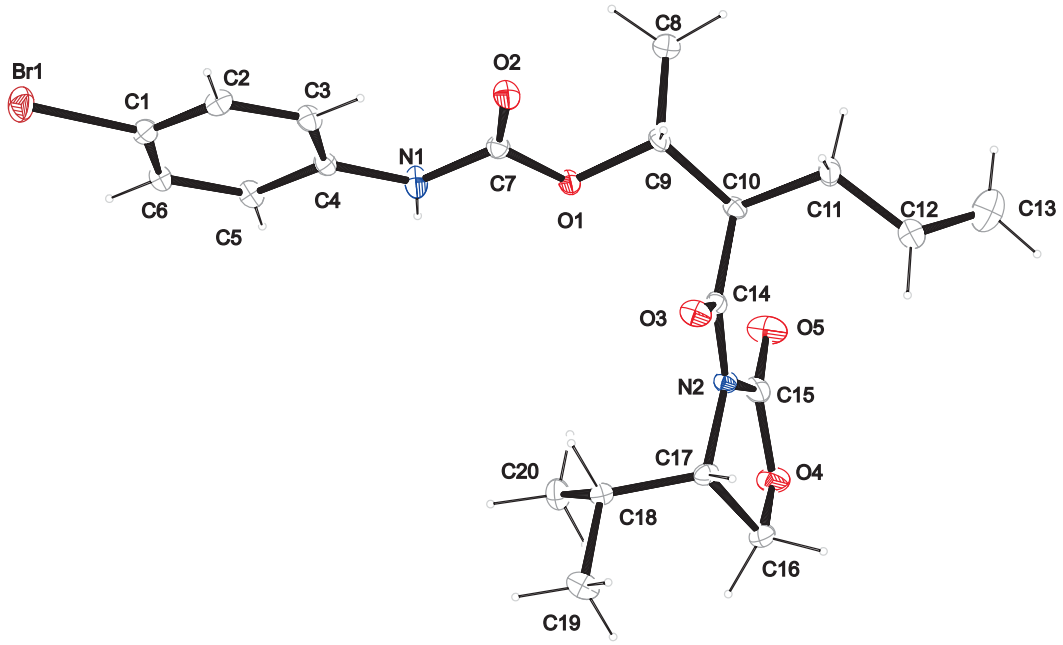
CCDC 934937 contains the supplementary crystallographic data for carbamate **443**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table A1.12 Crystallographic data for carbamte **443**.

net formula	$C_{20}H_{25}BrN_2O_5$
M_r/g mol^{-1}	453.327
crystal size/mm	0.31 × 0.22 × 0.16
T/K	173(2)
Radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	orthorhombic
space group	$P2_12_12_1$
a/Å	5.9917(2)
b/Å	9.7824(4)
c/Å	36.0498(14)
α/°	90
β/°	90
γ/°	90
V/Å^3	2112.99(14)
Z	4
calc. density/g cm^{-3}	1.42505(9)
μ/mm^{-1}	1.978
absorption correction	'multi-scan'
transmission factor range	0.93697–1.00000
refls. Measured	8750
R_{int}	0.0340
mean σ(I)/I	0.0838
θ range	4.17–26.33
observed refls.	2799
x, y (weighting scheme)	0.0131, 0
hydrogen refinement	mixed
Flack parameter	0.013(6)
refls in refinement	4003
parameters	259

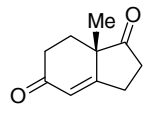
restraints	1
$R(F_{obs})$	0.0300
$R_w(F^2)$	0.0433
S	0.800
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.469
min electron density/e Å^{-3}	–0.329

C-bound H: constr., N-bound H: distance fixed to 0.88(1) Å, U(H) = 1.2 U(N).



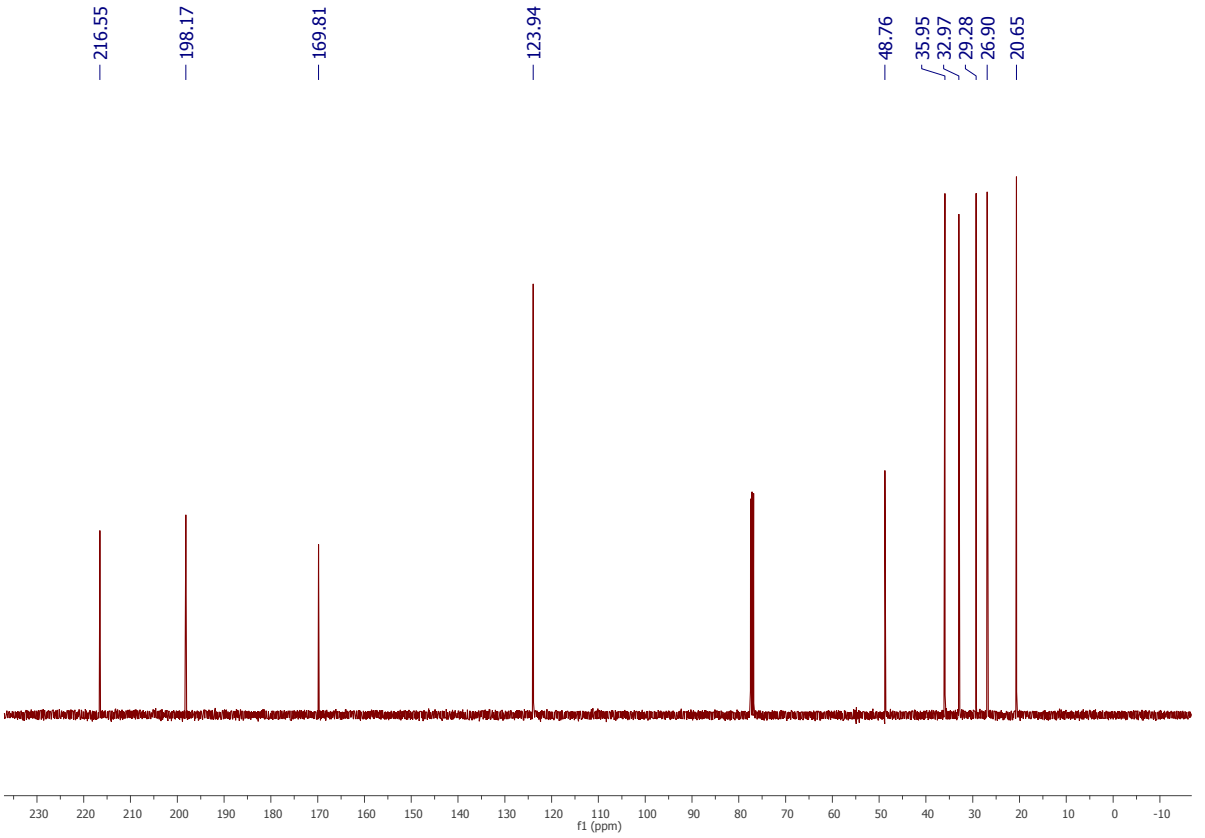
A2 ^{1}H AND ^{13}C NMR SPECTRA

^{1}H NMR ($CDCl_3$, 300 MHz):

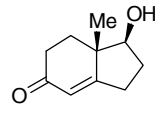


116
$C_{10}H_{12}O_2$
M = 164.20 g/mol

^{13}C NMR ($CDCl_3$, 75 MHz):

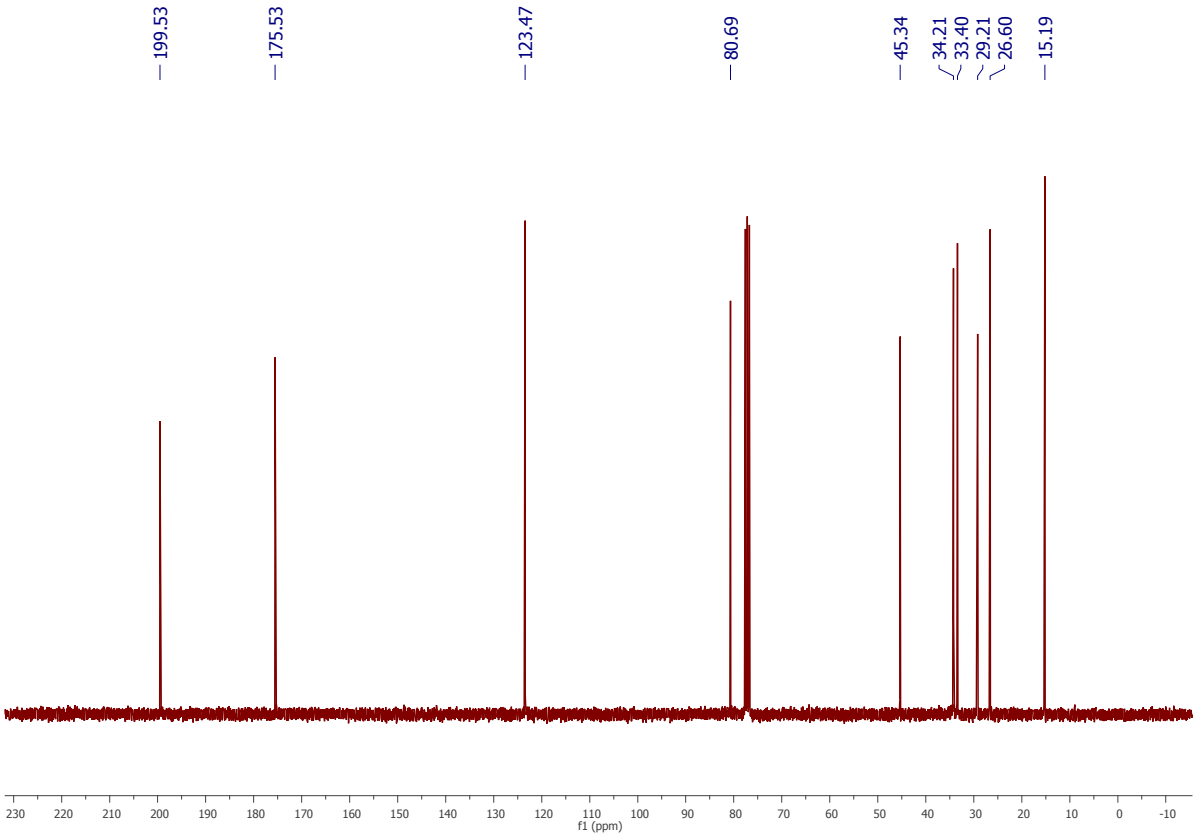


^{1}H NMR ($CDCl_3$, 300 MHz):

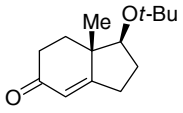


201
$C_{10}H_{14}O_2$
M = 166.22 g/mol

^{13}C NMR ($CDCl_3$, 75 MHz):

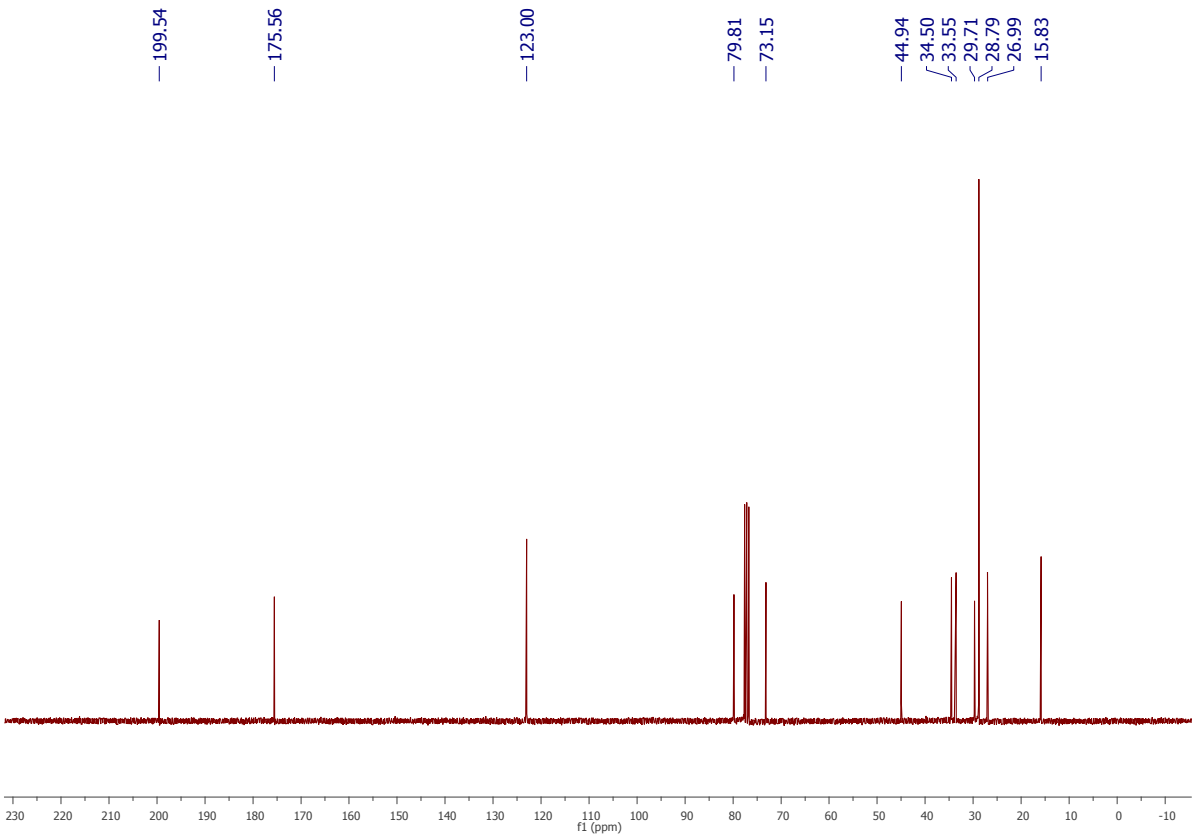


^{1}H NMR ($CDCl_3$, 300 MHz):

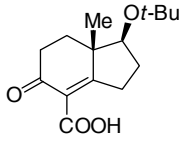


203
$C_{14}H_{22}O_2$
M = 222.32 g/mol

^{13}C NMR ($CDCl_3$, 75 MHz):

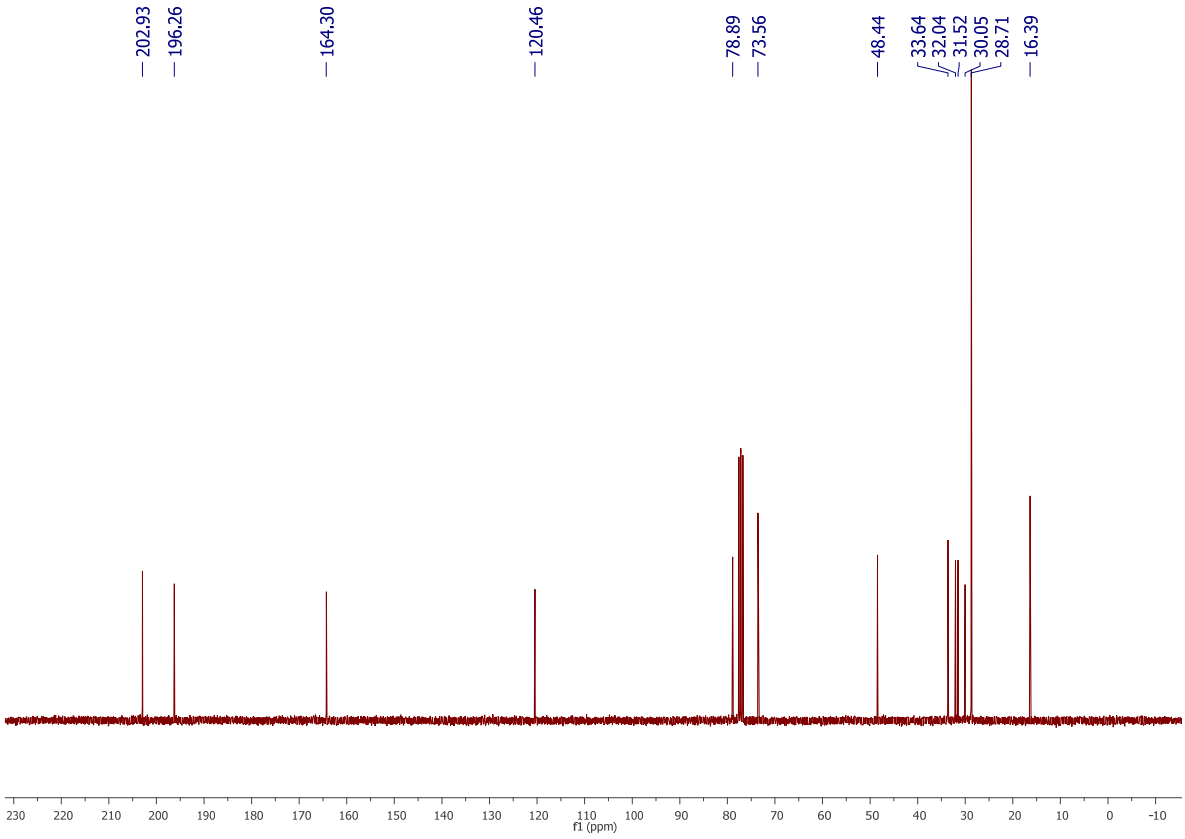


^{1}H NMR ($CDCl_3$, 300 MHz):

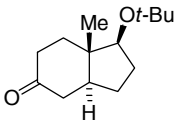


205
$C_{15}H_{22}O_4$
M = 266.33 g/mol

^{13}C NMR ($CDCl_3$, 75 MHz):

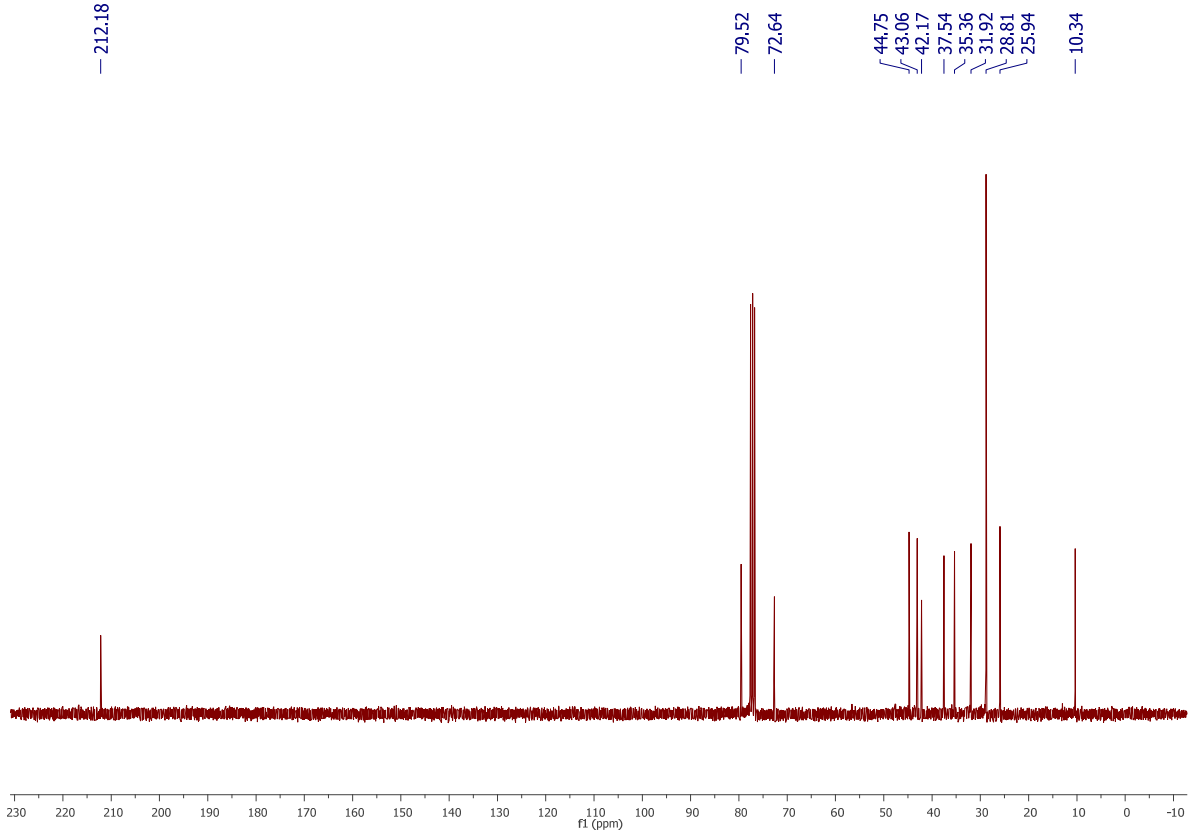


^{1}H NMR ($CDCl_3$, 400 MHz):

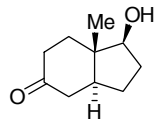


207
$C_{14}H_{24}O_2$
M = 224.34 g/mol

^{13}C NMR ($CDCl_3$, 100 MHz):

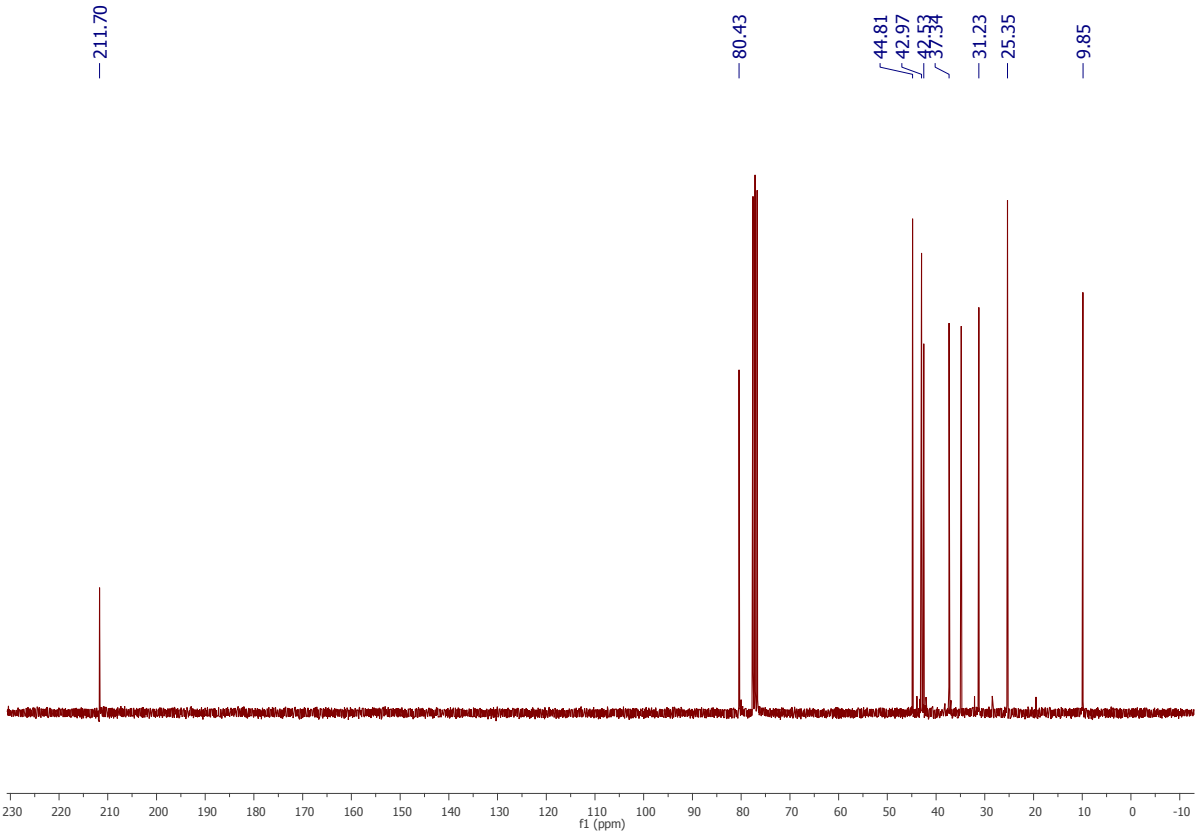


^{1}H NMR ($CDCl_3$, 300 MHz):

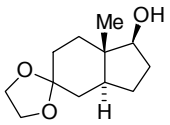


208
$C_{10}H_{16}O_2$
M = 168.23 g/mol

^{13}C NMR ($CDCl_3$, 75 MHz):

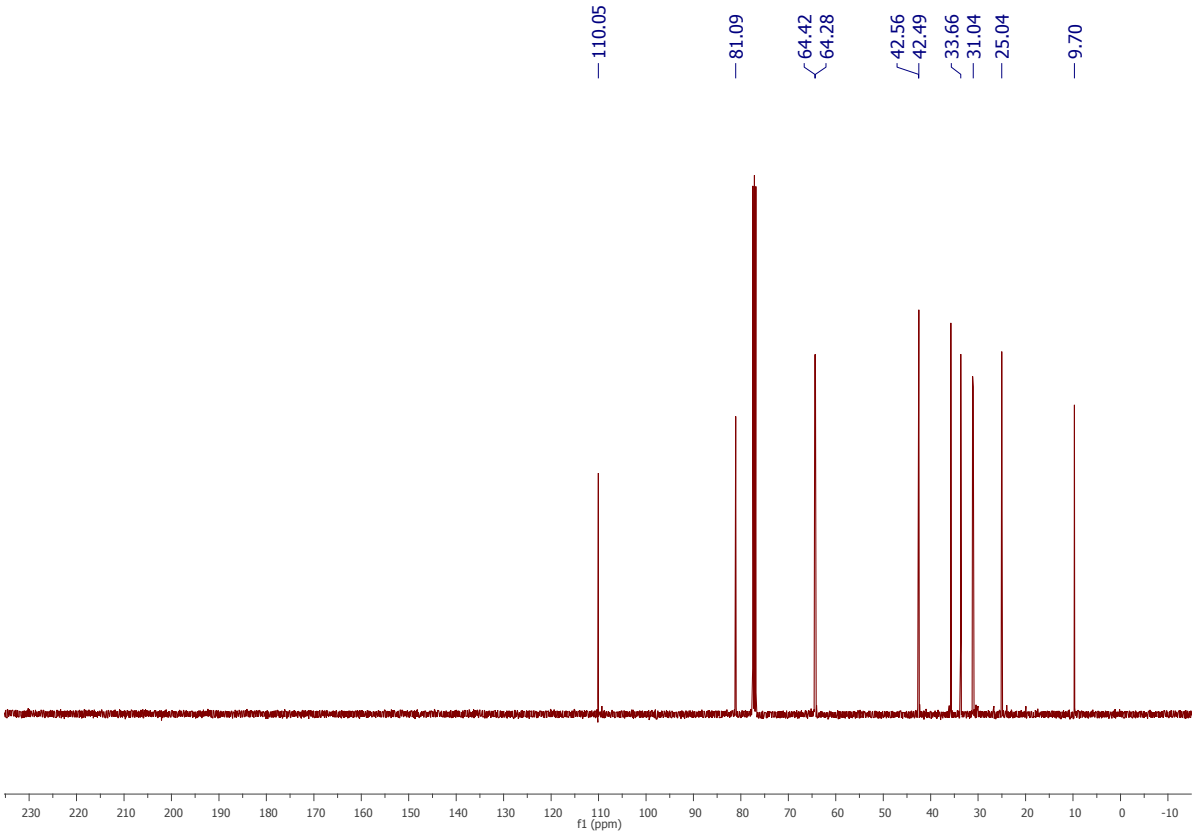


^{1}H NMR ($CDCl_3$, 400 MHz):

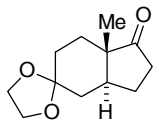


210
$C_{12}H_{20}O_3$
M = 212.29 g/mol

^{13}C NMR ($CDCl_3$, 100 MHz):

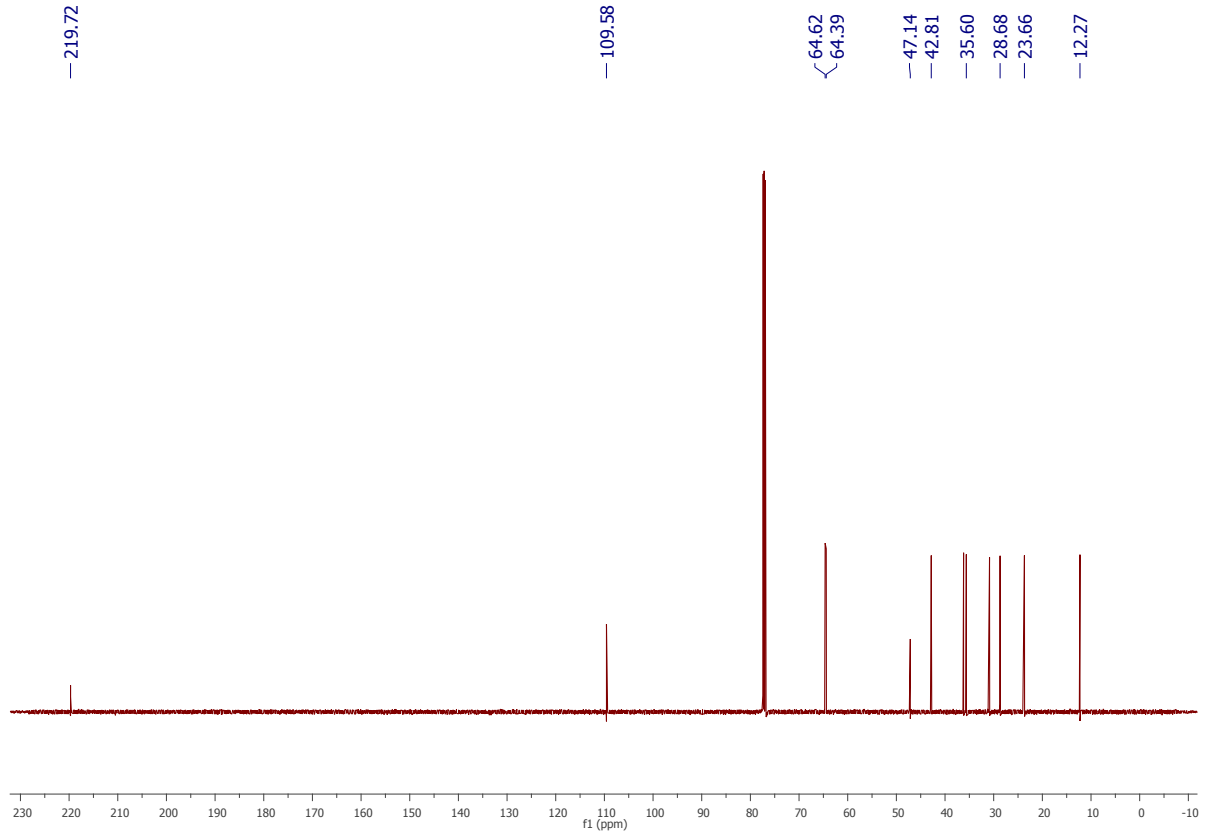


^{1}H NMR ($CDCl_3$, 600 MHz):

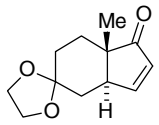


195
$C_{12}H_{18}O_3$
M = 210.27 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

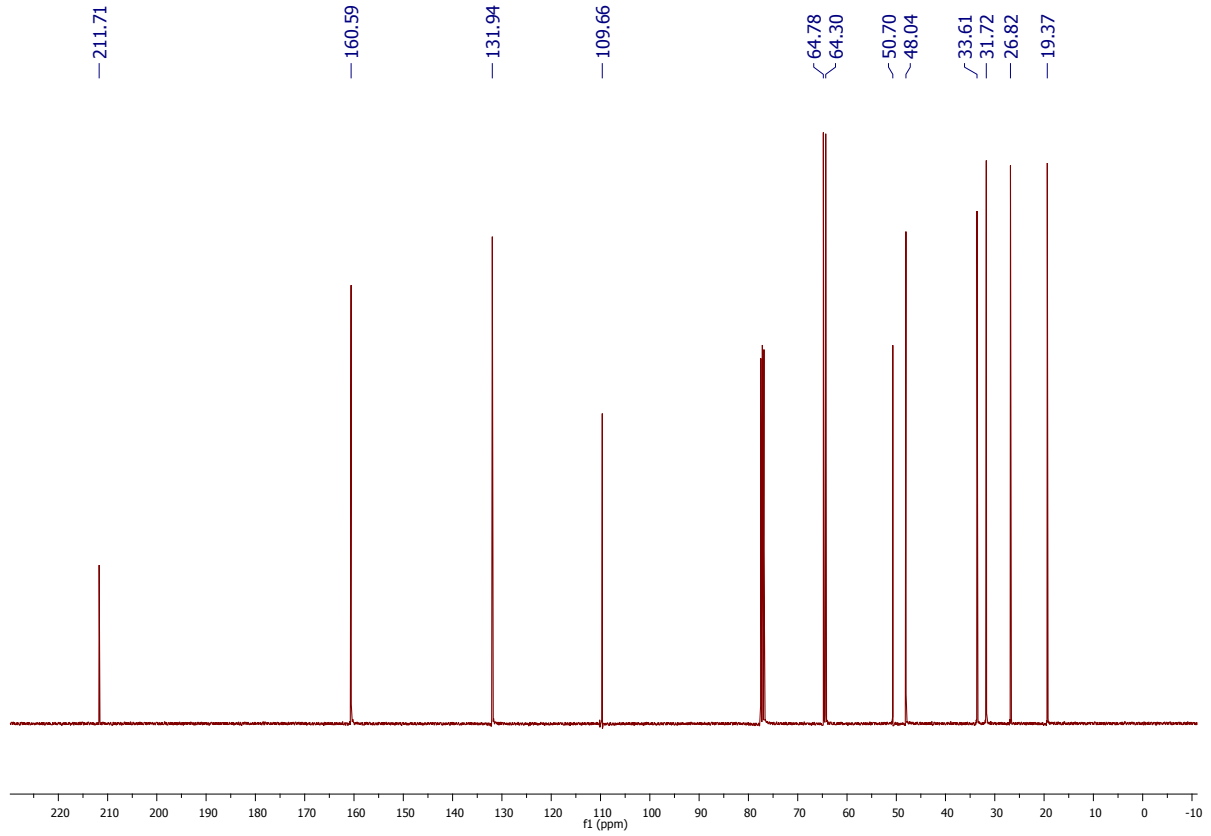


^{1}H NMR ($CDCl_3$, 600 MHz):

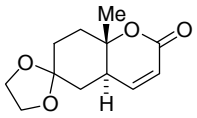


194
$C_{12}H_{16}O_3$
M = 208.25 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

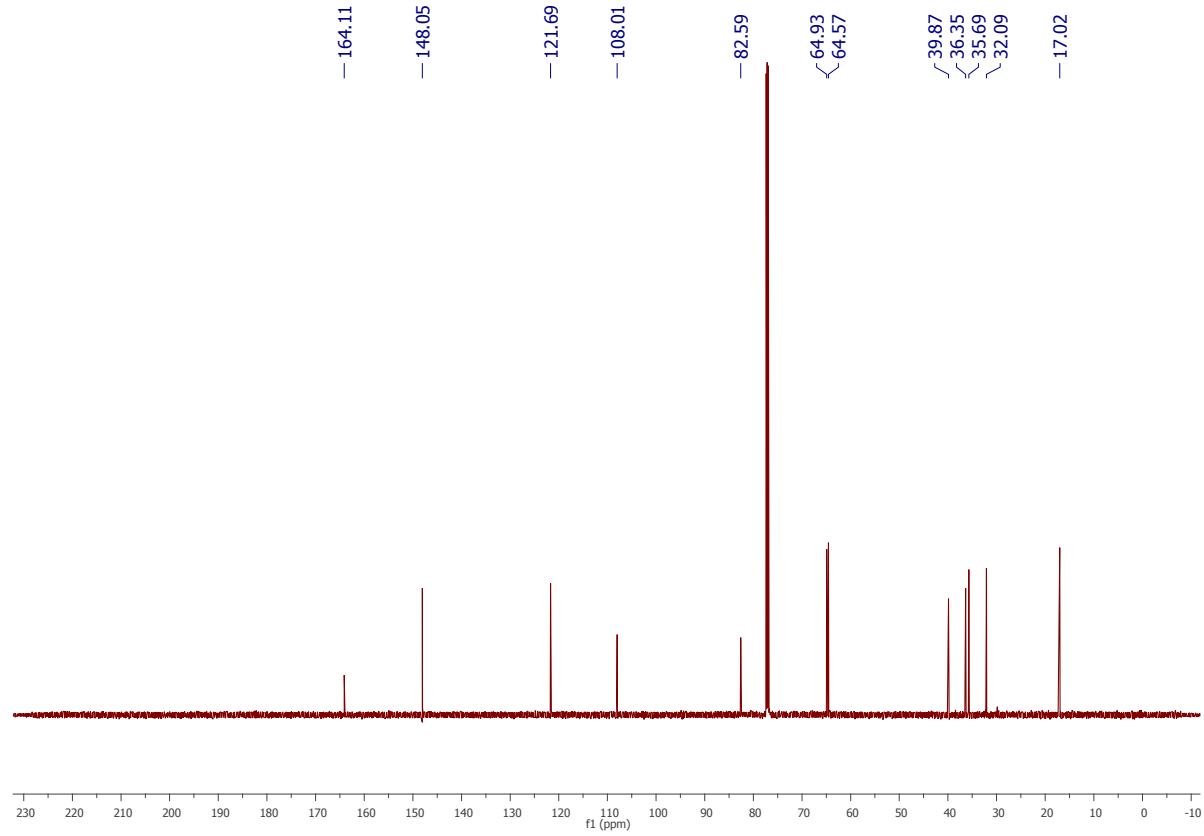


^{1}H NMR ($CDCl_3$, 600 MHz):

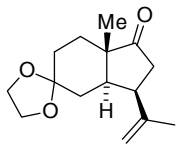


217
$C_{12}H_{16}O_4$
M = 224.25 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

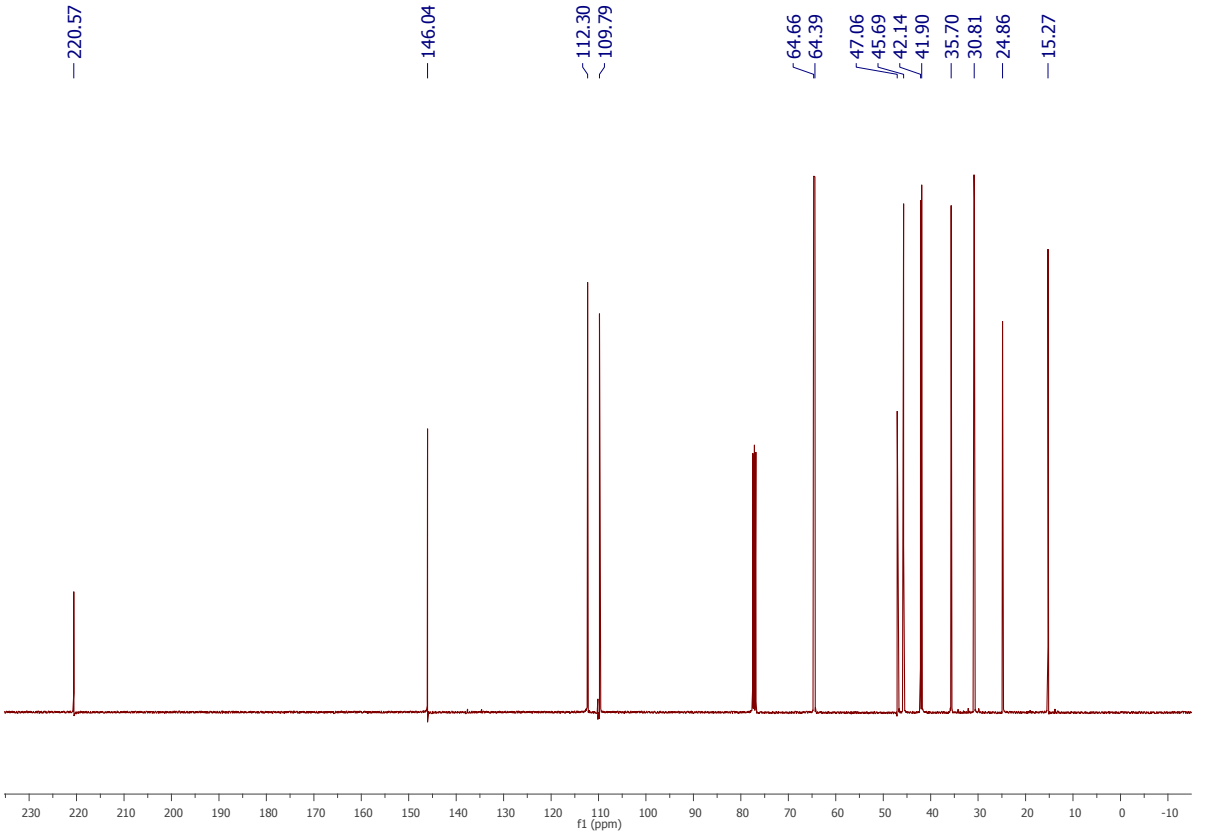


^{1}H NMR ($CDCl_3$, 600 MHz):

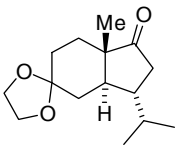


220
$C_{15}H_{22}O_3$
M = 250.33 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

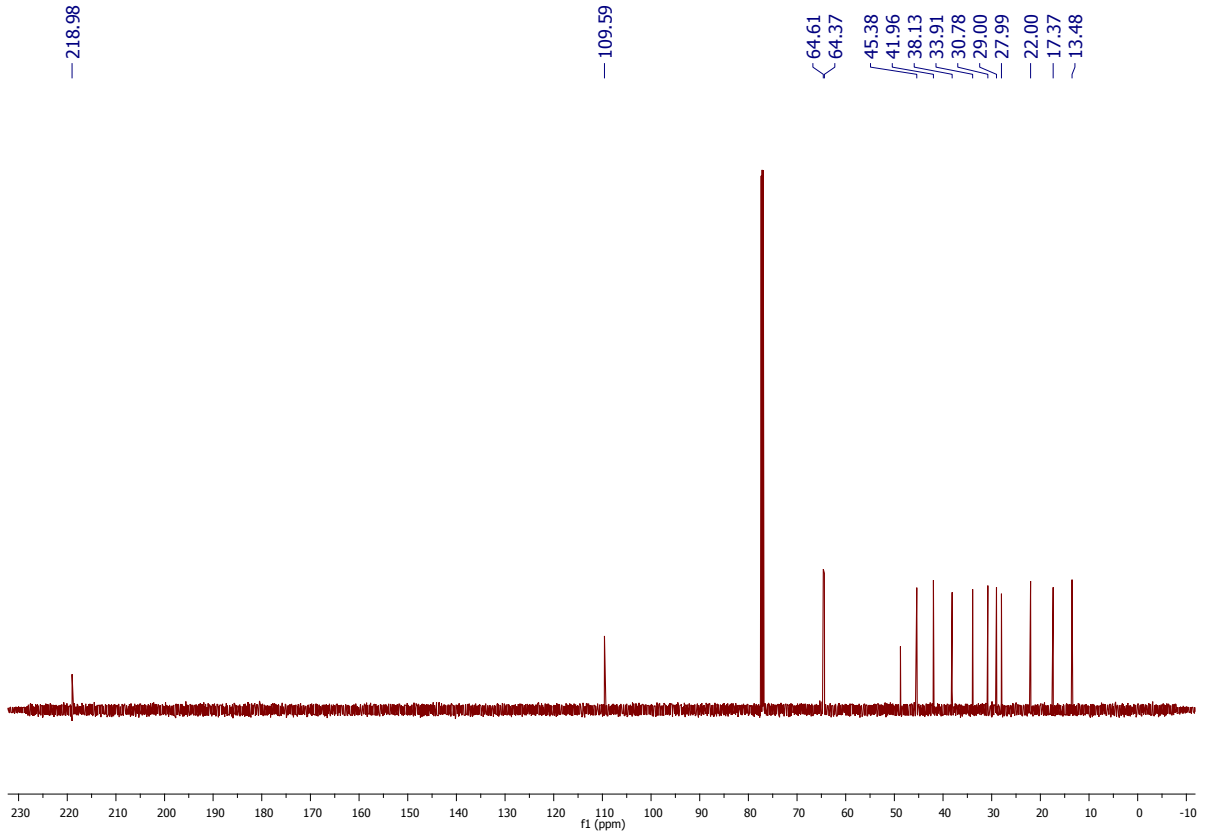


^{1}H NMR ($CDCl_3$, 600 MHz):

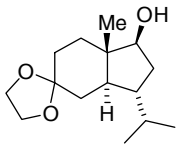


222
$C_{15}H_{24}O_3$
M = 252.35 g/mol

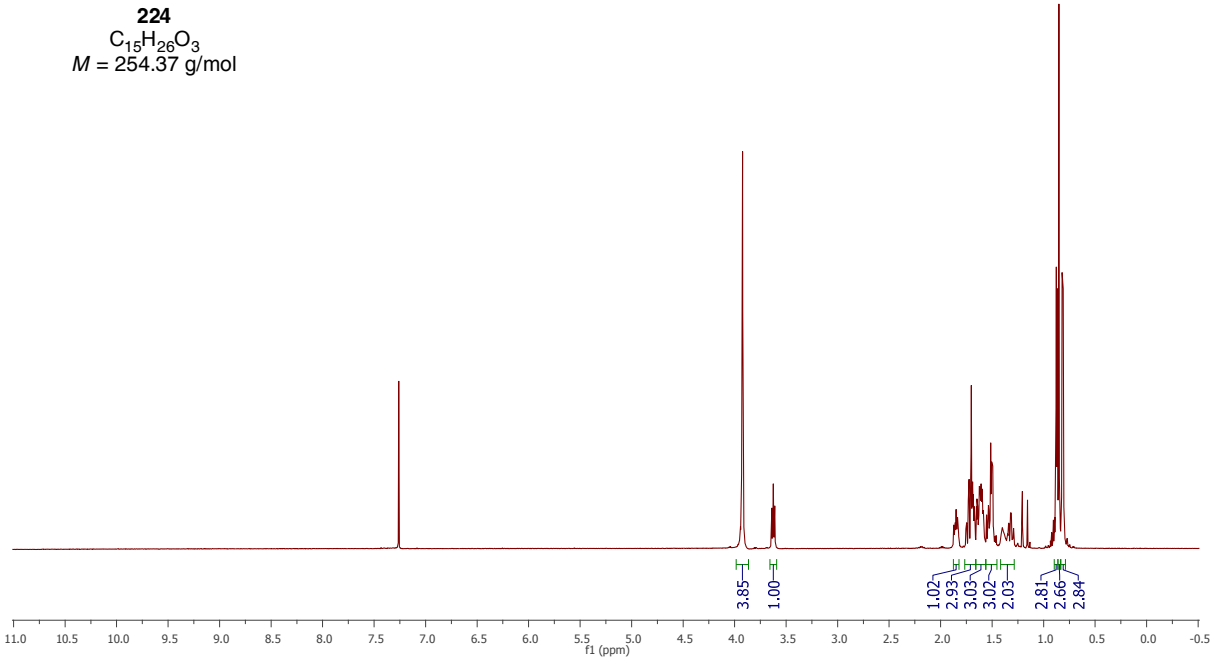
^{13}C NMR ($CDCl_3$, 150 MHz):



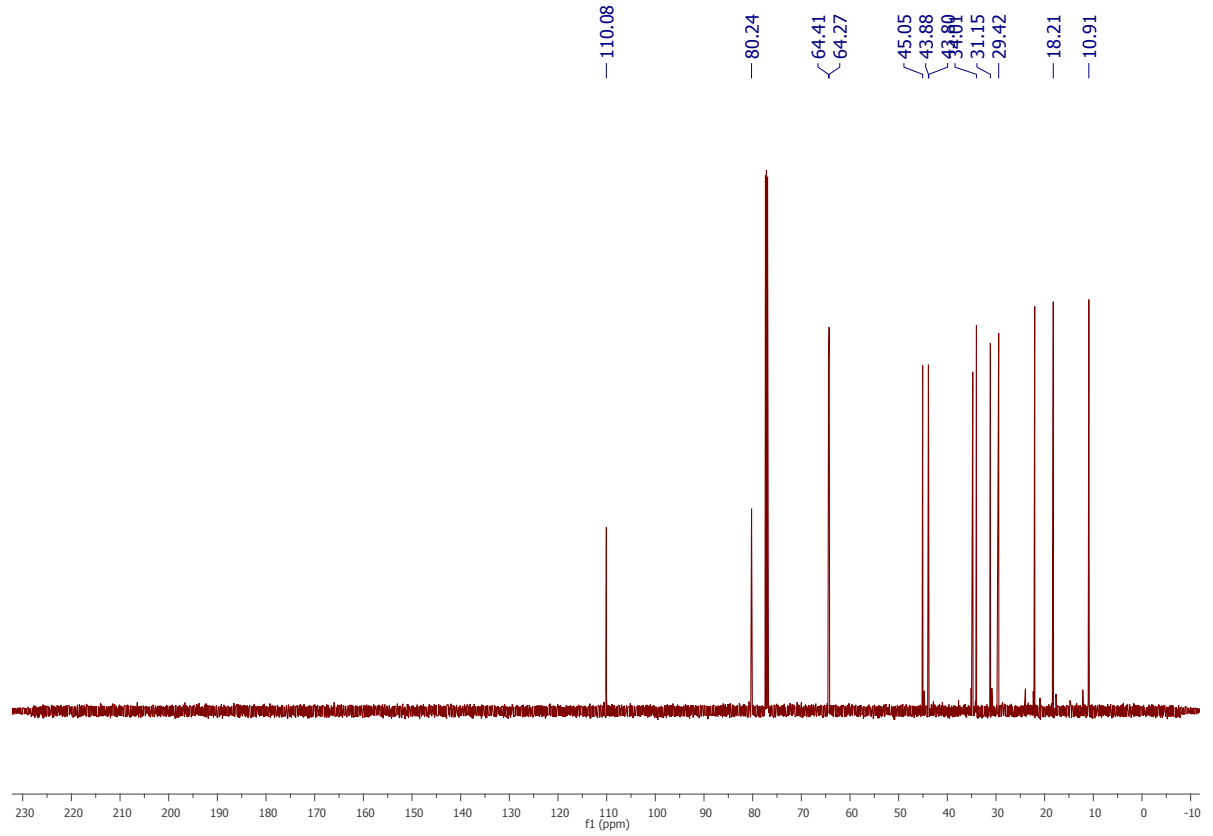
^{1}H NMR ($CDCl_3$, 600 MHz):



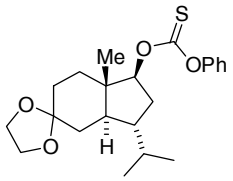
224
$C_{15}H_{26}O_3$
M = 254.37 g/mol



^{13}C NMR ($CDCl_3$, 150 MHz):

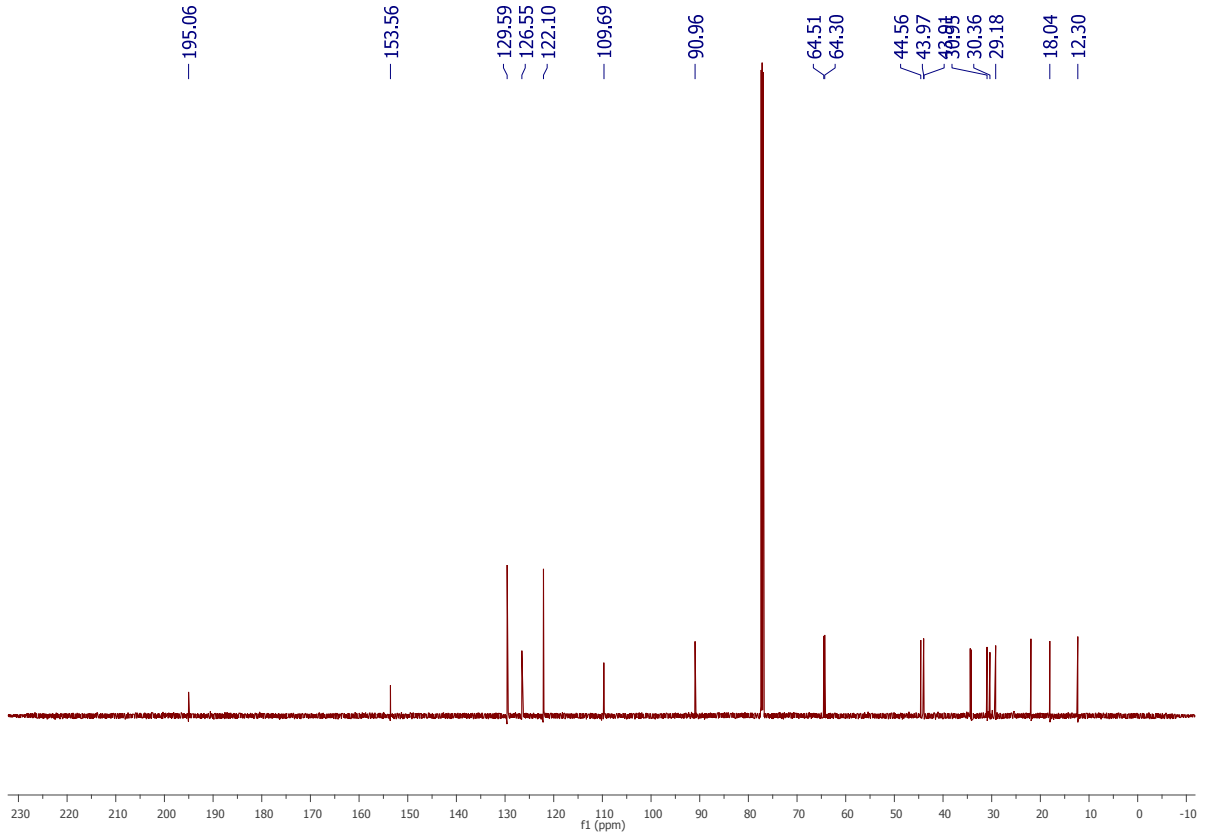


^{1}H NMR ($CDCl_3$, 600 MHz):

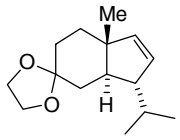


227
$C_{22}H_{30}O_4S$
M = 390.54 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

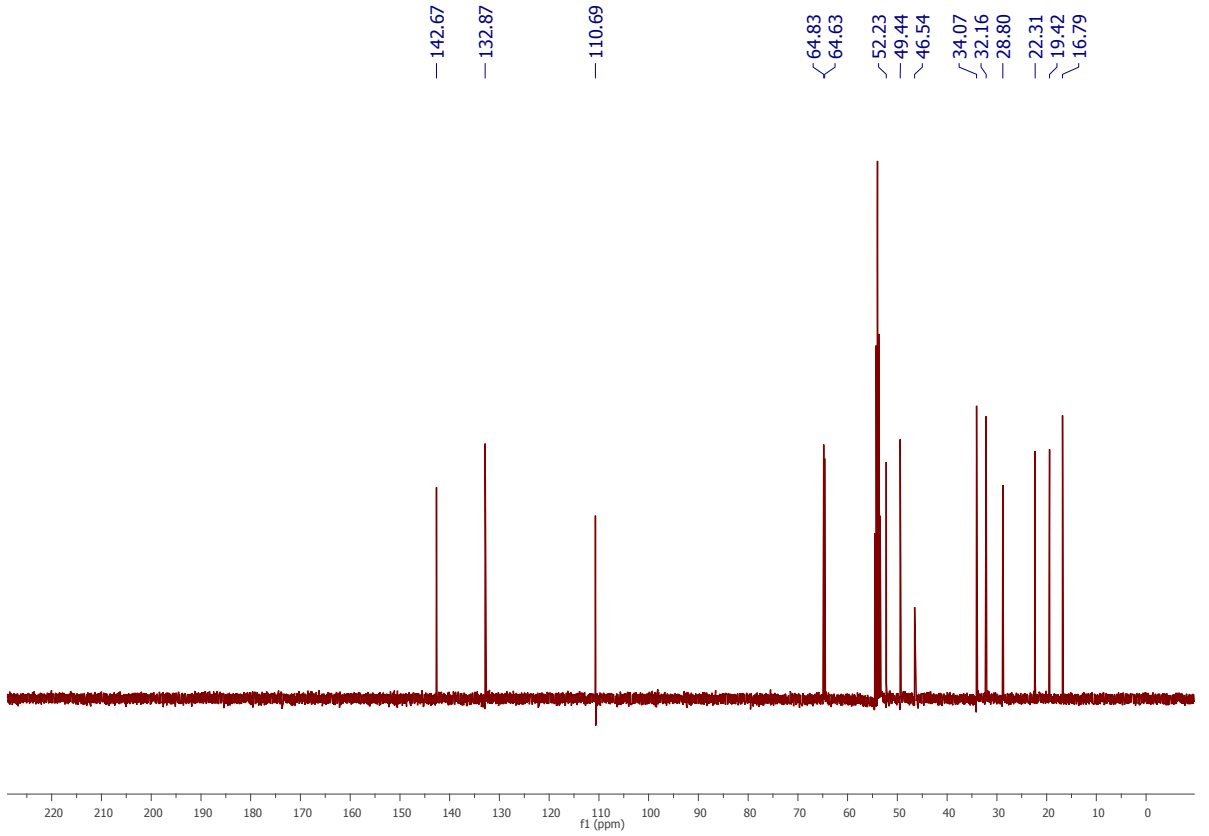


^{1}H NMR (CD_2Cl_2, 400 MHz):

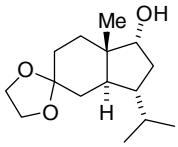


225
$C_{15}H_{24}O_2$
M = 236.35 g/mol

^{13}C NMR (CD_2Cl_2, 100 MHz):

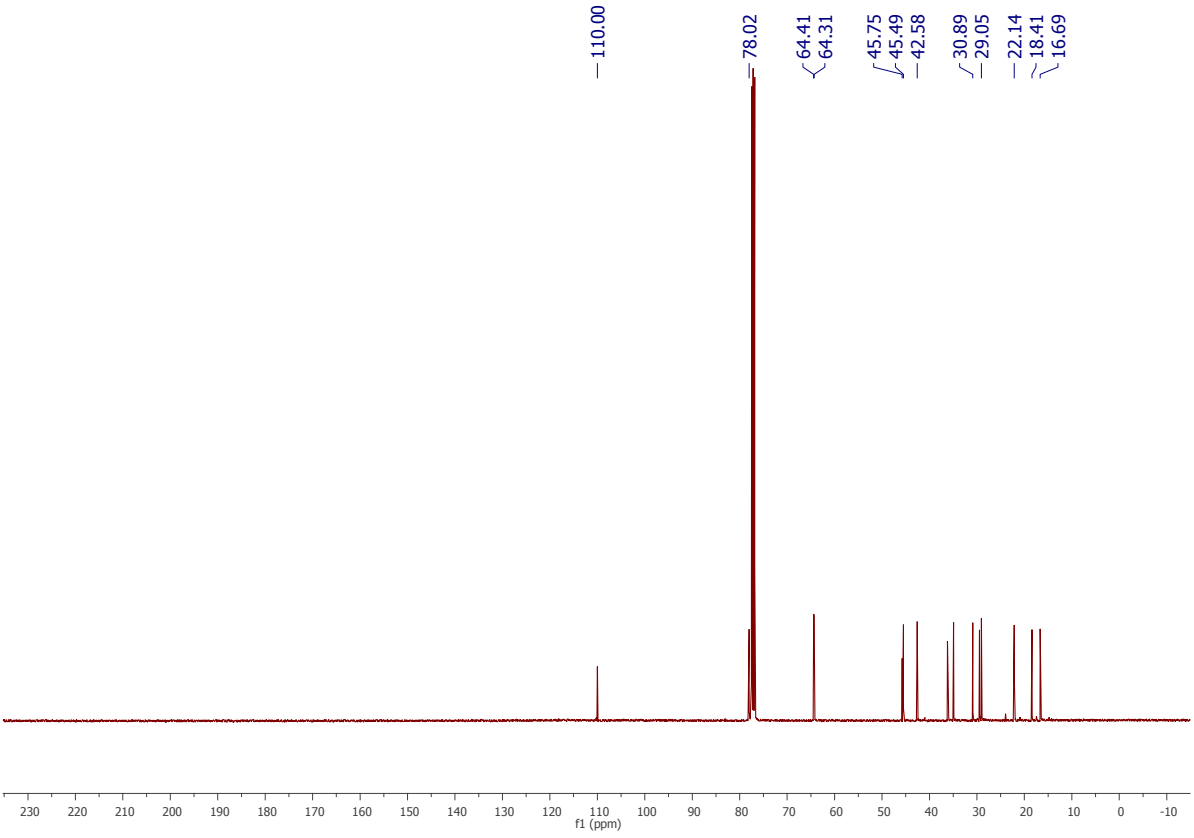


^{1}H NMR ($CDCl_3$, 600 MHz):

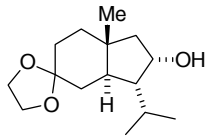


232
$C_{15}H_{26}O_3$
M = 254.37 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

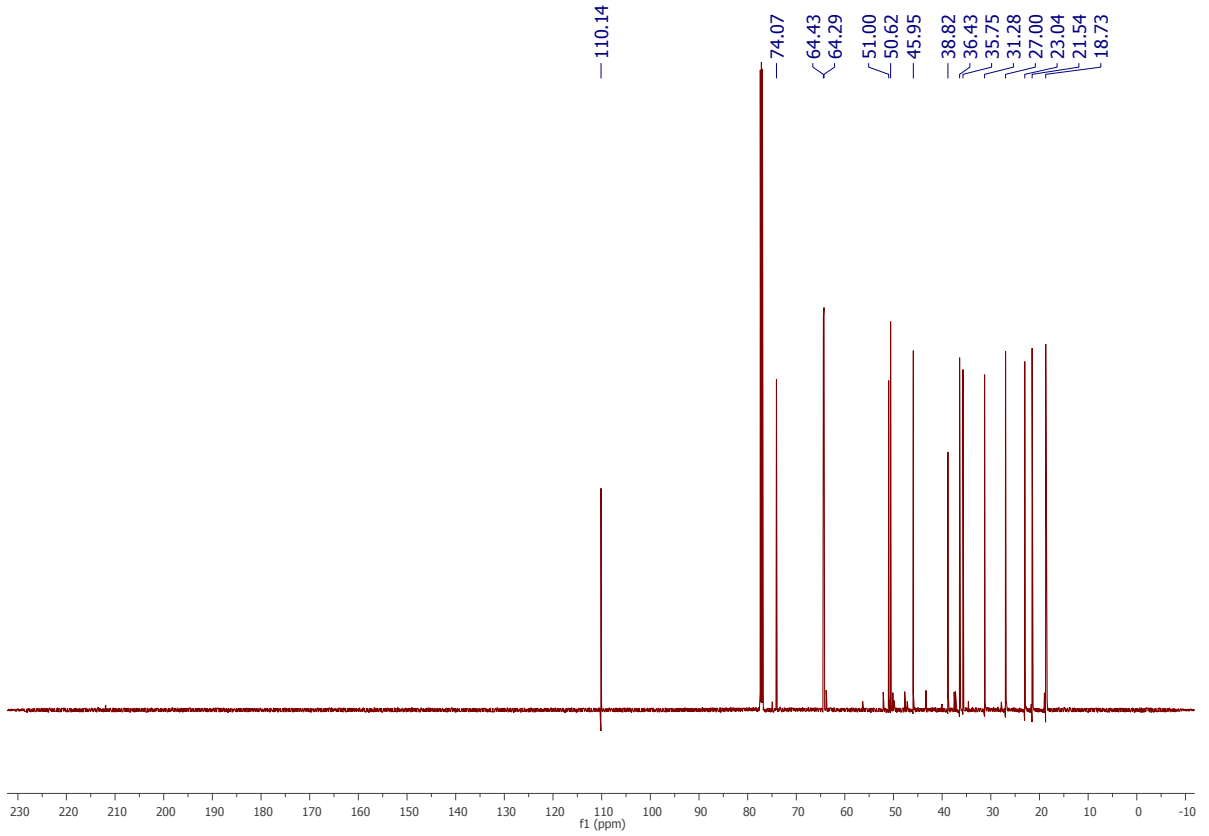


^{1}H NMR ($CDCl_3$, 600 MHz):

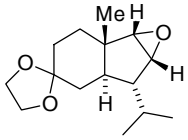


233
$C_{15}H_{26}O_3$
M = 254.37 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

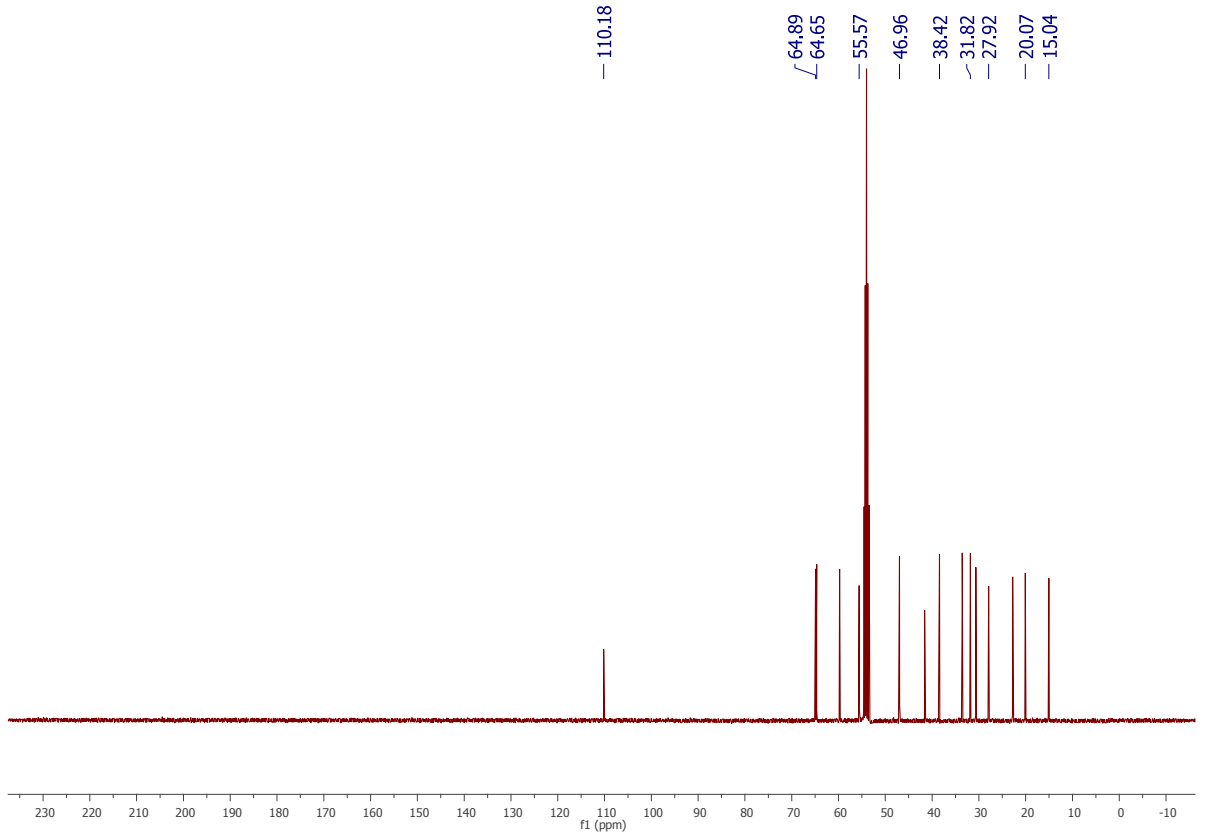


^{1}H NMR (CD_2Cl_2, 400 MHz):

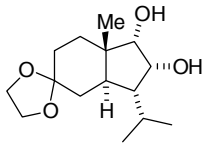


239
$C_{15}H_{24}O_3$
M = 252.35 g/mol

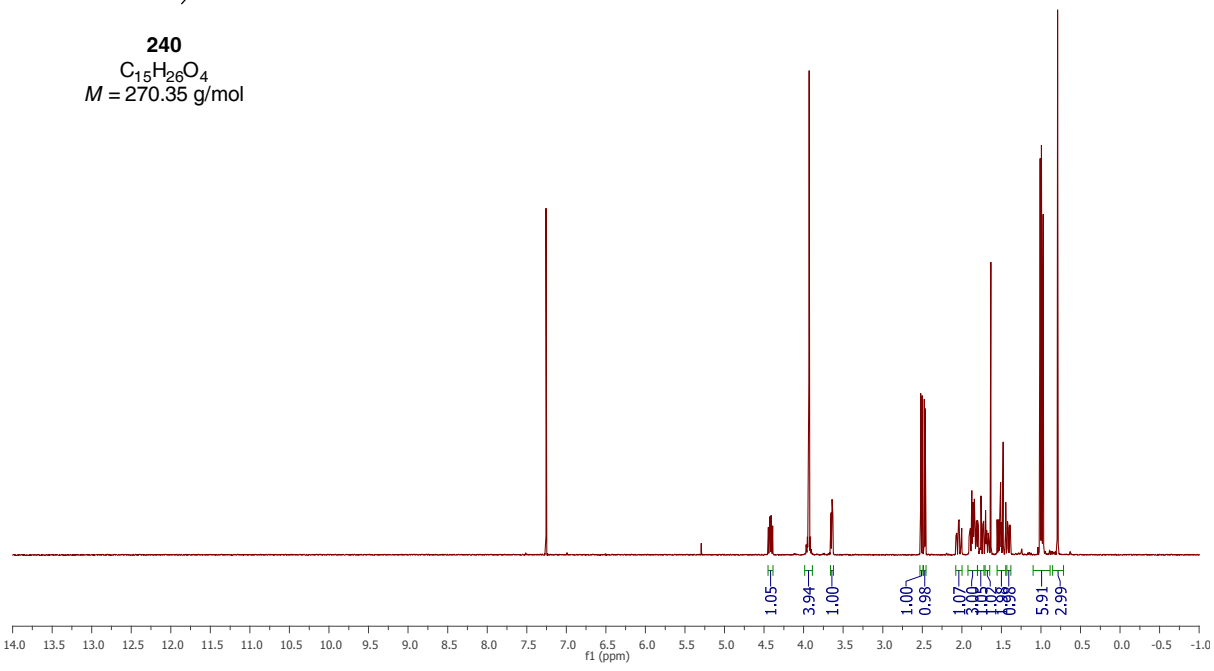
^{13}C NMR (CD_2Cl_2, 100 MHz):



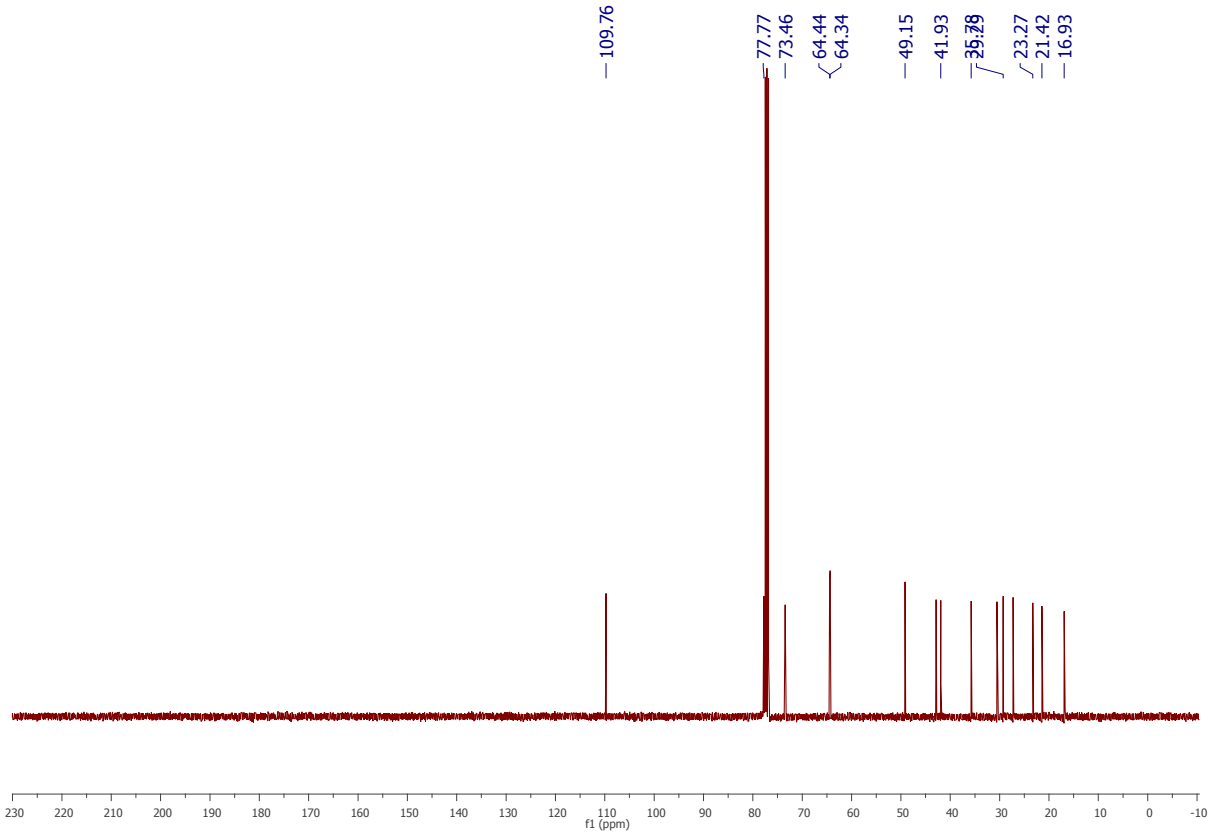
^{1}H NMR ($CDCl_3$, 400 MHz):



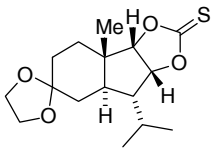
240
$C_{15}H_{26}O_4$
M = 270.35 g/mol



^{13}C NMR ($CDCl_3$, 100 MHz):

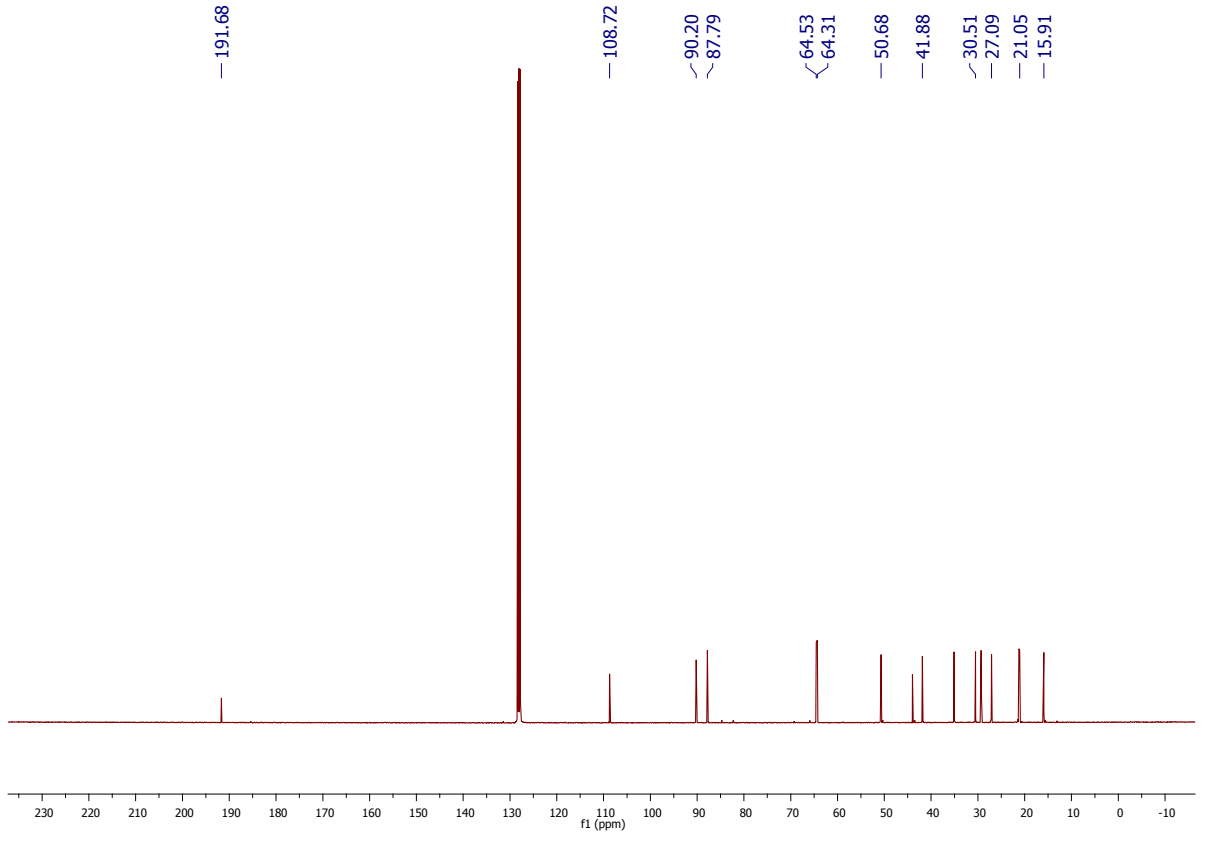


^{1}H NMR (C_6D_6, 400 MHz):

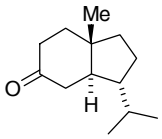


242
$C_{15}H_{24}O_4S$
M = 312.42 g/mol

^{13}C NMR (C_6D_6, 100 MHz):

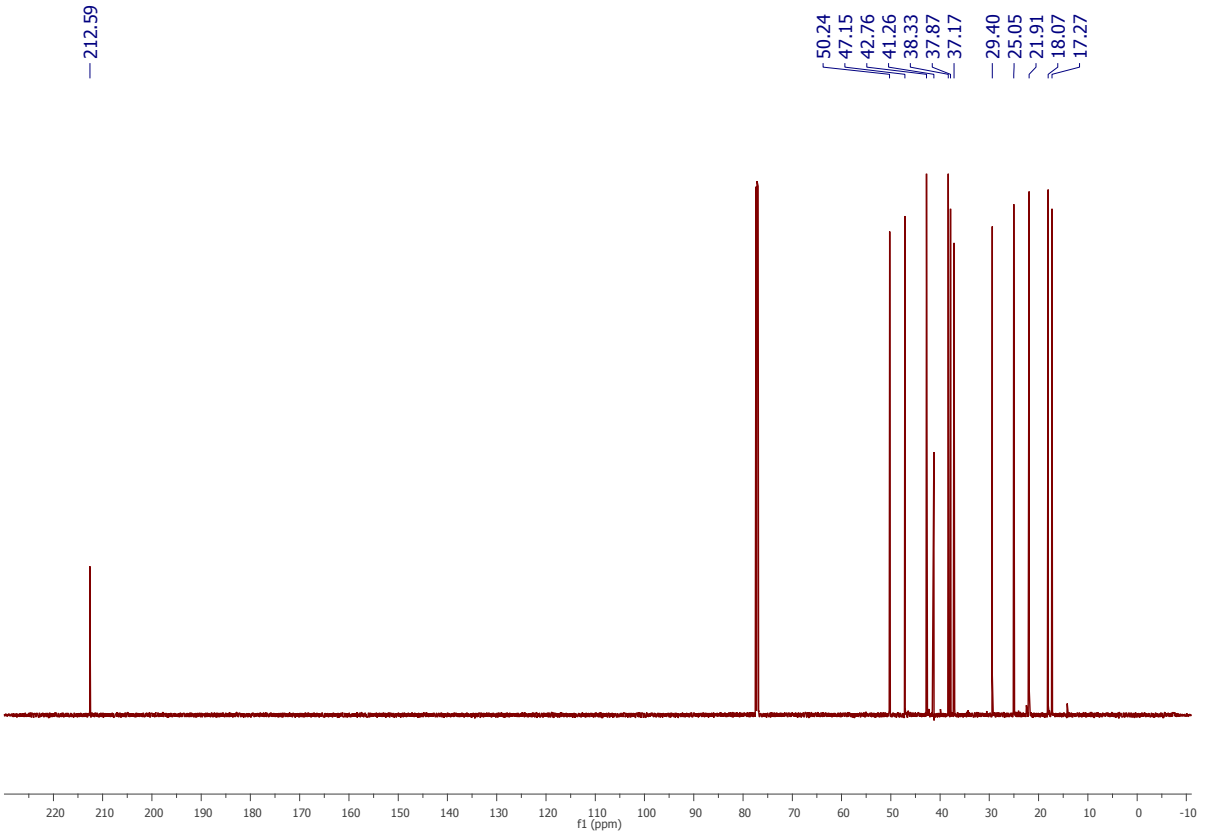


^{1}H NMR ($CDCl_3$, 600 MHz):

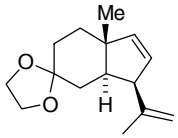


ent-**141**
$C_{13}H_{22}O$
M = 194.31 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

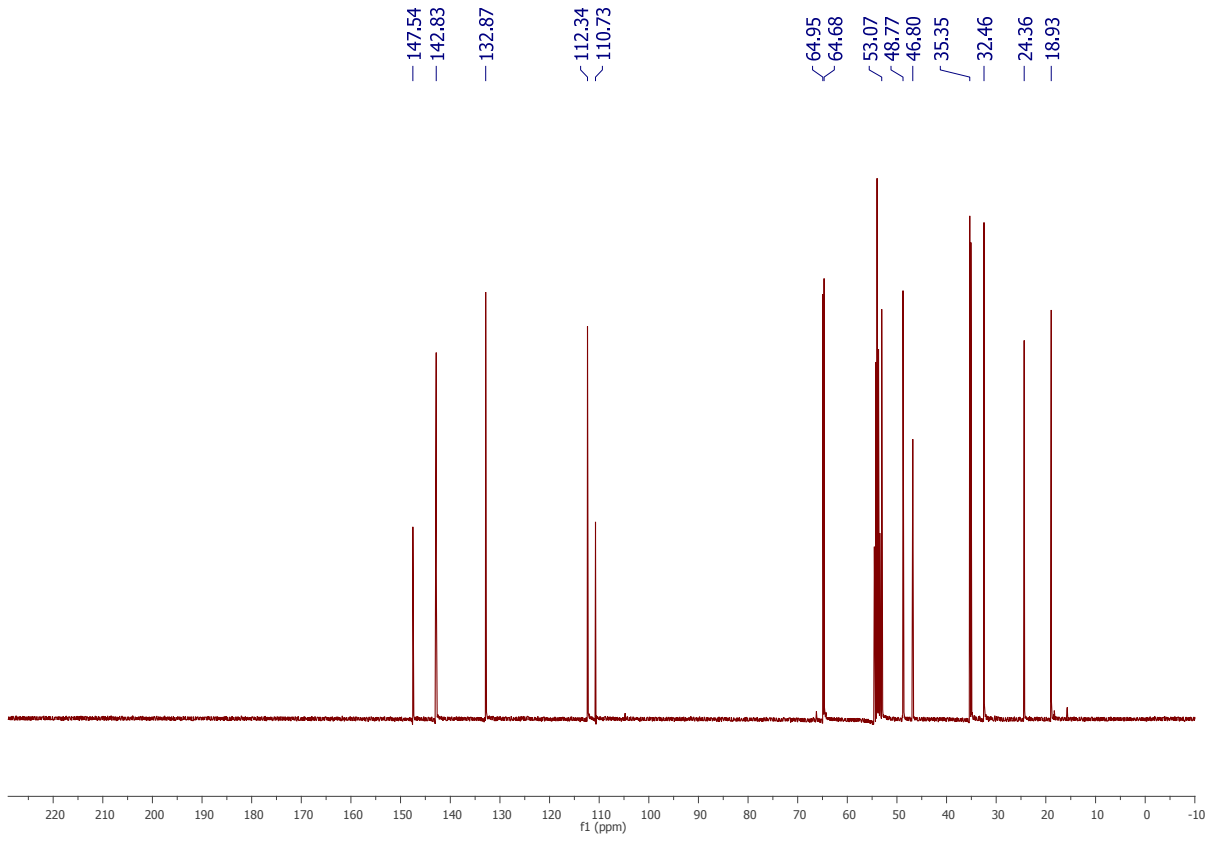


^{1}H NMR (CD_2Cl_2, 400 MHz):

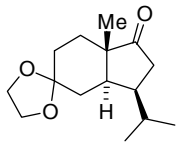


245
$C_{15}H_{22}O_2$
M = 234.33 g/mol

^{13}C NMR ($CDCl_2$, 100 MHz):

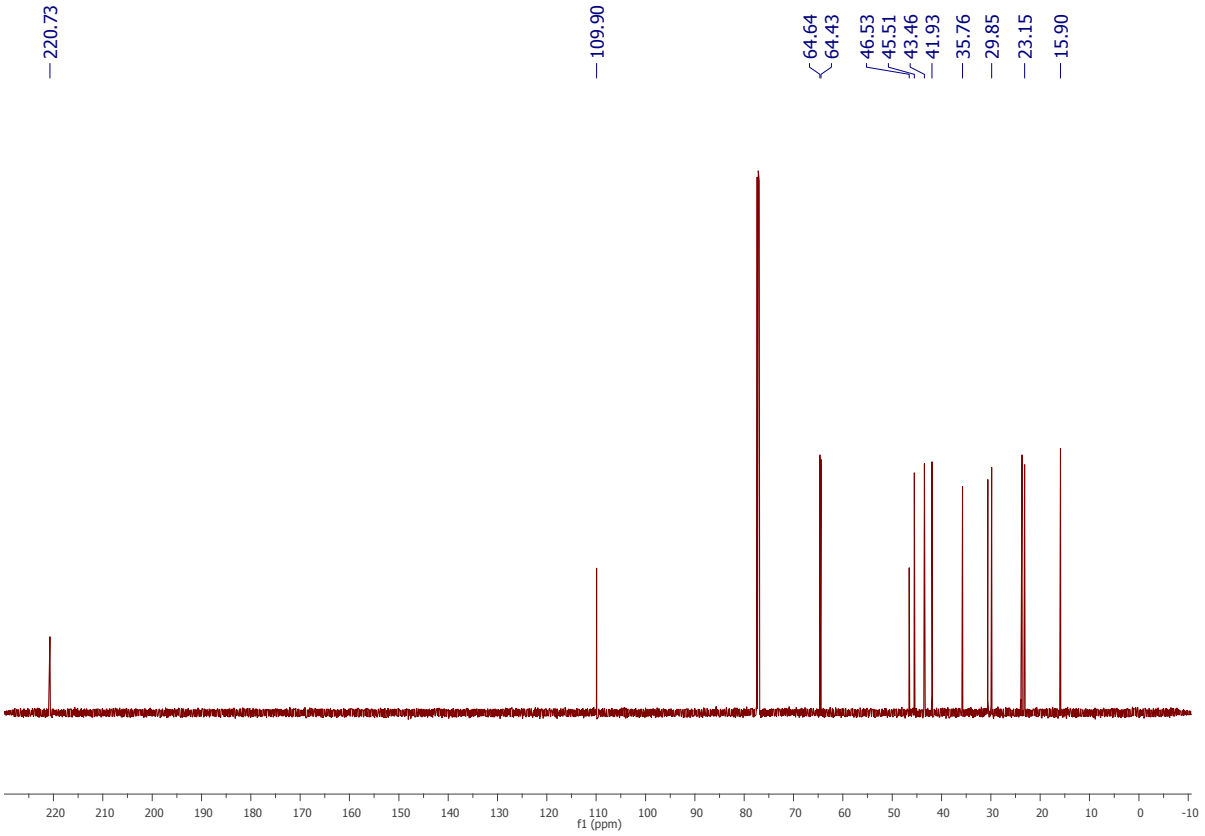


^{1}H NMR ($CDCl_3$, 600 MHz):

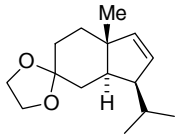


246
$C_{15}H_{24}O_3$
M = 252.35 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

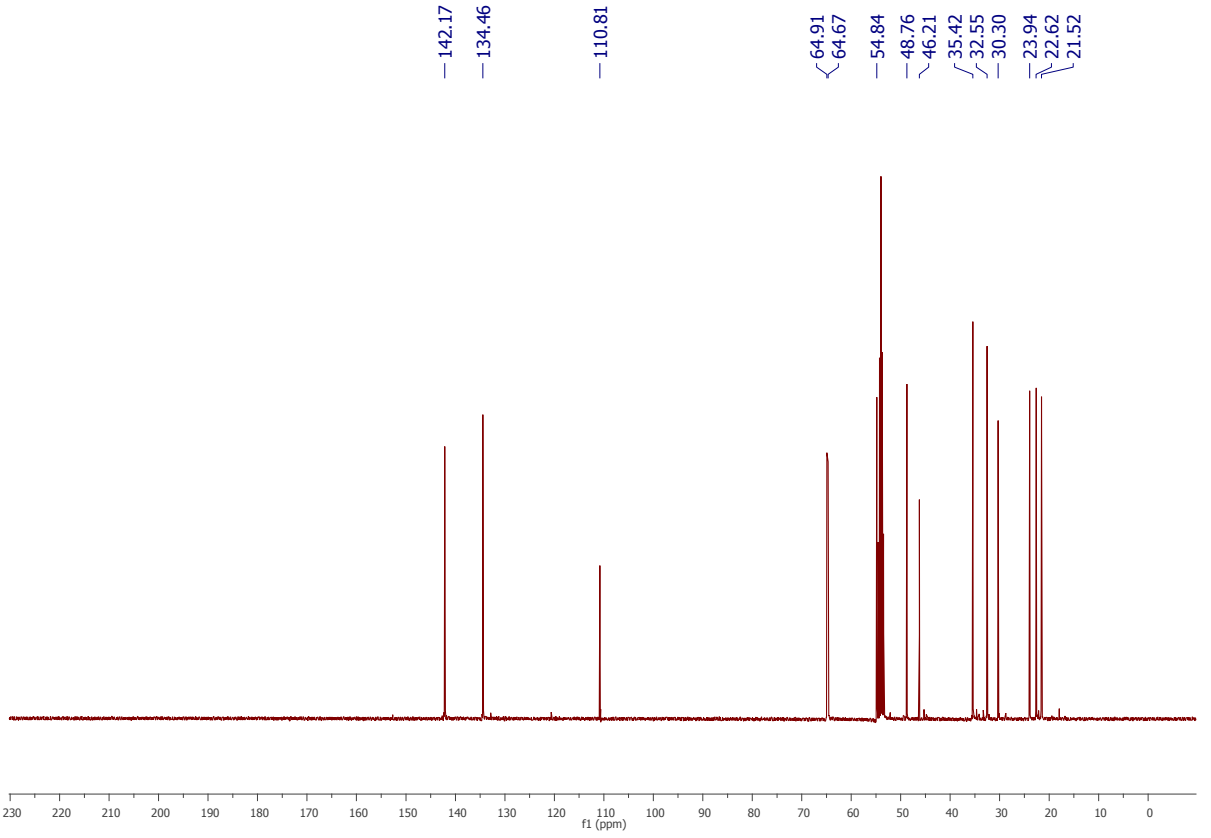


^{1}H NMR (CD_2Cl_2, 400 MHz):

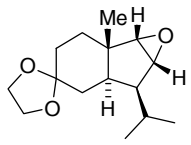


221
$C_{15}H_{24}O_2$
M = 236.35 g/mol

^{13}C NMR (CD_2Cl_2, 100 MHz):

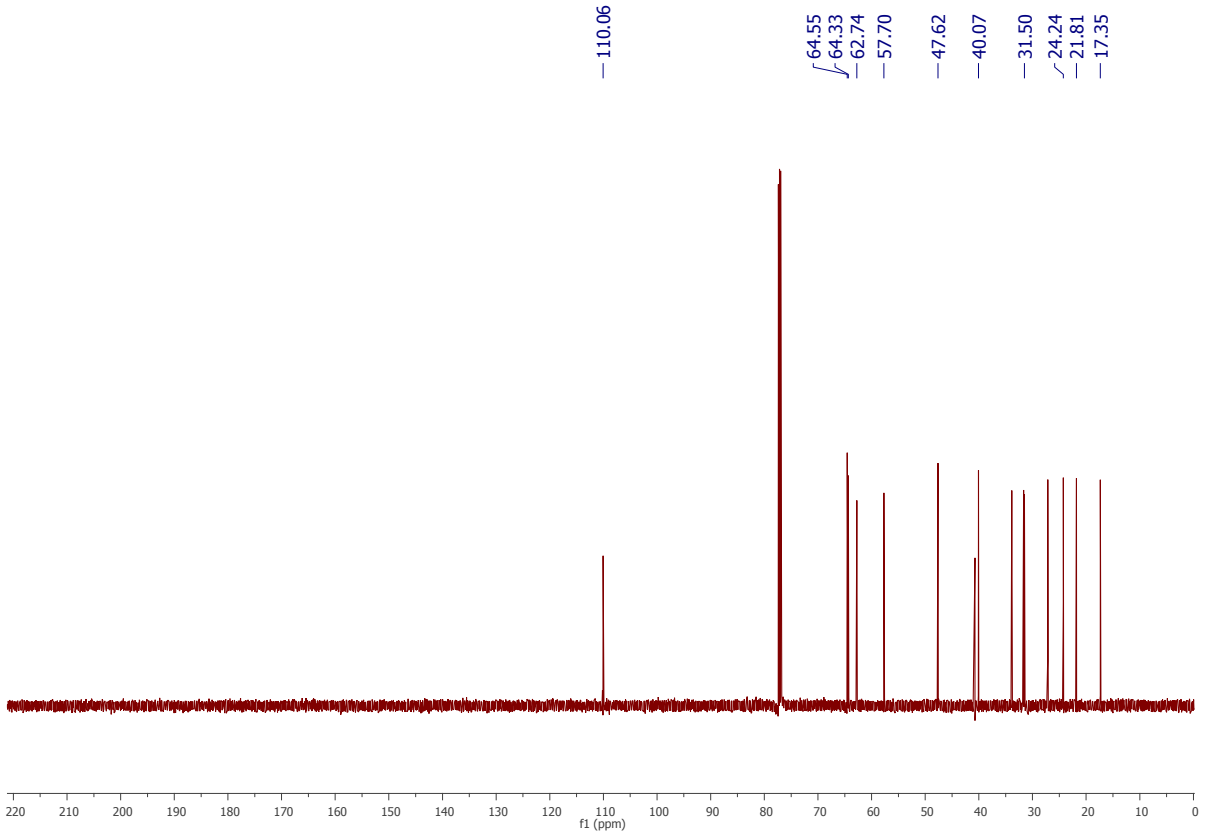


^{1}H NMR ($CDCl_3$, 600 MHz):

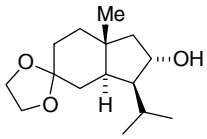


250
$C_{15}H_{24}O_3$
M = 252.35 g/mol

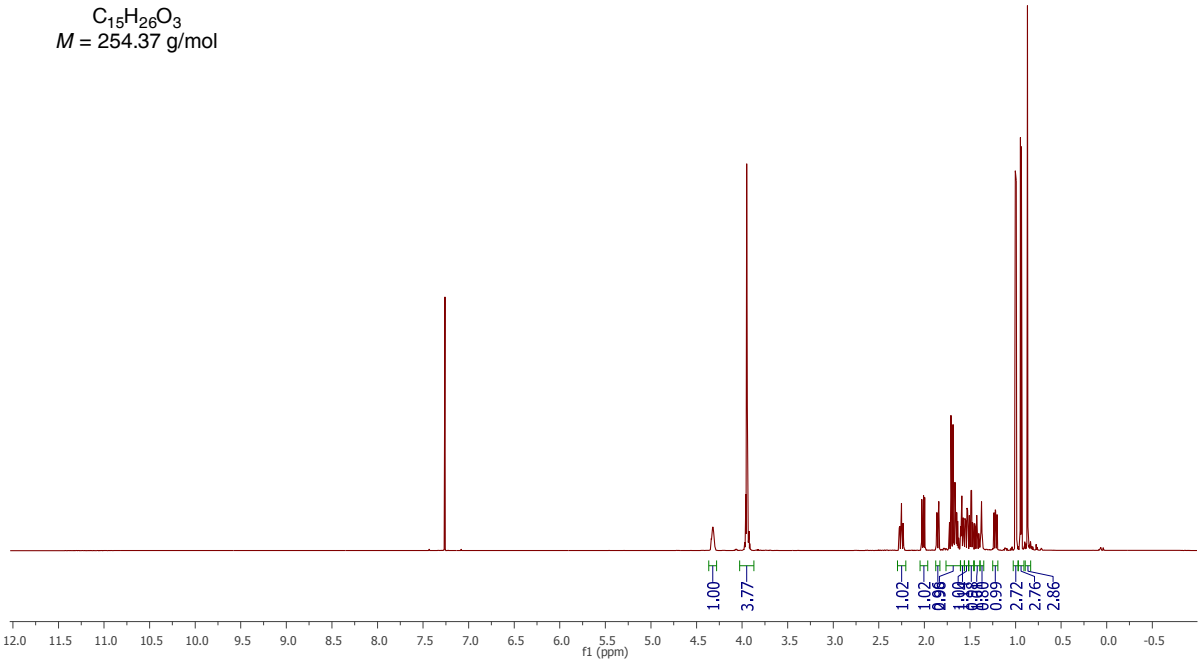
^{13}C NMR ($CDCl_3$, 150 MHz):



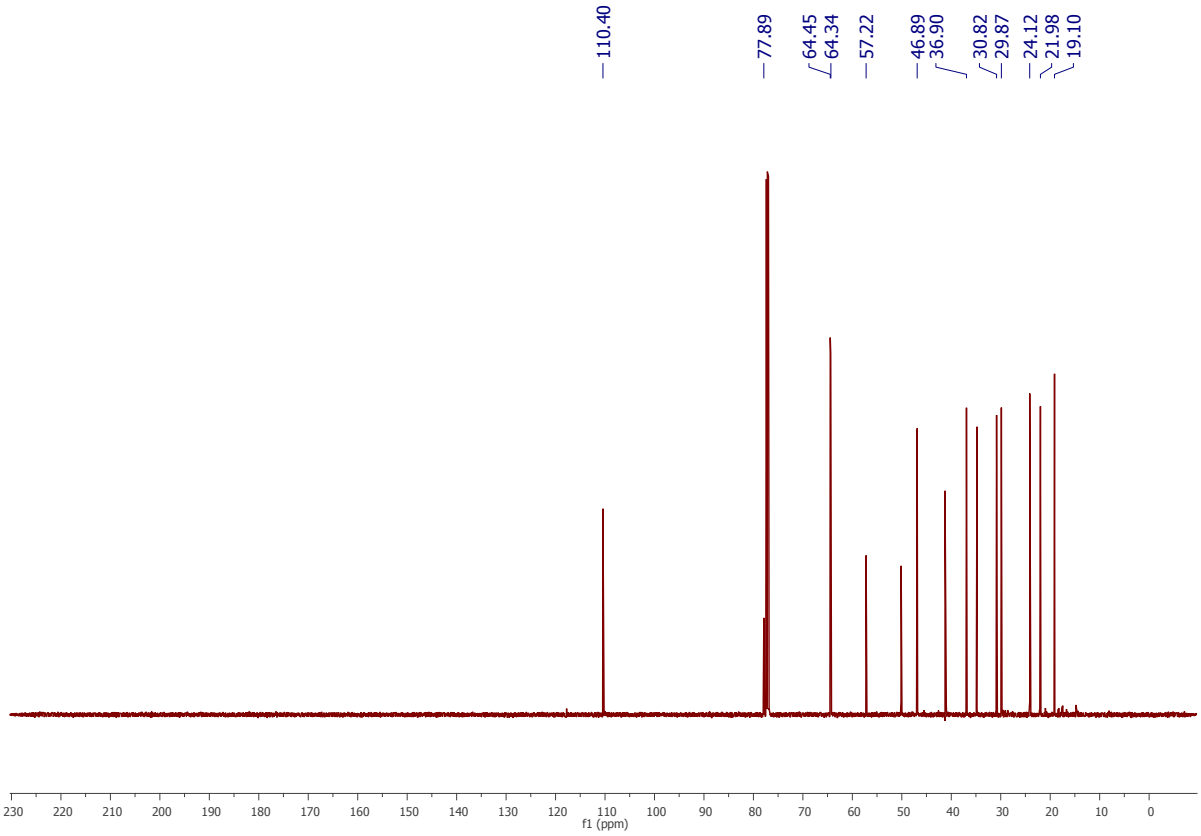
^{1}H NMR ($CDCl_3$, 600 MHz):



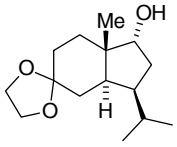
192
$C_{15}H_{26}O_3$
M = 254.37 g/mol



^{13}C NMR ($CDCl_3$, 150 MHz):



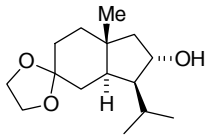
^{1}H NMR ($CDCl_3$, 600 MHz):



251

$C_{15}H_{26}O_3$

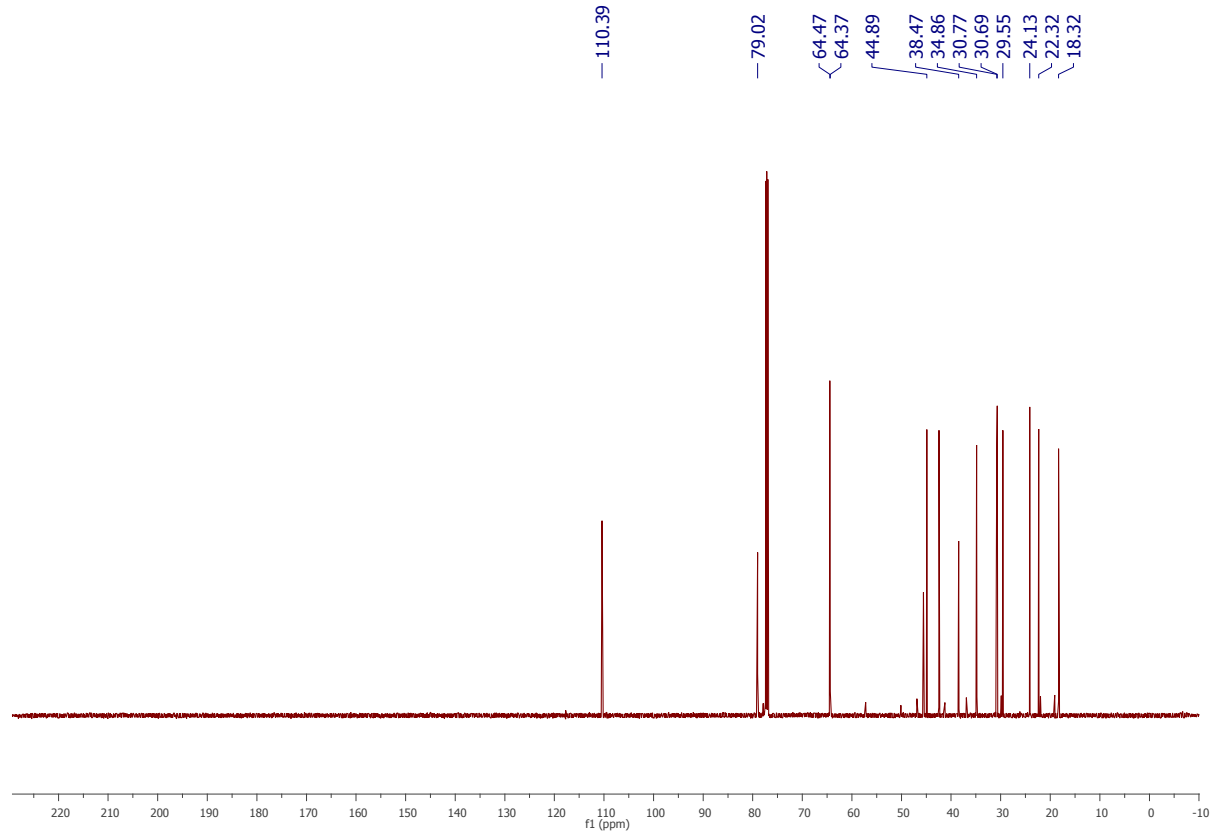
M = 254.37 g/mol



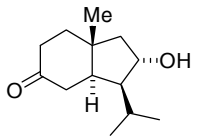
192

7.1 : 1

^{13}C NMR ($CDCl_3$,150 MHz):

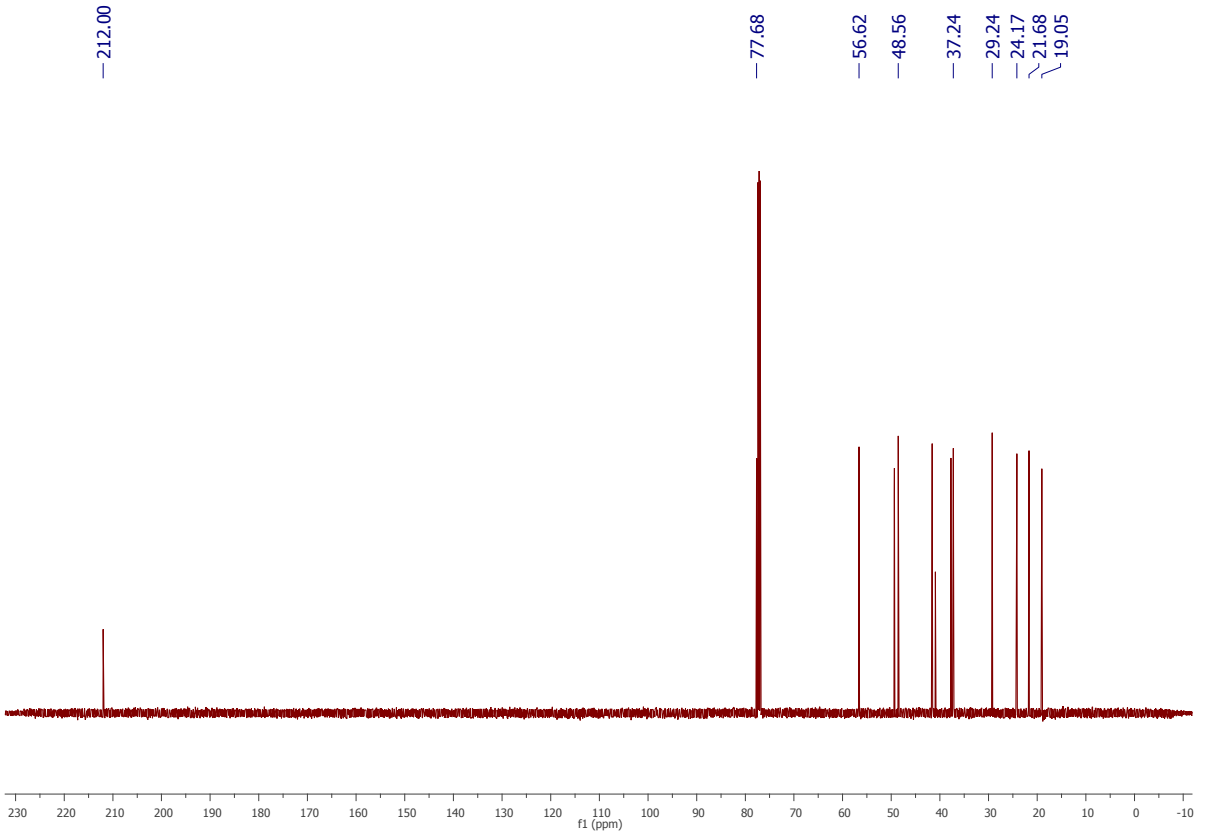


^{1}H NMR ($CDCl_3$, 600 MHz):

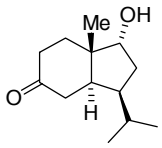


255
$C_{13}H_{22}O_2$
M = 210.31 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

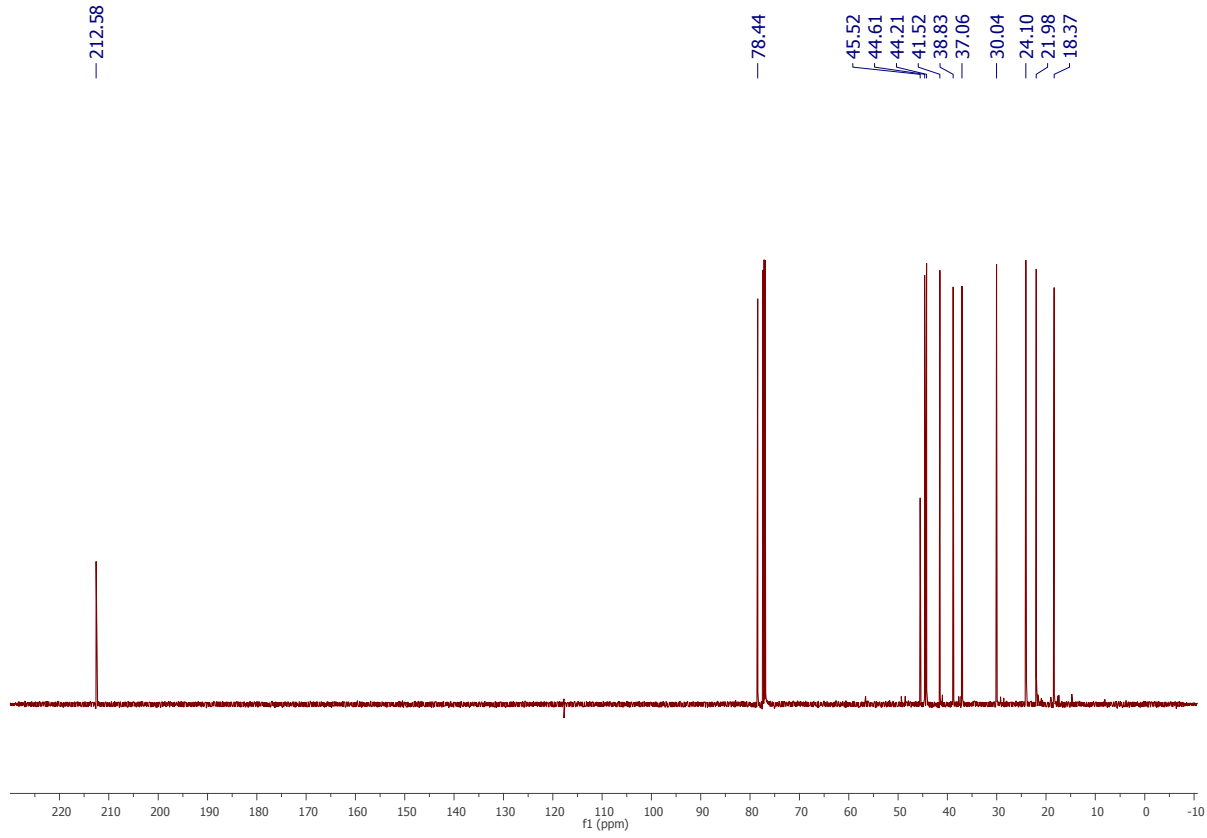


^{1}H NMR ($CDCl_3$, 600 MHz):

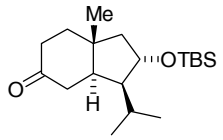


256
$C_{13}H_{22}O_2$
M = 210.31 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

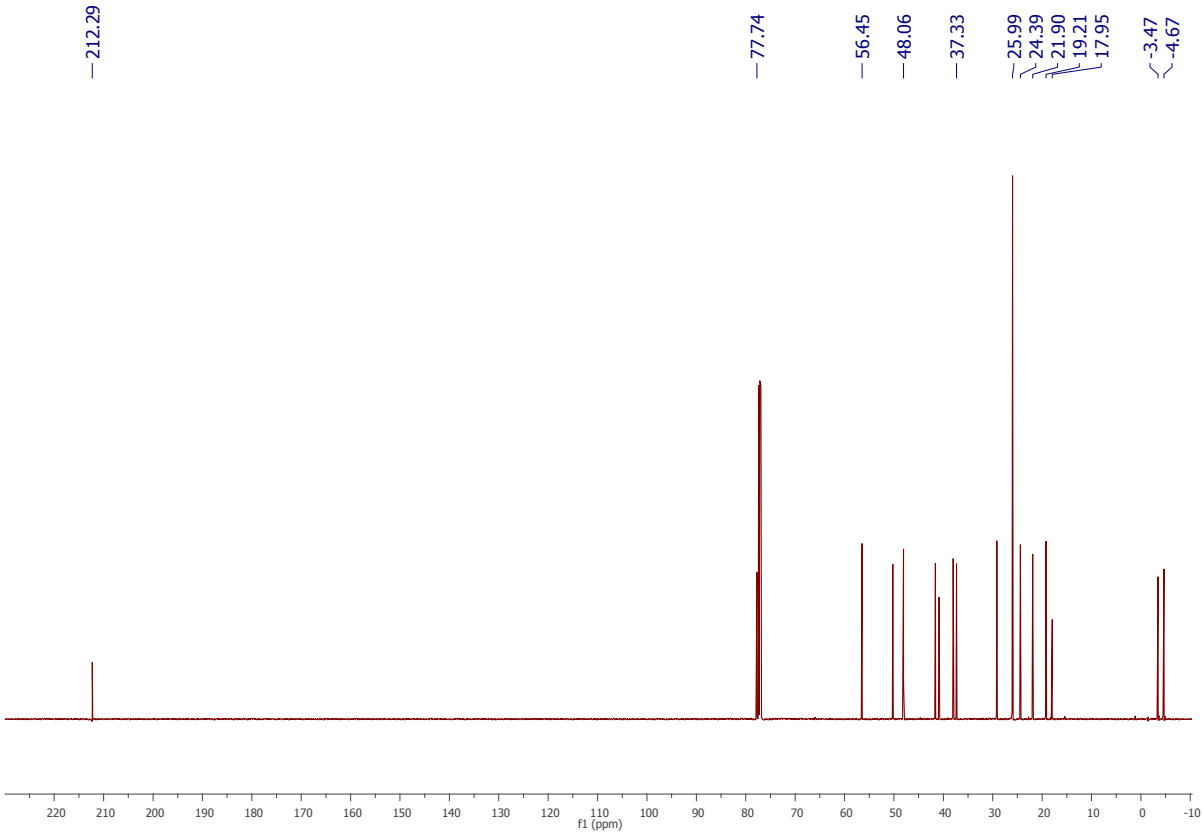


^{1}H NMR ($CDCl_3$, 600 MHz):

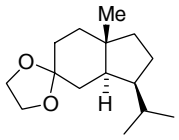


191
$C_{19}H_{36}O_2Si$
M = 324.57 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

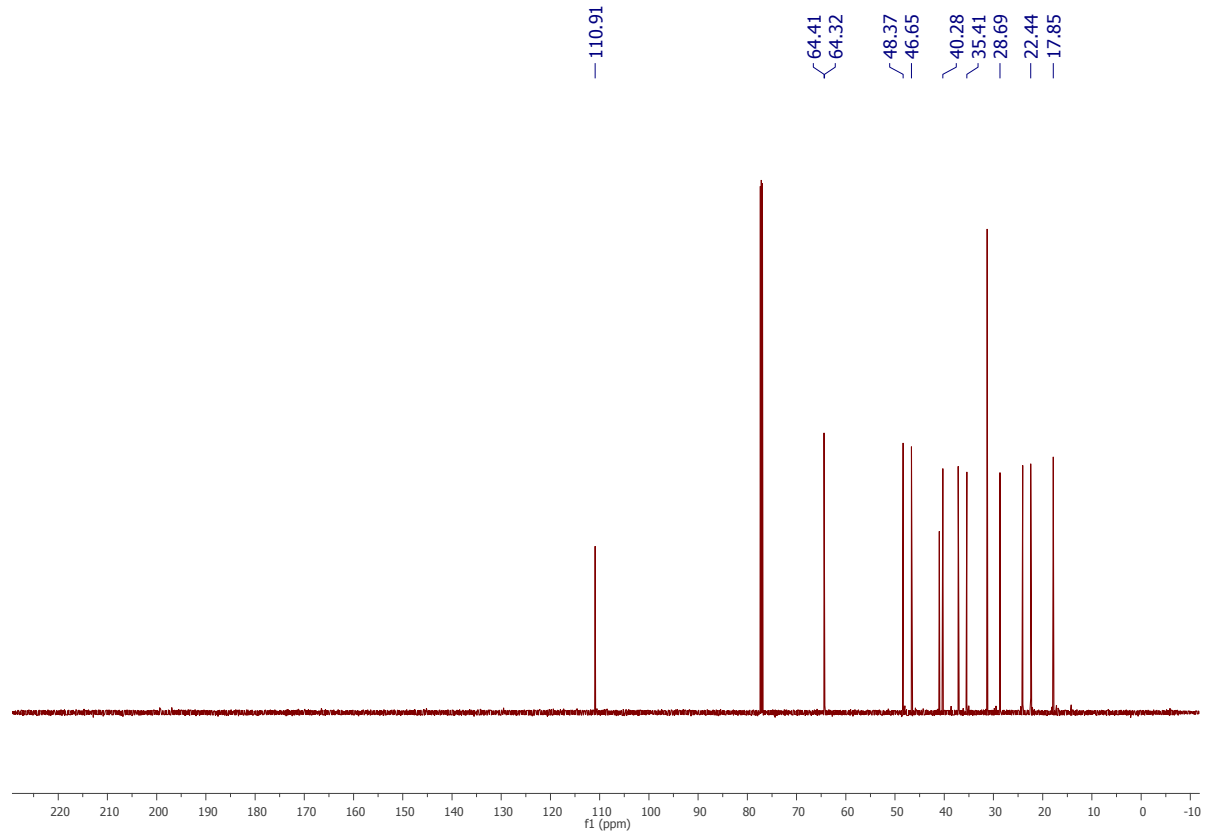


^{1}H NMR ($CDCl_3$, 600 MHz):

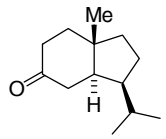


257
$C_{15}H_{26}O_2$
M = 238.37 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

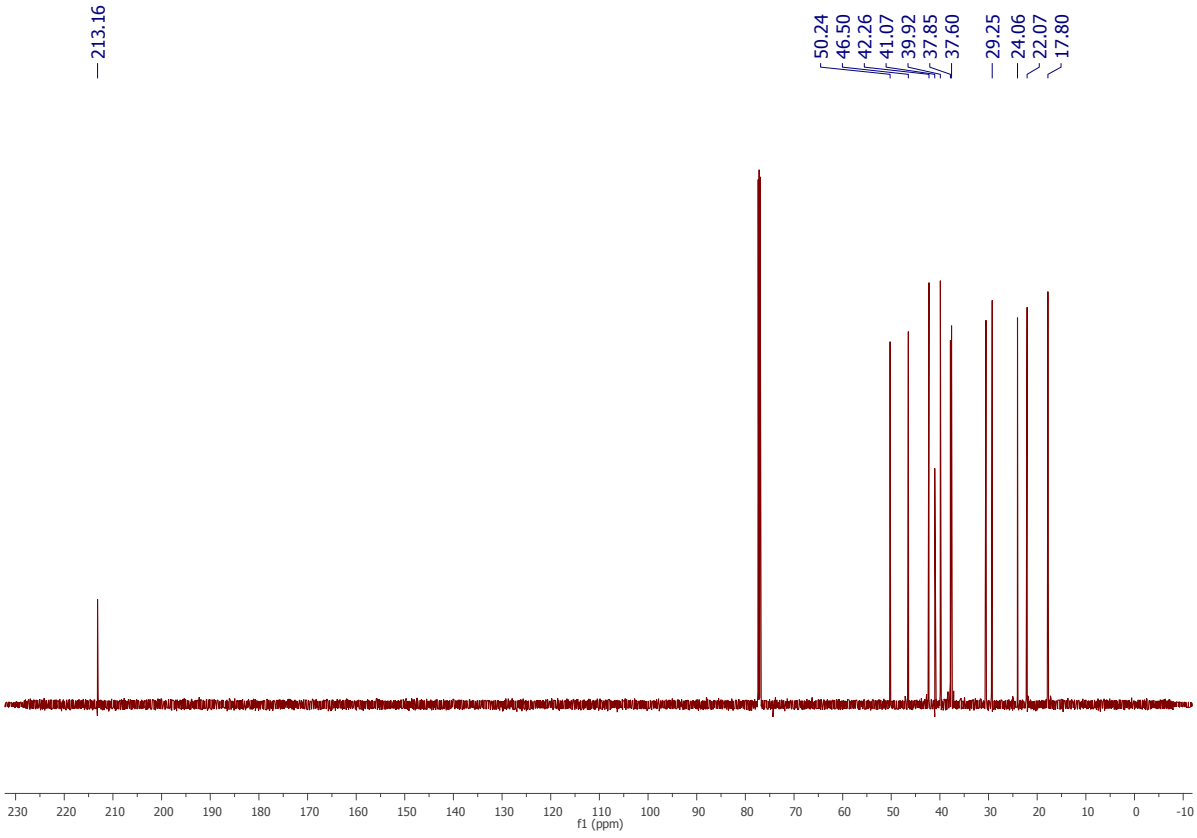


^{1}H NMR ($CDCl_3$, 600 MHz):

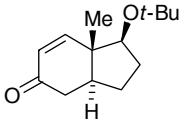


190
$C_{13}H_{22}O$
M = 194.31 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

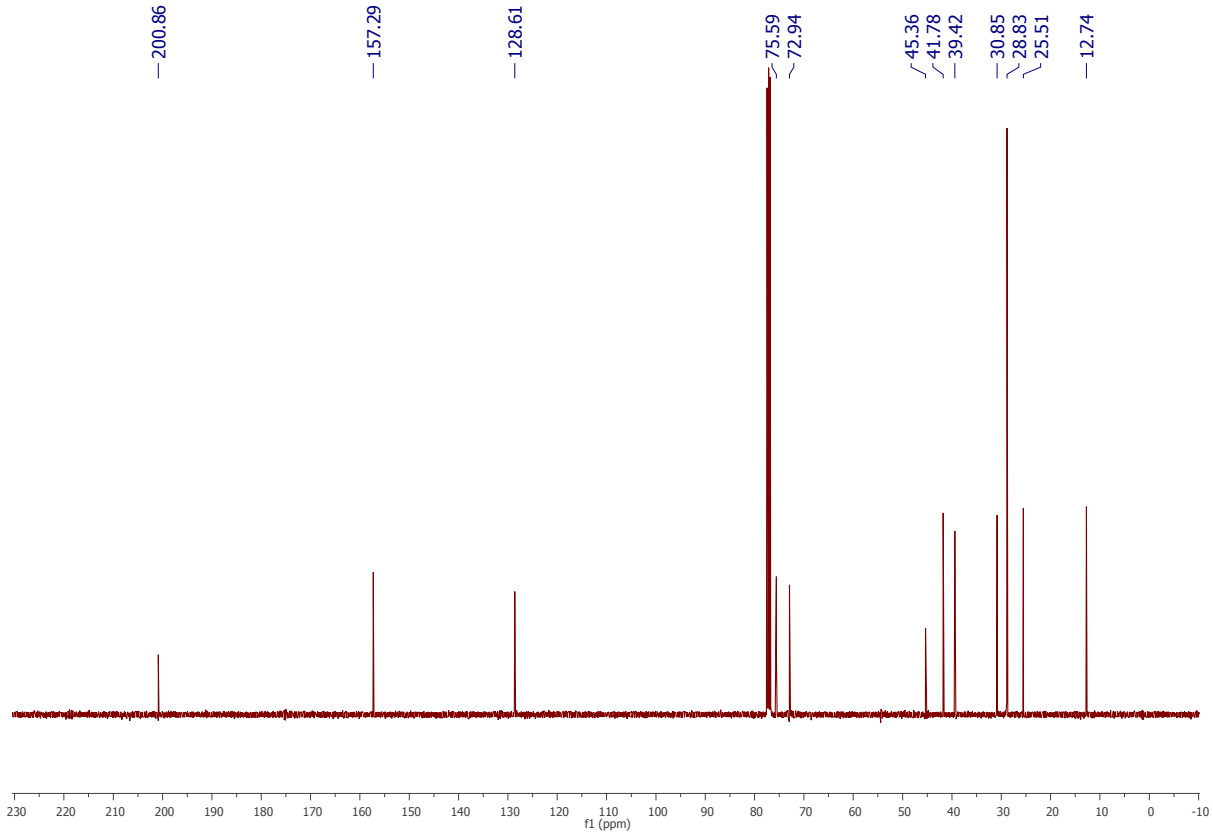


^{1}H NMR ($CDCl_3$, 100 MHz):

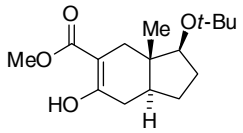


273
$C_{14}H_{22}O_2$
M = 222.32 g/mol

^{13}C NMR ($CDCl_3$, 75 MHz):

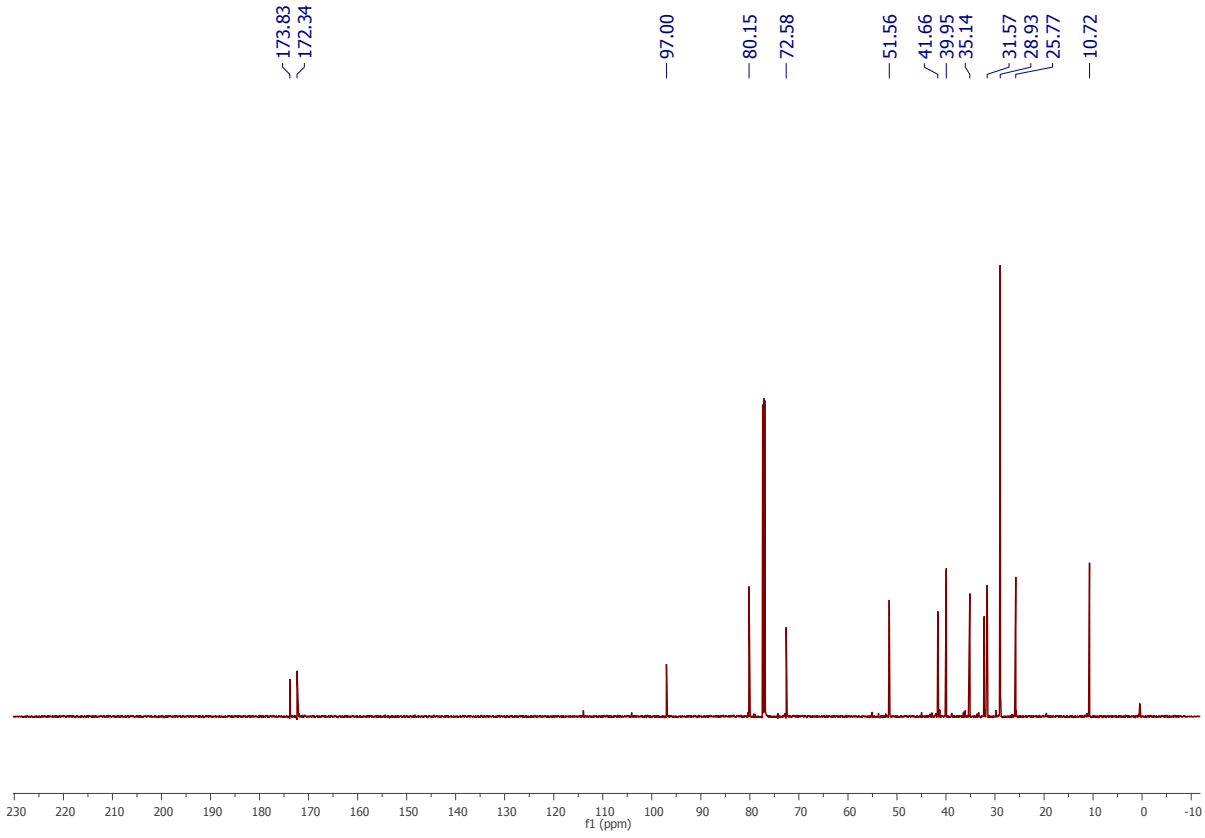


^{1}H NMR ($CDCl_3$, 600 MHz):

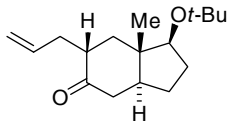


276
$C_{16}H_{26}O_4$
M = 282.38 g/mol

^{13} C NMR ($CDCl_3$, 100 MHz):

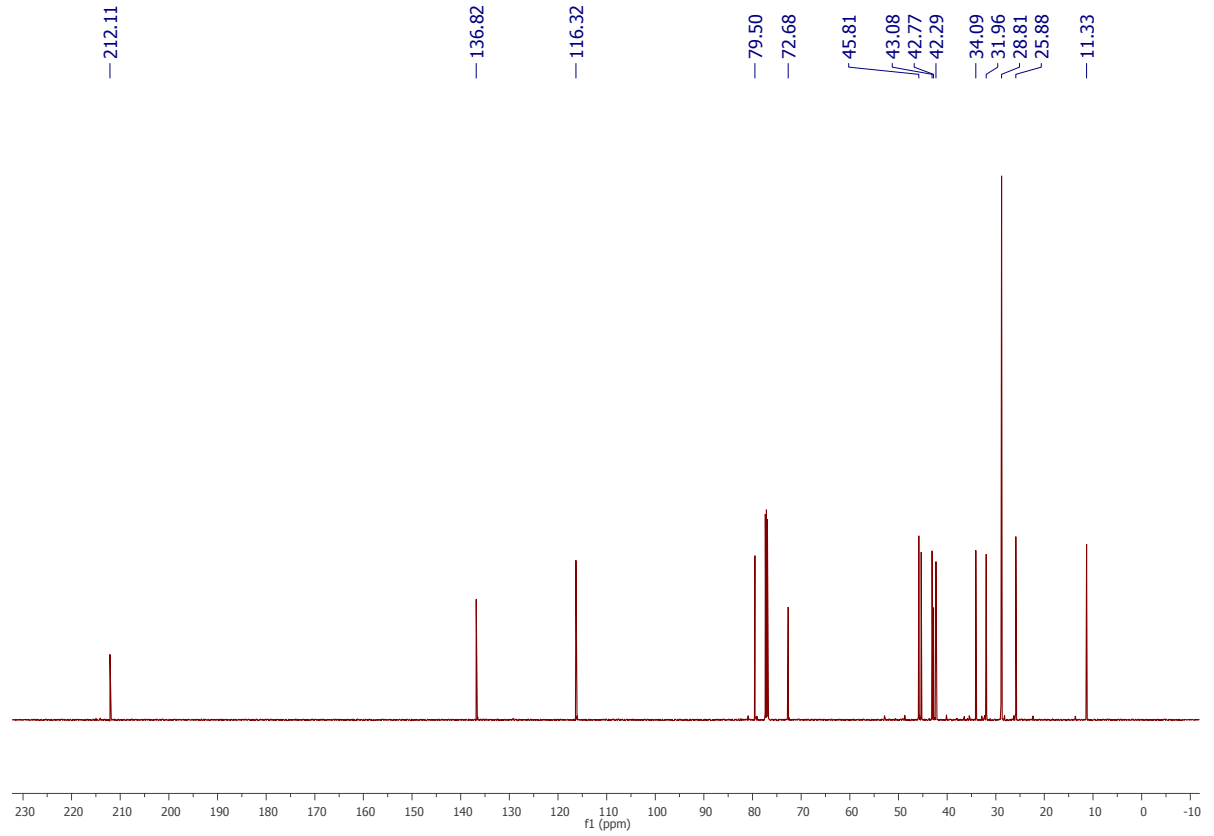


^{1}H NMR ($CDCl_3$, 600 MHz):

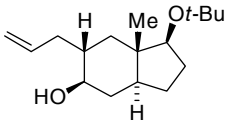


280
$C_{17}H_{28}O_2$
M = 264.40 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

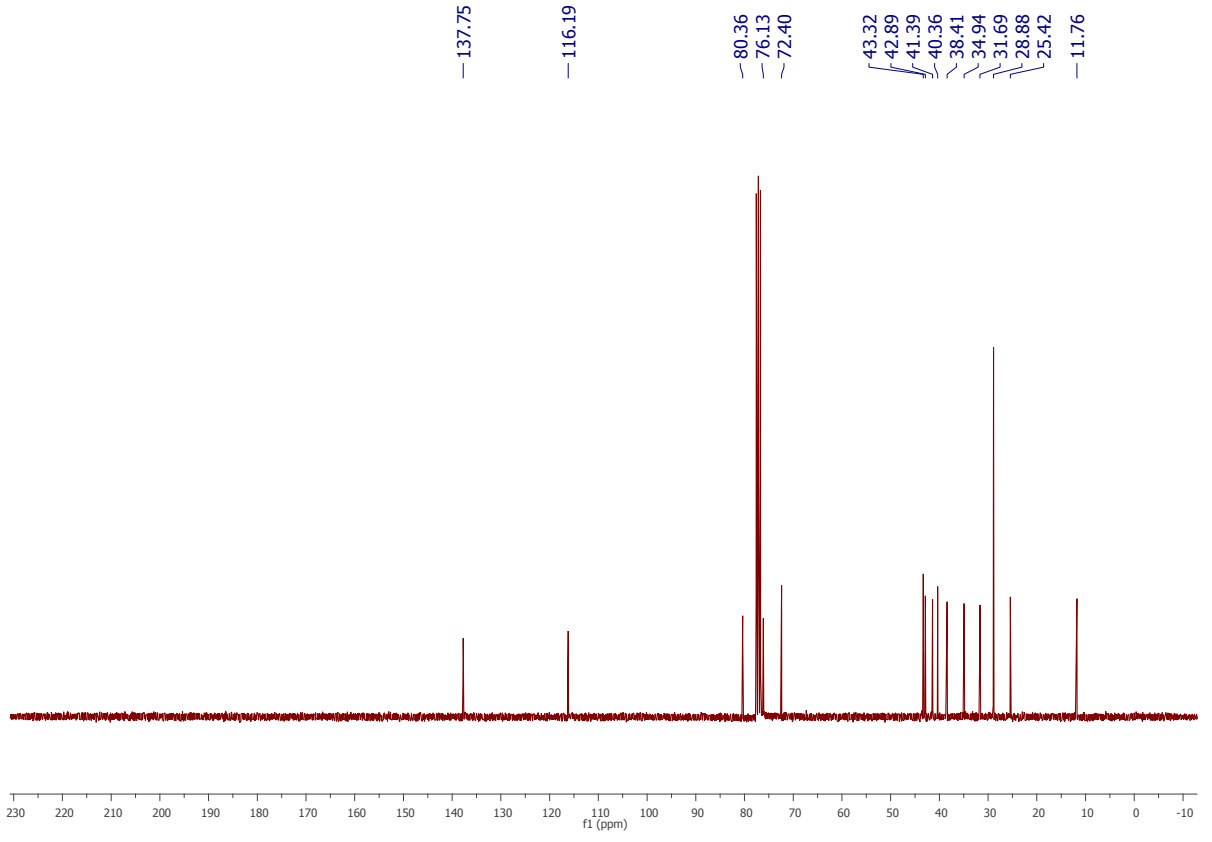


^{1}H NMR ($CDCl_3$, 600 MHz):

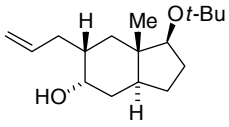


286
$C_{17}H_{30}O_2$
M = 266.42 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

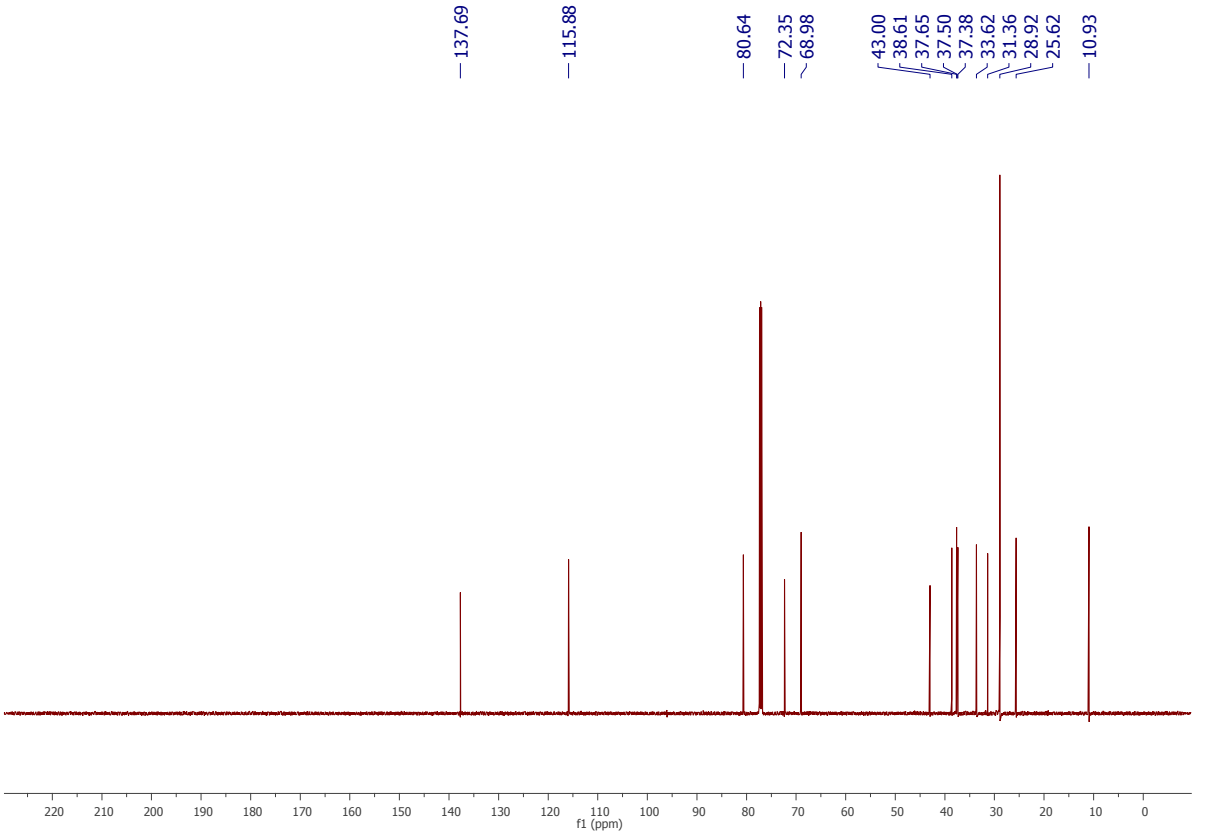


^{1}H NMR ($CDCl_3$, 600 MHz):

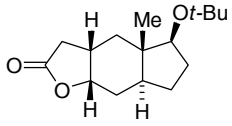


288
$C_{17}H_{30}O_2$
M = 266.42 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

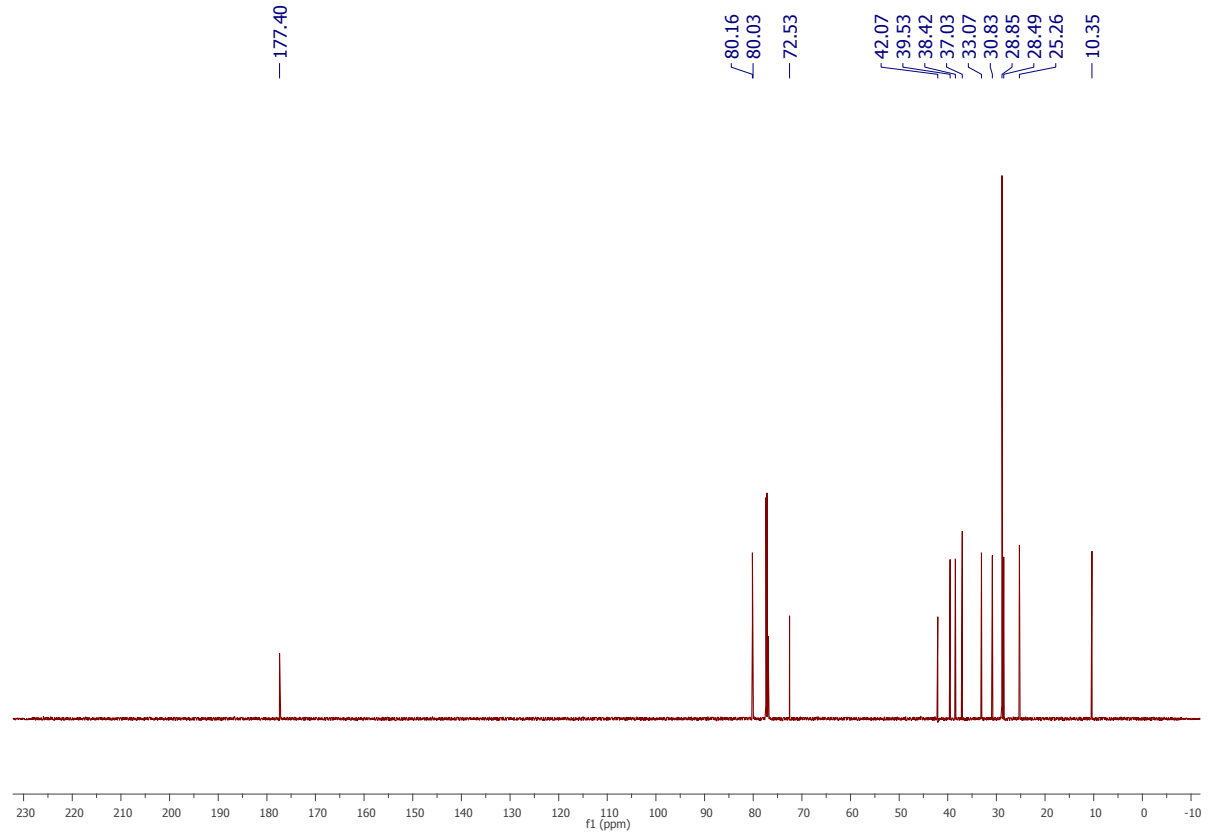


^{1}H NMR ($CDCl_3$, 600 MHz):

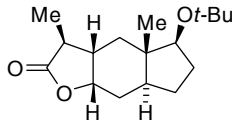


290
$C_{16}H_{26}O_3$
M = 266.38 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

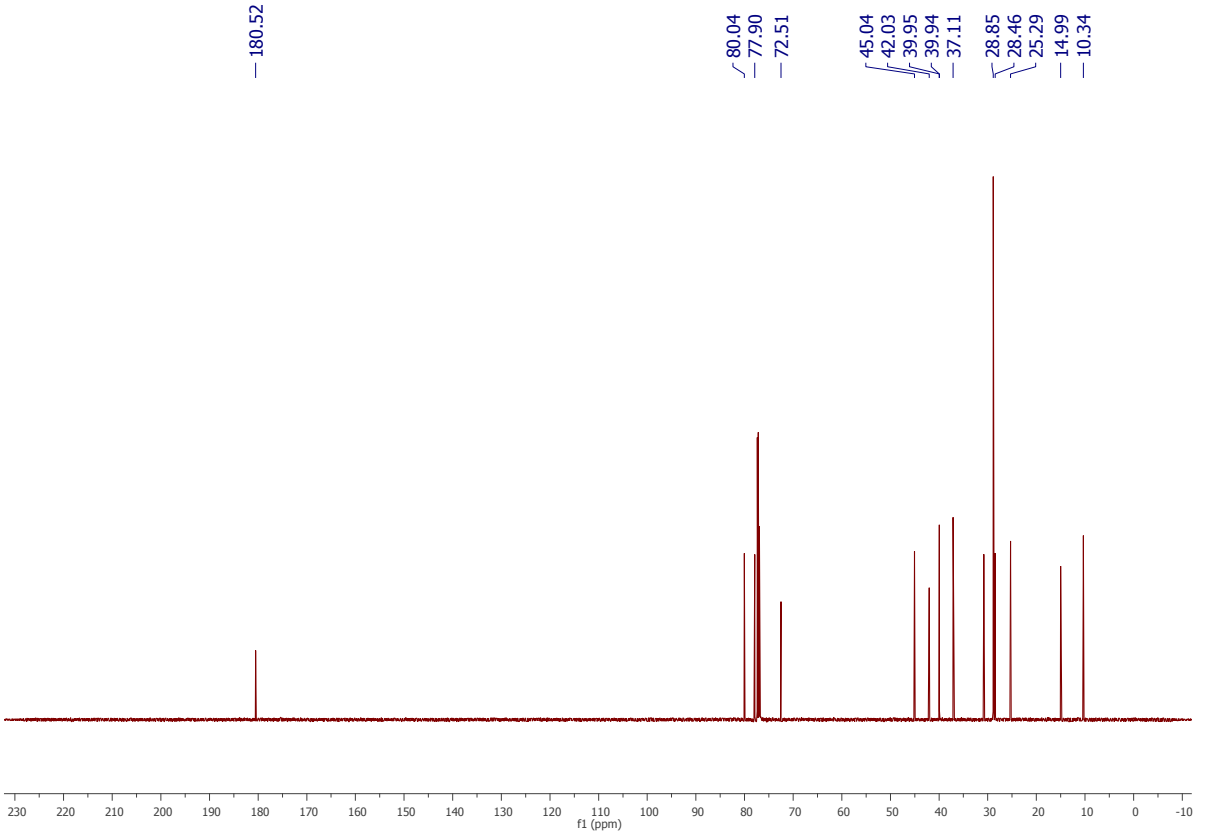


^{1}H NMR ($CDCl_3$, 600 MHz):

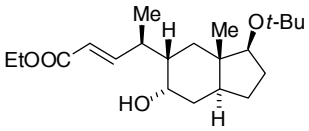


291
$C_{17}H_{28}O_3$
M = 280.40 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

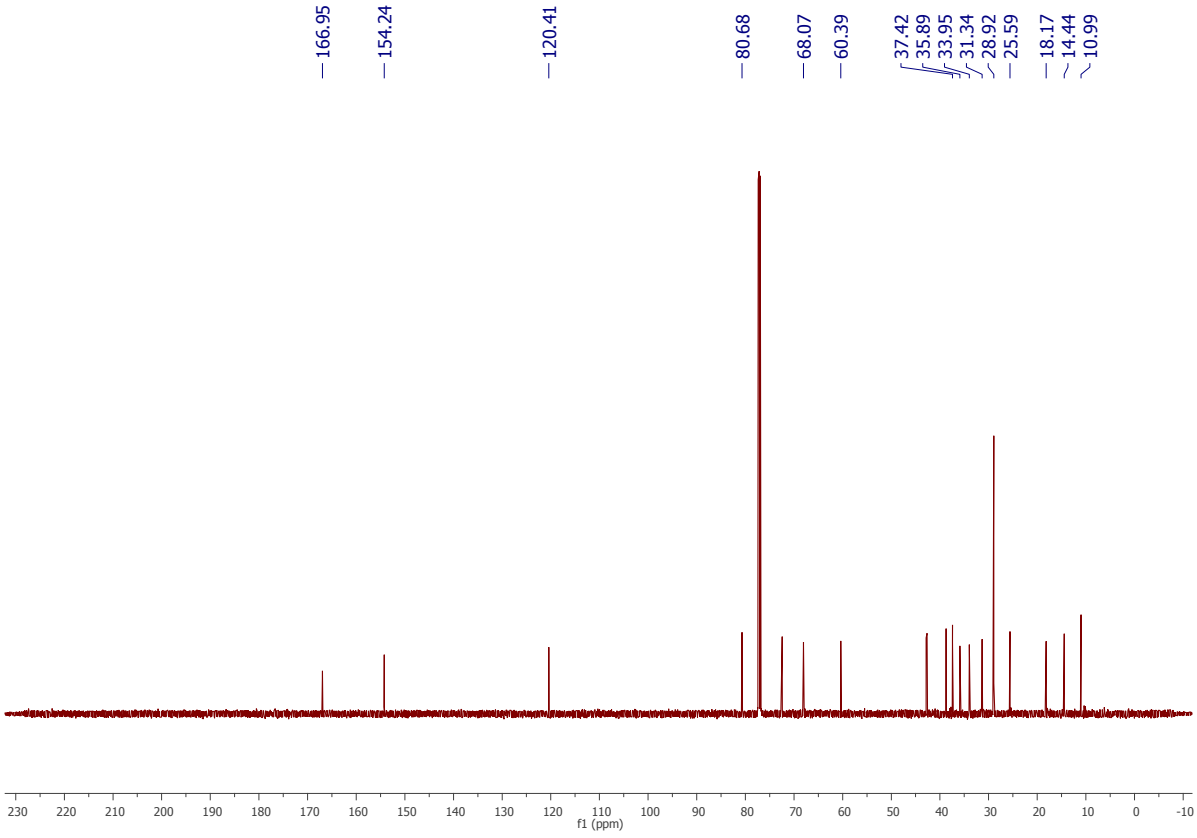


^{1}H NMR ($CDCl_3$, 600 MHz):

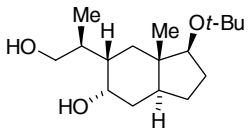


295
$C_{21}H_{36}O_4$
M = 352.51 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

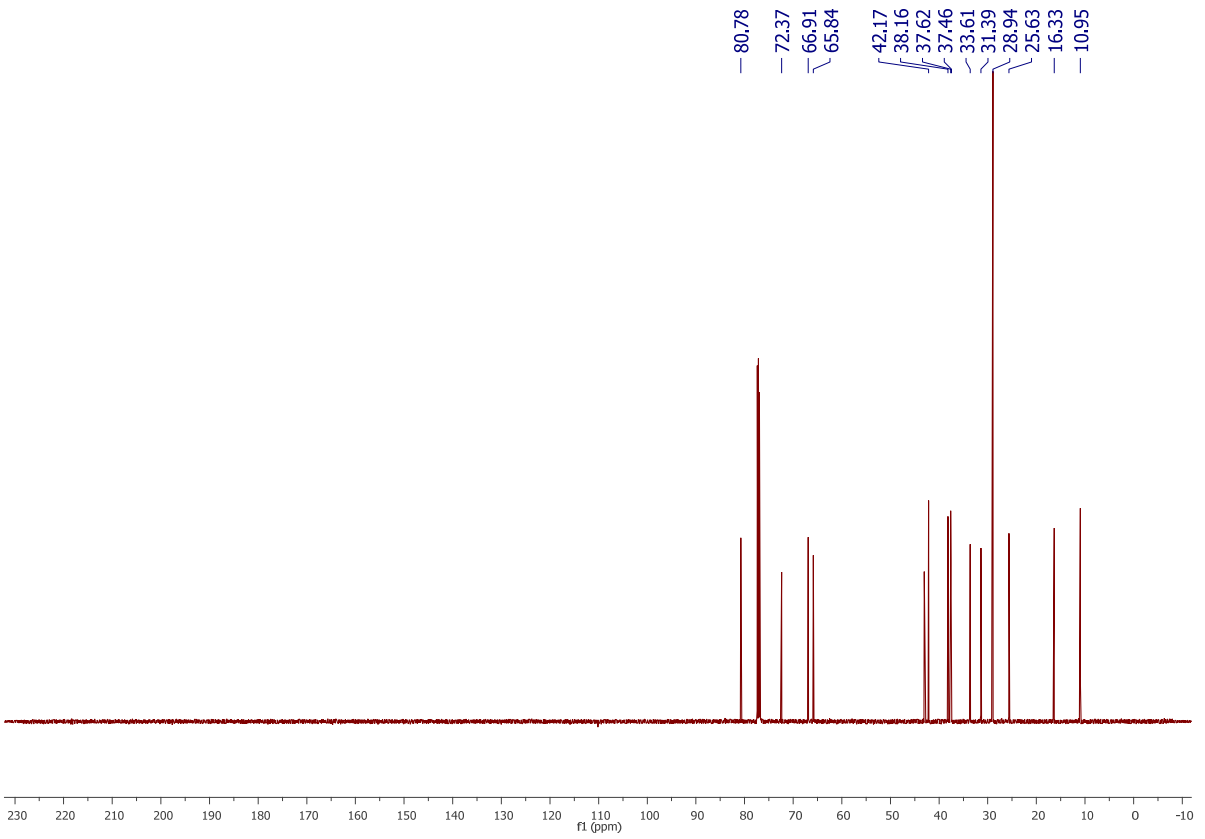


^{1}H NMR ($CDCl_3$, 600 MHz):

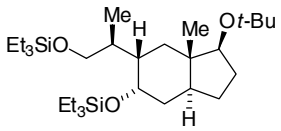


296
$C_{17}H_{32}O_3$
M = 284.43 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

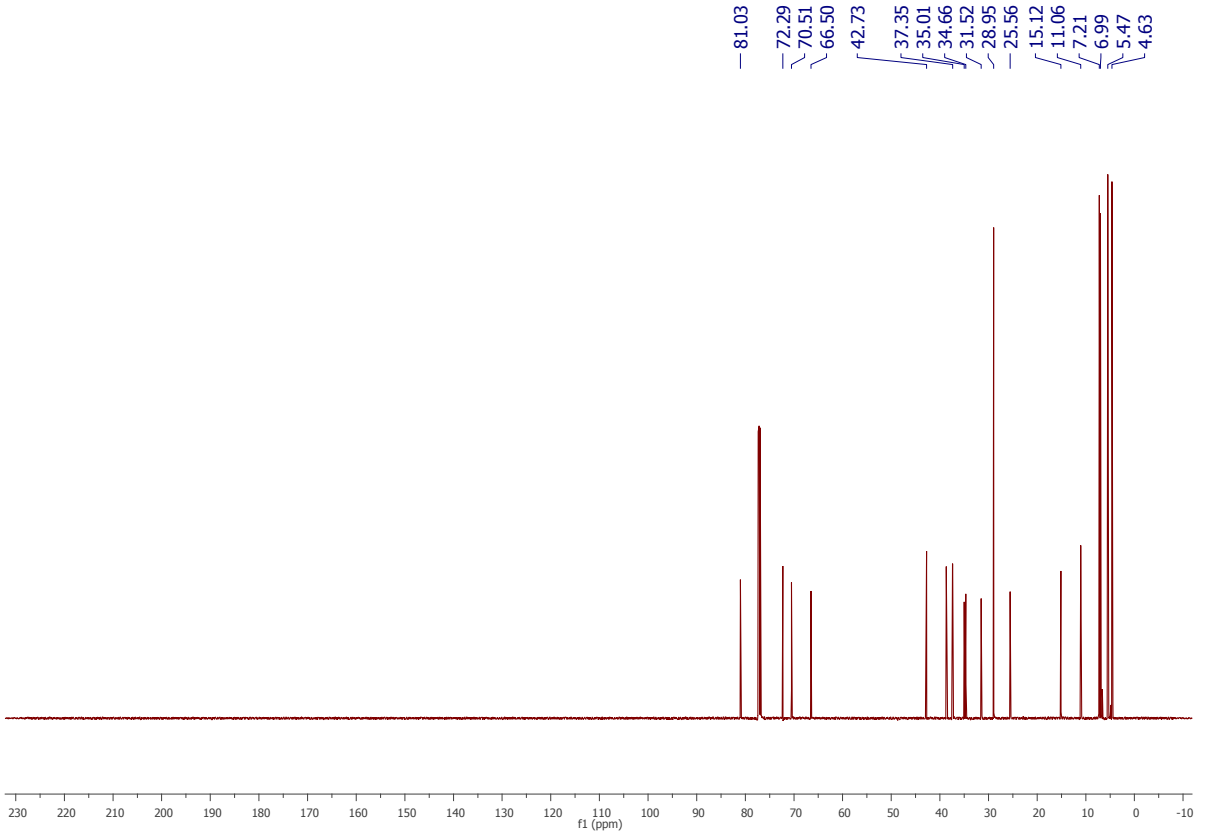


^{1}H NMR ($CDCl_3$, 600 MHz):

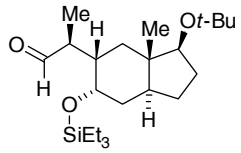


297
$C_{29}H_{60}O_3Si_2$
M = 512.96 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

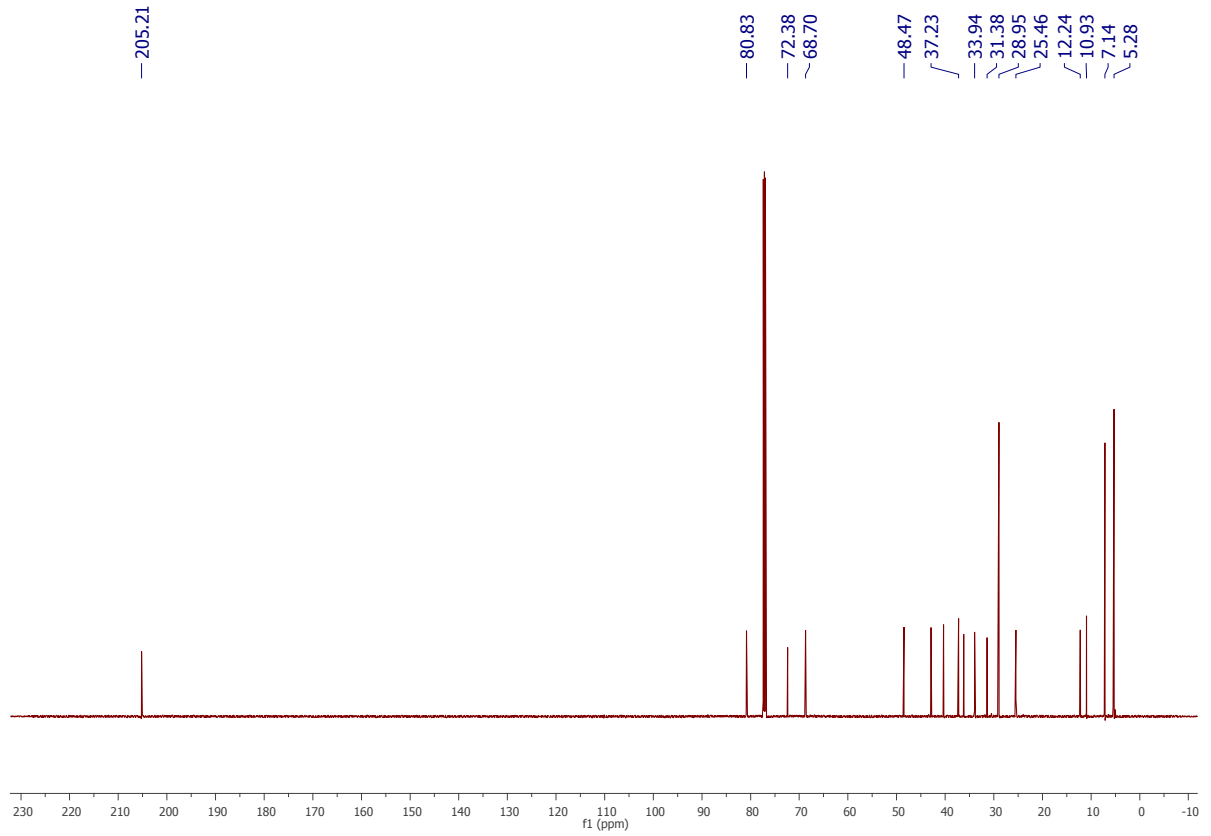


^{1}H NMR ($CDCl_3$, 600 MHz):

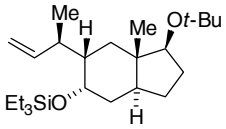


298
$C_{23}H_{44}O_3Si$
M = 296.68 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

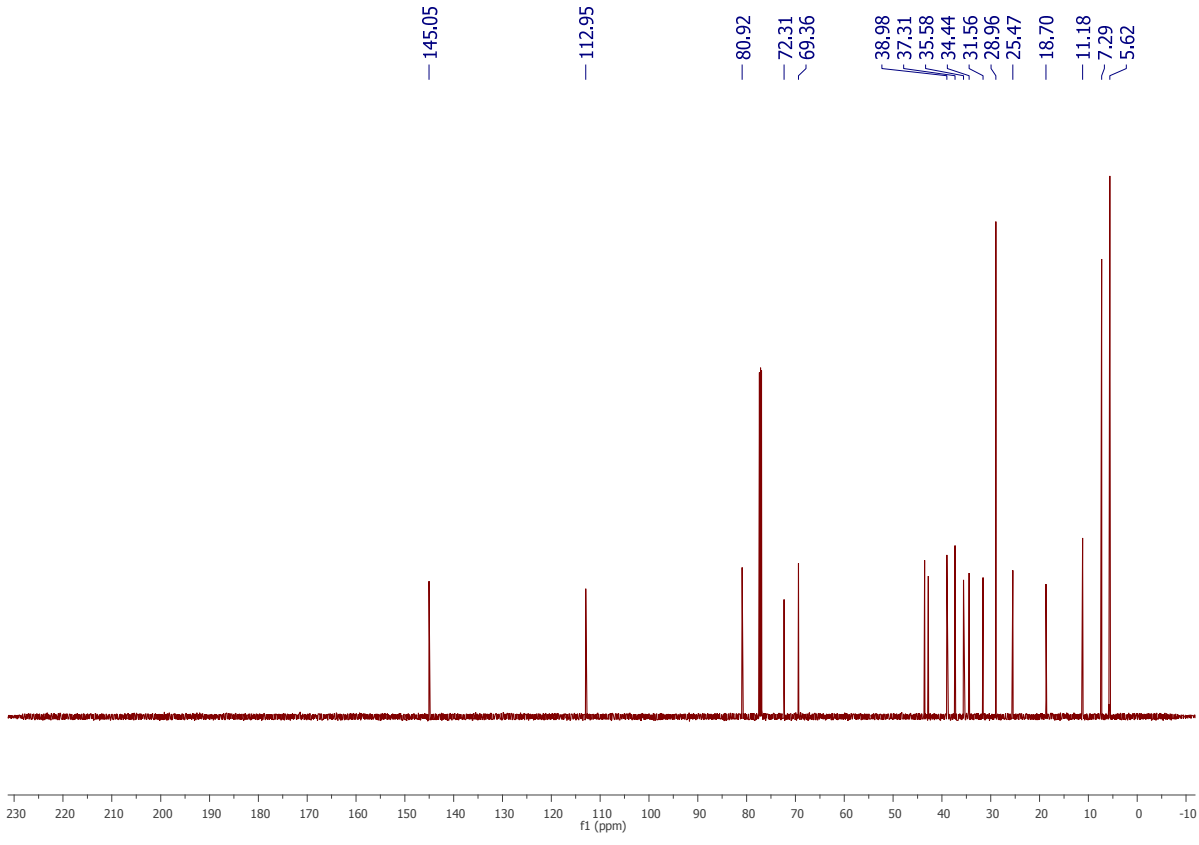


^{1}H NMR ($CDCl_3$, 600 MHz):

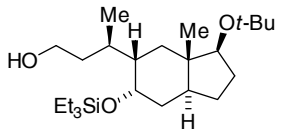


299
$C_{24}H_{46}O_2Si$
M = 394.71 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

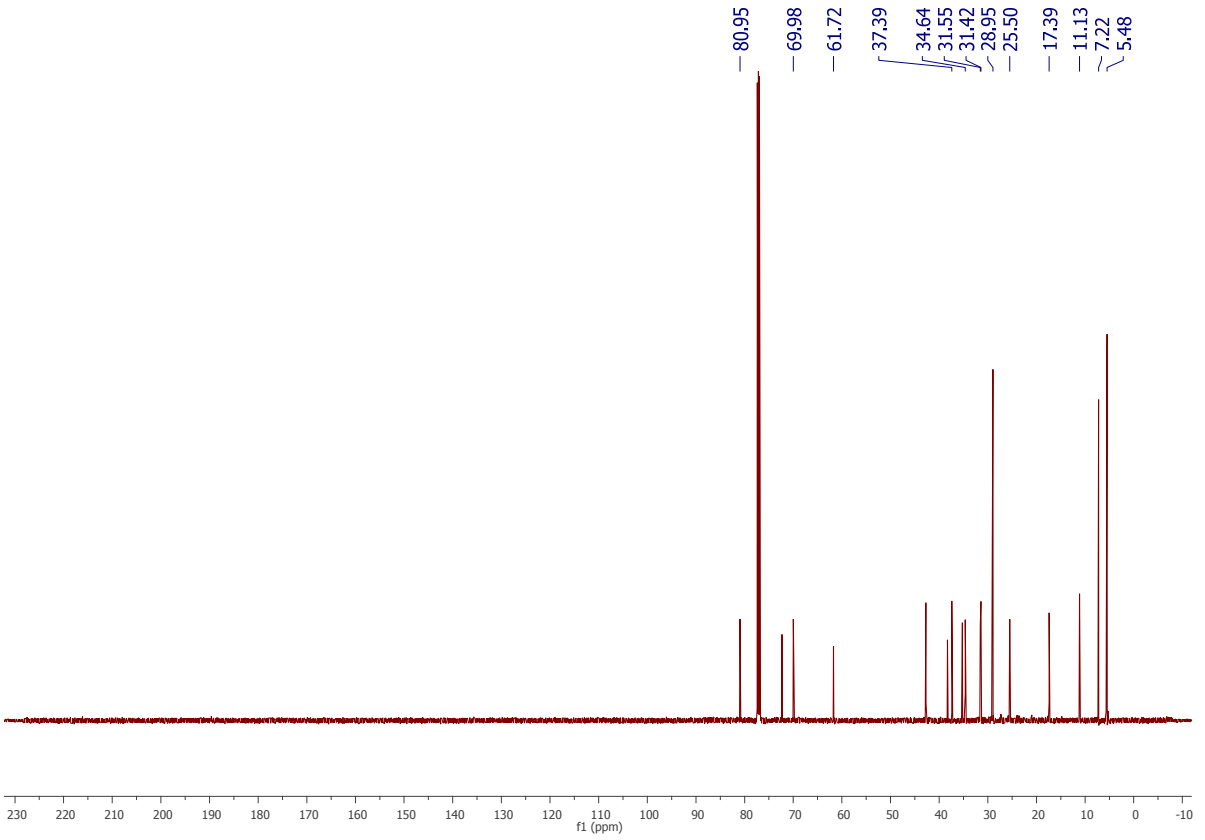


^{1}H NMR ($CDCl_3$, 600 MHz):

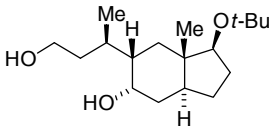


300
$C_{24}H_{48}O_3Si$
M = 412.72 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

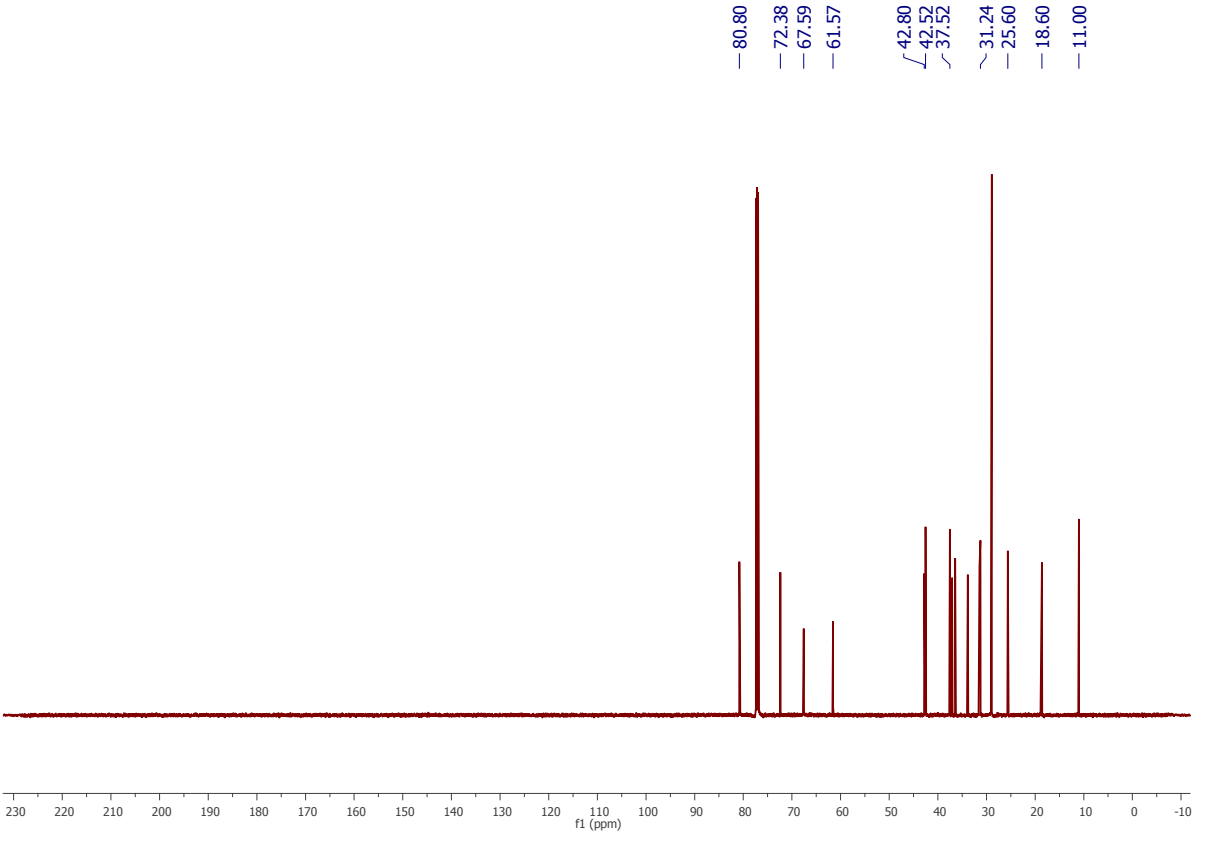


^{1}H NMR ($CDCl_3$, 600 MHz):

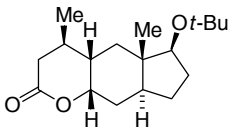


458
$C_{18}H_{34}O_3$
M = 298.46 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

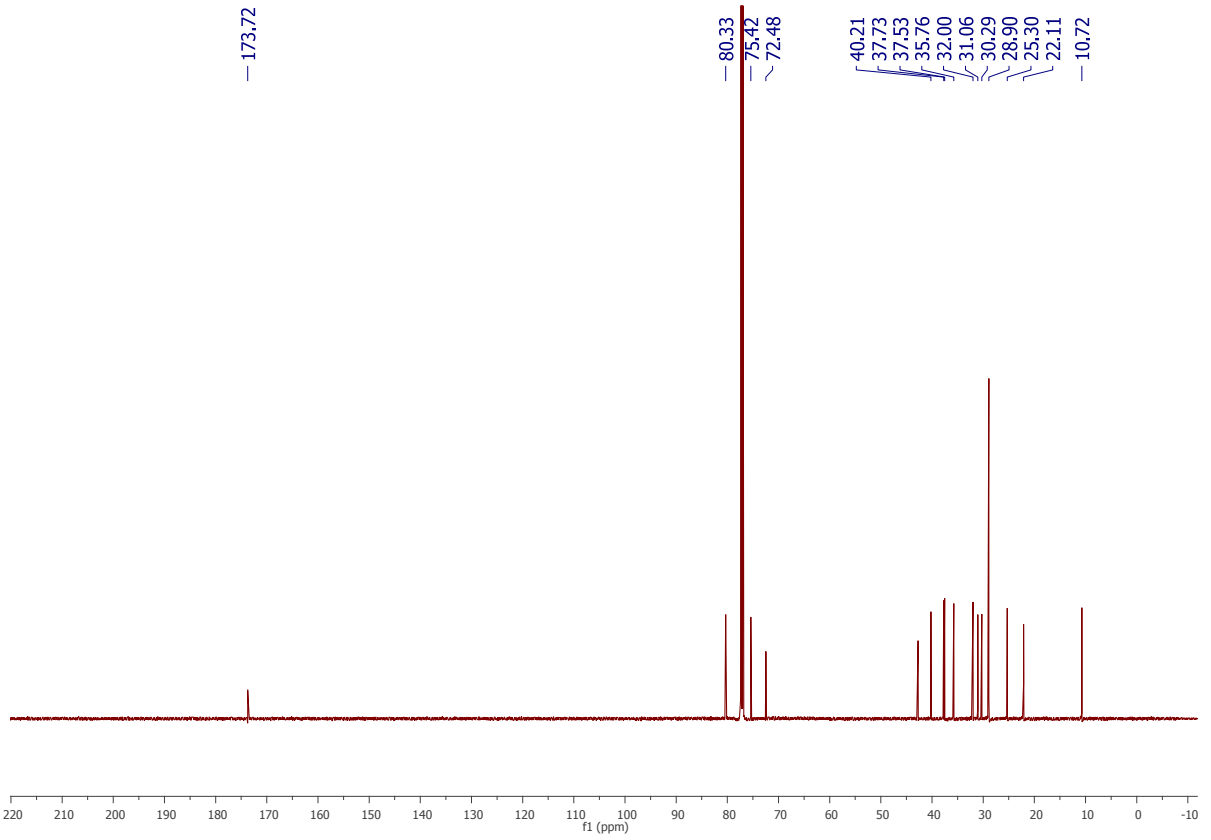


^{1}H NMR ($CDCl_3$, 600 MHz):

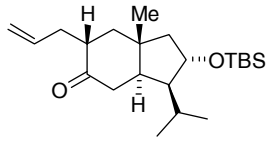


301
$C_{18}H_{30}O_3$
M = 294.43 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

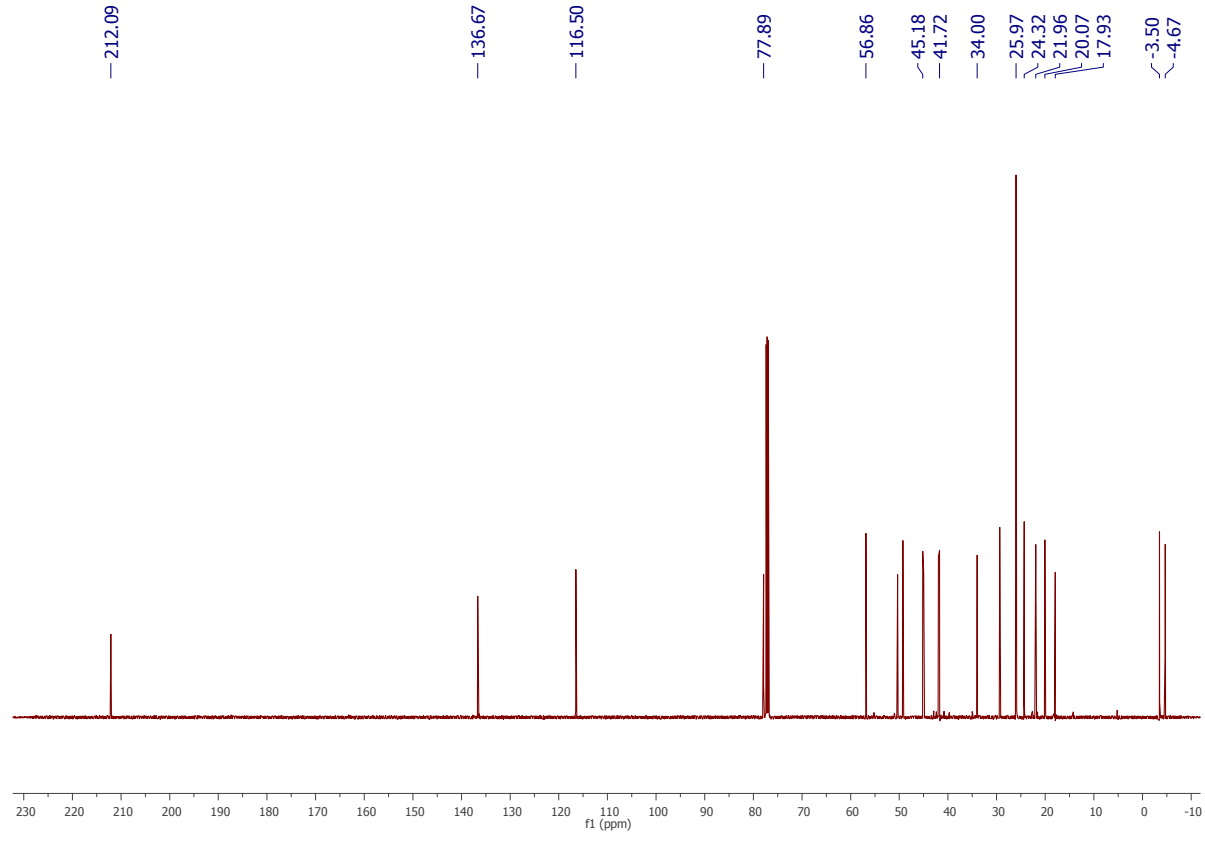


^{1}H NMR ($CDCl_3$, 600 MHz):

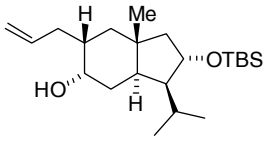


302
$C_{22}H_{40}O_2Si$
M = 364.64 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

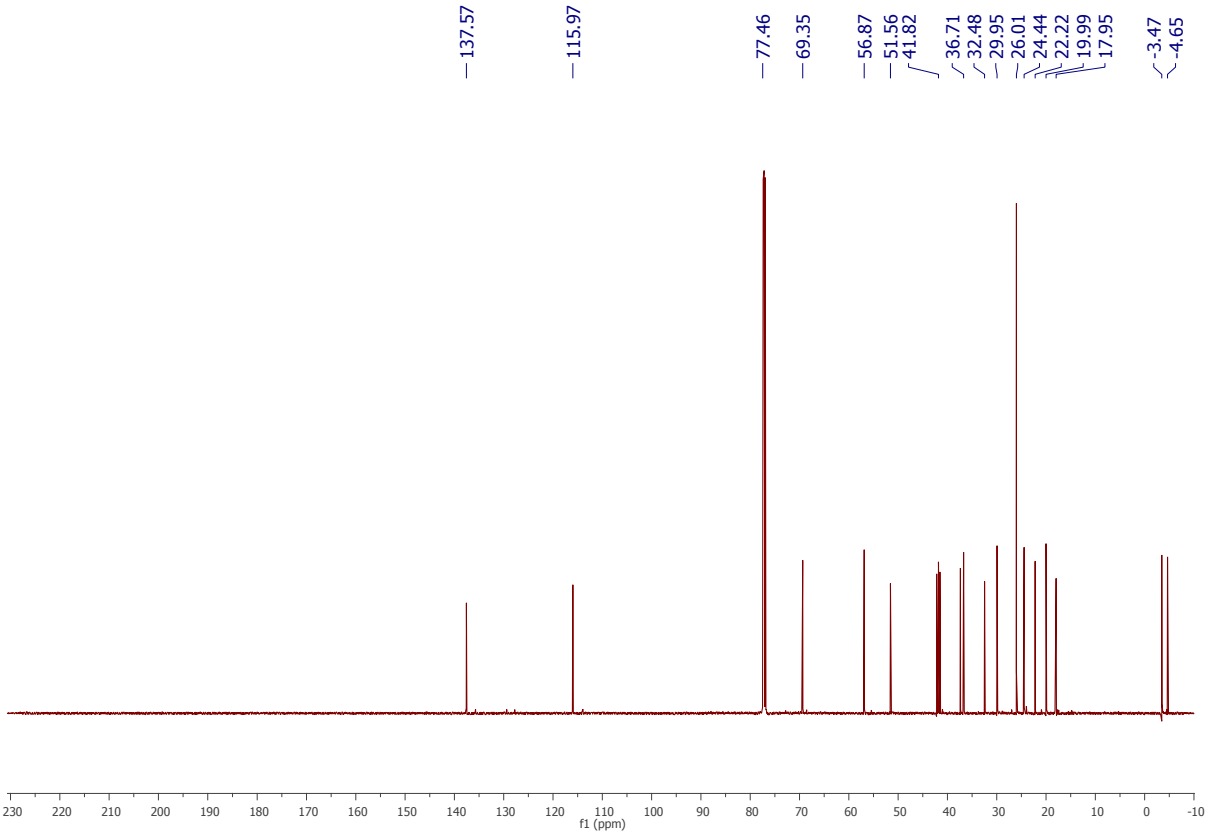


^{1}H NMR ($CDCl_3$, 600 MHz):

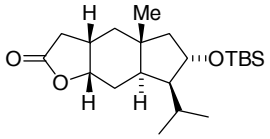


303
$C_{22}H_{42}O_2Si$
M = 366.65 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

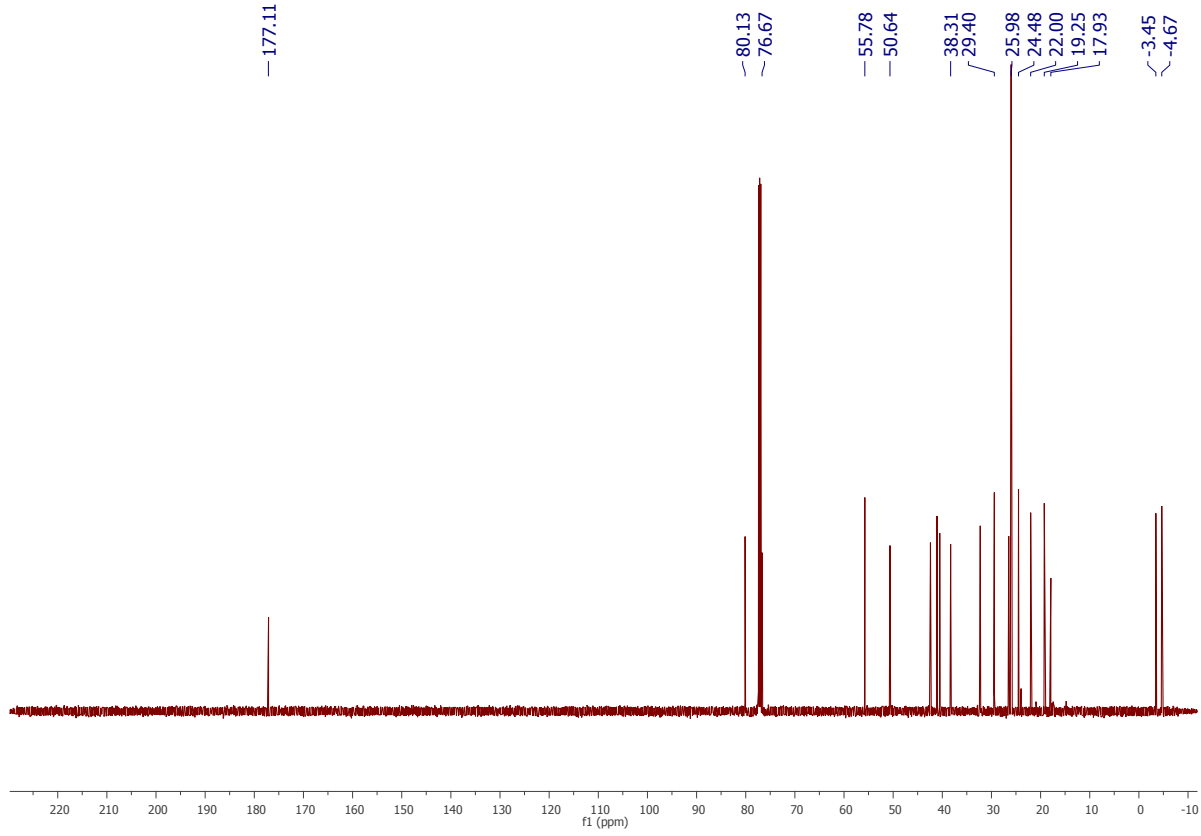


^{1}H NMR ($CDCl_3$, 600 MHz):

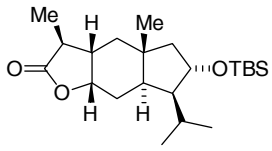


304
$C_{21}H_{38}O_3Si$
M = 366.61 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

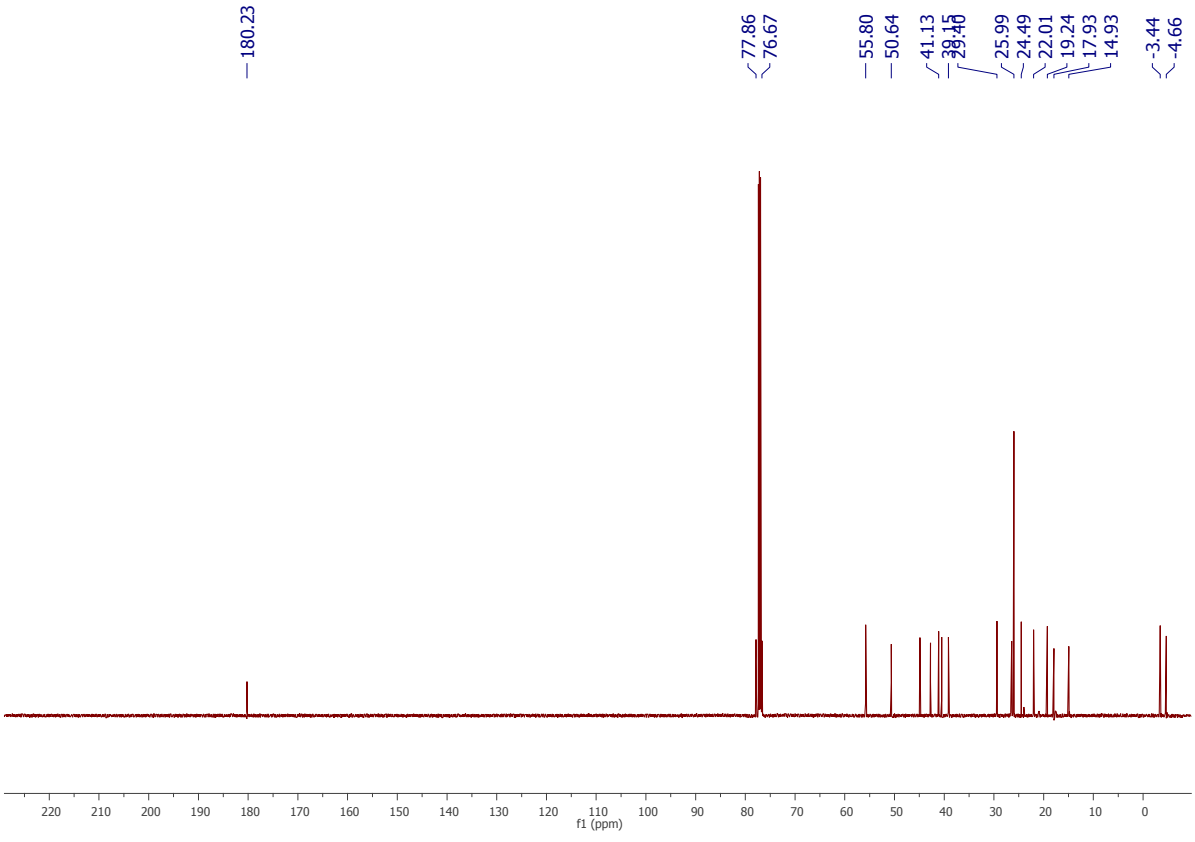


^{1}H NMR ($CDCl_3$, 600 MHz):

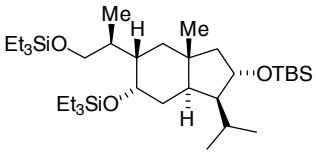


269
$C_{22}H_{40}O_3Si$
M = 380.64 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

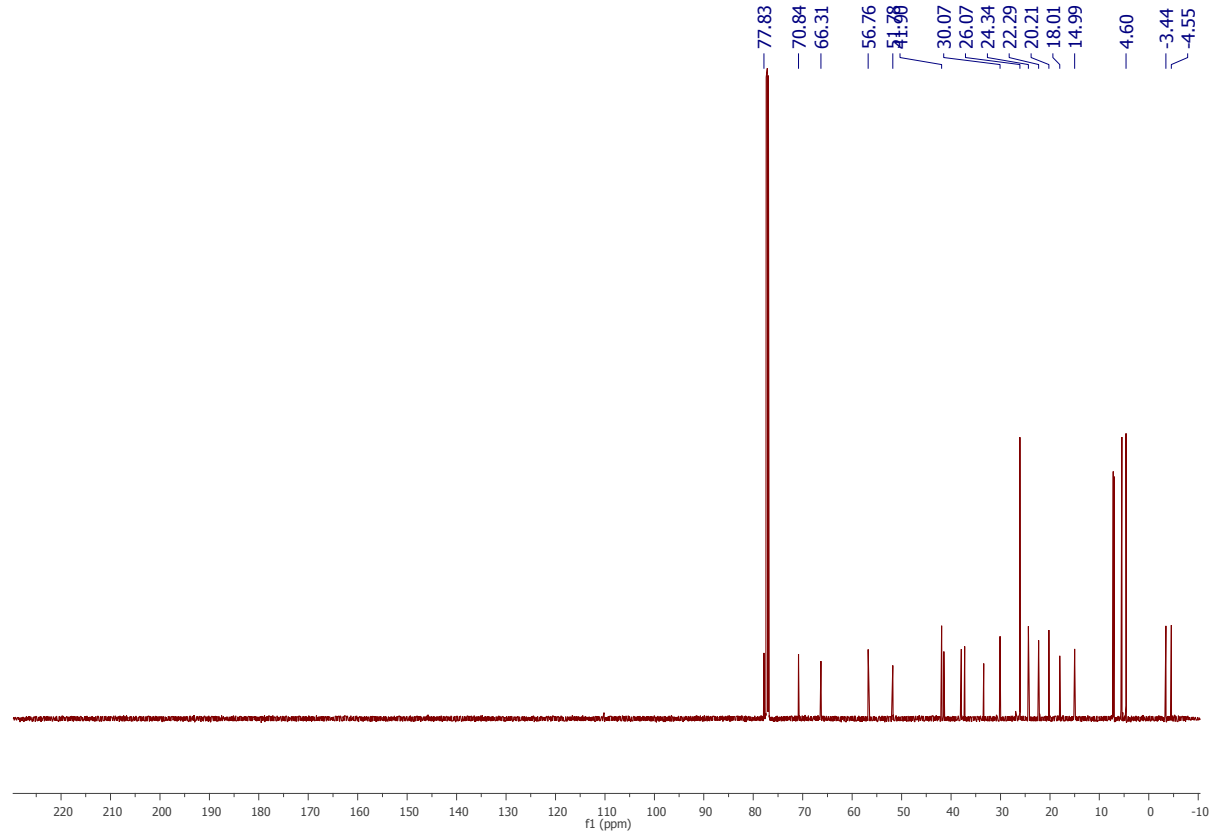


^{1}H NMR ($CDCl_3$, 600 MHz):

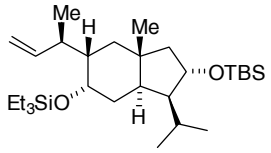


305
$C_{34}H_{72}O_3Si_3$
M = 613.19 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

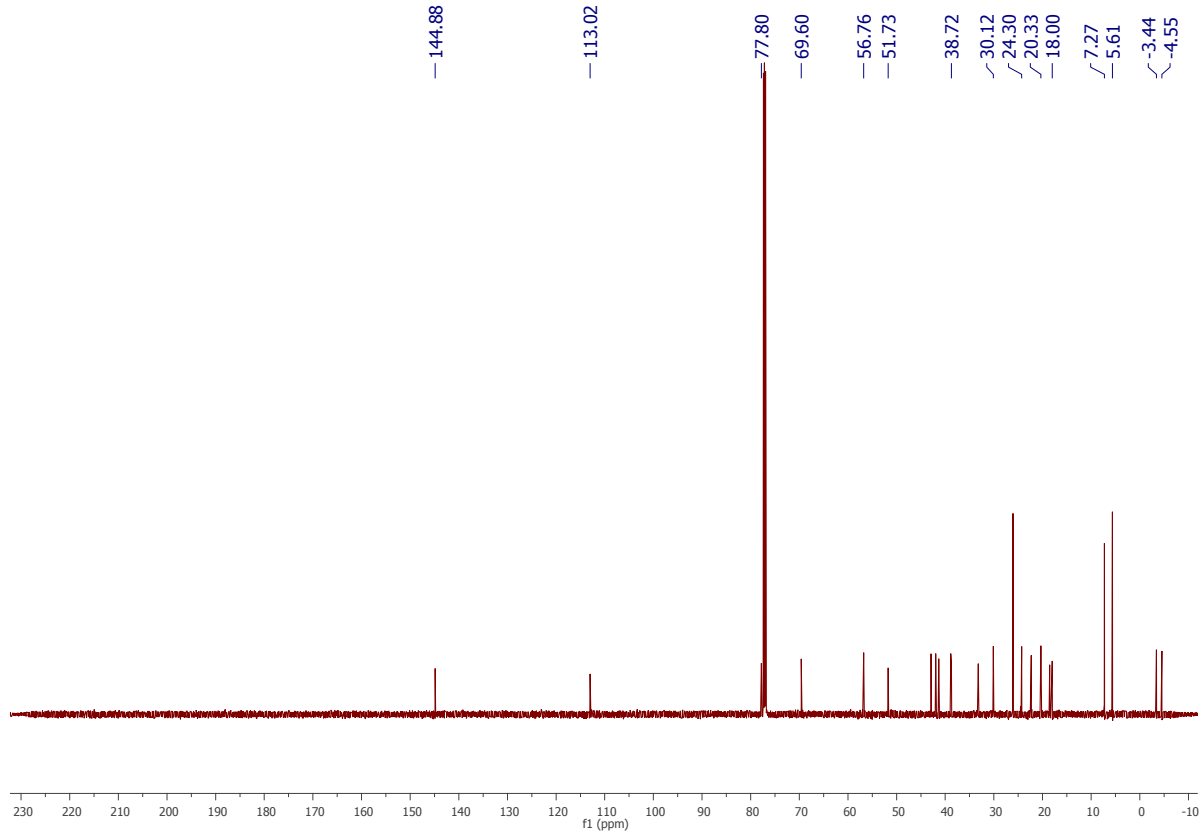


^{1}H NMR ($CDCl_3$, 600 MHz):

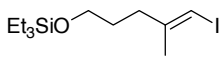


268
$C_{29}H_{58}O_2Si_2$
M = 494.94 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

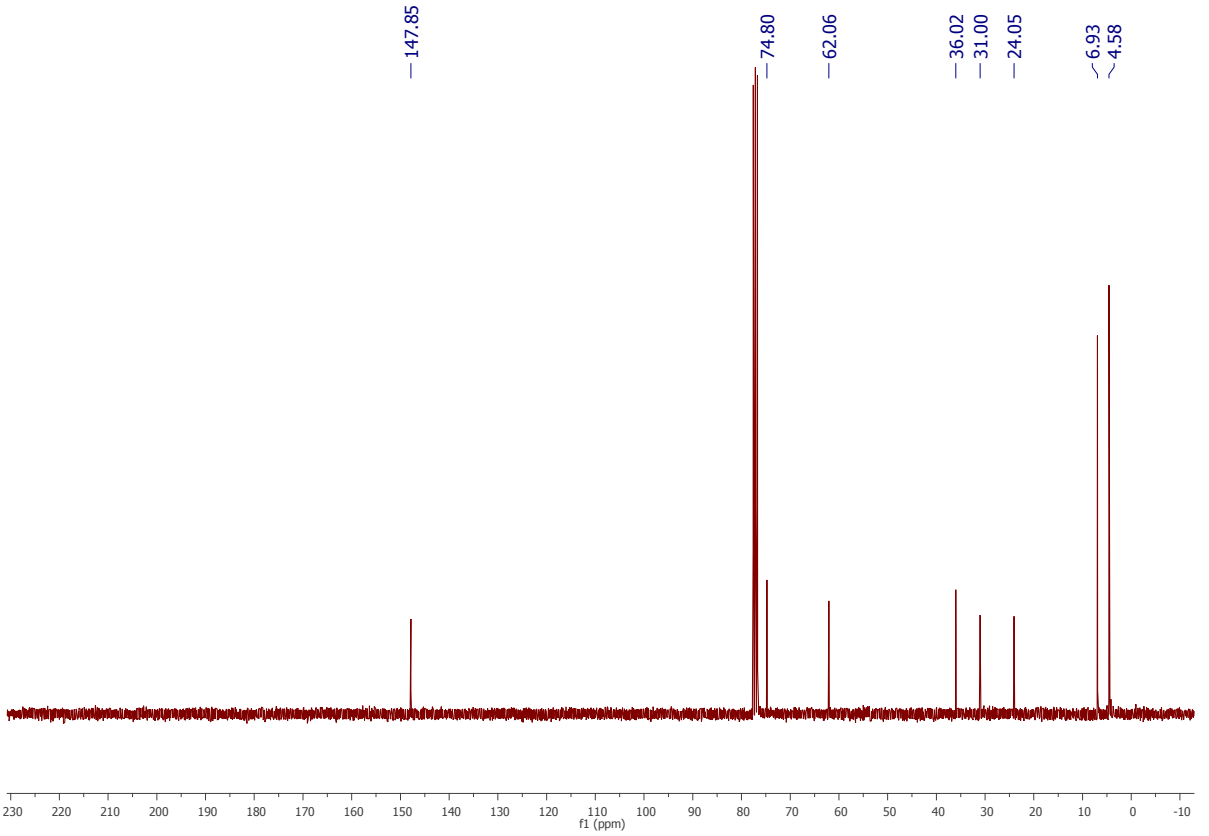


^{1}H NMR ($CDCl_3$, 300 MHz):

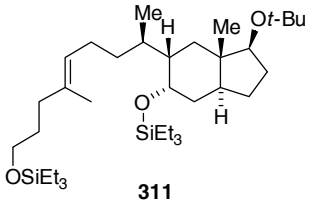


308
$C_{12}H_{25}IOSi$
M = 340.32 g/mol

^{13}C NMR ($CDCl_3$, 75 MHz):



^{1}H NMR ($CDCl_3$, 600 MHz):

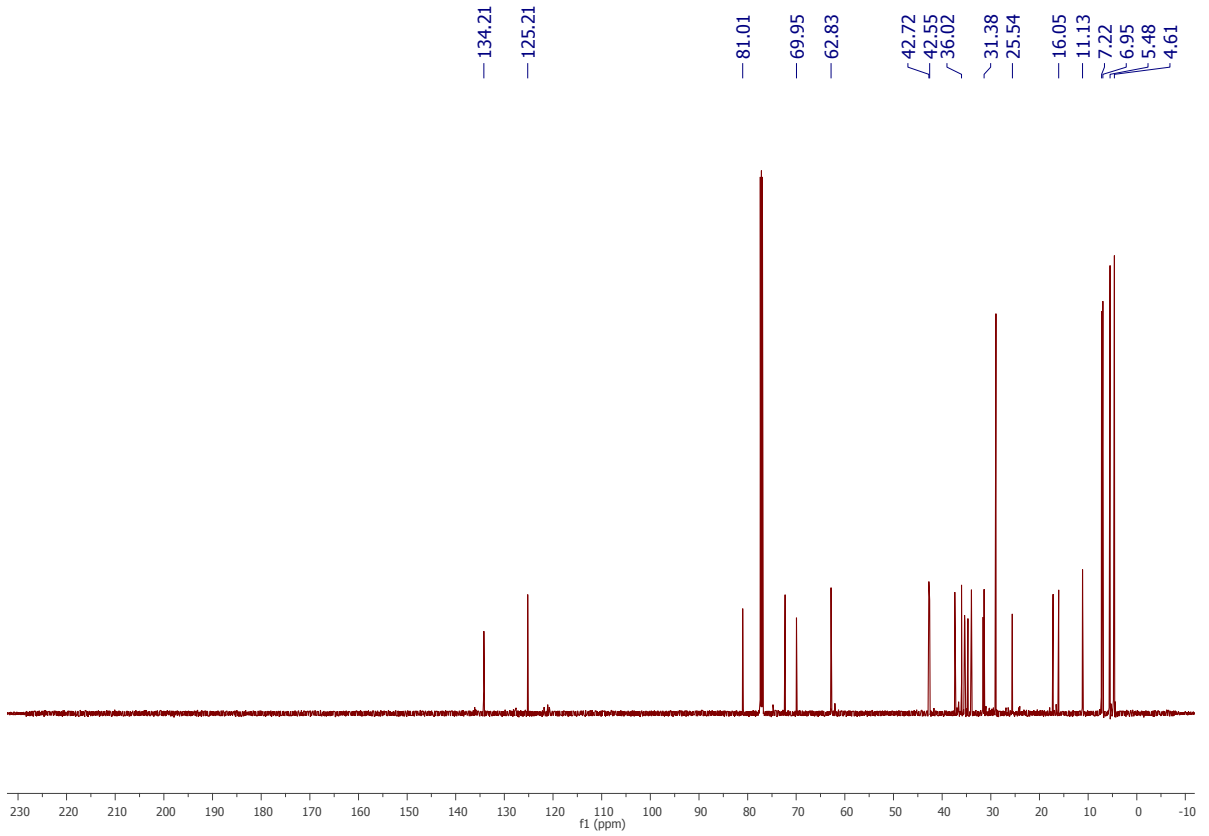


311

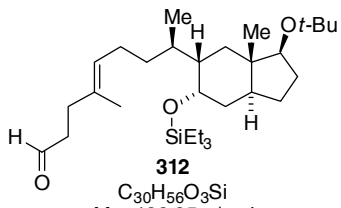
$C_{36}H_{72}O_3Si_2$

M = 609.13 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):



^{1}H NMR ($CDCl_3$, 600 MHz):

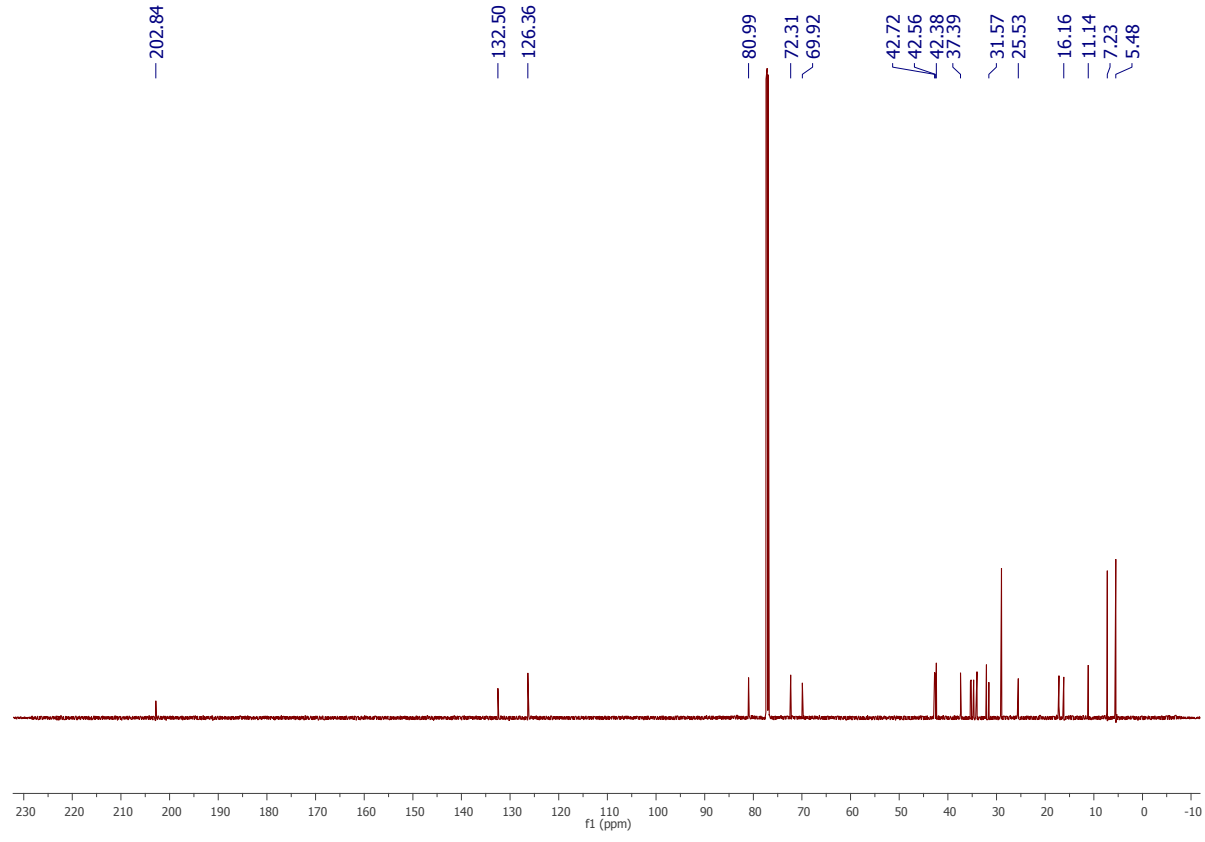


312

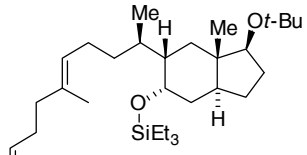
$C_{30}H_{56}O_3Si$

M = 492.85 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):



^{1}H NMR ($CDCl_3$, 600 MHz):

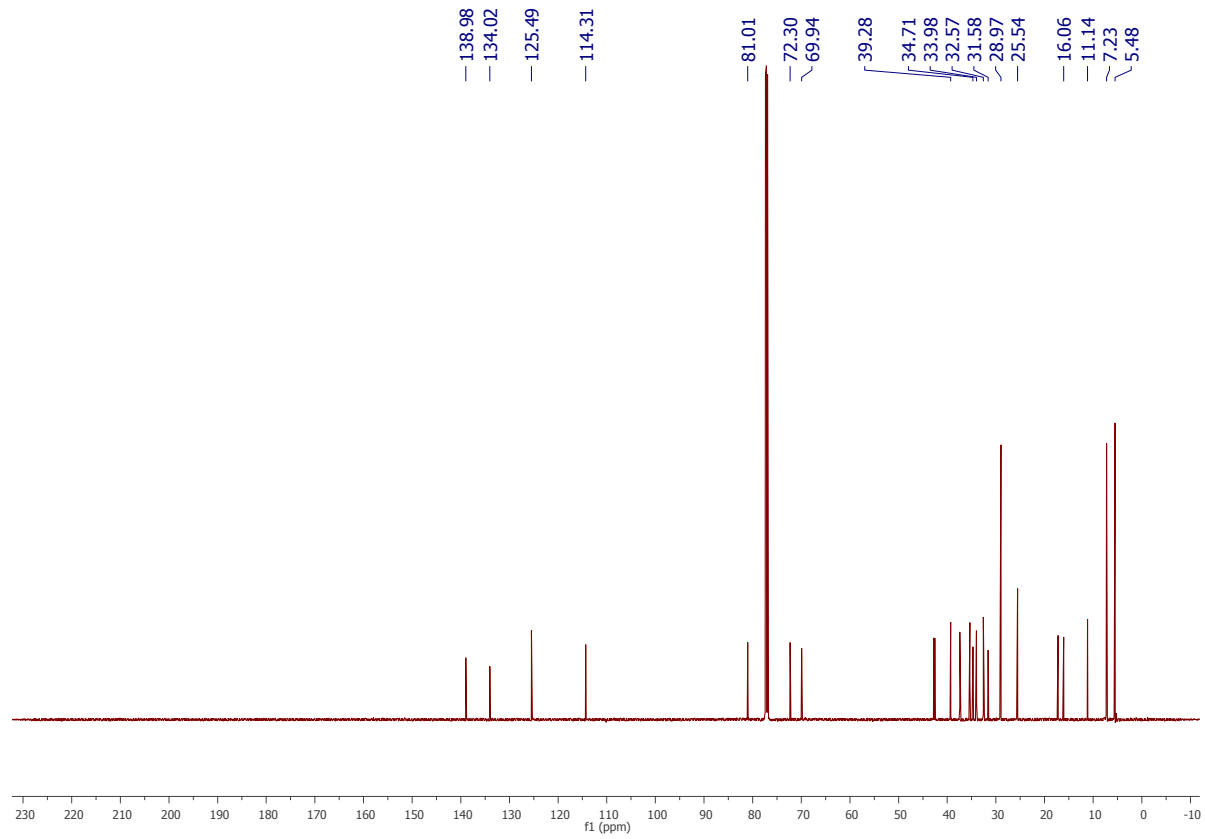


317

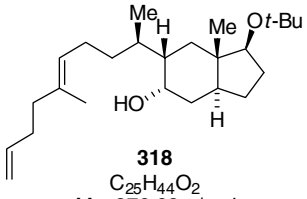
$C_{31}H_{58}O_2Si$

M = 490.88 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

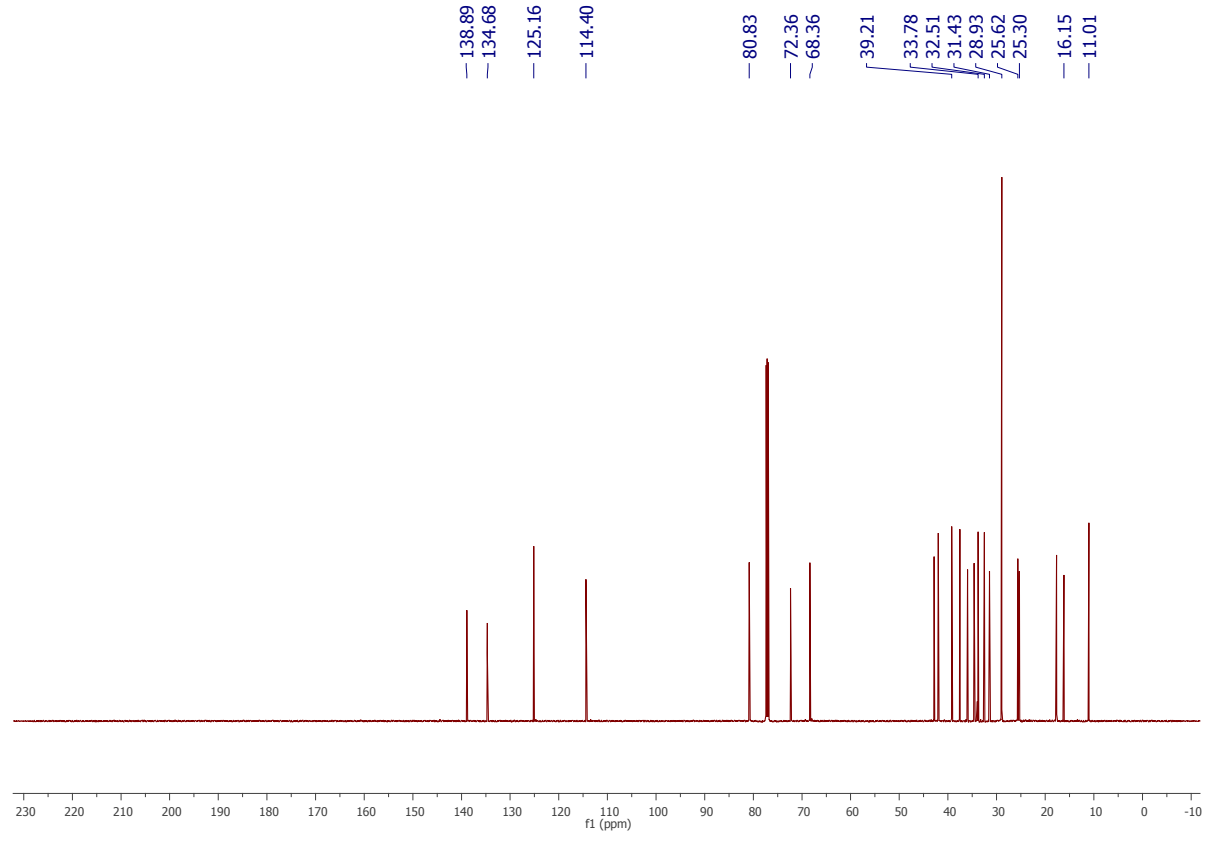


^{1}H NMR ($CDCl_3$, 600 MHz):

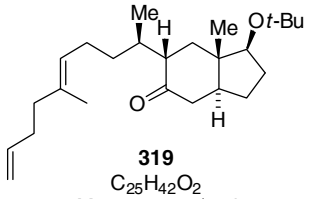


318
$C_{25}H_{44}O_2$
M = 376.62 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

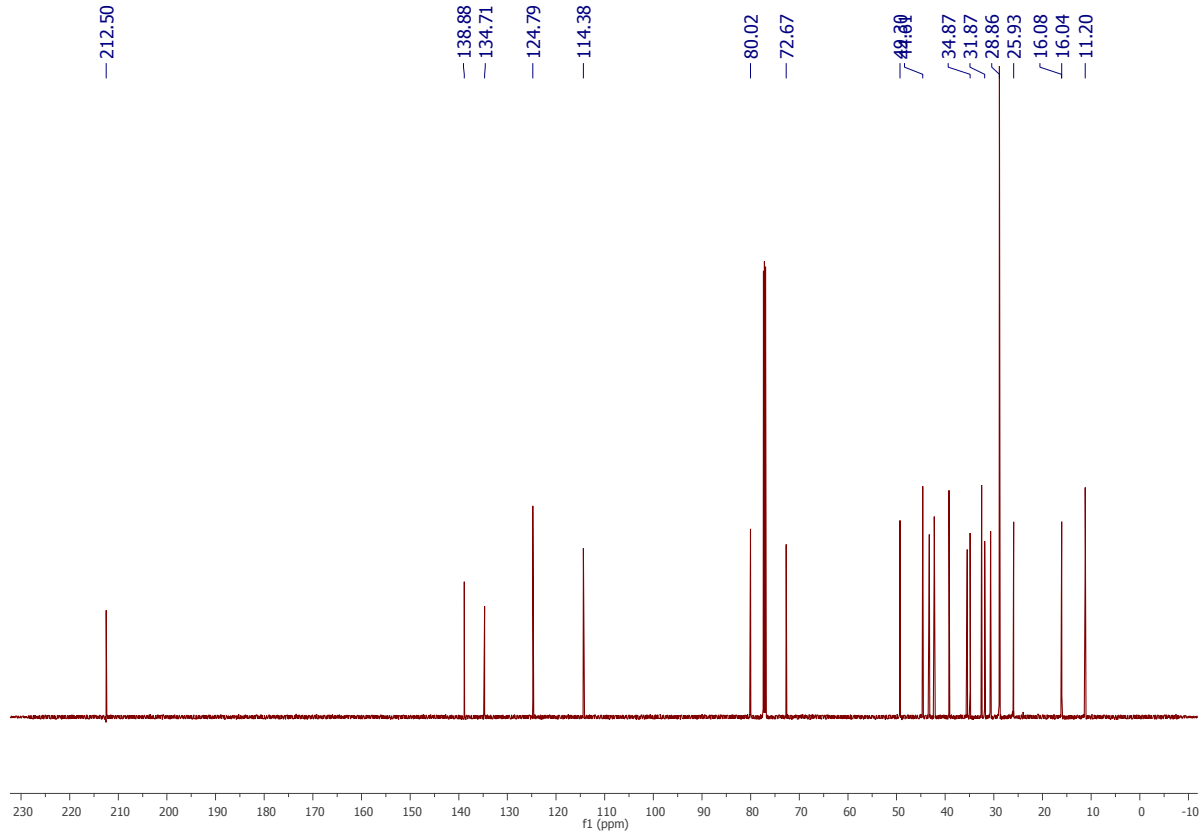


^{1}H NMR ($CDCl_3$, 600 MHz):

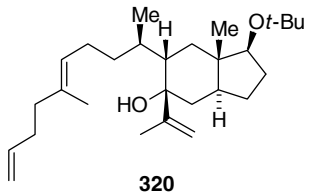


319
$C_{25}H_{42}O_2$
M = 374.60 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

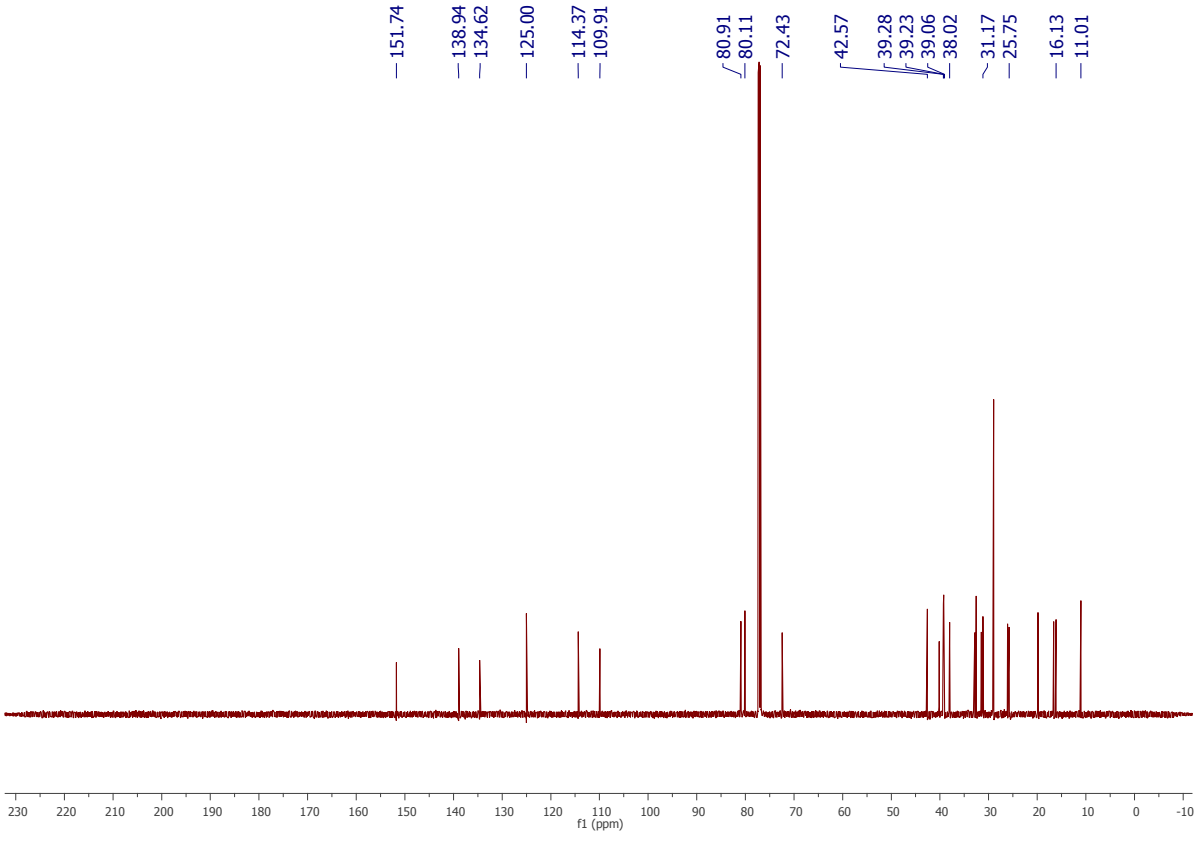


^{1}H NMR ($CDCl_3$, 600 MHz):

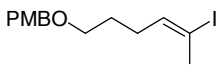


320
$C_{28}H_{48}O_2$
M = 416.68 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

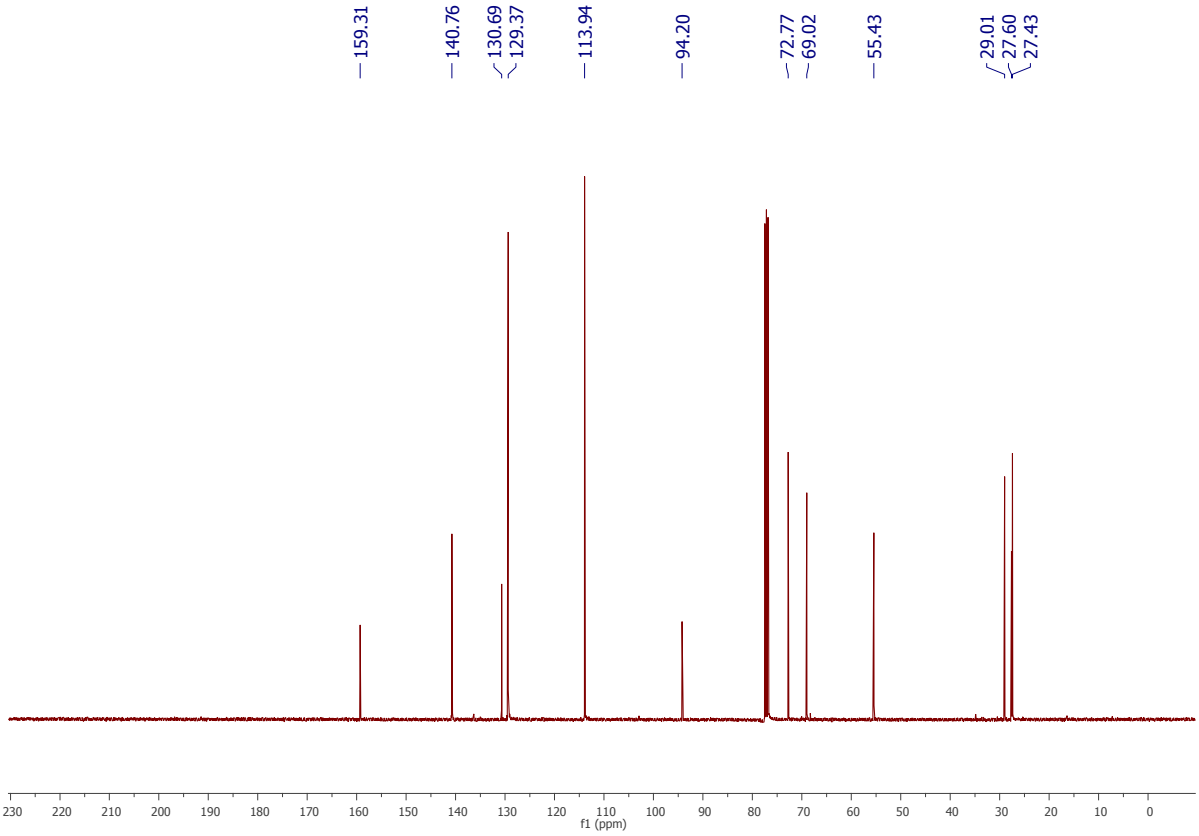


^{1}H NMR ($CDCl_3$, 400 MHz):

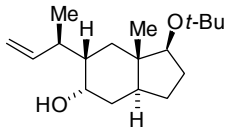


330
$C_{14}H_{19}IO_2$
M = 346.20 g/mol

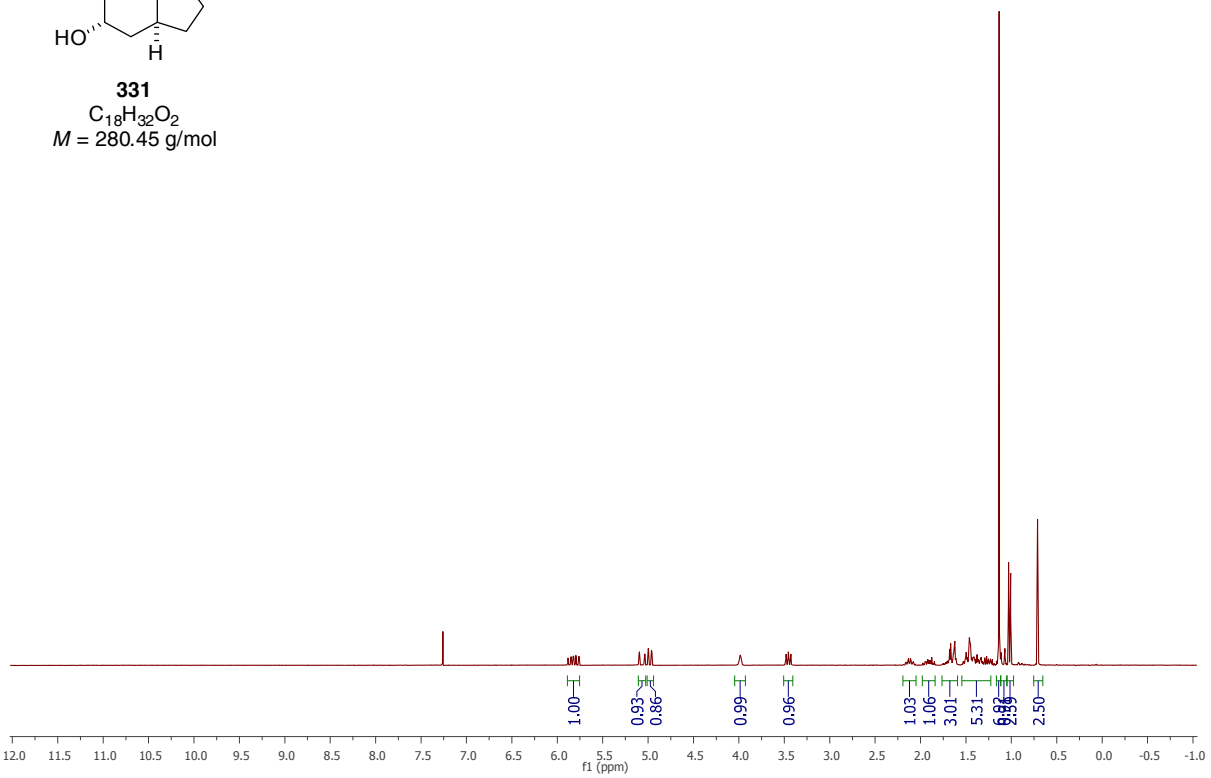
^{13}C NMR ($CDCl_3$, 100 MHz):



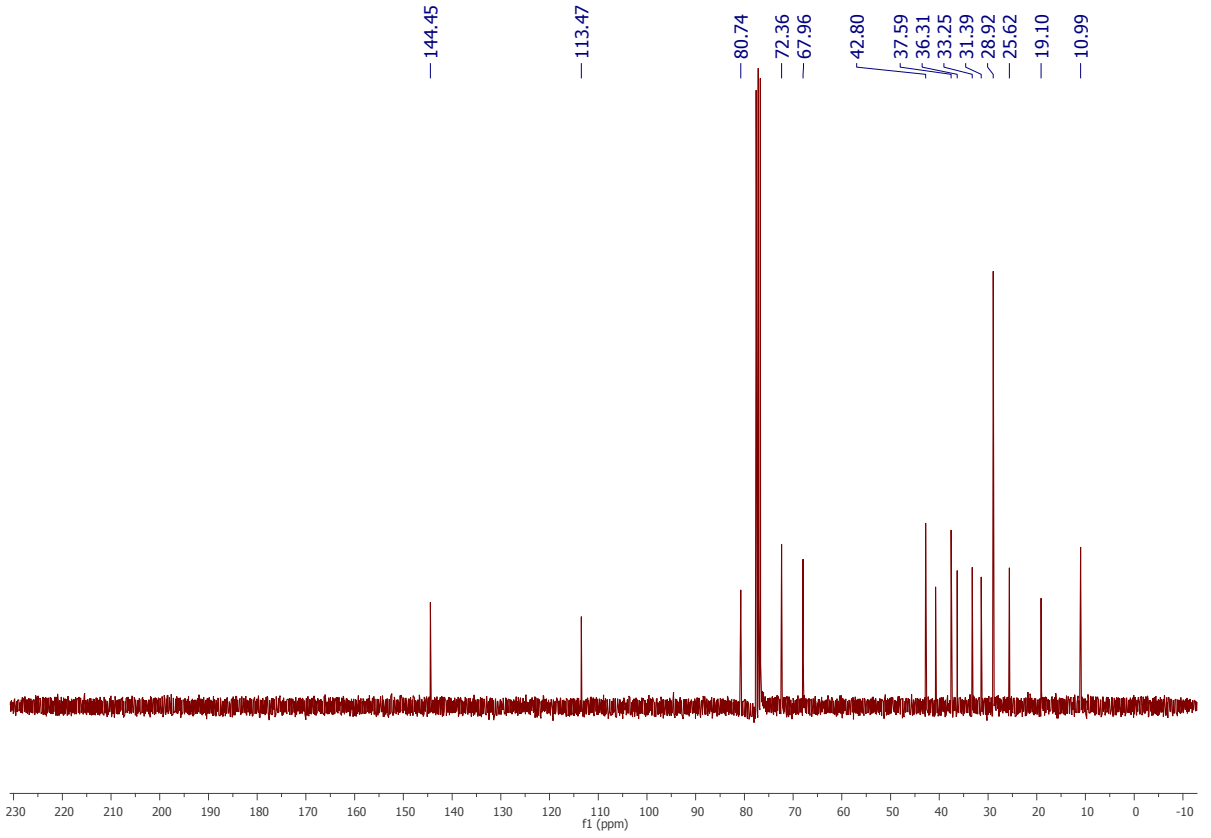
^{1}H NMR ($CDCl_3$, 300 MHz):



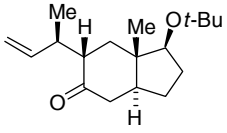
331
$C_{18}H_{32}O_2$
M = 280.45 g/mol



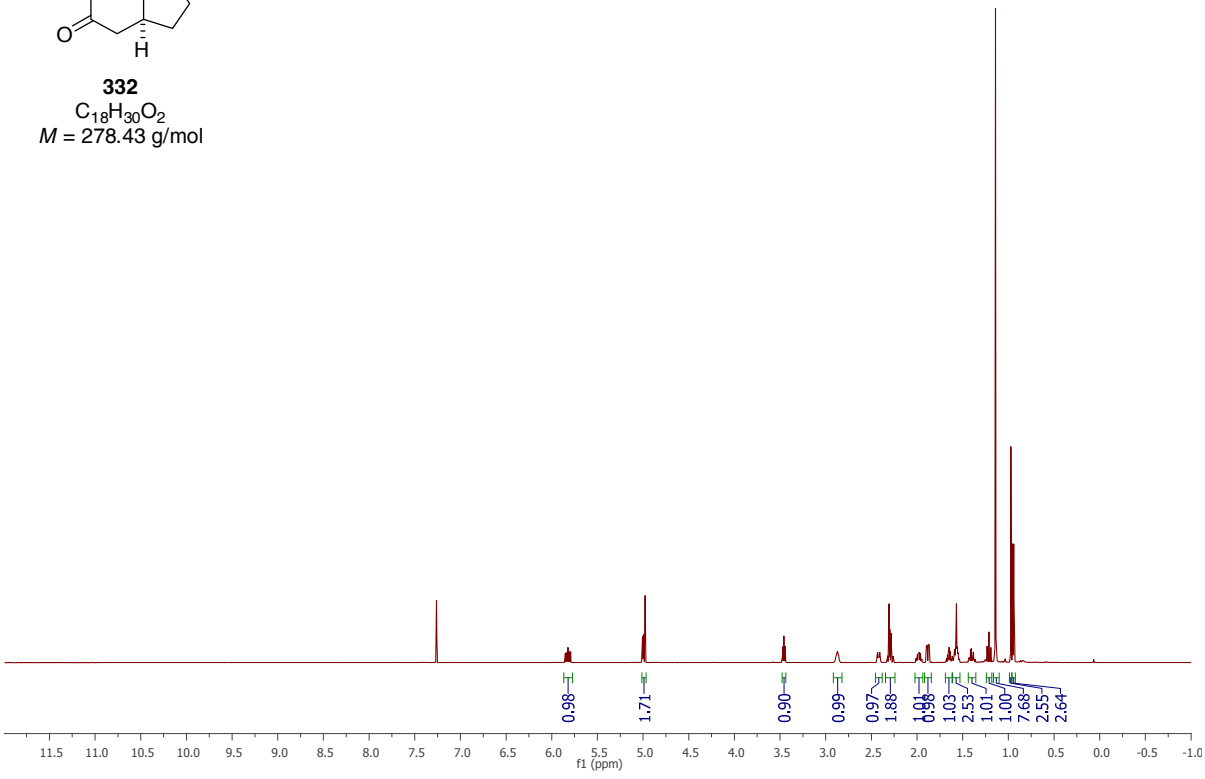
^{13}C NMR ($CDCl_3$, 75 MHz):



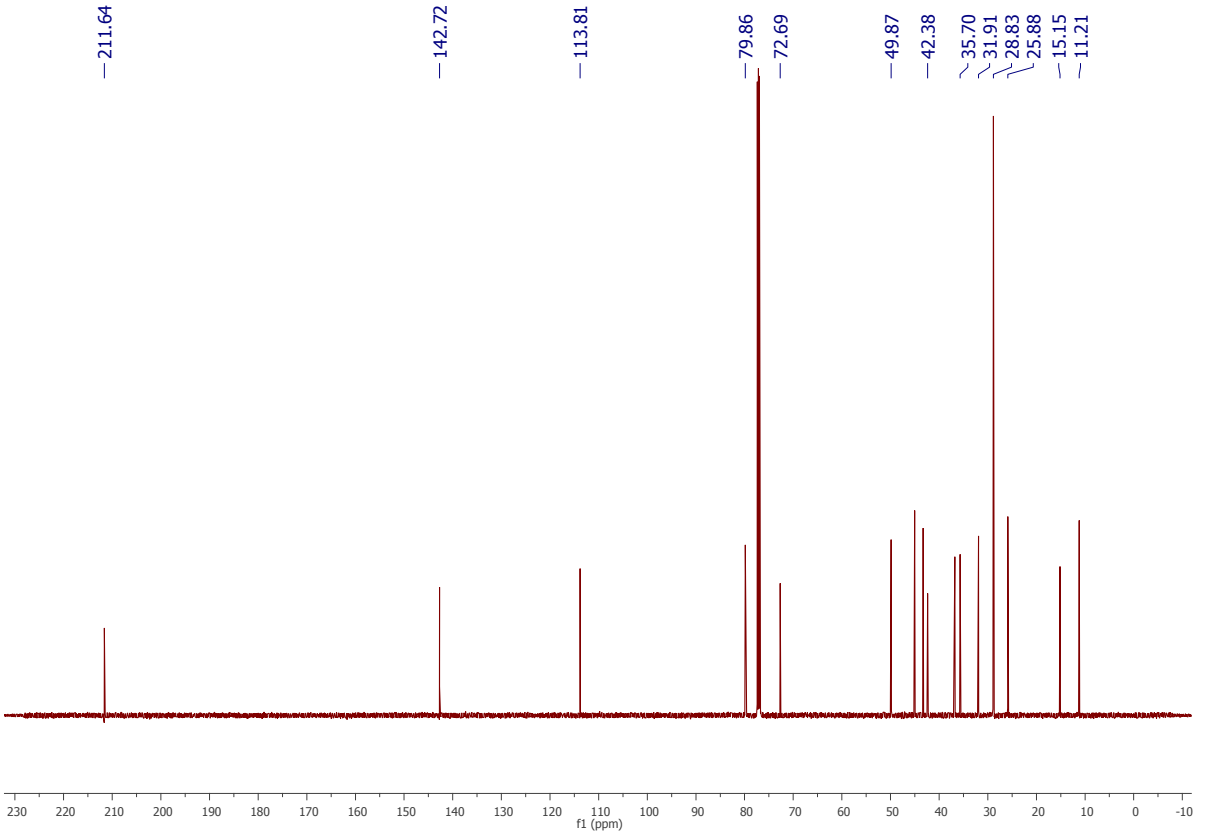
^{1}H NMR ($CDCl_3$, 600 MHz):



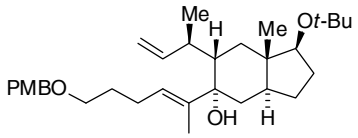
332
$C_{18}H_{30}O_2$
M = 278.43 g/mol



^{13}C NMR ($CDCl_3$, 150 MHz):

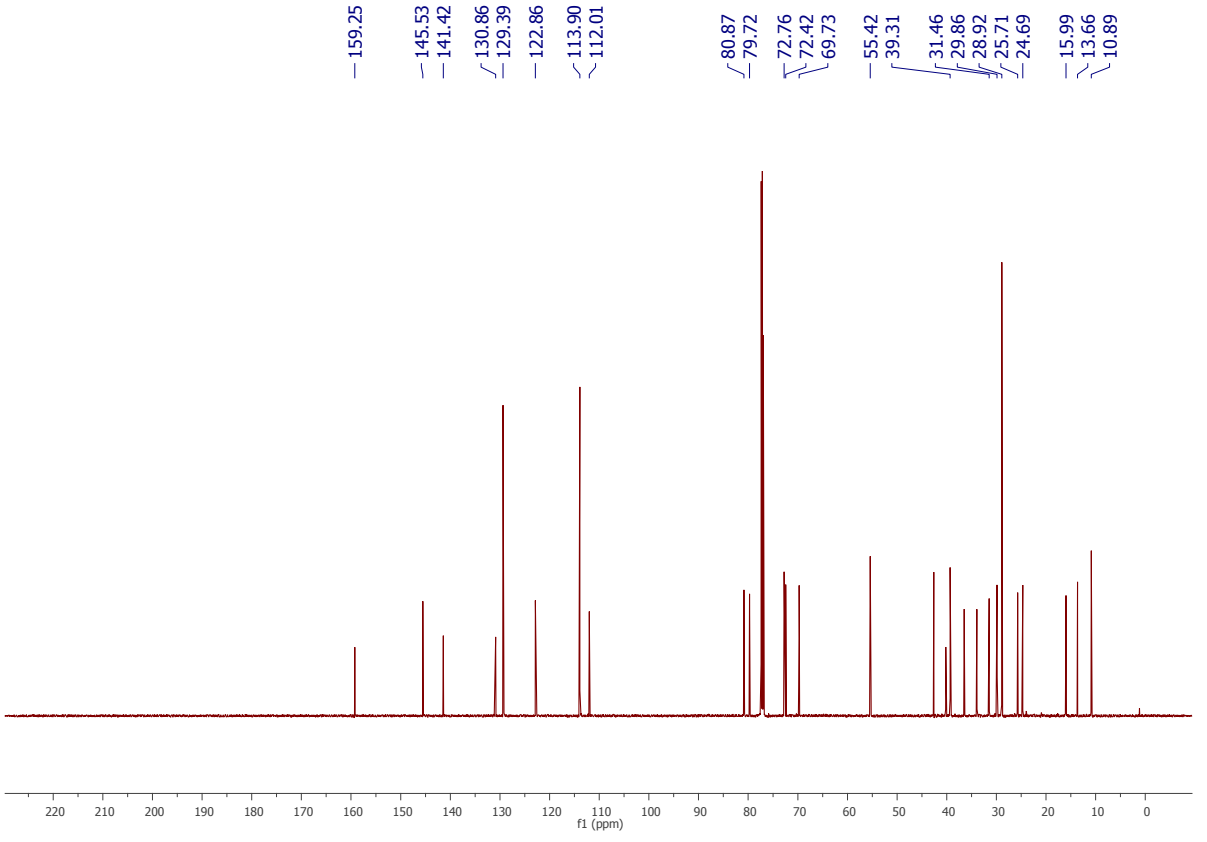


^{1}H NMR ($CDCl_3$, 600 MHz):

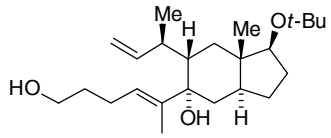


333
$C_{32}H_{50}O_4$
M = 498.74 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

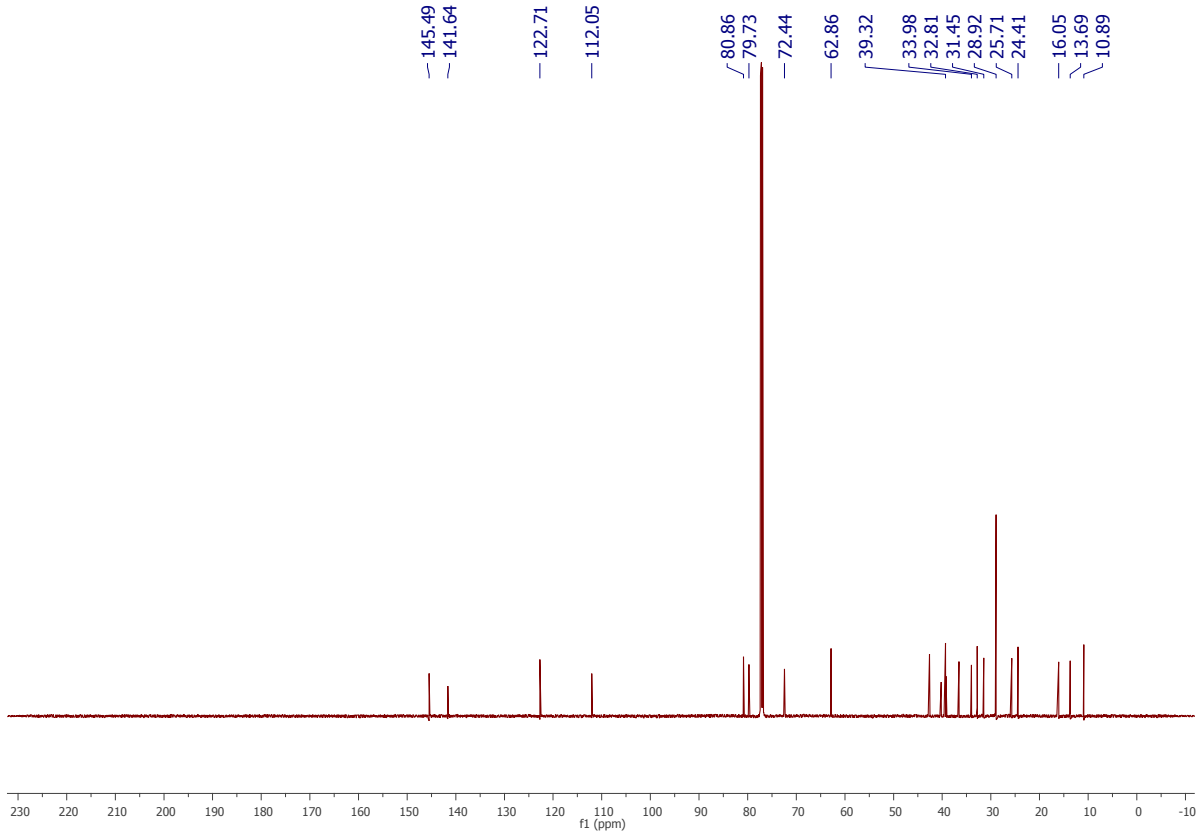


^{1}H NMR ($CDCl_3$, 600 MHz):

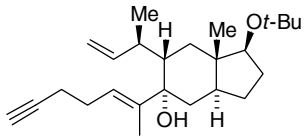


334
$C_{24}H_{42}O_3$
M = 378.59 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

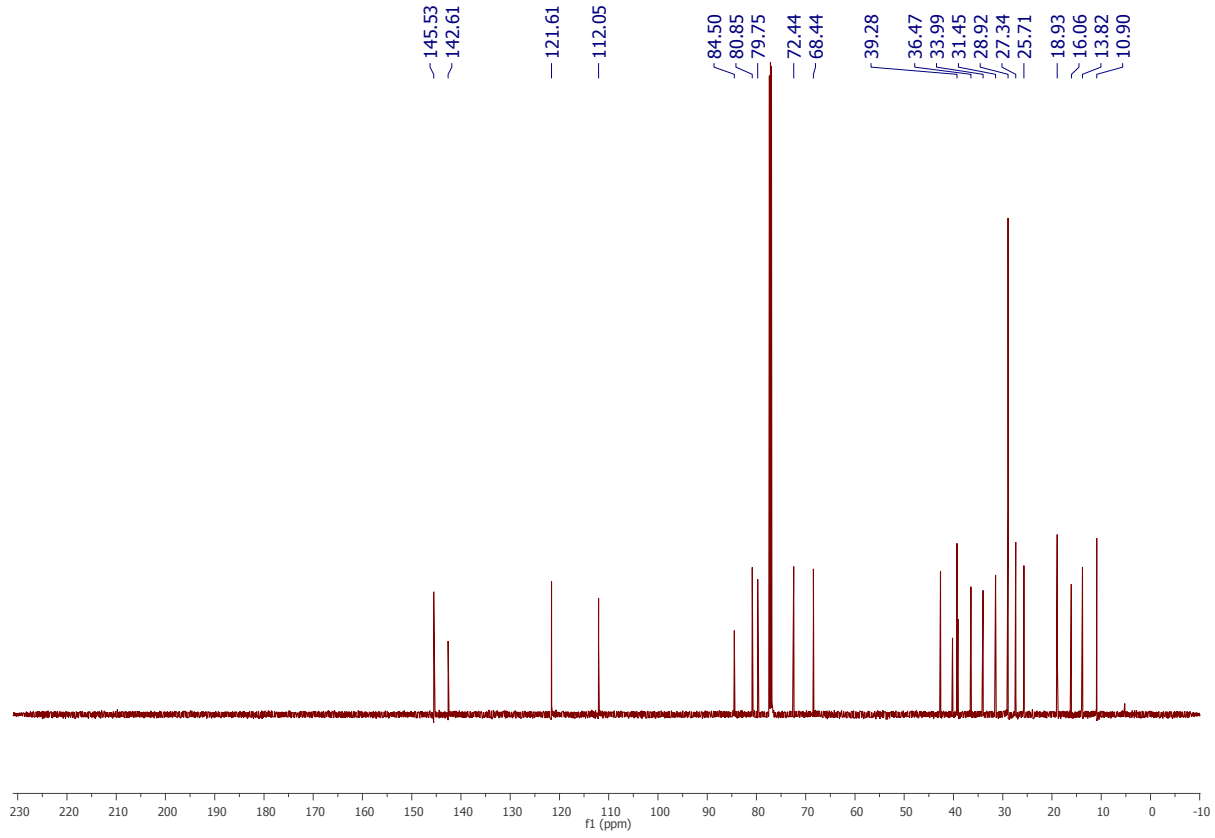


^{1}H NMR ($CDCl_3$, 600 MHz):

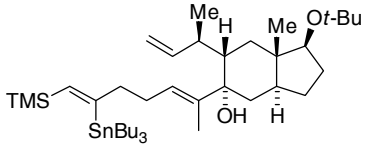


337
$C_{25}H_{40}O_2$
M = 372.58 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

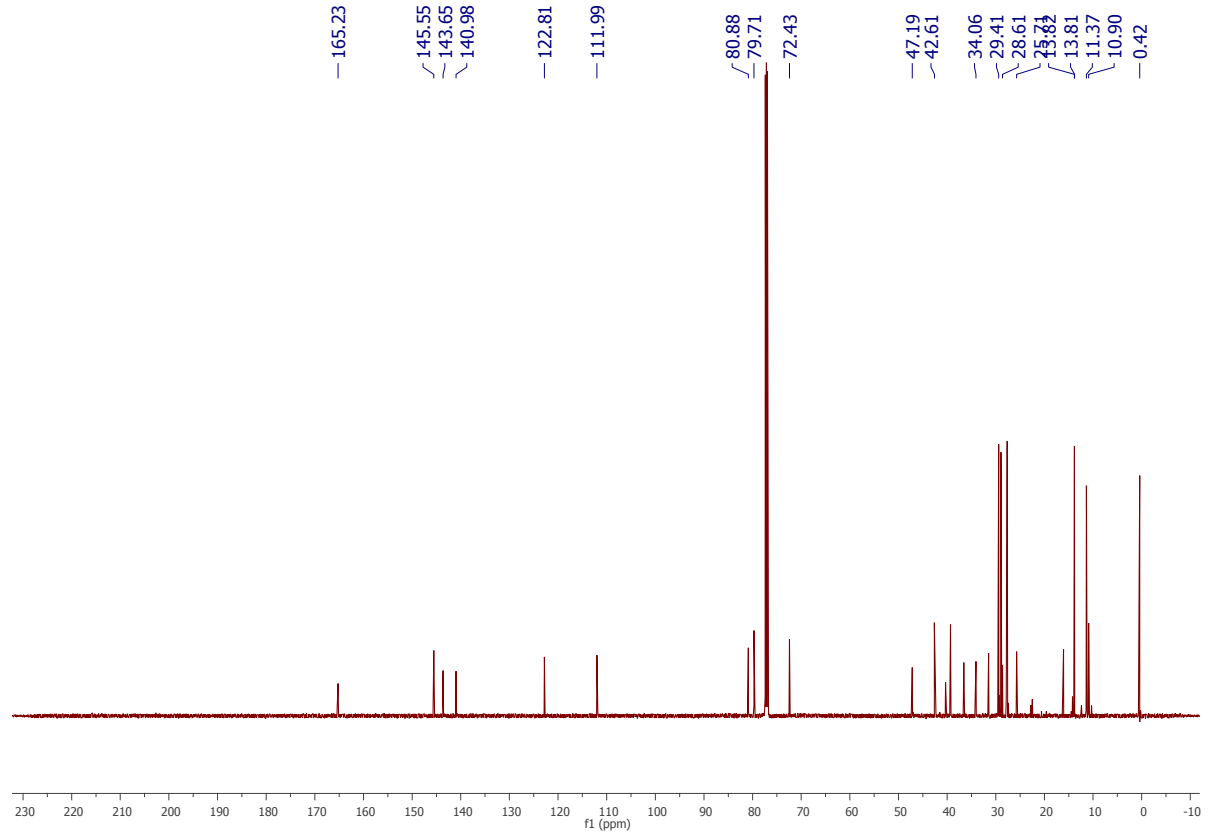


^{1}H NMR ($CDCl_3$, 600 MHz):

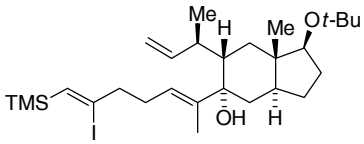


340
$C_{40}H_{76}O_2SiSn$
M = 735.83 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

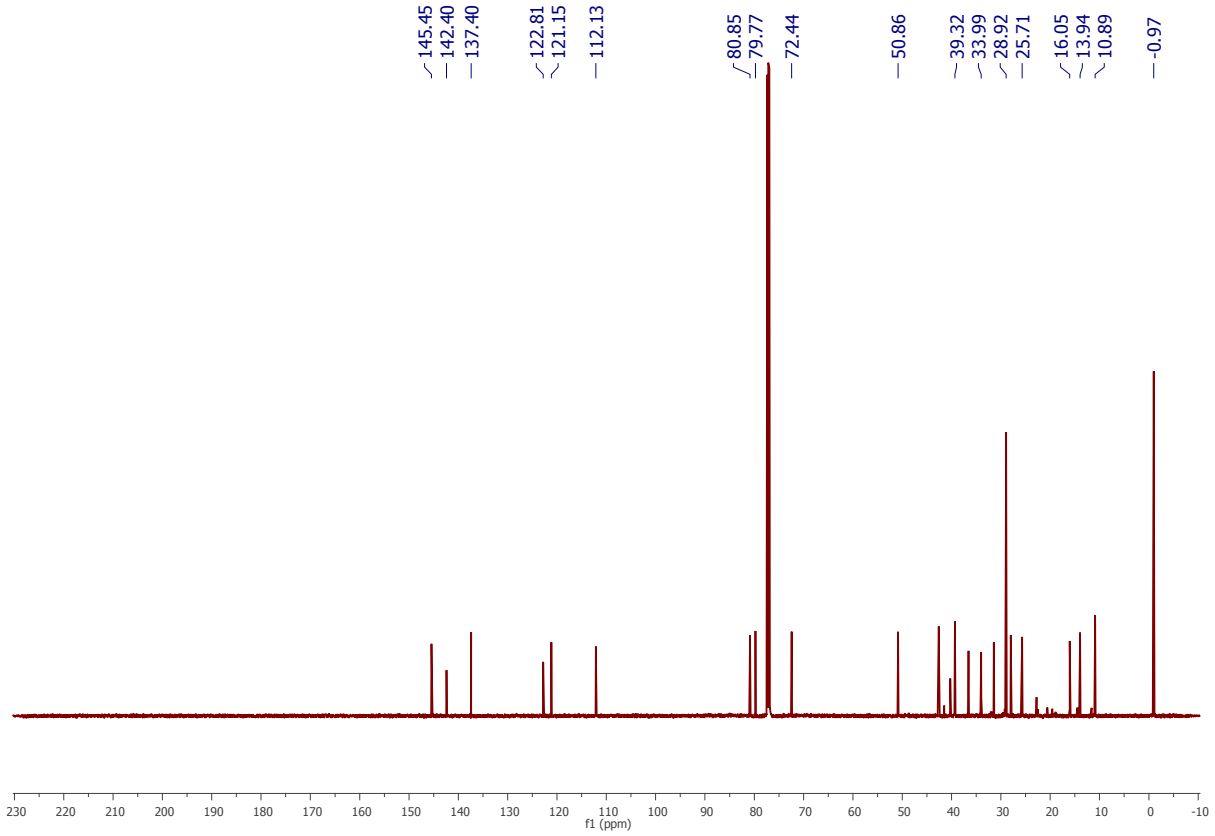


^{1}H NMR ($CDCl_3$, 600 MHz):

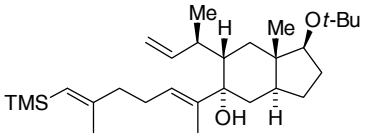


342
$C_{28}H_{49}IO_2Si$
M = 572.68 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

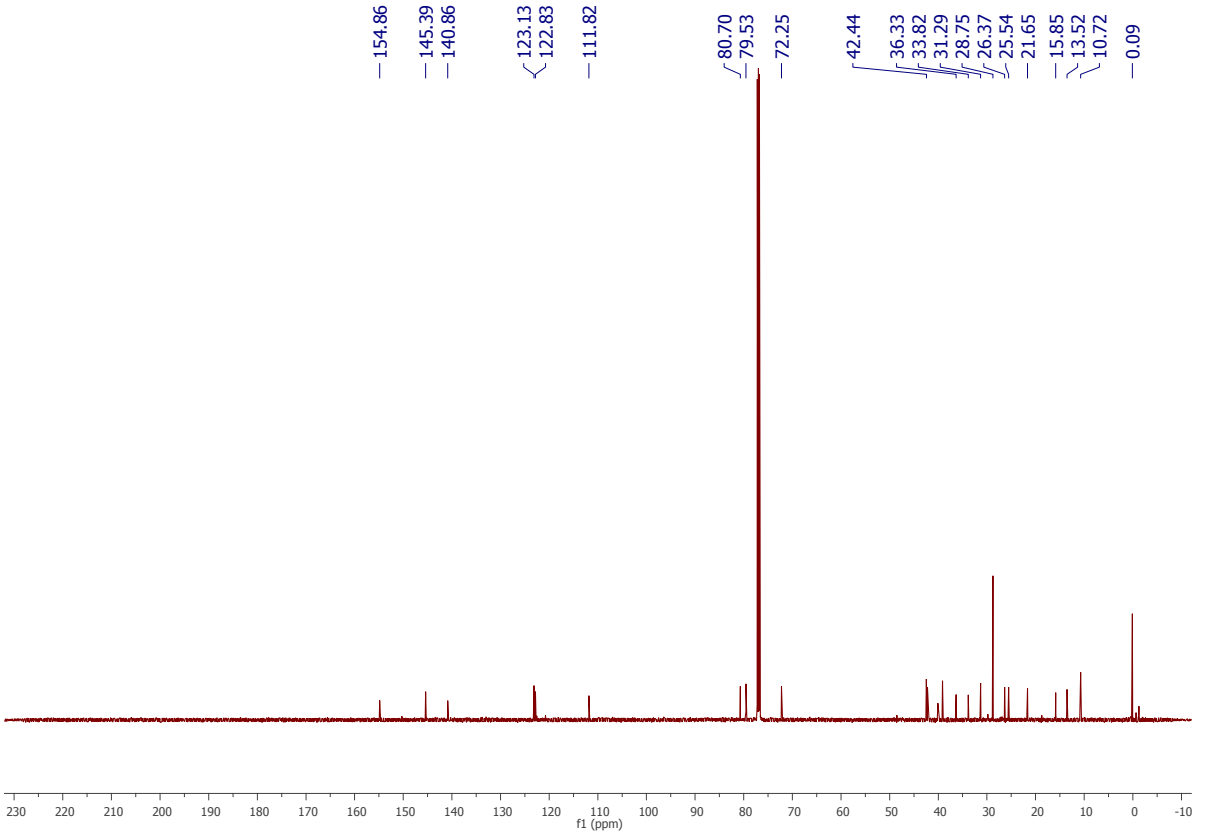


^{1}H NMR ($CDCl_3$, 600 MHz):

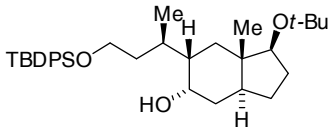


343
$C_{29}H_{52}O_2Si$
M = 460.81 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):



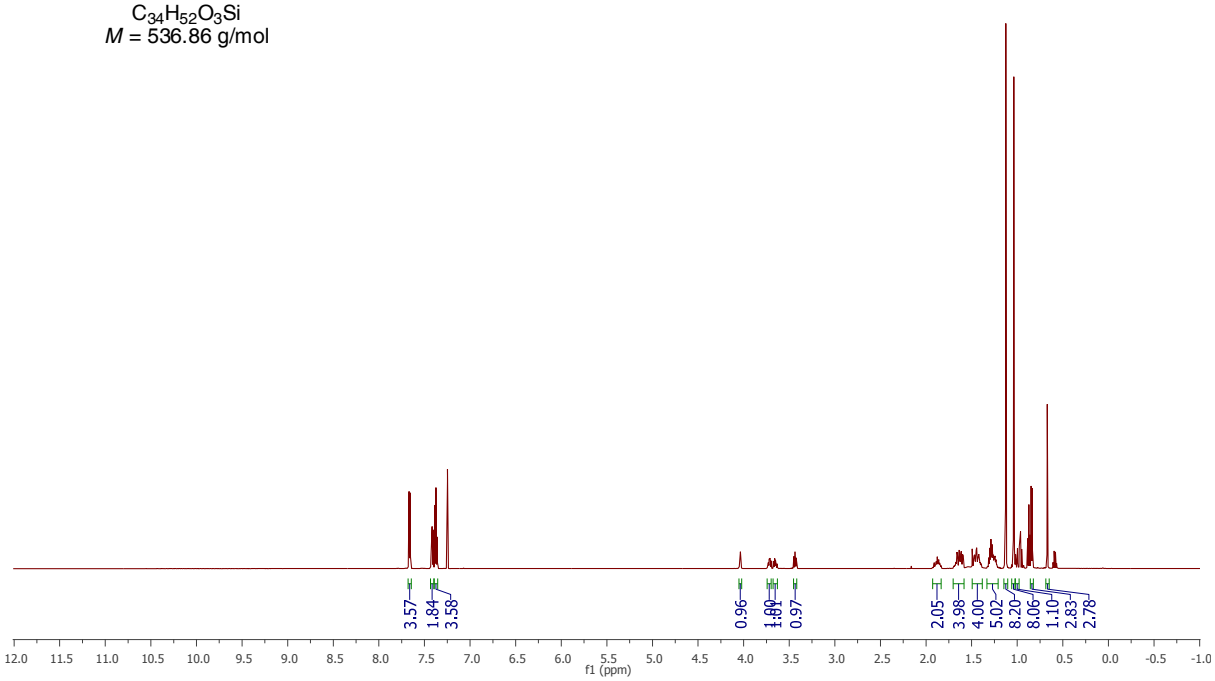
^{1}H NMR ($CDCl_3$, 600 MHz):



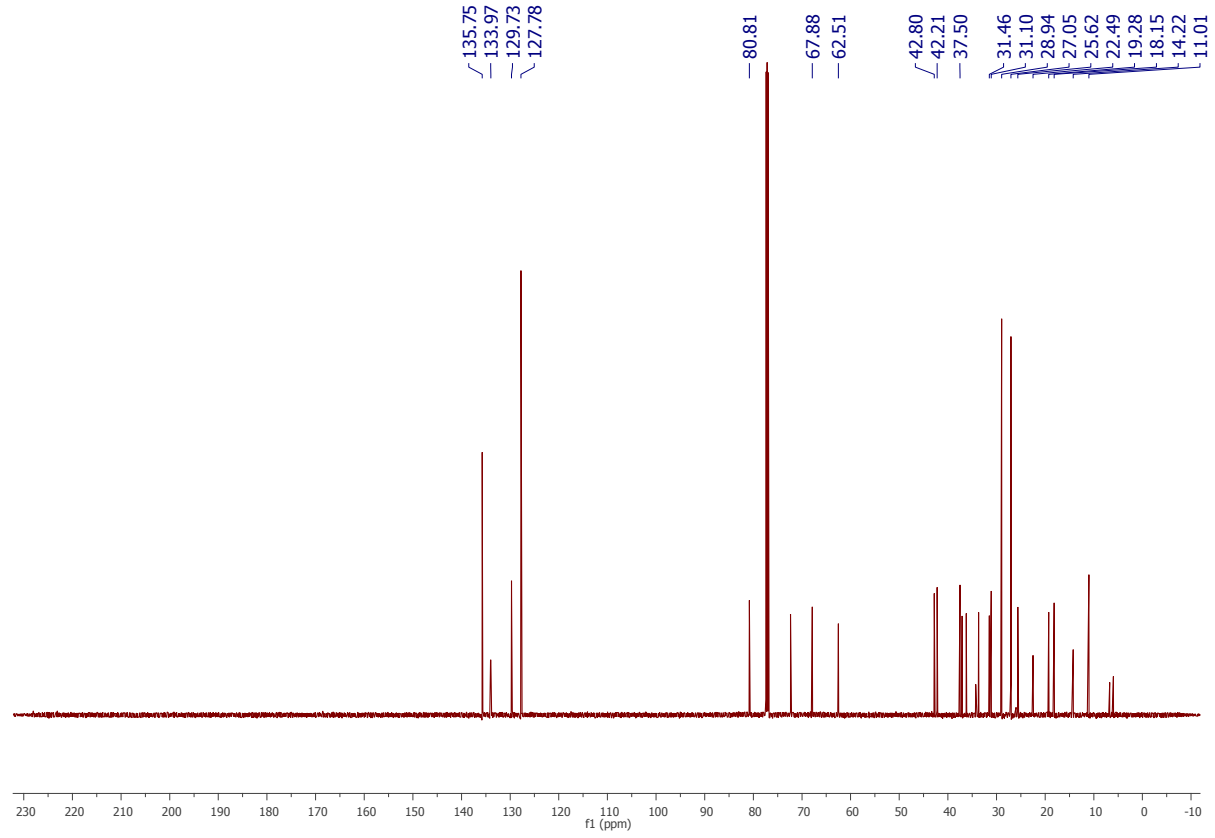
346

$C_{34}H_{52}O_3Si$

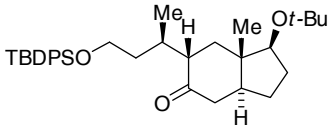
M = 536.86 g/mol



^{13}C NMR ($CDCl_3$, 150 MHz):



^{1}H NMR ($CDCl_3$, 600 MHz):

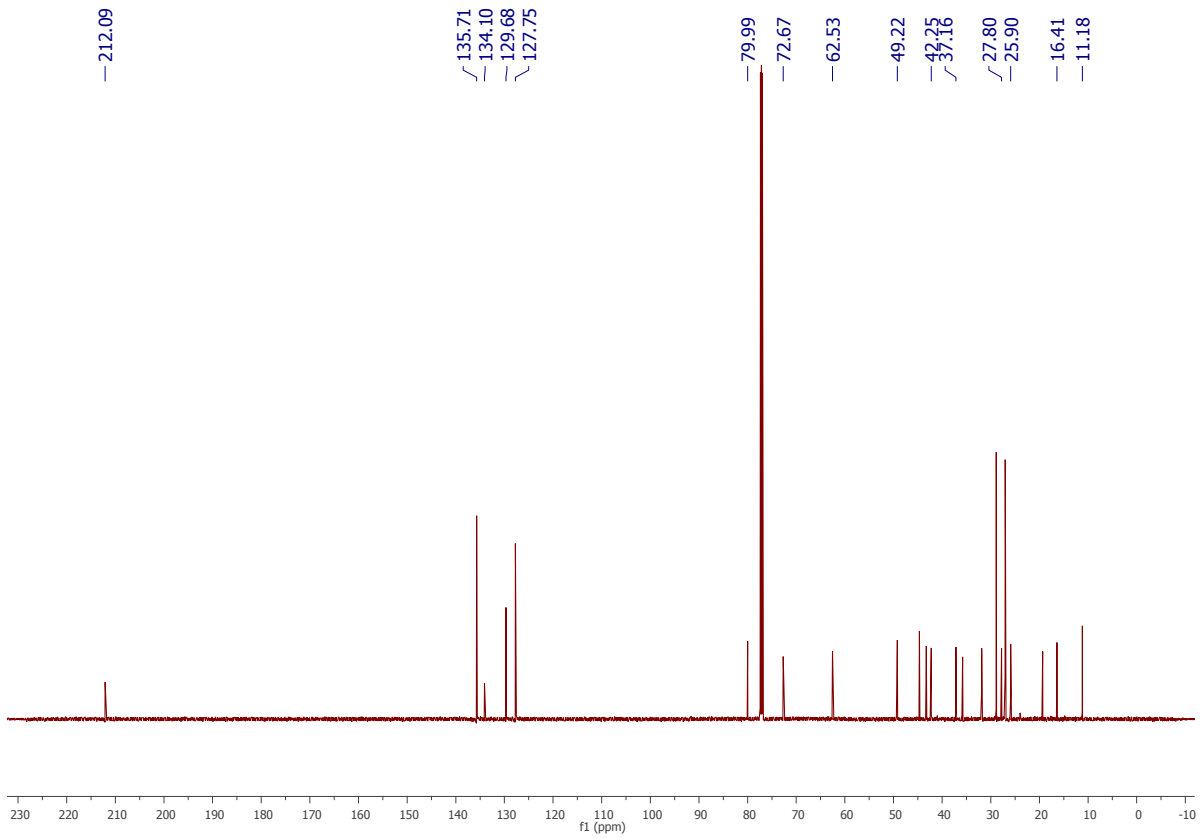


347

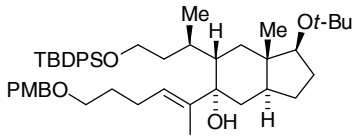
$C_{34}H_{50}O_3Si$

M = 534.85 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):



^{1}H NMR ($CDCl_3$, 600 MHz):

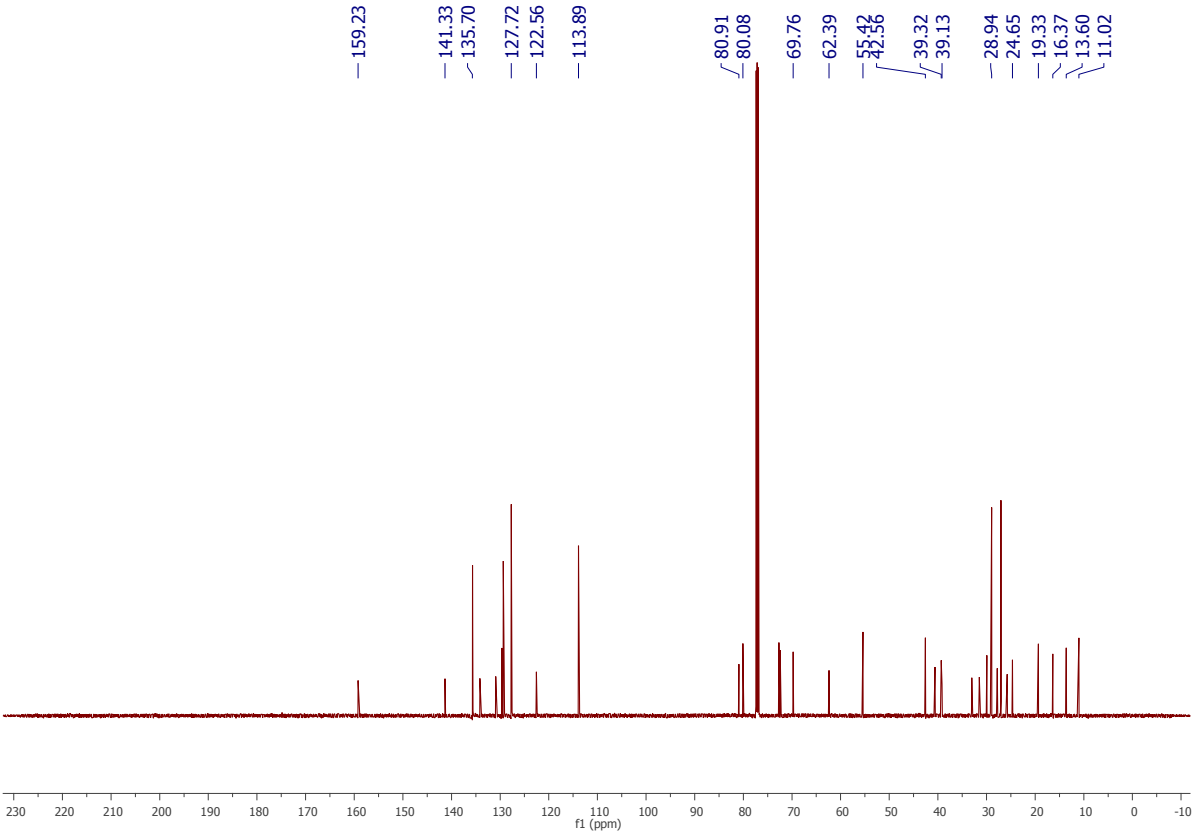


348

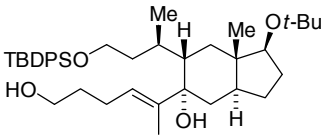
$C_{48}H_{70}O_5Si$

M = 755.15 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

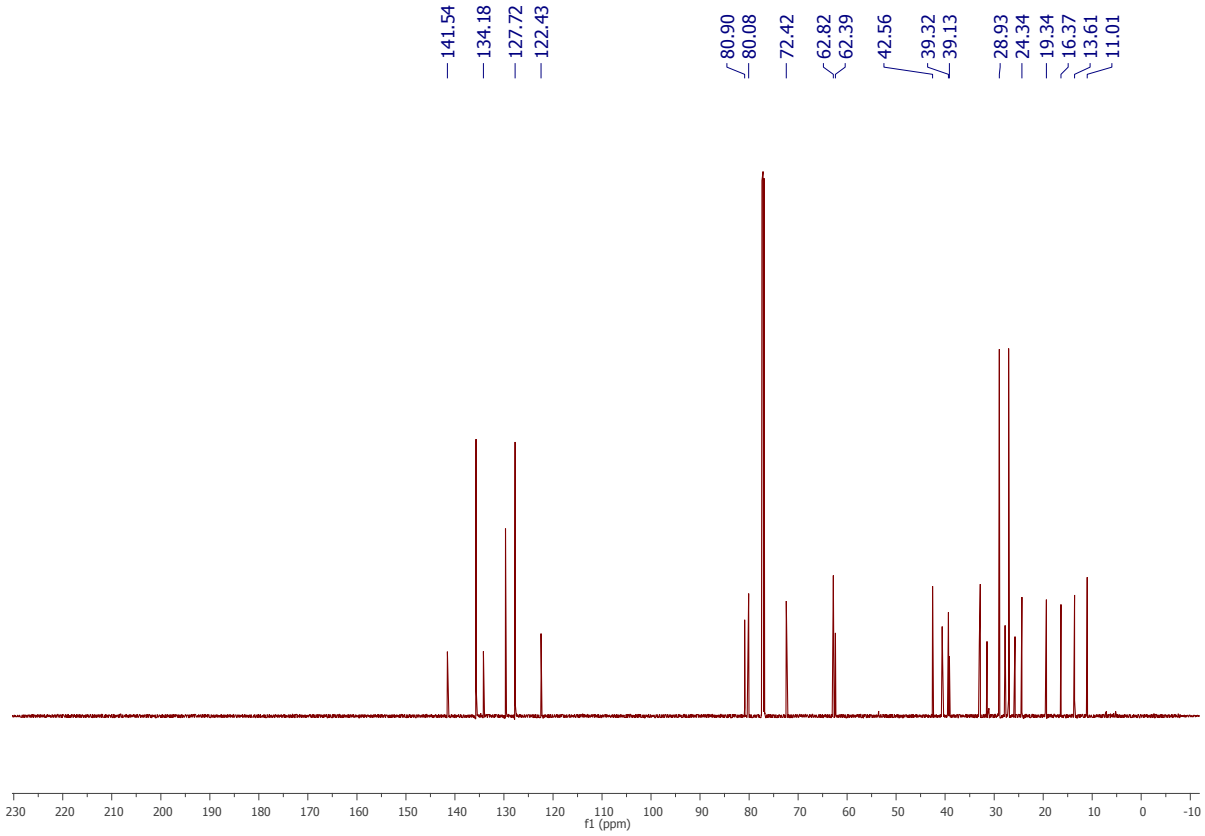


^{1}H NMR ($CDCl_3$, 600 MHz):

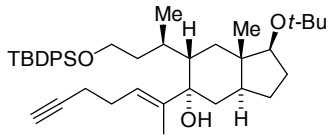


349
$C_{40}H_{62}O_4Si$
M = 635.00 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

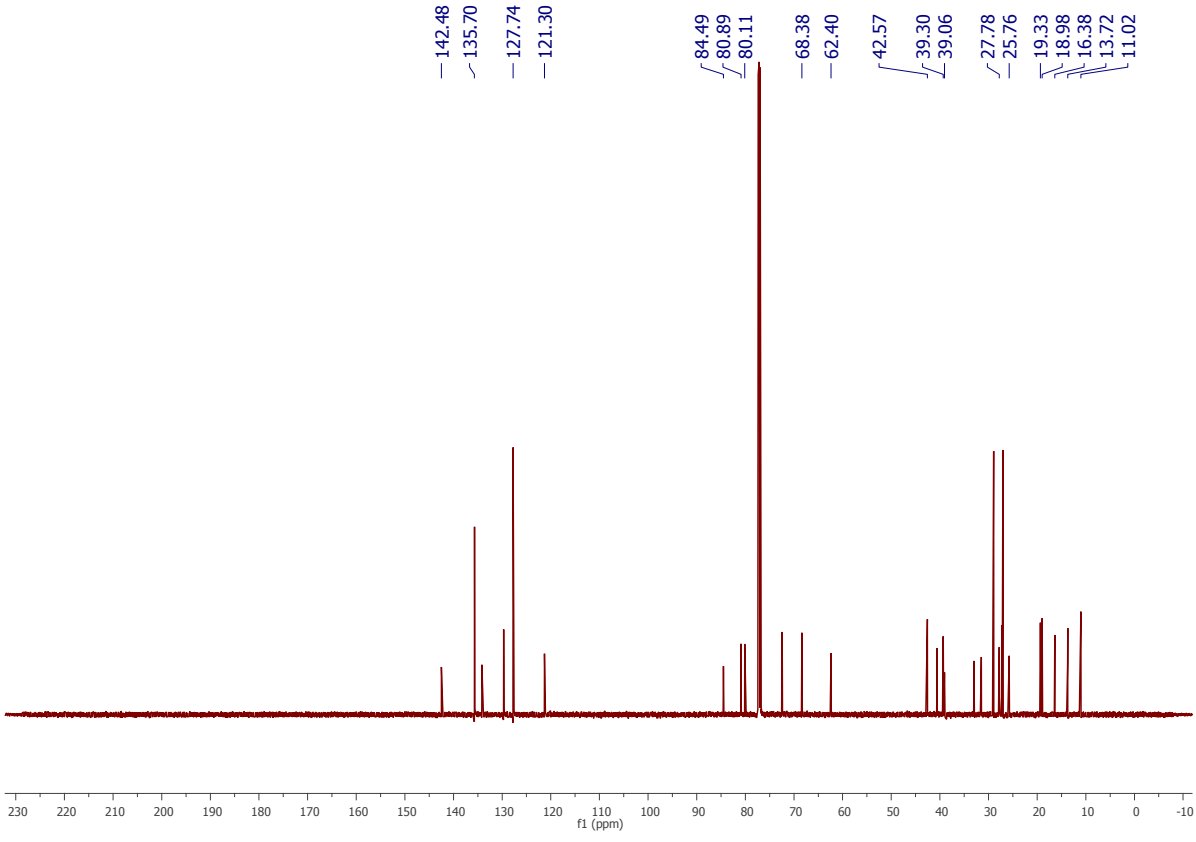


^{1}H NMR ($CDCl_3$, 600 MHz):

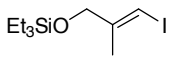


350
$C_{41}H_{60}O_3Si$
M = 629.00 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

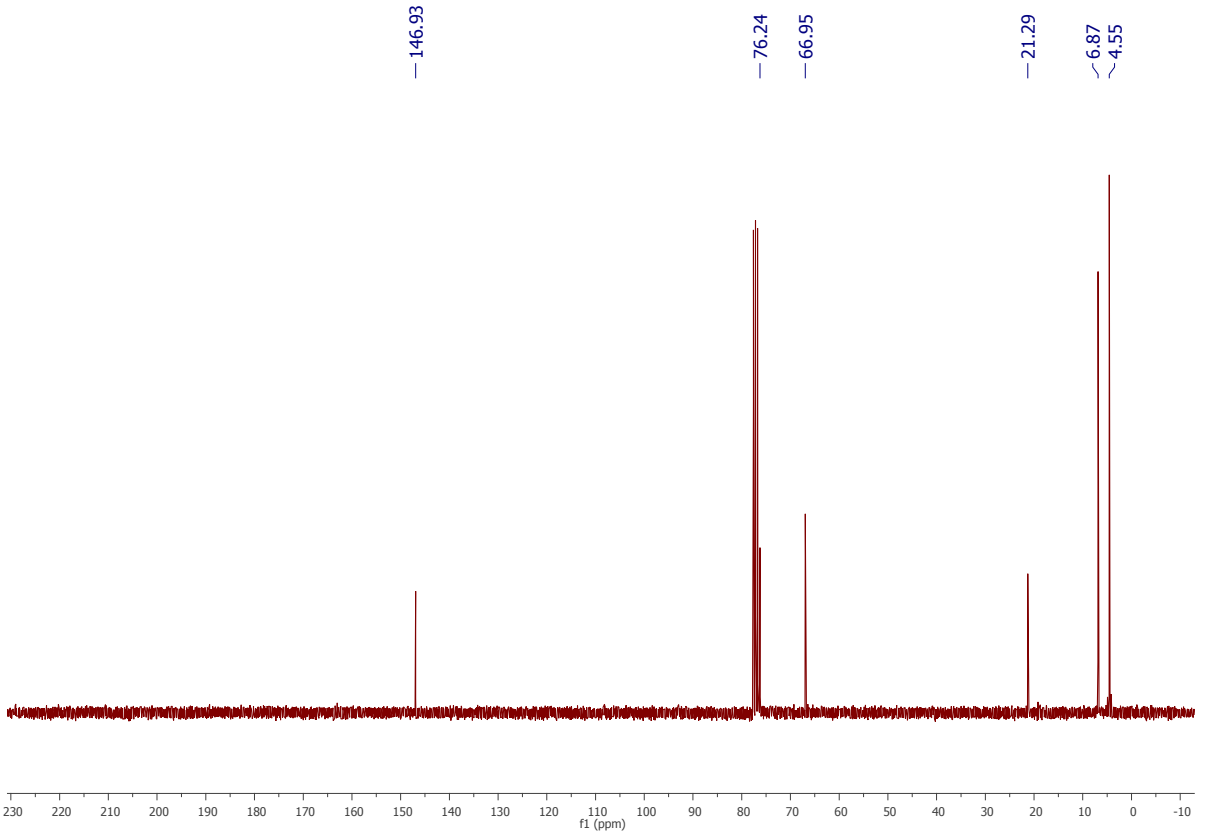


^{1}H NMR ($CDCl_3$, 300 MHz):

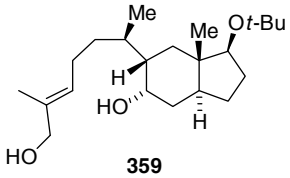


357
$C_{10}H_{21}IOSi$
M = 312.26 g/mol

^{13}C NMR ($CDCl_3$, 75 MHz):

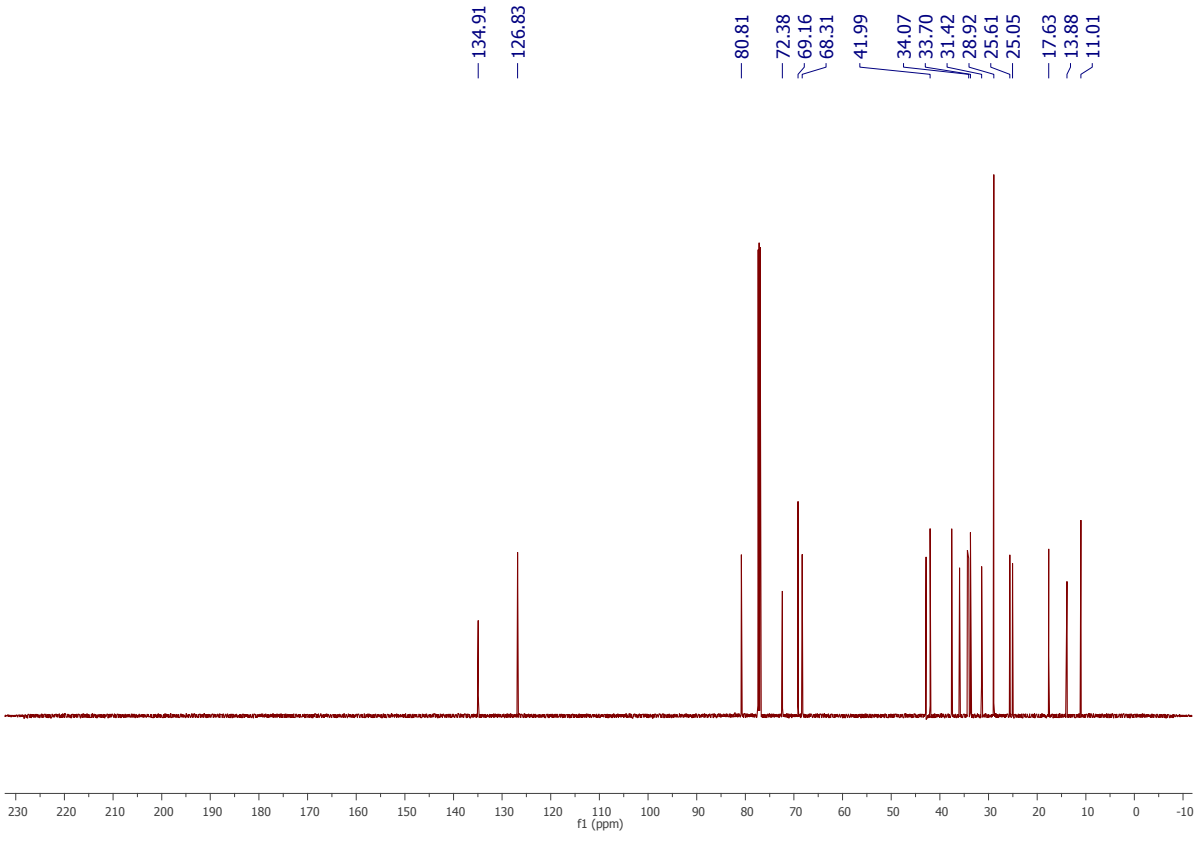


^{1}H NMR ($CDCl_3$, 600 MHz):

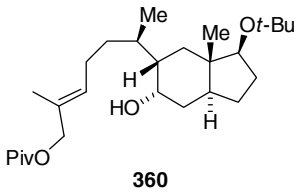


359
$C_{22}H_{40}O_3$
M = 352.55 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

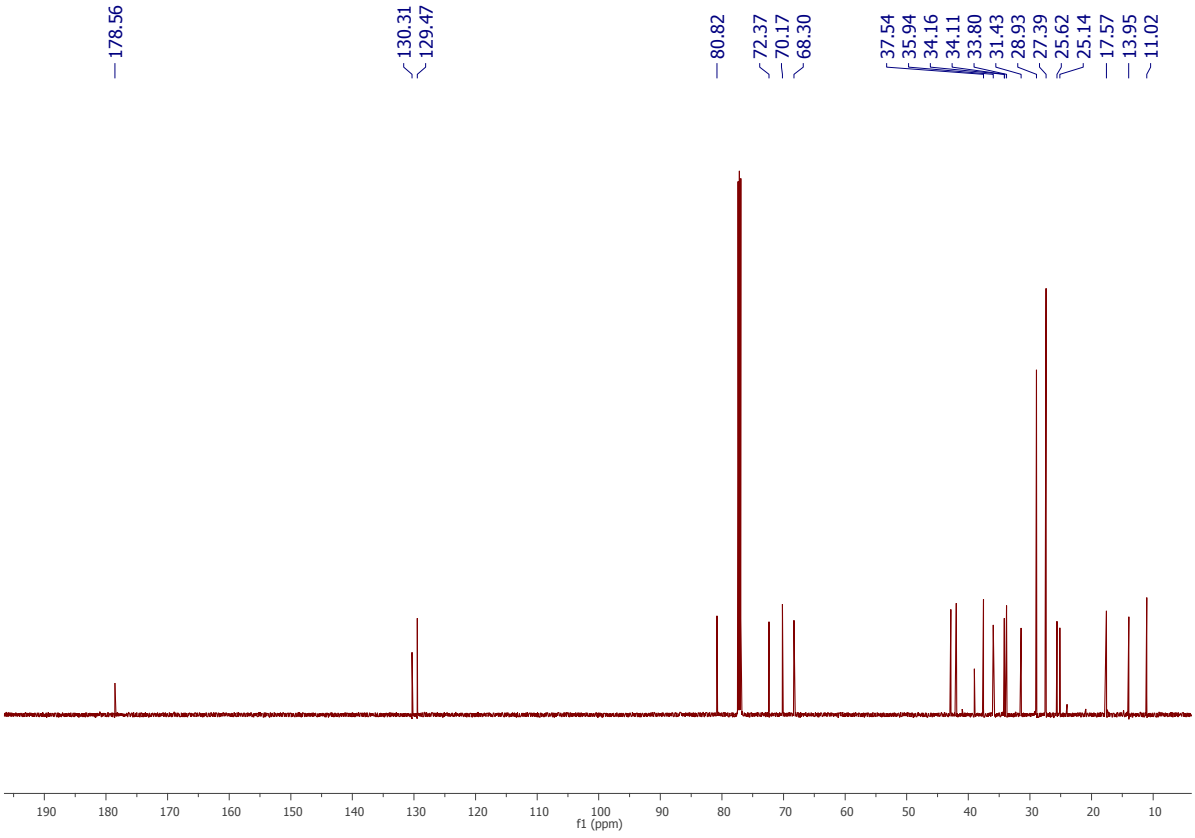


^{1}H NMR ($CDCl_3$, 600 MHz):

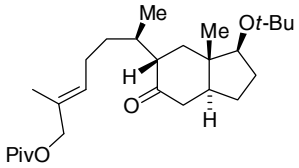


360
$C_{27}H_{48}O_4$
M = 436.67 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

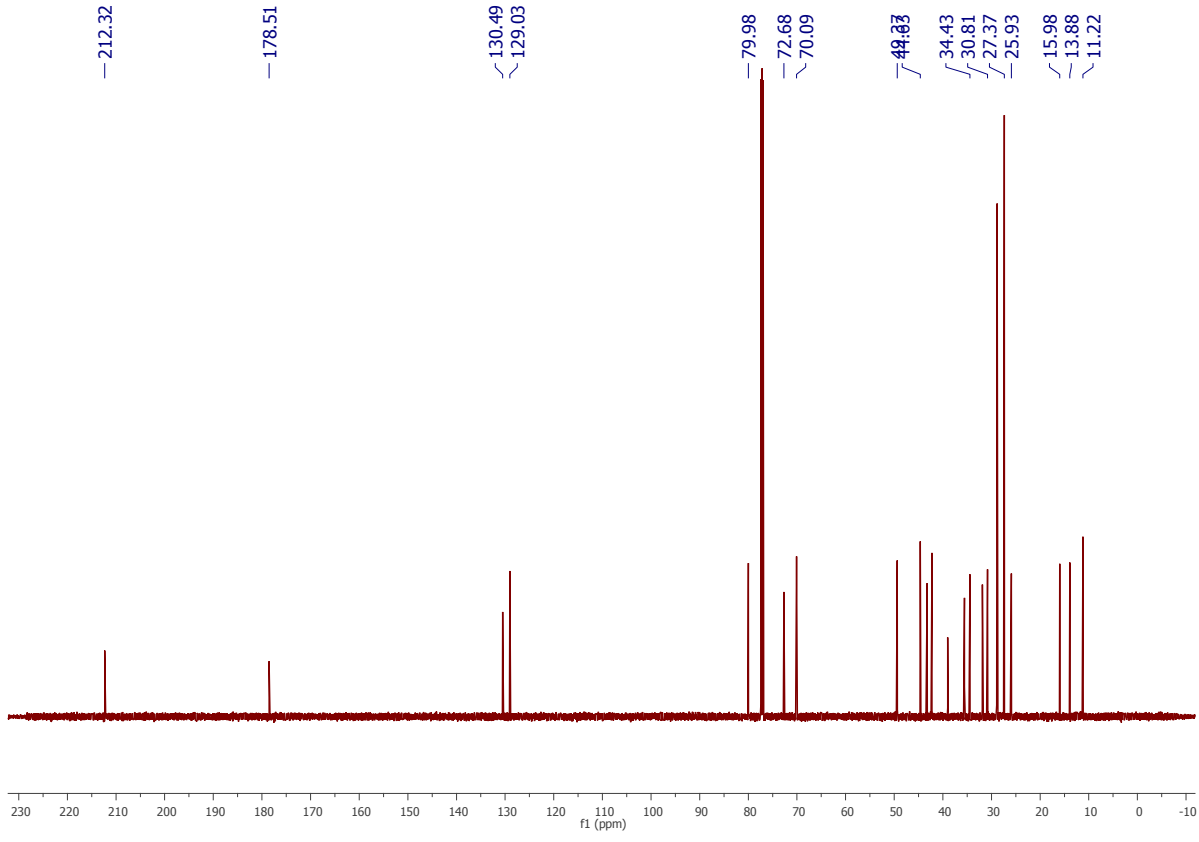


^{1}H NMR ($CDCl_3$, 600 MHz):

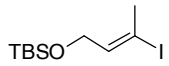


361
$C_{27}H_{46}O_4$
M = 434.65 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

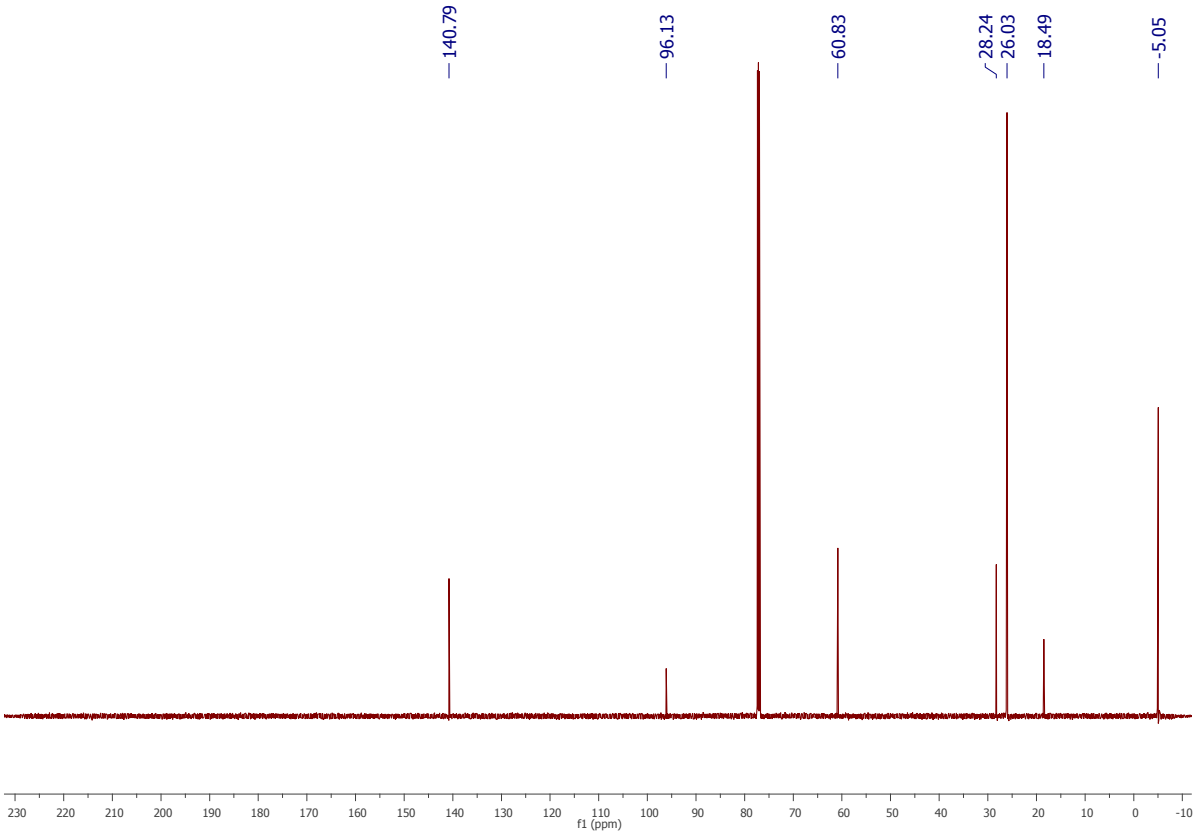


^{1}H NMR ($CDCl_3$, 600 MHz):

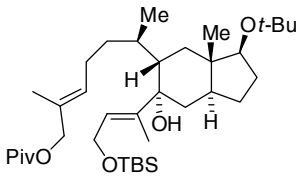


364
$C_{10}H_{21}IOSi$
M = 312.26 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

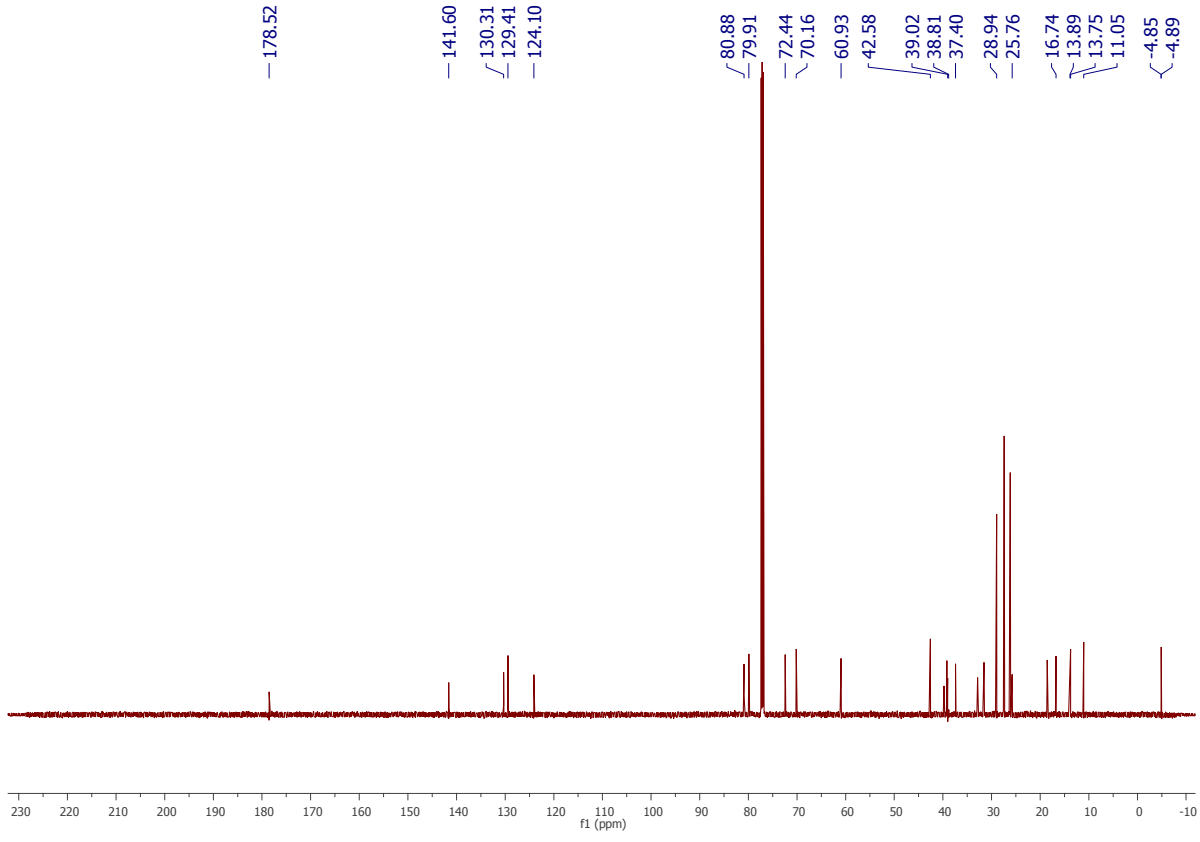


^{1}H NMR ($CDCl_3$, 600 MHz):

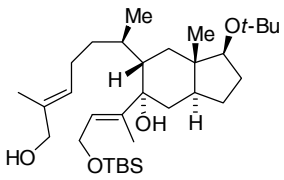


365
$C_{37}H_{68}O_5Si$
M = 621.02 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):



^{1}H NMR ($CDCl_3$, 600 MHz):

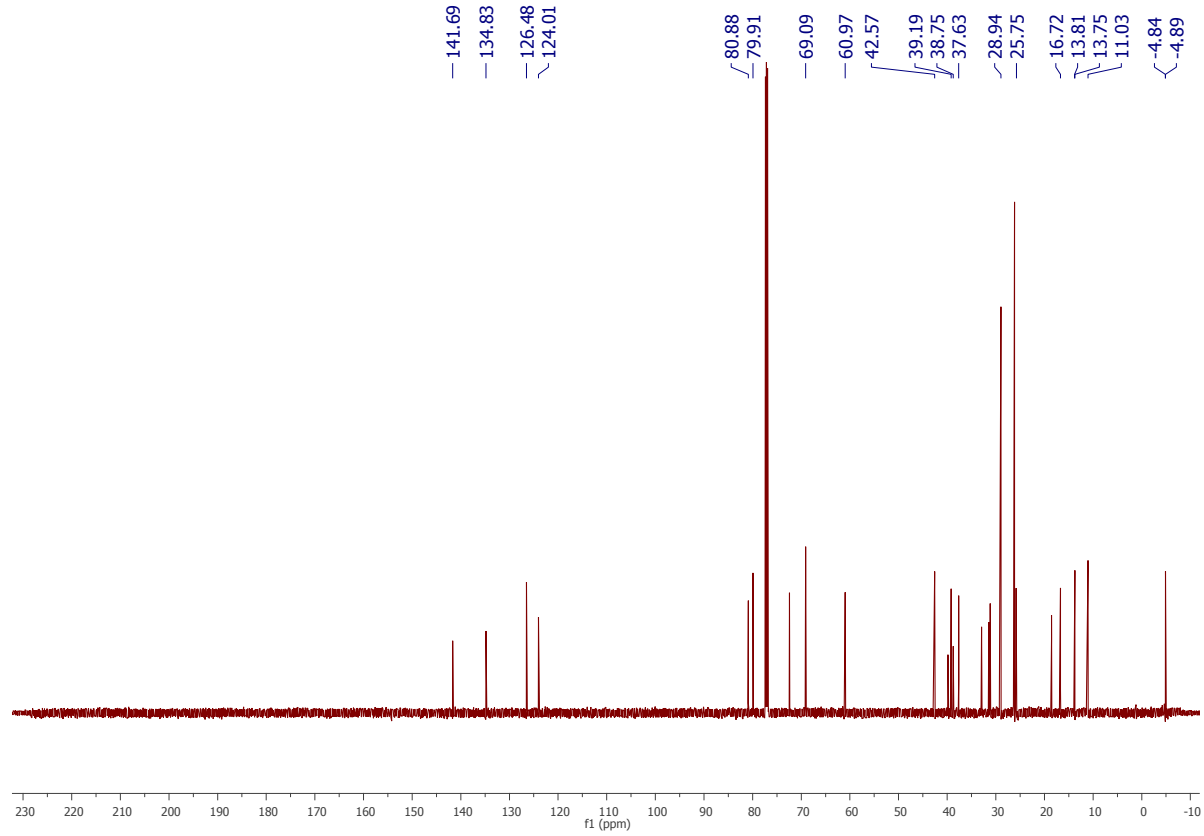


366

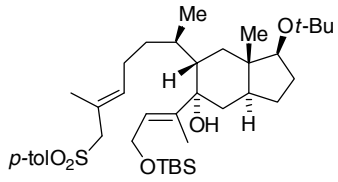
$C_{32}H_{60}O_4Si$

M = 536.90 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

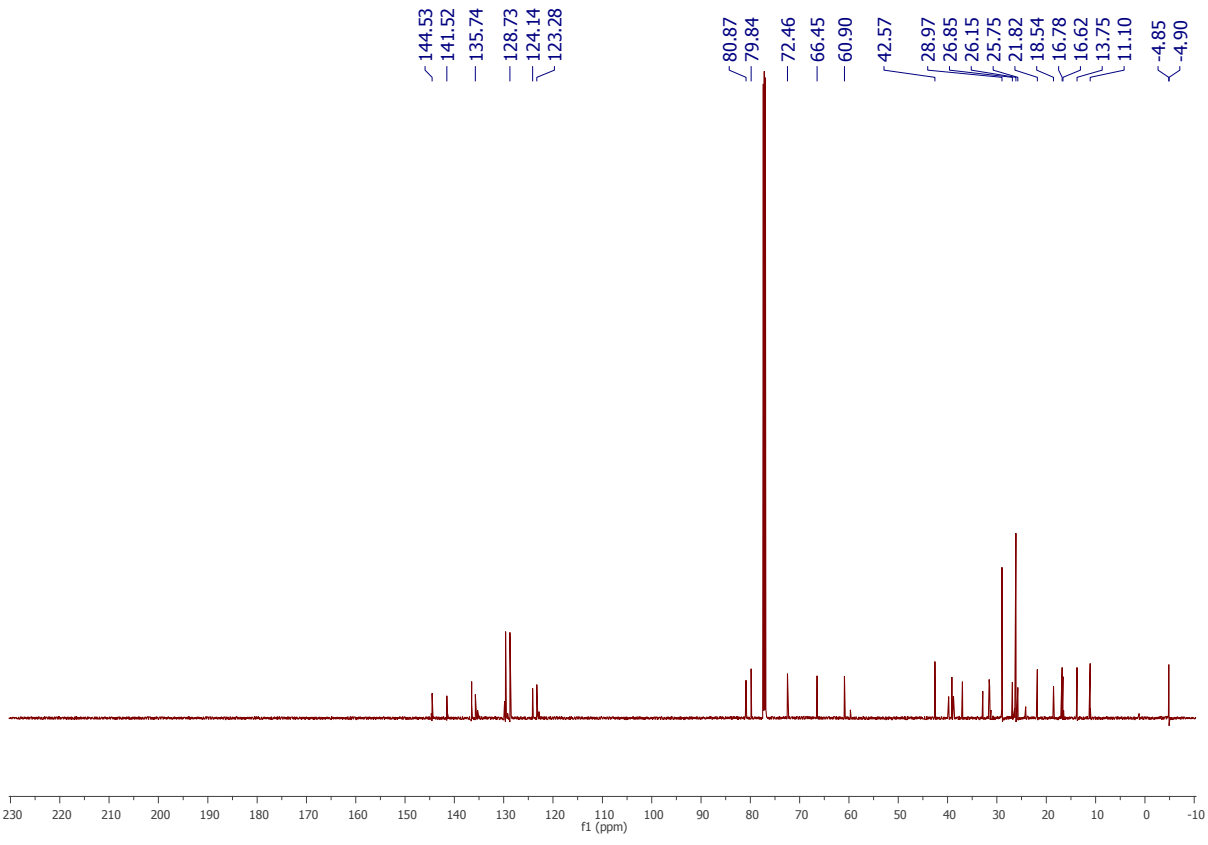


^{1}H NMR ($CDCl_3$, 600 MHz):

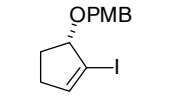


367
$C_{39}H_{66}O_5SSi$
M = 675.09 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

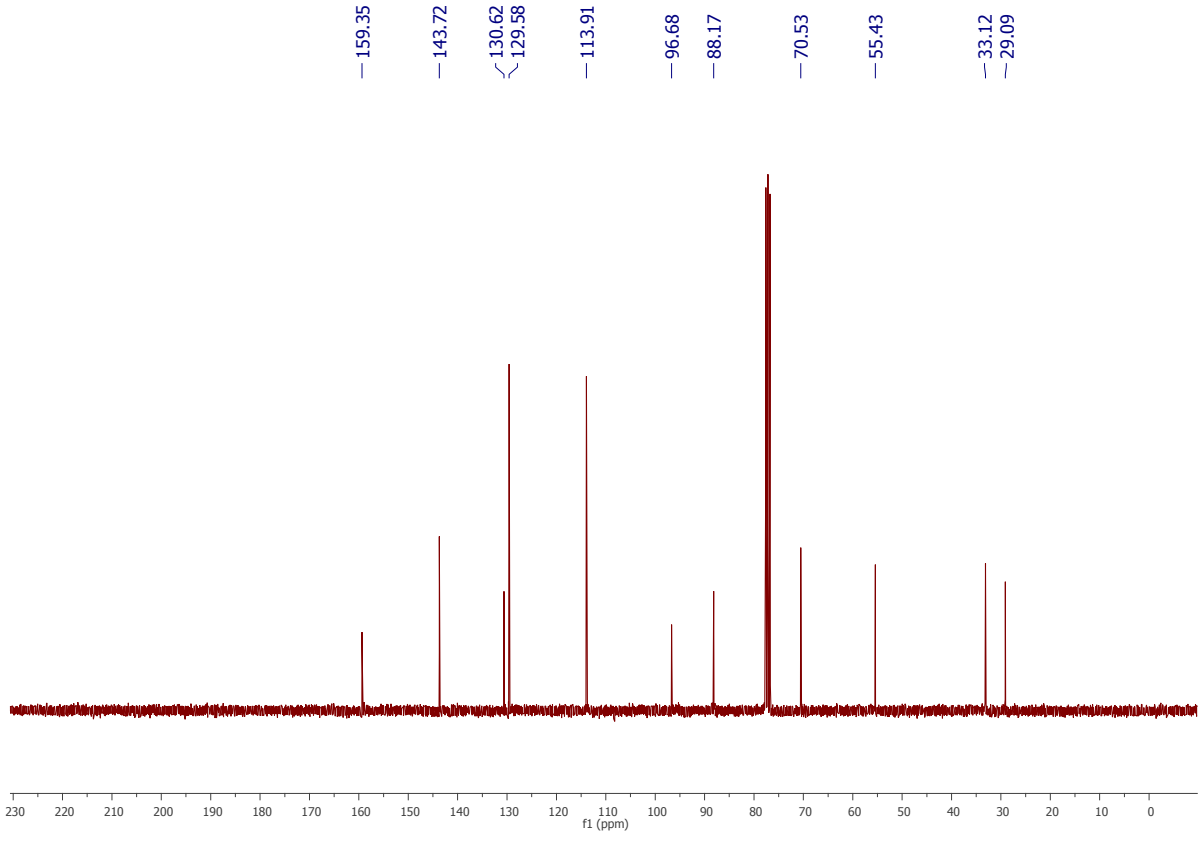


^{1}H NMR ($CDCl_3$, 300 MHz):

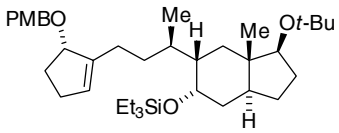


378
$C_{13}H_{15}IO_2$
M = 330.16 g/mol

^{13}C NMR ($CDCl_3$, 75 MHz):

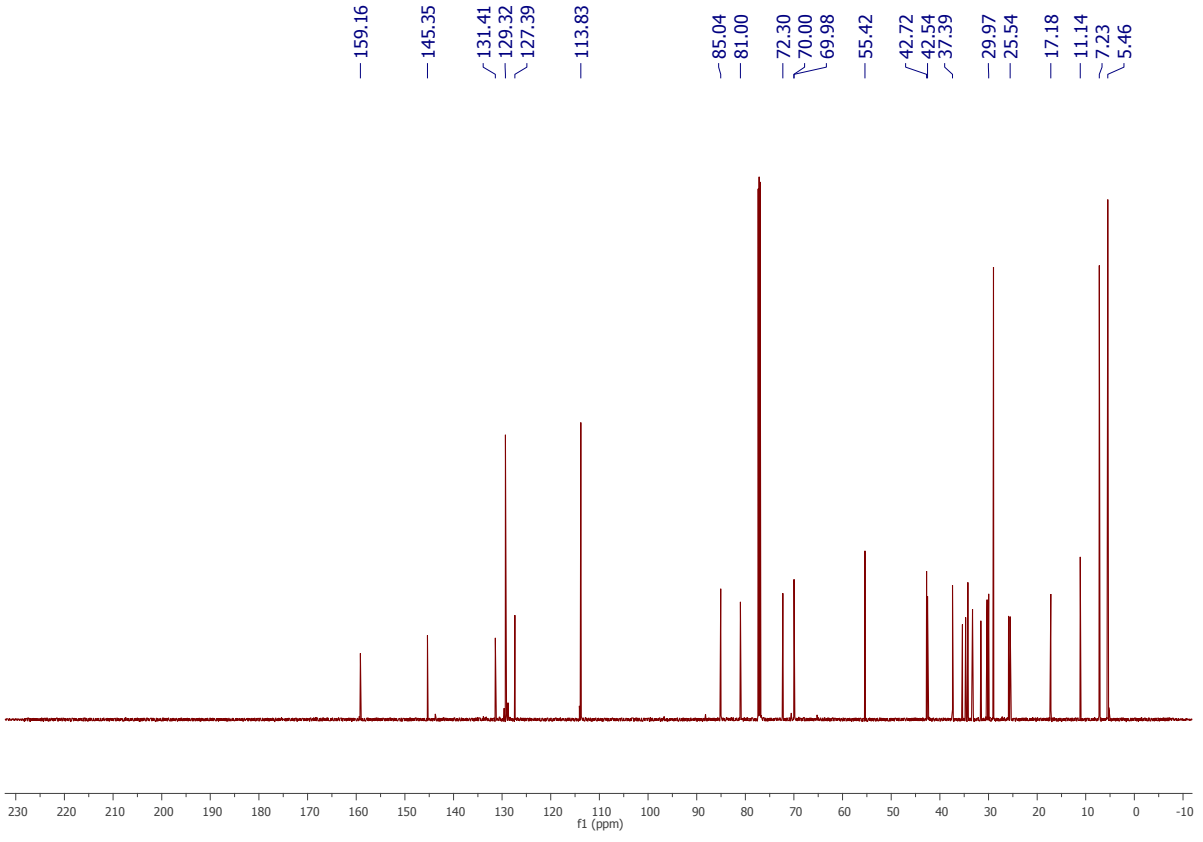


^{1}H NMR ($CDCl_3$, 600 MHz):

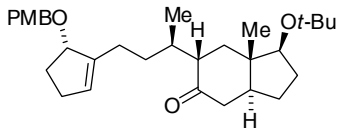


379
$C_{37}H_{62}O_4Si$
M = 598.97 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

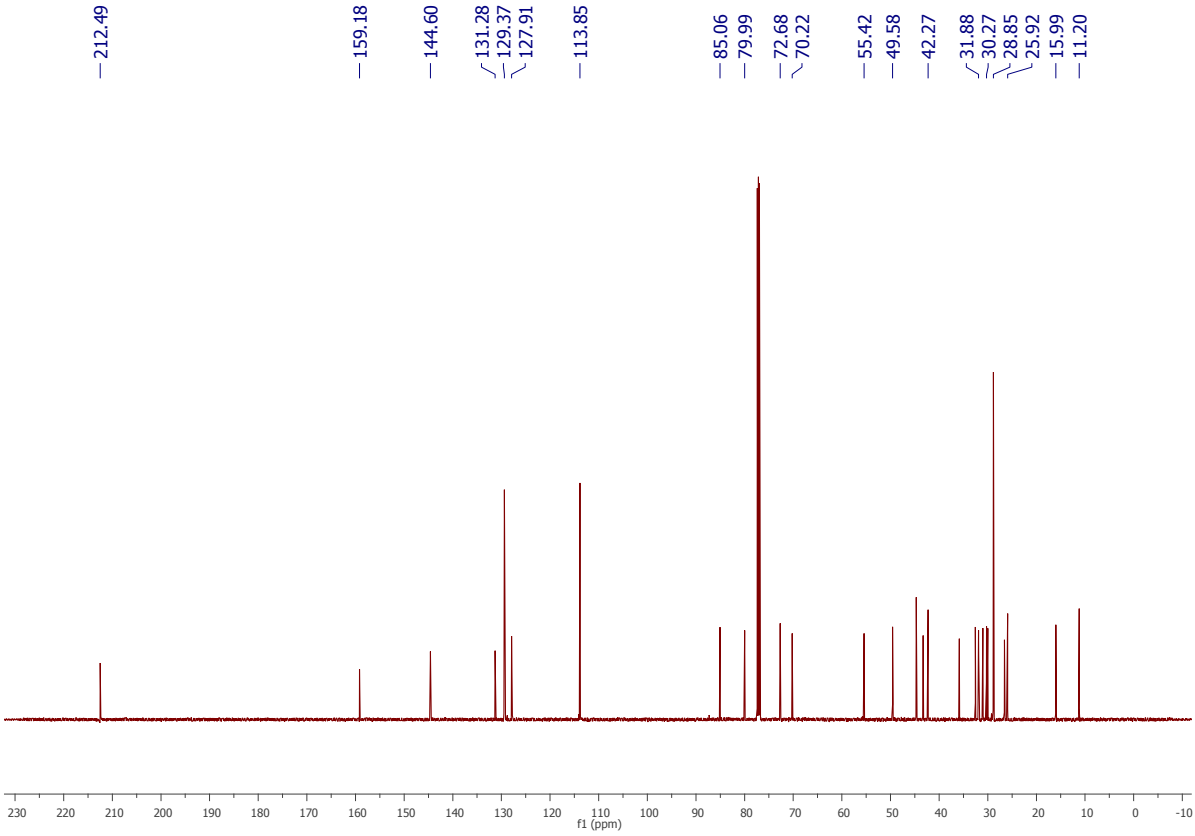


^{1}H NMR ($CDCl_3$, 600 MHz):

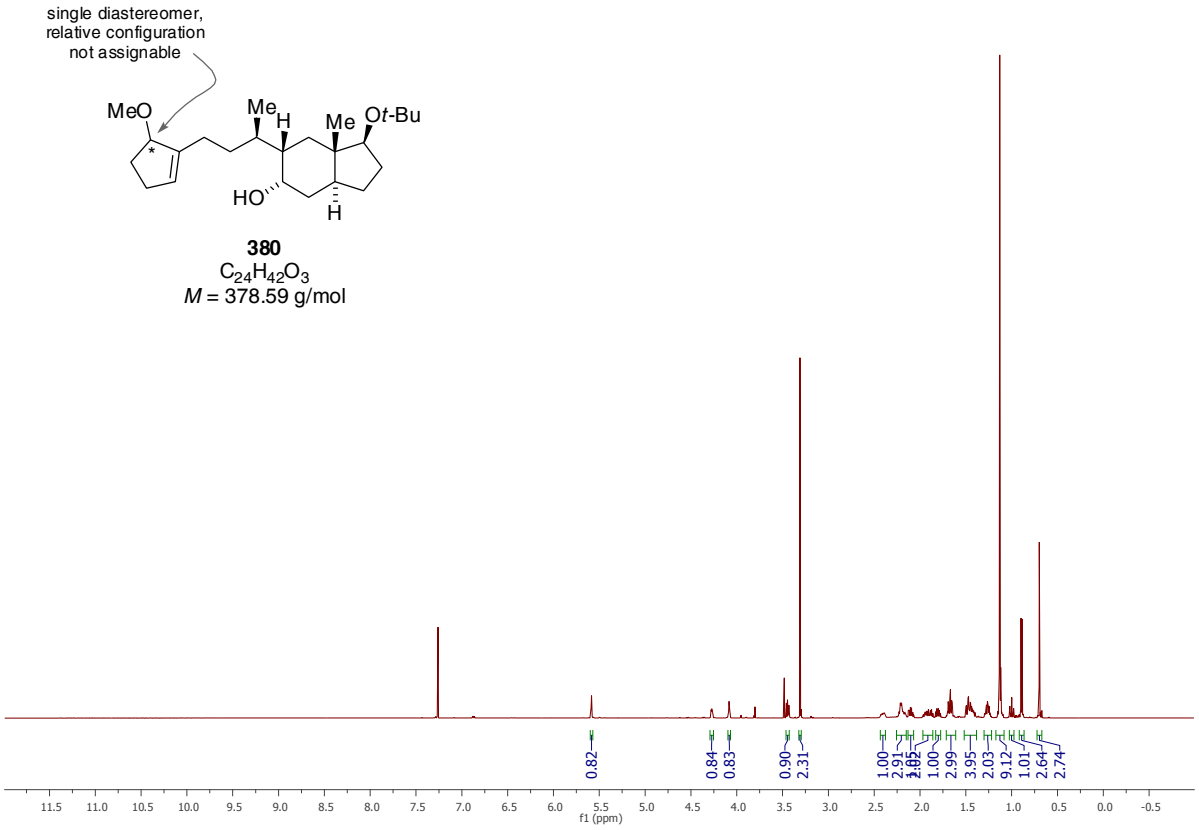


382
$C_{31}H_{46}O_4$
M = 482.69 g/mol

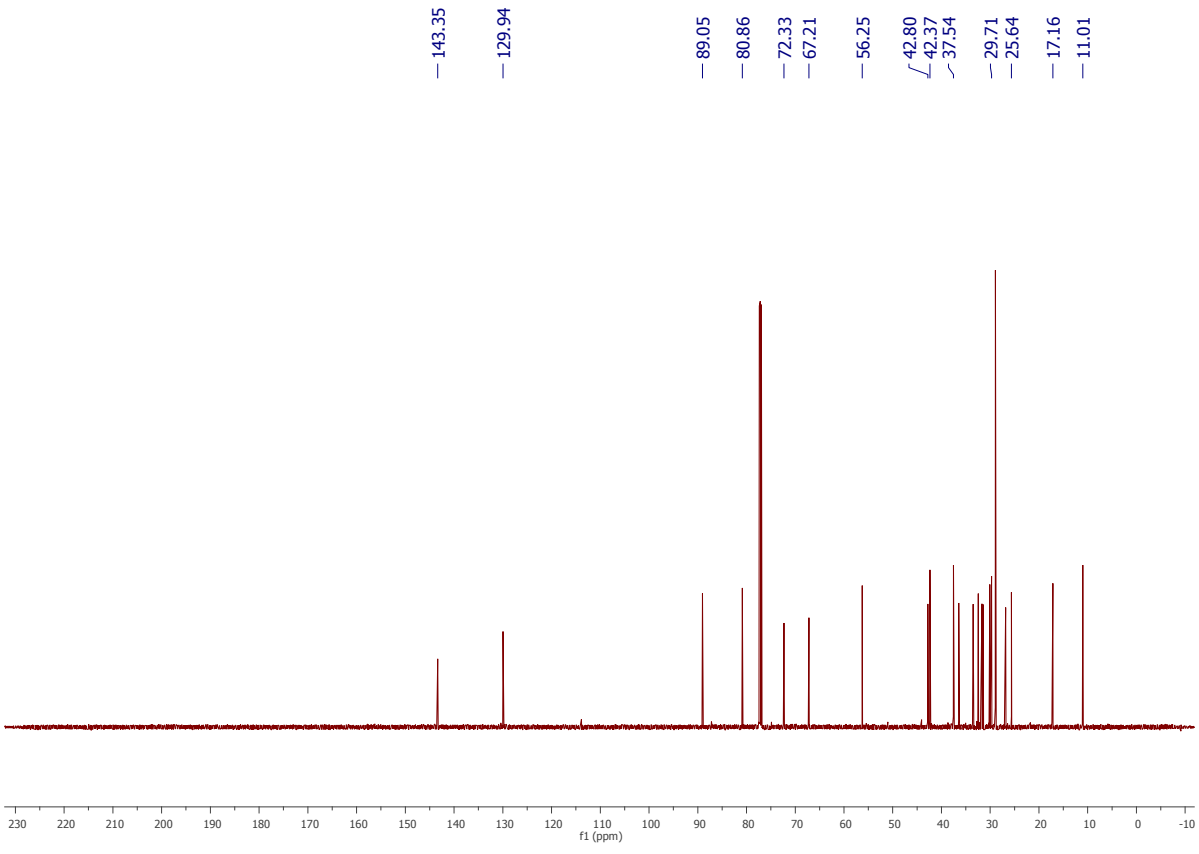
^{13}C NMR ($CDCl_3$, 150 MHz):



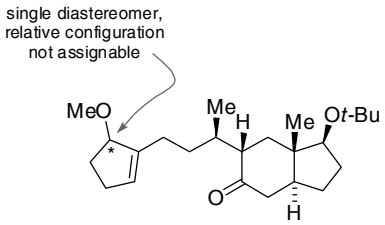
^{1}H NMR ($CDCl_3$, 600 MHz):



^{13}C NMR ($CDCl_3$, 150 MHz):

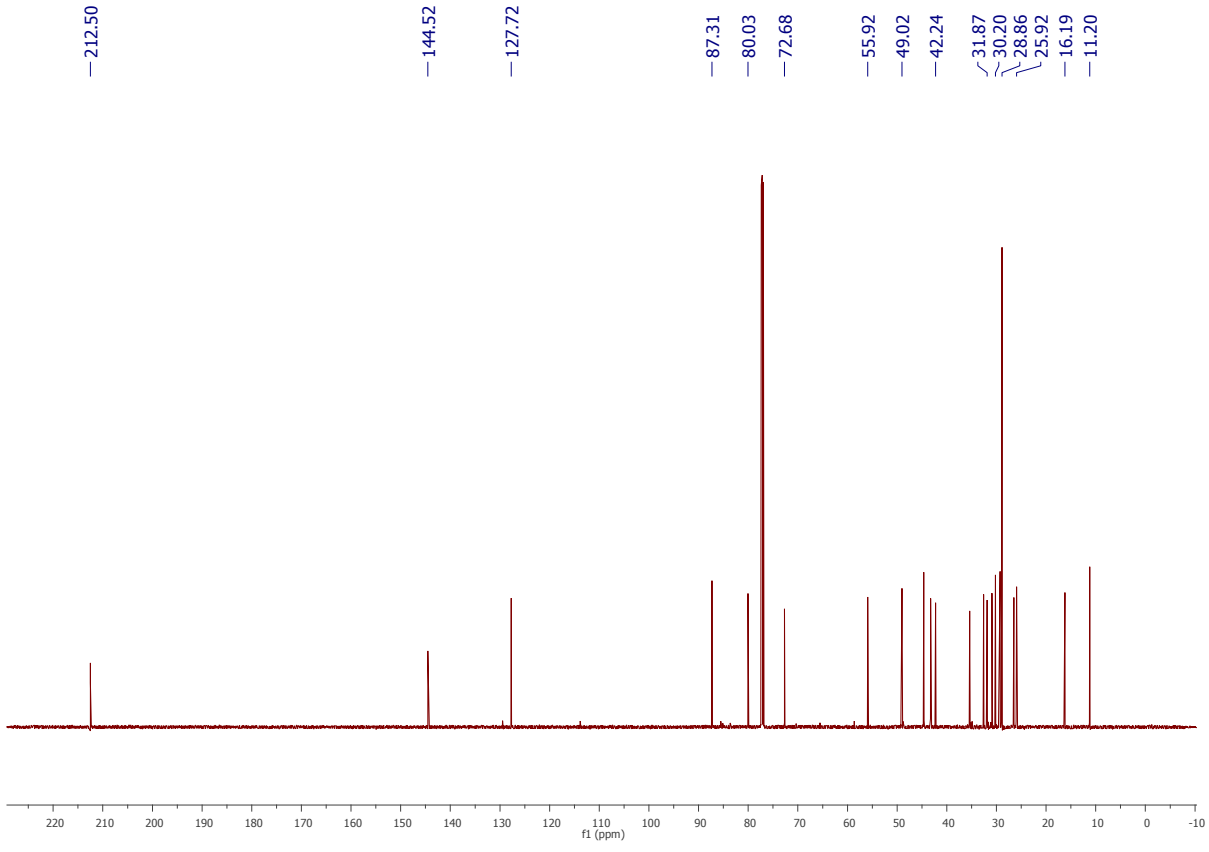


^{1}H NMR ($CDCl_3$, 600 MHz):

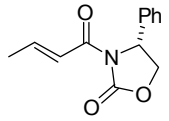


385
$C_{24}H_{40}O_3$
M = 376.57 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

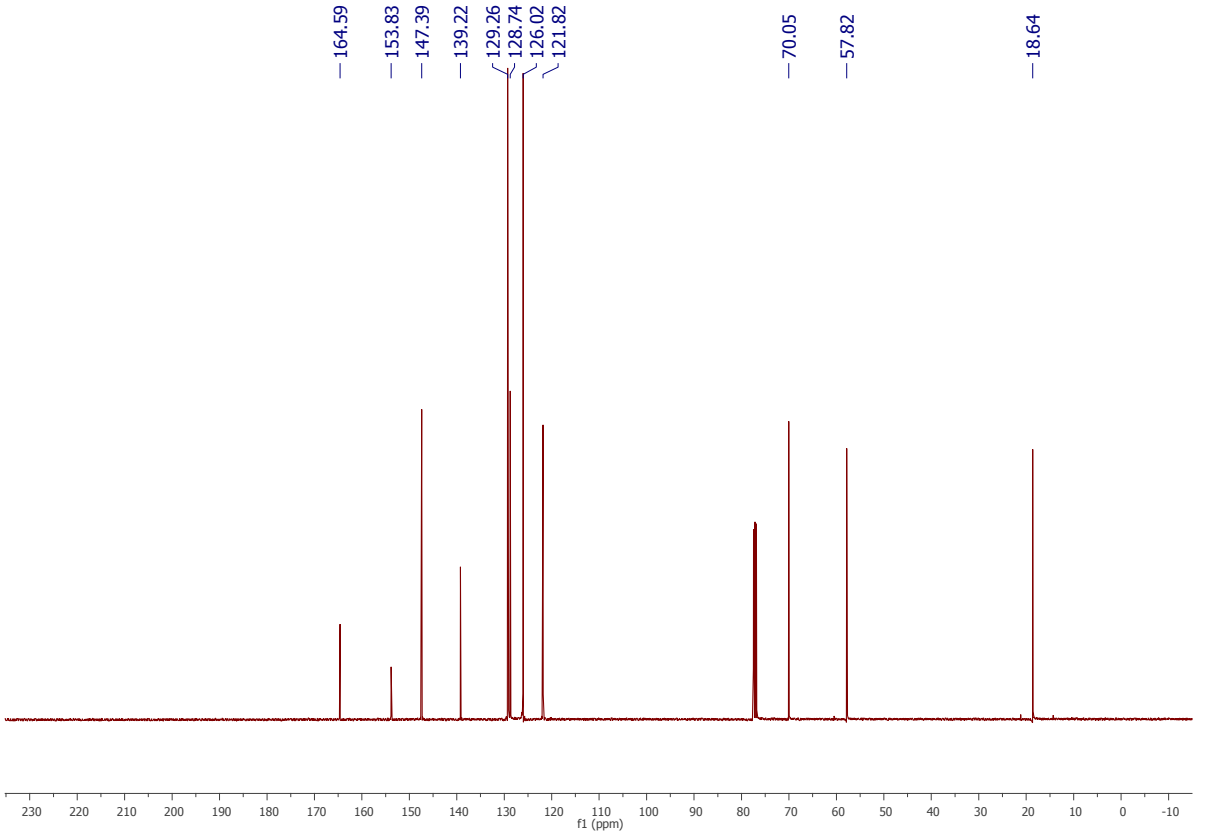


^{1}H NMR ($CDCl_3$, 400 MHz):

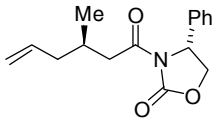


399
$C_{13}H_{13}NO_3$
M = 231.25 g/mol

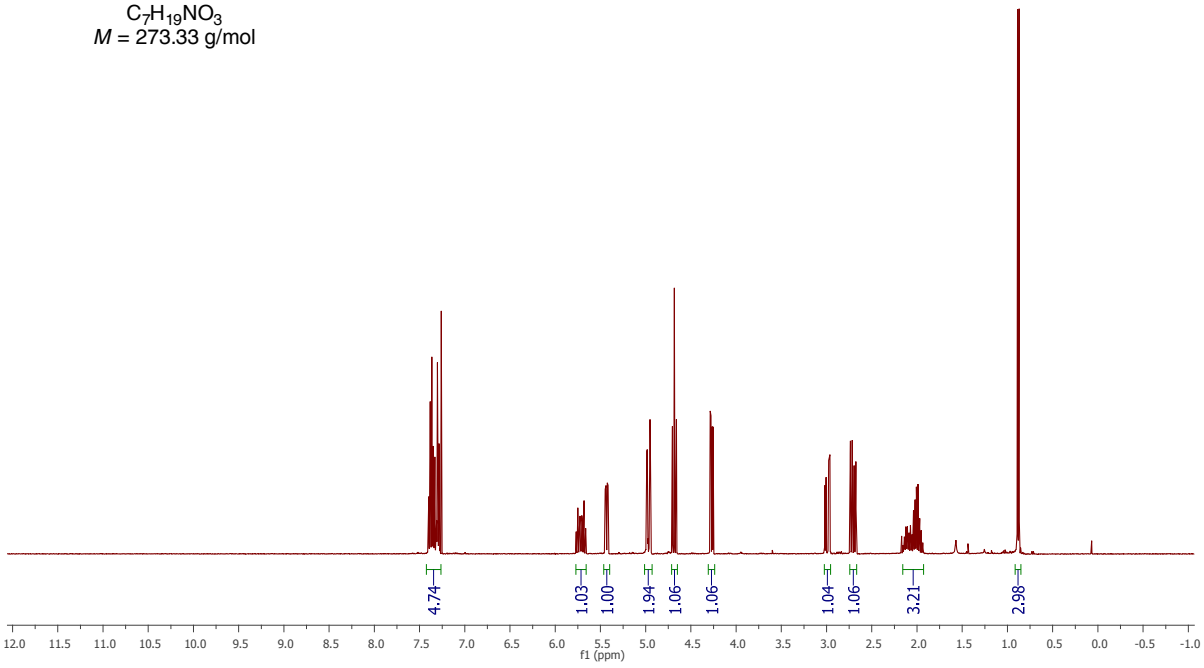
^{13}C NMR ($CDCl_3$, 100 MHz):



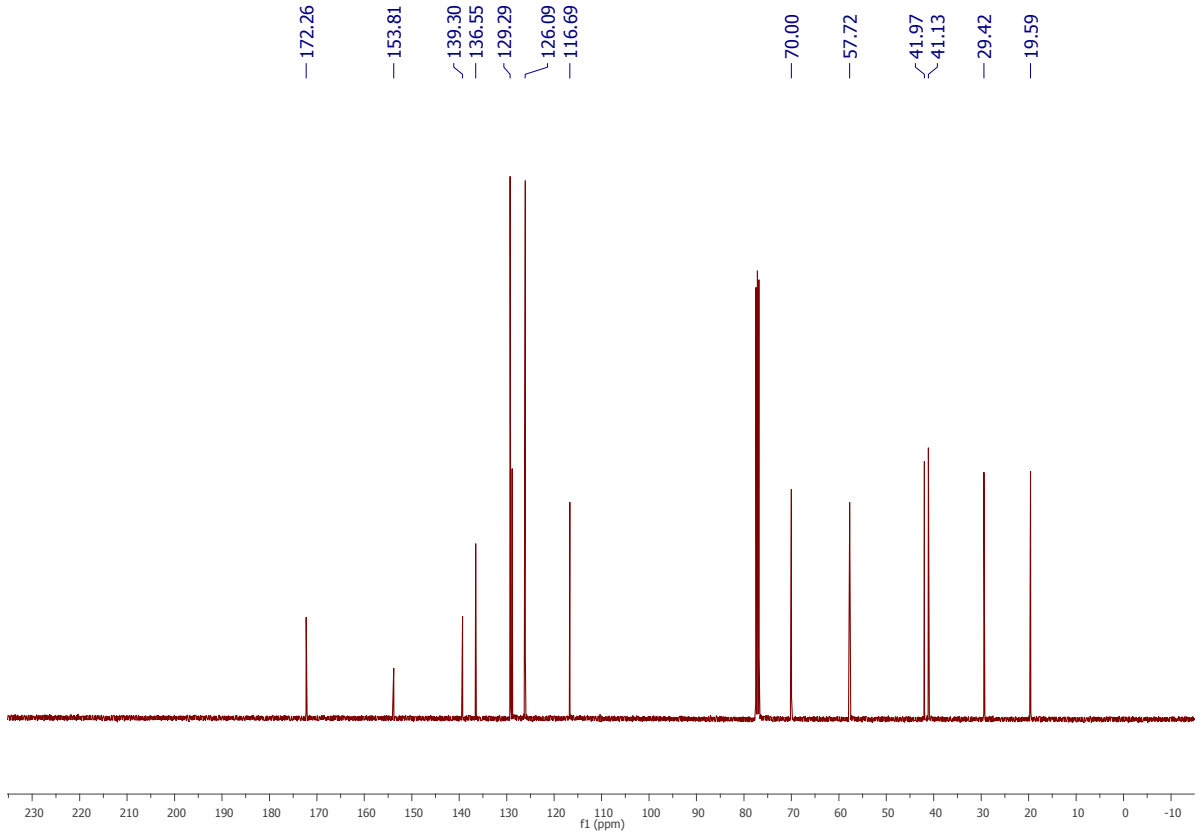
^{1}H NMR ($CDCl_3$, 400 MHz):



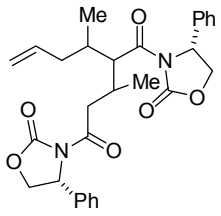
400
$C_7H_{19}NO_3$
M = 273.33 g/mol



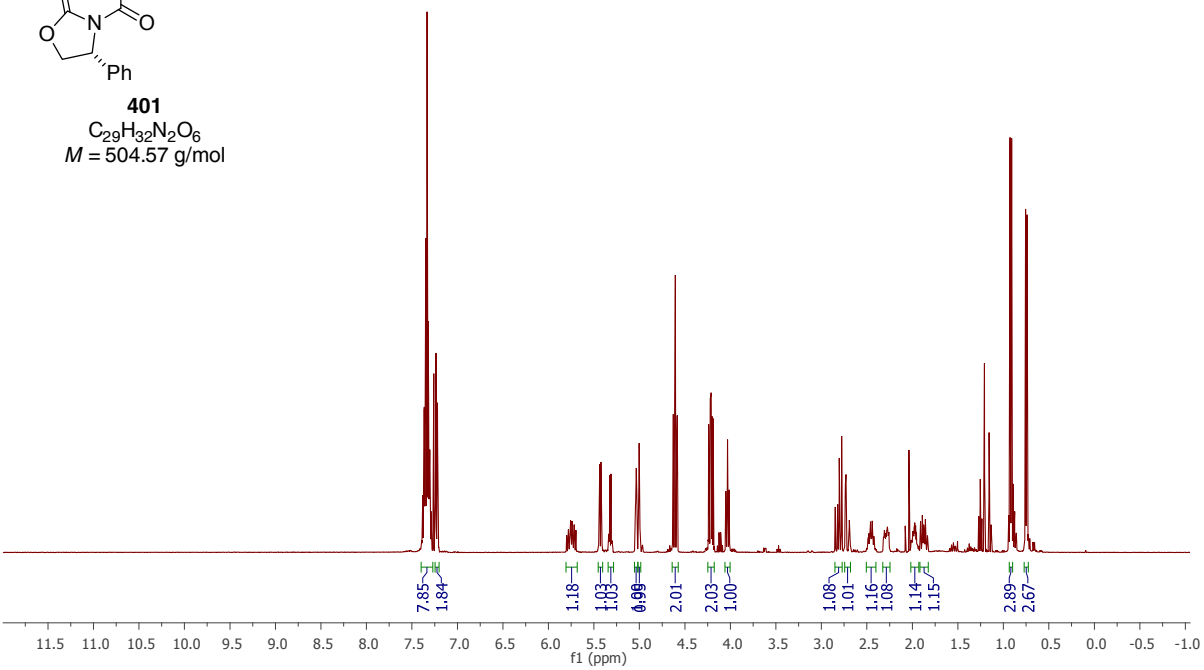
^{13}C NMR ($CDCl_3$, 100 MHz):



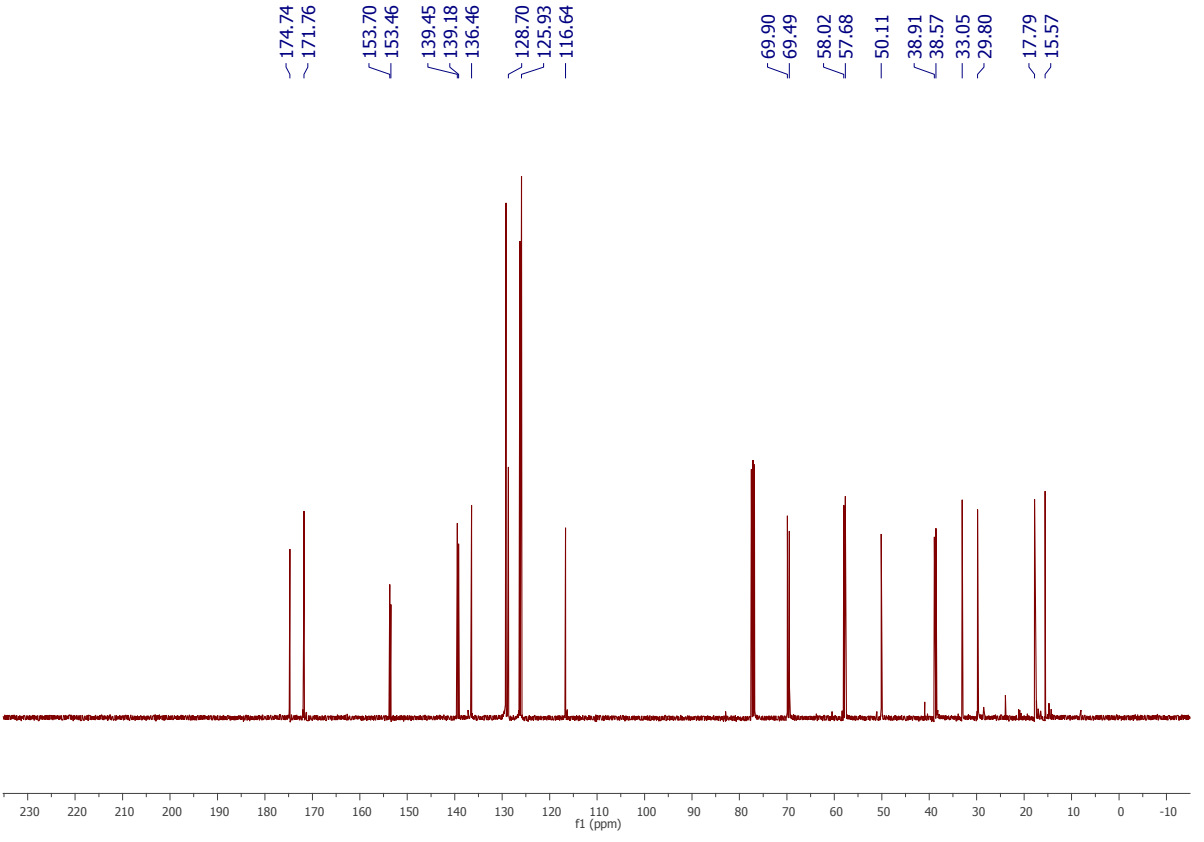
^{1}H NMR ($CDCl_3$, 400 MHz):



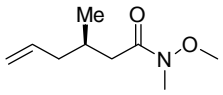
401
$C_{29}H_{32}N_2O_6$
M = 504.57 g/mol



^{13}C NMR ($CDCl_3$, 100 MHz):

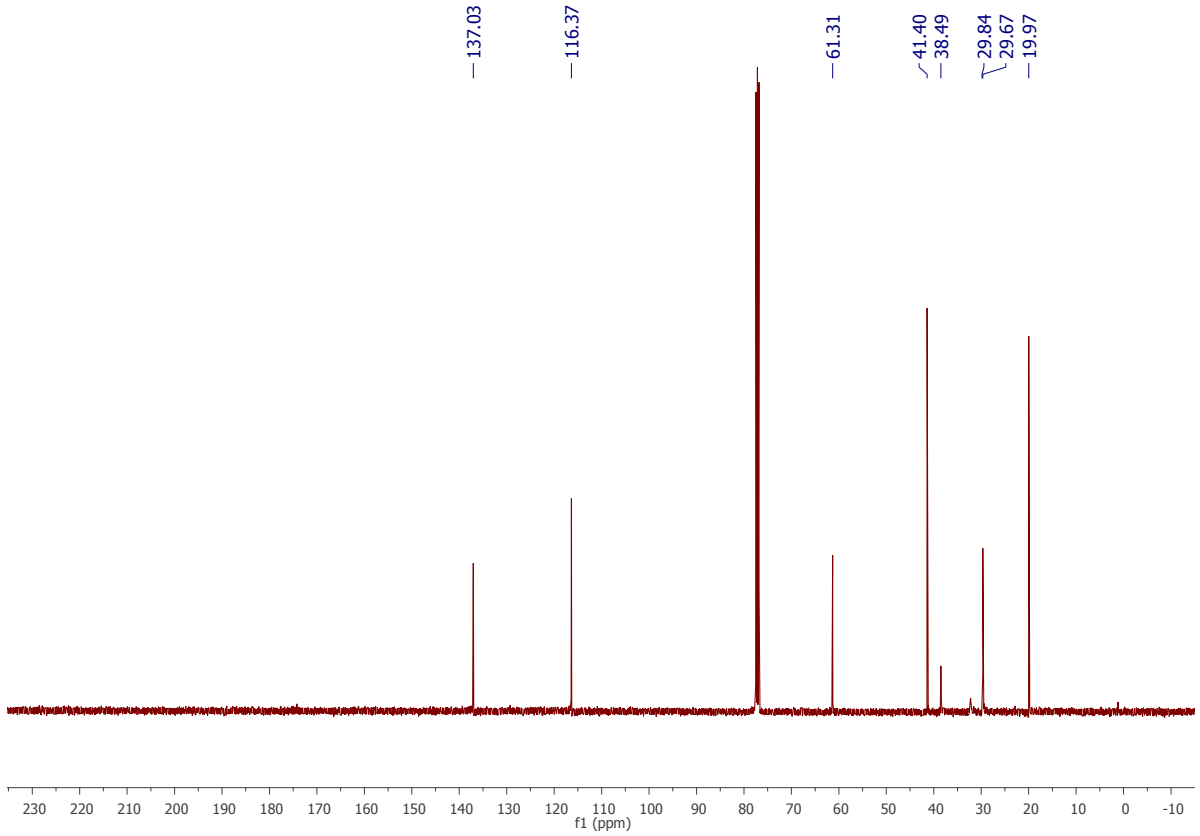


^{1}H NMR ($CDCl_3$, 400 MHz):

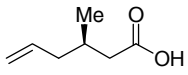


402
$C_9H_{17}NO_2$
M = 171.24 g/mol

^{13}C NMR ($CDCl_3$, 100 MHz):

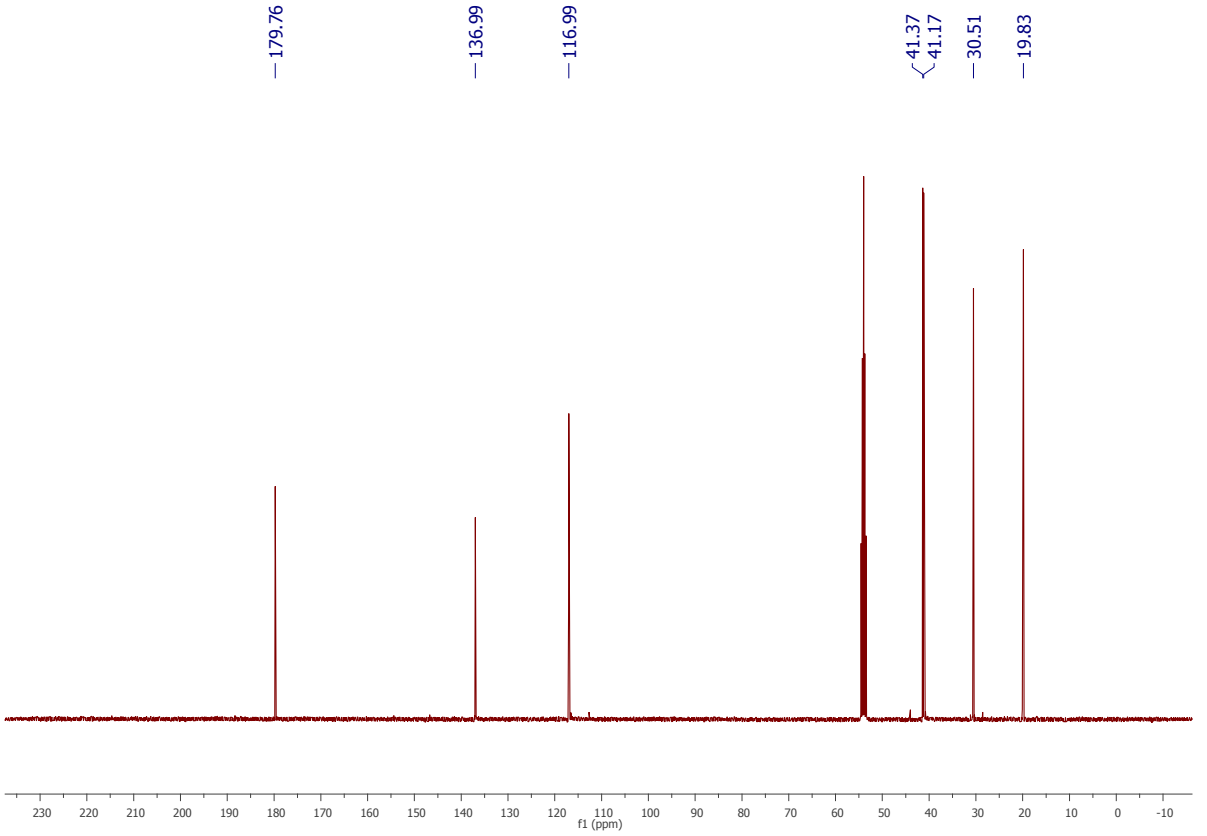


^{1}H NMR (CD_2Cl_2, 400 MHz):

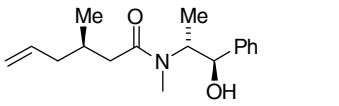


404
$C_7H_{12}O_2$
M = 128.17 g/mol

^{13}C NMR (CD_2Cl_2, 100 MHz):



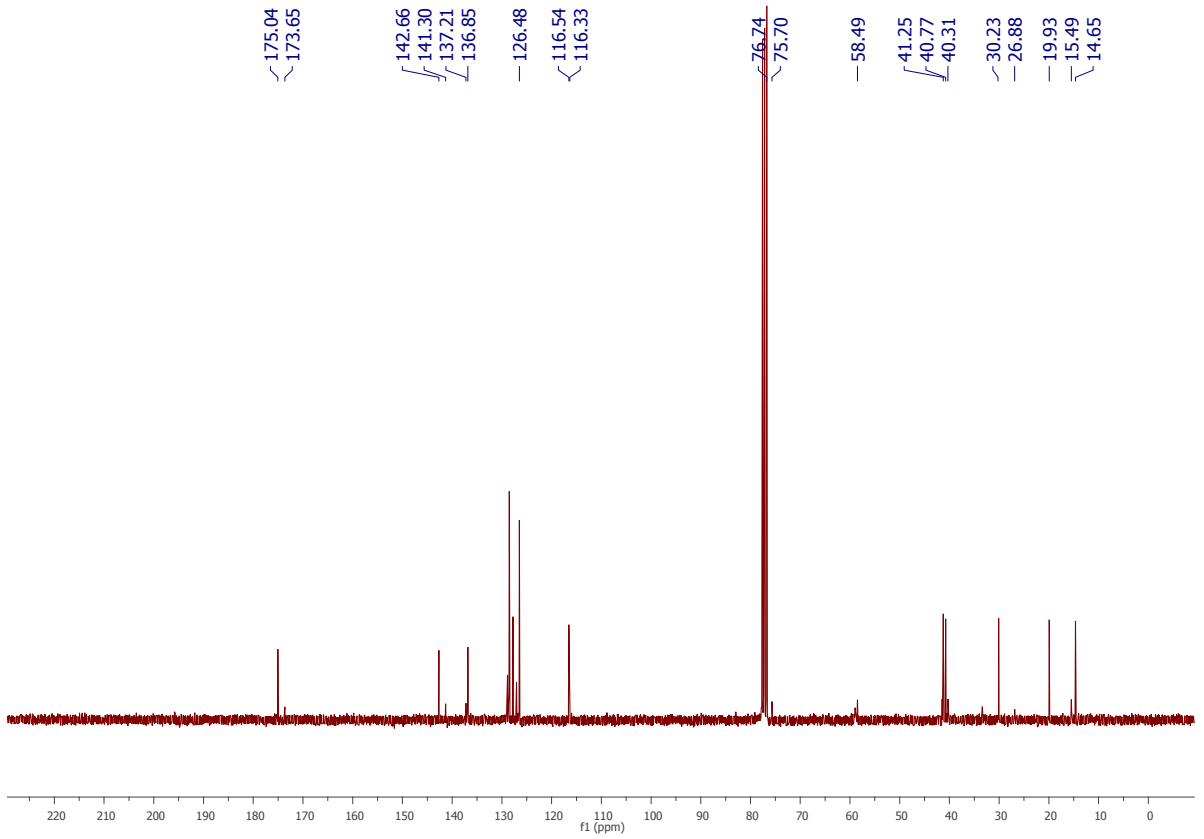
^{1}H NMR ($CDCl_3$, 300 MHz):



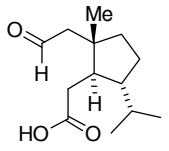
392
$C_{17}H_{25}NO_2$
M = 275.39 g/mol

3.6:1 mixture of rotamers

^{13}C NMR ($CDCl_3$, 75 MHz):

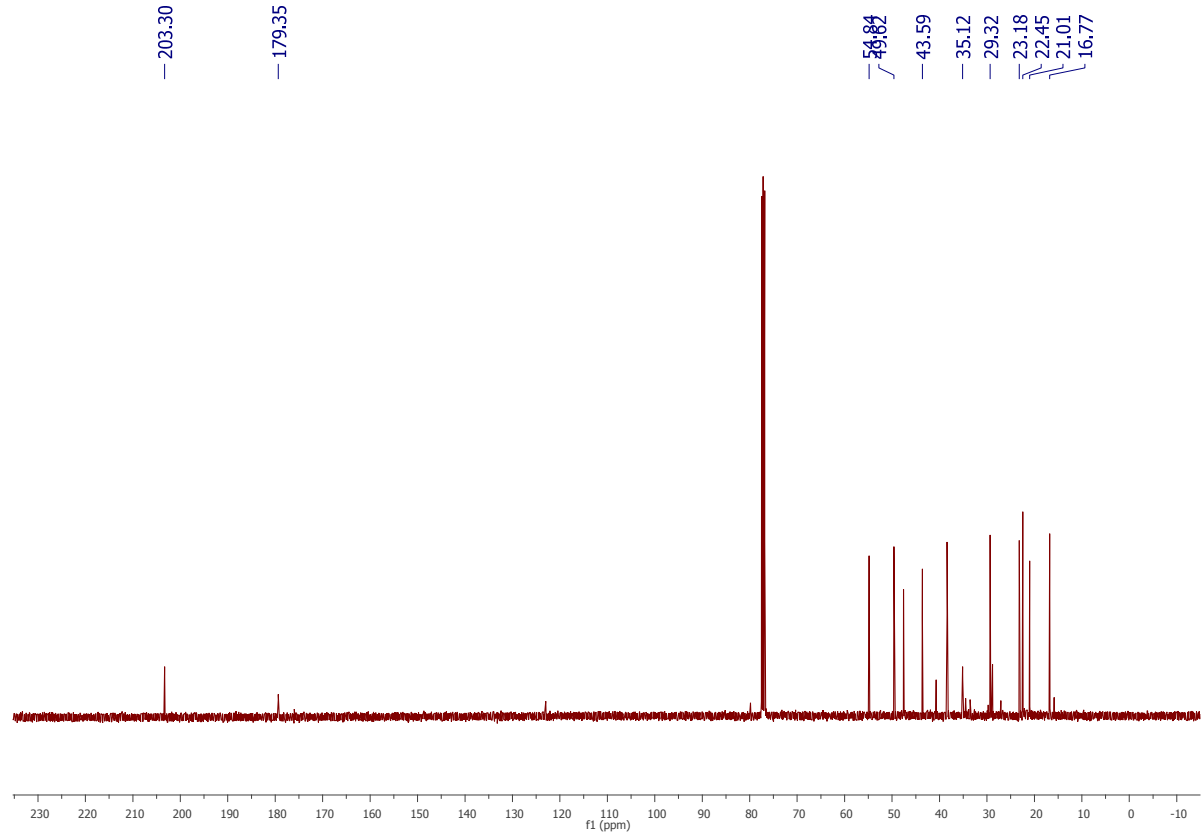


^{1}H NMR ($CDCl_3$, 400 MHz):

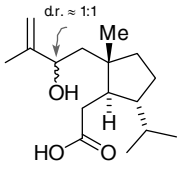


407
$C_{13}H_{22}O_3$
M = 226.31 g/mol

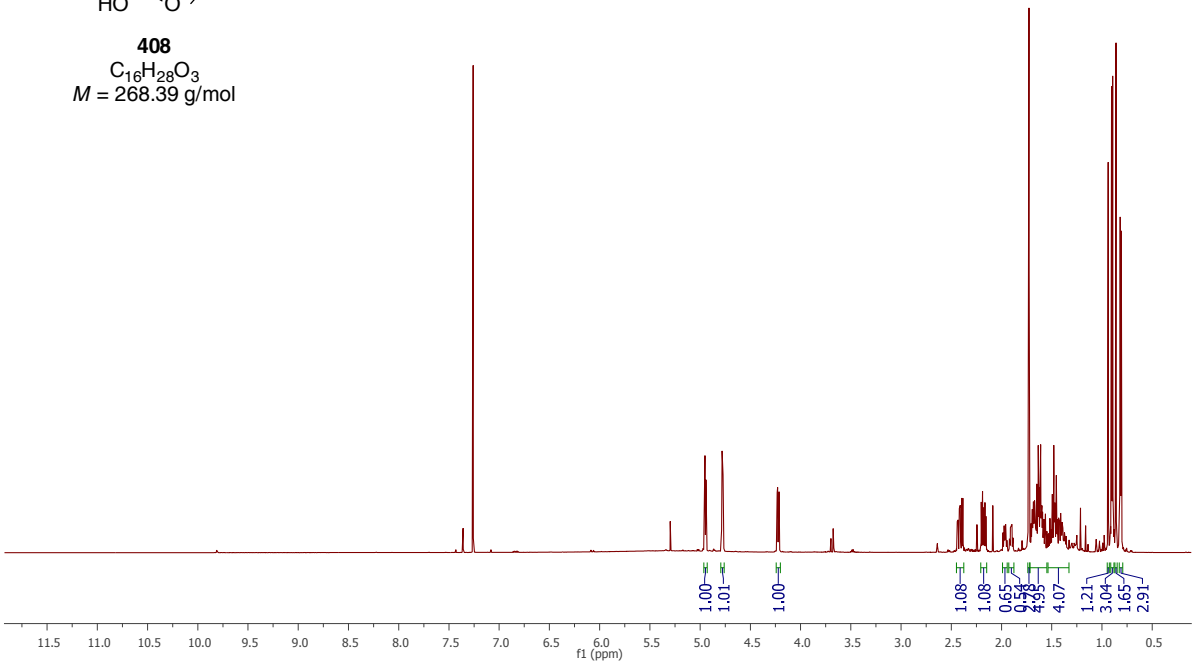
^{13}C NMR ($CDCl_3$, MHz):



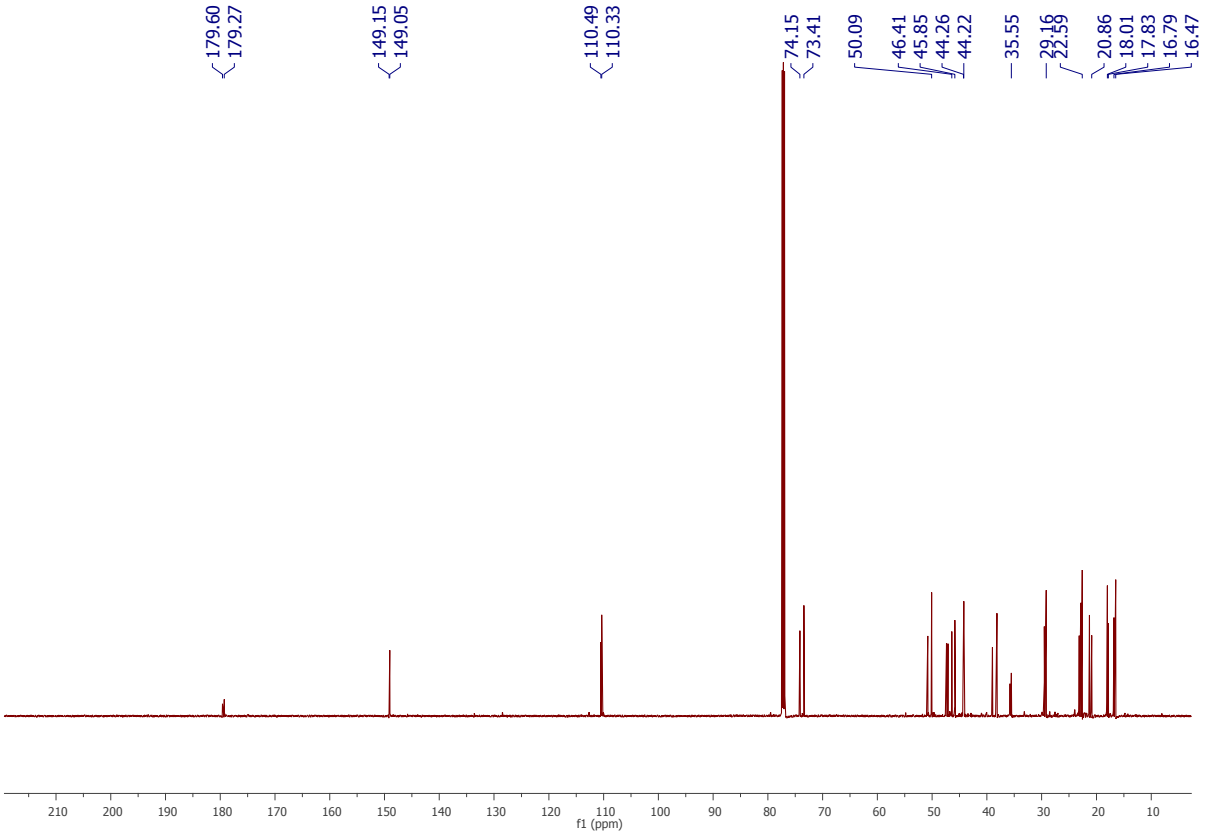
^{1}H NMR ($CDCl_3$, 600 MHz):



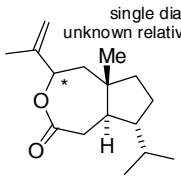
408
$C_{16}H_{28}O_3$
M = 268.39 g/mol



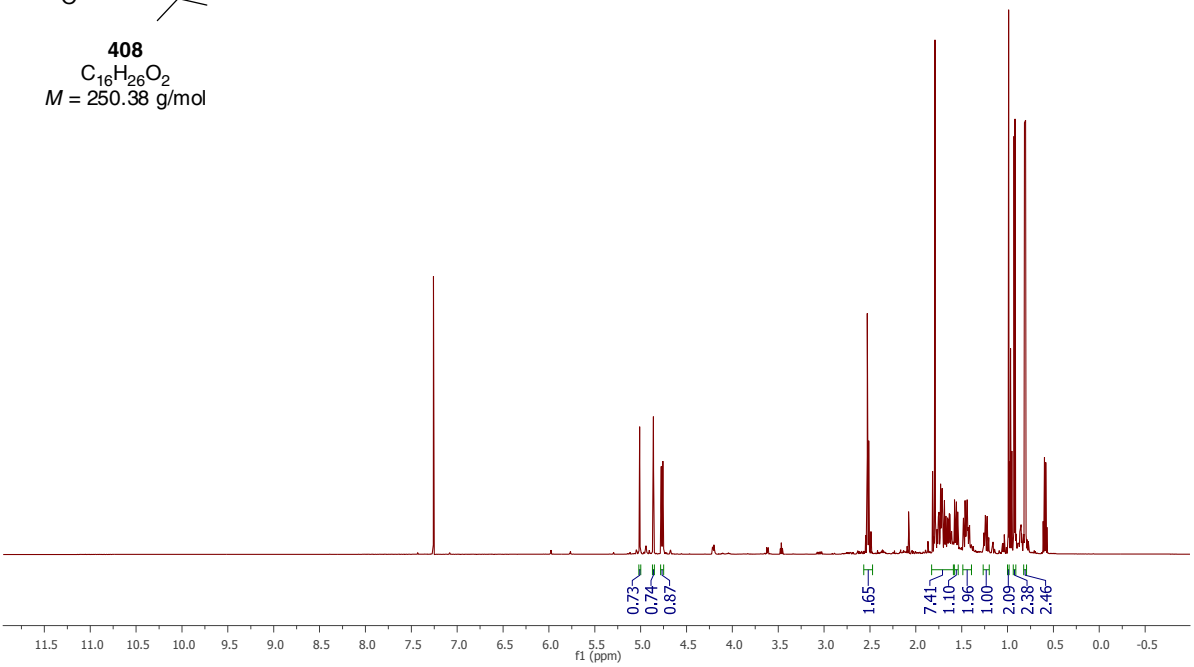
^{13}C NMR ($CDCl_3$, 150 MHz):



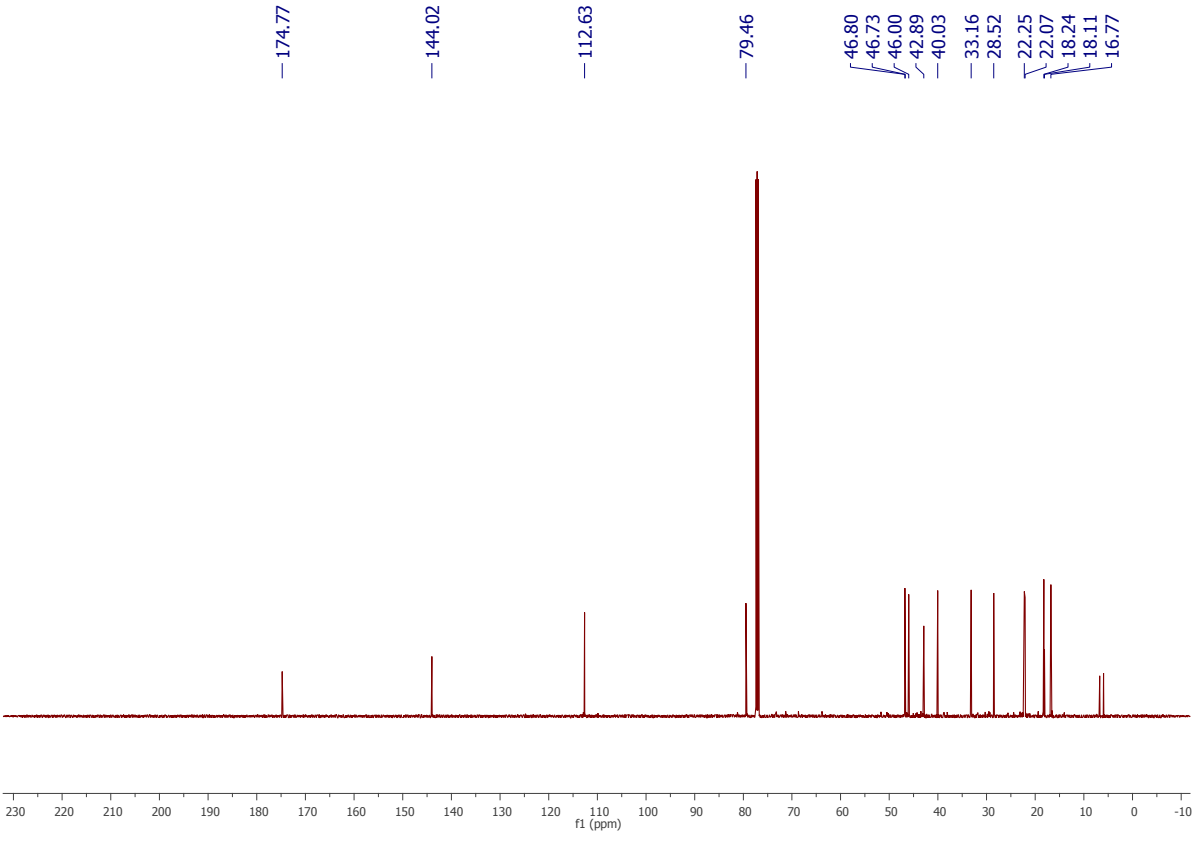
^{1}H NMR ($CDCl_3$, 600 MHz):



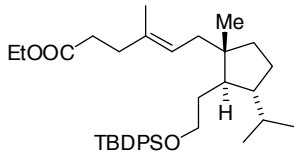
408
$C_{16}H_{26}O_2$
M = 250.38 g/mol



^{13}C NMR ($CDCl_3$, 150 MHz):

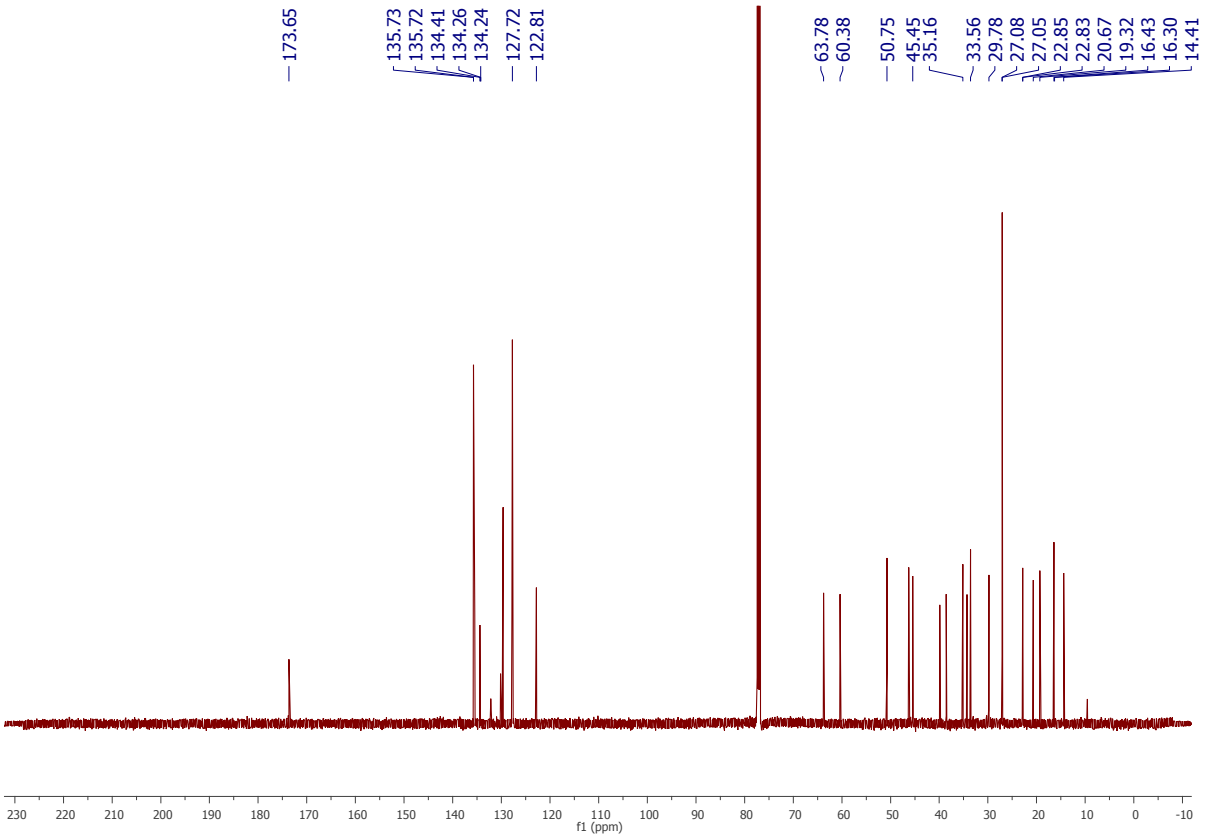


^{1}H NMR ($CDCl_3$, 600 MHz):

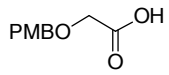


412
$C_{36}H_{54}O_3Si$
M = 562.90 g/mol

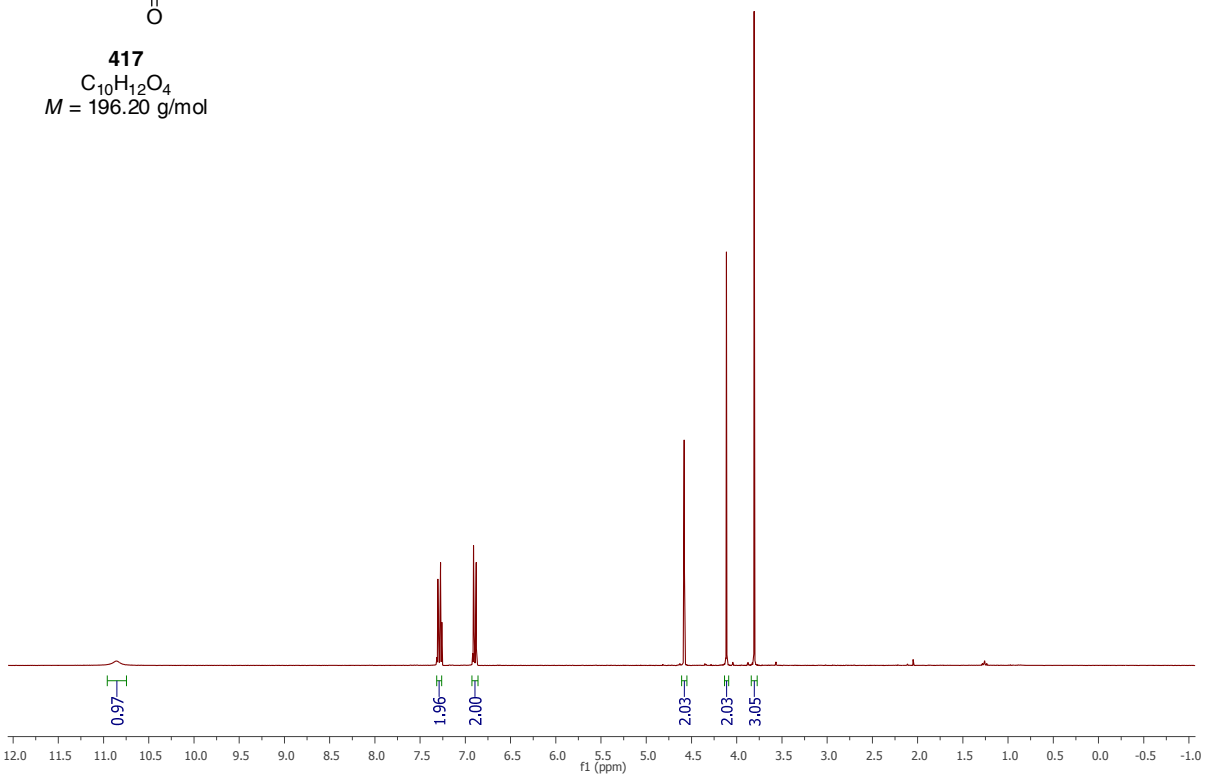
^{13}C NMR ($CDCl_3$, 150 MHz):



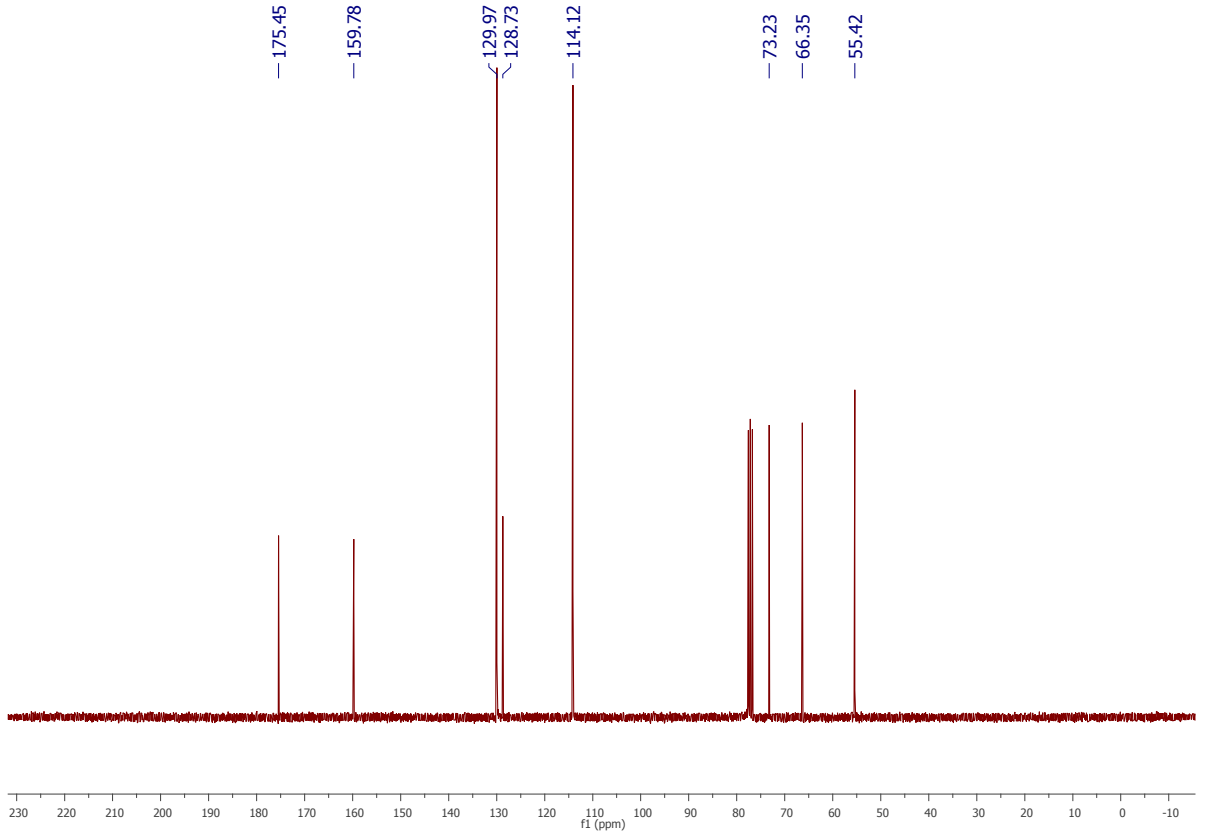
^{1}H NMR ($CDCl_3$, 300 MHz):



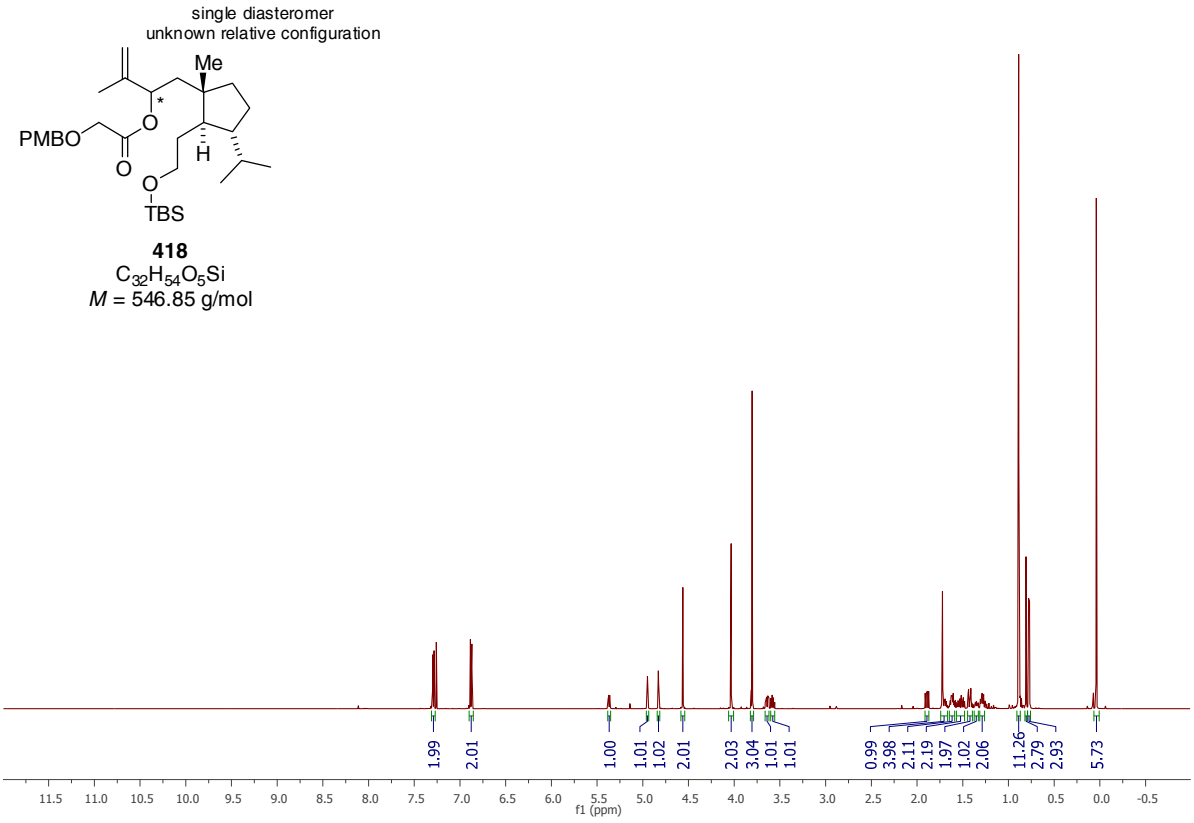
417
$C_{10}H_{12}O_4$
M = 196.20 g/mol



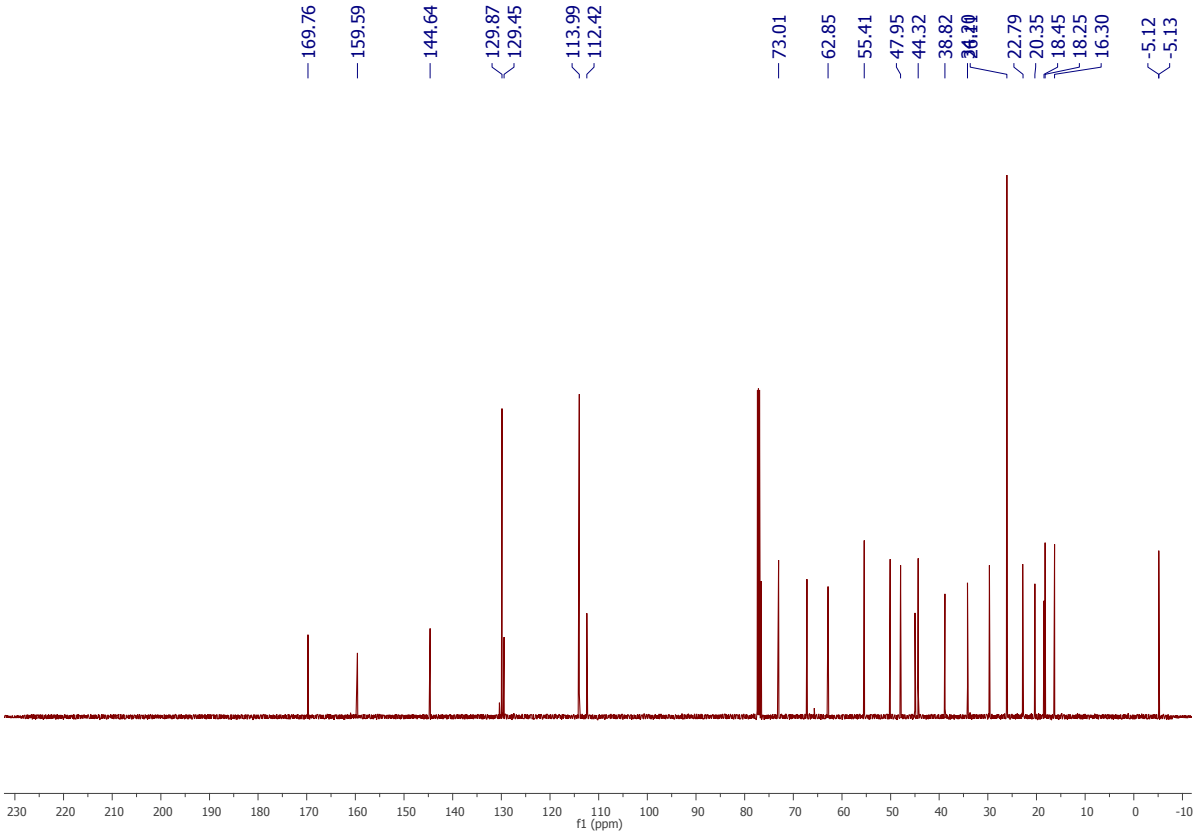
^{13}C NMR ($CDCl_3$, 75 MHz):



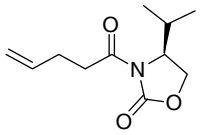
^{1}H NMR ($CDCl_3$, 600 MHz):



^{13}C NMR ($CDCl_3$, 150 MHz):

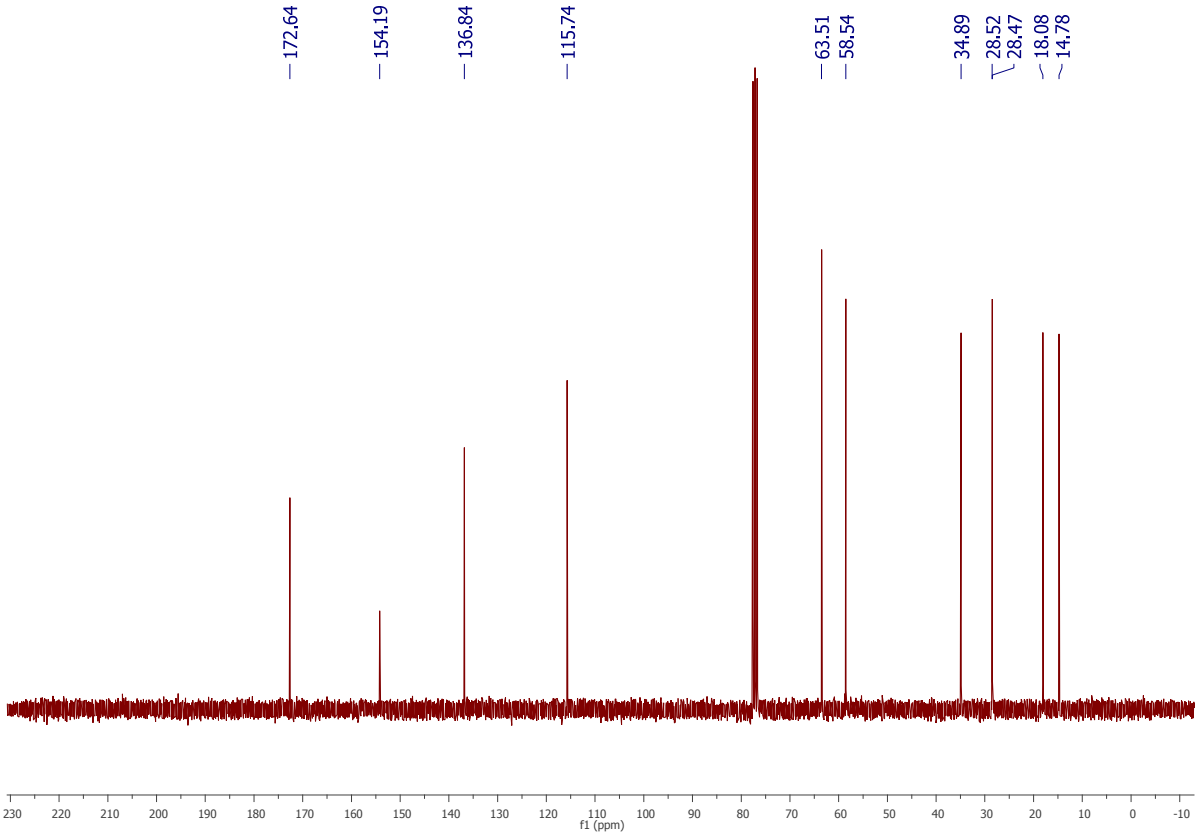


^{1}H NMR ($CDCl_3$, 300 MHz):

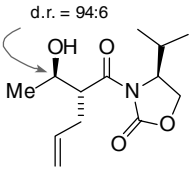


434
$C_{11}H_{17}NO_3$
M = 211.26 g/mol

^{13}C NMR ($CDCl_3$, 75 MHz):

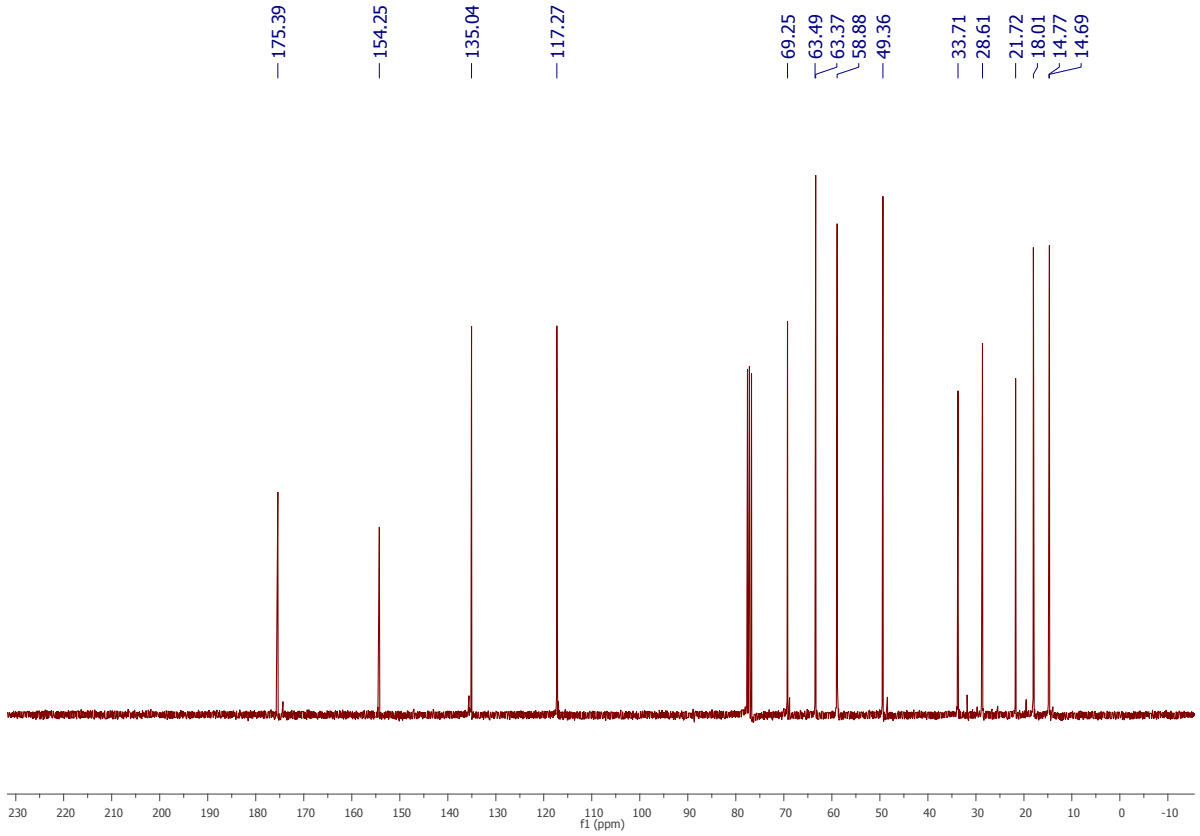


^{1}H NMR ($CDCl_3$, 600 MHz):

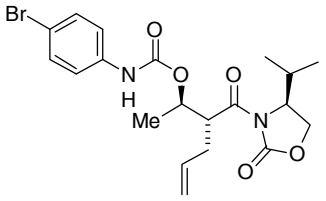


439
$C_{13}H_{21}NO_4$
M = 255.31 g/mol

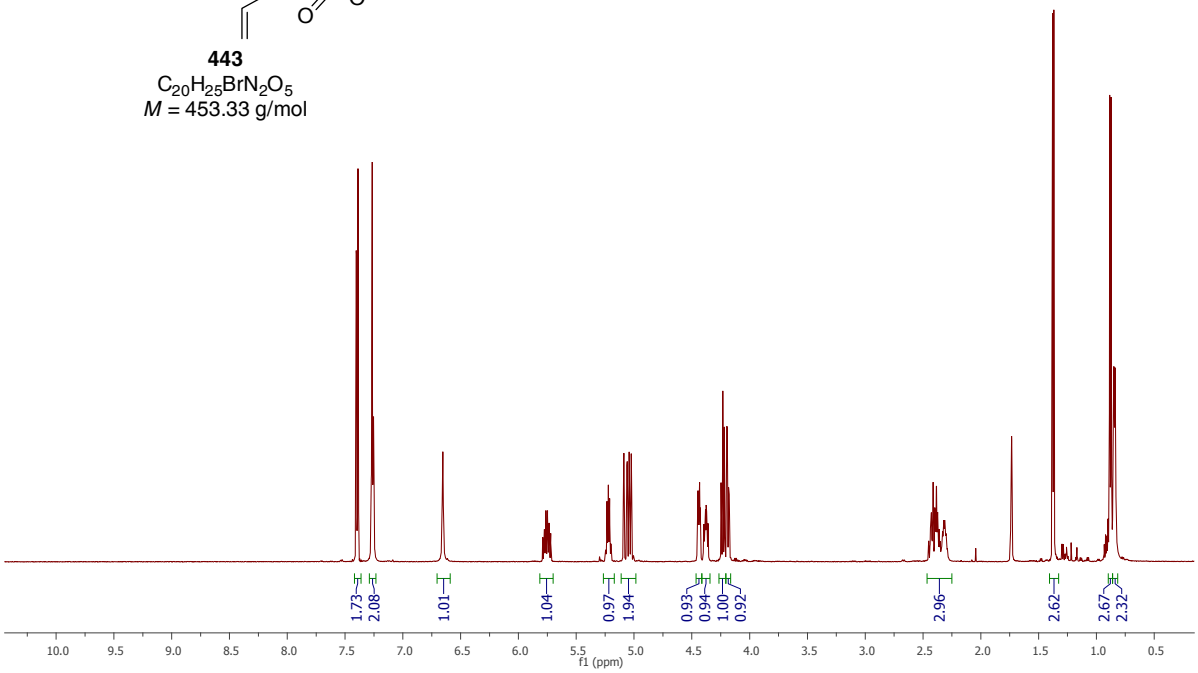
^{13}C NMR ($CDCl_3$, 75 MHz):



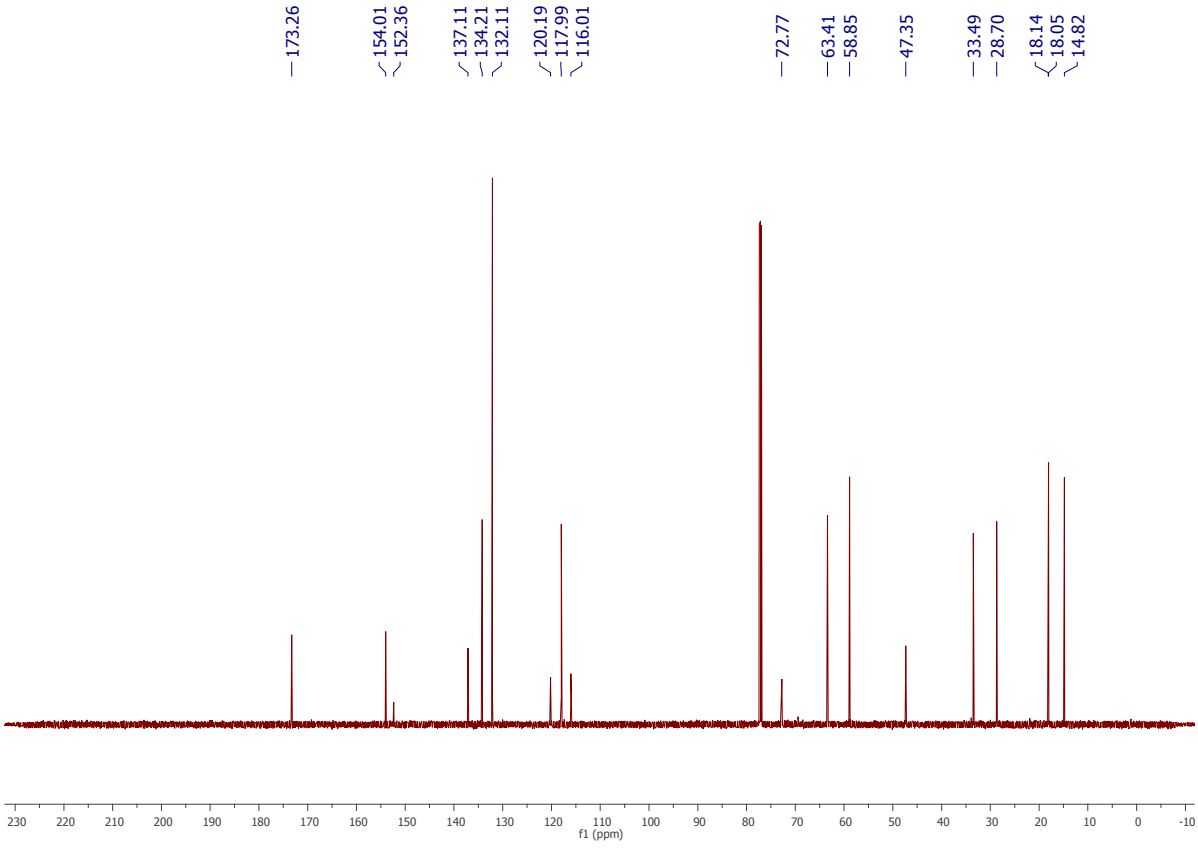
^{1}H NMR ($CDCl_3$, 600 MHz):



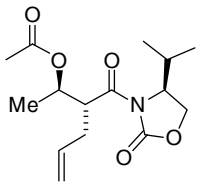
443
$C_{20}H_{25}BrN_2O_5$
M = 453.33 g/mol



^{13}C NMR ($CDCl_3$, 150 MHz):

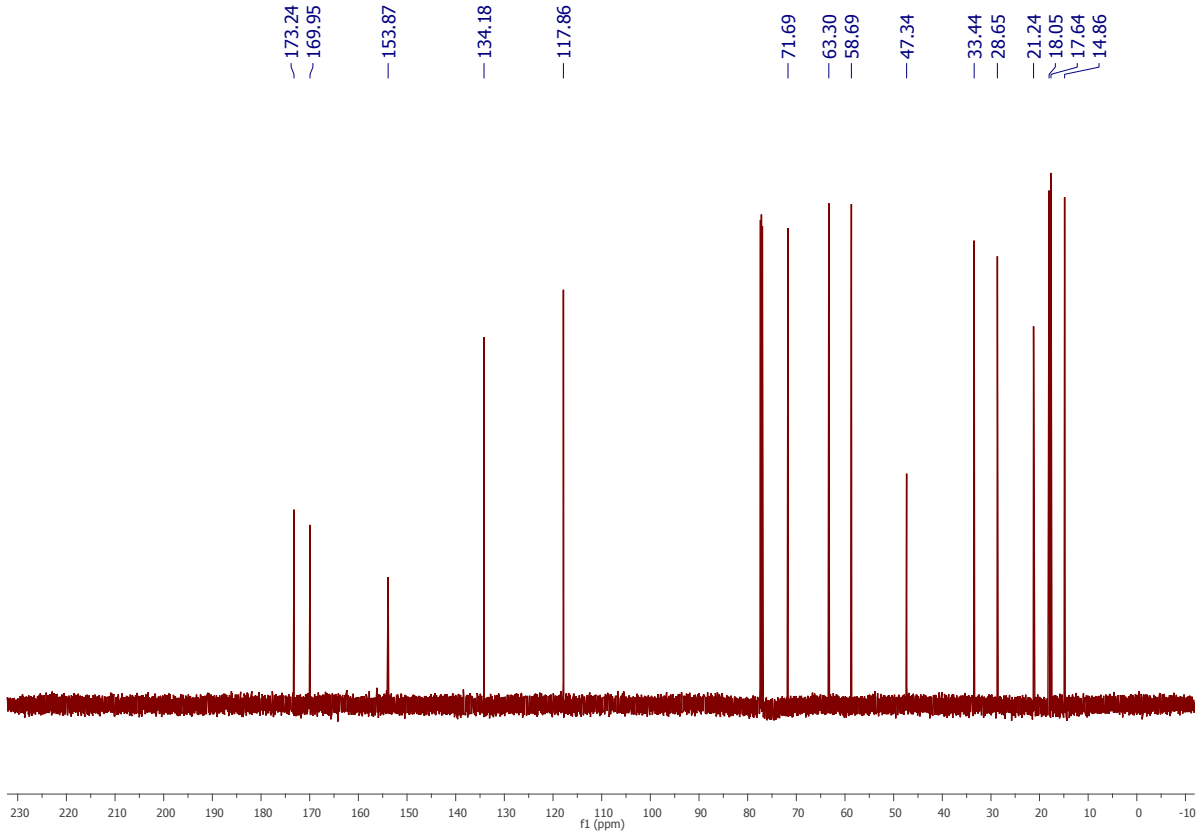


^{1}H NMR ($CDCl_3$, 600 MHz):

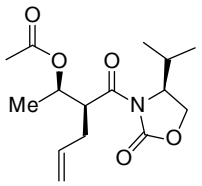


445
$C_{15}H_{23}NO_5$
M = 297.35 g/mol

^{13}C NMR ($CDCl_3$, 150 MHz):

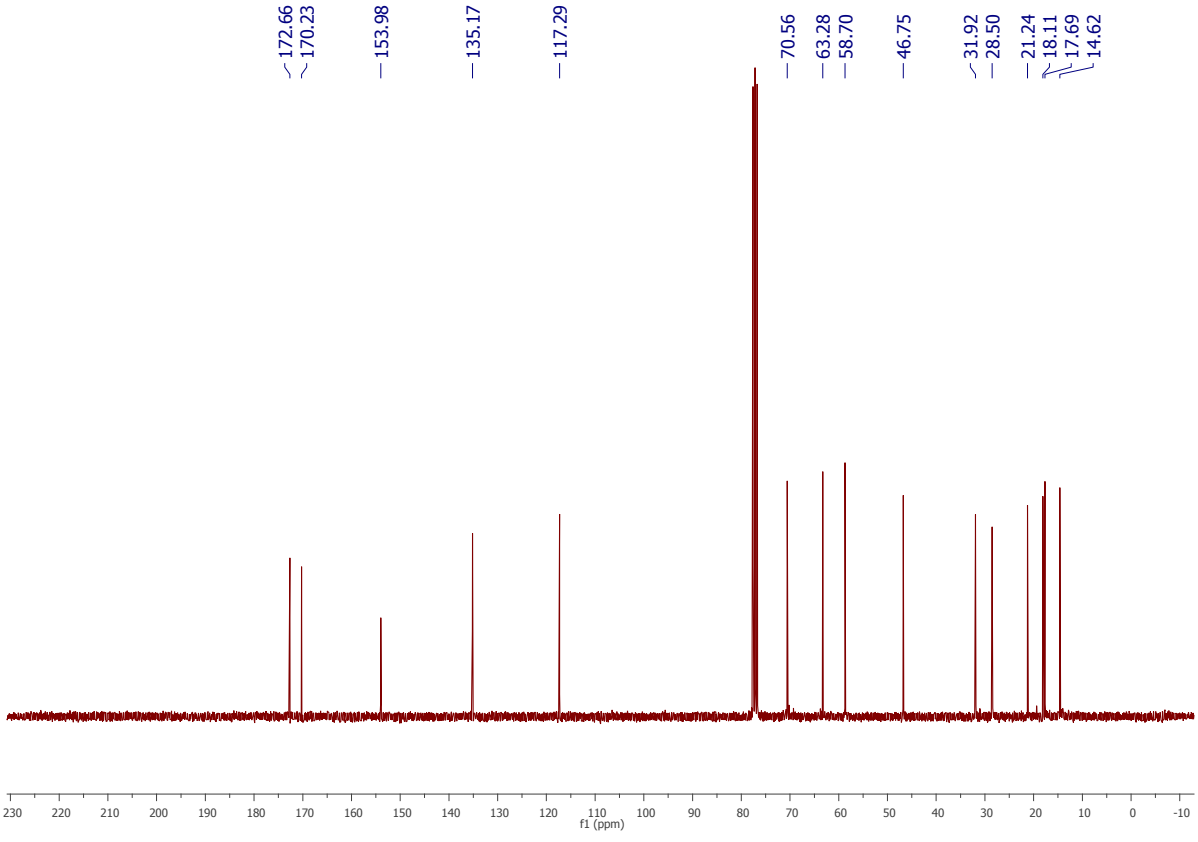


^{1}H NMR ($CDCl_3$, 300 MHz):

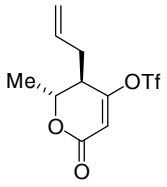


444
$C_{15}H_{23}NO_5$
M = 297.35 g/mol

^{13}C NMR ($CDCl_3$, 75 MHz):



^{1}H NMR ($CDCl_3$, 300 MHz):

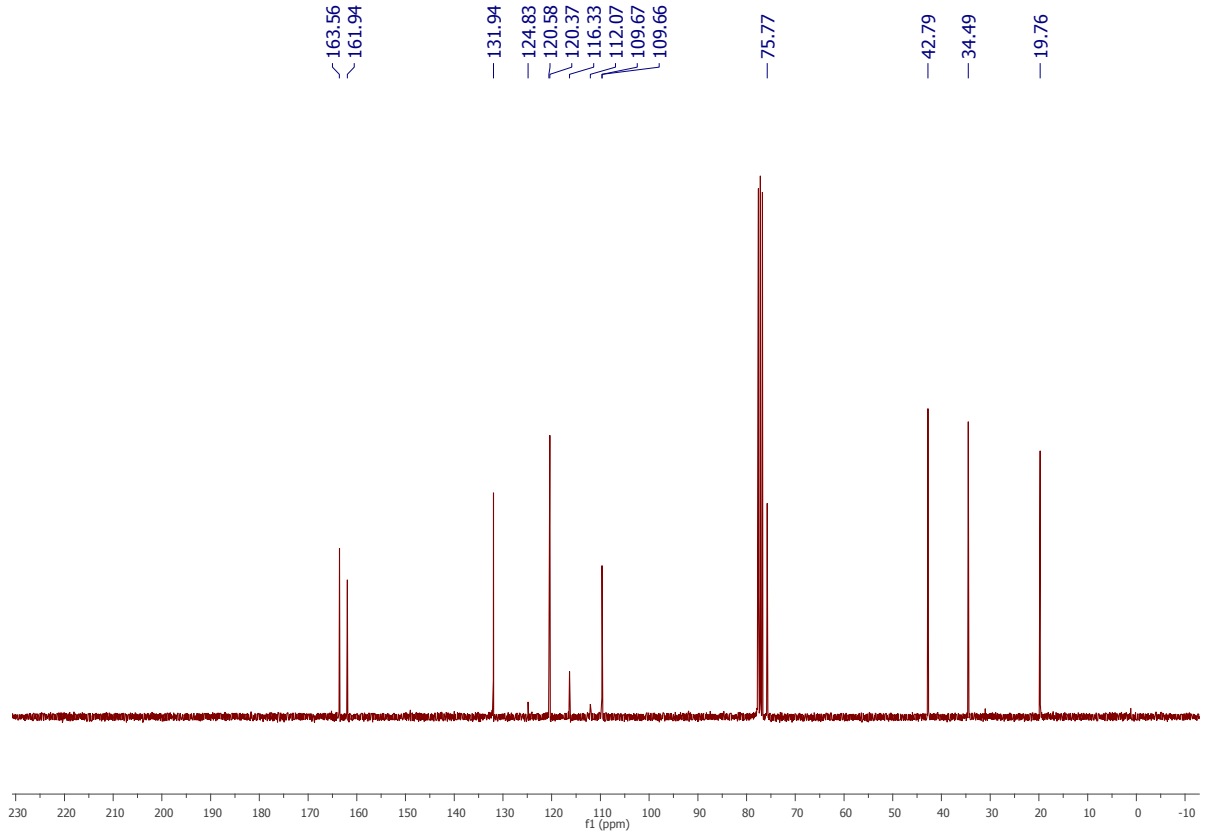


446

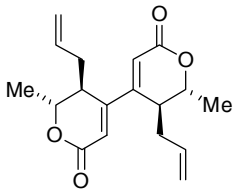
$C_{10}H_{11}F_3O_5S$

M = 300.25 g/mol

^{13}C NMR ($CDCl_3$, 75 MHz):



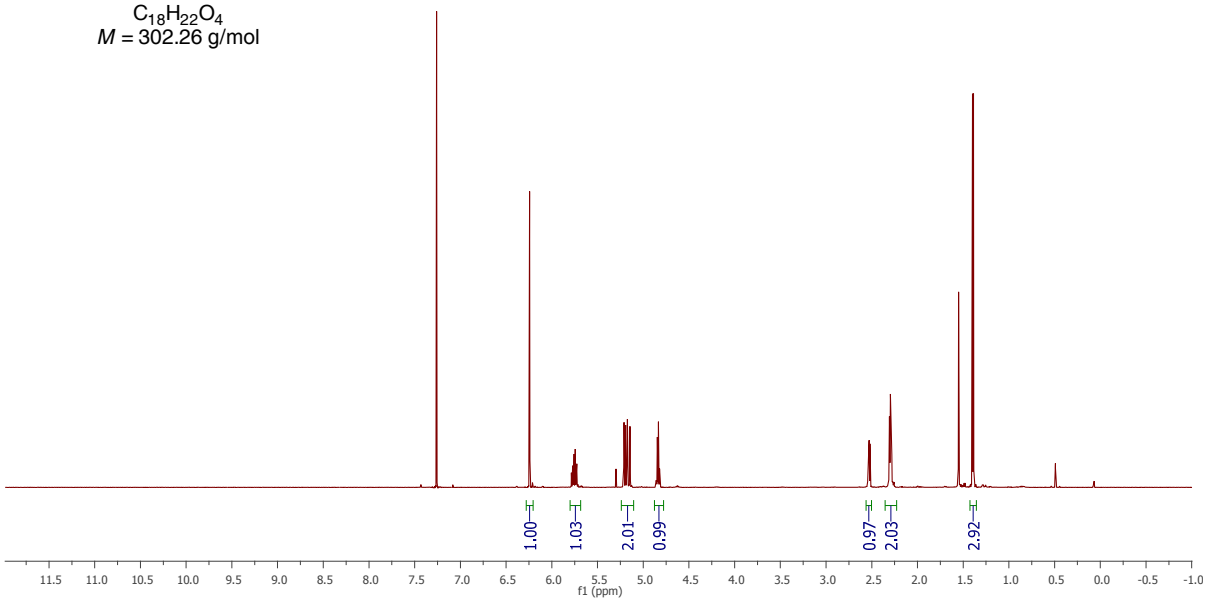
^{1}H NMR ($CDCl_3$, 600 MHz):



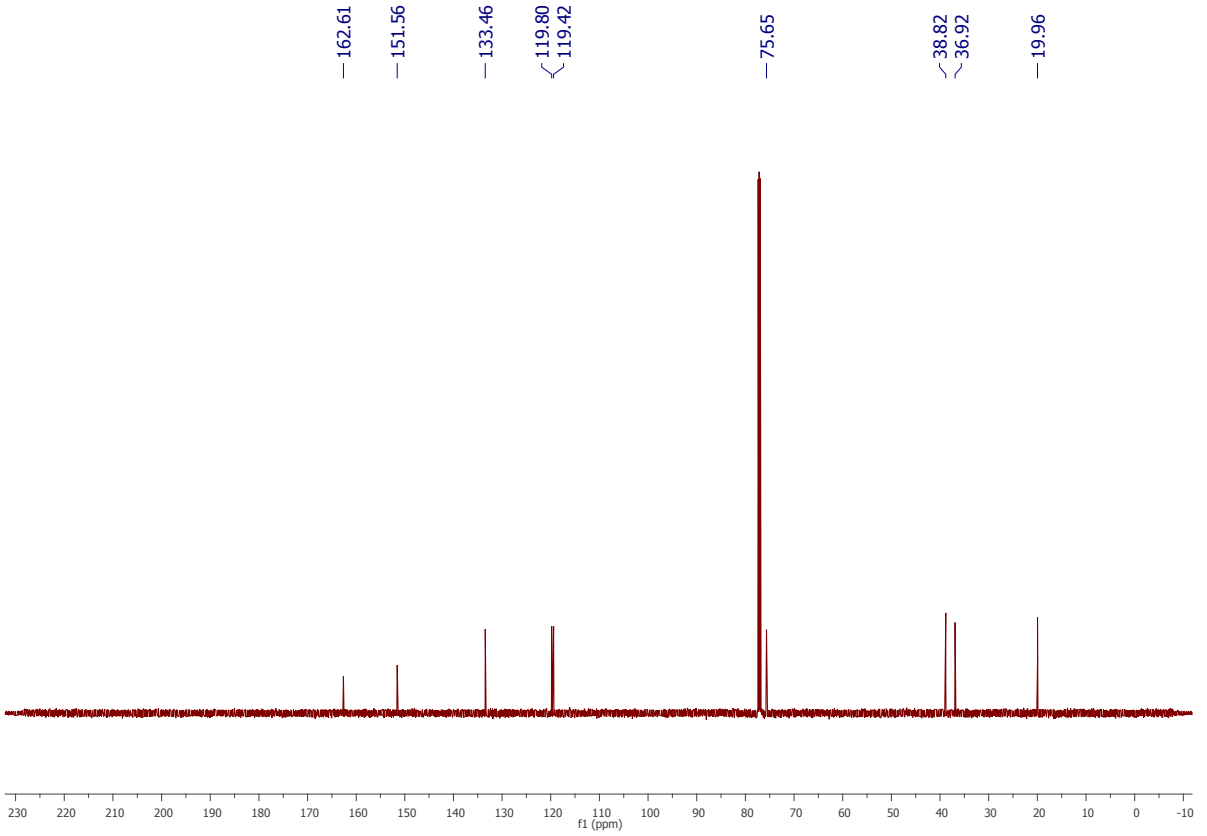
447

$C_{18}H_{22}O_4$

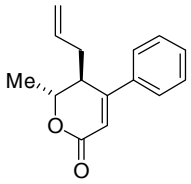
M = 302.26 g/mol



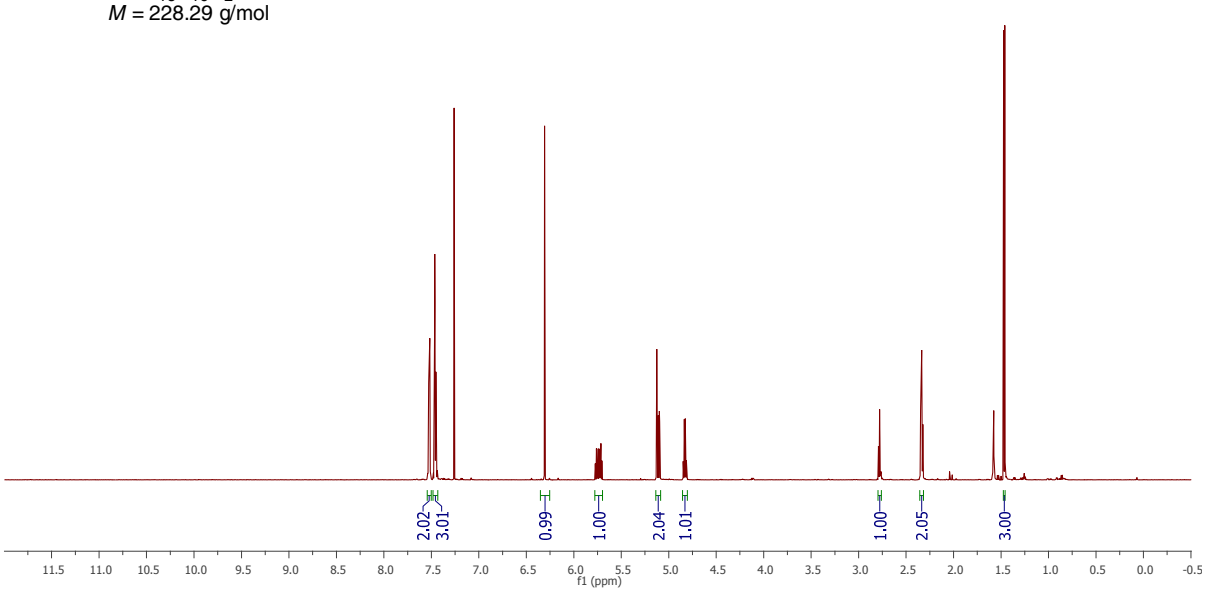
^{13}C NMR ($CDCl_3$, 150 MHz):



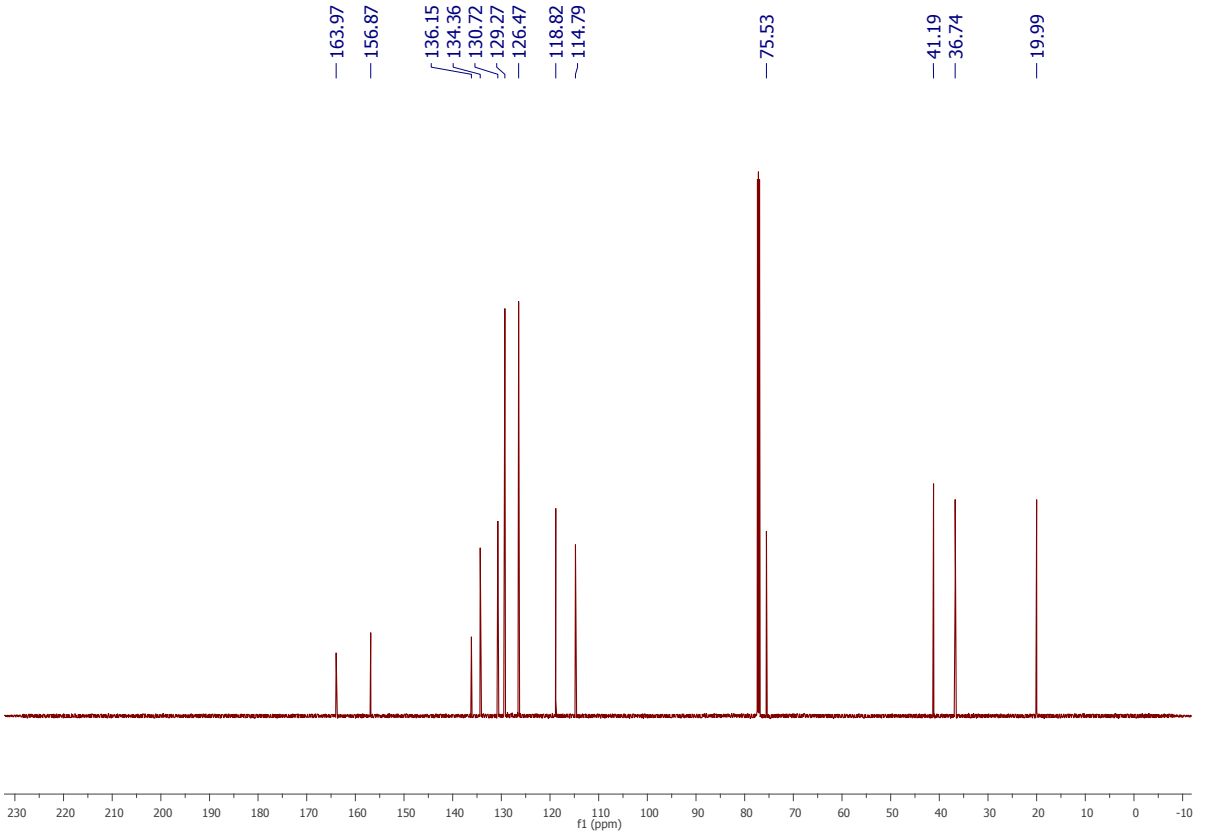
^{1}H NMR ($CDCl_3$, 600 MHz):



448
$C_{15}H_{16}O_2$
M = 228.29 g/mol



^{13}C NMR ($CDCl_3$, 150 MHz):



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Personal Data

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Languages:	German (native), English (fluent), Spanish (basic), French (basic).

Research Experience

09.2009 – present	Ph.D. student with Prof. Dr. Dirk Trauner, Faculty of Chemistry and Pharmacy, LMU Munich, Germany: 'A Unified Approach toward Astellatol, Nitiol and YW 3548'.
10.2008 – 04.2009	Diploma research with Prof. Dr. Martin Oestreich, Organic Chemistry Institute, WWU Münster, Germany: '$B(C_6F_5)_3$-Catalyzed Reduction of Ketones and Imines Using Silicon-Stereogenic Silanes: Stereoinduction by Single-Point-Binding'.
05.2008 – 07.2008	Research stay with Prof. Dr. Antonio M. Echavarren, Institut Català d'Investigació Chimiqua (ICIQ), Tarragona, Spain: 'Mechanistic Studies of the Intermolecular Reaction between functionalized 1,6-Enynes and Alkenes. Studies towards an Application of this Reaction in Natural Product Synthesis'.
11.2007 – 01.2008	Research stay with Prof. Dr. F. Ekkehardt Hahn, Institute for Inorganic and Analytical Chemistry, WWU Münster, Germany: 'Coordination Chemistry of Dithiolato Ligands and Benzimidazolinyl Carbenes'.
11.2006 – 01.2007	Research stay with Prof. Dr. Dieter Hoppe, Organic Chemistry Institute, WWU Münster, Germany: 'Preparation of (*R*)-2-(4-methoxybenzyloxy)-2-methylhex-5-enal and homoaldol reaction with *trans*-(5*R*)-crypytl carbamate'.

University Studies

23.04.2009	Diploma ('sehr gut').
10.2006 – 09.2008	Main studies in chemistry, WWU Münster, Germany.
06.09.2006	Prediploma ('sehr gut').
10.2004 – 09.2006	Basic studies in chemistry, WWU Münster, Germany

School Education & Civilian Service

09.2003 – 07.2004	Civilian Service, Hospital Pharmacy, University Hospital, Freiburg im Breisgau, Germany.
09.1994 – 06.2003	General qualification for university entrance (Abitur, 1.0), Wentzinger-Gymnasium, Freiburg im Breisgau, Germany.
09.1990 – 07.1994	Elementary School, Mühlmattenschule, Freiburg-Hochdorf, Germany.

Awards

08.2013	Participant of the 125th BASF International Summer Course.
26.09.2012	ORCHEM 2012 Poster Prize.
03.2010 – 04.2012	Predoctoral scholarship of the foundation *Stipendien-Fonds des Verbandes der chemischen Industrie e.V.*
02.2010	Ph.D. scholarship of the foundation *Universität Bayern e. V.* (declined).
27.06.2003	'Abitur'-book prizes in chemistry and mathematics, Wentzinger Gymnasium, Freiburg im Breisgau, Germany.

Scientific Employments

09.2009 – present	Scientific co-worker, Faculty of Chemistry and Pharmacy, LMU Munich, Germany.
10.2008 – 04.2009	Student assistant, Organic Chemistry Institute, WWU Münster, Germany.
10.2007 – 03.2008	Student assistant, Institute for Physical Chemistry, WWU Münster, Germany.

Teaching Experience

09.2009 – present	Supervision of two Bachelor students (Sebastian Rappenglück, Martin Rossa) and two F-Praktikanten (Thomas M. Wildenhof, Florian Weinzierl).
10.2012 – 03.2013	Scientific assistant for lecture 'Einführung in die Syntheseplanung' of Prof. Dr. Dirk Trauner, LMU Munich, Germany.
01.2012 – 03.2012	Supervision of lab course in basic organic chemistry, LMU Munich, Germany.
02.2011 – 03.2011	Supervision of lab course for prospective teachers, LMU Munich, Germany.
10.2009 – 02.2010	Supervision of lab course in basic organic chemistry, LMU Munich, Germany.
10.2007 – 03.2008	Tutor (mathematics for chemists), WWU Münster, Germany.

Publications

4. ‘A Unified Approach toward *trans*-Hydrindane Sesterterpenoids’, D. T. Hog, P. Mayer, D. Trauner, *J. Org. Chem.* **2012**, *76*, 5838–5843.

3. ‘Synthetic Approaches toward Sesterterpenoids’, D. T. Hog, R. Webster, D. Trauner, *Nat. Prod. Rep.* **2012**, *29*, 752–779.

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Conference Contributions

‘Synthetic Studies toward Astellatol’, D. T. Hog, P. Mayer, D. Trauner, poster presentation, ORCHEM 2012, Weimar, Germany, 24.09.2012 – 26.09.2012.

‘Synthetic Studies toward Astellatol’, D. T. Hog, P. Mayer, D. Trauner, oral & poster presentation, Regional Meeting of Scholarship Holders of the Foundation *Stipendien-Fonds der Chemischen Industrie e.V.*, Technische Universität München, Garching, Germany, 14.02.2012.

‘Synthetic Studies toward YW3548’, D. T. Hog, P. Mayer, D. Trauner, poster presentation, 22nd International Symposium: Synthesis in Organic Chemistry, Churchill College, Cambridge, United Kingdom, 11.07.2011 – 14.07.2011.

‘Recent Projects on Total Synthesis in the Trauner Group’, D. T. Hog, C. A. Kuttruff, F. Löbermann, T. J. Kimbrough, D. Trauner, poster presentation, Harvard-LMU Young Scientist Forum, Harvard University, Cambridge, MA, U.S.A., 23.07.2010 – 27.07.2010.

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