DISSERTATION

TOTAL SYNTHESES OF (±)-FAWCETTIMINE,

(±)-FAWCETTIDINE, (±)-LYCOFLEXINE,

AND (±)-LYCOPOSERRAMINE B

Submitted by

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ABSTRACT

TOTAL SYNTHESES OF (±)-FAWCETTIMINE, (±)-FAWCETTIDINE, (±)-LYCOFLEXINE, AND (±)-LYCOPOSERRAMINE B

The total syntheses of (±)-fawcettimine, (±)-lycoflexine, (±)-fawcettidine, and (±)-lycoposerramine B have been accomplished through an efficient, unified, and stereocontrolled strategy that required sixteen, sixteen, seventeen, and seventeen steps, respectively, from commercially available materials. The key transformations involve: 1) a Diels-Alder reaction between a 1-siloxy diene and an enone to construct the *cis*-fused 6,5-carbocycles with one all-carbon quaternary center, and 2) a Fukuyama-Mitsunobu reaction to form the azonine ring. Access to the enantioselective syntheses of these alkaloids can be achieved by kinetic resolution of the earliest intermediate via a Sharpless asymmetric dihydroxylation.

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Dedicated in the memory of my father

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List of Abbreviations

Ac	Acetyl
ADDP	1,1'-(Azodicarbonyl)dipiperidine
AIBN	2, 2'-Azobis(2-methylpropionitrile)
atm	Atmosphere
Bu	Butyl
Burgess reagent	Methyl *N*-(triethylammoniosulfonyl)carbamate
B-V	Baeyer-Villiger oxidation
brsm	Based on recovered starting material
Bz	Benzoyl
ca.	Circa
calcd.	Calculated
cat.	Catalytic
Cy	Cyclohexyl
DA	(±)-*trans*-1,2-Diaminocyclohexane
D-A	Diels-Alder reaction
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DEAD	Diethyl azodicarboxylate
decompd.	Decomposed
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutylaluminum hydride
DIPEA	*N*,*N*-Diisopropylethylamine
Diphos	Ethylenebis(diphenylphosphine)
DMAP	4-Dimethylaminopyridine
DMDO	Dimethyldioxirane
DMS	Dimethylsulfide
DMSO	Dimethyl sulfoxide
DMTST	Dimethyl(methylthio)sulfonium triflate
d.r.	Diastereomeric ratio
DTBMP	2,6-Di-*t*-butyl-4-methylpyridine
EG	Ethylene glycol
ESI	Electrospray ionization
Et	Ethyl
eq.	Equation
equiv.	Equivalent
Fmoc	Fluorenylmethoxycarbonyl
Fod	*tris*-(6,6,7,7,8,8,8)-Heptafluoro-2,2-dimethyl-3,5-octanedionate
G2	Grubbs catalyst, 2nd generation
GC	Gas chromatography
h	Hour(s)
hfc	3-(Heptafluoropropylhydroxymethylene)-(+)-camphorate
HG2	Hoveyda-Grubbs catalyst, 2nd generation
HMPA	Hexamethylphosphoramide

HNCO	Isocyanic acid
HRMS	High resolution mass spectroscopy
imid.	Imidazole
IR	Infrared spectroscopy
KHMDS	Potassium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
m	Milli
M	Moles per liter, mol/L; Mega
Martin sulfurane	Bis[α,α-bis(trifluoromethyl)benzyloxy]diphenylsulfur
m-CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
Mes	Mesityl
mol	Mole(s)
MOM	Methoxymethyl
m.p.	Melting point
Ms	Methanesulfonyl
MS	Molecular sieves; Mass spectroscopy
MW	Microwave
NaHMDS	Sodium bis(trimethylsilyl)amide
NIS	*N*-iodosuccinimide
NMO	4-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect spectroscopy
n.d.	Not determined
n.r.	No reaction
Ns	2-Nitrobenzenesulfonyl
ORD	Optical rotatory dispersion
P-	Polymer supported
PDC	Pyridinium dichromate
Ph	Phenyl
Piv	Pivaloyl
PPTS	Pyridine *p*-toluenesulfonate
psi	Pound per square inch
Py	Pyridyl
py.	Pyridine
quant.	Quantitative
RCM	Ring-closing metathesis
RRCM	Relay ring-closing metathesis
Ref.	Reference(s)
r.s.m.	Recovered starting material
r.t.	Room temperature
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl

TES	Triethylsilyl
Tf	Trifluorosulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TPAP	Tetrapropylammonium perruthenate
Ts	*para*-Toluenesulfonyl
wt.	Weight
Y	Yield
Å	Angstrom
v	Volume
Δ	Heat

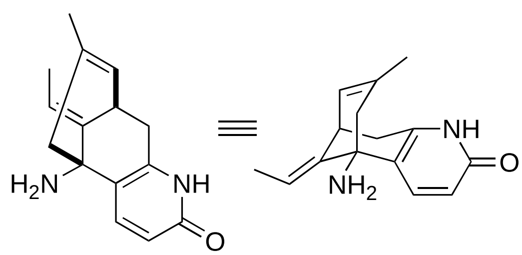
Chapter 1

Lycopodium Alkaloids

1.1 Introduction

Lycopodium (sensu lato) is a genus of club mosses also known as ground pines or creeping cedar, in the family *Lycopodiaceae*, a family of fern-allies.[1] There are more than 500 species for *Lycopodium* (s. l.), of which only about 50 species have been studied thus far. These low, evergreen, coarsely moss-like plants produce a large number of structurally related, yet diverse quinolizine-, pyridine-, or α-pyridone-type alkaloids.[2] By July 2008, about 250 *Lycopodium* alkaloids had been isolated[3] and the numbers continue to grow.[4] Some of the alkaloids, in particular Huperzine A (hupA), which was isolated by J. Liu and coworkers from the Chinese folk medicinal herb *Qian Ceng Ta* (whole plant of *Huperzia serrata* (*H. serrata*) (Thunb. Ex Murray) Trev., see Figure 1.1), were found to possess potent acetylcholinesterase inhibition activity,[5] and showed promising results for the treatment of Alzheimer's disease (AD).[6]

Huperzia serrata (Thunb. ex Murray) Trev.



huperzine A (*hupA*)

Figure 1.1. *H. serrata* (Thunb. Ex Murray) Trev.[7] and structure of hupA.

According to Ayer, A.W., *Lycopodium* alkaloids can be grouped into four classes: the lycopodine class, the lycodine class, the fawcettimine class and the miscellaneous class (Figure 1.2).[8] Representative compounds for these classes are lycopodine, lycodine, fawcettimine and phlegmarine, respectively.[2]

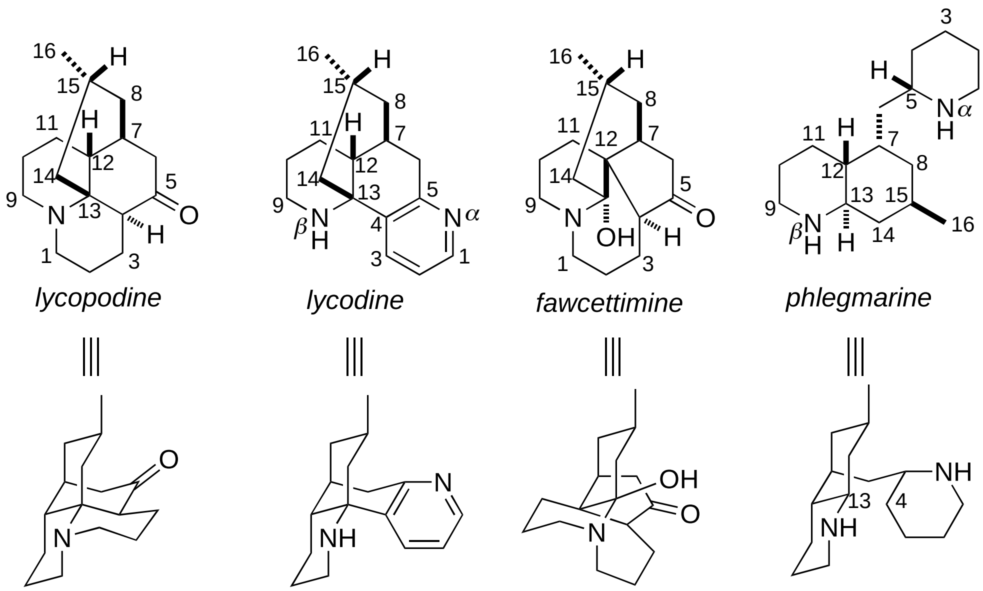
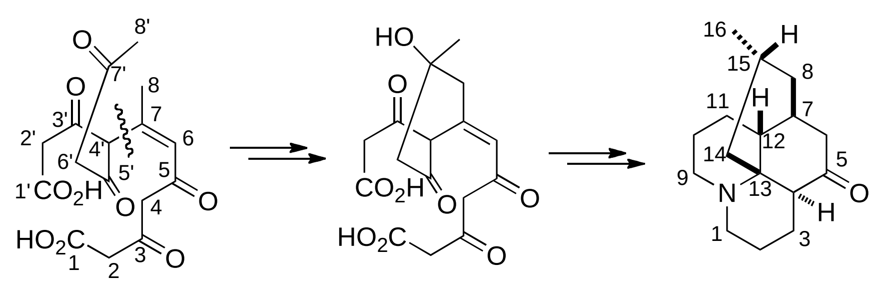


Figure 1.2. Representative compounds of the four classes of *Lycopodium* alkaloids.

The carbon numbering notation for the *Lycopodium* alkaloids is based on Conroy's biogenetic proposal, in which the skeletons of lycopodine and other *Lycopodium* alkaloids were suggested to be made up of two molecules of 3,5,7-triketooctanoic acid or its equivalent (Scheme 1.1).[9]

Scheme 1.1. Conroy's biogenetic proposal and the numbering notation for *Lycopodium* alkaloids.



1.1 **1.2** *lycopodine*

1.2 Fawcettimine Class

Since the isolation of the first member, fawcettimine (also known as Burnell's base), by Burnell, R. H. from *Lycopodium fawcettii* collected in the Blue Mountain Range of

Jamaica in 1959,[10] more than 80 alkaloids in this class have been isolated.[2,4c,11] Some of the alkaloids are selected and shown in Figure 1.3.

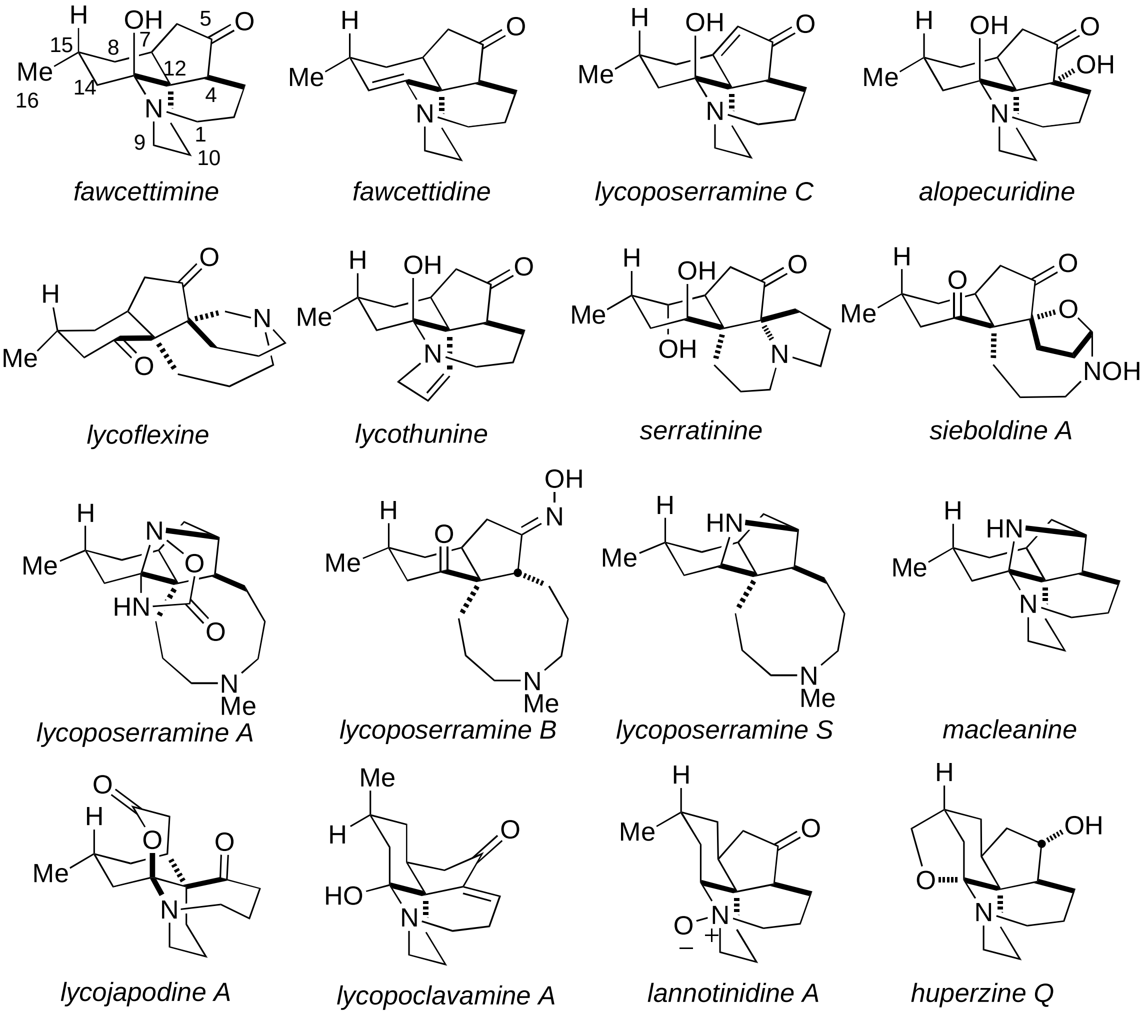
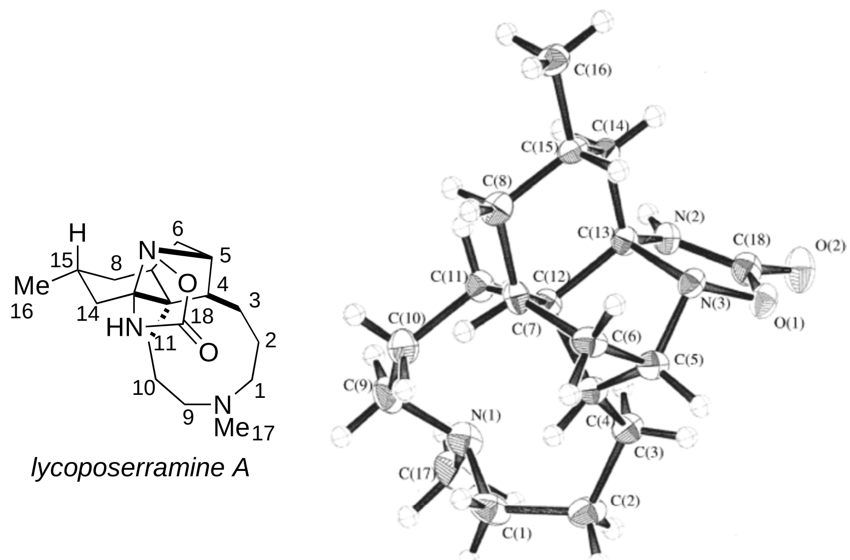


Figure 1.3. Selected fawcettimine class alkaloids.

Typically, members in this class contain a *cis*-fused 6,5-carbocyclic ring core connected to an azonine ring with an all-carbon quaternary center. The *N* atom of azonine ring can be methylated (for example: lycoposerramine A,[12] B[13]) or connected to *C*-13 to form carbinolamine (for example: fawcettimine, lycojapodine A[4]). For most of the alkaloids, the methyl group at *C*-15 adopted a *R* configuration. The only known exception is lycopoclavamine A, whose configuration at *C*-15 is *S*.[4c]

From those fawcettimine class alkaloids, lycoposerramine A was chosen as our ultimate target for total synthesis. Lycoposerramine A was isolated by Takayama, H. and coworkers from *Lycopodium serratum* Thunb = *Huperzia serrata* (Thunb.) Trev. in 2001 (Figure 1.4).[12] Its densely fused pentacyclic ring system (containing 5-, 6-, and 9-membered rings), as well as the 6 stereocenters (2 of them are quaternary centers) render it a challenging and charming target for total synthesis.[14] It is also the first natural product known to contain an oxadiazolidinone moiety, whose structure was verified by X-ray crystallographic analysis.[12]



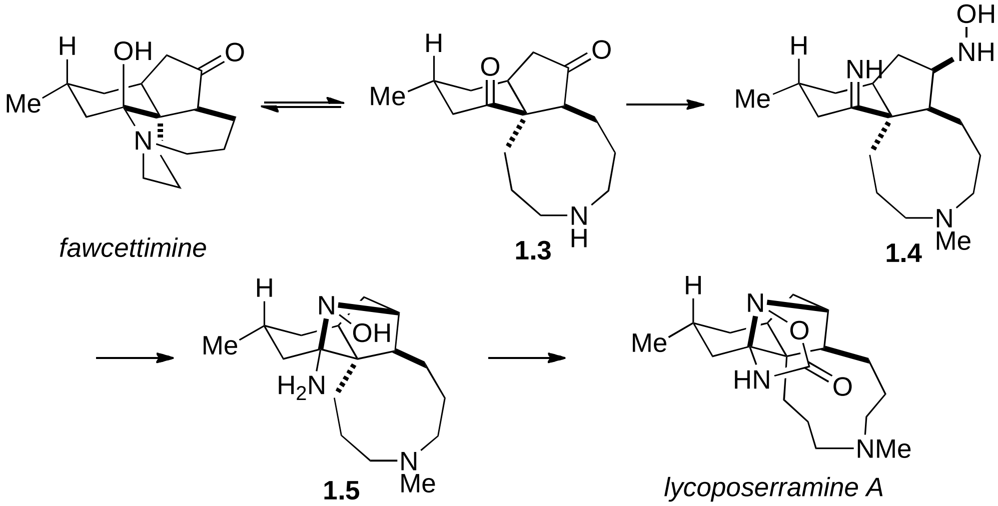
lycoposerramine A

X-ray structure of *lycoposerramine A*

Figure 1.4. Lycoposerramine A and its X-ray structure.[15]

The absolute configuration of lycoposerramine A was not determined in the isolation paper (ORD (c 0.00058 g/mL, $CHCl_3$) $[\Phi]_{589}$ −16°, $[\Phi]_{339}$ −154°, $[\Phi]_{256}$ −632°, $[\Phi]_{245}$ 0°, $[\Phi]_{230}$ +342°, $[\Phi]_{213}$ +89°). The authors suggested that lycoposerramine A could be biosynthetically derived from fawcettimine via *N*-methylation, selective hydroxylamine and imine formation followed by cyclization (Scheme 1.2). Thus, the absolute configuration of lycoposerramine A should be the same as fawcettimine.[12]

Scheme 1.2. Hypothetical biogenetic route from fawcettimine to lycoposerrramine A.



1.3 Bioactivities of *Lycopodium* Alkaloids

To date, the *Lycopodium* alkaloids are best known for their acetylcholinesterase (AChE) inhibitory activity, which is very useful for the treatment of Alzheimer's disease (AD).

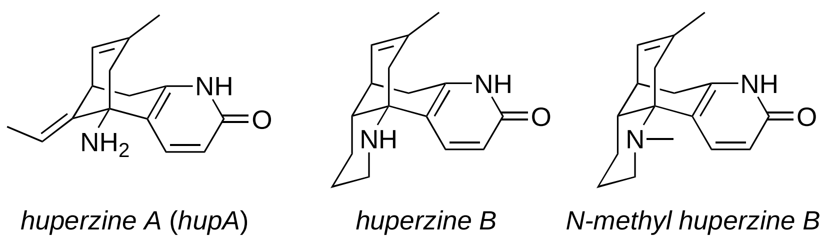


Figure 1.5. Some lycodine class alkaloids possessing AChE inhibitory activity.

Among those about 250 alkaloids, only a few members belonging to the lycodine class, such as huperzine A (hupA), huperzine B,[5] and *N*-methylhuperzine B,[16] were found to possess this activity (Figure 1.5).[2] In particular, hupA was found to be a reversible, potent, and selective acetylcholinesterase inhibitor (AChEi) and showed promise in the treatment of Alzheimer's disease (AD) and myasthenia gravis (MG).[5,6]

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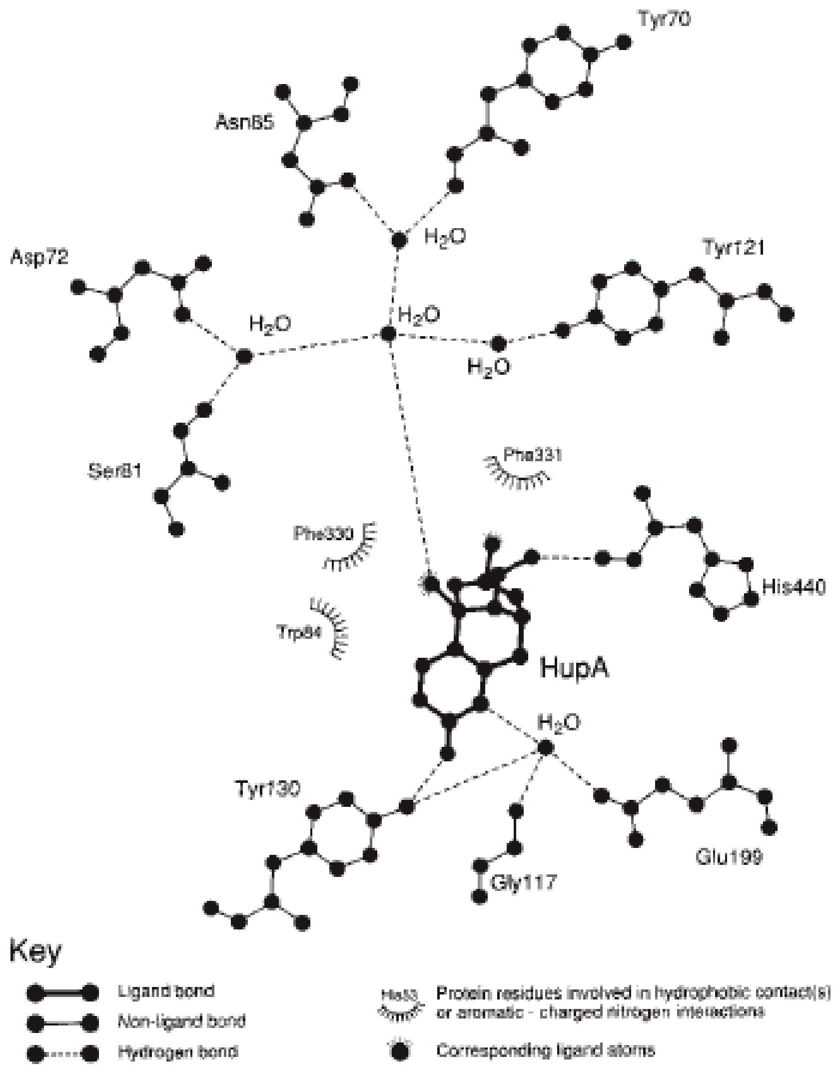


Figure 1.6. Schematic figure showing the principal interactions between TcAChE and hupA.[18]

The X-ray crystal structure of *Torpedo californica* AChE (TcAChE)-hupA complex shows that hupA binds tightly and specifically to the active-site gorge of AChE by direct hydrogen bonds, water molecule mediated hydrogen bonds, cation-π interactions, as well as hydrophobic interactions (Figure 1.6).[17]

The Tang group compared the inhibitory effects of hupA on AChE and BuChE with some known anti-AD drugs: tacrine, physostigmine, galantamine, and donepezil (Figure 1.7).

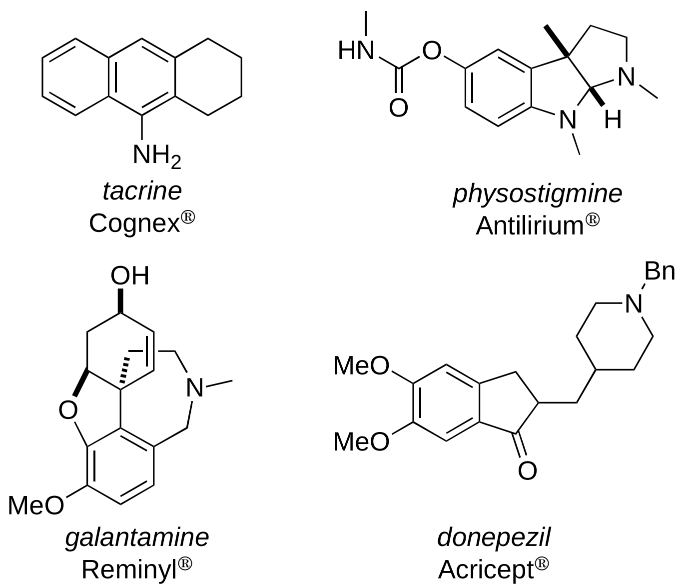


Figure 1.7. Some drugs used to treat Alzheimer's disease (AD).

It was found that hupA inhibited the activity of AChE in the rat cortex al low as 10 nM. The 50% inhibitory concentration (IC_{50}) was estimated to be 82 nM (Table 1.1). More significantly, hupA showed the highest BuChE/AChE ratio, which is desirable for anti-AD drugs that target the cholinergic system.[19]

Table 1.1. Effects of HupA and other cholinesterase inhibitors on AChE activity in the rat cortex and BuChE activity in rat serum *in vitro*.[20]

Cholinesterase inhibitor	$IC_{50}{}^{a}$ (μM)		Ratio of IC_{50} (BuChE/AChE)
	AChE	BuChE	
hupA	0.082	74.43	907.7
physostigmine	0.251	1.26	5.0
galantamine	1.995	12.59	6.3
donepezil	0.010	5.01	501.0
tacrine	0.093	0.074	0.8

[a] The cortex homogenate was preincubated for 5 min. with iso-OMPA 0.1 mM. The rate of color production was measured spectrophotometrically at 440 nm.

Double-blind and placebo-controlled clinical trials demonstrated that hupA produced significant improvements in memory deficiencies in aged patients and patients with AD. Furthermore, both animal and clinical safety testings showed that hupA was devoid of unexpected toxicity, particularly the dose-limiting hepatotoxicity induced by tacrine.[21]

HupA has been approved as the drug for treatment of AD in China, and is marketed in USA as a dietary supplement (as powdered *H. serrata* in tablet or capsule format).[2]

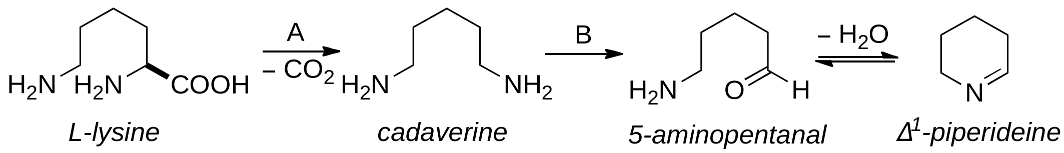
Besides the inhibition of AChE, some anti-microbial activities[22] and anti-cancer activity[23] were also reported for some of the Lycopodium alkaloids. However, no significant bioactivity was reported for our target molecule: lycoposerramine A.[12]

1.4 Biosynthesis of *Lycopodium* Alkaloids

To date, very few biosynthetic studies have been performed with *Lycopodium* alkaloids due to the difficulties in growing these plants. Club mosses are not abundant, grow very slowly and are only found in very specialized habitats. Wild plants that are transferred to greenhouse or other growth environments grow very slowly and do not survive for more than a few months.[2] In vitro tissue propagation of some of the species has just been achieved recently.[24]

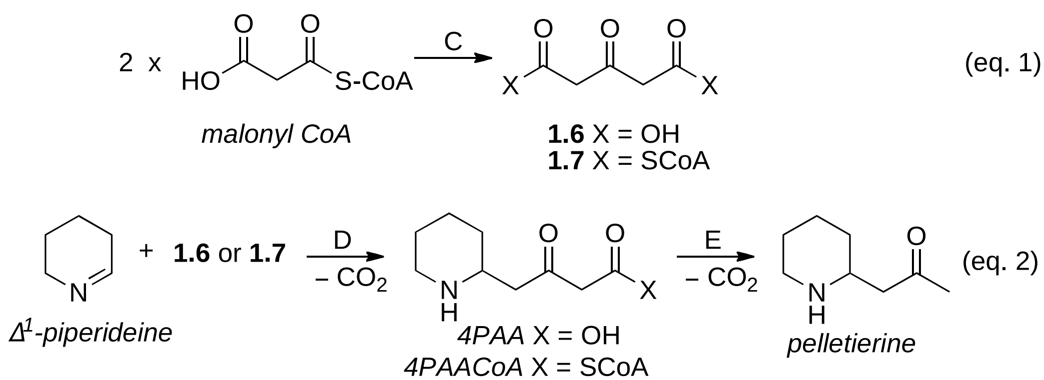
Despite these limitations, several feeding experiments were conducted on club mosses grown in the wild and have shed light on the biosynthetic route for this important group of alkaloids. It was found that the entry point of the biosynthetic pathway is the decarboxylation of L-lysine (by lysine decarboxylase, enzyme A) to form cadaverine. This could be converted to 5-aminopentanal (by diamine oxidase, enzyme B) followed by condensation to form Δ^1-piperideine (Scheme 1.3).[25]

Scheme 1.3. Proposed biosynthetic pathway to Δ^1-piperideine.



Alternatively, a Claisen condensation of two molecules of malonyl CoA could afford one molecule of acetonedicarboxylic acid CoA ester (by a ketosynthase, enzyme C), which could either be hydrolyzed to the free acid (**1.6**) or further activated to its bisCoA thioester (**1.7**) (eq. 1, Scheme 1.4).[26]

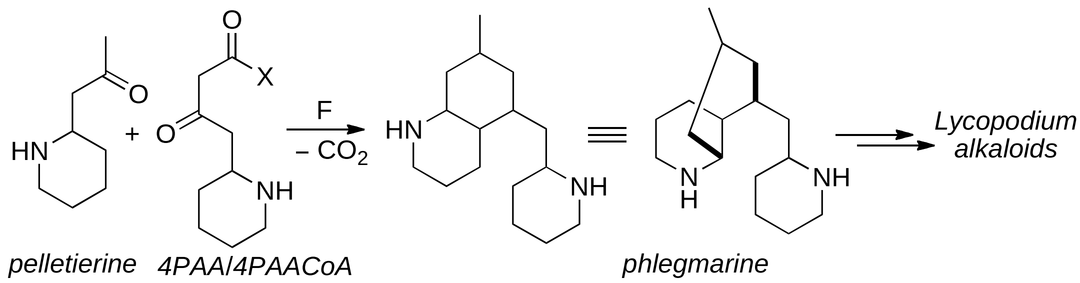
Scheme 1.4. Proposed biosynthetic pathway to pelletierine.



After condensation of **1.6** or **1.7** with Δ^1-piperideine by an unknown enzyme D, 4-(2-piperidyl)acetoacetate (4PAA) or 4-(2-piperidyl)acetoacetyl CoA (4PAACoA) could be formed. This could then be decarboxylated to give pelletierine (eq. 2, Scheme 1.4),[26] the first general intermediate to *Lycopodium* alkaloids.[2]

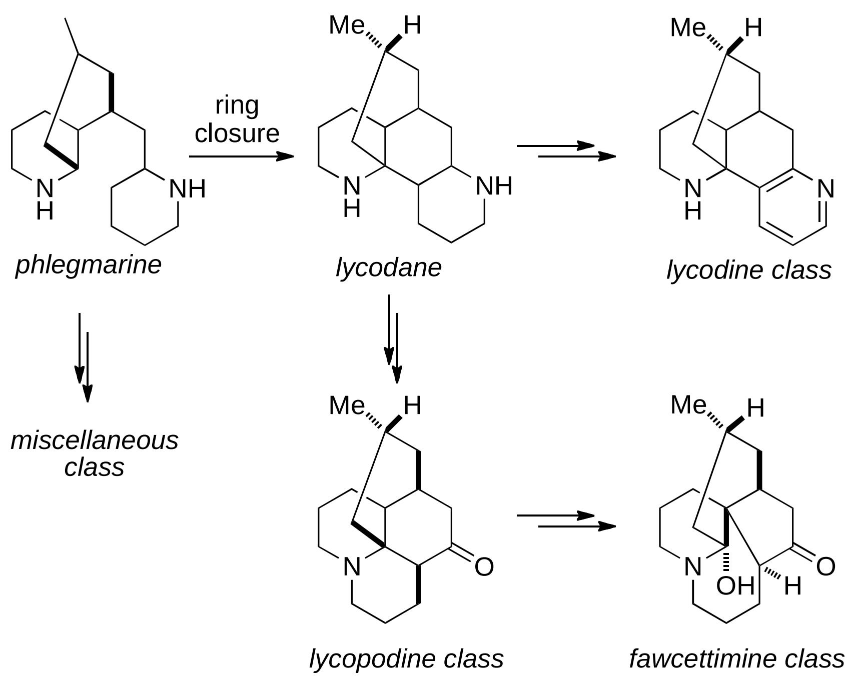
Pelletierine and 4PAA/4PAACoA or derivatives thereof, could then be coupled (by unknown enzyme(s) F) to afford phlegmarine, from which other *Lycopodium* alkaloids could be formed (Scheme 1.5).[26,27]

Scheme 1.5. Proposed biosynthetic pathway to *Lycopodium* alkaloids.



For example, phlegmarine could be cyclized to form lycodane, which could be oxidized to lycodine class alkaloids or rearranged to lycopodine class alkaloids (Scheme 1.6).[27] The conversion of lycopodine class to fawcettimine class alkaloids was also proposed.[28]

Scheme 1.6. Phlegmarine as the general intermediate to all *Lycopodium* alkaloids.



1.5 Conclusion

The *Lycopodium* alkaloids are a large group of structurally related, yet diverse quinolizine-, pyridine-, or α-pyridone-type alkaloids isolated from club moss *Lycopodium* (sensu lato). Some of the alkaloids, especially Huperzine A (hupA), were found to possess potent acetylcholinesterase inhibitory activity, and showed promising results in the treatment of Alzheimer's disease (AD). Due to the difficulties in growing club mosses, very few biosynthetic studies have been performed on the *Lycopodium* alkaloids. Some feeding experiments have showed that they are L-lysine derived alkaloids. From those *Lycopodium* alkaloids, lycoposerramine A was chosen as our ultimate target for total synthesis because of its challenging structural motif.

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Chapter 2

Synthetic studies of Fawcettimine Class Alkaloids

by Other Groups

2.1 Introduction

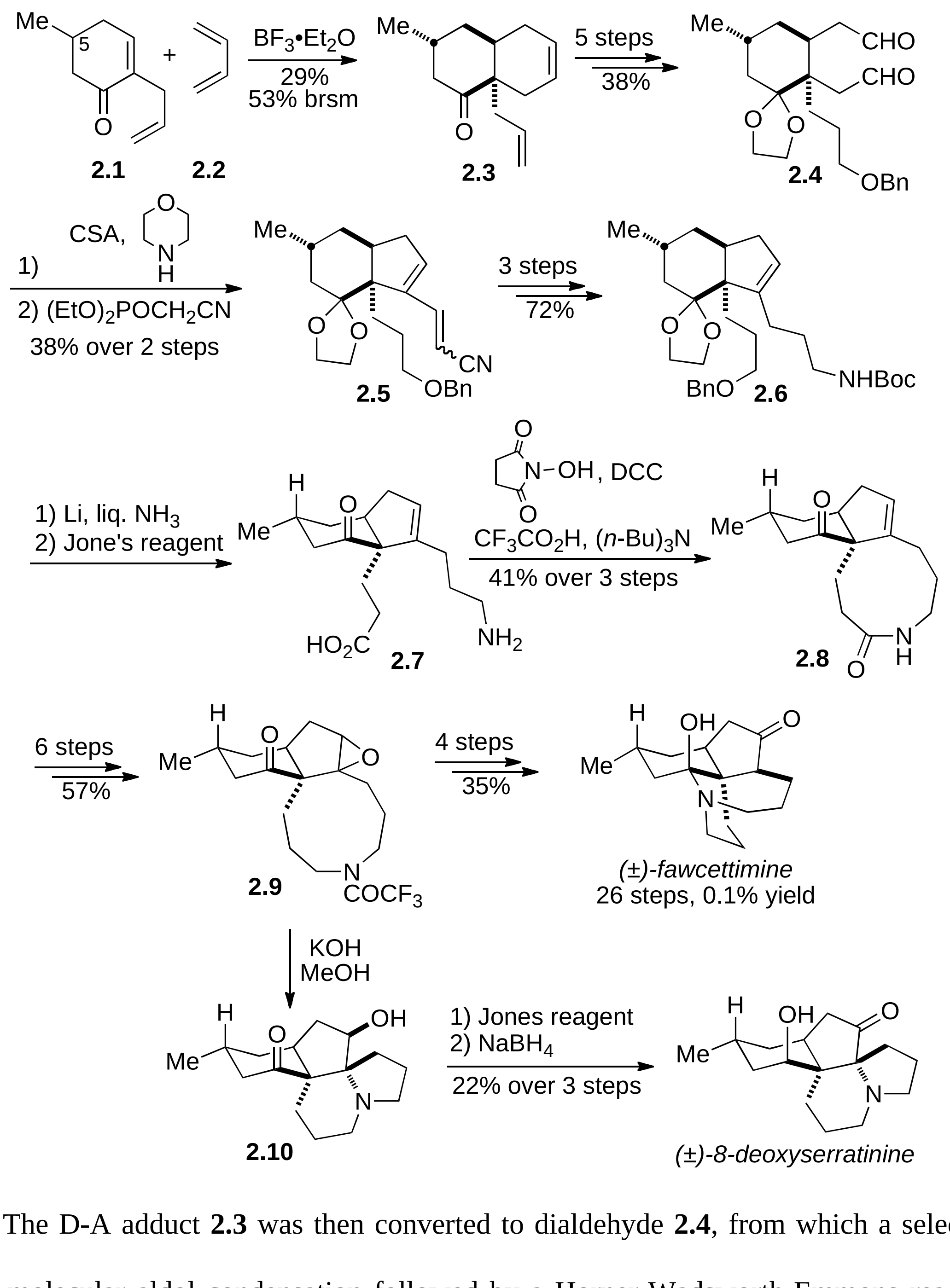
The fawcettimine class of *Lycopodium* alkaloids presents significant challenges for total synthesis and has been attracting increasing attention from the synthetic community.[1] For lycoposerramine A, our ultimate target, no total synthesis has been achieved. There is only a single reported synthesis of the tetracyclic core.[2] The total syntheses of other members of the family, such as fawcettimine, fawcettidine, lycoposeerramine B, lycoflexine, etc., have been accomplished. In particular, fawcettimine, the representative compound of this family, has inspired substantial interest from synthetic groups, resulting in five total (two racemic,[4a,4b,5] three enantioselective[7,9,13]) and two formal syntheses[3].

From a strategic vantage, the critical challenge in contemplating the synthesis of those fawcettimine class alkaloids is the formation of the *cis*-fused 6,5-carbocyclic core containing one all-carbon quaternary center. Some of the representative syntheses or synthetic approaches are selected and presented below.

2.2 Inubushi's syntheses of (±)-fawcettimine and (±)-8-deoxyserratinine

In 1979, the Inubushi group reported the first total syntheses of (±)-fawcettimine and (±)-8-deoxyserratinine (Scheme 2.1).[4a,4b] Their syntheses started with a Diels-Alder reaction (D-A) between enone **2.1** and 1,3-butadiene (**2.2**) to make D-A adduct **2.3**, with concurrent formation of the all-carbon quaternary center. The addition of **2.2** was found to take place stereoselectively from the opposite face of the *C*-5 methyl group of enone **2.1**.[4c] This strategy, using the *C*-5 methyl group to control the facial selectivity of cyclohex-2-en-1-ones, was widely adopted in later syntheses of fawcettimine and many other family members (*vide infra*).

Scheme 2.1. Total syntheses of (±)-fawcettimine and (±)-8-deoxyserratinine by the Inubushi group.



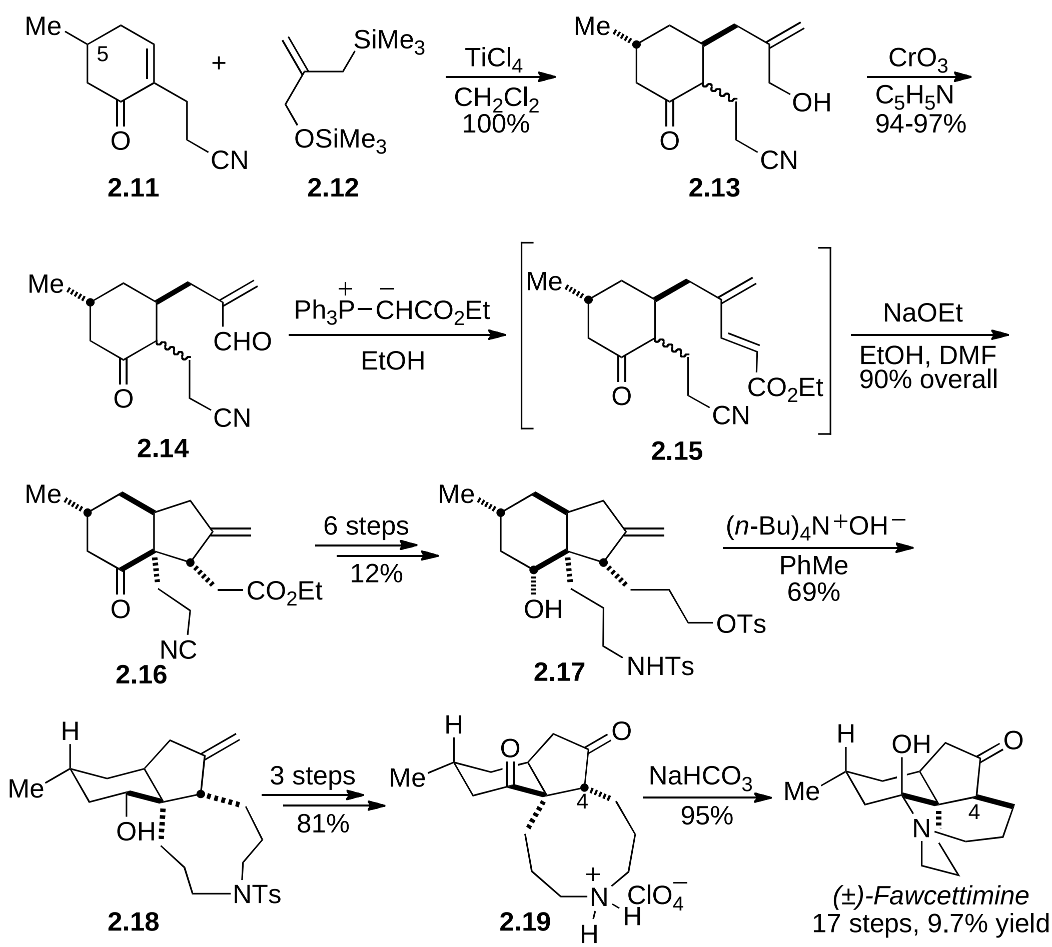
The D-A adduct **2.3** was then converted to dialdehyde **2.4**, from which a selective intra-molecular aldol condensation followed by a Horner-Wadsworth-Emmons reaction provided the *cis*-fused 6,5-carbocylcle **2.5**. Carbocycle **2.5** contains all of the carbon skeleton for fawcettimine and 8-deoxyserratinine, with the formation of the azonine ring being the main hurdle. To this end, **2.5** was converted to amino acid **2.7**, from which an intra-molecular lactam formation afforded the tricycle **2.8** in moderate yield. Tricycle **2.8** was then transformed to (±)-fawcettimine and (±)-8-deoxyserratinine in several steps, via the common intermediate epoxide **2.9**.

The Inubushi group accomplished the first total synthesis of (±)-fawcettimine in 26 steps, with a 0.1% overall yield from commercially available materials.

2.3 Heathcock's total synthesis of (±)-fawcettimine

In 1986, the Heathcock group reported a much more efficient synthesis of (±)-fawcettimine (Scheme 2.2).[5] Their synthesis began with a Sakurai reaction between cyano enone **2.11**[6] and allylsilane **2.12**. The *C*-5 methyl group of enone **2.11** guided the addition of **2.12** from the opposite face. The allylic alcohol **2.13** thus obtained was then oxidized to aldehyde **2.14**, which was converted to *cis*-fused 6,5-carbocylcle **2.16** by a one-pot Horner-Wadsworth-Emmons reaction and an intra-molecular Michael addition. After several steps, the *cis*-fused 6,5-carbocylcle **2.16** could be transformed to *N*,*O*-ditosyl derivative **2.17**, which set the stage for the construction of the azonine ring. When **2.17** was treated with tetra-*n*-butylammonium hydroxide in toluene under highly diluted condition, the intra-molecular S_N2 reaction took place smoothly, with azonine **2.18** isolated in good yield. Azonine **2.18** was then converted to the diketo amine perchlorate salt **2.19**, from which the stereocenter of *C*-4 was inverted and (±)-fawcettimine was obtained. The total synthesis required 17 steps from commercially available materials and was achieved in 9.7% overall yield.

Scheme 2.2. Total synthesis of (±)-fawcettimine by the Heathcock group.

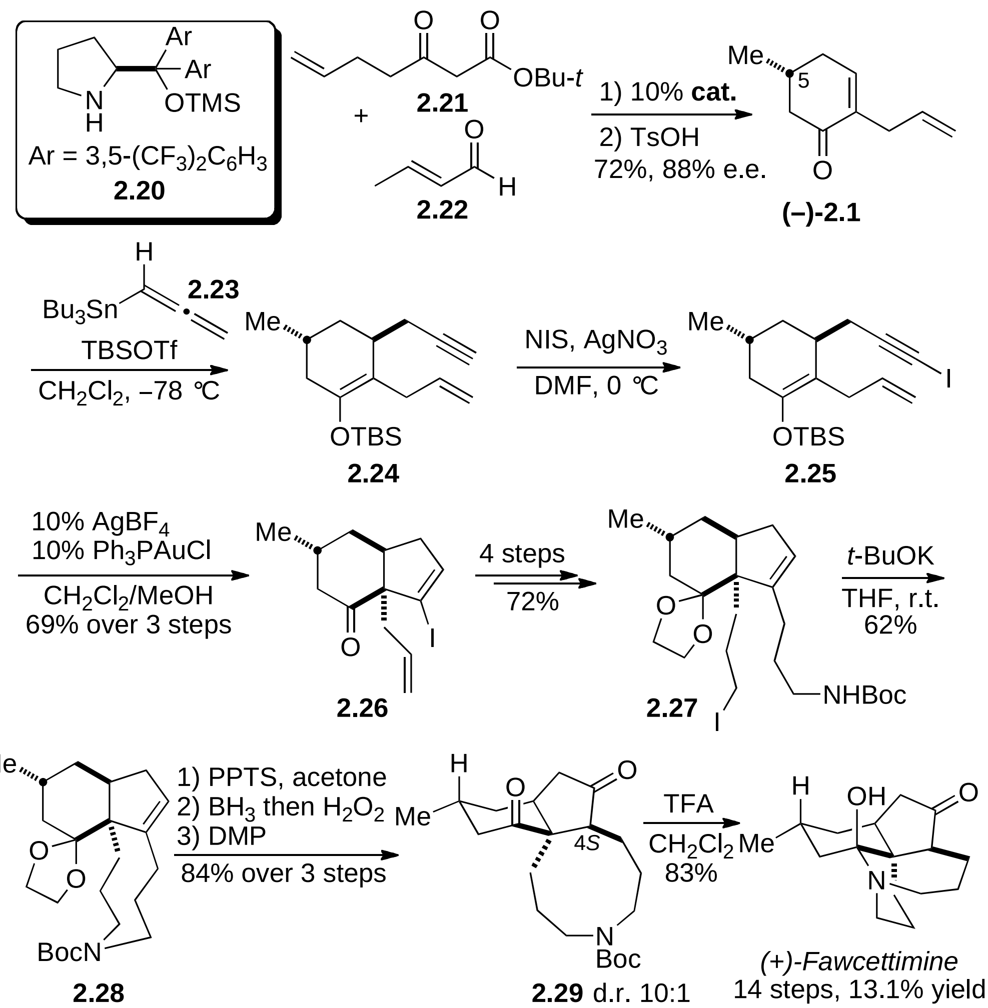


From their experiment, the Heathcock group concluded that the control of stereochemistry at *C*-4 is not necessary, since fawcettimine is the sole thermodynamic product. This landmark observation was exploited in the later reported syntheses of fawcettimine and many other family members, which dramatically improved the synthetic efficiency (*vide infra*).

2.4 Toste's total synthesis of (+)-fawcettimine

In 2007, the Toste group reported the first total synthesis of (+)-fawcettimine.[7] Their synthesis commenced with enantioenriched enone (**–**)-**2.1** (88% e.e.), which could be synthesized from **2.21** and **2.22** by a one-pot organocatalytic Robinson annulation and decarboxylation.[8]

Scheme 2.3. Total synthesis of (+)-fawcettimine by the Toste group.



From enone (**–**)-**2.1**, a *C*-5 methyl group directed, TBSOTf initiated conjugate addition of allenyltributylstannane (**2.23**) afforded TBS enol ether **2.24** stereoselectively, which was transformed to the *cis*-fused 6,5-carbocycle **2.26** by a sequential iodination and gold(I)-catalyzed cyclization. The *cis*-fused 6,5-carbocylcle **2.26** obtained was then converted to iodide **2.27** via several steps. Subsequent S_N2 reaction provided the azonine **2.28** in good yield, which was next converted to diketone **2.29** by a 3-step sequence: ketal deprotection, hydroboration/oxidation, and Dess-Martin oxidation.

It is worthy of note that the hydroboration step was found not to be stereoselective, which afforded a mixture of alcohols after H_2O_2 mediated oxidation. However, upon oxidation to ketone stage, a diastereomeric ratio (d.r.) of 10:1, in favor of the desired 4*S* epimer **2.29** was observed, which is consistent with the studies of the Heathcock group.

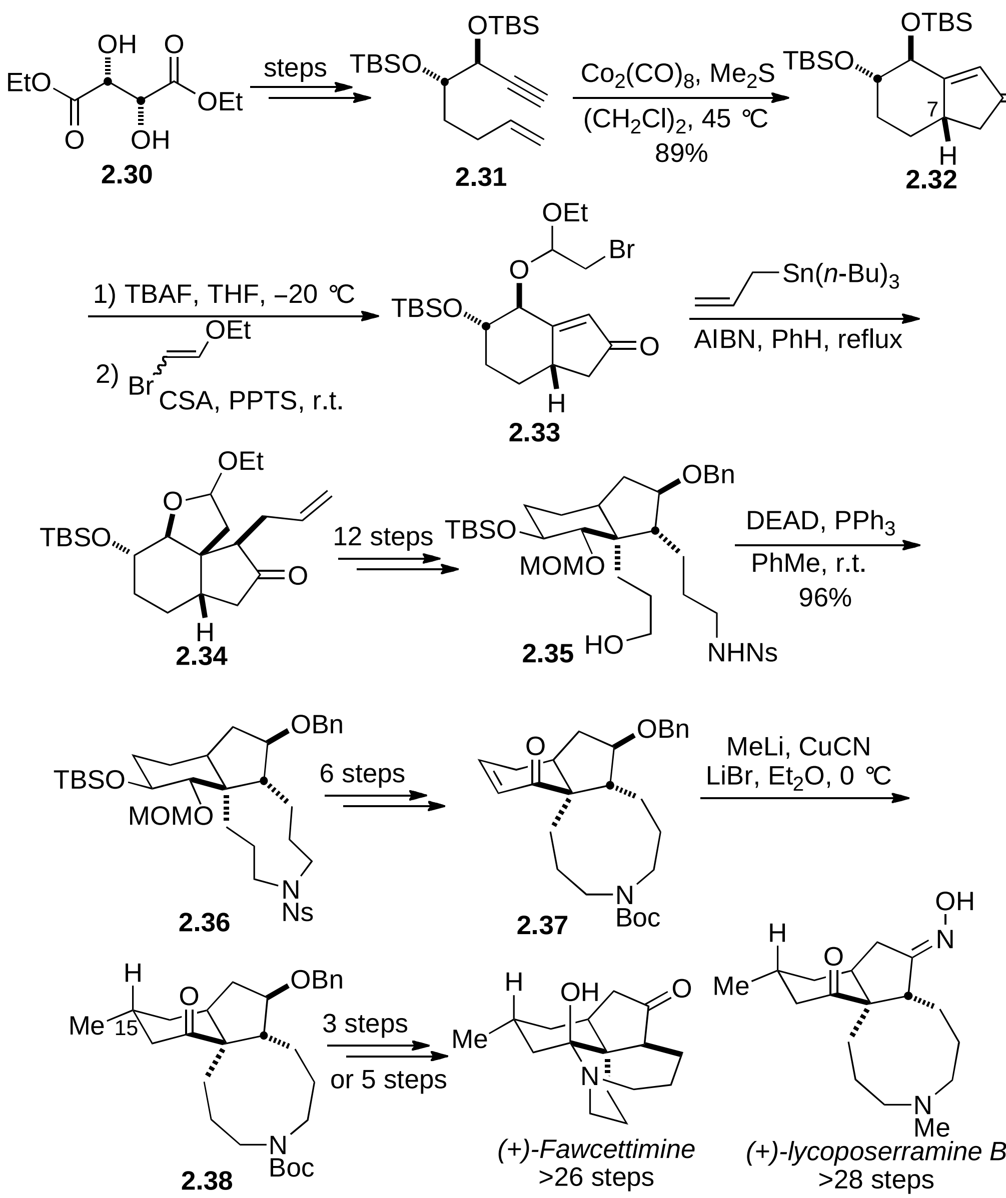
Finally, removal of the Boc group on **2.29** completed the first asymmetric synthesis of (+)-fawcettimine. This very efficient synthesis requires just 14 steps from commercially available materials and gives a 13.1% overall yield.

2.5 Mukai's syntheses of (+)-fawcettimine and (+)-lycoposerramine B

In 2010, the Mukai group reported their total synthesis of (+)-fawcettimine, as well as the first total synthesis of (+)-lycoposerramine B.[9] Their asymmetric synthesis relied on an intra-molecular Pauson-Khand reaction of enyne **2.31** to forge the 6,5-carbocycle **2.32**, which contains the desired stereochemistry at *C*-7 (fawcettimine numbering).[10a] The enyne **2.31** was obtained from (+)-diethyl L-tartrate (**2.30**) via several steps, which is a widely available and very cheap chiral source.[10b]

Installation of the all-carbon quaternary center for fawcettimine and lycoposerramine B on 6,5-carbocycle **2.32** followed a 3-step sequence: selective deprotection of one of the TBS ethers, acid catalyzed mixed ketal formation, and an intra-molecular radical cyclization/allyl coupling reaction cascade. Tricycle **2.34** obtained was converted to nosylate **2.35**, which was cyclized under Fukuyama-Mitsunobu reaction conditions (PPh_3, DEAD, PhMe, r.t.) to afford azonine **2.36** in 96% yield.

Scheme 2.4. Total synthesis of (+)-fawcettimine by the Mukai group.



Azonine **2.36** was next converted to enone **2.37** via several steps, which upon treatment with $Me_2Cu(CN)Li_2$ provided the conjugate addition product **2.38**. The addition of $Me_2Cu(CN)Li_2$ was found to be highly stereoselective, with **2.38** isolated as a single diastereomer, whose stereochemistry at *C*-15 is the desired *R* configuration. Tricycle **2.38** serves as the common intermediate, from which both (+)-fawcettimine and (+)-lycoposerramine B were synthesized.

Mukai's total syntheses of (+)-fawcettimine and (+)-lycoposerramine B require 26 and 28 steps respectively from enyne **2.31**.

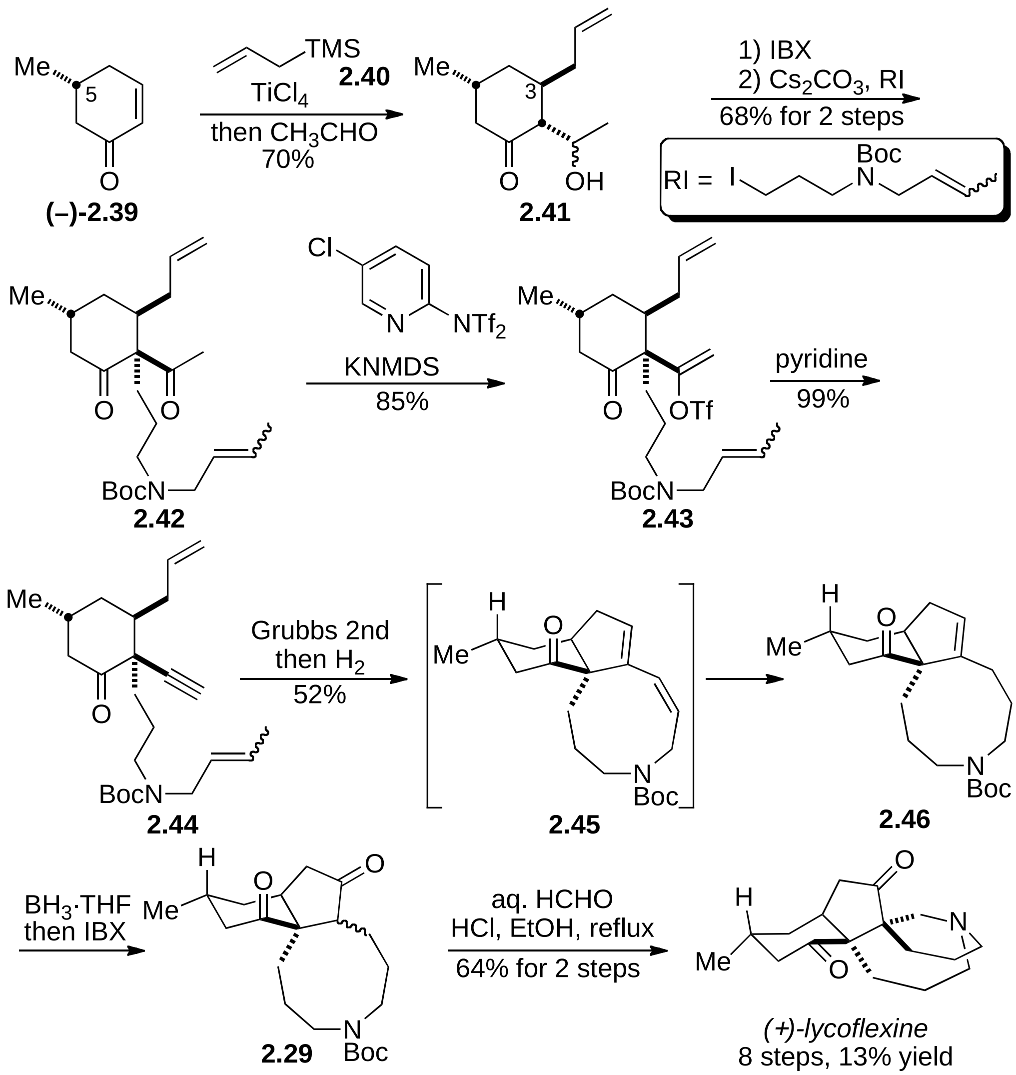
2.6 Ramharter's syntheses of (+)-lycoflexine

In 2010, the Ramharter group reported the first total synthesis of (+)-lycoflexine (Scheme 2.5).[11] Their synthesis started with a tandem Sakurai/aldol sequence that converted enone (–)-**2.39** into alcohol **2.41**. The *C*-5 methyl group of enone **2.39** controlled the addition of allyltrimethylsiliane (**2.40)** so that the stereochemistry at *C*-3 is secured. Oxidation followed by alkylation of **2.41** afforded carbamate **2.42**, with concurrent formation of the all-carbon quaternary center. The acyl group of **2.42** was next converted to an alkyne by a 2-step sequence: enol triflate formation and elimination. The dienyne **2.44** obtained was then submitted to an impressive one-pot dienyne ring-closing metathesis (RCM) and selective hydrogenation conditions, which provided azonine **2.46** in admirable 52% yield.

From **2.46**, a one-pot hydroboration and oxidation afforded diketone **2.29**, the same intermediate as in Toste's (+)-fawcettimine synthesis (Scheme 2.3), which was converted to (+)-lycoflexine by a one-pot Boc deprotection and biomimetic[12] Mannich reaction.

This remarkably concise total synthesis of (+)-lycoflexine requires only 8 steps from (–)-**2.39**, with an overall yield of 13%.

Scheme 2.5. Total synthesis of (+)-lycoflexine by the Ramharter group.

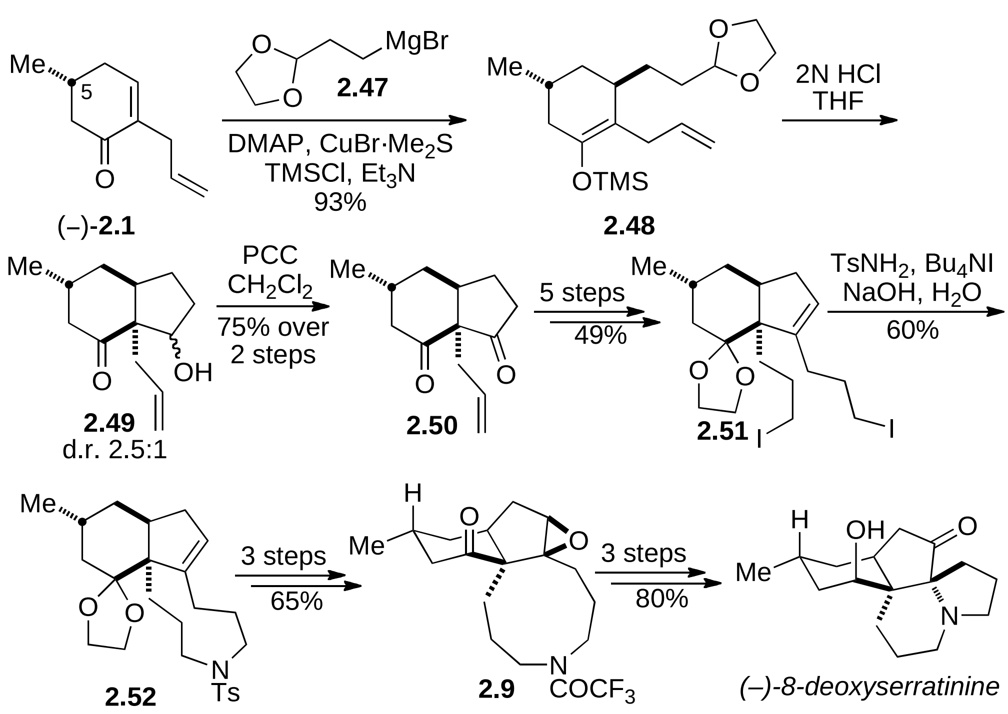


2.7 Yang's syntheses of (–)-8-deoxyserratinine, (+)-fawcettimine, and (+)-lycoflexine.

Quite recently, Yang Y. and coworkers reported their unified total synthesis of (–)-8-deoxyserratinine, (+)-fawcettimine, and (+)-lycoflexine (Scheme 2.6, 2.7).[13] The syntheses commenced with the conjugate addition of Grignard reagent **2.47** to enone (–)-**2.1**, the same enone used by the Toste group in their (+)-fawcettimine synthesis. Again, the C-5 methyl group of enone controlled the newly formed stereochemistry at C-3. The TMS enol ether obtained above, upon treatment with warm 2N HCl, underwent a cascade desilylation, acetal hydrolysis, and intra-molecular aldol cyclization to give *cis*-fused 6,5-carbocycle **2.49** (d.r. 2.5:1) with one all-carbon quaternary center in good yield. After several steps, **2.49** was converted to diiodide **2.51**, which could then be cyclized to afford azonine **2.52** in good yield.

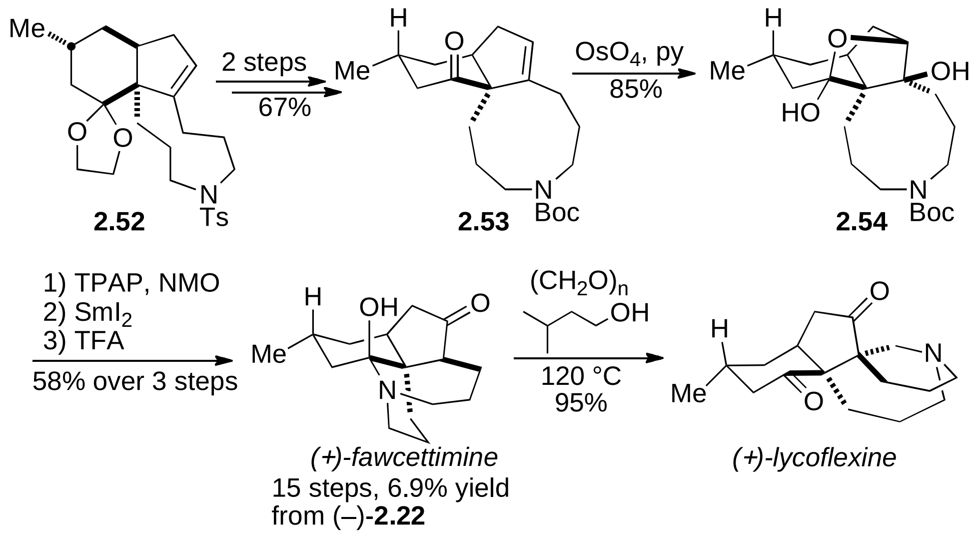
Azonine **2.52** was next converted to epoxide **2.9**, the same epoxide employed by Inubushi and coworkers in their (±)-8-deoxyserratinine synthesis. Following the procedures described by Inubushi, (–)-8-deoxyserratinine was synthesized.

Scheme 2.6. Yang's synthesis of of (–)-8-deoxyserratinine.



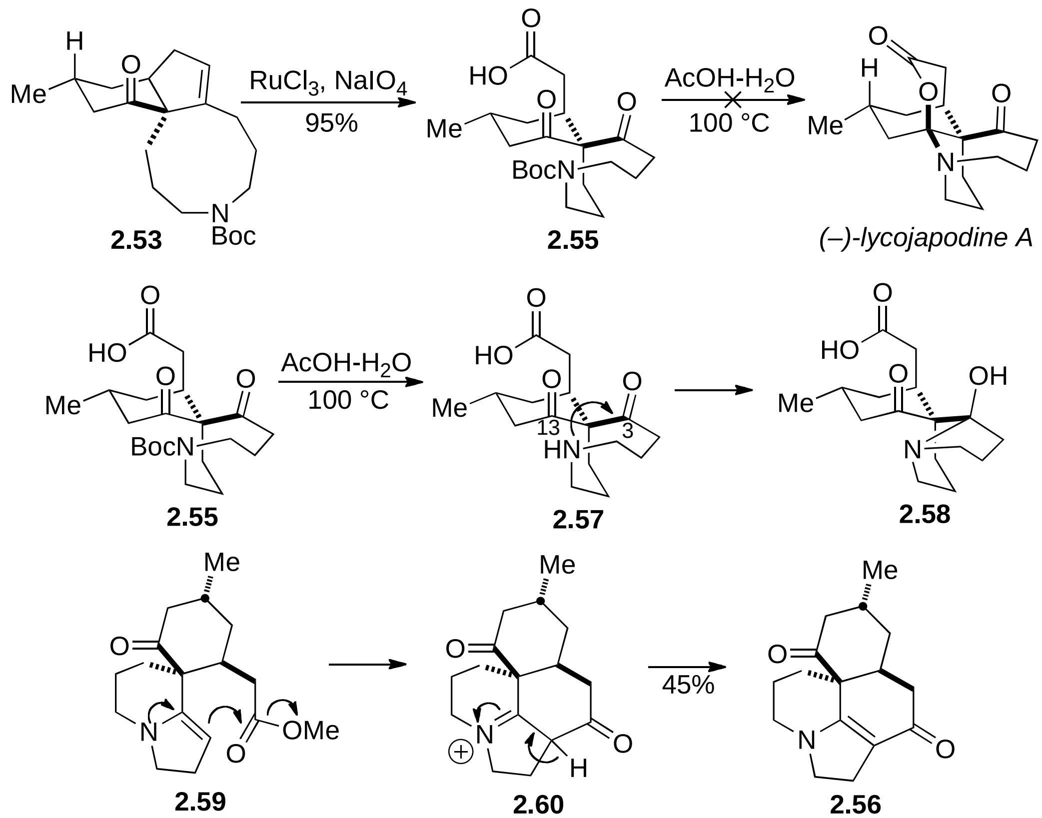
Azonine **2.52** also serves as the common intermediate to (+)-fawcettimine and (+)-lycoflexine (Scheme 2.7). In two steps, **2.52** was converted to carbamate **2.53**, which upon treatment with OsO_4 in pyridine provided, unexpectedly, lactol **2.54**. From **2.54**, the synthesis of (+)-fawcettimine was completed in a 3-step sequence: Ley oxidation, SmI_2 mediated reduction and TFA triggered Boc removal/cyclization. The Yang group accomplished the total synthesis of (+)-fawcettimine in 15 steps from (–)-**2.1**, with a 6.9% overall yield. From (+)-fawcettimine, a biomimetic Mannich reaction[12] afforded (+)-lycoflexine.

Scheme 2.7. Yang's syntheses of (+)-fawcettimine and (+)-lycoflexine.



The conversion of carbamate **2.53** to (–)-lycojapodine A was also attempted (Scheme 2.8).[14] To this end, the alkene moiety of **2.53** was cleaved by a combination of $RuCl_3$ and $NaIO_4$ to give keto acid **2.55**. However, subsequent biomimetic cyclization[15] of **2.55** by treatment of **2.55** in aqueous acetic acid at elevated temperature resulted in no formation of desired (–)-lycojapodine A. Instead, the unnatural alkaloid **2.56** was isolated in 45% yield. The mechanism for the formation of **2.56** was also proposed, in which the free amine of **2.57** attacked the *C*-3 but not the *C*-13 carbonyl to afford hemiaminal **2.58**. Hemiaminal **2.58** then underwent dehydration to form enamine **2.59**, which cyclized onto the ester side chain and rearranged to give **2.56**.[14]

Scheme 2.8. Attempted synthesis of (–)-lycojapodine A.

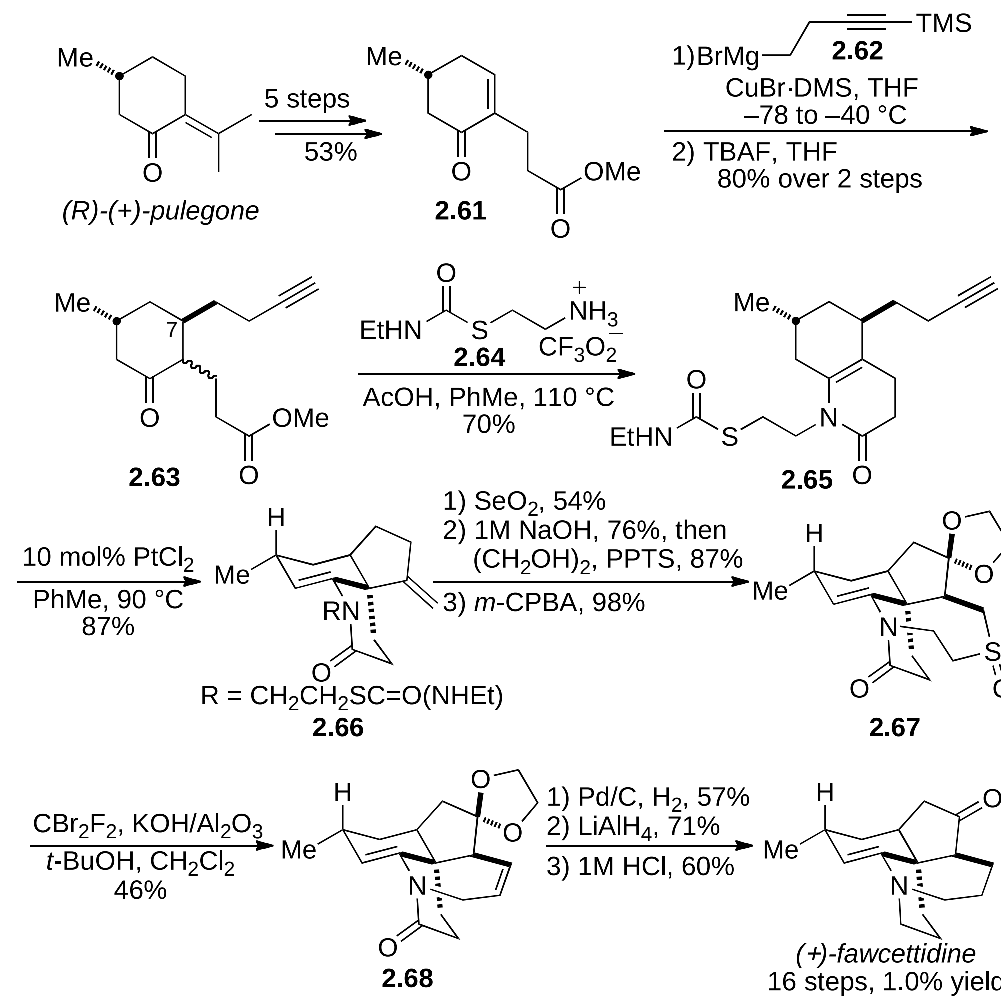


2.8 Dake's total synthesis of (+)-fawcettidine

In 2008, Dake G. R. and coworkers reported the first total synthesis of (+)-fawcettidine (Scheme 2.9).[16] Their asymmetric synthesis employs (*R*)-(+)-pulegone as the chiral source. In 5 steps, (*R*)-(+)-pulegone was transformed to enone **2.61**, which upon treatment with Grignard reagent **2.62** in the presence of CuBr·DMS followed by TBAF mediated desilylation afforded alkyne **2.63** in good yield. Again, the methyl group of enone **2.61** controlled the highly stereoselective formation of *C*-7 (fawcettimine numbering) stereocenter. Alkyne **2.63** obtained was then condensed with amine salt **2.64** to give enamide **2.65**, which underwent an intra-molecular annulation of enamide to alkyne upon treatment with catalytic amount of $PdCl_2$. Tricycle **2.66** was obtained in excellent yield, with concurrent formation of one all-carbon quaternary center. Tricycle **2.66** was next converted to sulfone **2.67** in a 3-step sequence: SeO_2 mediated allylic oxidation, NaOH triggered carbamate removal/conjugate addition, and *m*-CPBA promoted oxidation of sulfide to sulfone. From sulfone **2.67**, a Ramberg-Bäcklund reaction provided alkene **2.68** in moderate yield, from which (+)-fawcettidine was synthesized.

The Dake group accomplished the first total synthesis of (+)-fawcettidine in 16 steps, with a 1.0% overall yield.

Scheme 2.9. Dake's total synthesis of (+)-fawcettidine.

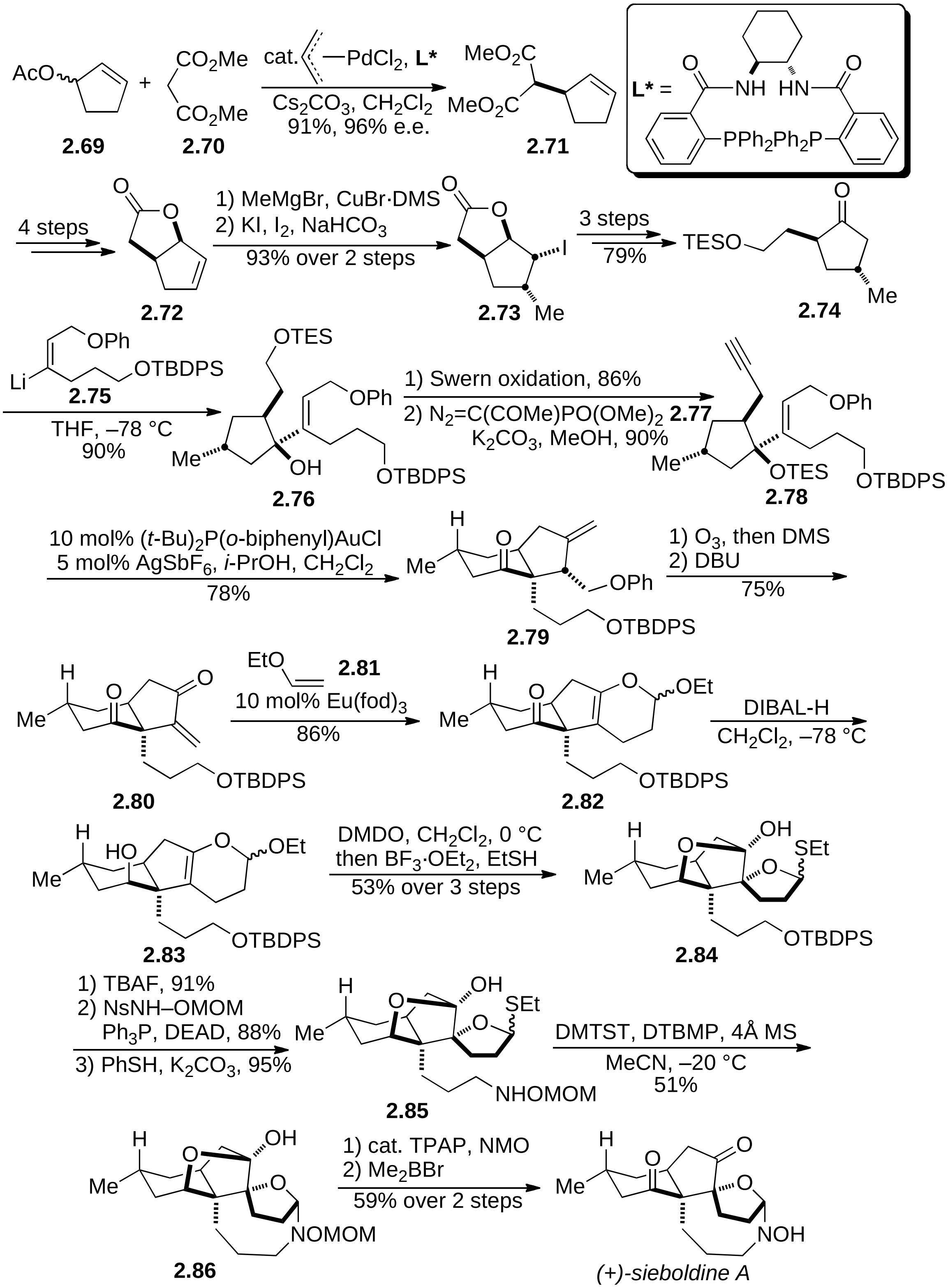


2.9 Overman's total synthesis of (+)-sieboldine A

In 2010, the Overman group reported the first total synthesis of (+)-sieboldine A (Scheme 2.10).[17] Their asymmetric synthesis began with the Tsuji-Trost reaction between 3-acetoxycyclopentene (**2.69**) and dimethyl malonate (**2.70**).[18] The alkylation product **2.71** obtained (96% e.e.) was then converted to cyclopentafuranone **2.72** under reported conditions.[19] Subsequent methylcuprate promoted S_N2' alkylation of **2.72** followed by iodolactonization afforded iodide **2.73**, which was transformed to cyclopentanone **2.74** in 3 steps. Addition of vinyl lithium reagent **2.75** to a solution of **2.74** in THF at –78 ºC delivered allylic alcohol **2.76** as a single diastereomer in excellent yield. Swern oxidation of the primary silyl ether of **2.76**, followed by condensation of the resulting aldehyde with Ohira-Bestmann reagent (**2.77)** afforded alkyne **2.78**, which upon treatment with cationic gold(I) catalyst produced the pinacol-terminated cyclization cascade product **2.79** in 78% yield. Bicycle **2.79** contains the *cis*-fused 6,5-carbocyclic core as well as the all-carbon quaternary center of sieboldine A.

From **2.79**, ozonolysis of the exomethylene group followed by DBU triggered elimination provided enone **2.80**, which was cyclized with ethyl vinyl ether (**2.81**) in the presence of catalytic amount of $Eu(fod)_3$ to give dihydropyran **2.82**. Reduction of the ketone group of **2.82**, followed by epoxidation and BF_3 promoted rearrangement in the presence of EtSH gave rise to thioglycoside **2.84** in 53% yield over 3 steps. Removal of the TBDPS group of **2.84**, followed by Fukuyama-Mitsunobu reaction and removal of the Ns group afforded MOM protected hydroxylamine **2.85**, which set the stage for the azonine ring formation.

Scheme 2.10. Overman's total synthesis of (+)-sieboldine A.



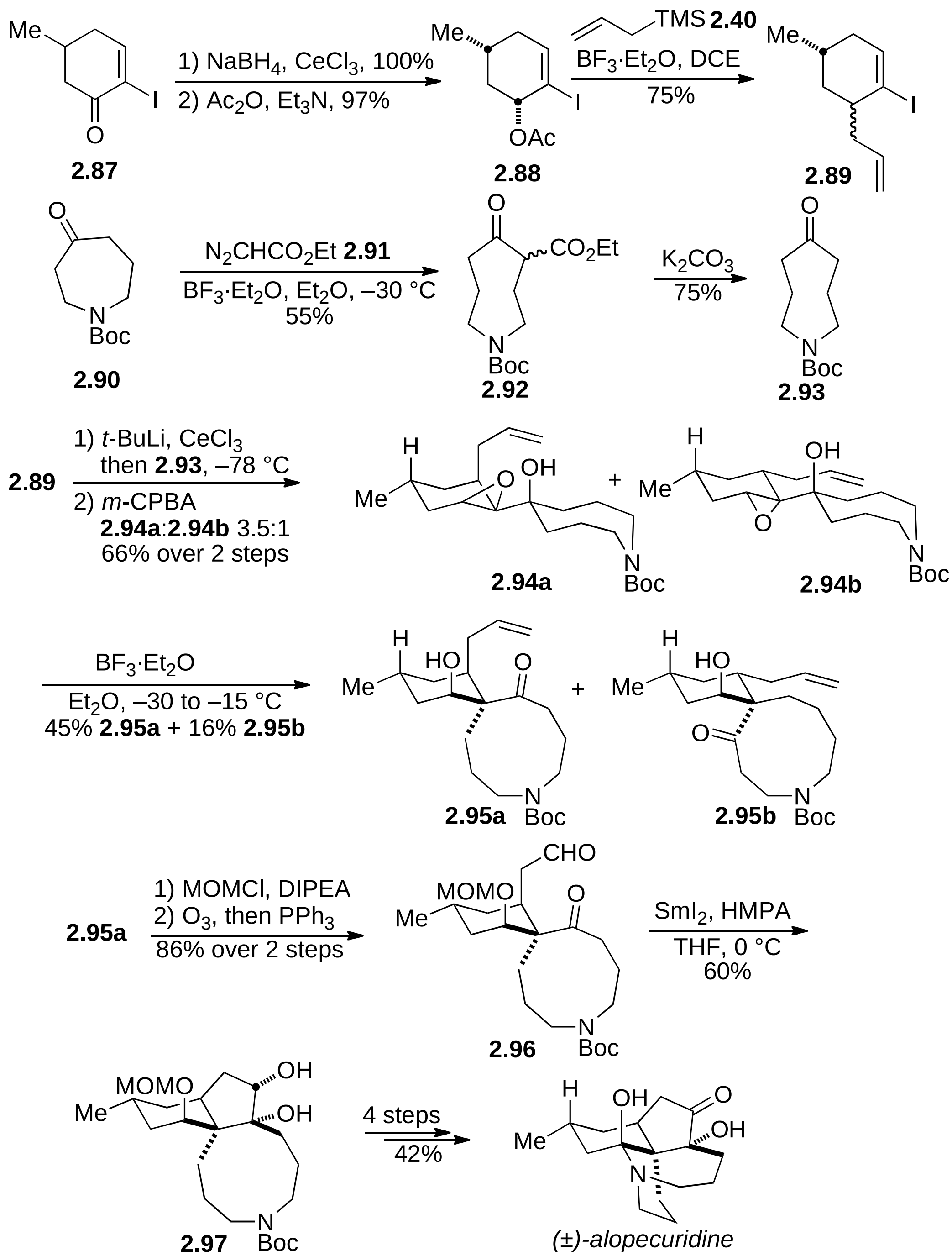
Exposure of **2.85** to dimethyl(methylthio)sulfonium triflate (DMTST) in the presence of 2,6-di-*t*-butyl-4-methylpyridine (DTBMP) at –20 ºC in acetonitrile provided azonine **2.86**, from which a Ley oxidation and removal of the MOM protecting group completed the first total synthesis of (+)-sieboldine A.

2.10 Tu's syntheses of (±)-alopecuridine and (±)-sieboldine A

In 2011, Tu Y. and coworkers reported the first total synthesis of (±)-alopecuridine as well as the biomimetic transformation of (±)-alopecuridine to (±)-sieboldine A.[20] Their synthesis began with the preparation of fragment **2.89** and **2.93** (Scheme 2.11). The fragment **2.89** was made from known iodide **2.87** in a 3-step sequence: Luche reduction of the enone, acetylation of the newly formed allylic alcohol, and BF_3 catalyzed allylation. The other fragment **2.93** was prepared from commercially available azepine **2.90** through a Tiffeneau-Demjanov type reaction with diazoacetic ester **2.91** and subsequent decarboxylation. After lithium iodide exchange, the resulting lithium salt of **2.89** was first transformed to cerium salt and then coupled to **2.93** followed by epoxidation to afford epoxide **2.94** as a mixture of inseparable diastereomers (**2.94a**:**2.94b** 3.5:1). When the diastereomers were treated with $BF_3 \cdot Et_2O$ in Et_2O at low temperature, a semipinacol reaction took place, with the desired azonine **2.95a** isolated in 45% yield. The undesired isomer **2.95b** could be readily separated from the reaction mixture.

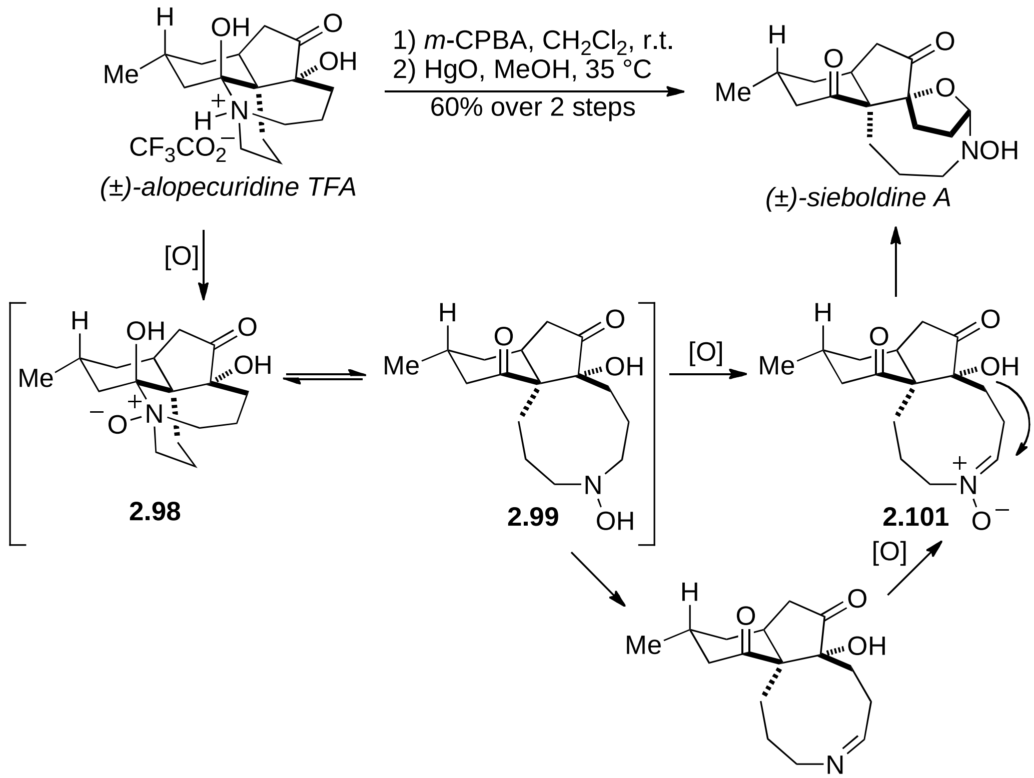
Azonine **2.95a** already contains the all-carbon quaternary center required for alopecuridine and sieboldine A syntheses. From **2.95a**, protection of the free alcohol as MOM ether followed by ozonolysis afforded keto aldehyde **2.96**.

Scheme 2.11. Tu's total synthesis of (±)-alopecuridine.



Upon treatment of **2.98** with SmI_2 at 0 ºC, a stereoselective intra-molecular pinacol coupling took place, with diol **2.97** isolated in 60% yield. Diol **2.97** contains the two contiguous quaternary centers for alopecuridine and sieboldine A. After some adjustment of the oxidation state as well as removal of the protecting groups, the first total synthesis of (±)-alopecuridine was accomplished.

Scheme 2.12. Biomimetic transformation of (±)-alopecuridine to (±)-sieboldine A.

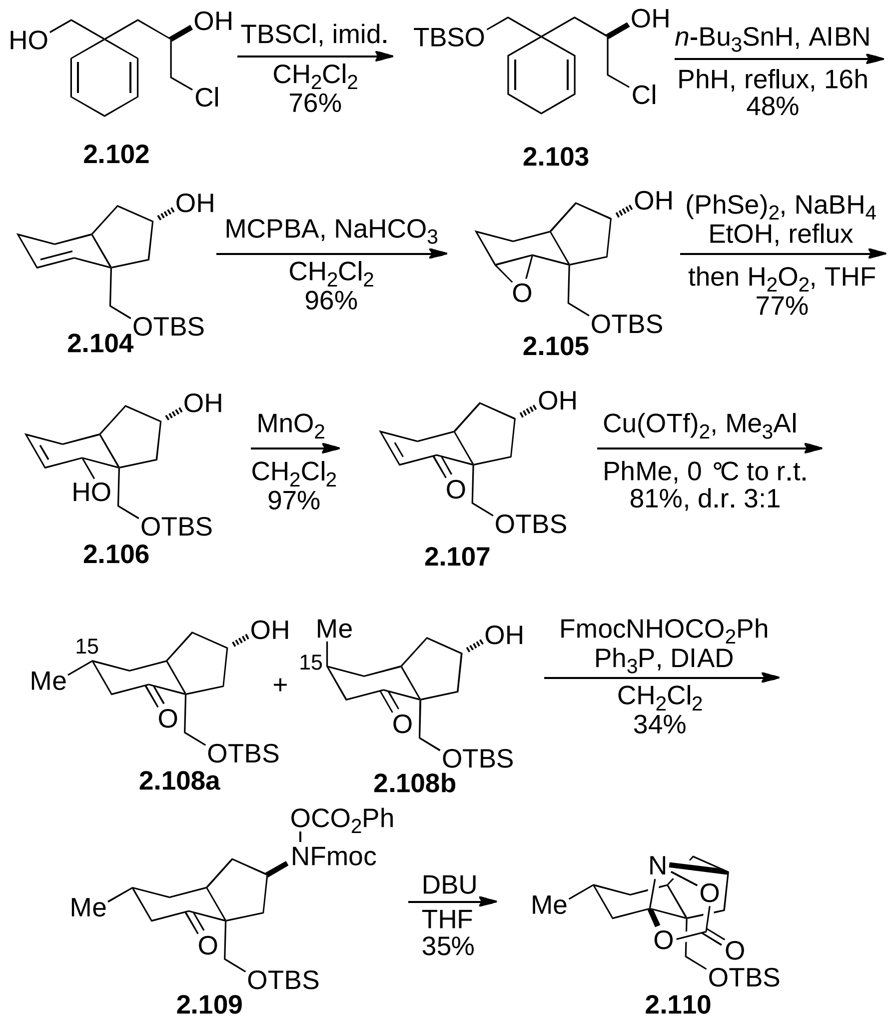


Based on Kobayashi's biosynthetic proposal,[21] Tu Y. and coworkers also achieved the biomimetic conversion of (±)-alopecuridine to (±)-sieboldine A (Scheme 2.12). In their 2-step oxidation sequence, (±)-alopecuridine TFA salt was first oxidized to the corresponding *N*-oxide **2.98** by *m*-CPBA. Intermediate **2.98** was found to be unstable during purification and was used in the next oxidation directly. Upon treatment of crude **2.98** or its equilibrating hydroxylamine form **2.99** with HgO in MeOH at elevated temperature, (±)-sieboldine A was isolated in 60% yield. In this second oxidation step, hydroxylamine **2.99** may undergo dehydration to form imine **2.100**, followed by oxidation to give nitrone **2.101**, from which an intra-molecular cyclization led to (±)-sieboldine A. The direct oxidation of **2.99** to **2.101** is another possibility.

2.11 Elliott's synthetic approach to lycoposerramine A

In 2009, The Elliott group reported their synthetic route to lycoposerramine A (Scheme 2.13).[2] Their synthesis started with diol **2.102**, from which a selective protection of the primary hydroxyl group as TBS ether followed by a radical cyclizaiton afforded the *cis*-fused 6,5-carbocycle **2.104** in moderate yield. The alkene functionality of **2.104** was then transformed to an enone moiety by a 3-step sequence: epoxidation, one-pot epoxide opening/selenoxide elimination, and allylic oxidation. The enone **2.107** obtained was then subjected to conjugate addition conditions ($Cu(OTf)_2$, Me_3Al, PhMe) to install the *C*-15 methyl group (fawcettimine numbering). However, an inseparable mixture of **2.108a** and **2.108b** was obtained with a diastereomeric ratio (d.r.) of 3:1, in favor of the desired stereoisomer **2.108a**. The mixture was carried on to the next Mitsunobu reaction. The hydroxylamine derivative **2.109** obtained above could be converted to dioxazolidinone **2.110** by DBU triggered Fmoc deprotection/cyclization process. However, all efforts to construct the oxadiazolidinone moiety, the challenging motif for lycoposerramine A, were met with failure.

Scheme 2.13. Elliott's synthetic approach to lycoposerramine A.



2.12 Conclusion

The fawcettimine class of *Lycopodium* alkaloids has been attracting significant attention from the synthetic community in the past 30 years, resulting in the total synthesis of several of the family members. In particular, fawcettimine, the parent compound of this family, has witnessed five total and two formal syntheses. From a strategic vantage, most of the reported syntheses of fawcettimine, as well as other members in the same group, adopted the strategy developed by the Inubushi group in their pioneering fawcettimine synthesis to construct the *cis*-fused 6,5-carbocyclic core with one all-carbon quaternary center. For lycoposerramine A, our ultimate target, no total synthesis has been achieved. There is only a single reported synthetic approach to the tetracyclic core.

2.13 References

1) For reviews, see: a) *The Lycopodium alkaloids*. Ayer, A. W. *Nat. Prod. Rep.* **1991**, *8*, 455–463. b) *The Lycopodium alkaloids*. Hirasawa, Y.; Kobayashi, J.; Morita, H. *Heterocycles* **2009**, *77*, 679–729. c) *Biomimetic synthesis of ornithine/arginine and lysine-derived alkaloids: selected examples.* Poupon, E.; Salame, R.; Yan, L.-H. in *Biomimetic Organic Synthesis*, Poupon, E.; Nay, B., Ed.; Wiley-VCH: Weinheim, **2011**, *vol.* 1, pp 44–60.

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Chapter 3

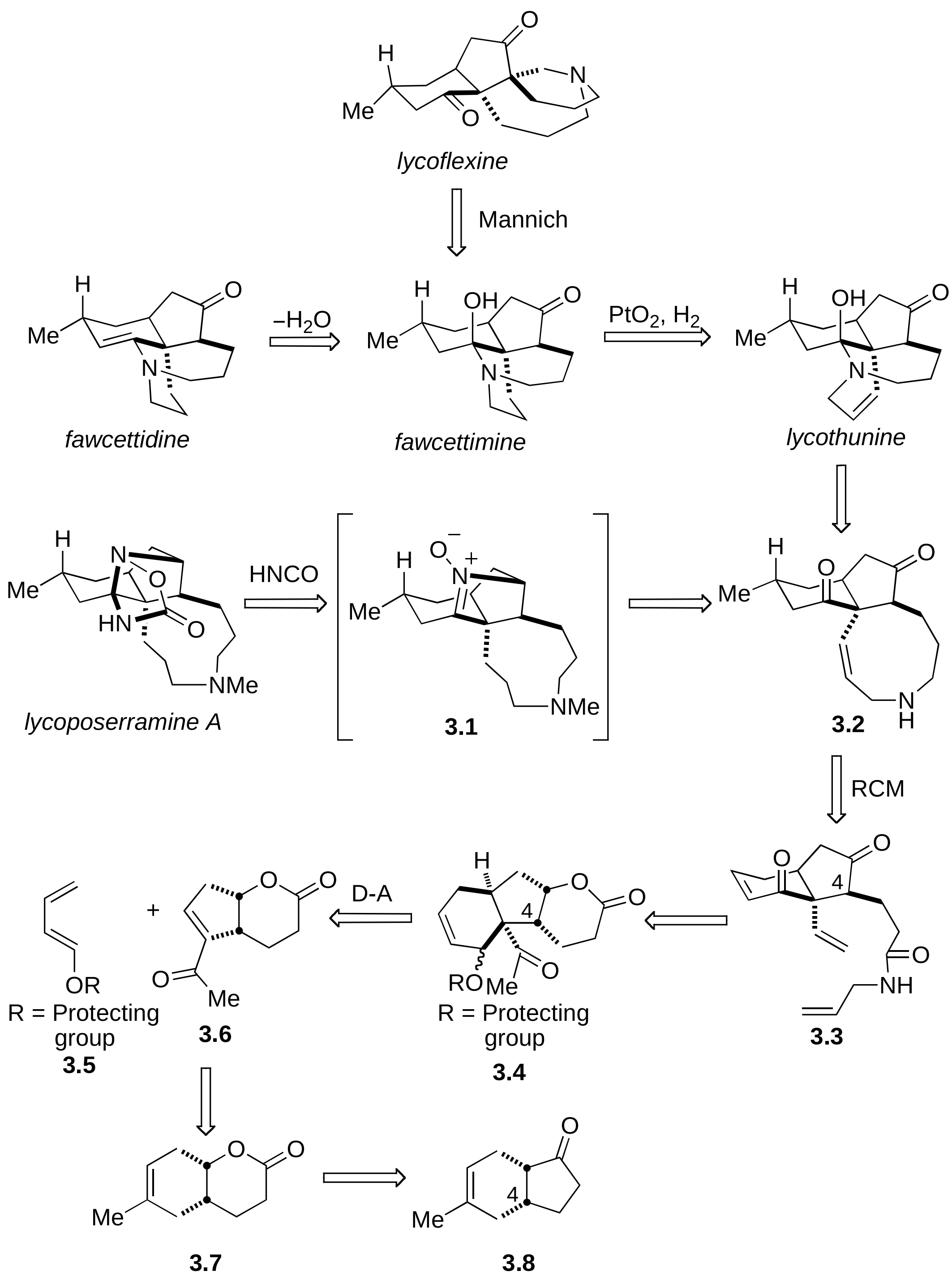
The First Generation Synthesis: RCM Approach

3.1 Retrosynthetic Analysis

As stated early in chapter one, we chose lycoposerramine A as our ultimate target for total synthesis. Given the structural similarity between lycoposerramine A and many other family members, a diversity oriented synthetic strategy that could target many of those alkaloids was pursued. Guided by the proposed biosynthetic pathway of lycoposerramine A,[1] we chose diketoamine **3.2** as the key intermediate in our synthetic route (Scheme 3.1). We envisioned that the 1,2,4-oxadiazolidin-5-one moiety could be assembled through a 1,3-dipolar cycloaddition between intermediate nitrone **3.1** and isocyanic acid (HNCO).[2] Nitrone **3.1** could be derived from diketoamine **3.2**, in which a selective oxime formation followed by reduction to form hydroxylamine are the key transformations. Diketoamine **3.2** could cyclize to afford lycothunine, from which the reduction of the C=C bond by PtO_2 and H_2 to form fawcettimine was reported.[3] Fawcettimine itself was viewed as the biosynthetic precursor to several other family members,[1,4] and the conversion of fawcettimine to fawcettidine[5] and lycoflexine[6] was already documented. Thus, our divergent oriented synthetic approach should enable us access to multiple targets of this family.

We envisioned that diketoamine **3.2** could be derived from amide **3.3**, in which an intra-molecular ring-closing metathesis (RCM) reaction was chosen to form the azonine ring. Amide **3.3** could be derived from lactone **3.4** with inversion of the stereocenter at *C*-4 (fawcettimine numbering). The ladder-like 6,5,6-fused rings of **3.4** suggested a Diels-Alder reaction between diene **3.5** and enone **3.6** to construct the *cis*-fused 6,5 carbocycles with one all-carbon quaternary center, which is characteristic to all of the fawcettimine class alkaloids. Enone **3.6** could be obtained from lactone **3.7**, which in turn could be made by Baeyer-Villiger (B-V) oxidation of known cyclopentanone **3.8**[7].

Scheme 3.1. Retrosynthetic analysis.

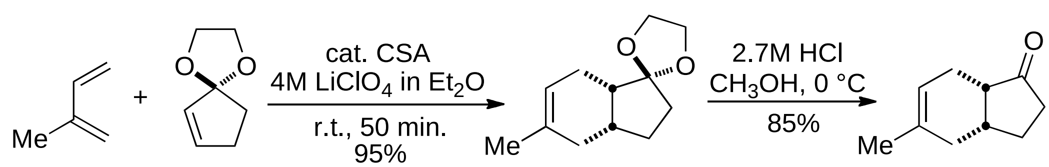


In our synthetic plan, the absolute stereochemistry of lycoposerramine A is controlled by the formation of *cis*-fused 6,5 carbocycles (intermediate **3.4**), which in turn is determined by the formation of *C*-4 stereogenic center (fawcettimine numbering) of cyclopentanone **3.8**. Thus, starting with the enantiomerically pure form of **3.8**, the asymmetric synthesis should also be achieved (*vide infra*). We chose racemic **3.8** to explore the proposed synthetic route first.

3.2 Attempt Synthesis of Enone 3.6

Our synthesis began with the known cyclopentanone **3.8**, which was readily synthesized in two steps from commercially available isoprene (**3.9**) and cyclopentenone ethylene ketal (**3.10**) under the reported procedures (Scheme 3.2).[7]

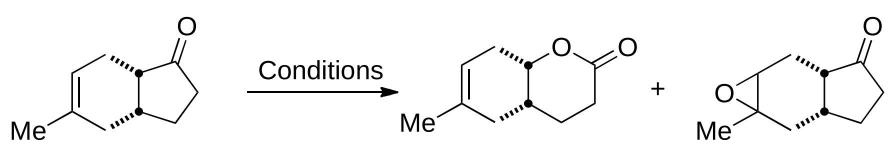
Scheme 3.2. Synthesis of cyclopentanone **3.8**.



3.9 **3.10** **3.11** **3.8**

The subsequent Baeyer-Villiger (B-V) oxidation[8] on cyclopentanone **3.8** to make lactone **3.7** was found to be difficult because of the competing epoxidation on the alkene moiety. When **3.8** was treated with *m*-CPBA, the most commonly resorted oxidant in this kind of reaction, only epoxide **3.12** was isolated (entry 1, 2, Table 3.1). $NaBO_3 \cdot 4H_2O$[9] in AcOH solvent gave a mixture of products, and no desired lactone **3.7** was isolated (entry 3). No reaction took place when H_2O_2 was employed as the oxidant, either at acidic or basic conditions (entry 4–6). We then turned our attention to bis(trimethylsilyl) peroxide ($(TMS)_2O_2$). In 1982, Noyori and coworkers reported that $(TMS)_2O_2$ and a catalytic amount of TMSOTf could react with ketones selectively in the presence of alkenes to afford B-V products in moderate yield.[10a] The Takai group found that a stoichiometric amount of $SnCl_4$ or $BF_3·OEt_2$ could catalyze this $(TMS)_2O_2$ mediated B-V oxidation.[10b] Later, Shibasaki reported that amine ligands such as *trans*-1,2-diaminocyclohexane (DA) could significantly improve the yields, with only a catalytic amount of $SnCl_4$ needed.[10c] We tried these $(TMS)_2O_2$ mediated B-V oxidations (entry 7– 9), and were pleased to find that the desired lactone **3.7** could be isolated in moderate yield under Shibasaki's conditions (entry 9).

Table 3.1. Baeyer-Villiger oxidation of cyclopentanone **3.8**.



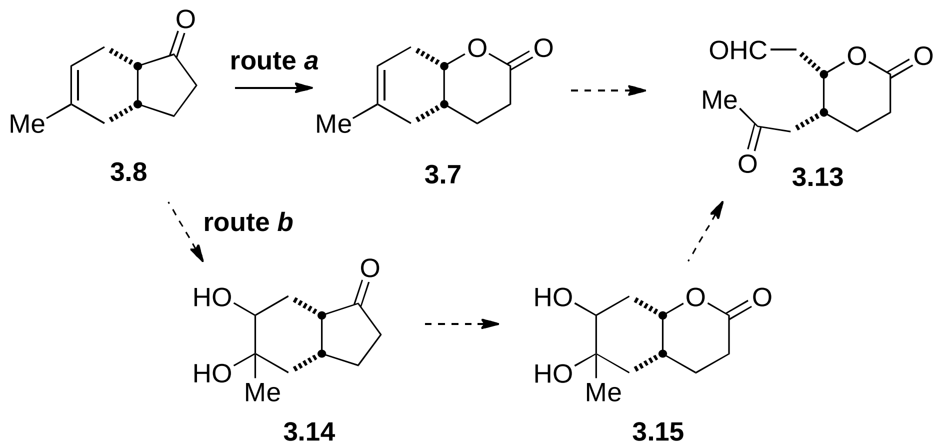
3.8 3.7 3.12

Entry	Conditions	Results[a]
1	*m*-CPBA, CH_2Cl_2, $NaHCO_3$, r.t.	90% **3.12**
2	*m*-CPBA, AcOH, r.t.	94% **3.12**
3	$NaBO_3·4H_2O$, AcOH, r.t.	messy, no **3.7**
4	H_2O_2, NaOH, MeOH, r.t.	n.r.
5	H_2O_2, $(n\text{-Bu})_4NOH$, PhH/H_2O, r.t.	n.r.
6	H_2O_2, CH_3COOH, THF, r.t.	n.r.
7	$(TMS)_2O_2$, $BF_3·Et_2O$, CH_2Cl_2, –78 °C	messy, no **3.7**
8	$(TMS)_2O_2$, $SnCl_4$, CH_2Cl_2, 0 °C	messy, no **3.7**
9	$(TMS)_2O_2$, cat. $SnCl_4$, DA, 4Å MS, CH_2Cl_2 0 °C	50% **3.7**, 59.5% brsm

[a] Isolated yield.

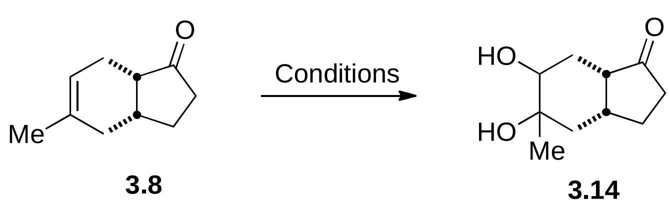
From lactone **3.7**, the synthesis of keto aldehyde **3.13** is straightforward, which just need cleavage of the C=C bond (route *a*, Scheme 3.3). However, during the screening of suitable oxidant to do a B-V oxidation on cyclopentanone **3.8**, we also envisioned an alternative approach to **3.13** (route *b*). The new route relied on a dihydroxylation of **3.8** to temporally mask the interfering alkene moiety. Subsequent B-V oxidation of the dihydroxylation product **3.14**, followed by diol cleavage could afford **3.13**. Since route *b* proved to be practical, the conversion of **3.7** to **3.13** via route *a* was not tried.

Scheme 3.3. Synthesis of keto aldehyde **3.13**.



Dihydroxylation of cyclopentanone **3.8** under conditions reported by Kobayashi,[11] using a catalytic amount of polymer supported OsO_4 (P-OsO_4) and NMO as the stoichiometric oxidant could afford diol **3.14** in good yield (entry 1, Table 3.2). Trimethylamine *N*-oxide dihydrate ($Me_3NO{\cdot}2H_2O$) worked less efficiently than NMO (entry 2). $KMnO_4$ in phase transfer catalysis conditions was also examined,[12] which only gave very low yield of desired product (entry 3).

Table 3.2. Dihydroxylation of cyclopentanone **3.8**.

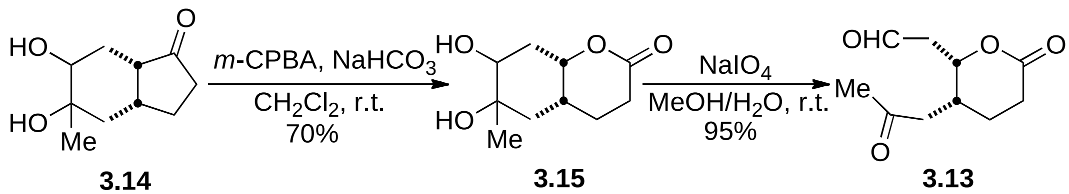


Entry	Conditions	Results[a]
1	5 mol% P-OsO_4, NMO, CH_3CN/acetone/H_2O, r.t.	82%, 88% brsm
2	5 mol% P-OsO_4, $Me_3NO{\cdot}2H_2O$, CH_3CN/acetone/H_2O, r.t.	24%, 26% brsm
3	$KMnO_4$, $BnEt_3NCl$, CH_2Cl_2, r.t., then 3% NaOH	20%

[a] Isolated yield.

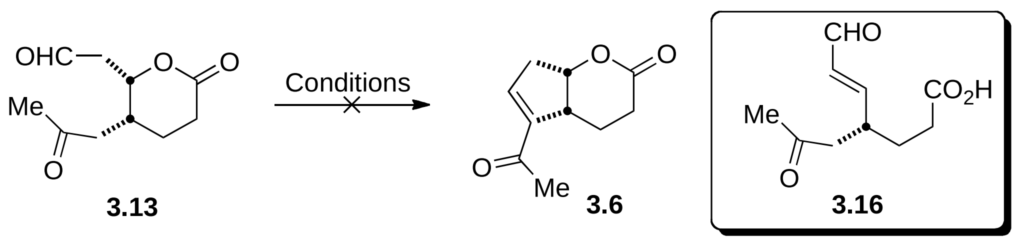
The following B-V oxidation of diol **3.14** went smoothly with *m*-CPBA as the oxidant, and gave lactone **3.15** in 70% yield (Scheme 3.4). Subsequent treatment of **3.15** with $NaIO_4$ could cleave the diol into keto aldehyde **3.13** in 95% yield.

Scheme 3.4. Synthesis of keto aldehyde **3.13**.



With keto aldehyde **3.13** in hand, the intra-molecular aldol condensation /dehydration process to form enone **3.6** was examined next. Unfortunately, **3.13** turned out to be prone to β-elimination, with α, β-unsaturated aldehyde **3.16** isolated as the sole product either at basic or acidic conditions (entry 2, 3, Table 3.3).

Table 3.3. Attempted synthesis of enone **3.6**.



Entry	Conditions	Results[a]
1	NaOH, 10 mol% (*n*-Bu)$_4$BF$_4$, PhH, reflux	messy, no **3.6**
2	5 mol% *t*-BuOK, THF, r.t.	60% **3.16**
3	5 mol% *p*-TsOH, CH_3CN, r.t.	45% **3.16**

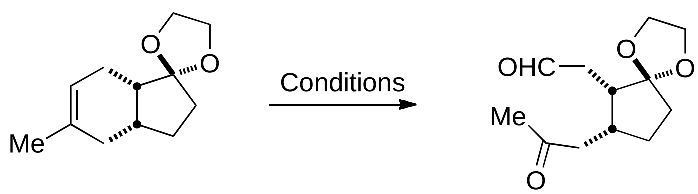
[a] Crude yield.

Realizing that β-elimination was unavoidable to keto aldehyde **3.13**, we didn't invest more time on its conversion to **3.6** and decided to put the B-V oxidation step off to a later stage (*vide infra*).

3.3 Synthesis of Enone 3.18 and Its Diels-Alder Reaction

Our new synthesis started with the cleavage of the C=C bond of ketal **3.11**. Surprisingly, the Lemieux-Johnson reagent (OsO_4 and $NaIO_4$)[13a] gave very low yield of desired keto aldehyde **3.17** (entry 1, Table 3.4). The yield could not be improved by addition of a catalytic amount of NMO (entry 2).[13b] Polymer supported OsO_4 (P-OsO_4) totally failed this time (entry 3, 4). We then turned our attention to ozonolysis[14]. When MeOH was used as the solvent, only trace amount of **3.17** was detected. CH_2Cl_2 as cosolvent or solvent could improve the yield slightly (entry 6, 7). Ph_3P worked less efficiently than Me_2S as the reducing reagent (entry 8). The acid labile ethylene ketal moiety of **3.11** may be responsible for the low yields obtained for above reactions.[7]

Table 3.4. Synthesis of keto aldehyde **3.17**.



3.11 3.17

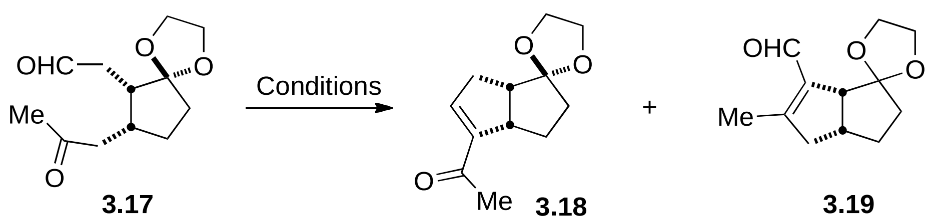
Entry	Conditions	Results[a]
1	1 mol% OsO_4, $NaIO_4$, THF/H_2O, r.t.	15%
2	1 mol% OsO_4, 10 mol% NMO, $NaIO_4$, MeCN/H_2O, r.t.	12%, 20% brsm
3	3 mol% P-OsO_4, $NaIO_4$, THF/H_2O, r.t.	0%
4	3 mol% P-OsO_4, $NaIO_4$, dioxane/H_2O, r.t.	0%
5	O_3, MeOH, –78 °C then Me_2S	trace
6	O_3, MeOH/CH_2Cl_2, –78 °C then Me_2S	<10%
7	O_3, CH_2Cl_2, –78 °C then Me_2S	30%
8	O_3, CH_2Cl_2, –78 °C then Ph_3P	25%
9	3.5 mol% $RuCl_3 \cdot xH_2O$, $NaIO_4$, $(ClCH_2)_2$/H_2O, r.t.	59%
10[b]	1 mol% $RuCl_3 \cdot xH_2O$, $NaIO_4$, $(ClCH_2)_2$/H_2O, r.t.	75%

[a] Isolated yield. [b] Using mechanical stirrer.

To our delight, when Yang's conditions (cat. $RuCl_3 \cdot xH_2O$, $NaIO_4$, $(ClCH_2)_2/H_2O$)[15] were attempted, **3.17** could be isolated in 59% yield. The yield could be further improved to 75% when a mechanical stirrer was employed (entry 9, 10).

Compared to keto aldehyde **3.13**, the intra-molecular aldol condensation/dehydration of **3.17** was met with less difficulty. When **3.17** was treated with KOH in H_2O at room temperature for 3 hours, desired enone **3.18** and undesired α, β-unsaturated aldehyde **3.19** (**3.18**:**3.19** = 1:2.27) were isolated as an inseparable mixture in 91% combined yield (entry 1, Table 3.5). It was quickly found that **3.18** is the thermodynamic product and **3.19** is the kinetic product. The ratio of **3.18** could be increased either by elongated reaction time or elevated temperature. However, the yield dropped with those factors because of the unwanted inter-molecular reactions. The optimal result could be obtained by treatment of **3.17** with 4 equiv. of KOH in reflux H_2O for 15 hours (entry 7).

Table 3.5. Synthesis of enone **3.18**.



Entry	Conditions	**3.18**:**3.19**[a,b,c]
1	20 equiv. KOH, H_2O, r.t., 3h	1:2.27 (91%)
2	20 equiv. KOH, H_2O, r.t., 25h	1:1.56 (83%)
3	20 equiv. KOH, H_2O, r.t., 14d	1:0.31 (78%)
4	20 equiv. KOH, H_2O, 60–70 °C, 11h	1:0.14 (67%)
5	20 equiv. KOH, H_2O, 60–70 °C, 25h	1:0.02 (60%)
6	20 equiv. KOH, 20 mol% pyrogallol, $MeOH/H_2O$, 60–70°C, 25h	1:0.05 (45%)
7	4 equiv. KOH, H_2O, reflux, 15h	1:0.02 (79%)
8	2 equiv. KOH, H_2O, reflux, 15h	1:0.04 (68%)
9	25 mol% KOH, H_2O, 60–70 °C, 18h	1:1.38 (76%)

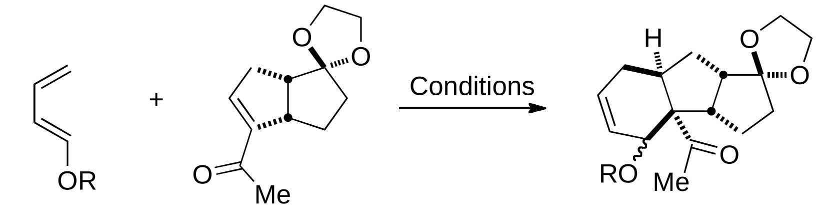
[a] Ratio was determined by ^1H NMR. [b] Yield in parenthesis was combined yield for **3.18** and **3.19**. [c] Isolated yield.

It is worth noting that O_2 is detrimental to this reaction and thus must be carefully removed.[16] A catalytic amount of pyrogallol was added with the hope that it could act as O_2 scavenger, but no beneficial effect was observed (entry 6).

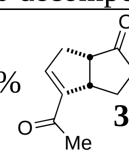
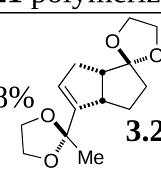
Although undesired **3.19** could not be separated from **3.18** at this moment, it was found that **3.19** did not participate in the next Diels-Alder reaction and could be removed in that step (*vide infra*).

The Diels-Alder reaction (D-A)[17] between enone **3.18** and two commercially available dienes: 1-(trimethylsiloxy)-1,3-butadiene (**3.20**) and 1-acetoxy-1,3-butadiene (**3.21**) was investigated next. When **3.18** was treated with **3.20** in refluxing toluene for 10 hours, no reaction took place (entry 1, Table 3.6). Microwave heating at 120 °C in CH_2Cl_2 for 1 hour also gave no reaction (entry 2). On the other hand, Lewis acids such as $ZnCl_2$ or $EtAlCl_2$ could either decompose the diene **3.20** or remove the ketal protecting group of enone **3.18** (entry 3, 4). With these initial failures, we focused on more harsh thermal conditions. The breakthrough was made by heating enone **3.18** with a large excess of diene **3.20** in xylene in a sealed tube for elongated time. Desired adduct **3.22** could be isolated in low yield together with most of enone **3.18** recovered (entry 5). The yield could be improved by running the reaction under neat conditions (entry 6, 7). However, higher temperatures (> 190 °C) resulted in significant loss of yield, presumably due to the decomposition of the product or the starting material (entry 8).

Table 3.6. Diels-Alder reaction between enone **3.18** and dienes.



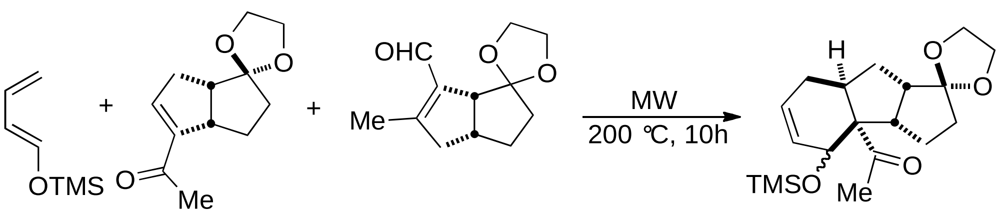
3.20 R = TMS
3.21 R = OAc
3.18
3.22 R = TMS
3.23 R = OAc

Entry	Conditions	Results[a]
1	2.4 equiv. **3.20**, PhMe, reflux, 10h	n.r.
2	2 equiv. **3.20**, CH_2Cl_2, MW, 120 °C, 1h	n.r.
3	6 equiv. **3.20**, 25 mol% $ZnCl_2$, CH_2Cl_2, 0 °C, 3h	**3.20** decomposed
4	2 equiv. **3.20**, 2.5 equiv. $EtAlCl_2$, CH_2Cl_2, –78 °C, 1h	41%  **3.24**
5[b]	10 equiv. **3.20**, xylene, 170 °C, 4d	15% **3.22**, 75% brsm
6[b]	10 equiv. **3.20**, neat, 160 °C, 7d	36% **3.22**, 65% brsm
7[b]	10 equiv. **3.20**, neat, 190 °C, 3d	30% **3.22**, 67% brsm
8[b]	10 equiv. **3.20**, neat, 240 °C, 10h	9% **3.22**
9[b]	10 equiv. **3.20**, neat, MW, 190 °C, 9h	48% **3.22**, 69% brsm
10[b]	10 equiv. **3.20**, neat, MW, 200 °C, 16h	37% **3.22**, 55% brsm
11	1.5 equiv. **3.21**, PhMe, reflux, 3d	**3.21** decomposed
12	10 equiv. **3.21**, neat, MW, 200 °C, 4h	**3.21** polymerized
13[b]	4.5 equiv. **3.21**, EG, 145 °C, 3d	18%  **3.25**

[a] Isolated yield. [b] Sealed tube reaction.

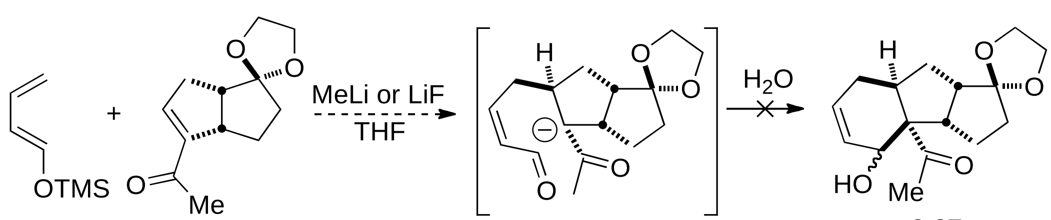
To our delight, compared to reactions conducted under elevated temperatures, microwave (MW)[18] shortened the Diels-Alder reaction time and improved the yield dramatically. Thus, the optimal result was obtained by running the reaction in a microwave reactor at 190 °C for 9 hours with adduct **3.22** isolated in 48% yield (69% brsm) (entry 9). Moreover, when a mixture of enone **3.18** and α, β-unsaturated aldehyde **3.19** (**3.18**:**3.19** = 1:1.56) was subjected to this optimized condition, only adduct **3.22** was isolated, with no adduct between **3.20** and **3.19** was detected (Scheme 3.5). Thus, **3.19** could be removed from **3.18** at this step.

Scheme 3.5. Diels-Alder reaction between diene **3.20** and a mixture of **3.18** and **3.19**.



Compared to 1-(trimethylsiloxy)-1,3-butadiene (**3.20**), 1-acetoxy-1,3-butadiene (**3.21**) gave no desired adduct **3.23** when heated with **3.18** in toluene or neat by microwave. Diene **3.21** was found to be unstable in both conditions (entry 11, 12). Ethylene glycol (EG) was also tested, which was reported to be a good solvent for inter-molecular Diels-Alder reactions involving relatively hydrophobic dienes and dienophiles.[19] However, when **3.21** and **3.18** was heated in EG at 145 °C for 3 days, only diethylene ketal **3.25** was isolated (entry 13).

Scheme 3.6. Attempted Michael addition/aldol condensation between diene **3.20** and enone **3.18**.

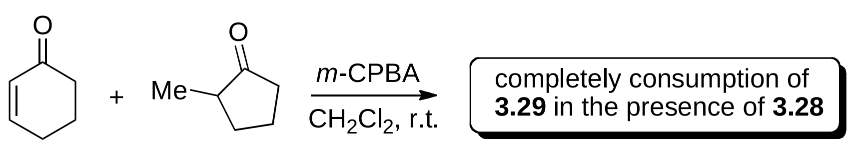


Besides a Diels-Alder reaction, the possibility of successive Michael addition/aldol condensation between diene **3.20** and enone **3.18** to form adduct **3.27** was also tested.[20] It was hoped that when diene **3.20** was treated with MeLi or LiF, the butadienolate generated could add to enone **3.18** to form intermediate **3.26**, followed by an intra-molecular aldol condensation to afford **3.27** (Scheme 3.6). Unfortunately, no trace of desired **3.27** was observed.

3.4 Synthesis of Alkene 3.34

With the D-A adduct **3.22** in hand, we had already constructed the *cis*-fused 6,5-carbocycles with one all-carbon quaternary center, which is characteristic to all of the fawcettimine class alkaloids. Efforts were then focused on the formation of the azonine ring. As illustrated in our retrosynthetic analysis (Scheme 1), a ring-closing metathesis (RCM) was planned to fulfill the task. Before this step, however, a Baeyer-Villiger oxidation to convert cyclopentanone to lactone is necessary. The time to introduce this critical reaction in our synthetic route definitely needed careful consideration.

Scheme 3.7. Model study for Baeyer-Villiger reaction.

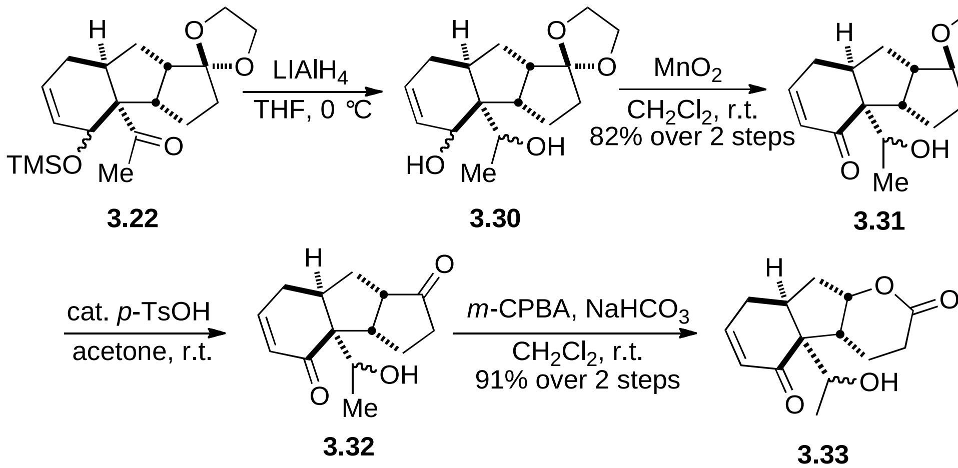


3.28 **3.29**

Since alkenes are nucleophilic and carbonyls are electrophilic, we envisioned that the conjugation of these two groups should render the resulting enone less reactive towards either nucleophiles or electrophiles. A model study using a mixture of cyclohex-2-enone (**3.28**) and 2-methylcyclopentanone (**3.29**) further verified our consideration. When a mixture of **3.28** and **3.29** was subjected to *m*-CPBA in CH_2Cl_2 at room temperature, TLC showed that cyclopentanone **3.29** was completely consumed while cyclopentenone **3.28** was totally remained (Scheme 3.7). Hence, the selective Baeyer-Villiger oxidation of cyclopentanone in the presence of cyclohexenone is possible.

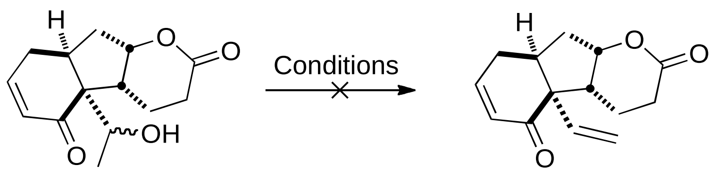
Encouraged by this preliminary result, we decided to put the Baeyer-Villiger reaction on the ketoenone oxidation state of our substrate (Scheme 3.8). To this end, Diels-Alder adduct **3.22** was first reduced to diol **3.30** by $LiAlH_4$ reduction. The subsequent selective allylic oxidation of diol **3.30** to enone **3.31** could be achieved by treatment of **3.30** with activated MnO_2 in CH_2Cl_2 (82% over 2 steps). After removal of the ethylene ketal protecting group, the resulting ketoenone **3.32** was tested for the selective Baeyer-Villiger reaction. To our delight, when **3.32** was treated with *m*-CPBA in CH_2Cl_2 at room temperature in the presence of $NaHCO_3$, desired lactone **3.33** was isolated as the sole product in 91% yield over 2 steps. Since the enone moiety is close to the all-carbon quaternary center, the steric hindrance may also play a role in this highly selective Baeyer-Villiger reaction.

Scheme 3.8. Synthesis of lactone **3.33**.



With lactone **3.33** in hand, efforts were then put on its dehydration to form alkene **3.34**. When **3.33** was subjected to Martin sulfurane[21] in benzene at room temperature or Burgess reagent[22] in different solvents at elevated temperatures, no desired alkene **3.34** was detected (entry 1–4, Table 3.7). No reaction was observed when **3.33** was treated with $SOCl_2$ in pyridine solvent at room temperature (entry 5).[23] Moreover, Mitsunobu dehydration conditions[24] (entry 6) and Monson's conditions[25] (entry 7) were also tested, with no alkene **3.34** formed in both cases. Apparently, the neighboring all-carbon quaternary center rendered the secondary hydroxyl group so hindered that bulky reagents could not access it.

Table 3.7. Attempted dehydration of lactone **3.33**.

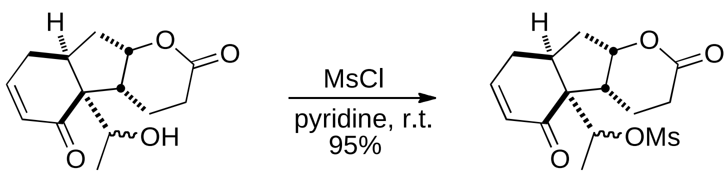


3.33 **3.34**

Entry	Conditions	Results
1	Martin sulfurane, PhH, r.t.	no **3.34**
2	Burgess reagent, CH_3CN, 60 °C	no **3.34**
3	Burgess reagent, PhMe, 60 °C	no **3.34**
4	Burgess reagent, THF, 60 °C	no **3.34**
5	$SOCl_2$, pyridine, r.t.	n.r.
6	Ph_3P, DEAD, THF, reflux	no **3.34**
7	HMPA, 180 °C	no **3.34**

Since there was no way to perform the dehydration on **3.33** directly, we then turned our attention to those two steps approaches. Treatment of lactone **3.33** with mesyl chloride (MsCl) in pyridine at room temperature gave mesylate **3.35** in 95% yield (Scheme 3.9).

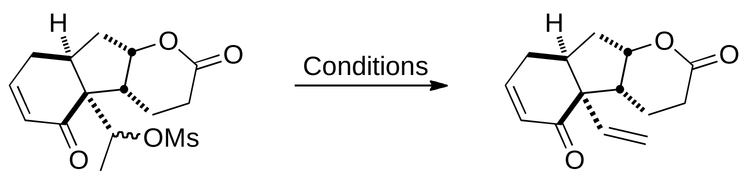
Scheme 3.9. Synthesis of mesylate **3.35**.



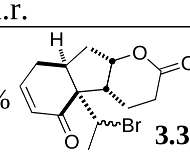
3.33 **3.35**

Subsequent elimination of mesylate **3.35** to form alkene **3.34** was met with failure, initially. When **3.35** was treated with DBU in toluene at room temperature, no reaction took place. At reflux temperatures, the reaction turned very messy and no trace of **3.34** was detected (entry 1, 2, Table 3.8). Other bases, such as *t*-BuOK or AcONa[26a], also failed to deliver **3.34** (entry 3–5). No reaction was observed when **3.35** was subjected to silica gel[26b] or $(CH_3CN)_2PdCl_2$[26c] (entry 6, 7).

Table 3.8. Synthesis of alkene **3.34** from mesylate **3.35**.



3.35 **3.34**

Entry	Conditions	Results[a]
1	DBU, PhMe, r.t.	n.r.
2	DBU, PhMe, reflux	no **3.34**
3	*t*-BuOK, DMSO, r.t.	no **3.34**
4	*t*-BuOK, *t*-BuOH/THF, 0 °C	no **3.34**
5	AcONa, AcOH, reflux	no **3.34**
6	Silica gel, CH_2Cl_2, r.t.	n.r.
7	$(CH_3CN)_2PdCl_2$, PhH, reflux	n.r.
8	Li_2CO_3, LiBr, DMF, reflux, 1h	34% **3.34** + 25%  **3.36**
9	Li_2CO_3, LiBr, DMF, reflux, 5h	41% **3.34** + 15% **3.36**
10	Li_2CO_3, LiBr, DMF, 130 ˚C, 20h	61%
11	Li_2CO_3, DMF, reflux, 6h	< 20%
12	Li_2CO_3, LiBr, DMF, 210 ˚C, MW, 8min.	65%

[a] Isolated yield.

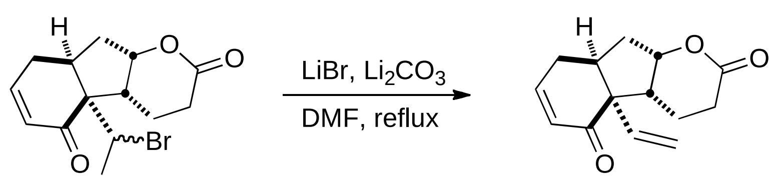
It was reported that LiBr in DMF could act as a strong base to trigger the elimination of secondary mesylates to form alkenes.[27] Gratifyingly, when **3.35** was treated with LiBr and Li_2CO_3 in refluxing DMF for 1 hour, desired alkene **3.34** could be isolated in 34% yield together with bromide **3.36** in 25% yield (entry 8). After 5 hours, the yield of alkene

3.34 increased to 41% while the yield of bromide **3.36** dropped to 15% (entry 9). The reaction was pushed to completion at 130 °C for 20 hours, with **3.34** isolated as the sole product in 61% yield (entry 10).

The conversion of **3.35** to **3.34** possibly goes through the substitution of **3.35** by LiBr to form bromide **3.36** first, followed by elimination of HBr to form **3.34**. Bromide **3.36** as the reactive intermediate was verified by our control experiment, which showed that when **3.36** was subjected to the reaction condition, alkene **3.34** could be obtained (Scheme 3.10). However, direct elimination of methanesulfonic acid (MsOH) from **3.35** is still possible, since in the absence of LiBr, alkene **3.34** was still isolated in lower yield (entry 11).

Finally, it was found that the reaction time could be shortened greatly by microwave (MW) heating, with the reaction completed in 8 minutes and the yield slightly improved to 65% (entry 12). This microwave assisted procedure stands out as our optimized reaction condition.

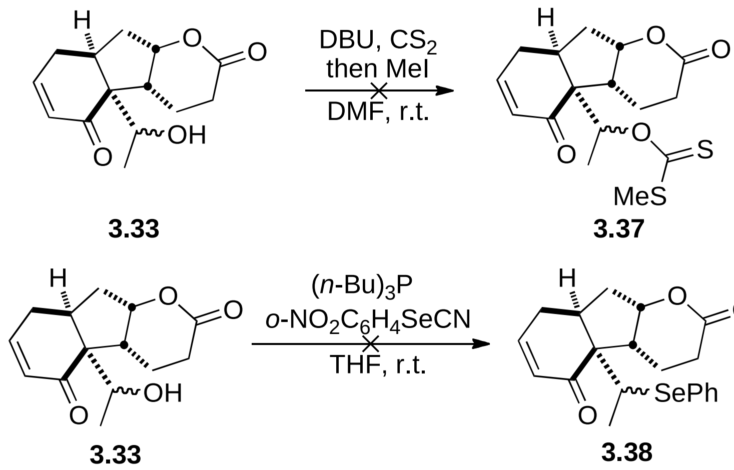
Scheme 3.10. Synthesis of alkene **3.34** from bromide **3.36**.



3.36 3.34

Compared to the mesylate formation/elimination sequence, the xanthate formation/ elimination[28] and Grieco elimination[29] were also attempted (Scheme 3.11). However, no desired xanthate **3.37** or selenide **3.38** was isolated under the reaction conditions.

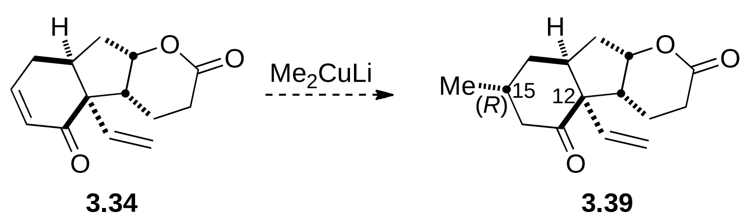
Scheme 3.11. Attempted synthesis of xanthate **3.37** and **3.38**.



3.5 Installation of *C*-15 Methyl Group

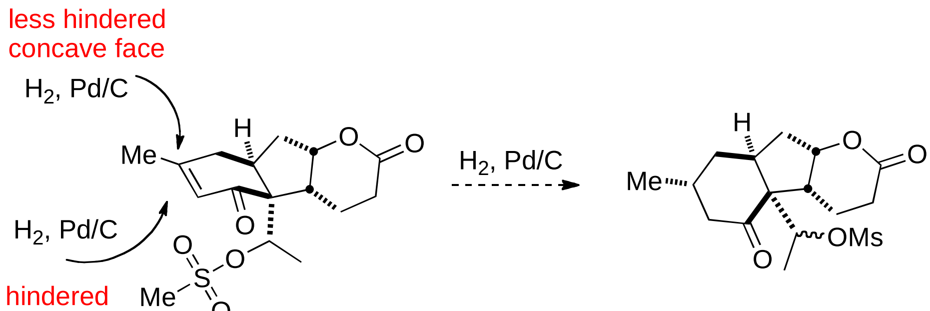
With alkene **3.34** in hand, the installation of *C*-15 methyl group (fawcettimine numbering) was investigated next. A Michael addition using Me_2CuLi to add the methyl group from the convex face of the 6,5-carbocycle was planned originally and expected to deliver ketone **3.39** with the required *R* configuration at *C*-15 (Scheme 3.12). However, the *C*-12 vinyl group may block the approach of Me_2CuLi from that face so that the facial selectivity can be eroded.

Scheme 3.12. Envisioned Michael addition by Me_2CuLi.



On the other hand, since we already obtained alkene **3.34** by mesylate elimination, we envisioned that the mesylate group could be utilized further to block the convex face of the fused 6, 5-carbocycle (Scheme 3.13). Thus, hydrogenation of mesylate **3.40** could only take place from the more available concave face to provide ketone **3.41** with correct *R* configuration at *C*-15.

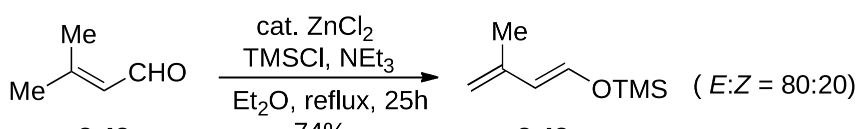
Scheme 3.13. Envisioned hydrogenation of enone **3.39**.



3.40 **3.41**

To make enone **3.40**, diene **3.43** needs to substitute diene **3.20** in the corresponding Diels-Alder reaction (*vide infra*). Diene **3.43** (mixtures, *E*:*Z* = 80:20) is a known compound and can be easily made in one step from commercially available 3-methyl-2-butenal (**3.41**) under reported conditions (Scheme 3.14).[30]

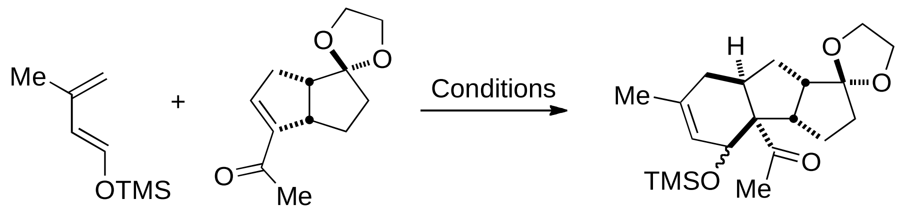
Scheme 3.14. Synthesis of diene **3.43**.



3.42 **3.43**

The following Diels-Alder reaction between diene **3.43** and enone **3.18** went smoothly under the above optimized conditions for diene **3.20**, affording adduct **3.43** in moderate yield together with recovered enone **3.18** (entry 1, Table 3.9). Further optimization was focused on reaction temperature, time and equivalency of diene used (entry 2–6). The best result was obtained when enone **3.18** was treated with 2.5 equivalent of diene **3.42** in a microwave reactor without solvent at 180 °C for 9 hours, with adduct **3.43** (d.r. = 1.0 (*endo*): 0.4 (*exo*)) isolated in 74% yield (92.5% brsm) (entry 5).

Table 3.9. Diels-Alder reaction between diene **3.42** and enone **3.18**.



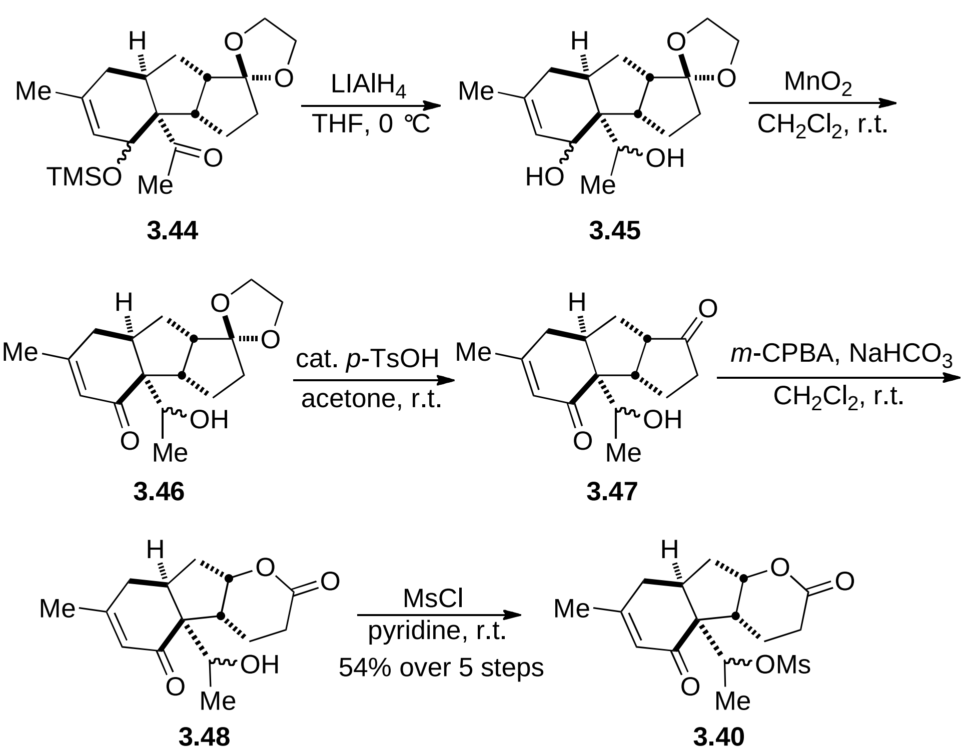
3.43 **3.18** **3.44**

Entry	Conditions	Results[a, b]
1[c]	10 equiv. **3.43**, neat, MW, 195 °C, 6h	35%, 76% brsm
2[c]	10 equiv. **3.43**, neat, MW, 200 °C, 16h	18%, 28% brsm
3[c]	6 equiv. **3.43**, neat, MW, 185 °C, 9h	56%, 65% brsm
4[c]	6 equiv. **3.43**, neat, MW, 130 °C, 10h	18%, 51% brsm
5[d]	2.5 equiv. **3.43**, neat, MW, 180 °C, 9h	74%, 92.5% brsm
6[d]	2 equiv. **3.43**, neat, MW, 180 °C, 10h	58%, 89% brsm

[a] Isolated yield. [b] Sealed tube reaction. [c] Reaction performed on < 0.5 g scale of **3.18**. [d] Reaction performed on > 1.0 g scale of **3.18**.

From Diels-Alder adduct **3.44**, the synthesis of enone **3.39** can follow the same sequence as for enone **3.35** (Scheme 3.15).

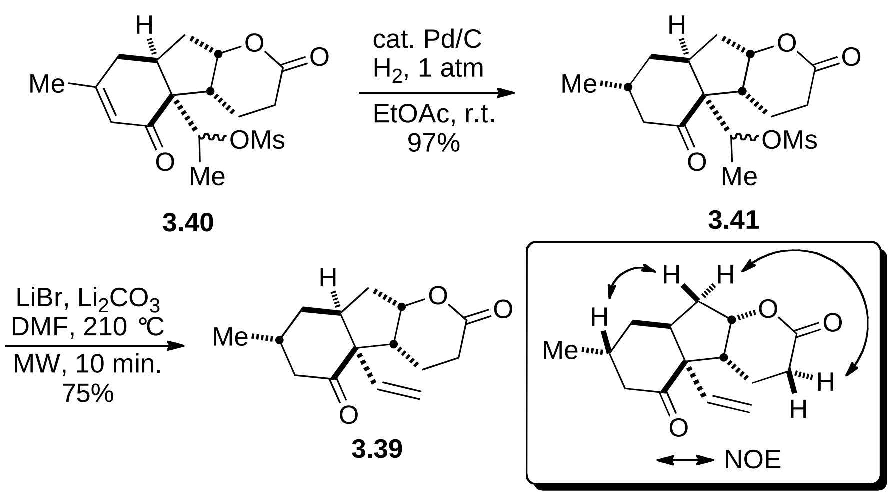
Scheme 3.15. Synthesis of enone **3.39**.



Reduction of **3.44** by $LiAlH_4$ followed by allylic oxidation by MnO_2, provided enone **3.46**. The ketal group of **3.46** was then removed by a catalytic amount of *p*-TsOH in acetone. Cyclopentanone **3.47** obtained was then subjected to a Baeyer-Villiger reaction to afford lactone **3.48**. Treatment of **3.48** with MsCl in pyridine provided mesylate **3.40** in 54% overall yield over above 5 steps.

With mesylate **3.40** in hand, the idea of hydrogenation of the enone moiety to set the *C*-15 methyl group (fawcettimine numbering) could now be tested. To our delight, the desired hydrogenation could be effected by treatment of **3.40** with a catalytic amount of Pd/C under atmospheric pressure of H_2 in EtOAc at room temperature. Mesylate **3.41** obtained was then subjected directly to above optimized conditions for mesylate elimination (LiBr, Li_2CO_3, DMF, 210 ˚C, MW, 8min.). To our delight, alkene **3.39** was isolate as a single diastereomer in 75% yield and the stereochemistry at *C*-15 (fawcettimine numbering) was confirmed to be *R* by NOESY.

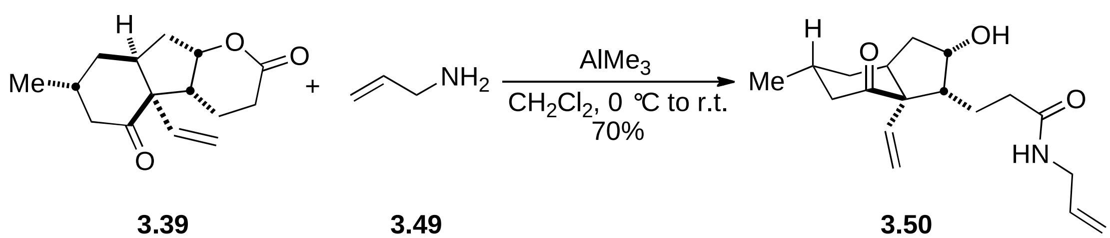
Scheme 3.16. Synthesis of alkene **3.39**.



3.6 Attempted RCM Approach to Form the Azonine Ring

With alkene **3.39** in hand, the formation of the azonine ring could now be focused on.[31] As illustrated early in our retrosynthetic analysis (Scheme 3.1, *vide supra*), a ring-closing metathesis (RCM) was conceived to fulfill the task. To this end, alkene **3.39** was reacted with allyl amine (**3.49**) in the presence of $AlMe_3$[32] to give diene **3.50** in 70% yield (Scheme 3.17). It is worth noting that diene **3.50** contains all of the carbon skeletons for fawcettimine. Only azonine formation and several oxidation state adjustment steps are required to complete the synthesis of this alkaloid.

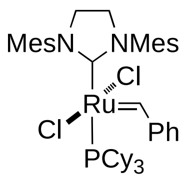
Scheme 3.17. Synthesis of diene **3.50**.



3.39 **3.49** **3.50**

From diene **3.50**, the essential RCM reaction to construct the azonine ring was investigated. The literature search revealed that there are only limited reports about formation of medium-sized heterocycles via RCM reactions. For example, Lemcoff and Bittner reported that treatment of quinone derivative **3.51** with 5 mol% Grubbs 2nd generation catalyst (G2) in toluene at elevated temperature could deliver the diazonine fused quinone **3.52** in 89% yield (eq. 1, Scheme 3.18).[33a] Hsung also showed that azonine fused triazole **3.54** could be obtained in moderate yield when triazole derivative **3.53** was subjected to 10 mol% G2 in CH_2Cl_2 at reflux temperature for 12 hours (eq. 2).[33b] Moreover, the Bewley group demonstrated that *N*-allyl amide side chain of **3.55** could take part in the RCM reaction to form 12-membered lactam **3.56** in good yield (eq. 3).[33c]

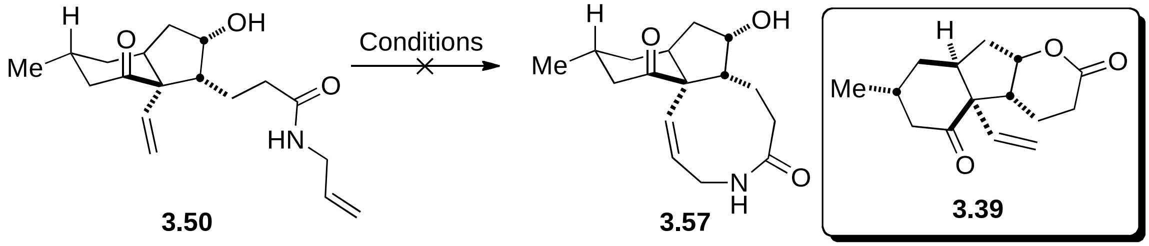
Scheme 3.18. Selected examples for RCM reaction.



G2

With those precedents, diene **3.50** was subjected to standard RCM conditions (cat. G2, solvent, Δ). It was found that in refluxing CH_2Cl_2, no reaction took place when 15 mol% G2 was used (entry 1, Table 3.10). When much harsher conditions (30 mol% G2, PhMe, reflux, 4h) were employed, alkene **3.39** was detected as the only product (entry 2). Even at lower temperature, the formation of **3.39** still dominated (entry 3).

Table 3.10. Attempted RCM on diene **3.50**.



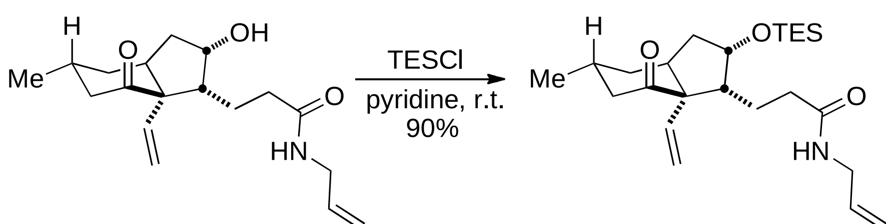
Entry	Conditions	Results[a]
1	15 mol% G2, CH_2Cl_2, reflux, 6h	n.r.
2	30 mol% G2, PhMe, reflux, 4h	**3.38** only
3	30 mol% G2, PhMe, 50 °C, 5h	**3.38** only

[a] Determined by crude ^{1}H NMR or TLC.

The occurrence of alkene **3.39** was the result of the loss of allylamine moiety from diene **3.50**. One possible explanation is that G2 serves as the Lewis acid catalyst to activate the amide carbonyl group toward attack of the nearby hydroxyl group. To prevent this unwanted lactone formation, efforts were then put on the protection of the hydroxyl group and subsequent azonine formation via RCM.

The mask of the secondary hydroxyl group on diene **3.50** as a silyl ether was attempted first. When **3.50** was treated with TESCl in pyridine, the TES ether **3.58** could be isolated in 90% yield (Scheme 3.19). Compared to TES ether, the corresponding TMS ether was too unstable to be isolated.

Scheme 3.19. TES protection of diene **3.50**.

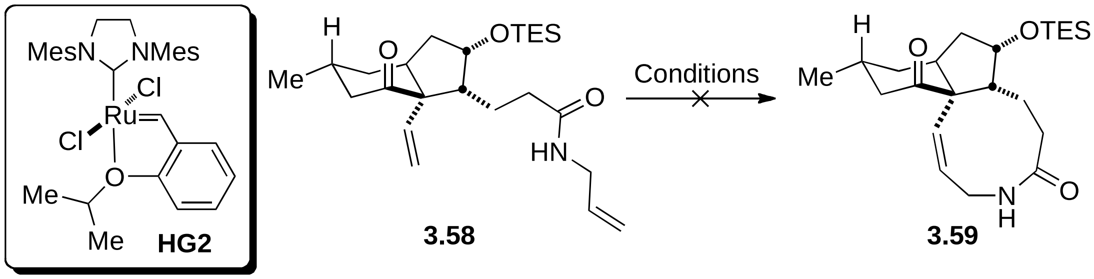


3.50 3.58

With the secondary hydroxyl group on diene **3.58** now protected, RCM to form the azonine was then examined. However, to our surprise, when **3.58** was subjected to 20 mol% G2 in toluene at 40~50 °C for 2 days, alkene **3.39** was the only product detected from the crude reaction mixture (entry 1, Table 3.11). The Hoveyda-Grubbs 2[nd] generation catalyst (HG2) was also tested on diene **3.58**. Under the reaction conditions

(20 mol% HG2, PhMe, 50 °C, 5h), the complete consumption of **3.58** was observed. Unfortunately, no desired azonine **3.59** was formed (entry 2).

Table 3.11. Attempted RCM on diene **3.58**.

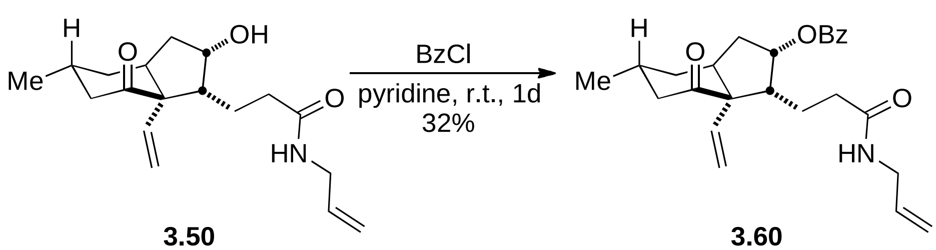


Entry	Conditions	Results[a]
1	20 mol% G2, PhMe, 40~50 °C, 2d	**3.39** only
2	20 mol% HG2, PhMe, 50 °C, 5h	no **3.59**

[a] Determined by crude ^{1}H NMR.

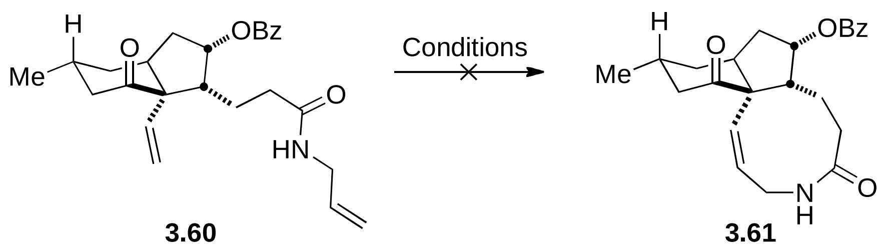
The loss of the TES group prompted us to use other protecting groups. Benzoyl (Bz) group was tried next, since the corresponding benzoyl ester should be more stable to Lewis acid conditions than the TES ether. The protection could be done by treatment of diene **3.50** with benzoyl chloride in pyridine at room temperature for one day, with desired diene **3.60** isolated in low yield (Scheme 3.19). Efforts were not put on the optimization of this reaction at this moment.

Scheme 3.20. Benzoyl protection of diene **3.50**.



The following RCM on diene **3.60** proved to be unfruitful. When **3.60** was treated with 25 mol% G2 in toluene at 80 °C for 6h, no reaction took place (entry 1, Table 3.12). Total consumption of starting material was observed when the reaction was heated at reflux for 1 day. Again, alkene **3.39** was observed as the major product from crude ^{1}H NMR, with no trace of desired **3.61** detected (entry 2).

Table 3.12. Attempted RCM on diene **3.60**.



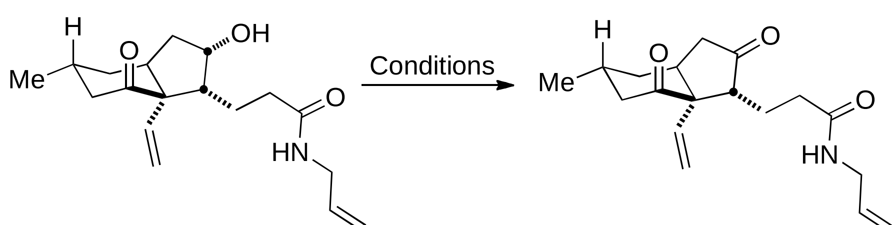
3.60 **3.61**

Entry	Conditions	Results[a]
1	25 mol% G2, PhMe, 80 °C, 6h	n.r.
2	25 mol% G2, PhMe, reflux, 1d	**3.39** only

[a] Determined by crude ^{1}H NMR or TLC.

In light of the easy formation of alkene **3.39**, we turned our attention to oxidation of the hydroxyl group of **3.50** to a ketone group. Treatment of **3.50** with Dess-Martin periodinane (DMP) in CH_2Cl_2 gave diketone **3.62** in moderate yield (entry 1, Table 3.13). To our surprise, under Ley oxidation conditions (10 mol% TPAP, NMO, 4Å MS, CH_2Cl_2, r.t., 1h), alkene **3.39** was still isolated, together with desired diketone **3.62** (entry 2). The basic 4-methylmorpholine generated may catalyze the formation of alkene **3.39**.

Table 3.13. Oxidation of diene **3.50**.



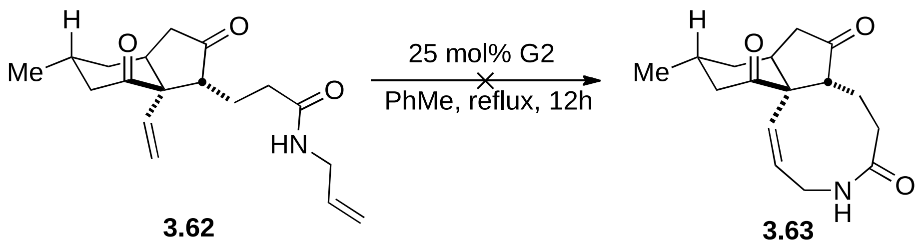
3.50 **3.62**

Entry	Conditions	Results[a]
1	1.5 equiv. DMP, CH_2Cl_2, r.t., 2h	57% **3.62**
2	10 mol% TPAP, NMO, 4Å MS, CH_2Cl_2, r.t., 1h	50% **3.62** + 37% **3.38**

[a] Isolated yield.

Unfortunately, the subsequent RCM failed again on diene **3.62**. Under the reaction conditions (25 mol% G2, PhMe, reflux, 12h), the starting material was completely consumed and provided a byproduct without the allylic side chain, with no desired azonine **3.63** observed (Scheme 3.21).

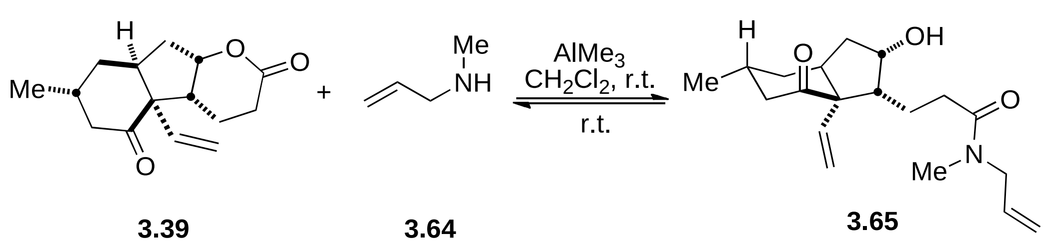
Scheme 3.21. Attempted RCM on diketone **3.62**.



3.62 **3.63**

The synthesis of diene **3.65**, which has a *N*-Me group, was also attempted. When alkene **3.38** was treated with *N*-allylmethylamine (**3.64**) in the presence of $AlMe_3$ in CH_2Cl_2, desired diene **3.65** could be isolated in moderate yield. However, it was found that **3.65** was not stable and could lose the *N*-allylmethylamine moiety to regenerate the starting alkene **3.39** upon standing at room temperature (Scheme 3.22). The repulsion between the crowded vinyl group and the amide side chain on diene **3.65** may account for the labile amide group. In light of the instability of diene **3.65**, RCM was not tested on this substrate.

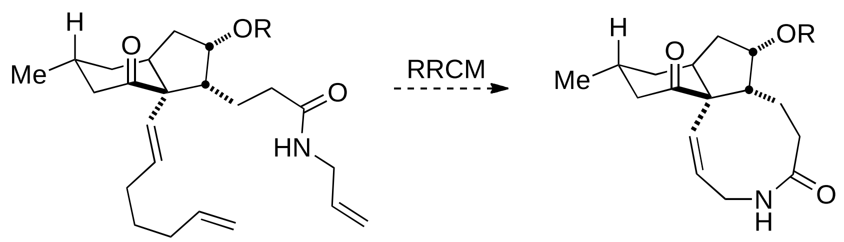
Scheme 3.22. Synthesis of diene **3.65**.



3.39 **3.64** **3.65**

From above unsuccessful RCM attempts, we realized that the vinyl group close to the all-carbon quaternary center is too hindered to react with the ruthenium catalyst. One potential solution is to use Hoye's relay ring-closing metathesis (RRCM) strategy (Scheme 3.23).[34] However, since the installation of the additional side chain may need several additional steps and the prospect of this RRCM is still unclear for substrate like **3.66**, this route was not pursued. Instead, we turned our attention to homologation on alkene **3.39** (*vide infra*).

Scheme 3.23. Envisioned RRCM to construct the azonine ring.

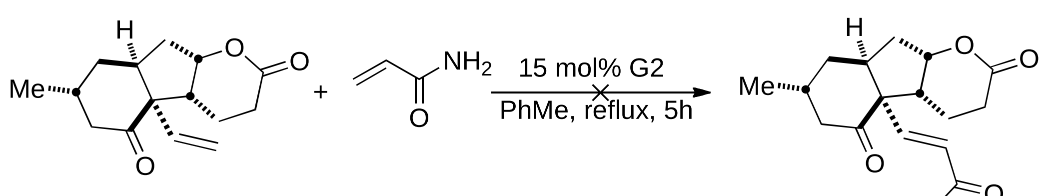


3.66 R = protecting group **3.67**

3.7 Attempted Homologation on Alkene 3.39

A cross metathesis (CM) between alkene **3.39** and acrylamide (**3.68**) was tried first, with the hope that the nitrogen atom belonging to the azonine ring could be simultaneously installed (Scheme 3.24). However, when **3.39** and **3.68** was treated with 15 mol% G2 in refluxing toluene for 5 hours, no CM product was observed, with alkene **3.39** completely recovered.

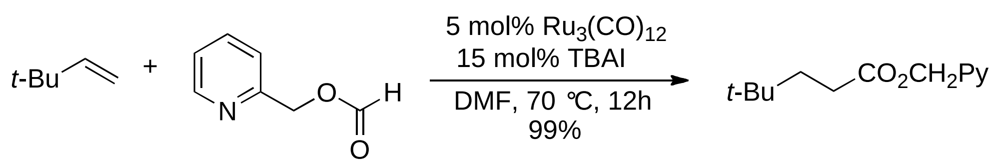
Scheme 3.24. Attempted CM on alkene **3.39**.



3.39 **3.68** **3.69**

The Chang group reported a novel chelation-assisted hydroesterification of alkenes via ruthenium catalyst. For example, when 3,3-dimethyl-1-butene (**3.70**) and 2-pyridyl-methyl formate (**3.71**) were treated with a catalytic amount of $Ru_3(CO)_{12}$ and TBAI in DMF at 70 °C for 12 hours, almost quantitative yield of ester **3.72** could be obtained (Scheme 3.25).[35]

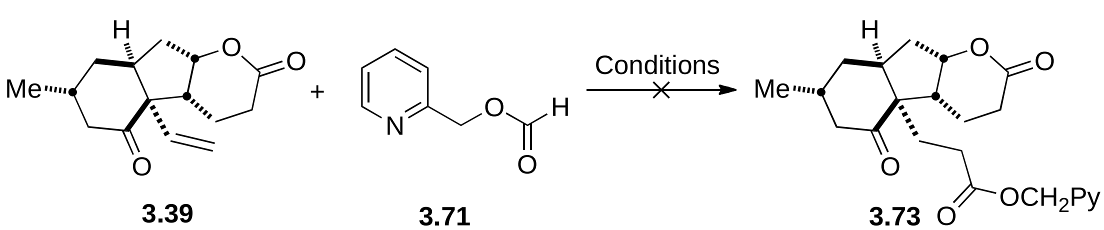
Scheme 3.25. Ru-catalyzed hydroesterification of alkene.



3.70 **3.71** **3.72**

We applied these hydroesterification conditions to alkene **3.39**, however, no desired ester **3.73** was obtained, with alkene **3.39** totally recovered (entry 1, Table 3.14). The same results were achieved when the reaction was conducted in DMSO at 110 °C with an increased load of catalysts $Ru_3(CO)_{12}$ and TBAI (entry 2). Further increasing the amount of **3.71** and raising the reaction temperature brought no beneficial effect (entry 3). Finally, the neat reaction condition with a large excess of 2-pyridyl-methyl formate (**3.71**) was tested. Unfortunately, no trace amount of desired ester **3.73** could be detected (entry 4).

Table 3.14. Attempted hydroesterification on alkene **3.39**.



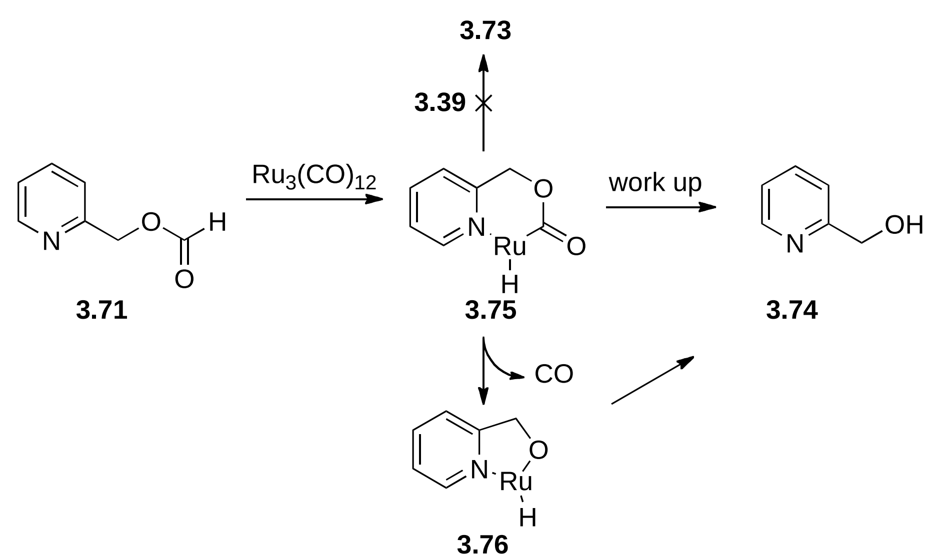
3.39 **3.71** **3.73**

Entry	Conditions[a]	Results
1	5 mol% $Ru_3(CO)_{12}$, 15 mol% TBAI, 1.5 equiv. **3.71**, DMF, 70–80 °C, 12h	no **3.73** **3.39** recovered
2	20 mol% $Ru_3(CO)_{12}$, 25 mol% TBAI, 1.5 equiv. **3.71**, DMSO, 110 °C, 12h	no **3.73** **3.39** recovered
3	20 mol% $Ru_3(CO)_{12}$, 25 mol% TBAI, 4 equiv. **3.71**, DMSO, 140 °C, 16h	no **3.73** **3.39** recovered
4	5 mol% $Ru_3(CO)_{12}$ 20 equiv. **3.71**, neat, 140 °C, 12h	no **3.73** **3.39** recovered

[a] Sealed tube reaction.

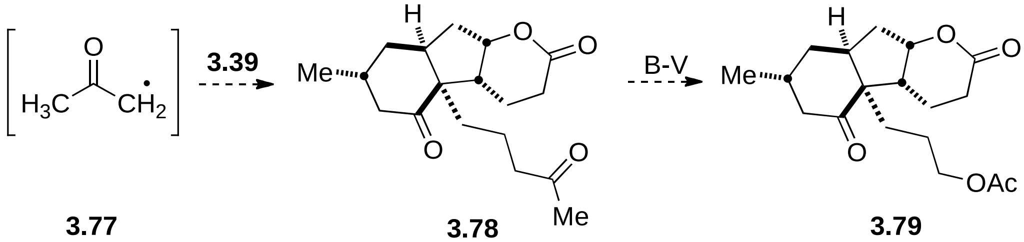
For all of the above screened hydroesterification reaction conditions, alkene **3.39** was completely recovered and the conversion of **3.71** to 2-pyridinemethanol (**3.74**) was observed. The appearance of **3.74** is not surprising, since the Ru insertion intermediate (**3.75**) may give **3.74** upon work up or lose one molecule of CO followed by reductive elimination to provide **3.74** (Scheme 3.26).[35a] The complete recovery of **3.39** showed that the vinyl group attached to the *C*-12 all-carbon quaternary center is too hindered to react with Ru insertion intermediate **3.75**. In view of the steric requirement for most of the organometallic catalysts, metal catalyzed homologation of alkene **3.39**, such as hydroformylation, were not further attempted.

Scheme 3.26. Proposed mechanism for the formation of 2-pyridinemethanol (**3.74**).



Lastly, a two-step sequence involving addition of acetonyl radical (**3.77**) to alkene **3.39** followed by Baeyer-Villiger oxidation (B-V) of adduct **3.78** to form acetate **3.79** was envisioned and tested (Scheme 3.27).

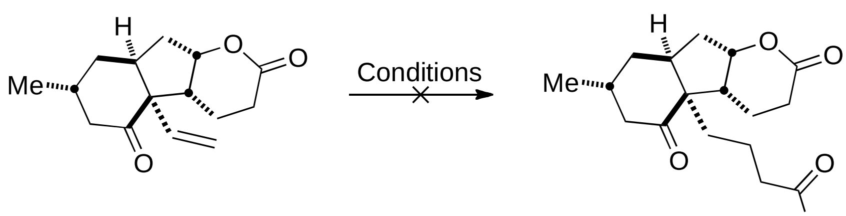
Scheme 3.27. Envisioned two-step synthesis of acetate **3.79**.



3.77 3.78 3.79

However, no reaction took place when **3.39** was treated with excess of acetone in the presence of reported catalysts such as $Ce(SO_4)_2{\cdot}4H_2O$[36a], Ag(II)O[36b], or Mn(III)$(OAc)_3{\cdot}2H_2O$[36c]. In all of the cases, alkene **3.39** was totally recovered (entry 1–3, Table 3.15).

Table 3.15. Attempted addition of acetonyl radical to alkene **3.39**.



3.39 3.78

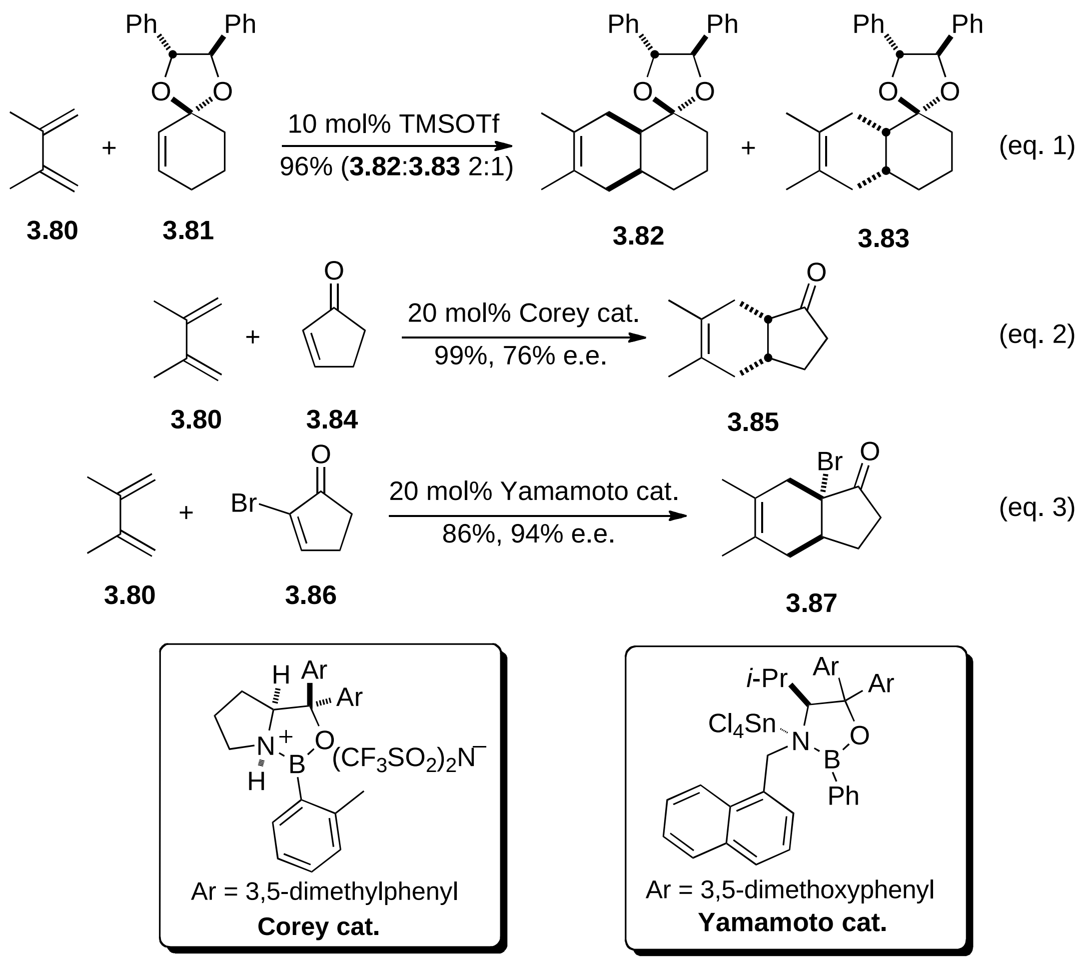
Entry	Conditions	Results
1	2.0 equiv. $Ce(SO_4)_2{\cdot}4H_2O$, acetone/H_2O (*v*/*v* 7:1), reflux, 20h	n.r.
2[a]	2.0 equiv. Ag(II)O, acetone, reflux, 12h	n.r.
3[a,b]	2.5 equiv. Mn(III)$(OAc)_3{\cdot}2H_2O$, acetone, MW, 120 °C, 5h	n.r.

[a] acetone as solvent. [b] Sealed tube reaction.

3.8 Towards asymmetric synthesis

As stated early in our retrosynthetic analysis (Scheme 1, *vide supra*), the asymmetric version of our synthesis can be achieved if enantiomeric pure **3.8** is employed. A search of literature shows that there is no reported asymmetric synthesis of cyclopentanone **3.8** or its ketal **3.11**. Some close related examples are shown in Scheme 3.28.

Scheme 3.28. Selected examples of asymmetric D-A of enone or enone ketal.

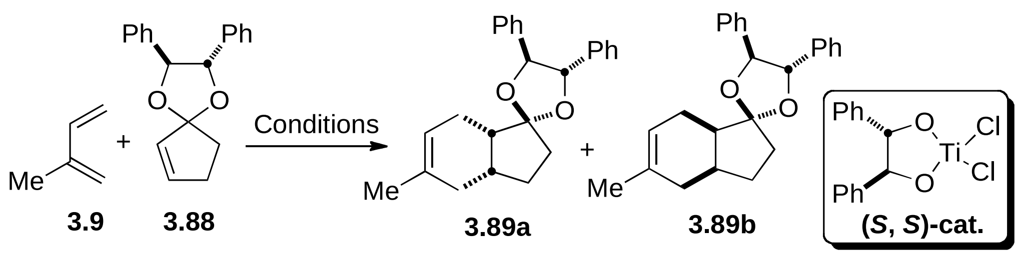


For instance, Anderson and coworkers reported the asymmetric Diels-Alder reaction (D-A) between 2,3-dimethyl-1,3-butadiene (**3.80**) and chiral ketal **3.81** to afford adduct **3.82** and **3.83** (d.r. 2:1) (eq. 1).[37] The Corey group showed that their proline derived oxazaborolidine catalyst could catalyze the asymmetric Diels-Alder reaction (D-A) between **3.80** and cyclopent-2-enone (**3.84**), with excellent yield of **3.85** in good e.e. obtained (eq. 2).[38a,b,c] Shibatomi and Yamamoto also demonstrated that their valine derived oxazaborolidine catalyst was effective towards the reaction between **3.80** and 2-bromocyclopent-2-enone (**3.86**) to give **3.87** in excellent yield and e.e. (eq. 3).[39]

The chiral auxiliary strategy was attempted first. To this end, (*S*, *S*)-hydrobenzoin derived chiral ketal **3.88** was treated with excess of isoprene (**3.9**) and a catalytic amount of TMSOTf in CH_2Cl_2 at –78 °C, the conditions used by Anderson, J.C. and coworkers.[37] Excellent yield of D-A adduct **3.89a** and **3.89b** were obtained. However, the diastereoselectivity is not satisfactory (entry 1, Table 3.16). Higher concentration of **3.88** could slightly improve the diastereoselectivity, which is in agreement with Anderson's observation (entry 2).

$TiCl_4$ as the Lewis acid catalyst was tried next and unsatisfactory d.r. was again observed. However, the diastereoselectivity was reversed at this moment (entry 3). Finally, the (*S*, *S*)-hydrobenzoin derived titanium catalyst ((*S*, *S*)-cat.) was used with the hope that a chiral auxiliary could bring some beneficial effect. Unfortunately, no improvement in d.r. was observed. It is interesting to note that the diastereoselectivity can be reversed with higher temperature (entry 4, 5).

Table 3.16. Diels-Alder reaction of isoprene (**3.9**) and ketal **3.88**.

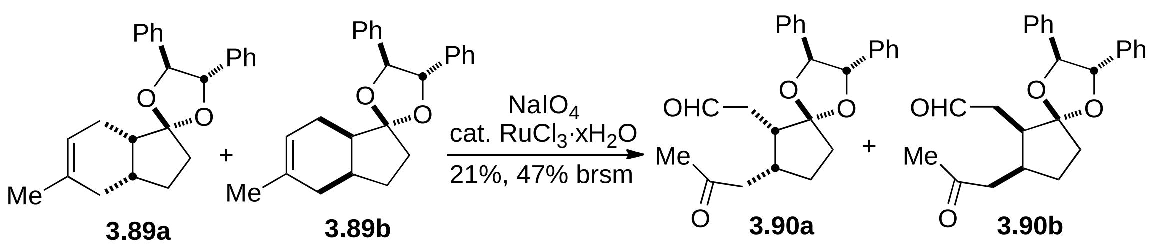


Entry	Conditions	Yield[a,b]	d.r.(**3.89a**:**3.89b**)
1	10 mol% TMSOTf, CH_2Cl_2, 0.1 M, −78 °C, 25h	100% (90%)	2.08:1
2	10 mol% TMSOTf, CH_2Cl_2, 1.0 M, −78 °C, 25h	100% (96%)	2.76:1
3	10 mol% $TiCl_4$, CH_2Cl_2, −78 °C, 2h	15%	0.67:1
4	20 mol% (*S*, *S*)-cat., CH_2Cl_2, −78 °C, 1d	6%	0.53:1
5	20 mol% (*S*, *S*)-cat., CH_2Cl_2,0−4 °C, 2d	41%	1.18:1

[a] Yield is determined by crude ^{1}H NMR. [b] Yield in parenthesis is isolated yield.

The D-A adducts **3.89a** and **3.89b** were found to be inseparable by chromatography or crystallization. Their subsequent conversion to keto aldehydes was problematic, with very low yield of desired products **3.90a** and **3.90b** obtained, which were found also to be inseparable upon chromatography (Scheme 3.29).

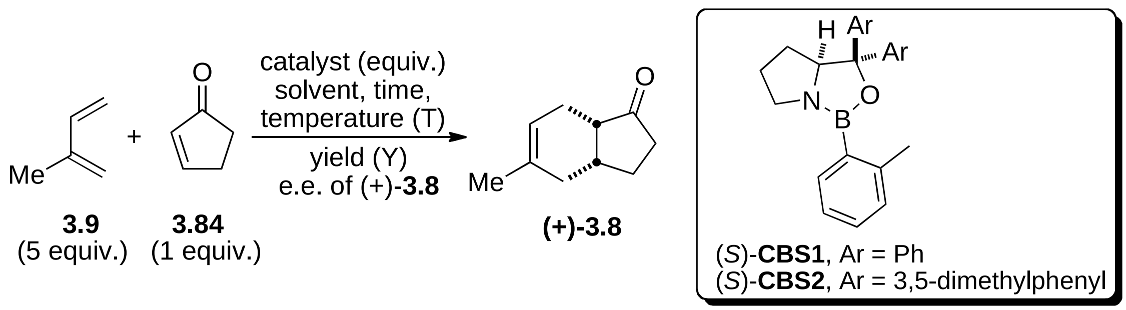
Scheme 3.29. Synthesis of keto aldehyde **3.90a** and **3.90b**.



In view of above encountered difficulties, this chiral auxiliary strategy was not pursued any further. Instead, efforts were put on Corey's oxazaborolidine catalyzed Diels-Alder reaction (D-A) of isoprene (**3.9**) and cyclopent-2-enone (**3.84**).[38] To our delight, when **3.84** and excess of **3.9** were treated with 20 mol% of (*S*)-(–)-*o*-Tolyl-CBS-oxazaborolidine ((*S*)-**CBS1**) in the presence of 18 mol % of Tf_2NH[38c] as an activator in toluene at −25 °C for 3 days, (+)-**3.8** was isolated in 52% yield and 73.5% e.e. (entry 1, Table 3.17). The temperature around −25 °C was found to be optimal, since no reaction took place at −40 °C while e.e. dropped to 48.6% at room temperature (entry 2, 3).

Switching the solvent from PhMe to CH_2Cl_2 brought little impact on yield and e.e. (entry 4). Compared to (*S*)-**CBS1**, (*S*)-**CBS2** gave slightly better e.e. of (+)-**3.8**, which is in agreement with the reported results (entry 5).[38c] Since there is no significant improvement for the yield or the e.e. of (+)-**3.8** when (*S*)-**CBS2** was employed, further optimization was focused on the use of (*S*)-**CBS1**, which is commercially available as 0.5 M solution in toluene.

Table 3.17. Catalytic asymmetric synthesis of (+)-**3.8** by Corey catalysts.



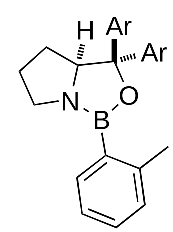
Entry	Catalyst	Equiv. (mol %)	Solvent	Time	T (°C)	e.e. (%)	Y[a,b] (%)
1	(*S*)-**CBS1**/Tf_2NH	20	PhMe	3d	–25	73.5	52
2	(*S*)-**CBS1**/Tf_2NH	20	PhMe	1d	–40	–	n.r.
3	(*S*)-**CBS1**/Tf_2NH	20	PhMe	40h	r.t.	48.6	15
4	(*S*)-**CBS1**/Tf_2NH	20	CH_2Cl_2	3d	–20	71.6	56
5	(*S*)-**CBS2**/Tf_2NH	20	CH_2Cl_2	7d	–20	73.5	60
6	(*S*)-**CBS1**/Tf_2NH	20	CH_2Cl_2	10d	–30	77.3	38
7	(*S*)-**CBS1**/Tf_2NH	10	CH_2Cl_2	4d	–20	37.2	40
8	(*S*)-**CBS1**/Tf_2NH	5	CH_2Cl_2	3d	–20	3.8	49
9	(*S*)-**CBS1**/$AlBr_3$	5	PhMe	3d	–20	70.6	14
10	(*S*)-**CBS1**/$AlBr_3$	5	CH_2Cl_2	4d	–30	65.4	5
11	(*S*)-**CBS1**/$AlBr_3$	5	PhMe/CH_2Cl_2	30h	–42	81.9	7
12	(*S*)-**CBS1**/$AlBr_3$	5	PhMe/Et_2O	4d	–20	63.9	21
13	(*S*)-**CBS1**/$AlBr_3$	5	PhMe/CH_3CN	4d	–20	75.2	9
14	(*S*)-**CBS1**/TMSOTf	10	PhMe	1d	–78	65.9	24
15	(*S*)-**CBS1**/TfOH	20	PhMe	1d	–30	73.8	3

[a] Isolated yield. [b] Yield is not accurate because of the low boiling point of (+)-**3.8**.

In CH_2Cl_2, running the reaction at −30 °C could improve the product e.e. to 77.3%. However, the reaction became extremely sluggish at this temperature, which provided (+)-**3.8** in only 38% yield for 10 days (entry 6). When less amounts of catalyst were used, sharp drop of e.e.s were observed (entry 7, 8). Interestingly, the product yields were not affected.

$AlBr_3$ as the activator for (*S*)-**CBS1** was reported to give a more efficient catalyst, in which the load of catalyst could be decreased to 4 mol% without erosion of yield or enantioselectivity.[38d] The use of (*S*)-**CBS1**/$AlBr_3$ as catalyst was thus examined in regards to different solvent as well as temperatures (entry 9–13). Unfortunately, no significant improvement for enantioselectivity was detected. Isoprene (**3.9**) was found to be incompatible with this catalyst system, which polymerized in all of the conditions examined. As a complementary to Tf_2NH or $AlBr_3$, TMSOTf or TfOH[38e] as the activator to (*S*)-**CBS1** was also attempted. Both gave unsatisfactory results (entry 14, 15).

The further possible direction for optimization of this catalyzed asymmetric Diels-Alder reaction (D-A) between **3.9** and **3.84**, is to use other oxazaborolidines such as (*S*)-**CBS3** or (*S*)-**CBS4** (Figure 3.1). Due to time constraints, those two oxazaborolidines were not tested.



(*S*)-**CBS3**, Ar = Naphthyl
(*S*)-**CBS4**, Ar = 3,5-bis(trifluoromethyl)phenyl

Figure 3.1. Other potential oxazaborolidines.

It is worthy of note that according to the model proposed by Corey and coworkers (Figure 3.2),[38a,b,c] the absolute stereochemistry of the above (*S*)-**CBS1** or (*S*)-**CBS2** mediated asymmetric Diels-Alder adduct (+)-**3.8** was assigned as shown.

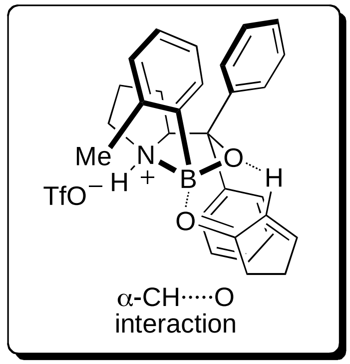
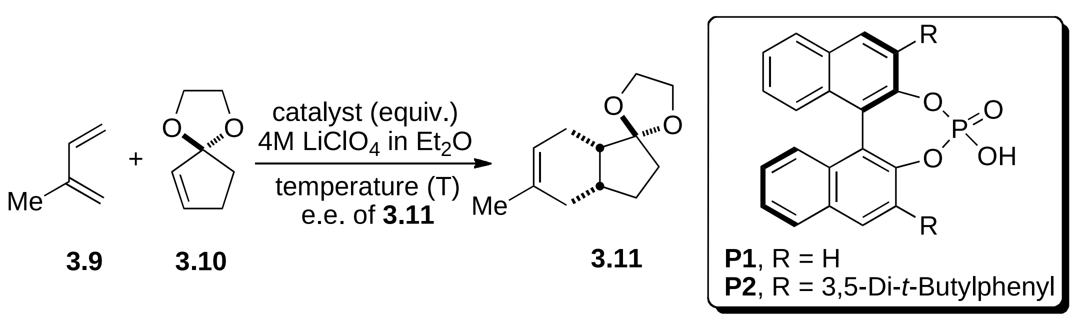


Figure 3.2. Proposed model of complexation of **3.84** with (*S*)-**CBS1**.

In the previous synthesis of **3.11**, a catalytic amount of (1*S*)-(+)-camphorsulfonic acid (CSA) was added as the catalyst (Scheme 3.2, *vide supra*). We noticed that the adduct **3.11** is not a true racemate. In fact, a 1.0% e.e. was detected, which is in agreement with Chapuis' observation.[40] We wondered if other chiral acids could catalyze this ionic Diels-Alder reaction (D-A) and improve the enantioselectivity. To this end, chiral phosphoric acids (**P1** and **P2**) were attempted (Table 3.18). Unfortunately, no significant e.e. improvement was achieved even at −78 °C, which showed that the proton itself catalyzed the reaction and the counter chiral anion had little effect.

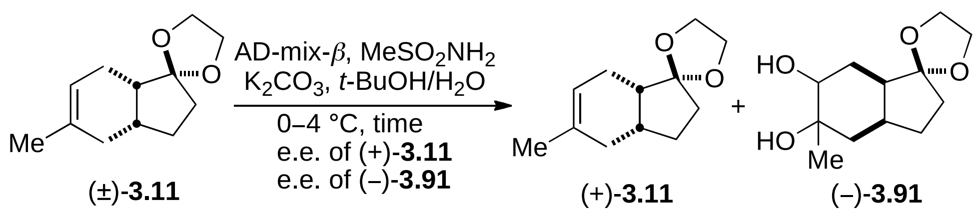
Table 3.18. Attempted catalytic asymmetric synthesis of **3.11**.



Entry	**Catalyst**	**Equiv.** (mol %)	**T** (°C)	**e.e.** (%)
1	**P1**	0.25	r.t.	<1.0
2	**P1**	0.25	–78 °C	<1.0
3	**P2**	0.05	–30 °C	2.0

Finally, we came up with the idea that a Sharpless asymmetric dihydroxylation (Sharpless AD)[41] could be employed to afford kinetic resolution[42] on substrate (±)-**3.11**. One advantage of this kinetic resolution is that the dihydroxylation product can be converted to ketoaldehyde and reenter our synthetic route (*vide infra*).

Table 3.19. Sharpless asymmetric dihydroxylation on (±)-**3.11**.[a]

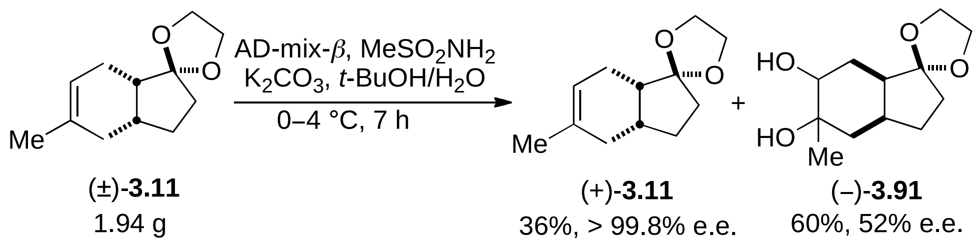


Entry	**Time** (h)	**e.e.** of (+)-**3.11**[b,c]	**e.e.** of (–)-**3.91**[c,d]
1	1	13.0%	n.d.
2	2	24.2%	n.d.
3	3	42.1%	n.d.
4	4	56.8%	n.d.
5	5	76.3%	n.d.
6	6	89.0%	n.d.
7	7	96.9%	n.d.
8	8	98.5%	n.d.
9	13	> 99.4% (33%)	n.d. (67%)

[a] Reaction was performed on 67 mg of (±)-**3.11**. [b] e.e. was measured by GC. [c] Yield in parenthesis is isolated yield. [d] e.e. was determined by conversion of (–)-**3.91** to (–)-**3.17** and measured e.e. by HPLC.

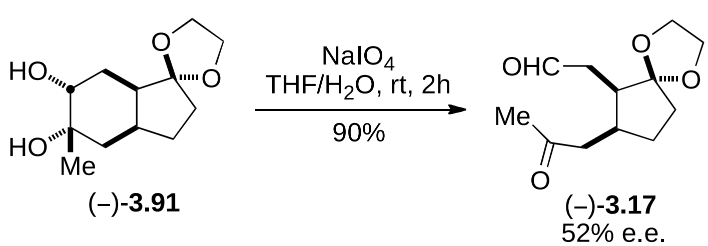
To our delight, when (±)-**3.11** (67 mg scale) was subjected to the Sharpless AD conditions (AD-mix-β, $MeSO_2NH_2$, K_2CO_3, t-BuOH/H_2O (*v*/*v* 1:1), 0–4 °C), an increase of e.e. for (+)-**3.11** was observed along with reaction time (Table 3.19). At 13 hours, (+)-**3.11** was isolated in 33% yield and greater than 99.4% e.e.

Scheme 3.30. Sharpless asymmetric dihydroxylation on (±)-**3.11** (1.94 g scale).



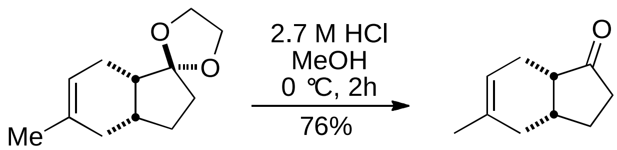
More satisfyingly, when this kinetic resolution was performed on a larger scale (1.94 g of (±)-**3.11**), (+)-**3.11** in 33% yield and greater than 99.8% e.e. was isolated at 7 hour (Scheme 3.30). The corresponding diol (–)-**3.91** was obtained in 60% yield. Since direct measurement of e.e. for (–)-**3.91** was met with failure by GC, HPLC or ^{1}H NMR analysis (using Eu(hfc)$_3$), (–)-**3.91** was converted to (–)-**3.17**, from which the e.e. of (–)-**3.91** was determined to be 52% (Scheme 3.31). The enantioenriched (–)-**3.17** could be used in the syntheses of the antipode of alkaloids.

Scheme 3.31. Synthesis of (–)-**3.17** from (–)-**3.91**.



The absolute stereochemisty of the above kinetic resolution product (+)-**3.11** was assigned to be as shown by conversion of (+)-**3.11** to (+)-**3.8** and comparison of its optical rotation with the above (*S*)-**CBS1** mediated asymmetric Diels-Alder adduct (Scheme 3.32).

Scheme 3.32. Conversion of (+)-**3.11** to (+)-**3.8**.



(+)-**3.11**
95.0% e.e.

(+)-**3.8**
92.3% e.e.

The AD-mix-α catalyzed kinetic resolution of (**±**)-**3.11**, which should afford (**–**)-**3.11** and (+)-**3.91** in theory, was not studied due to time constraints.

3.9 Conclusion

For our first generation synthetic approach, a unified and diversity oriented strategy that can target lycoposerramine A as well as several other family members was presented. Through a microwave assisted Diels-Alder reaction between silyoxydiene and enone, the *cis*-fused 6,5-cycle with one all-carbon quaternary center was constructed in high yield. The stereoselective introduction of the *C*-15 methyl group was achieved via a mesylate controlled hydrogenation of an enone moiety. However, due to the steric hindrance brought by the neighboring all-carbon quaternary center, all efforts to form the azonine ring by RCM reaction were met with failure. The one-carbon elongations of the hindered vinyl group were also not successful. The asymmetric version of our synthetic approach was achieved by kinetic resolution of the earliest intermediate by a Sharpless dihydroxylation.

3.10 References

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Chapter 4

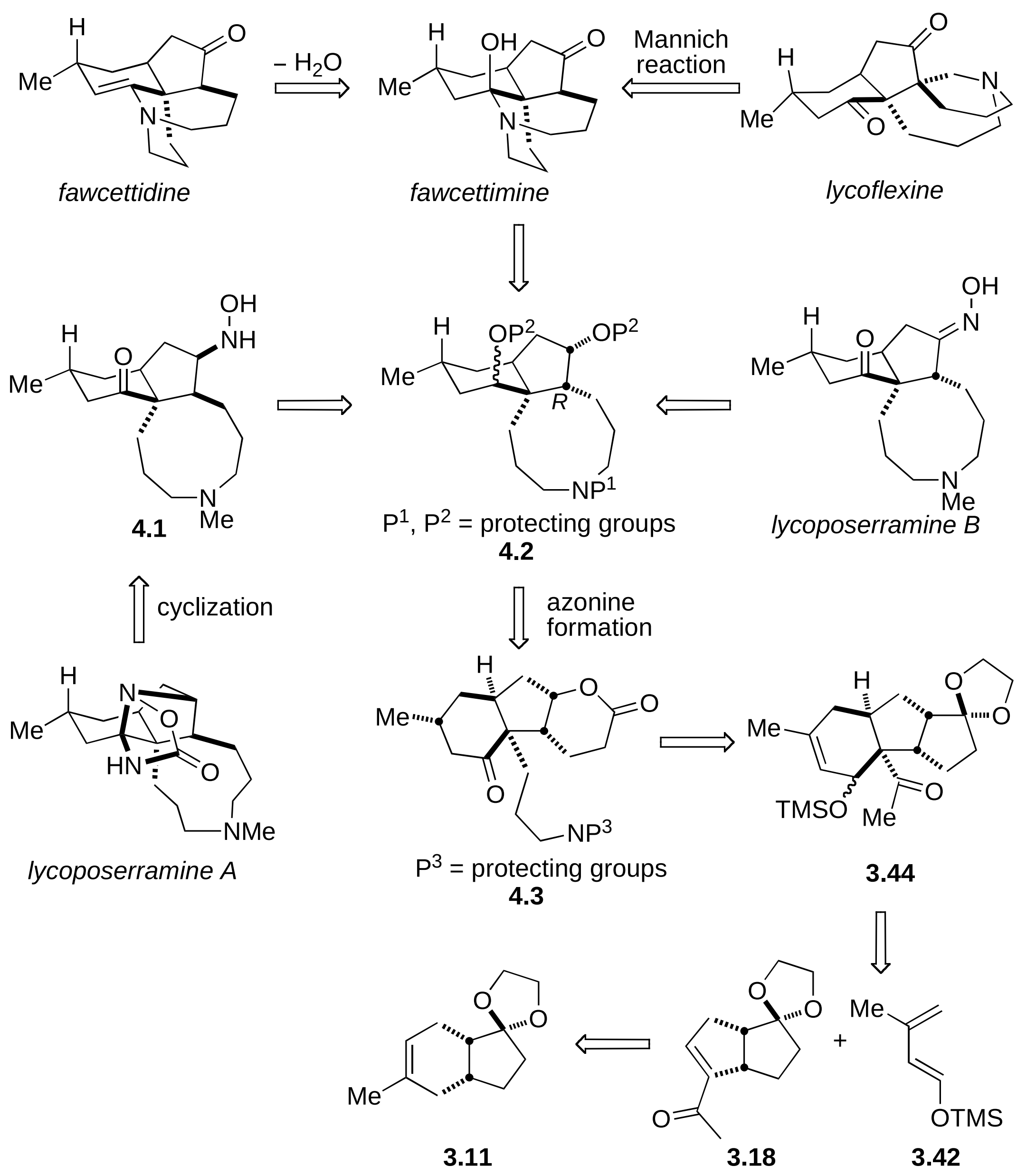
The Second Generation Synthesis:

Fukuyama-Mitsunobu Approach

4.1 Modified Retrosynthetic Analysis

In light of the failures encountered in our first generation synthetic approach (Chapter 3), the steric hindrance brought by the *C*-12 all-carbon quaternary center (fawcettimine numbering) was appreciated in our modified synthetic approach.

Scheme 4.1. Modified retrosynthetic analysis.

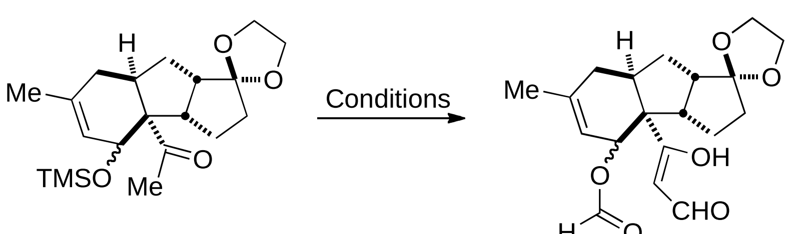


As shown in Scheme 4.1, a homologation of D-A adduct **3.44** (Chapter 3) or its derivatives, followed by cyclization to afford azonine **4.2** was the key strategic change to our second-generation retrosynthetic analysis. The advantage of this early step homologation is that the azonine formation site is now three-carbons away from the *C*-12 all-carbon quaternary center so that the steric hindrance can be minimized. Azonine **4.2**, with the *R* configuration at *C*-4, could be converted to lycoposerramine B. When this stereocenter is inverted, **4.2** could serve as the common intermediate to lycoposerramine A and fawcettimine. Since the conversion of fawcettimine to fawcettidine or lycoflexine has already been documented,[1] our synthetic route should enable us the access to those two alkaloids as well.

4.2 Homologation

The homolotation of D-A adduct **3.44** could be effected by treatment of **3.44** with NaH in THF at room temperature in the presence of ethyl formate (HCO_2Et)[2a] , with formate **4.4** (enol form) isolated in 47% yield (entry 1, Table 4.1). The trimethylsilyl group of **3.44** was found to be incompatible with the reaction conditions. The yield of **4.4** could be improved dramatically if less sterically demanding methyl formate (HCO_2Me)[2b] was employed (entry 2).

Table 4.1. Homologation on D-A adduct **3.44**.



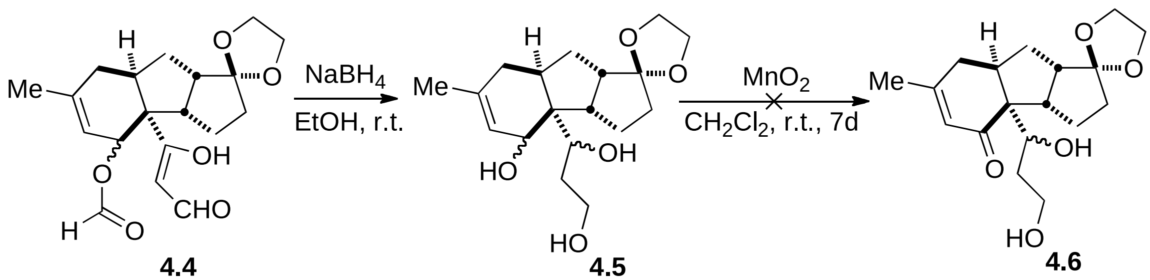
3.44 **4.4**

Entry	Conditions	Results[a]
1	6 equiv. NaH, 10 equiv. HCO_2Et, THF, r.t.	47%
2	15 equiv. NaH, 40 equiv. HCO_2Me, THF, r.t.	80%

[a] Isolated yield.

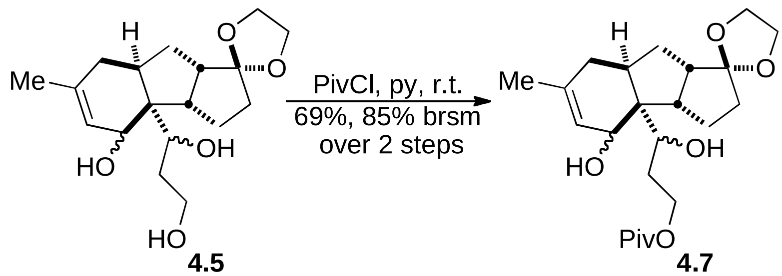
Formate **4.4**, when treated with $NaBH_4$ in ethanol at room temperature was converted to triol **4.5** (Scheme 4.2). Unfortunately, the selective allylic oxidation of triol **4.5** to form enone **4.6** could not be realized this time by treatment of **4.5** with activated MnO_2 in CH_2Cl_2 even with prolonged reaction time.

Scheme 4.2. Attempted synthesis of enone **4.6**.



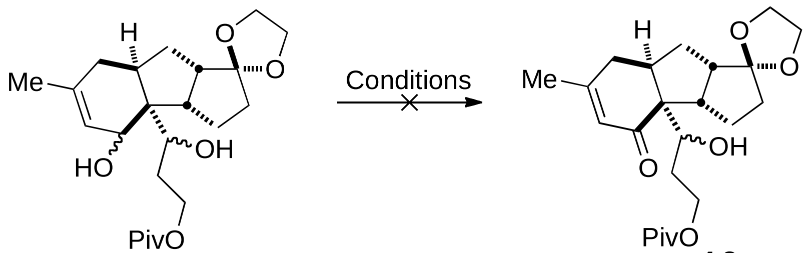
On the other hand, the selective protection of the primary hydroxyl group of triol **4.5** as the pivolate could be effected by treatment of **4.5** with pivaloyl chloride in pyridine solvent at room temperature (Scheme 4.3).

Scheme 4.3. Synthesis of pivolate **4.7**.



The selective allylic oxidation of **4.7** was attempted. However, under standard reaction conditions (MnO_2 or $BaMnO_4$, CH_2Cl_2, r.t.), no reaction took place (entry 1, 2, Table 4.2). When PDC was used, the oxidation of *C*-11 hydroxy group (fawcettimine numbering) was observed, with no desired enone **4.8** detected from the reaction mixture (entry 3).

Table 4.2. Attempted selective allylic oxidation of pivolate **4.7**.



4.7 4.8

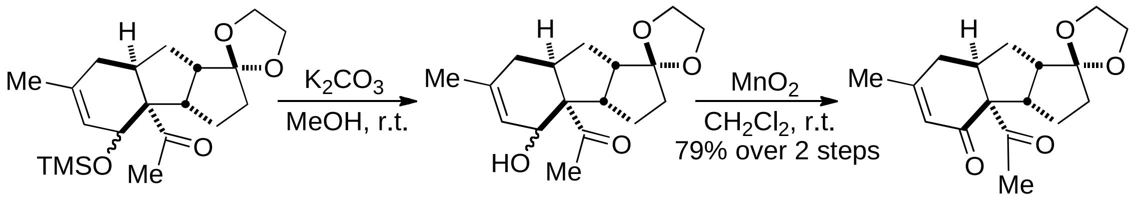
Entry	Conditions	Results[a]
1	MnO_2, CH_2Cl_2, r.t., 2d	n.r.
2	$BaMnO_4$, CH_2Cl_2, r.t., 1d	n.r.
3	PDC, CH_2Cl_2, r.t., 8h	no **4.8**

[a] Determined by crude ^{1}H NMR.

The unfruitful selective allylic oxidation of triol **4.5** and pivolate **4.7** was again attributed to the steric hindrance brought by the neighboring *C*-12 all-carbon quaternary center.

To avoid the troublesome selective allylic oxidation problem, we decided to put the homologation to a later stage. To this end, D-A adduct **3.44** was subjected to K_2CO_3 in MeOH solvent at room temperature to give allylic alcohol **4.9** (Scheme 4.4). Subsequent allylic oxidation by MnO_2 afforded enone **4.10** in 79% yield over 2 steps.

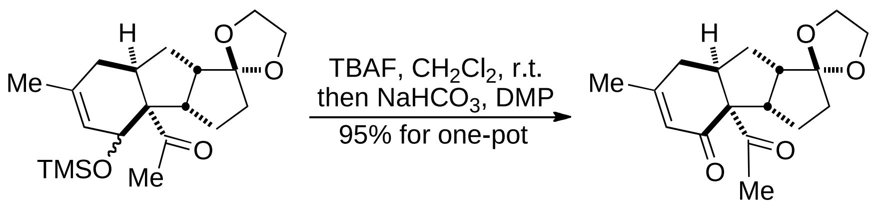
Scheme 4.4. Synthesis of enone **4.10**.



3.44 4.9 4.10

It was found that the conversion of **3.44** to **4.10** can be done more conveniently in a one-pot manner by treatment of **3.44** with TBAF to remove the TMS group followed by in-situ oxidation of the newly formed allylic alcohol by Dess-Martin periodinane (DMP)[3]. Enone **4.10** was isolated in 95% yield for this one-pot procedure (Scheme 4.5).

Scheme 4.5. One-pot synthesis of enone **4.10** from D-A adduct **3.44**.



3.44 **4.10**

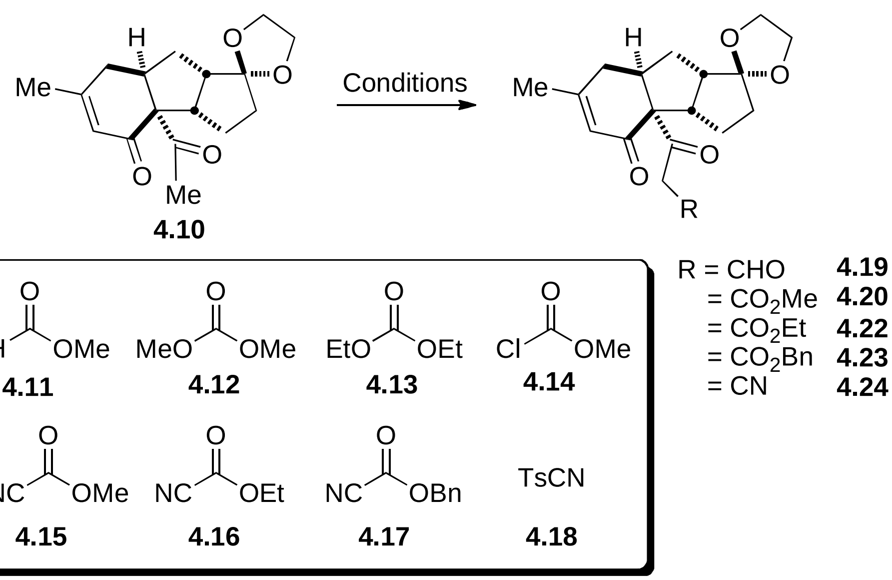
With enone **4.10** in hand, the selective homologation of the acetyl group could now be investigated. The previous homologation conditions for D-A adduct **3.44** (15 equiv. NaH, 40 equiv. **4.11**, THF) were tested first. It was found that no reaction took place at room or elevated temperature, with enone **4.10** totally recovered (entry 1–2, Table 4.3). Carbonates such as dimethyl carbonate (**4.12**) and diethyl carbonate (**4.13**) were examined next. However, the only promising result was obtained when enone **4.10** was treated with excess NaH in the presence of **4.12** in DMF, with trace of β-keto ester **4.20** detected from the crude ^{1}H NMR. In most of the cases, no reaction took place and enone **4.10** was totally recovered (entry 3–7).

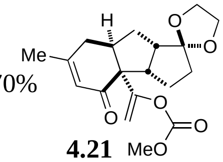
We then turned our attention to the more electrophilic methyl chloroformate (**4.14**). When enone **4.10** was subjected to excess of NaH and **4.14** in refluxing THF for 5 hours, no reaction took place (entry 8). To our surprise, when **4.10** was treated with 1.2 equiv. of KHMDS in THF at –78 °C followed by quenching with **4.14**, enol carbonate **4.21**, instead of homologation product **4.20**, was isolated in 70% yield (entry 9).

Mander's reagent (methyl cyanoformate, **4.15**)[4], which was reported to give superior yields of *C*-acylation products for sterically hindered substrates, was examined next. To our delight, under the reaction conditions (1.1 equiv. LiHMDS, 1.2 equiv. **4.15**, THF, **–**78 °C to r.t., 10h), desired β-keto ester **4.20** was isolated in 18% yield together with some recovered starting material (entry 10). The yield of **4.20** could be greatly improved if Et_2O was used as the solvent (entry 12). Other bases such as NaHMDS or LDA gave relatively lower yields of **4.20** (entry 11, 13).

It is worth noting that under the same conditions as for methyl cyanoformate (**4.15**), methyl chloroformate (**4.14**) totally failed to afford trace amount of desired **4.20** (entry 14). Other cyanoformates, such as Ethyl cyanoformate (**4.16**) and benzyl cyanoformate (**4.17**) were also screened, however, both cyanoformate were found to be less efficient than **4.15** (entry 15, 16).

Table 4.3. Homologation of enone **4.10**.



Entry	Conditions	Results[a,b]
1	15 equiv. NaH, 40 equiv. **4.11**, THF, r.t., 3h	n.r.
2	15 equiv. NaH, 40 equiv. **4.11**, THF, reflux, 6h	n.r.
3	6 equiv. NaH, 10 equiv. **4.12**, THF, reflux, 5h	n.r.
4[c]	3 equiv. KHMDS, 10 equiv. **4.12**, THF, –78 °C to r.t., 19h	no **4.20**
5	3 equiv. NaH, 6 equiv. **4.12**, DMF, r.t., 5h	trace **4.20**
6	10 equiv. NaH, 20 equiv. **4.13**, PhMe, reflux, 30h	n.r.
7[c]	2.5 equiv. KHMDS, 2 equiv. **4.13**, THF, –78 °C to r.t., 30h	n.r.
8	15 equiv. NaH, 40 equiv. **4.14**, THF, reflux, 5h	n.r.
9[c]	1.2 equiv. KHMDS, 1.4 equiv. **4.14**, THF, –78 °C to r.t., 22h	70%  **4.21**
10[e]	1.1 equiv. LiHMDS, 1.2 equiv. **4.15**, THF, –78 °C to r.t., 10h	18% (42%) **4.20**
11[d]	1.1 equiv. NaHMDS, 1.2 equiv. **4.15**, THF, –78 °C to r.t., 12h	23% (38%) **4.20**
12[e]	1.1 equiv. LiHMDS, 1.2 equiv. **4.15**, Et_2O, –78 °C to r.t., 7h	41% (68%) **4.20**
13	1.1 equiv. LDA, 1.2 equiv. **4.15**, Et_2O, –78 °C to r.t., 5h	37% (59%) **4.20**
14[e]	1.1 equiv. LiHMDS, 1.2 equiv. **4.14**, Et_2O, –78 °C to r.t., overnight	no **4.20**
15[e]	1 equiv. LiHMDS, 1 equiv. **4.16**, Et_2O, –78 °C to r.t., 4h	33% (62%) **4.22**
16[e]	1 equiv. LiHMDS, 1 equiv. **4.17**, Et_2O, –78 °C to r.t., 6h	24% (34%) **4.23**
17[e]	1.1 equiv. LiHMDS, 1.1 equiv. **4.18**, Et_2O, –78 °C to r.t., 6h	23% (26%) **4.24**
18[f]	1.2 equiv. LiHMDS, 1.2 equiv. **4.15**, Et_2O, –78 °C to r.t., overnight	60% (94%) **4.20**

[a] Isolated yield. [b] Yield in parenthesis is based on recovered **4.10**. [c] KHMDS (0.5 M in toluene) solution was used. [d] NaHMDS (1.0 M in THF) solution was used. [e] LiHMDS (1.0 M in THF) solution was used. [f] LiHMDS solid was used.

Instead of forming a β-keto ester, tosyl cyanide (**4.18**) was also attempted with the hope that the nitrogen atom belonging to the azonine ring could be simultaneously installed. However, the desired β-keto cyanide **4.24** was obtained in very low yield (entry 17).

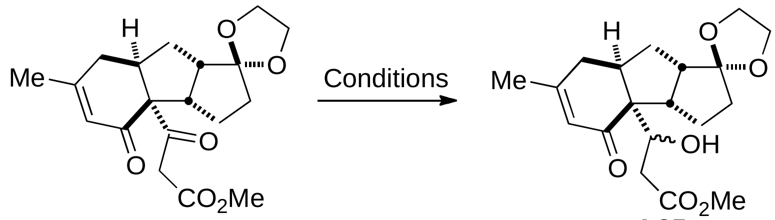
Finally, we were pleased to find that solid LiHMDS, instead of LiHMDS solution (1.0 M in THF), could improve the yield of **4.20** dramatically (entry 18). Under these optimized conditions, *β*-keto ester **4.20** could be obtained in 60% yield (94% based on recovered starting material).

4.3 Azonine formation by Fukuyama-Mitsunobu cyclization

With the homologation product **4.20** now secured, efforts were then put on the azonine formation, before which, the *C*-15 stereocenter (fawcettimine numbering) needs to be installed. To avoid significant strategic changes, the previous developed mesylate group controlled hydrogenation of enone (Scheme 3.16, Chapter 3) was adopted here to set the required stereochemistry of *C*-15. To this end, the selective reduction of *β*-keto ester **4.20** to *β*-hydroxy ester **4.25** in the presence of an enone moiety needs to be realized.

In 1988, Ward and coworkers reported the use of excess $NaBH_4$ in $MeOH/CH_2Cl_2$ (*v*/*v* 1:1) at −78 °C to reduce ketones selectively in the presence of enones.[5] This conditions was applied to our *β*-keto ester **4.20**. We were pleased to find that desired *β*-hydroxy ester **4.25** was obtained in 40% yield with some recovered starting material (entry 1, Table 4.4). The reaction was found to be extremely sluggish when 1 equiv. of $ZnCl_2$ was added (entry 2). Finally, by running the temperature at −42 °C, the reaction was found to complete in 4.5 hours, with **4.25** isolated in 83% yield (entry 3). This selective reduction was not optimized further.

Table 4.4. Selective reduction of β-keto ester **4.20**.



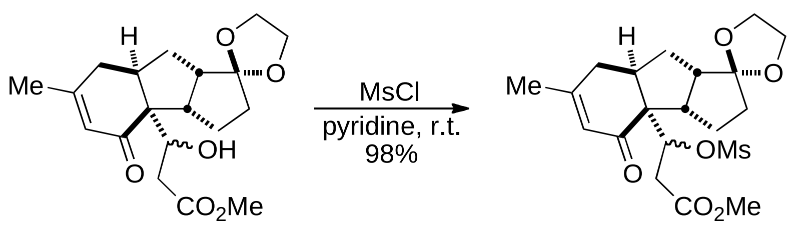
4.20 **4.25**

Entry	Conditions	Results[a]
1	10 equiv. $NaBH_4$, CH_2Cl_2/MeOH (*v*/*v* 1:1), –78 °C, 10h	40%
2	200 wt. % $NaBH_4$, 1 equiv. $ZnCl_2$, CH_2Cl_2/MeOH (*v*/*v* 1:1), –78 °C, 5h	< 10%
3	100 wt. % $NaBH_4$, CH_2Cl_2/MeOH (*v*/*v* 1:1), –42 °C, 4.5h	83%

[a] Isolated yield.

From β-hydroxy ester **4.25**, mesylate formation went smoothly to give mesylate **4.26**, which set the stage for the hydrogenation to install the *C*-15 stereocenter (fawcettimine numbering) (Scheme 4.6).

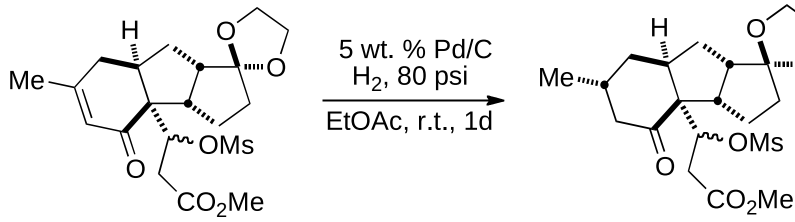
Scheme 4.6. Synthesis of mesylate **4.26**.



4.25 **4.26**

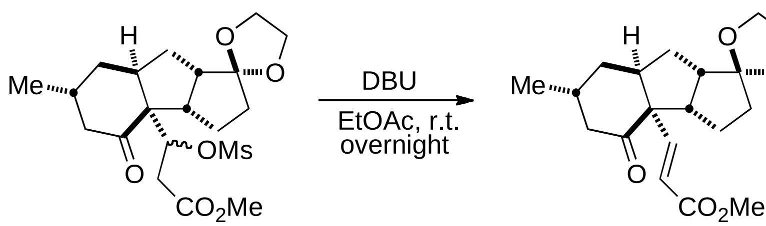
Under the same conditions (5 wt.% Pd/C, 1 atm. H_2, EtOAc, r.t.) for previous reduction of substrate **3.40** (Chapter three), no reduction of mesylate **4.26** was observed this time. Fortunately, the reduction went smoothly under 80 psi of H_2 and afforded cyclohexanone **4.27** exclusively (Scheme 4.7).

Scheme 4.7. Hydrogenation of mesylate **4.26**.



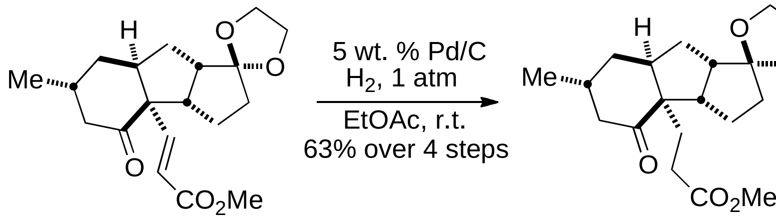
Since the mesylate of **4.27** is located at the β-position of the ester group, we envisioned that a base could trigger the β-elimination to deliver α, β-unsaturated ester **4.28**. This β-elimination should be superior to our previous developed microwave assisted mesylate elimination conditions (Li_2CO_3, LiBr, DMF, 210 ˚C, MW, 8min). To our delight, when **4.27** was treated with 1.2 equiv. of DBU in EtOAc at room temperature overnight, the desired α, β-unsaturated ester **4.28** (*Z* form only) could be obtained as anticipated (Scheme 4.8).

Scheme 4.8. β-Elimination of mesylate **4.27**.



From α, β-unsaturated ester **4.28**, subsequent hydrogenation went smoothly without incident. Subjection of **4.28** to standard hydrogenation conditions (cat. Pd/C, H_2, 1 atm., EtOAc, r.t.) provided ester **4.29** as a single diastereomer in 63% yield over 4 steps (Scheme 4.9).

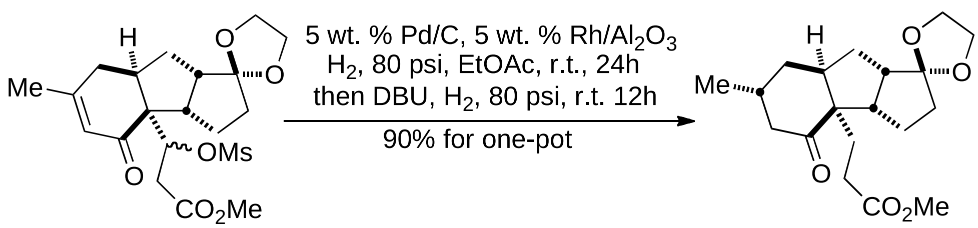
Scheme 4.9. Hydrogenation of α, β-unsaturated ester **4.28**.



4.28 **4.29**

To our delight, the more convenient one-pot conversion of mesylate **4.26** to ester **4.29** could also be achieved without erosion of efficiency, provided that a catalytic amount of Rh/Al_2O_3 was added as a co-catalyst (Scheme 4.10). Control experiments showed that in the absence of Rh/Al_2O_3, the in-situ hydrogenation of α, β-unsaturated ester **4.28** to ester **4.29** was very sluggish.

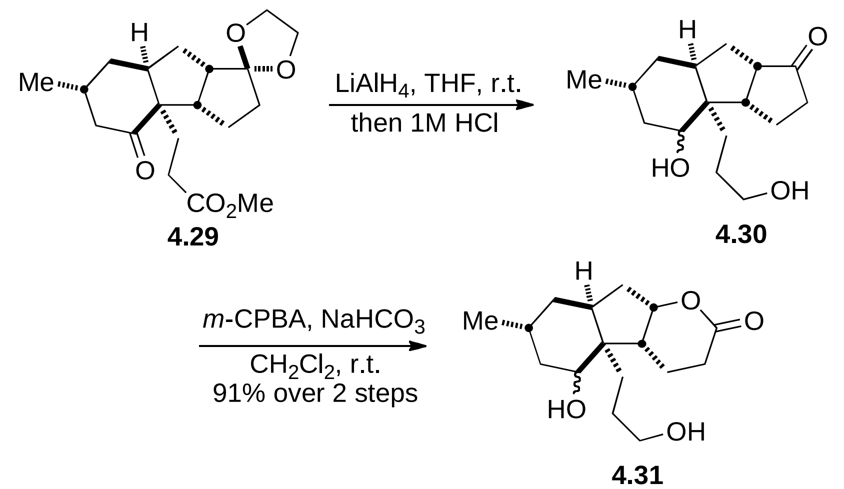
Scheme 4.10. One-pot synthesis of ester **4.29** from mesylate **4.26**.



4.26 **4.29**

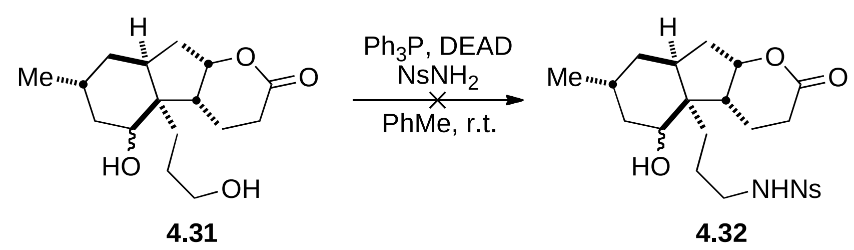
From ester **4.29**, $LiAlH_4$ mediated reduction followed by acidic workup delivered diol **4.30** (Scheme 4.11). The unmasked cyclopentanone was then subjected to standard Baeyer-Villiger oxidation conditions (*m*-CPBA, $NaHCO_3$, CH_2Cl_2, r.t.) afforded lactone **4.31** in 91% yield over 2 steps.

Scheme 4.11. Synthesis of lactone **4.31**.



With lactone **4.31** in hand, Fukuyama-Mitsunobu reaction[6] to install the *N*-atom belonging to the azonine ring was eagerly attempted. Unfortunately, when **4.31** was treated with 2-nitrobenzenesulfonamide ($NsHH_2$), Ph_3P and DEAD in anhydrous toluene at room temperature, no desired nosyl amide **4.32** was isolated (Scheme 4.12). The intra-molecular ether formation turned out to be a significant side reaction, which necessitates the protection of the reactive secondary hydroxyl group.

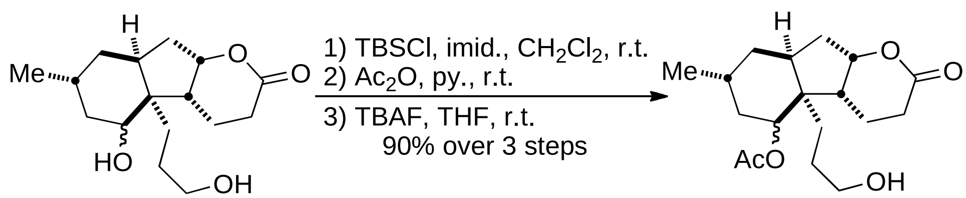
Scheme 4.12. Attempted synthesis of nosyl amide **4.32**.



The selective protection of the secondary hydroxyl group was achieved by a 3-step sequence (Scheme 4.13). That is, the primary hydroxyl group was first protected as its TBS ether. The secondary hydroxyl group was then treated with acetic anhydride (Ac_2O) in pyridine with catalytic amount of DMAP as catalyst to form the corresponding acetate.

Finally, the primary TBS protecting group was removed by TBAF. The whole sequence went smoothly without incident, with **4.33** isolated in 90% yield over 3 steps.

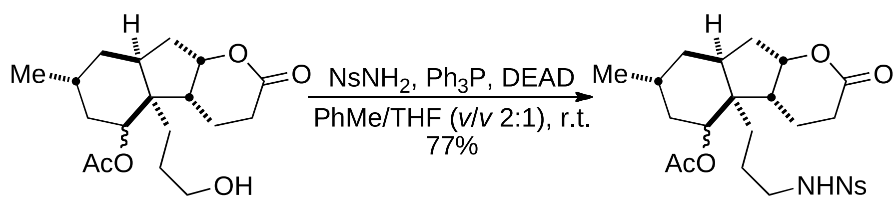
Scheme 4.13. Synthesis of primary alcohol **4.33**.



4.31 **4.33**

As anticipated, with the protection of the secondary hydroxyl group as its acetate, the intended Fukuyama-Mitsunobu reaction of primary alcohol **4.33** took place smoothly, providing nosyl amide **4.34** in 77% yield (Scheme 4.14).

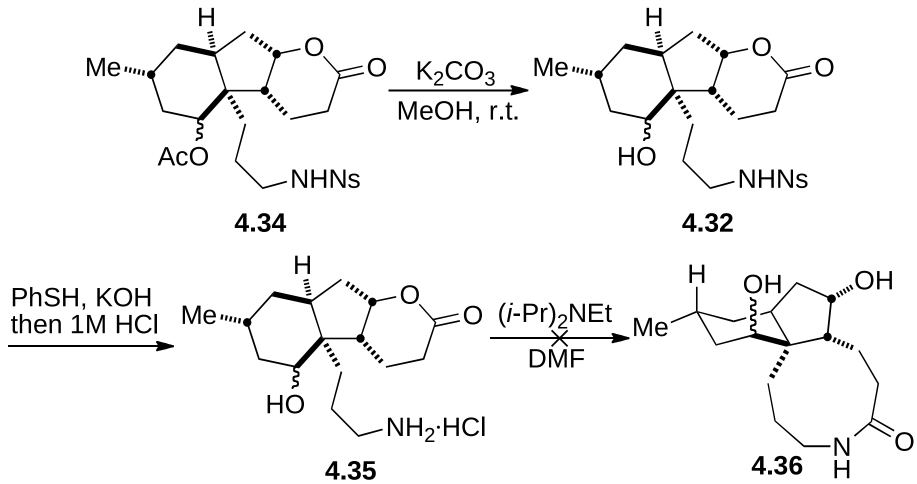
Scheme 4.14. Fukuyama-Mitsunobu reaction to make nosyl amide **4.34**.



4.33 **4.34**

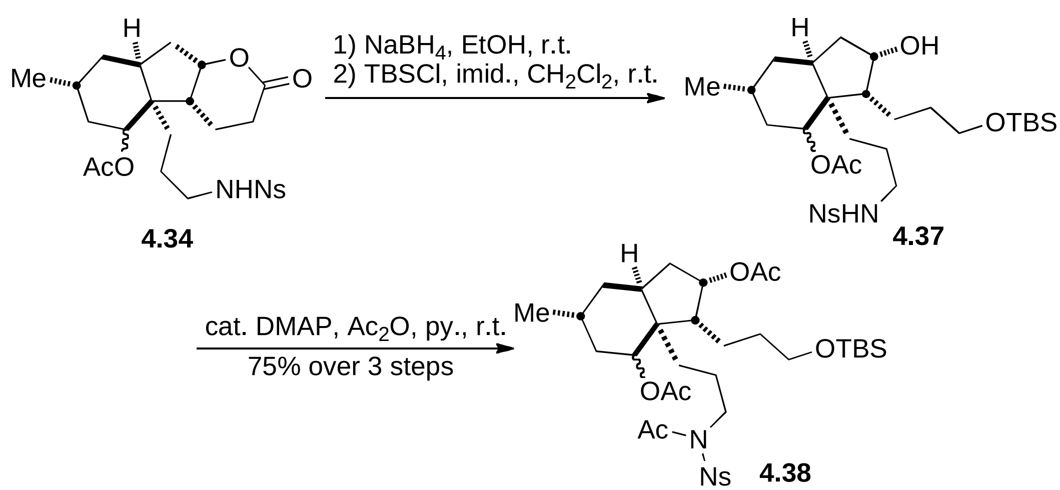
We were intrigued by the possibility of an intra-molecular amine to lactone addition to form the 9-membered lactam. To this end, both of the acetyl and the nosyl group of **4.34** were removed (Scheme 4.15). Amino lactone **4.35** obtained was then heated with Hünig base ((i-Pr)$_2$NEt) in DMF with the hope that an intra-molecular lactam formation could take place. Unfortunately, no desired lactam **4.36** was observed.

Scheme 4.15. Attempted intra-molecular cyclization to make lactam **4.36**.



Without deviation from this unsuccessful intra-molecular lactam formation, we turned our attention to a second Fukuyama-Mitsunobu reaction to form the azonine ring.[7] The sequence used before to differentiate primary and secondary hydroxyl groups was resorted to again (Scheme 4.16). Thus, the lactone moiety of nosyl amide **4.34** was reduced, and the newly formed primary alcohol was temporarily protected as its TBS ether **4.37**.

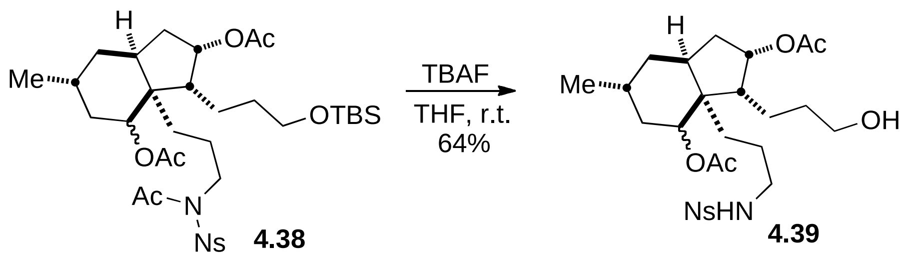
Scheme 4.16. Synthesis of triacetate **4.38**.



The secondary hydroxyl group of **4.37** was then treated with acetic anhydride in pyridine in the presence of a catalytic amount of DMAP. Unexpectedly, the nosyl amide was also acylated under the reaction conditions, with triacetate **4.38** isolated in 75% yield over this 3-step sequence.

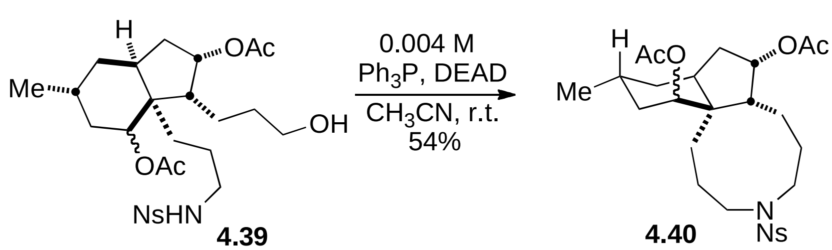
Fortunately, under the conditions to remove the primary TBS group (TBAF, THF, r.t.), the acetyl on the nosyl amide group of **4.38** could be removed simultaneously, providing nosylamino alcohol **4.39** in 64% yield (Scheme 4.17).

Scheme 4.17. Synthesis of nosylamino alcohol **4.39**.



To our delight, when the diluted solution of nosylamino alcohol **4.39** was treated with excess of Ph_3P and DEAD at room temperature in CH_3CN, the desired azonine **4.40** could finally be isolated in 54% yield (Scheme 4.18).

Scheme 4.18. Synthesis of azonine **4.40**.

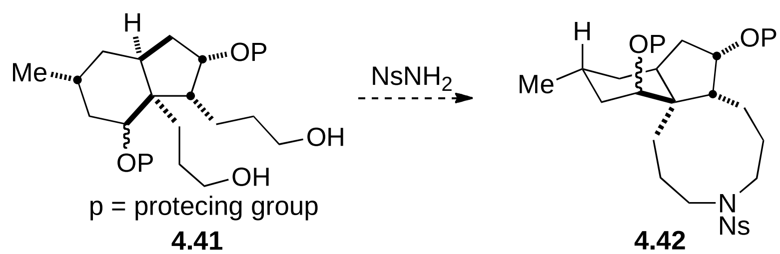


With azonine **4.40** in hand, the total synthesis of fawcettimine is just steps away, which only requires removal of the acetyl and nosyl protecting groups as well as the oxidation of the resulting diol to diketone. However, the current synthesis of **4.40** is quite lengthy, which requires 20 steps from commercially available materials. To avoid those tedious protecting and deprotecting steps, efforts were then put on the double Fukuyama-Mitsunobu approach to form azonine **4.40**.

4.4 Azonine formation by double Fukuyama-Mitsunobu reaction

To improve the efficiency of our synthesis, we envisioned that a double (inter- then intra-molecular) Fukuyama-Mitsunobu reaction[6b,6c] on diol **4.41** could be utilized to construct the azonine **4.42** (Scheme 4.19).

Scheme 4.19. Envisioned double Fukuyama-Mitsunobu reaction to form azonine **4.42**.



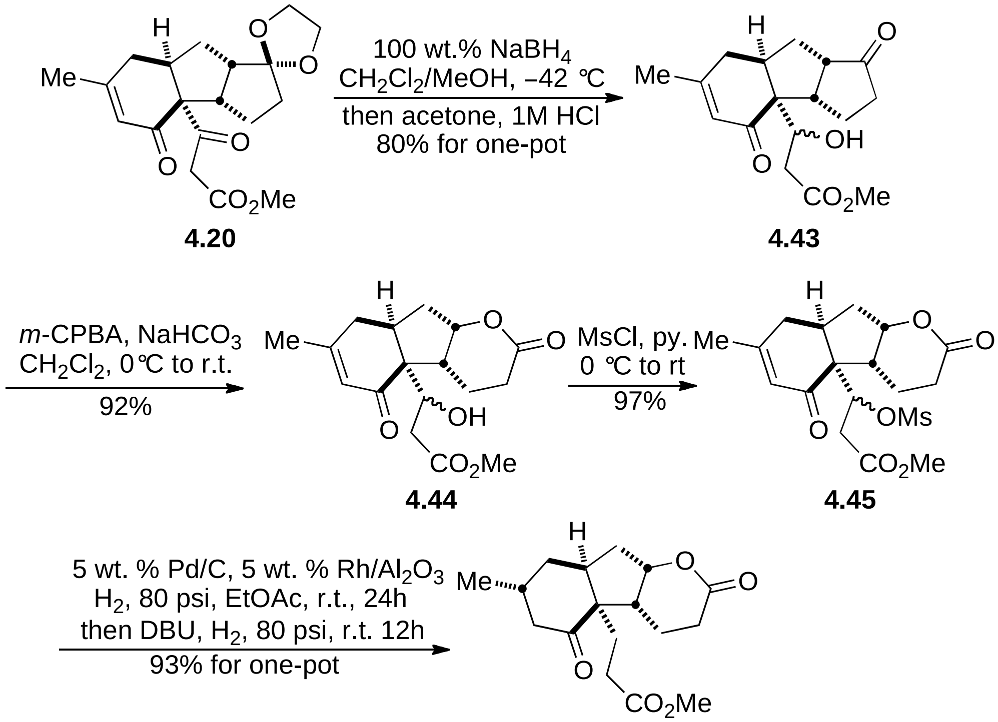
p = protecing group

4.41

4.42

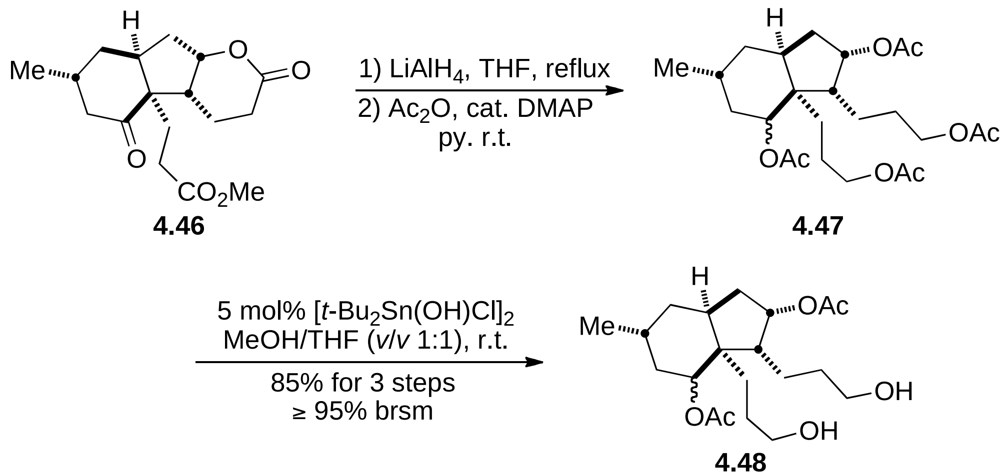
The strategy developed before to install the *C*-15 stereocenter (fawcettimine numbering) is totally adopted here (Scheme 4.20). Thus, a one-pot selective reduction of β-keto ester **4.20** under modified Ward's conditions (100 wt. % $NaBH_4$, $MeOH/CH_2Cl_2$ (*v*/*v* 1:1), –42 °C, 4.5h), followed by acidic work up gave β-hydroxy ester **4.43** in 81% yield. Subsequent Baeyer-Villiger oxidation and mesylate formation afforded mesylate **4.45**, which was then subjected to our optimized one-pot enone hydrogenation/β-elimination/α, β-unsaturated ester hydrogenation process to give lactone **4.46** in 93% yield as a single diastereomer.

Scheme 4.20. Synthesis of lactone **4.46**.



As the structure of **4.46** now secured, we turned out attention to a double (inter- then intra-molecular) Fukuyama-Mitsunobu reaction to construct the azonine ring. Instead of the 3-step sequence (TBS ether formation/acetylation/TBS removal) used above for the synthesis of primary alcohol **4.33** (Scheme 4.12, *vide supra*), Otera's selective deacetylation[8] was attempted (Scheme 4.21). To this end, lactone **4.46** was fully reduced ($LiAlH_4$, THF, reflux) and then protected as the tetraacetate (Ac_2O, cat. DMAP, py., r.t.). When tetraacetate **4.47** obtained was subjected to Otera's conditions (5 mol% [*t*-$Bu_2Sn(OH)Cl]_2$, MeOH/THF (*v*/*v* 1:1), r.t., 30h), we were pleased to find that desired diol **4.48** could be isolated in 85% yield over 3 steps from **4.46**. The side products of the deacetylation step could be acetylated and recycled.

Scheme 4.21. Synthesis of diol **4.48**.

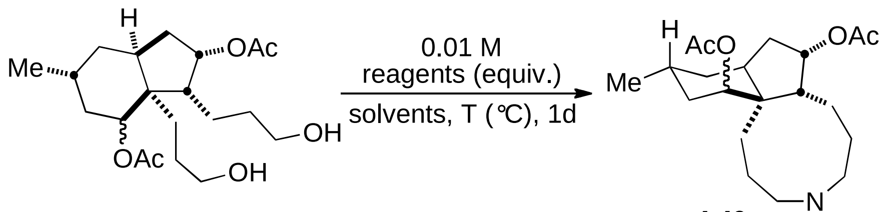


The subsequent double Fukuyama-Mitsunobu reaction to form azonine **4.40** from diol **4.48** was then subjected to extensive screening of reaction conditions. The effect of different solvents was compared first. It was found that the reaction performed best in DMSO or acetonitrile (CH_3CN) (entry 1−7, Table 4.5). To our surprise, no desired azonine **4.40** was observed when the reaction was conducted in DMSO solvent at 80 °C, with diol **4.48** totally recovered (entry 8). Compared to a 40% DEAD solution (40 wt. % in toluene), pure DEAD (97% DEAD) or DIAD gave lower yields of **4.40** (9−11). Other phosphines, such as (n-Bu)$_3$P, (Me_2N)$_3$P, or Diphos failed to yield any Fukuyama-Mitsunobu reaction product under the same conditions as Ph_3P did (entry 12−14).

The combination of (n-Bu)$_3$P and 1,1'-(Azodicarbonyl)dipiperidine (ADDP), which was reported to have enhanced reactivity over Ph_3P and DEAD,[9] was also examined. However, no reaction was observed (entry 15).

Finally, the relative ratios of $NsNH_2$, Ph_3P and DEAD to diol **4.48** were adjusted. The usage of 4 equiv. $NsNH_2$, 6 equiv. Ph_3P and 6 equiv. DEAD was found to be optimal (entry 7, 16−20).

Table 4.5. Optimization of double Fukuyama-Mitsunobu reaction to form azonine **4.40**.



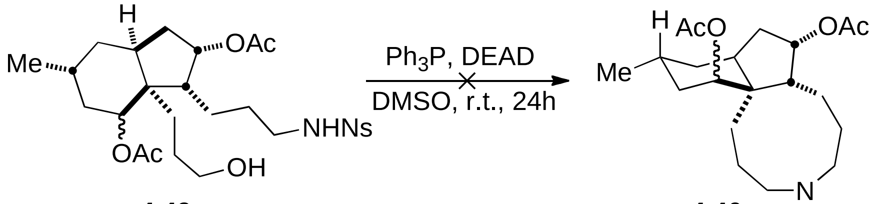
4.48 **4.40**

Entry	Reagent (equiv.)	Solvent	T (°C)	Yield[a]
1	$NsNH_2$ (4), Ph_3P (6), 40% DEAD (6)	THF/PhMe	r.t.	23%
2	$NsNH_2$ (4), Ph_3P (6), 40% DEAD (6)	THF	r.t.	24%
3	$NsNH_2$ (4), Ph_3P (6), 40% DEAD (6)	CH_2Cl_2	r.t.	20%
4	**$NsNH_2$ (4), Ph_3P (6), 40% DEAD (6)**	**CH_3CN**	**r.t.**	**36%**
5	$NsNH_2$ (4), Ph_3P (6), 40% DEAD (6)	DMF	r.t.	33%
6[b]	$NsNH_2$ (4), Ph_3P (6), 40% DEAD (6)	py.	r.t.	25%
7	**$NsNH_2$ (4), Ph_3P (6), 40% DEAD (6)**	**DMSO**	**r.t.**	**38%**
8[b]	$NsNH_2$ (4), Ph_3P (6), 40% DEAD (6)	DMSO	80	n.r.
9	$NsNH_2$ (4), Ph_3P (6), 97% DEAD (6)	DMSO	r.t.	16%
10	$NsNH_2$ (4), Ph_3P (6), DIAD (6)	DMSO	r.t.	28%
11	$NsNH_2$ (4), Ph_3P (6), DIAD (6)	CH_3CN	r.t.	19%
12[b]	$NsNH_2$ (4), $(n\text{-Bu})_3P$ (6), 40% DEAD (6)	DMSO	r.t.	n.r.
13[b]	$NsNH_2$ (4), $(Me_2N)_3P$ (6), 40% DEAD (6)	DMSO	r.t.	n.r.
14[b]	$NsNH_2$ (4), Diphos (6), 40% DEAD (6)	DMSO	r.t.	n.r.
15[b]	$NsNH_2$ (4), $(n\text{-Bu})_3P$ (6), ADDP (6)	DMSO	r.t.	n.r.
16	$NsNH_2$ (4), Ph_3P (10), 40% DEAD (10)	DMSO	r.t.	26%
17	$NsNH_2$ (6), Ph_3P (6), 40% DEAD (6)	DMSO	r.t.	23%
18	$NsNH_2$ (4), Ph_3P (5), 40% DEAD (5)	DMSO	r.t.	26%
19	$NsNH_2$ (3), Ph_3P (6), 40% DEAD (6)	DMSO	r.t.	20%
20	$NsNH_2$ (2), Ph_3P (4), 40% DEAD (4)	DMSO	r.t.	16%

[a] Yield was determined by ^{1}H NMR and was not accurate. [b] Diol **4.48** was recovered.

The major byproduct from this double Fukuyama-Mitsunobu reaction is nosylamide **4.49**, which failed to yield enen trace amounts of azonine **4.40** when resubmitted to the reaction conditions, with **4.49** totally recovered (Scheme 4.22).

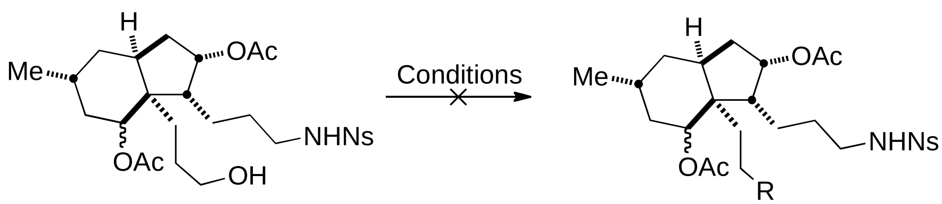
Scheme 4.22. Attempted synthesis of azonine **4.40** from nosylamide **4.49**.



4.49 **4.40**

All efforts to convert **4.49** to mesylate **4.50** or chloride **4.51** were not successful (entry 1–2, Table 4.6). Attempted Dess-Martin oxidation of **4.49** to aldehyde **4.52** was also met with failure (entry 3). The primary hydroxyl group of **4.49** was found to be too hindered to take part in those reactions.

Table 4.6. Attempted reaction of nosylamide **4.49**.



4.49

4.50 R = CH_2OMs
4.51 R = CH_2Cl
4.52 R = CHO

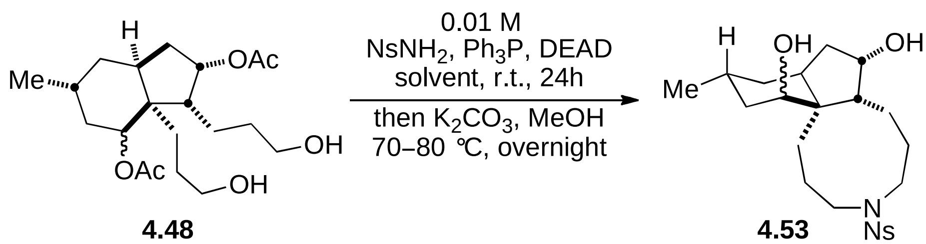
Entry	Conditions	Results[a]
1	4 equiv. MsCl, py., r.t., 4d	n.r.
2	20 equiv. $SOCl_2$, PhMe, r.t., 3d	n.r.
3	1.5 equiv. DMP, $NaHCO_3$, CH_2Cl_2, r.t., 2d	n.r.

[a] Nosylamide **4.49** totally recovered.

Another issue worthy of note is that azonine **4.40** co-spotted with $NsNH_2$ upon column chromatography, which rendered its isolation a significant challenge. To avoid this isolation problem, azonine **4.40** was in-situ deacylated by addition of excess K_2CO_3 and methanol followed by heating the resulting mixture at 70–80 °C overnight. Diol **4.53** was thus isolated in 38% yield for this one-pot procedure (entry 1, Table 4.6).

Although pyridine (py.) was not identified as the ideal solvent from our above solvent screening, it was noticed that less byproducts were formed in this solvent (entry 6, Table 4.5, *vide supra*). We were thus intrigued by the possible beneficial effect of pyridine as the co-solvent and conducted another survey for solvent combinations. Even though no favorable effect was observed when pyridine was added to DMSO as co-solvent (entry 2–4, Table 4.7), we were pleased to find that the combination of CH_3CN and pyridine improved the yield of azonine significantly (entry 5–8). The highest yield of **4.53** (50%) was achieved when a 5:1 (*v*/*v*) combination of CH_3CN and pyridine was used as the solvent (entry 7).

Table 4.7. Optimization of one-pot conversion of **4.48** to **4.53**.



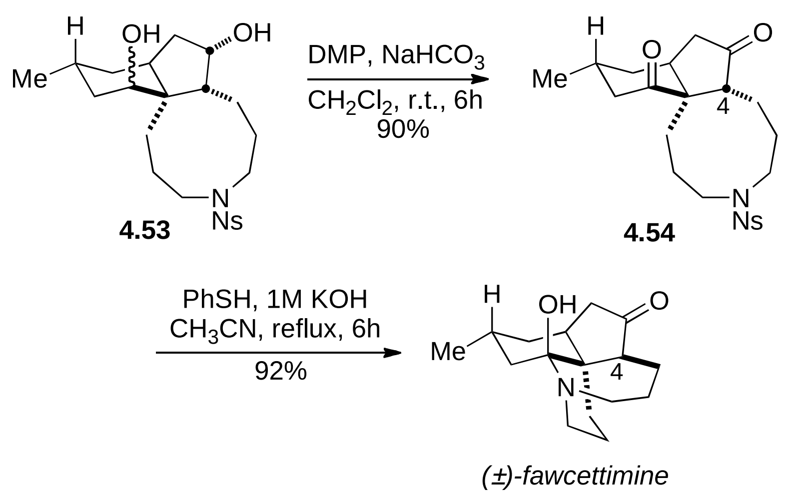
Entry	Solvent (*v*/*v*)	Yield[a]
1	DMSO	38%
2	DMSO/py. (1:1)	30%
3	DMSO/py. (3:1)	35%
4	DMSO/py. (6:1)	25%
5	CH_3CN/py. (1:1)	27%
6	CH_3CN/py. (3:1)	48%
7	**CH_3CN/py. (5:1)**	**50%**
8	CH_3CN/py. (6:1)	47%

[a] Isolated yield.

4.5 Synthesis of (±)-fawcettimine, (±)-fawcettidine, (±)-lycoflexine, and (±)-lycoposerramine B

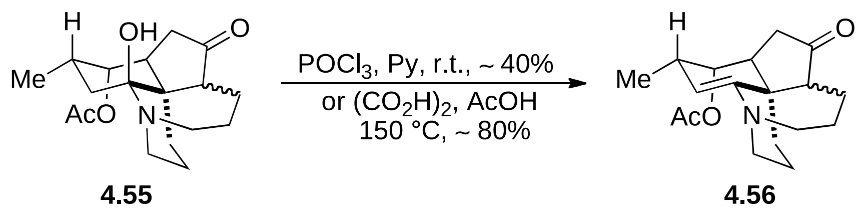
With a concise synthesis of diol **4.53** now achieved (14 steps from commercially available materials), efforts were then put on its conversion to a variety of fawcettimine class alkaloids. The synthesis of (±)-fawcettimine itself proved to be straightforward. Dess-Martin oxidation of diol **4.53** provided diketone **4.54**, which upon treatment with PhSH under basic conditions removed the nosyl group to afford (±)-fawcettimine (Scheme 4.23). It was noticed that the inversion of *C*-4 stereogenic center occurred at the stage when the (±)-fawcettimine hydrobromide salt was made, which is in agreement with Heathcock's observation that a trace amount of acid is crucial to this inversion.[10]

Scheme 4.23. Synthesis of (±)-fawcettimine.



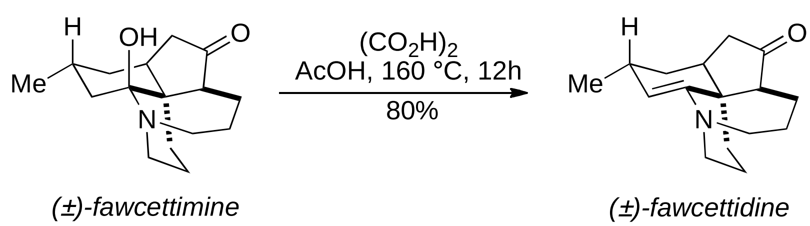
From (±)-fawcettimine, the dehydration by $POCl_3$/pyridine to form (±)-fawcettidine was already reported.[1a] However, no yield and experimental details were given for this procedure. In a similar transformation, acetylaposerratinine (**4.55**) was dehydrated to give anhydroacetylaposerratinine (**4.56**), in which the dehydration with oxalic acid in acetic acid solvent at elevated temperature gave better yield of **4.56** than $POCl_3$/pyridine (Scheme 4.24).[11]

Scheme 4.24. Dehydration of acetylaposerratinine (**4.55**).



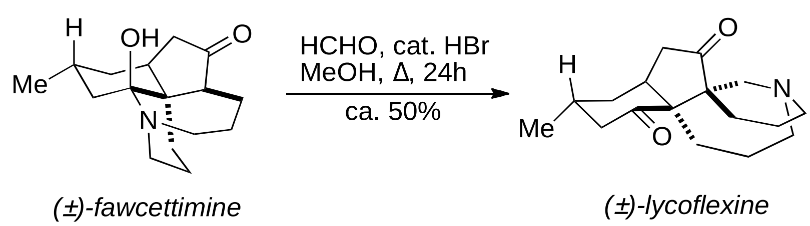
We applied the oxalic acid mediated dehydration conditions (oxalic acid, AcOH, 160 °C, 12h) to (±)-fawcettimine and were pleased to find that (±)-fawcettidine could be isolated in 80% yield (Scheme 4.25). In contrast, Burgess reagent,[12] the commonly utilized dehydration agent for tertiary alcohols, failed to give trace amounts of (±)-fawcettidine.

Scheme 4.25. Synthesis of (±)-fawcettidine.



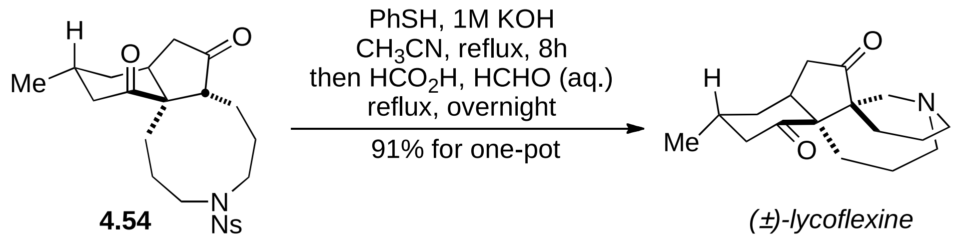
The conversion of (±)-fawcettimine to (±)-lycoflexine via a Mannich reaction was reported by Ayer, W. A. and coworkers in 1973 (Scheme 4.26).[1b] This biomimetic transformation was adopted in two recently reported total syntheses of this alkaloid.[13]

Scheme 4.26. Ayer's synthesis of (±)-lycoflexine from (±)-fawcettimine.



In our case, we were pleased to find that the deprotection of the nosyl group and subsequent Mannich reaction could be done in one-pot manner to afford (±)-lycoflexine in 91% yield (Scheme 4.27).

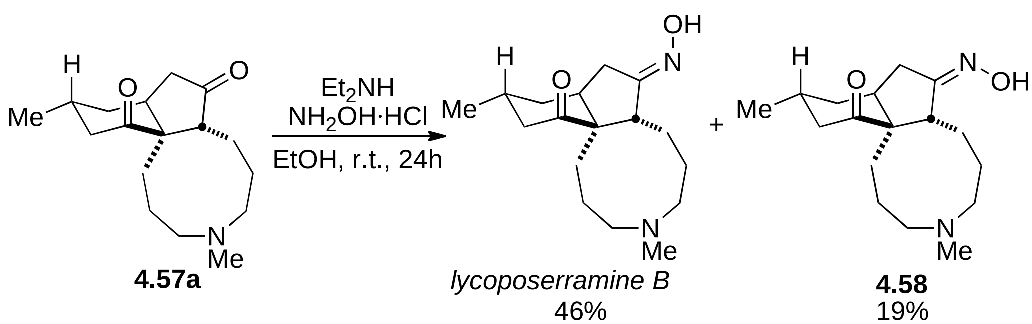
Scheme 4.27. Synthesis of (±)-lycoflexine.



Since diol **4.53** contains the *R* configuration at *C*-4 (fawcettimine numbering), its conversion to lycoposerramine B was executed next.

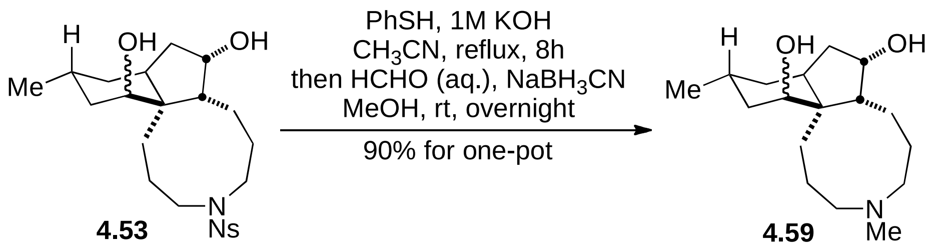
In their lycoposerramine B isolation paper, the Takayama group reported that a selective oxime formation on diketoamine **4.57a** could afford lycoposerramine B in 46% yield together with its isomer **4.58** in 19% yield (Scheme 4.28).[14] This strategy was also utilized in the recent reported total synthesis of (+)-lycoposerramine B.[15]

Scheme 4.28. Reported synthesis of lycoposerramine B from diketo amine **4.57a**.



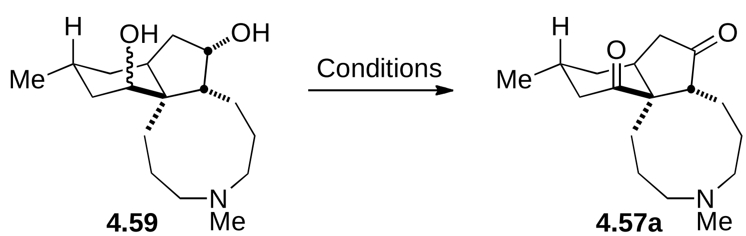
Thus, our synthesis of lycoposerramine B can now be reduced to the formation of known diketoamine **4.57a**. To this end, the nosyl group on **4.49** needs to be removed and a methyl group must be installed. We were pleased to find that those two steps could be conveniently conducted in a one-pot manner, with tertiary amine **4.59** isolated in 90% yield (Scheme 4.29).

Scheme 4.29. Synthesis of tertiary amine **4.59**.



With **4.59** in hand, an oxidation was all that remained for the conversion of **4.59** to diketoamine **4.57a**. However, this oxidation proved to be a nontrivial step. Oxidants, such as Dess-Martin periodenane (DMP), PCC,[16] CrO_3[17] or TPAP/NMO (Ley oxidation) all failed to give the desired oxidation product (entry 1–4, Table 4.8). Finally, it was found that the Swern oxidation could provide **4.57a** in high yield (entry 5). Since **4.57a** is prone to be oxidized in the air or by column chromatography, the crude was used directly in the next selective oxime formation step.

Table 4.8. Oxidation of tertiary amine **4.59**.

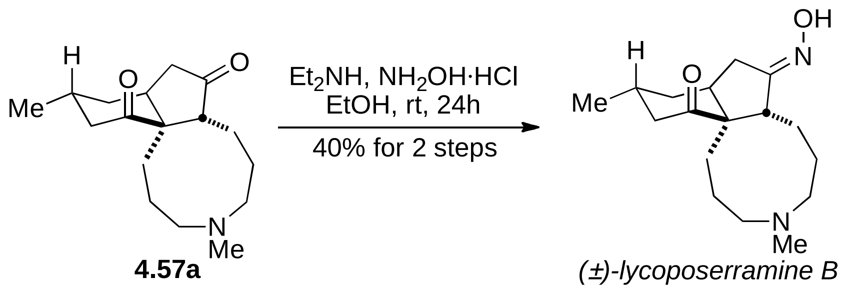


Entry	Conditions	Results[a]
1	DMP, CH_2Cl_2, r.t.	no **4.57a**
2	PCC, CH_2Cl_2, r.t.	no **4.57a**
3	CrO_3, $AcOH/H_2O$ (*v*/*v* 4:1), r.t.	no **4.57a**
4	cat. TPAP, NMO, 4Å MS, CH_2Cl_2, r.t.	no **4.57a**
5	$(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, then NEt_3	**4.57a** obtained

[a] Determined by TLC and crude ^1H NMR.

Following the procedure described by Takayama and coworkers,[14] (±)-lycoposerramine B was isolated in 40% yield over 2 steps from **4.59** together with some of its isomer, **4.58** (Scheme 4.30).

Scheme 4.30. Synthesis of (±)-lycoposerramine B.

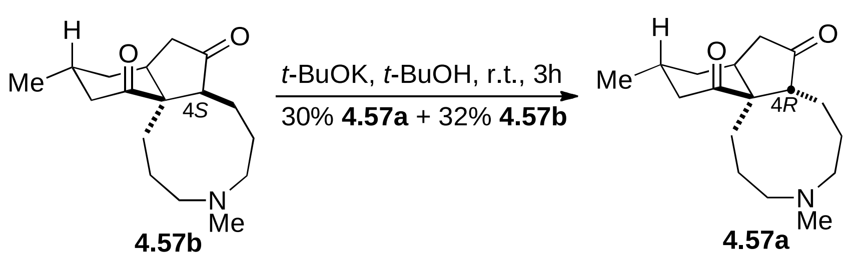


4.6 Synthetic Efforts Towards lycoposerramine A

Our synthetic efforts towards lycoposerramine A followed the hypothetical biogenetic route proposed by Takayama and coworkers.[18] From diketoamine **4.57a**, the inversion of *C*-4 stereogenic center was investigated first.

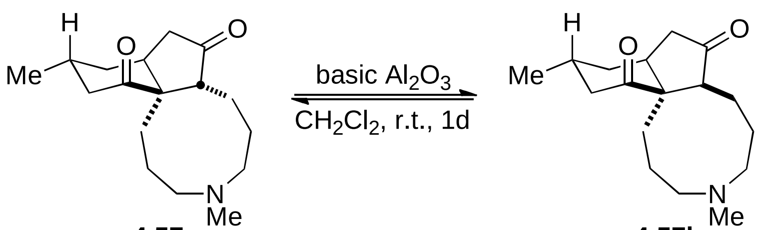
In their synthesis of lycoposerramine B from serratinine, the Takayama group found that when **4.57b** was treated with *t*-BuOK in *t*-BuOH at room temperature, the epimer **4.57a** could be isolated in 30% yield together with recovered **4.57b** in 32% yield (Scheme 4.31).[14]

Scheme 4.31. Epimerization of **4.57b** reported by Takayama.



However when these conditions (*t*-BuOK, *t*-BuOH, r.t.) were applied to the crude **4.57a** obtained from above Swern oxidation of **4.59**, the reaction was found to be extremely sluggish. Fortunately, during our attempted purification of **4.57a**, we observed the epimerization of **4.57a** on basic aluminum oxide (Al_2O_3) column. Thus, basic Al_2O_3 in CH_2Cl_2 was tested on crude **4.57a** (Scheme 4.32). To our delight, an equilibrium of **4.57a** and **4.57b** (near 1:1 ratio) was arrived at after one day. Due to the issue of difficult separation of these two epimers, the equilibrated mixture was used in the next step directly.

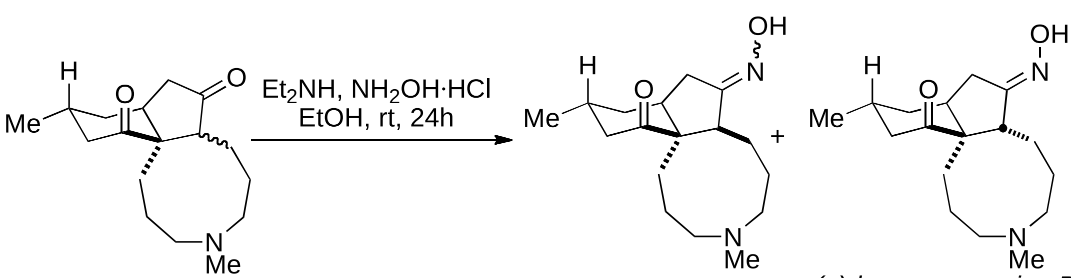
Scheme 4.32. Epimerization of diketoamine **4.57a**.



4.57a 4.57b

When a mixture of **4.57a** and **4.57b** was treated with $NH_2OH{\cdot}HCl$ in the presence of excess Et_2NH, both the desired oxime **4.60** and (±)-lycoposerramine B were obtained and easily separated, together with some other isomers (Scheme 4.33).

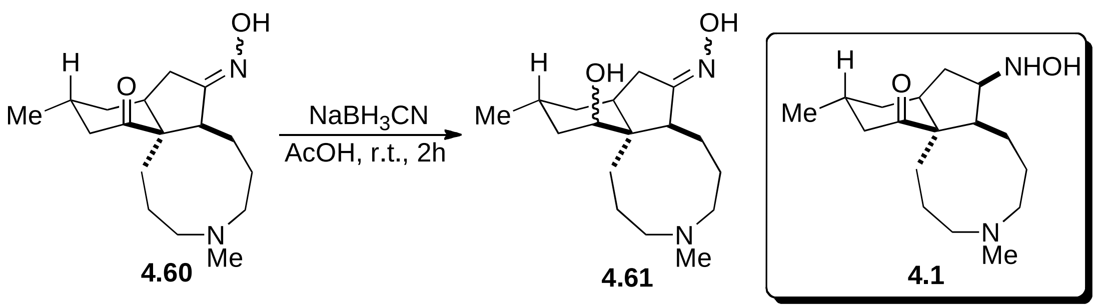
Scheme 4.33. Synthesis of oxime **4.60** and (±)-lycoposerramine B from a mixture of **4.57a** and **4.57b**.



4.57a + **4.57b** **4.60** *(±)-lycoposerramine B*

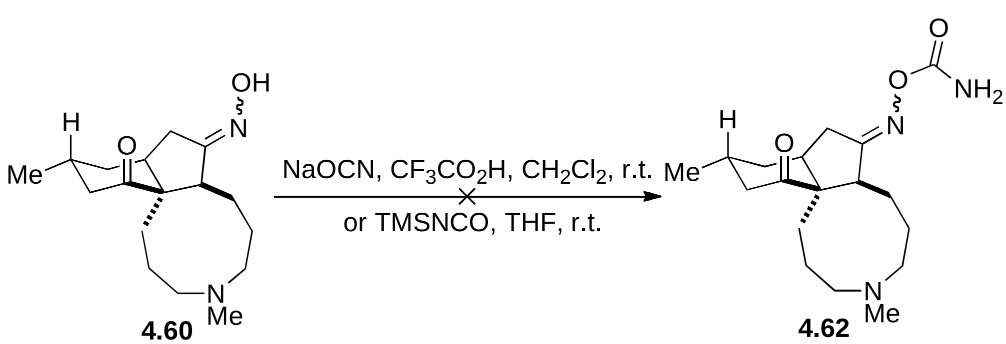
From **4.60**, the selective reduction of the oxime moiety in the presence of ketone was expected to be a trivial step, given the steric hindrance of the ketone brought by the neighboring all-carbon quaternary center. To our surprise, when **4.60** was treated with $NaBH_3CN$ in acetic acid at room temperature, the standard selective oxime reduction conditions, only hydroxyloxime **4.61** was isolated (Scheme 4.34). The formation of desired hydroxylamine **4.1** was not observed. The reduction of **4.60** needs further investigation.

Scheme 4.34. Reduction of oxime **4.60**.



From oxime **4.60**, the urethane formation was also attempted. Unfortunately, under the reported conditions (NaOCN and CF_3CO_2H in CH_2Cl_2[19a] or TMSNCO in THF[19b]), no desired **4.62** was obtained (Scheme 4.35).

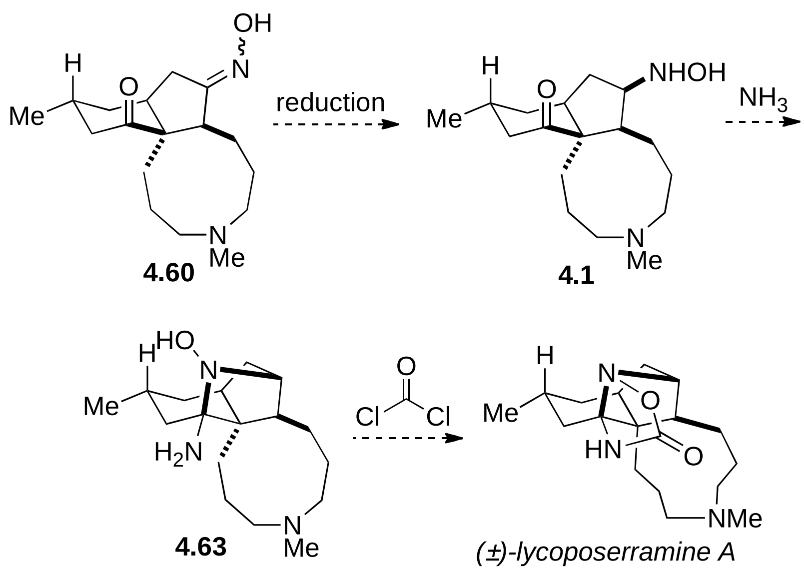
Scheme 4.35. Attempted urethane formaiton from oxime **4.60**.



4.7 Future work

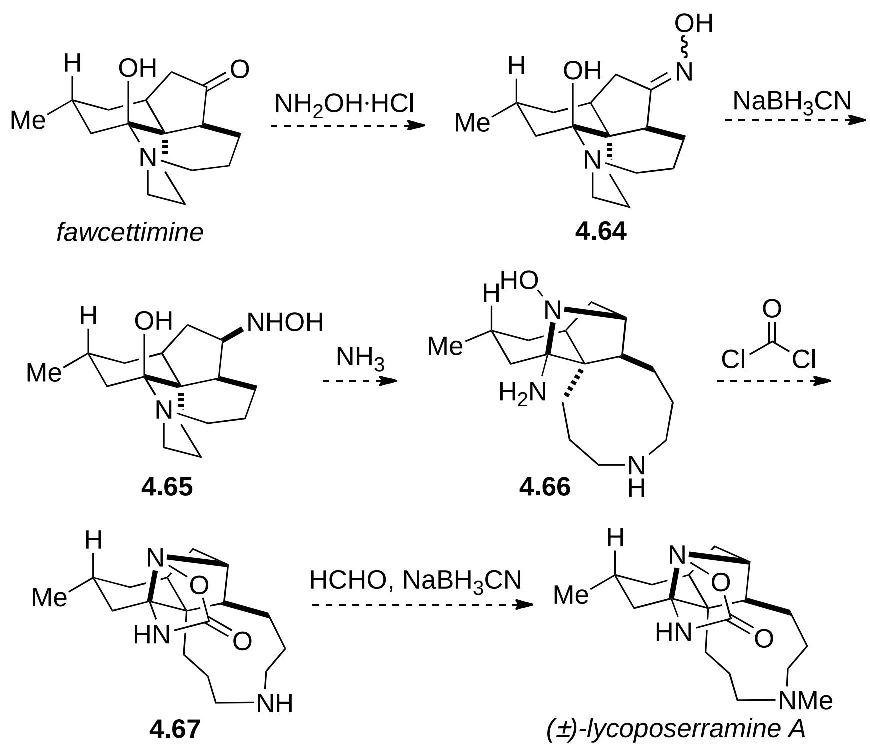
Our future plan for the synthesis of (±)-lycoposerramine A from **4.60** is shown in Scheme 4.36. As mentioned early, the conditions for the selective reduction of the oxime moiety in the presence of the ketone need to be screened. Once the structure of hydroxylamine **4.1** is secured, treatment of **4.1** with liquid ammonia should trigger the imine formation and a cascade intra-molecular cyclization to afford aminal **4.63**, which could then react with phosgene to provide (±)-lycoposerramine A.

Scheme 4.36. Future work for (±)-lycoposerramine A synthesis from **4.60**.



Alternatively, (±)-fawcettimine with the *C*-13 ketone already protected as its hemiaminal form could react with $NH_2OH{\cdot}HCl$ to give oxime **4.64** (Scheme 4.37). When **4.64** is treated with $NaBH_3CN$, the reduction of the hemiaminal moiety is expected to be slower than the oxime and hydroxylamine **6.65** should be obtained. Subsequent treatment of **4.65** with liquid ammonia should trigger the opening of hemiaminal and the ketone liberated could condense with ammonia to form an imine followed by an intra-molecular cyclization to give aminal **4.66**. The loss of water may be the driving force for this cascade reaction. From **4.66**, cyclization with phosgene to construct the oxadiazolidinone moiety followed by reductive amination to install the *N*-Me group should finish the synthesis of (±)-lycoposerramine A.

Scheme 4.37. Future work for (±)-lycoposerramine A synthesis from (±)-fawcettimine.



4.8 Conclusion

Through the homologation of enone **4.10**, the steric hindrance brought by the all-carbon quaternary center was minimized and the azonine formation was realized by a Fukuyama-Mitsunobu reaction. Thus, the total syntheses of (±)-fawcettimine, (±)-lycoflexine, (±)-fawcettidine, and (±)-lycoposerramine B have been accomplished through an efficient, unified, and stereocontrolled strategy that required sixteen, sixteen, seventeen, and seventeen steps, respectively, from commercially available materials.

Combined with the successful kinetic resolution of the earliest intermediate by a Sharpless asymmetric dihydroxylation (Chapter 3), the enantioselective syntheses of these alkaloids can also be achieved. The synthesis of other family members, especially lycoposerramine A, is undertaken.

4.9 References

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2) For examples, see: a) *Total synthesis of (±)-pisiferic acid.* Banerjee, A. K.; Hurtado, H. S.; Laya, M. M.; Acevedo, J. C.; Alvárez, J. G. *J. Chem. Soc., Perkin Trans. I* **1988**, 931–938. b) *Diazoaldehyde chemsitry. Part 1. Transdiazotization of acylacetaldehydes in neutral-to-acidic medium. A direct approach to the synthesis of α-diazo-β-oxoaldehydes*. Sezer, Ö.; Anac, O. *Helv. Chim. Acta*. **1994**, *77*, 2323–2334.

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5) *A general method for the selective reduction of ketones in the presence of enones.* Ward, D. E.; Rhee, C. K.; Zoghaib, W. M. *Tetrahedron Lett.* **1988**, *29*, 517–520.

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cladiell-11-ene-3,6,7-triol, and (–)-deacetoxyalcyonin acetate. Kim, H.; Lee, H.; Kim, J.; Kim, S.; Kim, D. *J. Am. Chem. Soc.* **2006**, *128*, 15851–15855.

13) a) *Synthesis of the Lycopodium alkaloid (+)-lycoflexine*. Ramharter, J.; Weinstabl, H.; Mulzer, J. *J. Am. Chem. Soc.* **2010**, *132*, 14338–14339. b) *Application of the Helquist annulation in Lycopodium alkaloid synthesis: unified total syntheses of (–)-8-deoxyserratinnine, (+)-fawcettimine, and (+)-lycoflexine.* Yang, Y.; Shen, L.; Huang, J.; Xu, T.; Wei, K. *J. Org. Chem.* **2011**, *76*, 3684–3690.

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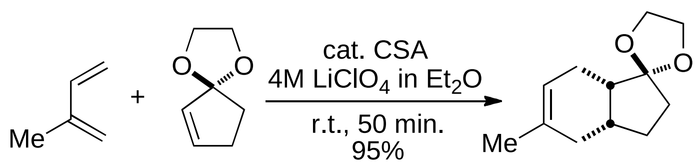
Chapter 5

Experimental Section

5.1 General Considerations

All reactions were performed in single-neck round bottom flasks fitted with rubber septa under positive pressure of argon, unless otherwise noted. Organic solutions were concentrated under reduced pressure by rotary evaporation below 50 °C at 20 mmHg. Analytical and preparative thin-layer chromatography (PTLC) was performed using glass plates pre-coated with a 0.25-mm layer of silica gel impregnated with a fluorescent indicator (254 nm). Reaction progress was followed by TLC analysis and visualized by UV light and/or submersion in standard TLC stains ($KMnO_4$, Vanillin, Anisaldehyde, etc.) followed by heating on a hot plate (~200 °C). Flash column chromatography was conducted as described by Still and coworkers using 60 Å (230-400 mesh), standard grade silica gel purchased from Sorbtech. ^{1}H and ^{13}C NMR spectra were obtained using Varian 300 MHz or 400 MHz spectrometers. The chemical shifts are given in parts per million (ppm) relative to TMS at δ 0.00 ppm or to residual $CDCl_3$ δ 7.27 ppm for proton spectra and relative to $CDCl_3$ at δ 77.23 ppm for carbon spectra, unless otherwise noted. IR spectra were recorded on a Perkin-Elmer 1600 FTIR as thin films in CH_2Cl_2. Mass spectra were obtained using a Fisons VG Autospec spectrometer. Enantiomeric Excess (e.e.) values were measured on a Varian 3800 Gas Chromatograph or Agilent 1100 series HPLC device. Optical rotations were recorded on a Perkin-Elmer 24 polarimeter at a wavelength of 589 nm. Melting points were measured on a MELTEMP capillary melting point apparatus and are uncorrected. Microwave assisted reactions were performed on CEM Discover Reactor. $LiClO_4$ was purchased from Aldrich (ACS reagent, ≥95.0%) and heated in oven (120 ºC) for three days before use. (*S*)-(–)-*o*-Tolyl-CBS-oxazaborolidine solution (0.5 M in toluene) was purchased from Aldrich. $ClCH_2CH_2Cl$ was purchased from Mallinckrodt Baker, Inc. (ACS grade). Anhydrous ethanol (EtOH) was purchased from Pharmco-Aaper. Dess-Martin periodinane,[1] and Otera's catalyst[2] were prepared according to the literature procedures. All other materials were obtained from Aldrich or VWR and used without further purification. Dichloromethane (CH_2Cl_2), tetrahydrofuran (THF), toluene (PhMe), benzene (PhH), *N*,*N*-dimethylforamide (DMF), acetonitrile (CH_3CN), triethylamine (Et_3N), *N*,*N*-diisopropylamine, pyridine, dimethyl sulfoxide (DMSO) and methanol (MeOH) were all purified by a LabContour solvent purification system.

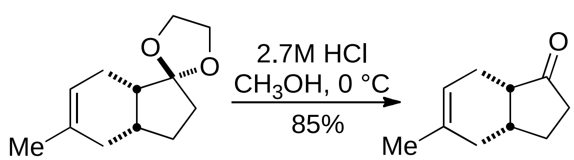
5.2 Experimental Procedures Relevant to Chapter 3



3.9 **3.10** **3.11**

Compound 3.11. Following the procedure described by Hailes,[3] to an oven dried 500 mL round-bottomed flask with reflux condenser, $LiClO_4$ (136.18 g, 1.28 mol) and Et_2O (320 mL) was added. After stirring at room temperature for 1.5 h, isoprene (**3.9**) (32 mL, 320 mmol, 4.0 equiv.), 2-cyclopenten-1-one ethylene ketal (**3.10**) (9.46 mL, 80 mmol, 1.0 equiv.) and camphorsulfonic acid in THF (0.5 M, 0.37 mL, 0.23 mol%) were added. The resulting solution was stirred for additional 50 minutes before NEt_3 (0.40 mL) was added to quench the reaction. Cold water (200 mL) was added cautiously and the organic layer was separated. The aqueous layer was extracted with Et_2O (2 x 200 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure (~15 mmHg, rotavap water bath temp. 0–5 ºC). The crude obtained was purified by flash column chromatography (hexanes/EtOAc 50:1) to afford title compound (14.76 g, 95%) as a colorless oil (R_f = 0.57, hexanes/EtOAc 10:1). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.36–5.40 (m, 1H), 3.80–3.96 (m, 4H), 2.26–2.37 (m, 1H), 1.66–2.18 (m, 8H), 1.64 (S, 3H), 1.39–1.52 (m, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 132.2, 119.8, 119.2, 64.9, 64.0, 41.4, 35.0, 34.0, 31.9, 27.1, 24.1, 22.3.

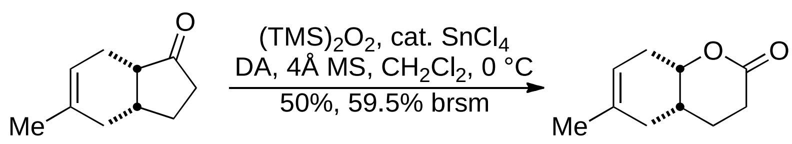
(^{1}H NMR filename: pan101-002; ^{13}C NMR filename: pan101-t002; notebook #: 01344, 01373)



3.11 **3.8**

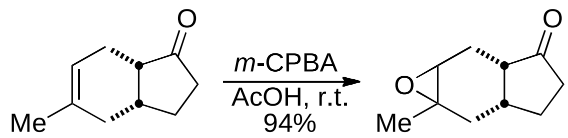
Compound 3.8. Following the procedure described by Hailes,[3] to a 50-mL round-bottomed flask, **3.11** (0.740 g, 3.81 mmol, 1.0 equiv.) was dissolved in MeOH (ACS grade, 20 mL) at 0 ºC (ice-water bath). aq. HCl solution (2.7 M, 1.18 mL) was added drop by drop. The resulting mixture was stirred at 0 ºC for 2.5 hours before sat. $NaHCO_3$ (30mL) was added. The mixture was extracted with hexanes (3 x 50 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration and concentration at reduced pressure (~15 mmHg, rotavap water bath temp. 0–5 ºC), the crude obtained was purified by flash column chromatography (hexanes/EtOAc 50:1) to afford **3.8** (0.488 g, 85%, contains ca. 7% isomer) as a colorless oil (R_f = 0.38, hexanes/EtOAc 10:1). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.31 (br s, 1H), 2.44–2.55 (m, 1H), 1.93–2.39 (m, 8H), 1.72–1.81 (m, 1H), 1.61 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 220.0, 132.4, 118.9, 46.7, 34.3, 33.0, 30.9, 26.6, 24.1, 21.9.

(^{1}H NMR filename: pan202-4a-1-1; ^{13}C NMR filename: pan202-4a-1-t1; notebook #: 00054, 01534)



Compound 3.7. To a 10-mL round-bottomed flask with magnetic stirring bar (flame-*vacuo*-Ar dried) was added CH_2Cl_2 (3 mL), (±)-*trans*-1,2-diaminocyclohexane (DA) (0.5 M in THF, 0.20 mL, 0.1 mmol, 32 mol%), $SnCl_4$ (1.0 M in CH_2Cl_2, 98 μL, 98 μmol, 32 mol%). The resulting mixture was stirred at 0 °C (ice-water bath) and $(TMS)_2O_2$ (1.0 M in CH_2Cl_2, 0.62 mL, 0.62 mmol, 2.0 equiv.) was added. After 10 minutes, **3.8** (0.0465 g in 2 mL CH_2Cl_2, 0.31 mmol, 1.0 equiv.) was added slowly via syringe. The ice-water bath was removed and the reaction was stirred at room temperature for 5 days. Solid Na_2SO_3 (0.117 g) was added to quench the reaction and the suspension was stirred for 3 hours before filtered over a short pad of silica and washed with EtOAc (25 mL). The filtrate was concentrated at reduced pressure (~15 mmHg, rotavap water bath temp. 0–5 ºC) and the crude obtained was purified by flash column chromatography (hexanes/EtOAc 4:1) to afford recovered **3.8** (0.0076 g, 16%) and **3.7** (0.0255 g, 50%, contains ca. 7% isomer) as a colorless oil (R_f = 0.31, hexanes/EtOAc 2:1). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.24–5.28 (m, 1H), 4.56 (td, *J* = 4.5, 3.0 Hz, 1H), 2.52–2.68 (m, 2H), 2.13–2.49 (m, 3H), 1.83–2.08 (m, 3H), 1.68–1.80 (m, 1H), 1.66 (app s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 132.57, 116.72, 76.18, 31.79, 30.51, 29.90, 27.19, 23.51.

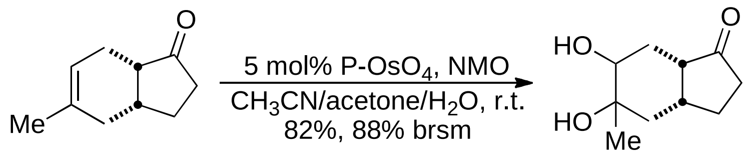
(^{1}H NMR filename: panpan01-07-1; ^{13}C NMR filename: panpan01-t07-1; notebook #: 00178)



3.8 **3.12**

Compound 3.12. To a stirred solution of **3.8** (0.0458 g, 0.305 mmol, 1.0 equiv.) in AcOH (ACS grade, 1.5 mL) was added *m*-CPBA (77%, 0.0752 g, 0.336 mmol, 1.1 equiv.). The reaction was stirred at room temperature for 40 minutes and then sat. $Na_2S_2O_3$ (1 mL) and sat. $NaHCO_3$ (40 mL) were added. The mixture was extracted with EtOAc (3 x 10 mL) and the combined organic layer was washed with brine (10 mL), dried over dried over anhydrous $MgSO_4$. After filtration and concentration, the crude obtained was purified by flash column chromatography (hexanes/EtOAc 6:1) to afford **3.12** (0.475 g, d.r. 1: 0.13, 94%) as a colorless oil (R_f = 0.27 (major), 0.16 (minor), hexanes/EtOAc 4:1). **^{1}H NMR** (major isomer, 300 MHz, $CDCl_3$): δ 2.90 (d, *J* = 3 Hz, 1H), 2.53–2.63 (m, 1H), 2.08–2.45 (m, 5H), 1.91–2.02 (m, 2H), 1.68–1.76 (m, 1H), 1.30–1.35 (m, 1H), 1.26 (s, 3H); **^{13}C NMR** (major isomer, 75 MHz, $CDCl_3$) δ 219.14, 57.59, 45.31, 33.31, 31.72, 31.55, 25.34, 23.07, 20.78; **^{1}H NMR** (minor isomer, 300 MHz, $CDCl_3$): δ 2.96 (d, *J* = 3.3 Hz, 1H), 2.58–2.67 (m, 1H), 2.34–2.52 (m, 2H), 1.90–2.22 (m, 5H), 1.65–1.74 (m, 2H), 1.27 (s, 3H).

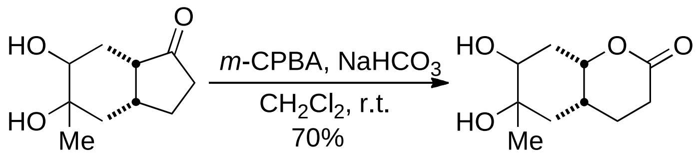
(^{1}H NMR filename: panpan01-01-1, panpan01-01-2; ^{13}C NMR filename: panpanct01-05; notebook #: 00155, 00166)



3.8 **3.14**

Compound 3.14. To a solution of **3.8** (0.0586 g, 0.39 mmol, 1.0 equiv.) in $H_2O/CH_3COCH_3/CH_3CN$ (*v*/*v*/*v* 1:1:1, 4 mL) was added NMO (0.1828 g, 1.56 mmol, 4.0 equiv.) and OsO_4 on poly(4-vinylpyridine) (0.23 mmol/g, 0.0848 g, 5 mol%). The suspension was stirred at room temperature for 2 days and then filtered over sintered glass funnel, washed with MeOH (5 mL). To the filtrate was added water (20 mL) and the resulting mixture was extracted with hexanes (2 x 5 mL). The hexanes layer was combined and concentrated at reduced pressure (~15 mmHg, rotavap water bath temp. 0–5 ºC) to give recovered **3.8** (0.0043 g, 7%). The water layer was concentrated to dryness and the crude obtained was purified by flash column chromatography (hexanes/EtOAc 1:2) to afford **3.14** (0.587 g, 82%, 88% brsm) as a colorless oil (inseparable diastereomers, d.r. 1:0.13; R_f = 0.17, hexanes/EtOAc 1:2). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.41 (dd, *J* = 11.1, 4.8 Hz, 0.15H), 3.22 (dd, *J* = 11.4, 5.1 Hz, 1H), 2.63–2.74 (m, 1H), 2.43–2.56 (m, 0.32H), 1.93–2.40 (m, 10H), 1.34–1.87 (m, 5.1H), 1.20 (s, 2.9H), 1.19 (s, 0.5H), 0.98 (dd, *J* = 14.4, 12.9 Hz, 1.2H); **^{13}C NMR** (major isomer, 75 MHz, $CDCl_3$) δ 219.82, 71.63, 71.33, 50.14, 39.32, 34.19, 31.92, 27.38, 26.89, 24.98.

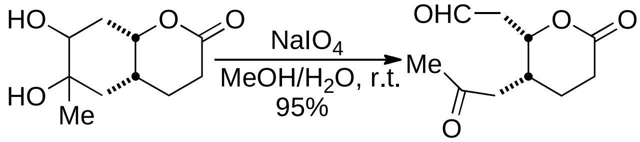
(^{1}H NMR filename: panpan003-010; ^{13}C NMR filename: panpan003-010c; notebook #: 00042, 00046)



3.14 **3.15**

Compound 3.14. (Note: open flask reaction) To a 25-mL round-bottomed flask equipped with reflux condenser, **3.14** (0.0201 g, 0.11 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (ACS grade, 5 mL). The solution was stirred at room temperature and $NaHCO_3$ (0.0739 g, 0.88 mmol, 8.0 equiv.) was added followed by *m*-CPBA (70%, 0.0538 g, 0.22 mmol, 2.0 equiv.). After 2 days at room temperature, Na_2SO_3 (0.0555 g) was added to quench the reaction. The mixture was filtered over a cotton plug to remove all of the salts and washed with CH_2Cl_2 (5 mL). The filtrate was concentrated and the crude obtained was purified by flash column chromatography (CH_2Cl_2/MeOH 97:3) to afford **3.15** (0.0154 g, 70%) as a pale yellow oil (inseparable diastereomers, d.r. 1:0.17; R_f = 0.19, CH_2Cl_2/MeOH 94:6). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 4.55–4.58 (m, 0.97H), 3.75 (dd, *J* = 11.4, 5.1 Hz, 1H), 3.56–3.59 (m, 0.15H), 3.48 (dd, *J* = 11.7, 4.8 Hz, 0.17H), 2.46–2.54 (m, 2.4H), 2.31–2.41 (m, 2.3H), 2.04–2.20 (m, 3.7H), 1.86–1.97 (m, 2H), 1.44–1.67 (m, 4.2H), 1.23–1.29 (m, 5.3H); **^{13}C NMR** (major isomer, 75 MHz, $CDCl_3$) δ 78.90, 71.24, 69.98, 37.34, 34.28, 27.49, 27.24, 26.47, 23.67.

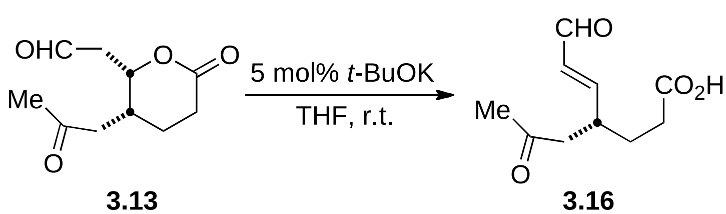
(^{1}H NMR filename: panpan004-005; ^{13}C NMR filename: panpan004-005c; notebook #: 00049, 00074)



3.15 **3.13**

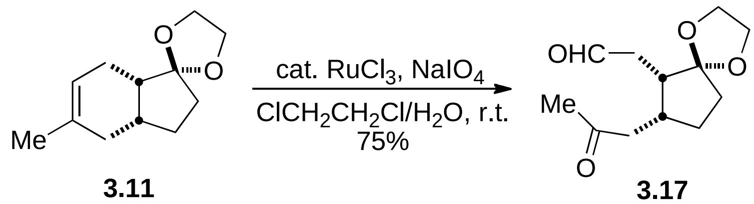
Compound 3.13. To a stirred solution of **3.15** (0.0136 g, 68 μmol, 1.0 equiv.) in MeOH/H_2O (*v*/*v* 1:1, 3 mL) was added $NaIO_4$ (0.0458 g, 210 μmol, 3.1 equiv.). After stirring at room temperature for 3 h, EtOAc (20 mL) was added. The mixture was washed with brine (2 x 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to give **3.13** (0.0130 g, 95%) as a colorless oil, which is pure enough and used in the next step without further purification. (R_f = 0.23, EtOAc). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.76 (t, *J* = 1.2 Hz, 1H), 5.01 (ddd, *J* = 8.1, 5.1, 3.0 Hz, 1H), 2.33–2.82 (m, 8H), 2.18 (s, 3H), 1.60–1.71 (m, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 206.09, 198.28, 170.87, 76.18, 45.89, 41.88, 30.63, 29.84, 27.08, 24.64.

(^{1}H NMR filename: panpan005-003; ^{13}C NMR filename: panpan005-003c; notebook #: 00068)



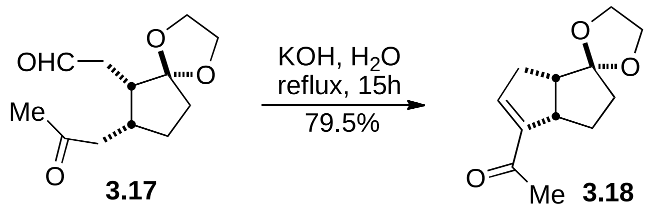
Compound 3.16. To a stirred solution of **3.13** (0.0099 g, 50 μmol, 1.0 equiv.) in THF was added *t*-BuOK (0.1 M in THF, 25 μL, 2.5 μmol, 5 mol%). After stirring at room temperature for 5 h, the mixture was filtered over a short pad of silica, washed with EtOAc (14 mL). The filtrate was concentrated to give crude **3.16** (0.0062 g) as a pale yellow oil. (R_f = 0.10, EtOAc). The crude **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.49 (d, *J* = 7.5 Hz, 1H), 6.68 (dd, *J* = 15.6, 8.4 Hz, 1H), 6.12 (ddd, *J* = 15.6, 7.8, 1.2 Hz, 1H) shows the presence of the *trans*-unsaturated aldehyde moiety.

(crude ^{1}H NMR filename: panpan006-001; notebook #: 00082)



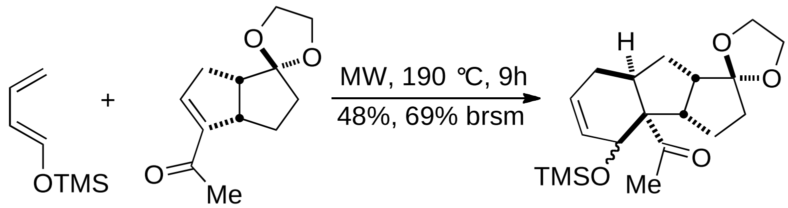
Compound 3.17. To a 2000-mL three-neck round-bottomed flask equipped with mechanical stirrer, **3.11** (5.06 g, 26.05 mmol, 1.0 equiv.), and $RuCl_3 \cdot xH_2O$ (0.054g, 0.26 mmol, 1.0 mol%) were dissolved in $ClCH_2CH_2Cl$ (130 mL) and H_2O (104 mL). The resulting mixture was stirred vigorously at room temperature. $NaIO_4$ (11.142g, 52.09 mmol, 2.0 equiv.) was then added in portions over 5 minutes. After 3 hours at room temperature, sat. $Na_2S_2O_3$ (50 mL) was added. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layer was dried over anhydrous $MgSO_4$. After filtration and concentration, the crude obtained was purified by flash column chromatography (hexanes/EtOAc, 2:1) to afford **3.17** (4.42 g, 75%) as a colorless oil. (R_f = 0.23, hexanes/EtOAc 2:1). **IR** (thin film): 3413, 2956, 2888, 1716, 1413, 1358, 1289, 1121 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.70 (dd, *J* = 2.7, 1.5 Hz, 1H), 3.73–3.91 (m, 4H), 2.60–2.74 (m, 2H), 2.30–2.48 (m, 3H), 2.16–2.24 (m, 1H), 2.10 (s, 3H), 1.71–2.02 (m, 3H), 1.23–1.36 (m, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 208.13, 202.17, 117.73, 65.00, 64.51, 45.44, 43.66, 39.71, 34.56, 34.16, 30.39, 27.67; **HRMS** (ESI) calcd. for $C_{12}H_{19}O_4$ $[M+H]^+$ 227.1278 found 227.1276.

(^{1}H NMR filename: panpan102-012; ^{13}C NMR filename: panpan102-t008; notebook #: 00098, 00114, 01374)



Compound 3.18. To a 1000-mL round-bottomed flask equipped with reflux condenser, was added keto aldehyde **3.17** (3.30g, 58.86 mmol, 1.0 equiv.) and H_2O (740 mL). The mixture was stirred at room temperature and oxygen was removed under reduced pressure (~15 mmHg) for 20 minutes. The flask was refilled with Ar and the *vacuo*-Ar cycle was repeated for three times. Solid KOH (3.30g, 51.2 mmol, 3.5 equiv.) was added and the *vacuo*-Ar cycle was repeated for another two times. The resulting pale yellow solution was gently refluxed for 15 hours, cooled to room temperature, and extracted with EtOAc (3 x 100 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4. After filtration and concentration, the crude obtained was purified by flash column chromatography (hexanes/EtOAc, 4:1) to afford **3.18** (2.44 g, 79.5%) as a yellow oil. (R_f = 0.17, hexanes/EtOAc 4:1). **IR** (thin film): 2960, 2883, 1708, 1666, 1619, 1435, 1373, 1107 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.61–6.62 (m, 1H), 3.77–4.00 (m, 4H), 3.45–3.55 (m, 1H), 2.48–2.78 (m, 3H), 2.28 (s, 3H), 1.90–2.11 (m, 1H), 1.51–1.70 (m, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 196.56, 147.52, 144.11, 118.51, 65.13, 64.19, 47.15, 47.09, 35.20, 33.55, 28.44, 27.29; **HRMS** (ESI) calcd. for $C_{12}H_{17}O_3$ $[M+H]^+$ 209.1172 found 209.1176.

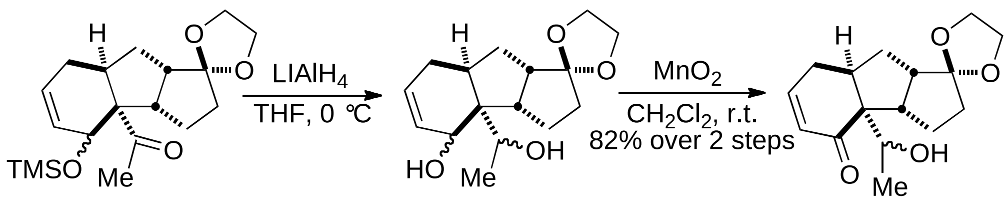
(^{1}H NMR filename: panpan103-013; ^{13}C NMR filename: panpan103-t039-1; notebook #: 00131, 01284)



3.20 **3.18** **3.22**

Compound 3.22. To a 10-mL CEM Discover reaction vessel with magnetic stirring bar, enone **3.18** (g, mmol, 1.0 equiv.) and diene **3.20** (g, mmol, 2.5 equiv.) were added. The vessel was flushed with Ar, capped and put in a microwave reactor. The mixture was heated to 190 ºC and kept at this temperature with high speed stirring for 9 hours. After cooling to room temperature, the pale yellow solution was transferred to a 25-mL round-bottomed flask by pipette. A short-path distillation head was attached and the volatiles (contain diene **3.20** and crotonaldehyde) were removed (~100 ºC/4 mmHg for 0.5 hour). The residue was purified by flash column chromatography (hexanes/EtOAc, 7:1 to 2:1) to afford recovered **3.18** (g, %) and **3.22** (g, %, % brsm) as a pale yellow oil (inseparable diastereomers, d.r. 1:0.6; R_f = 0.21, hexanes/EtOAc 6:1). **IR** (thin film): 3029, 2957, 2883, 1697, 1426, 1350, 1251, 1222, 1093 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.70–5.77 (m, 0.67H), 5.58–5.68 (m, 1.5H), 5.39–5.45 (m, 0.94H), 4.34 (app d, J = 5.1 Hz, 0.57H), 4.13–4.19 (m, 1H), 3.84–3.98 (m, 6H), 3.01 (dt, *J* = 8.7, 6.9 Hz, 0.97H), 2.82 (q, *J* = 8.7 Hz, 0.6H), 2.35–2.61 (m, 4.7H), 2.14 (s, 2.6H), 2.11 (s, 1.6H), 1.98–2.08 (m, 0.74H), 1.59–1.96 (m, 8H), 1.41 (td, *J* = 13.2, 10.8 Hz, 1.2H), 1.01–1.19 (m, 1.7H), 0.18 (s, 7.5H), 0.16 (s, 4.8H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 211.32, 210.02, 129.55, 128.62, 127.92, 125.91, 118.39, 118.24, 70.18, 66.48, 65.16, 65.08, 64.88, 64.40, 64.35, 49.18, 48.49, 46.84, 46.78, 36.41, 36.04, 35.47, 33.87, 32.39, 31.85, 31.81, 28.24, 27.08, 26.20, 26.04, 0.64, 0.35; **HRMS** (ESI) calcd. for $C_{19}H_{30}NaO_4Si$ $[M+]^+$ 373.1806 found 373.1803.

(^{1}H NMR filename: panpan104-005-2, pan104-016; ^{13}C NMR filename: pan104-t016; notebook #: 00140, 01708)

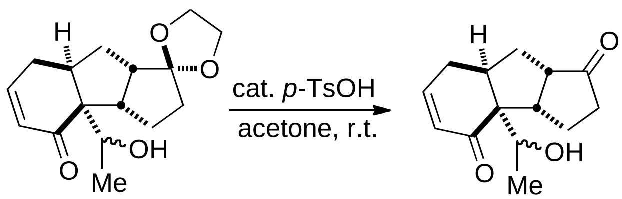


Compound 3.31. To a stirred solution of **3.22** (0.0782 g, 0.223 mmol, 1.0 equiv.) in THF (3.6 mL) at 0 ºC (ice-water bath) was added $LiAlH_4$ (1.0 M in THF, 0.49 mL, 0.49 mmol, 2.2 equiv.). The mixture was stirred at 0 ºC for 10 minute then allowed to warm to room temperature. After stirring at room temperature for 5 h, the reaction was quenched by addition of H_2O (19 μL), 15% NaOH (19 μL) and H_2O (57 μL). The resulting slurry was stirred for additional 1h and then filtered over Büchner funnel at reduced pressure and washed with EtOAc. The filtrate was concentrated to yield crude **3.30**, which was used in the next step without further purification.

To a solution of crude **3.30** (0.223 mmol, 1.0 equiv., theoretical) obtained above in CH_2Cl_2 (ACS grade, 3 mL) at room temperature was added MnO_2 (85%, activated, Aldrich; 0.183 g, 2.10 mmol, 10.0 equiv.). The suspension was stirred for 8 hours at room temperature, filtered over Büchner funnel at reduced pressure and washed with EtOAc. The filtrate was concentrated and the crude obtained was purified by flash column chromatography (hexanes/EtOAc 2:1) to afford **3.31** (0.051 g, 82% over 2 steps) as a colorless oil (inseparable diastereomers, d.r. 1:0.19; R_f = 0.36, hexanes/EtOAc 1:1). **^{1}H**

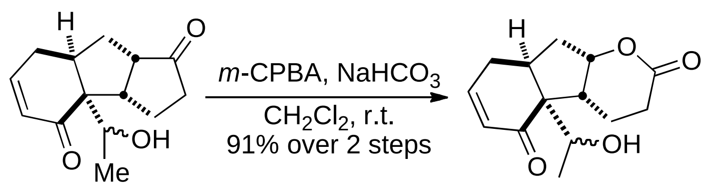
NMR (300 MHz, $CDCl_3$): δ 6.80–6.88 (m, 1H), 6.06–6.10 (m, 1H), 3.84–3.92 (m, 4H), 3.16–3.32 (m, 1H), 2.24–2.66 (m, 4H), 1.36–2.07 (m, 8H), 1.17 (d, J = 6.6 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 148.38, 130.26, 70.68, 65.01, 64.43, 62.67, 49.46, 46.46, 37.58, 35.87, 32.70, 28.28, 25.00, 20.25.

(^{1}H NMR filename: 106-c002; ^{13}C NMR filename: panpan106-ct002; notebook #: 00179)



Compound 3.32. To a solution of **3.31** (0.052 g, 0.187 mmol, 1.0 equiv.) in acetone (ACS grade, 5 mL) was added p-TsOH·H_2O (0.0071 g, 37 μmol, 20 mol%). The solution was stirred at room temperature for 6 hours then filtered over a short pad of silica, washed with EtOAc. The filtrate was concentrated to give crude **3.32**, which was used directly in the next step without further purification. An analytical sample was purified by preparative thin-layer chromatography (PTLC) (hexanes/EtOAc 2:1) and obtained as a colorless oil (diasteromers, d.r. 1:0.18; R_f = 0.24, hexanes/EtOAc 1:1). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.87–6.94 (m, 1H), 6.11–6.15 (m, 1H), 3.83–3.93 (m, 1H), 3.44–3.52 (m, 1H), 2.41–2.69 (m, 4H), 2.27–2.38 (m, 3H), 2.11 (ddd, J = 14.1, 9.0, 4.5 Hz, 1H), 1.85–1.98 (m, 1H), 1.66–1.77 (m, 1H), 1.58 (br, s, 1H), 1.21 (d, J = 6.6 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$, major diastereomer): δ 221.26, 203.09, 148.50, 130.18, 70.22, 63.37, 48.48, 47.91, 39.47, 36.87, 35.02, 27.97, 23.35, 20.33; MS (FAB) m/z (%): 154.1 (100), 235.2 (23) $[M+H]^+$.

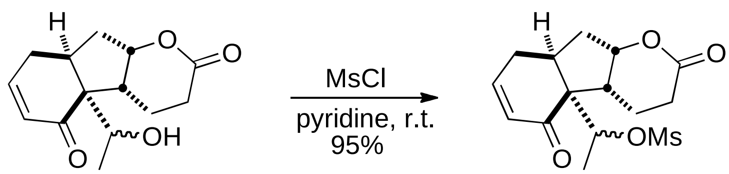
(^{1}H NMR filename: panpan106-003-1; ^{13}C NMR filename: panpan107-ct002; notebook #: 00184, 00211)



Compound 3.33. (Note: open flask reaction) To a 25-mL round-bottomed flask equipped with reflux condenser, crude **3.32** (0.187 mmol, 1.0 equiv., theoretical) obtained above was dissolved in CH_2Cl_2 (ACS grade, 5 mL). $NaHCO_3$ (0.0781 g, 0.930 mmol, 5 equiv.) was added and the mixture was stirred at 0 ºC (ice-water bath). *m*-CPBA (77%, 0.0542 g, 0.242 mmol, 1.3 equiv.) was then added and the reaction was allowed to warm to room temperature on its own. After stirring at room temperature for 2 days, sat. $Na_2S_2O_3$ (4 mL) and sat. $NaHCO_3$ (10 mL) were added and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration and concentration, the crude obtained was purified by flash column chromatography (hexanes/EtOAc 1:2) to give **3.33** (0.0426 g, 91% over 2 steps) as a colorless oil (inseparable diasteromers, d.r. 1:0.18; R_f = 0.23, hexanes/EtOAc 1:2). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.96 (ddt, *J* = 10.2, 5.4, 1.8 Hz, 1H), 6.88 (ddt, *J* = 5.4, 4.8, 1.8 Hz, 0.18H), 6.13–6.18 (m, 0.86H), 6.06–6.11 (m, 0.24H), 4.57–4.66 (m, 0.99H), 4.46 (ddd, J = 11.4, 4.2, 2.1 Hz, 0.10H), 4.24 (td, J = 12.0, 2.1 Hz, 0.14H), 3.99–4.06 (m, 0.27H), 3.76–3.88 (m, 0.88H), 2.80–3.20 (m, 2.5H), 2.52–2.77 (m, 2.9H), 2.11–2.50 (m, 4.8H), 1.62–2.09 (m, 3.9H), 1.18 (m, 3.5H); **^{13}C NMR** (75 MHz, $CDCl_3$, major diastereomer): δ 203.02, 171.87, 149.26, 130.59, 79.69, 70.54, 61.36, 45.00, 39.94,

35.20, 30.34, 28.42, 20.25, 19.46; **^{13}C NMR** (75 MHz, $CDCl_3$, minor diastereomer): δ 200.97, 172.56, 149.15, 129.64, 79.92, 71.33, 61.22, 43.83, 39.05, 36.89, 30.22, 28.79, 21.04, 19.33; **HRMS** (FAB) calcd. for $C_{14}H_{17}O_4$ $[M{-}H]^-$ 249.11323 found 249.11317.

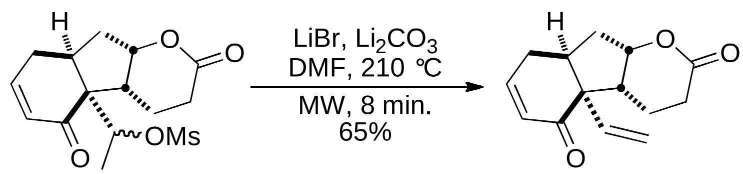
(^{1}H NMR filename: panpan107-003; ^{13}C NMR filename: panpan107-t003; notebook #: 00187, 00213)



3.33 **3.35**

Compound 3.35. To a stirred solution of **3.33** (0.0520 g, 0.21 mmol, 1.0 equiv.) in pyridine (4 mL) at 0 ºC (ice-water bath) was added MsCl (97 μL, 1.25 mmol, 6.0 equiv.). The ice-water bath was removed and the reaction was stirred at room temperature for 9 hours. Sat. $NaHCO_3$ (10 mL) was added and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration and concentration, the crude obtained was purified by flash column chromatography (hexanes/EtOAc 1:2) to give **3.33** (0.0649 g, 95%) as a colorless oil (d.r. 1:0.18; R_f = 0.28, 0.30, hexanes/EtOAc 1:2). **^{1}H NMR** (300 MHz, $CDCl_3$, major diastereomer): δ 6.90 (ddt, *J* = 9.9, 5.4, 1.8 Hz, 1H), 6.00–6.05 (m, 1H), 5.08 (q, *J* = 6.6 Hz, 1H), 4.65 (td, *J* = 7.8, 3.0 Hz, 1H), 3.32–3.41 (m, 1H), 3.05 (s, 3H), 2.89–2.99 (m, 1H), 2.64 (dt, *J* = 16.5, 3.3 Hz, 1H), 1.92–2.44 (m, 6H), 1.70–1.85 (m, 1H), 1.43 (d, *J* = 6.6 Hz, 3H).

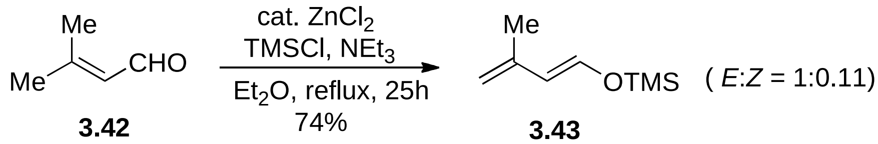
(^{1}H NMR filename: panpan108-007-1; notebook #: 00222, 00322)



3.35 **3.34**

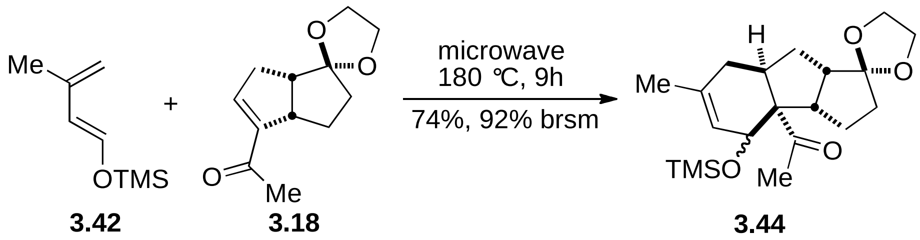
Compound 3.38. To a 10-mL CEM Discover reaction vessel with magnetic stirring bar was added **3.35** (39 μmol, 1.0 equiv.) in DMF (1 mL), Li_2CO_3 (0.0174 g, 235 μmol, 6 equiv.), and LiBr (1.0 M in DMF, newly made, 157 μL, 157 μmol, 4.0 equiv.). The vessel was flushed with Ar, capped and put in a microwave reactor. The mixture was heated to 210 ºC and kept at this temperature with high speed stirring for 8 minutes. After cooling to room temperature, the pale brown solution was partitioned between water (20 mL) and Et_2O (8 mL). The organic layer was separated and the water layer was extracted with Et_2O (2 x 8 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration and concentration, the crude obtained was purified by flash column chromatography (hexanes/EtOAc 6:1) to give **3.38** (0.0059 g, 65%) as a colorless oil (R_f = 0.23, hexanes/EtOAc 2:1). **^{1}H NMR** (100 MHz, $CDCl_3$) δ 6.72–6.78 (m, 1H), 5.99–6.04 (m, 1H), 5.65 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.26 (d, *J* = 10.8 Hz, 1H), 5.13 (d, *J* = 17.4 Hz, 1H), 4.67 (app td, *J* = 7.2, 0.9 Hz, 1H), 3.41 (dt, *J* = 12.3, 7.5 Hz, 1H), 2.77–2.87 (m, 1H), 2.63–2.74 (m, 1H), 2.53–2.59 (m, 1H), 2.37–2.46 (m, 1H), 2.19–2.31 (m, 1H), 2.06–2.12 (m, 1H), 1.86–1.98 (m, 2H), 1.35–1.50 (m, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 173.68, 146.61, 135.49, 127.87, 118.20, 79.94, 61.62, 43.27, 37.74, 37.46, 30.52, 25.66, 21.71; **HRMS** (FAB) calcd. for $C_{14}H_{17}O_3$ $[M+H]^+$ 233.11722 found 233.11622.

(^{1}H NMR filename: panpan108-024; ^{13}C NMR filename: panpan108-t021-11; notebook #: 00324, 00329)



Compound 3.43. Following the procedure described by Duhamel,[4] to a 500-mL 2 necked round-bottomed flask equipped with reflux condenser and glass stopper was added $ZnCl_2$ (0.30 g, 2.2 mmol, 0.8 mol%). The condenser was connected to vacuum and the flask was heated by a bunsen burner until all the solid $ZnCl_2$ melted. After cooling to room temperature, the flask was charged with Argon. Et_2O (60 mL), 3-methylcrotonaldehyde (**3.42**) (24 mL, 250 mmol, 1.0 equiv.), NEt_3 (40 mL, 287.5 mmol, 1.15 equiv.), and TMSCl (34.9 mL, 275 mmol, 1.10 equiv.) were added successively. The suspension was stirred at gentle reflux for 25 hours. After cooling to room temperature, hexanes (200 mL) was added and the triethylamine hydrochloride precipitate was removed by filtering over sintered glass funnel under reduced pressure and washed with hexanes (50 mL). The filtrate was concentrated by rotavap and the residue was distilled under reduced pressure to give **3.43** (55–65 ºC/20 mmHg, 30.96 g, 79%, *E*:*Z* = 1.0:0.11) as a colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$, *E* isomer): δ 6.53 (dt, J = 12.3, 0.6 Hz, 1H), 5.79 (dd, J = 12.3, 0.6 Hz, 1H), 4.66–4.76 (m, 2H), 1.81 (dd, J = 1.2, 0.6 Hz, 3H), 0.22 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$, *E* isomer): δ 141.96, 140.20, 116.34, 111.72, 18.92, 0.63.

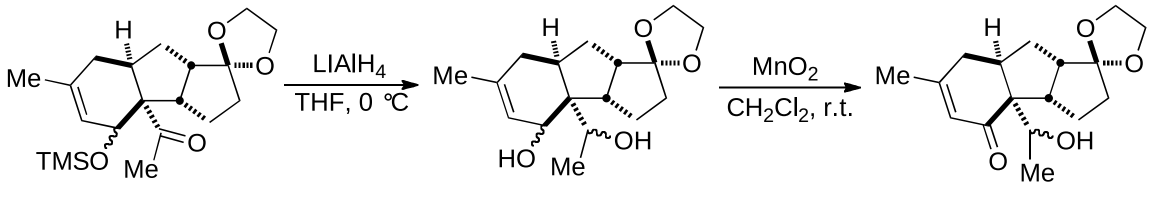
(^{1}H NMR filename: pan104-104; ^{13}C NMR filename: pan104-t104; notebook #: 00333, 01051, 01569)



Compound 3.44. To a 10-mL CEM Discover reaction vessel with magnetic stirring bar, diene **3.42** (2.08g, 13.28 mmol, 2.5 equiv.) and enone **3.18** (1.11g, 5.31 mmol, 1.0 equiv.) were added. The vessel was flushed with Ar, capped and put in microwave reactor. The mixture was heated to 180 ºC and kept at this temperature with high speed stirring for 9 hours. After cooling to room temperature, the pale yellow solution was transferred to a 25-mL round-bottomed flask by pipette. A short-path distillation head was attached and the volatiles (contain diene **3.42** and 3-methyl-2-butenal (**3.41**)) were removed (~100 ºC/4 mmHg for 0.5 hour). The residue was purified by flash column chromatography (hexanes/EtOAc, 7:1 to 2:1) to afford recovered **3.18** (0.21g, 19%) and **3.44** (1.44g, 74%, 92% brsm) as a pale yellow oil (inseparable diastereomers, d.r. 1:0.42; R_f = 0.23, hexanes/EtOAc 2:1). **IR** (thin film): 2957, 1696, 1350, 1251, 1096, 1065 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.30–5.32 (m, 0.42H), 5.07 (app s, 1H), 4.29 (br d, *J* = 5.4 Hz, 0.42H), 4.09–4.10 (m, 1H), 3.77–3.91(m, 5.9H), 2.92 (td, *J* = 8.4, 8.0 Hz, 1.1H), 2.75 (q, J = 8.7 Hz, 0.44H), 2.23–2.52 (m, 4.6H), 2.06(s, 3.2H), 2.03 (s, 1.1H), 1.46–1.88 (m, 13H), 1.26–1.38 (m, 1H), 0.93–1.10 (m, 1.5H), 0.12(s, 8.9H), 0.09 (s, 3.1H); **^{13}C NMR** (75 MHz, $CDCl_3$, major diastereomer): δ 211.31, 135.58, 123.15, 118.34, 70.87, 67.55, 65.12, 64.31, 46.77, 46.75, 36.80, 35.41, 32.38, 31.83, 26.06, 23.22, 0.39; **^{13}C NMR** (75 MHz, $CDCl_3$, minor diastereomer): δ 209.87, 137.26, 120.89, 118.18, 65.04, 64.84,

64.81, 49.19, 48.26, 36.02, 34.53, 32.04, 30.88, 28.18, 26.21, 24.06, 0.69; **HRMS** (ESI) calcd. for $C_{20}H_{32}NaO_4Si$ $[M+Na]^+$ 387.1962 found 387.1963.

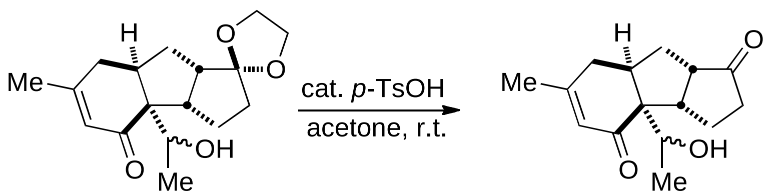
(^{1}H NMR filename: panpan104-401-1; ^{13}C NMR filename: panpan104-401-t1; notebook #: 01385)



Compound 3.46. To a solution of D-A adduct **3.44** (0.436g, 1.20 mmol, 1.0 equiv.) in THF (24 mL) at 0 ºC (ice-water bath) was added $LiAlH_4$ (0.10 g, 2.63 mmol, 2.2 equiv.) in one portion. The reaction mixture was stirred at at 0 ºC for 10 minute then allowed to warm to room temperature. After stirring at room temperature for 5 h, the reaction was quenched by successive addition of H_2O (100 μL), 15% NaOH (100 μL) and H_2O (300 μL). The resulting slurry was stirred for additional 1h and then filtered over Büchner funnel at reduced pressure and washed with EtOAc. The filtrate was concentrated to yield crude **3.45**, which was used in the next step without further purification.

To a solution of crude **3.45** (1.20 mmol, 1.0 equiv., theoretical) obtained above in CH_2Cl_2 (ACS grade, 24 mL) at room temperature was added MnO_2 (85%, activated, Aldrich; 1.25 g, 14.36 mmol, 12.0 equiv.). The suspension was stirred for 1d at room temperature, filtered over Büchner funnel at reduced pressure and washed with EtOAc. The filtrate was concentrated and the crude obtained was purified by flash column chromatography (hexanes/EtOAc 2:1) to afford **3.46** (d.r. 1: 0.20, 0.316 g, 90%) as a colorless oil (R_f = 0.17, 0.13, hexanes/EtOAc 2:1). Analytical data for major isomer: **IR** (thin film): 3475, 2969, 2881, 1642, 1437, 1380, 1354, 1318, 1209, 1157, 1104, 1040 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.92 (s, 1H), 3.79–3.90 (m, 4H), 2.78 (br d, *J* = 7.6 Hz), 2.52–2.58 (m, 1H), 2.38–2.43 (m, 1H), 2.18–2.27 (m, 2H), 1.76–2.06 (m, 7H), 1.59–1.67 (m, 2H), 1.49 (dt, *J* = 13.6, 11.2 Hz, 1H), 1.11 (d, *J* = 6.8, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 203.92, 160.26, 126.96, 118.32, 70.68, 64.93, 64.34, 61.31, 49.75, 46.58, 37.75, 35.79, 33.36, 33.01, 24.96, 24.82, 20.30; **HRMS** (ESI) calcd. for $C_{17}H_{25}O_4$ $[M+H]^+$ 293.1753 found 293.1747.

(^{1}H NMR and ^{13}C NMR filename: pan306-1, notebook #: 00551)

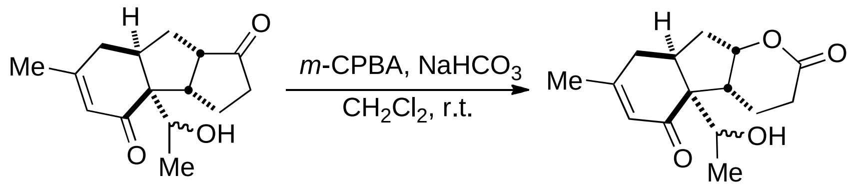


3.46 **3.47**

Compound 3.47. To a solution of **3.46** (0.334 g, 1.142 mmol, 1.0 equiv.) in acetone (ACS grade, 23 mL) was added *p*-TsOH·H_2O (0.043 g, 0.228 mmol, 20 mol%). The reaction was stirred at room temperature for 16 hours then filtered over a short pad of silica, washed with EtOAc. The filtrate was concentrated to give crude **3.47** (R_f = 0.24, hexanes/EtOAc 1:1), which was used directly in the next step without further purification. An analytical sample was purified by flash column chromatography (hexanes/EtOAc 2:1) and obtained as a colorless oil (inseparable diasteromers, d.r. 1:0.18). **IR** (thin film): 3424, 2939, 1734, 1654, 1458, 1435, 1381, 1275, 1257, 1236, 1157, 1118, 1060 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.99 (m, 0.91H), 5.96 (br s, 0.16H), 3.82–3.89 (m, 1.2H), 3.39–3.48 (m, 1.3H), 2.86–2.96 (m, 1.3H), 2.56–2.63 (m, 1.4H), 2.40–2.52 (m, 2.4H), 2.23–2.36 (m, 4.7H), 2.01–2.14 (m, 2.2H), 1.98 (s, 3H), 1.95 (s, 0.7H), 1.81–1.86 (m, 1.1H), 1.69–1.77 (m, 1.3H), 1.27 (d, *J* = 6.4 Hz, 0.7H), 1.18 (d, *J*

=6.4 Hz, 3H); **^{13}C NMR** (major diastereomer, 100 MHz, $CDCl_3$): δ 221.02, 203.05, 160.66, 127.14, 70.54, 62.01, 49.20, 48.06, 39.37, 37.20, 35.43, 33.25, 24.95, 23.51, 20.45; **HRMS** (ESI) calcd. for $C_{15}H_{21}O_3$ $[M+H]^+$ 249.1491 found 249.1485.

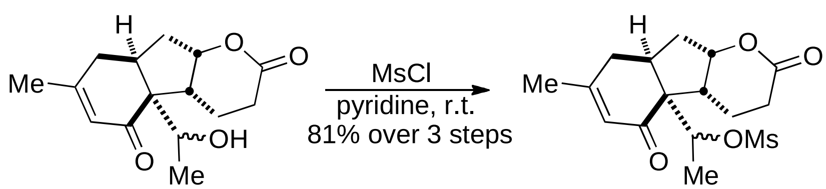
(^{1}H NMR and ^{13}C NMR filename: pan306-2-2, notebook #: 00345, 01685)



3.47 **3.48**

Compound 3.48. (Note: open flask reaction) To a 100-mL round-bottomed flask equipped with reflux condenser, crude **3.47** (1.142 mmol, 1.0 equiv., theoretical) obtained above was dissolved in CH_2Cl_2 (ACS grade, 25 mL). $NaHCO_3$ (0.480 g, 5.71 mmol, 5 equiv.) was added and the mixture was stirred at 0 ºC (ice-water bath). *m*-CPBA (77%, 0.384 g, 1.713 mmol, 1.5 equiv.) was then added in 2 portions and the reaction was allowed to warm to room temperature on its own. After stirring at room temperature for 36 hours, sat. $Na_2S_2O_3$ (4 mL) and sat. $NaHCO_3$ (10 mL) were added and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic layer was washed with brine (15 mL), dried over anhydrous Na_2SO_4. After filtration and concentration, the crude **3.48** obtained was used directly in the next step without further purification. An analytical sample was purified by flash column chromatography (hexanes/EtOAc 1:1.5) and obtained as a colorless oil (inseparable diasteromers, d.r. 1:0.18; R_f = 0.21, hexanes/EtOAc 1:2). **IR** (thin film): 3456, 2938, 1735, 1650, 1433, 1384, 1245, 1187, 1134, 1069 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.03 (m, 1H), 5.94 (m, 0.18H), 4.56–4.61 (m, 1.2H), 4.43–4.47 (m, 0.25H), 4.20–4.26 (m, 0.25H), 4.02 (q, *J* = 6.4 Hz, 0.25H), 3.76–3.83 (m, 1.2H), 3.06–3.21 (m, 1H), 2.96–3.04 (m, 1.2H), 2.70–2.95 (m, 1.1H), 2.56–2.66 (m, 3.3H), 2.41–2.51 (m, 0.5H), 2.14–2.38 (m, 5.1H), 1.92–2.02 (m, 5.1H), 1.66–1.90 (m, 2.1H), 1.19 (d, J = 6.4 Hz, 0.57H), 1.14 (d, J = 6.8 Hz, 3.2H); **^{13}C NMR** (major diastereomer, 100 MHz, $CDCl_3$): δ 202.86, 171.71, 161.70, 127.38, 79.68, 70.55, 59.76, 45.04, 40.02, 35.35, 33.55, 30.24, 25.00, 20.26, 19.42; **HRMS** (ESI) calcd. for $C_{15}H_{21}O_4$ $[M+H]^+$ 265.1440 found 265.1450.

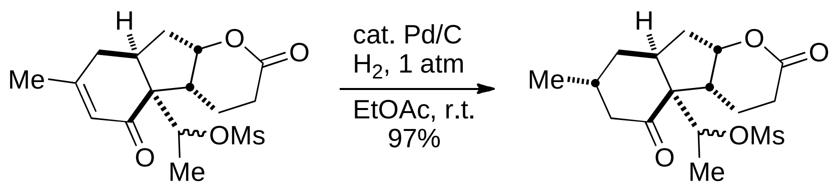
(^{1}H NMR and ^{13}C NMR filename: pan306-3-2, notebook #: 00346, 01691)



3.48 **3.40**

Compound 3.40. To a stirred solution of crude **3.48** (1.142 mmol, 1.0 equiv., theoretical) in pyridine (12 mL) at 0 ºC (ice-water bath) was added MsCl (0.35 mL, 4.56 mmol, 4.0 equiv.). The ice-water bath was removed and the reaction was stirred at room temperature for 1 day. Sat. $NaHCO_3$ (15 mL) was added and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration and concentration, the crude was purified by flash column chromatography (hexanes/EtOAc 1:1) to afford **3.40** (d.r. 1:0.18, 0.316 g, 81% over 3 steps) as a pale yellow oil (R_f = 0.18, 0.12, hexanes/EtOAc 1:1). Analytical data for major isomer: **IR** (thin film): 1737, 1656, 1432, 1335, 1247, 1173, 1135, 1054, 1018, 965 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.87 (s, 1H), 5.01 (q, J = 6.8 Hz, 1H), 4.61 (td, J = 7.8, 3.2 Hz, 1H), 3.32 (dt, J = 12.8, 6.8 Hz, 1H), 3.03 (s, 3H), 2.96–3.02 (m, 1H), 2.84–2.91 (m, 1H), 2.61 (dt, J = 16.4, 3.2 Hz, 1H), 2.20–2.31 (m, 2H), 2.05–2.13 (m, 2H), 1.97 (s, 3H), 1.86–1.93 (m, 1H), 1.76 (dq, J = 12.4, 3.2 Hz, 1H), 1.42 (d, J = 6.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 197.96, 172.26, 160.73, 124.35, 79.21, 76.85, 60.83, 40.96, 39.52, 36.86, 35.47, 30.56, 30.50, 24.61, 20.33, 18.03; **HRMS** (ESI) calcd. for $C_{16}H_{22}NaO_6S$ $[M+Na]^+$ 365.1035 found 365.1032.

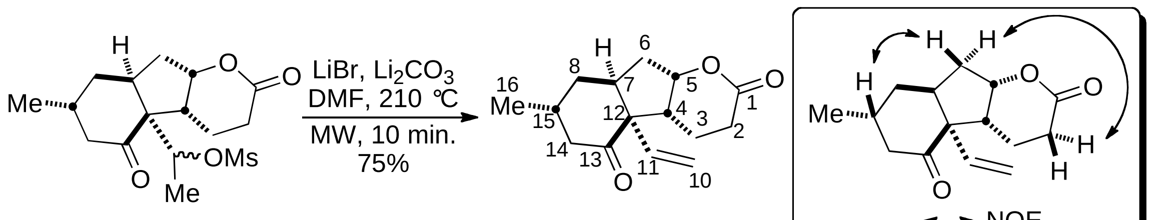
(^{1}H NMR and ^{13}C NMR filename: pan306-4-1, notebook #: 00348, 01694)



3.40 **3.41**

Compound 3.41. To a stirred solution of **3.40** (0.105 g, 0.308 mmol, 1.0 equiv.) in EtOAc (ACS grade, 4 mL) was added 5 wt. % Pd/C (0.105 g). A balloon of H_2 was applied and the reaction mixture was stirred at room temperature for 1 day. The mixture was then filtered over Büchner funnel at reduced pressure and washed with EtOAc. The filtrate was concentrated to give crude **3.41**, which was used directly in the next step without further purification. An analytical sample was purified by flash column chromatography (hexanes/EtOAc 1.5:1) and obtained as a colorless oil (R_f = 0.23, 0.14, hexanes/EtOAc 1:1). **IR** (thin film): 2957, 1736, 1704, 1457, 1339, 1246, 1176, 1129, 1104, 1053 cm^{-1}; **^{1}H NMR** (major diastereomer, 400 MHz, $CDCl_3$): δ 5.32 (q, J = 6.8 Hz, 1H), 4.63 (td, J = 7.4, 3.6 Hz, 1H), 3.35 (dt, J = 11.6, 7.2 Hz, 1H), 3.07 (s, 3H), 2.94–3.00 (m, 1H), 2.58 (dt, J = 16.4, 3.2 Hz, 1H), 2.38–2.42 (m, 1H), 2.28 (ddd, J = 16.4, 14.4, 5.2 Hz, 1H), 1.97–2.19 (m, 4H), 1.71–1.89 (m, 4H), 1.34 (d, J = 6.8 Hz, 3H), 1.06 (d, J = 6.4 Hz, 3H); **^{13}C NMR** (major diastereomer, 100 MHz, $CDCl_3$): δ 210.67, 172.45, 79.63, 75.80, 65.29, 48.06, 39.59, 39.49, 39.30, 35.40, 31.51, 30.44, 30.14, 22.26, 20.13, 18.31; **^{1}H NMR** (minor diastereomer, 400 MHz, $CDCl_3$): δ 4.96 (q, *J* = 6.8 Hz, 1H), 4.59 (dt, *J* = 8.4, 6.8 Hz, 1H), 3.07 (s, 3H), 2.89–2.97 (m, 1H), 2.65–2.71 (m, 1H), 2.50 (ddd, *J* = 14.4, 3.6, 2.0 Hz, 1H), 1.68–2.41 (m, 10H), 1.33 (d, *J* = 6.8 Hz, 3H), 1.06 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** (minor diastereomer, 100 MHz, $CDCl_3$): δ 211.35, 170.58, 81.39, 79.62, 61.83, 50.26, 41.87, 40.90, 39.66, 37.88, 34.94, 29.95, 28.86, 22.48, 18.86, 18.80; **HRMS** (ESI) calcd. for $C_{16}H_{24}NaO_6S$ $[M+Na]^+$ 367.1191 found 367.1193.

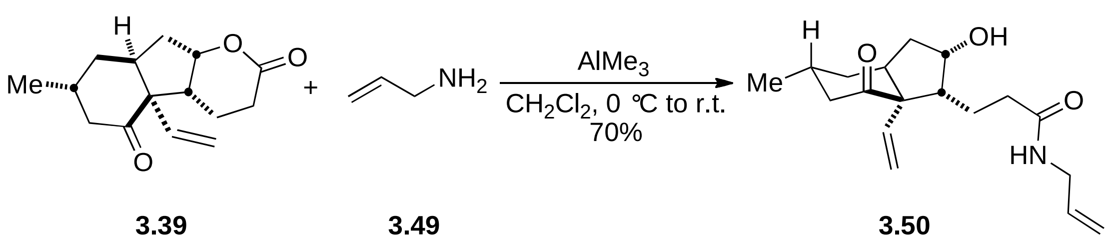
(^{1}H NMR filename: pan306-5-1; ^{13}C NMR filename: pan306-5-t1; notebook #: 00354, 01696)



3.41 **3.39**

Compound 3.39. To a 10-mL CEM Discover reaction vessel with magnetic stirring bar were added crude **3.41** (0.308 mmol, 1.0 equiv., theoretical) in DMF (3 mL), Li_2CO_3 (0.1278 g, 1.730 mmol, 6 equiv.), and LiBr (1.0 M in DMF, newly made, 1.15 mL, 1.15 mmol, 4.0 equiv.). The vessel was flushed with Ar, capped and put in microwave reactor. The mixture was heated to 210 ºC and kept at this temperature with high speed stirring for 10 minutes. After cooling to room temperature, the pale brown solution was partitioned between water (40 mL) and Et_2O (10 mL). The organic layer was separated and the water layer was extracted with Et_2O (2 x 10 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration and concentration, the crude obtained was purified by flash column chromatography

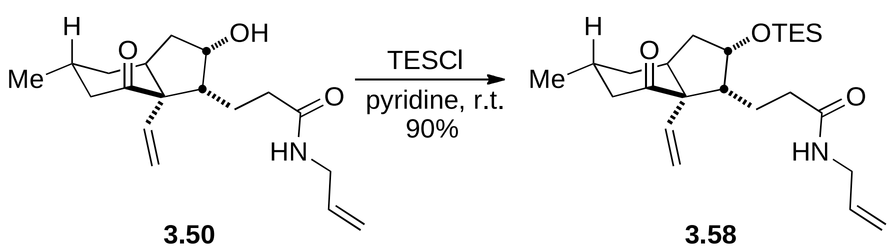
(hexanes/EtOAc 6:1) to give **3.39** (0.0574 g, 75%) as a colorless oil (R_f = 0.23, hexanes/EtOAc 4:1). **IR** (thin film): 2955, 1746, 1703, 1457, 1331, 1248, 1187, 1130, 1033 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 5.60 (*C*-11H, dd, *J* = 18.0, 10.8 Hz, 1H), 5.28 (*C*-10H, d, *J* = 10.8 Hz, 1H), 5.02 (*C*-10H, d, *J* = 17.6 Hz, 1H), 4.62 (*C*-5H, dt, *J* = 6.8, 0.8 Hz, 1H), 3.38 (*C*-4H, dt, *J* = 11.6, 7.6 Hz, 1H), 2.70–2.77 (*C*-7H, m, 1H), 2.45 (*C*-2H, dt, *J* = 16.0, 3.6 Hz, 1H), 2.14–2.30 (*C*-14, 2H, m, 3H), 1.94–2.06 (*C*-15H, m, 1H), 1.91 (*C*-6H, ddd, *J* = 14.4, 6.8, 0.8 Hz, 1H), 1.54–1.81 (*C*-3, 8, 6H, m, 4H), 1.28–1.39 (*C*-3H, m, 1H), 0.94 (*C*-16H, d, *J* = 6.4 Hz, 3H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 211.28 (*C*-13), 173.72 (*C*-1), 137.54 (*C*-11), 119.28 (*C*-10), 80.37 (*C*-5), 63.98 (*C*-12), 47.36 (*C*-14), 42.76 (*C*-7), 41.12 (*C*-4), 36.63 (*C*-6), 32.27 (*C*-8), 30.46 (*C*-2), 30.15 (*C*-15), 22.52 (*C*-16), 21.74 (*C*-3); **HRMS** (ESI) calcd. for $C_{15}H_{21}O_3$ $[M+H]^+$ 249.1485 found 249.1481.
(^{1}H, ^{13}C NMR, gCOSY filename: pan110-7-1; NOESY, HSQCAD filename: pan110-7-2; notebook #: 00391, 01703)



3.39 **3.49** **3.50**

Compound 3.50. To a 10-mL flame dried round-bottomed flask, CH_2Cl_2 (0.8 mL) was added and the flask was cooled to 0 ºC (ice-water bath). Me_3Al (2.0 M in toluene, 156 μL, 313 μmol, 3.0 equiv.) was added. After stirring at 0 ºC for 30 minutes, **3.39** (0.0259 g, 104 μmol, 1.0 equiv.) in CH_2Cl_2 (1.4 mL) was added dropwise. The ice-water bath was removed and the reaction was allowed to warm to room temperature on its own. After 2.5 hours at room temperature, TLC showed complete consumption of the **3.39**. MeOH (170

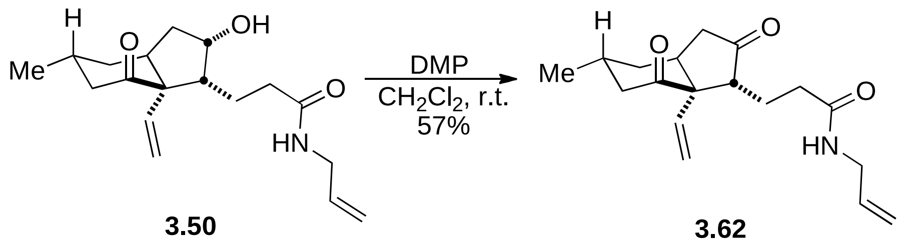
μL) was added to quench the reaction. The mixture was filtered over a short pad of silica, washed with EtOAc (10 mL). The filtrate was concentrated and the residue was purified by flash column chromatography (hexanes/EtOAc 6:1) to give **3.50** (0.0222 g, 70%) as a colorless oil (R_f = 0.08, hexanes/EtOAc 1:1). **IR** (thin film): 3333, 2924, 1700, 1639, 1543, 1419, 1334, 1225 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.10 (br s, 1H), 5.80–5.88 (m, 1H), 5.74 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.01–5.27 (m, 3H), 4.84 (d, *J* = 17.6 Hz, 1H), 4.05 (s, 1H), 3.80–3.88 (m, 3H), 2.92–2.96 (m, 1H), 2.36–2.46 (m, 2H), 2.14–2.28 (m, 3H), 1.69–1.98 (m, 4H), 1.58–1.66 (m, 2H), 1.48 (td, *J* = 13.2, 3.2 Hz, 1H), 0.98 (d, *J* = 6.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 215.14, 174.35, 141.18, 134.24, 116.70, 116.20, 71.61, 62.34, 51.71, 48.93, 44.35, 42.29, 39.07, 35.55, 34.14, 29.07, 22.38, 21.93. (^{1}H and ^{13}C NMR filename: pan306-7-1; notebook #: 00362, 01710)



3.50 **3.58**

Compound 3.58. To a stirred solution of **3.50** (0.0026 g, 8.5 μmol, 1.0 equiv.) in pyridine (1.0 mL) was added TESCl (7.1 μL, 42.4 μmol, 5.0 equiv.). After stirring at room temperature for 2 hours, sat. $NaHCO_3$ (3 mL) was added and the mixture was extracted with Et_2O (3 x 5 mL). The combined organic layer was washed with brine (5 mL) and dried over anhydrous Na_2SO_4. After filtration and concentration, the crude **3.58** obtained (0.0032 g, 90%) was used in the next step without further purification. **^{1}H NMR** (300 MHz, CD_3OCD_3, crude): δ 7.00–7.09 (br s, 1H), 5.69–5.90 (m, 2H), 4.84–5.19 (m, 4H), 4.21 (dt, J = 4.5, 3.3 Hz, 1H), 3.76–3.83 (m, 2H), 2.44 (dt, J = 8.7, 5.4 Hz, 1H), 1.54–2.35 (m, 12H), 0.92–1.04 (m, 12H), 0.62 (q, J = 7.8 Hz, 6H).

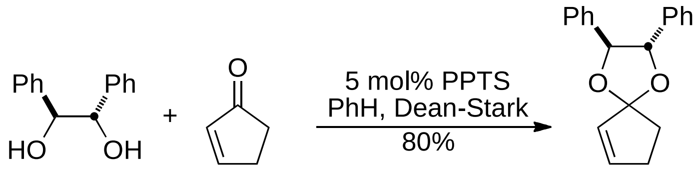
(^{1}H NMR filename: panpan112-c006; notebook #: 00372, 00374)



3.50 **3.62**

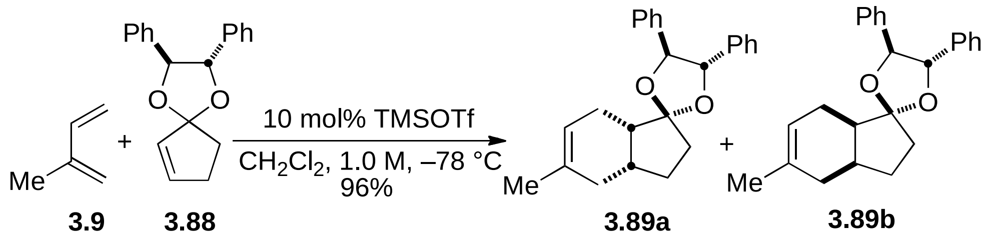
Compound 3.62. To a stirred solution of **3.50** (0.0225 g, 73.6 μmol, 1.0 equiv.) in CH_2Cl_2 (3.0 mL) at room temperature was added Dess-Martin periodinane (0.0468 g, 110.0 μmol, 1.5 equiv.). After 2 hours, sat $Na_2S_2O_3$ (1 mL) and sat. $NaHCO_3$ (2 mL) were added and the mixture was extracted with EtOAc (3 x 5 mL). The combined organic layer was washed with brine (3 mL) and dried over anhydrous Na_2SO_4. After filtration and concentration, the residue was purified by flash column chromatography (hexanes/EtOAc 6:1) to give **3.62** (0.0149 g, 67%) as a colorless oil (R_f = 0.14, hexanes/EtOAc 1:1). **IR** (thin film): 3313, 2956, 2924, 1737, 1703, 1654, 1541, 1456, 1420, 1378, 1225, 1129 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.74–5.96 (m, 3H), 5.42 (d, J = 10.8 Hz, 1H), 5.08–5.24 (m, 3H), 3.84–3.93 (m, 2H), 2.96–3.08 (m, 2H), 2.21–2.49 (m, 5H), 2.07 (ddd, J = 19.2, 12.0, 1.2 Hz, 2H), 1.78–1.94 (m, 3H), 1.45–1.59 (m, 1H), 1.03 (d, J = 6.6 Hz, 3H).

(^{1}H NMR filename: pan306-8-1; notebook #: 00392, 01710)

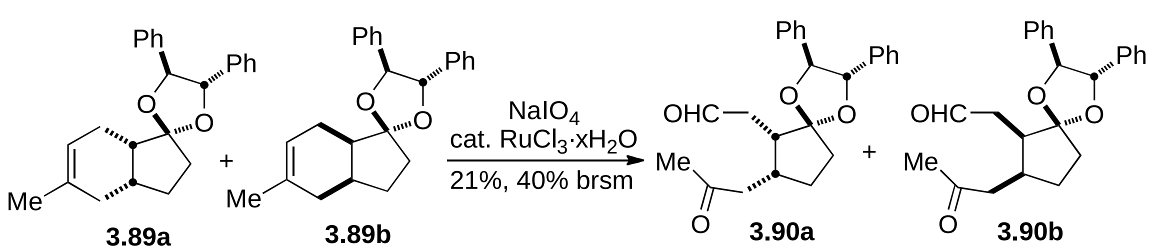


Compound 3.88. Following the procedure described by Mash,[5] to a 100-mL round-bottomed flask with Dean-Stark distillation head and condenser was added benzene (60 mL), cyclopent-2-enone (**3.84**, 3.52 mL, 42 mmol, 2.8 equiv.), (*S*, *S*)-hydrobenzoin (3.214 g, 15 mmol, 1.0 equiv.) and PPTS (0.189 g, 0.75 mmol, 5 mol%). The mixture was heated to reflux and the water was removed azeotropically. After 3 days, TLC showed complete consumption of (*S*, *S*)-hydrobenzoin. The reaction was cooled to r.t. and sat. $NaHCO_3$ (30 mL) was added. The organic layer was separated and the water layer was extracted with EtOAc (3 x 15 mL). The combined organic layer was washed with brine (20 mL) and dried over anhydrous Na_2SO_4. After filtration and concentration, the crude **3.88** obtained was purified by flash column chromatography (hexanes/EtOAc, 10:1) to afford title compound (4.18g, 80%) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.25–7.40 (m, 10H), 6.25 (app dt, *J* = 5.4, 2.4 Hz, 1H), 6.05 (app dt, *J* = 5.4, 2.1 Hz, 1H), 4.81 (s, 2H), 2.51–2.60 (m, 2H), 2.37–2.48 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 137.82, 137.04, 136.92, 131.37, 128.57, 128.44, 128.40, 126.86, 126.81, 121.40, 85.91, 85.47, 35.84, 29.92.

(^{1}H NMR filename: panpan101-2a-1; ^{13}C NMR filename: panpan101-2a-t1; notebook #: 01285, 01361.)

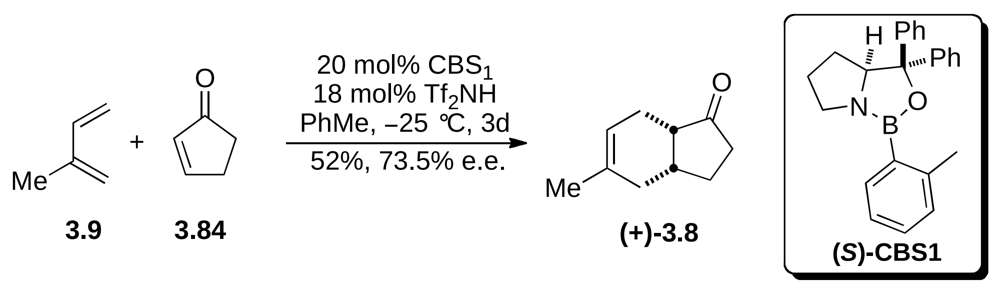


Compound 3.89a and 3.89b. To a 10-mL long neck round-bottomed flask with chiral ketal **3.88** (0.410 g, 1.47 mmol, 1.0 equiv.) was added CH_2Cl_2 (1.47 mL) and isoprene (**3.9**, 0.74 mL, 7.36 mmol, 5 equiv.). The solution was stirred at –78 ºC (dry ice/acetone bath) and TMSOTf (26 μL, 147 μmol, 10 mol%) was added. After 25 h at –78 ºC, TLC showed complete consumption of **3.88**. NEt_3 (0.20 mL) was added and the flask was warmed to room temperature. The solution was applied to flash column chromatography directly (hexanes/EtOAc, 30:1) to afford title compounds (0.488 g, 96%) as a colorless oil (inseparable mixture, d.r. = 2.08:1). **IR** (thin film): **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.17–7.36 (m, 17H), 5.47–5.49 (m, 1H), 5.39–5.44 (m, 0.48H), 4.62–4.73 (m, 3.1 H), 1.97–2.56 (m, 11H), 1.51–1.91 (m, 11H); **^{13}C NMR** (major isomer, 75 MHz, $CDCl_3$): δ 137.26, 136.81, 132.36, 128.50, 128.45, 128.35, 128.22, 127.00, 126.69, 120.51, 119.26, 85.67, 43.36, 35.85, 34.93, 32.11, 27.18, 24.04, 22.66. ; **HRMS** (ESI) calcd. for
(^{1}H NMR filename: pan101-3a-3-1; ^{13}C NMR filename: pan101-3a-4-t1; notebook #: 01313, 01391.)



Compound 3.90a/3.90b. To a solution of **3.89a**/**3.89b** mixture (0.099 g, 264 μmol, 1.0

equiv.) in $ClCH_2CH_2Cl$ (ACS grade, 1.32 mL) and H_2O (1.06 mL) was added $RuCl_3{\cdot}xH_2O$ (0.0019 g, 9.1 μmol, 3.5 mol%) and $NaIO_4$ (0.113 g, 528 μmol, 2.0 equiv.). The reaction was stirred vigorously at room temperature for 34 hours, then sat. $Na_2S_2O_3$ (2 mL) was added. The mixture was extracted with EtOAc (2 x 6 mL) and the combined organic layer was dried over anhydrous $MgSO_4$. After filtration and concentration, the residue was purified by flash column chromatography (hexanes/EtOAc, 3:1) to afford recovered **3.89a**/**3.89b** (0.054 g) and title compounds (0.021 g, 21%, 47% brsm) as a colorless oil (inseparable diastereomers, d.r. = 0.3:1). **IR** (thin film): **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.89 (t, *J* = 1.8 Hz, 0.3H), 9.86 (dd, *J* = 3.0, 1.5 Hz, 1H), 7.28–7.39 (m, 14H), 7.14–7.26 (m, 7.2H), 4.57–4.80 (m, 4.6H), 2.95–3.06 (m, 1.5H), 2.34–2.90 (m, 9.8H), 1.94–2.32 (m, 14H), 1.37–1.56 (m, 3.8H); **^{13}C NMR** (major isomer, 75 MHz, $CDCl_3$): δ 208.36, 202.20, 137.29, 135.95, 128.87, 128.78, 128.67, 128.44, 127.37, 126.55, 118.02, 85.70, 85.17, 45.80, 43.96, 40.05, 35.60, 33.65, 30.50, 28.22; **HRMS** (ESI) calcd. For (^{1}H NMR filename: pan101-4a-2; ^{13}C NMR filename: pan101-4a-t3; notebook #: 01333, 01397.)

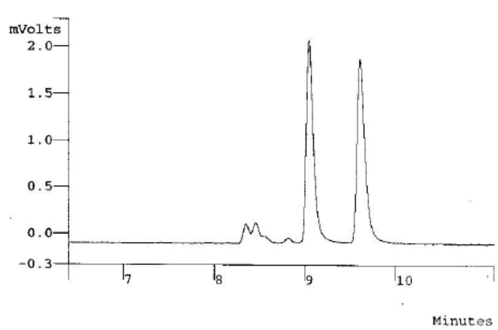


Compound (+)-3.8 from 3.9 and 3.84. Following the procedure described by Corey,[6] to a 50-mL long neck round-bottomed flask with magnetic stirring bar (flame-*vacuo*-Ar dried) was added PhMe (1 mL) and (*S*)-(–)-*o*-Tolyl-CBS-oxazaborolidine solution ((*S*)-

CBS1, 0.80 mL, 0.4 mmol, 20 mol%). The flask was cooled to –25 ºC (Cryocooler) and Tf_2NH solution (0.2 M in PhMe, newly made, 1.80 mL, 0.36 mmol, 18 mol%) was added. After 10 minutes at –25 ºC, isoprene (**3.9**, 1.0 mL, 10 mmol, 5 equiv.) and cyclopent-2-enone (**3.84**, 168 μL, 2 mmol, 1 equiv.) were added. The mixture was stirred at –25 ºC for 3 days and then quenched with NEt_3 (56 μL). After warming to room temperature, the solvent was removed by rotary evaporation (~15 mmHg, rotavap water bath temp. 0–5 ºC) and the residue was purified by flash column chromatography (hexanes/EtOAc 10:1) to afford title compound (0.157 g, 52%, 73.5% e.e.) as a colorless oil. The absolute stereochemistry of (+)-**3.8** was temporally assigned as shown according to the model proposed by Corey's group.

Analytical data for (+)-**3.8**: $[\alpha]_D$ = +9.8° (c 8.32, $CHCl_3$), 73.5% e.e.

GC condition: Column: Chiraldex B-DM (Cat. No. 77023), Adv. Separation Technologies, Inc. **Oven:** 130 °C; **Carrier:** Helium, head pressure 15 psi; **Detection:** FID 250 °C.



Peak No	Peak Name	Ret. Time (min)	Result ()	Area (counts)
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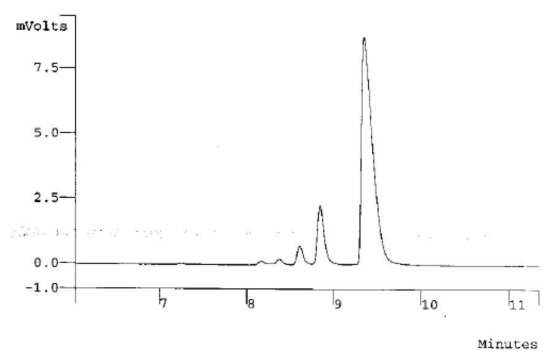
2		9.602	52.3485	11957
	Tota		100.0000	22841



Peak No	Peak Name	Ret. Time (min)	Result ()	Area (counts)
1		8.841	13.2593	11805
2		9.346	86.7407	77228
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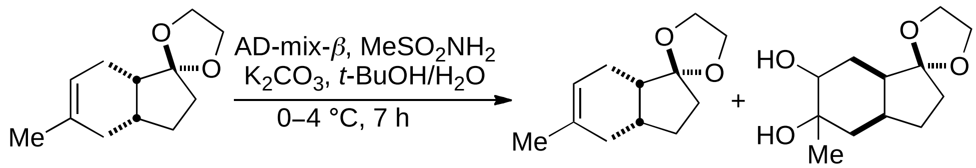
(notebook #: 01448)

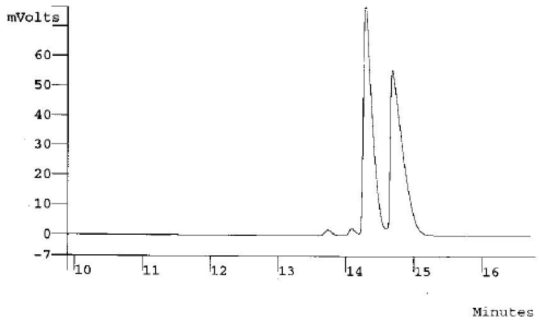


(±)-**3.11** 1.94 g — (+)-**3.11** 36%, > 99.8% e.e. — (–)-**3.91** 60%, 52% e.e.

Kinetic resolution of (±)-3.11. To a 500-mL round-bottomed flask, (±)-**3.11** (1.94 g, 10 mmol, 1.0 equiv.), methanesulfonamide (0.951 g, 10 mmol, 1.0 equiv.), and K_2CO_3 (4.146 g, 30 mmol, 3 equiv.) were dissolved in *t*-BuOH/H_2O (*v*/*v* 1:1, 100 mL). The mixture was stirred at 0 °C and AD-mix-*β* (1.41g/mmol, 14.1 g) was added in one portion. After stirring at 0–4 °C for 7 hours, sat. $Na_2S_2O_3$ (50 mL) was added and the mixture was extracted with hexanes (2 x 100 mL). The combined hexanes extract layer was washed successively with H_2O (4 x 50 mL) and brine (40 mL), dried over anhydrous Na_2SO_4. After filtration and concentration at reduced pressure (~15 mmHg, rotavap water bath temp. 0–5 ºC), the crude (+)-**3.11** was obtained, which also contains a little (**–**)-**3.91**. All of the aqueous layers were combined and added NaCl until saturation. The aqueous layer was then extracted with $CHCl_3$ (3 x 50 mL). The combined $CHCl_3$ extract layer was dried over anhydrous Na_2SO_4, filtered and concentrated to give crude (**–**)-**3.91**. The crude (+)-**3.11** obtained above was purified by flash column chromatography (hexanes/EtOAc 50:1) to afford (+)-**3.11** (0.67 g, 36%) as a colorless oil. After eluting all of the (+)-**3.11**, crude (**–**)-**3.91** was loaded to the same column and chromatographed (THF/hexanes/EtOAc 1:1:1) to yield (**–**)-**3.91** (1.104g, 60%) as a colorless oil.

Analytical data for (+)-**3.11**: $[\alpha]_D$ = +12.4° (*c* 16.23, $CHCl_3$), > 99.8% e.e.

GC condition: Column: Chiraldex B-DM (Cat. No. 77023), Adv. Separation Technologies, Inc. **Oven:** 130 °C; **Carrier:** Helium, head pressure 15 psi; **Detection:** FID 250 °C.



Peak No	Peak Name	Ret. Time (min)	Result ()	Area (counts)
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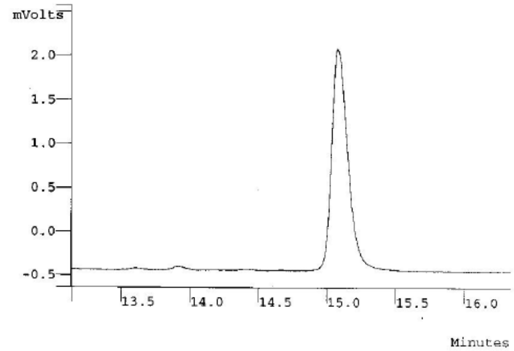
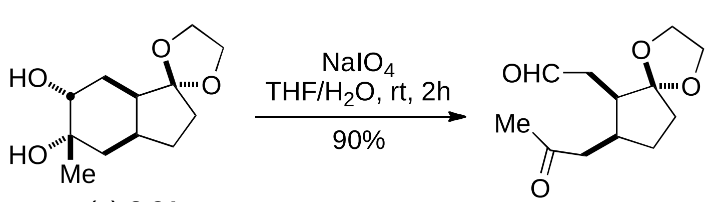
	Tota		**100.0000**	**1290927**



Peak No	Peak Name	Ret. Time (min)	Result ()	Area (counts)
1		14.671	0.0538	11
2		15.079	99.9462	21077
	Tota		**100.0000**	**21088**

Analytical data for **(–)-3.91**: **IR** (film): 3424, 2940, 1438, 1329, 1208, 1153, 1120, 1044, 1014 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.73–4.04 (m, 5H), 2.18–2.40 (m, 2H), 1.54–1.96 (m, 8H), 1.34–1.48 (m, 2H), 1.24 (d, *J* = 0.3Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 118.68, 72.33, 71.73, 65.17, 64.23, 45.96, 40.08, 35.74, 32.75, 28.01, 27.63, 27.27; **HRMS** (ESI) calcd. for $C_{12}H_{20}NaO_4$ $[M+Na]^+$ 251.1254 found 251.1250.

(^{1}H NMR filename: pan202-2-1; ^{13}C NMR filename: pan202-2-t1; notebook #: 01531, 01540)

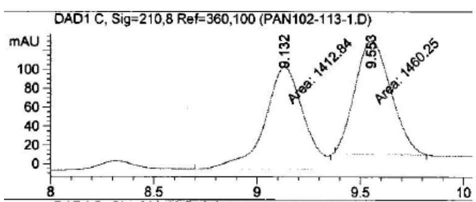


(–)-**3.91** (–)-**3.17**

Compound (–)-3.17 from (–)-3.91. To a 25-mL round-bottomed flask, (–)-**3.91** (kinetic resolution product, 0.129g, 0.70 mmol, 1.0 equiv.) was dissolved in THF (ACS grade, 4 mL) and H_2O (3 mL). The mixture was stirred vigorously at room temperature and then $NaIO_4$ (0.225 g, 1.05 mmol, 1.5 equiv.) was added in one portion. After 2 hours the reaction was quenched with sat. $Na_2S_2O_3$ (5 mL) and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic layer was washed with brine (5 mL) and dried over anhydrous $MgSO_4$. After filtration and concentration, the residue was purified by flash column chromatography (hexanes/EtOAc 2:1) to afford (–)-**3.17** (0.144 g, 90%) as a colorless oil.

Analytical data for (–)-**7**: $[\alpha]_D$ = –11.3° (*c* 3.38, $CHCl_3$), 52% e.e.

HPLC condition: Column: CHIRALPAK® IA (Column No. IA00CE-ML034), Chiral Technologies, Inc., 90 : 10 Hex : *i*-PrOH, 1 mL/min.



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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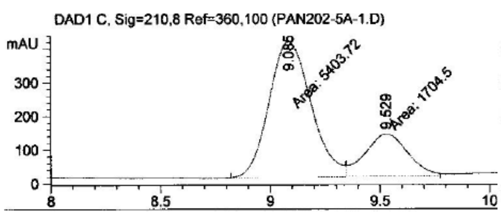
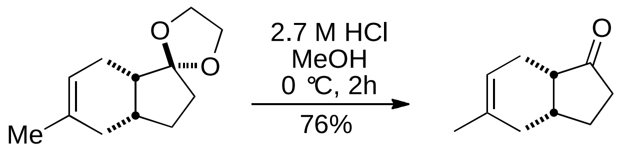
2	9.553	MM	0.2022	1460.25122	120.39056	50.8250
Totals :				2873.09619	228.24681	



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.085	MM	0.2228	5403.72168	404.28656	76.0207
2	9.529	MM	0.2248	1704.50171	126.35725	23.9793
Totals :				7108.22339	530.64381	

(notebook #: 01535)



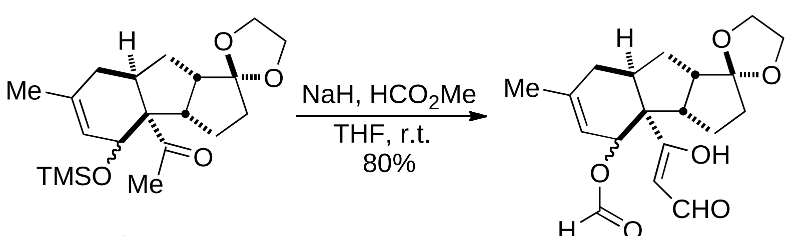
(+)-**3.11**
95.0% e.e.

(+)-**3.8**
92.3% e.e.

Compound (+)-3.8 from (+)-3.11. Following the procedure described by Hailes,[3] to a stirred solution of (+)-**3.11** (95.0% e.e., 0.157 g, 0.81 mmol, 1.0 equiv.) in MeOH (ACS grade, 4 mL) at 0 ºC was added dropwise aq. HCl solution (2.7 M, 0.25 mL, 0.675 mmol, 0.8 equiv.). The reaction was stirred at 0 ºC for 2 hours then sat. $NaHCO_3$ (8mL) was added. The mixture was extracted with hexanes (3 x 15 mL) and the combined organic layer was washed with brine (10 mL), dried over anhydrous $MgSO_4$. After filtration and concentration (~15 mmHg, rotavap water bath temp. 0–10 ºC), the crude obtained was purified by flash column chromatography (hexanes/Et_2O, 15:1) to afford (+)-**3.8** (0.092 g, 76%, 92.3% e.e.) as a colorless oil. $[\alpha]_D$ = +21.5° (*c* 3.57, $CHCl_3$).

(notebook #: 01534)

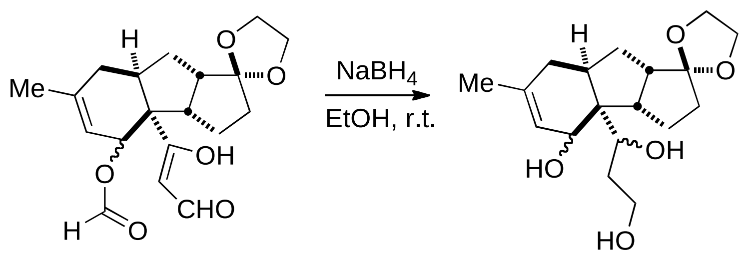
5.3 Experimental Procedures Relevant to Chapter 4



3.44 **4.4**

Compound 4.4. To a 25 mL round-bottomed flask with magnetic stirring bar (flame-*vacuo*-Ar dried) was added NaH (60% in mineral oil, 0.1139 g, 2.85 mmol, 15 equiv.) and pentane (4 mL). The suspension was stirred at room temperature for 5 minutes and the pentane was removed by pipette. **3.44** (0.0692 g, 190 μmol, 1.0 equiv.) in THF (5 mL) and HCO_2Me (0.47 mL, 7.59 mmol, 40 equiv.) were added via syringe. The mixture was stirred at room temperature for 1 day and then filtered over a short pad of silica, washed with EtOAc (20 mL). The filtrate was concentrated and the crude obtained was purified by flash column chromatography (hexanes/EtOAc, 4:1) to afford **4.4** (0.0527 g, 80%) as a colorless oil (R_f = 0.39, hexanes/EtOAc 2:1). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.90 (s, 1H), 8.07 (s, 1H), 5.26–5.30 (m, 1H), 4.97–5.03 (m, 1H), 3.84–4.01 (m, 4H), 3.01 (dt, *J* = 13.8, 7.2 Hz, 1H), 2.90 (q, *J* = 8.4 Hz, 1H), 2.66 (t, *J* = 9.6 Hz, 1H), 2.15–2.27 (m, 1H), 1.96–2.06 (m, 1H), 1.71–1.89 (m, 2H), 1.67 (s, 3H), 1.44–1.62 (m, 3H), 1.22–1.42 (m, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 188.00, 168.29, 141.91, 117.76, 117.27, 115.90, 83.35, 65.25, 64.53, 55.12, 47.83, 47.04, 36.20, 35.72, 30.49, 29.72, 24.38, 23.44.

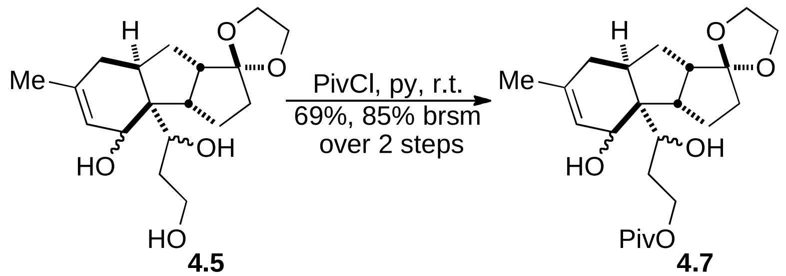
(^{1}H NMR filename: panpan105-302-1; ^{13}C NMR filename: panpan105-302-t1; notebook #: 00418, 00427)



4.4 **4.5**

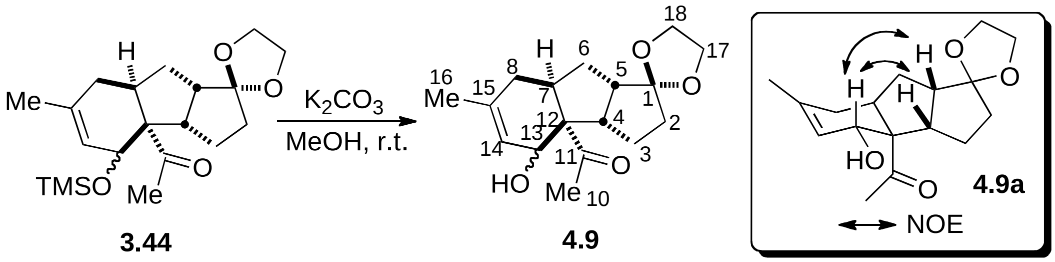
Compound 4.5. To a stirred solution of **4.4** (0.0508 g, 146 μmol, 1.0 equiv.) in absolute EtOH (2 mL) was added $NaBH_4$ (0.0165 g, 437 μmol, 3.0 equiv.). The solution was stirred at room temperature for 2 hours and sat. NH_4Cl (8 mL) was added. The mixture was extracted with EtOAc (3 x 10 mL) and the combined organic layer was dried over anhydrous $MgSO_4$. After filtration and concentration, the crude **4.5** (R_f = 0.19, 0.11, hexanes/EtOAc 2:1) obtained was used in subsequent reactions without further purification.

(notebook #: 00456, 00464)



Compound 4.7. To a solution of **4.5** (0.0471 g, 145 μmol, 1.0 equiv., theoretical) in pyridine (1.5 mL) was added pivaloyl chloride (179 μL, 1.45 mmol, 10 equiv.). The reaction was stirred at room temperature for 2 days and sat. $NaHCO_3$ (5 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the combined organic layer was washed with brine (5 mL), dried over anhydrous Na_2SO_4. After filtration and concentration, the crude obtained was purified by flash column chromatography (hexanes/EtOAc, 2:1) to afford recovered **4.5** (0.0088 g, 19%) and **4.4** (0.0411 g, 69%, 85% brsm) as a pale yellow solid. (inseparable diastereomers, d.r. 5.4:1; R_f = 0.78, hexanes/EtOAc 1:2). **^{1}H NMR** (300 MHz, $CDCl_3$, diastereomers): δ 5.24–5.30 (m, 1.0H), 4.69 (dd, *J* = 11.4, 3.6 Hz, 0.11H), 4.51 (dd, *J* = 11.4, 4.5 Hz, 0.93H), 4.28–4.34 (m, 0.27H), 4.00–4.13 (m, 0.42H), 3.84–3.97 (m, 5.8H), 3.75 (dd, *J* = 11.4, 4.5 Hz, 0.99H), 3.38–3.50 (m, 1.9H), 2.94 (dt, *J* = 9.9, 7.5Hz, 1.0H), 2.55–2.67(m, 2.1H), 2.49 (br s, 0.84H), 1.97–2.16 (m, 3.0H), 1.69–1.95 (m, 4.0H), 1.49–1.68 (m, 5.9H), 1.19–1.34 (m, 2.4H), 1.17 (s, 8.8H); **^{13}C NMR** (75 MHz, $CDCl_3$, major diastereomer): δ 136.75, 122.02, 118.15, 76.42, 68.28, 65.11, 64.49, 63.99, 62.65, 48.29, 48.02, 47.39, 41.95, 37.60, 35.73, 29.96, 29.23, 27.37, 26.05, 23.43.

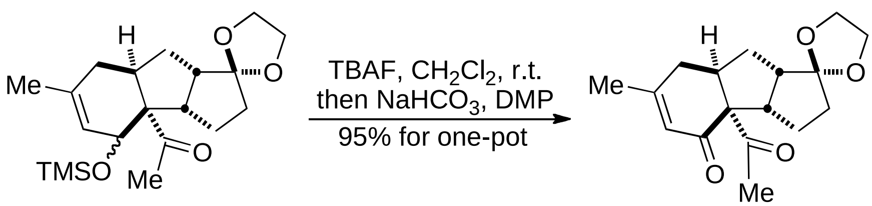
(^{1}H NMR filename: panpan106-322-1; ^{13}C NMR filename: panpan106-322-t1; notebook #: 00458, 00465)



Compound 4.9. To a solution of **3.44** (0.289 g, 0.792 mmol, 1.0 equiv.) in MeOH (ACS grade, 16 mL) was added K_2CO_3 (0.329 g, 2.377 mmol, 3 equiv.). The mixture was stirred at room temperature for 4 hours and then concentrated to remove all of the solvent. The residue was partitioned between EtOAc (40 mL) and brine (10 mL). The organic layer was separated, dried over anhydrous Na_2SO_4. After filtration and concentration, the crude **4.9** (R_f = 0.23, 0.17, hexanes/EtOAc 2:1) obtained was used in the next step without further purification. An analytical sample was purified by flash column chromatography (hexanes/EtOAc 4:1), with one pure diastereomer **4.9a** (R_f = 0.23, hexanes/EtOAc 2:1) was obtained as a colorless oil and fully characterized. **IR** (thin film): 3444, 2959, 2880, 1692, 1438, 1352, 1318, 1221, 1161, 1104, 1065, 1022 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.38 (*C*-14H, app t, *J* = 1.6 Hz, 1H), 4.06 (*C*-13H, br s, 1H), 3.84–3.98 (*C*-17,18H, m, 4H), 3.44 (OH, br s, 1H), 3.17 (*C*-4H, q, *J* = 8.8 Hz, 1H), 2.64 (*C*-7H, dt, *J* = 13.2, 8.0 Hz, 1H), 2.58 (*C*-5H, t, *J* = 10.0 Hz, 1H), 2.38 (*C*-8H, dd, *J* = 18.8, 7.6 Hz, 1H), 2.17 (*C*-16H, s, 3H), 1.99 (*C*-6H, ddd, *J* = 13.6, 8.0, 2.0 Hz, 1H), 1.90 (*C*-8H, br d, *J* = 18.8 Hz), 1.73–1.84 (*C*-2,3H, m, 2H), 1.66 (*C*-16H, d, *J* = 1.6 Hz, 3H), 1.57–1.63 (*C*-2H, m, 1H), 1.43 (*C*-6H, td, *J* = 13.2, 10.4 Hz, 1H), 1.13–1.23 (*C*-3H, m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 215.56 (*C*-11), 134.52 (*C*-15), 125.23 (*C*-14), 118.17 (*C*-1), 70.45 (*C*-13), 65.20 (*C*-17 or *C*-18), 64.53 (*C*-17 or *C*-18), 62.98 (*C*-12),

48.03 (*C*-4), 46.84 (*C*-5), 37.70 (*C*-7), 36.14 (*C*-2), 32.44 (*C*-6), 31.65 (*C*-8), 31.62 (*C*-10), 26.39 (*C*-3), 23.15 (*C*-16); **HRMS** (ESI) calcd. for $C_{17}H_{24}NaO_4$ $[M+Na]^+$ 315.1572 found 315.1565.

(^{1}H NMR, ^{13}C NMR, gCOSY, and HSQCAD filename: pan105-114-1; NOESY filename: pan105-114-2; notebook #: 00497, 01705.)

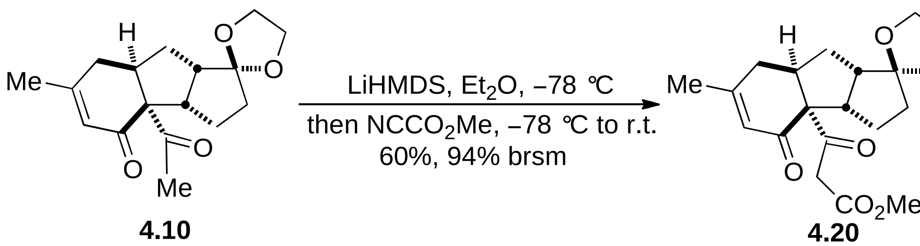


3.44 **4.10**

Compound 4.10. To a solution of **3.44** (1.556 g, 4.27 mmol, 1.0 equiv.) in CH_2Cl_2 (ACS grade, 43 mL) was added TBAF (1.228 g, 4.70 mmol, 1.1 equiv.). The reaction was stirred at room temperature for 12 hours and $NaHCO_3$ (1.434g, 17.07 mmol, 4.0 equiv.) was added. Dess-Martin periodinane (2.534 g, 5.98 mmol, 1.4 equiv.) was then added in portions over 5 minutes. The suspension was stirred for 6 hours then quenched with sat. $Na_2S_2O_3$ (10 mL) and sat. $NaHCO_3$ (20 mL). After stirring for another 6 hours, the organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (hexanes/EtOAc, 4:1) to afford **4.10** (1.18g, 95%, R_f = 0.28, hexanes/EtOAc 4:1) as a white solid. m.p. = 111–113 °C; **IR** (thin film): 2959, 2888, 1702, 1658, 1355, 1197, 1094 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.81–5.83 (m, 1H), 3.80–3.91 (m, 4H), 3.64 (q, *J* = 8.7 Hz, 1H), 2.73–2.92 (m, 2H), 2.39 (t, *J* = 9.9 Hz, 1H), 2.15 (d, *J* = 19.2 Hz, 1H), 2.03 (s, 3H), 1.87 (s, 3H), 1.81 (td, *J* = 6.0, 1.5 Hz, 1H), 1.67–

1.76 (m, 2H), 1.53–1.65 (m, 1H), 1.38 (td, J = 13.2, 10.5 Hz, 1H), 0.99–1.11 (m, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 204.38, 196.13, 161.54, 124.74, 117.96, 73.93, 65.15, 64.45, 46.70, 46.63, 37.16, 35.74, 32.03, 30.25, 27.67, 25.17, 24.69; **HRMS** (ESI) calcd. for $C_{17}H_{23}O_4$ $[M+H]^+$ 291.1591 found 291.1595.

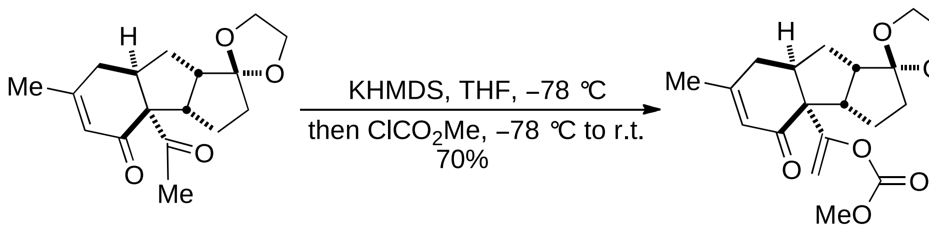
(^{1}H NMR filename: panpan105-306-1; ^{13}C NMR filename: panpan105-306-t1; notebook #: 00471, 01392)



Compound 4.20. To a stirred solution of **4.10** (0.6663 g, 2.295 mmol, 1.0 equiv.) in Et_2O (23 mL) at –78 ºC (dry ice/acetone bath) was added solid LiHMDS (Aldrich, 0.4608 g, 2.754 mmol, 1.2 equiv.). The solution was stirred at –78 ºC for 40 minutes before cooling bath was removed. The flask was allowed to warm to room temperature over 20 minutes and then cooled down to –78 ºC. Methyl cyanoformate (0.22 mL, 2.754 mmol, 1.2 equiv.) was added and the solution was allowed to warm to room temperature on its own with stirring overnight. Sat. $NaHCO_3$ (12 mL) was then added to quench the reaction. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organic layer was washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (hexanes/EtOAc, 7:1 to give **4.20** then 1:1 to give recovered **4.10**) to afford recovered **4.10** (0.2392 g, 36%) and **4.20** (0.4814 g, 60%, 94% brsm) as a colorless oil (contains ~8% enol ester forms, R_f = 0.14, hexanes/EtOAc 4:1). **IR** (thin film): 2955,

2888, 1746, 1703, 1658, 1437, 1321, 1236, 1152, 1017 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 12.37 (s, 0.08H), 5.84 (s, 1H), 5.05 (s, 0.08H), 3.79–3.90 (m, 6.3H), 3.77 (s, 0.76H), 3.50–3.70 (m, 4.9), 3.44 (d, J = 2.4 Hz, 2H), 2.64–3.02 (m, 3.1H), 2.06–2.55 (m, 3.5H), 2.04 (s, 0.84H), 1.98 (s, 0.49H), 1.34–1.88 (m, 13H), 0.96–1.12 (m, 1.8H); **^{13}C NMR** (75 MHz, $CDCl_3$, *β*-keto ester form): δ 198.90, 195.39, 167.66, 162.08, 124.84, 117.72, 73.67, 65.14, 64.47, 52.45, 47.26, 46.83, 46.31, 37.06, 35.76, 31.84, 30.13, 25.13, 24.80; **HRMS** (ESI) calcd. for $C_{19}H_{25}O_6$ $[M+H]^+$ 349.1646 found 349.1644.

(^{1}H NMR filename: panpan106-501; ^{13}C NMR filename: panpan106-t501; notebook #: 00953, 01398, 01341)

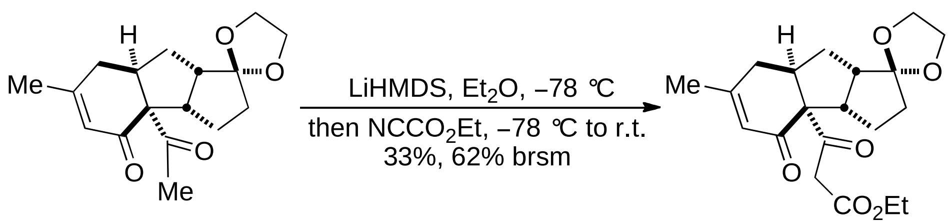


4.10 **4.21**

Compound 4.21. To a stirred solution of **4.10** (0.0617 g, 212 *μ*mol, 1.0 equiv.) in THF (4 mL) at –78 ºC (dry ice/acetone bath) was added KHMDS (0.5M in toluene, 467 *μ*L, 234 *μ*mol, 1.1 equiv.). The solution was stirred at –78 ºC for 1 hour before cooling bath was removed. The flask was allowed to warm to room temperature over 30 minutes and then cooled down to –78 ºC. Methyl chloroformate (20 *μ*L, 255 *μ*mol, 1.1 equiv.) was added and the solution was allowed to warm to room temperature on its own with stirring overnight. The brown solution was filtered over a short pad of silica, washed with Et_2O (15 mL). The filtrate was concentrated and the residue was purified by flash column chromatography (hexanes/EtOAc, 6:1) to give **4.21** (0.0518 g, 70%) as a colorless oil (R_f

= 0.22, hexanes/EtOAc 4:1). **^{1}H NMR** (300 MHz, $CDCl_3$, rotamers): δ 6.12 (s, 0.73H), 5.82 (d, *J* = 1.2 Hz, 0.99H), 5.60–5.65 (m, 1H), 4.94–5.01 (m, 1.6H), 3.83–3.96 (m, 12H), 2.98–3.13 (m, 2.7H), 2.75–2.84 (m, 0.83H), 2.41–2.62 (m, 2.6H), 2.26 (dd, *J* = 15.9, 2.4Hz, 0.82H), 2.19 (s, 2.1H), 2.18 (s, 2.9H), 2.04 (ddd, *J* = 13.2, 7.5, 1.8 Hz, 1.2H), 1.46–1.84 (m, 11.2H), 1.03–1.25 (m, 2.5H); **^{13}C NMR** (75 MHz, $CDCl_3$, rotamers): δ 204.43, 146.06, 145.58, 139.04, 127.85, 124.61, 121.89, 118.45, 117.96, 116.35, 65.87, 65.21, 65.19, 65.15, 64.48, 64.40, 55.69, 48.51, 47.96, 45.98, 45.87, 41.18, 38.40, 35.76, 35.16, 31.93, 29.62, 29.32, 28.74, 28.10, 25.94, 25.17, 21.16; **HRMS** (ESI) calcd. for $C_{19}H_{25}O_6$ $[M+H]^+$ 349.1646 found 349.1647.

(^{1}H NMR filename: panpan106-325-1; ^{13}C NMR filename: panpan106-325-t1; notebook #: 00489, 00501)

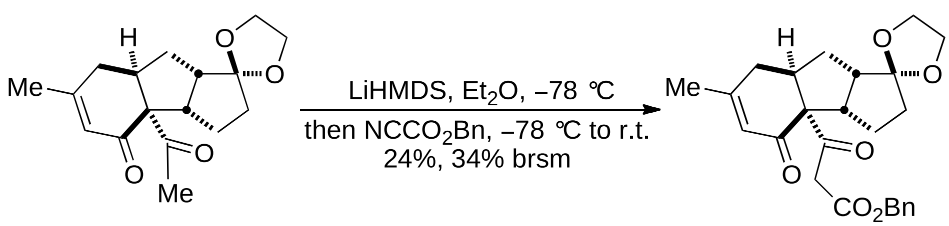


4.10 **4.22**

Compound 4.22. To a stirred solution of **4.10** (0.0078 g, 27 μmol, 1.0 equiv.) in Et_2O (2 mL) at –78 ºC (dry ice/acetone bath) was added LiHMDS (1.0 M in THF, 27 μL, 27 μmol, 1.0 equiv.). The solution was stirred at –78 ºC for 1 hour before cooling bath was removed. The flask was allowed to warm to room temperature over 20 minutes and then cooled down to –78 ºC. Ethyl cyanoformate (2.7 μL, 27 μmol, 1.0 equiv.) was added and the solution was allowed to warm to room temperature on its own over 3 hours. Sat. $NaHCO_3$ (6 mL) was then added to quench the reaction. The mixture was extracted with

EtOAc (2 x 5 mL). The combined organic layer was washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by preparative TLC (hexanes/CH_2Cl_2/Et_2O 3:3:1) to give recovered **4.10** (0.0037 g, 47%) and **4.22** (0.0032 g, 33%, 62% brsm) as a pale yellow oil (R_f = 0.25, hexanes/CH_2Cl_2/ Et_2O 3:3:1). **^{1}H NMR** (300 MHz, $CDCl_3$, β-keto ester form): δ 5.86–5.89 (m, 1H), 5.45 (q, J = 5.7 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 3.86–3.90 (m, 4H), 5.60–5.68 (m, 1H), 3.46 (d, J = 3.6 Hz, 2H), 2.89–3.00 (m, 1H), 2.76–2.87 (m, 1H), 2.43 (t, J = 10.2 Hz, 1H), 2.14 (d, J = 19.8 Hz, 1H), 1.91 (s, 3H), 1.69–1.88 (m, 4H), 1.60–1.67 (m, 1H), 1.22 (t, J = 7.2 Hz, 3H).

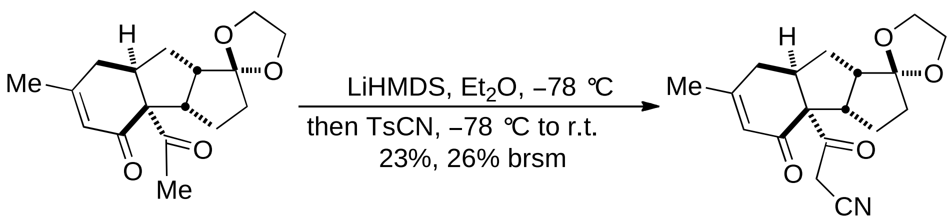
(^{1}H NMR filename: panpan105-107-1; notebook #: 00808)



4.10 4.23

Compound 4.23. To a stirred solution of **4.10** (0.0079 g, 27 μmol, 1.0 equiv.) in Et_2O (2 mL) at –78 ºC (dry ice/acetone bath) was added LiHMDS (1.0 M in THF, 27 μL, 27 μmol, 1.0 equiv.). The solution was stirred at –78 ºC for 1 hour before cooling bath was removed. The flask was allowed to warm to room temperature over 20 minutes and then cooled down to –78 ºC. Benzyl cyanoformate (4.0 μL, 27 μmol, 1.0 equiv.) was added and the solution was allowed to warm to room temperature on its own overnight. Sat. $NaHCO_3$ (6 mL) was then added to quench the reaction. The mixture was extracted with EtOAc (2 x 5 mL). The combined organic layer was washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by preparative TLC (hexanes/EtOAc 2:1) to give recovered **4.10** (0.0023 g, 30%) and **4.23** (0.0028 g, 24%, 34% brsm) as a pale yellow oil (R_f =0.12, hexanes/EtOAc 4:1). **^{1}H NMR** (300 MHz, $CDCl_3$, β-keto ester form): δ 7.28–7.43 (m, 5H), 5.79–5.83 (m, 1H), 5.11 (s, 2H), 3.82–3.93 (m, 4H), 3.58–3.68 (m, 1H), 3.53 (d, J = 10.8 Hz, 1H), 2.90–2.99 (m, 1H), 2.74–2.84 (m, 1H), 2.42 (t, J = 9.9 Hz, 1H), 2.14–2.21 (m, 1H), 1.66–1.91 (m, 6H), 1.59–1.65 (m, 1H), 1.37–1.49 (m, 2H), 1.02–1.16 (m, 1H).

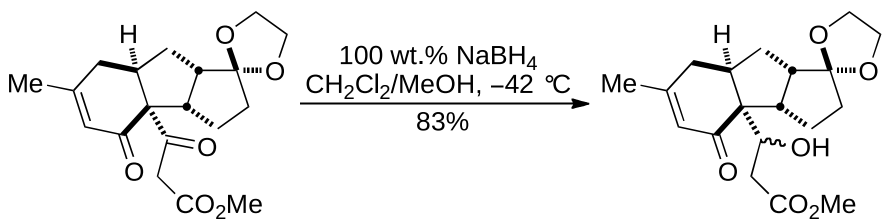
(^{1}H NMR filename: panpan105-109-1; notebook #: 00814)



4.10 4.24

Compound 4.24. To a stirred solution of **4.10** (0.0370 g, 127 μmol, 1.0 equiv.) in Et_2O (5 mL) at –78 ºC (dry ice/acetone bath) was added LiHMDS (1.0 M in THF, 140 μL, 140 μmol, 1.1 equiv.). The solution was stirred at –78 ºC for 1 hour before cooling bath was removed. The flask was allowed to warm to room temperature over 20 minutes and then cooled down to –78 ºC. *p*-Toluenesulfonyl cyanide (0.0231 g, 127 μmol, 1.0 equiv.) was added and the solution was allowed to warm to room temperature on its own with stirring overnight. Sat. $NaHCO_3$ (6 mL) was then added to quench the reaction. The mixture was extracted with EtOAc (3 x 5 mL). The combined organic layer was washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (hexanes/EtOAc, 2:1) to give recovered **4.10** (0.0044 g, 12%) and **4.24** (0.0092 g, 23%, 26% brsm) as a pale yellow oil (R_f =0.12, hexanes/EtOAc 2:1). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.87–5.92 (m, 1H), 3.83–3.96 (m, 4H), 3.52–3.62 (m, 2H), 2.92–3.01 (m, 1H), 2.76–2.86 (m, 1H), 2.44 (t, *J* = 9.6 Hz, 1H), 2.00–2.27 (m, 2H), 1.65–1.94 (m, 7H), 1.46 (td, *J* = 13.2, 10.5 Hz, 1H), 1.02–1.14 (m, 1H).

(^{1}H NMR filename: panpan105-108-2; notebook #: 00816, 00849)

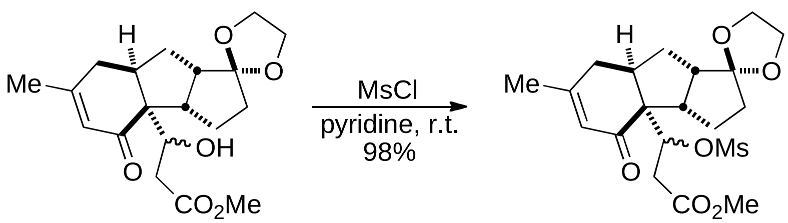


4.20 **4.25**

Compound 4.25. To a stirred solution of *β*-keto ester **4.20** (0.217 g, 0.622 mmol, 1.0 equiv.) in CH_2Cl_2 (4 mL) and MeOH (4 mL) at –42 ºC (dry ice/CH_3CN bath) was added $NaBH_4$ (0.217 g, 5.74 mmol, 9.2 equiv.). The solution was stirred at –42 ºC for 4.5 hours. TLC showed complete consumption of **4.20**. Acetone (4 mL) was added to quench the additional $NaBH_4$. The reaction was allowed to warm to room temperature over 3 hours and sat. NH_4Cl (20 mL) was added. After stirring at room temperature for 1 hour, the mixture was extracted with EtOAc (3 x 15 mL). The combined organic layer was washed with brine (10 mL) and dried over anhydrous Na_2SO_4. After filtration and concentration, the residue obtained was purified by flash column chromatography (hexanes/EtOAc, 2:1) to afford **4.43** (0.180 g, 83%) as a colorless oil (inseparable diastereomers, dr 1:0.20; R_f = 0.16, hexanes/EtOAc 2:1). **IR** (thin film): 3485, 2955, 2888, 1737, 1653, 1437, 1352, 1293, 1209, 1172, 1114, 1091, 1070, 1026 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.87 (s, 0.17H), 5.77 (s, 0.84H), 4.02–4.23 (m, 1.14H), 3.78–3.87 (m, 5.4H), 3.69 (s, 0.54H), 3.61

(s, 3H), 3.06–3.23 (m, 2.5H), 2.66–2.75 (m, 1H), 2.47–2.59 (m, 2.5H), 2.31–2.40 (m, 1.3H), 2.01–2.24 (m, 3H), 1.70–1.89 (m, 7.5H), 1.53–1.60 (m, 1.7H), 1.36–1.47 (m, 1.7H), 0.93–1.12 (m, 1.6H); **^{13}C NMR** (75 MHz, $CDCl_3$, major diastereomer): δ 202.10, 173.61, 159.76, 125.23, 118.25, 68.80, 65.00, 64.32, 60.81, 52.04, 46.50, 46.19, 38.24, 37.14, 35.80, 32.02, 30.84, 24.68, 24.61; **HRMS** (ESI) calcd. for $C_{19}H_{26}NaO_6$ $[M+Na]^+$ 373.1622 found 373.1618.

(^{1}H NMR filename: panpan206-1-1; ^{13}C NMR filename: pan206-1-t1; notebook #: 00852, 01556)

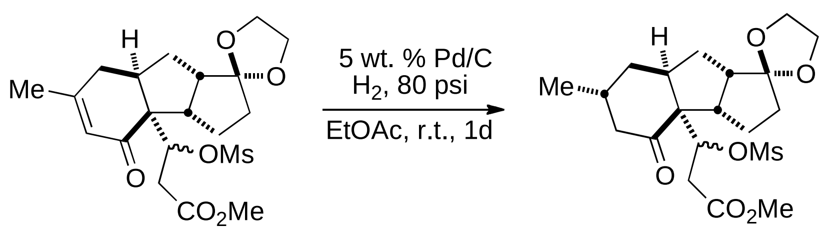


4.25 **4.26**

Compound 4.26. To a stirred solution of **4.25** (0.165 g, 0.47 mmol, 1.0 equiv.) in pyridine (4.7 mL) at 0 ºC (ice-water bath) was added MsCl (146 μL, 1.88 mmol, 4 equiv.). The solution was allowed to warm to room temperature on its own overnight with stirring. Sat. $NaHCO_3$ (10 mL) was added carefully and the mixture was extracted with EtOAc (3 x 6 mL). The combined organic layer was washed with brine (10 mL) and dried over anhydrous Na_2SO_4. After filtration and concentration, the residue obtained was purified by flash column chromatography (hexanes/EtOAc, 2:1) to afford **4.45** (0.197 g, 98%) as a colorless oil (inseparable diastereomers, dr 1:0.16; R_f = 0.19, hexanes/EtOAc 2:1). **IR** (thin film): 2957, 1738, 1656, 1438, 1342, 1289, 1205, 1172, 1094, 1021 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$, major diastereomer): δ 5.85 (s, 0.19H), 5.72 (s, 1H), 5.17–

5.24 (m, 1.2H), 3.73–3.83 (m, 5.8H), 3.61 (s, 0.56H), 3.58 (s, 2.8H), 3.12–3.25 (m, 1.3H), 3.00 (s, 0.43H), 2.98 (s, 3H), 2.79–2.89 (m, 2.3H), 2.59–2.70 (m, 2.2H), 2.10–2.24 (m, 2.6H), 1.80–1.88 (m, 2.4H), 1.63–1.76 (m, 4.1H), 1.50–1.57 (m, 1.6H), 1.24–1.42 (m, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$, major diastereomer): δ 198.96, 171.20, 160.80, 123.88, 117.71, 77.68, 65.03, 64.36, 60.82, 52.27, 46.37, 44.75, 39.30, 37.38, 36.30, 30.68, 29.64, 24.92, 24.65; **HRMS** (ESI) calcd. for $C_{20}H_{28}NaO_6S$ $[M+Na]^+$ 451.1403 found 451.1405.

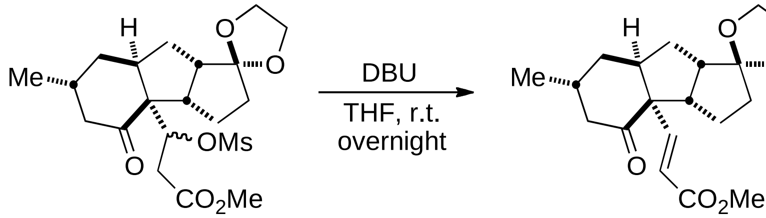
(^{1}H NMR filename: pan206-2-1; ^{13}C NMR filename: pan206-2-t1; notebook #: 00915, 01573)



4.26 **4.27**

Compound 4.27. To a 10-mL vial, **4.26** (0.0043 g, 10 μmol, 1.0 equiv.) was dissolved in EtOAc (ACS grade, 2 mL). 5 wt. % Pd/C (0.0043 g) was added and the vial was put in a hydrogenation vessel. H_2 (80 psi) was filled and then released. This process was repeated twice and the vessel was filled with H_2 (80 psi) and sealed. After stirring at room temperature for 1 day, H_2 was released and the mixture was filtered over Büchner funnel at reduced pressure and washed with EtOAc. The filtrate was concentrated and the crude **4.27** obtained was used in the next step without further purification. The ^{1}H NMR (300 MHz, $CDCl_3$) of crude **4.27** shows that the enone was reduced.

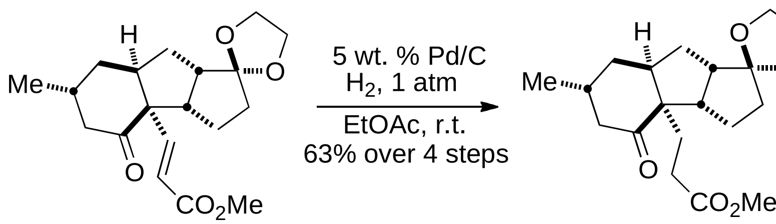
(^{1}H NMR filename: pan106-398-c1; notebook #: 00821)



4.27 **4.28**

Compound 4.28. To a stirred solution of crude **4.27** (10 μmol, 1.0 equiv., theoretical) obtained above in THF (ACS grade, 1.5 mL) was added DBU (0.1 M in THF, 120 μL, 12 μmol, 1.2 equiv.). The reaction was stirred at room temperature overnight and filtered over a short pad of silica, washed with EtOAc (5 mL). The filtrate was concentrated and the crude **4.28** obtained was used in the next step without further purification. The ^{1}H NMR (300 MHz, $CDCl_3$) of crude **4.28** shows that the presence of *trans*-α, β-unsaturated ester (J = 16.2 Hz).

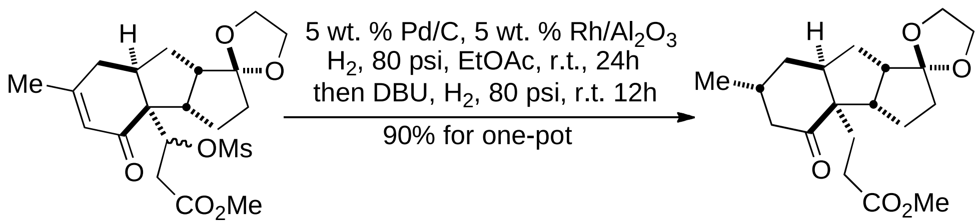
(^{1}H NMR filename: panpan106-399-c1; notebook #: 00823)



4.28 **4.29**

Compound 4.29 from 4.28. To a stirred solution of **4.28** (10 μmol, 1.0 equiv., theoretical) obtained above in EtOAc (ACS grade, 2 mL) was added 5 wt. % Pd/C (0.0043 g). A balloon of H_2 was attached and the reaction was stirred at room temperature for 12 hours. The mixture was filtered over a short pad of silica and washed

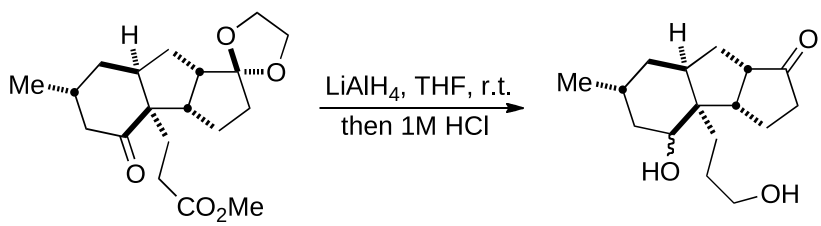
with EtOAc (5 mL). The filtrate was concentrated to give crude **4.29**, the ^{1}H NMR (300 MHz, $CDCl_3$) of which showed the *trans*-α, β-unsaturated ester moiety was reduced.
(^{1}H NMR filename: pan106-400-c1; notebook #: 00826)



4.26 **4.29**

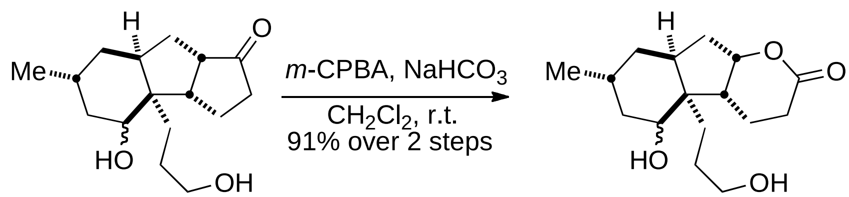
Compound 4.29 from 4.26. To a 100-mL hydrogenation vessel, **4.26** (0.201 g, 0.47 mmol, 1.0 equiv.) was dissolved in EtOAc (ACS grade, 7 mL). 5 wt. % Pd/C (0.2 g) and 5 wt. % Rh/Al_2O_3 (0.2 g) were added and the vessel was sealed. H_2 (80 psi) was filled and then released. This process was repeated twice and the vessel was refilled with H_2 (80 psi) and sealed. After stirring at room temperature for 1 day, H_2 was released and TLC showed complete consumption of **4.26**. DBU (84 μL, 0.56 mmol, 1.2 equiv.) was then added and the vessel was resealed, refilled with H_2 (80 psi). The reaction was stirred at room temperature for another 12 hours and then filtered over Büchner funnel at reduced pressure and washed with EtOAc. The filtrate was concentrated and the residue obtained was purified by flash column chromatography (hexanes/EtOAc, 4:1) to afford title compound (0.142 g, 90%) as a colorless oil (R_f = 0.29, hexanes/EtOAc 4:1). **IR** (thin film): 2955, 1737, 1702, 1438, 1317, 1173, 1127, 1094, 1019 cm^{-1}; ^{1}**H NMR** (300 MHz, $CDCl_3$): δ 3.80–3.88 (m, 4H), 3.59 (s, 3H), 3.14–3.23 (m, 1H), 2.35 (t, *J* = 9.9 Hz, 1H), 2.02–2.27 (m, 6H), 1.83–1.96 (m, 1H), 1.52–1.78 (m, 7H), 1.20–1.33 (m, 2H), 0.96 (d, *J* = 6.3 Hz, 3H); ^{13}**C NMR** (75 MHz, $CDCl_3$, major diastereomer): δ 214.80, 173.67, 118.18, 65.01, 64.43, 60.54, 51.86, 46.89, 46.22, 45.88, 43.14, 36.09, 31.75, 30.39, 30.33, 29.01, 28.03, 24.28, 22.69; **HRMS** (ESI) calcd. for $C_{19}H_{29}O_5$ $[M+H]^+$ 337.2015 found 337.2017.

(^{1}H NMR filename: pan206-3-2; ^{13}C NMR filename: pan206-3-t2; notebook #: 00922, 01577)



4.29 **4.30**

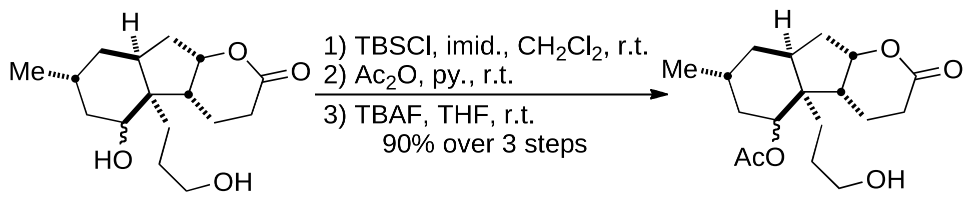
Compound 4.30. To a stirred solution of **4.29** (0.148 g, 0.44 mmol, 1.0 equiv.) in THF (4.5 mL) at room temperature was added $LiAlH_4$ (0.033 g, 0.88 mmol, 2.0 equiv.) in two portions. The reaction was stirred at room temperature for 12 hours then acetone (3 mL) was added to quench the additional $LiAlH_4$. After stirring for 1 hour, 1M HCl was added slowly to adjust the pH to 3 (pH paper) and the mixture was stirred overnight. Brine (10 mL) was added and the mixture was extracted with EtOAc (3 x 8 mL). The combined organic layer was washed successively with sat. $NaHCO_3$ (8 mL) and brine (8 mL), dried over anhydrous Na_2SO_4. After filtration and concentration, the crude **4.30** was obtained and used in the next step without further purification. An analytical sample was purified by flash column chromatography (hexanes/EtOAc, 1:2) and obtained as a colorless oil (R_f = 0.10, hexanes/EtOAc 1:2). **IR** (thin film): 3385, 2951, 2919, 1729, 1459, 1052, 1022 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 3.67–3.72 (m, 1H), 3.57–3.64 (m, 1H), 3.49 (dd, J = 12.0, 3.6 Hz, 1H), 3.19 (dt, J = 10.4, 8.4 Hz, 1H), 2.71–2.77 (m, 1H), 2.18–2.28 (m, 2H), 1.53–2.10 (m, 12H), 1.46–1.50 (m, 1H), 1.24–1.38 (m, 2H), 1.11 (ddd, J = 14.0, 12.4, 4.4 Hz, 1H), 0.93 (d, J = 6.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 222.81, 74.30, 64.31, 51.50, 48.59, 47.79, 44.30, 40.29, 39.90, 32.22, 32.03, 29.54, 26.91, 26.86, 23.30, 22.29; **HRMS** (ESI) calcd. for $C_{16}H_{25}O_2$ $[M+H–H_2O]^+$ 249.1855 found 249.1850. (^{1}H NMR and ^{13}C NMR filename: pan206-4-s1; notebook #: 00935, 01597)



4.30 **4.31**

Compound 4.31. (Note: open flask reaction) To a 25-mL round-bottomed flask equipped with reflux condenser, **4.43** (0.44 mmol, 1.0 equiv., theoretical) was dissolved in CH_2Cl_2 (ACS grade, 4.4 mL). $NaHCO_3$ (0.221 g, 2.63 mmol, 6.0 equiv.) was added and the reaction was cooled to 0 ºC (ice-water bath). *m*-CPBA (77%, 0.197 g, 0.88 mmol, 2.0 equiv.) was then added and the reaction was allowed to warm to room temperature on its own. After 24 hours, sat. $Na_2S_2O_3$ (4 mL) was added to quench the reaction. Sat. Na_2CO_3 (6 mL) was added and the mixture was extracted EtOAc (3 x 10 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration and concentration, the residue was purified by flash column chromatography (hexanes/EtOAc, 1:2 to 1:3) to afford **4.31** (0.113 g, 91% over 2 steps) as a colorless oil (R_f = 0.11, EtOAc). **IR** (thin film): 3386, 2950, 2923, 1722, 1460, 1325, 1244, 1195, 1176, 1114, 1053 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.91 (td, J = 7.6, 2.4 Hz, 1H), 3.58–3.70 (m, 2H), 3.48 (dd, J = 12.0, 4.0 Hz, 1H), 2.76 (dt, J = 12.4, 7.2 Hz, 1H), 2.58 (dt, J = 16.8, 2.8 Hz, 1H), 1.90–2.29 (m, 7H), 1.24–1.86 (m, 9H), 1.12 (ddd, J = 14.0, 12.4, 4.8 Hz, 1H), 0.94 (d, J = 6.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 173.69, 81.82, 74.97, 63.92, 50.23, 45.21, 41.21, 39.96, 36.57, 32.40, 30.86, 28.90, 26.85, 25.81, 22.23, 20.56; **HRMS** (ESI) calcd. for $C_{16}H_{27}O_4$ $[M+H]^+$ 283.1909 found 283.1905.

(^{1}H NMR and ^{13}C NMR filename: pan206-5-2; notebook #: 00937, 01614)



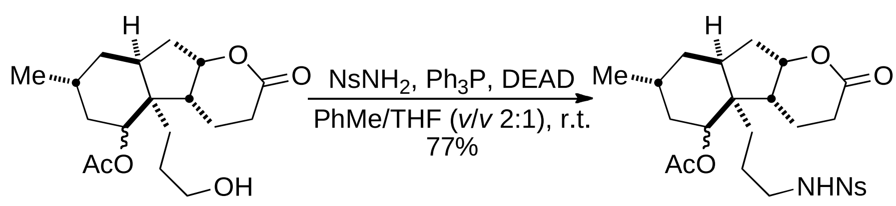
4.31 **4.33**

Compound 4.33. To a stirred solution of **4.31** (0.110 g, 0.39 mmol, 1.0 equiv.) in CH_2Cl_2 (5 mL) was added imidazole (0.040 g, 0.58 mmol, 1.5 equiv.) and TBSCl (0.070 g, 0.47 mmol, 1.2 equiv.). The reaction was stirred at room temperature for 6 hours and sat. $NaHCO_3$ (10 mL) was added. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 7 mL). The combined organic layer was washed with brine (6 mL) and dried over anhydrous Na_2SO_4. After filtration and concentration, the crude TBS ether was obtained and used in the next step directly.

To a stirred solution of TBS ether (0.39 mmol, 1.0 equiv., theoretical) in pyridine (5 mL) was added acetic anhydride (0.11 mL, 1.17 mmol, 3.0 equiv.). After 6 hours at room temperature, sat $NaHCO_3$ (10 mL) was added slowly to quench the reaction. The mixture was extracted with EtOAc (3 x 10 mL) and the combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration and concentration, the crude acetate was obtained and used in the next step directly.

To a stirred solution of acetate (0.39 mmol, 1.0 equiv., theoretical) in THF (ACS grade, 6 mL) was added TBAF (0.106 g, 0.41 mmol, 1.2 equiv.). After 16 hours at room temperature, the mixture was filtered over a short pad of silica and washed with EtOAc (10 mL). The filtrate was concentrated and the crude obtained was purified by flash column chromatography (hexanes/EtOAc, 1:2 to 1:3) to afford **4.33** (0.114 g, 90% over 3 steps) as a colorless oil (R_f = 0.11, hexanes/EtOAc 1:2). **IR** (thin film): 3437, 2953, 1730, 1553, 1458, 1374, 1246, 1197, 1175, 1026 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.95–4.99 (m, 1H), 4.77 (dd, *J* = 12.0, 4.0 Hz, 1H), 3.60–3.70 (m, 2H), 2.58 (dt, *J* = 16.4, 3.2 Hz, 1H), 2.18–2.36 (m, 4H), 2.07 (s, 3H), 1.53–2.00 (m, 11H), 1.38–1.46 (m, 1H), 1.14–1.22 (m, 1H), 0.94 (d, J = 6.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 173.14, 171.16, 81.48, 76.51, 63.66, 49.21, 44.67, 41.53, 36.38, 36.02, 31.96, 30.62, 29.26, 26.63, 26.61, 21.95, 21.51, 20.06; **HRMS** (ESI) calcd. for $C_{18}H_{28}NaO_5$ $[M+Na]^+$ 347.1834 found 347.1820.

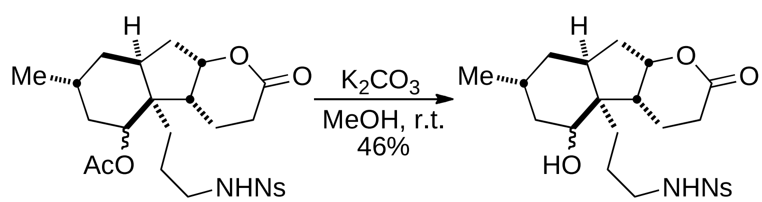
(^{1}H NMR filename: pan206-6-2; ^{13}C NMR filename: pan206-6-t1; notebook #: 00946, 00948, 00951, 01665, 01669, 01671)



4.33 **4.34**

Compound 4.34. To a stirred solution of **4.33** (0.058 g, 178 μmol, 1.0 equiv.), 2-nitrobenzenesulfonamide (0.054 g, 267 μmol, 1.5 equiv.), and Ph_3P (0.065 g, 249 μmol, 1.4 equiv.) in THF (1 mL) and toluene (2 mL) at room temperature was added dropwise DEAD (40 wt. % in toluene, 114 μL, 249 μmol, 1.4 equiv.). After stirring at room temperature for 1 day, all of the volatiles were removed by rotavap. To the residue, EtOH

(1 mL) was added and the precipitate was filtered over a cotton plug, washed with EtOH (3 mL). The filtrate was concentrated and the residue obtained was purified by flash column chromatography (hexanes/EtOAc, 1:2) to give **4.34** (0.070 g, 77%; R_f = 0.29, hexanes/EtOAc 1:2) as a colorless oil. **IR** (thin film): 2954, 1726, 1593, 1542, 1419, 1366, 1342, 1245, 1166, 1125, 1058, 1026 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$, major diastereomer): δ 9.57 (br s, 1H), 8.11–8.15 (m, 1H), 7.84–7.88 (m, 1H), 7.73–7.78 (m, 2H), 5.44 (t, J = 6.0 Hz, 1H), 4.90–4.94 (m, 1H), 4.72 (dd, J = 12.0, 4.0 Hz, 1H), 3.08 (q, J = 6.4 Hz, 2H), 2.54 (dt, J = 16.4, 3.2 Hz, 1H), 2.15–2.31 (m, 4H), 2.03 (s, 3H), 1.04–1.95 (m, 11H), 0.91 (d, J = 6.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$, major diastereomer): δ 172.90, 171.00, 148.26, 133.85, 132.97, 131.18, 125.54, 99.63, 81.27, 76.25, 49.20, 44.86, 44.48, 41.68, 36.34, 35.97, 31.87, 30.53, 27.73, 26.62, 26.59, 21.91, 21.48, 20.14; **HRMS** (ESI) calcd. for $C_{24}H_{33}N_2O_8S$ $[M+H]^+$ 509.1958 found 509.1967.
(^{1}H NMR and ^{13}C NMR filename: pan206-7-1, notebook #: 00902, 01683)

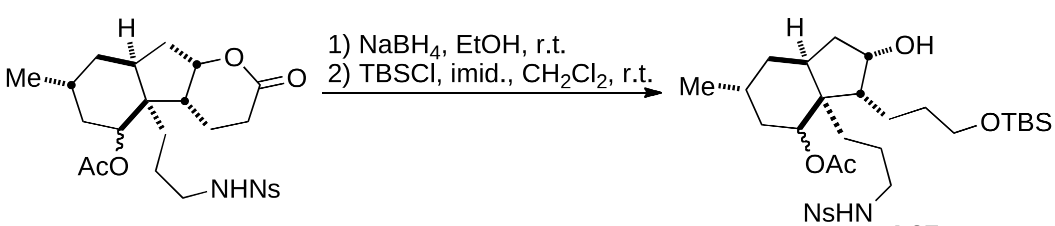


4.34 **4.32**

Compound 4.32. To a solution of **4.34** (0.0211 g, 41.5 μmol, 1.0 equiv.) in MeOH (ACS grade, 2 mL) was added K_2CO_3 (0.023 g, 166.0 μmol, 4.0 equiv.). The mixture was stirred at room temperature for 1 day and then concentrated to remove all of the solvent. Brine (5 mL) and 1M HCl (2 mL) were added and the mixture was extracted with EtOAc (3 x 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by preparative TLC (hexanes/EtOAc 1:2) to afford recovered **4.34** (0.010 g, 47%) and **4.32** (0.009 g, 46%) as a colorless oil (R_f = 0.12, hexanes/EtOAc 1:2). **IR** (thin film): 3356, 2925, 1724, 1542, 1414, 1364, 1340, 1244, 1166, 1124 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.10–8.16 (m, 1H), 7.84–7.90 (m, 1H), 7.72–7.79 (m, 2H), 5.47 (t, *J* = 6.0 Hz, 1H), 4.85–4.91 (m, 1H), 3.50 (dd, *J* = 12.0, 3.9 Hz, 1H), 3.02–3.13 (m, 2H), 2.71 (dt, *J* = 12.3, 7.2 Hz, 1H), 2.57 (app dt, *J* = 16.8, 3.0 Hz, 1H), 2.07–2.28 (m, 3H), 1.88–1.98 (m, 2H), 1.44–1.83 (m, 9H), 1.30–1.37 (m, 1H), 0.98–1.08 (m, 1H), 0.92 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$, major diastereomer): δ 173.22, 134.06, 133.75, 132.98, 131.29, 125.61, 81.53, 74.84, 49.99, 45.14, 45.03, 40.98, 40.13, 36.54, 32.37, 30.78, 29.92, 26.81, 26.72, 26.54, 22.15, 20.61; **HRMS** (ESI) calcd. for $C_{22}H_{31}N_2O_7S$ $[M+H]^+$ 467.1852 found 467.1845.

(^{1}H NMR filename: panpan106-412-4; ^{13}C NMR filename: pan207-1-t3; notebook #: 00910, 01693)

Compound 4.35.

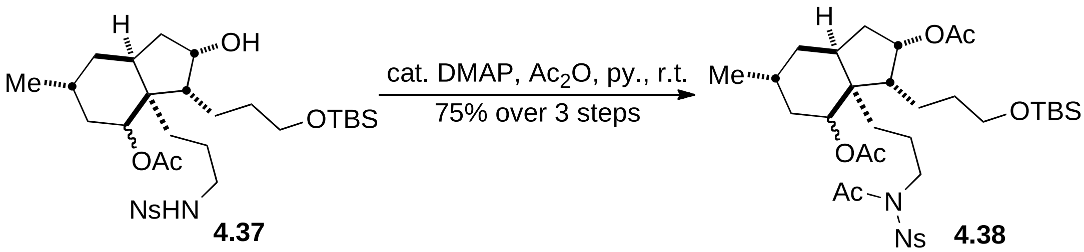


4.34 4.37

Compound 4.37. To a stirred solution of **4.34** (0.060 g, 118 μmol, 1.0 equiv.) in absolute EtOH (4 mL) at room temperature was added $NaBH_4$ (0.026 g, 687 μmol, 5.8 equiv.). The reaction was stirred at room temperature for 12 hours, then sat. NH_4Cl (6 mL) was added. The mixture was extracted with EtOAc (3 x 6 mL) and the combined organic layer was washed with brine (6 mL), dried over anhydrous Na_2SO_4. After filtration and concentration, the crude diol was obtained (R_f = 0.12, hexanes/EtOAc 1:2) and used in the next step directly.

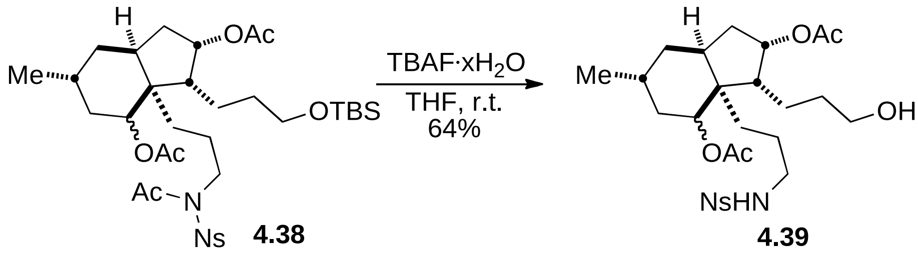
To a stirred solution of diol (118 μmol, 1.0 equiv., theoretical) obtained above in CH_2Cl_2 (5 mL) was added imidazole (0.0482 g, 708 μmol, 6.0 equiv.) and TBSCl (0.0709 g, 472 μmol, 4.0 equiv.). The reaction was stirred at room temperature for 5 hours and then sat. $NaHCO_3$ (10 mL) was added. The mixture was extracted with EtOAc (3 x 7 mL). The combined organic layer was washed with brine (6 mL) and dried over anhydrous Na_2SO_4. After filtration and concentration, the crude obtained was used in the next step directly without further purification. An analyticcal sample was purified by preparative TLC (hexanes/EtOAc, 3:1) to give **4.37** as a colorless oil (R_f = 0.30, hexanes/EtOAc 2:1). **IR** (thin film): 3356, 2929, 1727, 1543, 1461, 1364, 1249, 1167, 1093, 1024 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.13–8.18 (m, 1H), 7.85–7.90 (m, 1H), 7.72–7.78 (m, 2H), 5.29 (t, *J* = 6.0 Hz, 1H), 4.68 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.24 (t, *J* = 4.4 Hz, 1H), 3.58–3.68 (m, 2H), 3.06–3.17 (m, 2H), 2.33–2.39 (m, 1H), 2.03 (s, 3H), 1.36–1.79 (m, 15H), 1.26 (br s, 1H), 0.80–1.13 (m, 14H), 0.06 (s, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.14, 148.39, 134.20, 133.65, 132.95, 131.35, 125.60, 81.96, 72.51, 63.40, 55.64, 46.54, 45.08, 39.40, 38.14, 36.65, 33.42, 32.02, 27.12, 26.16, 25.91, 25.28, 22.14, 21.87, 21.50, 18.58, 5.09, 5.13; **HRMS** (ESI) calcd. for $C_{30}H_{50}N_2NaO_8SSi$ $[M+Na]^+$ 649.2955 found 649.2961.

(^{1}H NMR filename: pan208-1-1; ^{13}C NMR filename: pan208-1-t2; notebook #: 00933, 01070, 01702, 01706)



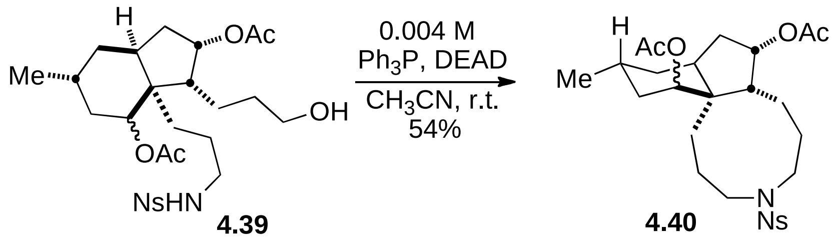
Compound 4.38. To a stirred solution of **4.37** (118 μmol, 1.0 equiv., theoretical) in pyridine (3 mL) was added acetic anhydride (67 μL, 708μmol, 6.0 equiv.). After stirring at room temperature overnitht, sat $NaHCO_3$ (10 mL) was added slowly to quench the reaction. The mixture was extracted with EtOAc (3 x 10 mL) and the combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration and concentration, the crude obtained was purified by flash column chromatography (hexanes/EtOAc, 3:1) to give **4.38** (0.0630 g, 75% over 3 steps) as a colorless oil (R_f = 0.38, hexanes/EtOAc 2:1). **IR** (thin film): 2954, 1732, 1544, 1459, 1369, 1240, 1171, 1095, 1022 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 8.34–8.39 (m, 1H), 7.75–7.82 (m, 3H), 5.24–5.26 (m, 1H), 4.73 (dd, *J* = 11.6, 4.0 Hz, 1H), 3.79 (t, *J* = 8.0 Hz, 2H), 3.52–3.61 (m, 2H), 2.36–2.42 (m, 1H), 2.30 (s, 3H), 2.06 (s, 6H), 1.39–1.94 (m, 14H), 1.14–1.23 (m, 2H), 0.94 (d, *J* = 6.4 Hz, 3H), 0.89 (s, 9H), 0.04 (d, *J* = 1.2 Hz, 6H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 171.04, 170.72, 170.18, 148.17, 134.76, 134.19, 133.37, 132.17, 124.79, 82.09, 75.97, 63.50, 54.32, 48.91, 46.62, 39.86, 36.64, 36.46, 33.44, 32.58, 27.21, 26.88, 26.20, 24.63, 24.32, 22.92, 22.12, 21.49, 21.45, 18.56, –5.07. **HRMS** (ESI) calcd. for $C_{34}H_{54}N_2NaO_{10}SSi$ $[M+Na]^+$ 733.3161 found 733.3155.

(^{1}H NMR filename: pan209-1-1; ^{13}C NMR filename: pan209-1-t1; notebook #: 01007, 01091)



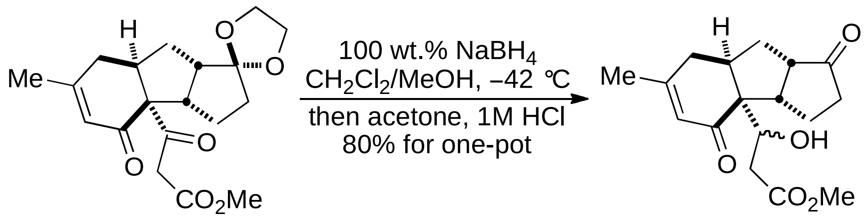
Compound 4.39. To a stirred solution of **4.38** (0.0375 g, 48 μmol, 1.0 equiv.) in THF (ACS grade, 3 mL) at room temperature was added TBAF·xH_2O (0.0150 g, 57 μmol, 1.2 equiv.). After 4 days at room temperature, the mixture was filtered over a short pad of silica, washed with EtOAc (15 mL). The filtrate was concentrated and the crude obtained was purified by flash column chromatography (hexanes/EtOAc, 1:2) to give **4.39** (0.0171 g, 64%) as a colorless oil (R_f = 0.14, hexanes/EtOAc 1:1). **IR** (thin film): 3320, 2953, 1728, 1543, 1441, 1372, 1246, 1166, 1126, 1023 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.13–8.19 (m, 1H), 7.84–7.90 (m, 1H), 7.73–7.79 (m, 2H), 5.55 (t, J = 6.0 Hz, 1H), 5.27 (t, J = 4.4 Hz, 1H), 4.74 (dd, J = 12.0, 4.4 Hz, 1H), 3.56–3.67 (m, 2H), 3.06–3.17 (m, 2H), 2.26–2.36 (m, 1H), 2.04 (s, 6H), 1.92–1.97 (m, 1H), 1.85 (td, J = 13.6, 4.4 Hz, 1H), 1.39–1.75 (m, 13H), 1.05–1.18 (m, 2H), 0.91 (d, J = 6.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.14, 170.72, 148.32, 133.95, 133.74, 132.96, 131.34, 125.53, 81.33, 75.95, 62.65, 53.13, 46.81, 44.74, 40.36, 36.69, 36.31, 33.30, 32.08, 27.07, 26.21, 25.40, 22.45, 22.11, 21.54, 21.50; **HRMS** (ESI) calcd. for $C_{26}H_{38}N_2NaO_9S$ $[M+Na]^+$ 577.2190 found 577.2211.

(^{1}H NMR filename: pan210-1-1; ^{13}C NMR filename: pan210-1-t2; notebook #: 00972, 01104, 01720)



Compound 4.40. To a stirred solution of **4.39** (0.0171 g, 31 μmol, 1.0 equiv.), and Ph_3P (0.0404 g, 154 μmol, 5.0 equiv.) in CH_3CN (7.5 mL) at room temperature was added dropwise DEAD (40 wt. % in toluene, 70 μL, 154 μmol, 5.0 equiv.). After stirring at room temperature for 1 day, all of the volatiles were removed by rotavap. The residue was purified by flash column chromatography (hexanes/EtOAc, 1:1) to give **4.40** (0.0090 g, 54%; R_f = 0.24, hexanes/EtOAc 1:1) as a colorless oil. **IR** (thin film): 2925, 2854, 1730, 1546, 1458, 1374, 1248, 1166, 1028 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.90–7.94 (m, 1H), 7.65–7.72 (m, 2H), 7.56–7.59 (m, 1H), 5.30–5.39 (m, 1H), 4.86–4.93 (m, 1H), 3.42–3.62 (m, 2H), 2.85–3.04 (m, 2H), 1.07–2.24 (m, 23H), 0.90 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.00, 170.59, 133.64, 131.85, 131.48, 130.85, 124.10, 75.91, 75.80, 50.73, 50.42, 46.04, 45.96, 42.49, 36.22, 33.65, 32.22, 29.94, 28.88, 26.86, 24.76, 24.10, 22.06, 21.66, 21.42, 16.99; **HRMS** (ESI) calcd. for $C_{26}H_{36}N_2NaO_8S$ $[M+Na]^+$ 559.2085 found 559.2093.

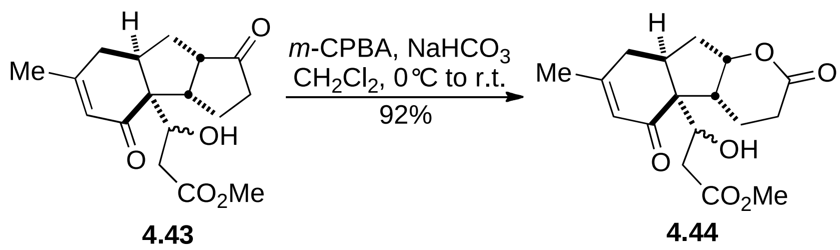
(^{1}H NMR filename: panpan106-428-1; ^{13}C NMR filename: panpan106-428-t1; notebook #: 01028, 01116)



4.20 **4.43**

Compound 4.43. To a stirred solution of *β*-keto ester **4.20** (0.214 g, 0.613 mmol, 1.0 equiv.) in CH_2Cl_2 (4 mL) and MeOH (4 mL) at –42 ºC (dry ice/CH_3CN bath) was added $NaBH_4$ (0.214 g, 5.66 mmol, 9.2 equiv.). The solution was stirred at –42 ºC for 4.5 hours. TLC showed complete consumption of **4.20**. Acetone (4 mL) was added to quench the additional $NaBH_4$. The reaction was allowed to warm to room temperature over 3 hours and 1 M HCl (6 mL) was added to adjust the pH to 1.0 (pH paper). The mixture was stirred at room temperature overnight and then extracted with EtOAc (3 x 15 mL). The combined organic layer was washed with sat. $NaHCO_3$ (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4. After filtration and concentration, the residue obtained was purified by flash column chromatography (hexanes/EtOAc, 2:1) to afford **4.43** (0.150 g, 80%) as a colorless oil (inseparable diastereomers, dr 1:0.14; R_f = 0.28, hexanes/EtOAc 1:1). **IR** (thin film): 3470, 2953, 1735, 1653, 1437, 1173, 1116 cm^{-1}; ^{1}**H NMR** (300 MHz, $CDCl_3$, major diastereomer): δ 5.79 (s, 1H), 4.12 (br d, *J* = 10.8 Hz, 1H), 3.62 (s, 3H), 3.37–3.46 (m, 2H), 2.71–2.79 (m, 1H), 2.51–2.62 (m, 2H), 2.33–2.46 (m, 2H), 2.15–2.24 (m, 3H), 2.03–2.14 (m, 1H), 1.87–1.99 (m, 5H), 1.63–1.77 (m, 1H); ^{13}**C NMR** (75 MHz, $CDCl_3$, major diastereomer): δ 221.52, 201.11, 173.43, 159.94, 125.25, 68.28, 61.38, 52.13, 47.88, 45.10, 39.76, 38.19, 36.41, 32.89, 31.53, 24.68, 23.38; **HRMS** (ESI) calcd. for $C_{17}H_{23}O_5$ $[M+H]^+$ 307.1540 found 307.1542.

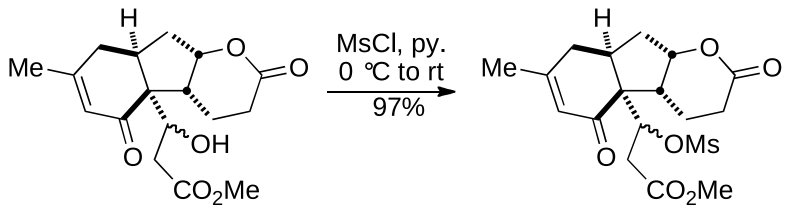
(^{1}H NMR filename: pan107-004; ^{13}C NMR filename: pan107-t004; notebook #: 00909, 01413)



Compound 4.44. (Note: open flask reaction) To a 100-mL round-bottomed flask equipped with reflux condenser, *β*-hydroxy ester **4.43** (0.595 g, 1.94 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (ACS grade, 20 mL). $NaHCO_3$ (0.978 g, 11.64 mmol, 6 equiv.) was added and the reaction was cooled to 0 ºC (ice-water bath). *m*-CPBA (77%, 0.739 g, 3.30 mmol, 1.7 equiv.) was then added in portions over 5 minutes and the reaction was allowed to warm to room temperature on its own. After 24 hours, sat. $Na_2S_2O_3$ (6 mL) was added to quench the reaction. Sat. Na_2CO_3 (14 mL) was added and the mixture was extracted EtOAc (3 x 20 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (hexanes/EtOAc, 1:1 to 1:2) to afford **4.44** (0.575 g, 92%) as a colorless oil (inseparable diastereomers, dr 1:0.14; R_f = 0.12, hexanes/EtOAc 1:1). **IR** (thin film): 3383, 1736, 1648, 1437, 1071 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$, major diastereomer): δ 5.82 (s, 1H), 4.78–4.51 (m, 1H), 4.11 (br d, *J* = 10.8 Hz, 1H), 3.58 (s, 3H), 2.99–3.08 (m, 1H), 2.92 (td, *J* = 9.6, 5.4 Hz, 1H), 2.01–2.60 (m, 9H), 1.89 (s, 3H), 1.78–1.87 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$, major diastereomer): δ 201.05, 172.78, 172.40, 160.87, 125.71, 79.66, 68.50, 59.83, 52.14, 42.50, 38.00, 34.89, 31.84,

30.42, 24.80, 19.98; **HRMS** (ESI) calcd. for $C_{17}H_{23}O_6$ $[M+H]^+$ 323.1489 found 323.1488.

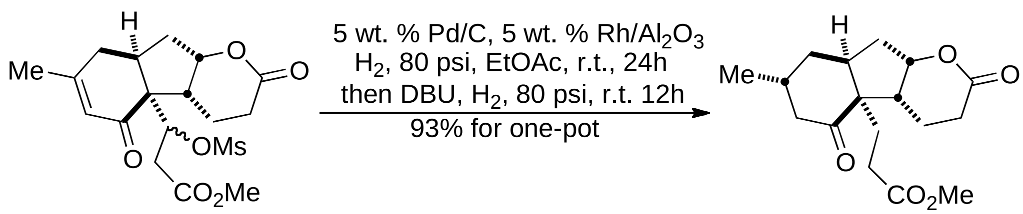
(^{1}H NMR filename: pan108-001; ^{13}C NMR filename: pan108-t001; notebook #: 01419)



4.44 **4.45**

Compound 4.45. To a stirred solution of **4.44** (0.410 g, 1.27 mmol, 1.0 equiv.) in pyridine (13 mL) at 0 ºC (ice-water bath) was added MsCl (0.40 mL, 5.09 mmol, 4 equiv.). The solution was allowed to warm to room temperature on its own overnight with stirring. Sat. $NaHCO_3$ (15 mL) was added carefully and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic layer was washed with brine (15 mL) and dried over anhydrous Na_2SO_4. After filtration and concentration, the residue obtained was purified by flash column chromatography (hexanes/EtOAc, 2:1) to afford **4.45** (0.494 g, 97%) as a colorless oil (inseparable diastereomers, dr 1:0.18; R_f = 0.19, hexanes/EtOAc 2:1). **IR** (thin film): 2954, 1738, 1654, 1437, 1339, 1249, 1172, 1131, 1021 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$, major diastereomer): δ 5.81 (s, 1H), 5.27 (dd, *J* = 8.4, 3.0 Hz, 1H), 4.54 (td, *J* = 8.4, 3.3 Hz, 1H), 3.61 (s, 3H), 3.19 (dt, *J* = 13.2, 6.6 Hz, 1H), 3.01 (s, 3H), 2.94–2.96 (m, 1H), 2.80–2.88 (m, 1H), 2.63–2.72 (m, 1H), 2.55 (dt, *J* = 16.8, 3 Hz, 1H), 1.97–2.29 (m, 4H), 1.93 (s, 3H), 1.67–1.88 (m, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$, major diastereomer): δ 197.83, 171.82, 170.76, 161.82, 124.24, 79.03, 76.62, 60.46, 52.49, 41.16, 39.26, 36.96, 36.82, 35.34, 30.46, 30.37, 24.78, 20.47; **HRMS** (ESI) calcd. for $C_{18}H_{24}NaO_8S$ $[M+Na]^+$ 423.1084 found 423.1076.

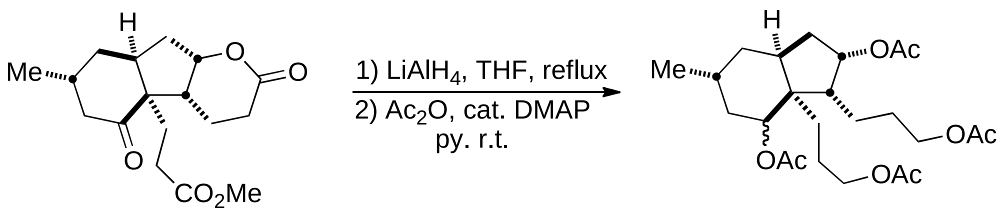
(^{1}H NMR filename: pan109-002; ^{13}C NMR filename: pan109-t002; notebook #: 01250, 01428)



4.45 **4.46**

Compound 4.46. To a 100-mL hydrogenation vessel, **4.45** (0.494 g, 1.23 mmol, 1.0 equiv.) was dissolved in EtOAc (ACS grade, 13 mL). 5 wt. % Pd/C (0.494 g) and 5 wt. % Rh/Al_2O_3 (0.494 g) were added and the vessel was sealed. H_2 (80 psi) was filled and then released. This process was repeated twice and the vessel was refilled with H_2 (80 psi) and sealed. After stirring at room temperature for 1 day, H_2 was released and TLC showed complete consumption of **4.45**. DBU (0.28 mL, 1.85 mmol, 1.5 equiv.) was then added and the vessel was resealed, refilled with H_2 (80 psi). The reaction was stirred at room temperature for another 12 hours and then filtered over Büchner funnel at reduced pressure and washed with EtOAc. The filtrate was concentrated and the residue obtained was purified by flash column chromatography (hexanes/EtOAc, 2:1) to afford title compound (0.353 g, 93%) as a white solid (R_f = 0.16, hexanes/EtOAc 2:1). m.p. = 78–80 °C; **IR** (thin film): 2955, 1737, 1699, 1437, 1248, 1191, 1132, 1033 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 4.65 (td, *J* = 7.8, 3.0 Hz, 1H), 3.63 (s, 3H), 3.20 (dt, *J* = 13.2, 6.9 Hz, 1H), 2.60 (dt, *J* = 16.5, 3.0 Hz, 1H), 2.43–2.53 (m, 1H), 2.24–2.35 (m, 4H), 1.99–2.19 (m, 2H), 1.67–1.96 (m, 7H), 1.49 (qd, *J* = 13.3, 3.3 Hz, 1H), 1.02 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 213.63, 173.06, 172.61, 80.01, 60.20, 52.14, 46.96, 43.59, 38.86, 36.49, 31.89, 30.42, 30.09, 29.94, 27.54, 22.45, 19.62; **HRMS** (ESI) calcd. for $C_{17}H_{25}O_5$ $[M+H]^+$ 309.1697 found 309.1698.

(^{1}H NMR filename: pan106-366-6; ^{13}C NMR filename: pan106-366-t6; notebook #:01257)

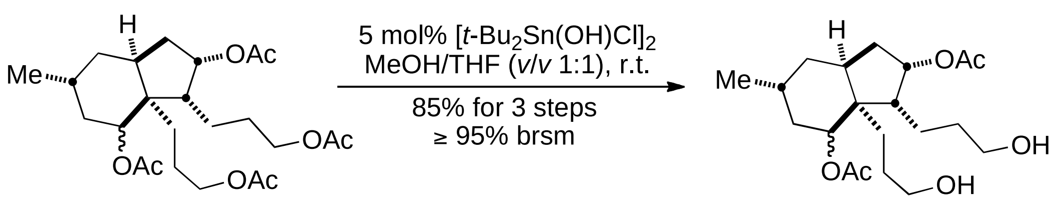


4.46 **4.47**

Compound 4.47. To a 50-mL oven dried round-bottomed flask equipped with reflux condenser, **4.46** (0.204 g, 0.66 mmol, 1.0 equiv.) was dissolved in THF (14 mL) and stirred at room temperature. $LiAlH_4$ (0.075 g, 1.98 mmol, 3 equiv.) was added in one portion and the mixture was refluxed overnight. After cooling to room temperature the reaction was quenched by successive addition of H_2O (75 μL), 15% NaOH (75 μL), and H_2O (225 μL). The resulting slurry was stirred for another 4 hours and then filtered over Büchner funnel at reduced pressure, washed with EtOAc. After concentration, the crude tetraol obtained was used in the next step without further purification.

To a stirred solution of the tetraol obtained from above (0.66 mmol, theoretical, 1.0 equiv.) in pyridine (7 mL) were added one crystal of DMAP and Ac_2O (0.50 mL, 5.30 mmol, 8 equiv.). The reaction was stirred at room temperature for 1 day and then quenched with sat. $NaHCO_3$ (10 mL). The mixture was extracted with EtOAc (3 x 10 mL), washed with brine (10 mL), and dried over anhydrous Na_2SO_4. After filtration and concentration, the crude obtained was used in the next step directly without further purification. An analytic sample was purified by flash column chromatography (hexanes/EtOAc, 2:1) to afford **4.47** as a colorless oil (inseparable diastereomers, dr 9:1; R_f = 0.14, hexanes/EtOAc 4:1). **IR** (thin film): 2956, 1737, 1458, 1370, 1239, 1024 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$, major diastereomer): δ 5.17 (app t, *J* = 4.2 Hz, 1H), 4.63 (dd, *J* = 11.4, 3.9 Hz, 1H), 3.86–4.05 (m, 4H), 2.24–2.32 (m, 1H), 1.982 (s, 3H), 1.961 (s, 3H), 1.957 (s, 3H), 1.948 (s, 3H), 1.79–1.87 (m, 1H), 1.22–1.76 (m, 13H), 1.04–1.16 (m, 2H), 0.84 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$, major diastereomer): δ 171.22, 171.13, 170.92, 170.42, 81.51, 75.69, 65.26, 64.60, 53.32, 46.52, 39.86, 36.44, 36.30, 33.17, 28.12, 27.02, 24.75, 24.22, 22.74, 22.05, 21.40, 21.36, 21.16, 21.09; **HRMS** (ESI) calcd. for $C_{24}H_{42}NO_8$ $[M+NH_4]^+$ 472.2905 found 472.2900.

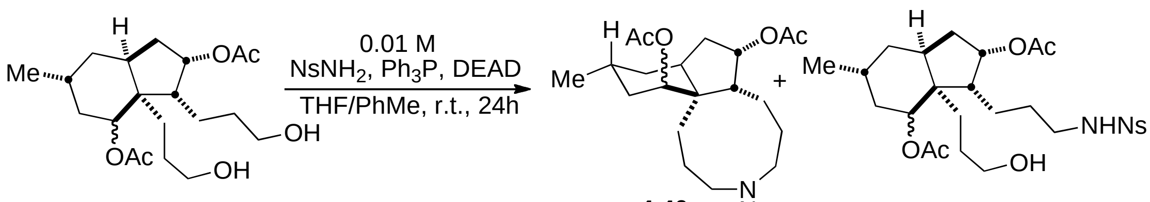
(^{1}H NMR filename: pan112-001; ^{13}C NMR filename: pan112-t001; notebook #: 01336, 01340, 01417)



4.47 **4.48**

Compound 4.48. To a stirred solution of **4.47** (0.66 mmol, theoretical, 1.0 equiv.) obtained above in MeOH (ACS grade, 3.3 mL) and THF (ACS grade, 3.3 mL) was added Otera's catalyst ($[t\text{-}Bu_2Sn(OH)Cl]_2$) (0.019 g, 33 μmol, 5 mol%). The reaction was stirred at room temperature for 30 hours and NEt_3 (50 μL) was added to quench the reaction. After concentration, the residue was purified by flash column chromatography (hexanes/EtOAc/THF, 1:2:0.5) to afford recovered materials (0.052 g, contains mono- or tri- acetate, which could be recycled by reacetylation to **4.47**) and **4.48** (0.208 g, 85% for 3 steps, ≥ 95% brsm) as a colorless oil (inseparable diasteromers, dr 9:1; R_f = 0.07, hexanes/EtOAc 1:2). **IR** (thin film): 3386, 2951, 2871, 1734, 1457, 1375, 1242, 1052, 1023 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$, major diastereomer): δ 5.24 (t, *J* = 4.5 Hz, 1H), 4.70 (app dd, *J* = 12.0, 4.2 Hz, 1H), 3.47–3.74 (m, 4H), 2.71 (br s, 2H), 2.31–2.40 (m, 1H), 2.007 (s, 3H), 2.004 (s, 3H), 1.76–1.94 (m, 2H), 1.32–1.74 (m, 12H), 1.08–1.25 (m, 2H), 0.87 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$, major diastereomer): δ 171.37, 170.93, 81.66, 76.17, 63.56, 62.60, 53.26, 46.66, 40.13, 36.63, 36.25, 33.17, 32.18, 28.75, 27.09, 24.08, 22.50, 22.14, 21.55, 21.52; **HRMS** (ESI) calcd. for $C_{20}H_{38}NO_6$ $[M+NH_4]^+$ 388.2694 found 388.2696.

(^{1}H NMR filename: pan113-001; ^{13}C NMR filename: pan113-t001; notebook #: 01336, 01342, 01425)



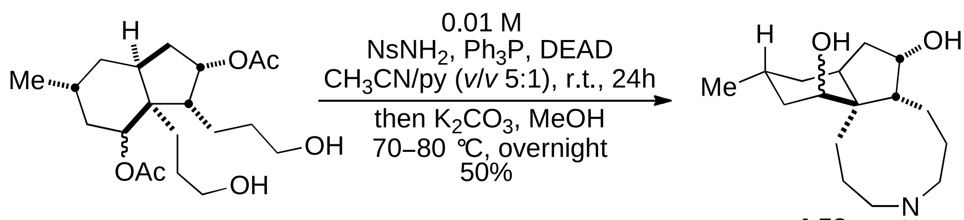
4.48 **4.40** **4.49**

Compound 4.49. To a stirred solution of **4.48** (0.0039 g, 10.5 μmol, 1.0 equiv.), 2-nitrobenzenesulfonamide (0.0085 g, 42 μmol, 4.0 equiv.), and Ph_3P (0.0165 g, 63 μmol, 6.0 equiv.) in THF (0.5 mL) and toluene (1 mL) at room temperature was added DEAD (40 wt. % in toluene, 29 μL, 63 μmol, 6.0 equiv.). The reaction was stirred at room temperature for 1 day. All of the solvents were removed by rotavap and to the residue was added Et_2O (1 mL). The white precipitate was removed by filtering through a filter funnel with a cotton plug and washed with Et_2O (3 mL). The filtrate was concentrated and the crude obtained was purified by preparative TLC (hexanes/EtOAc 1:1) to give

4.40 (0.0013 g, 23%; R_f = 0.34, hexanes/EtOAc 1:1) and **4.49** (0.0035 g, 60%, d.r. 6:1) as a pale yellow oil (R_f = 0.23, hexanes/EtOAc 1:1).

Data for **4.49** (major diastereomer): **IR** (thin film): 3334, 2953, 1727, 1542, 1415, 1368, 1245, 1166, 1126, 1077, 1023 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$, *N*-nosyl rotamers): δ 8.11–8.21 (m, 1.8H), 7.83–7.90 (m, 1.7H), 7.70–7.80 (m, 3.6H), 5.48 (t, *J* = 6.0 Hz, 1H), 5.39 (t, *J* = 6.0 Hz, 1H), 5.231 (t, *J* = 4.4 Hz, 1H), 4.71 (dd, *J* = 12.0, 4.0 Hz, 1H), 3.00–3.18 (m, 4H), 2.28–2.37 (m, 1H), 2.07 (s, 3H), 2.06 (s, 3H), 1.90–1.95 (m, 1H), 1.83 (td, *J* = 13.6, 4.4 Hz, 1H), 1.07–1.73 (m, 14H), 0.92 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$, *N*-nosyl rotamers): δ 171.26, 170.81, 148.29, 133.87, 133.74, 133.05, 133.01, 131.38, 131.37, 125.54, 125.50, 98.82, 81.45, 75.58, 53.33, 46.80, 44.73, 43.92, 40.26, 36.73, 36.38, 33.28, 29.33, 27.07, 26.37, 25.27, 23.32, 22.10, 21.57, 21.52.

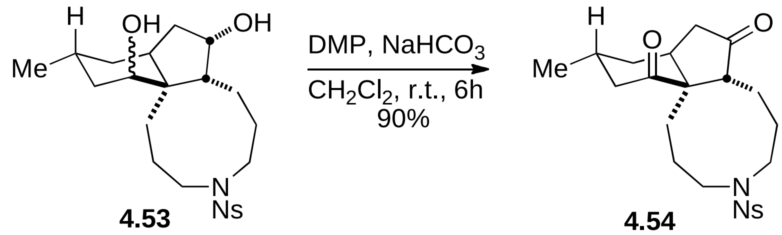
(^{1}H NMR and ^{13}C NMR filename: pan106-429-4-1notebook #: 01057, 01062)



4.48 **4.53**

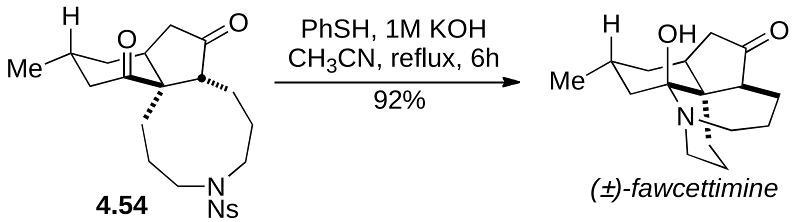
Compound 4.53. To a stirred solution of **4.48** (0.0876 g, 236 μmol, 1.0 equiv.), 2-nitrobenzenesulfonamide (0.191 g, 0.94 mmol, 4.0 equiv.), and Ph_3P (0.372 g, 1.42 mmol, 6.0 equiv.) in CH_3CN (20 mL) and pyridine (4 mL) at 0 °C was added DEAD (40 wt. % in toluene, 0.65 mL, 1.42 mmol, 6.0 equiv.) over 10 minutes. The reaction was allowed to warm to room temperature on its own with stirring for 24 hours. MeOH (24 mL) and K_2CO_3 (0.326 g, 10.0 equiv.) were then added. A reflux condenser was added and the suspension was stirred with gentle reflux overnight. After cooling to room temperature, the stirring bar was removed and the solution was concentrated. The residue was partitioned between EtOAc (15 mL) and brine (15 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. To the residue, EtOH (3 mL) was added and the additional $NsNH_2$ was precipitated as white solid. The solid was removed by filtering over a filter funnel with a cotton plug and washed with EtOH (3 x 3 mL). The filtrate was concentrated and the residue obtained was purified by flash column chromatography (hexanes/EtOAc, 1:1 to 1:2) to afford **4.53** (0.054 g, 52%; R_f = 0.07, hexanes/EtOAc 1:2) as a white solid contaminated with trace amount of Ph_3PO. An analytic sample was further purified by preparative TLC (hexanes/EtOAc 1:2). **IR** (thin film): 3385, 2925, 1545, 1373, 1343, 1164 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.91–7.96 (m, 1H), 7.64–7.72 (m, 2H), 7.56–7.62 (m, 1H), 4.62 (dt, *J* = 8.4, 6.0 Hz, 1H), 3.67–3.78 (m, 1H), 3.47–3.55 (m, 2H), 3.13 (ddd, *J* = 14.8, 9.6, 4.8 Hz, 1H), 2.95 (dt, *J* = 13.2, 4.0 Hz, 1H), 1.51–2.31 (m, 16H), 1.22–1.31 (m, 2H), 1.06–1.14 (m, 1H), 0.92 (d, *J* = 6.4, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 133.51, 132.08, 131.45, 130.90, 124.08, 74.11, 73.02, 51.83, 50.79, 48.04, 46.39, 42.46, 40.38, 36.91, 32.80, 29.50, 27.41, 24.55, 24.47, 22.28, 16.47; **HRMS** (ESI) calcd. for $C_{22}H_{33}N_2O_5S$ $[M+H]^+$ 453.2059 found 453.2061.

(^{1}H NMR filename: pan115-004-1; ^{13}C NMR filename: pan115-t005; notebook #: 01429, 01433)



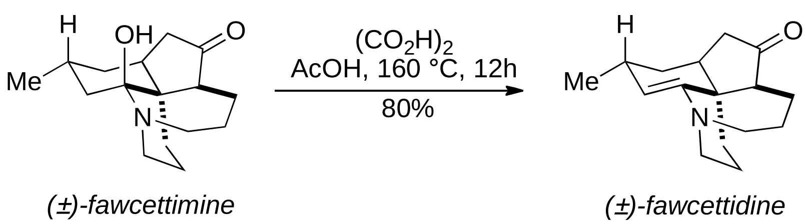
Compound 4.54. To a stirred solution of **4.53** (0.022 g, 49 μmol, 1.0 equiv.) in CH_2Cl_2 (ACS grade, 2 mL) were added $NaHCO_3$ (0.033 g, 0.39 mmol, 8.0 equiv.) and Dess-Martin periodinane (0.084 g, 0.20 mmol, 4.0 equiv.). The suspension was stirred at room temperature for 6 hours then sat. $Na_2S_2O_3$ (3 mL) and sat. $NaHCO_3$ (3 mL) were added. After stirring for additional 1 hour, the mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layer was washed with brine (5 mL) and dried over anhydrous Na_2SO_4. After filtration and concentration, the residue obtained was purified by flash column chromatography (hexanes/EtOAc, 1:1) to afford **4.54** (0.0195 g, 90%) as a white solid. m.p. = 232–235 °C (decompd.); **IR** (thin film): 2924, 1737, 1700, 1544, 1439, 1373, 1347, 1168, 1128 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.92 (dd, *J* = 5.7, 2.0 Hz, 1H), 7.66–7.74 (m, 2H), 7.59 (dd, *J* = 5.4, 2.0 Hz, 1H), 3.63 (td, *J* = 12.8, 4.8 Hz, 1H), 3.52 (ddd, *J* = 15.2, 6.0, 4.0 Hz, 1H), 2.91–2.99 (m, 2H), 2.82 (dt, *J* = 13.6, 4.0 Hz, 1H), 2.60–2.66 (m, 1H), 1.60–2.41 (m, 13H), 1.48–1.54 (m, 1H), 1.23–1.34 (m, 1H), 1.09 (d, *J* = 6.0 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 218.70, 213.95, 148.88, 133.96, 131.59, 131.12, 130.94, 124.22, 60.33, 50.14, 49.38, 46.79, 45.49, 42.42, 39.62, 31.20, 30.23, 29.72, 24.97, 22.54, 22.07, 20.94; **HRMS** (ESI) calcd. for $C_{22}H_{29}N_2O_6S$ $[M+H]^+$ 449.1741 found 449.1735.

(^{1}H NMR filename: pan116-005-1; ^{13}C NMR filename: pan116-t006; notebook #: 01527)



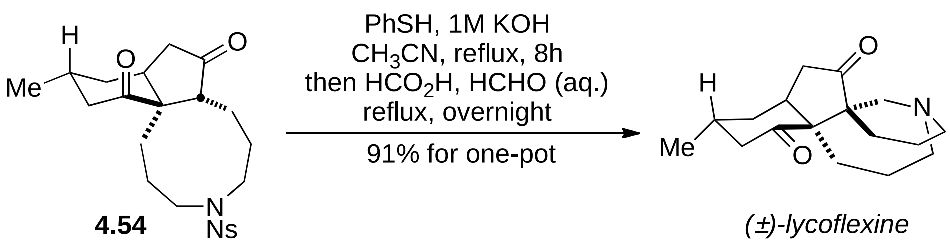
(±)-Fawcettimine. To a 10-mL round-bottomed flask equipped with reflux condenser, **4.54** (0.0127 g, 30 μmol, 1.0 equiv.) was dissolved in CH_3CN (3 mL). KOH (1.0 M, 300 μmol, 0.30 mL, 10 equiv.) and PhSH (15 μL, 150 μmol, 5 equiv.) were added. The reaction was stirred at gentle reflux for 6 hours then cooled to room temperature. EtOAc (8 mL) was added and the mixture was extracted with 1 M HCl (3 x 4 mL). The combined aqueous layer was added solid Na_2CO_3 until saturation. The resulting mixture was extracted with 3% MeOH in $CHCl_3$ (3 x 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4. After filtration and concentration, the residue obtained was dissolved in CH_2Cl_2 and added HBr (0.1 M in H_2O, 0.30 mL, 30 μmol). After standing at room temperature overnight, all of the volatiles were removed under vacuum. To the solid obtained, a minimum amount of Et_2O was added, rinsed and removed by pipette. The (±)-fawcettimine hydrobromide salt remained was dissolved in CH_2Cl_2 and dried over anhydrous K_2CO_3 overnight. After filtration and concentration, (±)-fawcettimine (0.0073 g, 92%) was obtained as a pale yellow foam (R_f = 0.35, *n*-BuOH/AcOH/H_2O 7:2:2). **IR** (thin film): 3287, 2923, 2856, 1735, 1637, 1458, 1340, 1264, 1144, 1100, 1056 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.76–3.85 (m, 1H), 3.58–3.70 (br, 1H), 3.40 (td, *J* = 14.2, 4.0 Hz, 1H), 3.03 (dd, *J* = 14.4, 4.8 Hz, 1H), 2.81–2.86 (m, 1H), 2.60 (dd, *J* = 18.0, 13.6 Hz, 1H), 1.82–2.35 (m, 11H), 1.37–1.76 (m, 5H), 1.00 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 218.16, 59.87, 54.69, 50.59, 48.13, 43.39, 42.46, 41.65, 34.77, 31.80, 29.92, 27.55, 26.61, 23.94, 21.81, 20.90; **HRMS** (ESI) calcd. for $C_{16}H_{26}NO_2$ $[M+H]^+$ 264.1958 found 264.1962. Analytical data for (±)-fawcettimine hydrobromide: ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 10.01 (br s, 1H), 5.80 (s, 1H), 4.18 (br s, 1H), 3.51–3.64 (m, 1H), 3.21 (br d, J = 11.2 Hz, 1H), 3.02 (br s, 1H), 2.81 (d, J = 12.4 Hz, 1H), 2.60 (dd, J = 16.8, 12.4 Hz, 1H), 1.82–2.46 (m, 12H), 1.75 (br d, J = 14.0 Hz, 1H), 1.64 (d, J = 12.8 Hz, 1H), 1.48 (td, J = 13.4, 4.8 Hz, 1H), 1.05 (d, J = 6.0 Hz, 3H); ^{13}**C NMR** (75 MHz, $CDCl_3$): δ 216.16, 96.33, 59.22, 55.98, 51.56, 47.68, 43.29, 41.20, 40.27, 33.54, 31.38, 26.75, 24.19, 23.96, 21.64, 19.19.

(^{1}H NMR filename: pan117-002, pan117-1; ^{13}C NMR filename: pan117-t003, pan106-428-t19; notebook #: 01377, 01536)



(±)-Fawcettidine. To a 10-mL round-bottomed flask equipped with reflux condenser, fawcettimine (0.0054 g, 20 μmol, 1.0 equiv.) and oxalic acid (0.0540 g, 0.6 mmol, 29.0 equiv.) were dissolved in AcOH (2 mL). Oxygen was carefully removed through a freeze-pump-thaw cycles for 3 times. The flask was refilled with Ar and the reaction was stirred at 160 °C for 12 hours. After cooling to room temperature, *n*-heptane was added and all the volatiles were removed under vacuum. To the residue, aq. 5% $NH_3{\cdot}H_2O$ solution (5 mL) was added and the resulting mixture was extracted with 3% MeOH in $CHCl_3$ (4 x 4 mL). The combined organic layer was dried over anhydrous Na_2SO_4. After filtration and concentration, the crude obtained was purified by flash column chromatography (basic alumina, hexanes/EtOAc, 2:1 then 3% MeOH in $CHCl_3$) to afford title compound (0.0040 g, 80%) as a white foam (R_f = 0.24, MeOH/$CHCl_3$ 5:95). **IR** (thin film): 2924, 2848, 1737, 1662, 1549, 1447, 1328, 1302, 1253, 1216, 1193, 1169, 1149, 1105, 1030 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.69 (d, *J* = 4.8 Hz, 1H), 2.97–3.15 (m, 4H), 2.74 (ddd, *J* = 16.8, 7.6, 1.6 Hz, 1H), 2.22–2.36 (m, 2H), 2.05–2.20 (m, 3H), 1.82–2.00 (m, 2H), 1.54–1.79 (m, 3H), 1.21–1.41 (m, 4H), 1.06 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 219.11, 146.23, 127.41, 60.61, 56.47, 52.22, 46.39, 44.34, 39.41, 37.51, 34.39, 31.64, 29.41, 27.95, 24.06, 21.07; **HRMS** (ESI) calcd. for $C_{16}H_{24}NO$ $[M+H]^+$ 246.1852 found 246.1855.

(^{1}H NMR filename: pan121-4; ^{13}C NMR filename: pan121-t4; notebook #:01451, 01542)

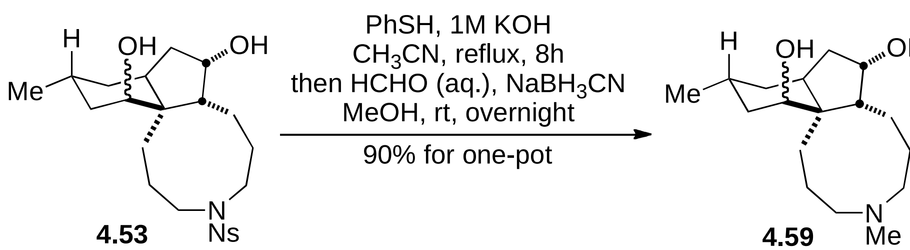


4.54

(±)-lycoflexine

(±)-Lycoflexine. To a 10-mL round-bottomed flask equipped with reflux condenser, **4.54** (0.0024 g, 5.3 μmol, 1.0 equiv.) was dissolved in CH_3CN (2 mL). KOH (1.0 M, 42 μmol, 42 μL, 8.0 equiv.) and PhSH (2.7 μL, 26 μmol, 5.0 equiv.) were added. The reaction was stirred at gentle reflux for 8 hours then cooled to room temperature. H_2O (1 mL), HCO_2H (16 μL, 424 μmol, 80 equiv.), and 37% HCHO (aq., 34 μL, 424 μmol, 80 equiv.) were added. The resulting mixture was stirred at gentle reflux overnight before all of the volatiles were removed at vacuum. The residue was dissolved in EtOAc (10 mL) and extracted with 1 M HCl (3 x 4 mL). The combined aqueous layer was added solid

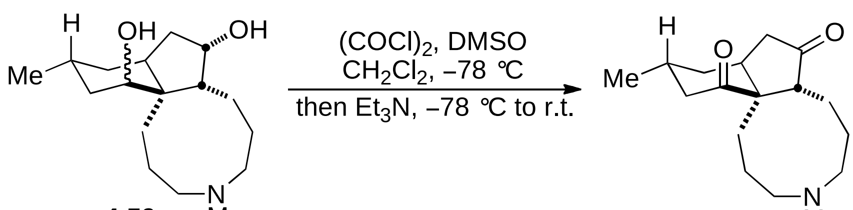
Na_2CO_3 until saturation. The mixture was then extracted with 3% MeOH in $CHCl_3$ (3 x 4 mL) and the combined organic layer was dried over anhydrous Na_2SO_4. After filtration and concentration, the residue was purified by flash column chromatography (basic alumina, hexanes/EtOAc, 1:2 then 3% MeOH in $CHCl_3$) to afford title compound (0.0013 g, 91%) as a white solid (R_f = 0.23, *n*-BuOH/AcOH/H_2O 7:2:2). **IR** (thin film): 2924, 2853, 1727, 1699, 1456, 1352, 1208, 1174, 1127, 1063 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.19 (ddd, *J* = 14.4, 2.8, 1.2 Hz, 1H), 3.13 (ddd, *J* = 13.6, 8.0, 4.0 Hz, 1H), 2.94–3.02 (m, 1H), 2.78–2.91 (m, 2H), 2.61–2.72 (m, 2H), 2.19–2.42 (m, 6H), 2.06–2.17 (m, 2H), 1.91–2.01 (m, 2H), 1.71–1.89 (m, 3H), 1.56–1.64 (m, 1H), 1.31–1.36 (m, 1H), 1.04 (d, *J* = 6.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 218.62, 214.06, 60.84, 58.69, 56.91, 53.81, 53.52, 46.92, 40.53, 40.30, 36.43, 31.46, 29.53, 28.22, 26.26, 22.59, 19.57; **HRMS** (ESI) calcd. for $C_{17}H_{26}NO_2$ $[M+H]^+$ 276.1958 found 276.1962.
(^{1}H NMR filename: pan118-4; ^{13}C NMR filename: pan118-t4; notebook #:01410, 01416)



Compound 4.59. To a 25-mL round-bottomed flask equipped with reflux condenser, **4.53** (0.0310 g, 69 μmol, 1.0 equiv.) was dissolved in CH_3CN (ACS grade, 4 mL). KOH (1.0 M, 0.55 mmol, 0.55 mL, 8 equiv.) and PhSH (35 μL, 0.35 mmol, 5 equiv.) were added. The reaction was stirred at gentle reflux for 8 hours then cooled to room temperature and added MeOH (ACS grade, 4 mL), aq. HCHO (37%, 154 μL, 2.07 mmol,

30 equiv.), and $NaBH_3CN$ (0.013 g, 0.21 mmol, 3 equiv.). After stirring at room temperature overnight, aq. HCl (1.0 M, 2.0 mL) was added and the mixture was extracted with 1M HCl (3 x 3 mL). The combined aqueous layer was added solid Na_2CO_3 until saturation. The resulting mixture was extracted with 5% MeOH in $CHCl_3$ (4 x 4 mL) and the combined organic layer was dried over anhydrous Na_2SO_4. After filtration and concentration, the residue was purified by flash column chromatography (basic alumina, 3% MeOH in $CHCl_3$) to afford **4.59** (0.0175 g, 90%) as a white solid. **IR** (thin film): 3356, 2925, 2869, 1721, 1660, 1455, 1376, 1273, 1107, 1066 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): 4.58–4.66 (m, 1H), 3.59–3.66 (m, 1H), 2.51–2.76 (m, 3H), 2.17–2.47 (m, 6H), 1.81–2.14 (m, 5H), 1.11–1.74 (m, 12H), 0.93 (d, J = 6.3 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 74.41, 73.83, 55.82, 51.93, 47.95, 46.80, 43.33, 39.36, 37.65, 33.02, 28.43, 27.49, 26.73, 25.82, 22.42, 19.62; **HRMS** (ESI) calcd. for $C_{17}H_{32}NO_2$ $[M+H]^+$ 282.2428 found 282.2434.

(^{1}H NMR filename: pan106-442-9-1; ^{13}C NMR filename: pan106-442-9-t1; notebook #:01439, 01611, 01641)

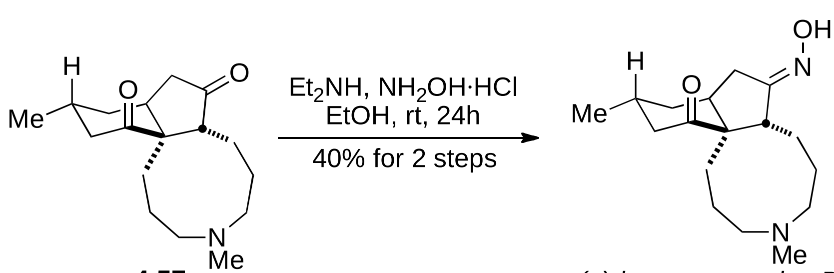


4.59 **4.57a**

Compound 4.57a. To a 15-mL flame dried round-bottomed flask, CH_2Cl_2 (1.0 mL) was added and the flask was cooled to –78 ºC (dry ice/acetone bath). $(COCl)_2$ (21 μL, 250 μmol, 5.0 equiv.) and DMSO (36 μL, 501 μmol, 10.0 equiv.) were added. The mixture was stirred at –78 ºC for 30 minutes then **4.59** (0.0141 g, 50 μmol, 1.0 equiv.) in CH_2Cl_2

(3.0 mL) was added *via* syringe. The mixture was stirred at –78 ºC for 1 hour and then NEt_3 (140 μL, 1.0 mmol, 20.0 equiv.) was added. After 20 minutes at –78 ºC, the reaction was allowed to warm to room temperature and stirred at room temperature for 1 hour. EtOAc (10 mL) was added and the mixture was washed with 1M HCl (3 x 3 mL). The combined water layer was added solid Na_2CO_3 until saturation. The resulting mixture was extracted with 5% MeOH in $CHCl_3$ (3 x 4 mL) and the combined organic layer was dried over anhydrous Na_2SO_4. After filtration and concentration, the crude **4.57a** obtained was used immediately in the next step without further purification. An analytic sample was purified by flash column chromatography (3% MeOH in CH_2Cl_2) to give **4.57a** as a colorless oil. ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 2.90 (d, J = 5.2 Hz, 1H), 2.49–2.62 (m, 2H), 2.04–2.45 (m, 12H), 1.72–1.99 (m, 5H), 1.31–1.52 (m, 3H), 1.12–1.20 (m, 1H), 1.07 (d, J = 6.4 Hz, 3H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 220.38, 214.38, 60.91, 55.02, 50.44, 48.96, 46.87, 44.52, 42.75, 39.64, 31.34, 30.44, 28.33, 25.54, 22.66, 22.57, 21.91; **HRMS** (ESI) calcd. for $C_{17}H_{28}NO_2$ $[M+H]^+$ 278.2115 found 278.2110.

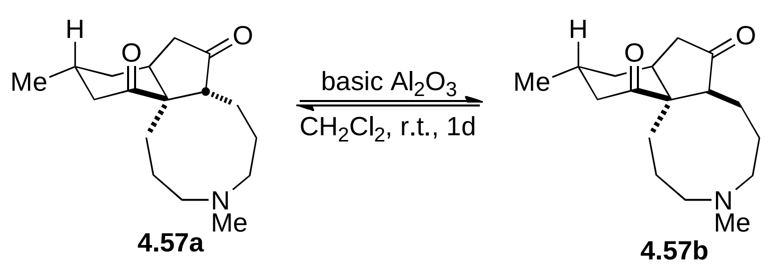
(^{1}H NMR and ^{13}C NMR filename: pan106-442-17-s2, notebook #: 01617, 01646)



4.57a *(±)-lycoposerramine B*

(±)-Lycoposerramine B. Following the procedure described by Harayama and Takayama,[7] to a solution of crude **4.57a** (15.2 μmol, theoretical) in EtOH (1.5 mL) was added Et_2NH (7.9 μL, 76 μmol, 5.0 equiv.). The mixture was stirred at room temperature for 3 hours then $NH_2OH{\cdot}HCl$ (0.2 M in EtOH, 83.5 μL, 1.1 equiv.) was added. After 24 hours at room temperature, the reaction was quenched with chilled sat. $NaHCO_3$ (3 mL) and extracted with 5% MeOH in $CHCl_3$ (4 x 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4. After filtration and concentration, the residue was chromatographed (10% MeOH in $CHCl_3$) to afford crude (±)-lycoposerramine B. The crude was rechromatographed ($NH_3{\cdot}H_2O$/MeOH/$CHCl_3$ 0.05/5/95) to afford pure (±)-lycoposerramine B (1.8 mg, 40%) as a colorless oil. **IR** (thin film): 2918, 2849, 1702, 1451, 1369, 1268, 1210, 1139, 1076 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.18 (d, *J* = 3.2 Hz, 1H), 2.66 (app td, *J* = 13.6, 3.6 Hz, 1H), 2.55 (ddd, *J* = 18.8, 9.2, 0.8 Hz, 1H), 2.38–2.45 (m, 1H), 2.18–2.36 (m, 8H), 1.96–2.16 (m, 4H), 1.55–1.80 (m, 5H), 1.43–1.50 (m, 1H), 1.15–1.40 (m, 3H), 1.04 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 213.97, 169.82, 61.87, 55.20, 48.67, 46.99, 44.52, 43.06, 31.80, 30.09, 29.93, 28.86, 27.70, 25.71, 25.64, 22.62, 21.58; **HRMS** (ESI) calcd. for $C_{17}H_{29}N_2O_2$ $[M+H]^+$ 293.2224 found 293.2226.

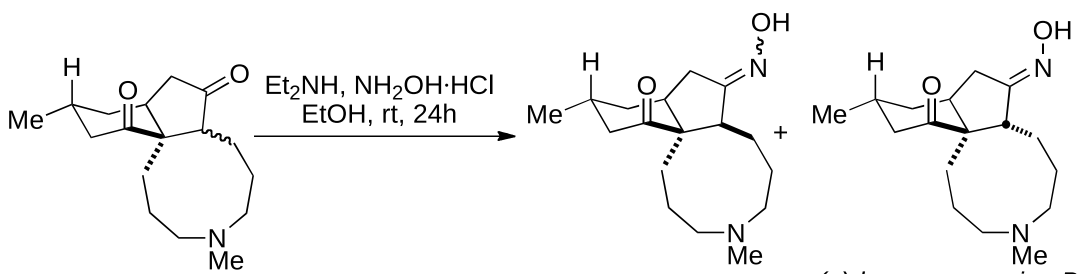
(^{1}H NMR filename: pan120-2; ^{13}C NMR filename: pan120-t2; notebook #:01523, 01543)



Compound 4.57b. To a stirred solution of crude **4.57a** (0.0104 g, obtained from Swern oxidation of **4.59**) in CH_2Cl_2 was added basic Al_2O_3 (150 mesh, 0.0520 g, 500 wt.%). After stirring at room temperature for 1 day, the suspension was filtered over sintered

glass funnel and washed with 3% MeOH in CH_2Cl_2 (5 mL). The filtrate was concentrated to give a mixture of **4.57a** and **4.57b** as a colorless oil (d.r. 1:1), which was used immediately in the next step without further purification. An analytic sample was purified by flash column chromatography (1% MeOH in CH_2Cl_2) to give recovered **4.57a** (R_f = 0.20, 3% MeOH in $CHCl_3$ 3 times) and **4.57b** (R_f = 0.27, 3% MeOH in $CHCl_3$ 3 times) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.18–2.56 (m, 11H), 1.89–2.15 (m, 5H), 1.81 (td, J = 14.4, 4.8 Hz, 1H), 1.63–1.73 (m, 2H), 1.52–1.60 (m, 3H), 1.27–1.37 (m, 2H), 1.06 (d, J = 6.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 216.40, 214.98, 60.78, 58.38, 57.38, 55.35, 47.15, 45.94, 42.32, 38.81, 31.71, 31.50, 30.92, 29.93, 27.41, 23.60, 22.47.

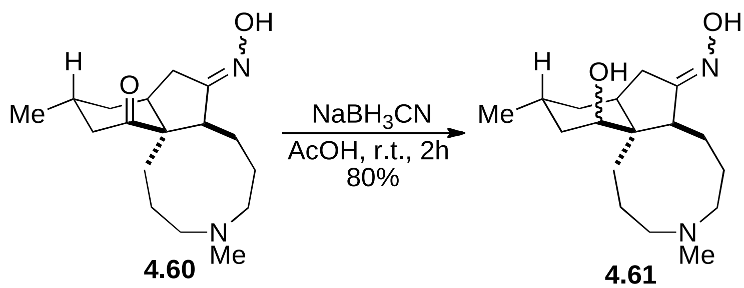
(^{1}H NMR and ^{13}C NMR filename: pan106-442-17-s1, notebook #: 01649)



4.57a + **4.57b** **4.60** *(±)-lycoposerramine B*

Compound 4.60. To a solution of crude mixture of **4.57a** and **4.57b** (17.3 μmol, theoretical) in EtOH (1.2 mL) was added Et_2NH (18 μL, 173 μmol, 10.0 equiv.). The mixture was stirred at room temperature for 3 hours then $NH_2OH{\cdot}HCl$ (0.2 M in EtOH, 95 μL, 1.1 equiv.) was added. After 24 hours at room temperature, the reaction was quenched with chilled sat. $NaHCO_3$ (3 mL) and extracted with 5% MeOH in $CHCl_3$ (4 x 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4. After filtration and concentration, the residue was chromatographed (MeOH/$CHCl_3$ 2.5:97.5 to 10:90) to afford crude (±)-lycoposerramine B and **4.60** (0.0018 g, 35%) as a colorless oil. **IR** (thin film): 3264, 2924, 2785, 1702, 1453, 1375, 1267, 1227, 1129, 1067 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.94–7.21 (br s, 1H), 2.76–2.78 (m, 1H), 2.52–2.62 (m, 2H), 2.40–2.46 (m, 1H), 2.19–2.32 (m, 8H), 2.02–2.17 (m, 5H), 1.64–1.74 (m, 3H), 1.48–1.58 (m, 2H), 1.30–1.40 (m, 2H), 1.03 (d, *J* = 6.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 214.89, 166.84, 60.84, 58.34, 55.03, 48.37, 47.63, 45.98, 43.00, 31.82, 30.93, 30.39, 29.93, 29.11, 27.04, 25.13, 22.54, 22.30.

(^{1}H NMR and ^{13}C NMR filename: pan120-4-4-1, notebook #: 01658)



Compound 4.61. To a stirred solution of **4.60** (0.0018 g, 6.2 μmol, 1.0 equiv.) in CH_3CO_2H (ACS grade, 0.5 mL) was added $NaBH_3CN$ (0.2 M in THF, newly made, 31 μL, 6.2 μmol, 1.0 equiv.). After 2 hours at room temperature, sat. $NaHCO_3$ (4 mL) was added carefully. $NaHCO_3$ powder was then added slowly until saturation. The mixture was extracted with 5% MeOH in $CHCl_3$ (4 x 5 mL) and the combined organic layer was dried over anhydrous Na_2SO_4. After filtration and concentration, the residue was chromatographed (7*N* NH_3 in MeOH/$CHCl_3$ 3:97) to give **4.61** (0.0014 g, 80%) as a colorless oil. **IR** (thin film): 3265, 2924, 2784, 1654, 1559, 1541, 1508, 1457, 1375, 1231, 1023 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.16 (br s, 1H), 4.25 (br s, 1H), 3.52 (dd, *J* = 12.0, 4.4 Hz, 1H), 3.22–3.31 (m, 1H), 2.27–2.66 (m, 8H), 2.17–2.25 (m, 1H),

2.10 (dd, J = 14.4, 8.4 Hz, 1H), 1.85–2.00 (m, 3H), 1.46–1.81 (m, 8H), 1.09–1.26 (m, 2H), 0.93 (d, J = 6.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 168.60, 70.17, 63.95, 59.19, 58.10, 54.03, 49.79, 47.22, 41.93, 41.00, 31.94, 29.79, 28.69, 26.24, 25.54, 24.78, 22.19; **HRMS** (ESI) calcd. for $C_{17}H_{31}N_2O_2$ $[M+H]^+$ 295.2380 found 295.2371.
(^{1}H NMR and ^{13}C NMR filename: pan120-7-2-1, notebook #: 01675)

5.4 References

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2) *Hydroxid-halogenid-verbindungen des di-t-butyl-substituierten zinns.* Puff, H.; Hevendehl, H.; Höffer, K.; Reuter, H.; Schuh, W. *J. Organomet. Chem.* **1985**, *287*, 163–178.

3) *Synthesis of methyl epijasmonate and cis-3-(2-oxopropyl-2-(pent-2Z-enyl)-cyclopentan-1-one*. Hailes, H. C.; Isaac, B.; Javaid, M. H. *Tetrahedron* **2001**, *57*, 10329–10333.

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6) *Triflimide activation of a chiral oxazaborolidine leads to a more general catalytic system for enantioselective Diels-Alder addition*. Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388–6390.

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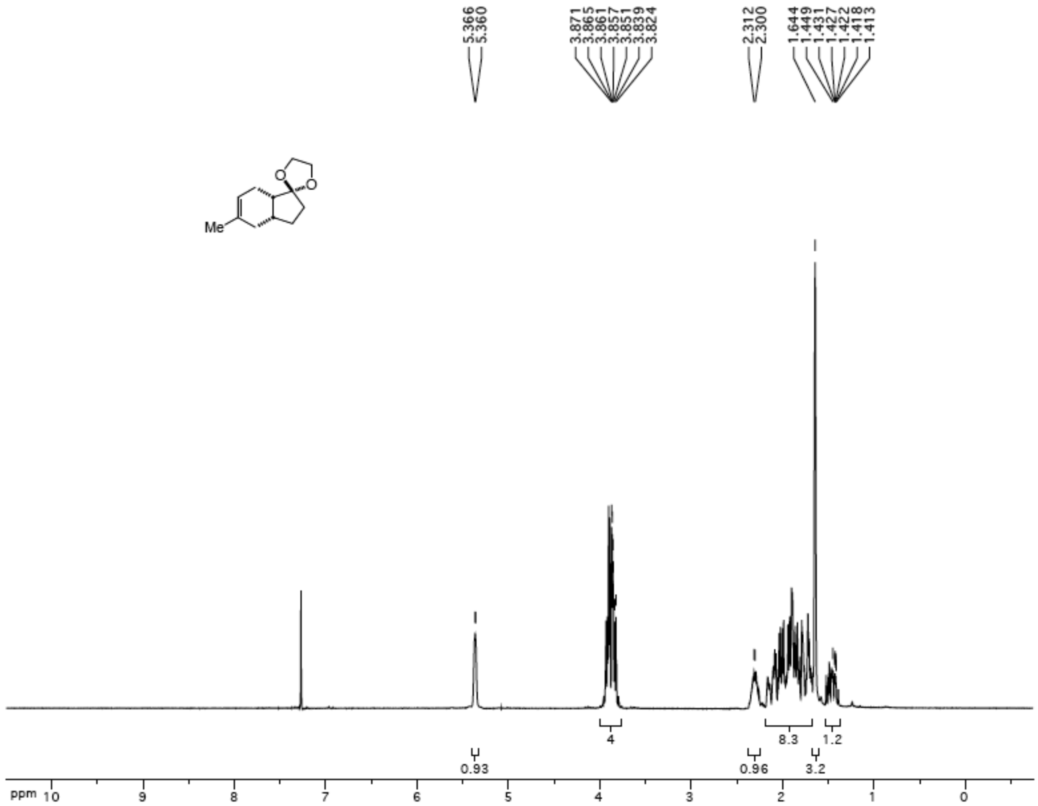
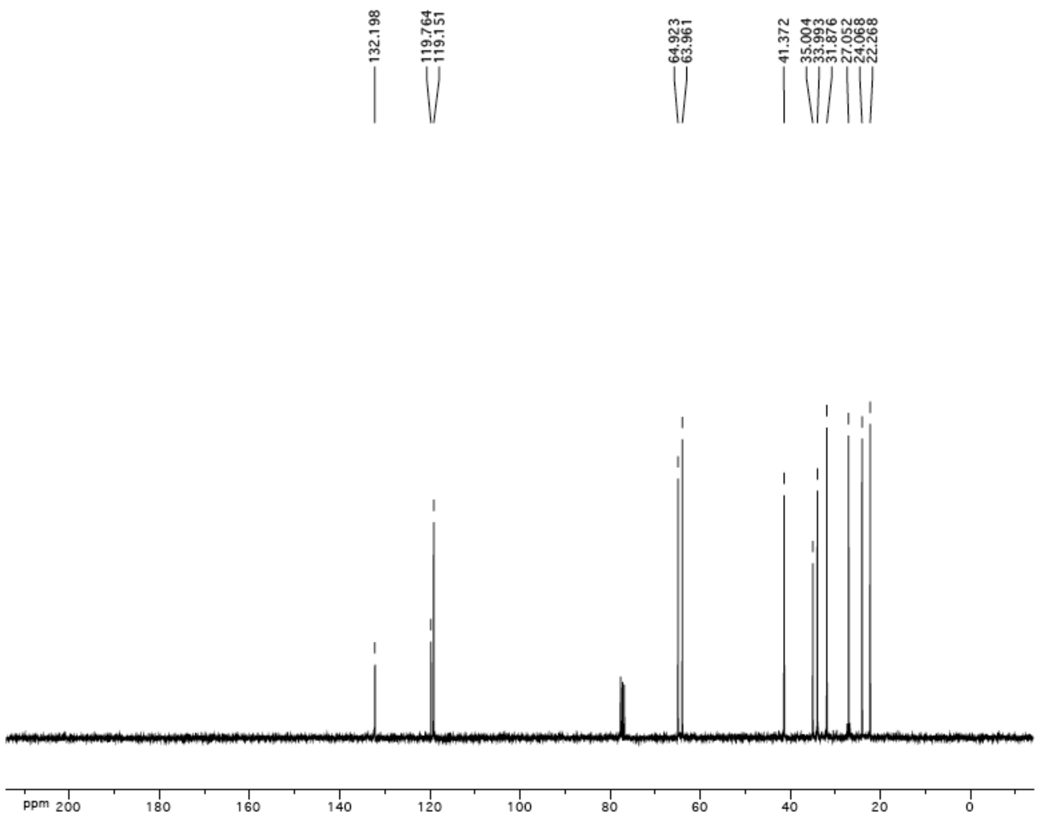
Appendix I

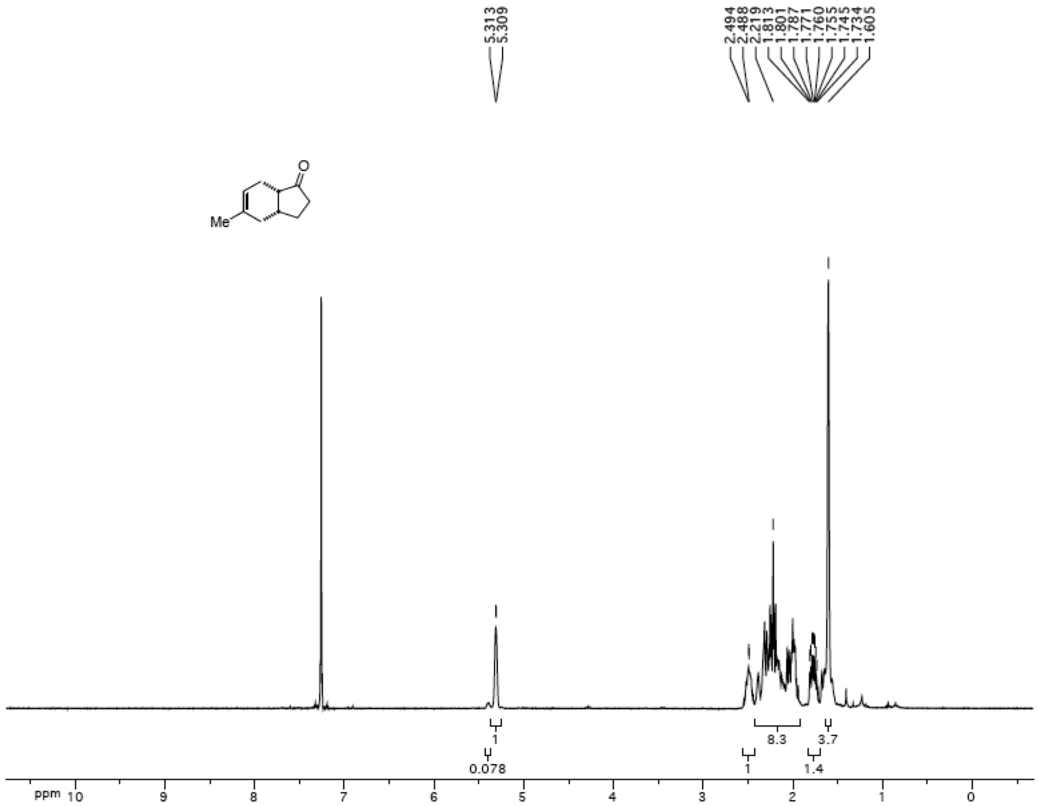
Spectra relevant to Chapter 3

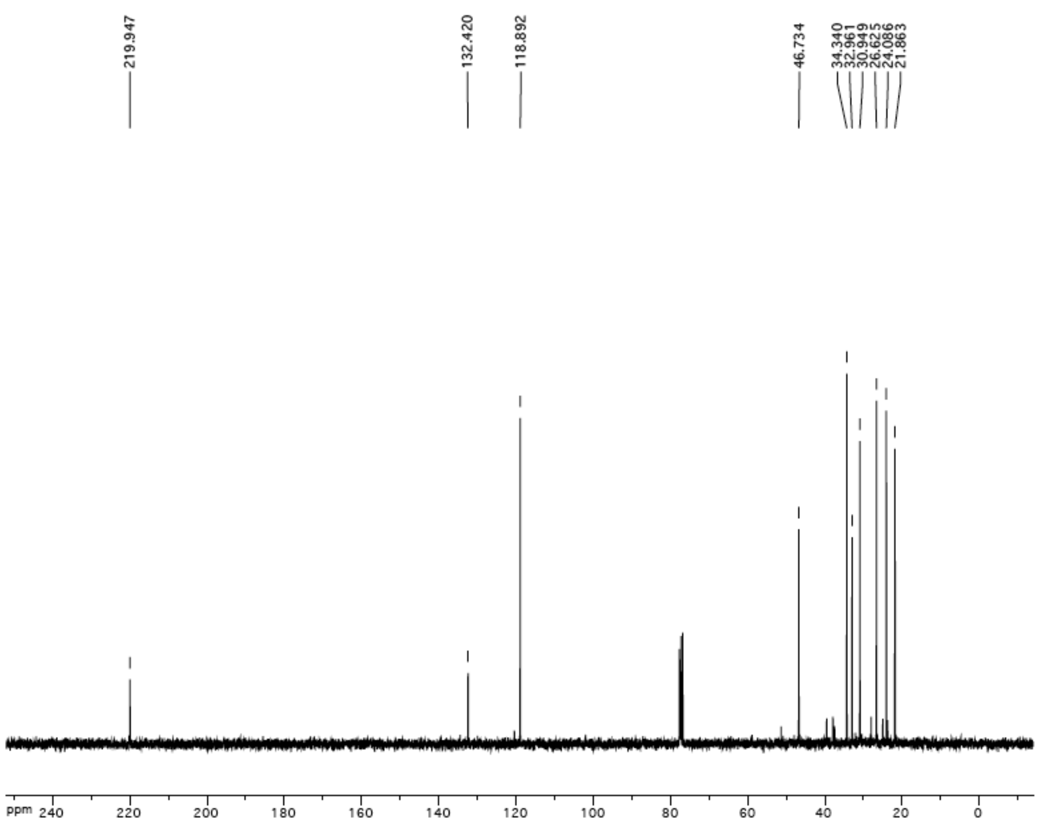
^{1}H and ^{13}C NMR spectra for **3.11**



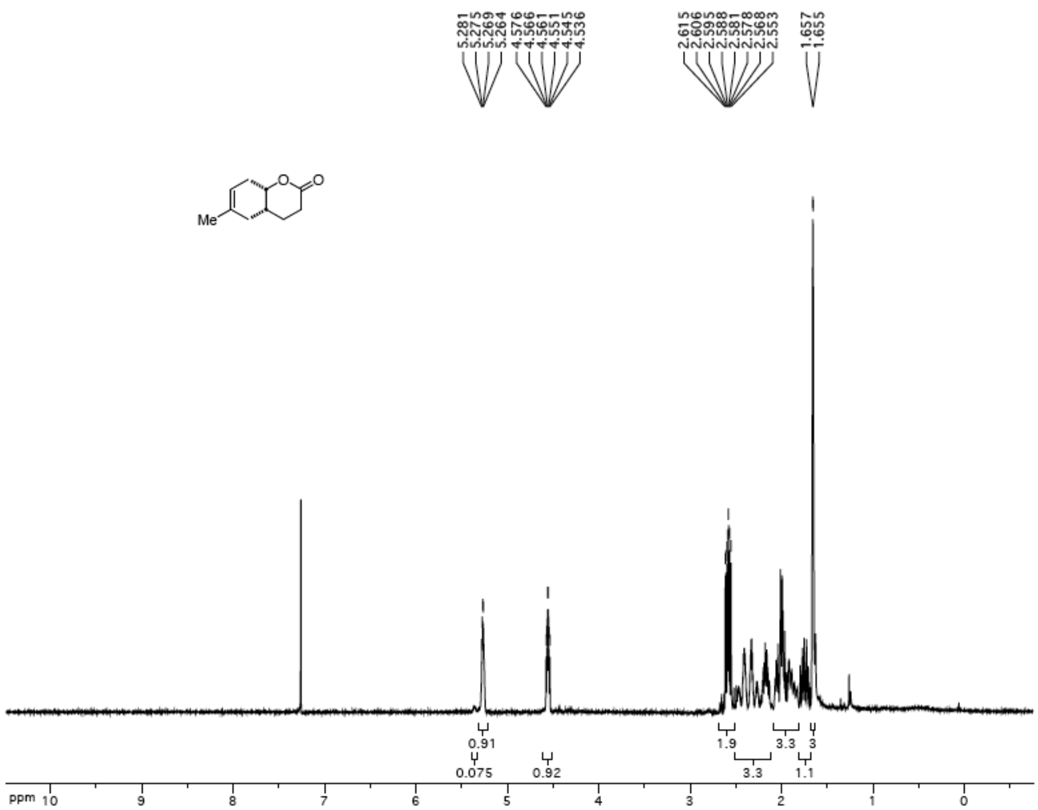


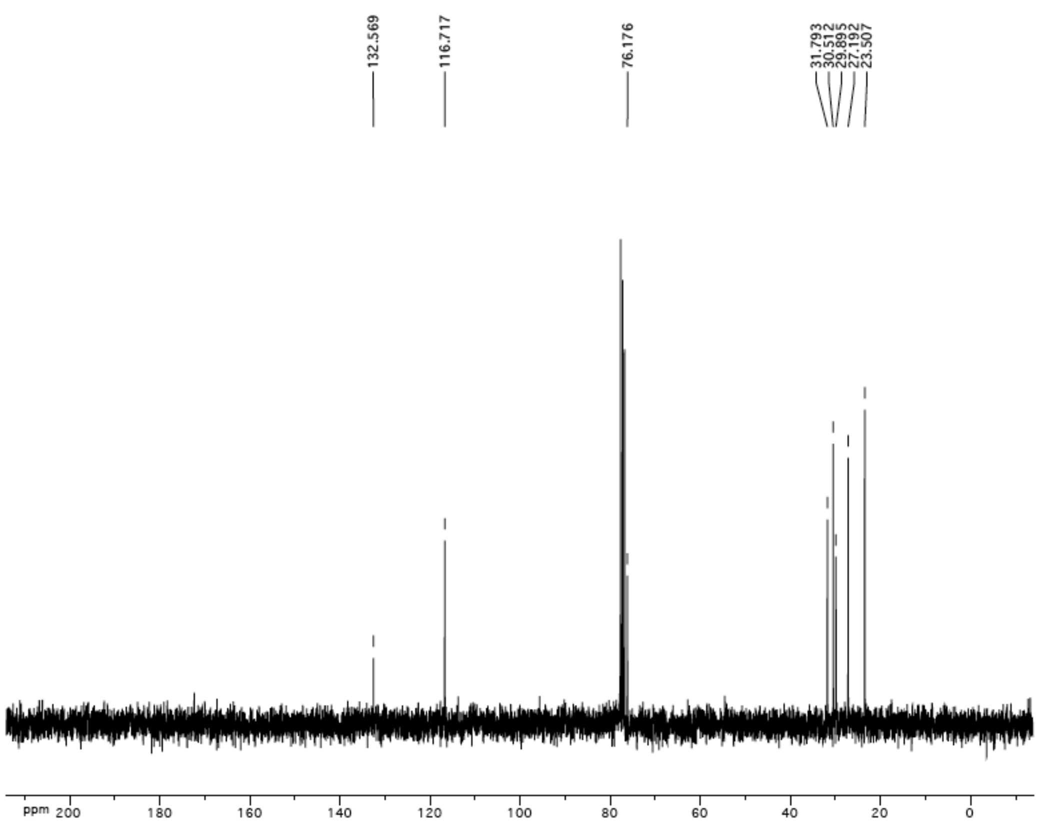
^{1}H and ^{13}C NMR spectra for **3.8**



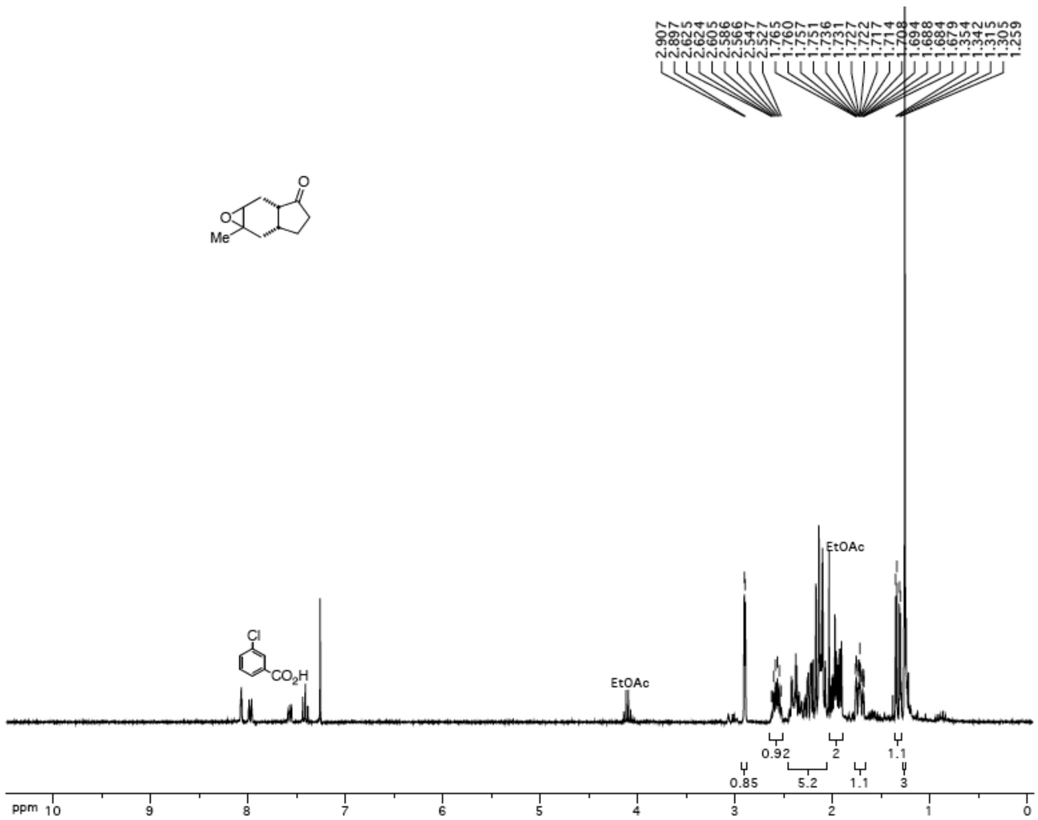


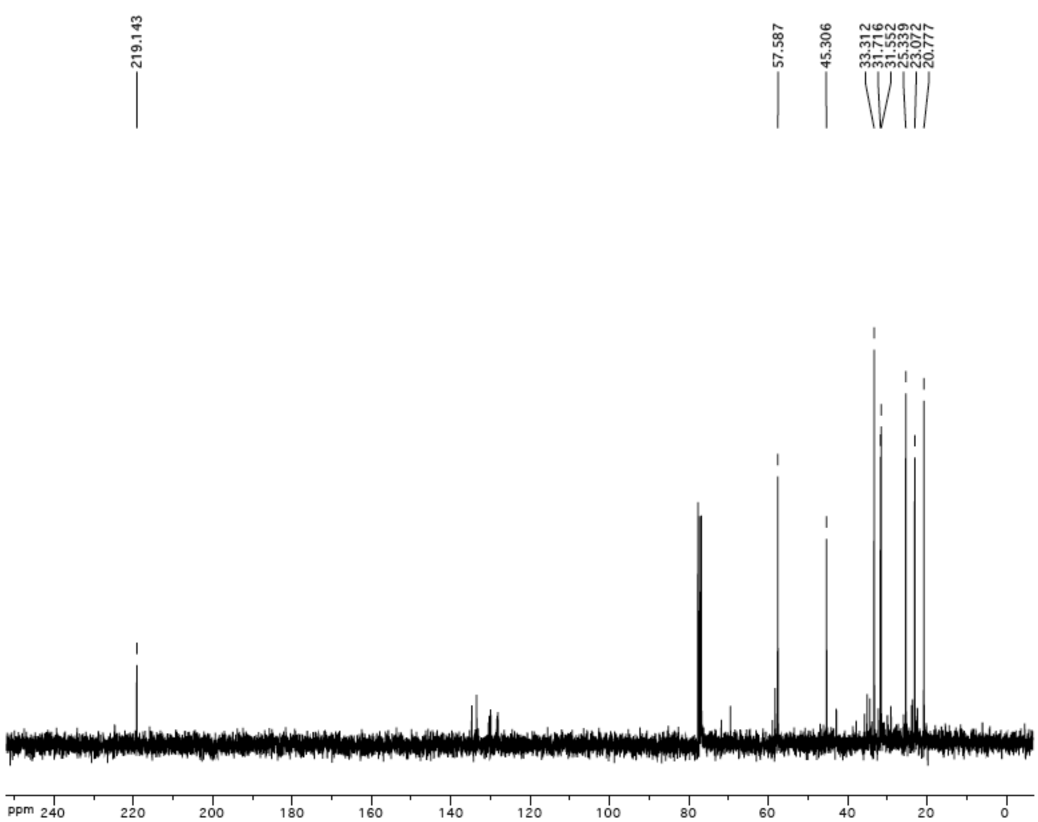
^{1}H and ^{13}C NMR spectra for **3.7**



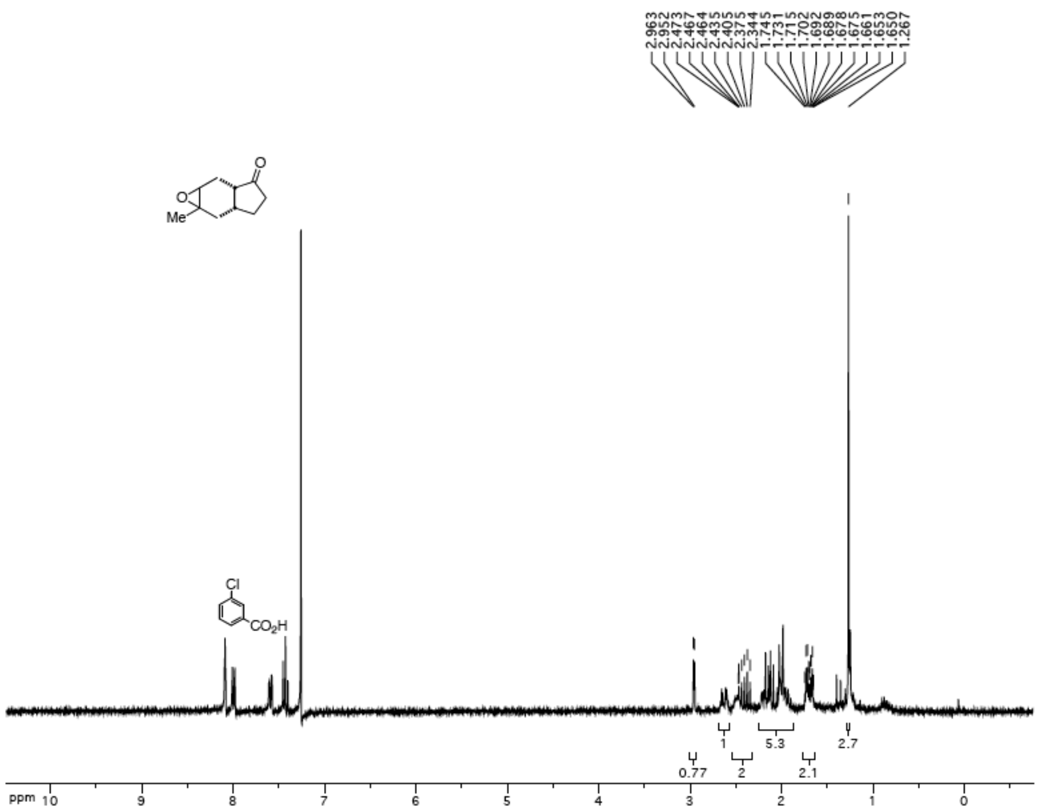


^{1}H and ^{13}C NMR spectra for **3.12** (major isomer)

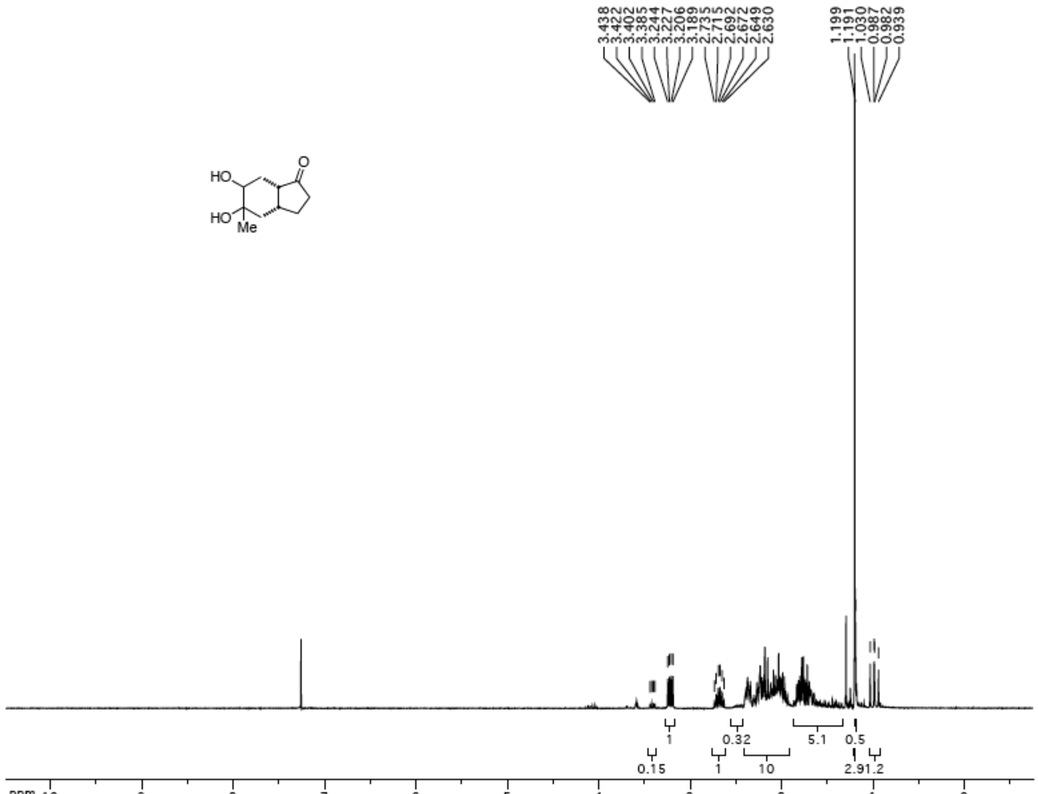


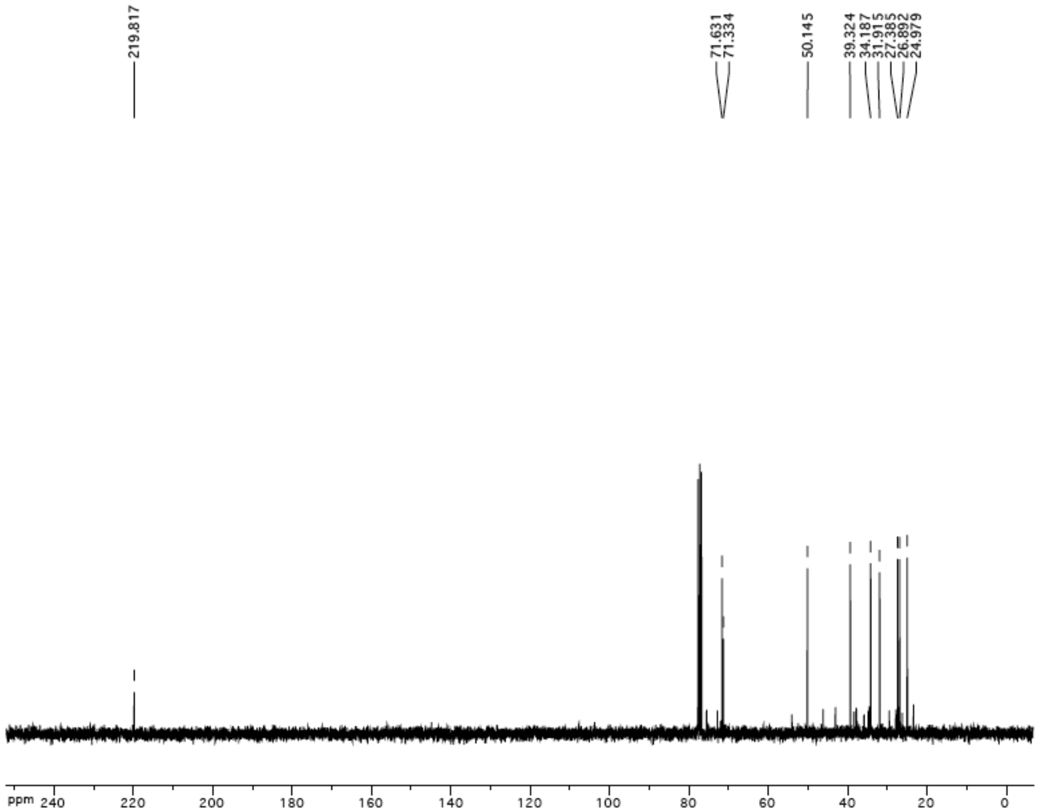


[1]H spectrum for **3.12** (minor isomer)

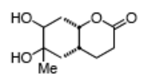


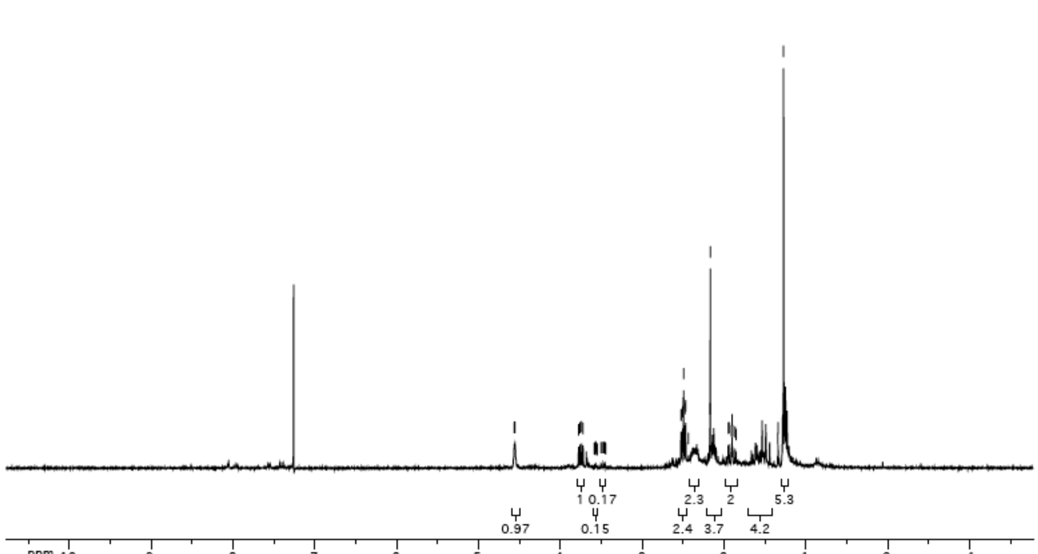
[1]H and [13]C NMR spectra for **3.14**

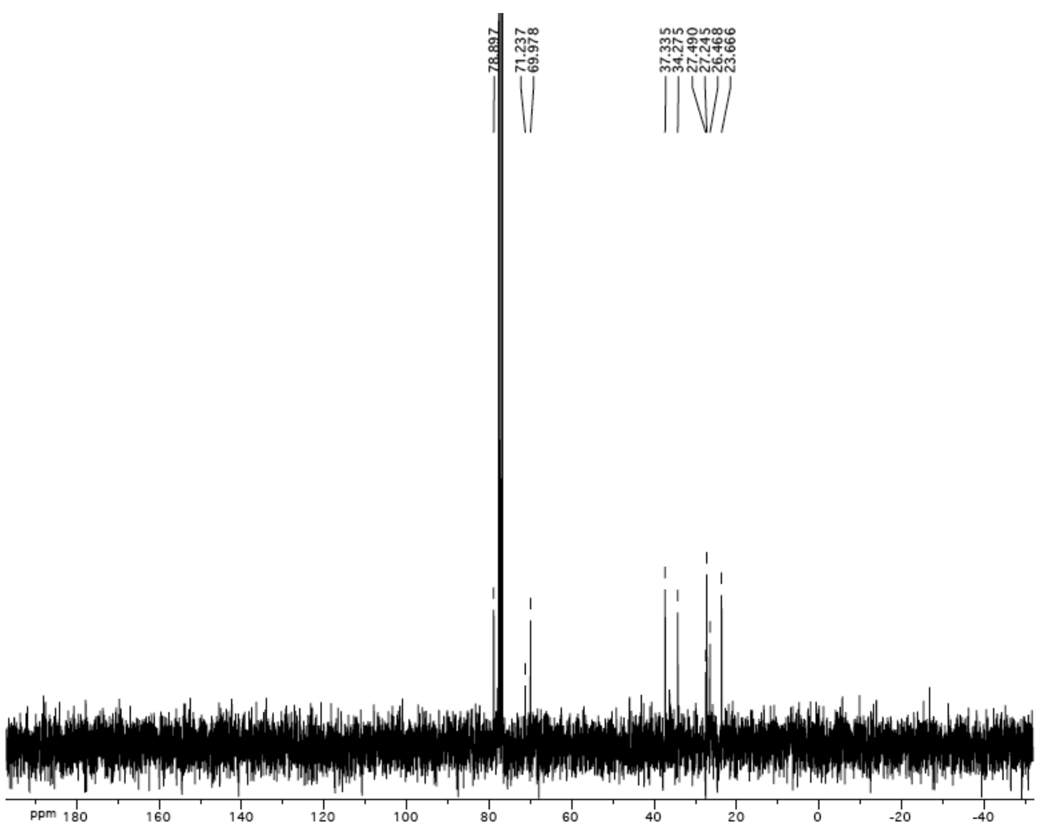




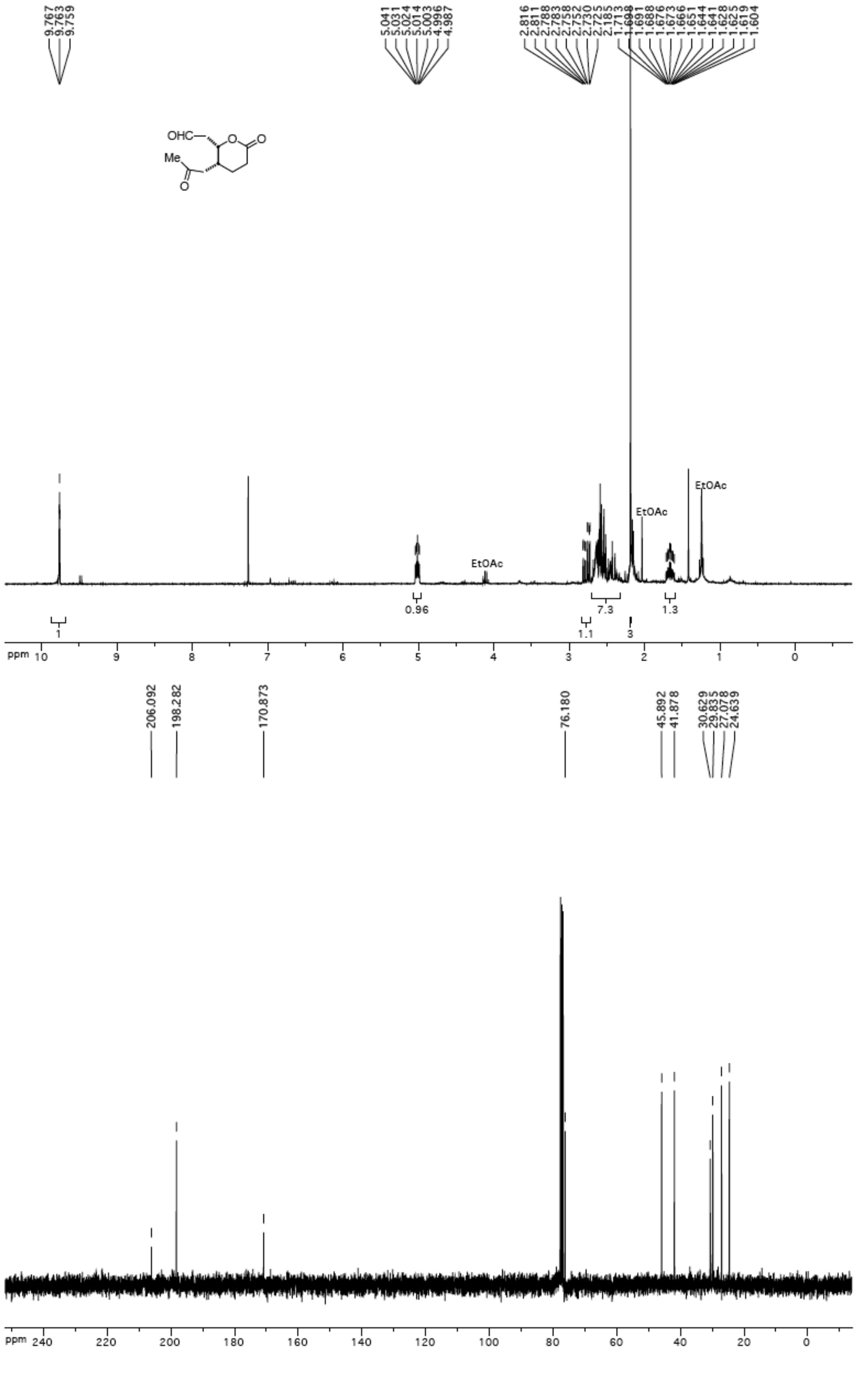
^{1}H and ^{13}C NMR spectra for **3.15**



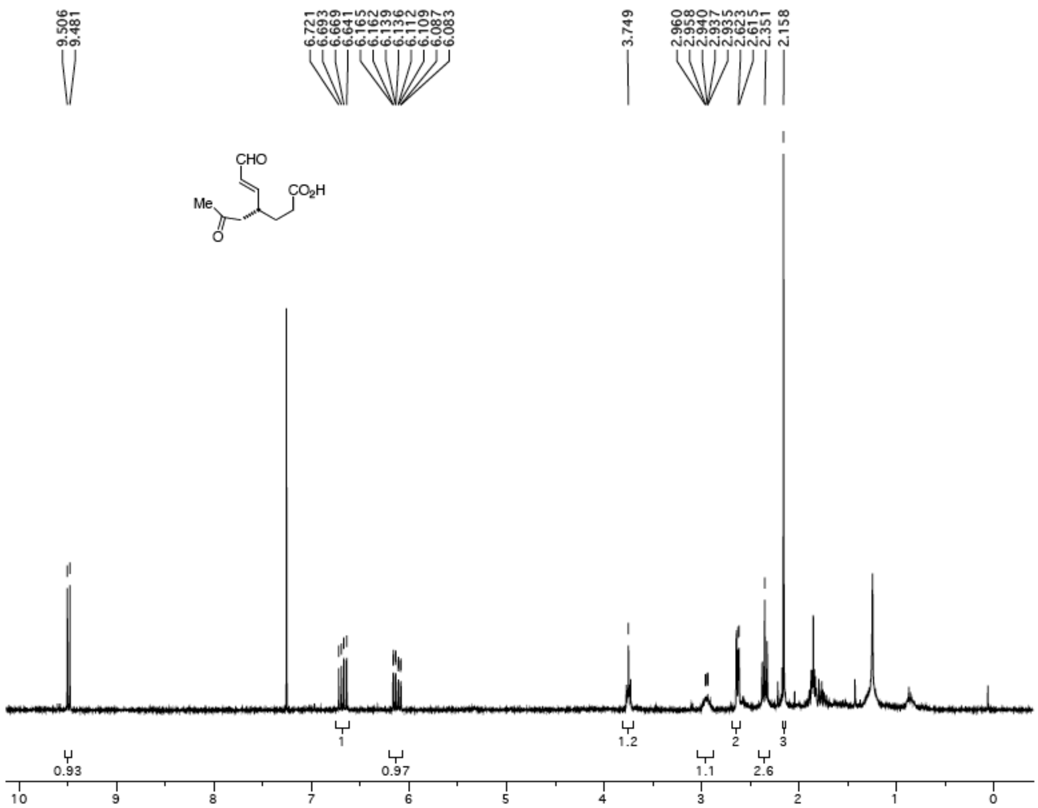




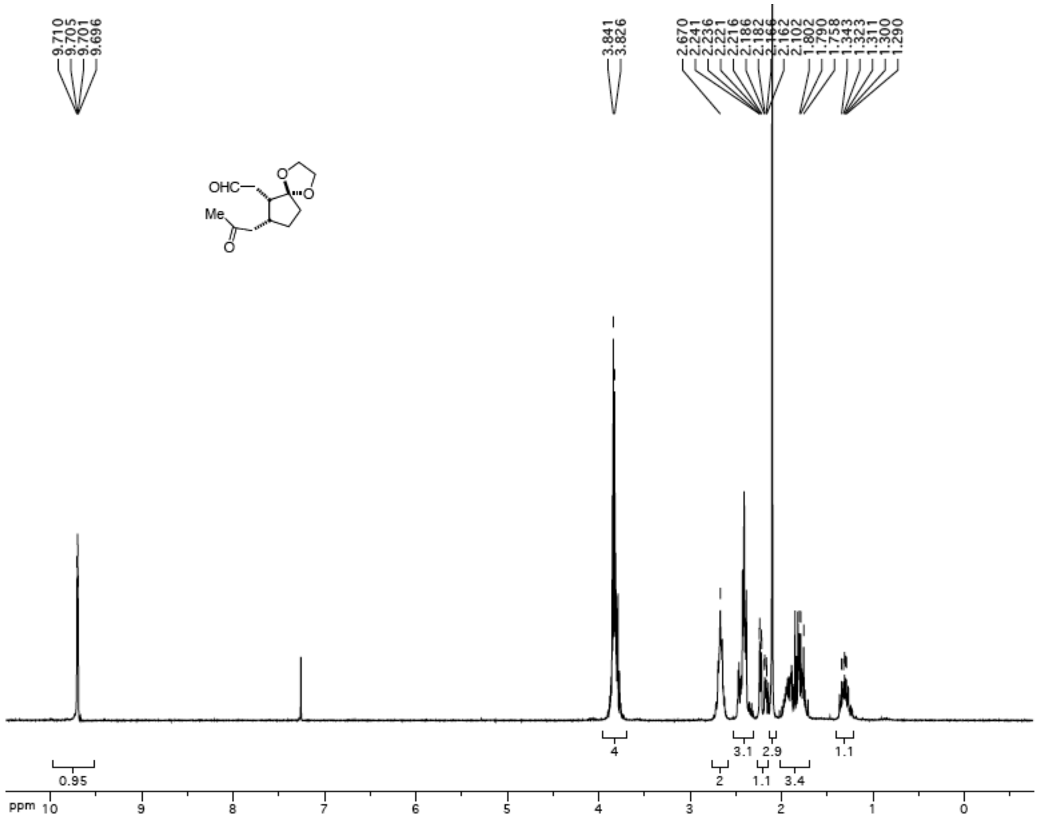
^{1}H and ^{13}C NMR spectra for **3.13**

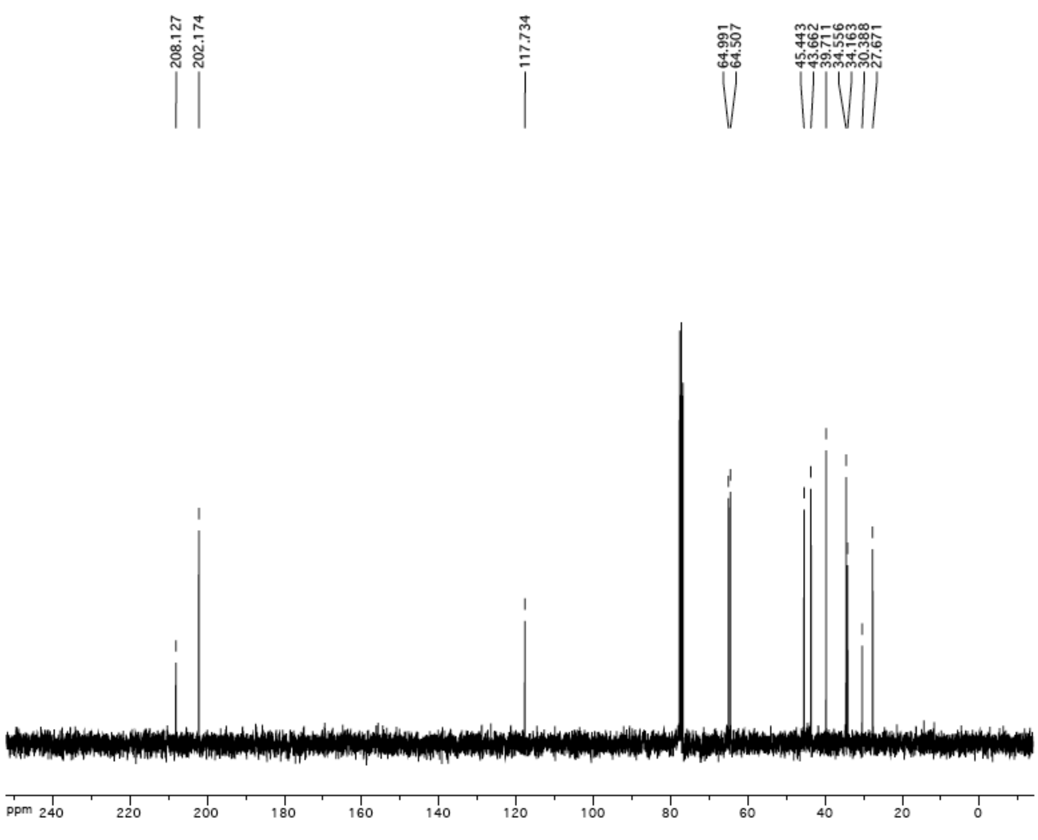


Crude ^{1}H NMR spectrum for **3.16**

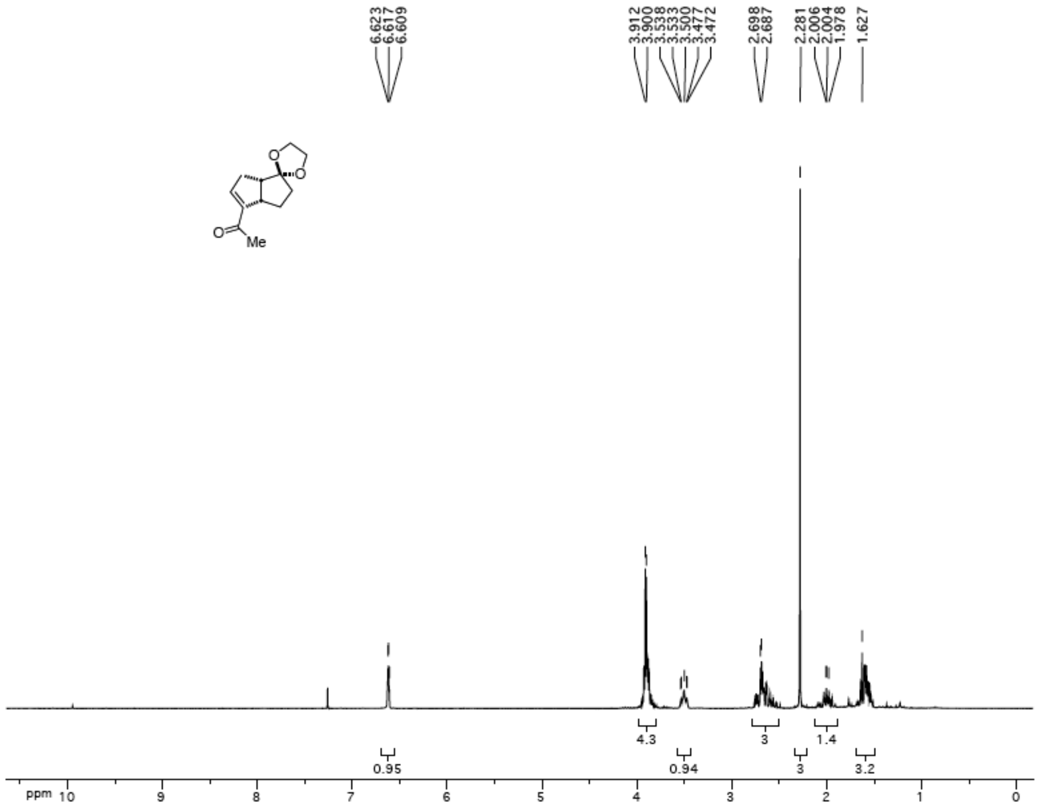


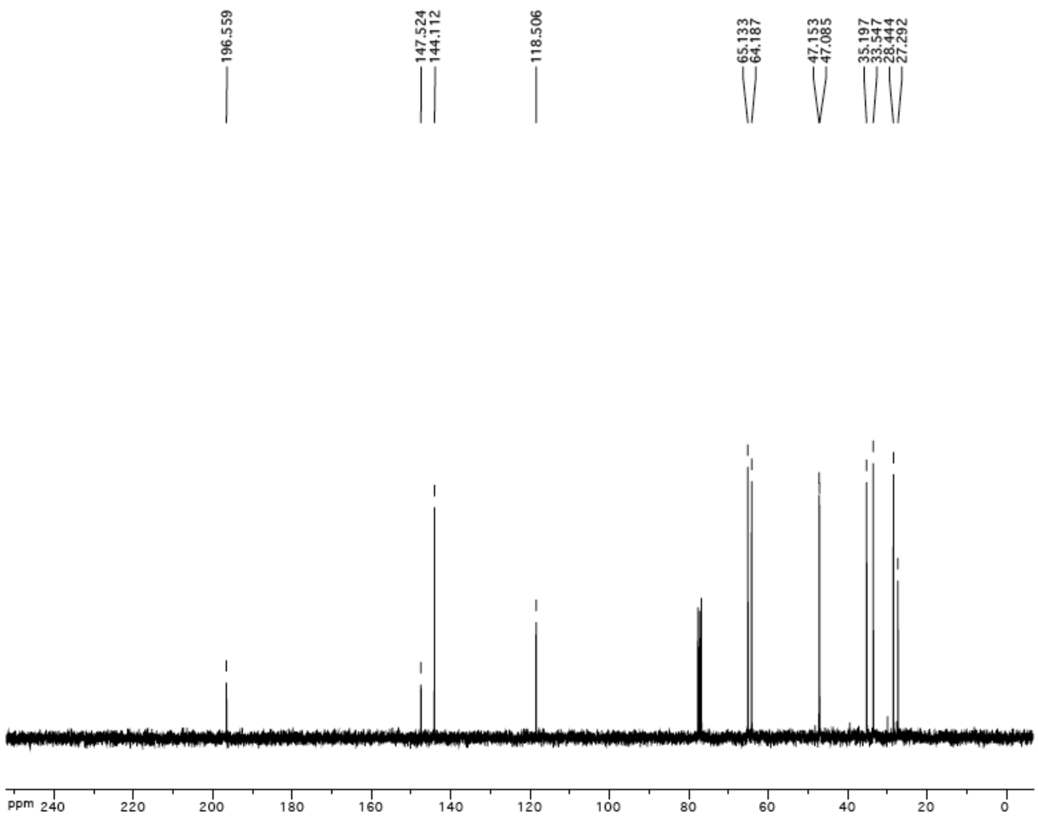
^{1}H and ^{13}C NMR spectra for **3.17**



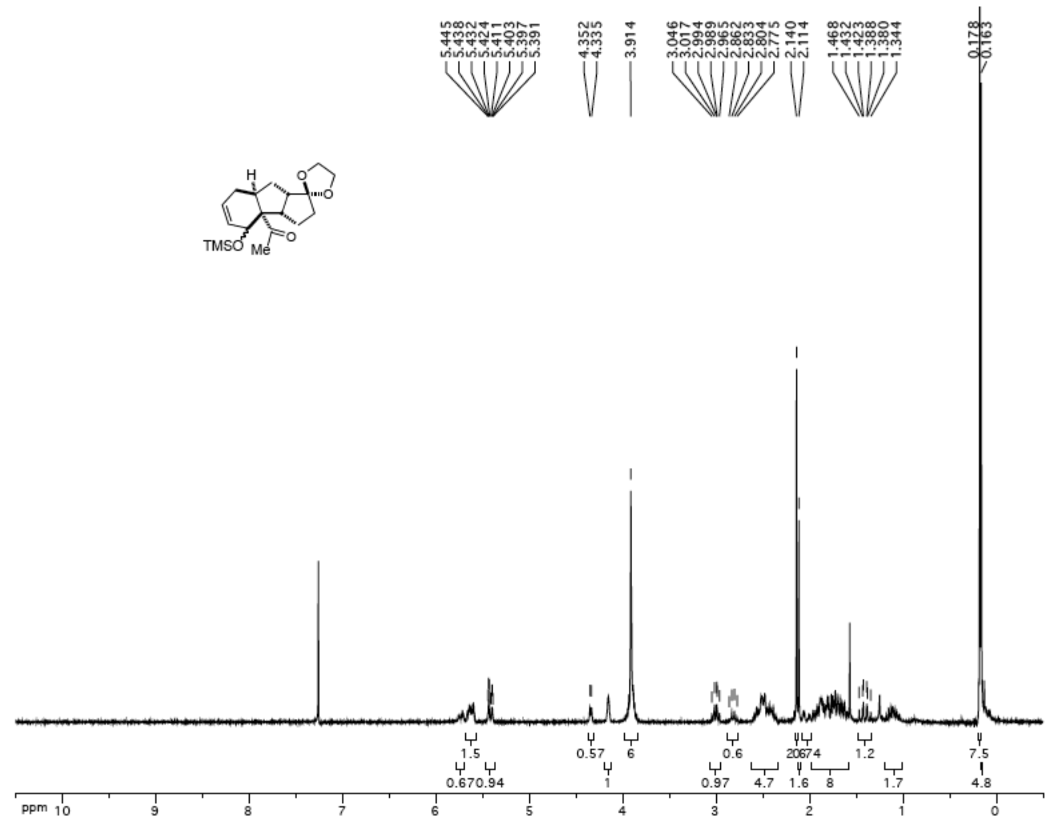


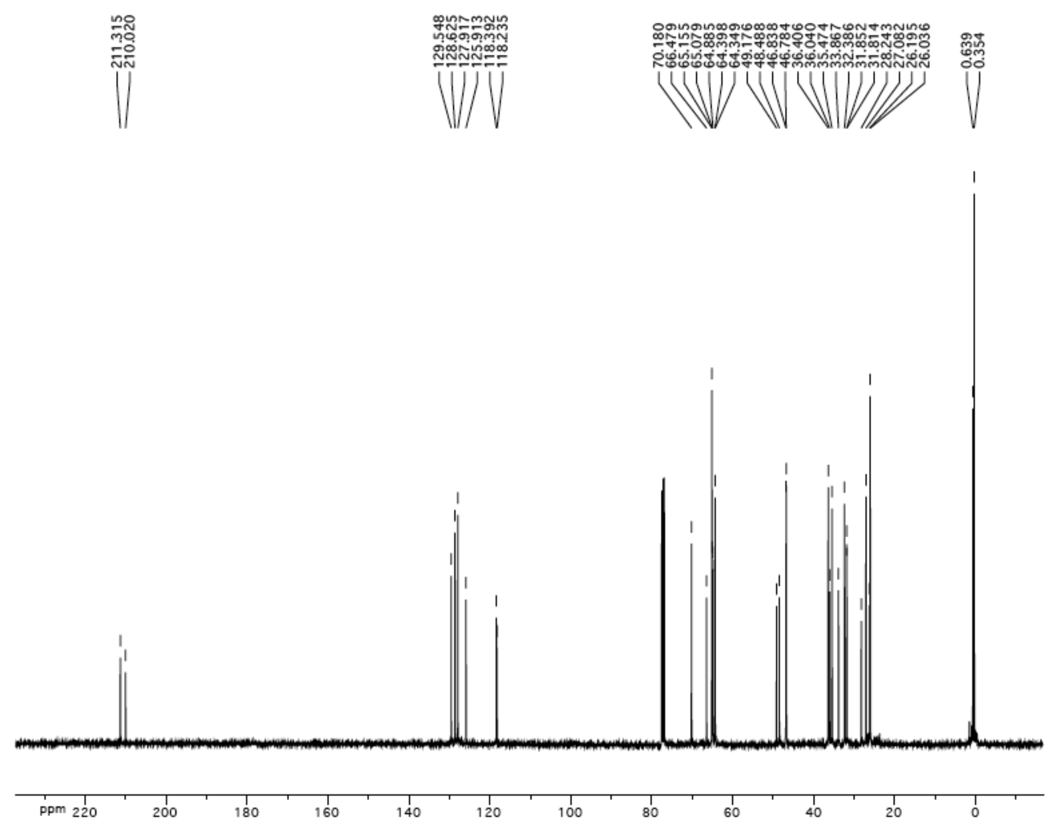
^{1}H and ^{13}C NMR spectra for **3.18**



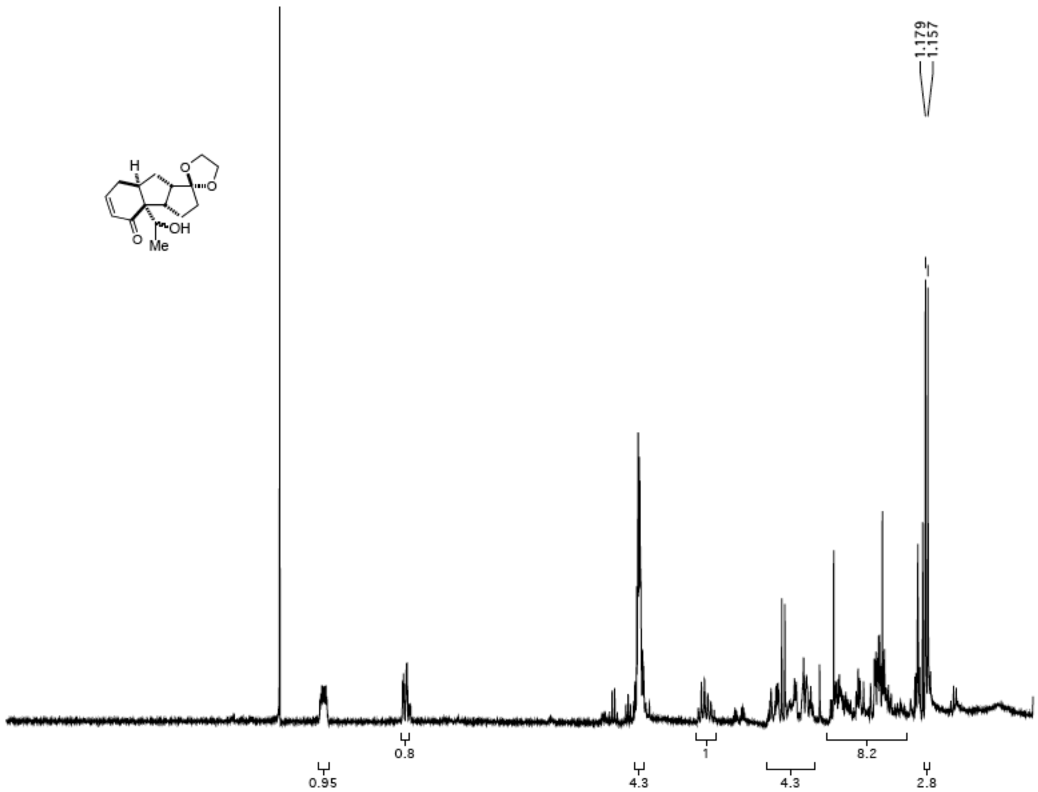


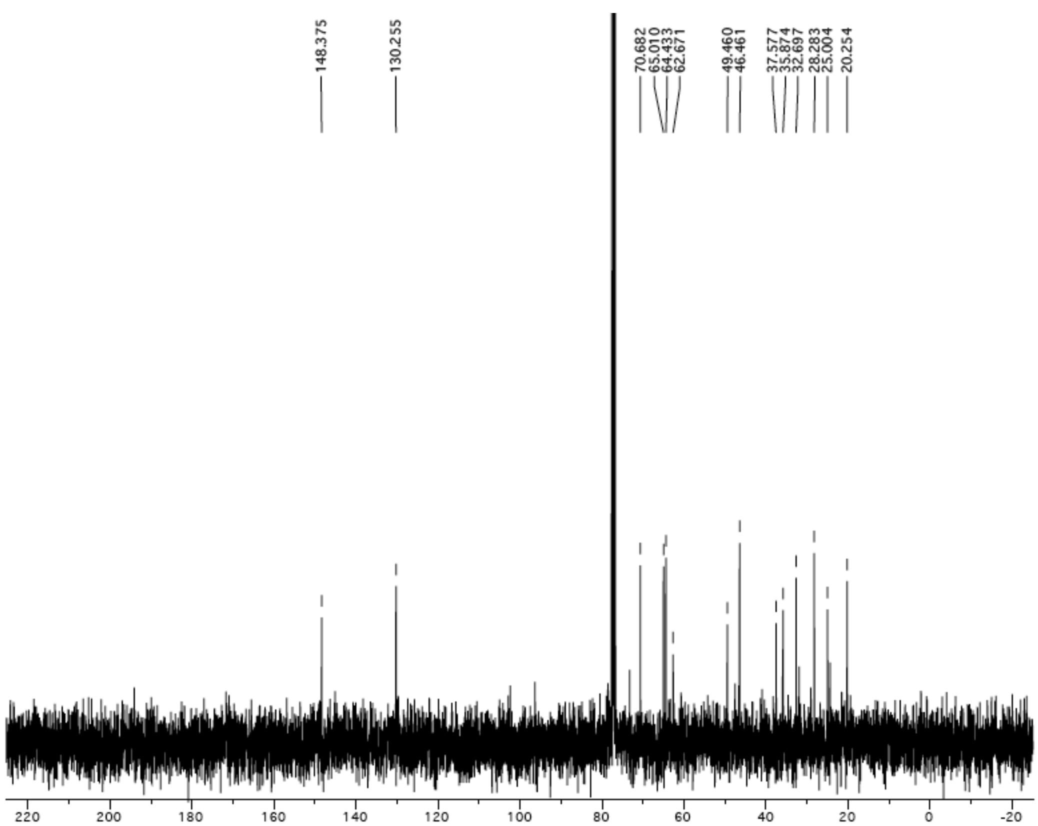
^{1}H and ^{13}C NMR spectra for **3.22**



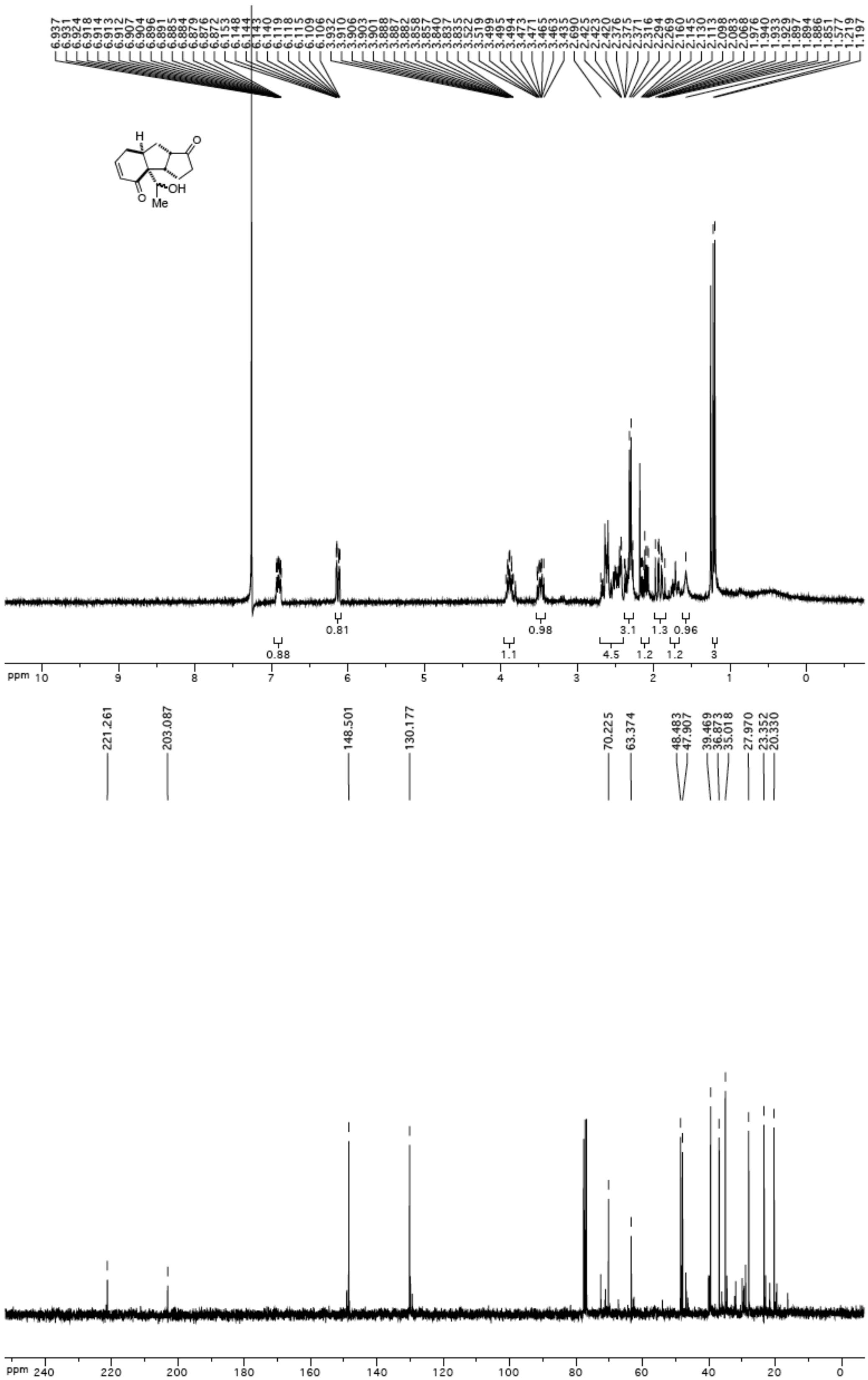


^{1}H and ^{13}C NMR spectra for **3.31**





[1]H and [13]C NMR spectra for **3.32**



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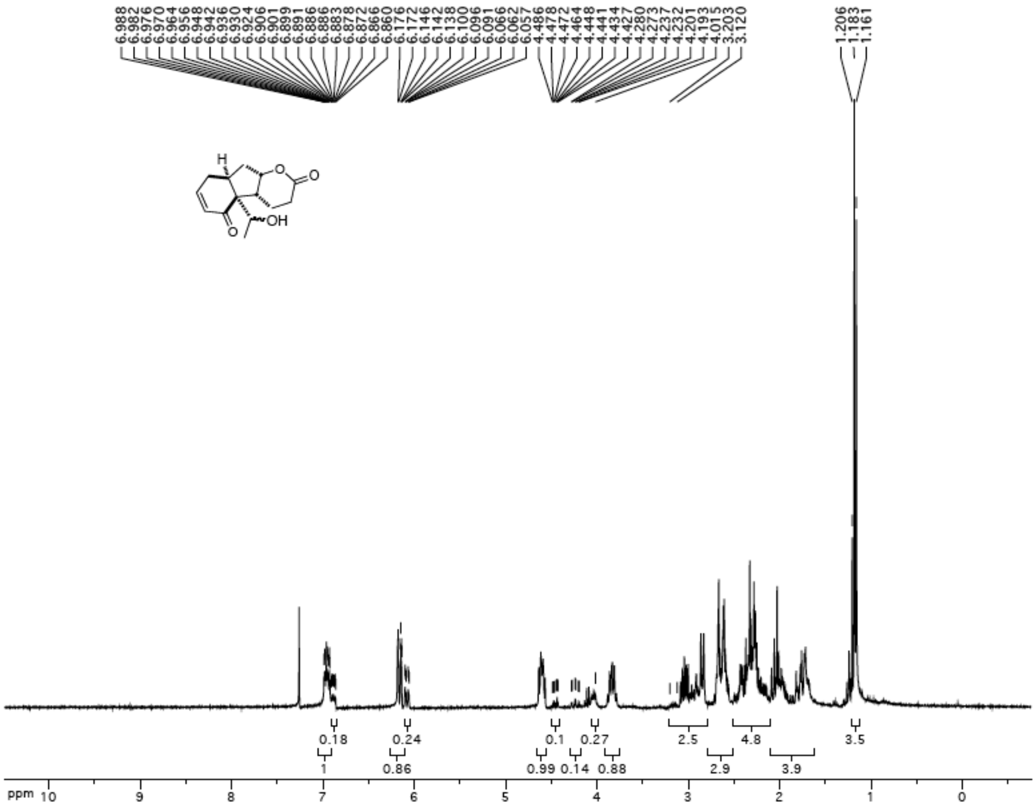
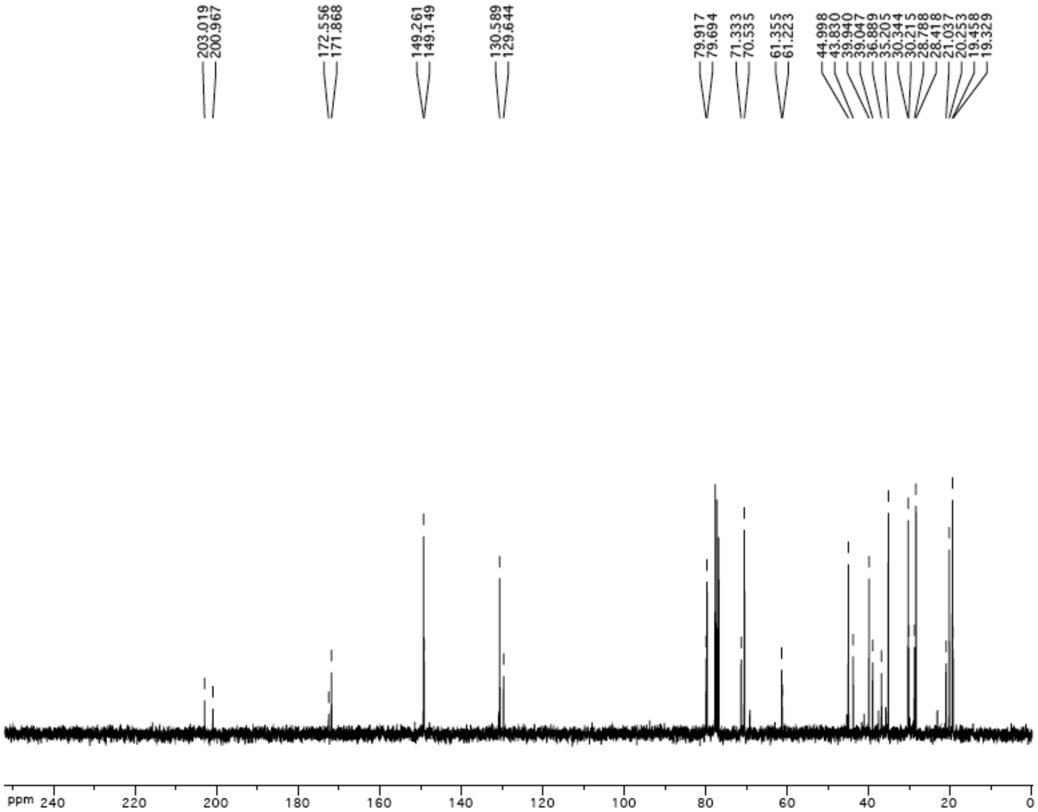
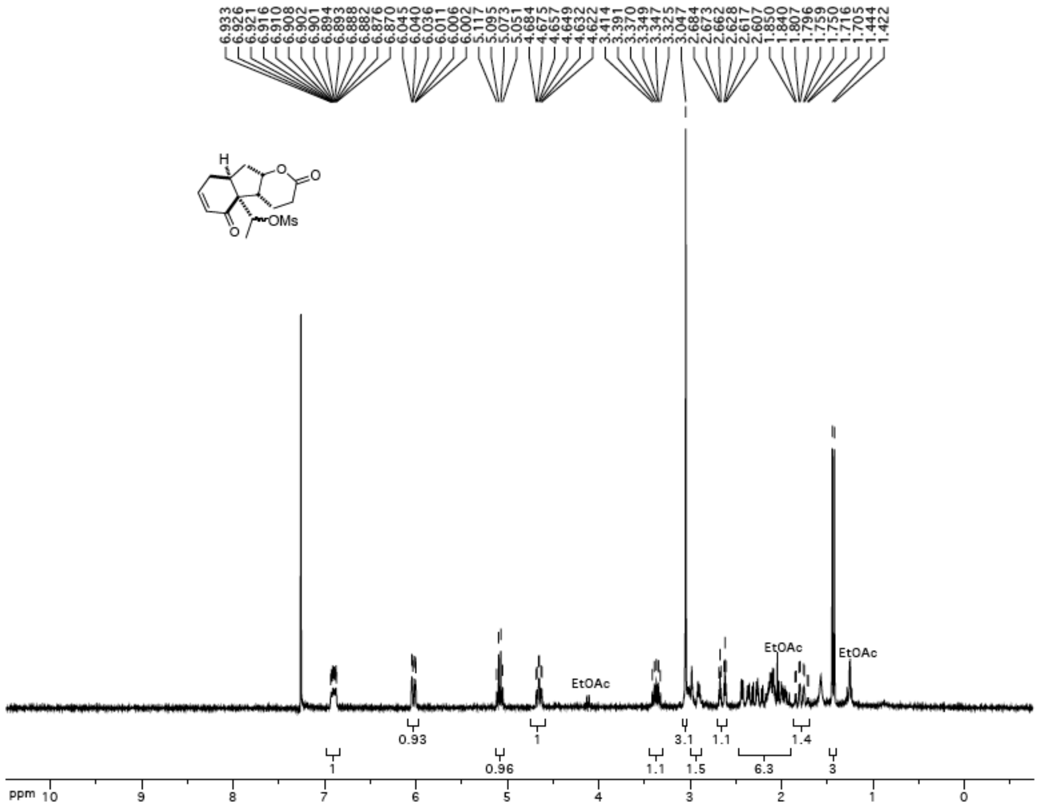
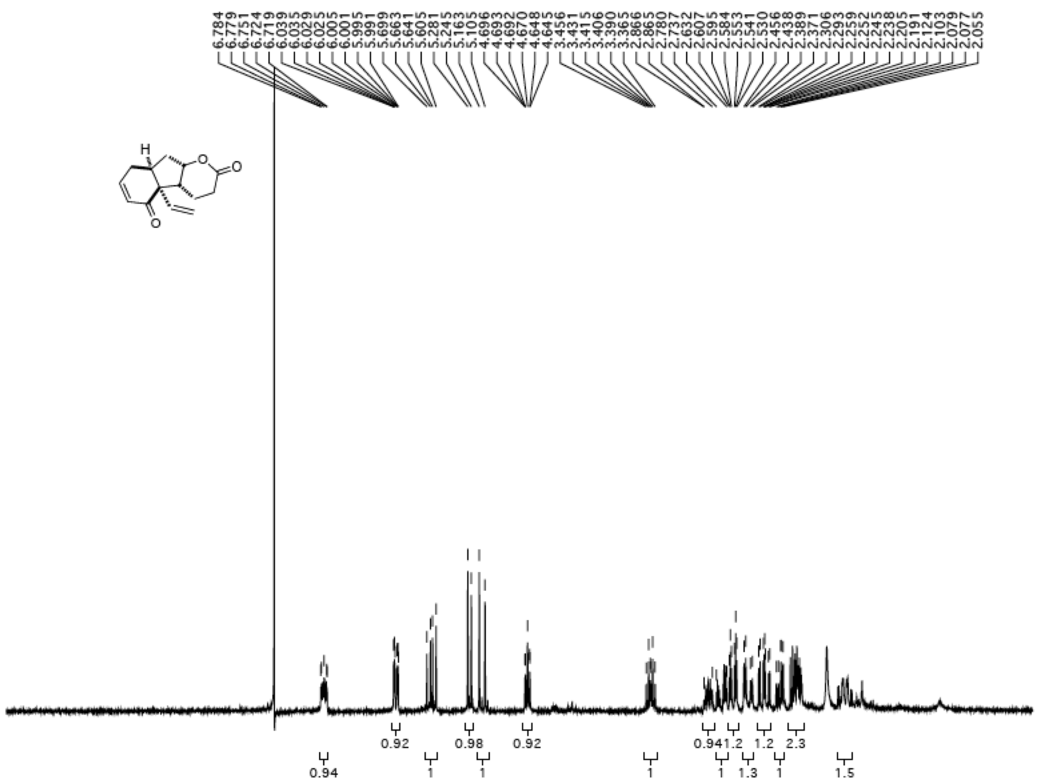


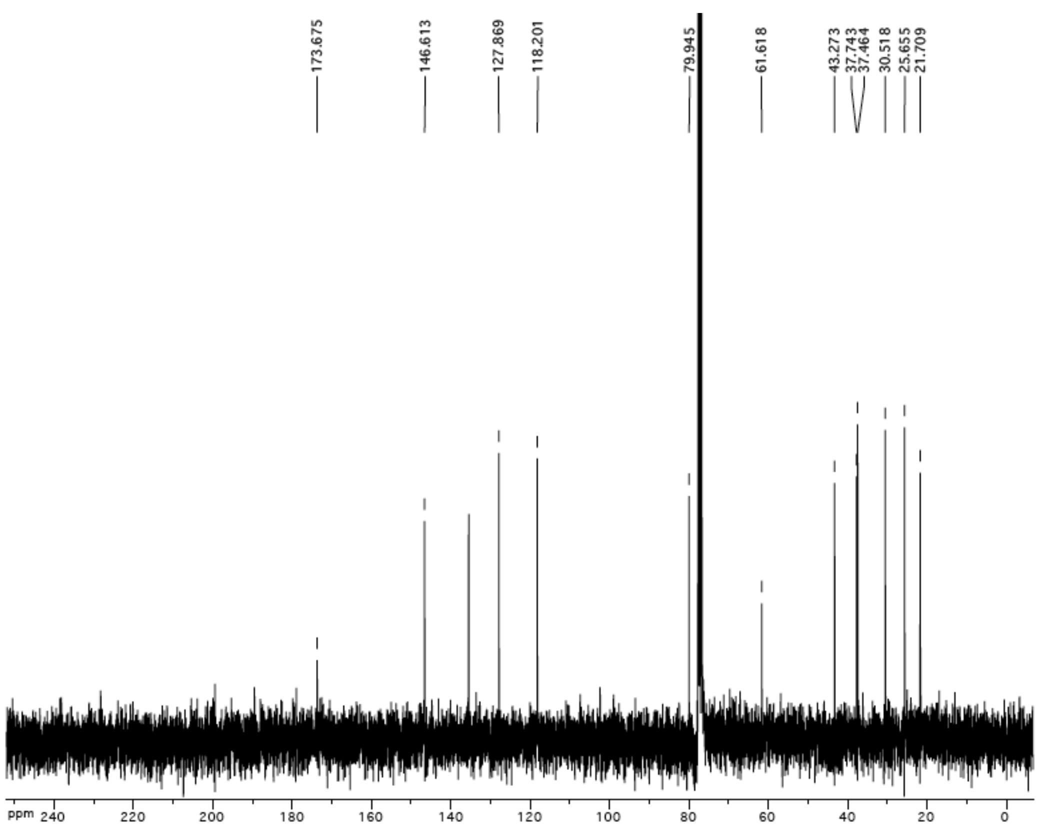


[1]H NMR spectrum for **3.35**

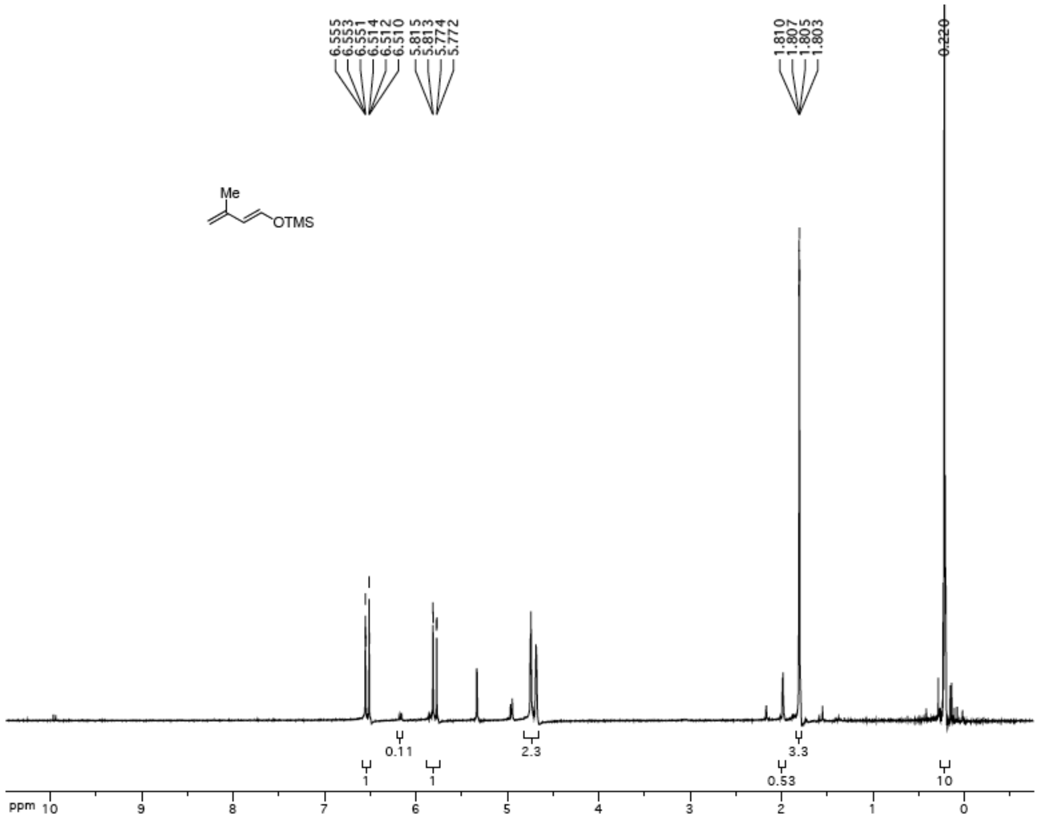


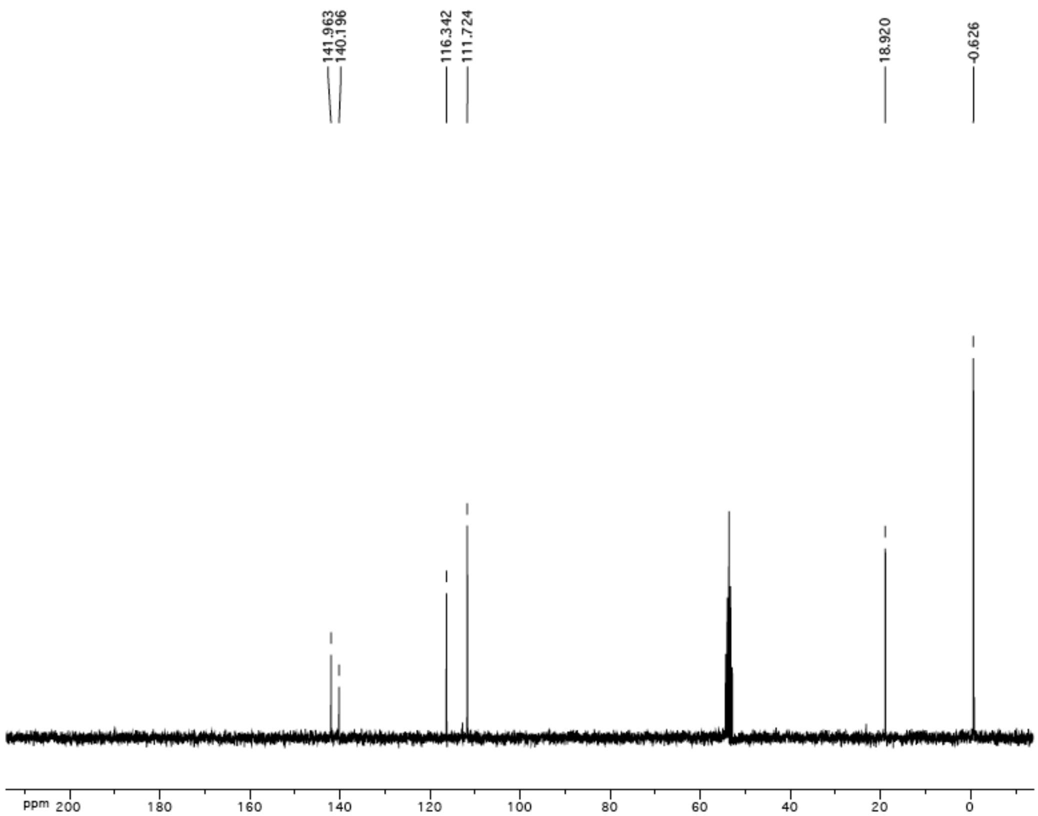
[1]H and [13]C NMR spectra for **3.34**



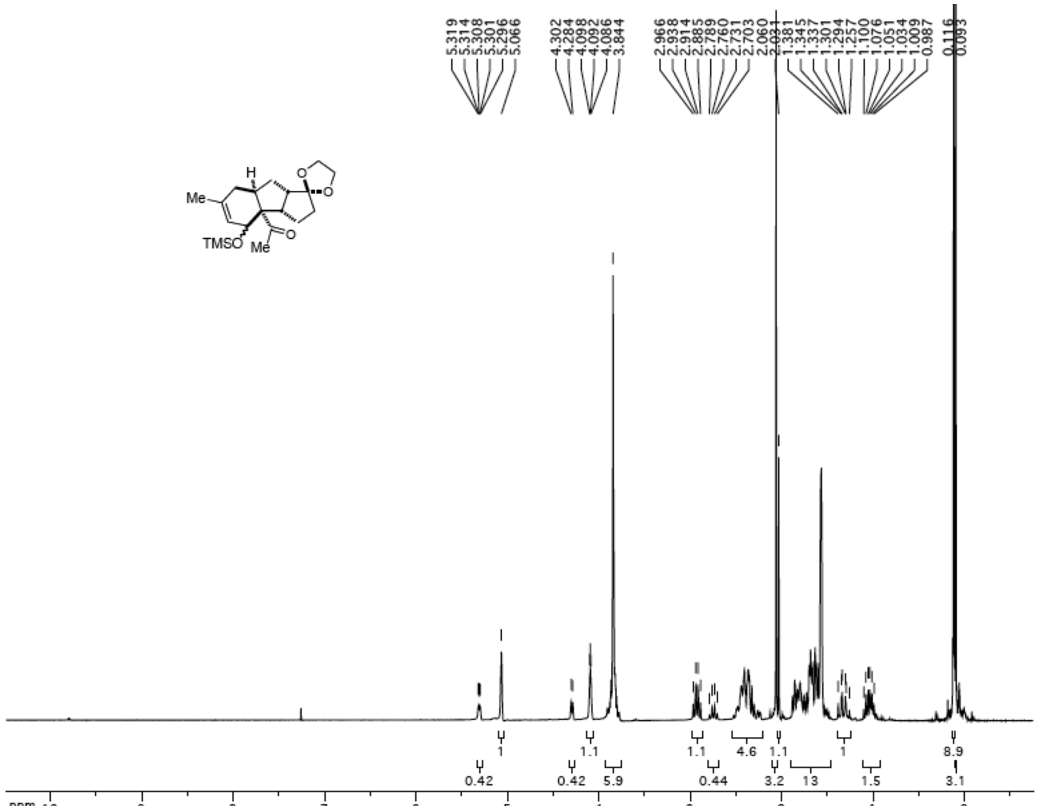


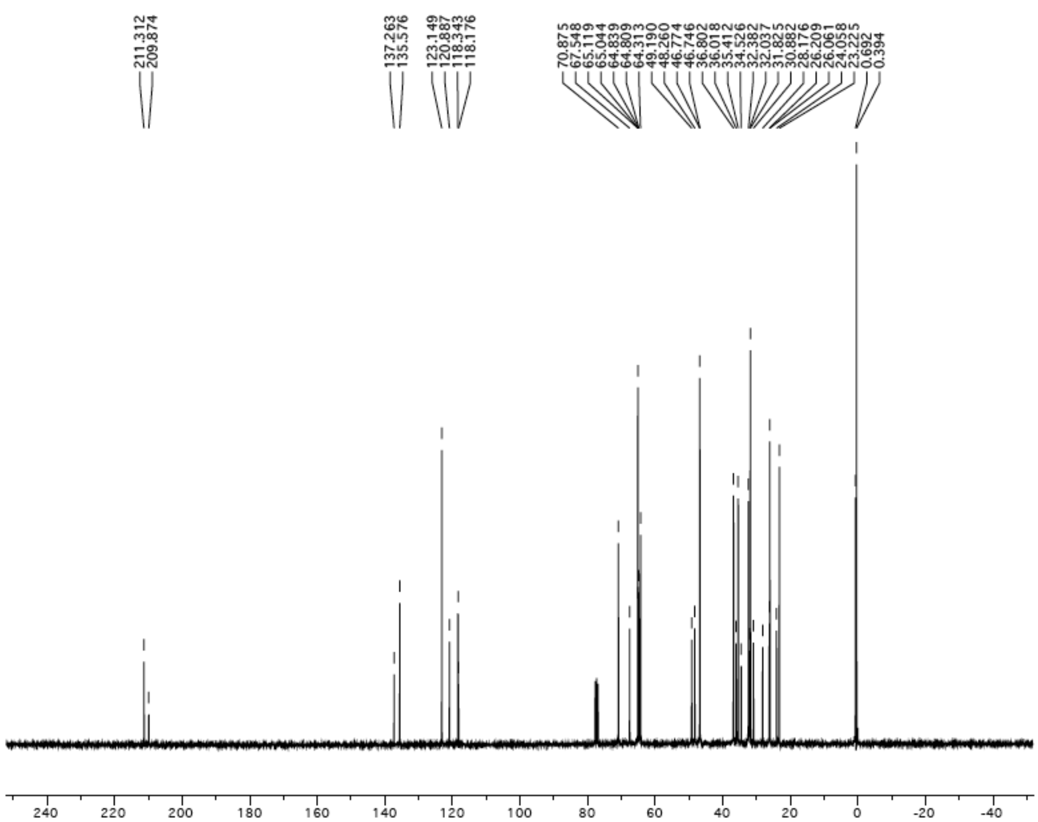
[1]H and [13]C NMR spectra for **3.43**



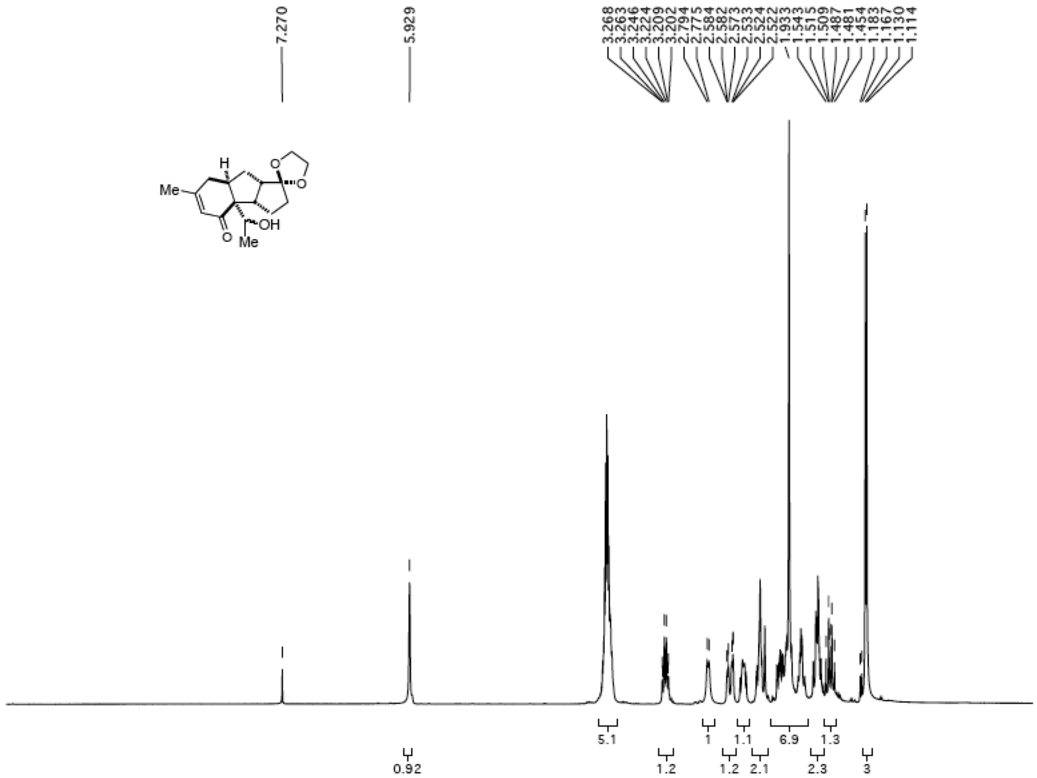


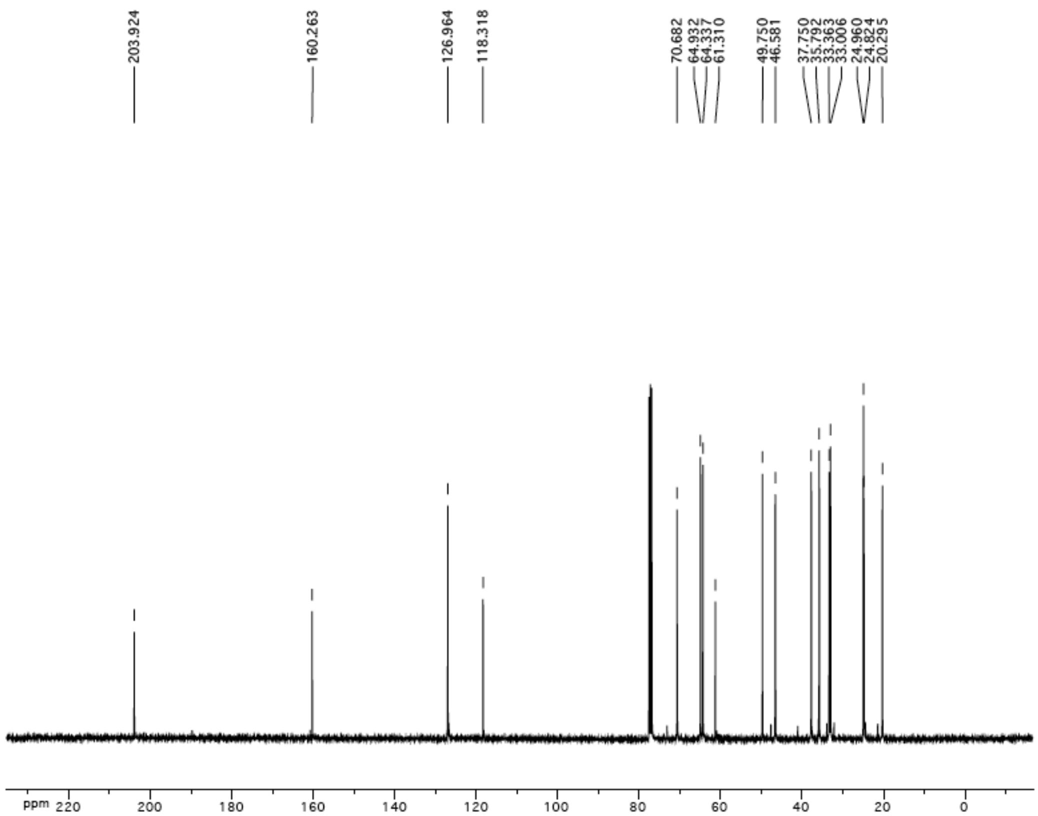
[1]H and [13]C NMR spectra for **3.44**



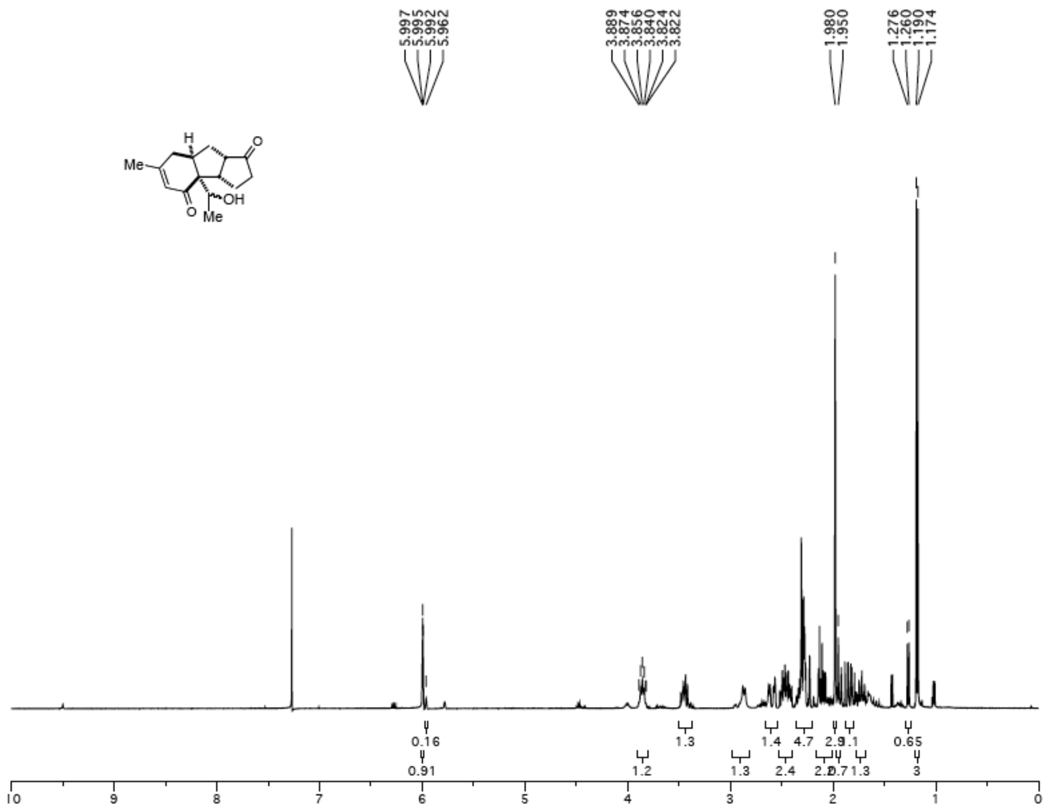


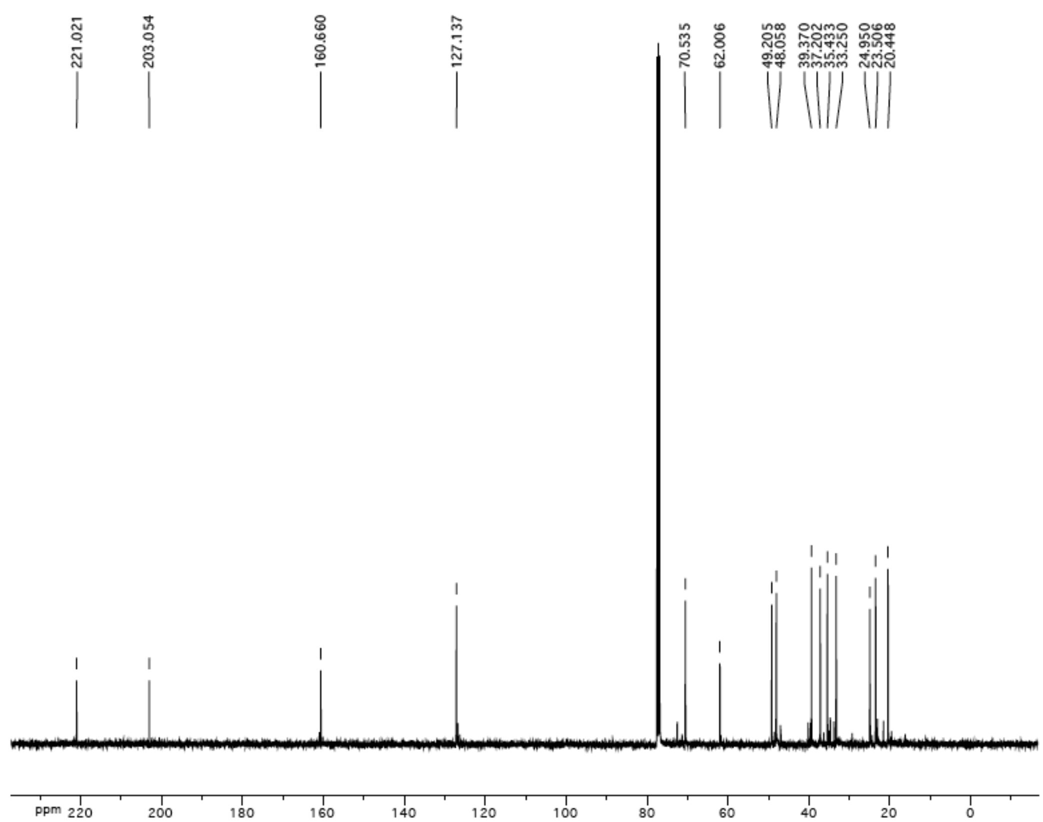
[1]H and [13]C NMR spectra for **3.46**



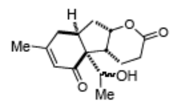


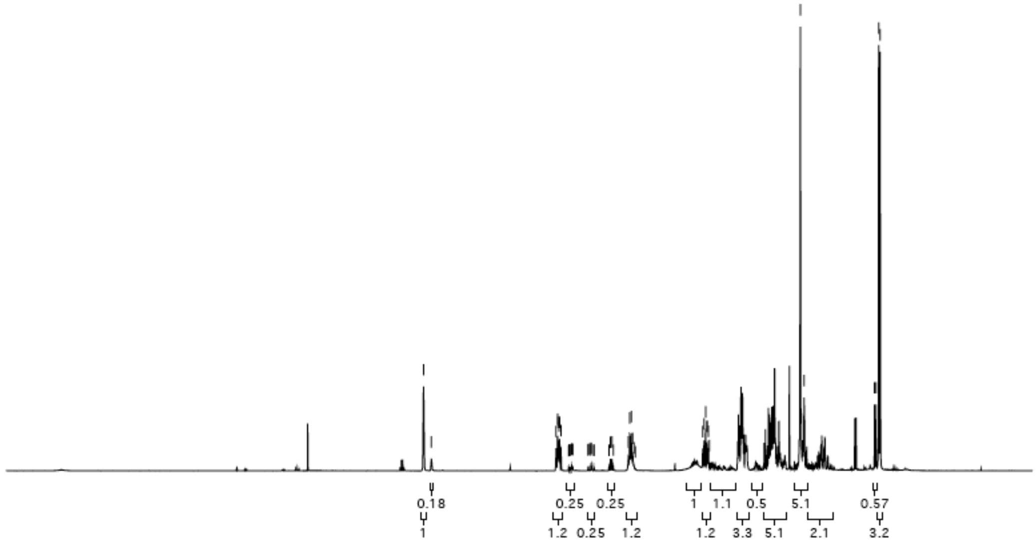
^{1}H and ^{13}C NMR spectra for **3.47**

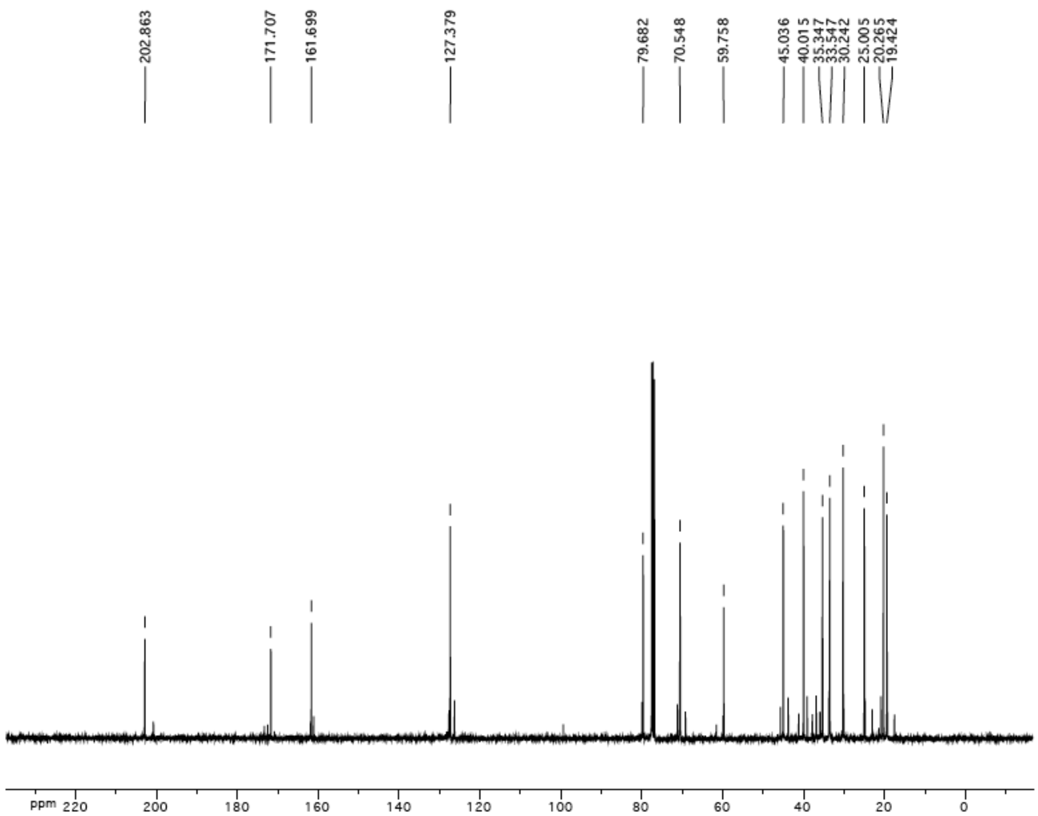




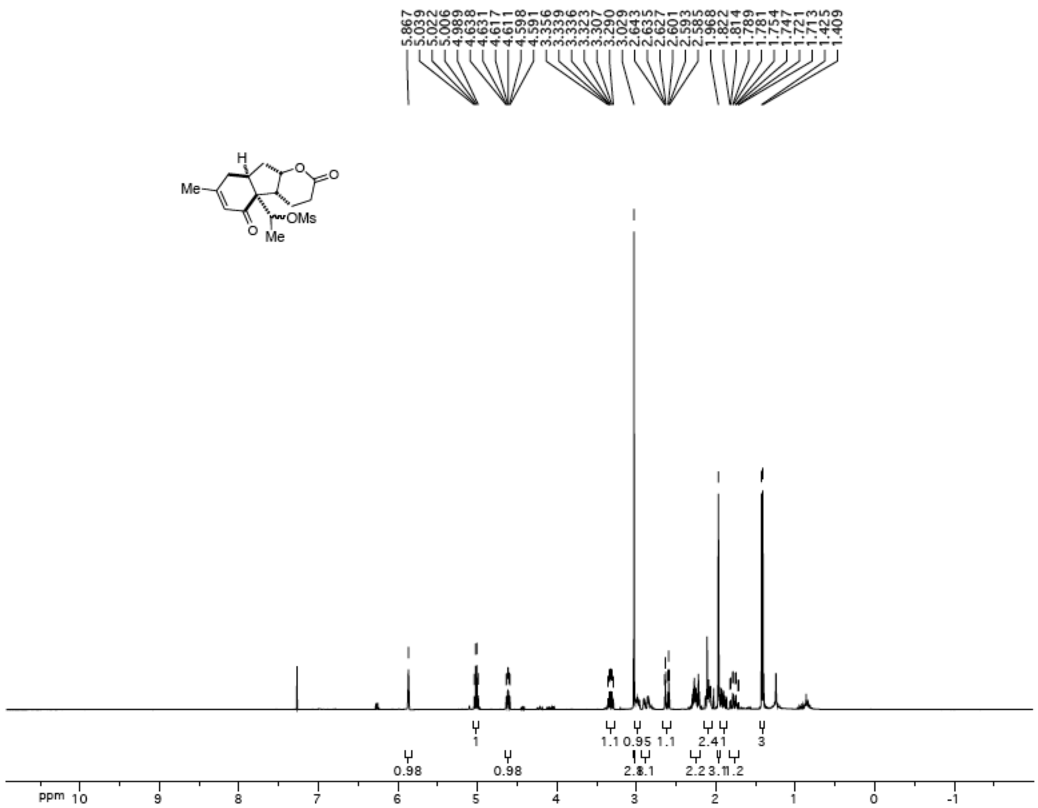
^{1}H and ^{13}C NMR spectra for **3.48**

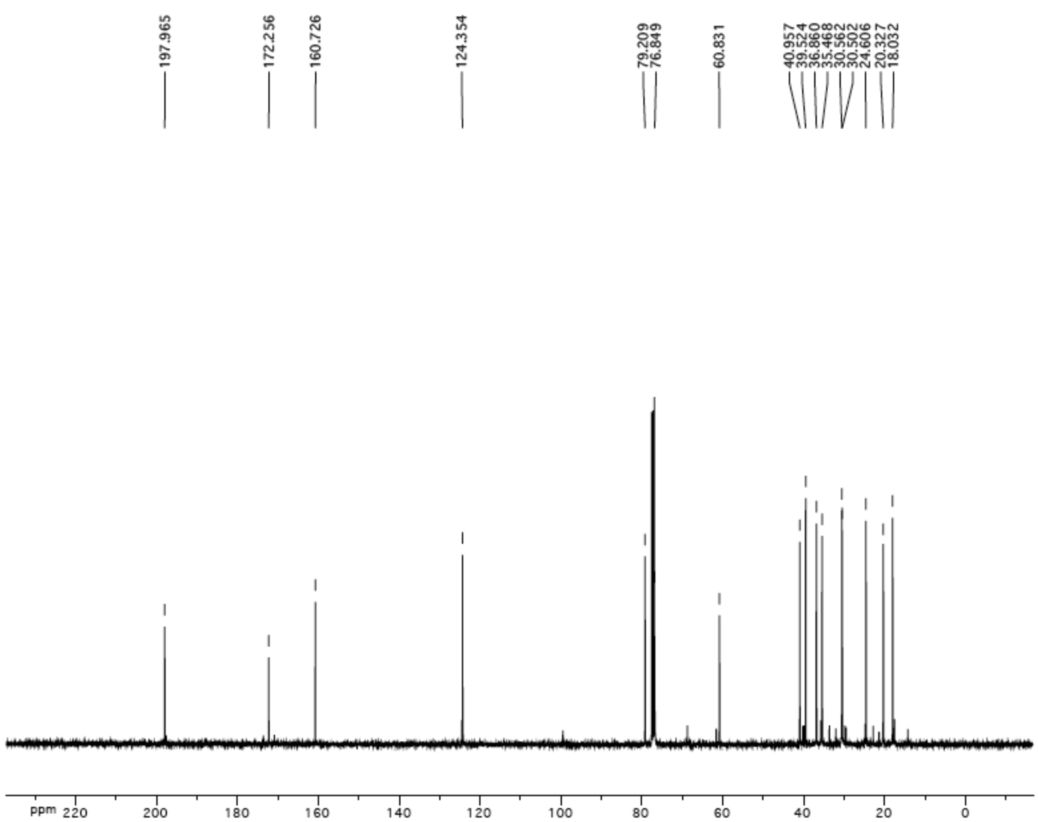




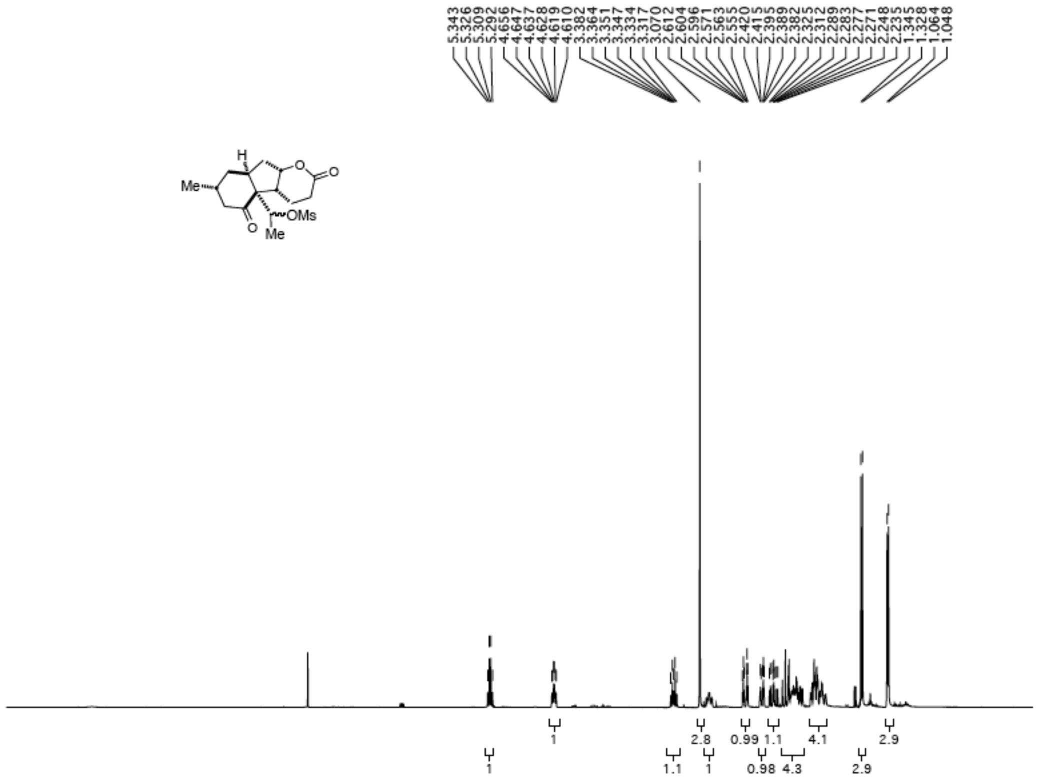


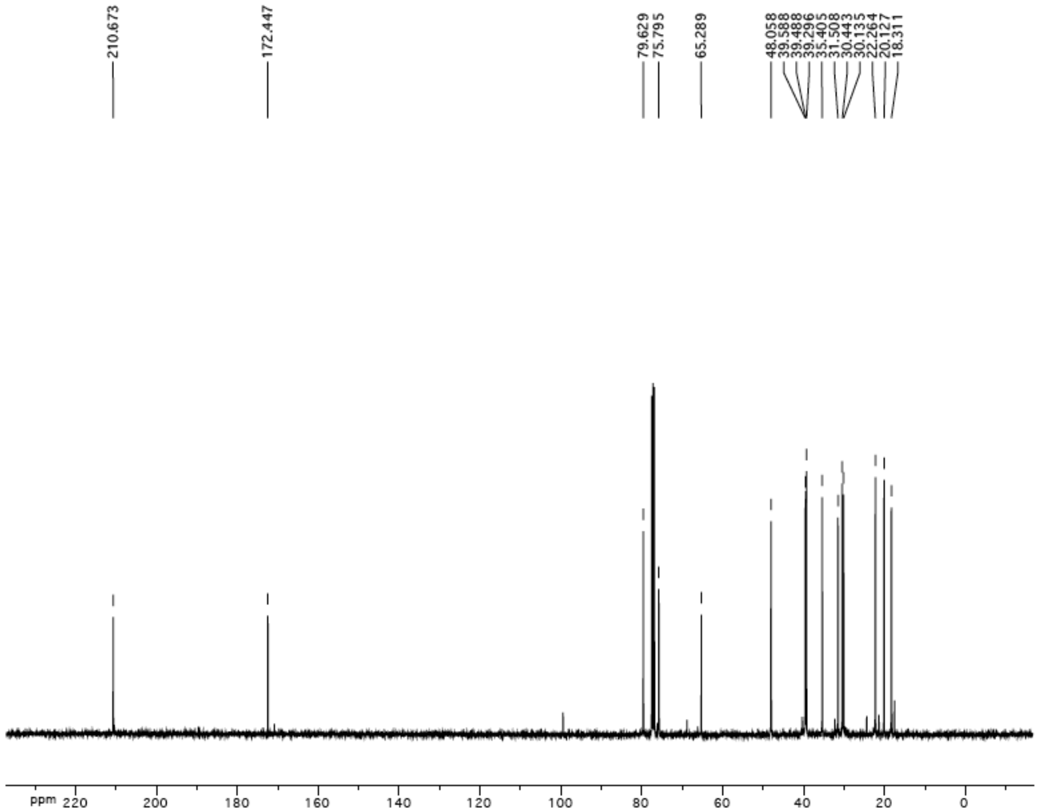
^{1}H and ^{13}C NMR spectra for **3.40**



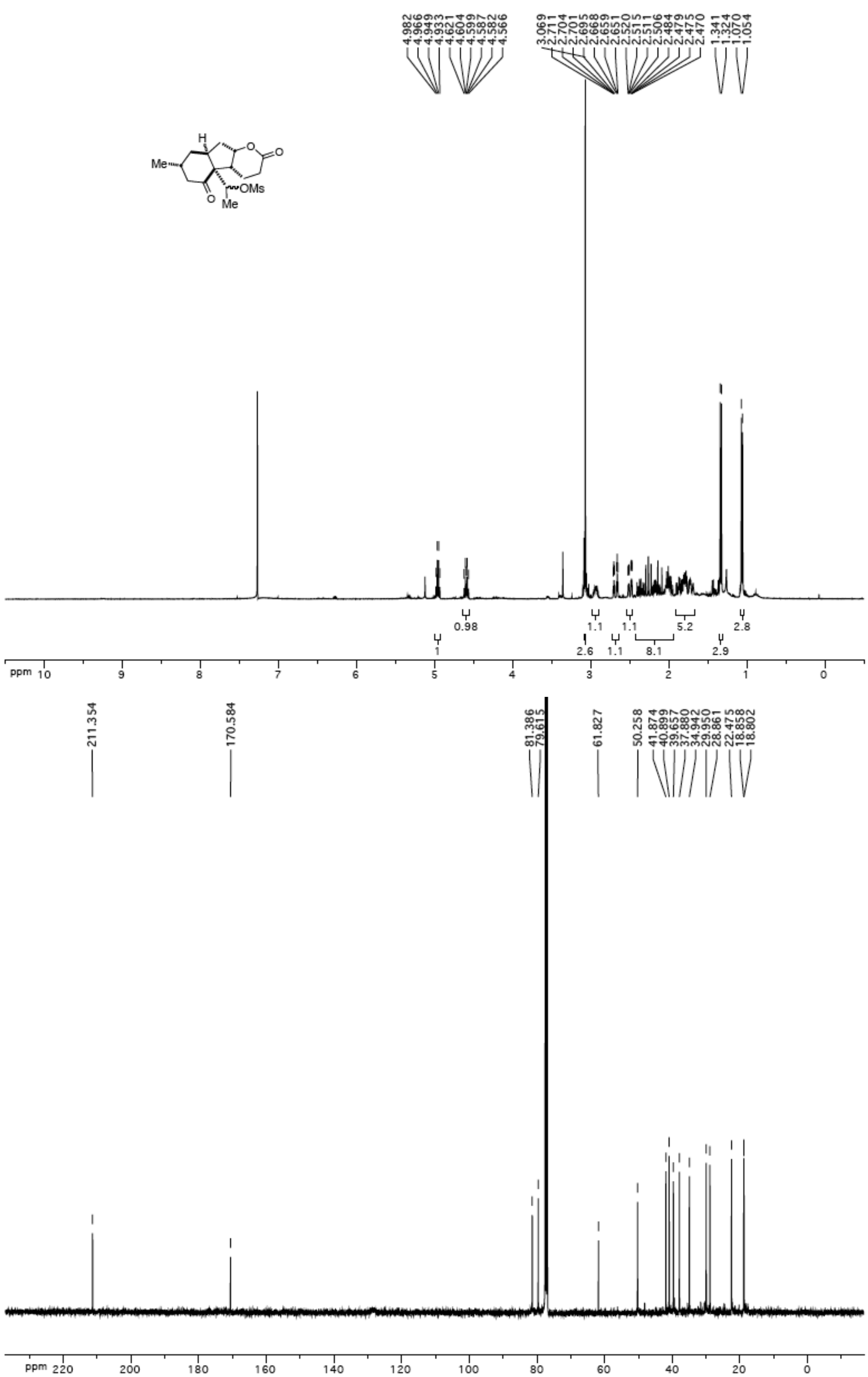


[1]H and [13]C NMR spectra for **3.41** (major diastereomer)

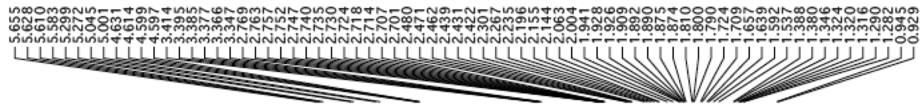


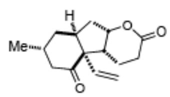


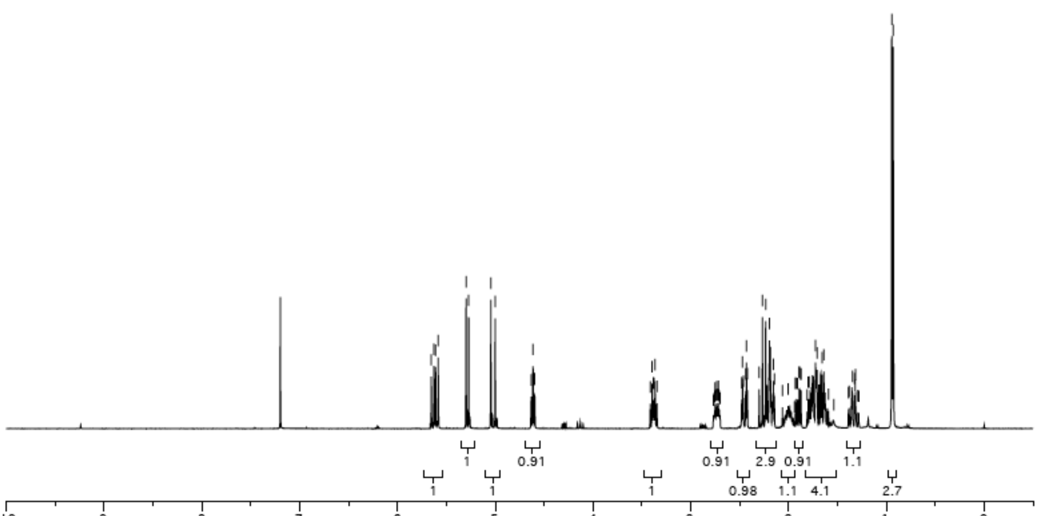
^{1}H and ^{13}C NMR spectra for **3.41** (minor diastereomer)

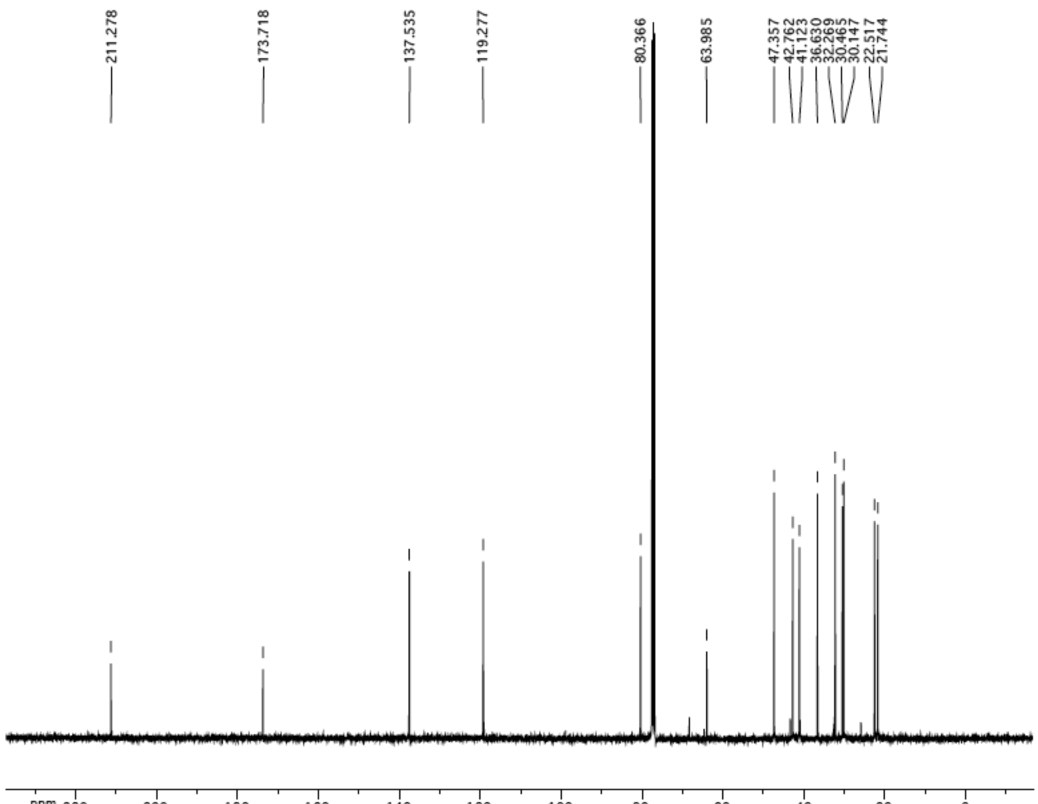


^{1}H and ^{13}C NMR spectra for **3.39**

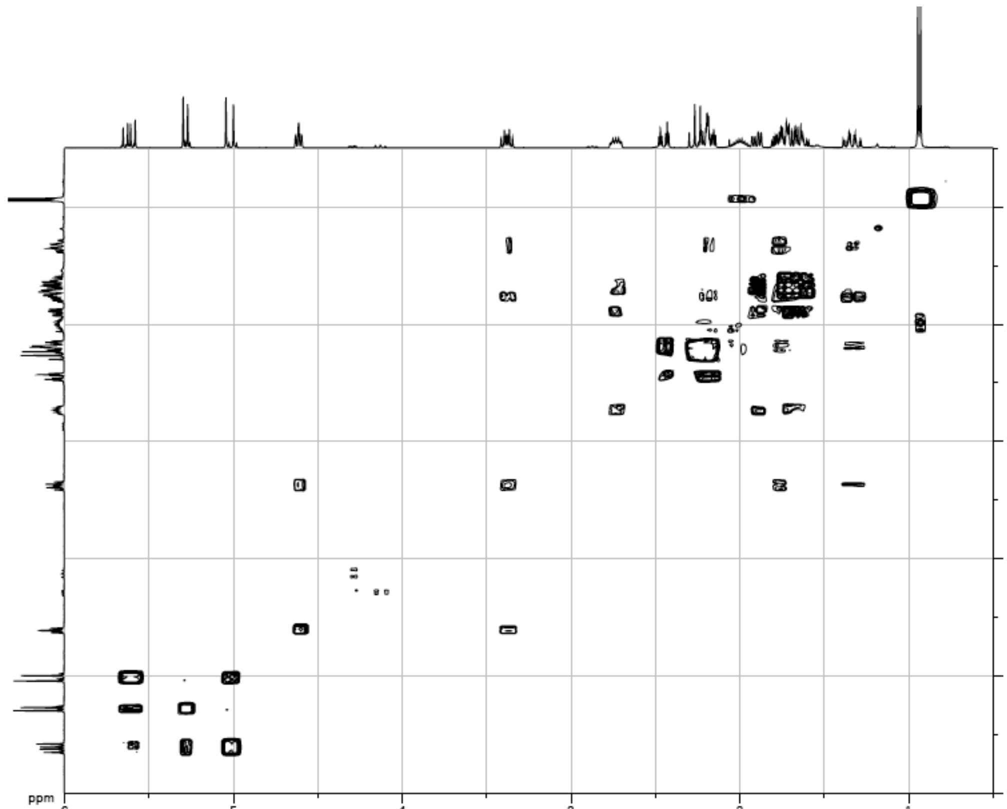


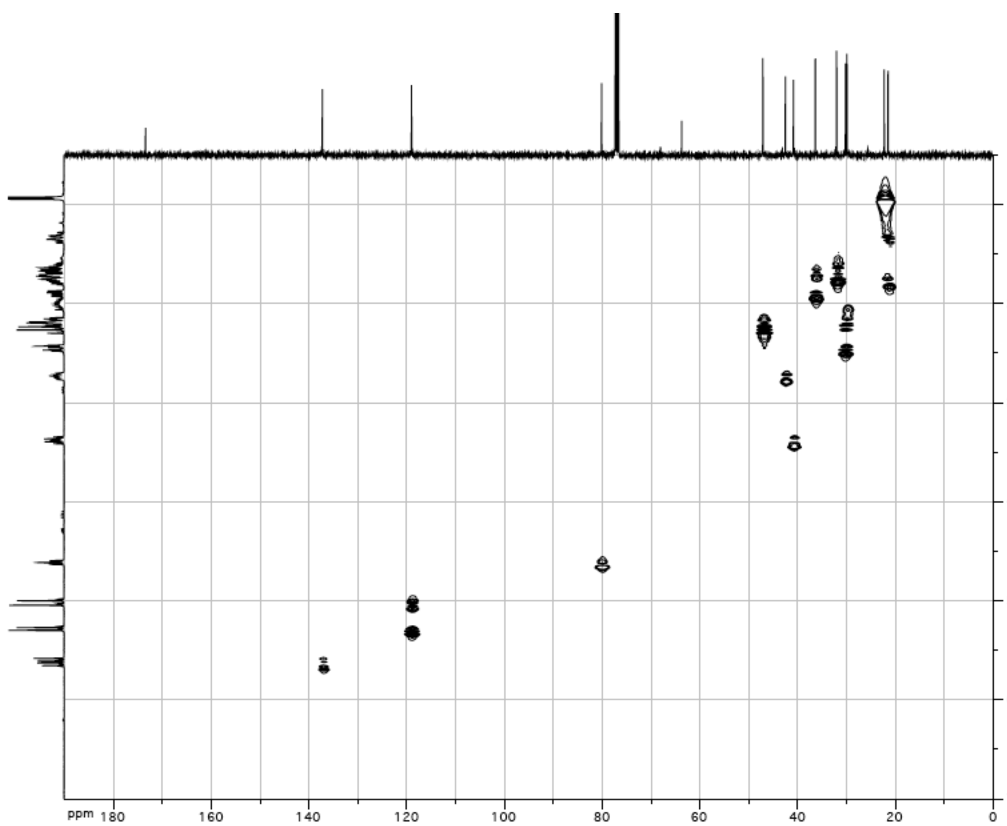




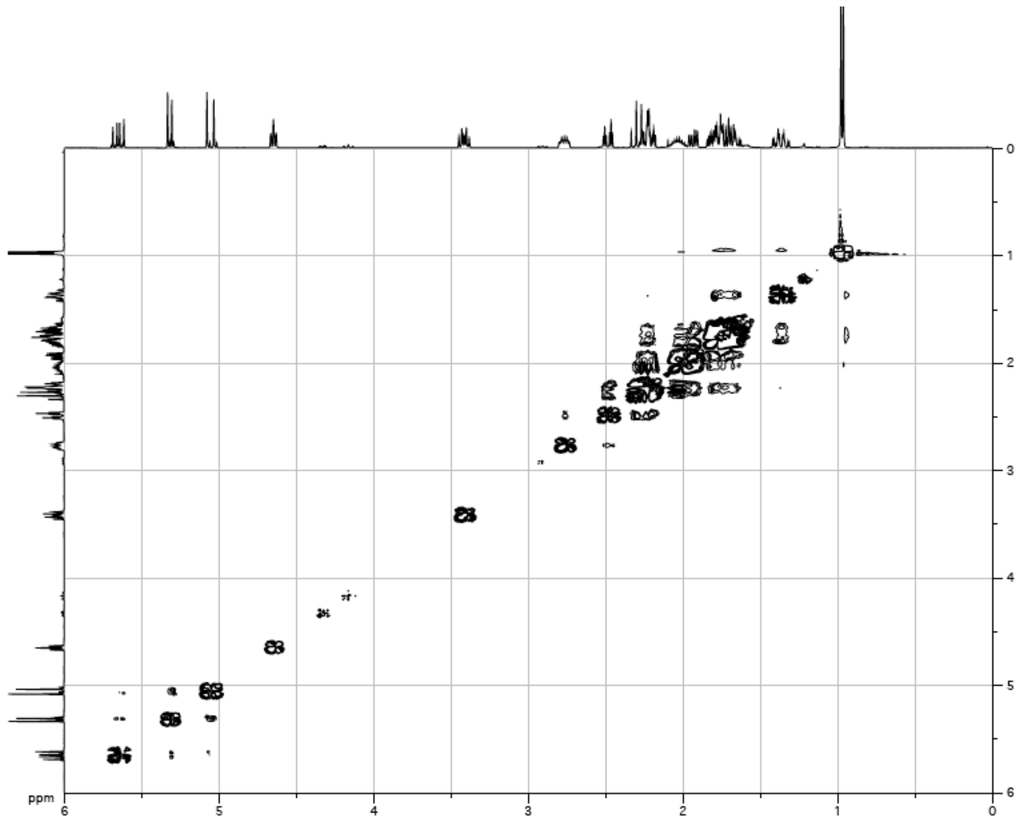


gCOSY and HSQCAD for **3.39**

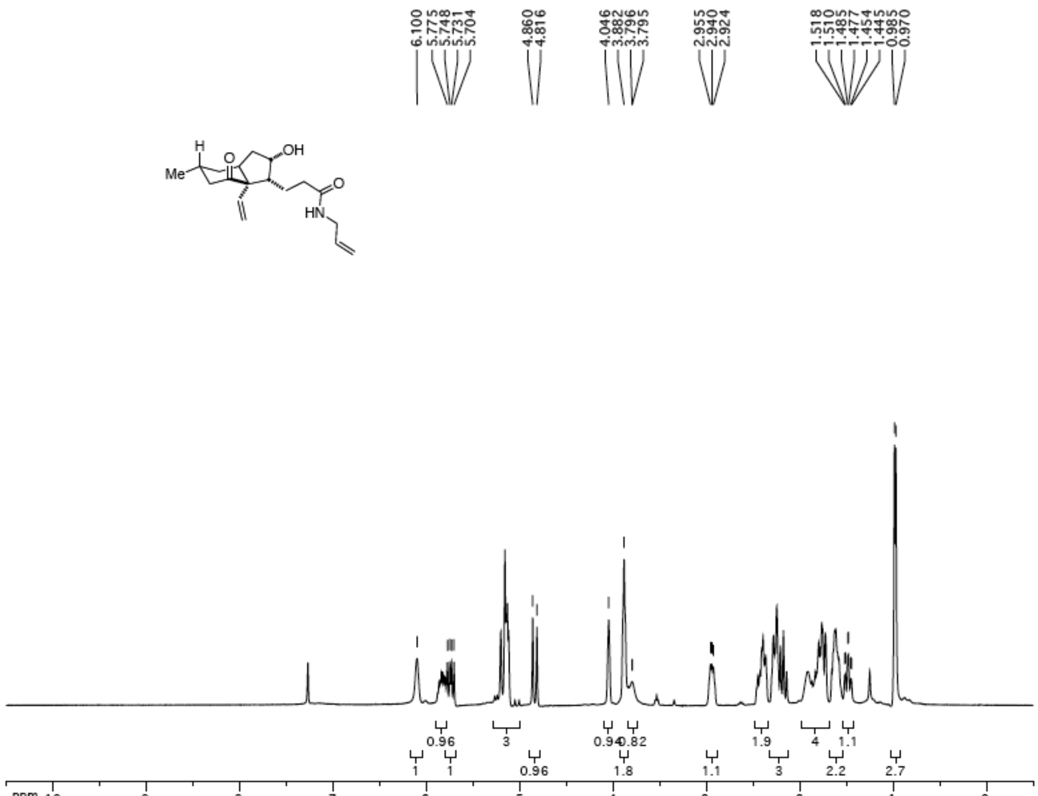


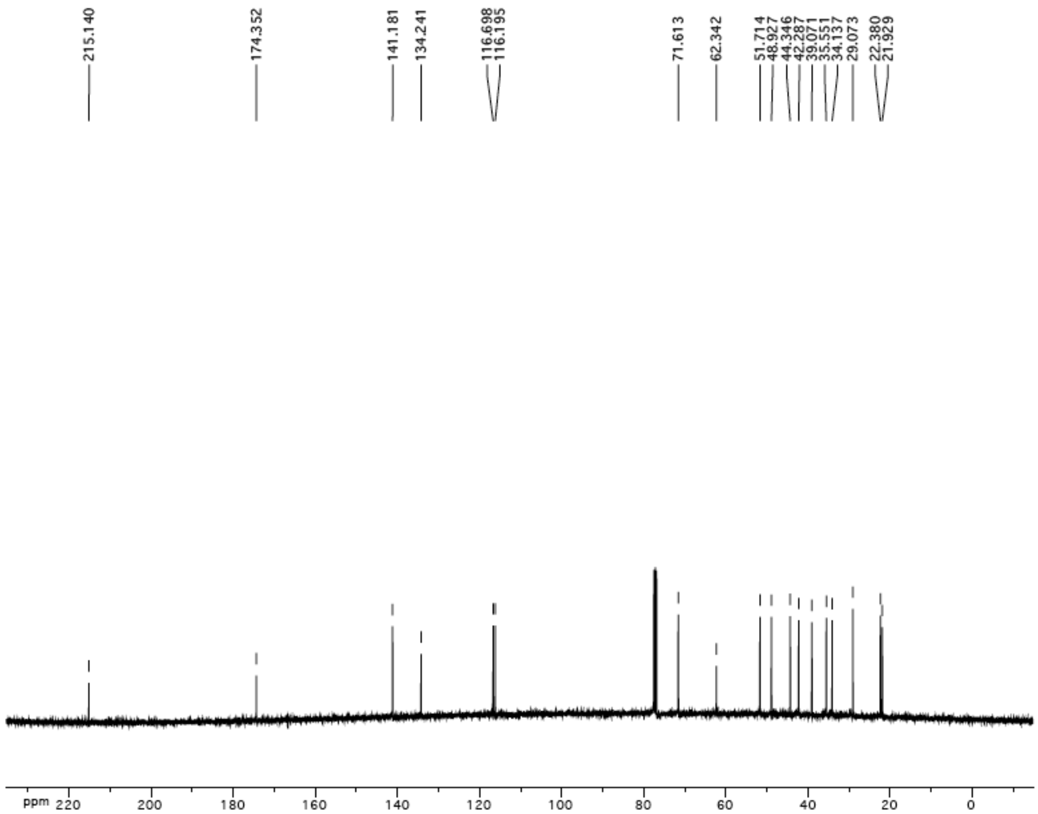


NOESY for **3.39**

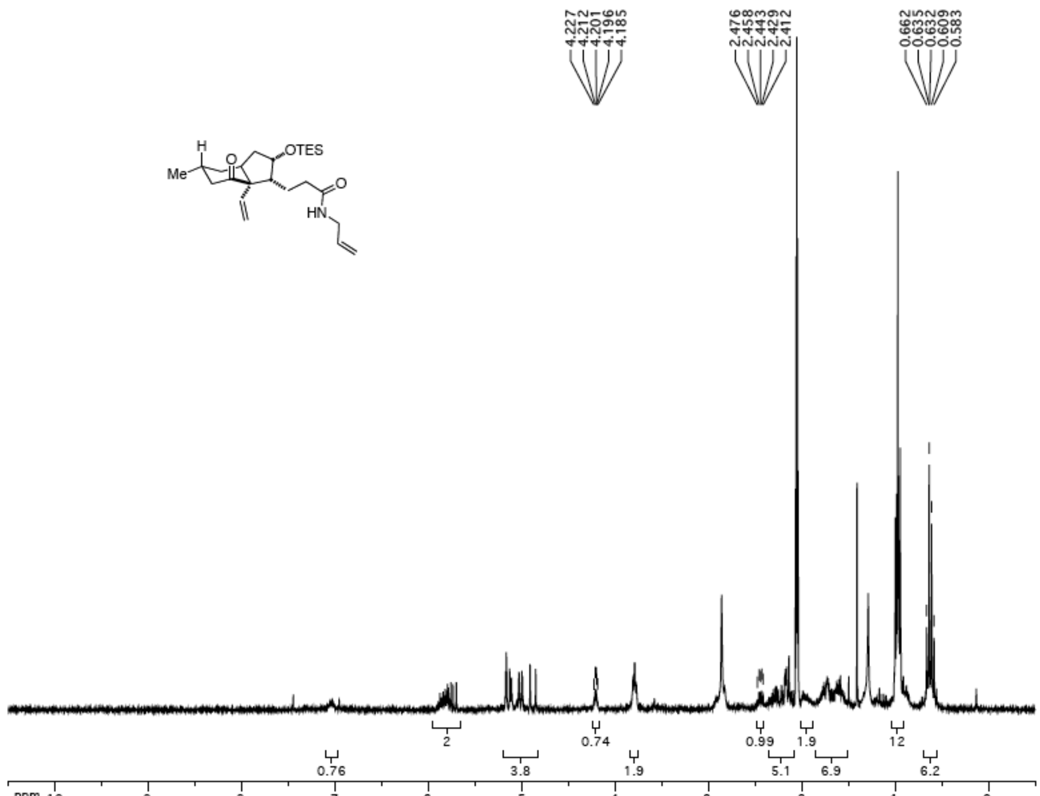


^{1}H and ^{13}C NMR spectra for **3.50**

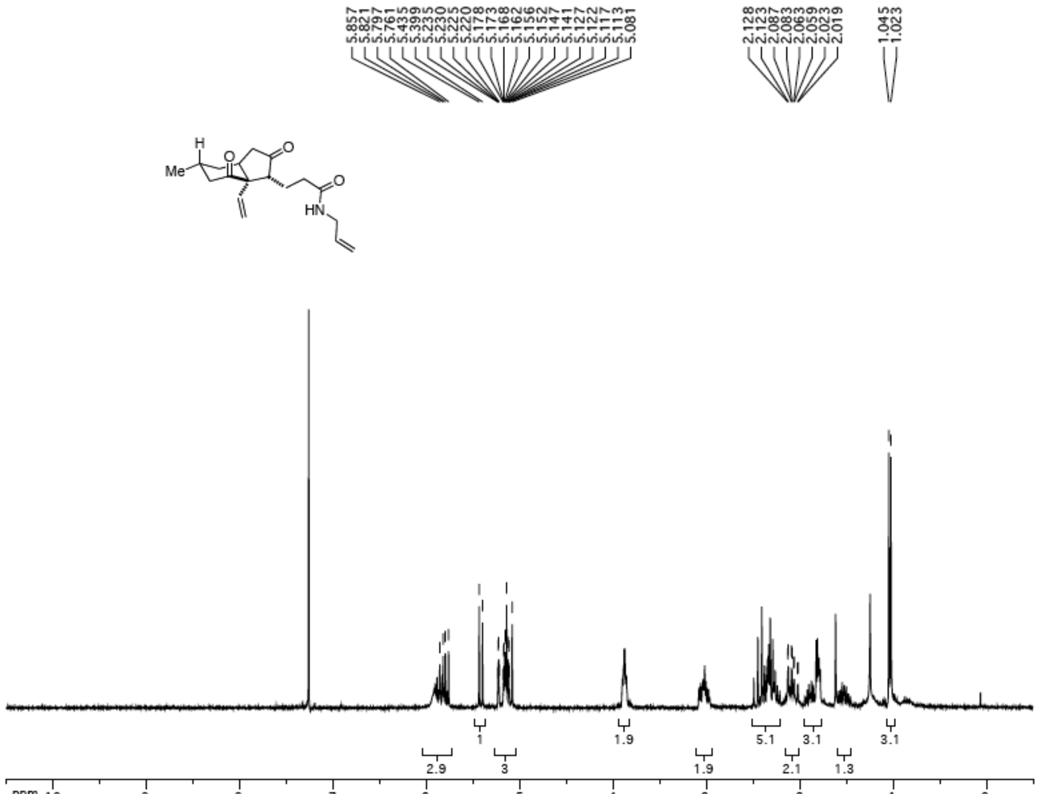




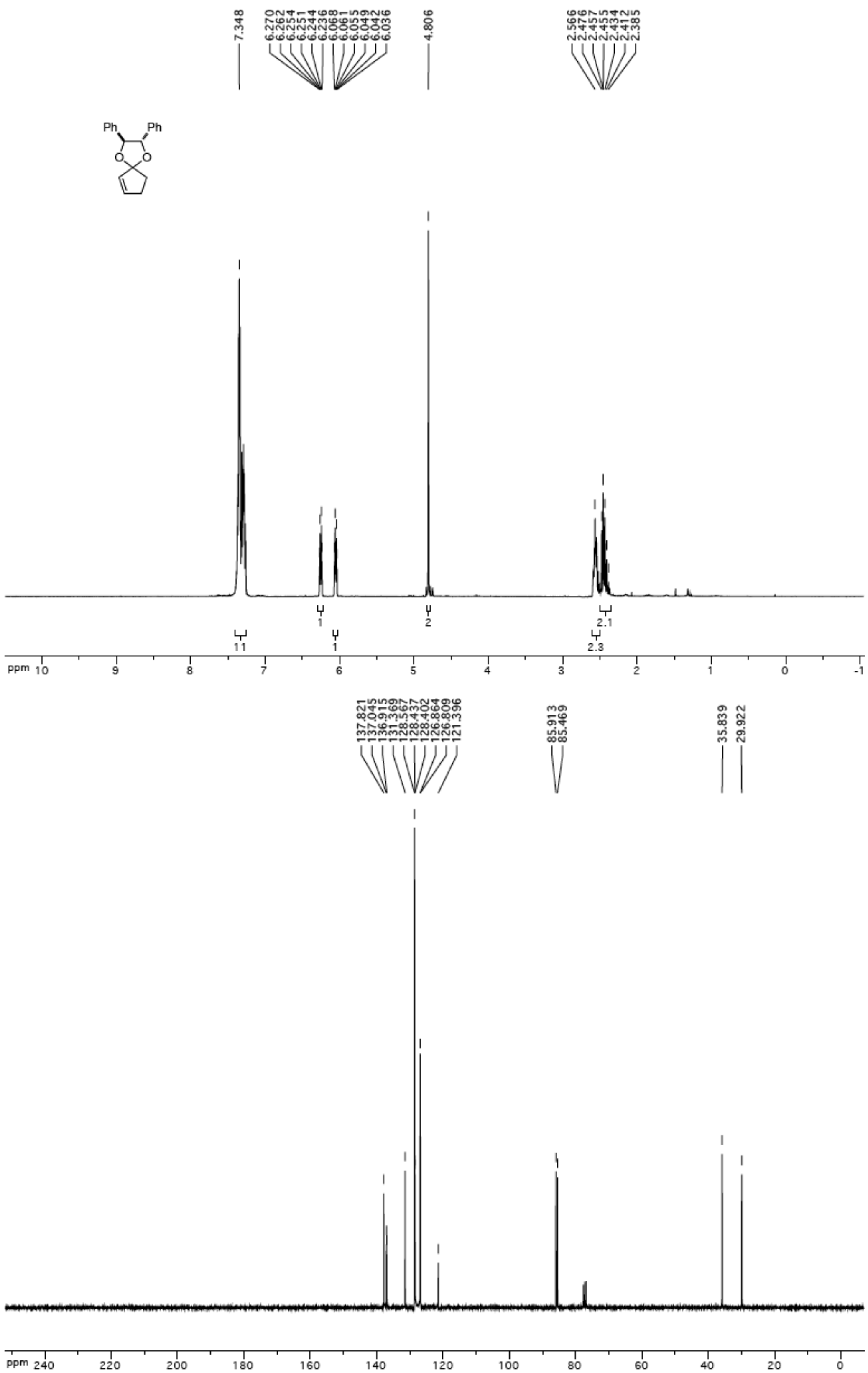
[1]H NMR spectrum for crude **3.58**



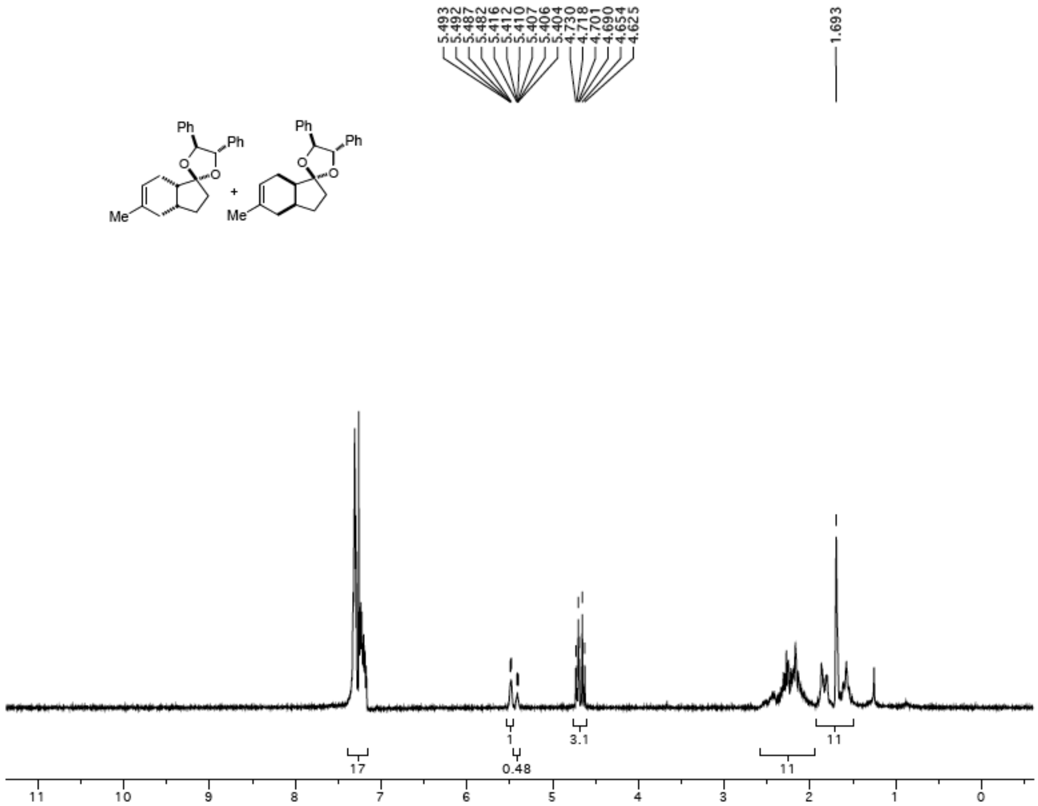
[1]H NMR spectrum for **3.62**

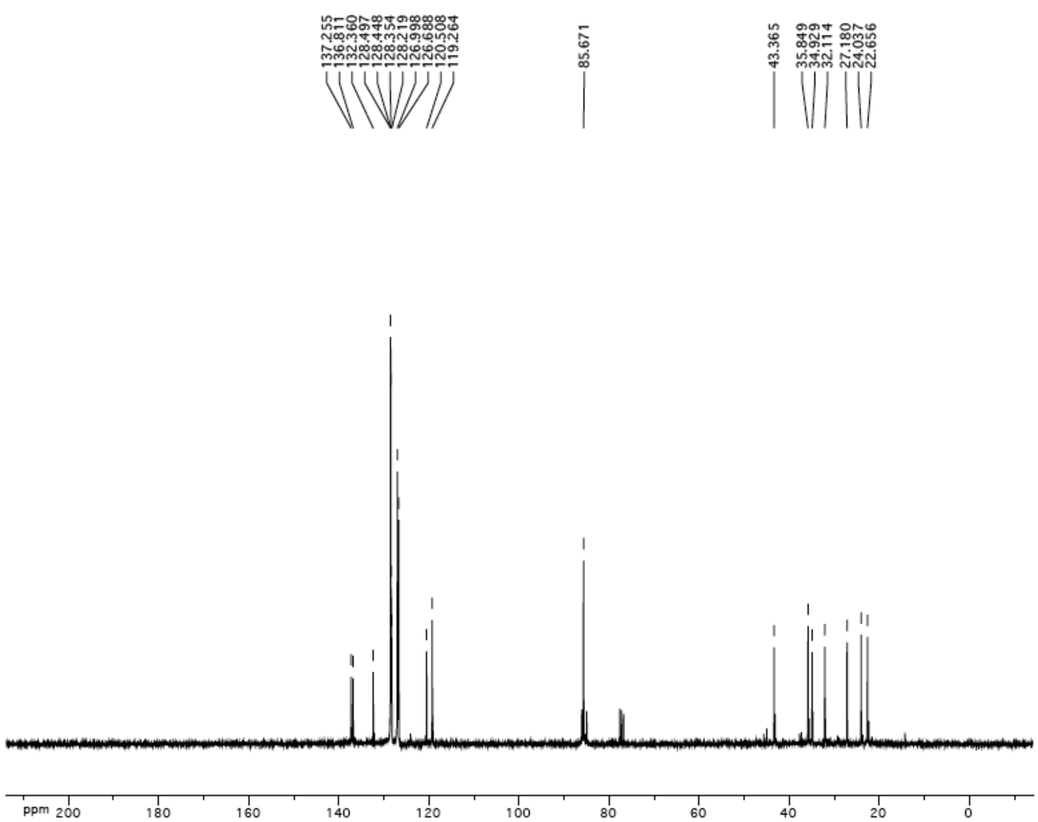


^{1}H and ^{13}C NMR spectra for **3.88**

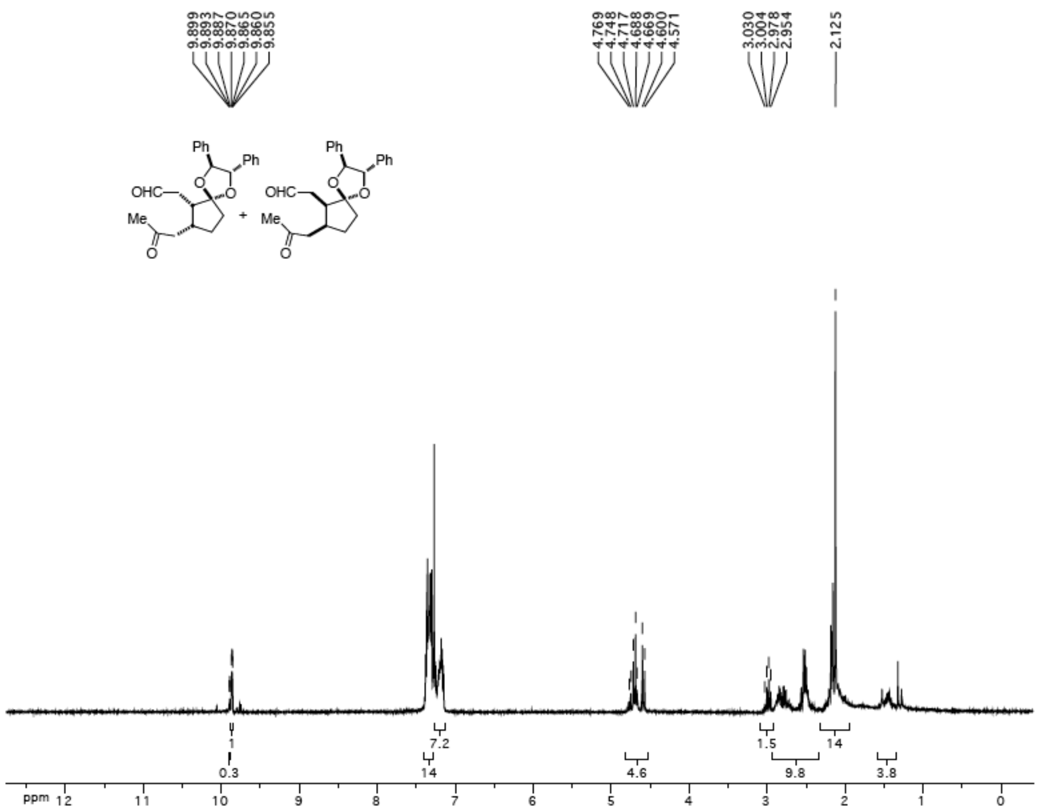


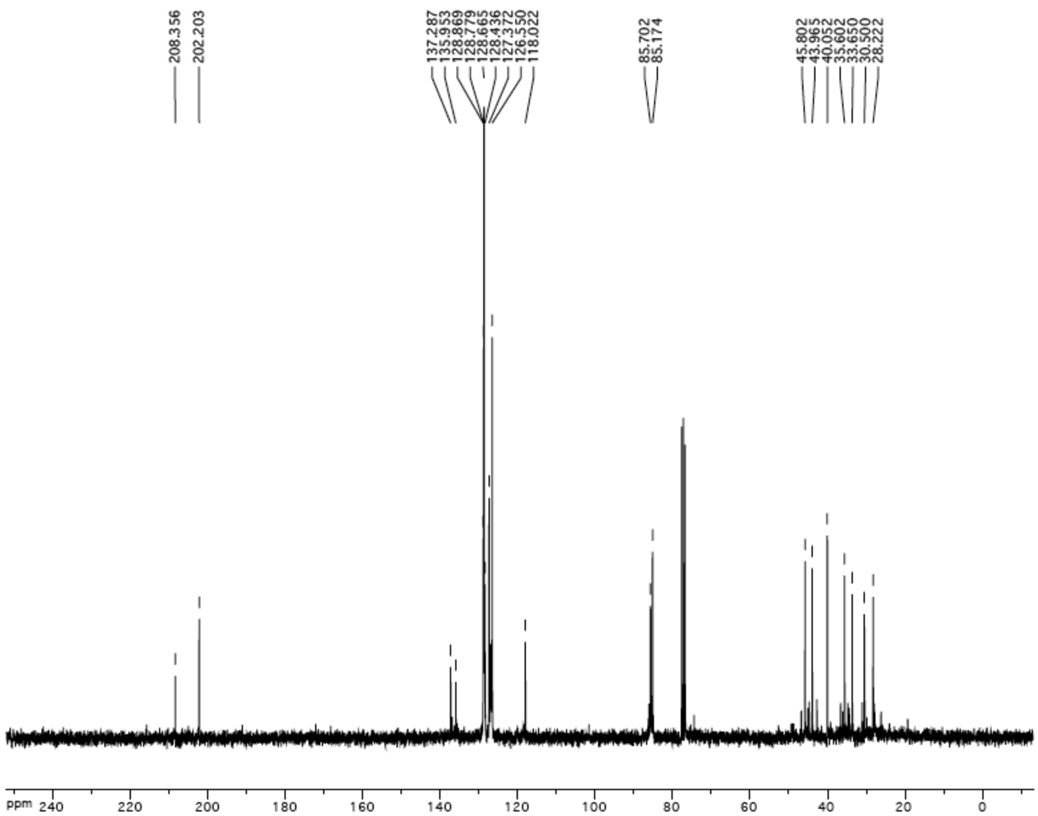
[1]H and [13]C NMR spectra for **3.89a** and **3.89b**



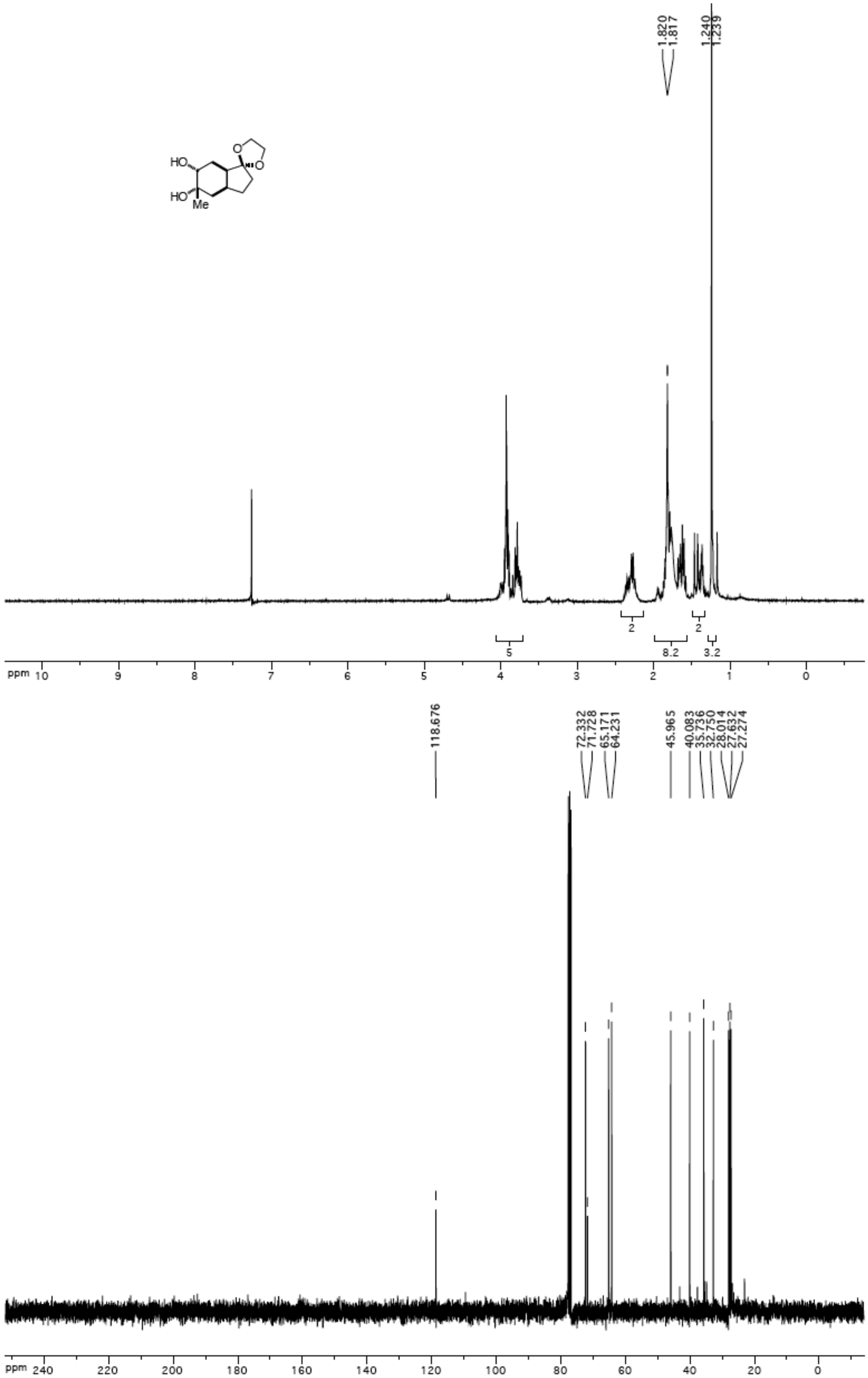


[1]H and [13]C NMR spectra for **3.90a** and **3.90b**





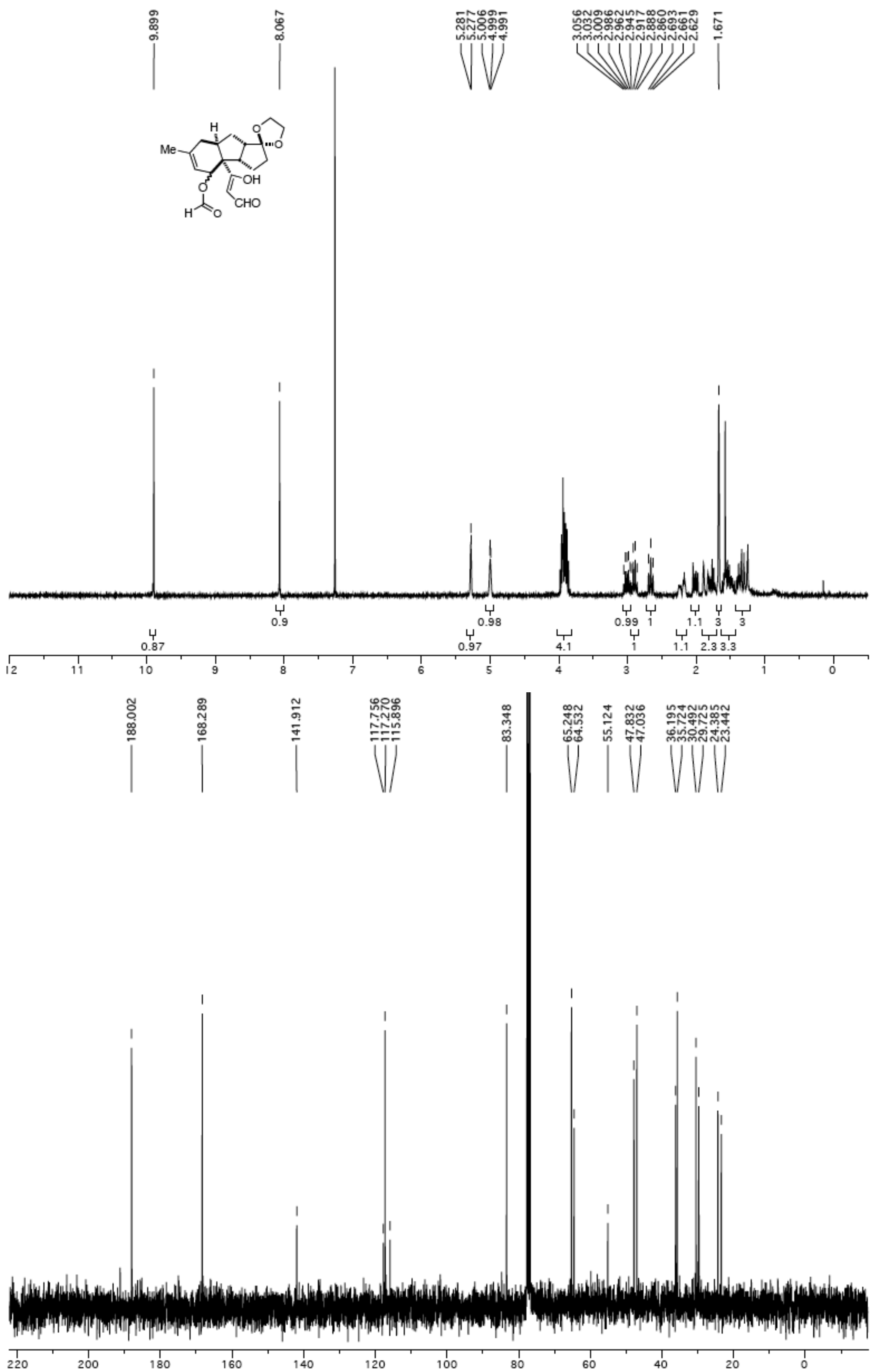
[1]H and [13]C NMR spectra for **3.91**



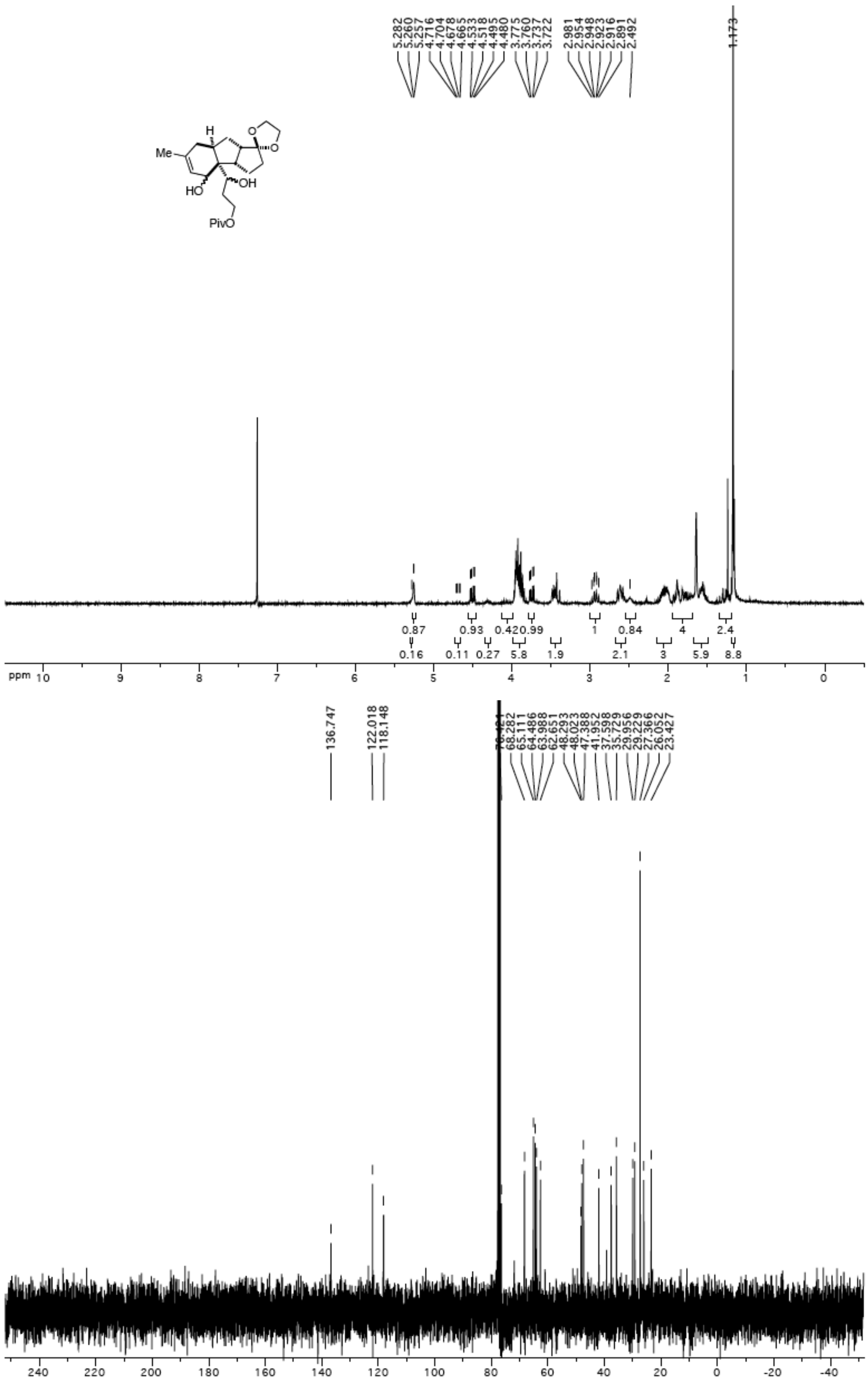
Appendix II

Spectra relevant to Chapter 4

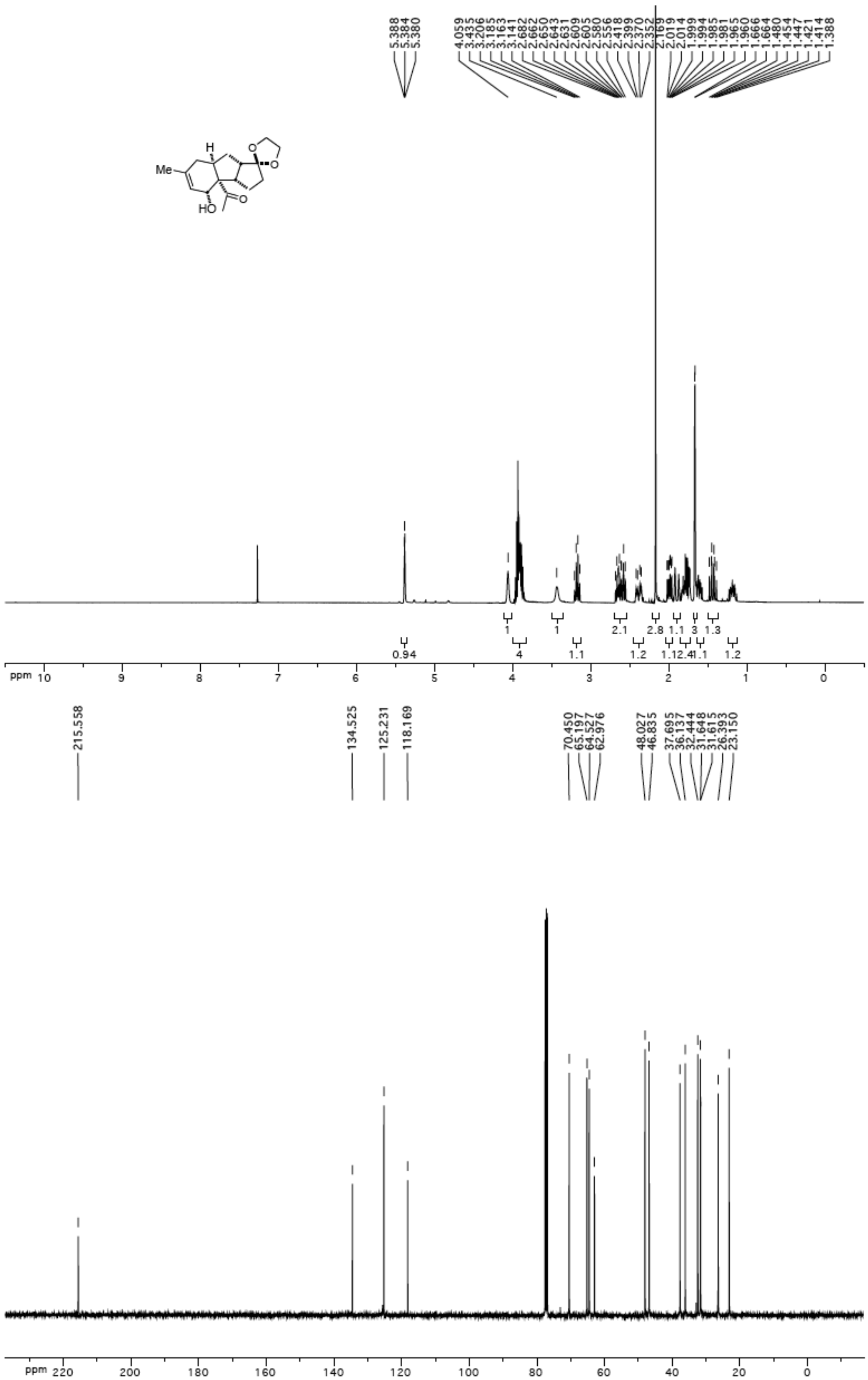
[1]H and [13]C NMR spectra for **4.4**



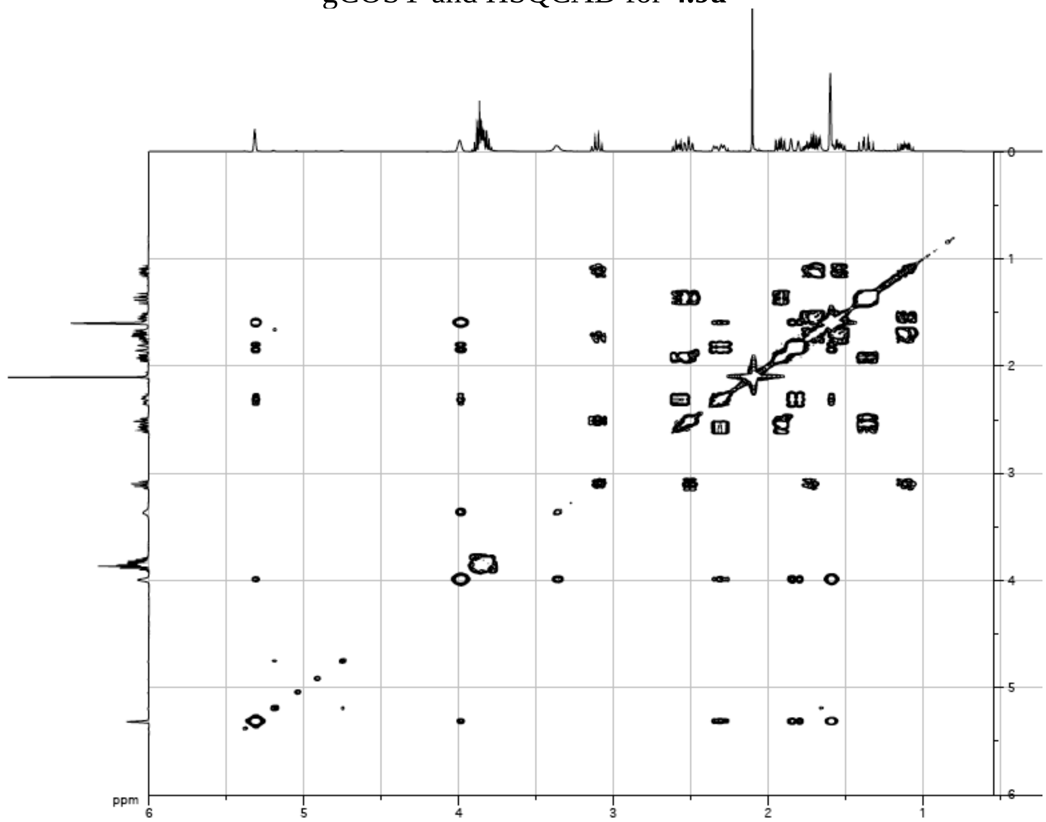
^{1}H and ^{13}C NMR spectra for **4.7**

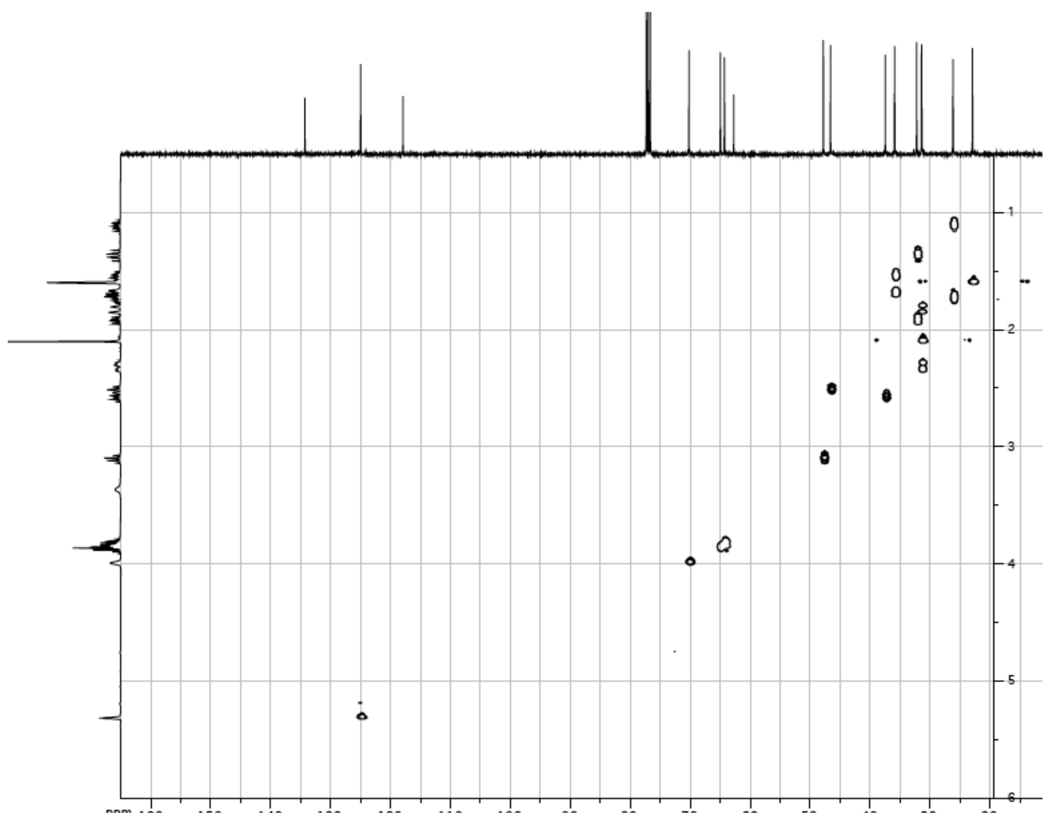


^{1}H and ^{13}C NMR spectra for **4.9a**

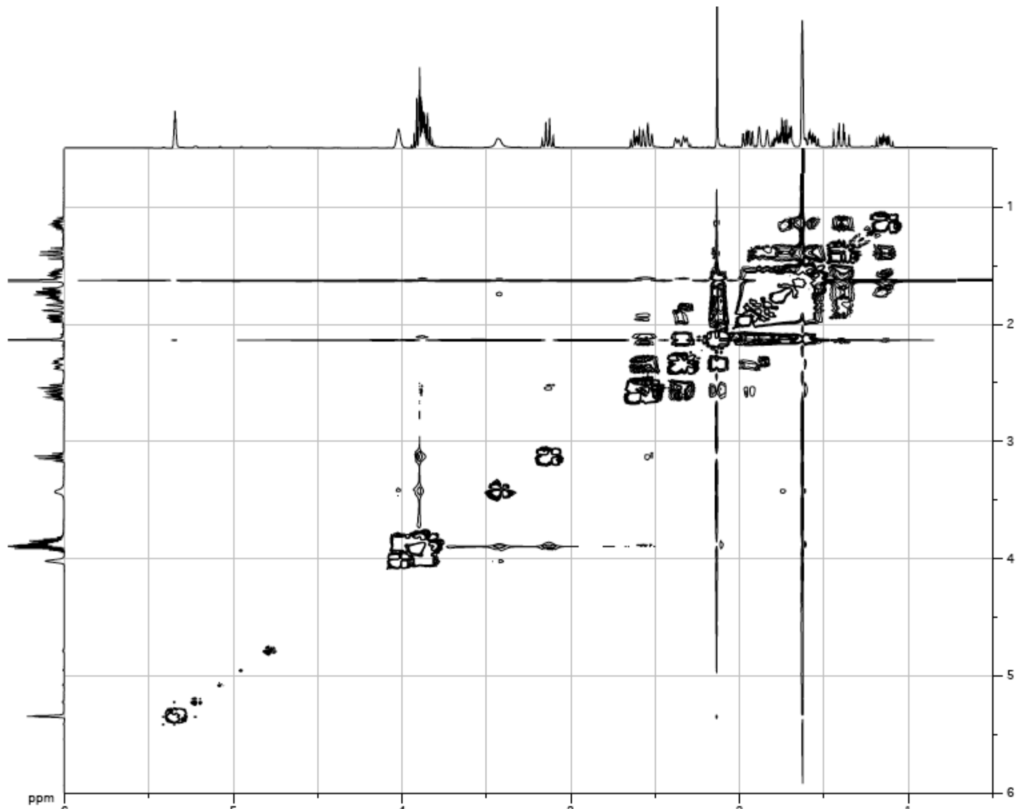


gCOSY and HSQCAD for **4.9a**

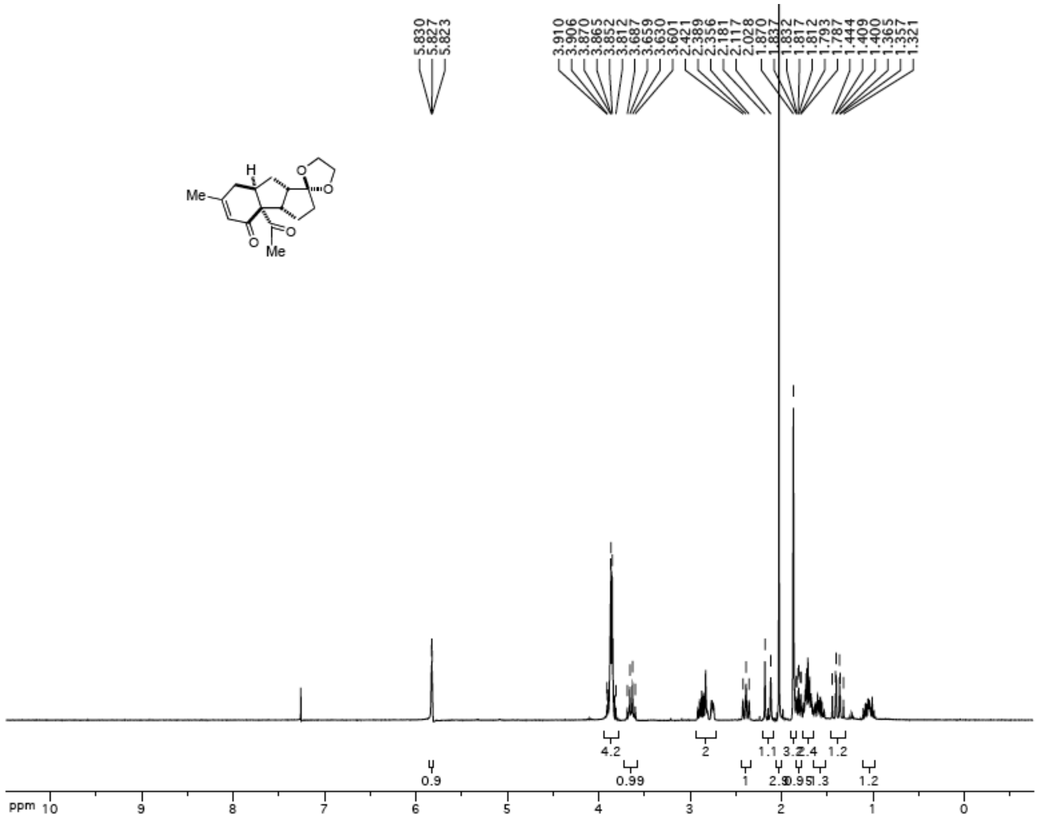


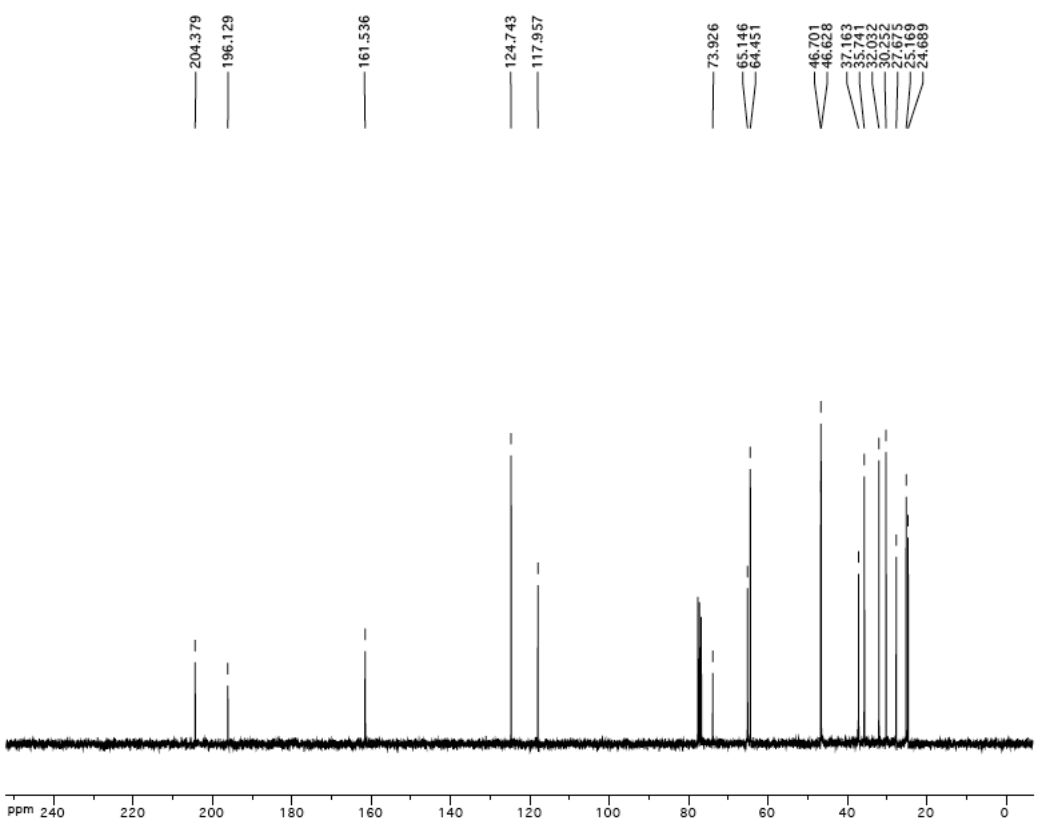


NOESY for **4.9a**

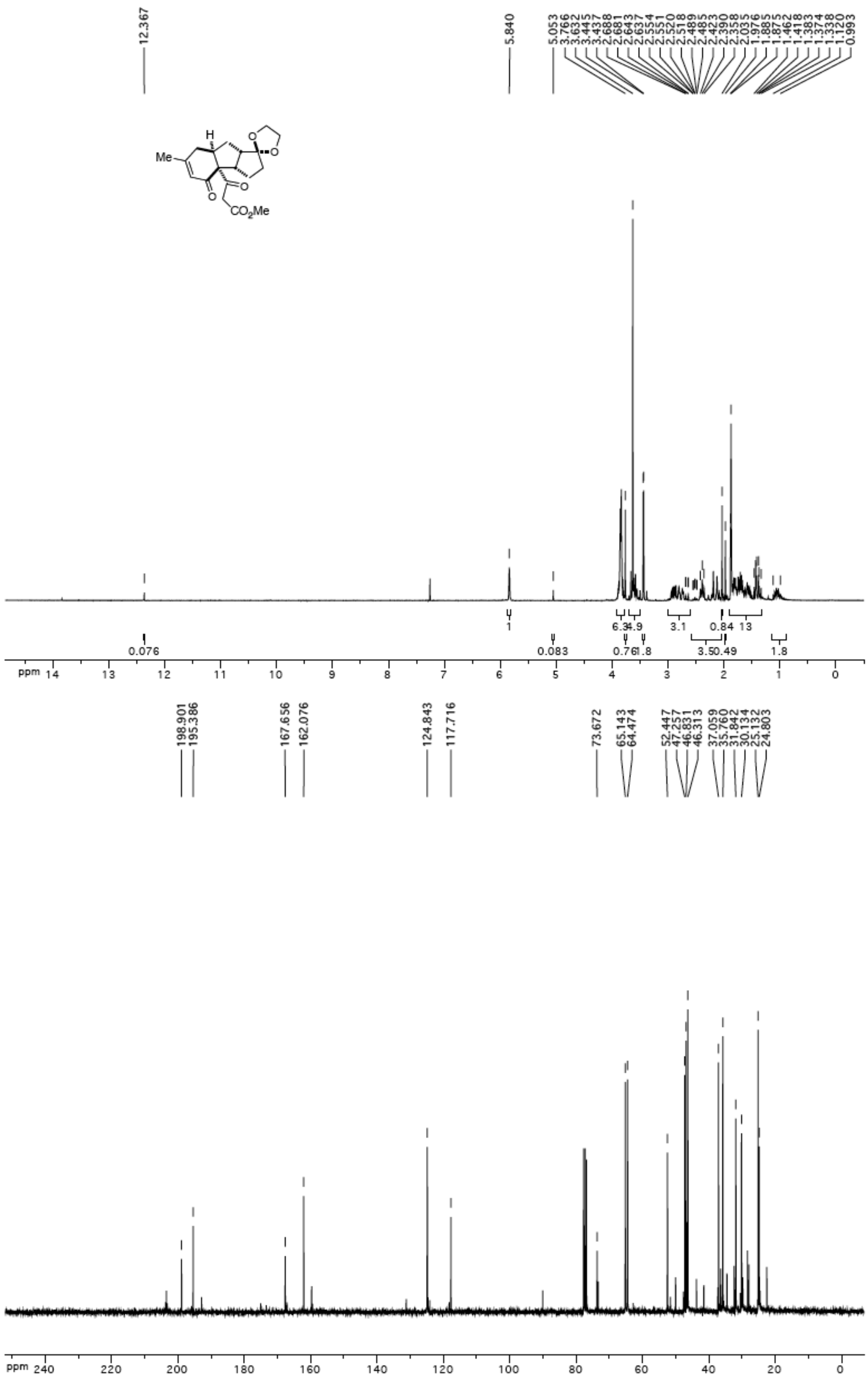


^{1}H and ^{13}C NMR spectra for **4.10**

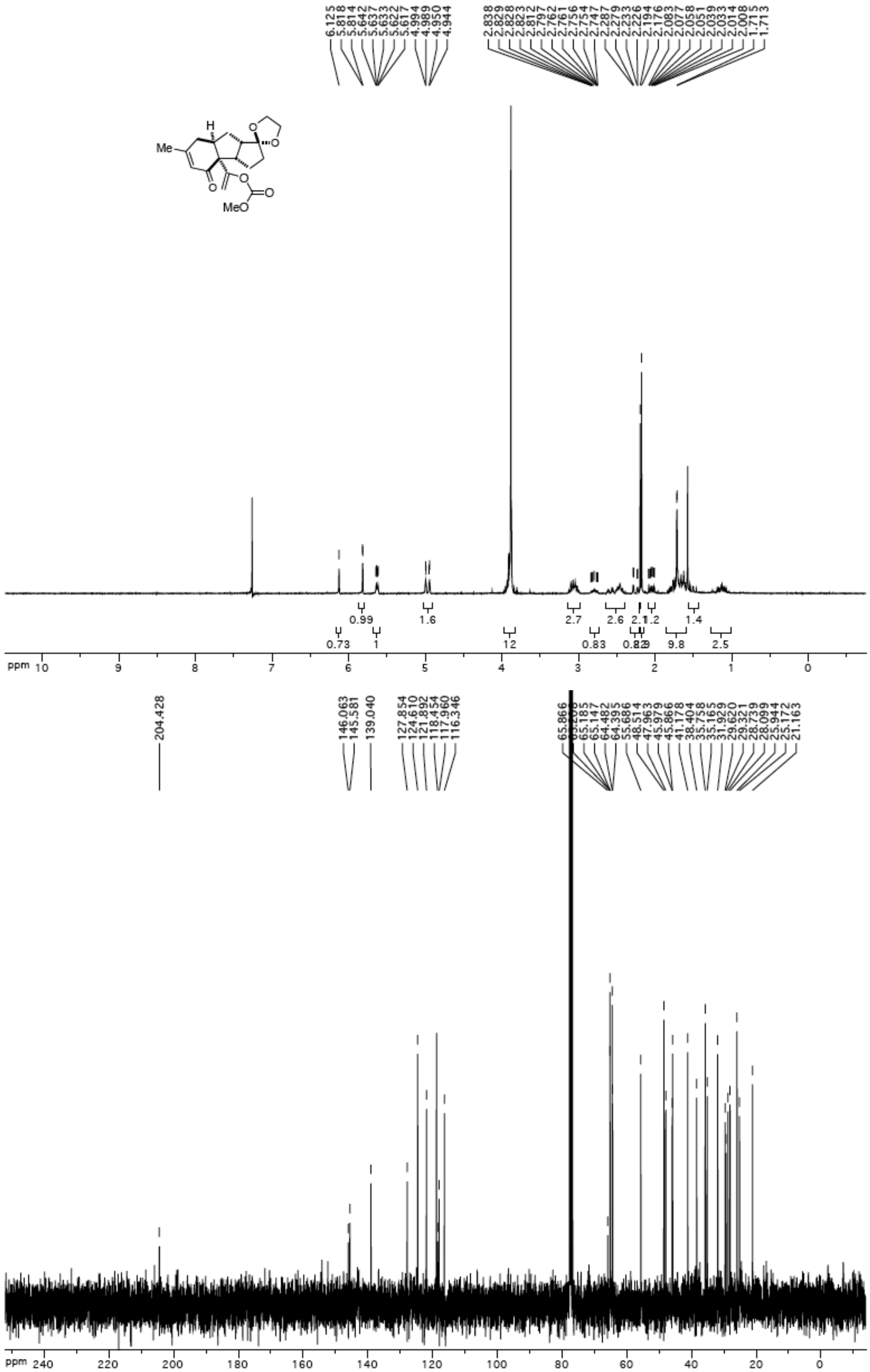




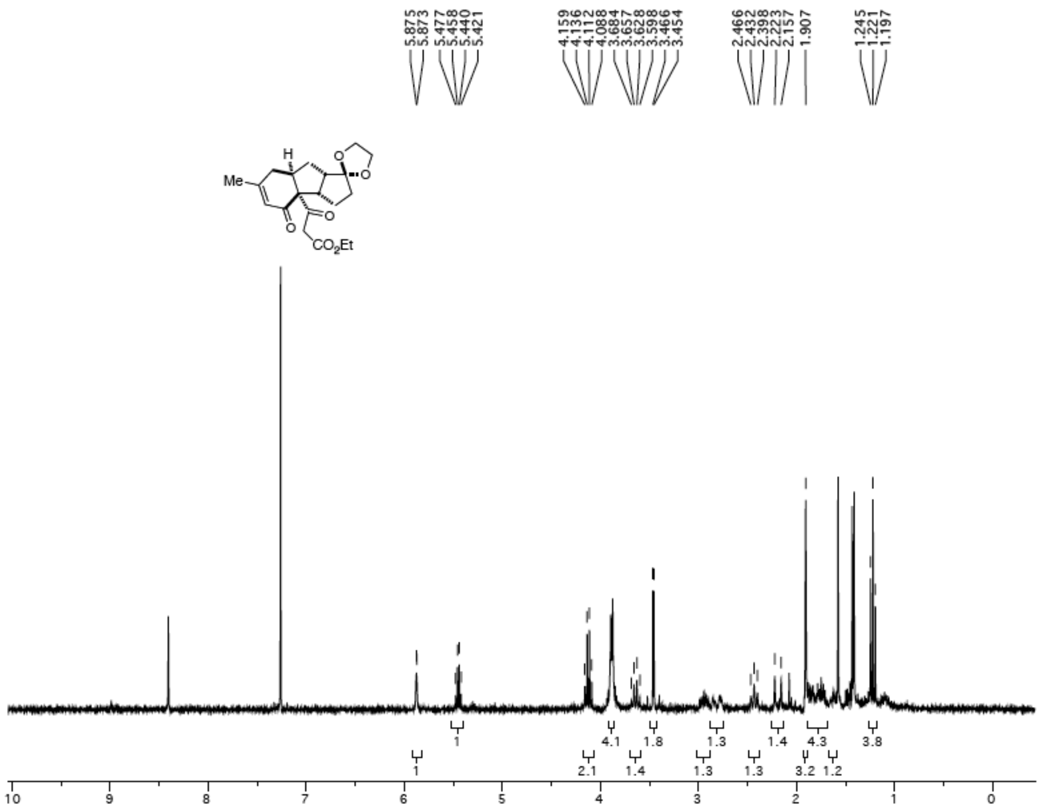
^{1}H and ^{13}C NMR spectra for **4.20**



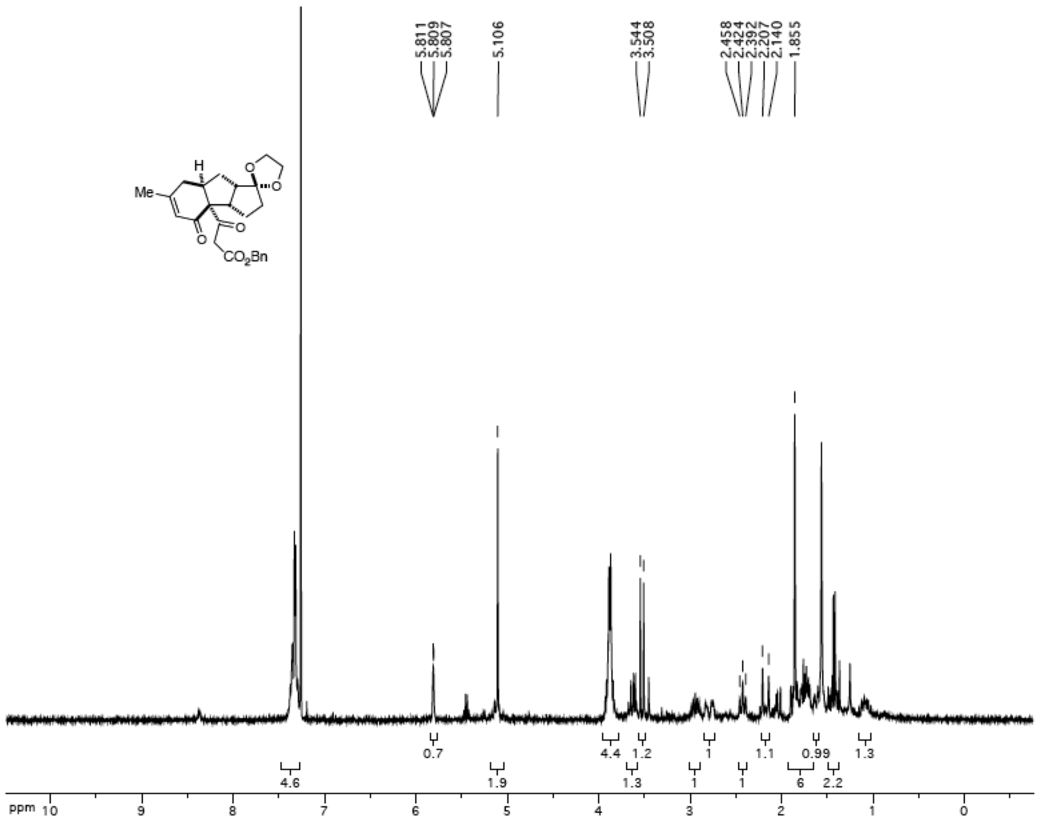
[1]H and [13]C NMR spectra for **4.21**



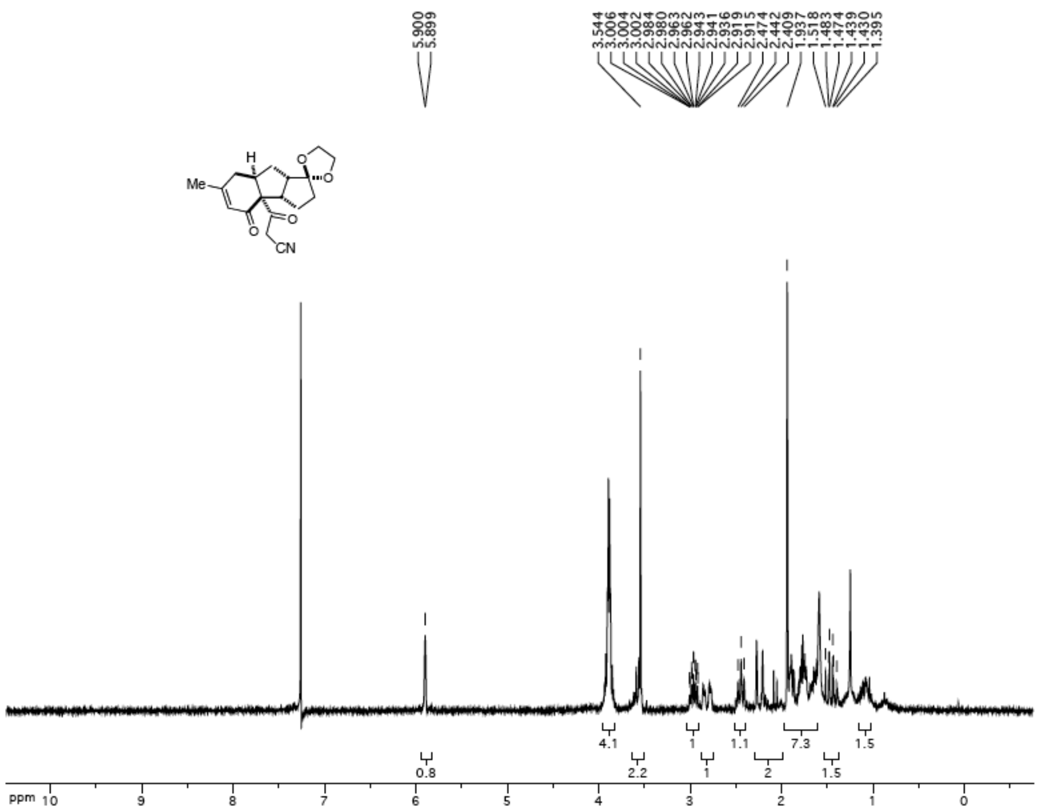
^{1}H spectrum for **4.22**



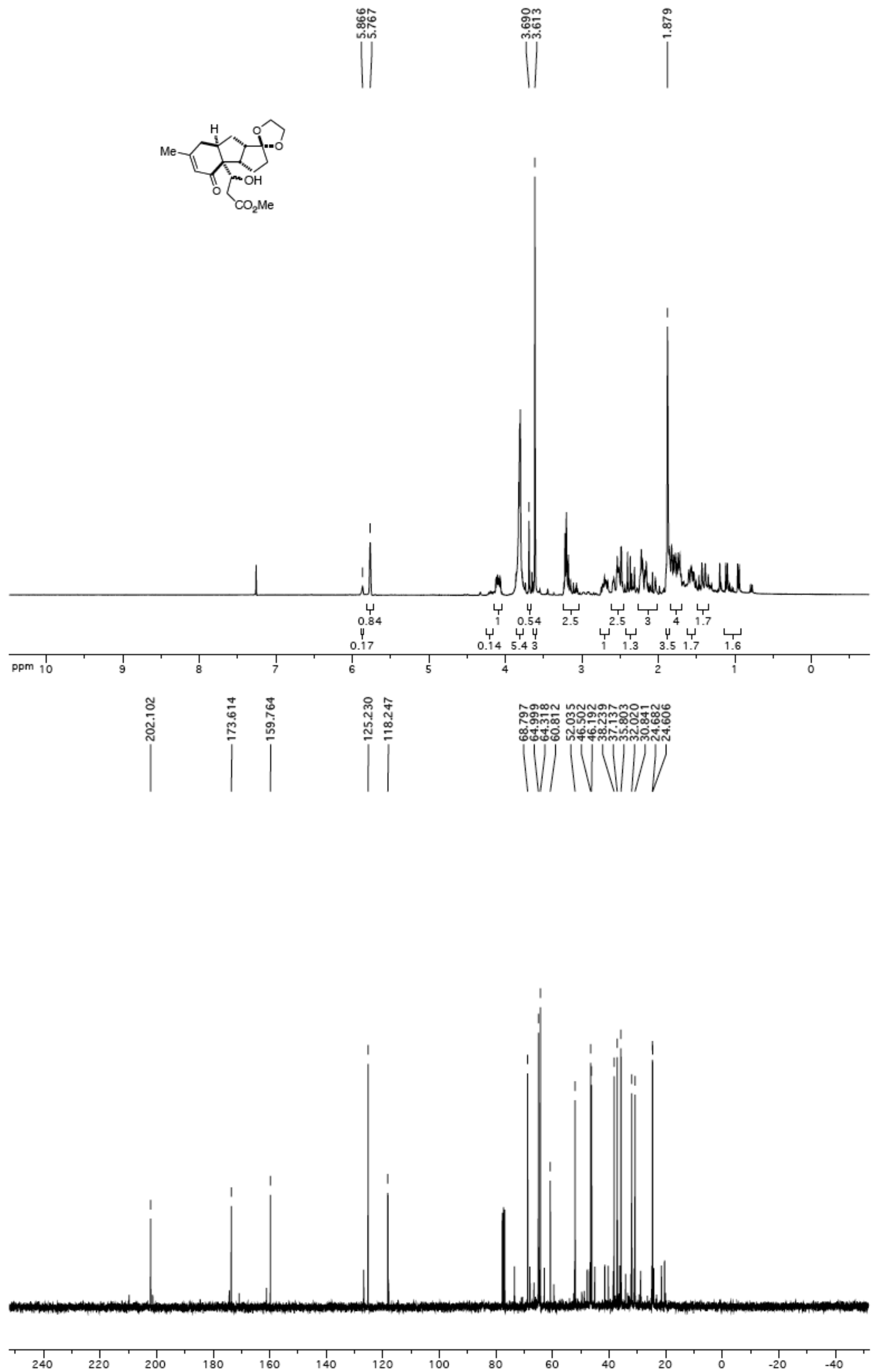
^{1}H spectrum for **4.23**



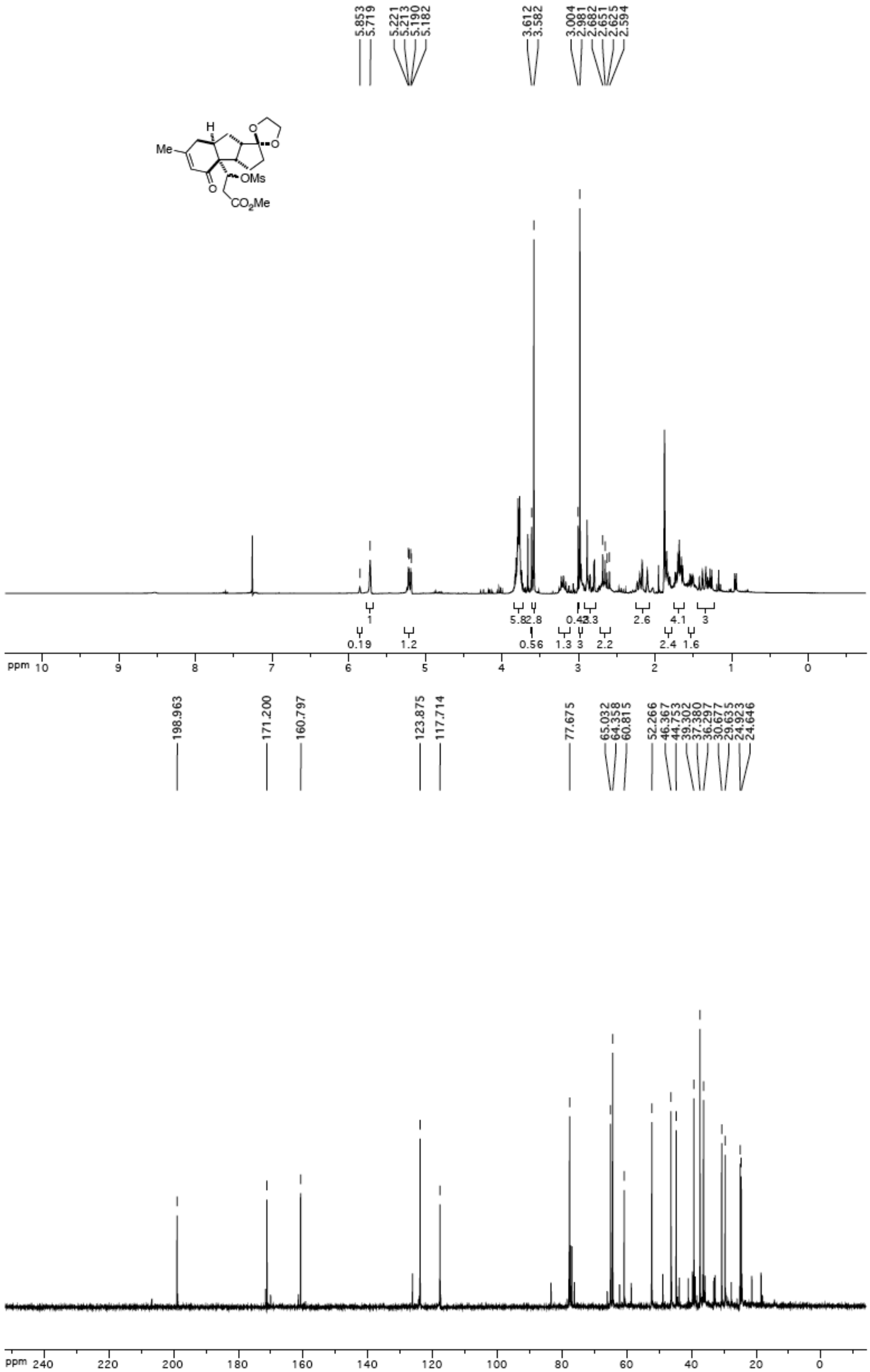
^{1}H spectrum for **4.24**



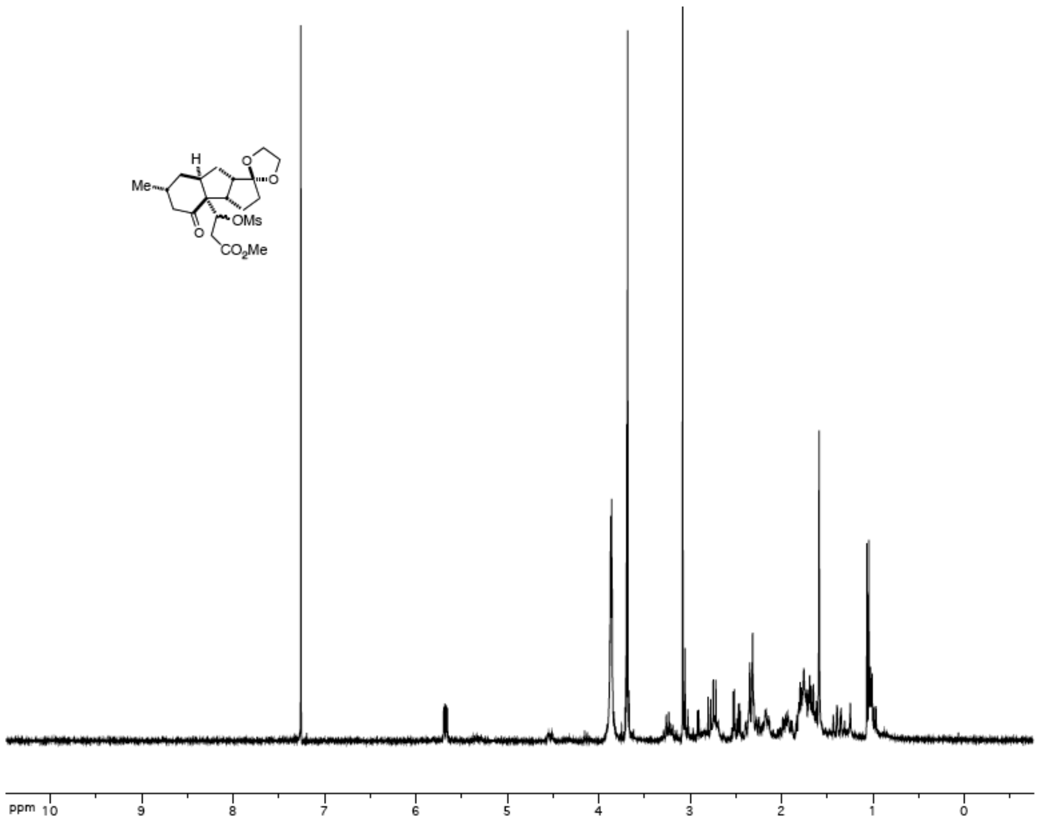
^{1}H and ^{13}C NMR spectra for **4.25**



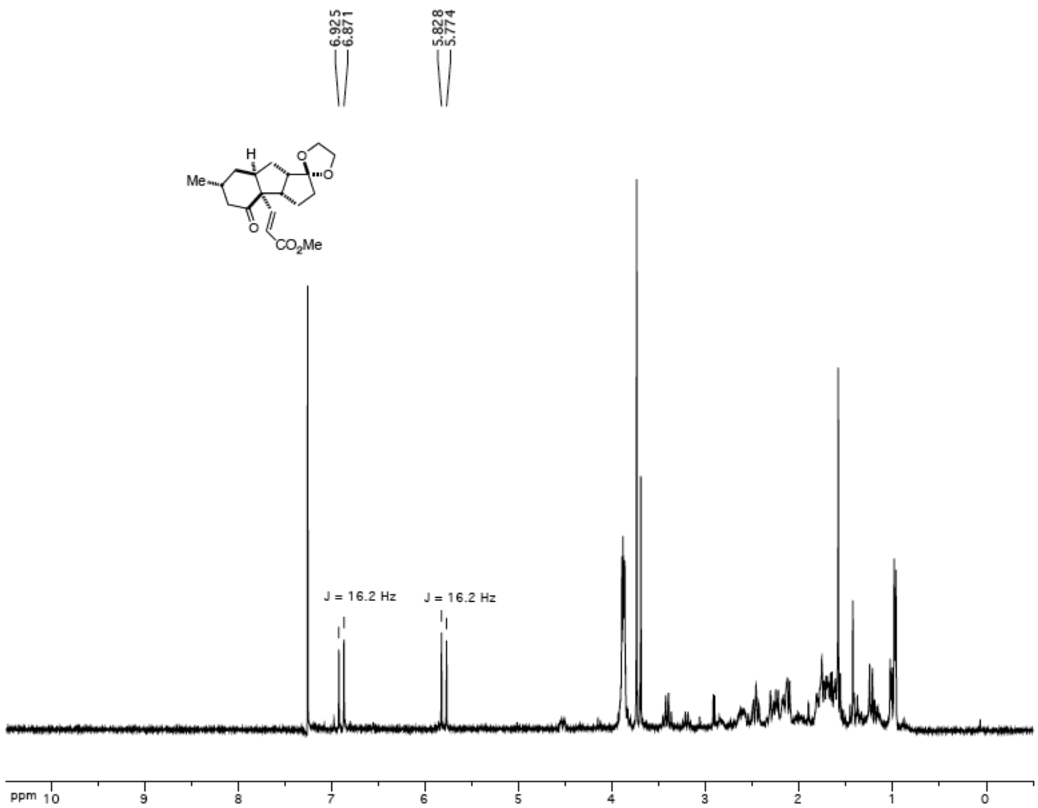
^{1}H and ^{13}C NMR spectra for **4.26**



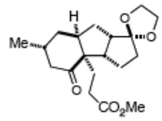
[1]H NMR spectrum for crude **4.27**

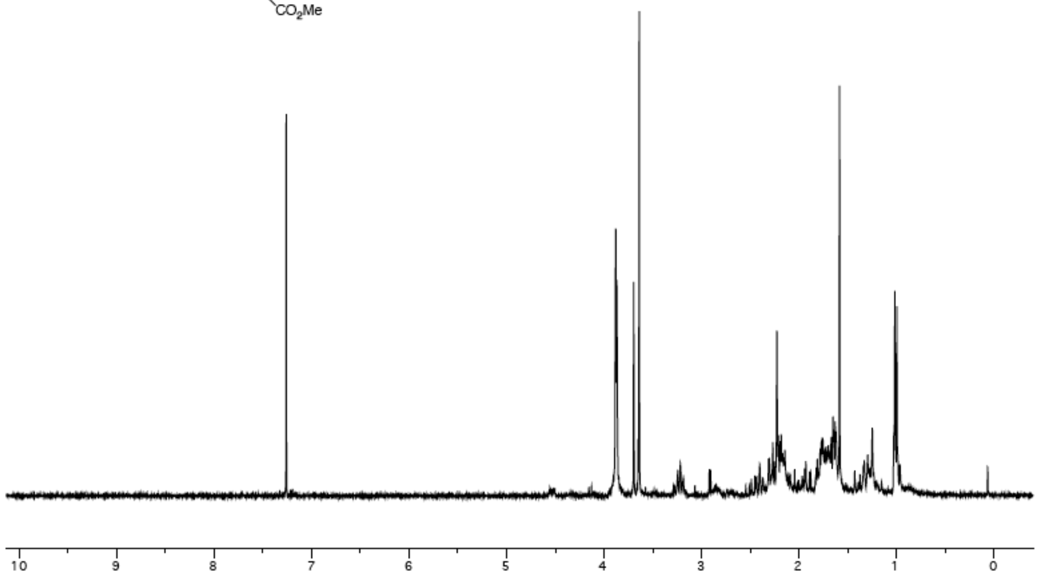


^{1}H NMR spectrum for crude **4.28**

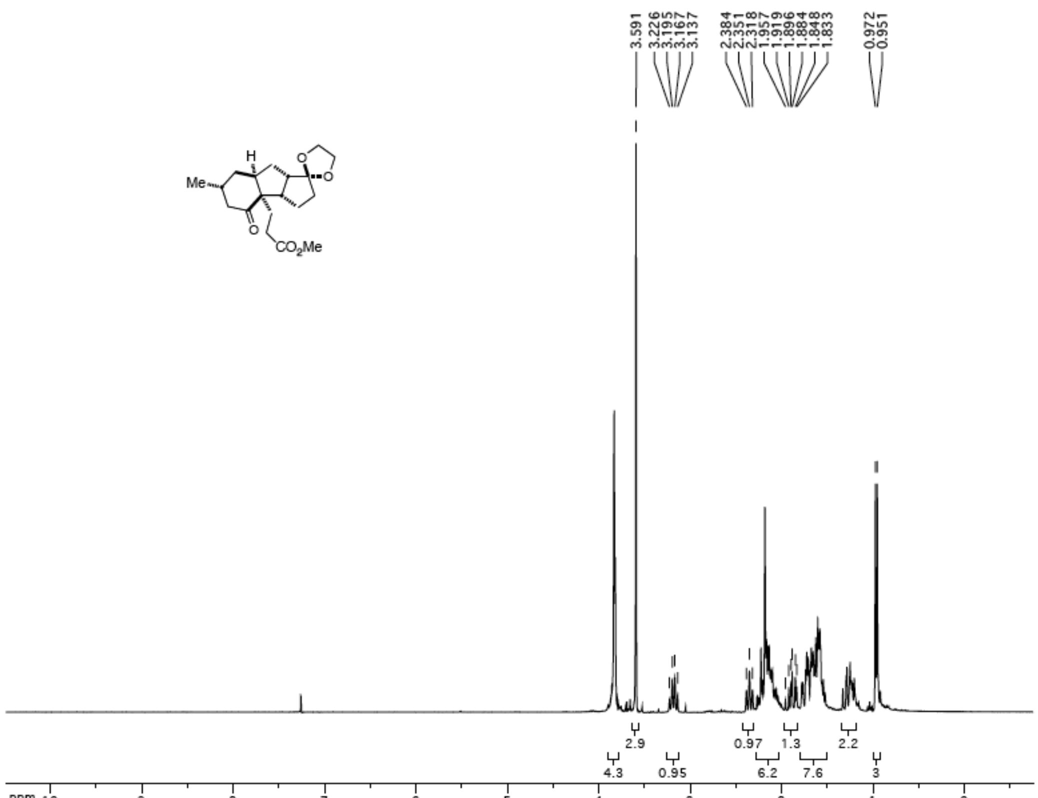


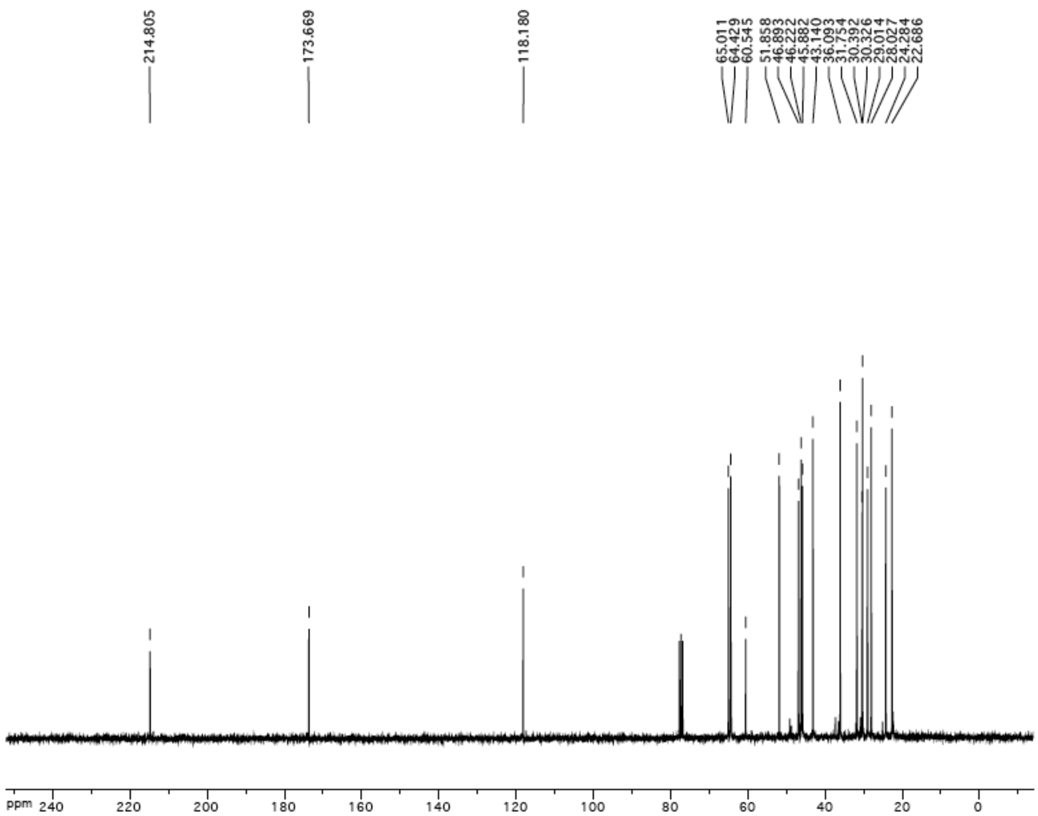
[1]H NMR spectrum for crude **4.29**



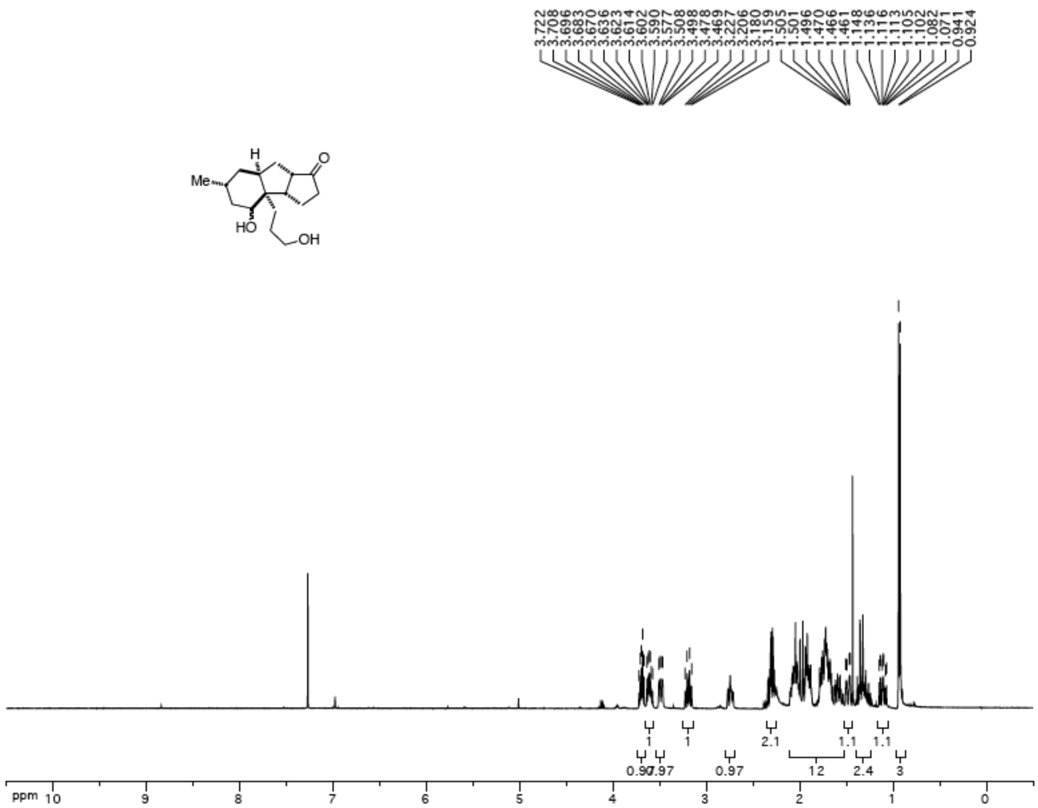


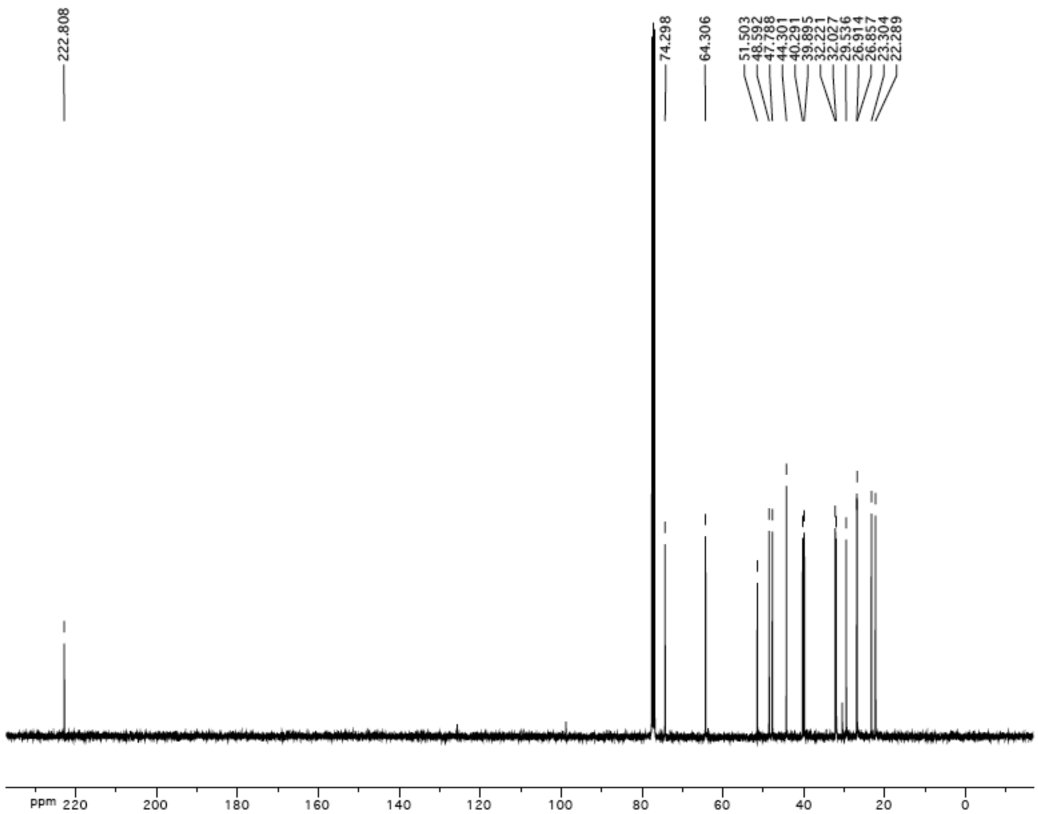
^{1}H and ^{13}C NMR spectra for **4.29**



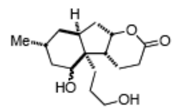


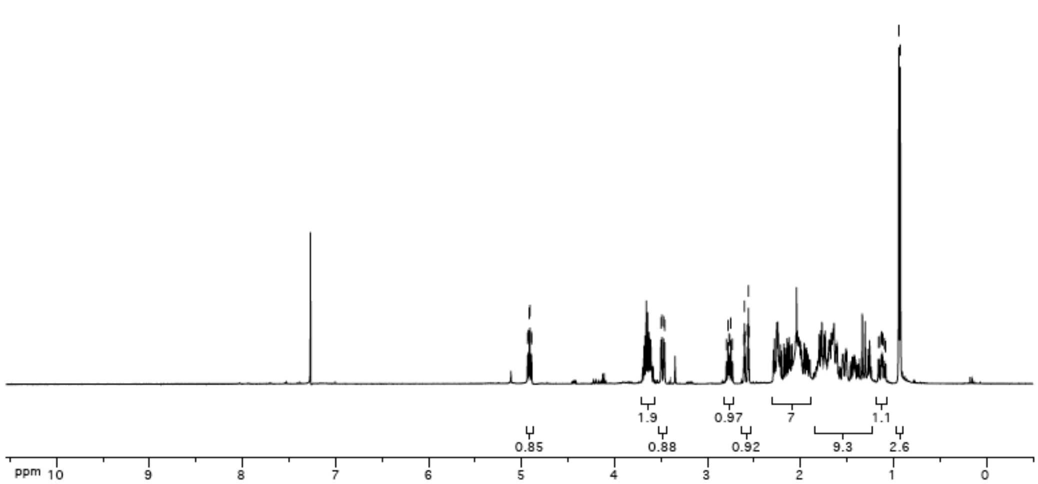
^{1}H and ^{13}C NMR spectra for **4.30**

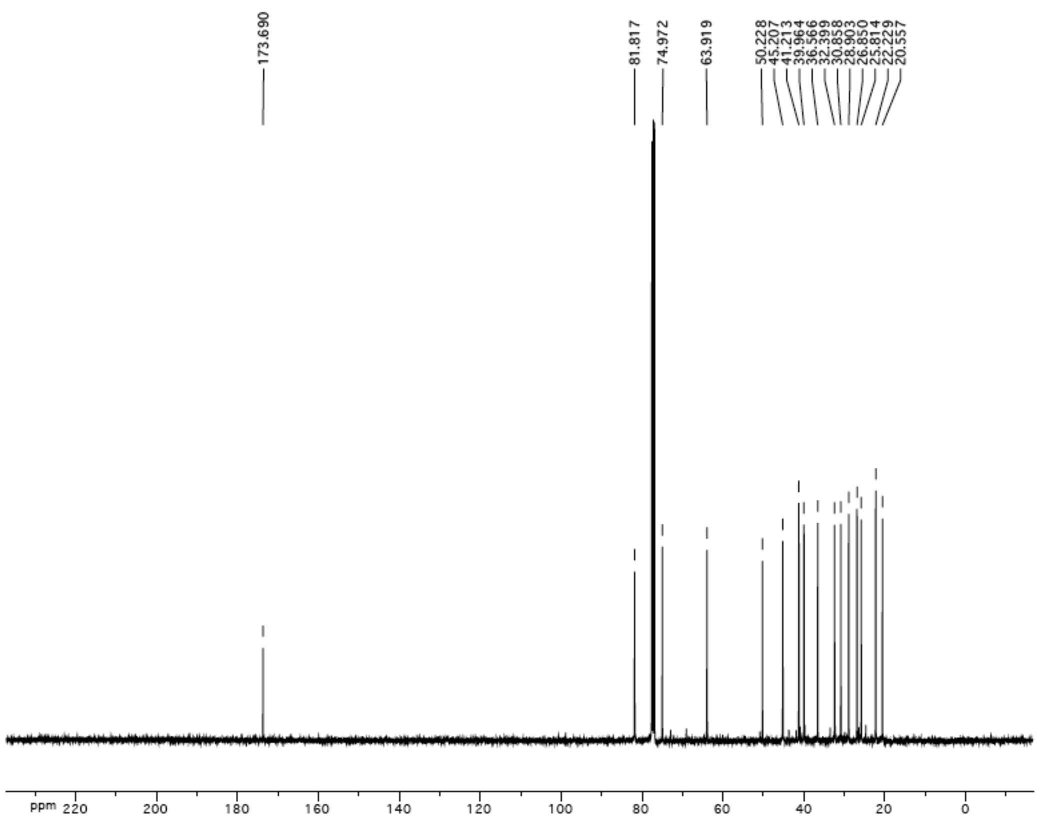




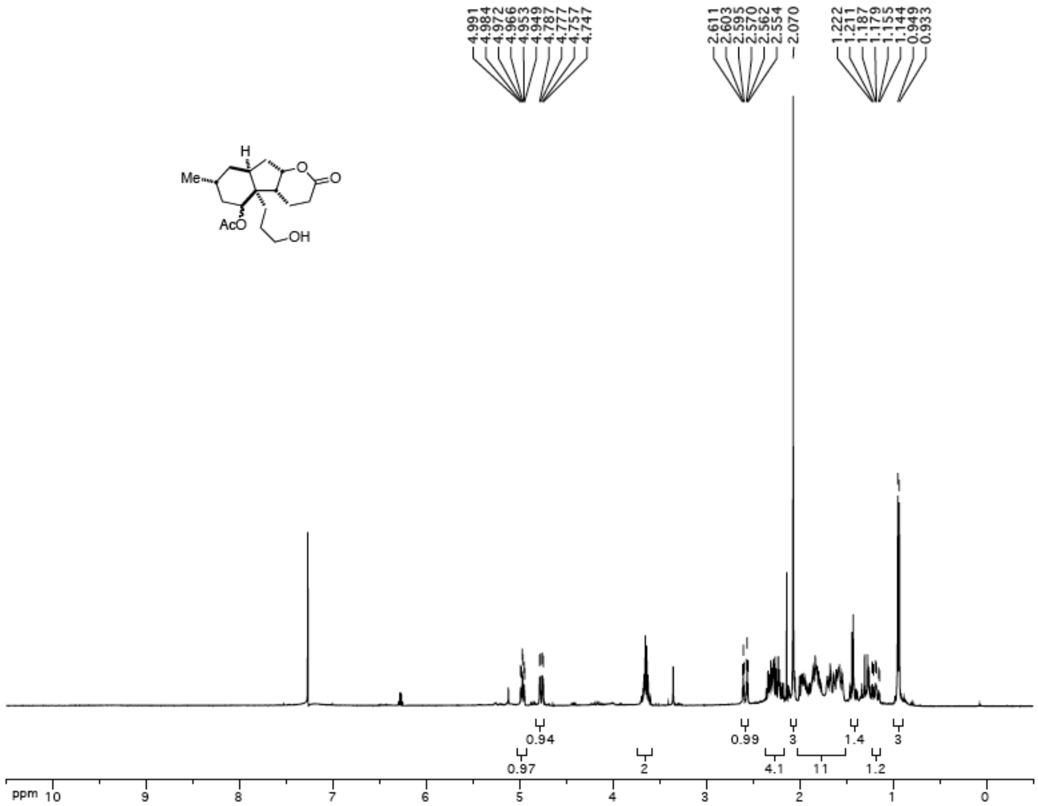
^{1}H and ^{13}C NMR spectra for **4.31**

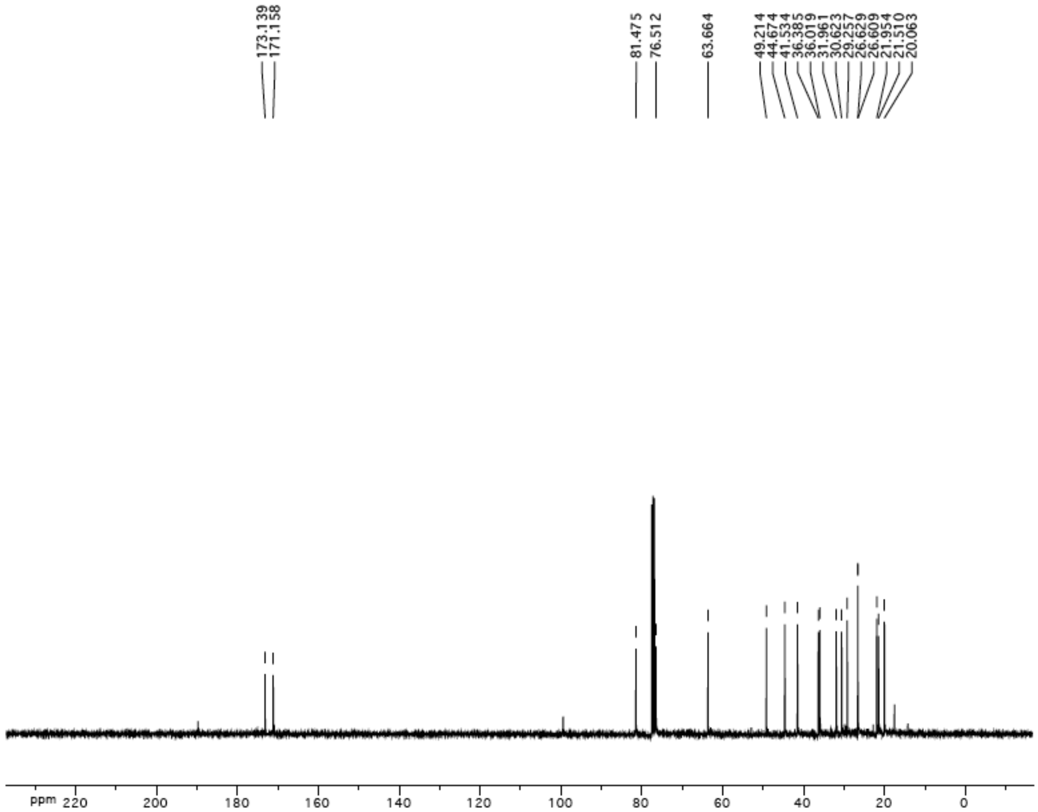




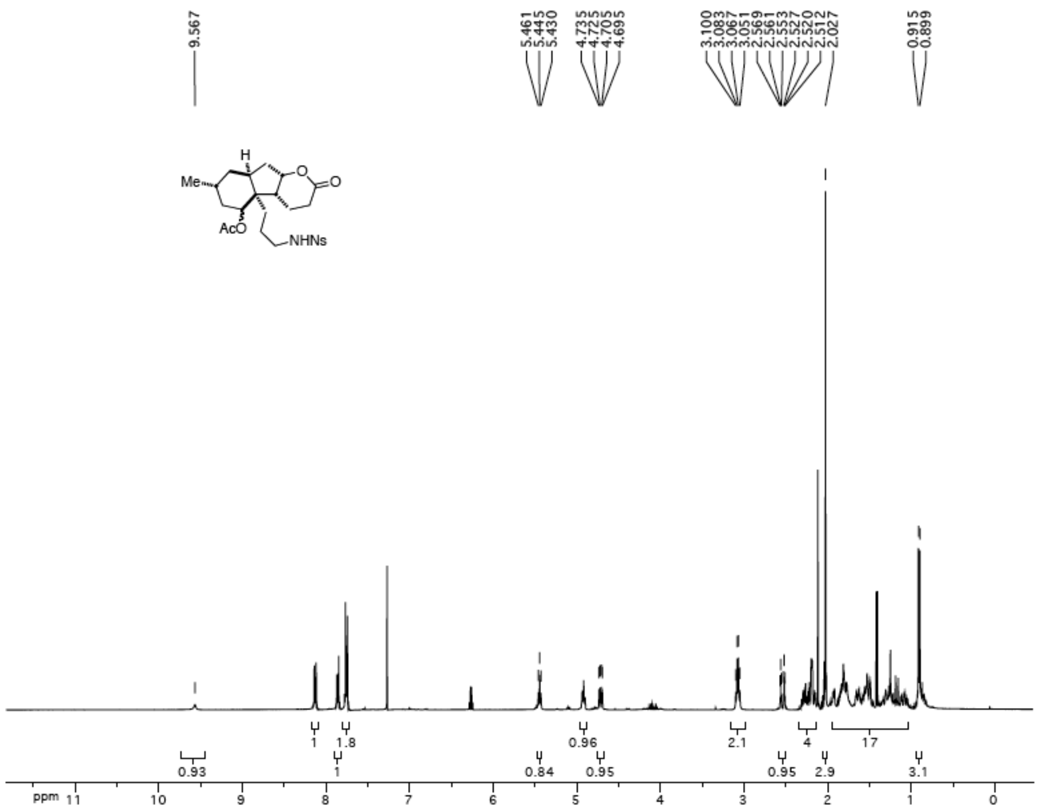


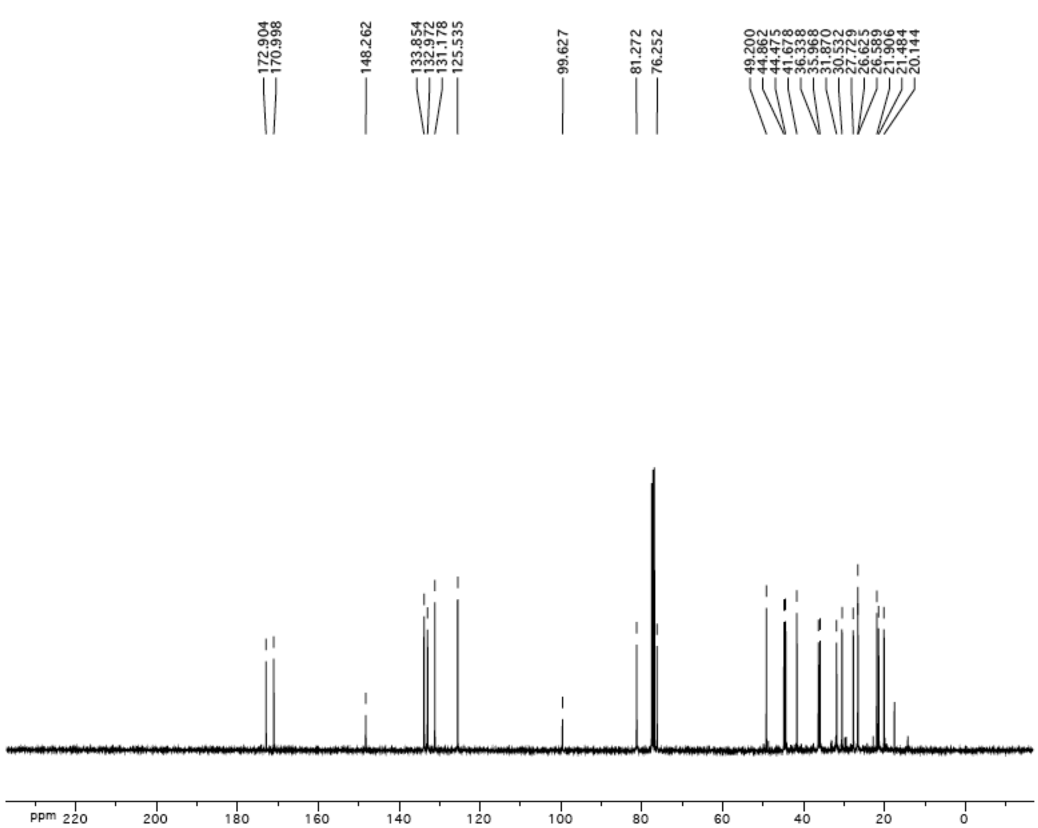
^{1}H and ^{13}C NMR spectra for **4.33**



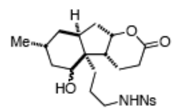


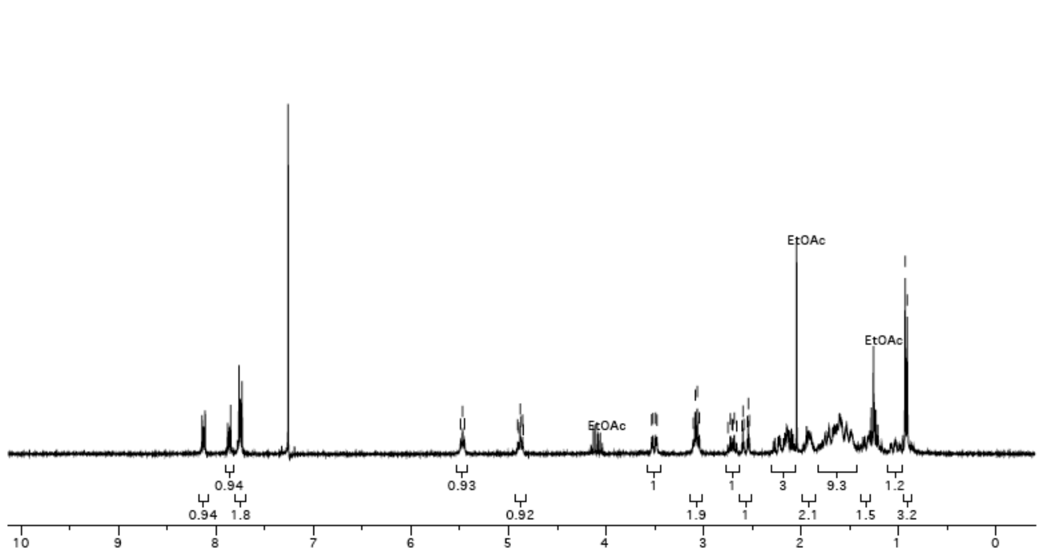
^{1}H and ^{13}C NMR spectra for **4.34**

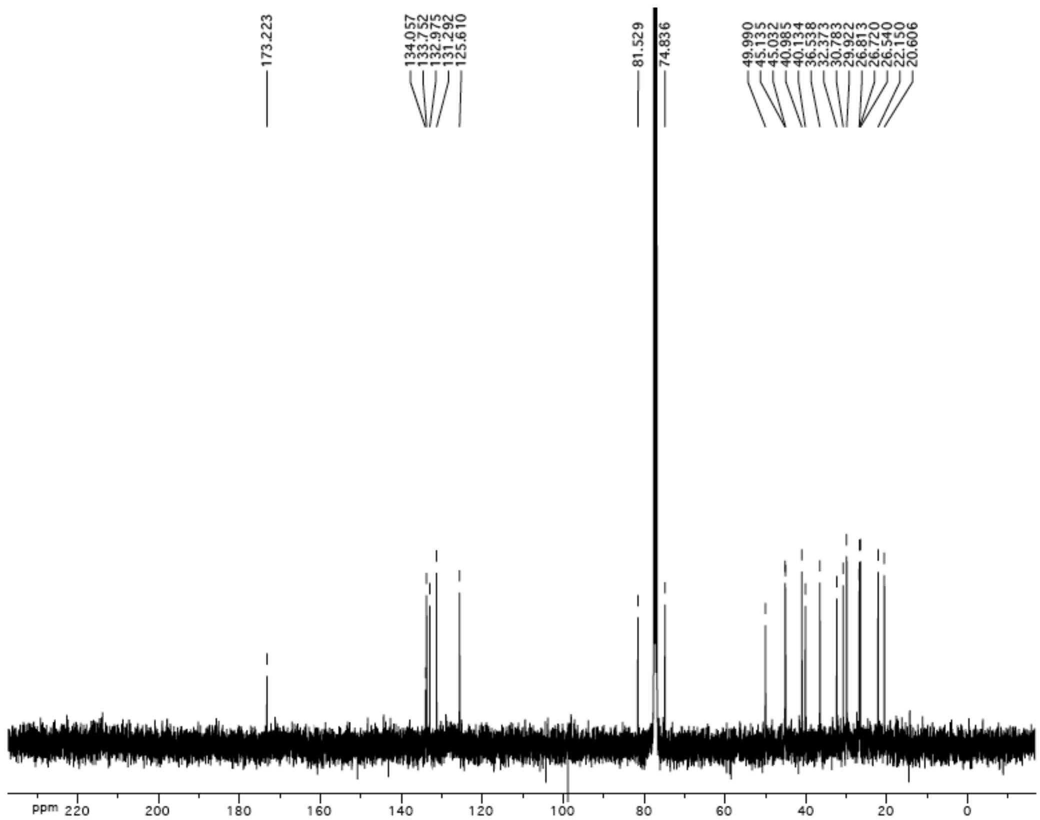




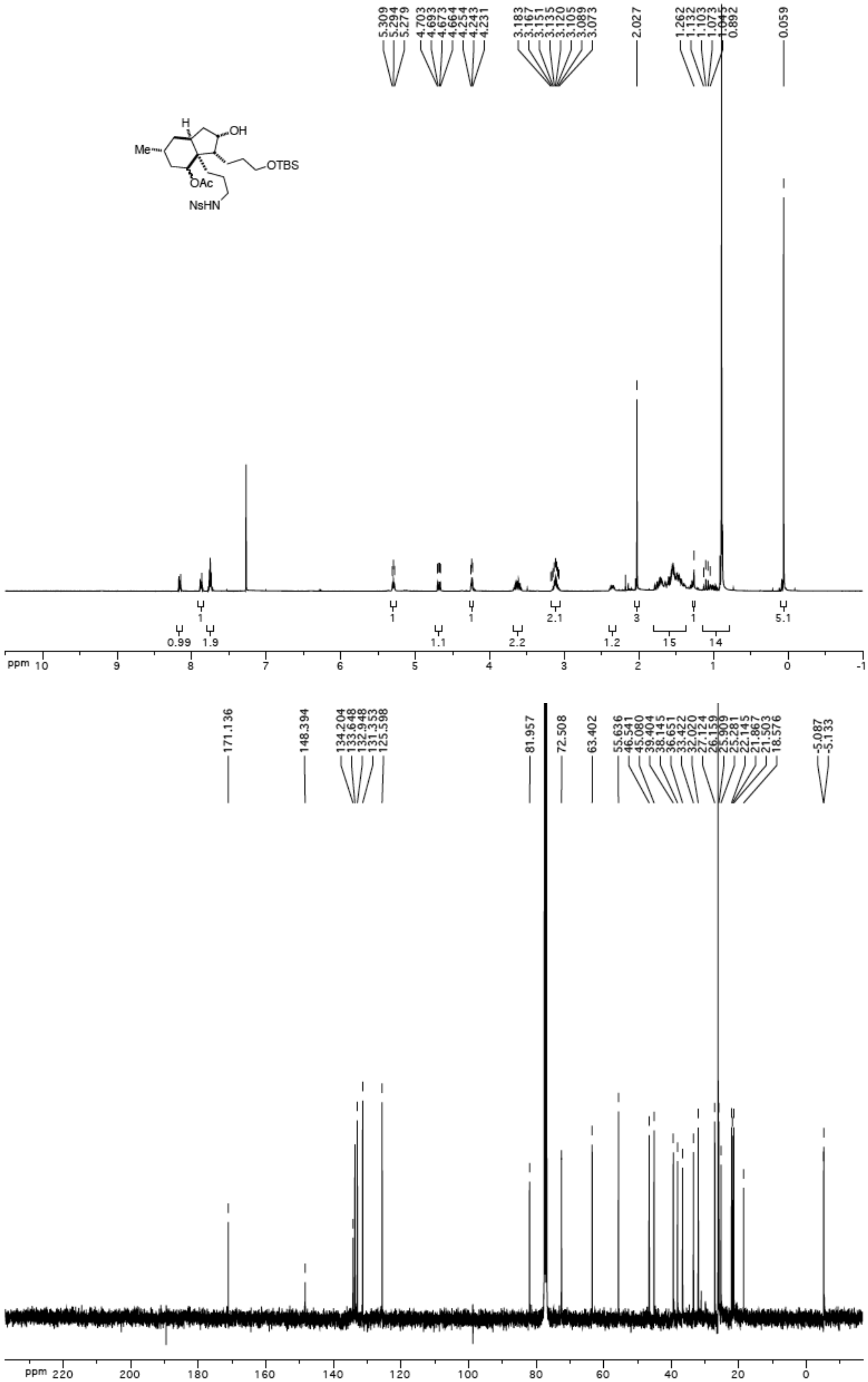
^{1}H and ^{13}C NMR spectra for **4.32**



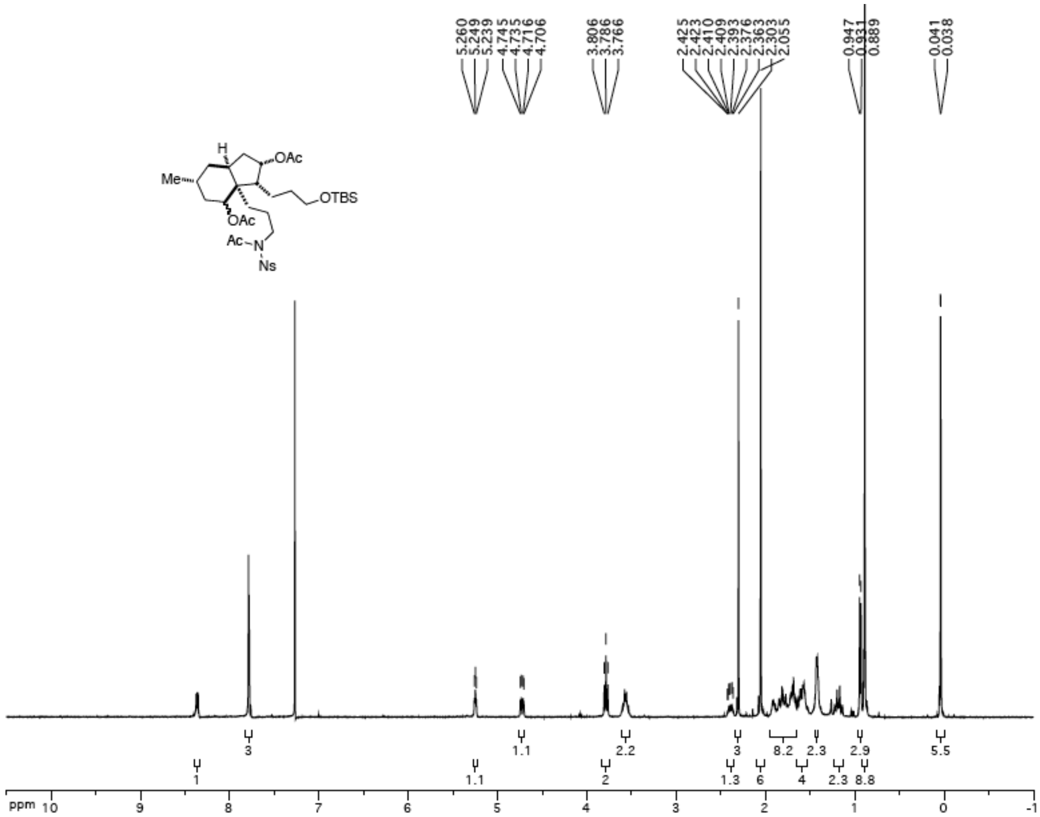


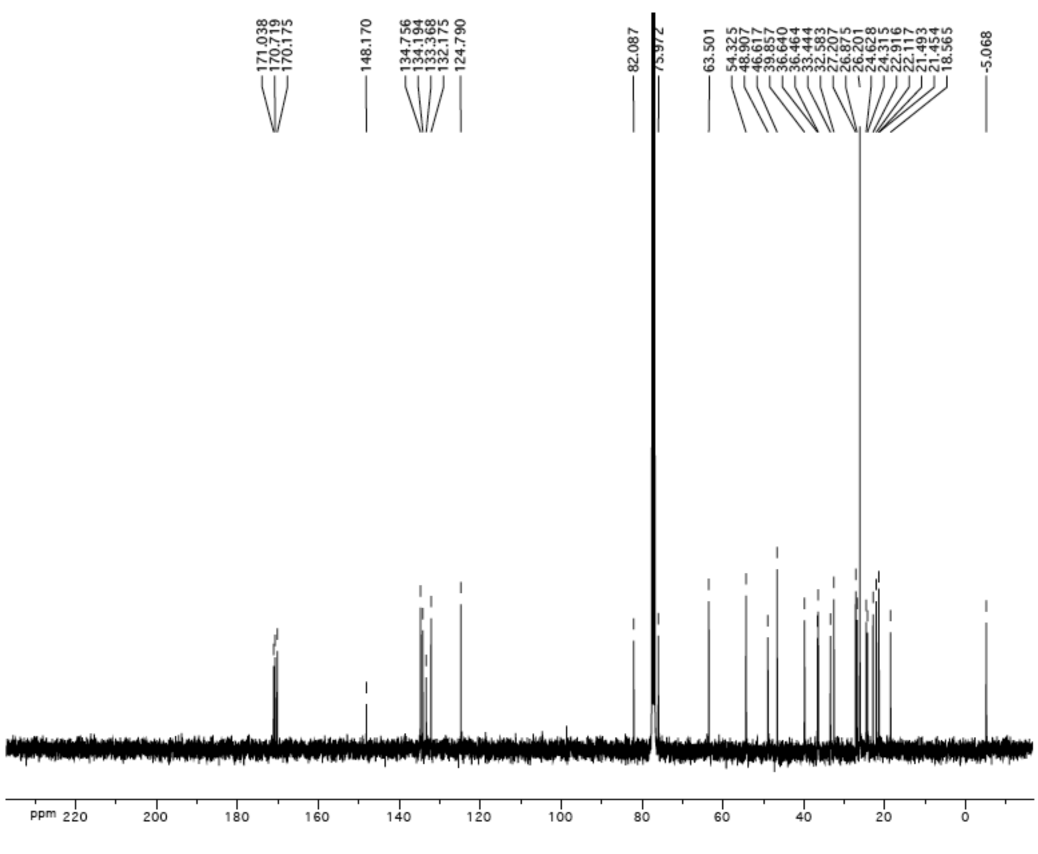


^{1}H and ^{13}C NMR spectra for **4.37**

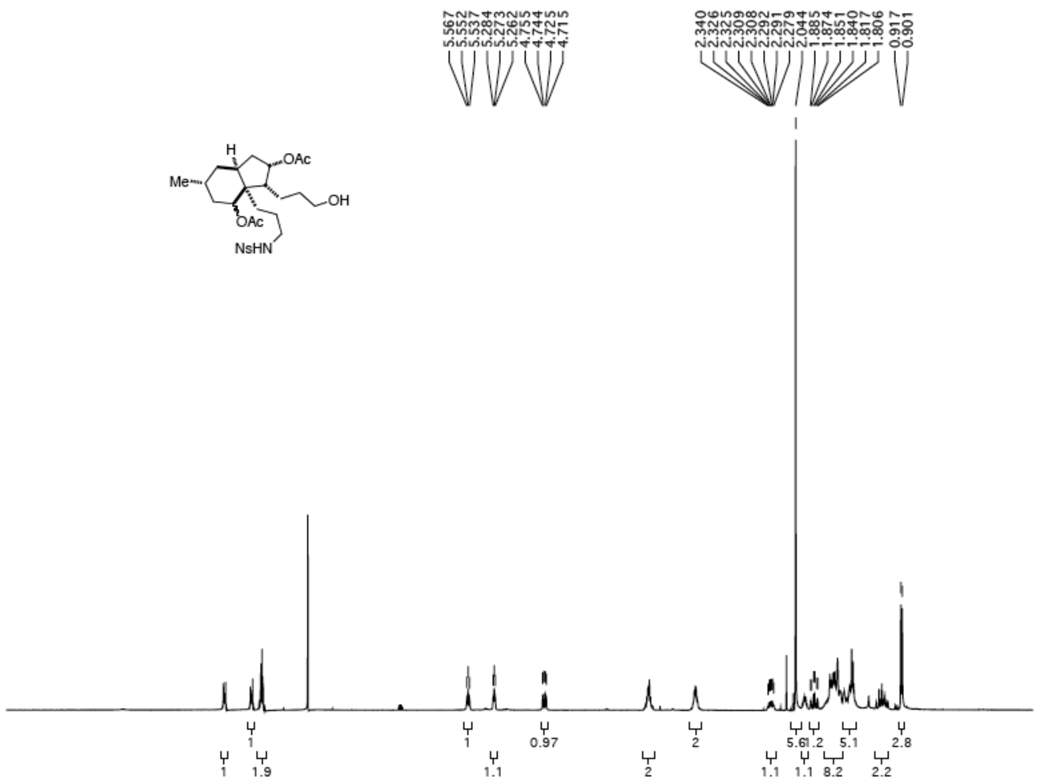


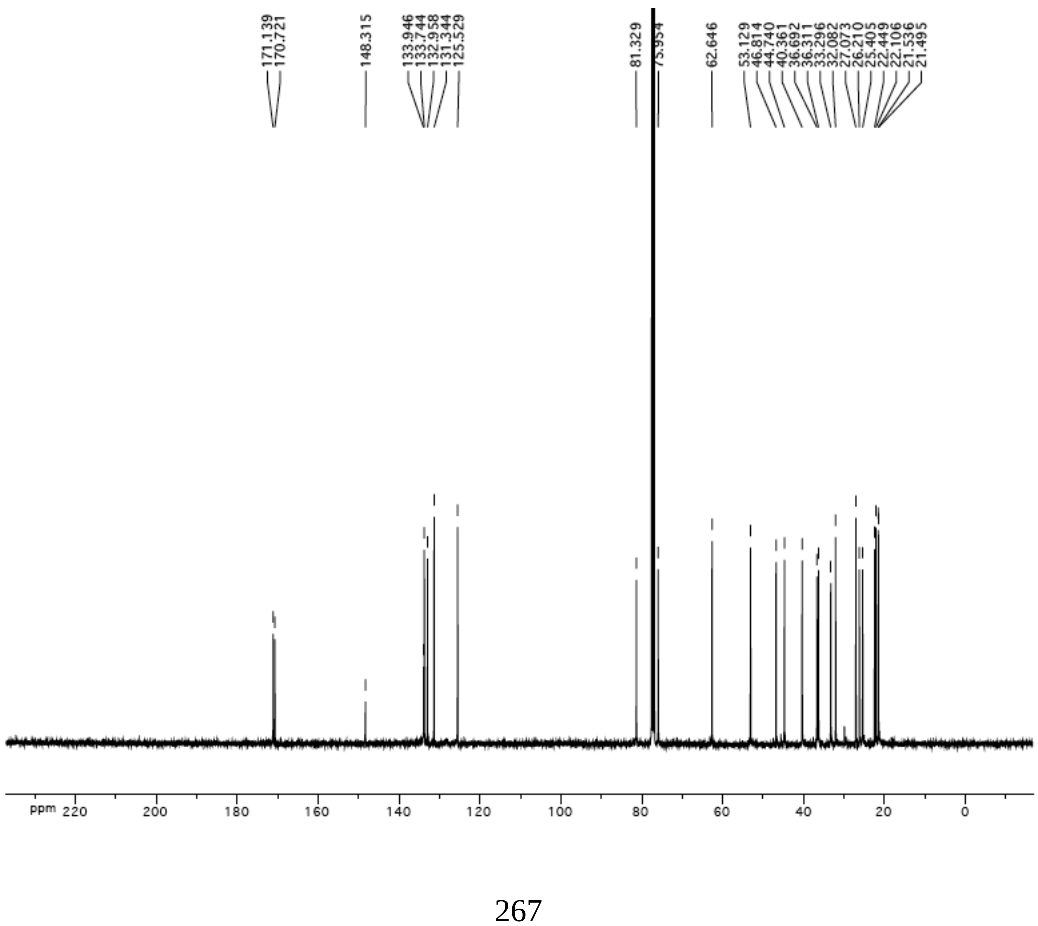
[1]H and [13]C NMR spectra for **4.38**



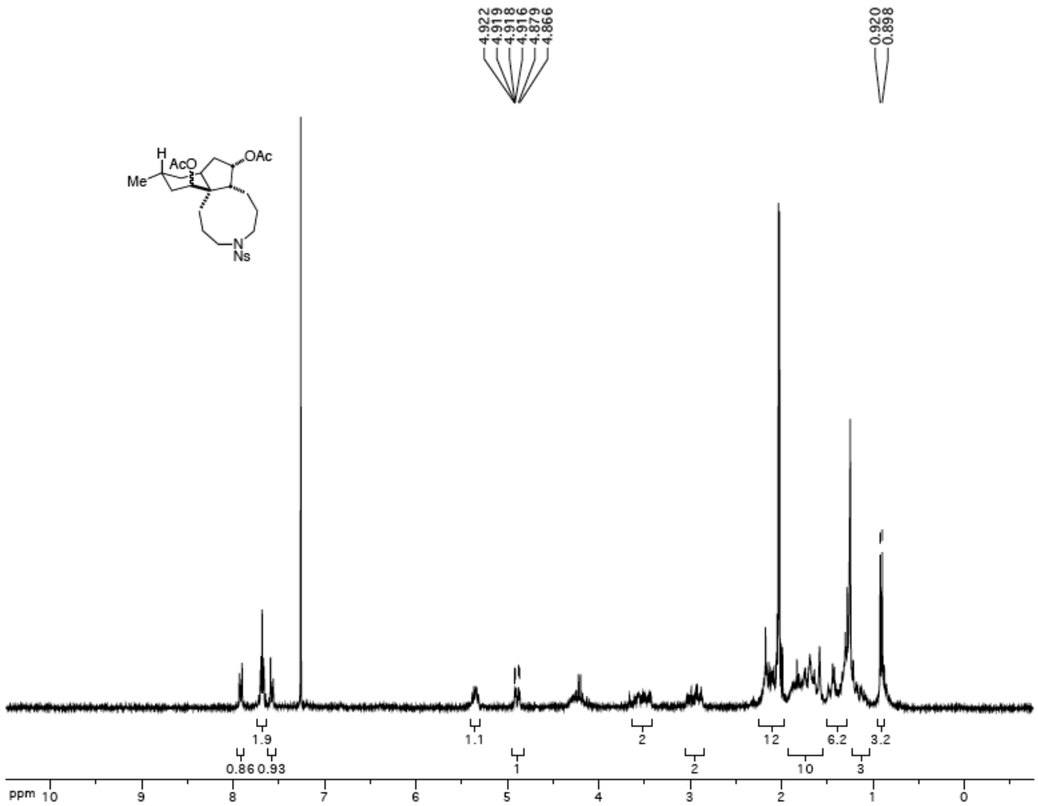


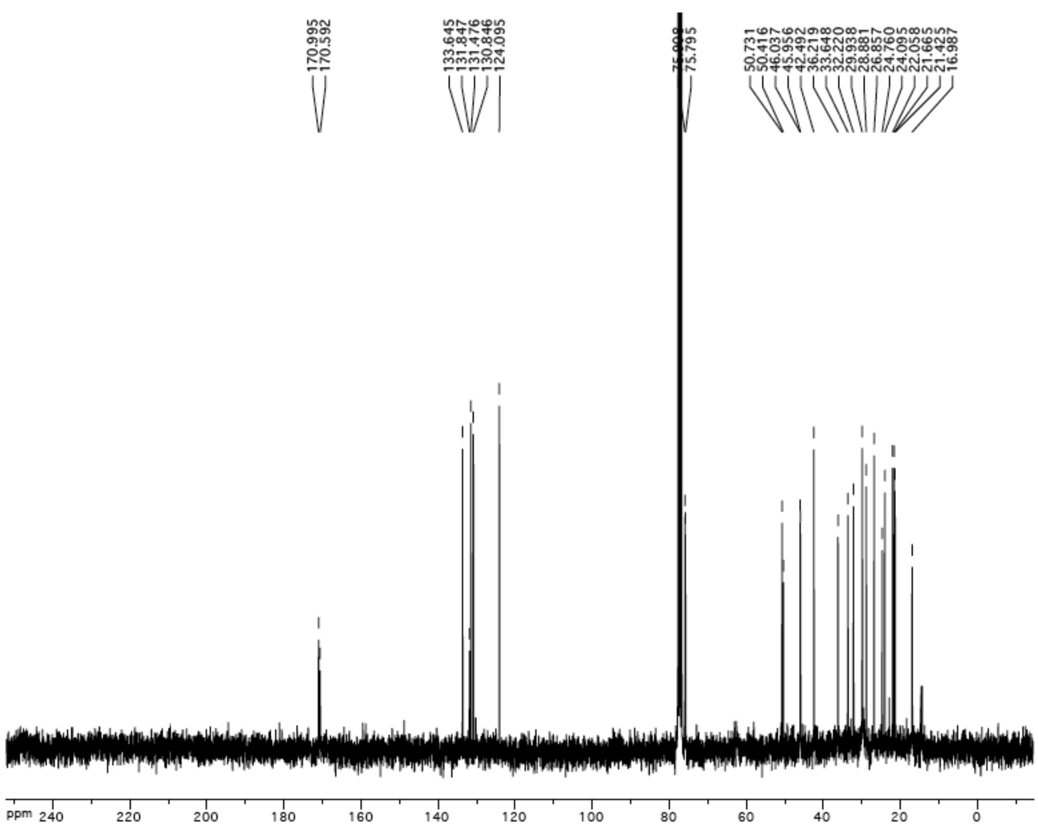
^{1}H and ^{13}C NMR spectra for **4.39**



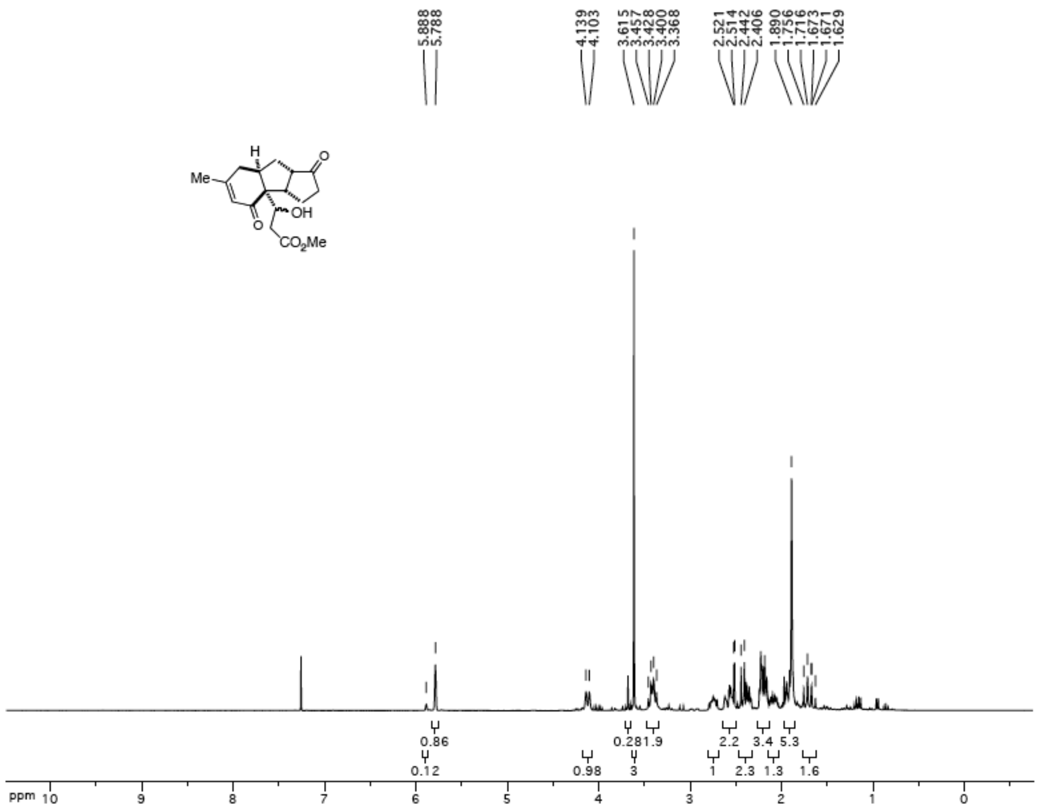


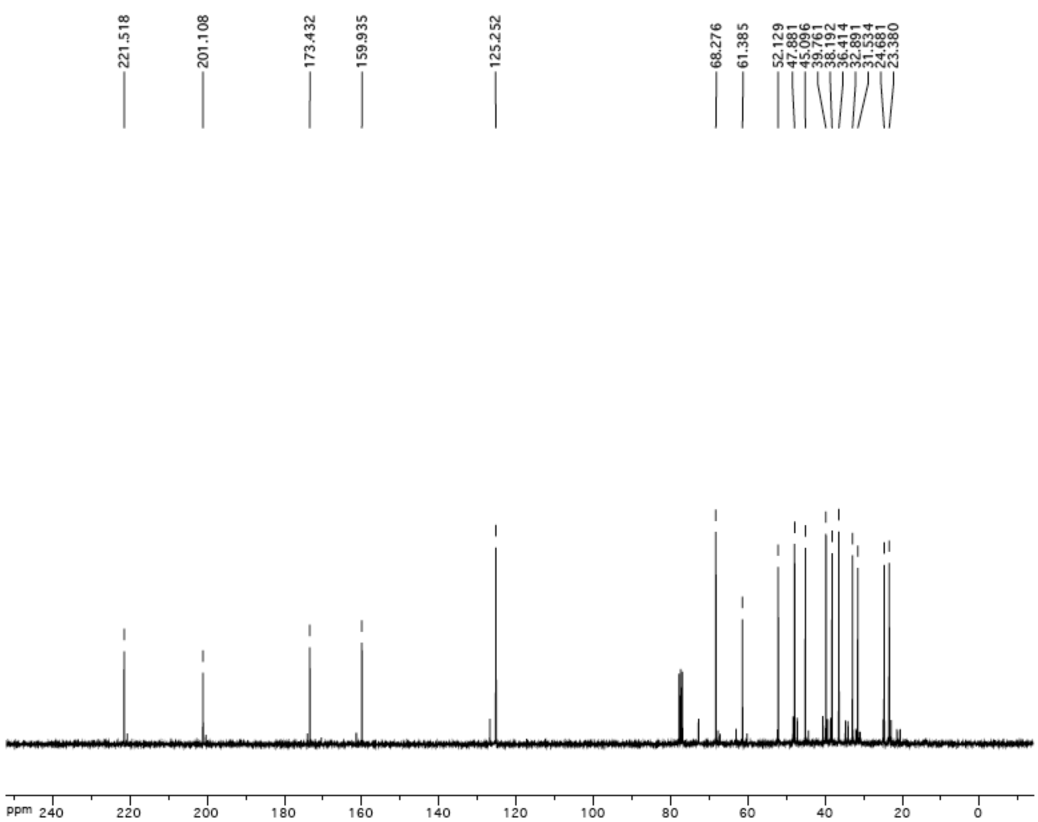
[1]H and [13]C NMR spectra for **4.40**



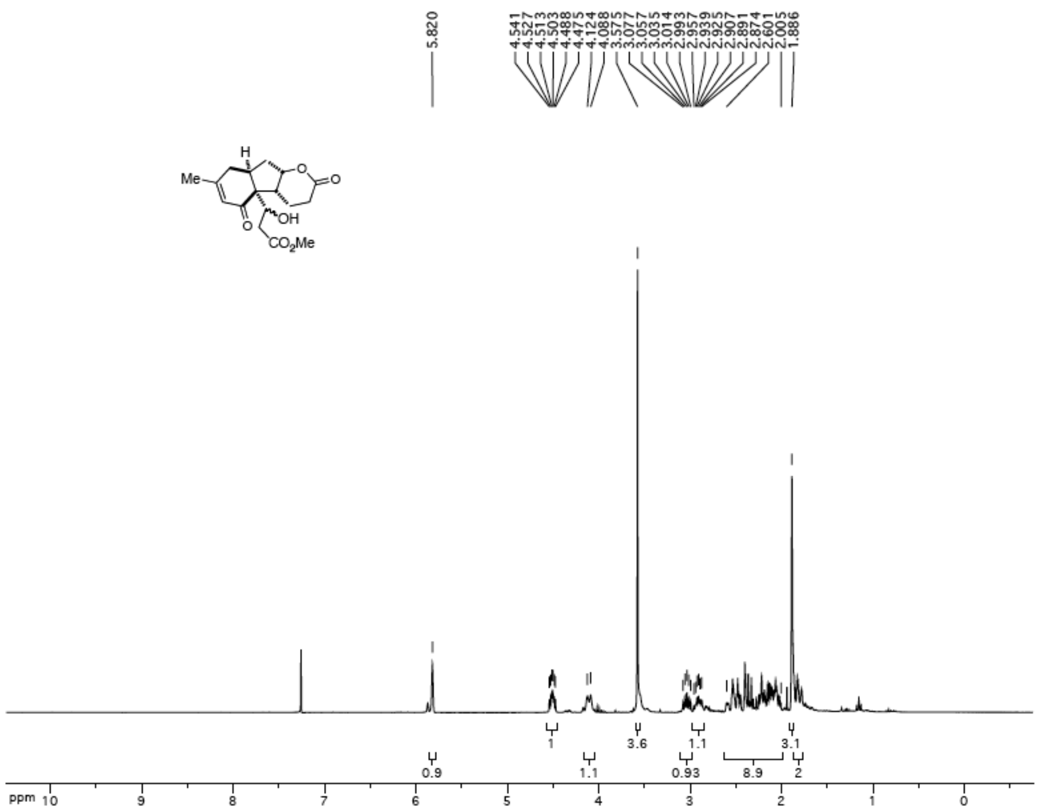


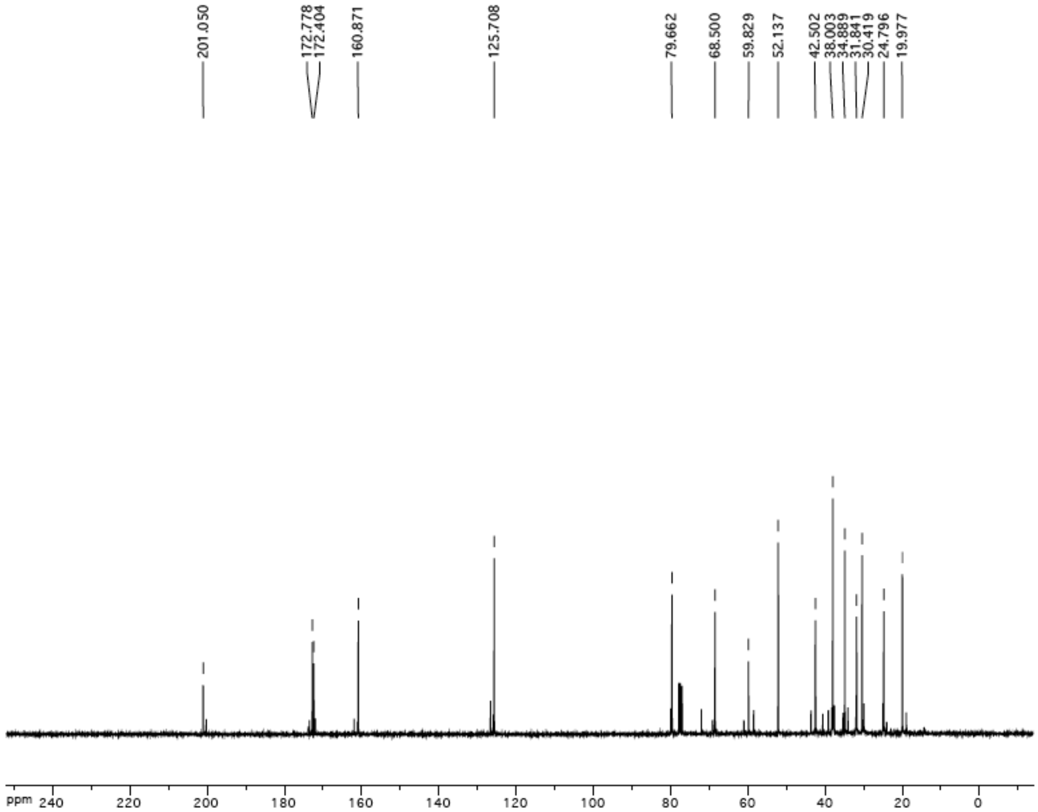
^{1}H and ^{13}C NMR spectra for **4.43**



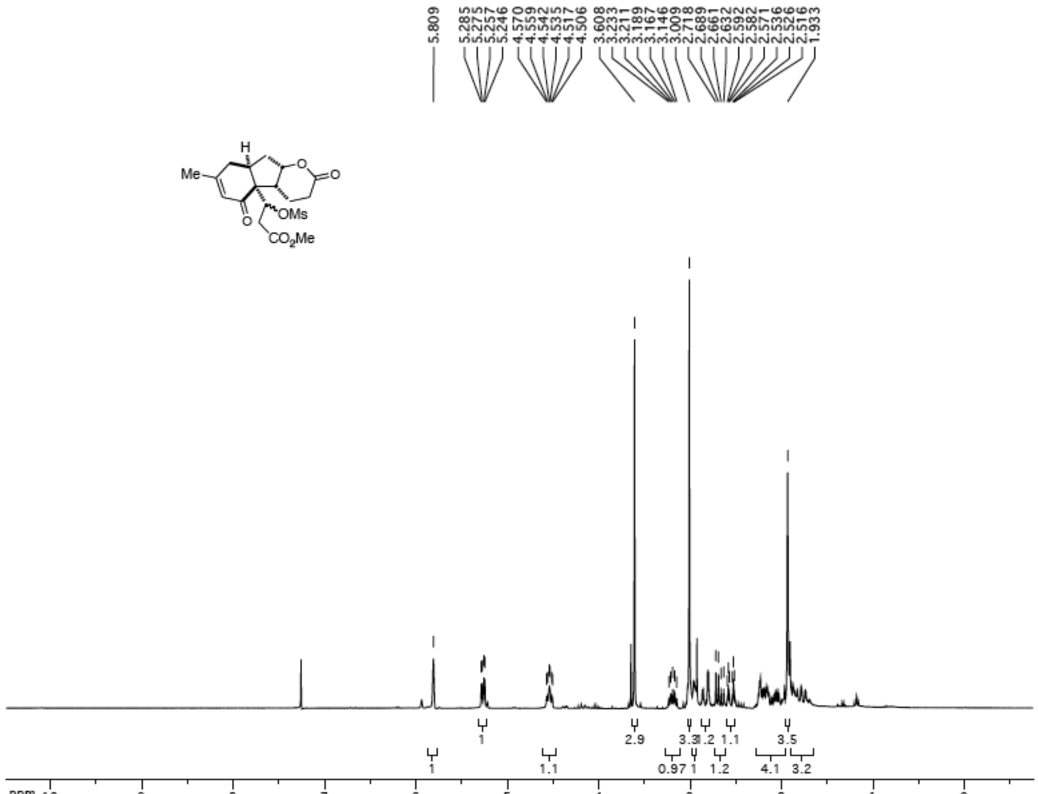


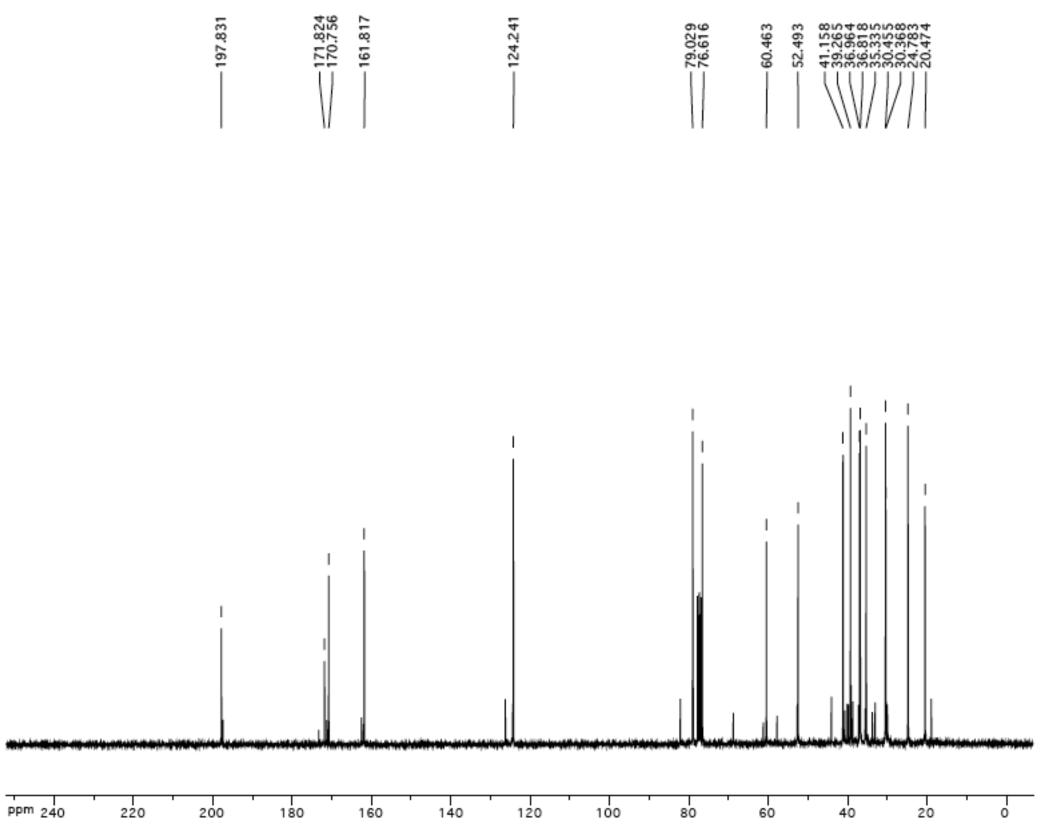
^{1}H and ^{13}C NMR spectra for **4.44**



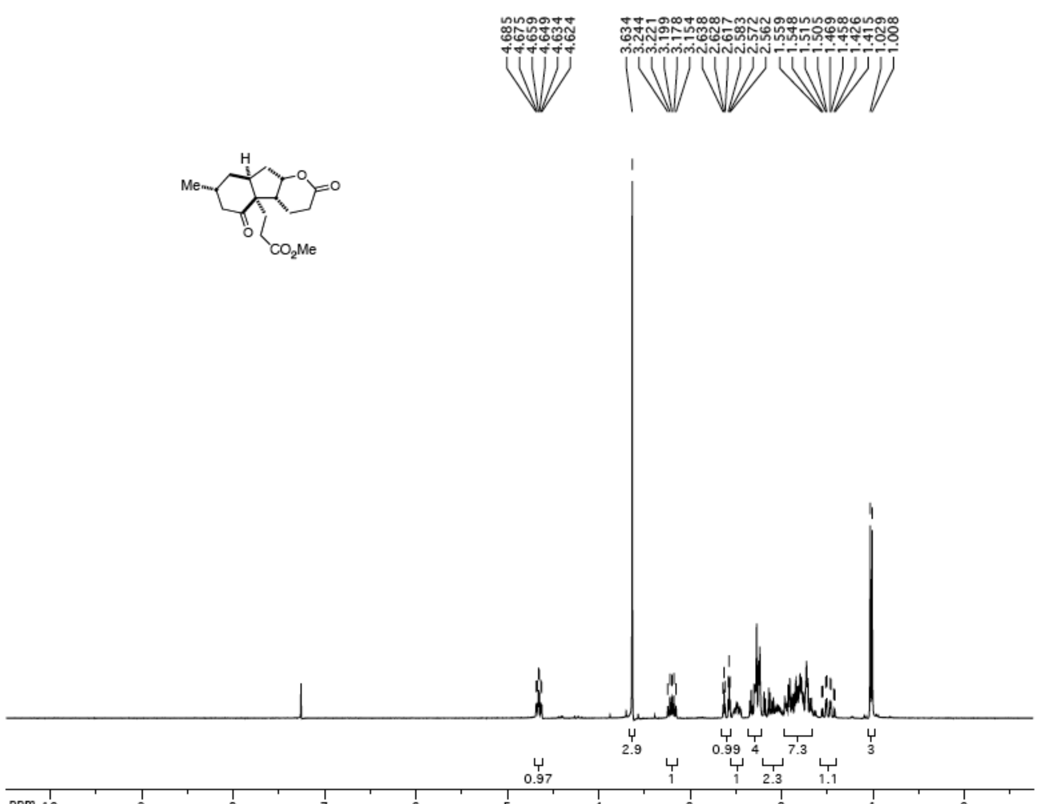


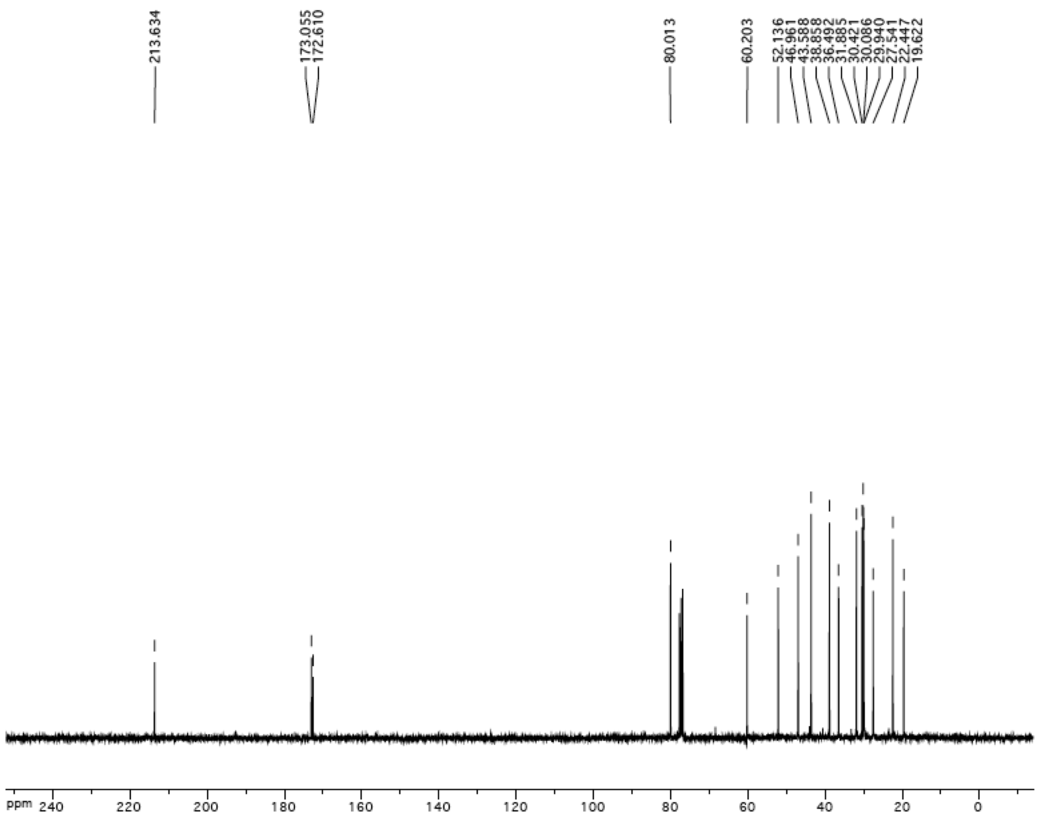
^{1}H and ^{13}C NMR spectra for **4.45**



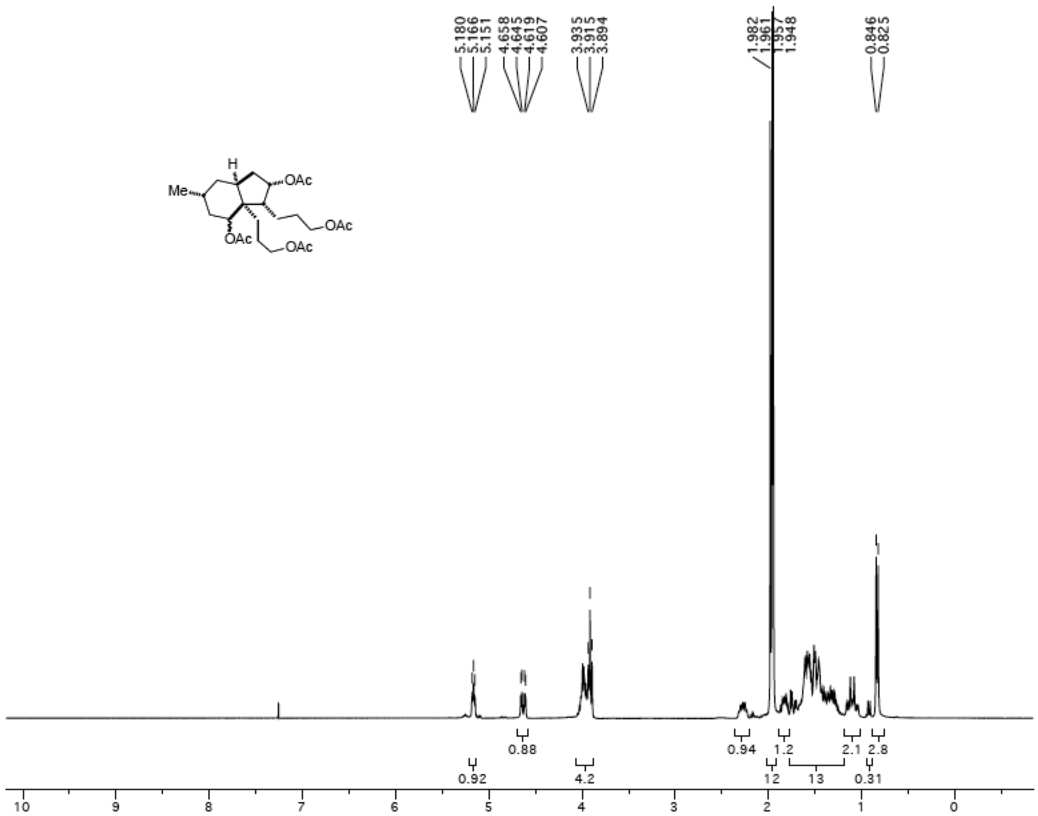


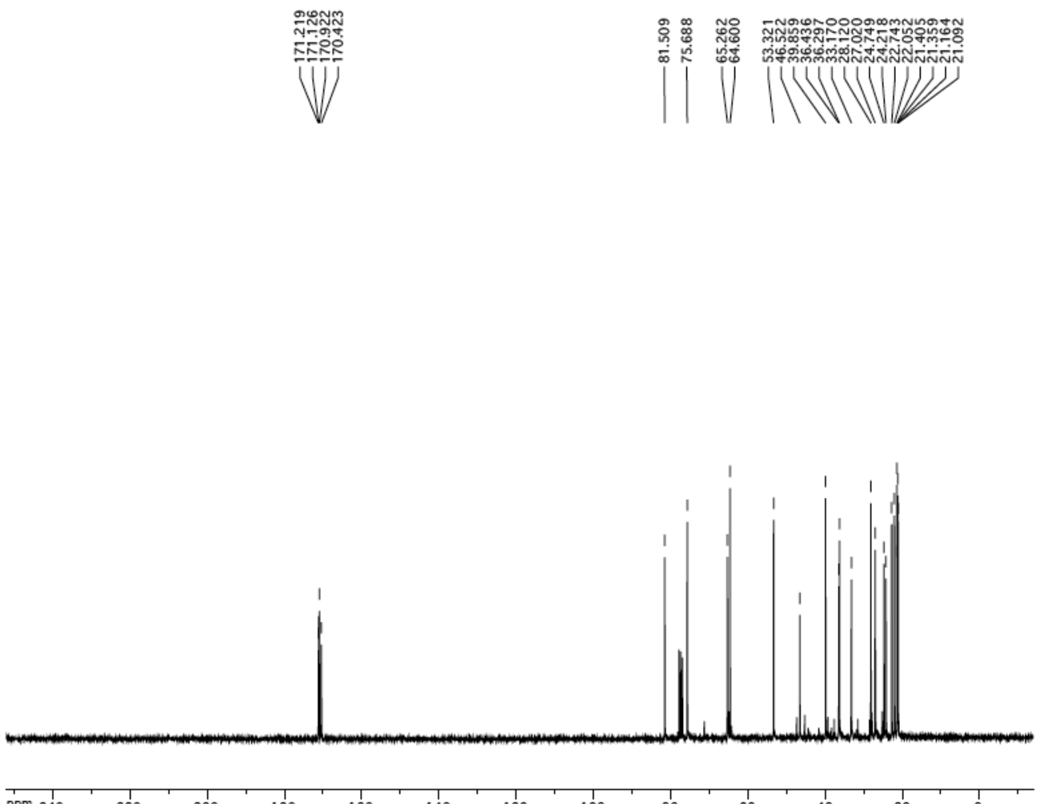
[1]H and [13]C NMR spectra for **4.46**



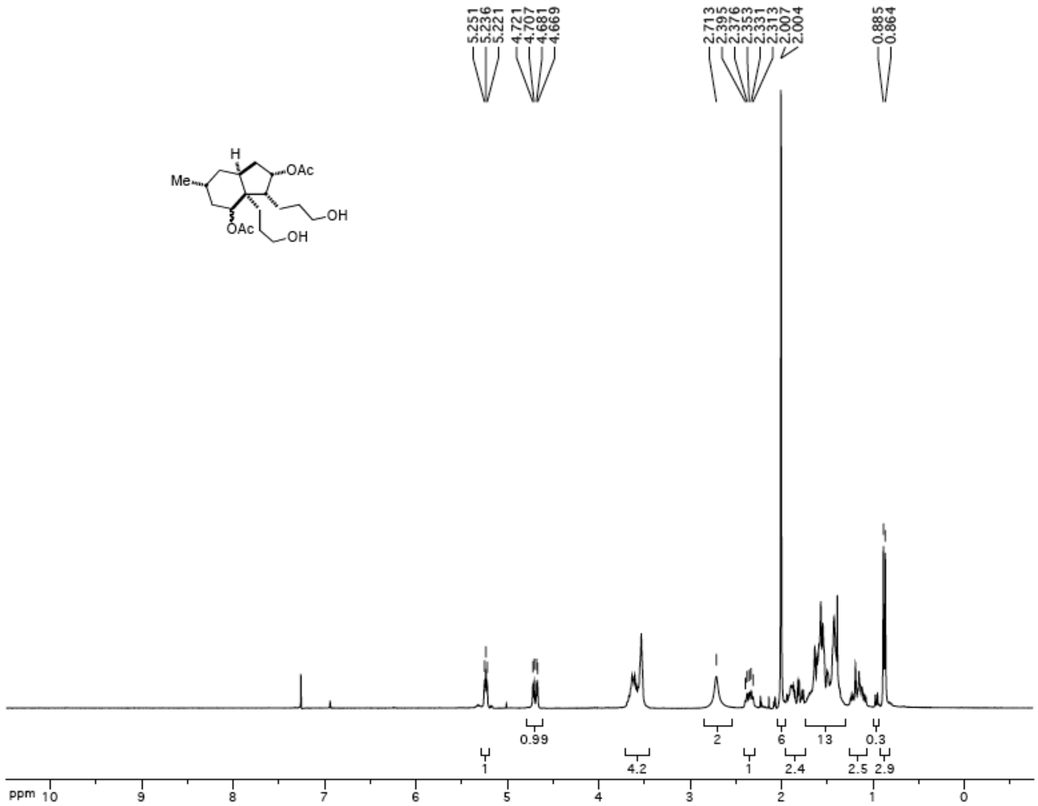


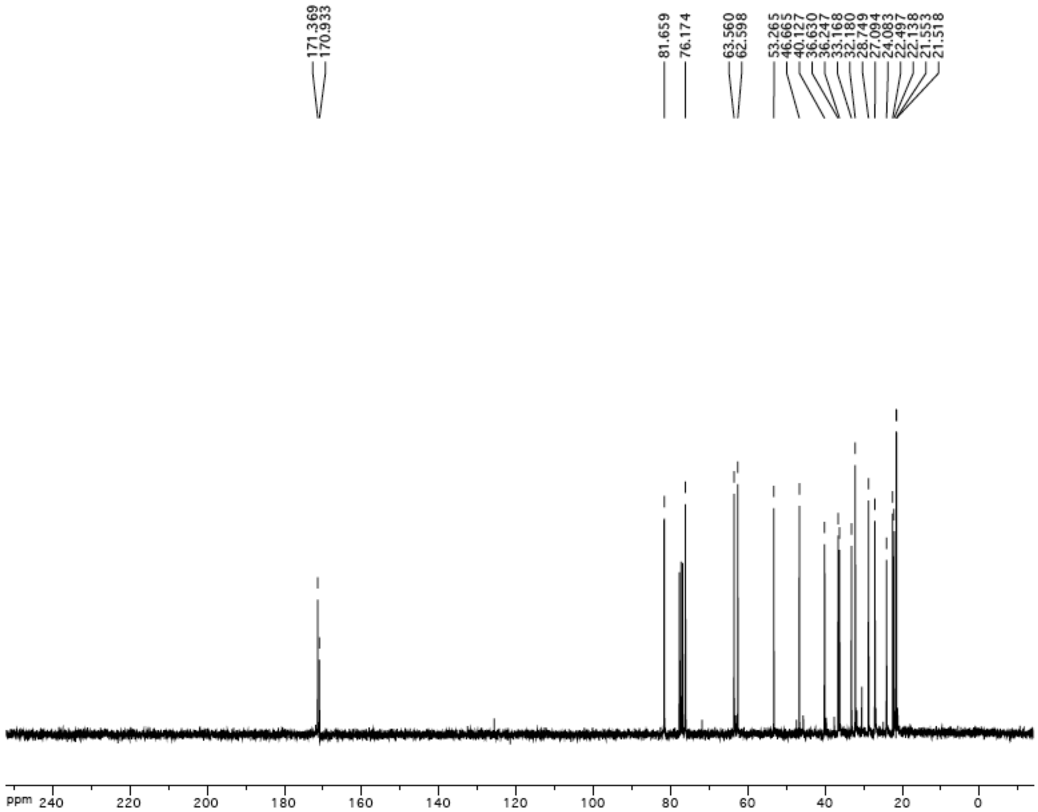
^{1}H and ^{13}C NMR spectra for **4.47**



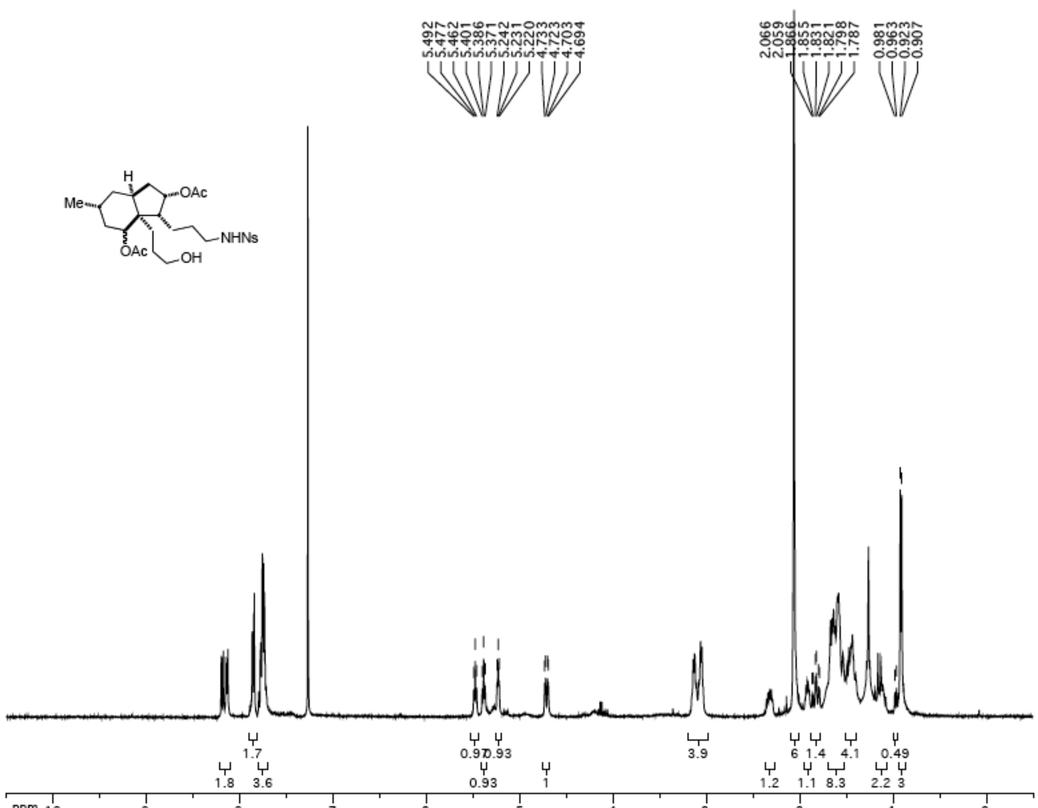


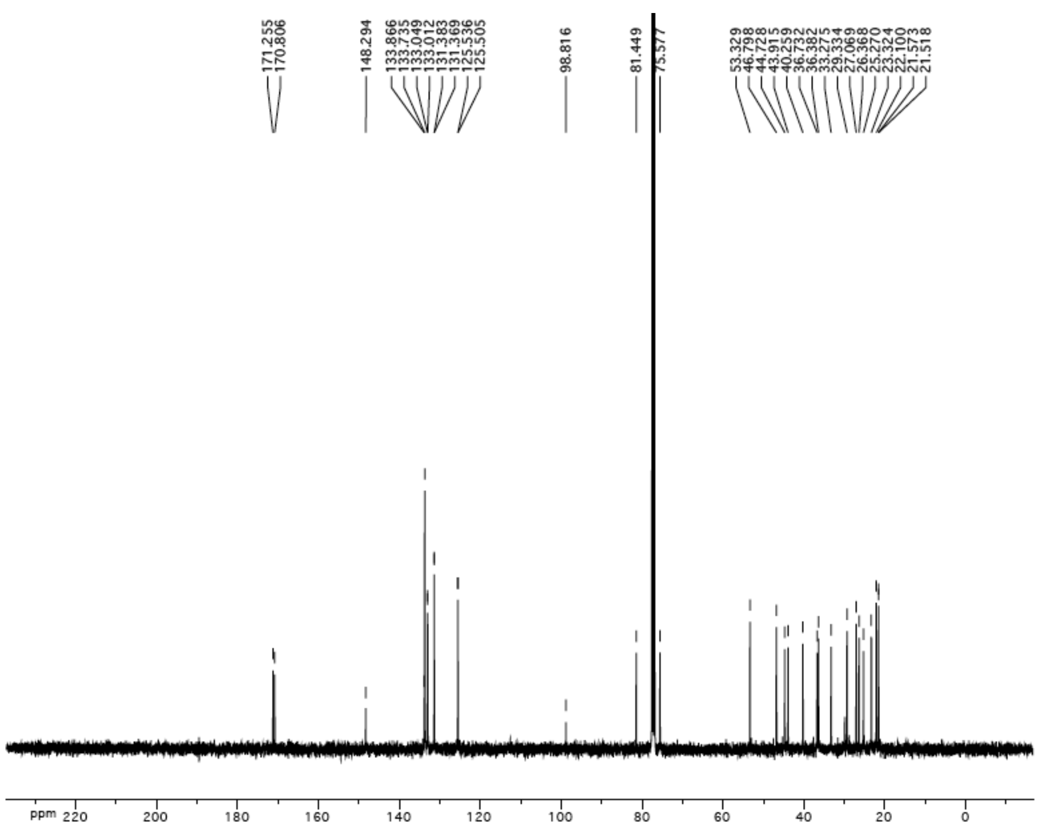
^{1}H and ^{13}C NMR spectra for **4.48**



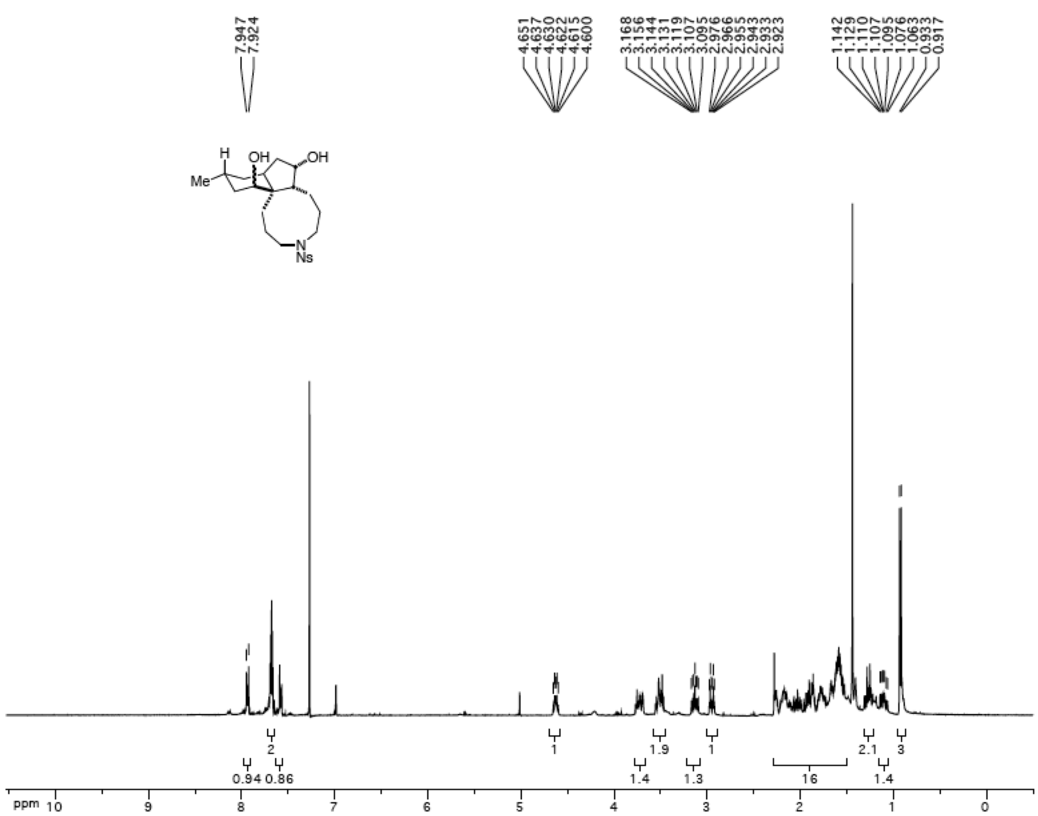


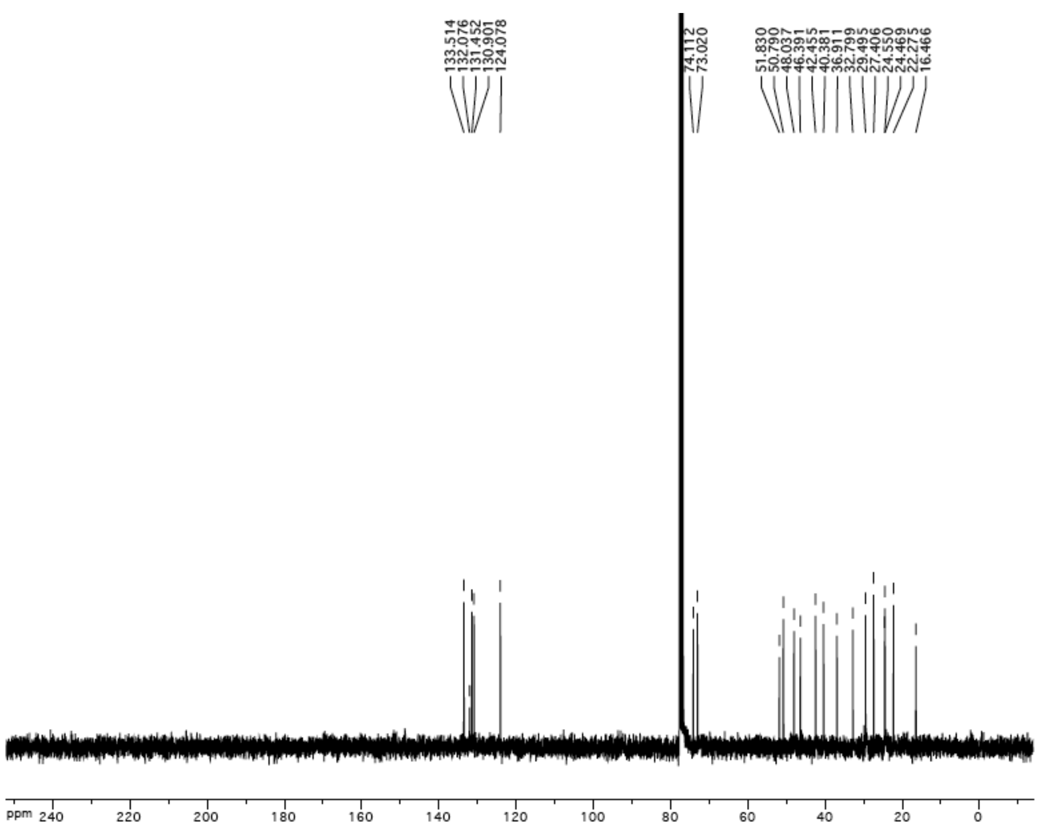
^{1}H and ^{13}C NMR spectra for **4.49**



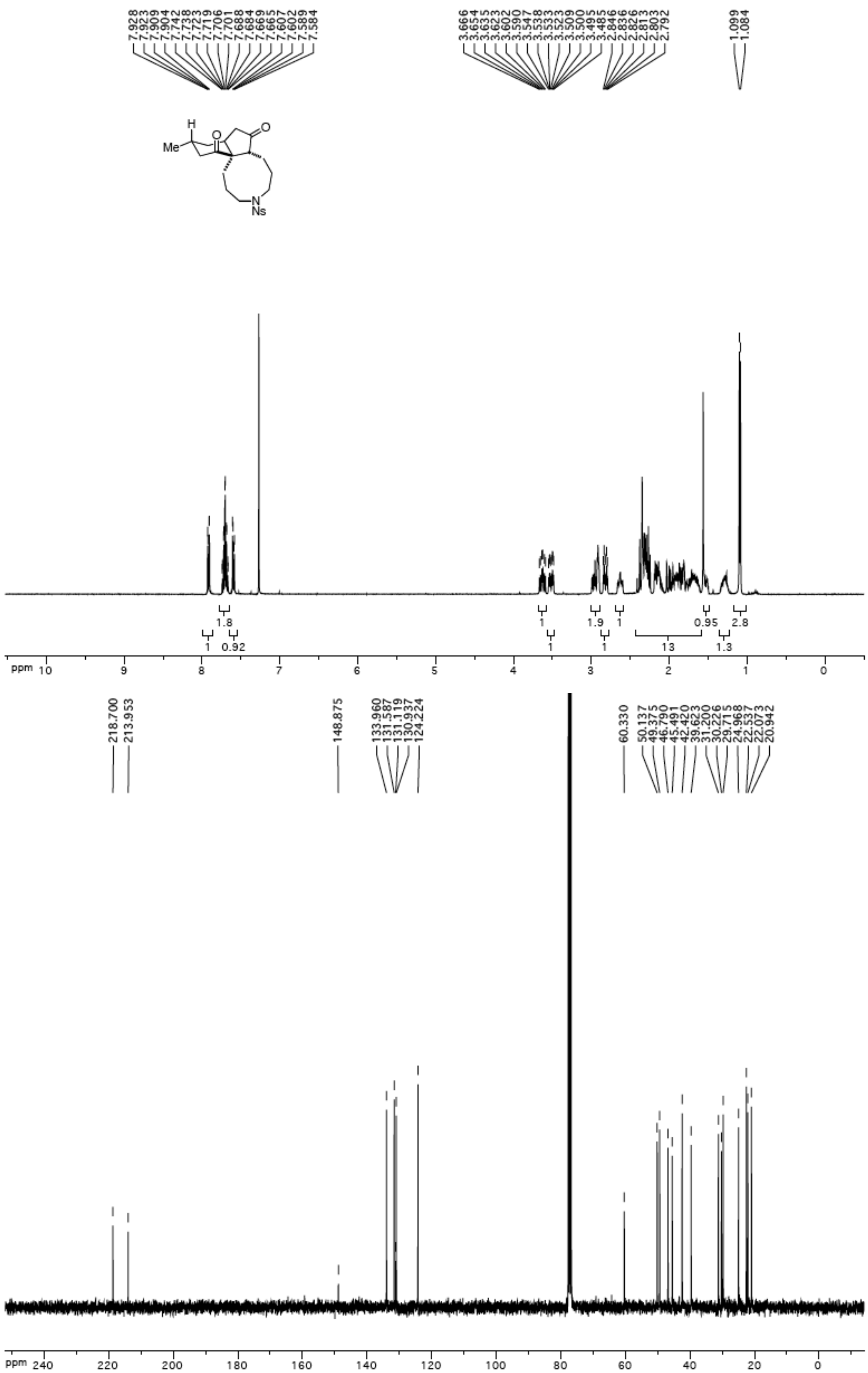


[1]H and [13]C NMR spectra for **4.53**

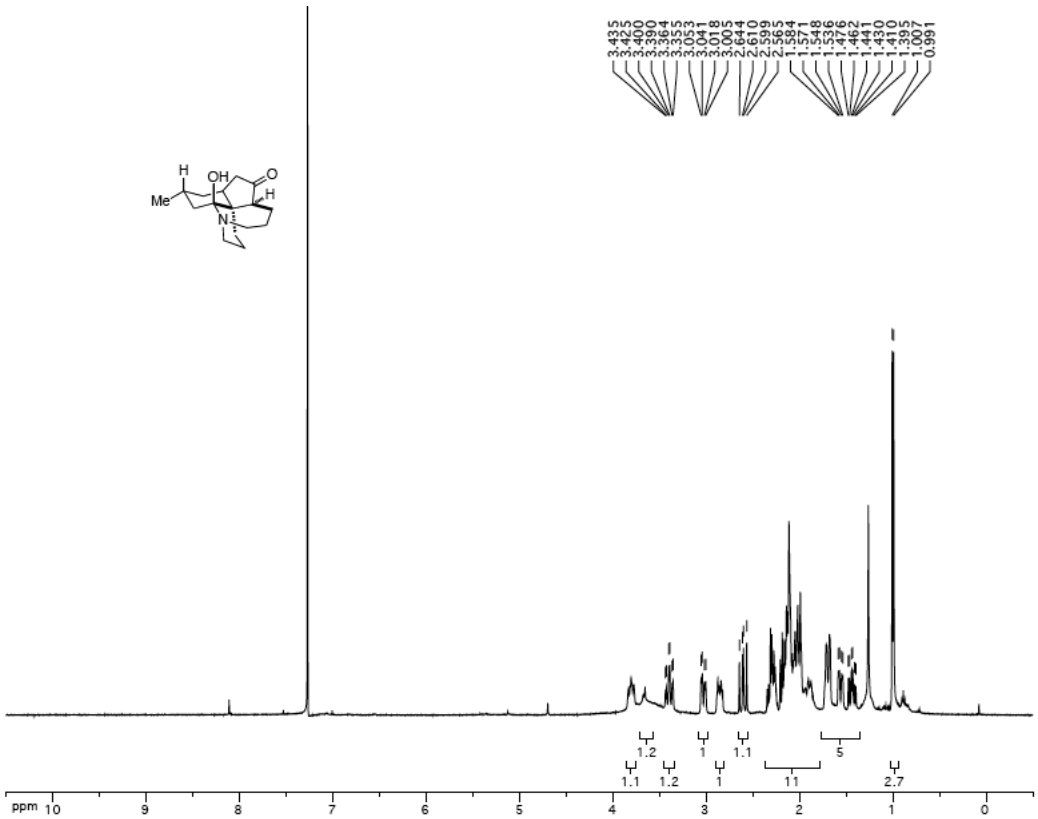




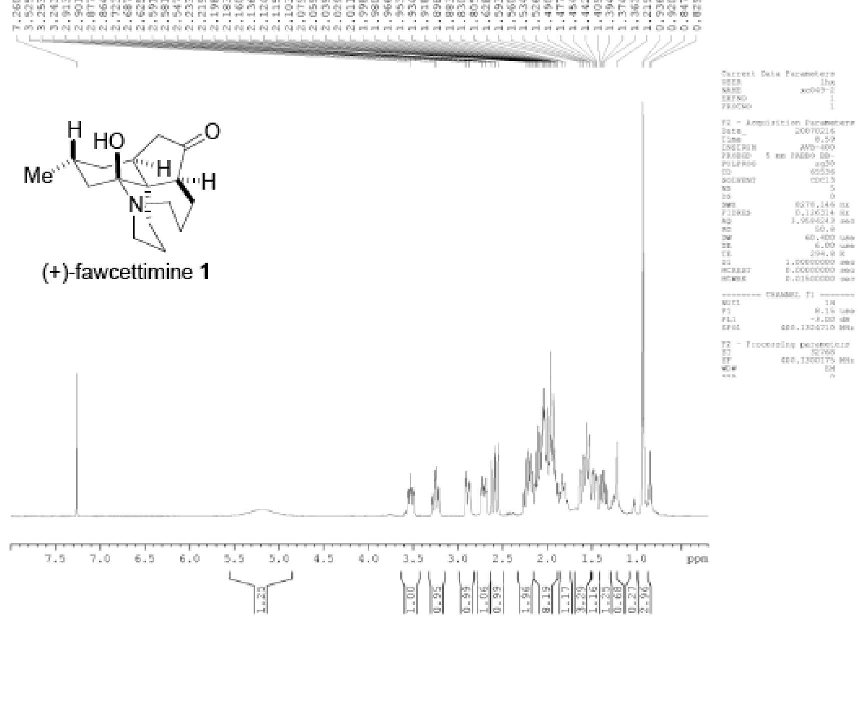
^1H and ^{13}C NMR spectra for **4.54**



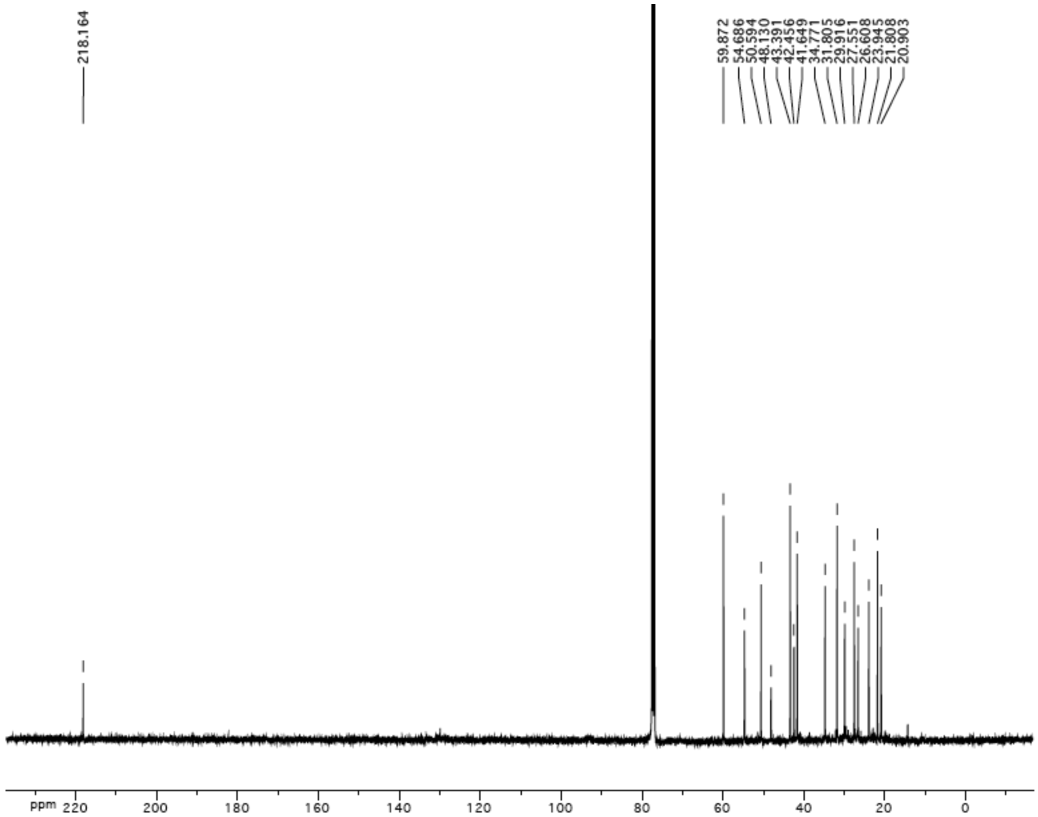
[1]H NMR spectrum for (±)-fawcettimine



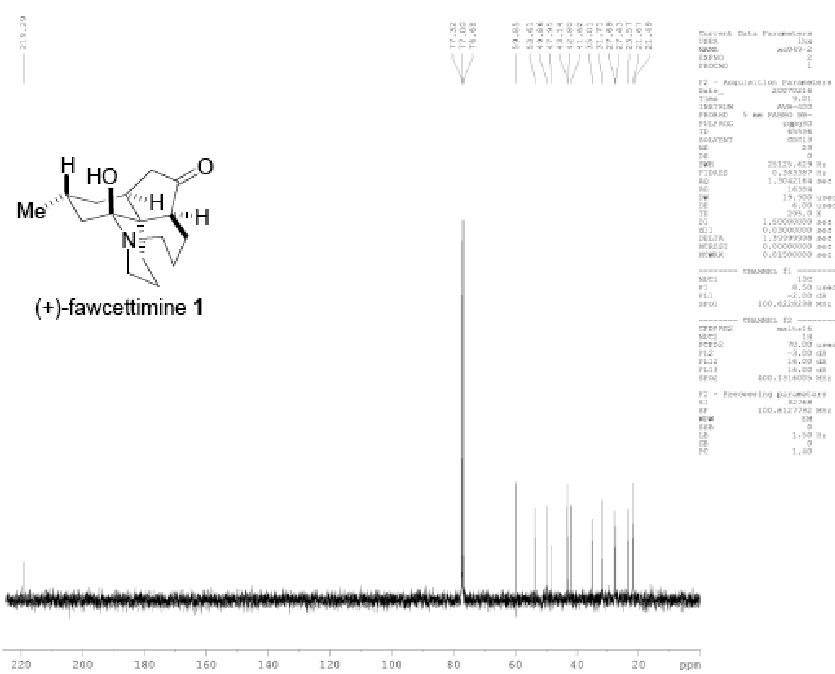
[1]H NMR spectrum for (+)-fawcettimine reported by Toste



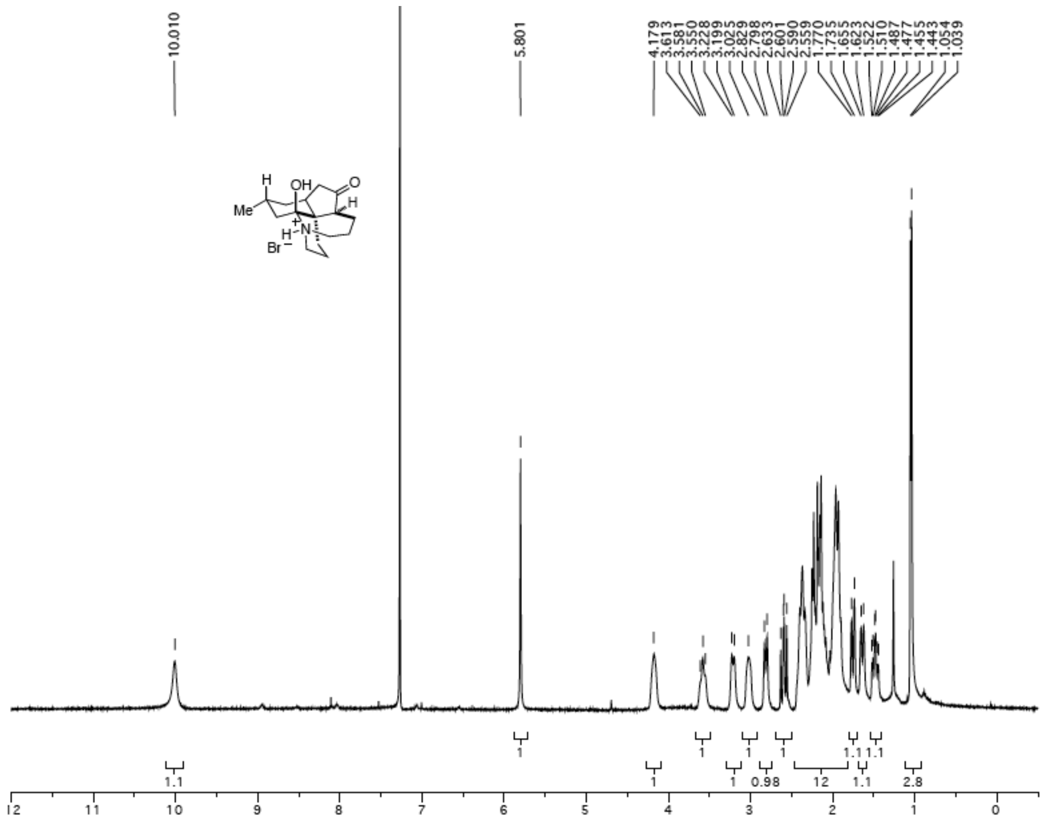
^{13}C NMR spectrum for (±)-fawcettimine



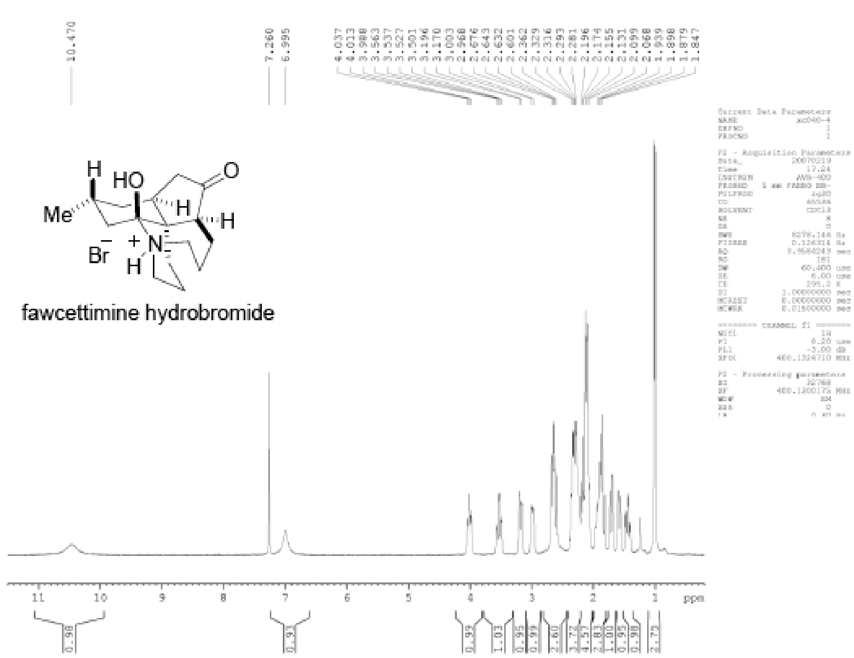
^{13}C NMR spectrum for (+)-fawcettimine reported by Toste



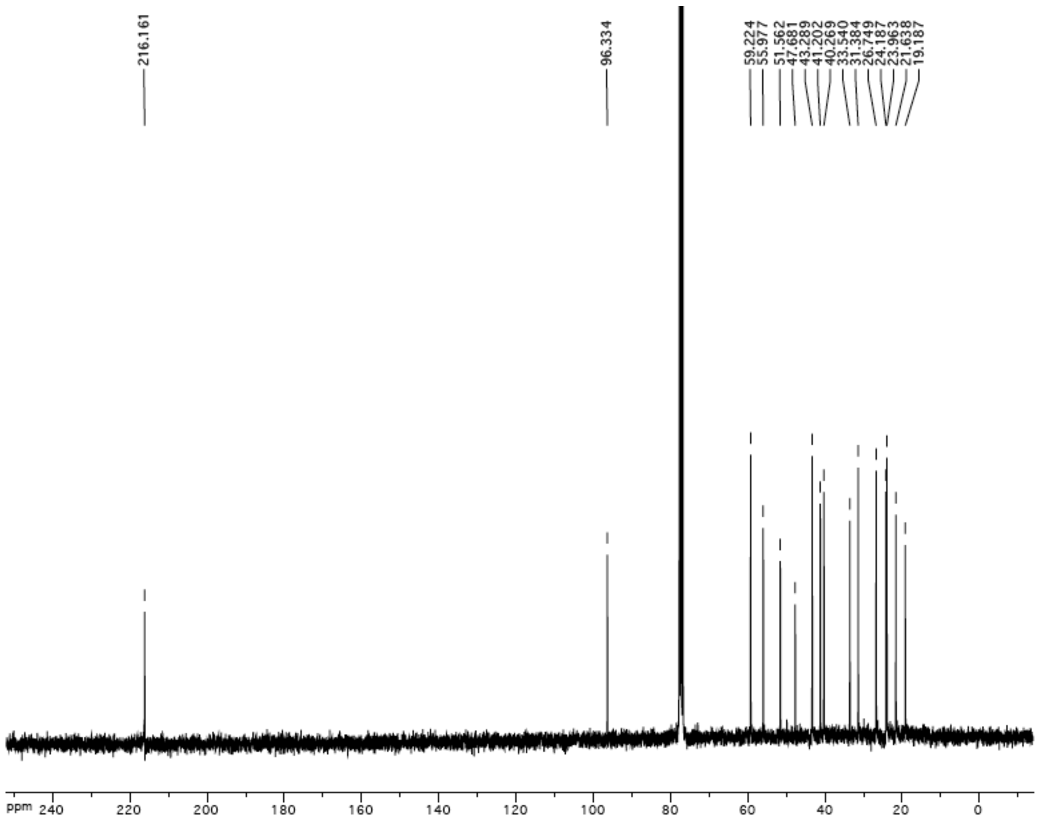
[1]H NMR spectrum for (±)-fawcettimine hydrobromide



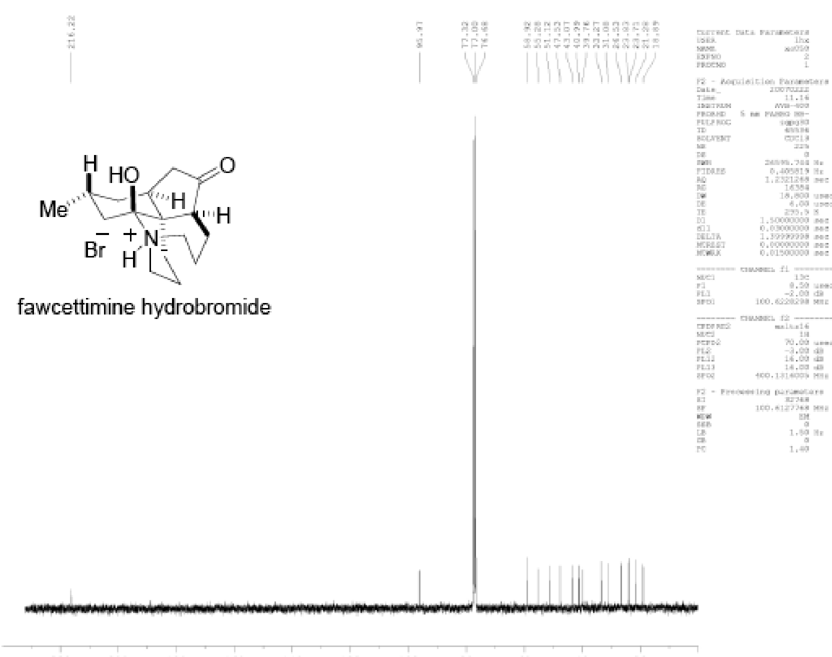
[1]H NMR spectrum for (+)-fawcettimine hydrobromide reported by Toste



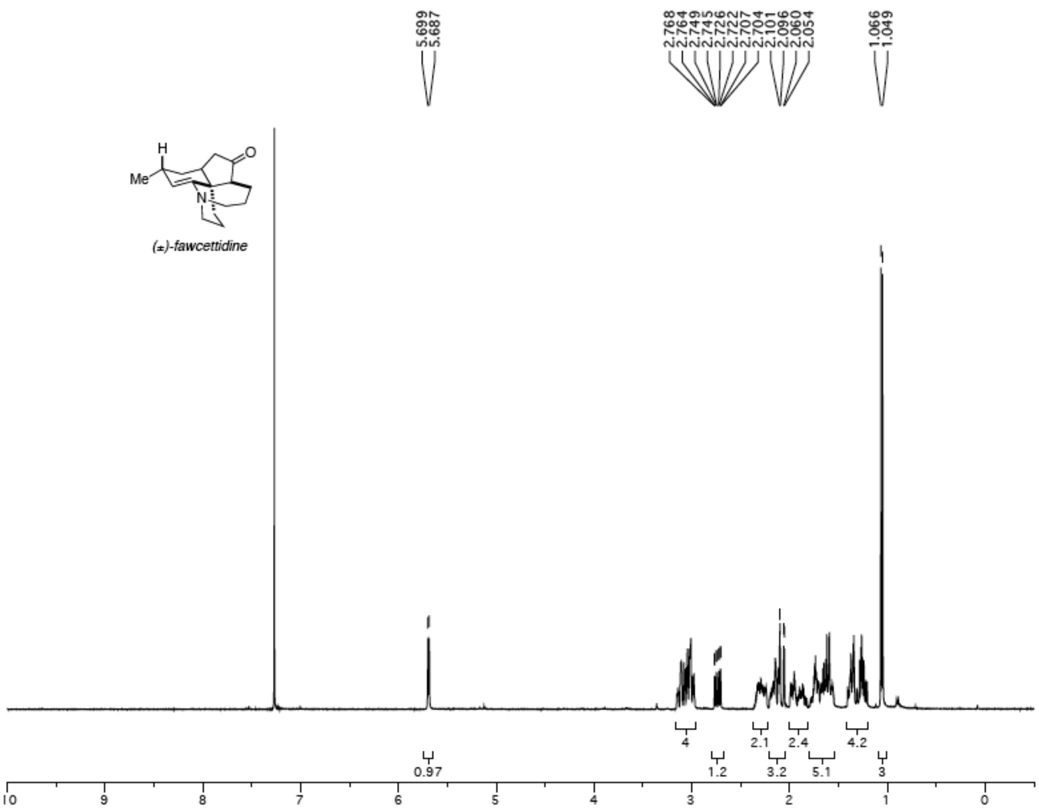
[13]C NMR spectrum for (±)-fawcettimine hydrobromide



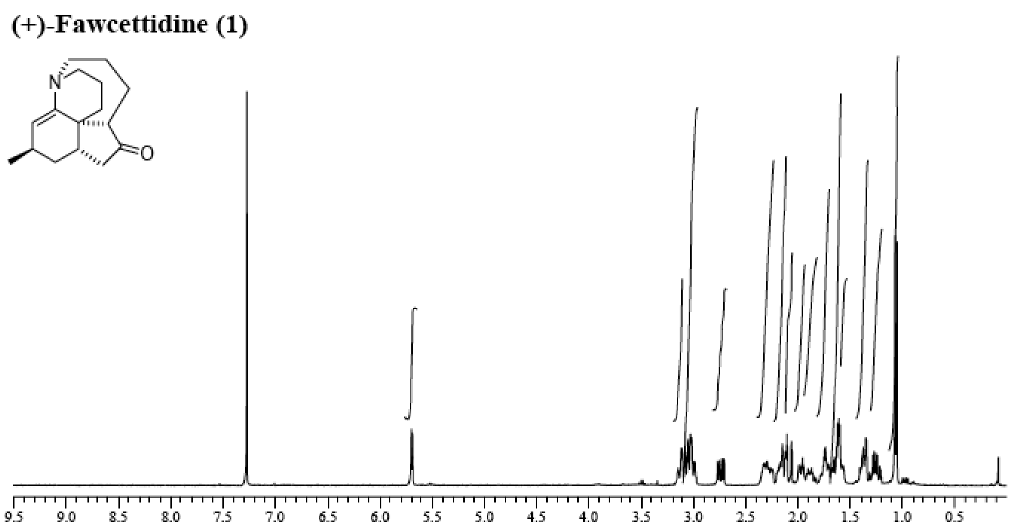
[13]C NMR spectrum for (+)-fawcettimine hydrobromide reported by Toste



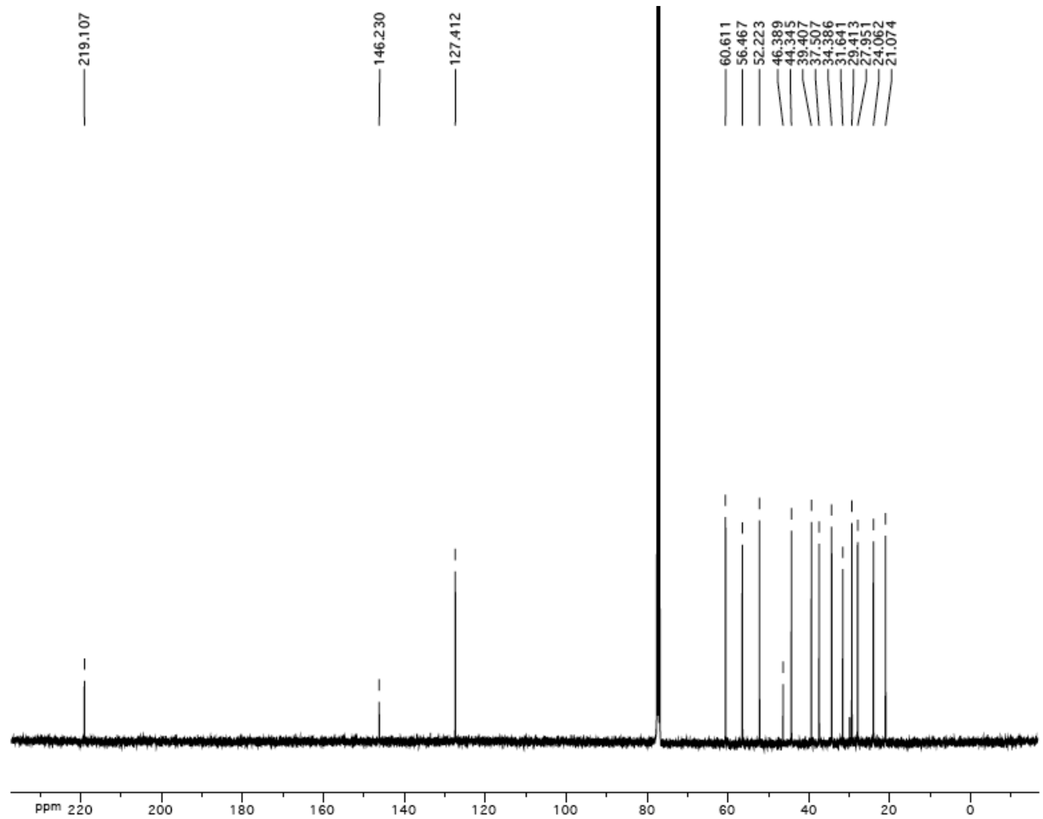
[1]H NMR spectrum for (±)-fawcettidine



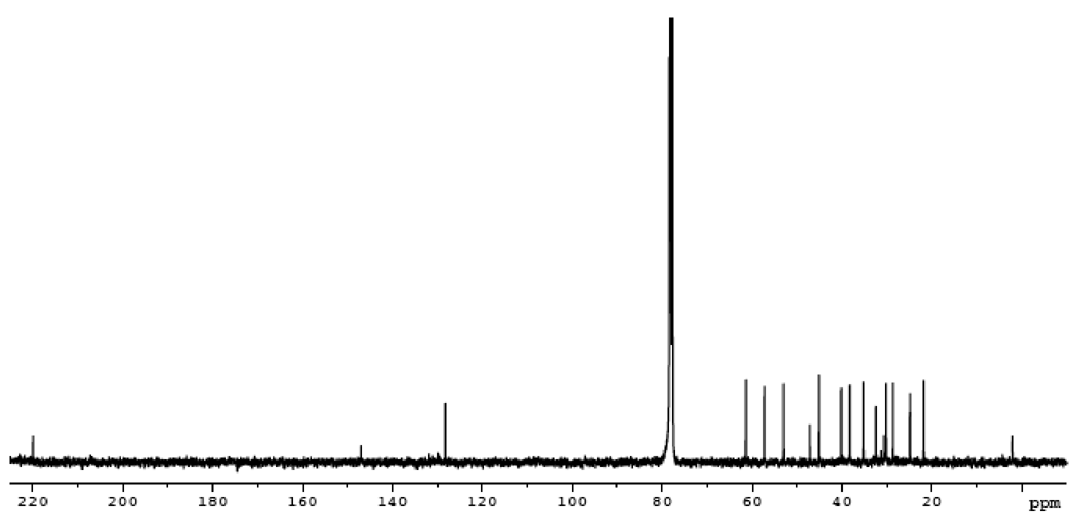
[1]H NMR spectrum for (+)-fawcettidine reported by Dake



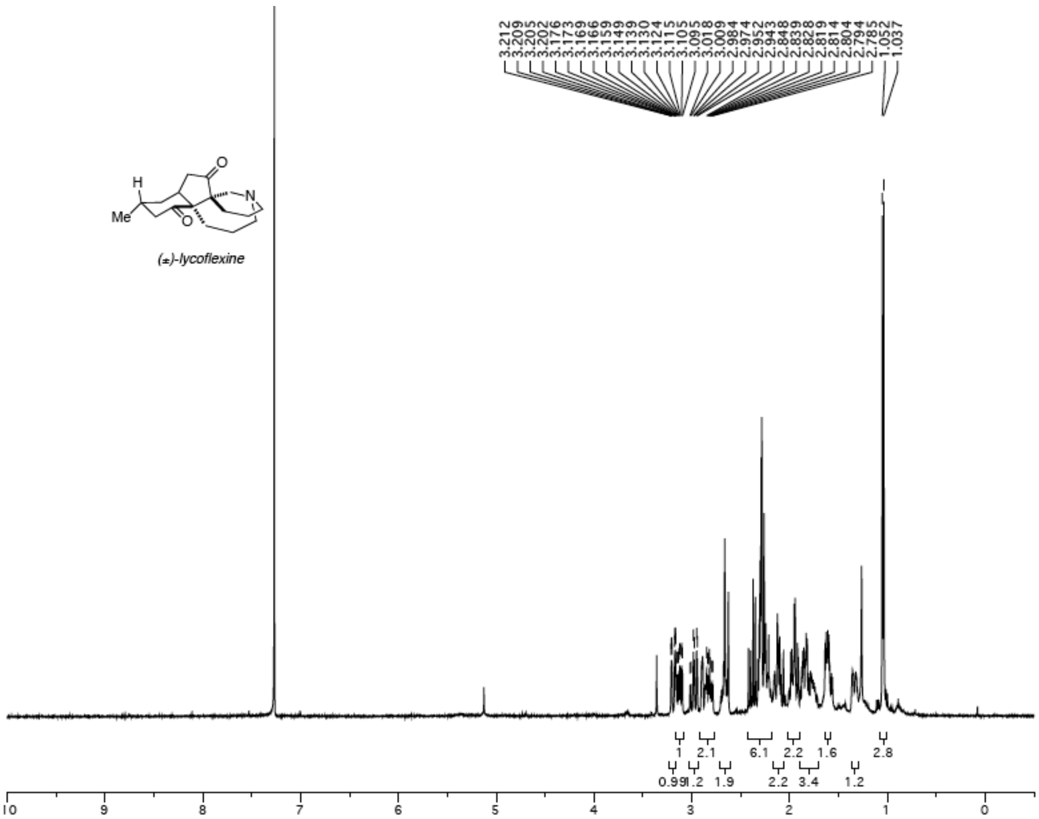
^{13}C NMR spectrum for (±)-fawcettidine



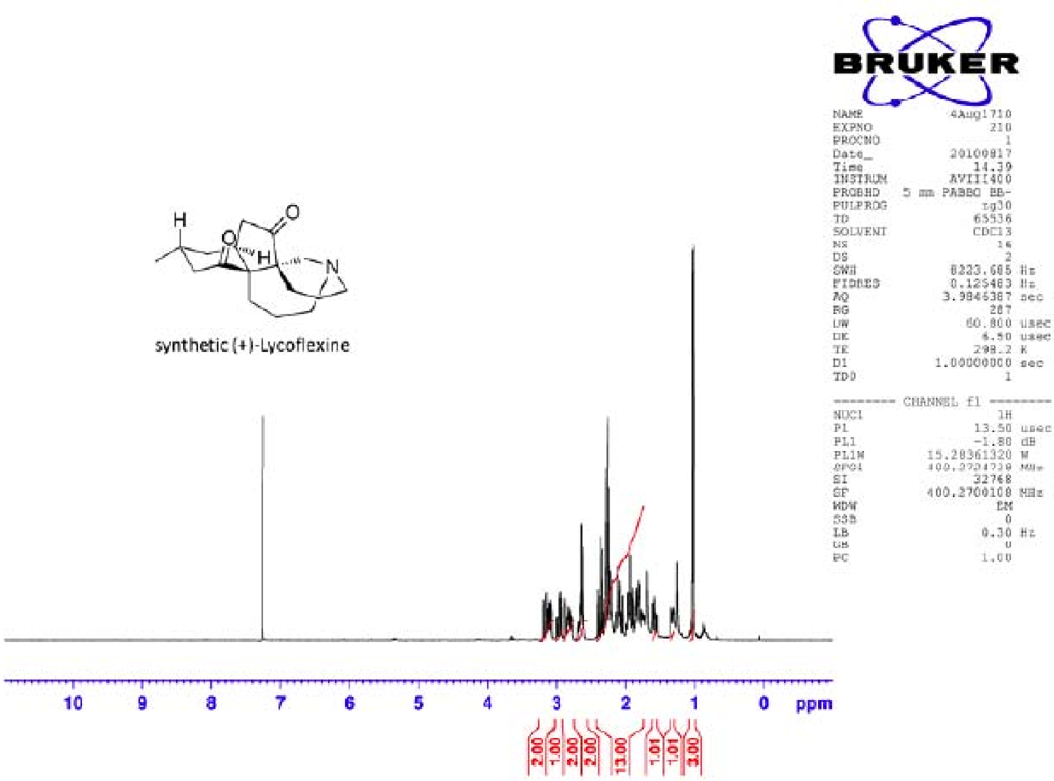
^{13}C NMR spectrum for (+)-fawcettidine reported by Dake



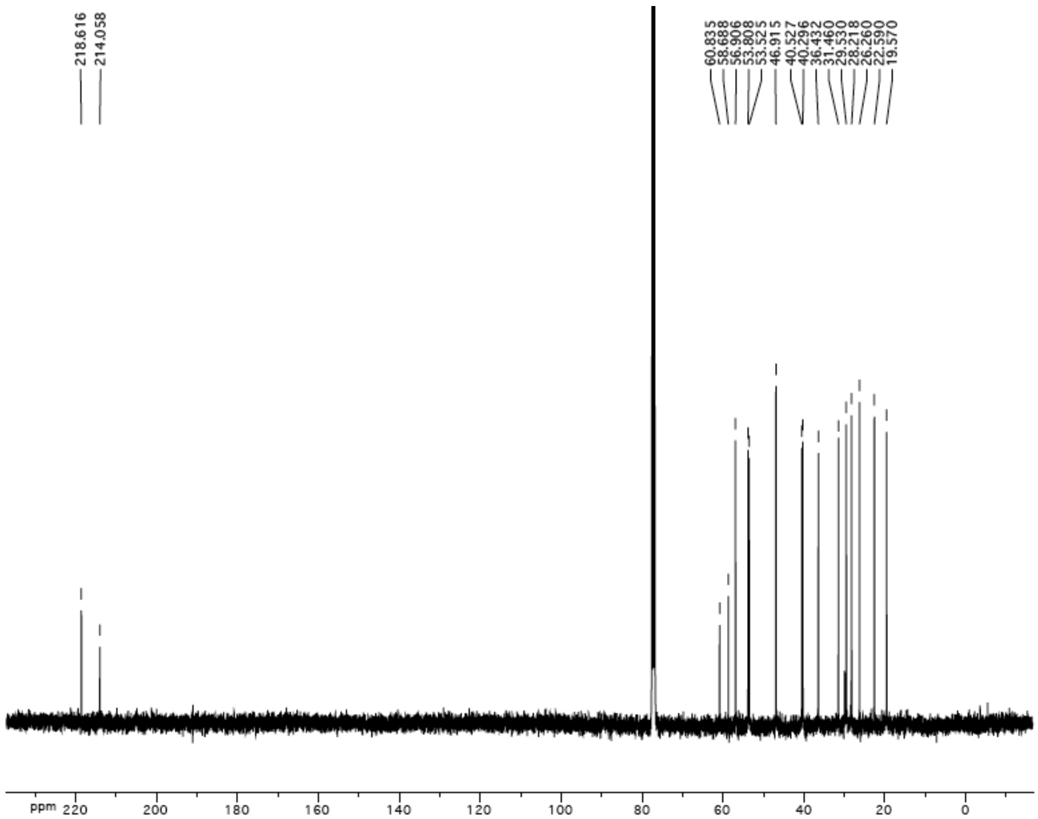
^{1}H NMR spectrum for (±)-lycoflexine



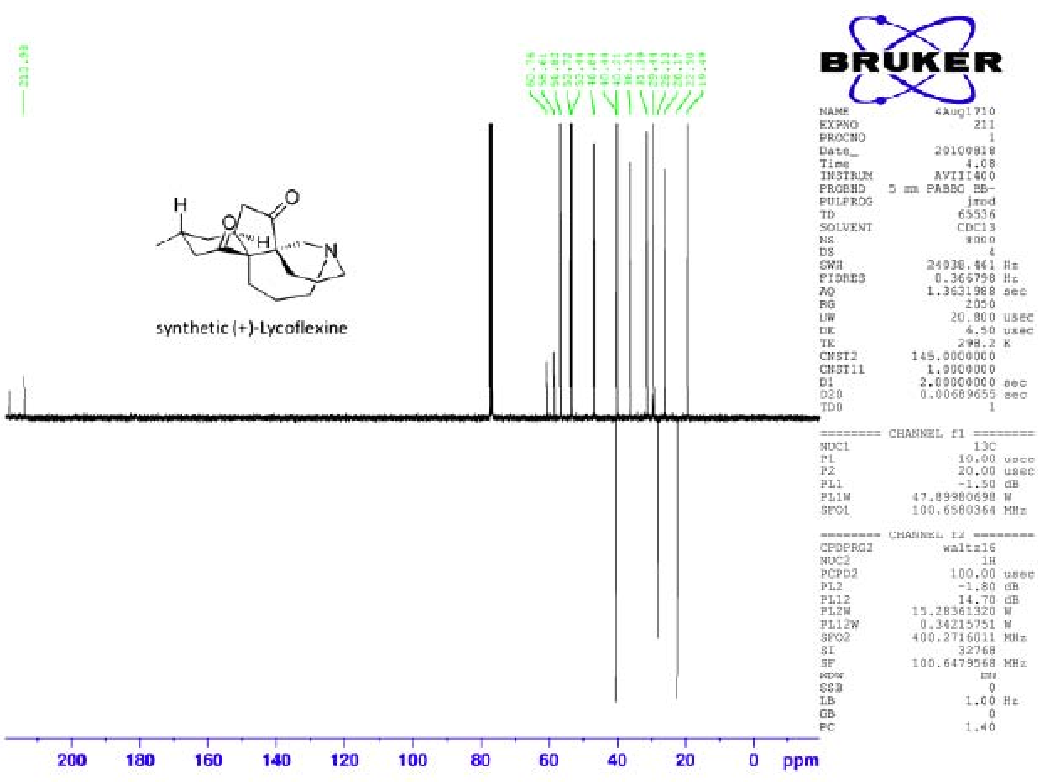
^{1}H NMR spectrum for (+)-lycoflexine reported by Ramharter



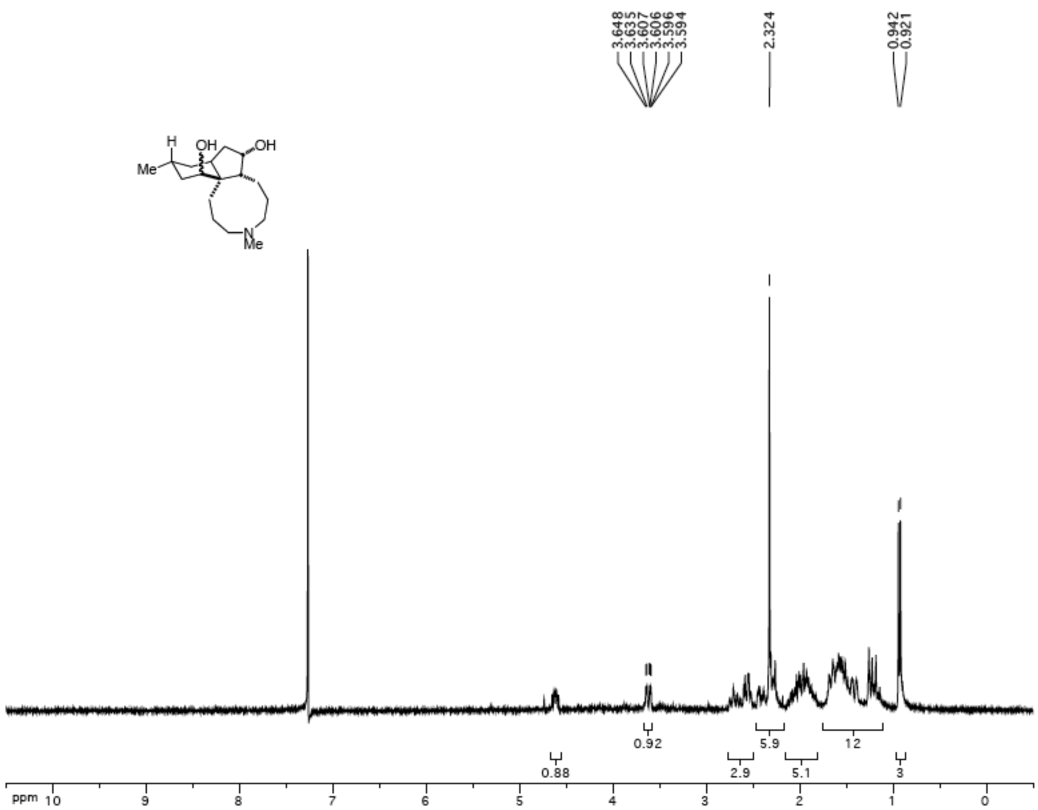
^{13}C NMR spectrum for (±)-lycoflexine

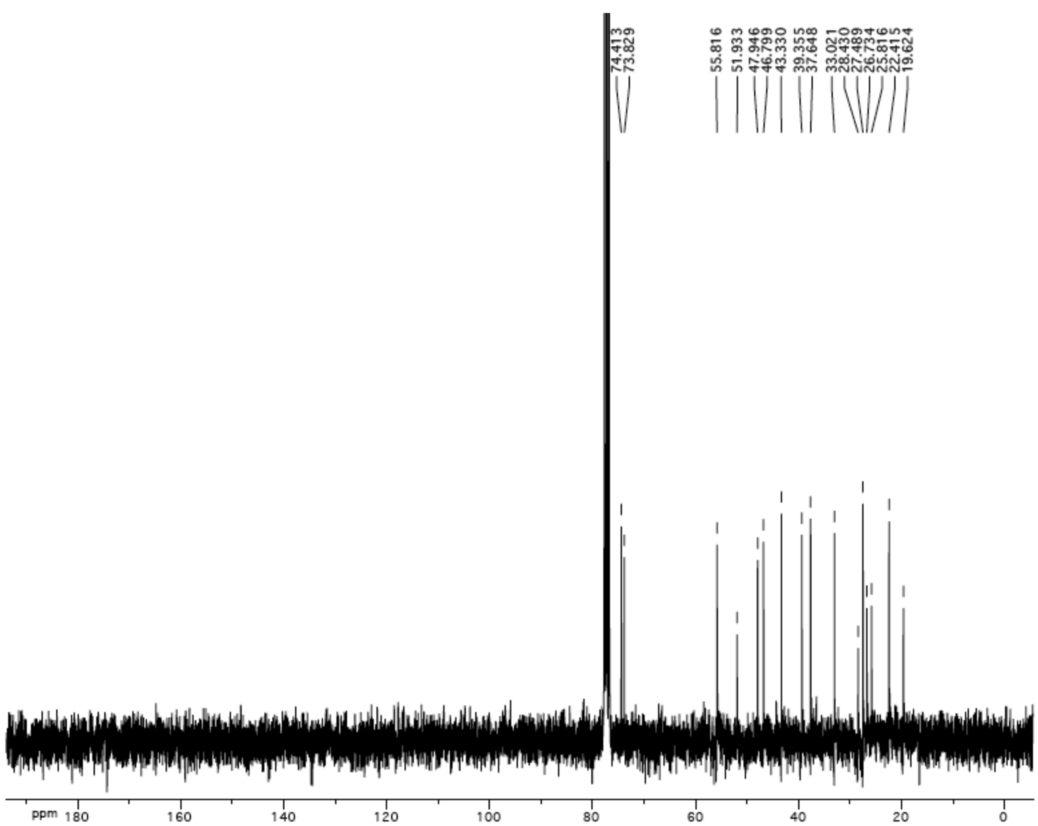


^{13}C NMR spectrum for (+)-lycoflexine reported by Ramharter

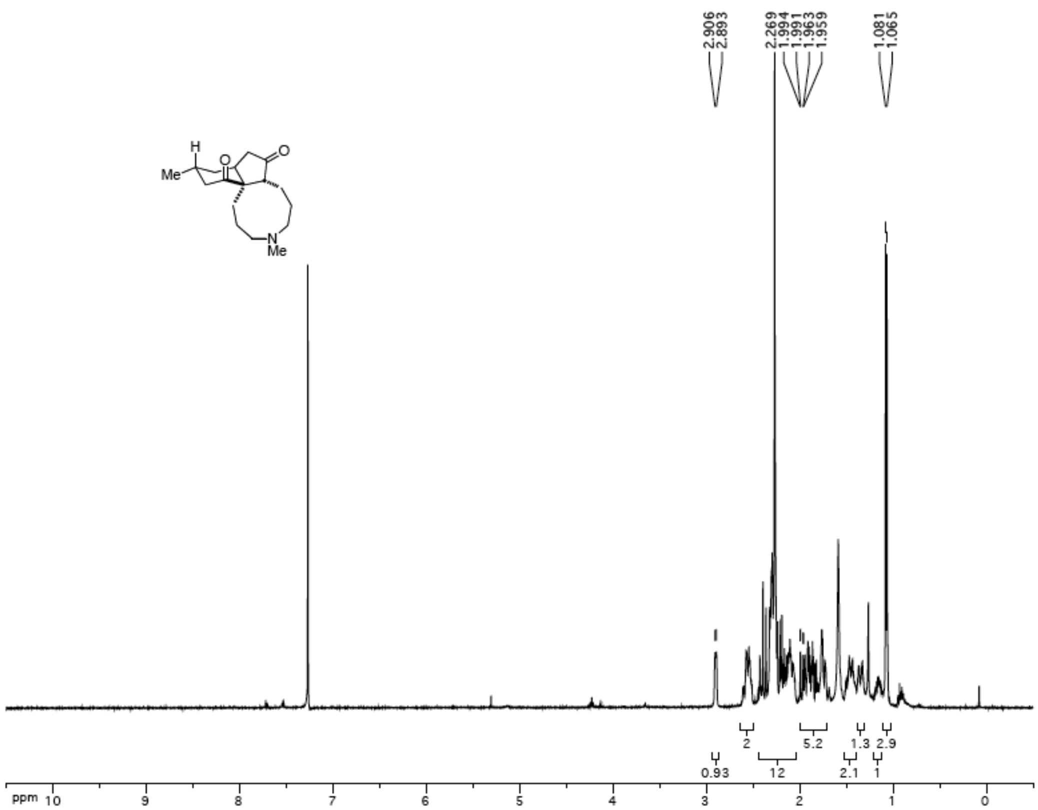


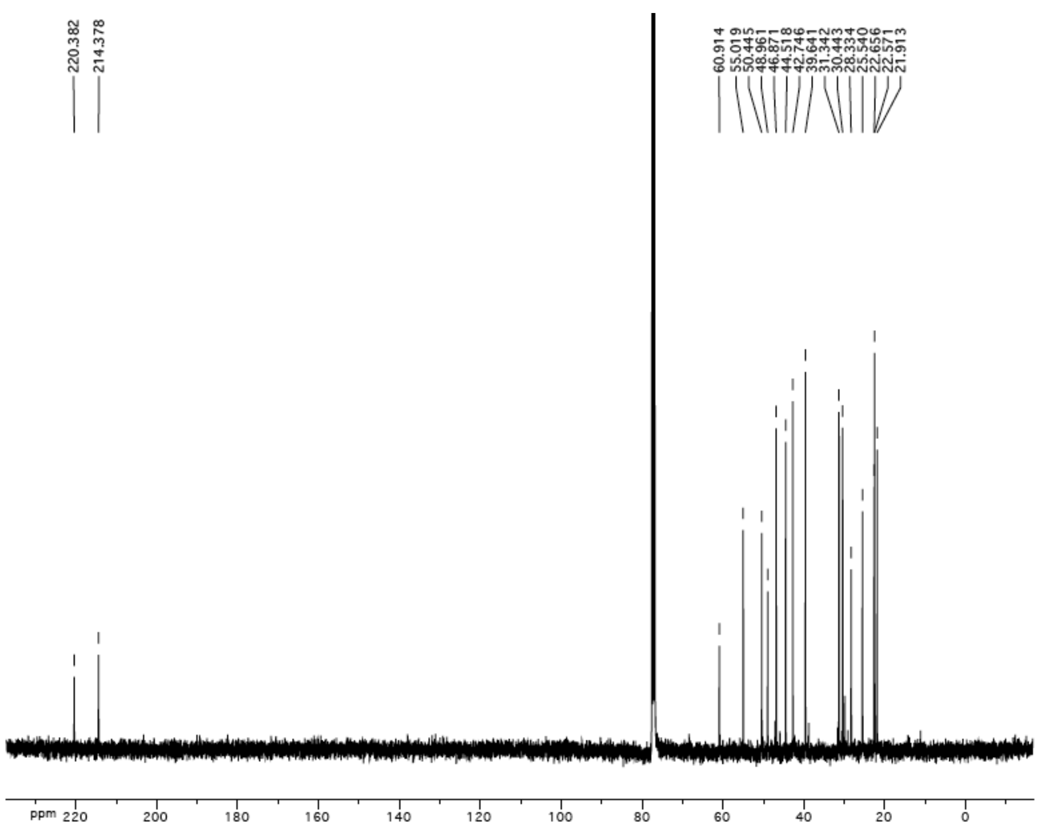
^{1}H and ^{13}C NMR spectra for **4.59**



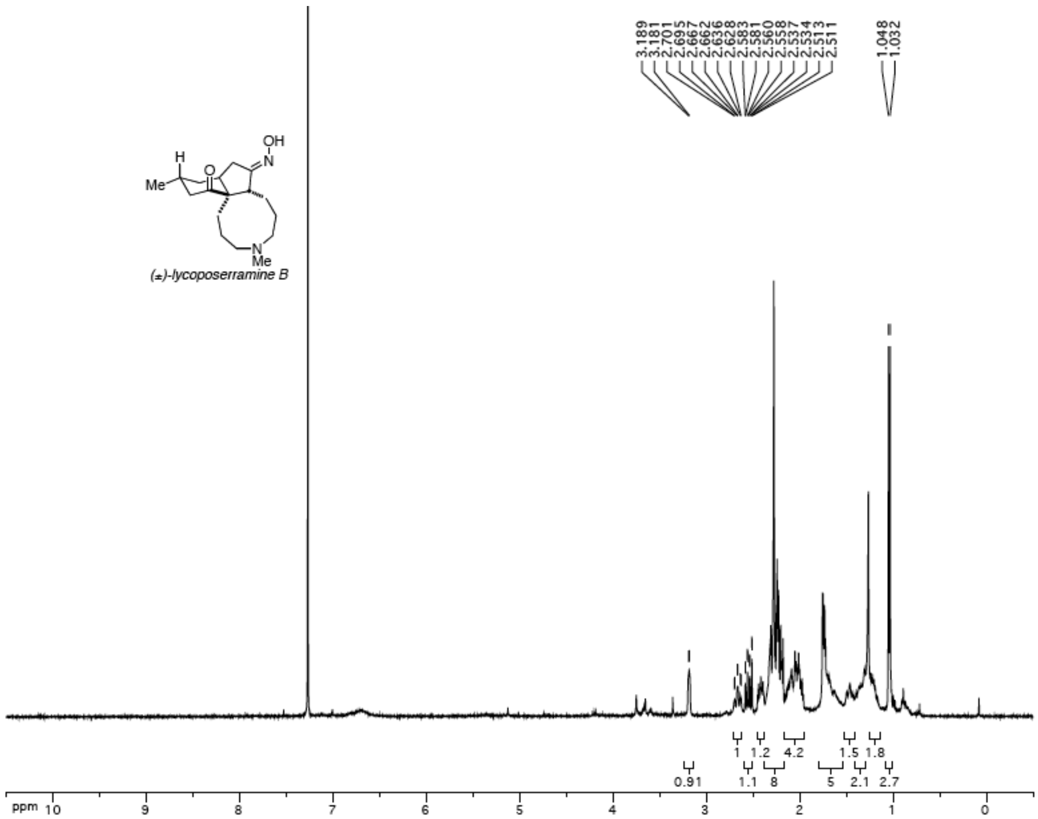


^{1}H and ^{13}C NMR spectra for **4.57a**

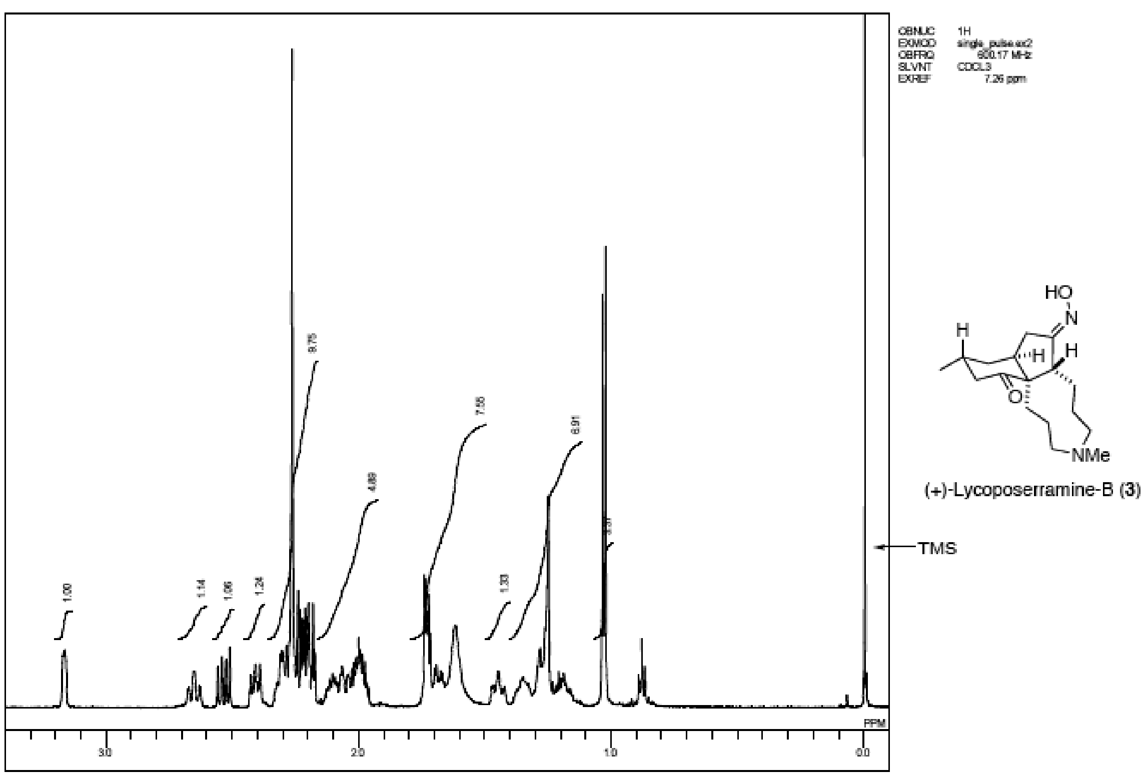




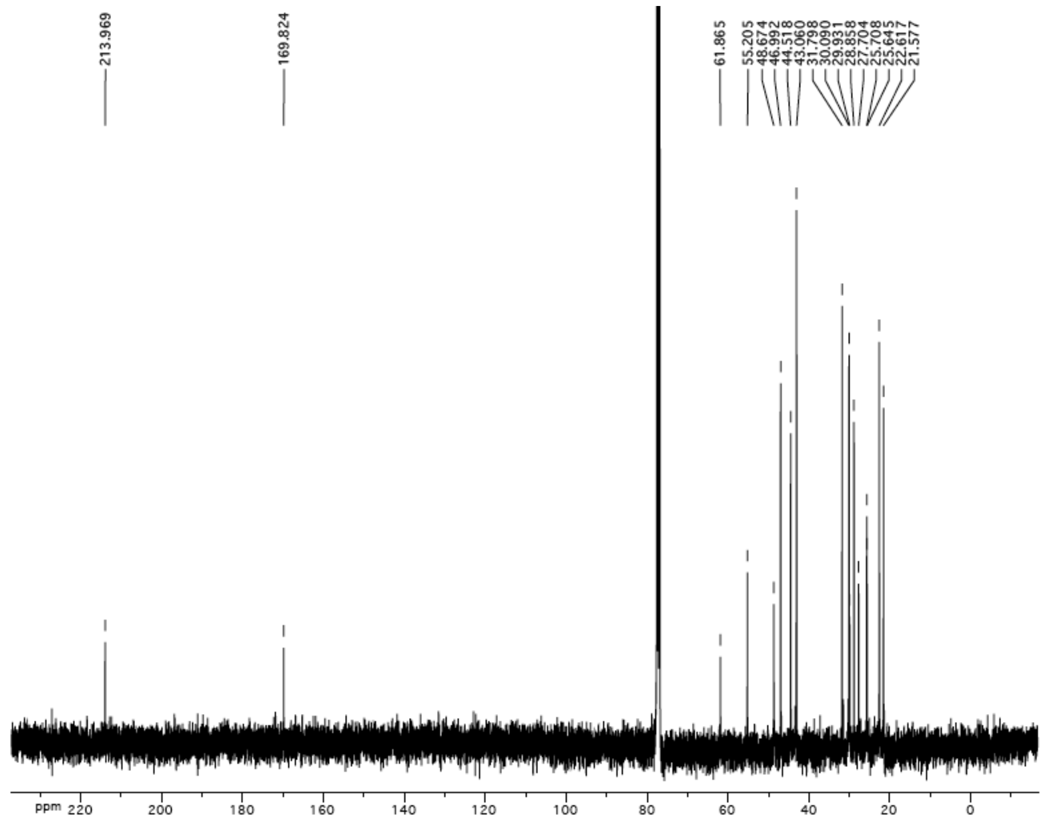
[1]H NMR spectrum for (±)-lycoposerramine B



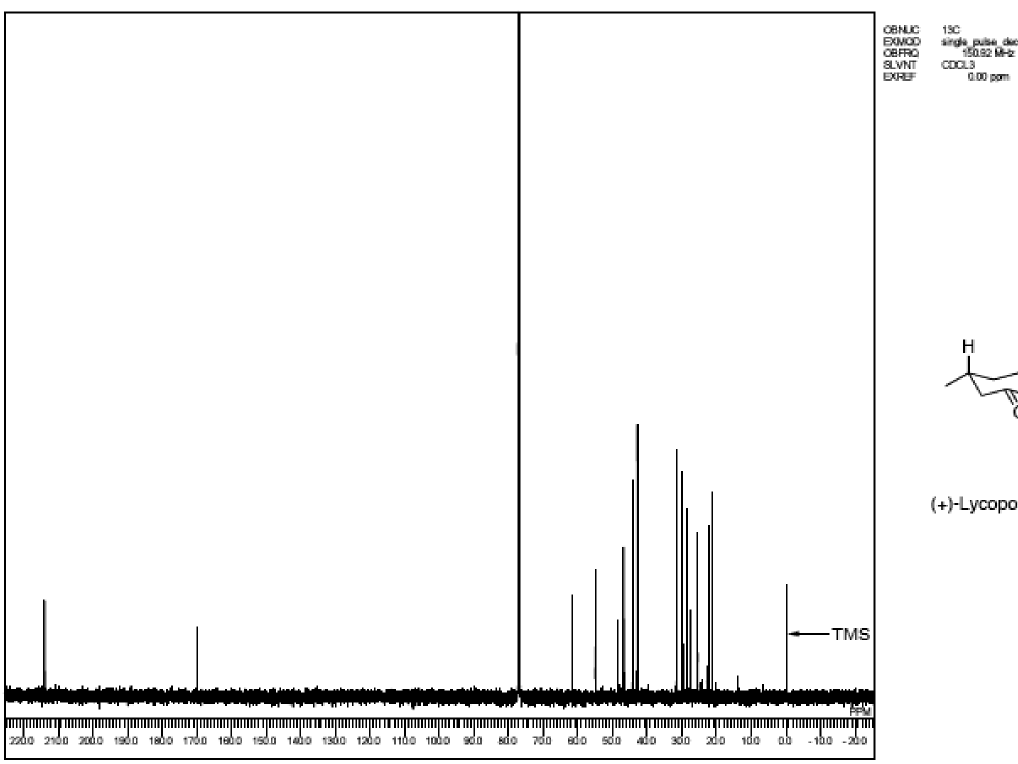
[1]H NMR spectrum for (+)-lycoposerramine B reported by Mukai

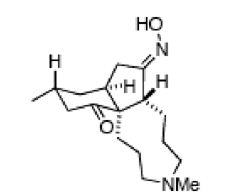


^{13}C NMR spectrum for (±)-lycoposerramine B



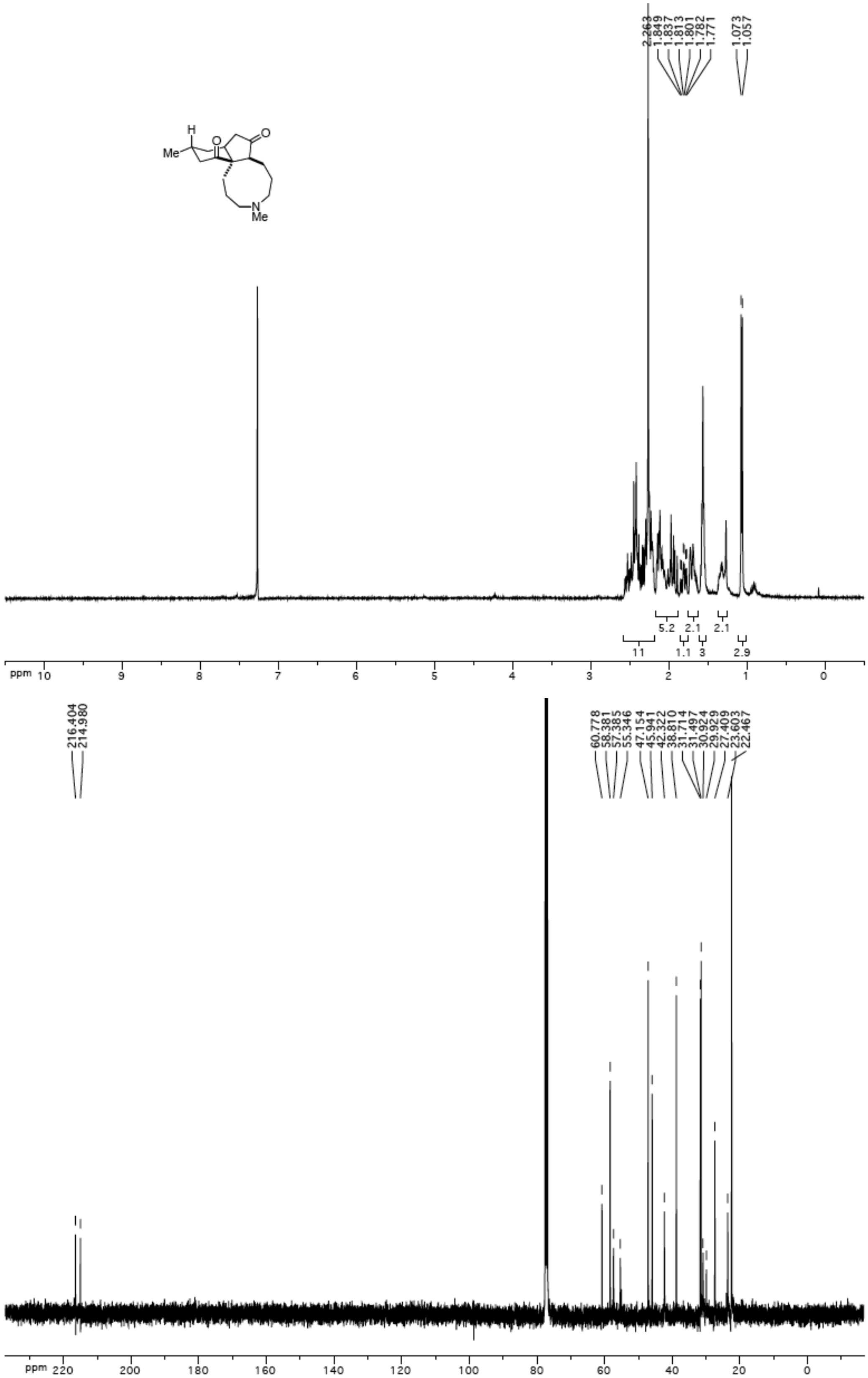
^{13}C NMR spectrum for (+)-lycoposerramine B reported by Mukai



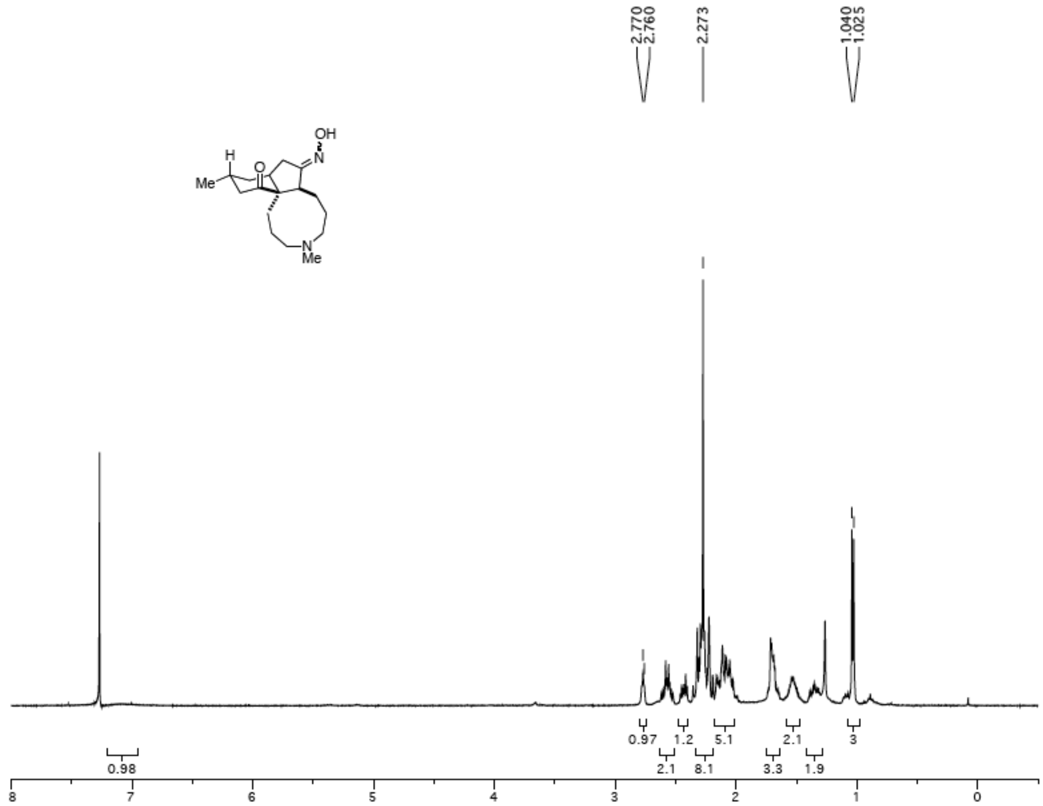


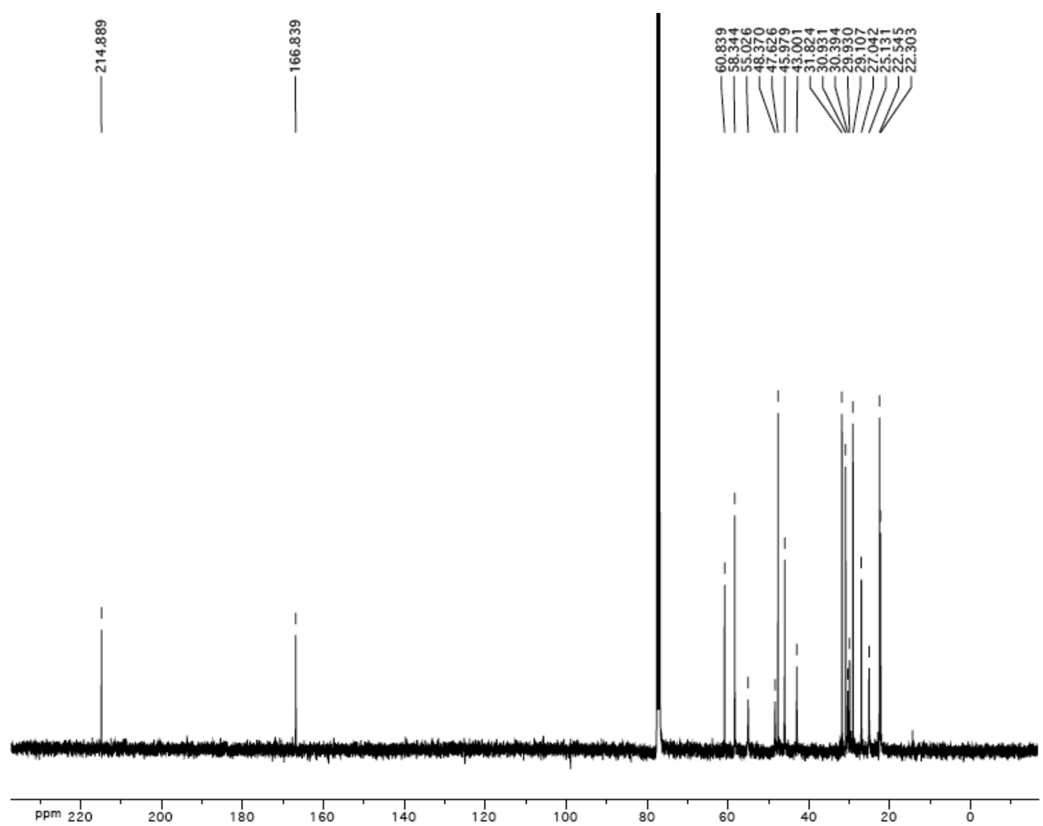
(+)-Lycoposerramine-B (**3**)

^{1}H and ^{13}C NMR spectra for **4.57b**



[1]H and [13]C NMR spectra for **4.60**





^{1}H and ^{13}C NMR spectra for **4.61**