Progress Toward the Total Synthesis of the Phomoidrides

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Abstract

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2005

An advanced approach toward the total synthesis of the Phomoidrides is presented. Following extensive use of model studies, the current method employs several novel tandem reactions to rapidly assemble the Phomoidride skeleton, containing the fully functionalized side-chains, bridgehead olefin moiety and most of the functionality found in the natural products.

The first key transformation is a tandem phenolic oxidation/intramolecular Diels-Alder reaction that creates five new stereocenters in a single step. A novel bromoacetal cascade cyclization was employed to complete the isotwistane core that was the precursor to the bicyclo[4.3.1] decadiene core of the phomoidrides. By utilizing Samarium(II) Iodide (SmI_2), this could be achieved in a novel "top-down" 5-*endo*-trig/5-*exo*-tet cascade cyclization sequence. Also employing SmI_2, a novel xanthate fragmentation was successful in generating the bridgehead olefin and bicyclic Phomoidride core. Several additional transformations are also described leading to a highly functionalized system, with only a few transformations remaining in the total synthesis of the Phomoidrides.

To my family

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I would like to thank my advisor Professor John L. Wood for all his support and advice. I would also like to thank my thesis committee, Professors Frederick E. Ziegler and John F. Hartwig for reviewing my thesis.

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List of Abbreviations

p-ABSA	4-acetamidobenzenesulfonyl azide
AcOH	acetic acid
app.	apparent
aq	aqueous
Bn	benzyl
br	broad
Bu	butyl
C	carbon
°C	degrees Celsius
calcd	calculated
CCl_4	carbon tetrachloride
$CDCl_3$	chloroform-*d*
CDI	1,1'-carbonyldiimidazole
CH_2N_2	diazomethane
CH_3CN	acetonitrile
$CHCl_3$	chloroform
CH_2Cl_2	methylene chloride
CI	chemical ionization
δ	chemical shift in ppm downfield from Me_4Si
d	doublet
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
dd	doublet of doublets
ddd	doublet of doublets of doublets
DEAD	diethyl azodicarboxylate
DIBALH	diisobutylaluminum hydride
DMAD	dimethylacetylene dicarboxylate
DMAP	4-(dimethylamino)pyridine
DMDO	dimethyldioxirane
DMF	dimethyl formamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dt	doublet of triplets
ea.	each
EI	electron impact
equiv	equivalent
Et	ethyl
Et_2O	ethyl ether
EtOAc	ethyl acetate

Et_3N	triethylamine
FAB	fast atom bombardment
FTIR	Fourier transform infrared
g	gram(s)
GDP	guanosine diphosphate
GTP	guanosine triphosphate
h	hour(s)
H	hydrogen
Hz	hertz
HCl	hydrochloric acid
HMDS	potassium bis(trimethylsilyl)amide
HMPA	hexamethylphosphoric triamide
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrum
J	coupling constant
L	liter(s)
LDA	lithium diisopropylamide
LiOH	lithium hydroxide
lit.	literature
LTA	lead(IV) acetate
μ	micro
m	milli, medium (FTIR), multiplet (NMR)
M	moles per liter
Me	methyl
MeOH	methanol
$MgSO_4$	magnesium sulfate
mp	melting point
MHz	megahertz
min	minute(s)
mol	mole(s)
mp	melting point
m/z	mass to charge ratio
NH_4Cl	ammonium chloride
NaCl	sodium chloride
NaH	sodium hydride
$NaHCO_4$	sodium bicarbonate
NaOH	sodium hydroxide
Na_2SO_4	sodium sulphate
NIS	N-iodosuccinimide
NMO	4-methylmorpholine N-oxide
NMR	nuclear magnetic resonance
O	oxygen
OAc	acetate
p	para
pH	hydrogen ion concentration
PPh_3	triphenylphosphine

ppm	parts per million
ppt	precipitate
q	quartet
quint.	quintuplet
$Rh_2(OAc)_4$	rhodium(II) acetate dimer
$Rh_2(OOctc)_4$	rhodium(II) octanoate dimer
$RuCl_3$	ruthenium(III) chloride
s	singlet (NMR), strong (FTIR)
sext.	sextuplet
SmI_2	samarium diiodide
soln	solution
t	triplet
td	triplet of doublets
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBSOTf	*tert*-butyldimethylsilyl trifluoromethylsulfonate
TES	triethylsilyl
Tf_2O	triflic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMPA	trimethyl phosphonoacetate
TPAP	tetrapropylammonium perruthenate
TsOH	toluenesulfonic acid
w	weak

Chapter 1

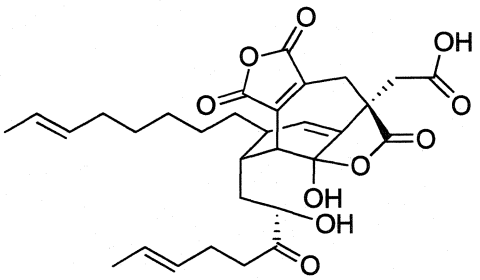
Phomoidrides A and B: Background and Introduction

1.1 Phomoidrides: Isolation and Background.

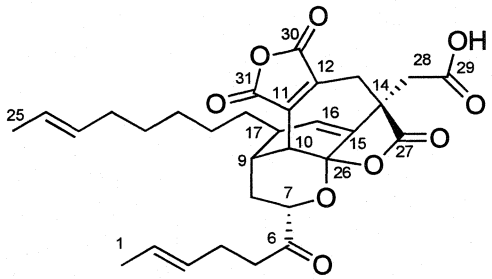
1.1.1 Isolation and Classification.

In 1995, researchers at Pfizer in Groton, Connecticut reported the isolation and characterization of two novel natural products, CP-225,917 (**1**) and CP-263,114 (**2**) (Figure 1.1) from the fermentation of an unidentified fungus discovered on twigs of *Juniperus ashei*[1] found in a scrub forest in Dripping Springs, Texas.[2, 3] This unidentified fungus, which was deposited with the American Type Culture Collection under the accession number 74256 (ATCC 74256), is believed to belong to the *Phoma* genus, a classification which led to these compounds being given the names Phomoidride A (**1**) and Phomoidride B (**2**). This name is a hybridization of the names *Phoma* and nonadride, as the nonadrides are the family of natural products to which the phomoidrides were most closely related. [2]

Figure 1.1 Phomoidrides A and B.



CP-225,917 (**1**)
(Phomoidride A)

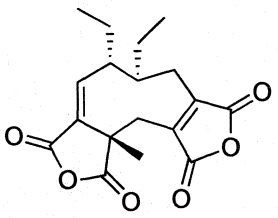


CP-263,114 (**2**)
(Phomoidride B)

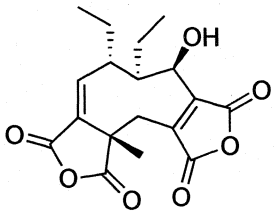
1.1.2 The Nonadrides.

Some representative nonadrides are shown in Figure 1.2. Glaucanic acid (**3**),[4] glauconic acid (**4**),[5] and byssochlamic acid (**5**)[6] were originally named the nonadrides by Barton because they were believed to arise by the dimerization of two nine-carbon units (hence *nona-*) and they all contained bisanhydride moieties (hence *–dride*). While none of the other members of this class come from the dimerization of nine-carbon units, they have been classified as nonadrides due to the similarities in their proposed biosyntheses.[4-14]

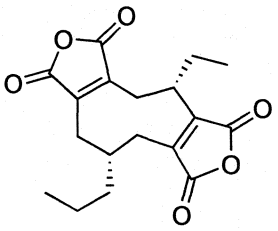
Figure 1.2 The Nonadrides.



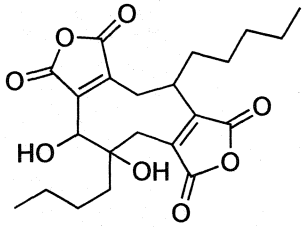
Glaucanic acid (**3**)



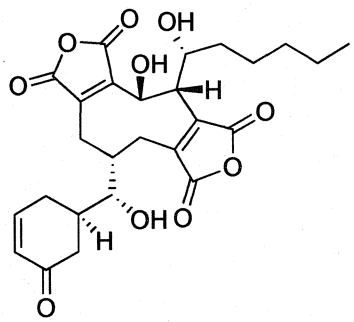
Glauconic acid (**4**)



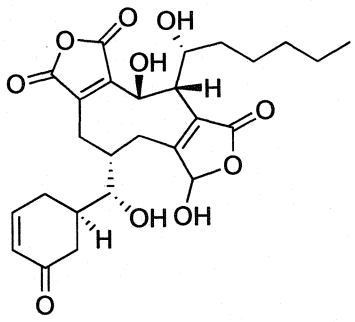
Byssochlamic acid (**5**)



Casteneinolide (**6**)



Rubratoxin B (**7**)



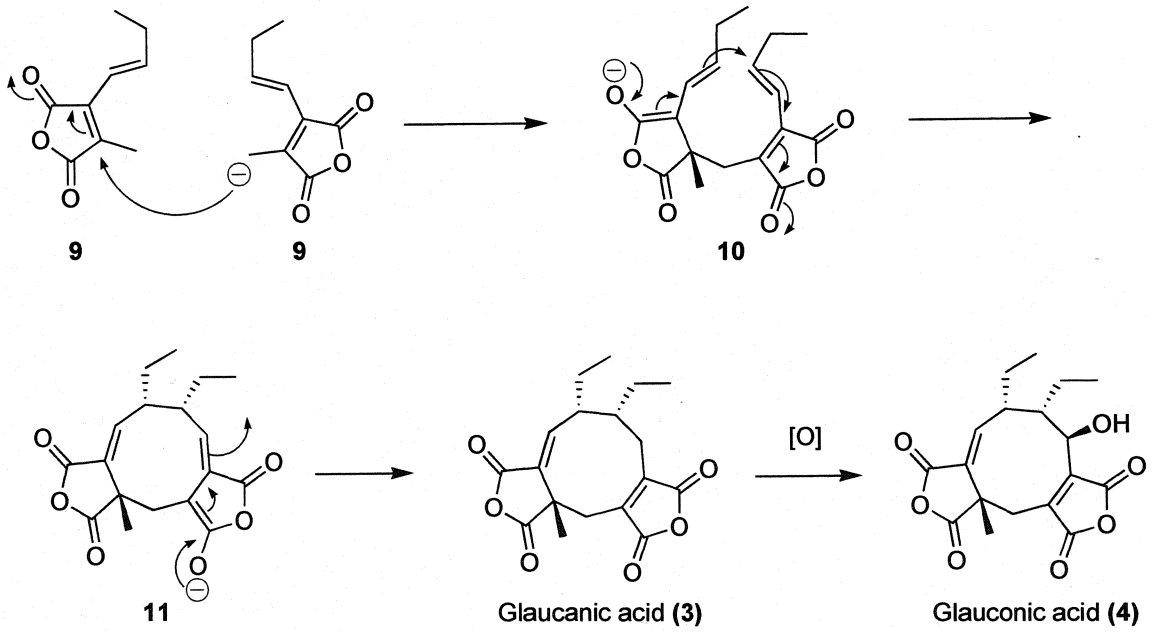
Rubratoxin A (**8**)

1.2 Proposed Biosyntheses.

1.2.1 Barton's Proposed Biosynthesis of Glaucanic Acid.

Barton and Sutherland's proposed biosynthesis of glaucanic acid (**3**) is shown in Scheme 1.1.[4, 5] It was suggested that C_9 anhydride **9** dimerizes by sequential Michael additions to give **3** via **10** and **11**. Glauconic acid (**4**) comes from subsequent enzymatic oxidation of glaucanic acid (**3**). The other nonadrides (**6**, **7**, **8**) are believed to come from similar dimerization mechanisms, but in which the dimerization happens in a "head-to-tail" manner, rather than the "head-to-head" manner proposed for **3**.

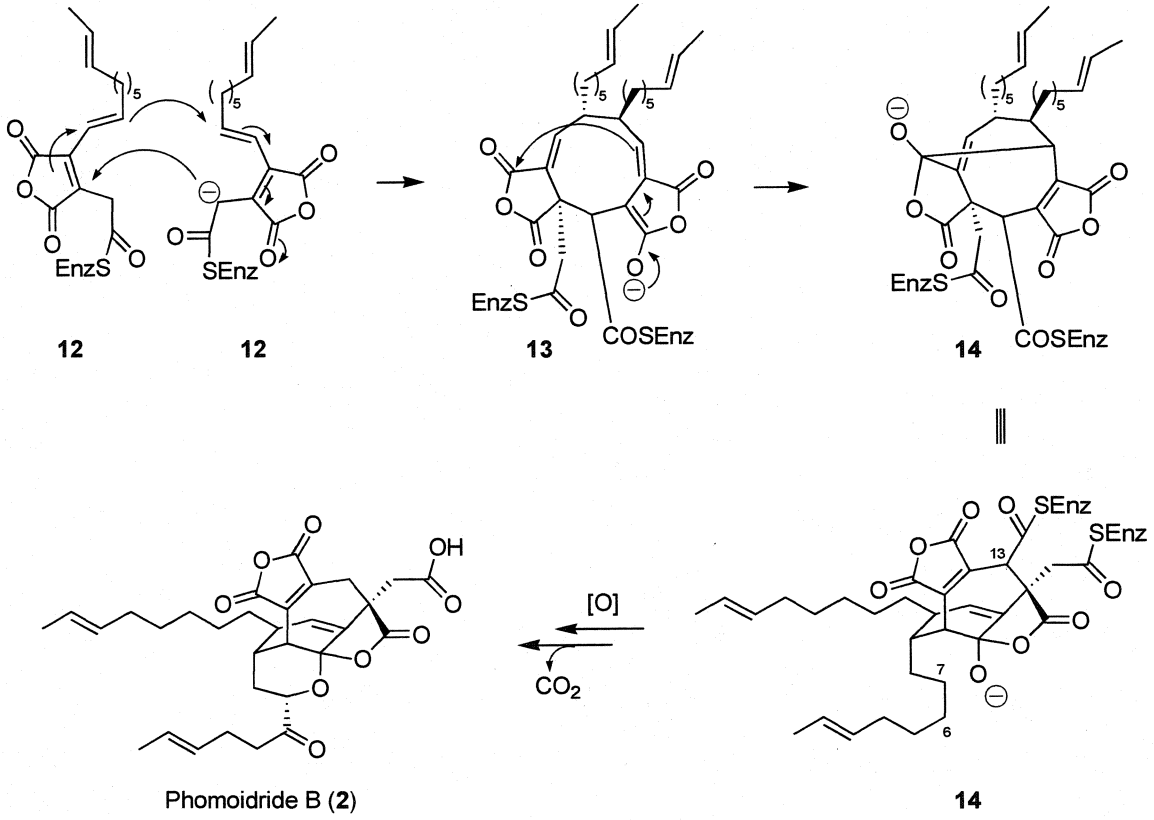
Scheme 1.1 Barton's Proposed Biosynthesis of Glaucanic acid.



1.2.2 Kaneko's Proposed Biosynthesis of Phomoidrides A and B.

The phomoidrides (**1**, **2**) are the most structurally complex nonadrides, bearing little resemblance to their structurally simpler relatives, but the proposed biosynthesis of the phomoidrides is in fact very similar to that of glauconic acid. Glaucanic acid (**3**), glauconic acid (**4**) and byssochlamic acid (**5**) are thought to be formed from the dimerization of C_9 anhydride precursor **9**, which comes from the condensation of oxaloacetic acid and a hexenoic acid. In the report of their initial isolation, Kaneko and co-workers suggested that the phomoidrides would arise similarly from the combination of C_{16} anhydride **12**, which would be formed from the condensation of oxaloacetic acid and a C_{12} acid. [2, 9, 15]

Scheme 1.2 Kaneko's Proposed Biosynthesis of the Phomoidrides.

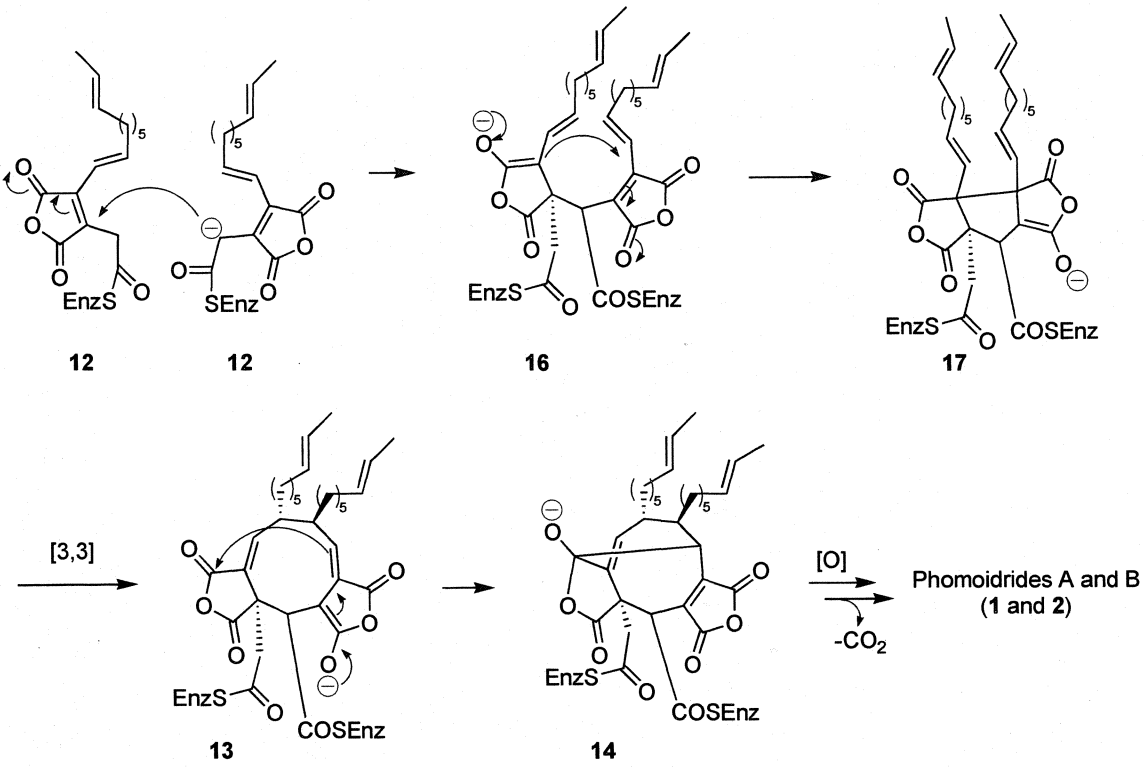


This C_{16} anhydride (**12**) can dimerize in a "head-to-head" manner to provide the nine-membered ring intermediate **13**. While the other nonadrides are believed to tautomerize at this point (**11**γ **3**, Scheme 1.1), the phomoidrides undergo a transannular Dieckmann cyclization (**13**γ **14**, Scheme 1.2) to give the bicyclo[4.3.1]decene core, including the bridgehead olefin. Subsequent decarboxylation at C(13) and enzymatic oxidation at C(6) and C(7) furnish the phomoidrides.

1.2.3 Shair's Proposed Biosynthesis of the Phomoidrides.

Shair and co-workers proposed a slightly different sequence of bond forming events in the biosynthetic scheme.[16] (Scheme 1.3) They suggested that the initial dimerization forms a five-membered ring (**17**), which can then undergo Cope rearrangement to provide cyclononadiene **13**, an intermediate common to both biosynthetic proposals. While differentiation of these two mechanisms would be difficult, the Shair group completed a total synthesis of the phomoidrides (*vide infra*), in which the key step was a tandem sequence involving the [3,3] rearrangement of a similar divinylcyclopentane, followed by a transannular Dieckmann cyclization.[17]

Scheme 1.3 Shair's Proposed Biosynthesis of the Phomoidrides.



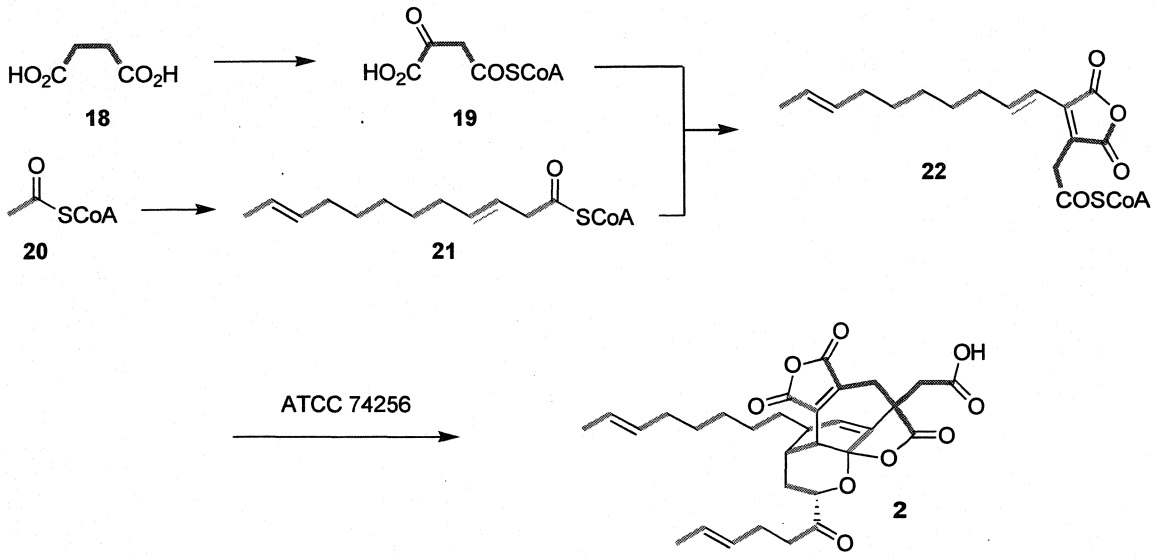
1.3 Biosynthetic Studies.

1.3.1 Sulikowski's ^{13}C Labeling Studies.

The Sulikowski group performed extensive studies on the biosynthetic origins of the phomoidrides.[18-22] They first studied the potential origins of the proposed monomeric C_{16} anhydride precursor **12** (Scheme 1.4). This was suggested to arise from the condensation of oxaloacetyl-CoA (**19**) and a C_{12} dienoic acid (**21**), which would come from acetyl-CoA either through polyketide or fatty acid biosynthesis pathways.[23] They tested this hypothesis by selectively feeding suspended whole cells of ATCC 74256 either ^{13}C labeled succinic acid or ^{13}C labeled acetic acid.[18] Labeled acetic acid provides

labeled acetyl-CoA (**20**), while labeled succinic acid (**18**) leads to labeled oxaloacetyl-CoA (**19**) via the citric acid cycle.

Scheme 1.4 Sulikowski's ^{13}C Labeling studies.



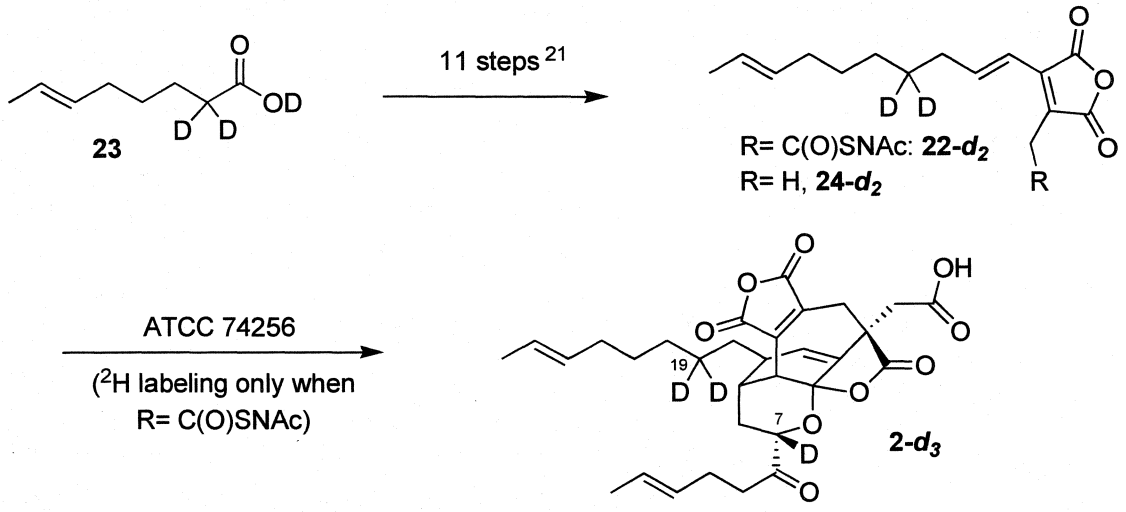
As highlighted in Scheme 1.4, these experiments showed that seven of the carbons (labeled in blue) found in the phomoidrides arise from succinic acid, with the remaining 24 (labeled in red) coming from acetic acid. This labeling study provided evidence for a dimerization mechanism followed by decarboxylation.

1.3.2 Sulikowski's ^{2}H Labeling Studies.

Specific evidence for this biosynthetic pathway came when Sulikowski synthesized C_{16} anhydride **22**, selectively labeled with two deuterium atoms at C(7).[21] Upon feeding this monomer to a broth of ATCC 74256, the phomoidrides produced were selectively labeled with ^{2}H at C(7) and C(19) (Scheme 1.5). In a separate experiment, a C(7) deuterated analog of this C_{16} anhydride that had been decarboxylated (**24-d_2**) was

fed to the same broth, and in this case, no ^{2}H labeling was observed in the isolated product. This provided conclusive evidence that decarboxylation occurs after the dimerization step.

Scheme 1.5 Sulokowski's ^{2}H Labeling Studies.

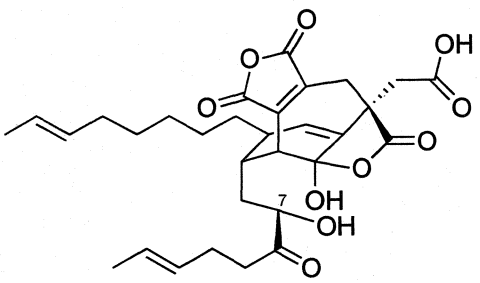


1.3.3 Phomoidrides C and D.

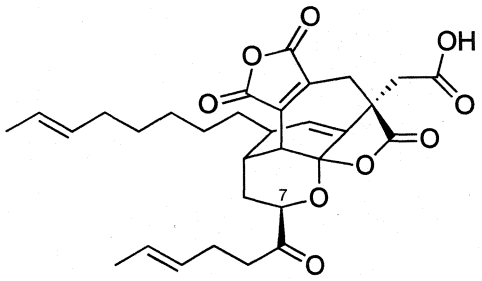
While the Sulikowski group was studying the biosynthesis of the phomoidrides, many other groups were undertaking efforts toward their total synthesis. The Danishefsky group was close to achieving this goal when they produced a compound that was very similar, but not identical to a trace sample of authentic **2** provided by Pfizer.[24] Their compound was found to be a diastereomer of **2** in which C(7), the point of attachment for the lower side-chain, was epimerized. They also discovered that this diastereomer was thermodynamically preferred, and that treatment of naturally-derived **2** under basic conditions afforded epimerization of the C(7) center, an observation that led them to suggest that the C(7) epimers of **1** and **2** might also be natural products. Upon

careful examination of the trace samples of several fermentation broths of ATCC 74256, they found that these epimers (**26** and **27**) could, in fact, be detected in varying amounts (5-30%).[24]

Figure 1.3 Phomoidrides C and D.



Phomoidride C, **26**



Phomoidride D, **27**

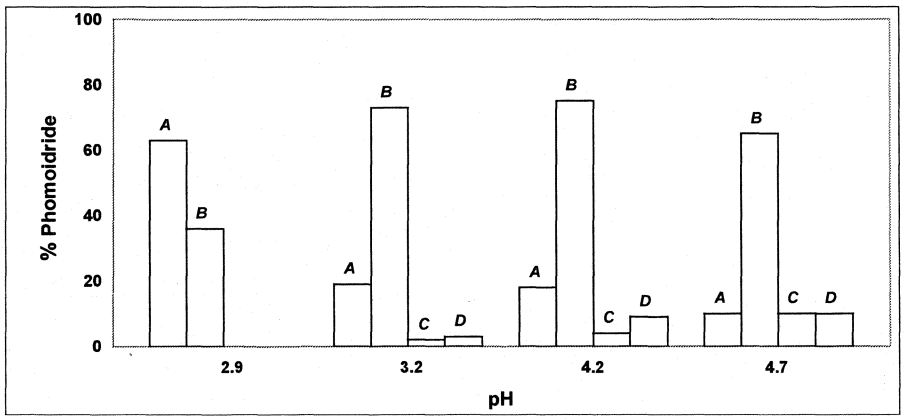
The Sulikowski group expanded on these observations by carefully re-investigating the fermentation of ATCC 74256. They were able to isolate and characterize the minor diastereomers reported by Danishefsky, and they named these phomoidrides C and D (**26** and **27**).[20]

1.3.4 pH Dependence on Distribution of Phomoidrides A-D.

The ratios of phomoidrides A-D produced by ATCC 74256 were found to be strongly dependant on the pH of the fermentation medium (Figure 1.4).[20] Production of the phomoidrides by the fungus proceeded efficiently only in the pH range between 3 and 5, and in this range the major isolate was always phomoidride B. Below pH 3, the rate of production slowed significantly, leading to an inverted product ratio: the rate of production of **2** became slower than the rate of hydrolysis of **2** to **1**. At the higher end of

this pH range (~4.7) the production of phomoidrides C and D becomes significant (~10% each). This finding led Sulikowski to suggest that phomoidride B is the initially formed secondary metabolite, with phomoidrides A, C and D arising from this, depending on the pH of the medium. Further evidence for the hypothesis that phomoidrides A,C, and D arise from phomoidride B is the time-dependant conversion of **2** to **1** when the pH was maintained at 7 or greater. [20]

Figure 1.4 pH Dependence on the Distribution of Phomoidrides A-D.

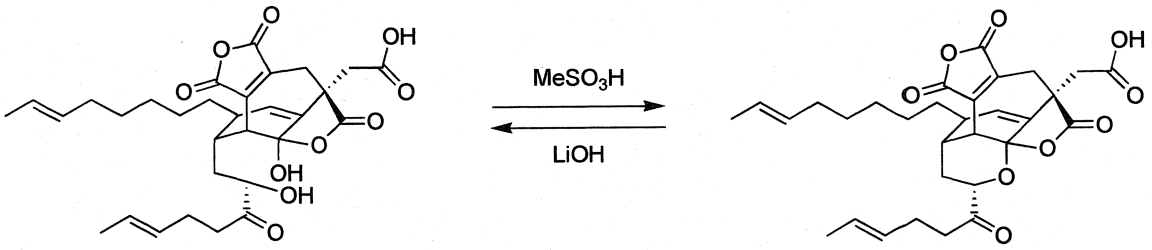


1.4 Interconversion of the Phomoidrides.

1.4.1 Interconversion of Phomoidrides A and B.

In the report of the initial isolation, the Pfizer team showed that **1** could be converted to **2** by treatment with catalytic methanesulfonic acid (Scheme 1.6).[2] Subsequently, Nicolaou established that the reverse reaction occurred upon treatment with lithium hydroxide.[25]

Scheme 1.6 Interconversion of Phomoidrides A and B.

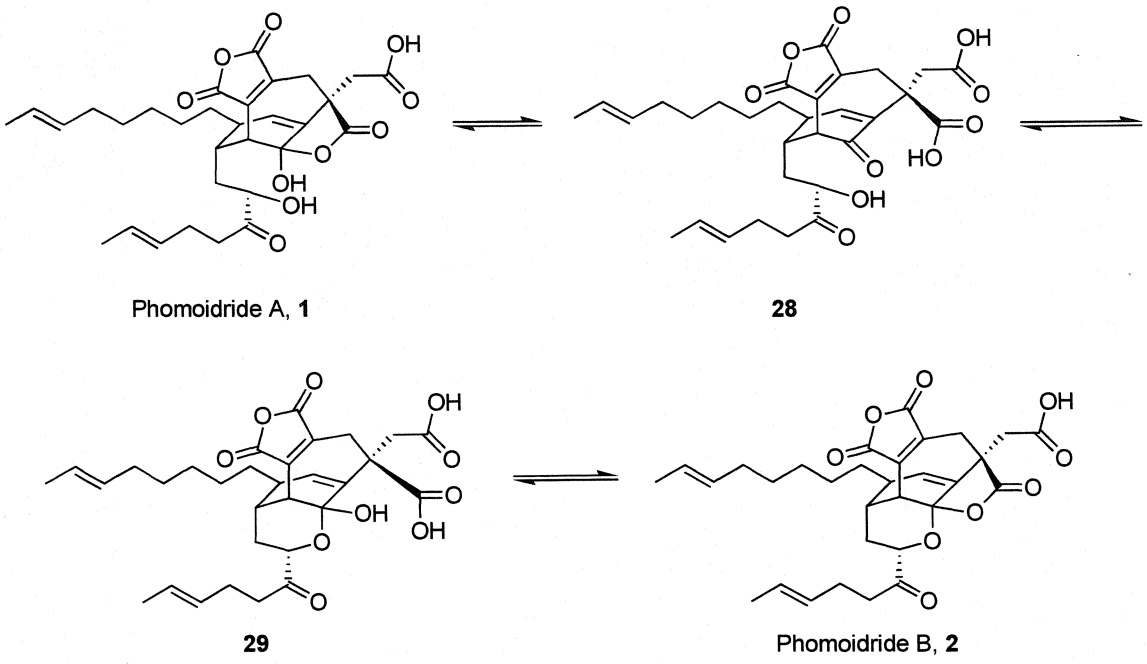


Phomoidride A, **1**

Phomoidride B, **2**

Sulikowski proposed a mechanism for this interconversion that proceeds through open-chain ketone **28**[20] (Scheme 1.7). Under acidic conditions, **1** (phomoidride A) would undergo ring-chain tautomerization to **28**. Tautomerization to lactol **29** would allow for rapid lactonization to **2** (phomoidride B). In the reverse direction, treatment of **2** with aqueous base would provide open-chain compound **28** via lactol **29**. This would tautomerize to **1** (phomoidride A), which is the thermodynamically favored tautomer.

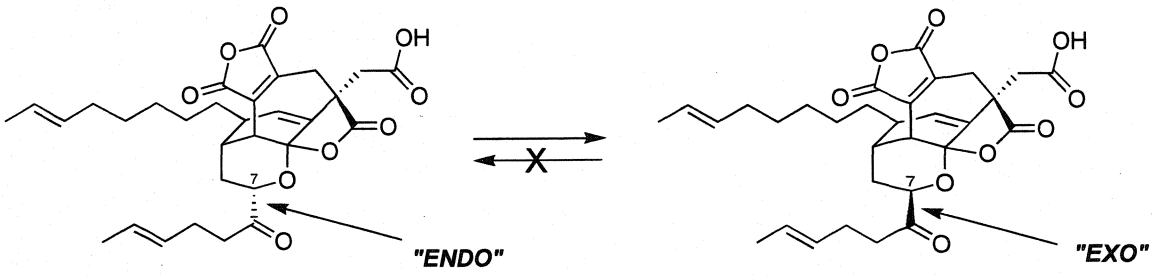
Scheme 1.7 Mechanism of Phomoidride A/B Interconcversion.



1.4.2 Interconversion of Phomoidrides B and D.

Danishefsky showed that phomoidride D (**27**) was thermodynamically preferred and was readily converted to phomoidride B (**2**), while the reverse reaction did not take place.[24, 26] This is readily understood in terms of the increased strain expected from placing the C(7) side-chain in the *endo* orientation.(Scheme 1.8)

Scheme 1.8 Phomoidride B/D Interconversion.

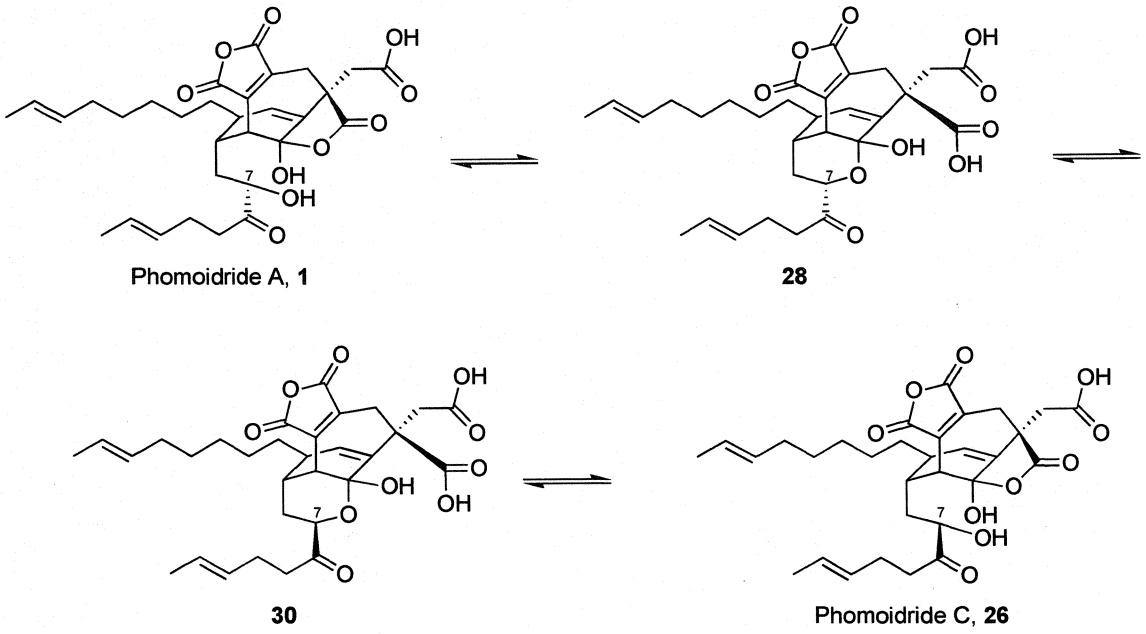


Phomoidride B, **2** Phomoidride D, **27**

1.4.3 Interconversion of Phomoidrides A and C.

The reasoning behind the thermodynamic preference for the *exo* orientation of the side-chain (phomoidride C (**26**)) in the open-chain compounds (phomoidride A/ phomoidride C) was not as readily apparent as for their ring-closed relatives (i.e. phomoidrides B/D). Sulikowski proposed, however, that the epimerization of these open-chain compounds could be understood in that the closed-ring tautomer of **1**, pyran **28** (Scheme 1.9), should prefer to have the C(7) side-chain in the less crowded *exo*-orientation in a manner analogous to the epimerization of **2** to **27** (Scheme 1.8). [20]

Scheme 1.9 Phomoidride A/C Interconversion.



1.5 Biological Activity.

1.5.1 Overview.

At the time of their initial isolation, phomoidrides A and B were found to have very interesting biochemical properties; both inhibit the enzyme squalene synthase (phomoidride A (**1**): IC_{50} of 43μM and phomoidride B (**2**): IC_{50} of 320μM) as well as the enzyme Ras farnesyl transferase (phomoidride A (**1**): IC_{50} of 6μM and phomoidride B (**2**): IC_{50} of 20μM).[2, 3] These are both biologically relevant targets, as inhibition of squalene synthase (SQS) might be useful in the fight against cardiovascular disease, and inhibition of Ras farnesyltransferase is an active area of research in the battle against cancer. To our knowledge, the biological activities of phomoidrides C and D have never been assayed.

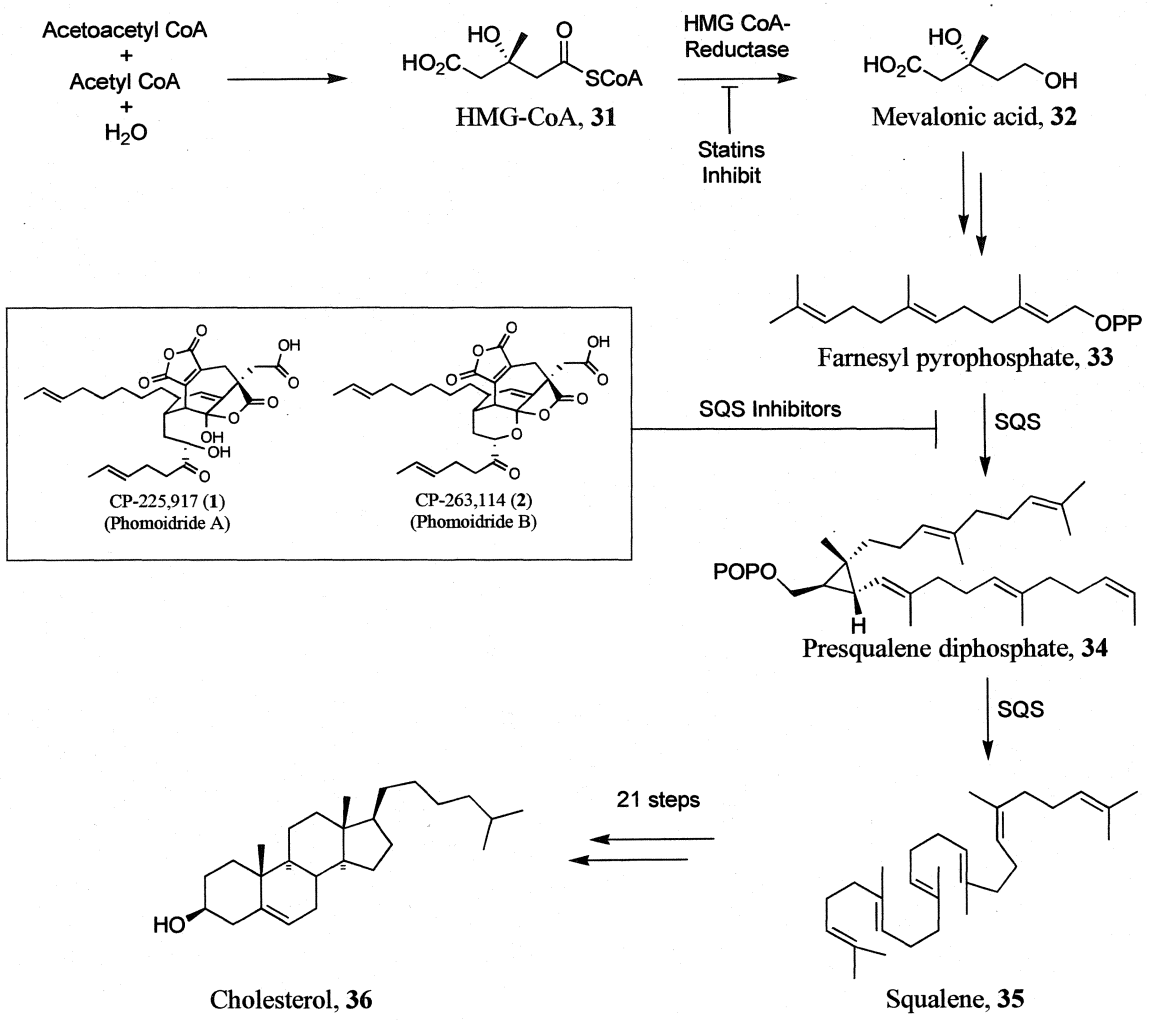
1.5.2 Squalene Synthase and Cardiovascular Disease.

Cardiovascular disease is the number one cause of death and disability in most western nations, with over 50 million Americans suffering from cardiovascular (CV) problems. Chronic hypercholesterolemia is one of the key risk factors for CV disease. In humans, 70% of serum cholesterol is derived from endogenous biosynthesis (as opposed to dietary sources) and therefore inhibition of cholesterol biosynthesis is an important goal for the pharmaceutical industry. [27, 28]

Toward this end, inhibitors of HMG-CoA reductase, which catalyzes the rate-limiting step in cholesterol biosynthesis, have been developed. These drugs, known as the statins, have been extremely successful and include the blockbusters simvastatin (Zocor®, Merck), pravastatin (pravachol®, Sankyo/Bristol-Myers Squibb), lovastatin (Mevacor®, Merck), fluvastatin (Lescol®, Novartis), and atorvastatin (Lipitor®, Pfizer).

While HMG-CoA reductase is the rate-limiting step in cholesterol biosynthesis, squalene synthase (SQS) occurs downstream from HMG-CoA reductase and is the first committed step toward the synthesis of cholesterol, in which two molecules of farnesyl pyrophosphate (FPP, **33**) are joined to form first presqualene diphosphate (**34**) and then squalene (**35**) (Figure 1.5). Inhibition of this enzyme might be another interesting target in the battle against hypercholesterolemia. Phomoidrides A and B (**1** and **2**) are reported to reversibly bind to the enzyme (SQS) via a FPP binding site in either the free enzyme, or one which is bound to a single FPP. Further mechanistic studies toward understanding this activity are reported to be underway.[3]

Figure 1.5 Cholesterol Biosynthesis and Inhibition.

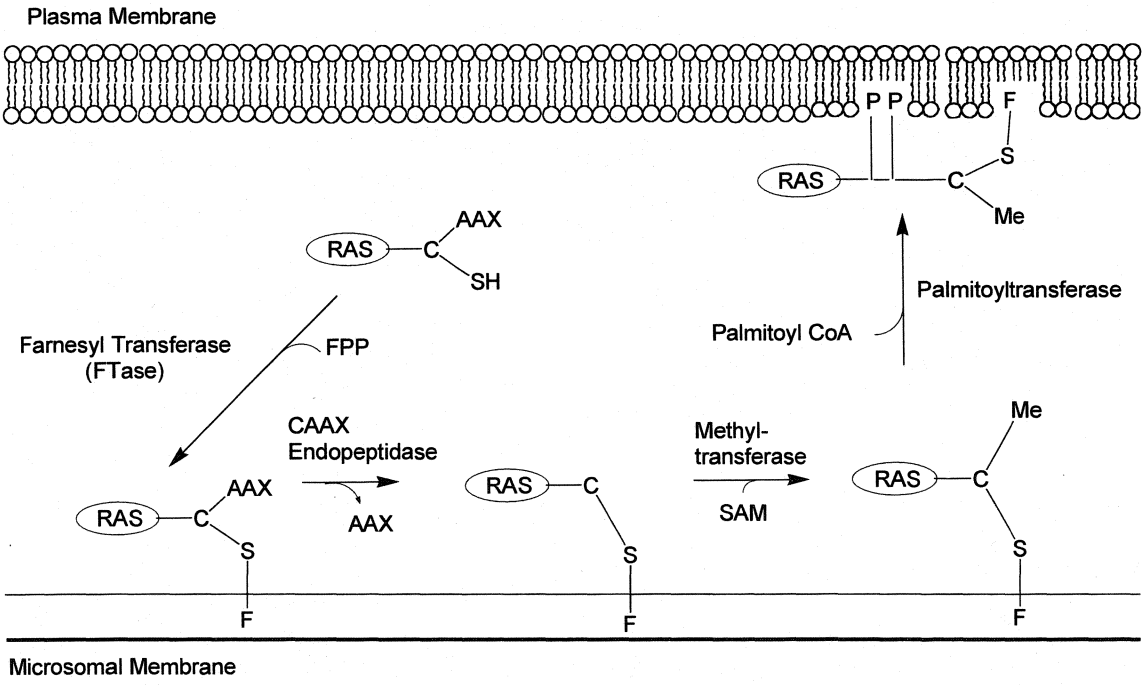


1.5.3 Inhibition of Ras-Farnesyltransferase.

Mutations in the Ras proto-oncogene are found in 20%-30% of all human cancers, making Ras is an important target for anti-cancer research.[29, 30] One potential area for therapeutic intervention would be the disruption of the post-translational modification of Ras that is required for its activity.[31] Newly formed Ras is a cytosolic protein, but its

activity is dependent on its relocation to the plasma membrane. The first step in the post-translational journey to the plasma membrane is farnesylation of a cysteine residue near the carboxyl terminus of Ras by Ras farnesyltransferase (FTase), which allows Ras to associate with an intracellular membrane (Figure 1.6). Next, a CAAX endopeptidase cleaves the AAX tripeptide at the carboxyl terminus, and a methyltransferase methylates the newly formed carboxyl terminus. This methylation initiates translocation of Ras to the plasma membrane, where Ras is further lipidated by a palmitoyltrasnsferase, thus anchoring Ras in the plasma membrane.

Figure 1.6 Post-translational Modification of Ras.



Once attached to the plasma membrane, Ras becomes activated by exchanging GDP for GTP, which is aided by a guanine nucleotide exchange factor (GEF). It was believed that if initial farnesylation of Ras is inhibited, it would never be able to reach its

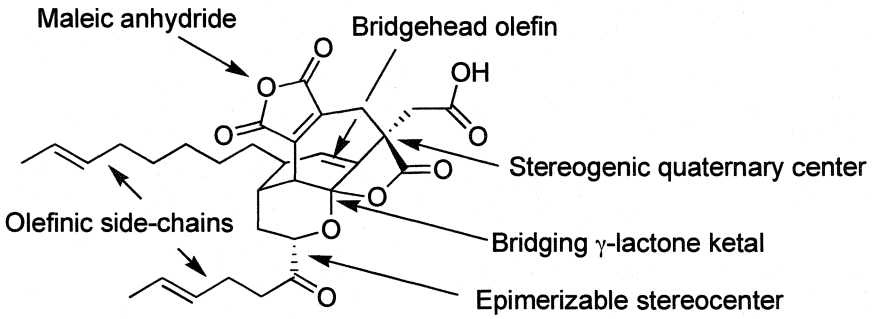
active state. While this remains an area of intense interest, thus far results of clinical trials involving Ras FTase inhibitors have been somewhat unsuccessful.[31]

1.6 Synthetic Studies.

1.6.1 Synthetic Challenges.

Along with their interesting biological profiles, the phomoidrides possess a unique skeleton containing many interesting structural features. As with the other nonadrides, a maleic anhydride is fused to a cyclononadiene core, however unlike their simpler relatives, the phomoidrides contain many other interesting and unusual features, such as a bridgehead olefin, bridging γ-lactone ketal, olefinic side-chains, stereogenic quaternary center, and epimerizable stereocenter. Most notable among these features is the bridgehead olefin moiety. While this is often referred to as an "anti-Bredt" olefin, this is a misnomer, as Bredt's rule only refers to rings with fewer than eight atoms.[32-37]

Figure 1.7 Synthetic Challenges.



Phomoidride B, **2**

1.6.2 Synthetic Efforts Toward the Phomoidrides.

This unique combination of biochemical and structural properties has prompted a great deal of interest in the phomoidrides as synthetic targets. To date, four groups have reported total syntheses of the phomoidrides (Nicolaou,[25, 38-47] Danishefsky,[24, 26, 48-51] Shair[16, 17, 52] and Fukuyama[53-55]) and at least a dozen other research groups have published approaches toward the bicyclo[4.3.1]decadiene core of the phomoidrides.[15, 56-89] These efforts have recently been reviewed.[90]

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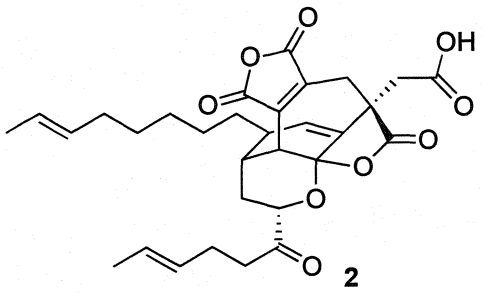
Chapter 2

Phomoidrides: Model Studies

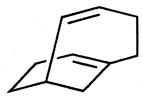
2.1 Synthetic challenges.

While many challenges were associated with the synthesis of the phomoidrides (e.g, the bridgehead olefin, the olefinic side-chains, the epimerizable stereocenter, the stereogenic quaternary center, the bridging α-latone ketal, free carboxylic acid and the maleic anhydride), the construction of the bicyclo[4.3.1]decadiene core containing the bridgehead olefin was of the utmost significance. As a result, our initial efforts were focused upon the construction of this core structure (**40**). In order to explore the synthesis of this core structure (**40**), a model system was employed, in which the remaining complex functionality found in the phomoidrides was avoided.

Scheme 2.1 Phomoidride B and Bicyclo[4.3.1]decadiene Core.



2



Bicyclo[4.3.1]decadiene
40

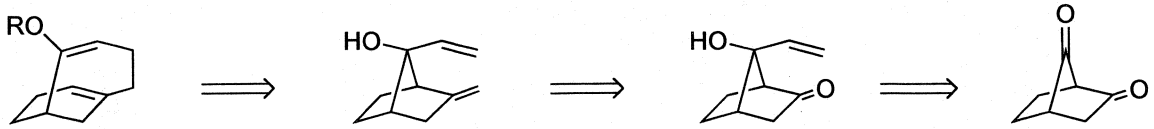
2.2 Preliminary Model Studies. [1, 2, 3]

2.2.1 Oxy-Cope.

2.2.1.1 Oxy-Cope Retrosynthesis.

One potential retrosynthetic approach to the bicyclo[4.3.1]decene core was a [3,3] sigmatropic rearrangement, which could be used to deliver the desired both the bicyclic core and the bridgehead olefin.

Scheme 2.2 Retrosynthesis: Oxy-Cope Disconnection.



42 **43** **44** **45**

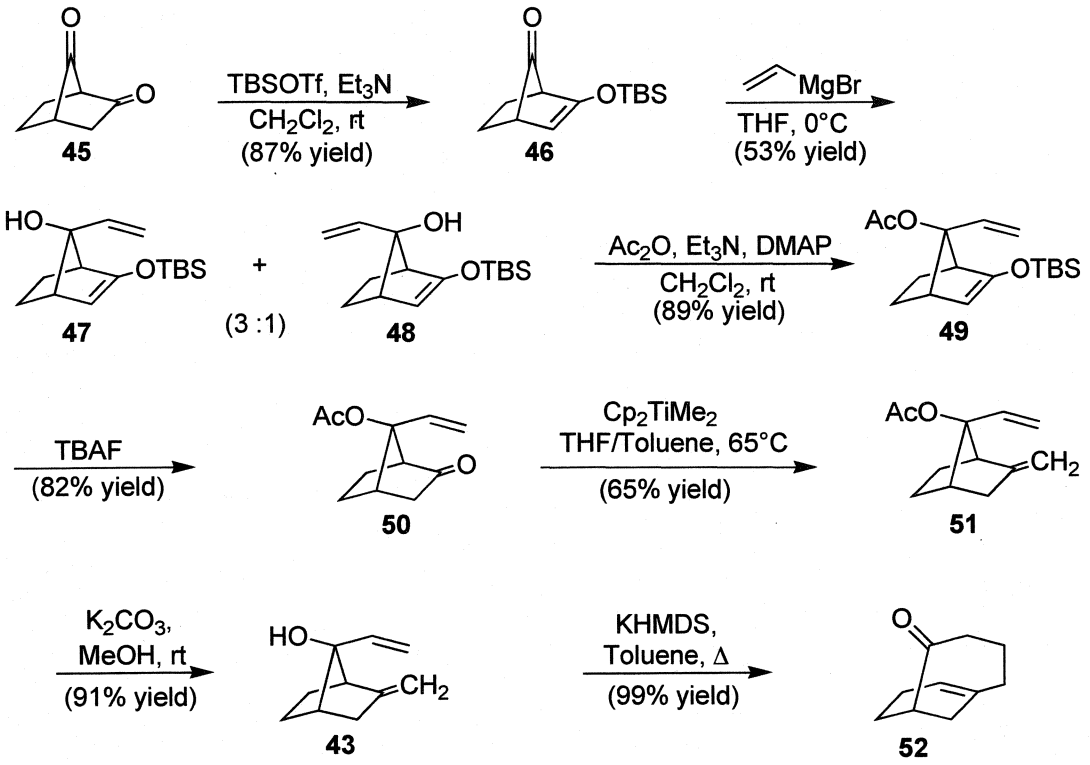
Scheme 2.2 shows a simple retrosynthesis to test the desired [3,3] rearrangement. In this case an oxy-Cope disconnection was envisioned, with the substrate for the oxy-Cope rearrangement (**43**) arising from diketone **45** by olefination and vinyl grignard addition.

2.2.1.2 Oxy-Cope Model System.

Synthesis of model substrate **43** commenced by differentiating the two ketones of **45**[4] *via* protection the enolizable ketone as its TBS-enol ether and subsequent addition of vinyl grignard (Scheme 2.3). This afforded tertiary alcohols **47** and **48** in a 3:1 ratio, favoring the desired isomer **47**. Following protection of the tertiary alcohol of **47** as its acetate (**49**), and deprotection of the TBS-enol ether, the remaining ketone was reacted with Petasis' reagent[5] to afford the desired diene (**51**). Deprotection of the acetate gave the dienol substrate for the anionic oxy-Cope reaction (**43**), which upon treatment with

KHMDS in refluxing toluene provided rearrangement product **52**, containing the bicyclo[4.3.1] decene core and the bridgehead olefin.

Scheme 2.3 Oxy-Cope: Synthesis and Evaluation.

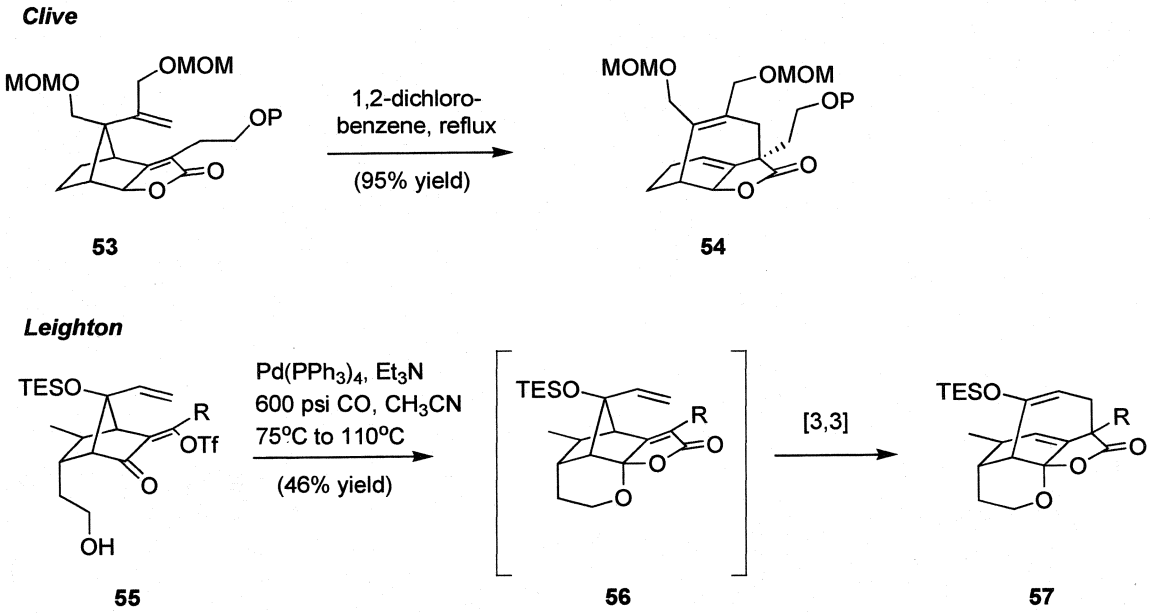


2.2.1.3 Clive and Leighton's [3,3]-Rearrangement Strategies.

Unfortunately, efforts to perform this rearrangement on more complex substrates were unsuccessful, a result which was in accord with the observations made by two other research groups. Concurrent to our findings, both the Clive[6-13] and Leighton[14-16] groups had been independently approaching the synthesis of the phomoidrides by a [3,3] sigmatropic rearrangement strategy. Scheme 2.4 depicts the key step in both Clive's (**53**α **54**) and Leighton's (**55**α **57**) synthetic efforts. They observed that extraordinary measures were required to achieve the desired rearrangement on all but the simplest

substrates. Both groups found it necessary to incorporate ring-strain in the starting material by forming the butenolide, thus allowing the [3,3] rearrangement to proceed under relatively mild conditions.

Scheme 2.4 Clive and Leighton's [3,3]-Rearrangement Strategies.

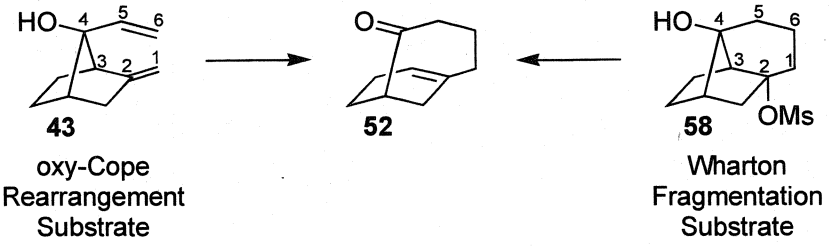


2.2.2 Transition from an Oxy-Cope Rearrangement to a Wharton Fragmentation.

Unable to perform the desired rearrangement on a suitably functionalized substrate, we next turned to finding an alternative route to the phomoidride core that would be efficient, mild, and tolerant to the diverse functionality found in the phomoidrides. One potential solution evolved from the oxy-Cope model system: ketone **52** might arise from a Wharton fragmentation[17] instead of a sigmatropic rearrangement. This would be equivalent to performing the [3,3] rearrangement in a stepwise manner, first forming the bond between C(1) and C(6) and then breaking the C(3)-C(4) bond to

unveil the phomoidride core (not phomoidride numbering, see Scheme 2.5 for numbering sequence).

Scheme 2.5 Transition from an Oxy-Cope to a Wharton Fragmentation.

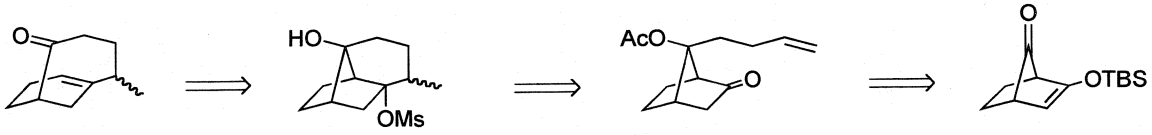


2.2.3 First Wharton Fragmentation System.

2.2.3.1 Retrosynthetic Analysis Based on Wharton Fragmentation.

Retrosynthetic analysis showed that construction of a Wharton fragmentation model system could proceed in a manner similar to the oxy-Cope system. The substrate for the Wharton fragmentation (**60**) could arise from the 6-*exo-trig* ketyl radical cyclization of ketone **61**, which, in analogy to the earlier model system, would come from the addition of a homoallylic nucleophile to ketone **46**.

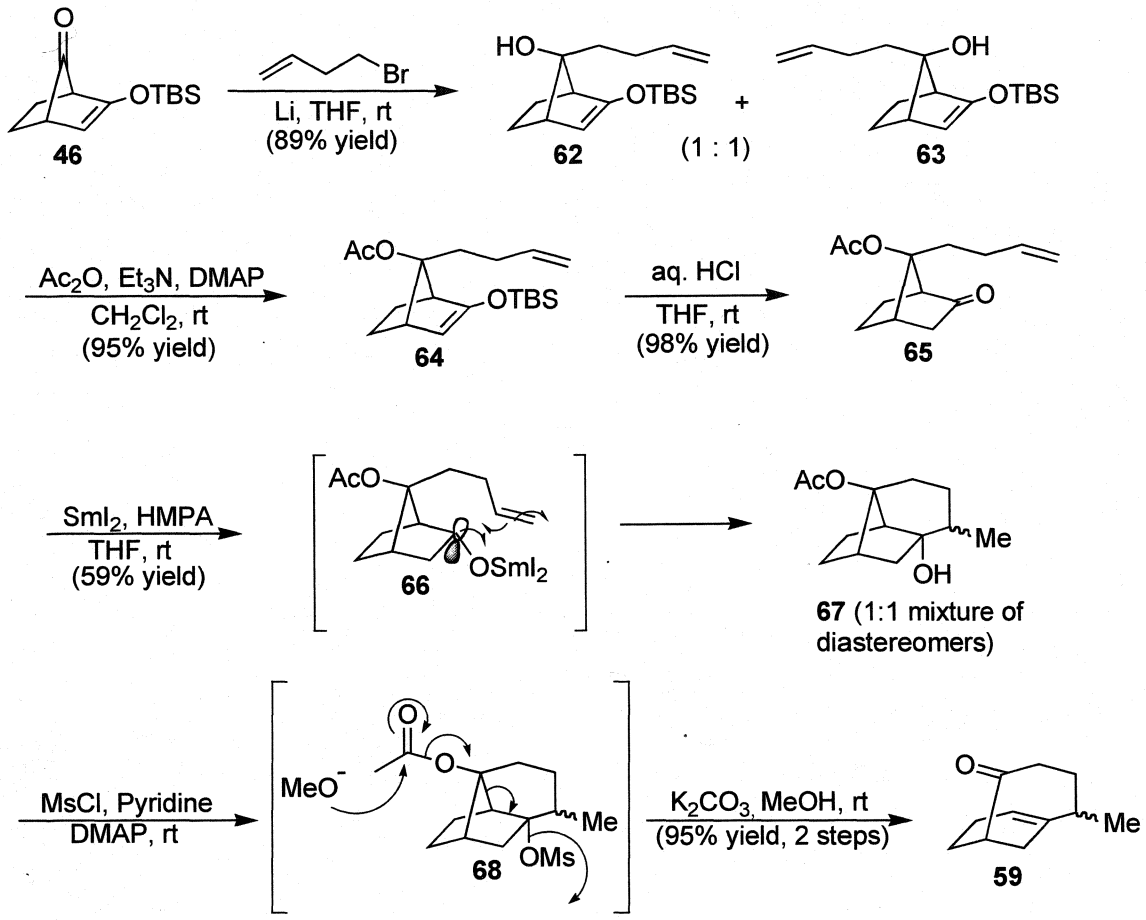
Scheme 2.6 Retrosynthesis: First Wharton Fragmentation Model System.



2.2.3.2 Synthesis of the First Model Wharton Fragmentation Substrate.

Ketone **46**, an intermediate previously employed in the oxy-Cope model system, was treated with lithio-3-butene to afford the bis-homoallylic tertiary alcohols **62** and **63** as a 1:1 mixture of diastereomers (Scheme 2.7). Following separation, protection of **62** as the acetate and deprotection of the ketone, a ketyl was generated upon treatment of **65** with samarium(II) iodide (SmI_2) in the presence of HMPA.[18, 19] Subsequent 6-*endo-trig* cyclization delivered tertiary alcohol **67**, containing the tricyclic core of the fragmentation precursor, and formation of the mesylate (**68**) occurred under standard conditions. Finally, exposure to potassium carbonate in methanol deprotected the acetate, and simultaneously promoted fragmentation to give ketone **59**, which possessed the bicyclo[4.3.1]decene core of the phomoidrides. This fragmentation provided the desired core under very mild conditions, a noteworthy attribute of this method that might make it amenable to use in more highly functionalized system.

Scheme 2.7 First Wharton Fragmentation System.



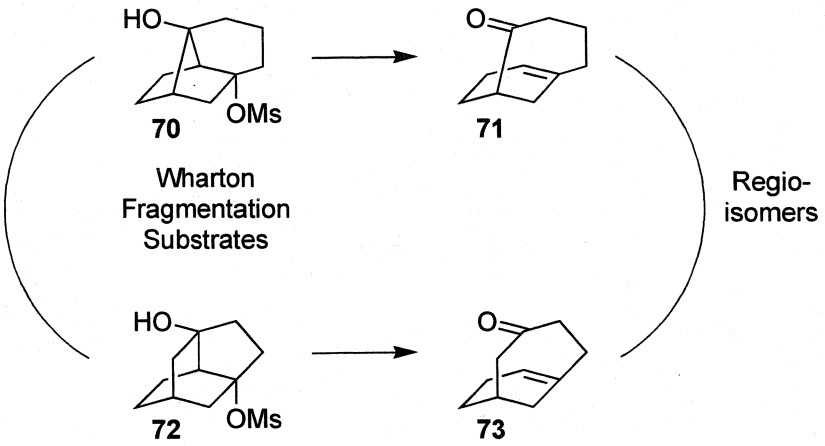
2.2.4 Transition to a New Wharton Fragmentation.

2.2.4.1 Transition From a [2.2.1] to a [2.2.2] Based Fragmentation.

While the Wharton fragmentation was an expeditious way to form the [4.3.1] core in the model system, there were few methods available for the construction of the highly functionalized bicyclo[2.2.1]heptane precursor that would be required for the total synthesis of the phomoidrides. The synthetic plane was therefore reassessed in order to find a method that would be both mild like the Wharton fragmentation, but also could be performed on a substrate that would be accessible in a highly functionalized form. Once

again, the synthetic plan evolved, this time upon realization that an analogous fragmentation might be achieved from the isomeric isotwistane[20] precursor (Scheme 2.8).

Scheme 2.8 Transition from a [2.2.1] to a [2.2.2] Based Fragmentation.

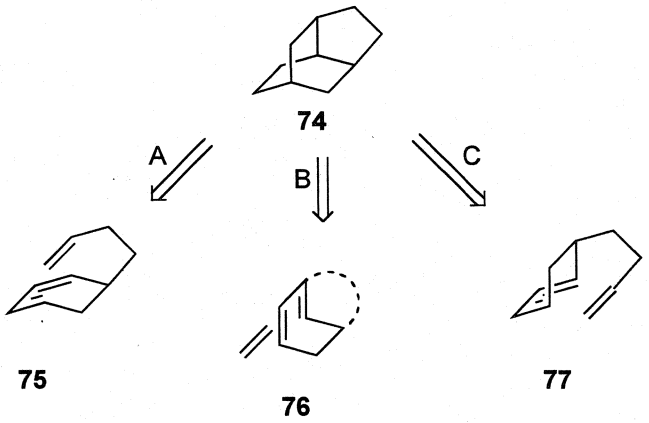


Mesylate **72**, containing a bicyclo[2.2.2]octane based isotwistane skeleton, could potentially undergo a Wharton fragmentation to provide ketone **73**, which is isomeric to the former fragmentation product (**71**), differing only in the position of the ketone.

2.2.4.2 Isotwistane Disconnections via Diels-Alder Reaction.

It was envisioned that the bicyclo[2.2.2]octane core of isotwistane **72** could arise from a number of routes, and specifically, the Diels-Alder reaction seemed promising. It was noted that the isotwistane core contained three possible Diels-Alder disconnections (**74α 75-77**), two of which (paths A and C, Scheme 2.9) could be performed in an intramolecular manner to provide the isotwistane directly.

Scheme 2.9 Isotwistane Disconnections Based on a Diels-Alder Reaction.

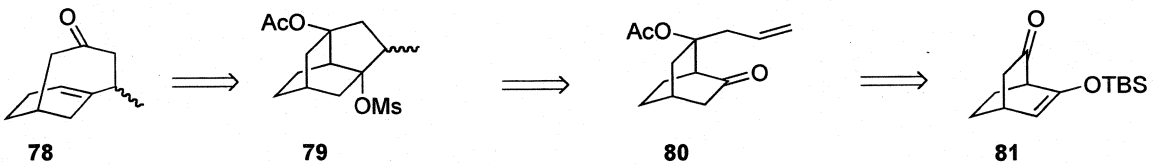


2.2.5 Second Wharton Fragmentation Model System.

2.2.5.1 Revised Retrosysnthesis Based on an Isotwistane Skeleton.

Before exploring Diels-Alder methods for the formation of isotwistanes, it was necessary to test the feasibility of performing a Wharton fragmentation on an isotwistane substrate. Retrosynthetic analysis for this revised model system proceeded along the same lines as the previous system. Thus, fragmentation of mesylate **79** would be the key step, with the requisite isotwistane structure being formed by a ketyl radical cyclization, the substrate for which could be formed by the addition of an allyl to ketone **81**.

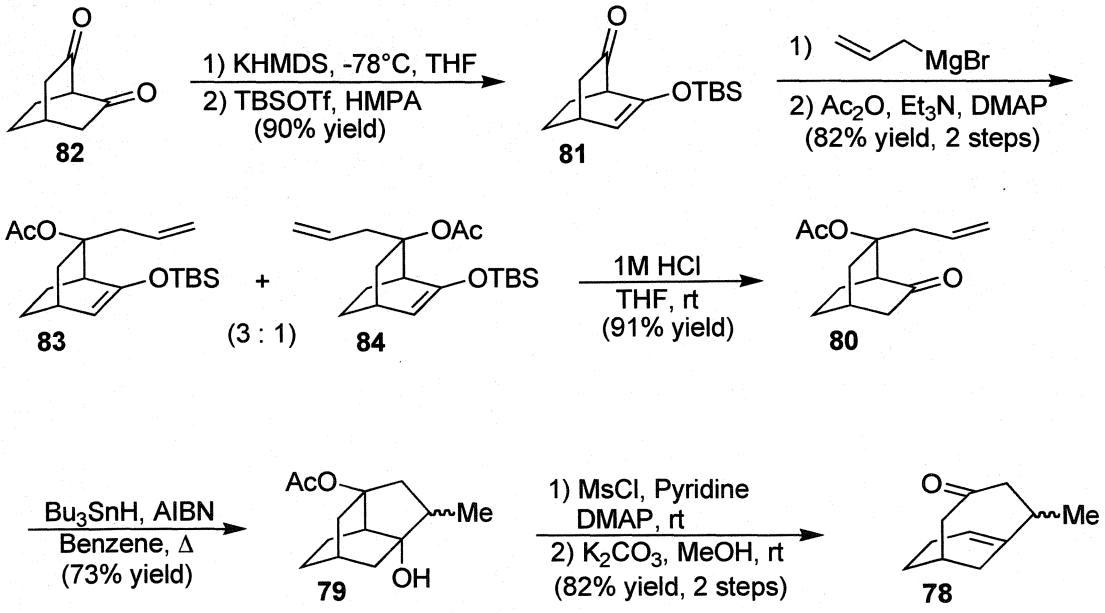
Scheme 2.10 Retrosynthesis: Second Wharton Fragmentation System.



2.2.5.2 Synthesis of the Second Model Wharton Fragmentation System.

Construction of the model system began with known diketone **82**,[21] which was desymmetrized by formation of the mono-TBS enol ether (**81**) (Scheme 2.11). Addition of allyl grignard was followed by acetate protection, and desilylation gave ketone **80**, the substrate for ketyl radical cyclization. Treatment of ketone **80** with Bu_3SnH and AIBN in refluxing benzene generated the corresponding ketyl,[22] which underwent radical cyclization in the *5-exo-trig* mode to afford isotwistane **79**. Mesylate formation again proceeded under standard conditions, and finally, treatment with K_2CO_3 in methanol effected acetate deprotection and fragmentation to efficiently give bicyclic ketone **78.**

Scheme 2.11 Isotwistane-based Wharton Fragmentation Model System.



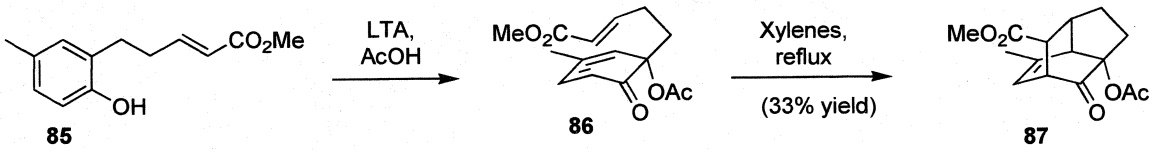
2.3 Intermediate Model Studies.

2.3.1 Tandem Phenolic Oxidation/ IMDA Reaction.

2.3.1.1 Yates Tandem Phenolic Oxidation/ IMDA Example.

As indicated previously, the reason for choosing the isotwistane-based fragmentation substrate was the hope that such a substrate could constructed in a facile manner. In fact, one example from Yates describes the synthesis of an isotwistane structure in a single step via a tandem phenolic oxidation/intramolecular Diels-Alder (IMDA) reaction (Scheme 2.12).[23] In this case, phenol **85** was treated with Lead(IV) acetate (LTA) in acetic acid to effect a phenolic oxidation, delivering triene (**86**), which upon heating in xylenes underwent an IMDA reaction to give isotwistane **87**.

Scheme 2.12 Yates' Tandem Phenolic Oxidation/IMDA Example.



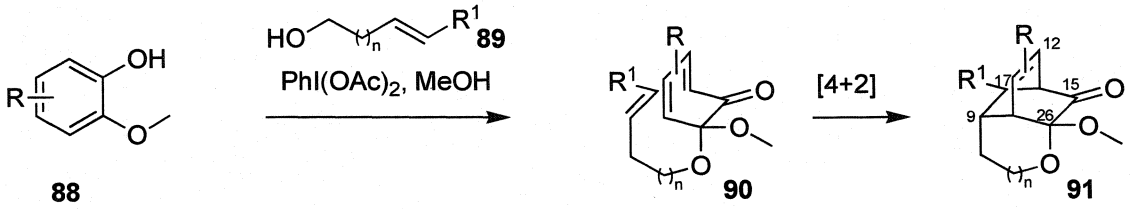
85 **86** **87**

2.3.1.2 Liao's Phenolic Oxidation/IMDA Approach.

One major limitation in the application of Yates' method to the synthesis of the phomoidrides was the lack of a good handle for the installation of the two side-chains in a stereodefined arrangement. In a similar phenolic oxidation/IMDA sequence however, Liao employed a system in which the dienophile was tethered through an ether linkage, rather than an all-carbon linkage (**88α** **91**, Scheme 2.13).[24-27] This method would not incorporate the final five-membered ring of the isotwistane, but would rather install the six-membered pyran ring, bridging C(9) to C(26). Importantly, the use of an *E*-

homoallylic alcohol could provide the correct stereochemical arrangement at C(9) and C(17)[25] and allow for the two side-chains to be installed.

Scheme 2.13 Liao's Hypervalent Iodine Oxidation/IMDA.

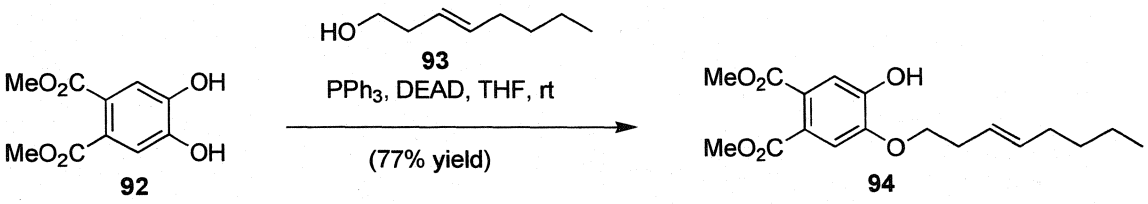


2.3.1.3 Application Toward the Synthesis of the Phomoidrides.

In the event that this type of phenolic oxidation/IMDA reaction was to be applied to the phomoidrides, the remaining five-membered ring of the isotwistane (bridging C(15)α C(12)) would need to be installed separately. This could potentially be formed from the corresponding bicyclo[2.2.2]octene via a 5-*exo-trig* radical cyclization as in the earlier model systems (**80α 79**, Scheme 2.11).

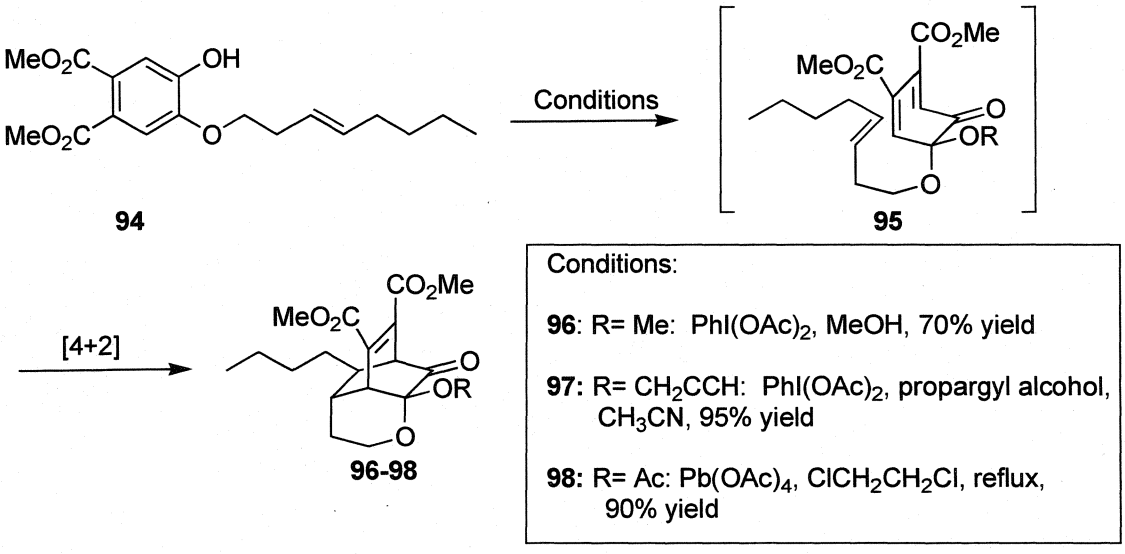
A second problem with Liao's method was the need to use excess dienophile (**89**) as the trapping agent, as this is quite uneconomical if a complex dienophile is required. A potential solution would be to tether the dienophile as an aryl ether, and use a simpler, cheaper alcohol as the trapping agent. To test this idea, a related and readily available model system was synthesized (Scheme 2.14).

Scheme 2.14 Construction of the Phenolic Oxidation Substrate.



Mitsunobu coupling of known homoallylic alcohol **93**[28] and known catechol **92**[29-31] provided phenol **94**. Gratifyingly, treatment of this phenol (**94**) with iodobenzene diacetate (IBDA) in the presence of excess alcohol as a trapping agent provided the desired bicyclo[2.2.2]octene core via a tandem phenolic oxidation/IMDA reaction sequence (Scheme 2.15, R=Me:**96**, R=propargyl:**97**). Furthermore, this type of reaction was not limited to using alcohols as the trapping agents, as it was found that by employing LTA in place of IBDA, trapping with acetate was also effective (**94α 98**).

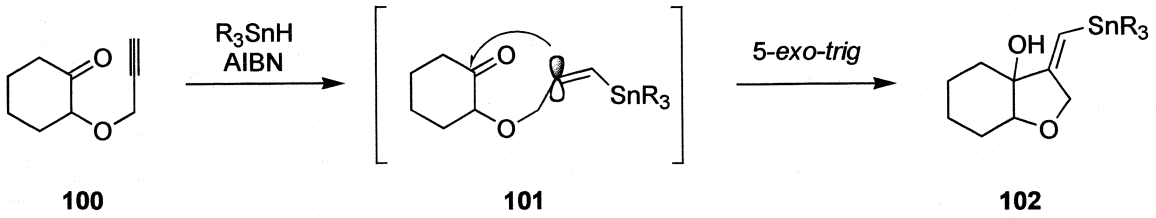
Scheme 2.15 Phenolic Oxidation/ IMDA.



2.3.2 Incorporation of the C(26)-C(15) Ring.

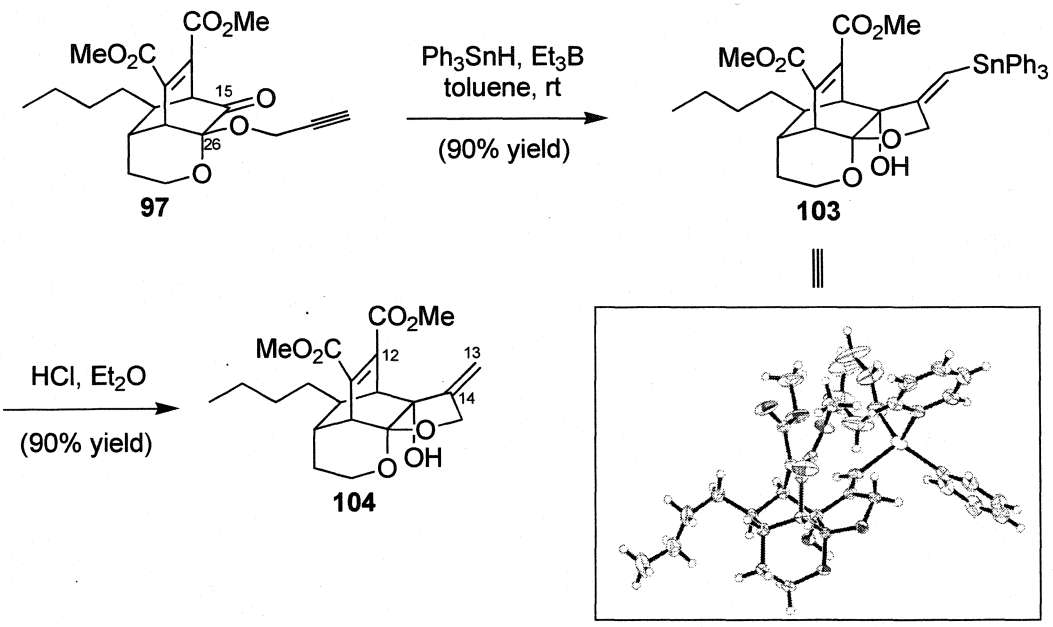
With tricyclic acetals (**96-98**) now in hand, completion of the isotwistane structure was considered. At this point, it was realized that the appropriate choice of trapping agent in this reaction might provide a handle for the incorporation of the C(15)α C(26) ring. (Scheme 2.17) For this reason, propargyl alcohol was employed (**94**α **97**, scheme 2.15), as work by Nishida showed that propargyl ethers could serve as precursors to vinyl radicals for radical cyclization into ketones (**100**α **102**, scheme 2.16).[32]

Scheme 2.16 Nishida's Vinylstannane Cyclization into Ketones.



Treatment of propargyl acetal **97** with Ph_3SnH in the presence of BEt_3 as a radical initiator provided vinylstannane **103**, the product of a 5-*exo-trig* radical cyclization (Scheme 2.17). As expected from the work of Nishida, vinylstannane **103** was obtained as a single diastereomer, in which the triphenyltin moiety was *trans* to the newly formed carbon-carbon bond. This arrangement was confirmed by single-crystal X-Ray analysis of vinylstannane **103**. Subsequent protodestannylation was accomplished by exposure of **103** to anhydrous HCl in ether to afford **104**.

Scheme 2.17 Vinylstannane Cyclization and X-Ray.



2.3.3 Installation of the C(12)-C(14) Ring of the Isotwistane.

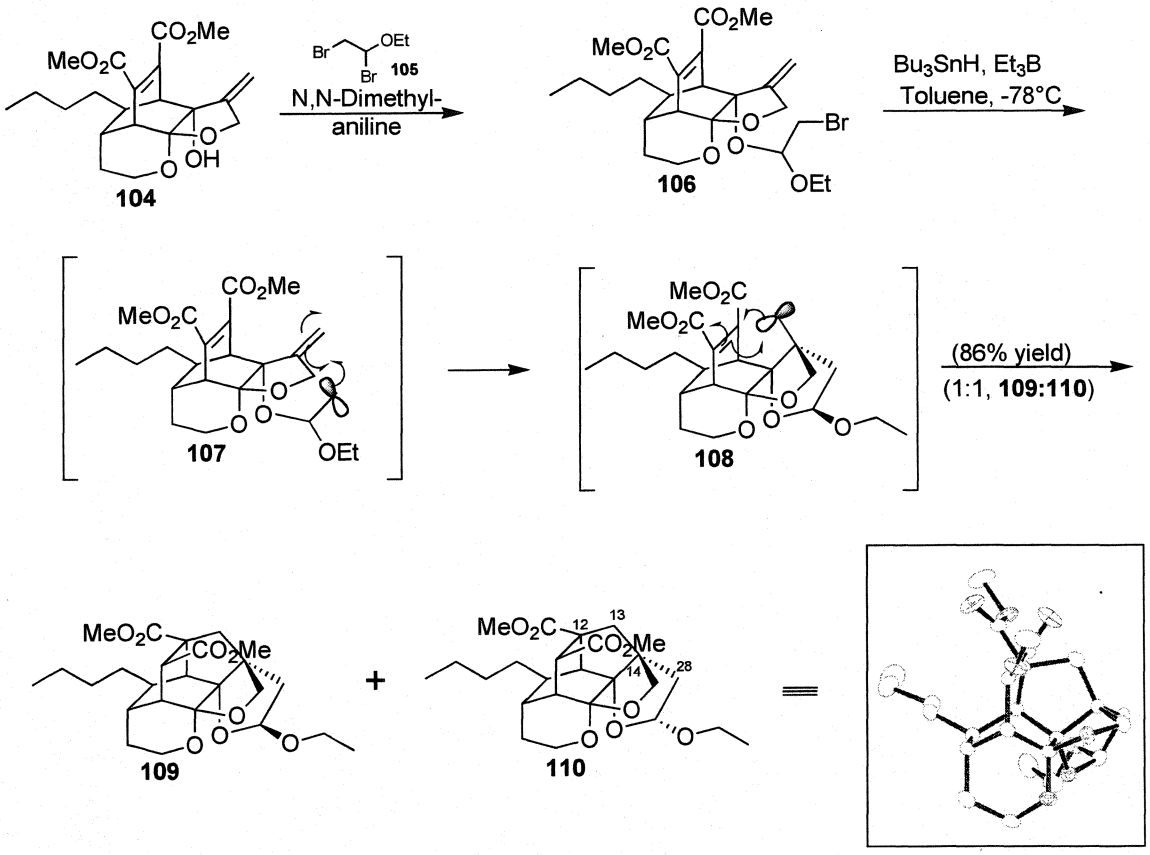
Attention was next turned to the formation of the final five-membered ring (bridging C(12)α C(14)) of the isotwistane precursor. Having successfully employed radical cyclization reactions for the construction of this ring in earlier systems (i.e. **80α 79**, Scheme 2.11) it was hoped that this type of reaction could also be used to close the final ring in the present system. Toward this end, it was believed that it would be possible to derivatize the C(15) tertiary alcohol such that a radical cascade could install both the C(14) quaternary center, and the bond between C(12) and C(13) to complete the isotwistane. Thus, the alcohol was functionalized as its Stork bromoacetal.[33-37]

Formation of the bromoacetal proceeded under standard conditions[38] to afford **106** as an inseparable mixture of diastereomers at the acetal position (Scheme 2.18). Subsequent treatment with Bu_3SnH and AIBN delivered polycycles **109/110** in good

yield as an inconsequential 1:1 mixture of diastereomers at the acetal position. It is believed that this reaction takes place by formation of the primary radical (**107**) from the bromoacetal, which undergoes a 5-*exo-trig* radical cyclization into the exocyclic olefin, forming a new primary radical (**108**). A second radical cyclization, also in the 5-*exo-trig* mode, into the maleate, thus completes the isotwistane core. Remarkably, this reaction formed two critical carbon-carbon bonds (C(12)α C(13) and C(14)α C(28)) and also set the stereochemistry at the important C(14) quaternary center. It is important to stress the accomplishment of having installed the C(14) stereogenic quaternary center, as other groups have struggled with this in their efforts toward the synthesis of the phomoidrides.[39]

The mixture of diastereomers **109** and **110**, could be readily separated by column chromatography. One of the diastereomers (**110**, acetal in the α-position) was found to be a crystalline solid, allowing for structure confirmation by single-crystal X-Ray analysis (Scheme 2.18).

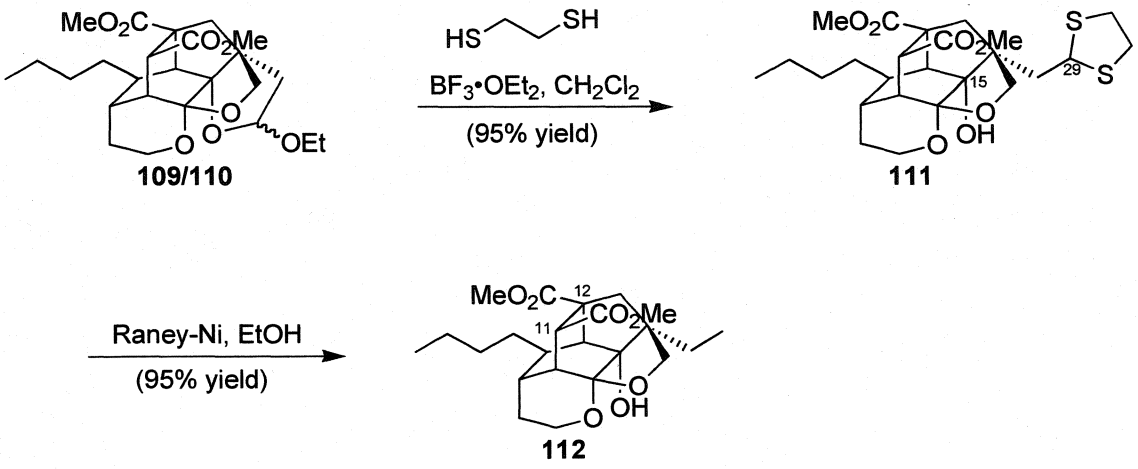
Scheme 2.18 Cascade Cyclization.



2.3.4 Unveiling the C(15) Tertiary Alcohol.[40, 41]

Treatment of the mixture of acetals **109** and **110** with ethanedithiol and $BF_3 \cdot OEt_2$ promoted a transacetalization to give **111**, in which C(29) is protected as its dithiolane and the tertiary alcohol at C(15) is unveiled (Scheme 2.19). Prior to attempting any fragmentation reactions, the dithiolane moiety was removed by reduction with Raney Nickel to give isotwistane **112**. The reason for this simplification was twofold: to remove any potential incompatibilities, and to clear the proton NMR spectrum of any resonances that might interfere with detection of the bridgehead olefin peak.

Scheme 2.19 Dithiolane Formation and Reduction.



2.3.5 Investigating New Fragmentation Possibilities.

2.3.5.1 Overview.

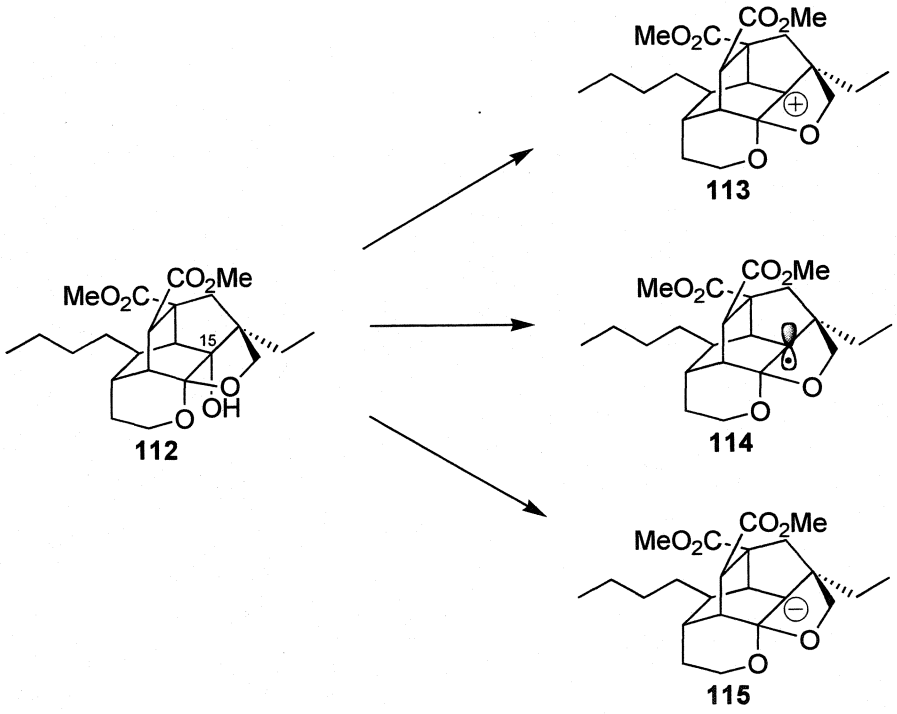
Unlike previous model systems, this system had esters at both C(11) and C(12), which were incorporated for three reasons. First, the use of a symmetrical catechol (**92**) greatly simplified the construction of this system. Second, it was believed that using the diester would accelerate the tandem phenolic oxidation / IMDA sequence, as this was expected to be an inverse electron demand Diels-Alder reaction,[42] and third, it was believed that the diester motif would allow facile access to the maleic anhydride. The downside to having these esters at C(11) and C(12) was that this system did not contain the tertiary alcohol at C(12) that was used to trigger the Wharton fragmentation in the previous model systems.

Although this system could not be advanced using the previously employed Wharton fragmentation, armed with the knowledge that isotwistanes could show a

propensity to fragment to the bicyclo[4.3.1]decene structure, it was possible to optimistically consider other methods to accomplish this goal.

The tertiary alcohol at C(15) of **112** was regarded as a handle to install a variety of functional groups that could potentially impart a carbocationic (**113**), radical (**114**) or carbanioinic (**115**) charcter to C(15) (Scheme 2.20), thus leading to a variety of fragmentation possibilities.

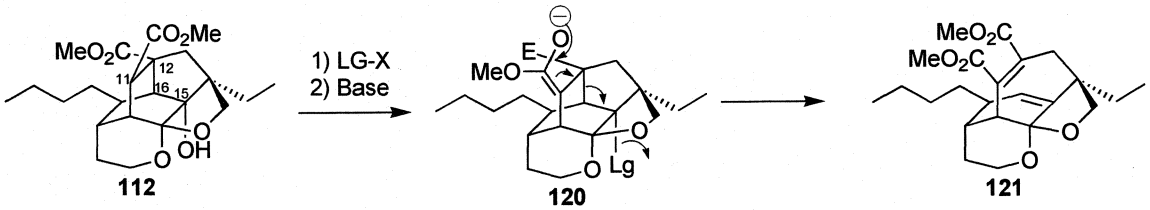
Scheme 2.20 New Isotwistane Fragmentation Possibilities.



2.3.5.2 "Top-Down" Fragmentation.

In the first approach, it was thought that a good leaving group such as a mesylate or halide at C(15) would impart carbocationic character to this position, thus promoting fragmentation in a strategy that would be similar to the previous Wharton fragmentation. Scheme 2.21 depicts how fragmentation might occur in a "top-down" manner by deprotonation of **112** at C(11). It was speculated however, that deprotonation at C(11) was unlikely to lead to fragmentation, as there would be very poor orbital overlap between the enolate (**120**) and the C(12)α C(16) bond which was to be broken.

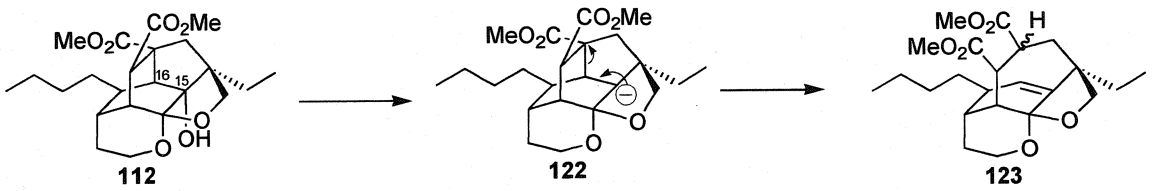
Scheme 2.21 "Top-Down" Fragmentation.



2.3.5.3 "Bottom-up" Fragmenation.

Alternatively, formation of a radical or anion at C(15) could potentially lead to a "bottom-up" fragmentation, in which the bridgehead olefin is installed, the C(12)-C(16) bond is cleaved and an enolate (or radical) is formed at C(12) (**112**α **123**, Scheme 2.22). This would be assured of having good orbital overlap, and stabilization of the anion (or radical) by the ester at C(12) might provide assistance to this reaction.

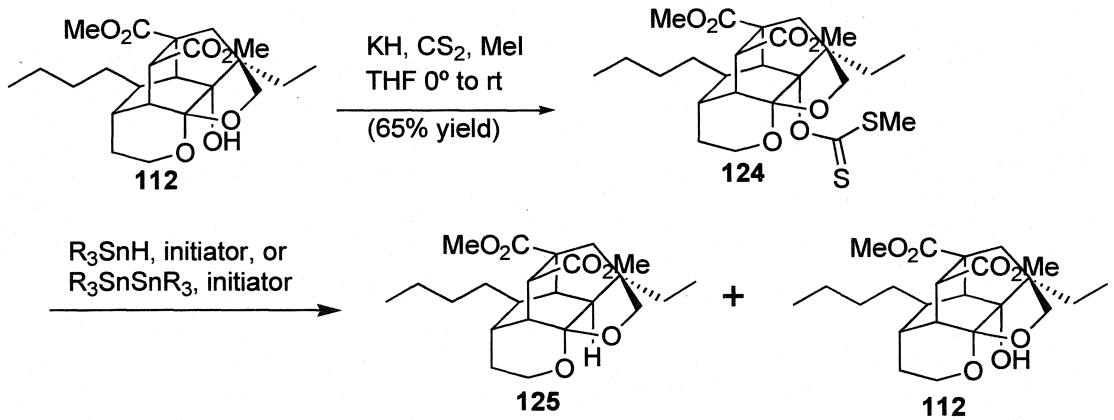
Scheme 2.22 "Bottom-up" fragmentation.



2.3.5.4 Xanthate Fragmenation Attempts with Tin-Hydride Methods.

Unfortunately, efforts to derivatize alcohol **112** at C(15) for the exploration of new fragmentation methods were rendered difficult by the inaccessibility of this alcohol, which in addition to being tertiary is also flanked on two sides by quaternary centers. Eventually however, it was discovered that the *S*-methyl dithiocarbonate (methyl xanthate, **124**) could be installed upon successive treatment with KH, CS_2 and CH_3I (Scheme 2.23).[43]

Scheme 2.23 Xanthate formation.

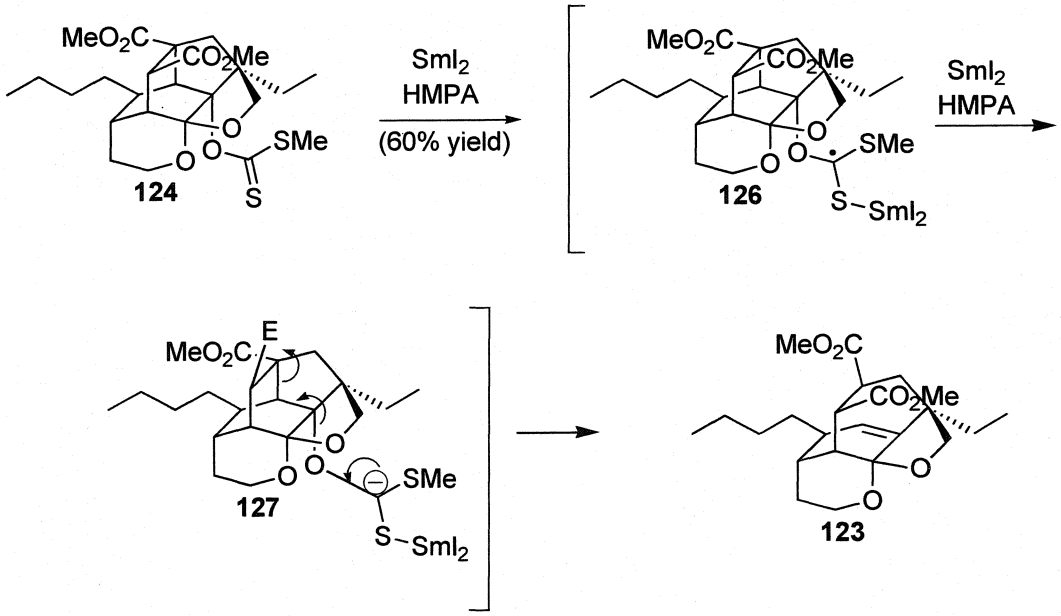


While this xanthate was expected to be a good precursor to a radical at C(15), standard radical conditions afforded none of the desired fragmentation product, the only isolable products being reduced isotwistane **125** and alcohol **112**.[43]

2.3.5.5 Xanthate Fragmentation with SmI_2/HMPA.

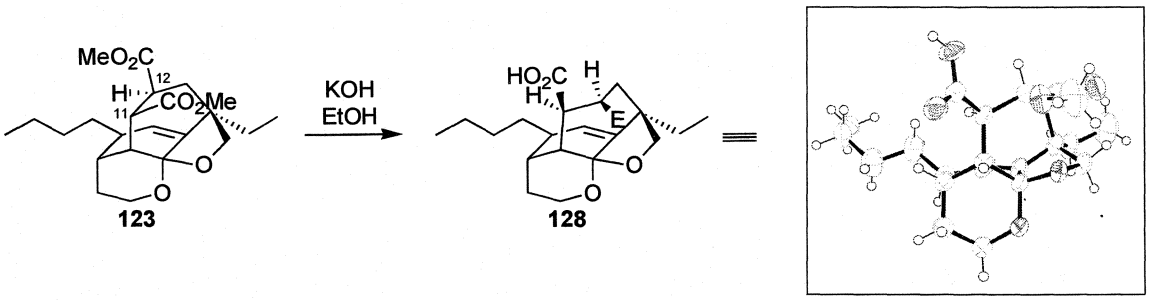
Although standard radical conditions were ineffective, after a great deal of experimentation, it was found that when xanthate **124** was treated with SmI_2 and HMPA, the desired fragmentation reaction proceeded in 60% yield (Scheme 2.24).[44] In light of the fact that standard radical conditions did not afford fragmented product (but did clearly form the radical, as evidenced by the isolation of reduced compound **125**), and the requirement of HMPA as an additive in this reaction (HMPA increases the reduction potential of the samarium reagent),[45] it is likely that this reaction was proceeding through a two-electron process. It is believed that two sequential one-electron additions to the xanthate form a species such as **127** (via **126**), which can fragment, *from the bottom-up*, to give **123**, containing the desired bicyclo[4.3.1]decene core of the phomoidrides including the bridgehead olefin.

Scheme 2.24 Mechanism of Xanthate Fragmentation with SmI_2/HMPA.



The structure of fragmentation product **123** was initially assigned by extensive NMR study (^{1}H NMR, ^{13}C NMR, COSY, HMQC, HMBC, NOE), and was later confirmed when saponification of a single ester led to a crystalline product. Single-crystal X-ray analysis showed the bicyclo[4.3.1]decene core containing the bridgehead olefin, and also established that the C(11) and C(12) esters are *cis* to one another[46].

Scheme 2.25 Structure Conformation by X-Ray Crystallography.



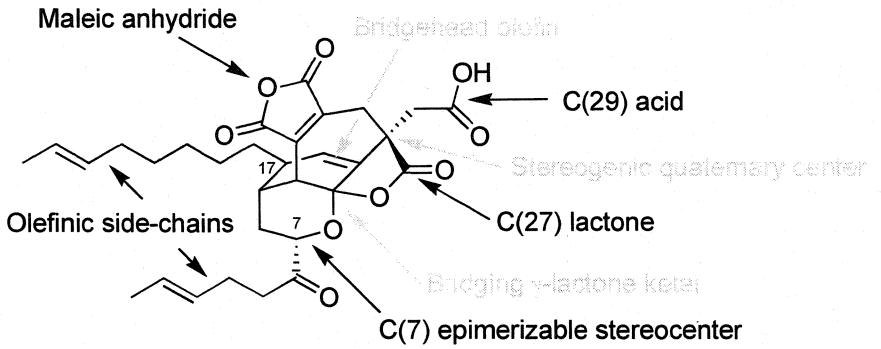
This fragmentation proved that the bicyclo[4.3.1]decene core could be accessed from the corresponding isotwistane in either a "top-down"(Wharton) or a "Bottom-up" (xanthate/SmI_2) manner. This validated the choice of including esters at C(11) and C(12), and allowed for work toward the total synthesis to proceed by next evaluating how the remaining functionality could be incorporated.

2.4 Remaining Challenges.

Having established a concise route toward the assembly of the carbocyclic core of the phomoidrides, our attention turned to addressing the remaining challenges in the synthesis. As outlined in Figure 2.1, several important features were not incorporated into the previously discussed model systems, including the olefinic side-chains, the

maleic anhydride, C(7) epimerizable stereocenter, and the C(29) acid and the C(27) lactone.

Figure 2.1 Remaining Challenges.



Among the remaining challenges, most notable are the two side-chains; the upper side-chain (connected to the core at C(17)) was truncated to an *n*-butyl group in the model compounds, while the lower side-chain (attached at C(7)) was not included at all. Additionally, the lower side-chain had the challenge of containing a ketone at C(6), and thus an epimerizable stereocenter at C(7), its point of attachment to the phomoidride core. The other remaining challenges, including the C(29) acid, C(27) lactone, and the maleic anhydride installation all required oxidation state adjustments. Along these lines, we envisioned the remaining obstacles as being divided into two groups: those to be addressed from the beginning of the synthesis, and those that could be incorporated post-fragmentation. The maleic anhydride incorporation and the C(29) acid installation would fall into the latter category, while the two side-chains would necessarily be included from the beginning. The C(27) lactone could potentially be installed either via a late-stage oxidation, or by inclusion of the correct oxidation state from the beginning of the

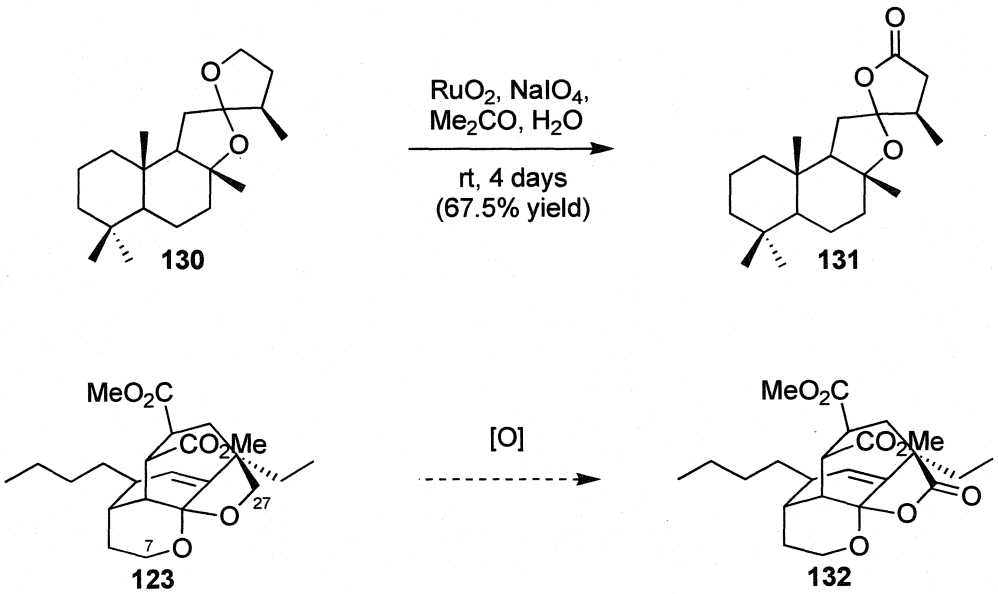
synthetic sequence. Before tackling the other challenges, it was decided to first determine the best occasion for the installation of the lactone.

2.5 Lactone Installation.

2.5.1 Acetal Oxidation.

Initial attempts at construction of the lactone were focused on oxidation of the C(27) methylene at various stages. One possibility was to perform an oxidation of an advanced intermediate such as **123**. This type of acetal oxidation was well precedented (**130**α **131**, Scheme 2.26),[47] but was unlikely to be successful on a compound such as **123** for a number of reasons. To wit, fragmentation product **123**, containing sensitive functionality such as the bridgehead olefin, was ill-equipped to handle the harsh oxidative conditions required, and furthermore, all compounds in this series have multiple acetal sites (i.e. C(7) as well as C(27)) that could be oxidized.

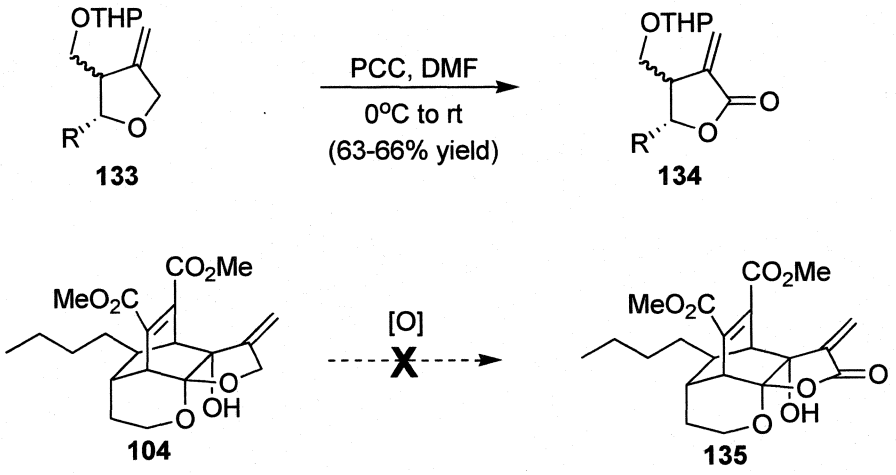
Scheme 2.26 Lactone Installation by Acetal Oxidation.



2.5.2 Lactone Installation by Allylic Oxidation.

Another possibility to install the C(27) lactone was to perform the oxidation prior to the cascade cyclization (Scheme 2.27). At this point, the C(27) methylene is allylic and should be significantly more reactive than the methylene at C(7). Although this type of allylic oxidation of ethers is well precedented under mild conditions,[48] attempts to oxidize **104** at C(27) were met with no success.

Scheme 2.27 Lactone Incorporation by Allylic Oxidation.

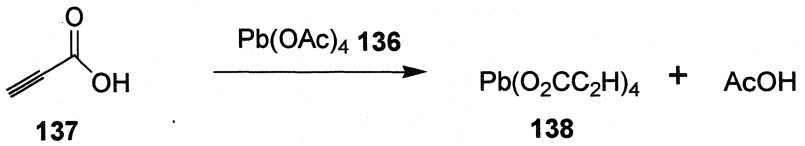


2.5.3 Lactone Installation via the Propiolate Ester.

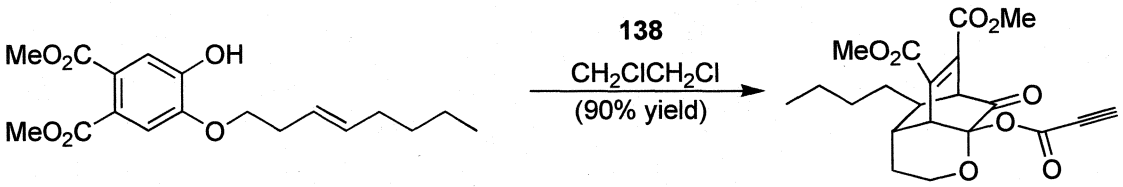
Since the oxidation of C(27) was not fruitful, it was necessary to include this oxidation state earlier in the synthesis. In the tandem phenolic oxidation/IMDA sequence, a variety of conditions were effective. While conditions employing IBDA and propargyl alcohol were previously used, LTA also performed effectively in this reaction (**94**α **98**, Scheme 2.15), and served to install the correct (acid) oxidation state at C(27). Yates and others have shown that addition of excess carboxylic acid promotes a metathesis in which the added acid displaces the acetate ligands on the lead.[49, 50] This

newly formed Lead (IV) tetracarboxylate (**138**) can then function similarly to LTA, with the added acid acting as the trapping agent.

Scheme 2.28 Formation of the Propiolate Pseudoester.



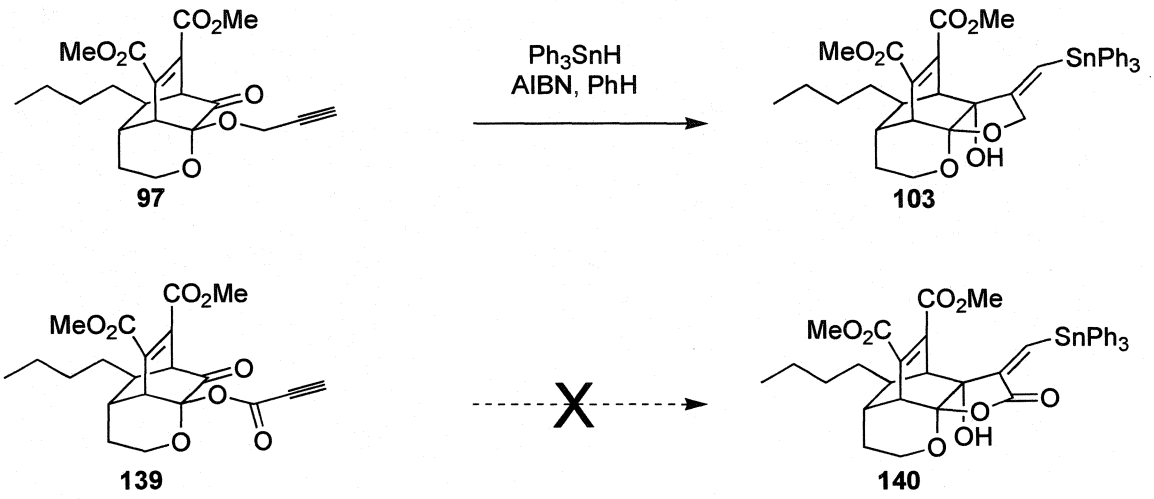
137 **138**



94 **139**

When applied to our system, it was found that premixing excess propiolic acid and LTA followed by addition of phenol **94** provided propiolate pseudoester **139**. Unfortunately, however, when propiolate pseudoester **139** was treated under the previously optimized cyclization conditions, none of the desired *exo*-methylene lactone was formed. Several other attempts to achieve this cyclization were similarly unsuccessful (Scheme 2.29).[51]

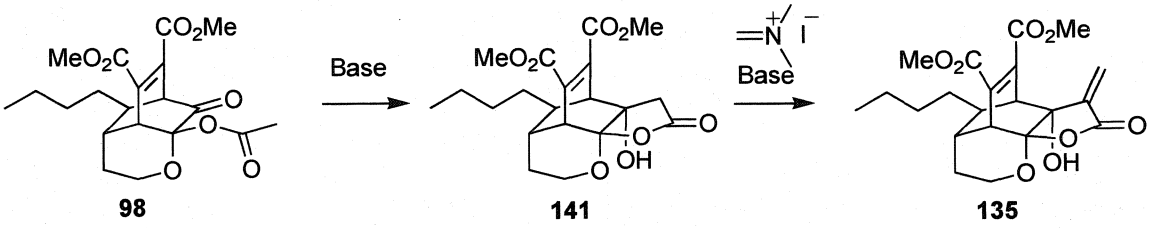
Scheme 2.29 Propiolate Cyclization Attempts.



2.5.4 Lactone Formation by Tandem Aldol-Mannich-Hofmann Sequence.

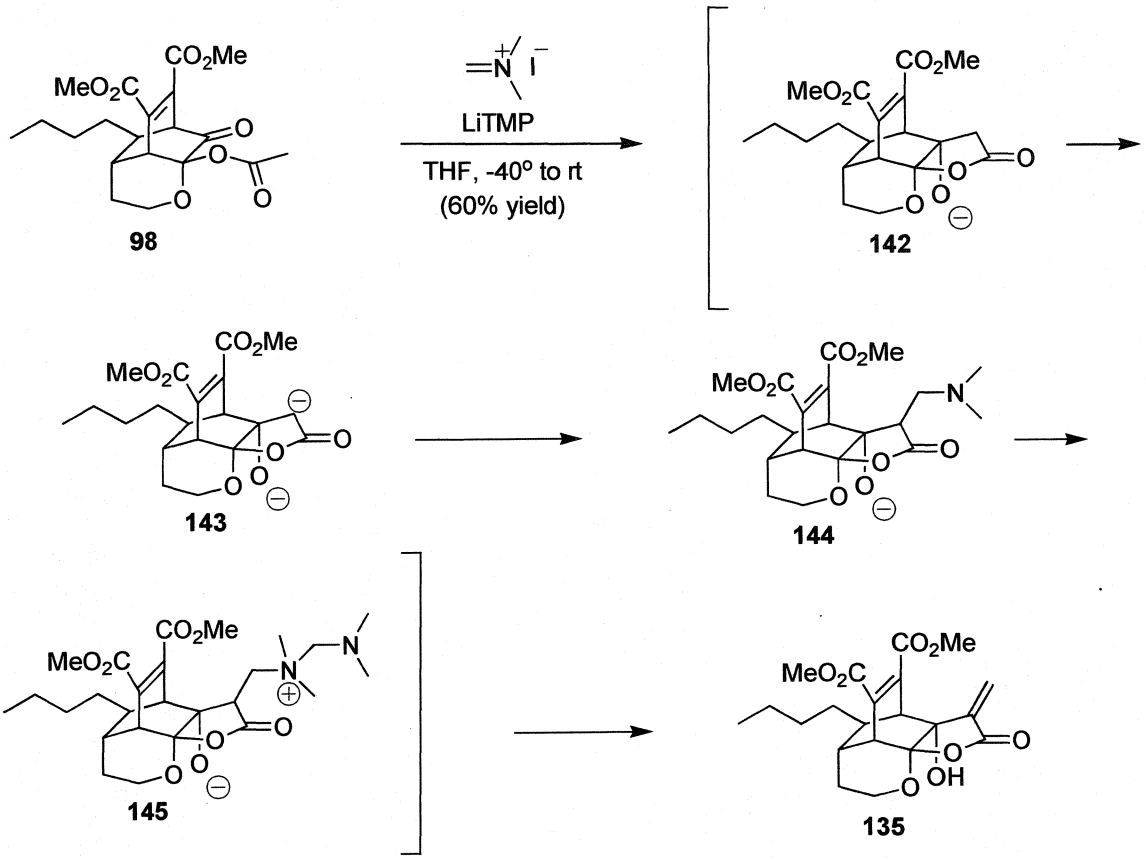
Failure to advance propiolate ester **139** to the *exo*-methylene lactone forced us to abandon this radical cyclization strategy, and our attention turned to using acetate **98** directly. Scheme 2.30 shows that this could potentially be used to form the lactone ring (**141**) by aldol cyclization, and **135** by subsequent α-methylenation.

Scheme 2.30 Aldol-Mannich Sequence.



Since both of these transformations would likely require similar basic conditions, it was imagined that they might be carried out in a one-pot reaction sequence. To our satisfaction, treatment of mixture of acetate **98** and Eschenmoser's salt with LTMP gave *exo*-methylene lactone **135** in 60% yield (Scheme 2.31).

Scheme 2.31 Tandem Aldol-Mannich-Hofmann Reaction.



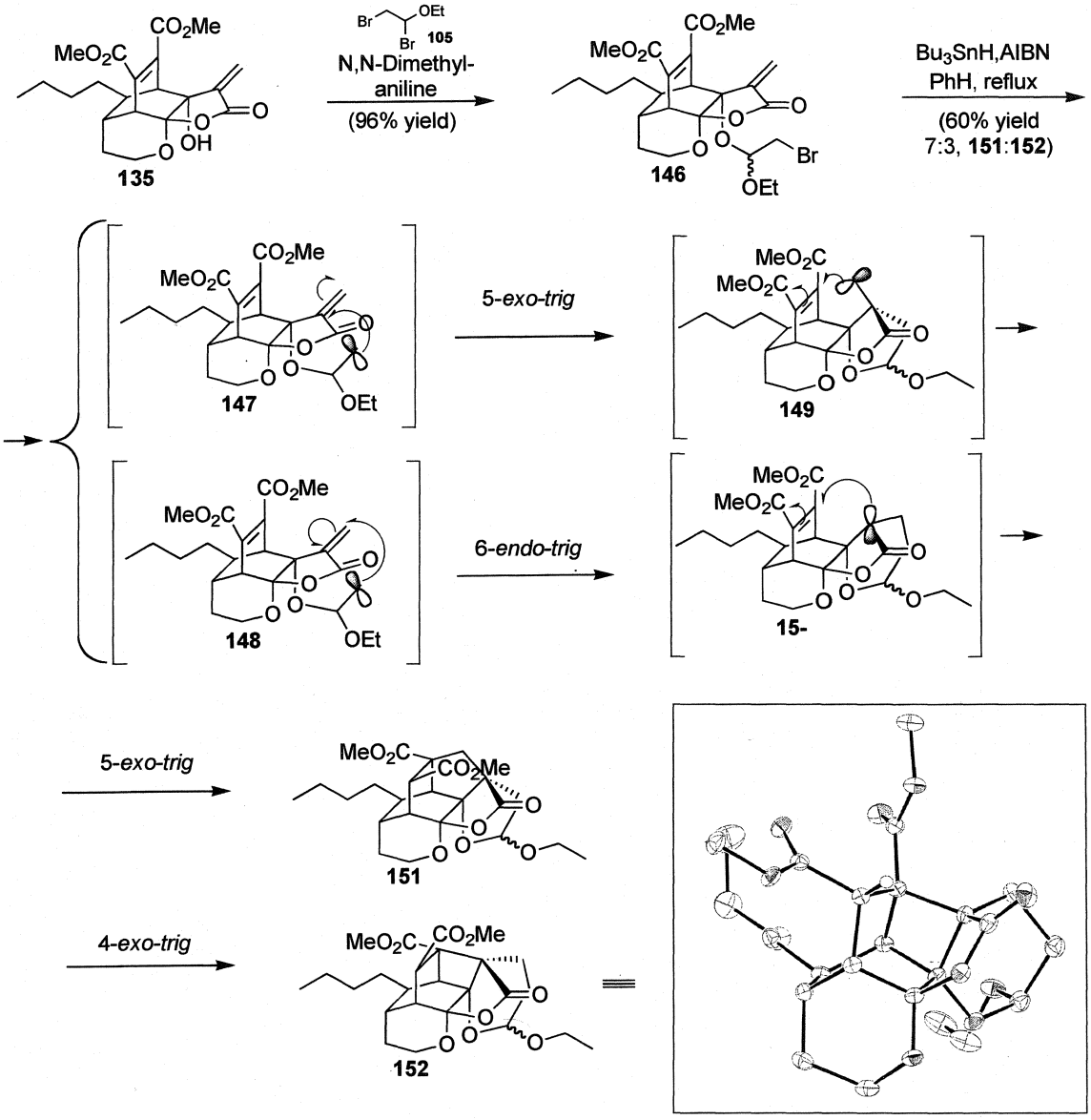
Presumably, this reaction occurs first by enolization and aldol cyclization into the ketone to provide **142**, which is again deprotonated to provide dianion **143**, which then undergoes a Mannich reaction with Eschenmoser's salt. It has been reported that in cases such as this, in which a large excess of the Eschenmoser's salt is present, the elimination is facilitated by further alkylation of the resultant tertiary amine (**144**) with another equivalent of Eschenmoser's salt.[52] While the yield in this sequence was somewhat lower than the cyclization in the previous model system (which lacked the correct oxidation state at C(27)), it allowed access to the desired *exo*-methylene lactone in only one step from the product of the tandem phenolic oxidation/ IMDA sequence.

2.6 Advancing the lactone.

2.6.1 Radical Cascade Cyclization on the Lactone.

Lactone **135** was next advanced through the rest of the sequence employed in the previous model system. Bromoacetal formation proceeded as before to give bromoacetal **146**, and treatment with Bu_3SnH and AIBN provided the desired 5-*exo-trig*, 5-*exo-trig* radical cascade product **151** as a mixture of diastereomers at the ethyl acetal, albeit in significantly lower yield than before (Scheme 2.32). The main impurity, **152**, was determined to be the result of an undesired 6-*endo-trig,* 4-*exo-trig* radical cascade, also found as a mixture of diastereomers at C(29). One diastereomer of this unusual cyclization product was found to be a crystalline solid, and its structure was thus confirmed by single crystal X-Ray analysis. Presumably, the carbonyl of the lactone increases the propensity for this system to undergo 6-*endo-trig* cyclization during the first step.

Scheme 2.32 Bromoacetal Cascade Cyclization of Lactone 135.

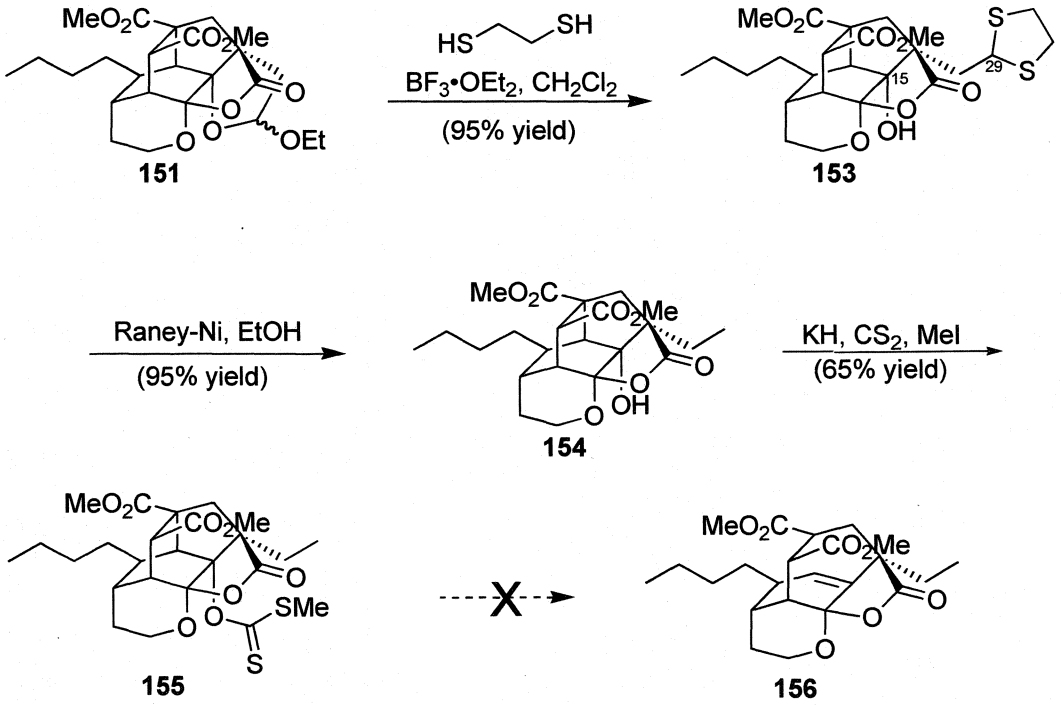


2.6.2 Attempted Fragmentation.

Although the yield of the cascade cyclization was lower than expected due to the unanticipated side product, it still proved reasonably efficient in allowing access to material to test the crucial fragmentation step. Advancing in an analogous manner to

before, acetal **151** was treated with ethanedithiol and BF_3•OEt_2 in dichloromethane to afford dithiolane **153** (Scheme 2.33). Treatment of **153** with Raney-Ni next reduced C(29) to afford tertiary alcohol **154**, thus allowing for incorporation of the xanthate moiety under the previously optimized conditions. Unfortunately, when xanthate **155** was treated with SmI_2 and HMPA, none of the desired fragmentation product was formed.

Scheme 2.33 Attempted Fragmentation.

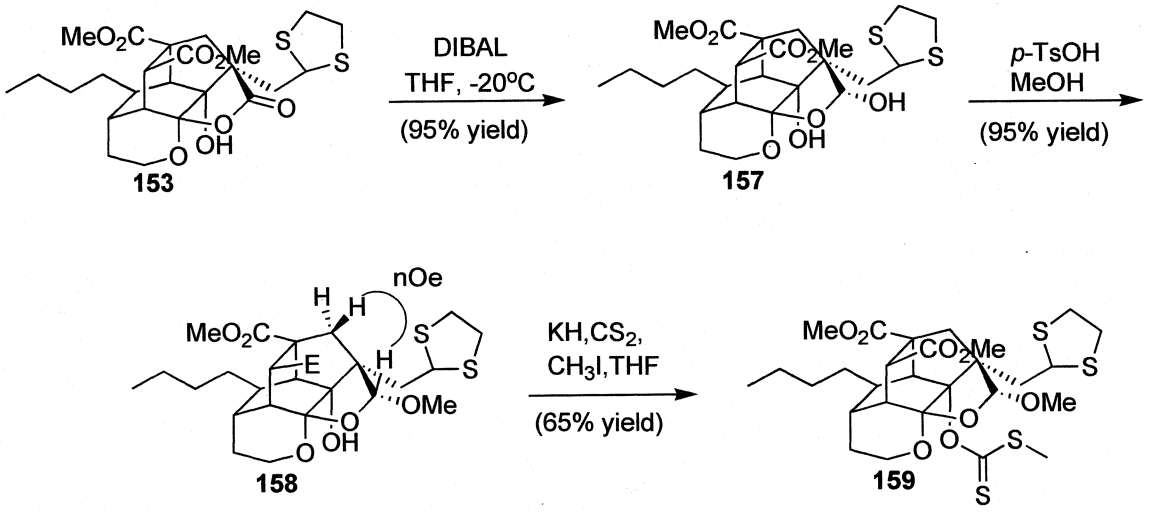


2.6.3 Protection of the Lactone.

The only difference between the successful fragmentation (see **124**α **123**, Scheme 2.23) and this unsuccessful attempt, was the oxidation state at C(27). There seemed to be two possible causes to this different reactivity: either due to stabilization of the reactive intermediate (anion or radical) from the newly neighboring carbonyl at C(27), or due to

the different steric strain caused by changing the hybridization of C(27) from an sp^3 to an sp^2 center. To solve this problem, lactone **153** was reduced to the corresponding lactol (**157**) by treatment with DIBAL in THF. Exposure of this to catalytic *p*-TsOH in methanol then gave methyl acetal **158** in excellent yield as a single diasteromer. The orientation of the methyl acetal was determined down (as shown) by 1D NOE experiments, showing an NOE between the acetal methine and the C(13) methylene (Scheme 2.34).

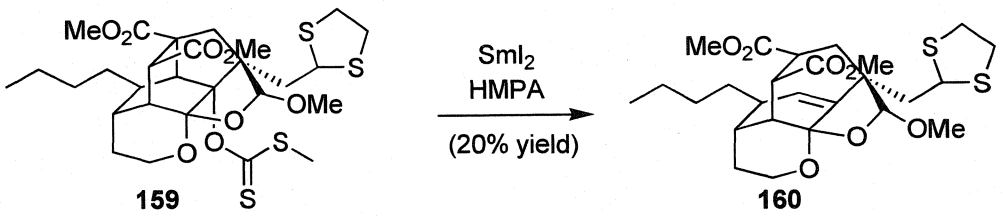
Scheme 2.34 Reduction of the Acetal and Xanthate Formation.



2.6.4 Acetal Fragmentation

Xanthate formation proceeded as before to make **159**, which upon treatment with a mixture of SmI_2 and HMPA, resulted in the desired fragmentation reaction to afford bicyclo[4.3.1]decene **160** in 20% yield. Although this yield was low, it was encouraging that the desired fragmentation, which was completely unsuccessful on the lactone (**155**), worked on this protected variant.

Scheme 2.35 Xanthate Fragmentation of Acetal 159.



2.7 Conclusions.

The evolution of a synthetic approach to the phomoidrides has been described. Initially, a rather naïve retrosynthetic plan (oxy-Cope) was replaced with the milder Wharton fragmentation. Further development transformed the initial fragmentation approach, which was centered on a [2.2.1] bicyclic system, to the fragmentation of a more easily accessible isotwistane, to provide a regioisomeric bicyclo[4.3.1]decene product.

In order to address the inclusion of some of the key structural features found in the phomoidrides, several tandem reaction sequences were employed. A tandem phenolic oxidation/IMDA sequence provided the [2.2.2]bicyclic core around which the isotwistane would be constructed. A tandem radical cascade completed the isotwistane, including the stereocontrolled construction of the difficult C(14) quaternary center. Finally, a xanthate based fragmentation, in which the fragmentation is initiated from the bottom-up, provided yet another method to access the bicyclo[4.3.1]decene core of the phomoidrides.

Several of the remaining challenges in the synthesis of the phomoidrides have been considered. The incorporation of the C(27) oxidation state, which was not possible to introduce by oxidation or by analogy with the earlier method (5-*exo-trig* cyclization)

was installed in a novel one-pot procedure involving tandem aldol and Mannich reactions, with *in situ* Hofmann elimination. This system, differing from the former in only one position (i.e. the lactone at C(27)), was found to have substantially different reactivity in the other key steps in the sequence. The radical cascade cyclization was rendered less efficient by the formation of a significant amount of a side product resulting from 6-*endo-trig*, 4-*exo-trig* cascade cyclization, and the critical fragmentation step did not work at all on the substrate containing the lactone. The latter problem was overcome by protection of this lactone as its methyl acetal, allowing for fragmentation to occur, albeit in modest yield.

2.8 References.

1. This chapter is a review of work done by others in the Wood Group (Drs. Jon T. Njardarson, David A. Spiegel and Munenori Inoue) and more detailed discussions of this work, along with experimental details, may be found in references 2, 3, 39 and 40.

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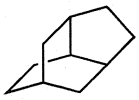
20. Isotwistane is Tricyclo[4.3.1.0(3,7)]decane



Isotwistane
Tricyclo[4.3.1.$0^{3,7}$]decane

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Chapter 3

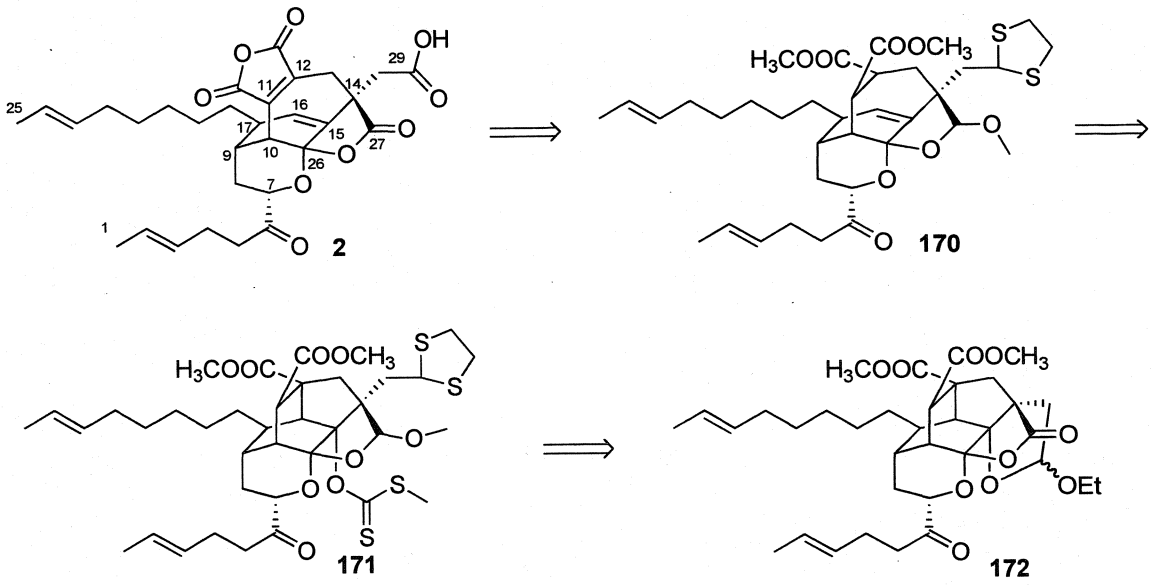
Progress Toward the Phomoidrides:

Construction of a Fully-Functionalized Isotwistane Precursor

3.1 Retrosynthetic Analysis.

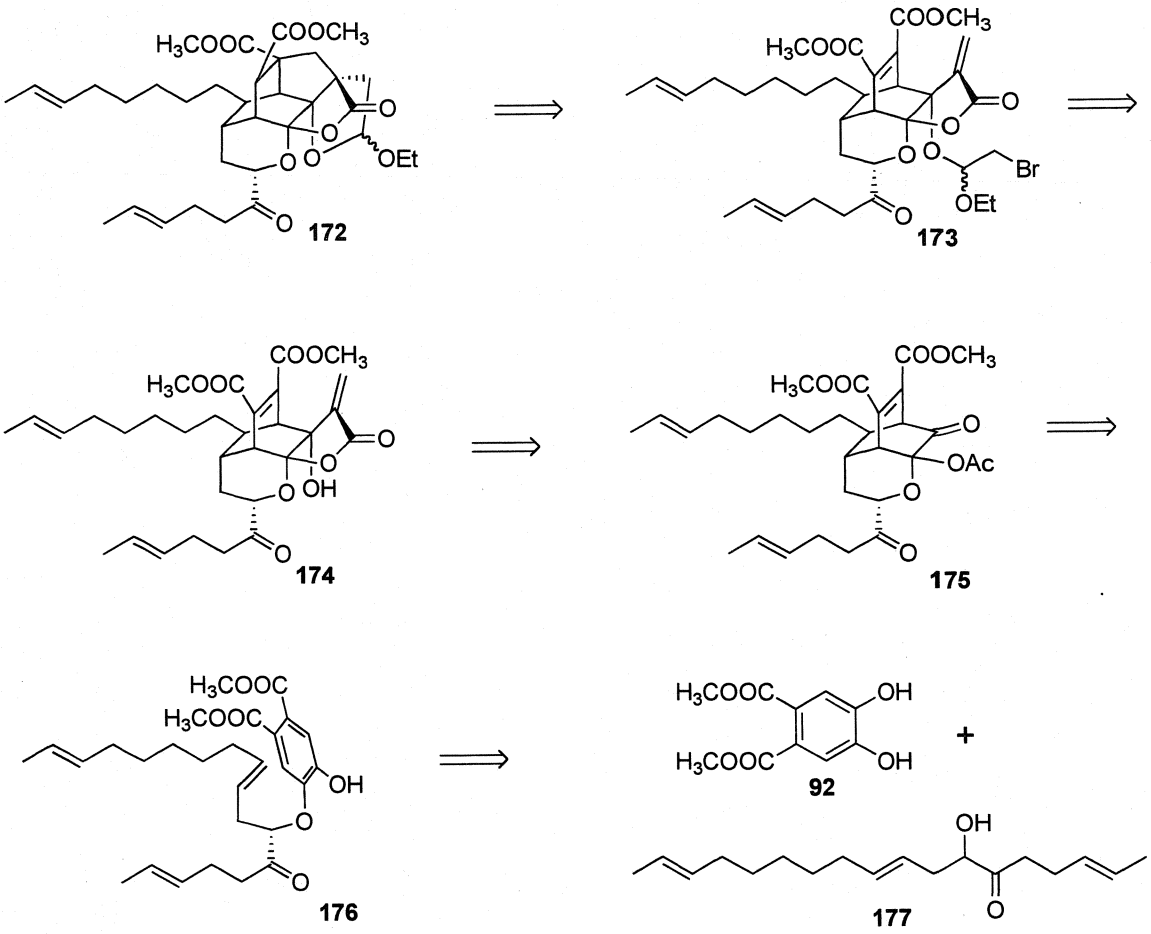
In the previous chapter, several model systems employed in the evolution of a synthetic route to the phomoidrides were discussed. Up to this point, a complete retrosynthetic analysis has not been discussed, but now a viable retrosynthesis can be envisioned based upon the information learned from the model studies.

Scheme 3.1 Retrosynthesis, Part 1.



The C(29) acid, C(27) lactone, maleate olefin, and anhydride moieties were all poised for late-stage introduction from a fragmentation product such as **170** (Scheme 3.1). This intermediate, containing the bicyclo[4.3.1]decene core of the phomoidrides and the important bridgehead olefin, would be unveiled by samarium(II) iodide (SmI_2) promoted fragmentation of xanthate **171**. As was shown in model studies, this xanthate could come in several steps from an ethyl acetal such as **172**, which in turn would arise via a cascade cyclization of a bromoacetal derived from lactone **174** (Scheme 3.2). Formation of lactone **174** might proceed, as in the model studies, from acetate **175**, which would be formed by a tandem phenolic oxidation/ intramolecular Diels-Alder (IMDA) sequence from ether **176**. Finally, ether **176** could be accessed from the coupling of catechol **92** and C_{18} δ-hydroxyketone **177**.

Scheme 3.2 Retrosynthesis, Part 2.



3.2 Synthesis of the Fully Functionalized Side-Chains.

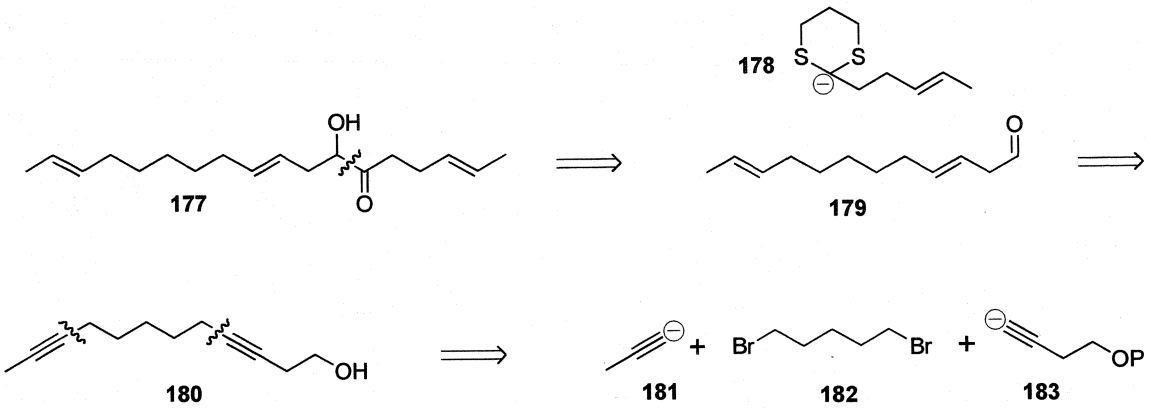
3.2.1 First-Generation Approach.

3.2.1.1 First Generation Retrosynthesis of the C_{18} δ-Hydroxyketone.

While catechol **92** was employed in the model systems, δ-hydroxyketone **177** was not, and therefore required further retrosynthetic analysis. A first-generation retrosynthesis of δ-hydroxyketone **177** is presented in Scheme 3.3. The key disconnection was proposed to be an umpolung dithane addition to a δ,δ-unsaturated

aldehyde (**179**), which would be obtained from the diynyl alcohol **180**. Finally, **180** would be formed by two acetylide alkylations of 1,5-dibromopentane (**182**).

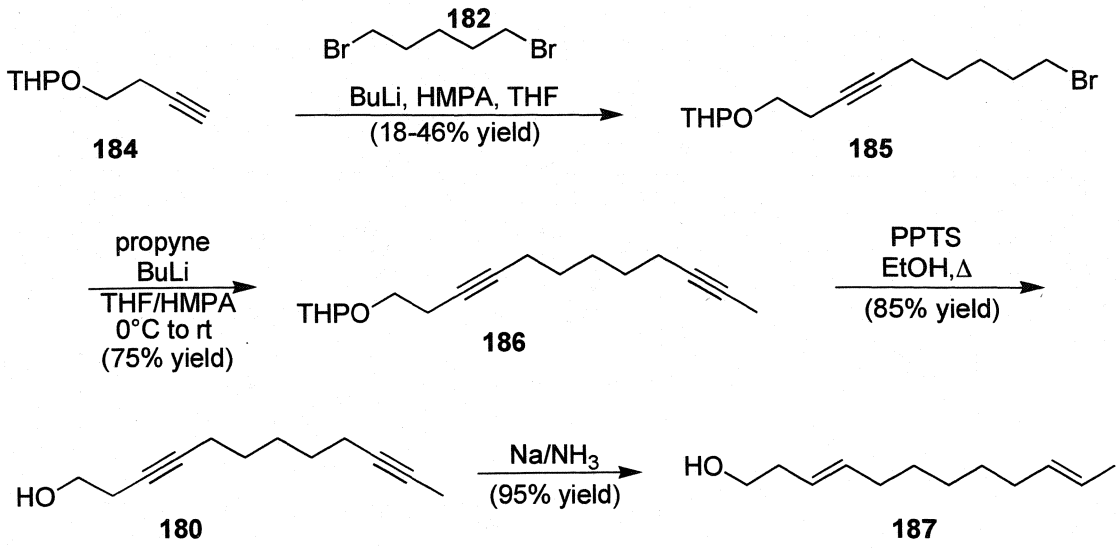
Scheme 3.3 First-Generation Retrosynthesis of the Full Side-Chains.



3.2.1.2 First-Generation Approach to the Side-Chains.

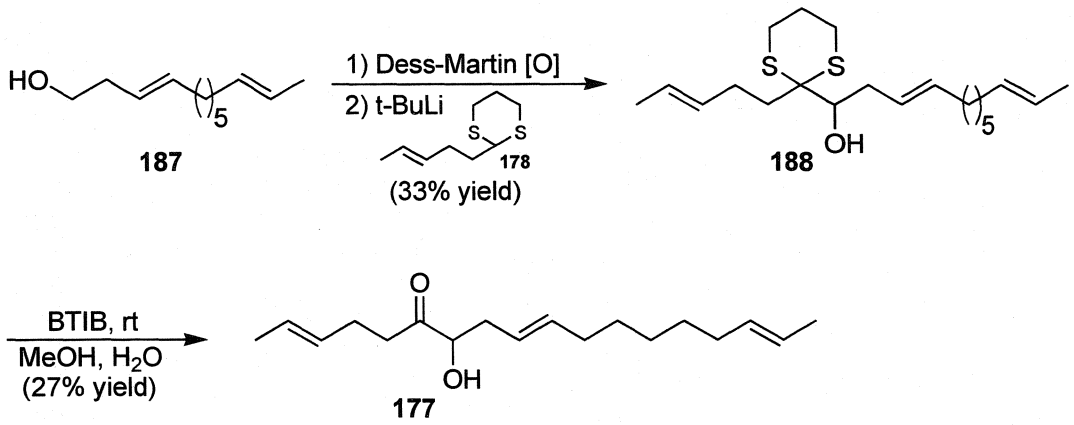
In the forward sense, the synthesis commenced with alkylation of commercially available THP-protected butynol **184** with 1,5-dibromopentane to afford bromide **185** in modest yield (Scheme 3.4). Subsequent displacement of the second bromide with propynyl lithium furnished diyne **186**, which upon deprotection, gave diynyl alcohol **180**. Finally, exposure of **180** to dissolving metal reduction conditions furnished the desired *trans-trans* dienyl alcohol **187**.

Scheme 3.4 First-Generation Synthesis of Primary Alcohol 187.



The sequence proceeded with Dess-Martin oxidation of alcohol **187** to the aldehyde, which reacted in an umpolung fashion with known lithio thioacetal **178** to give secondary alcohol **188** (Scheme 3.5). Next, dithiane deprotection according to Stork's method, employing bis-trifluoroacetoxy iodobenzene (BTIB) in methanol, furnished the desired C_{18} δ-hydroxyketone **177**. This secondary alcohol contained all the carbons found in both side-chains (C(1)δ C(9) and C(17)δ C(25) Scheme 3.1), but unfortunately this sequence was very low yielding (2.5% over seven steps).

Scheme 3.5 Dithiane Addition to Form δ-Hydroxyketone 177.



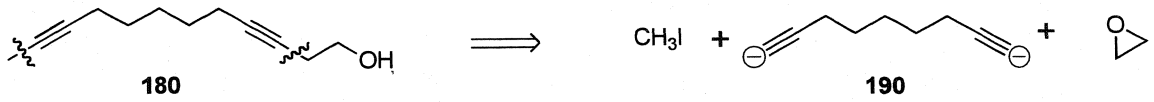
The poor yield of this route was not acceptable for the initial stages of a synthesis. The very first step provided the greatest challenge in terms of scale-up (Scheme 3.4 **184**δ **185**), proceeding with an average yield of less than 46%. Additionally, this reaction required large amounts of toxic HMPA as a cosolvent, needed to be purified by flash chromatography, and at the maximum scale provided only 5g of product. One problem appeared to be that elimination of bromide by the basic acetylide anion was competitive with substitution.

3.2.2 Second-Generation Approach to the Full Side-Chains.

3.2.2.1 Revised Retrosynthesis.

Due to difficulties in preventing elimination of the dibromopentane, an alternate route was devised in which elimination could not occur. Scheme 3.6 shows a revised retrosynthesis of **180**, in which 1,8-nonadiyne would be alkylated successively with iodomethane and ethylene oxide.

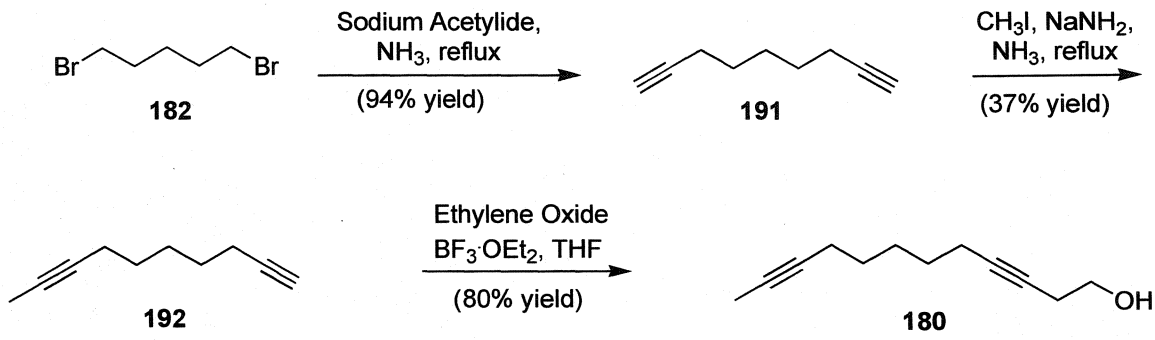
Scheme 3.6 Second-Generation Retrosynthesis of the Primary Alcohol.



3.2.2.2 Second-Generation Approach to the Full Side-Chains.

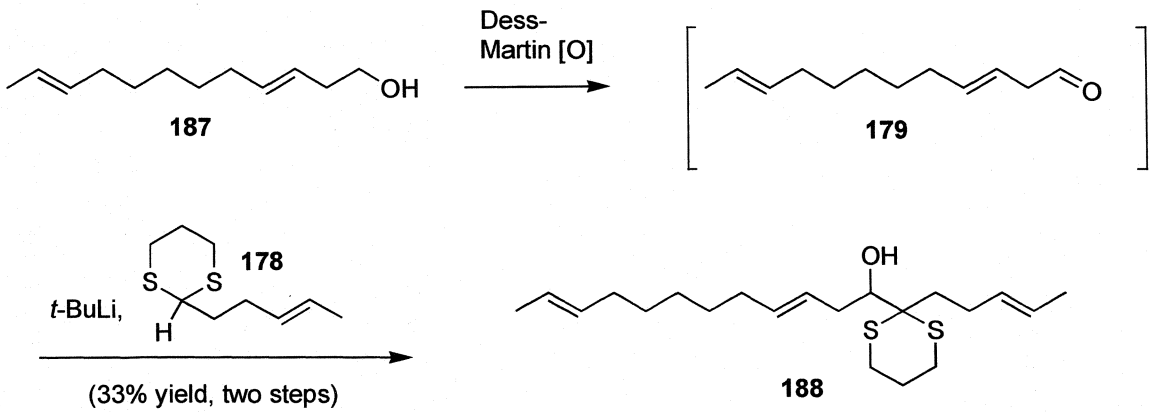
While the requisite 1,8-nonadiyne (**191**) is commercially available, it can be prepared in a very economical manner by reaction of 1,5-dibromopentane (**182**) with excess sodium acetylide (Scheme 3.7) Next, treatment of diyne **191** with sodium amide and iodomethane in liquid ammonia provided monomethyl diyne **192** in 40% yield. Although the yield was again modest, and the separation was difficult, this route had distinct advantages. Material scale-up was facile, as this alkylation step was performed at high concentration, used inexpensive reagents, and was purified by distillation rather than chromatography. As a result, this reaction could be performed on greater than 2 mole scale without difficulty.

Scheme 3.7 Second-Generation Approach to the Primary Alcohol.



Monomethyl diyne **192** was next deprotonated with *n*-butyllithium to form the acetylide anion, which was treated with ethylene oxide and $BF_3 \cdot OEt_2$. This efficiently provided the diynyl alcohol **180**, which, as shown previously in Scheme 3.4, could be reduced under dissolving metal conditions to give **187**. Thus, the synthesis of the requisite primary alcohol (**187**) was improved over the initial route.

Scheme 3.8 Elaboration to the Secondary δ-Hydroxyketone.



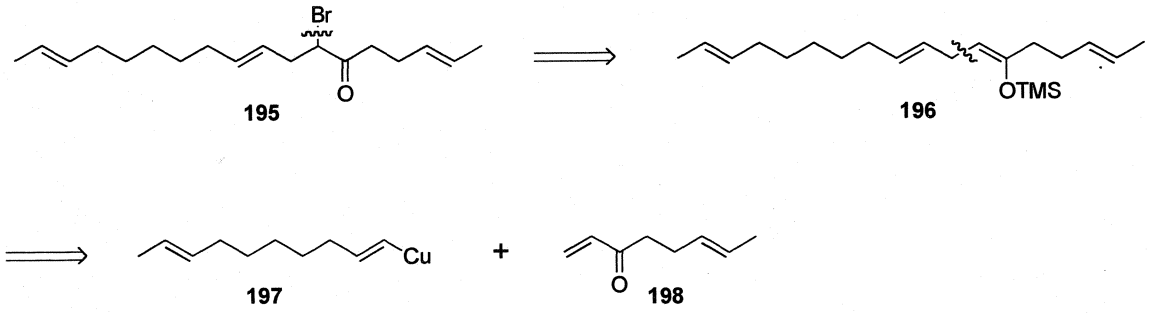
The key step in the formation of the secondary δ-hydroxyketone **177** from primary alcohol **187** was the umpolung addition of lithio dithiane **178** to aldehyde **179**. Unfortunately, both oxidation of alcohol **187** and dithiane addition were made difficult by the instability of aldehyde **179**. Unfortunately, all efforts to optimize this sequence were unsuccessful. Furthermore, the deprotection of the dithiane to the ketone was also inefficient (although no significant effort was made to improve this, given the inefficiency of the previous step). Thus, it was decided that in order to provide ample quantities of C_{18} δ-hydroxyketone **177**, the retrosynthetic sequence would need to be altered.

3.2.3 Third-Generation Approach to the Full Side-Chains.

3.2.3.1 Retrosynthesis.

A third-generation retrosynthesis of this C_{18} triene focused on the δ-bromoketone **195** rather than the δ-hydroxyketone (**177**). As shown in Scheme 3.9, it was envisioned that the bromide could be installed by bromination of a TMS-enol ether (**196**), which could then come from the TMSCl-accelerated conjugate addition of organocopper reagent **197** to enone **198**.

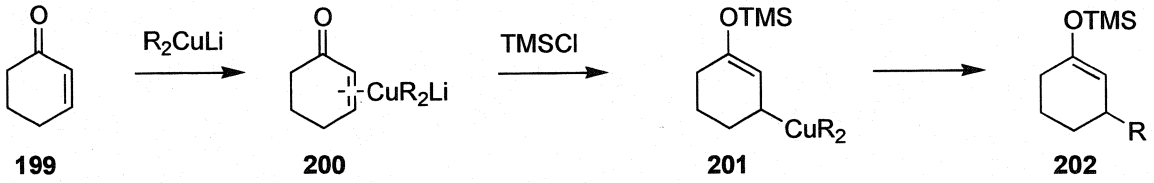
Scheme 3.9 Third-Generation Retrosynthesis of the Full Side-Chains.



3.2.3.2 TMSCl Accelerated Conjugate Additions.

In 1985, Corey and Boaz reported that chlorotrimethylsilane greatly accelerated the conjugate addition of cuprates to enones. They suggested that the copper reagent first reversibly forms a d-δ* complex with the enone (**200**), which is then silylated in the rate determining step to give a Cu(III) δ-adduct (**201**). Finally, reductive elimination forms the C-C bond at the δ position (**202**).

Scheme 3.10 Corey's Proposed Rationale for TMSCl Acceleration of 1,4 Additions.



199 **200** **201** **202**

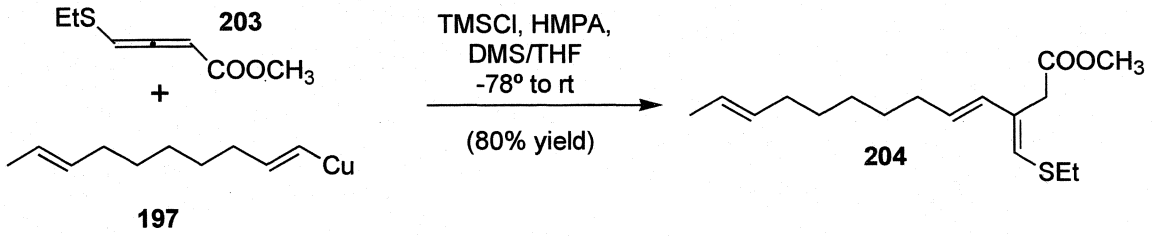
Since their initial report, several other mechanisms have been proposed for this reaction. The most straightforward was Kuwajima's proposal that the increased rate was due to Lewis acid activation of the enone carbonyl. Snyder and Bertz have suggested that the chlorosilane reagent activates the copper reagent, and Lipshutz has presented another alternative mechanism in which the chloride of the chlorosilane acts as a Lewis base, associating with the lithium cation, thus resulting in a "push-pull" effect that increases the reactivity of the cuprate reagent. A recent study on the kinetic isotope effects in this reaction however, suggests that the most likely mechanism is actually the one originally proposed by Corey and Boaz.

The use of TMSCl has two very beneficial effects in this reaction. First, by trapping as a silyl enol ether, the two sides of the ketone are differentiated, thus allowing further transformations to be carried out in a regioselective manner. Second, the use of chlorosilanes gives considerable rate enhancements, allowing systems that are normally unreactive to successfully participate in conjugate addition reactions, meaning that even neutral organocopper reagents can be used. This is important because standard cuprate reagents require the use of two equivalents of alkyllithium, which is very uneconomical in a case where a complex nucleophile is necessary. The use of a stoichiometric copper

reagent, if possible, would provide a simpler solution than the use of "dummy" ligands or higher order reagents.

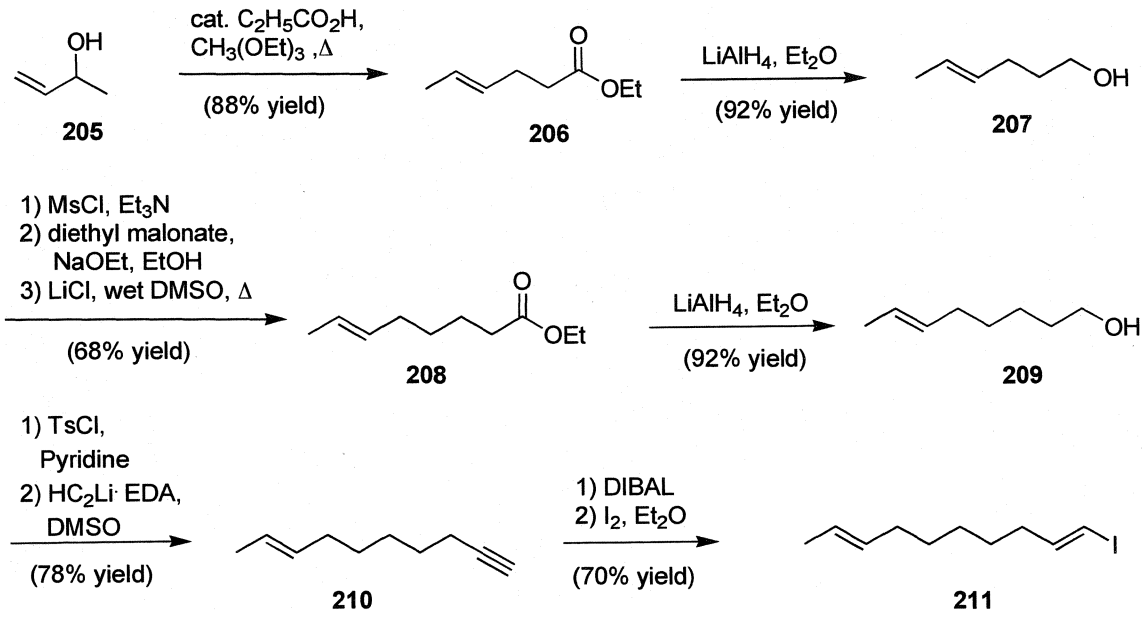
3.2.3.3 Fukuyama's Synthesis of Vinyl-Copper Reagent 197.

Scheme 3.11 Fukuyama's Use of Vinylcopper Reagent 197.



The alkenylcopper reagent **197** required in our retrosynthesis is actually a known compound from Fukuyama's synthesis of the phomoidrides (Scheme 3.11, **197**δ **204**). The alkenylcopper reagent was formed from vinyl iodide **211**, Fukyama's synthesis of which is presented in Scheme 3.12. The synthesis commenced with an orthoester-Claisen rearrangement of 3-buten-2-ol, providing ethyl ester **206**, which was then reduced with $LiAlH_4$ to alcohol **207**. Formation of the mesylate, addition of malonate and decarboxylation provided the homologated ester **208**. Reduction again with $LiAlH_4$ gave alcohol **209**. Tosylation and reaction with lithium acetylide gave enyne **210**, which was then converted to vinyl iodide **211** upon hydroalumination with DIBAL and cleavage of the resultant alkenylaluminate with iodine.

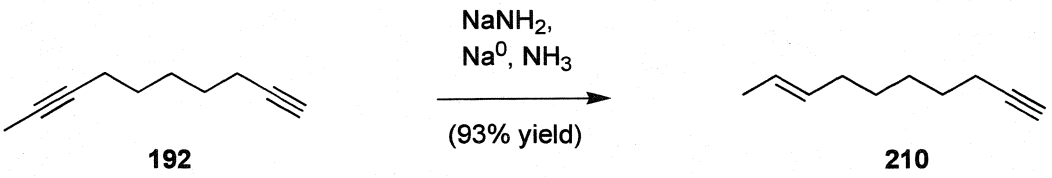
Scheme 3.12 Fukuyama's Synthesis of Vinyl Iodide 211.



3.2.3.4 Mono-Reduction of Diyne 192.

While Fukuyama's route allows for synthesis of ample quantities of vinyl iodide **211**, the penultimate intermediate **210** is only one oxidation state removed from diyne **192**, which was already available to us from our previous route. Conversion of diyne **192** to enyne **210** would require reduction of the internal alkyne in the presence of a terminal alkyne. Fortunately, it was found that this could be accomplished according to the method of Dobson and Raphael, in which terminal alkynes are protected from reduction as their acetylide anions.

Scheme 3.13 Mono-Reduction of Diyne 192.

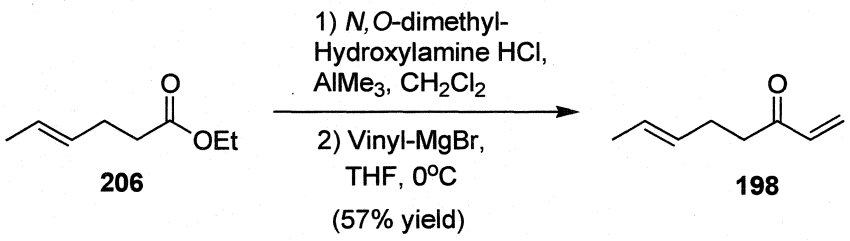


In the event, a solution of monomethyl diyne **192** in ammonia was treated first with sodium amide to form the acetylide anion, and then with metallic sodium to give enyne **210** in 93% yield. While the product of this reaction (**210**) was often contaminated with small amounts of over-reduction product (1,8–decadiene), this side-product did not participate in the subsequent step (formation of vinyl iodide **211**) and was easily separated by distillation at that point.

3.2.3.5 Synthesis of Vinyl Ketone 198.

Our attention next turned to the other partner in the conjugate addition reaction, the δ,δ-unsaturated ketone (**198**). This compound was made in a two-step sequence from ester **206** by Weinreb's amide formation and vinyl grignard addition.

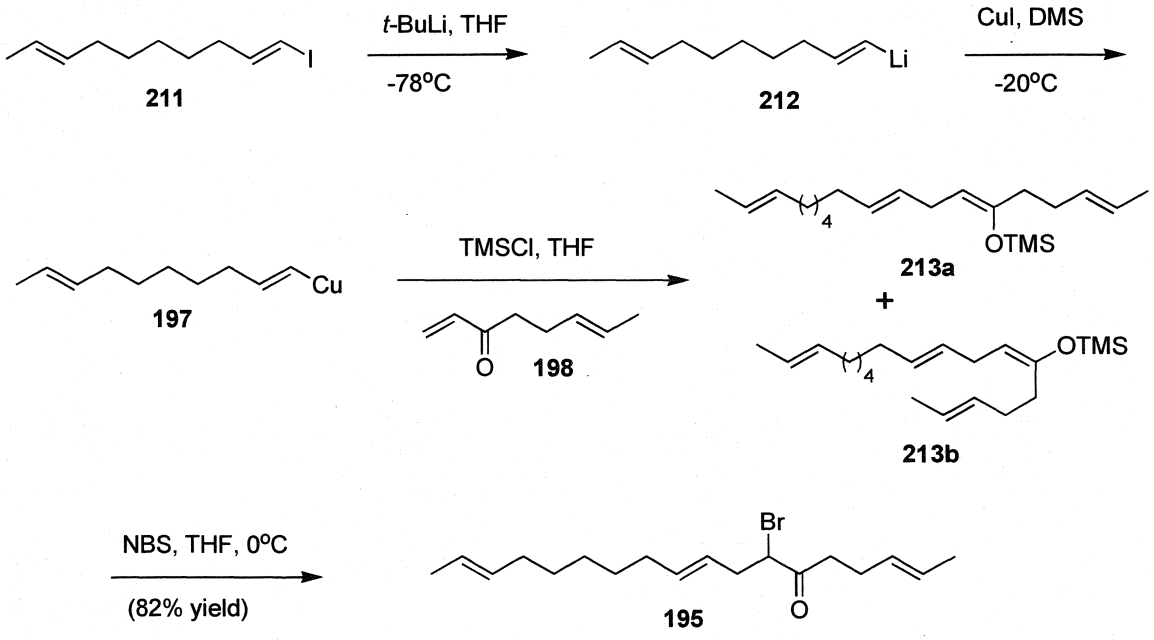
Scheme 3.14 Synthesis of Vinyl Ketone 198.



3.2.3.6 Conjugate Addition to Form The C_{18} Side-Chain.

With both coupling partners in hand, our attention turned to the critical conjugate addition step. Treatment of vinyl iodide **211** with *tert*-butyllithium promoted halogen-metal exchange to form the corresponding vinyllithium (**212**), which upon treatment with a solution of CuI in DMS was transmetallated to the vinylcopper reagent **197**. A mixture of δ,δ-unsaturated ketone **198** and chlorotrimethylsilane was next added, affording TMS-enol ethers **213a** and **213b**, which were formed as a 3:1 mixture favoring the Z-enol ether (**213a**). Finally, this crude mixture of TMS-enol ethers was brominated with NBS in THF to give the desired δ-bromoketone **195** in 82% overall yield. This reaction proceeded reproducibly on up to ten-gram scale to allow for suitable quantities of this key intermediate to be formed.

Scheme 3.15 Conjugate Addition.

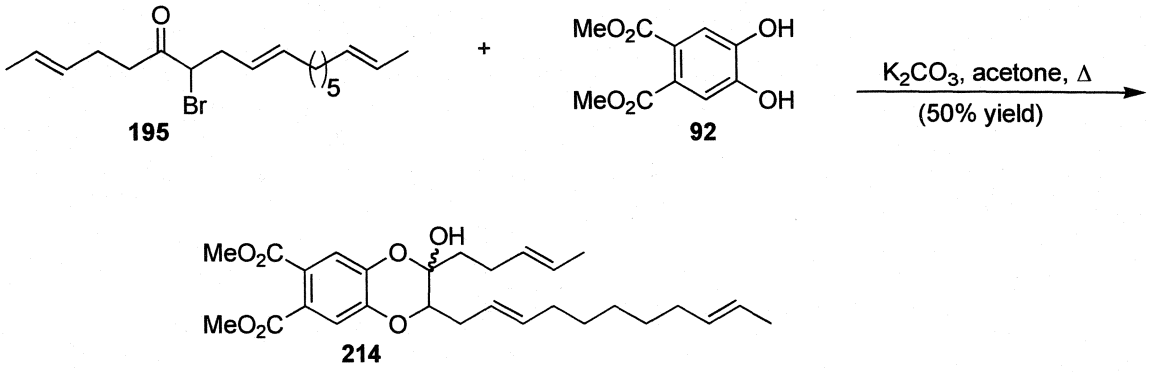


3.3 Advancing Toward the Phenolic Oxidation.

3.3.1 Coupling δ-Bromoketone 195 with Catechol 92.

Progress toward the phenolic oxidation commenced with the coupling of δ-bromoketone **195** and catechol **92**. This reaction proceeded to give the hemiacetal product **214** in modest yield. It was determined that the hemiacetal nature of **214** could potentially complicate the next key phenolic oxidation step (in which the free phenol was desired), so the decision was made to protect the ketone. A strategy was devised that would address both the protection of the ketone and improving the poor yield in the alkylation step by first mono-protecting catechol **92**.

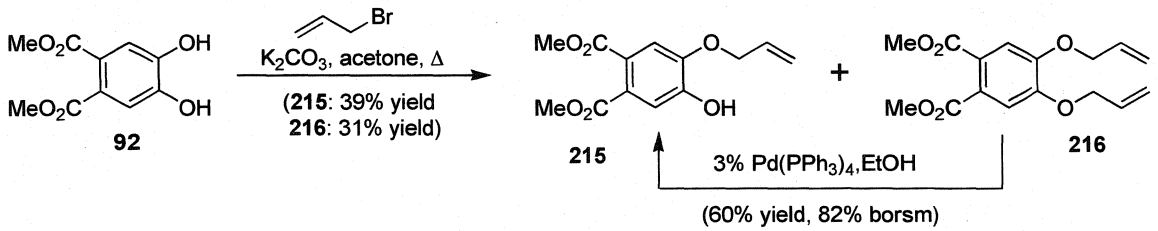
Scheme 3.16 Coupling of δ-Bromoketone 195 with Catechol 92.



3.3.2 Protection of the Catechol, and Coupling to δ-Bromoketone 195.

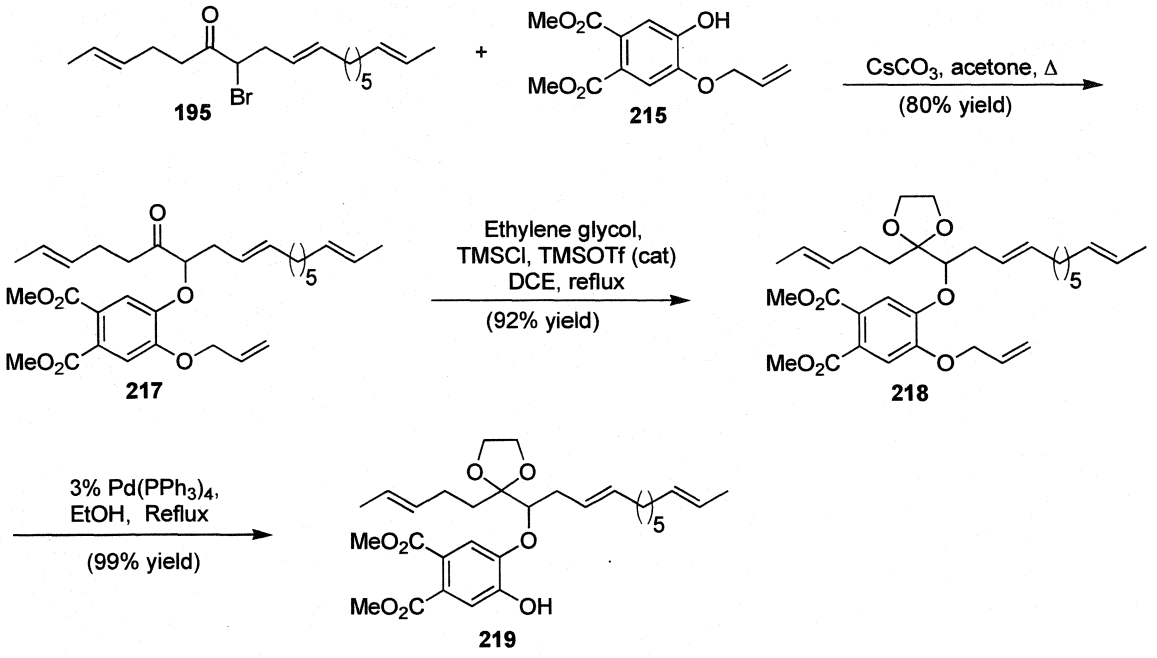
Catechol **92** was protected as its monoallyl ether **215** by treatment with allyl bromide and potassium carbonate in refluxing acetone (Scheme 3.17). Although the yield was not exceptional, the remainder of the material was either the starting catechol or the bis-allyl phenol **216**, which could be easily recycled.

Scheme 3.17 Protection of the Catechol.



The coupling of mono-allyl phenol **215** with δ-bromoketone **195** proceeded smoothly upon refluxing with cesium carbonate in acetone to give ether **217** (Scheme 3.18). Protection of the ketone as its dioxolane was extremely sluggish under standard conditions, but proceeded efficiently under modified Noyori conditions. Thus, treatment of ketone **217** with ethylene glycol, chlorotrimethylsilane and catalytic TMS triflate in refluxing dichloroethane provided ketal **218**. Deprotection of the allyl ether was accomplished by heating a solution of **218** to reflux in ethanol in the presence of 3% $Pd(PPh_3)_4$.

Scheme 3.18 Synthesis of the Phenolic Oxidation Precursor.



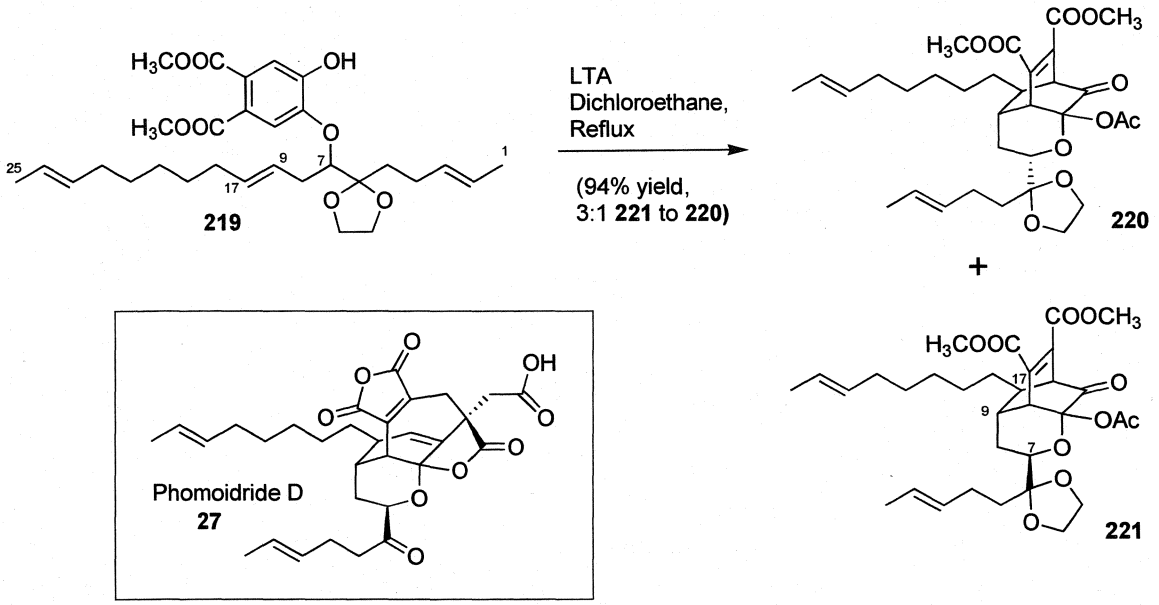
3.4 Phenolic oxidation.

3.4.1 Initial Result.

Having access to the requisite phenol **219**, the stage was now set to try the key phenolic oxidation step on the fully functionalized system. In the event, phenol **219** was treated with lead(IV) acetate (LTA) in refluxing dichloroethane. This initiated the desired phenolic oxidation reaction to form a reactive ortho-quinone monoketal (*vide infra*), which readily underwent an intramolecular Diels-Alder (IMDA) reaction with the central (C(9)-C(17)) *E*-olefin in the side-chain to provide acetates **220** and **221** in 94% yield. Remarkably, the single steroeocenter (C(7)) in the starting material influences the

stereochemical course of this reaction, as the products are formed in a 3:1 ratio, favoring **221**, containing the phomoidride C/D stereochemistry at C(7).

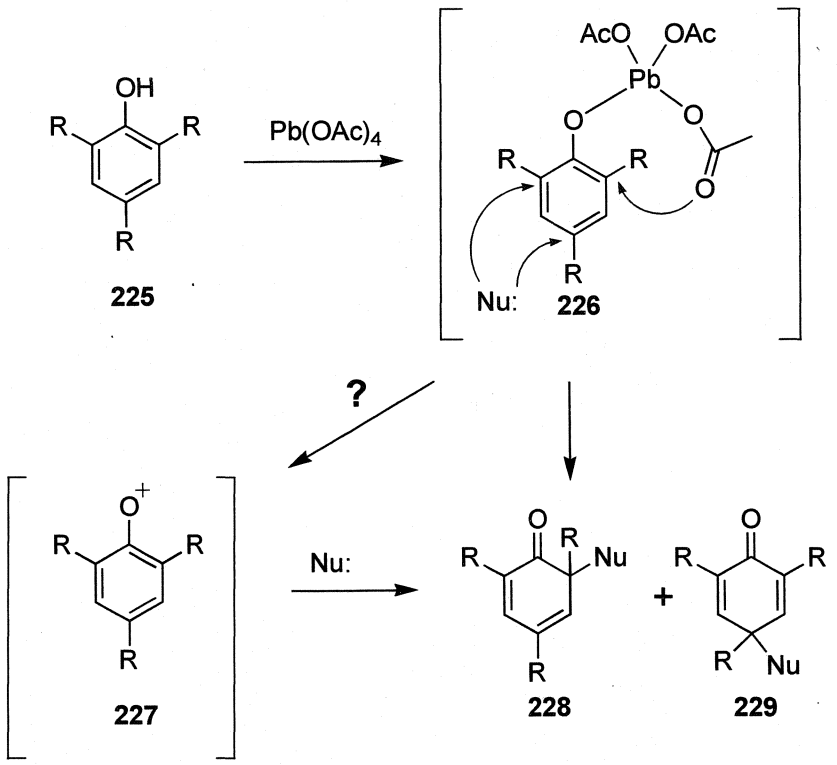
Scheme 3.19 Phenolic Oxidation of a Fully Functionalized System.



3.4.2 Mechanism of Phenolic Oxidation with LTA.

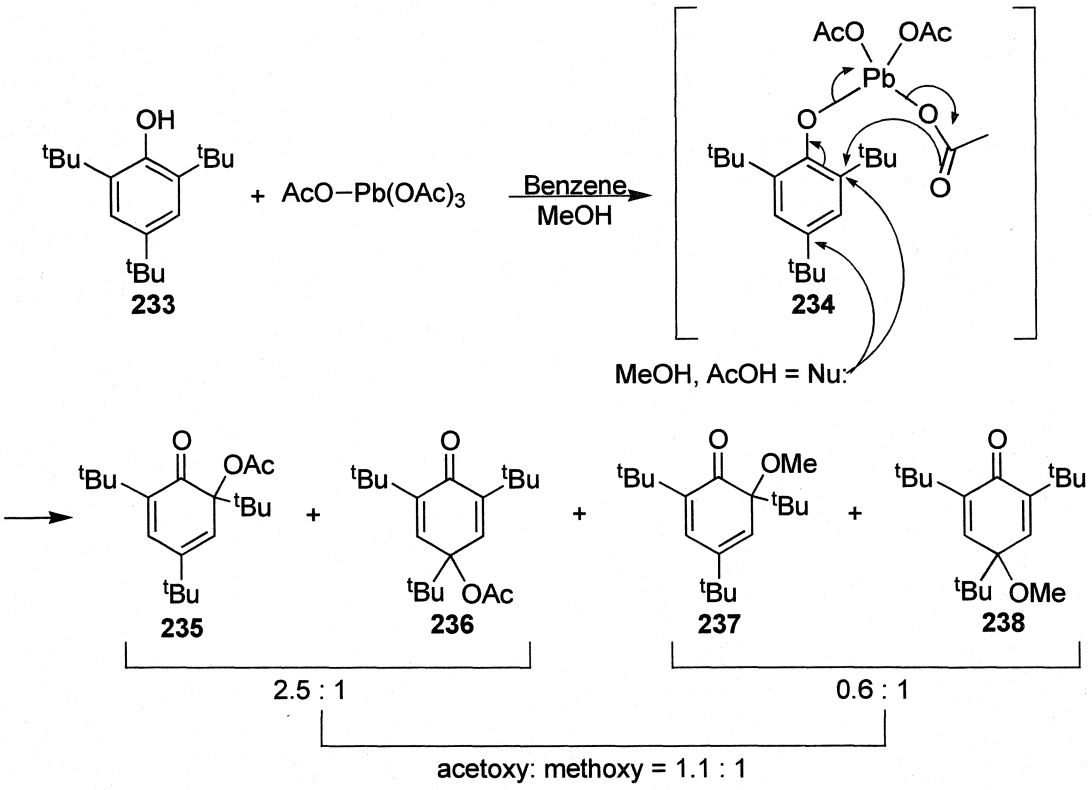
Although the exact mechanism of LTA-promoted phenolic oxidations is unclear, it is generally believed that it involves a mechanism such as is shown in Scheme 3.20. Thus, the first step is ligand exchange, where the phenol displaces one of the acetates to form intermediate **226**. The remainder of the mechanism includes nucleophilic attack at the *ortho* or *para* positions, and oxidation, wherein the phenol-lead bond is cleaved to give the reduced lead(II) acetate. The timing of these last steps is uncertain; both initial oxidation to the phenoxonium (**226**δ **227**) and concerted nucleophilic trapping and oxidation (**226**δ **228, 229**) have been proposed. It is also been suggested that the acetate trapping could be an intramolecular event.

Scheme 3.20 Mechanism for Phenolic Oxiation with LTA.



Norman and Harrison suggested that more than one mechanism might be taking place, depending on the exact reaction conditions (Scheme 3.21). They showed that oxidation of 2,4,6-tri-*tert*-butyl phenol (**233**) with LTA in acetic acid, benzene or dichloromethane gave a 2.5:1 ratio favoring the *ortho*-substituted product **235** over the *para*-product **236**, but when the same reaction was performed in a mixture of benzene and methanol, a mixture of four products was formed: acetates **235** and **236**, still in the 2.5:1 ratio favoring *ortho* substitution, and methyl ethers **237** and **238** formed in a 0.6:1 ratio *favoring para substitution.*

Scheme 3.21 Harrison and Norman's Example.



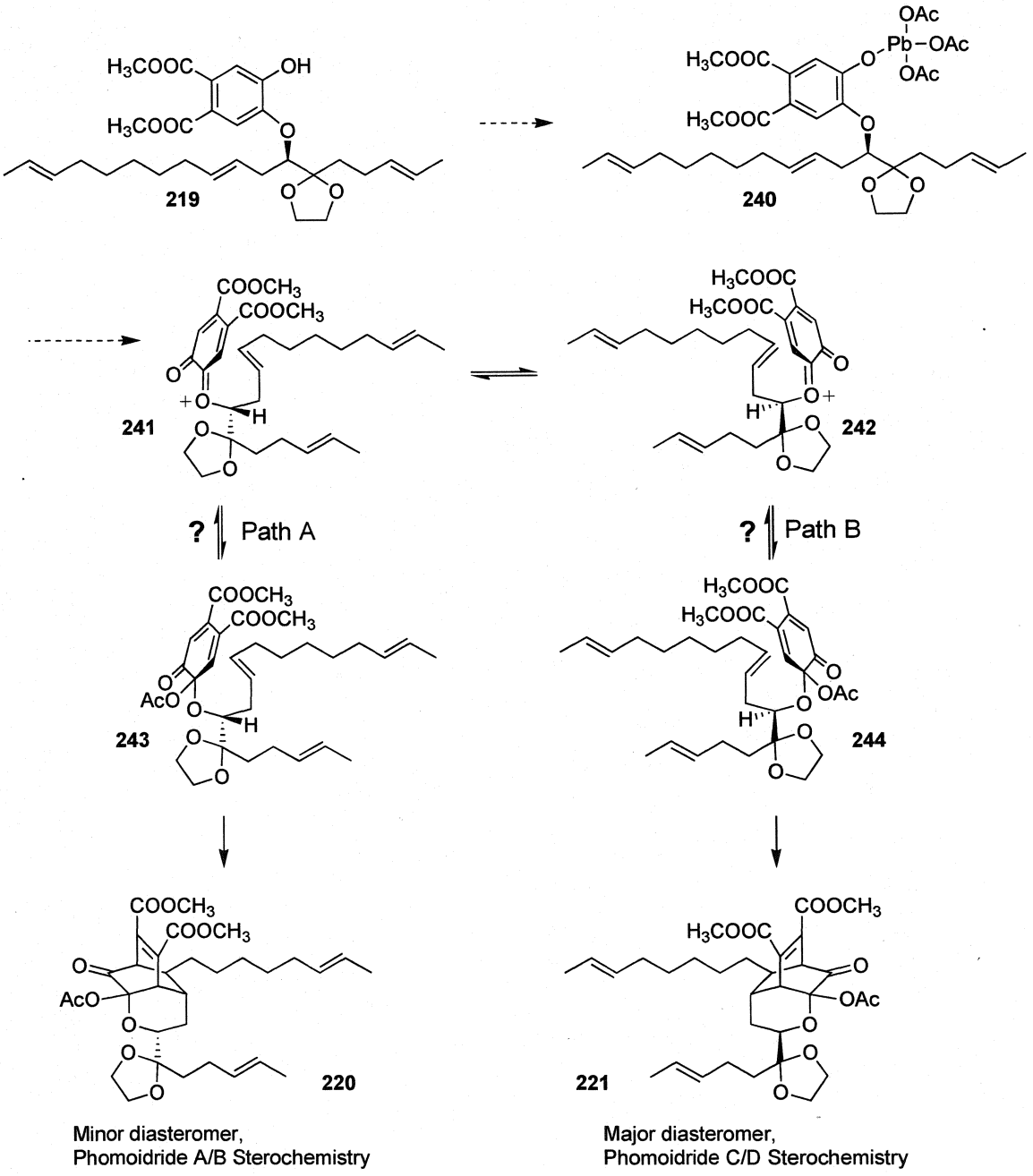
These results could be explained if two different mechanisms were operating: *intra*molecular addition of acetate would explain the 2.5:1 ratio of acetate trapping products, while methanol trapping is most likely *inter*molecular and the 0.6:1 ratio suggests that the *para* position is more accessible, as would be expected if the oxidation and trapping steps were concerted, with the bulky lead triacetate blocking the *ortho* positions.

3.4.3 Origins of Diastereoselectivity.

Because the exact nature of the phenolic oxidation mechanism is unclear, it is difficult to explain the origin of the diastereoselectivity observed in this tandem phenolic oxidation/IMDA reaction, but two main possibilities were recognized.

Diastereoselectivity could arise from either facial selectivity in the acetate trapping, or, if the trapping is reversible, from differences in the rates of the two possible Diels-Alder reactions (Scheme 3.22).

Scheme 3.22 Origins of Diasteroselectivity.



Minor diasteromer,
Phomoidride A/B Sterochemistry

Major diasteromer,
Phomoidride C/D Sterochemistry

3.4.3.1 Facial Selectivity in the Trapping Step.

If the oxidation proceeded through a discrete phenoxonium ion, a structure such as **241/242** would be formed, which could then be trapped by acetate to provide **243** and **244** (Scheme 3.22). If the trapping was irreversible, the facial selectivity of the acetate trapping would determine the ratio of products formed. Similar arguments of facial selectivity might be made if the trapping step was concerted, or even intramolecular.

3.4.3.2 Reversible Trapping Could Lead to Diastereoselectivity.

The second possibility as to the origin of the observed diastereoselectivity would involve interconversion between acetates **243** and **244**, which might occur if the trapping step (**241**δ **243**, or **242**δ **244**) is reversible. If the rate of interconversion of these acetate pseudoesters was fast, then differences in the rates of the two Diels-Alder reactions (**243**δ **220**, and **244**δ **221**) would lead to diastereoselectivity. In this case the selectivity could be rationalized by examining the conformation of the tetrahydropyran ring formed in this reaction. If the C(7) side-chain is to be equatorial, path A (leading to the Phomoidride A/B stereochemistry) would necessitate a boat–like conformation in which the C(7) side-chain is in the crowded *endo* orientation, while path B (phomoidride C/D stereochemistry) would be in a more favored a chair-like conformation, with the side-chain *exo* to the bicyclic ring system.

Preliminary efforts to determine the exact nature of the origin of the diastereoselectivity were inconclusive, and all efforts to improve on this selectivity, were unsuccessful. Although phoimoidride B was envisioned to be our initial target, given our inability to improve, or reverse the selectivity in this step, the decision was made to take advantage of the diastereoselectivity in this reaction and advance the major product (**221**)

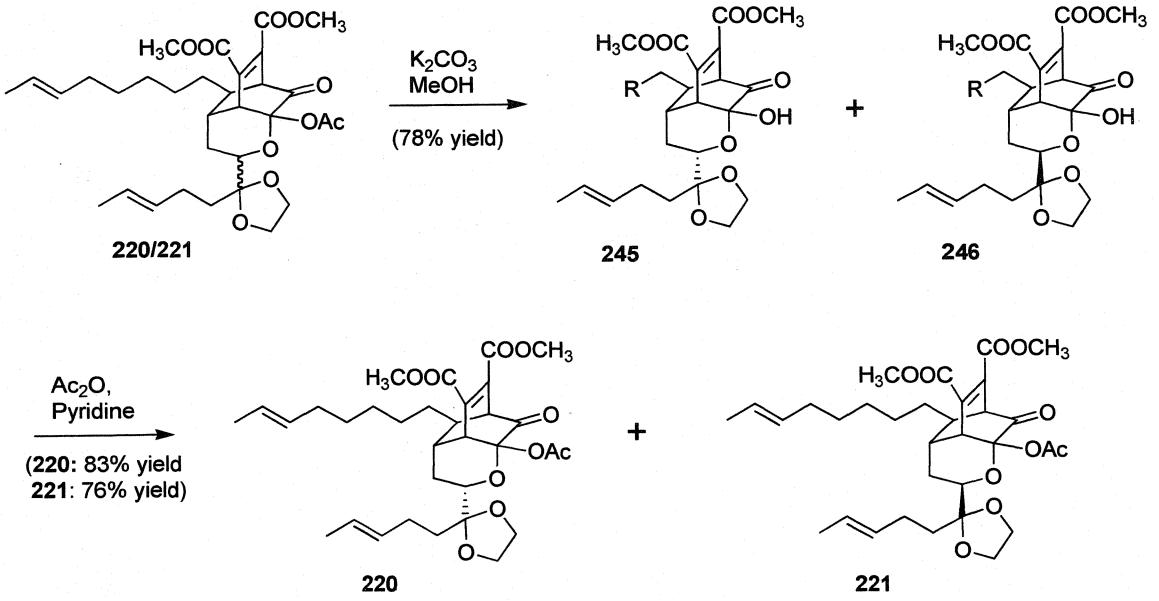
toward a total synthesis of phomoidrides C and D, which would also be a formal synthesis of phomoidrides A and B. As will be apparent later, following this path was a fortuitous decision (*vide infra*).

3.5 Formation of the Lactone.

3.5.1 Purification and Stability of Acetates 220 and 221.

An important note is that acetates **220** and **221** were sensitive toward both acidic and basic conditions, and were not separable by column chromatography. In order to characterize these two compounds, it was necessary to first cleave the acetate by treatment with K_2CO_3 in MeOH (Scheme 3.23). This gave lactols **245** and **246**, which were easily separable. These lactol diastereomers were then independently converted to their respective acetates (**220** and **221**) upon treatment with Ac_2O in pyridine. While this transformation was relatively efficient, the subsequent steps were usually carried out on a mixture of acetate diastereomers **220** and **221**.

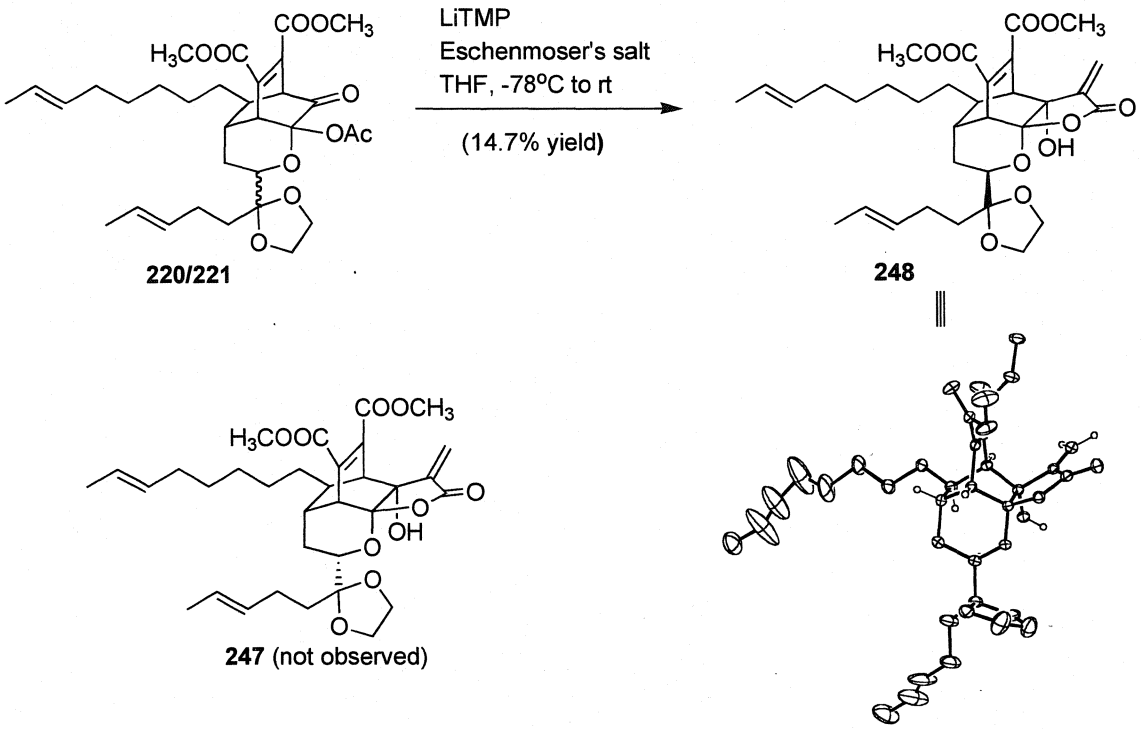
Scheme 3.23 Purification of Acetates 220 and 221.



3.5.2 Tandem Aldol-Mannich-Hofmann.

Having successfully accomplished the first key step on the fully functionalized system, attention was next turned to the formation of the lactone ring. The mixture of acetate diastereomers **220** and **221** was treated with Eschenmoser's salt and LTMP in the previously employed tandem aldol-Mannich-Hofmann reaction. Unfortunately, this reaction occurred in very poor yield (14.7%) and only afforded lactone **248**, the product derived from the major acetate diastereomer (**221**). This product, however was obtained as a crystalline solid, and its structure was confirmed by single-crystal X-Ray analysis.

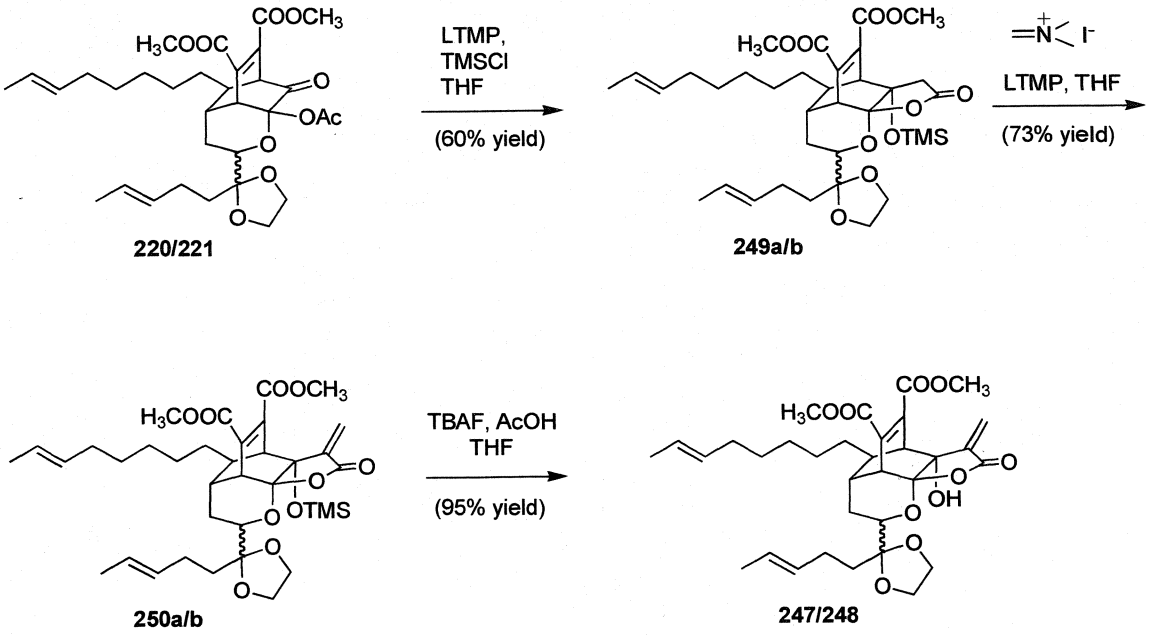
Scheme 3.24 Tandem Aldol-Mannich-Hofmann Sequence.



3.5.3 Sequential Aldol and Mannich Reactions.

The first modification made to improve this sequence was to separate the steps into sequential aldol and Mannich reactions. As in the model system, two potential problems were the instability of the acetate starting material, and the possibility of retro-aldol ring opening. These difficulties were mitigated by performing the aldol reaction in the presence of TMSCl, which trapped the resulting tertiary alcohol as its TMS ether **249**, thus preventing retro-aldol ring opening (Scheme 3.25). Mannich reaction and desilylation followed in a straightforward manner to provide lactones **247** and **248**. This route was an improvement from the tandem reaction, but the aldol reaction was still difficult to reproduce and yields were often affected by the instability of the acetate.

Scheme 3.25 Sequential Aldol and Mannich Reactions.

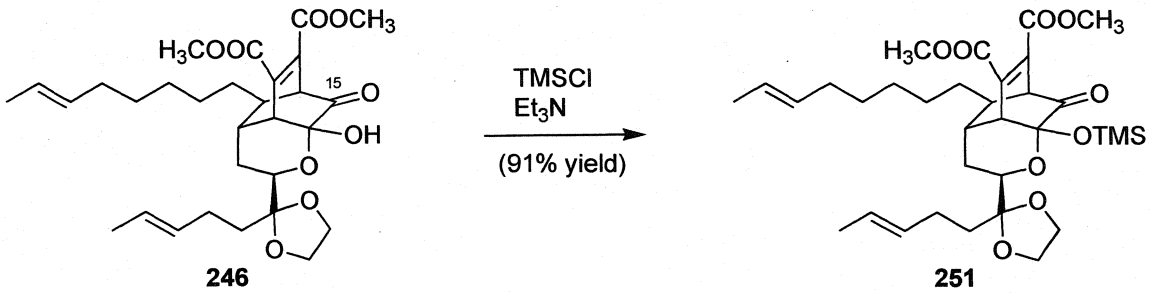


3.5.4 Intermolecular Aldol Reaction.

3.5.4.1 Synthesis of the Substrate for Intermolecular Aldol reacion.

One key problem with both of the previous routes to *exo*-methylene lactone **248** was the sensitivity of acetate **221**. If the bond between C(14) and C(15) were to be formed in an *intra*molecular manner, this is unavoidable. If, however, this bond were formed in an *inter*molecular manner, performing delicate operations on the sensitive acetate structure might be avoided. Toward this end, lactol **246**, formed by the methanolysis of the acetate (Scheme 3.25, **221**δ **246**), was protected as its TMS ether **251** (Scheme 3.26).

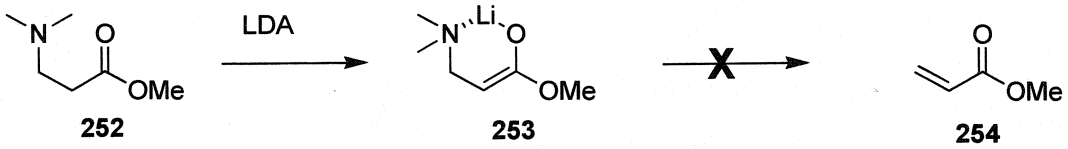
Scheme 3.26 Protection of the Lactol.



3.5.4.2 δ-Acrylate Synthetic Equvalents.

Ideally, an δ-acrylate anion might be used to form the C(14)-C(15) bond. These types of anions are rare however, as they are unstable and therefore ineffective as nucleophiles. Several δ-acrylate synthetic equivalents have been developed for this reason, the most effective being the lithium enolate of 3-(dimethylamino) propionate (**253**) (Scheme, 3.27). This enolate (**253**) is stable for several days at ambient temperature and shows no propensity to eliminate the δ-dimethylamino group.

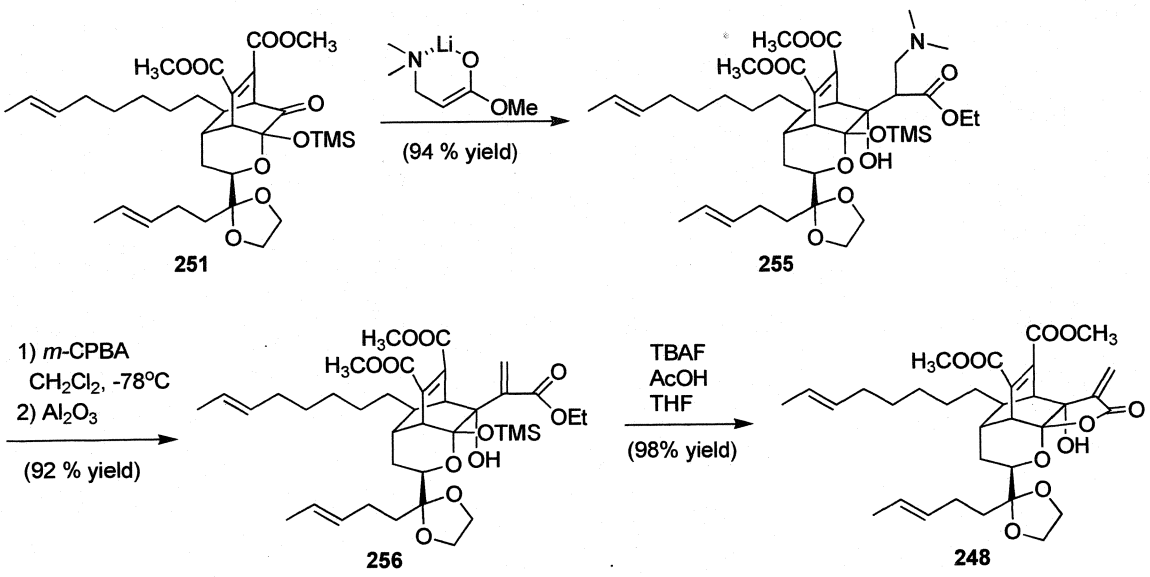
Scheme 3.27 δ-Acrylate Anion Synthons.



3.5.4.3 Intermolecular Aldol Reaction.

In the event, enolate **253** reacted smoothly with TMS-ether **251** to give **255** (Scheme 3.28). This addition to the C(15) ketone of **251** occurs in a highly diastereoselective manner, as the undesired diastereomer at C(15) (not shown) cannot be detected in the ^{1}H NMR of the crude reaction mixture. Hofmann elimination under standard conditions (MeI, $NaHCO_3$) gave a substantial amount of retro aldol product (**251**). Therefore a Cope elimination was employed, in which the tertiary amine was selectively oxidized to the N-oxide by treatment with *m*-CPBA in CH_2Cl_2 at –78°C (careful control of the temperature was necessary to prevent epoxidation of the side-chain olefins). Filtration over basic alumina then provided δ,δ-unsaturated ester **256** in good yield, with no detectable retro-aldol product formed. Finally, treatment with TBAF gave the lactone (**248**) via desilylation and lactonization. By avoiding alkylation conditions that employ the delicate acetate pseudoester, this sequence provided an increased yield over the previous routes, and importantly, had the advantage of being much more reproducible, robust, and scalable.

Scheme 3.28 Intermolecular Aldol Reaction.

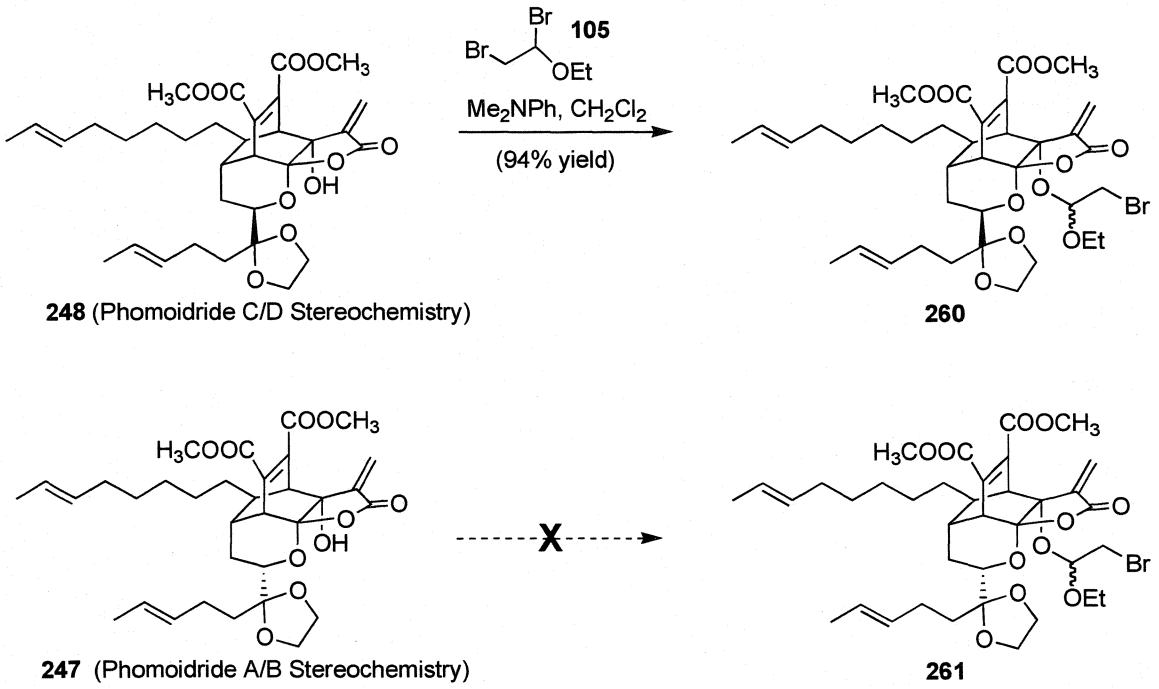


3.6 Cascade Cyclization.

3.6.1 Bromoacetal Formation.

Treatment of tertiary alcohol **248** with dibromoethyl ethyl ether and dimethylaniline gave bromoacetal **260** as an inconsequential mixture of diastereomers at the acetal position (Scheme 3.29). Interestingly, the minor diastereomer of the *exo*-methylene lactone (**247**, phomoidride A/B stereochemistry at C(7)) failed to react under these conditions. Presumably, this is due to the increased steric bulk around the tertiary alcohol due to the C(7) side-chain being in the *endo* orientation. For this reason, it was fortunate that the tandem phenolic oxidation/IMDA reaction afforded acetate **221**, containing the phomoidride C/D stereochemistry, as the major product (*vide supra*).

Scheme 3.29 Bromoacetal Formation.



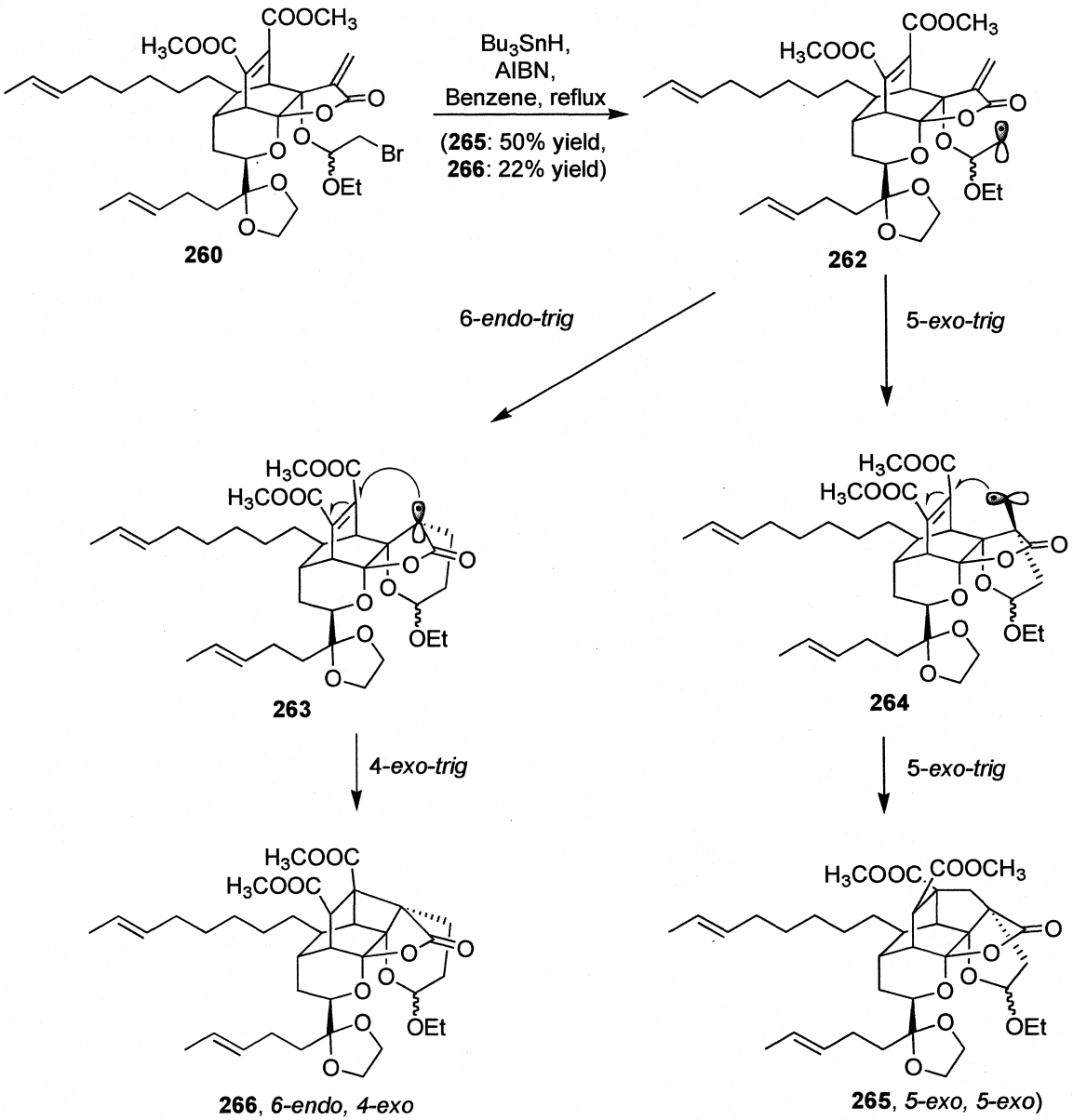
3.6.2 Cascade Cyclization.

As in the model systems, the bromoacetal was subjected to Bu_3SnH and AIBN at reflux in benzene to give the desired 5-*exo-trig*, 5-*exo-trig* cascade cyclization product **265** along with the undesired 6-*endo-trig*, 4-*exo-trig* cascade cyclization product **266**, both as mixtures of diastereomers at the acetal position. As was the case in the model system, this ratio could not be improved upon through varying the reaction conditions. At this point, every carbon-carbon bond found in the phomoidrides has been formed.

Although the acetal diastereomers were inseparable, the 6-*endo-trig*, 4-*exo-trig* cascade cyclization product **266**, could be enriched in one diastereomer upon treatment with *p*-TsOH in ethanol. Unfortunately, efforts to similarly epimerize the desired 5-*exo-*

trig, 5-*exo-trig* cascade cyclization product **265** were unsuccessful, leading to complex mixtures of products.

Scheme 3.30 Cascade Cyclization.



3.7 Conclusions.

Substantial use of model studies, as outlined in Chapter 2, has led to a novel route toward the phomoidrides. Many changes were needed in the transition from model studies to the fully functionalized system. A new synthesis of the C_{18} side-chain unit was necessary, and a tandem conjugate addition/ bromination sequence was developed for this purpose. The key phenolic oxidation/ IMDA step efficiently provided the desired acetate, but with the phomoidride C/D stereochemistry at C(7), and the tandem aldol-Mannich-Hofmann sequence that was employed in previous systems was abandoned for a more robust alkylation approach. Finally, another key reaction, the desired 5-*exo-trig*, 5-*exo-trig* cascade cyclization afforded an advanced intermediate in which every carbon-carbon bond found in the natural product is in place. Subsequent chapters will focus on the efforts to convert of this acetal (via fragmentation) to phomoidride D.

3.8 Experimental Section.

3.8.1 Materials and Methods.

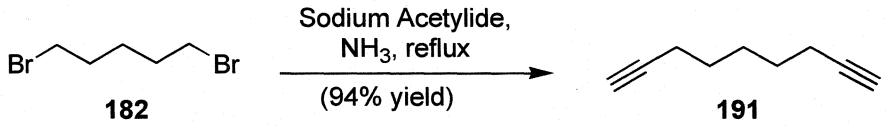
Unless stated otherwise, reactions were performed in flame dried glassware under a nitrogen atmosphere, using freshly distilled solvents. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl. Methylene chloride (CH_2Cl_2) and triethylamine (Et_3N) were distilled from calcium hydride. All other commercially obtained reagents were used as received.

Unless stated otherwise, all reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using E. Merck silica gel 60 F_{254} precoated plates (0.25 mm). Column or flash chromatography was performed with the indicated solvents using

silica gel (230-400 mesh) purchased from Bodman. In general, the chromatography guidelines reported by Still et al. were followed. Infrared spectra were recorded on a Midac M1200 FTIR. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX-500 or Bruker Avance DPX-400 spectrometer. Chemical shifts are reported relative to internal chloroform (^{1}H, δ 7.26 ppm; ^{13}C, δ 77.23 ppm) or Benzene (^{1}H, δ 7.16 ppm; ^{13}C, δ 128.06 ppm). High resolution mass spectra were performed at the University of Illinois Mass Spectrometry Center. Single-crystal X-ray analyses were performed by Dr. Christopher Incarvito of Yale University.

3.8.2 Preparative Procedures.

Preparation of Diyne 191 (IMMIII-141):

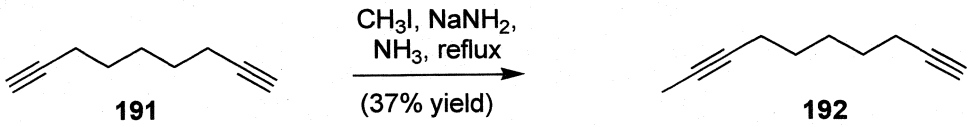


182 **191**

Diyne 191. In a 6L, 3-neck flask equipped with two dry-ice condensers and a mechanical stirrer, 3L of ammonia was condensed at –78°C (an inlet for ammonia was provided by connecting one of the dry-ice condensers via a Claisen-head, thus providing essentially a 4-neck flask). Upon completion of the condensation, one of the dry-ice condensers was removed. Acetylene was bubbled through this solution for 15 min. (Note: Acetylene cylinders contain significant amounts of acetone; thus it must be purified by using 4 cold traps in series) At this point sodium (117g, 5.04 mol, 2.74 equiv)

was added in small pieces (ca. 10mm x 5mm x 5mm) over 30 min. Upon complete addition of sodium, Acetylene was passed through the reaction for an additional 5 min, and the gas inlet was replaced with a dropping funnel charged with 1,5-dibromopentane (200mL, 1.84 mmol, 1 equiv). Dibromopentane was added over 45 min, and the reaction was then let to warm to reflux over 3h. The reaction was quenched by slow addition of conc. NH_4OH (300mL) followed by careful addition of water (1.5L). Once the frost on the outside of the flask had melted, the mixture was transferred to a 6L separatory funnel, and carefully extracted with pentane (3X 1L) The combined organics were dried over Na_2SO_4 and then concentrated *in vacuo*. Distillation at 20mmHg provided **191** as a clear liquid (206g, 94% yield) which was consistent with commercially available material in both ^{13}C and $^{1}HNMR$.

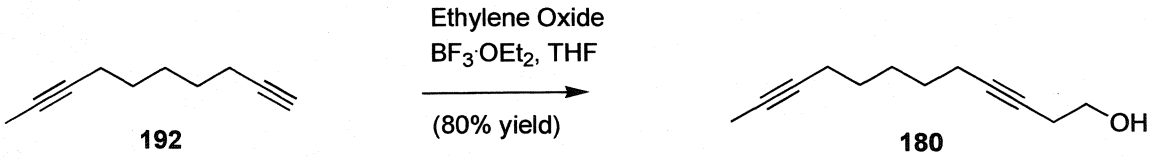
Preparation of Diyne 192 (NTII-206):



Diyne 192.This reaction could be carried out on larger scale (up to 2.2 mol, 300ml of 1,8-nonadiyne) without any substantial difficulty. Ammonia was condensed into a 3L, 3-neck flask equipped with a dry-ice condenser. When 1.5L was collected, the ammonia inlet was removed, and sodium amide (95.8g, 2.46 mol, 1.5 equiv) was added. Next, an addition funnel (not pressure-equalized) was attached, and 1,8-nonadiyne (**191**) (198.5g, 1.65 mol, 1 equiv) was added over 20 min. The funnel was rinsed with ether (50

mL) and then charged with iodomethane (113g, 1.82 mol, 1.82 equiv), and the iodomethane was added slowly over a period of 1.5 h. The mixture was allowed to stir an additional 2 h, at which time NH_4Cl (44.1g, 0.825 mol, 0.5 equiv) was added with care. Next, water (500mL) was slowly added via the dropping funnel. Once the frost on the outside of the flask had melted, the mixture was transferred to a 2l separatory funnel, and carefully extracted with pentane (3X 200mL) the organic layer was washed with 6N HCl until it remained acidic. The combined organics were wased successively with aqueous $NaHCO_3$ (200 mL), and brine (200 mL). The solvent was removed *in vacuo* to give 190 g of a mixture of **191**, **192** and 2,9-undecadiyne that was distilled through a Vigreux column at 6 mmHg to give recovered **191** (first fraction, 71.2g, 36% yield), mixed fractions (second fraction, 37.2g, 17% yield) and the title compound **192** (81.0g, 37% yield) consistent both ^{13}C and ^{1}HNMRwith the literature reports.

Preparation of Diyne-Alcohol 180 (IMMIII-36):

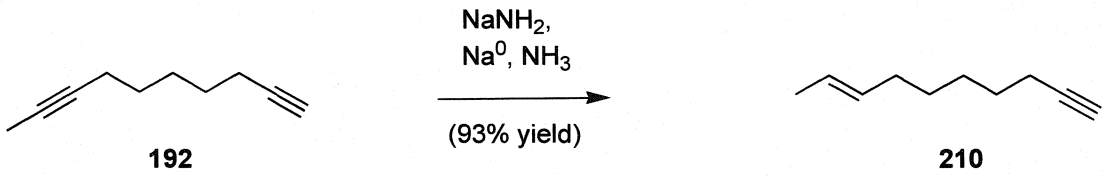


192 180

Diyne-alcohol 180. To a stirred solution of 1,8-decadiyne (6.7 g, 50 mmol, 1 equiv) in THF (500 mL) at –78°C was added a 2.5 M solution of n-BuLi in hexane (24 mL, 60 mmol, 1.2 equiv). This mixture was allowed to stir for 1.5h at this temperature, at which time BF_3•Et_2O (7.8 mL, 55 mmol, 1.1 equiv) was added. After a additional 20

min, ethylene oxide (9g, 204 mmol, 4.1 equiv) was added slowly by cannula over 35 min. (Note: the ethylene oxide was measured by condensing into a tared flask maintained at –78°C. It was then transferred to the reaction mixture by placing the tip of a cannula just *above* the surface of the liquid, with the other tip of the cannula *below* the surface of the reaction mixture. In this manner the ethylene oxide is slowly added to the reaction mixture as it warms from –78°C to ~0° C. If the addition was not sufficiently rapid, a 25°C water bath was used to accelerate the process.) Following the addition, the mixture was stirred an additional 3h at –78°C, at which time the mixture was quenched by the addition of aqueous NH_4Cl (200 mL). The mixture was transferred to a separatory funnel and extracted with EtOAc (3x 200 mL). The combined organics were washed with brine (200 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* to provide an oil that was purified by silica gel chromatography (20-30% EtOAc/Hexanes eluent) to furnish **180** (6.8 g, 80% yield) as a clear oil.

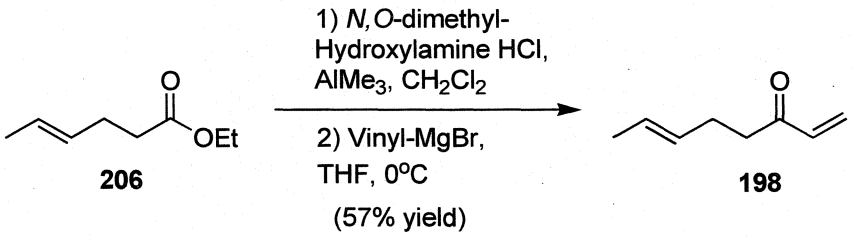
Preparation of Eneyne 210 (IMMIII-223):



Eneyne 210. A dry 3-neck 1l flask was equipped with a dry-ice condenser (with a KOH drying tube) and charged with sodium amide (14.6g, 375 mmol, 2.5 equiv) followed by ammonia (500 mL). Diyne **192** (20.1g, 150 mmol, 1 equiv) was added in one portion and the mixture was allowed to stir at reflux for 1h. Sodium (6.9g, 300

mmol, 2.0 equiv) was added over 1 h. After the addition was complete, stirring continued for 5 min, at which time the blue color had disappeared. The reaction was quenched by careful addition of methanol (50 mL) followed by water (100 mL). Once the frost on the outside of the flask had melted, the mixture was transferred to a separatory funnel, and carefully extracted with pentane (3x 100 mL) The combined organics were dried over Na_2SO_4 and then concentrated *in vacuo*. Distillation at 20mmHg provided **210** as a clear liquid (19g, 93% yield).

Preparation of Vinyl Ketone 198 (TSI-38):

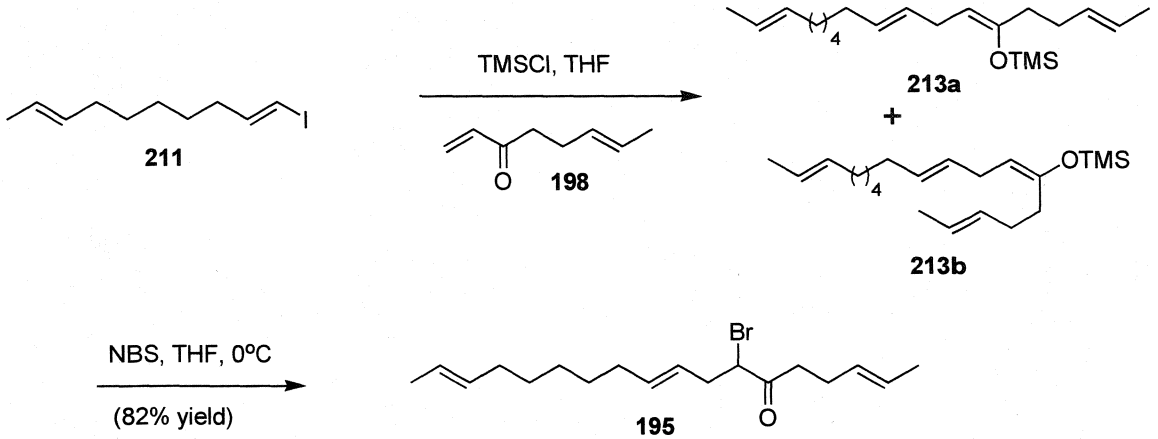


Vinyl Ketone 198. To a solution of N,O-Dimethylhydroxylamine HCl (23.7g, 243 mmol, 1.5 equiv) in CH_2Cl_2 (161 mL) was added $AlMe_3$ (2.0M in heptane, 121.4 mL, 243 mmol, 1.5 equiv) at –78°C over 10 min. The reaction mixture was warmed to rt and maintained at rt for 1h, at which point it was cooled to 0°C. Ethyl ester **206** (23g, 161.9 mmol, 1.0 equiv) was then added dropwise over 10 min, and the reaction was allowed to warm to rt. After stirring at rt for 2.5h, the mixture was cooled to –78°C and treated with water (5 mL) and 1N HCl (300 mL). After warming to rt, the mixture was transferred to a separatory funnel, an additional 200 mL HCl was added, and the layers were separated. The aqueous layer was extracted with Et_2O (3x 250 mL), the combined

organic layer was washed with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), and dried over Na_2SO_4. and the solvent was removed *in vacuo*. The crude product was dissolved in THF (162 mL, 1.0M) and cooled to –78°C. Vinyl magnesium bromide (1.0M in THF, 162 mL, 162 mmol, 1.0 equiv) was then added dropwise over 10 min. The reaction mixture was warmed to 0°C and maintained at that temperature for 1h, at which time it was poured into 1N HCl (300 mL) at 0°C and stirred for 20 min. The layers were separated, and the aqueous portion was extracted with Et_2O (3x 200 mL), the combined organic layer was washed with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), and dried over Na_2SO_4. and the solvent was removed *in vacuo*. Distillation under reduced pressure (0.5 mmHg) afforded vinyl ketone **198** (11g, 54.7% yield) as a clear liquid (bp 35-40°C at 0.5 mmHg).

Vinyl Ketone 198. FTIR (thin film/NaCl) 3022 (w), 2963 (s), 2936 (m), 2919 (m), 2857 (w), 1734 (m), 1701 (s), 1684 (s), 1616 (m), 1437 (w), 1401 (m), 1316 (w), 1184 (w), 1090 (w), 965 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.28 (dd, *J*=17.7, 10.6 Hz, 1H), 6.15 (dd, *J*=17.6,1.2 Hz, 1H), 5.77 (d, *J*=1.2, 1H), 5.74 (d, *J*=1.3, 1H), 5.44-5.30 (m, 2H), 2.57 (t, *J*=7.3, 2H), 2.25-2.19 (m, 2H), 1.59-1.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.26, 136.59, 129.60, 128.04, 125.9, 39.44, 26.87, 17.9. Satisfactory HRMS could not be obtained for this compound.

Preparation of δ-Bromoketone 195 (TSII-78):



TMS-Enol Ethers 213a and 213b. To a stirred solution of vinyl iodide **211** (6.6g, 18.9 mmol, 1.0 equiv) in THF (95 mL) at –78°C was added *t*-BuLi (1.7M in pentane, 35 mL 59.5 mmol, 3.15 equiv) slowly until the color of the mixture turned yellow. At this time, a few drops of additional **211** were added until the yellow color of the reaction mixture disappeared. Stirring at –78°C continued for 20 min, at which time the reaction was warmed to –40°C and maintained at that temperature for 30 min. The mixture was then re-cooled to –78°C and kept at that temperature for 10 min. A solution of CuI (5.71g, 22.7 mmol, 1.2 equiv) in DMS (36.7 mL, 378 mmol, 20 equiv) was then added over 10 min stirring was maintained at –78°C for 10 min more, followed by warming again to –40°C and keeping the reaction at that temperature for 30 min, at which point it was again re-cooled to –78°C. After stirring at –78°C for 10 min, a solution of vinyl ketone **198** (2.79g, 17 mmol, 0.9 equiv) and TMSCl (7.19 mL, 42.7 mmol, 2.25 equiv), in THF (10 mL) was added. The reaction was kept at –78°C for 2h, warmed to

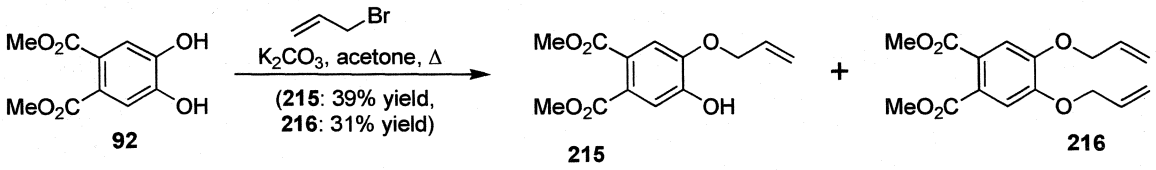
–40°C, kept at –40°C for 1h, warmed to 0°C, kept at 0°C for 2h, warmed to rt, and kept at rt for 2h. At this time, the reaction was again cooled to –78°C, and treated with Et_3N (15mL) and water (10 mL) and pentane (100 mL). The layers were separated, and the organic layer was washed with brine (2x 100 mL) dried over Na_2SO_4, filtered, concentrated *in vacuo*, and kept under vacuum for 1h to remove all traces of DMS (DMS solublizes the Cu salts, making work up difficult). At this time, pentane (100 mL) was added and the mixture was filtered through Celite. The Celite was then washed with pentane (4x 50 mL) and concentrated. At this point, an analytical sample of TMS-enol ethers **213a** and **213b** could be obtained by silica gel chromatography (Hexanes eluent) to afford **213a** and **213b** in a 3:1 ratio, favoring **213a**, as an inseparable mixture.

δ-Bromoketone 195. The unpurified foregoing reaction mixture was dissolved in THF (100mL) and cooled to 0°C, and NBS (5g, 28.3 mmol, 1.5 equiv) was added in one portion. The reaction was stirred at 0°C for 5 min, and then treated with pentane (150 mL) and water (25 mL). The phases were separated, the organic layer was washed with water (2x 25 mL), the combined organics were dried over Na_2SO_4, and then concentrated *in vacuo*. Purification by silica gel chromatography (0%-10% EtOAc/hexanes) gave δ-Bromoketone **195** (6.277g, 81.9% yield) as a clear oil.

TMS-enol ethers 213a and 213b. FTIR (thin film/NaCl) 3021 (w), 2959 (m), 2925 (s), 2854 (m), 1673 (w), 1451 (w), 1438 (w), 1252 (s), 1163 (m), 1008 (w), 965 (s), 844 (s), 753 (w) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 5.39-5.21 (m, 6H), 4.82 (t, *J*=7.7 Hz, 0.25H), 4.65 (t, *J*=7.2 Hz, 0.75H), 2.96-2.92 (m, 1.5H), 2.75-2.71 (m, 0.5H), 2.35-2.21 (m, 2.5H). 2.16-2.11 (m, 1.5H), 2.05-1.95 (m, 4H), 1.63-1.55 (m, 6H), 1.4-1.25 (m, 6H), 0.20 (s, 2.25H), 0.17 (s, 6.75H); ^{13}C NMR (125 MHz, C_6D_6) δ 152.22, 150.55,

131.97, 131.95, 131.31, 131.07, 130.49, 130.45, 129.93, 129.69, 128.57, 125.34, 125.25, 124.86, 124.83, 106.99, 105.37, 37.30, 33.08, 33.06, 32.99, 32.95, 31.93, 30.75, 30.70, 30.50, 29.99, 29.97, 29.95, 29.87, 29.25, 29.15, 29.11, 18.12, 18.09, 0.78, 0.52. Satisfactory HRMS could not be obtained for this compound.

Preparation of Phenols 215 and 216 (TSII-118):



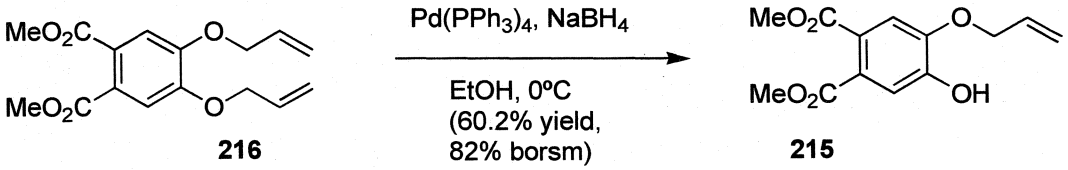
Phenols 215 and 216. To a solution of catechol **92** (50g, 221.2 mmol, 1 equiv) in acetone (221 mL, 1.0M) was added K_2CO_3 (30.6g, 221.2 mmol, 1.0 equiv) and Allyl bromide (19.2 mL, 221.2 mmol, 1.0 equiv). The reaction mixture was heated to reflux for 6h, at which time it was cooled to rt, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (10%-33% EtOAc/Hexanes eluent) gave diallyl phenol **216** (21.4g, 31.6% yield, eluting first) and monoallyl phenol **215** (23.1g, 39.3% yield, eluting second) as white crystalline solids.

Phenol 215. FTIR (thin film/NaCl) 3408 (br), 2952 (m), 1722 (s), 1612 (m), 1580 (m), 1437 (s), 1361 (w), 1306 (s), 1201 (s), 1125 (s), 994 (m), 783 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (s, 1H), 7.21 (s, 1H), 6.1-5.98 (m, 2H), 5.14 (ddd, *J*=17.2, 2.8, 1.4 Hz, 1H), 5.35 (dd *J*=10.5, 1.1 Hz, 1H), 4.66 (dt, *J*=5.49, 1.4 Hz, 2H), 3.87 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.19, 167.67, 148.25,

147.02, 131.87, 126.91, 123.91, 119.49, 115.39, 112.74, 70.23, 52.79, 52.77. HRMS (ESI) *m/z* 267.0869 [calc'd for $C_{13}H_{15}O_6$ (M+H) 267.0869].

Bis-allyl Phenol 216. FTIR (thin film/NaCl) 2951 (w), 1724 (s), 1648 (w), 1598 (m), 1517 (m), 1435 (m), 1407 (w), 1353 (m), 1288 (s), 1196 (s), 1131 (m), 1054 (w), 993 (m), 931 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.16 (s, 1H), 6.02 (dddd, *J*=17.25, 10.46, 5.3, 5.3 Hz,1H), 5.39 (dt, *J*=17.25, 1.3 Hz, 1H), 5.27 (dt, *J*=10.46, 1.3 Hz, 1H), 4.62 (dt, *J*=5.3, 1.3 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.86, 150.16, 132.41, 125.29, 118.40, 113.62, 69.92, 52.62. HRMS (ESI) *m/z* 307.1183 [calc'd for $C_{16}H_{19}O_6$ (M+H) 307.1182].

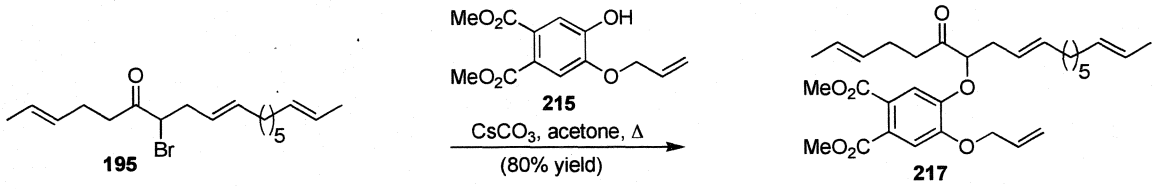
Recovery of Phenol 215 (TSI-142):



Phenol 215. To a solution of diallyl phenol **216** (1.14g, 3.72 mmol, 1 equiv) in EtOH (37 ml) was added $Pd(PPh_3)_4$ (43 mg, 0.04 mmol, 0.01 equiv), The mixture was then cooled to 0°C, and $NaBH_4$ (70.4 mg, 1.9 mmol, 0.5 equiv) was added. The reaction was stirred at 0°C for 2h, and then quenched with water (5 mL), and extracted with EtOAc (3x 5 mL) the organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by silica gel chromatography (20%-50%

EtOAc/hexanes eluent) furnished recovered **216** (304mg, 26.7% yield, eluted first), and **215** (595mg, 60.2% yield, eluted second) as white solids.

Preparation of Ketone 217 (IMMIV-180):

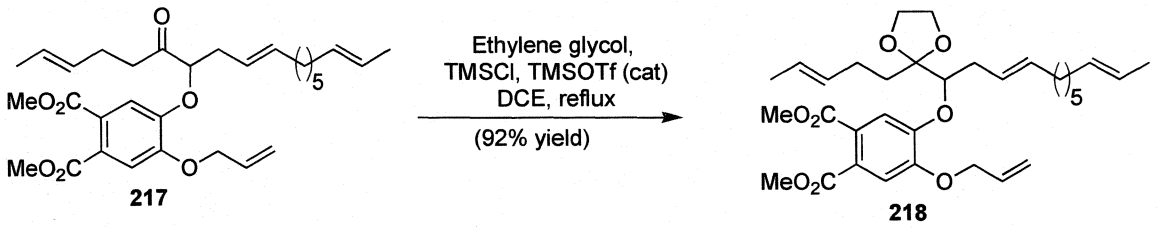


Ketone 217. A stirred solution of ketone **195** (3.3g, 9.67 mmol, 1.0 equiv), phenol **215** (2.60g, 9.67 mmol, 1.0 equiv), and $CsCO_3$ (3.15g, 9.67 mmol, 1.0 equiv) in acetone (25mL, 0.39M) was heated to reflux and maintained at that temperature for 4h. At that time the mixture was cooled to room temperature and the solids were removed by filtration. The organics were diluted with EtOAc (200 mL), washed with water (50 mL) and brine (50mL), and dried over Na_2SO_4, and the solvent was removed *in vacuo.* Purification via silica gel chromatography (25% EtOAc/Hexanes eluent) furnished **217** (4.03g, 80% yield).

Ketone 217. FTIR (thin film/NaCl) 2962 (s), 2854 (s), 1725 (s), 1599 (m), 1579 (m), 1514 (m), 1435 (m), 1405 (w), 1290 (m), 1192 (m), 1128 (m), 1056 (m), 968 (m), 934 (m), 800 (w), 784 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 1H), 7.12 (s, 1H), 6.03 (dddd, *J*=17.4, 10.5, 5.3, 5.3 Hz, 1H), 5.6-5.25 (m, 8H), 4.62 (dt *J*=5.3, 1.3, 1.3 Hz, 2H), 4.57 (t, *J*=5.78, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 2.71-253 (m, 4H), 2.2 (dd, *J*=13.3, 6.7) 2H, 1.64-1.56 (m, 6H), 1.35-1.19 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.92,

168.02, 167.36, 151.00, 149.35, 135.50, 132.29, 131.71, 129.62, 127.05, 126.16, 124.96, 124.81, 123.25, 118.52, 116.56, 114.11, 85.03, 69.99, 52.89, 52.80, 38.35, 35.77, 32.71, 29.61, 29.33, 29.30, 28.90, 28.87, 25.95, 18.13, 18.05. HRMS (ESI) *m/z* 527.3021 [calc'd for $C_{31}H_{43}O_7$ (M+H) 527.3009].

Preparation of Ketal 218 (IMMIV-250):



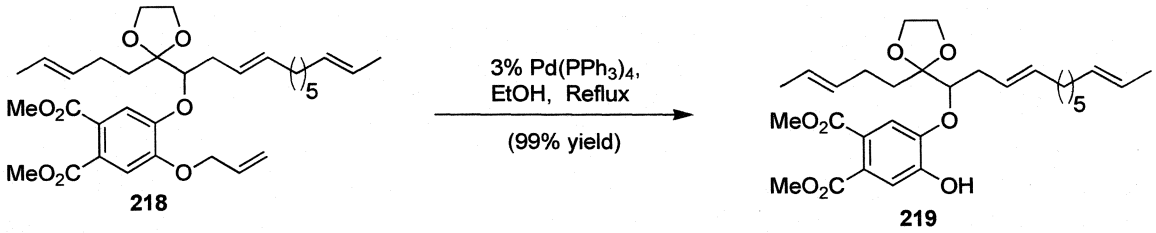
217 218

Ketal 218. To a stirred mixture of ketone **217** (8g, 15.19 mmol, 1.0 equiv), TMSCl (25 mL, 197 mmol, 12.9 equiv), and ethylene glycol (12 mL, 197 mmol, 12.9 equiv) in 1,2-dichloroethane (120 mL, 0.126M) at 0°C was added TMSOTf (0.4 mL, 2.2 mmol, 0.15 equiv). The mixture was heated to reflux and maintained at that temperature for 3h, at which time it was cooled to 0°C and quenched by the addition of Et_3N (50 mL), then water (200 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2x 200 mL). The combined organics were washed with brine and dried over Na_2SO_4, and the solvent was removed *in vacuo*. Purification via silica gel chromatography (25% EtOAc/Hexanes eluent) furnished **218** (8.0 g, 92% yield) as a clear oil.

Ketal 218. FTIR (thin film/NaCl) 3083 (w), 3018 (m), 2926 (s), 2854 (s), 1727 (s), 1597 (s), 1575 (m), 1515 (s), 1435 (s), 1405 (m), 1346 (s), 1281 (s), 1193 (s), 1129 (s), 1051 (m), 968 (m), 926 (m), 880 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (s,

1H), 7.15 (s, 1H), 6.03 (dddd, *J*=17.14, 10.4, 5.2, 5.2 Hz, 1H), 5.56-5.35 (m, 8H), 5.28 (dd, *J*=10.4, 1.3 Hz, 1H), 4.6 (dd, *J*=5.2, 1.0 Hz, 2H), 4.51 (t, 5.2 Hz, 1H), 4.27 (dd, *J*=7.6, 4.5 Hz, 1H), 4.09-4.03 (m, 1H), 4.0-3.85 (m, 10H), 2.47-2.43 (m, 2H), 2.05-2.03 (m, 2H), 1.98-1.87 (m, 6H),, .78-1.58 (m, 8H), 1.30-1.17 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.02, 151.47,150.68, 133.94, 132.86, 131.78, 131.75, 130.99, 130.97, 125.76, 125.16, 125.12, 124.70, 118.12, 115.87, 113.98, 111.37, 83.70, 83.68, 69.84, 66.35, 66.11, 52.71, 52.68, 34.32, 34.04, 32.70, 32.68, 29.59, 29.31, 28.88, 25.98, 18.11. HRMS (ESI) *m/z* 571.3273 [calc'd for $C_{33}H_{47}O_8$ (M+H) 571.3271].

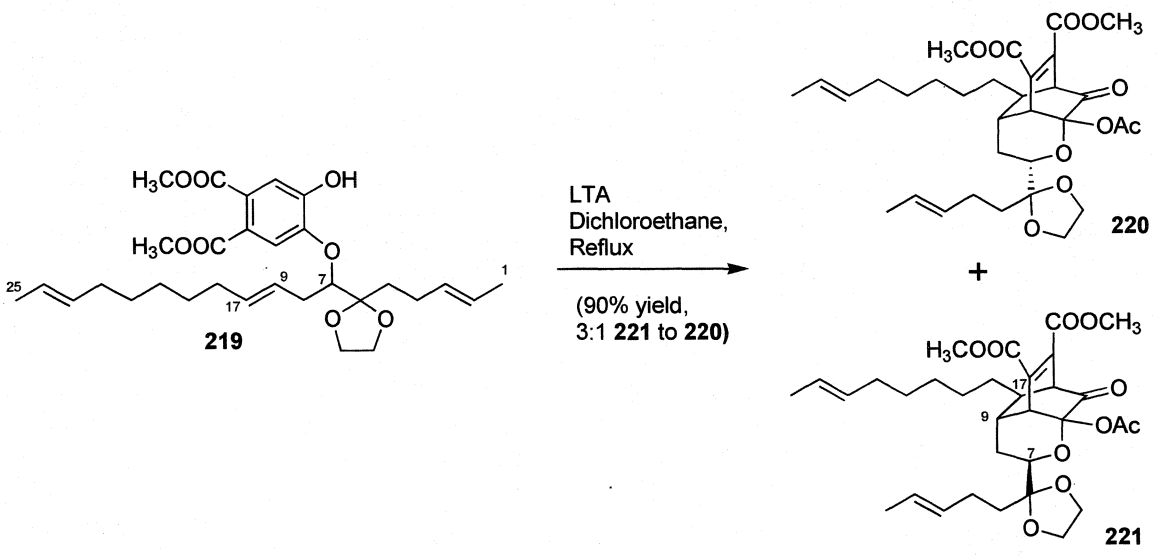
Preparation of Phenol 219 (IMMIV-183):



Phenol 219. A stirred mixture of allyl ether **218** (1.3g, 2.28 mmol, 1.0 equiv) and $Pd(PPh_3)_4$ (100mg, 0.087 mmol, 0.038 equiv) in EtOH (25 ml) was lightly degassed by repeating cycles of vacuum(~1-2 sec) and N_2 4 times. This was then heated to reflux, and maintained at that temperature for 3h, at which point the solvent was removed *in vacuo*. Purification via silica gel chromatography (25% EtOAc/Hexanes eluent) furnished **183** (1.2g, 99% yield) as a clear oil.

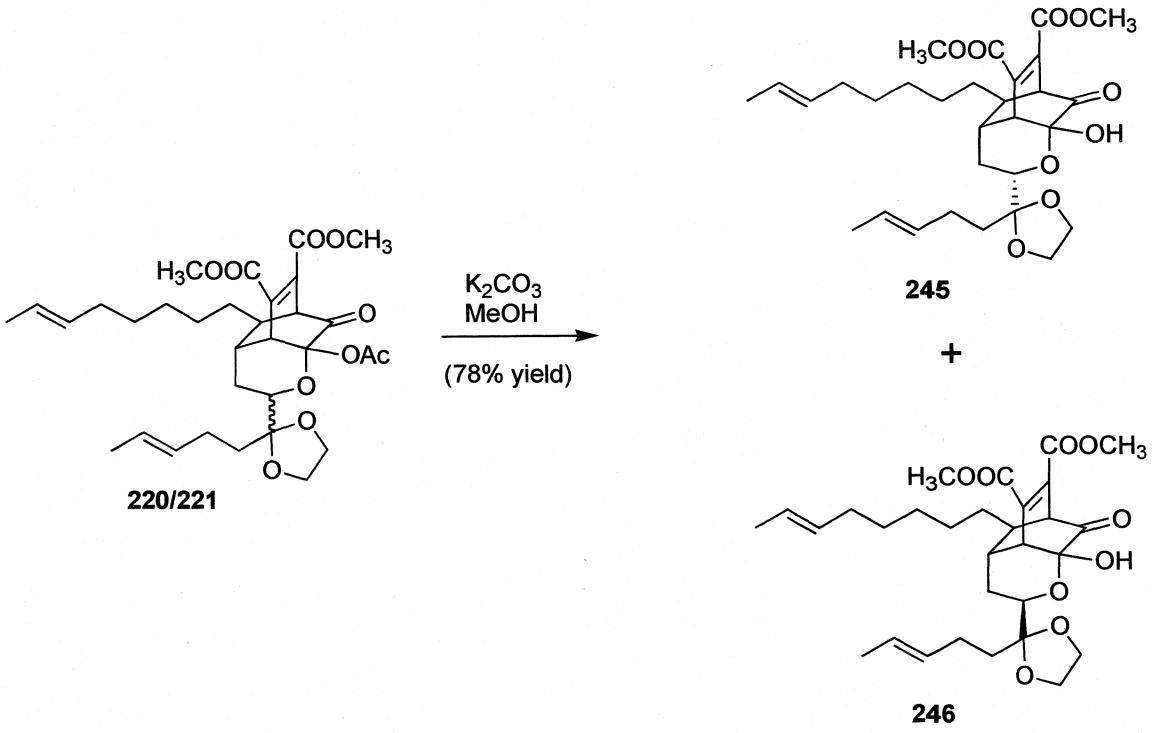
Phenol 219. FTIR (thin film/NaCl) 3422 (br), 2925 (s), 2854 (s), 1724 (s), 1613 (m), 1578 (s), 1511 (s), 1436 (s), 1364 (m), 1312 (w), 1258 (m), 1200 (m), 1121 (m), 1051 (m), 968 (m), 925 (m), 854 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.47 (s, 1H), 7.14 (s, 1H), 5.61-5.28 (m, 6H), 4.08-3.92 (m, 4H), 3.88 (s, 3H), 3.85 (s 3H), 2.49 (t *J*=6.62 Hz, 2H), 2.16-2.02 (m, 2H), 2.0-1.85 (m, 6H), 1.8-1.55 (m, 6H), 1.35-1.20 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.50, 167.21, 150.95, 147.92, 134.76, 131.73, 130.93, 130.47, 129.31, 125.61, 125.34, 124.76, 123.84, 122.72, 120.94, 116.53, 111.56, 86.04, 66.33, 66.23, 52.80, 52.59, 34.85, 34.14, 32.70, 32.62, 29.60, 29.55, 29.22, 29.18, 29.05, 28.93, 26.94, 25.91, 18.12. HRMS (ESI) *m/z* 531.2958 [calc'd for $C_{30}H_{43}O_8$ (M+H) 531.2958].

Preparation of Acetates 220 and 221 (NTII-98):



Acetates 220 and 221. To a stirred solution of phenol **219** (3.18g, 5.99 mmol, 1.0 equiv) at reflux in 1,2-Dichloroethane (32 mL) was added a solution of LTA (3.99g, 8.99mmol, 1.5 equiv) in 1,2-Dichloroethane (40 mL, total concentration of reaction 0.083M). The solution was maintained at reflux for 10 min, at which point it was cooled to rt and then concentrated *in vacuo*. Purification via silica gel chromatography (Short plug ~4cm, 25% EtOAc/Hexanes eluent) furnished an inseparable mixture of acetates **220** and **221** (3.31 g, 94% yield) as a clear oil.

Preparation of Lactols 245 and 246 (TSII-142):

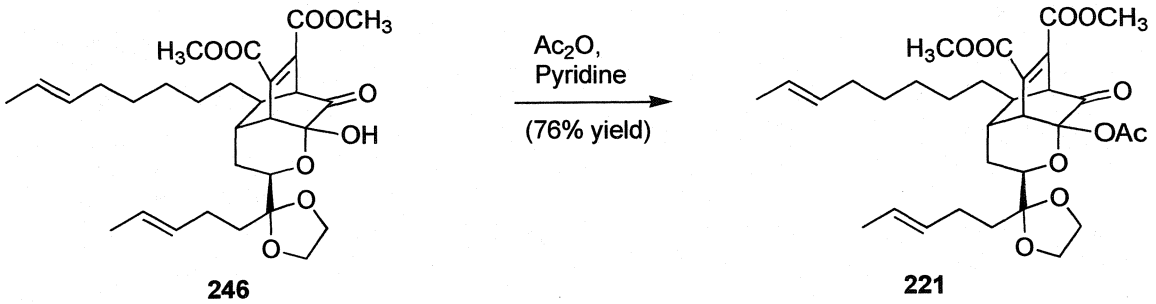


Lactols 245 and 246. To a solution of acetates **220/221** (56.2mg, 0.106 mmol, 1.0 equiv) in MeOH (5 mL) was added K_2CO_3 (29.3mg, 0.212 mmol, 2.0 equiv) at 0°C. the reaction mixture was warmed to rt, and stirred for 40 min. It was then cooled to 0°C, and quenched with 1N HCl (5 mL), and extracted with CH_2Cl_2 (3x 5 mL). The combined organic layer was wahed with brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by preparative TLC (33% EtOAc/Hexanes eluent) gave lactol **245** (11.2 mg, 19.4% yield, higher band) and lactol **246** (33.7 mg, 58.3% yield, lower band) as clear oils.

Lactol 245. FTIR (thin film/NaCl) 3436 (br), 2930 (s), 2856 (m), 1725 (s), 1634 (w), 1435 (m), 1364 (w), 1225 (s), 1172 (m), 1085 (m), 1043 (m), 967 (m), 925 (w), 736 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41 (m, 4H). 4.4-3.9 (m, 5H), 3.81 (s, 3H), 3.79 (s, 3H), 3.76 (s, 1H), 3.57 (d, *J*=1.2 Hz, 1H), 3.37 (d *J*=2.9 Hz, 1H), 2.12-1.9 (m, 8H), 1.78-1.55 (m, 10H), 1.35-1.22 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.30, 165.16, 165.06, 139.57, 134.82, 131.52, 130.91, 125.26, 125.05, 110.47, 89.65, 76.98, 73.07, 66.74, 66.13, 53.93, 52.88, 43.67, 41.90, 36.22, 35.72, 34.23, 32.67, 30.66, 29.59, 29.24, 27.20, 26.05, 18.12, 18.09. HRMS (ESI) *m/z* 547.2906 [calc'd for $C_{30}H_{43}O_9$ (M+H) 547.2907].

Lactol 246. FTIR (thin film/NaCl) 3200 (br), 2928 (s), 2855 (s), 1723 (s), 1699 (s), 1695 (s), 1642 (s), 1435 (s), 1357 (m), 1280 (m), 967 (m), 924 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.43-5.38 (m, 4H), 3.96 (s, 4H), 3.81 (s, 3H), 3.78 (s, 3H), 3.56 (d, *J*=2.5 Hz, 1H), 3.52 (s, 1H), 3.13 (d, *J*=3.2Hz, 1H), 2.1-1.75 (m, 9H), 1.7-1.55 (m, 8H), 1.42-1.20 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.84, 165.51, 165.12, 139.84, 133.28, 131.45, 130.98, 125.14, 125.08, 110.33, 89.86, 74.35, 66.47, 65.79, 53.84, 52.83, 52.80, 45.77, 40.78, 35.90, 39.94, 34.25, 32.62, 29.58, 29.11, 29.08, 27.06, 26.15, 18.09. HRMS (ESI) *m/z* 547.2913 [calc'd for $C_{30}H_{43}O_9$ (M+H) 547.2907].

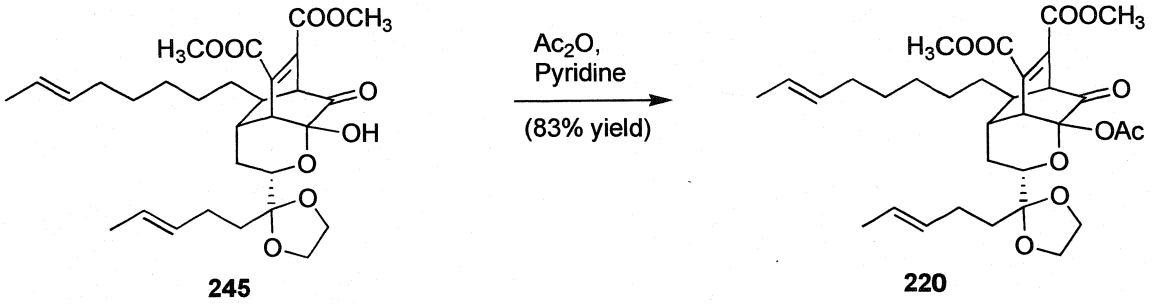
Preparation of Acetate 221 (IMM-265):



Acetate 221. To a stirred solution of **246** (100mg, 0.2 mmol, 1.0 equiv) in pyridine (3 mL) was added acetic anhydride (0.3 mL). The reaction was allowed to stir for 24h, at which point the solvent was removed *in vacuo*. Purification by silica gel chromatography (EtOAc/hexanes as eluent) furnished acetate **221** (79mg, 76% yield) as a clear oil.

Acetate 221. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.45-5.38 (m, 4H), 4.00-3.92 (m, 4H), 3.81 (s, 3H), 3.79 (s, 3H), 3.82-3.78 (m, 1H), 3.73 (d, *J*=3.6Hz, 1H), 3.61 (dd, *J*= 12.4, 2.6 Hz, 1H), 2.15-1.80 (m, 12H), 1.70-1.55 (m, 9 H), 1.4-.12 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.92, 168.51, 166.60, 163.98, 140.65, 131.65, 131.47, 131.13, 131.00, 125.19, 125.13, 125..09, 124.17, 110.36, 110.25, 92.04, 75.12, 66.85, 65.91, 53.90, 52.98, 52.85, 52.72, 45.22, 41.15, 36.13, 35.13, 34.15, 32.63, 29.62, 29.22, 29.18, 28.90, 27.06, 26.04, 21.52, 18.12. HRMS (ESI) *m/z* 589.3020 [calc'd for $C_{32}H_{45}O_{10}$ (M+H) 589.3013].

Preparation of Acetate 220 (IMM-267):

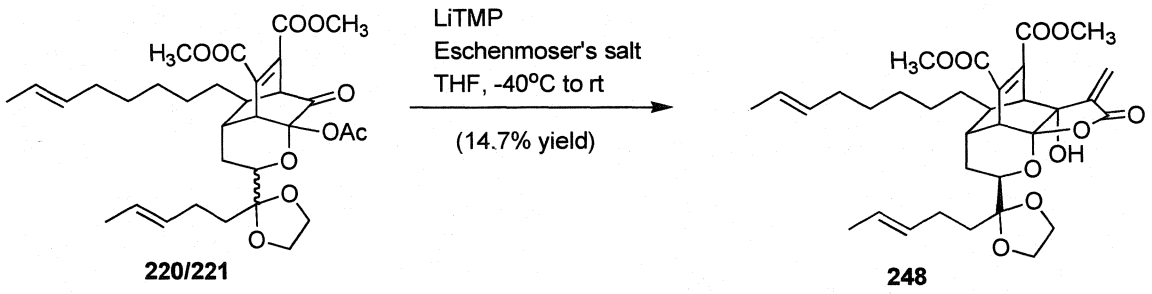


245 220

Acetate 220. To a stirred solution of **245** (100mg, 0.2 mmol, 1.0 equiv) in pyridine (3 mL) was added acetic anhydride (0.3 mL). The reaction was allowed to stir for 24h, at which point the solvent was removed *in vacuo*. Purification by silica gel chromatography (EtOAc/hexanes as eluent) furnished acetate **220** (87mg, 83% yield) as a clear oil.

Acetate 220. FTIR (thin film/NaCl) 2929 m 1749 s 1725 s 1434 m 1368 m 1283 s 1229 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.45-5.35 (m, 4H), 4.67-4.62 (m, 1H), 4.09 (d, *J*=3Hz, 1H), 4.08-3.82 (m, 4H), 3.86 (s, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.78-3.74 (m, 1H), 3.63 (d, *J*= 1.45Hz, 1H), 2.15-1.8 (m, 10H), 1.85-1.78 (m, 1H), 1.72-1.55 (m, 9H), 1.46-1.24 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.88, 170.00, 165.45, 164.70, 039.42, 133.29, 131.52, 131.01, 125.19, 125.10, 124.76, 118.59, 113.64, 110.43, 92.98, 75.88, 69.87, 66.78, 66.16, 53.90, 53.06, 52.95, 52.86, 52.76, 44.15, 39.38, 35.66, 35.36, 34.06, 32.67, 30.76, 29.60, 29.21, 27.16, 15.92, 21.86, 20.72, 18.13, 18.11. HRMS (ESI) *m/z* 589.3022 [calc'd for $C_{32}H_{45}O_{10}$ (M+H) 589.3013].

Preparation of Lactone 248 (IMMIV-189):



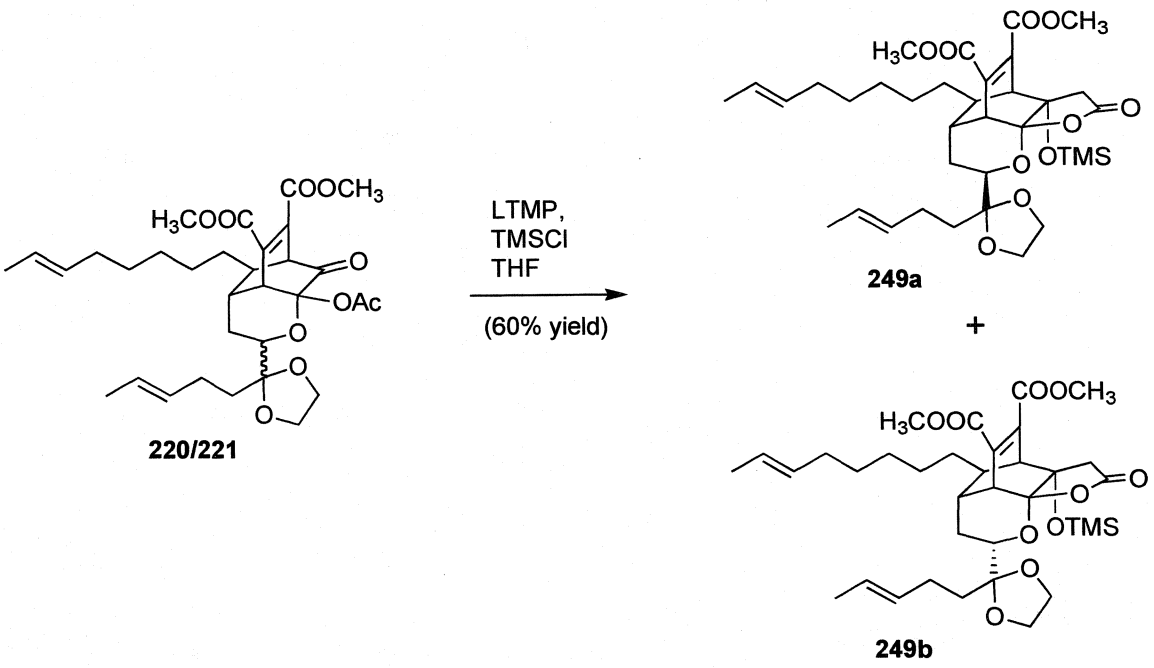
LTMP. To a cooled (-10°C) solution of 2,2,6,6-tetramethylpiperidine (115 μL, 0.68 mmol, 4.0 equiv) in THF (1.5 mL) was added *n*-BuLi (1.6M in hexane, 360 μL, 0.58 mmol, 3.4 equiv). This solution was stirred at -10°C for 30 min, at which time it was cooled to -40°C.

Lactone 248. To a mixture of **221/220** (100mg, 0.17 mmol, 1.0 equiv) and Eschenmoser's salt (189mg, 1.02 mmol, 6.0 equiv) was added THF (2.5 mL), and this was cooled to -40°C. The solution of LTMP was transferred to the second flask *via* cannula. This mixture was allowed to warm to rt over 1.5h, and then let stir overnight (~16h) at ambient temperature. It was then quenched with water (3 mL), diluted with EtOAc (10 mL), separated, and the aqueous layer was extracted with EtOAc (2x 10 mL) the combined organics were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification via silica gel chromatography (30% EtOAc/Hexanes eluent) furnished **248** (15mg, 14.7% yield) as a clear oil.

Lactone 248. FTIR (thin film/NaCl) 3420 (br), 2927 (s), 2855 (m), 1781 (s), 1733 (s), 1718 (s), 1457 (m), 1436 (m), 1280 (s), 1148 (m), 1088 (s), 1010 (m), 966 (m),

919 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.37 (s, 1H), 5.98 (s, 1H) 5.5-5.35 (m, 4H), 4.57 (dd, *J*=11.5, 3.7 Hz, 1H), 4.40 (s, 1H), 4.15-3.85 (m, 4H), 3.24 (s, 3H), 3.21 (s, 3H), 3.28 (d, *J*=1.7 Hz, 1H), 2.96 (d, *J*=2.6, 1H), 2.2-1.55 (m, 16H), 1.35-1.20 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.42, 165.71, 165.20, 140.78, 138.90, 136.92, 131.53, 130.80, 127.51, 125.43, 125.02, 110.97, 104.23, 76.66, 76.61, 66.52, 66.31, 52.76, 52.68, 48.33, 45.99, 37.68, 36.01, 35.82, 33.93, 32.66, 29.62, 29.61, 29.33, 27.37, 25.88, 18.14. HRMS (ESI) *m/z* 601.2999 [calc'd for $C_{33}H_{45}O_{10}$ (M+H) 601.2996].

Preparation of Lactones 249a and 249b (IMMIV-251):



LTMP. To a cooled (-10°C) solution of 2,2,6,6-tetramethylpiperidine (250 μL, 1.52 mmol, 1.8 equiv) in THF (10 mL) was added *n*-BuLi (1.5M in hexane, 620 μL, 0.93 mmol, 1.1 equiv). This solution was stirred at -10°C for 30 min, at which time it was cooled to -40°C.

Lactones 249a and 249b. A solution of **221/220** (100mg, 0.17mmol, 1.0 equiv) in THF (5mL) was cooled to –40°C. The solution of LTMP was added to this *via* cannula, over 12 min. After stirring for 30 min at –40°C, a solution of TMSCl (190μL, 1.52mmol, 1.8 equiv), Et_3N (210μL, 1.52 mmol, 1.8 equiv) in THF (3mL) was added. After allowing to warm to ambient temperature, this was stirred at rt for 2.5 h, at which

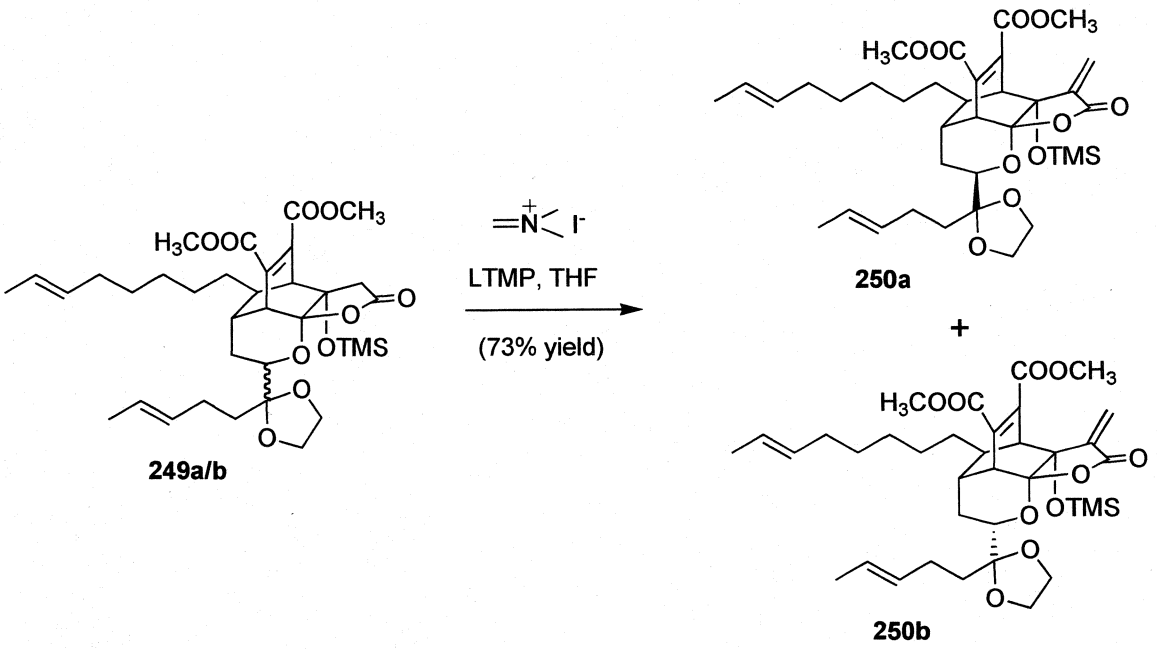
point it was quenched with water (10mL), diluted with EtOAc (20 mL) and separated. The aqueous was extracted with EtOAc (2x 20mL) the combined organics were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification via silica gel chromatography (25% EtOAc/Hexanes eluent) furnished **249a** (249mg, 45% yield, eluting first) and **249b** (81mg, 15% yield, eluting second) as clear oils.

Lactone 249a. FTIR (thin film/NaCl) 2955 (s), 2928 (s), 2855 (s), 2256 (w), 1790 (s), 1723 (s), 1646 (m), 1437 (m), 1364 (m), 1268 (s), 1218 (s), 1090 (s), 1071 (s), 1046 (m), 965 (m), 918 (m), 863 (s), 845 (s), 734 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.48-5.36 (m, 4H), 4.51 (dd, *J*=12.27,3.93 Hz, 1H), 4.10-3.94 (m, 4H), 3.81 (s, 3H), 3.75 (s, 3H), 3.00 (s, 1H), 2.97 (d, *J*=19 Hz, 1H), 2.80 (d, *J*=19 Hz, 1H), 2.2-1.6 (m, 18H), 1.4-1.2 (m, 8H), 0.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.05, 167.07, 164.63, 140.09, 136.43, 131.48, 130.94, 125.21, 125.05, 10.92, 106.97, 80.13, 76.76, 66.67, 66.48, 52.96, 52.75, 51.68, 45.43, 42.88, 37.78, 36.00, 35.95, 34.86, 32.72, 29.62, 25.48, 29.22, 27.35, 26.15, 18.14, 1.95. HRMS (ESI) *m/z* 661.3412 [calc'd for $C_{35}H_{53}O_{10}Si$ (M+H) 661.3408].

Lactone 249b. FTIR (thin film/NaCl) 2926 (s), 2853 (m), 1785 (s), 1721 (s), 1436 (m), 1268 (s), 1148 (s), 1093 (s), 967 (m), 863 (m), 843 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.50-5.35 (m, 4H), 4.22 (dd, *J*=1.73, 4.71 Hz, 1H), 4.08-3.92 (m, 4H), 3.82 (s, 3H), 3.75 (s, 3H), 3.56(d, *J*=3 Hz, 1H), 2.96 (d, *J*=1.65, 1H), 2.95 (d, *J*=19.5, 1H), 2.69 (d, *J*=19.5, 1H), 2.20-1.86 (m, 8H). 1.0-1.60 (m, 8H), 1.40-1.15 (m, 8H), 1.20 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.55, 167.2, 164.51, 142.13, 134.10, 131.52, 131.04, 125.28, 125.02, 110.41, 108.14, 79.86, 75.36, 66.49, 65.72, 53.02, 52.94, 52.85,

42.38, 42.16, 39.75, 36.19, 35.15, 33.85, 32.71, 30.21, 29.63, 29.24, 27.28, 25.97, 18.15, 18.09, 2.01. HRMS (ESI) *m/z* 661.3397 [calc'd for $C_{35}H_{53}O_{10}Si$ (M+H) 661.3408].

Preparation of Lactones 250a and 250b (IMMIV-252):



LTMP. To a cooled (-10°C) solution of 2,2,6,6-tetramethylpiperidine (300 μL, 1.8 mmol, 3.6 equiv) in THF (9 mL) was added *n*-BuLi (1.5M in hexane, 730 μL, 1.1 mmol, 2.2 equiv). This solution was stirred at -10°C for 30 min, at which time it was cooled to -40°C.

Lactones 250a and 250b. Second, in a separate flask, a mixture of **249a/249b** (325mg, 0.50 mmol, 1.0 equiv) and Eschenmoser's salt (555 mg, 3.0 mmol, 6.0 equiv) was azeotroped with benzene (3x 5mL) and then dried *in vacuo* for 1h. THF (7mL) was added to the mixture of **249a/249b** and Eschenmoser's salt, and this mixture was cooled to –40°C. The solution of LTMP was added to this *via* cannula, over 8 min. This mixture

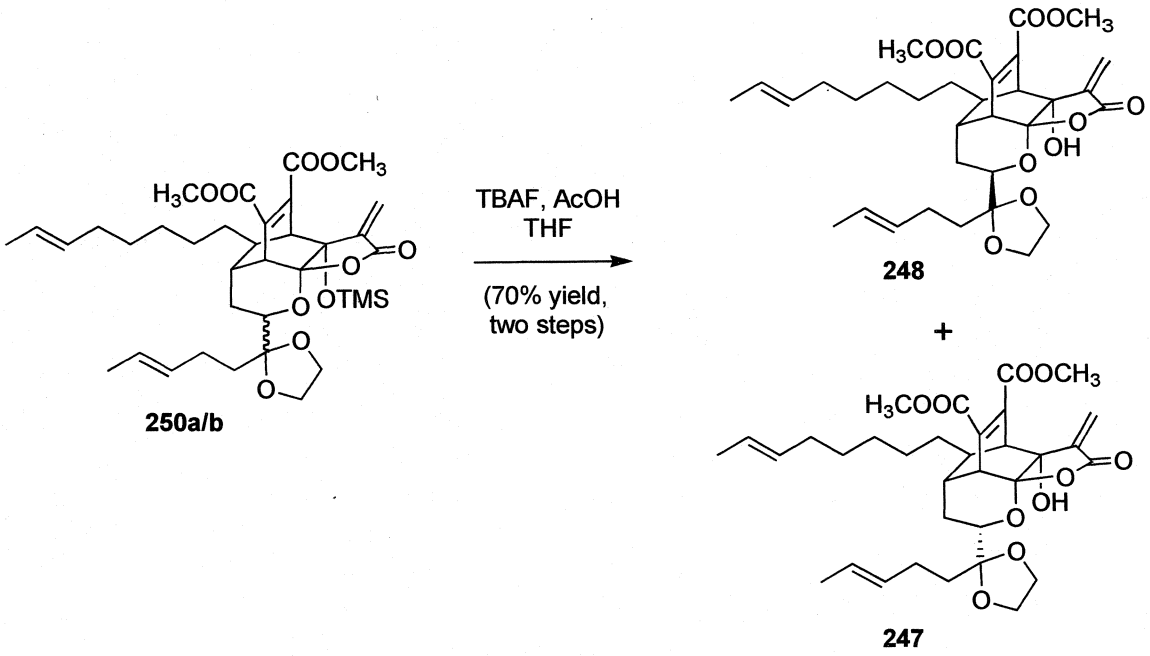
was allowed to warm to ambient temperature, and it was stirred at this temperature overnight (~16h). At that point it was quenched with water (10mL), diluted with EtOAc (20 mL) and separated. The aqueous was extracted with EtOAc (2x 20mL) the combined organics were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification via silica gel chromatography (25% EtOAc/Hexanes eluent) furnished **250a** (183mg, 56% yield, eluting first) and **250b** (57mg, 17% yield, eluting second) as clear oils.

Lactone 250a. FTIR (thin film/NaCl) 2954 (m), 2827 (s), 2825 (m), 1781 (s), 1723 (s), 1645 (w), 1437 (m), 1282 (s), 1151 (s), 1090 (s), 1050 (m), 1012 (m), 965 (w), 880 (w), 845 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.46 (s, 1H). 5.89 (s, 1H), 5.47-5.38 (m, 4H, 4.50 (dd, *J*=12.2, 3.84 Hz, 1H), 4.2-4.1 (m, 2H), 4.0-3.9 (m, 2H), 3.74 (s, 3H), 3.71 (s, 3H), 3.24 (d, *J*=2.2 Hz, 1H), 2.91 (d, *J*=2.67 Hz, 1H), 2.15-1.85 (m, 6H), 1.78 (m, 1H), 1.70-1.50 (m, 10H), 1.40-1.20 (m, 8H), 0.16 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.76, 165.92, 165.32, 139.87, 138.95, 136.93, 131.56, 130.99, 127.77, 125.30, 125.04, 110.97, 104.44, 78.44, 77.62, 67.09, 66.87, 52.70, 52.62, 50.49, 46.57, 38.11, 35.89, 35.67, 35.64, 32.76, 29.99, 29.67, 29.29, 27.38, 26.02, 18.14, 18.13, 1.96. HRMS (ESI) *m/z* 673.3417 [calc'd for $C_{36}H_{53}O_{10}Si$ (M+H) 673.3408].

Lactone 250b. FTIR (thin film/NaCl) 2953 (m), 2927 (s), 2854 (m), 1775 (s), 1772 (s), 1653 (w), 1436 (m), 1285 (s), 1144 (s), 1094 (s), 965 (w), 844 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.44 (s, 1H). 5.88 (s, 1H), 5.44-5.38 (m, 4H), 4.30 (dd, *J*=11.7, 4.4 Hz, 1H), 4.03-3.90 (m, 4H), 3.74 (s, 3H), 3.72 (s, 3H), 3.50 (d, *J*=3.1 Hz, 1H), 3.20 (d, *J*=1.7 Hz, 1H), 2.17-1.60 (m, 18H), 1.40-1.10 (m, 9H), 0.11 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.25, 163.76, 163.61, 137.96, 137.46, 134.17, 129.66,

129.01, 125.41, 123.27, 123.01, 108.45, 103.52, 76.26, 72.86, 64.49, 63.23, 50.78, 50.63, 49.99, 39.65, 39.20, 34.04, 33.80, 32.93, 30.81, 27.71, 27.30, 27.18, 25.30, 24.52, 16.18, 16.13, 0.02. HRMS (ESI) *m/z* 673.3394 [calc'd for $C_{36}H_{53}O_{10}Si$ (M+H) 673.3408].

Preparation of Lactones 247 and 248 (TSII-102):

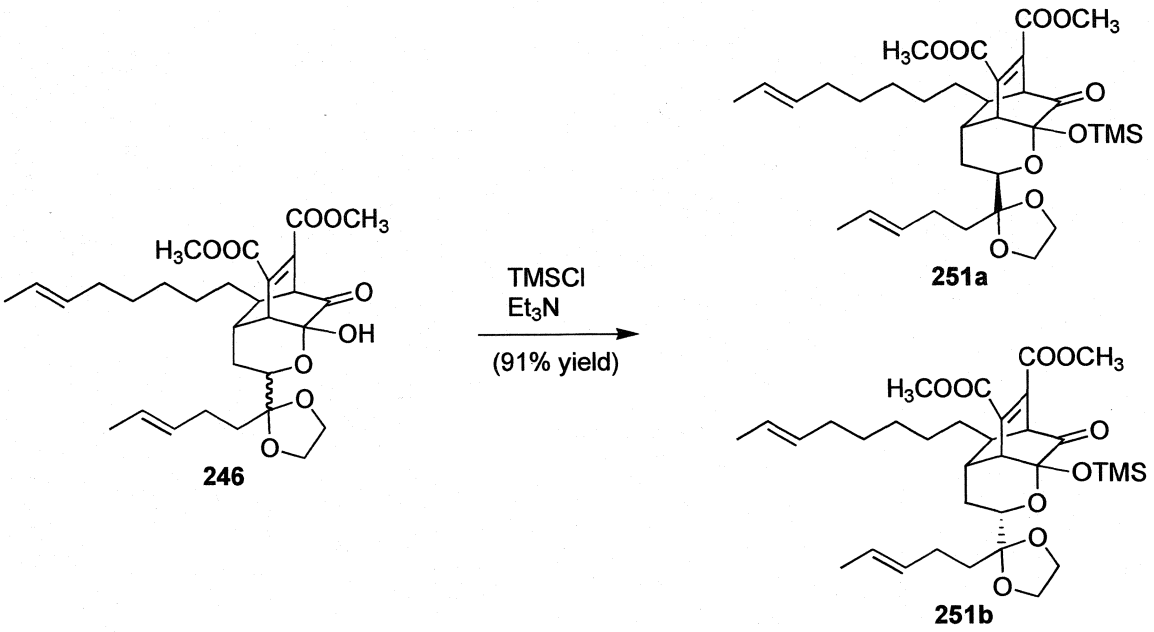


Lactones 247 and 248. To a solution of TMS-lactones **250a** and **250b** (984mg, 1.46 mmol, 1.0 equiv) in THF (7.3 mL) was added AcOH (377 μL, 7.3 mmol, 5.0 equiv) and TBAF (1.0M in THF, 2.6 mL, 2.6 mmol, 1.8 equiv) at 0°C. The mixture was warmedn to rt, stirred at rt for 2h, treated with EtOAc (5 mL) and water (2 mL) and separated. The aqueous layer was extracted with EtOAc (2x 5 mL), and the combined

organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification via silica gel chromatography (25%-50% EtOAc/Hexanes eluent) furnished **247** (181mg, 21% yield, eluting first) and **248** (653mg, 75% yield, eluting second) as clear oils.

Lactone 247. FTIR (thin film/NaCl) 3465 (br), 2928 (s), 2855 (m), 1778 (s), 1723 (s), 1646 (w), 1347 (m), 1372 (w), 1284 (s), 1143 (s), 1090 (s), 997 (m), 966 (s), 917 (m), 810 (w), 734 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.37 (s, 1H), 5.95 (s, 1H), 5.46-5.36 (m, 4H), 4.40 (dd, *J*=11.75,5.4 Hz, 1H), 4.08 (s, 1H), 4.05-3.95 (m, 4H), 3.75 (s, 3H), 3.72 (s, 3H), 3.56 (d, *J*=3.1, 1H), 3.29 (d, *J*=1.9, 1H), 2.20-1.90 (m, 6H), 1.82-1.56 (m, 10H), 1.34-1.20 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.04, 165.55, 165.26, 140.08, 139.32, 135.31, 131.52, 130.49, 126.96, 125.54, 125.00, 110.36, 103.46, 76.07, 74.83, 66.67, 66.25, 52.84, 52.69, 50.03, 42.55, 39.69, 35.92, 34.87, 34.58, 32.64, 30.03, 29.60, 29.23, 27.29, 27.25, 26.33, 18.14, 18.10. HRMS (ESI) *m/z* 601.3011 [calc'd for $C_{33}H_{45}O_{10}$ (M+H) 601.3013].

Preparation of TMS Acetals 251a and 251b (TSII-168):



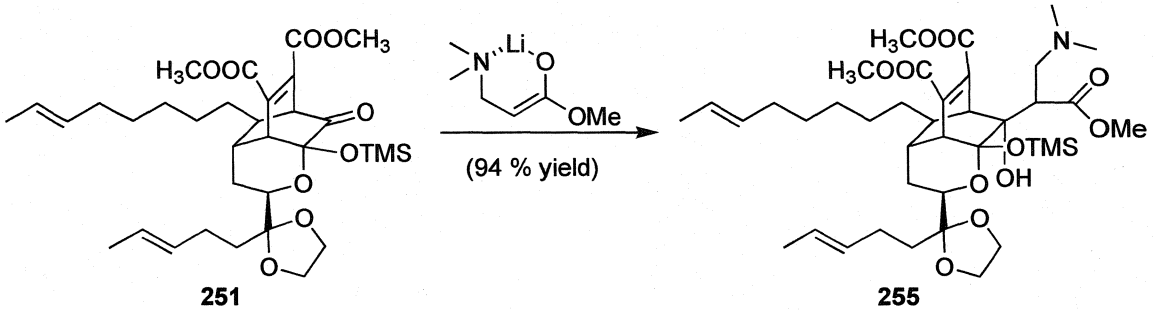
TMS Acetals 251a and 251b. To a solution of lactols **245/246** (2.1g, 4.04 mmol, 1.0 equiv) in CH_2Cl_2 (40 mL) at 0°C was added Et_3N (676 μL, 4.84 mmol, 1.2 equiv) and TMSCl (651 μL, 4.84 mmol, 1.2 equiv). The reaction mixture was stirred at 0°C for 5h, at which point additional Et_3N (169μL, 1.24 mmol, 0.3 equiv) and TMSCl (163 μL, 1.21 mmol, 0.3 equiv) were added. The reaction mixture was stirred at 0°C an additional hour, diluted with CH_2Cl_2 (20mL) treated with water (5mL) and saturated aqueous $NaHCO_3$ (5mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2x 20 mL) and the combined organic layer was wahed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification via silica gel chromatography (5%-50% EtOAc/Hexanes eluent) furnished TMS-acetal **251b** (131mg, 5.3% yield, eluting first),

TMS-Acetal **251a** (1012mg, 40.5% yield, eluting second), and lactols **245/246** (650mg, 29.5% yield, eluting third) as clear oils.

TMS Acetal251a. FTIR (thin film/NaCl) 2954 (s), 2929 (s), 2855 (s), 1736 (s), 1725 (s), 1643 (m), 1436 (m), 1355 (m), 1276 (s), 1250 (s), 1208 (s), 1188 (s), 1145 (m), 1083 (s), 1045 (m), 847 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.48-5.35 (,. 4H), 4.00-3.89 (m, 4H), 3.78 (s, 3H), 3.76 (s, 3H), 3.54 (dd, *J*=12.1, 2.3 Hz, 1H). 3.47 (d, *J*=2.5 Hz, 1H), 3.0 (d, *J*=3.4 Hz, 1H), 2.15-1.70 (m, 8H), 1.66-1.52 (m, 10H), 1.41-1.19 (m, 8H). 0.11 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.56, 165.92, 165.43, 140.37, 132.64, 131.46, 130.87, 125.00, 110.53, 91.66, 73.36, 66.26, 65.26, 55.27, 52.66, 52.46, 48.67, 41.39, 35.61, 34.98, 34.81, 32.59, 29.56, 29.11, 28.25, 27.06, 26.43, 18.10, 1.44. HRMS (ESI) *m/z* 619.3298 [calc'd for $C_{33}H_{51}O_9Si$ (M+H) 619.3302].

TMS Acetal 251b. FTIR (thin film/NaCl) 2954 (s), 2928 (s), 2855 (m), 1755 (s), 1725 (s), 1640 (w), 1436 (m), 1361 (w), 1277 (s), 1249 (s), 1185 (m), 1154 (w) 1082 (m), 1046 (s), 966 (m), 875 (m), 848 (s), 758 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.46-5.37 (m, 4H), 4.07-4.00 (m, 2H), 3.95-3.86 (m, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.46 (d, *J*=1.5 Hz, 1H), 3.19 (d, *J*=2.7 Hz, 1H), 2.12-1.92 (m, 8H), 1.71-1.55 (m, 10H), 1.34-1.20 (m, 8H), 0.12 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.80, 165.58, 165.36, 140.16, 134.07, 131.54, 130.87, 125.23, 124.98, 110.65, 91.37, 72.95, 66.56, 66.16, 54.94, 52.74, 52.63, 45.44, 44.00, 35.80, 35.52, 34.65, 32.65, 31.08, 29.57, 29.23, 27.23, 26.91, 26.05, 18.08, 1.47. HRMS (ESI) *m/z* 619.3306 [calc'd for $C_{33}H_{51}O_9Si$ (M+H) 619.3302].

Preparation of Ester 255 (TSII-186):



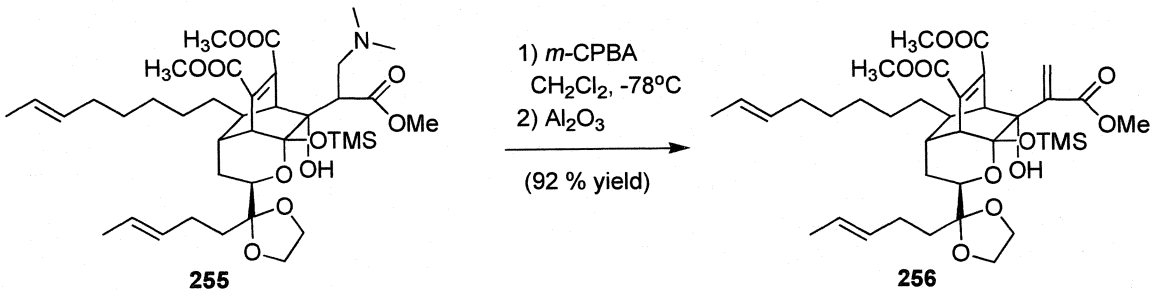
Enolate 253. To a solution of diisopropyamine (537 μL, 4.08 mmol, 2.5 equiv) in THF (5 mL) at –78°C was added *n*-BuLi (1.6M in hexane, 2.4 mL, 3.84 mmol, 2.4 equiv) dopwise over 5 min. The resultant mixture was stirred at –20°C for 5 min, and then cooled to –78°C. To this mixture was added methyl-3-(dimethylamino)propionate (515 μL, 3.6 mmol, 2.2 equiv) in THF (2 mL) dropwise over 5 min. The reaction mixture was stirred at –78°C for 30 min, 0°C for 15 min and rt for 15 min, and then cooled to –78°C.

Ester 255. A solution of TMS-ether ketone **251** (1.01g, 1.63 mmol, 1.0 equiv) in THF (5+3+2mL) was added dropwise to Enolate **253** over 10 min. The temperature was maintained at-78°C for 1h, at which time it was treated with EtOAc (5 mL) and Sat. NH_4Cl (3 mL), warmed to rt and separated. The aqueous layer was extracted with EtOAc (2x 10 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification via silica gel chromatography (5%-10% $MeOH/CH_2Cl_2$ eluent) furnished **255** (1.31g, 93.5% yield) as a clear oil.

Ester 255. FTIR (thin film/NaCl) 3467 (br), 2951 (s), 2928 (s), 2856 (m), 2772 (w), 1721 (s), 1644 (m), 1436 (m), 1347 (w), 1274 (s), 1249 (s), 1195 (m), 1169 (m),

1087 (m), 1071 (m), 1046 (m), 966 (w), 921 (w), 867 (w), 845 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.44-5.36 (m, 4H), 4.90 (dd, *J*=10.6, 5.2 Hz, 1H), 4.00-3.90 (m, 4H), 3.76 (s, 3H), 3.73 (s, 3H), 3.66 (s, 3H). 3.22 (dd, *J*=13.0, 8.3 Hz, 1H), 3.01 (d, *J*=1.7 Hz, 1H), 2.79-2.69 (m, 2H), 2.67 (d, *J*=2.5 Hz, 1H), 2.29-2.20 (m, 2H), 2.20 (s, 6H), 2.10-1.90 (m, 4H), 1.69-1.49 (m, 10H), 1.33-1.18 (m, 8H), 0.20 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.09, 166.54, 166.49, 139.71, 136.68, 131.75, 131.52, 124.78, 124.60, 111.49, 99.66, 80.74, 73.81, 66.05, 64.96, 60.09, 52.22, 52.16, 51.82, 50.73, 50.17, 49.11, 46.43, 37.11, 36.32, 34.88, 34.70, 32.72, 29.69, 29.50, 28.56, 27.40, 26.63, 18.12, 2.0. HRMS (ESI) *m/z* 750.4252 [calc'd for $C_{39}H_{64}O_{11}Si$ (M+H) 750.4249].

Preparation of Ester 256 (TSII-182):

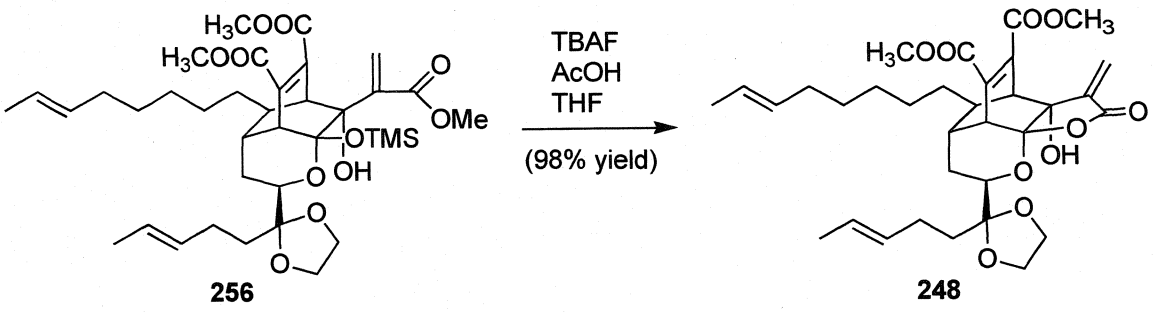


Ester 256. Before beginning the reaction, an alumina column was prepared: h=3cm, d=4.5cm, packed with CH_2Cl_2 (It is critical that the pad of alumina be short and thick). To a solution of tertiary amine **255** (767mg, 1.02mmol, 1.0equiv) in CH_2Cl_2 (5mL) at –78°C was added a solution of *m*-CPBA (275.5mg, 1.53mmol, 1.5 equiv) in

CH_2Cl_2 (5mL) dropwise over 5 min. The reaction was stirred at –78°C for 9 min, at which time basic alumina was added (1.5g), and the reaction mixture quickly moved to the prepared alumina column, and the reaction mixture was filtered through basic alumina using CH_2Cl_2 /MeOH (10:1) with careful monitoring by TLC. The collected fractions contained both the desired ester (**256**) and the non-eliminated N-oxide intermediate (base line spot on TLC). Upon rotary evaporation, the polar spot is converted to the desired compound (i.e. the base line spot disappears in the TLC). Purification via silica gel chromatography (25% EtOAc/Hexanes eluent) furnished **256** (664mg, 92.1% yield) as a clear oil.

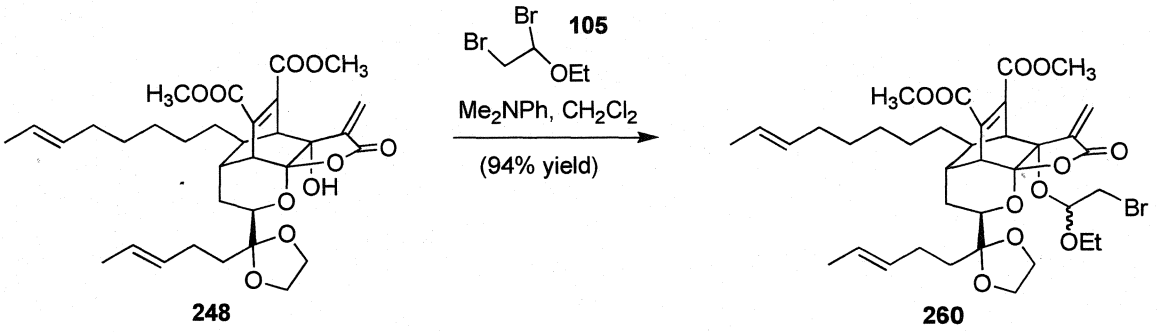
Ester 256. FTIR (thin film/NaCl) 3435 (br), 2953 (s), 2927 (s), 2855 (m), 1716 (s), 1644 (w), 1437 (m), 1321 (m), 1276 (s), 1249 (s), 1181 (m), 1100 (m), 1056 (m), 965 (m), 923 (m), 864 (m), 846 (m), 811 (w), 760 (w), 734 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.73 (s, 1H), 5.68 (s, 1H), 5.56 (s, 1H), 5.50-5.45 (m, 2H), 5.41-5.37 (m, 2H) 4.87 (dd, *J*=10.8, 5.4 Hz, 1H), 4.00-3.90 (m, 4H), 3.77 (s, 3H), 3.76 (s, 3H), 3.75 (s, 3H), 3.35 (d, *J*=1.7 Hz, 1H), 2.63 (d, *J*=2.6 Hz, 1H), 229 (m, 1H), 2.20-1.90 (m, 5H), 1.80-1.58 (m, 10H), 1.35-1.21 (m, 8H), 0.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.79, 167.71, 165.73, 143.89, 143.54, 132.85, 131.72, 131.34, 124.90, 124.85, 120.00, 111.43, 99.15, 82.15, 74.52, 66.30, 65.32, 52.58, 52.23, 52.01, 50.62, 46.03, 38.08, 36.10, 34.90, 34.75, 32.70, 29.71, 29.45, 28.28, 27.46, 26.79, 18.20, 18.15, 1.61. HRMS (ESI) *m/z* 705.3654 [calc'd for $C_{37}H_{57}O_{11}Si$ (M+H) 705.3670].

Preparation of Lactone 248 (TSII-212):



Lactone 248. To a solution of TMS-ether **256** (1.516g, 2.15 mmol, 1.0 equiv) in THF (21.5 mL) was added AcOH (616 μL, 10.75 mmol, 5 equiv) and TBAF (1.0 M in THF, 4.3 mL, 4.3 mmol, 2 equiv) at 0°C. The mixture was stirred at 0°C for 30 min, allowed to warm to rt, and stirred at rt for 2.5h. At that time an additional equivalent of TBAF was added (2.15 mL, 2.15 mmol, 1 equiv) and stirring continued fro 45 min, when a fourth equivalent of TBAF was added (2.15 mL, 2.15 mmol, 1 equiv). After an additional 15 min, water was added (50 mL), the reaction was diluted with EtOAc (50mL) and separated. The aqueous layer was extracted with EtOAc (2x 50 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification via silica gel chromatography (25%-33% EtOAc/Hexanes eluent) furnished **248** (1.26g, 98.1% yield) as a clear oil.

Preparation of Bromoacetal 260 (TSII-214):

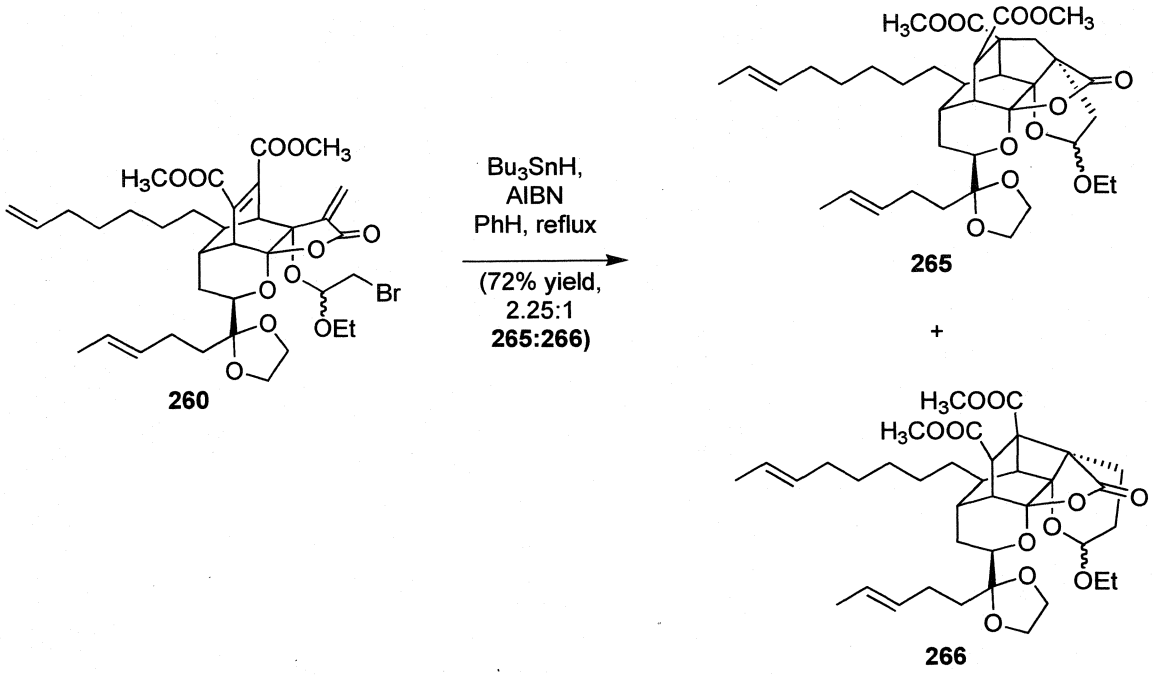


Bromoacetal 260. To a solution of tertiary alcohol **248** (1.52g, 2.53 mmol, 1.0 equiv) in CH_2Cl_2 (12.6 mL, 0.2M) was added N,N-dimethylaniline (1.61 mL, 12.65 mmol, 5 equiv) and dibromide **105** (1.7 mL, 12.65 mmol, 5.0 equiv) at rt. The reaction mixture was stirred at rt for 24 h, at which time it was treated with saturated aqueous $NaHCO_3$ (10 mL) and separated. The aqueous layer was extracted with CH_2Cl_2 (2x 20 mL), and the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification via silica gel chromatography (10%-33% EtOAc/Hexanes eluent) furnished **260** (1.79g, 93.7% yield) as a clear oil.

Bromoacetal 260. FTIR (thin film/NaCl) 2928 (m), 2825 (m), 1781 (s), 1721(s), 1652 (w), 1646 (w), 1436 (m), 1364 (w), 1282 (s), 1193 (w), 1148 (m), 1092 (s), 1071 (s), 1010 (m), 967 (m), 921 (w), 821 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.59 (s, 0.5H), 6.48 (s, 0.5H), 6.05 (s, 0.5H), 5.84 (s, 0.5H), 5.47-5.37 (m, 4H), 4.81 (dd, *J*=7.3, 3.4 Hz, 0.5H), 4.73 (dd, *J*=4.4, 2.8 Hz, 0.5H), 4.66 (dd, *J*=12.1, 3.7 Hz, 0.5H), 4.53 (dd, *J*=12.3, 4.1 Hz, 0.5H), 4.13-3.91 (m, 4H), 3.77 (dd, *J*=11.3, 4.5 Hz, 0.5H), 3.74 (s, 1.5H), 3.738 (s, 1.5H), 3.71 (s, 1.5H), 3.70 (s, 1.5H), 3.59 (dd, *J*=11.3, 2.8 Hz, 0.5H), 3.57 (d,

J=2.1 Hz, 0.5H), 3.55-3.31 (m, 3.5H), 2.94 (d, *J*=2.8 Hz, 0.5H), 2.91 (d, *J*= 2.7 Hz, 0.5H), 2.26 (m, 1H), 2.1-1.58 (m, 16H), 1.36-1.10 (m, 9H), 1.22 (t, *J*=7 Hz, 1.5H), 1.07 (t, *J*=7.0 Hz, 0.5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.51, 166.42, 165.85, 165.82, 165.18, 165.01, 139.18, 139.15, 136.71, 135.74, 135.16, 131.57, 131.54, 131.06, 130.91, 130.12, 126.91, 125.34, 125.15, 125.01, 125.00, 111.02, 110.85, 104.90, 104.20, 97.51, 97.80, 81.74, 80.90, 66.77, 66.73, 66.63, 61.32, 61.23, 52.74, 52.70, 52.67, 52.66, 48.55, 47.63, 46.76, 46.69, 38.24, 37.93, 35.88, 35.85, 35.36, 35.19, 35.01, 34.49, 32.72, 32.70, 32.45, 31.84, 29.65, 29.63, 29.28, 29.20, 27.29, 27.26, 26.07, 25.98, 18.12, 18.11, 15.26, 15.06. HRMS (ESI) *m/z* 751.2687 [calc'd for $C_{37}H_{52}O_{11}Br$ (M+H) 751.2693].

Preparation of Acetals 265 and 266 (IMMIV-259):



Acetals 265 and 266. To a solution of bromoacetal **260** (144mg, 0.19 mmol, 1.0 equiv) and Bu_3SnH (80 μL, 0.29 mmol, 1.5 equiv) in Benzene (6 mL, 0.03M) was added AIBN (8mg, 0.048 mmol, 0.25 equiv) at rt, and the reaction was heated to reflux. After 2.5h, no reaction was observed, so an additional 0.25 equiv of AIBN (8mg, 0.048 mmol, 0.25 equiv) was added. After 30 min more at reflux, still no reaction was observed, so additional portions of Bu_3SnH (80 μL, 0.29 mmol, 1.5 equiv) and AIBN (8mg, 0.048 mmol, 0.25 equiv) were added. After 2h more at reflux, the solvent was removed *in vacuo*, and the reaction was purified via silica gel chromatography (0%-20% EtOAc/Hexanes eluent) to furnish **266** (29mg, 22% yield, eluting first) and **265** (65mg, 50% yield, eluting second) as clear oils.

Acetal 265. FTIR (thin film/NaCl) 2928 (s), 2856 (m), 1789 (s), 1732 (s), 1436 (m), 1371 (m), 1257 (m), 1232 (s), 1148 (s), 1096 (m), 1041 (s), 995 (m), 733 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.42-5.27 (m, 5H), 4.18-3.77 (m, 6H), 3.70-3.59 (m, 7H), 3.49-3.37 (m, 2H), 3.31-3.24 (m, 1H), 3.16 (m, 3H), 3.04 (d, *J*=14.2 Hz, 1H), 2.88 (d, *J*=3 Hz, 1H), 2.69 (dd, *J*=5.7, 14Hz, 1H), 2.59-2.48 (m, 3H), 2.28 (d, *J*= 14.7 Hz, 1H), 2.25-1.38 (m, 19H), 1.29-1.05 (m, 11H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.73, 176.05, 174.18, 170.81, 170.76, 131.26, 131.08, 124.99, 124.92, 124.89, 124.76, 110.49, 110.48, 109.26, 107.13, 106.53, 97.57, 97.37, 75.52, 74.35, 66.46, 66.19, 66.081, 65.43, 64.05, 62.69, 59.06, 54.95, 53.44, 53.35, 52.85, 52.25, 52.22, 44.02, 43.67, 43.27, 43.47, 41.55, 41.52, 41.46, 39.55, 39.43, 35.16, 34.55, 34.08, 33.99, 33.87, 32.48, 32.45, 32.28, 30.76, 29.54, 29.46, 29.20, 29.16, 27.72, 27.60, 26.02, 25.82, 17.92, 15.14, 14.86. HRMS (ESI) *m/z* 673.3588 [calc'd for $C_{37}H_{53}O_{11}$ (M+H) 673.3588].

Acetal 266. FTIR (thin film/NaCl) 2927 (s), 2857 (m), 1784 (s), 1749 (s), 1438 (m), 1300 (m), 1267 (m), 1215 (s), 1144 (s), 1045 (m), 1002 (s), 854 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.47-5.38 (m, 4H), 4.92 (s, 1H), 4.14-3.94 (m, 5H), 3.75 (dd, (*J*=9.5, 7.1 Hz, 1H), 3.72 (s, 3H), 3.68 (s, 3H), 3.56 (d, *J*=2.5, 1H), 3.48 (dd, *J*=9.5, 7.1, 1H), 3.11 (d, *J*=4.9, 1H), 2.50 (m, 1H), 2.25-1.95 (m, 1H), 2.05-1.89 (m, 6H), 1.83-1.44 (m, 18H), 1.38-1.13 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.68, 170.86, 170.31, 131.77, 131.50, 124.97, 124.92, 110.52, 107.68, 96.82, 74.35, 73.64, 66.33, 65.37, 63.40, 55.68, 52.52, 52.41, 47.67, 43.97, 43.26, 42.46, 38.50, 34.26, 33.80, 33.53, 32.76, 31.37, 29.78, 29.72, 29.44, 28.10, 26.20, 26.11, 18.13, 15.20, 14.17. HRMS (ESI) *m/z* 673.3583 [calc'd for $C_{37}H_{53}O_{11}$ (M+H) 673.3588].

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40. This reaction could be carried out on larger scale (up to 2.2 mol, 300ml of 1,8-nonadiyne) without any substantial difficulty.

Appendix 1

Spectra Relevant to Chapter 3

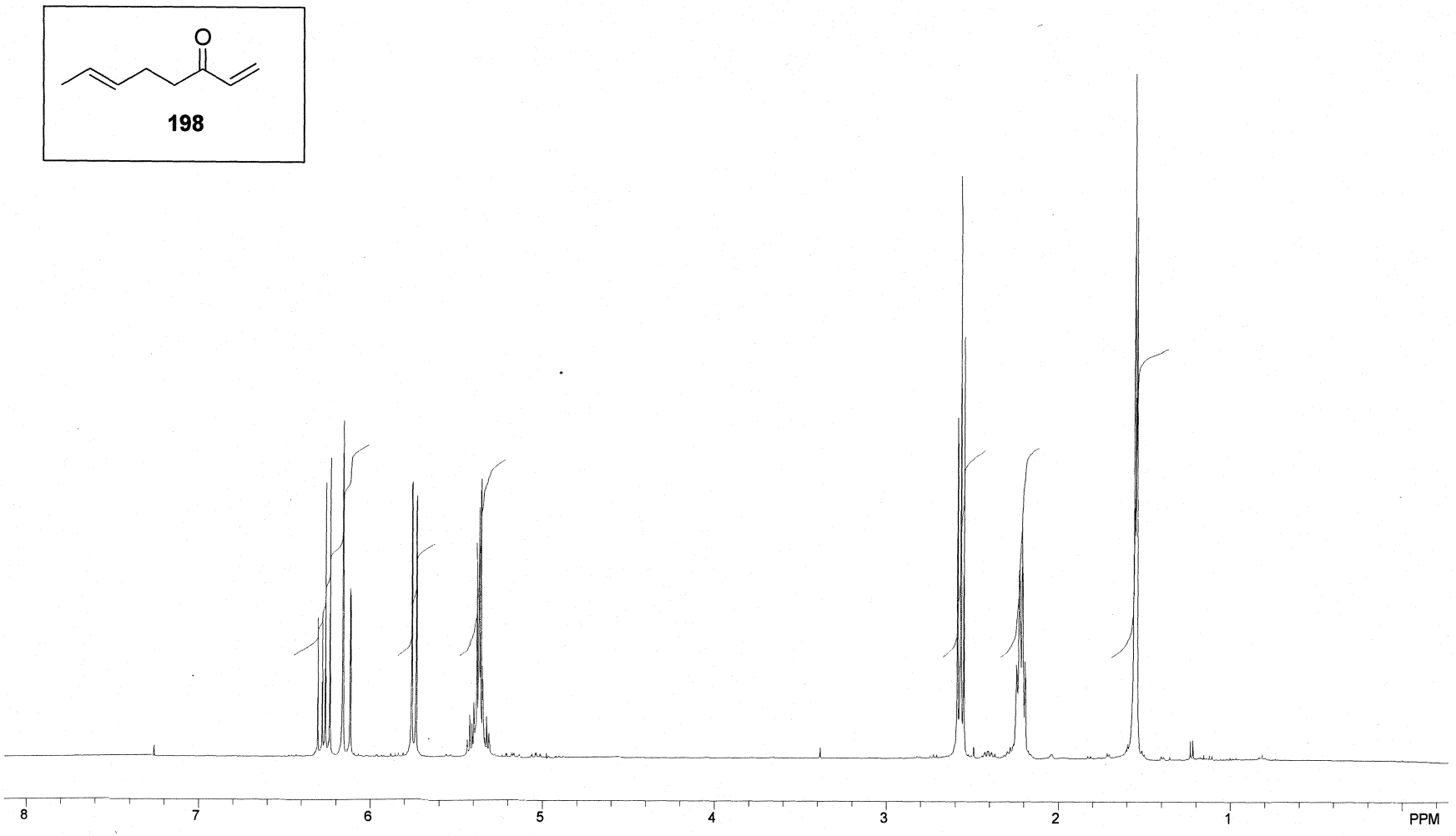


Figure A.1.1 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **198**.

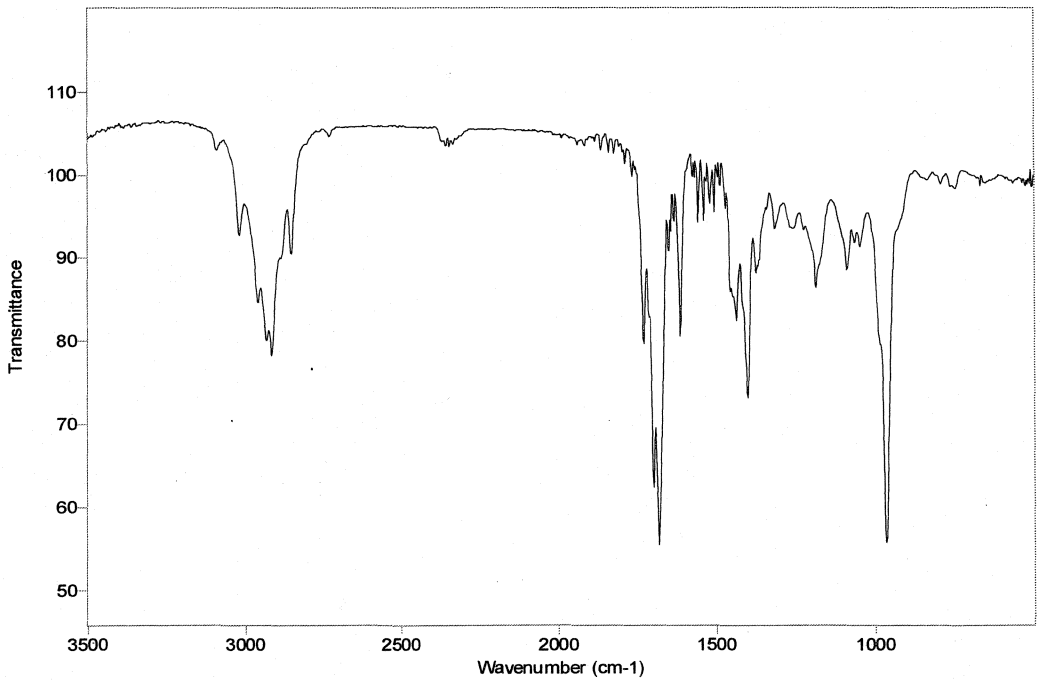


Figure A.1.2 FTIR Spectrum (thin film/NaCl) of Compound **198**.

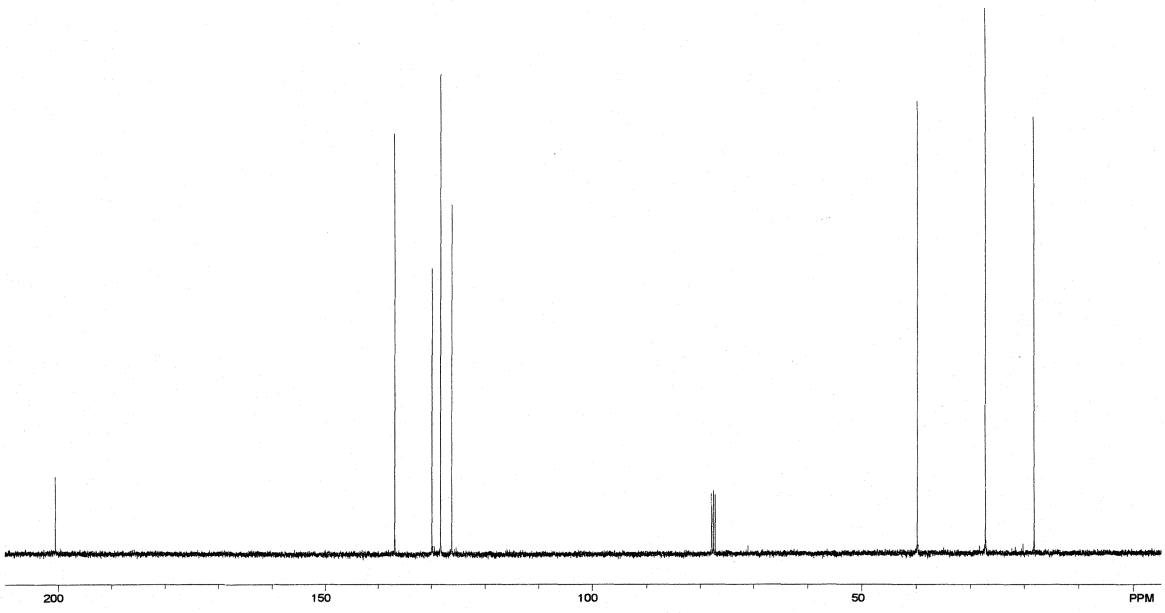


Figure A.1.3 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **198**.

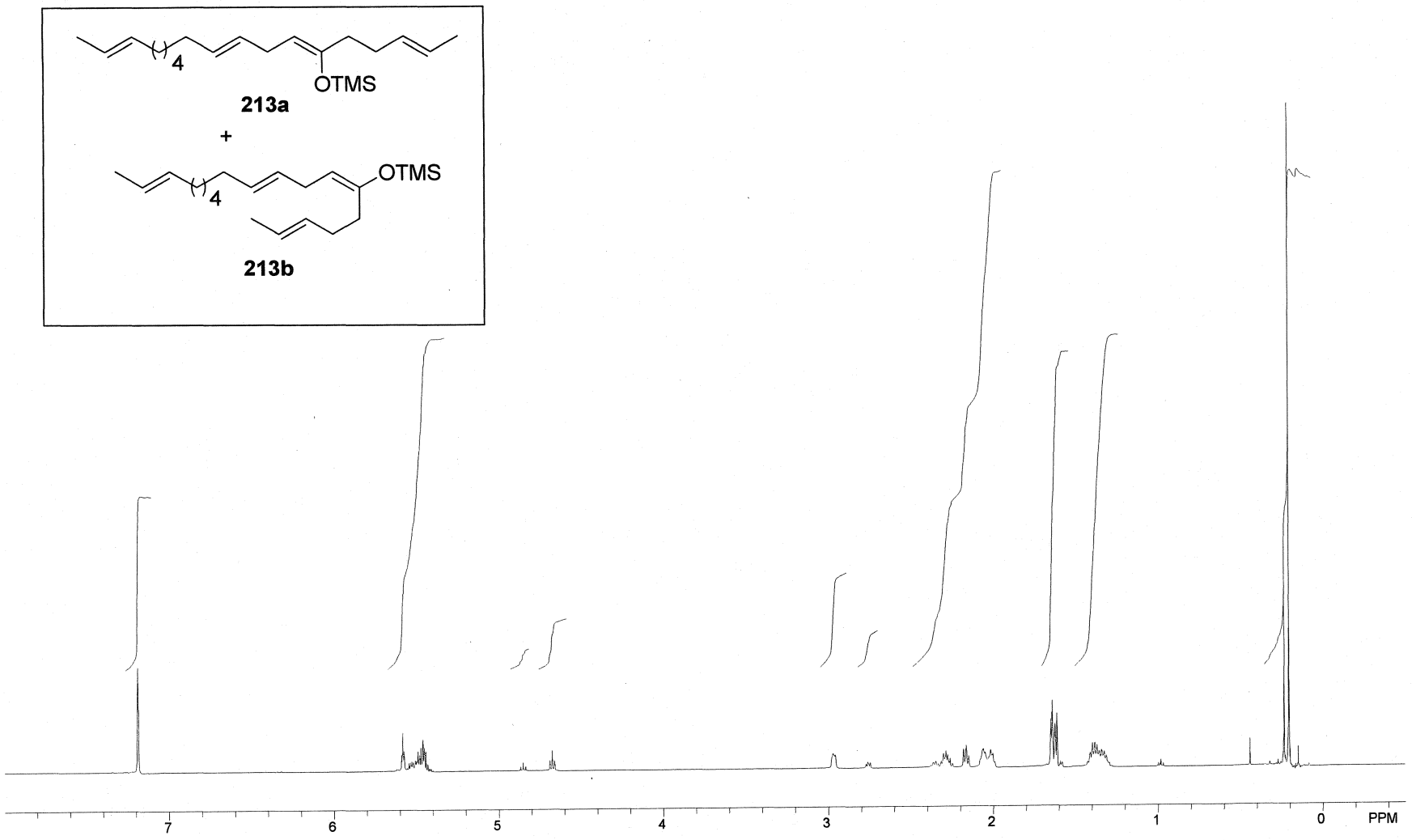


Figure A.1.4 ^{1}H NMR (500 MHz, C_6D_6) of Compound **213a/b**.

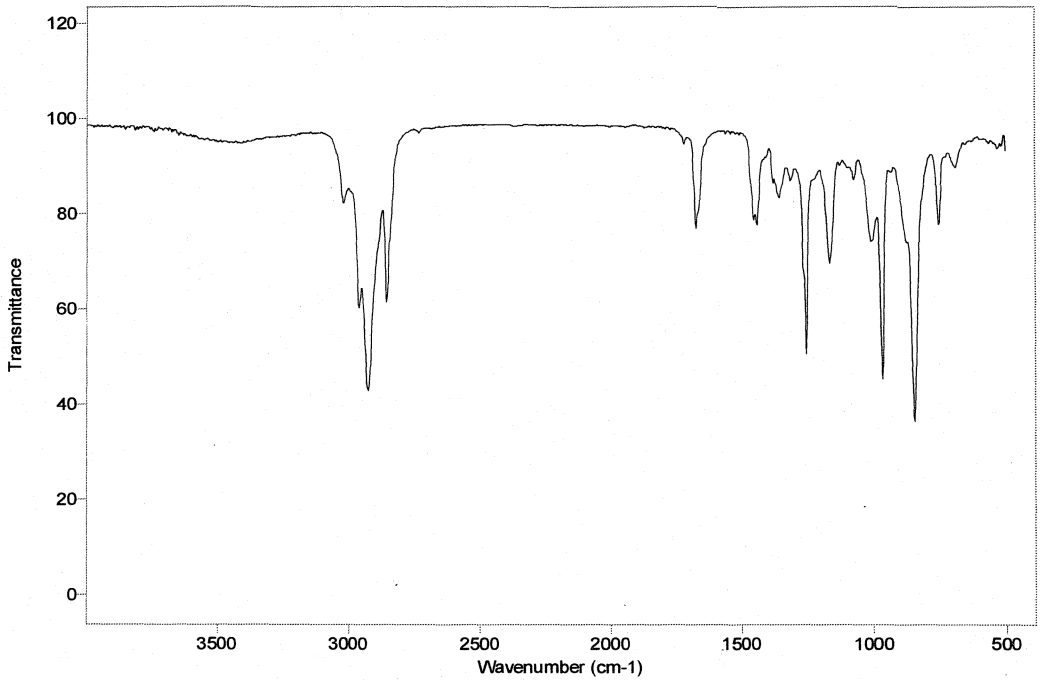


Figure A.1.5 FTIR Spectrum (thin film/NaCl) of Compound **213a/b**.

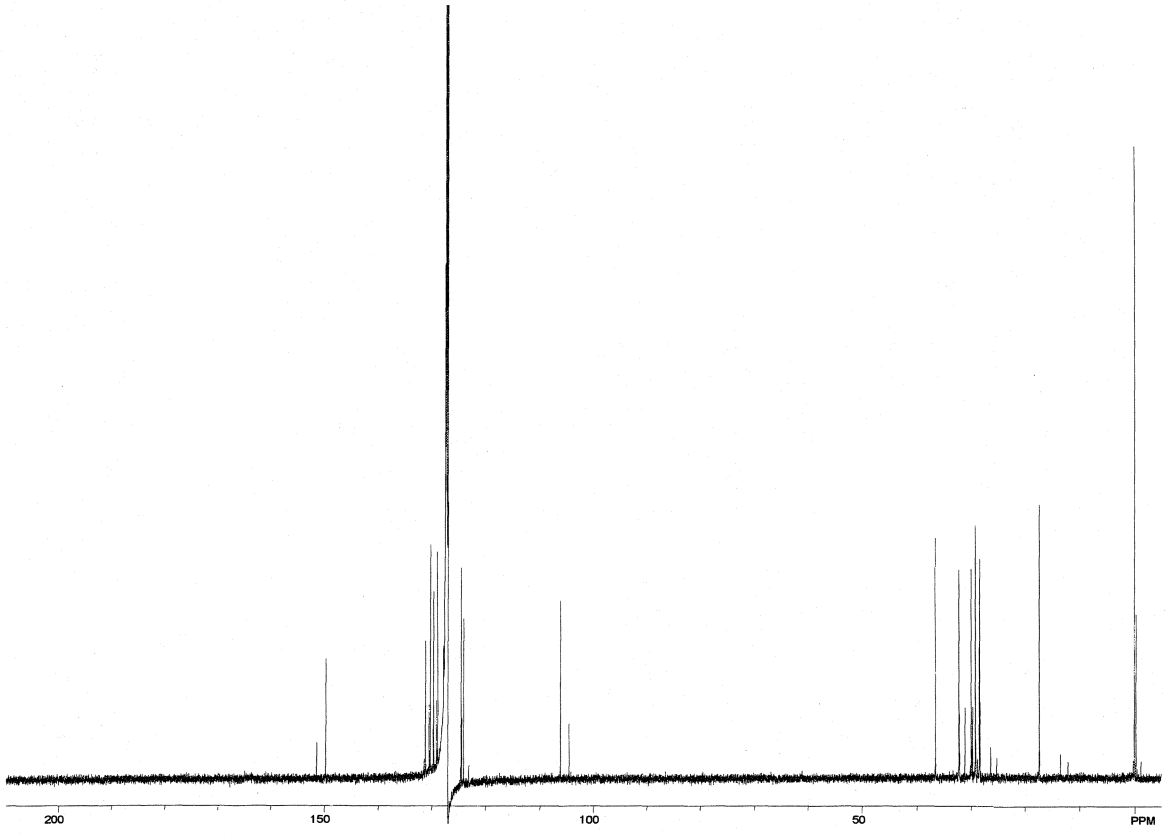


Figure A.1.6 ^{13}C NMR (125 MHz, C_6D_6) of Compound **213a/b**.

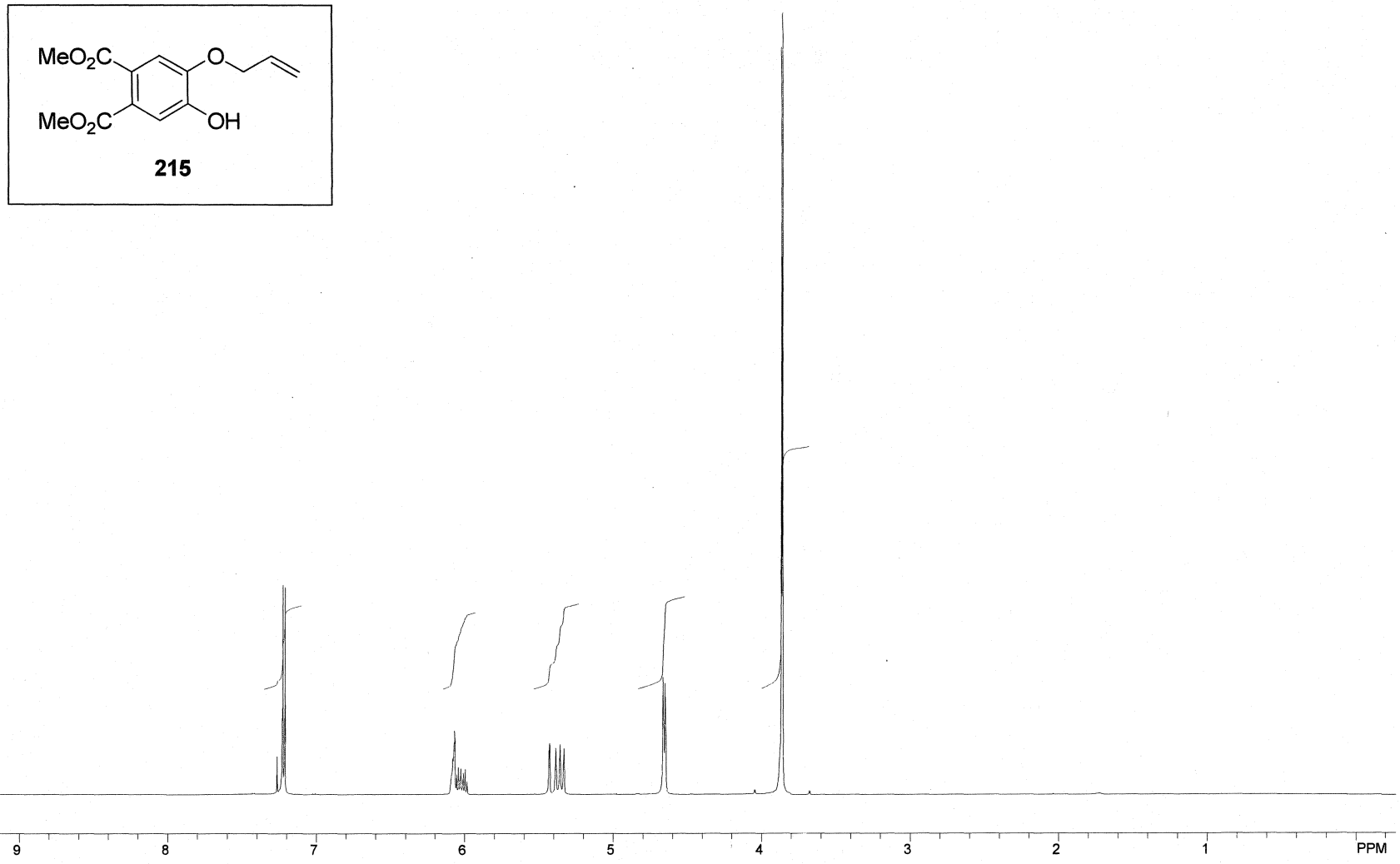


Figure A.1.7 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **215**.

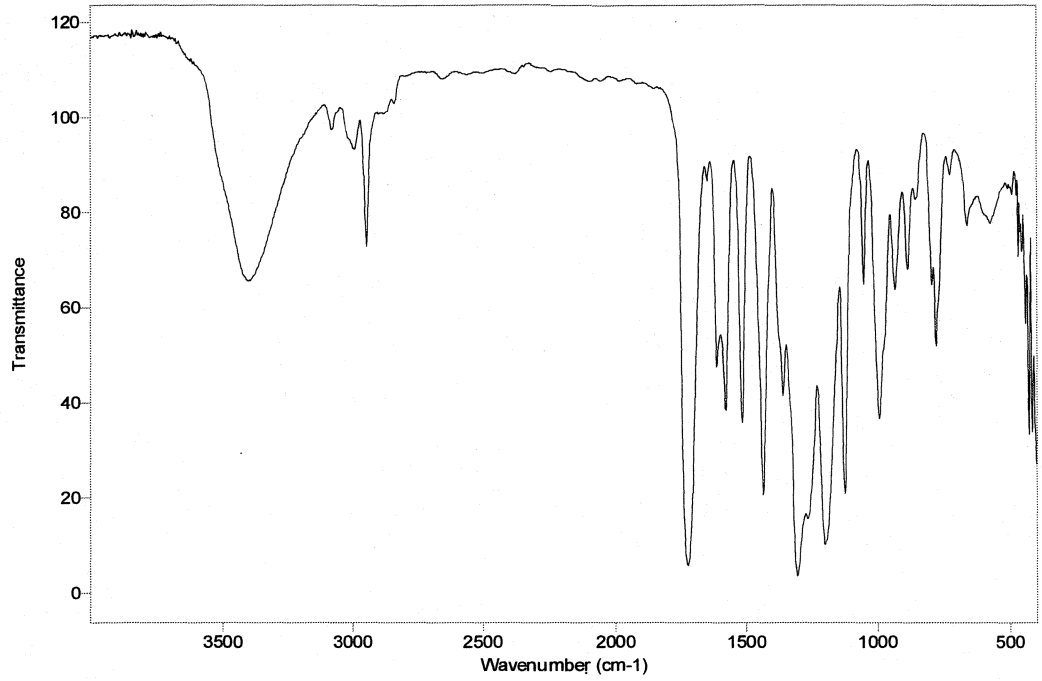


Figure A.1.8 FTIR Spectrum (thin film/NaCl) of Compound **215**.

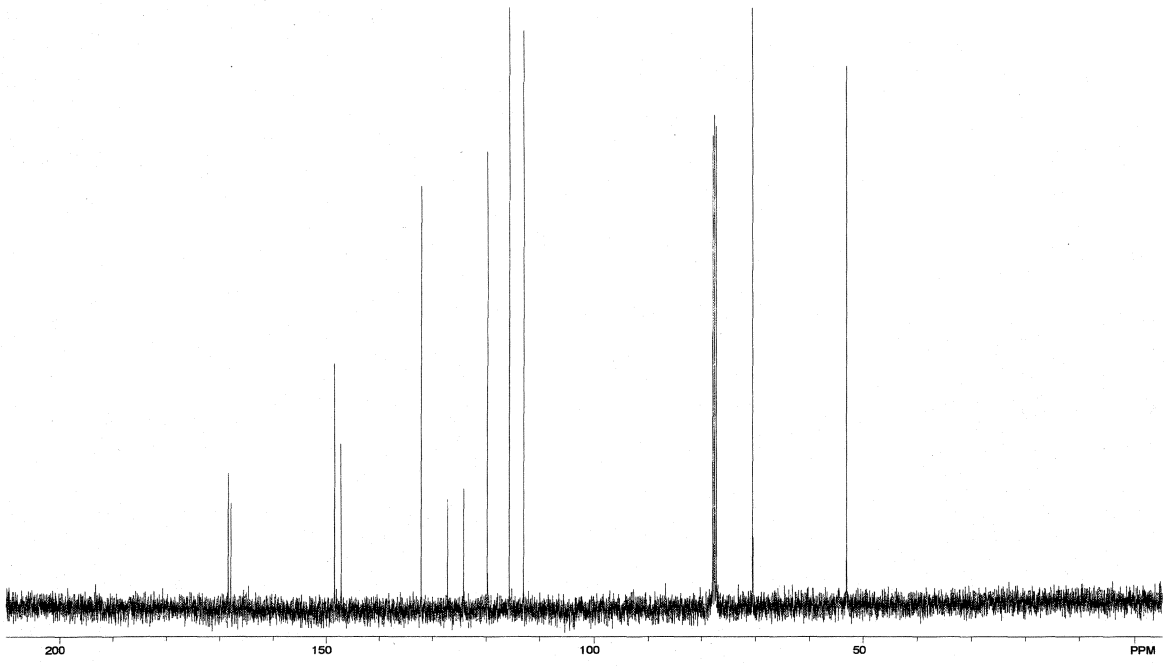


Figure A.1.9 ^{13}C NMR (125 MHz, C_6D_6) of Compound **215**.

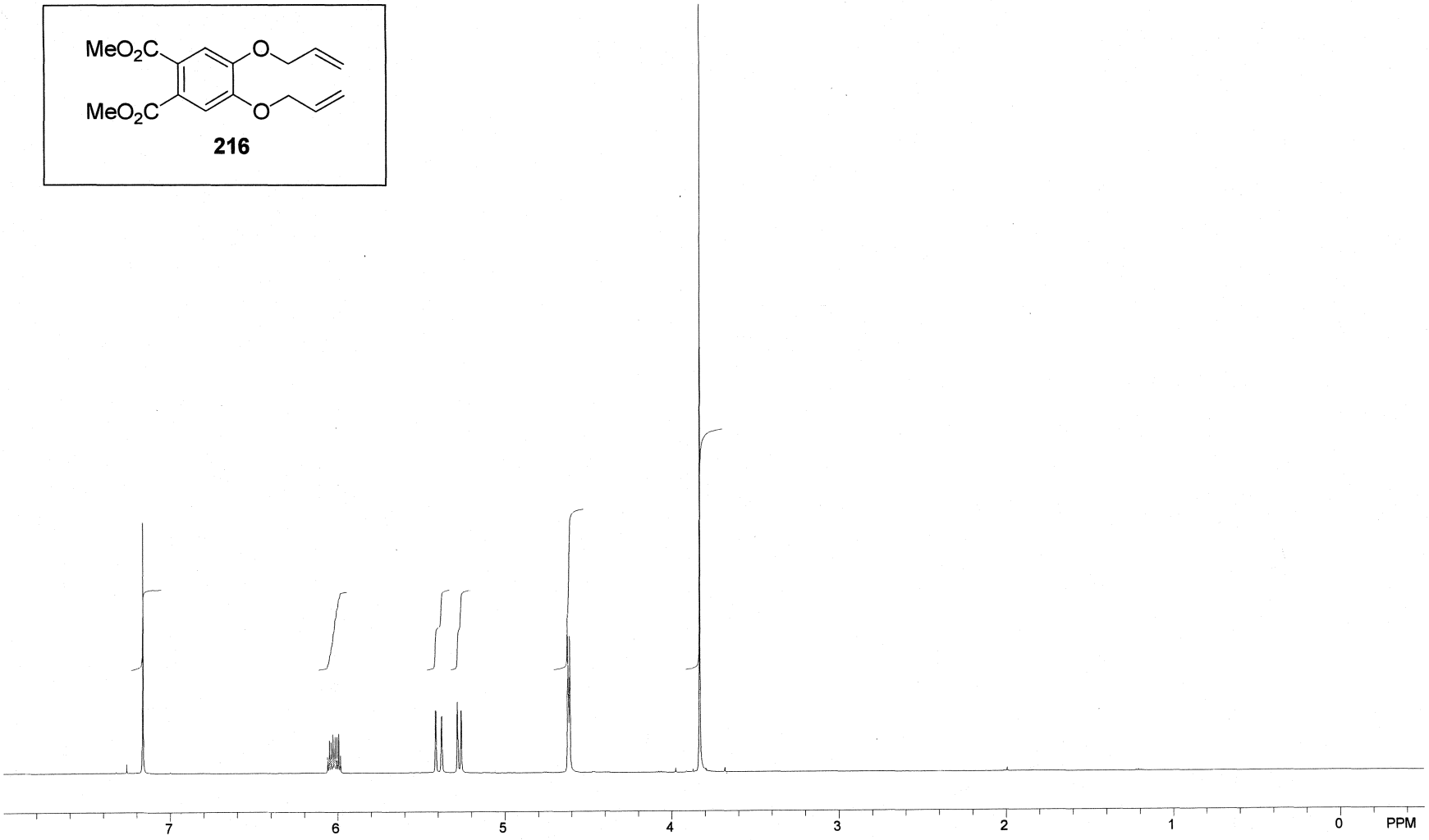


Figure A.1.10 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **216**.

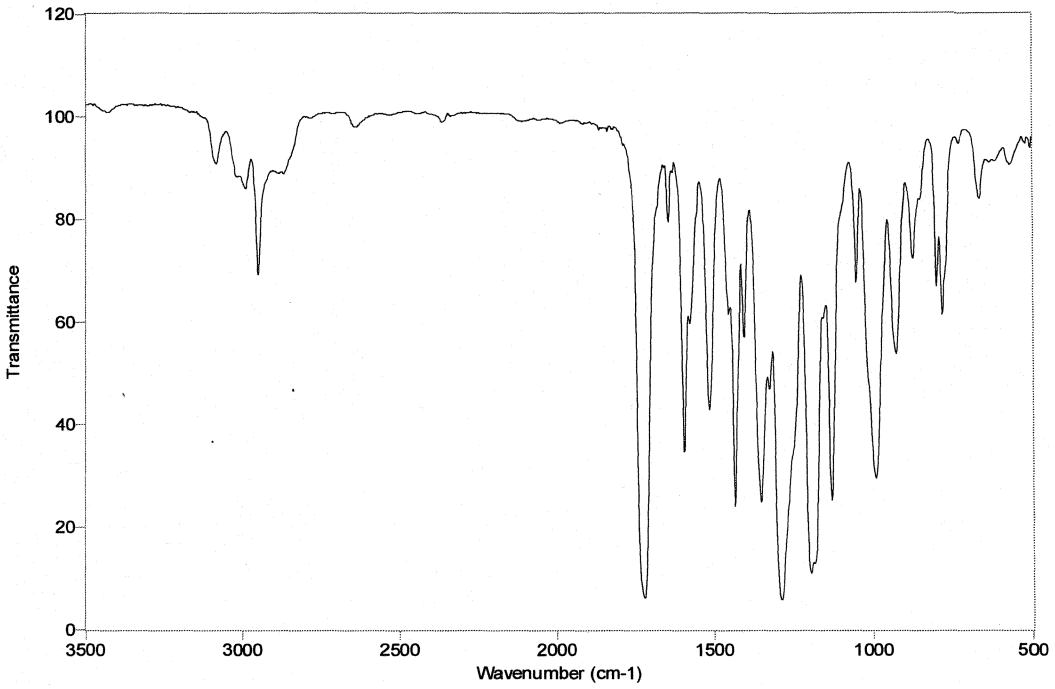


Figure A.1.11 FTIR Spectrum (thin film/NaCl) of Compound **216**.

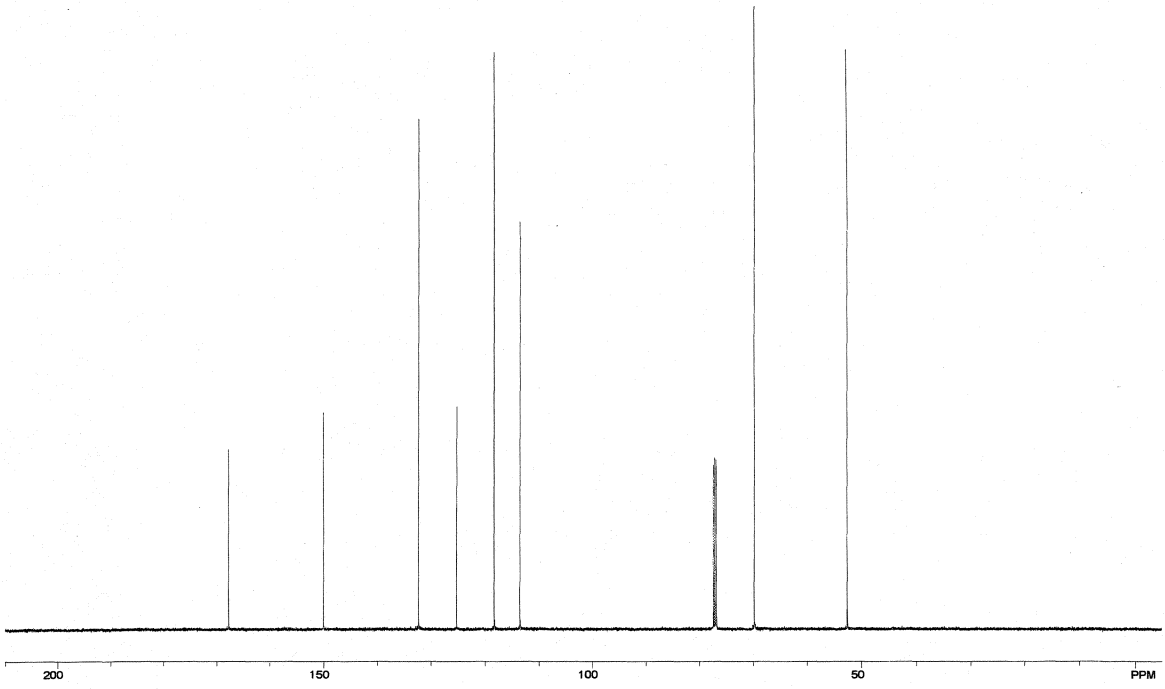


Figure A.1.12 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **216**.

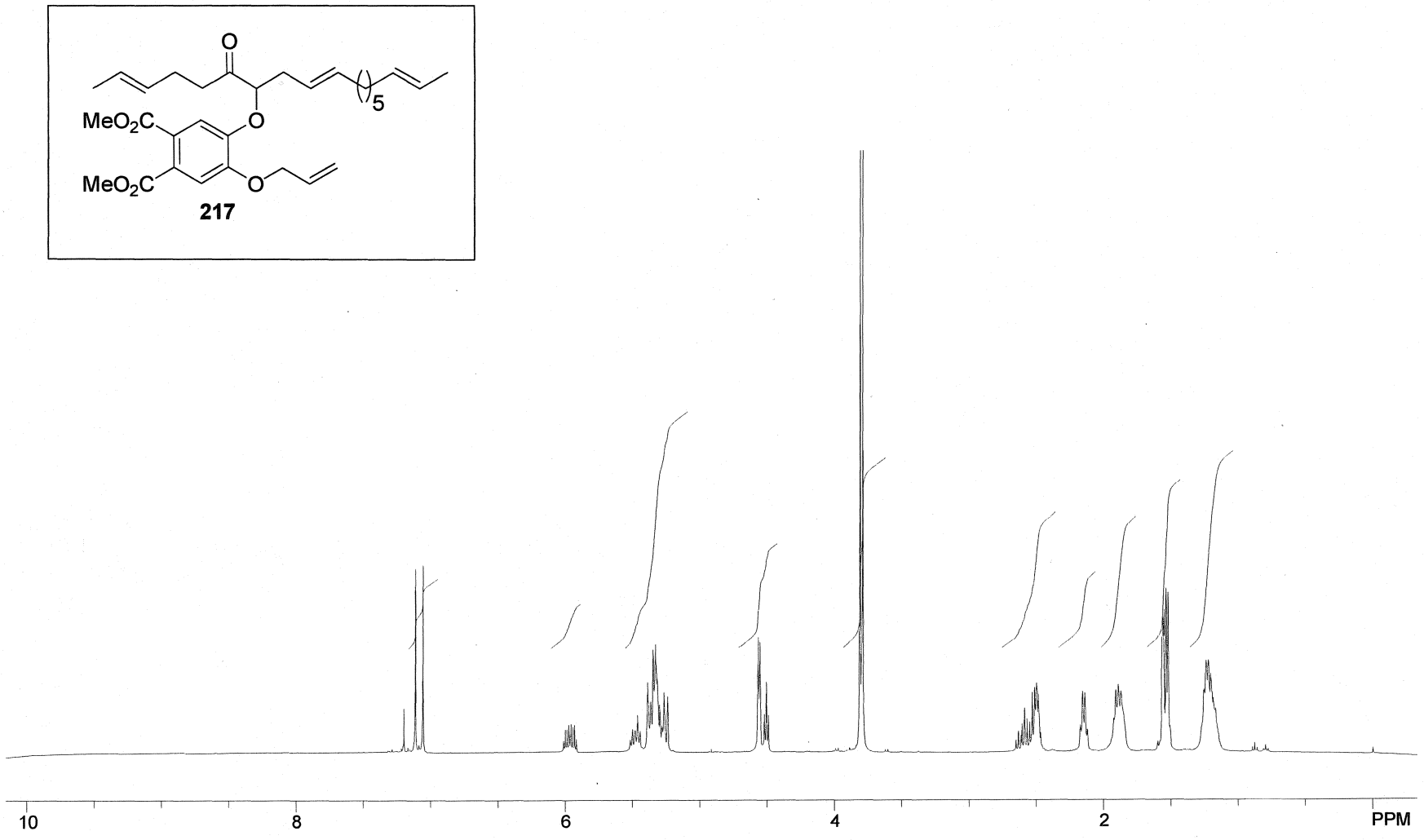


Figure A.1.13 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **217**.

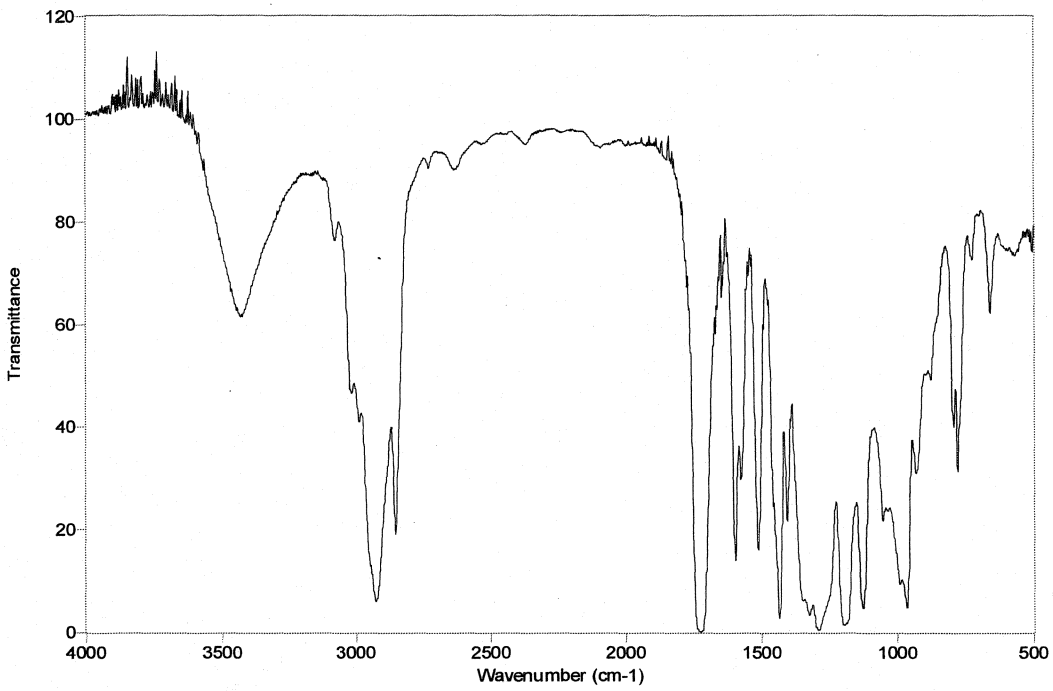


Figure A.14 FTIR Spectrum (thin film/NaCl) of Compound **217**.

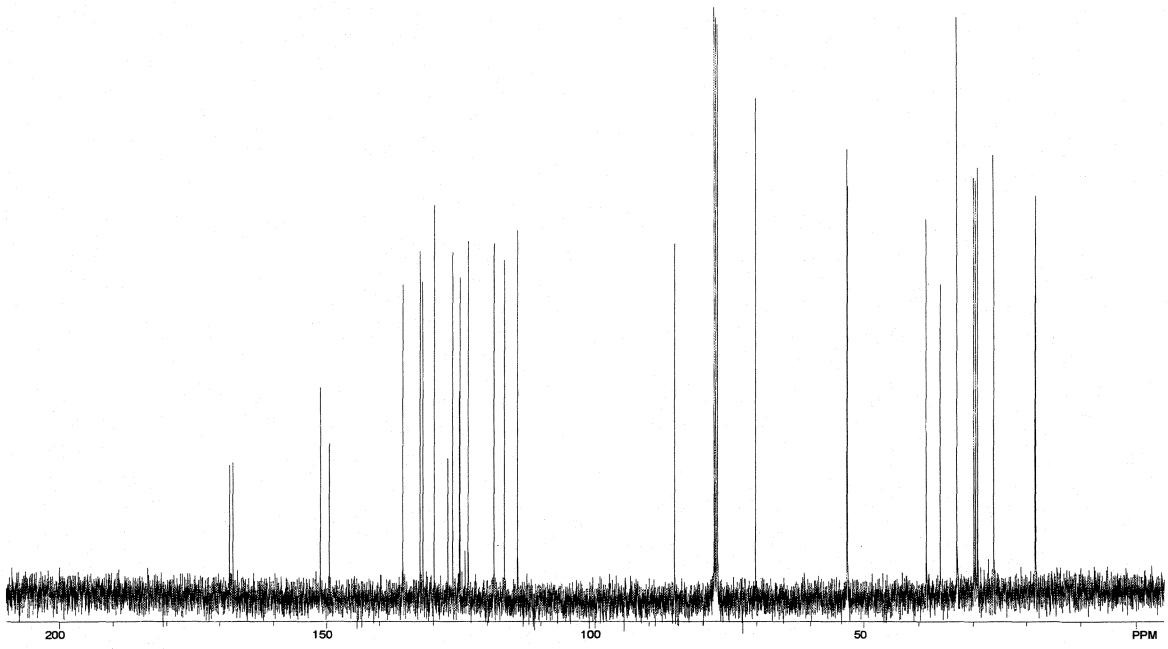


Figure A.1.15 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **217**

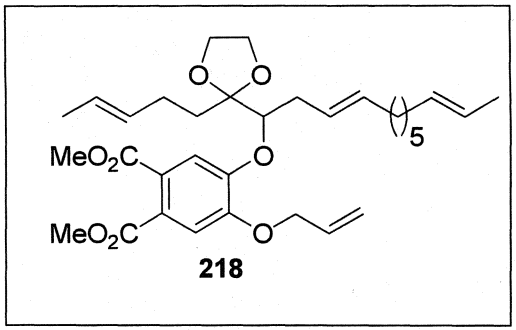


Figure A.1.16 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **218**.

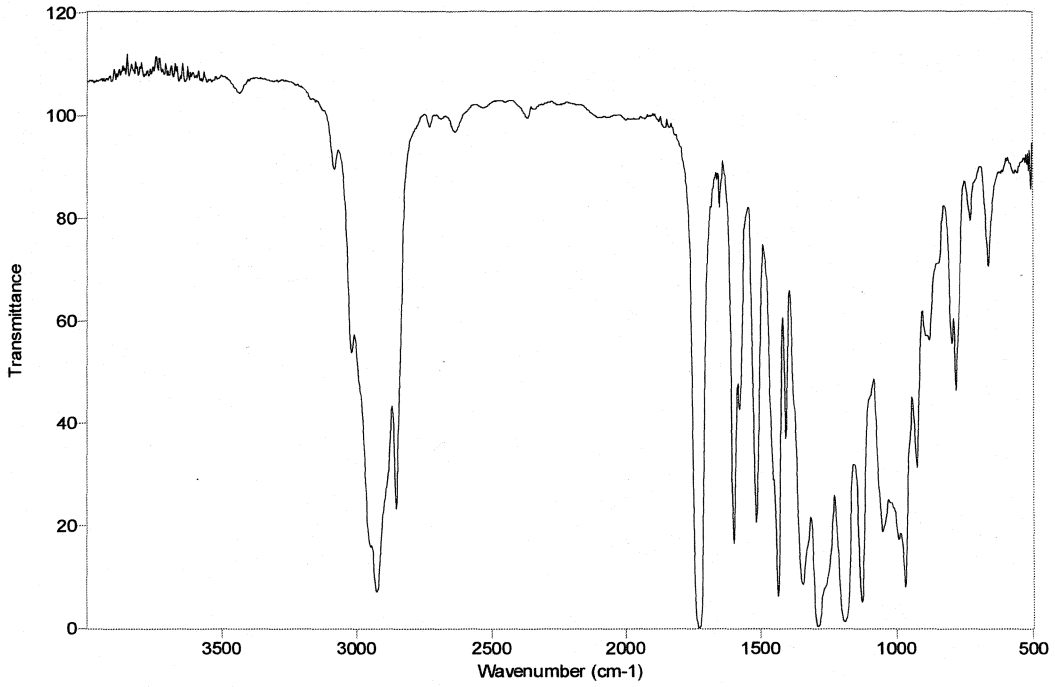


Figure A.1.17 FTIR Spectrum (thin film/NaCl) of Compound **218**.

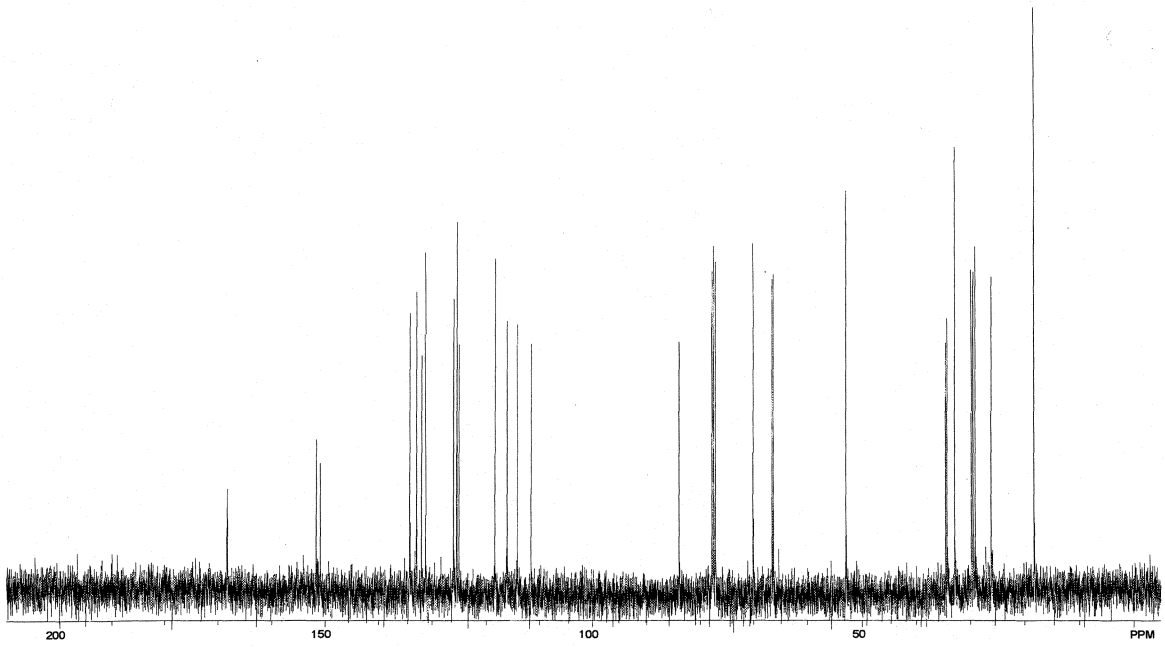


Figure A.1.18 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **218**.

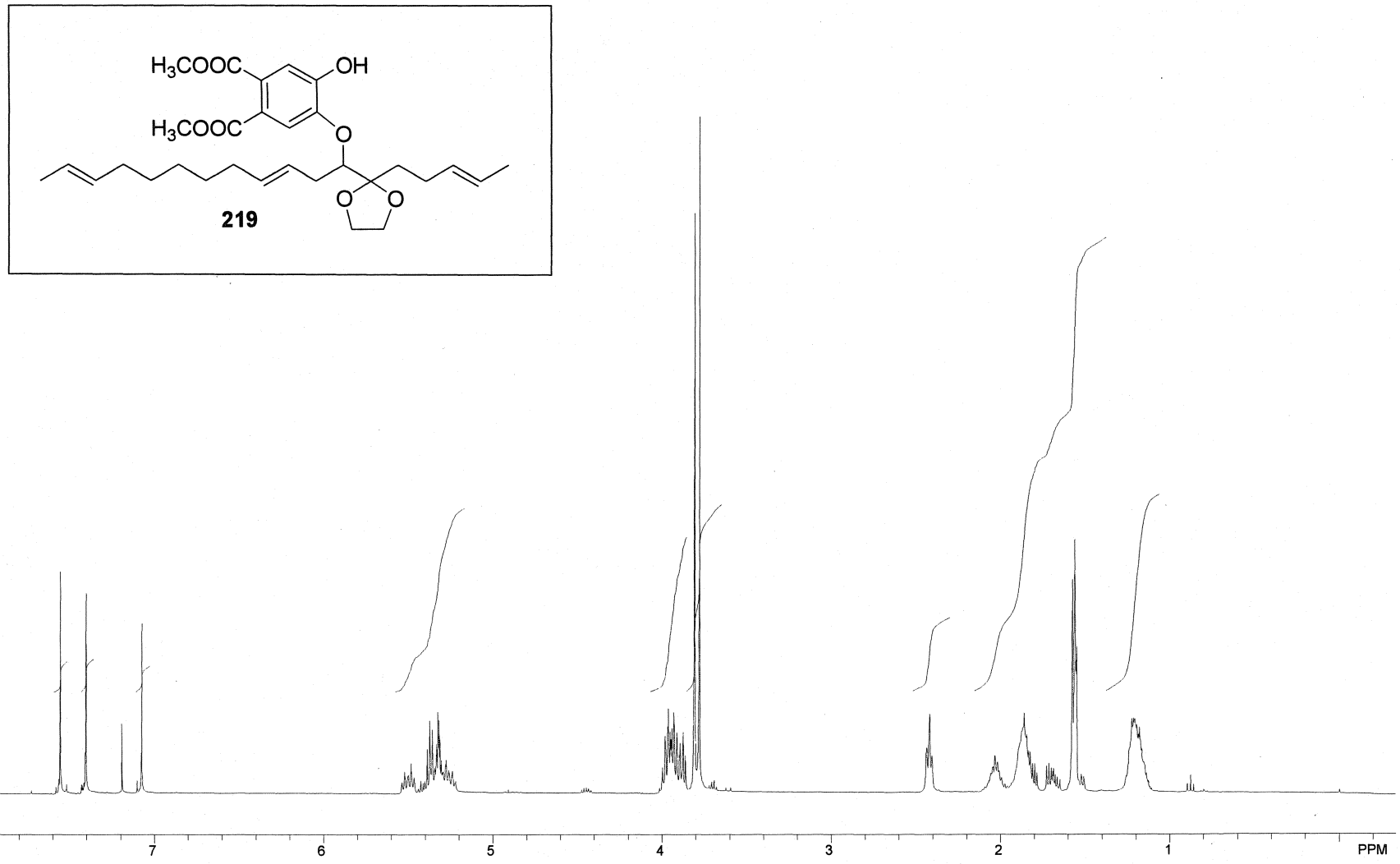


Figure A.1.19 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **219**.

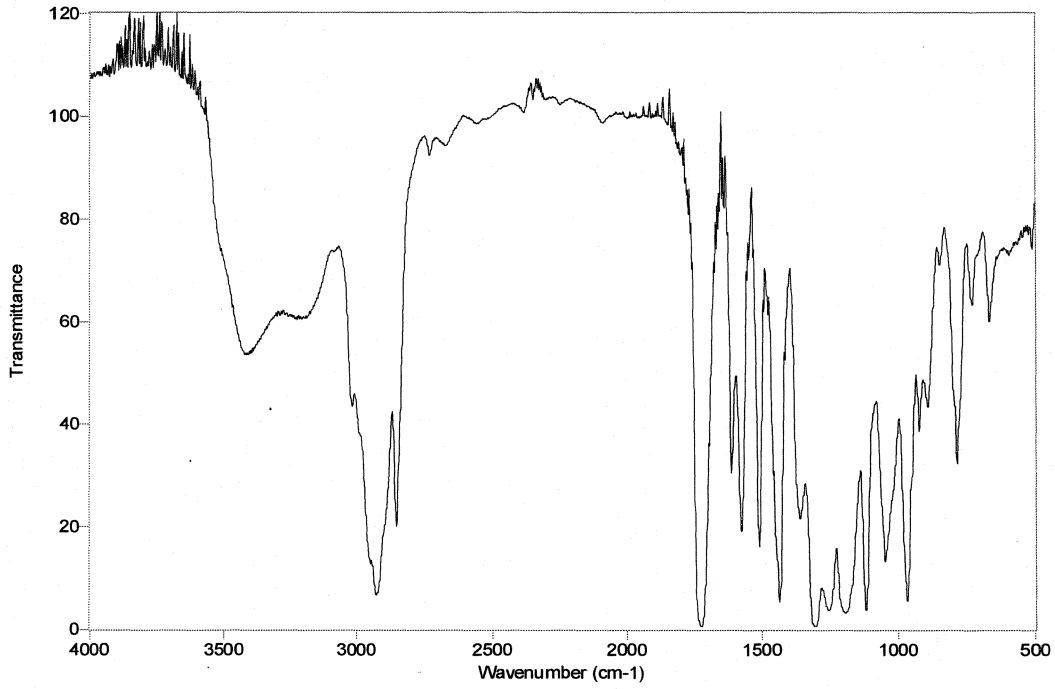


Figure A.1.20 FTIR Spectrum (thin film/NaCl) of Compound **219**.

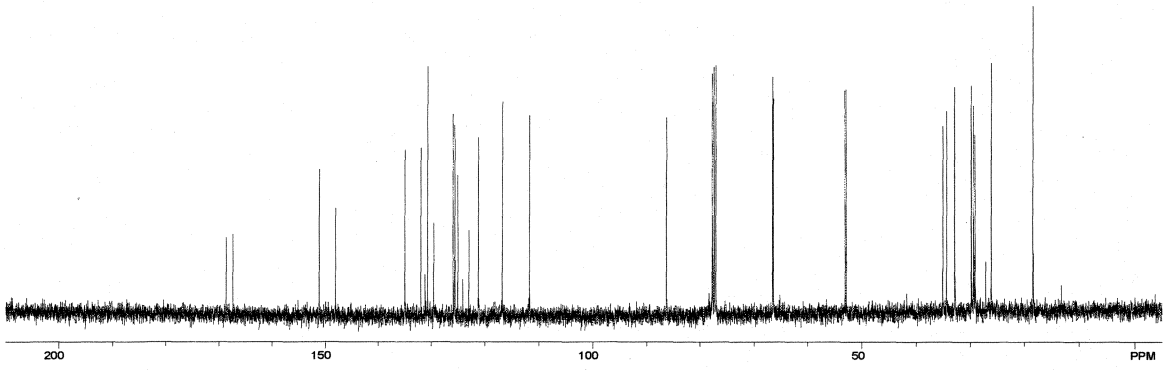
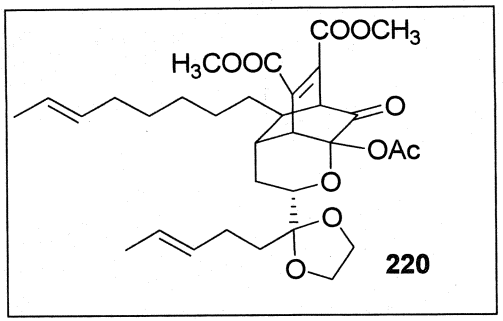


Figure A.1.21 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **219**.



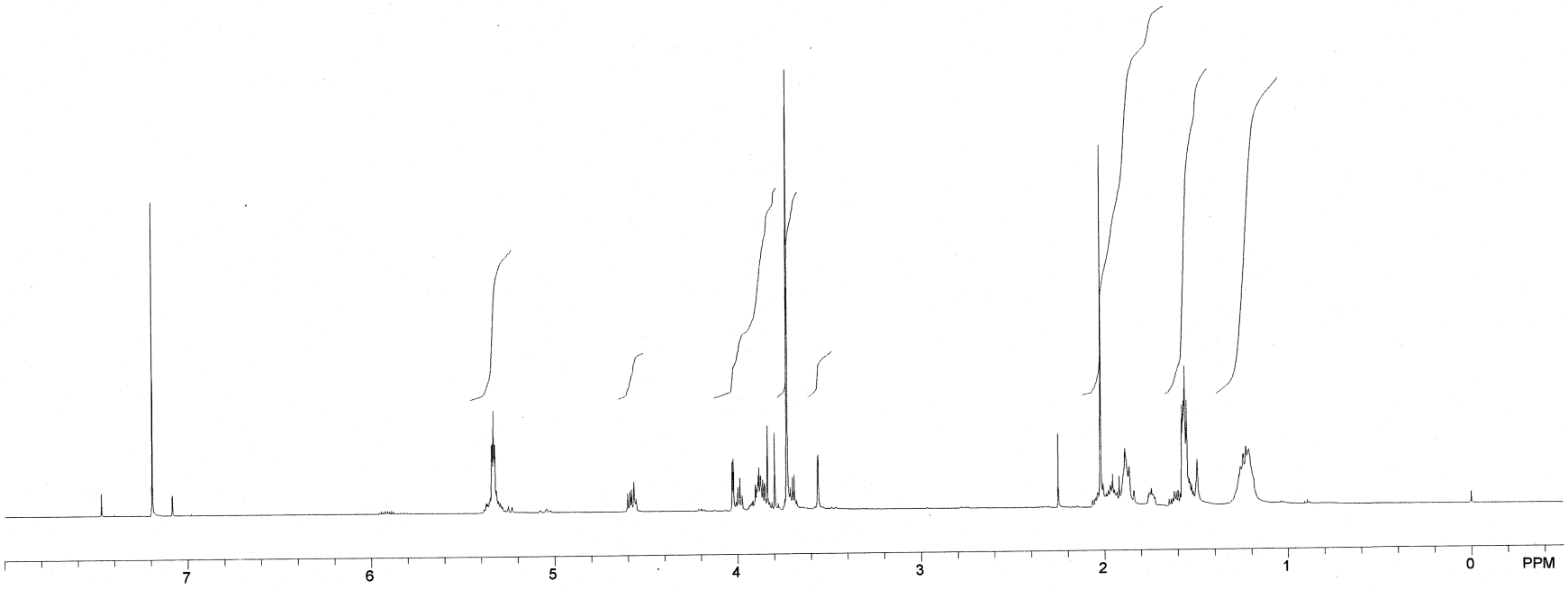


Figure A.1.22 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **220**.

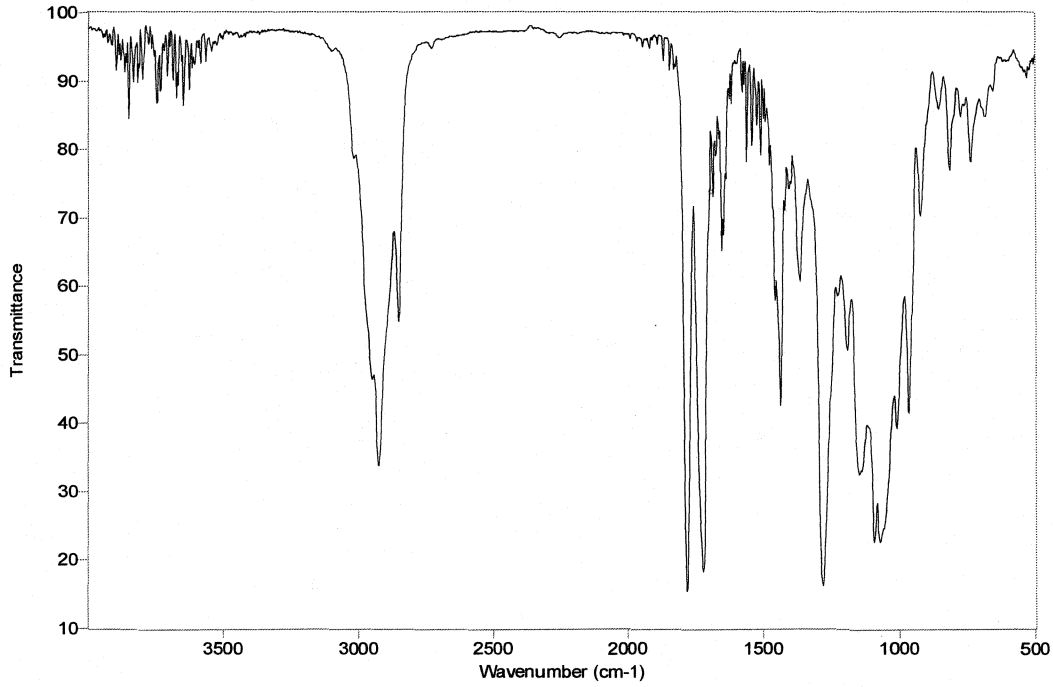


Figure A.1.23 FTIR Spectrum (thin film/NaCl) of Compound **220**.

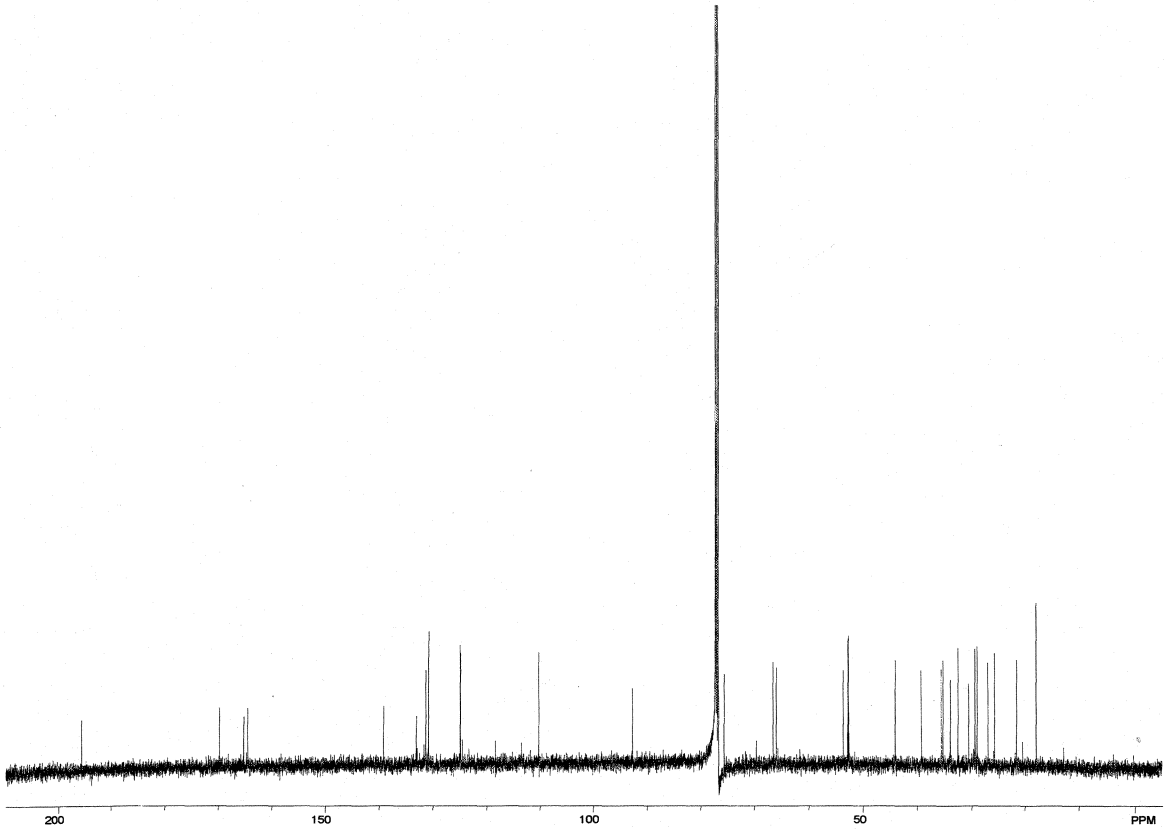


Figure A.1.24 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **220.**

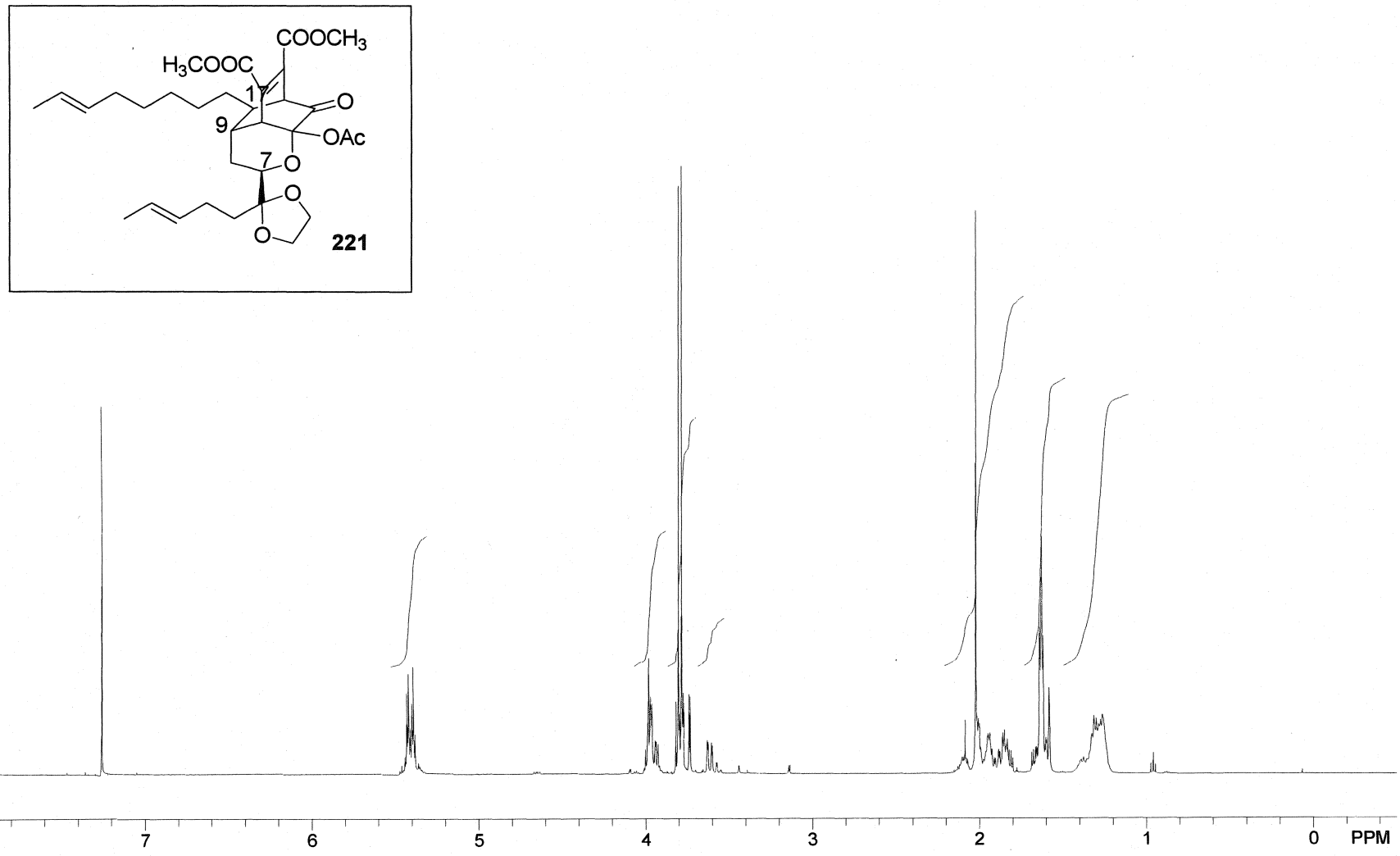


Figure A.1.25 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **221**.

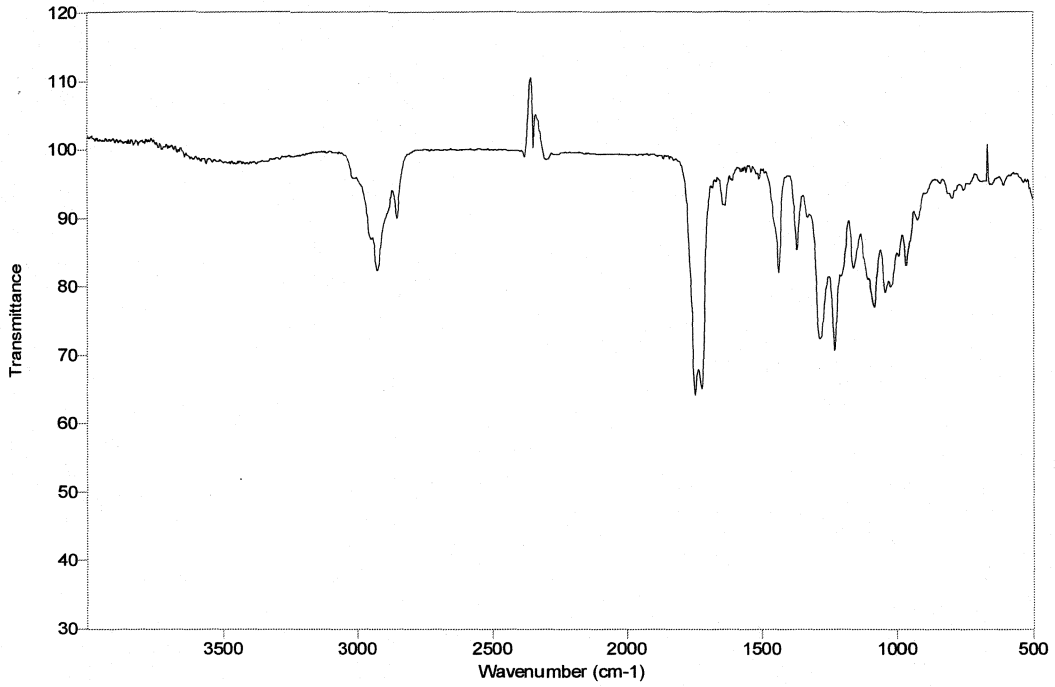


Figure A.1.26 FTIR Spectrum (thin film/NaCl) of Compound **221**.

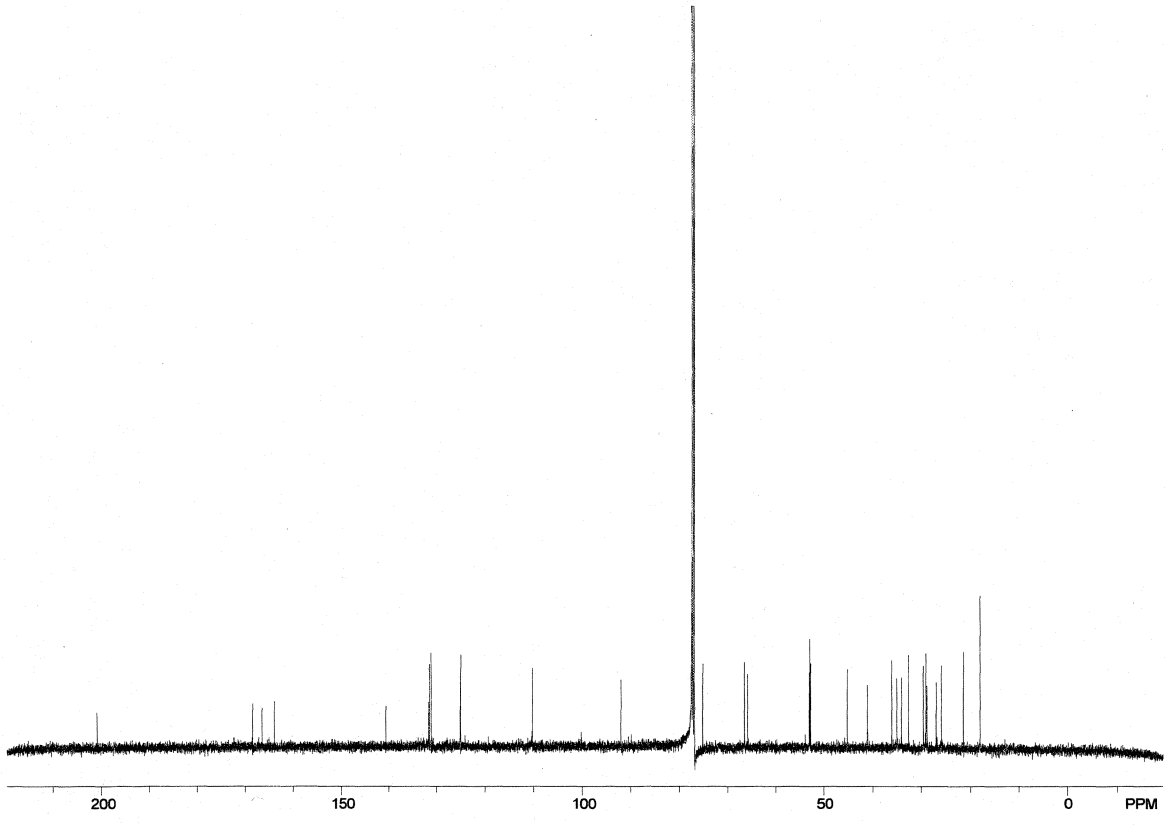


Figure A.1.27 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **221**.

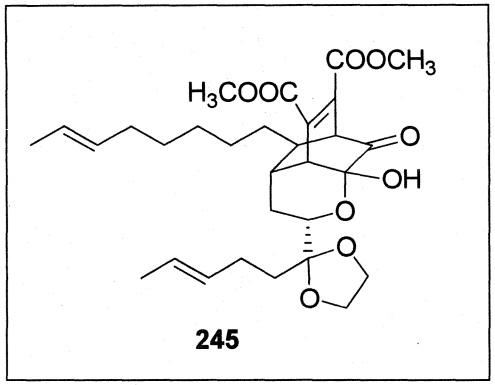


Figure A.1.28 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **245**.

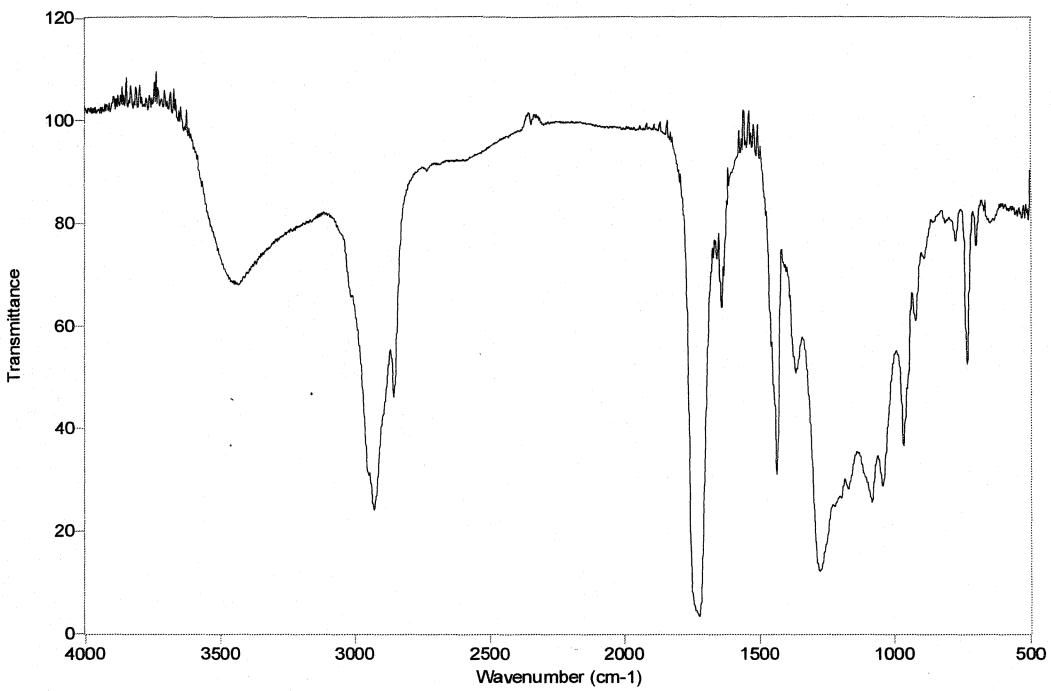


Figure A.1.29 FTIR Spectrum (thin film/NaCl) of Compound **245**.

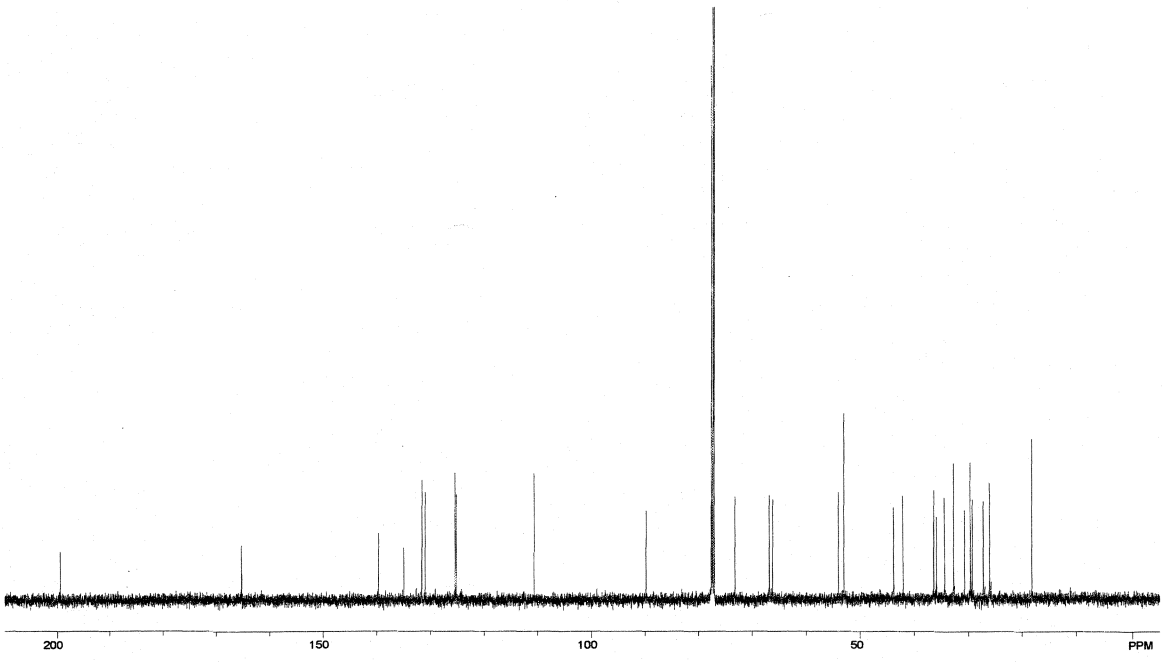


Figure A.1.30 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **245**.

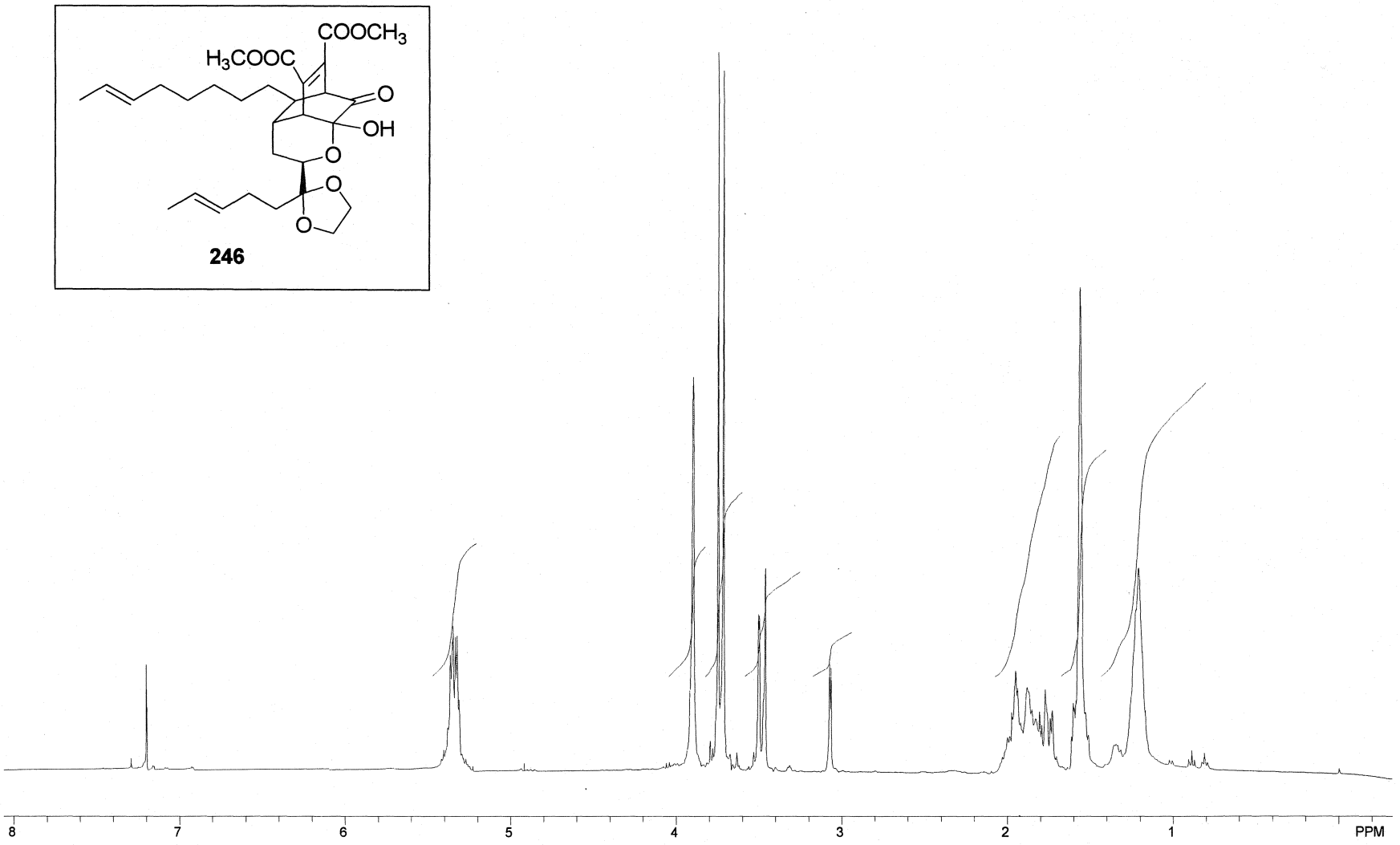


Figure A.1.31 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **246**.

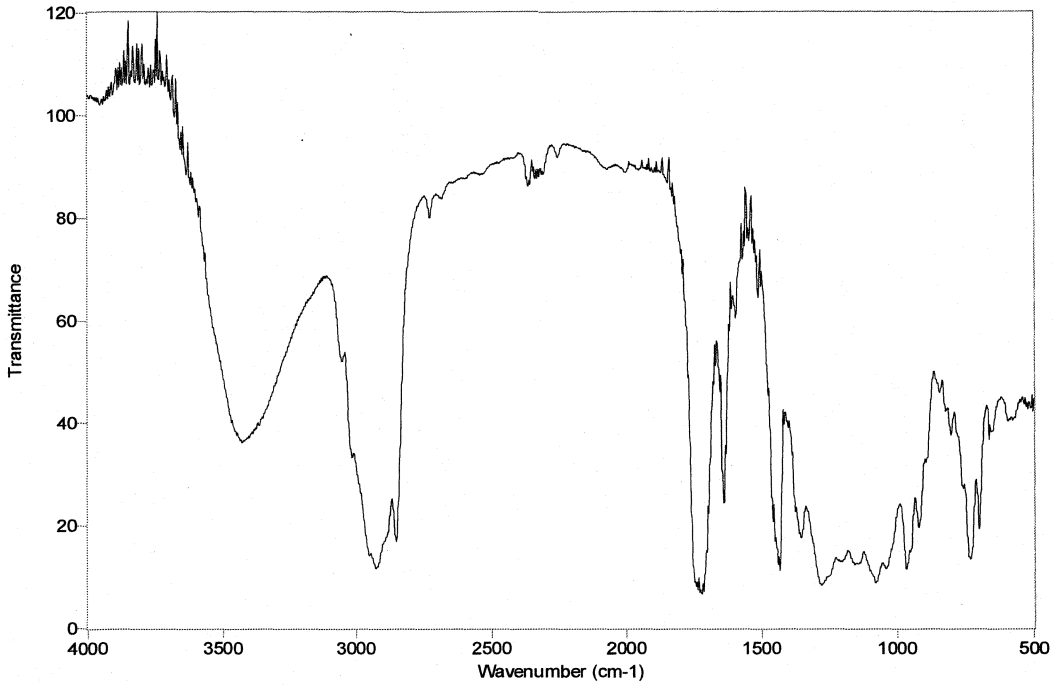


Figure A.1.32 FTIR Spectrum (thin film/NaCl) of Compound **246**.

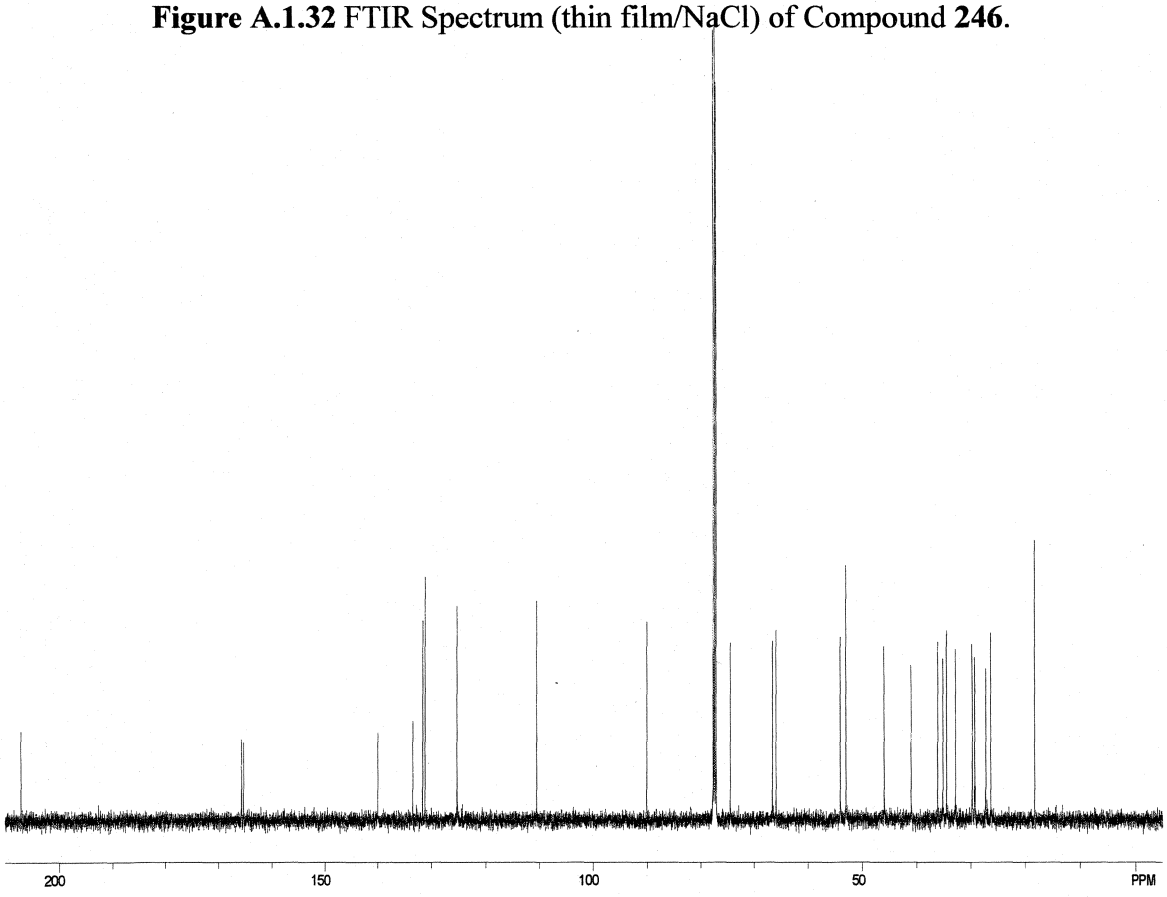


Figure A.1.33 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **246**.

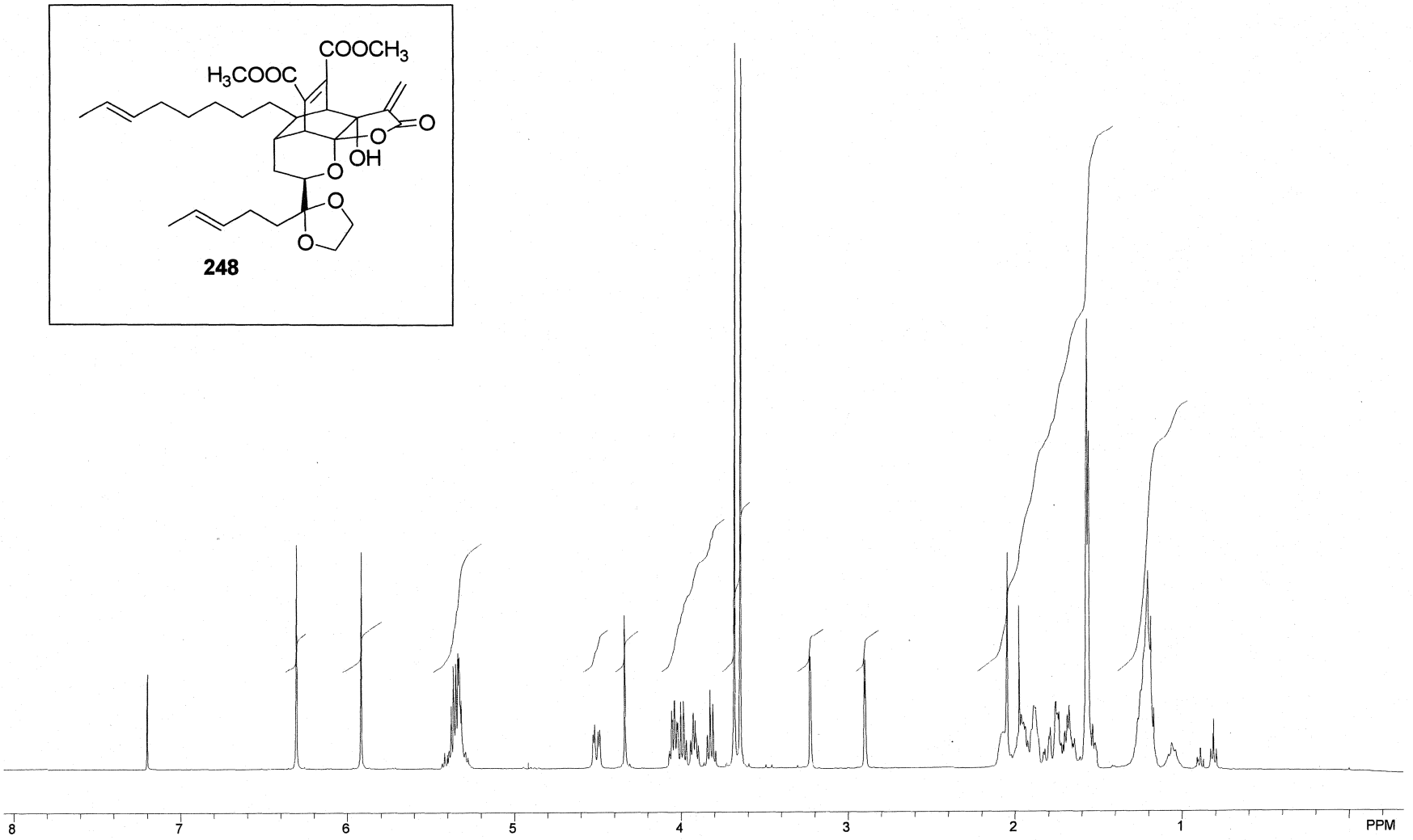


Figure A.1.34 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **248**.

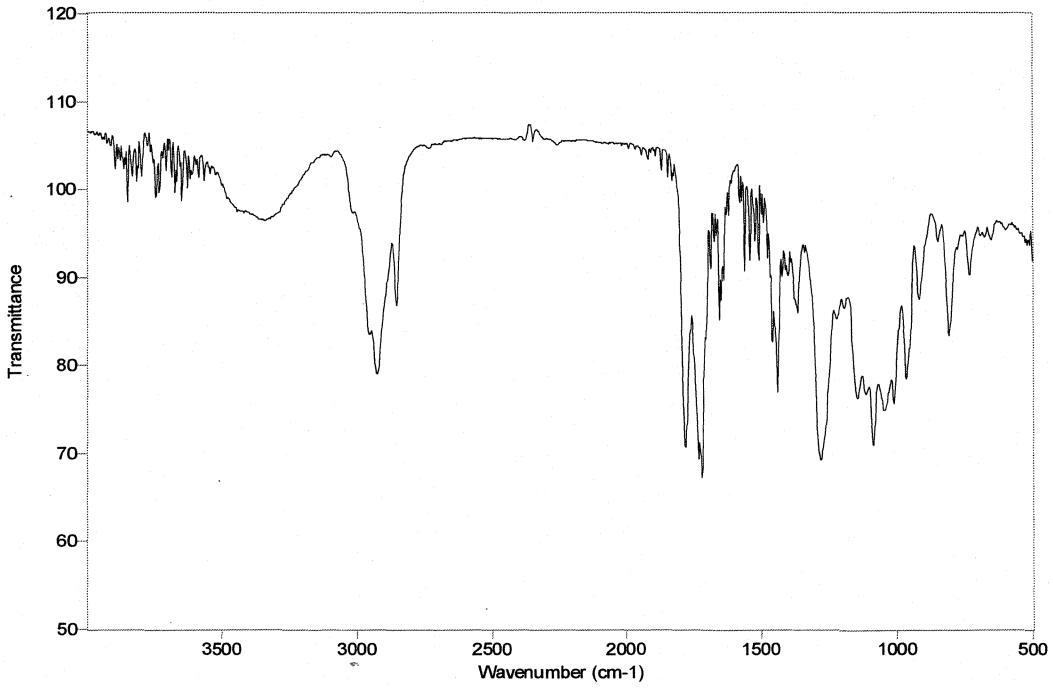


Figure A.1.35 FTIR Spectrum (thin film/NaCl) of Compound **248**.

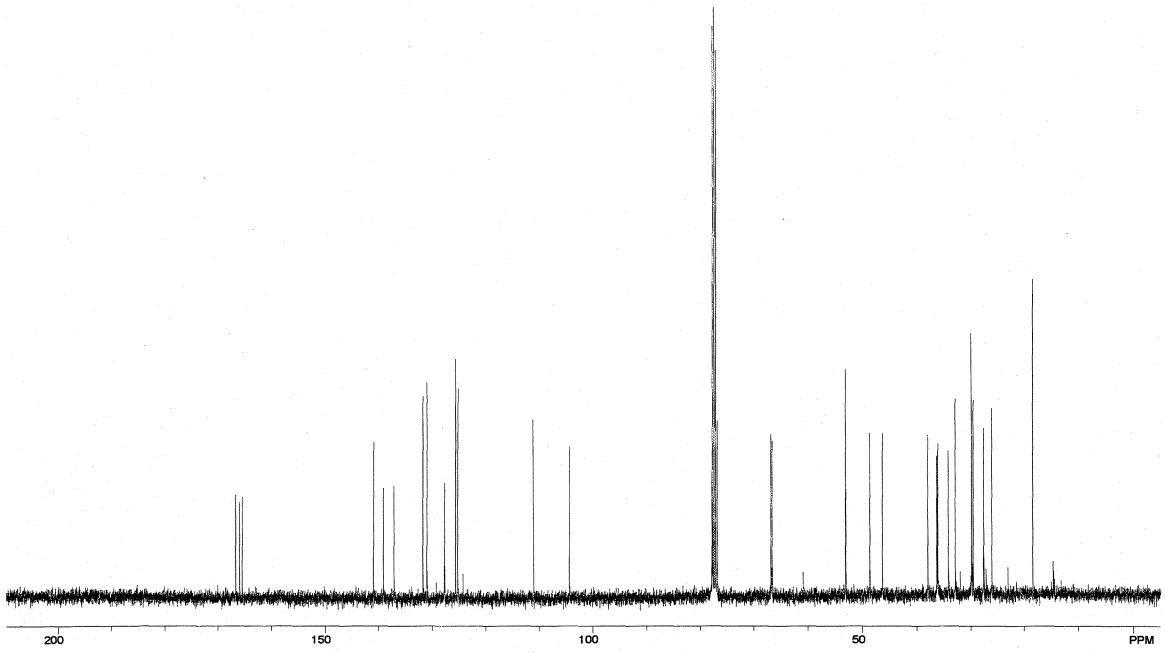
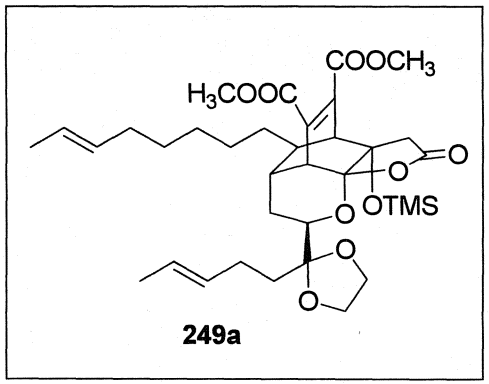


Figure A.1.36 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **248**.



249a

Figure A.1.37 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **249a**.

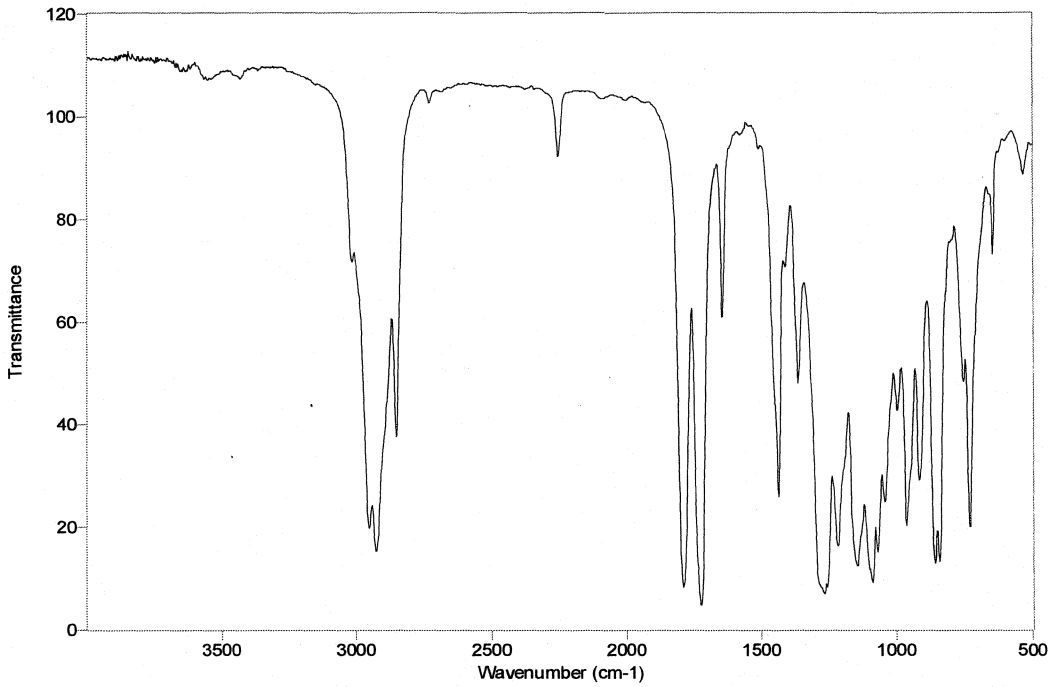


Figure A.1.38 FTIR Spectrum (thin film/NaCl) of Compound **249a**.

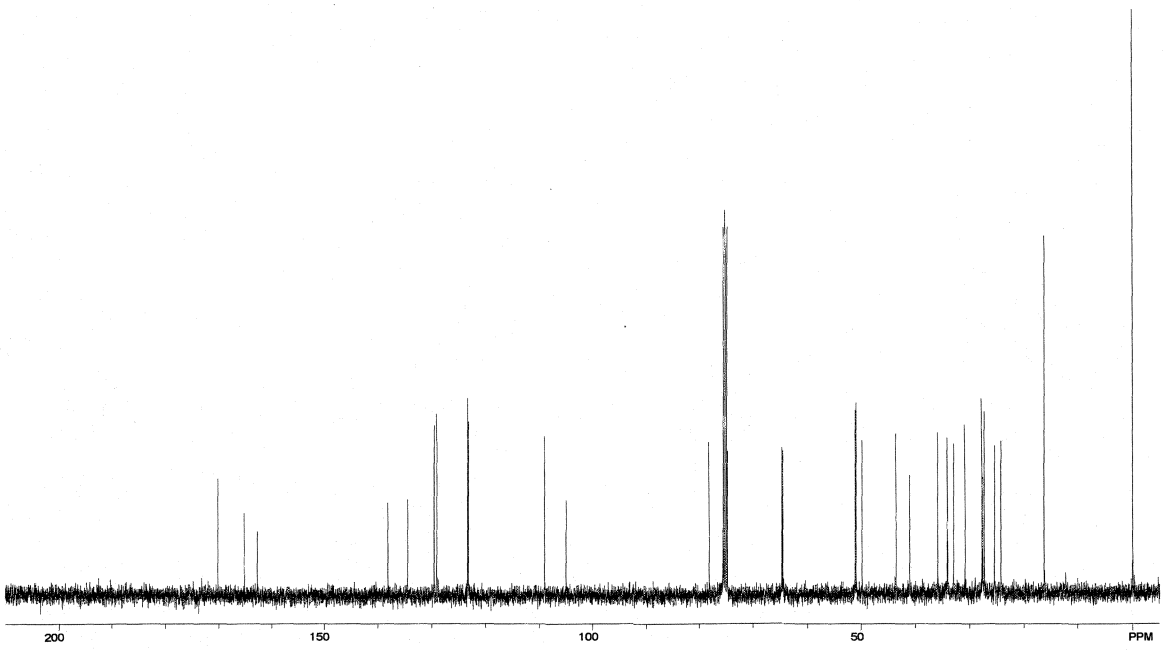
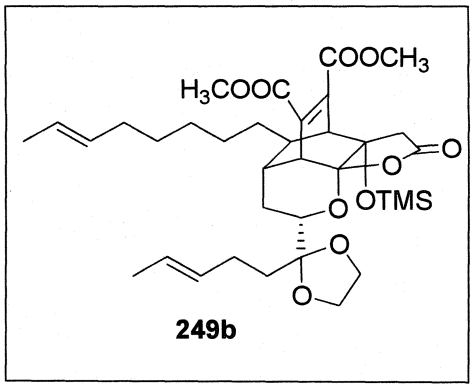


Figure A.1.39 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **249a**.



249b

Figure A.1.40 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **249b**.

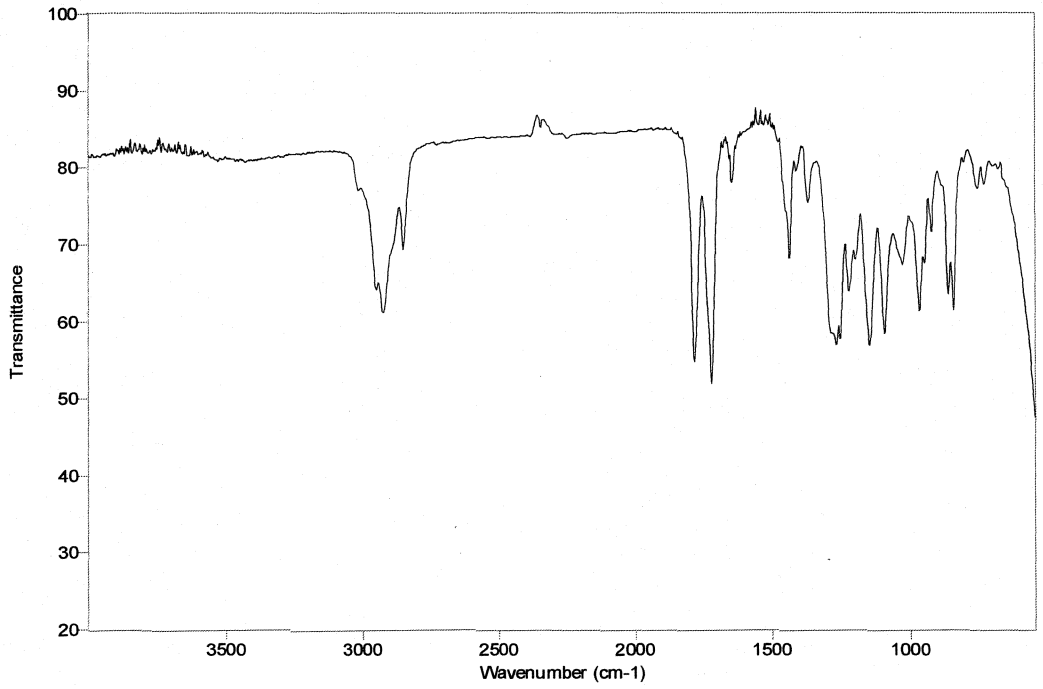


Figure A.1.41 FTIR Spectrum (thin film/NaCl) of Compound **249b**.

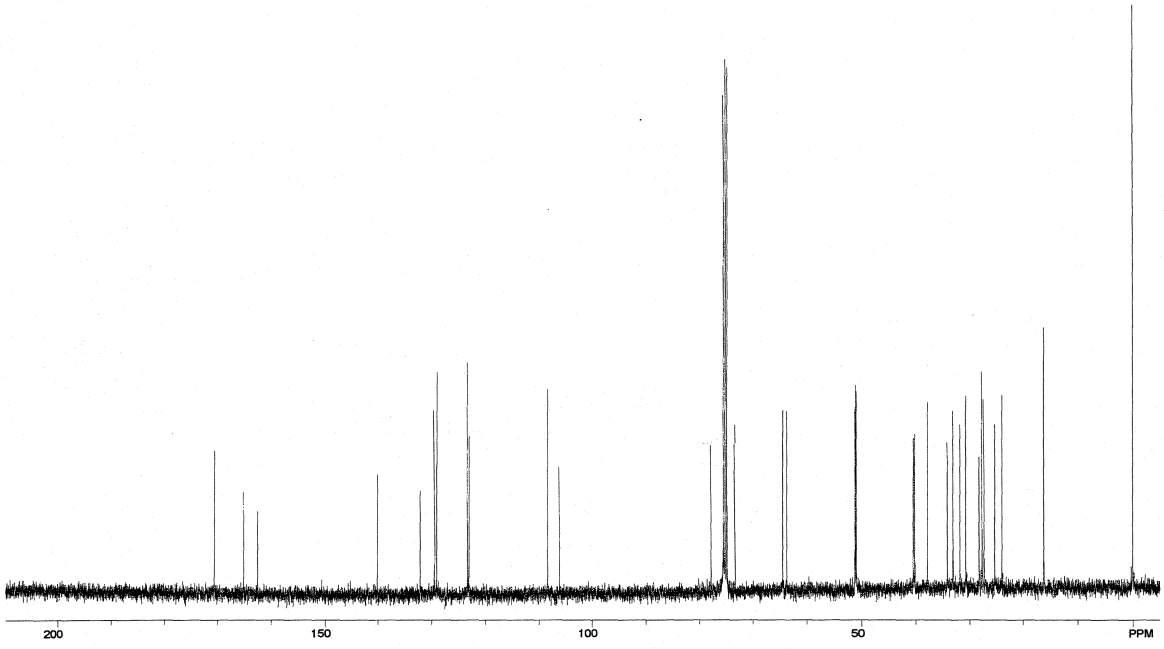


Figure A.1.42 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **249b**.

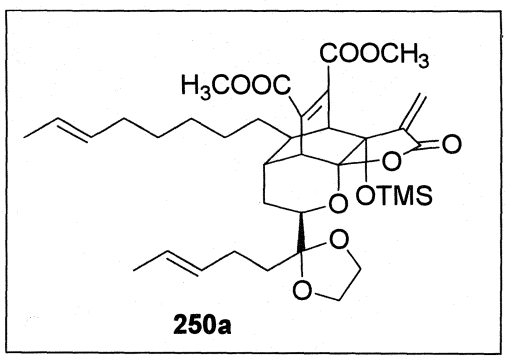


Figure A.1.43 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **250a**.

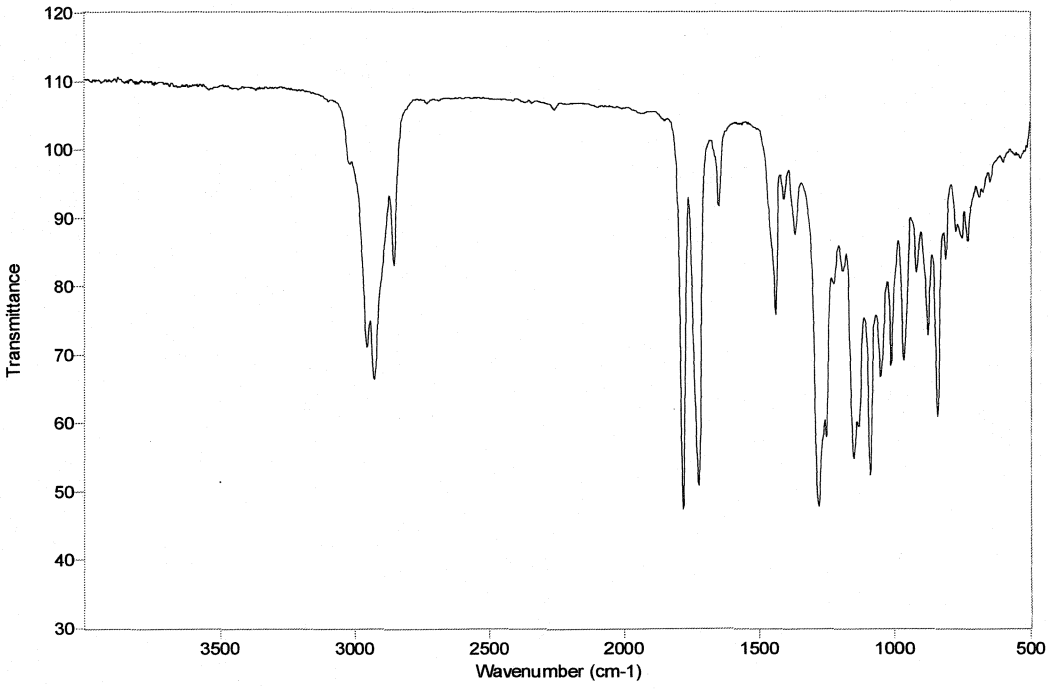


Figure A.1.44 FTIR Spectrum (thin film/NaCl) of Compound **250a**.

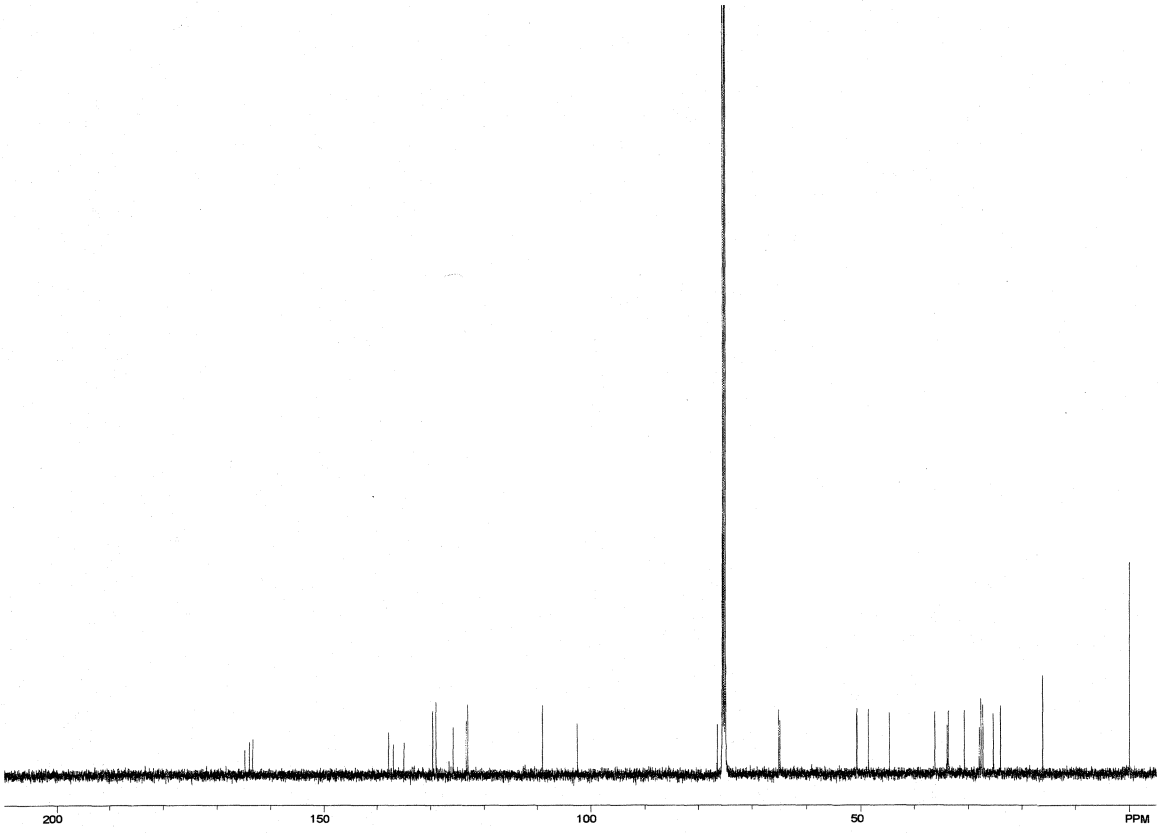


Figure A.1.45 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **250a**.

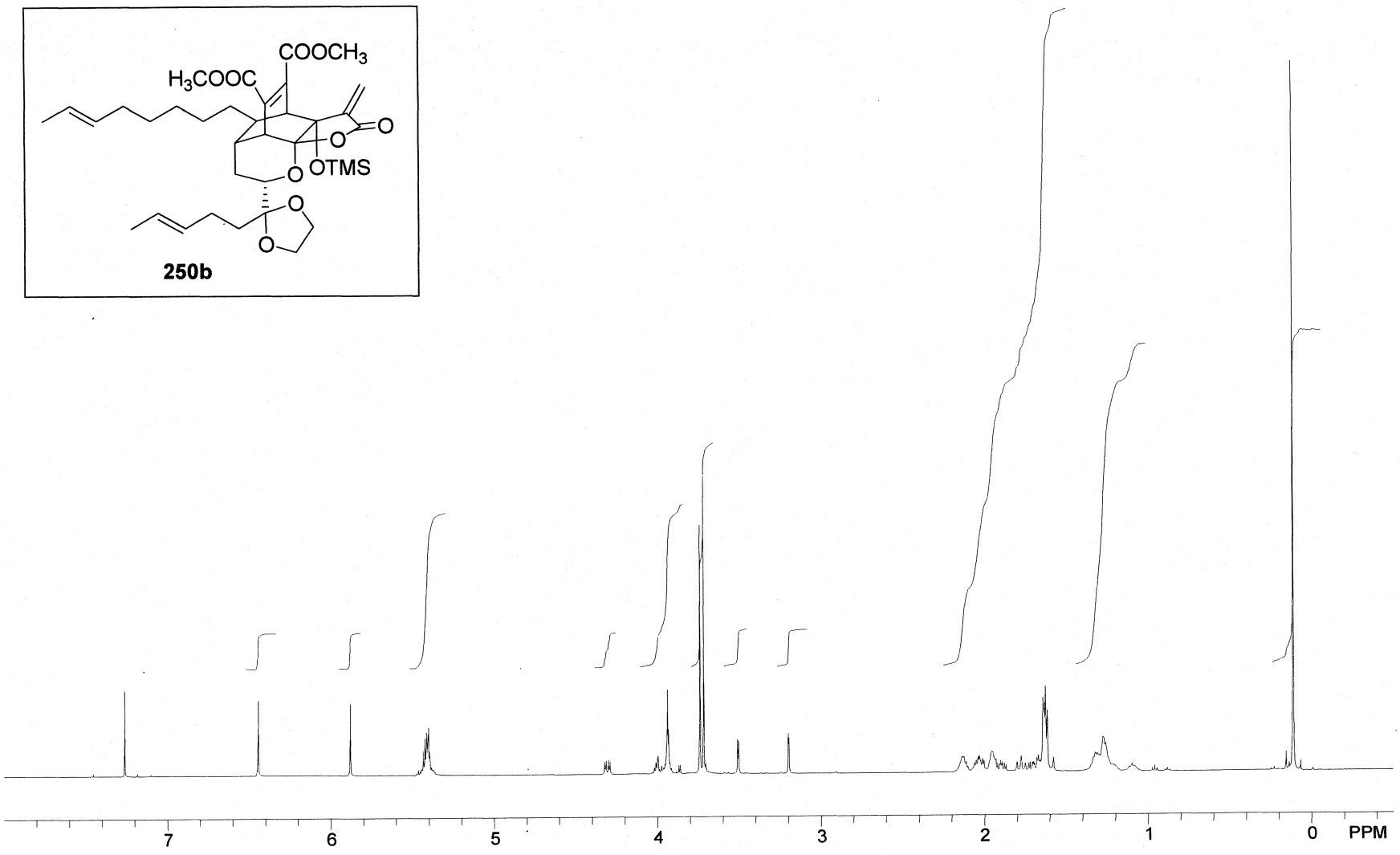


Figure A.1.46 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **250b**.

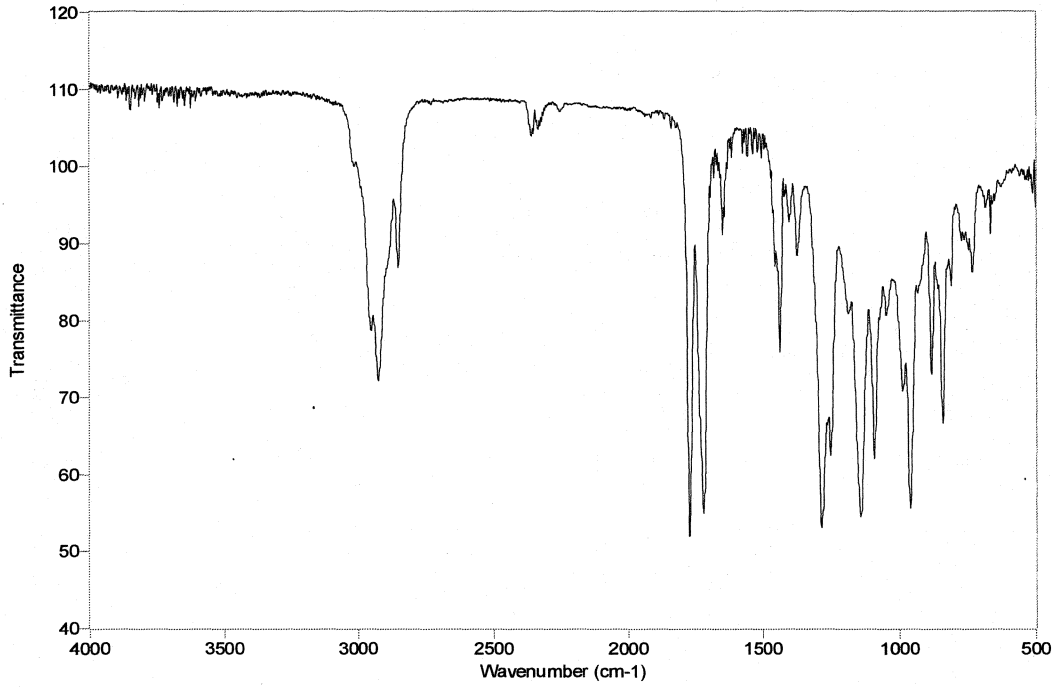


Figure A.1.47 FTIR Spectrum (thin film/NaCl) of Compound **250b**.

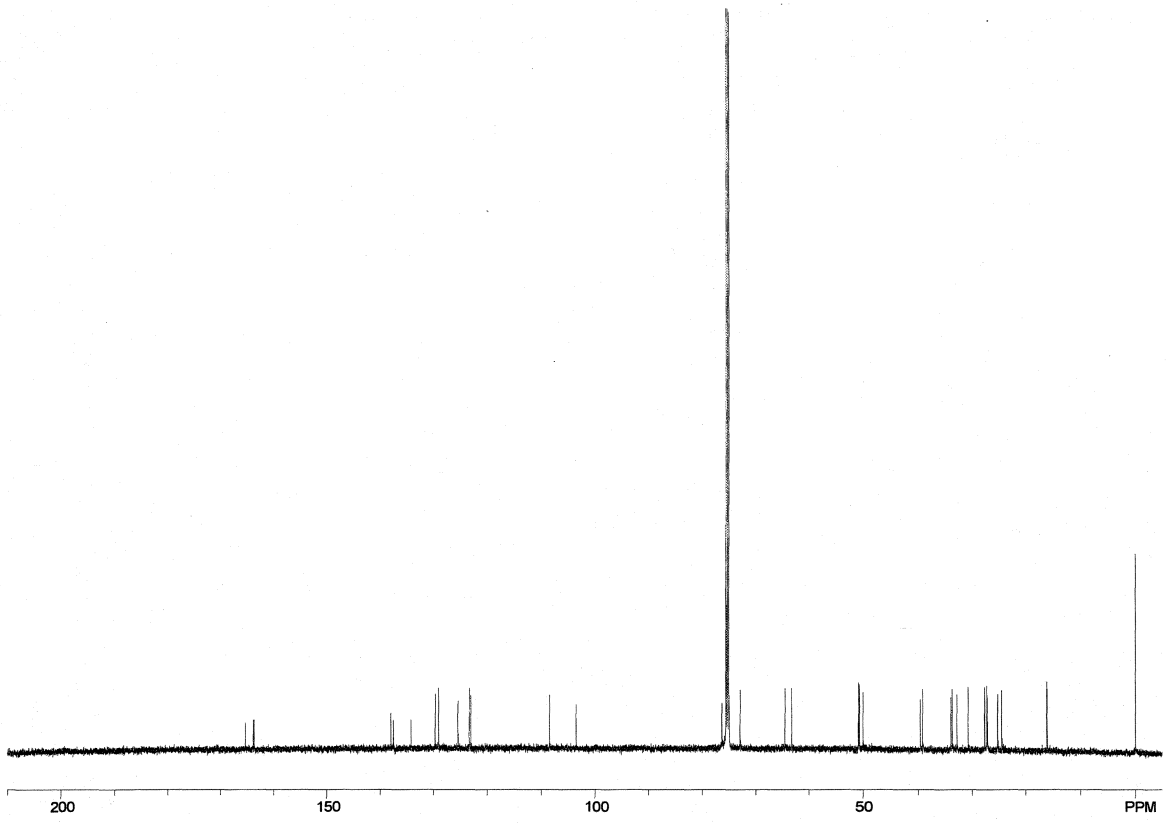


Figure A.1.48 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **250b**.

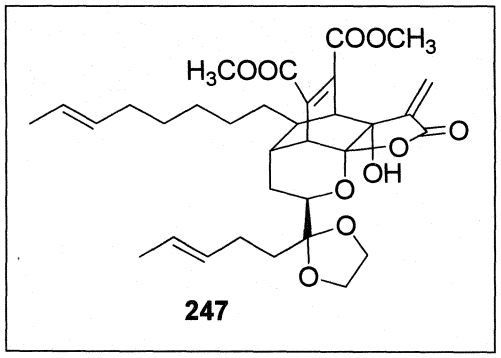


Figure A.1.49 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **247**.

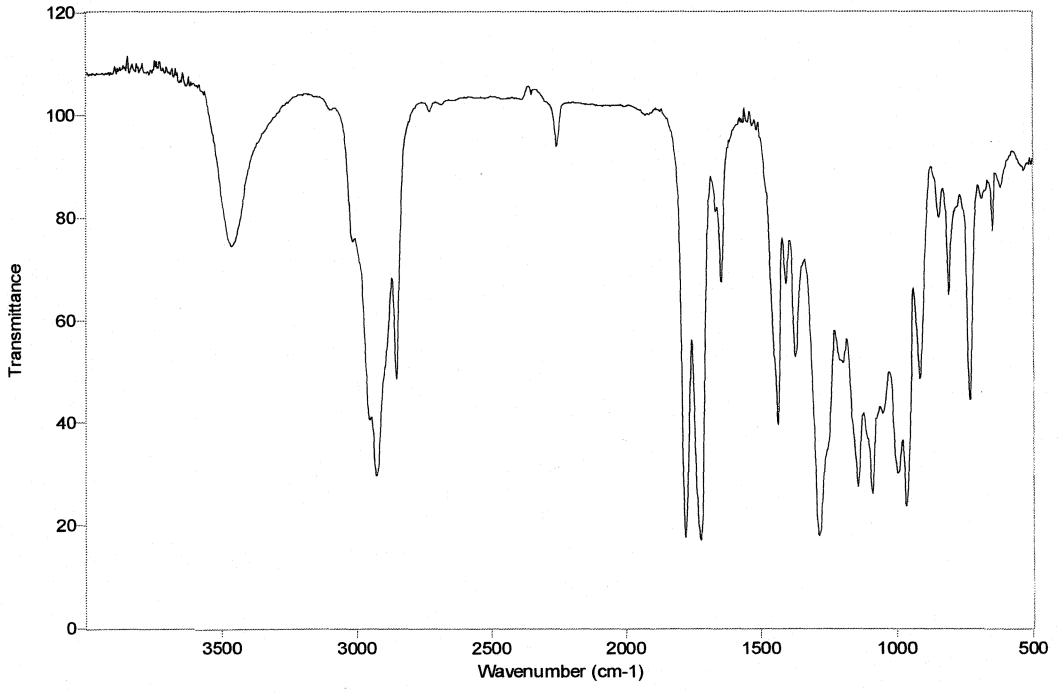


Figure A.1.50 FTIR Spectrum (thin film/NaCl) of Compound **247**.

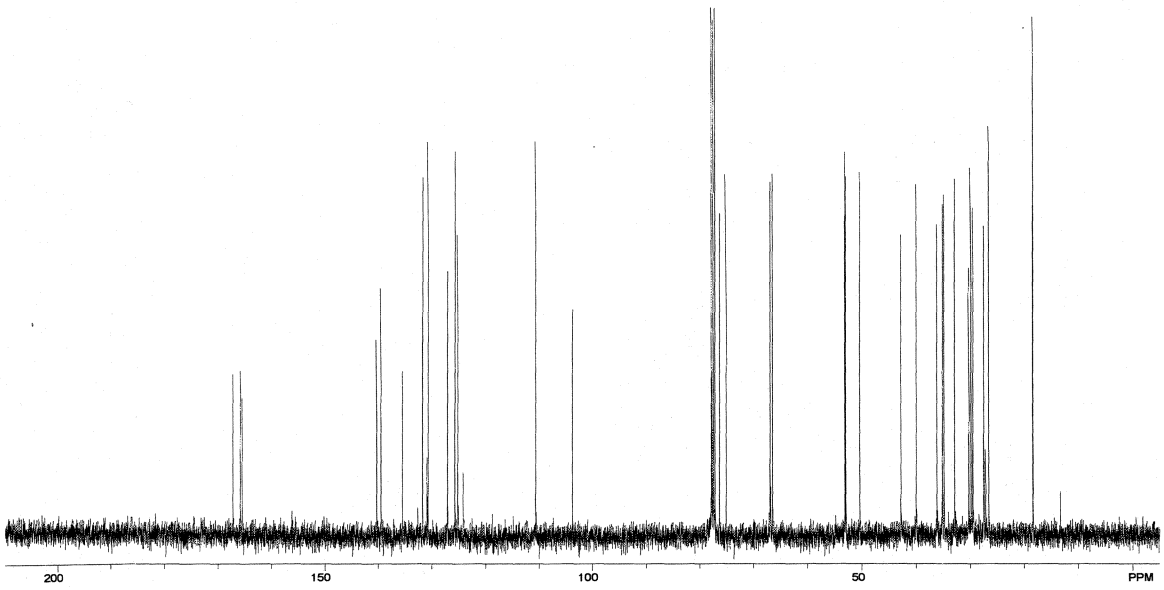


Figure A.1.51 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **247**.

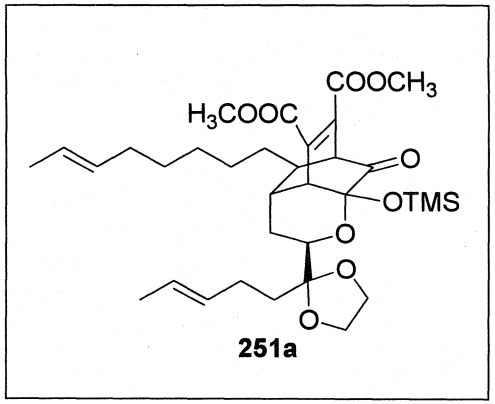


Figure A.1.52 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **251a**.

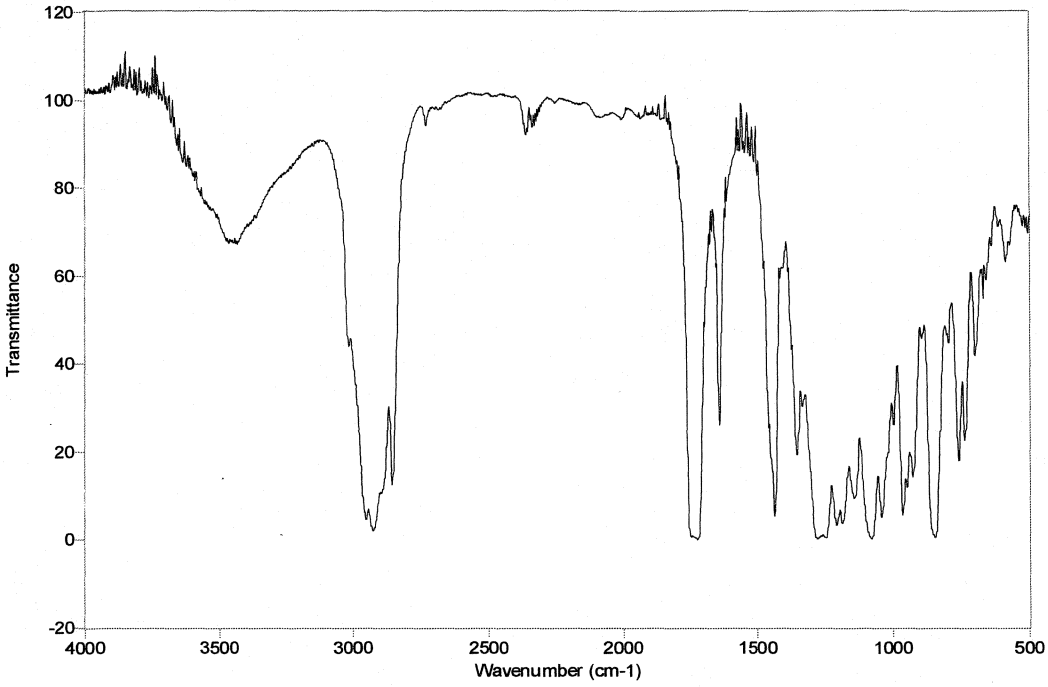


Figure A.1.53 FTIR Spectrum (thin film/NaCl) of Compound **251a**.

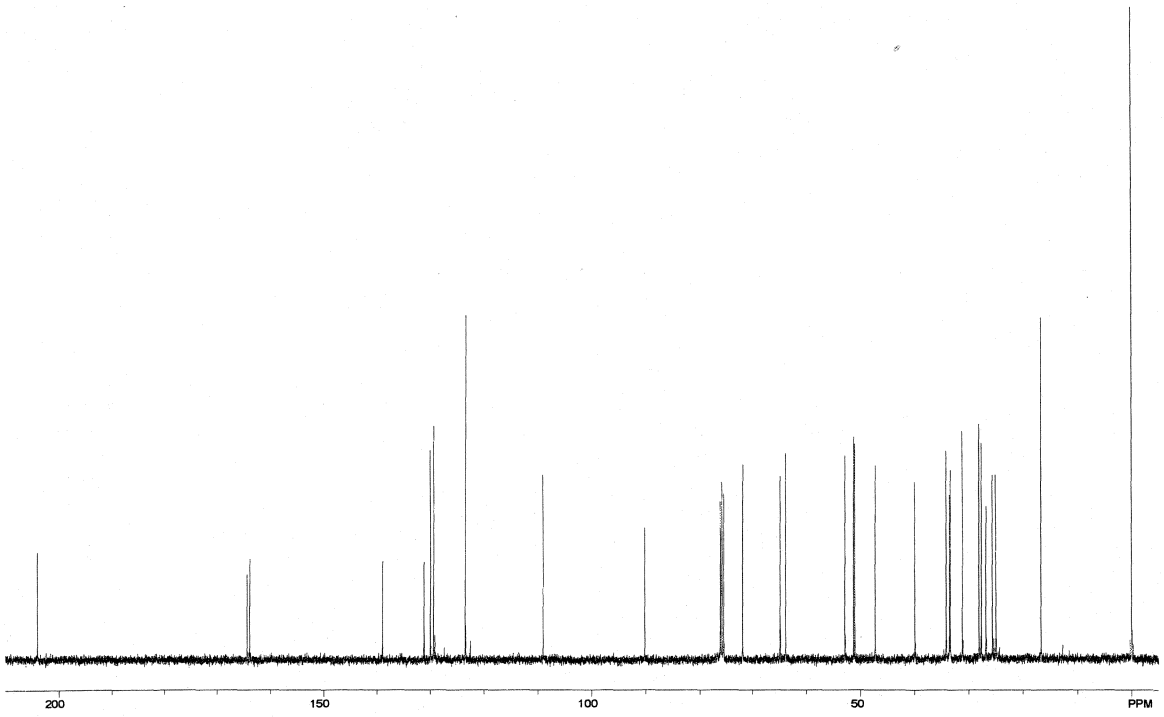


Figure A.1.54 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **251a**.

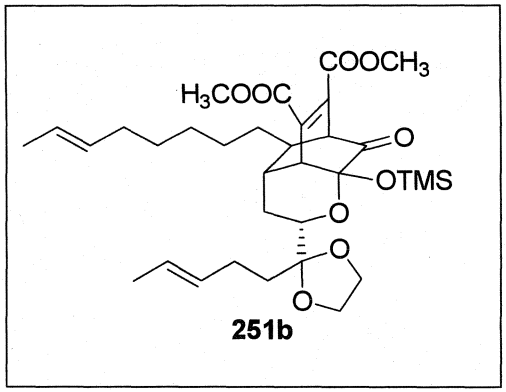


Figure A.1.55 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **251b**.

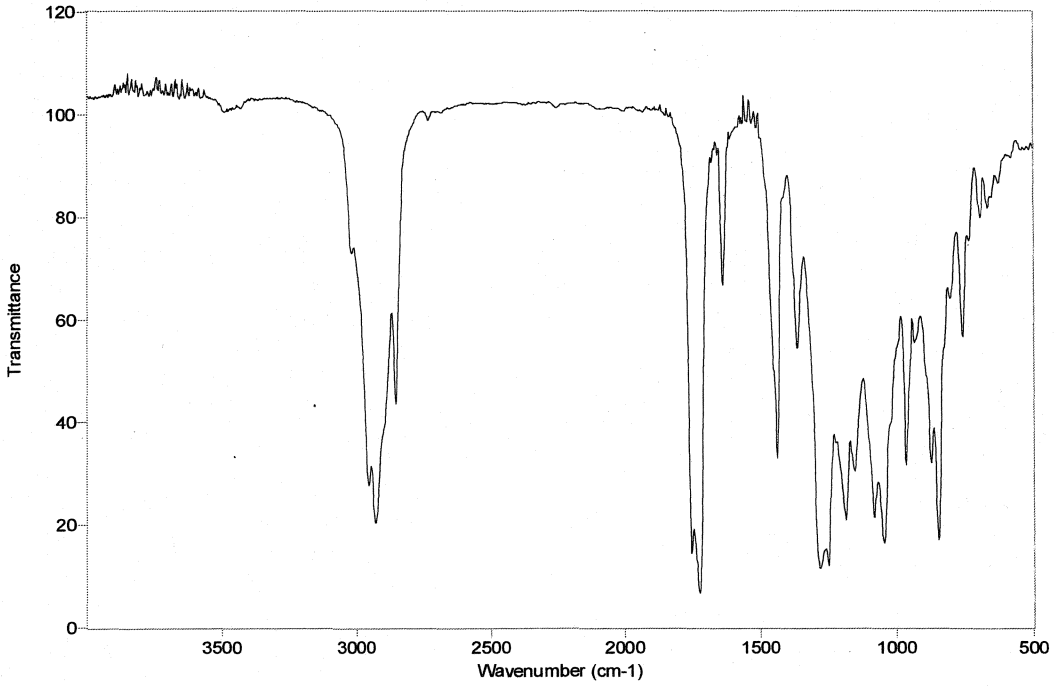


Figure A.1.56 FTIR Spectrum (thin film/NaCl) of Compound **251b**.

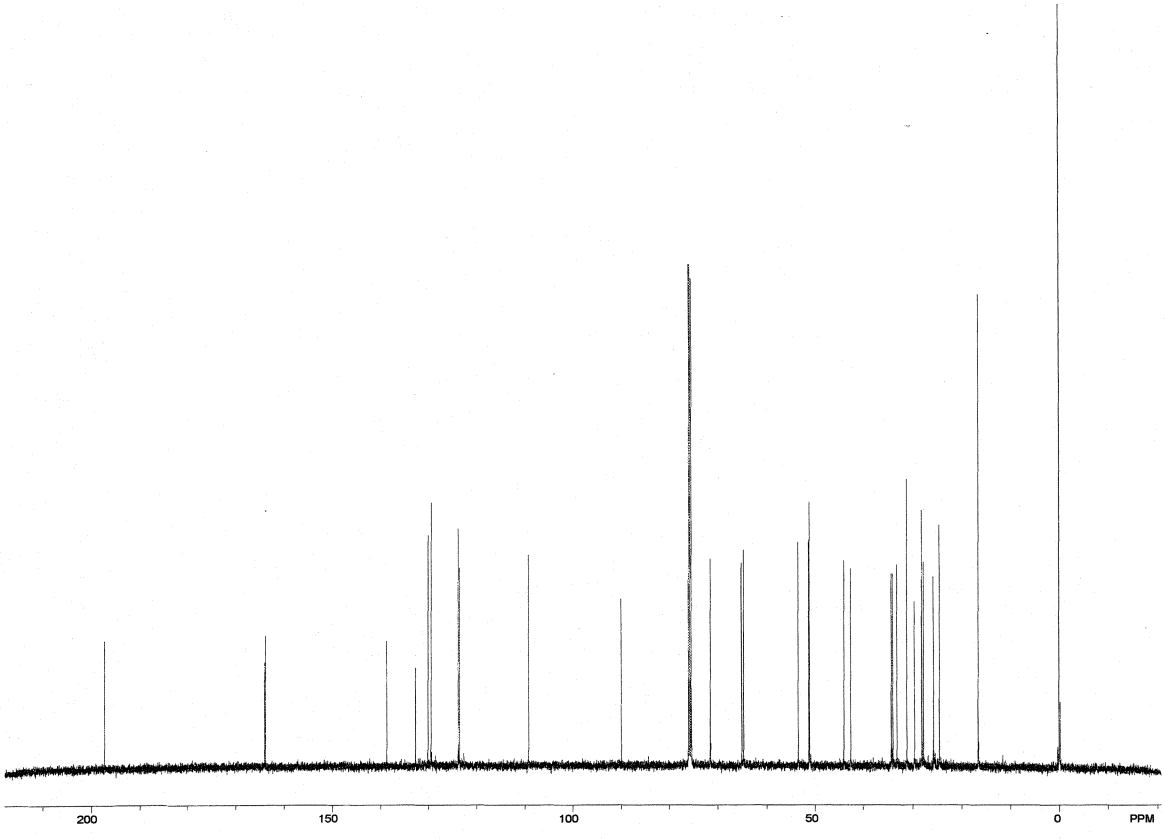


Figure A.1.57 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **251b**.

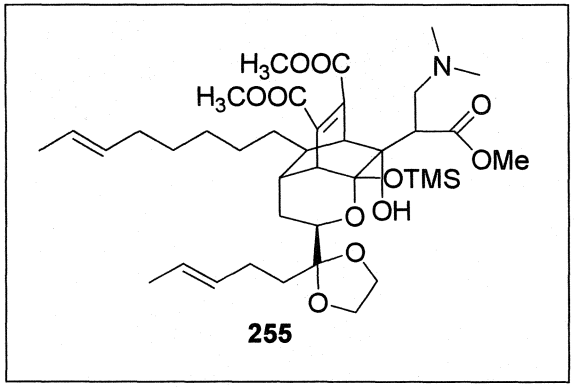


Figure A.1.58 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **255**.

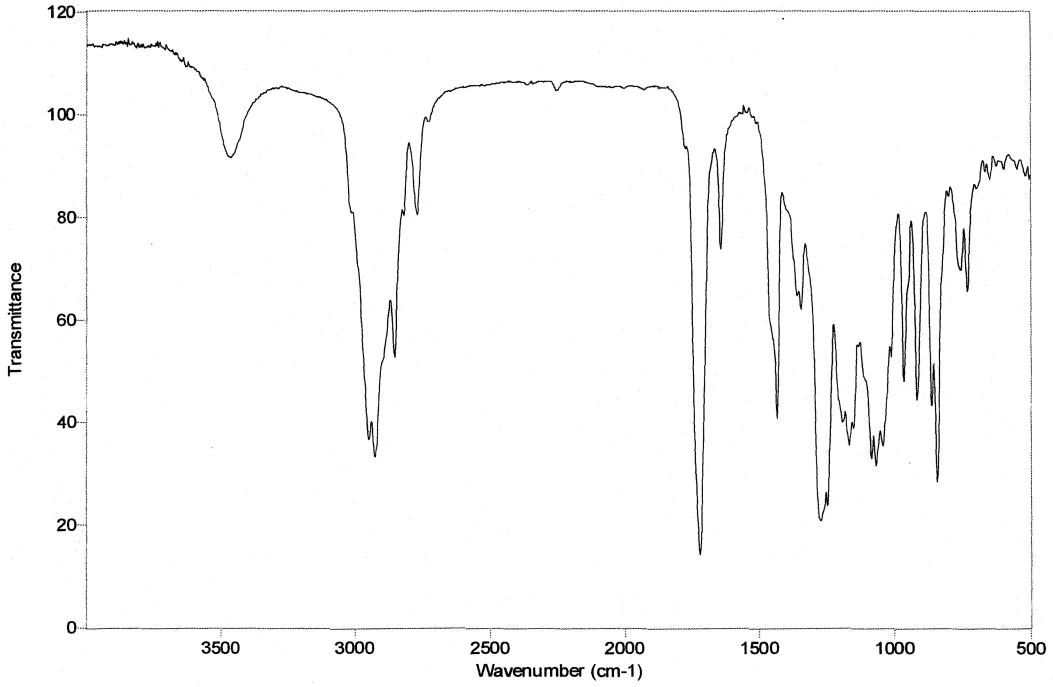


Figure A.1.59 FTIR Spectrum (thin film/NaCl) of Compound **255**.

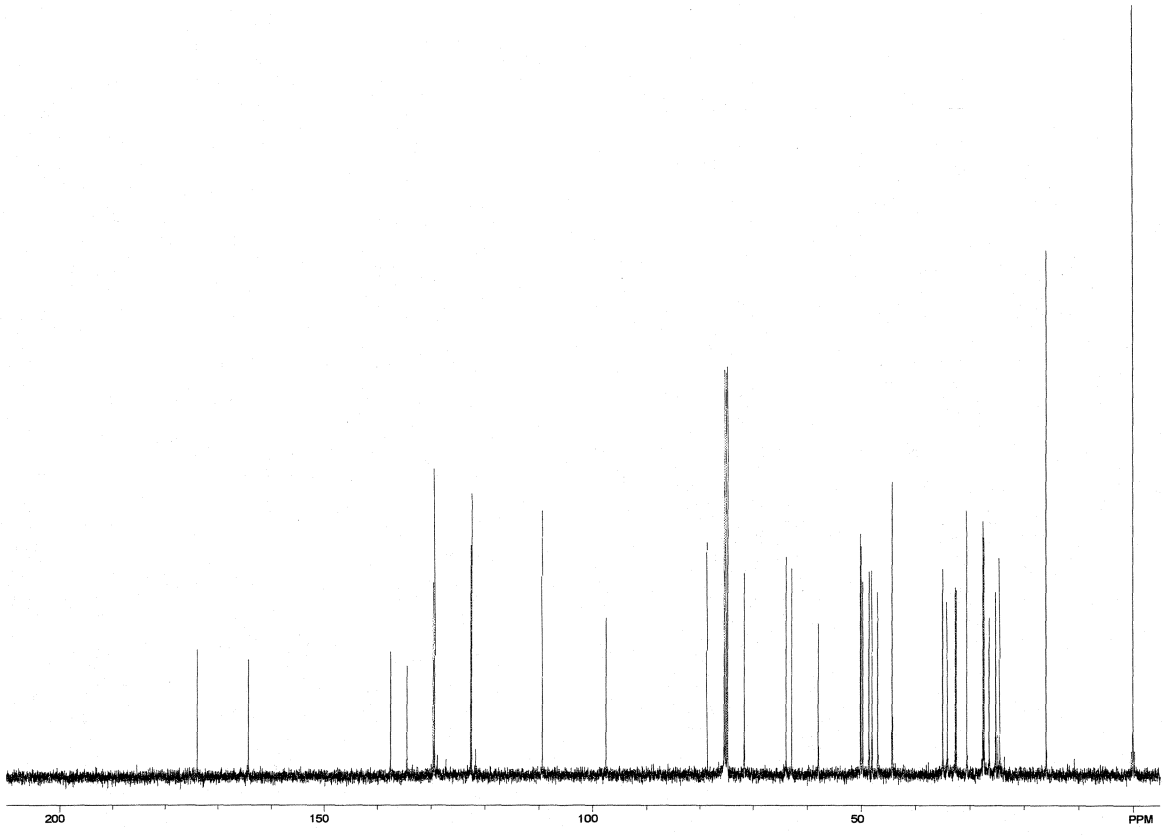


Figure A.1.60 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **255**.

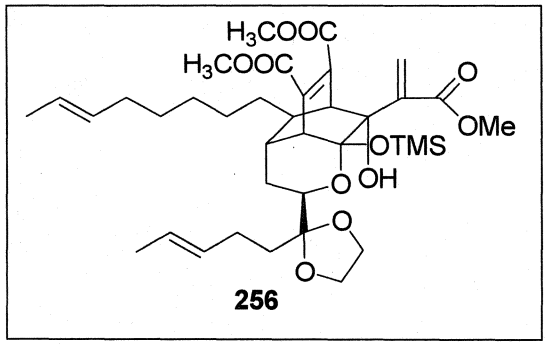


Figure A.1.61 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **256**.

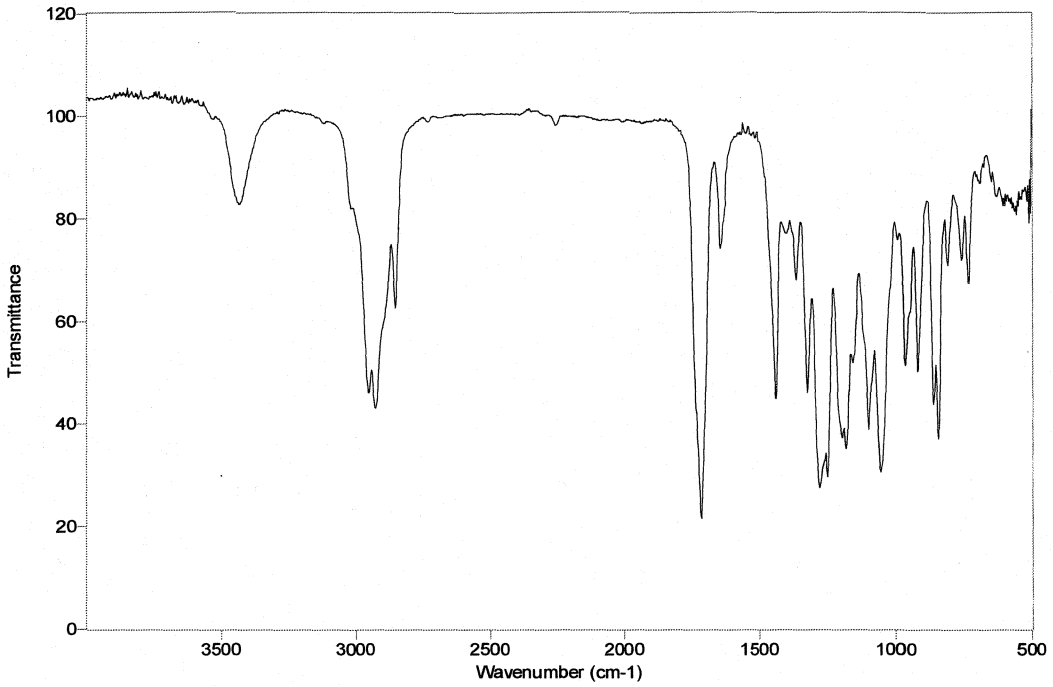


Figure A.1.62 FTIR Spectrum (thin film/NaCl) of Compound **256**.

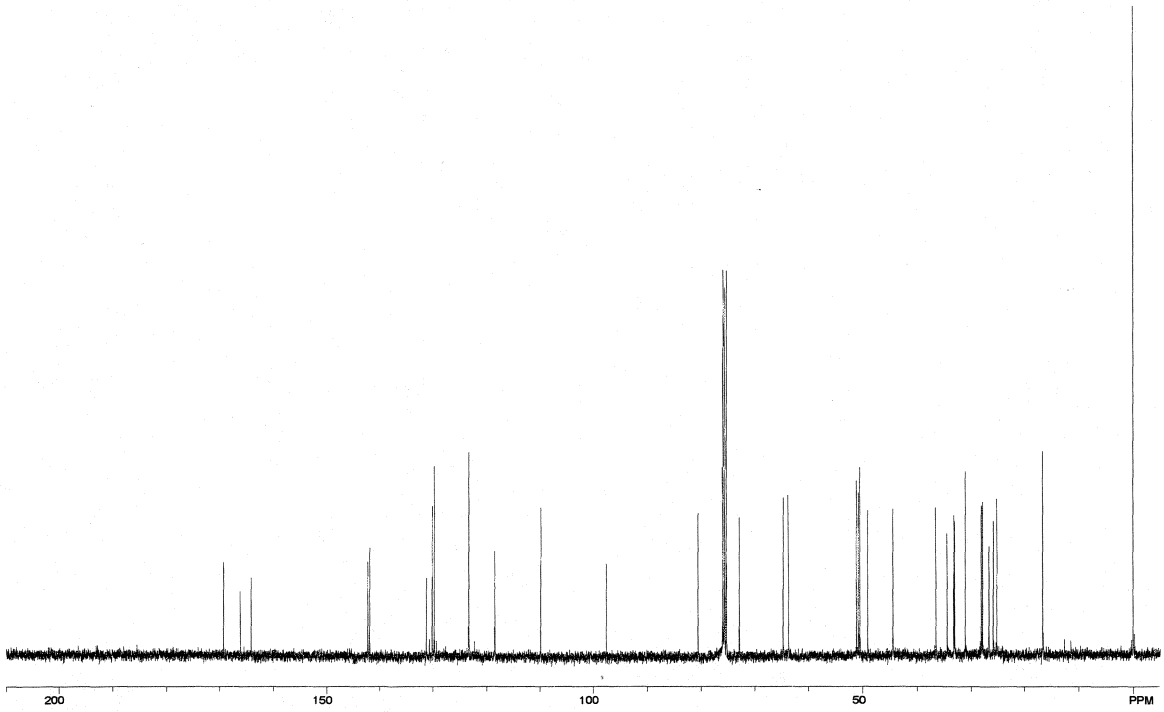


Figure A.1.63 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **256**.

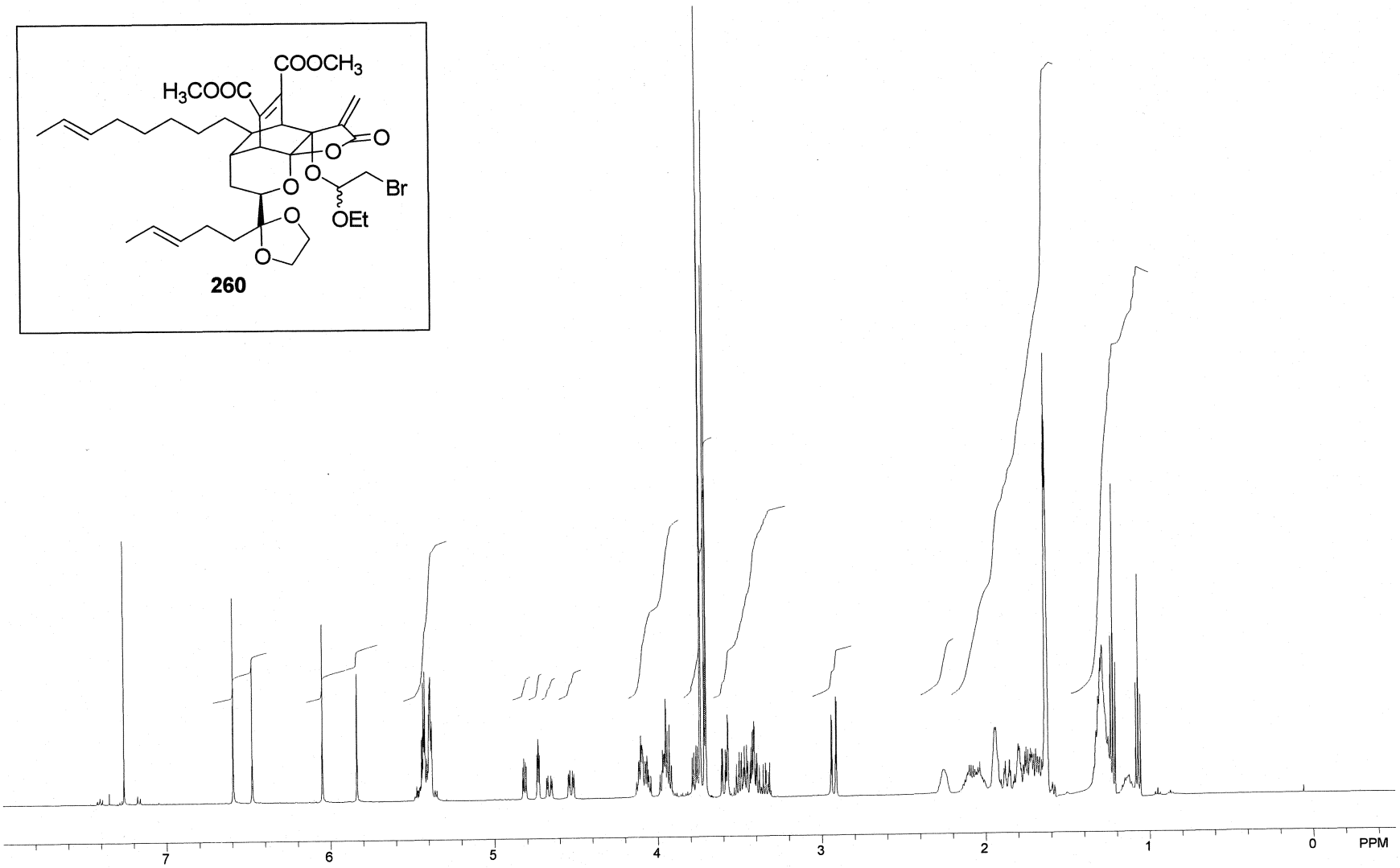


Figure A.1.64 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **260**.

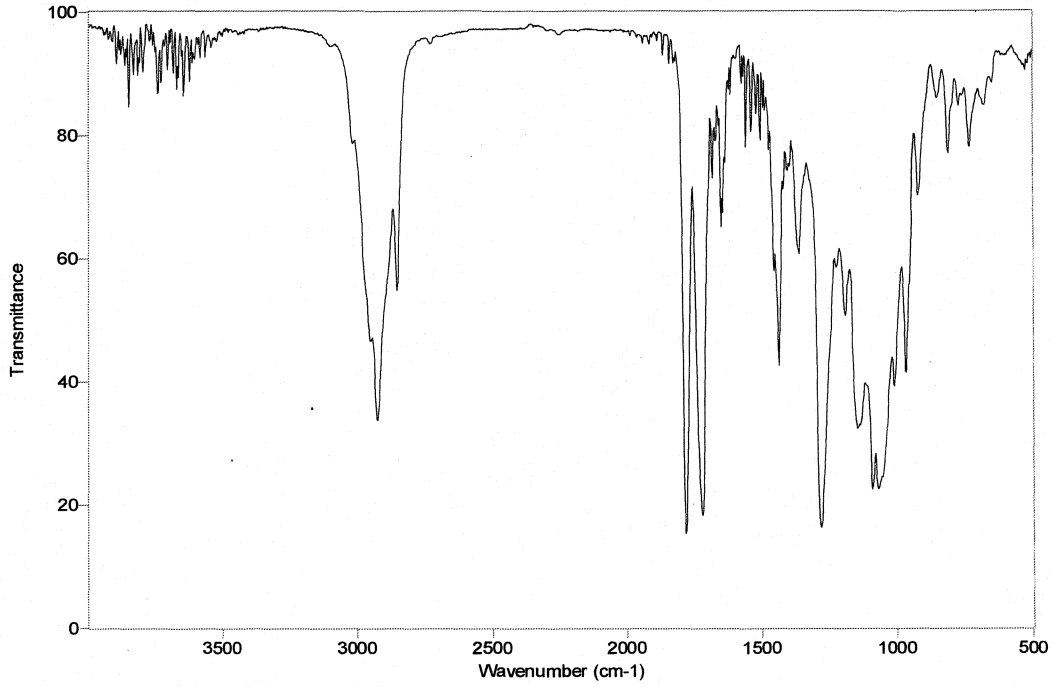


Figure A.1.65 FTIR Spectrum (thin film/NaCl) of Compound **260**.

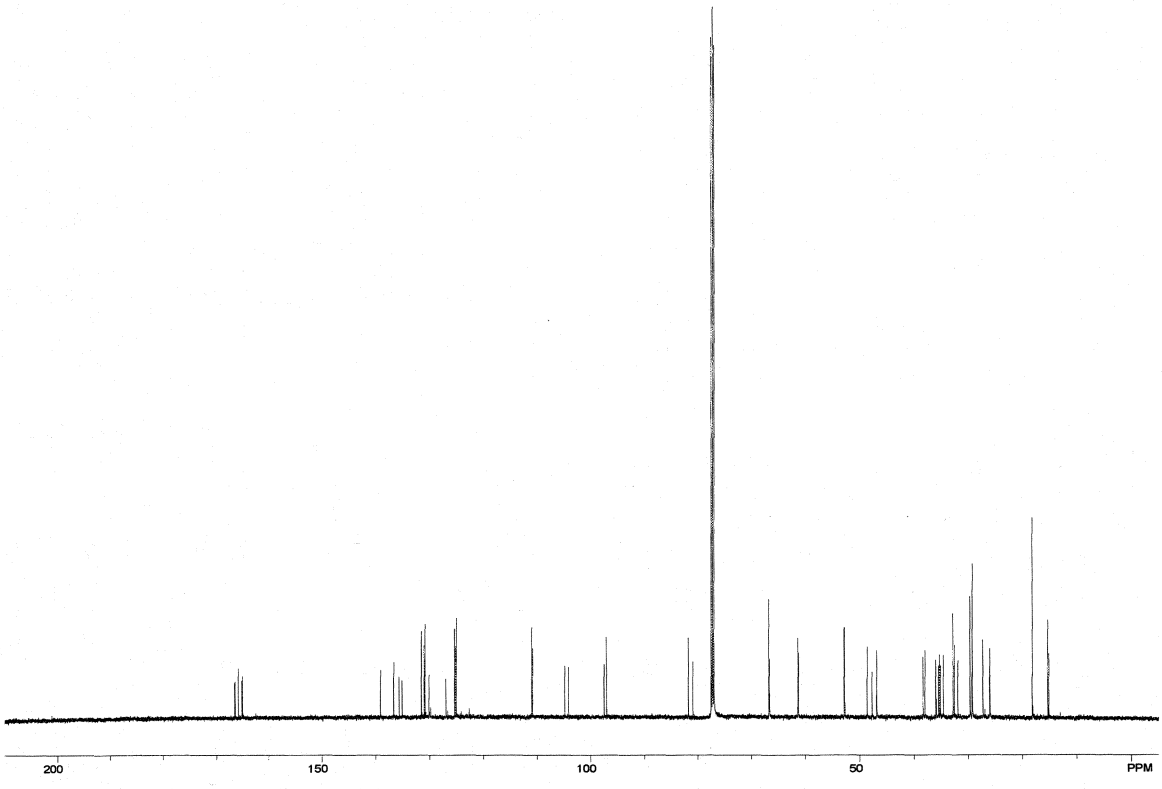
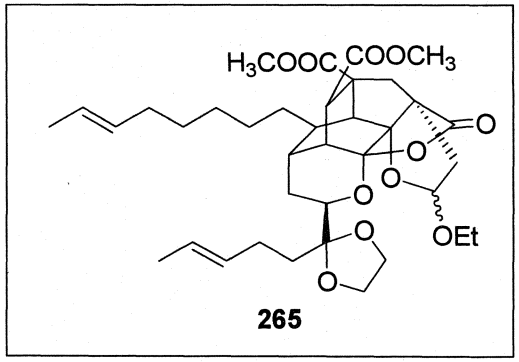


Figure A.1.66 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **260**.



265

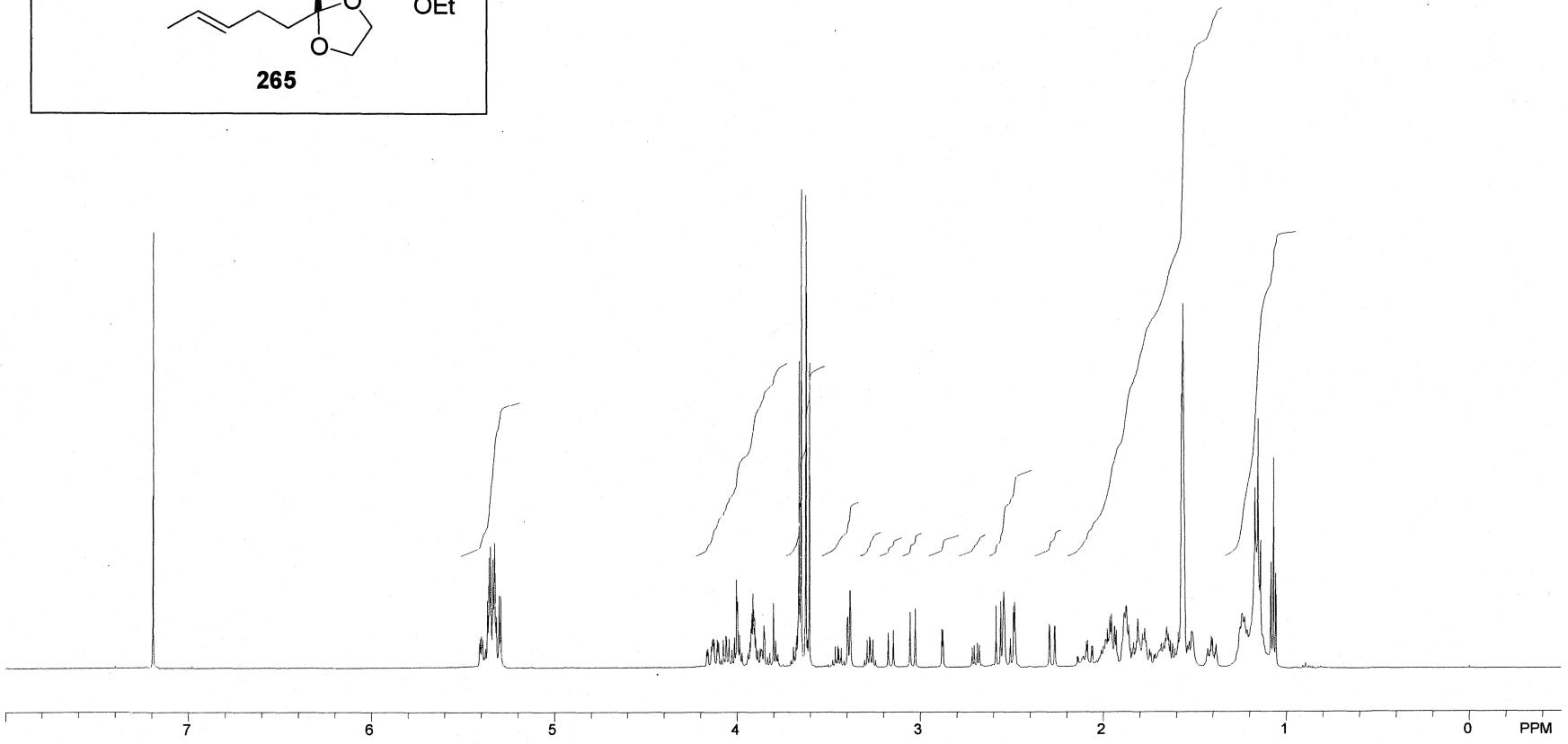


Figure A.1.67 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **265**.

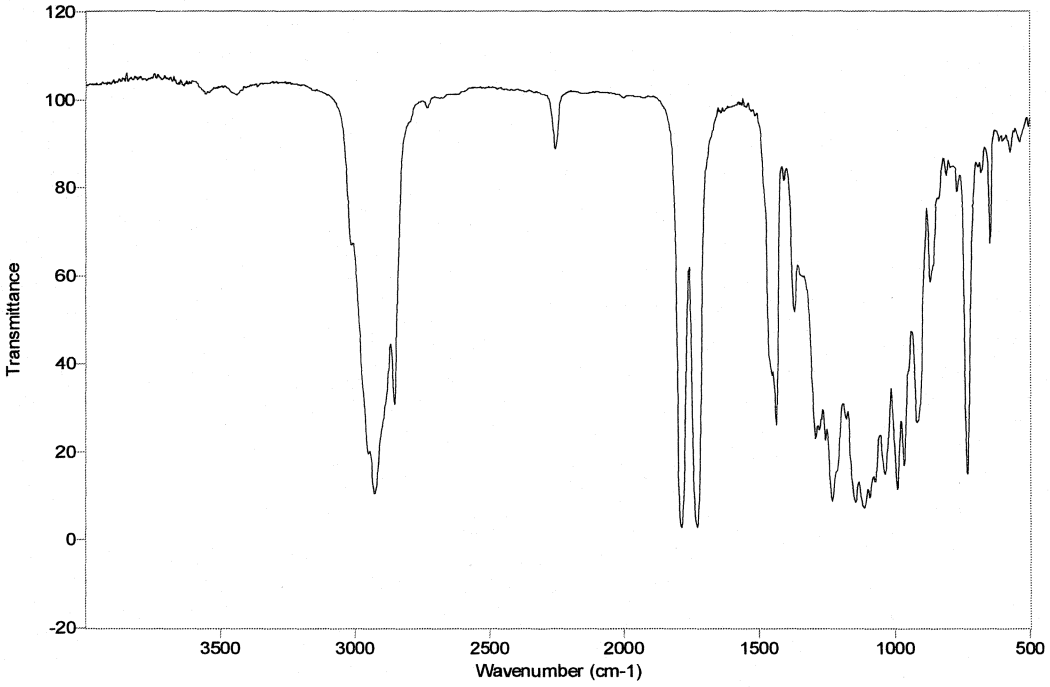


Figure A.1.68 FTIR Spectrum (thin film/NaCl) of Compound **265**.

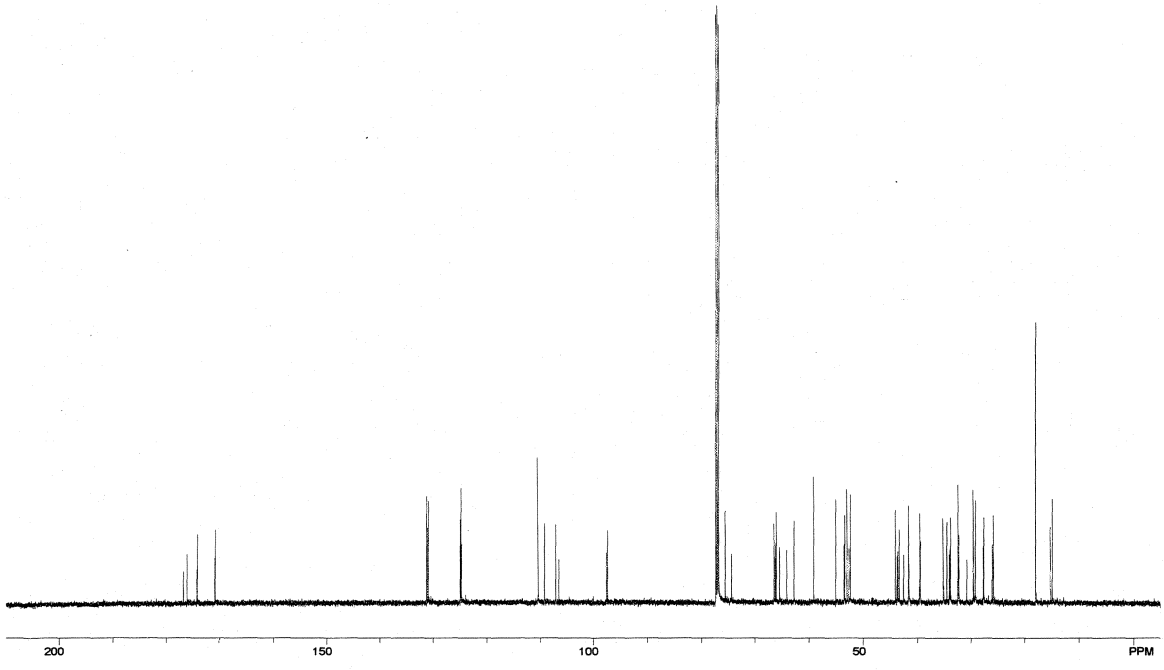


Figure A.1.69 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **265**.

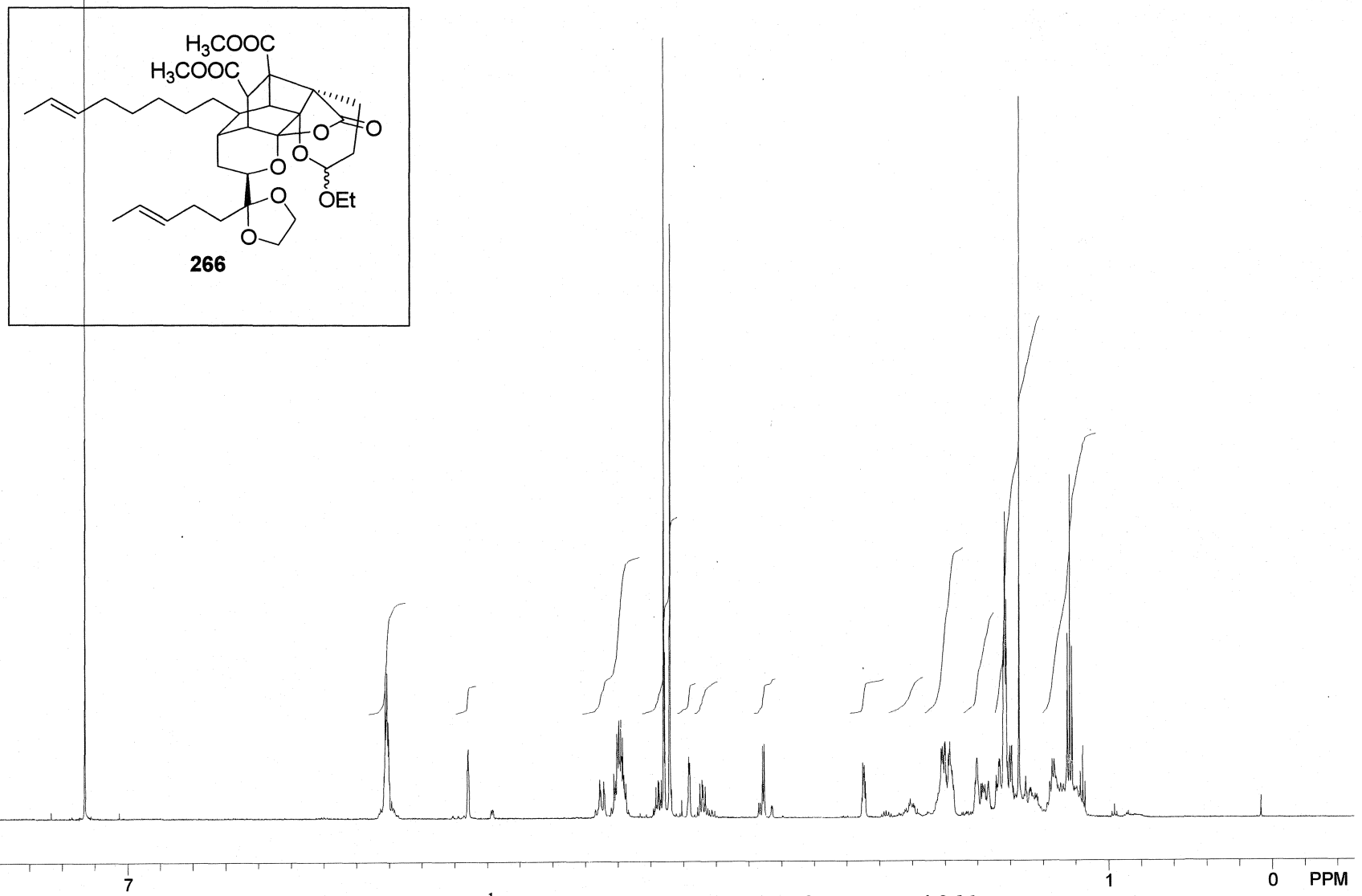


Figure A.1.70 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **266**.

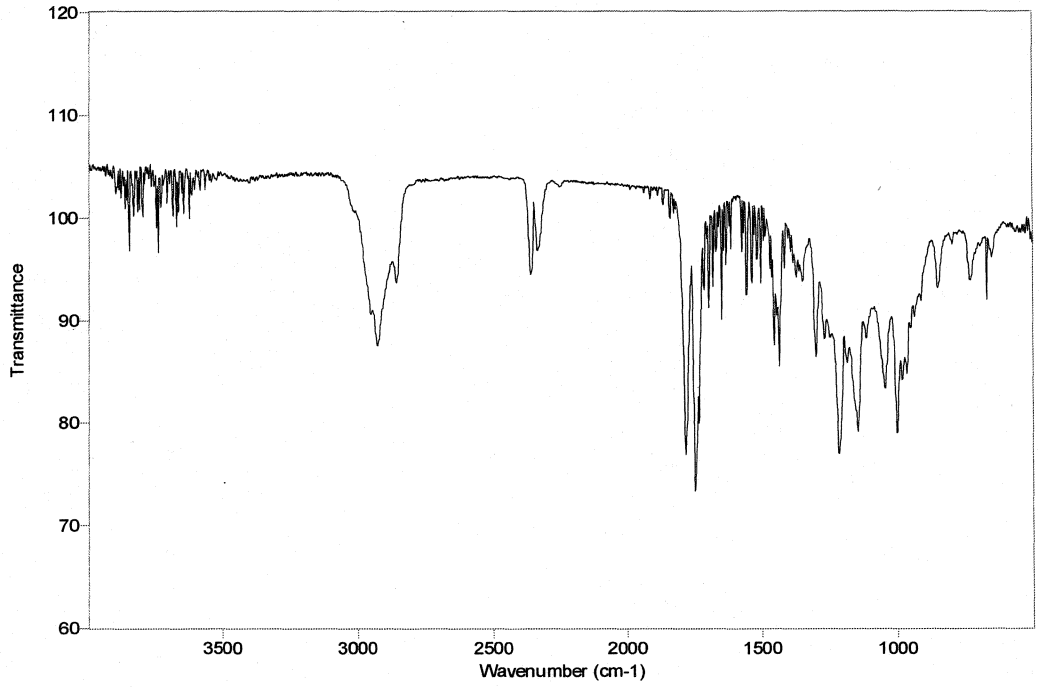


Figure A.1.71 FTIR Spectrum (thin film/NaCl) of Compound **266**.

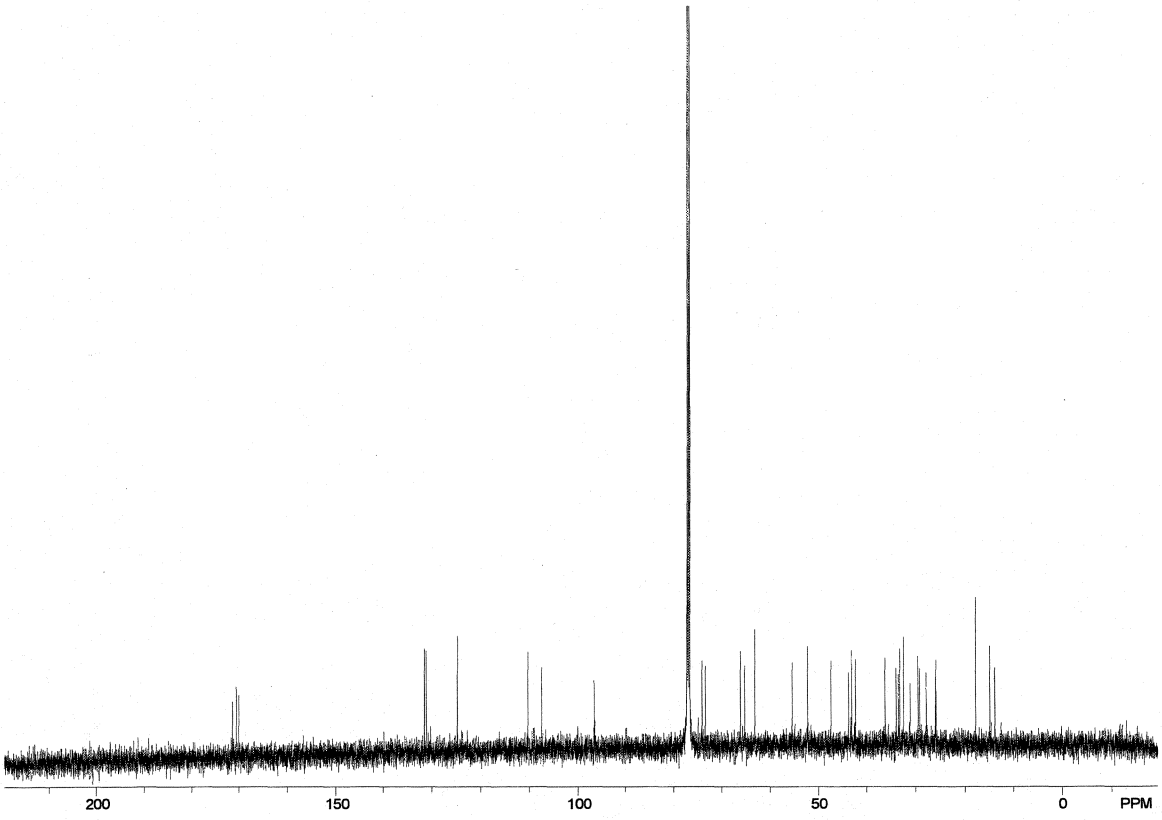


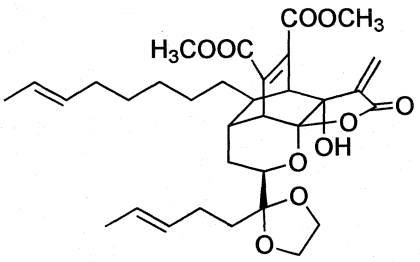
Figure A.1.72 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **266**.

Appendix 2

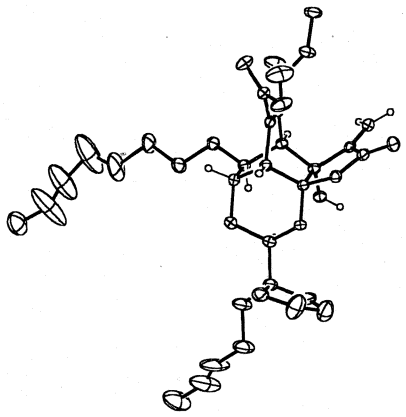
X-Ray Data relevant to Chapter 3

A.2.1 X-Ray Structure Report for Lactone 248.

A.2.1.1 Structure and ORTEP Plot of Lactone 248.



248



A.2.1.2 Reference Information

YALE CHEMICAL INSTRUMENTATION CENTER

X-Ray Structure Report

Reference Number: WOOD_IM02

May 14, 2003

A.2.1.3 Data Collection.

A colorless blade crystal of $C_{33}H_{44}O_{10}$ having approximate dimensions of 0.35 x 0.20 x 0.15 mm^3 was mounted with epoxy cement on the tip of a fine glass fiber. All measurements were made on a Nonius KappaCCD diffractometer with graphite monochromated Mo-Kπ radiation.

Cell constants and an orientation matrix for data collection corresponded to a triclinic cell with dimensions:

a = 7.7285(15) Å π = 95.50(3) °

b = 15.223(3) Å π = 94.23(3) °

c = 27.208(5) Å π = 100.07(3) °

V = 4572.6(16) $Å^3$

For Z = 4 and F.W. = 600.68, the calculated density is 1.277 g/cm^3. Based on a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be: *P*-1 (#2)

The data were collected at a temperature of 173(2) K to a maximum 2π value of 57.16 °. Seven omega scans consisting of 84, 84, 77, 66, 55, 66, and 17 data frames, respectively, were collected with a frame width of 0.9 ° and a detector-to-crystal distance, Dx, of 35.0 mm. Each frame was exposed twice (for the purpose of de-zingering) for a total of 108 seconds. The data frames were processed and scaled using the DENZO software package.[1]

A.2.1.4 Data Reduction.

A total of 26485 reflections were collected of which 15489 were unique and observed (R_{int} = 0.0585). The linear absorption coefficient, μ, for Mo-Kπ radiation is 0.94 cm^{-1} and no absorption correction was applied. The data were corrected for Lorentz and polarization effects.

A.2.1.5 Structure Solution and Refinement.

The structure was solved by direct methods and expanded using Fourier techniques[2]. The non-hydrogen atoms were refined anisotropically and hydrogen atoms were treated as idealized contributions. The final cycle of full-matrix least-squares refinement[3] on F was based on 15489 observed reflections ($I > 2.00\pi(I)$) and 783 variable parameters and converged with unweighted and weighted agreement factors of:

$$R = \pi \, ||Fo| - |Fc|| \, / \, \pi \, |Fo| = 0.0746$$

$$R_W = \{\pi[w \, (F_o^2 - F_c^2)^2] \, / \, \pi[w(F_o^2)^2]\}^{1/2} = 0.17.49$$

The maximum and minimum peaks on the final difference Fourier map corresponded to 0.500 and –0.447 $e^-/Å^3$, respectively.

A.2.1.6 REFERENCES.

(1) Z. Otwinowski and W. Minor, "Processing of X-Ray Diffraction Data Collected in Oscillation Mode," Methods in Enzymology, vol. 276: Macromolecular Crystallography, part A, 307-326, 1997, C.W. Carter, Jr. & R.M. Sweet, Eds., Academic Press.

(2) *Acta Cryst.* **A46** (1990) 467-473

(3) Least Squares function minimized:

$$\pi w(F_o^2 - F_c^2)^2$$

A.2.1.7 Structural Description

The compound crystallized in the triclinic space group *P*-1 with two crystallographically unique but chemically equivalent molecules in the asymmetric unit and four molecules in the unit cell. Ring 1 [C(1-6)] adopts a boat conformation as a

result of the two-carbon bridge between C(7) and C(10) and ring 2 [C(1, 2, 6, 16, 17)-O(8)] adopts the expected chair geometry. The lactone rings are planar with 0.011 and 0.030(') Å deviations and are offset by 119.1 and 118.6 ° from their respective bicyclo-octane cores. This feature is better illustrated in Figure **4**. The torsion angles about the C(7)-C(10) double bond are 0.5 ° for C(11-10-7-8) and 5.0 ° for C(11'-10'-7'-8').

The hydroxyl-protons, H(7) and H(7'), were located from the residual electron density map and refined with isotropic displacement parameters. O-H distances refined to 0.96(4) Å for O(7)-H(7) and 0.88(4) Å for O(7')-H(7').

The highly flexible alkyl chains, C(19-23) and C(26-33), in both unique molecules may occupy numerous orientations in the crystal-lattice and could not be effectively modeled. The atoms associated with these chains possess inflated thermal parameters and non-ideal C-C bond lengths as a result of the unresolvable positional disorder

There are no significant intermolecular contacts. ORTEPs, packing diagrams, and full crystallographic tables follow.

Figure A.2.1 First Unique Molecule.

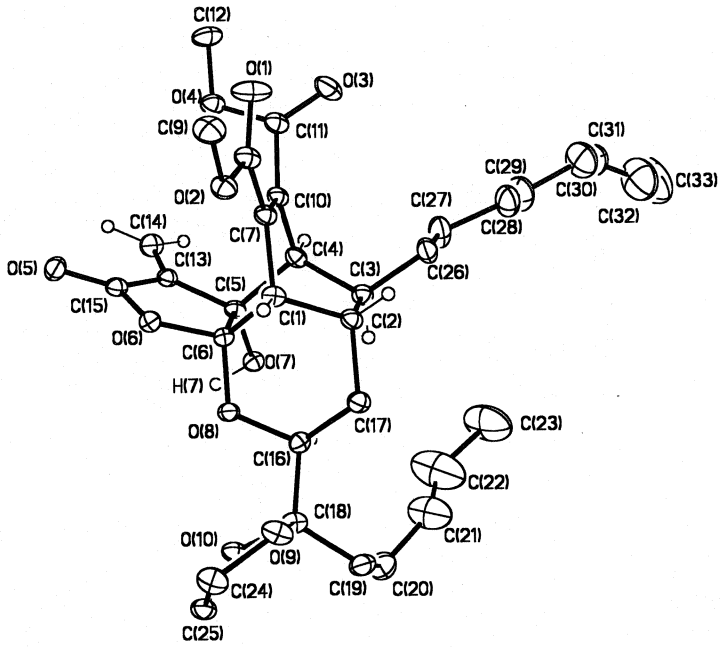


Figure A.2.2 Second Unique Molecule.

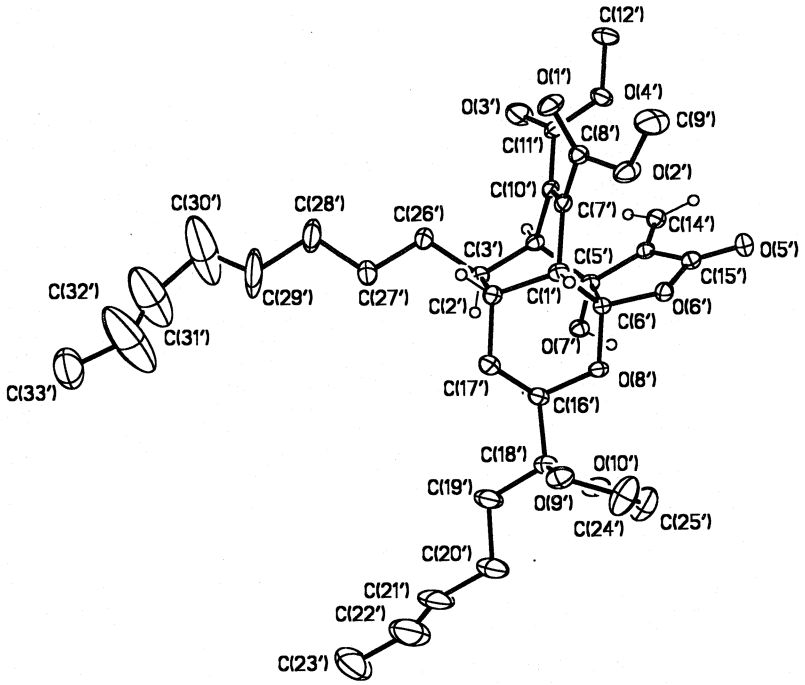


Figure A.2.3

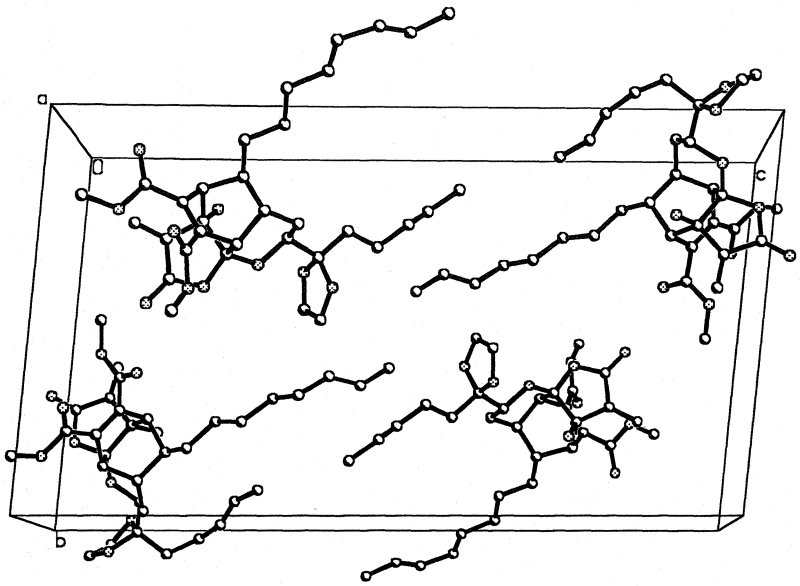


Figure A.2.4

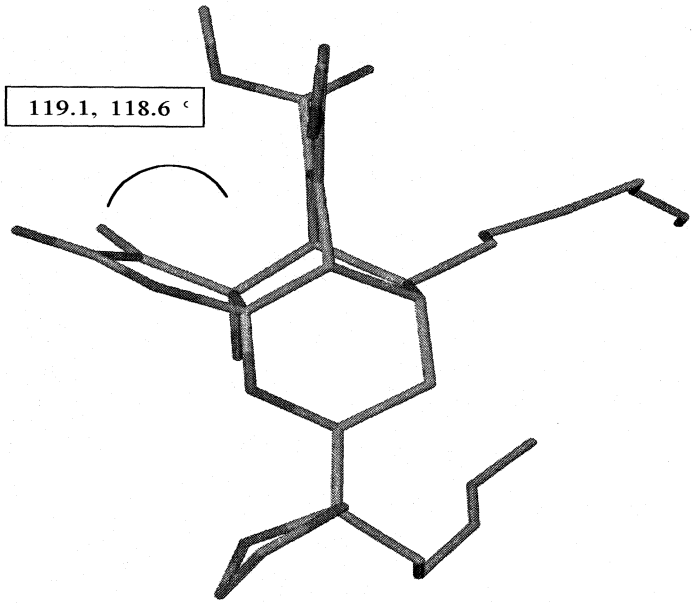


Figure A.2.5 Packing diagram – View down the a-axis

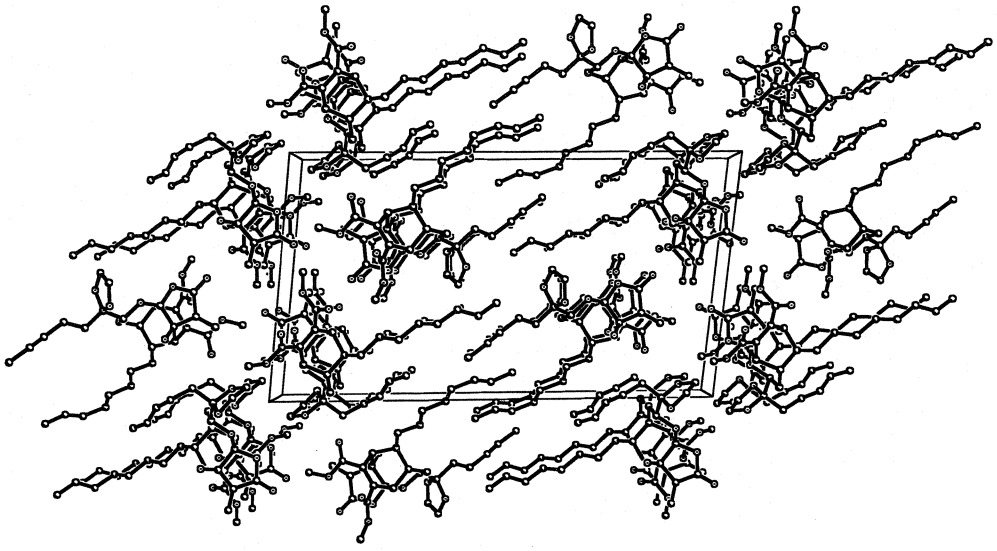


Figure A.2.6 Packing diagram – View down the b-axis

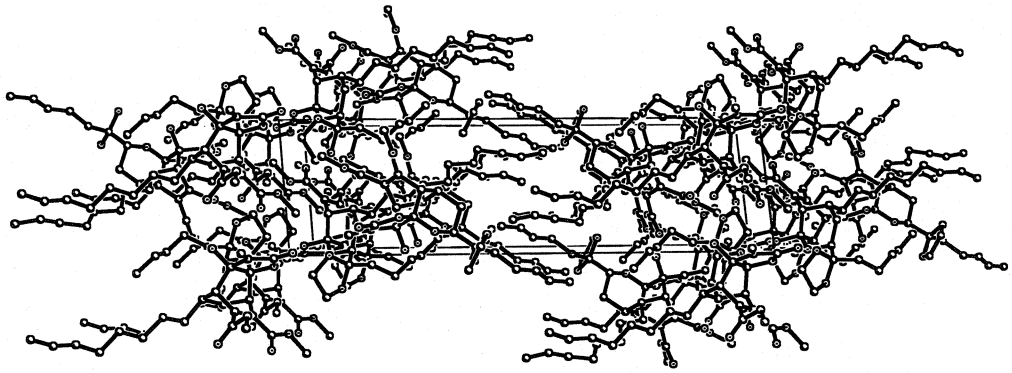


Figure A.2.7 Packing diagram – View down the c-axis

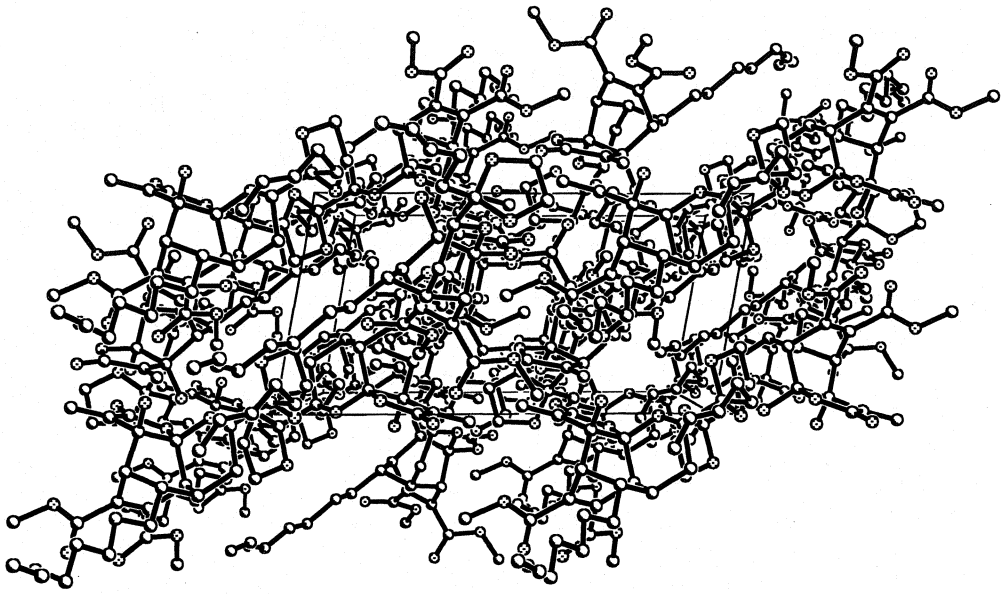


Table A.2.1. Crystal data and structure.

Identification code	wood_im02	
Empirical formula	C_{33} H_{44} O_{10}	
Formula weight	600.68	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.7285(15) Å	π= 95.50(3)°.
	b = 15.223(3) Å	π= 94.23(3)°.
	c = 27.208(5) Å	π= 100.07(3)°.
Volume	3123.8(11) $Å^3$	
Z	4	
Density (calculated)	1.277 g/cm^3	
Absorption coefficient	0.94 cm^{-1}	

F(000)	1288
Crystal size	0.35 x 0.20 x 0.15 mm^3
Theta range for data collection	2.27 to 28.58°.
Index ranges	-10<=h<=10, -20<=k<=20, -36<=l<=35
Reflections collected	26485
Independent reflections	15489 [R(int) = 0.0585]
Completeness to theta = 28.58°	96.8 %
Absorption correction	None
Max. and min. transmission	0.9861 and 0.9679
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	15489 / 0 / 783
Goodness-of-fit on F^2	1.063
Final R indices [I>2sigma(I)]	R1 = 0.0746, wR2 = 0.1749
R indices (all data)	R1 = 0.1648, wR2 = 0.2127
Largest diff. peak and hole	0.500 and -0.447 e.$Å^{-3}$

Table A.2.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3).
U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	6436(3)	7148(1)	339(1)	49(1)
O(2)	5436(2)	8305(1)	41(1)	32(1)
O(3)	5817(2)	6199(1)	1296(1)	45(1)
O(4)	3852(2)	5570(1)	655(1)	32(1)
O(5)	-391(2)	6367(1)	-268(1)	34(1)
O(6)	599(2)	7673(1)	194(1)	25(1)
O(7)	-708(2)	7313(1)	1353(1)	26(1)
O(8)	23(2)	8698(1)	770(1)	26(1)
O(9)	22(2)	10557(1)	838(1)	36(1)
O(10)	-2466(2)	9630(1)	1004(1)	30(1)
C(1)	3014(3)	8423(2)	783(1)	26(1)

C(2)	3358(3)	8824(2)	1332(1)	28(1)
C(3)	2924(3)	8058(2)	1667(1)	27(1)
C(4)	2299(3)	7150(2)	1337(1)	26(1)
C(5)	593(3)	7211(2)	1019(1)	23(1)
C(6)	1041(3)	8028(2)	706(1)	23(1)
C(7)	4062(3)	7680(2)	701(1)	26(1)
C(8)	5435(3)	7673(2)	350(1)	30(1)
C(9)	6845(4)	8378(2)	-282(1)	43(1)
C(10)	3695(3)	7022(2)	991(1)	26(1)
C(11)	4603(3)	6229(2)	998(1)	30(1)
C(12)	4610(4)	4759(2)	645(1)	42(1)
C(13)	-9(3)	6435(2)	627(1)	24(1)
C(14)	-441(3)	5575(2)	685(1)	35(1)
C(15)	-6(3)	6766(2)	136(1)	26(1)
C(16)	314(3)	9239(2)	1247(1)	25(1)
C(17)	2272(3)	9572(2)	1405(1)	29(1)
C(18)	-697(3)	10008(2)	1198(1)	28(1)
C(19)	-671(4)	10609(2)	1676(1)	37(1)
C(20)	-1536(4)	10168(2)	2104(1)	51(1)
C(21)	-368(7)	9829(4)	2456(2)	89(2)
C(22)	-117(9)	9207(6)	2641(2)	138(3)
C(23)	1100(9)	8953(5)	3013(2)	133(2)
C(24)	-1361(4)	10644(2)	481(1)	42(1)
C(25)	-3022(3)	10265(2)	702(1)	34(1)
C(26)	4476(4)	8034(2)	2045(1)	37(1)
C(27)	4078(5)	7334(2)	2406(1)	50(1)
C(28)	5482(5)	7421(2)	2834(1)	61(1)
C(29)	4950(6)	6798(3)	3231(1)	72(1)
C(30)	6355(6)	6802(3)	3641(2)	86(1)
C(31)	5747(7)	6261(3)	4036(2)	88(1)
C(32)	5847(7)	6509(5)	4496(2)	118(2)
C(33)	5305(10)	6012(6)	4866(3)	188(4)
O(1')	-8801(2)	5932(1)	-2256(1)	44(1)
O(2')	-7357(3)	4818(1)	-2434(1)	54(1)
O(3')	-5854(4)	8132(2)	-1573(1)	69(1)
O(4')	-6354(3)	6707(1)	-1413(1)	40(1)

O(5')	-2208(3)	4970(1)	-1662(1)	39(1)
O(6')	-2858(2)	5304(1)	-2429(1)	28(1)
O(7')	-502(2)	7413(1)	-2420(1)	29(1)
O(8')	-1842(2)	5934(1)	-3082(1)	30(1)
O(9')	-1614(3)	5421(1)	-4107(1)	45(1)
O(10')	921(2)	6043(2)	-3627(1)	48(1)
C(1')	-4789(3)	6093(2)	-2886(1)	27(1)
C(2')	-4662(3)	6897(2)	-3198(1)	31(1)
C(3')	-3900(3)	7779(2)	-2852(1)	30(1)
C(4')	-3507(3)	7550(2)	-2319(1)	26(1)
C(5')	-2146(3)	6925(2)	-2309(1)	25(1)
C(6')	-2880(3)	6073(2)	-2690(1)	26(1)
C(7')	-5836(3)	6270(2)	-2449(1)	26(1)
C(8')	-7495(3)	5668(2)	-2368(1)	29(1)
C(9')	-8879(5)	4171(2)	-2324(2)	76(1)
C(10')	-5171(3)	7024(2)	-2154(1)	26(1)
C(11')	-5860(3)	7347(2)	-1690(1)	30(1)
C(12')	-7191(4)	6937(2)	-973(1)	45(1)
C(13')	-1972(3)	6523(2)	-1828(1)	26(1)
C(14')	-1592(3)	6942(2)	-1374(1)	34(1)
C(15')	-2326(3)	5531(2)	-1938(1)	30(1)
C(16')	-1726(4)	6584(2)	-3438(1)	32(1)
C(17')	-3552(4)	6718(2)	-3626(1)	36(1)
C(18')	-673(4)	6237(2)	-3846(1)	37(1)
C(19')	-252(5)	6921(2)	-4208(1)	60(1)
C(20')	911(6)	6664(3)	-4604(1)	73(1)
C(21')	1068(10)	7240(4)	-5000(2)	143(3)
C(22')	1813(11)	7650(4)	-5238(2)	146(3)
C(23')	1965(10)	8222(4)	-5641(2)	134(2)
C(24')	-793(6)	4723(3)	-3967(2)	85(1)
C(25')	828(6)	5112(3)	-3684(2)	79(1)
C(26')	-5117(4)	8472(2)	-2870(1)	39(1)
C(27')	-5326(5)	8812(2)	-3372(1)	54(1)
C(28')	-6602(6)	9455(3)	-3400(2)	82(1)
C(29')	-6700(11)	9843(5)	-3916(2)	160(3)
C(30')	-7704(18)	10379(6)	-4019(3)	248(6)

C(31')	-7440(16)	10744(6)	-4526(3)	227(5)
C(32')	-7160(20)	10657(6)	-4915(3)	273(8)
C(33')	-7464(9)	11045(4)	-5377(2)	126(2)

Table A.2.3. Bond lengths [Å] and angles [°].

O(1)-C(8)	1.206(3)	C(5)-C(6)	1.577(3)
O(2)-C(8)	1.337(3)	C(7)-C(10)	1.339(4)
O(2)-C(9)	1.447(3)	C(7)-C(8)	1.479(4)
O(3)-C(11)	1.203(3)	C(10)-C(11)	1.500(4)
O(4)-C(11)	1.324(3)	C(13)-C(14)	1.322(4)
O(4)-C(12)	1.455(3)	C(13)-C(15)	1.471(4)
O(5)-C(15)	1.194(3)	C(16)-C(18)	1.527(4)
O(6)-C(15)	1.367(3)	C(16)-C(17)	1.525(3)
O(6)-C(6)	1.438(3)	C(18)-C(19)	1.513(4)
O(7)-H(7)	0.96(4)	C(19)-C(20)	1.536(4)
O(7)-C(5)	1.423(3)	C(20)-C(21)	1.459(6)
O(8)-C(6)	1.398(3)	C(21)-C(22)	1.153(7)
O(8)-C(16)	1.448(3)	C(22)-C(23)	1.456(7)
O(9)-C(24)	1.424(3)	C(24)-C(25)	1.506(4)
O(9)-C(18)	1.430(3)	C(26)-C(27)	1.525(4)
O(10)-C(18)	1.428(3)	C(27)-C(28)	1.512(4)
O(10)-C(25)	1.428(3)	C(28)-C(29)	1.536(5)
C(1)-C(7)	1.510(3)	C(29)-C(30)	1.497(5)
C(1)-C(6)	1.529(3)	C(30)-C(31)	1.469(6)
C(1)-C(2)	1.544(4)	C(31)-C(32)	1.267(6)
C(2)-C(17)	1.534(3)	C(32)-C(33)	1.361(8)
C(2)-C(3)	1.555(4)	O(1')-C(8')	1.199(3)
C(3)-C(26)	1.529(4)	O(2')-C(8')	1.313(3)
C(3)-C(4)	1.553(4)	O(2')-C(9')	1.466(4)
C(4)-C(10)	1.511(4)	O(3')-C(11')	1.207(3)
C(4)-C(5)	1.545(3)	O(4')-C(11')	1.311(3)
C(5)-C(13)	1.497(3)	O(4')-C(12')	1.443(3)

O(5')-C(15')	1.201(3)	C(27')-C(28')	1.509(5)
O(6')-C(15')	1.362(3)	C(28')-C(29')	1.576(7)
O(6')-C(6')	1.429(3)	C(29')-C(30')	1.257(9)
O(7')-H(7')	0.88(4)	C(30')-C(31')	1.548(11)
O(7')-C(5')	1.423(3)	C(31')-C(32')	1.097(10)
O(8')-C(6')	1.403(3)	C(32')-C(33')	1.460(9)
O(8')-C(16')	1.448(3)		
O(9')-C(24')	1.398(4)	C(8)-O(2)-C(9)	115.2(2)
O(9')-C(18')	1.420(4)	C(11)-O(4)-C(12)	115.4(2)
O(10')-C(25')	1.399(4)	C(15)-O(6)-C(6)	112.53(19)
O(10')-C(18')	1.419(3)	H(7)-O(7)-C(5)	112(2)
C(1')-C(7')	1.514(4)	C(6)-O(8)-C(16)	116.24(18)
C(1')-C(6')	1.537(3)	C(24)-O(9)-C(18)	109.13(19)
C(1')-C(2')	1.549(4)	C(18)-O(10)-C(25)	105.84(18)
C(2')-C(17')	1.528(4)	C(7)-C(1)-C(6)	109.6(2)
C(2')-C(3')	1.560(4)	C(7)-C(1)-C(2)	108.8(2)
C(3')-C(26')	1.533(4)	C(6)-C(1)-C(2)	105.3(2)
C(3')-C(4')	1.545(4)	C(17)-C(2)-C(1)	107.7(2)
C(4')-C(10')	1.513(4)	C(17)-C(2)-C(3)	114.4(2)
C(4')-C(5')	1.536(3)	C(1)-C(2)-C(3)	109.1(2)
C(5')-C(13')	1.505(4)	C(26)-C(3)-C(2)	111.8(2)
C(5')-C(6')	1.573(4)	C(26)-C(3)-C(4)	112.7(2)
C(7')-C(10')	1.336(4)	C(2)-C(3)-C(4)	109.5(2)
C(7')-C(8')	1.484(4)	C(10)-C(4)-C(5)	107.8(2)
C(10')-C(11')	1.479(4)	C(10)-C(4)-C(3)	108.3(2)
C(13')-C(14')	1.324(4)	C(5)-C(4)-C(3)	108.3(2)
C(13')-C(15')	1.483(4)	O(7)-C(5)-C(13)	112.34(19)
C(16')-C(17')	1.519(4)	O(7)-C(5)-C(4)	106.70(19)
C(16')-C(18')	1.530(4)	C(13)-C(5)-C(4)	114.0(2)
C(18')-C(19')	1.512(4)	O(7)-C(5)-C(6)	113.70(19)
C(19')-C(20')	1.519(5)	C(13)-C(5)-C(6)	102.7(2)
C(20')-C(21')	1.450(7)	C(4)-C(5)-C(6)	107.39(19)
C(21')-C(22')	1.072(7)	O(8)-C(6)-O(6)	103.50(18)
C(22')-C(23')	1.463(7)	O(8)-C(6)-C(1)	111.29(19)
C(24')-C(25')	1.422(6)	O(6)-C(6)-C(1)	108.64(19)
C(26')-C(27')	1.516(4)	O(8)-C(6)-C(5)	115.97(19)

O(6)-C(6)-C(5)	106.36(18)	C(3)-C(26)-C(27)	113.9(2)
C(1)-C(6)-C(5)	110.51(19)	C(28)-C(27)-C(26)	113.9(3)
C(10)-C(7)-C(8)	121.3(2)	C(27)-C(28)-C(29)	113.3(3)
C(10)-C(7)-C(1)	114.1(2)	C(30)-C(29)-C(28)	115.3(4)
C(8)-C(7)-C(1)	124.5(2)	C(31)-C(30)-C(29)	113.6(4)
O(1)-C(8)-O(2)	123.3(3)	C(32)-C(31)-C(30)	127.8(6)
O(1)-C(8)-C(7)	123.9(3)	C(31)-C(32)-C(33)	128.3(8)
O(2)-C(8)-C(7)	112.8(2)	C(8')-O(2')-C(9')	116.2(2)
C(7)-C(10)-C(11)	124.7(2)	C(11')-O(4')-C(12')	117.7(2)
C(7)-C(10)-C(4)	114.3(2)	C(15')-O(6')-C(6')	112.3(2)
C(11)-C(10)-C(4)	120.9(2)	H(7')-O(7')-C(5')	100(3)
O(3)-C(11)-O(4)	125.4(2)	C(6')-O(8')-C(16')	116.57(19)
O(3)-C(11)-C(10)	123.0(2)	C(24')-O(9')-C(18')	108.1(2)
O(4)-C(11)-C(10)	111.5(2)	C(25')-O(10')-C(18')	108.6(3)
C(14)-C(13)-C(15)	122.7(2)	C(7')-C(1')-C(6')	108.8(2)
C(14)-C(13)-C(5)	128.1(2)	C(7')-C(1')-C(2')	109.0(2)
C(15)-C(13)-C(5)	109.2(2)	C(6')-C(1')-C(2')	105.5(2)
O(5)-C(15)-O(6)	120.7(2)	C(17')-C(2')-C(1')	108.1(2)
O(5)-C(15)-C(13)	130.1(2)	C(17')-C(2')-C(3')	113.9(2)
O(6)-C(15)-C(13)	109.1(2)	C(1')-C(2')-C(3')	108.9(2)
O(8)-C(16)-C(18)	106.5(2)	C(26')-C(3')-C(4')	111.9(2)
O(8)-C(16)-C(17)	112.0(2)	C(26')-C(3')-C(2')	112.3(2)
C(18)-C(16)-C(17)	112.4(2)	C(4')-C(3')-C(2')	109.4(2)
C(16)-C(17)-C(2)	112.3(2)	C(10')-C(4')-C(5')	105.9(2)
O(10)-C(18)-O(9)	105.8(2)	C(10')-C(4')-C(3')	108.8(2)
O(10)-C(18)-C(19)	110.9(2)	C(5')-C(4')-C(3')	110.2(2)
O(9)-C(18)-C(19)	107.8(2)	O(7')-C(5')-C(13')	111.6(2)
O(10)-C(18)-C(16)	107.97(19)	O(7')-C(5')-C(4')	108.3(2)
O(9)-C(18)-C(16)	109.9(2)	C(13')-C(5')-C(4')	113.2(2)
C(19)-C(18)-C(16)	114.2(2)	O(7')-C(5')-C(6')	113.5(2)
C(18)-C(19)-C(20)	116.6(2)	C(13')-C(5')-C(6')	102.2(2)
C(21)-C(20)-C(19)	116.3(3)	C(4')-C(5')-C(6')	107.95(19)
C(22)-C(21)-C(20)	145.0(7)	O(8')-C(6')-O(6')	103.74(19)
C(21)-C(22)-C(23)	140.1(9)	O(8')-C(6')-C(1')	111.0(2)
O(9)-C(24)-C(25)	104.2(2)	O(6')-C(6')-C(1')	109.3(2)
O(10)-C(25)-C(24)	103.1(2)	O(8')-C(6')-C(5')	115.4(2)

O(6')-C(6')-C(5')	107.22(19)	C(17')-C(16')-C(18')	113.9(2)
C(1')-C(6')-C(5')	109.8(2)	C(16')-C(17')-C(2')	111.5(2)
C(10')-C(7')-C(8')	123.0(2)	O(9')-C(18')-O(10')	106.5(2)
C(10')-C(7')-C(1')	114.4(2)	O(9')-C(18')-C(19')	109.3(2)
C(8')-C(7')-C(1')	122.5(2)	O(10')-C(18')-C(19')	109.5(3)
O(1')-C(8')-O(2')	124.4(2)	O(9')-C(18')-C(16')	110.9(2)
O(1')-C(8')-C(7')	123.6(2)	O(10')-C(18')-C(16')	109.3(2)
O(2')-C(8')-C(7')	112.0(2)	C(19')-C(18')-C(16')	111.2(3)
C(7')-C(10')-C(11')	126.4(2)	C(18')-C(19')-C(20')	114.9(3)
C(7')-C(10')-C(4')	113.9(2)	C(21')-C(20')-C(19')	114.9(4)
C(11')-C(10')-C(4')	119.6(2)	C(22')-C(21')-C(20')	152.9(9)
O(3')-C(11')-O(4')	124.3(3)	C(21')-C(22')-C(23')	152.8(9)
O(3')-C(11')-C(10')	122.2(3)	O(9')-C(24')-C(25')	107.9(3)
O(4')-C(11')-C(10')	113.3(2)	O(10')-C(25')-C(24')	107.6(3)
C(14')-C(13')-C(15')	123.2(3)	C(27')-C(26')-C(3')	113.5(2)
C(14')-C(13')-C(5')	128.3(3)	C(28')-C(27')-C(26')	113.7(3)
C(15')-C(13')-C(5')	108.5(2)	C(27')-C(28')-C(29')	112.4(4)
O(5')-C(15')-O(6')	121.4(3)	C(30')-C(29')-C(28')	122.7(7)
O(5')-C(15')-C(13')	129.3(3)	C(29')-C(30')-C(31')	113.5(10)
O(6')-C(15')-C(13')	109.3(2)	C(32')-C(31')-C(30')	151.4(11)
O(8')-C(16')-C(17')	110.8(2)	C(31')-C(32')-C(33')	139.8(13)
O(8')-C(16')-C(18')	106.2(2)		

Symmetry transformations used to generate equivalent atoms:

Table A.4.1 Anisotropic displacement parameters ($Å^2 x\ 10^3$) for wood_im02. The anisotropic displacement factor exponent takes the form:

$-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	36(1)	36(1)	85(2)	20(1)	30(1)	16(1)
O(2)	25(1)	37(1)	35(1)	7(1)	8(1)	6(1)
O(3)	33(1)	32(1)	68(2)	8(1)	-12(1)	9(1)
O(4)	31(1)	23(1)	44(1)	4(1)	4(1)	7(1)
O(5)	41(1)	33(1)	28(1)	-1(1)	2(1)	8(1)
O(6)	28(1)	24(1)	25(1)	5(1)	4(1)	5(1)
O(7)	22(1)	27(1)	29(1)	4(1)	7(1)	2(1)
O(8)	24(1)	22(1)	31(1)	1(1)	2(1)	8(1)
O(9)	27(1)	31(1)	53(1)	19(1)	8(1)	5(1)
O(10)	25(1)	24(1)	43(1)	8(1)	4(1)	6(1)
C(1)	23(1)	22(1)	32(2)	8(1)	7(1)	2(1)
C(2)	21(1)	25(1)	36(2)	3(1)	0(1)	3(1)
C(3)	26(1)	25(1)	31(2)	3(1)	1(1)	5(1)
C(4)	25(1)	24(1)	31(1)	8(1)	-1(1)	4(1)
C(5)	19(1)	23(1)	28(1)	5(1)	5(1)	4(1)
C(6)	24(1)	21(1)	25(1)	3(1)	4(1)	6(1)
C(7)	20(1)	24(1)	34(2)	3(1)	2(1)	3(1)
C(8)	20(1)	24(1)	45(2)	5(1)	3(1)	1(1)
C(9)	32(2)	58(2)	42(2)	13(2)	17(1)	10(1)
C(10)	19(1)	22(1)	35(2)	2(1)	0(1)	2(1)
C(11)	20(1)	28(2)	41(2)	7(1)	5(1)	2(1)
C(12)	41(2)	27(2)	62(2)	2(1)	13(2)	14(1)
C(13)	20(1)	25(1)	29(1)	2(1)	2(1)	5(1)
C(14)	33(2)	32(2)	40(2)	4(1)	5(1)	4(1)
C(15)	22(1)	26(1)	30(2)	2(1)	4(1)	6(1)
C(16)	24(1)	23(1)	28(1)	2(1)	4(1)	1(1)
C(17)	26(1)	23(1)	37(2)	3(1)	1(1)	3(1)
C(18)	22(1)	22(1)	41(2)	7(1)	10(1)	1(1)
C(19)	32(2)	29(2)	50(2)	-3(1)	5(1)	8(1)
C(20)	50(2)	59(2)	44(2)	-2(2)	11(2)	15(2)

C(21)	98(3)	122(4)	72(3)	45(3)	38(3)	53(3)
C(22)	138(5)	231(8)	92(4)	86(5)	60(4)	107(5)
C(23)	164(5)	196(7)	77(3)	58(4)	22(3)	110(5)
C(24)	39(2)	43(2)	48(2)	17(2)	9(1)	10(1)
C(25)	32(1)	27(2)	43(2)	5(1)	0(1)	9(1)
C(26)	35(2)	35(2)	39(2)	2(1)	-10(1)	4(1)
C(27)	61(2)	39(2)	44(2)	8(2)	-15(2)	1(2)
C(28)	76(3)	48(2)	55(2)	5(2)	-23(2)	13(2)
C(29)	92(3)	57(2)	63(3)	15(2)	-18(2)	11(2)
C(30)	106(4)	92(3)	63(3)	21(3)	-17(3)	31(3)
C(31)	112(4)	94(4)	63(3)	14(3)	3(3)	39(3)
C(32)	115(4)	174(6)	66(3)	17(4)	7(3)	24(4)
C(33)	147(7)	284(11)	145(6)	85(7)	-2(5)	49(7)
O(1')	24(1)	41(1)	66(1)	3(1)	10(1)	8(1)
O(2')	45(1)	32(1)	91(2)	10(1)	35(1)	7(1)
O(3')	112(2)	40(1)	67(2)	9(1)	51(2)	31(1)
O(4')	51(1)	37(1)	35(1)	7(1)	21(1)	9(1)
O(5')	45(1)	36(1)	40(1)	13(1)	4(1)	10(1)
O(6')	29(1)	25(1)	32(1)	5(1)	4(1)	7(1)
O(7')	24(1)	29(1)	33(1)	3(1)	5(1)	0(1)
O(8')	28(1)	36(1)	27(1)	2(1)	9(1)	11(1)
O(9')	44(1)	50(1)	37(1)	-11(1)	2(1)	10(1)
O(10')	32(1)	67(2)	44(1)	-8(1)	8(1)	13(1)
C(1')	22(1)	30(2)	28(1)	-1(1)	1(1)	3(1)
C(2')	29(1)	38(2)	28(2)	7(1)	3(1)	10(1)
C(3')	33(1)	29(2)	32(2)	7(1)	8(1)	8(1)
C(4')	27(1)	25(1)	28(1)	-1(1)	5(1)	6(1)
C(5')	22(1)	26(1)	27(1)	1(1)	3(1)	2(1)
C(6')	25(1)	28(2)	26(1)	5(1)	6(1)	8(1)
C(7')	23(1)	28(1)	29(1)	5(1)	1(1)	7(1)
C(8')	24(1)	33(2)	29(2)	4(1)	3(1)	7(1)
C(9')	71(3)	36(2)	125(4)	16(2)	57(3)	-1(2)
C(10')	26(1)	29(2)	27(1)	4(1)	2(1)	11(1)
C(11')	29(1)	33(2)	32(2)	0(1)	4(1)	14(1)
C(12')	43(2)	62(2)	31(2)	1(2)	16(1)	7(2)
C(13')	19(1)	30(2)	31(2)	4(1)	3(1)	5(1)

C(14')	31(1)	39(2)	33(2)	6(1)	3(1)	9(1)
C(15')	24(1)	33(2)	33(2)	7(1)	5(1)	8(1)
C(16')	34(1)	36(2)	27(2)	4(1)	9(1)	6(1)
C(17')	39(2)	43(2)	28(2)	6(1)	6(1)	10(1)
C(18')	35(2)	46(2)	31(2)	-1(1)	6(1)	8(1)
C(19')	76(2)	62(2)	47(2)	10(2)	35(2)	17(2)
C(20')	84(3)	86(3)	58(2)	15(2)	42(2)	21(2)
C(21')	213(7)	143(5)	129(5)	74(5)	141(5)	98(5)
C(22')	256(9)	100(5)	114(5)	29(4)	114(5)	68(5)
C(23')	214(7)	110(4)	97(4)	49(4)	72(4)	41(4)
C(24')	81(3)	52(3)	117(4)	-12(2)	-19(3)	25(2)
C(25')	83(3)	75(3)	80(3)	-7(2)	-14(2)	37(2)
C(26')	47(2)	38(2)	38(2)	9(1)	6(1)	19(1)
C(27')	72(2)	55(2)	47(2)	20(2)	11(2)	31(2)
C(28')	116(4)	81(3)	67(3)	24(2)	-1(2)	66(3)
C(29')	273(9)	147(6)	101(4)	31(4)	-22(5)	157(6)
C(30')	530(20)	125(6)	104(6)	24(5)	-51(8)	120(9)
C(31')	411(16)	170(8)	97(6)	52(6)	-13(8)	38(9)
C(32')	580(20)	150(8)	70(5)	29(5)	2(9)	25(10)
C(33')	181(6)	115(5)	96(4)	28(3)	2(4)	62(4)

Table A.2.5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3).

	x	y	z	U(eq)
H(7)	-1890(50)	7100(30)	1197(14)	83(12)
H(1A)	3332	8896	557	31
H(2A)	4637	9097	1401	33
H(3A)	1915	8182	1856	33
H(4A)	2088	6643	1546	32
H(9A)	6744	8856	-494	64
H(9B)	6761	7807	-491	64
H(9C)	7986	8519	-82	64
H(12A)	3970	4312	381	63
H(12B)	4515	4516	965	63
H(12C)	5856	4902	583	63
H(14A)	-768	5142	403	42
H(14B)	-426	5389	1008	42
H(16B)	-205	8866	1501	30
H(17C)	2422	9818	1758	34
H(17D)	2726	10064	1209	34
H(19A)	-1269	11111	1602	44
H(19B)	574	10869	1792	44
H(20A)	-2108	10613	2289	61
H(20B)	-2479	9663	1960	61
H(21A)	553	10314	2583	107
H(22A)	-979	8698	2509	166
H(23A)	765	8311	3045	199
H(23B)	1052	9300	3333	199
H(23C)	2302	9078	2912	199
H(24A)	-1269	10300	159	50
H(24B)	-1331	11282	429	50
H(25A)	-3465	10740	904	40
H(25B)	-3958	9969	441	40
H(26A)	4831	8633	2237	45

H(26B)	5489	7910	1865	45
H(27A)	2939	7386	2540	60
H(27B)	3942	6729	2222	60
H(28A)	5738	8050	2990	73
H(28B)	6579	7282	2704	73
H(29A)	3910	6973	3378	86
H(29B)	4586	6177	3067	86
H(30A)	7353	6570	3500	103
H(30B)	6798	7429	3788	103
H(31A)	5216	5654	3933	105
H(32A)	6366	7118	4597	142
H(33A)	5520	6393	5183	282
H(33B)	5963	5519	4880	282
H(33C)	4041	5766	4799	282
H(7')	180(50)	7020(30)	-2367(14)	82(13)
H(1'A)	-5337	5518	-3092	33
H(2'A)	-5877	6934	-3338	37
H(3'A)	-2753	8048	-2971	36
H(4'A)	-3075	8110	-2088	32
H(9'A)	-8636	3561	-2384	114
H(9'B)	-9923	4226	-2537	114
H(9'C)	-9096	4292	-1975	114
H(12D)	-7498	6402	-801	68
H(12E)	-8265	7165	-1068	68
H(12F)	-6379	7400	-753	68
H(14C)	-1536	6606	-1098	40
H(14D)	-1376	7579	-1323	40
H(16A)	-1047	7171	-3273	38
H(17A)	-4159	6175	-3842	43
H(17B)	-3439	7230	-3826	43
H(19C)	339	7497	-4020	71
H(19D)	-1375	7020	-4374	71
H(20C)	2106	6672	-4443	88
H(20D)	432	6042	-4752	88
H(21B)	-121	7270	-5101	172
H(22B)	3004	7633	-5132	176

H(23D)	3213	8458	-5669	200
H(23E)	1342	8722	-5571	200
H(23F)	1440	7869	-5954	200
H(24C)	-570	4346	-4264	101
H(24D)	-1560	4339	-3765	101
H(25C)	874	4883	-3356	94
H(25D)	1834	4959	-3858	94
H(26C)	-6294	8198	-2780	47
H(26D)	-4637	8988	-2618	47
H(27C)	-4158	9117	-3452	65
H(27D)	-5739	8293	-3626	65
H(28C)	-6234	9958	-3133	98
H(28D)	-7792	9141	-3342	98
H(29C)	-5487	10143	-3961	192
H(29D)	-7002	9321	-4173	192
H(30C)	-7498	10891	-3756	298
H(30D)	-8944	10070	-4022	298
H(31B)	-7594	11350	-4471	273
H(32B)	-6534	10179	-4969	328
H(33D)	-6881	10754	-5638	189
H(33E)	-6979	11690	-5329	189
H(33F)	-8735	10953	-5475	189

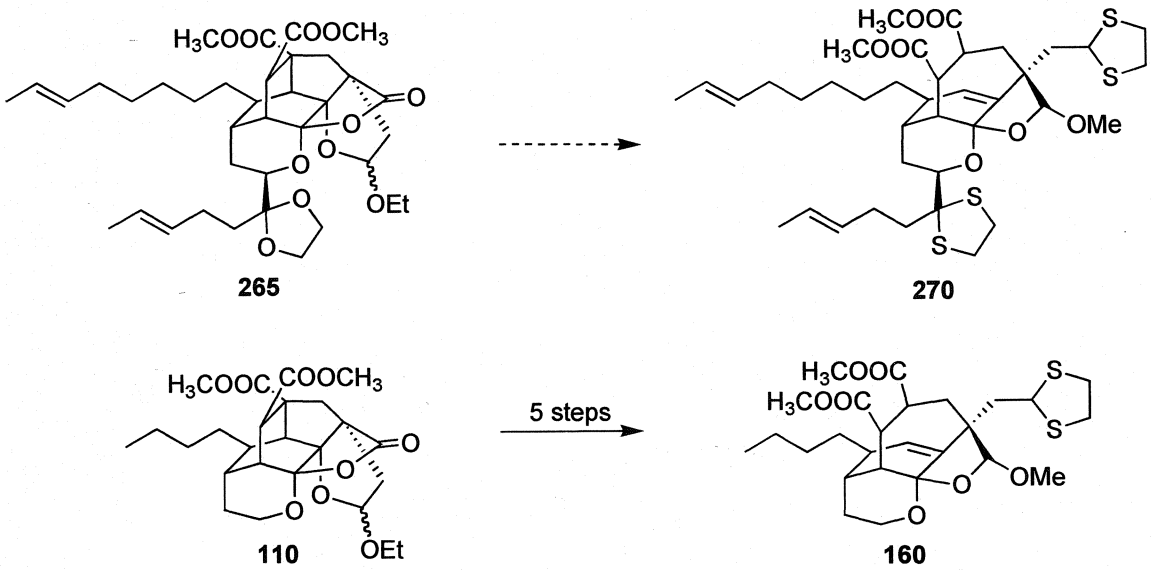
Chapter 4

The Serendipitous Discovery of a Novel SmI_2 Initiated Cascade Cyclization

4.1 Remaining Challenges.

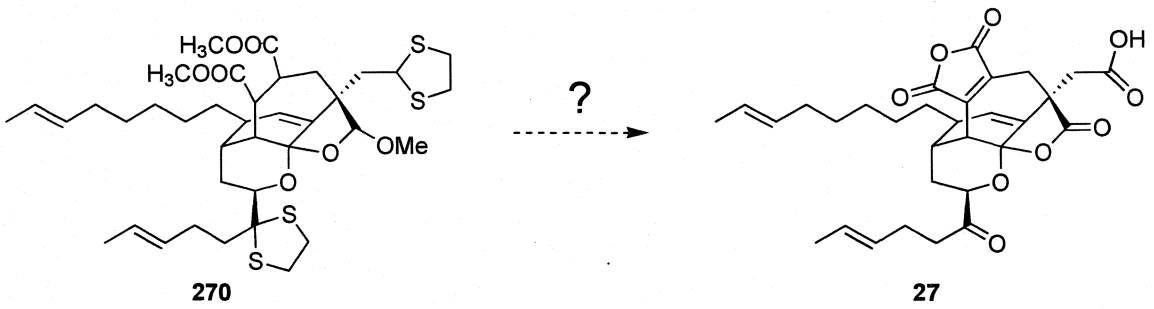
In the previous chapter, a fully functionalized intermediate (**265**) that contained every carbon-carbon bond found in the phomoidrides had been synthesized. Several of the remaining challenges had been previously addressed in the model studies (Scheme 4.1, **110δ 160**), including: 1) opening the acetal to free the tertiary hydroxyl, 2) protection of the lactone as its methyl acetal, and 3) xanthate formation and fragmentation.

Scheme 4.1 Remaining Challenges Which were Previously Addressed.



The remaining challenges that had not been addressed in model studies were the introduction of the maleate olefin, anhydride formation, deprotection of the dithiolanes, installation of the carboxylic acid and re-installation of the lactone (Scheme 4.2, **270**δ **27**).

Scheme 4.2 Unexplored Challenges.



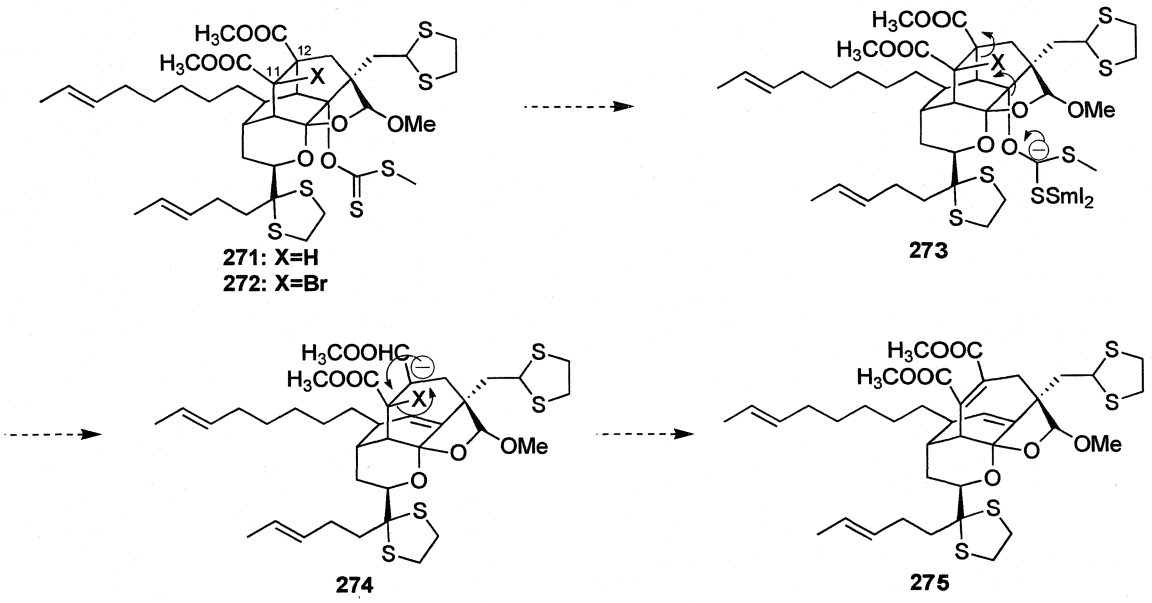
270 **27**

4.2 Fragmentation/Elimination Strategy for Installation of the Maleate.

4.2.1 Introduction.

As established in the model studies, the bridgehead olefin would be formed from the SmI_2/HMPA promoted fragmentation of a xanthate such as **271**. In this fragmentation, an anion (or radical) is produced at C(12) (**273**, Scheme 4.3). It was imagined that the maleate olefin between C(11) ands C(12) could be formed by eliminating a leaving group at C(11) directly during he fragmentation reaction (**274**δ **275**, Scheme 4.3). To test this idea, it would be necessary to incorporate a leaving group at C(11).

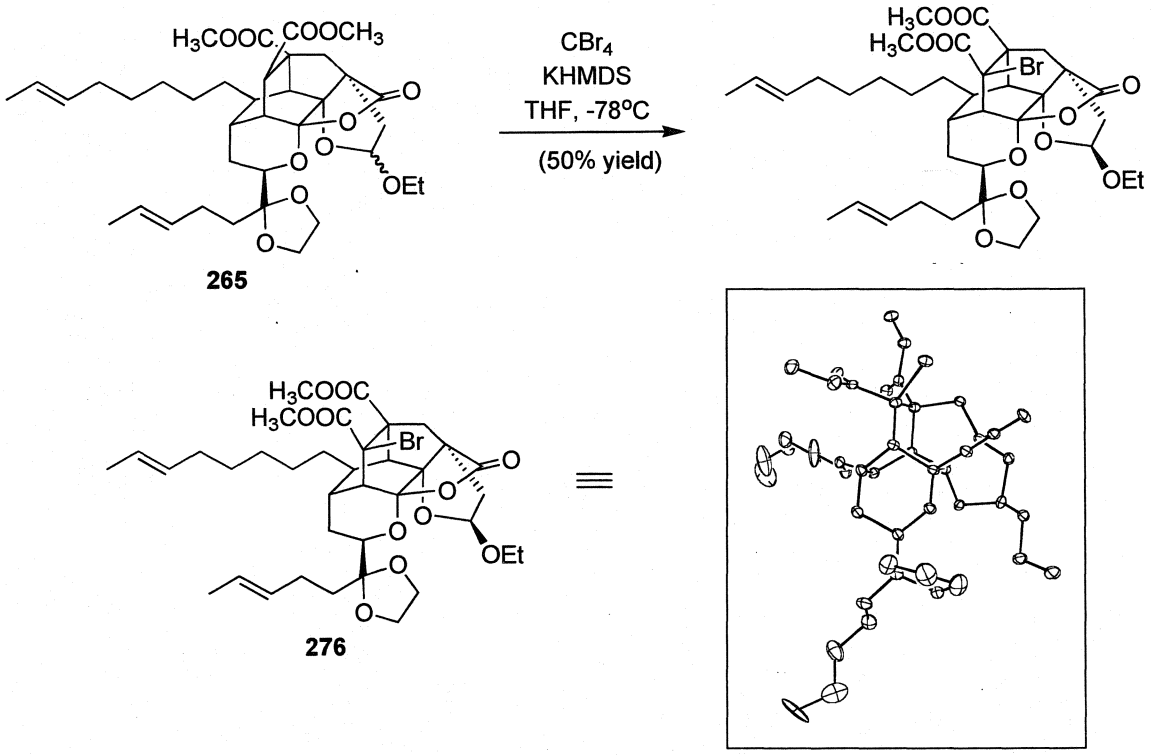
Scheme 4.3 Fragmentation/Elimination Strategy for Maleate Incorporation.



4.2.2 Formation of the C(11) Bromide.

In order to install a leaving group at C(11), ethyl acetal **265** was treated with KHMDS and CBr_4 in THF at –78°C, effectively installing a bromine atom at C(11) in moderate yield (Scheme 4.4). This reaction provided a single, crystalline product, **276**, whose structure was confirmed by single crystal X-ray analysis.

Scheme 4.4 Bromination of Acetal 265.

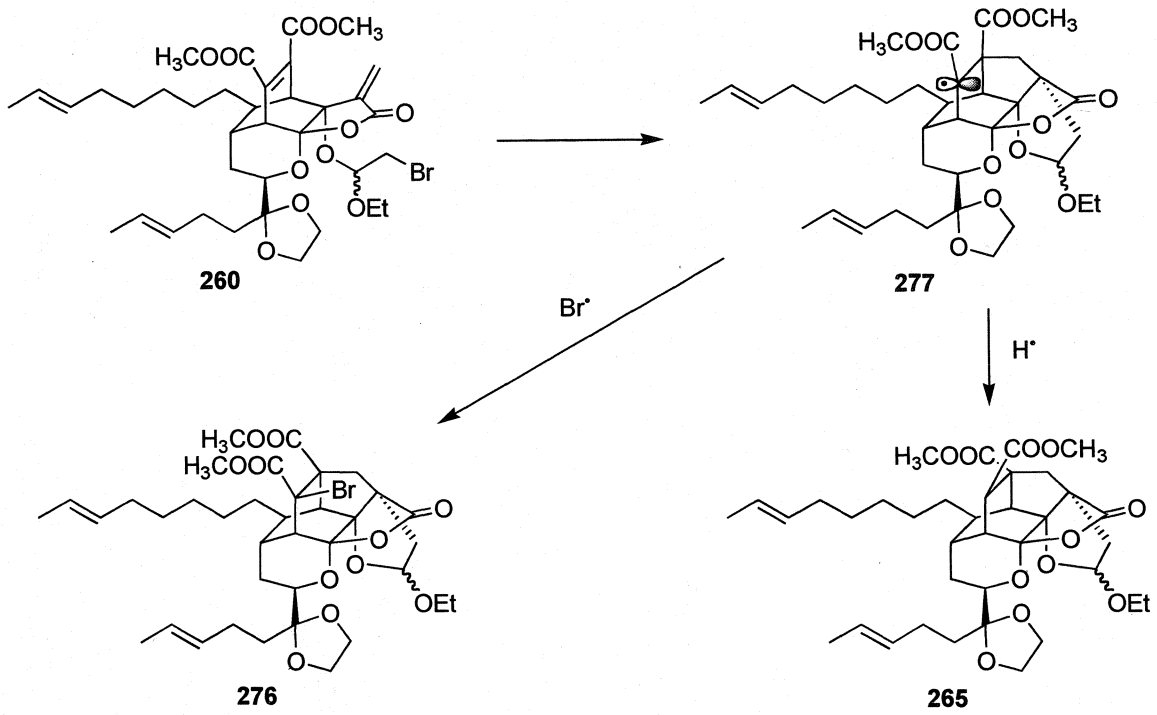


4.2.3 Atom-transfer Cyclization.

4.2.3.1 Rationale and Mechanism for Atom-transfer Cyclization.

Although bromination of **265** was an effective method to install the leaving group at C(11), it was envisioned that δ-bromoester **276** might be formed in a single step from bromoacetal **260** by an atom-transfer cyclization, if the ultimate radical in the cascade sequence, **277**was trapped with a halogen source rather than being reduced (Scheme 4.5, **277**δ **276**).

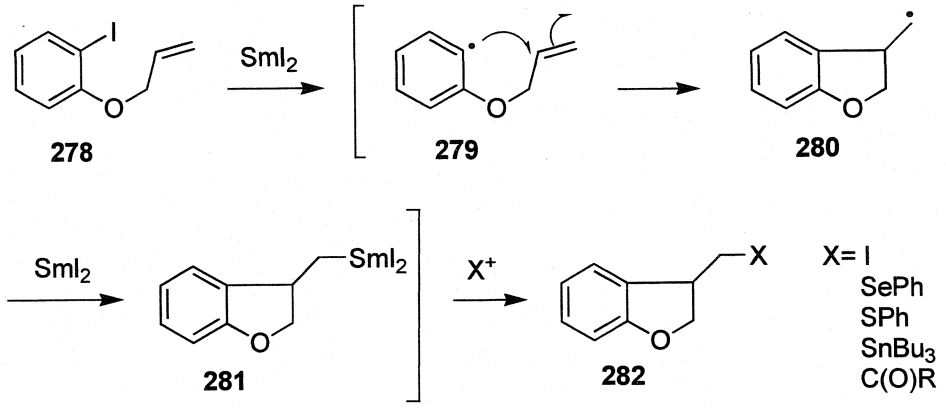
Scheme 4.4 Atom-transfer Cyclization.



4.2.3.2 The Use of SmI_2 in Atom-transfer Cyclizations.

Samarium(II) iodide (SmI_2) is uniquely well suited to perform "atom-transfer" reactions. Radicals can be formed from the halide and then undergo standard radical reactions, such as radical cyclization (Scheme 4.6 **278**δ **280**). Under proper circumstances, the resultant radical is further reduced to the organosamarium (**281**), which can react with a variety of electrophiles (**281**δ **282**).

Scheme 4.5 Atom-transfer Cyclization with SmI_2.

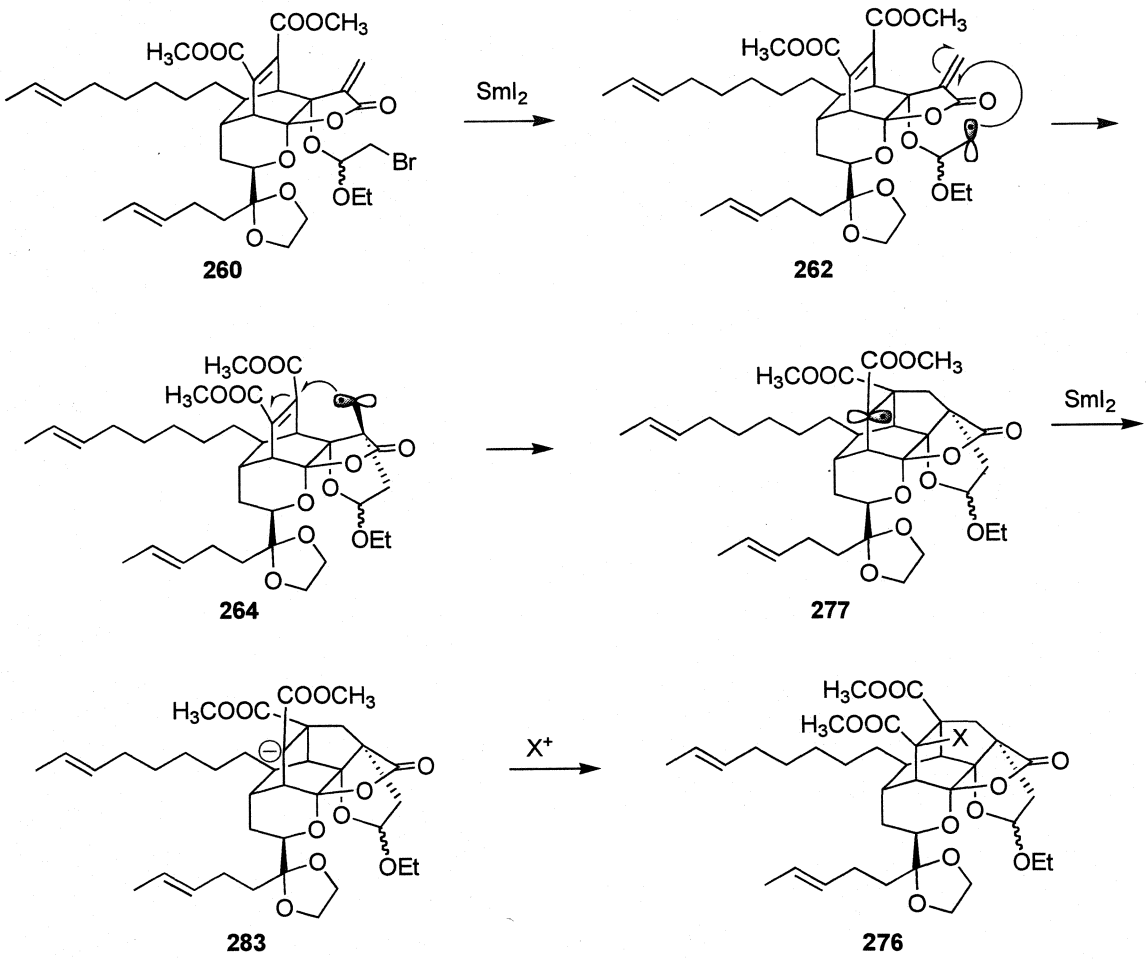


Although the products in these reactions might themselves be reactive toward SmI_2, there is little risk of this, as SmI_2 is itself quenched by the added electrophile. There are some limitations to this method, as the initially formed radical (i.e. **279**) must cyclize faster than it is reduced to the organosamarium.

4.2.3.3 Application Toward Bromoacetal Cyclization.

While over reduction of the initial radical might be a concern, the radical cyclization of bromoacetals with SmI_2/HMPA was precedented, so this was not expected to be problematic. Scheme 4.7 shows how this type of cyclization could be applied to the phomoidrides. The initially formed radical would undergo a 5-*exo-trig* cyclization to give **264**. This could undergo a second 5-*exo-trig* radical cyclization,This reaction might also proceed by reduction of 264 to the organosamarium, followed by michael addition into the maleate. This possibility was left out of Scheme 4.6 in the interest of clarity. followed by further reduction to the organosamarium to provide a samarium enolate that can then react with a suitable electrophile.

Scheme 4.6 Possible Atom-transfer Cyclization of Bromoacetal 260.

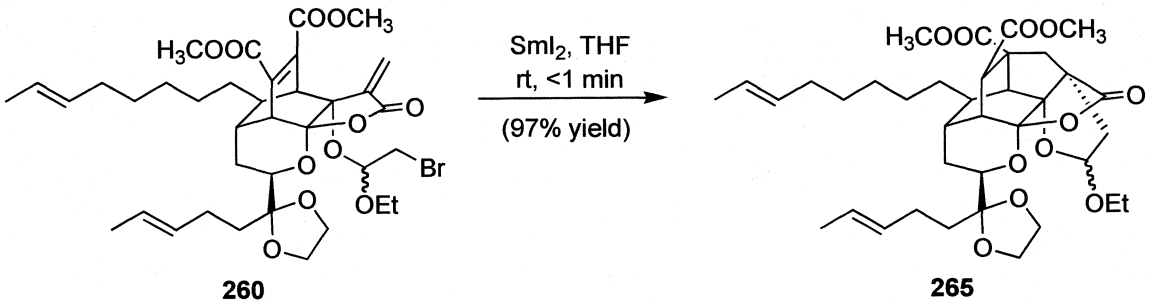


4.2.3.4 Control Experiment.

Before attempting this type of atom-transfer cyclization on our substrate (**260**), it was first necessary to ascertain whether the desired 5-*exo-trig*, 5-*exo-trig* cascade cyclization, which had previously been performed using tin hydride methods, could in fact occur with SmI_2. A control experiment was performed, using SmI_2 with no added electrophile.Although literature precedent clearly stated that HMPA was required for the

reaction of bromoacetals with SmI2, This reaction was first performed with no addatives, in the interest of avoiding the use of this toxic co-solvent. As is apparent, this was a serendipitous choice. To our delight, when bromoacetal **265** was added to a solution of SmI_2 in THF, the desired 5-*exo-trig*, 5-*exo-trig* cascade cyclization worked extremely well, providing acetal **265** in 96% yield (compare to 54% yield via tin-hydride methods). Furthermore, the undesired 6-*endo-trig*, 4-*exo-trig* product could not be detected in the reaction mixture. Along with the increased yield, this reaction also had the benefit of being very easy to perform, taking place very rapidly at ambient temperature, without any toxic or hard to remove reagents or solvents, and requiring only removal of the inorganic salts to afford very pure material.

Scheme 4.7 SmI_2 Promoted Cascade Cyclization of Bromoacetal 260.



260 **265**

4.3 Mechanism of the Cascade Cyclization.

4.3.1 Mechanistic Considerations.

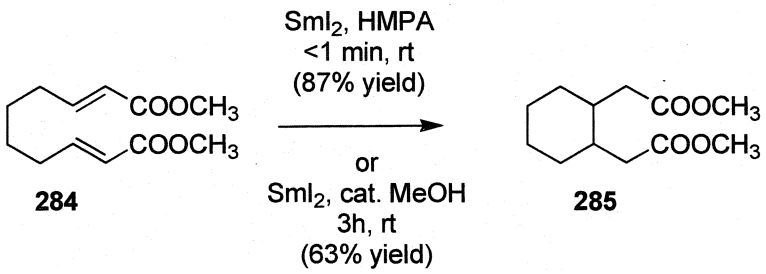
The excellent yield and selectivity of this reaction were somewhat puzzling, as there was no obvious reason for the 5-*exo-trig*, 5-*exo-trig* cyclization mode to be enhanced. (In fact, the 6-*endo-trig*, 4-*exo-trig* cyclization was expected to be enhanced by

the Lewis acidity of the samarium reagent.) Along with the superb effectiveness of this reaction, we were also surprised by the mild conditions required for its completion, as it was performed at ambient temperature, without any additives, and was complete in less than one minute.

This intriguing combination of increased selectivity, and the ease with which this reaction was performed led us to question the mechanism. Alkyl bromides are relatively unreactive toward SmI_2, being reduced only when heated, or when HMPA is added as a cosolvent. In fact, the literature report of bromoacetal cyclizations with SmI_2 states that HMPA is essential for this reaction to proceed at a reasonable rate.

In addition, it is well precedented that δ,δ-unsaturated esters can react with SmI_2, to afford a vinylogous ketyl. Cyclization precursor **260** has two δ-δ-unsaturated esters, the maleate and the *exo*-methylene lactone. This allowed for the possibility that the cascade sequence might be initiated by vinylogous ketyl formation rather than bromide reduction. (*vide infra*). In fact, the reductive δ-coupling of bis-δ,δ-unsaturated esters has been reported (Scheme 4.9).

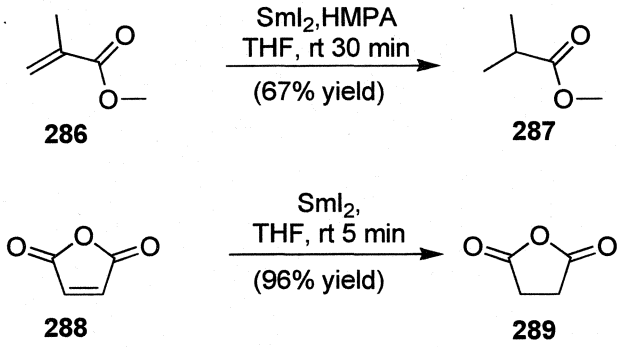
Scheme 4.8 Reductive Coupling of Bis-δ,δ-unsaturated Esters.



284 **285**

Finally, the reduction of δ,δ-unsaturated esters by SmI_2 has been studied, and it was shown that while most δ,δ-unsaturated acid derivatives require HMPA for reduction by SmI_2, those in which two carbonyls are attached directly to the olefin (e.g. a maleate) are readily reduced without any additives. (Scheme 4.10)

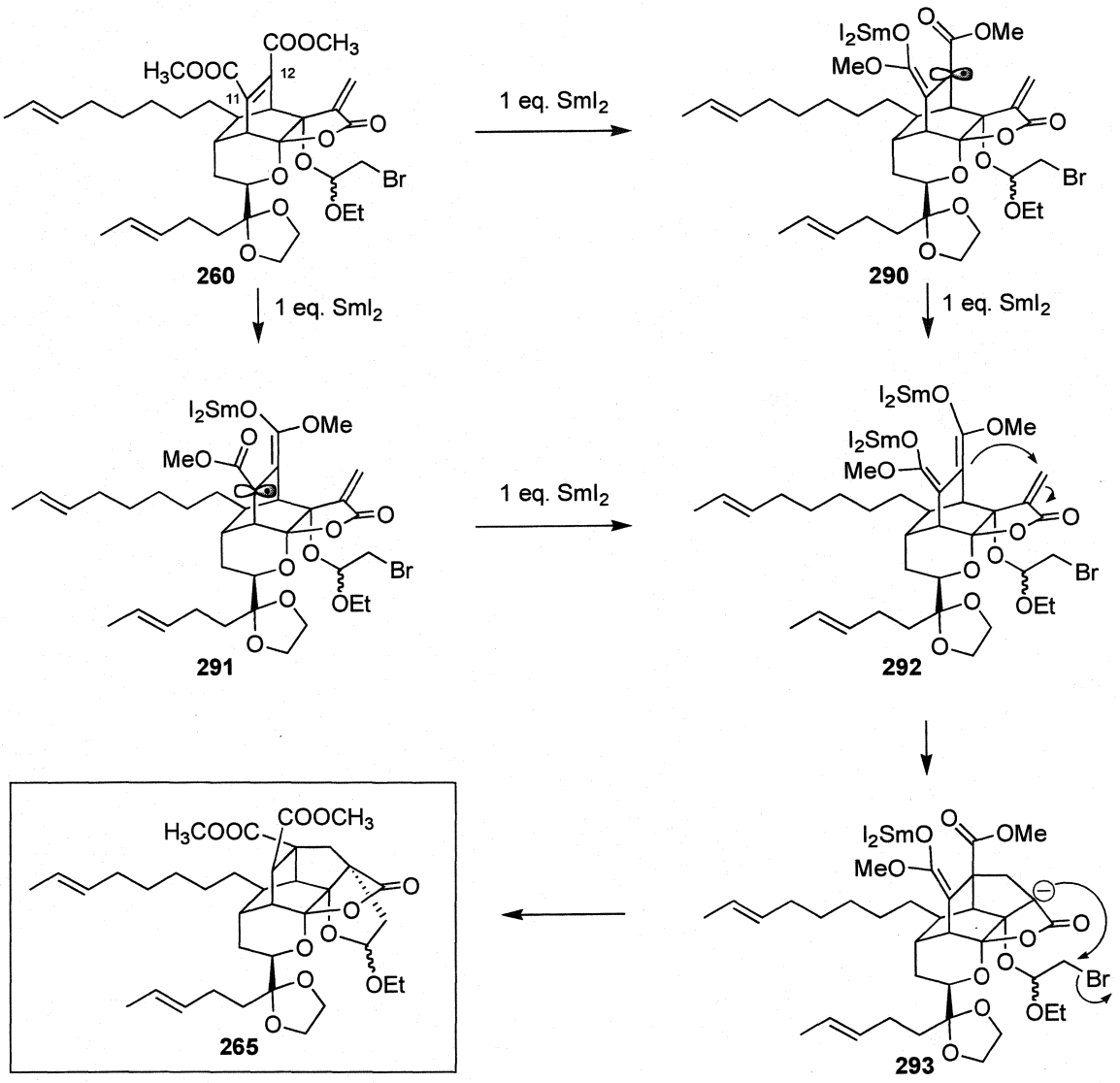
Scheme 4.9 Conjugate Reductions with SmI_2.



4.3.2 Proposed Mechanism.

This combination of information suggested that the most reactive moiety toward SmI_2 was the maleate, and that observed cyclization was, in fact, taking place by a different mechanism than was originally planned. Thus, as depicted in Scheme 4.11, reduction of the C(11)-C(12) maleate would form bis-enolate **292** via the vinylogous ketyl **290** or **291**. This bis-enolate (**292**) could then undergo a 5-*endo-trig* cyclization into the *exo*-methylene lactone (**292δ 293**), giving an enolate that could then undergo a 5-*exo-tet* displacement of the bromide, thus completing the cyclization to **265**. It is possible that the initial cyclization is a radical event, in which case the resultant C(14) radical would be reduced to the enolate prior to the second cyclization. This mechanism was not depicted in the interest of clarity.

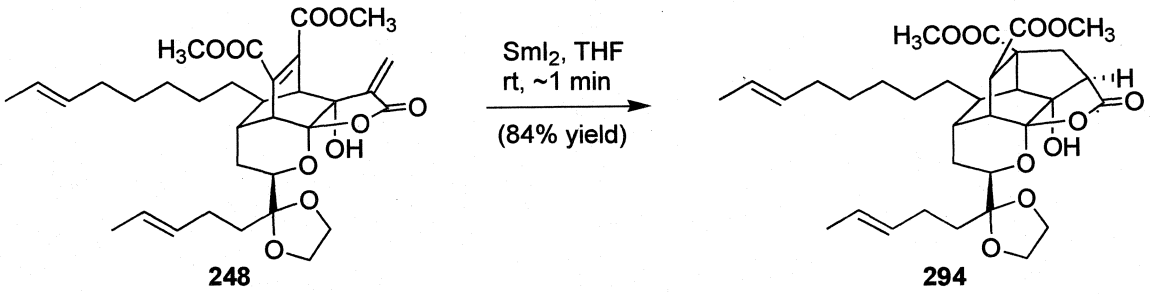
Scheme 4.10 Potential "Top-Down" Cascade Cyclization Mechanism.



4.3.3 Testing the Proposed Mechanism.

To test our hypothesis, two experiments were carried out. The first was designed to test if the cyclization could, in fact, proceed from the top-down. Thus, *exo*-methylene lactone **248** was subjected to the same reaction conditions (SmI_2, THF, rt ~1 min). This cleanly underwent the proposed cyclization to give isotwistane **294**, proving that the bromoacetal moiety was not required for cyclization (Scheme 4.11).

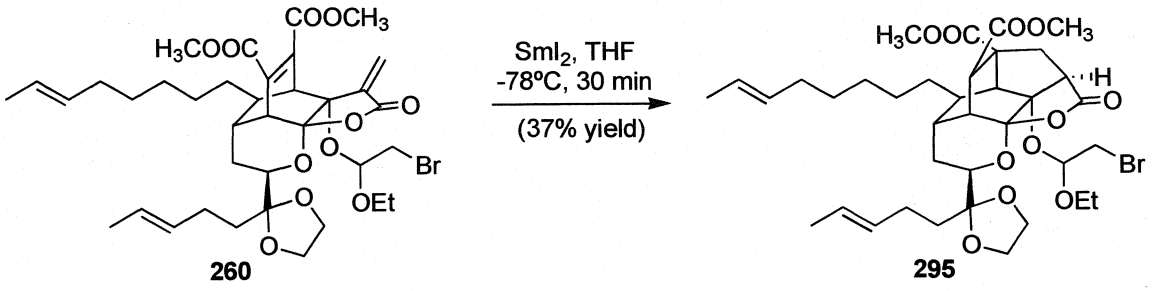
Scheme 4.11 Cyclization of Lactone 248.



While the conversion of **248** to **294** showed that the bromoacetal was not required for cyclization to form the isotwistane, it did not prove that the "bottom-up" cyclization was not taking place when the bromoacetal substrate (**260**) was employed. For this reason, an additional experiment was performed, in which bromoacetal **260** was treated with SmI_2 at –78°C for 30 minutes. This reaction gave a mixture of products from which bromoacetal **295** was isolated (Scheme 4.12). Bromoacetal **295** has undergone the "top" cyclization to form the isotwistane, but not the "bottom" cyclization of the complete

cascade. This was proof that the SmI_2 promoted cyclization of **260** to **265** does not take place from the "bottom-up" as originally planned, and as occurs with Bu_3SnH.

Scheme 4.12 Low-temperature Cyclization of Bromoacetal 260.



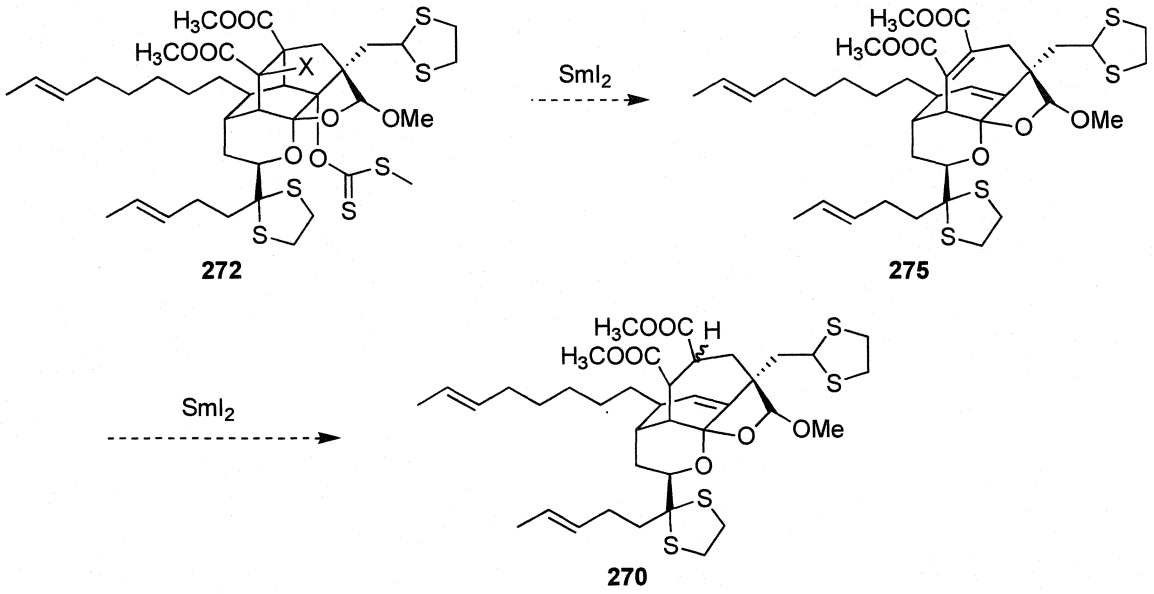
Interestingly, this cascade sequence involves a 5-*endo-trig* cyclization, which, according to Baldwin's rules for ring closure is a disfavored process. Several successful examples of 5-*endo-trig* cyclizations have appeared in the literature however, and these have recently been reviewed. Also, recent theoretical work has suggested that the 5-*endo-trig* cyclization may, in fact, be a *favored* mode of cyclization.

4.4 Implications for the Fragmentation/Elimination Sequence.

Literature precedent, along with these studies, showed that SmI_2 reduces maleates very rapidly. As a result, the original idea to perform the fragmentation reaction with concomitant elimination to form the maleate would likely be unsuccessful (Scheme 4.3). Since SmI_2 was used in the xanthate fragmentation, the maleate that would hopefully be formed in this reaction (**275**) would most definitely be reduced under the reaction

conditions to **270**, which is the product that would formed upon fragmentation of the non-brominated system.

Scheme 4.13 Maleate Reduction in a Fragmentation/Elimination Strategy.



4.5 Conclusion.

In an attempt to perform an "atom-transfer" cyclization of the Stork bromoacetal **260** in the key cascade cyclization step, SmI_2 was employed as a reductant, and gave **265** in excellent yield under very mild and simple conditions. The reaction was found to proceed *via* a completely different mechanism than was previously employed. When tin hydride conditions are used, acetal **265** is produced by a "bottom-up" 5-*exo-trig*, 5-*exo-trig* mechanism, whereas SmI_2 promoted a "top-down" cascade sequence which was initiated by reduction of the very reactive maleate moiety, which is followed by a 5-*endo-trig* cyclization and a 5-*exo-tet* intramolecular alkylation. These results showed that the

pursuit a strategy in which the maleate would be unveiled during the fragmentation would likely not be fruitful.

4.6 Experimental Section.

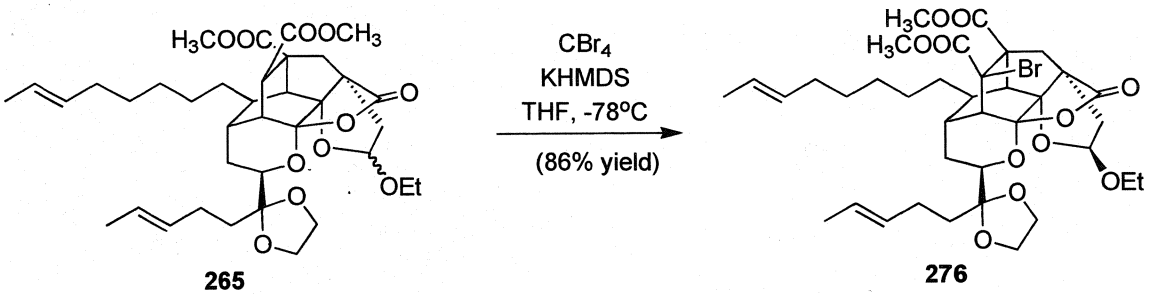
4.6.1 Materials and Methods.

Unless stated otherwise, reactions were performed in flame dried glassware under a nitrogen atmosphere, using freshly distilled solvents. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl. Methylene chloride (CH_2Cl_2) and triethylamine (Et_3N) were distilled from calcium hydride. All other commercially obtained reagents were used as received.

Unless stated otherwise, all reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using E. Merck silica gel 60 F_{254} precoated plates (0.25 mm). Column or flash chromatography was performed with the indicated solvents using silica gel (230-400 mesh) purchased from Silicycle. In general, the chromatography guidelines reported by Still et al. were followed. Infrared spectra were recorded on a Midac M1200 FTIR. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX-500 or Bruker Avance DPX-400 spectrometer. Chemical shifts are reported relative to internal chloroform (^1H, δ 7.26 ppm; ^{13}C, δ 77.23 ppm). High resolution mass spectra were performed at the University of Illinois Mass Spectrometry Center. Single-crystal X-ray analyses were performed by Dr. Christopher Incarvito of Yale University.

4.6.2 Preparative Procedures.

Preparation of δ-Bromoester 276 (TSII-260):

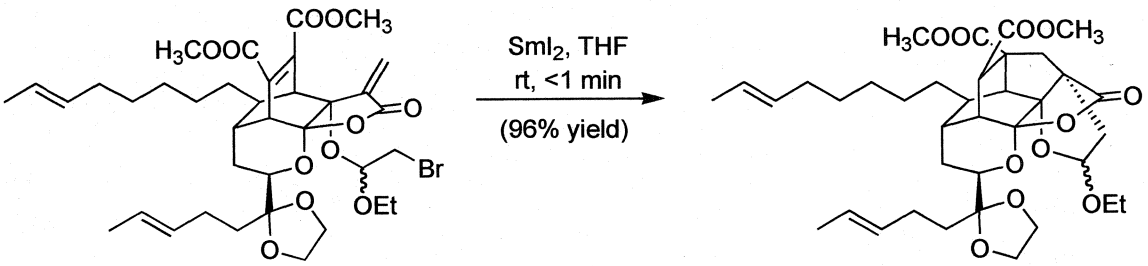


δ-Bromoester 276. To a solution of ethyl acetal **265** (124.5 mg, 0.185 mmol, 1.0 equiv) and CBr_4 (307mg, 0.555 mmol, 3.0 equiv) in THF (2mL) at –78°C was added KHMDS (0.5M in toluene, 1.11mL, 0.925 mmmol, 5.0 equiv). The reaction mixture was stirred at –78°C for 13 min, quenched with saturated aqueous NH_4Cl (2 mL) and diluted with EtOAc (2mL). The phases were separated, and the aqueous layer was extracted with EtOAc (2x 10 mL). The combined organic layers were washed with brine (10ml), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by silica gel chromatography furnished δ-bromoester **276** (70.0 mg, 50.4% yield) as a foamy solid.

δ-Bromoester 276. FTIR (thin film/NaCl) 2927 (m), 2855 (w), 1794 (s), 1742 (s), 1242 (m), 1003 (m), 735 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.45-5.35 (m, 5H), 4.25 (dd, *J*=12.0, 3.3 Hz, 1H), 4.13-4.07 (m, 2H), 3.96-3.87 (m, 2H), 3.79 (s, 3H), 3.67 (s, 3H), 3.37-3.33 (m, 1H), 3.14 (d, *J*=15 Hz, 1H), 2.72-2.63 (m, 3H), 2.15-1.18 (m, 27H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.10, 172.38, 169.51, 131.57, 130.76, 125.14, 124.67, 110.41, 108.83, 106.71, 97.99, 76.30, 76.16, 76.06, 75.27, 66.62, 66.30, 63.91, 62.76, 60.07, 57.52, , 53.70, 52.09, 51.44, 49.90, 43.09 36.64, 34.67.33.77, 32.89, 32.61,

31.64, 29.62, 29.19, 28.06, 25.81, 17.98, 17.96, 14.89. HRMS (ESI) *m/z* 751.2687 [calc'd for $C_{37}H_{52}O_{11}Br$ (M+H) 751.2693].

Preparation of Acetal 265 (TSII-253):



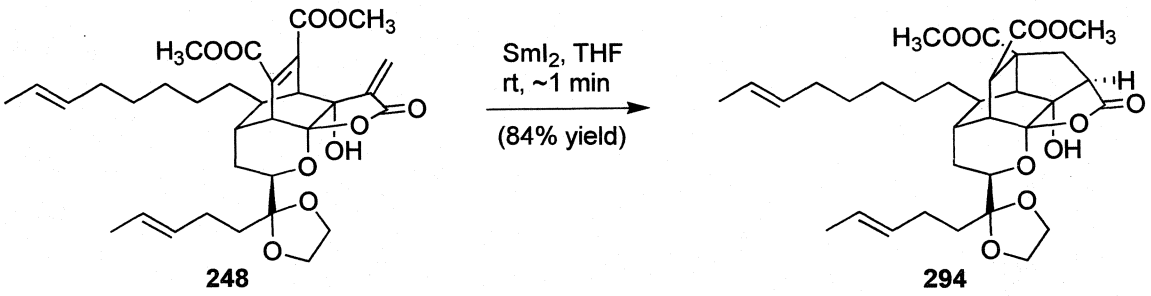
260 **265**

Preparation of 0.1M SmI_2 in THF. Samarium metalNote: Sm metal was either purchased from Strem Chemical as a "powder" or freshly filed from a samarium ingot. In either case, the appearance of the samarium should be that of shiny metallic filings. If the samarium has a "powdery" appearance, it is a sign that the metal has become oxidized. (2.6 g, 17.3 mmol, 1.75 equiv) was placed in a flame-dried 250ml flask and lightly flame-dried under vacuum. THF (100 ml) was then added, and the mixture was lightly degassed by three repetitions of cycles of vacuum (1-2 sec), and nitrogen refilling. 1,2-Diiodoethane (2.8g, 9.95 mmol, 1.0 equiv) was added in one portion, and the degassing sequence was repeated. The time required for initiation of the reaction was variable, but always fastest when freshly filed samarium was employed. Within 30 minutes of the addition of diiodoethane, the reaction mixture should begin to turn a blue-green color. Eventually, the color will change to a deep Prussian blue, which is characteristic of THF solutions of SmI_2. After 3h of stirring, the reagent was deemed to

be of a good quality, and stirring was halted, allowing the excess samarium metal to settle to the bottom. When using this reagent (i.e. transferring by syringe), care was taken to try to take only the supernatant.

Acetal 265. To a solution of SmI_2 in THF (80.5 ml, 8.05 mmol, 3.4 equiv) was added a solution of bromoacetal **260** (1.79g, 2.37 mmol, 1.0 equiv) in THF (5+3+3 ml=11 ml). The reaction mixture was stirred at rt for 10 min, treated with saturated aqueous NH_4Cl (20 ml), 1.0N HCl (5 ml) and EtOAc (20 ml) and the phases were separated. The aqueous layer was extracted with EtOAc (2x 20 ml). The combined organic layers were washed with brine (30 ml) dried over Na_2SO_4 and concentrated *in vacuo*. Purification via silica gel chromatography (20%-33% EtOAc/Hexanes eluent) furnished **265** (2.83g, 96.9% yield) as a pale yellow oil.

Preparation of Isotwistane 294 (IMMIV-243):

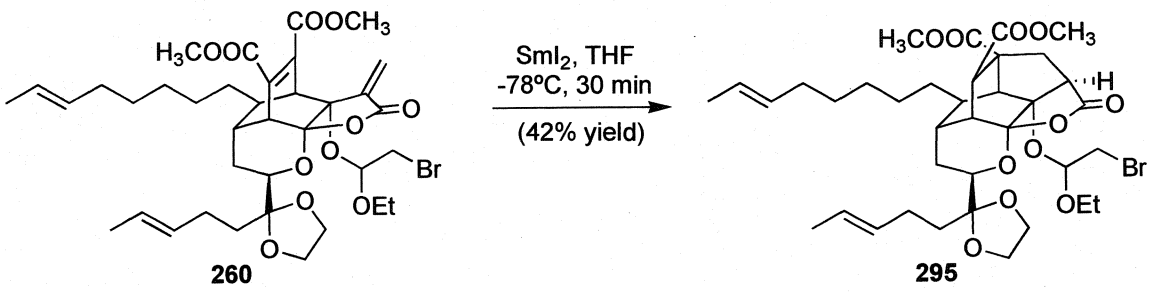


Isotwistane 294. To a solution of SmI_2 in THF (5 ml, 0.5 mmol, 5.0 equiv) was added a solution of tertiary alcohol **248** (60mg, 0.1 mmol, 1.0 equiv) in THF (0.5+ 0.3 ml = 0.8 ml). The reaction mixture was stirred at rt for 10 min, treated with saturated aqueous NH_4Cl (2 ml), 1.0N HCl (0.5 ml) and EtOAc (5 ml) and the phases were separated. The aqueous layer was extracted with EtOAc (2x 5 ml). The combined

organic layers were washed with brine (5 ml) dried over Na_2SO_4 and concentrated *in vacuo*. Purification via silica gel chromatography (20%-33% EtOAc/Hexanes eluent) furnished **265** (50.5mg, 84% yield) as a colorless oil.

Isotwistane 294. FTIR (thin film/NaCl) 3431 (br), 2927 (m), 2855 (w), 1787 (s), 1731 (s), 1436 (m), 1366 (w), 1285 (m), 1213 (s), 1151 (m), 1100 (m), 1071 (m), 968 (m), 927 (w), 736 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.49-5.38 (m, 4H), 4.29 (dd, *J*=12.1, 3.4 Hz, 1H), 4.07-3.89 (m, 4H), 3.78 (s, 3H), 3.68 (s, 3H), 3.63 (s, 1H), 3.54 (s, 1H), 3.03 (dd, *J*=10.7, 3.0 Hz, 1H), 2.78-2.69 (m, 2H), 2.66 (d, *J*=2.6 Hz, 1H), 2.51 (d, *J*=1.6 Hz, 1H), 2.39-1.92 (m, 4H), 1.84-1.72 (m, 4H), 1.67-1.49 (m, 10H), 1.36-1.19 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.20, 174.79, 170.87, 131.47, 130.91, 125.42, 125.12, 110.77, 107.67, 85.83, 76.45, 66.66, 66.33, 53.31, 53.10, 52.48, 51.12, 50.11, 44.77, 40.53, 39.48, 35.68, 35.30, 33.94, 33.07, 32.66, 31.43, 29.69, 29.36, 27.85, 25.95, 18.12. HRMS (ESI) *m/z* 625.2991 [calc'd for $C_{33}H_{46}O_{10}Na$ (M+Na) 625.2989].

Preparation of Bromoacetal 295 (IMMIV-259):



Bromoacetal 295. To a solution of SmI_2 in THF (5 ml, 0.5 mmol, 5.0 equiv) at –78°C was added a solution of bromoacetal **260** (75mg, 0.1 mmol, 1.0 equiv) in THF (0.5+0.3 ml = 0.8ml). The reaction mixture was stirred at –78°C for 30 min, treated with saturated aqueous NH_4Cl (2 ml), 1.0N HCl (0.5 ml) and EtOAc (2 ml), and warmed to rt, at which point the phases were separated. The aqueous layer was extracted with EtOAc (2x 5 ml). The combined organic layers were washed with brine (5 ml) dried over Na_2SO_4 and concentrated *in vacuo*. Purification via silica gel chromatography (25% EtOAc/Hexanes eluent) furnished **265** (28mg, 37% yield) as a pale yellow oil.

Bromoacetal 295. ^1H NMR (500 MHz, $CDCl_3$) δ 5.48-5.35 (m, 4H), 5.20 (t, *J*=4.5 Hz, 1H), 4.26 (dd, *J*=12.2, 3.4 Hz, 1H), 4.16-3.91 (m, 4H), 3.74 (s, 3H), 3.68 (s, 3H), 3.68-3.57 (m, 5H), 3.50 (s, 1H), 2.78-2.64 (m, 3H), 2.15-1.45 (m, 22H), 1.34-1.29 (m, 12H), 1.24 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.94, 174.84, 170.84, 131.47, 130.87, 125.42, 125.11, 110.87, 108.81, 98.84, 90.00, 77.80, 76.53, 66.88, 66.72, 61.90, 54.50, 53.10, 52.50, 50.30, 46.71, 44.49, 41.42, 39.67, 36.13, 35.23, 34.92, 33.21, 32.70, 32.46, 31.80, 29.92, 29.67, 29.32, 29.15, 27.80, 26.07, 18.13, 15.42. HRMS (ESI) *m/z* 753.2851 [calc'd for $C_{37}H_{54}O_{11}Br$ (M+H) 753.2849].

4.7 References.

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3. Molander, G. A.; Harris, C. R., Sequenced reactions with samarium(II) iodide. *Tetrahedron* **1998,** 54, (14), 3321-3354.

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6. This reaction might also proceed by reduction of 264 to the organosamarium, followed by michael addition into the maleate. This possibility was left out of Scheme 4.6 in the interest of clarity.

7. Although literature precedent clearly stated that HMPA was required for the reaction of bromoacetals with SmI_2, This reaction was first performed with no additives, in the interest of avoiding the use of this toxic co-solvent. As is apparent, this was a serendipitous choice.

8. Kagan, H. B.; Namy, J. L.; Girard, P., Divalent Lanthanide Derivatives in Organic-Synthesis .2. Mechanism of SmI_2 Reactions in Presence of Ketones and Organic Halides. *Tetrahedron* **1981,** 37, 175-180.

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13. It is possible that the initial cyclization is a radical event, in which case the resultant C(14) radical would be reduced to the enolate prior to the second cyclization. This mechanism was not depicted in the interest of clarity.

14. Baldwin, J. E., Rules for Ring-Closure. *Journal of the Chemical Society-Chemical Communications* **1976**, (18), 734-736.

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18. Note: samarium metal was either purchased from Strem Chemical as a "powder" or freshly filed from a samarium ingot. In either case, the appearance of the samarium should be that of shiny metallic filings. If the samarium has a "powdery" appearance, it is a sign that the metal has become oxidized.

Appendix 3

Spectra Relevant to Chapter 4

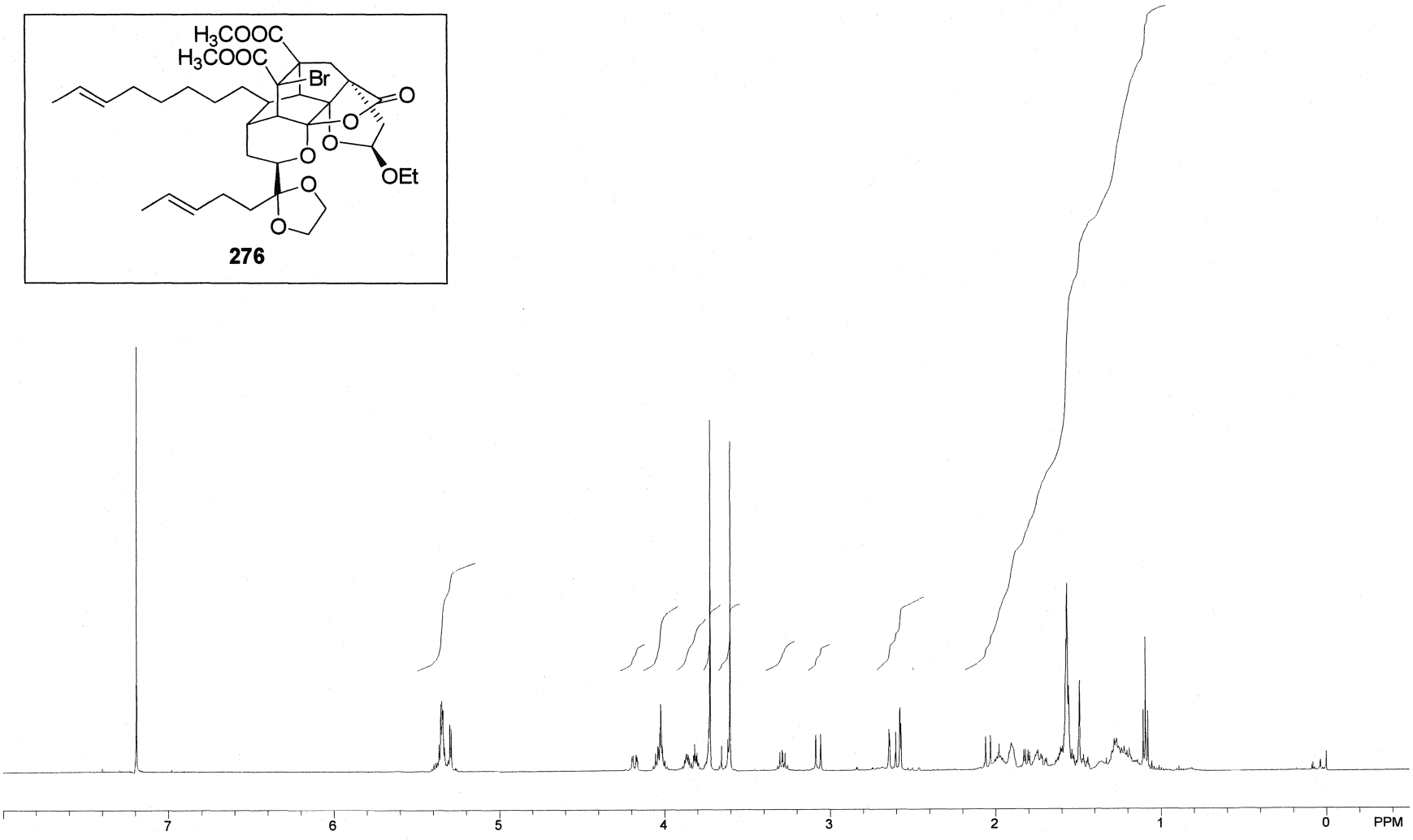


Figure A.3.1 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **276**.

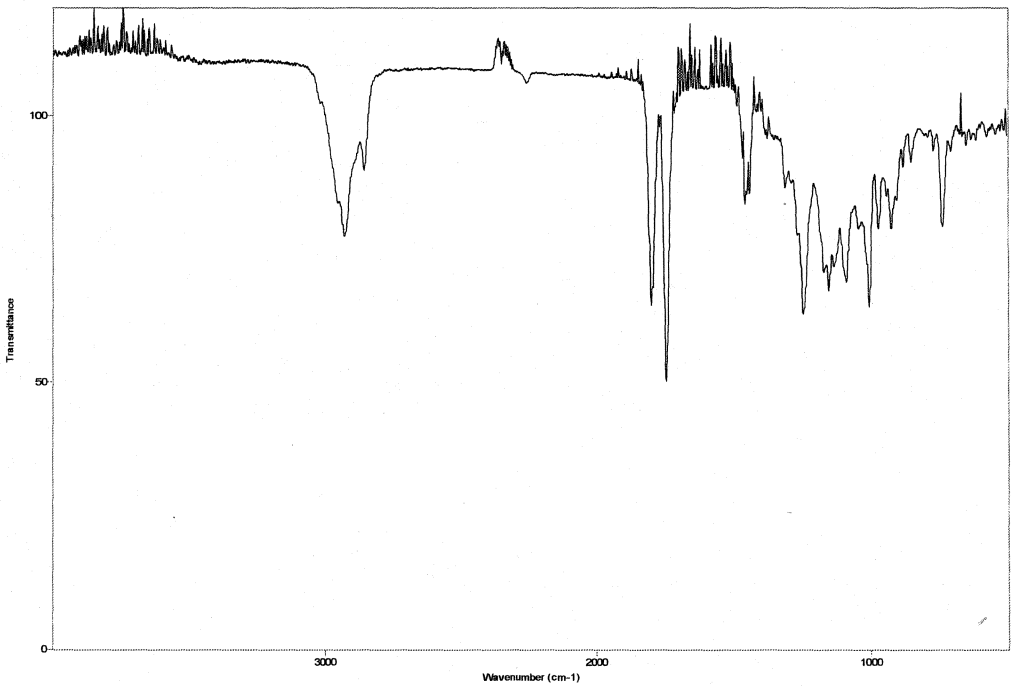


Figure A.3.2 FTIR Spectrum (thin film/NaCl) of Compound **276**.

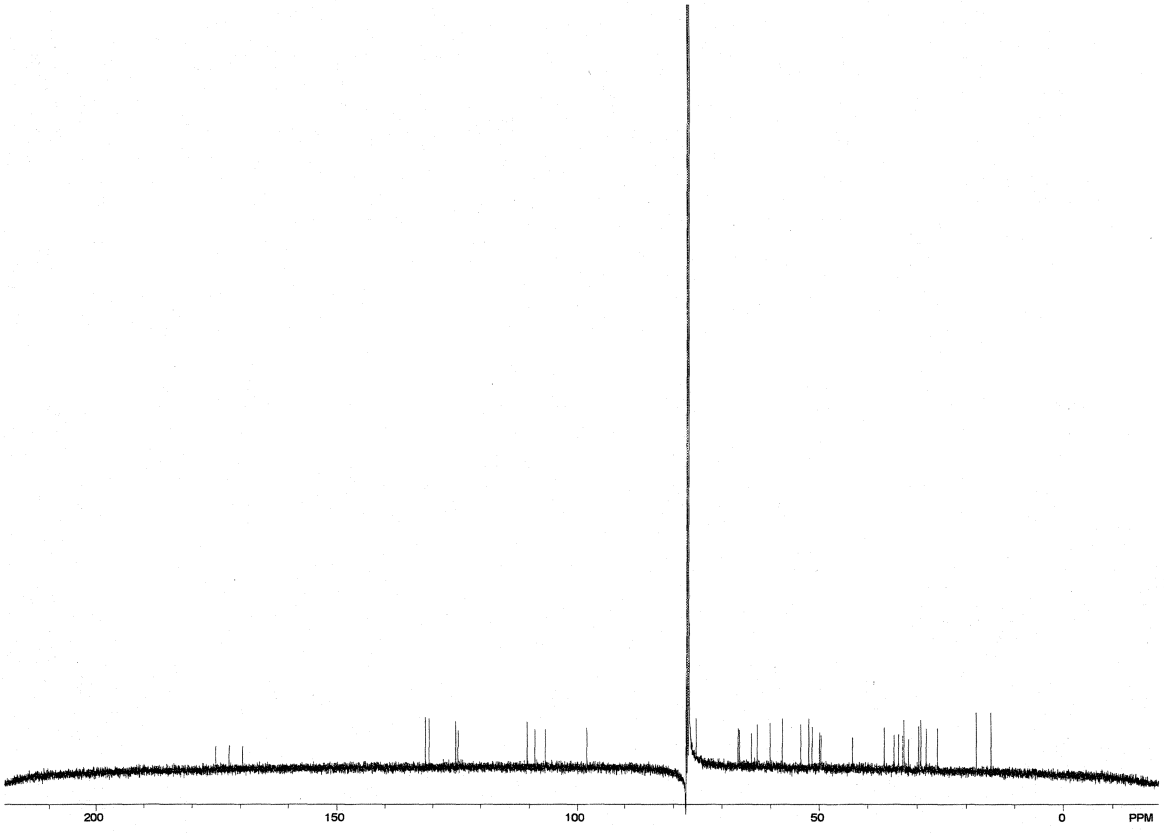


Figure A.3.3 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **276**.

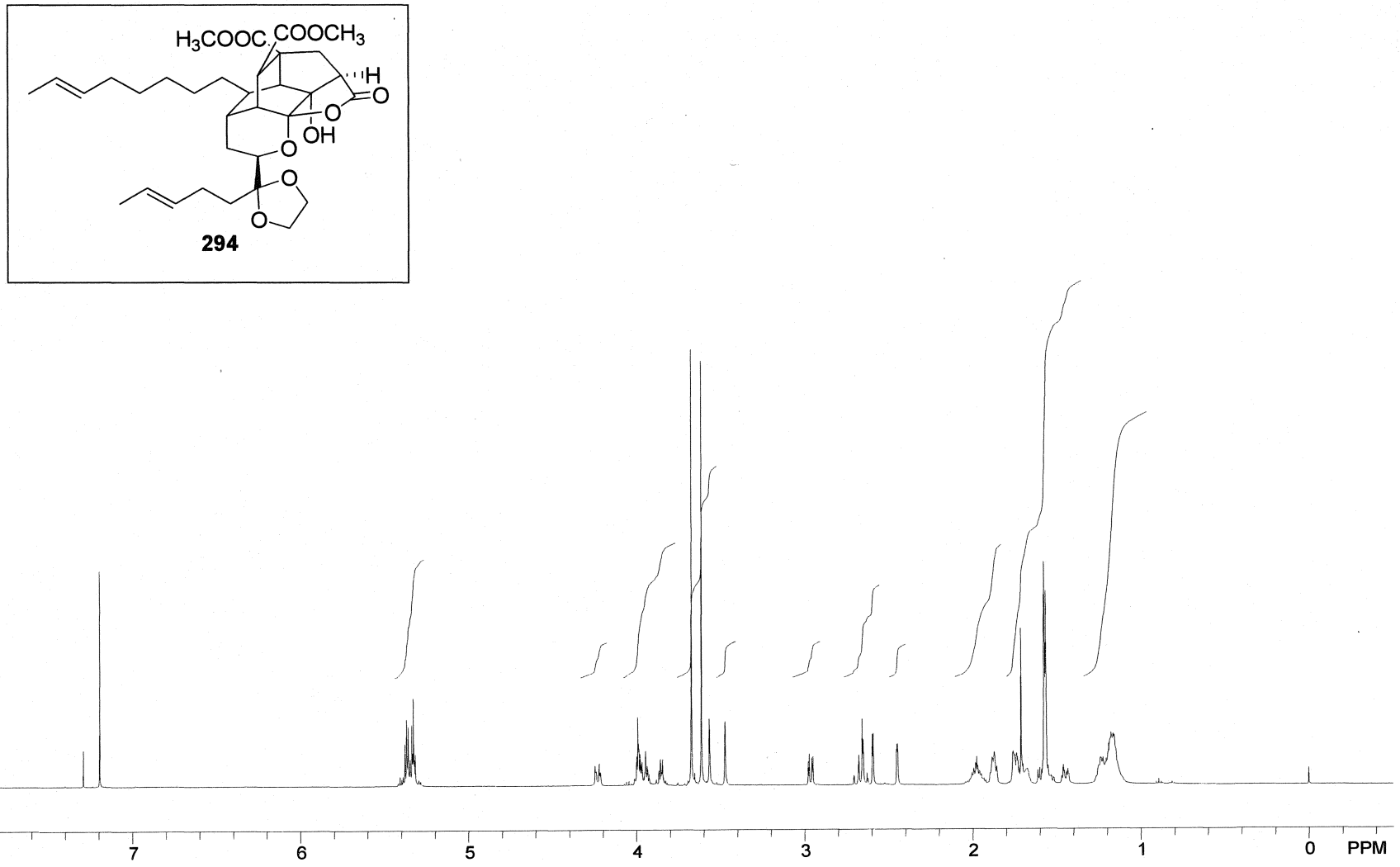


Figure A.3.4 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **294**.

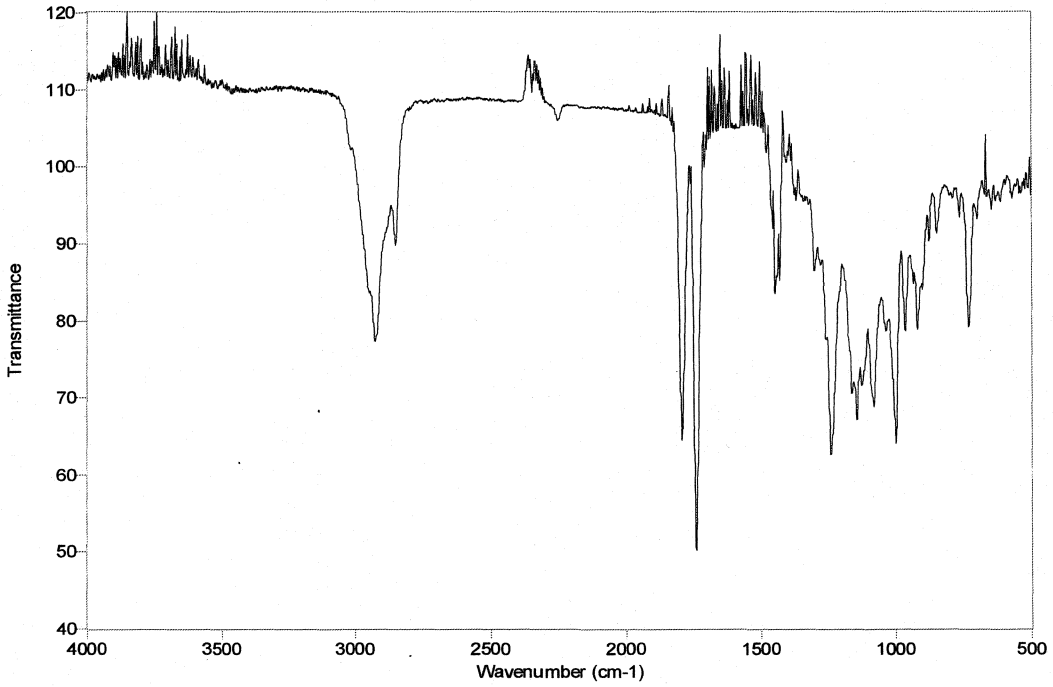


Figure A.3.5 FTIR Spectrum (thin film/NaCl) of Compound **294**.

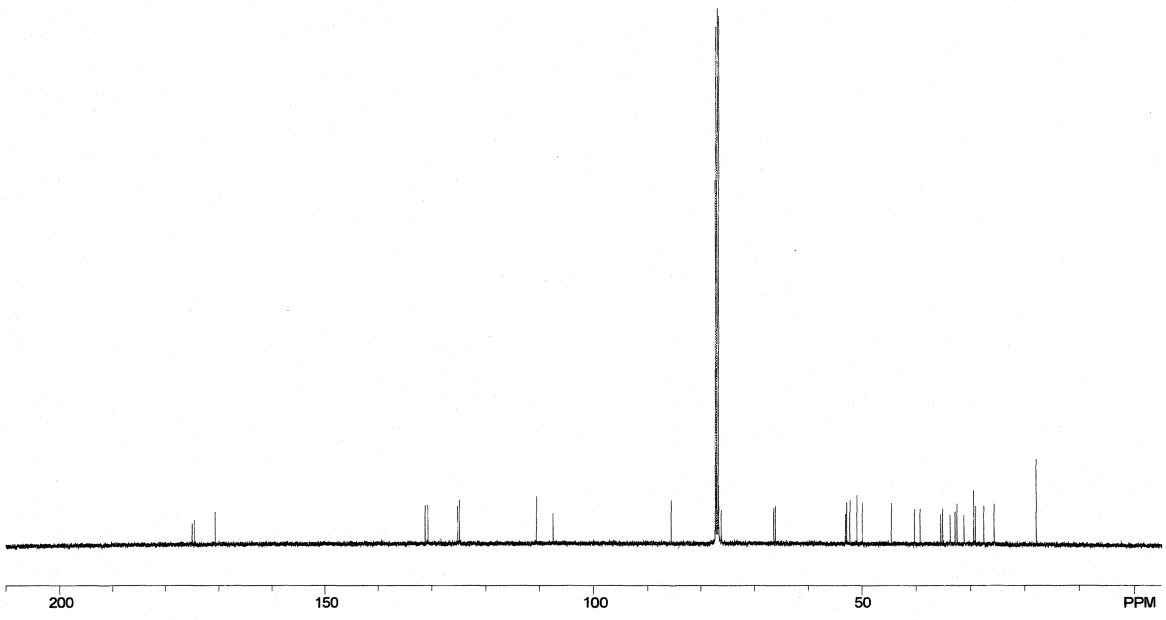


Figure A.3.6 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **294**.

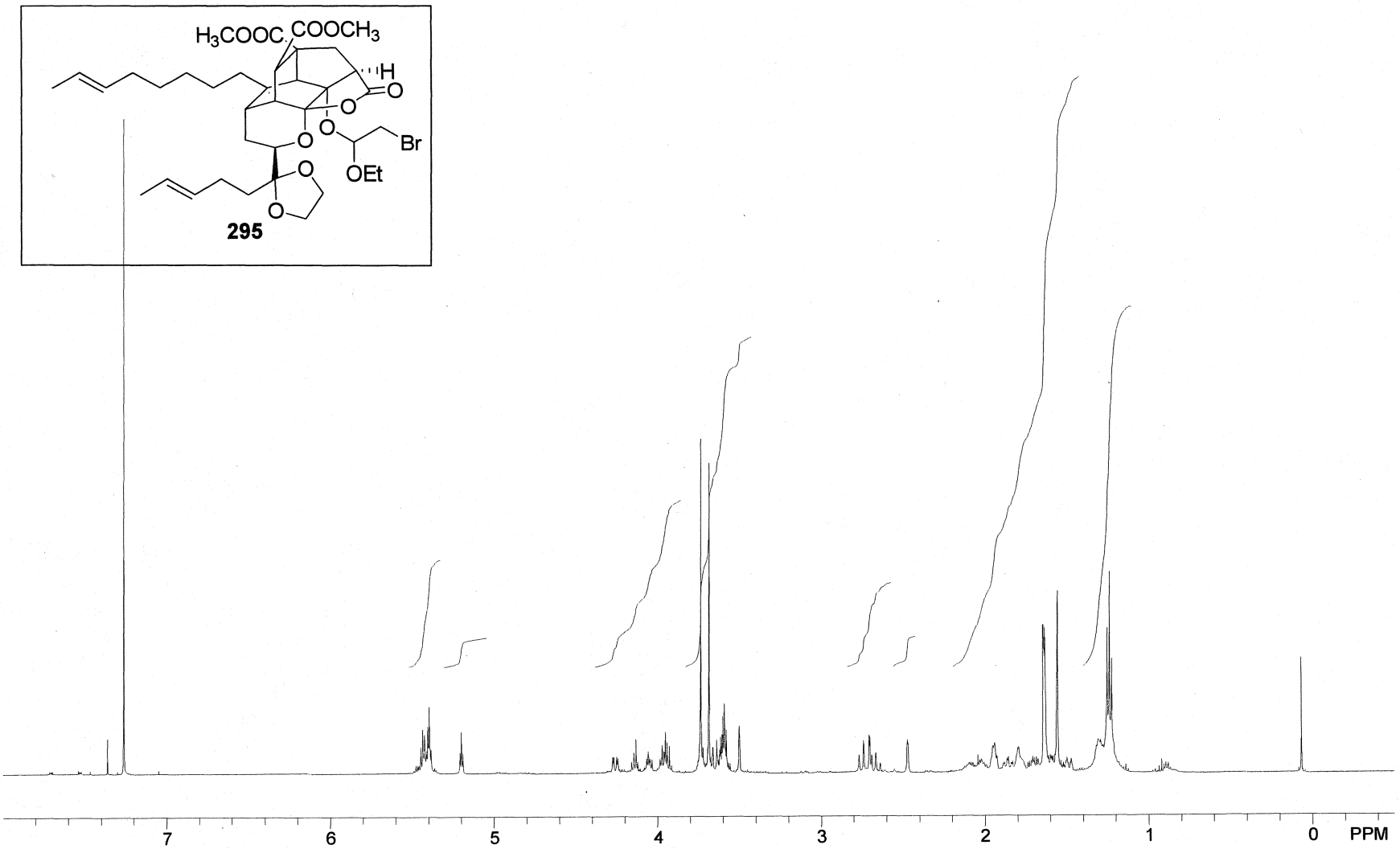


Figure A.3.7 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **295**.

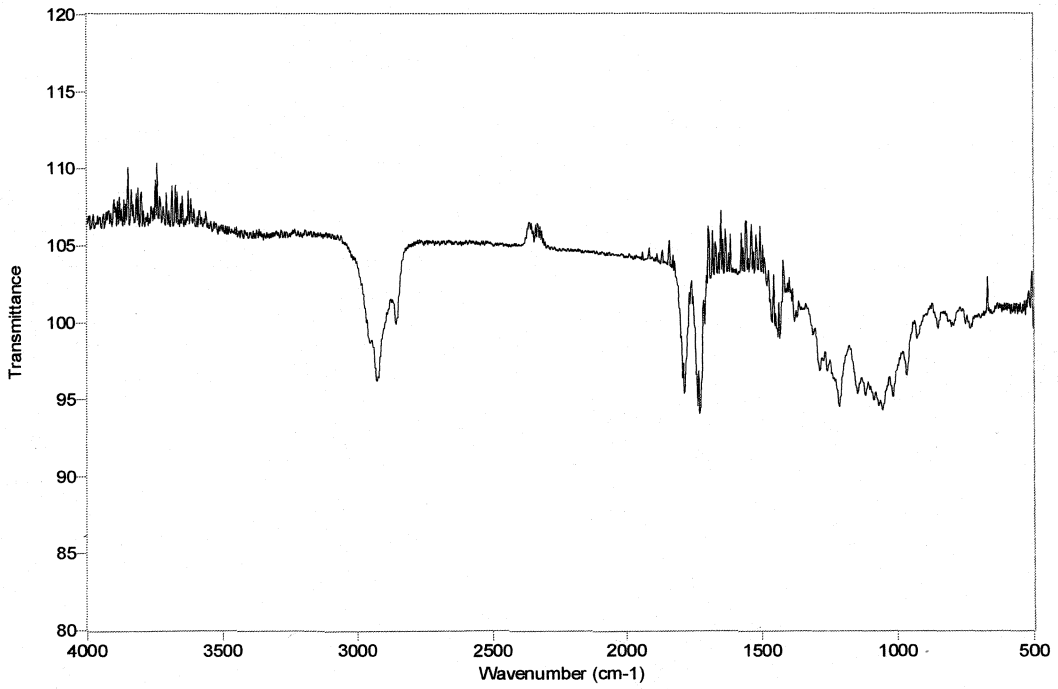


Figure A.3.8 FTIR Spectrum (thin film/NaCl) of Compound **295**.

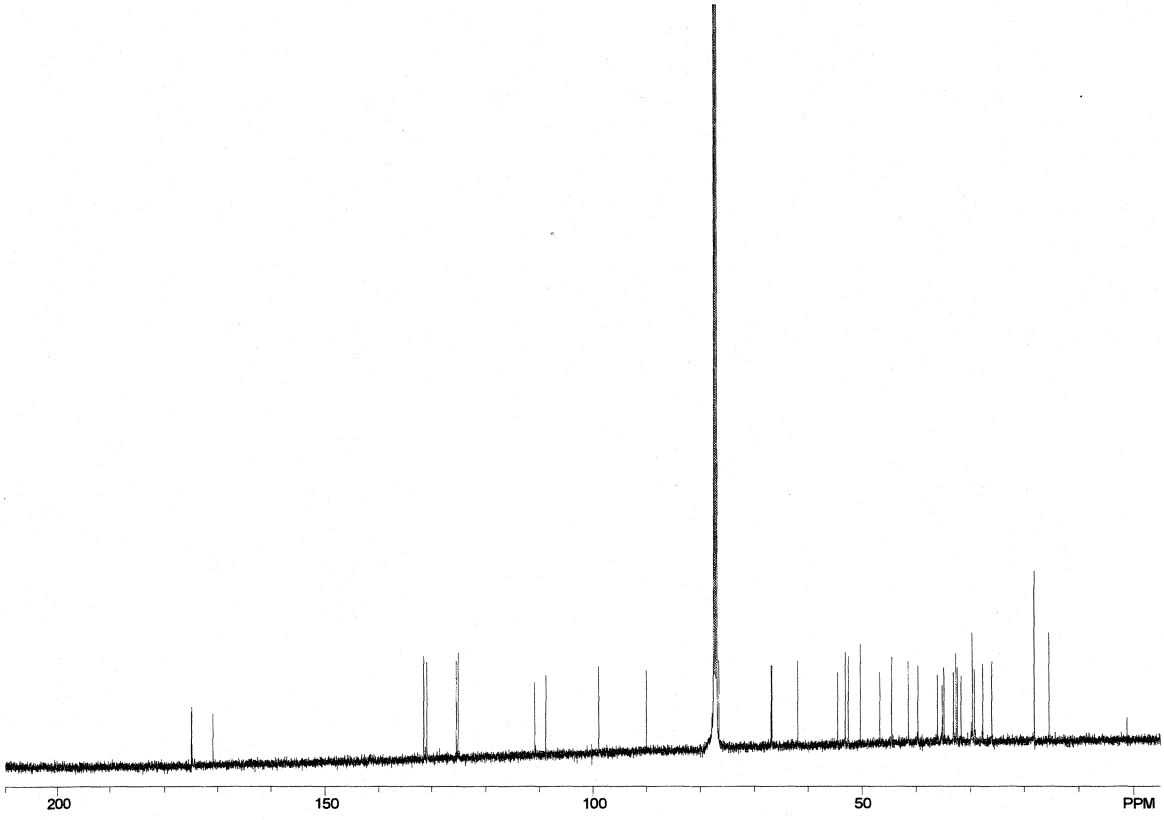


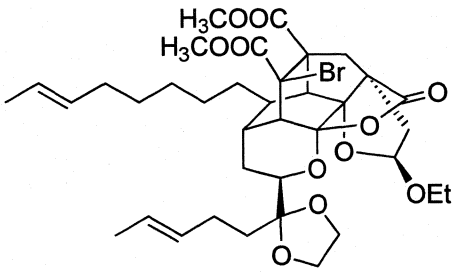
Figure A.3.9 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **295**.

Appendix 4

X-Ray Data Relevant to Chapter 4

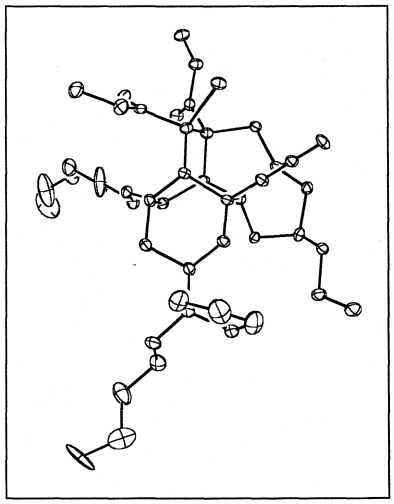
A.4.1 X-Ray Structure Report for Acetal 276.

A.4.1.1 Structure and ORTEP Plot For Lactone 276.



276

≡



A.4.1.2 Reference Information.

YALE CHEMICAL INSTRUMENTATION CENTER

X-Ray Structure Report

Reference Number: WOOD_IM04

March 31, 2003

A.4.1.3 Data Collection

A colorless blade crystal of $C_{37}H_{51}BrO_{11}$ having approximate dimensions of 0.20 x 0.10 x 0.08 mm^3 was mounted with epoxy cement on the tip of a fine glass fiber. All measurements were made on a Nonius KappaCCD diffractometer with graphite monochromated Mo-Kπ radiation.

Cell constants and an orientation matrix for data collection corresponded to a primitive monoclinic cell with dimensions:

$a = 8.1933(16)$ Å $\quad \pi = 90$ °

$b = 16.725(3)$ Å $\quad \pi = 94.05(3)$ °

$c = 26.311(5)$ Å $\quad \pi = 90$ °

$V = 3596.5(12)$ Å^3

For Z = 4 and F.W. = 751.69, the calculated density is 1.388 g/cm^3. Based on a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be $P2_1/n$ (#14).

The data were collected at a temperature of 173(2) K to a maximum 2π value of 56.50 °. Five omega scans consisting of 126, 126, 99, 40, and 98 data frames, respectively, were collected with a frame width of 0.6 ° and a detector-to-crystal distance, Dx, of 35.0 mm. Each frame was exposed twice (for the purpose of de-zingering) for a total of 120 s. The data frames were processed and scaled using the DENZO software package.[1]

A.4.1.4 Data Reduction

A total of 15672 reflections were collected of which 8854 were unique and observed (R_{int} = 0.0563). The linear absorption coefficient, μ, for Mo-Kπ radiation is 12.03 cm^{-1}, and no absorption correction was applied. The data were corrected for Lorentz and polarization effects.

A.4.1.5 Structure Solution and Refinement

The structure was solved by direct methods and expanded using Fourier techniques[2]. The non-hydrogen atoms were refined anisotropically, and hydrogen atoms

were treated as idealized contributions. The final cycle of full-matrix least-squares refinement[3] on F was based on 8854 observed reflections ($I > 2.00\pi(I)$) and 460 variable parameters and converged with unweighted and weighted agreement factors of:

$$R = \pi \, ||Fo| - |Fc|| \, / \, \pi \, |Fo| = 0.0807$$

$$R_W = \{\pi[w \, (F_o^2 - F_c^2)^2] \, / \, \pi[w(F_o^2)^2]\}^{1/2} = 0.2008$$

The maximum and minimum peaks on the final difference Fourier map corresponded to 0.743 and –0.800 $e^-/Å^3$ respectively.

A.4.1.6 REFERENCES

(1) Z. Otwinowski and W. Minor, "Processing of X-Ray Diffraction Data Collected in Oscillation Mode," Methods in Enzymology, vol. 276: Macromolecular Crystallography, part A, 307-326, 1997, C.W. Carter, Jr. & R.M. Sweet, Eds., Academic Press.

(2) *Acta Cryst.* **A46** (1990) 467-473

(3) Least Squares function minimized: $\pi w(F_o^2 - F_c^2)^2$

A.4.1.7 Structural Description.

The compound crystallized in the monoclinic space group $P2_1/n$ with one molecule in the asymmetric unit and four molecules in the unit cell.

Consistent with the previously characterized compounds wood_im02 and wood_im03, ring 1 [C(1-6)] adopts a boat conformation as a result of the two-carbon bridge between C(7) and C(10) and ring 2 [C(1, 2, 6, 20, 21)-O(9)] adopts the expected chair geometry. The lactone ring, C(5, 6, 14, 15)-O(5, 6), is planar with a mean deviation of 0.056 Å. The torsion angles about the C(7)-C(10) bond are 24.8 ° for C(8-7-10-11),

146.9 ° for C(8-7-10-13), 89.6 ° for Br(1)-C(7-10-11), and 32.5 ° for Br(1)-C(7-10-13). These features are better illustrated in Figure **3**.

Positional disorder exists within the linear alkyl chains. Carbon atoms C(24-27) were effectively modeled with alternative positions as illustrated in Figure **4**. This minor component (40%) was refined with isotropic displacement parameters and the carbon-carbon bonds in both components were restrained to ideal lengths. An effective representation of the disorder among carbon atoms C(30-37) could not be modeled. The irresolvable positional disorder affords inflated displacement parameters and atypical bond lengths. Carbon-carbon distances in this chain were also retrained to ideal lengths.

There are no significant intermolecular contacts. ORTEPs, packing diagrams and full crystallographic tables follow.

Figure A.4.1

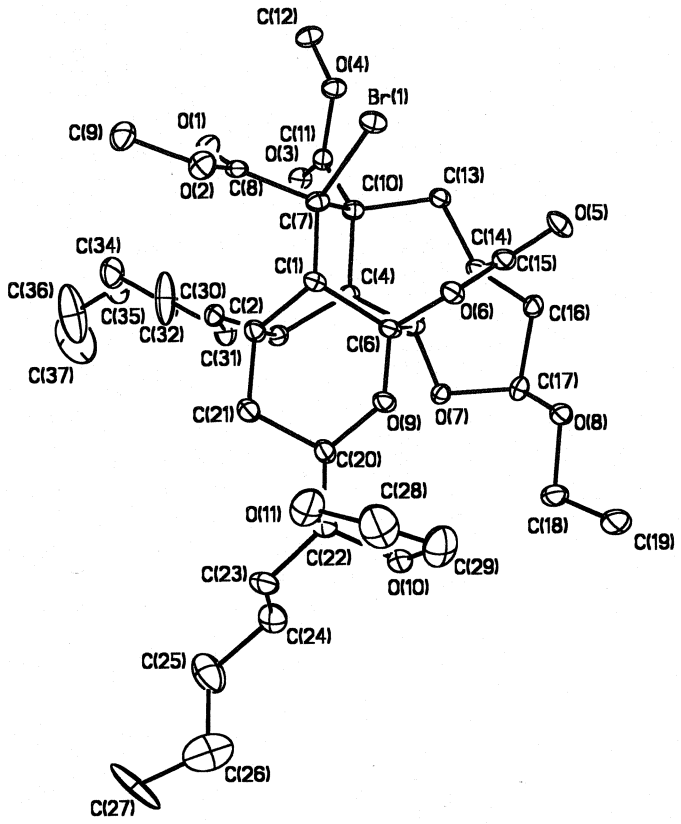


Figure A.4.2

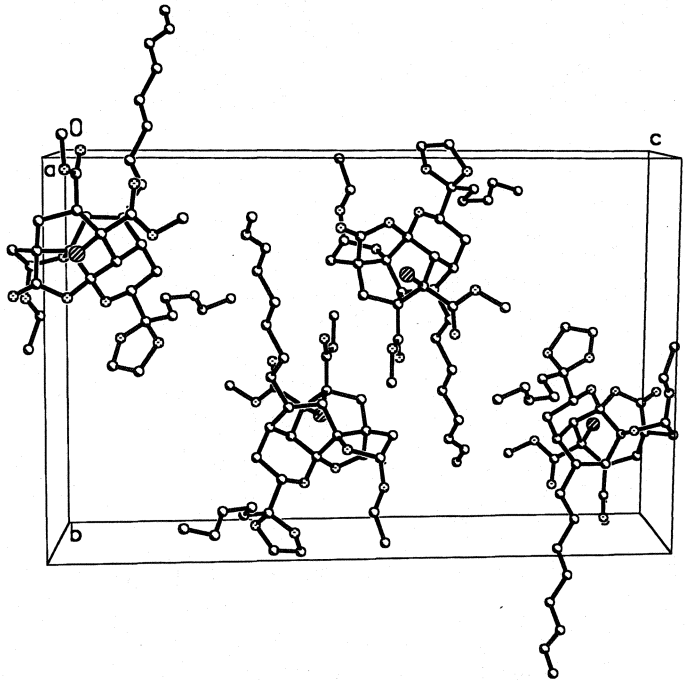


Figure A.4.3

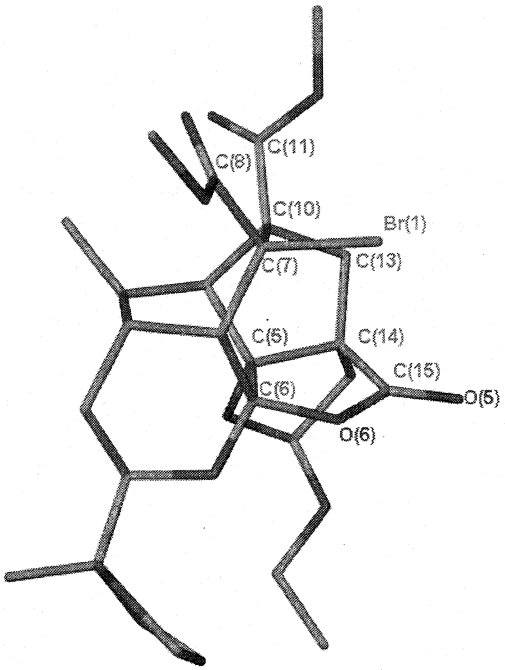


Figure A.4.4

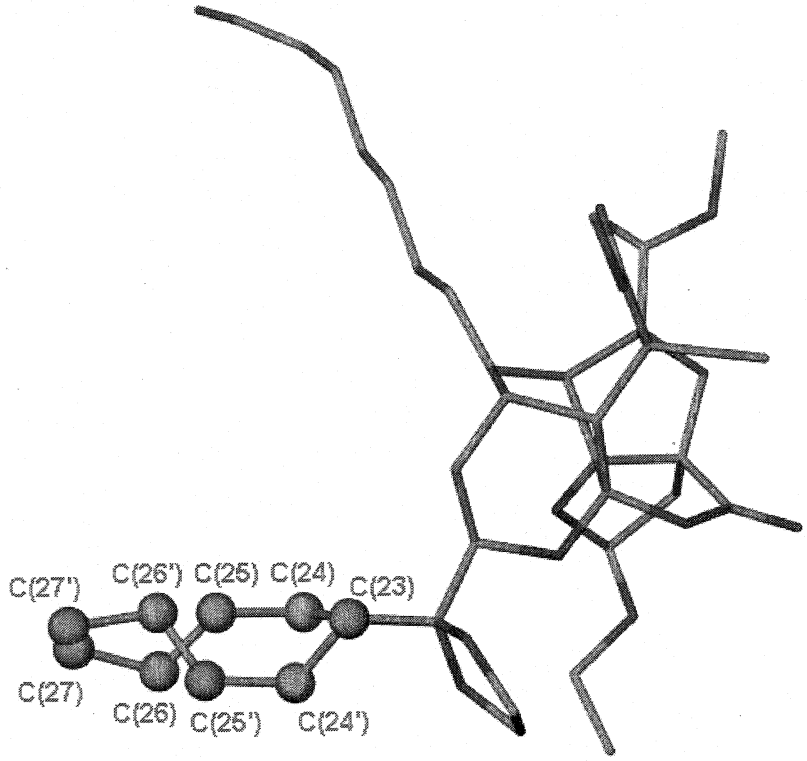


Figure A.4.5 Packing diagram – View down the a-axis

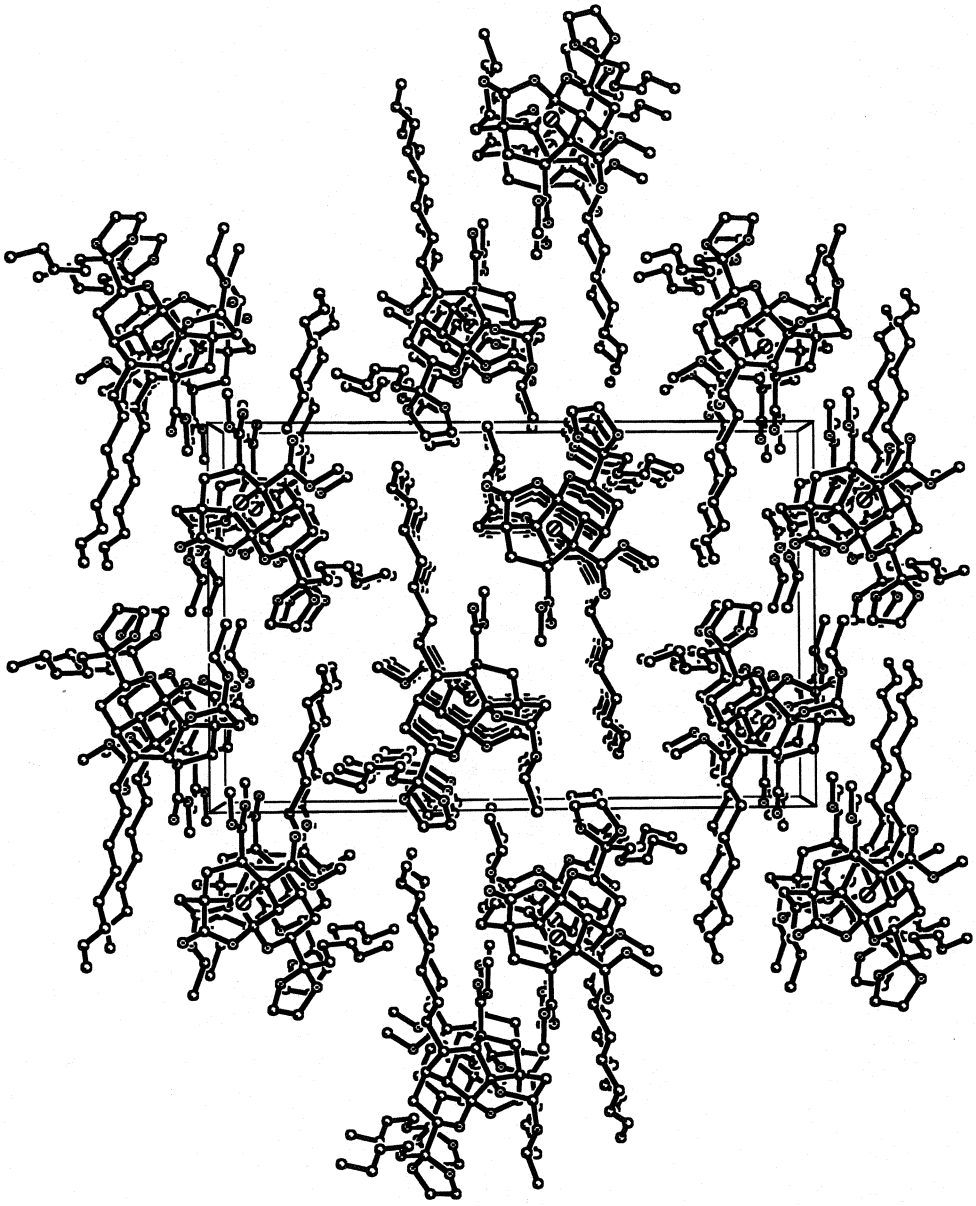


Figure A.4.6 Packing diagram – View down the b-axis

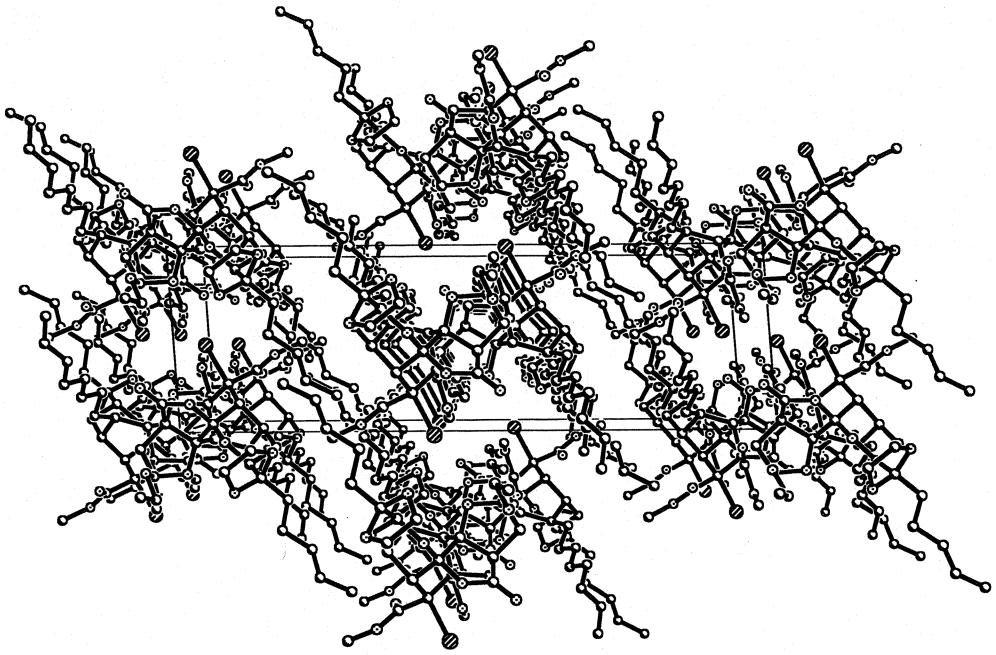


Figure A.4.7 Packing diagram – View down the c-axis

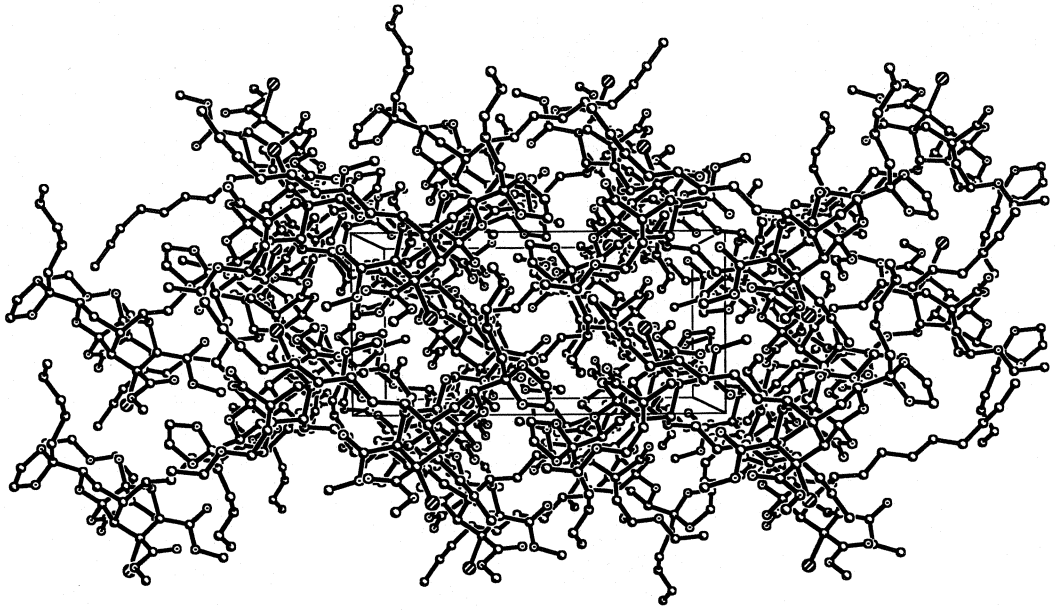


Table A.4.1. Crystal data and structure refinement for Acetal 276.

Identification code	wood_im04	
Empirical formula	$C_{37}H_{51}BrO_{11}$	
Formula weight	751.69	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 8.1933(16) Å	π= 90°.
	b = 16.725(3) Å	π= 94.05(3)°.
	c = 26.311(5) Å	π= 90°.
Volume	3596.5(12) $Å^3$	
Z	4	
Density (calculated)	1.388 g/cm^3	
Absorption coefficient	12.03 cm^{-1}	
F(000)	1584	
Crystal size	0.20 x 0.10 x 0.08 mm^3	
Theta range for data collection	2.44 to 28.25°.	
Index ranges	-10<=h<=10, -21<=k<=22, -35<=l<=34	
Reflections collected	15672	
Independent reflections	8854 [R(int) = 0.0563]	
Completeness to theta = 28.25°	99.5 %	
Absorption correction	None	
Max. and min. transmission	0.9099 and 0.7949	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	8854 / 8 / 460	
Goodness-of-fit on F^2	1.238	
Final R indices [I>2sigma(I)]	R1 = 0.0807, wR2 = 0.2008	
R indices (all data)	R1 = 0.1496, wR2 = 0.2251	
Largest diff. peak and hole	0.743 and -0.800 $e.Å^{-3}$	

Table A.4.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for Acetal 276. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	9695(1)	2878(1)	5670(1)	41(1)
O(1)	8185(4)	4461(2)	6473(1)	48(1)
O(2)	9189(4)	3291(2)	6764(1)	49(1)
O(3)	5963(4)	5194(2)	5616(1)	38(1)
O(4)	8496(4)	4800(2)	5458(1)	38(1)
O(5)	7511(4)	1793(2)	4625(1)	47(1)
O(6)	6676(4)	1699(2)	5414(1)	36(1)
O(7)	3021(4)	2514(2)	5243(1)	33(1)
O(8)	3154(4)	1499(2)	4636(1)	40(1)
O(9)	4737(4)	1499(2)	5936(1)	35(1)
O(10)	2254(5)	449(3)	6093(2)	66(1)
O(11)	4270(7)	453(3)	6737(2)	85(2)
C(1)	6648(5)	2566(3)	6160(2)	32(1)
C(2)	5359(6)	2915(3)	6504(2)	35(1)
C(3)	4253(6)	3523(3)	6199(2)	34(1)
C(4)	4759(5)	3569(3)	5654(2)	29(1)
C(5)	4641(5)	2743(3)	5399(2)	33(1)
C(6)	5631(5)	2109(3)	5738(2)	31(1)
C(7)	7663(5)	3268(3)	5962(2)	33(1)
C(8)	8366(5)	3745(3)	6427(2)	32(1)
C(9)	9845(7)	3705(4)	7220(2)	57(2)
C(10)	6585(5)	3782(3)	5570(2)	31(1)
C(11)	6950(6)	4666(3)	5575(2)	32(1)
C(12)	9002(6)	5620(3)	5444(2)	47(1)
C(13)	6647(5)	3535(3)	4994(2)	32(1)
C(14)	5613(6)	2778(3)	4921(2)	32(1)
C(15)	6686(6)	2038(3)	4946(2)	37(1)
C(16)	4298(6)	2754(3)	4484(2)	37(1)
C(17)	2920(6)	2294(3)	4709(2)	37(1)
C(18)	1870(7)	996(3)	4816(2)	50(1)

C(19)	2094(8)	169(3)	4629(3)	64(2)
C(20)	3586(6)	1710(3)	6301(2)	38(1)
C(21)	4410(6)	2217(3)	6719(2)	41(1)
C(22)	2966(9)	896(4)	6508(2)	64(2)
C(23)	1834(9)	982(5)	6910(3)	118(4)
C(24)	236(12)	1346(6)	6769(3)	57(3)
C(25)	-745(14)	1352(10)	7227(4)	96(5)
C(26)	-2113(15)	905(9)	7330(6)	122(6)
C(27)	-2920(20)	1126(14)	7805(6)	102(10)
C(24')	217(12)	556(9)	6898(6)	59(4)
C(25')	-1100(20)	677(11)	7256(7)	93(7)
C(26')	-1520(20)	1391(10)	7492(6)	59(4)
C(27')	-2710(50)	1300(40)	7897(17)	170(20)
C(28)	4434(13)	-242(5)	6431(3)	108(3)
C(29)	3381(12)	-169(4)	5994(3)	93(3)
C(30)	4105(6)	4327(3)	6480(2)	38(1)
C(31)	2824(7)	4898(3)	6274(2)	50(1)
C(32)	3035(13)	5727(5)	6556(3)	114(4)
C(33)	2047(13)	6362(4)	6415(3)	99(3)
C(34)	2306(11)	7137(4)	6696(3)	86(2)
C(35)	1099(13)	7754(5)	6556(3)	97(3)
C(36)	160(20)	8131(7)	6858(4)	171(6)
C(37)	-1235(19)	8613(11)	6760(6)	212(8)

Table A.4.3. Bond lengths [Å] and angles [°] for Acetal 276.

Br(1)-C(7)	1.993(4)	C(10)-C(13)	1.576(6)
O(1)-C(8)	1.213(6)	C(13)-C(14)	1.528(6)
O(2)-C(8)	1.317(6)	C(14)-C(15)	1.517(7)
O(2)-C(9)	1.456(6)	C(14)-C(16)	1.519(7)
O(3)-C(11)	1.208(5)	C(16)-C(17)	1.520(7)
O(4)-C(11)	1.343(6)	C(18)-C(19)	1.484(8)
O(4)-C(12)	1.435(6)	C(20)-C(21)	1.511(7)
O(5)-C(15)	1.190(6)	C(20)-C(22)	1.565(8)
O(6)-C(15)	1.356(6)	C(22)-C(23)	1.463(9)
O(6)-C(6)	1.426(5)	C(23)-C(24)	1.468(5)
O(7)-C(5)	1.414(5)	C(23)-C(24')	1.503(5)
O(7)-C(17)	1.449(6)	C(24)-C(25)	1.495(5)
O(8)-C(17)	1.358(5)	C(25)-C(26)	1.390(5)
O(8)-C(18)	1.452(6)	C(26)-C(27)	1.500(5)
O(9)-C(6)	1.380(5)	C(24')-C(25')	1.499(5)
O(9)-C(20)	1.435(5)	C(25')-C(26')	1.400(5)
O(10)-C(22)	1.415(7)	C(26')-C(27')	1.501(6)
O(10)-C(29)	1.422(9)	C(28)-C(29)	1.394(11)
O(11)-C(22)	1.401(9)	C(30)-C(31)	1.493(7)
O(11)-C(28)	1.425(9)	C(31)-C(32)	1.576(9)
C(1)-C(6)	1.542(6)	C(32)-C(33)	1.370(10)
C(1)-C(7)	1.550(6)	C(33)-C(34)	1.501(9)
C(1)-C(2)	1.554(6)	C(34)-C(35)	1.458(12)
C(2)-C(21)	1.532(7)	C(35)-C(36)	1.310(14)
C(2)-C(3)	1.549(7)	C(36)-C(37)	1.406(17)
C(3)-C(4)	1.521(6)		
C(3)-C(30)	1.542(6)	C(8)-O(2)-C(9)	115.0(4)
C(4)-C(5)	1.537(6)	C(11)-O(4)-C(12)	116.4(4)
C(4)-C(10)	1.568(6)	C(15)-O(6)-C(6)	112.6(3)
C(5)-C(14)	1.536(6)	C(5)-O(7)-C(17)	109.8(3)
C(5)-C(6)	1.573(6)	C(17)-O(8)-C(18)	114.1(4)
C(7)-C(8)	1.536(7)	C(6)-O(9)-C(20)	117.5(3)
C(7)-C(10)	1.566(6)	C(22)-O(10)-C(29)	106.7(6)
C(10)-C(11)	1.509(6)	C(22)-O(11)-C(28)	106.8(6)

C(6)-C(1)-C(7)	114.2(4)	C(11)-C(10)-C(13)	104.2(4)
C(6)-C(1)-C(2)	104.5(3)	C(4)-C(10)-C(13)	99.9(3)
C(7)-C(1)-C(2)	108.3(4)	C(7)-C(10)-C(13)	115.8(4)
C(21)-C(2)-C(3)	113.5(4)	O(3)-C(11)-O(4)	123.1(4)
C(21)-C(2)-C(1)	108.2(4)	O(3)-C(11)-C(10)	125.8(4)
C(3)-C(2)-C(1)	110.0(4)	O(4)-C(11)-C(10)	110.6(4)
C(4)-C(3)-C(30)	116.3(4)	C(14)-C(13)-C(10)	106.4(3)
C(4)-C(3)-C(2)	109.5(4)	C(15)-C(14)-C(16)	112.9(4)
C(30)-C(3)-C(2)	112.7(4)	C(15)-C(14)-C(13)	110.9(4)
C(3)-C(4)-C(5)	110.7(4)	C(16)-C(14)-C(13)	118.3(4)
C(3)-C(4)-C(10)	118.0(4)	C(15)-C(14)-C(5)	105.4(4)
C(5)-C(4)-C(10)	100.0(3)	C(16)-C(14)-C(5)	103.7(4)
O(7)-C(5)-C(4)	113.5(4)	C(13)-C(14)-C(5)	104.1(4)
O(7)-C(5)-C(14)	107.7(4)	O(5)-C(15)-O(6)	122.7(4)
C(4)-C(5)-C(14)	107.7(3)	O(5)-C(15)-C(14)	127.3(5)
O(7)-C(5)-C(6)	114.7(3)	O(6)-C(15)-C(14)	109.8(4)
C(4)-C(5)-C(6)	110.1(4)	C(14)-C(16)-C(17)	103.0(4)
C(14)-C(5)-C(6)	102.4(3)	O(8)-C(17)-O(7)	112.7(4)
O(9)-C(6)-O(6)	103.2(3)	O(8)-C(17)-C(16)	108.9(4)
O(9)-C(6)-C(1)	111.6(4)	O(7)-C(17)-C(16)	104.8(4)
O(6)-C(6)-C(1)	110.6(3)	O(8)-C(18)-C(19)	108.9(4)
O(9)-C(6)-C(5)	116.5(4)	O(9)-C(20)-C(21)	110.1(4)
O(6)-C(6)-C(5)	107.0(4)	O(9)-C(20)-C(22)	105.2(4)
C(1)-C(6)-C(5)	107.8(4)	C(21)-C(20)-C(22)	111.9(4)
C(8)-C(7)-C(1)	107.9(4)	C(20)-C(21)-C(2)	111.7(4)
C(8)-C(7)-C(10)	113.7(4)	O(11)-C(22)-O(10)	108.2(6)
C(1)-C(7)-C(10)	110.2(3)	O(11)-C(22)-C(23)	104.1(6)
C(8)-C(7)-Br(1)	101.6(3)	O(10)-C(22)-C(23)	111.3(5)
C(1)-C(7)-Br(1)	111.3(3)	O(11)-C(22)-C(20)	110.7(5)
C(10)-C(7)-Br(1)	111.9(3)	O(10)-C(22)-C(20)	108.5(5)
O(1)-C(8)-O(2)	124.2(4)	C(23)-C(22)-C(20)	113.9(6)
O(1)-C(8)-C(7)	123.4(4)	C(22)-C(23)-C(24)	117.2(7)
O(2)-C(8)-C(7)	112.4(4)	C(22)-C(23)-C(24')	122.7(8)
C(11)-C(10)-C(4)	114.3(4)	C(24)-C(23)-C(24')	54.6(7)
C(11)-C(10)-C(7)	115.4(4)	C(23)-C(24)-C(25)	108.6(7)
C(4)-C(10)-C(7)	106.4(4)	C(26)-C(25)-C(24)	129.8(13)

C(25)-C(26)-C(27)	115.9(11)	C(30)-C(31)-C(32)	110.1(5)
C(25')-C(24')-C(23)	126.7(13)	C(33)-C(32)-C(31)	120.7(7)
C(26')-C(25')-C(24')	127.1(18)	C(32)-C(33)-C(34)	118.4(8)
C(25')-C(26')-C(27')	115(3)	C(35)-C(34)-C(33)	114.6(8)
C(29)-C(28)-O(11)	108.5(7)	C(36)-C(35)-C(34)	127.2(8)
C(28)-C(29)-O(10)	106.5(7)	C(35)-C(36)-C(37)	132.1(11)
C(31)-C(30)-C(3)	117.5(4)		

Symmetry transformations used to generate equivalent atoms:

Table A.4.4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for Acetal 276. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	31(1)	41(1)	52(1)	4(1)	9(1)	4(1)
O(1)	53(2)	39(2)	49(2)	-4(2)	-8(2)	-5(2)
O(2)	49(2)	51(2)	44(2)	6(2)	-8(2)	4(2)
O(3)	39(2)	29(2)	48(2)	0(2)	6(2)	3(2)
O(4)	35(2)	29(2)	51(2)	1(2)	7(2)	-3(1)
O(5)	56(2)	37(2)	51(2)	-1(2)	31(2)	8(2)
O(6)	41(2)	28(2)	41(2)	0(2)	14(2)	1(1)
O(7)	32(2)	31(2)	37(2)	-8(1)	4(1)	-4(1)
O(8)	44(2)	33(2)	44(2)	-5(2)	13(2)	-6(2)
O(9)	41(2)	26(2)	38(2)	0(1)	13(2)	-5(1)
O(10)	82(3)	64(3)	55(2)	-21(2)	30(2)	-39(2)
O(11)	139(5)	44(3)	71(3)	19(2)	-10(3)	-22(3)
C(1)	30(2)	30(2)	35(3)	3(2)	8(2)	-1(2)
C(2)	43(3)	30(2)	32(3)	-2(2)	10(2)	-2(2)
C(3)	31(2)	32(2)	39(3)	-7(2)	4(2)	0(2)
C(4)	25(2)	28(2)	35(2)	-1(2)	5(2)	-2(2)
C(5)	30(2)	24(2)	45(3)	0(2)	7(2)	-3(2)
C(6)	30(2)	26(2)	37(3)	0(2)	12(2)	-3(2)
C(7)	24(2)	32(2)	44(3)	-1(2)	4(2)	2(2)

C(8)	25(2)	34(3)	37(3)	3(2)	4(2)	-7(2)
C(9)	57(4)	67(4)	46(3)	3(3)	-11(3)	-7(3)
C(10)	30(2)	28(2)	36(3)	2(2)	4(2)	-1(2)
C(11)	39(3)	26(2)	30(2)	2(2)	2(2)	-2(2)
C(12)	48(3)	29(3)	64(4)	4(2)	4(3)	-13(2)
C(13)	31(2)	31(2)	37(3)	-1(2)	8(2)	-1(2)
C(14)	35(2)	27(2)	36(3)	1(2)	11(2)	-3(2)
C(15)	42(3)	26(2)	43(3)	-1(2)	11(2)	-6(2)
C(16)	49(3)	29(3)	34(3)	-3(2)	6(2)	-5(2)
C(17)	44(3)	30(3)	36(3)	-7(2)	-2(2)	0(2)
C(18)	49(3)	40(3)	64(4)	-3(3)	13(3)	-13(3)
C(19)	79(4)	36(3)	80(4)	-5(3)	27(4)	-17(3)
C(20)	45(3)	37(3)	33(3)	-2(2)	11(2)	0(2)
C(21)	47(3)	40(3)	37(3)	-3(2)	13(2)	-5(2)
C(22)	85(5)	60(4)	51(4)	-12(3)	28(3)	-41(4)
C(23)	153(8)	123(7)	90(6)	-53(5)	79(6)	-102(7)
C(24)	72(7)	46(6)	51(6)	14(5)	3(5)	3(5)
C(25)	72(8)	147(15)	71(8)	4(9)	19(7)	31(9)
C(26)	77(10)	78(11)	210(20)	4(12)	-9(12)	15(9)
C(27)	66(9)	160(19)	88(11)	89(13)	63(9)	79(11)
C(28)	152(9)	72(6)	101(7)	6(5)	25(6)	7(6)
C(29)	144(8)	47(4)	87(6)	-3(4)	0(6)	-3(5)
C(30)	48(3)	32(3)	35(3)	-8(2)	6(2)	-6(2)
C(31)	61(3)	43(3)	46(3)	-7(3)	5(3)	14(3)
C(32)	185(9)	102(6)	49(4)	-34(4)	-21(5)	88(7)
C(33)	181(9)	59(4)	57(4)	-13(4)	19(5)	-2(5)
C(34)	116(7)	71(5)	75(5)	-27(4)	25(5)	-12(5)
C(35)	156(9)	71(5)	68(5)	11(4)	26(5)	-10(5)
C(36)	322(19)	121(9)	71(6)	6(6)	23(9)	119(11)
C(37)	199(15)	290(20)	155(12)	37(13)	34(11)	87(15)

Table A.4.5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for acetal 276.

	x	y	z	U(eq)
H(1A)	7384	2186	6360	38
H(2A)	5950	3203	6795	42
H(3A)	3130	3286	6175	41
H(4A)	4022	3950	5456	35
H(9A)	10411	3321	7452	86
H(9B)	8948	3955	7389	86
H(9C)	10618	4117	7126	86
H(12A)	10137	5649	5350	71
H(12B)	8921	5862	5781	71
H(12C)	8293	5911	5192	71
H(13A)	6196	3967	4768	39
H(13B)	7789	3429	4913	39
H(16A)	4691	2473	4185	45
H(16B)	3944	3300	4381	45
H(17A)	1841	2462	4541	44
H(18A)	785	1202	4687	61
H(18B)	1922	999	5193	61
H(19A)	1225	-175	4745	96
H(19B)	3161	-35	4762	96
H(19C)	2044	170	4255	96
H(20A)	2649	2011	6127	45
H(21A)	5172	1880	6935	50
H(21B)	3572	2430	6937	50
H(23A)	2382	1307	7187	142
H(23B)	1642	445	7052	142
H(24A)	-343	1034	6492	68
H(24B)	384	1899	6647	68
H(25A)	-378	1717	7487	115
H(26A)	-2515	485	7112	147
H(27A)	-3862	776	7842	153

H(27B)	-3284	1683	7782	153
H(27C)	-2133	1062	8101	153
H(24C)	-308	651	6553	71
H(24D)	484	-21	6915	71
H(25B)	-1726	218	7332	111
H(26B)	-1092	1895	7402	71
H(27D)	-2826	1809	8073	256
H(27E)	-2303	891	8143	256
H(27F)	-3777	1131	7740	256
H(28A)	5577	-294	6337	129
H(28B)	4152	-725	6624	129
H(29A)	2795	-678	5920	112
H(29B)	4003	-28	5697	112
H(30A)	3897	4209	6838	45
H(30B)	5177	4600	6483	45
H(31A)	1726	4678	6324	60
H(31B)	2918	4974	5904	60
H(32A)	2913	5628	6922	136
H(32B)	4179	5902	6525	136
H(33A)	900	6194	6448	118
H(33B)	2165	6467	6049	118
H(34A)	2291	7032	7066	104
H(34B)	3406	7345	6633	104
H(35A)	984	7898	6206	117
H(36A)	472	8066	7210	205
H(37A)	-1716	8737	7082	318
H(37B)	-2039	8328	6534	318
H(37C)	-921	9111	6597	318

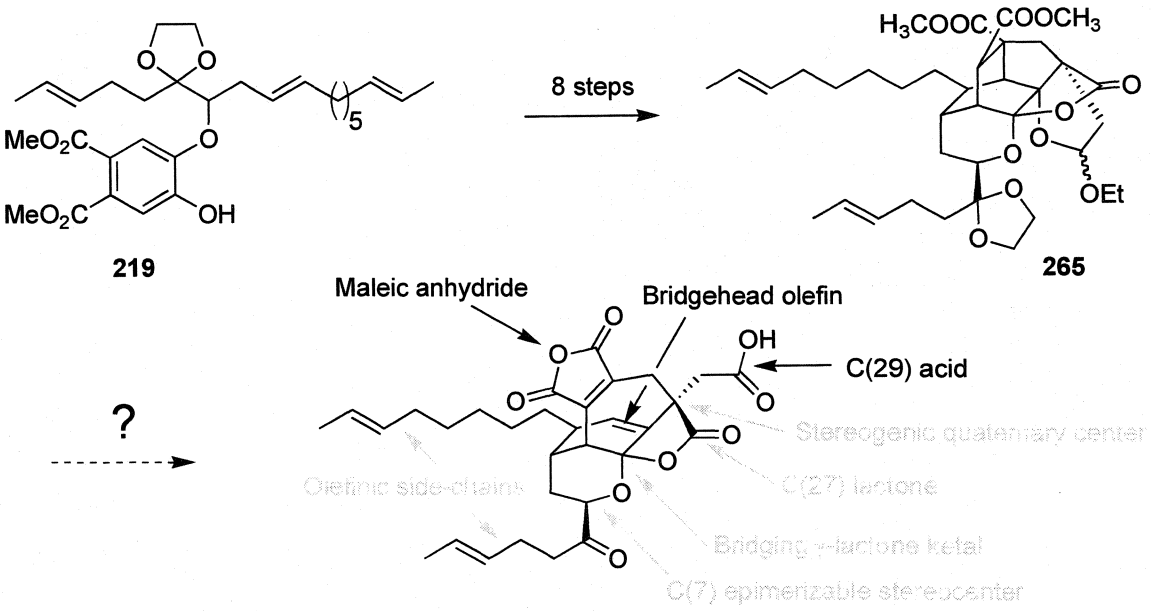
Chapter 5

Endgame Planning for the Synthesis of Phomoidride D

5.1 Remaining Challenges.

In the preceding chapters, information learned from model studies was applied toward the construction of a fully functionalized phomoidride precursor. These efforts provided acetal **265**, which contains all the carbon-carbon bonds found in the phomoidrides, including both full side-chains and most of the correct oxidation states.

Scheme 5.1 Remaining Challenges.

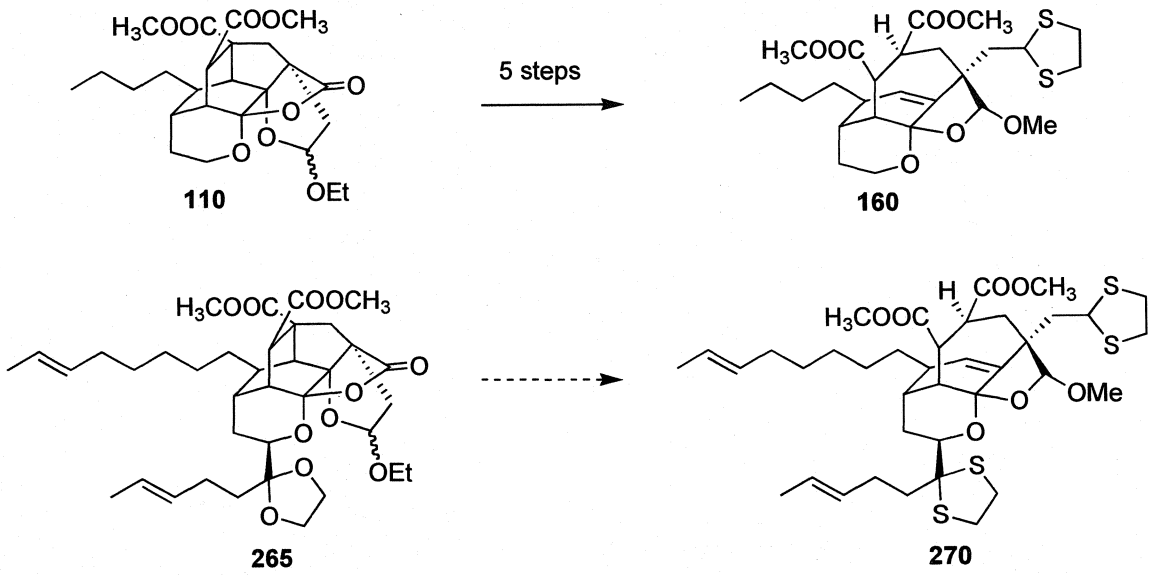


Phomoidride D, **27**

In model systems, we showed the elaboration of isotwistane-type structures to install the bridgehead olefin in a bicyclo[4.3.1]decene core (**110δ** **160**, Scheme 5.2). This chapter will discuss the application of these model studies to the fully functionalized

system (**265**), to produce an intermediate such as **270**, and the further conversion of this substrate to phomoidride D.

Scheme 5.2 Model System Precedent for Advancing Acetal 265.



5.2 Advancing Through the Xanthate Fragmentation.

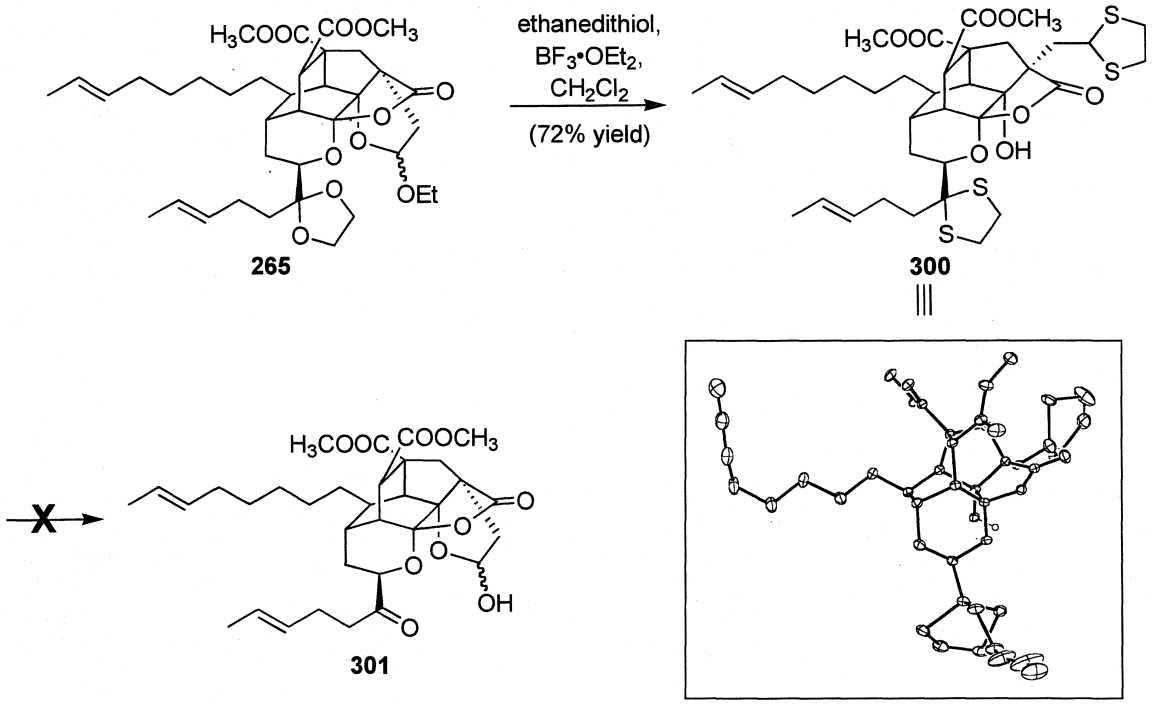
5.2.1 Formation of the bis-Dithiolane.

As with model systems, the first step along this route was transacetalization with ethanedithiol to provide bis-dithiolane **300**, thus freeing the tertiary alcohol at C(15). During this process, the dioxolane at C(6) was also inadvertently converted to the dithiolane, but this was seen as a relatively benign event. Fortunately, this reaction provided **300** as a crystalline solid, thus allowing its structure to be confirmed by single-crystal X-Ray analysis.

Before advancing this compound any further, the decision was made to work out conditions for deprotection of the dithiolanes. Unfortunately, under a variety of standard

conditions for dithiolane deprotection,[1] none of the desired deprotection product (**301**) was observed.

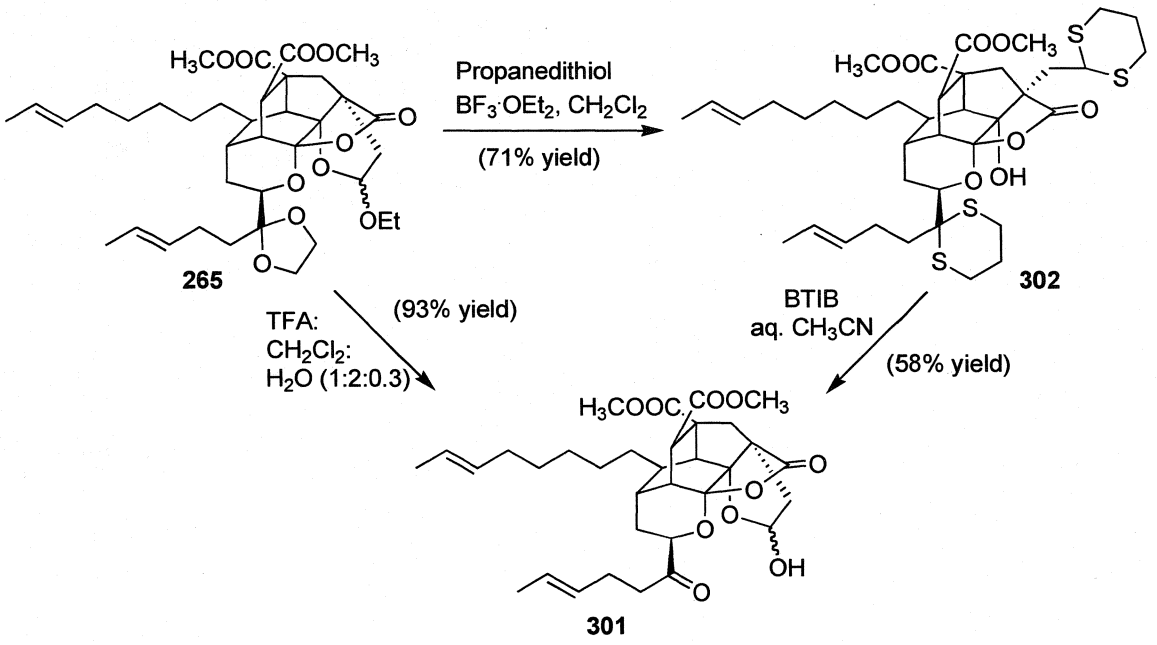
Scheme 5.3 Dithiolane Formation and X-Ray Structure.



5.2.2 Formation of the bis-Dithiane.

By employing propanedithiol in place of ethanedithiol, bis-dithane (the six-membered ring variant) was provided, in good yield (Scheme 5.4). This could then be deprotected using Stork's conditions ($PhI(OCCF_3)_2$ in aqueous CH_3CN)[2] to give the lactol **301**, the structure of which was confirmed by independent synthesis from ethyl acetal **265**.

Scheme 5.4 Dithiane Formation and Deprotection.

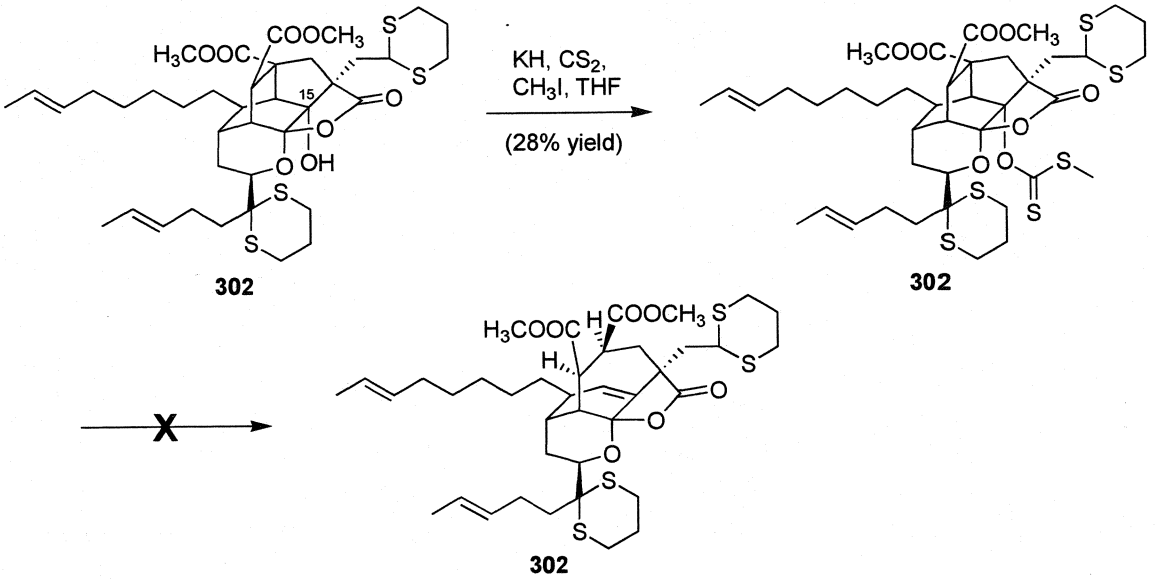


5.2.3 Xanthate Fragmentation.

5.2.3.1 Fragmentation Attempt with the Lactone Xanthate.

With confidence that the dithiane protecting groups could be removed under mild conditions in the late stages of the synthesis, the decision was made to advance this substrate. In model systems, it was necessary to protect the lactone as its methyl acetal prior to successful fragmentation, but it was prudent to try the fragmentation on the lactone before including additional steps for lactone reduction, protection, deprotection and oxidation. Thus, the C(15) tertiary alcohol of lactone **302** was derivatized as its methyl xanthate, by treatment with KH, followed by CS_2 and CH_3I. Unfortunately, as anticipated, fragmentation with this substrate was not successful.

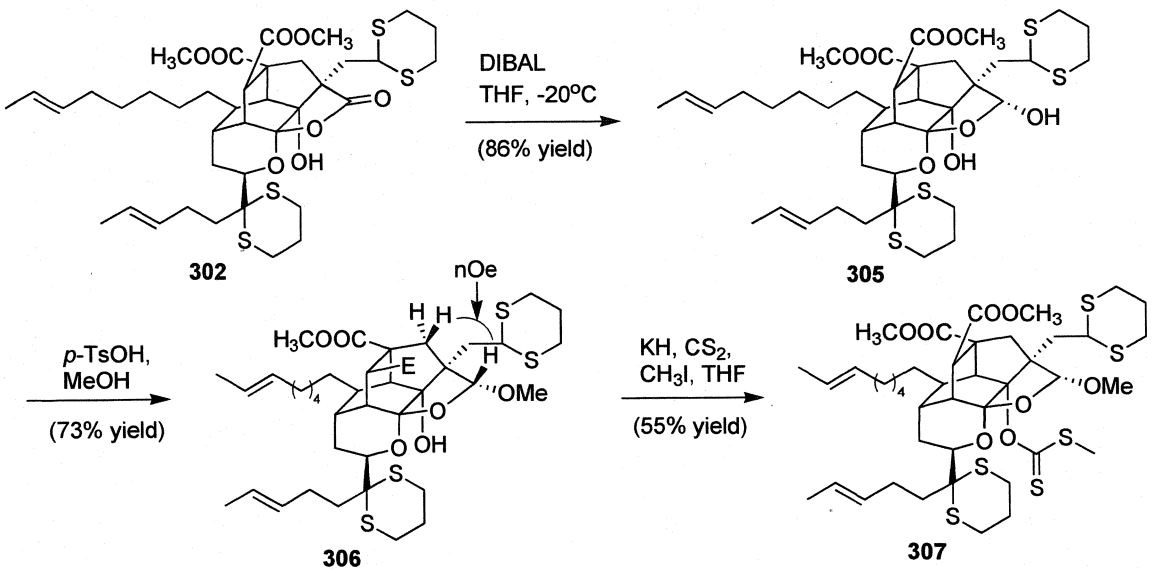
Scheme 5.5 Lactone Fragmentation.



5.2.3.2 Xanthate Fragmentation of Methyl Acetal 307.

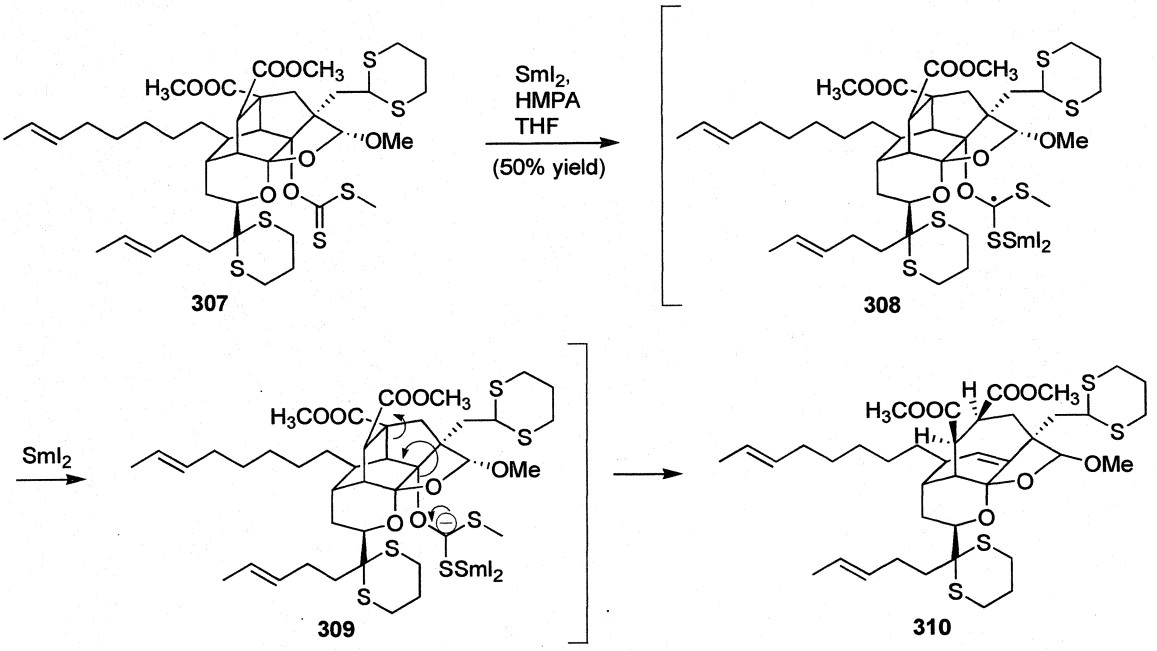
As in the model system, the lactone (**302**) was selectively reduced upon exposure to DIBAL at –20°C to give lactol **305** (Scheme 5.6). Subsequent treatment with *p*-TsOH in methanol provided the methyl acetal **306** as a single diastereomer. The stereochemistry at C(27) was determined to be as depicted in Scheme 5.6 (methoxy down) by 1D NOE experiments, which showed an NOE between the C(27) methine and the δ-proton of C(13). Again the methyl xanthate was incorporated by sequential treatment with KH, CS_2 and CH_3I.

Scheme 5.6 Lactone Reduction and Xanthate Fragmentation.



Exposure of xanthate **307** to a solution of SmI_2 and HMPA in THF gave the desired fragmentation product, **310**, in 60% yield.(Scheme 5.7) As detailed in Chapter 2 (see Scheme 2.24, Chapter 2), this reaction likely occurs via an anionic mechanism, in which the xanthate is reduced to the ketyl (**308**), and then again to the anion (**309**), which fragments in a "bottom-up" direction, providing the bridgehead olefin and bicyclo[4.3.1]decene core of the phomoidrides. It was unclear why the key fragmentation step worked significantly better on this system than on the most advanced model compound (i.e. 20% yield **159δ 160**, Scheme 2.36).

Scheme 5.7 Successful Fragmentation.



This point was an important milestone in the synthesis, as it is equivalent to the furthest point realized in the model systems. The bridgehead olefin, the full olefinic side-chains, the C(26) bridging ketal, and the C(14) quaternary center have all been installed. Furthermore, this system contains synthetic handles for the incorporation of the remaining features (i.e. C(27) lactone, C(29) acid, C(6) ketone, C(11)-C(12) maleate).

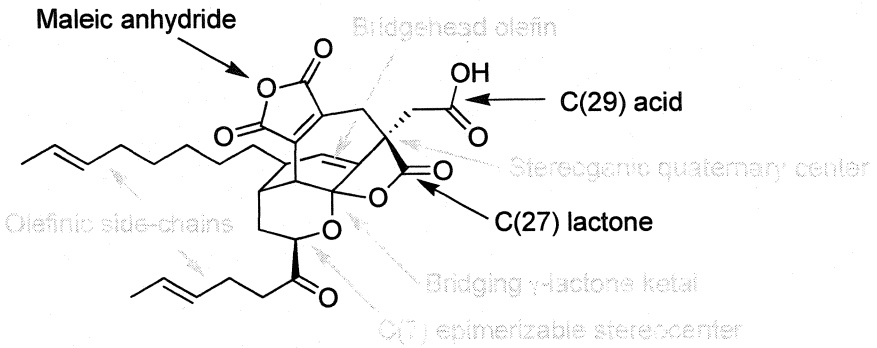
5.3 Advancing the Fragmentation Product.

5.3.1 Remaining Challenges.

In completing the synthesis of phomoidride D from **310**, the challenges remaining were the deprotection of the dithanes, deprotection of the methyl acetal, oxidation of C(27) and C(29) to the acid oxidation state, oxidation to form the maleate olefin, and

anhydride formation. Among these challenges, only deprotection of the dithianes had been previously explored.

Figure 5.1 Unexplored Remaining Challenges.

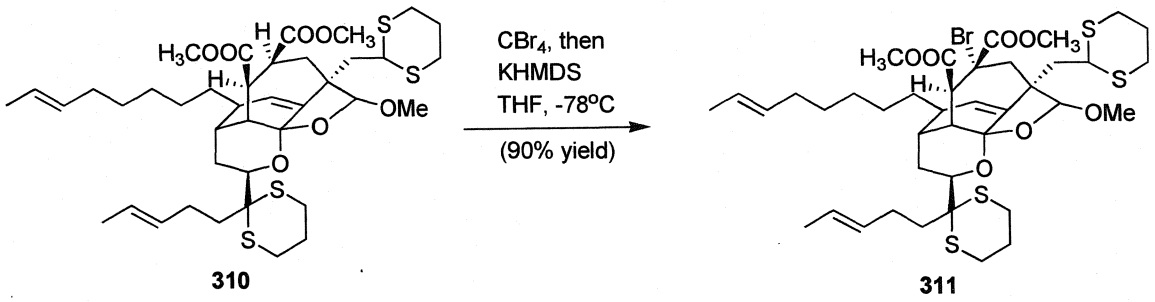


Phomoidride D, **27**

5.3.2 Efforts to Install the Maleate Olefin.

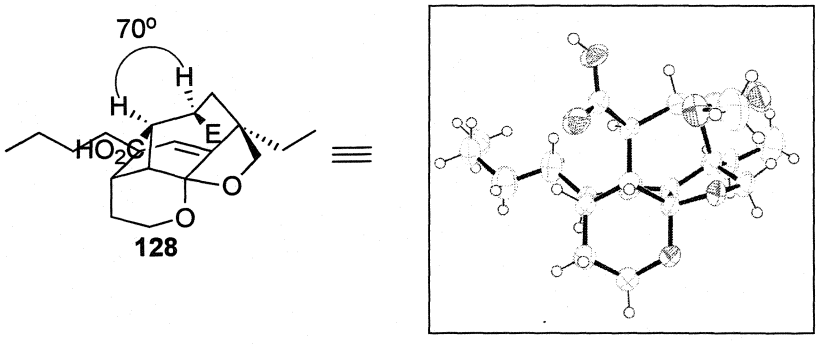
The most challenging transformation remaining was believed to be the installation of the maleate olefin. The initial strategy was to halogenate either C(11) or C(12), which could be eliminated to give the maleate, but treatment of **310** under basic conditions led to complex mixtures of unidentified products. Furthermore, the range of potential electrophiles was limited to those that would be compatible with the oxidatively reactive bridgehead olefin and dithiane moieties. It was eventually found that adding the electrophile prior to the base was essential to performing this reaction successfully. Thus, using CBr_4 as the electrophile[3] and KHMDS as the base provided **311** as a single diastereomer.

Scheme 5.8 Bromination of the Fragmentation Product.



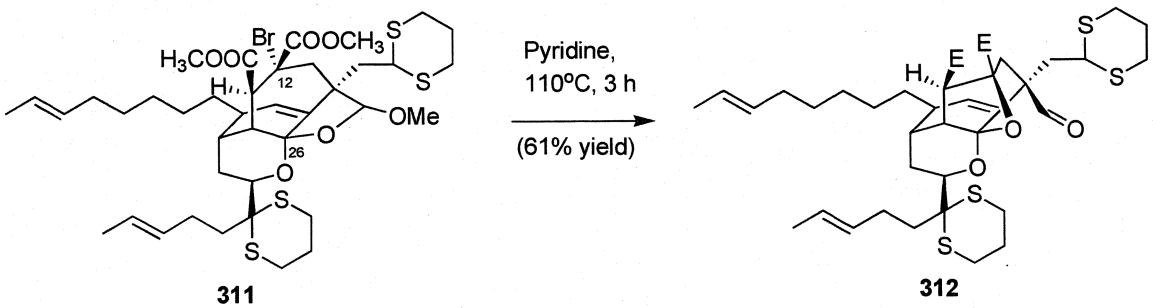
Of course, the bromine atom was installed with the intention of being eliminated under basic conditions. Unfortunately, a variety of efforts toward this end were unsuccessful, usually leading to complex mixtures of unidentifiable products. While unfortunate, this was not entirely unexpected, as bromide **311** was rather strained, and the alignment between the proton at C(11) and the bromine atom at C(12) was expected to be poor. In an earlier model system, X-ray analysis of the fragmentation product showed a torsional angle of 70° between the protons at C(11) and C(12), and a similar alignment was expected in bromide **311** (Figure 5.2).

Figure 5.2 X-Ray of Model Fragmentation Product 128.



One attempt at elimination that proceeded cleanly was the reaction of **311** with pyridine at 110°C, which gave aldehyde **312**, in which the methyl acetal was deprotected, and the resultant lactol at C(26) cyclized into C(12), displacing the bromide.[4] This was not at all expected, but the structure was assigned by extensive NMR study (^{1}H NMR, ^{13}C NMR, DEPT, HMQC, HMBC, NOE). This assignment provided further support to the structural assignment of bromide **311**, which in analogy to model compound **128** (Figure 5.2), must have C(12) relatively close to the lactol at C(26). This also suggests that the bromide is, indeed, in the δ-position, as would be required for direct substitution.

Scheme 5.9 An Unusual Reaction.

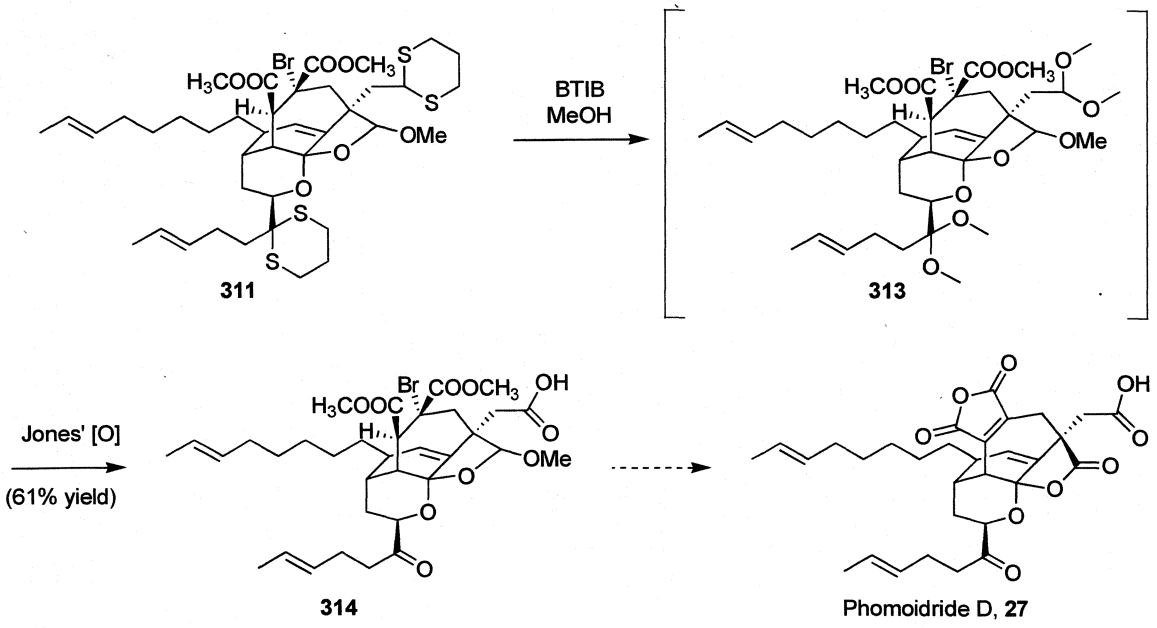


5.3.3 Addressing the Remaining Functionality.

Our inability to eliminate bromide **311** directly to the maleate led us to change course and first address the other remaining challenges in the synthesis. Toward this end, bis-dithiane **311** was treated with BTIB in methanol to give a compound that was believed to be the bis-dimethyl acetal **313**, which was somewhat unstable to silica gel chromatography and therefore not fully characterized. Instead this material was subjected directly to Jones' oxidation, affording keto-acid **314**. Unfortunately, even after prolonged exposure to Jones' reagent at elevated temperatures, the methyl acetal at C(27)

was stable. Thus, the goal of deprotecting C(27), C(29) and C(6) together with concomitant oxidation at C(27) and C(29) was only partially successful. While the dithiane moieties can be easily removed, and the acid unveiled by oxidation with Jones' reagent, additional efforts would be required to provide the lactone at C(27).

Scheme 5.10 Dithiane Deprotection and Oxidation.



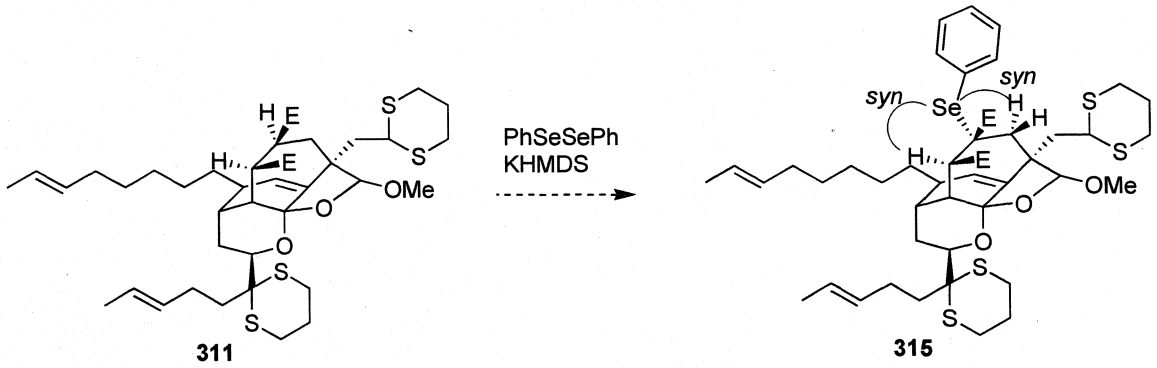
5.4 Future Work.

5.4.1 Maleate Incorporation.

Three challenges remain in the total synthesis of phomoidride D: installation of the maleate (by elimination of the C(12) bromide), anhydride formation (which is precedented)[5] and re-installation of the C(27) lactone. While attempts to eliminate the bromide have thus far been unsuccessful, these efforts have not been exhaustive, and this

remains a viable option for the incorporation of the maleate. Another possibility for installing the maleate would be to use a different electrophile in the oxidation of **310**. Potentially, incorporation of a phenylselenide (**315**) might allow for elimination to occur via a *syn* elimination, which might be more readily accomplished than the *anti* elimination of the bromide.

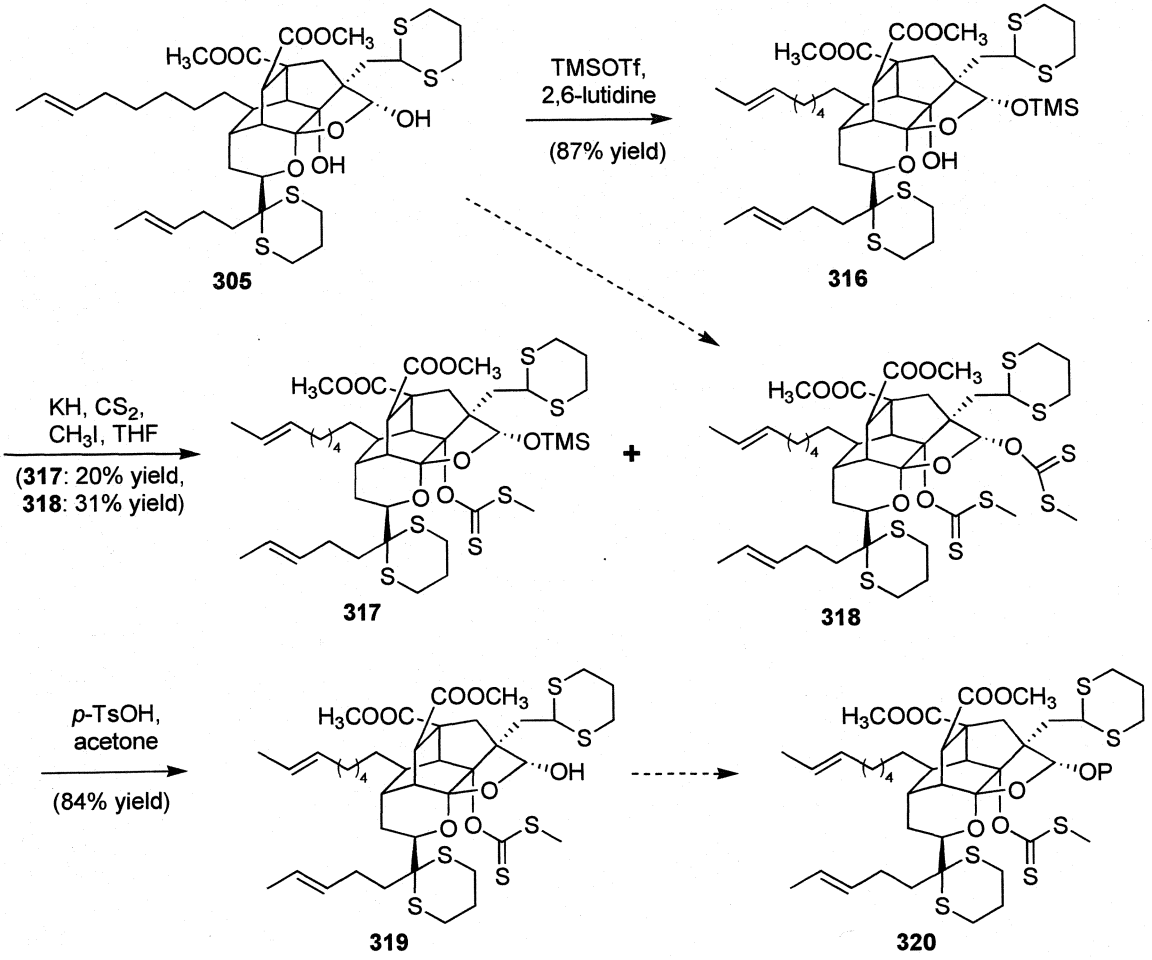
Scheme 5.11 Syn-Elimination Possibility.



5.4.2 Re-installation of the C(27) Lactone.

The other remaining challenge was the oxidation of the C(27) methyl acetal to the lactone. It was somewhat disappointing that **314** was stable to Jones' reagent, as this was expected to accomplish this hydrolysis and oxidation. Recent work has focused on the use of other protecting groups (besides methyl) for this C(27) acetal. Initially, TMS was chosen, but this was unsatisfactory in the xanthate-forming step (**316**δ **317**) giving a variable mixture of TMS-xanthate **317**, bis-xanthate **318** and recovered **316**.

Scheme 5.12 Formation of the TMS-Xanthate 317.

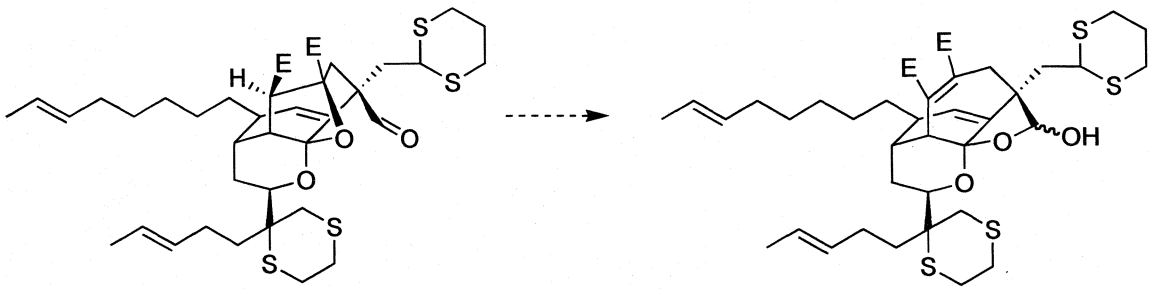


Fortunately, it was discovered that the bis-xanthate **318** could be efficiently transformed into the mono-xanthate lactol **319**. The free lactol of **319** should be readily functionalizable, allowing us to efficiently screen protecting groups. Current efforts are directed at the direct formation of bis-xanthate **318** from lactol **305**.

5.4.3 Advancing Aldehyde 312.

An alternate strategy for the completion of the synthesis would employ aldehyde **312**, the product of the unusual reaction of bromide **311** with pyridine (Scheme 5.9). In this system, the problem of deprotection is solved, but it is replaced with the challenge of performing an elimination to open the cyclic ether of **312**.

Scheme 5.13 Advancing Aldehyde 312.

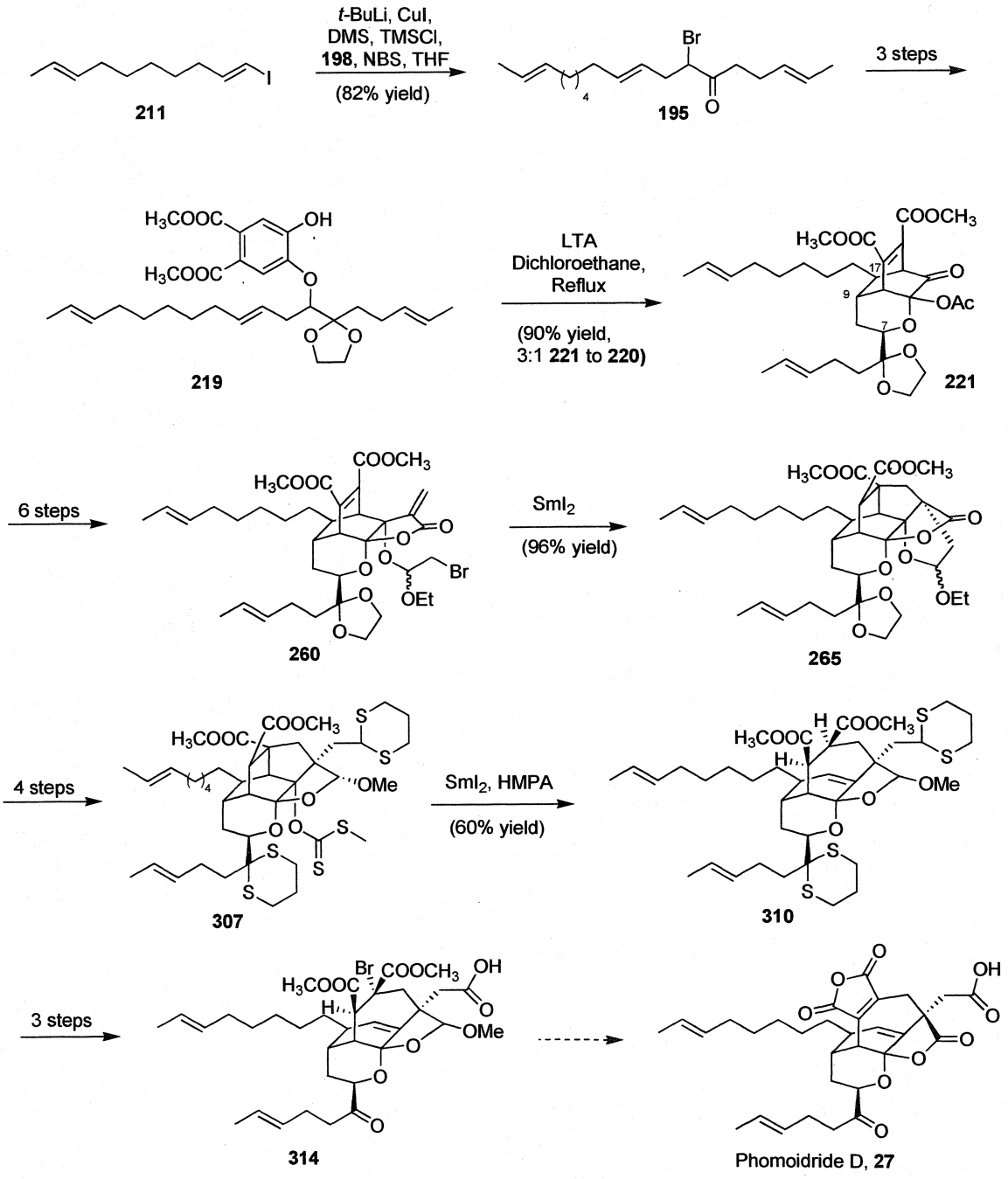


312 **321**

5.5 Conclusion.

Early work in our laboratory heavily utilized model systems to explore potential routes to the bicyclo[4.3.1]decene core of the phomoidrides. This use of model systems allowed a strategy to evolve which gave very efficient access to a bicyclo[4.3.1]decene core that incorporated several of the other features found in the phomoidrides (Scheme 5.2, **160**), including the C(14) quaternary center, bridging ketal, model C(17) side-chain and bridgehead olefin). With a great deal of information learned from these model systems, efforts toward the synthesis commenced (Scheme 5.14).

Scheme 5.14 Summary.



An efficient route to δ-bromoketone **211** was developed, employing a tandem conjugate addition/bromination sequence. After three steps, **211** afforded phenol **219**, which upon treatment with LTA underwent a tandem phenolic oxidation/IMDA sequence to give acetates **221** and **220** in a 3:1 ratio, favoring **221**, which contained the phomoidride D orientation at C(7). This was advanced through a sequence involving an intermolecular aldol addition, Cope elimination, desilylation and bromoacetal formation, setting the stage for the next key step, which was a tandem cascade reaction that could be carried out two different ways. Using standard tin-hydride conditions, a 5-*exo-trig,* 5-*exo-trig* cascade sequence that proceeds from the "bottom-up" occurs, providing **265** along with the unwanted 6-*endo-trig,* 4-*exo-trig* cascade cyclization product. It was found that employing SmI_2 instead, gave **265** exclusively, and that this reaction follows a completely different mechanism, in which maleate reduction leads to a 5-*endo-trig* cyclization followed by a 5-*exo-tet* intramolecular alkylation. Several more transformations give xanthate **307**, which upon exposure to SmI_2/HMPA gives the fragmentation product **310**. This was advanced to acid **314**, which requires only bromide elimination and acetal hydrolysis/oxidation to complete the total synthesis of phomoidride D.

5.6 Experimental Section.

5.6.1 Materials and Methods.

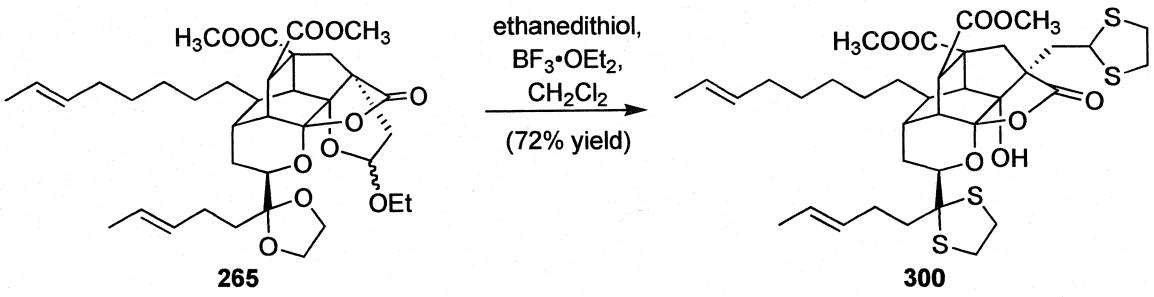
Unless stated otherwise, reactions were performed in flame dried glassware under a nitrogen atmosphere, using freshly distilled solvents. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl. Methylene

chloride (CH_2Cl_2) and triethylamine (Et_3N) were distilled from calcium hydride. All other commercially obtained reagents were used as received.

Unless stated otherwise, all reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using E. Merck silica gel 60 F_{254} precoated plates (0.25 mm). Column or flash chromatography was performed with the indicated solvents using silica gel (230-400 mesh) purchased from Silicycle. In general, the chromatography guidelines reported by Still et al. were followed. Infrared spectra were recorded on a Midac M1200 FTIR. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX-500 or Bruker Avance DPX-400 spectrometer. Chemical shifts are reported relative to internal chloroform (^1H, δ 7.26 ppm; ^{13}C, δ 77.23 ppm). High resolution mass spectra were performed at the University of Illinois Mass Spectrometry Center. Single-crystal X-ray analyses were performed by Dr. Christopher Incarvito of Yale University.

5.6.2 Preparative Procedures.

Preparation of Bis-dithiolane 300 (NTII-294):

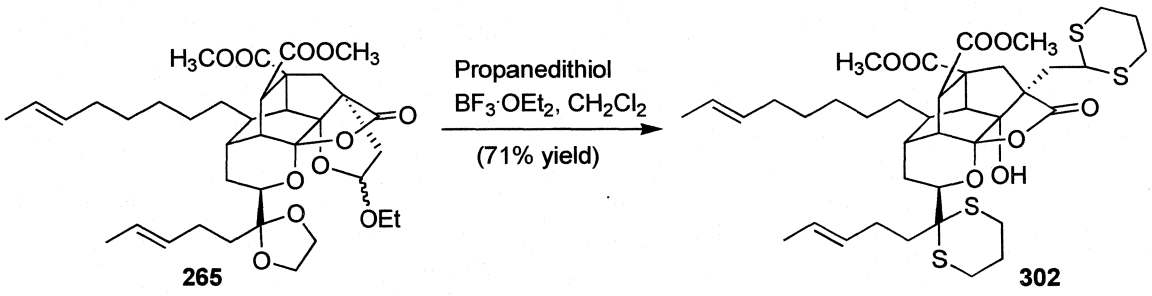


Bis-dithiolane 300. To a cooled (0°C) solution of ethyl acetal **265** (157mg, 0.233mmol, 1.0 equiv) in CH_2Cl_2 (4 mL) was added ethanedithiol (195 μL, 2.33 mmol, 10 equiv) and then BF_3•OEt_2 (148 μL, 1.17 mmol, 5.0 equiv). After stirring 30 min at 0°C, saturated aqueous $NaHCO_3$ (3 mL) was added, and the reaction was extracted with EtOAc (3x 10 mL). The combined organic layers were washed with brine (5 mL) and dried over Na_2SO_4, and the solvent was removed *in vacuo*. Purification via silica gel chromatography (20%-40% EtOAc/Hexanes eluent) furnished **300** (127mg, 72% yield) as a white foam.

Bis-dithiolane 300. FTIR (thin film/NaCl) 3242 (br), 2926 (s), 2853 (m), 1775 (s), 1730 (s), 1434 (m), 1366 (w), 1275 (m), 1231 (m), 1168 (m), 1091 (m), 1067 (m), 992 (m), 911 (w) 732 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.51-5.38 (m, 4H), 5.01 (dd, *J*=8.8, 4.1 Hz, 1H), 4.63 (dd, *J*=9.4, 3.0 Hz, 1H), 4.01 (s, 1H), 3.73 (s, 3H), 3.69 (s, 3H), 3.33-3.20 (m, 8H). 3.00 (d, *J*=14.2 Hz, 1H), 2.58-2.49 (m, 4H), 2.36-2.23 (m, 3H), 2.16-2.07 (m, 1H), 1.95-1.74 (m, 7H). 1.64-1.57 (m, 7H), 1.35-1.18 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.15, 174.86, 170.88, 131.49, 130.68, 125.66, 125.10, 106.79,

85.83, 80.44, 78.22, 74.14, 53.32, 53.26, 53.16, 52.51, 49.30, 49.22, 44.31, 44.08, 42.68, 40.91, 40.50, 40.37, 39.80, 38.76, 38.62, 38.46, 35.35, 33.53, 32.85, 32.67, 29.92, 29.68, 29.45, 29.32, 27.79, 18.17, 18.14. HRMS (ESI) *m/z* 753.2633 [calc'd for $C_{37}H_{53}O_8S_4$ (M+H) 753.2623].

Preparation of Bis-dithiane 302 (IMMV-293):

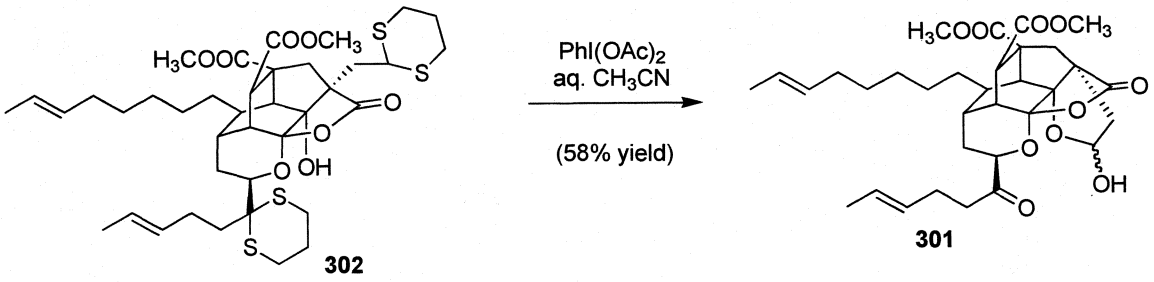


Bis-dithiane 302. To a cooled (-10°C) solution of ethyl acetal **265** (360mg, 0.53mmol, 1.0 equiv) in CH_2Cl_2 (5.4 mL) was added propanedithiol (540 µL, 5.38 mmol, 10.1 equiv) and then BF_3•OEt_2 (148 µL, 1.17 mmol, 2.2 equiv). The reaction mixture was allowed to warm to rt, and after 2h, was quenched by the addition of saturated aqueous $NaHCO_3$ (3 mL) The reaction was extracted with CH_2Cl_2 (3x 10 mL). The combined organic layers were washed with brine (5 mL) and dried over Na_2SO_4. and the solvent was removed *in vacuo*. Purification via silica gel chromatography (25% EtOAc/Hexanes eluent) furnished **300** (296mg, 71% yield) as a white foam.

Bis-dithiane 302. FTIR (thin film/NaCl) 3488 (br), 2925 (s), 2854 (m), 2257 (w), 1779 (s), 1731 (s), 1435 (m), 1375 (w), 1276 (m), 1231 (s), 1160 (m), 1147 (m), 1087 (m), 994 (m), 967 (m), 910 (m) 732 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.46-5.31

(m, 4H), 4.79 (dd, *J*=12.1, 3.1 Hz, 1H), 4.48 (dd, *J*=8.3, 6.7 Hz, 1H), 3.73 (s, 3H), 3.69 (s, 3H), 3.62 (s, 1H), 3.51 (s, 1H), 3.40-3.28(m, 2H), 3.00 (d, *J*=14.2 Hz, 1H), 2.91-2.77 (m, 4H), 2.63-2.49 (m, 7H), 2.30-2.25 (m, 2H), 2.14-1.74 (m, 12H), 1.65-1.29 (m, 8H), 1.33-1.18 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.24, 174.76, 170.83, 131.41, 130.31, 126.02, 125.10, 106.40, 85.98, 84.21, 53.75, 53.20, 53.17, 52.79, 52.50, 49.02, 45.14, 44.43, 42.11, 40.92, 39.52, 39.21, 38.05, 35.23, 33.70, 32.64, 32.33, 29.65, 29.30, 29.22, 28.71, 27.77, 27.67, 27.46, 25.45, 24.99, 18.10. HRMS (ESI) *m/z* 781.2936 [calc'd for $C_{39}H_{57}O_8S_4$ (M+H) 781.2936].

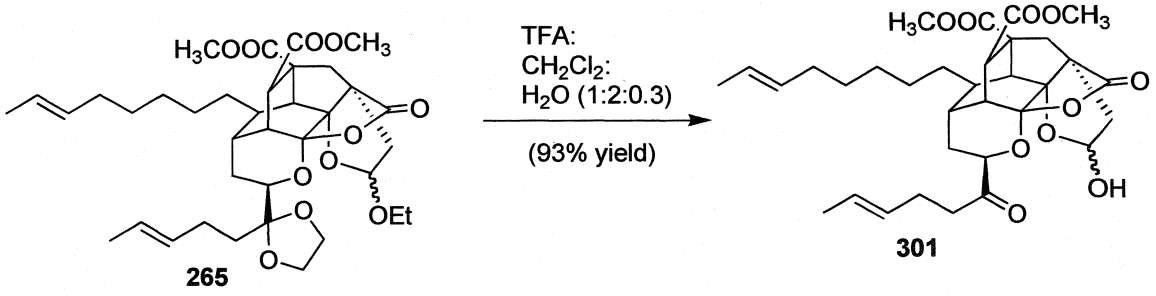
Preparation of Lactol 301 (IMMV-218):



Lactol 301. To a solution of bis-dithiane **302** (4.1 mg, 0.005 mmol, 1 equiv) in a mixture of $CH_3CN/CH_2Cl_2/H_2O$ (8:1:1, 150 μL) at 0°C was added Ca_2CO_3 (22mg, 0.22 mmol, 44 equiv) followed by $PhI(OCCF_3)_2$ (11.4mg, 0.0027 mmol, 5.3 equiv). After 2 min, a saturated aqueous solution of $NaHCO_3$ (500 μL) was added, and the reaction was extracted with EtOAc (3x 5 mL). The combined organics were washed with brine (2 mL) dried over Na_2SO_4, and concentrated *in vacuo*. Purification by silica gel chromatography (25%-100% EtOAc/hexanes eluent) gave **301** (1.8mg, 58% yield) as a clear oil.

Lactol 301. FTIR (thin film/NaCl) 3472 (br), 2927 (s), 2855 (m), 2256 (w), 1792 (s), 1733 (s), 1456 (m), 1436 (m), 1364 (w), 1294 (w), 1231 (s), 1149 (s), 1121 (s), 1083 (s), 1033 (w), 997 (s), 968 (m), 919 (w), 733 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.78 (d, *J*=4.2, 1H), 5.50-5.36 (m, 4H), 4.56 (dd, *J*= 11.8, 4 Hz, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 3.48 (s, 1H), 3.17 (d, *J*=14.2, 1H), 2.81-2.59 (m, 6H), 2.40 (d, *J*=14.2 Hz, 1H), 2.23 (d, *J*=6.8, 2H), 2.04 (dd *J*=12.9, 3.9 Hz, 1H), 1.94 (m, 4H), 1.80-1.60 (m, 13H), 1.33-1.15 (m, 14H). ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.86, 176.13, 173.94, 170.71, 131.38, 129.65, 126.31, 125.15, 106.63, 104.92, 97.75, 77.49, 58.75, 55.10, 53.17, 52.95, 52.58, 43.94, 43.80, 41.47, 41.38, 39.32, 38.10, 35.22, 33.69, 33.66, 32.58, 29.61, 29.30, 27.78, 26.12, 18.11, 18.07. HRMS (ESI) *m/z* 601.3014 [calc'd for $C_{33}H_{45}O_{10}$ (M+H) 601.3013].

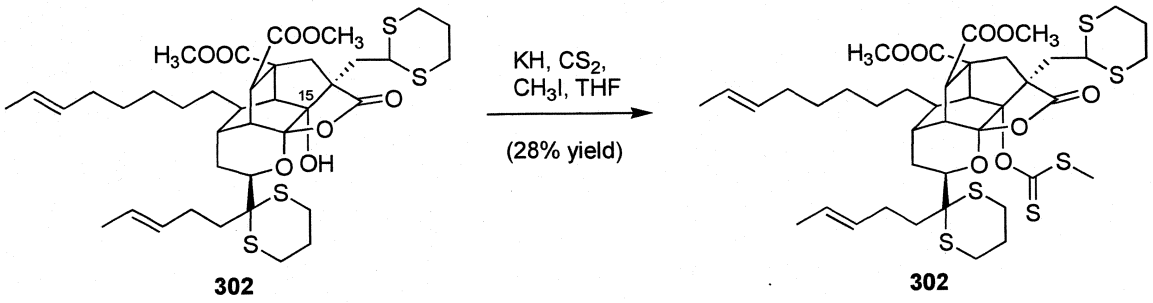
Preparation of Lactol 301 (TSII-226):



Lactol 301. A solution of acetal **265** (14.1mg, 0.021 mmol, 1.0 equiv) in TFA/ CH_2Cl_2/ H_2O (1:2:0.3, 1.1mL) was allowed to stir overnight at rt. The reaction mixture was treated with a saturated aqueous solution of $NaHCO_3$ (1mL) and CH_2Cl_2 (2mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2x 2mL), the

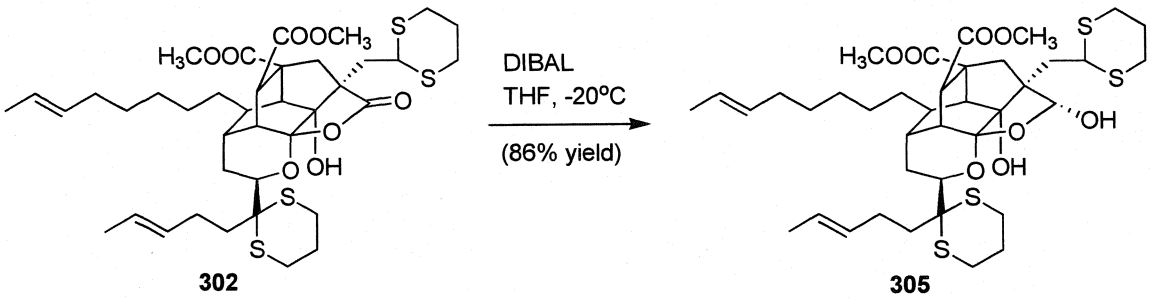
combined organic layers were dried over Na_2SO_4, and the solvent was removed *in vacuo*. Purification by silica gel chromatography (20%-33% EtOAc/hexanes eluent) provided lactol **301** (11.7mg, 92.9% yield) as a clear oil.

Preparation of Xanthate 304 (TSIII-132):



Xanthate 304. To a mixture of KH (12.9mg, 0.323mmol, 5.0 equiv) in THF (1mL) at 0°C was added a solution of lactone **302** (49.9 mg, 0.0646 mmol, 1.0 equiv) in THF (1mL +0.5mL). The reaction mixture was allowed to react at rt for 15 min, and then cooled to 0°C. After stirring at 0°C for 15 min, CS_2 (36.6μL, 0.65mmol, 10 equiv) was added, and the reaction was warmed to rt. After stirring at rt for 15 min, the reaction was cooled to 0°C, and stirred for 15 min, at which time CH_3I (40μL, 0.65mmol, 10 equiv) was added. The reaction was stirred at rt for 30 min, at which point MeOH (1mL) and a saturated aqueous solution of NH_4Cl (1mL) were added. The mixture was extracted with EtOAc (3x 5mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by silica gel chromatography (1%-2% EtOAc/Benzene eluent) furnished xanthate **302** (15.8 mg, 28% yield) as a clear oil.

Preparation of Lactol 305 (IMMV-295):

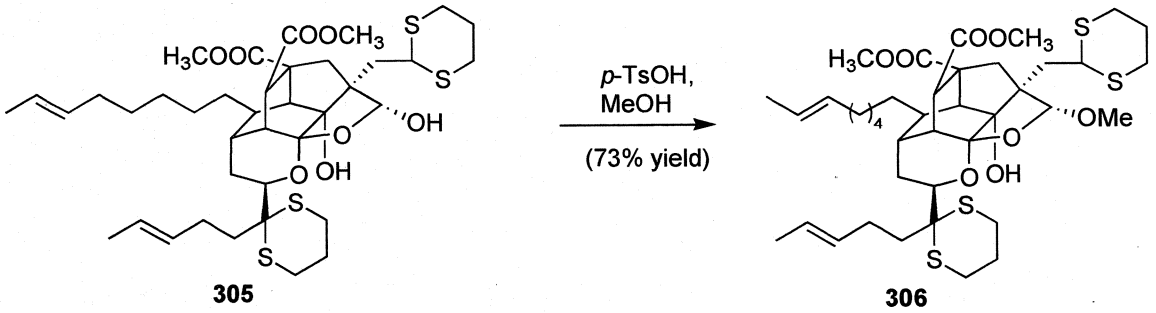


Lactol 305. To a solution of lactone **302** (143mg, 0.20mmol, 1.0 equiv) in THF (3mL) at –50°C was added DIBAL (1.0M in hexanes, 1mL, 1mmol, 5.0 equiv). The reaction was allowed to slowly warm to –25°C. After 45 min, the reaction was quenched with a 10% aqueous solution of Rochelle's salt (3mL) and allowed to stir overnight. After ~16h, EtOAc (10mL) was added and the phases were separated. The aqueous layer was extracted with EtOAc (2x 5mL) and the combined organics were washed with brine, dried over Na_2SO_4, and the solvent was removed *in vacuo*. Purification by silica gel chromatography (20%-40% EtOAc/hexanes eluent) gave lactol **305** (122mg, 86% yield) as a white foam.

Lactol 305. FTIR (thin film/NaCl) 3494 (br), 2525 (s), 2855 (m), 1730 (s), 1437 (m), 1231 (s), 1082 (s), 1004 (m), 968 (m), 910 (w), 732 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.46-5.29 (m, 4H), 5.23 (s, 1H), 4.92 (dd *J*=11.6, 3.0 Hz, 1H), 4.17 (dd *J*=8.6, 5.8 Hz, 1H), 3.71 (s, 3H), 3.65 (s, 3H), 3.33-3.16 (m, 4H), 2.96-2.77 (m, 5H), 2.68-2.38 (m, 4H), 2.24 (m, 1H), 2.13-1.75 (m, 13H), 1.72-1.48 (m, 10H), 1.31-1.14 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.24, 171.99, 131.45, 130.56, 125.71, 124.93, 108.05, 102.05, 88.20, 79.90, 55.09, 54.76, 52.95, 51.99, 51.62, 49.36, 45.74, 44.22, 40.26, 39.78,

39.55, 38.41, 37.15, 35.41, 34.23, 32.62, 32.41, 31.01, 30.70, 29.64, 29.23.27.81, 27.69, 27.55, 27.14, 25.63, 25.14, 18.11. HRMS (ESI) *m/z* 805.2923 [calc'd for $C_{39}H_{58}O_8S_4Na$ (M+Na) 805.2912].

Preparation of Acetal 306 (IMMV-299):

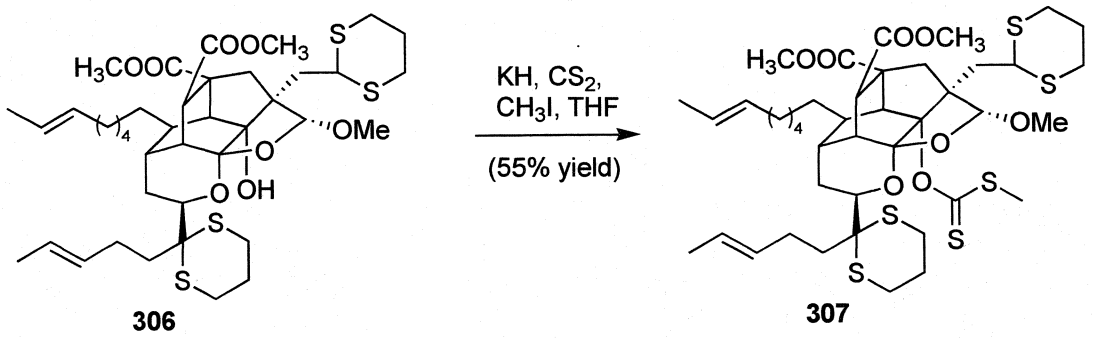


Acetal 306. To a solution of lactol **305** (107mg, 0.137 mmol, 1.0 equiv) in MeOH (2 mL) was added *p*-TsOH (30mg, 0.159 mmol, 1.16 equiv). The mixture was heated to reflux overnight, cooled to rt, quenched with a saturated aqueous solution of $NaHCO_3$ (1 mL) and extracted with EtOAc (3x 10 mL). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by silica gel chromatography furnished methyl acetal **306** (79.8 mg, 73% yield) as a white foam.

Acetal 306. FTIR (thin film/NaCl) 3540 (br), 2926 (s), 2854 (s), 1729 (s), 1434 (m), 1230 (m), 1165 (w), 1094 (s), 998 (w), 967 (m), 911 (m), 733 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.46-5.33 (m, 4H), 4.91 (dd, *J*=12.2, 3.5 Hz, 1H), 4.71 (s, 1H), 4.09 (dd, *J*=10.2, 4.3 Hz, 1H), 3.72 (s, 3H), 3.68 (s, 3H), 3.33 (s, 3H), 3.23-3.16 (m, 3H), 2.94 (ddd, *J*=13.9, 11.8, 2.5 Hz, 1H), 2.86-2.77 (m, 4H), 2.66-2.59 (m, 2H), 2.55 (d, *J*=2.5 Hz, 1H), 2.48-2.42 (m, 3H), 2.35 (d, *J*=15.0, 1H), 2.29-2.22 (m, 1H), 2.14-2.09 (m, 2H),

2.02-1.75 (m, 9H), 1.74-1.53 (m, 10H), 1.32-1.17 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.33, 172.12, 131.52, 130.75, 125.61, 126.96, 108.47, 107.61, 88.14, 79.47, 55.46, 55.11, 54.53, 52.92, 51.99, 51.47, 49.46, 45.90, 44.45, 40.45, 40.14, 39.26, 38.24, 37.21, 35.54, 34.30, 32.64, 32.57, 32.51, 31.22, 30.63, 29.67, 29.28, 27.86, 27.78, 27.09, 25.72, 25.13, 18.10, 18.09. HRMS (ESI) *m/z* 819.3059 [calc'd for $C_{40}H_{60}O_8S_4Na$ (M+Na) 819.3069].

Preparation of Xanthate 307 (IMMVI-71):

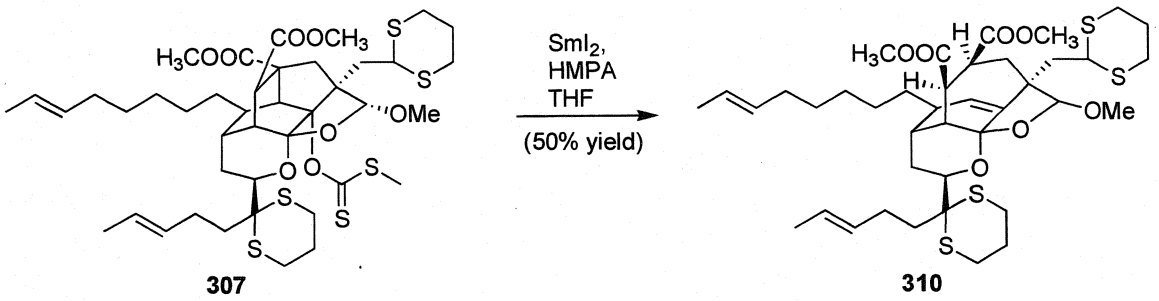


Xanthate 307. To a mixture of KH (31.3mg, 0.783 mmol, 5.4 equiv) in THF (2 mL) at 0°C was added a solution of acetal **306** (115 mg, 0.144 mmol, 1.0 equiv) in THF (1 mL+1 mL+0.5 mL). The reaction mixture was allowed to react at rt for 15 min, and then cooled to 0°C. After stirring at 0°C for 15 min, CS_2 (80 μL, 1.33 mmol, 9.2 equiv) was added, and the reaction was warmed to rt. After stirring at rt for 15 min, the reaction was cooled to 0°C, and stirred for 15 min, at which time CH_3I (90 μL, 1.44 mmol, 10 equiv) was added. The reaction was stirred at rt for 2h, at which point MeOH (1 mL) and a saturated aqueous solution of NH_4Cl (1 mL) were added. The mixture was extracted

with EtOAc (3x 5 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by silica gel chromatography (1.25% EtOAc/Benzene eluent) furnished xanthate **307** (70.8 mg, 55% yield) as a clear oil.

Xanthate 307. FTIR (thin film/NaCl) 2960 (s), 2925 (s), 2854 (m), 1733 (s), 1455 (m), 1435 (m), 1374 (w), 1261 (s), 1208 (s), 1102 (s), 1017 (s), 967 (m), 940 (w), 910 (m), 865 (w), 799 (s), 734 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.47-5.33 (m, 4H), 4.15 (d, *J*=2.6 Hz, 1H), 4.67 (s, 1H), 4.46 (dd, *J*=11.4, 3.7 Hz, 1H), 4.06 (dd, *J*=9.1, 5.3 Hz, 1H), 3.75 (s, 3H), 3.70 (s, 3H), 3.61-3.46 (m, 2H), 3.32 (s, 3H), 3.20 (s, 1H), 2.92 (ddd, *J*=14.0, 11.9, 2.5 Hz, 1H), 2.85-2.74 (m, 5H), 2.63-2.50 (m, 12H), 2.19 (ddd, *J*=12.5, 12.3, 4.5 Hz, 1H), 2.16-1.96 (m, 4H), 1.96-1.78 (m, 7H), 1.76-1.57 (m, 10H), 1.48 (dt, *J*=12.7, 3.7 Hz, 1H), 1.31-1.14 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.58, 176.06, 172.19, 131.61, 131.00, 125.62, 124.97, 108.56, 108.54, 102.71, 83.08, 57.97, 55.12, 54.85, 53.19, 52.08, 48.39, 48.10, 44.65, 44.53, 41.26, 39.98, 39.16, 39.02, 38.78, 35.53, 34.40, 33.09, 32.74, 31.38, 30.92, 29.69, 29.39, 28.01, 27.78, 27.61, 27.19, 25.73, 25.47, 20.35, 18.18, 18.14. HRMS (ESI) *m/z* 909.2686 [calc'd for $C_{42}H_{62}O_8S_6Na$ (M+Na) 909.2667].

Preparation of Fragmentation Product 310 (IMMVI-72):



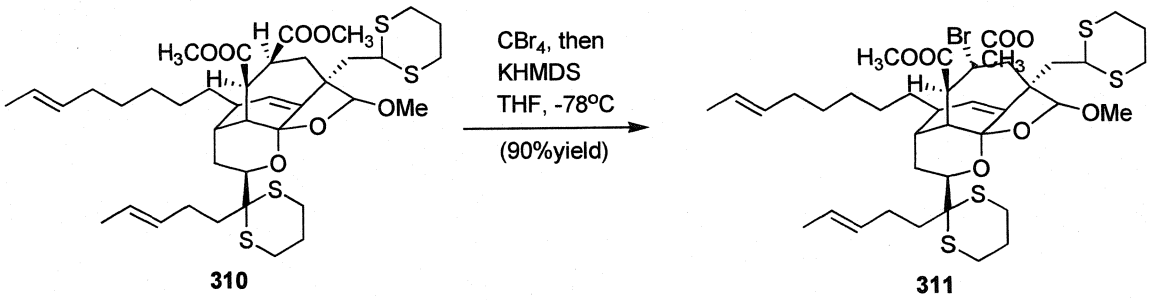
Preparation of 0.1M SmI_2 in THF. Samarium metal[6] (2.6 g, 17.3 mmol, 1.75 equiv) was placed in a flame-dried 250mL flask and lightly flame-dried under vacuum. THF (100 mL) was then added, and the mixture was lightly degassed by three repetitions of cycles of vacuum (1-2 sec), and nitrogen refilling. 1,2-Diiodoethane (2.8g, 9.95 mmol, 1.0 equiv) was added in one portion, and the degassing sequence was repeated. The time required for initiation of the reaction was variable, but always fastest when freshly filed samarium was employed. Within 30 minutes of the addition of diiodoethane, the reaction mixture should begin to turn a blue-green color. Eventually, the color will change to a deep Prussian blue, which is characteristic of THF solutions of SmI_2. After 3h of stirring, the reagent was deemed to be of a good quality, and stirring was halted, allowing the excess samarium metal to settle to the bottom. When using this reagent (i.e. transferring by syringe), care was taken to try to take only the supernatant.

Fragmentation Product 310. To a solution of freshly prepared SmI_2 in THF (25 mL, 2.5mmol, 31 equiv) was added HMPA (6.1 mL, 35 mmol, 439 equiv). To this purple solution was added a solution of xanthate **310** (70.8 mg, 0.08 mmol, 1.0 equiv) in THF (4.4 mL) *via* syringe pump over 1h. After the complete addition of **310**, the reaction was

stirred an additional 15 min, and then treated with a saturated aqueous solution of NH_4Cl (10 mL), the mixture was extracted with EtOAc (3x 10 mL). The combine organic phases were washed with water (10x 10 mL), and brine (10 mL) dried over Na_2SO_4, and concentrated *in vacuo*. Purification by silica gel chromatography (2.5% EtOAc/benzene eluent) furnished fragmentation product **311** (30.2mg, 50% yield) as a clear oil.

Fragmentation Product 310. FTIR (thin film/NaCl) 2926 (s), 2853 (m), 2255 (w), 1731 (s), 1435 (m), 1368 (w), 1330 (w), 1275 (m), 1241 (s), 1193 (s), 1135 (w), 1100 (s), 1039 (m), 971 (s), 910 (m), 805 (w), 733 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.52 (br, 1H), 5.48-5.35 (m, 4H), 4.96 (s, 1H), 4.20 (dd, *J*=10.5, 4.0 Hz, 1H), 3.77 (dd, *J*=11.5, 2.0 Hz, 1H), 3.70 (s, 3H), 3.64 (s, 3H), 3.49 (m, 1H), 3.31 (s, 3H), 2.99-2.72 (m, 10H), 2.62 (dd, *J*=7.9 2.0 Hz, 1H), 2.43 (dd, *J*=14.7, 10.6 Hz, 1H), 2.39 (s, 1H), 2.22-2.16 (m, 1H), 2.11-1.84 (m, 14H), 1.78-1.75 (m, 1H), 1.66-1.59 (m, 7H), 1.42-1.24 (m, 12H), 1.07 (d, *J*=13.4, 5.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.98, 172.72, 142.77, 131.57, 131.27, 126.33, 125.27, 125.06, 107.10, 104.46, 74.89, 56.48, 54.90, 54.32, 52.41, 51.93, 46.56, 45.15, 43.85, 41.57, 41.32, 39.89, 39.07, 38.30, 36.91, 36.19, 34.92, 32.69, 30.85, 30.30, 29.92, 29.63, 29.58, 29.27, 28.55, 27.70, 26.18, 25.76, 25.54, 22.91, 18.21, 18.14. HRMS (ESI) *m/z* 803.3122 [calc'd for $C_4H_{58}O_7S_4Na$ (M+Na) 803.3120].

Preparation of δ-Bromoester 311 (IMMVI-85):



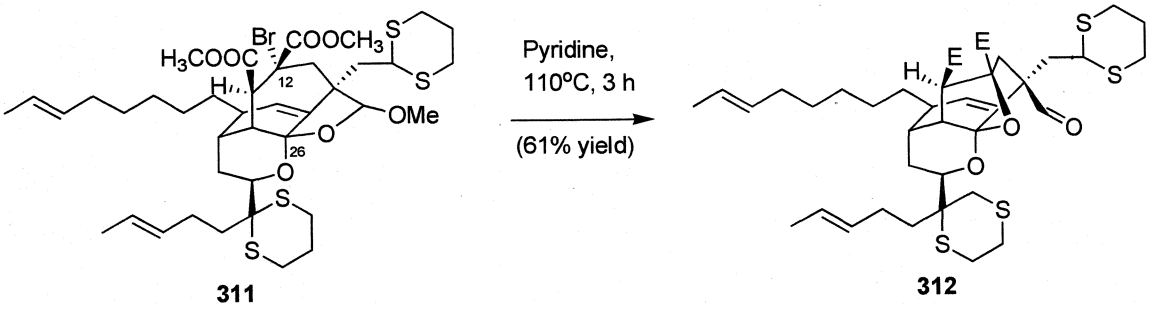
310 311

δ-Bromoester 311. To a solution of fragmentation product **311** (22mg, 0.028 mmol, 1 equiv) and CBr_4 (90mg, 0.272 mmol, 9.7 equiv) in THF (3 mL) at –78°C was added KHMDS (0.5M in toluene, 600 μL, 0.3 mmol, 10.7 equiv). The mixture was allowed to stir for 50 min at –78°C, at which point it was quenched by the addition of MeOH (0.5 mL) and saturated aqueous NH_4Cl (1 mL). The mixture was warmed to rt, and extracted with EtOAc (3x 5 mL). The combined organic phases were washed with brine (3 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by silica gel chromatography (0%-5% EtOAc/benzene eluent) gave δ-bromoester **311** (22mg, 89.8% yield) as a clear oil.

δ-Bromoester 311. FTIR (thin film/NaCl) 2928 (s), 2854 (m), 1751 (m), 1733 (s), 1436 (m), 1259 (m), 1151 (m), 1104 (s), 1054 (m), 967 (s), 911 (m), 803 (w), 733 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.62 (br, 1H), 5.47-5.336 (m, 4H), 4.99 (s, 1H), 4.19 (dd, *J*=10.9, 3.7 Hz, 1H), 3.82 (s, 3H), 3.77 (dd, *J*=11.6, 2.3 Hz, 1H), 3.71 (s, 3H), 3.50 (d, *J*=13 Hz, 1H), 3.33 (s, 3H), 2.98 (ddd, *J*=14.1, 11.3, 2.4 Hz, 1H), 2.91-2.73 (m, 9H), 2.39 (dd, *J*=15.2, 11.0 Hz, 1H), 2.20-1.85 (m, 15H), 1.73 (m, 1H), 1.66-1.30 (m, 24H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.90, 140.96, 131.55, 131.13, 127.68, 125.34, 125.12,

106.57, 103.71, 77.80, 74.86, 63.96, 56.95, 56.38., 56.02, 55.12, 54.80, 52.90, 51.98, 43.96, 43.46.41.74, 37.99, 37.08, 36.81, 35.71, 34.49, 32.74, 30.85, 30.23, 29.70, 29.34, 28.48, 27.68, 26.17, 26.13, 25.67, 25.42, 18.20, 18.15. HRMS (ESI) *m/z* 859.2403 [calc'd for $C_{40}H_{60}O_7S_4$ (M+H) 859.2405].

Preparation of Aldehyde 312 (IMMVI-86):

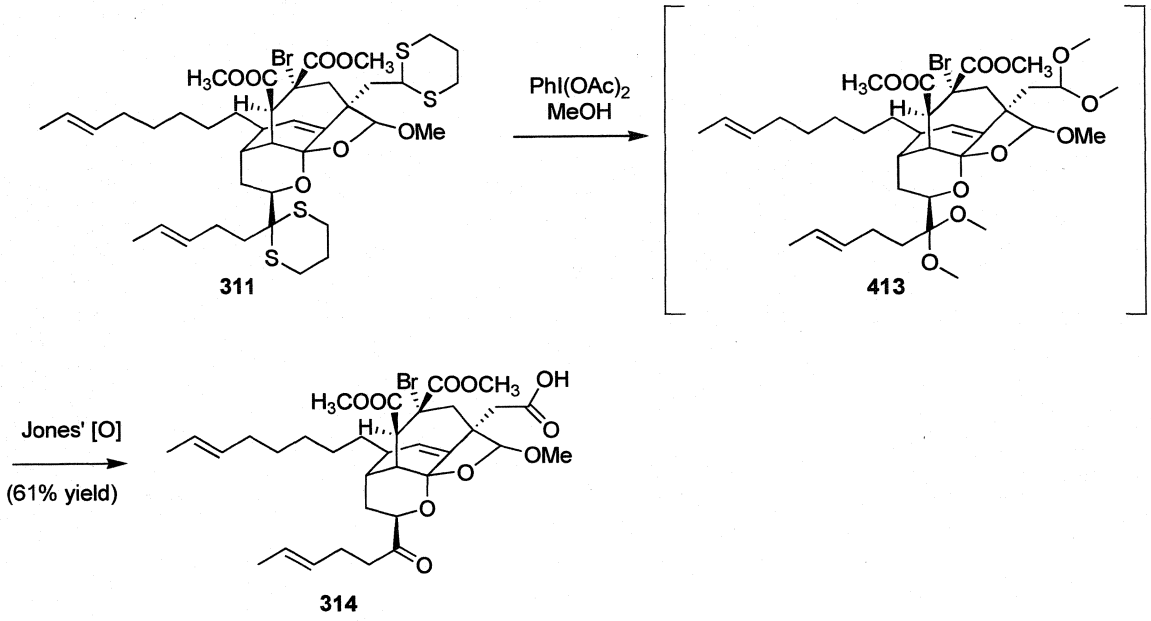


Aldehyde 312. A solution of δ-bromoester **311** (22mg, 0.025mmol, 1.0 equiv) in pyridine (2mL, 24.22 mmol, 989 equiv) in a sealed vial was heated to 115°C for 5h. The mixture was then cooled to rt, the solvent removed *in vacuo*, the residue dissolved in EtOAc (10mL) and washed with aqueous $NaHCO_3$ (1mL) and brine (1mL). The organic phase was dried over Na_2SO_4 and concented *in vacuo*. Purification by preparative TLC (5% EtOAc/hexanes eluent) gave aldehyde **312** (12mg, 61% yield) as a yellow oil.

Aldehyde 312. FTIR (thin film/NaCl) 2925 (s), 2852 (m), 1772 (m), 1739 (s), 1717 (s), 1436 (m), 1261 (m), 1169 (m), 1077 (m), 1014 (m), 967 (s), 909 (m), 800 (w), 733 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.85 (s, 1H), 5.99 (s, 1H), 5.43-5.28 (m, 4H), 4.11 (dd, *J*=11.8, 2.2 Hz, 1H), 3.89 (t, *J*=7.1Hz, 1H), 3.66 (s, 3H), 3.59 (s, 3H), 3.24 (s, 1H, 3.00-2.90 (m, 2H),2.76-2.42 (m, 10H), 2.30-1.70 (m, 20H), 1.60-1.20 (m, 24H); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 200.34, 172.54, 170.50, 136.74, 134.58, 131.68, 130.83, 128.75, 125.91, 125.35, 101.85, 80.70, 77.11, 76.93, 57.76, 55.35, 53.97, 53.05, 52.81, 48.22, 41.89, 40.79, 39.90, 37.30, 36.85, 35.52, 33.82, 32.88, 30.11, 29.76, 29.45, 28.60, 27.93, 27.32, 27.03, 25.34, 25.27, 18.41, 18.39. HRMS (ESI) *m/z* 765.2978 [calc'd for $C_{39}H_{57}O_7S_4$ (M+H) 765.2987].

Preparation of Acid 314 (IMMVI-155/157):

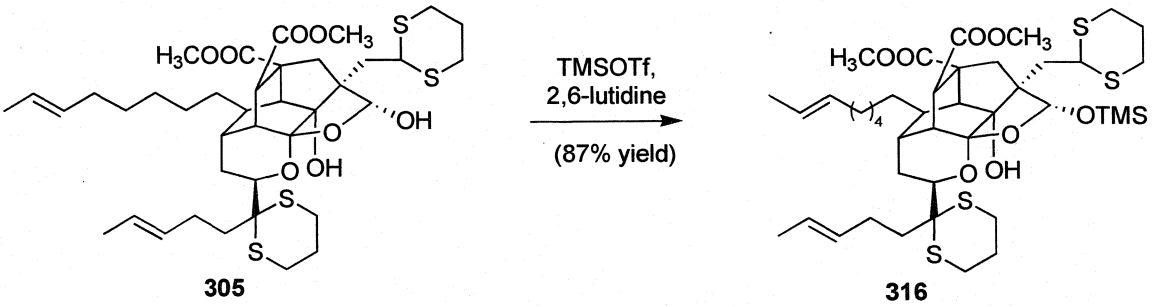


Acid 314. To a solution of δ-bromoester **311** (30mg, 0.035 mmol, 1.0 equiv) in CH_2Cl_2 (300 μL) was added MeOH (3 mL) and BTIB (120mg, 0.28 mmol, 8 equiv). After 1 min, the mixture was treated with an aqueous solution of $NaHCO_3$ (1 mL) and extracted with EtOAc (3x 10 mL). The combined organic phases were washed with brine (3mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting product, which was believed to be the bis-dimethyl acetal **313**, was unstable to silica gel chromatography, and was therefore carried on directly. Thus, the product of the foregoing reaction was dissolved in acetone (3 mL) and to this was added Jones' reagent [prepared from 13.5g CrO_3, and 12.5 mL H_2SO_4, diluted to 100 mL; 4N, (150 μL, 0.6 mmol, 17 equiv)]. After stirring for 30 min, an additional portion of Jones' reagent was added (150 μL). After an additional 30 min, the reaction was quenched by the addition of isopropanol (100 μL), diluted with EtOAc (10 mL) and separated. The aqueous phase was extracted with

EtOAc (3x 5 mL). The combined organic phases were washed with water (2x 2 mL) and brine (3 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by silica gel chromatography (25% EtOAc/hexanes + 1% AcOH) furnished acid **314** (16mg, 61% yield) as a colorless oil.

Acid 314. FTIR (thin film/NaCl) 2926 (s), 2855 (m), 1734 (s), 1457 (m), 1436 (m), 1112 (m), 967 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.79 (s, 1H), 5.32-5.28 (m, 4H), 5.02 (s, 1H), 3.92 (dd, *J*=10.9, 3.4 Hz, 1H), 3.67-3.59 (m, 4H), 3.21 (s, 3H), 2.76-2.45 (m, 10H), 2.14-1.16 (m, 30H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.61, 169.30, 138.49, 130.22, 128.62, 127.12, 124.72, 123.94, 105.30, 103.08, 75.68, 75.39, 75.03, 61.15, 55.86, 54.03, 52.57, 51.71, 50.92, 42.41, 40.02, 36.99, 36.47, 35.35, 33.78, 33.69, 31.47, 28.69, 28.41, 28.00, 27.08, 24.97, 16.93, 16.90. HRMS (ESI) *m/z* 717.2243 [calc'd for $C_{34}H_{47}O_{10}BrNa$ (M+Na) 717.2250].

Preparation of TMS-Acetal 316 (TSIII-88):

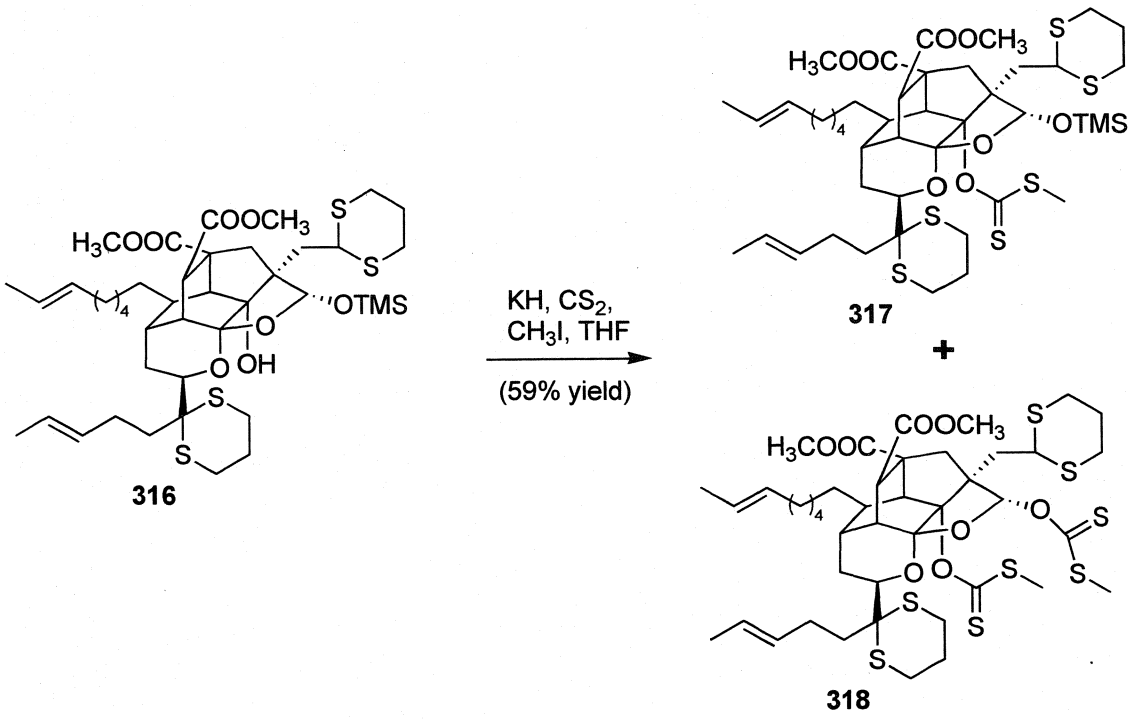


TMS-Acetal 316. To a solution of lactol **305** (38 mg, 0.0489 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) at –78°C was added 2,6-lutidine (57.5 μL, 0.49 mmol, 10.0 equiv) and TMSOTf (44.3 μL, 0.245 mmol, 5.0 equiv). The reaction mixture was stirred at –78°C for 5 min, treated with water (1 mL) warmed to rt and separated. The aqueous phase was

extracted with CH_2Cl_2 (2x 5 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by silica gel chromatography (5%-20% EtOAc/hexanes eluent) furnished TMS-acetal **316** (36mg, 86.7% yield) as a colorless oil.

TMS-Acetal 316. FTIR (thin film/NaCl) 3519 (br), 2949 (m), 2926 (s), 2854 (m), 2733 (s), 1735 (m), 1250 (m), 1231 (m), 1163 (w), 1085 (s), 1010 (m), 973 (m), 910 (m), 871 (m), 860 (m), 633 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.45-5.37 (m, 4H), 5.08 (s, 1H), 4.96 (dd, *J*=11.6, 3.1 Hz, 1H), 4.11 (dd, *J*=7.4, 6.8 Hz, 1H), 3.72 (s, 3H), 3.69 (s, 3H), 3.18 (s, 1H), 2.99-2.76 (m, 8H), 2.75-2.62 (m, 2H), 2.57 (d, *J*=2.5 Hz, 1H), 2.51 (d, *J*=15.0 Hz, 1H), 2.44 (d, *J*=15 Hz, 1H), 2.40 (d, *J*=2.1 Hz, 1H), 2.35 (dd, *J*=14.5, 7.8 Hz, 1H), 2.30-2.15 (m, 2H), 2.12-2.04 (m, 3H), 1.95-1.69 (m, 12H), 1.66-1.58 (m, 8H), 1.32-1.18 (m, 10H), 0.20 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.62, 172.18, 131.58, 131.16, 125.52, 124.99, 108.44, 102.69, 88.23, 74.96, 56.91, 55.23, 52.90, 51.89, 51.84, 49.41, 45.94, 45.00, 40.71, 40.44, 39.53, 38.66, 35.64, 35.34, 34.14, 32.72, 32.39, 31.53, 31.33, 29.72, 29.68, 29.37, 28.31, 27.95, 26.38, 25.74, 24.88, 18.16, 18.13, 0.70. HRMS (ESI) *m/z* 877.3321 [calc'd for $C_{42}H_{66}O_8S_4NaSi$ (M+Na) 877.3308].

Preparation of TMS-Xanthate 317 and bis-Xanthate 318 (TSIII-92):



TMS-Xanthate 317 and bis-Xanthate 318. To a mixture of KH (9.2 mg, 0.23 mmol, 5.0 equiv) in THF (1 mL) at 0°C was added a solution of acetal **316** (39.2 mg, 0.46 mmol, 1.0 equiv) in THF (1 mL). The reaction mixture was allowed to react at rt for 15 min, and then cooled to 0°C. After stirring at 0°C for 15 min, CS_2 (27.5 μL, 0.46 mmol, 10.0 equiv) was added, and the reaction was warmed to rt. After stirring at rt for 15 min, the reaction was cooled to 0°C, and stirred for 15 min, at which time CH_3I (28.5 μL, 0.46 mmol, 10 equiv) was added. The reaction was stirred at rt for 1h, at which point a saturated aqueous solution of NH_4Cl (1 mL) was added. The mixture was extracted with EtOAc (3x 5 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by silica gel chromatography (Two purifications were required; first 10%-35% EtOAc/hexanes eluent was used to separate

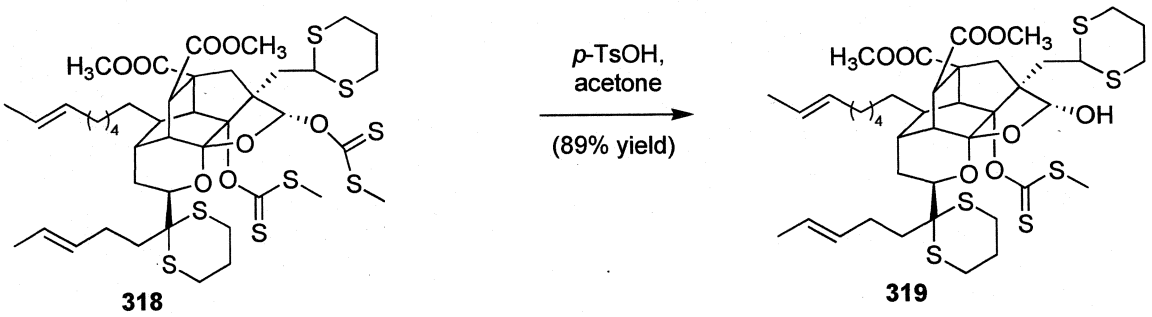
the unreacted starting material (**316**), then the mixed fractions of **317** and **318** were resubjected to silica gel chromatography using Benzene as the eluent) furnished TMS-xanthate **317** (8.8 mg, 20.3% yield), and bis-xanthate **318** (13.8mg, 31.2% yield) as clear oils.

TMS-Xanthate 317. FTIR (thin film/NaCl) 2925 (s), 2853 (m), 1733 (s), 1436 (m), 1249 (s), 1210 (s), 1104 (s), 1068 (s), 1013 (s), 966 (m), 896 (m), 871 (s), 847 (s), 733 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.47-5.36 (m, 4H), 5.09 (m, 1H), 5.06 (s, 1H), 4.31 (dd, *J*=12, 4.2 Hz, 1H), 4.04 (dd, *J*=7.8, 5.7 Hz, 1H), 3.74 (s, 3H), 3.70 (s, 3H), 3.16 (m, 3H), 2.90-2.62 (m, 8H), 2.57 (s, 3H), 2.50-2.10 (m, 10H), 2.00-1.50 (m, 30H), 1.32-1.15 (m, 16H) ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.44, 176.27, 172.26, 131.65, 131.19, 125.48, 124.95, 109.45, 108.44, 103.41, 102.60, 77.81, 59.14, 56.79, 55.23, 53.13, 51.92, 48.86, 48.35, 44.50, 41.50, 40.54, 39.47, 39.26, 38.25, 35.55, 34.36, 32.93, 32.75, 31.46, 31.25, 30.55, 29.71, 29.43, 29.38, 28.16, 27.62, 27.15, 27.07, 25.70, 25.12, 20.38, 18.18, 18.14, 0.59. HRMS (ESI) *m/z* 967.2917 [calc'd for $C_{44}H_{68}O_8S_6SiNa$ (M+Na) 967.2908].

Bis-Xanthate 318. FTIR (thin film/NaCl) 2925 (s), 2854 (m), 2231 (w), 1733 (s), 1435 (m), 1376 (w), 1301 (m), 1202 (s), 1098 (s), 1056 (s), 1020 (s), 966 (m), 909 (s), 865 (m), 733 (s), 648 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.54 (s, 1H), 5.41-5.37 (m, 4H), 5.27 (d, *J*=2.16 Hz, 1H), 4.54 (dd, *J*=12.0, 4.7 Hz, 1H), 3.95 (t, *J*=6.2 Hz, 1H), 3.78 (s, 3H), 3.73 (s, 3H), 3.76-3.68 (m, 1H), 3.57-3.44 (m, 2H), 3.26 (s, 1H), 3.00-2.20 (m, 24H), 2.10-1.65 (m, 11H), 1.62-1.05 (m, 30H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.10, 175.53, 171.76, 131.53, 130.72, 125.78, 125.04, 110.61, 105.50, 101.57, 84.50, 77.48, 76.64, 76.45, 58.14, 54.07, 53.38, 52.31, 48.41, 47.64, 44.33, 44.23, 40.84, 40.67, 39.92,

39.06, 38.94, 35.47, 34.42, 32.89, 32.75, 31.65, 31.49, 30.54, 29.67, 29.34, 29.20, 28.23, 27.57, 27.31, 25.47, 25.35, 20.65, 19.01, 18.13. HRMS (ESI) *m/z* 985.2087 [calc'd for $C_{43}H_{62}O_8S_8Na$ (M+Na) 985.2018].

Preparation of Xanthate 319 (TSIII-166):



Xanthate 319. To a solution of bis-xanthate **318** (8.6 mg, 8.93 μmol, 1.0 equiv) in acetone (500 μL) was added *p*-TsOH (34.0 mg, 178.6 μmol, 20 equiv). The reaction was stirred at rt for 10h, at which time it was treated with a saturated aqueous solution of $NaHCO_3$ (1 mL). The mixture was extracted with EtOAc (3x 3 mL). The combined organic layer was washed with brine (5 mL) dried over Na_2SO_4 and concentrated *in vacuo*. Purification by silica gel chromatography (2%-3% EtOAc/Benzene eluent) furnished lactol **319** (6.5mg, 84.1% yield) as a clear oil.

Xanthate 319. FTIR (thin film/NaCl) 3455 (br), 2924 (s), 2853 (m), 1734 (s), 1653 (w), 1436 (m), 1208 (s), 1103 (m), 1059 (s), 1009 (m), 965 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.47-5.33 (m, 4H), 5.16 (s, 1H), 5.12 (d, *J*=2.2 Hz, 1H), 4.45 (dd, *J*=11.8, 4.2 Hz, 1H), 4.19 (t, *J*=7.0 Hz, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 3.46-3.32 (m, 2H), 3.23 (s, 1H), 2.94-2.77 (m, 4H), 2.73-2.50 (m, 8H), 2.41-2.24 (m, 4H), 2.13-2.05 (m, 2H), 1.95-

1.79 (m, 8H), 1.77-1.45 (m, 12H), 1.32-1.15 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.80, 175.84, 171.91, 131.57, 130.84, 125.75, 125.02, 109.29, 102.63, 102.56, 82.31, 58.49, 55.30, 53.27, 52.14, 48.47, 47.89, 44.63, 44.16, 40.64, 39.77, 38.95, 38.75, 35.46, 34.52, 32.74, 32.71, 31.11, 31.01, 29.92, 29.69, 29.37, 28.04, 27.87, 27.69, 27.59, 25.68, 25.32, 20.58, 18.16, 18.14. HRMS (ESI) *m/z* 895.2552 [calc'd for $C_{41}H_{60}O_8S_6Na$ (M+Na) 895.2510].

5.6 References.

1. Greene, T. W.; Wuts, P. G. M., *Protectzive groups in organic synthesis*. 3rd ed.; Wiley: New York, 1999; 'Vol.' p xxi, 779 p.

2. Stork, G.; Zhao, K., A Simple Method of Dethioacetalization. *Tetrahedron Letters* **1989,** 30, (3), 287-290.

3. Arnold, R. T.; Kulenovic, S. T., Carbanion Halogenations with Carbon Tetrahalides - Alpha-Halo Esters. *Journal of Organic Chemistry* **1978,** 43, (19), 3687-3689.

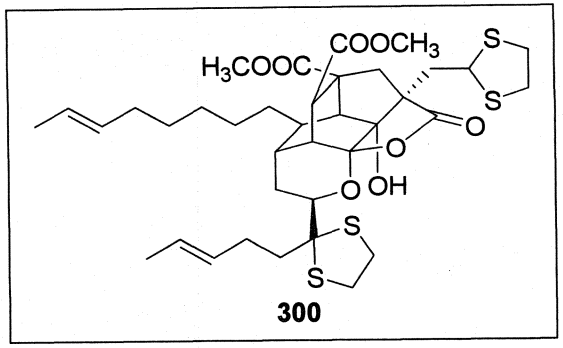
4. It is also possible that this reaction proceeds via elimination of the bromide and michael addition of the free lactol.

5. Meng, D. F.; Tan, Q.; Danishefsky, S. J., Discovery through total synthesis - Epimerization at C7 in the CP compounds: Is (7S)-CP-263,114 a fermentation product? *Angewandte Chemie-International Edition* **1999,** 38, (21), 3197-3201.

6. Note: Sm metal was either purchased from Strem Chemical as a "powder" or freshly filed from a samarium ingot. In either case, the appearance of the samarium should be that of shiny metallic filings. If the samarium has a "powdery" appearance, it is a sign that the metal has become oxidized.

Appendix 5

Spectra Relevant to Chapter 5



300

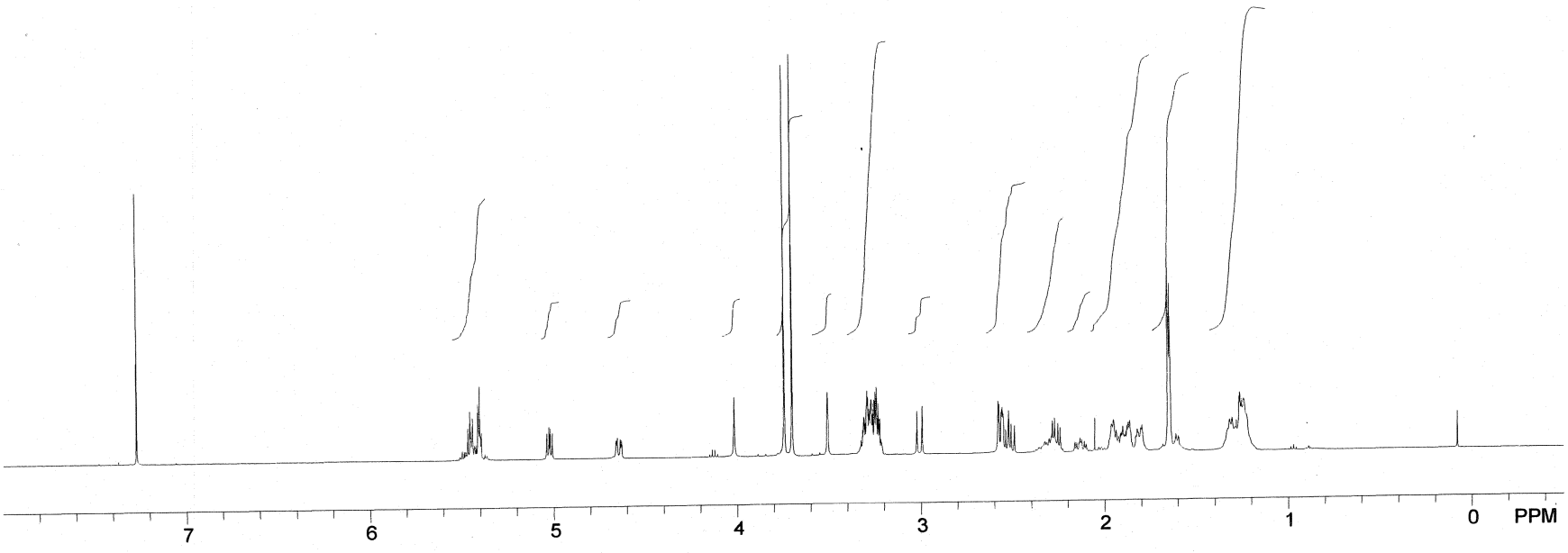


Figure A.5.1 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **300**.

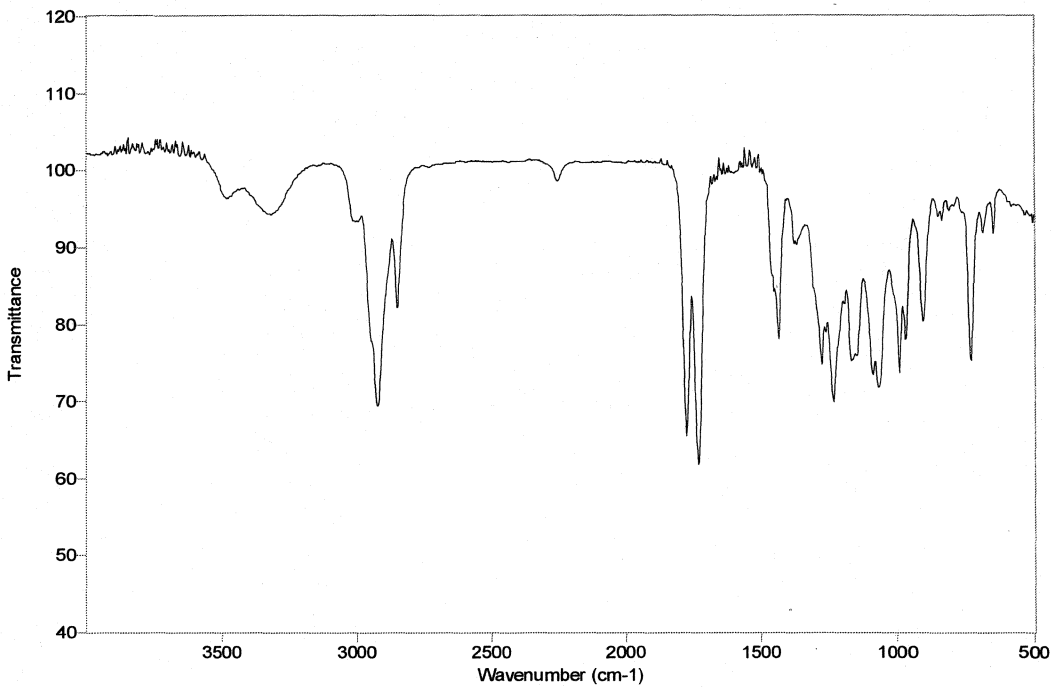


Figure A.5.2 FTIR Spectrum (thin film/NaCl) of Compound **300**.

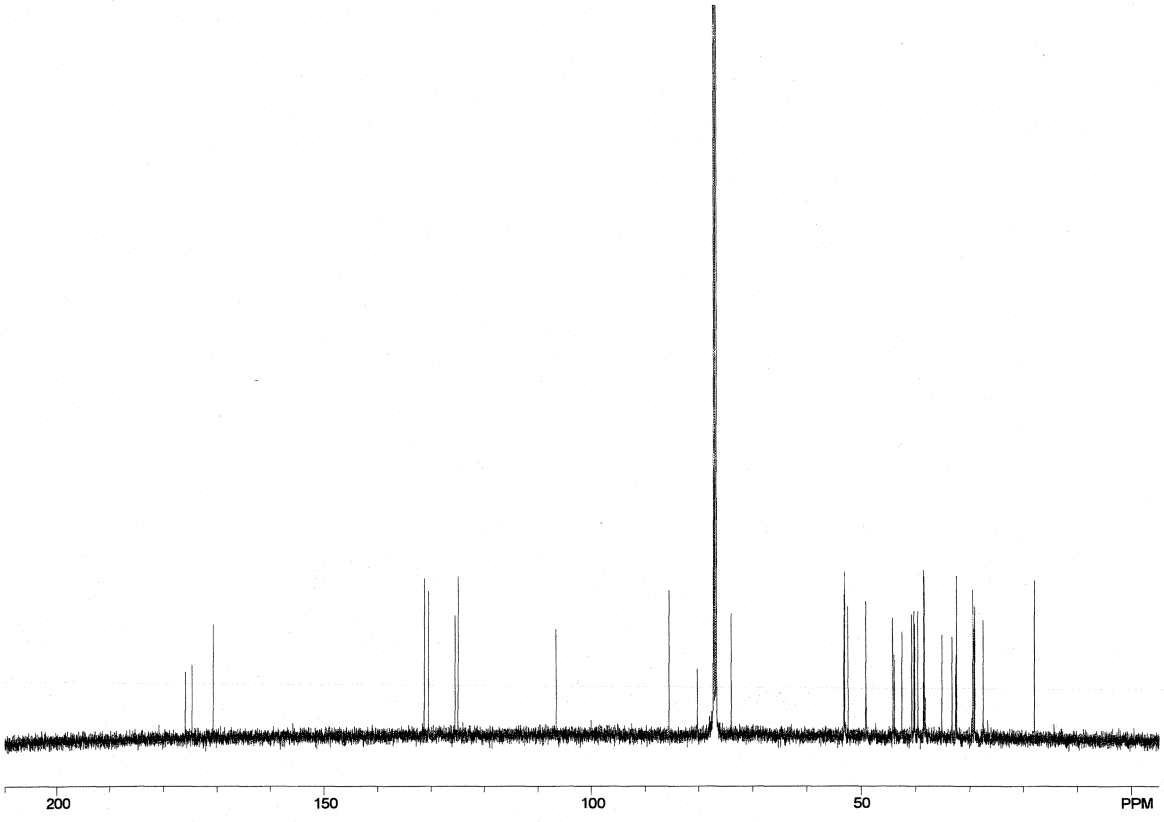
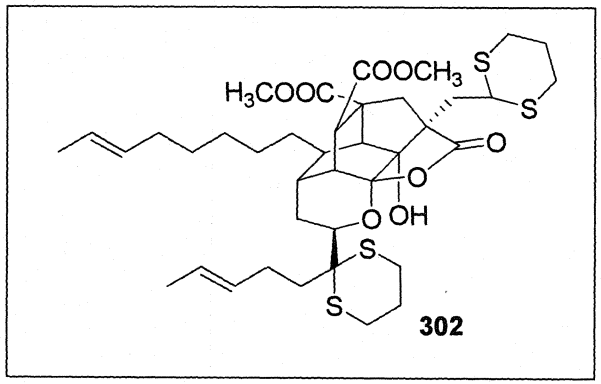


Figure A.5.3 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **300**.



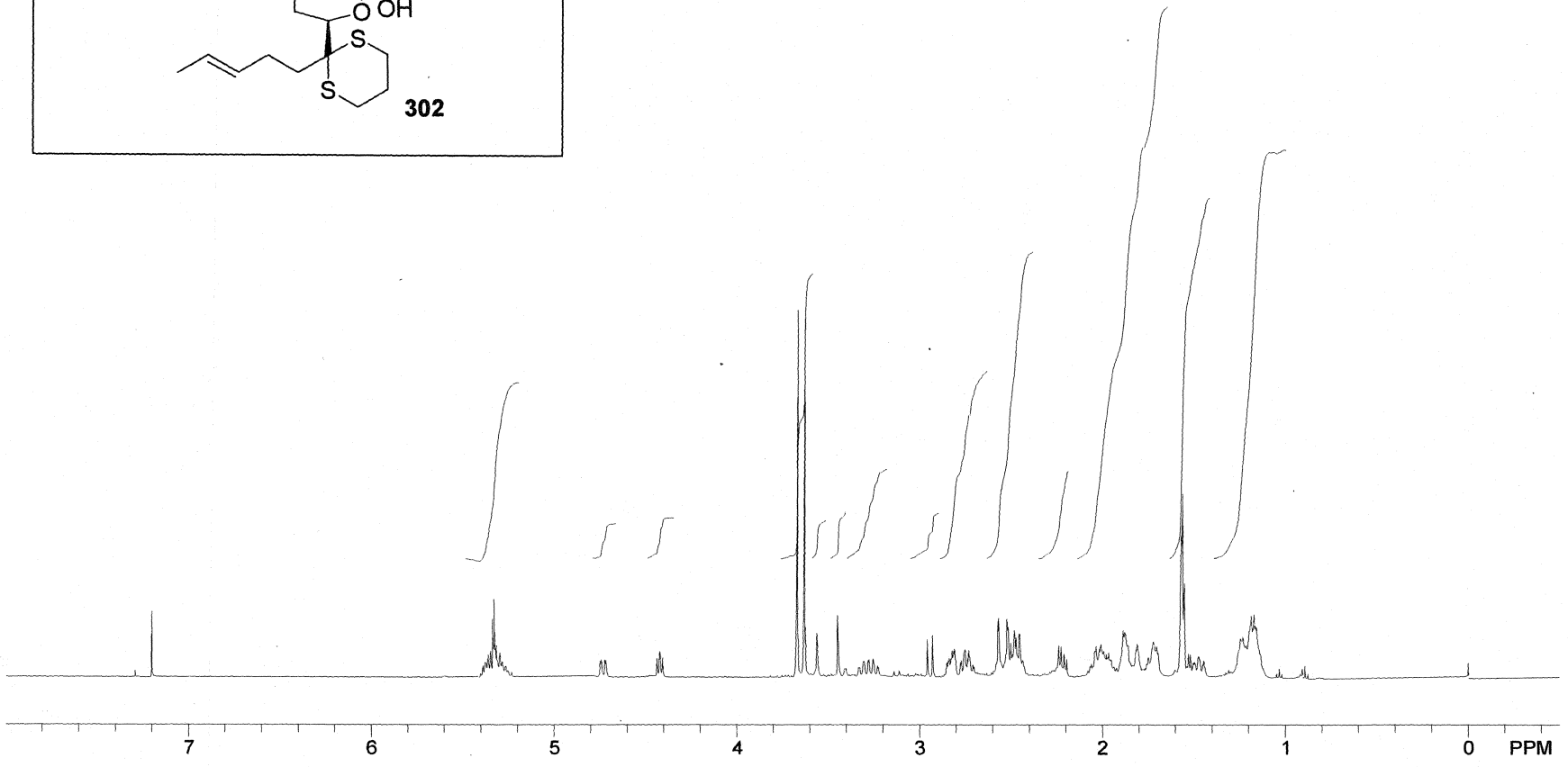


Figure A.5.4 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **302**.

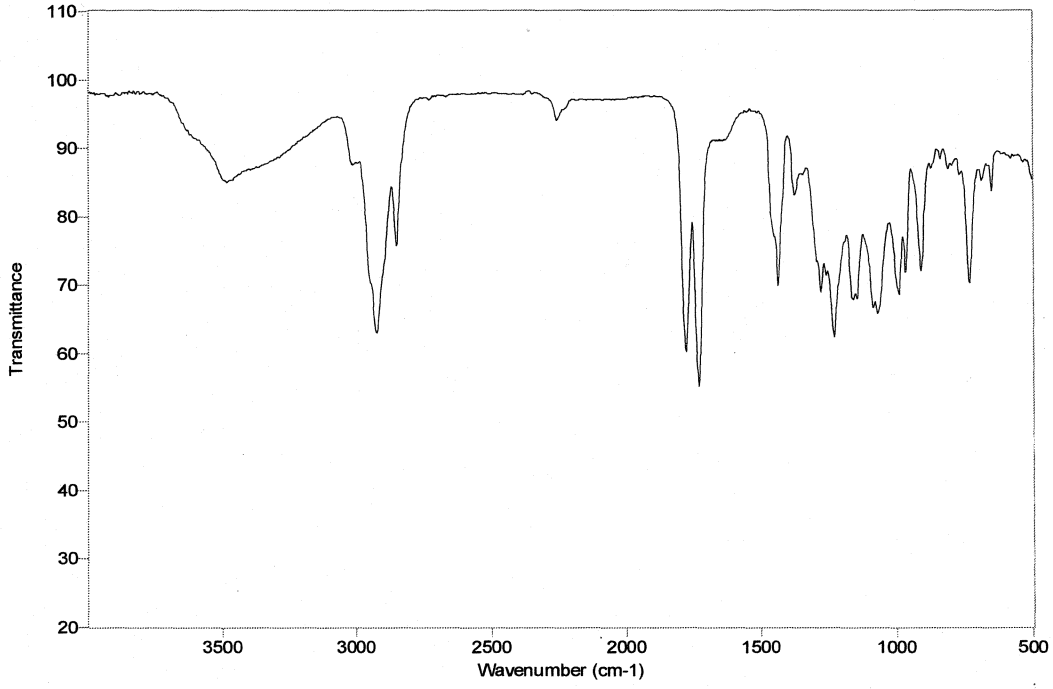


Figure A.5.5 FTIR Spectrum (thin film/NaCl) of Compound **302**.

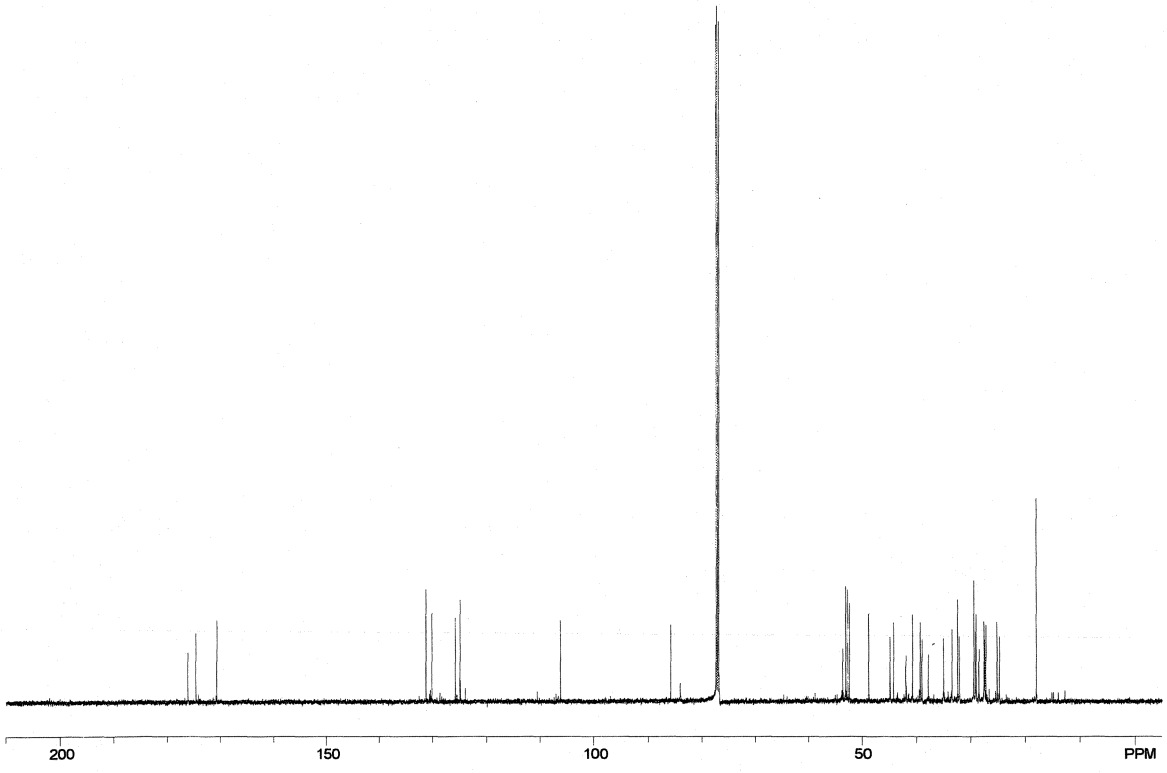


Figure A.5.6 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **302**.

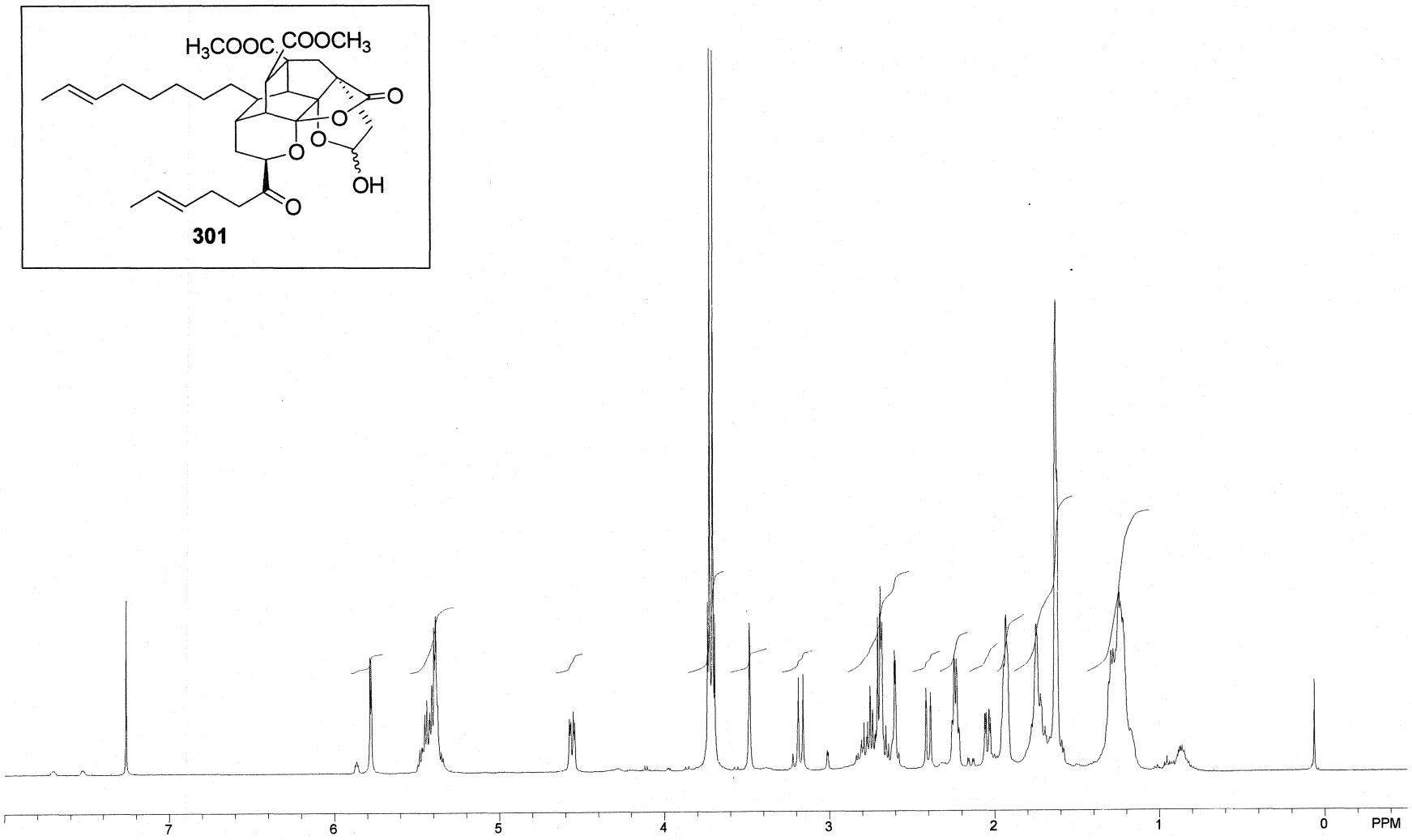


Figure A.5.7 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **301**.

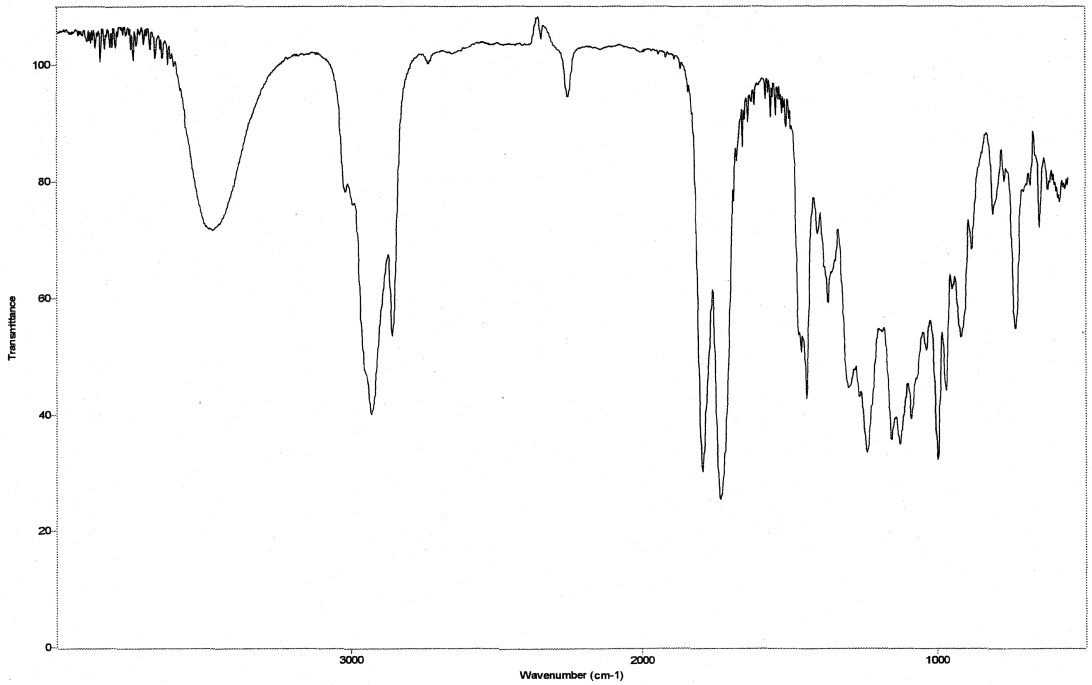


Figure A.5.8 FTIR Spectrum (thin film/NaCl) of Compound **301**.

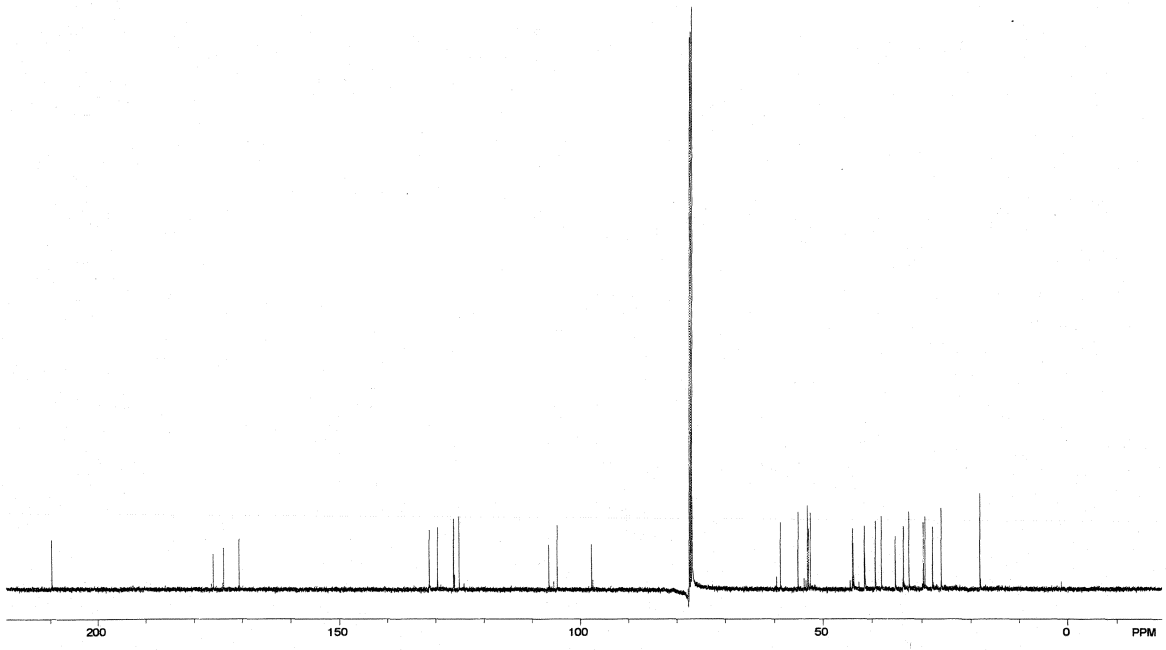


Figure A.5.9 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **301**.

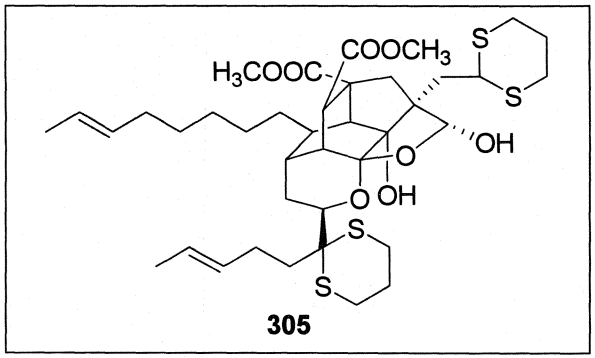


Figure A.5.10 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **305**.

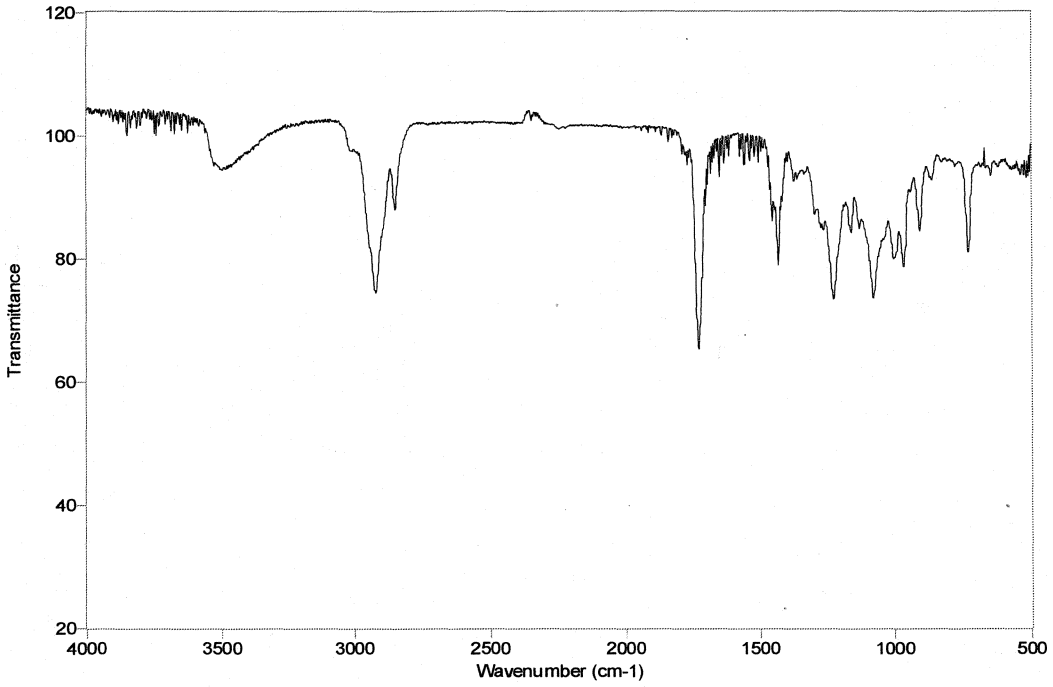


Figure A.5.11 FTIR Spectrum (thin film/NaCl) of Compound **305**.

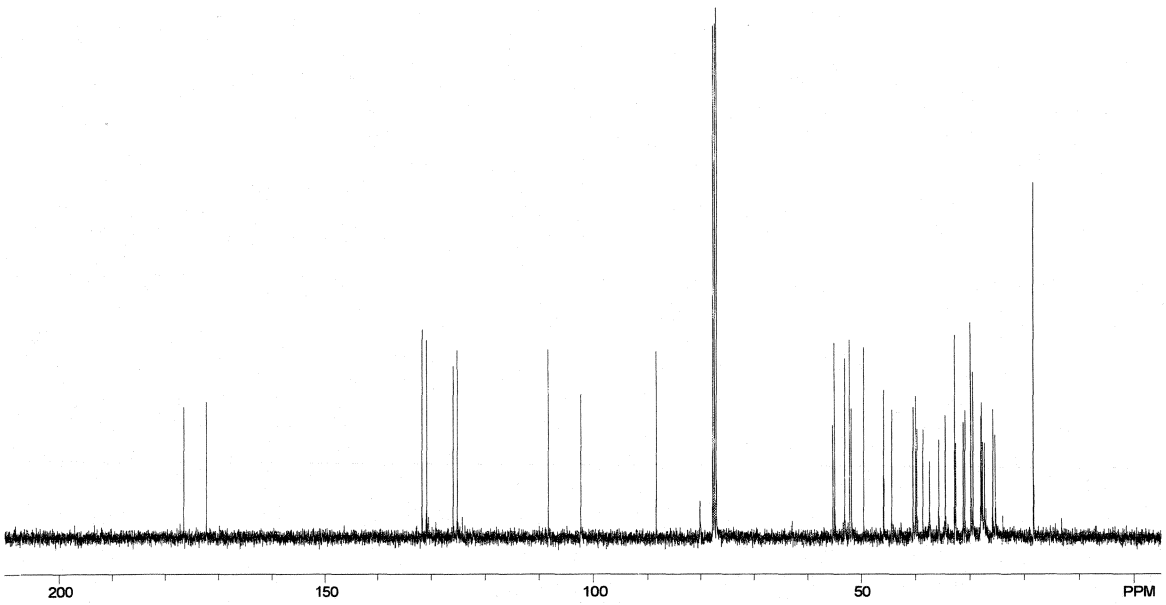


Figure A.5.12 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **305**.

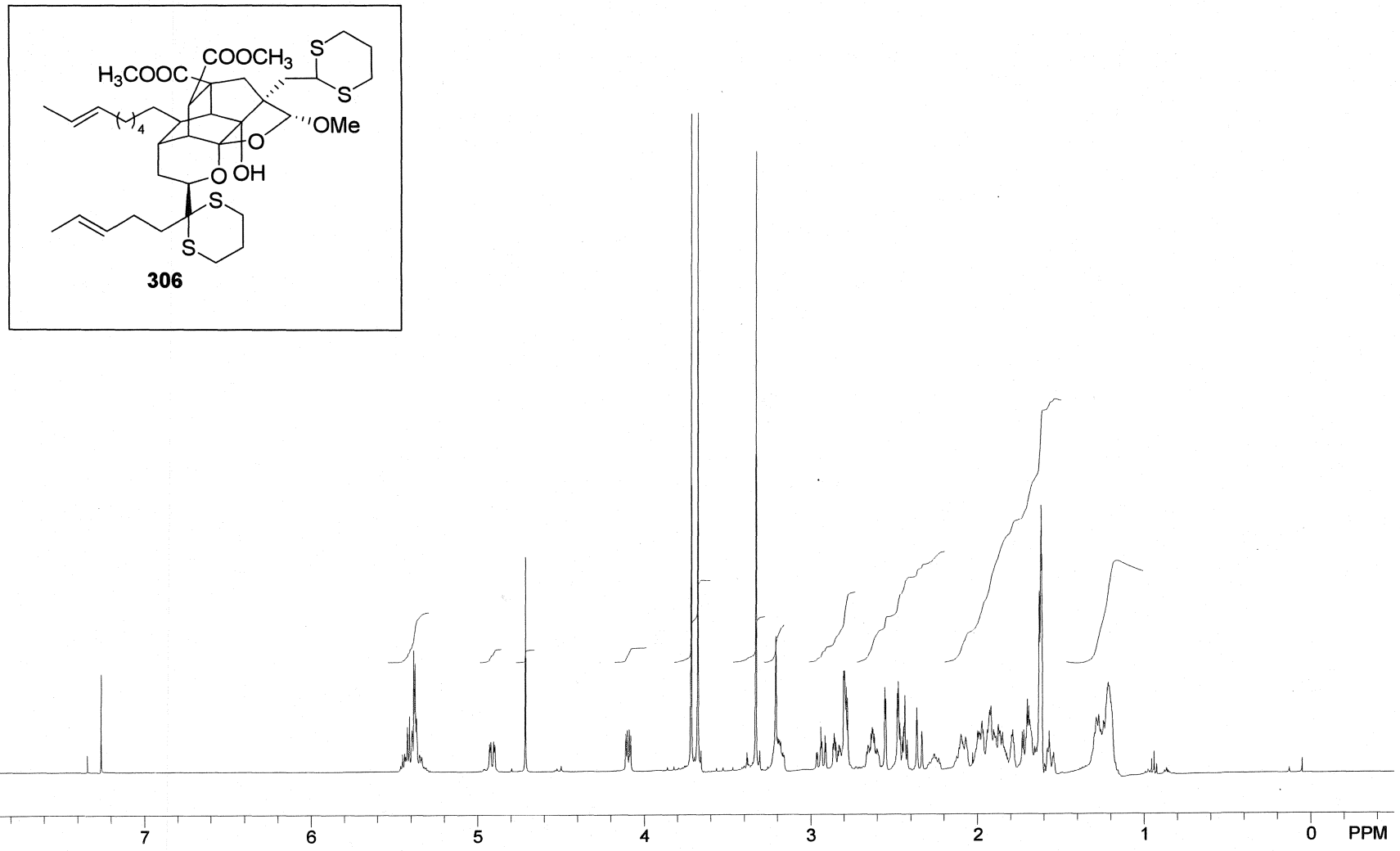


Figure A.5.13 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **306.**

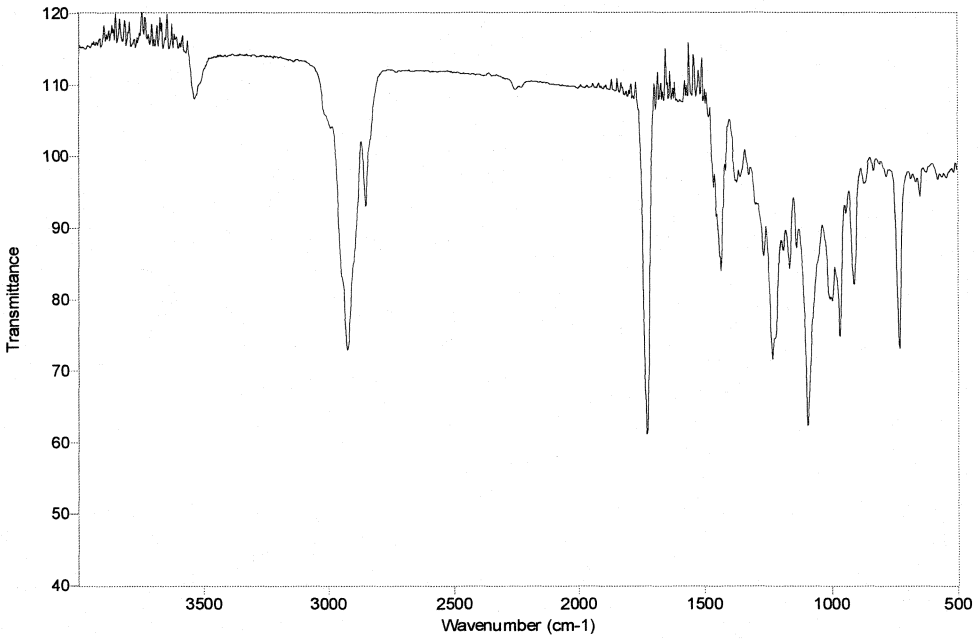


Figure A.5.14 FTIR Spectrum (thin film/NaCl) of Compound **306**.

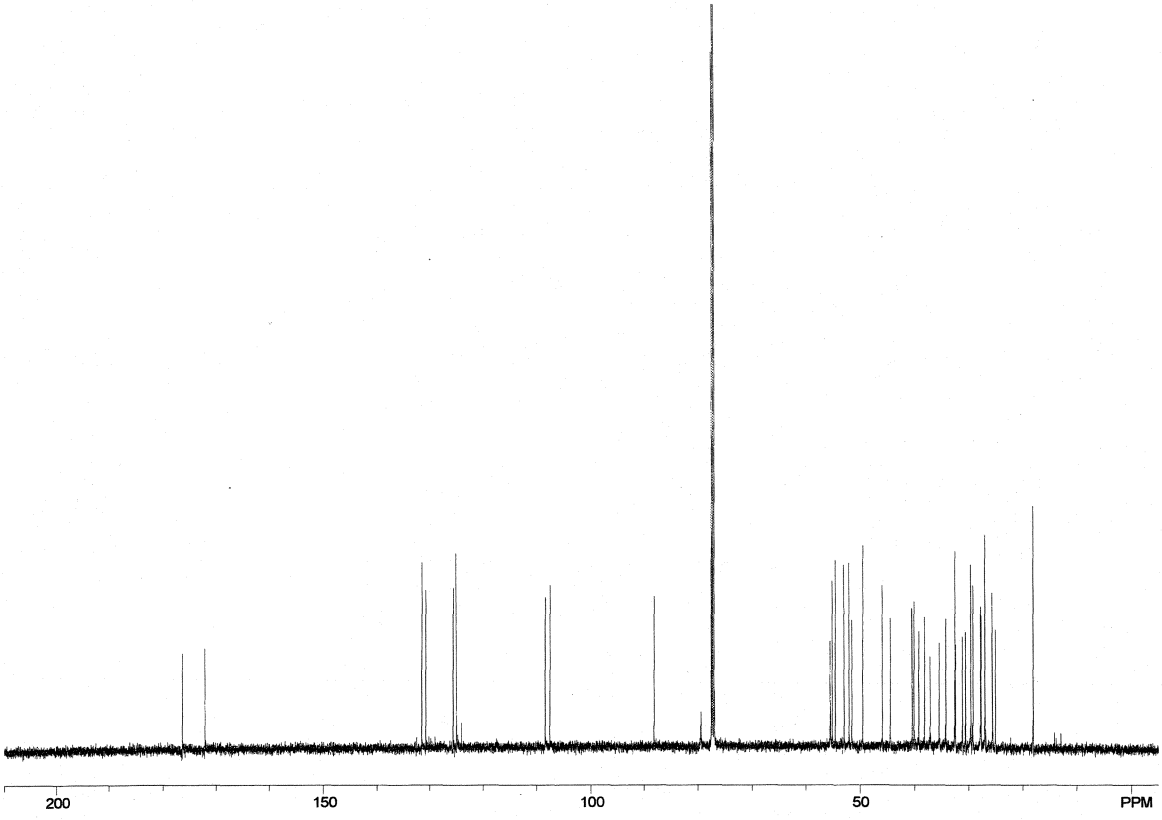


Figure A.5.15 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **306**.

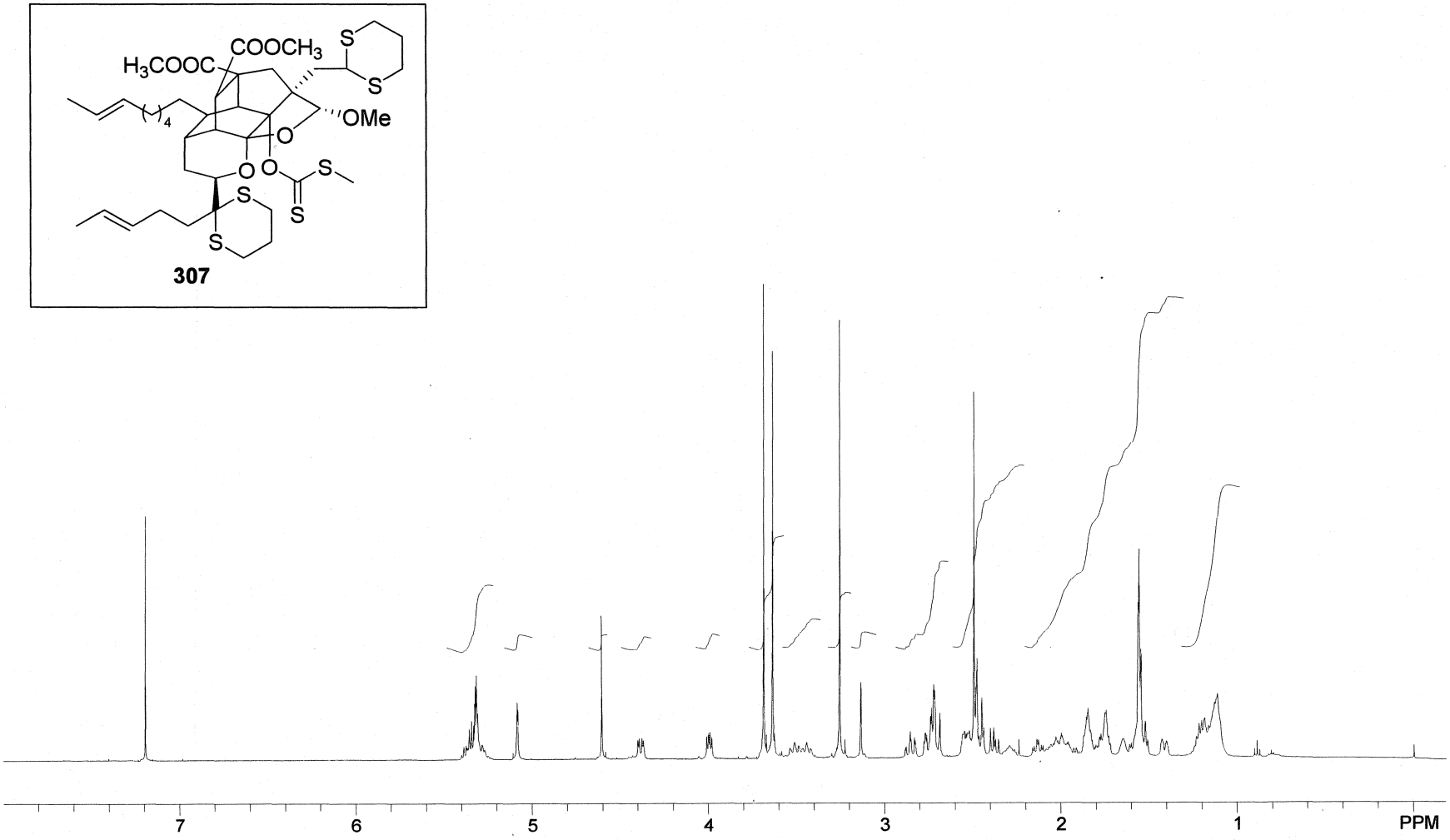


Figure A.5.16 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **307.**

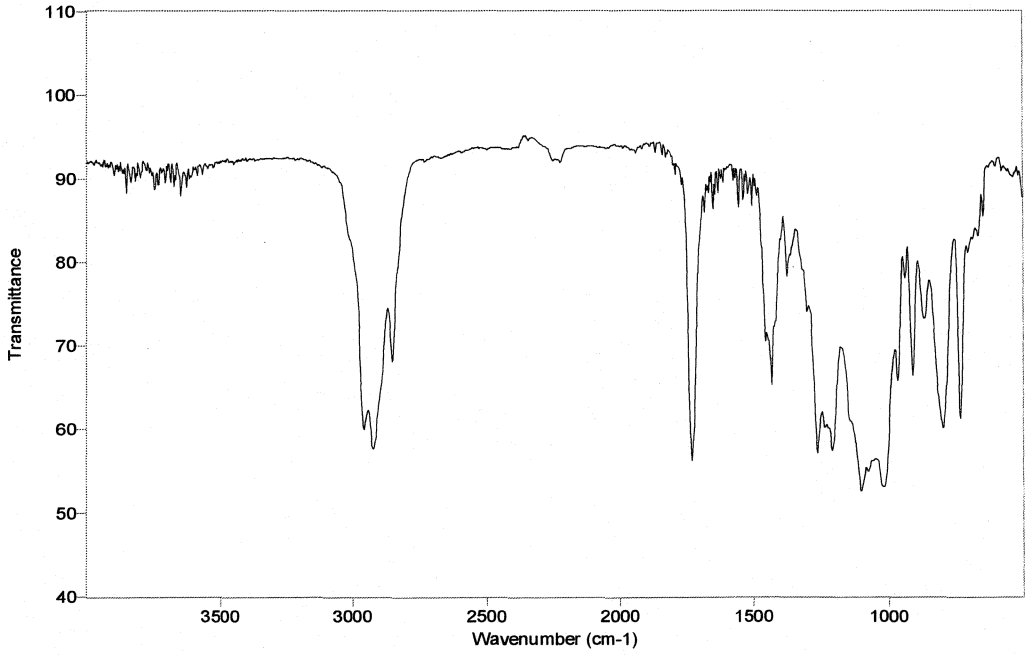


Figure A.5.17 FTIR Spectrum (thin film/NaCl) of Compound **307**.

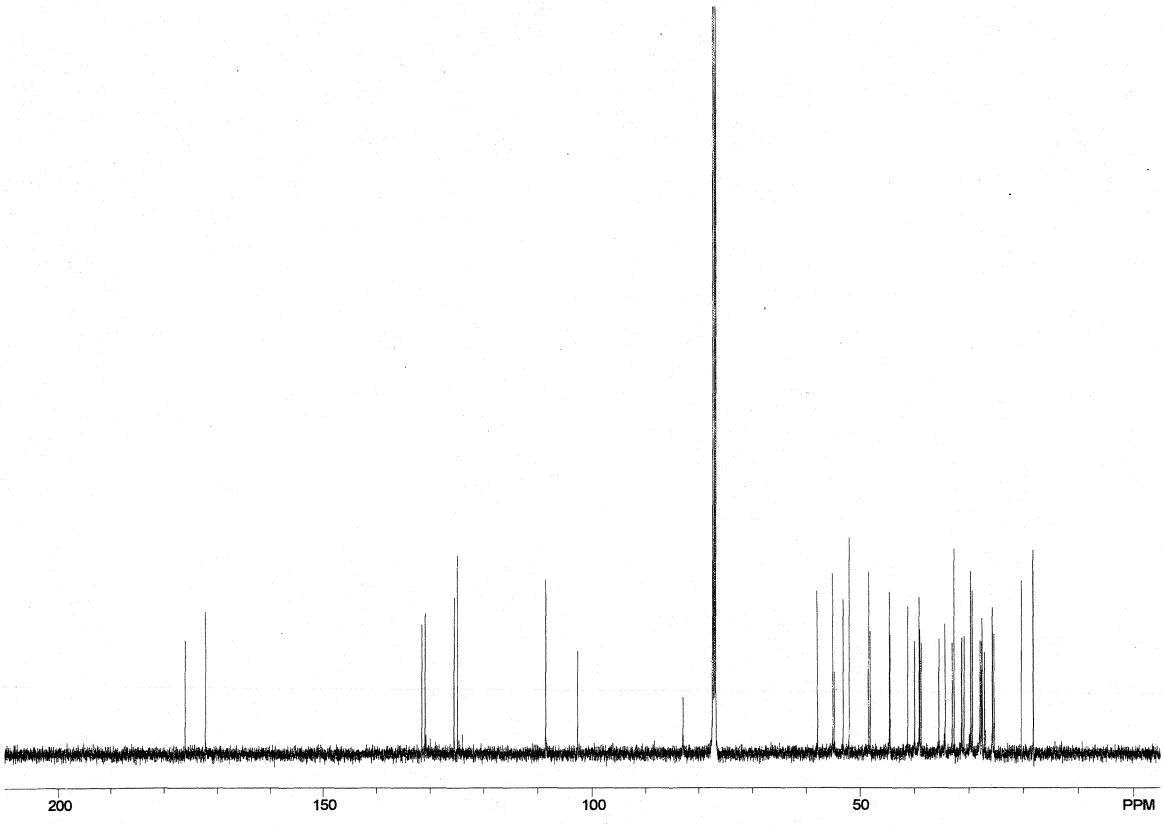


Figure A.5.18 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **307**.

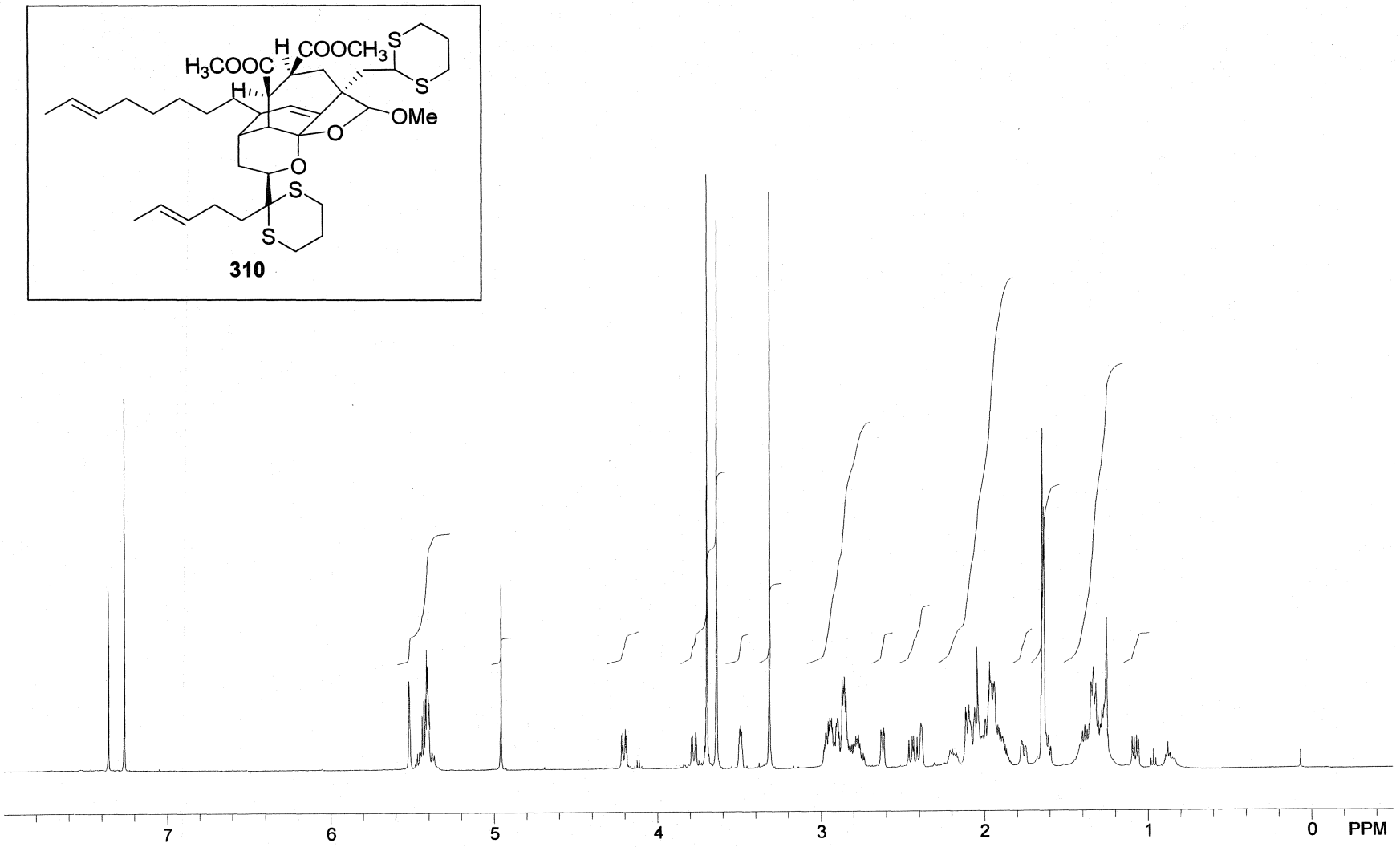


Figure A.5.19 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **310.**

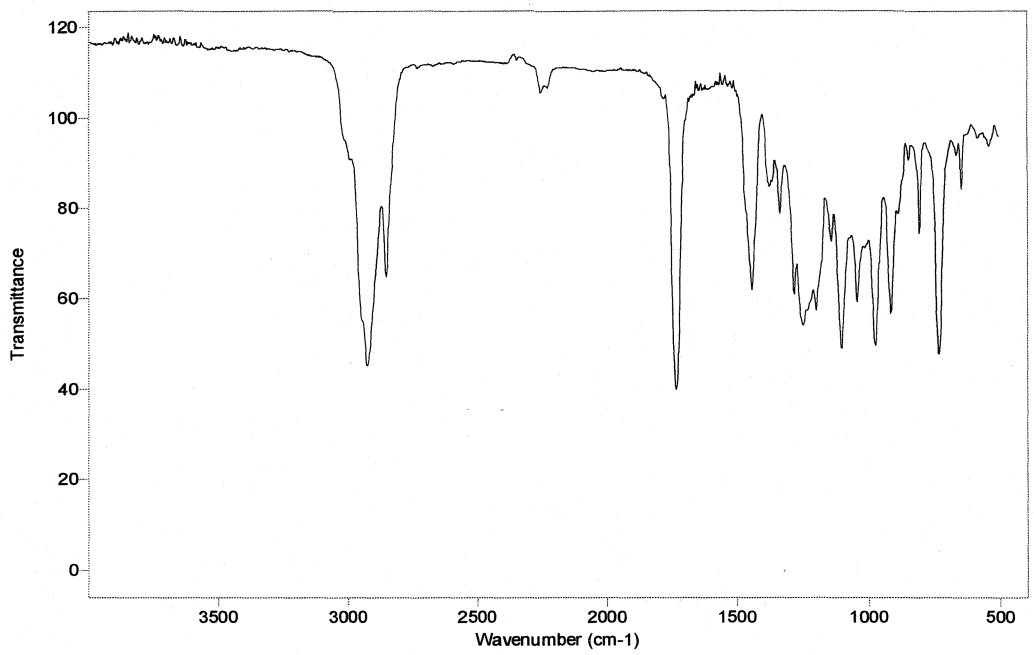


Figure A.5.20 FTIR Spectrum (thin film/NaCl) of Compound **310**.

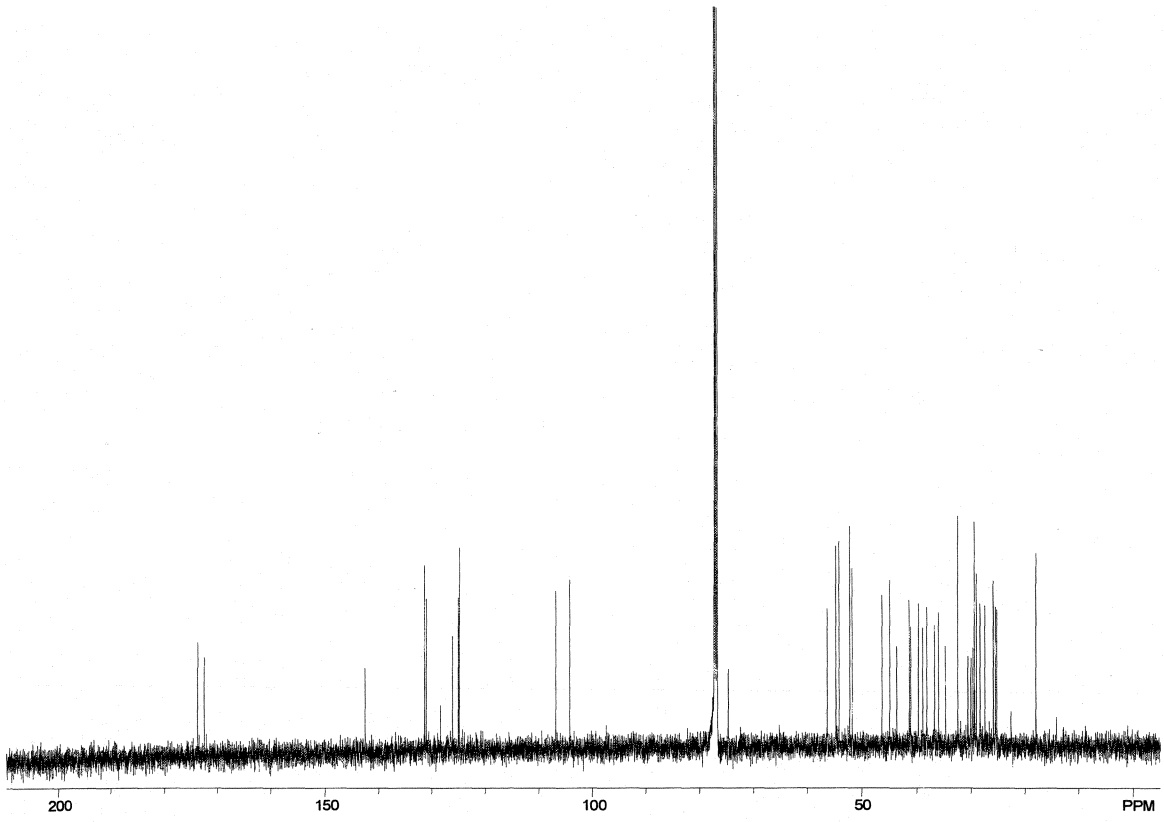


Figure A.5.21 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **310**.

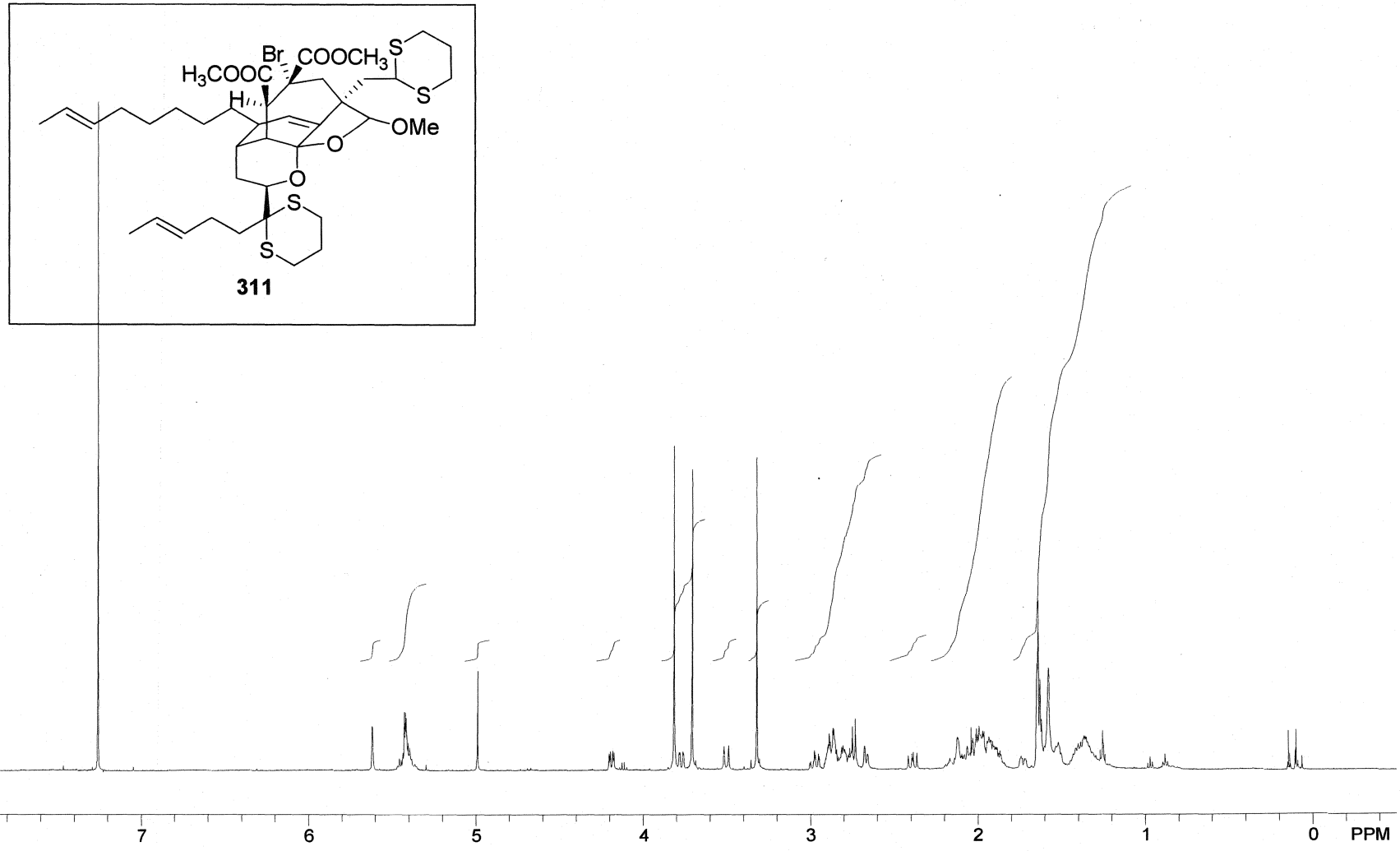


Figure A.5.22 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **311.**

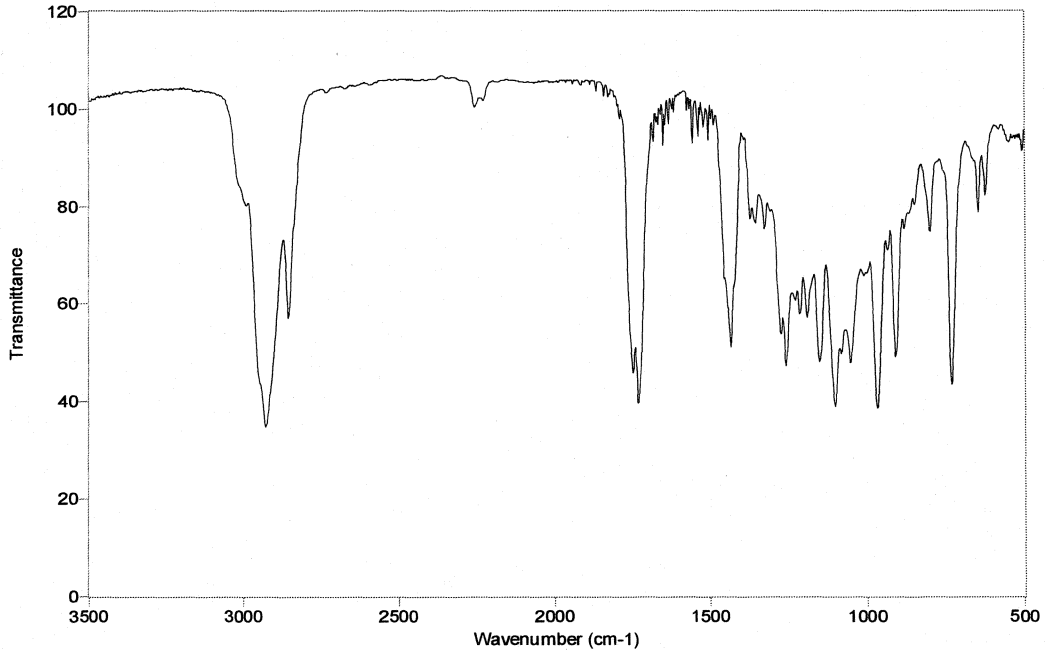


Figure A.5.23 FTIR Spectrum (thin film/NaCl) of Compound **311**.

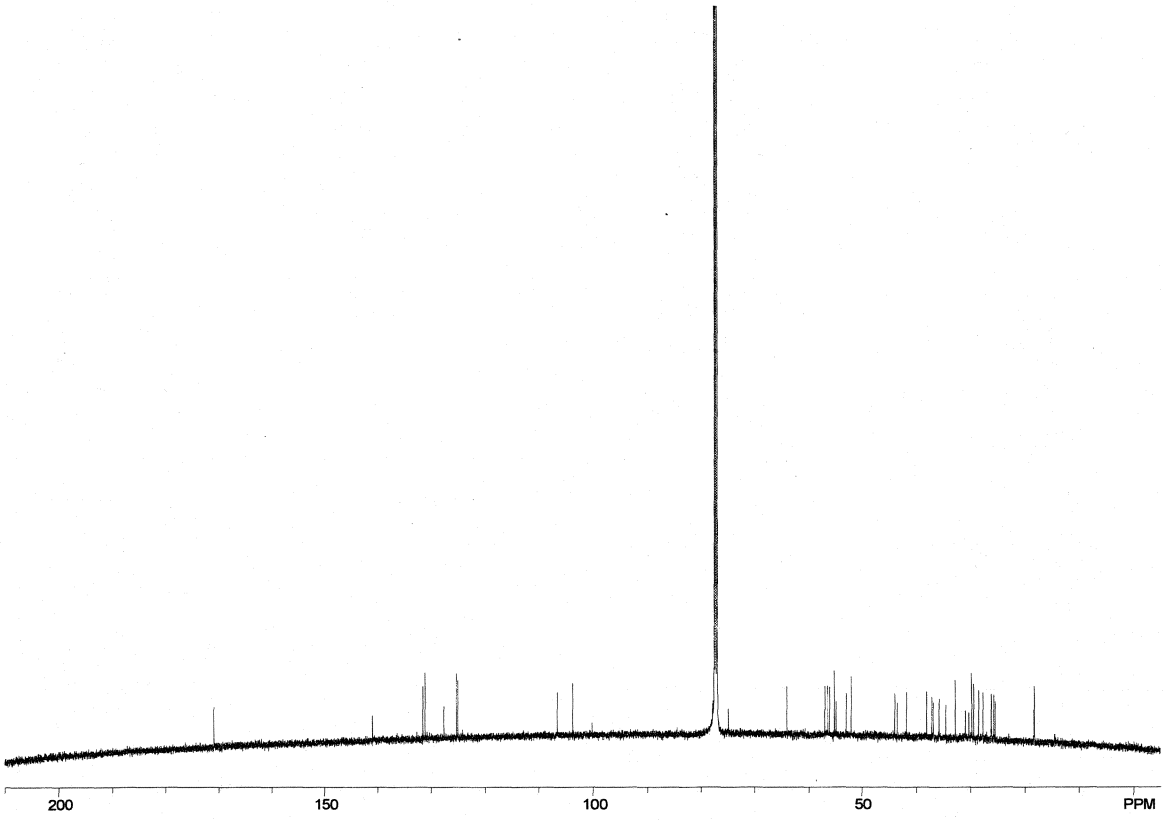


Figure A.5.24 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **311**.

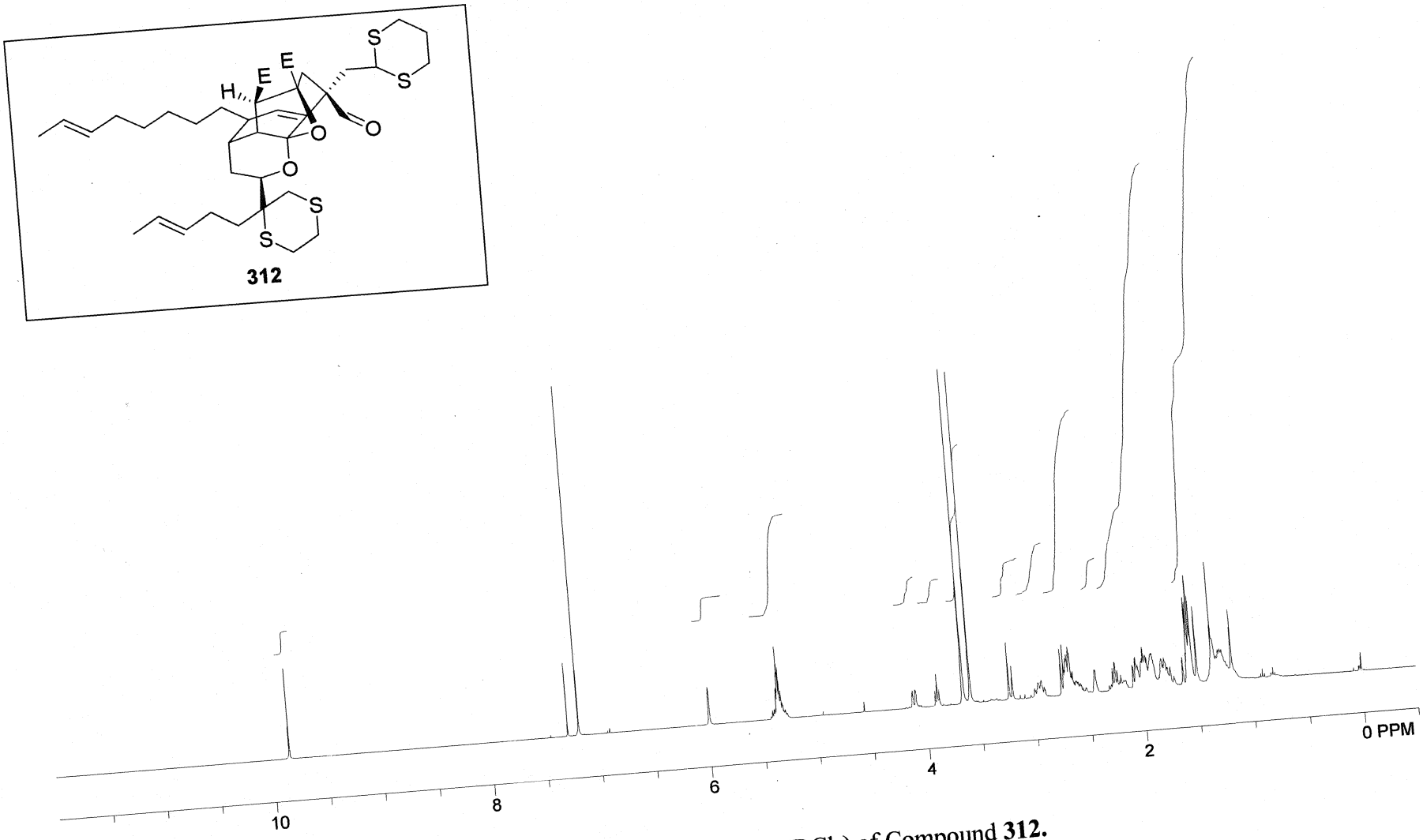


Figure A.5.25 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **312.**

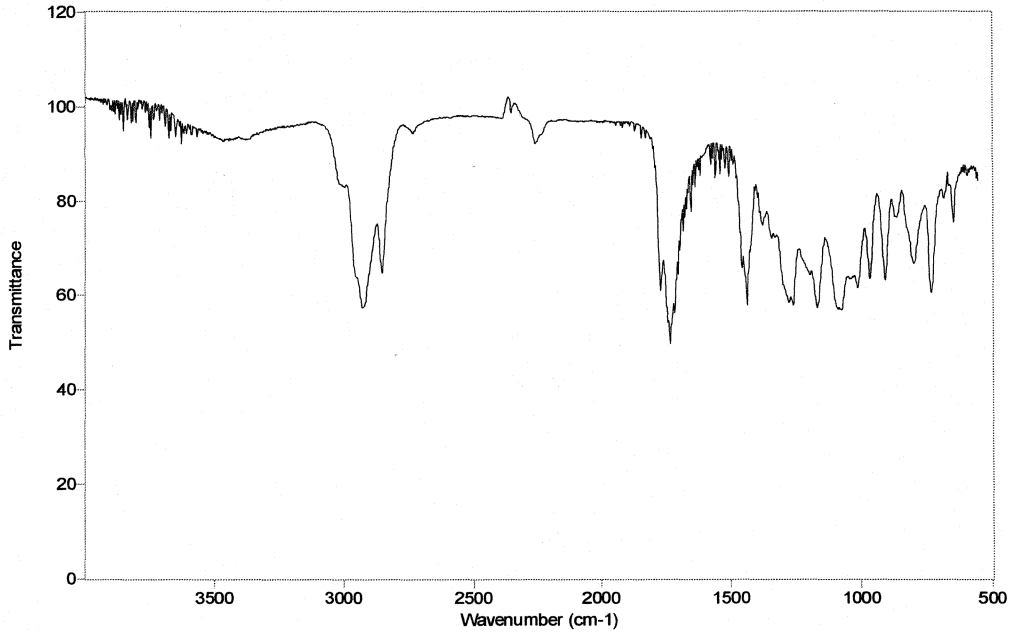


Figure A.5.26 FTIR Spectrum (thin film/NaCl) of Compound **312**.

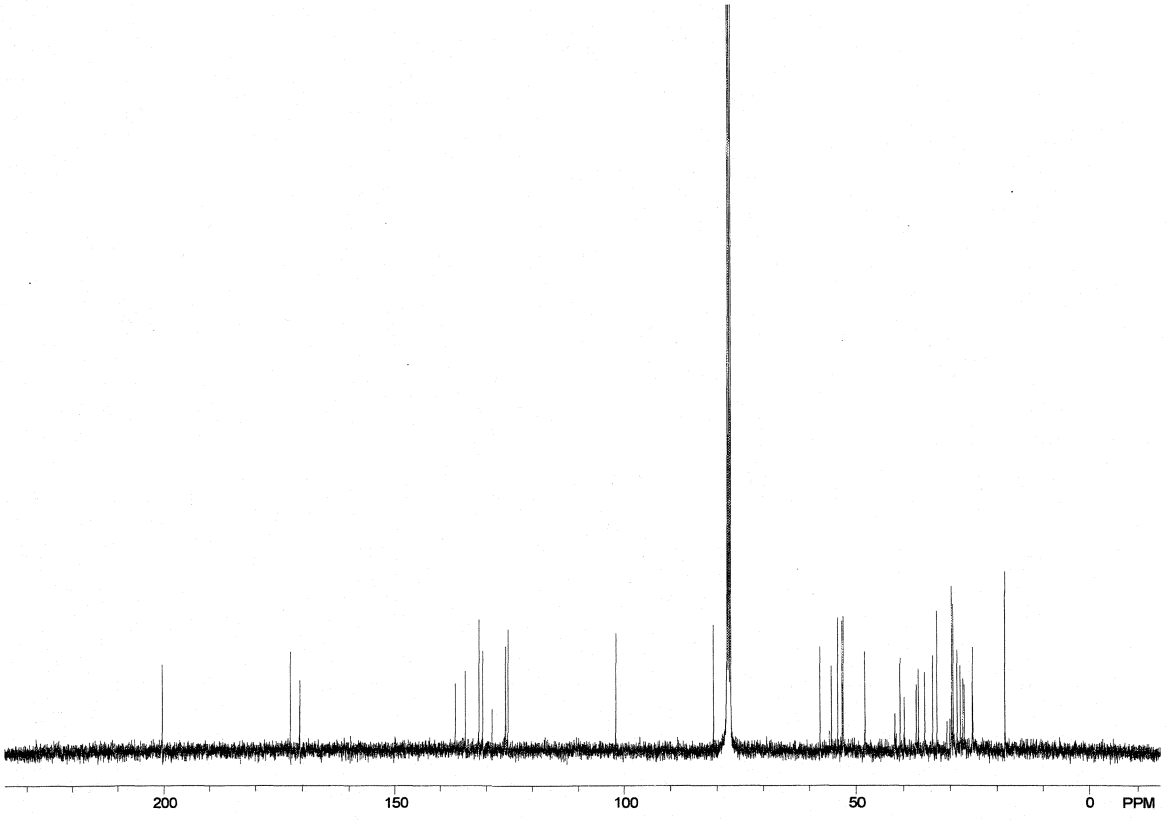


Figure A.5.27 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **312**.

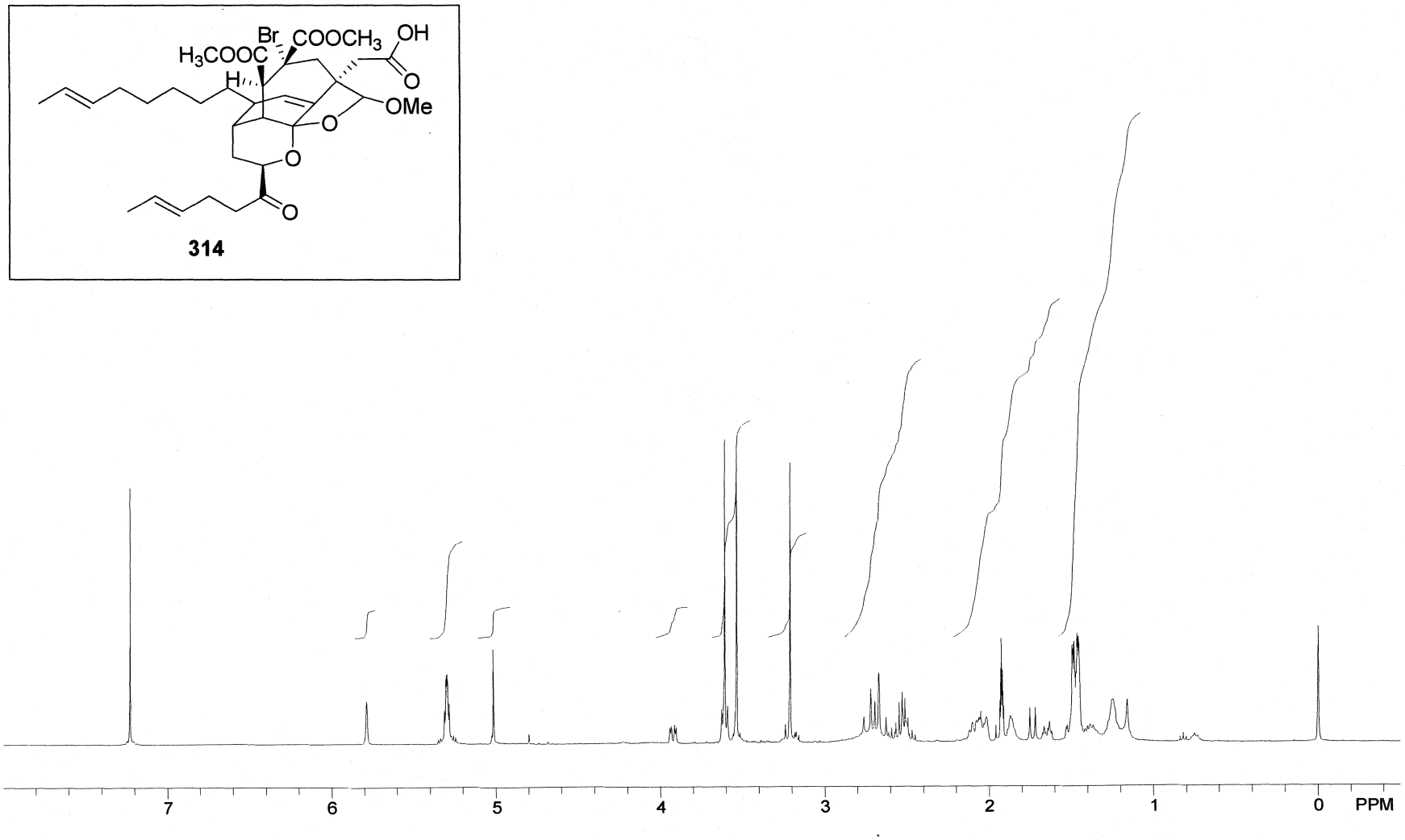


Figure A.5.28 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **314.**

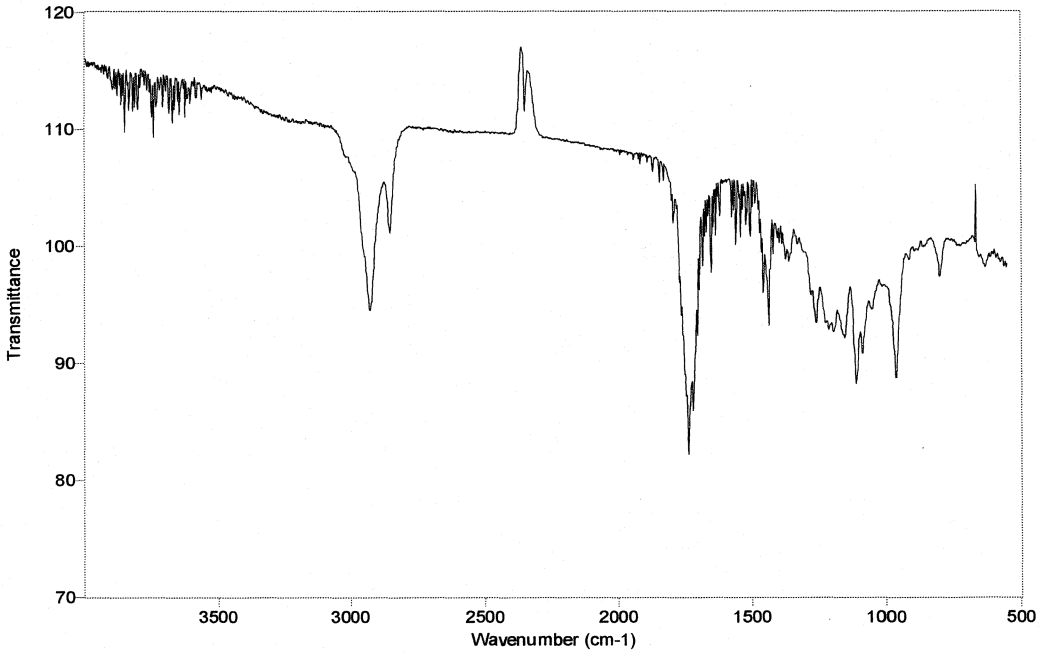


Figure A.5.29 FTIR Spectrum (thin film/NaCl) of Compound **314**.

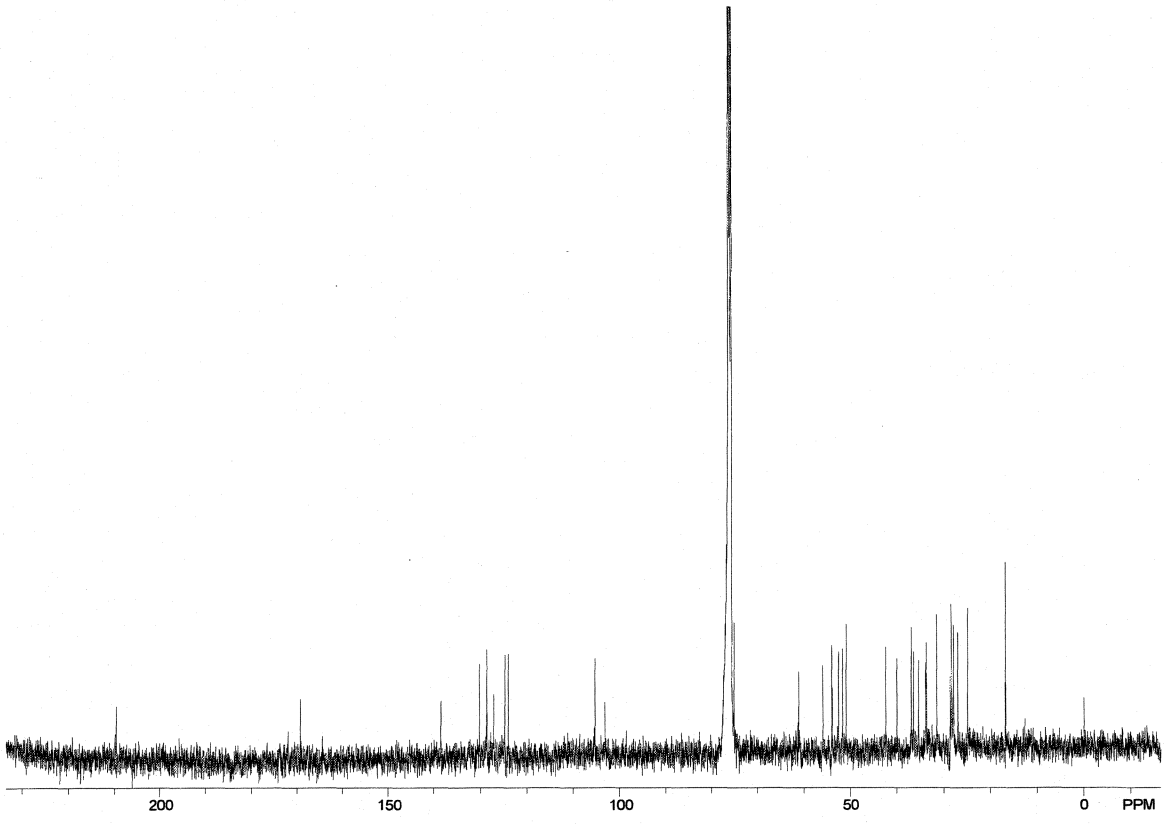


Figure A.5.30 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **314**.

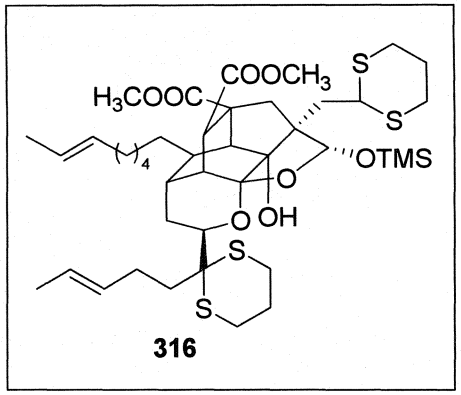


Figure A.5.31 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **316.**

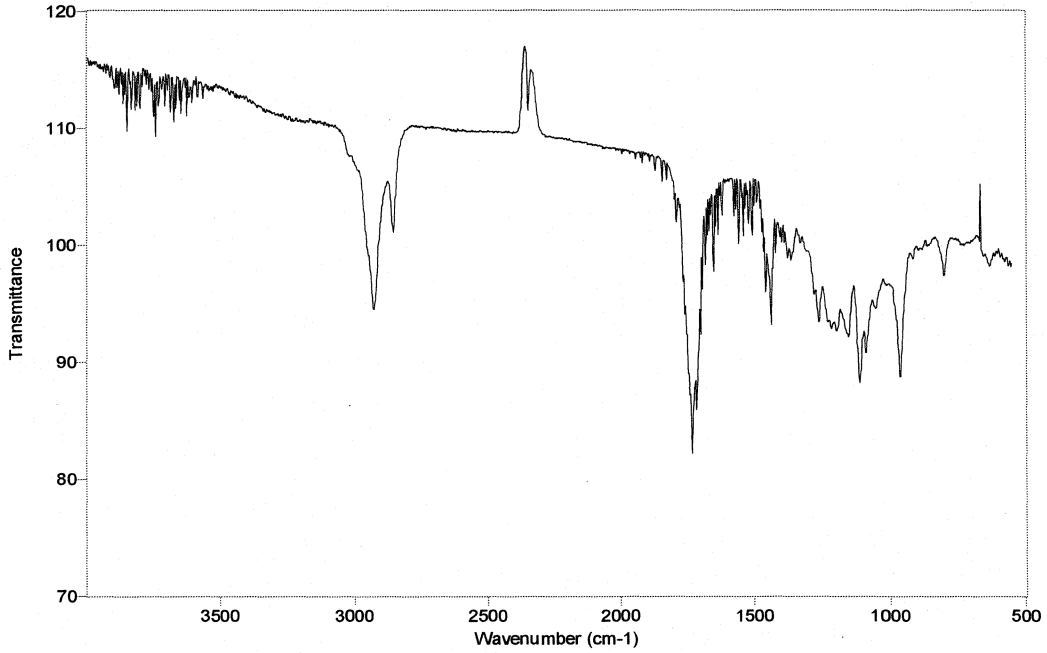


Figure A.5.32 FTIR Spectrum (thin film/NaCl) of Compound **316**.

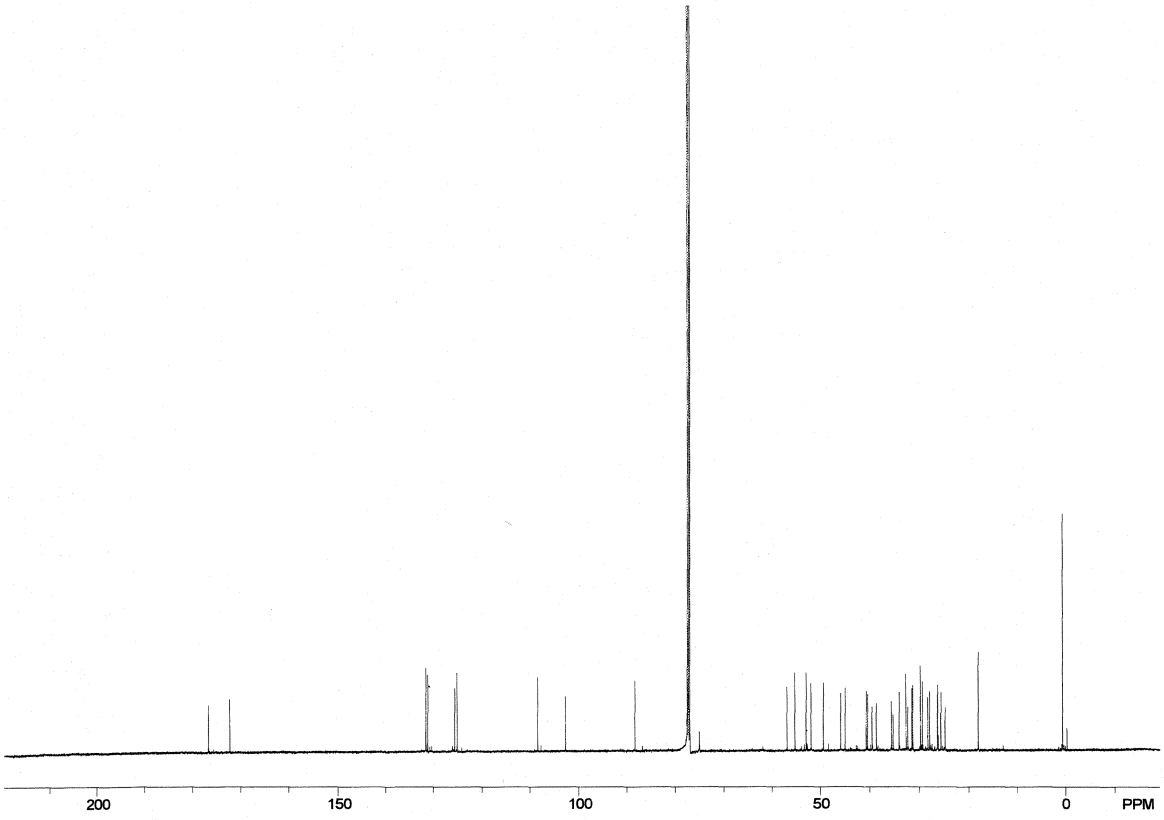


Figure A.5.33 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **316**.

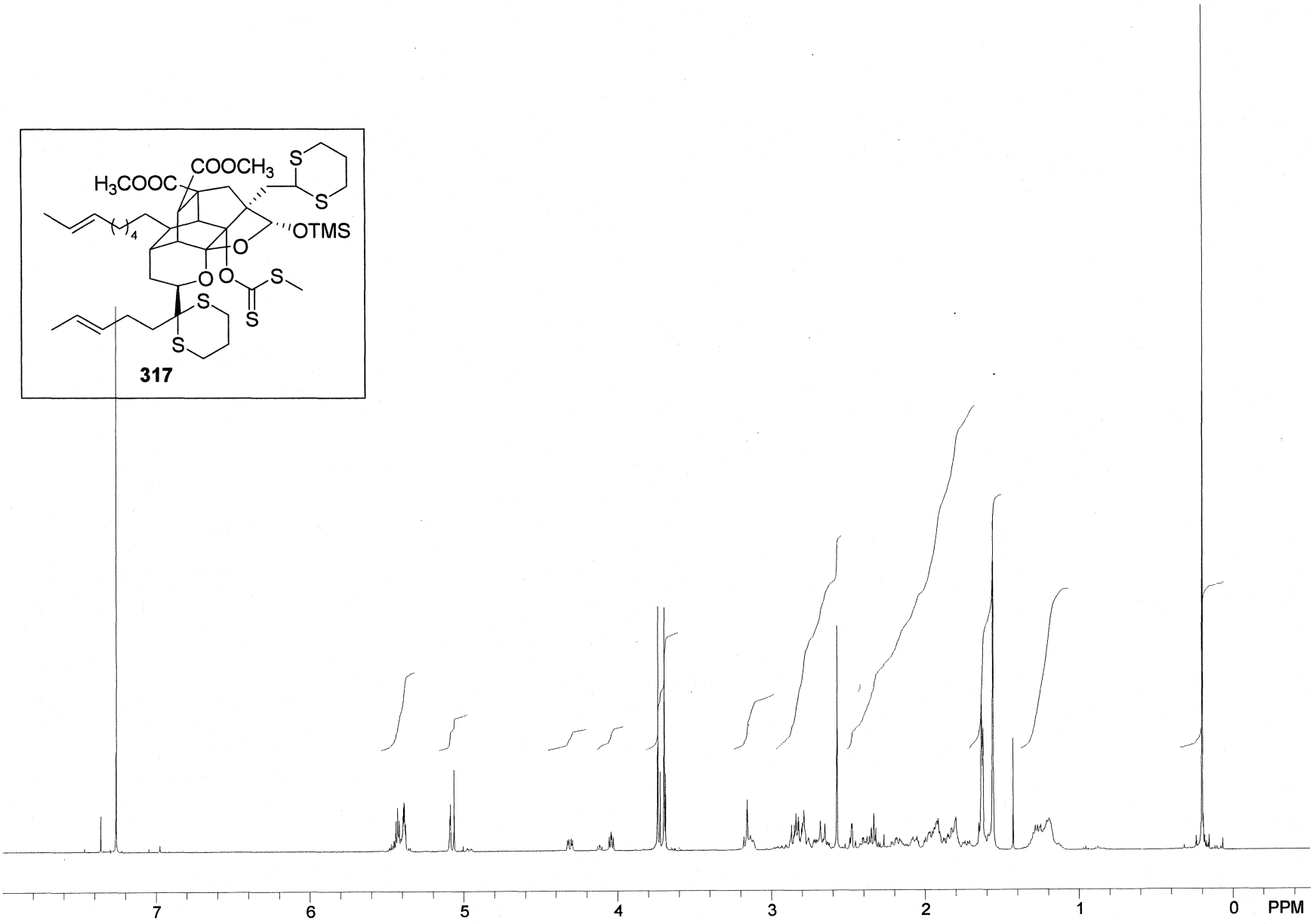


Figure A.5.34 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **317.**

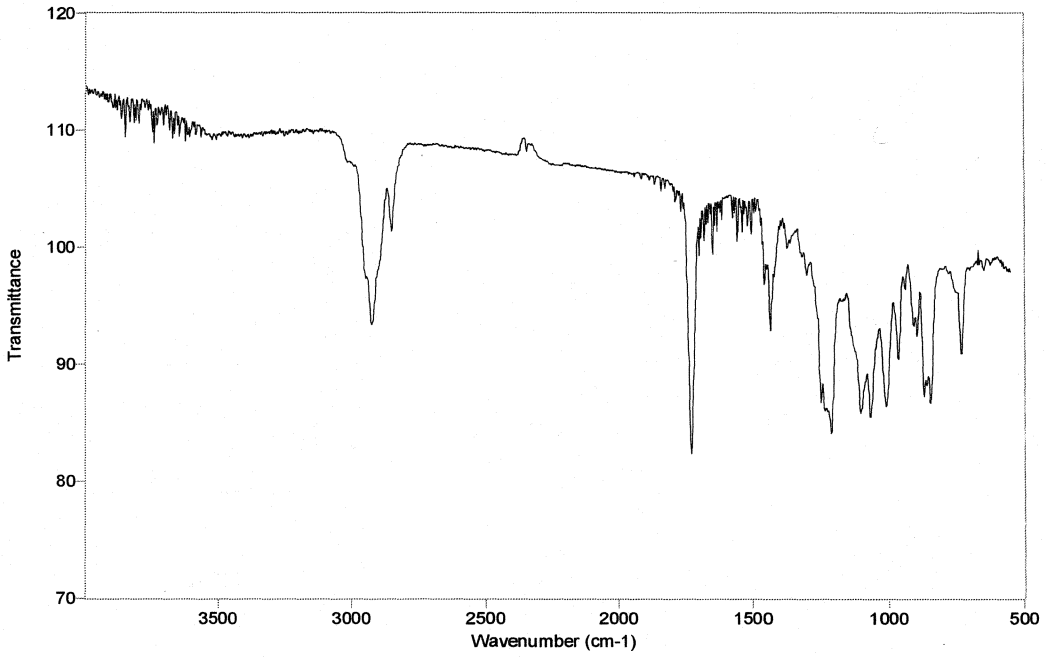


Figure A.5.35 FTIR Spectrum (thin film/NaCl) of Compound **317**.

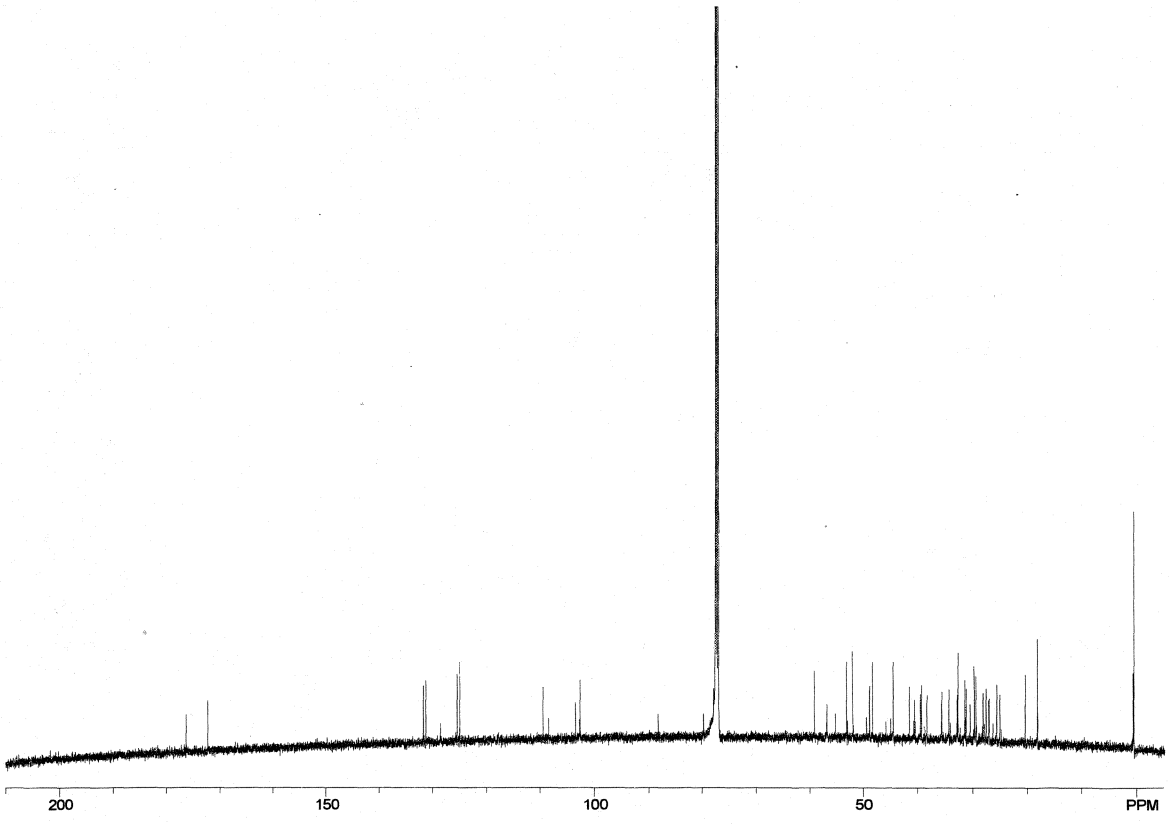


Figure A.5.36 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **317**.

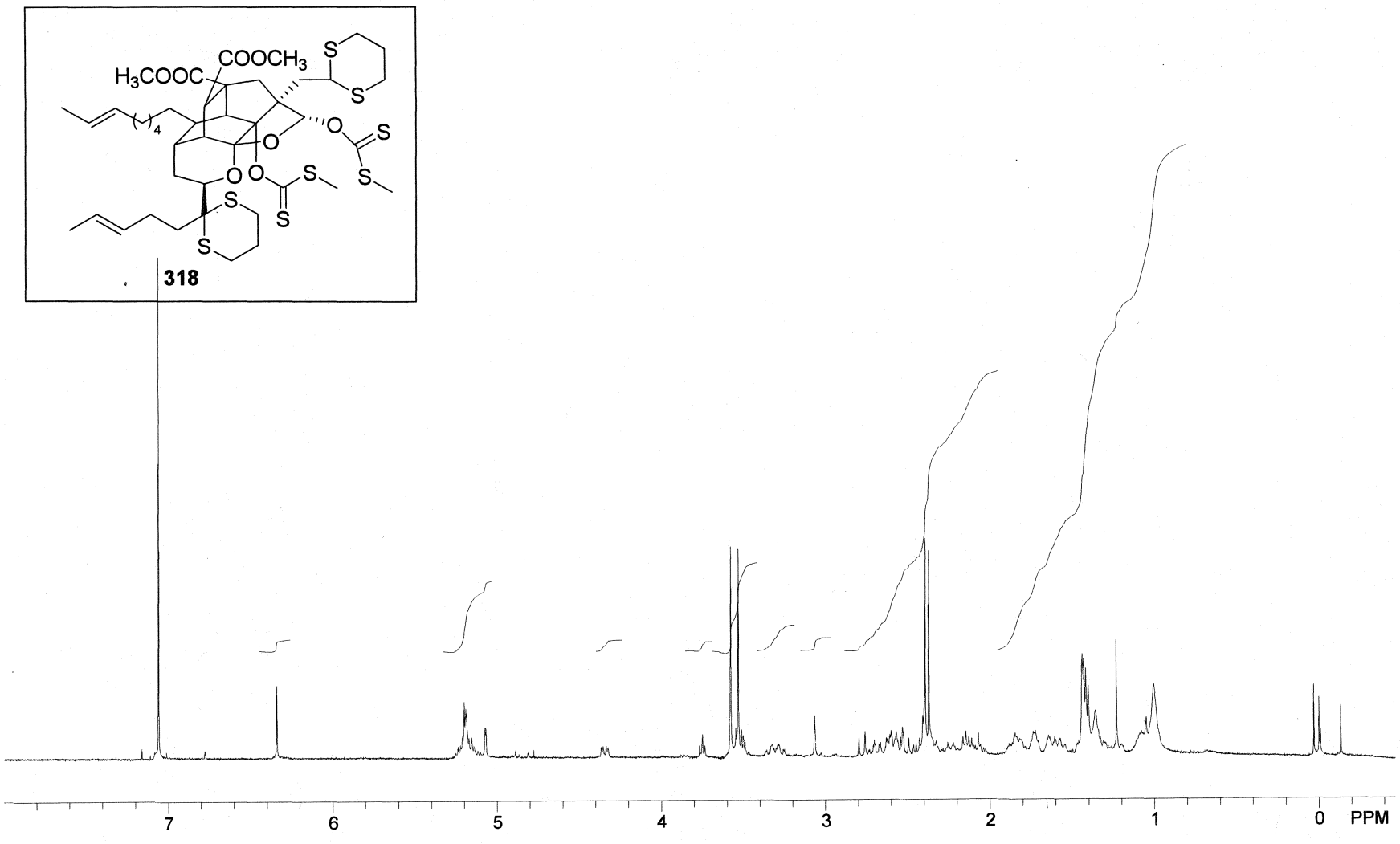


Figure A.5.37 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **318.**

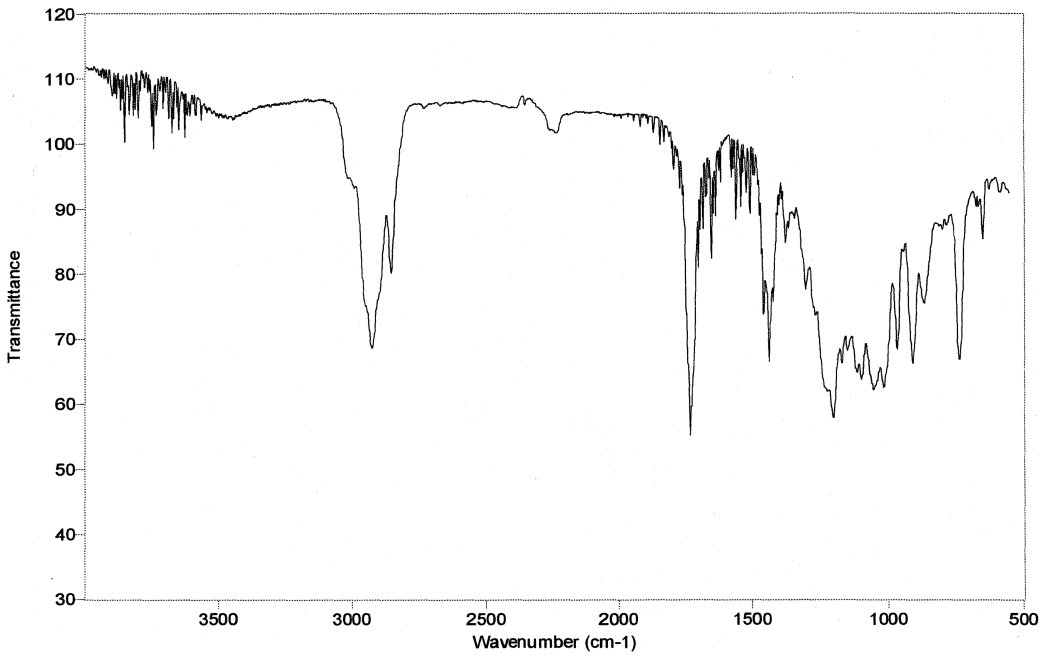


Figure A.5.38 FTIR Spectrum (thin film/NaCl) of Compound **318**.

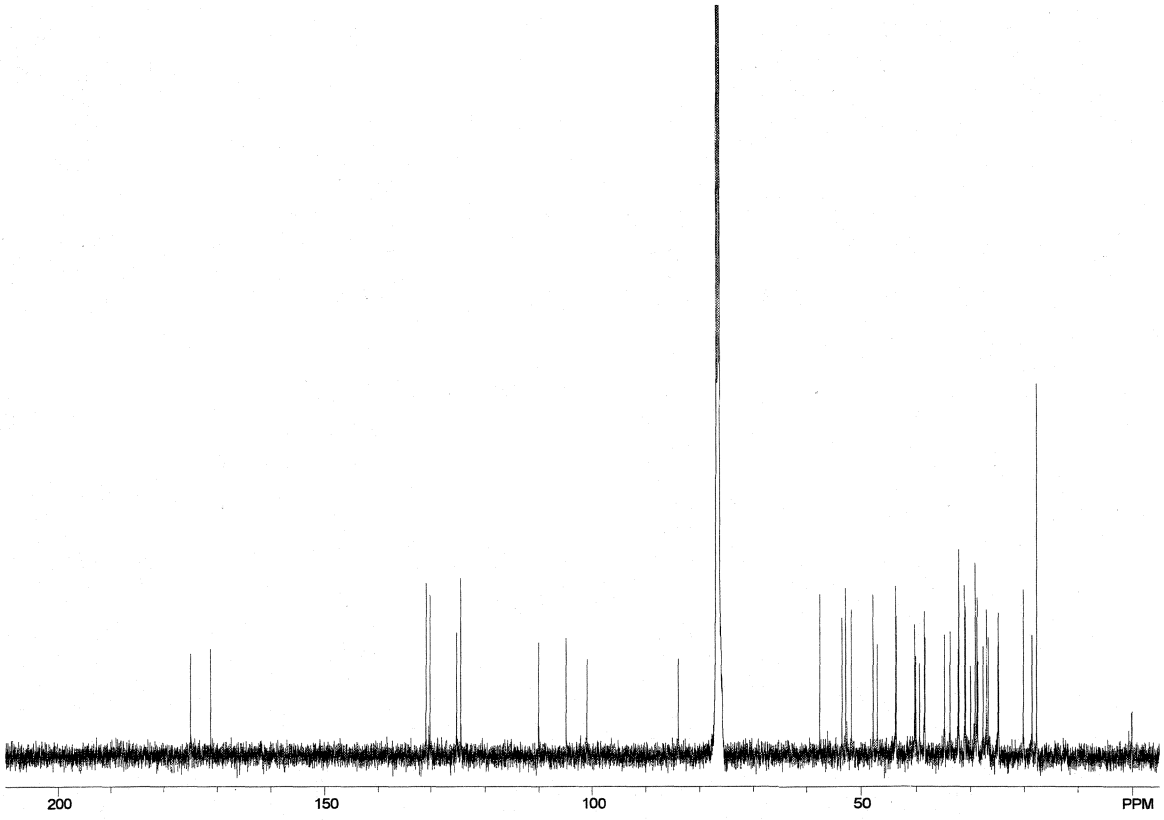


Figure A.5.39 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **318**.

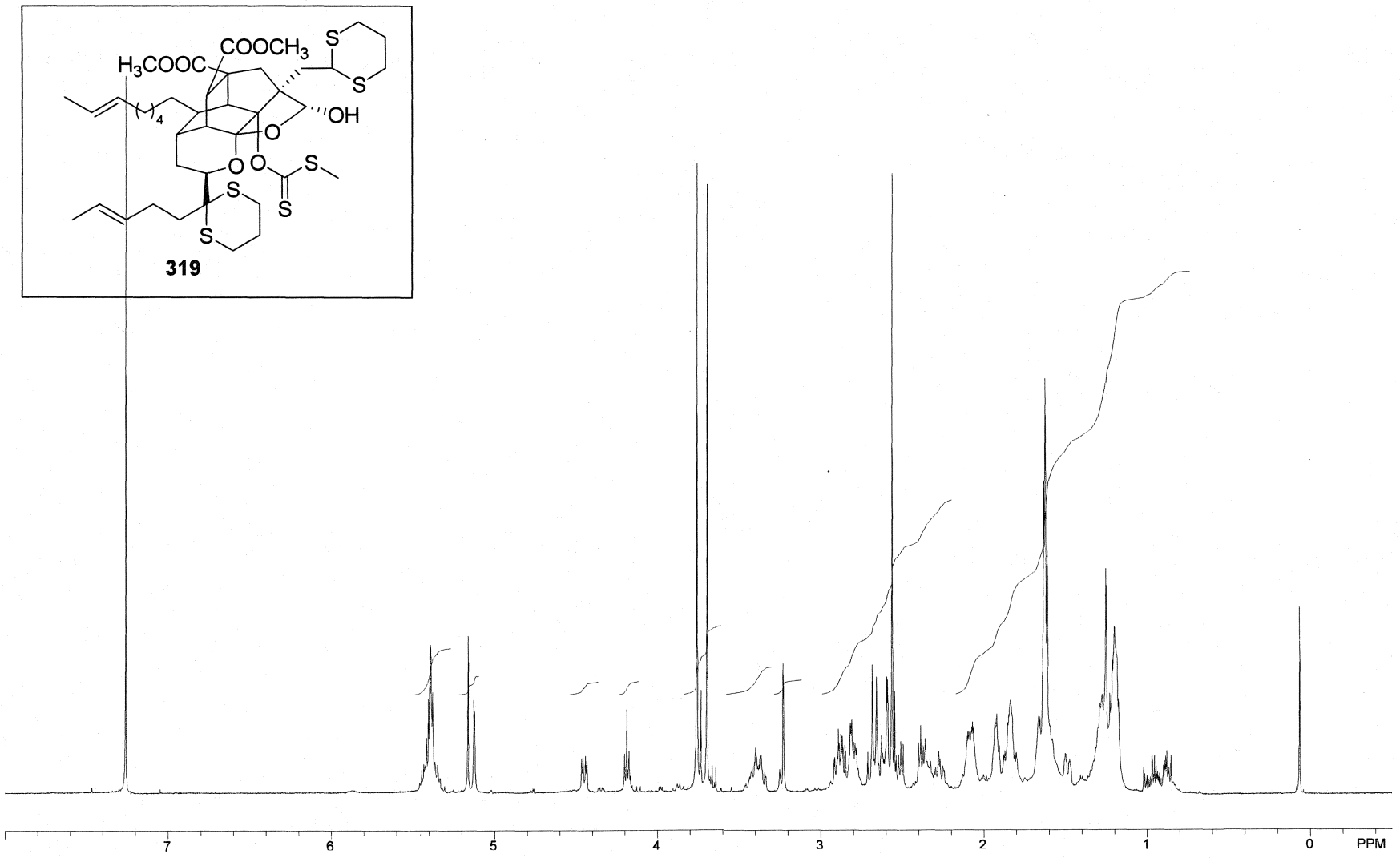


Figure A.5.40 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **319.**

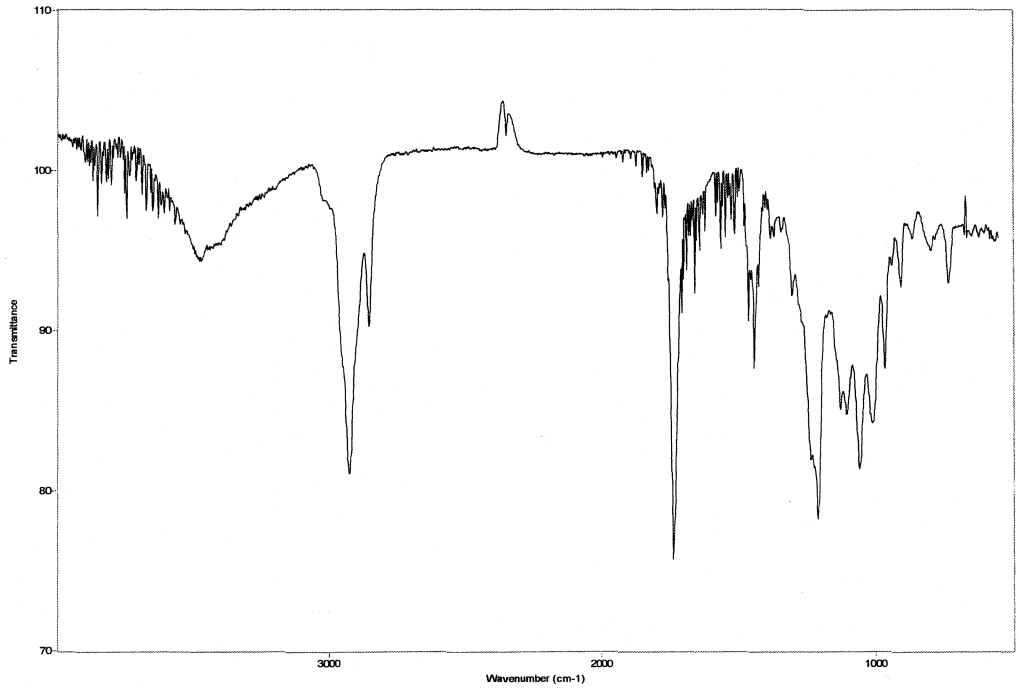


Figure A.5.41 FTIR Spectrum (thin film/NaCl) of Compound **319**.

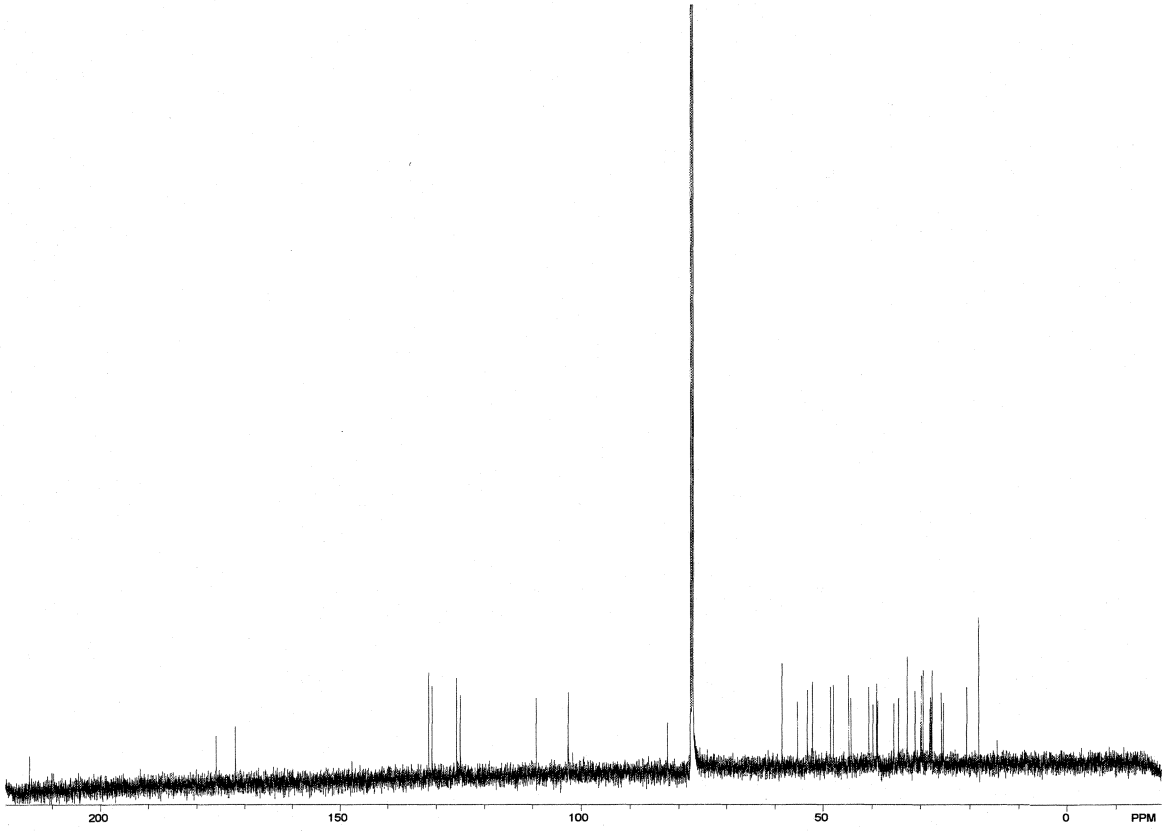


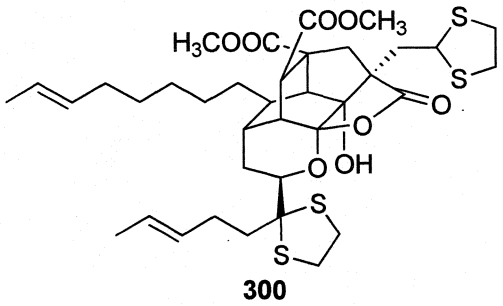
Figure A.5.42 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **319**.

Appendix 6

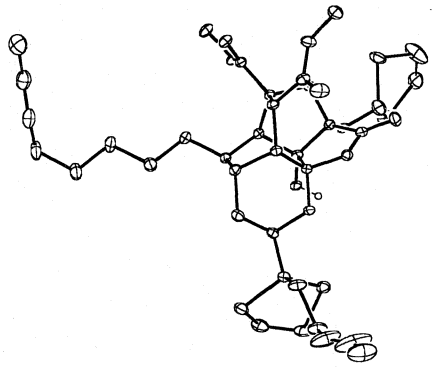
X-Ray Data Relevant to Chapter 5

A.6.1 X-Ray Structure Report for Dithiolane 300.

A.6.1.1 Structure and ORTEP Plot of Dithiolane 300.



300



A.6.1.2 Reference Information.

YALE CHEMICAL INSTRUMENTATION CENTER

X-Ray Structure Report

Reference Number: WOOD_IM03

September 25, 2003

A.6.1.3 Data Collection.

A colorless needle crystal of $C_{37}H_{52}O_8S_4$ having approximate dimensions of 0.25 x 0.10 x 0.10 mm^3 was mounted with epoxy cement on the tip of a fine glass fiber. All measurements were made on a Nonius KappaCCD diffractometer with graphite monochromated Mo-Kπ radiation.

Cell constants and an orientation matrix for data collection corresponded to a primitive monoclinic cell with dimensions:

$a = 21.990(4)$ Å $\quad \pi = 90^{o}$

$b = 15.567(3)$ Å $\quad \pi = 97.75(3)^{o}$

$c = 22.168(4)$ Å $\quad \pi = 90^{o}$

$V = 7519(3)$ Å^3

For Z = 8 and F.W. = 753.03, the calculated density is 1.330 g/cm^3. Based on a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be $P2_1/n$ (#14).

The data were collected at a temperature of 173(2) K to a maximum 2π value of 54.50 °. Four omega scans consisting of 53, 58, 58, and 15 data frames, respectively, were collected with a frame width of 1.3 ° and a detector-to-crystal distance, Dx, of 35.0 mm. Each frame was exposed twice (for the purpose of de-zingering) for a total of 260 s. The data frames were processed and scaled using the DENZO software package.[1]

A.6.1.4 Data Reduction.

A total of 27281 reflections were collected of which 16750 were unique and observed (R_{int} = 0.0710). The linear absorption coefficient, μ, for Mo-Kπ radiation is 3.03 cm^{-1}, and no absorption correction was applied. The data were corrected for Lorentz and polarization effects.

A.6.1.5 Structure Solution and Refinement.

The structure was solved by direct methods and expanded using Fourier techniques[2]. The non-hydrogen atoms were refined anisotropically, and hydrogen atoms were treated as idealized contributions. The final cycle of full-matrix least-squares refinement[3] on F was based on 16750 observed reflections ($I > 2.00\pi(I)$) and 896 variable parameters and converged with unweighted and weighted agreement factors of:

$$R = \pi \, ||Fo| - |Fc|| \, / \, \pi \, |Fo| = 0.0717$$

$$R_W = \{\pi[w \, (F_o^2 - F_c^2)^2] \, / \, \pi[w(F_o^2)^2]\}^{1/2} = 0.1646$$

The maximum and minimum peaks on the final difference Fourier map corresponded to 0.957 and –0.723 $e^-/Å^3$ respectively.

A.6.1.6 REFERENCES

(1) Z. Otwinowski and W. Minor, "Processing of X-Ray Diffraction Data Collected in Oscillation Mode," Methods in Enzymology, vol. 276: Macromolecular Crystallography, part A, 307-326, 1997, C.W. Carter, Jr. & R.M. Sweet, Eds., Academic Press.

(2) *Acta Cryst.* **A46** (1990) 467-473

(3) Least Squares function minimized:

$$\pi w(F_o^2 - F_c^2)^2$$

A.6.1.7 Structural Description.

The compound crystallized in the monoclinic space group $P2_1/n$ with two crystallographically unique but chemically equivalent molecules in the asymmetric unit and eight molecules in the unit cell. Consistent with the previously characterized compound wood_im02, ring 1 [C(1-6)] adopts a boat conformation as a result of the two-carbon bridge between C(7) and C(10) and ring 2 [C(1, 2, 6, 16, 17)-O(8)] adopts the expected chair geometry. The lactone rings are planar with 0.076 and 0.081(') Å deviations, slightly higher than the values in wood_im02. The decrease in planarity is caused by the formation of an additional ring to the bicyclo-octane core. This feature is better illustrated in Figure **4**. The torsion angles about the C(7)-C(10) bond are 86.5 ° for C(8-7-10-11) and 87.0 ° for C(7'-8'-10'-11').

The hydroxyl-protons, H(7) and H(7'), were located from the residual electron density map and refined with isotropic displacement parameters. No geometrical restraints were applied to the O-H bonds, which refined to distances of 0.87(5) Å for O(7)-H(1) and 0.82(4) Å for O(7')-H(1'). Hydrogen bonds, 2.21 Å, between this proton and O(3/3') of an adjacent molecule form infinitely extending chains in the crystal lattice as illustrated in Figure **5**.

The highly flexible alkyl chains, C(24-27) and C(30-37), in both unique molecules may occupy numerous orientations in the crystal-lattice and could not be effectively modeled. The atoms associated with these chains possess inflated thermal parameters and non-ideal C-C bond lengths as a result of the unresolvable positional disorder. One sulfur atom of the first independent molecule, S(2), is disordered over two

positions with an occupancy ratio of 80:20. The minor component was refined with isotropic displacement parameters.

ORTEPs, packing diagrams and full crystallographic tables follow.

Figure A.6.1 First Independent Molecule.

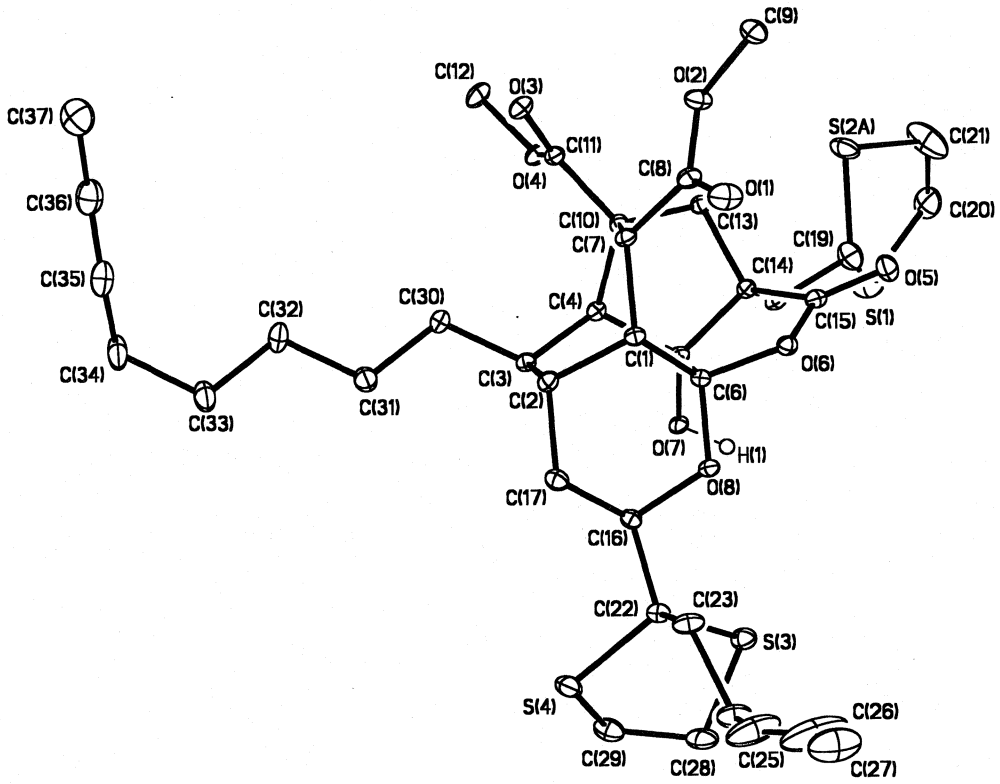


Figure A.6.2 Second Independent Molecule.

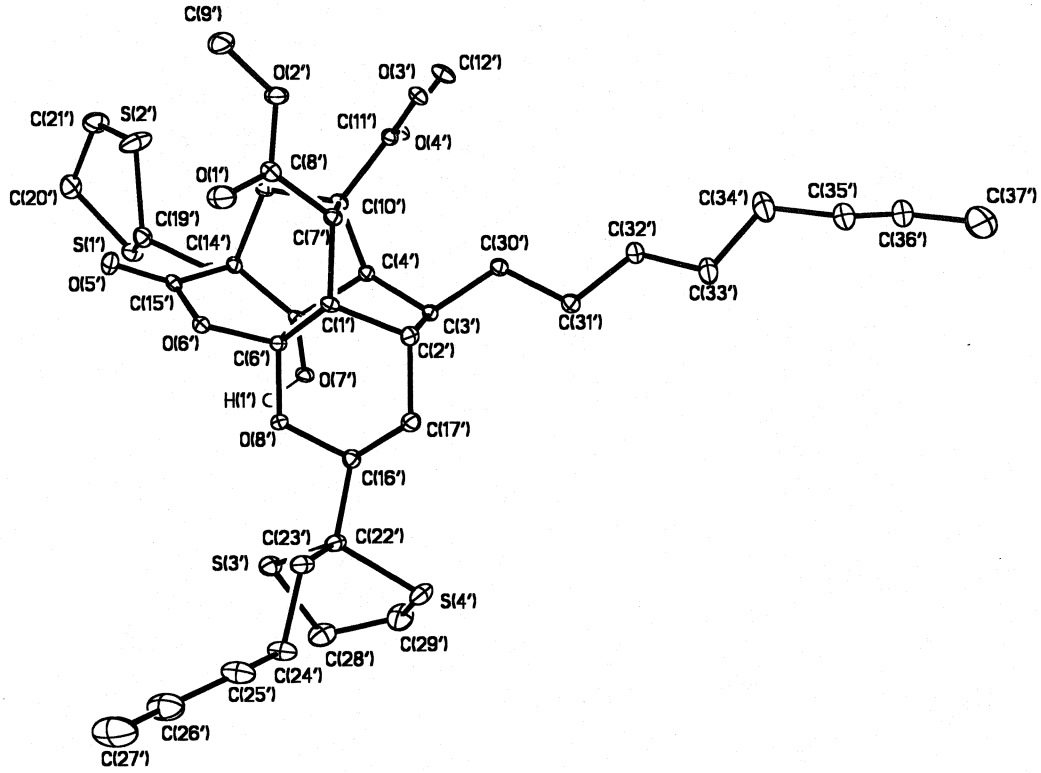


Figure A.6.3

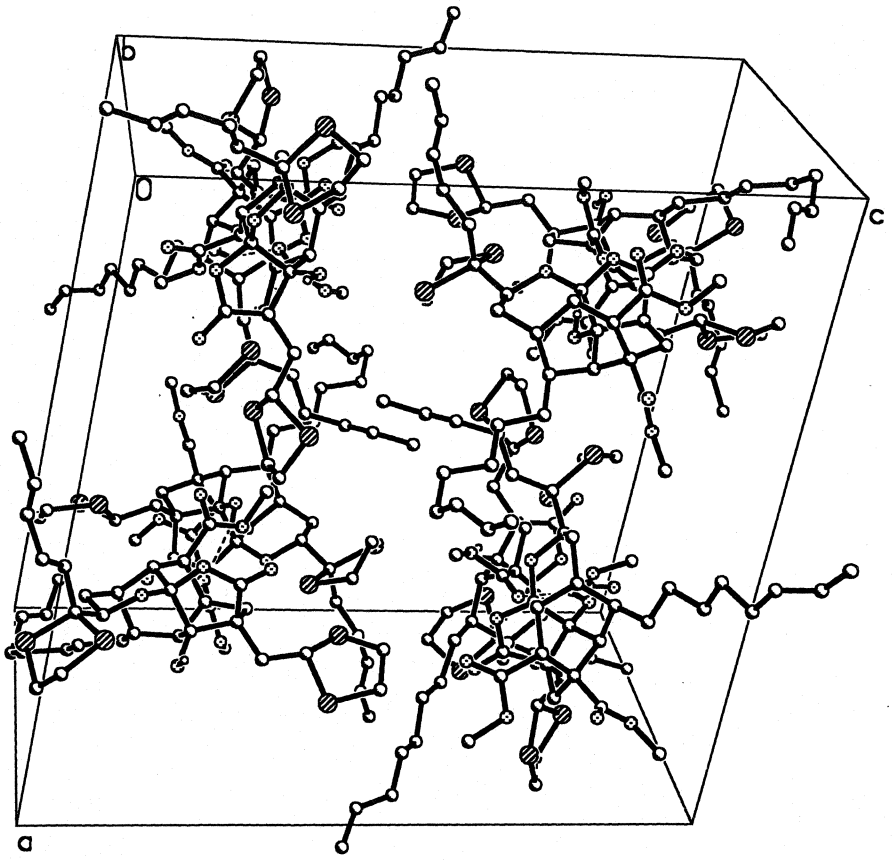
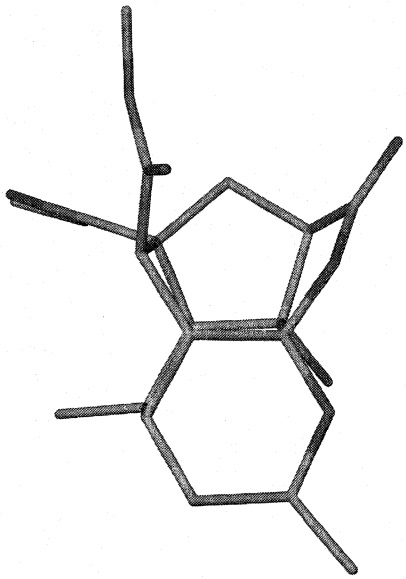
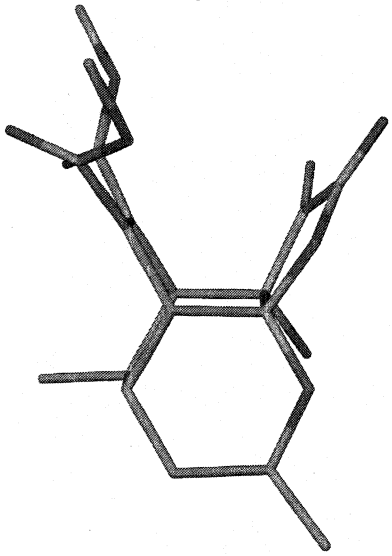


Figure A.6.4



IM03



IM02

Figure A.6.5

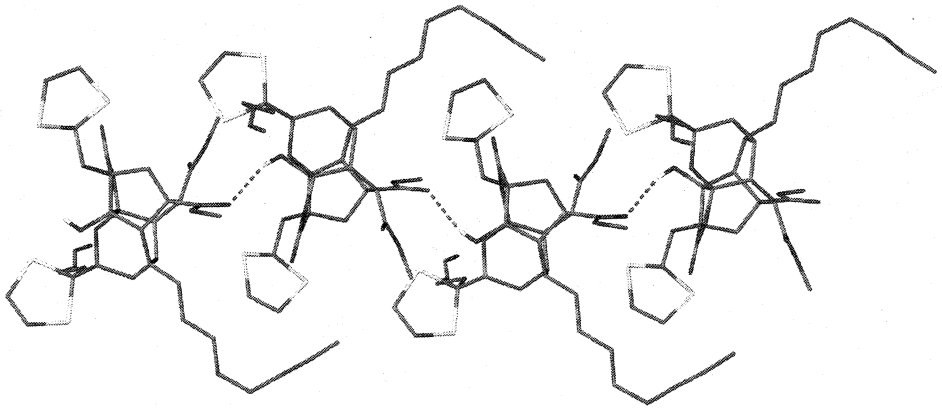


Figure A.6.6 Packing diagram – View down the a-axis

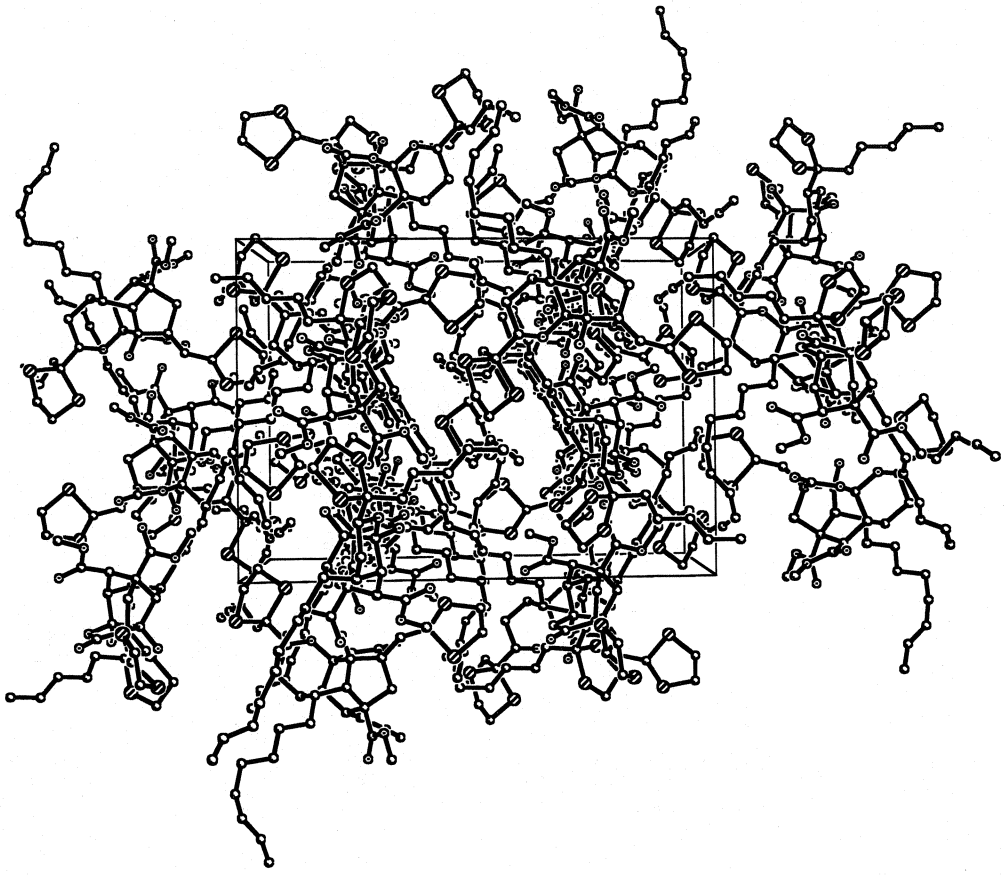


Figure A.6.7 Packing diagram – View down the b-axis

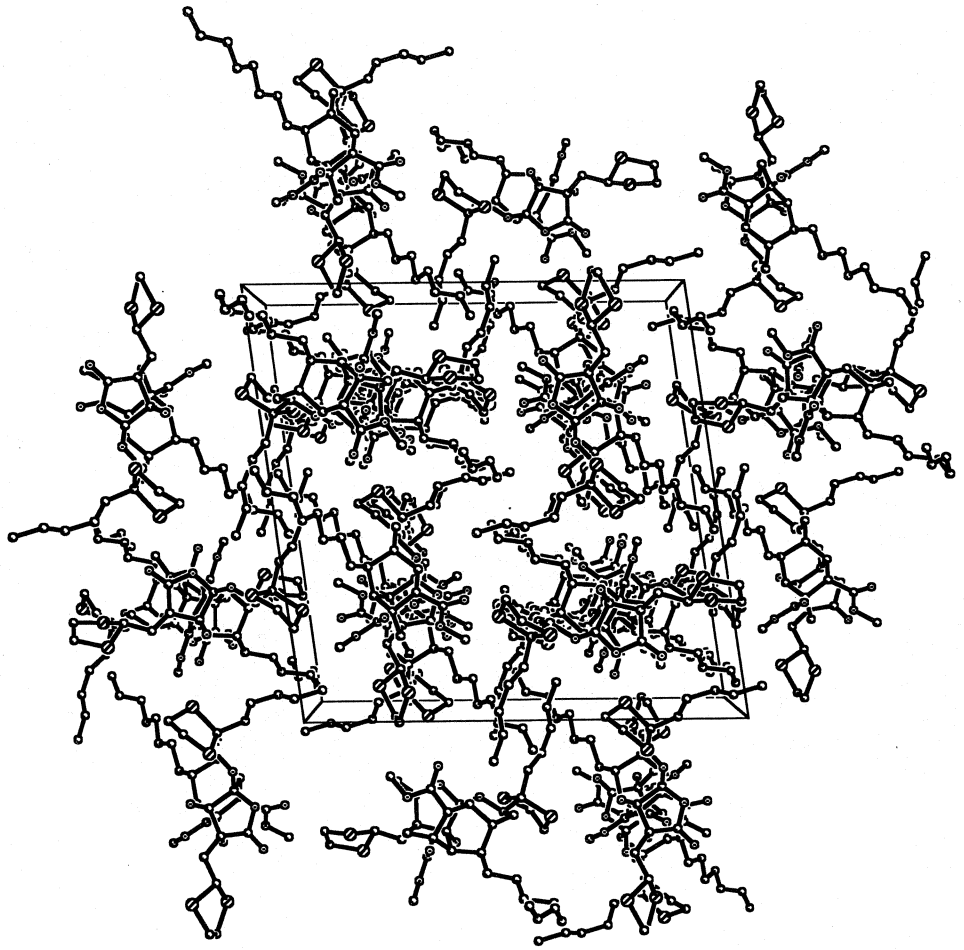


Figure A.6.8 Packing diagram – View down the c-axis

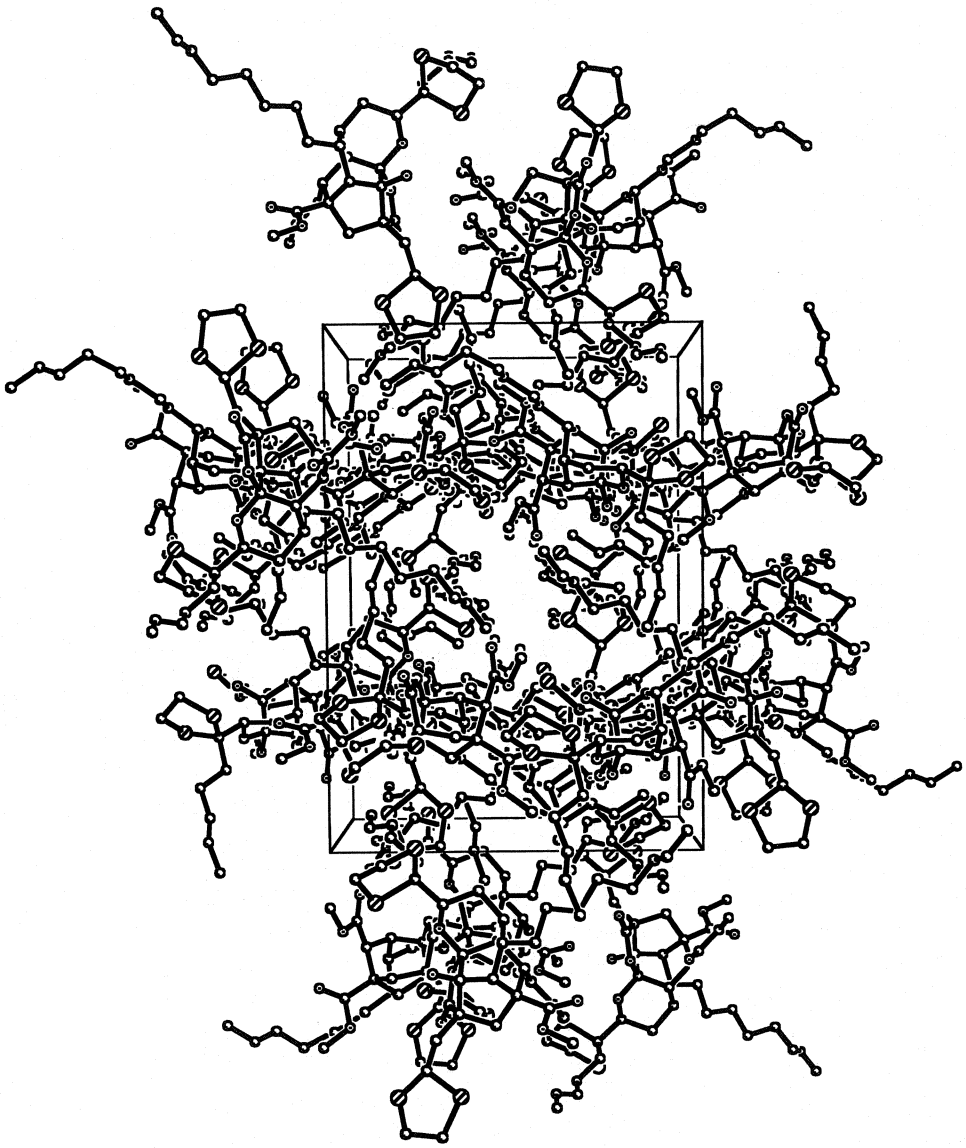


Table A.6.1. Crystal data and structure refinement for wood_im03.

Identification code	wood_im03	
Empirical formula	$C_{37} H_{52} O_8 S_4$	
Formula weight	753.03	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 21.990(4) Å	π= 90°.
	b = 15.567(3) Å	π= 97.75(3)°.
	c = 22.168(4) Å	π= 90°.
Volume	7519(3) $Å^3$	
Z	8	
Density (calculated)	1.330 g/cm^3	
Absorption coefficient	3.03 cm^{-1}	
F(000)	3216	
Crystal size	0.25 x 0.10 x 0.10 mm^3	
Theta range for data collection	2.27 to 27.25°.	
Index ranges	-28<=h<=28, -18<=k<=20, -28<=l<=28	
Reflections collected	27281	
Independent reflections	16750 [R(int) = 0.0710]	
Completeness to theta = 27.25°	99.5 %	
Absorption correction	None	
Max. and min. transmission	0.9704 and 0.9281	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	16750 / 0 / 896	
Goodness-of-fit on F^2	1.040	
Final R indices [I>2sigma(I)]	R1 = 0.0717, wR2 = 0.1646	
R indices (all data)	R1 = 0.1542, wR2 = 0.2028	
Largest diff. peak and hole	0.957 and -0.723 $e.Å^{-3}$	

Table A.6.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for wood_im03. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	8280(1)	855(1)	4248(1)	58(1)
S(2A)	7757(1)	2513(1)	4430(1)	48(1)
S(2B)	7312(6)	1998(9)	4319(6)	132(4)
S(3)	7093(1)	392(1)	787(1)	33(1)
S(4)	7477(1)	1353(1)	-257(1)	37(1)
O(1)	6058(1)	4392(2)	2135(1)	44(1)
O(2)	6733(1)	4824(2)	2915(1)	32(1)
O(3)	7908(1)	5536(2)	2570(1)	30(1)
O(4)	8668(1)	4654(2)	2930(1)	30(1)
O(5)	6544(1)	2173(2)	3164(1)	35(1)
O(6)	6616(1)	2463(2)	2195(1)	23(1)
O(7)	8028(1)	1793(2)	2040(1)	22(1)
O(8)	6946(1)	2037(2)	1335(1)	22(1)
C(1)	7001(2)	3552(2)	1566(2)	21(1)
C(2)	7474(2)	3657(2)	1118(2)	24(1)
C(3)	8130(2)	3552(2)	1465(2)	23(1)
C(4)	8092(2)	3338(2)	2135(2)	20(1)
C(5)	7713(2)	2527(2)	2203(2)	21(1)
C(6)	7066(2)	2647(2)	1805(2)	22(1)
C(7)	7131(2)	4225(2)	2073(2)	22(1)
C(8)	6578(2)	4464(2)	2370(2)	26(1)
C(9)	6236(2)	5149(3)	3214(2)	39(1)
C(10)	7740(2)	3999(2)	2492(2)	21(1)
C(11)	8102(2)	4816(2)	2665(2)	22(1)
C(12)	9048(2)	5391(3)	3100(2)	40(1)
C(13)	7665(2)	3469(2)	3075(2)	22(1)
C(14)	7548(2)	2527(2)	2863(2)	21(1)
C(15)	6865(2)	2342(2)	2784(2)	25(1)
C(16)	7299(2)	2102(2)	832(2)	23(1)
C(17)	7308(2)	3018(2)	595(2)	27(1)

C(18)	7941(2)	1878(2)	3275(2)	26(1)
C(19)	7751(2)	1658(3)	3885(2)	43(1)
C(20)	8114(3)	1023(3)	5012(2)	64(2)
C(21)	7733(3)	1804(4)	5049(2)	88(2)
C(22)	7018(2)	1424(2)	373(2)	25(1)
C(23)	6352(2)	1642(3)	121(2)	34(1)
C(24)	5996(2)	934(3)	-257(2)	40(1)
C(25)	5396(3)	1234(4)	-557(3)	79(2)
C(26)	4894(3)	1174(5)	-538(4)	111(3)
C(27)	4290(2)	1524(4)	-831(3)	71(2)
C(28)	7417(2)	-217(3)	218(2)	45(1)
C(29)	7862(2)	355(3)	-51(2)	45(1)
C(30)	8538(2)	4328(2)	1385(2)	28(1)
C(31)	8672(2)	4449(3)	733(2)	36(1)
C(32)	9046(2)	5254(3)	635(2)	39(1)
C(33)	9136(2)	5381(3)	-29(2)	45(1)
C(34)	9465(2)	6221(3)	-141(2)	53(1)
C(35)	9100(2)	7006(3)	-30(2)	48(1)
C(36)	9267(2)	7600(3)	375(2)	54(1)
C(37)	8905(3)	8362(3)	516(2)	64(2)
S(1')	4316(1)	1936(1)	3274(1)	35(1)
S(2')	4404(1)	3520(1)	2579(1)	63(1)
S(3')	775(1)	1345(1)	2335(1)	35(1)
S(4')	-264(1)	2394(1)	2645(1)	39(1)
O(1')	2240(2)	5021(2)	997(1)	52(1)
O(2')	2801(1)	5946(2)	1600(1)	37(1)
O(3')	2586(1)	6521(2)	2795(1)	26(1)
O(4')	3021(1)	5628(2)	3520(1)	29(1)
O(5')	3123(1)	2992(2)	1531(1)	32(1)
O(6')	2151(1)	3317(2)	1609(1)	22(1)
O(7')	2040(1)	2825(2)	3051(1)	24(1)
O(8')	1295(1)	2975(2)	1981(1)	24(1)
C(1')	1543(2)	4487(2)	1942(2)	21(1)
C(2')	1098(2)	4647(2)	2407(2)	25(1)
C(3')	1467(2)	4612(2)	3061(2)	22(1)
C(4')	2138(2)	4364(2)	3026(2)	21(1)

C(5')	2194(2)	3513(2)	2692(2)	20(1)
C(6')	1781(2)	3574(2)	2059(2)	21(1)
C(7')	2056(2)	5171(2)	2045(2)	22(1)
C(8')	2365(2)	5343(2)	1488(2)	26(1)
C(9')	3105(2)	6194(3)	1091(2)	50(1)
C(10')	2490(2)	4974(2)	2642(2)	21(1)
C(11')	2699(2)	5802(2)	2982(2)	21(1)
C(12')	3239(2)	6373(2)	3881(2)	34(1)
C(13')	3065(2)	4436(2)	2544(2)	23(1)
C(14')	2855(2)	3482(2)	2508(2)	22(1)
C(15')	2755(2)	3213(2)	1848(2)	22(1)
C(16')	808(2)	3086(2)	2356(2)	25(1)
C(17')	564(2)	4008(2)	2300(2)	28(1)
C(18')	3293(2)	2892(2)	2927(2)	24(1)
C(19')	3891(2)	2634(2)	2706(2)	32(1)
C(20')	5032(2)	2099(3)	2992(2)	44(1)
C(21')	5120(2)	3046(3)	2900(2)	51(1)
C(22')	347(2)	2360(2)	2163(2)	28(1)
C(23')	78(2)	2412(3)	1488(2)	33(1)
C(24')	-371(2)	1705(3)	1258(2)	42(1)
C(25')	-563(2)	1715(3)	588(2)	51(1)
C(26')	-490(3)	1095(4)	206(2)	70(2)
C(27')	-686(3)	1106(5)	-473(2)	98(2)
C(28')	286(2)	859(3)	2826(2)	49(1)
C(29')	18(2)	1553(3)	3171(2)	53(1)
C(30')	1429(2)	5450(2)	3417(2)	25(1)
C(31')	785(2)	5730(2)	3529(2)	28(1)
C(32')	819(2)	6548(2)	3903(2)	35(1)
C(33')	231(2)	7028(3)	3927(2)	43(1)
C(34')	380(2)	7892(3)	4252(2)	58(1)
C(35')	-141(2)	8430(3)	4347(3)	63(2)
C(36')	-250(3)	8727(4)	4898(4)	90(2)
C(37')	-721(3)	9221(5)	5062(4)	121(3)

Table A.6.3. Bond lengths [Å] and angles [°] for wood_im03.

S(1)-C(20)	1.799(5)	C(7)-C(8)	1.506(5)
S(1)-C(19)	1.820(4)	C(7)-C(10)	1.563(5)
S(2A)-C(21)	1.768(6)	C(10)-C(11)	1.522(5)
S(2A)-C(19)	1.796(5)	C(10)-C(13)	1.560(5)
S(2B)-C(19)	1.545(14)	C(13)-C(14)	1.551(5)
S(2B)-C(21)	1.778(14)	C(14)-C(15)	1.516(5)
S(3)-C(28)	1.799(4)	C(14)-C(18)	1.545(5)
S(3)-C(22)	1.845(4)	C(16)-C(17)	1.520(5)
S(4)-C(29)	1.798(4)	C(16)-C(22)	1.537(5)
S(4)-C(22)	1.833(4)	C(18)-C(19)	1.507(5)
O(1)-C(8)	1.196(4)	C(20)-C(21)	1.485(8)
O(2)-C(8)	1.333(4)	C(22)-C(23)	1.535(5)
O(2)-C(9)	1.443(4)	C(23)-C(24)	1.533(5)
O(3)-C(11)	1.208(4)	C(24)-C(25)	1.471(7)
O(4)-C(11)	1.327(4)	C(25)-C(26)	1.113(8)
O(4)-C(12)	1.440(4)	C(26)-C(27)	1.499(8)
O(5)-C(15)	1.198(4)	C(28)-C(29)	1.505(6)
O(6)-C(15)	1.360(4)	C(30)-C(31)	1.526(5)
O(6)-C(6)	1.429(4)	C(31)-C(32)	1.531(5)
O(7)-H(1)	0.87(5)	C(32)-C(33)	1.525(6)
O(7)-C(5)	1.408(4)	C(33)-C(34)	1.531(6)
O(8)-C(6)	1.408(4)	C(34)-C(35)	1.500(7)
O(8)-C(16)	1.446(4)	C(35)-C(36)	1.306(7)
C(1)-C(6)	1.506(5)	C(36)-C(37)	1.485(7)
C(1)-C(7)	1.535(5)	S(1')-C(20')	1.789(4)
C(1)-C(2)	1.541(5)	S(1')-C(19')	1.823(4)
C(2)-C(17)	1.533(5)	S(2')-C(21')	1.797(4)
C(2)-C(3)	1.549(5)	S(2')-C(19')	1.828(4)
C(3)-C(30)	1.531(5)	S(3')-C(28')	1.797(4)
C(3)-C(4)	1.533(5)	S(3')-C(22')	1.852(4)
C(4)-C(5)	1.531(5)	S(4')-C(29')	1.805(5)
C(4)-C(10)	1.565(5)	S(4')-C(22')	1.826(4)
C(5)-C(14)	1.555(5)	O(1')-C(8')	1.197(4)
C(5)-C(6)	1.581(5)	O(2')-C(8')	1.341(4)

O(2')-C(9')	1.438(5)	C(25')-C(26')	1.307(7)
O(3')-C(11')	1.207(4)	C(26')-C(27')	1.509(7)
O(4')-C(11')	1.332(4)	C(28')-C(29')	1.490(7)
O(4')-C(12')	1.452(4)	C(30')-C(31')	1.535(5)
O(5')-C(15')	1.193(4)	C(31')-C(32')	1.516(5)
O(6')-C(15')	1.371(4)	C(32')-C(33')	1.501(6)
O(6')-C(6')	1.427(4)	C(33')-C(34')	1.539(6)
O(7')-H(1')	0.82(4)	C(34')-C(35')	1.458(7)
O(7')-C(5')	1.403(4)	C(35')-C(36')	1.358(8)
O(8')-C(6')	1.412(4)	C(36')-C(37')	1.378(8)
O(8')-C(16')	1.451(4)		
C(1')-C(6')	1.524(5)	C(20)-S(1)-C(19)	96.8(2)
C(1')-C(2')	1.535(5)	C(21)-S(2A)-C(19)	93.5(3)
C(1')-C(7')	1.544(5)	C(19)-S(2B)-C(21)	102.5(8)
C(2')-C(17')	1.532(5)	C(28)-S(3)-C(22)	97.34(19)
C(2')-C(3')	1.564(5)	C(29)-S(4)-C(22)	98.44(19)
C(3')-C(30')	1.532(5)	C(8)-O(2)-C(9)	116.5(3)
C(3')-C(4')	1.537(5)	C(11)-O(4)-C(12)	116.2(3)
C(4')-C(5')	1.530(5)	C(15)-O(6)-C(6)	112.8(3)
C(4')-C(10')	1.550(5)	H(1)-O(7)-C(5)	104(3)
C(5')-C(14')	1.563(5)	C(6)-O(8)-C(16)	117.1(3)
C(5')-C(6')	1.569(5)	C(6)-C(1)-C(7)	112.4(3)
C(7')-C(8')	1.511(5)	C(6)-C(1)-C(2)	106.6(3)
C(7')-C(10')	1.555(5)	C(7)-C(1)-C(2)	108.9(3)
C(10')-C(11')	1.531(5)	C(17)-C(2)-C(1)	107.8(3)
C(10')-C(13')	1.555(5)	C(17)-C(2)-C(3)	114.7(3)
C(13')-C(14')	1.555(5)	C(1)-C(2)-C(3)	109.4(3)
C(14')-C(15')	1.509(5)	C(30)-C(3)-C(4)	113.1(3)
C(14')-C(18')	1.547(5)	C(30)-C(3)-C(2)	112.3(3)
C(16')-C(17')	1.531(5)	C(4)-C(3)-C(2)	109.6(3)
C(16')-C(22')	1.540(5)	C(5)-C(4)-C(3)	112.1(3)
C(18')-C(19')	1.519(5)	C(5)-C(4)-C(10)	100.3(3)
C(20')-C(21')	1.504(6)	C(3)-C(4)-C(10)	116.2(3)
C(22')-C(23')	1.536(5)	O(7)-C(5)-C(4)	110.6(3)
C(23')-C(24')	1.519(5)	O(7)-C(5)-C(14)	115.3(3)
C(24')-C(25')	1.490(6)	C(4)-C(5)-C(14)	106.9(3)

O(7)-C(5)-C(6)	112.9(3)	C(17)-C(16)-C(22)	116.0(3)
C(4)-C(5)-C(6)	107.9(3)	C(16)-C(17)-C(2)	111.1(3)
C(14)-C(5)-C(6)	102.7(3)	C(19)-C(18)-C(14)	118.5(3)
O(8)-C(6)-O(6)	103.7(3)	C(18)-C(19)-S(2B)	138.8(6)
O(8)-C(6)-C(1)	111.8(3)	C(18)-C(19)-S(2A)	117.2(3)
O(6)-C(6)-C(1)	111.1(3)	S(2B)-C(19)-S(2A)	43.6(5)
O(8)-C(6)-C(5)	113.5(3)	C(18)-C(19)-S(1)	108.3(3)
O(6)-C(6)-C(5)	106.4(3)	S(2B)-C(19)-S(1)	112.0(6)
C(1)-C(6)-C(5)	110.1(3)	S(2A)-C(19)-S(1)	105.3(2)
C(8)-C(7)-C(1)	114.0(3)	C(21)-C(20)-S(1)	111.0(3)
C(8)-C(7)-C(10)	118.2(3)	C(20)-C(21)-S(2A)	113.1(4)
C(1)-C(7)-C(10)	110.0(3)	C(20)-C(21)-S(2B)	108.5(6)
O(1)-C(8)-O(2)	123.1(3)	S(2A)-C(21)-S(2B)	41.7(5)
O(1)-C(8)-C(7)	124.6(3)	C(23)-C(22)-C(16)	111.6(3)
O(2)-C(8)-C(7)	112.2(3)	C(23)-C(22)-S(4)	109.4(3)
C(11)-C(10)-C(13)	110.0(3)	C(16)-C(22)-S(4)	109.4(3)
C(11)-C(10)-C(7)	109.8(3)	C(23)-C(22)-S(3)	112.9(3)
C(13)-C(10)-C(7)	115.8(3)	C(16)-C(22)-S(3)	105.6(2)
C(11)-C(10)-C(4)	113.5(3)	S(4)-C(22)-S(3)	107.78(18)
C(13)-C(10)-C(4)	100.7(3)	C(24)-C(23)-C(22)	115.6(3)
C(7)-C(10)-C(4)	106.8(3)	C(25)-C(24)-C(23)	112.3(4)
O(3)-C(11)-O(4)	122.8(3)	C(26)-C(25)-C(24)	142.2(9)
O(3)-C(11)-C(10)	124.8(3)	C(25)-C(26)-C(27)	141.1(10)
O(4)-C(11)-C(10)	112.4(3)	C(29)-C(28)-S(3)	107.8(3)
C(14)-C(13)-C(10)	106.3(3)	C(28)-C(29)-S(4)	107.7(3)
C(15)-C(14)-C(18)	114.2(3)	C(31)-C(30)-C(3)	113.4(3)
C(15)-C(14)-C(13)	109.7(3)	C(30)-C(31)-C(32)	114.2(3)
C(18)-C(14)-C(13)	112.5(3)	C(33)-C(32)-C(31)	112.6(4)
C(15)-C(14)-C(5)	104.1(3)	C(32)-C(33)-C(34)	113.1(4)
C(18)-C(14)-C(5)	111.9(3)	C(35)-C(34)-C(33)	113.2(4)
C(13)-C(14)-C(5)	103.6(3)	C(36)-C(35)-C(34)	125.6(5)
O(5)-C(15)-O(6)	120.4(3)	C(35)-C(36)-C(37)	127.0(5)
O(5)-C(15)-C(14)	129.0(3)	C(20')-S(1')-C(19')	93.8(2)
O(6)-C(15)-C(14)	110.4(3)	C(21')-S(2')-C(19')	98.89(19)
O(8)-C(16)-C(17)	111.4(3)	C(28')-S(3')-C(22')	98.86(19)
O(8)-C(16)-C(22)	104.6(3)	C(29')-S(4')-C(22')	98.1(2)

C(8')-O(2')-C(9')	116.1(3)	C(11')-C(10')-C(7')	111.2(3)
C(11')-O(4')-C(12')	115.3(3)	C(4')-C(10')-C(7')	107.0(3)
C(15')-O(6')-C(6')	112.2(3)	C(11')-C(10')-C(13')	109.0(3)
H(1')-O(7')-C(5')	107(3)	C(4')-C(10')-C(13')	102.8(3)
C(6')-O(8')-C(16')	117.0(3)	C(7')-C(10')-C(13')	113.9(3)
C(6')-C(1')-C(2')	105.8(3)	O(3')-C(11')-O(4')	123.7(3)
C(6')-C(1')-C(7')	113.0(3)	O(3')-C(11')-C(10')	125.3(3)
C(2')-C(1')-C(7')	107.9(3)	O(4')-C(11')-C(10')	111.0(3)
C(17')-C(2')-C(1')	109.6(3)	C(14')-C(13')-C(10')	106.3(3)
C(17')-C(2')-C(3')	114.4(3)	C(15')-C(14')-C(18')	114.5(3)
C(1')-C(2')-C(3')	108.6(3)	C(15')-C(14')-C(13')	108.5(3)
C(30')-C(3')-C(4')	111.1(3)	C(18')-C(14')-C(13')	112.3(3)
C(30')-C(3')-C(2')	113.0(3)	C(15')-C(14')-C(5')	104.1(3)
C(4')-C(3')-C(2')	110.1(3)	C(18')-C(14')-C(5')	112.8(3)
C(5')-C(4')-C(3')	112.4(3)	C(13')-C(14')-C(5')	103.7(3)
C(5')-C(4')-C(10')	100.8(3)	O(5')-C(15')-O(6')	120.3(3)
C(3')-C(4')-C(10')	115.3(3)	O(5')-C(15')-C(14')	129.1(3)
O(7')-C(5')-C(4')	110.2(3)	O(6')-C(15')-C(14')	110.4(3)
O(7')-C(5')-C(14')	115.4(3)	O(8')-C(16')-C(17')	110.1(3)
C(4')-C(5')-C(14')	106.9(3)	O(8')-C(16')-C(22')	105.2(3)
O(7')-C(5')-C(6')	113.5(3)	C(17')-C(16')-C(22')	117.1(3)
C(4')-C(5')-C(6')	107.8(3)	C(16')-C(17')-C(2')	110.1(3)
C(14')-C(5')-C(6')	102.4(3)	C(19')-C(18')-C(14')	117.4(3)
O(8')-C(6')-O(6')	102.8(2)	C(18')-C(19')-S(1')	108.6(3)
O(8')-C(6')-C(1')	111.1(3)	C(18')-C(19')-S(2')	115.4(3)
O(6')-C(6')-C(1')	111.0(3)	S(1')-C(19')-S(2')	106.7(2)
O(8')-C(6')-C(5')	114.0(3)	C(21')-C(20')-S(1')	108.7(3)
O(6')-C(6')-C(5')	107.0(3)	C(20')-C(21')-S(2')	109.6(3)
C(1')-C(6')-C(5')	110.6(3)	C(23')-C(22')-C(16')	112.6(3)
C(8')-C(7')-C(1')	113.7(3)	C(23')-C(22')-S(4')	110.6(3)
C(8')-C(7')-C(10')	115.9(3)	C(16')-C(22')-S(4')	109.0(3)
C(1')-C(7')-C(10')	110.0(3)	C(23')-C(22')-S(3')	111.3(3)
O(1')-C(8')-O(2')	122.1(3)	C(16')-C(22')-S(3')	105.8(2)
O(1')-C(8')-C(7')	126.5(3)	S(4')-C(22')-S(3')	107.35(19)
O(2')-C(8')-C(7')	111.4(3)	C(24')-C(23')-C(22')	115.9(3)
C(11')-C(10')-C(4')	112.6(3)	C(25')-C(24')-C(23')	114.3(4)

C(26')-C(25')-C(24')	126.5(5)	C(33')-C(32')-C(31')	117.2(3)
C(25')-C(26')-C(27')	126.4(6)	C(32')-C(33')-C(34')	108.7(4)
C(29')-C(28')-S(3')	108.4(3)	C(35')-C(34')-C(33')	116.6(4)
C(28')-C(29')-S(4')	108.6(3)	C(36')-C(35')-C(34')	124.2(6)
C(3')-C(30')-C(31')	116.2(3)	C(35')-C(36')-C(37')	131.0(8)
C(32')-C(31')-C(30')	110.4(3)		

Symmetry transformations used to generate equivalent atoms:

Table A.6.4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for wood_im03. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	86(1)	44(1)	39(1)	12(1)	-8(1)	12(1)
S(2A)	81(1)	40(1)	25(1)	0(1)	15(1)	12(1)
S(3)	41(1)	26(1)	30(1)	-1(1)	1(1)	2(1)
S(4)	51(1)	36(1)	26(1)	-5(1)	10(1)	4(1)
O(1)	24(2)	55(2)	51(2)	-18(2)	-5(1)	3(1)
O(2)	28(1)	35(2)	32(2)	-11(1)	4(1)	5(1)
O(3)	31(2)	19(1)	39(2)	1(1)	1(1)	0(1)
O(4)	24(1)	24(1)	39(2)	-3(1)	-6(1)	-5(1)
O(5)	27(2)	48(2)	29(2)	1(1)	7(1)	-5(1)
O(6)	20(1)	24(1)	23(1)	-3(1)	1(1)	-1(1)
O(7)	25(1)	13(1)	29(1)	-1(1)	6(1)	4(1)
O(8)	25(1)	20(1)	20(1)	-4(1)	1(1)	-1(1)
C(1)	20(2)	19(2)	22(2)	-2(2)	0(2)	2(1)
C(2)	26(2)	20(2)	25(2)	1(2)	2(2)	0(2)
C(3)	26(2)	18(2)	27(2)	-2(2)	7(2)	0(2)
C(4)	15(2)	20(2)	25(2)	0(2)	-1(2)	1(1)
C(5)	22(2)	16(2)	24(2)	0(2)	2(2)	4(1)
C(6)	25(2)	21(2)	20(2)	-4(2)	5(2)	-2(2)
C(7)	28(2)	15(2)	24(2)	-1(2)	1(2)	1(2)

C(8)	27(2)	19(2)	32(2)	-1(2)	2(2)	5(2)
C(9)	36(2)	39(3)	46(3)	-8(2)	17(2)	3(2)
C(10)	22(2)	17(2)	23(2)	3(2)	4(2)	2(1)
C(11)	26(2)	19(2)	21(2)	0(2)	1(2)	0(2)
C(12)	33(2)	32(2)	54(3)	-6(2)	-1(2)	-16(2)
C(13)	23(2)	19(2)	22(2)	0(2)	1(2)	1(2)
C(14)	23(2)	20(2)	19(2)	1(2)	0(2)	-1(2)
C(15)	26(2)	21(2)	26(2)	-4(2)	3(2)	-1(2)
C(16)	24(2)	26(2)	18(2)	-1(2)	1(2)	2(2)
C(17)	31(2)	30(2)	21(2)	0(2)	2(2)	2(2)
C(18)	33(2)	18(2)	25(2)	0(2)	-2(2)	-1(2)
C(19)	45(3)	50(3)	32(2)	12(2)	5(2)	6(2)
C(20)	89(4)	64(4)	36(3)	16(3)	1(3)	-18(3)
C(21)	107(5)	128(6)	30(3)	21(3)	13(3)	47(5)
C(22)	28(2)	24(2)	23(2)	-3(2)	1(2)	3(2)
C(23)	33(2)	33(2)	33(2)	-12(2)	-9(2)	4(2)
C(24)	39(3)	41(3)	36(2)	-11(2)	-11(2)	6(2)
C(25)	43(3)	65(4)	120(6)	-50(4)	-27(3)	9(3)
C(26)	59(4)	93(5)	166(8)	-81(5)	-42(5)	21(4)
C(27)	41(3)	80(4)	83(4)	-34(3)	-20(3)	15(3)
C(28)	70(3)	27(2)	39(3)	-9(2)	5(2)	11(2)
C(29)	51(3)	46(3)	39(3)	-8(2)	9(2)	14(2)
C(30)	28(2)	24(2)	32(2)	3(2)	3(2)	-3(2)
C(31)	40(2)	34(2)	35(2)	3(2)	11(2)	2(2)
C(32)	38(2)	38(2)	42(3)	14(2)	5(2)	-8(2)
C(33)	52(3)	43(3)	43(3)	13(2)	18(2)	0(2)
C(34)	59(3)	49(3)	55(3)	22(2)	24(3)	-4(2)
C(35)	45(3)	48(3)	52(3)	21(3)	7(2)	-3(2)
C(36)	52(3)	57(3)	53(3)	15(3)	1(3)	-3(3)
C(37)	65(4)	68(4)	58(3)	11(3)	2(3)	9(3)
S(1')	27(1)	26(1)	50(1)	3(1)	-3(1)	3(1)
S(2')	28(1)	49(1)	113(1)	38(1)	16(1)	4(1)
S(3')	32(1)	25(1)	47(1)	7(1)	5(1)	1(1)
S(4')	26(1)	42(1)	51(1)	12(1)	11(1)	1(1)
O(1')	67(2)	61(2)	30(2)	-9(2)	11(2)	-29(2)
O(2')	47(2)	35(2)	31(2)	-4(1)	12(1)	-19(1)

O(3')	34(2)	16(1)	26(1)	0(1)	2(1)	0(1)
O(4')	42(2)	20(1)	22(1)	1(1)	-4(1)	-6(1)
O(5')	29(2)	41(2)	26(1)	-4(1)	8(1)	4(1)
O(6')	23(1)	21(1)	23(1)	-2(1)	3(1)	-1(1)
O(7')	29(2)	16(1)	27(1)	3(1)	5(1)	-4(1)
O(8')	19(1)	23(1)	30(1)	-4(1)	6(1)	-4(1)
C(1')	23(2)	16(2)	24(2)	1(2)	0(2)	-1(1)
C(2')	22(2)	22(2)	29(2)	4(2)	2(2)	5(2)
C(3')	24(2)	17(2)	24(2)	1(2)	6(2)	1(2)
C(4')	23(2)	18(2)	22(2)	0(2)	5(2)	1(2)
C(5')	27(2)	12(2)	21(2)	4(1)	1(2)	0(1)
C(6')	21(2)	20(2)	21(2)	-2(2)	5(2)	-4(2)
C(7')	21(2)	19(2)	24(2)	0(2)	1(2)	1(2)
C(8')	32(2)	23(2)	21(2)	2(2)	1(2)	0(2)
C(9')	66(3)	49(3)	38(3)	-4(2)	24(2)	-22(2)
C(10')	24(2)	17(2)	21(2)	1(1)	1(2)	0(2)
C(11')	25(2)	20(2)	19(2)	-1(2)	5(2)	-1(2)
C(12')	50(3)	23(2)	26(2)	-5(2)	-7(2)	-9(2)
C(13')	24(2)	16(2)	29(2)	3(2)	2(2)	-2(2)
C(14')	25(2)	16(2)	24(2)	2(2)	5(2)	2(2)
C(15')	28(2)	14(2)	24(2)	0(2)	2(2)	2(2)
C(16')	25(2)	24(2)	26(2)	1(2)	4(2)	2(2)
C(17')	24(2)	28(2)	32(2)	0(2)	5(2)	0(2)
C(18')	21(2)	19(2)	30(2)	-1(2)	0(2)	-2(2)
C(19')	29(2)	29(2)	36(2)	-2(2)	1(2)	5(2)
C(20')	28(2)	46(3)	54(3)	-3(2)	-2(2)	13(2)
C(21')	28(2)	49(3)	73(4)	1(3)	0(2)	-3(2)
C(22')	21(2)	26(2)	37(2)	3(2)	4(2)	-3(2)
C(23')	28(2)	30(2)	42(2)	2(2)	2(2)	-6(2)
C(24')	43(3)	38(3)	42(3)	4(2)	-3(2)	-16(2)
C(25')	55(3)	49(3)	45(3)	6(2)	-9(2)	-21(2)
C(26')	73(4)	84(4)	49(3)	3(3)	1(3)	-31(3)
C(27')	110(5)	140(6)	41(3)	-3(4)	0(3)	-68(5)
C(28')	47(3)	40(3)	61(3)	22(2)	9(2)	0(2)
C(29')	61(3)	50(3)	52(3)	17(2)	18(3)	3(2)
C(30')	28(2)	20(2)	27(2)	2(2)	6(2)	0(2)

C(31')	30(2)	22(2)	31(2)	1(2)	6(2)	1(2)
C(32')	38(2)	31(2)	39(2)	-7(2)	13(2)	0(2)
C(33')	50(3)	37(3)	43(3)	-4(2)	14(2)	11(2)
C(34')	71(4)	46(3)	59(3)	-12(3)	17(3)	13(3)
C(35')	53(3)	43(3)	96(5)	-15(3)	23(3)	5(2)
C(36')	71(4)	55(4)	156(7)	-39(4)	59(4)	-7(3)
C(37')	119(6)	92(5)	166(8)	-70(5)	68(6)	-29(5)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for wood_im03.

	x	y	z	U(eq)
H(1)	7780(20)	1370(30)	2080(20)	56(15)
H(1A)	6578	3639	1345	25
H(2A)	7436	4252	946	29
H(3A)	8319	3045	1285	28
H(4A)	8516	3256	2354	24
H(7A)	7231	4760	1856	27
H(9A)	6402	5398	3607	59
H(9B)	5956	4677	3278	59
H(9C)	6012	5591	2959	59
H(12A)	9454	5200	3291	60
H(12B)	8857	5745	3388	60
H(12C)	9093	5730	2736	60
H(13A)	8042	3508	3373	26
H(13B)	7316	3689	3268	26
H(16A)	7731	1929	981	27
H(17A)	6899	3164	375	33
H(17B)	7611	3064	305	33
H(18A)	7955	1337	3043	31
H(18B)	8365	2104	3348	31
H(19A)	7330	1403	3817	51

H(20A)	7894	516	5145	77
H(20B)	8504	1085	5291	77
H(21A)	7877	2111	5433	106
H(21B)	7302	1628	5062	106
H(23A)	6129	1784	467	41
H(23B)	6352	2163	-135	41
H(24A)	6242	730	-571	48
H(24B)	5934	443	11	48
H(25A)	5458	1611	-880	95
H(26A)	4826	766	-236	134
H(27A)	3957	1261	-642	107
H(27B)	4236	1391	-1267	107
H(27C)	4283	2148	-774	107
H(28A)	7632	-730	405	54
H(28B)	7089	-410	-103	54
H(29A)	7993	81	-415	54
H(29B)	8230	458	249	54
H(30A)	8335	4853	1514	34
H(30B)	8932	4260	1656	34
H(31A)	8277	4478	460	43
H(31B)	8897	3939	614	43
H(32A)	8835	5763	775	47
H(32B)	9453	5210	886	47
H(33A)	8730	5375	-284	54
H(33B)	9377	4894	-159	54
H(34A)	9862	6240	128	63
H(34B)	9553	6230	-568	63
H(35A)	8714	7076	-275	58
H(36A)	9662	7539	602	65
H(37A)	9144	8701	837	96
H(37B)	8522	8172	656	96
H(37C)	8810	8715	150	96
H(1')	2026(19)	2390(30)	2835(19)	41(14)
H(1'A)	1321	4535	1519	25
H(2'A)	927	5239	2339	29
H(3'A)	1283	4148	3290	26

H(4'A)	2365	4321	3447	25
H(7'A)	1843	5720	2124	26
H(9'A)	3413	6635	1221	75
H(9'B)	2802	6424	766	75
H(9'C)	3306	5691	940	75
H(12D)	3467	6183	4268	51
H(12E)	2888	6723	3959	51
H(12F)	3509	6715	3658	51
H(13C)	3219	4610	2163	28
H(13D)	3397	4521	2888	28
H(16B)	986	2987	2789	30
H(17C)	280	4106	2603	34
H(17D)	335	4098	1889	34
H(18C)	3395	3185	3324	29
H(18D)	3067	2361	3001	29
H(19B)	3794	2304	2317	38
H(20C)	5372	1871	3287	52
H(20D)	5032	1790	2601	52
H(21C)	5432	3137	2623	61
H(21D)	5268	3321	3295	61
H(23C)	-133	2971	1416	40
H(23D)	422	2402	1242	40
H(24C)	-179	1142	1373	50
H(24D)	-741	1759	1465	50
H(25B)	-759	2222	421	61
H(26B)	-293	589	372	83
H(27D)	-585	554	-647	147
H(27E)	-471	1569	-657	147
H(27F)	-1130	1202	-556	147
H(28C)	-46	531	2581	59
H(28D)	526	458	3112	59
H(29C)	335	1786	3488	64
H(29D)	-322	1321	3372	64
H(30C)	1610	5915	3195	30
H(30D)	1687	5387	3817	30
H(31C)	525	5828	3134	33

H(31D)	593	5269	3747	33
H(32C)	994	6402	4326	42
H(32D)	1111	6942	3741	42
H(33C)	-46	6687	4151	51
H(33D)	21	7129	3509	51
H(34C)	620	7773	4654	70
H(34D)	647	8225	4012	70
H(35B)	-424	8583	4000	75
H(36B)	51	8567	5228	108
H(37D)	-656	9317	5503	182
H(37E)	-1112	8922	4949	182
H(37F)	-731	9775	4851	182

Appendix 7

Notebook Cross Reference.

The following notebook cross reference has been included to facilitate access to the original spectroscopic data obtained for the compounds presented in this work. For each compound a folder name is given (e.g., IMMC-XX) which corresponds to an original notebook reference. For each spectrum a code (i.e.: H for ^{1}H NMR, C for ^{13}C NMR and IR for FTIR) and a number are given. The notebook, spectral data and disks are stored in the Wood Group archives.

Table A.7.1 Compounds Appearing in Chapter 3.

Compound	Notebook	^{1}H NMR	^{13}C NMR	FTIR
198	TSI-38	198H	198C	48IR
213a/213b	TS-78	213a/bH	213a/bC	88bIR
215	TSII-118	215H	215C	34IR
216	TSII-118	216H	216C	72IR
217	IMMIV-180	195H	195C	40IR
218	IMMIV-250	218H	218C	50IR
219	IMMIV-183	219H	219C	42IR
220	NTII-98	220H	220C	92bIR
221	NTII-98	221H	221C	74IR
245	TSII-142	245H	245C	52IR

246	TSII-142	246H	246C	54IR
248	IMMIV-189	248H	248C	44dIR
249a	IMMIV-251	249aH	249aC	38IR
249b	IMMIV-251	249bH	249bC	31IR
250a	IMMIV-252	250aH	250aC	36IR
250b	IMMIV-252	250bH	250bC	124IR
247	TSII-102	247H	247C	32IR
251a	TSII-168	251aH	251aC	56bIR
251b	TSII-168	251bH	251bC	68IR
255	TSII-186	255H	255C	60IR
256	TSII-182	256H	256C	60IR
260	TSII-214	260H	260C	94bIR
265	IMMIV-259	265H	265C	82IR
266	IMMIV-259	266H	266C	96cIR

Table A.7.2 Compounds Appearing in Chapter 4.

Compound	Notebook	^{1}H NMR	^{13}C NMR	FTIR
276	TSII-260	276H	276C	270IR
294	IMMIV-243	294H	294C	294IR
295	IMMIV-259	295H	295C	266bIR

Table A.7.3 Compounds Appearing in Chapter 5.

Compound	Notebook	^{1}H NMR	^{13}C NMR	FTIR
300	NTII-294	300H	300C	80cIR
302	IMMV-293	302H	302C	64IR

301	IMMV-218	301H	301C	301IR
305	IMMV-295	305H	305C	66IR
306	IMMV-299	306H	306C	70IR
307	IMMVI-71	307H	307C	90gIR
310	IMMVI-72	310H	310C	100IR
311	IMMVI-85	311H	311C	104eIR
312	IMMVI-86	312H	312C	312eIR
314	IMMVI-155	314H	314C	314eIR
316	TSIII-88	316H	316C	122IR
317	TSIII-92	317H	317C	317IR
318	TSIII-92	318H	318C	318IR

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About the Author

Ivar Michael McDonald was born August 22, 1977 in Putnam, Connecticut to Dennis McDonald and Ida Berris. Ivar grew up in the neighboring towns of Brooklyn and Killingly, Connecticut, attending the public school systems of both towns, graduating from Killingly High School in June of 1995.

Following high school, the author attended Boston University, where he earned his B.A. degree in Chemistry in 1999, graduating *summa cum laude* .

In the fall of 1999 he started his studies towards a doctoral degree in chemistry at Yale University. In the spring of 2000 he joined the research group of professor John L. Wood, and has spent his time in the Wood group focusing on the total synthesis of the phomoidrides.

The author has accepted a position as a drug discovery chemist at Bristol-Myers Squibb in Wallingford, Connecticut. Following graduation in May 2005, the author will marry his long-time sweetheart Kate Stellitano.