DISSERTATION


SYNTHETIC APPROACH TOWARDS CEPHALEZOMINE A AND

PHOMOIDRIDE D



Submitted by

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ABSTRACT

SYNTHETIC APPROACH TOWARDS CEPHALEZOMINE A AND

PHOMOIDRIDE D

Two synthetic approaches towards cephalezomine A and phomoidride D are described separately.

The first approach towards cephalezomine A invented a new method for the synthesis of 3-butoxy-1-chlorobutenone and successful constructed α-$O$ and ß$^{'}$-$N$ disubstituted dienone for a designed key intermediate of cascade cyclization by Eschenmoser coupling of thiolactam and 3-butoxy-1-chlorobutenone.

The second approach towards phomoidride D systematically studied the electronic effects of different ester substituents for the phenolic oxidation and inverse electron demand Diels-Alder reaction, which resulted in the synthesis of functionalized bicyclic [2.2.1] intermediate. Base on this, a new route for the synthesis of precursor of Grob fragmentation has been established towards the total synthesis of phomoidride D by samarium diiodide mediated radical cascade cyclization.

To my parents and friends

# Acknowledgments

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# List of Abbreviations

| | |
|---|---|
| AcOH | acetic acid |
| aq. | aqueous |
| Bn | benzyl |
| BTIB | bis(trifluoroacetoxy)-iodobenzene |
| Bu | butyl |
| C | carbon |
| ºC | degree Celsius |
| calcd' | calculated |
| CDCl$_3$ | chloroform-*d* |
| CH$_2$N$_2$ | diazomethane |
| CH$_3$CN | acetonitrile |
| CHCl$_3$ | chloroform |
| *m*-CPBA | 3-chloroperoxybenzoic acid |
| δ | chemical shift in ppm downfield from Me$_4$Si |
| DCM | dichloromethane |
| DCE | dichloroethane |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DCC | 1,3-dicyclohexylcarbodiimide |
| dd | doublet of doublets |
| ddd | doublet of doublets of doublets |
| DDQ | 2,3-dichloro-5,6-dicyanobenzoquinone |
| DEAD | diethyl azodicarboxylate |
| DIBAL-H | diisobutylaluminum hydride |
| DIEA | N,N-diisopropylethylamine |
| DMAP | 4-(dimehylamino)pyridine |
| DMF | dimethyl formamide |

| | |
|---|---|
| DMSO | dimethyl sulfoxide |
| dt | doublet of triplets |
| equiv. | equivalent |
| Et | ethyl |
| Et$_2$O | ethyl ether |
| EtOAc | ethyl acetate |
| Et$_3$N | triethylamine |
| FTIR | Fourier transform infrared |
| g | gram(s) |
| h | hours |
| H | Hydrogen |
| Hz | Hertz |
| HCl | Hydrochloric acid |
| KHMDS | potassium bis(trimethylsilyl) amide |
| HMPA | hexamethylphosphoric triamide |
| HRMS | high-resolution mass spectrum |
| *J* | coupling constant |
| L | liter(s) |
| LAH | lithium aluminum hydride |
| LDA | lithium diisopropylamide |
| Lawesson's reagent | 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane2,4-disulfide |
| LiOH | lithium hydroxide |
| μ | micro |
| m | milli, multiplet(NMR) |
| M | moles per liter |
| Me | methyl |
| MeOH | methanol |

| | |
|---|---|
| mol | moles |
| MS | mesylate |
| *m/z* | mass to charge ratio |
| NMO | 4-methylmorpholine N-oxide |
| NMR | nuclear magnetic resonance |
| Ns | nosylate (2-nitrobenzenesulfonate) |
| O | oxygen |
| OAC | acetate |
| PivCl | pivaloyl Chloride |
| PMB | *p*-methoxybenzyl |
| PPh$_3$ | triphenylphosphine |
| PTSA | *p*-Toluenesulfonic acid |
| py. | pyridine |
| q | quartet |
| SmI$_2$ | samarium diiodide |
| t | triplet |
| td | triplet of doublets |
| TBAF | tetrabutylammounium fluoride |
| TBS | *ter*t-butyldimethylsilyl |
| TBSOTf | *ter*t-butyldimethylsilyl trifluomethylsulfonate |
| Tf$_2$O | triflic anyhydride |
| THF | tertrahydrofuran |
| TLC | thin layer chromatography |
| TMS | trimehtylbutylsilyl |
| TMSOTf | trimethylbutylsilyl trifluomethylsulfonate |
| TPAP | trimethylpropyl ammonium perruthenate |

# Chapter 1


# Cephalezomine A Chemistry and Biology


## 1.1 Background and Introduction


## 1.1.1 Cephalezomines: Isolation and Structural Characterization

In 2000, Jun'ichi Kobayashi and co-workers reported the isolation and structural elucidation of cephalezomines A-F (**1-6**) from the leaves of *Cephalotaxus harringtonine var nana* in Japan (**Figure 1.1.1.1**).[1] Additional compounds, cephalezomines G-M (**7-12**) and bis- cephalezomines A-E (**13-17**), were isolated and structure elucidated by the same group in 2002 and 2004.[2,3]

*Figure 1.1.1.1 Cephalezomines Natural Products*
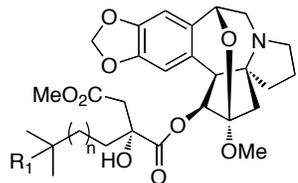
**Cephalezomine A-B**

**1**: n=2, R$_1$=OH, **A**
**2**: n=2, R$_1$= H, **B**
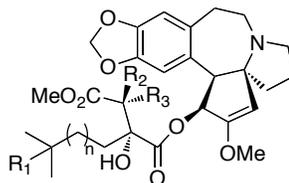
**Cephalezomine C-F**

**3**: n=1, R$_1$=OH, R$_2$=OH, R$_3$=H; **C**
**4**: n=1, R$_1$=OH, R$_2$=H, R$_3$=OH; **D**
**5**: n=2, R$_1$=OH, R$_2$=OH, R$_3$=H; **E**
**6**: n=2, R$_1$= H, R$_2$=OH, R$_3$=H; **F**
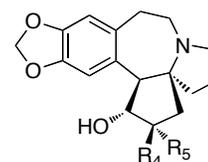
**Cephalezomine G-H**

**7**: R$_4$=H, R$_5$=OH, **G**
**8**: R$_4$=OH, R$_5$=H, **H**
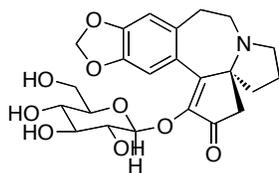
**9**: Cephalezomine J
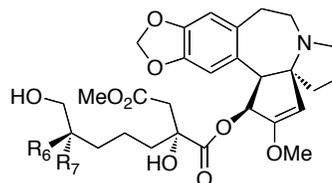
**Cephalezomine K-L**

**10**: R$_6$=OH, R$_7$=H, **K**
**11**: R$_6$=H, R$_7$=OH, **L**
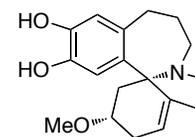
**12**: Cephalezomine M
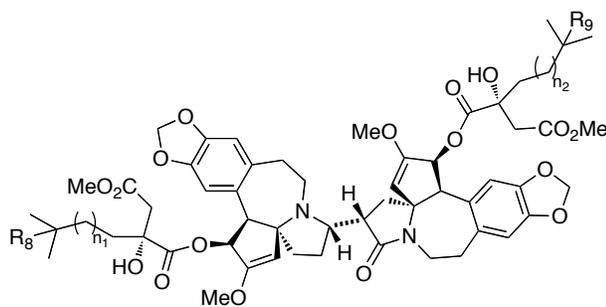
**Bis Cephalezomine A-E**

**13**: n$_1$=2, n$_2$=1, R$_8$=R$_9$=OH, **Bis-A**
**14**: n$_1$=1, n$_2$=2, R$_8$=R$_9$=OH, **Bis-B**
**15**: n$_1$=n$_2$=1, R$_8$=R$_9$=OH, **Bis-C**
**16**: n$_1$=2, n$_2$=1, R$_8$=OH,R$_9$=H, **Bis-D**
**17**: n$_1$=1, n$_2$=2, R$_8$=H,R$_9$=OH, **Bis-E**

Cephalezomines are members of the *Cephalotaxus* alkaloid family found in higher plants of the genus *Cephalotexus*.[4] Structurally related *Cephalotaxus* alkaloids are known as drupacine (**18**),[5] cephalotaxine (**19**),[6] 11-hydroxycephalotaxine (**20**),[5] harringtonine (**21**),[7] deoxyharringtonine (**22**)[7] and homoharringtonine (**23**)[7] (**Figure 1.1.1.2**). Some of the latter, such as **21**, **22** and **23**, display potent antileukemic activity

upon intraperitoneal injection in mice.[8] Recently, clinical studies of *Cephalotaxus* alkaloids in China have shown that intravenous administration can affect various types of acute leukemia.[9, 10]

*Figure 1.1.1.2 Cephalotexus alkaloids*



**18**: **Drupacine**

**19**: **Cephalotaxine**

**20**:**11-Hydroxycephalotaxine**

**21**: n=1, R=OH; **Harringtonine**
**22**: n=1, R=H;   **Deoxyharringtonine**
**23**: n=2, R=OH; **Homoharringtonine**
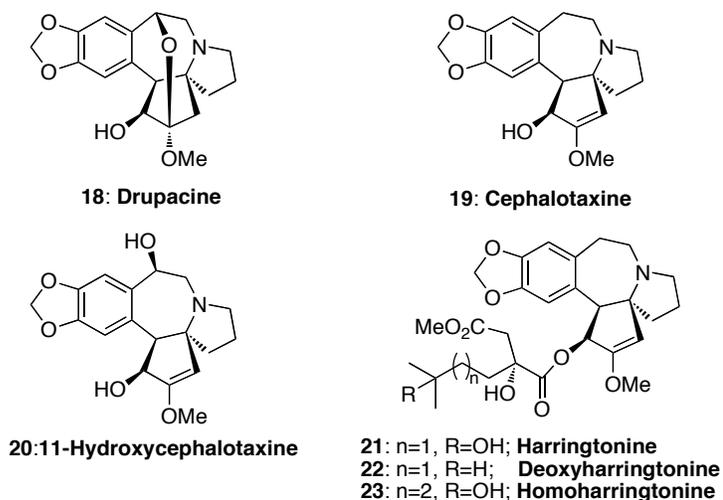
## 1.1.2 *Cephalotexus* Alkaloids Biosynthesis

Ronald Parry and co-workers have utilized the method of isotope-labeled precursor incorporation to study the biosynthesis of the *Cephalotexus* Alkaloids in *Cephalotaxus harringtonia*.[11] It had been established that in the early stage of biosynthesis (from **24**, **25** to **28**), cephalotaxine is biosynthesized from one molecule each of tyrosine (**24**) and phenylalanine (**25**) (**Scheme 1.1.2.1**). The hypothesis predicted that cephalotaxine should come from **24** and **25** via a 1-phenethyltetrahydroisoquinoline derivative (**26**), oxidative phenol coupling product (**27**) and dienone (**28**). This hypothesis is based on results obtained while investigating the biosynthesis of colchicine.[12] In the late stage of biosynthesis (from **28** to **19**), loss of one carbon atom from dienone (**28**) *via*

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a ring contraction formed the D ring of cephalotaxine. It has been suggested that the ring

contraction of **28** might result from a benzilic acid rearrangement.[13]


*Scheme 1.1.2.1 Cephalotaxine Biosynthesis*
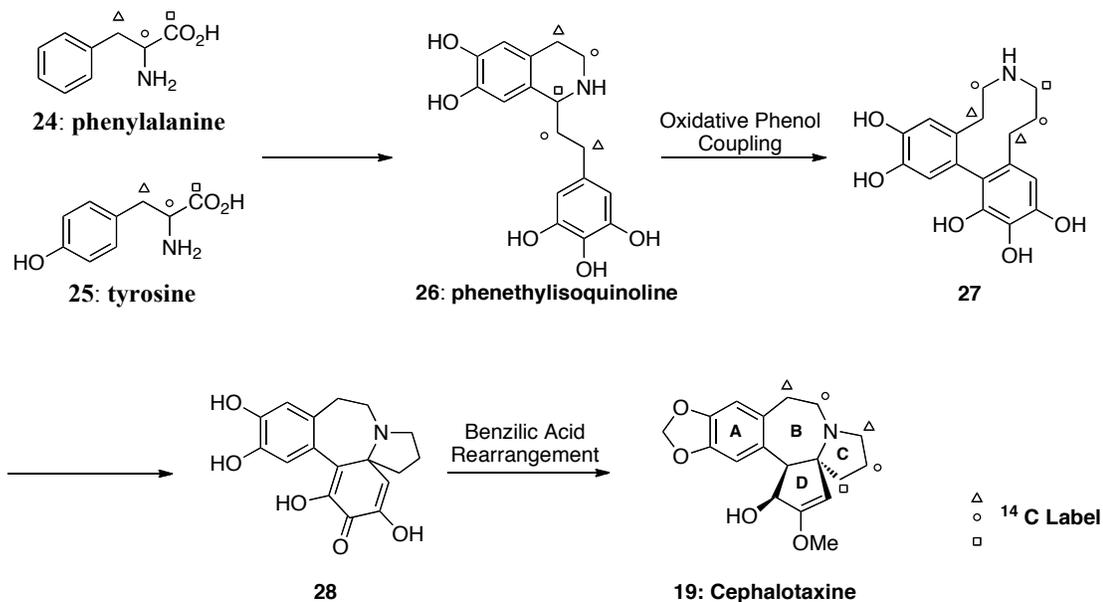


The biosynthesis of the acyl side chain of deoxyharringtonine (**21**) was proposed

to involve a pathway that begins with leucine (**29**) (**Scheme 1.1.2.2**).[14] Diacid (**31**) should

be an intermediate in the biosynthesis of the acyl side chain of deoxyharringtonine (**36**)

and carbon atoms (3-8) of diacid (**31**) should be derived from leucine. This hypothesis

was supported by the isolation of labeled **31** by feeding ^{14}C leucine (**29**) to *Cephalotaxus*

*harringtonia*. The latter ^{14}C experiment also indicated that diacid **33** lies on the

biosynthetic pathway to **36**.

*Scheme 1.1.2.2 Acyl Side Chain of Deoxyharringtonine Biosynthesis*
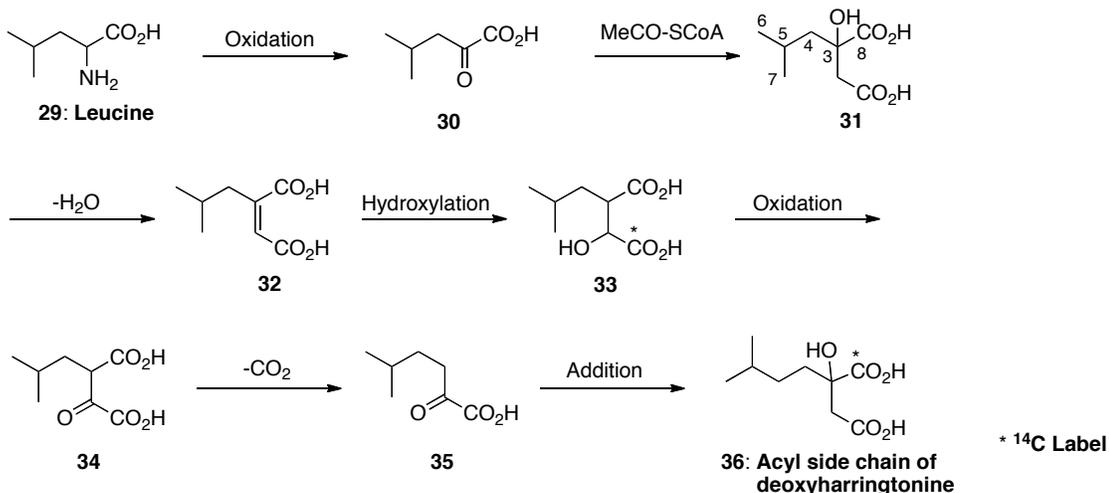


The $^{14}$C labeling experiment also clearly established that the acyl side chain of harringtonine is derived *in vivo* from the acyl side chain of deoxyharringtonine, probably by direct oxidative hydroxylation (**Scheme 1.1.2.3**). The acyl side chain of homoharringtonine was predicted to be derived by homologation of the acyl side chain of deoxyharringtonine with subsequent oxidative hydroxylation.

*Scheme 1.1.2.3 Acyl Side Chains of Harringtonine and Homoharringtonine Biosynthesis*
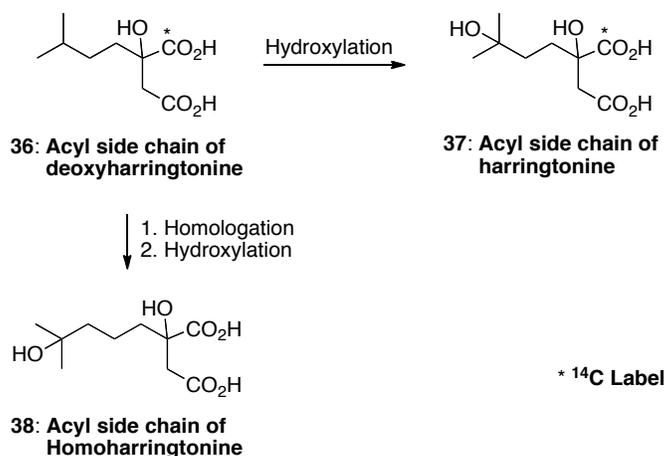
## 1.1.3 Biological Activity of the Cephalezomines

Several members of cephalezomine family display potent biological activity. The cytotoxicity of cephalezomines A-M and bis-cephalezomines A-E is shown in **Table 1.1.3**.[1,2,3] In general, monomeric cephalezomines display greater potency than the dimeric ones. This study also showed that cephalotaxine-type compounds lacking either the side chain acid or sugar moiety exhibit weak cytotoxicity.[1]

*Table 1.1.3 Cytotoxicity of Cephalezomines*

| Compound | IC$_{50}$ ($\mu$g/mL) | | Compound | IC$_{50}$ ($\mu$g/mL) | |
|---|---|---|---|---|---|
| | L1210 | KB | | L1210 | KB |
| A | 0.067 | 0.020 | K | 1.2 | 0.036 |
| B | 0.030 | 0.024 | L | 3.6 | 0.044 |
| C | 0.88 | 0.078 | M | >30 | 13 |
| D | 7.6 | 0.40 | Bis-A | 1.9 | |
| E | 0.68 | 0.18 | Bis-B | 1.9 | |
| F | 0.10 | 0.084 | Bis-C | 2.6 | |
| G | 8.0 | >30 | Bis-D | 3.1 | |
| H | 8.6 | >30 | Bis-E | 3.7 | |
| J | 12 | 5.6 | | | |

## 1.2 Cephalezomine A: Structure and Synthesis

## 1.2.1 Structural Features

The structure of cephalezomine A (**1**) contains a drupacine-type skeleton and an acyl side chain (**Figure 1.2.1**). It is known that drupacine derives from 11-hydroxycephalotaxine (**20**).[6] In terms of reported syntheses towards cephalezomine A (**1**),

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the descriptions below will focus on two parts: the acyl side chain and heterocyclic core (11-oxidized-cephalotaxine-type skeleton).

*Figure 1.2.1 Cephalezomine A Structure Features*



**1**: Cephalezomine A
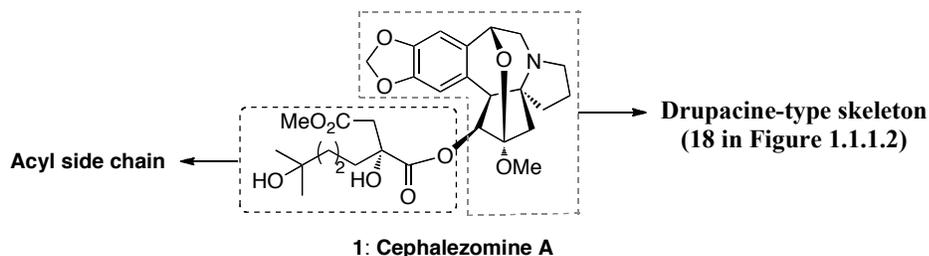
## 1.2.2 Synthetic Routes to Related Acyl Side Chains

In 1973, Weinreb and co-workers reported the synthesis of the acid side chain of deoxyharringtonine (**Scheme 1.2.2.1**).[15] First, epoxidation of benzylmethylitaconate **41** by *m*-CPBA gave epoxide **42**. Treatment with an organo-copper reagent prepared from isobutyl lithium **43** and cuprous iodide produced tertiary alcohol **44**. Finally, hydrogenolysis of benzyl ester **44** using Adams' catalyst produced acid **45**.

*Scheme 1.2.2.1 Weinreb's Procedure for the Synthesis of Acid Side Chain*
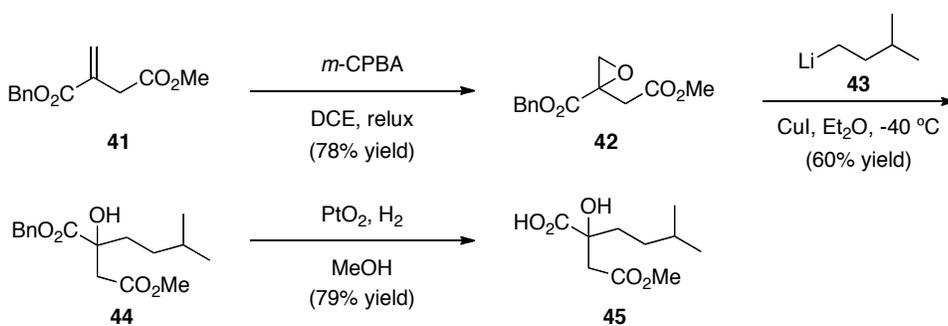
In 1982, Hudlicky and co-workers reported the synthesis of homoharringtonine (**23**) commencing with cephalotaxine (**19**).[16] During the synthesis, they described the preparation of acyl side chain (**Scheme 1.2.2.2**). Ozonolysis of methylcyclohexene **46** gave an intermediate ketoaldehyde which was subjected to an intramolecular aldol condensation, followed by oxidation of the resultant aldehyde to acid **47**. Ozonolysis of **47** gave the ketopyruvate **48**. Generation of the acid chloride from substrate **48**, followed by exposure to cephalotaxine formed cephalotaxine ester **49**. This ester was difficult to purify by chromatography due to decomposition, therefore no yield was reported. To this crude intermediate was added the zinc reagent derived from methyl bromoacetate, followed by treatment with MeLi or MeMgBr to produce homoharringtonine (**23**).

*Scheme 1.2.2.2 Hudlicky's Procedure for the Synthesis of Acid Side Chain*
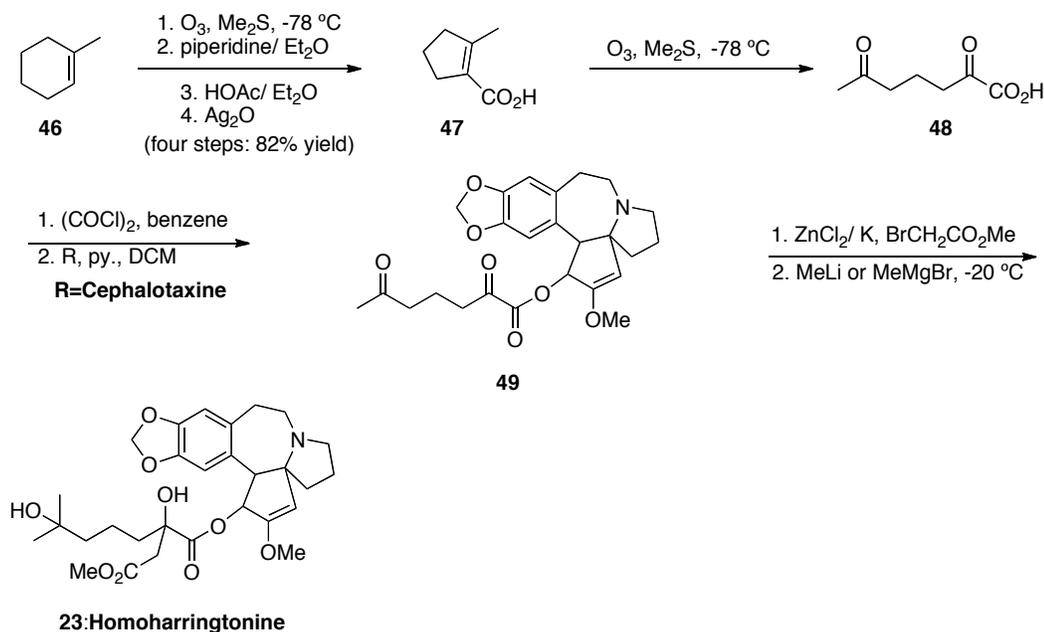


In 2006, as part of reported total synthesis of (-)-deoxyharringtonine (**22**), Gin described the preparation of the acyl side chain (**Scheme 1.2.2.3**).[17] Commencing with

commercially available *D*-malic acid **50**, acetal **51** was afforded in a two-step procedure. Alkylation of **51** followed by acetal opening gave γ-hydroxy acid **52**. Lactone **53** was produced *via* Yamaguchi lactonization[18] followed by alkene hydrogenation and removal of benzyl group. Coupling of **53** with cephalotaxine *via* the Yamaguchi protocol yielded ester **54**. Methanolysis concluded the synthesis of (-)-deoxyharringtonine (**22**).

*Scheme 1.2.2.3 Gin's Procedure for the Synthesis of Acid Side Chain*
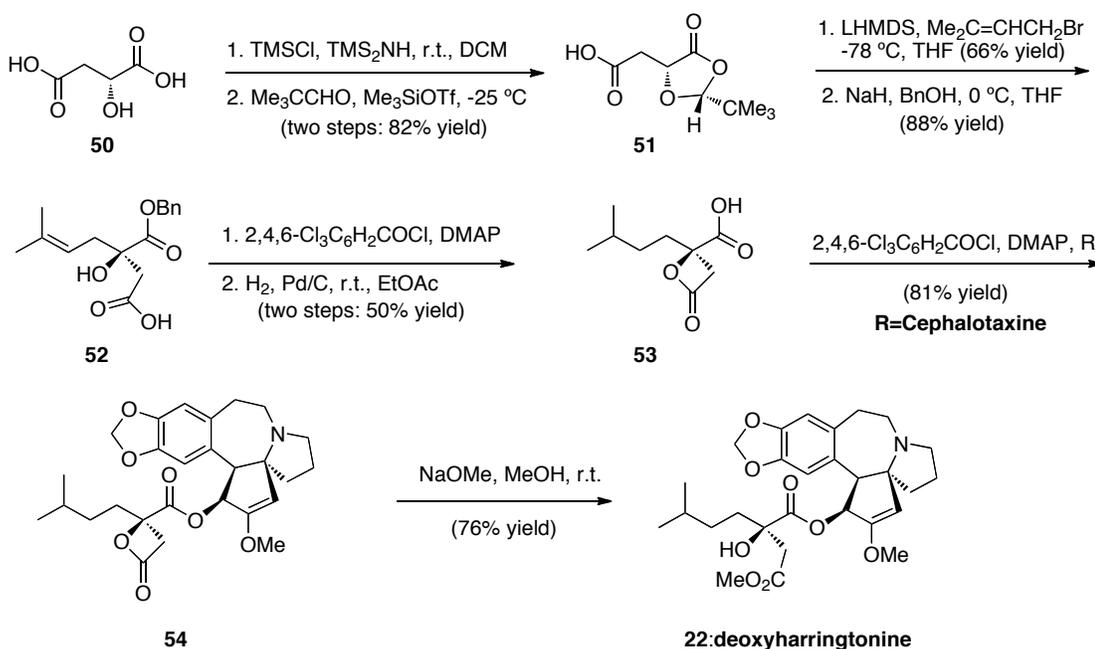


## 1.2.3 Synthetic Routes to the Tetracyclic Core of Cephalezomine A

The significant anticancer activities and intriguing chemical structures have made the *Cephalotaxus* alkaloids attractive targets for synthetic chemists. Since the report of the first total synthesis of cephalotaxine by Weinreb and Semmelhack in 1972,[19,20] a number of innovative synthetic strategies have been developed towards the synthesis of the cephalotaxine core ring system. One of the most commonly employed strategic

approaches involves forming the B-ring of cephalezomine A core ring system (**55**) from an *N*-spirocyclic intermediate (**56**, **Scheme 1.2.3.1**).

*Scheme 1.2.3.1 B Ring Closure of a N-Spiro Cyclic Precursor*



**55**: Cephalezomine A core ring          **56**: N-Spiro intermediate
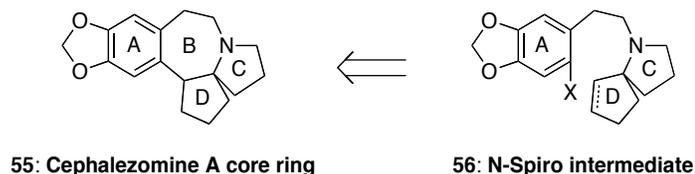
Typical B ring closure approaches include Friedel-Crafts- and Heck-type cyclization strategies.

 *Kuehne's total synthesis of dl-cephalotaxine*: Lactam **57** was ring-contracted to the spiro C, D ring of **58** in the presence of Pb(OAc)$_4$ (**Scheme 1.2.3.2**). Further transformation of **58** furnished acetate **59** which was utilized as substrate in the illustrated palladium mediated coupling to furnish the B-ring of **60**.[21]

*Scheme 1.2.3.2 Friedel-Crafts Cyclization for B Ring Closure: Kuehne's Work*
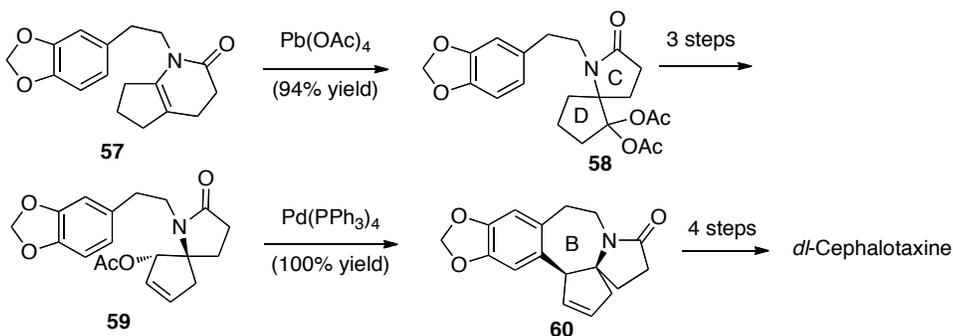


 *Sha's approach towards total synthesis of dl-cephalotaxine*: An intramolecular cyclization of **61** in the presence of PTSA gave the spiro C, D ring of **62** (**Scheme**

**1.2.3.3**). Ozonolysis, followed by deprotection produced **63**, which, upon alkylation, provided cyclization precursor **64**. Friedel-Crafts cyclization in the presence of polyphosphoric acid completed the construction of **65**.[22]

*Scheme 1.2.3.3 Friedel-Crafts Cyclization for B Ring Closure: Sha's Work*
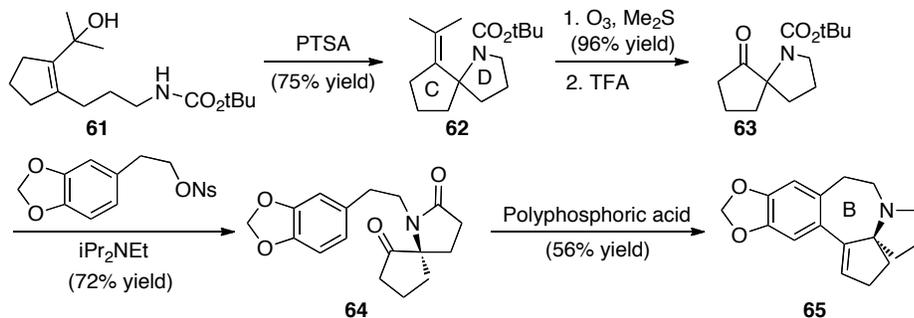


*Mori's total synthesis of (-)-cephalotaxine*: Vinyl iodide **66** was cyclized in the presence of Me$_3$SiSnBu$_3$ and CsF to form the spirocyclic C, D-ring system in allylic alcohol **67** (**Scheme 1.2.3.4**). The B-ring of **68** was closed by Friedel-Crafts cyclization in the presence of polyphosphoric acid.[23]

*Scheme 1.2.3.4 Friedel-Crafts Cyclization for B Ring Closure: Mori's Work*
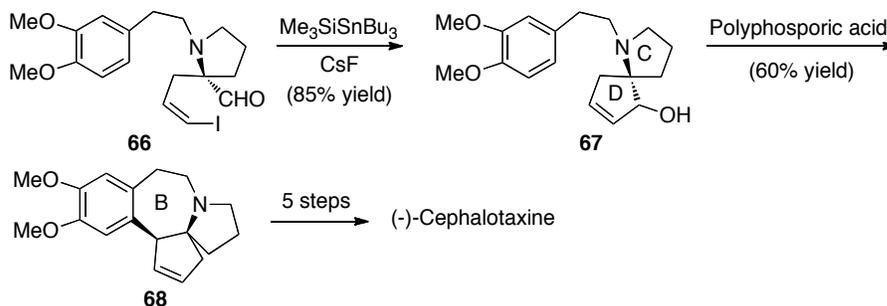
*Royer's total synthesis of (-)-cephalotaxine*: Expansion of the cyclobutane ring in **69** under acidic conditions gave ketone **70** which possesses the spirocyclic C, D-ring system (**Scheme 1.2.3.5**). This substrate was further advance to allylic alcohol **71** which upon exposure to the Lewis acid SnCl₄ underwent B-ring closure to furnish **72**.[24]

***Scheme 1.2.3.5 Friedel-Crafts Cyclization for B Ring Closure: Royer's Work***
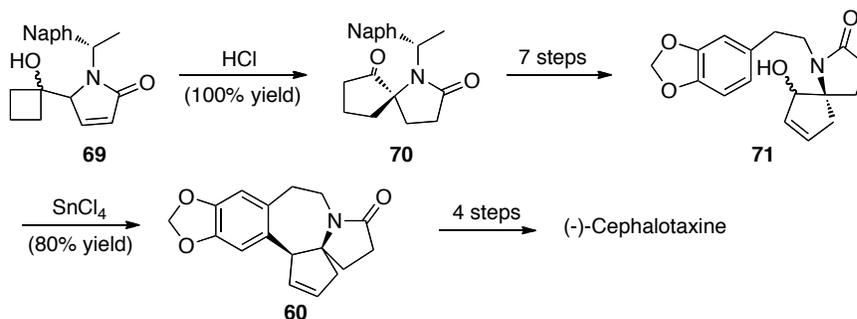


*Li's formal total synthesis of dl-cephalotaxine*: The Li group reported that Friedel-Crafts type alkylation occurs upon exposure of **72** to TfOH and forms ketone **73** which, in five steps can be converted to cephalotaxine (**Scheme 1.2.3.6**).[25]

***Scheme 1.2.3.6 Friedel-Crafts Cyclization for B Ring Closure: Li's Work***
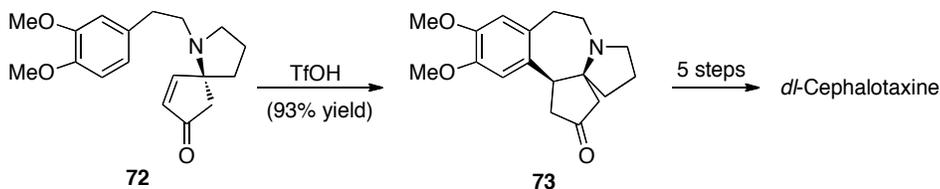


*Hayes's first formal total synthesis of (-)-cephalotaxine*: Hayes reported that treatment of **74** with deprotonated TMSCHN₂ furnishes carbene intermediate **75**, which undergoes intramolecular C-H insertion to give the spirocyclic C, D-ring system in **76**

(**Scheme 1.2.3.7**). Further transformation of **76** produces an allylic alcohol (**78**) which, upon exposure to Lewis acid SnCl₄ undergoes B-ring closure to produce **68**.[26]

*Scheme 1.2.3.7 Friedel-Crafts Cyclization for B Ring Closure: Hayes's Work*
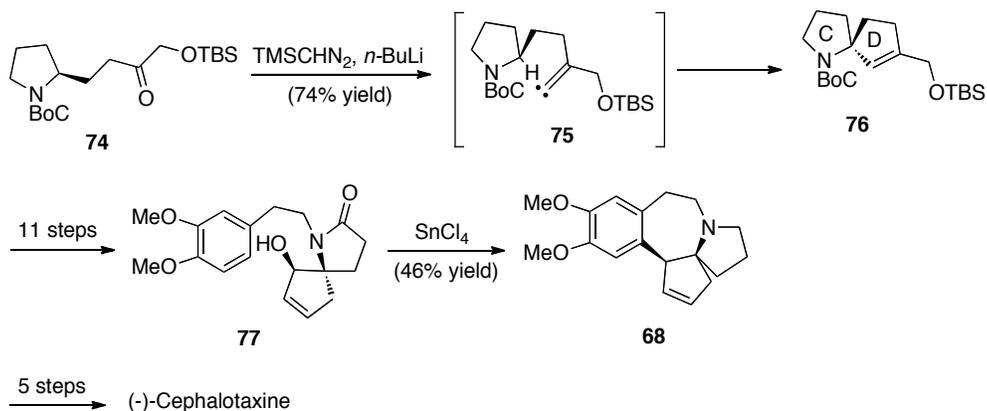


*Hayes's second formal total synthesis of (-)-cephalotaxine*: An intramolecular C-H insertion of the vinyl carbene derived from vinyl chloride **78** produced the spirocyclic ring of **79** (**Scheme 1.2.3.8**). Iodination of **79** provided **80** and set the stage for an intramolecular Heck cyclization that furnished tetracycle **81**.[27]

*Scheme 1.2.3.8 Heck Cyclization for B Ring Closure: Hayes's Work*
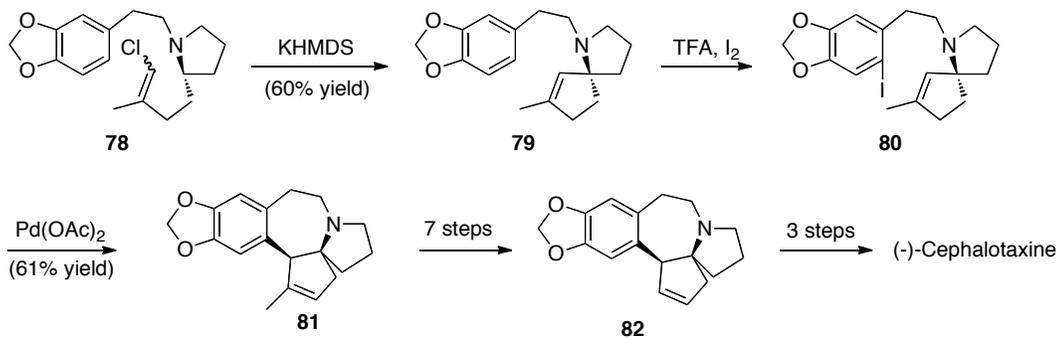
*Tietze's formal total synthesis of (-)-cephalotaxine*: Tietze reported that an intramolecular amination of the π-allyl intermediate derived from allylic acetate **83** produces the spirocyclic C, D-ring of **84** (**Scheme 1.2.3.9**). An intramolecular Heck cyclization was then used to close the B-ring and form **82**.[28]

*Scheme 1.2.3.9 Heck Cyclization for B Ring Closure: Tietze's Work*
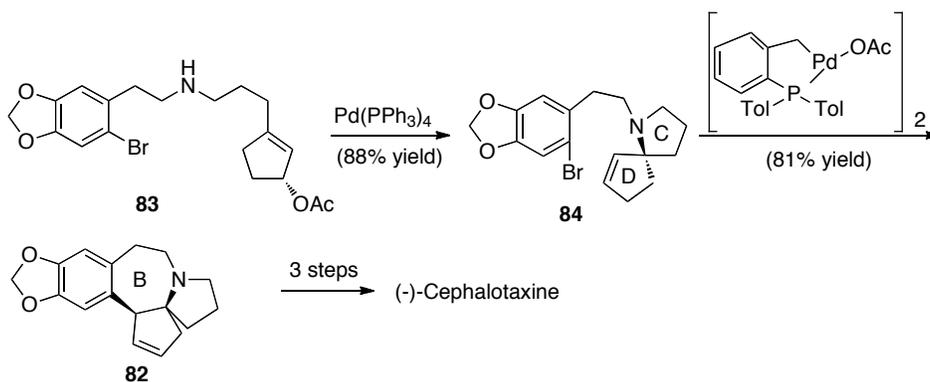


*Stoltz's total synthesis of (-)-cephalotaxine and (-)-drupacine*: Stoltz applied an intramolecular Heck cyclization to advance **85** to intermediate **86**. One of the unique features of the Stoltz synthesis is the inclusion of alcohol at *C*-11 which allows for eventual access to both the cephalotaxine and drupacine ring systems (**Scheme 1.2.3.10**).[29]

*Scheme 1.2.3.10 Heck Cyclization for B Ring Closure: Stoltz's Work*
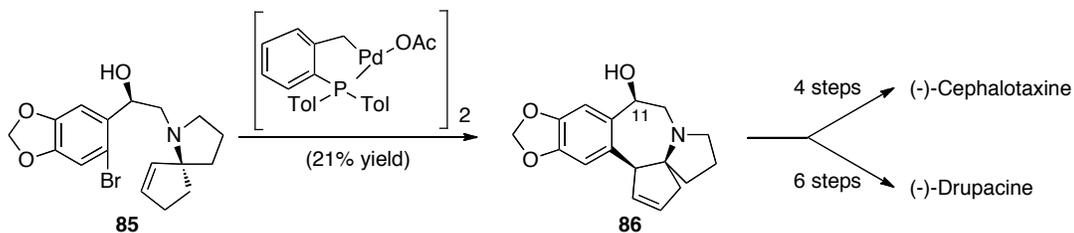
*Semmelhack's total synthesis of dl-cephalotaxine*: Semmelhack reported that the B-ring in intermediate **87** could be produced upon exposure of **88** to a variety of reaction conditions (**Scheme 1.2.3.11**). The best yield was achieved by photo-$S_{RN}^{1}$ reaction in the presence of base.[31]

**Scheme 1.2.3.11 Semmelhack's synthesis**
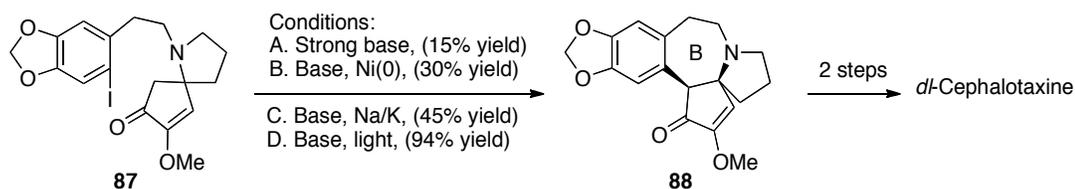


In addition to approaches that assemble the spirocyclic C, D-ring system prior to formation of the B-ring, there are, several reports of strategies leading to the cephalotaxine ring system wherein construction of the spirocycle occurs at a later stage. These include:

*Wienreb's total synthesis of dl-cephalotaxine*: In this synthesis, Friedel-Crafts type reaction of aldehyde **90** produced enamine **91** (**Scheme 1.2.3.12**). In a subsequent 4-steps **91** was converted to diketone **92** which upon exposure to $Mg(OMe)_2$ underwent Nazarov cyclization to furnish **93**. [19, 30]

*Scheme 1.2.3.12 Weinreb's Synthesis*
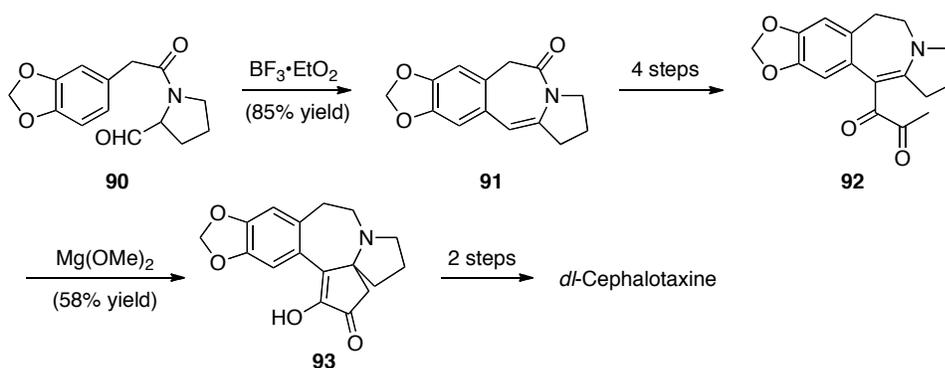


*Hanaoka's total synthesis of dl-cephalotaxine*: Hanaoka reported that exposure of carboxylic acid **94** to polyphosphoric acid induced a Friedel-Crafts acylation which furnished ketone **95** (**Scheme 1.2.3.13**). Conversion of **95** in 3-steps to vinyl chloride **96** set the stage for acid mediated cyclization to furnish **97**.[32]

*Scheme 1.2.3.13 Hanaoka's synthesis*
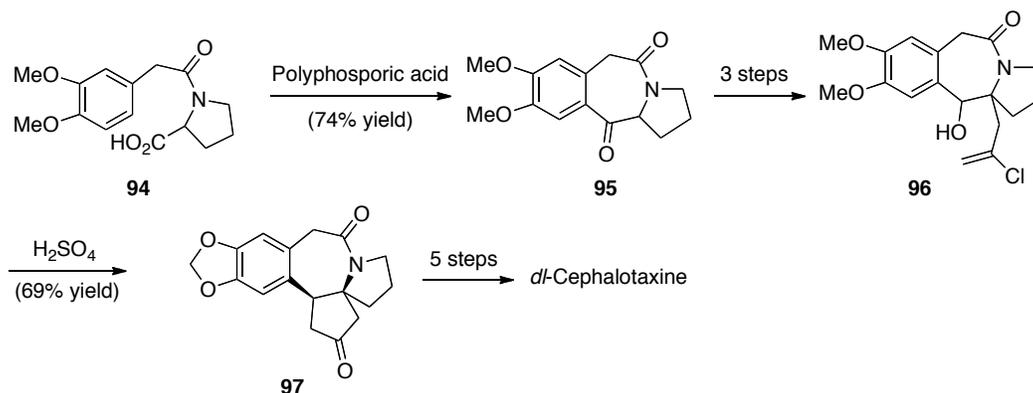


*Fuchs' total synthesis of dl-cephalotaxine and drupacine*: Oxidation of hydroxamic acid **98** to the corresponding acylnitroso species followed by intramolecular

16

hetero Diels-Alder reaction formed **99**. Intermediate **99** was converted to cephalotaxine and drupacine in 10 and 9 steps respectively. (**Scheme 1.2.3.14**).[33]

*Scheme 1.2.3.14 Fuchs' Synthesis*
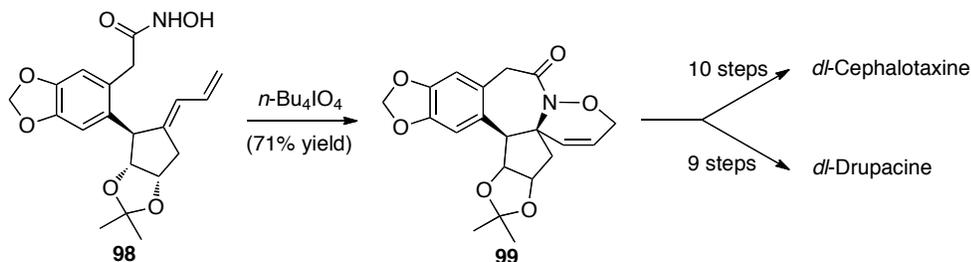


*Bryce's approach towards the total synthesis of dl-cephalotaxine*: Lactam-aldehyde **100** was cyclized to hemiaminal **102** by treatment with DIBAL-H. The reaction was believed to occur through an aluminum complex, which is either monocoordinated (to the aldehyde oxygen) or chelated (to both the aldehyde and lactam oxygens). Such a complex (e.g., **101**) would activate the carbonyl group of the aldehyde to nucleophilic attack by the lactam nitrogen. (**Scheme 1.2.3.15**).[34]

*Scheme 1.2.3.15 Bryce's Approach*
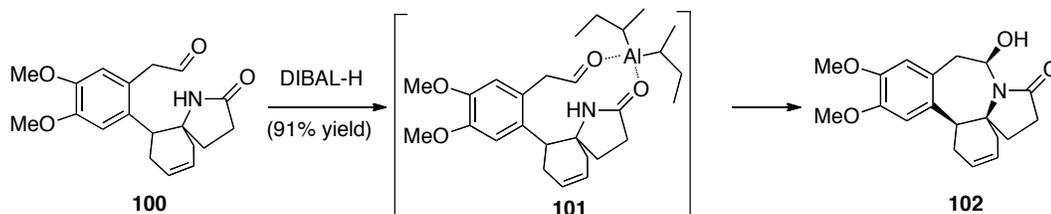


*Mariano's total synthesis of dl-cephalotaxine*: Macrocyclization of **103** gave intermediate **104** (**Scheme 1.2.3.16**). Hydrogenolysis to remove the benzyl protecting

group, was followed by transannular conjugate addition of the free amine to provide ketone **93**.[35]

*Scheme 1.2.3.16 Mariano's Synthesis*
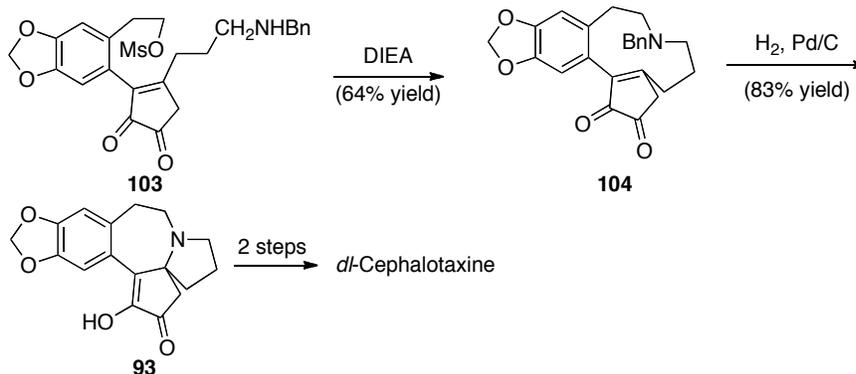


*Nagasaka' formal total synthesis of dl-cephalotaxine*: In Nagasaka's formal synthesis it was reported that treatment of isoindoquinoline **105** with SO$_2$Cl$_2$ produces ring-expansion product **106** (**Scheme 1.2.3.17**). Further advancement of **106** furnished β-keto ester **107** which, upon exposure to TiCl$_4$ and NIS (*N*-iodosuccinimde) undergoes ring-closure to **108**.[36]

*Scheme 1.2.3.17 Nagasaka's Synthesis*
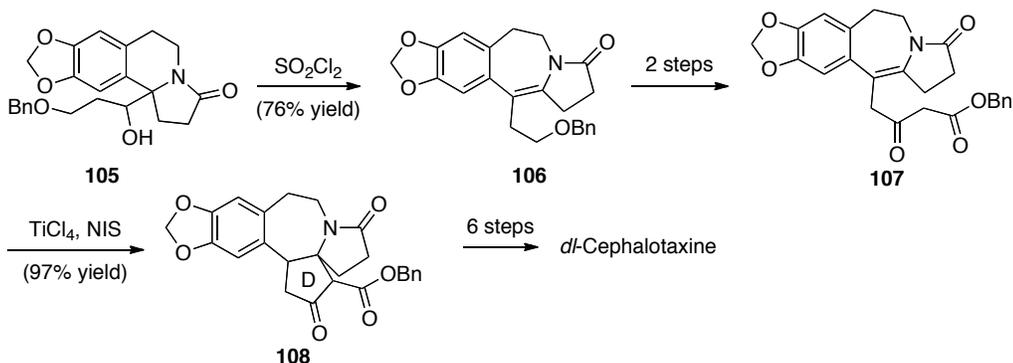
*Li's formal total synthesis of dl-cephalotaxine*: In an interesting ring-expansion/contraction approach, Li reported that exposure of intermediate **109** to zinc and acetic acid rearranged product **110** (**Scheme 1.2.3.18**).[37]

*Scheme 1.2.3.18 Li's Synthesis*
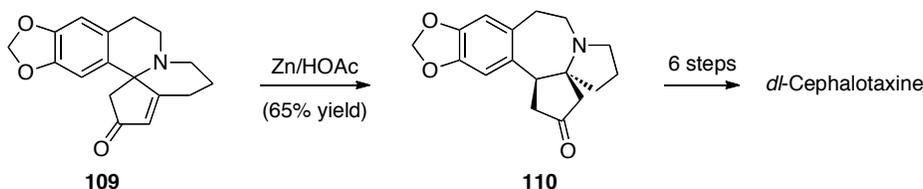


*Ishibashi's total synthesis of (-)-cephalotaxine*: In Ishibashi's total synthesis, a radical cascade cyclization was applied to transform aryl iodide **111** to **112** wherein construction of the B and C rings has occurred *via* a sequential 7-*endo*, 5-*endo-trig* cyclization (**Scheme 1.2.3.19**).[38]

*Scheme 1.2.3.19 Ishibashi's Synthesis*
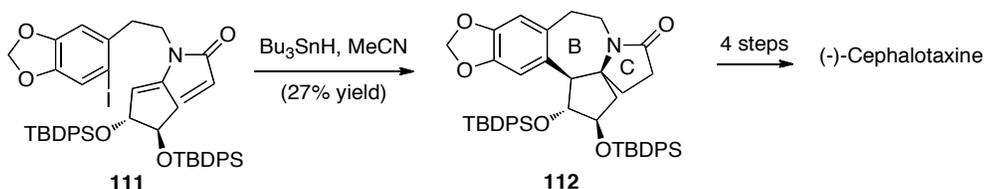


*Gin's total synthesis of (-)-cephalotaxine and (-)-dehydroxyharringtonine*: Gin reported that the B-ring found in intermediate **113** can be produced from aziridine **114** *via* [3,3]-rearrangement (**Scheme 1.2.3.20**). Subsequent alkylation with TMSCH$_2$I sets the stage for a [2+3] cyclization with vinyl sulfonate to complete the construction of the C ring in substrate **115**.[39]

## Scheme 1.2.3.20 Gin's Synthesis



**113**
1. Cs$_2$CO$_3$
   (76% yield)
2. TMSCH$_2$I
   (75% yield)

**114**

PivCl, AgOTf, TBAT

SO$_2$Ph

(77% yield)

**115**

9 steps → (-)-Cephalotaxine

Acylation → (-)-Degydroxyharringtonine
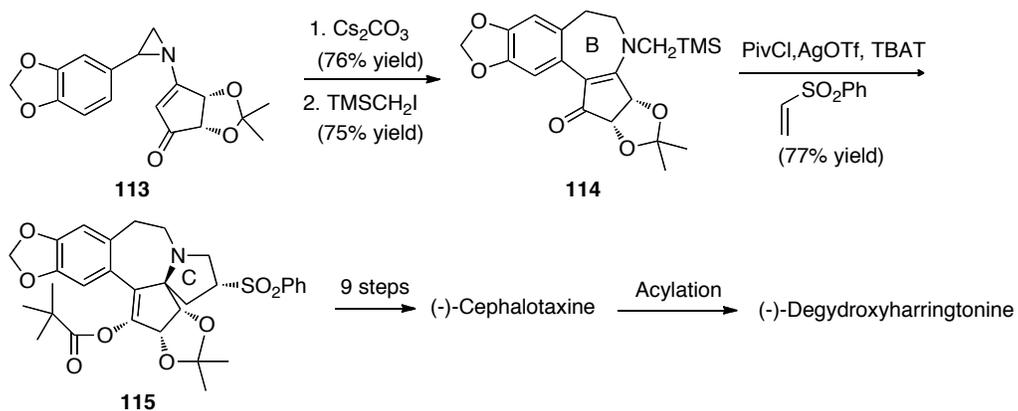
## 1.3 Conclusions

Many research groups have initiated synthetic studies of the *Cephalotaxus* alkaloids due to their significant biological activities and interesting chemical structures. From the investigation of these compact molecular templates, new chemical transformations and methodologies have been developed.

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# Chapter 2

## Approach Towards the Total Synthesis of Cephalezomine A

Given that cephalezomine A has dramatic biological activities and is isolated in low yield[1] coupled with the fact that it has yet to succumb to total synthesis, led us to target this fascinating and challenging natural product.

### 2.1 Retrosynthetic Analysis I

The retrosynthetic analysis of cephalezomine A (**1**) is outlined in **Scheme 2.1.1**. Retrosynthetic cleavage of the ester bond in cephalezomine A (**1**) furnishes the acyl side chain (**150**) and drupacine (**18**). It is known that drupacine (**18**) can be prepared from 11-hydroxycephelotaxine (**20**) in one step.[2] In our retro synthetic analysis, 11-hydroxycephelotaxine (**20**) derives from the cyclization of substrate **152**. In the forward sense, exposure of dienone **152** to Lewis Acid conditions is envisioned to furnish cationic intermediate **151** *via* a Nazarov cylization. This intermediate could, in turn, undergo a Friedel- Crafts type cyclization to form 11-hydroxycephelotaxine (**20**). Disubstituted dienone **152** is seen as arising from **153** by nucleophilic addition of an $\alpha$- lithio vinyl ether to Weinreb amide **153** which will derive from the union of epoxide **154** and vinylogous urea **155**.

*Scheme 2.1.1 Retrosynthetic Analysis I*

**1**: Cephalezomine A    **150: Acyl side chain**    **18: Drupacine**

*Nazarov cyclization*    LA=Lewis Acid    *Friedel- Crafts cyclizaion*

**152**    **151**    **20: 11-hydroxycephalotaxine**

**153**    **154**    **155**
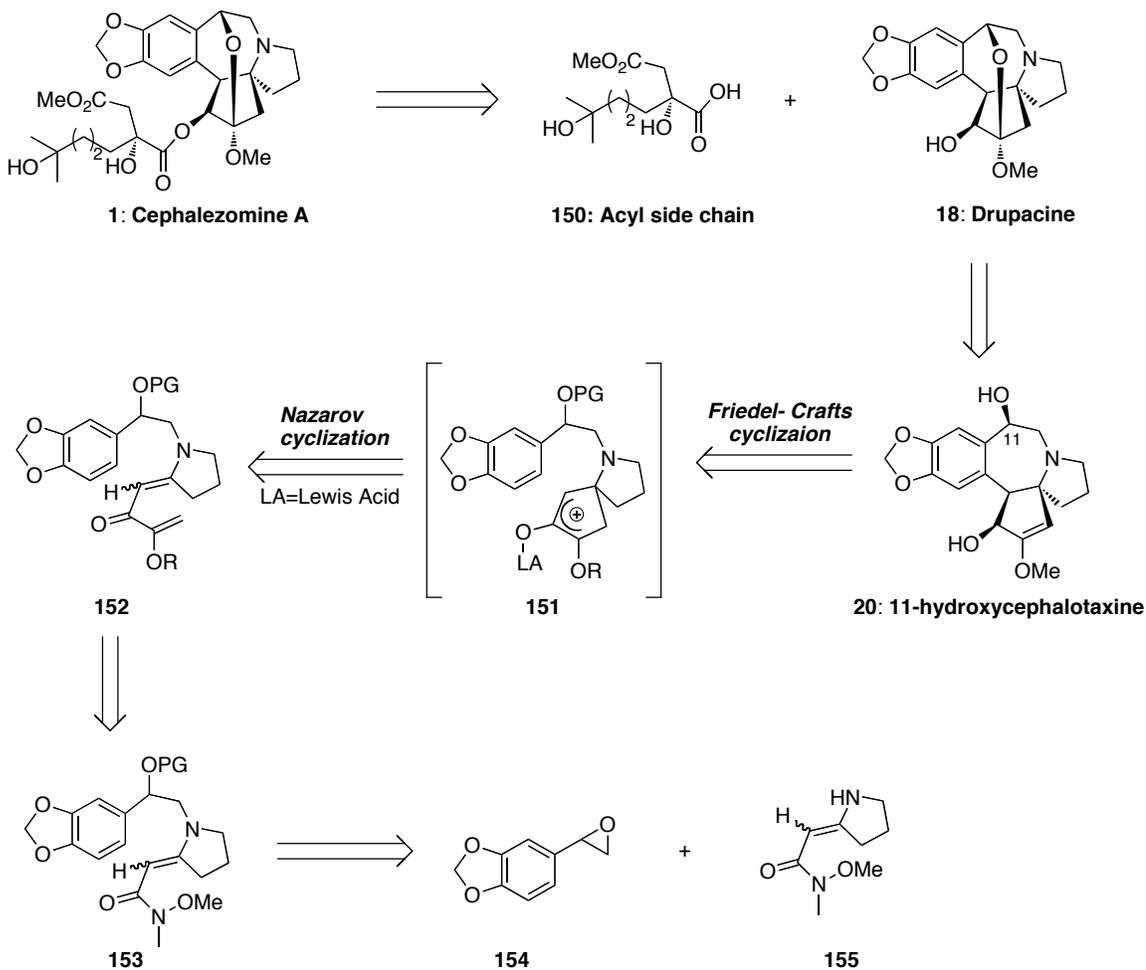
## 2.2 Synthesis of Dienone 152

## 2.2.1 Coupling of an Epoxide and a Vinylogous Amide

One of the coupling precursors, epoxide **154** was prepared from piperonal (**156**) in good yield by a Johnson-Corey-Chaykovsky reaction (**Scheme 2.2.1**).[3] The remaining coupling partner vinylogous urea **155** was prepared by treatment of 2-methyl-1-pyrroline (**157**) with LDA, followed by addition of dimethylcarbamic chloride. Attempts to couple epoxide **154** and vinylogous amide **155** were conducted under numerous conditions.

Unfortunately, no desired coupling product **158** was observed and starting material was either recovered or decomposed. The poor nucleophile character of the vinylogous urea nitrogen was not unexpected and similar reactivity was observed upon exposure of pyrrolidin-2-one (**159**) to epoxide **154**. Given that the nucleophile (vinylogous urea **155**) was seen as the least variable substrate, we next explored alteration of the electrophile.

*Scheme 2.2.1 Coupling of Epoxide and Vinylogous amide*
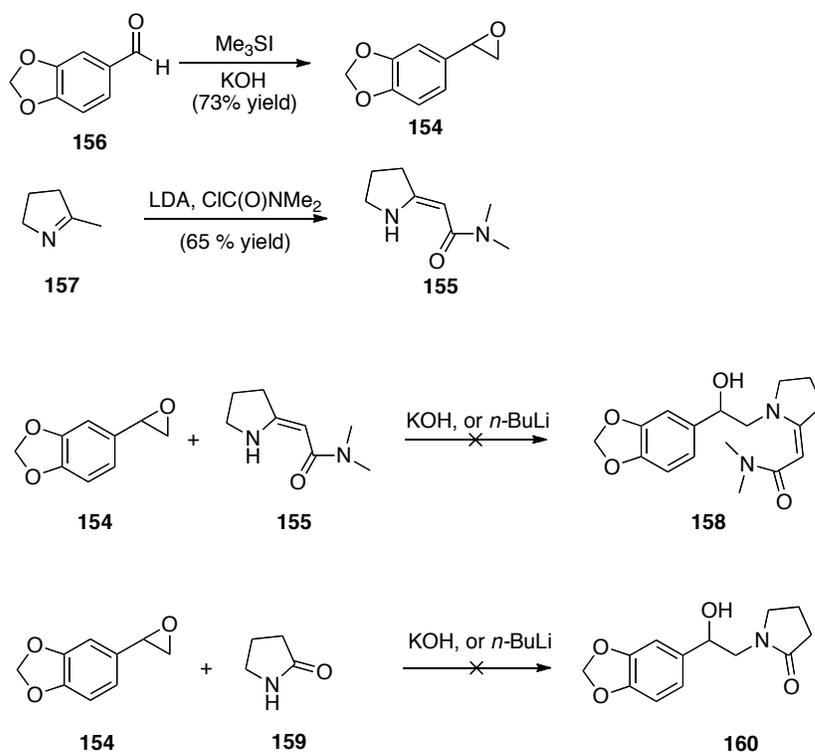


## 2.2.2 Coupling of an $\alpha$-Bromo Ketone and a Vinylogous Urea

In considering other possible eletrophiles, we first explored $\alpha$-bromo ketone **162**. The preparation of **162** began with addition of MeMgBr to piperonal (**156**) and oxidation of newly formed secondary alcohol to ketone **161** (**Scheme 2.2.2**). Treatment of ketone **161** with bromine produced $\alpha$-bromo ketone **162** in excellent yield[4] and the latter could

be readily protected as its ethylene glycol acetal to provide an additional electrophile substrate **163**.

***Scheme 2.2.2 Preparation of Bromo Ketone***
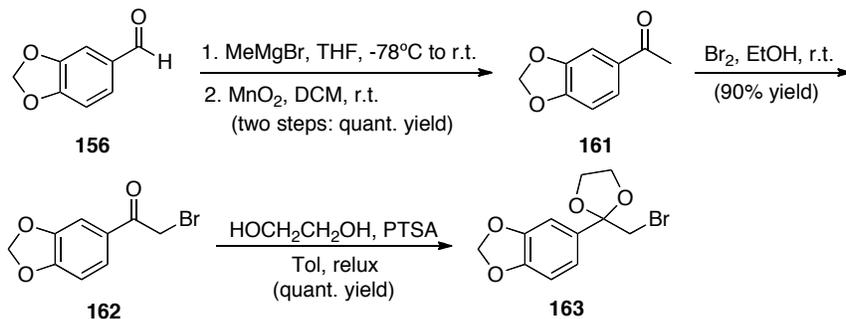


As illustrated in **Table 2.2.2**, our efforts to engage vinylogous urea **155** with the more reactive $\alpha$-bromo ketone **162** were unsuccessful. Under basic conditions ($K_2CO_3$, $Cs_2CO_3$, $n$-BuLi), bromo ketone **162** decomposed and vinylogous urea **155** was recovered. Under milder conditions (EtOH or $Et_3N$), both of the starting materials were recovered. Given these results, we turned to another electrophile: bromide **163**, which is more stable under harsh conditions; however, only starting material was recovered upon exposure to either mild or strong basic conditions. Although less desirable, at this stage addressing the nucleophilicity of the vinylogous urea **155** became the next step.

*Table 2.2.2 Coupling Conditions of Bromo Ketone and Vinylogous Urea*



**162**, X= -O-
**163**, X=-OCH₂CH₂O-

**155**

**164**, X= -O-
**165**, X=-OCH₂CH₂O-
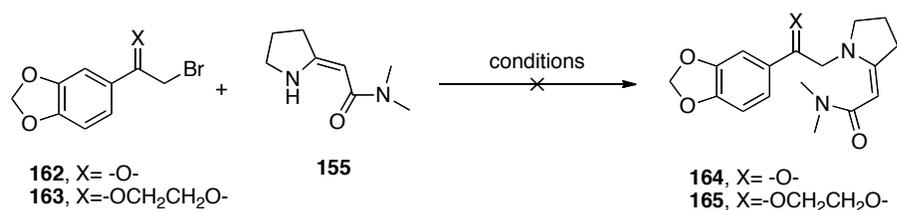
| conditions | results |
| --- | --- |
| K$_2$CO$_3$, DMF or MeCN, r.t. | **162**, decomposed; **155**, recovered |
| Cs$_2$CO$_3$,DMF or MeCN, r.t. | **162**, decomposed; **155**, recovered |
| NaH,THF, r.t. | **162**, decomposed; **155**, recovered |
| KOH, *n*-Bu$_4$NI, MeCN or THF, r.t | **162**, decomposed; **155**, recovered |
| *n*-BuLi, -78ºC, THF | **162**, decomposed; **155**, recovered |
| *n*-BuLi, -78ºC to r.t., THF | **162**, decomposed; **155**, decomposed |
| EtOH, r.t. | **162**, recovered; **155**, recovered |
| Et$_3$N, DCM, r.t. | **162**, recovered; **155**, recovered |
| AgOAc,or AgOTf or AgNO$_3$, Tol/THF or MeCN, r.t | **162**, decomposed; **155**, recovered |
| K$_2$CO$_3$, DMF, r.t. | **163**, recovered; **155**, recovered |
| *n*-BuLi, -78ºC to r.t., THF | **163**, recovered; **155**, recovered |

## 2.2.3 Coupling of an *α*-Bromo Ketone with an Amide

Since pyrrolidin-2-one (**159**) has been reported to serve effectively as a nucleophile in coupling reactions with α-halogenated ketones at room temperature,[5] we decided to explore its coupling with bromo ketone **162**. From a retrosynthetic perspective (**Scheme 2.2.3.1**), this change to a less functionalized nucleophile requires further manipulation of vinylogous urea **153** to produce requisite dienone **152**. To this end, it was

envisioned that an Eschenmoser coupling of α-halo amide **166** and thiolactam **167** would

deliver intermediate **153** *via* an addition-elimination process.

*Scheme 2.2.3.1 Revised Coupling Retrosynthetic Analysis*
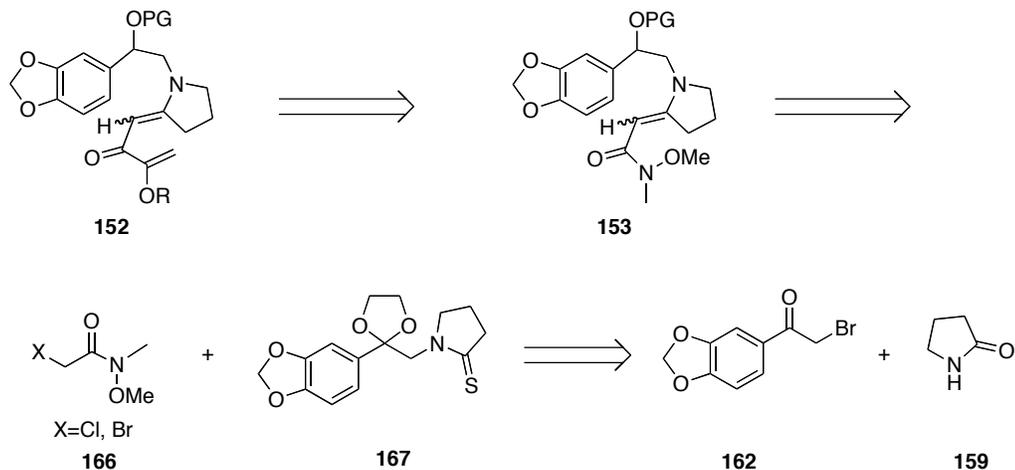


In practice, initial studies on the coupling of **162** and pyrrolidin-2-one (**159**) to

yield **168** using NaH were modestly successful (56% yield). Further study revealed that

using 2-methoxy-1-pyrroline (**169**)[5] as nucleophile instead of amide **159** results in a

significantly improved yield.  Protection of **168** using ethylene glycol gave **170**.

*Scheme 2.2.3.2 Coupling of Bromo Ketone with Amide*
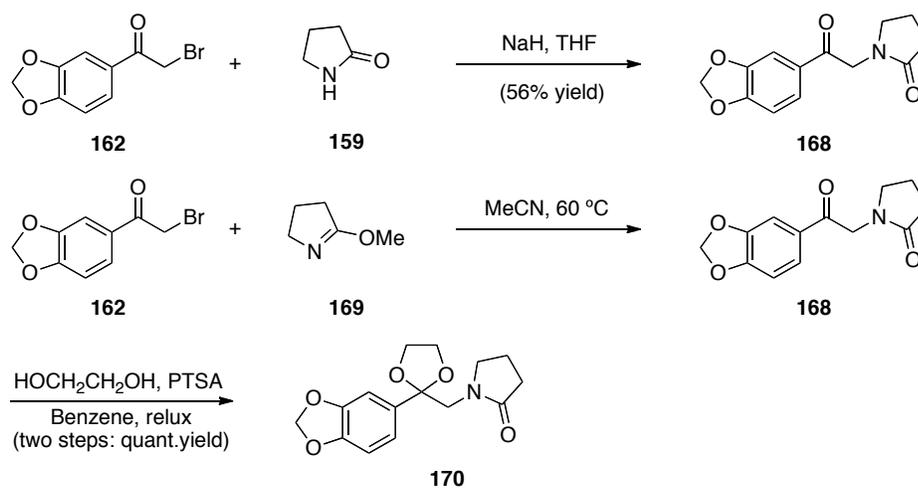


Having set the stage for the planned coupling (see **170** to **153** in **Scheme 2.2.3.3**),

we first explored the use of lactam **171** to establish our ability to effect a coupling of α-

halo amide **166**.

*Scheme 2.2.3.3 Proposed Model Study on the Coupling of Substrate 170 with 166*
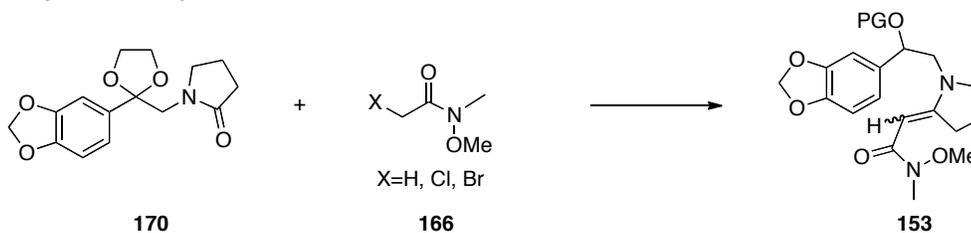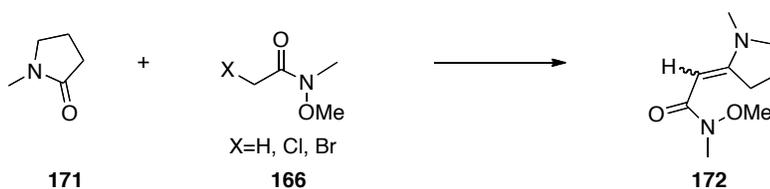
In preliminary studies we explored the direct coupling of **171** to form the vinylogous urea **172** or amide **175** (**Scheme 2.2.3.4**). Different nucleophiles, such as depronated *N*-methoxy-*N*-methylacetamide **173** and silyl enol ether **174**,[6] were investigated. However, no desired product was observed. Coupling also failed when the corresponding ammonium salt **176**, which was produced by methylation of amide **171**.

*Scheme 2.2.3.4 Addition and Elimination for the Coupling Study*
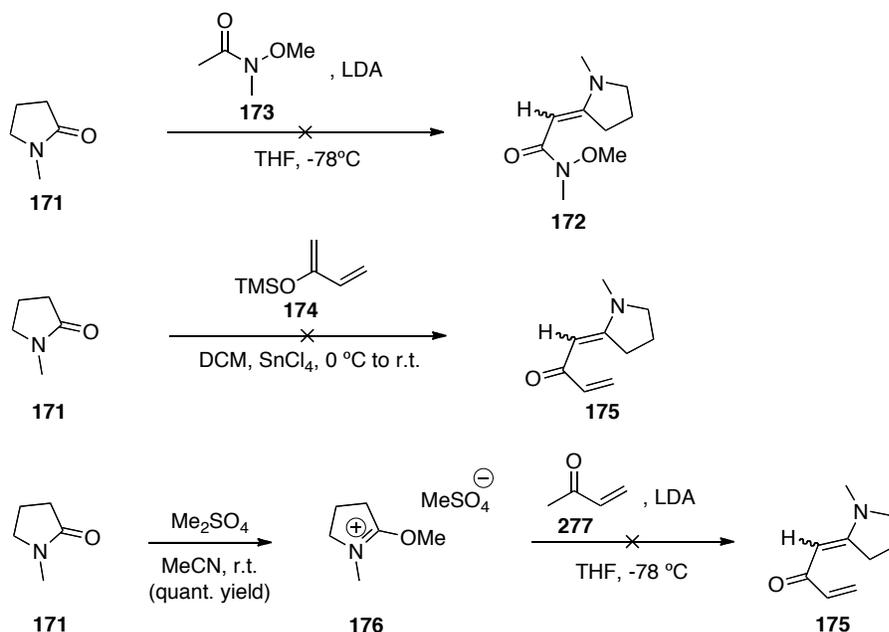


We next turned to the Eschenmoser Coupling[9] and set the stage for this coupling *via* the conversion of lactam **171** to thiolactam **177** by treatment with Lawesson's reagent.[7] Subsequent coupling of **177** with either an α-bromo amide[8] or ester produced the coupling product (e.g. amide **179** or ester **180** , **Scheme 2.2.3.5**). However, the product **179** was difficult to separate from triphenyl phosophine sulfide, which was produced in the coupling reaction.

*Scheme 2.2.3.5 Model Study on Eschenmoser Coupling*
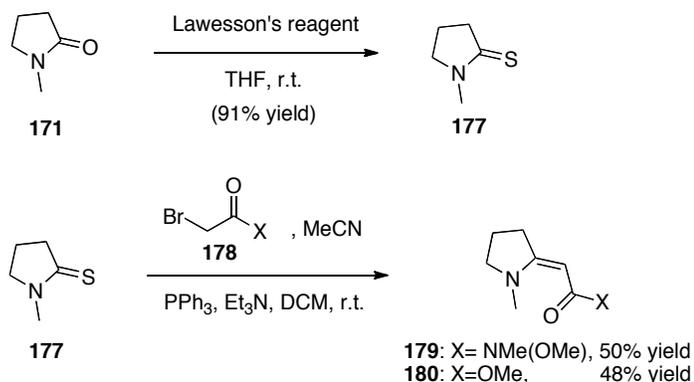


Further optimization of the coupling (**Table 2.2.3**) identified triethyl phosphite as the best phosphorus source; Eschenmoser coupling under these conditions proceeds in higher yield and purification of the desired product is greatly simplified.

*Table 2.2.3 Optimized Eschenmoser Coupling for Model*



| R$_3$P | Results |
|--------|---------|
| PPh$_3$ | S.M. + P. |
| (EtO)$_3$P | yield: 87% |
| Et$_3$P | None P. |
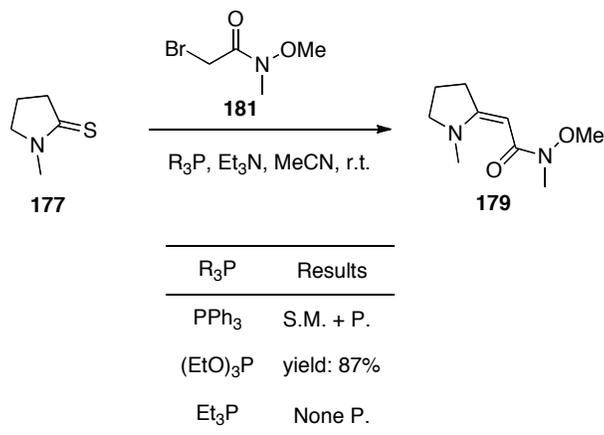
As illustrated in **Scheme 2.2.3.6**, the conditions developed in our model study proceeded effectively in the real system. In the event, conversion of lactam **170** to thiolactam **167**, followed by Eschenmoser coupling gave precursor **182** in excellent yield.

Interestingly, purification of this product was easily achieved even when PPh₃ was employed.

*Scheme 2.2.3.6 Eschenmoser Coupling for Real System*
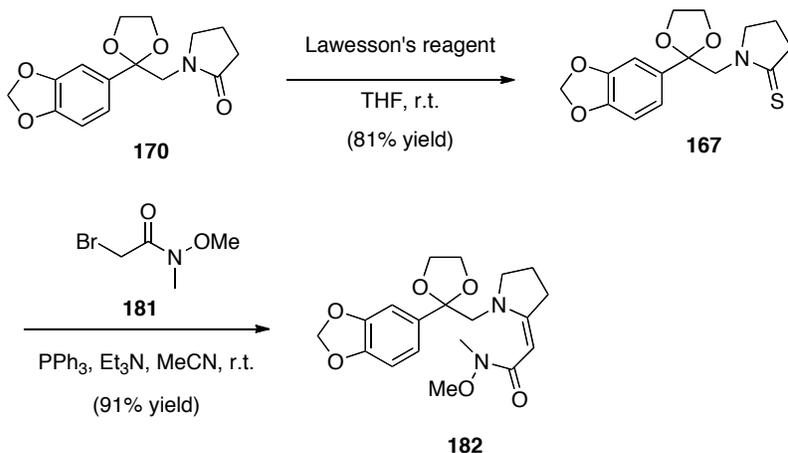


## 2.2.4 Efforts to Access Dienone 152 from Weinreb Amide 182

Our exploration into the transformation of Weinreb amide **153** to dienone **152** (as illustrated in the retrosynthetic analysis **scheme 2.2.3.1**) began with model substrate **179**. Exposure of **179** to more than 3 equivalent of lithio vinyl ether[10] or vinyl magnesium bromide[11] resulted only in isolation of recovered starting material (**Table 2.2.4**).

*Table 2.2.4 Nucleophilic Addition Failure in Model for Synthesis of Dienone*
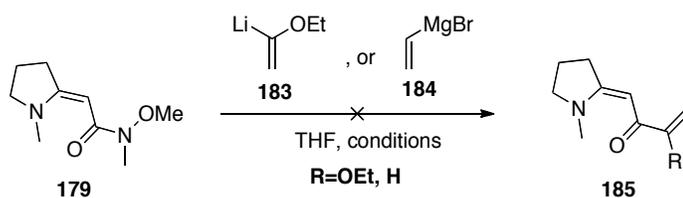


| conditions | results |
|---|---|
| 3 eq of Nu., -78ºC to r.t. | S.M. recovered |
| 12 eq of Nu., r.t. | S.M. recovered |
| 3eq of Nu., reflux | S.M. decomposed |
| 3eq of Nu. , 2eq BF$_3$·OEt$_2$, -78 ºC to r.t. | S.M. decomposed |
| 3eq of Nu. , 2eq Me$_3$Al, -78 ºC to r.t. | S.M. recovered |

Unfortunately, as illustrated in **Scheme 2.2.4**, similar results were obtained in the real system. Since the difficult nucleophilic addition was likely due the decreased reactivity of the vinylogous urea, we turned to an alternative wherein the vinyl group would be introduced prior to Eschenmoser coupling.

*Scheme 2.2.4 Nucleophilic Addition Failure in Real System for Synthesis of Dienone*
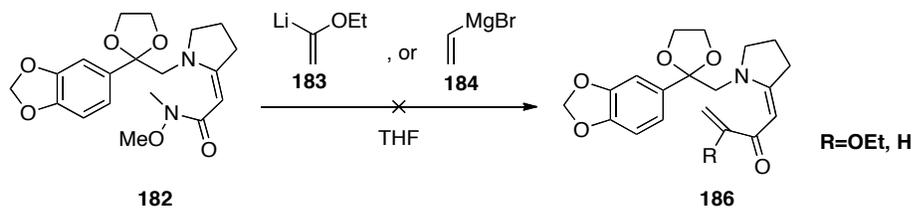
## 2.2.5 Changing the Order of Events: Eschenmoser Coupling of Enones

Since Eschenmoser Coupling with α-halogenated amides or esters has been reported, we were optimistic about coupling the α-halogenated enone **187** with thiolactam **167** to form dienone **152** (**Scheme 2.2.5.1**).

*Scheme 2.2.5.1 Revised Coupling Retrosynthetic Analysis*



**152**                                **167**                                **187**

X=Cl, Br, R=H, Et or Bu
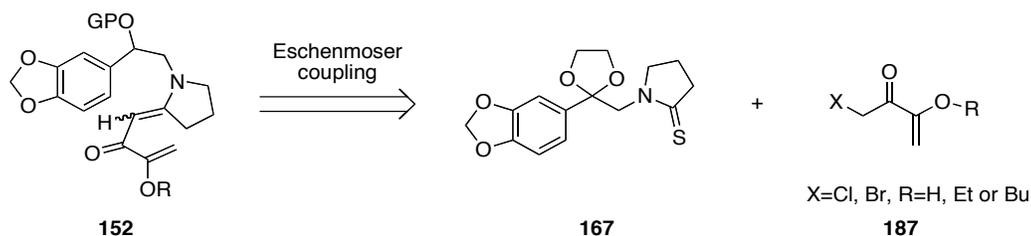
Implementation of this idea required preparation of the α-halo ketone **187**. To this end, our first approach was to attempt the nucleophilic addition of a lithium, magnesium or zinc, vinyl metal species to bromoacetyl bromide (**188**, **Scheme 2.2.5.2**). Unfortunately, no desired product (**190**) was obtained.

*Scheme 2.2.5.2 Approach to Bromo Enone by Vinyl Nucleophile Addition*



**188**                                **190**
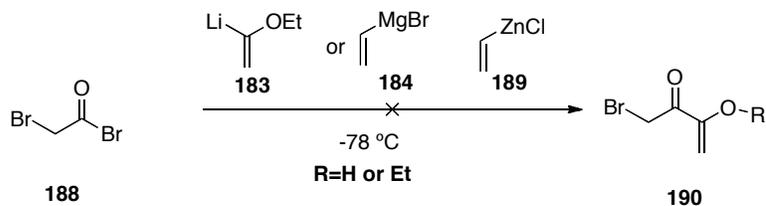
Turning to an alternative approach involving bromination of an intact enone system we were delighted to find several examples of in the literature describing the bromination of methyl vinyl ketones. For example, Li demonstrated that vinyl ketone **191** furnished

bromide **193** upon treatment with tri[pyrrolidine-2-one] hydrobromide (**192)** at -78 ºC

(**Scheme 2.2.5.3**).[12] Given our need for a terminal alkenyl ketone, we explored Li's

conditions on methyl vinyl ketone **194**; however, the undesired dibromide **196** was the

only observed product.

*Scheme 2.2.5.3 Approach to Bromo Enone via Bromination Process I*
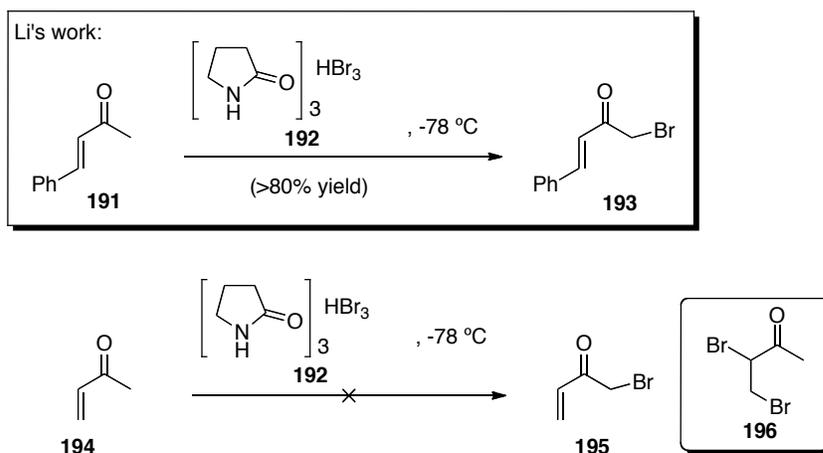


In a different report, Herman described that treatment of TMS silyl enol ether **197**

with NBS produced bromination product **193** (**Scheme 2.2.5.4**).[13] Exploring these

conditions on TMS silyl enol ether **194**, we observed only starting material

decomposition and no desired product.

*Scheme 2.2.5.4 Approach to Bromo Enone via Bromination Process II*
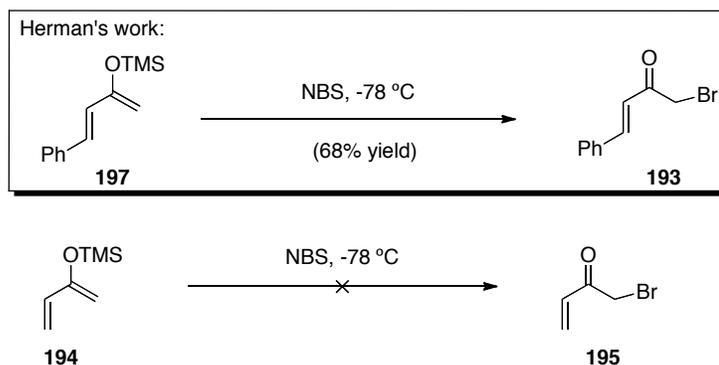


A more relevant example was found in the work of Danishefsky who reported that addition of ethylene (**198**) to chloroacetyl chloride (**199**) followed by elimination produced product **200** in good yield (**Scheme 2.2.5.5**). [14] In repeating this experiments, we did obtain some of the desired product **200**. However, the yield was poor.

*Scheme 2.2.5.5 Approach to Chloro Enone via Friedel –Crafts Addition*
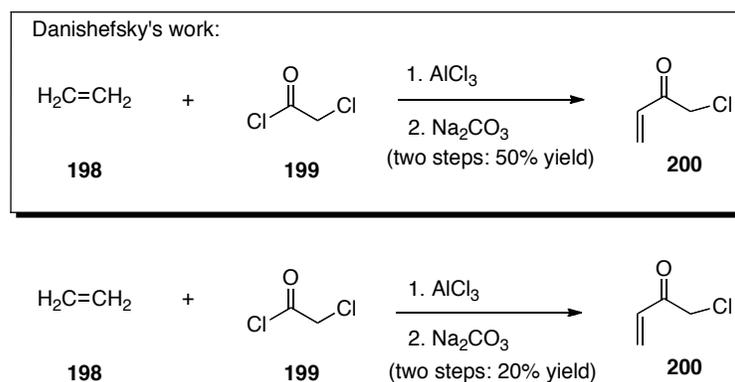


In a more recent report, Ram described that the treatment of allylic alcohol **201** with cuprous chloride to give α-chloro enone **202** in good yield (**Scheme 2.2.5.6**).[15] The mechanism is believed to involve a copper(I) carbenoid mediated 1,2-H shift process. Since our coupling target was α-chloro alkoxy-enone **209** or **210**, the exploration of

42

Ram's procedure requires the preparation of alkoxy-allylic alcohol **205** or **206** as illustrated in **Scheme 2.2.5.6**. Addition of litho vinyl ether **204** to DMF (**203**) produced aldehyde **205** or **206**, which upon exposure to chloroform under basic conditions furnished the corresponding allylic alcohol **207** or **208** in good yield. At this point we were delighted to find that the application of Ram's procedure to **207** or **208** furnished the desired α-Chloro alkoxy-enone **209** or **210** in good yield. Since ethoxyl enone **209** is volatile at room temperature, we employed butoxyl enone **210** in subsequent studies.

*Scheme 2.2.5.6 Synthesis of Chloro Enone via Copper(I) Carbenoid 1,2 H Shift Process*
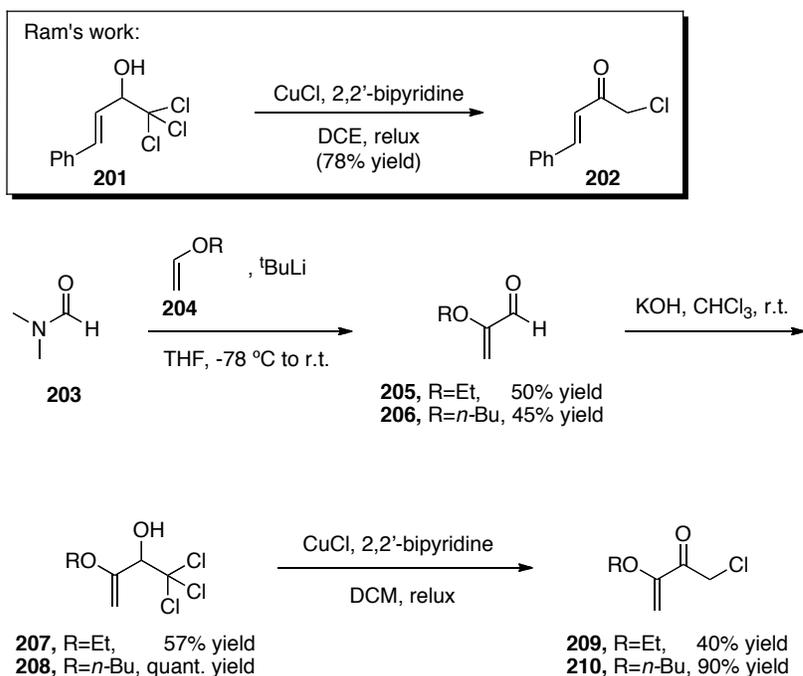


Impressively, Eschenmoser coupling of **167** with **210** gave the desired key precursor **211** and set the stage for investigation of the Nazarov cyclization (**Scheme 2.2.5.7**).

*Scheme 2.2.5.7 Eschenmoser Coupling of 102 with 120*



## 2.3 Nazarov Cyclization of Dienone 211

Recent reports by West[16] describing the successful tandem Nazarov cyclization/ Friedel-Crafts reaction of heavily substituted dienone **213** left us encouraged at prospects of employing dienone **211** in a similar reaction (**Scheme 2.3.1**). We were additionally encouraged by recent studies from Frontier describing the benefits of electron donating substituents.[17] Unfortunately, despite similarity to West's system and presence of additional electron donating substituent's, the Nazarov cyclization failed for our substrate **211** under standard Lewis acid conditions (TiCl$_4$ or BF$_3$•OEt$_2$ at room temperature). At lower temperature, only starting material was observed and when the temperature was increased to 0 ºC, NMR monitoring indicated only decomposition. Given that West's substrates lack both alkoxy and *N*-substituted functional groups, we decided to investigate the Nazarov cyclization on model systems wherein these two dienone substituents are present individually.

*Scheme 2.3.1 Nazarov Cylization Studies on the Real System*



West's work:

212 → 213

R$_1$=Me, R$_2$=H , 99% yield
R$_1$=Et, R$_2$=Me, 99% yield
R$_1$=R$_2$=(CH$_2$)$_4$,99% yield

211 → 214

TiCl$_4$, or BF$_3$•OEt$_2$
-78 °C to r.t.
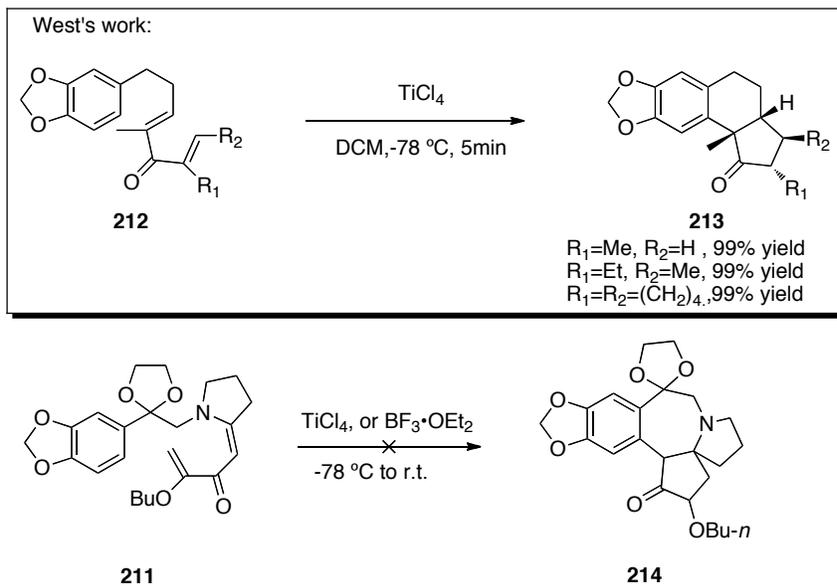
To explore the effects of an alkoxy substituent, model system dienone **217** was prepared by addition of lithio vinyl ether to the Weinreb amide derived from benzoyl chloride (**Scheme 2.3.2**). Additionally, model system **220** was prepared by addition of lithiated vinyl ether to piperine (**219**). Interestingly, both model dienone **217** and **220** underwent smooth cyclization under Lewis acid conditions. These results indicated that alkoxy substituents in the $\alpha$-position were not deleterious to Nazarov cyclization. Noteworthy was the decrease in yield for the cyclization of **220** compared to **217**. Based on studies by Sharpen this was expected.[18]

***Scheme 2.3.2 Nazarov Cylization Model Test for Alkoxy Group***
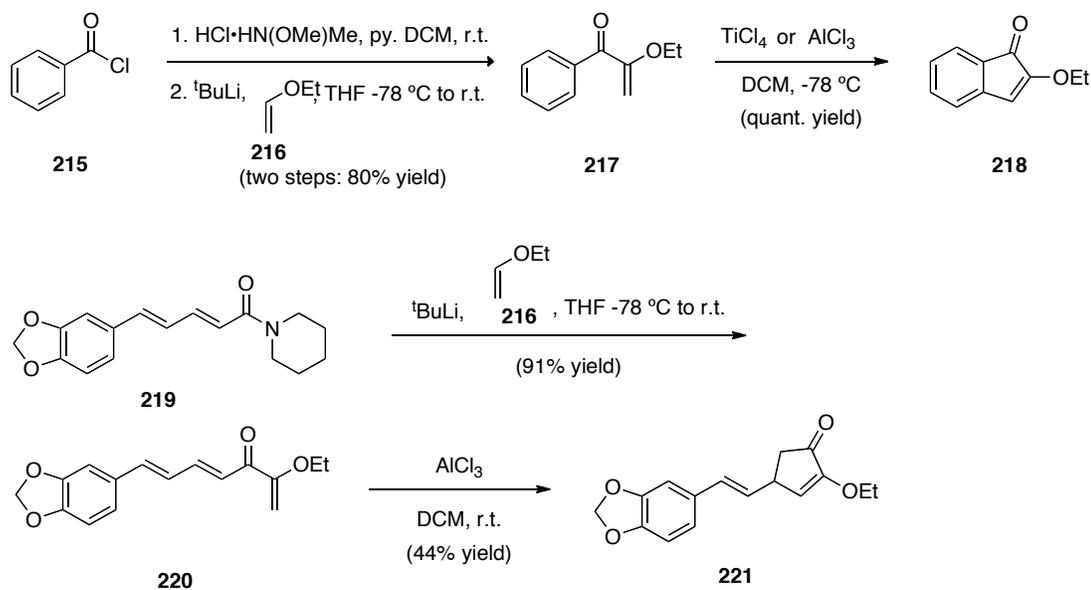


To investigate the effect of the vinylogous amide substituent on Nazarov

cyclization, we prepared model **175** (**Scheme 2.3.3**). In a first attempt to this end,

treatment of acryloyl chloride with lithiated 2-methyl-1-pyrroline (**157**) gave undesired

product amide **224** via *N*-acylation. In a second attempt, acryloyl chloride (**225**) was

pretreated with *N*, *O*-dimethylhydroxylamine hydrochloride (**226**) to yield Weinreb

amide **227**.With this substrate, addition of lithiated 2-methyl-1-pyrroline furnished the

desired vinylogous amide **223** which, upon, methylation delivered dienone **175**.

*Scheme 2.3.3 Synthesis Model with N-Substituted Group for Nazarov Cyclization Test*

**Route 1:**



**Route 2:**
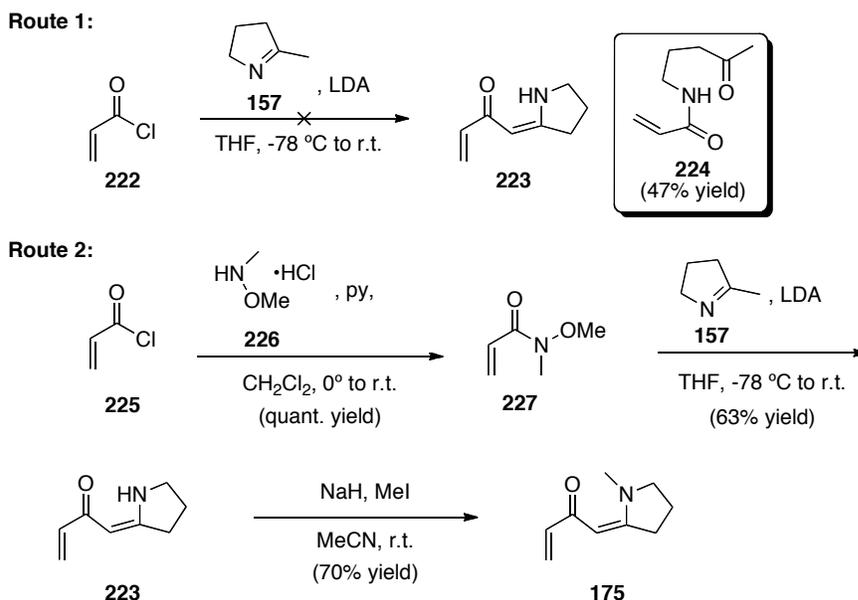


With the model substrate dienone **175** in hand, a variety of conditions were explored in order to produce spiro ketone **228** by Nazarov cyclization. Conditions include Lewis acid: SiO$_2$,[19a(7)] AlCl$_3$,[18] Et$_2$AlCl or Me$_3$Al,[20(1)] TiCl$_4$ or BF$_3$•OEt$_2$,[19a(8)] PdCl$_2$(MeCN)$_2$ or Pd(OAc)$_2$,[19a(3)] Sc(OTf)$_3$,[19a(9)] FeCl$_3$,[19a(1),a(2)] Cu(OTf)$_2$,[19a(4),] Yb(OTf)$_3$[19a(6)] TBSOTf;[19a(5)] TFA[19b(1),20(1),(2)] and HCOOH/H$_3$PO$_4$.[19b(1),(2)] Unfortunately, under all of the conditions no desired product was observed. Starting material was recovered or decomposed (**Table 2.3**). This result led us to believe that the vinylogous amide substituent was the culprit in our failed Nazarov cylization.

*Table 2.3 Nazarov Cyclization Test with N-Substituted Model 175*
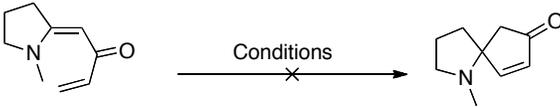


| conditions | results |
|---|---|
| $SiO_2$, r.t. | S.M. recovered |
| $AlCl_3$, 0° or r.t. or reflux | S.M. recovered; decomposed (reflux) |
| $Et_2AlCl$ or $Me_3Al$, -78 °C to r.t. | S.M. recovered |
| $TiCl_4$ or $BF_3 \cdot OEt_3$, -78°C to r.t. | decomposed . |
| $PdCl_2(MeCN)_2$ or $Pd(OAc)_2$, r.t. | S.M. recovered |
| $Sc(OTf)_3$ | decomposed |
| $FeCl_3$ | decomposed |
| $Cu(OTf)_2$, r.t. or 50° | S.M. recovered |
| $Yb(OTf)_3$ | S.M. recovered |
| TBSOTf, -78° to r.t. | S.M. recovered |
| TFA, r.t. | S.M. recovered |
| $HCOOH$, $H_3PO_4$ | decomposed |

As a third model system we prepared a dienone containing both of the alkoxy and vinylogous amide substituents. To prepare dienone **231**, dimethyl carbamic chloride (**229**) was treated with lithiated vinyl ether, followed by addition of lithiated 2-methyl-1-pyrroline. Methylation of intermediate **230** gave desired dienone **231** (**scheme 2.3.4**). Nazarov cyclization was only conducted under the $TiCl_4$ conditions that proved successful for dienone **217**. Unfortunately, only the diketone **233** was produced and none of the spiro product **232** was observed.

*Scheme 2.3.4 Nazarov Cyclization Test with O, N-Substituted Model 231*
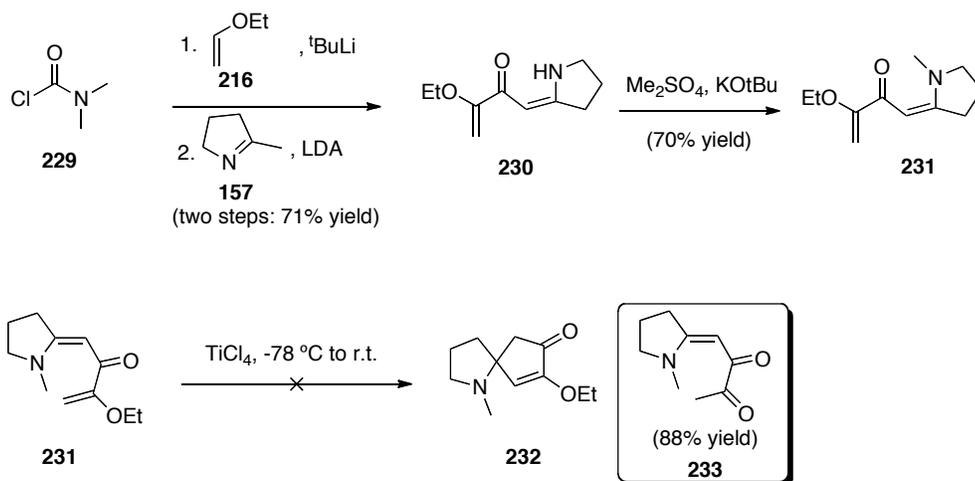


Results from the above studies indicated that altering the electronic nature of the amine might impact the Nazarov cyclization. To investigate this possibility, it was decided to attempt converting the vinylogous amide to a vinylogous imide prior to Nazarov cyclization. Access to this new Nazarov substrate (**235**) was gained simple through a simple peptide coupling of **234** and **230**  (**Scheme 2.3.5**). [21]

*Scheme 2.3.5 Preparation of Deactivated N-Substituted Dienone*
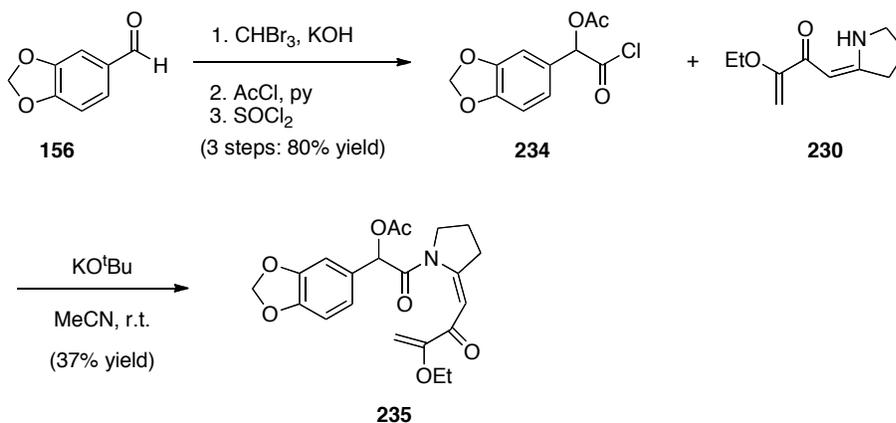
Unfortunately, under Lewis acid promoted Nazarov cyclization conditions **235** was found to deliver none of the desired product **236**. Only decomposition of the starting material was observed (**Scheme 2.3.6**). Based on these results the Nazarov cyclization route was abandoned and alternatives were considered.

*Scheme 2.3.6 Nazarov Cyclization Test with Deactivated N-Substituted Dienone 235*
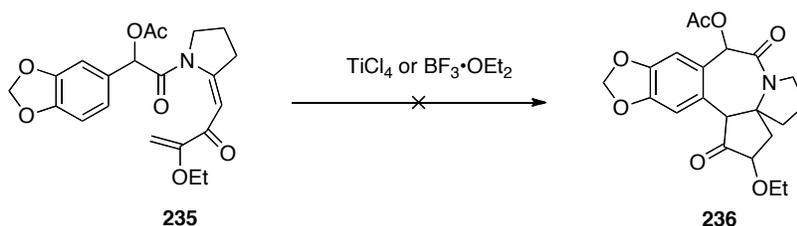


## 2.4 Considering an Alternative Strategy

The failure of the Nazarov cyclization approach coupled with recent success with tandem radical reactions in the Wood group[22] led us to consider an alternative approach (**Scheme 2.4.1**). As illustrated in retrosynthetic fashion, this approach relies on the same bond construction as the Nazarov cyclization strategy; however in this radical based approach one can view bond formation as moving from the aromatic moiety to the vinylogous amide system (substrate **239** to **238** to **237**). Importantly, although the underlying chemistry is quite different, the substrates required for the radical approach are fairly similar to those employed in our studies of the Nazarov cyclization. Thus great advantage could be taken of previously developed chemistry.

*Scheme 2.4.1 Alternative Strategy: Radical Cyclization Approach*



**20**: **11-hydroxyCephalotaxine**

**237**

**238**

**239**
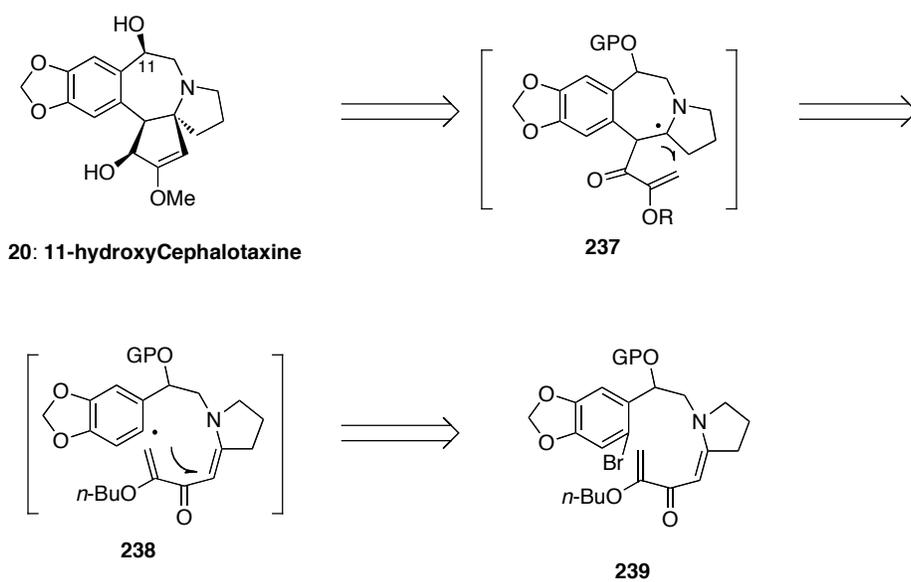
In the forward sense, preparation of the radical cyclization substrate began with bromination of piperonal (**Scheme 2.4.2**). The desired bromide **240** was taken through a 7-step sequence similar to that employed for substrate **211**. In the end, substrate **247** and **248** were accessed in good yield.

## Scheme 2.4.2 Preparation for Radical Cyclization
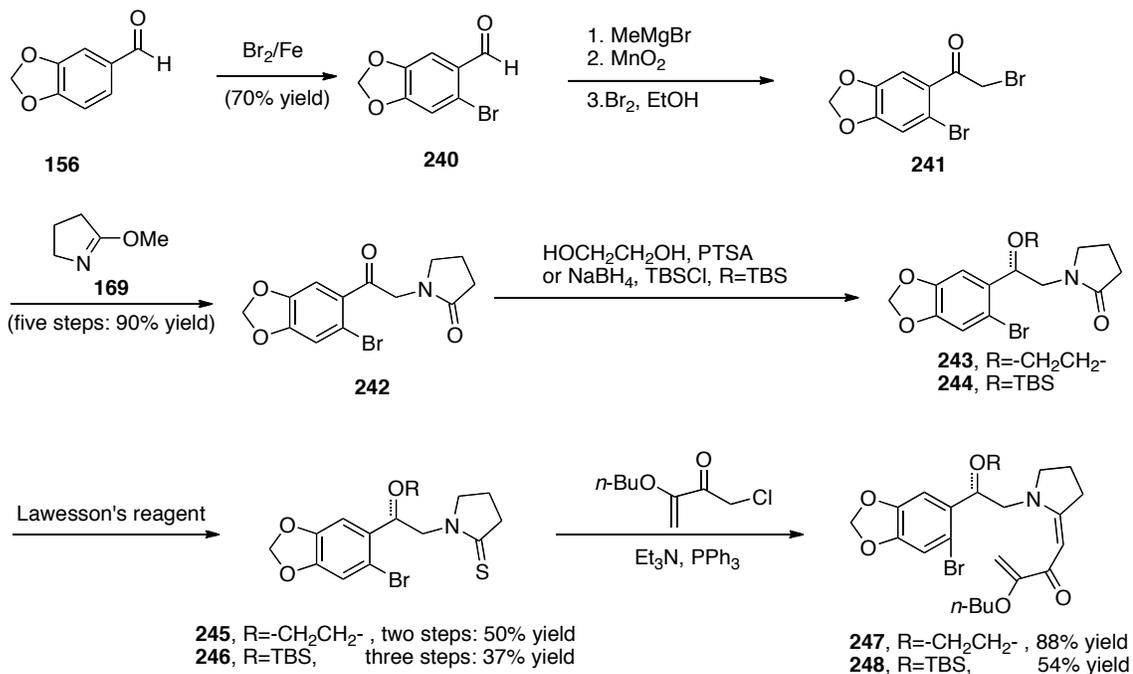


With radical cyclization substrates **247** and **248** in hand, we were disappointed to find that in the presence of Bu₃SnH/ AIBN or SmI₂ neither gave the desired product **249** (**Scheme 2.4.2**). Under the Bu₃SnH/AIBN conditions,[22,23] reductive debromination products were observed whereas under the SmI₂ conditions,[22,24] the starting materials were found to decompose.

## Scheme 2.4.2 Radical Cyclization Approach
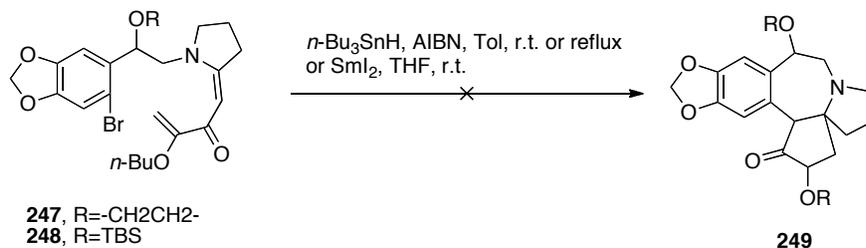
## 2.5 Conclusions

Efforts to assemble the core structure found in 11-hydroxycephalotaxine (**20**) using either a tandem Nazarov/ Friedel-Crafts cyclization or radical cascade sequence failed. Despite the failure of the key steps, considerable chemistry was developed in the course of the assembling the requisite intermediates.

## 2.6 Experimental Section

### 2.6.1 Materials and Methods

**General.** Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF) was dried either by distillation from sodium/benzophenone or by passing through activated alumina columns. Methylene chloride (DCM), diethyl ether (Et$_2$O), benzene (PhH), toluene (Tol) and acetonitrile (MeCN) were dried by passing through activated alumina columns. Dimethylformamide (DMF) was dried over activated molecular sieves or by passing through activated alumina columns. MeOH was distilled over magnesium oxide. All other commercially obtained reagents were used as received. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm). Flash chromatography was performed with indicated solvents using silica gel (particle size 0.032-0.063) purchased from Silicycle. Microwave experiments were performed using a Biotage Initiator® or CEM Discover microwave reactor. $^1$H NMR spectra were recorded at 500 MHz, 400 MHz or 300 MHz using a Bruker AM-500, Bruker Avance DPX-500, Bruker AM-400, Varian Inova 400, Varian Inova 300 or Varian Mercury Inova 300 instrument. $^{13}$C NMR spectra were recorded at 125 MHz, 100 or 75 MHz using a Bruker AM-500, Bruker Avance DPX-500, Bruker AM-400, Varian Inova 400, Varian Inova 300 or Varian Mercury Inova 300 instrument. Chemical shifts are reported relative to internal chloroform ($^1$H, $\delta = 7.26$, $^{13}$C, $\delta = 77.1$) as indicated. Splitting patterns are reported as such, app = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet. Infrared spectra were recorded on a

Nicolet Avatar 320 FT-IR. High-resolution mass spectra were acquired at the Colorado State University CIF using an Agilent 6210 TOF LCMS.

## 2.6.2 Preparative Procedures

**Preparation of vinylogous amide 155**
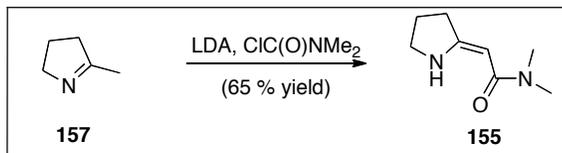


To a solution of diisopropylamine (280 μL, 2 mmol, 2.0 equiv.) in THF (1mL) at 0 ºC was added *n*-BuLi (1.25 mL, 2 mmol, 2.0 equiv., 1.6 M hexanes solution) dropwise over 5 minutes. The resultant mixture was stirred at 0 ºC for 10 minutes and then cooled to -78 ºC. To this LDA solution was added 2-methyl-pyrroline (**157**) (95 μL, 1.00 mmol, 1 equiv.). The solution was stirred for 1 hour. To this mixture was added dimethylcarbamic chloride (180 μL, 2 mmol, 2 equiv.). The reaction was stirred for three hours at -78 ºC and quenched by $H_2O$ (2 mL). The layers were separated and aqueous layer was washed with EtOAc (2 × 2 mL). The combined organic layers were washed with brine (4 mL) and dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%- 50% EtOAc/ Hexanes) to yield **155** (101mg, 65%) as brown oil.

**Vinylogous amide 155**: FTIR(NaCl/ thin film) 3343, 2925, 2877, 2361, 2339, 1624, 1567, 1516, 1369, 1310, 1294, 1144,1059, 762, 685 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.62- 8.49 (m, 1H), 4.66 (s, 1H), 3.43 (t, *J*=6.8 Hz, 2H), 2.90 (s, 6H), 2.53 (t,

$J$=7.7 Hz, 2H), 1.89 (dd, $J$=7.3, 14.5 Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 171.3, 164.1, 76.0, 46.8, 36.4, 32.5, 22.1;  HRMS (TOF LCMS) calc'd for C$_8$H$_{14}$N$_2$O [M+H] 155.1184, found 155.1178.

**Preparation of amide 168**
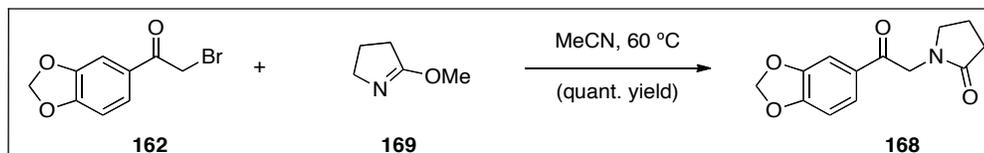


To a solution of **162** (18.8 g, 49.1 mmol, 1 equiv.) in MeCN (45 mL) was added 2-Methoxy-1-pyrroline (**169**) (7.3 g, 73.7 mmol, 1.5 equiv.). The mixture was heated to 60 ºC and stirred for 2 days.  The reaction was cooled to room temperature and concentrated by reducing pressure to yield pure **168** (12.5g) as brown oil.

**Amide 168**: FTIR (NaCl/ thin film) 2911, 1677, 1604, 1504, 1445, 1365, 1289, 1255, 1141, 1110, 1036, 931, 886 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.56 (dd, $J$=1.8, 8.2 Hz, 1H), 7.41 (d, $J$=1.6 Hz, 1H), 6.85 (d, $J$=8.2 Hz, 1H), 6.05 (s, 2H), 6.64 (s, 2H), 3.49 (t, $J$=6.9 Hz, 2H), 2.47 (t, $J$=7.8 Hz, 2H), 2.19-2.01 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 191.9, 175.9, 152.4, 148.4, 129.8, 124.6, 108.2, 107.8, 102.1, 48.9, 48.0, 30.5, 18.2; HRMS (TOF LCMS) calc'd for C$_{13}$H$_{14}$NO$_4$ [M+H] 248.0923, found 248.0922.

**Preparation of amide 170**
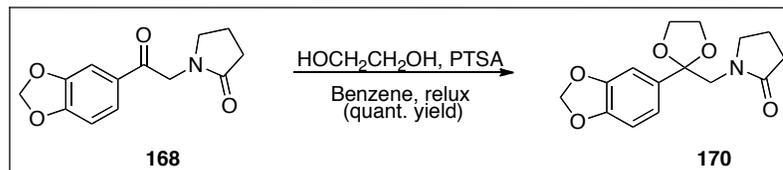


To a solution of **168** (1.8 g, 7.28 mmol, 1 equiv.) in Benzene (125 mL) was added

ethyl glycol (4.1 mL, 73.3 mmol, 10 equiv.) and *p*-Toluenesulfonic acid (180mg, 1.05

mmol, 0.14 equiv.). The mixture was heated to reflux and stirred for overnight.   The

mixture was cooled to room temperature and washed by saturated aqueous NaHCO$_3$ (2 ×

20 mL). The organic layer was dried by Na$_2$SO$_4$, filtered through Celite and concentrated

by reducing pressure to yield pure **170** (2.2g) as brown solid.

**Amide 170**: FTIR (NaCl/ thin film) 2892, 1686, 1488, 1437, 1248, 1175, 1103,

1036, 1000, 932, 812 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 6.98 (dd, *J*=1.2, 7.2 Hz, 1H),

6.97 (d, *J*=0.7 Hz, 1H), 6.76 (d, *J*=7.4 Hz, 1H), 5.95 (s, 2H), 4.02 (t, *J*=6.9 Hz, 2H), 3.80

(t, *J*=6.5 Hz, 2H), 3.62 (s, 2H), 3.45 (t, *J*=6.9 Hz, 2H), 2.29 (t, *J*=8.0, 2H), 1.98-1.87 (m,

2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 175.5, 147.8, 147.7, 134.3, 119.7, 109.4, 108.0,

106.8, 101.2, 64.8, 49.8, 49.0, 30.8, 18.6; HRMS (TOF LCMS) calc'd for C$_{15}$H$_{18}$NO$_5$

[M+H] 292.1185, found 292.1178.

**Preparation of vinylogous amide 180**
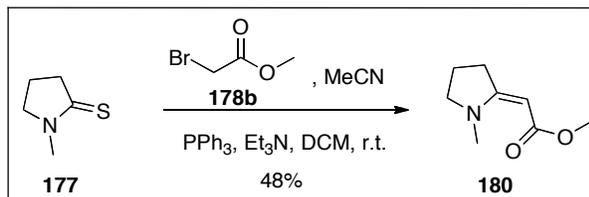


To a solution of **177** (230 mg, 2 mmol, 1 equiv.) in MeCN (800 μL) was added methyl 2-bromoacetate (**178b**) (38 μL, 4 mmol, 2 equiv.) at room temperature. The mixture was stirred for 1 day and was concentrated by reducing pressure. The residue was dissolved in DCM (800 μL) and was added Et$_3$N (340 μL, 2.4 mmol, 1.2 equiv.), PPh$_3$ (630mg, 2.4 mmol, 1.2 equiv.). The mixture was stirred for overnight and filtered through Celite, concentrated by reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%- 50% EtOAc/ Hexanes) to yield **180** (150 mg, 48%) as yellow oil.

**Vinylogous Amide 180**: FTIR (NaCl/ thin film) 2969, 2947, 2883, 1675, 1582, 1456, 1456, 1412, 1375, 1298, 1243, 1135, 1108, 1054, 980, 908, 778 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 4.46 (s, 1H), 3.61 (d, *J*=2.4 Hz, 3H), 3.37 (td, *J*=1.8, 7.8 Hz, 2H), 3.13 (td, *J*=1.8, 7.8 Hz, 2H), 3.79 (d, *J*=1.9 Hz, 3H), 1.99-1.89 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 169.8, 165.8, 77.2, 54.5, 50.0, 33.2, 32.5, 21.0; HRMS (TOF LCMS) calc'd for C$_8$H$_{14}$NO$_2$ [M+H] 156.1025, found 156.1020.

**Preparation of thiolactam 167**
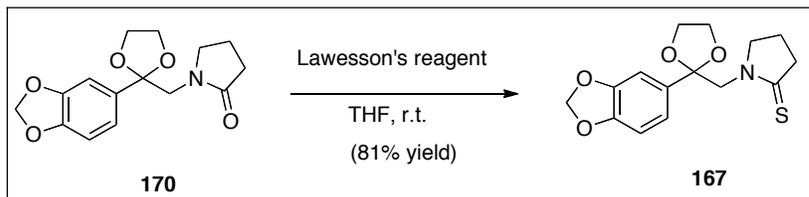


To a solution of **170** (675.4 mg, 2.32 mmol, 1 equiv.) in THF (2 mL) was added Lawesson's reagent (562.8 mg, 11.6 mmol, 0.5 equiv.) at room temperature. The mixture was stirred for overnight. The reaction was concentrated under reduced pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%- 50% EtOAc/ Hexanes) to yield **167** (580 mg, 81.4%) as orange solid.

**Thiol lactam 167**: FTIR (NaCl/ thin film) 2892, 1687, 1503, 1488, 1438, 1363, 1250, 1119, 1036, 934, 993, 812 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 6.95 (dd, $J$=1.6, 8.4, 1H), 6.95 (d, $J$=1.7 Hz, 1H), 6.70 (d, $J$=8.4, 1H), 5.89 (s, 2H), 4.14 (s, 2H), 3.98 (t, $J$=7.2 Hz, 2H), 3.75(t, $J$=7.1 Hz, 4H), 2.89 (t, $J$=7.8 Hz, 2H), 1.97-1.84 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 203.2, 147.7, 147.5, 133.5, 119.4, 108.8, 107.8, 106.6, 101.1, 64.5, 55.9, 53.7, 44.6, 20.0; HRMS (TOF LCMS) calc'd for C$_{15}$H$_{18}$NO$_4$S [M+H] 308.0957, found 308.0959.

**Preparation of vinylogous amide 182**
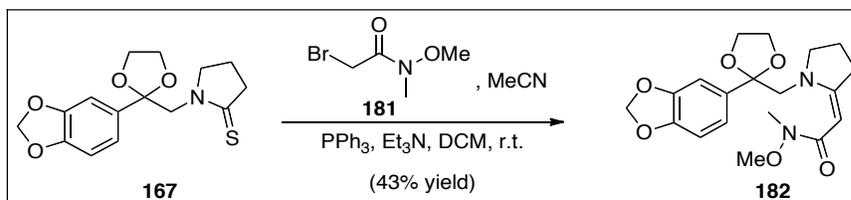
To a solution of **167** (190 mg, 0.62 mmol, 1 equiv.) in MeCN (250 μL) was added 2-bromo-N-methoxy-N-methylacetamide (**181**) (95 μL, 1 mmol, 1.62 equiv.) at room temperature. The mixture was stirred for 1 day and concentrated by reducing pressure. The residue was dissolved in DCM (250 μL) and was added Et$_3$N (100 μL mL, 0.74 mmol, 1.2 equiv.), PPh$_3$ (295 mg, 0.74 mmol, 1.2 equiv.). The mixture was stirred for overnight and filtered by Celite, concentrated by reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%- 50% EtOAc/ Hexanes) to yield **182** (100 mg, 43%) as yellow oil.

**Vinylogous Amide 182**: FTIR (NaCl/ thin film) 2890, 1634, 1573, 1487, 1435, 1387, 1246, 1168, 1099, 1035, 990 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 6.94- 6.88 (m, 2H), 6.72 (d, $J$=8.6 Hz, 1H), 5.91 (s, 2H), 5.23 (s, 1H), 3.99- 3.93 (m, 2H), 3.79- 3.73 (m, 2H), 3.64 (s, 3H), 3.48 (s, 2H), 3.27 (t, $J$=7.0 Hz, 2H), 3.12-3.05 (m, 5H), 1.83-1.74 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 172.1, 165.3, 147.7, 147.6, 134.5, 119.3, 109.8, 108.0, 106.5, 101.1, 77.9, 64.9, 61.0, 55.2, 54.1, 33.1, 32.2, 21.8; HRMS (TOF LCMS) calc'd for C$_{19}$H$_{25}$N$_2$O$_6$ [M+H] 377.1713, found 377.1705.

**Preparation of chloro ketone 210**
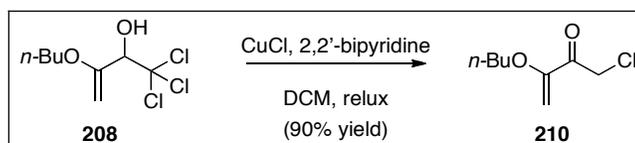


To a solution of **208** (644 mg, 2.60 mmol, 1 equiv.) in DCM (7 mL) was added CuCl (522 mg, 5.25 mmol, 2.02 equiv.) and 2,2'-bipyridine (785 mg, 5.03 mmol, 1.93 equiv.). The mixture was heated to reflux and stirred for 3 hours. Then the reaction was

cooled to room temperature and filtered through Celite by Et$_2$O (2 × 20mL). The solution was washed by H$_2$O (40 mL) and dried by Na$_2$SO$_4$, concentrated by reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 10%- 20% EtOAc/ Hexanes) to yield **210** (380 mg, 90%) as brown oil.

**Chloro ketone 210**: FTIR (NaCl/ thin film) 2960, 2936, 2874, 1732, 1614, 1465, 1398, 1368, 1313, 1264, 1062 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 5.29 (d, $J$=2.6 Hz, 1H), 4.51 (s, 2H), 4.46 (d, $J$=2.5 Hz, 1H), 3.76 (t, $J$=7.4 Hz, 2H), 1.82-1.59 (m, 2H), 1.56- 1.37 (m, 2H), 0.96 (t, $J$=7.4 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 189.0, 156.3, 92.1, 68.4, 47.3, 30.9, 19.5, 14.0; HRMS (TOF LCMS) calc'd for C$_8$H$_{14}$ClO$_2$ [M+H] 176.0682, found 177.0676.

**Preparation of dienone 211**
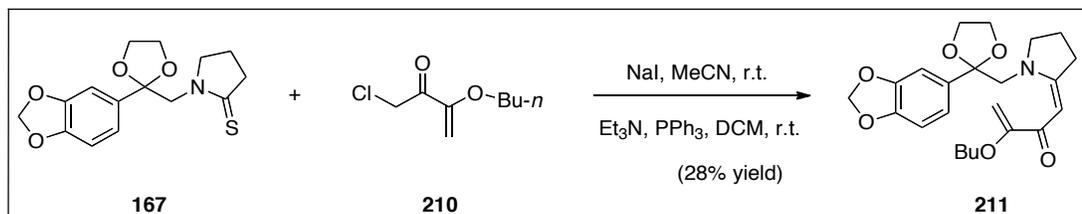


To a solution of **167** (224 mg, 0.73 mmol, 1 equiv.) in MeCN (1.6 mL) was added **210** (257 mg, 2.03 mmol, 2.8 equiv.) and NaI (240 mg, 1.60 mmol, 2.2 equiv.) at room temperature. The mixture was stirred for 1 day and concentrated by reducing pressure. The residue was dissolved in DCM (5 mL) and was added Et$_3$N (122 μL, 0.90 mmol, 1.2 equiv.), PPh$_3$ (230 mg, 0.90 mmol, 1.2 equiv.). The mixture was stirred for overnight and filtered by Celite, concentrated by reducing pressure. The residue was loaded onto silica

and purified by column chromatography (gradient elution, 50%:1% - 50% :10% EtOAc/ Hexanes: MeOH) to yield **211** (84 mg, 28%) as brown oil.

**Dienone 211 (rotamer)**: FTIR (NaCl/ thin film) 2957, 2890, 1705, 1544, 1487, 1436, 1287, 1247, 1036, 939, 812 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 6.96 (d, $J$=1.6 Hz, 1H), 6.95 (s, 1H), 6.75 (dd, $J$=1.7, 8.7 Hz, 1H), 5.95 (d, $J$=2.5 Hz, 2H), 5.83 (d, $J$=45.0 Hz, 1 H), 5.09 (d, $J$=1.4 Hz, 1H), 4.19 (d, $J$=1.3 Hz, 1H), 4.05- 3.93 (m, 2H), 3.86- 3.78 (m, 2H), 3.74 (t, $J$=6.3 Hz, 2H), 3.63 (s, 1H), 3.57 (s, 1H), 3.53- 3.38 (m, 2H), 3.24 (t, $J$=7.7 Hz, 2H), 1.99- 1.82 (m, 2H), 1.81- 1.70 (m, 2H), 1.63- 1.43 (m, 2H), 0.99 (t, $J$=7.5 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 183.6, 182.9, 171.1, 169.2, 161.0, 148.1, 148.0, 134.4, 133.9, 119.7, 119.5, 109.8, 109.4, 108.2, 108.2, 106.7, 101.4, 101.3, 86.7, 86.1, 83.5, 67.5, 65.1, 65.0, 55.0, 55.1, 54.7, 34.0, 33.8, 31.4, 21.6, 21.3, 19.7, 14.1; HRMS (TOF LCMS) calc'd for C$_{23}$H$_{30}$NO$_6$ [M+H] 416.2073, found 417.2066.

**Preparation of dienone 220**
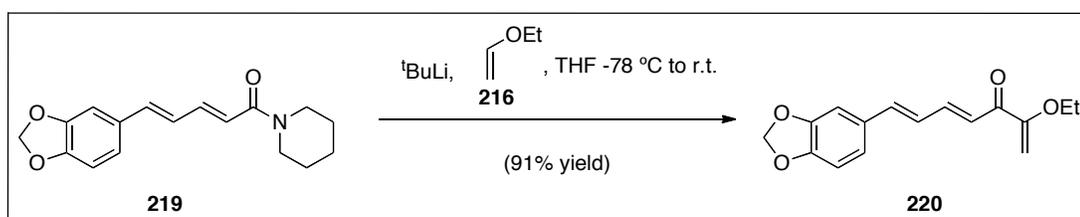


To a solution of vinyl ether (**216**) (1.60 mL, 16.5 mmol, 6.0 equiv.) in THF (20mL) at -78 ºC was added $^t$BuLi (4.85 ml, 8.25 mmol, 3.0 equiv., 1.7 M hexanes solution) dropwise over 5 minutes. The resultant mixture was stirred at -78 ºC for 30 minutes, and then warmed to 0 ºC and stirred for 2 hours. To a solution of piperine (**219**) (784 mg, 2.75 mmol, 1 equiv.) in THF (1 mL) was added lithio vinyl ether solution at -78

ºC and stirred for 15 minutes. The mixture was warmed to room temperature and stirred

for overnight. The reaction was quenched by $H_2O$ (5 mL). The layers were separated and

aqueous layer was washed with EtOAc (2 × 30 mL). The combined organic layers were

washed with brine (60 mL) and dried over $Na_2SO_4$, filtered through Celite and

concentrated under reduced pressure. The residue was loaded onto silica and purified by

column chromatography (gradient elution, 10%- 20% EtOAc/ Hexanes) to yield **220** (1 g,

100%) as brown solid.

**Dienone 220**: FTIR(NaCl/ thin film)  2980, 2900, 1667, 1607, 1575, 1503, 1489,

1447, 1372, 1329, 1296, 1254, 1217, 1080, 1038, 1001, 930, 853 cm$^{-1}$; $^1$H NMR (400

MHz, CDCl$_3$) δ 7.53 (dd, J=10.8, 15.1 Hz, 1H), 7.01 (s, 1H), 6.99- 6.71 (m, 5H), 6.00 (s,

2H), 5.25 (d, J=2.2 Hz, 1H), 4.49 (d, J=2.2 Hz, 1H), 3.85 (q, J=6.9 Hz, 2H), 1.42 (t,

J=6.9 Hz, 3H) ; $^{13}$C NMR (100 MHz, CDCl$_3$) δ 186.6, 158.5, 148.9, 148.5, 145.0, 142.0,

130.9, 125.6, 123.6, 123.4, 108.7, 106.0, 101.6, 91.4, 64.0, 14.6;  HRMS (TOF LCMS)

calc'd for $C_{16}H_{17}O_4$ [M+H] 273.1127, found 273.1125.


**Preparation of unsaturated ketone 221**
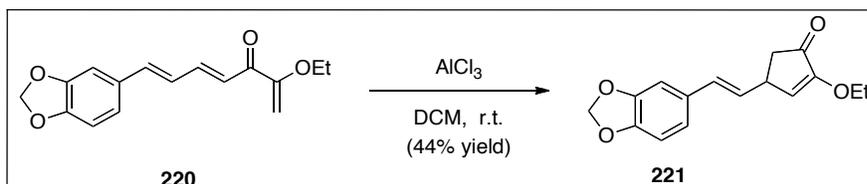


To a solution of **220** (272.3 mg, 1 mmol, 1 equiv.) in DCM (27 mL) was added

AlCl$_3$ (13.4 mg, 0.1 mmol, 0.1 equiv.) at room temperature. The mixture was stirred for 4

days, filtered through Celite and concentrated under reduced pressure. The residue was

loaded onto silica and purified by column chromatography (gradient elution, 10%- 25% EtOAc/ Hexanes) to yield **221** (120 mg, 44%) as orange oil.

**Ketone 221**: FTIR(NaCl/ thin film)  2980, 2895, 17616, 1621, 1503, 1489, 1446, 1250, 1119, 1037, 965, 927 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 6.88 (s, 1H), 6.81- 6.67 (m, 2H), 6.39 (d, $J$=15.7 Hz, 1H), 6.26 (d, $J$=3.0 Hz, 1H), 5.94 (s, 2H), 5.87 (dd, $J$=8.4, 15.7 Hz, 1H), 4.01- 3.85 (m, 2H), 3.61- 3.45 (m, 1H), 2.77 (dd, $J$=6.5, 19.3 Hz, 1H), 2.24 (dd, $J$=2.0, 9.2 Hz, 1H), 1.41 (t, $J$=7.0 Hz, 3H) ; $^{13}$C NMR (100 MHz, CDCl$_3$) δ 201.9, 156.6, 148.3, 147.4, 131.3, 130.3, 129.6, 1295, 121.0, 108.5, 105.7, 101.3, 66.0, 40.7, 37.8, 14.5;  HRMS (TOF LCMS) calc'd for C$_{16}$H$_{17}$O$_4$ [M+H] 273.1127, found 273.1122.

**Preparation of amine 233**
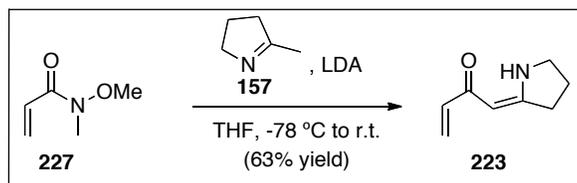


To a solution of diisopropylamine (179 μL, 1.20 mmol, 5.3 equiv.) in THF (1mL) at 0 ºC was added *n*-BuLi (750 μL, 1.20 mmol, 5.3 equiv., 1.6 M hexanes solution) dropwise over 5 minutes. The resultant mixture was stirred at 0 ºC for 10 minutes, and then cooled to -78 ºC. To this LDA solution was added 2-methyl-pyrroline (**157**) (100 μL, 1.05 mmol, 4.6 equiv.). The mixture was stirred at -78 ºC for 1 hour. To this mixture was added to **227** (57.5 mg, 0.23 mmol, 1 equiv.) and the mixture was stirred for three hours at -78 ºC. The reaction was quenched by H$_2$O (2 mL). The layers were separated and aqueous layer was washed with EtOAc (2 × 2 mL). The combined organic layers

were washed with brine (4 mL) and dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 50- 67% EtOAc/ Hexanes) to yield **223** (30 mg, 44%) as brown oil.

**Vinylogous amide 223**: FTIR(NaCl/ thin film) 3278, 1607, 1540, 1505, 1396, 1330, 1298, 1257, 1144, 1045, 987, 939, 806, 774, 739 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 10.30- 10.10 (m, 1H), 6.27 (dd, J=1.2, 17.3 Hz, 1H), 6.05 (dd, J=1.7, 17.1 Hz, 1H), 5.39 (d, J=10.4 Hz, 1H), 5.16 (s, 1H), 3.55 (t, J=8.1 Hz, 2H), 2.60 (t, J=7.8 Hz, 2H), 1.95 (dd, J=7.9, 15.4 Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 186.0, 169.4, 137.9, 122.3, 89.6, 47.4, 32.5, 21.2; HRMS (TOF LCMS) calc'd for $C_8H_{11}NO$ [M+H] 138.0919, found 138.0910.

**Preparation of vinylogous amide 230**
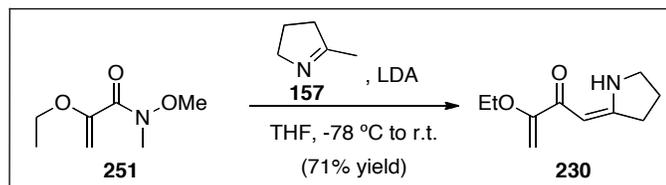


To a solution of diisopropylamine (340 µL, 2.43 mmol, 1.15 equiv.) in THF (2mL) at 0 ºC was added *n*-BuLi (1.5 ml, 2.32 mmol, 1.1 equiv., 1.6 M hexanes solution) dropwise over 5 minutes. The resultant mixture was stirred at 0 ºC for 10 minutes, and then cooled to -78 ºC. To this LDA solution was added 2-methyl-pyrroline (**157**) (200 µL, 2.11 mmol, 1 equiv.) The mixture was stirred at -78 ºC for 1 hour. To this mixture was added **251** (304 mg, 2.11 mmol, 1 equiv.) and the solution was warmed to room

temperature and stirred for overnight. The reaction was quenched by H$_2$O (2 mL). The layers were separated and aqueous layer was washed with EtOAc (2 × 2 mL). The combined organic layers were washed with brine (4 mL) and dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%- 50% EtOAc/ Hexanes) to yield **230** (240 mg, 62.7%) as brown solid.

**Vinylogous amide 230**: FTIR(NaCl/ thin film) 2978, 1700, 1600, 1534, 1507, 1377, 1282, 1225, 1127, 1061, 977, 794 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 10.3- 10.1 (m, 1H), 5.71 (s, 1H), 5.11 (s, 1H), 4.24 (s, 1H), 3.79 (q, *J*=6.9 Hz, 2H), 3.61 (t, *J*=6.9 Hz, 2H), 2.00 (t, *J* =7.7 Hz, 2H), 2.05- 1.93 (m, 2H), 1.36 (t, *J*=6.9 Hz, 3H) ; $^{13}$C NMR (100 MHz, CDCl$_3$) δ 183.6, 170.2, 159.6, 87.1, 85.4, 63.5, 47.9, 33.0, 21.4, 14.6;  HRMS (TOF LCMS) calc'd for C$_{10}$H$_{15}$NO$_2$ [M+H] 182.1181, found 182.1176.


**Preparation of vinylogous amide 231**
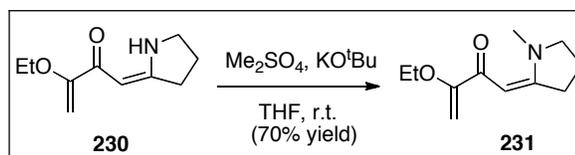


To a solution of **230** (100mg, 0.55 mmol, 1 equiv.) in THF (3 mL) was added KO$^t$Bu (68mg, 0.61 mmol, 1.1 equiv.) and Me$_2$SO$_4$ (60 μL, 0.63 mmol, 1.1 equiv.) at room temperature. The mixture was stirred for 2 days ad quenched by H$_2$O (1mL). The layers were separated and aqueous layer was washed with EtOAc (2 × 5 mL). The combined organic layers were washed with brine (10 mL) and dried over Na$_2$SO$_4$, filtered through Celite and concentrated under reduced pressure. The residue was loaded onto

silica and purified by column chromatography (gradient elution, 33%- 67% EtOAc/ Hexanes) to yield **231** (75 mg, 69.6%) as orange solid.

**Vinylogous amide 231**: FTIR(NaCl/ thin film) 2976, 2919, 1637, 1594, 1493, 1443, 1376, 1269, 1060, 984, 858, 802 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 5.63 (s, 1H), 5.12 (s, 1H), 4.21 (s, 1H), 3.80 (q, $J$=6.9 Hz, 2H), 3.46- 3.35 (m, 2H), 3.30 (t, $J$ =7.6, 2H), 2.92 (s, 3H), 2.03- 1.89 (m, 2H), 1.37 (t, $J$=6.9 Hz, 3H) ; $^{13}$C NMR (100 MHz, CDCl$_3$) δ 183.1, 168.8, 160.8, 87.0, 84.7, 63.5, 54.8, 33.9, 33.5, 20.9, 14.6; HRMS (TOF LCMS) calc'd for C$_{11}$H$_{18}$NO$_2$ [M+H] 196.1338, found 196.1336.

**Preparation of diaketone 233**
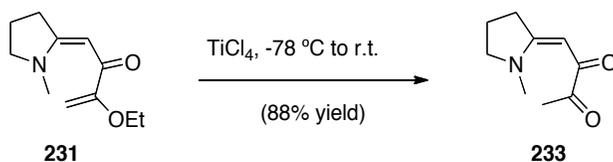


To a solution of **231** (28 mg, 0.14 mmol, 1 equiv.) in DCM (15 mL) at -78°C was added TiCl$_4$ (140 μL, 0.14 mmol, 1 equiv.) dropwise. Then the mixture was warmed to room temperature and stirred for overnight. The reaction was quenched by H$_2$O (15 mL). The organic was dried by Na$_2$SO$_4$ and concentrated by reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 50%- 75% EtOAc/ Hexanes) to yield **233** (21 mg, 88%) as orange oil.

**Diaketone 233**: FTIR (NaCl/ thin film) 2924, 1701, 1653, 1559, 1457, 1419, 1301 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 5.69  (s, 1H), 3.51 (t, $J$=6.4 Hz, 2H), 3.31 (t, $J$=7.8 Hz, 2H), 2.98  (s, 3H), 2.38  (s, 3H), 3.31 (dd, $J$=7.7, 15.4 Hz, 2H); $^{13}$C NMR (100

MHz, CDCl$_3$) δ 210.7, 201.3, 167.4, 82.5, 55.3, 34.1, 33.8, 24.7, 20.7; HRMS (TOF LCMS) calc'd for C$_9$H$_{14}$NO$_2$ [M+H] 168.1025, found 168.1020.

**Preparation of dienone 235**
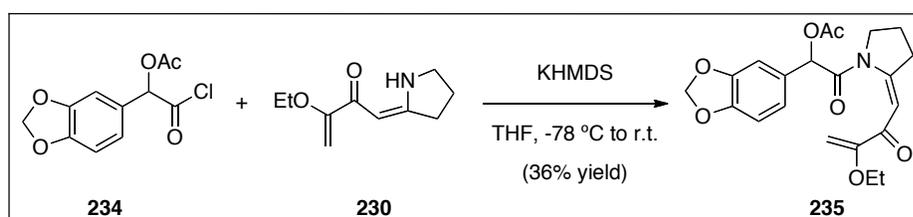


To a solution of **230** (87mg, 0.48 mmol, 1 equiv.) in THF (5 mL) was added KHMDS (1.05 mL, 0.53 mmol, 1.1 equiv.) at -78 ºC and the mixture was stirred for 10min. To the mixture was added **234** (186.2mg, 0.73 mmol, 1.5 equiv.) was at -78 ºC dropwise over 5 min. Then the mixture was warmed to room temperature and stirred for overnight. The reaction was quenched by H$_2$O (1 mL). The layers were separated and aqueous layer was washed with EtOAc (2 × 5 mL). The combined organic layers were washed with brine (10 mL) and dried over Na$_2$SO$_4$, filtered through Celite and concentrated under reduced pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%- 50% EtOAc/ Hexanes) to yield **235** (70 mg, 36.3%) as yellow oil.

**Dienone 235**: FTIR(NaCl/ thin film) 2979, 2895, 1742, 1697, 1666, 1568, 1504, 1490, 1446, 1393, 1371, 1309, 1232, 1104, 1039, 935, 864, 810 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.00 (s, 1H), 6.95 (d, *J*=1.5 Hz, 1H), 6.90 (dd, *J*=1.5, 7.9 Hz, 1H), 6.81 (d, *J*=7.9 Hz, 1H), 5.99 (s, 2H), 5.98 (s, 1H), 5.16 (d, *J*=2.3 Hz, 1H), 4.42 (d, *J*=2.3 Hz, 1H), 3.90- 3.87 (m, 1H), 3.81 (q, *J* =7.0 Hz, 2H), 3.54- 3.45 (m, 1H), 3.24- 3.05 (m, 2H),

2.17 (s, 3H), 2.04- 1.78 (m, 2H), 1.4 (t, $J$=7.0 Hz, 3H) ; $^{13}$C NMR (100 MHz, CDCl$_3$) δ

188.1, 170.7, 168.1, 159.4, 158.6, 149.1, 148.6, 125.9, 123.3, 109.1, 108.8, 103.9, 101.7,

90.4, 75.0, 63.8, 49.0, 31.9, 22.0, 20.9, 14.4; HRMS (TOF LCMS) calc'd for C$_{21}$H$_{24}$NO$_7$

[M+H] 402.1553, found 402.1553.


**Preparation of ketone 242**
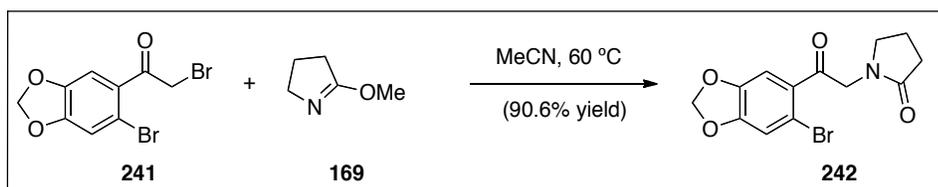


To a solution of **241** (1.75 g, 5.43 mmol, 1 equiv.) in MeCN (3 mL) was added 2-

Methoxy-1-pyrroline (**169**) (708 mg, 7.15 mmol, 1.3 equiv.). The mixture was heated to

60 ºC and stirred for 1 day.  The mixture was cooled to room temperature and

concentrated by reducing pressure to yield pure **242** (1.6g, 90.6%) as orange solid.

**Ketone 242**: FTIR (NaCl/ thin film) 2918, 1680, 1612, 1503, 1480, 1442, 1408,

1385, 1350, 1243, 1122, 1035, 932 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.05 (s, 1H),

7.04 (s, 1H), 6.05 (s, 2H), 4.59 (s, 2H), 3.50 (t, $J$=6.9 Hz, 2H), 2.45 (t, $J$=7.0 Hz, 2H),

2.16-2.04 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 196.2, 175.9, 151.0, 147.7, 131.8,

114.1, 112.2, 109.3, 102.7, 51.7, 47.9, 30.4, 18.2; HRMS (TOF LCMS) calc'd for

C$_{13}$H$_{13}$BrNO$_4$ [M+H] 326.0028, found 302.0024.

**Preparation of amide 243**
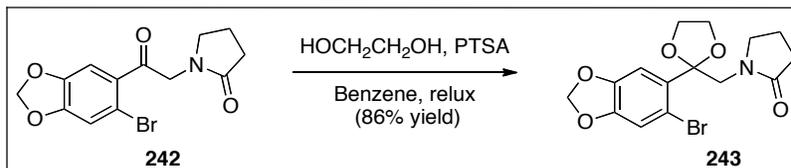


To a solution of **242** (580 mg, 1.78 mmol, 1 equiv.) in Benzene (40 mL) was added ethyl glycol (1.1 mL, 19.7 mmol, 11 equiv.) and *p*-Toluenesulfonic acid (44 mg, 0.257 mmol, 0.14 equiv.). The mixture was heated to reflux and stirred for overnight. The mixture was cooled to room temperature and washed by saturated aqueous $NaHCO_3$ (2 × 10 mL). The organic layer was dried by $Na_2SO_4$, filtered through Celite and concentrated by reducing pressure to yield pure **243** (565 mg, 86.0%) as brown solid.

**Amide 243**: FTIR (NaCl/ thin film) 2893, 1690, 1502, 1477, 1422, 1286, 1238, 1196, 1114, 1039, 1009, 931 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.17 (s, 1H), 7.03 (s, 1H), 5.97 (s, 2H), 4.03(t, *J*=6.9 Hz, 2H), 3.87 (s, 2H), 3.80 (t, *J*=6.7 Hz, 2H), 3.48 (t, *J*=7.0 Hz, 2H), 2.31 (t, *J*=8.0 Hz, 2H), 2.02-1.83 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 175.7, 148.5, 147.3, 132.2, 114.9, 111.9, 109.4, 108.8, 102.1, 64.7, 49.2, 47.6, 30.8, 18.7; HRMS (TOF LCMS) calc'd for C$_{15}$H$_{17}$BrNO$_5$ [M+H] 370.0290, found 370.0281.

**Preparation of alcohol 252**
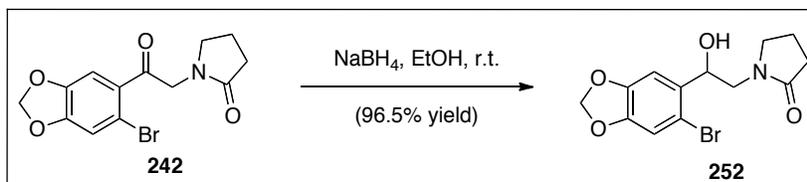
To a solution of **242** (510 mg, 1.56 mmol, 1 equiv.) in EtOH (5 ml) was added NaBH4 (660 mg, 15.6, 10 equiv.) and the mixture was stirred for overnight at room temperature. The reaction was quenched by $H_2O$ (10 mL) and washed by EtOAc 2 × 10 mL). The combined organic layers was dried by $Na_2SO_4$, filtered through Celite and concentrated by reducing pressure to yield pure **252** (492 mg, 96.5%)

**Alcohol 252**: FTIR (NaCl/ thin film) 3338, 2906, 1664, 1501, 1475, 1421, 1288, 1237, 1111, 1036, 931, 876 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.17 (s, 1H), 6.03 (s, 1H), 5.97 (s, 2H), 5.13 (t, $J$=5.1 Hz, 1H), 4.90- 4.62 (m, 1H), 3.67- 3.35 (m, 3H), 3.26-3.10 (m, 1H), 2.43 (t, $J$=7.4 Hz, 2H), 2.11-1.86 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 178.1, 147.9, 147.8, 134.3, 112.5, 111.5, 108.0, 101.9, 72.9, 50.7, 49.6, 30.9, 18.6; HRMS (TOF LCMS) calc'd for C$_{13}$H$_{14}$BrNO$_4$Na [M+Na] 350.0004, found 349.9994.

**Preparation of amide 244**



**252**     TBSCl, Imidazole / DCM, r.t. (78% yield)     **244**
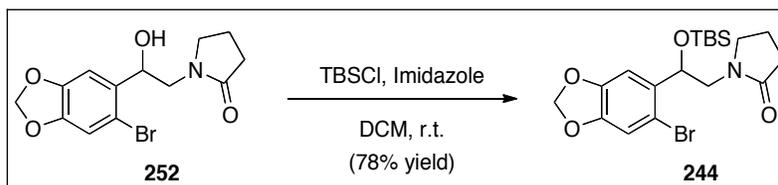
To a solution of **252** (700 mg, 2.27 mmol, 1 equiv.) in DCM (10 mL) was added TBSCl (772 mg, 5.44 mmol, 2.4 equiv.) and imidazole (2.98 g, 45.4 mmol, 20 equiv.) at room temperature. The mixture was stirred for 2 days and concentrated by reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 10%- 33% EtOAc/ Hexanes) to yield **244** (735 mg, 78.0%) as white solid.

**Amide 244**: FTIR (NaCl/ thin film) 2954, 2928, 2895, 2856, 1692, 1503, 1475, 1411, 1286, 1237, 1110, 1090, 1035, 940, 836 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.03 (s, 1H), 6.91 (s, 1H), 5.96 (dd, *J* =1.2 Hz, 2H), 5.19 (dd, *J*=4.3, 7.6 Hz, 1H), 3.56- 3.30 (m, 3H), 3.17 (dd, *J* =4.3, 13.7 Hz, 1H), 2.33 (t, *J*=8.0 Hz, 2H), 2.03-1.91 (m, 2H), 0.86 (s, 9H), 0.03 (s, 3H), 0.13 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 175.2, 147.8, 147.7, 135.2, 112.2, 111.9, 108.0, 101.8, 71.6, 50.2, 48.8, 31.0, 25.8, 18.3, 18.1, -4.76, -5.02; HRMS (TOF LCMS) calc'd for C$_{19}$H$_{29}$BrNO$_4$Si [M+H] 442.1049, found 442.1044.

**Preparation of thiol lactam 245**
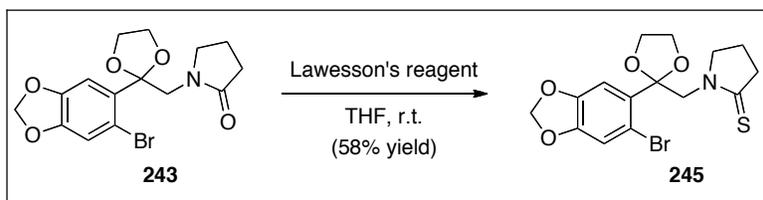


To a solution of **243** (2.90 g, 8.98 mmol, 1 equiv.) in THF (10 mL) was added Lawesson's reagent (1.90 g, 5.34 mmol, 0.6 equiv.) at room temperature. The mixture was stirred for overnight. The reaction was concentrated under reduced pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%- 50% EtOAc/ Hexanes) to yield **245** (2 g, 58.2%) as orange solid.

**Thiol lactam 245**: FTIR (NaCl/ thin film) 2892, 1501, 1477, 1238, 1201, 1223, 1033, 951 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.20 (s, 1H), 7.04 (s, 1H), 5.99 (s, 2H), 4.44 (s, 2H), 4.11- 3.99 (m, 2H), 3.88- 3.77 (m, 4H), 3.0 (t, *J*=7.6 Hz, 2H), 2.05- 1.91 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 203.9, 148.7, 147.5, 131.8, 114.9, 112.0, 109.0,

108.8, 102.1, 64.6, 56.6, 52.1, 45.0, 20.4; HRMS (TOF LCMS) calc'd for $C_{15}H_{17}BrNO_4S$ [M+H] 386.0062, found 386.0057.

**Preparation of thiol lactam 246**
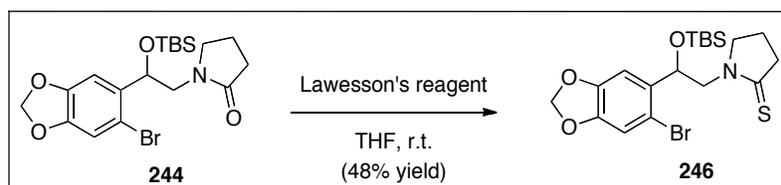


To a solution of **244** (52 mg, 0.12 mmol, 1 equiv.) in THF (0.2 mL) was added Lawesson's reagent (28.5 g, 0.07 mmol, 0.6 equiv.) at room temperature. The mixture was stirred for overnight. The reaction was concentrated under reduced pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%- 50% EtOAc/ Hexanes) to yield **246** (25 mg, 48.0%) as yellow oil.

**Thiol lactam 246**: FTIR (NaCl/ thin film) 2954, 2928, 2886, 2856, 1503, 1475, 1409, 1326, 1235, 1110, 1085, 1038, 936, 837 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.03 (s, 1H), 6.93 (s, 1H), 5.98 (dd, $J$=1.4, 10.4 Hz, 2H), 5.50 (dd, $J$=5.2, 7.5 Hz, 1H), 3.91 (dd, $J$=7.6, 13.0 Hz, 1H), 3.84- 3.76 (m, 1H), 3.70 (dd, $J$=5.2, 10.8 Hz, 1H), 3.56- 3.48 (m, 1H), 3.0 (t, $J$=7.9 Hz, 2H), 2.04- 1.95 (m, 2H), 0.87 (s, 9H), 0.06 (s, 3H), 0.11(s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 202.3, 148.1, 147.9, 135.1, 112.4, 112.3, 108.0, 101.9, 70.4, 57.2, 55.2, 45.1, 25.9, 20.1, 18.0, -4.8; HRMS (TOF LCMS) calc'd for $C_{19}H_{19}BrNO_3SSi$ [M+H] 458.0821, found 458.0812.

## Preparation of dienone 247
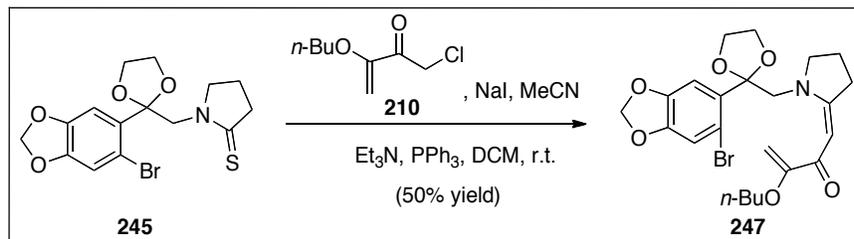


To a solution of **245** (191 mg, 0.50 mmol, 1 equiv.) in MeCN (4 mL) was added 3-butoxy-1-chlorobut-3-en-2-one (**210**) (131 mg, 0.75 mmol, 1.5 equiv.) and NaI (93 mg, 0.70 mmol, 1.4 equiv.) at room temperature. The mixture was stirred for 1 day and concentrated by reducing pressure. The residue was dissolved in DCM (2 mL) and was added Et$_3$N (170 µL, 0.60 mmol, 1.2 equiv.), PPh$_3$ (157 mg, 0.60 mmol, 1.2 equiv.). The mixture was stirred for overnight and filtered by Celite, concentrated by reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 50%:1% - 50% :10% EtOAc/ Hexanes: MeOH) to yield **247** (100 mg, 49.7%) as brown oil.

**Dienone 247**:  FTIR (NaCl/ thin film) 2957, 1709, 1593, 1537, 1502, 1477, 1305, 1238, 1198, 1119, 1004, 934, 847 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.14  (s, 1H), 7.02 (s, 1H), 6.05 (s, 1H), 5.97 (s, 2H), 5.09 (d, $J$=1.5 Hz, 1H), 4.19 (d, $J$=1.4 Hz, 1H), 4.02-3.95 (m, 2H), 3.84 (s, 2H), 3.82- 3.76 (m, 2H), 3.73 (t, $J$=6.5 Hz, 2H), 3.51 (t, $J$=7.3 Hz, 2H), 3.25 (t, $J$=7.6 Hz, 2H), 1.95- 1.84 (m, 2H), 1.79- 1.69 (m, 2H), 1.56- 1.44 (m, 2H), 0.96 (t, $J$=7.4 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 183.8, 169.3, 161.0, 148.7, 147.5, 132.2, 114.8, 111.7, 110.0, 108.6, 102.1, 86.7, 86.3, 67.6, 64.9, 54.9, 52.4, 33.8, 31.3,

21.6, 19.6, 14.0; HRMS (TOF LCMS) calc'd for $C_{23}H_{29}BrNO_6$ [M+H] 494.1178, found 494.1176.

**Preparation of dienone 248**
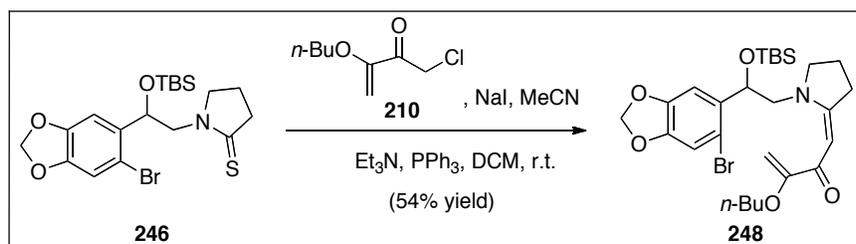


To a solution of **246** (60 mg, 0.13 mmol, 1 equiv.) in MeCN (1 mL) was added 3-butoxy-1-chlorobut-3-en-2-one (**210**) (46 mg, 0.20 mmol, 1.5 equiv.) and NaI (47 mg, 0.18 mmol, 1.4 equiv.) at room temperature. The mixture was stirred for 1 day and concentrated by reducing pressure. The residue was dissolved in DCM (1 mL) and was added $Et_3N$ (33 μL, 0.16 mmol, 1.2 equiv.), $PPh_3$ (62 mg, 0.16 mmol, 1.2 equiv.). The mixture was stirred for overnight and filtered by Celite, concentrated by reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 50%:1% - 50% :10% EtOAc/ Hexanes: MeOH) to yield **248** (40 mg, 54.0%) as brown oil.

**Dienone 248**: FTIR (NaCl/ thin film) 2956, 2931, 2859, 1547, 1504, 1475, 1400, 1390, 1288, 1237, 1111, 1094, 1035, 930, 837, 779 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.03 (s, 1H), 6.93 (s, 1H), 5.97 (dd, $J$=1.4, 15.9 Hz, 2H), 5.91 (s, 1H), 5.29 (dd, $J$=3.7, 8.5 Hz, 1H), 5.11 (d, $J$=1.6 Hz, 1H), 4.20 (d, $J$=1.6 Hz, 1H), 3.73 (td, $J$=1.2, 6.6 Hz, 2H), 3.65- 3.57 (m, 1H), 3.48- 3.25 (m, 5H), 2.00- 1.91 (m, 2H), 1.79- 1.71 (m, 2H), 1.53-

1.42 (m, 2H), 0.96 (t, $J$=7.4 Hz, 3H), 0.84 (s, 9H), 0.02 (s, 3H), 0.15 (s, 3H); $^{13}$C NMR

(100 MHz, CDCl$_3$) δ 183.4, 168.3, 161.0, 148.1, 148.0, 134.8, 112.3, 111.6, 107.8, 101.9,

86.8, 85.7, 71.2, 67.7, 54.9, 53.9, 34.2, 31.2, 25.8, 21.1, 19.7, 18.0, 14.1, -4.91, -4.99;

HRMS (TOF LCMS) calc'd for C$_{27}$H$_{41}$BrNO$_5$Si [M+H] 566.1937, found 566.1924.

## 2.7 Notes and References

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**Appendix I: Spectra Relevant to Chapter 2**
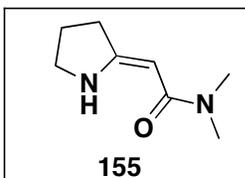
Figure A.2.1 1H NMR (400MHz, CDCl₃) of compound 155
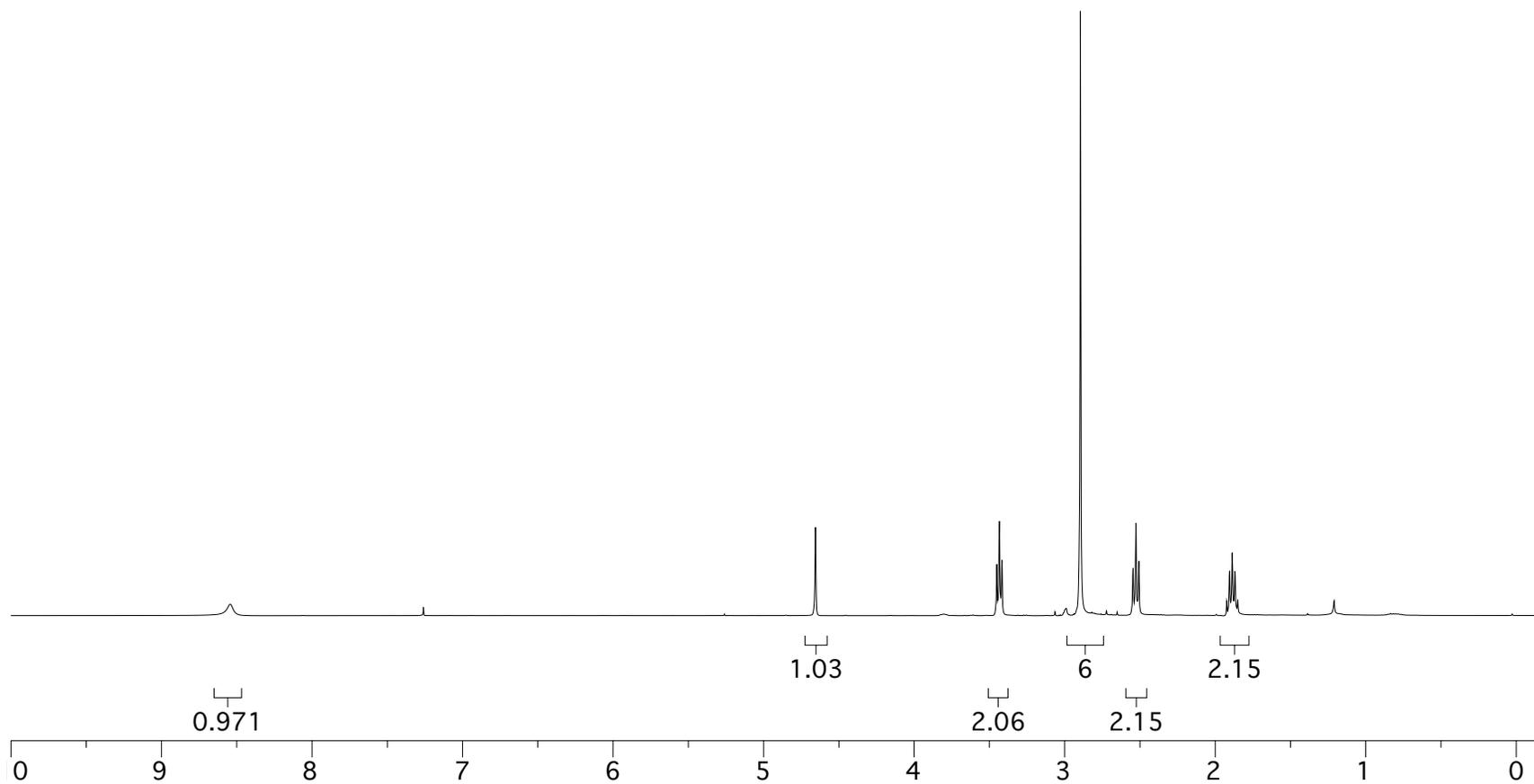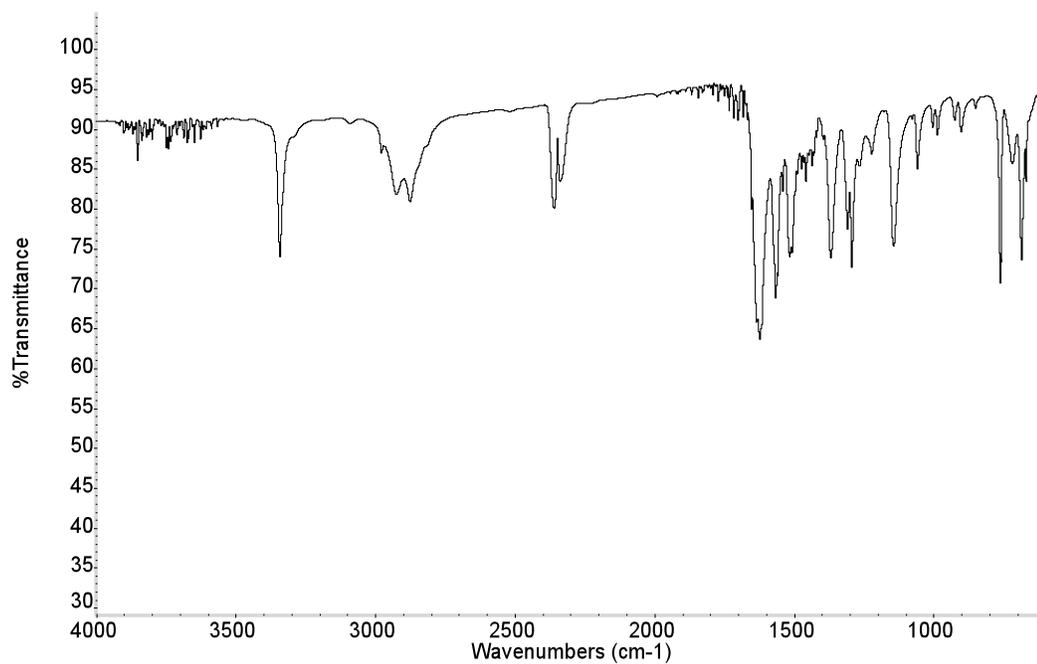
Figure A.2.2 Infrared Spectrum (thin film/NaCl) of compound **155**.
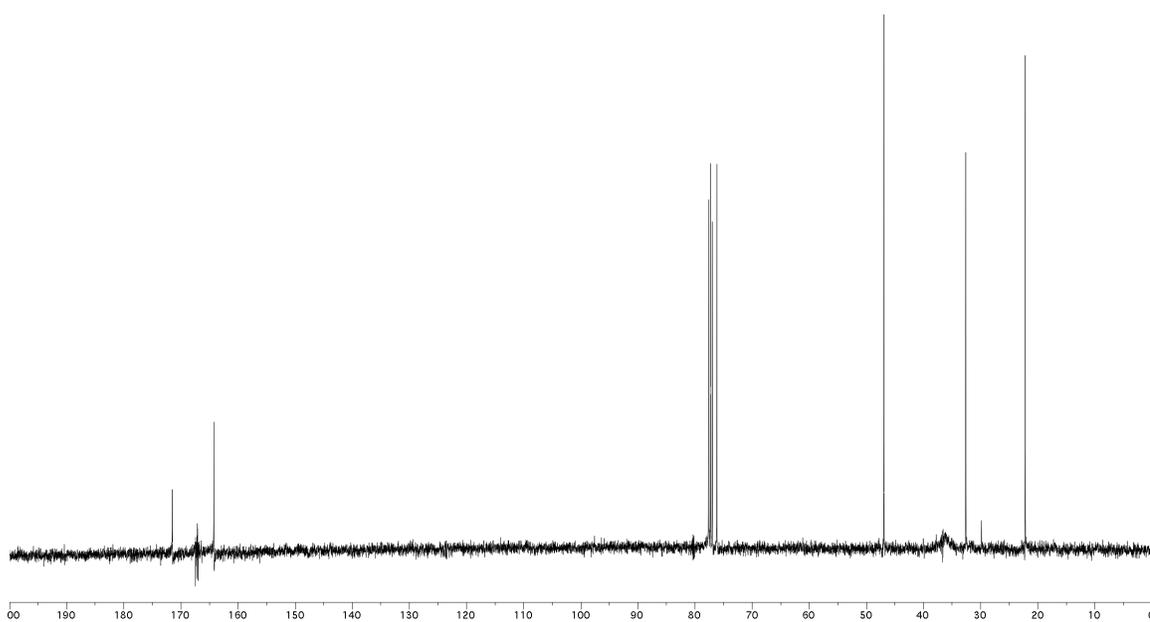


Figure A.2.3 ^{13}C NMR (125 MHz, CDCl$_3$) of compound **155**.

84
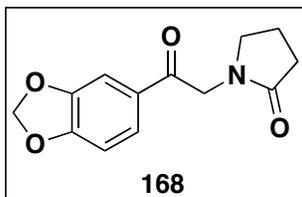
**Figure A.2.4 1H NMR (400MHz, CDCl$_3$) of compound 168**
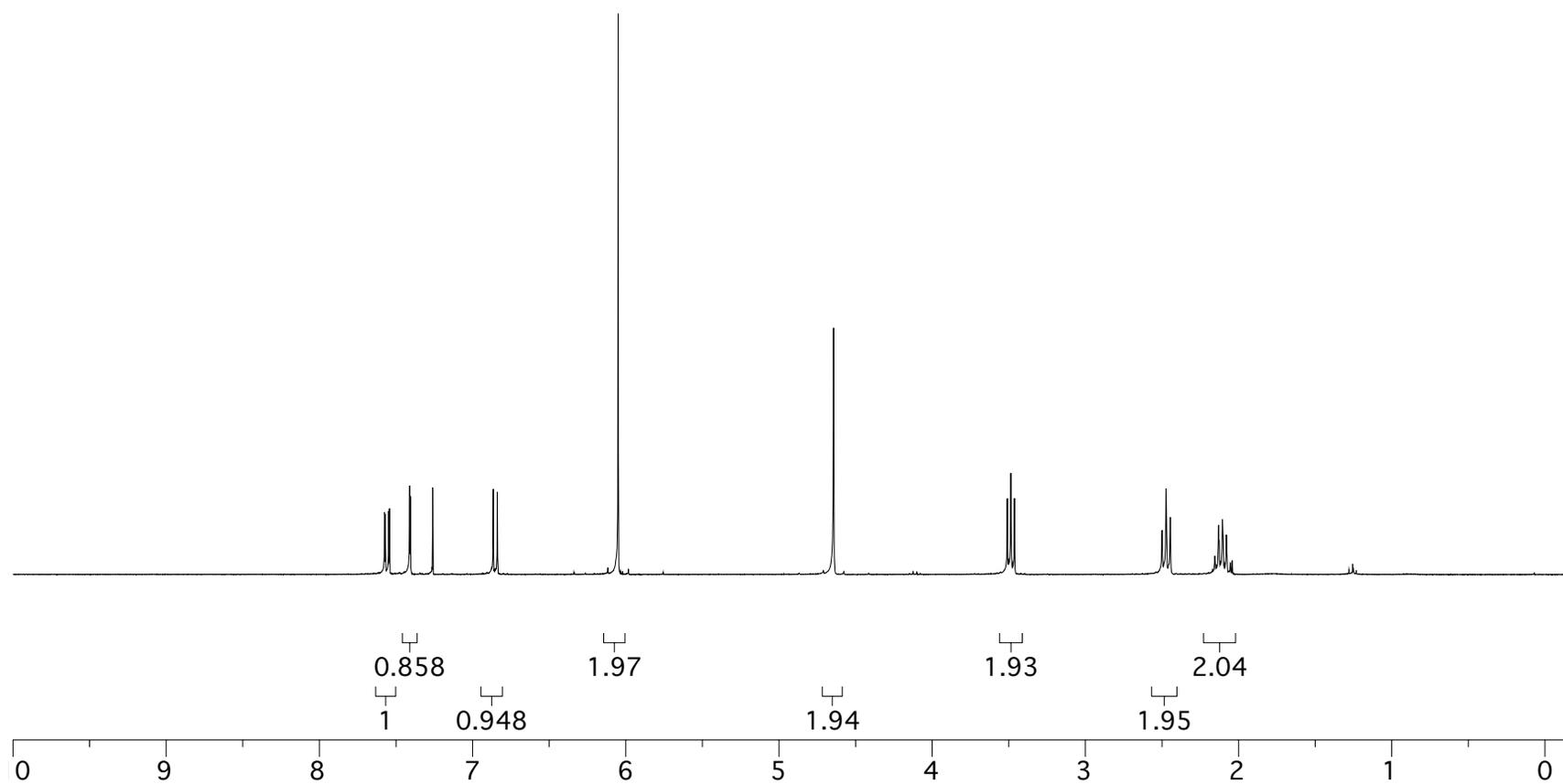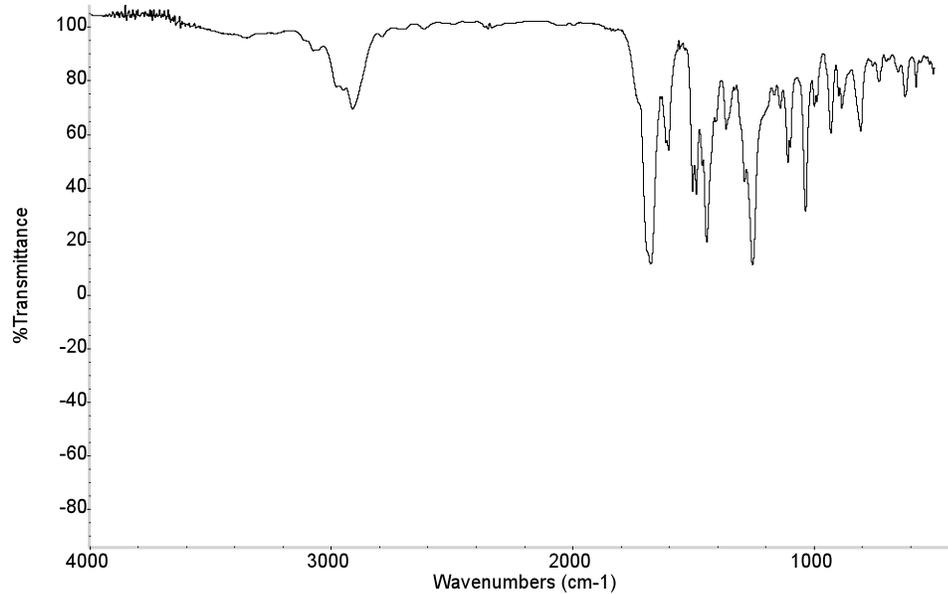
Figure A.2.5 Infrared Spectrum (thin film/NaCl) of compound **168**
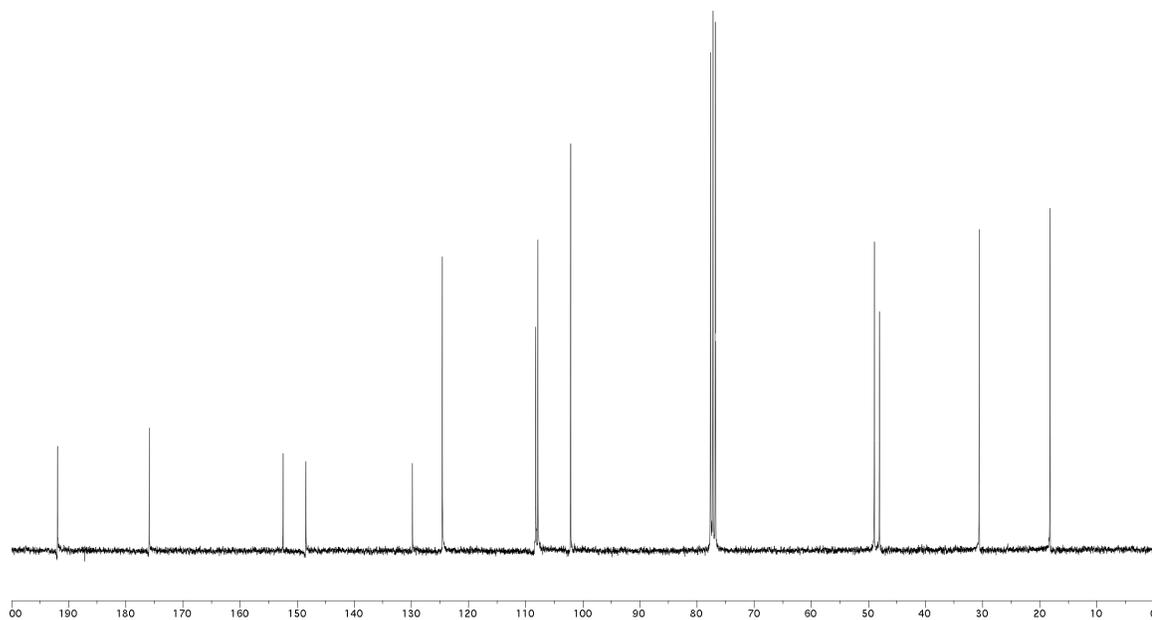


Figure A.2.6 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **168**
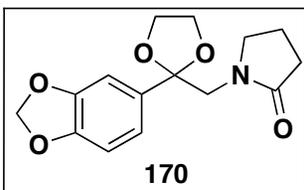
**Figure A.2.7 1H NMR (400MHz, CDCl₃) of compound 170**
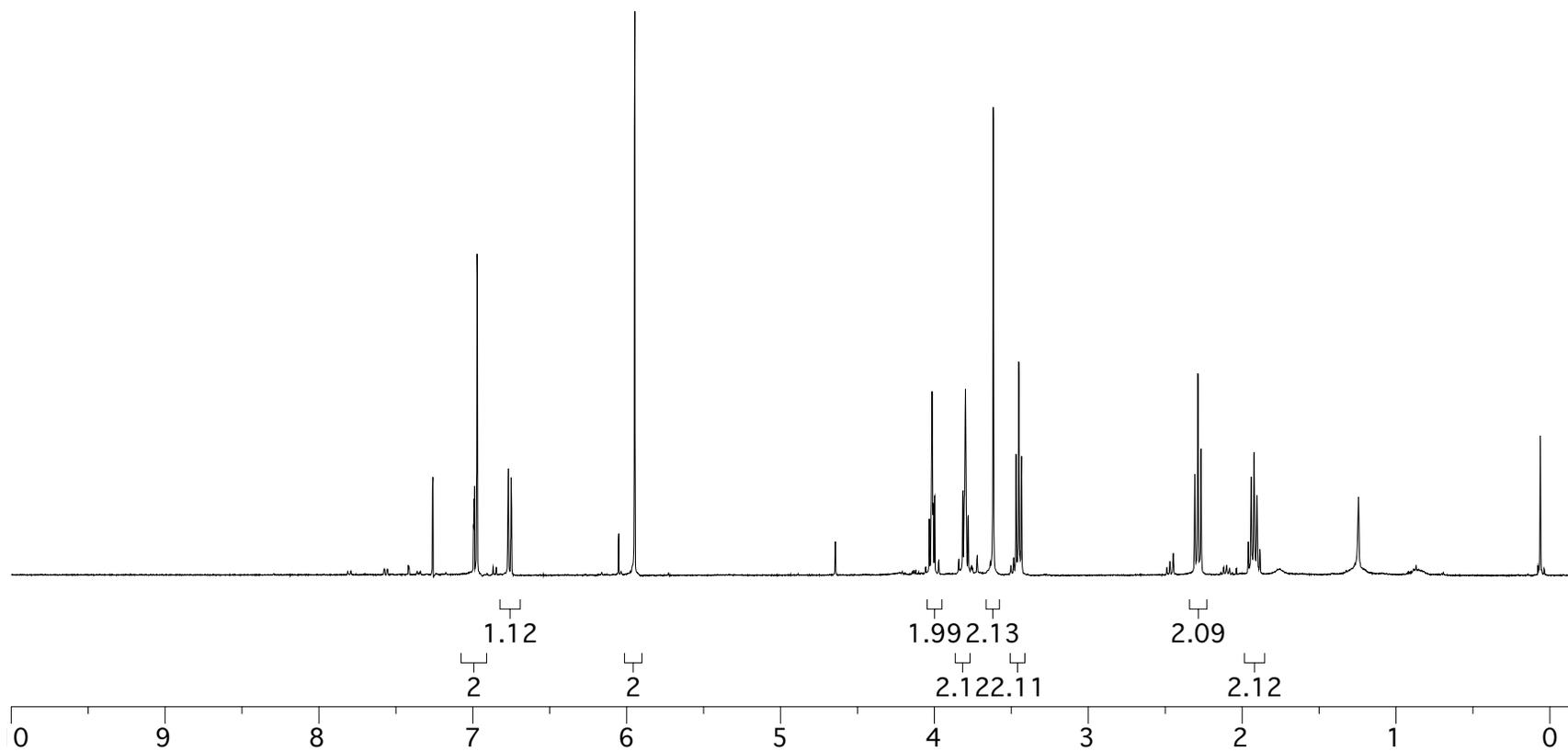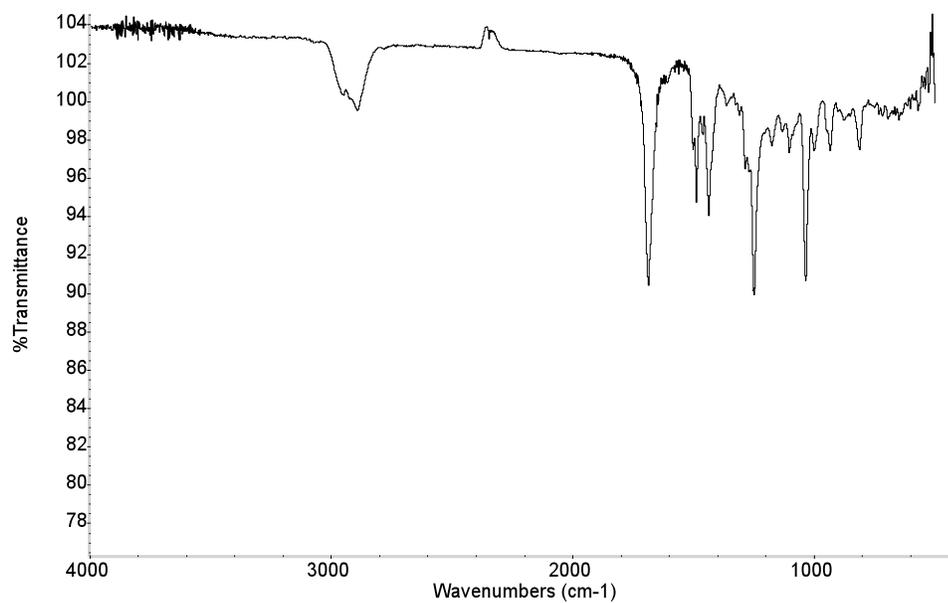
Figure A.2.8 Infrared Spectrum (thin film/NaCl) of compound **170**
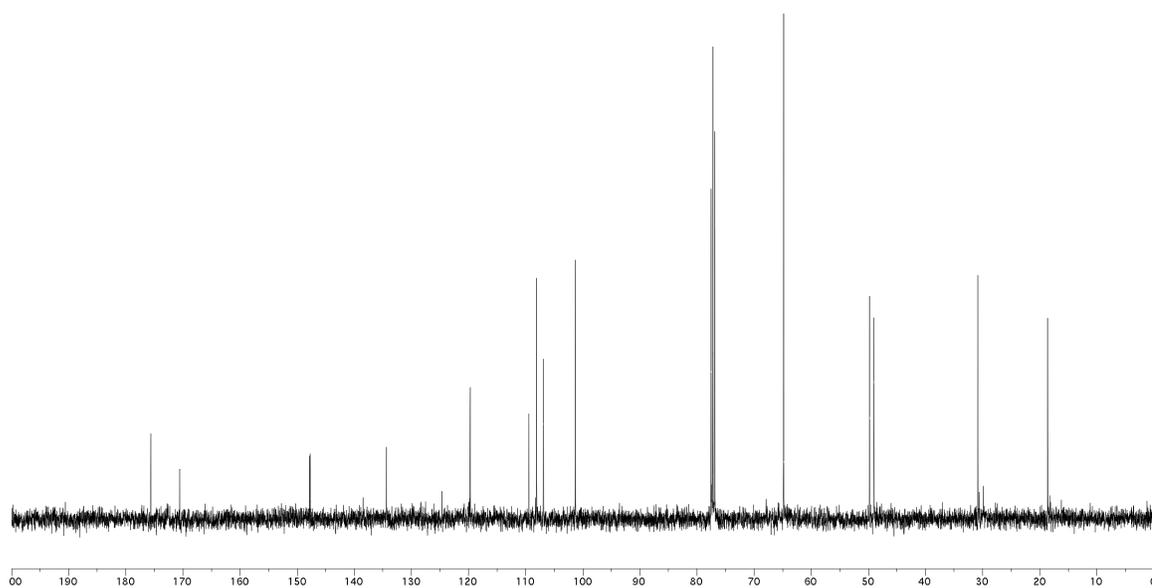


Figure A.2.9 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **170**
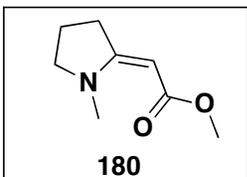
Figure A.2.10 1H NMR (400MHz, CDCl₃) of compound 180
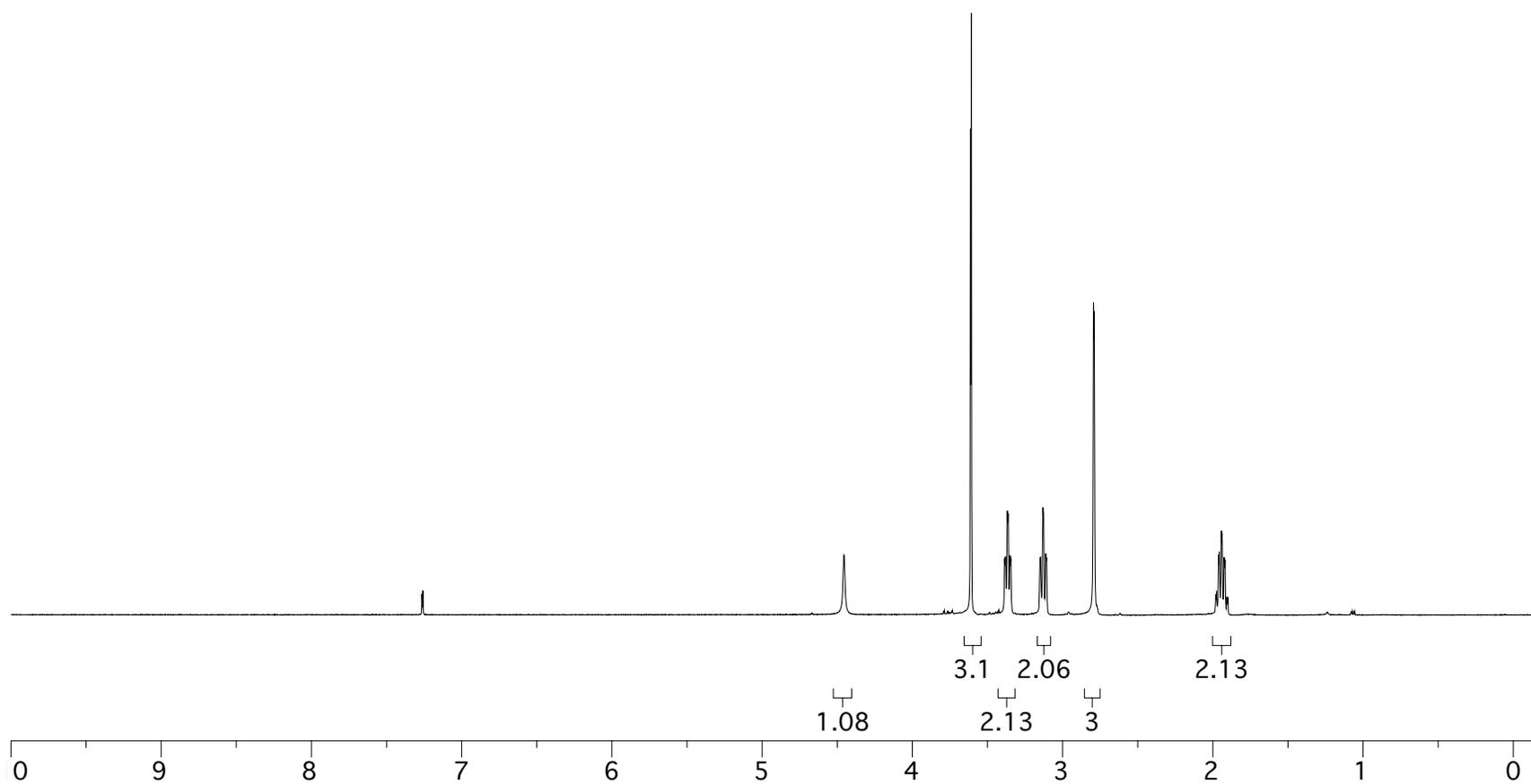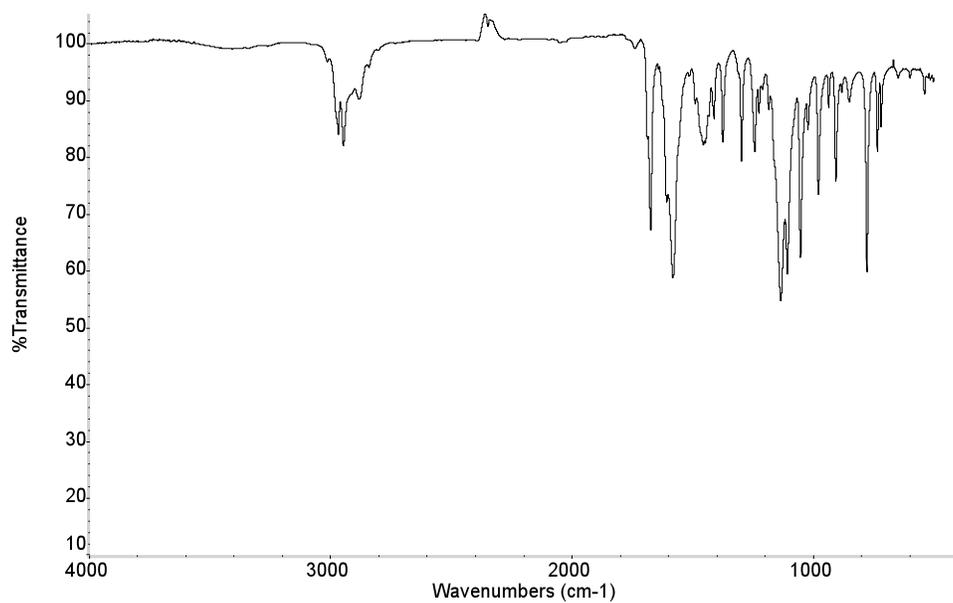
Figure A.2.11 Infrared Spectrum (thin film/NaCl) of compound **180**
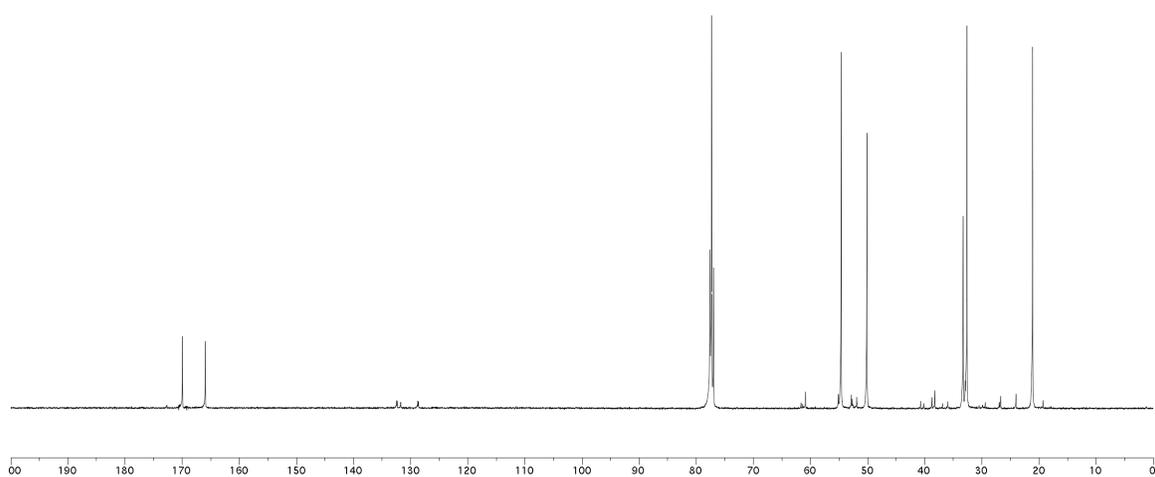


Figure A.2.12 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **180**
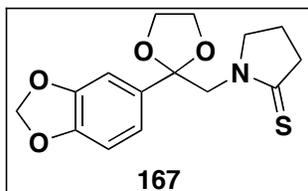
**Figure A.2.13 1H NMR (400MHz, CDCl$_3$) of compound 167**
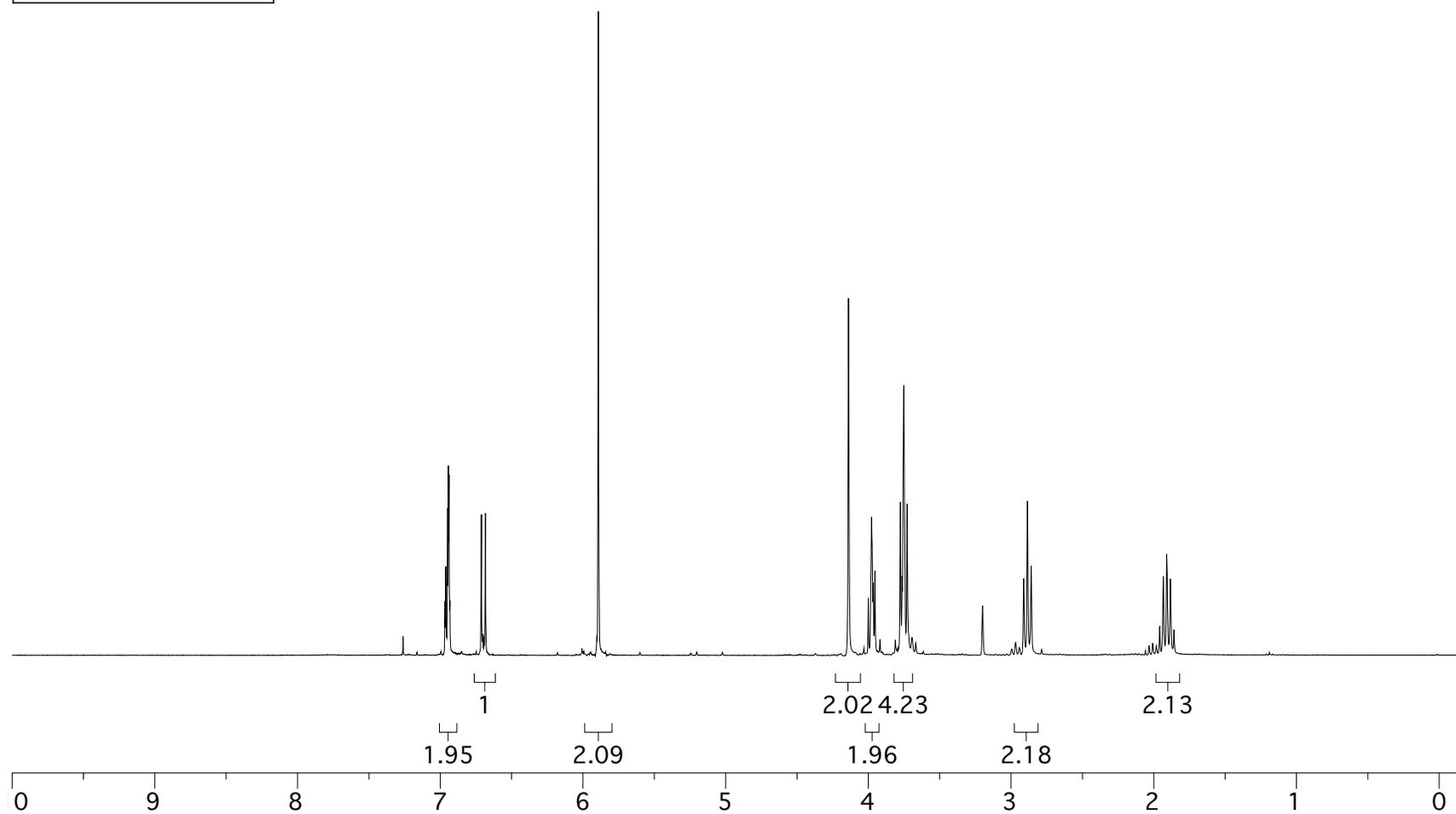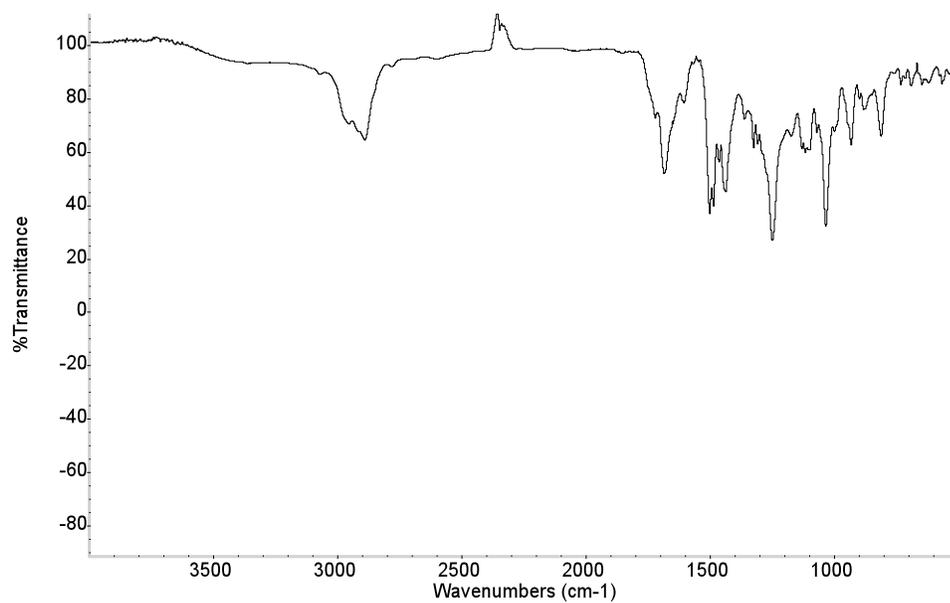
Figure A.2.14 Infrared Spectrum (thin film/NaCl) of compound **167**
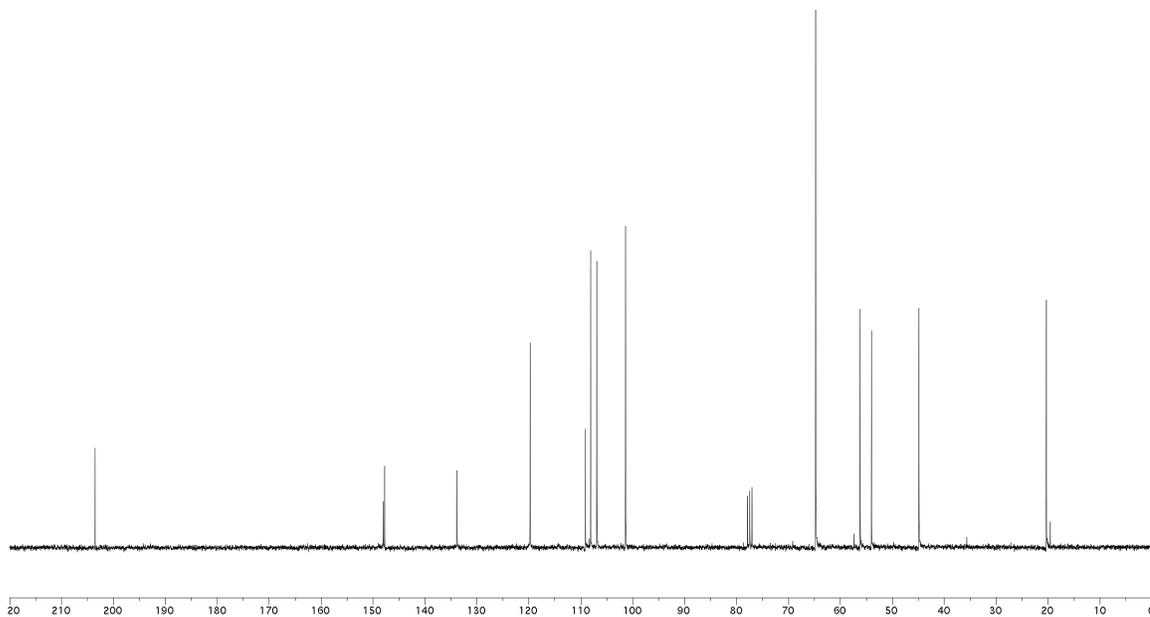


Figure A.2.15 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **167**
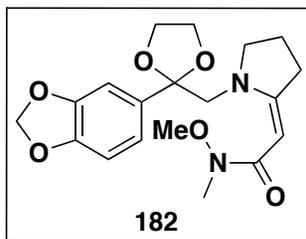
**Figure A.2.16 1H NMR (400MHz, CDCl₃) of compound 182**
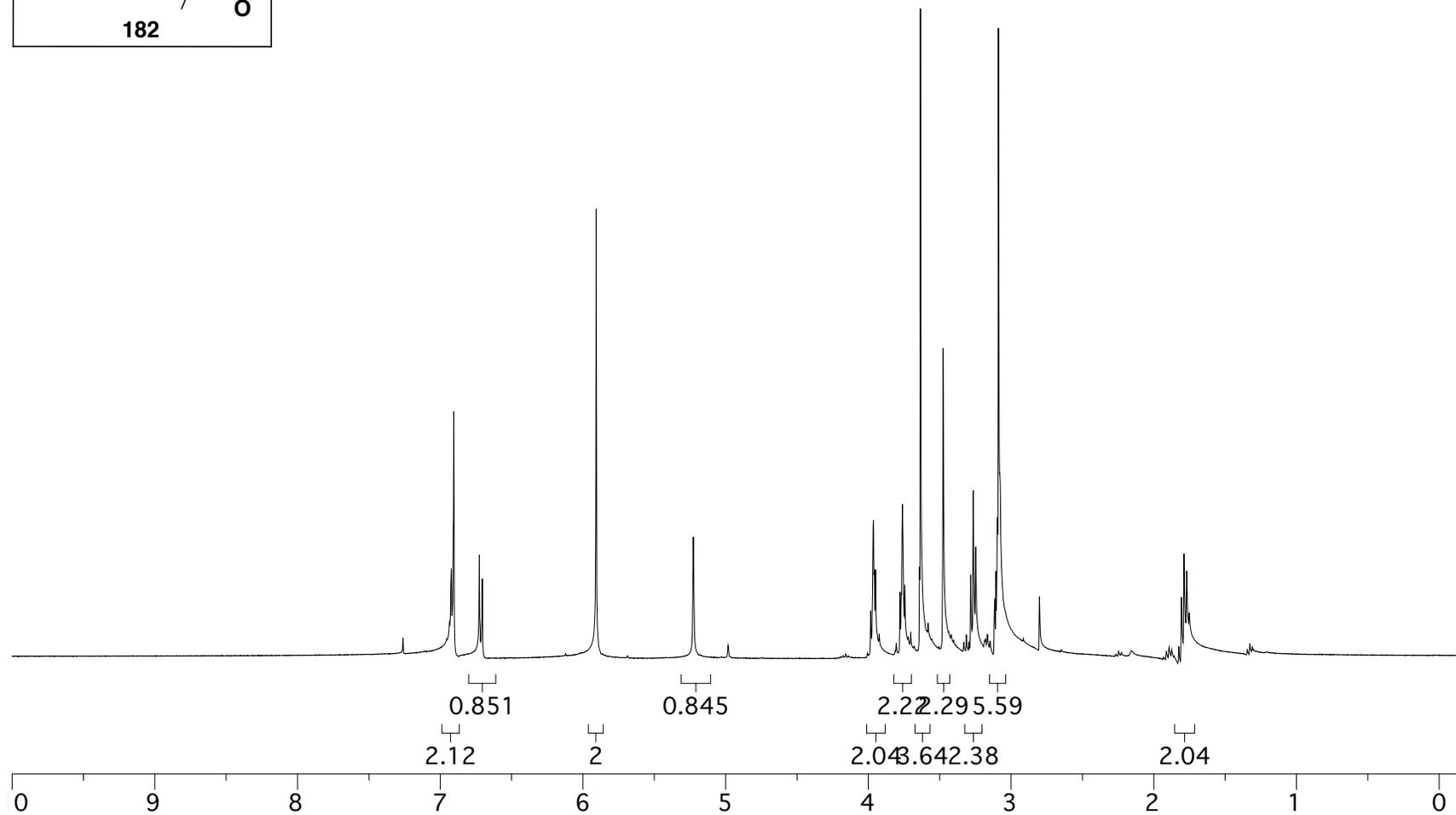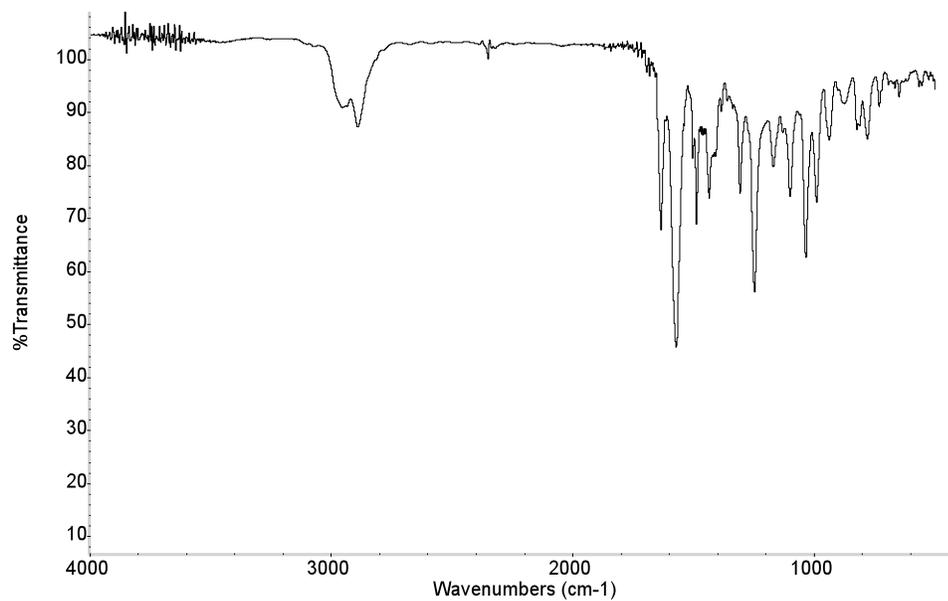
Figure A.2.17 Infrared Spectrum (thin film/NaCl) of compound **182**
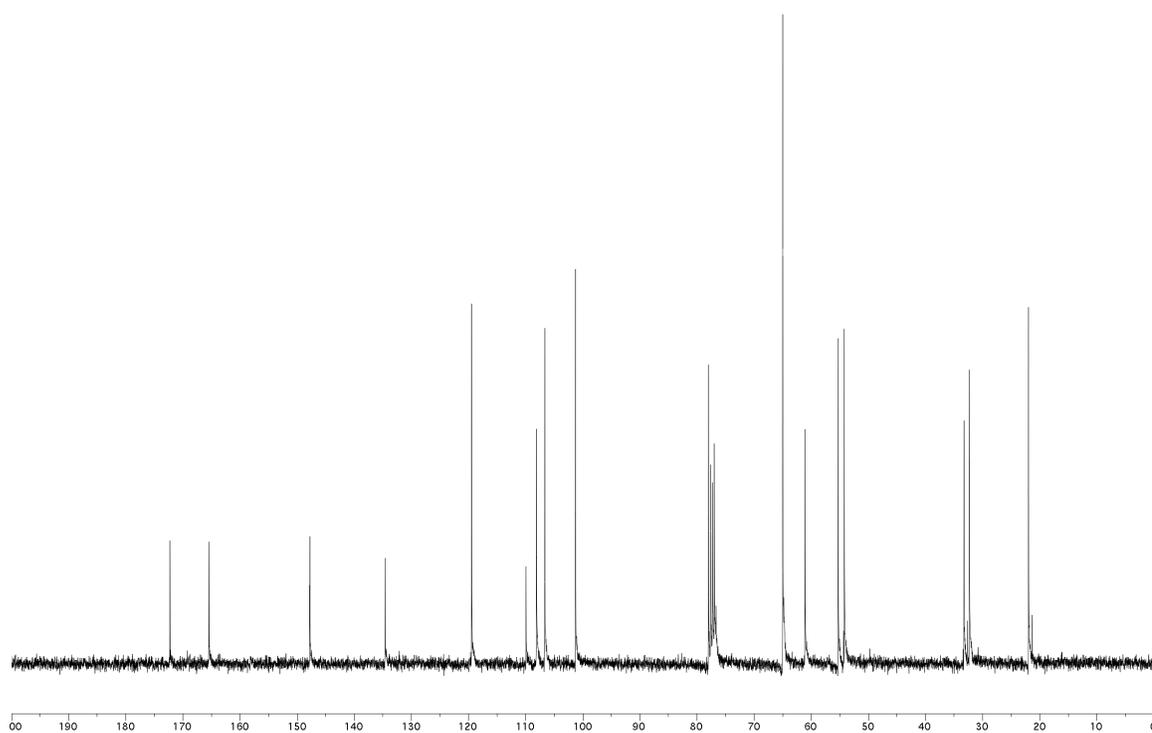


Figure A.2.18 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **182**
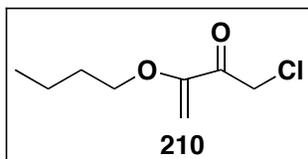
Figure A.2.19 1H NMR (400MHz, CDCl$_3$) of compound 210
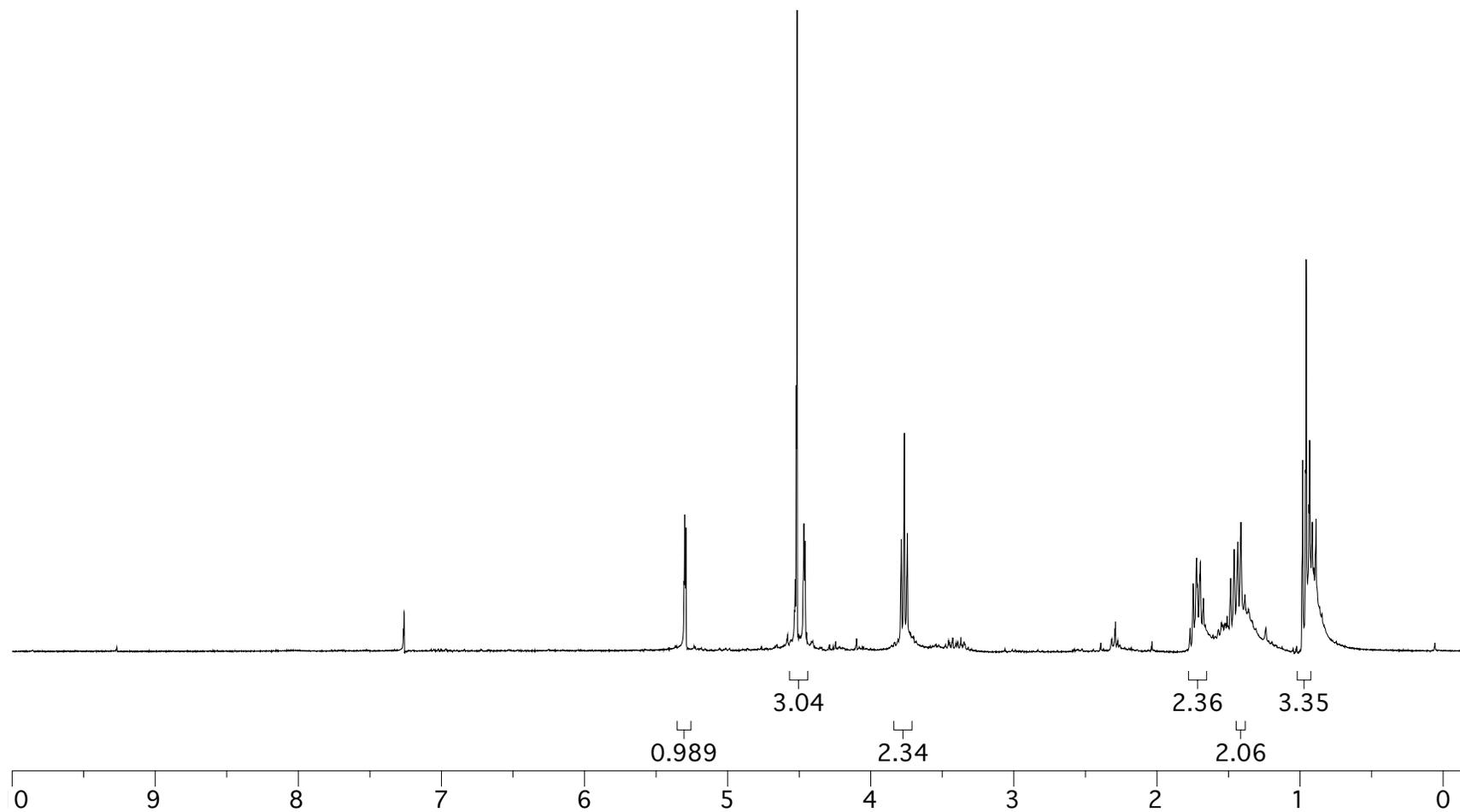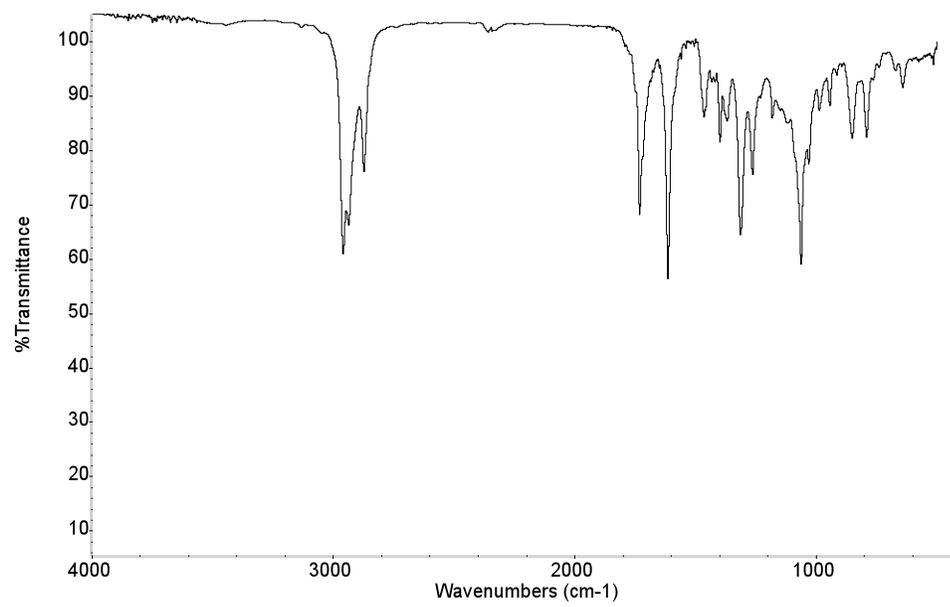
Figure A.2.20 Infrared Spectrum (thin film/NaCl) of compound **210**
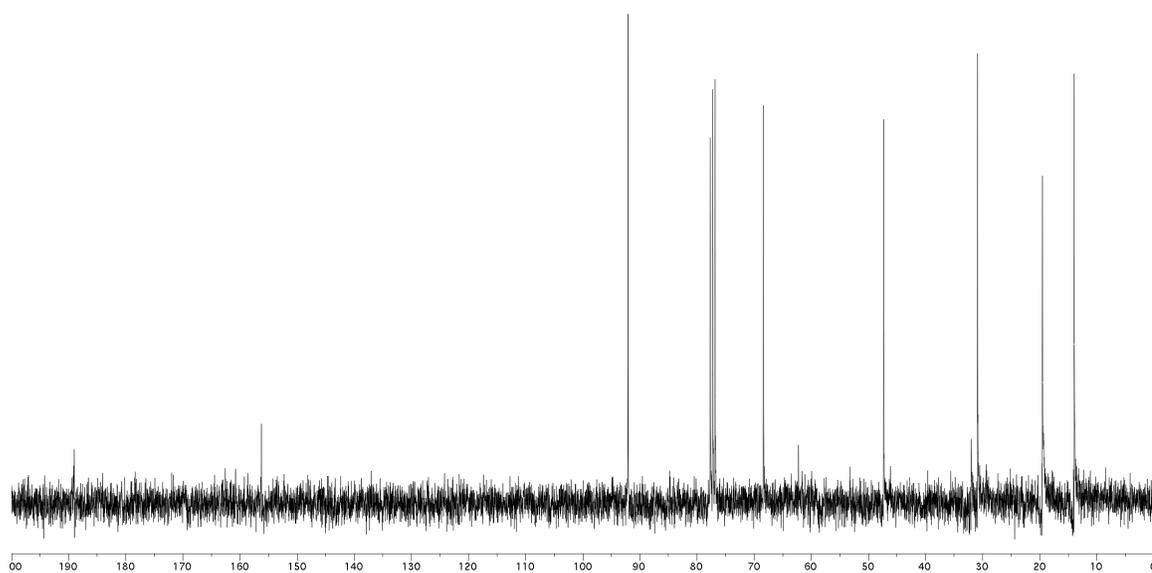


Figure A.2.21 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **210**

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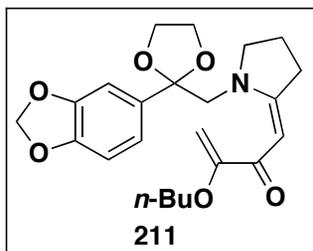
Figure A.2.22 1H NMR (400MHz, CDCl₃) of compound 211
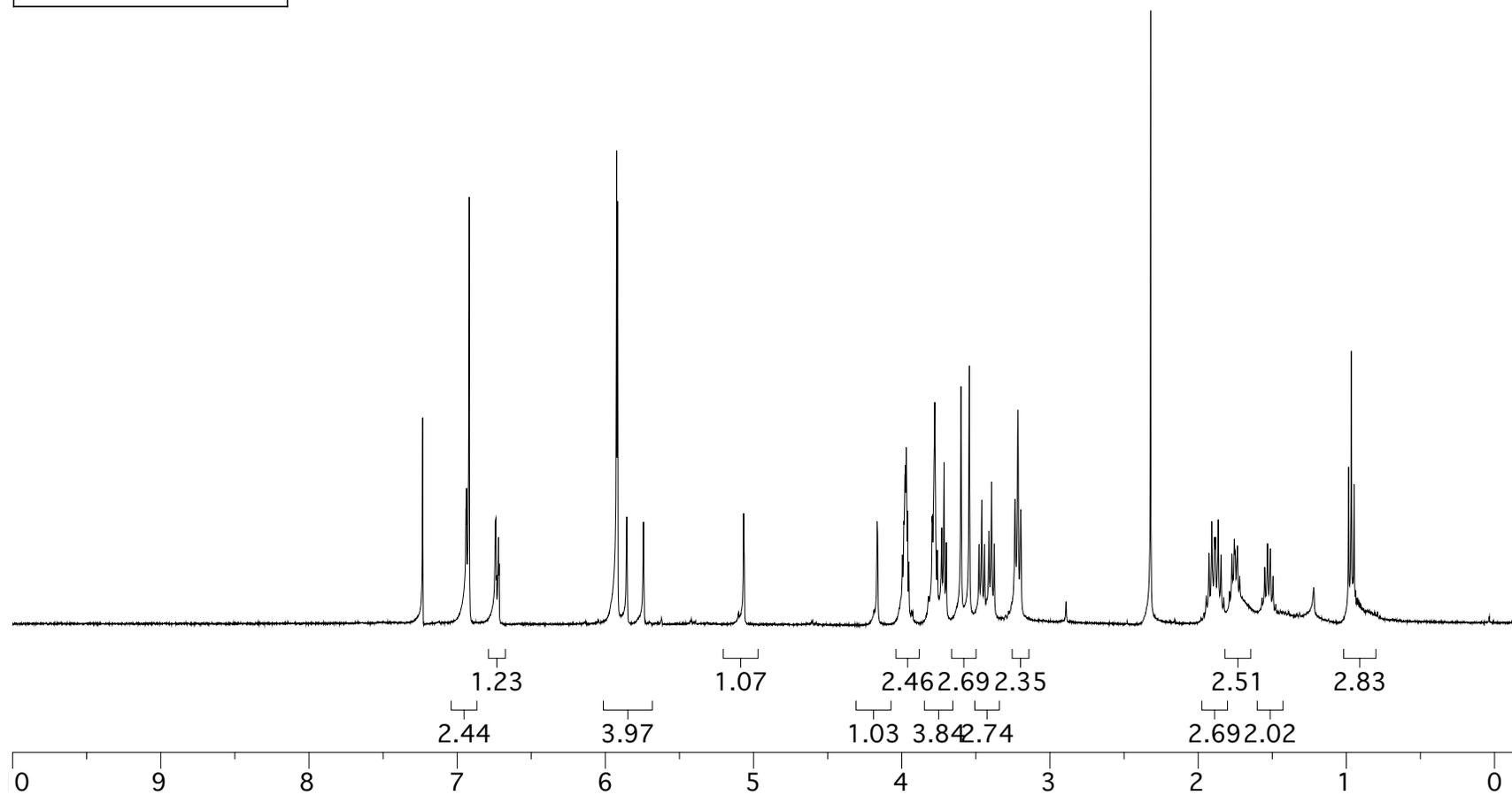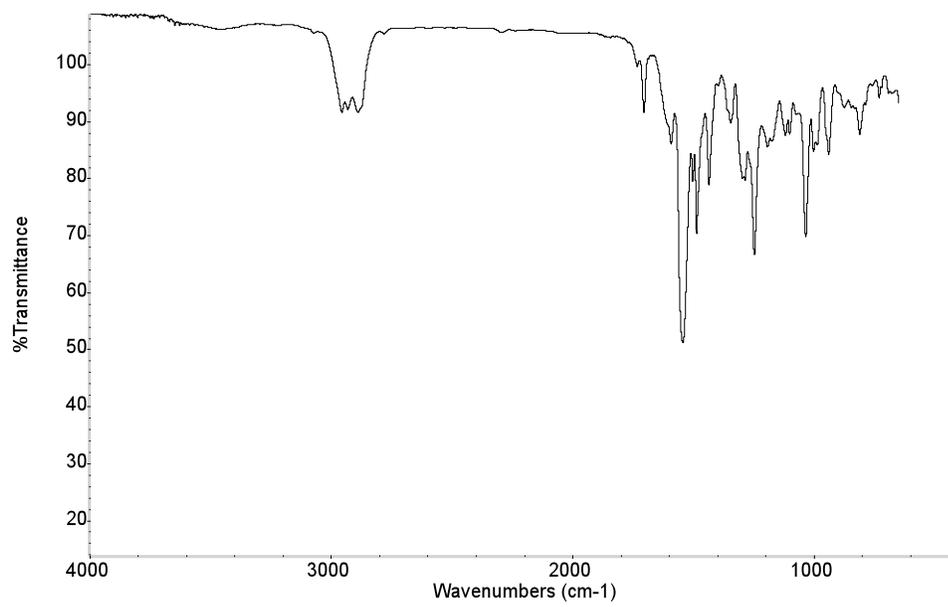
Figure A.2.23 Infrared Spectrum (thin film/NaCl) of compound **211**
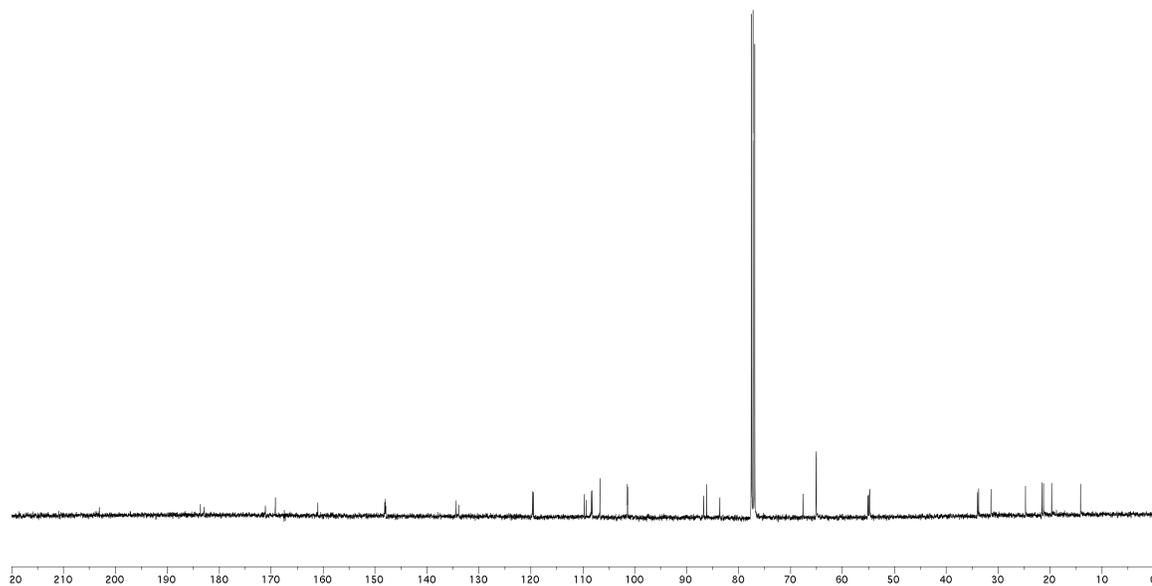


Figure A.2.24 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **211**
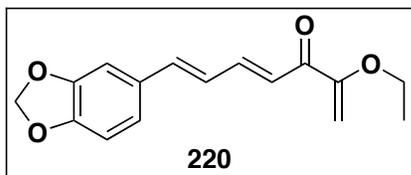
Figure A.2.25 1H NMR (400MHz, CDCl$_3$) of compound 220
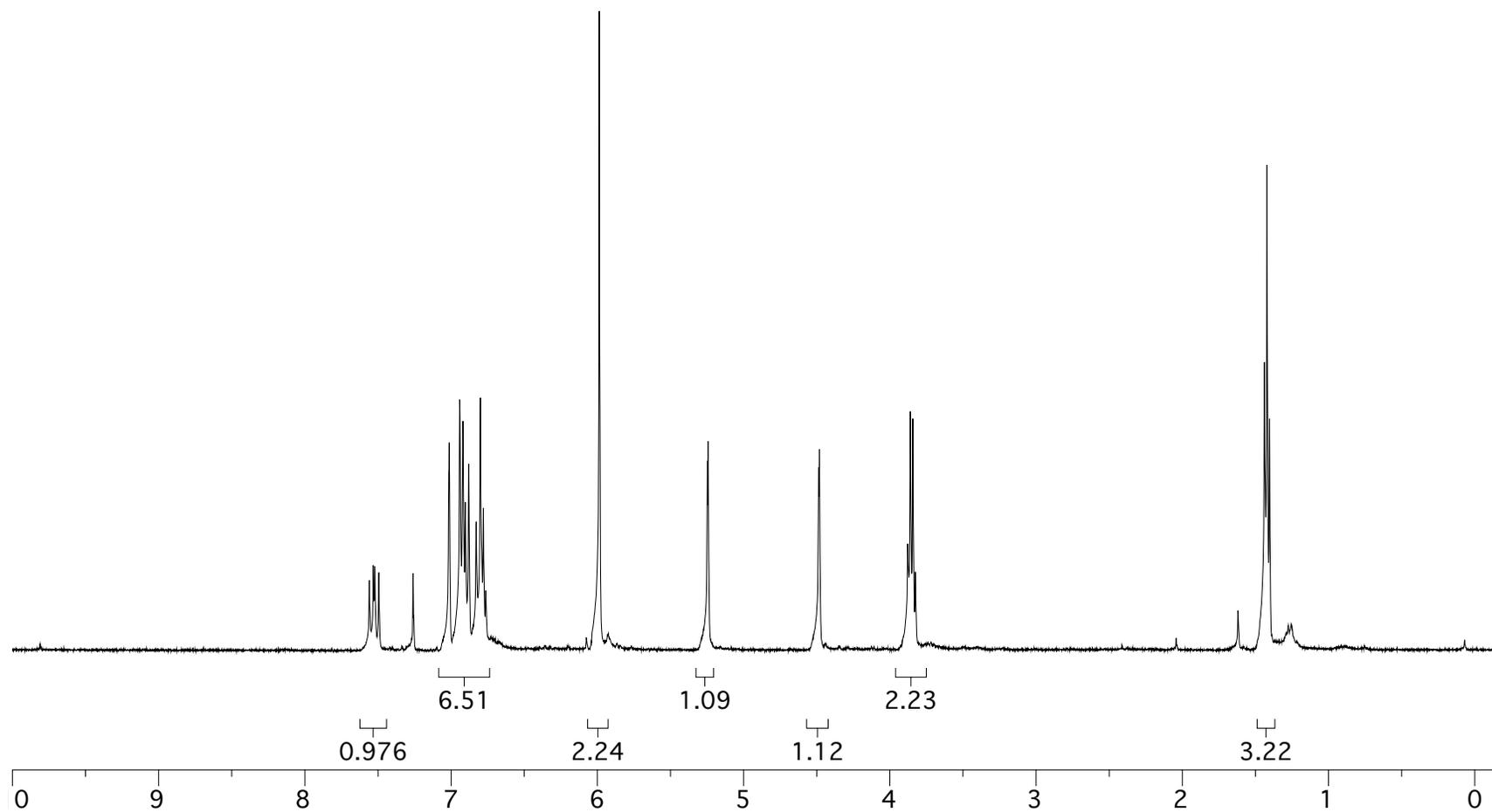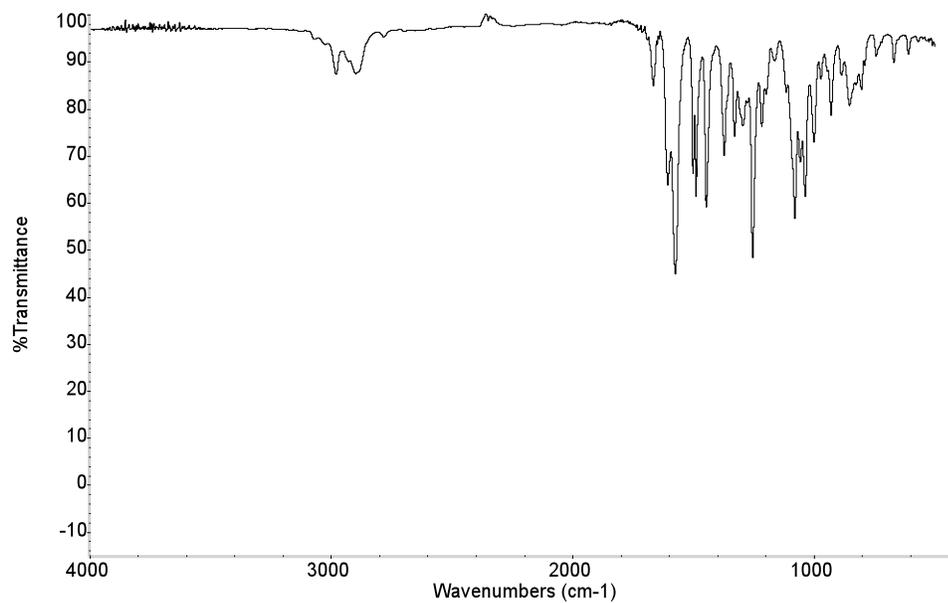
Figure A.2.26 Infrared Spectrum (thin film/NaCl) of compound **220**
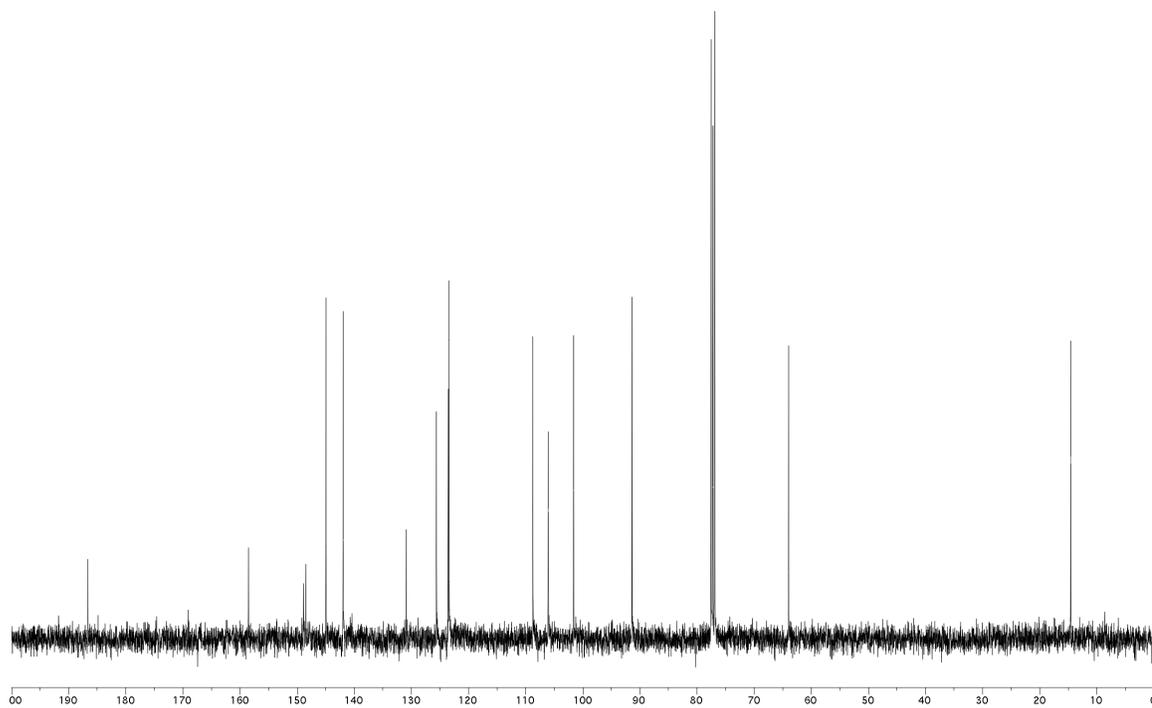


Figure A.2.27 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **220**
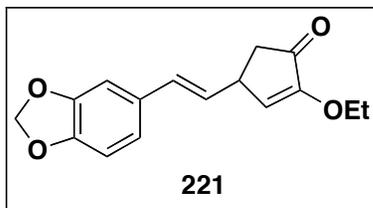
Figure A.2.28 1H NMR (400MHz, CDCl$_3$) of compound 221
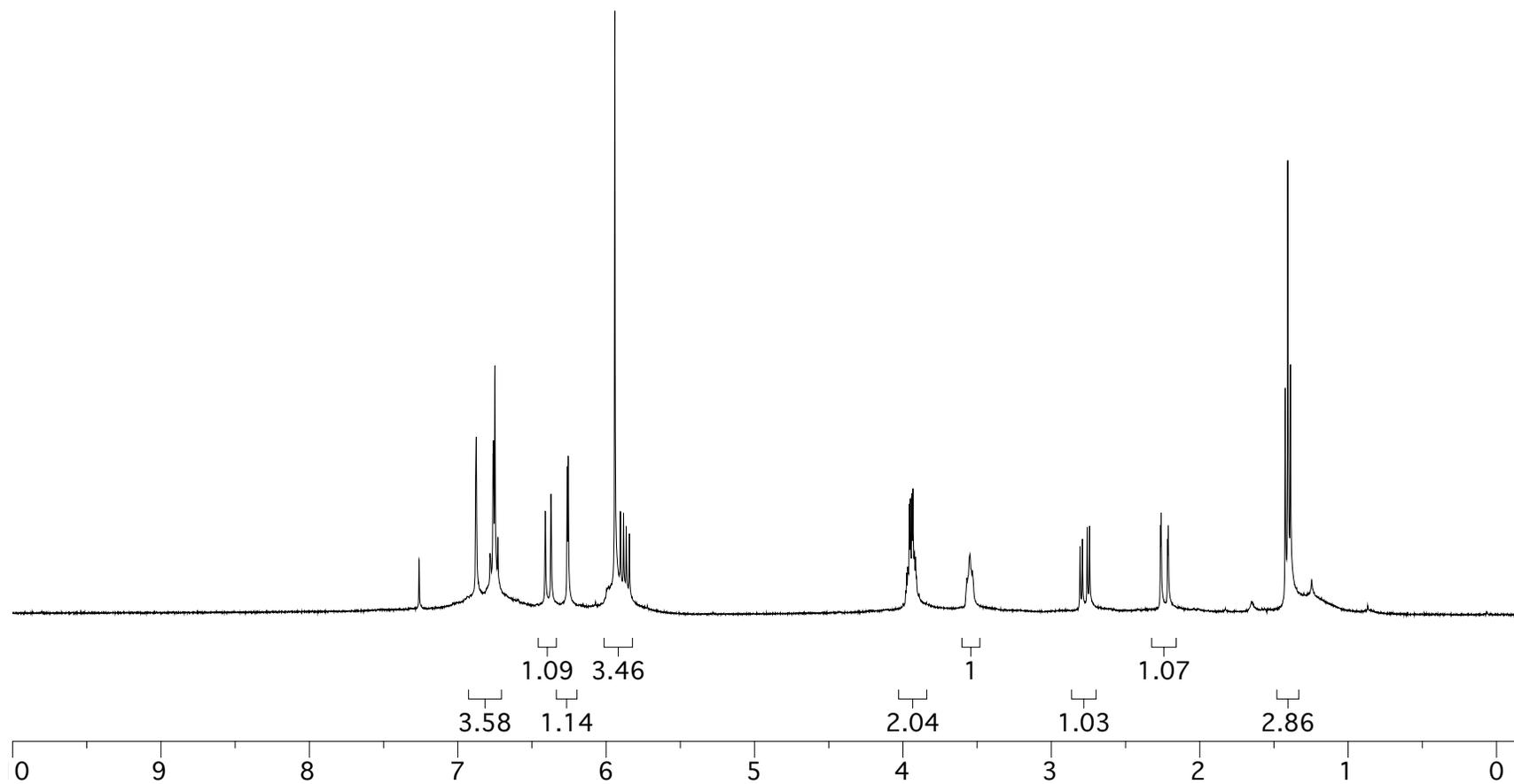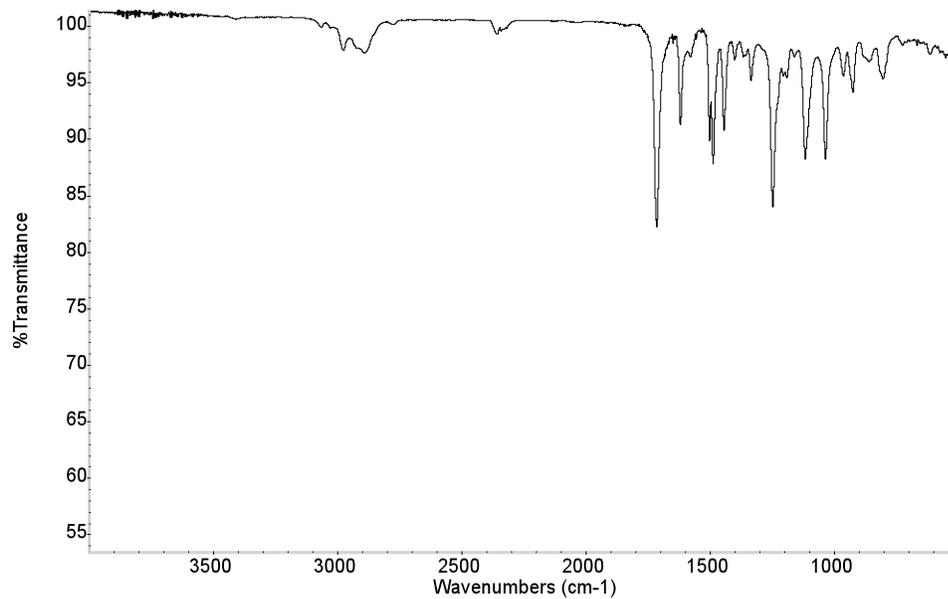
Figure A.2.29 Infrared Spectrum (thin film/NaCl) of compound **221**
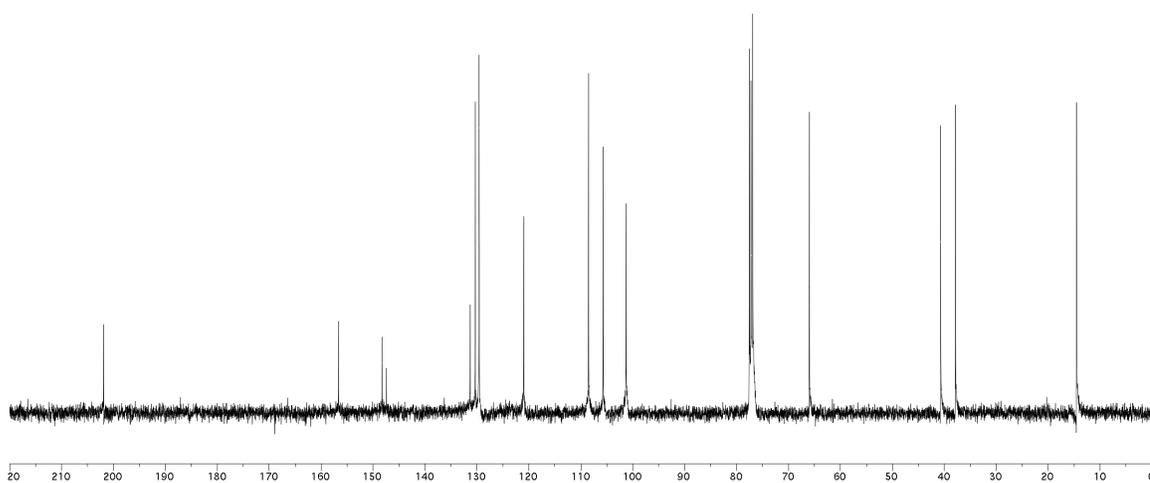


Figure A.2.30 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **221**
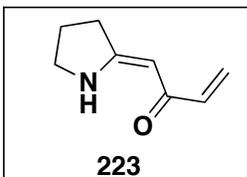
Figure A.2.31 1H NMR (400MHz, CDCl$_3$) of compound 223
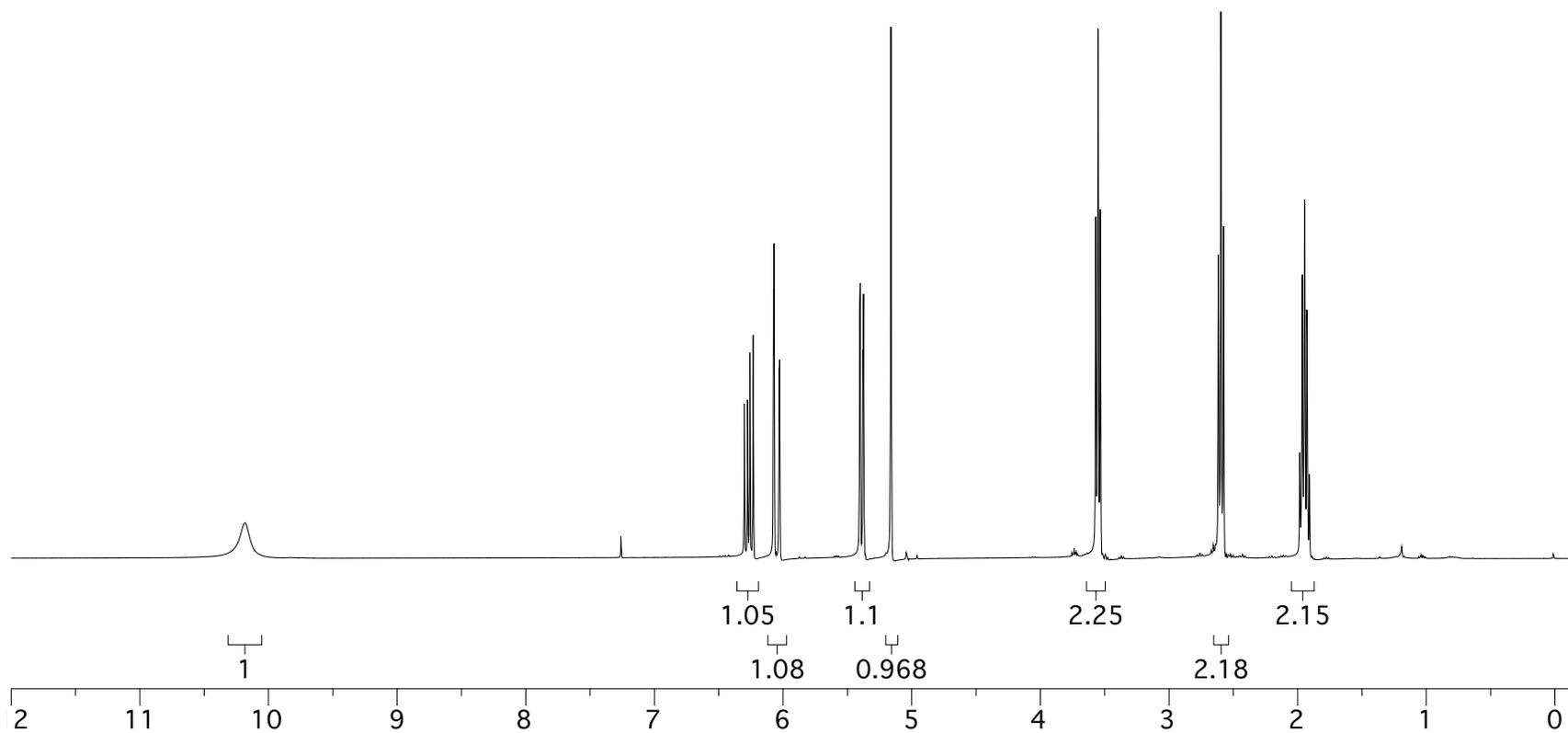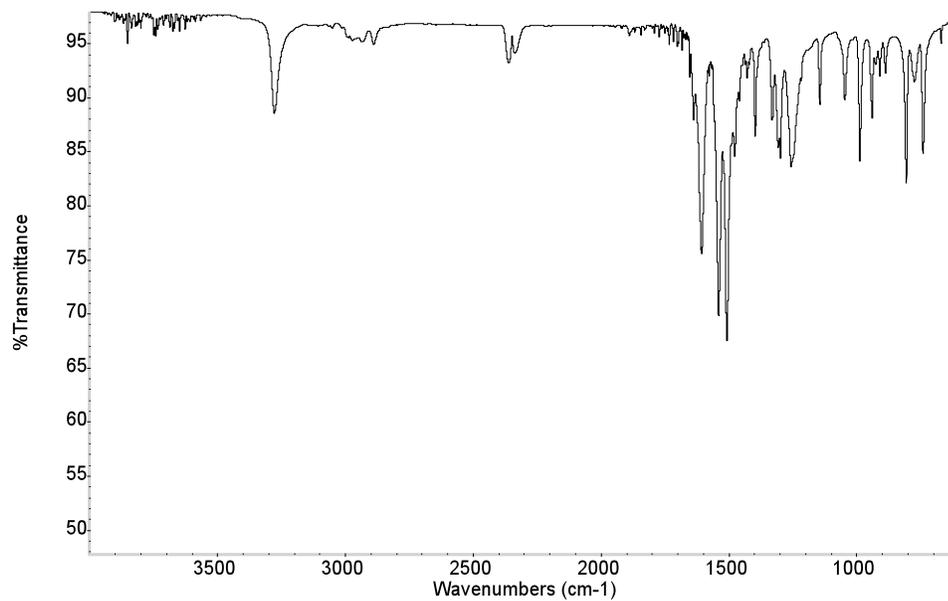
Figure A.2.32 Infrared Spectrum (thin film/NaCl) of compound **223**
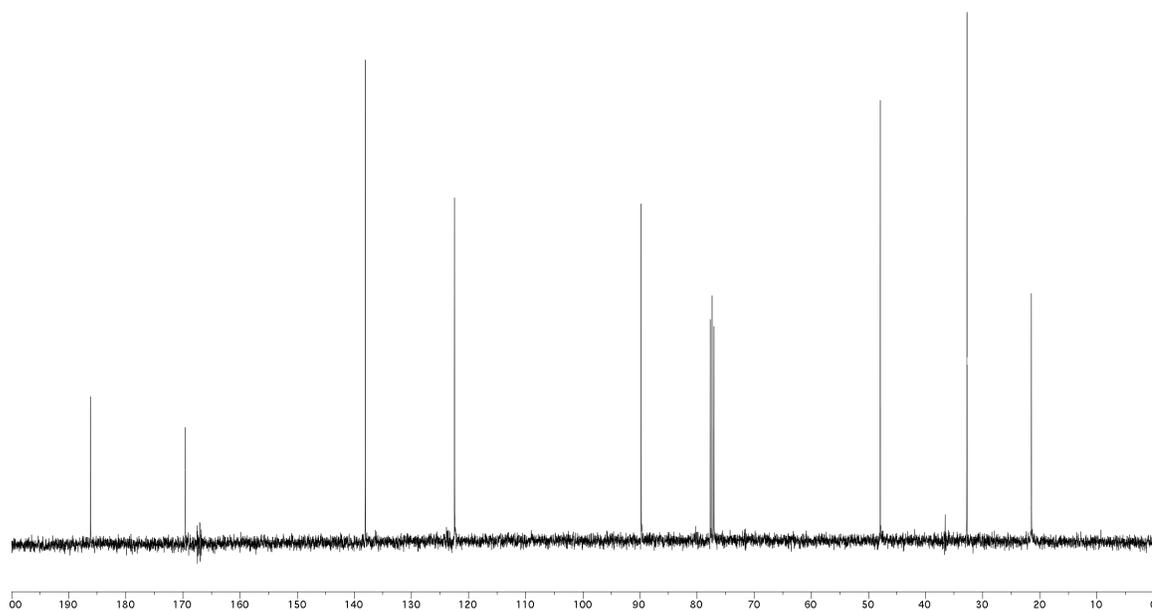


Figure A.2.33 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **223**
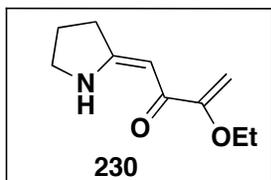
Figure A.2.34 1H NMR (400MHz, CDCl₃) of compound 230
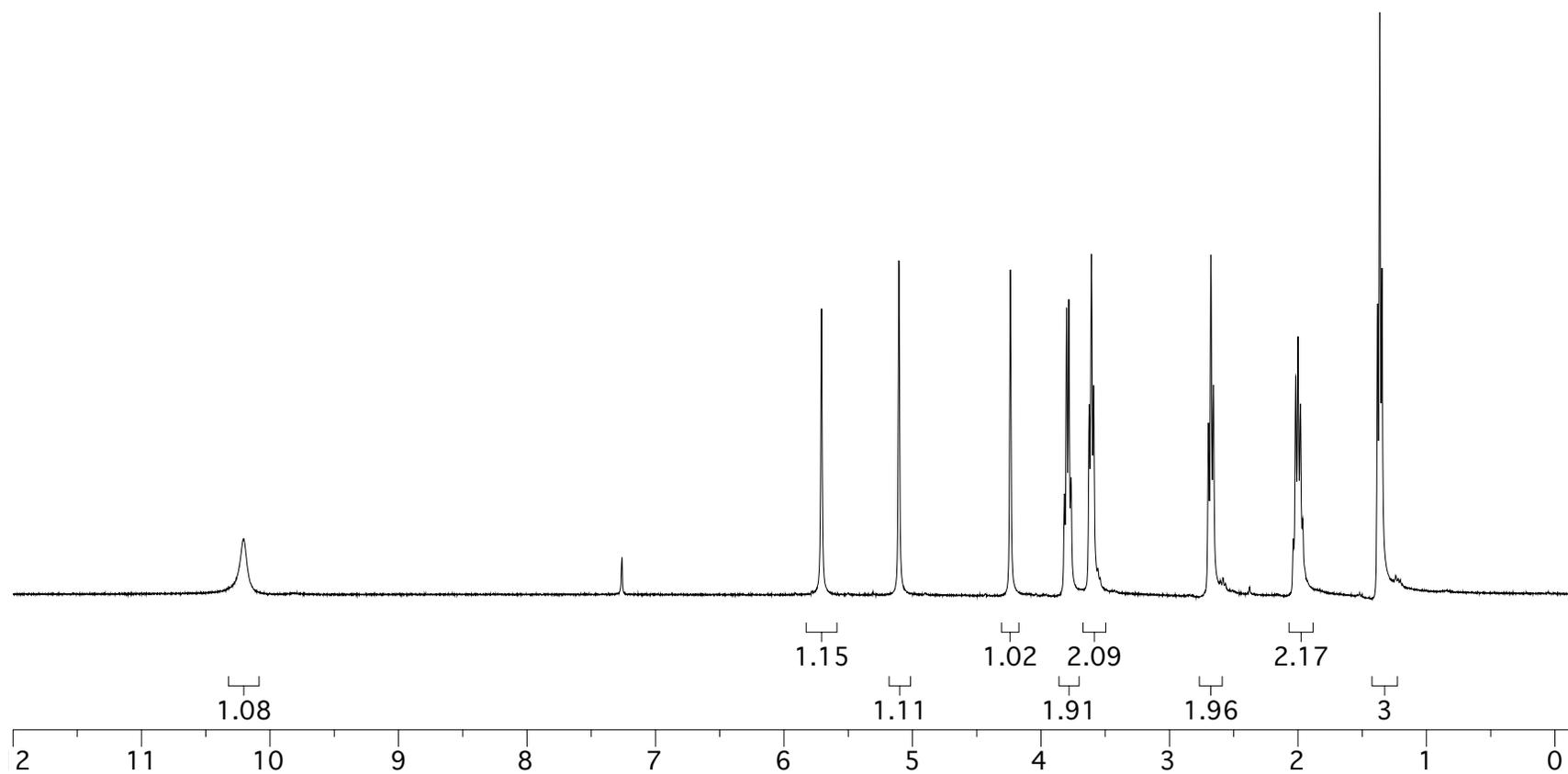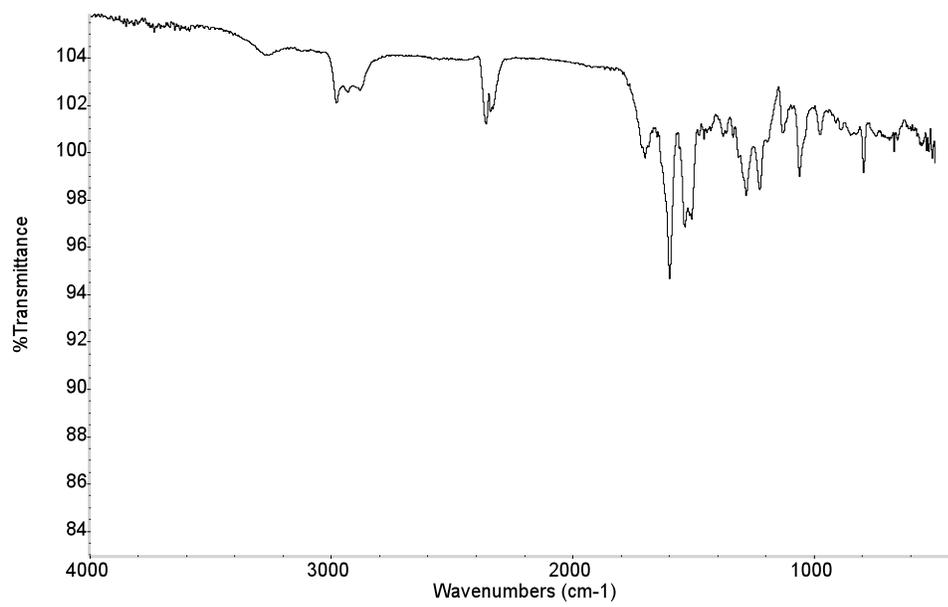
Figure A.2.35 Infrared Spectrum (thin film/NaCl) of compound **230**
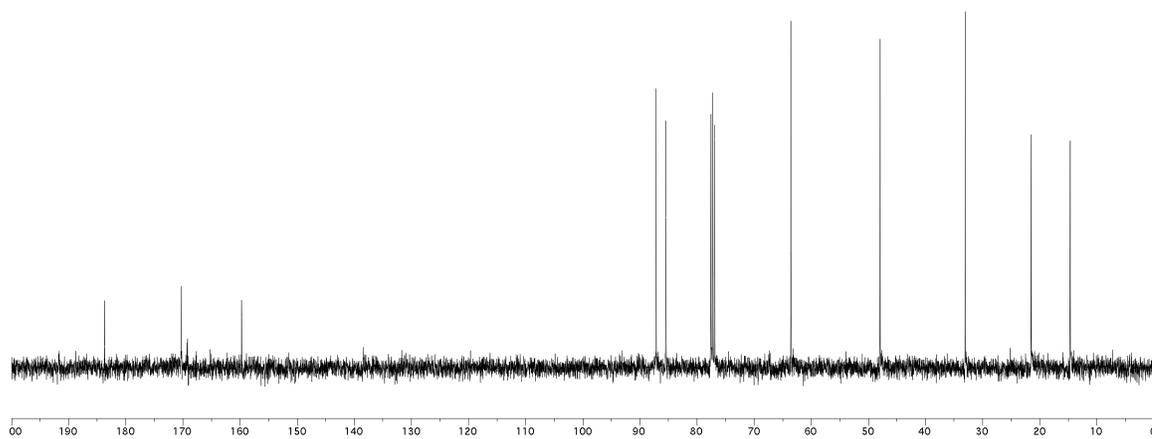


Figure A.2.36 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **230**

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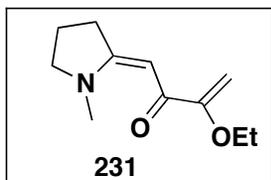
**Figure A.2.37 1H NMR (400MHz, CDCl₃) of compound 231**
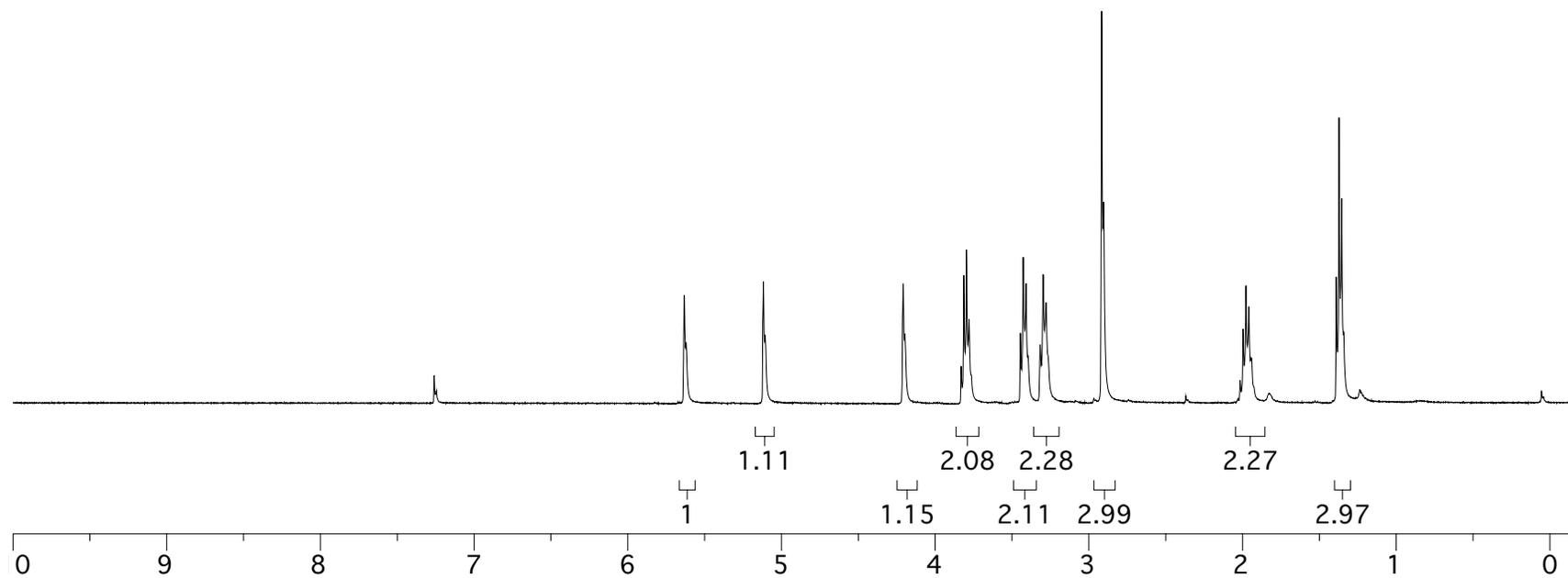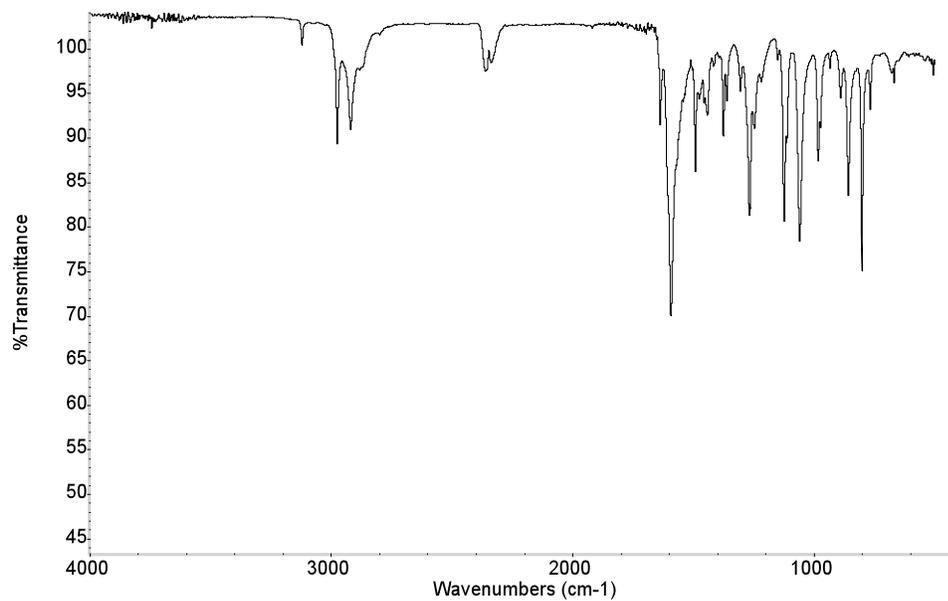
Figure A.2.38 Infrared Spectrum (thin film/NaCl) of compound **231**
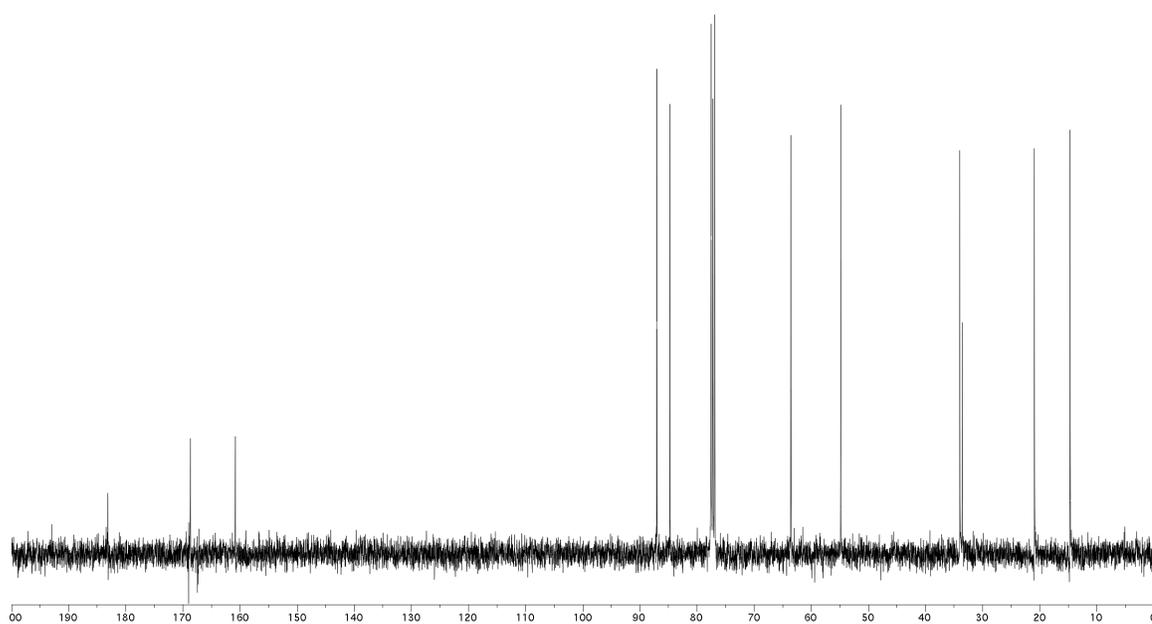


Figure A.2.39 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **231**
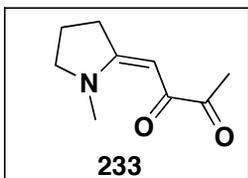
Figure A.2.40 1H NMR (400MHz, CDCl₃) of compound 233
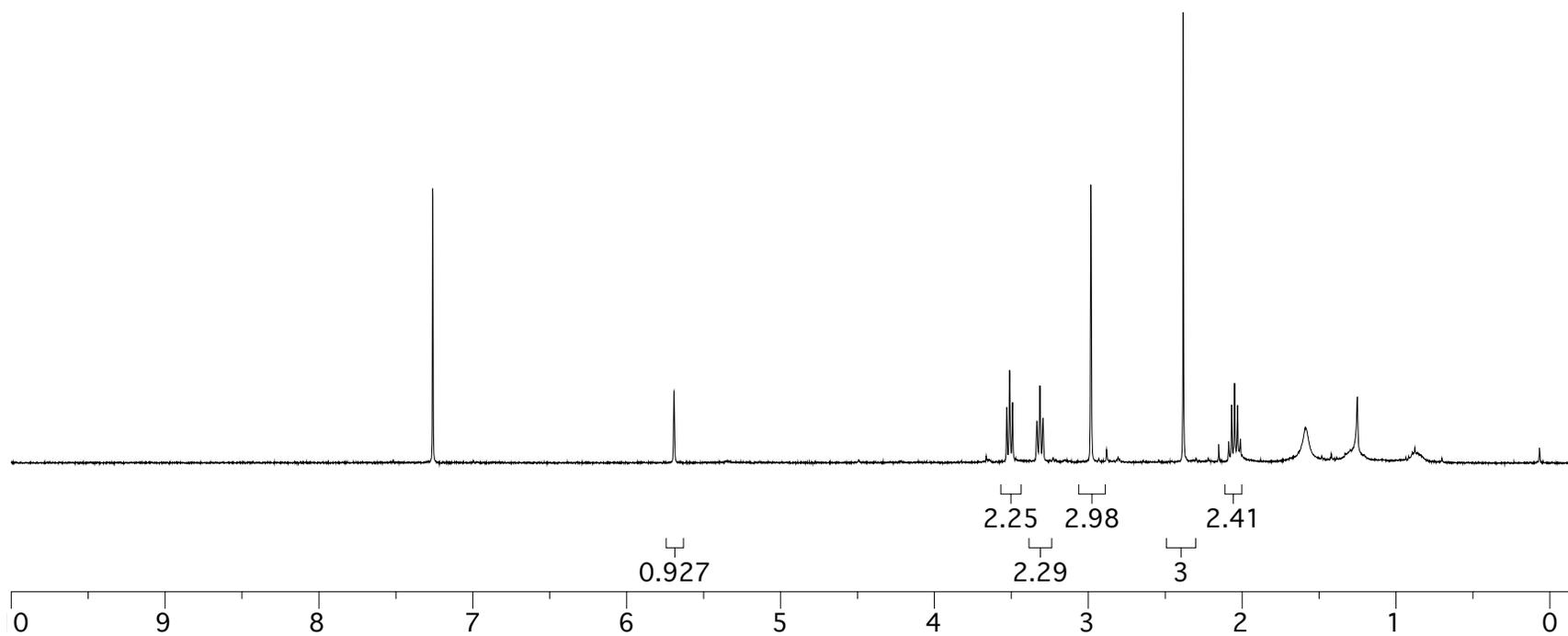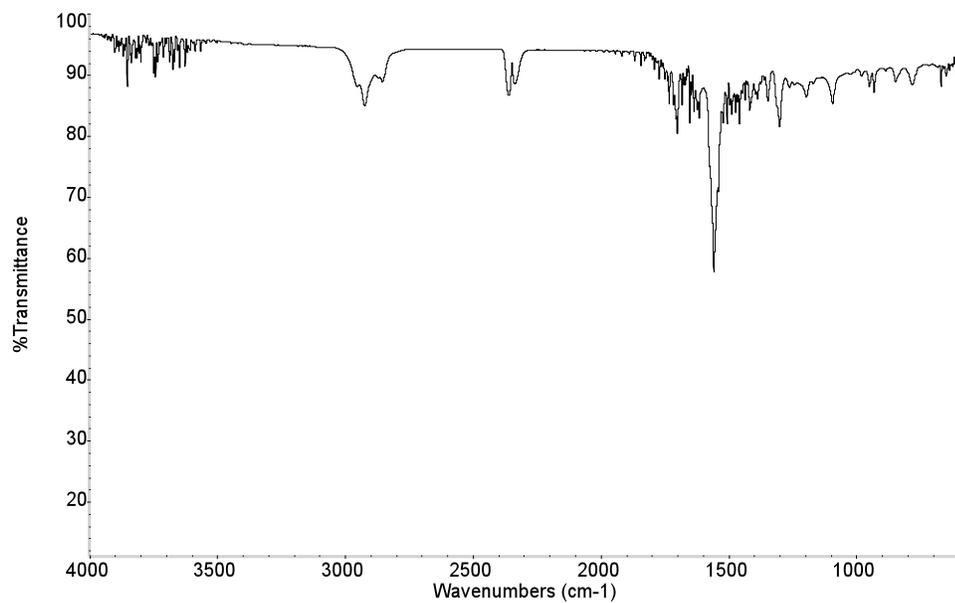
Figure A.2.41 Infrared Spectrum (thin film/NaCl) of compound **233**
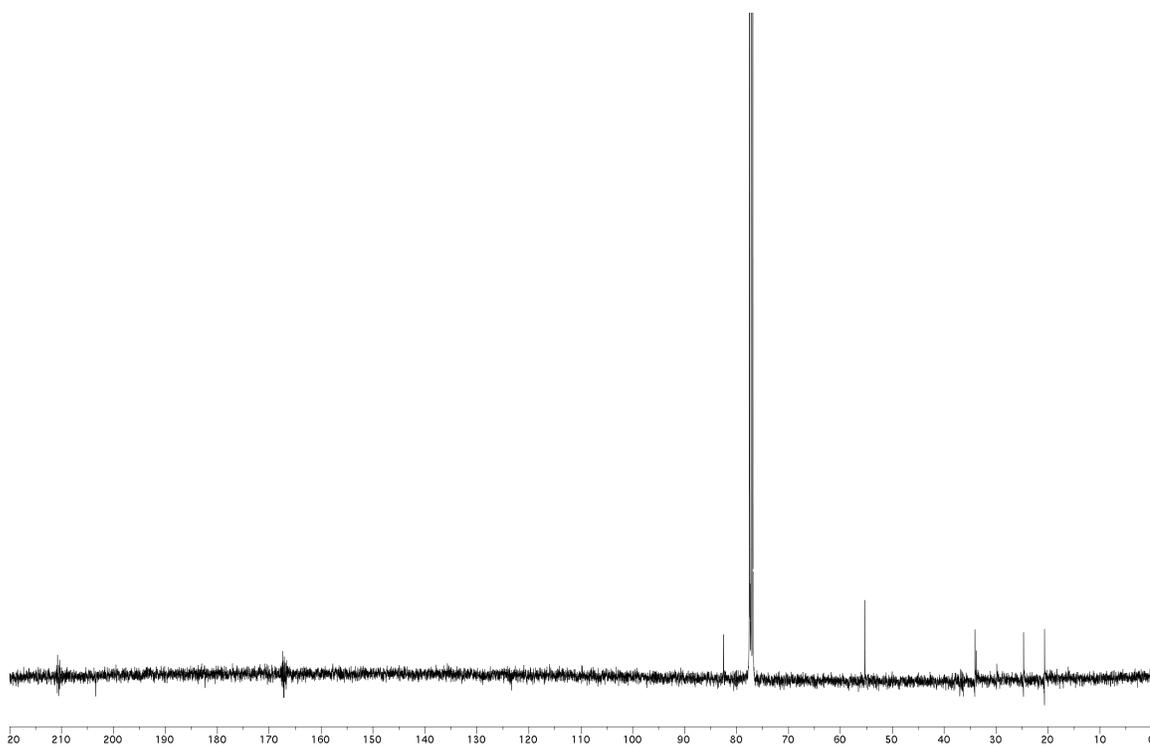


Figure A.2.42 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **233**
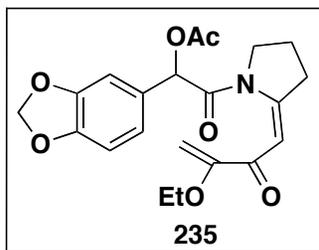
Figure A.2.43 1H NMR (400MHz, CDCl₃) of compound 235
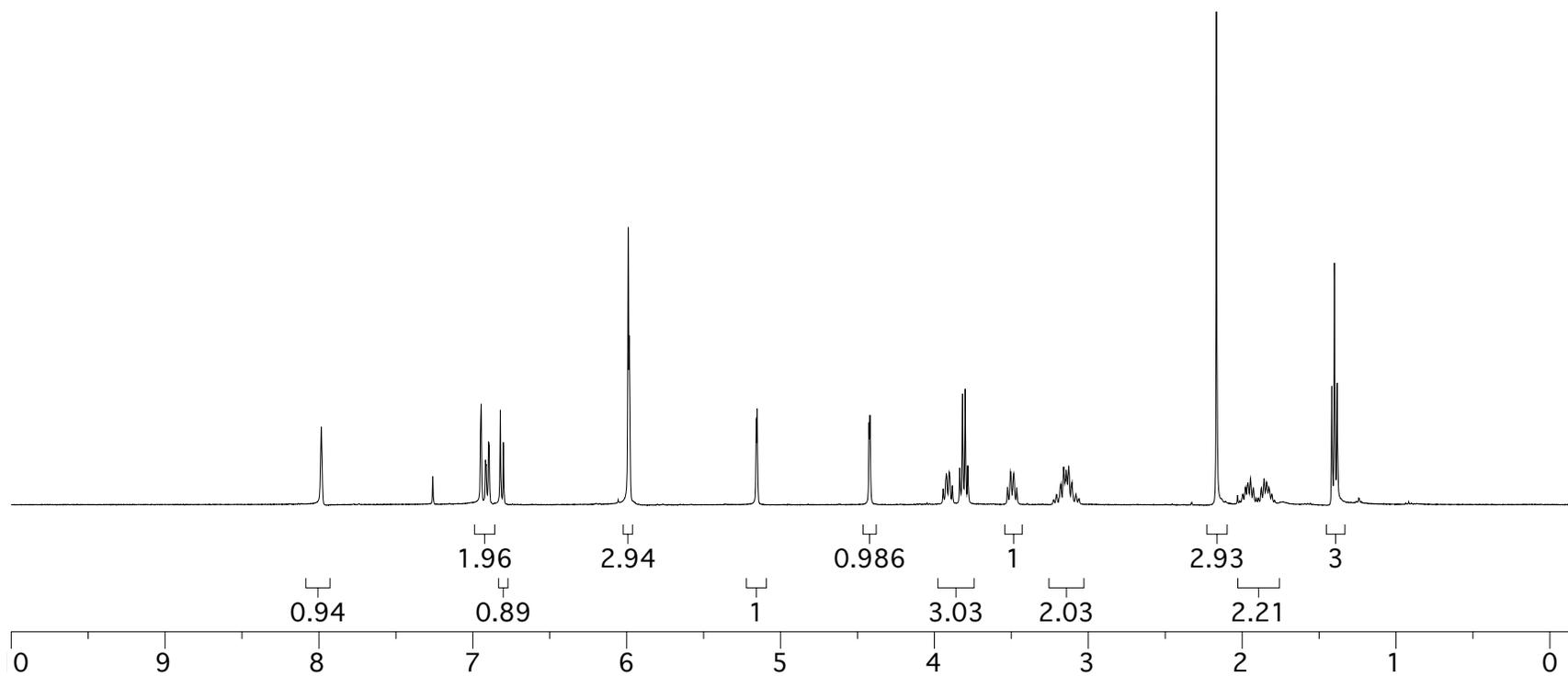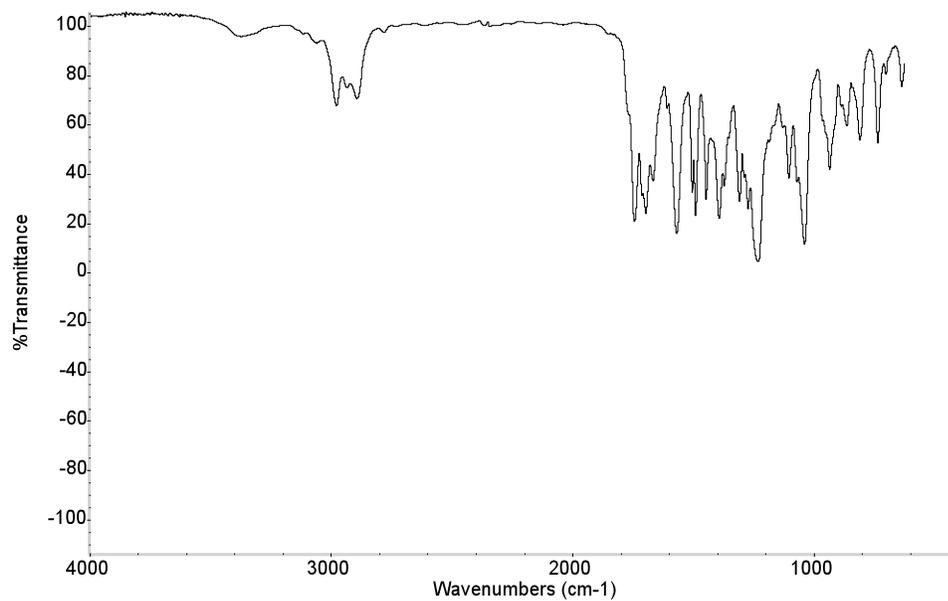
Figure A.2.44 Infrared Spectrum (thin film/NaCl) of compound **235**
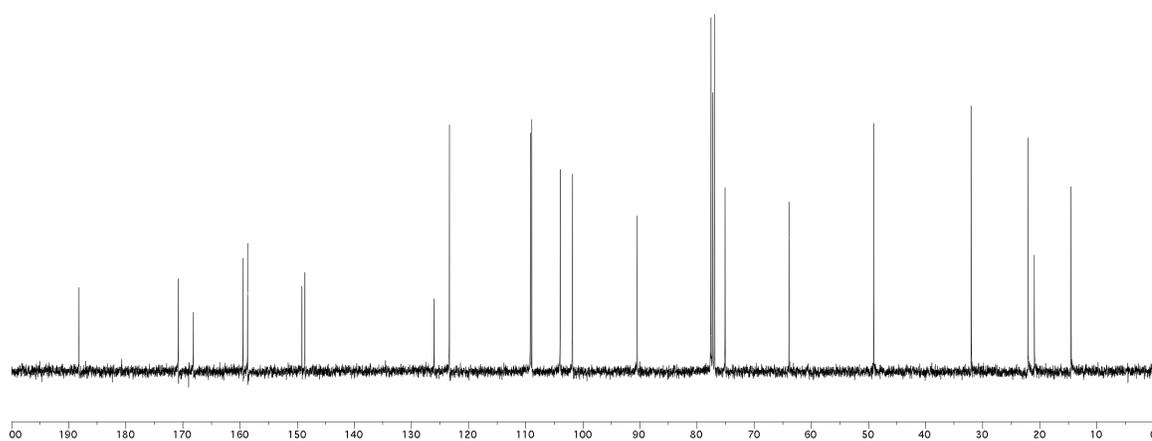


Figure A.2.45 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **235**
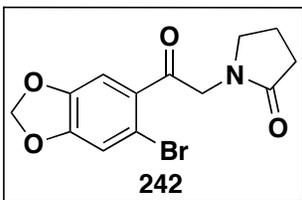
**Figure A.2.46 1H NMR (400MHz, CDCl₃) of compound 242**
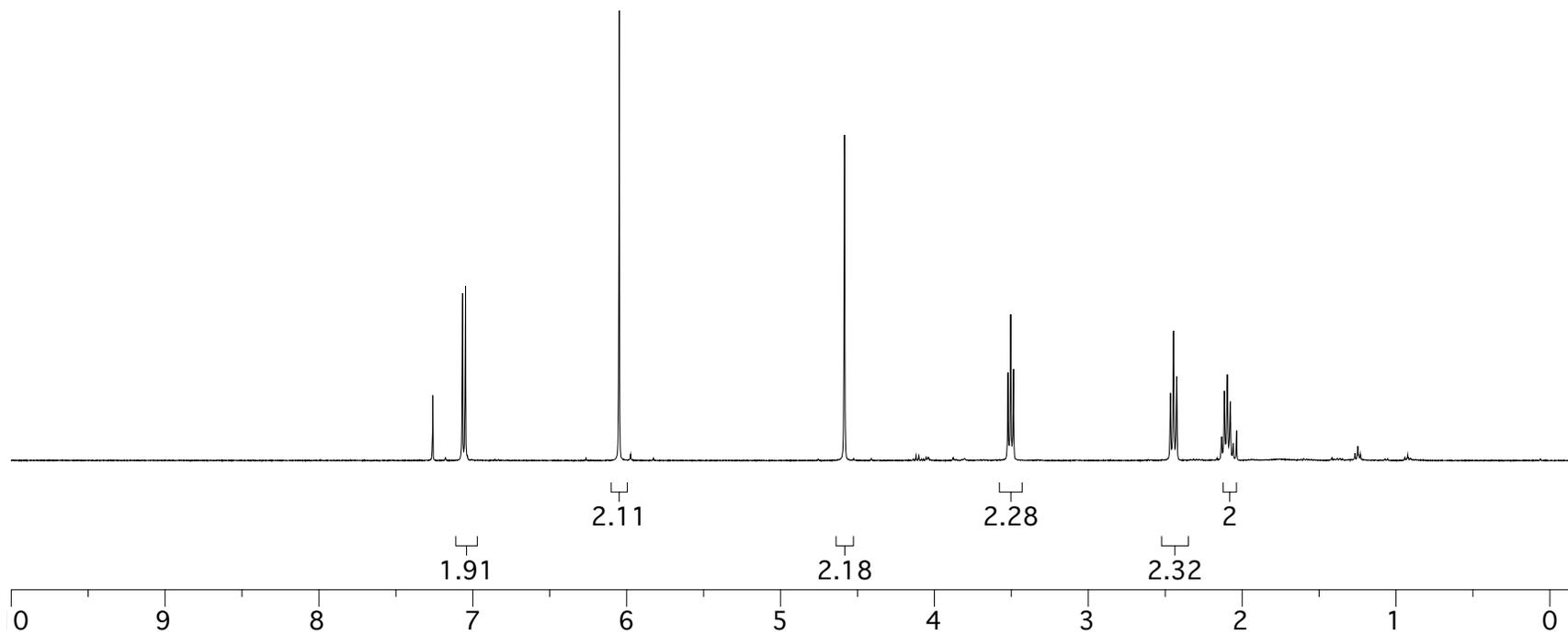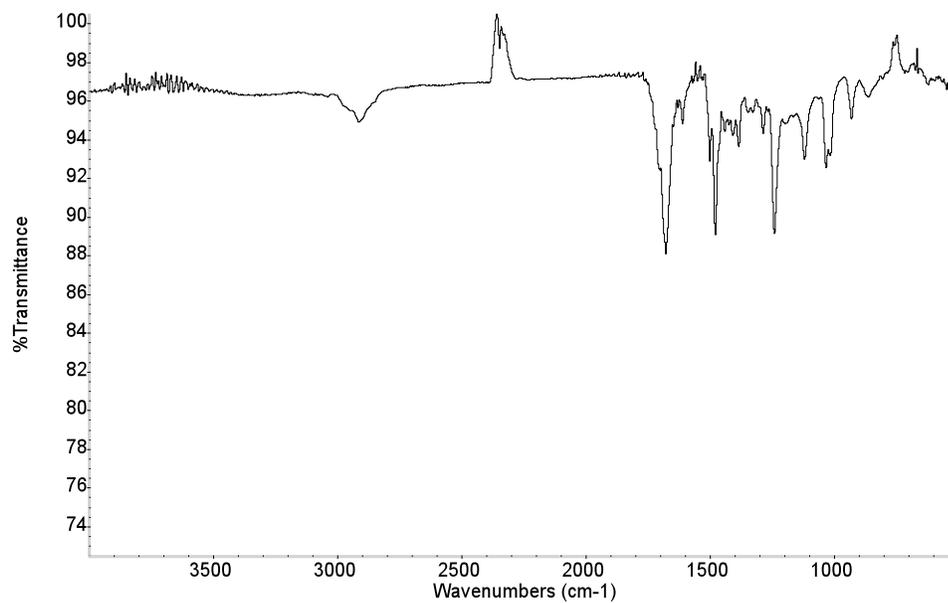
Figure A.2.47 Infrared Spectrum (thin film/NaCl) of compound **242**
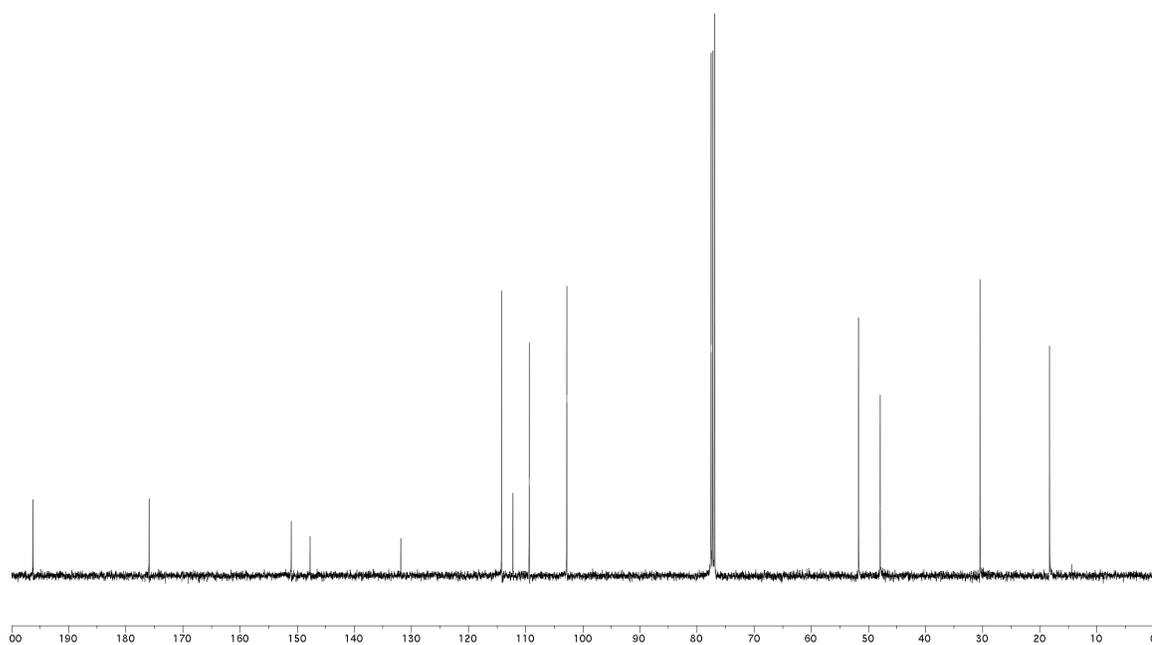


Figure A.2.48 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **242**
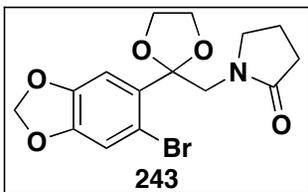
Figure A.2.49 1H NMR (400MHz, CDCl$_3$) of compound 243
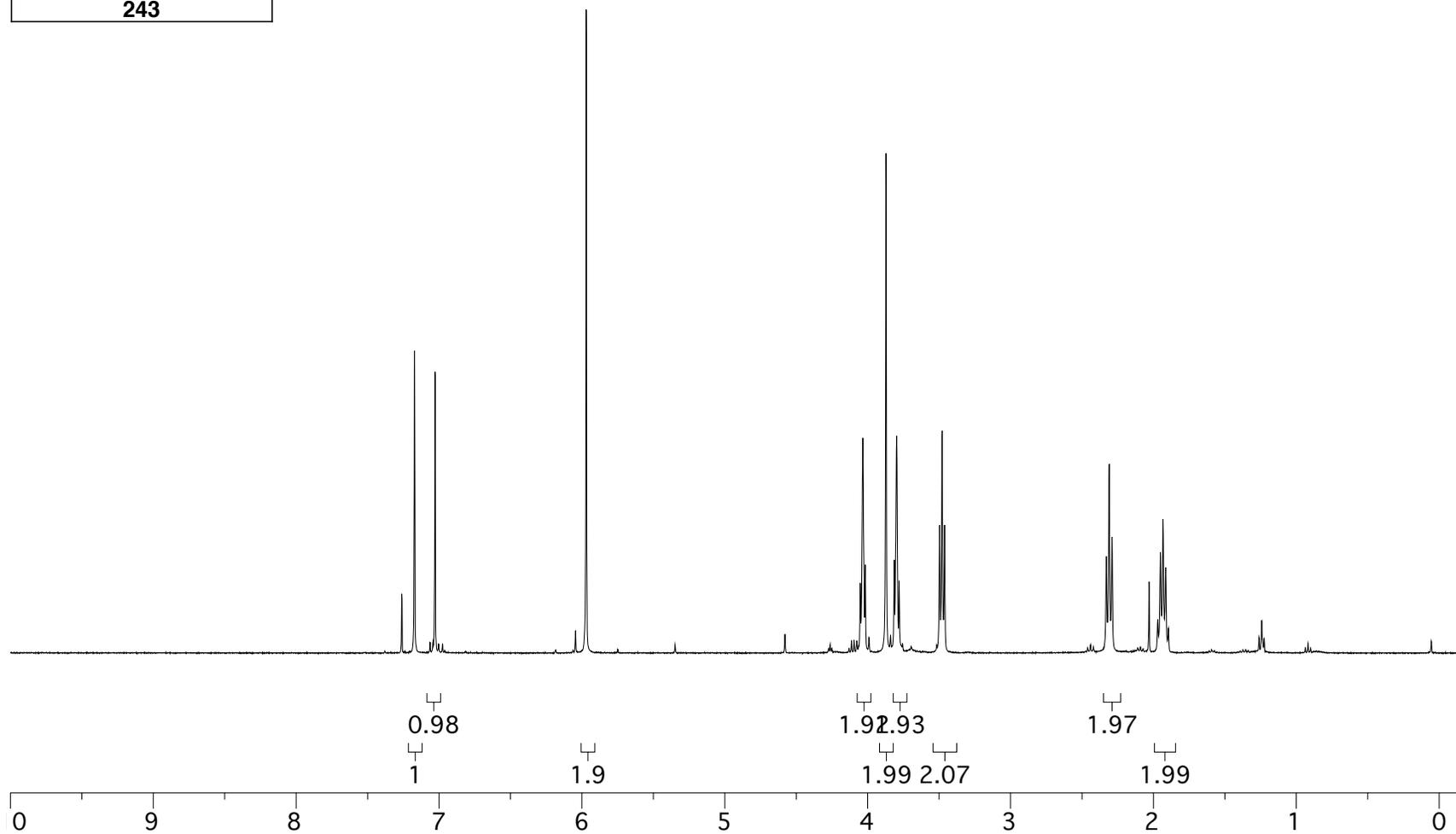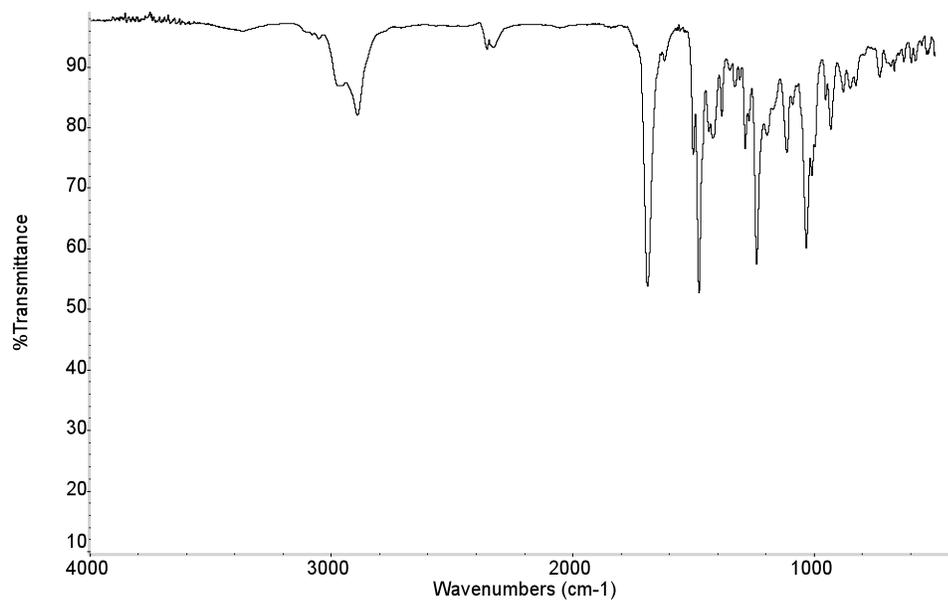
Figure A.2.50 Infrared Spectrum (thin film/NaCl) of compound **243**
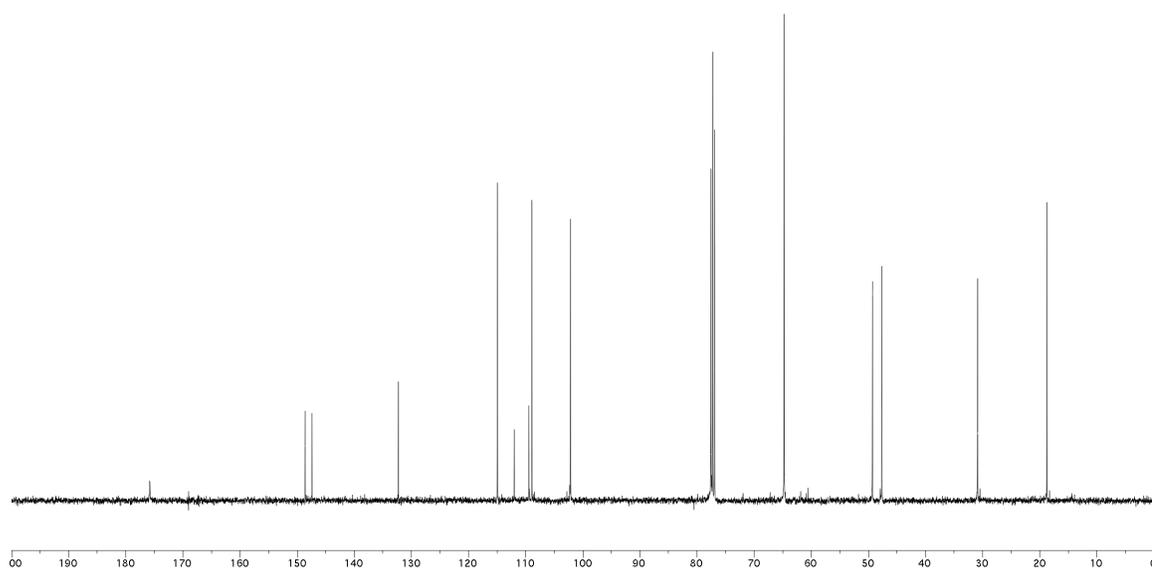


Figure A.2.51a $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **243**
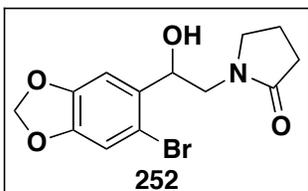
Figure A.2.52 1H NMR (400MHz, CDCl$_3$) of compound 252
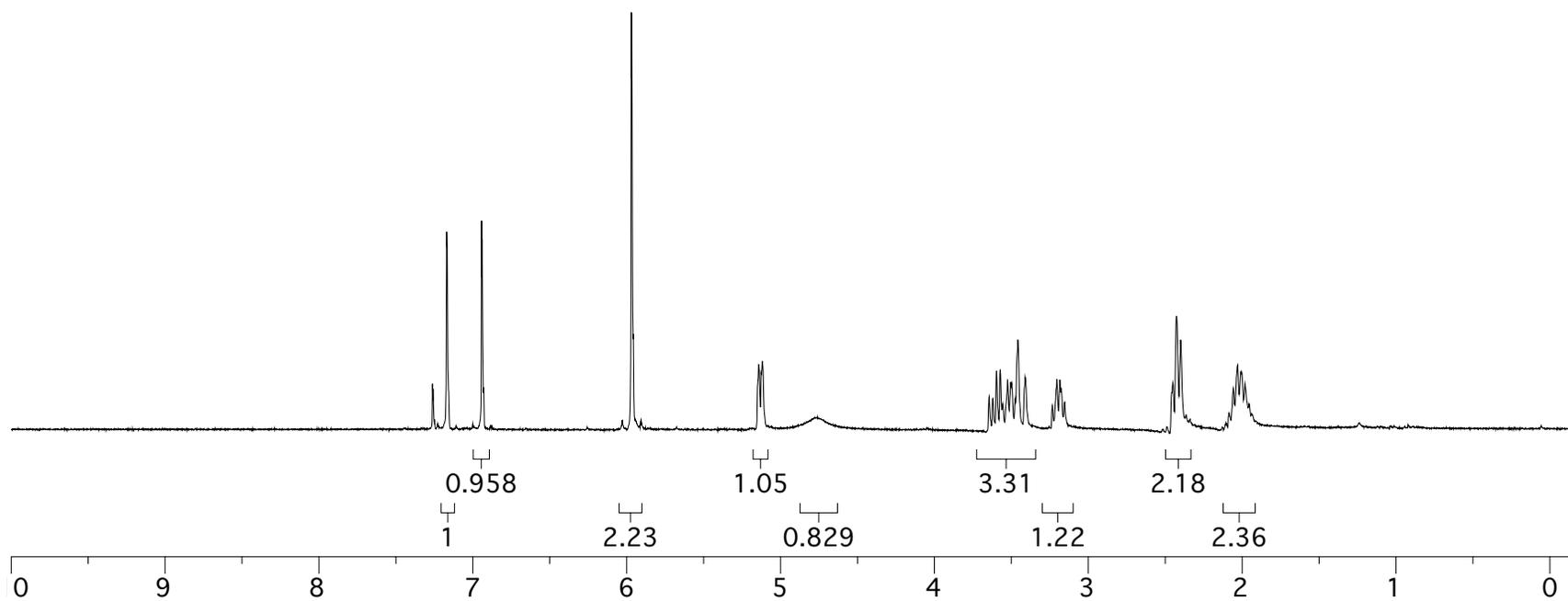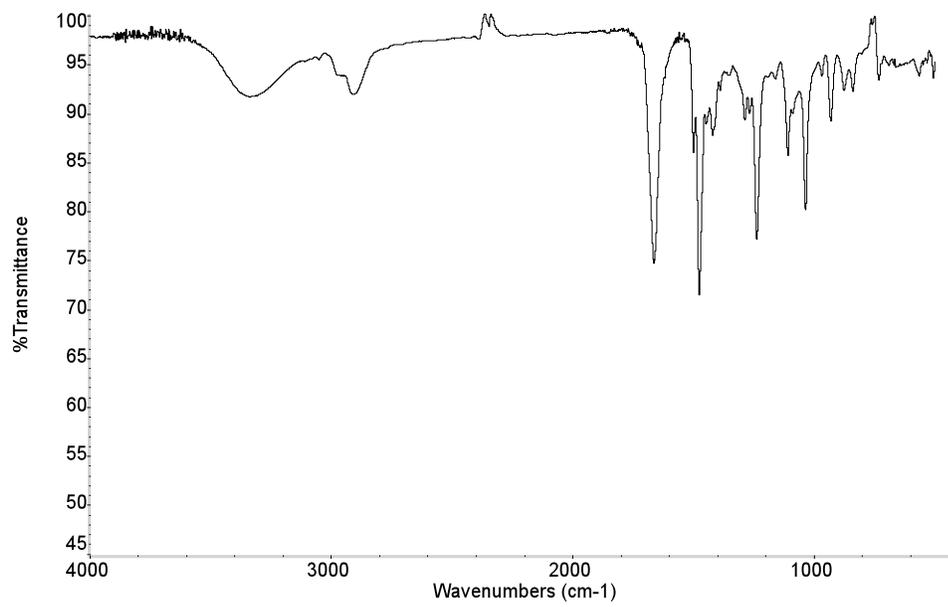
Figure A.2.53 Infrared Spectrum (thin film/NaCl) of compound **252**
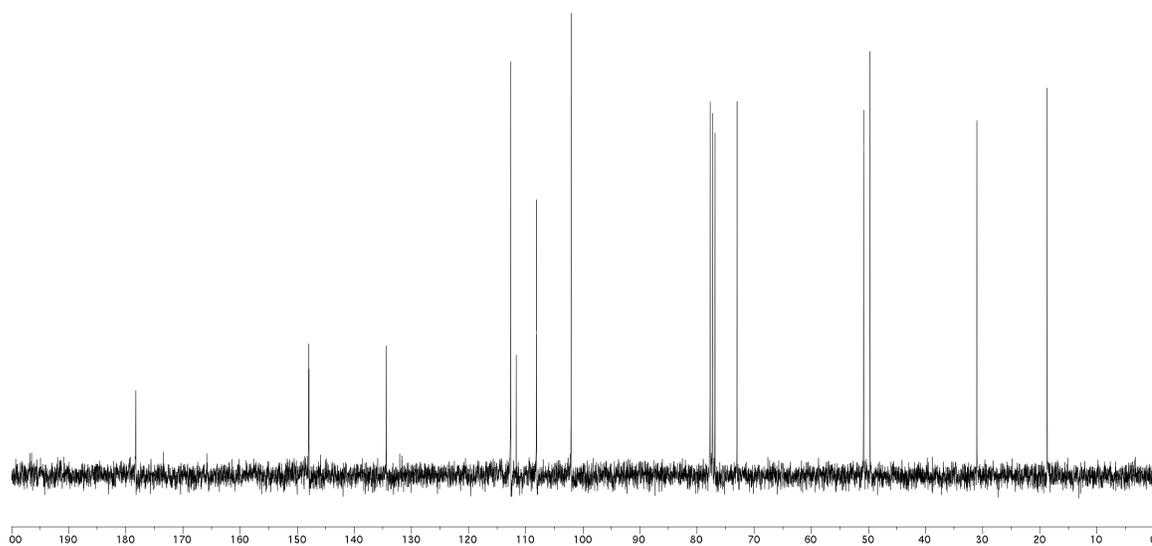


Figure A.2.54 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **252**
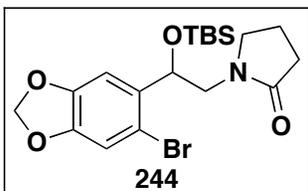
Figure A.2.55 1H NMR (400MHz, CDCl$_3$) of compound 244
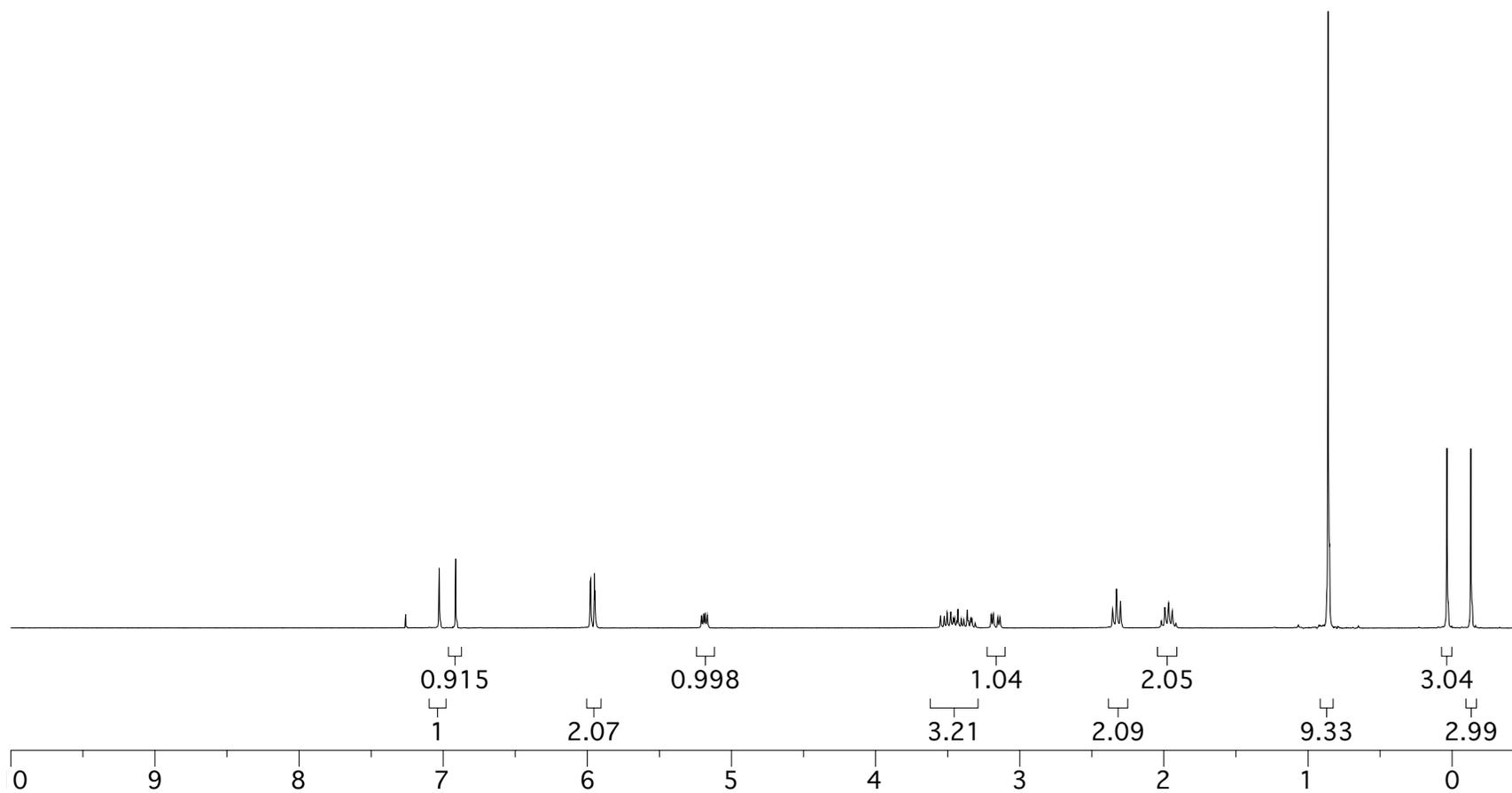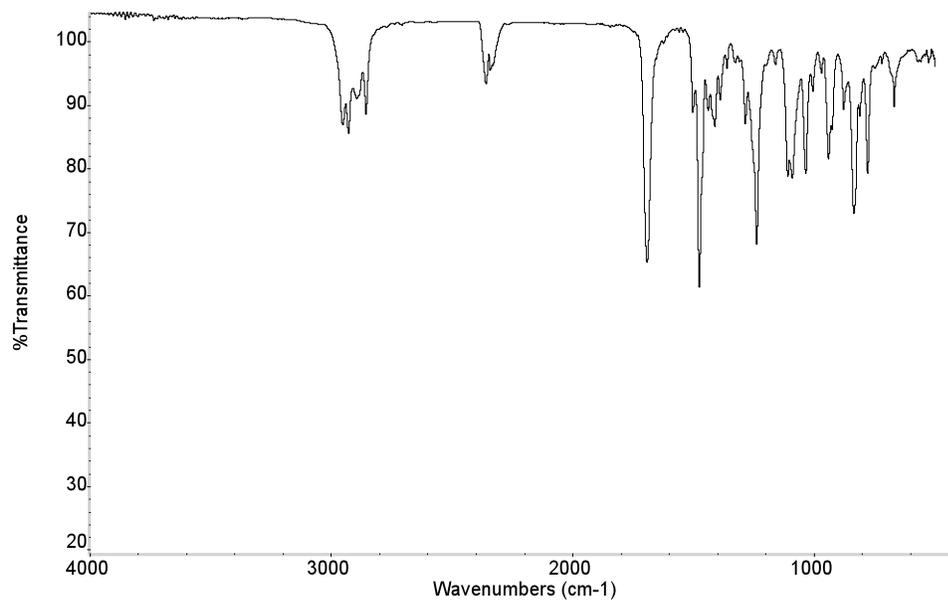
Figure A.2.56 Infrared Spectrum (thin film/NaCl) of compound **244**
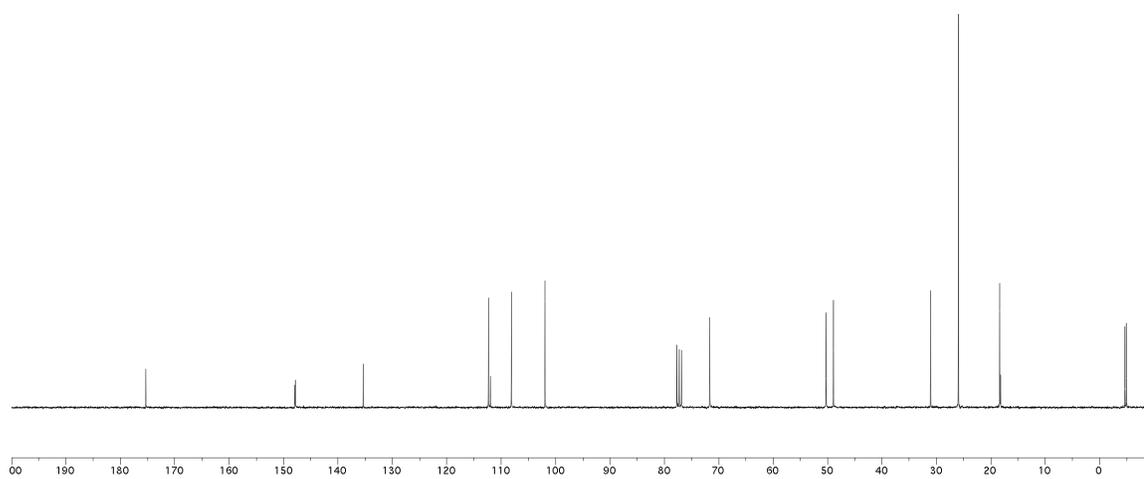


Figure A.2.57 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **244**
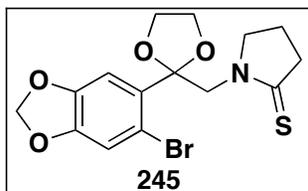
Figure A.2.58 1H NMR (400MHz, CDCl₃) of compound 245
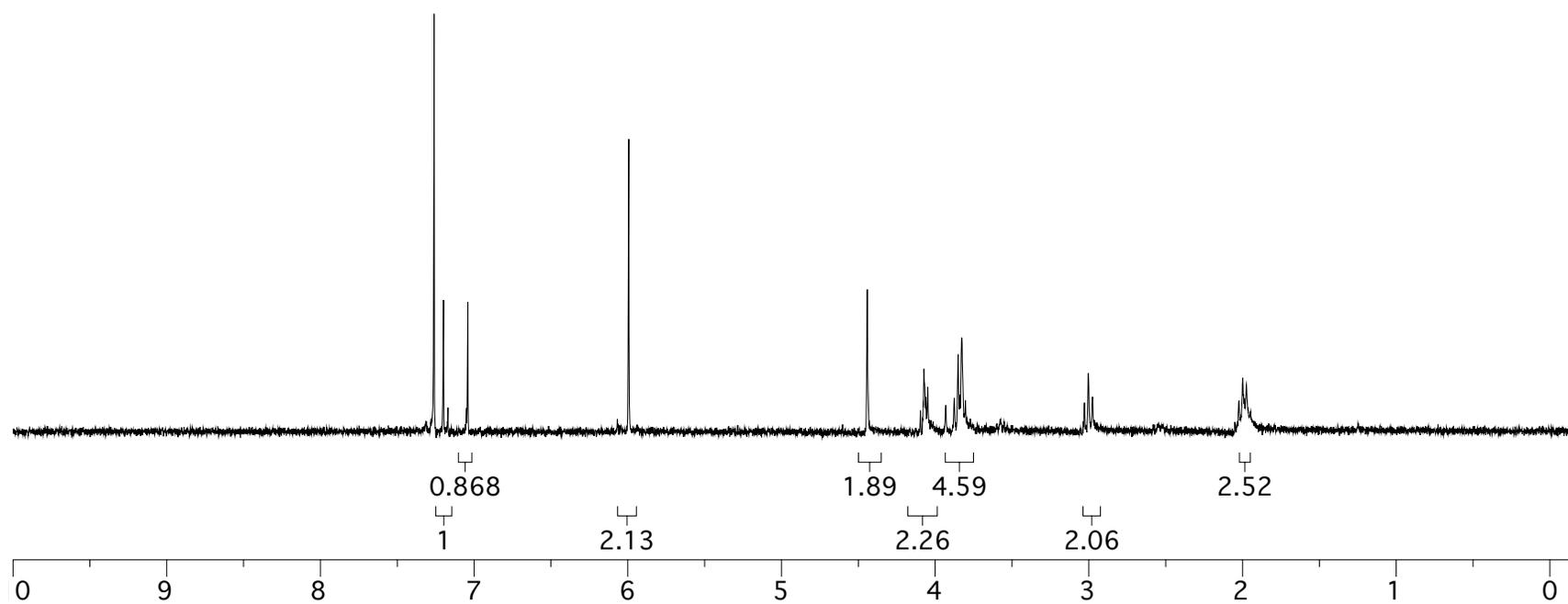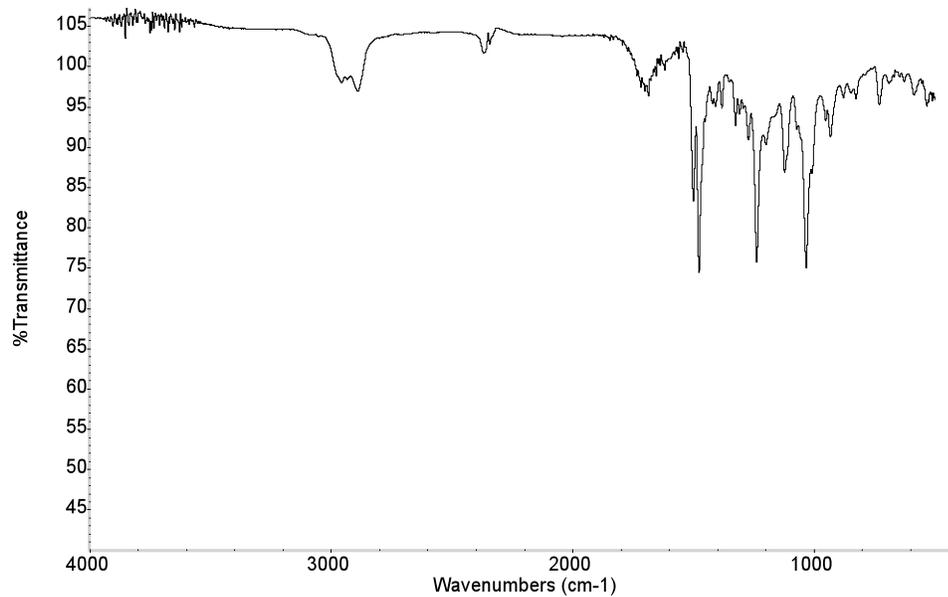
Figure A.2.59 Infrared Spectrum (thin film/NaCl) of compound **245**
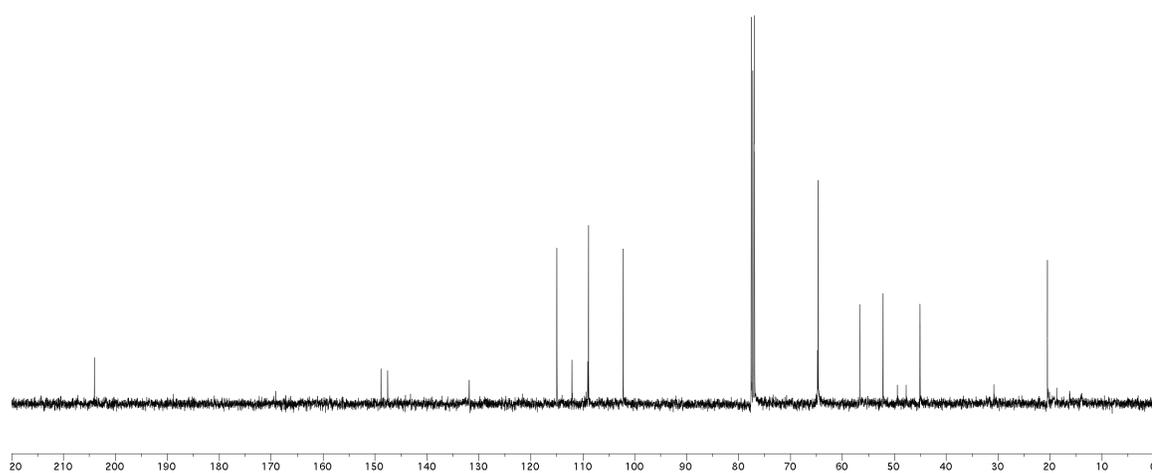


Figure A.2.60 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **245**

122
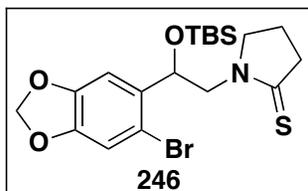
Figure A.2.61 1H NMR (400MHz, CDCl$_3$) of compound 246
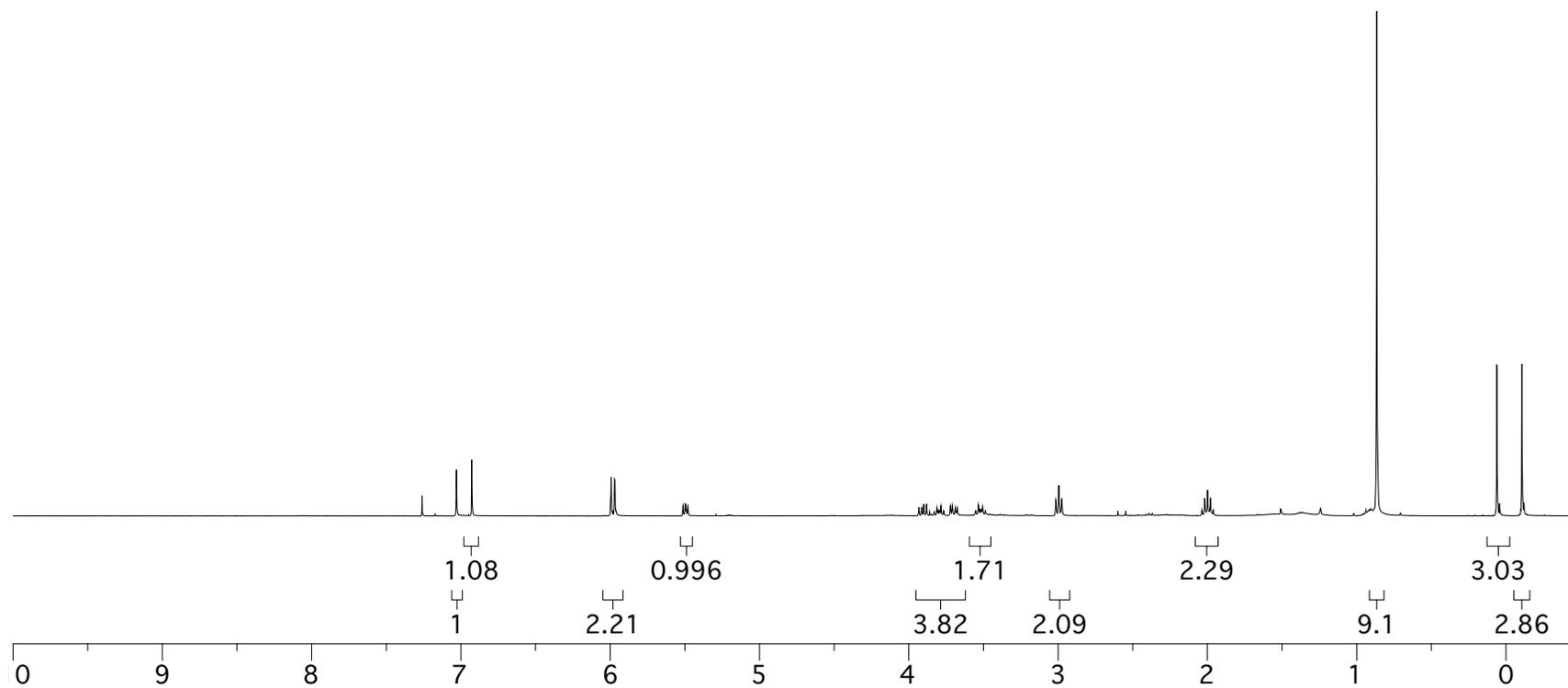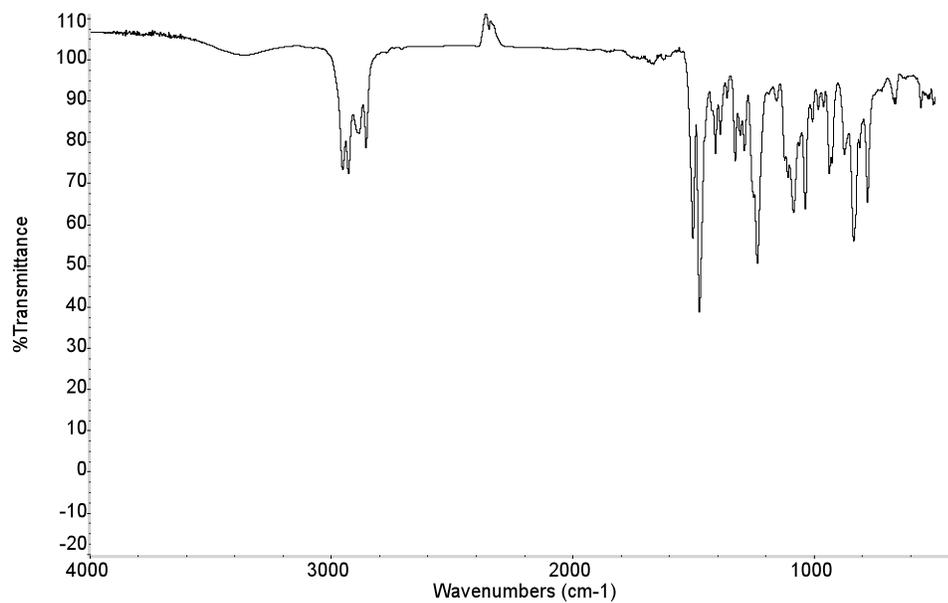
Figure A.2.62 Infrared Spectrum (thin film/NaCl) of compound **246**
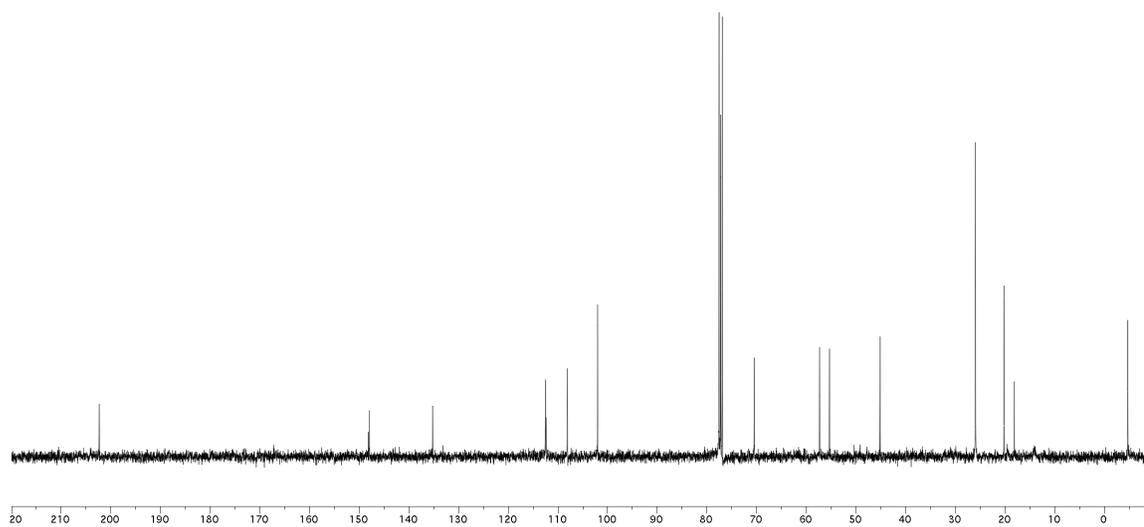


Figure A.2.63 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **246**
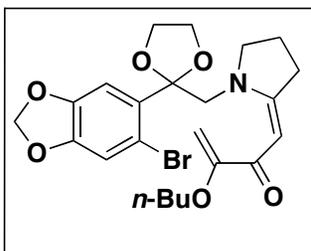
Figure A.2.64 1H NMR (400MHz, CDCl$_3$) of compound 247
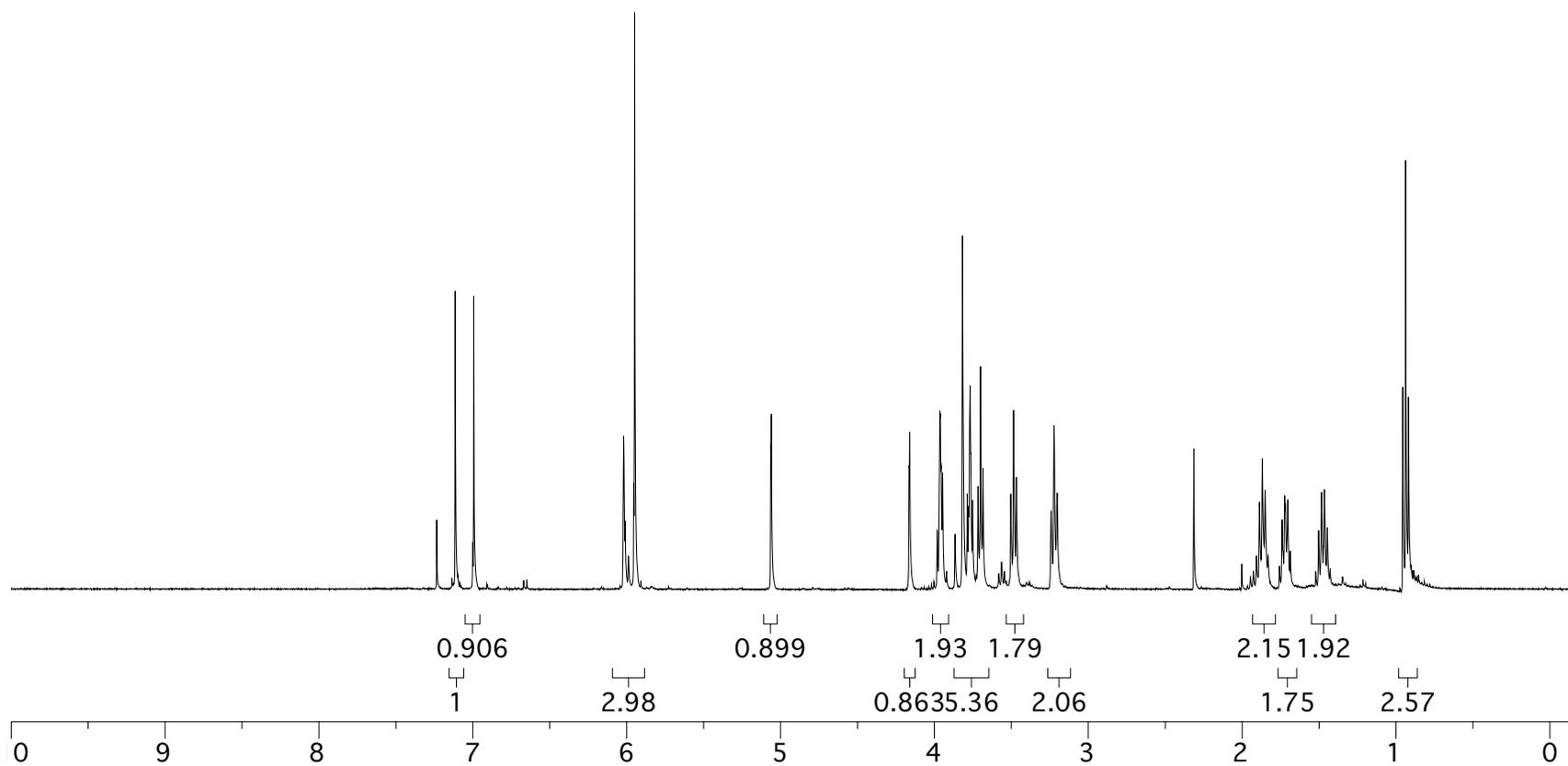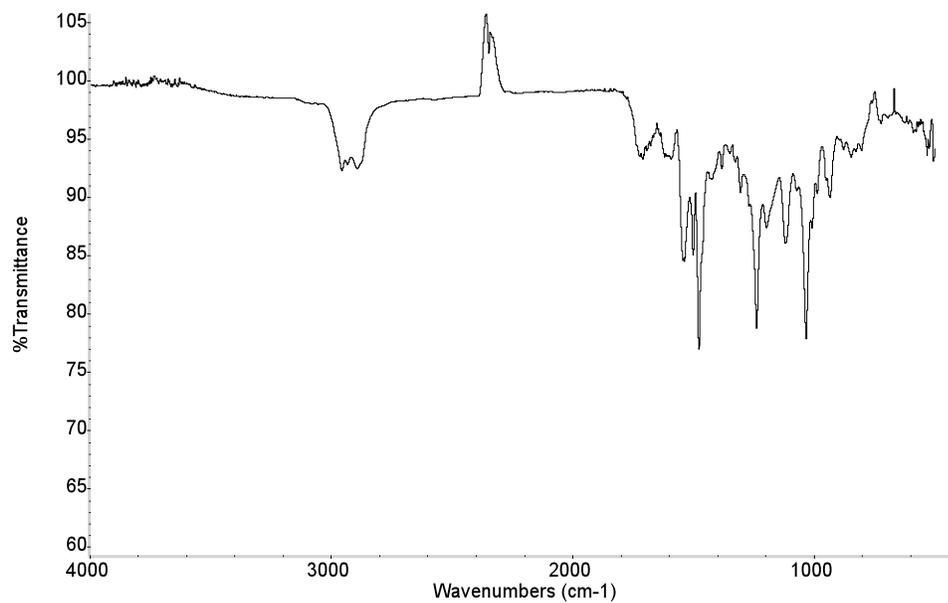
Figure A.2.65 Infrared Spectrum (thin film/NaCl) of compound **247**
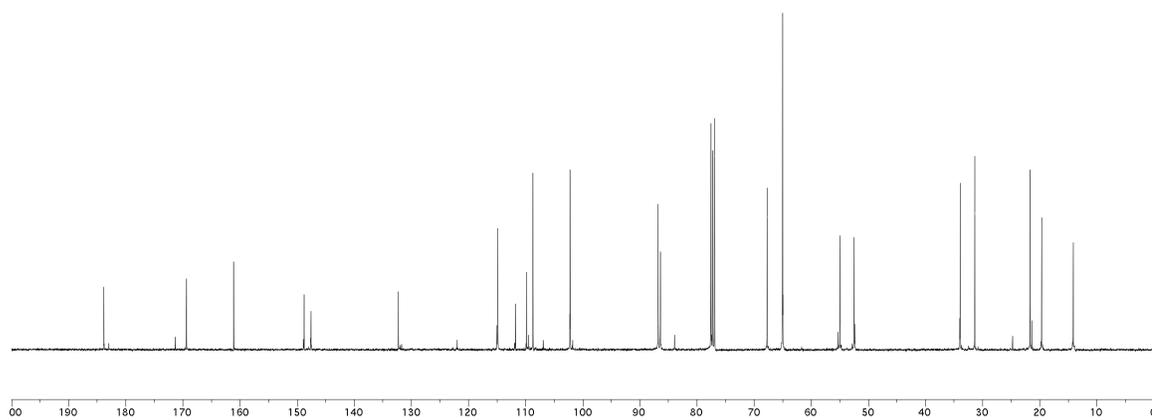


Figure A.2.66 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **247**
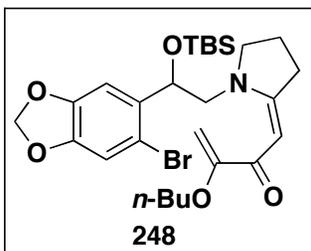
Figure A.2.67 1H NMR (400MHz, CDCl$_3$) of compound 248
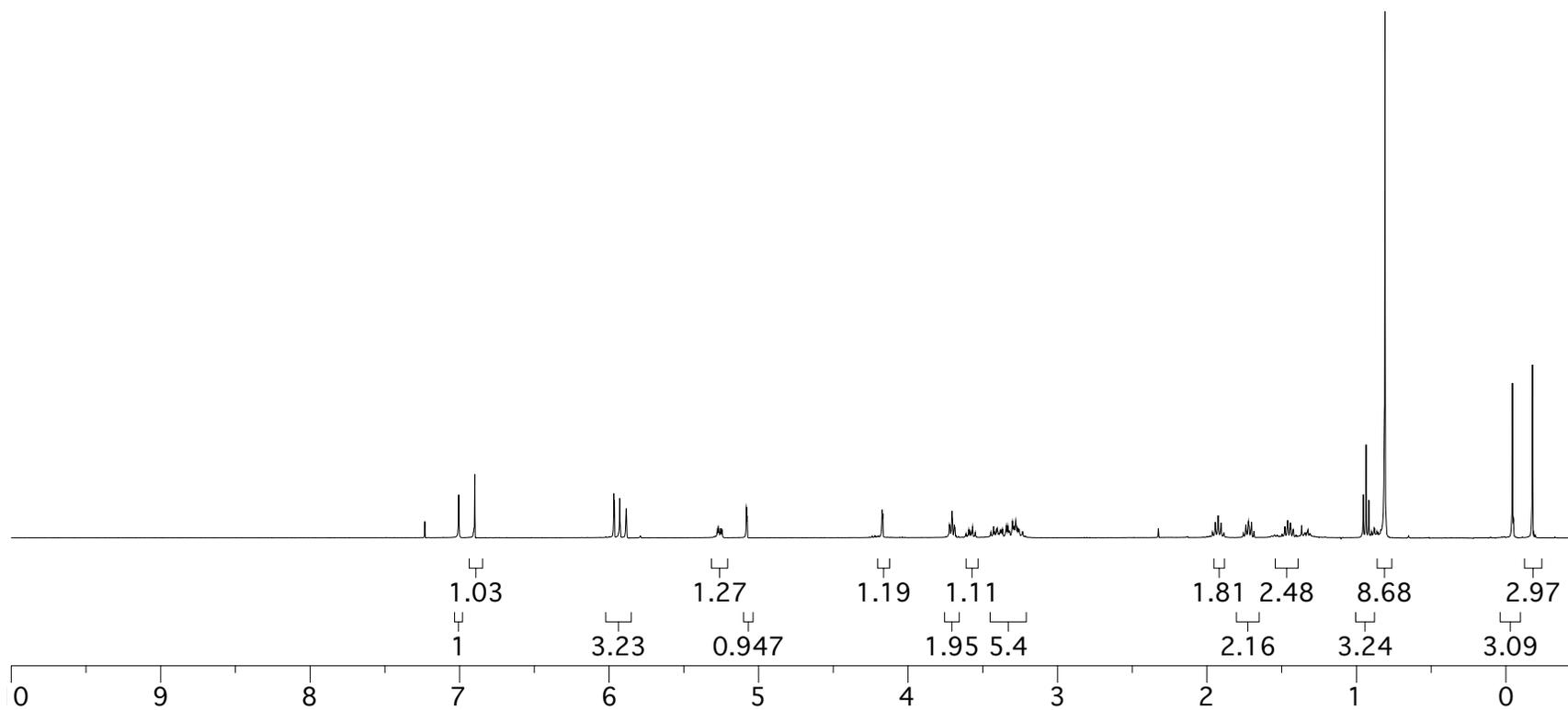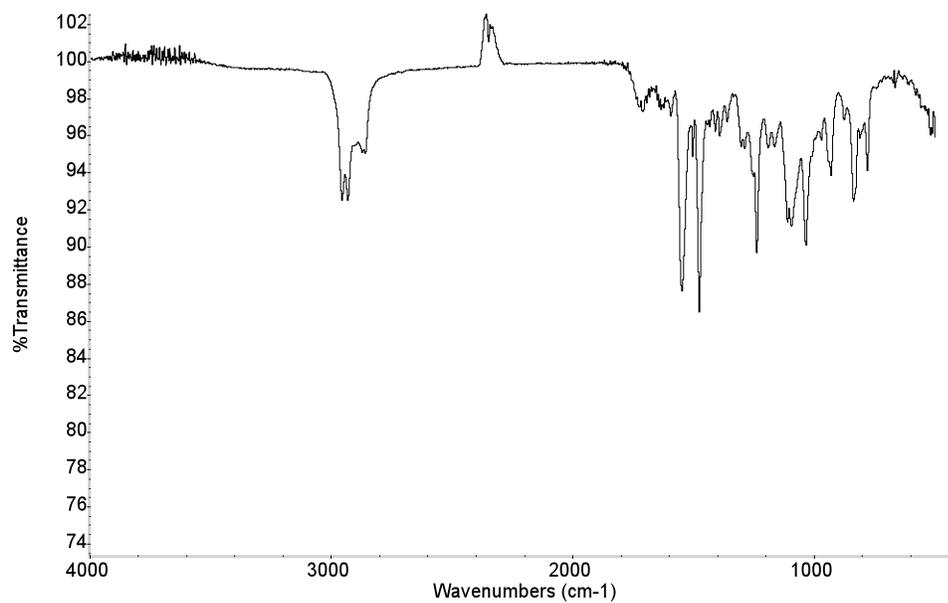
Figure A.2.68 Infrared Spectrum (thin film/NaCl) of compound **248**
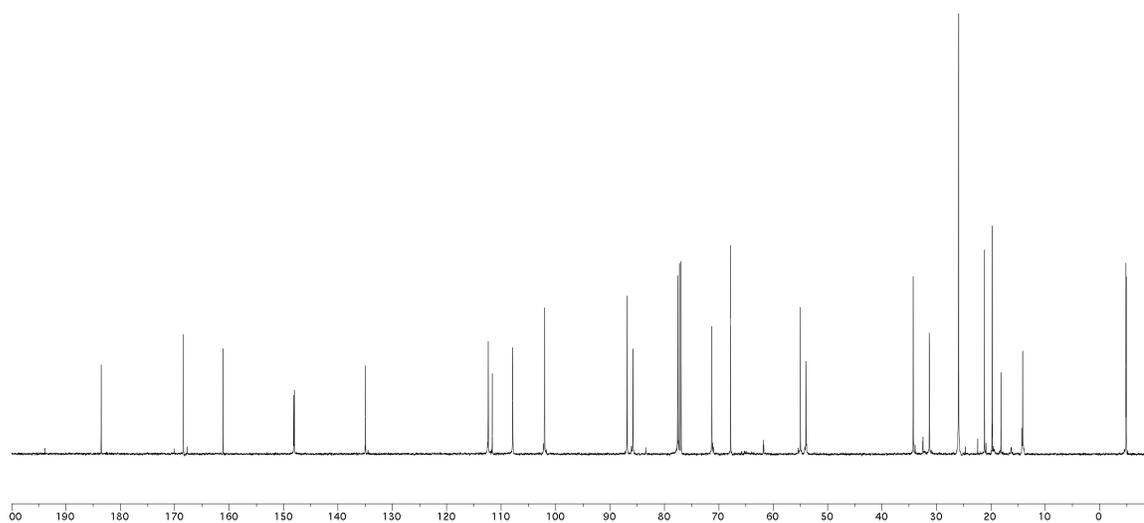


Figure A.2.69 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **248**

# Chapter 3

# Phomoidride Chemistry and Biology

## 3.1 Background and Introduction

### 3.1.1 Phomoidrides: Isolation and Structural Characterization

In 1995, researchers at Pfizer in Groton, Connecticut reported the isolation and characterization of phomoidride A (**300**) and phomoidride B (**301**) (**Figure 3.1.1**) from an unidentified fungus discovered on the twigs of *Juniperus ashei* trees in Dripping Springs, Texas.[1] In 1999, two additional compounds, phomoidride C (**302**) and phomoidride D (**303**) were found in the fungal broth.[2,3]

*Figure 3.1.1 Phomoidrides A-D*
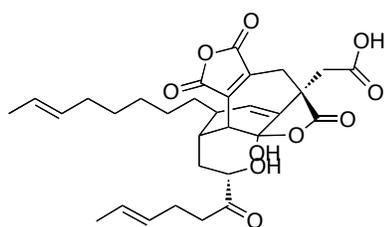


**300: Phomoidride A (CP-225, 917)**
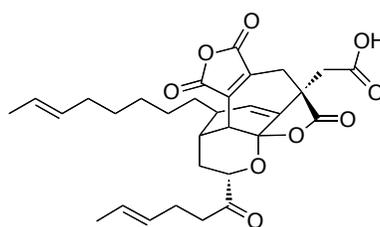
**301: Phomoidride B (CP-263, 114)**
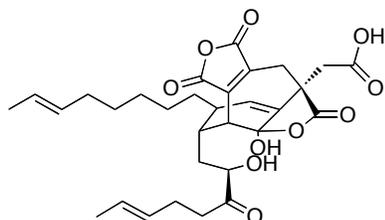
**302: Phomoidride C**
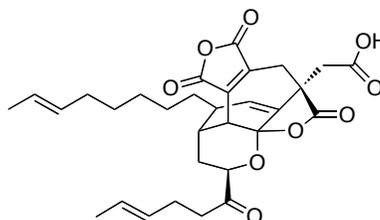
**303: Phomoidride D**

The phomoidrides are the members of the nonadride family of natural products. The name phomoidride derives from the name of the *phoma* genus, which exhibits characteristics of the phomoidride producing fungus. In addition, the name also reflects the classification of these fungal metabolites as nonadrides, a name given by Barton based on the observation that these compounds derive from dimerization of two nine-carbon natural products (nona-), containing bisanhydride rings (-dride).[4] Other members of the nonadride family have been found that are postulated to arise from a similar biosynthetic pathways (**Figure 3.1.2**).[5-10]

*Figure 3.1.2 Nonadride Family*



**304: Glaucanic acid**

**305: Cordyanhydride A**

**306: Cornexisitin**

**307: Rubratoxin A**

**308: Byssochlamic acid**
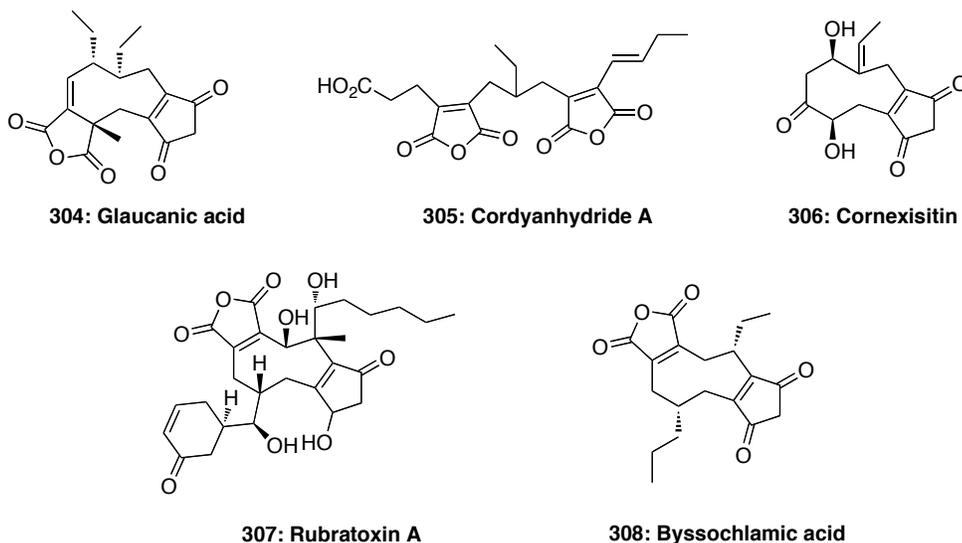
## 3.1.2 Phomoidride Biosynthesis

In Sulikowski's biosynthesis study of the phomoidride,[11-15] decarboxylative homodimerization of an unsaturated anhydride **313** is a key step (**Scheme 3.1.2**). Anhydride **313** could be derived from the condensation of oxaloacetyl-CoA (**310**, derived from succinic acid (**309**)) and diene **312** (derived from acetyl-CoA (**311**)). Dimerization of **313** followed by oxidation would afford the core of phomoidrides (**314**). Subsequent ether formation and thioester hydrolysis would furnish phomoidride B (**301**).

*Scheme 3.1.2 Biosynthesis of Phomoidride B*
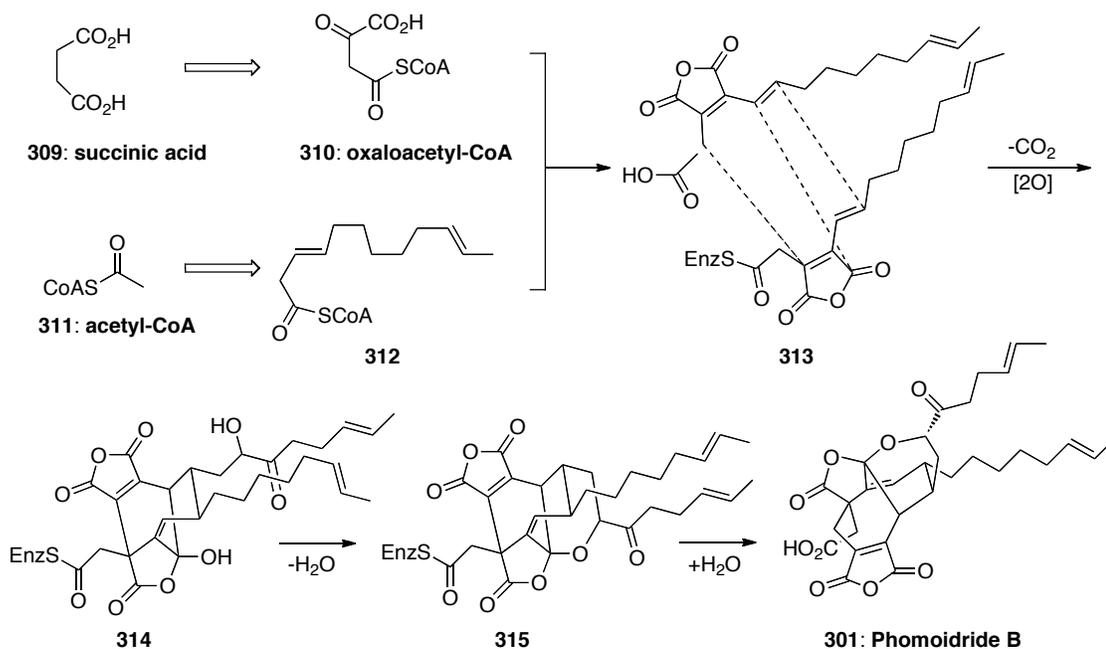


## 3.1.3 Biological Activity of the Phomoidrides

The phomoidrides display modest activity against the enzyme squalene synthase (phomoidride A $IC_{50}$ = 43 µM, phomoidride B $IC_{50}$ = 160 µM),[16] an enzyme that catalyzes the synthesis of squalene (**317**) from farnesyl pyrophosphate (**316**) (**Scheme 3.1.3**). From a chemotherapy perspective, the inhibition of squalene synthase may serve to decrease the level of cholesterol (**318**) since squalene is a precursor in the biosynthesis of cholesterol.[17-19]

*Scheme 3.1.3 Biosynthesis of Cholesterol*



**316**: Farnesyl pyrophosphate

**317**: Squalene

**318**: Cholesterol
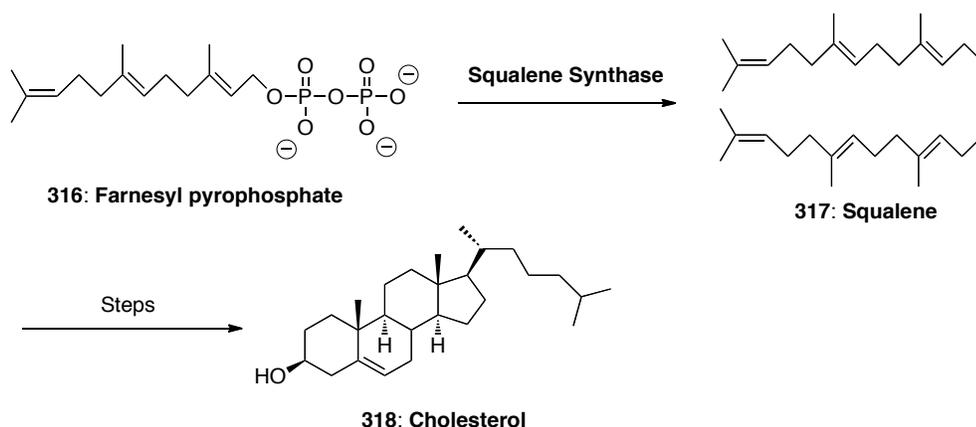
The phomoidrides also have shown biological activity against *ras* farnesyl transferase (phomoidride A $IC_{50} = 6$ μM, phomoidride B $IC_{50} = 20$ μM). Mutated forms of cellular *ras* genes are among the most common genetic abnormalities in human cancers, occurring in 90% of pancreatic carcinomas, 50% of colon carcinomas, and 20-30% of acute leukemias. Thus, inhibition of oncogenic *ras* activity is thought to be useful for anticancer treatment. One promising pharmacological approach against oncogenic *ras* activity would be interference of *ras* membrane localization. The crucial modification required for *ras* membrane association and transformation is the addition of a farnesyl moiety to the cysteine residue of a C-terminal CAAX motif in a reaction catalyzed by protein farnesyltransferase. Therefore, phomoidrides may have chemotherapeutic potential for inhibiting farnesyltransferase.[20-21]

## 3.2 Phomoidrides: Structure and Synthesis

## 3.2.1 Structural Features

In addition to their intriguing biological activity, the phomoidrides possess interesting structural features. For example, phomoidride D (**303**) contains a bicyclo [4.3.1] decadiene moiety with a maleic anhydride, bridgehead olefin, all-carbon quaternary center, bridging lactone ketal, an epimerizable stereocenter and two olefinic side chains (**Figure 3.2.1**). The complicated structure makes phomoidrides challenging targets for synthetic chemists.

*Figure 3.2.1 Phomoidride D Structural Features*
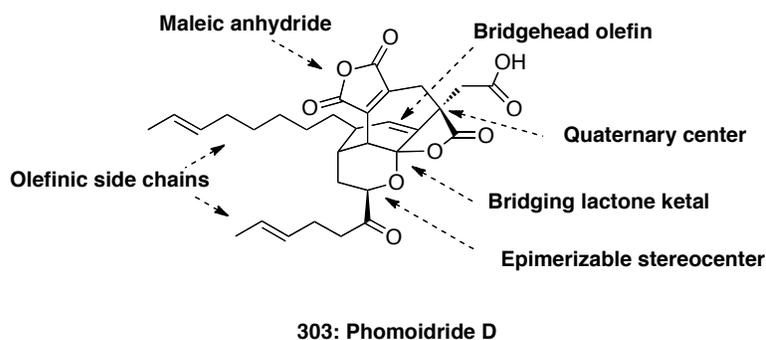


**303: Phomoidride D**

## 3.2.2 Phomoidrides Interconversion

Dabrah and co-workers reported the conversion of phomoidride A (**300**) to phomoidride B (**301**) by treatment with catalytic methanesulfonic acid (**scheme 3.2.2.1**).[1] Correspondingly, Nicolaou's group found that phomoidride B (**301**) can be converted to phomoidride A (**300**) upon exposure to LiOH.[22]

*Scheme 3.2.2.1 Phomoidride A and B Interconversion*



**300: Phomoidride A (CP-225, 917)**          **301: Phomoidride B (CP-263, 114)**
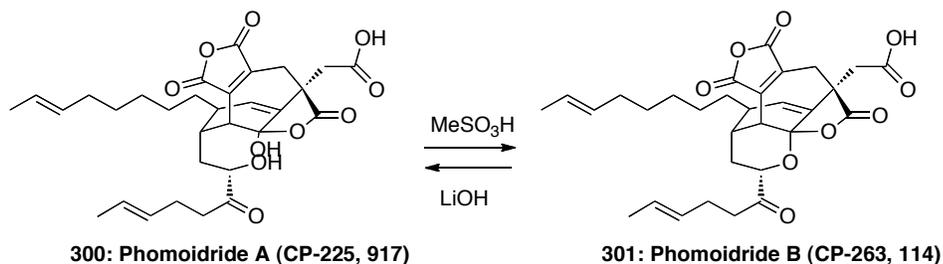
In an epimerization study, Danishefsky and co-workers reported that phomoidride
B could be epimerized to phomoidride D and phomoidride A can be epimerized to
phomoidride C (**Scheme 3.2.2.2**). The reverse epimerization, from phomoidride D to
phomoidride B or phomoidride C to phomoidride A, does not occur. However,
Danishefsky did demonstrate that Phomoidride D can be converted to phomoidride A in
seven steps (see **section 3.2.3.4** for details).[23]

*Scheme 3.2.2.2 Phomoidrides Epimerization*



**300: Phomoidride A (CP-225, 917)**          **302: Phomoidride C**

**301: Phomoidride B (CP-263, 114)**          **303: Phomoidride D**
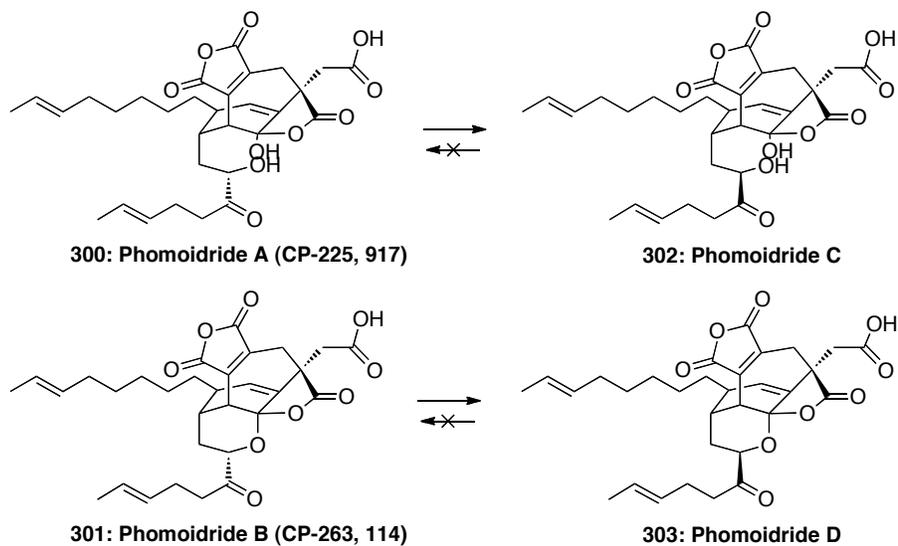
## 3.2.3 Synthetic Routes to the Phomoidrides

Numerous synthetic efforts have been made towards the total synthesis of the phomoidrides. To date, only four groups (Nicolaou, Fukuyama, Shair and Danishefsky) have reported completion of the total syntheses. In this dissertation, only the four completed total synthesis will be discussed since the other synthetic efforts have been summarized in a review article.[24]

## 3.2.3.1 K. C. Nicolaou's Route

K. C. Nicolaou reported the first total synthesis of phomoidride A and B in 1999.[22,29-44] Nicolaou's synthesis started with dimethyl malonate **320** (**Scheme 3.2.3.1.1**). Bis-alkylation, reduction of the diester and acetal formation gave acetonide **321**. Ozonolysis of alkene **321** produced an intermediate aldehyde, which underwent a modified aldol condensation with aldehyde **322** to yield enal **323**. The diene **324** for intramolecular Diels-Alder reaction was prepared from aldehyde **323** *via* PMB ether formation, deprotection of the primary alcohol and Parikh-Doering-oxidation.

*Scheme 3.2.3.1.1 Nicolaou Diene's Synthesis*
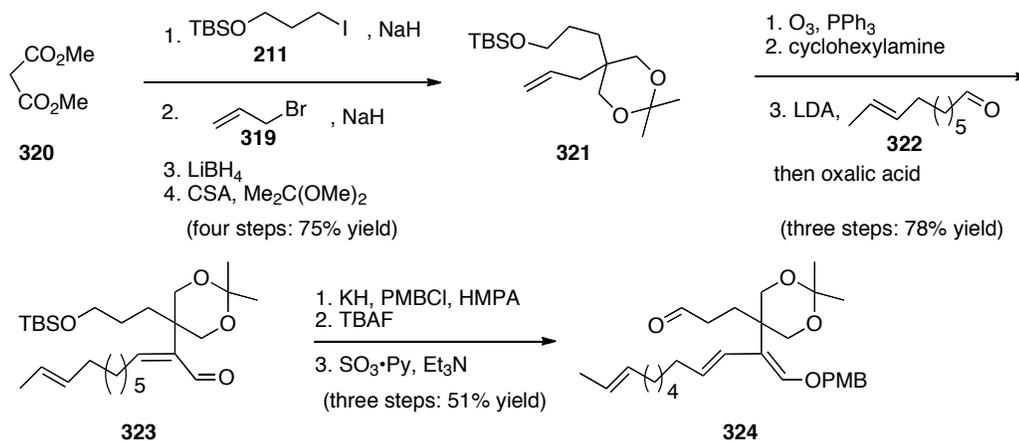
Diels-Alder product **327** was obtained from **325** *via* aldol addition of the vinyl

lithium reagent derived from vinyl iodide **326**, Dess-Martin oxidation, and aluminum

Lewis acid catalyzed [4+2] cycloaddition (**Scheme 3.2.3.1.2**). Removal of the bis TBS

ethers revealed an intermediate diol which underwent oxidative cleavage in the presence

of NaIO$_4$ to yield an aldehyde intermediate. Addition of the litho dithiane reagent **328** to

this aldehyde gave secondary alcohol **329**.

*Scheme 3.2.3.1.2 Nicolaou's Intramolecular Diels-Alder Reaction*
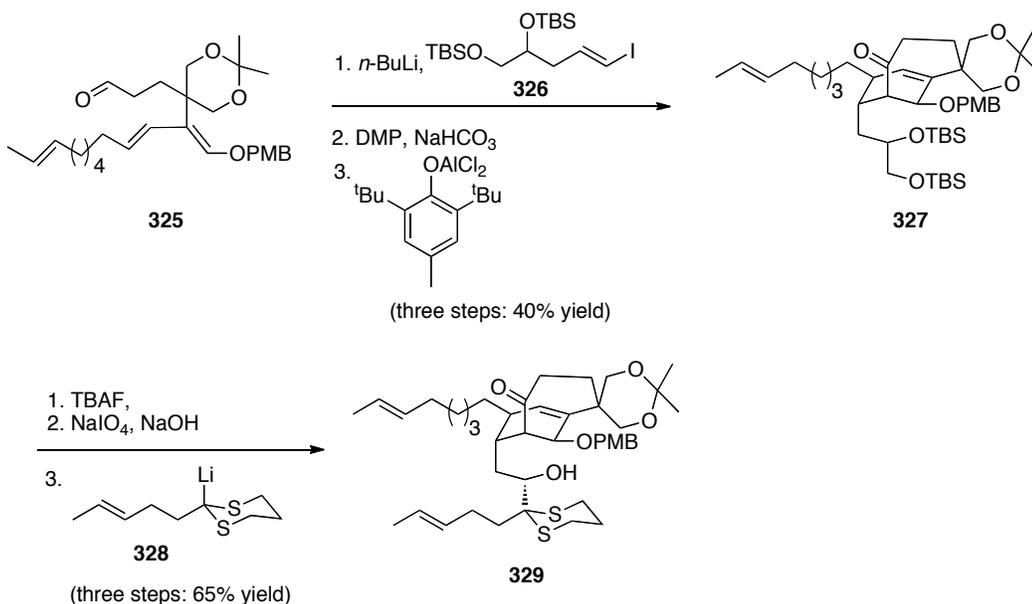


Installation of the maleic anhydride moiety commenced with alcohol **329**

(**Scheme 3.2.3.1.3**). TES ether protection, vinyl triflate formation using Comins reagent,

and Pd-mediated CO insertion, gave methyl ester **330**. Protecting group exchanged in the

presence of BTIB and MeOH, followed by ester reduction, directed epoxidation and

cyanide addition with Nagata's reagent opened the newly formed epoxide to yield diol

**331**. Treatment of diol **331** with MsCl, K$_2$CO$_3$ and oxalic acid furnished the maleic

anhydride moiety. Nicolaou believed that the anhydride was formed *via* the following transformations: (1) selective protection of primary alcohol by mesylation; (2) epoxide formation under the basic conditions; (3) epoxide opening via β-elimination; (4) 5-*exo-dig* cyclization on cyanide in the presence of acid; (5) double oxidation by exposure to air (6) hydrolysis to lose ammonia. After removal of dimethyl ketal and reprotection of the secondary alcohol as TBS ether, they prepared ketone **332**.

*Scheme 3.2.3.1.3 Nicolaou's Maleic Anhydride Synthesis*
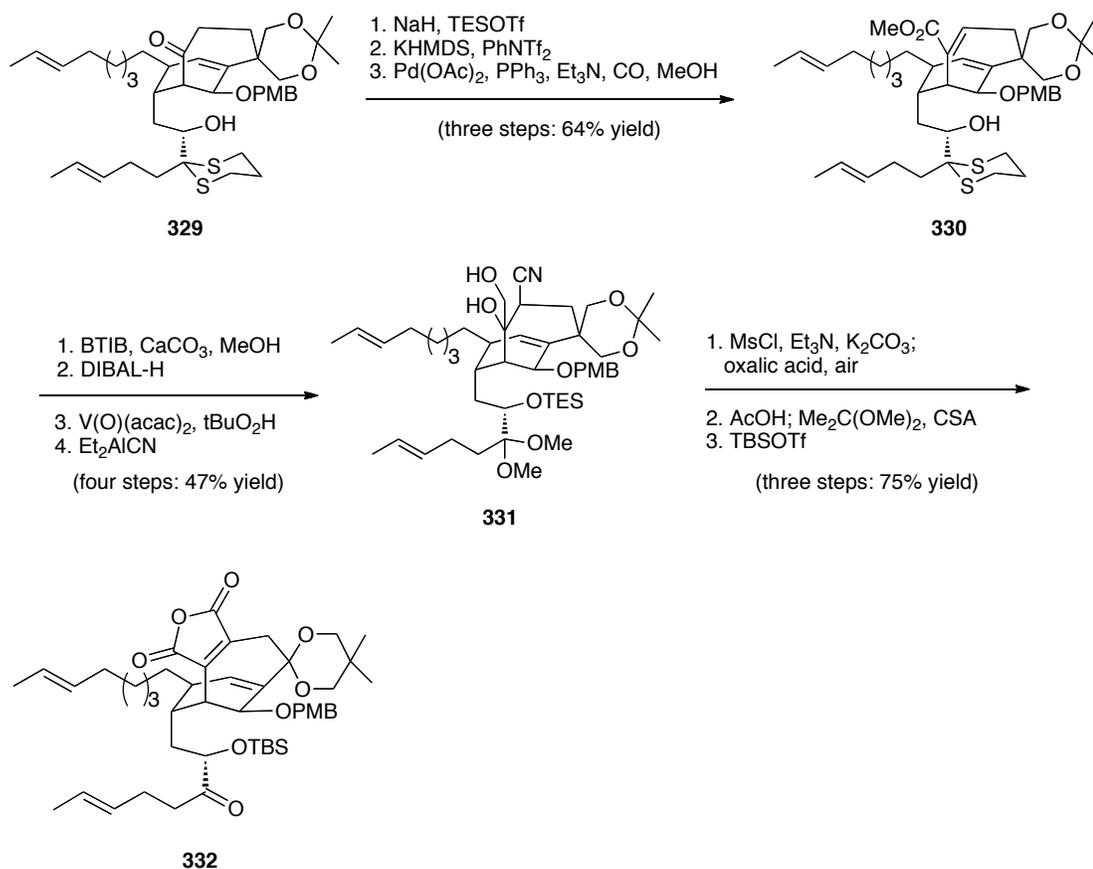


Treatment of ketone **332** with DDQ to remove the PMB protecting group was followed by PDC oxidation and removal of the acetonide in the presence of acetic acid to

give a diol which, underwent cyclization to form a hemiacetal. Protection of the

remaining alcohol as a TES ether provided hemiacetal **333** (**Scheme 3.2.3.1.4**). Bis

hemiacetal **334** was obtained by exposing **333** to the Dess-Martin reagent followed by

removal of the TES protecting group and MeSO₃H-mediated removal of the TBS ether.

*Scheme 3.2.3.1.4 Nicolaou's Bridging Ketal Synthesis*
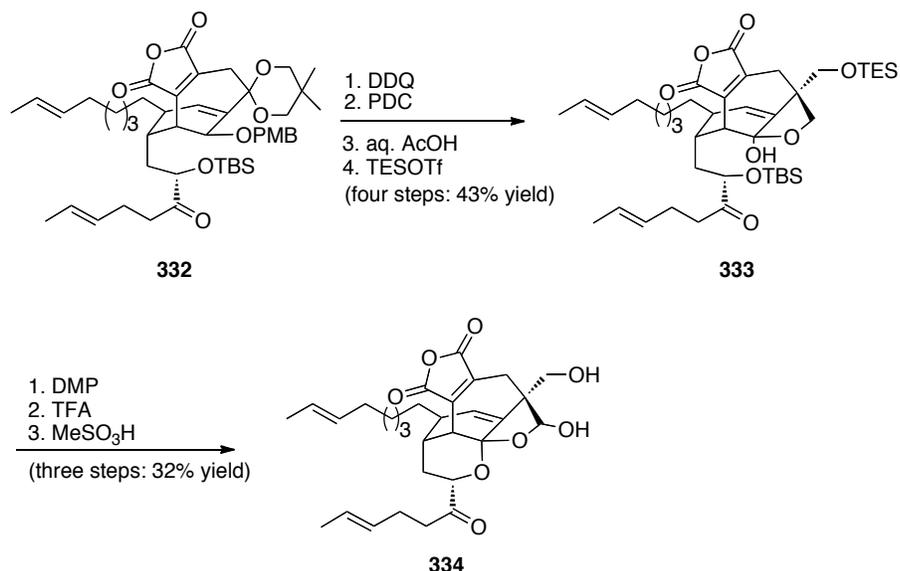


At this stage, oxidation of the primary alcohol, protection of the hemiacetal

alcohol and Pinnick oxidation yield an intermediate carboxylic acid which underwent

Arndt-Eistert homologation to furnish carboxylic acid **335** (**Scheme 3.2.3.1.5**).

Protection of carboxylic acid **335** as its indoline amide, removal of the TBS group,

oxidation of the hemiacetal to the corresponding lactone, oxidation of the indoline amide

to its indole derivative and hydrolysis of the derived indole amide to the acid gave the

natural product phomoidride A (**300**). In the presence of MeSO₃H, phomoidride A (**300**)

was converted to phomoidride B (**301**).

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*Scheme 3.2.3.1.5 Nicolaou's Phomoidride A and B Synthesis*



**334**

1. DMP
2. TBSOTf, 2,6-lutidine
3. NaClO$_2$, NaH$_2$PO$_4$, tBuOH
4. MsCl, Et$_3$N; CH$_2$N$_2$; Ag$_2$O, H$_2$O
   (four steps: 21% yield)

**335**

1. indoline, EDC, DMAP
2. TFA, H$_2$O
3. DMP, NaHCO$_3$
4. p-Chloranil
5. LiOH
   (five steps: 37% yield)

**300: Phomoidride A (CP-225, 917)**

MeSO$_3$H

(90% yield)

**301: Phomoidride B (CP-263, 114)**
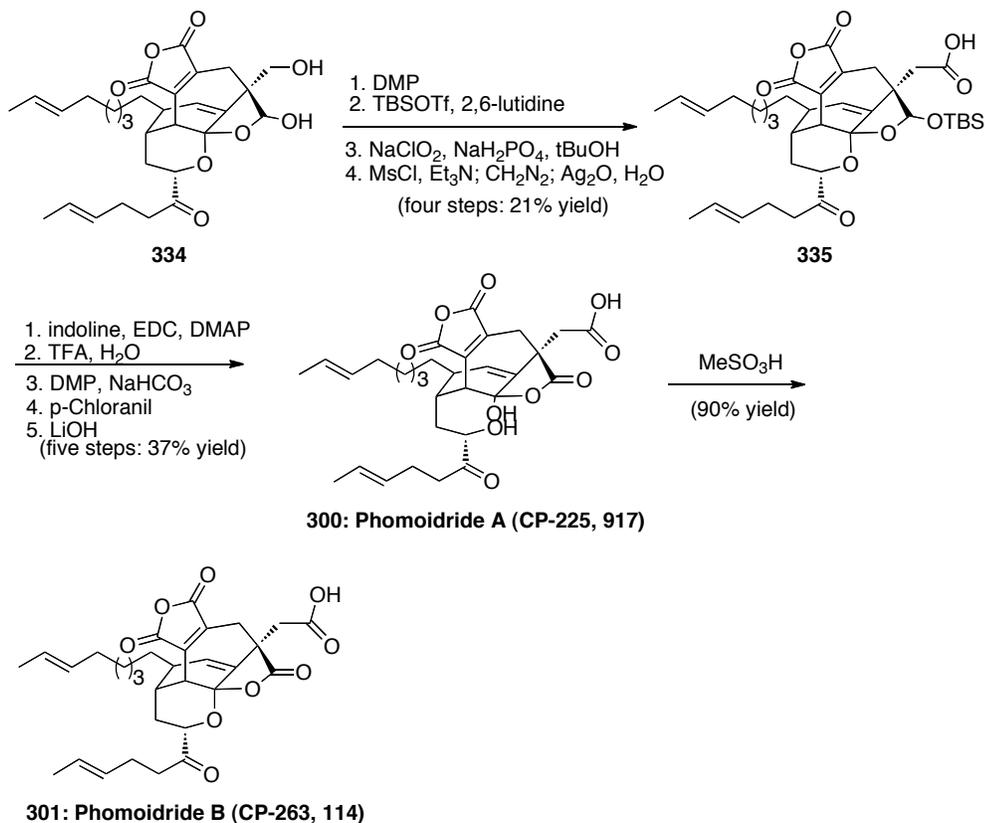
## 3.2.3.2 Fukuyama's Route

The second total synthesis of phomoidride B was reported by Fukuyama in 2000.[45-47] Fukuyama's synthesis commenced with the conversion of progargylic thioether **340** to the corresponding allene which was followed by nucleophilic addition of vinyl cuprate **341**, ester alkylation with Mander's reagent and Michael addition with a chiral oxazolidinone to give **342** (**Scheme 3.2.3.2.1**). Adol reaction between this intermediate and aldehyde **343** was followed by oxidation and intramolecular Diels-Alder reaction in the presence of ZnCl$_2$•OEt$_2$ to afford cycloaddition product **344**.

*Scheme 3.2.3.2.1 Fukuyama Intramolecular Diels- Alder Reaction*
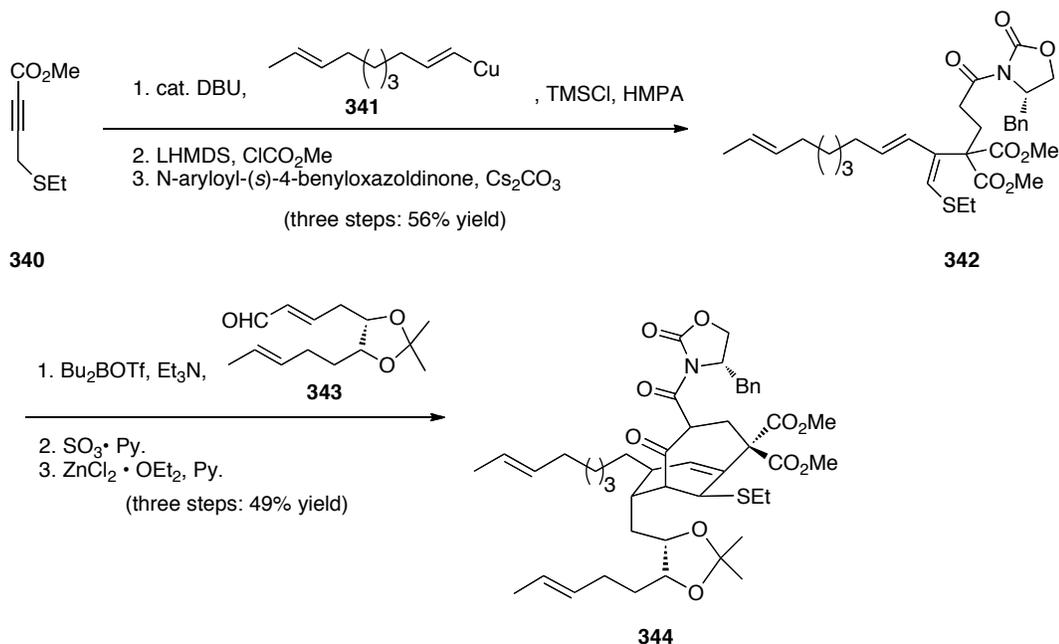


Proceeding forward with Diels- Alder product **344**, the chiral oxazolidinone functionality is displaced by allyl thioglycolate, followed by intramolecular adol addition, decarboxylation catalyzed by $Pd(OAc)_2$ and elimination of the tertiary alcohol to give thio lactone **345** (**Scheme 3.2.3.2.2**). Maleic anhydride formation was achieved by the formation of the TBS silyl enolether and treatment with NIS in the presence of $AgNO_3$. Selective hydrolysis of the less hindered methyl ester, produced carboxylate **346**.

*Scheme 3.2.3.2.2 Fukuyama's Maleic Anhydride Synthesis*
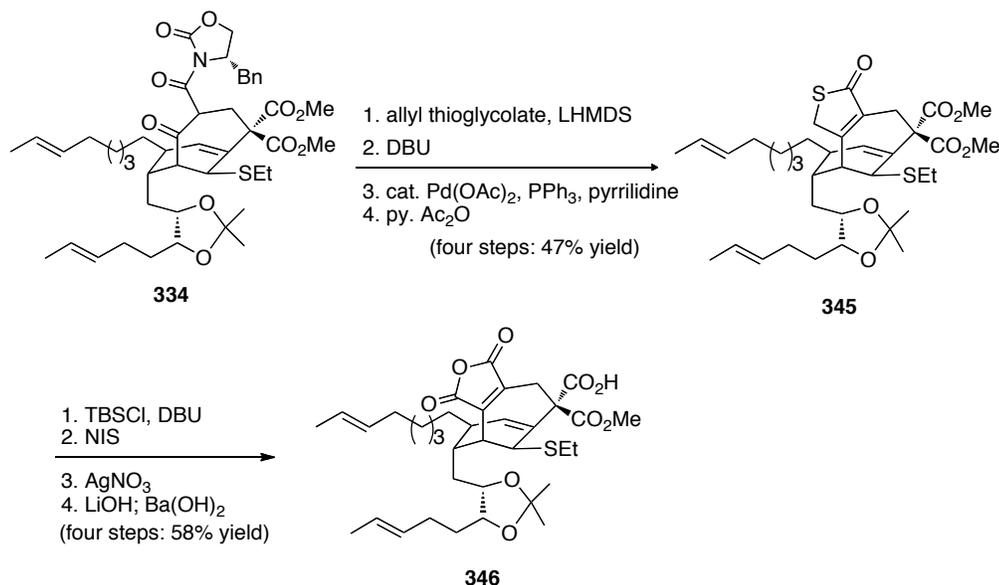


As in the Nicoloau's synthesis, an Arndt- Eistert homologation protocol was utilized to install the neopentyl carboxylic acid (**Scheme 3.2.3.2.3**). To this end, carboxylic acid **346** was converted to the corresponding diazoketone by treatment with $(COCl)_2$ and $CH_2N_2$. In the presence of the silver (I) salt $PhCO_2Ag$, the diazoketone was converted to the ketene, which formed the *tert*-Butyl ester in the presence of ${}^t$BuOH. Turning to the lactones, a Pummerer rearrangement converted the sulfide to its corresponding ketone which, upon treatment with acid, produced ketal **347**. Jones oxidation and deprotection of the *tert*-butyl ester gave the natural product phomoidride B (**301**).

*Scheme 3.2.3.2.3 Fukuyam's Phomoidride B Synthesis*



**346**

1. (COCl)$_2$, CH$_2$N$_2$
2. PhCO$_2$Ag, tBuOH

3. m-CPBA
4. TFAA, iPr$_2$NEt
5. aq. AcOH

(five steps: 28% yield)

**347**

1. Jones reagent
2. HCO$_2$H

(two steps: 96% yield)

**301**: **Phomoidride B (CP-263, 114)**
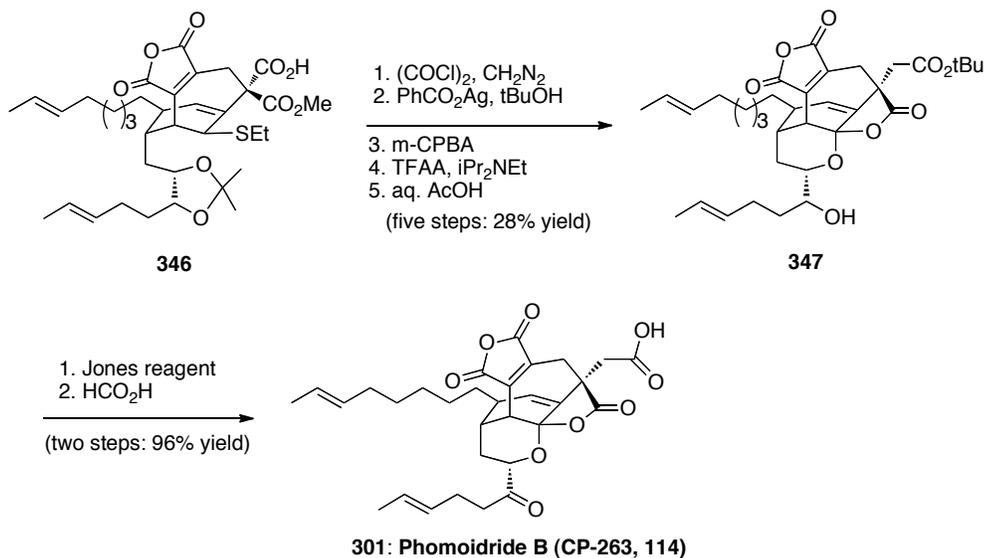
## 3.2.3.3 Shair's Route

In 2000, Shair published the third total synthesis of phomoidride B.[48-50] Shair's

synthesis started with a Stille coupling between vinyl iodide **350** and vinyl stannane **351**

which was followed by cuprate addition and alkylation with Mander's reagent to give

ketone **352** (**Scheme 3.2.3.3.1**). Enantiomerically pure ketone **352** was provided by an

efficient kinetic resolution using Corey's oxazaborolidine catalyst and catecholborane.

The resolved ketone, upon addition of Grignard reagent **353**, underwent oxy-Cope

rearrangement and subsequent transannular Dieckmann cyclization to furnish the [4.3.1]

core of phomoidride B (**354**).

*Scheme 3.2.3.3.1 Shair's Oxy-Cope Rearrangement/ Transannular Dieckmann Cascade*
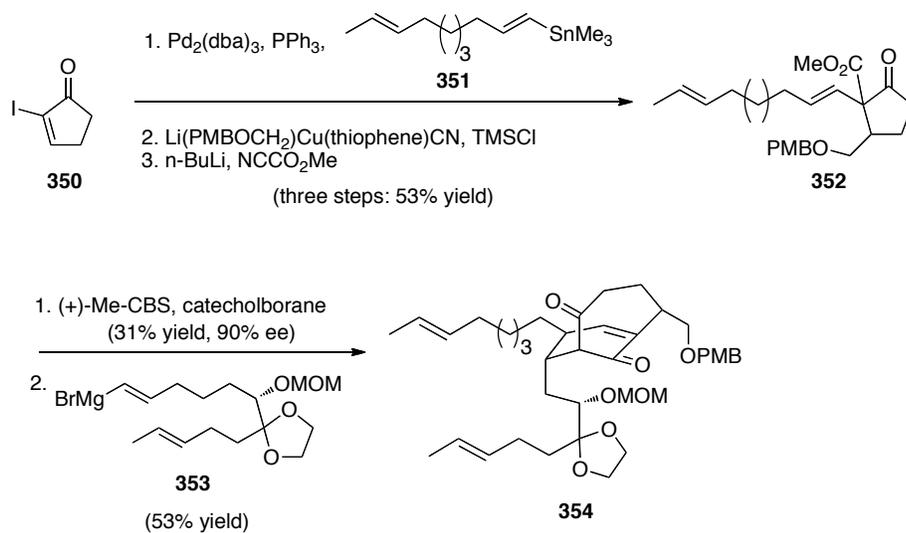


Treatment of ketone **354** with Mander's reagent, removal of the PMB group and oxidation yielded carboxylic acid **355**. The acid was converted to a MOM ester which, upon treatment with Mander's reagent yielded enol carbonate **356**. Exposure of **356** to TMSOTf and HC(OMe)$_3$ initiated a Fries-like rearrangement to furnish lactone **357**.

*Scheme 3.2.3.3.2 Shair's Fries Rearrangement*
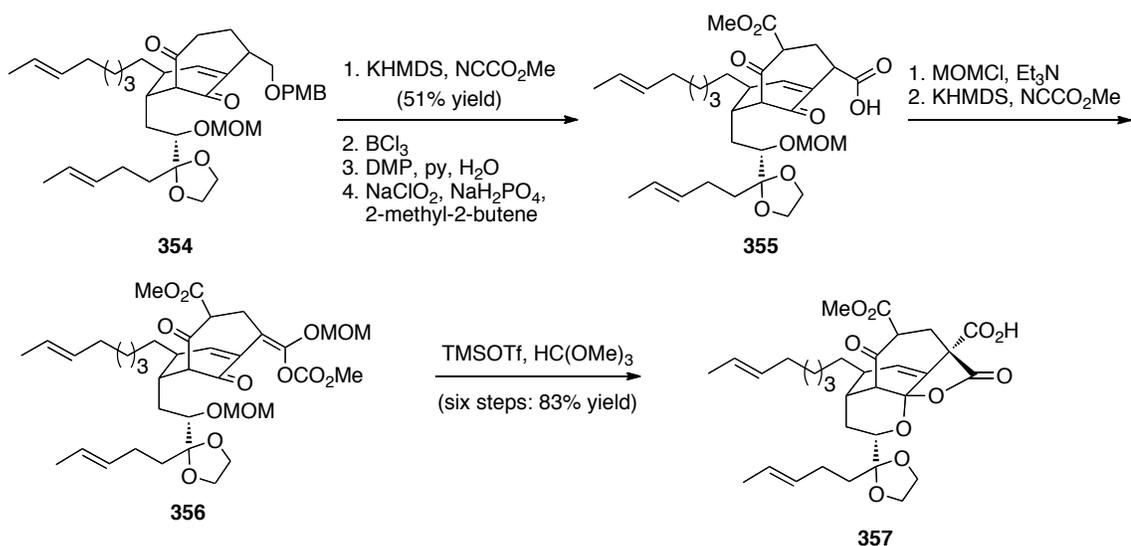


Similar to the previous two total syntheses, homologation of carboxylic acid **358** by mesylation, diazoketone formation and Wolf rearrangement gave *tert*-butyl ester **359**. Phomoidride B (**301**) was completed *via* enol triflate formation, palladium catalyzed CO insertion and deprotection of the *tert*-butyl ester.

*Scheme 3.2.3.3.3 Shair's Phomoidride B Synthesis*



**301**: **Phomoidride B (CP-263, 114)**
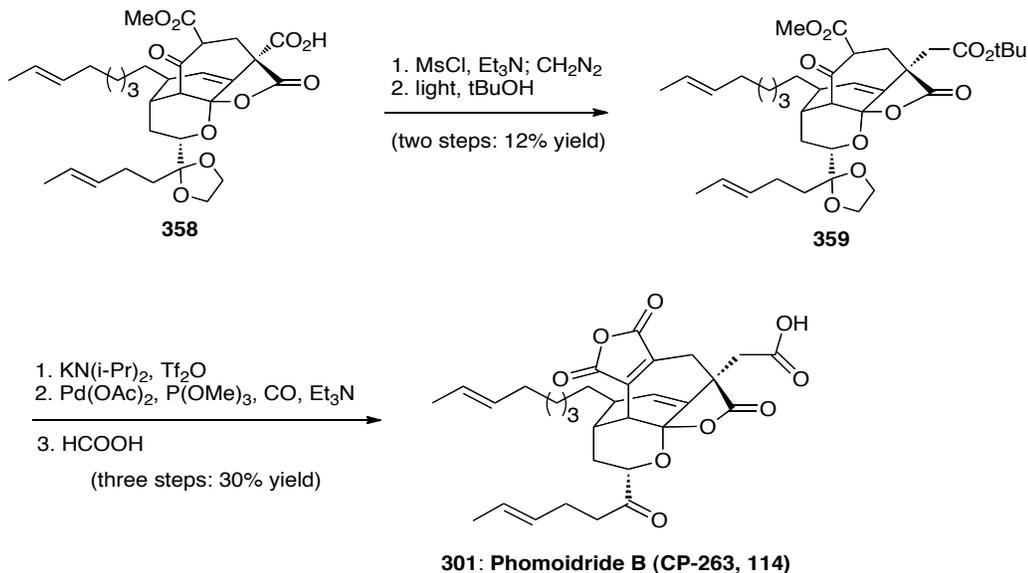
### 3.2.3.4 Danishesky's Route

The fourth total synthesis of the phomoidrides was reported by Danishefsky in 2000.[51-54] Danishefsky began by silylation of furan **360** at the 2-position followed by iodinating at the 4-position and mesylation of the alcohol (**Scheme 3.2.3.4.1**). The derived mesylate **361** was converted to the corresponding furanoaldehyde, which was in turn subjected to an aldol reaction with **362**. Protection of the newly formed alcohol as the TBS ether provided **364** which, upon Heck cyclization, ketone reduction and TBS protection provided key intermediate **364**. A two-step allylic oxidation/ iodination applied to the olefin gave vinyl iodide **365**. Palladium mediated coupling of **365** with trialkyl borane **366**, followed by selective removal of the TBS protecting group and Michael addition with allytrimethylsilane yielded olefin **367**.

## Scheme 3.2.3.4.1 Danishefsky's Heck Reaction to the Bicyclic Core
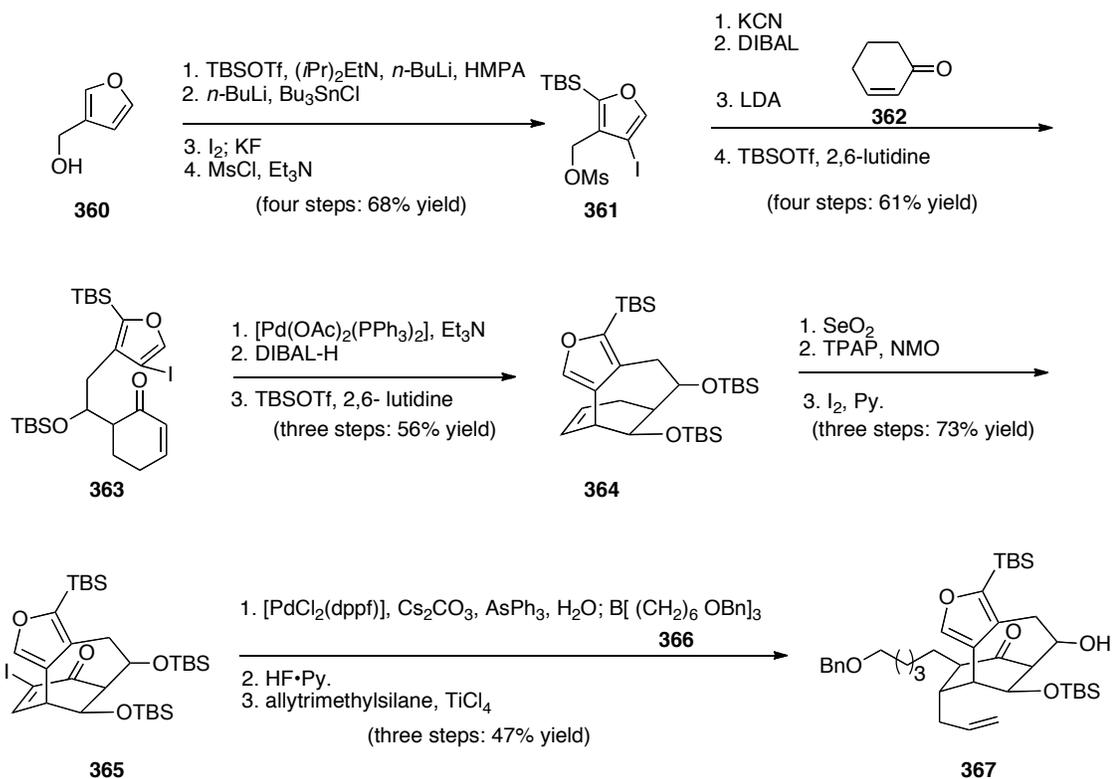


Reduction of ketone **367** with LAH, oxidation of the less hindered alcohol,

mesylation, and elimination with DBU gave bridgehead olefin **368** (**Scheme 3.2.3.4.2**).

Using Tebbe's reagent, the ketone was converted to the corresponding *exo*-methylene,

which upon [2+2] cycloaddition with 2,2- dichloroketene, reductive removal of the

chlorine atoms and removal of TBS protecting group produced alcohol **369**. The

unsymmetrical all-carbon quaternary center was constructed via a sequence that began

with treatment of cyclobutanone **369** with diphenyl disulfide.  This was followed by

oxidation of the allylic secondary alcohol to the corresponding ketone, Baeyer-Villiger

oxidation of the cyclobutanone with $H_2O_2$ and concomitant oxidation of the phenylsulfide

to its sulfoxide. The terminal olefin in the resultant intermediate was then oxidized with

OsO$_4$ and NMO to yield an intermediate diol the cyclized to the corresponding

hemiacetal **370**. The lactone **371** was formed *via* base-mediated rearrangement and

subsequent Swern oxidation.


*Scheme 3.2.3.4.2 Danishefsky Ketal synthesis*
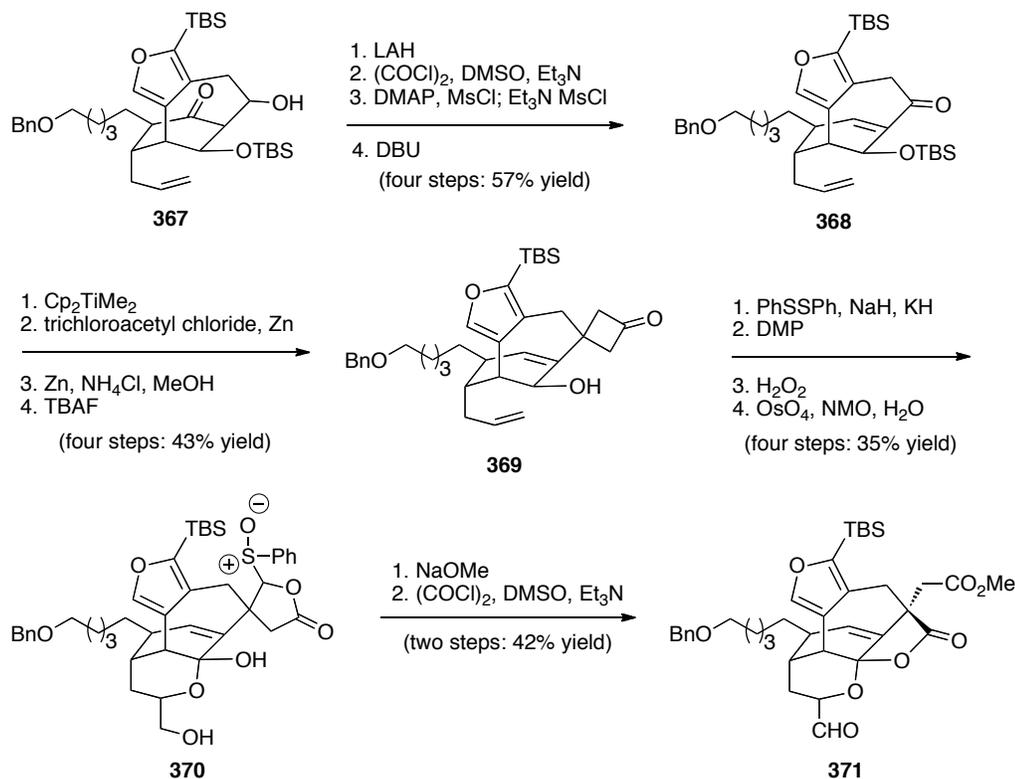


Danishefsky next turned toward installing the side chains.  To this end aldehyde

**371** was exposed to Grignard reagent **372** to furnish an alcohol which, upon oxidation,

oxidative removal of benzyl protecting group, oxidation of resultant primary alcohol and

finally olefin formation by treatment with 1,1- diiodomethane in the presence of CrCl$_2$,

gave olefin **373** (**Scheme 3.2.3.4.3**). Singlet oxygen oxidation of the furan ring, followed

by TPAP oxidation, hydrolysis of the methyl ester and subsequent reclosure of the acetal

with MeSO$_3$H furnished the natural product phomoidride D (**303**). As illustrated, in

another seven steps, phomoidride D (**303**) was converted to phomoidride A (**300**).

*Scheme 3.2.3.4.3 Danishefsky Phomoidride A and D synthesis*



**371**

1. [**372**] ⟶ MgBr

2. DMP
3. DDQ, H$_2$O
4. DMP
5. 1,1-diiodoethane, CrCl$_2$
   (five steps 20% yield)

**373**

1. light, O$_2$, Rose-Bengal, *i*Pr$_2$EtN
2. TPAP, NMO

3. LiOH
4. MeSO$_3$H
   (four steps: 40% yield)

**303**; **Phomoidride D**

1. TMSCHN$_2$
2. (TMSOCH$_2$)$_2$, TMSOTf

3. LiOH, TMSCHN$_2$
4. DMP, NaHCO$_3$
   (four steps: 51% yield)

**374**

1. LiAlH(O$^t$Bu)$_3$
2. LiOH

3. TFA, H$_2$O
   (three steps: 49% yield)

**300**; **Phomoidride A (CP-225, 917)**
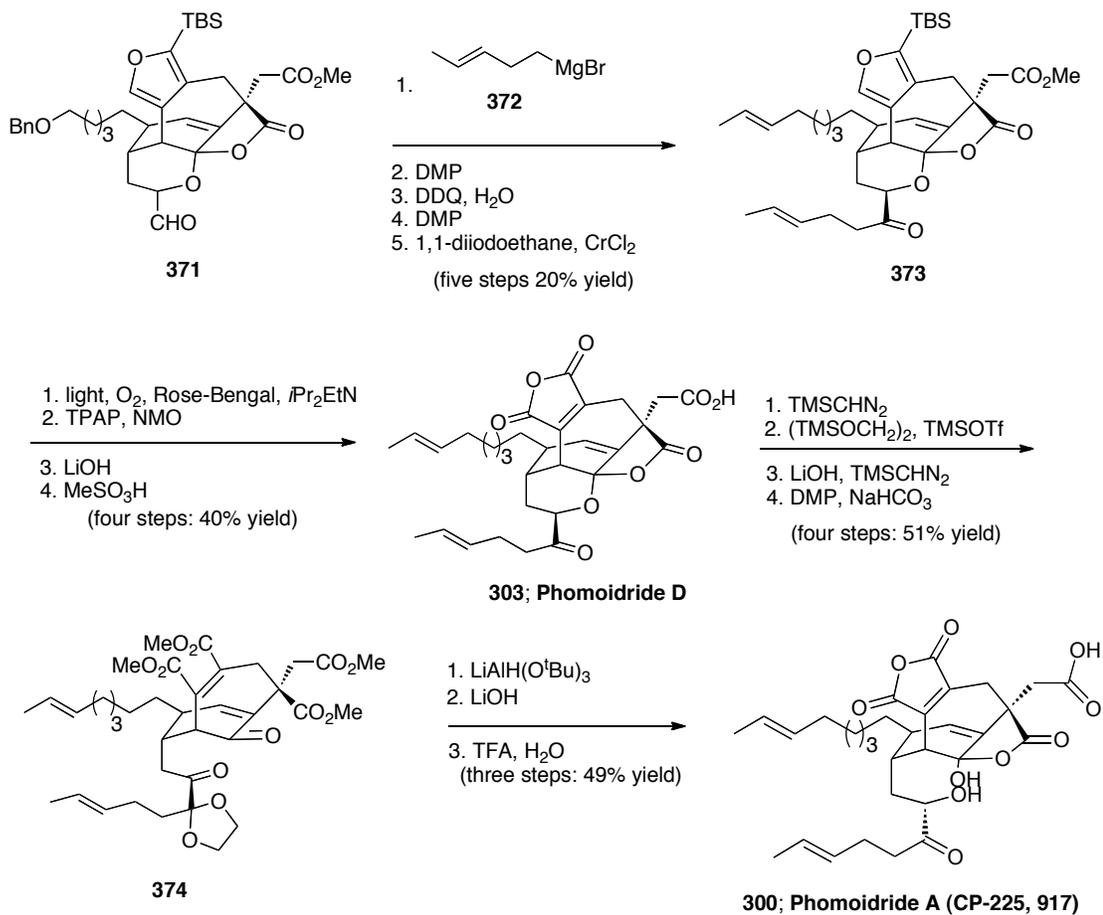
## 3.3 Conclusions

To date numerous synthetic efforts have been directed toward the phomoidrides and four total syntheses have been completed.  While in part, these investigations were motivated by an interesting biological profile, the fascinating structures innovative strategies and tactics they inspire are likely the true driving force being these synthetic efforts.  Further synthetic studies will likely provide more efficient access to these compounds, new structural analogs, and additional advances in both the strategies and tactics available to synthetic chemists.

## 3.4 Notes and References

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# Chapter 4

# Phomoidride Synthetic Studies from the Wood Group

## 4.1 Introduction

In the Wood Group, a total synthesis of the Phomoidrides has been ongoing for about ten years. Graduate students Jón Njardarson, David Spiegel, Ivar McDonald, and Barry Twenter, as well as several post-doctoral fellows and undergraduate students have worked on this project.[1-8] This chapter will first introduce their pioneering research and then discuss our current progress towards a total synthesis of the phomoidrides.

## 4.2 Previous Studies Towards the Total Synthesis of Phomoidrides

### 4.2.1 Synthetic Approach I: Diester Model

Illustrated in **Scheme 4.2.1** is a retrosynthetic analysis for phomoidride D (**303**) that was under investigation just prior to my joining the project. As indicated, phomoidride D (**303**) was expected to derive from diester **400**. Grob fragmentation[9] of intermediate **401** would give the [4.3.1] bicyclic core and install the bridgehead olefin. Opening the acetal in **402** and subsequent dithiane formation, followed by installation of a leaving group would yield the fragmentation precursor **401**. Intermediate **402** was expected to arise from radical cascade cyclization of bromide **403**. The latter would be produced from ketone **404** *via* aldol-type introduction of the carbons needed for

exomethylene lactone formation. Finally, the [2.2.2] bicyclic core found in **404** would be delivered through a tandem phenolic oxidation/Diels-Alder sequence applied to phenol **405** which, in turn, would be available from the coupling of phenol **406** and bromide **407**.

*Scheme 4.2.1 Retrosynthetic Analysis I of Total synthesis of Phomoidride D*
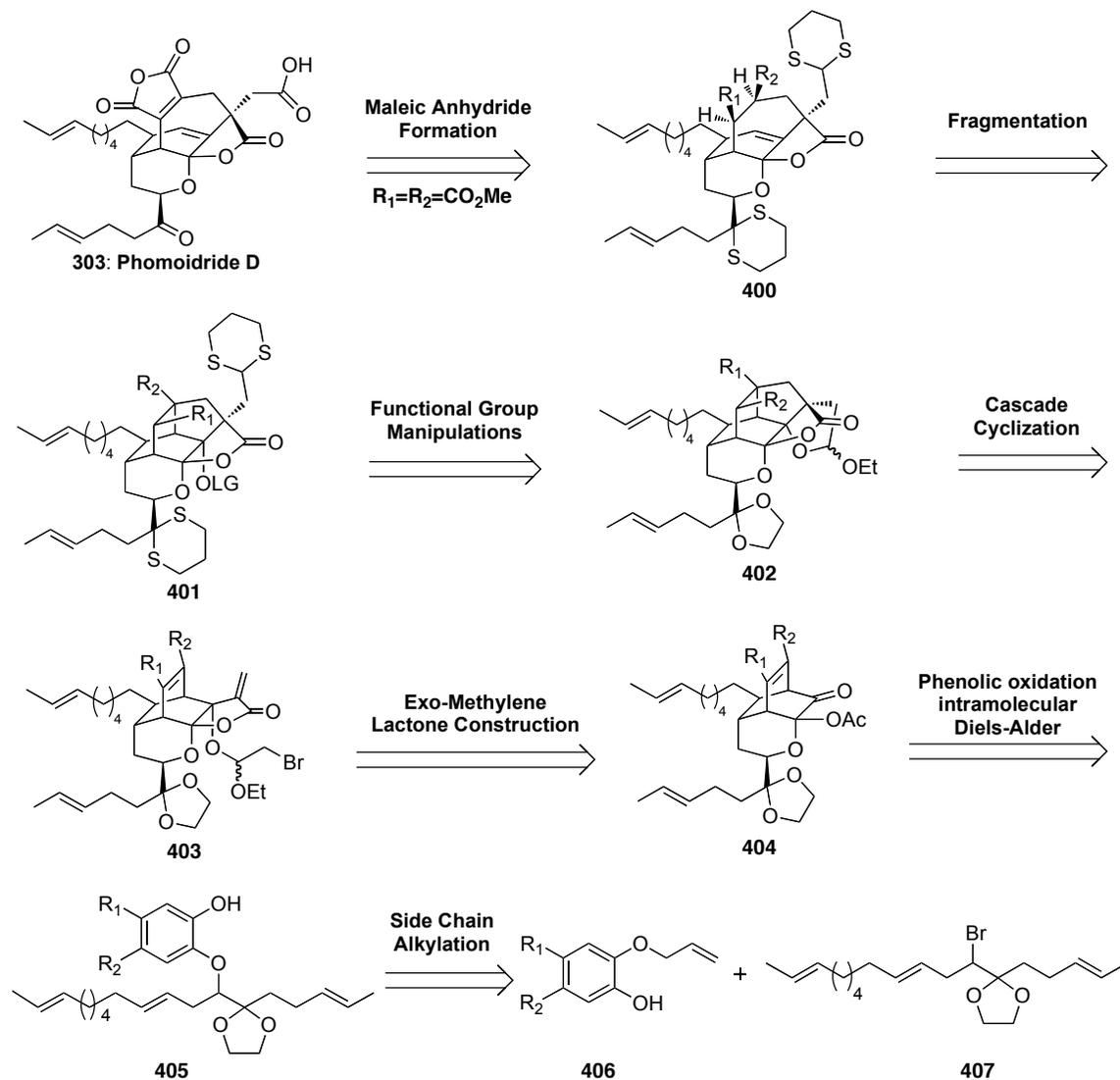
## 4.2.2 Development of Phenolic Oxidation/Diels-Alder Cascade Reaction

To investigate the planned synthetic route to the phomoidrides, a model system was employed wherein primary alcohol **408** replaced the more elaborate side-chain component **407**. Mitsunobu coupling of catechol **410** with **408** gave the corresponding mono alkylation product, phenol **411** (**Scheme 4.2.2.1**). Oxidation of **411** with Pb(OAc)$_4$ gave the intermediate diene **412** which underwent intramolecular [4+2] cycloaddtion to yield ketone **413**.[12-18] To maintain compatibility in subsequent transformations, the acetyl group was replaced by TMS to yield **414**.

*Scheme 4.2.2.1 Phenolic Oxidation and Diels- Alder Cycloaddition*
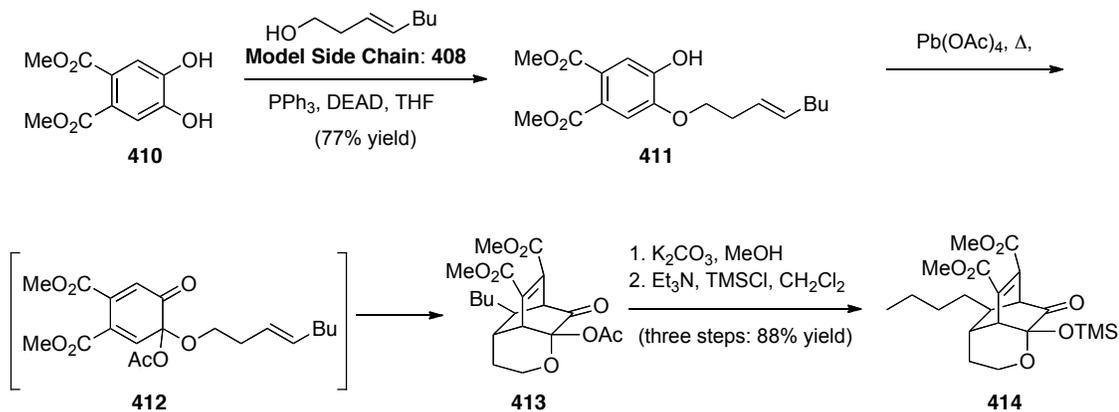


Aldol addition of enolate **415** [36-39] to ketone **414** gave tertiary alcohol **416** (**Scheme 4.2.2.2**). Introduction of the required exomethylene followed by *N*-oxidation (*m*-CPBA) and Cope elimination. The derived ester (**417**) was converted to lactone **418** following removal of the TMS protecting group and exposure to mild acid.

## Scheme 4.2.2.2 Exo-Methylene Lactone Construction
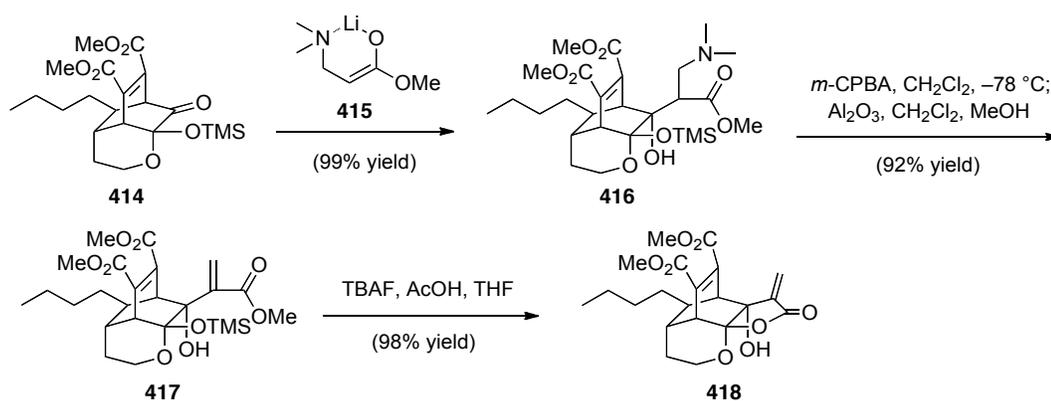


Alkylation of lactone **418** with Stork's bromoacetal (**419**) [20-23] gave radical cascade cyclization precursor **420** (**Scheme 4.2.2.3**). Treatment of **420** with SmI$_2$ yielded a cyclization product **423** resulting from a sequential 5-*endo-trig*, 5-*exo-tet* cyclization.[24-31] The cascade cyclization is highly efficient and is believed to occur via initial reduction of the maleate followed by addition to the exomethylene and substitution of the bromine.[3]

**Scheme 4.2.2.3 SmI₂ Cascade Cyclization**
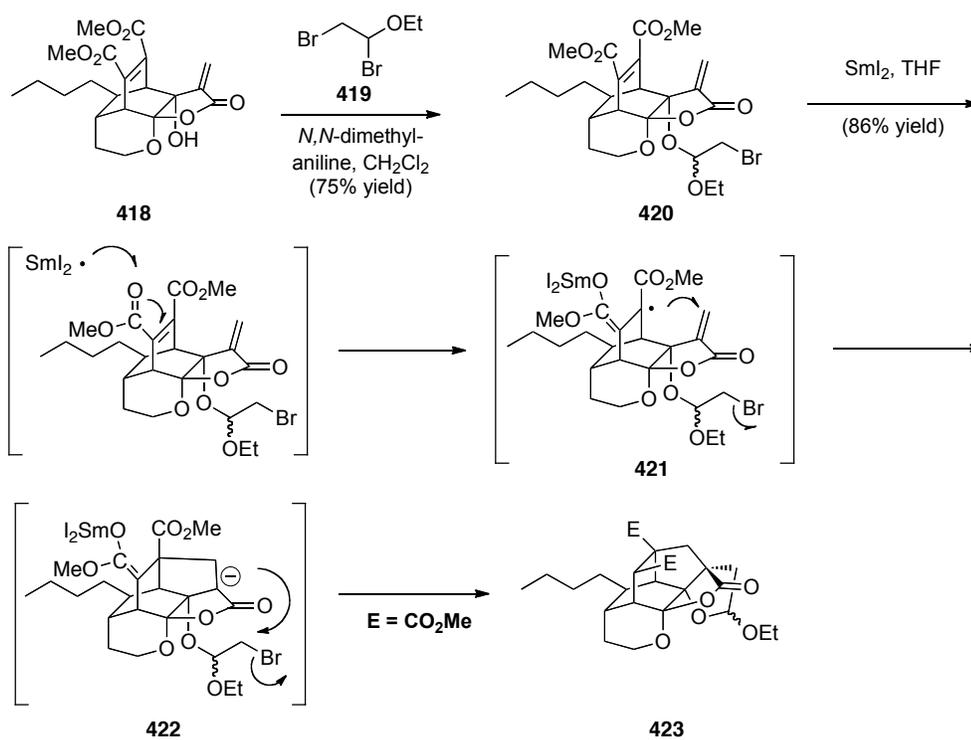


Opening of acetal **423** in the presence of BF₃•OEt₂ and propane-1,3-dithiol gave tertiary alcohol **424** (**Scheme 4.2.2.4**). Reduction of lactone **424** to the corresponding hemiacetal (**425**), followed by methylation gave acetal **426**. Treatment of **426** with KH, CS₂ and MeI furnished xanthate **427**.

## Scheme 4.2.2.4 Tertiary Xanthate Formation
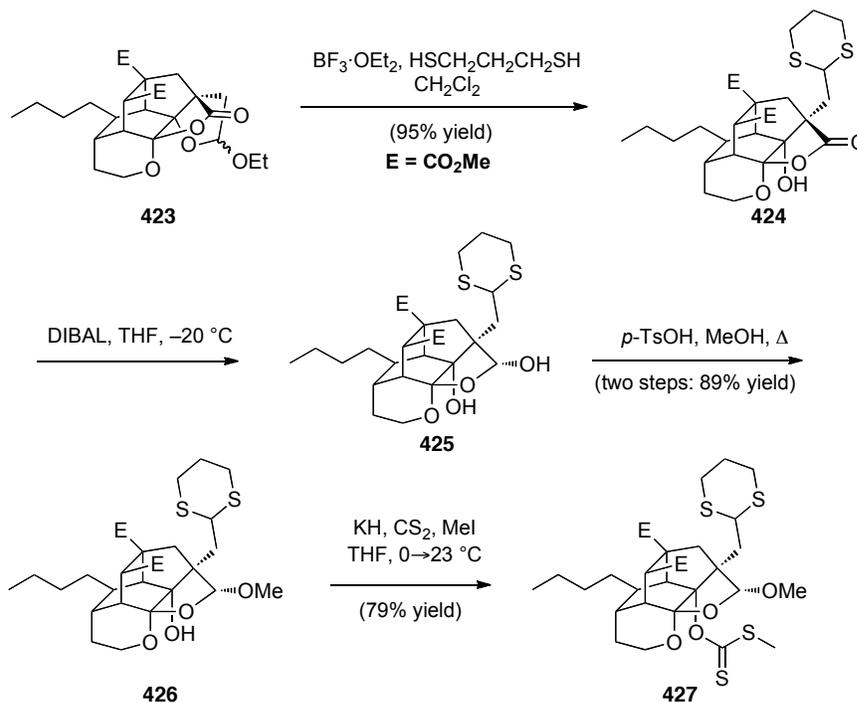


After considerable experimentation it was found that treatment of xanthate **427** with SmI$_2$ and HMPA produces the desired Grob fragmentation[9] product **428a**, as well as the byproduct **428b** resulting from reductive removal of the xanthate (**Scheme 4.2.2.5**).[32-33] Although the derived fragmentation product is the result of a two electron reduction, the exact nature of the intermediate undergoing fragmentation (radical or anionic) is not known.

## Scheme 4.2.2.5 Grob Fragmentation
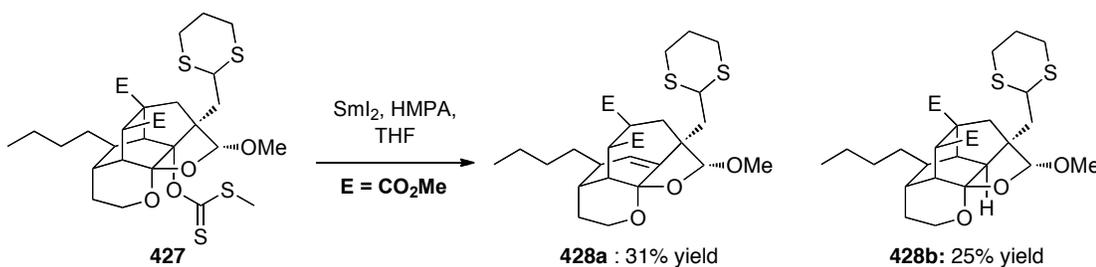
Numerous attempts were made to convert diester **428a** to olefin **429** (**Scheme 4.2.2.6**). Unfortunately, all efforts to effect this transformation were unsuccessful.

*Scheme 4.2.2.6 Maleic Anhydride Synthesis Approach*
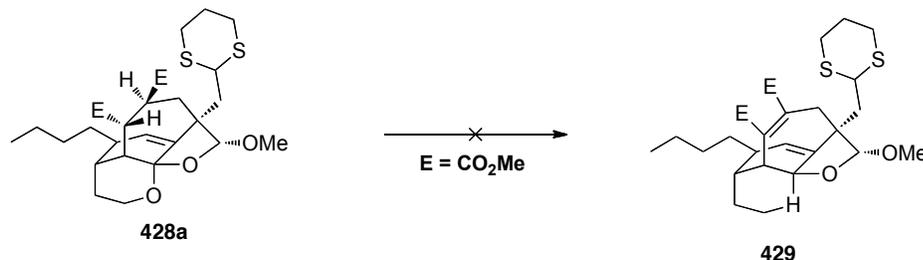


## 4.2.3 Synthetic Approach II: Ester and Benzyl Ether Model

Since attempts to install the maleic anhydride moiety were unsuccessful from substrate **428a**, an alternative approach targeting β- keto ester **432** as substrate was explored. In this approach it was envisioned that the maleic anhydride moiety in **430** would arise via a Pd(0)-catalyzed CO-insertion applied to the corresponding enol triflate **431** (**Scheme 4.2.3.1**). The requisite ß- Keto ester **432** would derive from a Wharton fragmentation [10-11] of tertiary alcohol **433**. Using similar procedures as the previous diester approach, **433** would be prepared from phenol **434** wherein the aromatic core possesses a single methyl ester and a benzyl ether. Alkylation of phenol **435** with iodide **436** would yield oxidation precursor **434**.

*Scheme 4.2.3.1 Retrosynthetic Analysis II: Model with Ester and OBn Substitution*
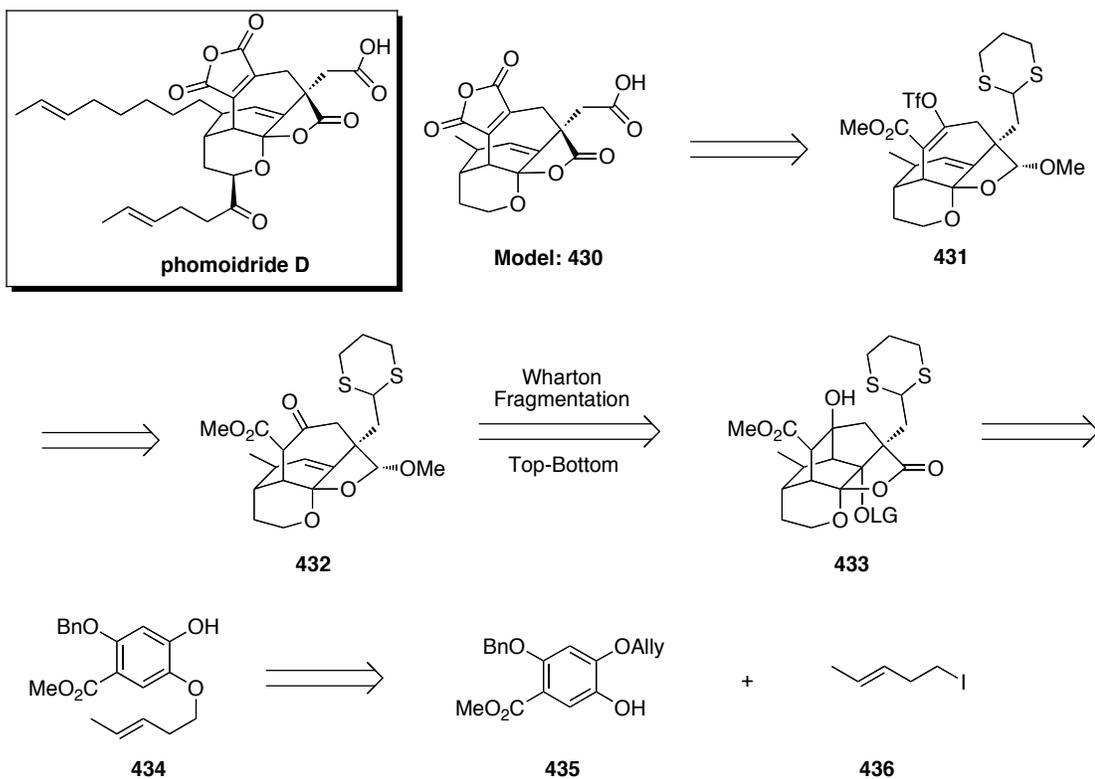


This approach commenced with 2,4-dihydroxy benzaldehyde (**440, Scheme 4.2.3.2**). Selective bis protection of the diphenol followed by Baeyer-Villiger oxidation and formate hydrolysis yielded phenol **441**. Regioselective bromination[34] and phenol alkylation with iodide **436**[35] gave aryl bromide **442**. Lithium-bromide exchange and trapping of the resulting aryl lithium species with methyl chloroformate was followed by removal of the allyl protecting group to provide **443**.[40] Phenolic oxidation and Diels-Alder cycloaddition was performed using Pb(OAc)$_4$ as the oxidant and produced bicycle **445** in excellent yield.

*Scheme 4.2.3.2 Phenolic Oxidation and Diels-Alder Cycloaddition*
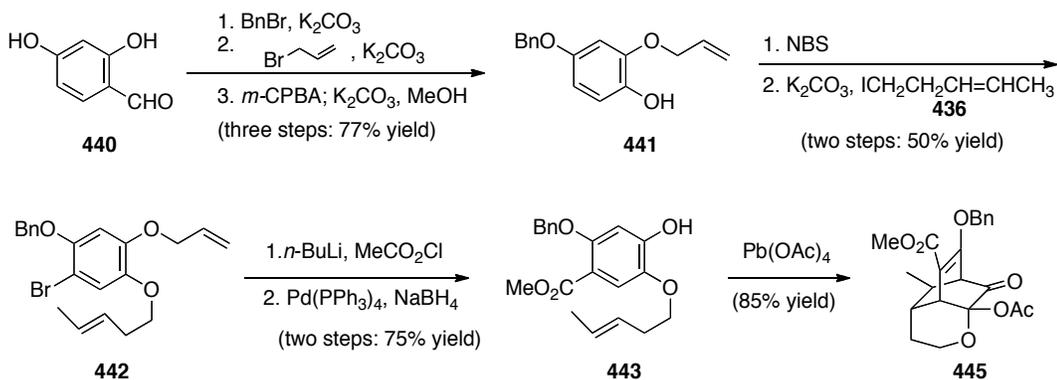


Using procedures similar to those employed in the diester approach, ketone **445** was converted to the corresponding lactone (**446**) wherein the Stork bromoacetal was poised for radical cascade cyclization. In contrast to the diester system, exposure of **446** to SmI$_2$ resulted in decomposition of the starting material (**Scheme 4.2.3.3**); however, treatment **446** with Bu$_3$SnH and AIBN furnished a 1:1 mixture of the desired 5-*exo-trig*, 5-*exo-trig* product **448** and an undesired 6-*endo-trig*, 4-*exo-trig* byproduct **447**.

*Scheme 4.2.3.3 Bu$_3$SnH Radical Cascade Cyclization*
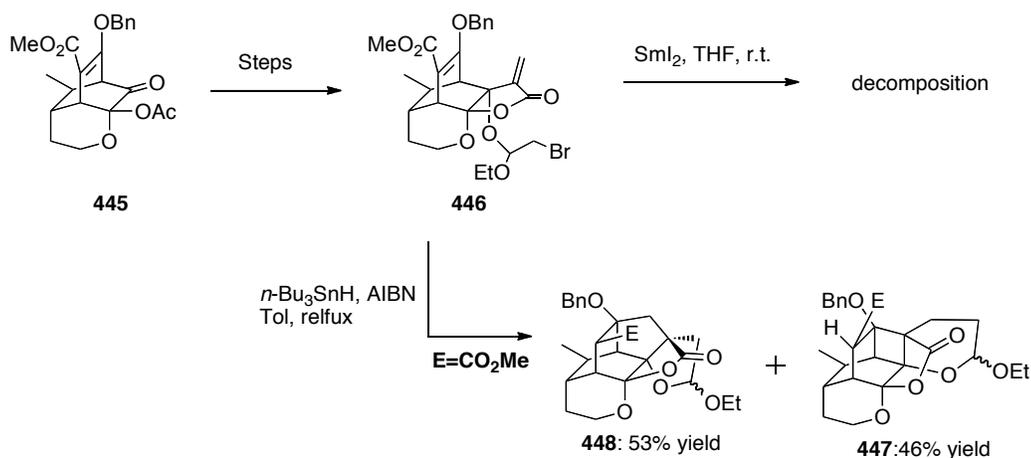
Following previously-established procedures, acetal **448** was converted to fragmentation precursor **449** (**Scheme 4.2.3.3**). However, efforts to fragment intermediate **449** led only to epimerization product **452**, the structure of which was confirmed by X-ray structure analysis.[4] The lack of fragmentation coupled with the observed epimerization product **452,** suggested the intermediacy of a retro-aldol process. Based on this unanticipated retro-aldol epimerization pathway, we reasoned that the ester group, although necessary for eventual installation of the maleic anhydride moiety, could not be present in the fragmentation substrate.

*Scheme 4.2.3.3 Approach to Wharton Fragmentation*
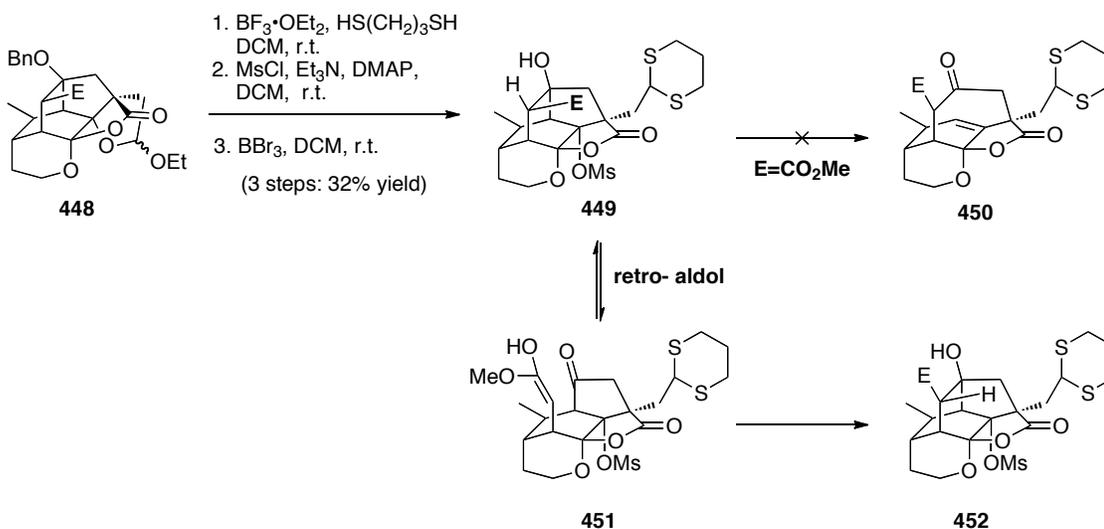


In an effort to remove the ester groups deleterious influence on the Wharton fragmentation, it was found that treatment of **452** with LAH selectively reduces the ester without affecting the lactone (**Scheme 4.2.3.4**). Importantly, the derived alcohol (**453**) undergoes smooth fragmentation to desired product **454** in good yield upon exposure KOH.

*Scheme 4.2.3.4 Wharton Fragmentation after Reduction of Methyl Ester*



**452** → (LAH, THF, r.t. (48-80% yield)) → **453** → (KOH, THF, r.t. (70% yield)) → **454**
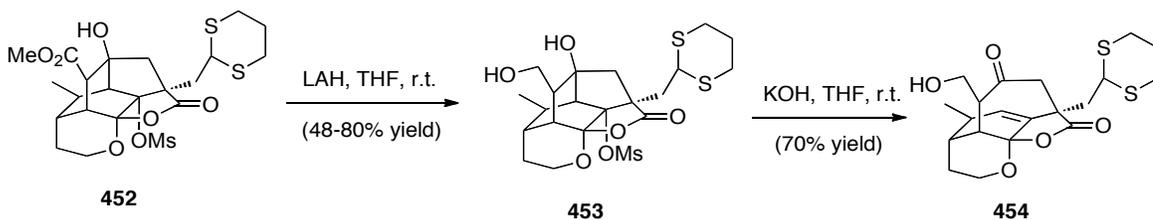
At this stage, completing the synthesis in the model system required oxidation of the primary alcohol **454** to the corresponding acid or aldehyde **455** (**Scheme 4.2.3.5**). Unfortunately, all conditions attempted resulted in recovery or decomposition of starting materials. The difficulty in manipulating **454** was further illustrated by several failed attempts to simply install a protecting group.

*Scheme 4.2.3.5 Attempted Further Modification of the Fragmentation Product*



**454** → (Oxidation ✗) → **455, R=CO₂H, CHO**

**454** → (Protection ✗) → **456**
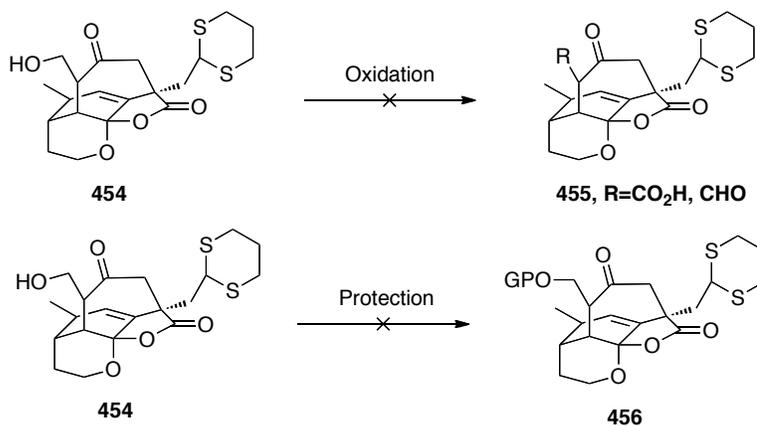
# 4.3 Current Approach Towards the Total Synthesis of the Phomoidrides

## 4.3.1 Proposed Solution for Removal Carboxylate

Given that our prior studies had established the need to remove the ester in **449** prior to fragmentation (see **Scheme 4.2.3.3**) and that removing the ester by reduction was a dead-end, a more dramatic modification of the synthetic plan was needed. Thus began my involvement with the project and as a first solution the complete removal of the ester group was proposed.

As illustrated in **Scheme 4.3.1**, it was envisioned that the proposed decarboxylated intermediate **462** could be accessed in two ways. One approach involved the decarboxylation of an intermediate similar to that already prepared in previous studies (i.e., **460** to **462**). Alternatively, we had the option of leaving out the $CO_2$ unit from the outset and bringing the synthesis through a more simplified intermediate **461**.

*Scheme 4.3.1 Proposed Solution to Remove of Carboxylate*
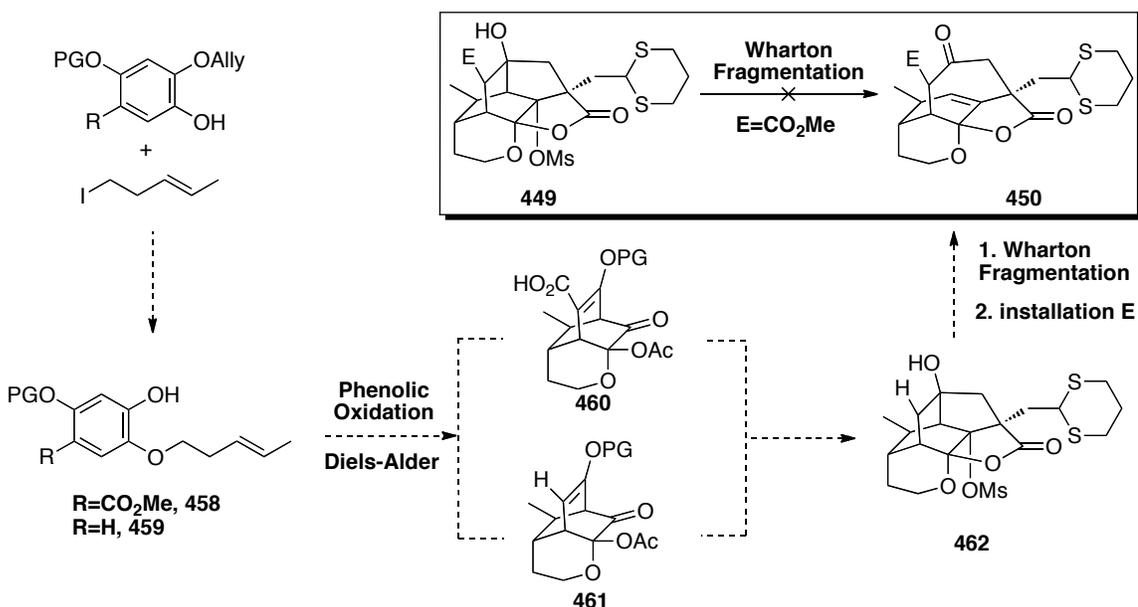
## 4.3.2 Decarboxylation Attempts

To determine whether the decarboxylation approach would be viable, we attempted to prepare substrate **464** (**Scheme 4.3.2**); however, hydrolysis of ester **463** to carboxylic acid **464** led only to decomposition of the starting material. As an alternative, we attempted to prepare acid **464** via an oxidation of the corresponding aldehyde (**465**). To this end, preparation of the **465** began with previously prepared aryl bromide **442**. Removal of the allyl protecting group, followed by exposure to *n*-BuLi and trapping of the derived dianion with DMF furnished benzaldehyde **466**. Oxidation of **466** and intramolecular Diels-Alder cycloaddition, yielded aldehyde **465**. Unfortunately, attempts to oxidize aldehyde **465** to carboxylic acid **464** under Pinnick conditions failed and only starting material was recovered.[41]

*Scheme 4.3.2 Proposed Solution to Remove Carboxylate*
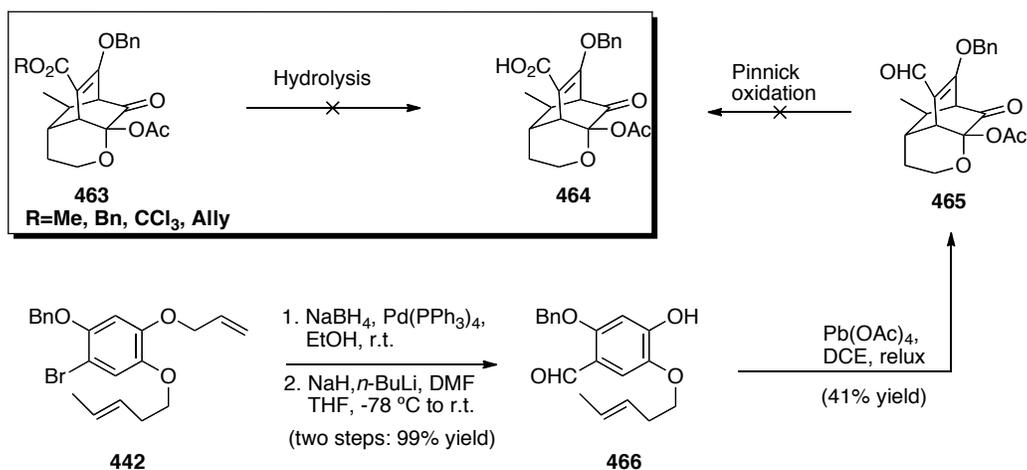
## 4.3.3 Initial Studies with Simplified Substrates

Given the difficulty of converting aldehyde **465** to carboxylic acid **464**, we began

to consider [2.2.2] bicyclic core structures that were devoid of a caboxylate moiety, such

as substrate **468**. In fact, efforts to prepare this intermediate are illustrative of the inherent

difficulties associated with this design change.  As can be seen in **Scheme 4.3.3**, phenol

**467** is readily available from deallylation of **442**; however, when **467** is exposed to

conditions expected to result in the tandem phenolic oxidation/Diels-Alder reaction, the

only observed product is **469**.  Thus, the electronic demands of  the intramolecular Diels-

Alder reaction are not met by this substrate.

*Scheme 4.3.3 Phenolic Oxidation and Diels- Alder reaction of bromide phenol 467*
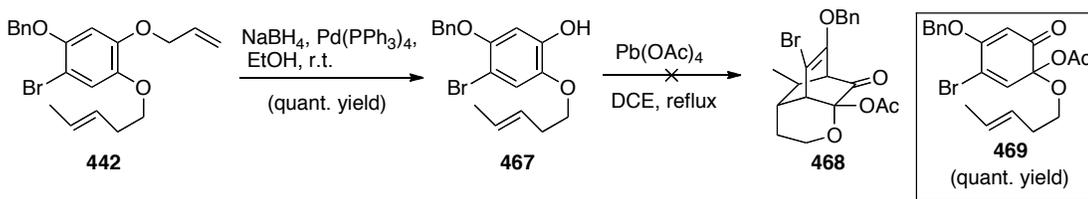


## 4.3.4 Tuning of the Diels-Alder Substrate

When one considers the successful phenolic oxidation/ Diels-Alder reactions of

di- and mono-ester substrates **411** and **443** in conjunction with the unsuccessful phenolic

oxidation/Diels-Alder of **467** (**Scheme 4.3.4.1**, inset), it becomes clear that an electron

withdrawing group must be present on the diene to enable the inverse electron demand

Diels-Alder process. Therefore, we began to develop an alternative route wherein an

electron withdrawing group replaces the benzyl ether at the 3- position (e.g., **470**,

**Scheme 4.3.4.1**).  In contrast to **443**, the C-4 functionalized monoester substrate, the

newly envisioned intermediate manifests an aldehyde as the electron withdrawing group.

The change in oxidation level was made in anticipation of employing a Baeyer-Villiger

oxidation to cleave the aldehyde and deliver the hydroxyl group required for Wharton

fragmentation (see **473** to **462** in **Scheme 4.3.4.1**).  In addition to incorporation of the

aldehyde, substrate **470** is unfunctionalized at C-4; this change was made to circumvent

complications akin to those encountered when trying to manipulate the C-4

hydroxymethyl group in **454** (*vide supra*, **Scheme 4.2.3.5**).  Overall, exposure of **470** to

the tandem penolic oxidation/ Diels-Alder was expected to deliver the [4+2] product **472**

*via* the intermediacy of acetate **471**.  Paralleling our previous routes, **472** would be

advanced to **473** via radical cascade chemistry applied to an exomethylene lactone.

Baeyer-Villiger oxidation, thioacetal formation and introduction of a mesylate group

would deliver **462** and set the stage for the Wharton fragmentation.

*Scheme 4.3.4.1 Synthetic Plan Using EWG for Diels- Alder Reaction*



**467, no D/A reaction**      **411, successful D/A reaction**      **443, successful D/A reaction**

**470**      **471**      **472**

**473**      **462**      **568**
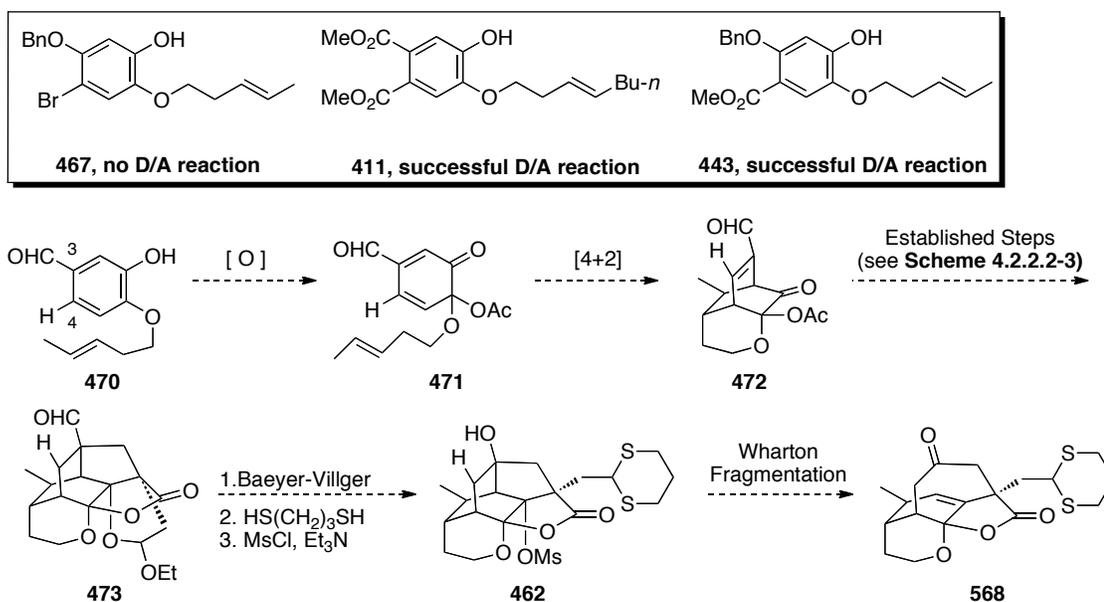
To investigate this plan, we set out to prepare phenol **470**. In an initial approach 3,4-dihydroxy benzaldehyde (**437**) was used as the starting material and selectively converted to the corresponding monoacetate (**474**) upon exposure to AcCl in the presence of NaOH (**Scheme 4.3.4.2**).[42] Unfortunately, efforts to alkylate the derived phenol (**474**) with iodide **436** only yielded an undesired bis alkylation product **475**. Eventually we discovered that, in contrast to acylation, alkylation of 3,4-dihydroxy benzaldehyde proceeds selectively at the C-4 phenolic oxygen; thus, simply treating with $K_2CO_3$ and iodide **436**, furnishes desired phenol **470** in reasonable yield.

*Scheme 4.3.4.2 Preparation of Phenol 470*
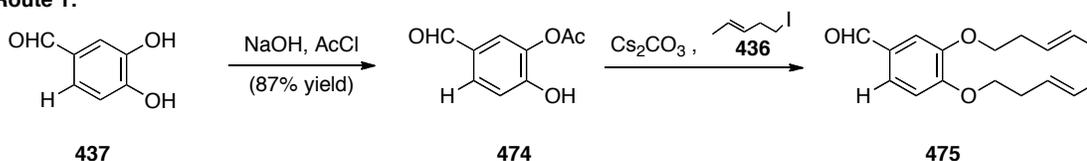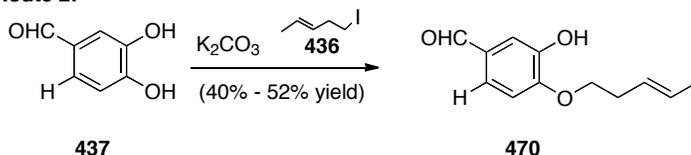


Proceeding with phenol **470**, we observed that the tandem phenolic oxidation/Diels-Alder reaction behaves differently at varied temperatures (**Table 4.3.4**). The highest yield for the desired [4+2] product **480** was observed in reactions performed at 90 ºC; however, efforts to improve the yield by running the reaction at warmer temperatures resulted in increasing amounts of rearomatized byproduct **481**; at 140 °C **481** was the only observed product.

*Table 4.3.4 Phenolic Oxidation and Diels- Alder Cycloaddition of Phenol 470*
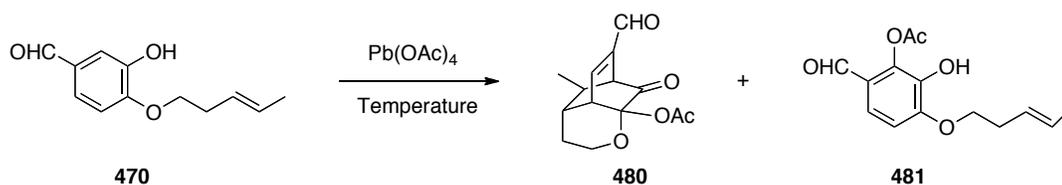


| Temperature | Yield(%) |
|---|---|
| 60 °C | **480**: 52% |
| 90 °C | **480**: 54% |
| 140 °C | **481**: 47% |

## 4.3.5 Chemoselectivity Issues in Advancing 480

   Although introduction of the aldehyde in **470** had served to meet the electronic demands of the Diels-Alder reaction, advancing the cycloadduct **480** required differentiation of the aldehyde and newly formed ketone moieties.  This differentiation was important given that aldol addition to the ketone with methyl 3-(dimethylamino) propanoate enolate was the next step.[36-39] Given the potential difficulties associated with eventual removal of many carbonyl protecting groups, we chose to first explore differentiation of the aldehyde and ketone by nucleophilic addition.  As illustrated in **Scheme 4.3.5.1**, this effort began by removal of the acetate and exposure of the derived hemiacetal (**482**) to either TMSCl followed by MeLi or NaH/MeLi. Given somewhat improved efficiency, the latter sequence was employed for material advancement and the derived diol **485** was protected as the corresponding bis silyl ether **486**.  Unfortunately, **486** failed to undergo subsequent aldol addition to produce **487**.

## Scheme 4.3.5.1 Intermolecular Addition for Differentiation of Enol 480
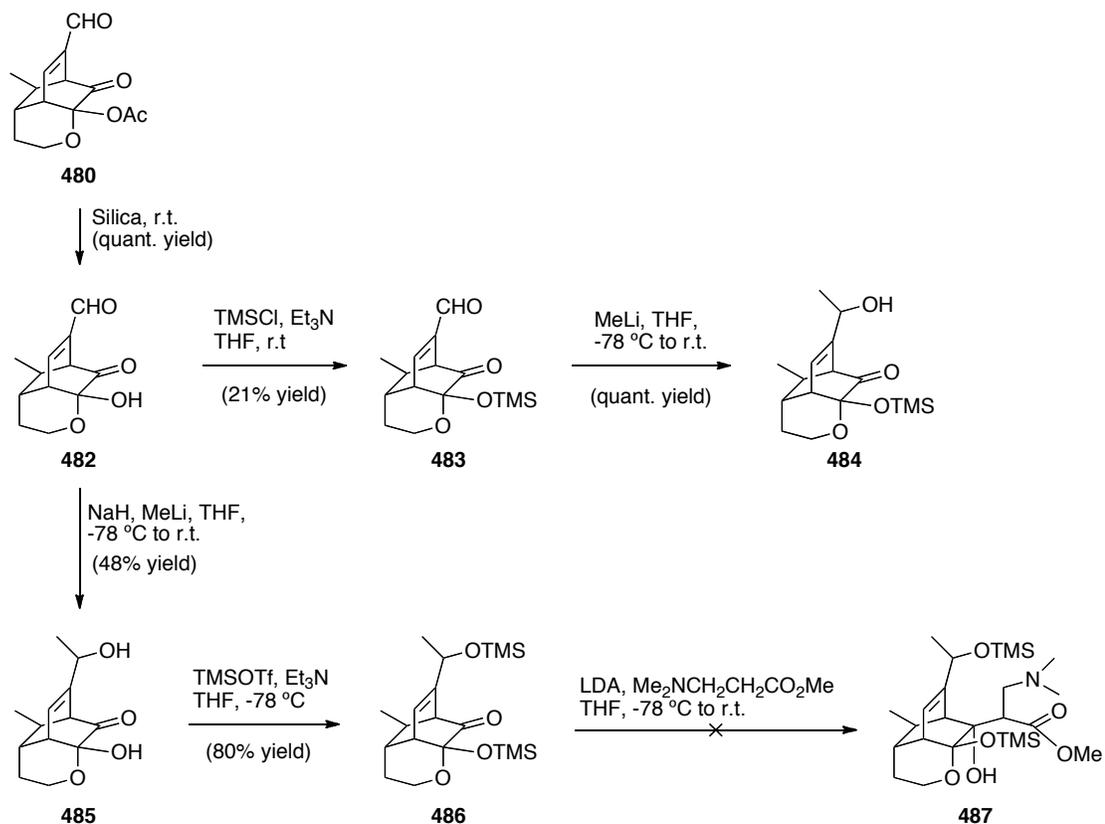


After the unsuccessful intermolecular aldol reaction to ketone **486**, we decided to attempt an intramolecular variant and explored the conversion of hemiacetyl **482,** to ester **488** by exposure to 2-bromoacryloyl chloride; unfortunately this acylation reaction failed (**Scheme 4.3.5.2**).

## Scheme 4.3.5.2 Attempted Intramolecular Addition of a Vinyl Bromide
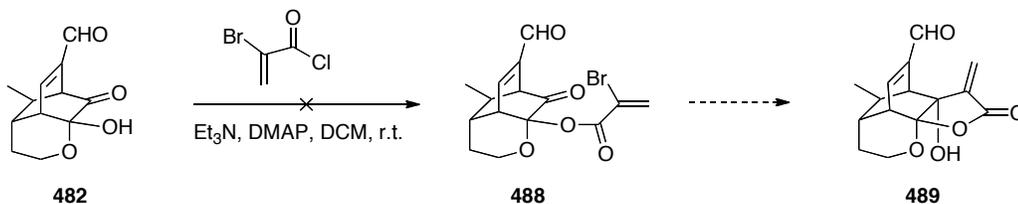
In a second attempt at intramolecular addition we explored the use of different

lead salts such as Pb(O₂CCH₂CH₃)₄ **494** [43-45] as oxidants in the tandem phenolic

oxidation/Diels-Alder reaction. Although this approach allowed quick access to the

desired ester (**490**), subsequent intramolecular aldol reaction to the lactone (**491**) failed

under a variety of different conditions (**Scheme 4.3.5.3**).

*Scheme 4.3.5.3 Intramolecular Addition for Differentiation of Enol 480 by Lead Salt*
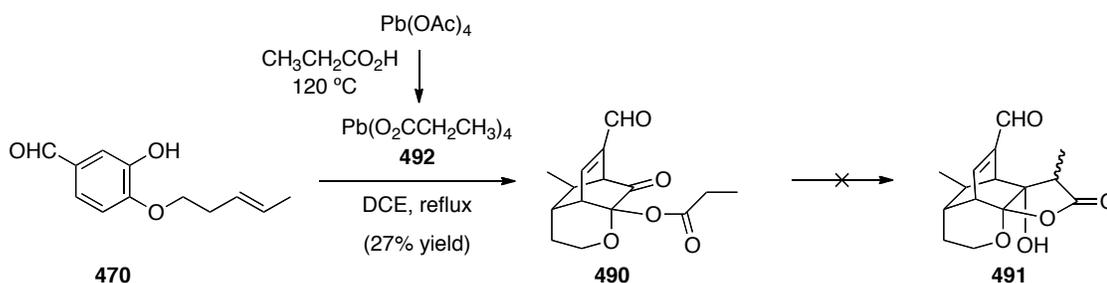


In a final attempt at intramolecular lactone formation we  exposed hemiacetal **482**

to ylide **497** and were delighted to find that butenolide **492** was produced in modest yield

(**Scheme 4.3.5.4**)..[47] Mechanistically this transformation is believed to begin with alcohol

addition to ketene **497** to furnish **493** which, in turn, undergoes  intramolecular Wittig

olefination *via* intermediate **494**.[46] Lactone **492** was produced after elimination of

triphenylphosphine oxide. Encouraged by this success we set out to explore preparation

of a more functionalized lactone system *via* treatment of **482** with cumulene **495**.  It was

hoped that the *in situ* generated cumulene would acylate hemiacteyl **482** and that the

derived intermediate would undergo intramolecular addition to directly furnish the

desired exomethylene lactone **489**. Unfortunately, these efforts resulted only in

decomposition of the starting material.

## Scheme 4.3.5.4 Attempt involving a Ketene and Cumulene

**Ph₃P=C=C=O Route:**
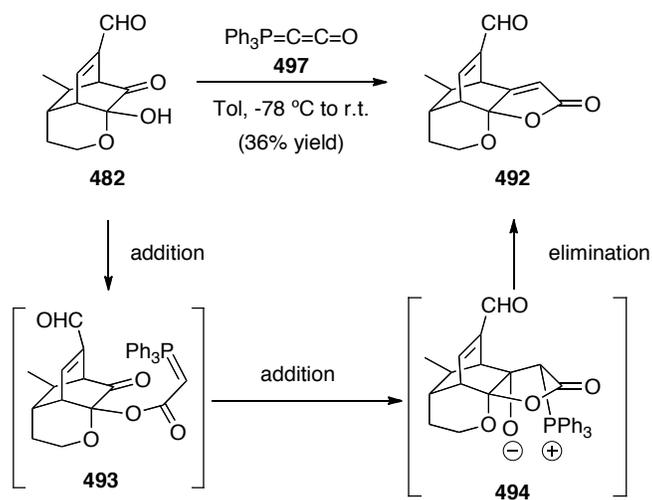


**Proposed C=C=C=O Route:**
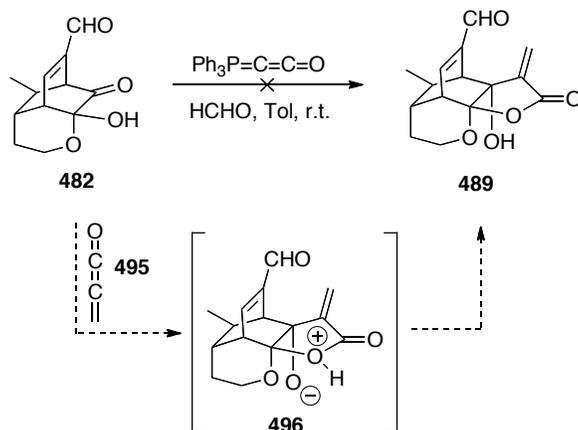


Experiencing only limited success with nucleophilic addition and intramolecular additions we next attempted to differentiate the aldehyde and ketone moieties in **480** via oxidation (**Scheme 4.3.5**). Attempt to transform the aldehyde to ketone **500** via a Baeyer-Villiger reaction using *m*-CPBA, H₂O₂, or CF₃CO₃H resulted in either recovery or decomposition of starting material.[48,49] Attempts to convert aldehyde **480** to its

corresponding carboxylic acid using the Pinnick oxidation resulted only in recovery of starting material.

*Scheme 4.3.5.5 Attempted Differentiation of Enol 480 via Oxidation*
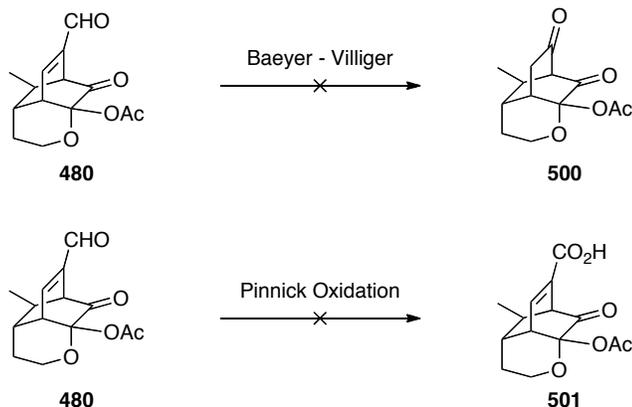


In a last approach to differentiate the carbonyl groups, an effort was made to effect conjugate reduction. To this end, it was hoped that conversion of **482** to the corresponding aldehyde **502** would provide a substrate suitable for subsequent Baeyer-Villiger oxidation and thus a variety of conditions for conjugate reduction were explored that included: L-selectride;[50] ([(PPh$_3$)CuH]$_6$;[51] (Ph$_3$P)RhCl, Et$_3$SiH;[52] NaBH$_6$, NiCl$_2$;[53] Mg or Zn/ MeOH;[54] Et$_3$SiH, CuCl; Al(O(2,5-Ph) Ph)$_3$, DIBAL, nBuLi;[55] Morpholine, Hantz reagent;[56] 9-BBN; pyridine, and; Pd/C, H$_2$ (**Table 4.3.5**). As illustrated in **Table 4.3.5** reduction using Pd/C and H$_2$ was the only successful result. Although, this condition provided a high yield of the desired product, potential lack of compatibility with the olefins present in the side chains in the real system led us to abandon this approach.

*Table 4.3.5 Reduction for Differentiation of Enol 482*
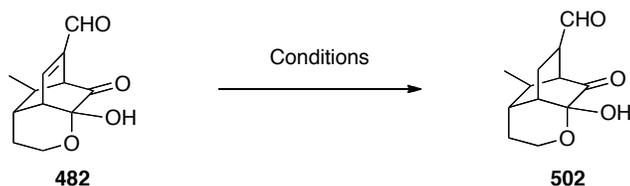


| Conditions | Results |
|---|---|
| L-selectride | decomposition |
| ([(PPh$_3$)CuH]$_6$ | S.M. recovered |
| (Ph$_3$P)RhCl, Et$_3$SiH | S.M. recovered |
| NaBH$_6$, NiCl$_2$ | S.M. recovered |
| Mg or Zn/ MeOH | decomposition |
| Et$_3$SiH, CuCl | S.M. recovered |
| Al(O(2,5-Ph) Ph)$_3$,DIBAL, *n*-BuLi | dicomposition |
| Morpholine, Hantz reagent | S.M. recovered |
| 9-BBN, Py | S.M. recovered |
| Pd/C, H$_2$ | **502**: 89% |

## 4.3.6 Diels- Alder Reaction of a Triflate-Containing Substrate

Efforts thus far have demonstrated the necessity of an electron withdrawing group (EWG) on the phenol for success in the phenolic oxidation/inverse electron demand Diels-Alder reaction. In addition, deleterious retro-aldol chemistry in attempted fragmentation reactions led us toward temporarily placing the EWG at C-3 of the aryl substrate. Although this latter maneuver worked with regard to the electronic demands of the Diels-Alder reaction, transforming the EWG (i.e., aldehyde) to a ketone-containing substrate (e.g., **513**) suite for a subsequent radical cascade cyclization proved unworkable. Based on this growing body of results we decided to explore the affect of electron withdrawing substituents attach to the aryl oxygen. If these "OEWGs" proved

capable of meeting the electronic demands of the Diels-Alder reaction, we could avoid

many of the deleterious issues encountered in our previous studies. As illustrated

retrosynthetically in **Scheme 4.3.6.1**, model system **430** was envisioned to derive from β

keto ester **510** *via* Pd(0) catalyzed CO insertion. Wharton fragmentation would deliver

**510** from **512** which, in turn, would be produced by application of a radical cascade

reaction to bromo acetyl **513**. Following the previous established procedures, bromo

acetal **513** would be derived from Diels-Alder product **514** which we hoped could be

produced from phenol **515** wherein an OEWG substituent would meet the electronic

demands of the tandem phenolic oxidation/Diels-Alder sequence.


*Scheme 4.3.6.1 Retrosynthetic Analysis III: Model with OEWG Substitution*
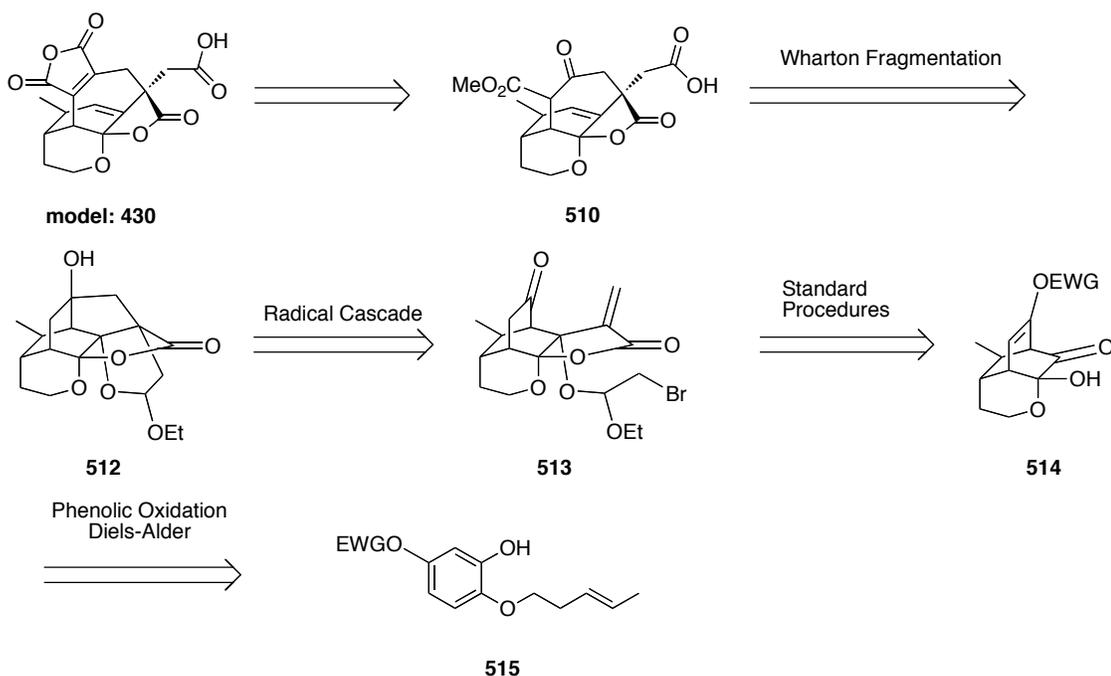



In accord with the above synthetic plan we began our studies by exploring the

effectiveness of OEWG substituents on the Diels-Alder reaction. To this end we first

explored the affect of incorporating a triflate group. As illustrated in **Scheme 4.3.6.2**, we

exposed the previously prepared phenol **470** to allylbromide to furnish benzaldehyde **516**.

Baeyer-Villiger oxidation of **516** in the presence of PhSeSePh and $H_2O_2$ produced a

mixture of the desired phenol **518** and byproduct epoxide **517**.[57] Isolation of **518** followed

by exposure to triflic anhydride furnished the corresponding triflate **519** which, upon

exposure to Pd(0) and $NaBH_4$ underwent smooth deallylation to afford **520**, the substrate

needed for the proposed tandem phenolic oxidation/Diels-Alder reaction. To our delight,

treatment of **520** with $Pb(OAc)_4$ produced desired [4+2] cycloaddition products **521** and

**522** in good yield. This result provided solid evidence that use of OEWG substitution on

the phenol ring was a suitable strategy in this inverse electronic demand Diels- Alder

reaction. Moreover, this substrate afforded better yields than previous model systems.

*Scheme 4.3.6.2 Preparation 1: Precursor for Phenolic Oxidation and Diels-Alder Reaction*
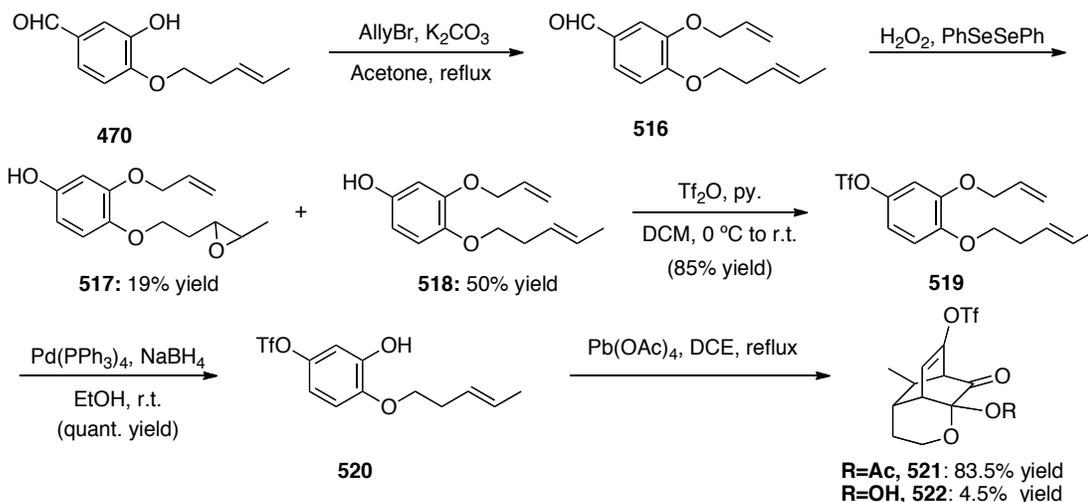


Although we were excited by this initial success, the observed over oxidation in

the Baeyer-Villiger oxidation of **516** left us a bit concerned about compatibility issues

with the olefins that would be present in the side chains of the real system (**Scheme 4.3.6.2**, inset).   Thus, rather than forge ahead with the model system we opted to explore an alternative route to **518**.  As illustrated in **Scheme 4.3.6.3**, we chose to explore a route eminating from 2,4-dihydroxy benzaldehyde (**440**) which, upon exposure to BOM-Cl can be selectively protected at the least hindered phenol to give aldehyde **525**. Subsequent allylation and Baeyer-Villiger oxidation delivers phenol **526**. Coupling of **526** with iodide **436** delivers phenol ether **527** and removal of the BOM protecting group then completes the construction of **518**.  Importantly, this approach to **518** is very short, proceeds in excellent yield and can be readily adapted to the phomoidride D (**303**) synthesis by simply incorporating a fully functionalized side-chain unit (i.e., **407**) in place of **436**. Having developed an alternative preparation of **518**, we turned toward completing the model study and advanced the Diels-Alder adduct (**521**) to the corresponding hemiacetyl (**522**) by exposure to silica gel.

*Scheme 4.3.6.3 Preparation 2: Precursor for Phenolic Oxidation and Diels- Alder Reaction*
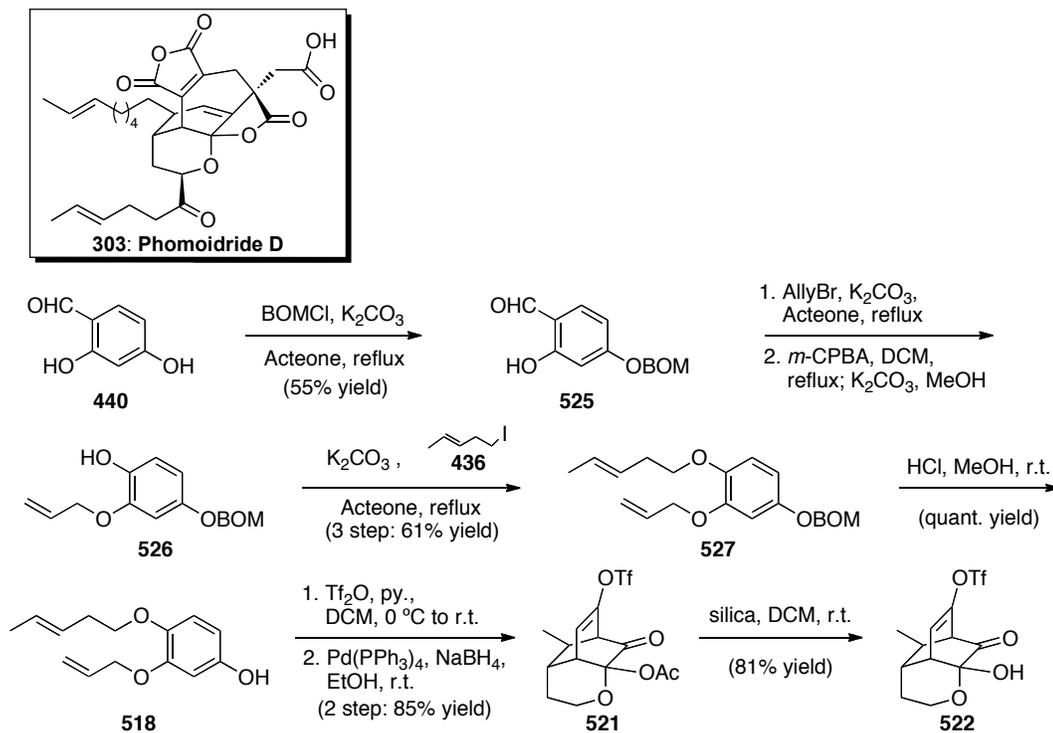
As illustrated in **Scheme 4.3.6.4**, intermediate **522** was advanced by protecting

the free alcohol as its TMS ether (**528**), followed by aldol addition and Cope elimination

to yield olefin **529** (**Scheme 4.3.6.4**). Removal of the TMS protecting group with TBAF

and AcOH was followed by spontaneous cyclization to provide lactone **530**.

Unfortunately, efforts to remove the triflate and deliver ketone **531** failed. The undesired

seco acid **532** was the only product observed.

## Scheme 4.3.6.4 Lactone Synthesis
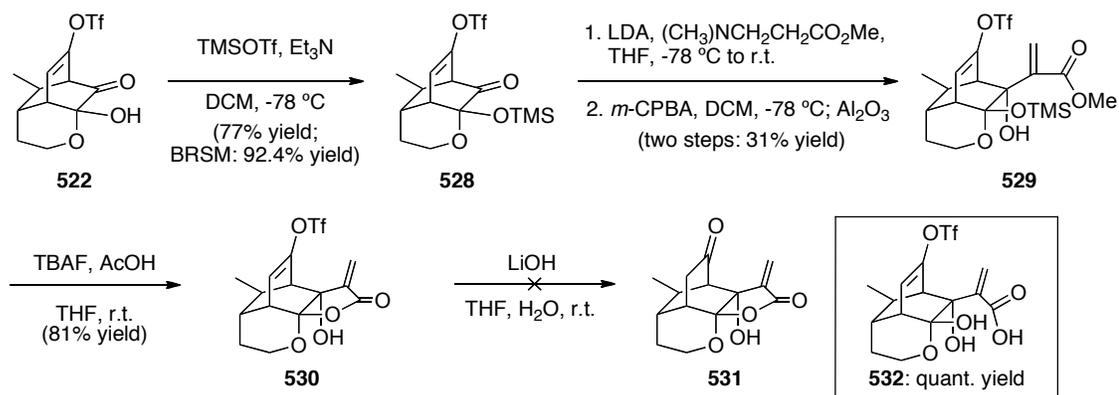


Somewhat surprised by the resiliency of the enol triflate we decided to explore this transformation in a simplified system. To this end model enoltriflate **535** was prepared and the conditions that were explored for its conversion to ketone **536** included: A) attempts to saponify under basic conditions (LiOH or KOH); B) initial transformation to the corresponding enamine via by Pd (0) or Cu (I) catalysis;[58-62] C) addition of amine nucleophiles such as DBU or NaNH$_2$, and;[63, 64] D) reductive cleavage of the O-S bond[65] (**Table 4.3.6.1**). Although several of these conditions produced some of the desired ketone, a combination of Pd(OAc)$_2$, BINAP, morpholine, and Cs$_2$CO$_3$ proved the most effective.

*Table 4.3.6.1 Triflate Removal Triflate in a Model.*



| Conditions | Results |
|---|---|
| LiOH, r.t. | decomposition |
| Pd(OAc)$_2$, BINAP, morphline, NaO$^t$Bu, Tol, reflux | decomposition |
| Pd(OAc)$_2$, BINAP, Cs$_2$CO$_3$, Tol, reflux | 26% |
| Pd(OAc)$_2$, BINAP, morphline, Cs$_2$CO$_3$, Tol, reflux | 46% |
| DBU, THF, r.t. | decomposition |
| NaNH$_2$, DMF, r.t. | 25% |
| Na(NH$_3$), -78 °C | trace |

Having had some success with the conversion of **535** to **536**, we applied a few of the more promising conditions to **528**, including: LiOH; Pd(OAc)$_2$, BINAP, morpholine, NaO$^t$Bu;[59] Pd(OAc)$_2$, BINAP, morpholine, Cs$_2$CO$_3$;[61] DBU;[63] Na(NH$_3$);[65] Pyridine; NaNH$_2$;[64] CuI, proline, morpholine, K$_3$PO$_4$ [62] (**Table 4.3.6.2**). Unfortunately, no desired product (**537**) was produced and starting material was either recovered or decomposed in all cases except the last, wherein an unexpected heterocyclic product (**538**) was observed.

*Table 4.3.6.2 Removal Triflate in the Real System 522*



**528** → Conditions → **537**
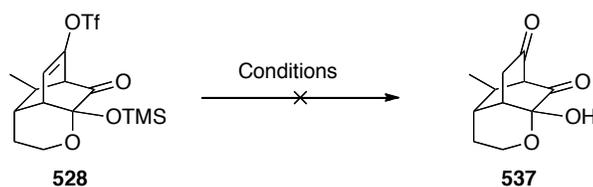
| Conditions | Results |
| --- | --- |
| LiOH, THF r.t. to reflux | decomposition |
| Pd(OAc)$_2$, BINAP, morphline, NaO$^t$Bu, Tol, reflux | decomposition |
| Pd(OAc)$_2$, BINAP, morphline, Cs$_2$CO$_3$, Tol, reflux | decomposition |
| DBU, THF, r.t. | decomposition |
| Na(NH$_3$), -78 °C | decomposition |
| Py. r.t. to reflux | S.M. recovered |
| NaNH$_2$, DMF, r.t. | decomposition |
| CuI, (-)-proline, morpholine, K$_3$PO$_4$, MeCN, reflux | <br>**538**: 39% yield |
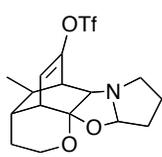
## 4.3.7 Investigation of Other OEWG Substituents

Due to the difficulties encountered while attempting to remove the triflate group, we decided to investigate other OEWG groups. To this end phenol **518** was acylated with different electron withdrawing groups, including: acetate, benzoylate, trifluoroacetate, phosphate, mesylate and nosylate to give the corresponding products **540** to **545**, respectively (**Table 4.3.7.1**).

*Table 4.3.7.1 Preparation of Substrate for Diels- Alder Reaction: Acylation*



| Conditions | Results (yield) |
|---|---|
| AcCl, py., DCM, r.t. | R=Ac, **540**: quant. |
| (NO₂-substituted benzoic acid), DCC, DMAP, DCM, r.t. | R= (acyl group), **541**: 33% |
| $(CF_3CO)_2O$, py., DCM, r.t. | R=OCCF₃, **542** |
| ClP(O)(OEt)₂, py, DCM, r.t. | R=P(O)(OEt)₂, **543**: 77 % |
| MsCl, py., DCM, r.t. | R=Ms, **544**: 55% |
| NsCl, py., DCM, r.t. | R=Ns, **545**: 79% |
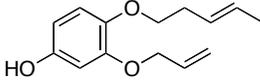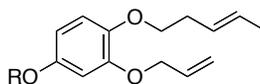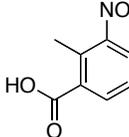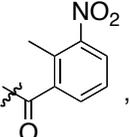
As illustrated in **Table 4.3.7.2**, derivatives **540**-**545**, could be deallylated to the corresponding phenols (**547**-**552**) using Pd(0) and either NaBH₄/EtOH or K₂CO₃/MeOH.[40,66]

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*Table 4.3.7.2 Preparation of Substrates for Diels-Alder Reaction: Deallylation*
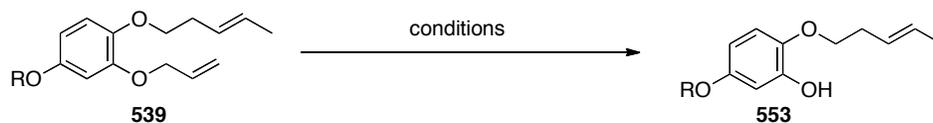


| Conditions | Results (yield) |
|---|---|
| Pd(PPh$_3$)$_4$, NaBH$_4$, EtOH, r.t | R=H, **546**: quant |
| Pd(PPh$_3$)$_4$, NaBH$_4$, EtOH, r.t | R=Ac, **547**: 98% |
| Pd(PPh$_3$)$_4$, NaBH$_4$, EtOH, r.t | R= , **548**: 10% |
| Pd(PPh$_3$)$_4$, NaBH$_4$, EtOH, r.t | R=OCCF$_3$, **549** |
| Pd(PPh$_3$)$_4$, NaBH$_4$, EtOH, r.t | R=P(O)(OEt)$_2$, **550**: 78 % |
| Pd(PPh$_3$)$_4$, K$_2$CO$_3$, MeOH, r.t. | R=Ms, **551**: 100% |
| Pd(PPh$_3$)$_4$, K$_2$CO$_3$, MeOH, r.t. | R=Ns, **552**: 92% |
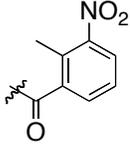
With a series of substrates in hand (i.e., **546**-**552**) the subsequent tandem phenolic oxidation/Diels-Alder addition was investigated. The first step, phenolic oxidation was found to work well for all substrates; however, the subsequent [4+2] cycloaddition was observed to proceeded with only three: phenol **550** (phosphate EWG), **551**(mesylate EWG), and **552** (nosylate EWG)  (**Table 4.3.7.3**). Of these successful substrates, the yield for **552** was best at 77% (combined).

*Table 4.3.7.3 Substrates 553 for Phenolic oxidation and Diels- Alder Reaction*
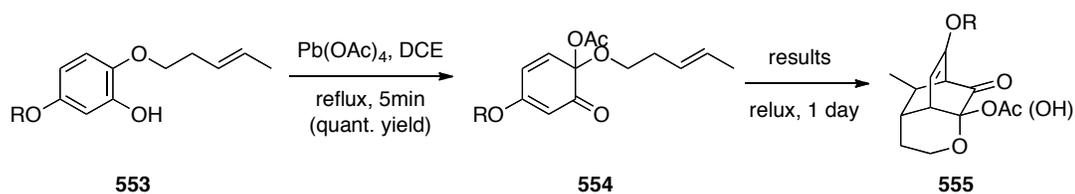


| Substrates: 553 | D/A product: yield |
|---|---|
| R=H, **546** | 0% |
| R=Ac, **547** | 0% |
| R= (2-methyl-3-nitrobenzoyl), **548** | 0% |
| R=OCCF$_3$, **549** | 0% |
| R=P(O)(OEt)$_2$, **550** | **556 (OH)**: 24% |
| R=Ms, **551** | **557(OAc)**: 42% |
| R=Ns, **552** | **558(OAc)**: 73%; **559(OH)**: 4% |
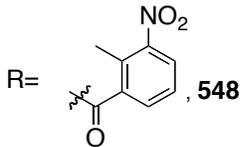
 

Our next challenge was to convert enolether **555** to the corresponding ketone **560**. To this end we chose to explore three conditions: LiOH; KOH; PhSH/KOH.[67] In the event, exposure of **521** (the enoltriflate) and **556-559** to the first two conditions resulted in no desired product (**Table 4.3.7.4**). However, for substrate **558**, exposure to PhSH/KOH furnished the desired ketone in excellent yield.

*Table 4.3.7.4 Conversion of Enolate 555 to Ketone 560*
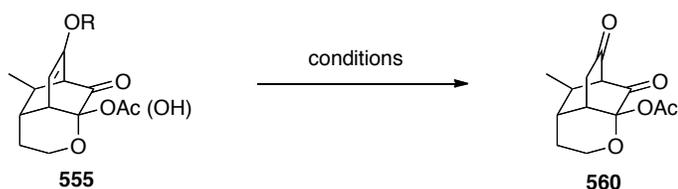


| substrates | conditions | results (yield) |
|---|---|---|
| R=Tf, **521(OAc)** | PhSH, KOH | decomposition |
| R=P(O)(OEt)₂, **556(OH)** | LiOH or KOH or PhSH, KOH | decomposition |
| R=Ms, **557(OAc)** | LiOH or KOH or PhSH, KOH | decomposition |
| R=Ns, **559(OH)** | LiOH or KOH | decomposition |
| R=Ns, **558(OAc)** | LiOH or KOH | decomposition |
| R=Ns, **559(OH)** | PhSH, KOH | 30% |
| R=Ns, **558(OAc)** | PhSH, KOH | 96% |

Proceeding with ketone **560**, our next goal was differentiation of the two ketone moieties. To this end, we began advancing **560** by removal of the acetate to provide hemiacetal **537**. Reprotection of **537** as the TMS ether (**561**) was followed by exposure to TBSOTf to produce silyl enolether **563**. With the two carbonyls effectively differentiated, the stage was set for the aldol addition/Cope elimination sequence. To our delight, **563** proved to be a superb substrate and furnished the desired ester **564** in 85% overall yield. Conversion of **564** to the corresponding exomethylene lactone (**531**) was followed by alkylation with Stork's bromo acetyl to provide radical cyclization precursor **513** (**Scheme 4.3.7.1**)

*Scheme 4.3.7.1 Synthesis of Lactone 531*
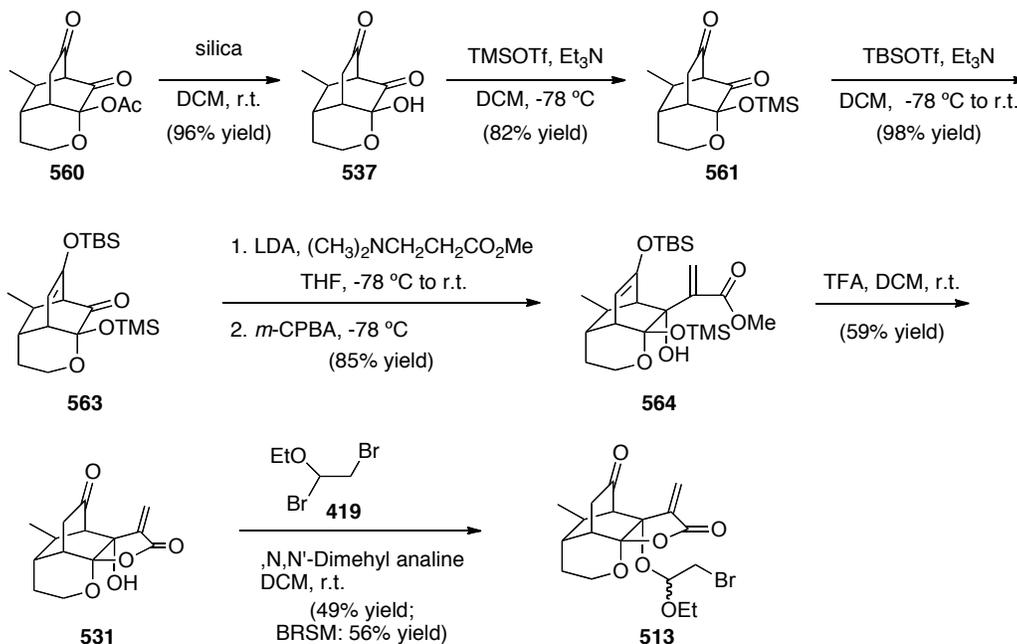


Treatment of **513** with SmI$_2$ gave tertiary alcohol **512**. Having accessed

cyclization product **512**, our next goal was to conduct the Wharton fragmentation. To this

end, the acetal in **512** was opened and converted to the corresponding dithiane (**566**) upon

exposure to BF$_3$•OEt$_2$ and 1,3-propanethiol. Unfortunately mesylation of **566** furnished

bis mesylate **567**, an intermediate which has to date proven unadvancable (**Scheme**

**4.3.7.2**).

*Scheme 4.3.7.2 Preparation Substrate 567 for Fragmentation*
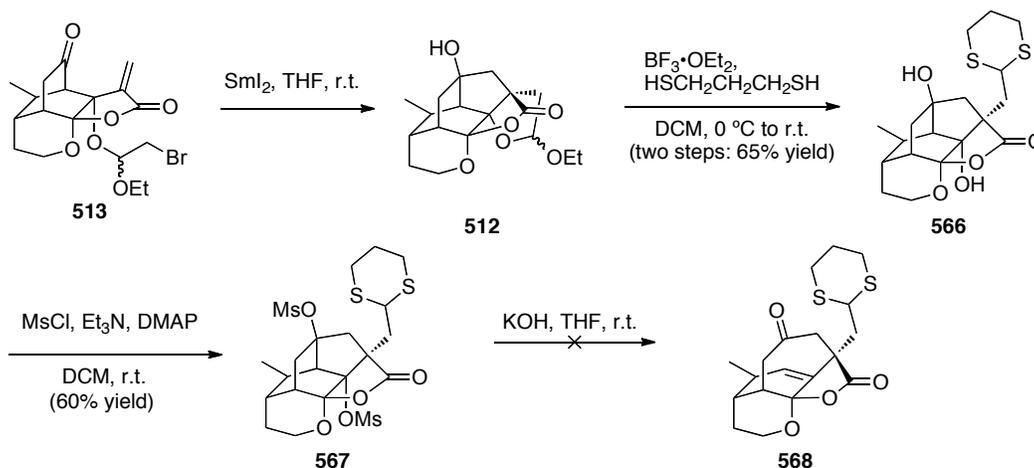


Given that selective alcohol funcitionalization had now presented itself as a problem we recognized that oxidation of the ethyl ketal to the corresponding lactone might provide an intermediate suited for fragmentation. Unfortunately, although conversion of acetal **512** to the corresponding hemiacetyl **570** was successful subsequent oxidation to **571** failed under numerous conditions (**Scheme 4.3.7.3**). As an alternative approach to delivering lactone **571**, we explored introduction of an alpha halo ester replacement for the bromo acetal. The derived ester (**585**) was seen as a potential precursor to **571** for *via* a radical cyclization akin to that initiated with the corresponding bromo acetal. However, efforts to prepare **585** by treatment of lactone **531** with 2-chloroacetic anhydride (**497**) gave undesired product **586**, from the product of an apparent [3,3] sigmatropic rearrangement of **585**.

## Scheme 4.3.7.3 Preparation Substrate 571 for Fragmentation
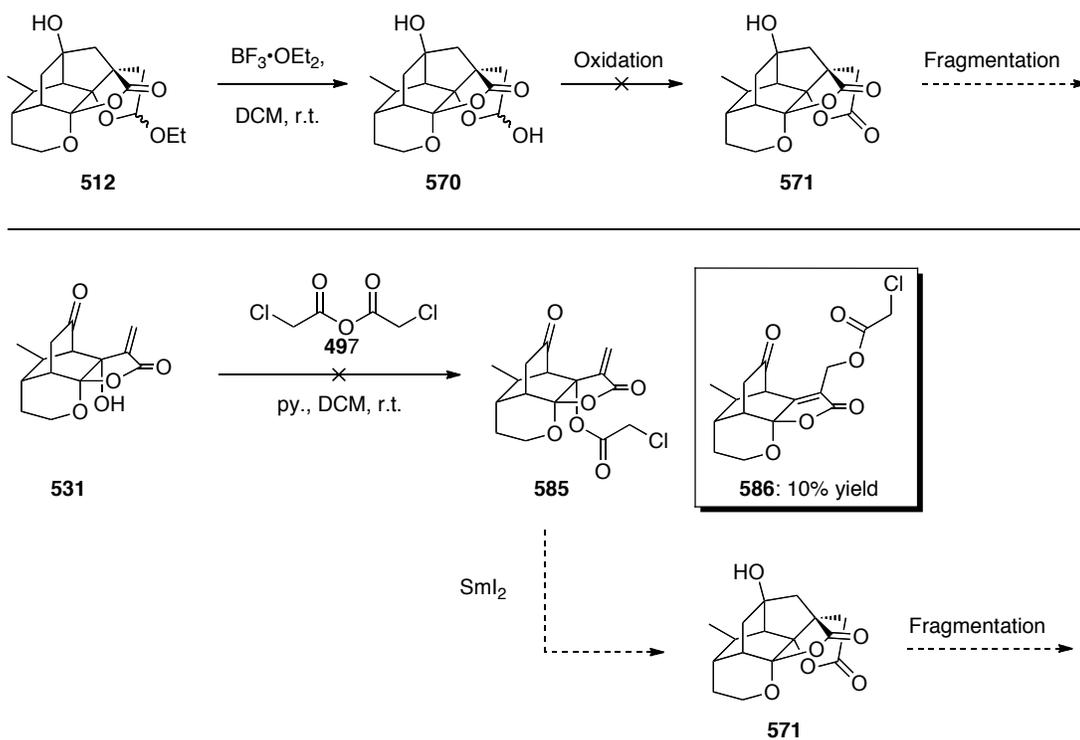


The final approach to prepare a substrate for Wharton fragmentation involved differentiating the two tertiary alcohols that would result following acetal opening of substrate **512** (**Scheme 4.3.7.4**).  Thus, acylation of the tertiary alcohol in **512** was followed by acetal opening/ dithiane formation, mesylation, and deacylation to furnish **572**.

## Scheme 4.3.7.4 Preparation of Substrate 572 for Fragmentation
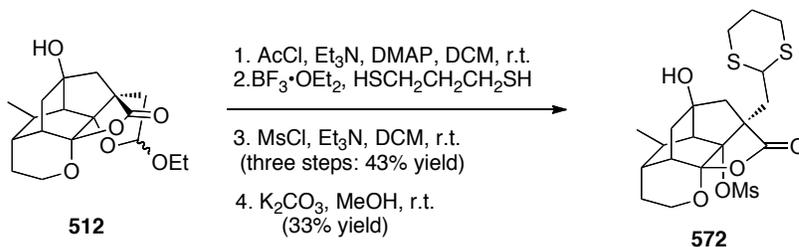
## 4.4 Future Plans

Future studies will focus on the fragmentation of mesylate **572** to the corresponding ketone **568**. Subsequent completion of the model system begin with homologation of **568** using Mander's reagent.  Conversion of the intermediate ß-keto ester to the corresponding enol triflate followed by palladium catalyzed CO insertion, will set the stage for dithane removal and oxidation using the Jones Reagent.

*Scheme 4.4 Future Plans*
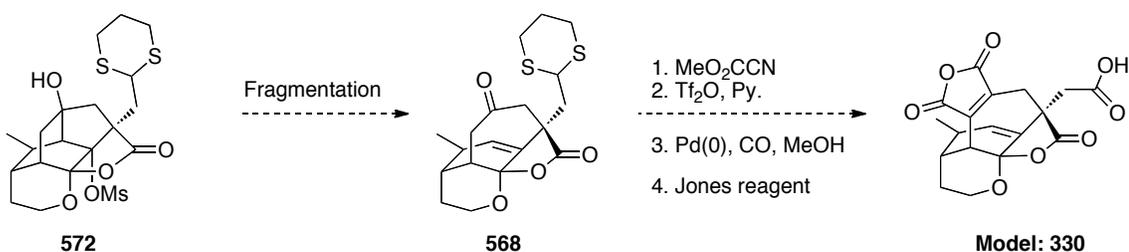


## 4.5 Conclusions

In this chapter, the previous Wood group synthetic efforts towards the total synthesis of the phomoidrides have been summarized. Based on these previous results, a new approach was developed wherein a deleterious ester group was removed and  a Wharton fragmentation enabled. Further refinement revealed that subtle electronic effects of a tandem phenolic oxidation/Diels-Alder sequence could be addressed by the incorporation of electron deficient sulfonates (e.g., a triflate or nosylate).

## 4.6 Experimental Section

## 4.6.1 Materials and Methods

**General.** Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF) was dried either by distillation from sodium/benzophenone or by passing through activated alumina columns. Methylene chloride (DCM), diethyl ether (Et$_2$O), benzene (PhH), toluene (Tol) and acetonitrile (MeCN) were dried by passing through activated alumina columns. Dimethylformamide (DMF) was dried over activated molecular sieves or by passing through activated alumina columns. MeOH was distilled over magnesium oxide. All other commercially obtained reagents were used as received. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm). Flash chromatography was performed with indicated solvents using silica gel (particle size 0.032-0.063) purchased from Silicycle. Microwave experiments were performed using a Biotage Initiator® or CEM Discover microwave reactor. $^1$H NMR spectra were recorded at 500 MHz, 400 MHz or 300 MHz using a Bruker AM-500, Bruker Avance DPX-500, Bruker AM-400, Varian Inova 400, Varian Inova 300 or Varian Mercury Inova 300 instrument. $^{13}$C NMR spectra were recorded at 125 MHz, 100 or 75 MHz using a Bruker AM-500, Bruker Avance DPX-500, Bruker AM-400, Varian Inova 400, Varian Inova 300 or Varian Mercury Inova 300 instrument. Chemical shifts are reported relative to internal chloroform ($^1$H, $\delta$ = 7.26, $^{13}$C, $\delta$ = 77.1) as indicated. Splitting patterns are reported as such, app = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet. Infrared spectra were recorded on a

Nicolet Avatar 320 FT-IR. High-resolution mass spectra were acquired at the Colorado State University CIF using an Agilent 6210 TOF LCMS.

## 4.6.2 Preparative Procedures

**Preparation of Compound 466**
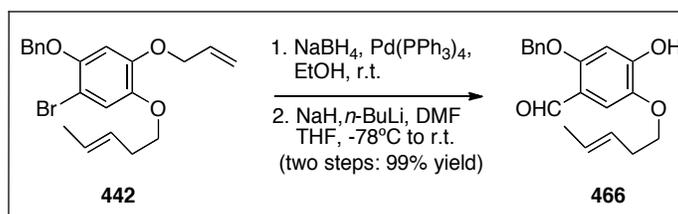


To a solution of **442** (403.0 mg, 1 mmol, 1 equiv.) in EtOH (10 mL) was added NaBH$_4$ (20 mg, 0.5 mmol, 0.5 equiv.) and Pd(PPh$_3$)$_4$ (29 mg, 0.03 mmol, 0.03 equiv.). The mixture was stirred overnight then filtered through Celite and concentrated under reducing pressure to give crude phenol (368.2 mg, 100%).

To a solution of crude phenol in THF (10 mL) was added NaH (26.4 mg, 1.1 mmol, 1.1 equiv.). The mixture was stirred for 5 min at room temperature then cooled to -78 °C. The solution was added to *n*-BuLi (0.75mL, 1.2 mmol, 1.2 equiv., 1.6 M) dropwise and stirred for 30 minutes. The mixture was added to DMF (0.23 mL, 3 mmol, 3 equiv.), stirred for 3 h at -78 °C then warmed to room temperature. The solution was stirred overnight and quenched by H$_2$O (1 mL). The layers were separated and the aqueous layer was washed with EtOAc (2 × 2 mL). The combined organic layers were washed with brine (4 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography

(gradient elution, 10%- 20% EtOAc/ Hexanes) to yield **466** (308.4 mg, 98.6%) as brown solid.

**Compound 466**: FTIR(NaCl/ thin film) 3308, 2935, 2874, 1662, 1585, 1506, 1456, 1290, 1216, 1138, 1025, 1290, 1216, 1138, 1025, 1024, 968, 736, 696 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 10.37 (s, 1H), 7.53- 7.31 (m, 6H), 6.64 (s, 1H), 6.52- 6.40 (m, 1H), 5.66- 5.38 (m, 2H), 5.11 (s, 2H), 4.05 (t, *J*=6.6 Hz, 2H), 2.56- 2.38 (m, 2H), 1.68 (t, *J*=6.2 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 188.2, 158.2, 153.5, 140.7, 136.2, 128.8, 128.6, 128.4, 127.5, 126.4, 117.9, 110.4, 100.4, 71.1, 69.4, 32.5, 18.1;  HRMS (TOF LCMS) calc'd for C$_{19}$H$_{21}$O$_4$ [M-H] 311.1283, found 311.1291.

**Preparation of Compound 465**
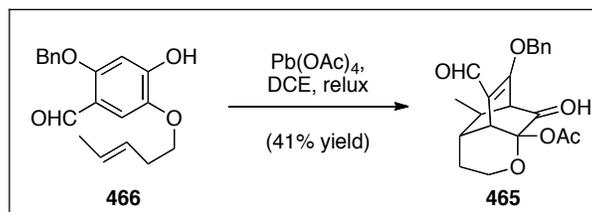


To a solution of **466** (43.5 mg, 0.14 mmol, 1 equiv.) in DCE (4.5 mL) was added Pb(OAc)$_4$ ( 225.7 mg, 0.17 mmol, 1.4 equiv.). The solution was heated to reflux and stirred overnight. The mixture was cooled to room temperature, filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%- 50% EtOAc/ Hexanes) to yield **465** (67.4 mg, 41%) as brown oil.

**Compound 465**: FTIR(NaCl/ thin film) 3402, 2959, 2927, 1741, 1662, 1616, 1456, 1374, 1221, 1178 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 10.00 (d, *J*= 4.2 Hz, 1H),

7.44- 7.29 (m, 5H), 5.28- 5.06 (m, 2H), 4.11- 3.98 (m, 1H), 3.75- 3.56 (m, 2H), 2.15-
1.90 (m, 6H), 1.83- 1.72 (m, 1H), 1.66- 1.50 (m, 1H), 1.00 (dd, $J$=4.2, 6.8 Hz, 3H); $^{13}$C
NMR (100 MHz, CDCl$_3$) δ 199.8, 184.4, 170.1, 169.1, 135.3, 129.0, 127.9, 127.6, 115.7,
94.0, 72.9, 62.0, 57.2, 38.7, 37.7, 36.9, 28.6, 20.9, 20.9;  HRMS (TOF LCMS) calc'd for
C$_{21}$H$_{22}$O$_6$ [M+H] 371.1495, found 371.1484.

## Preparation of Compound 470
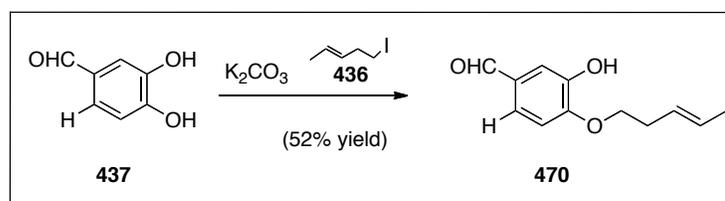


To a solution of 3,4-dihydroxy benzaldehyde (**437**) (6.9 g, 50 mmol, 5 equiv.) in
acetone (120 mL) was added K$_2$CO$_3$ (6.9 g, 50 mmol, 5 equiv.) and iodide **436** (1.96 g,
10 mmol, 1 equiv.). The solution was heated to reflux and stirred overnight. The mixture
was cooled to room temperature, filtered through Celite and concentrated under reducing
pressure. The residue was loaded onto silica and purified by column chromatography
(gradient elution, 10%- 20% EtOAc/ Hexanes) to yield **470** (867 mg, 52%) as yellow oil.

**Compound 470**: FTIR(NaCl/ thin film) 3409, 2937, 1686, 1609, 1586, 1569,
1461, 1276, 1203, 1126, 1015, 969 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 9.82 (s, 1H),
7.43 (d, $J$=1.8 Hz, 1H), 7.40 (dd, $J$=1.9, 8.1 Hz, 1H), 6.94 (d, $J$=8.2 Hz, 1H), 5.89 (s, 1H),
5.72- 5.34 (m, 2H), 4.12 (t, $J$=6.7 Hz, 2H), 2.57- 2.48 (m, 2H), 1.68 (dd, $J$=1.1, 6.3 Hz,
3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 191.2, 151.3, 146.4, 130.7, 128.8, 125.9, 124.6,

114.2, 111.3, 68.9, 32.4, 18.1; HRMS (TOF LCMS) calc'd for $C_{12}H_{13}O_3$ [M-H] 205.0865, found 205.0867.

**Preparation of Compound 482**
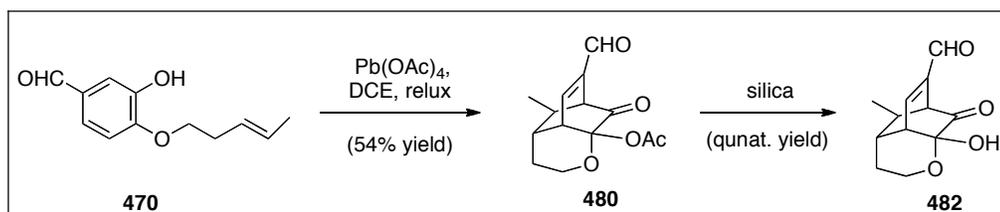


To a solution of **470** (180 mg, 0.87 mmol, 1 equiv.) in DCE (8.7 mL) was added Pb(OAc)$_4$ (394 mg, 0.89 mmol, 1.02 equiv.). The solution was heated to reflux and stirred overnight. The mixture was cooled to room temperature, filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%- 50% EtOAc/ Hexanes) to yield **480** (119 mg, 54%) as yellow oil.

To the residue in DCM (8 mL) was added silica (720 mg) and stirred for two days. The mixture was filtered through Celite and concentrated under reducing pressure to yield crude **482** (110 mg, 100%) as yellow oil.

**Compound 480**: FTIR(NaCl/ thin film) 2961, 2925, 1748, 1684, 1623, 1370, 1211, 1086, 1002 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 9.60 (s, 1H), 7.20 (dd, *J*=1.5, 6.8 Hz, 1H), 4.05 (ddd, *J*=1.6, 5.9, 12.9 Hz, 1H), 3.93 (dd, *J*=3.3, 6.8 Hz, 1H), 3.76 (s, 1H), 3.70 (dd, *J*=3.4, 12.4 Hz, 1H), 2.12- 1.95 (m, 2H), 1.98 (s, 3H), 1.85- 1.79 (m, 1H), 1.68- 1.61 (m, 1H), 0.88 (d, *J*=6.9 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 201.7, 188.6,

168.8, 147.9, 141.5, 92.9, 62.7, 50.7, 43.1, 37.3, 34.8, 28.2, 21.7, 20.1;   HRMS (TOF

LCMS) calc'd for $C_{14}H_{17}O_5$ [M+H] 265.1076, found 265.1071.

**Compound 482**: FTIR(NaCl/ thin film) 3419, 2961, 2927, 2871, 1742, 1680,

1622, 1374, 1092, 1064, 1008 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 9.62 (s, 1H), 7.36 (dd,

$J$=1.7, 6.8 Hz, 1H), 3.95 (ddt, $J$=1.2, 5.8, 12.6 Hz, 1H), 3.75 (t, $J$=2.1 Hz, 1H), 3.67 (td,

$J$=3.0, 12.7 Hz, 1H), 3.59 (s, 1H), 3.06 (dd, $J$=2.3, 6.7 Hz, 1H), 2.23- 2.11 (m, 1H), 2.05-

1.90 (m, 1H), 1.89- 1.81 (m, 1H), 1.73- 1.62 (m, 1H), 0.92 (d, $J$=6.9 Hz, 3H); $^{13}$C NMR

(100 MHz, CDCl$_3$) δ 208.5, 188.6, 151.1, 139.7, 89.9, 61.7, 50.5, 45.0, 37.0, 33.8, 28.5,

19.9;  HRMS (TOF LCMS) calc'd for $C_{12}H_{13}O_4$ [M-H] 221.0814, found 221.0818.

**Preparation of Compound 481**
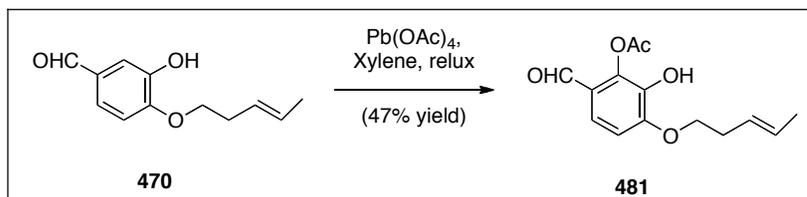


To a solution of **470** (4.12 mg, 0.02 mmol, 1 equiv.) in xylene (1.0 mL) was

added Pb(OAc)$_4$ (8.9 mg, 0.02 mmol, 1.02 equiv.). The solution was heated to reflux and

stirred overnight. The mixture was cooled to room temperature, filtered through Celite

and concentrated under reducing pressure. The residue was loaded onto silica and

purified by column chromatography (gradient elution, 10%- 20%EtOAc/ Hexanes) to

yield **481** (2.5 mg, 47%) as yellow solid.

**Compound 481**: FTIR(NaCl/ thin film) 2922, 2854, 1776, 1656, 1504, 1445,

1299, 1257, 1202, 1102, 969 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 11.27 (d, $J$=2.4 Hz,

1H), 9.74 (d, $J$=2.3 Hz, 1H), 7.40 (dd, $J$=2.4, 8.8 Hz, 1H), 6.61 (dd, $J$=2.3, 8.8 Hz, 1H),

5.66- 5.34 (m, 2H), 4.06 (td, $J$=2.2, 6.7 Hz, 2H), 2.47 (q, $J$=6.7 Hz, 2H), 2.34 (d, $J$=2.4

Hz, 3H), 1.68 (d, $J$=6.2 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 194.9, 168.4, 157.9,

155.1, 132.6, 128.6, 127.3, 125.9, 116.3, 104.7, 69.0, 32.4, 20.4, 18.2;  HRMS (TOF

LCMS) calc'd for C$_{14}$H$_{15}$O$_5$ [M-H] 263.0920, found 263.0923.


**Preparation of Compound 483**
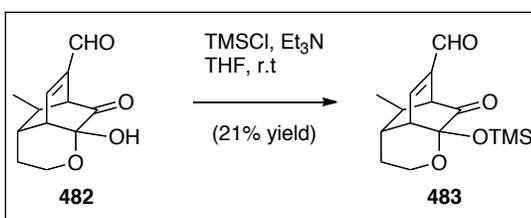


To a solution of **482** (74 mg, 0.33 mmol, 1 equiv.) in THF (3.3 mL) was added

TMSCl (84 μL, 0.66 mmol, 2 equiv.) and Et$_3$N (0.19 mL, 0.33 mmol, 2 equiv.) at room

temperature. The solution was stirred for 3 days. The mixture was filtered through Celite

and concentrated under reducing pressure. The residue was loaded onto silica and

purified by column chromatography (gradient elution, 10%- 20%EtOAc/ Hexanes) to

yield **483** (20 mg, 21%) as yellow oil.

**Compound 483**: FTIR(NaCl/ thin film) 2960, 2927, 2872, 1750, 1684, 1507,

1249, 1151, 995, 847 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 9.62 (s, 1H), 7.28 (dd, $J$=1.7

Hz, 6.8, 1H), 3.87 (dd, $J$=5.7, 12.7 Hz, 1H), 3.63 (s, 1H), 3.58 (dd, $J$=2.8, 12.7 Hz, 1H),

2.85 (dd, $J$=3.2, 6.8 Hz, 1H), 2.11- 2.02 (m, 1H), 1.93- 1.82 (m, 1H), 1.74- 1.70 (m, 1H),

1.59- 1.52 (m, 1H), 0.86 (d, $J$=7.0 Hz, 3H), 0.08 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ

206.6, 189.0, 151.8, 139.6, 91.7, 61.5, 51.2, 48.4, 37.1, 34.4, 28.6, 20.0, 1.7;   HRMS

(TOF LCMS) calc'd for $C_{15}H_{23}O_4Si$ [M+H] 295.1366, found 295.1396.

**Preparation of Compound 484**
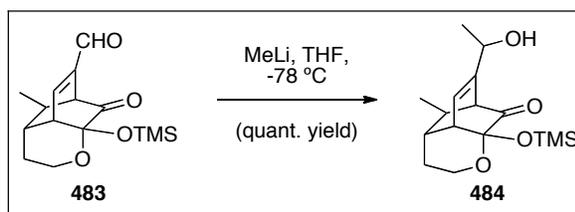


To a solution of **483** (14 mg, 0.048 mmol, 1 equiv.) in THF (0.5 mL) was added

MeLi (0.1 mL, 0.17 mmol, 3.5 equiv., 1.6M) at -78 ºC and the mixture was stirred for 1

hour. The reaction was quenched by $H_2O$ (1 mL). The layers were separated and the

aqueous layer was washed with EtOAc (2 × 2 mL). The combined organic layers were

washed with brine (4 mL), dried over $Na_2SO_4$, filtered through Celite and concentrated

under reducing pressure. The residue was loaded onto silica and purified by column

chromatography (gradient elution, 20%- 33% EtOAc/ Hexanes) to yield **484** (15 mg,

100%) as yellow oil.

**Compound 484**: FTIR(NaCl/ thin film) 3452, 2925, 2854, 1738, 1453, 1374,

1248, 1192, 1154, 1092, 1070, 990, 844 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 6.14 (dd,

*J*=2.4 Hz, 6.8, 1H), 4.36- 4.28 (m, 1H), 3.83 (dd, *J*=4.6, 11.4 Hz, 1H), 3.60 (td, *J*=2.9,

12.4 Hz, 1H), 3.09 (s, 1H), 2.51 (dd, *J*=3.3, 6.7 Hz, 1H), 2.05- 1.97 (m, 1H), 1.90- 1.79

(m, 1H), 1.69- 1.68 (m, 1H), 1.56- 1.44 (m, 2H), 1.24 (d, *J*=6.9 Hz, 3H), 0.97 (d, *J*=6.9

Hz, 3H), 0.1 (d, *J*=1.1 Hz, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 209.1, 141.7, 126.8, 92.4,

69.0, 61.3, 55.4, 45.6, 37.7, 34.2, 29.5, 21.9, 20.8, 1.8;  HRMS (TOF LCMS) calc'd for C$_{16}$H$_{26}$O$_4$SiNa [M+Na] 33.1498, found 33.1492.

**Preparation of Compound 485**
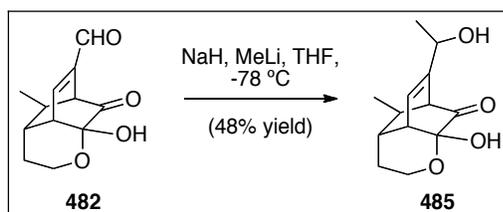


To a solution of **482** (98.9 mg, 0.45 mmol, 1 equiv.) in THF (4.5 mL) was added NaH (11.2 mg, 0.47 mmol, 1.1 equiv.) at room temperature. To this solution was added MeLi (0.83 mL, 1.35 mmol, 3 equiv., 1.6M) at -78 ºC and the mixture was stirred for 1 hour. The reaction was quenched by H$_2$O (2 mL). The layers were separated and the aqueous layer was washed with EtOAc (2 × 4 mL). The combined organic layers were washed with brine (8 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%- 50% EtOAc/ Hexanes) to yield **485** (51.3 mg, 48%) as yellow oil.

**Compound 485**: FTIR(NaCl/ thin film) 3402, 2967, 2928, 2870, 1733, 1456, 1374, 1170, 1088, 1023, 973 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 6.25 (dt, *J*=1.2 Hz, 6.8, 1H), 4.32 (ddd, *J*=1.1, 6.4, 12.8 Hz, 1H), 3.67 (td, *J*=3.3, 12.2 Hz, 1H), 3.11 (s, 1H), 2.70 (dd, *J*=3.3, 6.6 Hz, 1H), 2.14- 2.05 (m, 1H), 1.99- 1.88 (m, 1H), 1.78- 1.72 (m, 1H), 1.67- 1.59 (m, 1H), 1.27 (d, *J*=6.4 Hz, 3H), 1.00 (d, *J*=6.9 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 210.3, 142.6, 126.2, 90.6, 69.0, 61.6, 55.2, 42.5, 37.4, 33.4, 29.4, 21.6, 20.5; HRMS (TOF LCMS) calc'd for C$_{13}$H$_{17}$O$_4$ [M-H] 237.1127, found 237.1127.

## Preparation of Compound 490
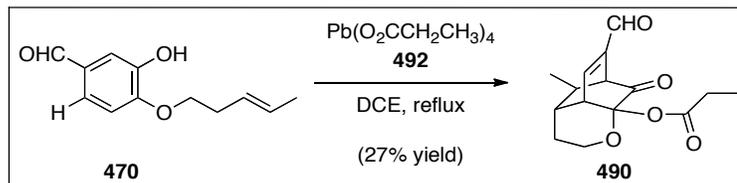


To a solution of **470** (33 mg, 0.16 mmol, 1 equiv.) in DCE (1.6 mL) was added Pb(O$_2$CCH$_2$CH$_3$)$_4$ (**492**) (112 mg, 0.22 mmol, 1.4 equiv.). The solution was heated to reflux and stirred overnight. The mixture was cooled to room temperature, filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%- 50% EtOAc/ Hexanes) to yield **490** (8.5 mg, 27%) as yellow oil.

**Compound 490**: FTIR(NaCl/ thin film) 2927, 1748, 1683, 1456, 1362, 1166, 1131, 1080 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 9.64 (s, 1H), 7.21 (dd, J=2.5 Hz, 6.8, 1H), 4.10 (ddd, J=2.0, 5.1, 11.2 Hz, 1H), 4.00 (dd, J=3.3, 12.2 Hz, 1H), 3.81 (s, 1H), 3.76 (td, J=3.6, 12.4 Hz, 1H), 2.30 (q, J=7.7, 2H), 2.19- 2.00 (m, 2H), 1.88- 1.82 (m, 1H), 1.73- 1.63 (m, 1H), 1.07 (d, J=7.6 Hz, 3H), 0.92 (d, J=7.0 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 201.7, 188.5, 169.0, 147.8, 141.6, 92.9, 62.7, 50.7, 43.2, 37.4, 34.8, 28.3, 28.2, 20.1, 8.9; HRMS (TOF LCMS) calc'd for C$_{15}$H$_{19}$O$_5$ [M+H] 279.1233, found 279.1222.

## Preparation of Compound 492
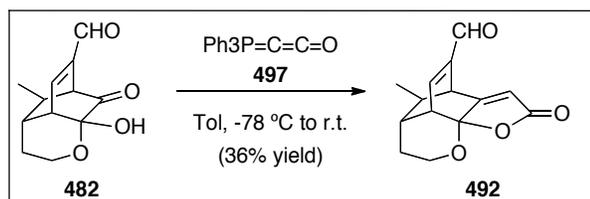
To a solution of **482** (45 mg, 0.49 mmol, 1 equiv.) in Tol (5 mL) was added phosphorus ketene **497** (164 mg, 0.54 mmol, 1.1 equiv.) at -78 ºC. The solution was warmed to room temperature and stirred overnight. The mixture was filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%- 50% EtOAc/ Hexanes) to yield **492** (16 mg, 36%) as yellow oil.

**Compound 492**: FTIR(NaCl/ thin film) 2958, 2926, 1783, 1680, 1649, 1453, 1358, 1166, 1150, 1117, 974, 876 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 9.45 (s, 1H), 7.12 (dd, $J$=1.2, 6.4 Hz, 1H), 5.39 (s, 1H), 4.20 (s, 1H), 4.06- 3.97 (m, 2H), 3.35 (dd, $J$=2.4, 6.5 Hz, 1H), 2.27- 2.19 (m, 1H), 2.07- 1.97 (m, 1H), 1.91- 1.82 (m, 1H), 1.58- 1.52 (m, 1H), 0.80 (d, $J$=7.0 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 187.5, 172.9, 172.7, 149.7, 147.9, 109.8, 104.8, 62.0, 40.1, 40.0, 39.1, 35.4, 27.9, 20.4;  HRMS (TOF LCMS) calc'd for C$_{14}$H$_{15}$O$_4$ [M+H] 247.0970, found 247.0961.

**Preparation of Compound 502**
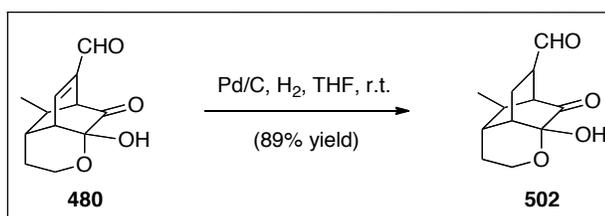


To a solution of **480** (mg, mmol, equiv.) in THF (mL) was added Pd/C (mg, mmol, mL), H$_2$ (1 atm) and the mixture was stirred overnight at room temperature. The mixture was filtered through Celite and concentrated under reducing pressure. The

residue was loaded onto silica and purified by column chromatography (gradient elution, 20%- 50% EtOAc/ Hexanes) to yield **502** (160 mg, 89%) as orange solid.

Compound **502**: FTIR(NaCl/ thin film) 3406, 2957, 2927, 2876, 1738, 1376, 1158, 1120, 1085, 1057 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 9.80 (s, 1H), 3.91 (dd, $J$=5.9, 12.5 Hz, 1H), 3.54 (td, $J$=3.1, 12.5 Hz, 1H), 3.00 (s, 1H), 2.65 (t, $J$=8.8 Hz, 1H), 2.28- 2.19 (m, 1H), 2.12- 2.07 (m, 1H), 2.01 (ddd, $J$=1.9, 8.0, 14.0 Hz, 1H), 1.97- 1.89 (m, 2H), 1.81- 1.75 (m, 1H), 1.42- 1.35 (m, 1H), 1.00 (d, $J$=7.3 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 213.6, 201.5, 94.0, 62.1, 49.9, 44.6, 38.5, 38.3, 31.9, 31.2, 21.9, 20.8; HRMS (TOF LCMS) calc'd for C$_{12}$H$_{15}$O$_4$ [M-H] 223.0970, found 223.0974.

**Preparation of Compound 516**
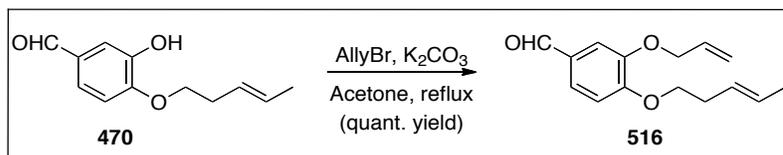


To a solution of **470** (1.15 g, 5.55 mmol, 1 equiv.) in acetone (11 mL) was added allyl bromide (0.60 mL, 7.21 mmol, 1.3 equiv.) and K$_2$CO$_3$ (1.54 g, 1.11 mmol, 2 equiv.) at reflux. The solution was stirred overnight and cooled to room temperature, filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 10%- 20% EtOAc/ Hexanes) to yield **516** (1.41 g, 100%) as brown solid.

Compound **516**: FTIR(NaCl/ thin film) 2936, 2728, 1688, 1596, 1584, 1436, 1270, 1168, 1133, 1014, 969, 929, 808 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 9.83 (s, 1H), 7.45 (d, $J$=1.9 Hz, 1H), 7.41 (dd, $J$=1.7, 8.0 Hz, 1H), 6.96 (d, $J$=8.2 Hz, 1H), 6.00 (ddt,

*J*=5.2, 10.4, 20.0 Hz, 1H), 5.66- 5.48 (m, 2H), 5.45 (dq, *J*=1.6, 17.4 Hz, 1H), 5.30 (dq,

*J*=1.6, 17.4 Hz, 1H), 4.64 (dt, *J*=1.4, 5.1 Hz, 2H), 4.09 (t, *J*=7.1 Hz, 2H), 2.60- 2.50 (m,

2H), 1.68 (dd, *J*=1.2, 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 191.0, 154.6, 148.9,

132.9, 130.0, 128.5, 126.9, 126.2, 117.9, 112.0, 111.9, 69.9, 68.9, 32.4, 18.2; HRMS

(TOF LCMS) calc'd for C$_{15}$H$_{19}$O$_3$ [M+H] 247.1334, found 247.1327.

**Preparation of Compound 517, 518**
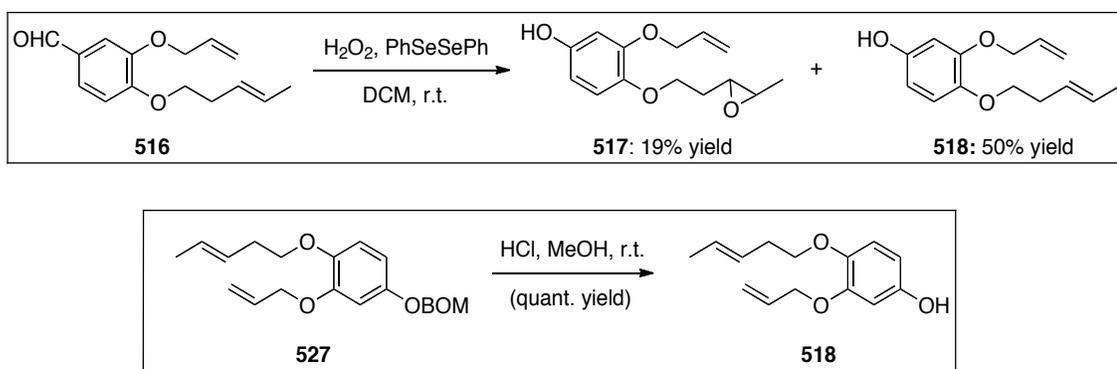


Method 1: to a solution of **516** (131 mg, 0.53 mmol, 1 equiv.) in DCM (8 mL)

was added PhSeSePh (6.8 mg, 0.02 mmol, 0.04 equiv.), H$_2$O$_2$ (0.70 ml, 0.86 mmol, 1.25

equiv., 30%) and the mixture was stirred at room temperature overnight. To the solution

was added 10% aqueous Na$_2$S$_2$O$_3$ (2mL). The layers were separated and the aqueous

layer was washed with DCM (2 × 8 mL). The combined organic layers were washed with

brine (16 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reducing pressure. The

residue was loaded onto silica and purified by column chromatography (gradient elution,

20%- 50% EtOAc/ Hexanes) to yield **517** (20 mg, 19%) as orange solid and **518** (47.4

mg, 50%) as pale yellow oil.

Method 2: to a solution of **527** (4.3 g, 12.13 mmol, 1 equiv.) in MeOH (350 mL) was added HCl (35 mL, conc.) and stirred at room temperature for 3h. The solution was neutralized by NaOH (90 mL, 2N). MeOH was removed under reducing pressure. The aqueous layer was washed with EtOAc (2 × 200 mL). The combined organic layers were washed with brine (400 mL) and dried over $Na_2SO_4$, filtered and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%- 50% EtOAc/ Hexanes) to yield **518** (3.0 g, 100%) as pale yellow oil.

**Compound 517**: FTIR(NaCl/ thin film) 3380, 2965, 2928, 1603, 1511, 1455, 1288, 1603, 1511, 1455, 1288, 1219, 1172, 1124, 1022, 931, 834 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 6.70 (d, $J$=8.6 Hz, 1H), 6.56- 6.51 (m, 1H), 6.43 (d, $J$=2.6 Hz, 1H), 6.31 (dq, $J$=2.5, 8.4 Hz, 1H), 6.00 (ddt, $J$=5.2, 10.4, 20.2 Hz, 1H), 5.38- 5.30 (m, 1H), 5.24- 5.18 (m, 1H), 4.48 (d, $J$=5.0 Hz, 2H), 4.08- 3.99 (m, 2H), 2.97- 2.87 (m, 2H), 2.14- 2.02 ( m, 1H), 1.93- 1.82 (m, 1H), 1.30 (d, $J$=5.1 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 151.3, 149.7, 142.1, 133.2, 117.7, 116.4, 106.8, 102.7, 69.7, 67.2, 57.7, 55.4, 32.2, 17.6; HRMS (TOF LCMS) calc'd for $C_{14}H_{17}O_4$ [M-H] 249.1127, found 247.1130.

**Compound 518**: FTIR(NaCl/ thin film) 3401, 2918, 1604, 1510, 1451, 1288, 1219, 1122, 1015, 968 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 6.70 (d, $J$=8.6 Hz, 1H), 6.45 (d, $J$=2.7 Hz, 1H), 6.33 (dd, $J$=2.8, 8.6 Hz, 1H), 6.04 (ddt, $J$=5.2, 10.5, 20.1 Hz, 1H), 5.62- 5.45 (m, 2H), 5.40 (dq, $J$=1.6, 17.3 Hz, 1H), 5.26 (dq, $J$=1.2, 10.6 Hz, 1H), 4.90 (s, 1H), 4.52 (dd, $J$=1.4, 5.1 Hz, 2H), 3.94 (t, $J$=7.0 Hz, 2H),  2.50- 2.42 (m, 2H), 1.67 (d, $J$=6.7 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 150.6, 150.0, 143.0, 133.4, 127.7, 127.0,

117.7, 116.5, 106.9, 103.1, 70.5, 70.6, 32.9, 18.2; HRMS (TOF LCMS) calc'd for

$C_{14}H_{19}O_3$ [M+H] 234.1334, found 235.1331.

**Preparation of Compound 519**
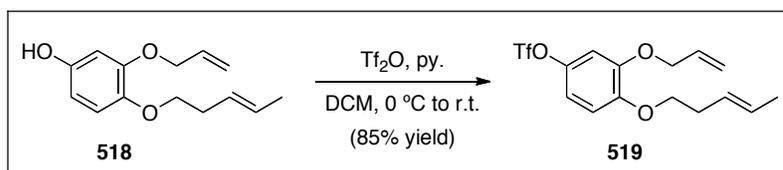


To a solution of **518** (447.1 mg, 1.90 mmol, 1 equiv.) in DCM (4 mL) was added

$Tf_2O$ (0.35 mL, 2.10, 1.1 equiv.) and pyridine (0.31 mL, 3.80 mmol, 2 equiv.) at 0 ºC.

The solution was warmed to room temperature and stirred overnight. The solvent was

removed under reducing pressure. The residue was loaded onto silica and purified by

column chromatography (gradient elution, 9%- 15% EtOAc/ Hexanes) to yield **519**

(592.3 mg, 85%) as pale yellow oil.

**Compound 519**: FTIR(NaCl/ thin film) 2923, 1608, 1508, 1422, 1217, 1142,

1018, 956, 860 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 6.88- 6.71 (m, 3H), 6.02 (ddt, $J$=5.1,

10.4, 20.8 Hz, 1H), 5.62- 5.44 (m, 2H), 5.40 (dq, $J$=1.5, 17.4 Hz, 1H), 5.29 (dq, $J$=1.0,

10.6 Hz, 1H), 4.56 (dt, $J$=1.3, 5.2 Hz, 2H), 3.98 (t, $J$=6.9 Hz, 2H),  2.53- 2.43 (m, 2H),

1.66 (dd, $J$=1.2, 6.7 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 149.3, 149.0, 143.0, 132.6,

128.3, 126.5, 118.4, 113.6, 113.5, 108.2, 70.4, 69.4, 32.6, 18.2; HRMS (TOF LCMS)

calc'd for $C_{12}H_{12}O_3$ [M-C3H5] 325.0358, found 325.0361.

**Preparation of Compound 520, 522**
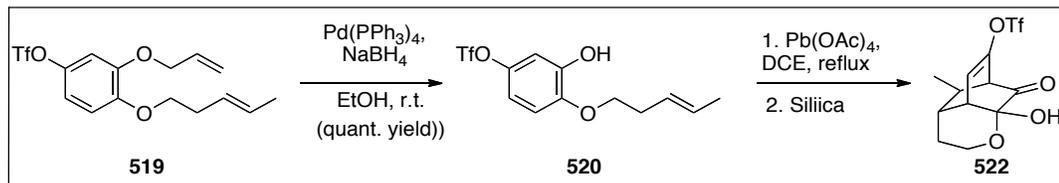


To a solution of **519** (592 mg, 1.62 mmol, 1 equiv.) in EtOH (1.6 mL) was added

NaBH$_4$ (30.6 mg, 0.81 mmol, 0.5 equiv.) and Pd(PPh$_3$)$_4$ (56 mg, 0.04 mmol, 0.03 equiv.).

The mixture was stirred overnight then filtered through Celite and concentrated under

reducing pressure to give crude phenol **520** (527 mg, 100%).

To a solution of crude phenol in DCE (16 mL) was added Pb(OAc)$_4$ (1.0 g, 2.27

mmol, 1.4 equiv.) at reflux. After stirring for 5 minuets, additional DCE (80 ml) was

added. The mixture was stirred overnight. NaBH$_4$ (20 mg, 0.5 mmol, 0.5 equiv.) and

Pd(PPh$_3$)$_4$ (29 mg, 0.03 mmol, 0.03 equiv.). The reaction was cooled to room temperature

then filtered through Celite and concentrated under reducing pressure. To this residue in

DCM (20 mL) was added silica (2.0 g) and stirred at room temperature overnight. The

mixture was filtered through Celite and concentrated under reducing pressure. The

residue was loaded onto silica and purified by column chromatography (gradient elution,

20%- 50% EtOAc/ Hexanes) to yield **522** (383.4 mg, 81%) as brown oil.

**Compound 520**: FTIR(NaCl/ thin film) 3521, 2937, 1608, 1505, 1422, 1275,

1219, 1142, 1106, 1019, 957, 866 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 6.88- 6.64 (m,

3H), 5.88- 5.72 (m, 1H), 5.68- 5.34 (m, 2H), 4.03 (t, $J$=6.5 Hz, 2H), 2.53- 2.35 (m, 2H),

1.67 (dd, $J$=1.2, 6.3 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 146.9, 145.8, 143.4, 128.8,

126.1, 112.7, 112.0, 108.4, 69.3, 32.5, 18.1; HRMS (TOF LCMS) calc'd for $C_{12}H_{12}O_3$ [M-H] 325.0358, found 325.0364.

**Compound 522**: FTIR(NaCl/ thin film) 3392, 2965, 2932, 2876, 1751, 1653, 1425, 1217, 1140, 1096, 901, 840 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 6.23 (dd, $J$=2.6, 7.6 Hz, 1H), 3.92 (dd, $J$=6.7, 12.6 Hz, 1H), 3.60 (td, $J$=3.0, 12.6 Hz, 1H), 3.62- 3.58 (m, 1H), 3.17 (q, $J$=2.5 Hz, 1H), 2.84 (dd, $J$=3.2, 7.6 Hz, 1H), 2.22- 2.12 (m, 1H), 2.05- 1.84 (m, 2H), 1.71- 1.66 (m, 1H), 1.15 (d, $J$=6.8 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 205.4, 145.1, 119.7, 90.1, 61.6, 57.8, 43.0, 37.2, 35.2, 28.7, 20.2; HRMS (TOF LCMS) calc'd for $C_{12}H_{12}F_3O_3S$ [M-H] 341.0307, found 341.0310.

**Preparation of Compound 525**
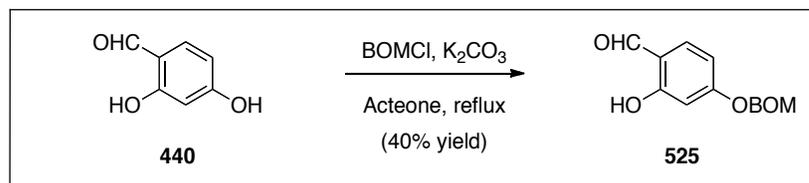


To a solution of 2,4-dihydroxy benzaldehyde (**440**) (37 g, 267.9 mmol, 1 equiv.) in acetone (1.4 L) was added BOMCl (25 g, 160.7 mmol, 0.6 equiv.) and K$_2$CO$_3$ (37 g, 267.9, 1 equiv.) at reflux. The mixture was stirred overnight. The reaction was cooled to room temperature then filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 5%- 10% EtOAc/ Hexanes) to yield **525** (15.1 g, 40%) as orange solid.

**Compound 525**: FTIR(NaCl/ thin film) 2923, 2854, 1651, 1629, 1578, 1501, 1453, 1216, 1157, 1087, 996, 957 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 11.37 (s, 1H).

9.75 (s, 1 H), 7.46 (d, $J$=8.6 Hz, 1H), 7.42- 7.30 (m, 5H), 6.69 (dd, $J$=2.2, 8.6 Hz, 1H), 6.65 (d, $J$=2.1 Hz, 1H), 5.34 (s, 2H), 4.72 (s, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 194.8, 164.6, 164.3, 136.9, 135.9, 128.7, 128.3, 128.2, 116.2, 109.3, 103.7, 92.1, 70.7; HRMS (TOF LCMS) calc'd for C$_{15}$H$_{13}$O$_4$ [M-H] 257.0814, found 257.0819.

**Preparation of Compound 526, 527**
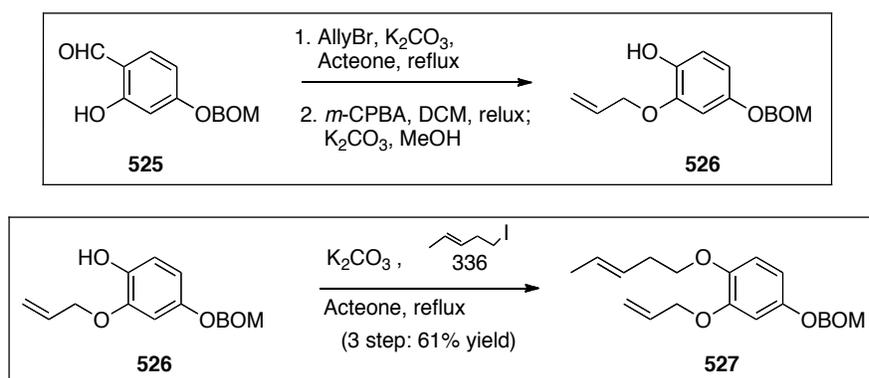


To a solution of **525** (2.9 g, 11.2 mmol, 1 equiv.) in acetone (23 mL) was added allyl bromide (1.23 mL, 14.6 mmol, 1.3 equiv.) and K$_2$CO$_3$ (3.1g, 22.4 mmol, 2 equiv.) at reflux. The mixture was stirred overnight. The reaction was cooled to room temperature then filtered through Celite and concentrated under reducing pressure. To this residue in DCM (82 mL) was added *m*-CPBA (4 g, 16.3 mmol, 1.4 equiv.) at reflux and stirred for 3 hours. The reaction was cooled to room temperature. DCM was removed under reducing pressure. To this residue in MeOH (20 mL) was added saturated aqueous Na$_2$CO$_3$ (200 mL) and stirred at room temperature overnight. The aqueous layer was washed with EtOAc (2 × 200 mL). The combined organic layers were washed with brine (400 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reducing pressure to yield crude **426** (2.7 g, 100%).

To a solution of crude **526** in acetone (41 mL) was added Cs$_2$CO$_3$ (9.4 g, 29.0 mmol, 2.5 equiv.), iodide **436** (5.55g, 29.0 mmol, 2.5 equiv.) at reflux and stirred overnight. The reaction was cooled to room temperature then filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%- 33% EtOAc/ Hexanes) to yield **4527** (2.5 g, 61%) as yellow oil.

**Compound 526**: FTIR(NaCl/ thin film) 3532, 3065, 3031, 2895, 1613, 1509, 1455, 1380, 1264, 1227, 1170, 1085, 1024, 933, 837 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.41- 7.28 (m, 5H), 6.87 (d, *J*=8.5 Hz, 1H), 6.70 (d, *J*=2.6 Hz, 1H), 6.57 (dd, *J*=2.6, 8.6 Hz, 1H), 6.08 (ddt, *J*=5.2, 10.5, 20.9 Hz, 1H), 5.34 (s, 2H), 5.39 (d, *J*=1.6 Hz, 1H), 5.32 (dd, *J*=1.2, 10.4 Hz, 1H), 5.24 (s, 2H), 4.75 (s, 2H), 4.57 (dd, *J*=1.2, 5.4 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 151.2, 146.0, 141.2, 137.6, 132.9, 128.7, 128.2, 128.1, 118.7, 114.7, 109.1, 102.9, 93.6, 70.0, 70.0; HRMS (TOF LCMS) calc'd for C$_{17}$H$_{17}$O$_4$ [M-H] 285.1127, found 285.1131.

**Compound 527**: FTIR(NaCl/ thin film) 2918, 2866, 1595, 1508, 1436, 1421, 1261, 1221, 1174, 1086, 928 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.45- 7.29 (m, 5H), 6.82 (d, *J*=8.6 Hz, 1H), 6.80 (d, *J*=2.8 Hz, 1H), 6.63 (dd, *J*=2.6, 8.5 Hz, 1H), 6.05 (ddt, *J*=5.2, 10.5, 20.9 Hz, 1H), 5.56-5.48 (m, 2H), 5.46- 5.37 (m, 1H), 5.31-5.24 (m, 1H), 5.22 (s, 2H), 4.72 (s, 2H), 4.60- 4.53 (m, 2H), 3.92 (t, *J*=6.9 Hz, 2H), 2.53- 2.43 (m, 2H), 1.68 (d, *J*=5.8 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 165.9, 152.2, 149.7, 144.3, 137.5, 133.5, 128.6, 128.2, 128.0, 127.7, 127.0, 117.6, 115.7, 108.0, 104.8, 93.3, 70.1, 70.0, 32.9, 18.2; HRMS (TOF LCMS) calc'd for C$_{22}$H$_{27}$O$_4$ [M+H] 355.1909, found 355.1896.

**Preparation of Compound 528**
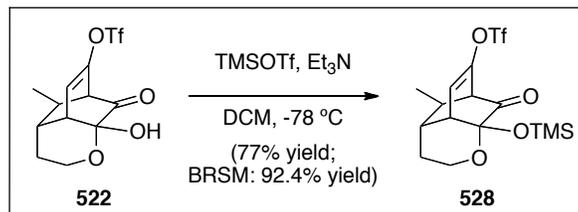


To a solution of **522** (348 mg, 1.02 mmol, 1 equiv.) in DCM (10 mL) was added TMSOTf (0.2 mL, 1.12 mmol, 1.1 equiv.) and Et$_3$N (0.17 mL, 1.12, 1.1 equiv.) at -78 ºC and stirred for 5 min. The reaction was quenched by aqueous NaHCO$_3$ (0.5 mL). The aqueous layer was washed with DCM (2 × 20 mL). The combined organic layers were washed with brine (40 mL) and dried over Na$_2$SO$_4$, filtered and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%- 33% EtOAc/ Hexanes) to yield **528** (349.4 mg, 77%) as green oil and recover starting material **522** (73.4 mg).

**Compound 528**: FTIR(NaCl/ thin film) 2962, 2931, 2875, 1575, 1653, 1427, 1218, 1141, 1092, 934, 847 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 6.15 (dd, $J$=2.8, 7.7 Hz, 1H), 3.86 (dd, $J$=5.7, 12.7 Hz, 1H), 3.52 (td, $J$=2.9, 12.8 Hz, 1H), 3.07 (t, $J$=2.7 Hz, 1H), 2.66 (dd, $J$=3.2, 7.7 Hz, 1H), 2.12- 2.04 (m, 1H), 1.94- 1.73 (m, 2H), 1.60- 1.51 (m, 1H), 1.11 (d, $J$=6.9 Hz, 3H), 0.11 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 203.8, 145.2, 119.3, 91.8, 61.3, 58.3, 45.9, 37.2, 35.6, 28.7, 20.2, 1.57; HRMS (TOF LCMS) calc'd for C$_{15}$H$_{21}$F$_3$O$_6$SSi [M+Na] 437.0678, found 437.0677.

## Preparation of Compound 529
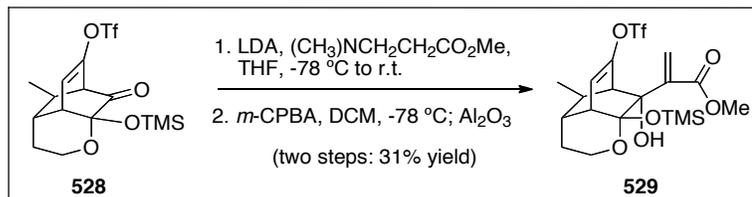


To a solution of diisopropylamine (0.62 mL, 4.42 mmol, 5.25 equiv.) in THF (3.4 mL) at −20 ºC was added *n*-BuLi (2.2 mL, 3.54 mmol, 4.2 equiv., 1.6 M hexanes solution) dropwise over 5 minutes. The resultant mixture was stirred at −20 ºC for 5 minutes, and then cooled to −78 ºC for 30 minutes. To this mixture was added methyl-3-(dimethylamino)propionate (0.73 mL, 3.0 mmol, 3.5 equiv.) dropwise over five minutes. The reaction mixture was stirred at −78 ºC for thirty minutes, 0 ºC for 15 min, and room temperature for 15 min, and then cooled to −78 ºC.

A solution of **528** (349 mg, 0.84 mmol) in THF (8.4 mL) was addedenolate dropwise over 1 minute at −78 °C. The solution was slowly warmed to room temperature and stirred for 1 hour. The reaction was quenched with 1M AcOH in THF (5mL) and allowed to warm to room temperature. At which point the reaction mixture was treated with H$_2$O (5mL) and EtOAc (5mL). The aqueous layer was extracted with EtOAc (2 x 10mL), and the combined organic layers were washed with brine (20 mL), dried over Na$_2$SO$_4$, and concentrated under reducing pressure.

To the solution of this residue solution in DCM (8.5 mL) was added *m*-CPBA (312 mg, 1.27 mmol, 1.5 equiv.) at -78 ºC and the mixture was stirred for 20 minutes. To the solution was added basic Al$_2$O$_3$ (400 mg) and stirred overnight at room temperature. The mixture was filtered through Celite and concentrated under reducing pressure. The

residue was loaded onto silica and purified by column chromatography (gradient elution, 5%- 10% EtOAc/ Hexanes) to yield **529** (132.6, mg, 31%) as colorless oil.

**Compound 529**: FTIR(NaCl/ thin film) 3440, 2959, 2926, 1710, 1663, 1424, 1323, 1214, 1143, 1055 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 5.88 (dd, $J$=2.7, 7.7 Hz, 1H), 5.85 (s, 1H), 5.62 (s, 1H), 5.50- 5.47 (m, 1H), 4.66 (td, $J$=4.7, 12.3 Hz, 1H), 3.92 (ddd, $J$=0.7, 7.1, 11.8 Hz, 1H), 3.77 (s, 1H), 2.76 (t, $J$=2.5 Hz, 1H), 2.58- 2.51 (m, 1H), 2.44 (dd, $J$=3.8, 7.6 Hz, 1H), 1.88- 1.66 (m, 3H), 1.05 (d, $J$=7.0 Hz, 3H), 0.09 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 167.6, 148.5, 143.4, 119.4, 114.7, 99.1, 82.3, 63.2, 52.1, 50.6, 47.1, 39.5, 29.1, 28.7, 20.9, 1.8; HRMS (TOF LCMS) calc'd for C$_{19}$H$_{26}$F$_3$O$_8$SSi [M-H] 499.1070, found 499.1081.

**Preparation of Compound 530**
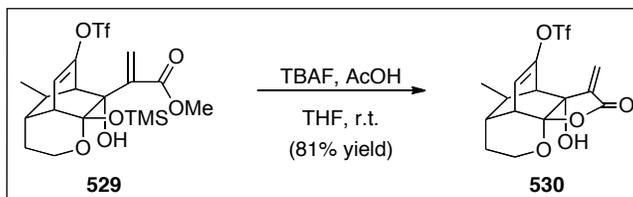


To a solution of **529** (132.6 mg, 0.27 mmol, 1 equiv.) in THF (2.6 mL) was added TBAF (1.32 mL, 1.35 mmol, 5 equiv.) and AcOH (76 μL, 1.35 mmol, 5 equiv.) at room temperature. The mixture was stirred overnight. The reaction was quenched by H$_2$O (2 mL). The aqueous layer was extracted with EtOAc (2 x 5mL), and the combined organic layers were washed with brine (10 mL), dried over Na$_2$SO$_4$, and concentrated under reducing pressure. The residue was loaded onto silica and purified by column

chromatography (gradient elution, 20%- 50% EtOAc/ Hexanes) to yield **530** (85.1 mg, 31%) as yellow solid.

**Compound 530**: FTIR(NaCl/ thin film) 3421, 2963, 2928, 1773, 1653, 1423, 1283, 1214, 1141, 1078, 1005, 907 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 6.46 (s, 1H), 6.01 (s, 1H), 5.86 (dd, $J$=2.7, 7.7 Hz, 1H), 4.47 (td, $J$=4.2, 11.3 Hz, 1H), 4.15- 4.05 (m, 1H), 3.28- 3.22 (m, 1H), 2.86 (dd, $J$=2.6, 7.4 Hz, 1H), 2.44- 2.33 (m, 1H), 2.06- 1.92 (m, 1H), 1.83- 1.71 (m, 2H), 1.07 (d, $J$=7.0 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 167.4, 166.2, 149.7, 140.6, 127.3, 113.3, 104.1, 64.2, 52.6, 42.6, 38.8, 31.4, 28.3, 20.7; HRMS (TOF LCMS) calc'd for C$_{15}$H$_{16}$F$_3$O$_7$S [M+H] 397.0569, found 397.0559.

**Preparation of Compound 538**



**528** → **538**

CuI, (-)-proline, morpholine, K$_3$PO$_4$, MeCN, reflux

(39% yield)
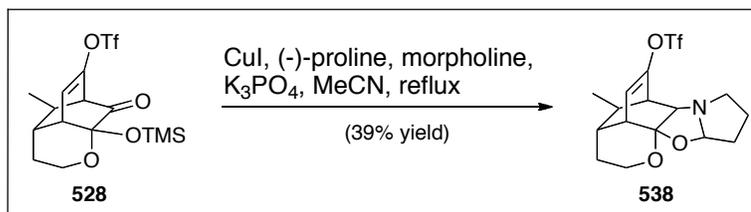
To a solution of **528** (53.6 mg, 0.13, 1 equiv.) in MeCN (1.30 mL) was added CuI (22mg, 0.13, 1 equiv.), (-)-proline (30mg, 0.26, 2 equiv.), NH$_4$OAc (22.5 mg, 0.26, 2 equiv.), K$_3$PO$_4$ (55 mg, 0.26, 2 equiv.) and morpholine (0.12 mL, 0.17 mmol, 1.1 equiv.). The mixture was heated to reflux and stirred overnight. The reaction was cooled to room temperature, filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%- 50% EtOAc/ Hexanes) to yield **538** (20 mg, 39%) as yellow solid.

**Compound 538**: FTIR(NaCl/ thin film) 2927, 2874, 1737, 1656, 1420, 1211, 1142, 1079, 834, 612 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 9.25 (dd, *J*=2.7, 7.6 Hz, 1H), 5.06 (t, *J*=3.3 Hz, 1H), 4.03 (dd, *J*=7.2, 12.5 Hz, 1H), 3.78 (td, *J*=3.2, 12.9 Hz, 1H), 3.31 (d, *J*=3.3 Hz, 1H), 3.19- 3.06 (m, 1H), 2.89- 2.77 (m, 1H), 2.69 (q, *J*=2.7 Hz, 1H), 2.62 (dd, *J*=2.8, 7.6 Hz, 1H), 1.96- 1.72 (m, 5H), 1.69- 1.54 (m, 2H), 1.53- 1.43 (m, 1H), 1.01 (d, *J*=6.9 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 151.0, 114.6, 110.4, 102.1, 72.7, 63.1, 57.7, 48.7, 44.5, 39.0, 35.0, 33.0, 28.3, 23.6, 21.0; HRMS (TOF LCMS) calc'd for C$_{16}$H$_{21}$F$_3$NO$_5$S [M+H] 395.1093, found 395.1096.

## Preparation of Compound 546
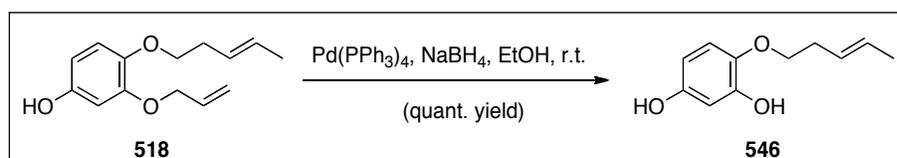


To a solution of **518** (156 mg, 0.67 mmol, 1 equiv.) in EtOH (4.7 mL) was added Pd(PPh$_3$)$_4$ (15.6 mg, 0.02 mmol, 0.03 equiv.) and NaBH$_4$ (8.8 mg, 0.34 mmol, 0.5 equiv.) at room temperature. The mixture was stirred overnight, filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%- 33% EtOAc/ Hexanes) to yield **546** (150 mg, 100%) as brown oil.

**Compound 546**: FTIR(NaCl/ thin film) 3404, 2936, 1607, 1510, 1469, 1386, 1296, 1219, 1148, 1117, 1022, 965, 846, 791 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 6.72 (d, *J*=8.6 Hz, 1H), 6.47 (d, *J*=1.9 Hz, 1H), 6.28 (dd, *J*=1.9, 8.7 Hz, 1H), 5.69- 5.41 (m, 2H), 4.80- 4.30 (m, 2H), 3.98 (t, *J*=6.5 Hz, 2H), 2.45 (q, *J*=6.2 Hz, 2H), 1.69 (d, *J*=6.2

Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 150.6, 147.1, 140.2, 128.5, 126.8, 113.9, 106.1, 102.9, 69.9, 32.8, 18.2; HRMS (TOF LCMS) calc'd for C$_{11}$H$_{13}$O$_3$ [M-H] 193.0865, found 193.0864.

**Preparation of Compound 540**
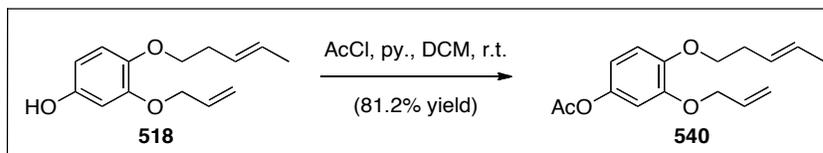


To a solution of **518** (94 mg, 0.40 mmol, 1 equiv.) in DCM (1 mL) was added AcCl (31 μL, 0.44 mmol, 1.1 equiv.) and pyridine (65 μL, 0.80 mmol) at room temperature. The mixture was stirred overnight, filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 10%- 20% EtOAc/ Hexanes) to yield **540** (90 mg, 81.2%) as orange oil.

**Compound 540**: FTIR(NaCl/ thin film) 2919, 2869, 1763, 1602, 1508, 1423, 1369, 1263, 1203, 1154, 1017 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 6.83 (d, *J*=8.5 Hz, 1H), 6..62 (dd, *J*=2.6, 5.4 Hz, 1H), 6.59 (d, *J*=2.6 Hz, 1H), 6.03 (ddt, *J*=5.1, 10.5, 20.9 Hz, 1H), 5.61- 5.43 (m, 2H), 5.39 (dq, *J*=1.5, 17.4 Hz, 1H), 5.24 (dq, *J*=1.3, 10.5 Hz, 1H), 4.53 (dt, *J*=1.5, 5.2 Hz, 2H), 3.96 (t, *J*=7.0 Hz, 2H), 2.50- 2.42 (m, 2H), 2.23 (s, 3H), 1.65 (dd, *J*=1.1, 5.9 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 169.8, 149.0, 146.8, 144.4, 133.1, 12.8, 126.7, 117.6, 114.1, 113.5, 108.5, 70.1, 69.4, 32.7, 21.1, 18.1; HRMS (TOF LCMS) calc'd for C$_{16}$H$_{21}$O$_4$ [M+H] 277.1440, found 277.1440.

**Preparation of Compound 547**
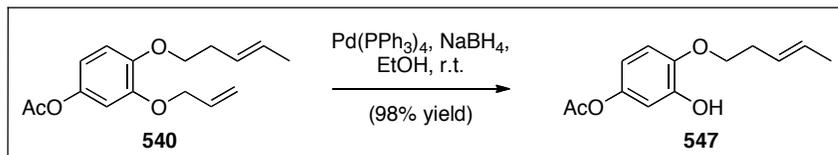


To a solution of **540** (59 mg, 0.21 mmol, 1 equiv.) in EtOH (2 mL) was added Pd(PPh$_3$)$_4$ (7.5 mg, 0.006 mmol, 0.03 equiv.) and NaBH$_4$ (4 mg, 0.11 mmol, 0.5 equiv.) at room temperature. The mixture was stirred overnight, filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%- 33% EtOAc/ Hexanes) to yield **547** (49.3 mg, 98%) as brown solid.

**Compound 547**: FTIR(NaCl/ thin film) 3451, 2935, 1762, 1605, 1505, 1370, 1280, 1207, 1140, 1015, 968 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 6.81 (d, J=8.7 Hz, 1H), 6..68 (d, J=2.8 Hz, 1H), 6.55 (d,d J=2.6, 8.7 Hz, 1H), 5.76- 5.74 (m, 1H), 5.67- 5.42 (m, 2H), 4.02 (t, J=6.7 Hz, 2H), 2.50- 2.42 (m, 2H), 2.26 (s, 3H), 1.65 (dq, J=1.2, 6.2 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 169.9, 146.6, 144.9, 143.9, 128.5, 126.5, 112.6, 112.3, 108.7, 69.3, 32.7, 21.2, 18.1; HRMS (TOF LCMS) calc'd for C$_{16}$H$_{15}$O$_4$ [M-H] 235.090, found 235.0974.

**Preparation of Compound 541**
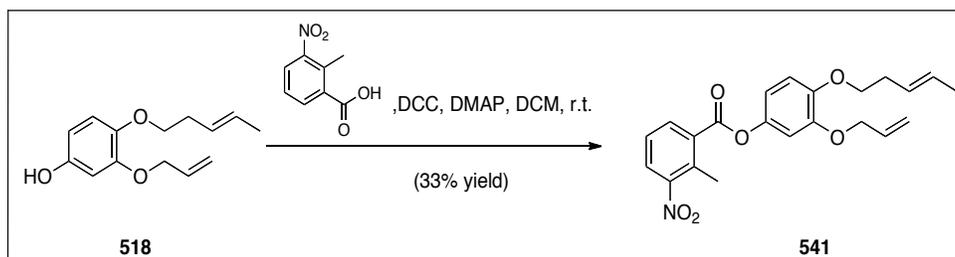
To a solution of 2-methyl-3-nitrobenzoic acid in DCM (1 mL) was added DCC (247.6 mg, 1.2 mmol, 1.2 equiv.) and DMAP (12.2 mg, 0.1 mmol, 0.1 equiv.) at room temperature. The mixture was stirred for 10 minutes. Then **518** (230 mg, 1 mmol, 1 equiv.) was added and stirred overnight. The reaction was filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 10%- 20% EtOAc/ Hexanes) to yield **541** (128 mg, 33%) as brown oil.

**Compound 541**: FTIR (NaCl/ thin film) 3083, 2920, 2869, 1742, 1603, 1530, 1506, 1251,1215, 1152, 1102, 1082, 1022 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.23 (dd, $J$=1.2, 8.0 Hz, 1H), 7.90 (dd, $J$=1.1, 8.1 Hz, 1H), 7.46 (t, $J$=8.1 Hz, 1H),6.92 (dd, $J$=1.7, 7.4 Hz, 1H), 6.77 (s, 1H), 6.76 (dd, $J$=2.7, 8.5 Hz, 1H), 6.07 (ddt, $J$=5.2, 10.2, 20.9 Hz, 1H), 5.66- 5.47 (m, 2H), 5.43 (dq, $J$=1.5, 17.2 Hz, 1H), 5.29 (dq, $J$=1.4, 10.5 Hz, 1H), 4.60 (dt, $J$=1.5, 5.2 Hz, 2H), 4.03 (t, $J$=7.0 Hz, 2H), 2.71 (s, 3H), 2.55- 2.49 (m, 2H), 1.69 (dd, $J$=1.1, 5.9 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 167.4, 165.0, 152.3, 149.3, 147.3, 144.2, 134.2, 134.0, 133.1, 132.5, 128.0, 127.4, 126.7, 117.9, 114.3, 113.6, 108.4, 70.3, 69.6, 32.7, 18.2, 16.4; HRMS (TOF LCMS) calc'd for C$_{22}$H$_{24}$NO$_6$ [M+H] 398.1604, found 398.1595.

**Preparation of Compound 548**



226
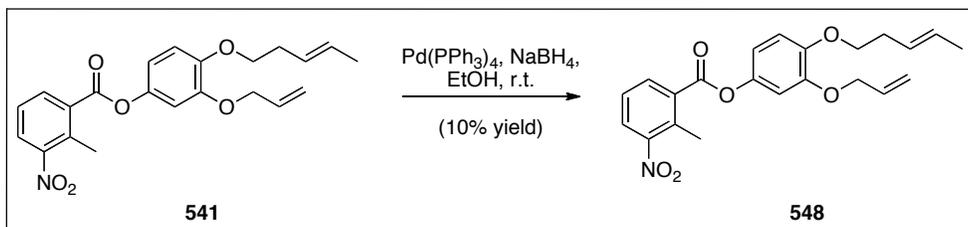
To a solution of **541** (128 mg, 0.33 mmol, 1 equiv.) in EtOH (3 mL) was added

Pd(PPh$_3$)$_4$ (11.4 mg, 0.01 mmol, 0.03 equiv.) and NaBH$_4$ (6.2 mg, 0.16 mmol, 0.5 equiv.)

at room temperature. The mixture was stirred overnight, filtered through Celite and

concentrated under reducing pressure. The residue was loaded onto silica and purified by

column chromatography (gradient elution, 20%- 33% EtOAc/ Hexanes) to yield **548**

(11.6 mg, 97%) as brown solid.

**Compound 548**: FTIR(NaCl/ thin film) 3465, 2924, 2855, 1742, 1605, 1536,

1504, 1354, 1276, 1217, 1141, 1022, 966 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.22 (dd,

*J*=2.4, 7.8 Hz, 1H), 7.91 (dd, *J*=2.5, 8.1 Hz, 1H), 7.47 (td, *J*=3.6, 7.9 Hz, 1H), 6.89(dd,

*J*=3.7, 8.6 Hz, 1H), 6.83- 6.79 (m, 1H), 6.72- 6.67 (m, 1H), 5.84- 5.80 (m, 1H), 5.69-

5,42 (m 2H), 4.12- 4.00 (m, 2H), 2.71 (d, *J*=1.5 Hz, 3H), 2.57- 2.44 (m, 2H), 1.74- 1.67

(m, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 165.1, 152.4, 146.9, 144.7, 144.3, 134.2, 134.0,

132.7, 128.7, 127.4, 126.8, 126.5, 112.6, 112.4, 108.7, 69.4, 32.7, 18.2, 16.5; HRMS

(TOF LCMS) calc'd for C$_{19}$H$_{18}$NO$_6$ [M-H] 356.1134, found 356.1141.

**Preparation of Compound 543**
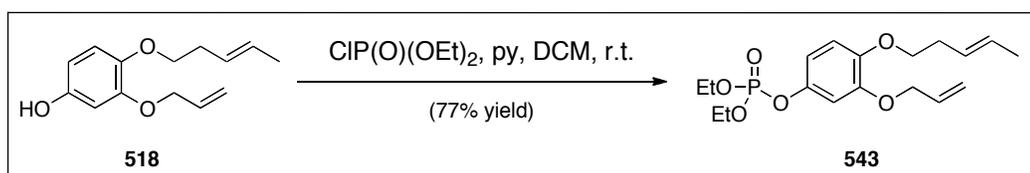


To a solution of **518** (295 mg, 1.26 mmol, 1 equiv.) in DCM (2 mL) was added

ClP(O)(OEt)$_2$ (0.36 mL, 2.52 mmol, 2 equiv.) and pyridine (0.2 mL, 2.52 mmol, 2equiv.)

at room temperature. The reaction was stirred overnight, filtered through Celite and

concentrated under reducing pressure. The residue was loaded onto silica and purified by

column chromatography (gradient elution, 33%- 50% EtOAc/ Hexanes) to yield **543** (140.3 mg, 77%) as brown oil.

**Compound 543**: FTIR(NaCl/ thin film) 2984, 2933, 1601, 1508, 1263, 1221, 1164, 1029, 981 cm$^{-1}$; $^{1}$H NMR (400 MHz, CDCl$_3$) δ 6.88- 6.68 (m, 3H), 6.05 (ddt, $J$=5.3, 10.5, 21.3 Hz, 1H), 5.63- 5.47 (m, 2H), 5.42 (dq, $J$=1.5, 17.4 Hz, 1H), 5.28 (dq, $J$=1.3, 10.4 Hz, 1H), 4.56 (dd, $J$=1.3, 5.2 Hz, 2H), 4.26- 4.14 (m, 4H), 3.97 (t, $J$=6.9 Hz, 2H), 2.53- 2.45 (m, 2H), 1.67 (dd, $J$=0.9, 6.0 Hz, 3H), 1.34 (t, $J$=7.0 Hz, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 149.3, 146.3, 144.8, 133.2, 127.9, 126.8, 117.8, 114.6, 112.0, 107.3, 70.1, 69.7, 64.7, 64.7, 32.8, 18.2, 16.3, 16.2; HRMS (TOF LCMS) calc'd for C$_{18}$H$_{28}$PO$_6$ [M+H] 371. 1624, found 371.1615.

**Preparation of Compound 550**
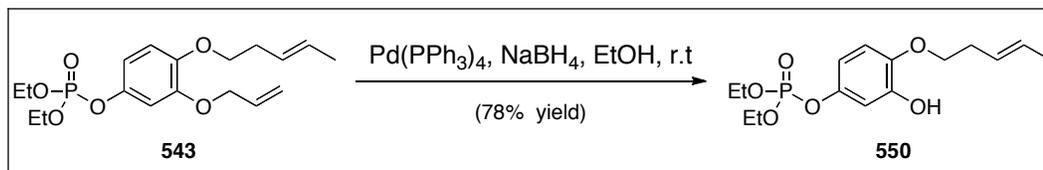


To a solution of **543** (80 mg, 0.22 mmol, 1 equiv.) in EtOH (2 mL) was added Pd(PPh$_3$)$_4$ (7.5 mg, 0.007 mmol, 0.03 equiv.) and NaBH$_4$ (4.1 mg, 0.11 mmol, 0.5 equiv.) at room temperature. The mixture was stirred overnight, filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 50%- 67% EtOAc/ Hexanes) to yield **550** (70 mg, 78.4%) as brown solid.

**Compound 550**: FTIR(NaCl/ thin film) 3399, 2985, 1602, 1507, 1257, 1238, 1031, 987 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 6.85- 6.66 (m, 3H), 5.86- 5.71 (m, 1H), 5.71- 5.39 (m, 2H), 4.29- 4.14 (m, 4H), 4.01 (t, $J$=7.5 Hz, 2H), 2.53- 2.39 (m, 2H), 1.69 (d, $J$=6.2 Hz, 3H), 1.35 (t, $J$=7.0 Hz, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 146.8, 145.0, 143.4, 128.6, 126.6, 112.7, 111.0, 107.4, 69.4, 64.7, 64.7, 32.7, 18.2, 16.3, 16.2; HRMS (TOF LCMS) calc'd for C$_{15}$H$_{22}$PO$_6$ [M-H] 329.1154, found 329.1165.

**Preparation of Compound 544**
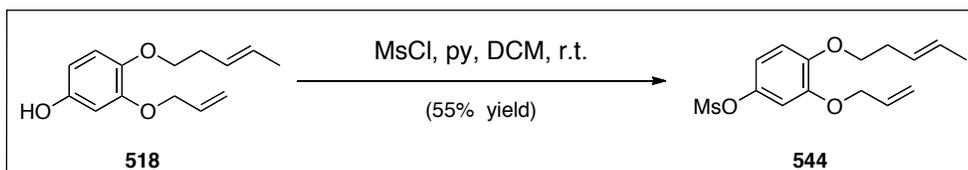


To a solution of **518** (69 mg, 0.29 mmol, 1 equiv.) in DCM (0.6 mL) was added MsCl (0.45 mL, 0.58 mmol, 2 equiv.) and pyridine (0.2 mL, 0.58 mmol, 2equiv.) at room temperature. The reaction was stirred overnight, filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%- 33% EtOAc/ Hexanes) to yield **544** (48.6 mg, 55%) as brown oil.

**Compound 544**: FTIR(NaCl/ thin film) 2938, 1601, 1508, 1422, 1366, 1262, 223, 1183, 1140, 1013, 968 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 6.93- 6.77 (m, 3H), 6.04 (ddt, $J$=5.0, 10.6, 22.0 Hz, 1H), 5.64- 5.46 (m, 2H), 5.42 (dq, $J$=1.8, 17.2 Hz, 1H), 5.29 (dq, $J$=1.0, 10.6 Hz, 1H), 4.58 (d, $J$=5.2 Hz, 2H), 4.00 (t, $J$=7.0 Hz, 2H), 3.10 (s, 3H), 2.54- 2.46 (m, 2H), 1.67 (d, $J$=6.0 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 149.3, 148.3,

142.9, 132.9, 128.2, 126.6, 118.2, 114.1, 113.9, 109.0, 70.3, 69.5, 37.2, 32.7, 18.2; HRMS (TOF LCMS) calc'd for $C_{15}H_{21}O_5S$ [M+H] 313.1110, found 313.1105.

**Preparation of Compound 551**
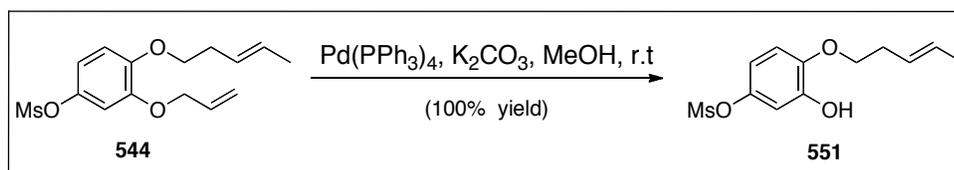


To a solution of **544** (37 mg, 0.12 mmol, 1 equiv.) in MeOH (1.2 mL) was added Pd(PPh$_3$)$_4$ (4 mg, 0.003 mmol, 0.03 equiv.) and K$_2$CO$_3$ (49 mg, 0.36 mmol, 3 equiv.) at room temperature. The mixture was stirred for 3 hours, filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 33%- 50% EtOAc/ Hexanes) to yield **551** (35 mg, 100%) as brown solid.

**Compound 551**:FTIR(NaCl/ thin film) 3466, 2938, 1604, 1505, 1366, 1277, 1230, 1180, 1129, 1020, 959, 832 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 6.94- 6.72 (m, 3H), 5.88- 5.75 (m, 1H), 5.70- 5.36 (m, 2H), 4.04 (t, *J*=7.6 Hz, 2H), 3.11 (s, 3H), 2.62- 2.36 (m, 2H), 1.69 (dd, *J*=1.3, 6.3 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 146.9, 145.2, 128.8, 126.3, 113.5, 112.3, 109.1, 69.3, 37.2, 32.6, 182.2; HRMS (TOF LCMS) calc'd for $C_{12}H_{17}O_5S$ [M+H] 273.0797, found 273.0795.

**Preparation of Compound 545**
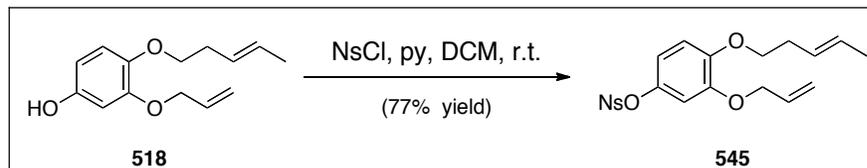


To a solution of **518** (5.5 g, 23.5 mmol, 1 equiv.) in DCM (46 mL) was added

NsCl (10.4 g, 47 mmol, 2 equiv.) and pyridine (9.5 mL, 117.5 mmol, 5 equiv.) at room

temperature. The reaction was stirred overnight, filtered through Celite and concentrated

under reducing pressure. The residue was loaded onto silica and purified by column

chromatography (gradient elution, 20%- 50% EtOAc/ Hexanes) to yield **545** (7.6 g, 79%)

as yellow oil.

**Compound 545**: FTIR(NaCl/ thin film) 3097, 2919, 1594, 1547, 1506, 1383,

1262, 1191, 1125, 852 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.97- 7.75 (m, 3H), 7.68-

7.54 (m, 1H), 6.81- 6.63 (m, 3H), 5.94 (ddt, *J*=5.2, 10.4, 21.0 Hz, 1H), 5.60- 5.40 (m,

2H), 5.33 (dq, *J*=1.3, 17.2 Hz, 1H), 5.21 (dq, *J*=1.3, 10.6 Hz, 1H), 4.46 (dt, *J*=1.3, 5.2 Hz,

2H), 3.93 (t, *J*=7.0 Hz, 2H), 2.49- 2.41 (m, 2H), 1.64 (dd, *J*=1.2, 6.1 Hz, 3H); $^{13}$C NMR

(100 MHz, CDCl$_3$) δ 149.1, 148.9, 148.4, 142.6, 135.5, 132.8, 132.5, 132.9, 128.4, 128.2,

126.5, 124.9, 118.1, 114.5, 113.5, 108.9, 70.1, 69.3, 32.7, 10.2; HRMS (TOF LCMS)

calc'd for C$_{20}$H$_{22}$NO$_7$S [M+H] 420.1117, found 420.1105.

**Preparation of Compound 552**
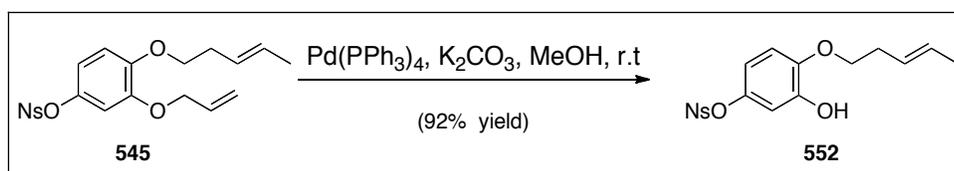
To a solution of **545** (1.16 g, 2.77 mmol, 1 equiv.) in MeOH (28 mL) was added

Pd(PPh$_3$)$_4$ (161 mg, 0.14 mmol, 0.05 equiv.) and K$_2$CO$_3$ (1.15 g, 8.31 mmol, 3 equiv.) at

room temperature. The mixture was stirred for 3 hours, filtered through Celite and

concentrated under reducing pressure. The residue was loaded onto silica and purified by

column chromatography (gradient elution, 50%- 67% EtOAc/ Hexanes) to yield **552**

(972.8 mg, 92.2%) as brown solid.

**Compound 552**: FTIR(NaCl/ thin film) 3501, 2939, 1604, 1546, 1503, 1443,

1276, 1230, 1192, 1124, 1109, 960, 832 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.90 (d, *J*=

8.5, 3H), 7.84- 7.78 (m, 2H), 7.70- 7.62 (m, 1H), 6.74 (d, *J*=2.5 Hz, 1H), 6.72 (s, 1H),

6.65 (dd, *J*=2.5, 8.9 Hz, 1H), 5.63- 5.39 (m, 2H), 3.99 (t, *J*=6.5 Hz, 2H), 2.57- 2.40 (m,

2H), 1.66 (dd, *J*=1.0, 6.3 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 148.9, 146.7, 145.4,

143.0, 135.7, 132.4, 132.2, 128.7, 128.4, 126.3, 125.0, 113.6, 112.1, 109.2, 69.2, 32.6,

18.2; HRMS (TOF LCMS) calc'd for C$_{17}$H$_{16}$NO$_7$S [M-H] 378.0648, found 378.0656.

**Preparation of Compound 556**
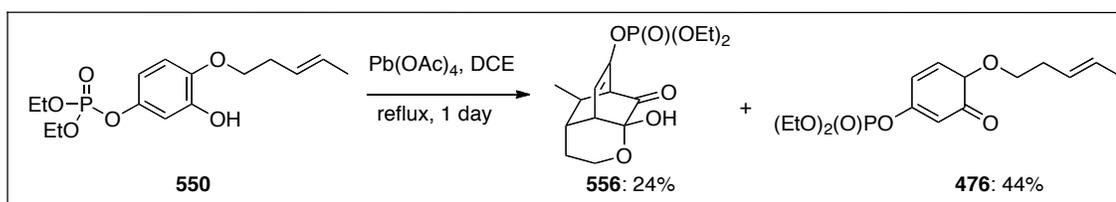


To a solution of **550** (89.3 mg, 0.22 mmol, 1 equiv.) in DCE (2.2 mL) was added

Pb(OAc)$_4$ (135 mg, 0.31 mmol, 1.4 equiv.). The solution was heated to reflux and stirred

overnight. The mixture was cooled to room temperature, filtered through Celite and

concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 50%- 67% EtOAc/ Hexanes) to yield **556** (20 mg, 24%) as yellow oil and **476** (35.5 mg, 44%) as yellow oiled.

**Compound 556**: FTIR(NaCl/ thin film) 3418, 2963, 2928, 1745, 1651, 1372, 1268, 1170, 1087, 1025, 972 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 5.90 (ddd, $J$= 1.6, 2.5, 7.4 Hz, 1H), 4.27- 4.09 (m, 4H), 3.90 (dd, $J$=5.3, 13.4 Hz, 1H), 3.61 (dt, $J$=3.2, 12.4 Hz, 1H), 3.08 (t, $J$=2.6 Hz, 1H), 2.70 (dd, $J$=3.3, 7.4 Hz, 1H), 2.14- 1.80 (m, 4H), 1.72- 1.58 (m, 1H), 1.41- 1.29 (m, 6H), 1.14 (d, $J$=6.9 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 207.8, 132.3, 111.3, 90.6, 65.1, 64.9, 61.5, 58.2, 42.2, 37.8, 34.8, 29.3, 20.2, 16.3, 16.2; HRMS (TOF LCMS) calc'd for C$_{15}$H$_{23}$PO$_7$ [M-H] 345.1103, found 345. 1113.

**Preparation of Compound 557**



551 → 557
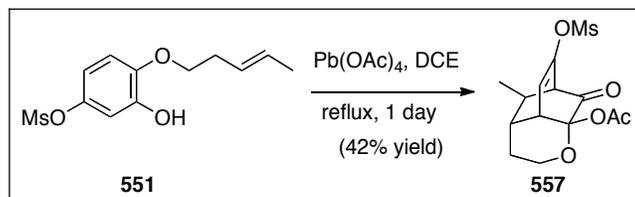
To a solution of **551** (158 mg, 0.58 mmol, 1 equiv.) in DCE (5.8 mL) was added Pb(OAc)$_4$ (362 mg, 0.81 mmol, 1.4 equiv.). The solution was heated to reflux and stirred overnight. The mixture was cooled to room temperature, filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 50%- 67% EtOAc/ Hexanes) to yield **557** (20 mg, 42.1%) as brown oil.

**Compound 557**: FTIR(NaCl/ thin film) 2961, 2936, 1743, 1650, 1368, 1183, 1120, 972, 817 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 5.99 (dd, $J$= 2.5, 7.6 Hz, 1H), 4.02 (dd, $J$=2.1, 12.5 Hz, 1H), 3.66 (td, $J$=3.6, 12.3 Hz, 1H), 3.54 (dd, $J$=3.4, 7.6 Hz, 1H), 3.16 (q, $J$=2.4 Hz, 1H), 3.12 (s, 3H), 2.13- 1.94 (m, 2H), 2.02 (s, 3H), 1.90- 1.84 (m, 1H), 1.67- 1.58 (m, 1H), 1.13 (d, $J$=6.9 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 200.4, 168.8, 146.7, 112.5, 93.5, 62.3, 57.9, 41.3, 38.2, 37.5, 35.9, 28.4, 21.6, 20.3; HRMS (TOF LCMS) calc'd for C$_{14}$H$_{19}$O$_7$S [M+H] 331.0852, found 331.0848.

**Preparation of Compound 558, 559**
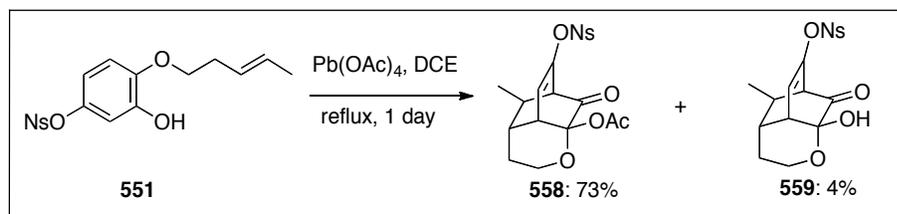


To a solution of **551** (972.8 mg, 2.56 mmol, 1 equiv.) in DCE (25 mL) was addedPb(OAc)$_4$ (1.59 , 3.58 mmol, 1.4 equiv.). The solution was heated to reflux and stirred overnight. The mixture was cooled to room temperature, filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 50%- 67% EtOAc/ Hexanes) to yield **558** (814.5 mg, 72.7%) as brown oil and **559** (45.2 mg, 4.2%) as yellow solid.

**Compound 558**: FTIR(NaCl/ thin film) 3418, 2959, 2926, 1743, 1545, 1385, 1251, 1193, 1110, 1022, 820 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.16- 8.02 (m, 1H), 7.91- 7.72 (m, 3H), 6.04 (dd, $J$=2.5, 7.6 Hz), 4.03 (ddd, $J$= 2.3, 6.6, 13.5 Hz, 1H), 3.76 (dd, $J$=2.2, 7.6 Hz, 1H), 3.62 (td, $J$=2.6, 12.2 Hz, 1H), 3.16 (t, $J$= 2.5 Hz, 1H), 2.07- 2.02

(m, 2H), 2.00 (s, 3H), 1.90- 1.5 (m, 1H), 1.67- 1.59 (m, 1H), 1.13 (d, $J$=6.9 Hz, 3H); $^{13}$C

NMR (100 MHz, CDCl$_3$) δ 200.0, 168.6, 146.0, 135.8, 132.4, 132.2, 128.5, 125.3, 117.0,

116.0, 93.4, 62.5, 57.4, 40.5, 37.3, 35.9, 28.4, 21.8, 20.2; HRMS (TOF LCMS) calc'd for

C$_{19}$H$_{19}$NO$_9$SNa [M+Na] 460.0678, found 460.0677.

**Compound 559**: FTIR(NaCl/ thin film) 3383, 2959, 2930, 1741, 1718, 1220,

1169, 1154, 1088, 1057 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 4.01 (dd, $J$= 5.1, 13.8 Hz,

1H), 3.68 (td, $J$=3.2, 12.0 Hz, 1H), 3.63- 3.63 (m, 1H), 3.51 (td, $J$=2.9, 12.5 Hz, 1H), 3.18

(t, $J$=3.5 Hz, 1H), 2.68 (dd, $J$=3.2, 7.4 Hz, 1H), 2.13- 2.04 (m, 1H), 1.95- 1.78 (m, 2H),

1.64- 1.56 (m, 1H), 1.12 (d, $J$=6.9 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 206.6, 148.5,

144.6, 135.9, 133.3, 132.4, 127.7, 125.1, 119.7, 90.2, 61.5, 57.8, 42.8, 37.1, 34.9, 28.8,

20.2; HRMS (TOF LCMS) calc'd for C$_{17}$H$_{21}$N$_2$O$_8$S [M+NH4] 413.1019, found

413.1025.


**Preparation of Compound 537**
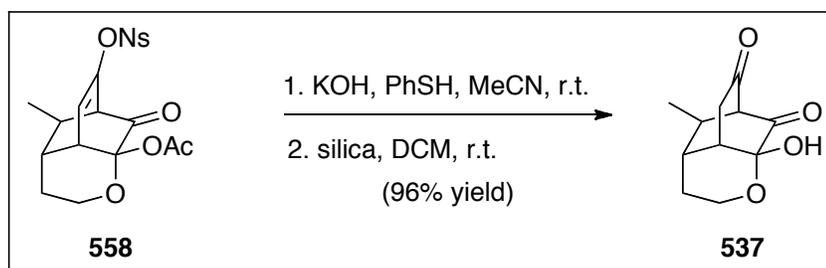


To a solution of **558** (470 mg, 1.08 mmol, 1 equiv.) in MeCN (5.4 mL) was added

PhSH (0.88 mL, 8.64 mmol, 8 equiv.) and KOH (120 mg, 2.16 mmol, 2 equiv.) at room

temperature. The mixture was stirred for 30 minutes and quenched by aqueous HCl (2

mL, 1N). The aqueous layer was washed by EtOAc (2 x 6mL), and the combined organic

layers were washed with brine (12 mL), dried over $Na_2SO_4$, and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%- 50% EtOAc/ Hexanes) to remove PhSH.

To the product mixture in DCM (20 mL) was added silica (2 g) and stirred at room temperature for 2 days. The solution was filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 33%- 67% EtOAc/ Hexanes) to yield **537** (370.5 mg, 96%) as brown oil.

**Compound 537**: FTIR(NaCl/ thin film) 3389, 2961, 1744, 1478, 1193, 1112, 1089, 822 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.01 (d, $J$= 7.7 Hz, 1H), 7.87- 7.80 (m, 2H), 7.76- 7.68 (m, 1H), 6.03 (dd, $J$=2.5, 7.6 Hz, 1H), 3.85 (dd, $J$=5.5, 12.5 Hz, 1H), 3.68- 3.55 (m, 1H), 3.22 (d, $J$=2.8 Hz, 1H), 2.85 (dd, $J$=3.6, 20.5 Hz, 1H), 2.40- 2.28 (m, 2H), 2.27- 2.17 (m, 1H), 2.14- 1.99 (m, 2H), 1.64- 1.54 (m, 1H), 1.11 (d, $J$=7.2 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 206.7, 203.6, 93.5, 71.0, 61.9, 39.7, 39.1, 37.3, 33.8, 30.8, 21.1; HRMS (TOF LCMS) calc'd for $C_{22}H_{28}NaO_8$ [M+M+Na] 443.1682, found 443.1687.

**Preparation of Compound 561**
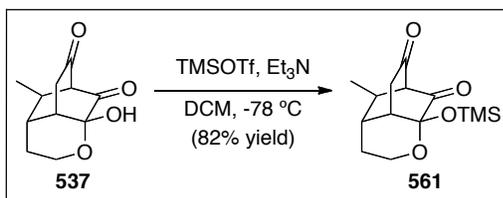
To a solution of **537** (89 mg, 0.42 mmol, 1 equiv.) in DCM (4.2 mL) was added TMSOTf (0.17 mL, 0.92 mmol, 2.2 equiv.) and Et$_3$N (0.14 mL, 0.92 mmol, 2.2 equiv.) at -78 ºC. The mixture was stirred for 5 min and quenched by saturated aqueous NaHCO$_3$ (0.5 mL). The aqueous layer was washed by DCM (2 x 5mL) and the combined organic layers were washed with brine (10 mL), dried over Na$_2$SO$_4$, and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%- 33% EtOAc/ Hexanes) to yield **561** (98.2 mg, 82.2%) as yellow oil.

**Compound 561**: FTIR(NaCl/ thin film) 2958, 1755, 1728, 1458, 1400, 1354, 1315, 1250, 1092, 939, 847 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 3.97 (dd, *J*= 4.8, 14.1 Hz, 1H), 3.63 (td, *J*=3.0, 12.5 Hz, 1H), 3.16 (d, *J*=3.0 Hz, 1H), 2.83 (dd, *J*=2.9, 19.7 Hz, 1H), 2.26 (dd, *J*=3.2, 19.6 Hz, 1H), 2.18- 2.11 (m, 2H), 2.06- 1.95 (m, 2H), 1.55- 1.49 (m, 1H), 1.08 (d, *J*=7.2 Hz, 3H), 0.15 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 205.1, 204.8, 95.5, 71.9, 61.9, 42.2, 39.8, 37.4, 34.3, 30.9, 21.3, 1.8; HRMS (TOF LCMS) calc'd for C$_{14}$H$_{22}$NaO$_4$Si [M+Na] 305.1185, found 305.1186.

**Preparation of Compound 563**
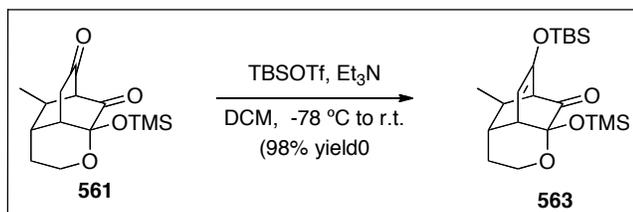


To a solution of **561** (60 mg, 0.21 mmol, 1 equiv.) in DCM (2.1 mL) was added TBSOTf (0.24 mL, 1.1 mmol, 5 equiv.) and Et$_3$N (0.16 mL, 1.1mmol, 5 equiv.) at -78 ºC.

The mixture was warmed to room temperature and stirred overnight. The reaction was quenched by saturated aqueous NaHCO$_3$ (0.5 mL). The aqueous layer was washed by DCM (2 x 2 mL), and the combined organic layers were washed with brine (4 mL), dried over Na$_2$SO$_4$, and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 5%- 10% EtOAc/ Hexanes) to yield **563** (77.8 mg, 92.3%) as yellow oil.

**Compound 563**: FTIR(NaCl/ thin film) 2957, 2929, 1749, 1725, 1643, 1250, 1193, 1153, 1091, 844 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 5.10 (dd, *J*= 2.2, 7.3 Hz, 1H), 3.82 (dd, *J*=6.1, 12.2 Hz, 1H), 3.55 (td, *J*=2.2, 12.7 Hz, 1H), 2.73 (t, *J*=2.3 Hz, 1H), 2.39 (dd, *J*=3.2, 7.3 Hz, 1H), 2.01- 1.92 (m, 1H), 1.91- 1.80 (m, 1H), 1.75- 1.70 (m, 1H), 1.53- 1.49 (m, 1H), 1.07 (d, *J*=7.0 Hz, 3H), 0.9 (s, 9H), 0.17 (s, 6H), 0.14 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 208.2, 149.7, 103.9, 93.2, 61.4, 44.8, 38.5, 34.9, 29.8, 25.7, 20.3, 18.1, 1.9, -4.4, -4.6; HRMS (TOF LCMS) calc'd for C$_{20}$H$_{37}$O$_4$Si$_2$ [M+H] 397.2230, found 397.2223.

**Preparation of Compound 564**
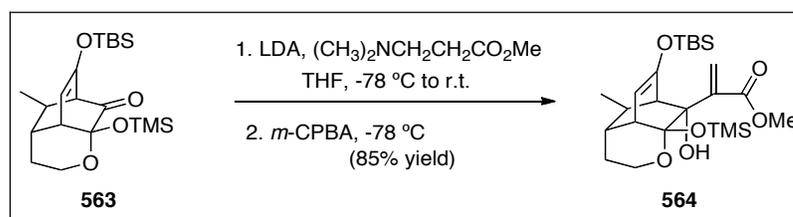


To a solution of diisopropylamine (0.14 mL, 1.03 mmol, 5.25 equiv.) in THF (1 mL) at −20 ºC was added *n*-BuLi (0.43 mL, 0.84 mmol, 4.2 equiv., 1.9 M hexanes solution) dropwise over 5 minutes.  The resultant mixture was stirred at −20 ºC for 5

minutes, and then cooled to –78 ºC for 30 minutes.  To this mixture was added methyl-3--
(dimethylamino)propionate (0.1 mL, 0.70 mmol, 3.5 equiv.) dropwise over five minutes.
The reaction mixture was stirred at –78 ºC for thirty minutes, 0 ºC for 15 min, and room
temperature for 15 min, and then cooled to –78 ºC.

A solution of **563** (77.8 mg, 0.2 mmol, 1equiv.) in THF (2 mL) was added enolate
dropwise over 1 min at –78 °C.  The solution was slowly warmed to room temperature
and stirred for  1 hour.  The reaction was quenched with 1M AcOH in THF (5mL) and
allowed to warm to room temperature.  At which point the reaction mixture was treated
with $H_2O$ (2 mL) and EtOAc (2 mL).  The aqueous layer was extracted with EtOAc (2 x
5mL), and the combined organic layers were washed with brine (10 mL), dried over
$Na_2SO_4$, and concentrated under reducing pressure.

To the solution of this residue solution in DCM (8.5 mL) was added *m*-CPBA
(170 mg, 0.70 mmol, 3.5 equiv.) at -78 ºC and stirred for 20 minutes. To the solution was
added basic $Al_2O_3$ (200 mg) and stirred overnight at room temperature. The mixture was
filtered through Celite and concentrated under reducing pressure. The residue was loaded
onto silica and purified by column chromatography (gradient elution, 5%- 10% EtOAc/
Hexanes) to yield **564** (80.2, mg, 84.7%) as colorless oil.

**Compound 564**: FTIR(NaCl/ thin film) 3451, 2955, 1705, 1652, 1322, 1258,
1180, 1023, 938, 911, 842 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 6.01 (s, 1H), 5.77 (s, 1H),
5.44- 5.31 (m, 1H), 4.74 (dd, *J*= 2.4, 7.1 Hz, 1H), 4.64 (td, *J*=4.4, 12.1 Hz, 1H), 3.85 (dd,
*J*=6.7, 11.4 Hz, 1H), 3.74 (s, 3H), 2.44 (t, *J*=2.3 Hz, 1H), 2.35 (ddd, *J*=2.3, 4.4, 9.2 Hz,
1H), 2.12 (dd, *J*=2.8, 7.1 Hz, 1H), 1.83- 1.73 (m, 1H), 1.67- 1.59 (m, 1H), 1.43- 1.37 (m,
1H), 0.95 (d, *J*=7.0 Hz, 3H), 0.93 (s, 9H), 0.18 (s, 3H), 0.14 (s, 3H), 0.06 (s, 9H); $^{13}$C

NMR (100 MHz, CDCl$_3$) δ 170.7, 153.0, 144.1, 119.7, 1006, 100.1, 82.3, 63.1, 52.9, 51.8, 45.9, 40.9, 29.7, 28.5, 25.7, 21.3, 18.0, 1.8, -4.8; HRMS (TOF LCMS) calc'd for C$_{24}$H$_{41}$O$_6$Si$_2$ [M-H] 481.2442, found 481.2455.

**Preparation of Compound 531**
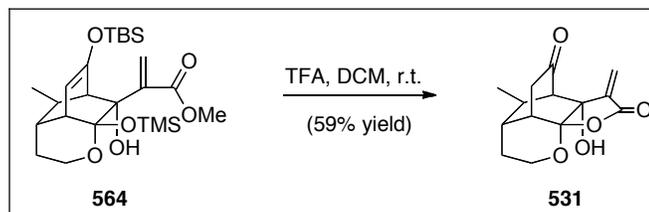


To a solution of **564** (80 mg, 0.17 mmol, 1 equiv.) in THF (1.6 mL) was added TBAF (1.67 mL, 1.7 mmol, 10 equiv.) and AcOH (95 μL, 1.7 mmol, 10 equiv.) at room temperature. The mixture was stirred overnight. The reaction was quenched by H$_2$O (2 mL). The aqueous layer was extracted with EtOAc (2 x 5mL). The combined organic layers were washed with brine (10 mL), dried over Na$_2$SO$_4$, and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%- 50% EtOAc/ Hexanes) to yield **531** (26 mg, 59%) as yellow solid.

**Compound 531**: FTIR(NaCl/ thin film) 3431, 2924, 1780, 1733, 1289, 1264, 1175, 1076, 1003 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 6.05 (s, 1H), 5.98 (s, 1H), 4.49 (ddd, $J$= 5.8, 9.1, 14.5 Hz, 1H), 4.23 (ddt, $J$=5.2, 11.5, 17.0 Hz, 1H), 3.42- 3.36 (m, 1H), 2.71 (d, $J$=2.2 Hz, 1H), 2.43- 2.37 (m, 2H), 2.20 (dd, $J$=3.4, 11.3 Hz, 1H), 2.14- 2.02 (m, 1H), 1.85- 1.73 (m, 2H), 1.31- 1.20 (m, 1H), 1.02 (d, $J$=7.2 Hz, 3H); $^{13}$C NMR (100

MHz, CDCl$_3$) δ 208.6, 166.0, 135.3, 130.1, 104.7, 74.6, 64.1, 61.8, 38.6, 38.3, 37.4, 31.0, 29.9, 20.8; HRMS (TOF LCMS) calc'd for C$_{14}$H$_{15}$O$_5$ [M-H] 263.0920, found 263.0922.

**Preparation of Compound 513**
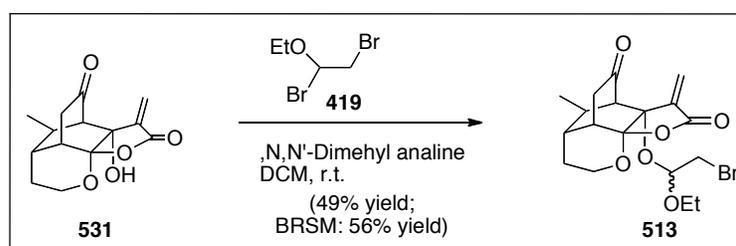


To a solution of **531** (76 mg, 0.29 mmol, 1 equiv.) in DCM (3 mL) was added **519** (0.37 mL, 2.9 mmol, 10 equiv.) and N,N'-Dimthyl analine (0.39 mL, 2.9 mmol, 20 equiv.) at room temperature. The mixture was stirred for 2 days and concentrated by reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%- 50% EtOAc/ Hexanes) to yield **513** (58.4 mg, 49%) as brown oil and starting material **531** (10 mg).

**Compound 513 (diastereomer)**: FTIR(NaCl/ thin film) 2972, 2929, 1777, 1732, 1286, 1189, 1106, 1071, 1039, 1066, 977 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 6.69 (s, 1H), 6.62 (s, 1H), 6.00 (s, 1H), 5.85 (s, 1H), 4.85 (t, *J*=4.3, 1H), 4.71 (dd, *J*=4.4, 16, 1H), 4.62 (dd, *J*= 6.1, 12.3 Hz, 1H), 4.53 (dd, *J*=6.1, 12.3 Hz, 1H), 4.14 (dd, *J*=6.6, 12.1 Hz, 2H), 3.56- 3.31 (m, 8H), 2.87 (d, *J*=2.4, 1H), 2.76 (*J*=2.4, 1H), 2.62- 2.48 (m, 2H), 2.26- 1.96 (m, 8H), 1.85- 1.78 (m, 2H), 1.72- 1.61 (m, 2H), 1.19  (t, *J*=7.1 Hz, 3H), 1.12 (t, *J*=7.0 Hz, 3H), 1.02 (d, *J*=1.7 Hz, 3H), 1.01 (d, *J*=1.7Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 208.7, 208.6, 165.8, 135.8, 135.4, 132.5, 130.3, 106.1, 97.3, 80.1, 79.7, 62.0,

61.8, 61.5, 61.4, 40.8, 40.4, 38.8, 38.3, 38.6, 38.5, 31.9, 31.8, 29.7, 29.6, 28.7, 28.2, 20.9, 25.2, 15.0; HRMS (TOF LCMS) calc'd for $C_{18}H_{23}NaBrO_6$ [M+Na] 437.0576, found 437.0568.

**Preparation of Compound 512**
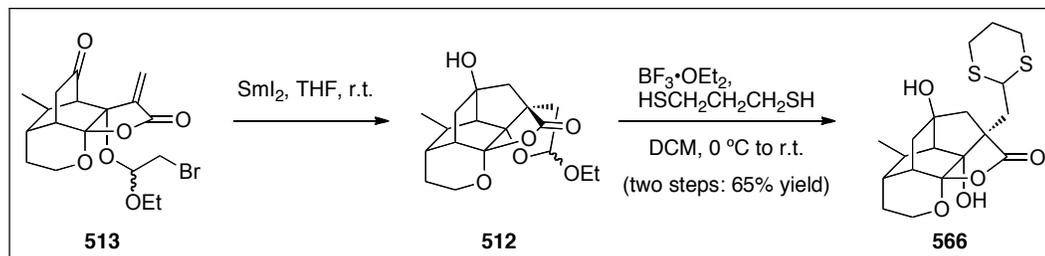


To a solution of $I_2$ (216.2 mg, 0.85 mmol, 1 equiv.) in THF (12 mL) was added samarium (186 mg, 0.94, 1.1 equiv.) at room temperature. The mixture was heated to reflux for 3 hours then cooled to room temperature. 0.07 M $SmI_2$ was ready for reaction.

To a solution of **513** (16 mg, 0.039 mmol, 1 equiv.) in THF (0.4 mL) was added $SmI_2$ solution (2.7 mL, 0.20 mmol, 5 equiv.) at room temperature. The mixture was stirred for 1 hour then quenched by saturated aqueous $NH_4Cl$ (0.5 mL) and HCl (0.1 mL, 1 N). At which point the reaction mixture was treated with $H_2O$ (2 mL) and EtOAc (2 mL). The aqueous layer was extracted with EtOAc (3 x 5mL), and the combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$, and concentrated under reducing pressure to yield crude **512**.

To a solution of **512** (half amount of last step rude product) in DCM (0.2 mL) was added BF₃•OEt₂ (6 μL, 0.048   mmol, 2.5 equiv.) and propane-1,3-dithiol (5 μL, 0.048 mmol, 2.5 equiv.) at 0 ºC. The mixture was warmed to room temperature and stirred

overnight. The reaction was quenched by $H_2O$ (10 µL). At which point the reaction mixture was treated with $H_2O$ (1 mL) and EtOAc (1 mL). The aqueous layer was extracted with EtOAc (3 x 1mL), and the combined organic layers were washed with brine (3 mL), dried over $Na_2SO_4$, and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 25%-50% EtOAc/ Hexanes) to yield **566** (5 mg, 65%) as yellow oil.

**Compound 512**: FTIR(NaCl/ thin film) 3457, 2918, 1778, 1726, 1480, 1462, 1451, 1358, 1327, 1299, 1273, 1174, 1109, 1080, 1027, 980 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 5.47 (dd, $J$=2.2, 5.7 Hz, 1H) 4.20 (td, $J$=3.1, 12.5 Hz, 1H), 3.99 (dd, $J$=6.0, 12.0 Hz, 1H), 3.78 (ddd, $J$=7.2, 9.8, 14.3 Hz, 1H), 3.53 (ddd, $J$=7.0, 9.8, 14.1 Hz, 1H), 2.72 (dd, $J$=6.8, 14.2 Hz, 1H), 2.32 (d, $J$=3.3 Hz, 1H), 2.30 (s, 1H), 2.19 (dd, $J$=2.3, 13.8 Hz, 1H), 2.13 (dd, $J$=2.2, 14.2 Hz, 1H), 2.10-2.07 (m, 1H), 2.01- 1.90 (m, 3H), 1.81 (q, $J$=3.4 Hz, 1H), 1.75- 1.65 (m, 2H), 1.48 (dt, $J$=3.2, 16.5 Hz, 1H), 1.28 (d, $J$=7.5 Hz, 3H), 1.22 (t, $J$=7.2 Hz, 3H) ;$^{13}$C NMR (100 MHz, CDCl$_3$) δ 177.7, 109.5, 106.9, 95.9, 77.9, 64.0, 63.0, 57.0, 53.9, 52.1, 44.3, 39.4, 38.4, 37.8, 30.7, 27.8, 21.0, 15.4; HRMS (TOF LCMS) calc'd for $C_{16}H_{19}O_5$ [M-C2H5O] 291.1233, found 291.1236.

**Preparation of Compound 586**



243
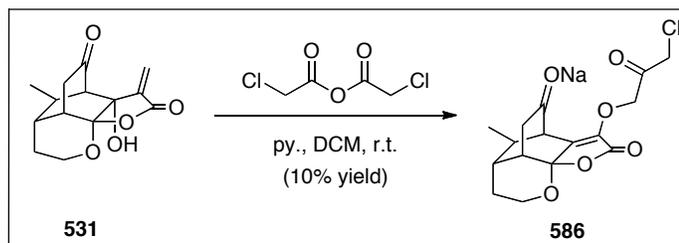
To a solution of **531** (16 mg, 0.06 mmol, 1 equiv.) in DCM (0.6 mL) was added 2-chloroacetic anhydride (20.5 mg, 0.12, 2 equiv.) and pyridine (20 μL, 0.02 mmol, 0.3 equiv.) at room temperature. The mixture was stirred overnight and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 25%- 67% EtOAc/ Hexanes) to yield **586** (2 mg, 10%) as yellow oil.

**Compound 586**: FTIR(NaCl/ thin film) 2960, 2361, 2339, 1743, 1546, 1439, 1387, 1194, 1088, 1023 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 4.89 (dd, $J$=14.0, 22.5 Hz, 1H) 4.20 (s, 2H), 4.14- 4.10 (m, 1H), 4.09 (d, $J$=3.2 Hz, 1H), 3.61 (d, $J$=1.8, Hz, 1H), 2.75 (q, $J$=2.2 Hz, 1H), 2.44- 2.36 (m, 1H), 2.32 (d, $J$=2.2 Hz, 1H), 2.25 (d, $J$=3.5 Hz, 1H), 2.30 (s, 1H), 1.99- 1.91 (m, 2H), 1.72- 1.65 (m, 1H), 1.01 (d, $J$=8.2 Hz, 3H),; $^{13}$C NMR (100 MHz, CDCl$_3$) δ 203.1, 171.3, 167.0, 158.9, 123.6, 105.8, 61.7, 57.6, 56.3, 40.5, 39.0, 38.0, 36.9, 32.5, 29.4, 19.4; HRMS (TOF LCMS) calc'd for C$_{16}$H$_{19}$O$_5$ [M+Na] 363.0611, found 363.0611.

**Preparation of Compound 580**
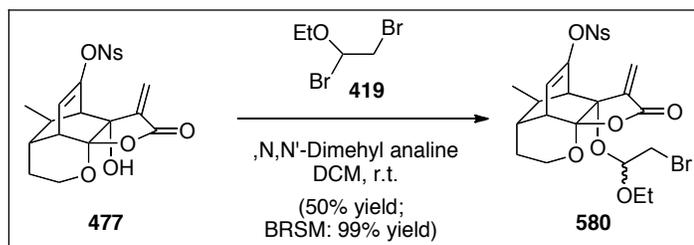


To a solution of **477** (100 mg, 0.22 mmol, 1 equiv.) in DCM (3 mL) was added **419** (0.32 mL, 4.40 mmol, 20 equiv.) and N,N'-Dimthyl analine (0.30 mL, 4.40 mmol, 20

equiv.) at room temperature. The mixture was stirred for 2 days and concentrated by reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%- 50% EtOAc/ Hexanes) to yield **580** (60 mg, 50%) as brown oil and starting material **477** (50 mg).

**Compound 580 (diastereomer)**: FTIR(NaCl/ thin film) 2974, 2928, 1775, 1651, 1547, 1390, 1367, 1284, 1195, 1123, 1075,905, 824 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.04 (dd, $J$=4.6, 7.7 Hz, 2H), 7.91- 7.82 (m, 4H), 7.79 (td, $J$=1.5, 7.3 Hz, 2H), 6.24 (s, 1H), 6.19 (s, 1H), 5.79 (s, 1H), 5.82 (s, 1H), 5.75 (ddd, $J$=2.6, 5.8, 7.9 Hz, 2H), 4.73 (ddd, $J$=4.0, 5.9, 8.0 Hz, 2H),  4.59 (td, $J$=3.6, 12.9 Hz, 1H), 4.47 (td, $J$=3.8, 12.1 Hz, 1H), 4.00 (q, $J$=5.6 Hz, 2H),  3.54- 3.32 (m, 8H),  3.00 (t, $J$=1.9 Hz, 1H), 2.84 (t, $J$=2.1 Hz, 1H), 2.63 (ddd, $J$=2.4, 7.7, 9.3 Hz, 2H), 2.46- 2.37 (m, 2H), 2.01-1.85 (m, 2H), 1.75- 1.58 (m, 4H), 1.22 (t, $J$=7.0 Hz, 3H), 1.07 (t, $J$=6.9 Hz, 3H), 0.98 (d, $J$=7.0 Hz, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 166.3, 149.6, 149.5, 148.5, 135.9, 135.2, 132.9, 131.7, 129.2, 129.0, 126.7, 125.3, 110.6, 110.5, 105.4, 104.8, 97.9, 97.0, 82.4, 81.9, 63.9, 63.6, 62.5, 61.2, 52.4, 52.3, 44.1, 43.6, 40.0, 39.7, 32.3, 32.0, 29.9, 29.6, 28.4, 20.8, 15.2, 15.0 ; HRMS (TOF LCMS) calc'd for C$_{24}$H$_{26}$NBrO$_{10}$NaS [M+Na] 622.0359, found 622.0358.

**Preparation of Compound 582**



580      PhSH, KOH, MeCN, r.t.      (100% yield)      582
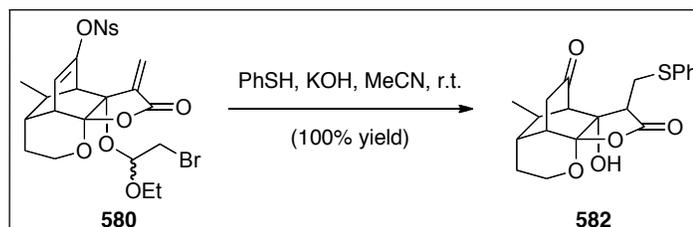
To a solution of **580** (31 mg, 0.052 mmol, 1 equiv.) in MeCN (0.7 mL) was added

PhSH (71 μL, 0.52 mmol, 10 equiv.) and KOH (7.5 mg, 0.10 mmol, 2 equiv.) at room

temperature. The mixture was stirred for 20 minutes then added H2O ( 1mL). The

aqueous layer was extracted with EtOAc (3 x 1mL), and the combined organic layers

were washed with brine (3 mL), dried over $Na_2SO_4$, and concentrated under reducing

pressure. The residue was loaded onto silica and purified by column chromatography

(gradient elution, 25%- 50% EtOAc/ Hexanes) to yield **582** (22 mg, 100%) as colorless

solid.

**Compound 582**: FTIR(NaCl/ thin film) 3456, 2958, 2927, 1778, 1728, 1200,

1057, 994, 740 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.48- 7.27 (m, 5H), 4.98- 4.75 (m,

1H), 4.45- 4.35 (m, 1H), 4.30- 4.15 (m, 1H), 3.38 (s, 1H), 3.36 (d, *J*=2.1 Hz, 1H), 2.87 (d,

*J*=2.2 Hz, 1H), 2.57- 2.51 (m, 2H), 2.41- 2.30 (m, 3H), 2.14- 2.01 (m, 1H),.1.92- 1.71 (m,

2H), 1.01 (d, *J*=7.2 Hz, 3H),;$^{13}$C NMR (100 MHz, CDCl$_3$) δ 209.6, 173.1, 134.6, 131.1,

129.4, 127.4, 105.4, 76.2, 63.8, 63.6, 50.0, 38.6, 36.7, 36.5, 33.0, 31.1, 29.8, 20.7; HRMS

(TOF LCMS) calc'd for $C_{20}H_{23}O_5S$ [M+H] 375.1266, found 375.1268.

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# Appendix II: Spectra Relevant to Chapter 4
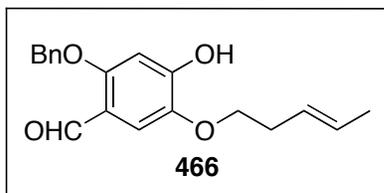
Figure A.4.1 $^1$H NMR (400MHz, CDCl$_3$) of compound 466
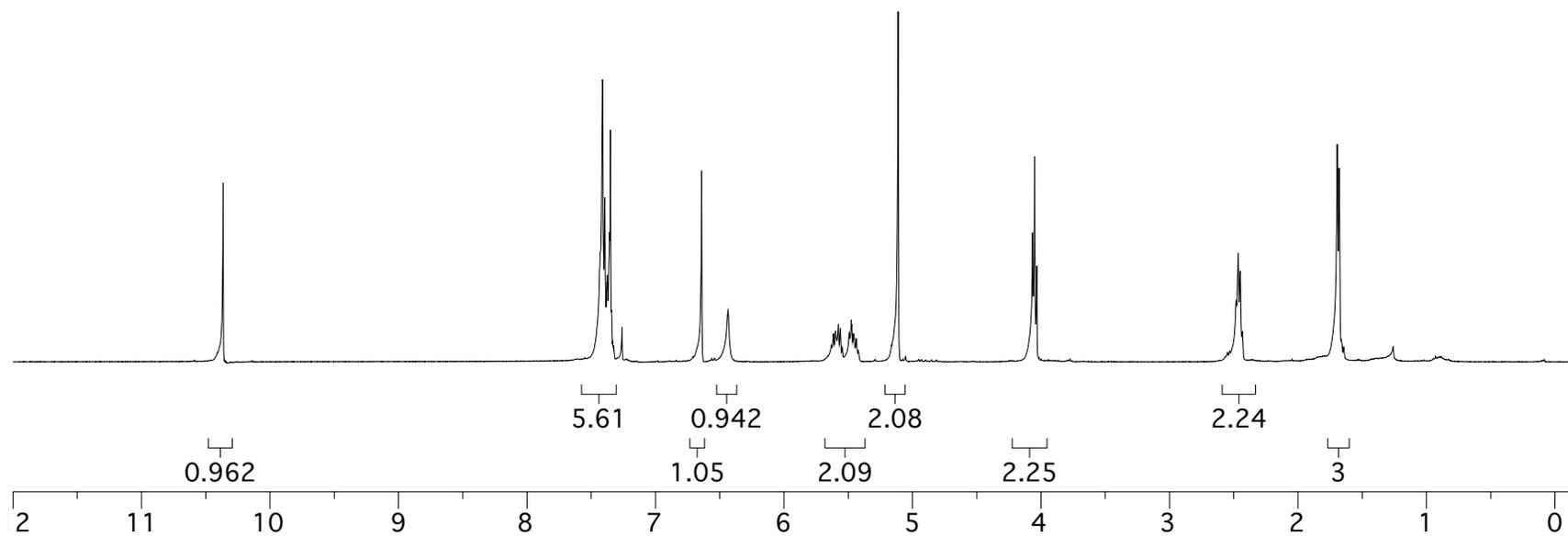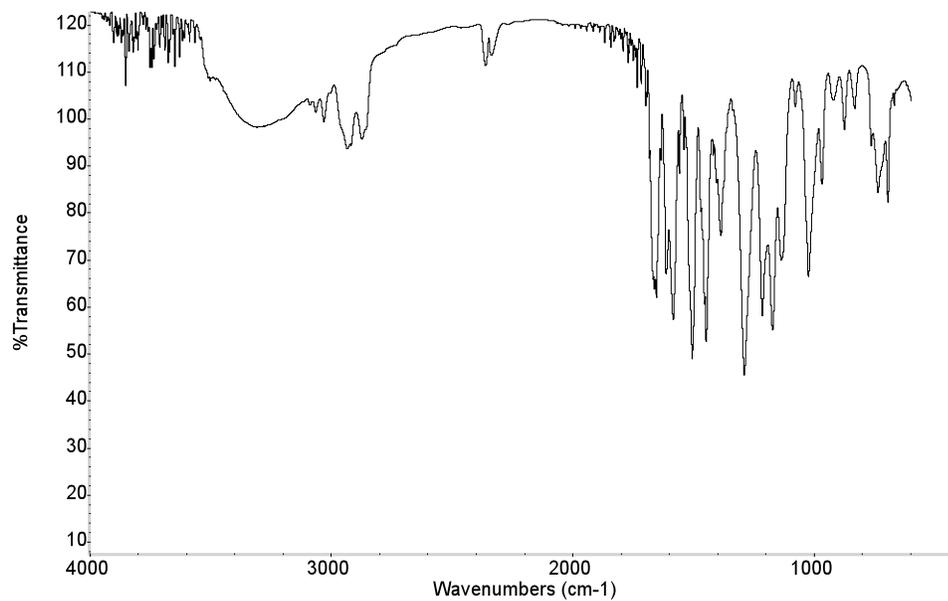
Figure A.4.2 Infrared Spectrum (thin film/NaCl) of compound **466**.
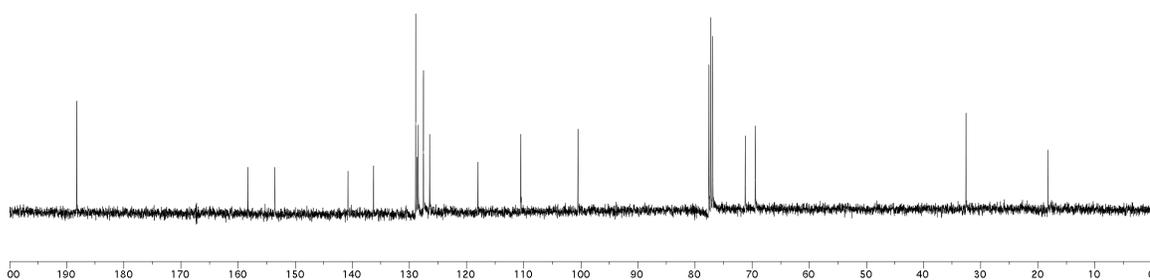


Figure A.4.3 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **466**.
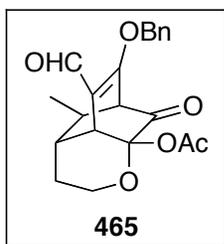
**Figure A.4.4** $^1$H NMR (400MHz, CDCl$_3$) of compound 465
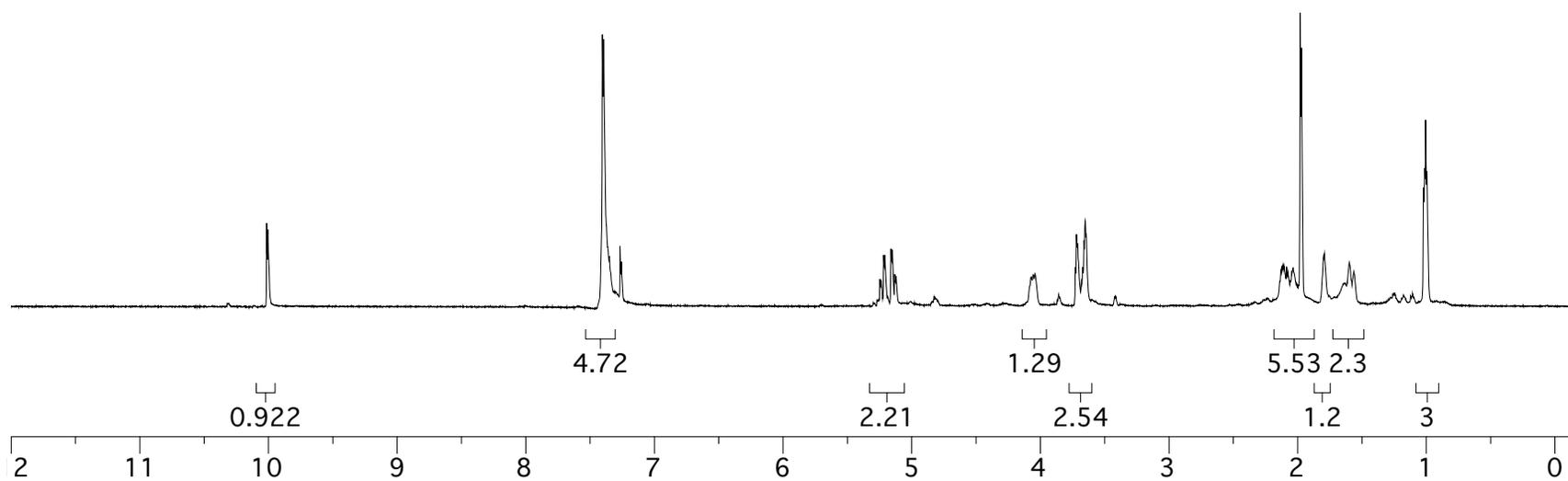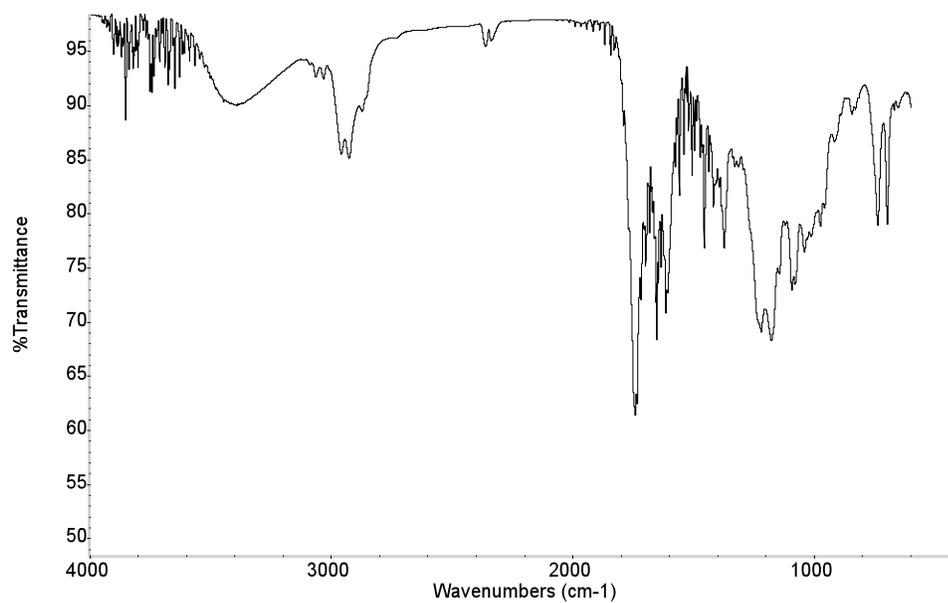
Figure A.4.5 Infrared Spectrum (thin film/NaCl) of compound **465**.
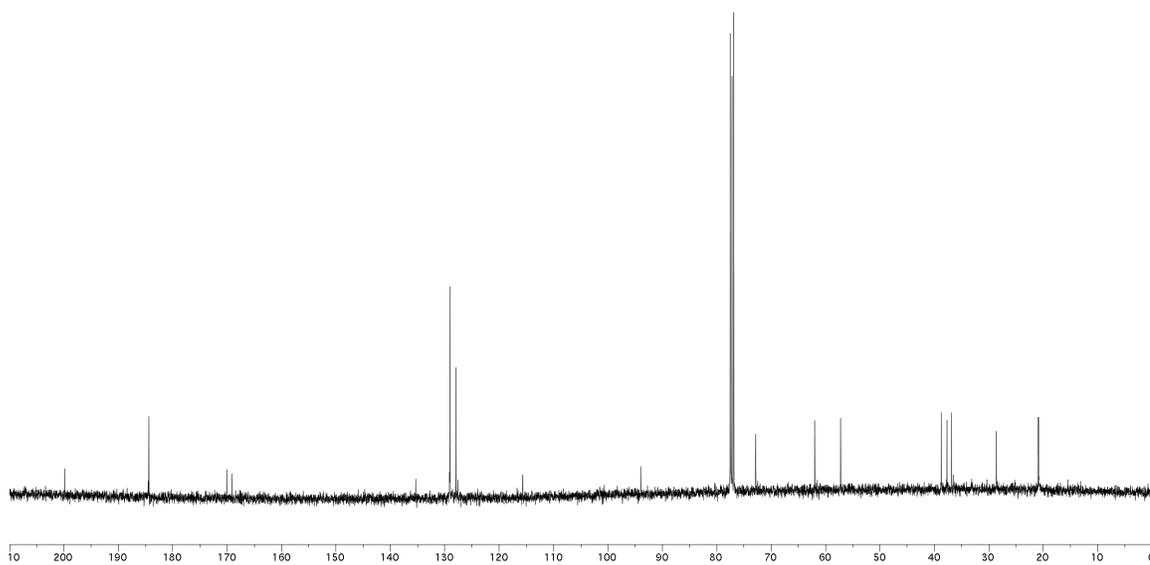


Figure A.4.6 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **465**.
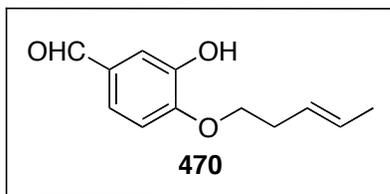
Figure A.4.7 $^1$H NMR (400MHz, CDCl$_3$) of compound 470
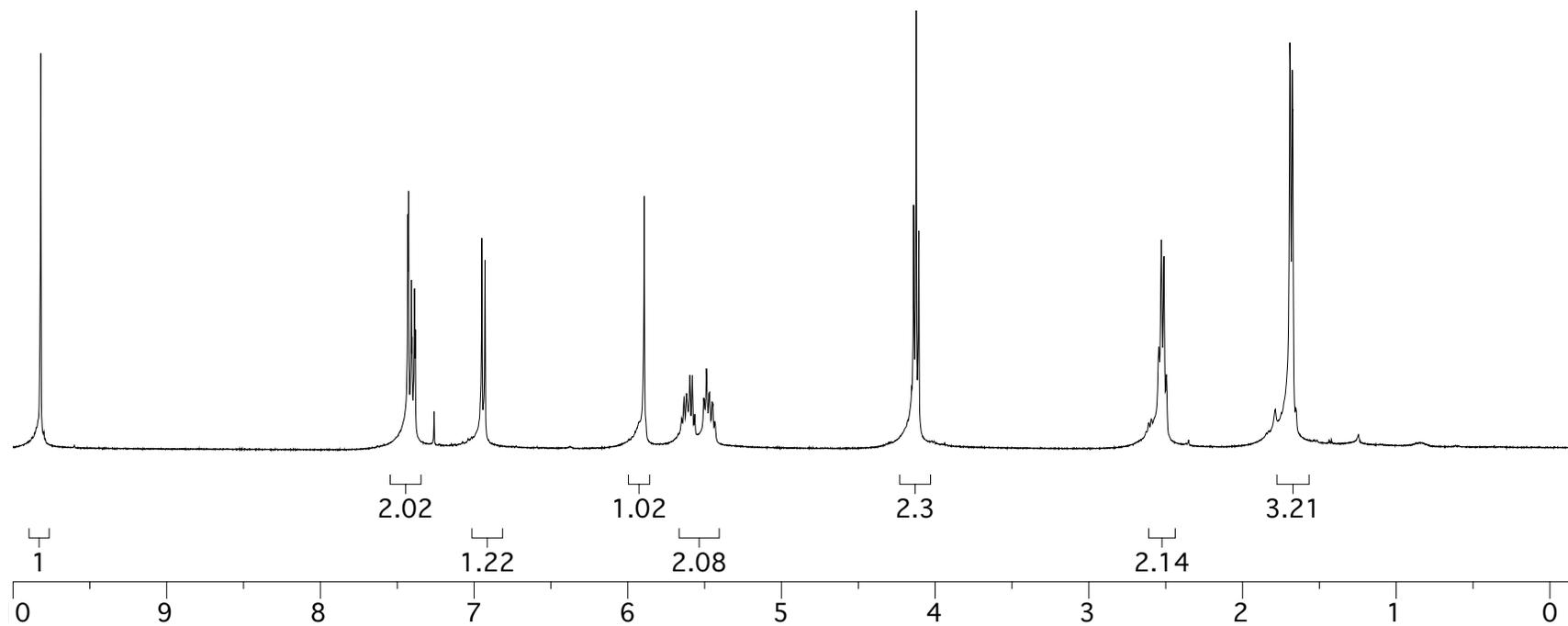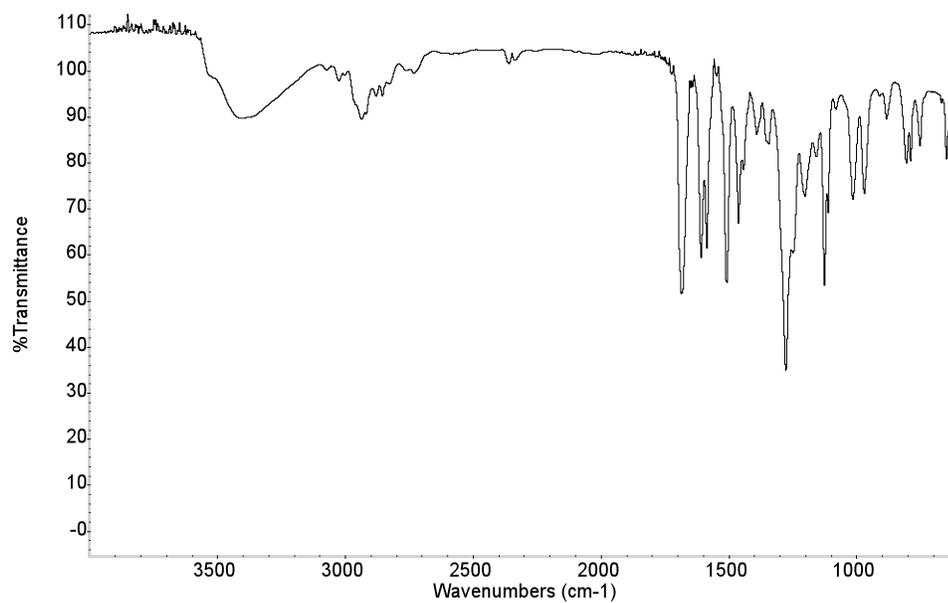
Figure A.4.8 Infrared Spectrum (thin film/NaCl) of compound **470**.
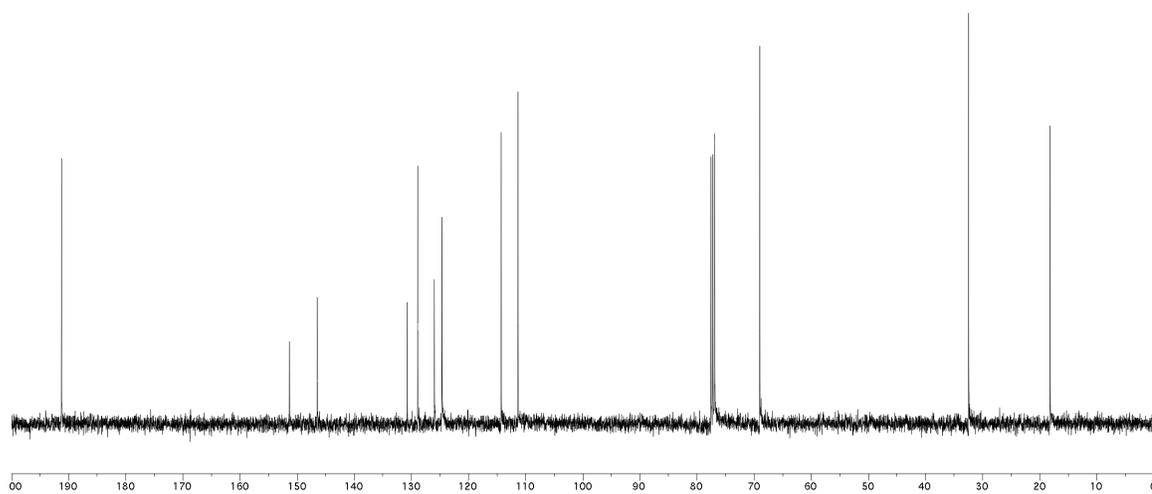


Figure A.4.9 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **470**.
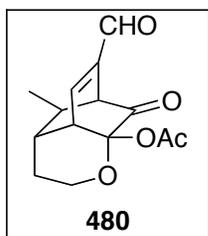
Figure A.4.10 $^1$H NMR (400MHz, CDCl$_3$) of compound 480
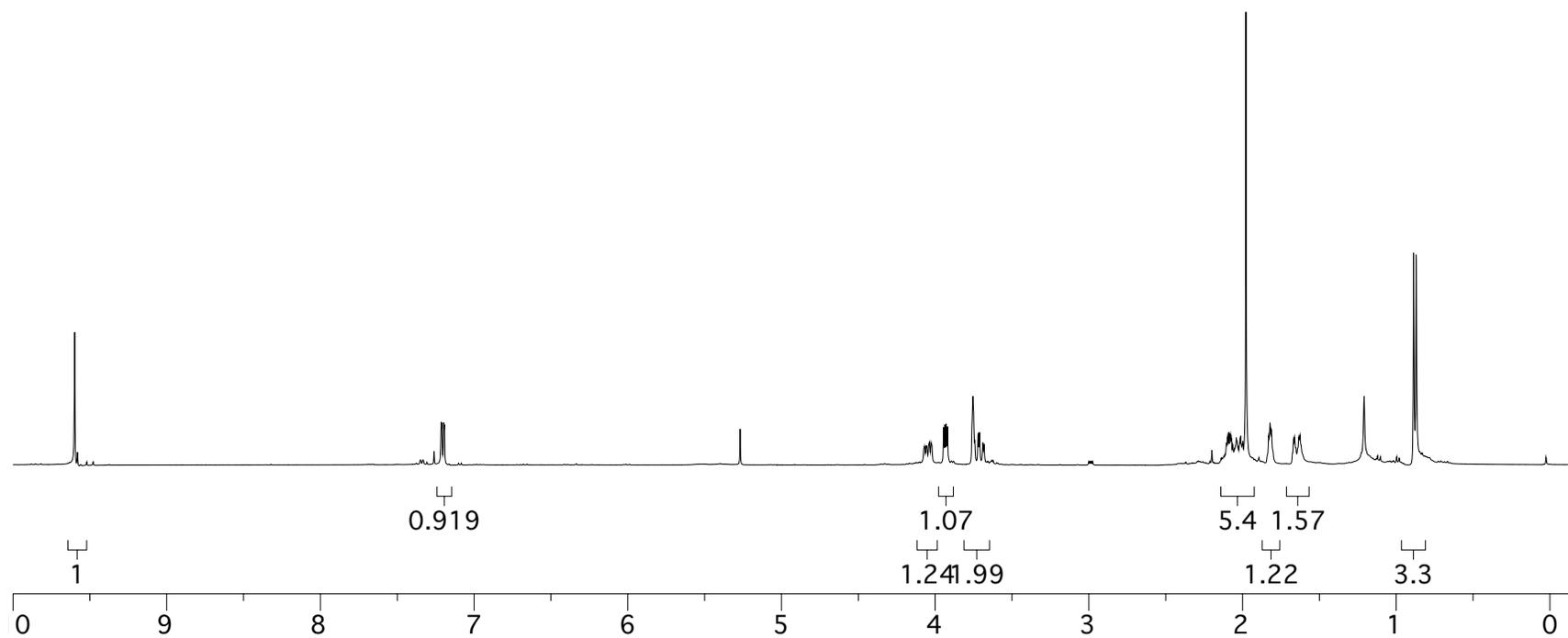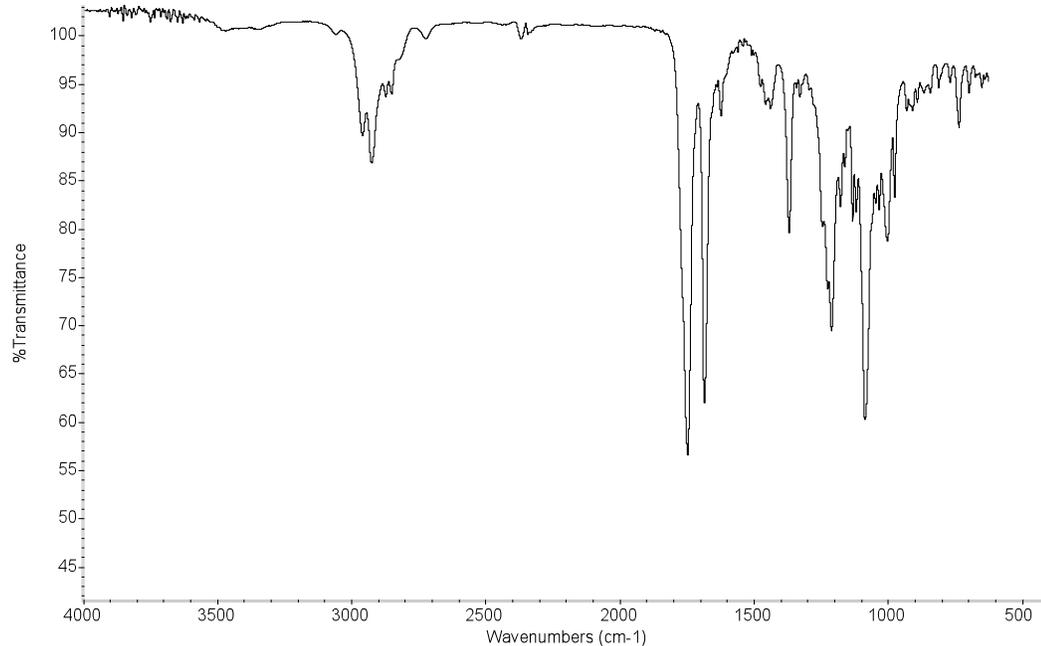
Figure A.4.11 Infrared Spectrum (thin film/NaCl) of compound **480**.
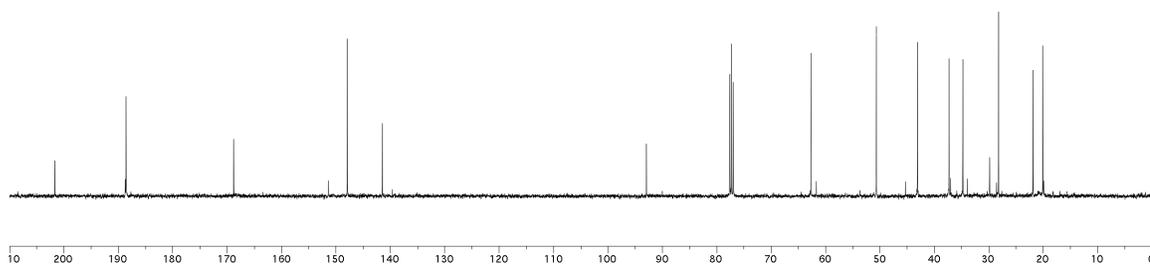


Figure A.4.12 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **480**.
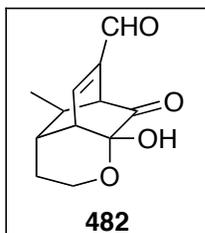
Figure A.4.13 ¹H NMR (400MHz, CDCl₃) of compound 482
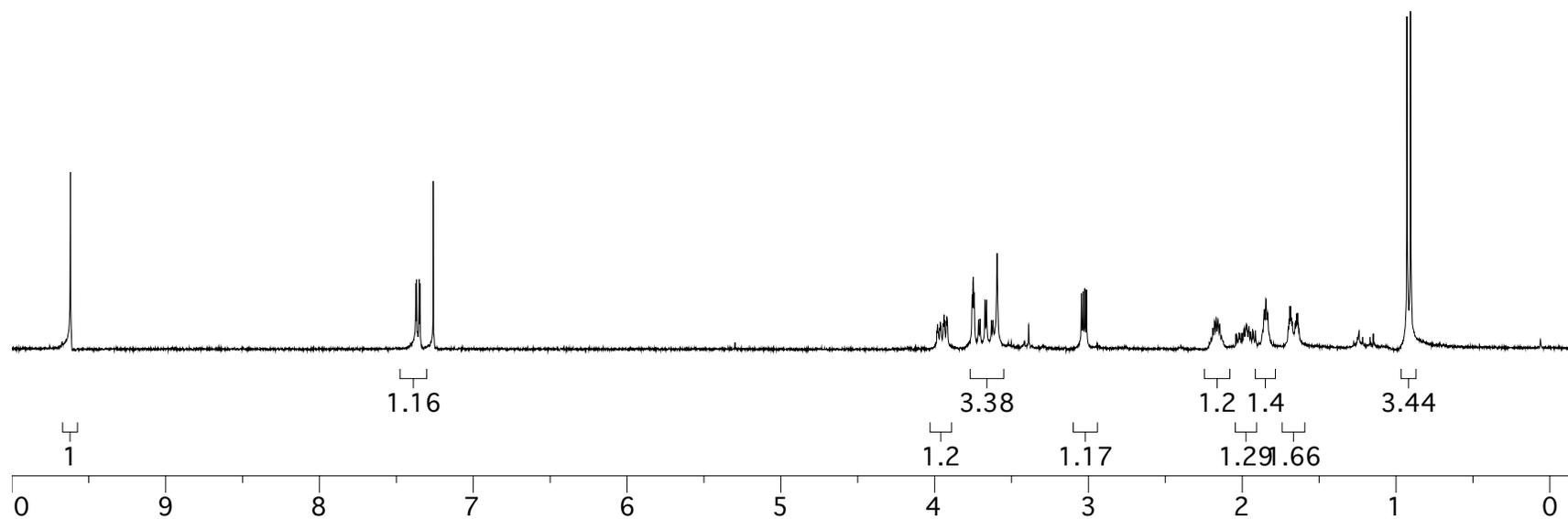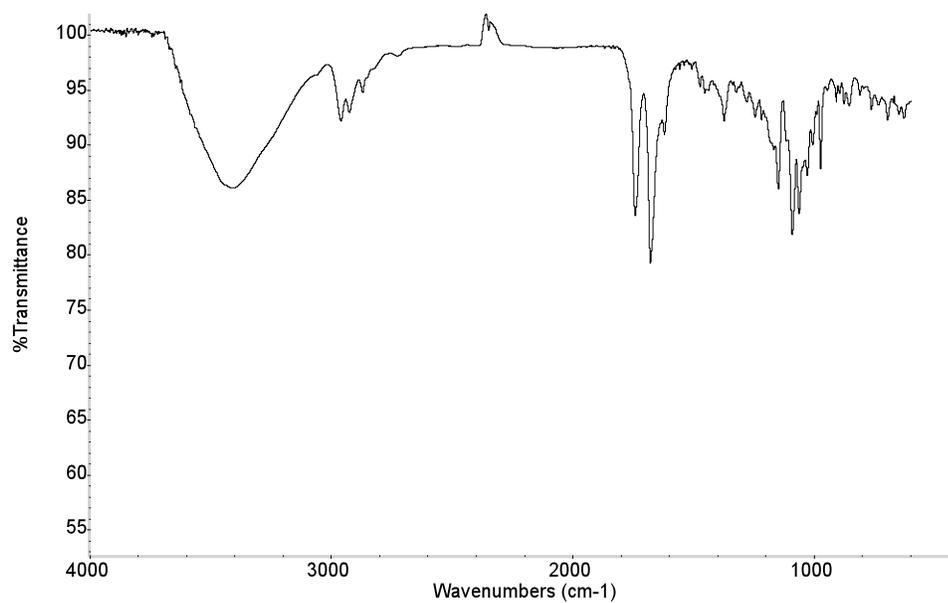
Figure A.4.14 Infrared Spectrum (thin film/NaCl) of compound **482**.
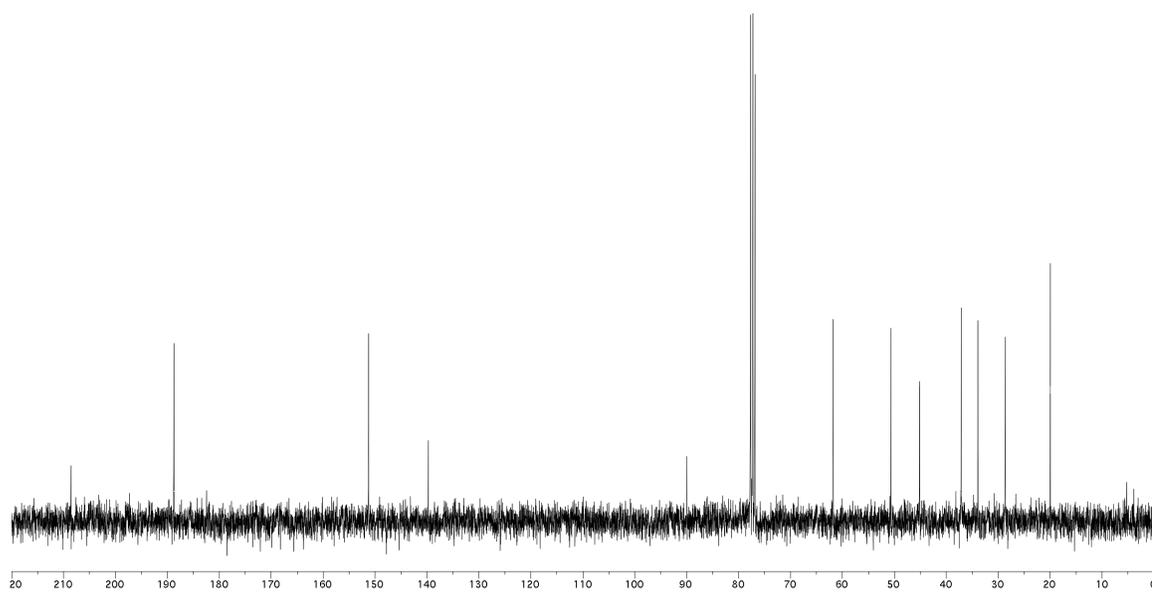


Figure A.4.15 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **482**.
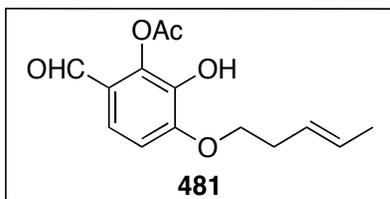
Figure A.4.16 $^1$H NMR (400MHz, CDCl$_3$) of compound 481
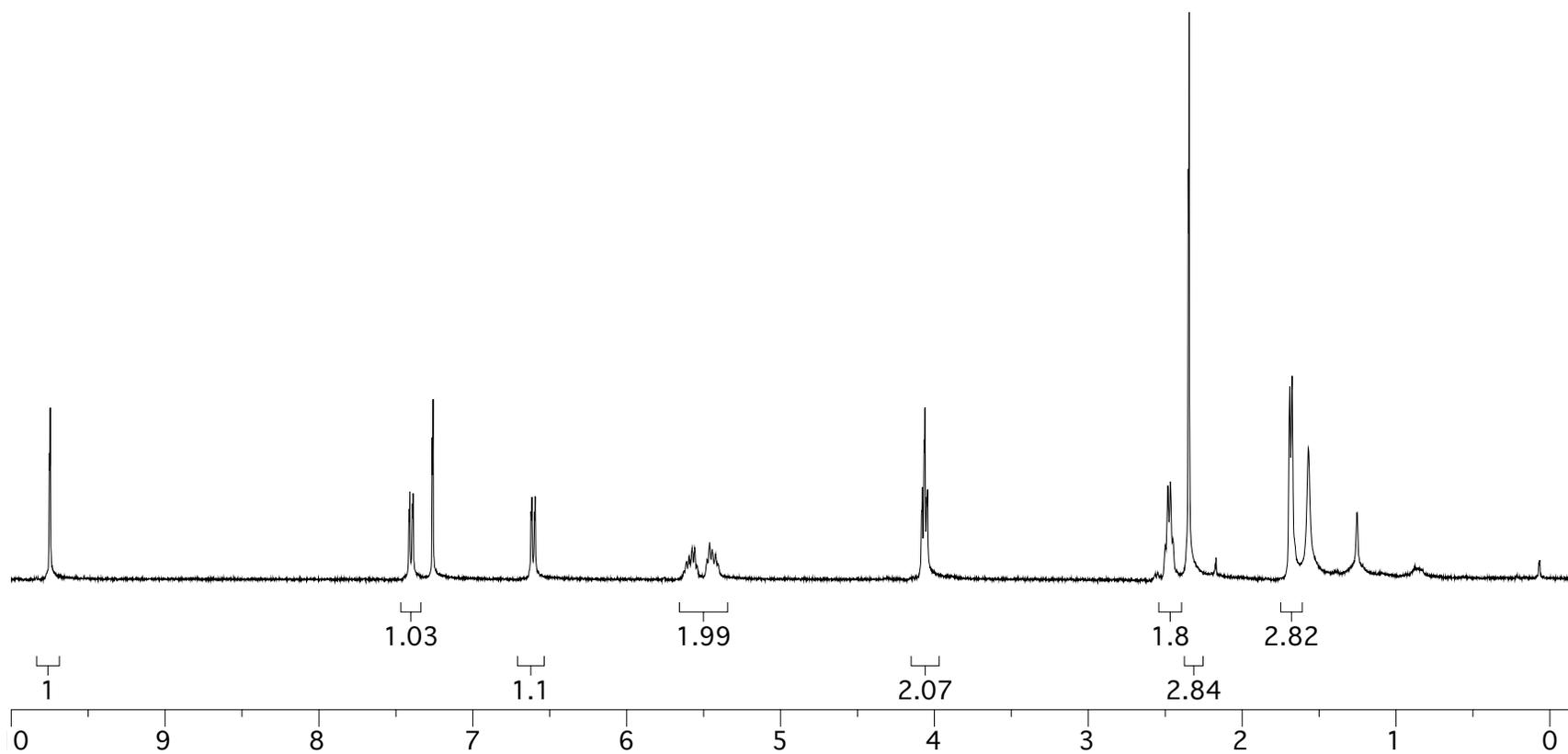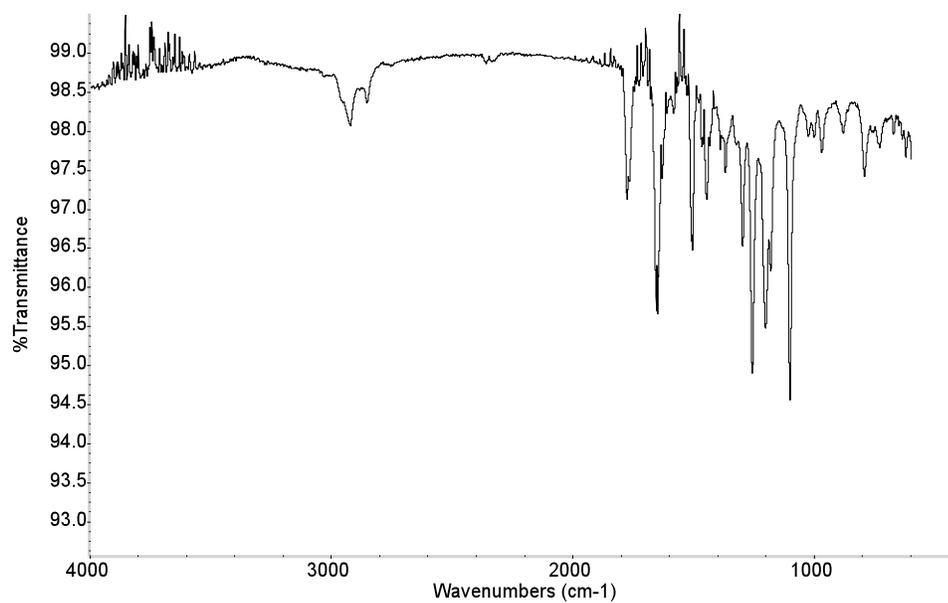
Figure A.4.17 Infrared Spectrum (thin film/NaCl) of compound **481**.
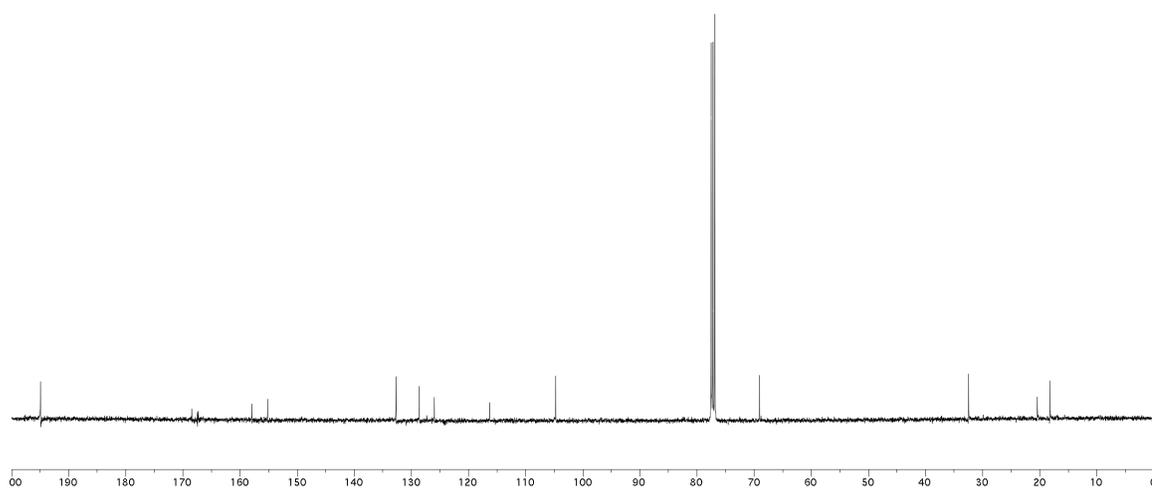


Figure A.4.18 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **481**.
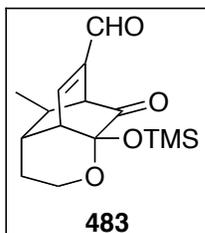
Figure A.4.19 $^1$H NMR (400MHz, CDCl$_3$) of compound 483
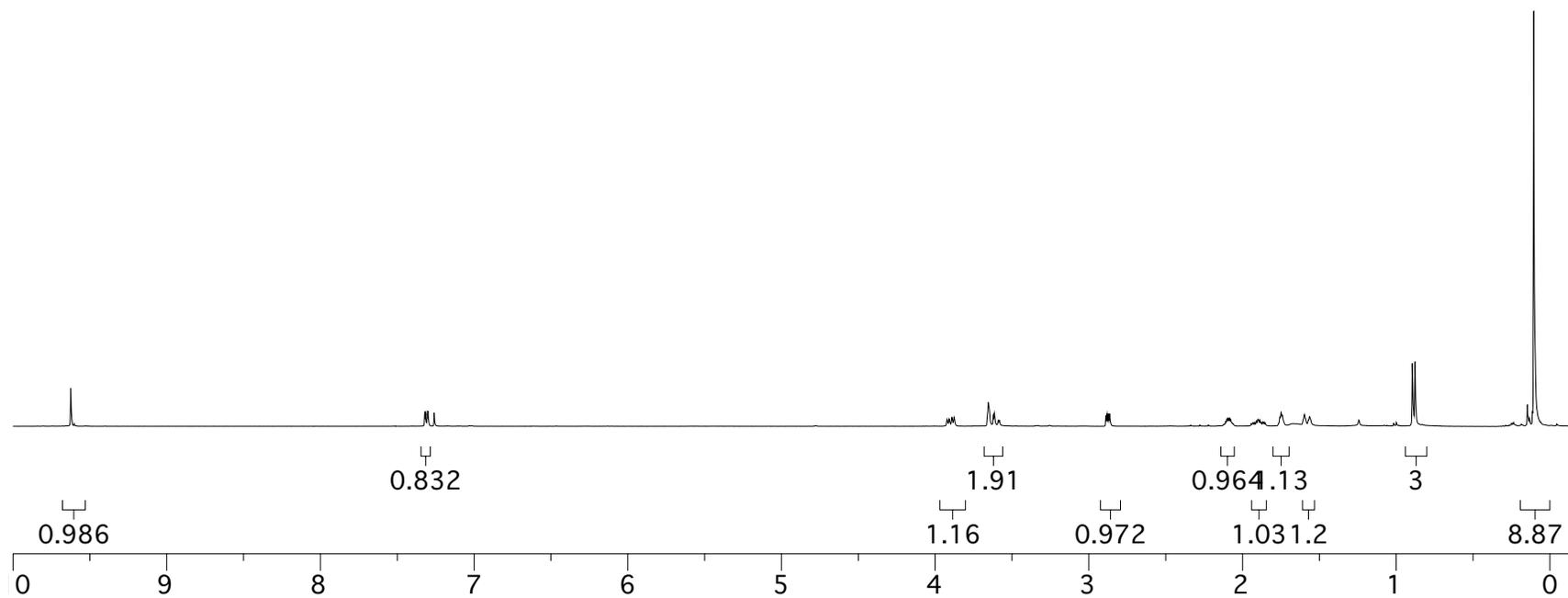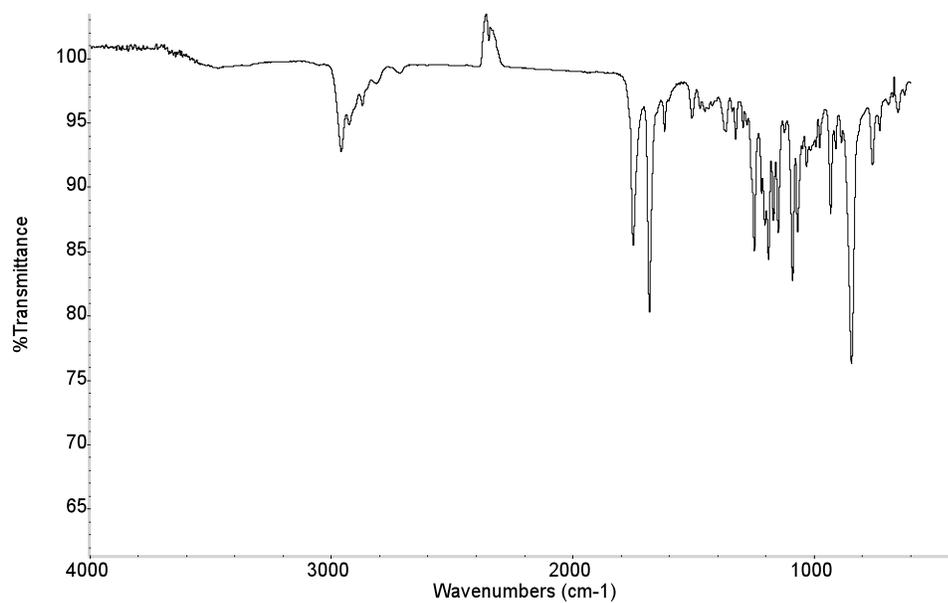
Figure A.4.20 Infrared Spectrum (thin film/NaCl) of compound **483**.
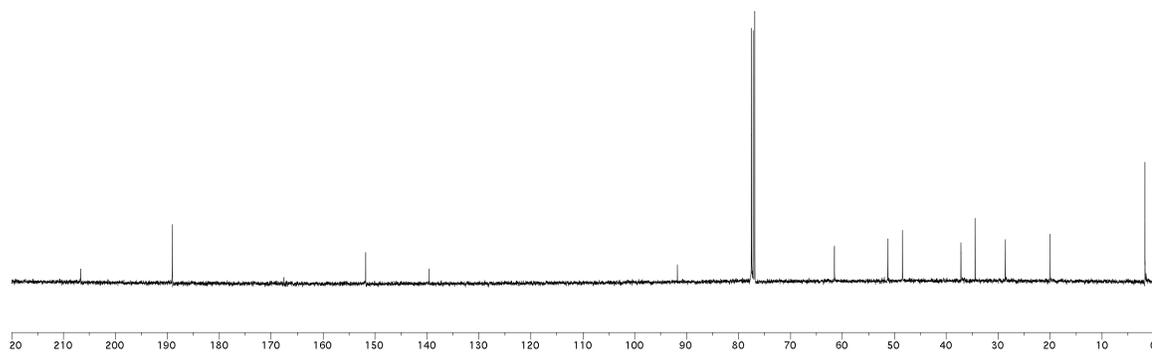


Figure A.4.21 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **483**.
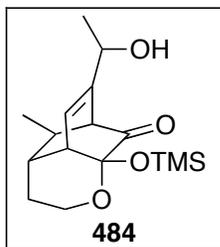
**Figure A.4.22 $^1$H NMR (400MHz, CDCl$_3$) of compound 484**
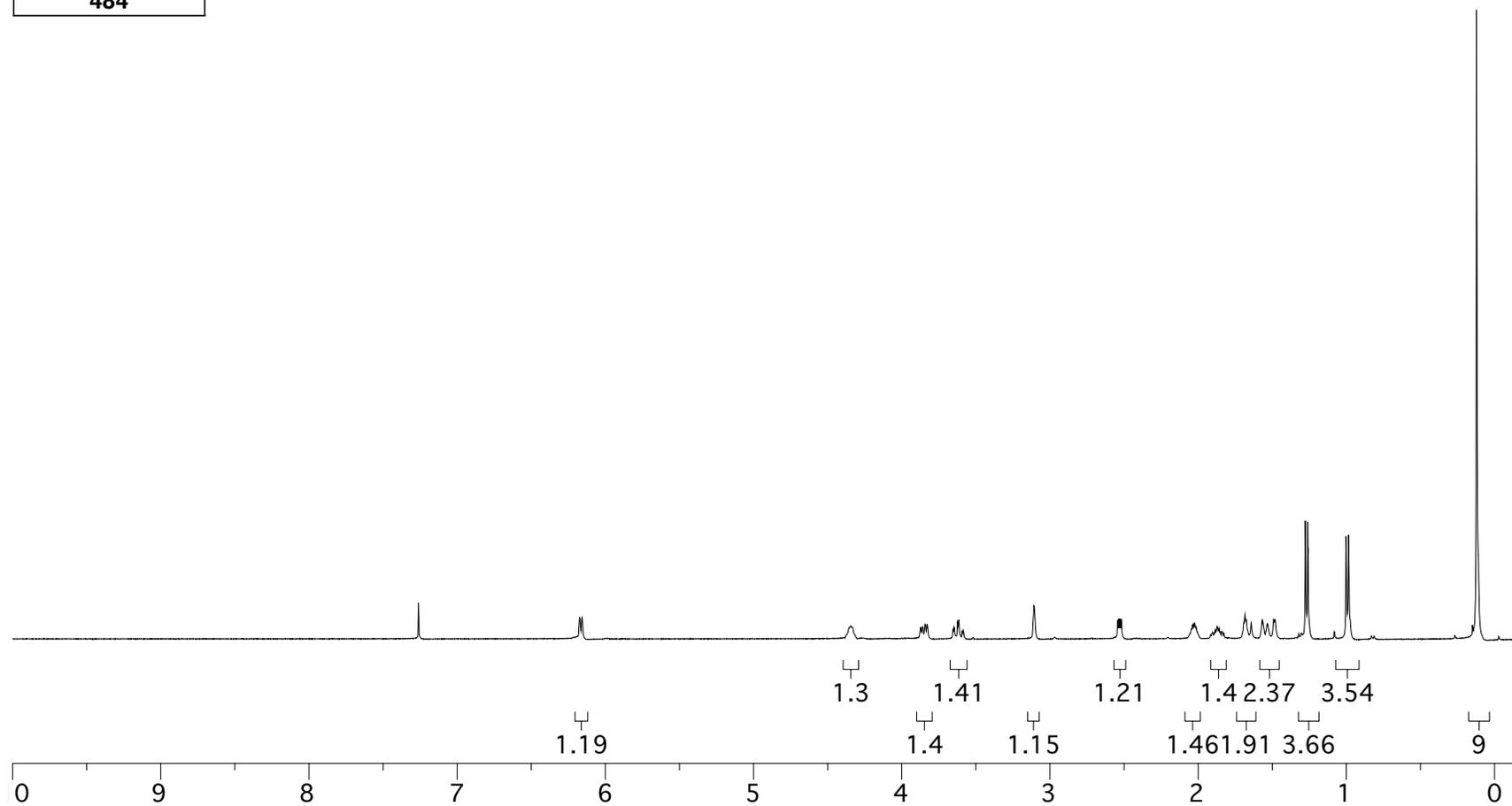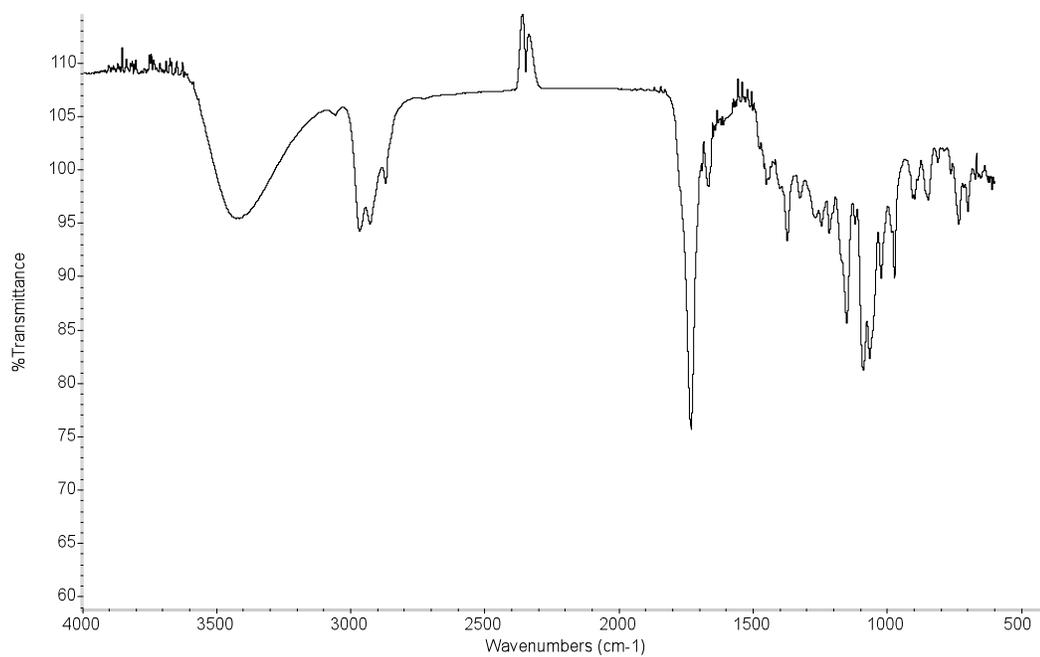
Figure A.4.23 Infrared Spectrum (thin film/NaCl) of compound **484**.
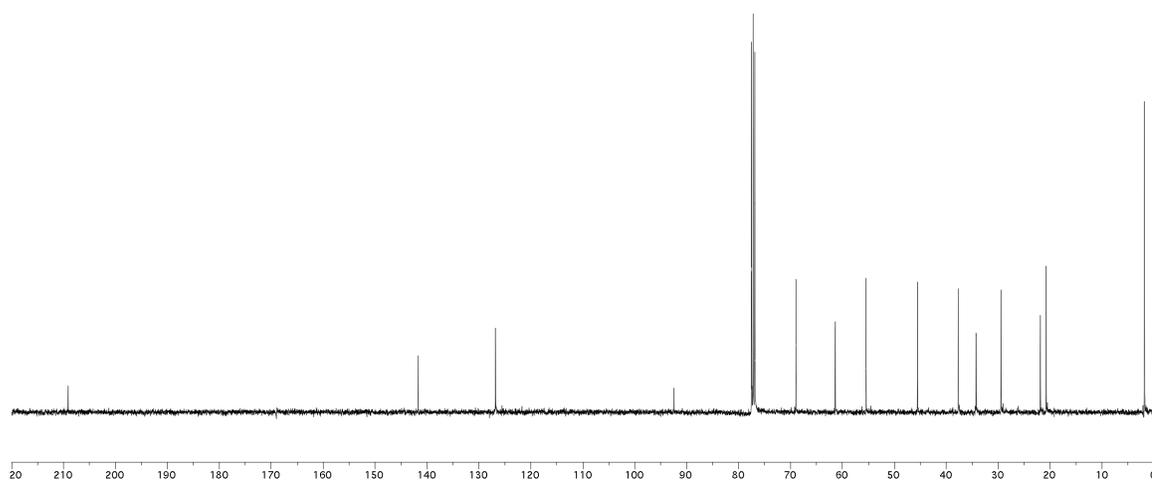


Figure A.4.24 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **484**.
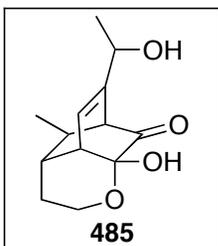
Figure A.4.25 ¹H NMR (400MHz, CDCl₃) of compound 485
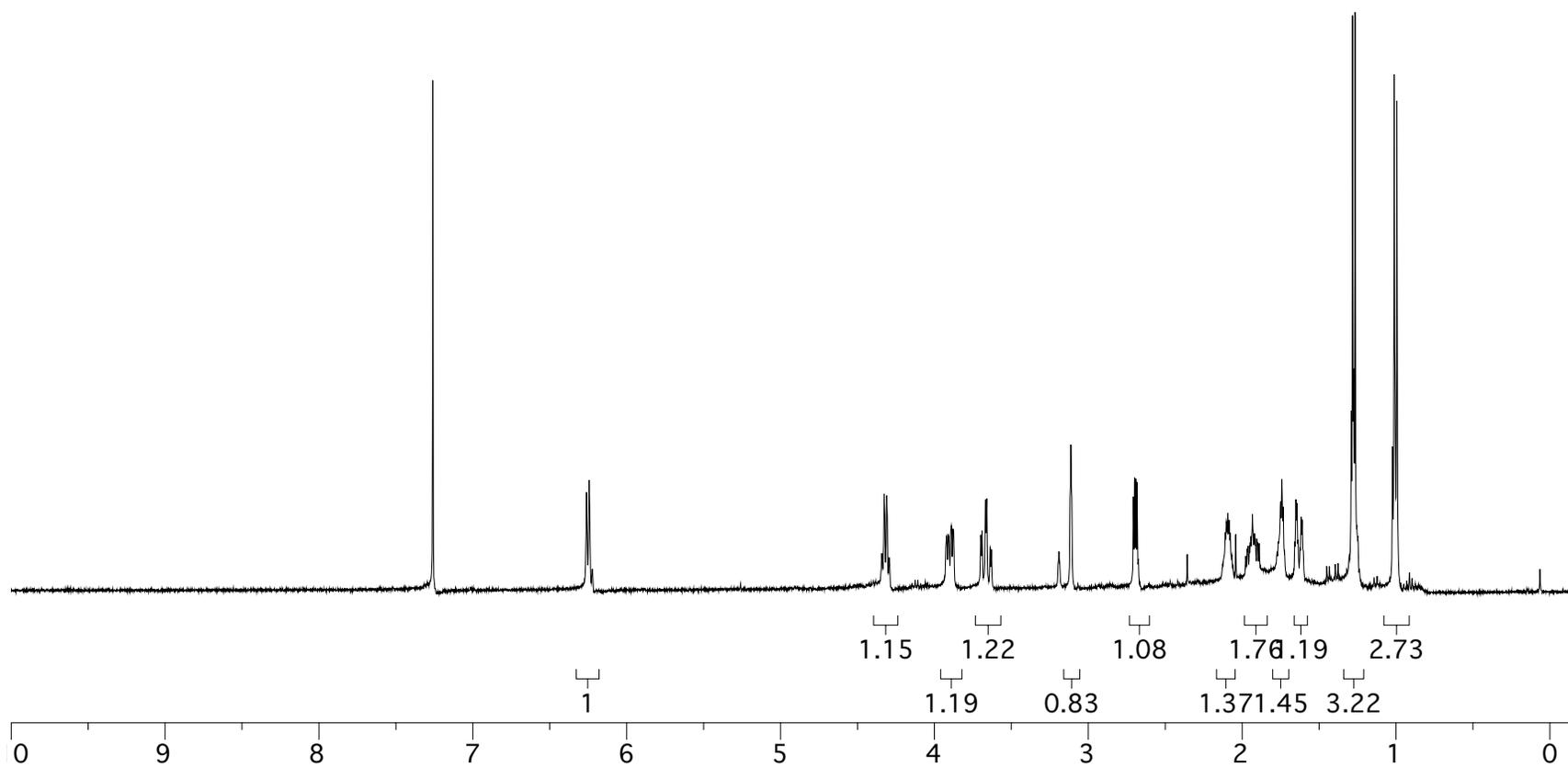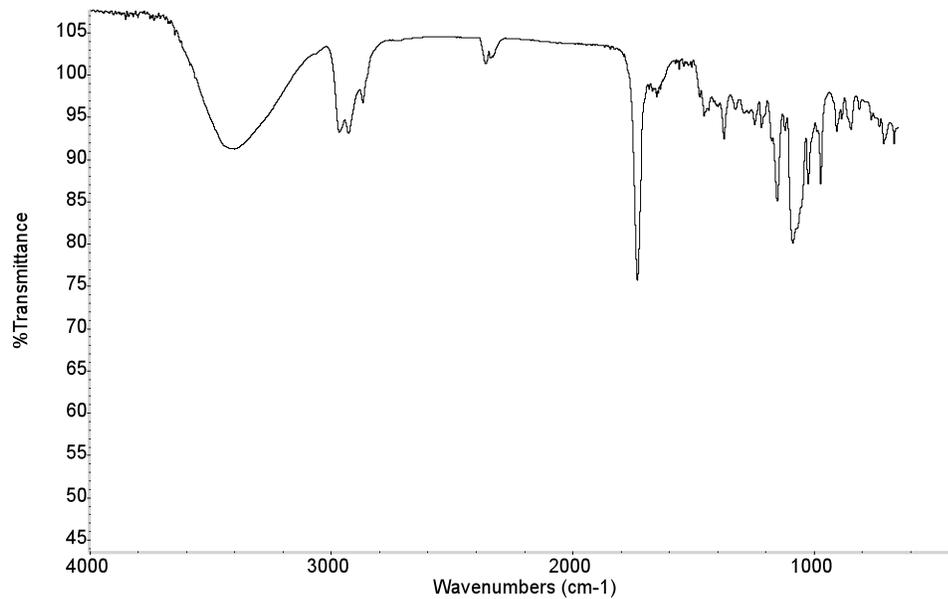
Figure A.4.26 Infrared Spectrum (thin film/NaCl) of compound **485**.
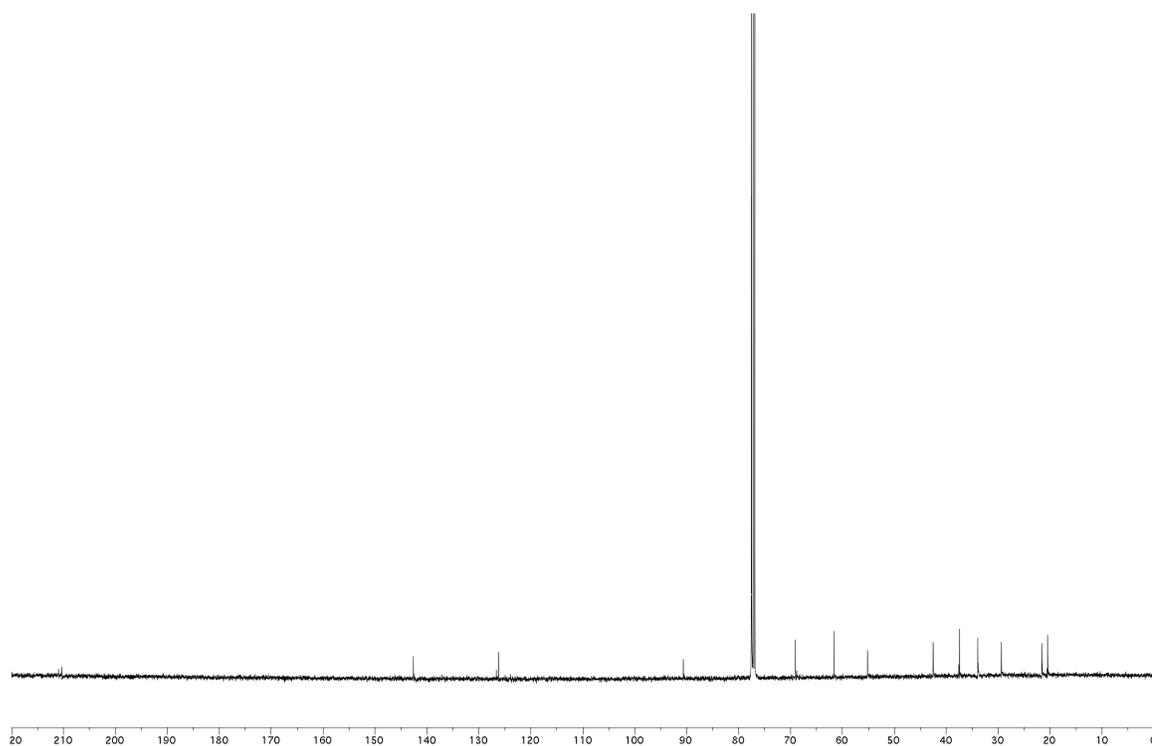


Figure A.4.27 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **485**.
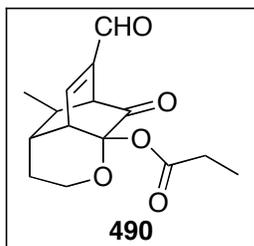
**Figure A.4.28 <sup>1</sup>H NMR (400MHz, CDCl₃) of compound 490**
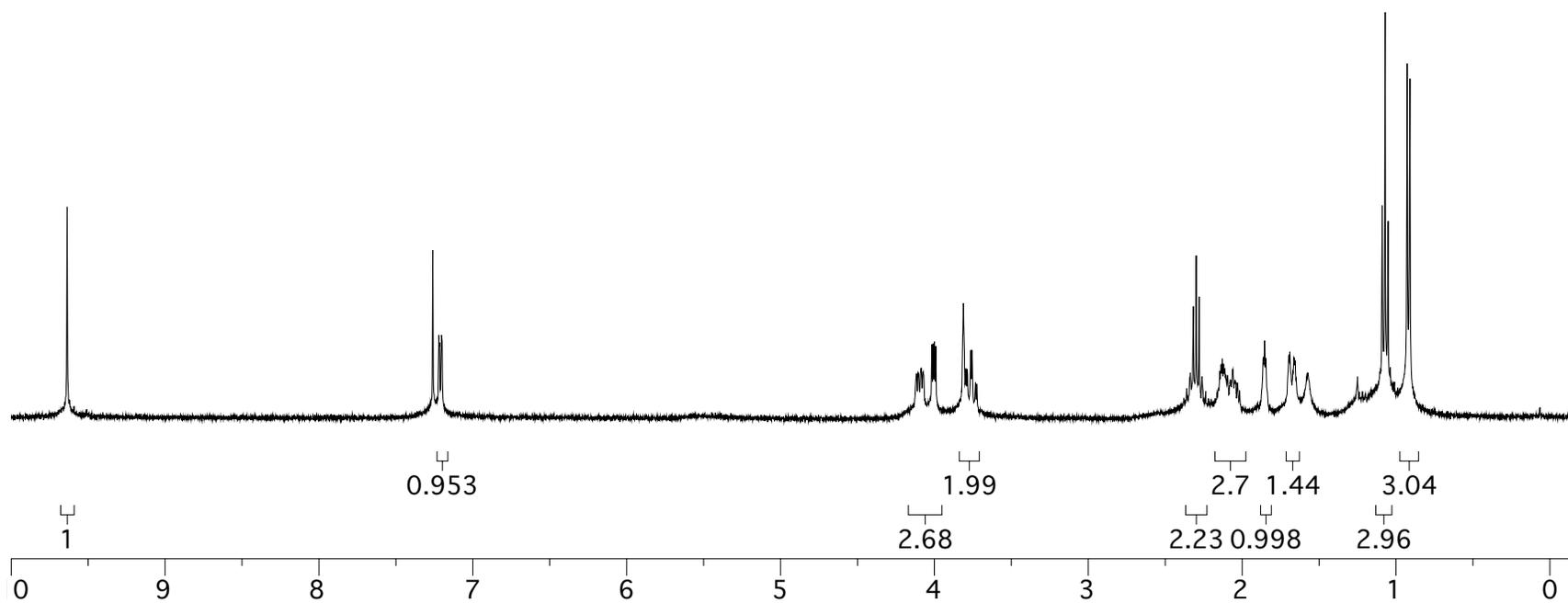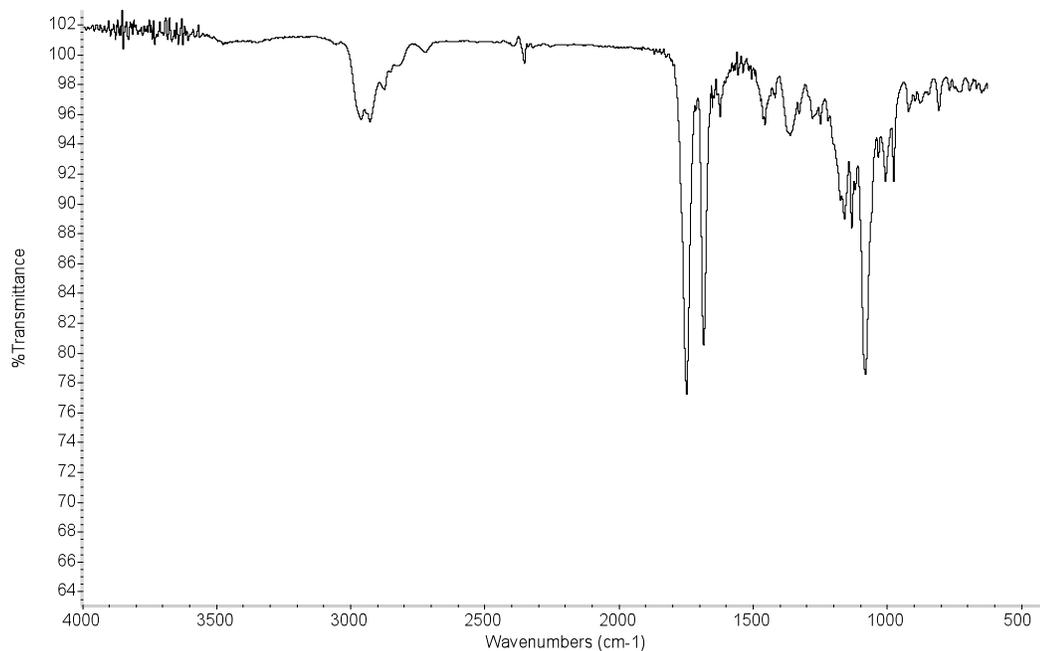
Figure A.4.29 Infrared Spectrum (thin film/NaCl) of compound **490**.
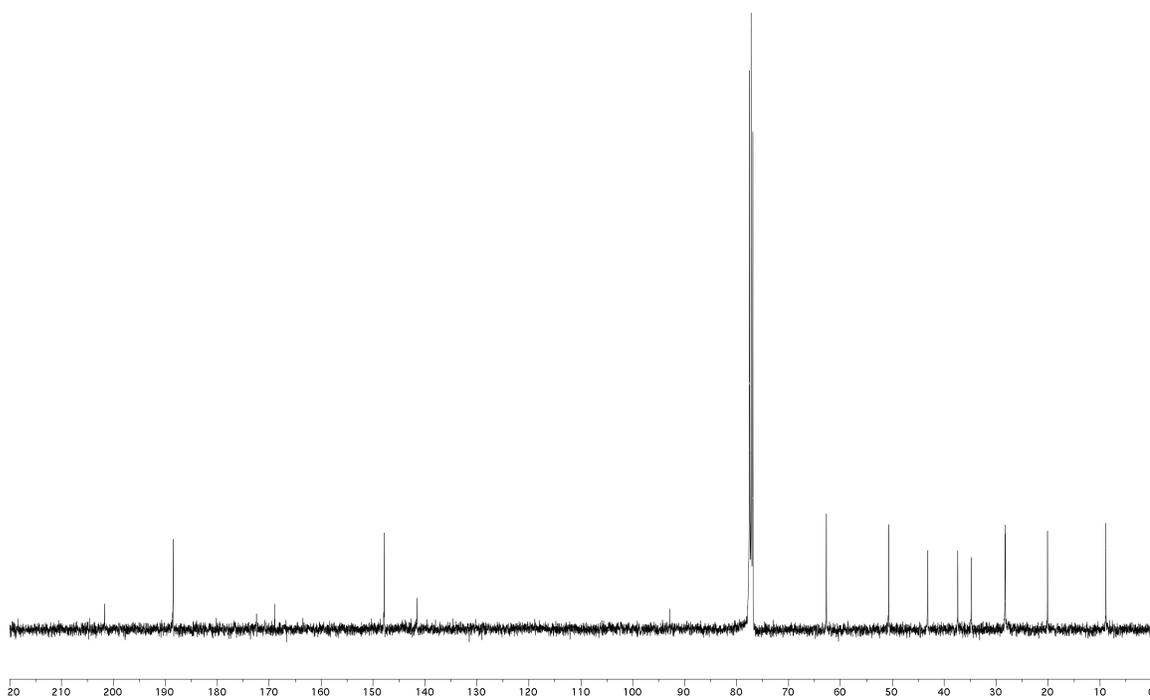


Figure A.4.30 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **490**.
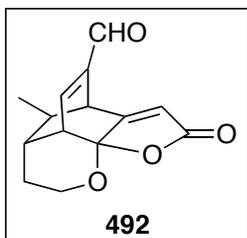
Figure A.4.31 $^1$H NMR (400MHz, CDCl$_3$) of compound 492
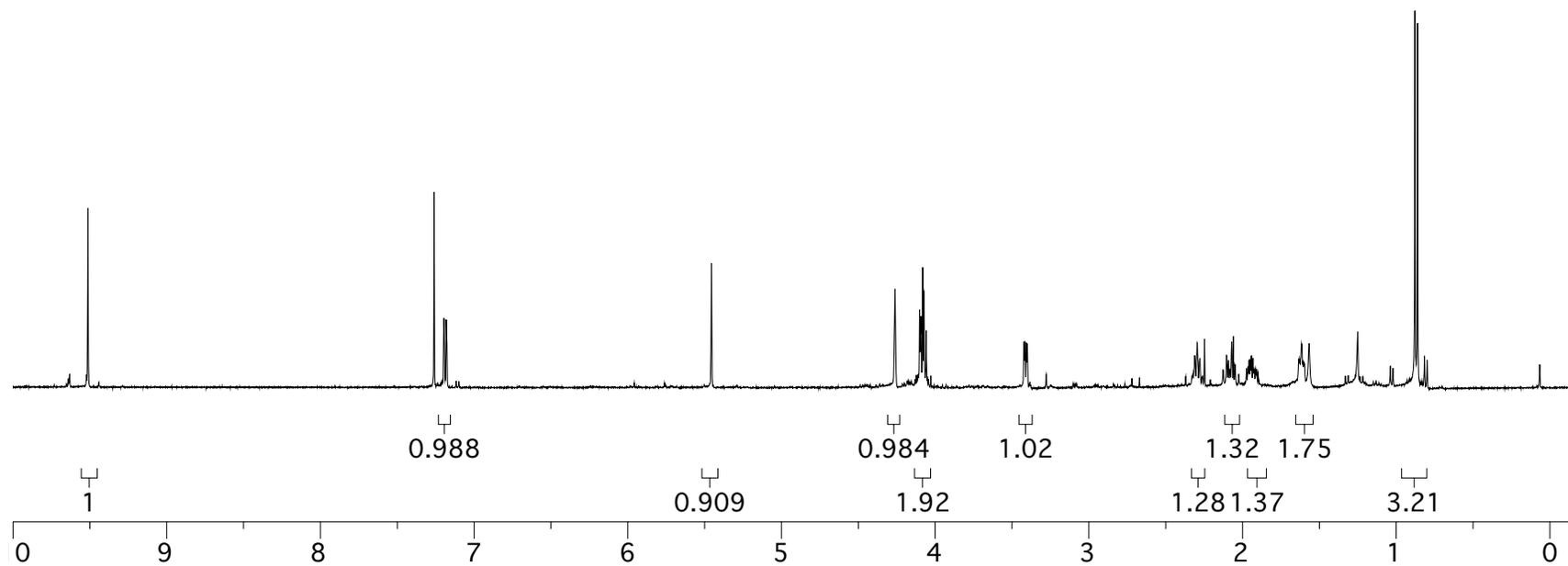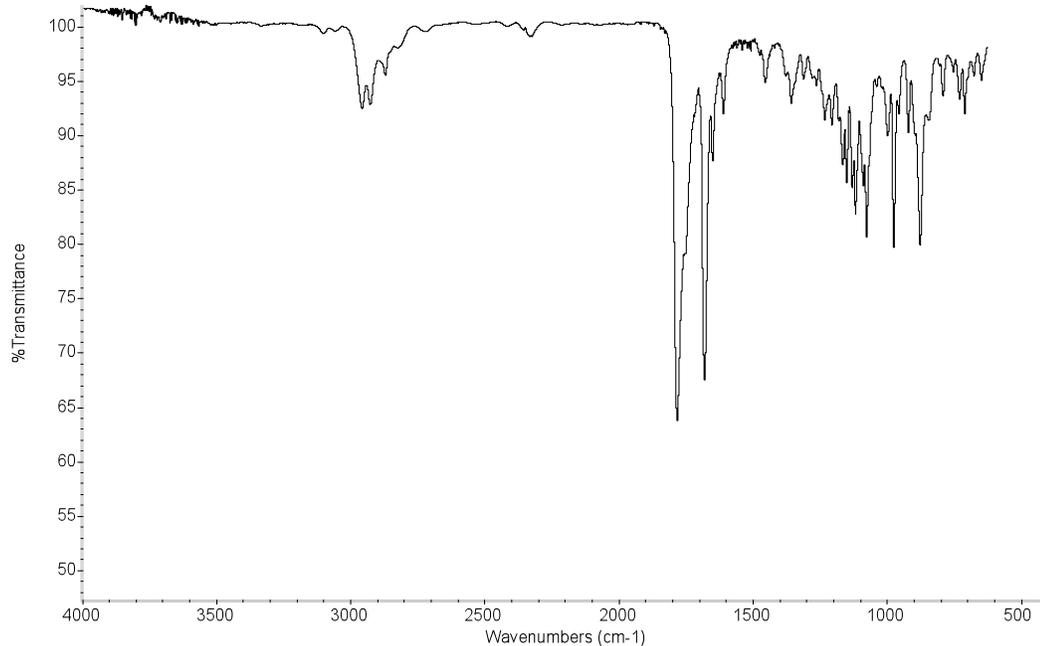
Figure A.4.32 Infrared Spectrum (thin film/NaCl) of compound **492**.
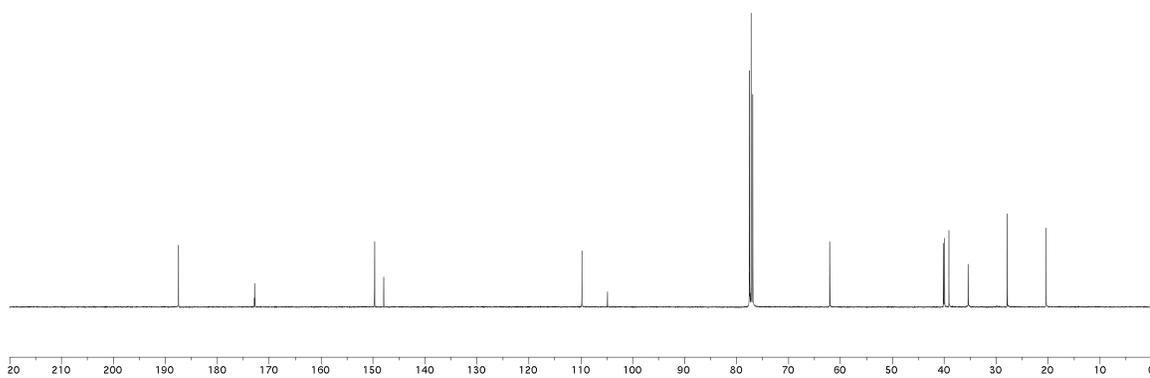


Figure A.4.33 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **492**.
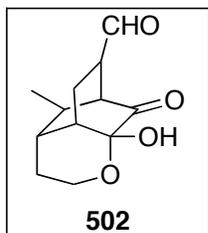
Figure A.4.34 $^1$H NMR (400MHz, CDCl$_3$) of compound 502
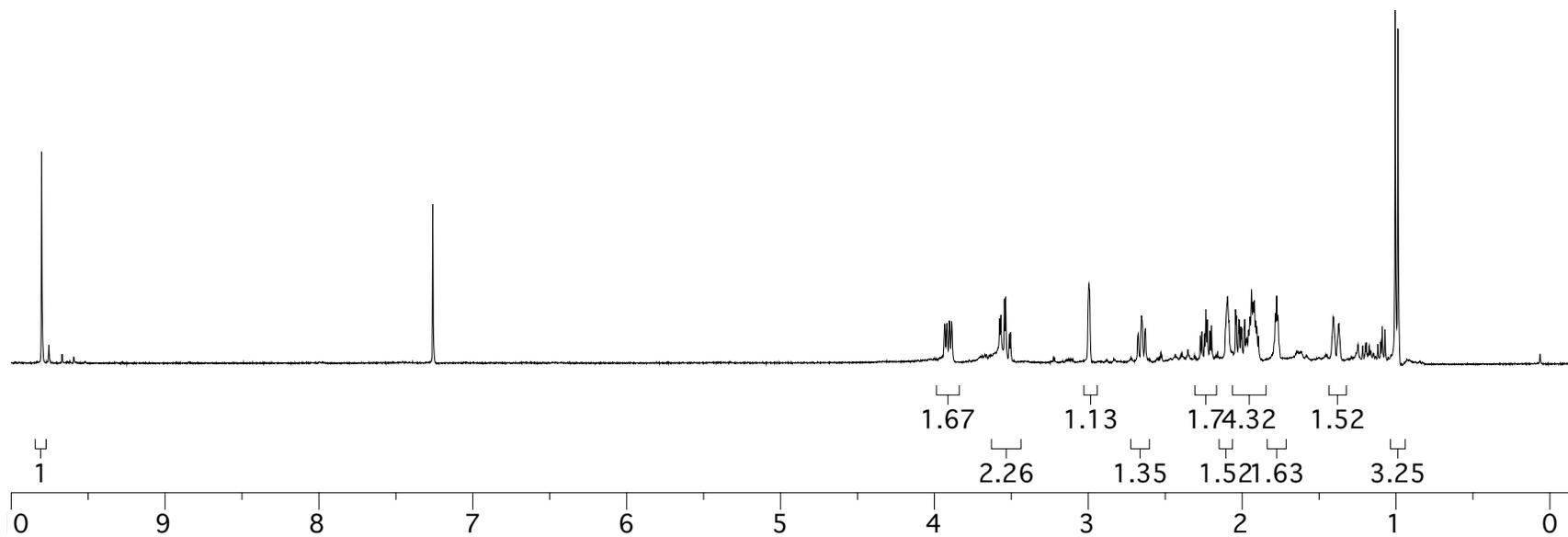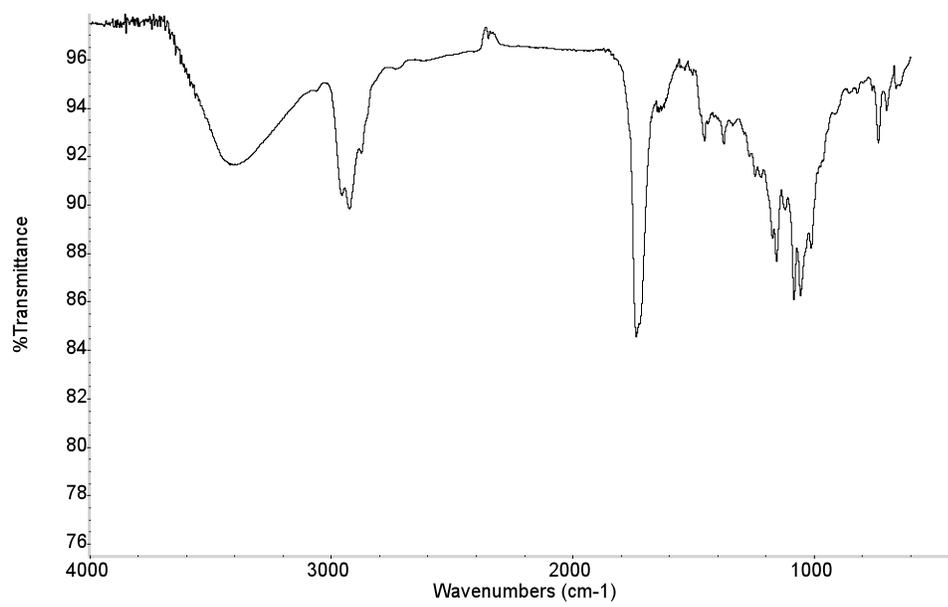
Figure A.4.35 Infrared Spectrum (thin film/NaCl) of compound **502**.
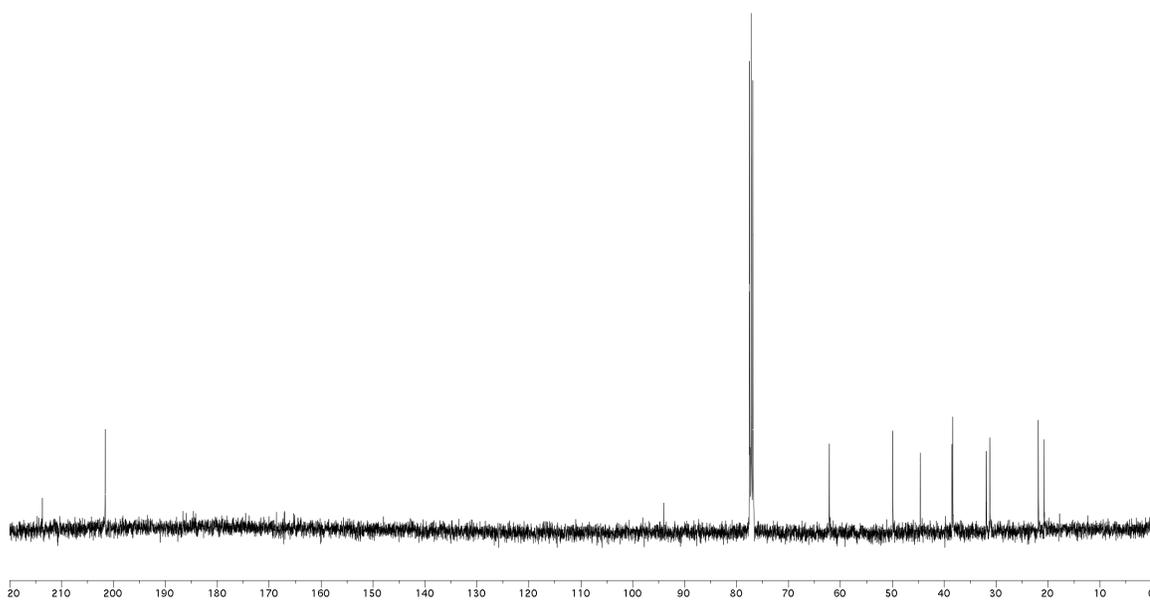


Figure A.4.36 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **502**.
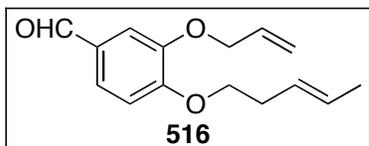
**Figure A.4.37 $^1$H NMR (400MHz, CDCl$_3$) of compound 516**
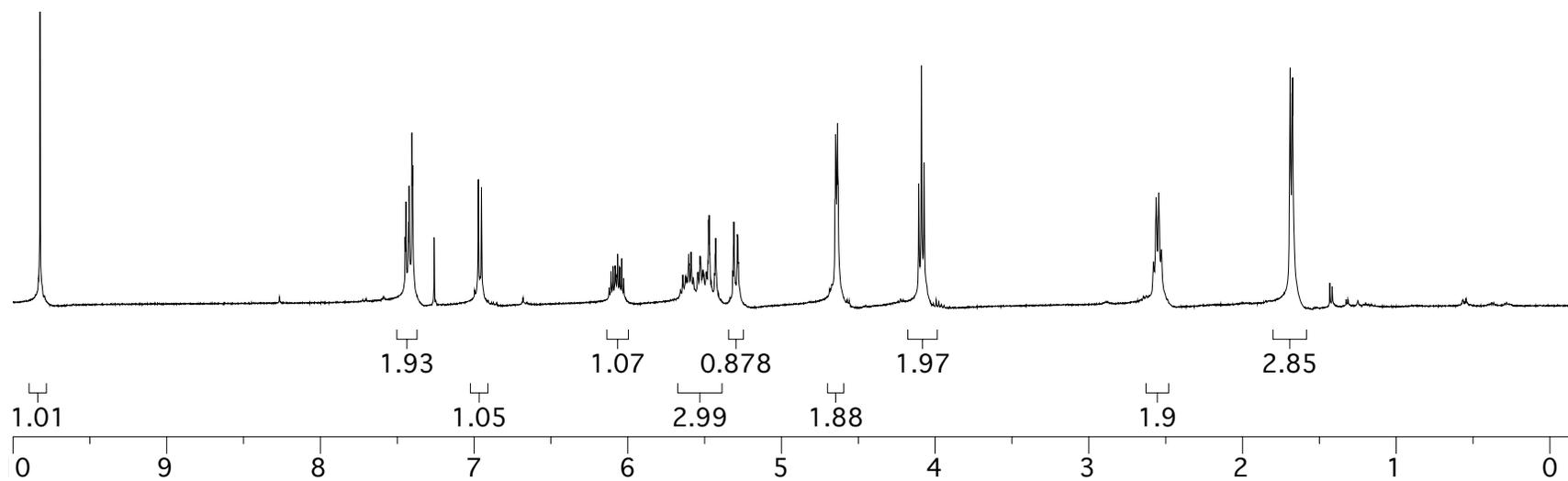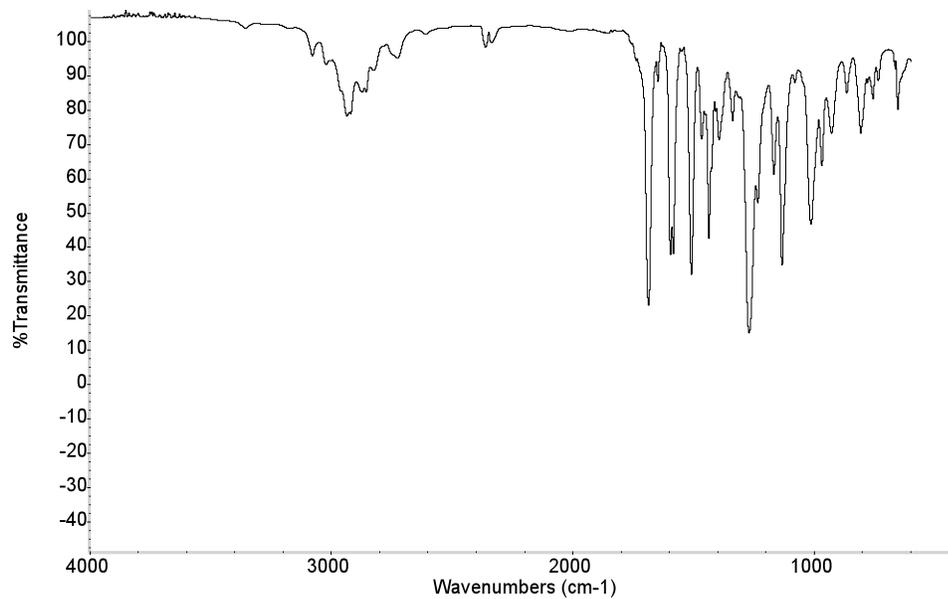
Figure A.4.38 Infrared Spectrum (thin film/NaCl) of compound **516**.
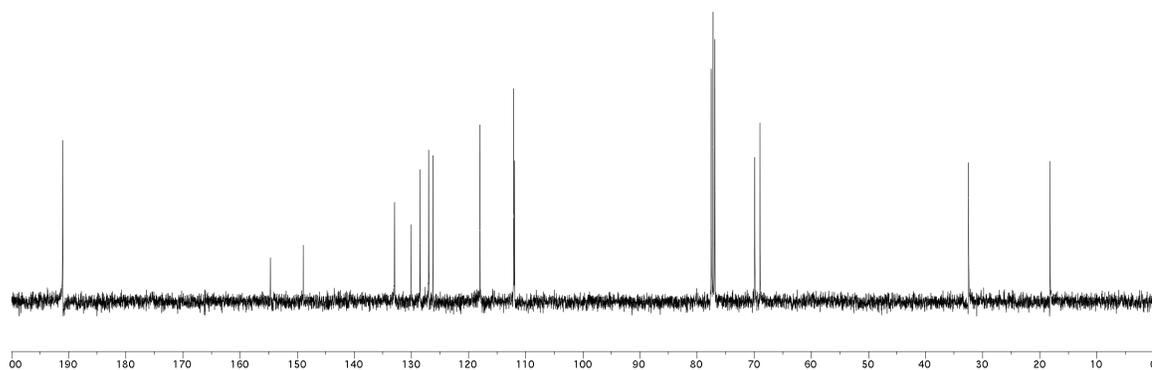


Figure A.4.39 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **516**.
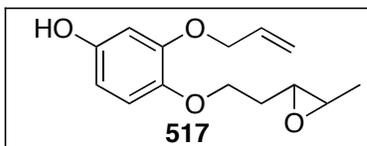
**Figure A.4.40** $^1$H NMR (400MHz, CDCl$_3$) of compound 517
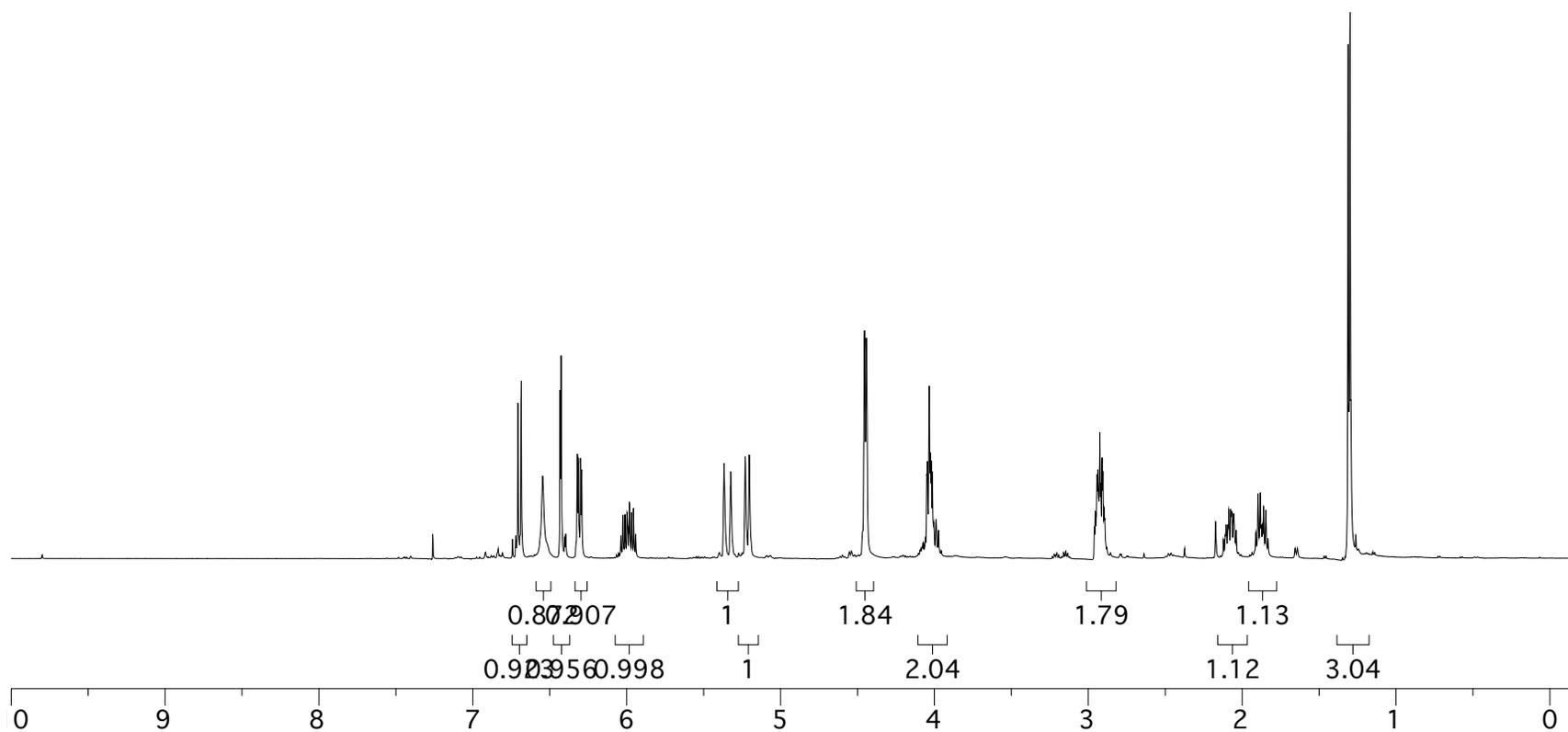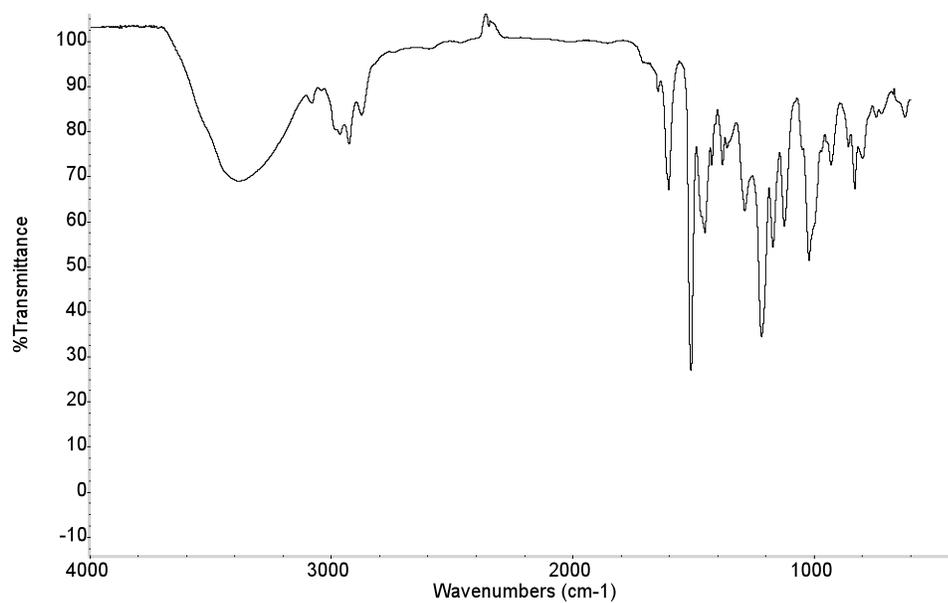
Figure A.4.41 Infrared Spectrum (thin film/NaCl) of compound **517**.
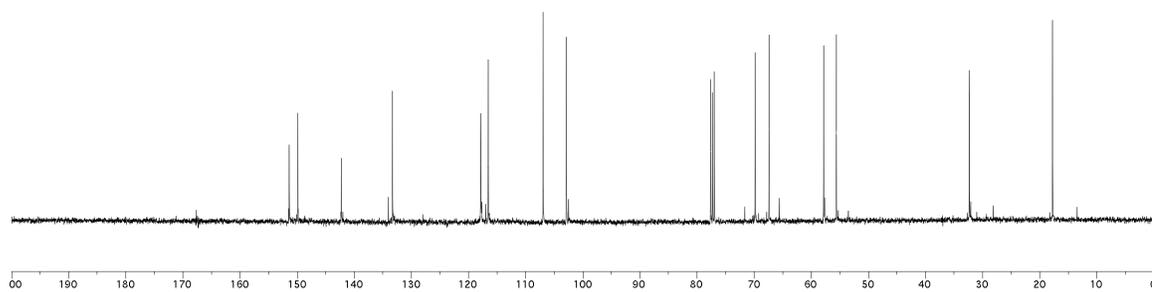


Figure A.4.42 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **517**.
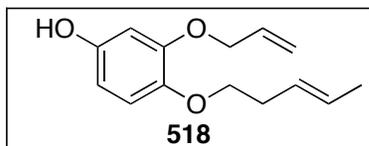
Figure A.4.43 $^1$H NMR (400MHz, CDCl$_3$) of compound 518
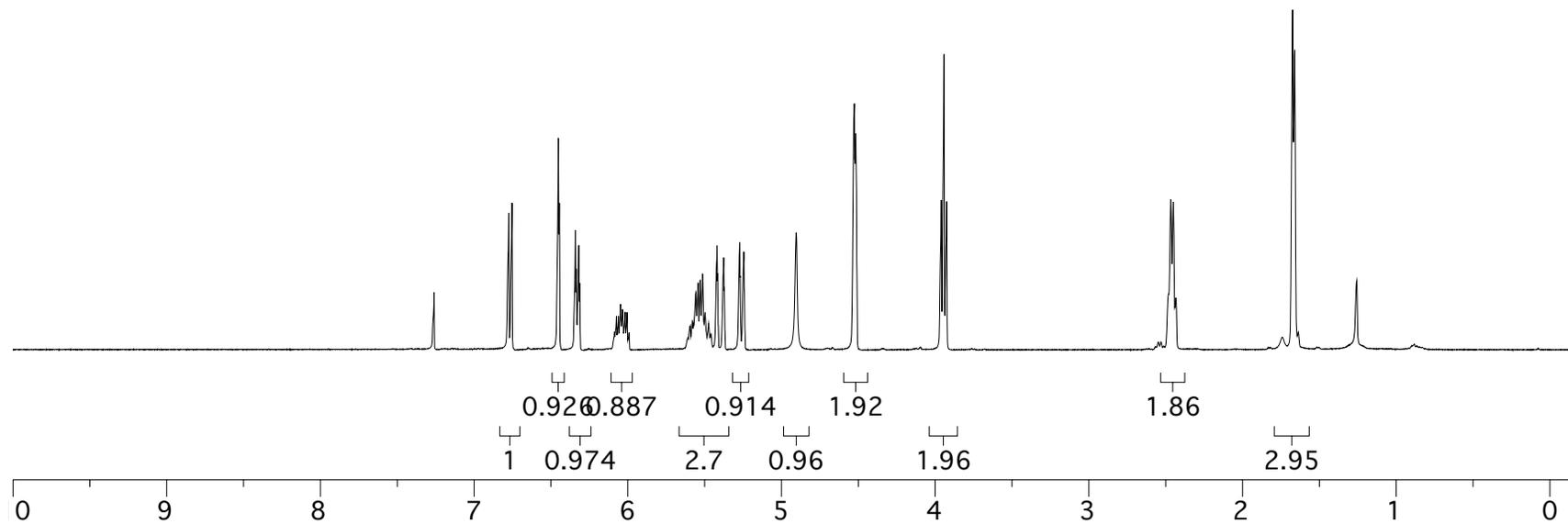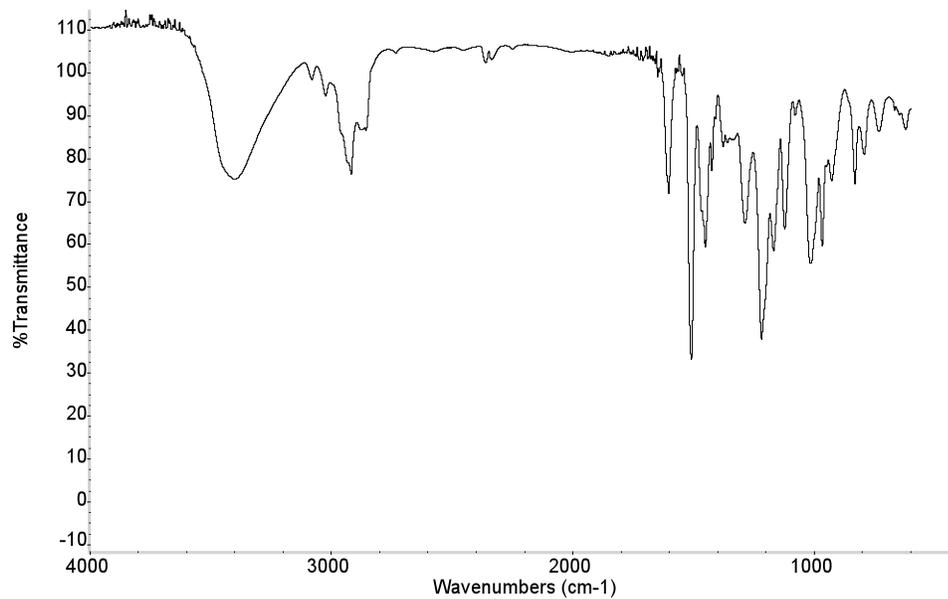
Figure A.4.44 Infrared Spectrum (thin film/NaCl) of compound **518**.
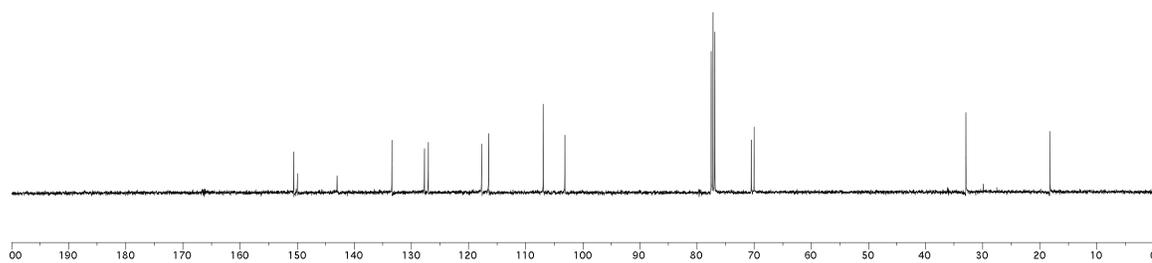


Figure A.4.45 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **518**.
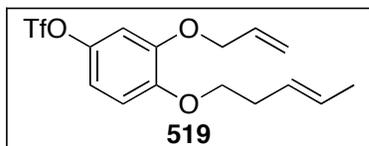
**Figure A.4.46 $^1$H NMR (400MHz, CDCl$_3$) of compound 519**
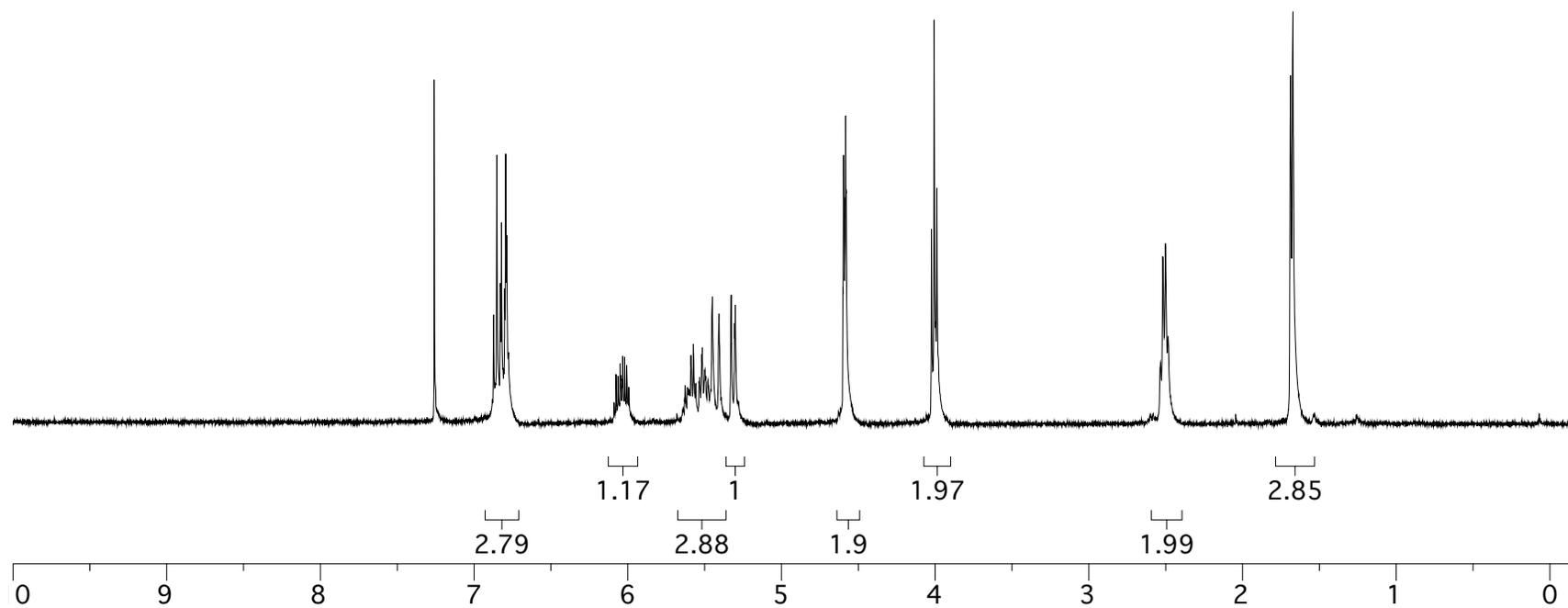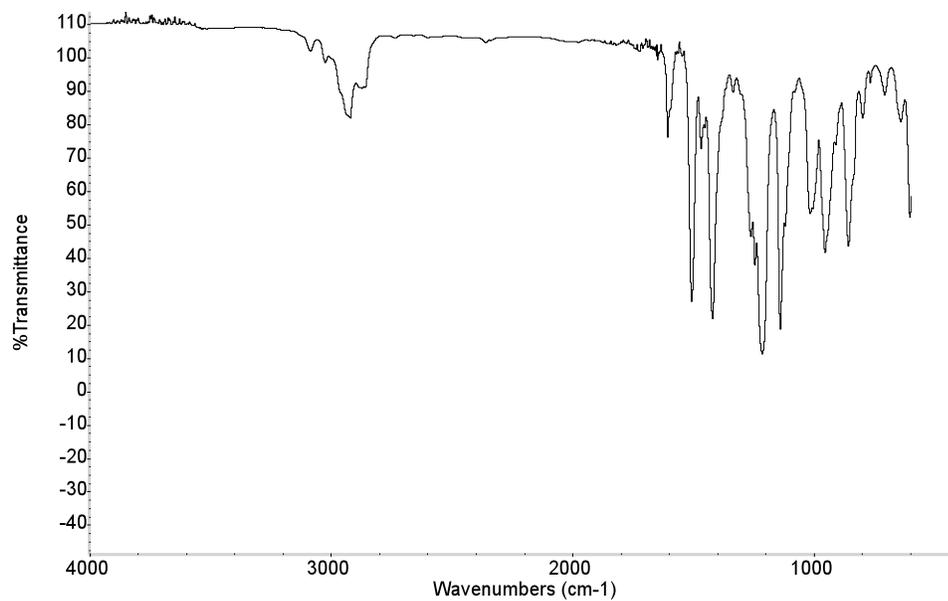
Figure A.4.47 Infrared Spectrum (thin film/NaCl) of compound **519**.
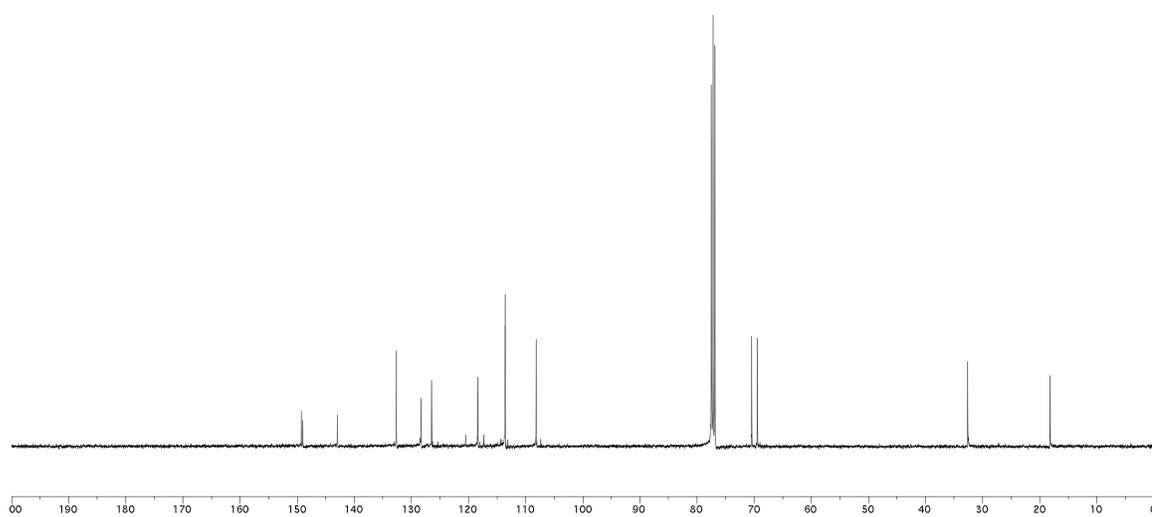


Figure A.4.48 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **519**.
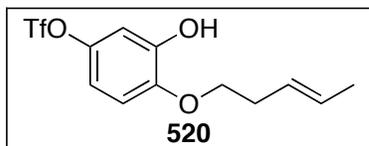
Figure A.4.49 $^1$H NMR (400MHz, CDCl$_3$) of compound 520
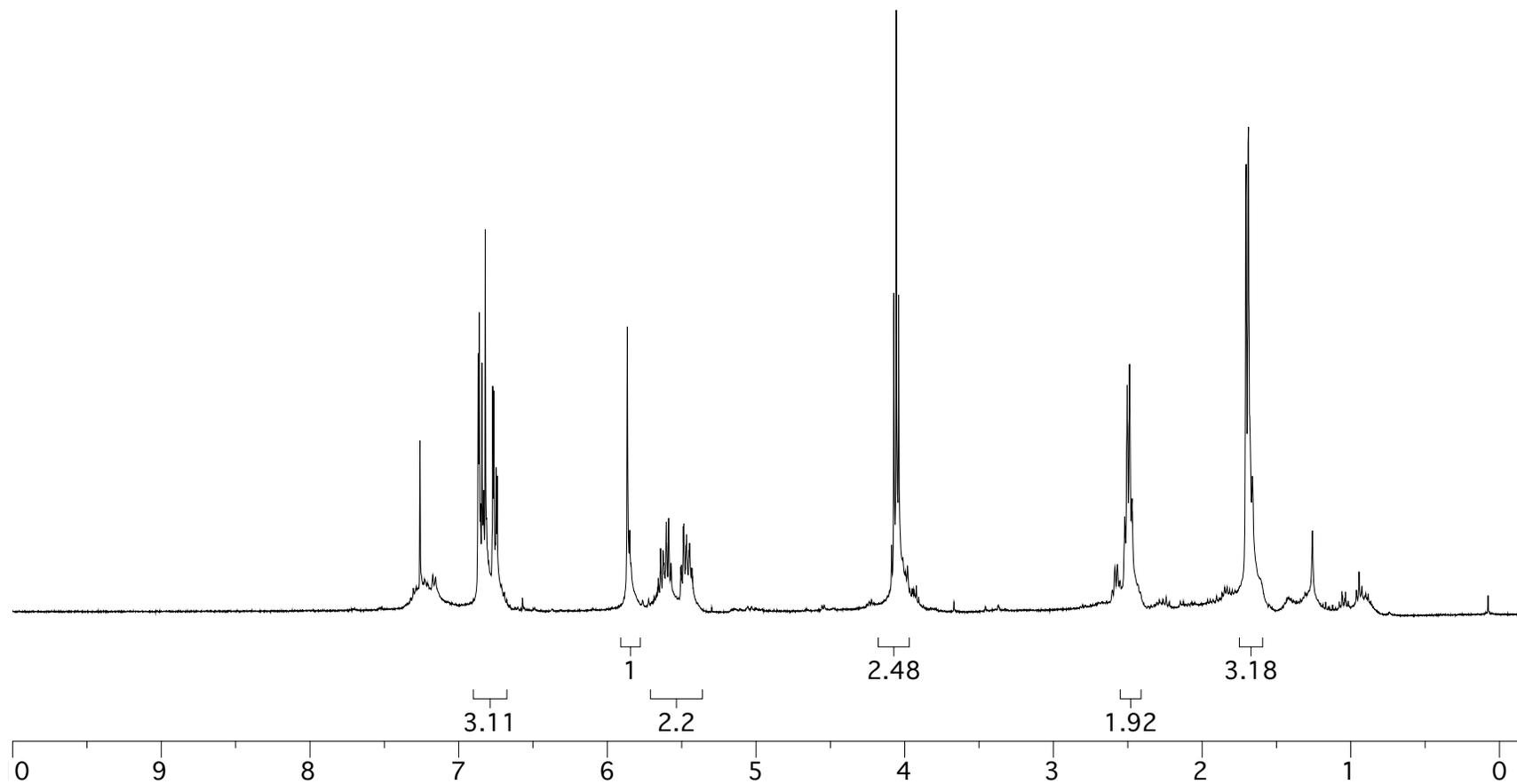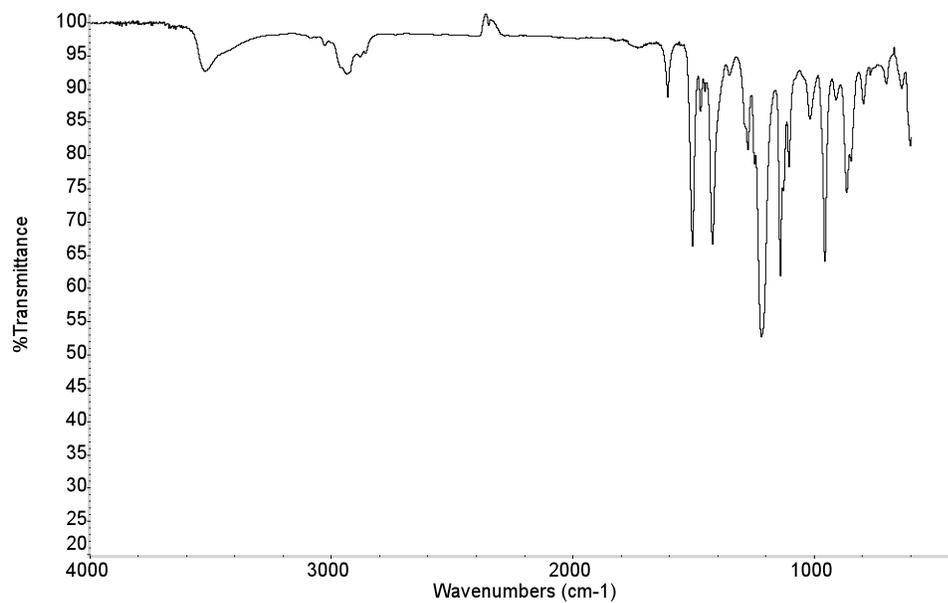
Figure A.4.50 Infrared Spectrum (thin film/NaCl) of compound **520**.
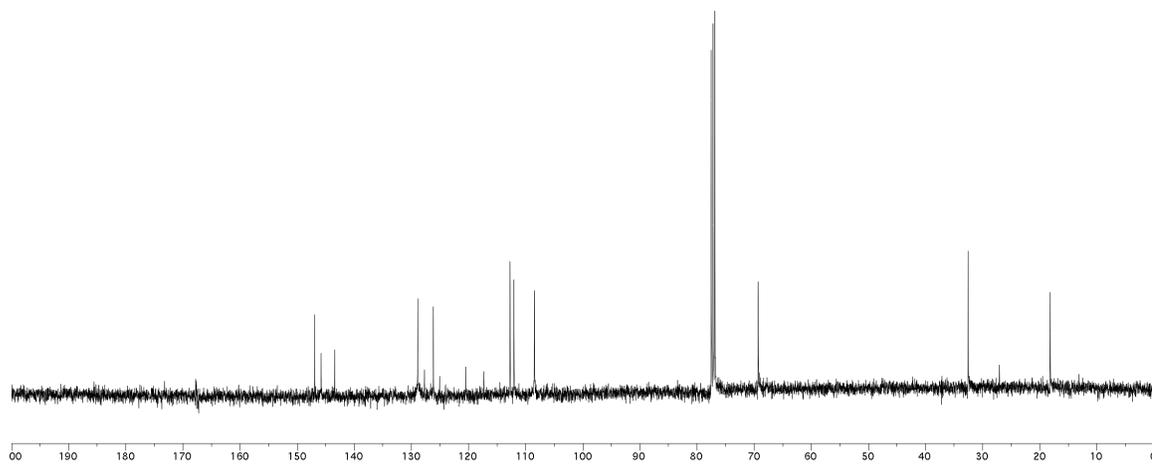


Figure A.4.51 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **520**.
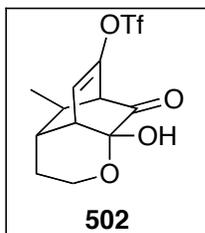
**Figure A.4.52** $^{1}$H NMR (400MHz, CDCl$_3$) of compound **502**
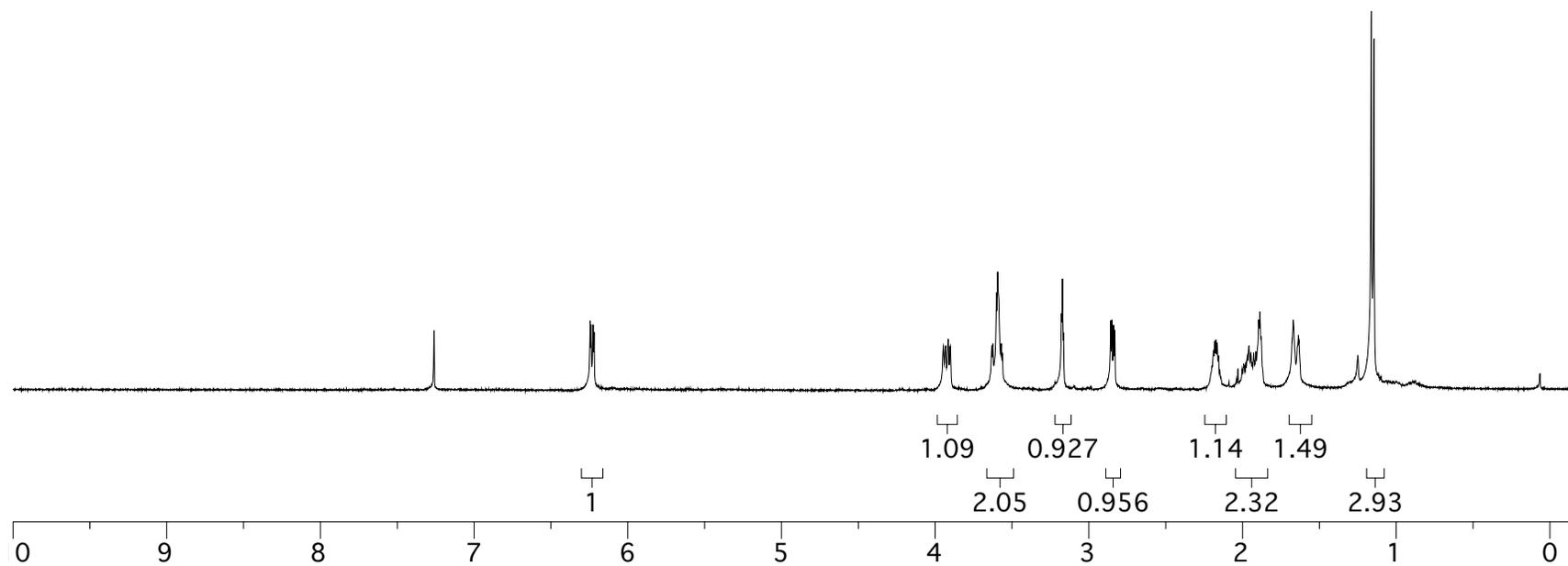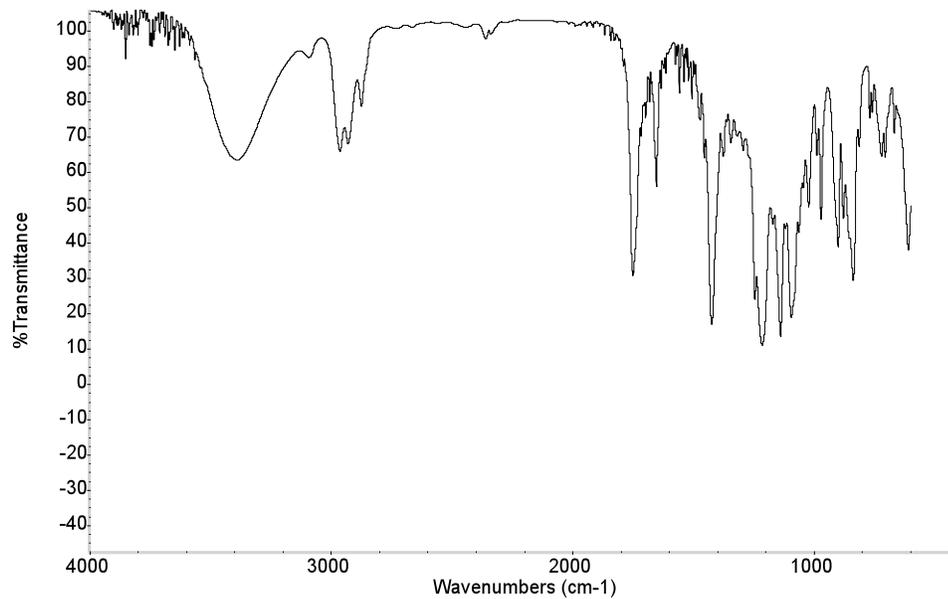
Figure A.4.53 Infrared Spectrum (thin film/NaCl) of compound **522**.
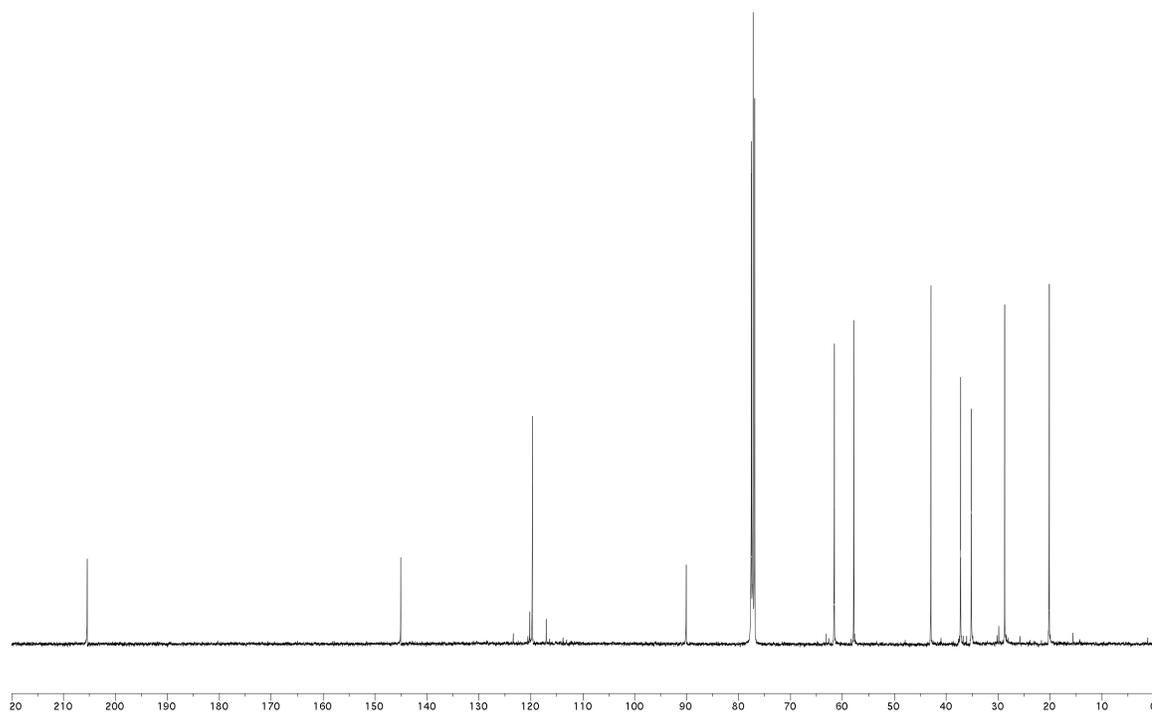


Figure A.4.54 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **522**.
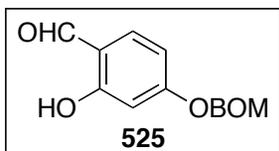
Figure A.4.55 $^1$H NMR (400MHz, CDCl$_3$) of compound 525
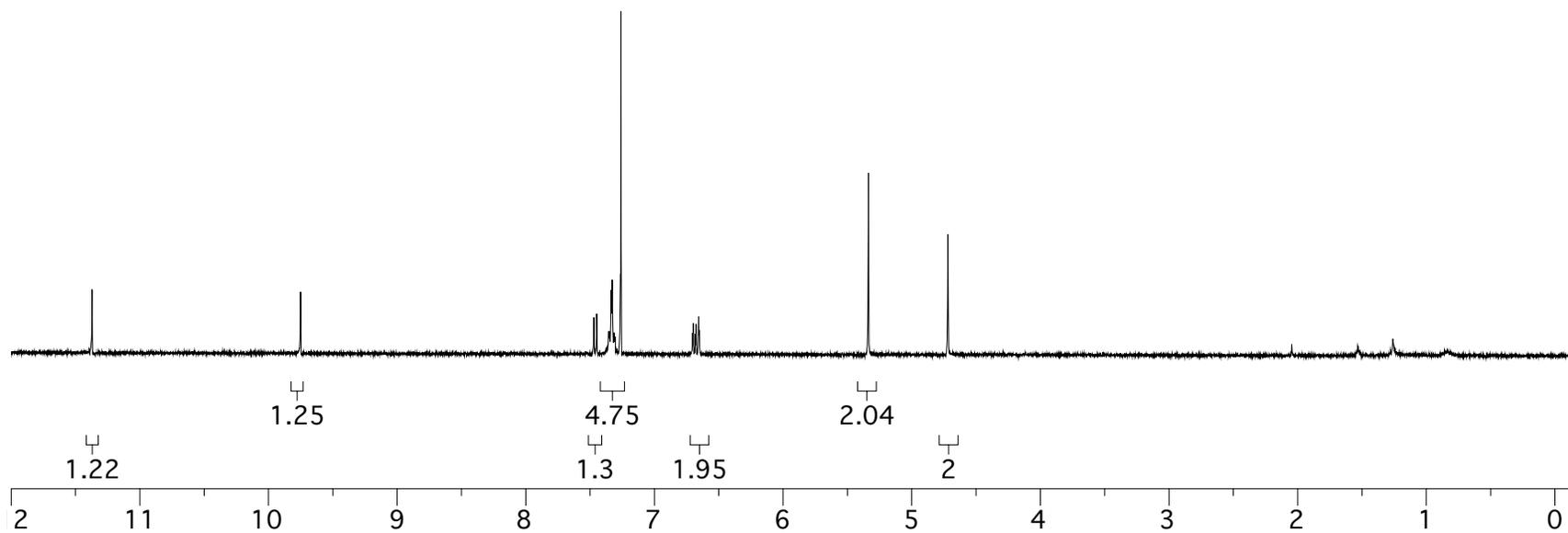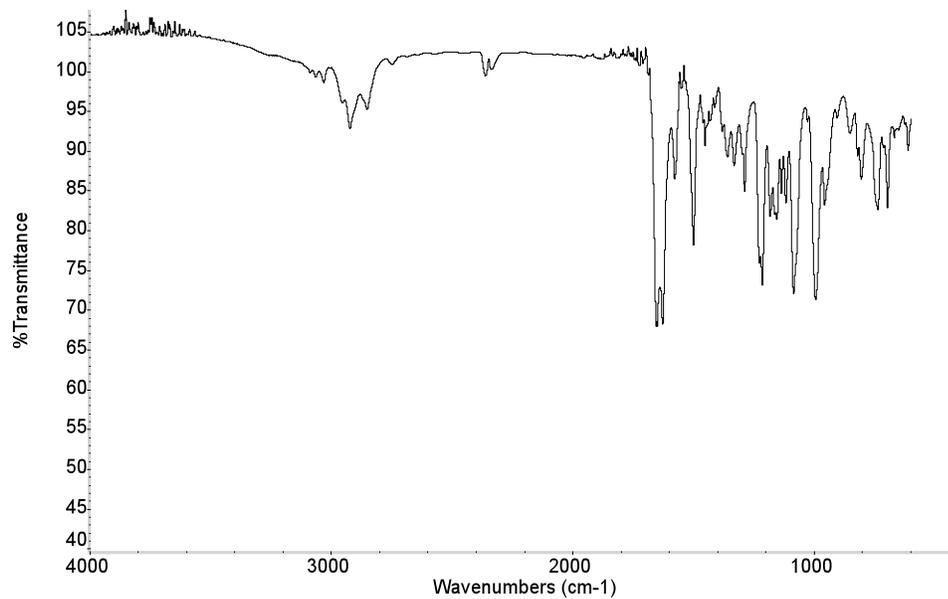
Figure A.4.56 Infrared Spectrum (thin film/NaCl) of compound **525**.
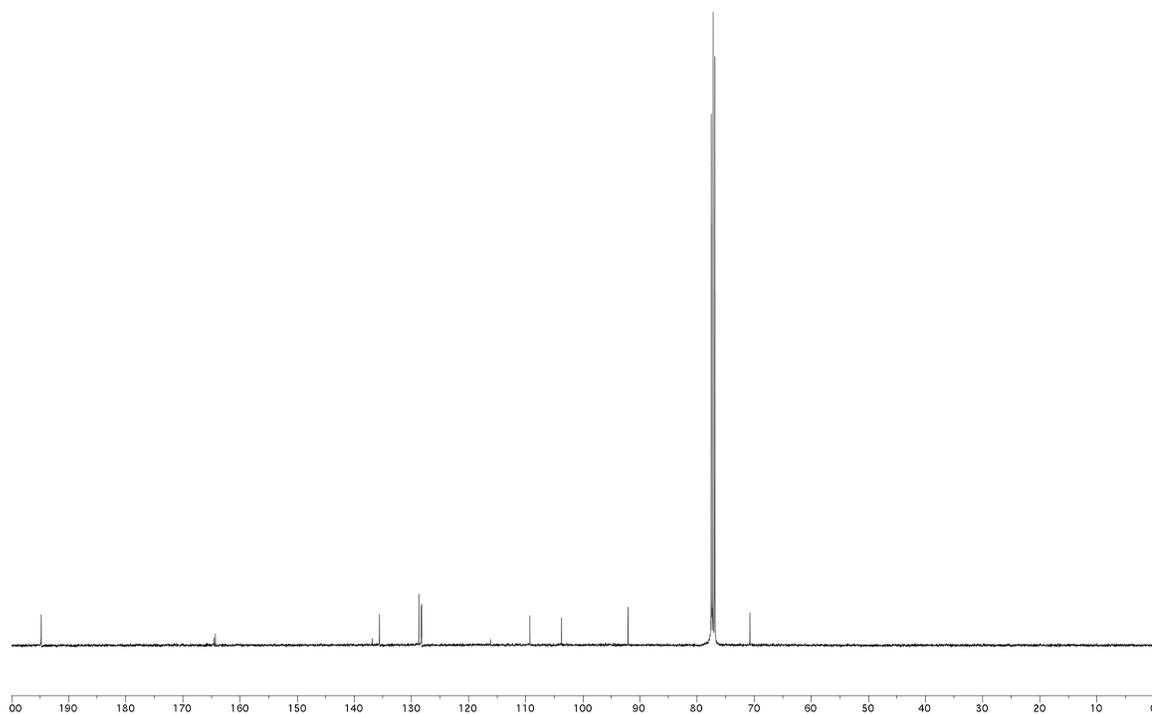


Figure A.4.57 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **525**.
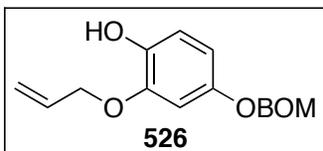
Figure A.4.58 $^1$H NMR (400MHz, CDCl$_3$) of compound 526
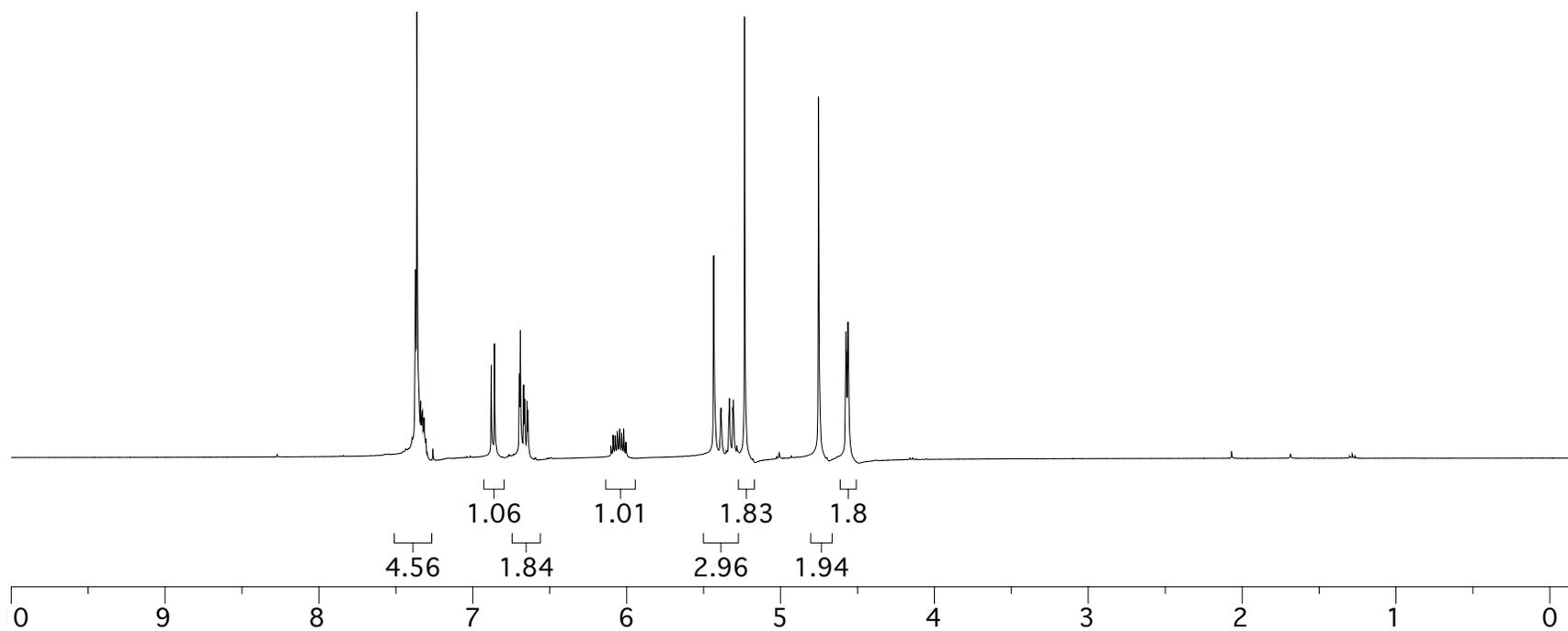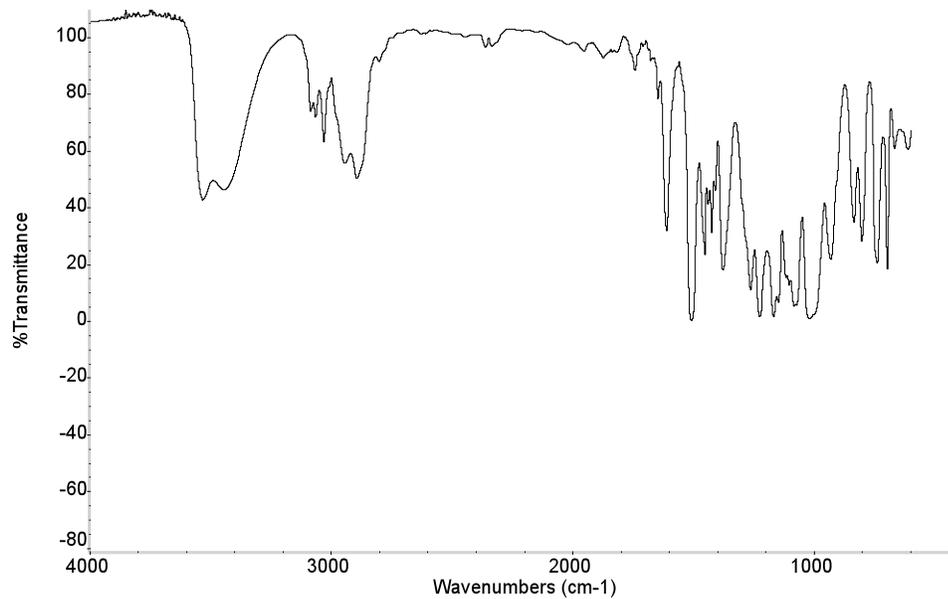
Figure A.4.59 Infrared Spectrum (thin film/NaCl) of compound **526**.
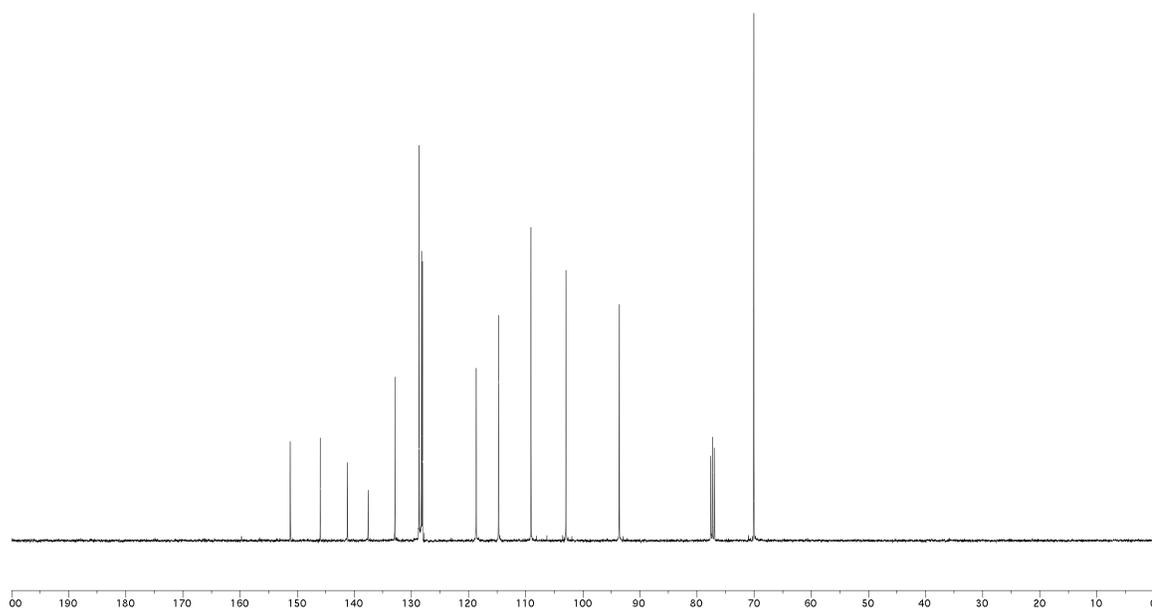


Figure A.4.60 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **526**.
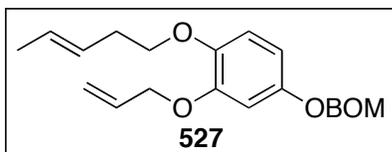
Figure A.4.61 $^1$H NMR (400MHz, CDCl$_3$) of compound 527
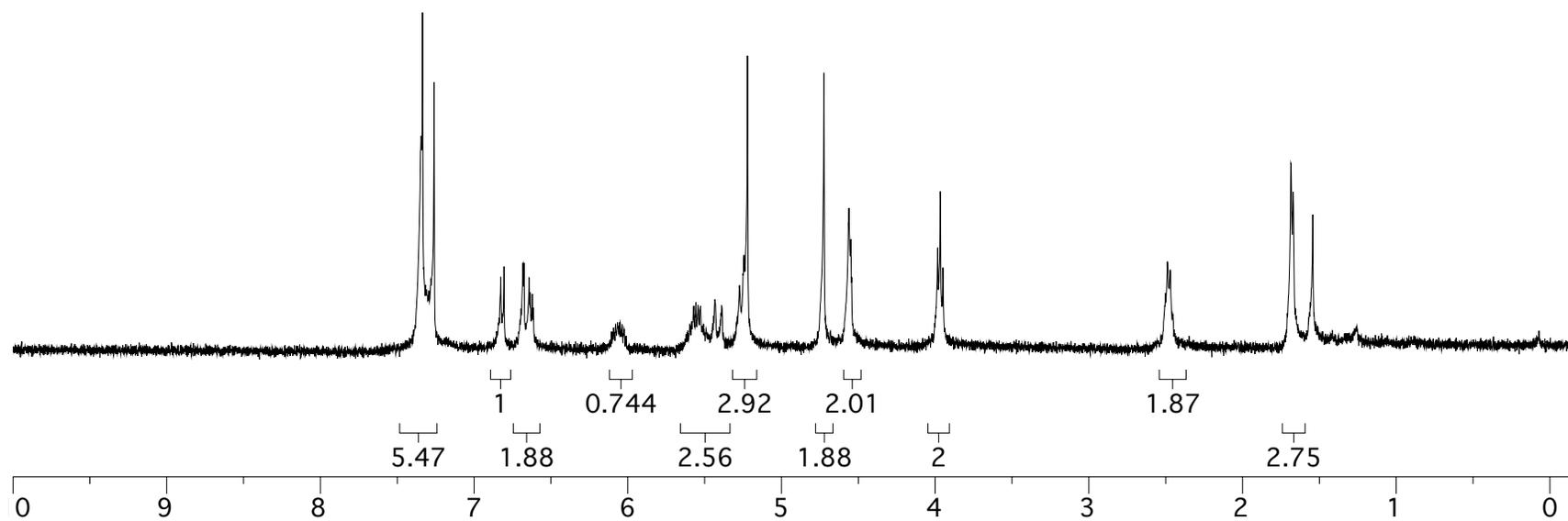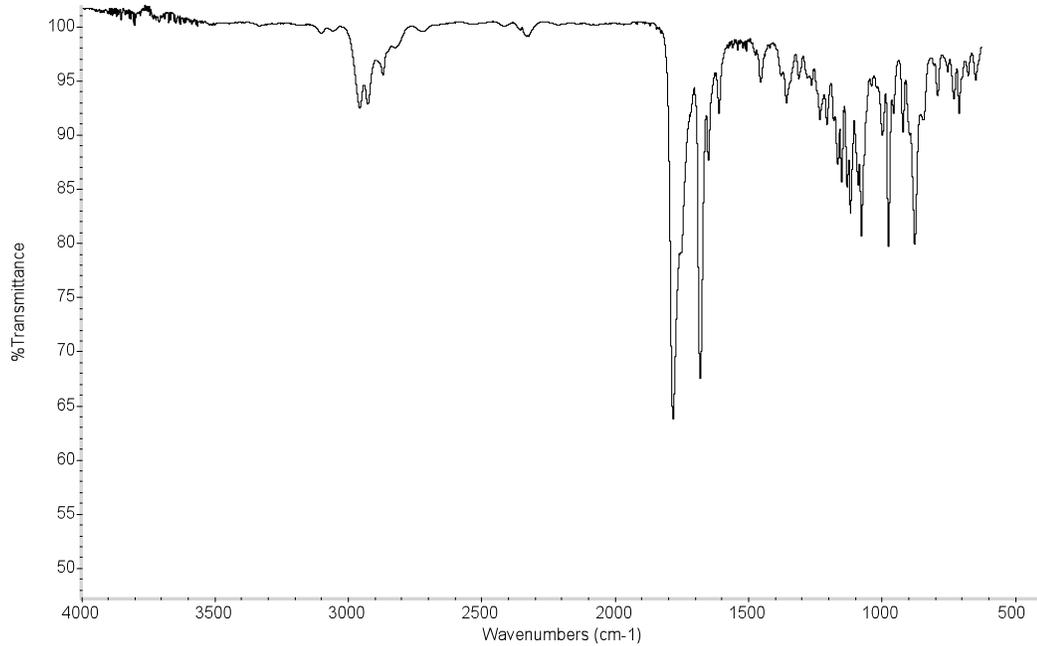
Figure A.4.62 Infrared Spectrum (thin film/NaCl) of compound **527**.
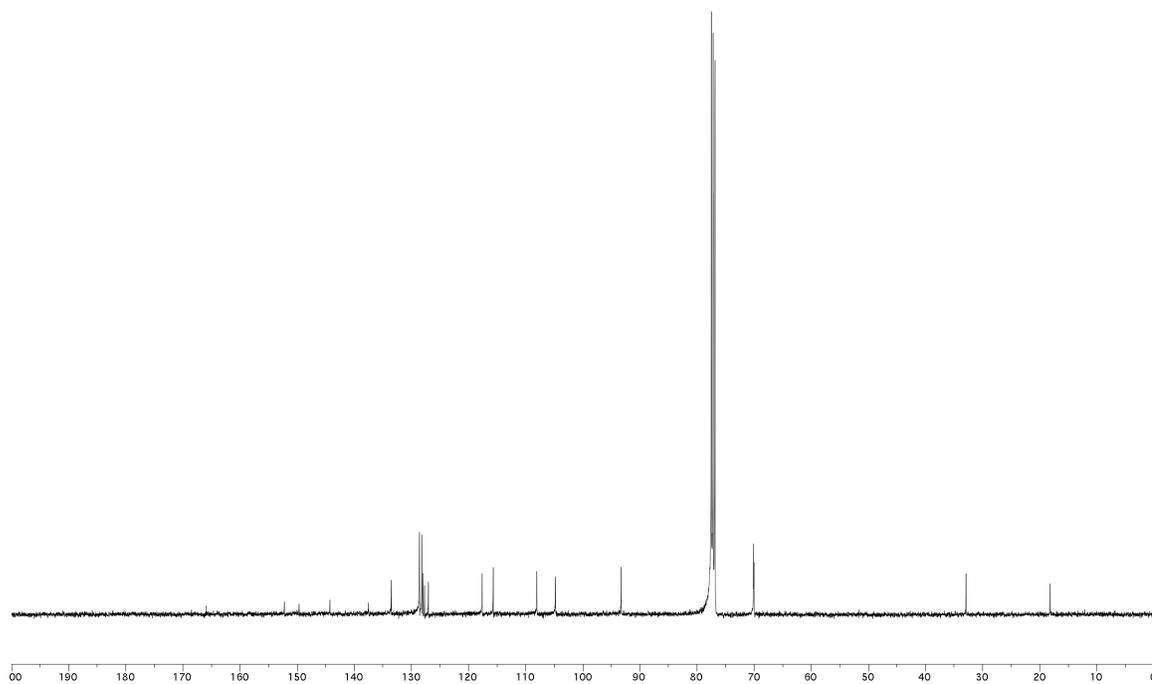


Figure A.4.63 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **527**.
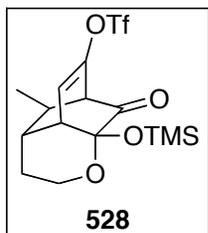
Figure A.4.64 $^1$H NMR (400MHz, CDCl$_3$) of compound 528
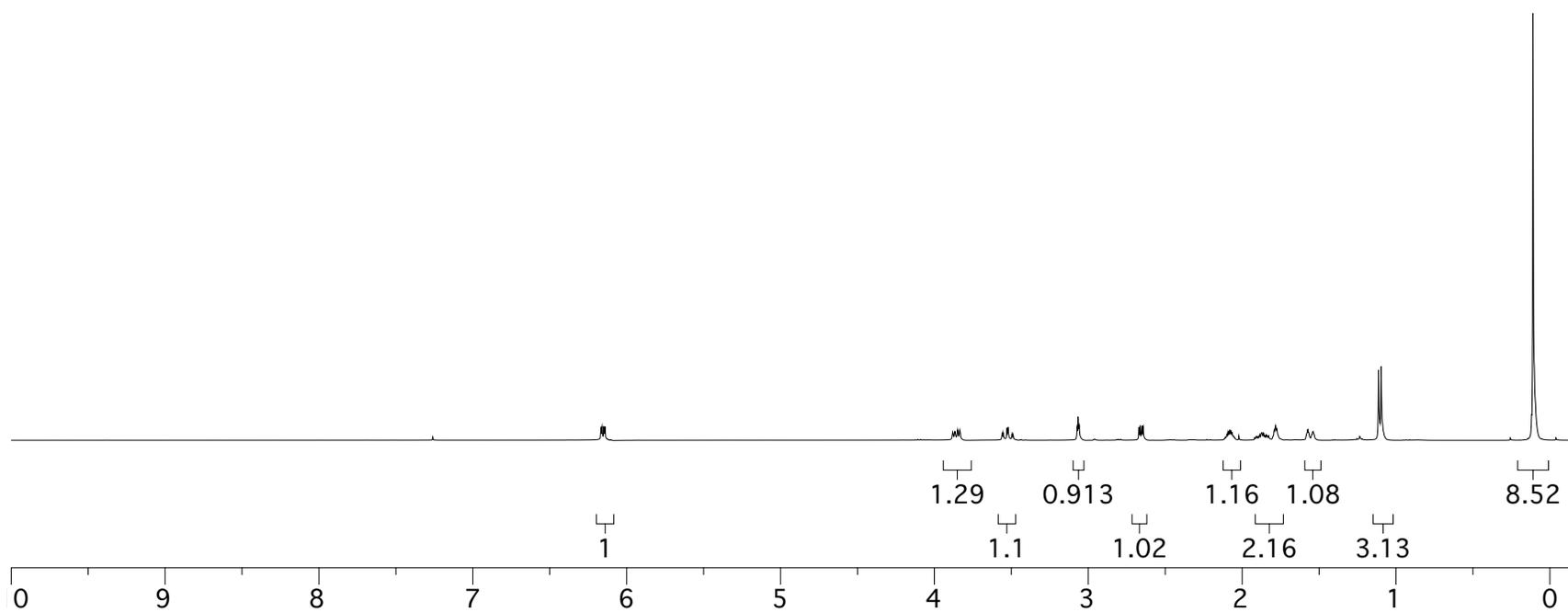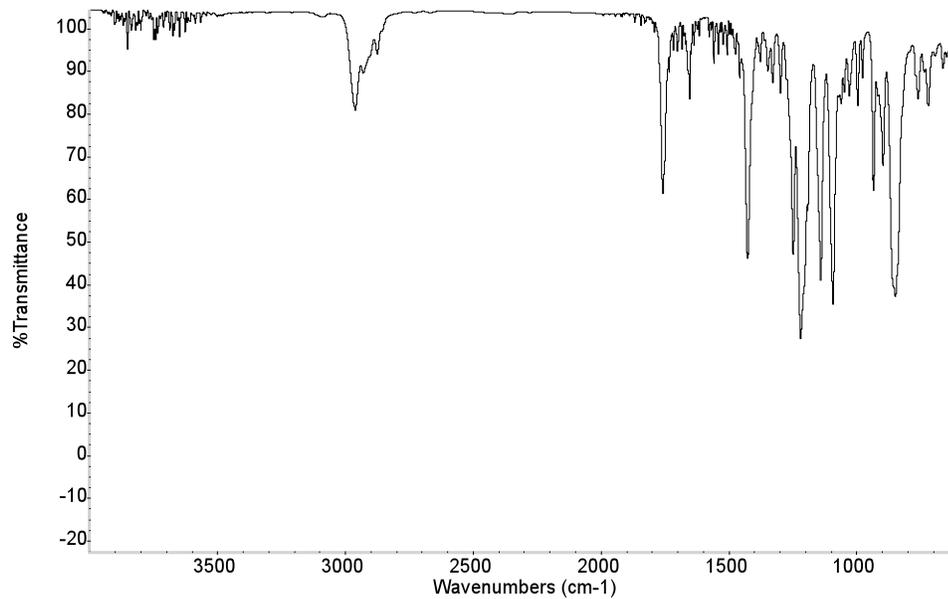
Figure A.4.65 Infrared Spectrum (thin film/NaCl) of compound **528**.
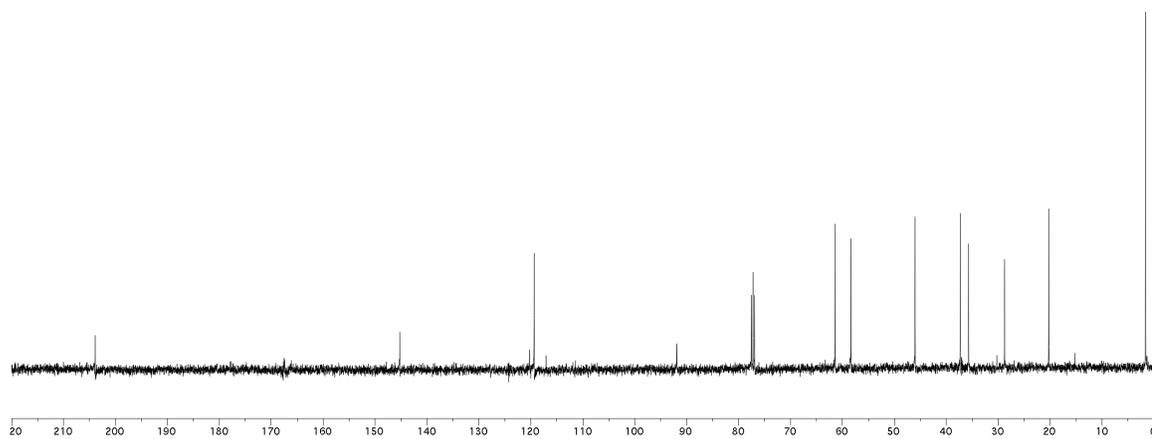


Figure A.4.66 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **528**.
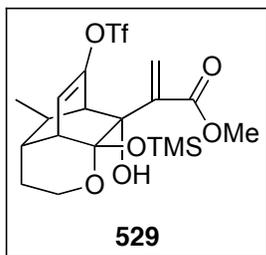
Figure A.4.67 $^{1}$H NMR (400MHz, CDCl$_3$) of compound 529
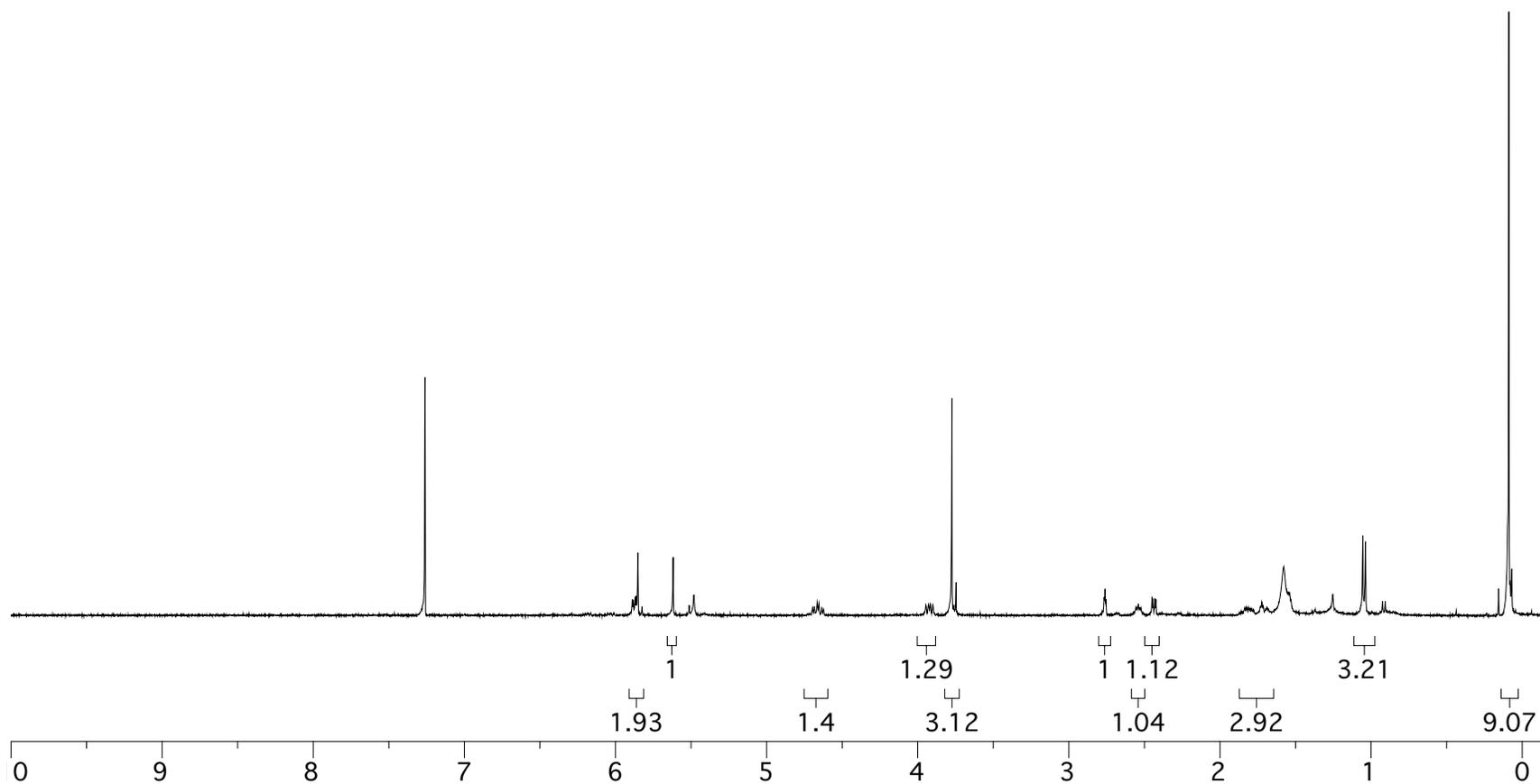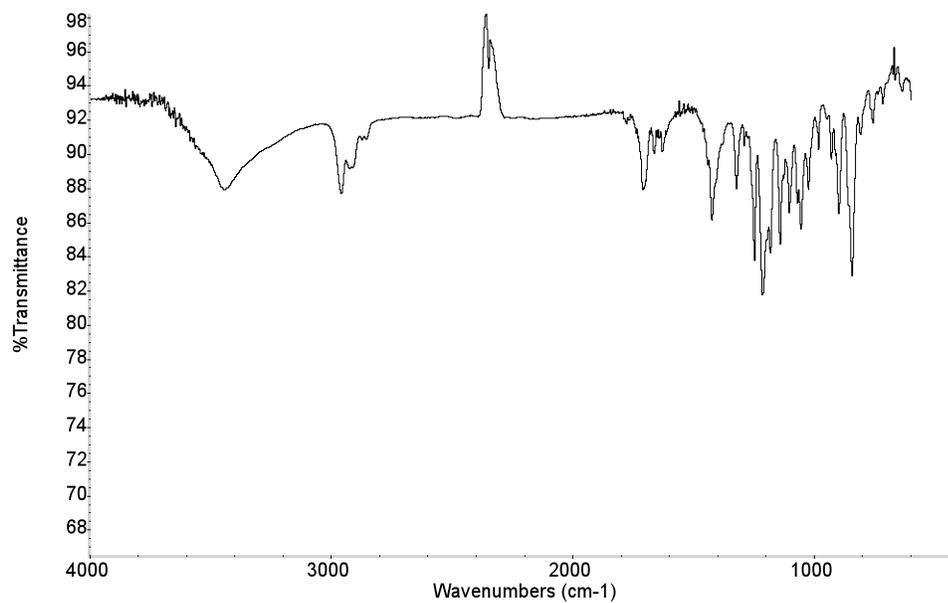
Figure A.4.68 Infrared Spectrum (thin film/NaCl) of compound **529**.
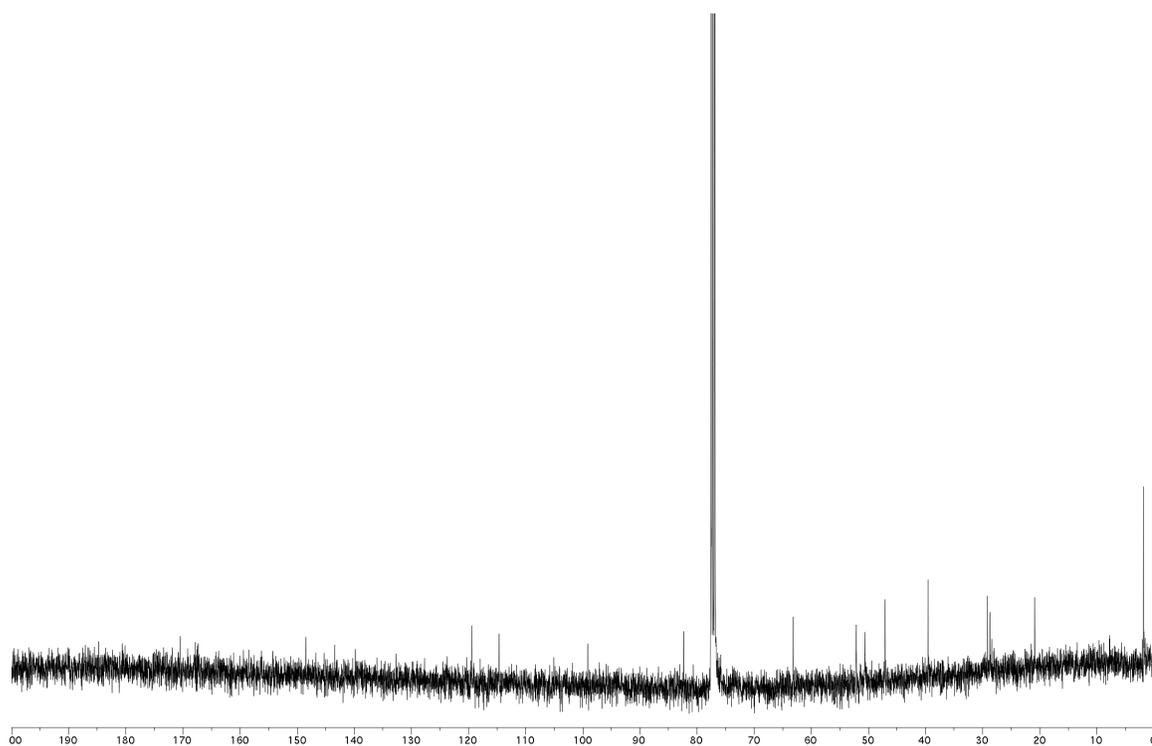


Figure A.4.69 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **529**.
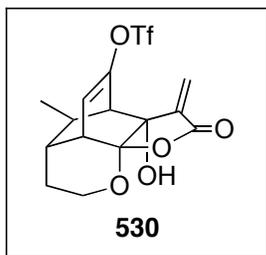
Figure A.4.70 $^1$H NMR (400MHz, CDCl$_3$) of compound 530
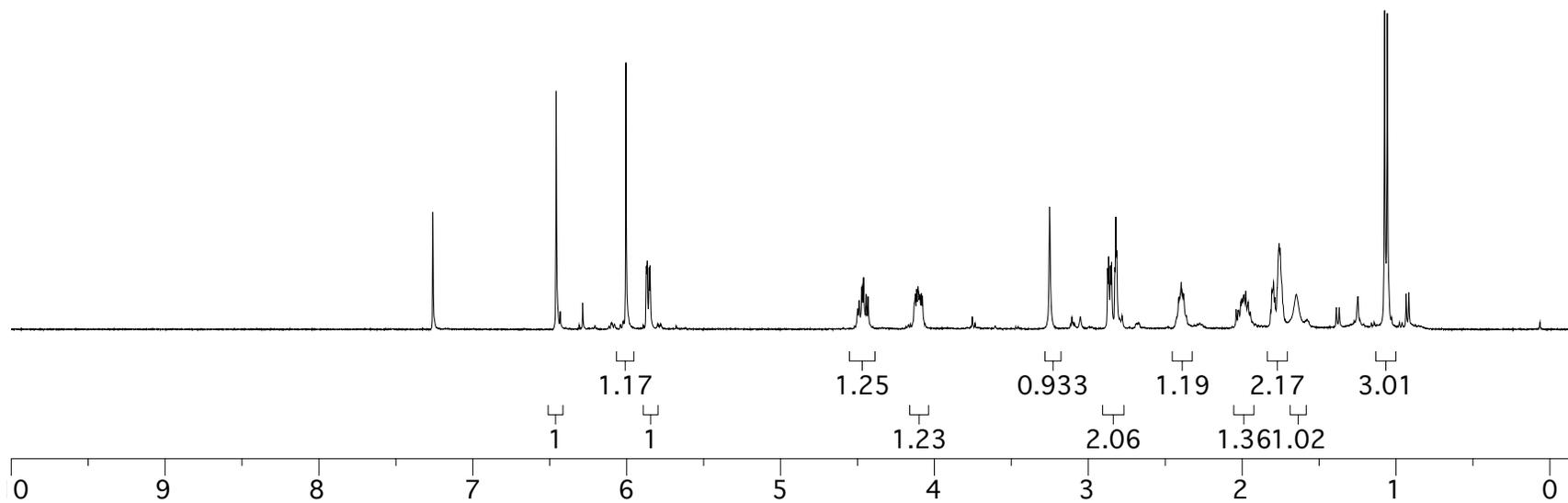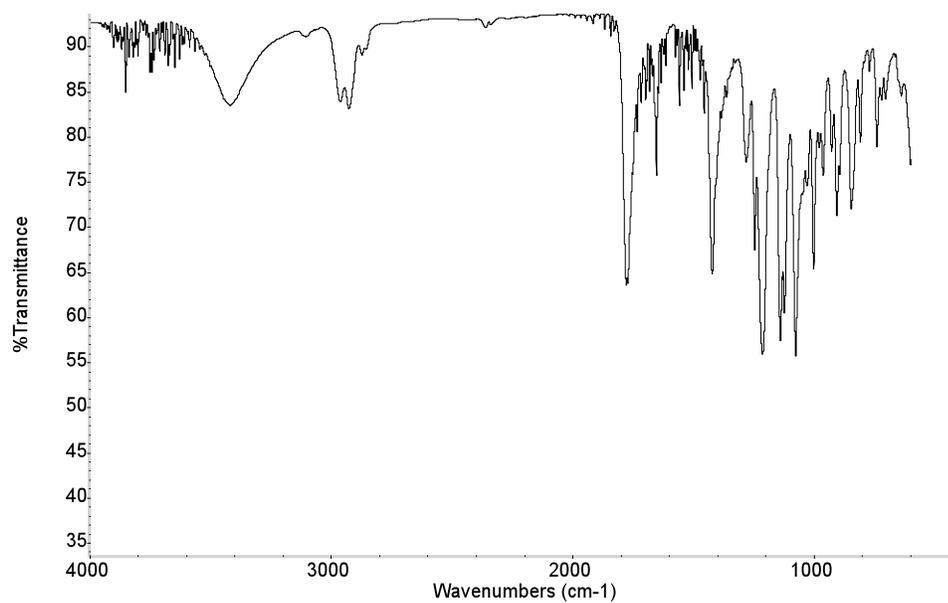
Figure A.4.71 Infrared Spectrum (thin film/NaCl) of compound **530**.
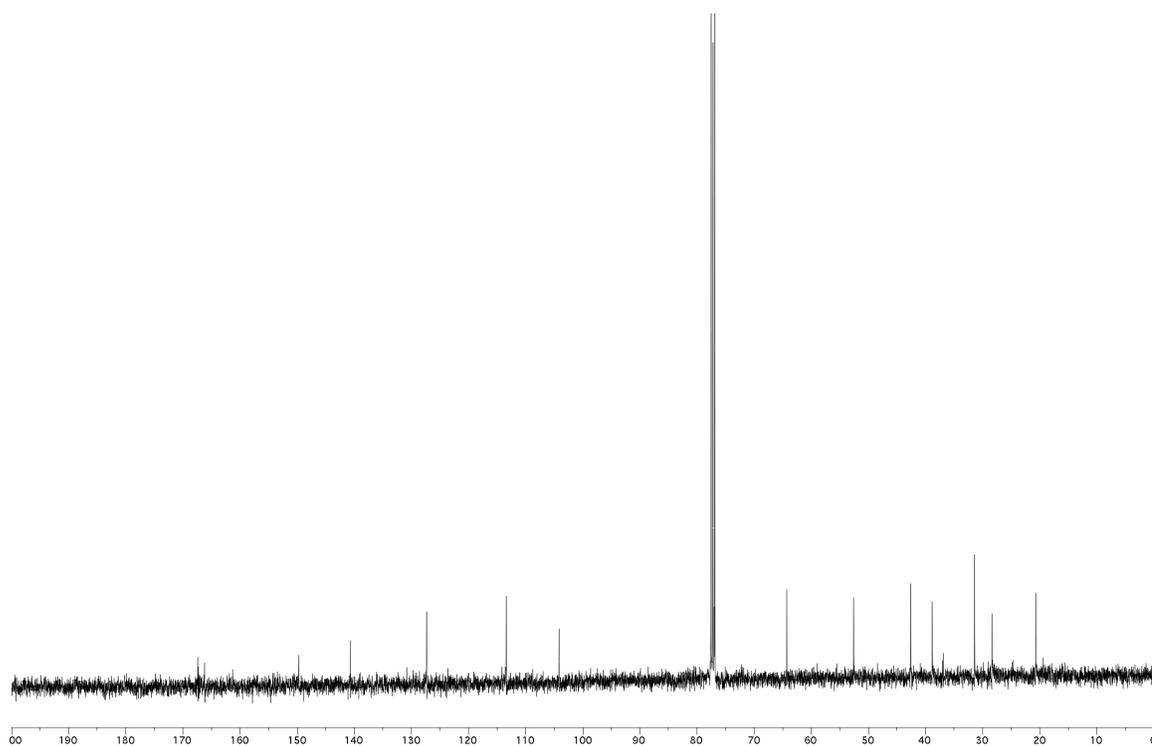


Figure A.4.72 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **530**.
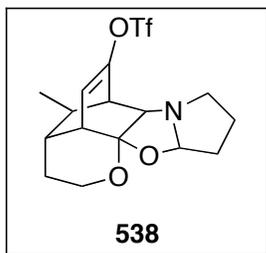
Figure A.4.73 $^1$H NMR (400MHz, CDCl$_3$) of compound **538**
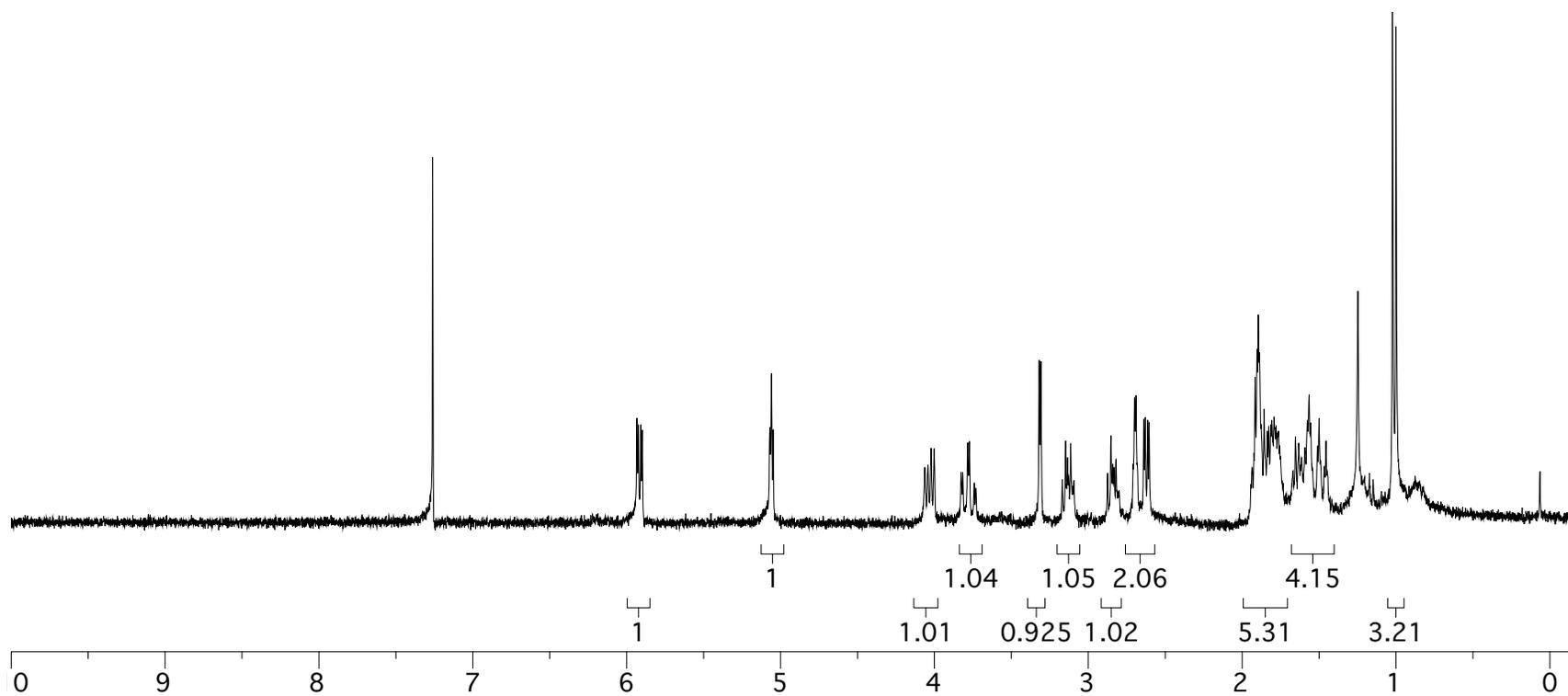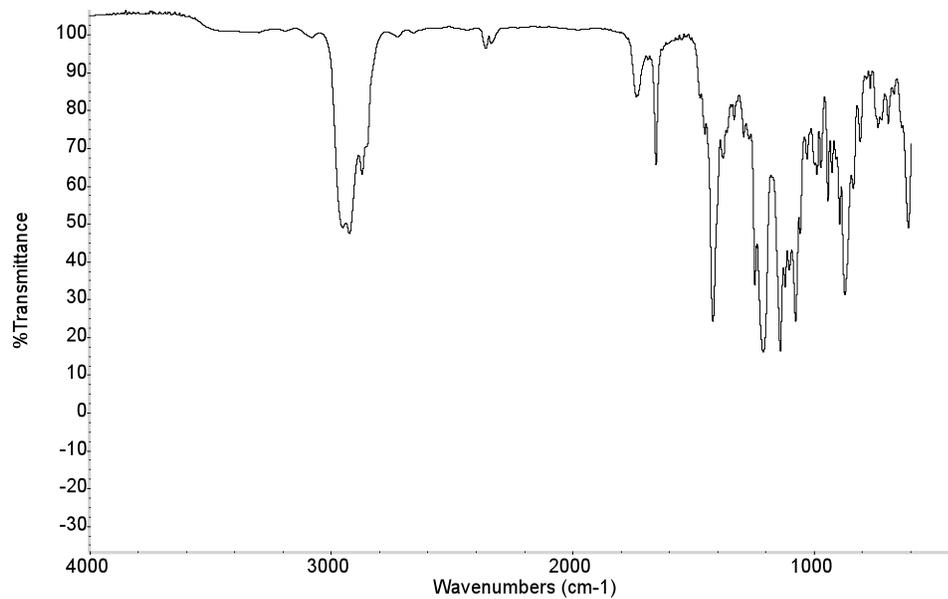
Figure A.4.74 Infrared Spectrum (thin film/NaCl) of compound **538**.
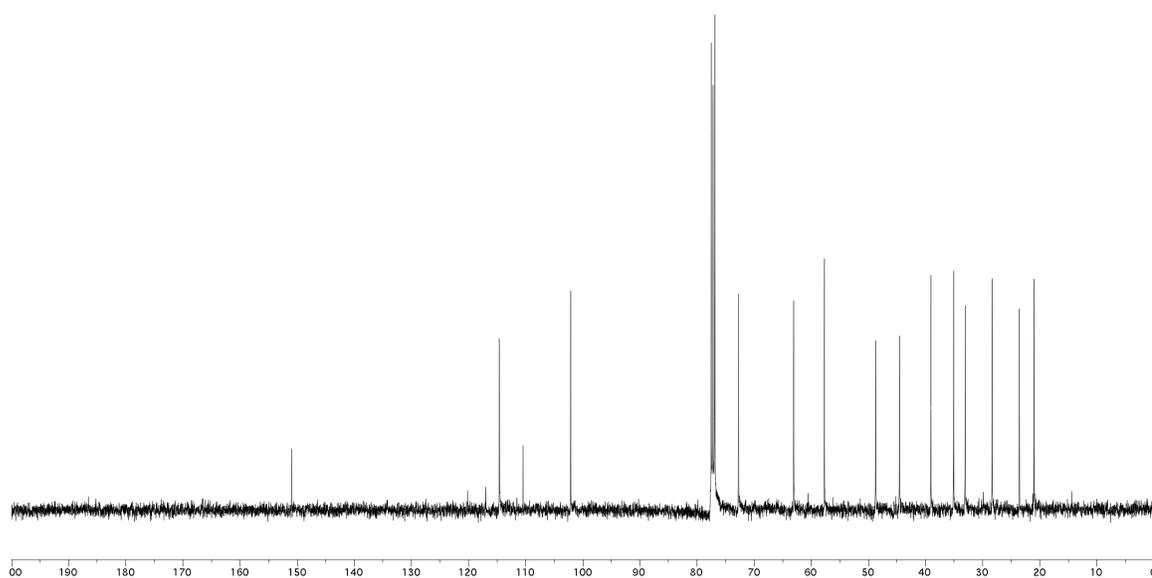


Figure A.4.75 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **538**.
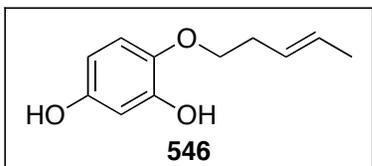
Figure A.4.76 $^1$H NMR (400MHz, CDCl$_3$) of compound 546
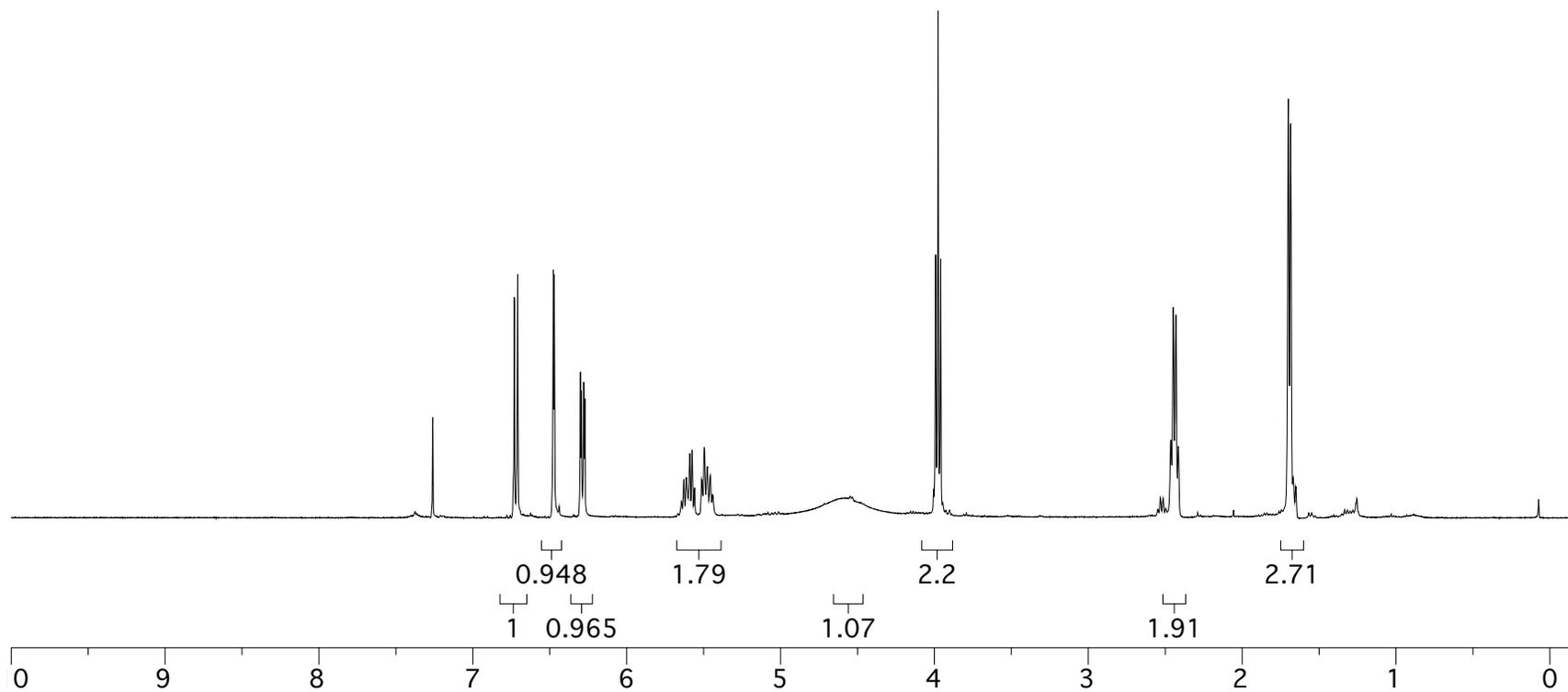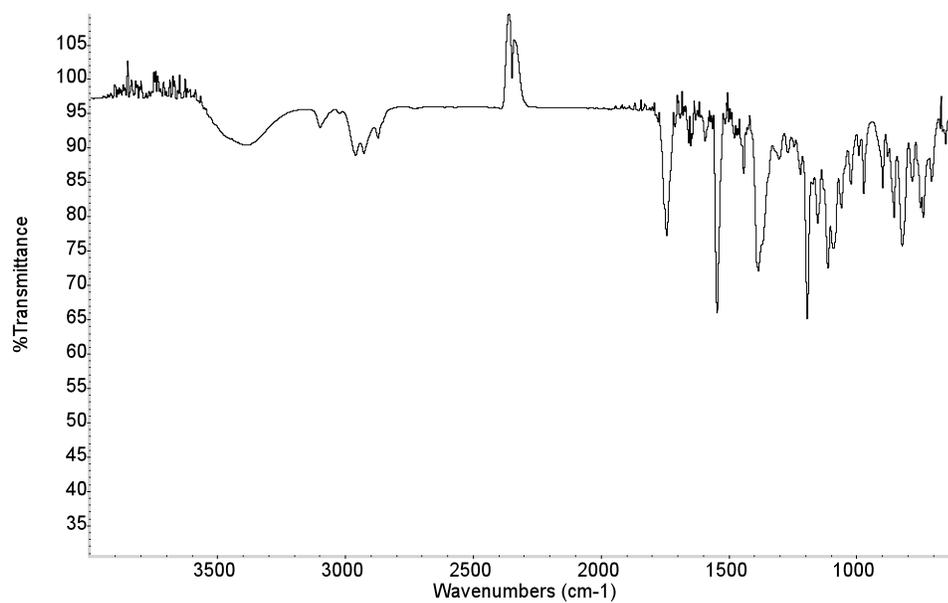
Figure A.4.77 Infrared Spectrum (thin film/NaCl) of compound **546**.
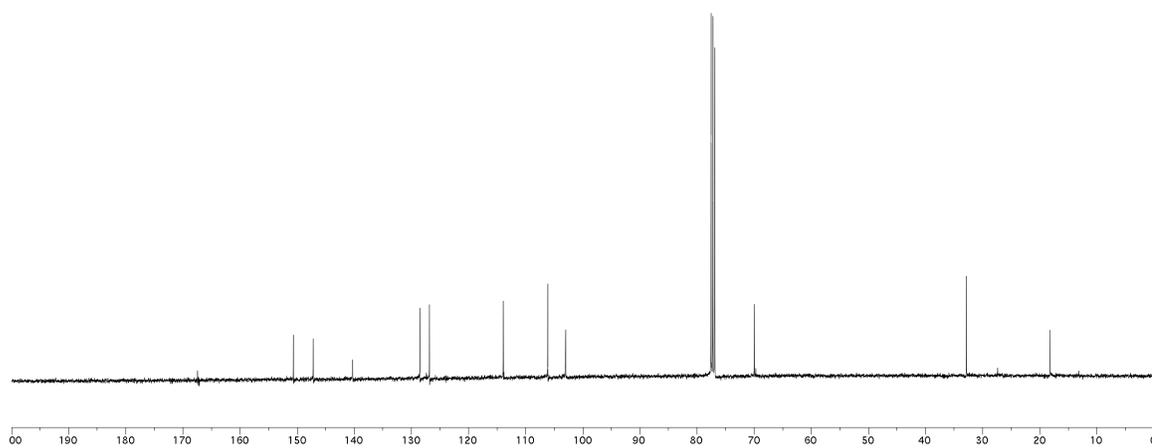


Figure A.4.78 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **546**.
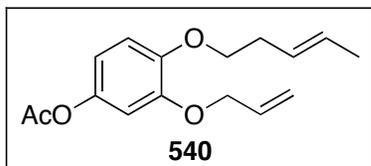
Figure A.4.79 $^1$H NMR (400MHz, CDCl$_3$) of compound 540
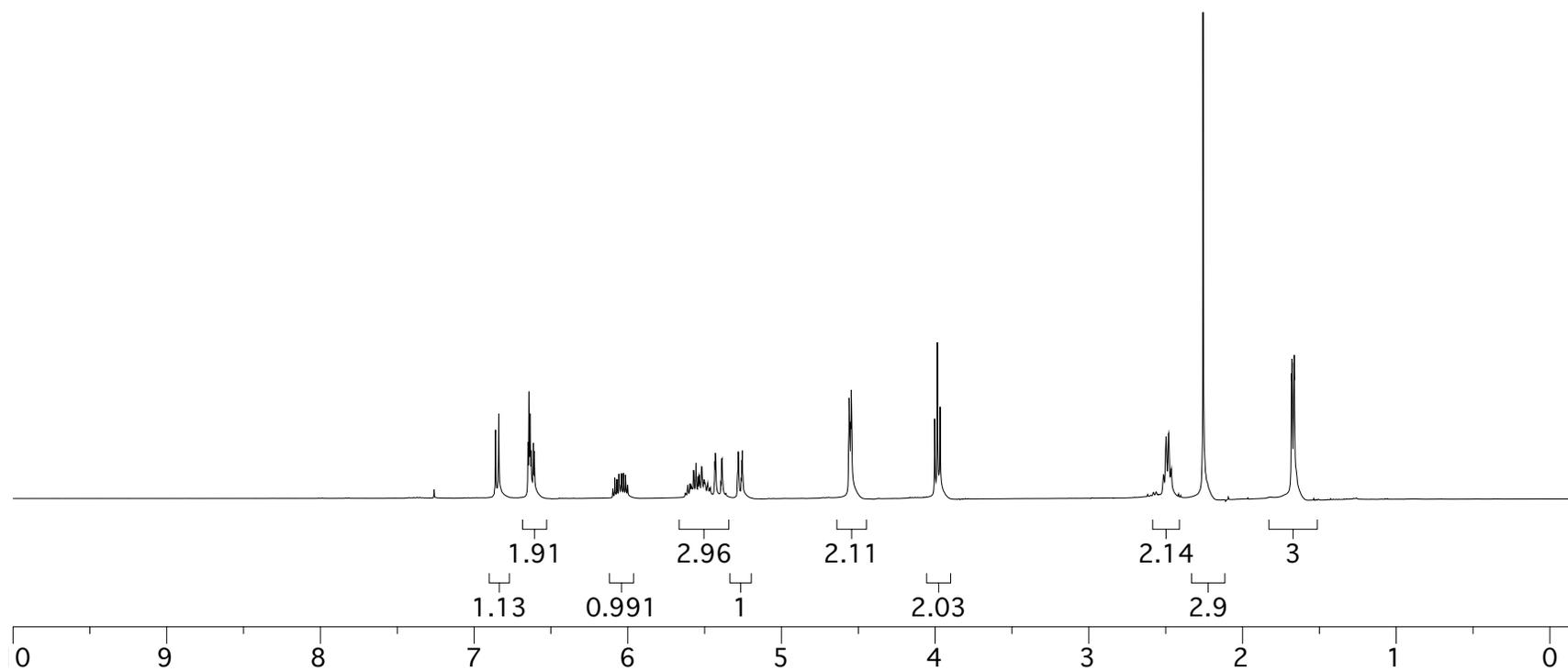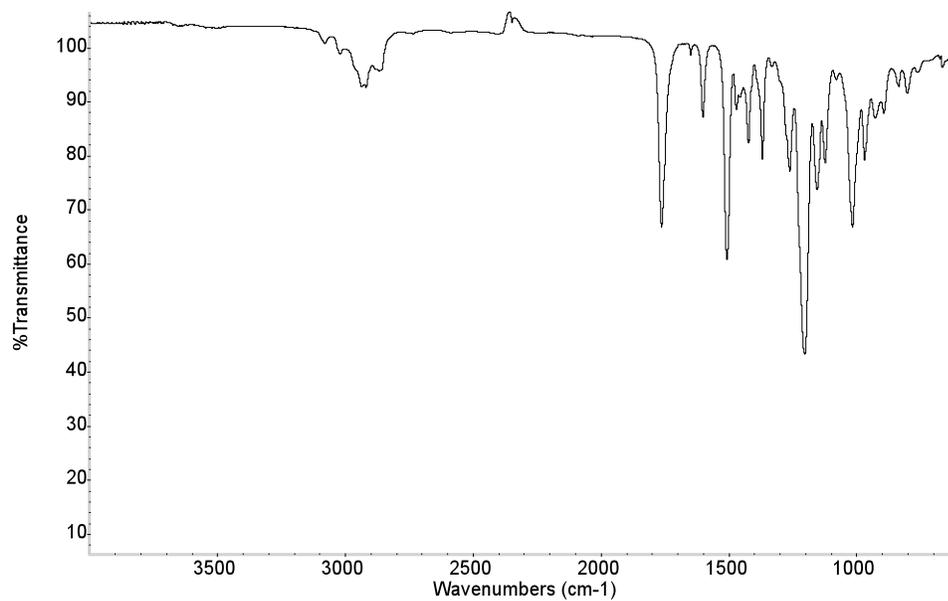
Figure A.4.80 Infrared Spectrum (thin film/NaCl) of compound **540**.
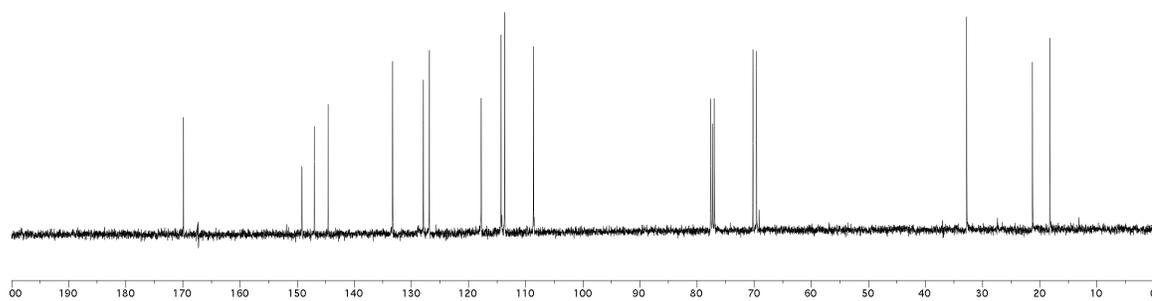


Figure A.4.81 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **540**.
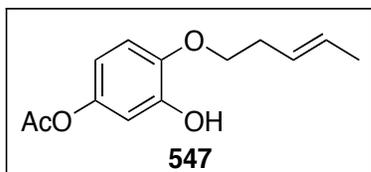
Figure A.4.82 $^1$H NMR (400MHz, CDCl$_3$) of compound 547
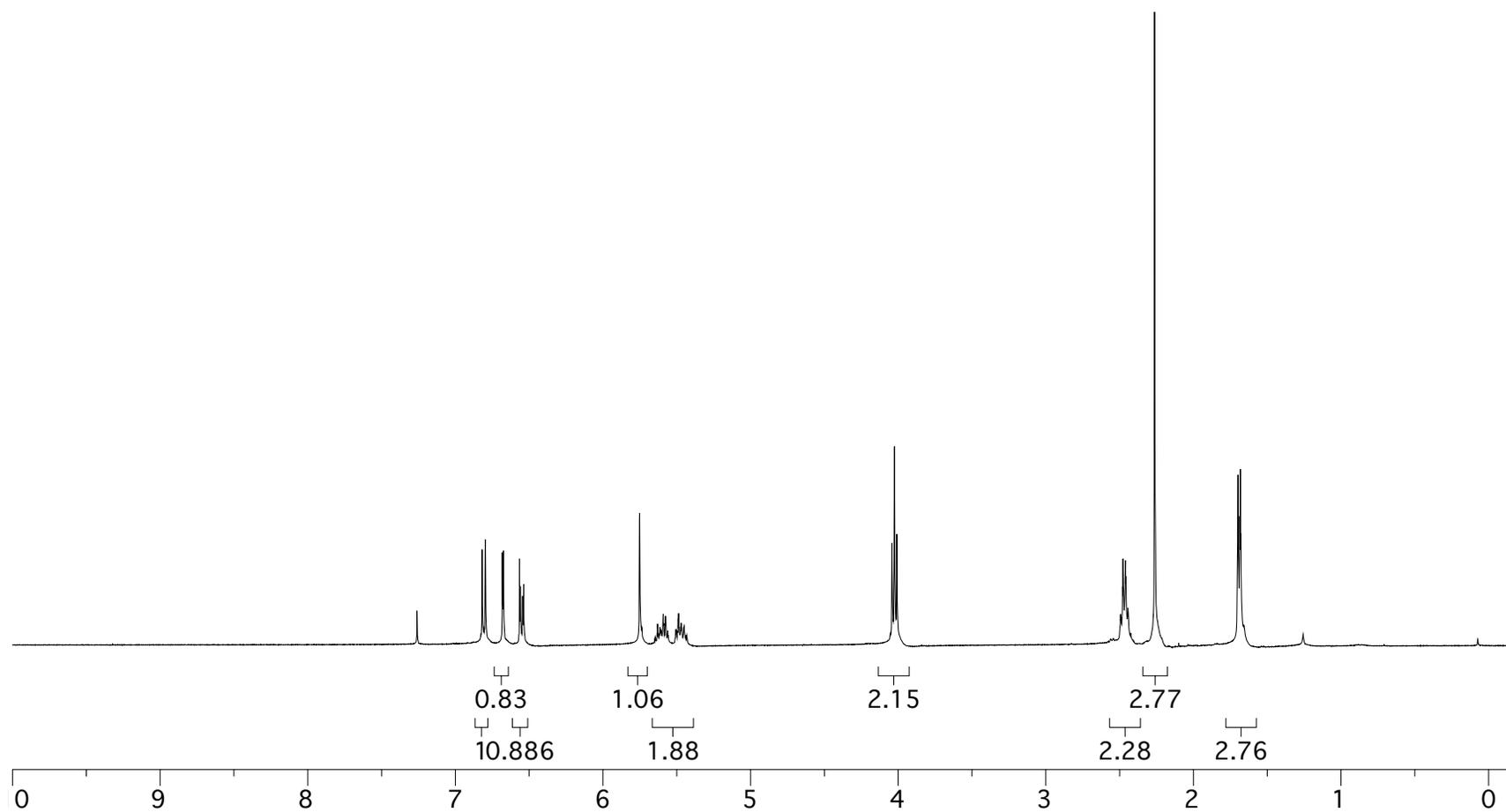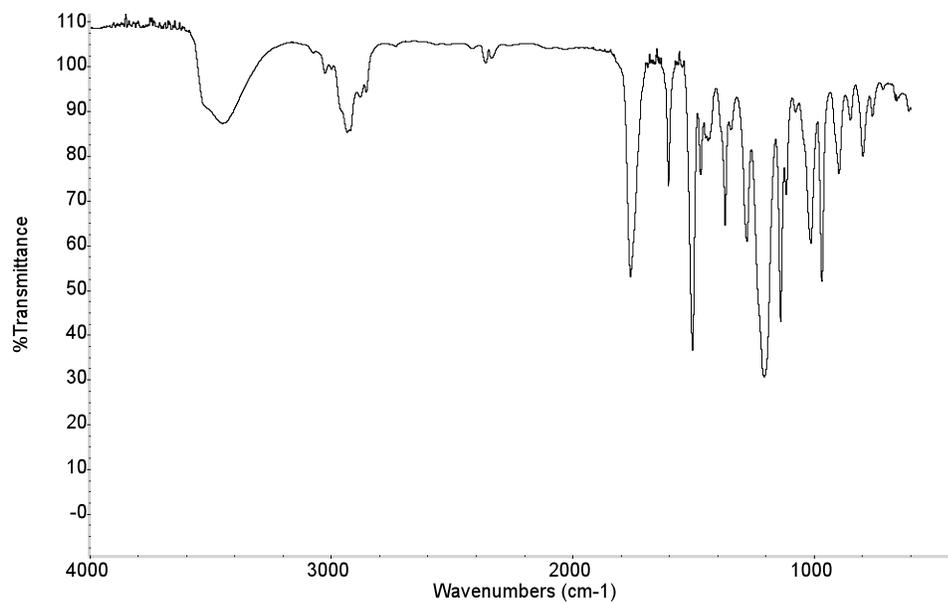
Figure A.4.83 Infrared Spectrum (thin film/NaCl) of compound **547**.
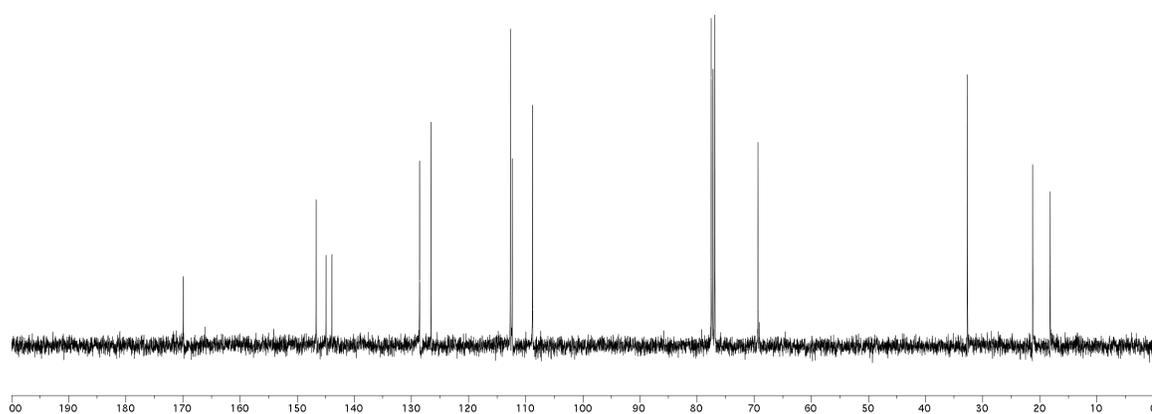


Figure A.4.84 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **547**.
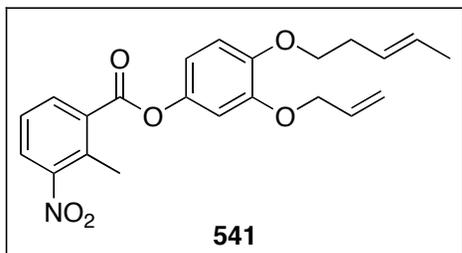
**Figure A.4.85** $^1$H NMR (400MHz, CDCl$_3$) of compound **541**
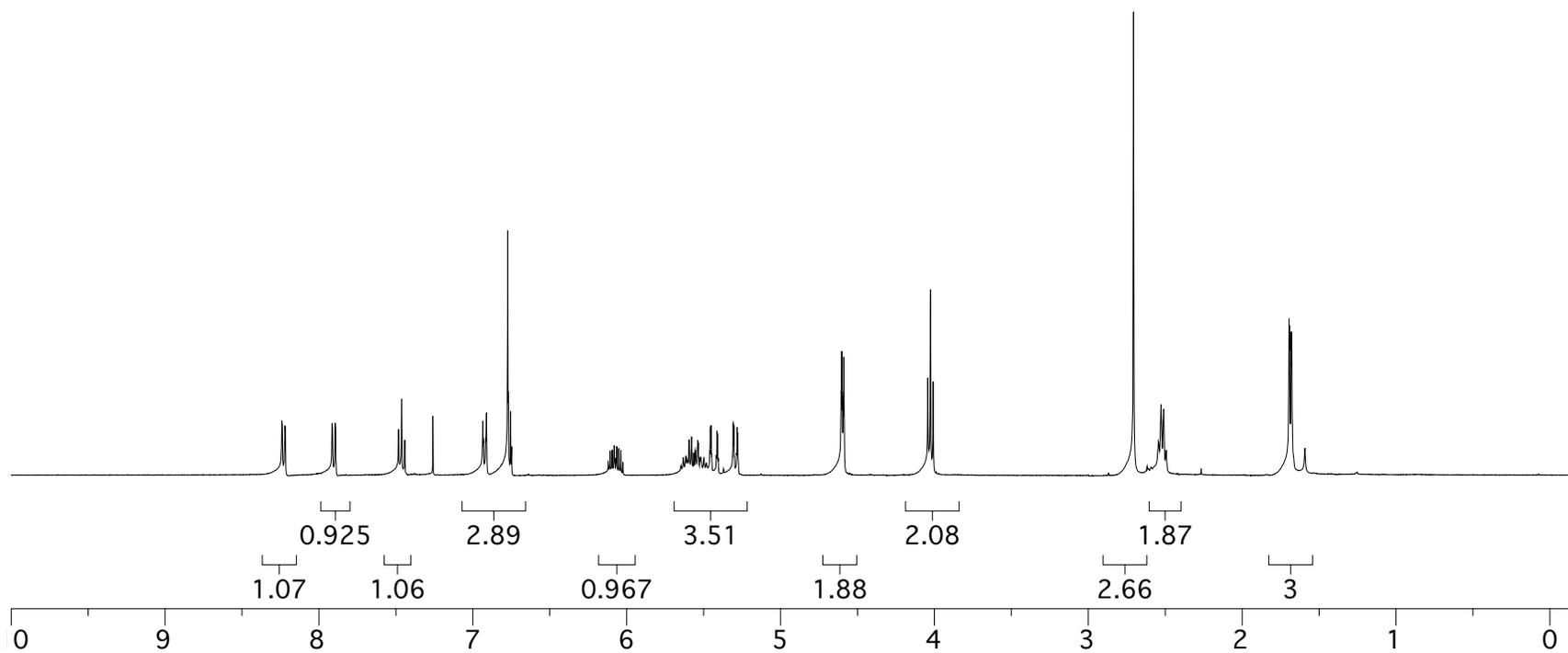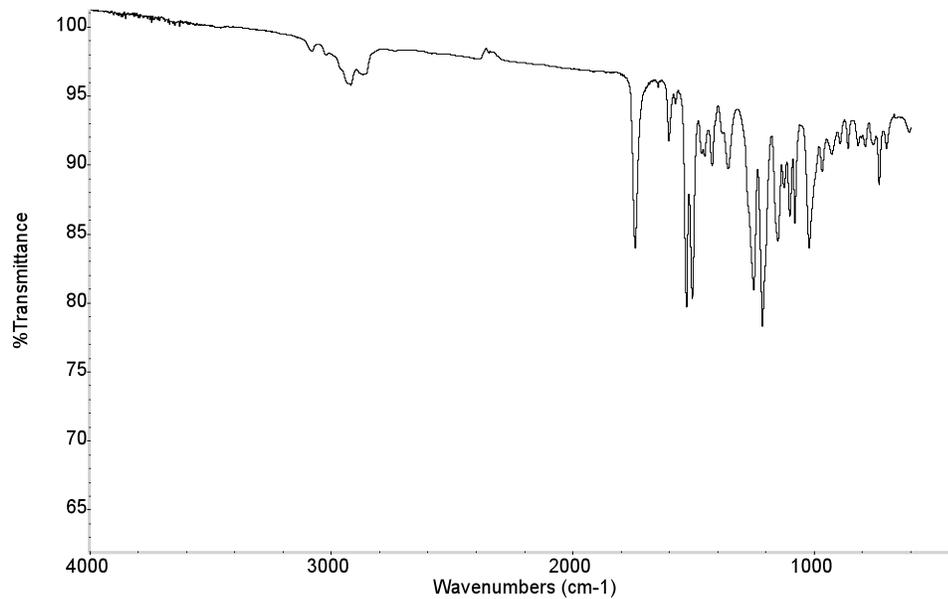
Figure A.4.86 Infrared Spectrum (thin film/NaCl) of compound **541**.
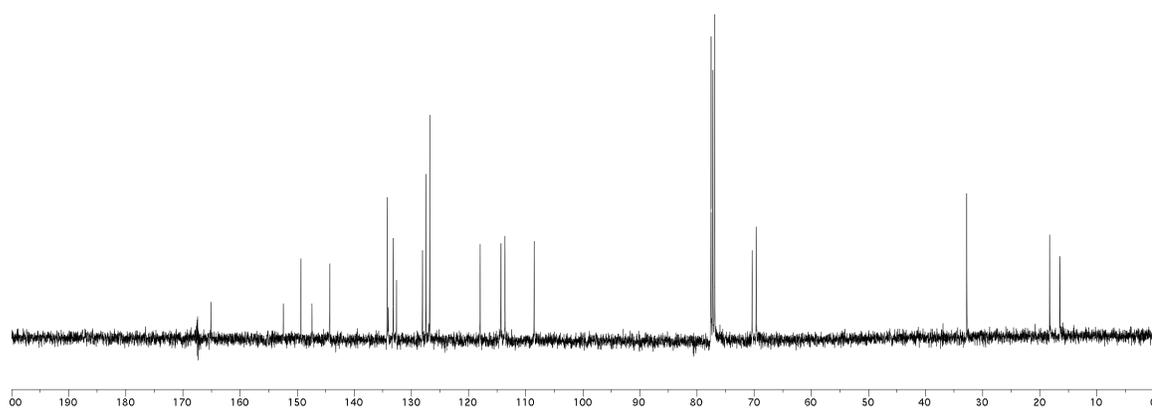


Figure A.4.87 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **541**.
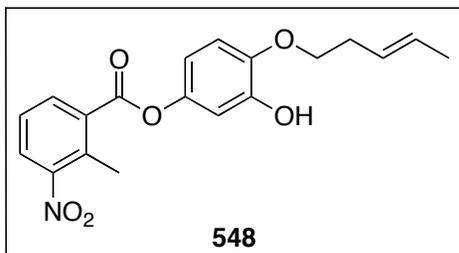
Figure A.4.88 $^1$H NMR (400MHz, CDCl$_3$) of compound 548
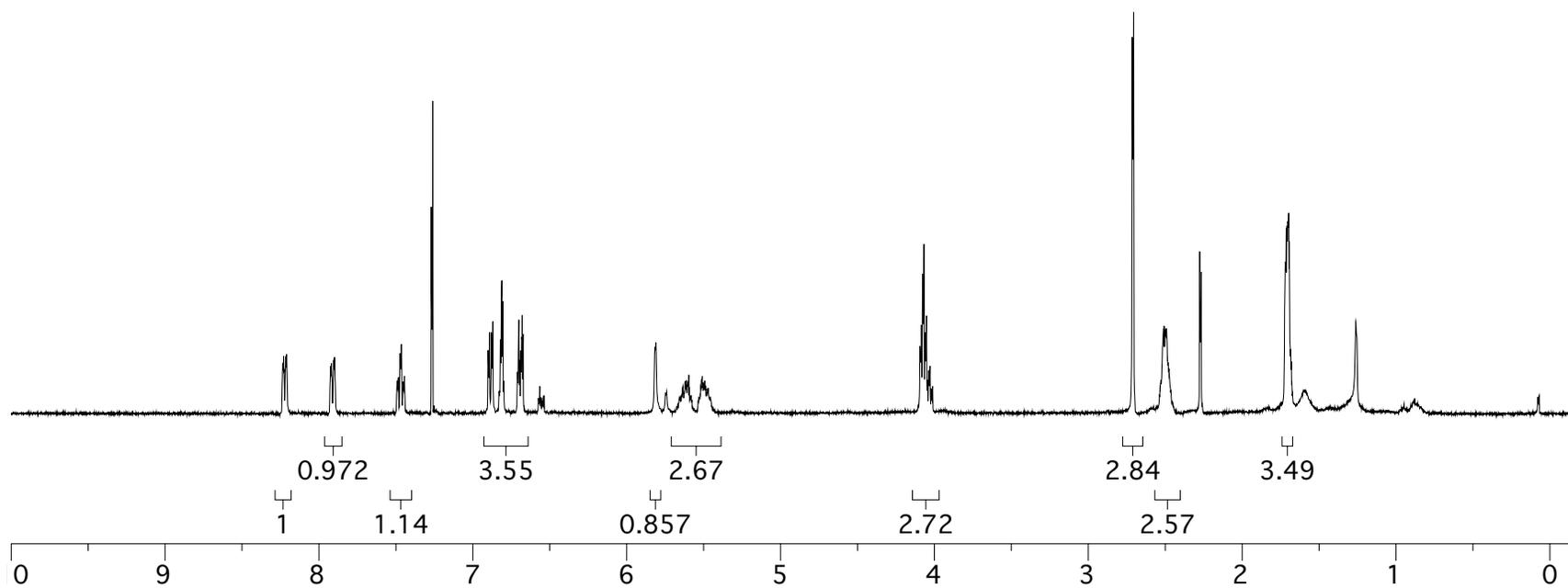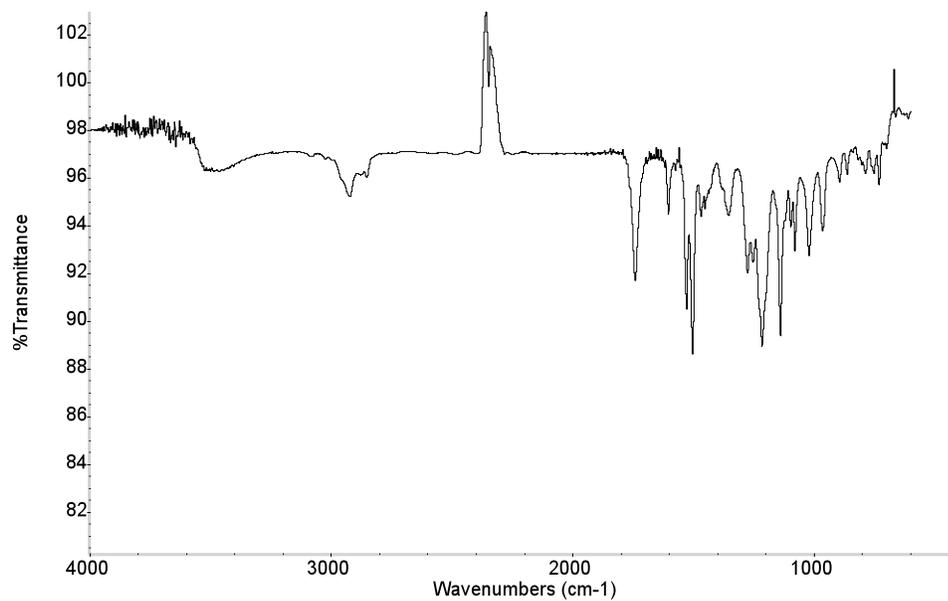
Figure A.4.89 Infrared Spectrum (thin film/NaCl) of compound **548**.
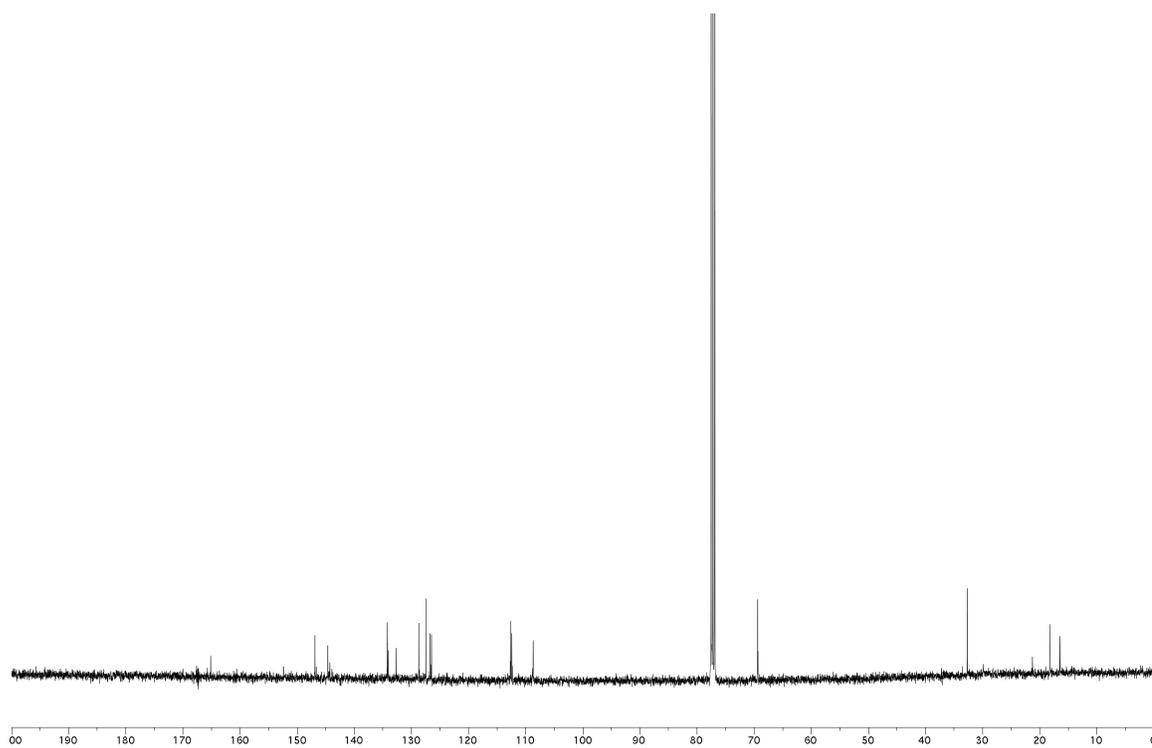


Figure A.4.90 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **548**.
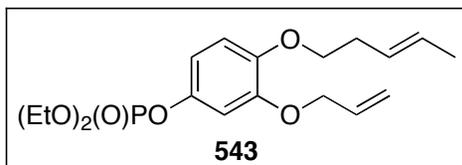
Figure A.4.91 $^1$H NMR (400MHz, CDCl$_3$) of compound 543
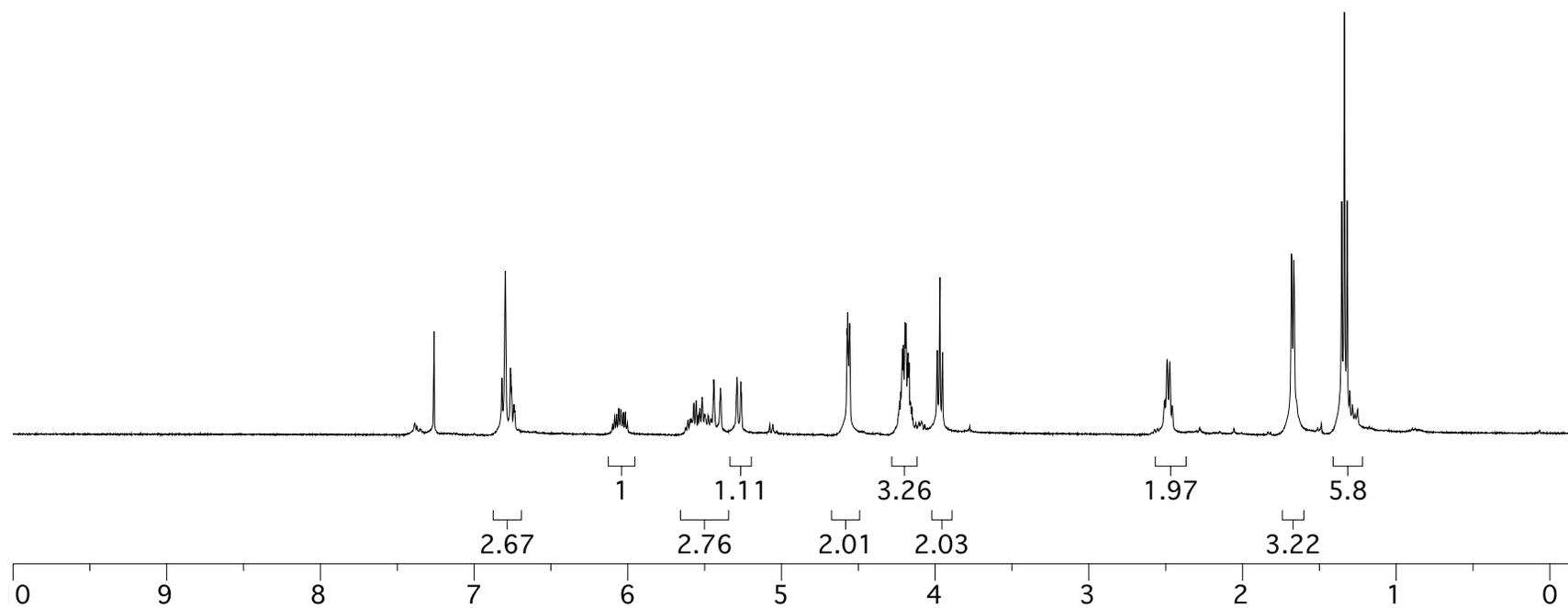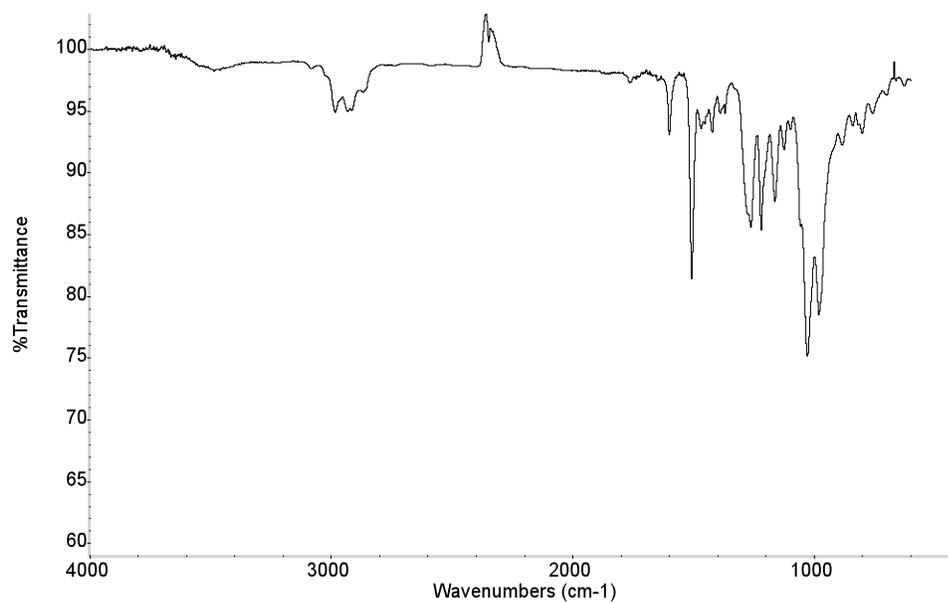
Figure A.4.92 Infrared Spectrum (thin film/NaCl) of compound **543**.
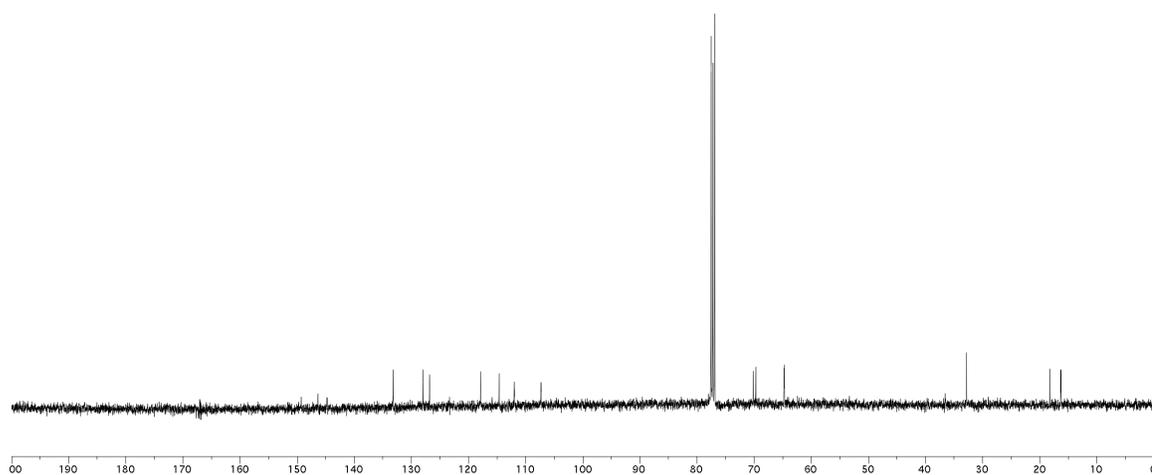


Figure A.4.93 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **543**.
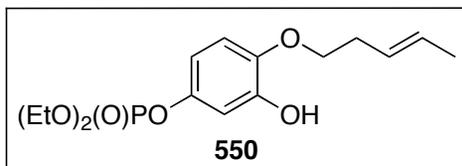
Figure A.4.94 $^1$H NMR (400MHz, CDCl$_3$) of compound 550
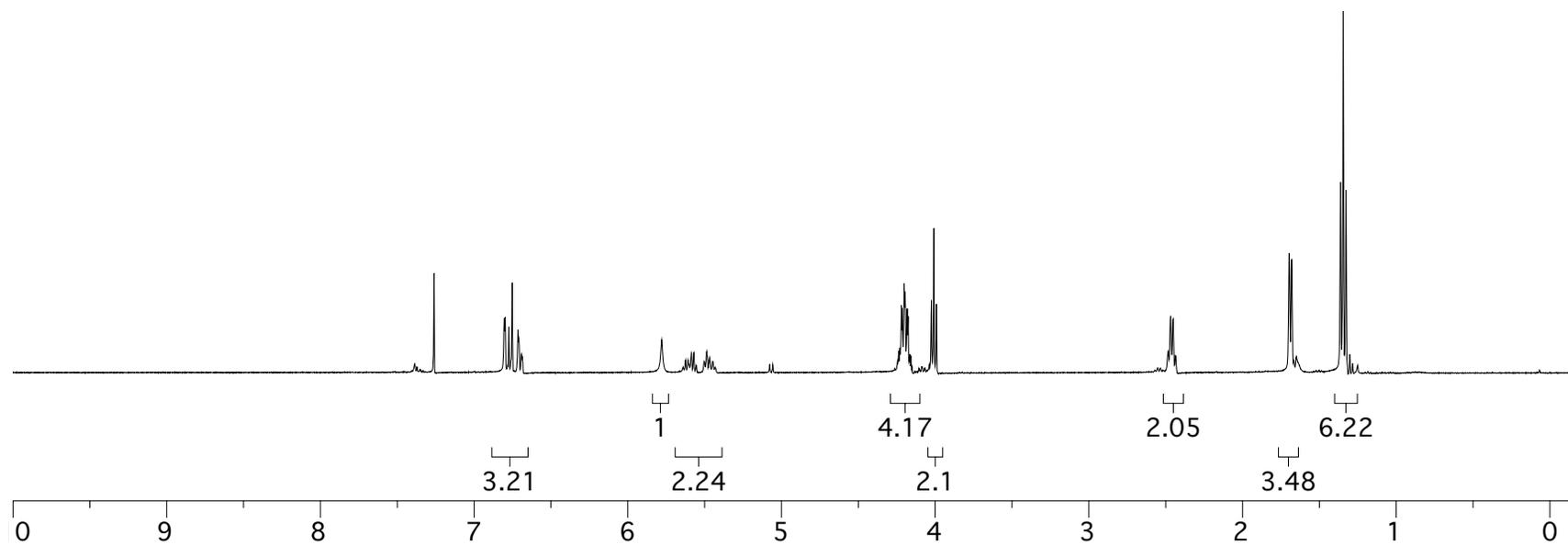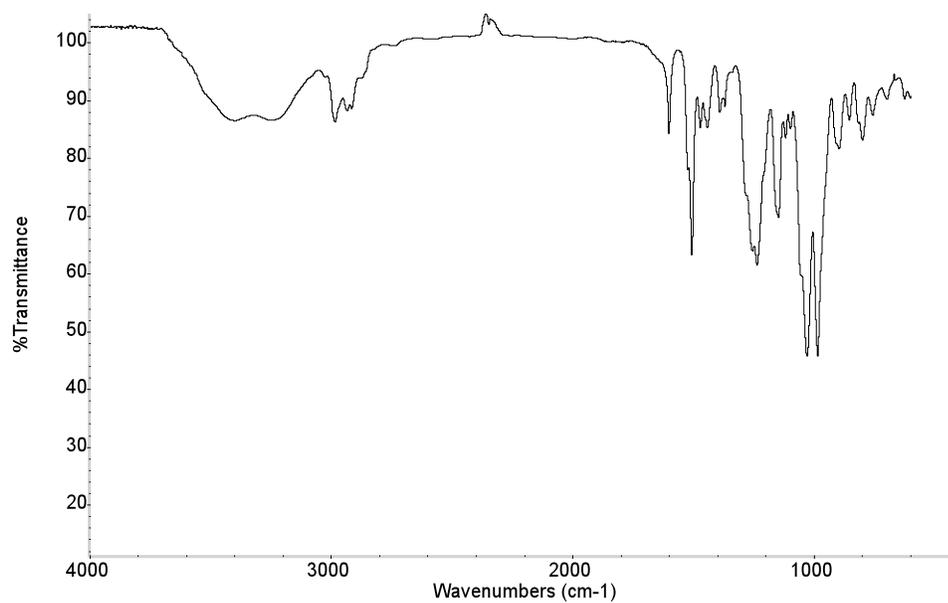
Figure A.4.95 Infrared Spectrum (thin film/NaCl) of compound **550**.
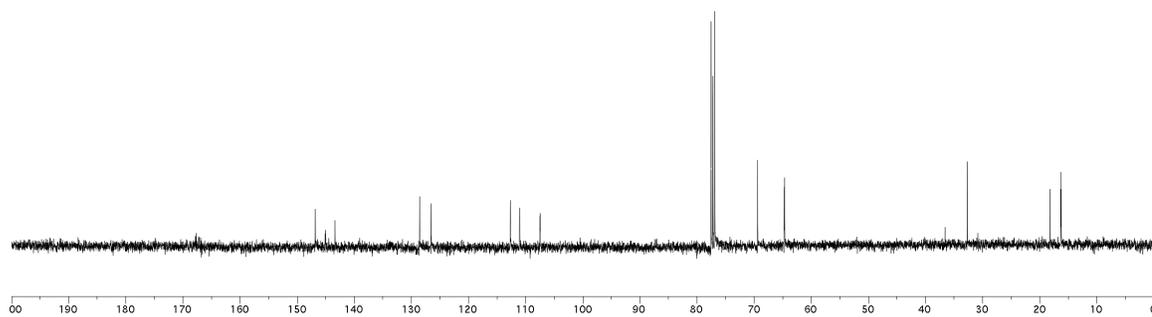


Figure A.4.96 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **550**.
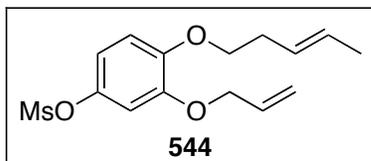
Figure A.4.97 $^1$H NMR (400MHz, CDCl$_3$) of compound 544
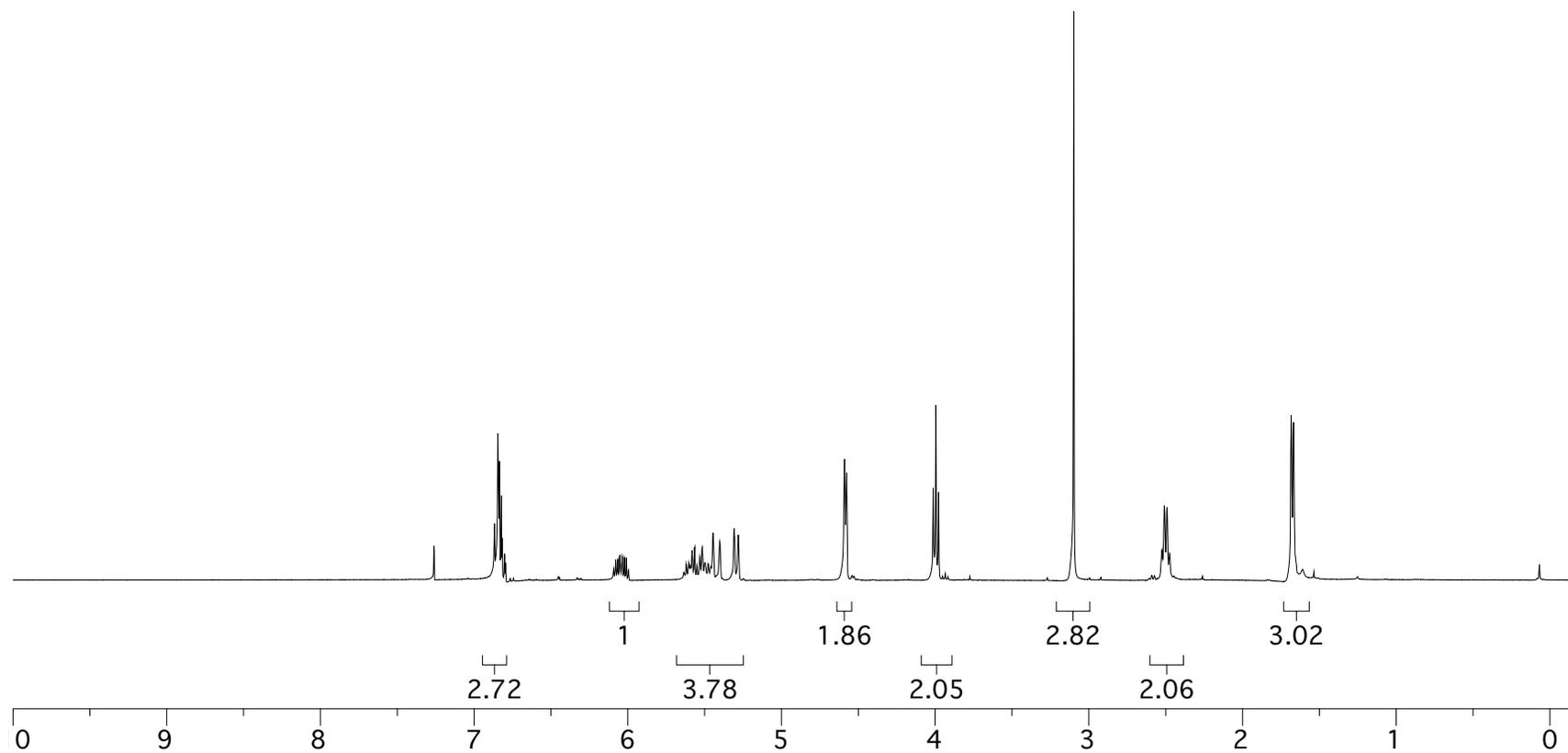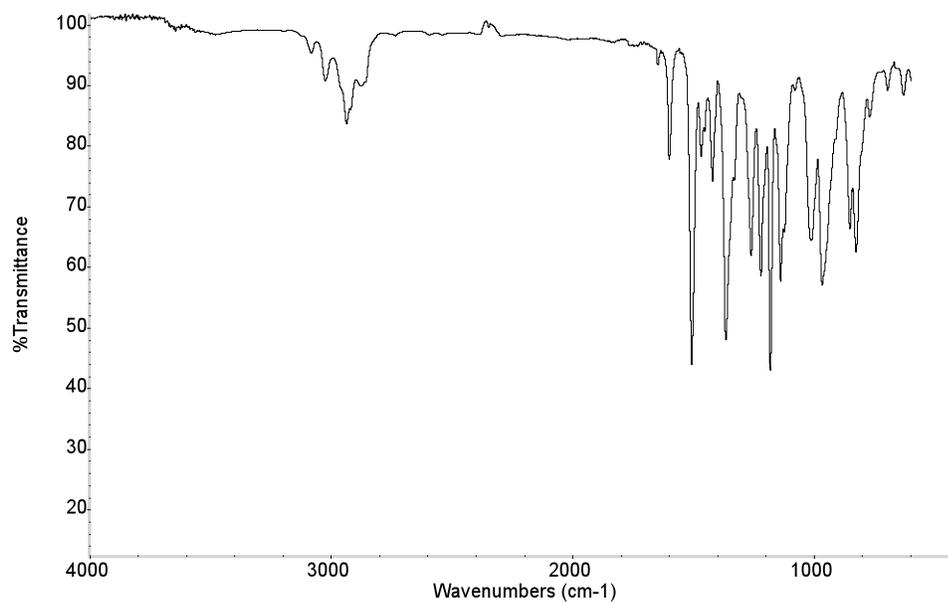
Figure A.4.98 Infrared Spectrum (thin film/NaCl) of compound **544**.
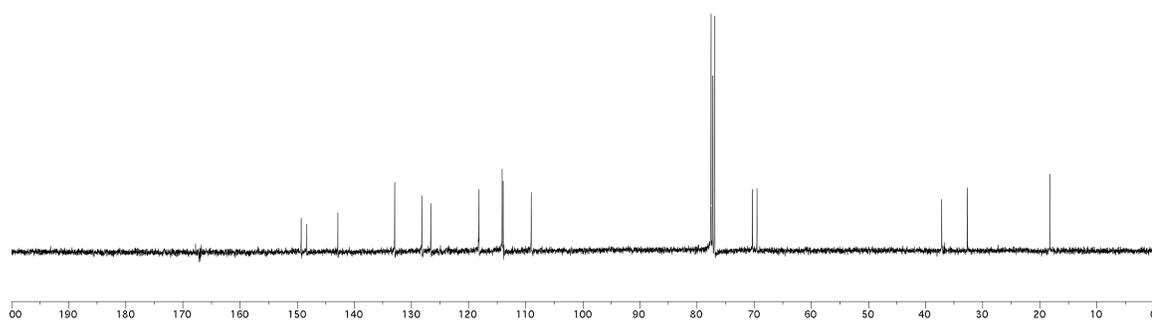


Figure A.4.99 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **544**.
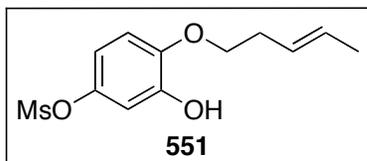
Figure A.4.100 $^1$H NMR (400MHz, CDCl$_3$) of compound 551
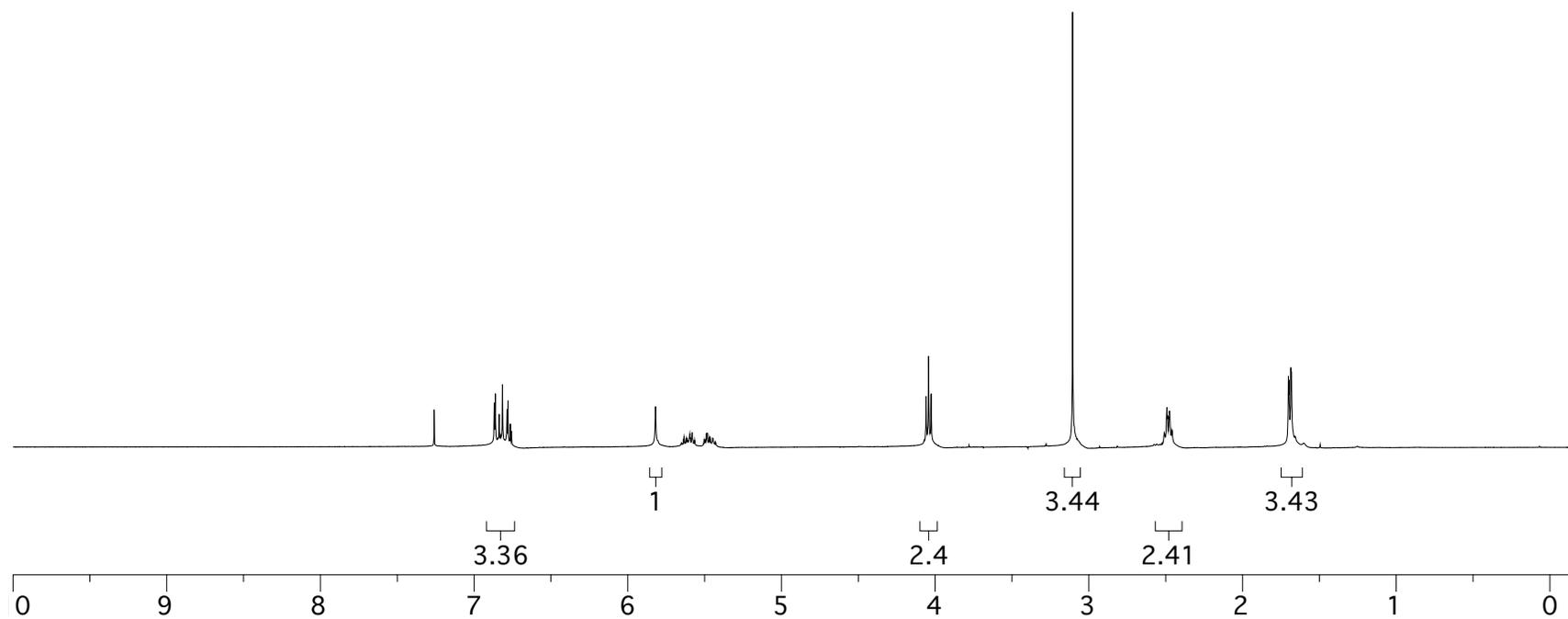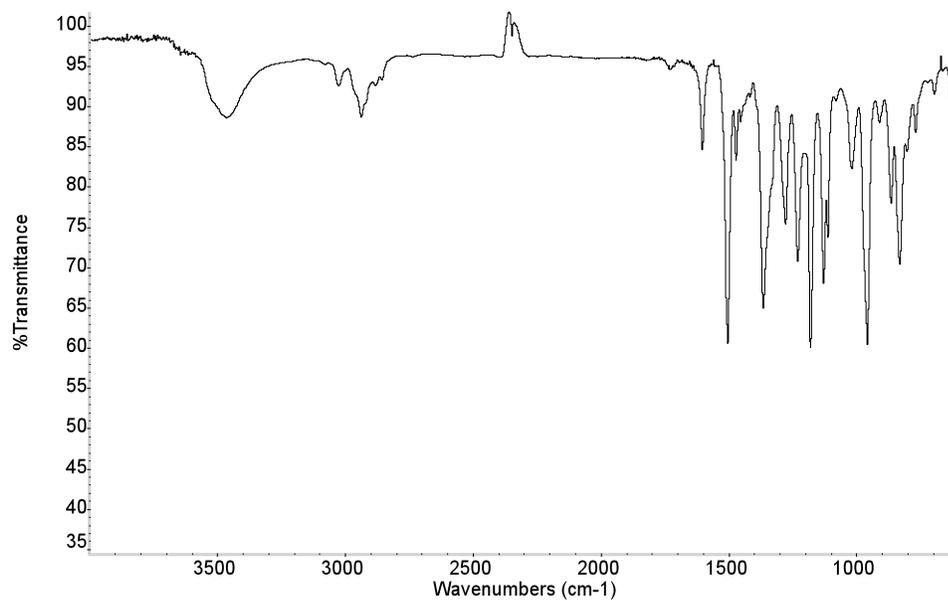
Figure A.4.101 Infrared Spectrum (thin film/NaCl) of compound **551**.
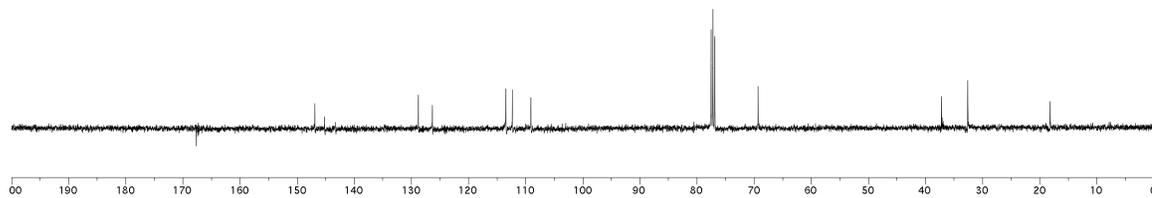


Figure A.4.102 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **551**.
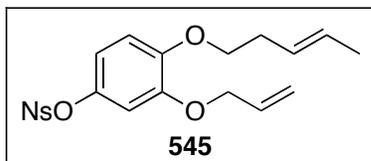
Figure A.4.103 $^1$H NMR (400MHz, CDCl$_3$) of compound 545
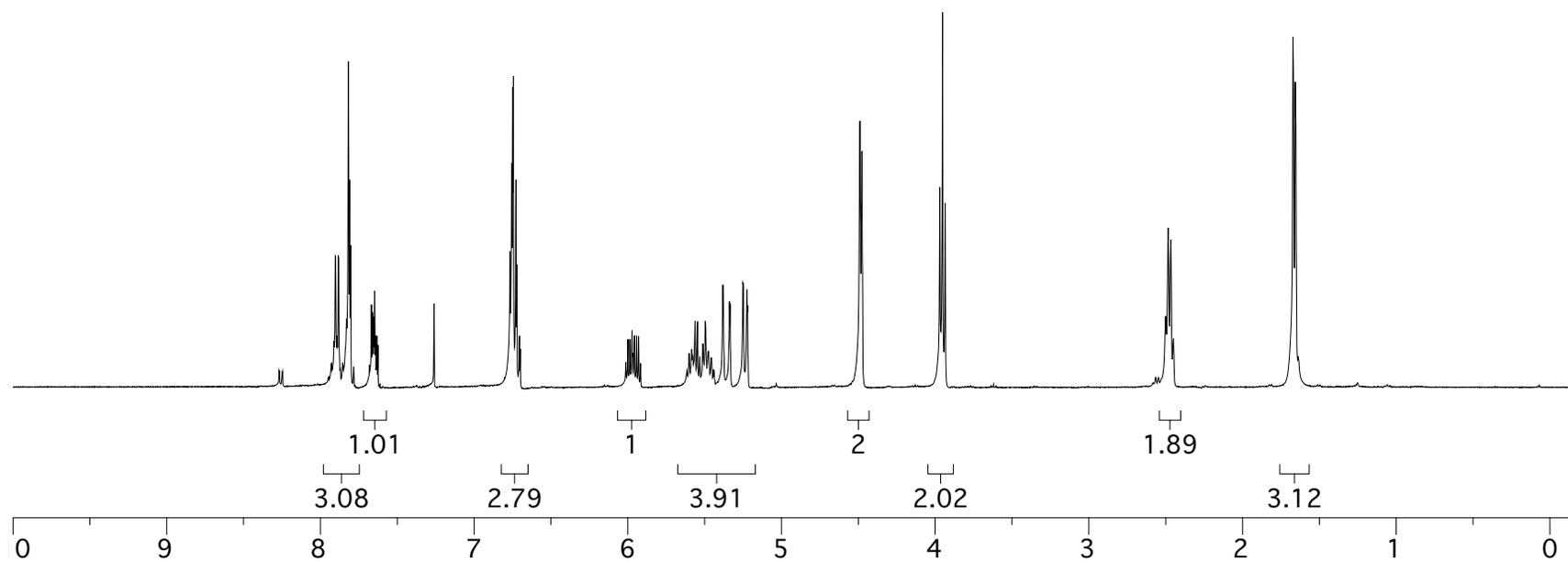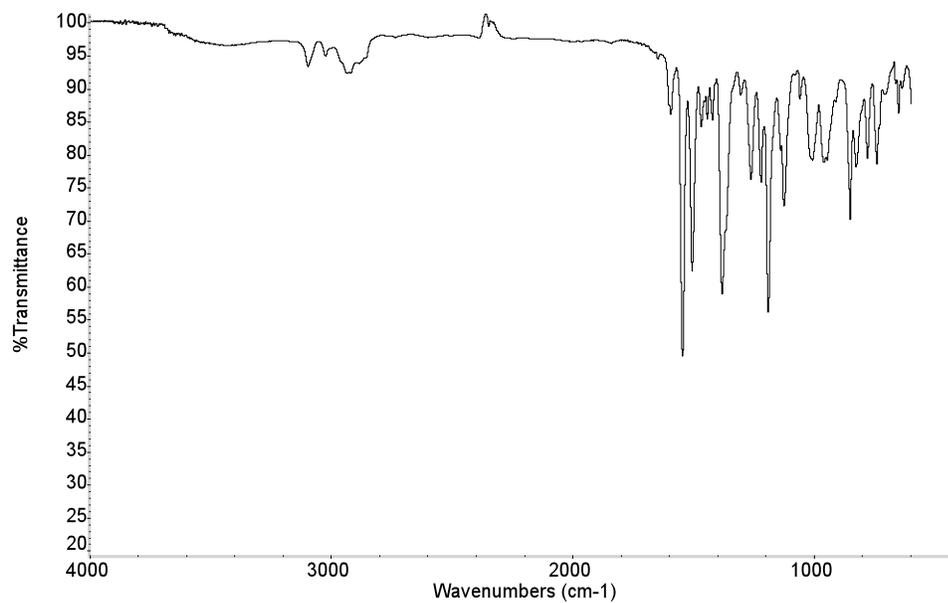
Figure A.4.104 Infrared Spectrum (thin film/NaCl) of compound **545**.
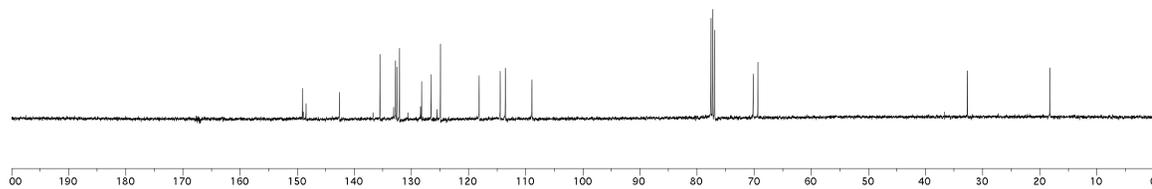


Figure A.4.105 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **545**.
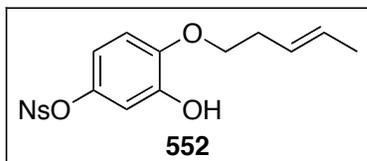
Figure A.4.106 $^1$H NMR (400MHz, CDCl$_3$) of compound 552
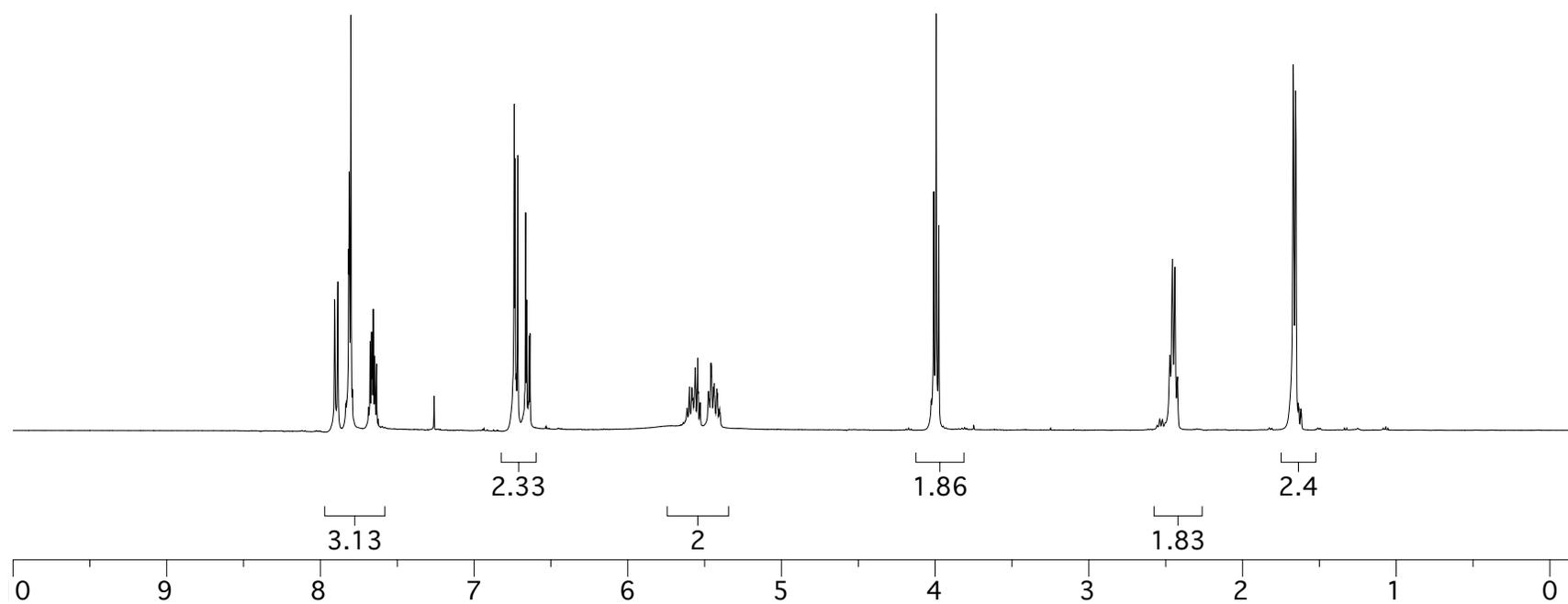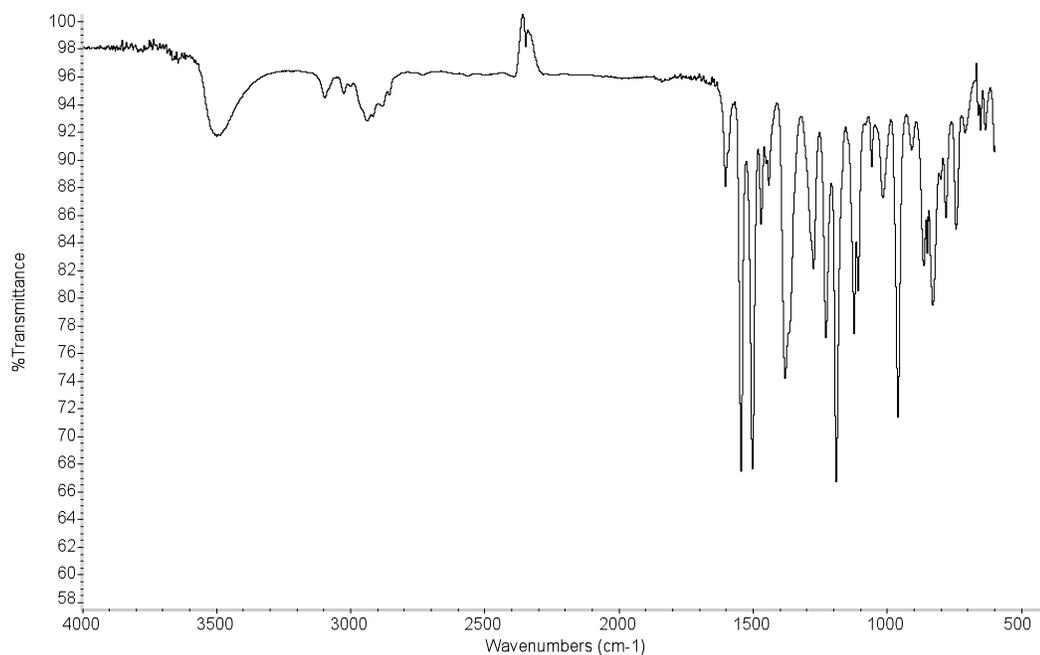
Figure A.4.107 Infrared Spectrum (thin film/NaCl) of compound **552**.
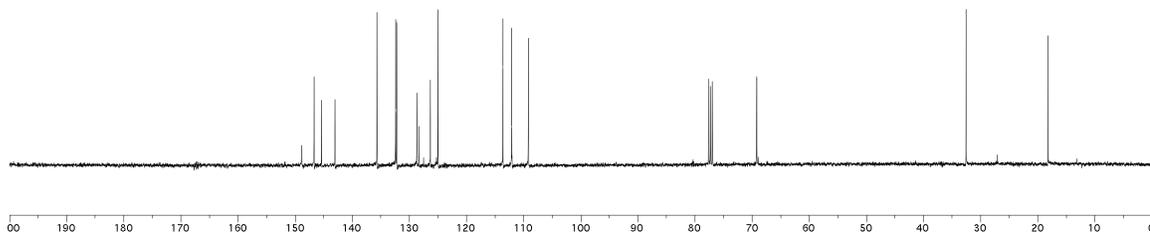


Figure A.4.108 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **552**.
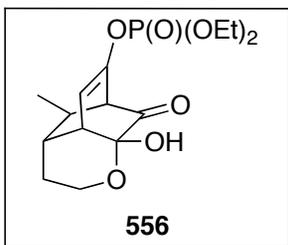
Figure A.4.109 $^1$H NMR (400MHz, CDCl$_3$) of compound 556
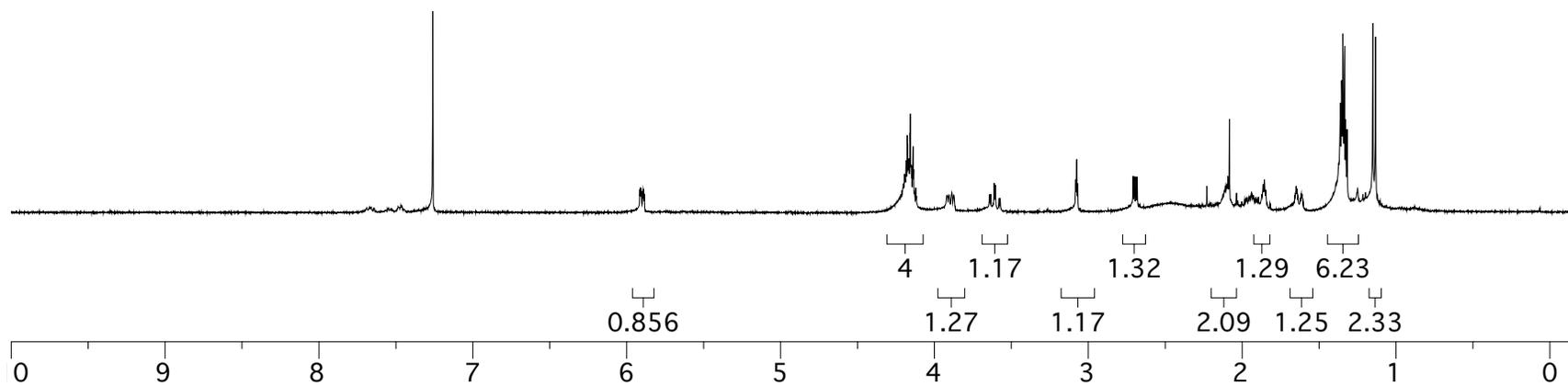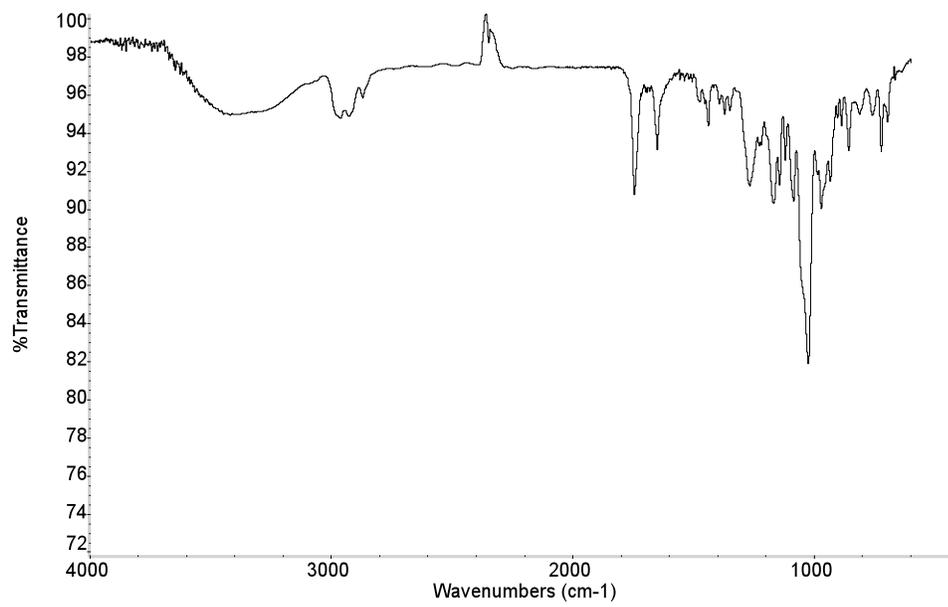
Figure A.4.110 Infrared Spectrum (thin film/NaCl) of compound **556**.
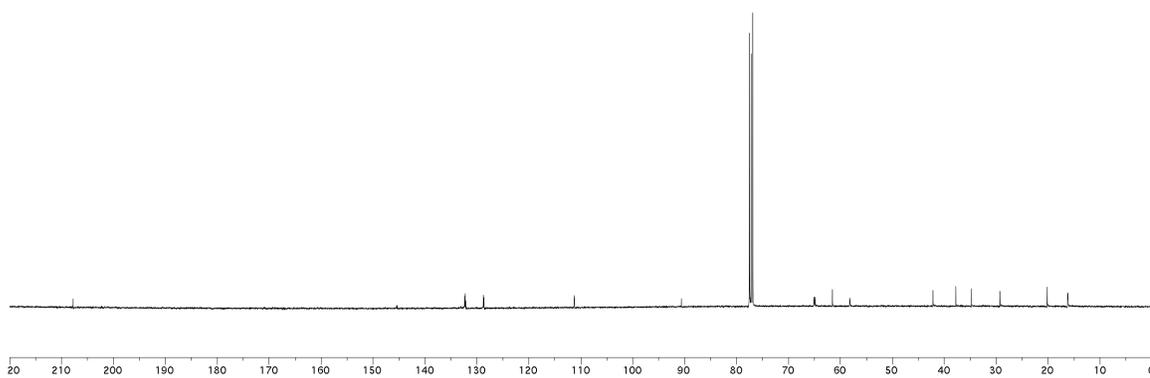


Figure A.4.111 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **556**.
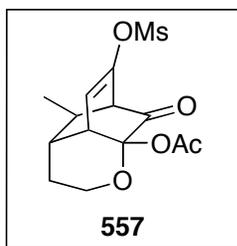
**Figure A.4.112 $^1$H NMR (400MHz, CDCl$_3$) of compound 557**
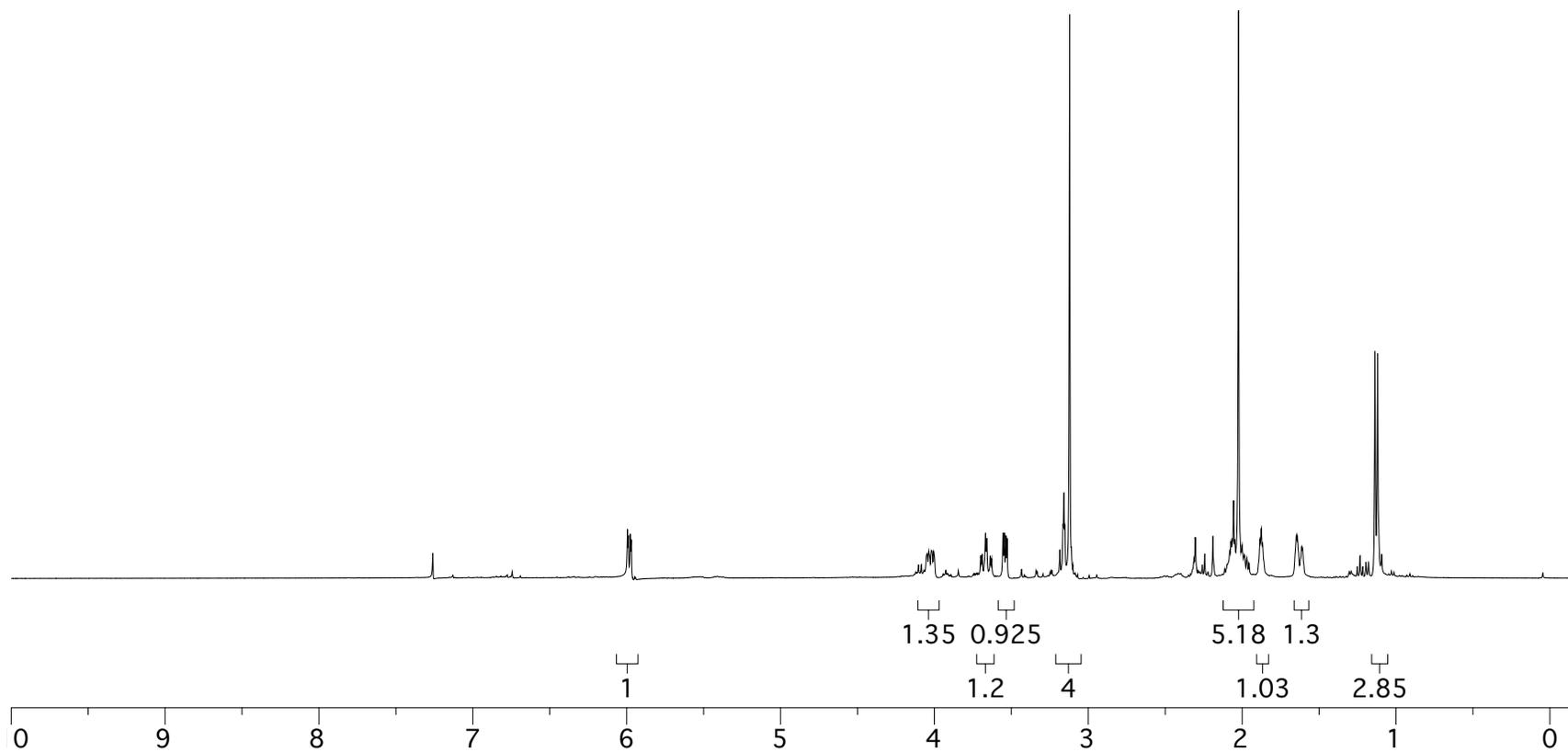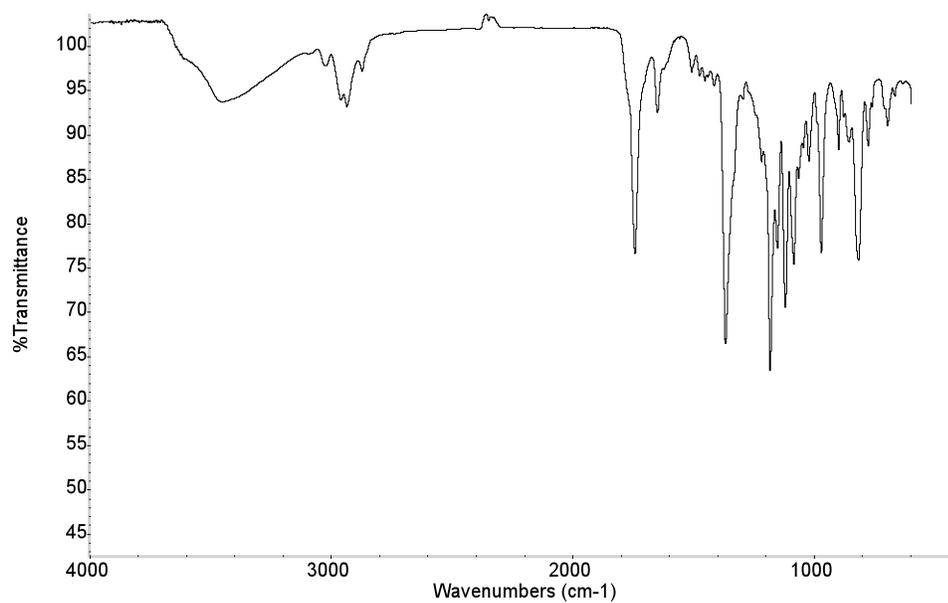
Figure A.4.113 Infrared Spectrum (thin film/NaCl) of compound **557**.
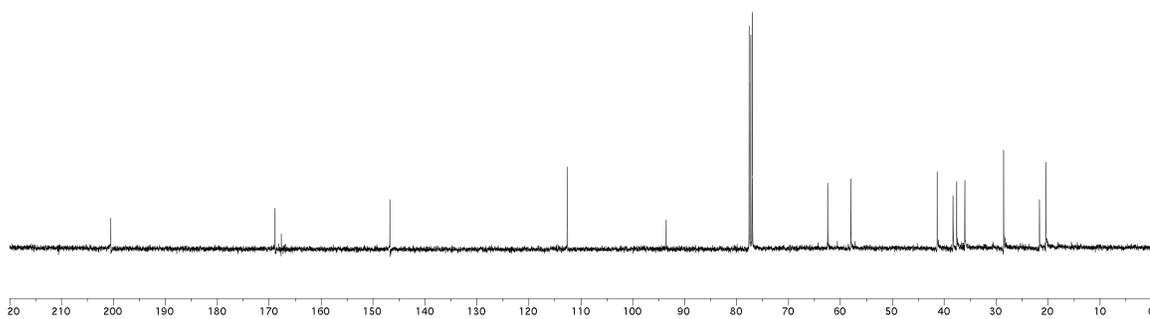


Figure A.4.114 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **557**.
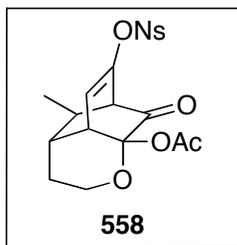
Figure A.4.115 $^1$H NMR (400MHz, CDCl$_3$) of compound 558
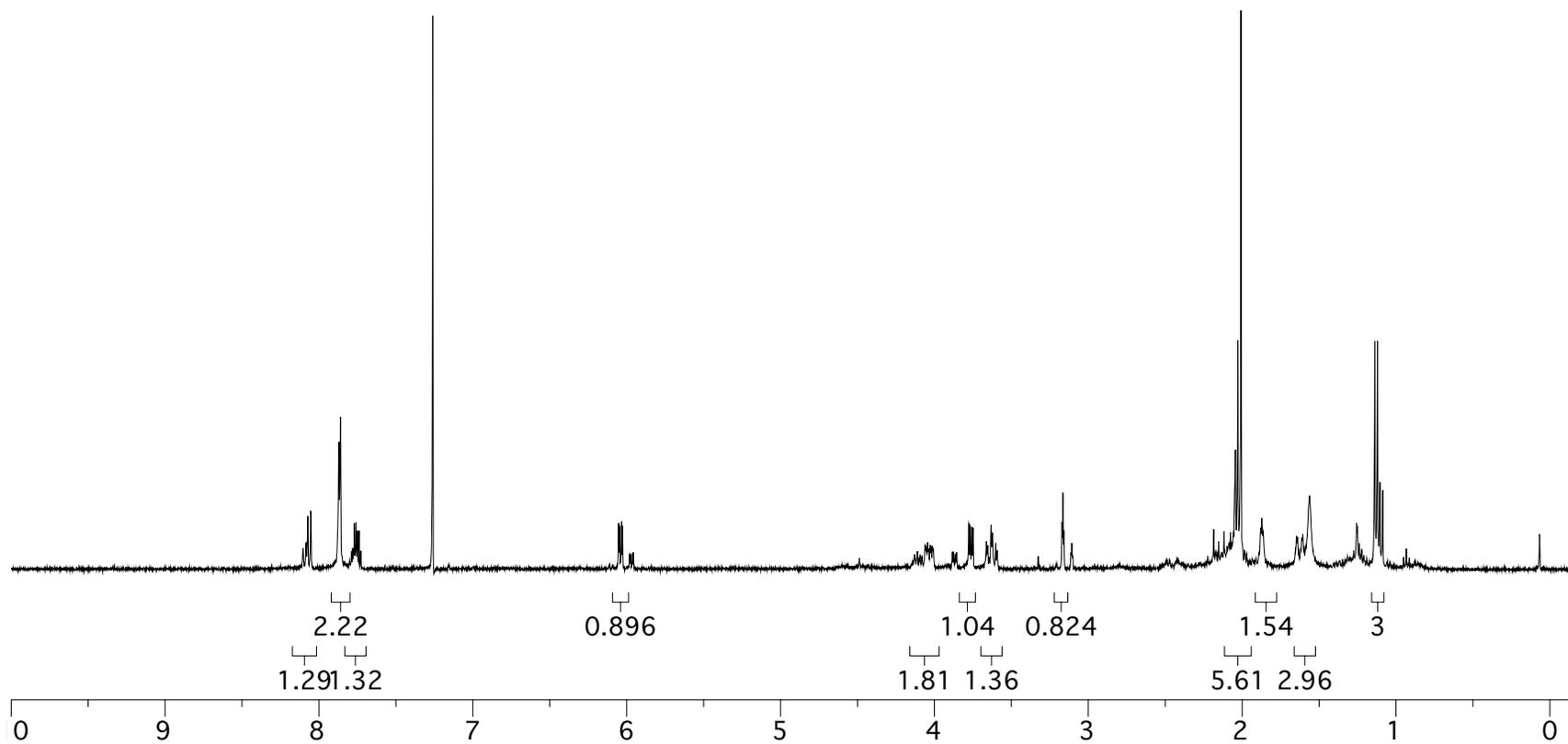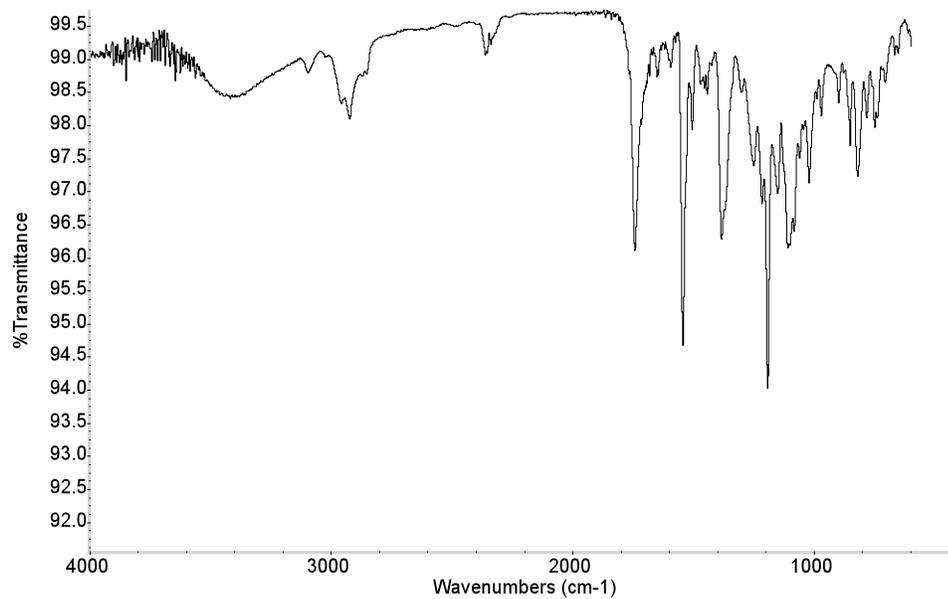
Figure A.4.116 Infrared Spectrum (thin film/NaCl) of compound **558**.
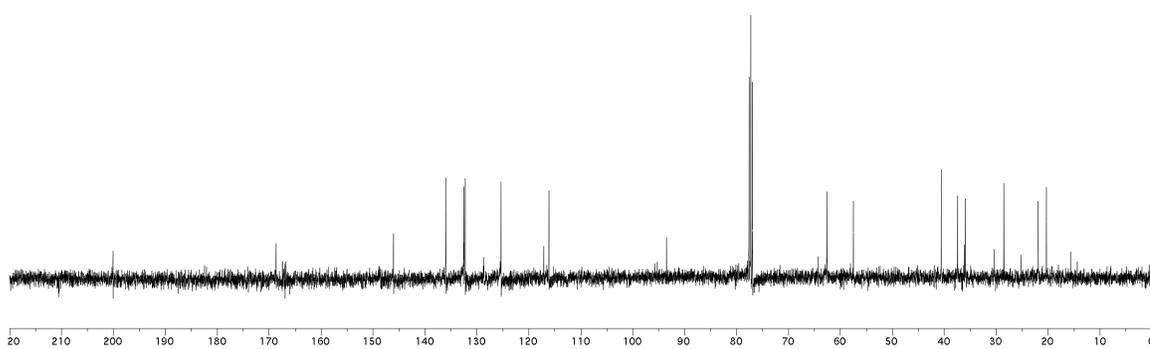


Figure A.4.117 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **558**.
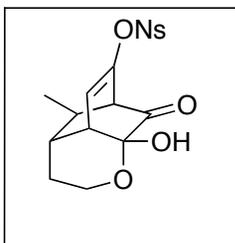
Figure A.4.118 $^1$H NMR (400MHz, CDCl$_3$) of compound 559
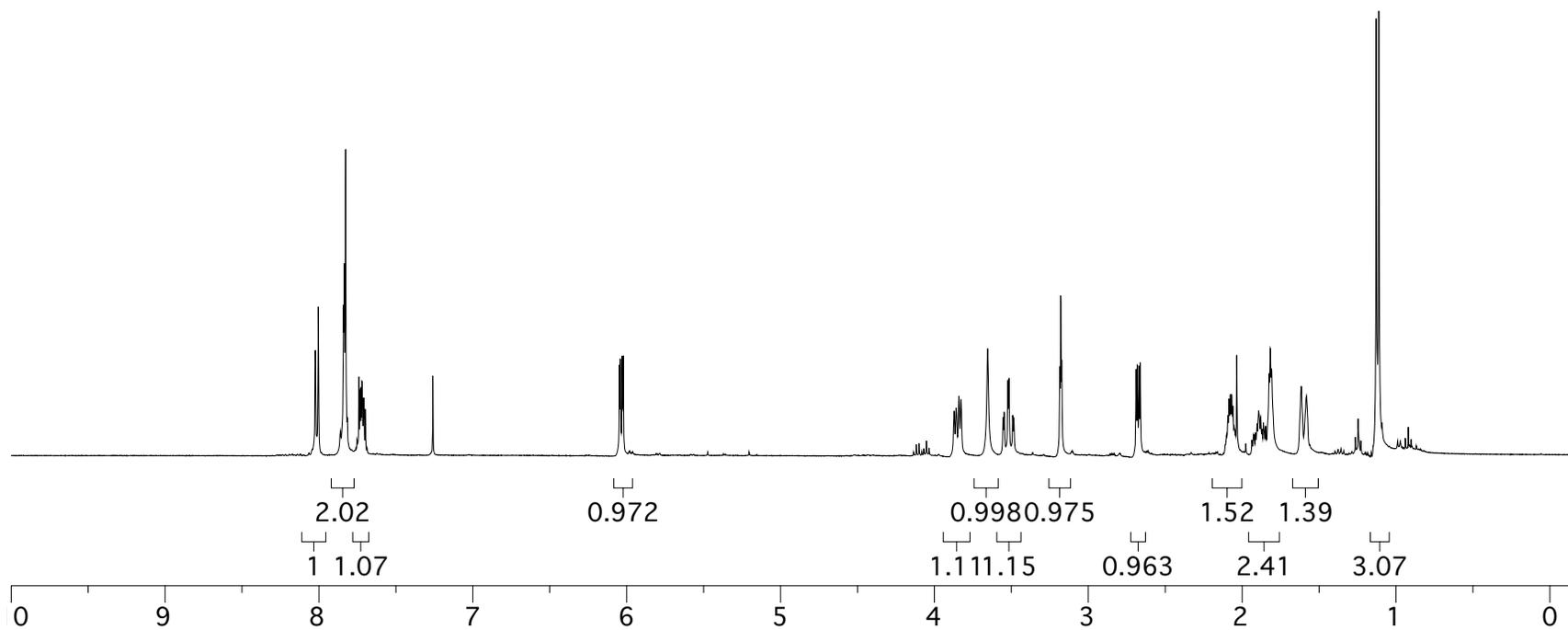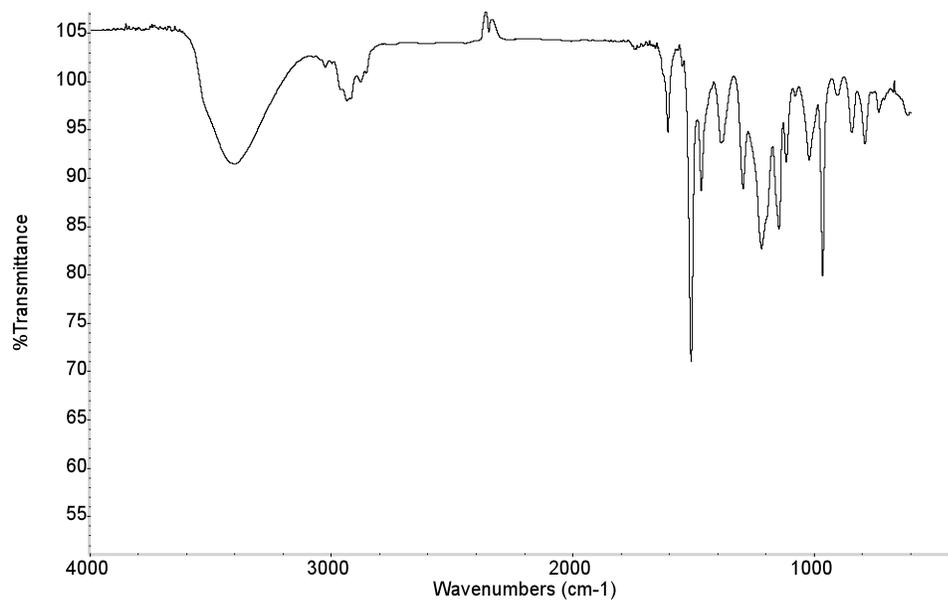
Figure A.4.119 Infrared Spectrum (thin film/NaCl) of compound **559**.
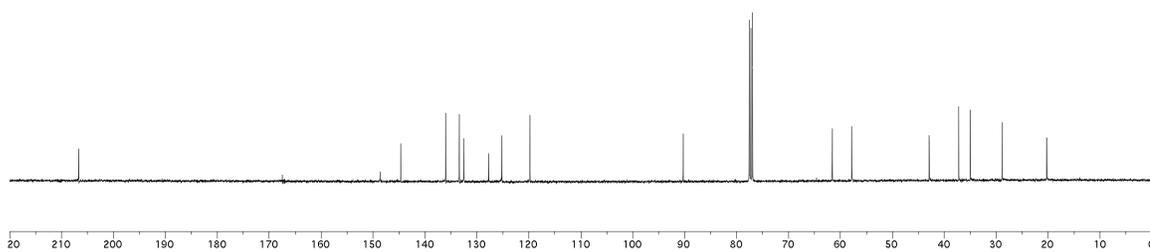


Figure A.4.120 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **559**.
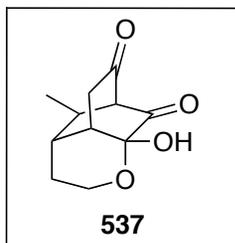
**Figure A.4.121** $^1$H NMR (400MHz, CDCl$_3$) of compound 537
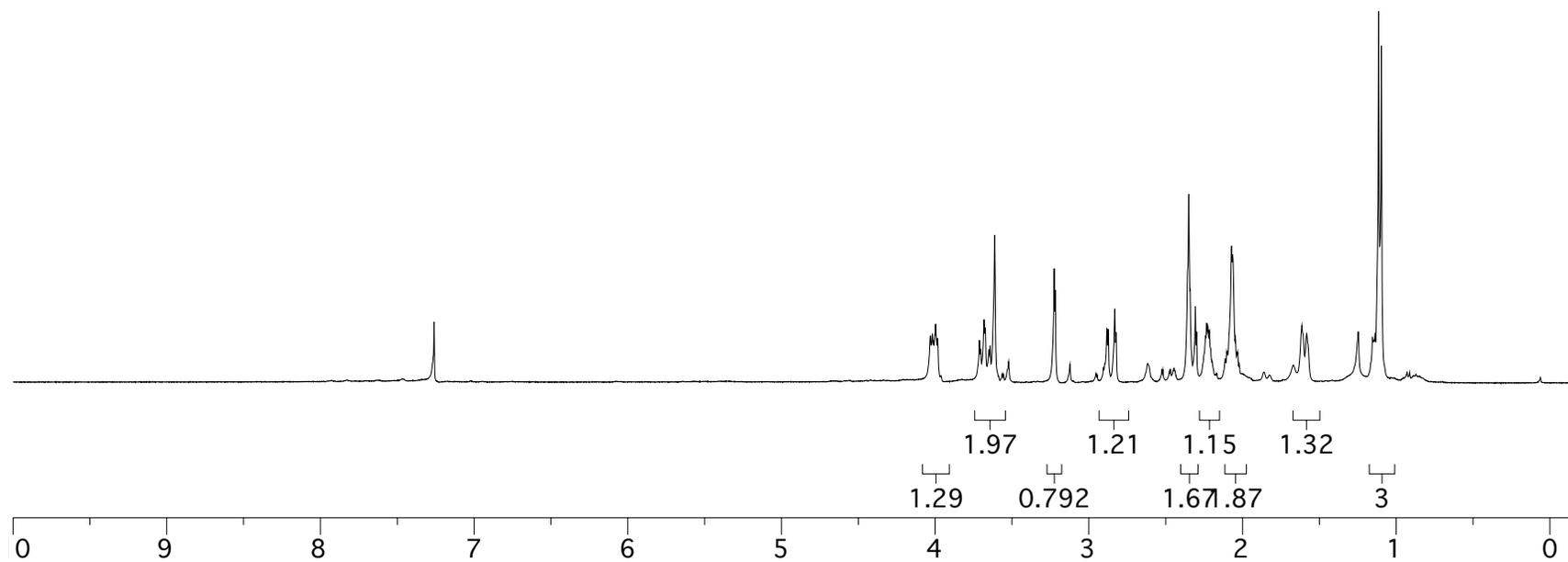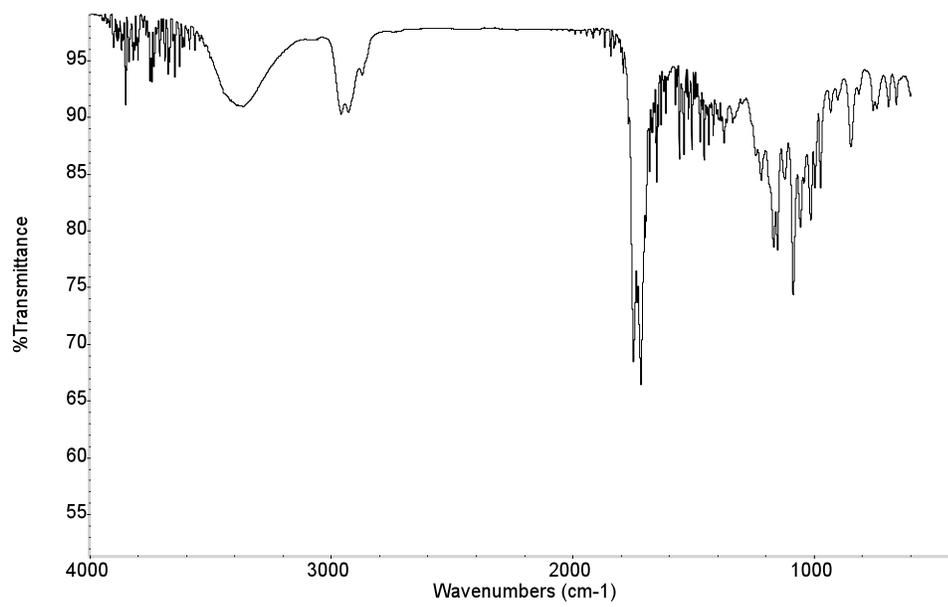
Figure A.4.122 Infrared Spectrum (thin film/NaCl) of compound **537**.
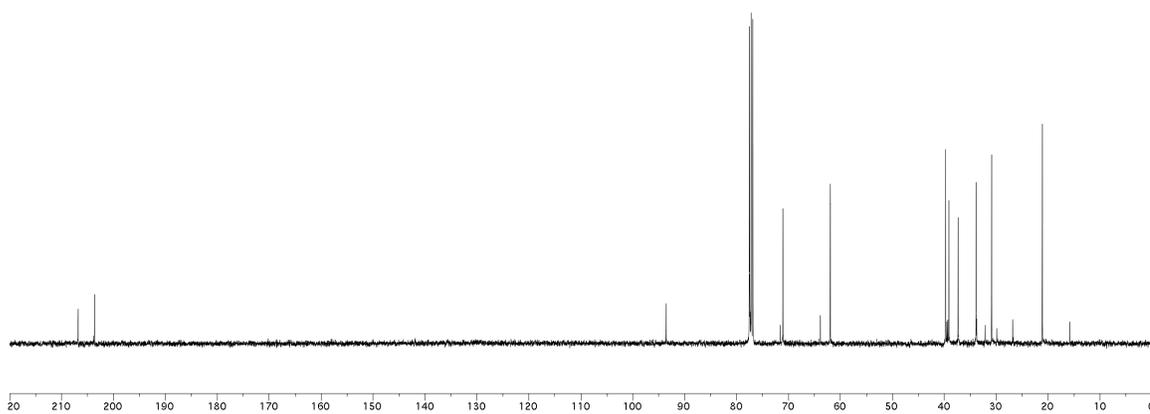


Figure A.4.123 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **537**.
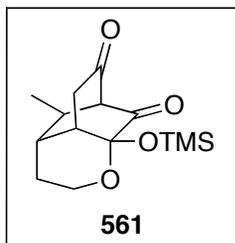
**Figure A.4.124** $^1$H NMR (400MHz, CDCl$_3$) of compound **561**
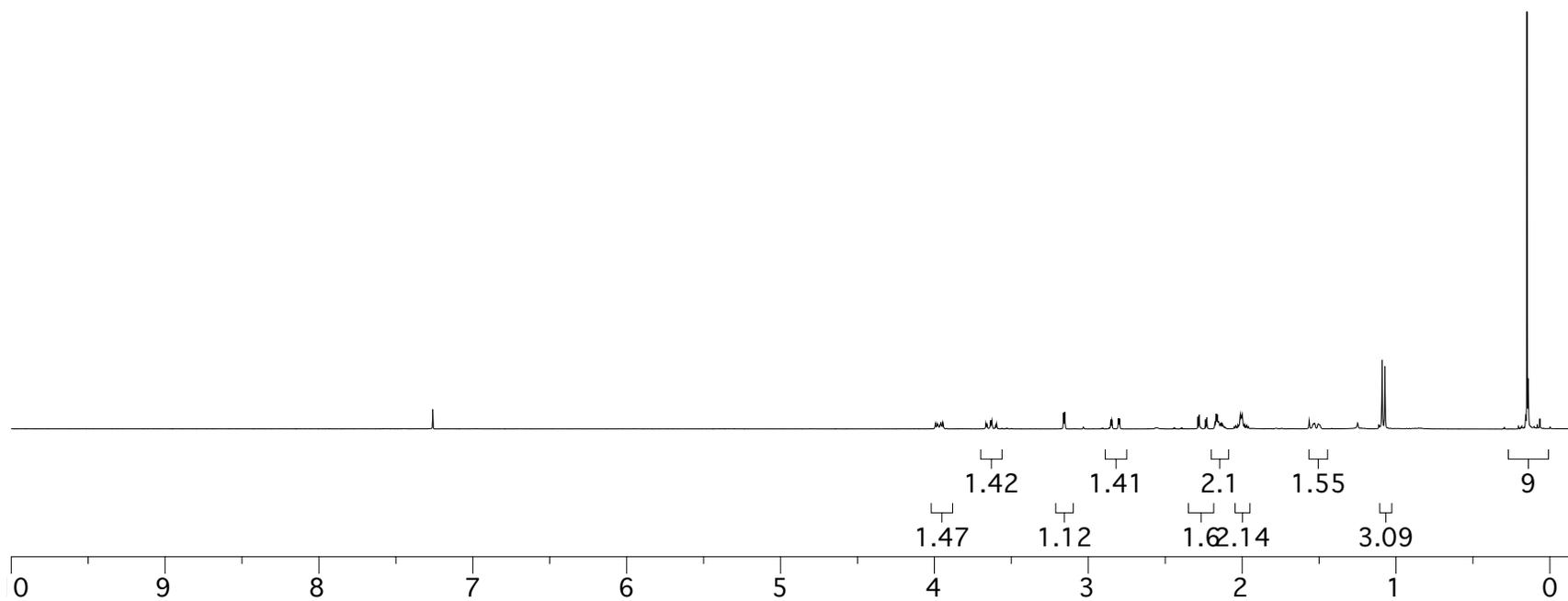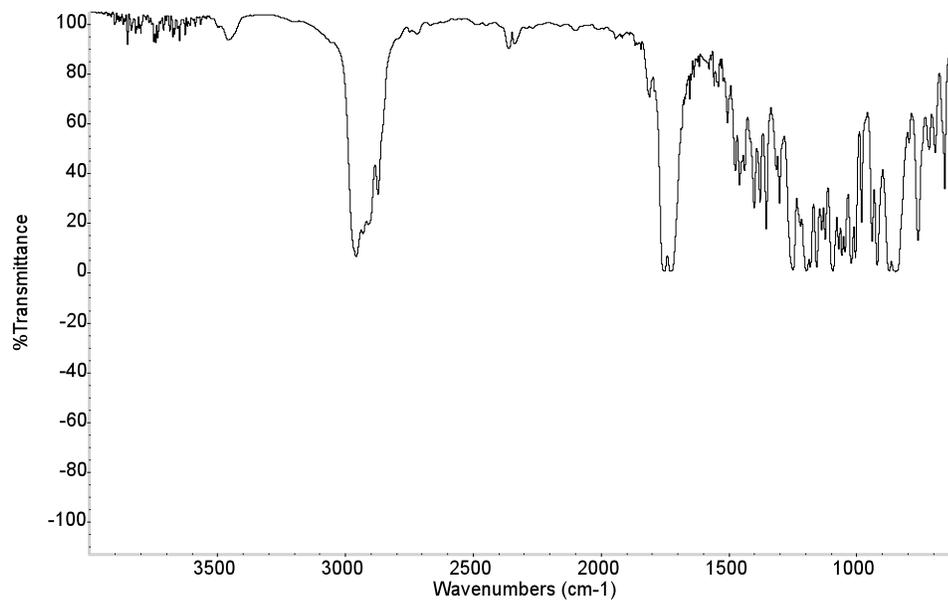
Figure A.4.125 Infrared Spectrum (thin film/NaCl) of compound **561**.
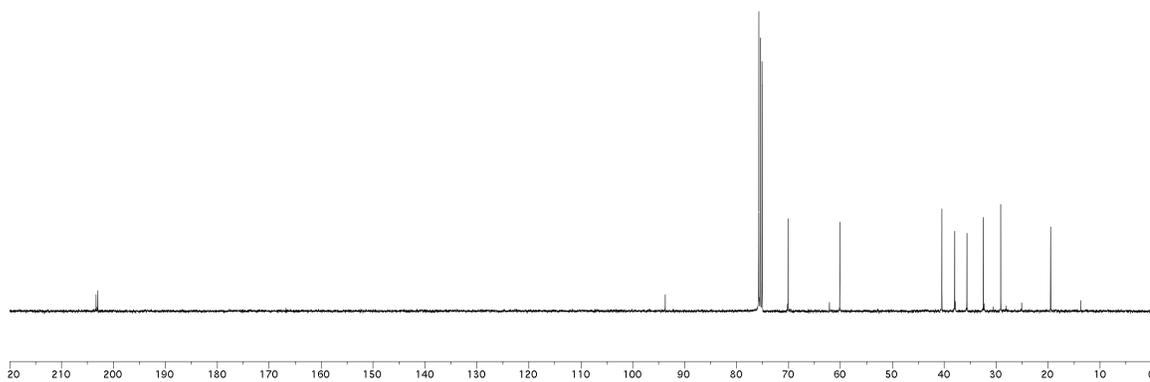


Figure A.4.126 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **561**.
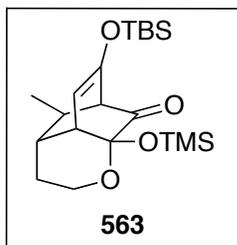
**Figure A.4.127** $^1$H NMR (400MHz, CDCl$_3$) of compound **563**
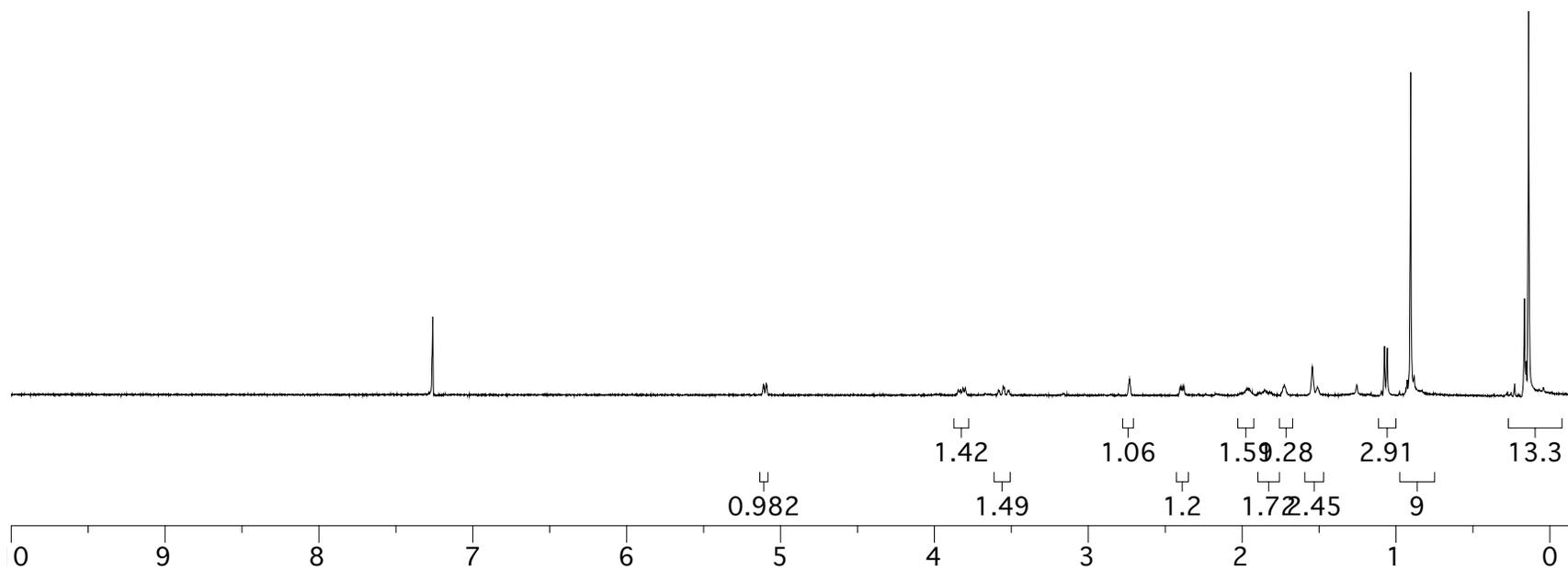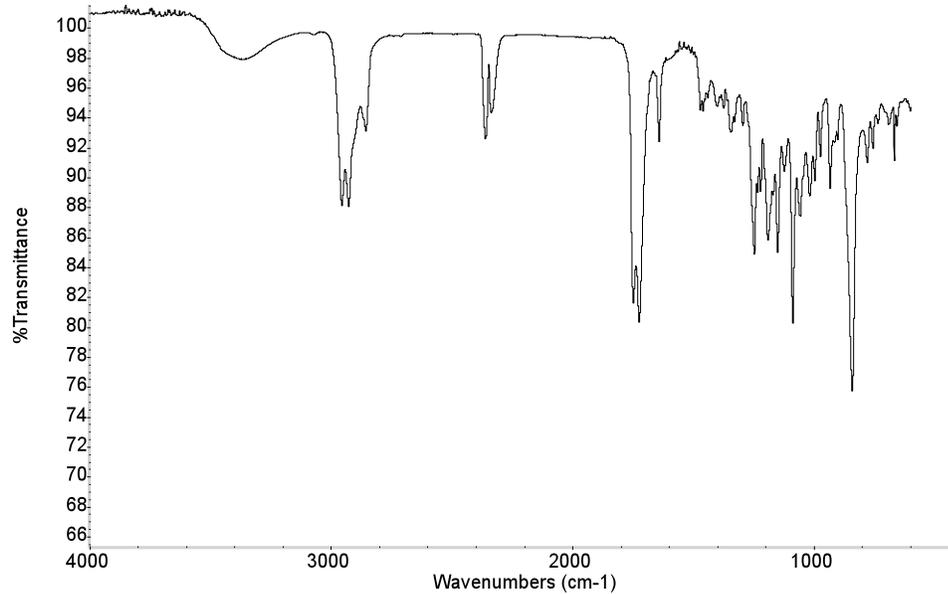
Figure A.4.128 Infrared Spectrum (thin film/NaCl) of compound **563**.
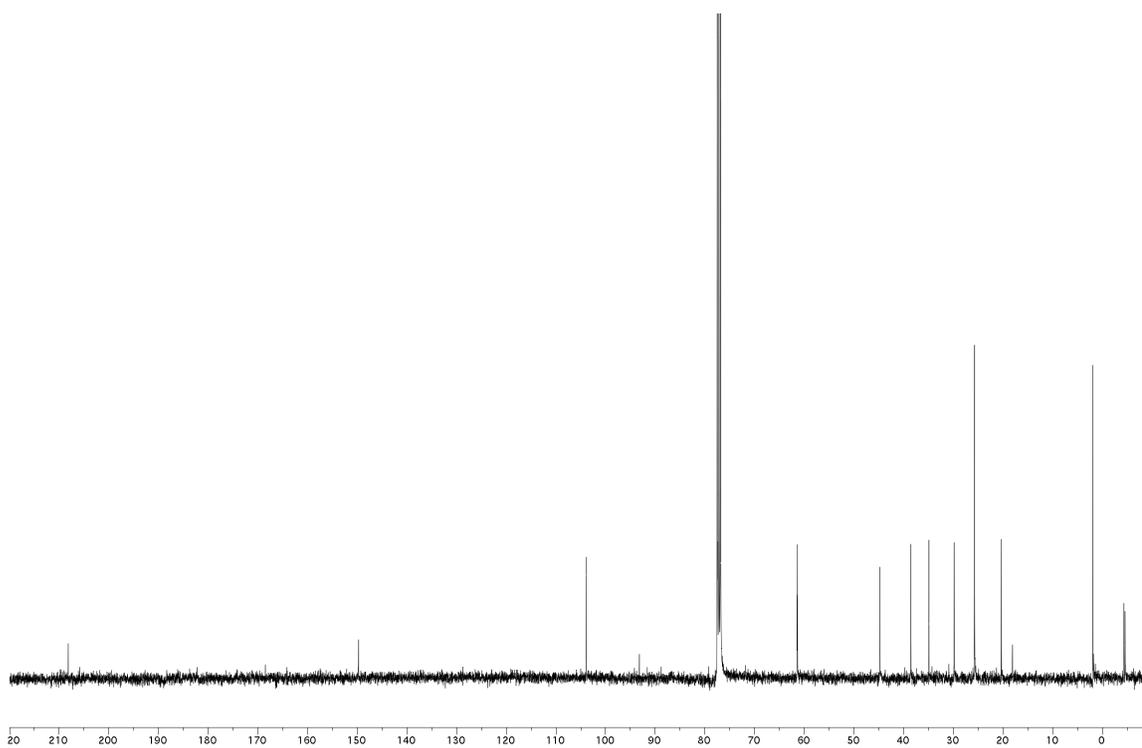


Figure A.4.129 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **563**.
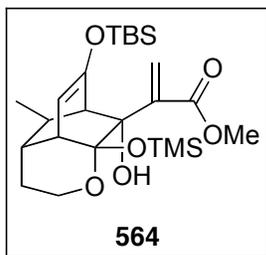
**Figure A.4.130 $^{1}$H NMR (400MHz, CDCl$_3$) of compound 564**
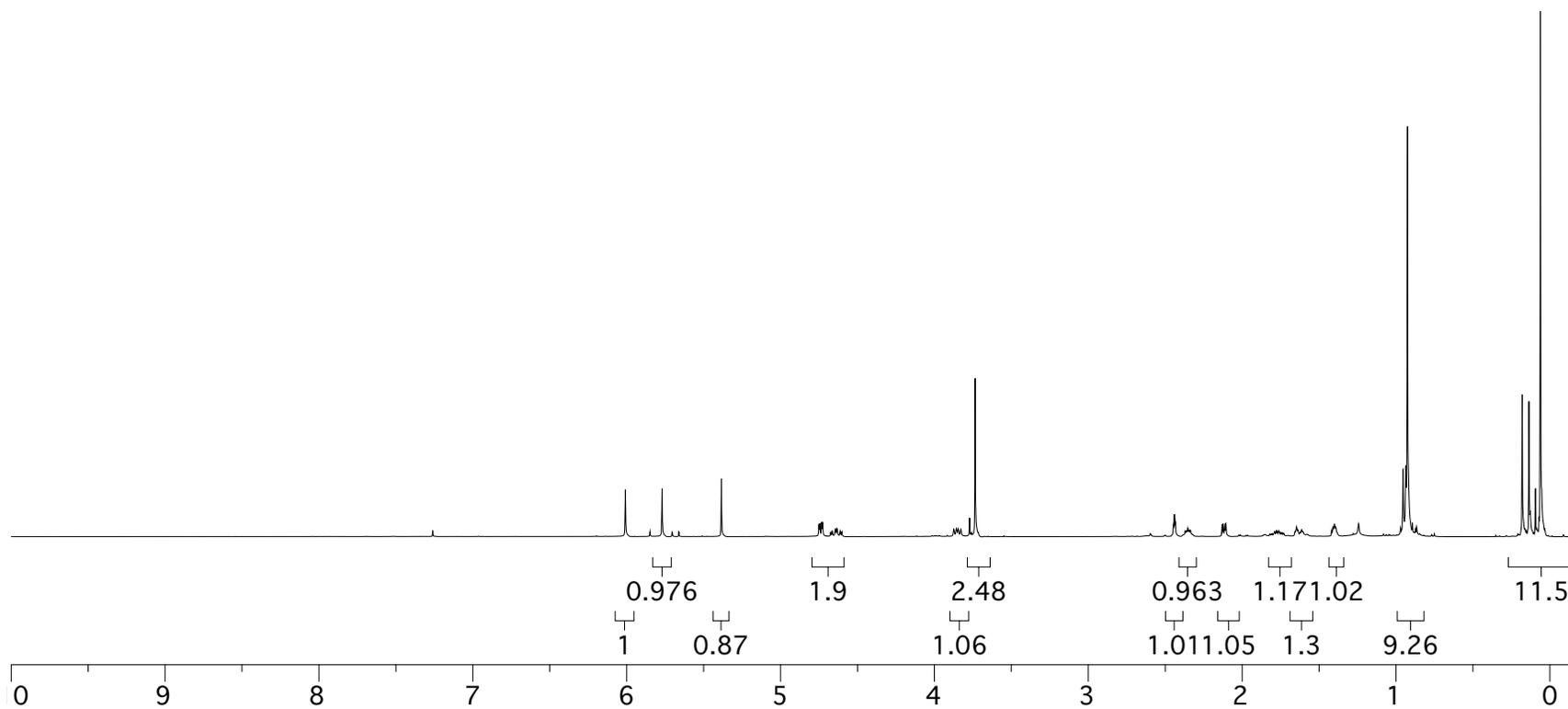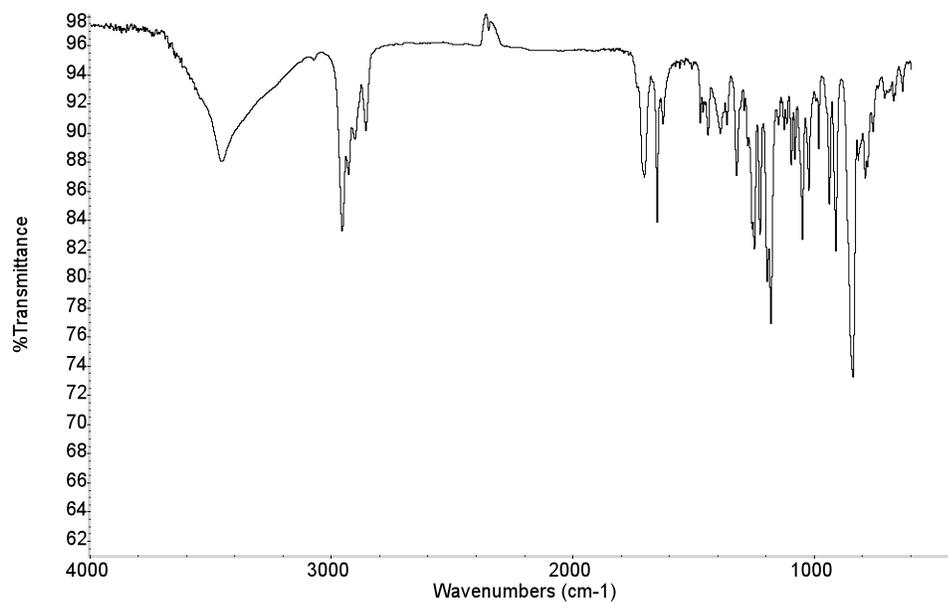
Figure A.4.131 Infrared Spectrum (thin film/NaCl) of compound **564**.
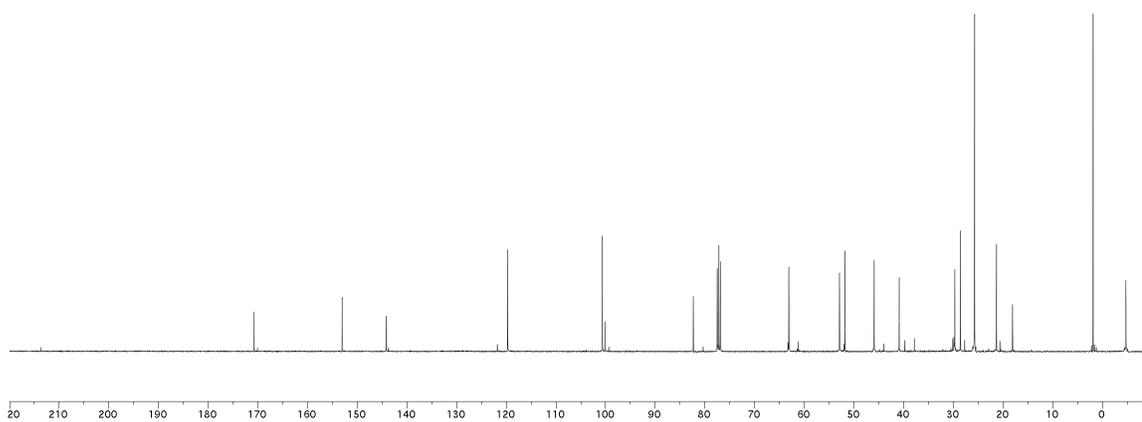


Figure A.4.132 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **564**.
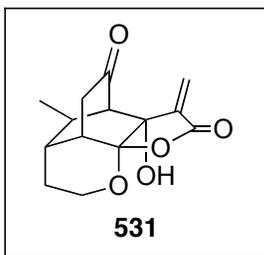
**Figure A.4.133 $^{1}$H NMR (400MHz, CDCl$_3$) of compound 531**

531
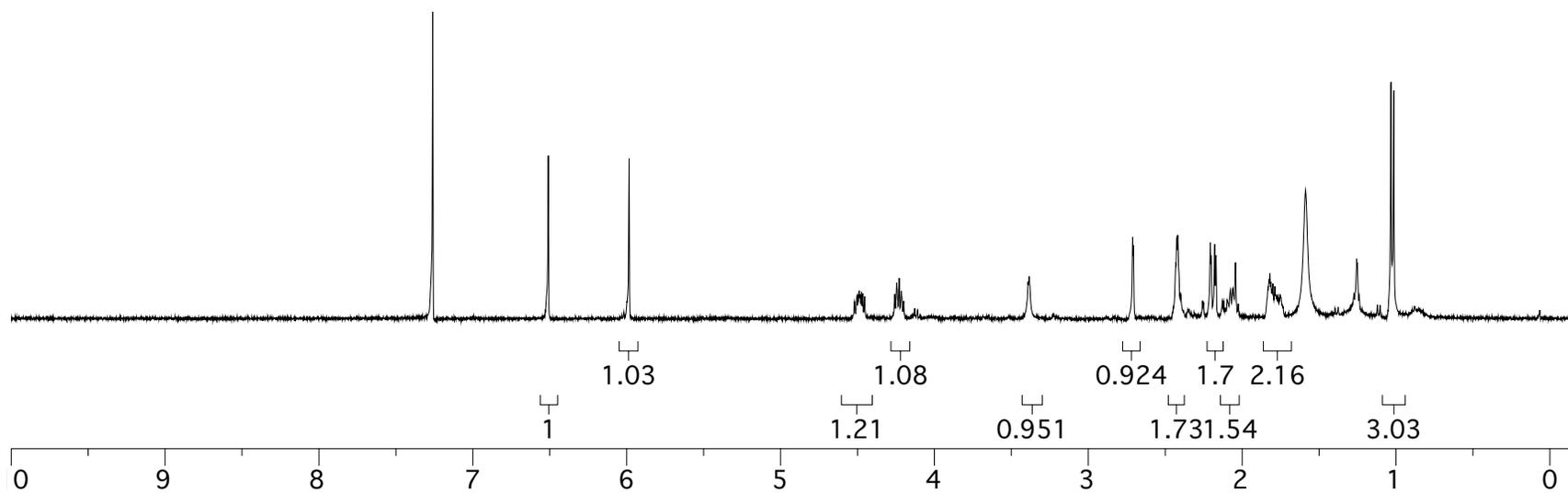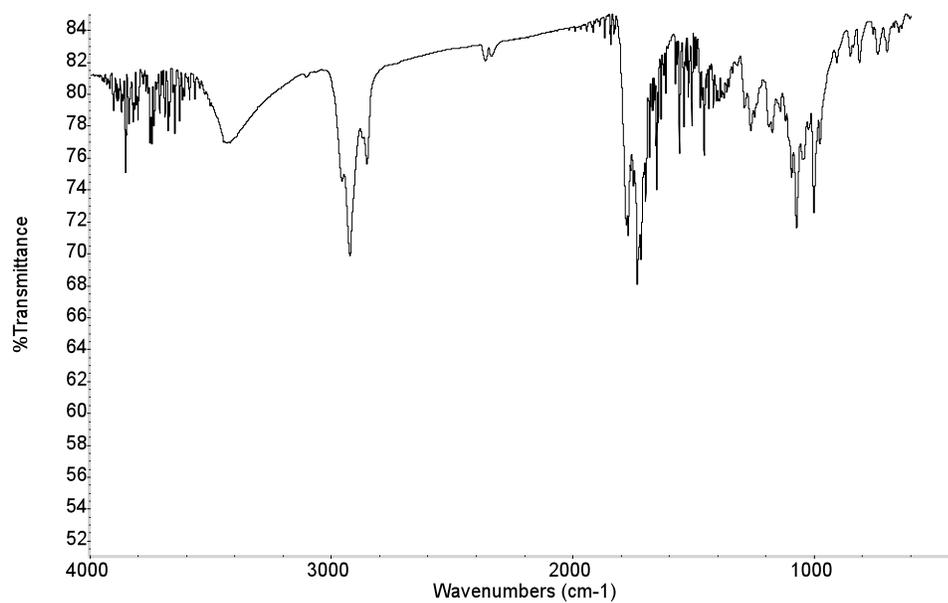
Figure A.4.134 Infrared Spectrum (thin film/NaCl) of compound **531**.
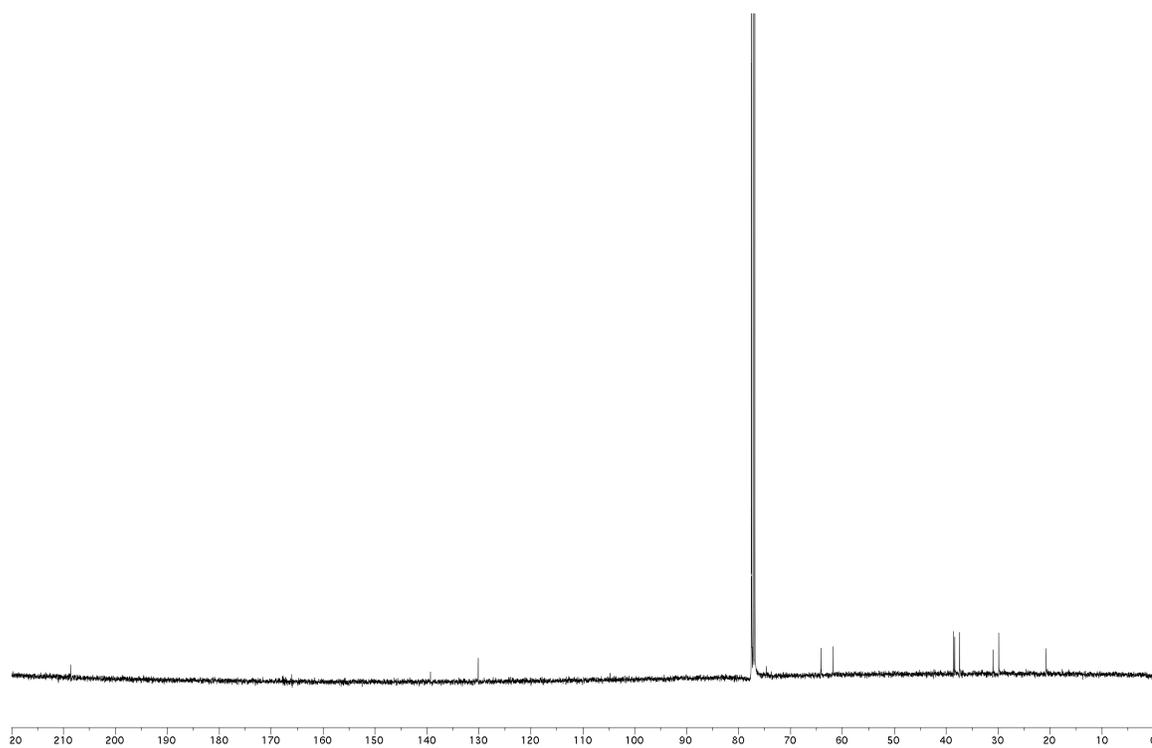


Figure A.4.135 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **531**.
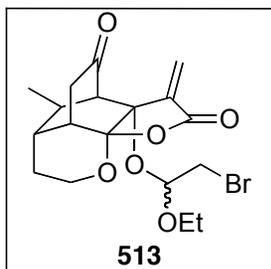
Figure A.4.136 $^1$H NMR (400MHz, CDCl$_3$) of compound 513
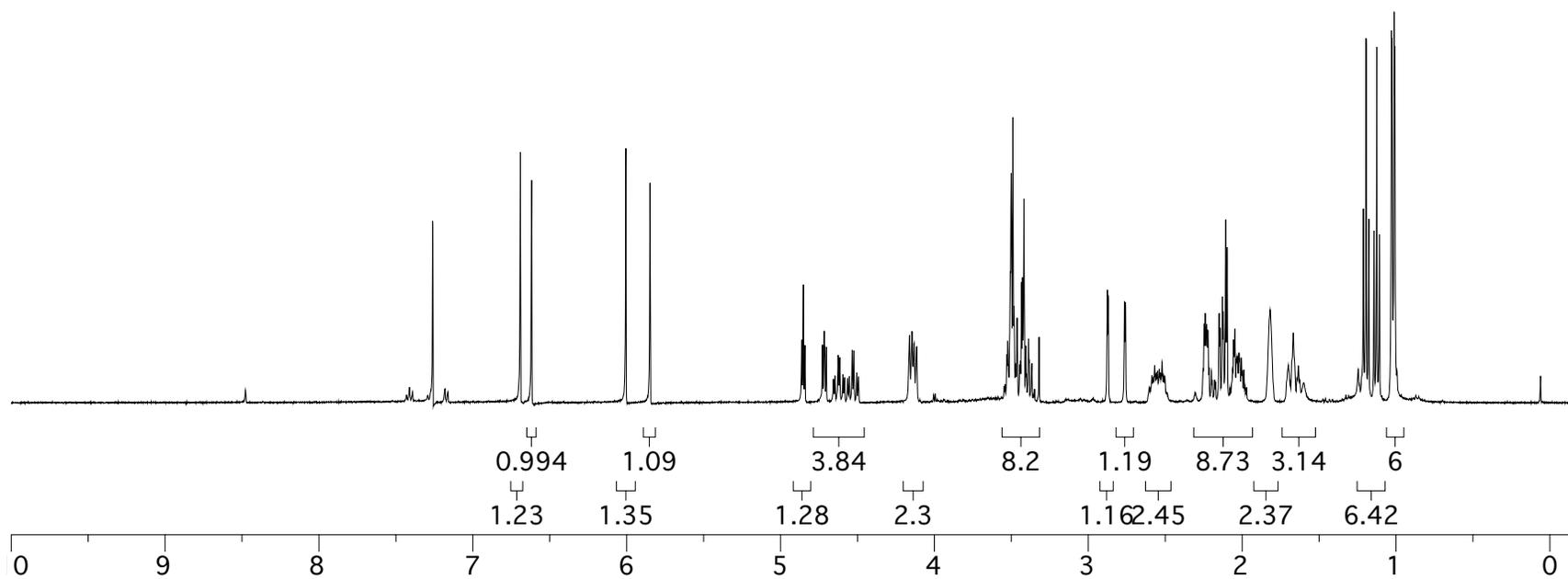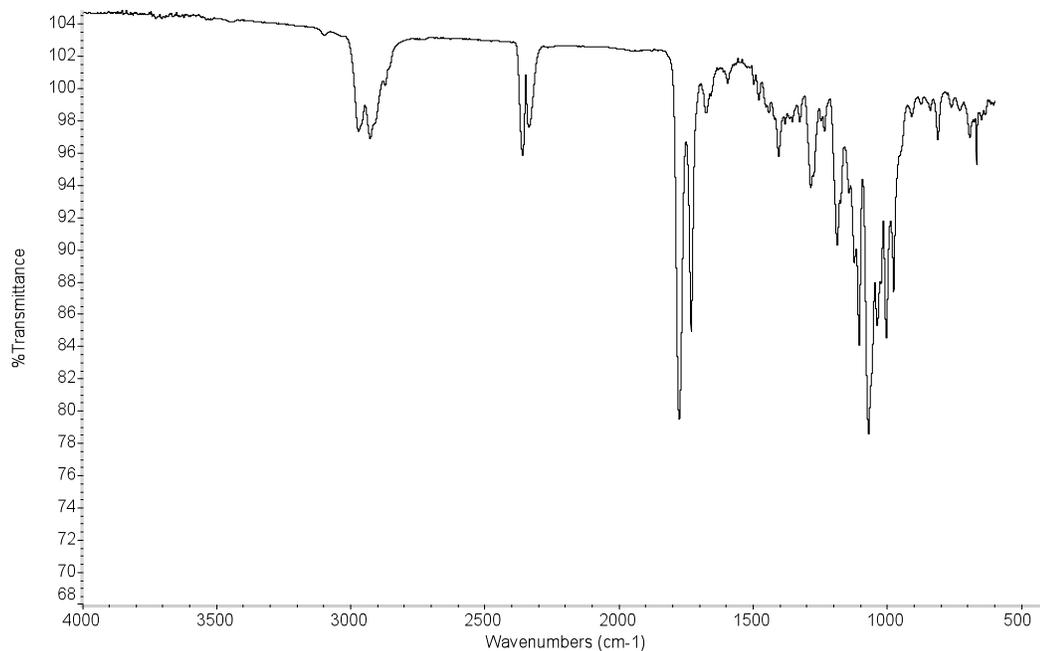
Figure A.4.137 Infrared Spectrum (thin film/NaCl) of compound **513**.
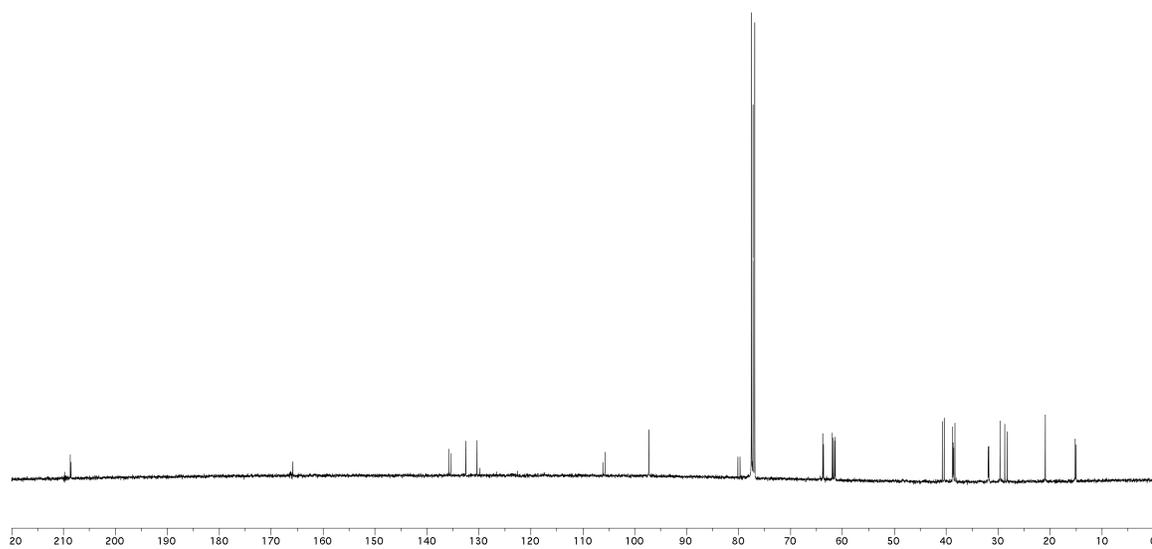


Figure A.4.138 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **513**.
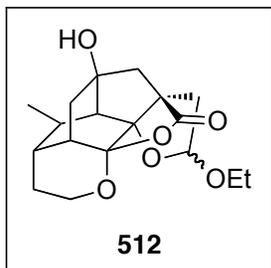
Figure A.4.139 ^{1}H NMR (400MHz, CDCl3) of compound **512**
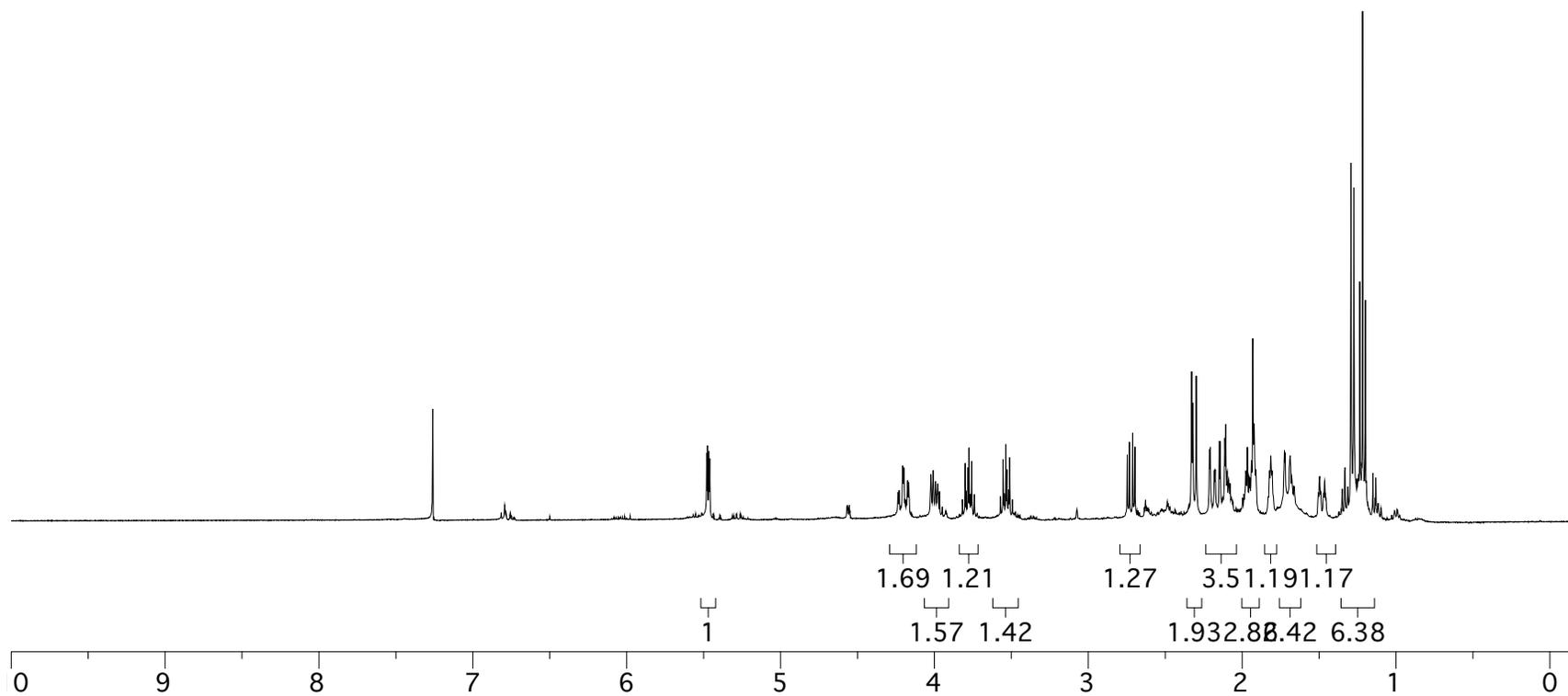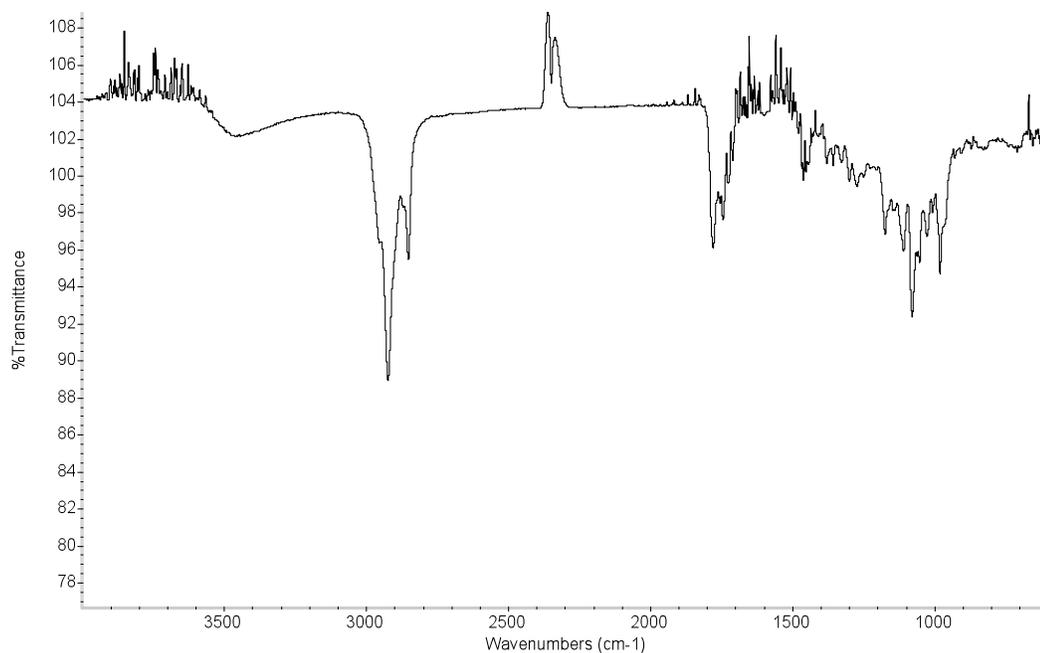
Figure A.4.140 Infrared Spectrum (thin film/NaCl) of compound **512**.
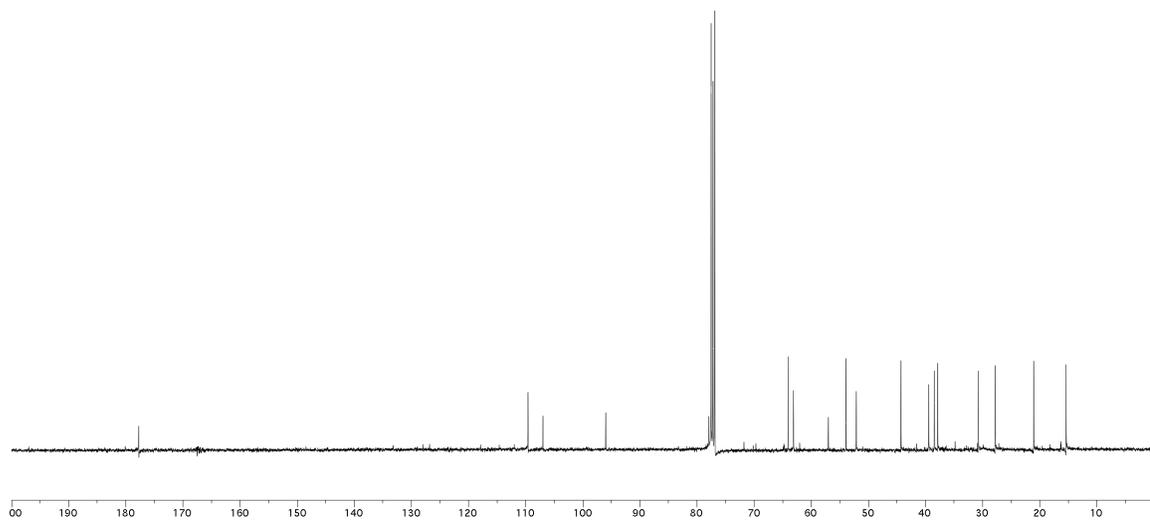


Figure A.4.141 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **512**.
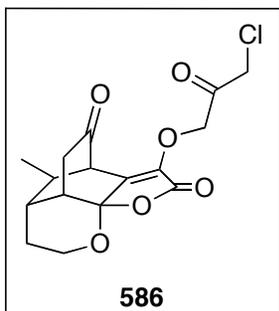
**Figure A.4.142 $^1$H NMR (400MHz, CDCl$_3$) of compound 586**
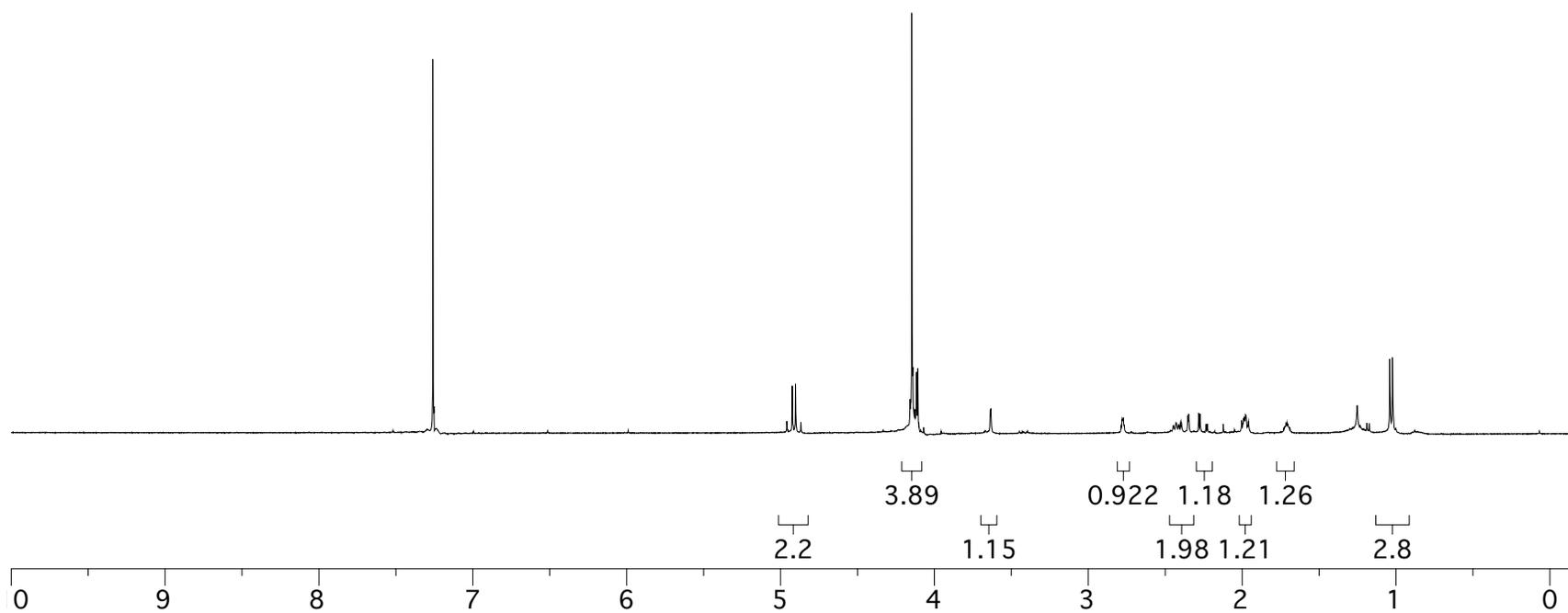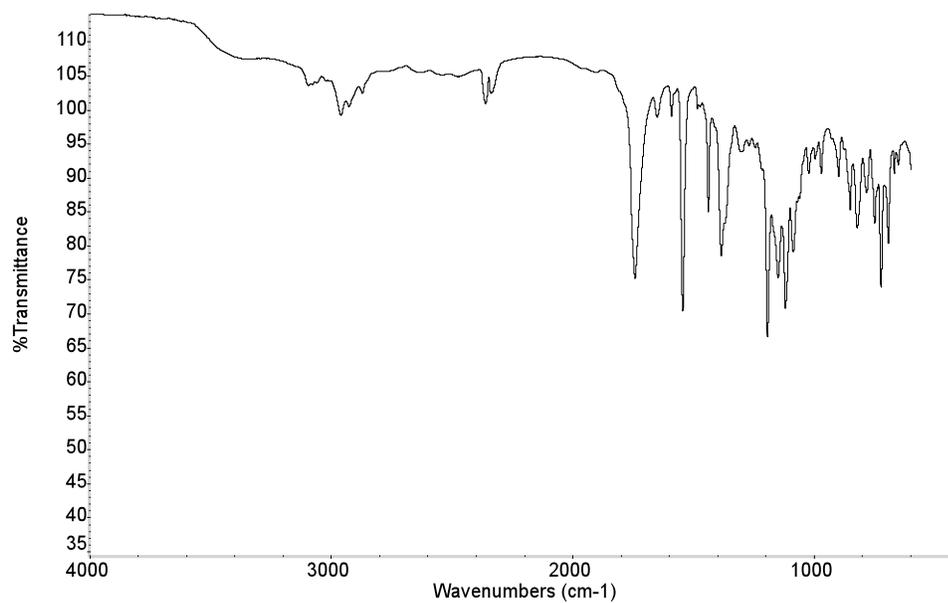
Figure A.4.143 Infrared Spectrum (thin film/NaCl) of compound **586**.
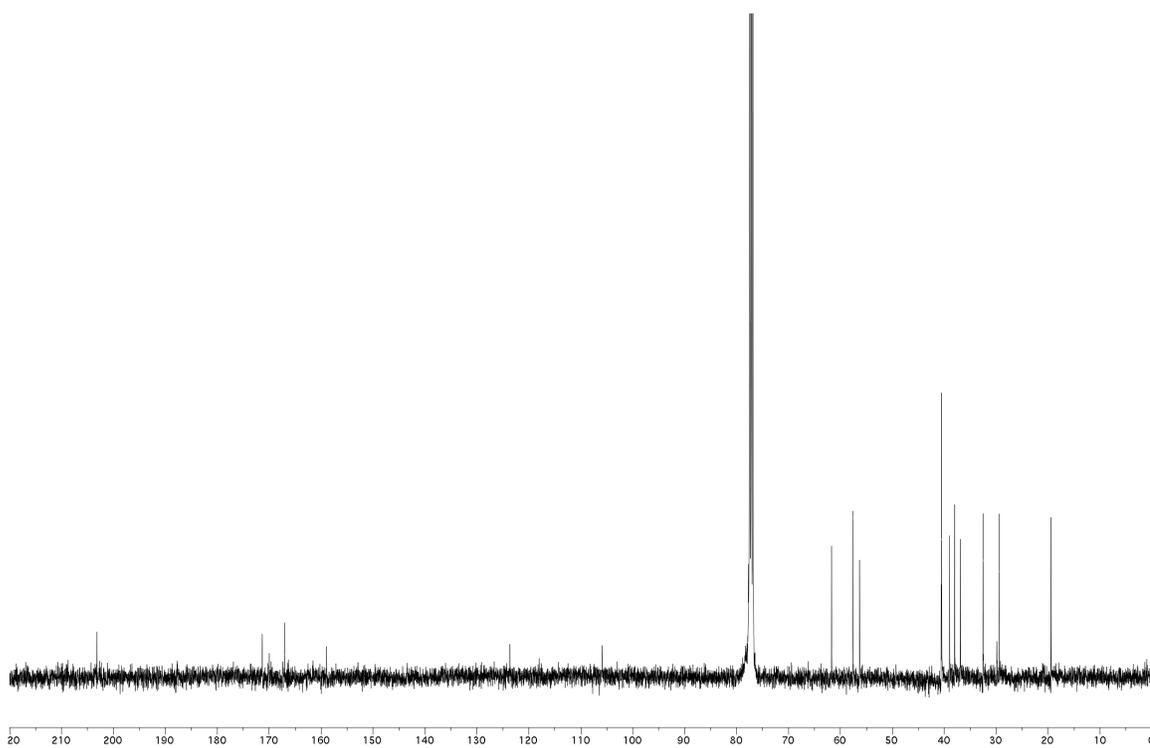


Figure A.4.144 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **586**.
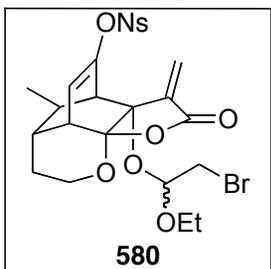
Figure A.4.145 $^1$H NMR (400MHz, CDCl$_3$) of compound 580
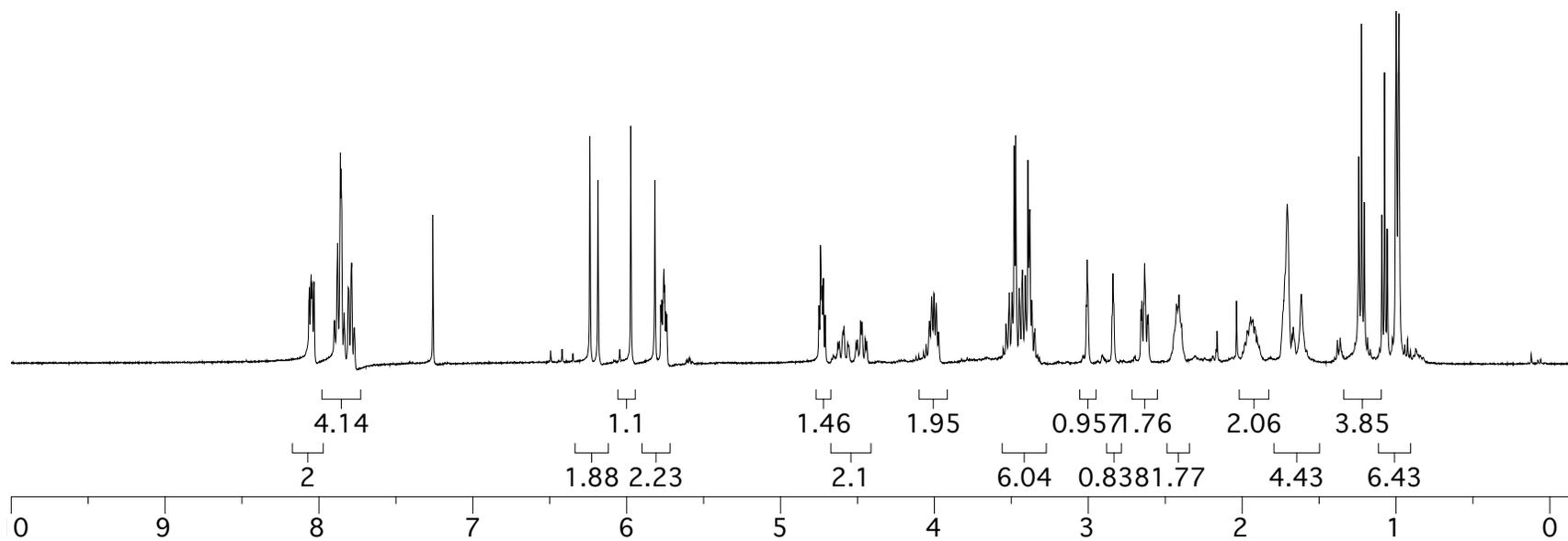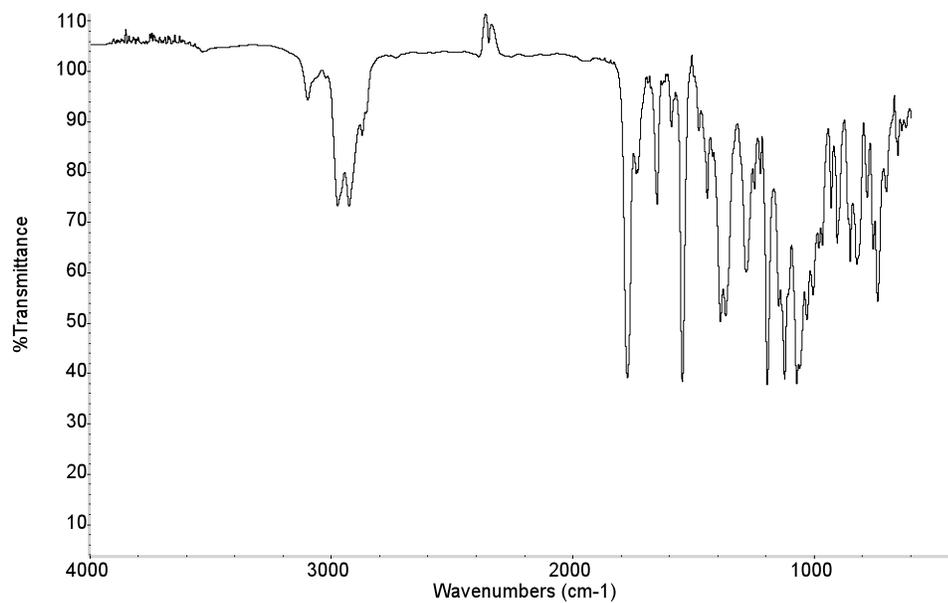
Figure A.4.146 Infrared Spectrum (thin film/NaCl) of compound **580**.
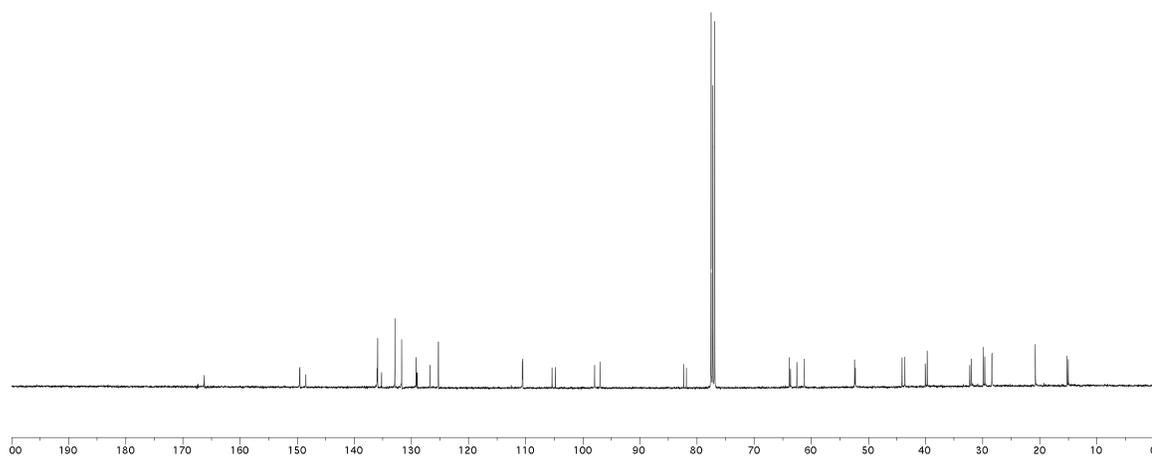


Figure A.4.147 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **580**.
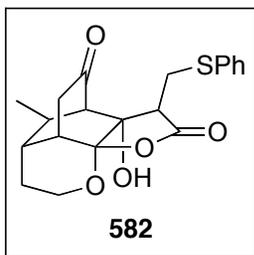
Figure A.4.148 $^1$H NMR (400MHz, CDCl$_3$) of compound 582
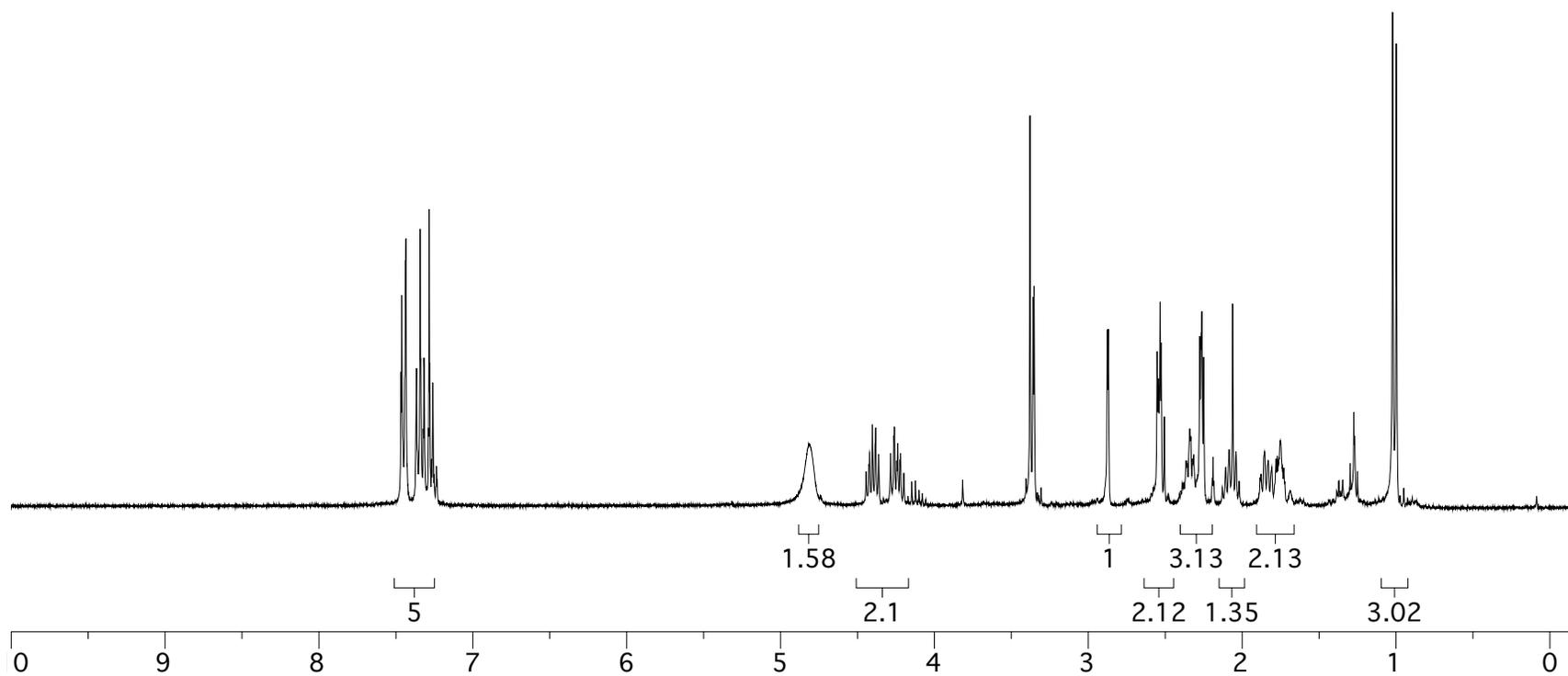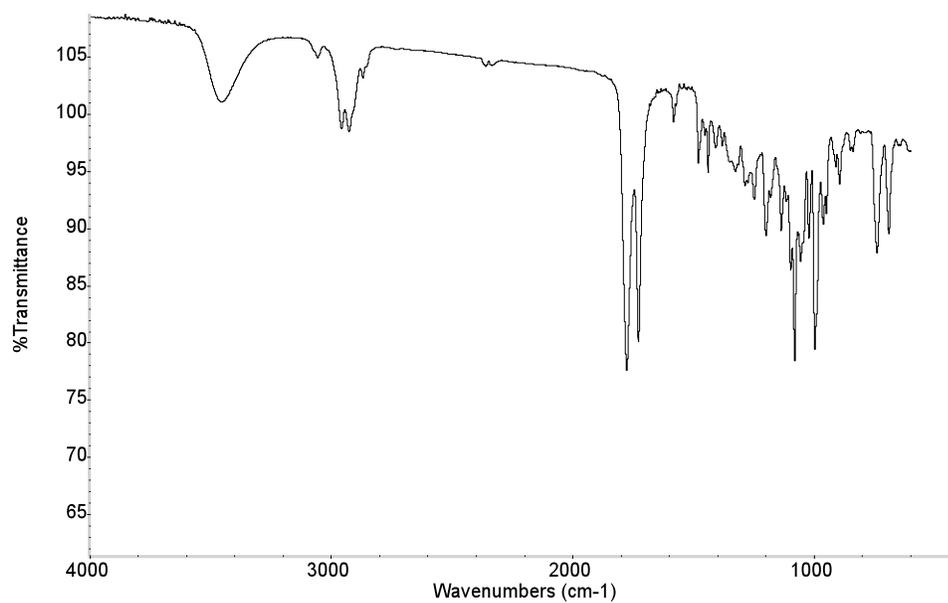
Figure A.4.149 Infrared Spectrum (thin film/NaCl) of compound **582**.
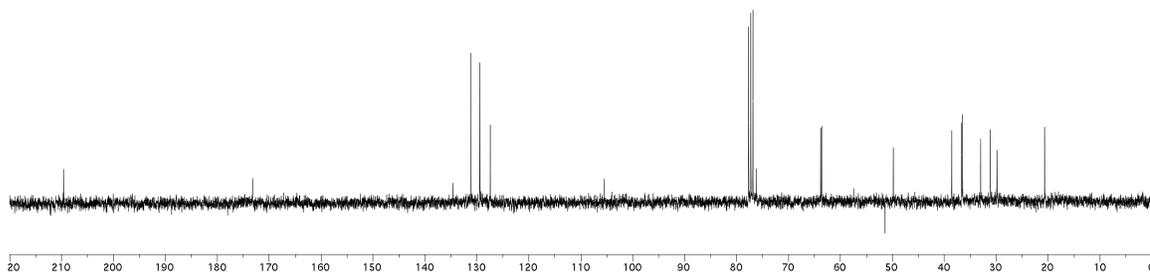


Figure A.4.150 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound **582**.

# About the Author

Ping Dong was born on July 13, 1978 to Jinghuan Zhang and Wangliang Dong. Ping Dong was raised in Fushun city of Liaoning province at the northeast of China. Ping Dong began his education at Fushun Town 4th elementary school. After 6 years study, he enter Fushun City 25th middle school for 3 years study. After passing the high school entrance examination in 1994, he was admitted to Fushun City 2nd middle school for further education.

After 3 years' study, Ping passed the national undergraduate entrance examination to begin his undergraduate study at Xiamen University in 1997. In this peaceful and beautiful coast city in the southeast of China, Ping spent 4 years on studying in chemistry. For his interest on the new arising research field of nano-chemistry at that time, he decided to pursue a graduate study on nano materials synthesis by electronic chemistry in Xiamen University. In 2001, Ping joined Professor Zhonhua Lin's research group for studying the synthesis and growth mechanism of nano polyanaline in alumina template by electronic chemistry method where he began to show some interest on organic chemistry. After 3 years graduate study, he received M.S. degree in chemistry in 2004.

In the fall of 2005, Ping Dong joined Professor Fraser Fleming's research group for organic graduate study in Duquesne University, Pittsburg of PA. He spent a year for studying the Grignard reagent addition on substrates containing nitrile group and found out that he was really fascinated on the total synthesis of nature products. Therefore, Ping joined Colorado State University at Fort Collins, CO in the fall of 2006 where luckily he

began his graduate study and research on the total synthesis of nature products in Wood

Lab.  Ping Dong will receive his Doctorate Degree at fall in 2010.