DISSERTATION

PROGRESS TOWARD THE SYNTHESIS OF PROVIDENCIN

Submitted by

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ABSTRACT

PROGRESS TOWARD THE SYNTHESIS OF PROVIDENCIN

Providencin, a highly oxygenated diterpene, was isolated from the sea plume *Pseudopterogorgia kallos* in 2003 by Rodriguez and co-workers. Providencin was revealed to be a cembrane-based diterpene containing an unprecedented [12.2.0]hexadecane ring-system. Providencin was found to possess anti-cancer activity against human breast (MCF7), lung (NCI-H460) and CNS (SF-268) cancer cell lines. The unique structure and biological activity make providencin an attractive target for total synthesis and our work toward providencin began shortly after its isolation. The initial focus of each approach has centered on the unique *trans*-fused cyclobutanol moiety. A formal [2 + 2] cycloaddition is our chosen approach to the synthesis of the cyclobutane moiety. Further elaboration of our cyclobutane compounds has led to the synthesis of several highly functionalized intermediates. Our efforts toward the synthesis of providencin are discussed herein.

ACKNOWLEDGEMENTS

First and foremost, I must thank Professor John L. Wood for the opportunity to study organic chemistry in his group. It has been an honor and a privilege to work for John for the past 5 years. His knowledge of and passion for organic chemistry is a constant source of inspiration. I truly appreciated the time he spent with me discussing my chemistry.

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Finally, I wish to thank my family and friends for their love and support during my graduate career. Without their constant encouragement I could not have made it to this point. Thank you to Becca for being such a wonderful friend and carpool mate. Thank you to the Williams group women especially Jenni and T for always making me smile. An enormous thank you to my husband Greg for taking this arduous journey with me, I am forever grateful for your love and support.

ABOUT THE AUTHOR

Sarah was born on April 16th, 1983 to parents Philip and Laurie. Although they would divorce a few years later, Sarah always had the love and support of both parents and their new families. When Sarah was 8 she got a baby sister, Chelsea, who was of course the cutest baby in the whole world. Even though the family tree was now a bit complicated it provided a network of supportive people.

Beginning in her early elementary school years Sarah developed a love of math and science, which continued throughout her education. Sarah spent her 16th birthday at a chemistry competition for high school students. She would later graduate from Bear Creek High School, where she had spent several years in the band, had met her future husband and had pursued her love of math and science.

In the fall of 2001, Sarah began college at the Colorado School of Mines, with the hope of becoming a chemical engineer. As her schooling progressed it became apparent that Sarah's love of research made her better suited to chemistry than chemical engineering and she switched majors. After doing research in the Voorhees lab, Sarah decided to go to graduate school and was accepted by Colorado State University.

Prior to beginning her graduate career, Sarah interned at Array Biopharma and worked in the process group under Dr. Paul Nichols. After her first semester of graduate school Sarah joined the Wood group and anxiously awaited the arrival of the graduate students and boxes from Yale University. After the unpacking Sarah began work on the providencin project, which continued until 2010. Upon completion of her Ph.D., Sarah will begin post doctoral studies with Dr. Robert Williams at Colorado State University.

To my wonderful husband Greg

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LIST OF ABBREVIATIONS

Å	angstrom
Ac	acetate
AcOH	acetic acid
$AgClO_4$	silver perchlorate
$AgNO_3$	silver nitrate
AIBN	azobisisobutyronitrile
app	apparent
Ar	aryl
$AsPh_3$	triphenylarsine
9-BBN	9-borabicyclo[3.3.1]nonane
$BF_3•OEt_2$	boron trifluoride diethyl etherate
BH_3•DMS	borane dimethylsulfide complex
Bn	benzyl
br	broad
BT	benzothiazole
Bz	benzoyl
C	carbon
C_6H_6	benzene
CAN	cerium(IV) ammonium nitrate
cat.	catalytic
CCl_4	carbon tetrachloride
CH_2Cl_2	dichloromethane
CH_3CN	acetonitrile
CO	carbon monoxide
Cp_2ZrCl_2	bis(cyclopentadienyl)zirconium dichloride
$CrCl_2$	chromium(II) chloride
CSA	camphorsulfonic acid
CsF	cesium fluoride
CuCl	copper(I) chloride
CuI	copper(I) iodide
d	doublet
DCC	dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
dd	doublet of doublets
ddd	doublet of doublet of doublets
dddd	doublet of doublet of doublet of doublets
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DIBAL-H	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DME	dimethoxyethane
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMS	dimethylsulfide
DMSO	dimethylsulfoxide

dppf	1,1'-bis(diphenylphosphino)ferrocene
dt	doublet of triplet
DTBMP	2,6-di-tert-butyl-4-methylpyridine
ent	enantiomer
ESI–APCI	electrospray ionization – atmospheric pressure chemical ionization
Et	ethyl
Et_2AlCl	diethylaluminum chloride
Et_3N	triethylamine
EtOAc	ethyl acetate
EtOH	ethanol
g	gram
GGPP	geranylgeranyl pyrophosphate
h	hour(s)
H	hydrogen
H_2O	water
H_2O_2	hydrogen peroxide
H_2SO_4	sulfuric acid
HFIP	hexafluoroisopropanol
$Hg(OAc)_2$	mercury(II) acetate
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
HWE	Horner-Wadsworth-Emmons
Hz	hertz
hν	light
i-Bu_2AlCl	diisobutylaluminum chloride
IBX	2-iodoxybenzoic acid
Im	imidazole
i-Pr_2NEt	*N*,*N*-Diisopropylethylamine, Hünig's Base
i-PrMgCl	isopropyl magnesium chloride
IR	infrared
J	coupling constant
K_2CO_3	potassium carbonate
kg	kilogram
KHMDS	potassium bis(trimethylsilyl)amide
KO*t*-Bu	potassium *tert*-butoxide
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
$LiNCy_2$	lithium dicyclohexylamide
m	milli, multiplet (NMR), mid (IR)
*m*CPBA	meta-chloroperoxybenzoic acid
Me	methyl
Me_2CO	acetone
Me_2SO_4	dimethylsulfate
Me_3SI	trimethylsulfonium iodide
MeO_2CCN	methyl cyanoformate, Mander's reagent

MeOH	methanol
mg	milligram
min	minute(s)
mL	milliliter
mmol	millimole
MMTr	monomethoxytrityl
mol sieves	molecular sieves
mol	mole(s)
MOM	methoxymethyl ether
MsCl	methanesulfonyl chloride
$NaBH_4$	sodium borohydride
NaH	sodium hydride
$NaHCO_3$	sodium bicarbonate
NaHMDS	sodium bis(trimethylsilyl)amide
NaI	sodium iodide
$NaIO_4$	sodium periodate
NBS	N-bromosuccinimide
n-BuLi	*n*-butyllithium
NH_4Cl	ammonium chloride
NH_4F	ammonium fluoride
NHK	Nozaki-Hiyama-Kishi
NHMeOMe	*N*,*O*-dimethylhydroxylamine
nm	nanometer
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
O_3	ozone
ºC	degrees Celsius
OTf	triflate
$Pd(OAc)_2$	palladium(II) acetate
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium(0)
Pd_2dba_3	tris(dibenzylideneacetone)dipalladium(0)
$PdCl_2$	palladium(II) chloride
PG	protecting group
Ph	phenyl
Ph_3P	triphenylphosphine
$(PhSe)_2$	diphenyl diselenide
PhSeCl	phenyl selenyl chloride
Piv	pivaloyl
PMB	paramethoxybenzyl
PPh_3	triphenylphosphine
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
PTAP	phenyltrimethyl ammonium tribromide
PTB	pyridinium tribromide
*p*TSA	*p*-toluenesulfonic acid
Py	pyridine

q	quartet
quint.	quintuplet
RCM	ring-closing metathesis
R_f	retention factor
$RhCl(PPh_3)_3$	chlorotris(triphenylphosphine)rhodium(I), Wilkinson's catalyst
rt	room temperature
$RuCp(MeCN)_3PF_6$	tris(acetonitrile)cyclopentadienylruthenium(II) hexafluorophosphate
$RuO_2•XH_2O$	ruthenium(IV) oxide hydrate
s	singlet (NMR), strong (IR)
SeO_2	selenium dioxide
$SnCl_2$	tin(II) chloride
$SnMe_3$	trimethyltin
$SOCl_2$	thionyl chloride
t	triplet
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
t-BuLi	*tert*-butyllithium
tert	tertiary
TES	triethylsilyl
Tf_2O	triflic anhydride
TFA	trifluoroacetate, trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyrans
TIPS	triisopropylsilyl
TLC	thin layer chromatography
$TMSCHN_2$	trimethylsilyldiazomethane
TOF LCMS	time of flight liquid chromatography mass spectrometry
TPAP	tetrapropylammonium perruthenate
Tr	trityl
w	weak
δ	chemical shift
Δ	heat

Chapter 1

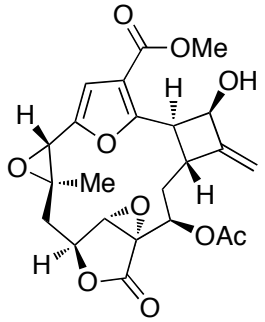
Providencin

1.1 Background

1.1.1 Isolation and Biological Activity

Providencin (**1**) was isolated in 2003 by Rodriguez and co-workers, from the Caribbean sea plume *Pseudopterogorgia kallos* (Figure 1.1.1.1).[1] The gorgonians encompass approximately 500 species of sea fans, sea plumes and sea whips found in oceans throughout the world.[2] *Pseudopterogorgia kallos* and related gorgonian octocorals have proven to be an abundant source of secondary metabolites that possess a diverse range of structural features and biological activities.[3]

Figure 1.1.1.1 Providencin (**1**)



Providencin (1)

Providencin was isolated as a colorless amorphous solid in 0.0012% yield from over 1 kg of dried *Pseudopterogorgia kallos* and its structure and relative stereochemistry

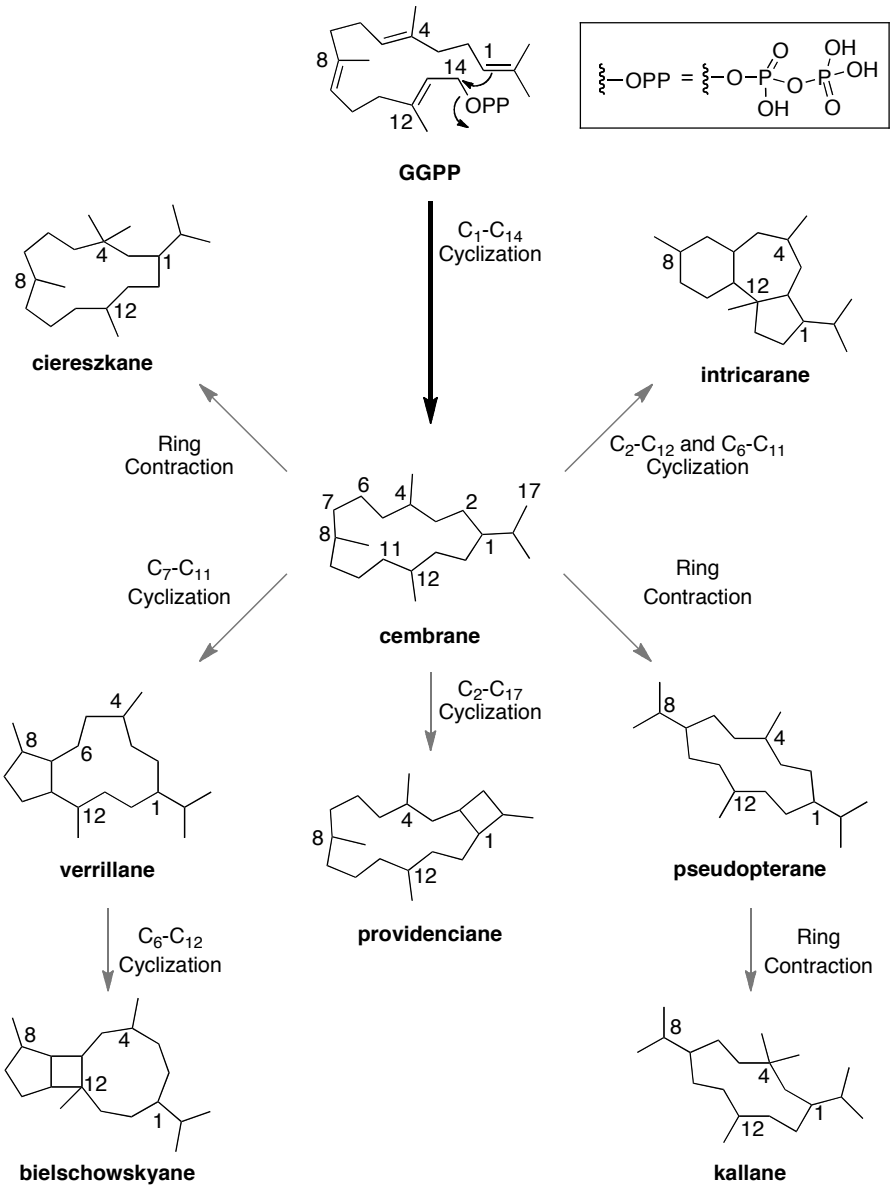
were determined through a combination of NMR spectroscopy and X-ray crystallographic analysis. These studies revealed **1** to be a highly oxygenated diterpene containing an unprecedented [12.2.0]hexadecane ring system. Some of the more intriguing structural features include the *trans*-fused cyclobutanol moiety, the tri-substituted furan and the epoxidized butenolide.[1]

Providencin was tested for biological activity and showed anti-cancer activity against human breast (MCF7), lung (NCI-H460) and CNS (SF-268) cancer cell lines. The growth inhibition of treated cells compared to untreated cells was 57, 39, and 94% respectively.[1] Unfortunately, the dearth of naturally occurring **1** has prevented further biological testing.

1.1.2 Related Compounds

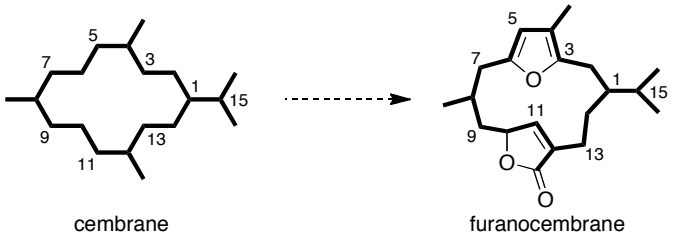
Providencin is one of several structurally intriguing natural products to be isolated from *Pseudopterogorgia kallos*. Rodriguez et al. have proposed that the carbon skeletons represented by **1** and six other compounds or classes of compounds share a common biogenic precursor (Figure 1.1.2.1).[1, 4] Cembrane-based compounds arise from the cyclization of geranylgeranyl pyrophosphate (GGPP).[4c] It has been proposed that cyclization or ring contraction of a cembrane skeleton leads to seven novel carbon skeletons. The providenciane carbon skeleton found in **1** results from a C_2-C_{17} cyclization of a cembrane-based compound.

Figure 1.1.2.1 Cembrane and related diterpene carbon skeletons



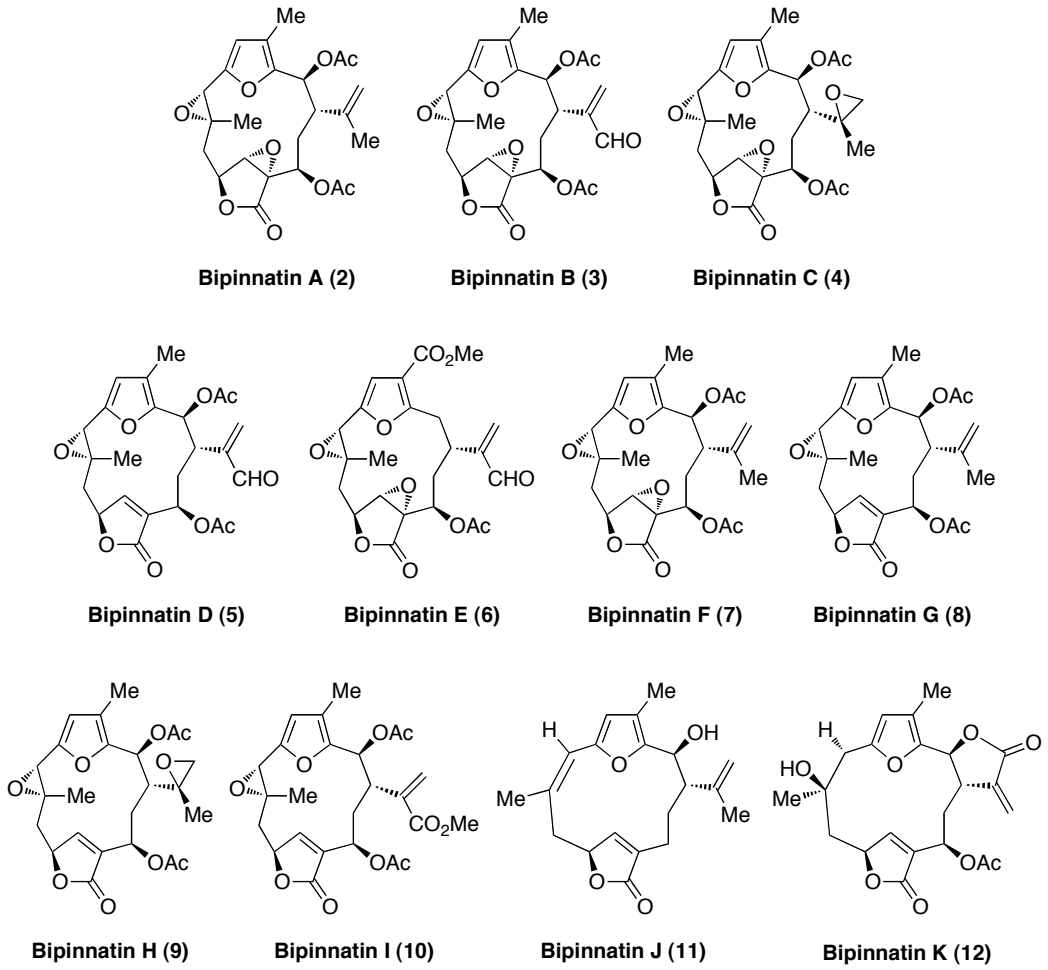
Providencin is closely related to a class of diterpenes with cembrane-based skeletons known as furanocembranoids. These compounds are typified by a polyoxygenated 14-membered macrocycle containing a furan ring and often a butenolide (Figure 1.1.2.2).[3]

Figure 1.1.2.2 Furanocembrane skeletal structure



It was discerned that providencin **1** most closely resembles some members of the bipinnatin family of natural products (Figure 1.1.2.3).[5] These furanocembranes were first isolated from *Pseudopterogorgia bipinnata* but the bipinnatins and their derivatives have also been found in other gorgonian species including *Pseudopterogorgia kallos*, from which **1** was isolated.

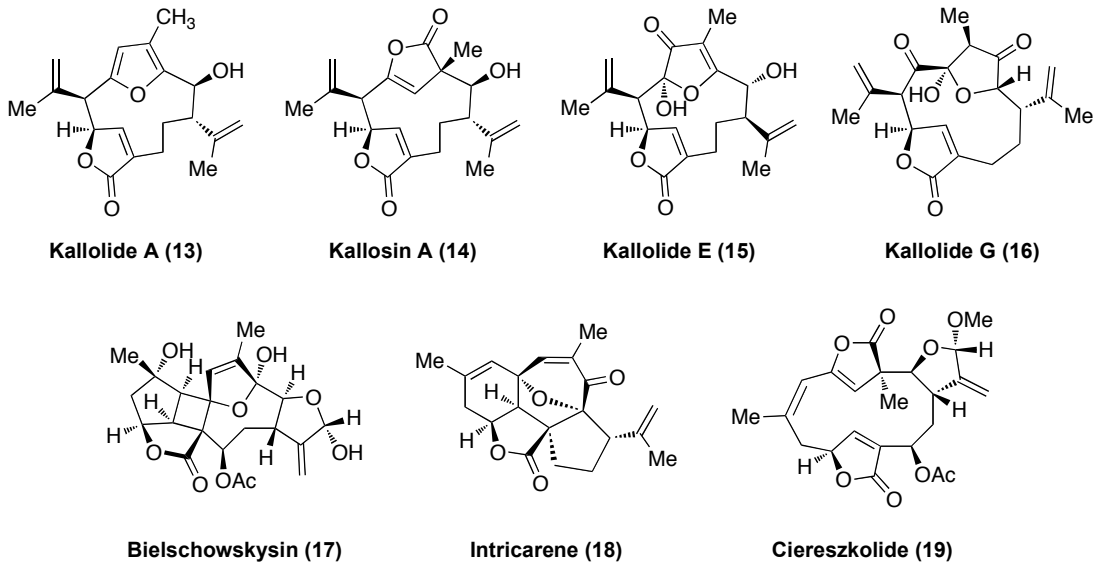
Figure 1.1.2.3 Bipinnatin family of natural products



In addition to providencin **1**, several other intriguing diterpene natural products have been isolated from *Pseudopterogorgia kallos* (Figure 1.1.2.4).[4, 6] These compounds show a wide variety of structural and biological characteristics and have therefore been the target of several synthetic studies. Kallolide A (**13**), the first and most abundant metabolite to be isolated from *Pseudopterogorgia kallos*, has potent anti-inflammatory activity and was synthesized in 1998 by Marshall and Liao.[6a, 7] Beilschowskysin (**17**) was found to have anti-malarial and anti-cancer activity. Several studies towards the cyclobutane-containing core have been published but there has been no total synthesis to date.[4c, 8] The study and synthesis of intricarene (**18**) and its proposed biogenic precursor,

bipinnatin J (**11**), have been accomplished by both the Trauner and Pattenden groups.[9] However, no specific synthetic work has been reported for kallosin A (**14**), kallolide E (**15**), kallolide G (**16**) or ciereszkolide (**19**).

Figure 1.1.2.4 Related *Pseudopterogorgia kallos* isolates



1.2 Synthesis of Relevant Structures

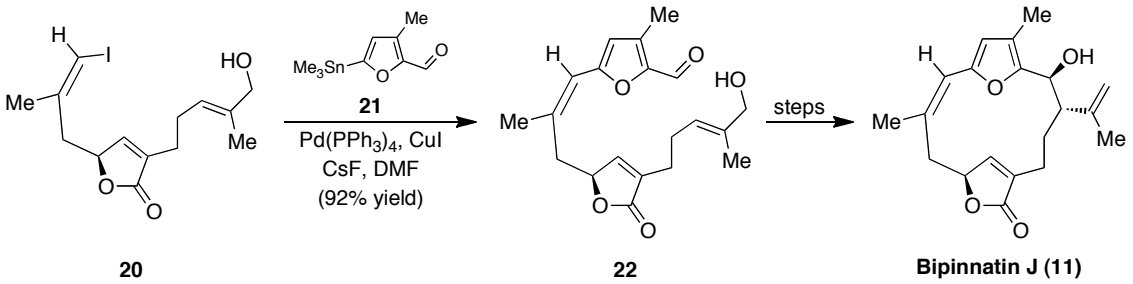
The synthesis of furanocembrane-based diterpenes has been the aim of several research groups. These synthetic studies have shown that a variety of distinctive approaches can effectively produce the various moieties found in these molecules. The main distinction in these approaches is whether or not the furan and/or butenolide moieties are introduced prior or subsequent to the macrocyclization.

1.2.1 Introduction of Furans in the synthesis of Furanocembranes

Marshall recognized two possible approaches to the introduction of the furan moiety in furanocembrane natural products.[10] The first method was to synthesize a furan substrate, which could then be homologated and undergo macrocyclization. This

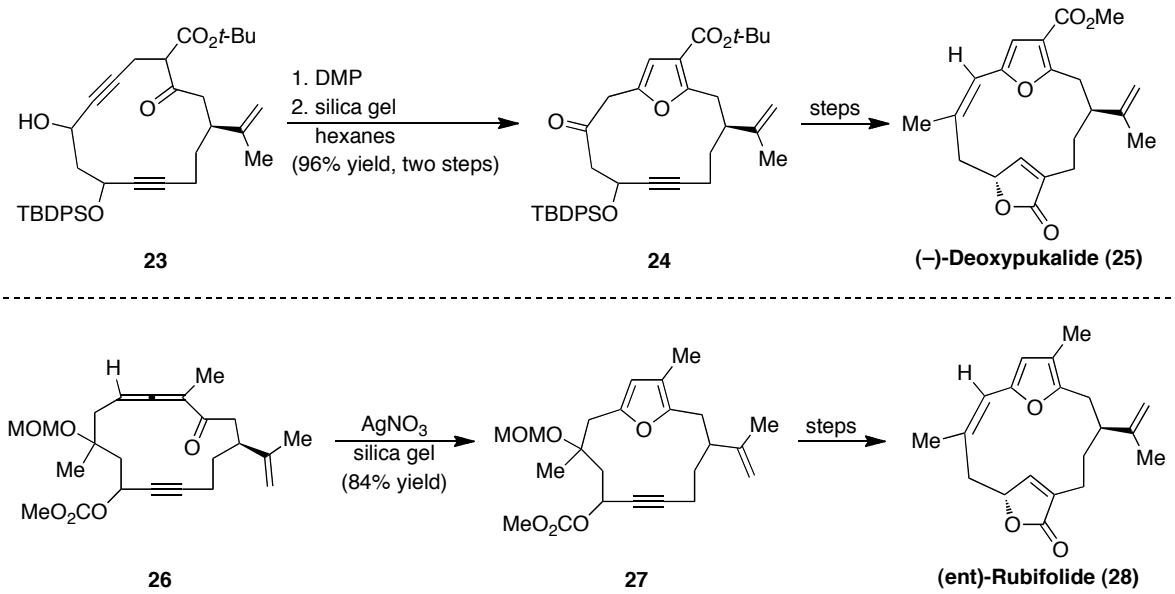
approach has been successfully demonstrated with the total synthesis of (±)-bipinnatin J (**11**) (Scheme 1.2.1.1).[11]

Scheme 1.2.1.1 Introduction of furan in the synthesis of Bipinnatin J (**11**)



The second method was to construct a macrocycle, containing the necessary functionalization in which to introduce the furan post-macrocyclization. Marshall has published two such approaches in the synthesis of (−)-deoxypukalide (**25**) and (*ent*)-rubifolide (**28**) (Scheme 1.2.1.2).[10, 12] In the synthesis of (−)-deoxypukalide (**25**), the macrocyclic ynone **23** was treated with silica gel to furnish the tri-substituted furan **24**. Alternatively, silver nitrate catalyzed the cyclization of allenone **26** to give furan **27** a precursor to (*ent*)-rubifolide (**28**).

Scheme 1.2.1.2 Furan formation in the synthesis of furanocembranes (**25**) and (**28**)

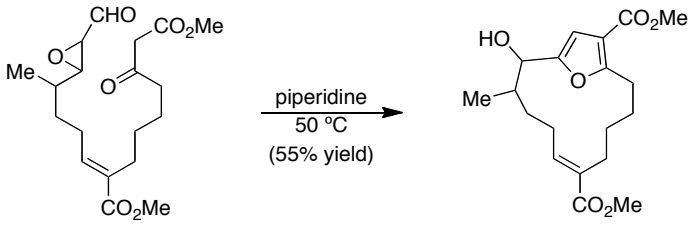


23 **24** **(–)-Deoxypukalide (25)**

26 **27** **(ent)-Rubifolide (28)**

A third approach, proposed by Tokoroyama and co-workers, was to combine the furan formation and macrocyclization into a single step.[13] A Feist-Bénary-type reaction of a tethered epoxy-aldehyde and β-ketoester **29** was shown to yield the macrocyclic furan **30** (Scheme 1.2.1.3). This particular approach has yet to be used in the total synthesis of a furanocembrane natural product.

Scheme 1.2.1.3 Feist-Bénary approach to furan formation/macrocyclization

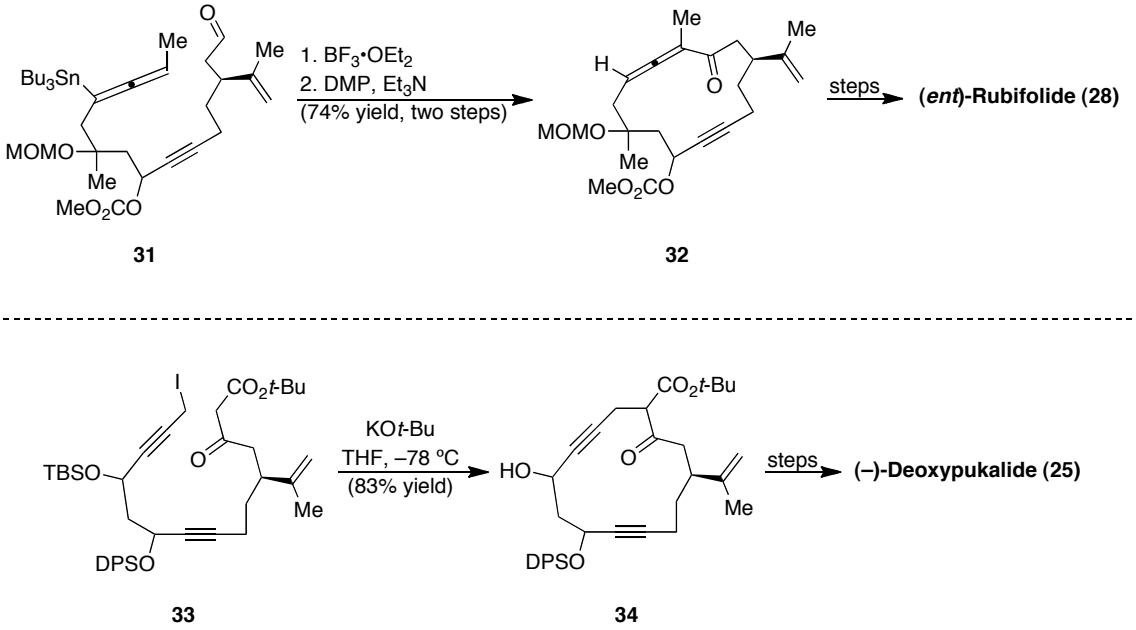


29 **30**

1.2.2 Macrocyclization in the Synthesis of Furanocembranes

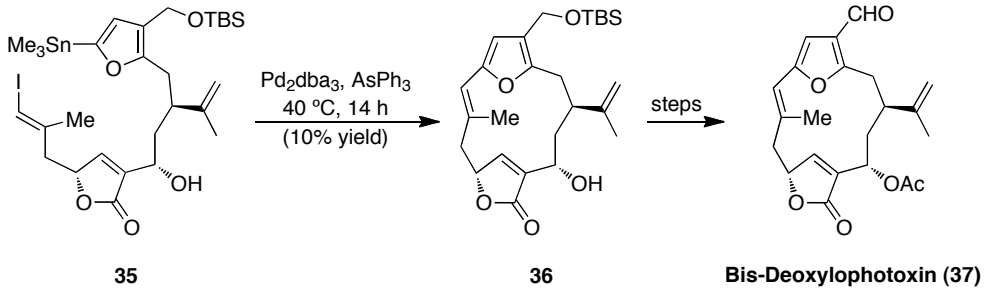
To date, reported approaches to the macrocyclic core of the furanocembranes involve either macrocyclization prior to formation of the furan or after the formation of the furan. As mentioned above, Marshall utilized the former approach in the syntheses of (–)-deoxypukalide (**25**) and (*ent*)-rubifolide (**28**) (Scheme 1.2.2.1).[10, 12] In the synthesis of (*ent*)-rubifolide (**28**), treatment of allenylstannane aldehyde **31** with BF_3•OEt_2 resulted in a cyclized homopropargylic alcohol. Subsequent oxidation and in situ isomerization of the alkyne to the allene resulted in the furan precursor allenone **32**. In the case of (–)-deoxypukalide (**25**) intramolecular alkylation of β-ketoester **33** furnished alkyne **34**, the furan precursor.

Scheme 1.2.2.1 Macrocyclization in the synthesis of (**28**) and (**25**)



Furan formation followed by macrocyclization has been used in several syntheses. An intramolecular Stille coupling, between a vinyl iodide and stannylfuran in substance **35** furnished macrocycle **36**, which was used by Pattenden and co-workers in the synthesis of bis-deoxylophotoxin (**37**) (Scheme 1.2.2.2).[14]

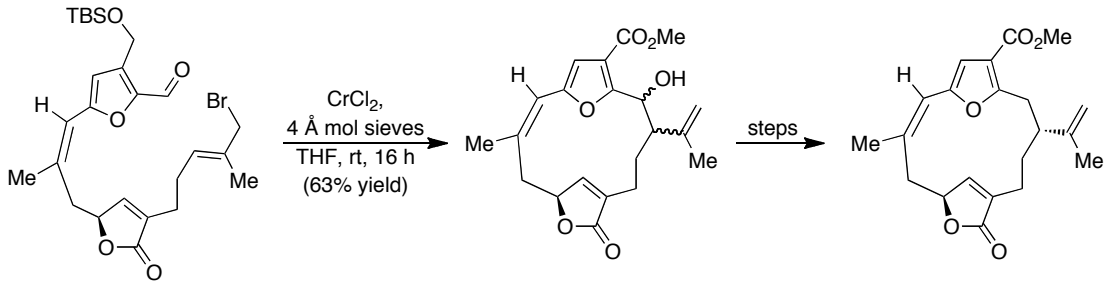
Scheme 1.2.2.2 Macrocyclization in the synthesis of Bis-Deoxylophotoxin (**37**)



Intramolecular cyclization of an allyl bromide and an aldehyde **38** under standard Nozaki-Hiyama-Kishi (NHK) conditions resulted in the desired homoallylic alcohols **39**

(Scheme 1.2.2.3). The Pattenden group used this approach in the synthesis of (+)-*Z*-deoxypukalide (**25**).[15]

Scheme 1.2.2.3 Macrocyclization in the synthesis of (+)-*Z*-Deoxypukalide (**25**)

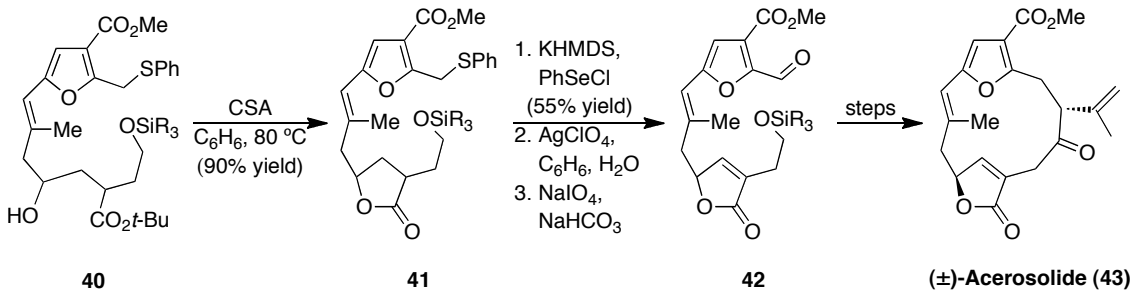


38 **39** **(+)-*Z*-Deoxypukalide (25)**

1.2.3 Introduction of Butenolide Moiety in the Synthesis of Furanocembranes

There have been several approaches to the butenolide moiety found in some of the furanocembrane natural products. One approach, used in the synthesis of (±)-acerosolide (**43**), involves lactonization of a γ-hydroxy ester **40** to a γ-lactone **41**. Conversion of the lactone to the selenide is followed by oxidation to the selenoxide, which subsequently undergoes elimination to yield the butenolide **42**. This approach has generally been used to introduce the butenolide prior to macrocyclization. Paquette, Pattenden and Rawal have favored this approach in the synthesis of bis-deoxylophotoxin (**37**), (±)-acerosolide (**43**) and (±)-bipinnatin J (**11**), respectively (Scheme 1.2.3.1).[11a, 14, 16]

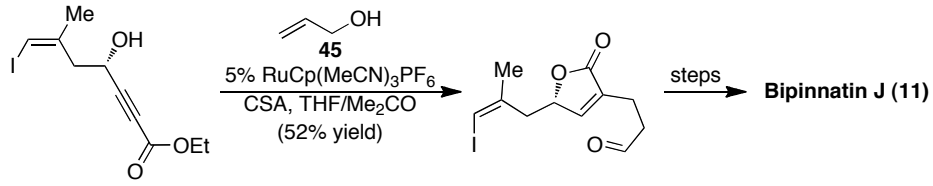
Scheme 1.2.3.1 Butenolide formation in the synthesis of (±)-Acerosolide (**43**)



40 **41** **42** **(±)-Acerosolide (43)**

Trauner and co-workers utilized another approach towards the butenolide moiety, which was synthesized prior to macrocyclization, involving a Trost enyne reaction.[11b] Propargyl alcohol **44** was treated with allyl alcohol **45** and catalytic ruthenium (II) under acidic conditions to give butenolide **46** (Scheme 1.2.3.2). This reaction was used in the synthesis of (±)-bipinnatin J (**11**).

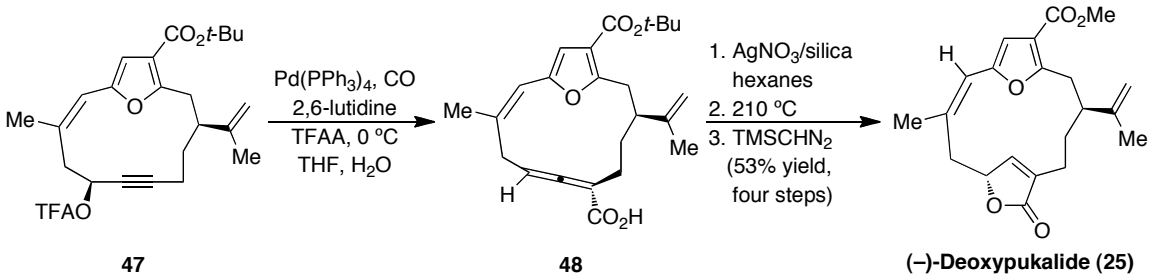
Scheme 1.2.3.2 Butenolide formation in the synthesis of Bipinnatin J (**11**)



44 **46**

Marshall took an independent approach and developed methodology to introduce the butenolide post macrocyclization. In this instance the macrocyclic alkyne **47** undergoes hydroxycarbonylation to give the allenoic acid **48**, which is treated directly with silver nitrate on silica to yield the butenolide. Marshall and co-workers have used this method to install the butenolide in the syntheses of (–)-deoxypukalide (**25**), (*ent*)-rubifolide (**28**) and kallolide A (**13**) (Scheme 1.2.3.3).[7, 10, 12]

Scheme 1.2.3.3 Butenolide formation in the synthesis of (–)-Deoxypukalide (**25**)



47 **48** **(–)-Deoxypukalide (25)**

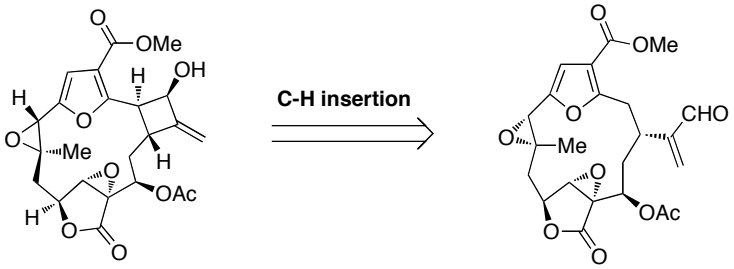
1.3 Previous Synthetic Work Towards Providencin

Three research groups have published work towards the synthesis of providencin (**1**). The Pattenden group from the University of Nottingham, the Mulzer group from the University of Vienna and the White group from Oregon State University have each taken different approaches toward the synthesis of this molecule.

1.3.1 Pattenden's Synthetic Work

In 2006, Pattenden and co-workers published the first synthetic work towards the synthesis of **1**.[17] They proposed that a radical C-H insertion reaction could be utilized to access the cyclobutanol moiety of **1**. They envisioned that **1** could be obtained by applying this reaction to bipinnatin E (**6**) (Scheme 1.3.1.1).

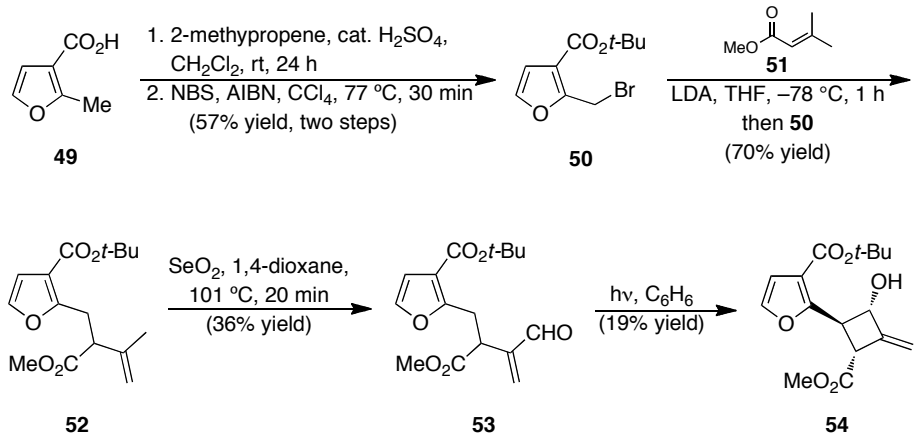
Scheme 1.3.1.1 Proposed biosynthesis of Providencin (**1**)



Providencin (1) **Bipinnatin E (6)**

To test this hypothesis, Pattenden and co-workers utilized a model system (Scheme 1.3.1.2). Starting with 2-methyl-3-furoic acid **49**, esterification and subsequent bromination gave furanmethyl bromide **50**. Deprotonation of methyl 3-methylbut-2-enoate **51** with LDA and treatment with bromide **50** gave the desired β,γ-unsaturated ester **52**. The radical cyclization precursor was obtained by oxidation of **52** with selenium dioxide. Irradiation of aldehyde **53** in benzene yielded the desired cyclobutanol **54** in 19% yield. Although the model study was successful, bipinnatin E (**6**) has not been synthesized and thus its conversion to **1** via the radical cyclization described above has yet to be demonstrated.

Scheme 1.3.1.2 Pattenden's synthesis of exo-methylene cyclobutanol **54**

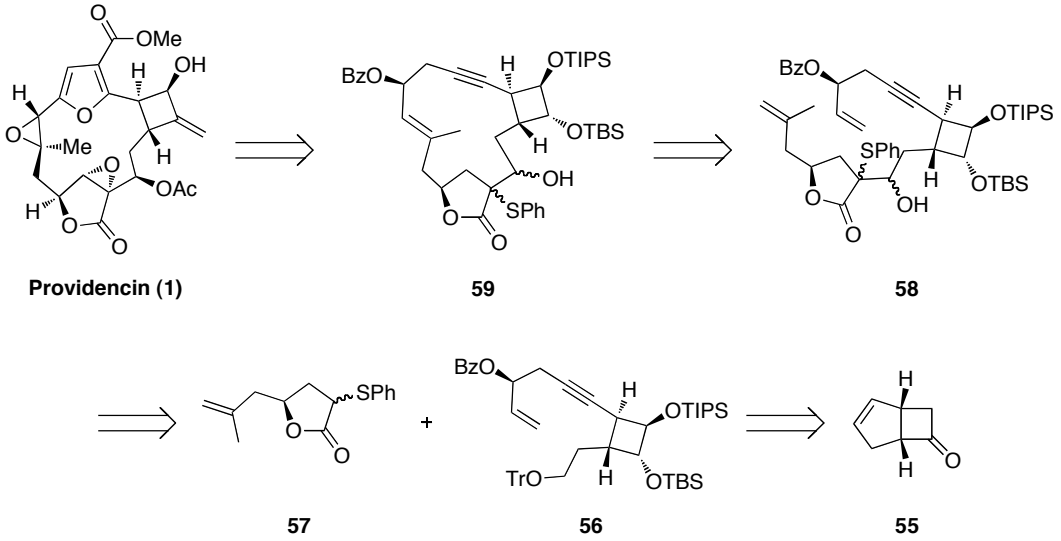


1.3.2 Mulzer's Synthetic Work

Mulzer and co-workers have published several papers regarding their work towards the synthesis of **1**.[18] In their initial retrosynthetic analysis they proposed starting with commercially available, chiral bicyclo[3.2.0]cyclo-hept-6-en-2-one **55**. Homologation of cyclobutanone **55** to cyclobutane **56** and subsequent combination with lactone **57** could provide diene **58**. Subsequent RCM could furnish compound **59**

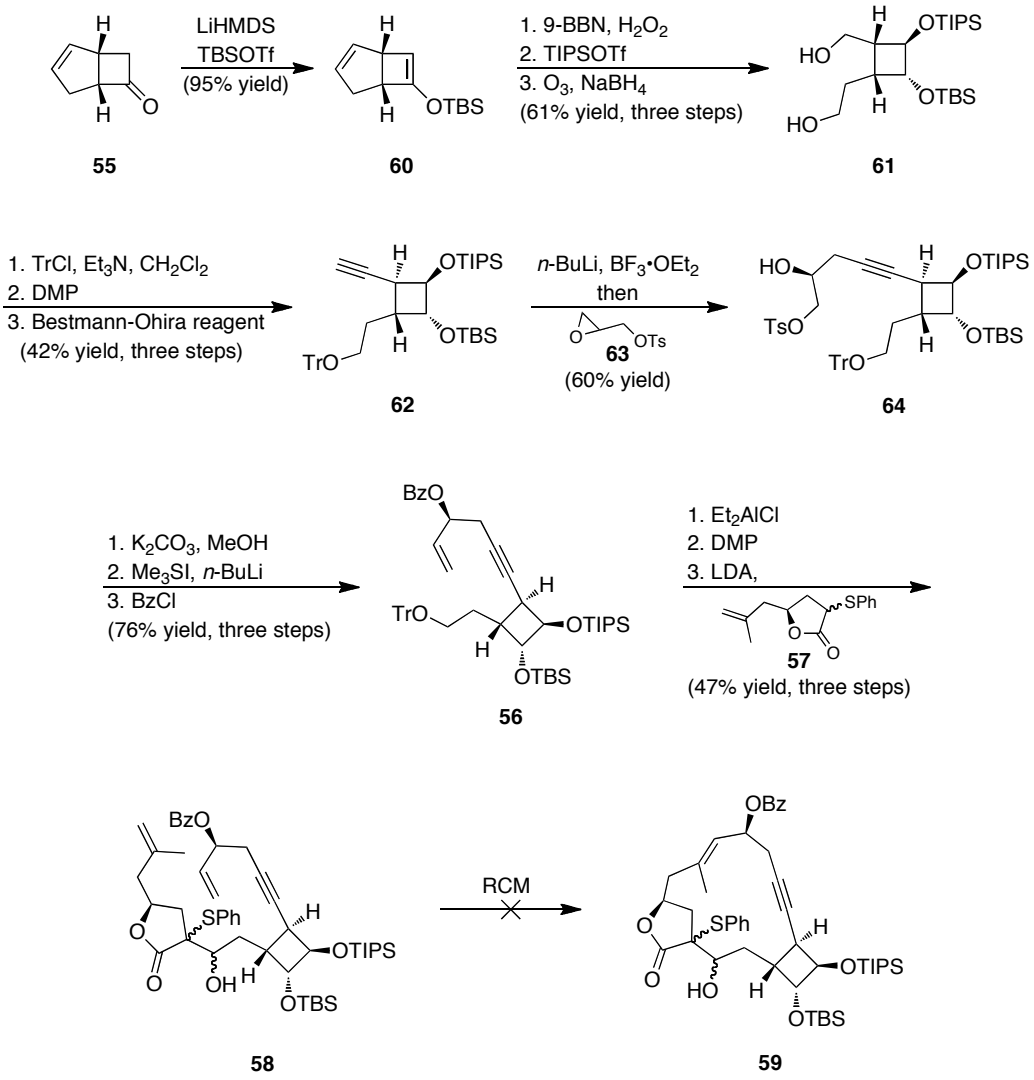
containing a [12.2.0]hexadecane ring system (Scheme 1.3.2.1). The [12.2.0]hexadecane ring system is unique to **1**.

Scheme 1.3.2.1 Mulzer's original retrosynthesis of Providencin (**1**)



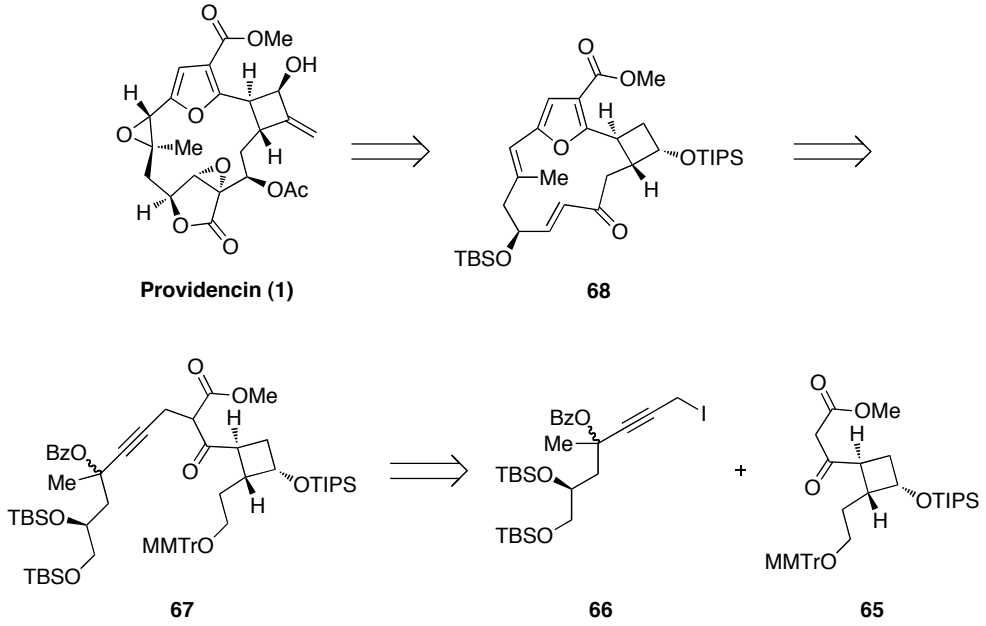
In the forward sense the synthesis began with the conversion of cyclobutanone **55** to the TBS-silyl enol ether **60** (Scheme 1.3.2.2). Hydroboration, silyl protection, ozonolysis and sodium borohydride reduction yielded bis-protected tetraol **61**. Mono-protection of **61** and oxidation of the remaining alcohol to the aldehyde was followed by conversion to the alkyne **62** using the Bestmann-Ohira reagent. Deprotonation of the alkyne **62** and treatment with epoxide **63** furnished **64**. Conversion to the protected allylic alcohol **56** was accomplished via formation of an epoxide and subsequent ring opening followed by benzoyl protection of the resultant alcohol. Deprotection and oxidation provided an aldehyde, which when exposed to deprotonated lactone **57** afforded the RCM-precursor. Unfortunately, all attempts to effect a ring closing metathesis were unsuccessful.

Scheme 1.3.2.2 Mulzer's attempted synthesis of macrocycle **59**



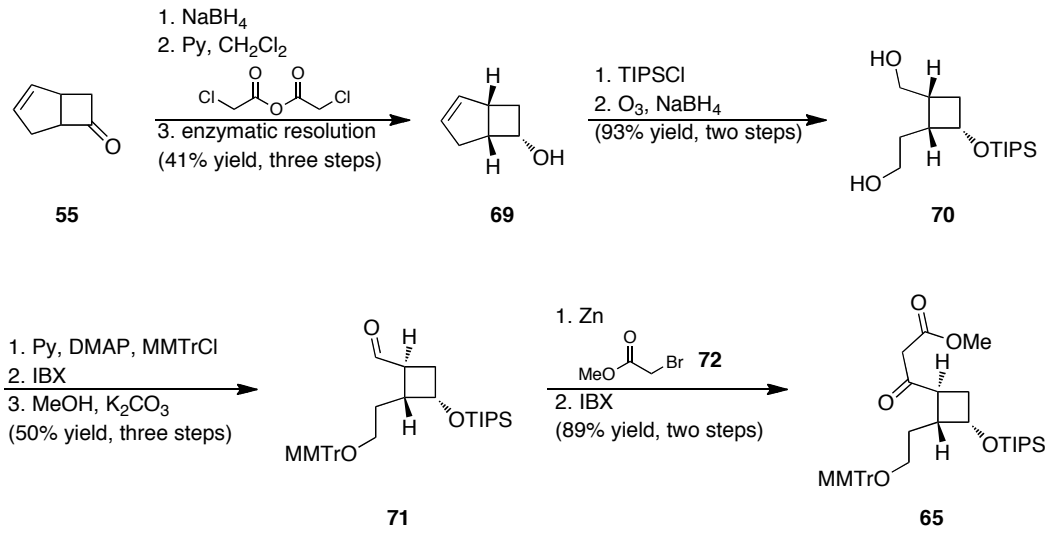
In a further attempt toward the synthesis of **1**, Mulzer and co-workers envisioned combining trans-cyclobutanol **65** and propargyl iodide **66** fragments via an alkylation reaction (Scheme 1.3.2.3). Further elaboration of **67** and subsequent ring-closing metathesis would give macrocycle **68**.

Scheme 1.3.2.3 Mulzer's second retrosynthesis of Providencin (**1**)



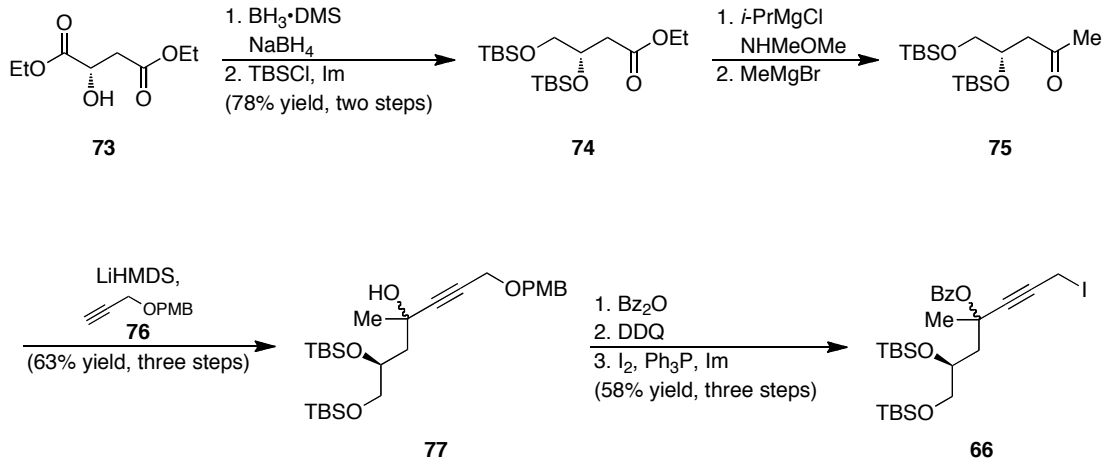
Synthesis of the *trans*-cyclobutanol **65** began with the commercially available racemic cyclobutanone **55** (Scheme 1.3.2.4). Reduction of the ketone and subsequent enzymatic resolution yielded enantiomerically pure alcohol **69**. TIPS protection of alcohol **69** was followed by ozonolysis and treatment with sodium borohydride to furnish the triol **70**. Mono-protection with monomethoxytrityl chloride (MMTrCl), oxidation and successive epimerization gave aldehyde **71**. A Reformatsky reaction and IBX oxidation provided the *trans*-cyclobutanol coupling partner **65**.

Scheme 1.3.2.4 Mulzer's synthesis of β-ketoester **65**



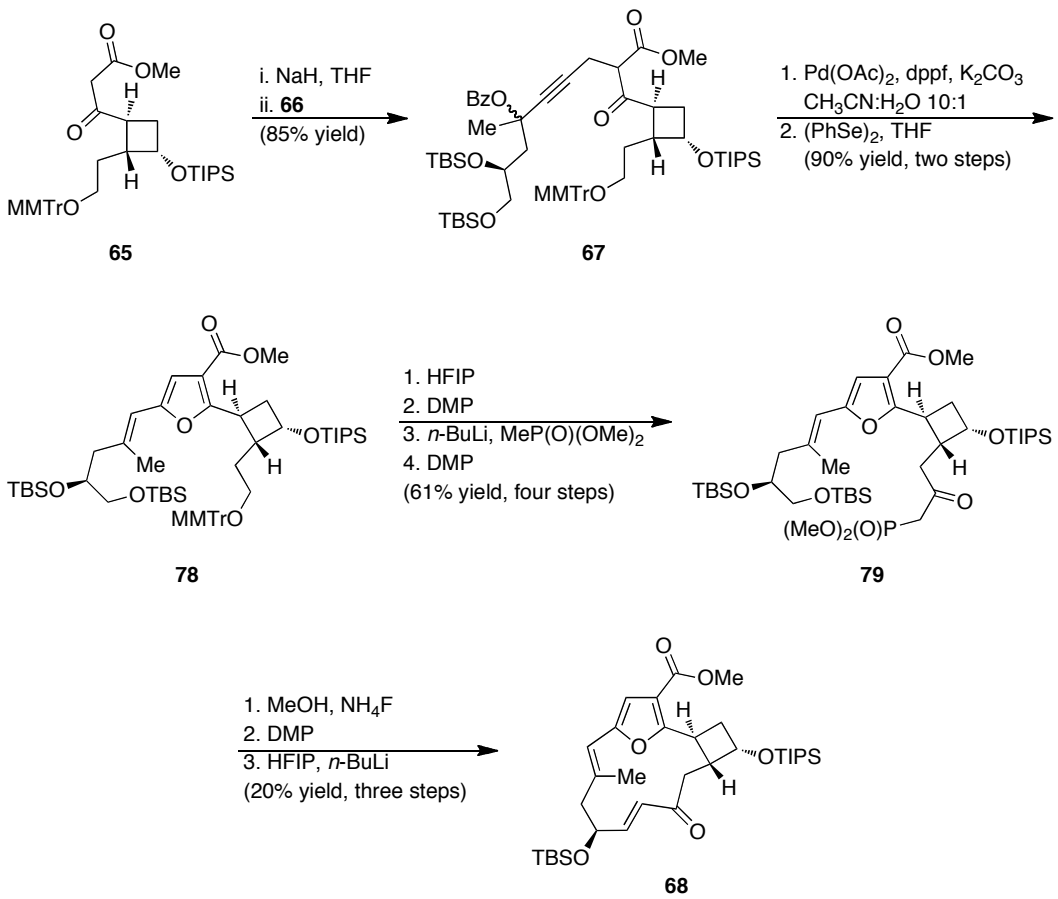
Synthesis of the propargyl iodide coupling partner **66** commenced with reduction of (*S*)-maleic ester **73** and bis-TBS protection of the resultant diol (Scheme 1.3.2.5). Conversion of the ester **74** to the Weinreb amide and treatment with methylmagnesium bromide provided the methyl ketone **75**. Addition of deprotonated alkyne **76** to methyl ketone **75** furnished the tertiary alcohol **77**. Benzoylation, PMB-removal and conversion to the propargyl iodide yielded the desired coupling partner **66**.

Scheme 1.3.2.5 Mulzer's synthesis of propargyl iodide **66**



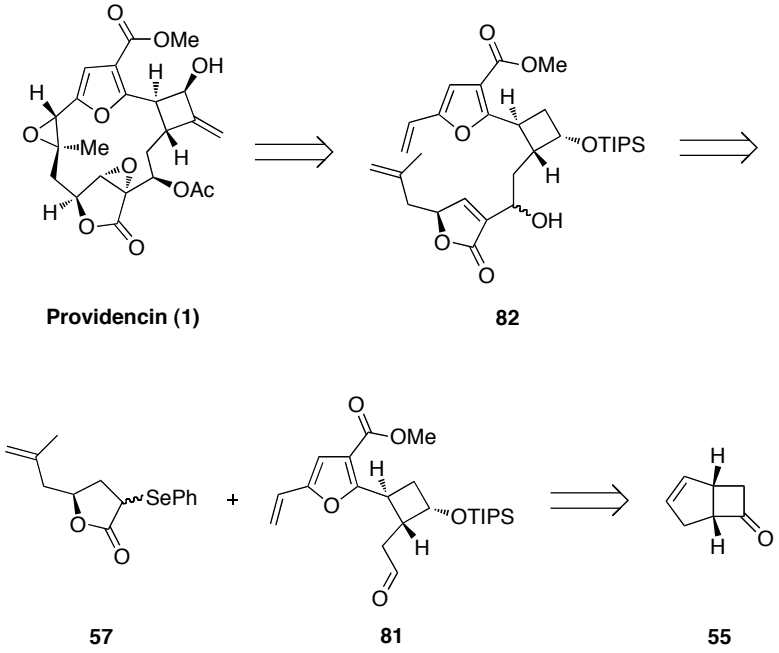
The coupling of the two fragments was accomplished through the alkylation of β-ketoester **65** with propargyl iodide **66** (Scheme 1.3.2.6). Wipf cyclization followed by selenium-mediated equilibration to the E-olefin generated furan **78**.[19] Removal of the MMTr group and oxidation to the aldehyde was followed by addition of the phosphonate and a second oxidation to give keto phosphonate **79**. The primary alcohol was deprotected and subsequently oxidized to the aldehyde followed by macrocyclization via an HWE reaction to give enone **68**. To date no further elaboration of this substrate has been published.

Scheme 1.3.2.6 Mulzer's synthesis of macrocycle **68**



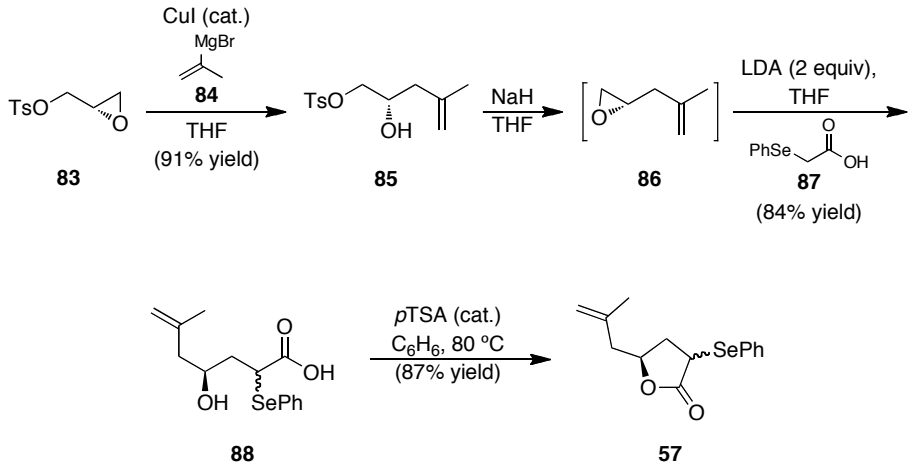
A third approach that Mulzer and co-workers took toward the synthesis of providencin **1** also involved a RCM approach to the macrocyclic core (Scheme 1.3.2.7). However, in this approach the RCM was envisioned to occur on a substrate in which the butenolide and furan moieties were already present. The RCM precursor **81** would arise from an aldol reaction between lactone **57** and aldehyde **81**. Cyclobutanone **55** would again be the starting point for the synthesis of the cyclobutyl furan.

Scheme 1.3.2.7 Mulzer's third retrosynthesis of Providencin (**1**)



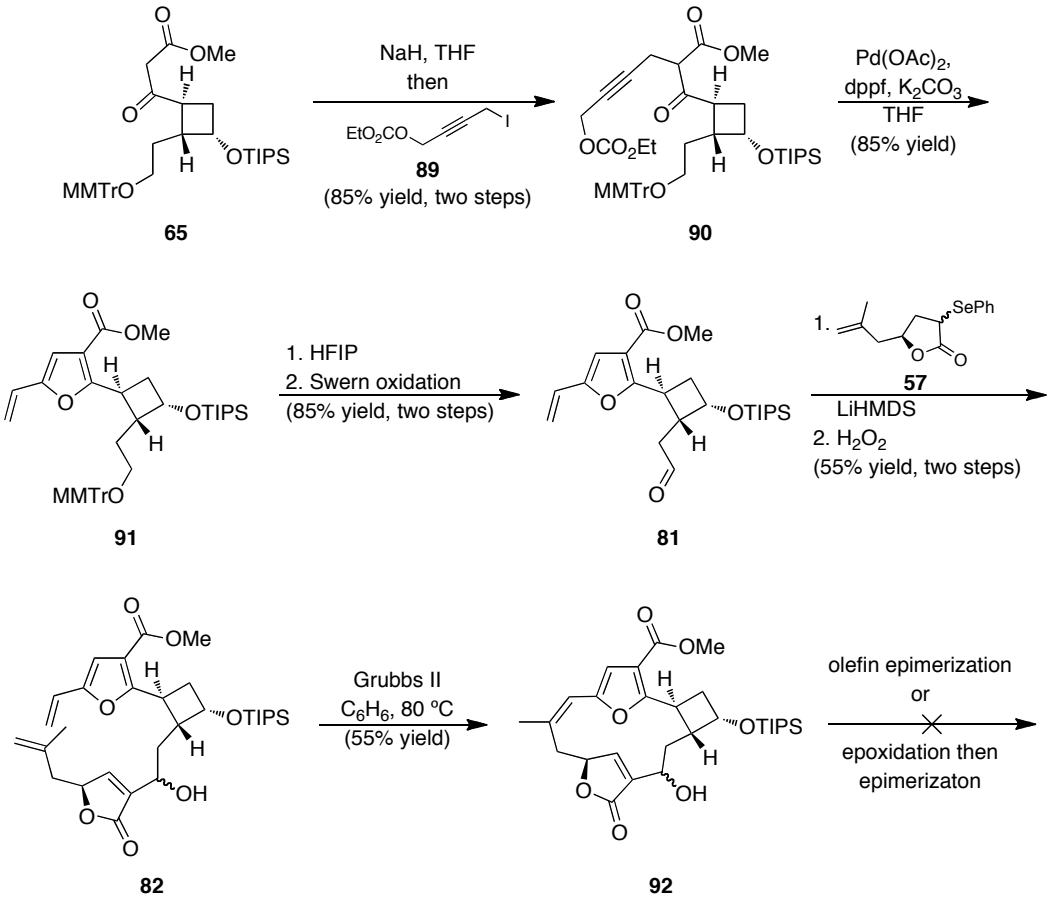
First, the lactone coupling partner **57** was synthesized in four steps from (*R*)-glycidyl tosylate **83** (Scheme 1.3.2.8). Cuprate addition to epoxide **83** provided the homoallylic alcohol that was then converted to the epoxide **86** upon treatment with sodium hydride. The epoxide was then treated with the dianion of (phenylseleno) acetic acid **87** to give the hydroxy acid **88** that underwent acid-catalyzed cyclization to the lactone **57** coupling partner.

Scheme 1.3.2.8 Mulzer's synthesis of α-seleno lactone **57**



Synthesis of the furan coupling partner **81** commenced with the alkylation of β-ketoester **65** was with propargyl iodide **89** (Scheme 1.3.2.9). Wipf cyclization furnished the alkenyl-furan **91**. Removal of the MMTr group was followed by oxidation to provide aldehyde **81**. Deprotonation of lactone **57** and treatment with aldehyde **84** gave the desired lactone, which upon treatment with hydrogen peroxide gave butenolide **82**. Treatment with Grubbs II catalyst furnished the *Z*-isomer of macrocycle **92** as a 1:1 mixture of diastereomers. All attempts to convert the *Z*-olefin to the *E*-olefin were unsuccessful. Similarly attempts to invert the configuration of *cis*-epoxides synthesized from the *Z*-olefin were also unsuccessful.

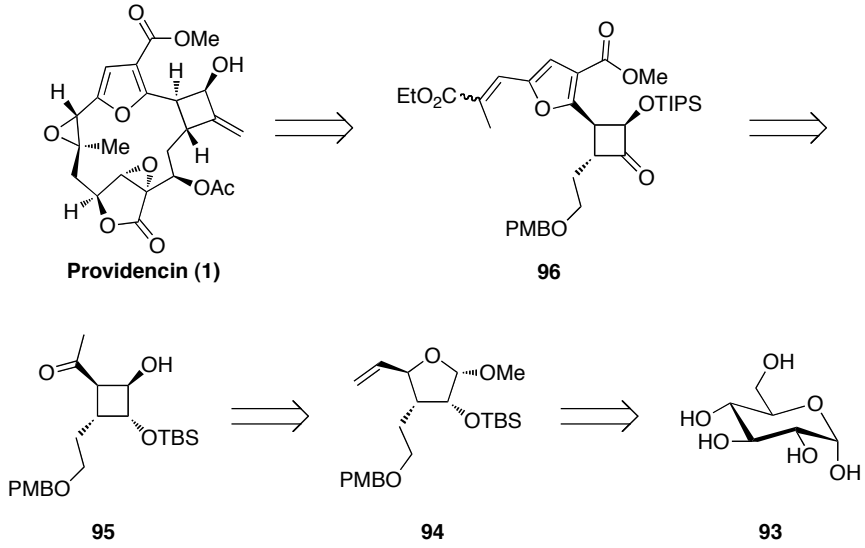
Scheme 1.3.2.9 Mulzer's synthesis of macrocycle **92**



1.3.3 White's Synthetic Work

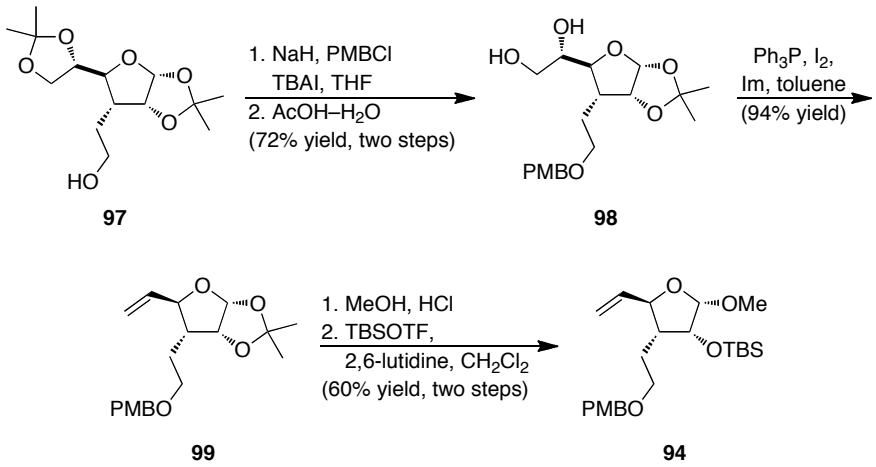
Most recently, White and co-workers published their work on the cyclobutyl furan sector of **1**.[20] The key step involved a zirconium-mediated deoxygenative ring-contraction of a glucose-derived furanoside **94** to yield a tetra-substituted cyclobutanol **95** for further elaboration (Scheme 1.3.3.1).

Scheme 1.3.3.1 White's retrosynthesis of Providencin (**1**)



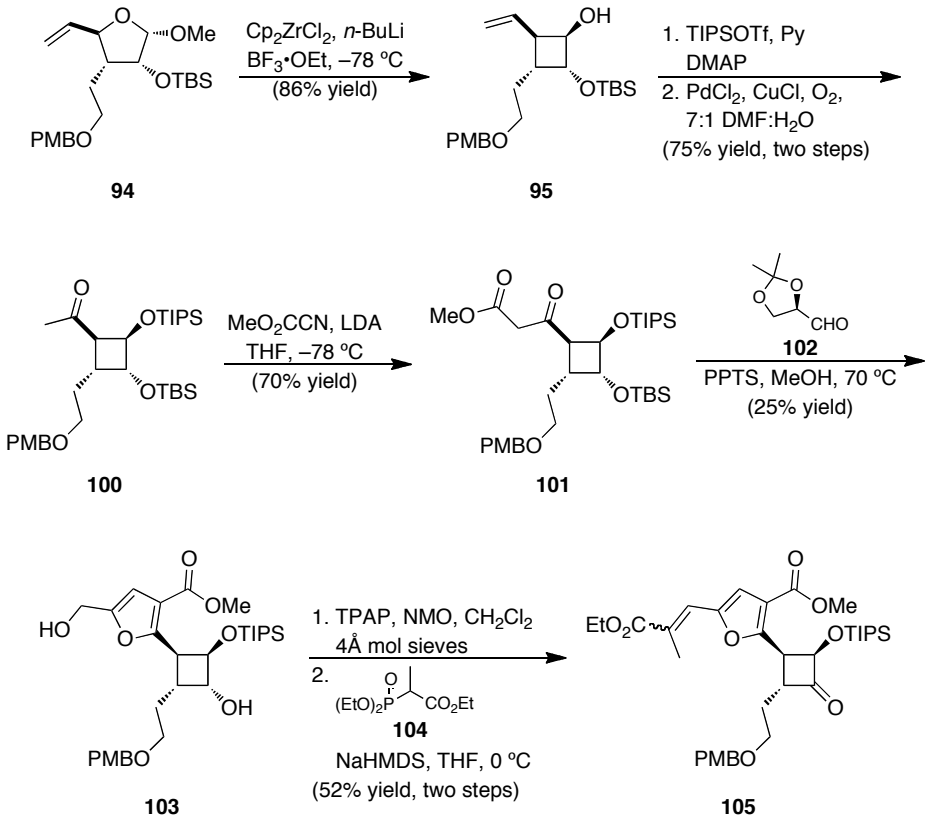
Synthesis of the furanoside **94** commenced with the four-step synthesis of the known alcohol **97** (Scheme 1.3.3.2). This alcohol was PMB-protected and the exo-cyclic acetonide was selectively removed. Reaction of diol **98** with iodine, triphenylphosphine and imidazole furnished the 2-vinyltetrahydofuran **99**. Subsequent methanolysis of the acetonide and TBS-protection of remaining alcohol gave the desired furanoside **94**.

Scheme 1.3.3.2 White's synthesis of furanoside **94**



Treatment of furanoside **94** with in situ generated dicyclopentadienylzirconium gave the desired cyclobutanol **95** in 86% yield with complete retention of stereochemistry (Scheme 1.3.3.3).[20] The secondary alcohol was protected as its silyl-ether and subsequent Wacker-oxidation yielded methyl ketone **100**. Deprotonation of **100** and treatment with methyl cyanoformate furnished β-ketoester **101**. Treatment of **101** with glyceraldehyde acetonide **102** and PPTS resulted in Knoevenagel condensation, followed by deprotection and cyclization give cyclobutyl furan **103**. Oxidation with TPAP gave an aldehyde, which was subjected to HWE-olefination and gave a 2.5:1 mixture of *E:Z* of olefins **105**. White reported that work is currently underway to elaborate cyclobutyl furan **105** to **1**.

Scheme 1.3.3.3 White's synthesis of 3-fur-2-yl-cyclobutanone **105**

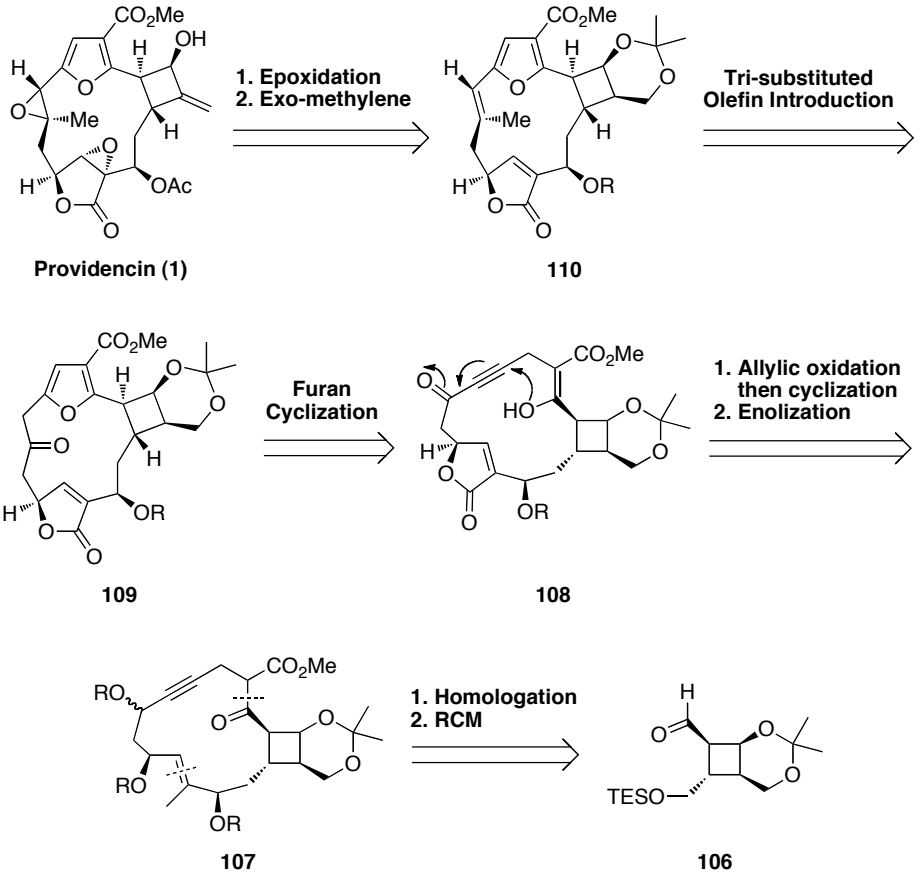


1.4 Previous Wood Group Efforts

1.4.1 First Generation Efforts

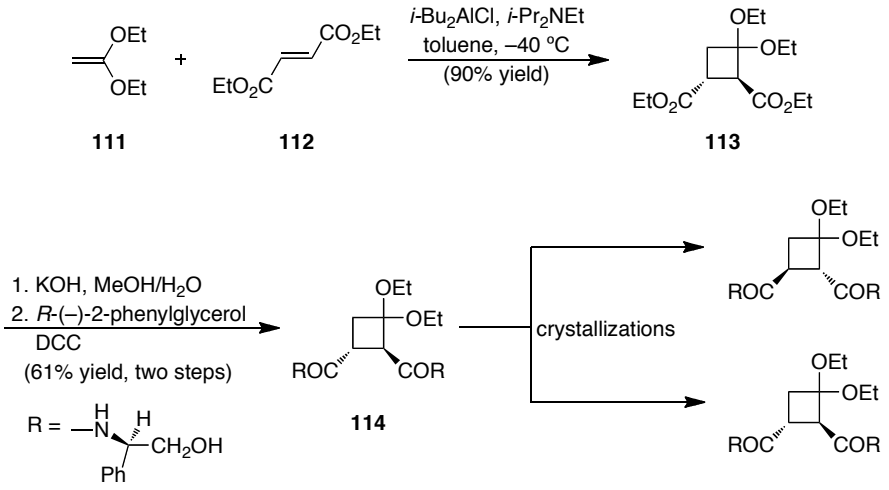
The Wood group effort towards the synthesis of **1** began shortly after its isolation in 2003.[21] The original retrosynthetic analysis calls for introduction of the exo-methylene and epoxides moieties at a late stage in the synthesis to avoid carrying these potentially sensitive moieties through many steps (Scheme 1.4.1.1). We anticipated that rigidity of macrocycle **110** would direct the epoxidations. The trisubstituted olefin was seen as arising from the methylation of a vinyl triflate generated from β-ketofuran **109**. The cyclization of enol **108** via Marshall's protocol would yield the desired β-ketofuran **109**. Allylic oxidation of **107** followed by lactonization and enolization could generate the furan precursor **108**. Homologation of cyclobutane **106** and RCM would furnish the macrocyclic core of **1**.

Scheme 1.4.1.1 Our original retrosynthetic approach to Providencin (**1**)



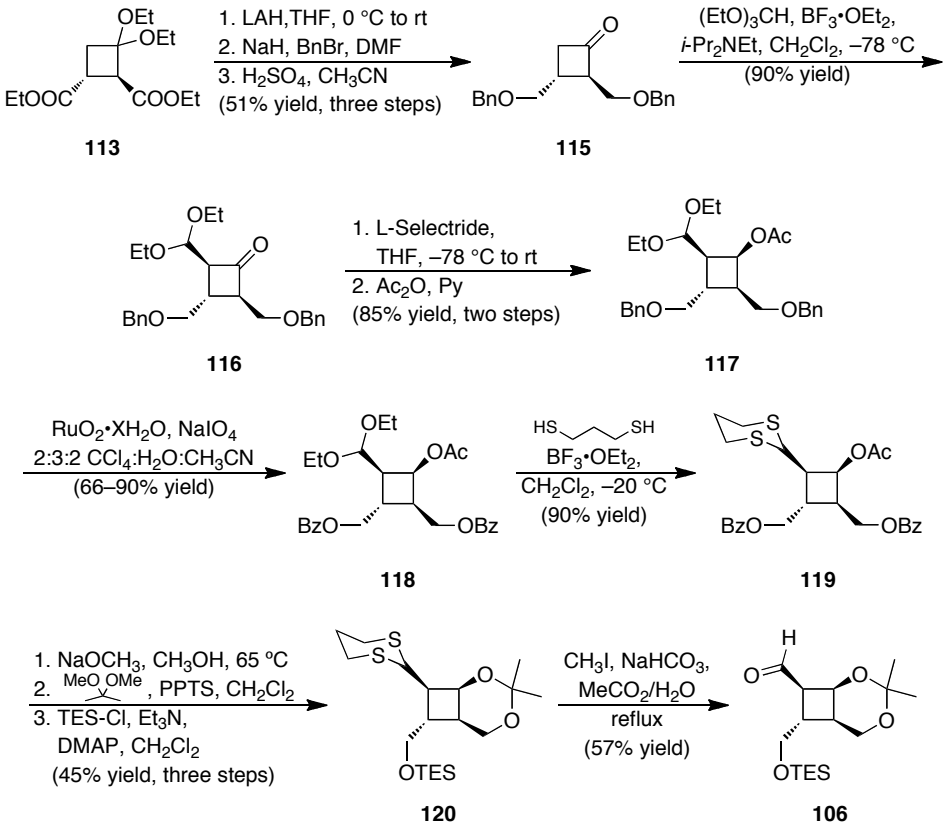
Our first synthetic efforts focused on preparing cyclobutane **106** (Scheme 1.4.1.2). In addition to the *trans*-ring fusion, the cyclobutane moiety of **1** contains both alcohol and exo-methylene moieties. Accordingly the design of cyclobutane **106** accounts for the *trans*-stereochemistry at C1 and C2 and incorporation of functional groups poised for further elaboration. We chose to pursue a [2 + 2] cycloaddition for generating the cyclobutane after finding a patent that described the aluminum-promoted [2 + 2] cycloaddition of ethyl ketene acetal (**111**) and diethylfumarate (**112**).[22] This reaction could be preformed on multigram scale and in good yield. Furthermore, Bisacchi and co-workers demonstrated that cyclobutane **113** could be resolved via the crystallization of the bis-amide derivatives **114**.[23]

Scheme 1.4.1.2 Lewis Acid promoted [2 + 2] cycloaddition



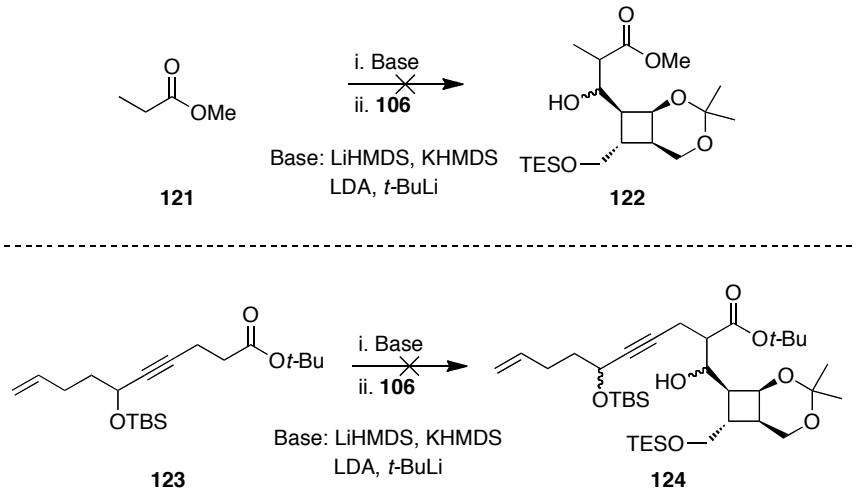
Reduction of diester **113** followed by diol protection and acetal removal furnished cyclobutanone **115** (Scheme 1.4.1.3). Advancement of **115** via formylation was accomplished using triethyl orthoformate in the presence of *i*-Pr_2NEt and BF_3•OEt_2, thus establishing the requisite trans-relationship at C1 and C2. Diastereoselective reduction of the ketone **116** from the least hindered side of the cyclobutanone followed by acylation of the resultant alcohol gave intermediate **117**. The benzyl-protecting groups were oxidized to benzoyl-protecting groups to facilitate more facile removal and the diethylacetal was subsequently replaced with a dithiane yielding **119**. The two benzoates and the acetate were concomitantly removed. The resultant triol was selectively protected by introduction of an acetonide on the 1,3-diol and protection of the remaining alcohol as its silyl ether. Dithiane **120** was converted to the corresponding aldehyde **106** by treatment with methyl iodide in aqueous base conditions. This sequence delivered a cyclobutane possessing an array of differentiable functional groups with the relative stereochemistry found in **1**.

Scheme 1.4.1.3 Elaboration of cyclobutane **113**



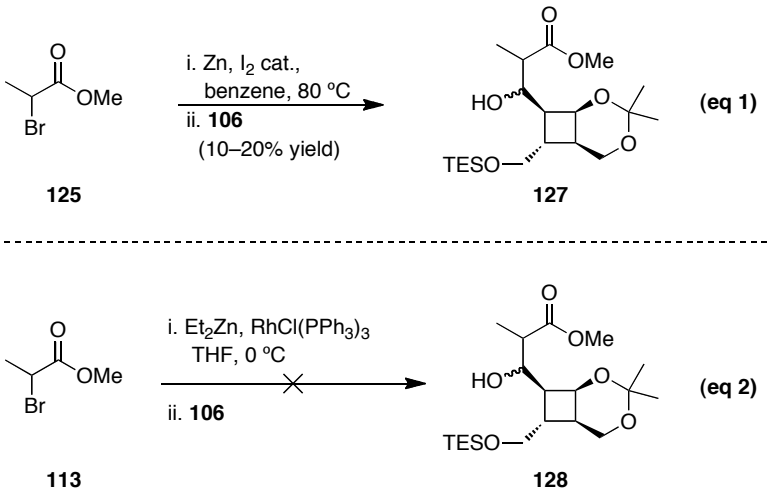
Unfortunately, attempts to effect an aldol reaction between aldehyde **106** and methyl propionate **121** or a more functionalized ester **123** were ineffective (Scheme 1.4.1.4). A screen of various bases and conditions for quenching the reaction failed to produce any desired product. Starting material **106** was the only compound recovered after work-up of these reactions.

Scheme 1.4.1.4 Attempted aldol reactions



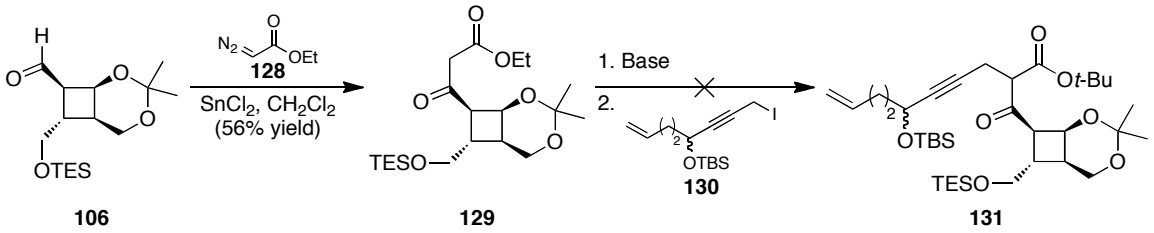
Our attention turned towards an approach emphasizing a Reformatsky reaction. A model system, utilizing α-bromo-methylpropionate **125**, was used to test the feasibility of this reaction with aldehyde **106** (Scheme 1.4.1.5). Under standard Reformatsky conditions a small amount of desired product was obtained; however, no starting material was recovered. Application of milder reaction conditions failed to produce any desired product (Scheme 1.4.1.5, eq 2).

Scheme 1.4.1.5 Attempted Reformatsky reactions



In a final attempt to utilize aldehyde **106**, we attempted a Roskamp reaction to produce the corresponding β-ketoester. Treatment of aldehyde **106** with ethyl diazoacetate and catalytic tin chloride yielded the desired β-ketoester **129** in modest yield (Scheme 1.4.1.6). However, attempts to alkylate β-ketoester **129** with propargyl iodide **130** or other electrophiles were unsuccessful under a variety of alkylation conditions. In most cases the β-ketoester **129** decomposed under the reaction conditions. Due to the difficulties encountered with the homologation of aldehyde **106**, we elected to revise our retrosynthetic approach.

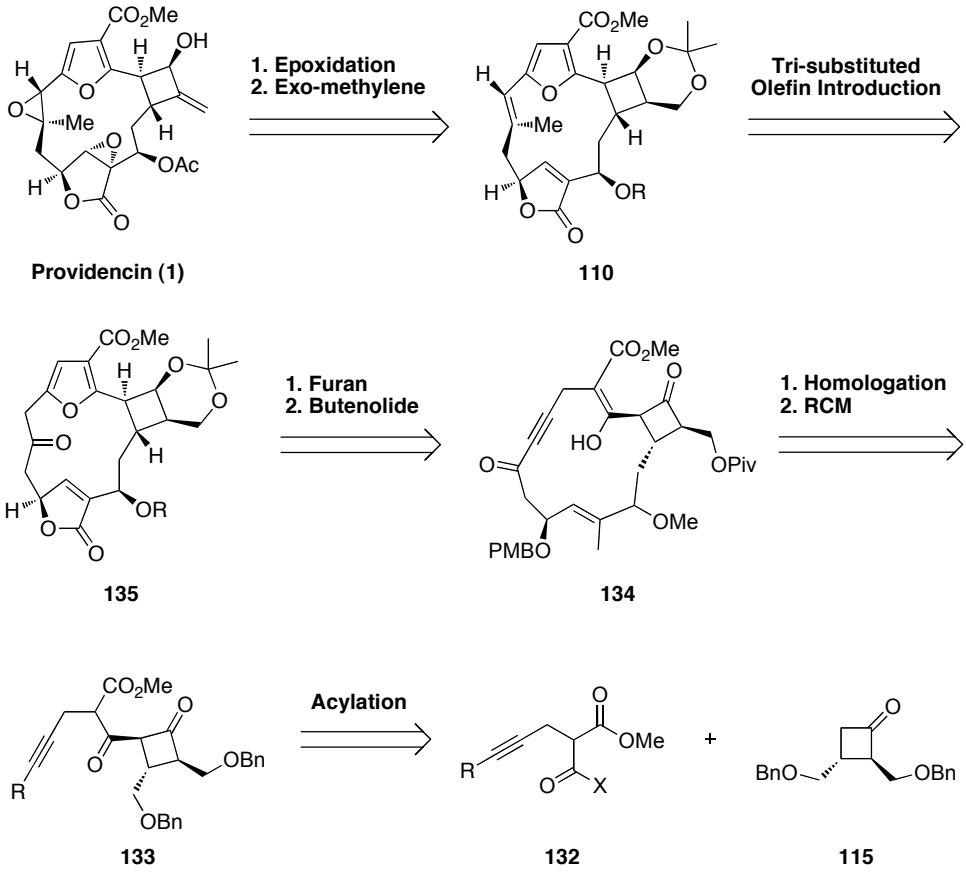
Scheme 1.4.1.6 Attempted alkylation of β-ketoester **129**



1.4.2 Second Generation Efforts

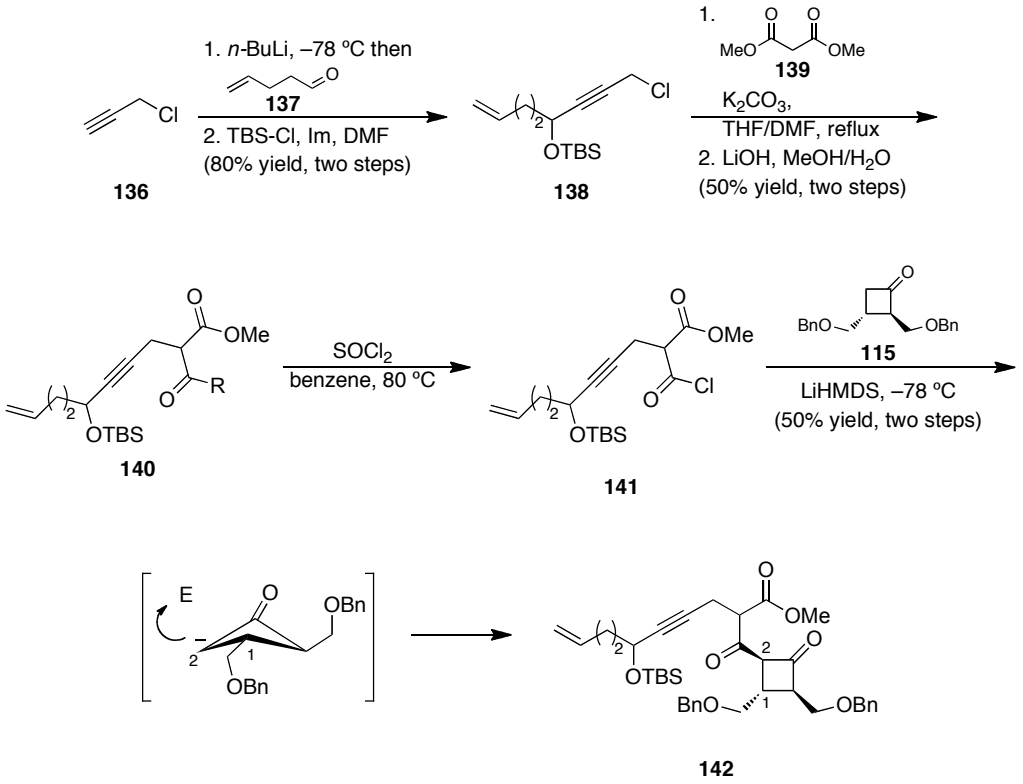
Upon review of our previous work we decided to pursue a course that would involve the acylation of a cyclobutanone **115** with a malonyl chloride **132** (Scheme 1.4.2.1). The macrocycle **134** would result from the homologation of **133** and subsequent RCM. The trisubstituted olefin precursor **135** could be obtained after furan cyclization and introduction of the butenolide. This retrosynthesis would then intercept the previously outlined retrosynthetic approach (Scheme 1.4.1.1).

Scheme 1.4.2.1 Our second retrosynthetic approach to Providencin (**1**)



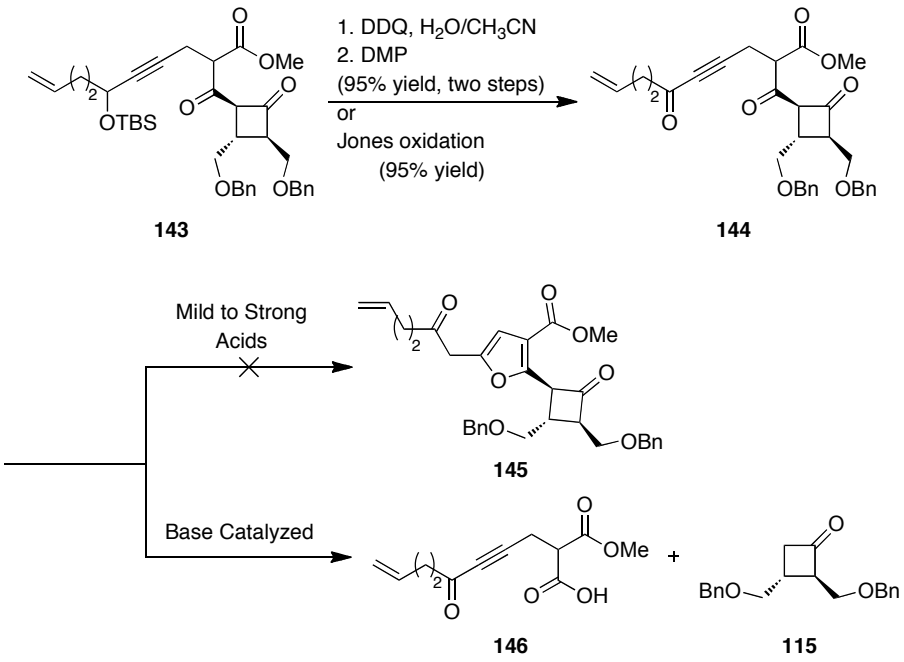
The synthesis of a malonyl chloride coupling partner **132** began with propargyl chloride **136** (Scheme 1.4.2.2). Deprotonation of propargyl chloride **136** was followed by treatment with 4-pentenal **137**, and subsequent TBS-protection furnished propargyl silyl ether **138**. Alkylation of dimethyl malonate **139** with propargyl chloride **138** followed by mono-hydrolysis yielded acid **140**, which was readily converted to the corresponding acid chloride **141**. Deprotonation of cyclobutanone **115** by LiHMDS followed by treatment with acid chloride **141** gave the functionalized cyclobutanone **142** in moderate yield. The relative *trans*-stereochemistry of the substituents on the C1 and C2 positions was achieved by approach of the electrophile from the opposite face of the substituent on C1.

Scheme 1.4.2.2 Acylation of cyclobutanone **115**



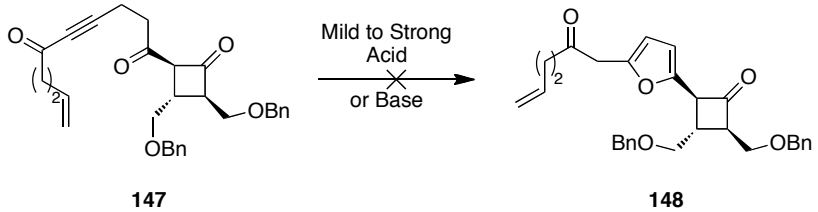
With substrate **142** in hand, we next attempted furan cyclization using Marshall's protocol. The TBS-protecting group was removed and the alcohol oxidized to give the alkynone **144** (Scheme 1.4.2.3). Unfortunately, all attempts to cyclize **144** to the furan under acidic conditions failed. Treatment of alkynone **144** under basic conditions resulted in cleavage to give cyclobutanone **115** and β–ketoester **146** fragments.

Scheme 1.4.2.3 Attempted furan cyclization



Concerned that the ester group was interfering with furan cyclization we prepared alkynone **147.** Attempts to cyclize alkynone **147** were also unsuccessful. In contrast to **144**, alkynone **147** proved stable but still unreactive to both acidic and basic conditions (Scheme 1.4.2.4). Despite these setbacks, we still hoped that the furan cyclization would be feasible on a substrate in which the macrocycle was already in place as demonstrated in the synthesis of (–)-deoxypukalide (**20**) (Scheme 1.2.1.2).

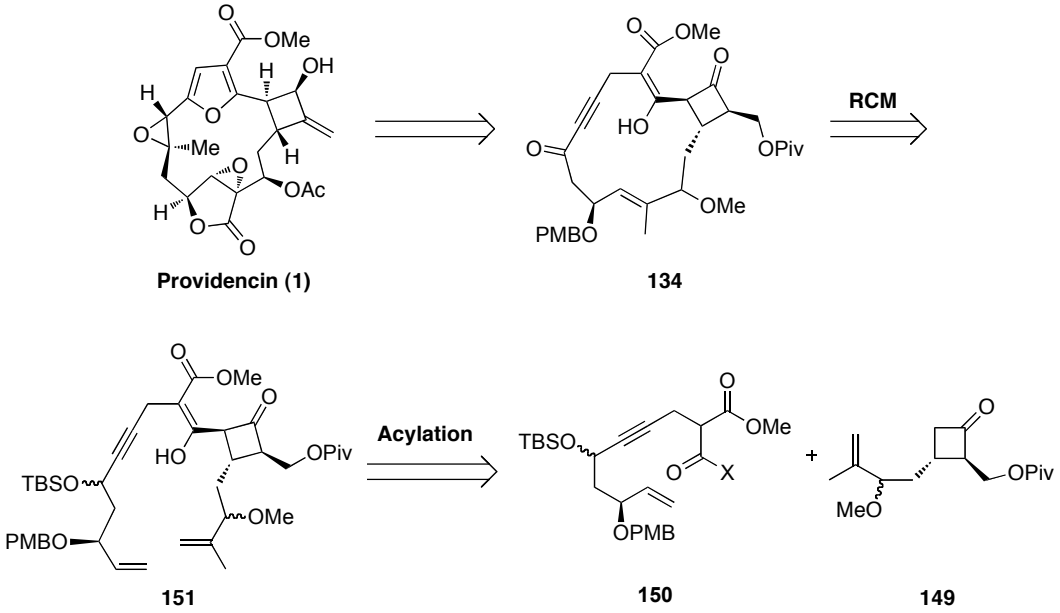
Scheme 1.4.2.4 Attempted furan cyclization



Given our success with the acylation of cyclobutanone **115**, we embarked upon the synthesis of a cyclobutanone **149** and acid chloride **150** for use in the acylation

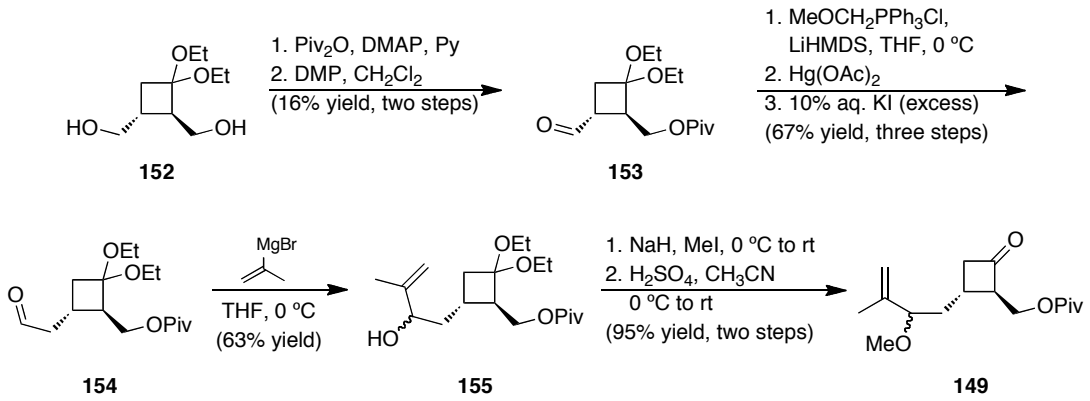
reaction (Scheme 1.4.2.5). Each was appended with an alkene and subsequent to acylation could undergo a RCM to furnish the macrocyclic core of **1**.

Scheme 1.4.2.5 Our third retrosynthetic approach to Providencin (**1**)



The synthesis of the cyclobutanone fragment **149** began with the previously synthesized diol **152** (Scheme 1.4.2.6). Mono-protection followed by oxidation gave aldehyde **153**. A Wittig olefination and subsequent selective deprotection furnished aldehyde **154**. The allylic alcohol **155** was obtained as a 1:1 mixture of diastereomers by treatment of **154** with propenyl magnesium bromide. Protection of the secondary alcohol and removal of the acetal provided the cyclobutanone coupling partner **149**.

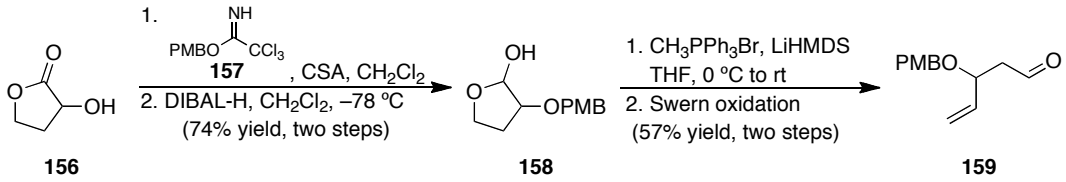
Scheme 1.4.2.6 Synthesis of cyclobutanone **149**



152 **153** **154** **155** **149**

Synthesis of the acid chloride coupling partner commenced with the PMB-protection of α-hydroxybutyrolactone **156** and subsequent reduction to the lactol **158** (Scheme 1.4.2.7). Methenylation of the lactol under Wittig conditions gave the primary alcohol that was subsequently oxidized to aldehyde **159**.

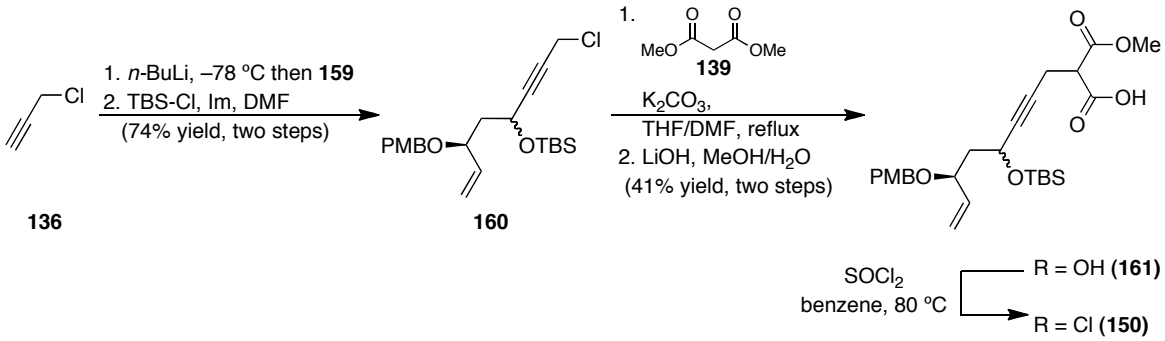
Scheme 1.4.2.7 Synthesis of aldehyde **159**



156 **158** **159**

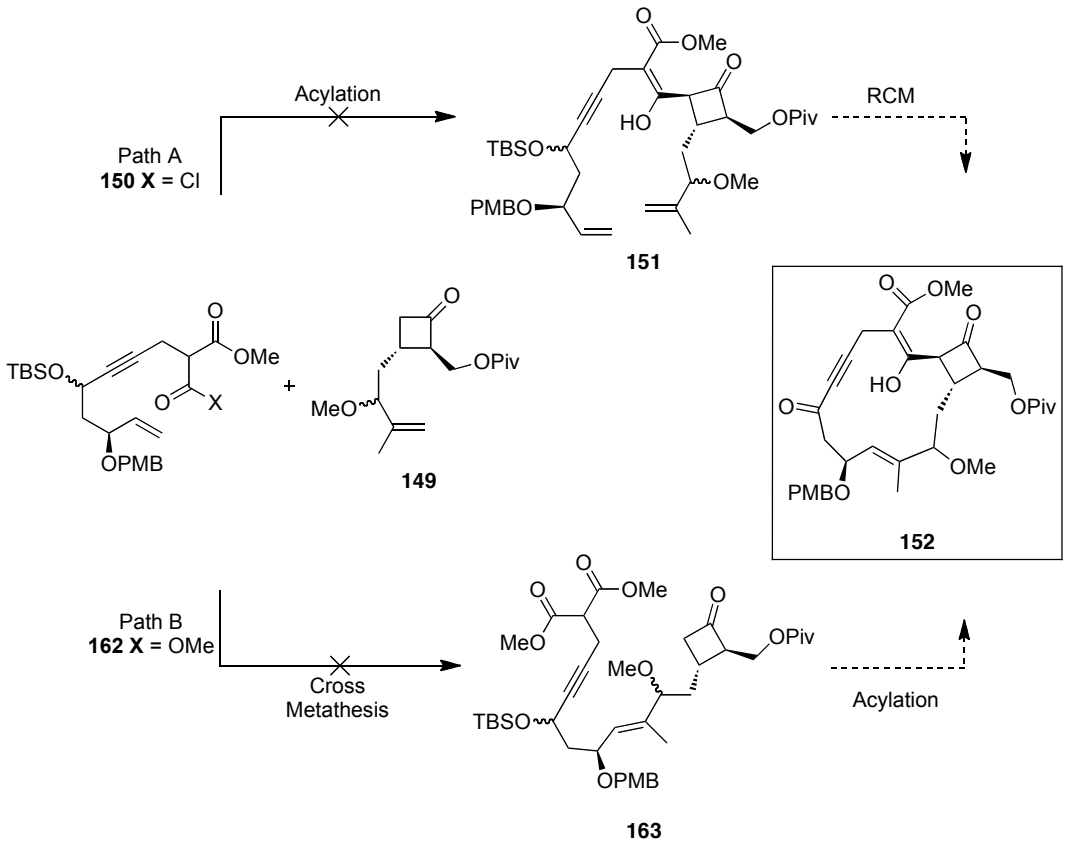
To complete the preparation of acid chloride coupling partner **150**, aldehyde **159** was treated with deprotonated propargyl chloride **136** to yield a secondary alcohol that was subsequently protected as its silyl ether **160** (Scheme 1.4.2.8). Alkylation of dimethyl malonate **139** with propargyl chloride **160** and mono-hydrolysis of the resultant ester provided acid **161**. Conversion to acid chloride **150** was accomplished through treatment of acid **161** with thionyl chloride. With both coupling partners in hand we set out to synthesize the macrocyclic core of **1**.

Scheme 1.4.2.8 Synthesis of acid chloride **150**



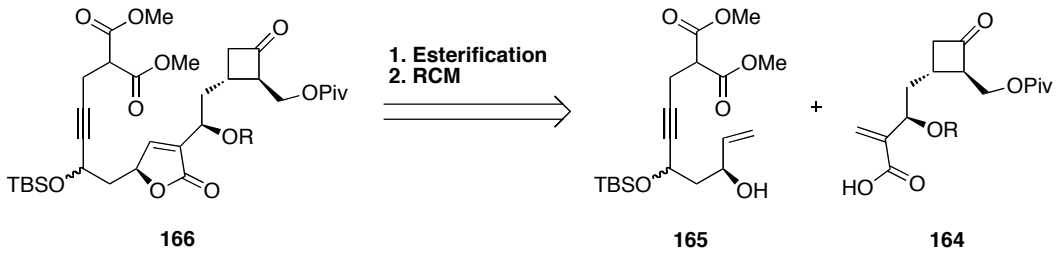
Our first attempt toward the coupling via acylation of cyclobutanone **134** with the acid chloride **140** generated from **139** met with limited success under a wide variety of conditions (Scheme 1.4.2.9). As an alternative to the acylation we attempted to couple the dimethyl malonate intermediate **162** and the cyclobutanone **149** via cross-metathesis. We were unsuccessful, even when the alkyne was protected as its cobalt hexacarbonyl complex. Under the reaction conditions the malonate **162** began to decompose but cyclobutanone **149** was recovered unchanged.

Scheme 1.4.2.9 Attempted coupling of **149** and **150**



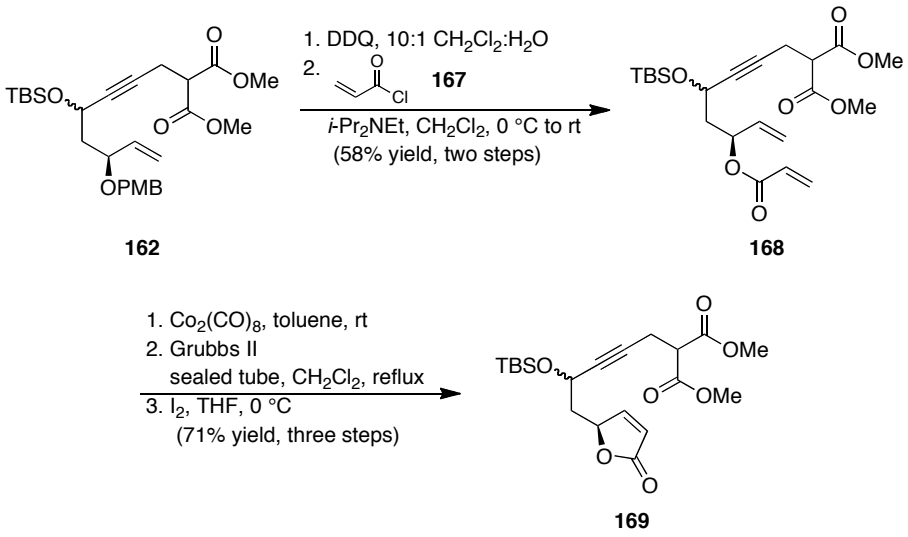
Given our failed attempts at coupling fragments **149** and **150** through acylation or **149** and **162** via cross-metathesis, we considered a new approach. In this instance, two fragments acid **164** and alcohol **165** could be coupled through an esterification reaction and a subsequent RCM would provide butenolide **166** (Scheme 1.4.2.10).

Scheme 1.4.2.10 Our fourth retrosynthetic approach to Providencin (**1**)



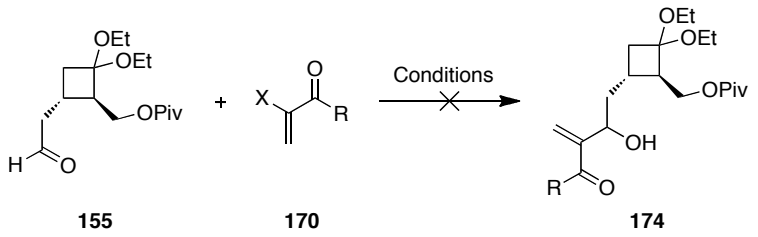
This sequence of esterification and RCM was tested on a simplified system wherein the previously prepared malonate **162** was used as a starting point (Scheme 1.4.2.11). Removal of the PMB-protecting group and subsequent acylation with acryloyl chloride furnished diene **168**. To prevent enyne-metathesis the alkyne was protected as its cobalt hexacarbonyl complex. Treatment with Grubbs 2nd generation catalyst in a sealed tube was followed by deprotection of the alkyne to give butenolide **169**.

Scheme 1.4.2.11 Esterification/RCM approach to butenolide **169**



Next we attempted to synthesize an appropriate coupling partner for the esterification and RCM sequence. Unfortunately, all attempts to elaborate aldehyde **155** using Baylis-Hillman, Nozaki-Hiyama-Kishi, and Grignard conditions were unsuccessful. Thus, without the necessary coupling partner **174** the esterification and RCM transformation could not be realized (Scheme 1.4.2.12).

Scheme 1.4.2.12 Attempted elaboration of cyclobutane **155**



155 **170** **174**

1.5 Conclusions

This chapter describes the isolation and properties of the highly oxygenated diterpene providencin **1**. Related compounds, synthesis of relevant moieties, and other groups' synthetic work toward the synthesis of **1** have also been discussed. In addition, our initial efforts toward the synthesis of this novel natural product have been reviewed.

We have demonstrated that a [2 + 2] cycloaddition is a powerful way to access functionalized cyclobutanes. However, homologation of our initial cyclobutane substrates was less efficient than hoped. We also observed a difficulty with the generation of furans from keto-alkynones in our system. Additionally, we have shown that cyclobutanones can be acylated in some instances, although this transformation failed to yield the desired product when more elaborate substrates were employed. Our inability to effect the coupling of advanced intermediates through acylation and cross-metathesis led us to consider esterification as an alternative means of coupling advanced intermediates. While we have successfully synthesized some advanced intermediates towards the total synthesis of providencin **1**, our failure to achieve the synthesis of the macrocyclic core of providencin caused us to review our approach to this molecule. Further efforts toward our goal will be outlined in the following chapters.

1.6 References

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Chapter 2

Construction of the Cyclobutyl Furan

2.1 Synthesis of Cyclobutanes

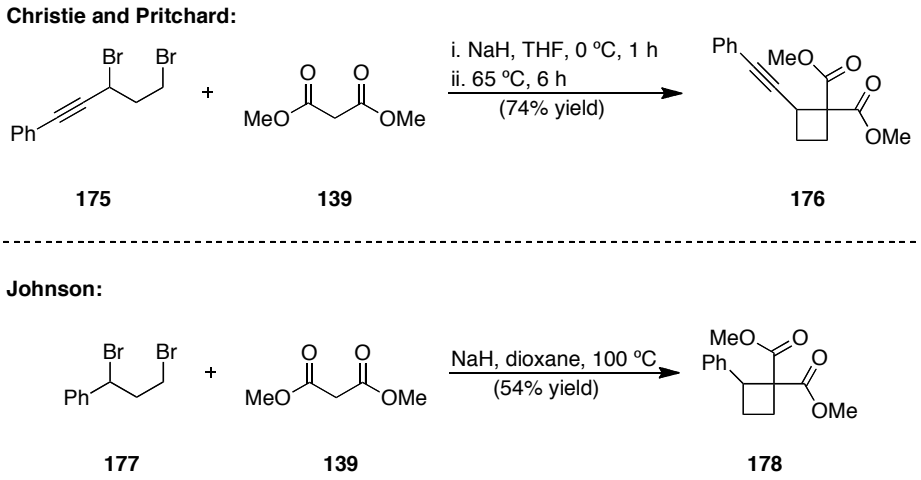
The *trans*-fused cyclobutanol moiety of providencin (**1**) is the most distinctive feature of this unprecedented [12.2.0]hexadecane ring system. It is, therefore, unsurprising that the major focus of synthetic efforts, including our own, towards **1** have focused on this aspect of the molecule. In general there are five major approaches to cyclobutane synthesis: [3 + 1] annulation, ring expansion, ring contraction, acyclic cyclization and [2 + 2] cycloadditions. The relative merits of each approach will be briefly discussed, with particular emphasis on our chosen approach, [2 + 2] cycloaddition.

2.1.1 [3 + 1] Annulation Reactions

The condensation of diethyl malonate with 1,3-dibromopropane was one of the earliest examples of cyclobutane synthesis.[1] This method is sometimes still used to synthesize cyclobutanes, as demonstrated by Christie and Pritchard, et al. and Johnson, et al. in their syntheses of 1,1-diestercyclobutanes (Scheme 2.1.1.1).[2] However, this approach suffers from several disadvantages, including: a lack of stereo-control, possible

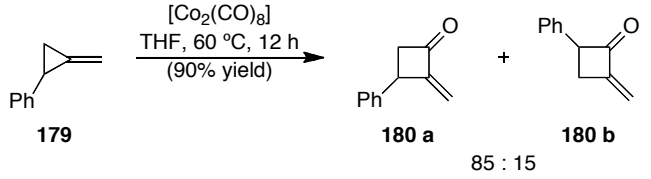
epimerization of stereocenters under basic reaction conditions, and the potential for oligomerization.

Scheme 2.1.1.1 [3 + 1] Annulation reaction with 1,3-dibromo compounds



Recently, de Meijere and co-workers demonstrated the synthesis of cyclobutanones via a [3 + 1] cyclization of methylenecyclopropanes with carbon monoxide (Scheme 2.1.1.2).[3] Treatment of an exo-methylene cyclopropane **179** with octacarbonyl dicobalt under an atmosphere of carbon monoxide provided a regioisomeric mixture of exo-methylene cyclobutanones **180**. While this is a unique approach to the synthesis of substituted cyclobutanes the yields and regioselectivities were often modest, and we felt the reaction scope was too limiting prompting us to consider alternative methods for accessing cyclobutane substrates.

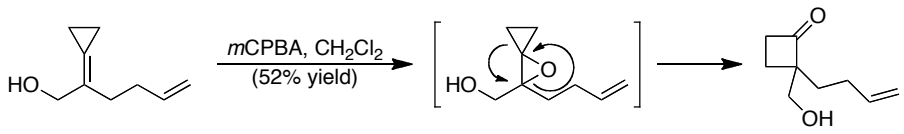
Scheme 2.1.1.2 [3 + 1] Cyclization of methylenecyclopropanes and carbon monoxide



2.1.2 Ring Expansion Reactions

The ring expansion of cyclopropanes is a second approach for the synthesis of cyclobutanes. One example of this is the conversion of an alkylidene-cyclopropane to a cyclobutanone.[1] Treatment of cyclopropane **181** with *m*CPBA generated an intermediate epoxide in situ which then underwent a ring expansion to give cyclobutanone **182** (Scheme 2.1.2.1).

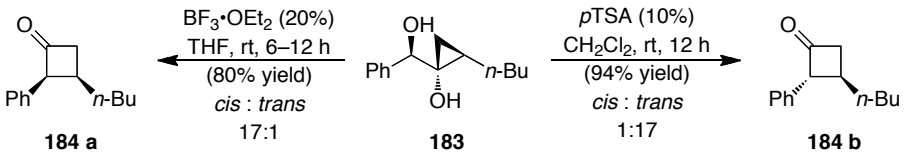
Scheme 2.1.2.1 Ring expansion of epoxidized alkylidene-cyclopropanes



181 **182**

Chiral cyclobutanones can be accessed through the use of an enantioselective epoxidation method, such as the Sharpless method. Cyclopropane ring expansion reactions can also be diastereoselective when chiral cyclopropane starting materials are employed. Hussain et al. have shown that treatment of a cyclopropanol **183** with a Lewis acid furnished primarily the *cis*-isomer of cyclobutanone **184 a** (Scheme 2.1.2.2).[4] The *trans*-isomer **184 b** was obtained by treating the same cyclopropanol with a Brönsted acid. The stereodivergence was proposed to arise from an epimerization of the product via enol formation under the protic acid conditions. While such methods can be useful in the synthesis of cyclobutanes, the nontrivial synthesis of hydroxy-cyclopropane substrates makes this approach less attractive.

Scheme 2.1.2.2 Ring expansion of cyclopropanol **183**

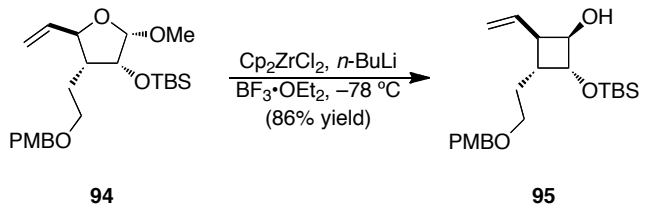


2.1.3 Ring Contraction Reactions

A third approach to cyclobutane synthesis, the ring contraction reactions of cyclopentanes and tetrahydropyrans is less widely used than other methods. Ring contraction of cyclopentane substrates generally involves a Wolff rearrangement, a Favorskii rearrangement, a Wagner-Meerwein rearrangement or a photodecarbonylation.[5] Such reactions are not generally useful for the synthesis of enantiomerically pure cyclobutanes unless the starting material is readily accessible from a chiral pool approach. The ring contraction of furanose-derived tetrahydrofurans allows for a more general approach toward the synthesis of chiral cyclobutanols and has the advantage of the retention of stereochemistry during the ring contraction reaction.

Taguchi et al. were among the first to show that ring contractions of tetrahydrofurans furnished cyclobutanols with good diastereoselectivity.[6] As described *vide supra*, White and co-workers have used a zirconium-mediated ring contraction reaction to convert tetrahydrofuran **94** to cyclobutanol **95** in good yield and with retention of stereochemistry (Scheme 2.1.3.1).[7] The enantiopure tetrahydrofuran was synthesized in eight steps from glucose.

Scheme 2.1.3.1 Ring contraction of tetrahydrofuran **94**

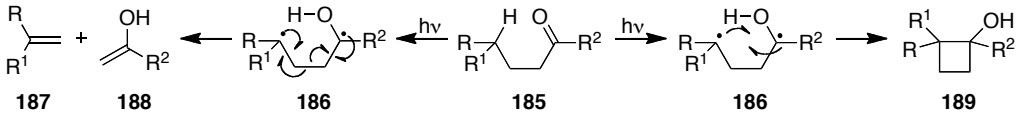


94 **95**

2.1.4 Cyclization of Acyclic Substrates

A fourth method to generate cyclobutanes utilizes ionic or radical cyclization of acyclic substrates. Unfortunately, such reactions generally result in the stereochemical equilibration of the reacting centers. However, the stereochemistry at the non-reacting centers of the cyclobutane is generally conserved.[5] One variation of acyclic cyclization is the Norrish-Yang photocyclization. In this reaction a carbonyl with a γ-hydrogen **185** can react to form a cyclobutanol **189**.[8] Abstraction of the γ-hydrogen by the excited carbonyl yields a diradical intermediate that can undergo either fragmentation or cyclization (Scheme 2.1.4.1).

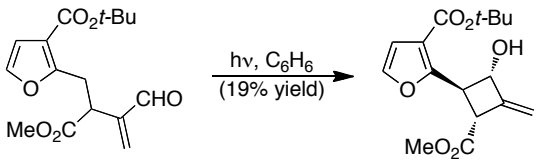
Scheme 2.1.4.1 Norrish-Yang photocyclization



187 **188** **186** **185** **186** **189**

Pattenden and co-workers have utilized this radical cyclization reaction to generate an exo-methylene cyclobutanol **54** such as the one found in **1** (Scheme 2.1.4.2).[9] While it is possible to synthesize chiral cyclobutanols from compounds that possess chiral centers at the 2- and/or 3-positions via this method it is not generally applicable. The potential for fragmentation products and other side reactions limits the general utility of this transformation.

Scheme 2.1.4.2 Norrish-Yang photocyclization of substrate **53**

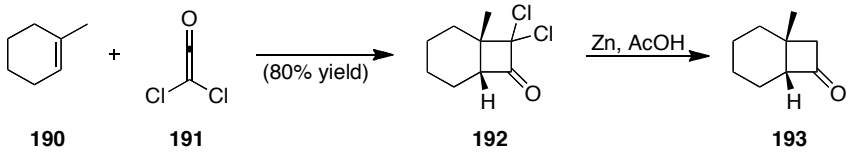


53 **54**

2.1.5 [2 + 2] Cycloaddition Reactions

The [2 + 2] cycloaddition reaction is arguably the most widely employed method for the synthesis of cyclobutane substrates. The photochemical [2 + 2] cycloaddition is allowed based on orbital symmetry considerations; however, such reactions are generally not regio- or stereoselective. The thermal [2 + 2] cycloaddition of alkenes is forbidden by orbital symmetry considerations. Formal thermal [2 + 2] cycloadditions, generally referred to simply as [2 + 2] cycloadditions, proceed via intermediates which are sufficiently long lived to undergo stereochemical equilibration and are typically not regioselective.[5] However, methods involving the [2 + 2] cycloaddition reaction of alkenes with ketenes and ketene equivalents circumvent both the regio- and stereochemical issues. While such reactions proceed via an asynchronous mechanism, the reactive intermediates are suitably short-lived, thus allowing the alkene-configuration to be retained in the cyclobutanone substrate.[5] Ketene-alkene cycloaddition reactions proceed regioselectively with the more nucleophilic carbon of the alkene adding to the carbonyl carbon of the ketene. One widely used substituted-ketene is dichloroketene (**191**).[5, 10] Dichloroketene (**191**) is widely used as a ketene surrogate due to its higher reactivity compared to the parent ketene. Furthermore, reduction of the 2,2-dichlorocyclobutanone **192** provides the corresponding saturated cyclobutanone product **193** (Scheme 2.1.5.1).

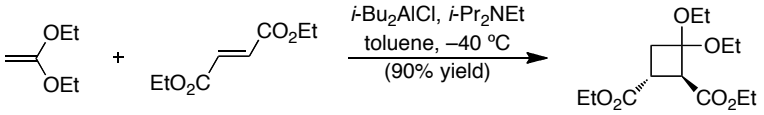
Scheme 2.1.5.1 [2 + 2] cycloaddition of (**190**) and (**191**) and subsequent reduction



190 **191** **192** **193**

Another alternative to a traditional [2 + 2] cycloaddition is a Lewis acid-promoted [2 + 2] cycloaddition reaction between an electron deficient alkene and an electron rich alkene (Scheme 2.1.5.2). One such example is the Lewis acid-promoted cycloaddition of diethyl fumarate **112** and ketene diethylacetal **111** that has been previously used by our group in earlier work towards the synthesis of **1** (Scheme 1.4.1.2).[11]

Scheme 2.1.5.2 [2 + 2] cycloaddition of (**111**) and (**112**)



111 **112** **113**

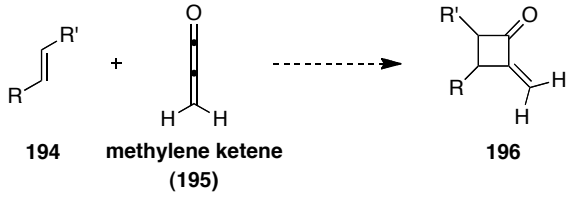
2.2 Ketene Cycloadditions Towards the Synthesis of Providencin

2.2.1 Methylene Ketene

The [2 + 2] cycloaddition reaction allows the rapid buildup of molecular complexity and is therefore an attractive strategy for cyclobutane synthesis. We postulated it might be possible to introduce both the exo-methylene and oxygen moieties of the cyclobutane in one step via a [2 + 2] cycloaddition; thus methylene ketene (**195**) would be an ideal coupling partner (Scheme 2.2.1.1). However, methylene ketene (**195**) is difficult to generate and is so reactive that only dimers and oligomers of it have ever

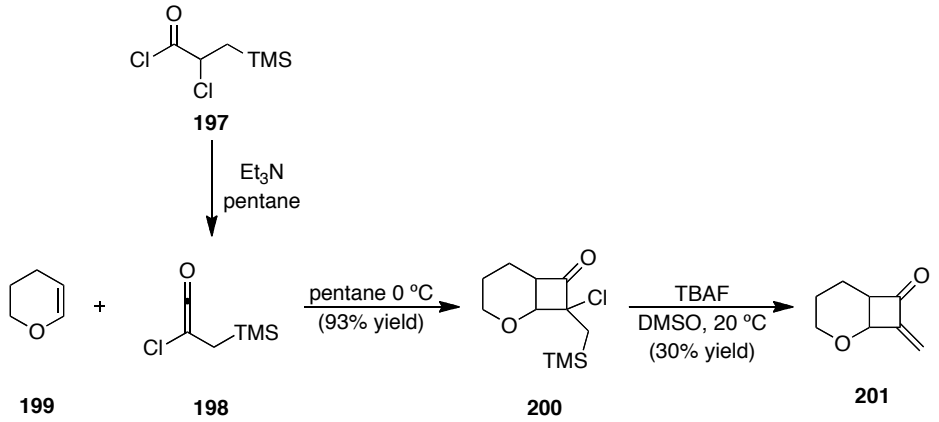
been observed. To date, no [2 + 2] cycloaddition between methylene ketene (**195**) and an alkene has been observed.

Scheme 2.2.1.1 [2 + 2] cycloaddition of methylene ketene (**195**) and an alkene



Paquette and co-workers reported chloro[(trimethylsilyl)methyl]ketene **198** as a substitute for the elusive methylene ketene (**195**).[12] They demonstrated that chloro[(trimethylsilyl)methyl]ketene **198** could be generated via dehydrohalogenation of α-chloro acid chloride **197**, which could then undergo the [2 + 2] cycloaddition with dihydropyran **199** to provide cyclobutanone **200**. Subsequent TBAF-mediated elimination gave exomethylene cyclobutanone **201** in modest yield (Scheme 2.2.1.2).

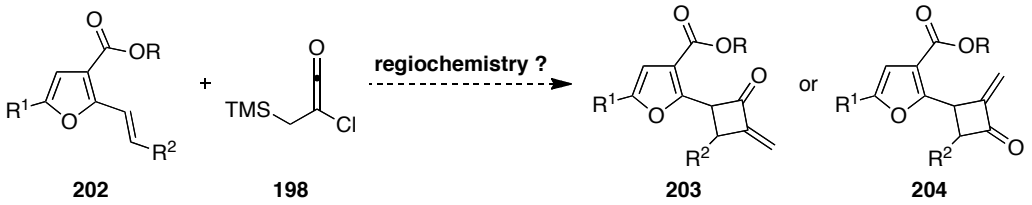
Scheme 2.2.1.2 Chloro[(trimethylsilyl)methyl]ketene as a methylene ketene equivalent



We were intrigued by the potential of such a reaction toward the synthesis of providencin (**1**). The use of chloro[(trimethylsilyl)methyl]ketene **198** toward the synthesis of **1** could allow for the introduction of the cyclobutane on an advanced

intermediate, perhaps one with the furan and/or macrocycle already in place. To further investigate the [2 + 2] cycloaddition between a 2-vinylfuran and a ketene, we employed the more accessible dichloroketene (**191**) and hoped with this substrate to establish the regiochemical preference upon the reaction between a furyl alkene and a ketene (Scheme 2.2.1.3).

Scheme 2.2.1.3 Regiochemical outcome of [2 + 2] cycloaddition of **202** and **198**

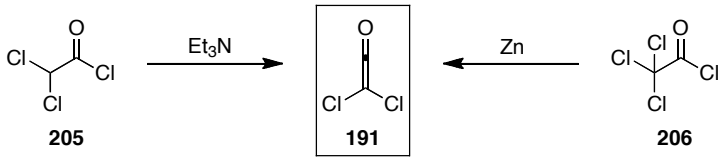


202 **198** **203** **204**

2.2.2 Dichloroketene

Dichloroketene (**191**) is one of the most widely used ketenes and has proven particularly useful when applied in [2 + 2] cycloaddition reactions.[10] Dichloroketene (**191**) must be generated in situ, and in the presence of the alkene with which it is to be reacted to prevent ketene dimerization. The two primary methods for generating **191** are dehydrohalogenation of dichloroacetyl chloride (**205**) using triethylamine or dehalogenation of trichloroacetyl chloride (**206**) using activated zinc (Scheme 2.2.1.1).[13] We chose the latter method because the reagents are commercially available, relatively inexpensive and this method is more widely used.[10]

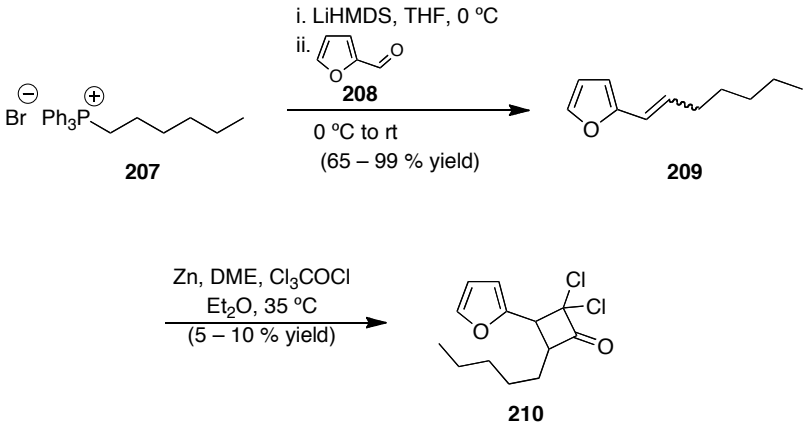
Scheme 2.2.1.1 Synthesis of dichloroketene (**191**)



205 **191** **206**

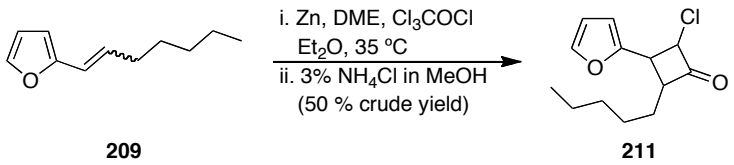
First we prepared a test substrate vinylfuran **209**. Wittig olefination of hexyltriphenylphosphonium bromide (**207**) with furfural (**208**) provided furyl alkene **209** (Scheme 2.2.1.2). Alkene **209** was treated with dichloroketene (**191**), generated in situ by reduction of trichloroacetyl chloride (**206**) with zinc. This indeed resulted in formation of a cyclobutanone **210**. However, the cyclobutanone proved to be unstable and it underwent decomposition upon exposure to silica gel.

Scheme 2.2.1.2 [2 + 2] Cycloaddition of furyl alkene **209** and dichloroketene (**191**)



We postulated that reduction of the dichloride might furnish a more stable cyclobutanone. Thus, after completion of the [2 + 2] cycloaddition, 3% NH_4Cl in methanol was added the reaction mixture and the resultant solution brought to reflux for an additional 15 minutes (Scheme 2.2.1.3). Upon work-up, we were able to isolate a mono-chloro cyclobutanone product **211** that was more stable than the dichlorocyclobutanone **210**, however its propensity toward decomposition on silica was problematic.

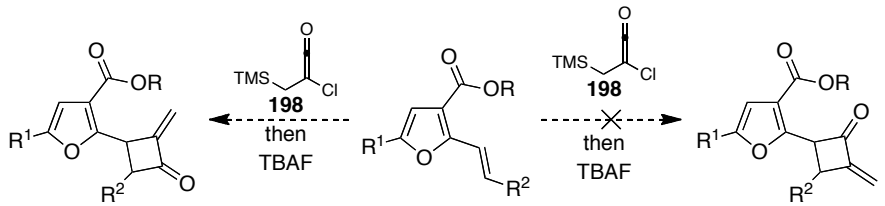
Scheme 2.2.1.3 [2 + 2] Cycloaddition and in situ reduction



209 **211**

In spite of the instability of these compounds we were able to confirm the formation of a [2 + 2] product and the regiochemical outcome through NMR studies. This analysis confirmed the presence of 3-furylcyclobutanone **211** wherein the furan and ketone are 1,3-disposed **(**Scheme 2.2.1.3**)**. Given that our plan for preparing **1** called for a [2 + 2] cycloaddition between a vinylfuran **202** and chloro[(trimethylsilyl)methyl]-ketene **198** to generate a 2-furylcyclobutanone **203** (Scheme 2.2.1.4), we were disappointed by the observed regiochemical outcome.

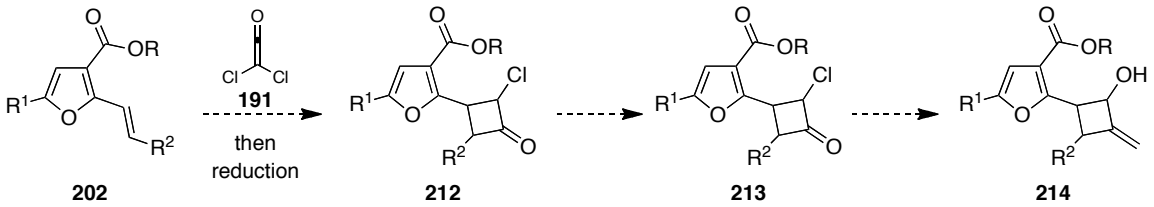
Scheme 2.2.1.4 Regiochemical outcome of proposed [2 + 2] cycloaddition



204 **202** **203**

However, the successful preparation of 3-furylcyclobutanone **211** inspired an alternative approach to the synthesis of the cyclobutyl furan portion of **1**. Thus, we now envisioned that cycloaddition between vinylfuran **202** and dichloroketene (**191**) could yield 3-furylcyclobutanone **212** which could then undergo olefination to furnish an exo-methylene cyclobutane **213** (Scheme 2.2.2.5). Subsequent installation of the alcohol would provide the furyl cyclobutanol portion of **1.**

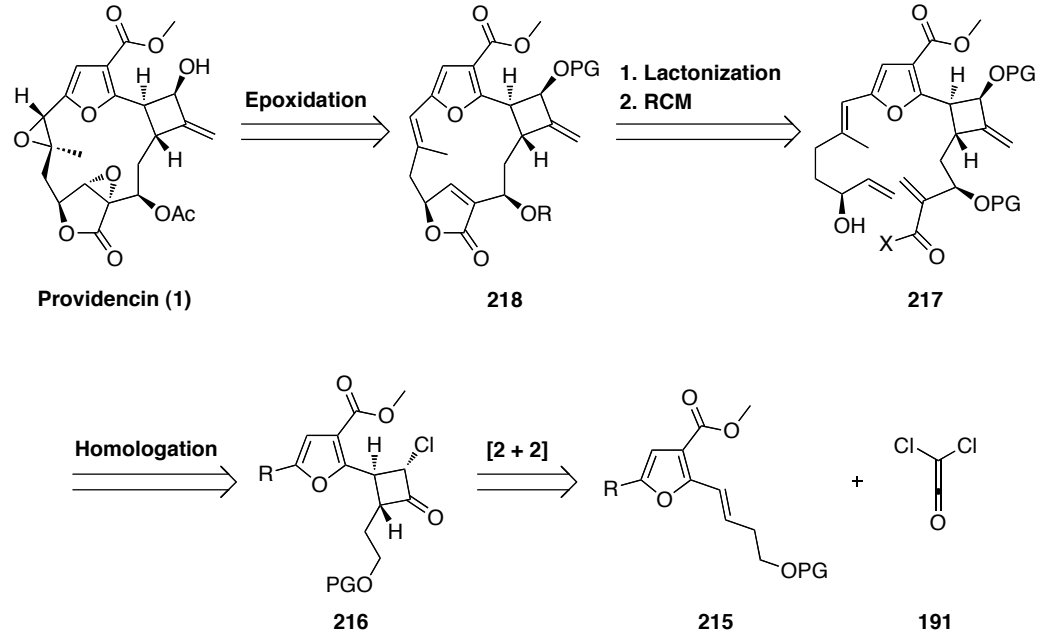
Scheme 2.2.2.5 Proposed synthesis of an exo-methylene cyclobutanol



2.3 Functionalized Furans

Having decided to utilize the [2 + 2] reaction with dichloroketene to synthesize the cyclobutyl furan moiety in providencin**,** we developed a new retrosynthetic approach (Scheme 2.3.1). As illustrated, the revised plan again calls for introduction of the epoxide moieties at a late stage in the synthesis. Macrolactonization and subsequent RCM would provide the butenolide-containing macrocyclic core **218** of **1**. The macrolactonization precursor **217** would arise from elaboration of cyclobutyl furan **216**. A [2 + 2] cycloaddition of dichloroketene (**191**) with alkenyl furan **215** would provide cyclobutanone **216**. Thus, our primary efforts focused on constructing a vinyl furan substrate **215** on which to effect the [2 + 2] cycloaddition. This furan **215** would possess the appropriate ester functionality and a handle at C-5 of the furan for further elaboration.

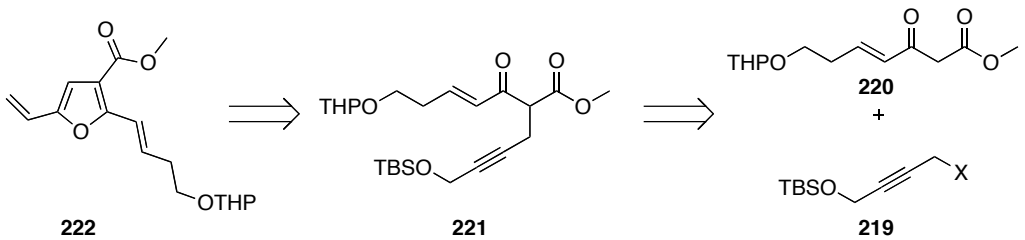
Scheme 2.3.1 Retrosynthetic approach to Providencin (**1**) utilizing [2 + 2] cycloaddition



2.3.1 Alkynone Cyclization to Furnish Furans

We began by investigating the synthesis of 2,3,5-trisubstituted furans. We initially intended to use the cyclization of an alkynone **221** to access a fully functionalized furan **222**. The alkynone **221** would be the result of an alkylation of a β-ketoester **220** (Scheme 2.3.1.1).

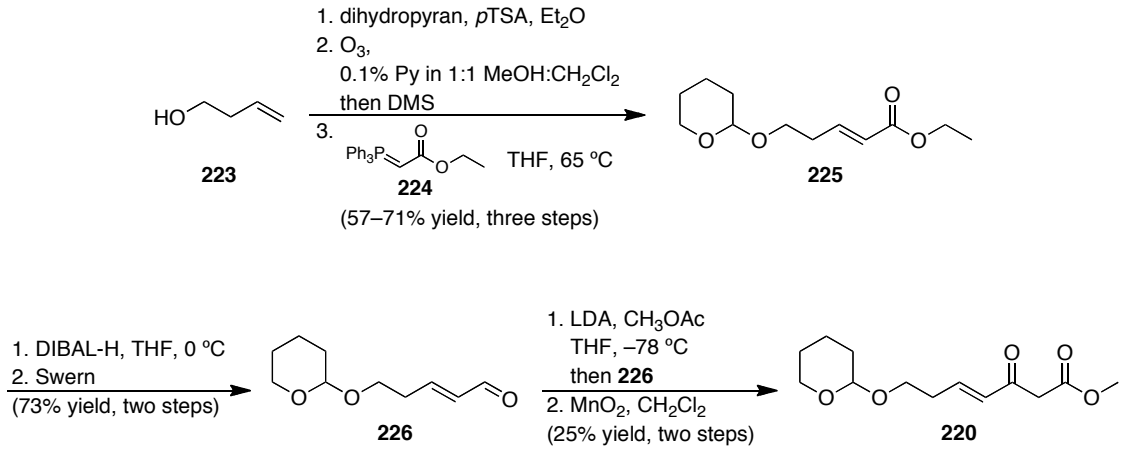
Scheme 2.3.1.1 Retrosynthetic approach to the synthesis of furan **222**



Our synthesis of β-ketoester **220** began with the protection of 3-buten-1-ol **223** as its THP-ether (Scheme 2.3.1.2). Ozonolysis of the alkene, followed by olefination

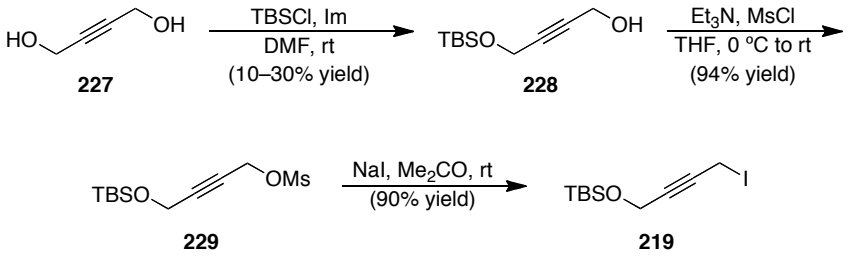
furnished α,β-unsaturated ester **225**. A reduction/oxidation sequence provided aldehyde **226**. Aldol reaction of methyl acetate and aldehyde **226** gave an allylic alcohol that was directly oxidized to yield β-ketoester **220**.

Scheme 2.3.1.2 Synthesis of β-ketoester **220**



The propargyl iodide coupling partner was synthesized in three steps from 2-butyn-1,4-diol **227** (Scheme 2.3.1.3). The diol was mono-protected as its silylether **228** and the remaining alcohol was converted to the iodide via the mesylate **229** to provide propargyl iodide **219**.

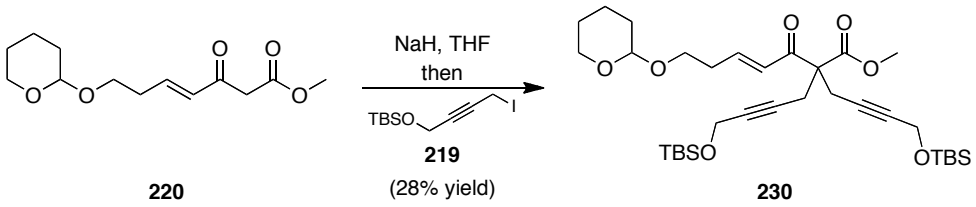
Scheme 2.3.1.3 Synthesis of propargyl iodide **219**



Attempts to mono-alkylate β-ketoester **220** with iodide **219** were unsuccessful. Initial attempts yielded primarily bis-alkylated product **230**, along with recovered iodide and decomposition products (Scheme 2.3.1.4). Even when a substoichiometric amount of

iodide was used, the bis-alkylation product still predominated. Attempts to alkylate β-ketoester **220** with the iodide **219** derived from the mesylate **229** in situ, resulted in decomposition of **220**. Attempts to utilize KO*t*-Bu instead of NaH or to change the order of addition also resulted in decomposition of β-ketoester **220**. The difficulties with the alkylation reaction, coupled with our previous difficulties with alkynone cyclization (Scheme 1.4.2.3), led us to reevaluate our approach to the furyl alkene.

Scheme 2.3.1.4 Alkylation of **220** with **219**

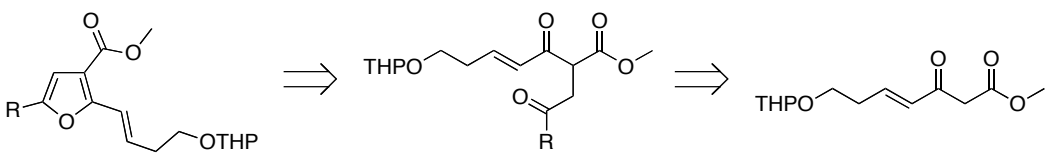


220 **219** (28% yield) **230**

2.3.2 Paal–Knorr Synthesis of Furans

Our next attempt at the furyl alkene employed a more commonly used method for the synthesis of furans: the acid-catalyzed cyclization of 1,4-dicarbonyls, known as the Paal-Knorr furan synthesis.[14] We envisioned converting the β-ketoester **220** (or a similar β-ketoester) to a 1,4-diketone **231**. Subsequent cyclization of the 1,4-diketone **231** would provide the furan **232** (Scheme 2.3.2.1).

Scheme 2.3.2.1 Revised retrosynthetic approach to furyl alkene

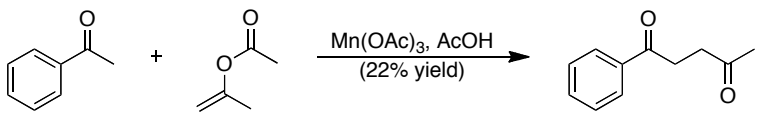


232 **231** **220**

We began to investigate the synthesis of 1,4-diketones such as **231** and were most interested in methods that would utilize previously prepared β-ketoester **220** as substrate and provide products with the 5-position of the furan poised for further elaboration.

One such method is the addition of ketones to vinylic acetates in the presence of one-electron oxidants. Heiba and Dessau have demonstrated the synthesis of 1,4-diketones from the reaction of a ketone and isopropenyl acetate **234** in the presence of manganic acetate (Scheme 2.3.2.2).[15] Unfortunately, these reactions showed low yields and poor selectivity when applied to 2-alkanones.

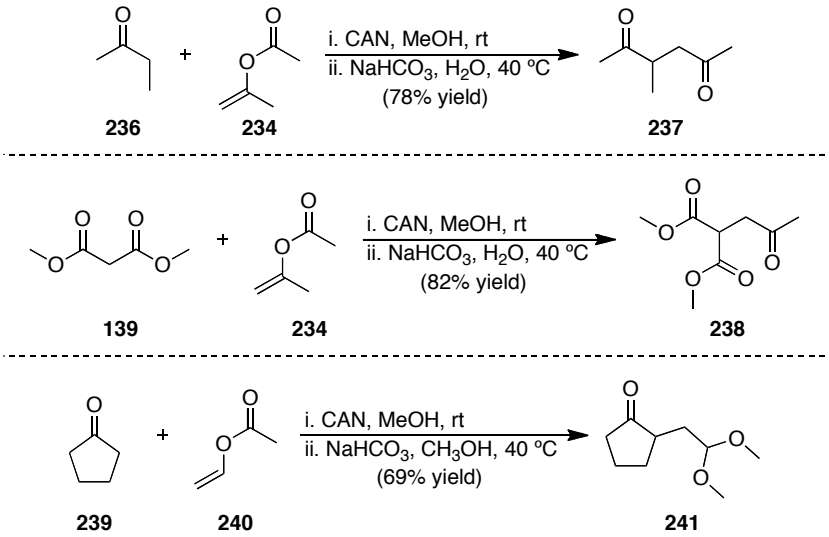
Scheme 2.3.2.2 Heiba and Dessau synthesis of 1,4-diketones



233 **234** **235**

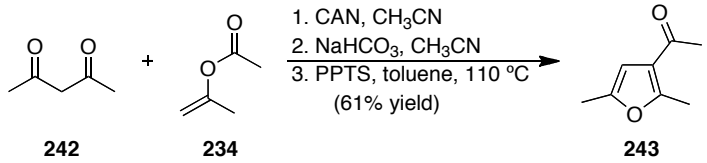
Baciocchi and Ruzziconi et al. greatly expanded the scope and utility of this reaction by replacing the manganic acetate with cerium(IV) ammonium nitrate (CAN) (Scheme 2.3.2.3).[16] Yields and regioselectivity were significantly improved with the addition occurring primarily at the more substituted position of the 2-alkanone. Malonates were also successfully converted to 1,4-dicarbonyl compounds. They also demonstrated that vinyl acetate **240** could be used in place of isopropenyl acetate **234** to obtain 4-keto dimethylacetals such as **241**.

Scheme 2.3.2.3 Baciocchi and Ruzziconi synthesis of 1,4-dicarbonyls



In a further extension of this chemistry, Baciocchi and Ruzziconi have demonstrated the possibility of accessing furan substrates **243** from 1,3-dicarbonyls **242** and isopropenyl acetates **234** (Scheme 2.3.2.4).[16b] The initial CAN reaction gave a dihydrofuran that subsequently underwent elimination to the furan upon heating with PPTS. By changing either the 1,3-dicarbonyl or the vinyl substrates they were able to access 3-substituted, 2,3-disubstituted, 2,3,4-trisubstitued or 2,3,5-trisubstitued furans.

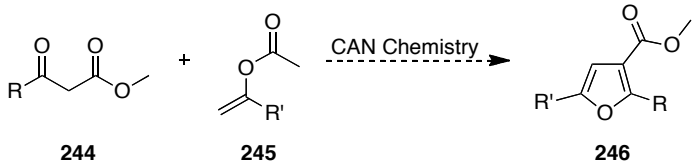
Scheme 2.3.2.4 Synthesis of 2,3,5-trisubstituted furan **243**



Based on these precedents we envisioned accessing a 2,3,5-trisubstituted furan, with an ester at the 3-position, utilizing the oxidative coupling chemistry (Scheme 2.3.2.5). We sought to demonstrate that a β-ketoester **244** and a vinyl acetate **245** could

be reacted under conditions similar to those of Baciocchi and Ruzziconi to furnish a 2,3,5-trisubstituted furan **246**.

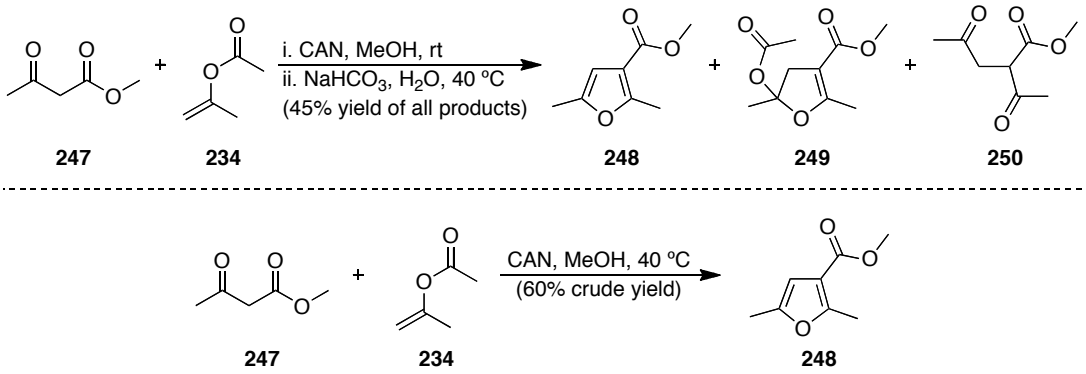
Scheme 2.3.2.5 Proposed synthesis of 2,3,5-trisubstituted furan **246**



244 **245** **246**

Towards this end, CAN was added to a methanolic solution of methyl acetoacetate **247** and isopropenyl acetate **234** at room temperature (Scheme 2.3.2.6). This mixture was then treated with aqueous sodium bicarbonate and heated to 40 ºC for two hours. Upon work-up and purification three products were identified: furan **248**, dihydrofuran **249** and 1,4-diketone **250**. To our satisfaction we also found that heating the reaction to reflux overnight provided furan **248** as the primary product.

Scheme 2.3.2.6 Synthesis of 2,3,5-trisubstituted furan **248**



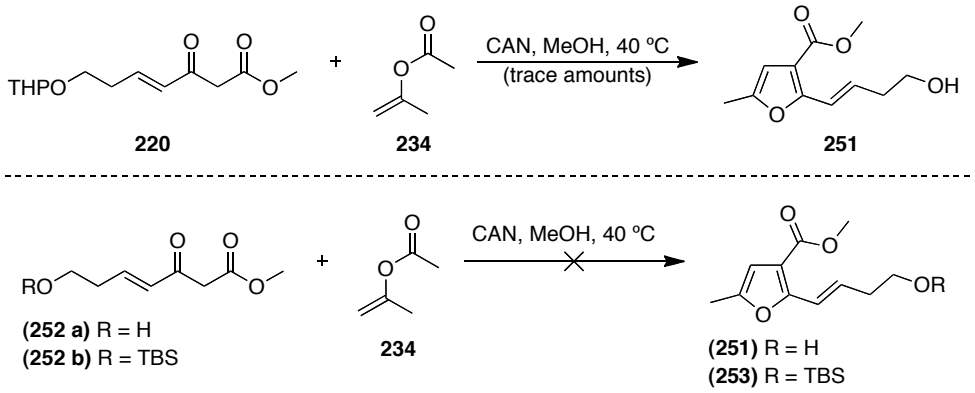
247 **234** **248** **249** **250**

247 **234** **248**

Having prepared a 2,3,5-trisubstiuted furan using a β-ketoester **247** and isopropenyl acetate **234**, we set out to investigate the reaction using more functionalized substrates. Unfortunately, attempts to effect the transformation on our previously synthesized β-ketoester **220** only resulted in a trace amount of furan lacking the THP-

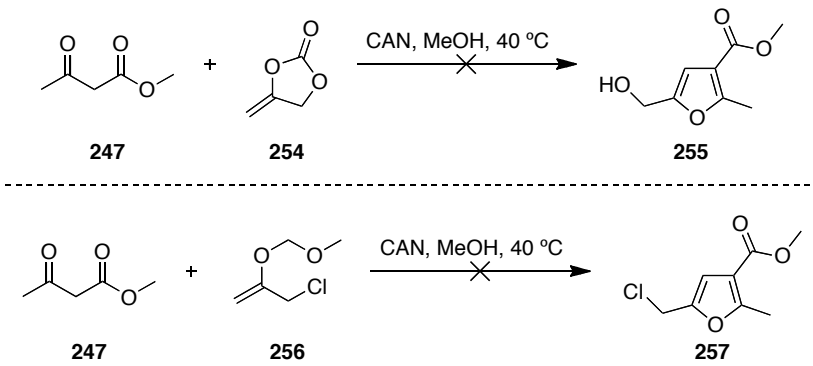
protecting group **251** (Scheme 2.3.2.7). Attempting the reaction on the free alcohol **252 a** or the TBS-protected alcohol **252 b** resulted in no furan products and decomposition of the starting materials.

Scheme 2.3.2.7 Attempted synthesis of furyl alkenes



As an alternative we attempted to incorporate vinyl carbonate and vinyl ether substrates into the oxidative coupling reaction. In the event, reaction of known compounds **254** and **256** with methyl acetoacetate **247** in the presence of CAN did not result in the formation of any addition or furan products.[17] The vinyl substrates were found to decompose under the reaction conditions (Scheme 2.3.2.8).

Scheme 2.3.2.8 Attempted synthesis of alternatively substituted furans

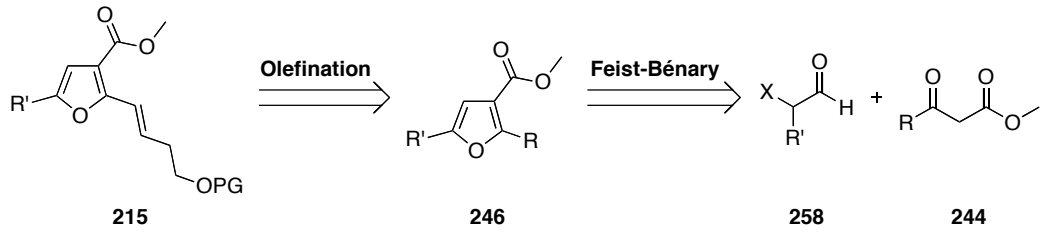


In summary, we have demonstrated the feasibility of the synthesis of 2,3,5-trisubstitued furans from simple substrates via the oxidative coupling between β-ketoester **247** and isopropenyl acetate **234**. However, we were unable to effect the same transformation on more highly functionalized β-ketoesters and vinyl ethers. Thus we chose to investigate an alternative approach to access the alkenyl furan substrate **232**.

2.3.3 A Feist-Bénary Approach to Synthesis of Functionalized Furans

Another classic method for the synthesis of poly-substituted furans is the Feist-Bénary reaction. A generic Feist-Bénary reaction involves the synthesis of furans through the reaction of β-ketoesters and α-halo carbonyl compounds.[14] This approach would allow for access to a highly functionalized furan **246** from a β-ketoester **244** and α-halo aldehyde **258**. Elaboration of furan substrate **246** could furnish alkenyl furan **215** (Scheme 2.3.3.1).

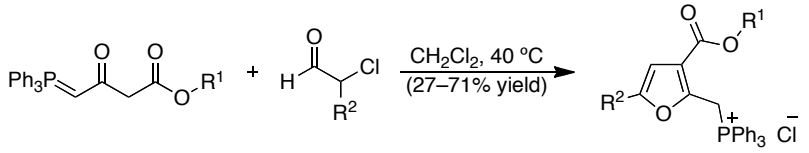
Scheme 2.3.3.1 A Feist-Bénary approach to the synthesis of a vinyl furan



Many modifications to the Feist-Bénary reaction have been reported. As mentioned previously (Scheme 1.2.1.3) the use of an epoxy aldehyde in lieu of an α-halo carbonyl results in a 2,3,5-trisubstituted furan with a handle at the 2-postion and a methyl alcohol moiety at the 5-position of the furan.[18] Langer and co-workers have shown that (2,4-dioxobutylidene)-phosphoranes **259** and α-chloro aldehydes **260** will undergo the

Feist-Bénary reaction to give (2-furyl)-methylphosphonium chlorides **261** (Scheme 2.3.3.2).[19]

Scheme 2.3.3.2 Feist-Bénary approach to (2-furyl)-methylphosphonium chlorides

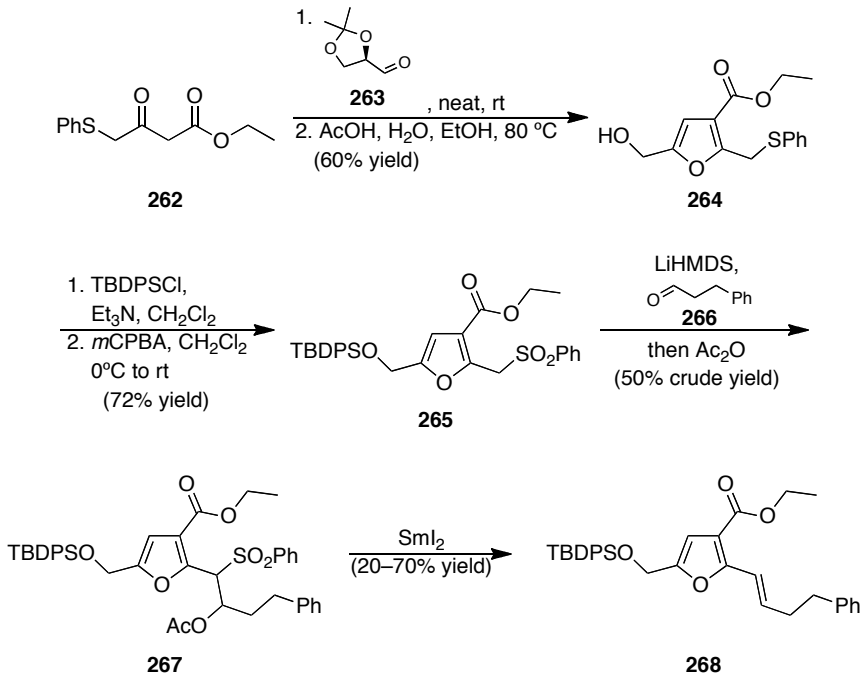


259 **260** **261**

The great versatility of the Feist-Bénary reaction, along with its many variations makes it well suited for our synthesis of the furan moiety. As such, furan **264** appeared to be a good starting point, wherein the sulfide could provide a handle for subsequent introduction of an olefin chain via a Julia-olefination. Paquette and co-workers have previously synthesized **264** in their synthesis of (±)-11,*O*(3)-dihydropseudopterolide.[20] In their variation, the reaction of glyceraldehyde acetonide **263** and β-ketoester **262**, followed by acid-catalyzed cyclization, furnished tri-substituted furan **264** (Scheme 2.3.3.3).

We prepared furan **264** following Paquette's protocol. Advancement of furan **264** commenced with protection of the alcohol as its silyl ether and subsequent oxidation gave sulfone **265** (Scheme 2.3.3.3). Deprotonation and treatment with hydrocinnamaldehyde **266** was followed by addition of acetic anhydride to furnish acetate **267**. Reductive elimination with SmI_2 allowed access to the fully functionalized alkenyl furan **268**.

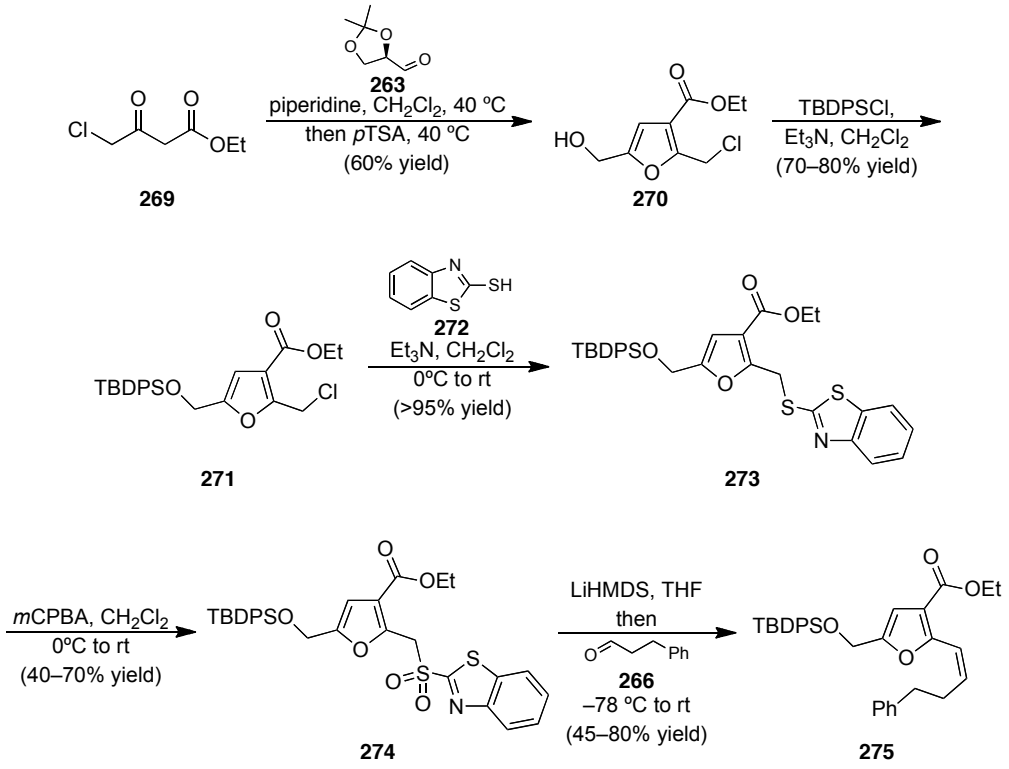
Scheme 2.3.3.3 Synthesis of alkenyl furan **268**



We were very please to have accessed a fully functionalized alkenyl furan **268**. However, the irreproducibility of the reductive elimination coupled with the necessary use of stoichiometric amounts of samarium metal, prompted us to investigate a modified Julia-olefination. Julia and co-workers discovered that using heteroaryl sulfones in place of phenyl sulfones allows for one-pot olefination reactions.[21] We elected to employ a benzothiazol-2-yl sulfone. We initially attempted to synthesize the sulfone in the same way we had previously synthesized phenyl sulfone **265** (Scheme 2.3.3.3). However, we found the furan forming reaction to be quite low yielding. We subsequently modified the procedure so that the benzothiazol-2-yl moiety was introduced following furan cyclization. In this case ethyl 4-chloroacetaldehyde **269** was condensed with glyceraldehyde acetonide **263** in the presence of a catalytic amount of piperidine (Scheme 2.3.3.4). Then *p*TSA was added directly to the reaction to induce cyclization and furnish

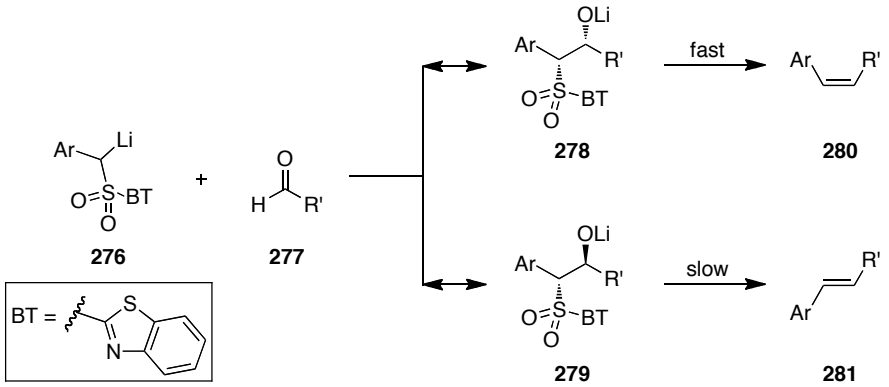
furan **270**. The alcohol was protected as its silyl ether **271**, and the chloride was displaced with benzothiazole **272**. Oxidation of sulfide **273** to sulfone **274** was accomplished with *m*CPBA. Deprotonation of the sulfone and subsequent treatment with hydrocinnamaldehyde furnished alkene **275**.

Scheme 2.3.3.4 Synthesis of alkenyl furan **275** via modified Julia-olefination



To our surprise in this instance the olefination yielded the *cis*-alkene rather than the *trans*-alkene as the primary product. The outcome of the olefination depends on the stereochemistry of the initial addition into the aldehyde, with *syn* β-alkoxysulfones **278** leading to (*Z*)-olefins **280** and *anti* β-alkoxysulfones **279** leading to (*E*)-olefins **281** (Scheme 2.3.3.5). [22] However, in the case of benzylic sulfones the addition is reversible, and since the elimination of *syn* β-alkoxysulfones to (*Z*)-olefins is faster, the product ratio heavily favors the (*Z*)-olefin product.

Scheme 2.3.3.5 Stereochemistry of modified Julia-olefination

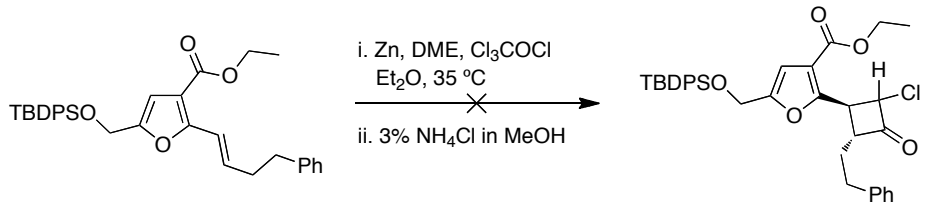


2.4 Attempted [2 + 2] Cycloadditions

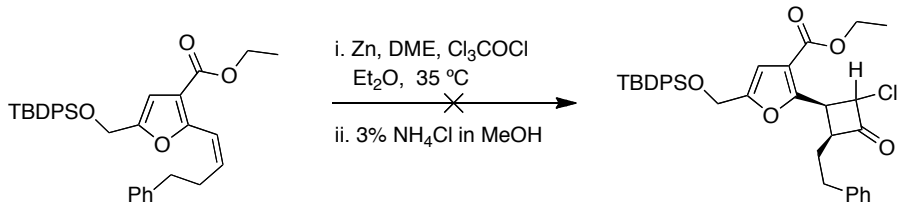
2.4.1 Dichloroketene Cycloadditions

With both the *cis* and *trans*-alkenyl furans in hand we set out to attempt our [2 + 2] cycloaddition. Using the conditions developed on simplified substrate **209** (Section 2.2.2) we attempted the transformation using both *cis* and *trans*-olefin substrates (Scheme 2.4.1.1). Unfortunately, neither substrate underwent the desired [2 + 2] cycloaddition reaction. When the *trans*-alkene **268** was employed we recovered starting material and observed some decomposition. When the *cis*-alkene **275** was employed, only a small amount of *trans*-isomer **268** was recovered.

Scheme 2.4.1.1 Attempted [2 + 2] cycloaddition of alkenyl furans **268/275**



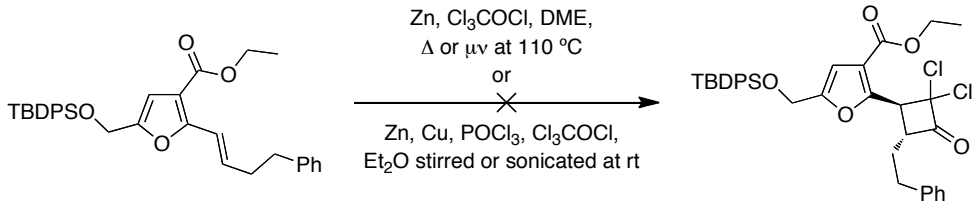
268 **282**



275 **283**

We employed alternative reaction conditions based on other literature precedent (Scheme 2.4.1.2).[23] Heating the reaction to higher temperatures or using microwave conditions resulted in no reaction. The Zn–Cu couple conditions resulted in decomposition of the starting materials.

Scheme 2.4.1.2 Additional [2 + 2] cycloaddition attempts



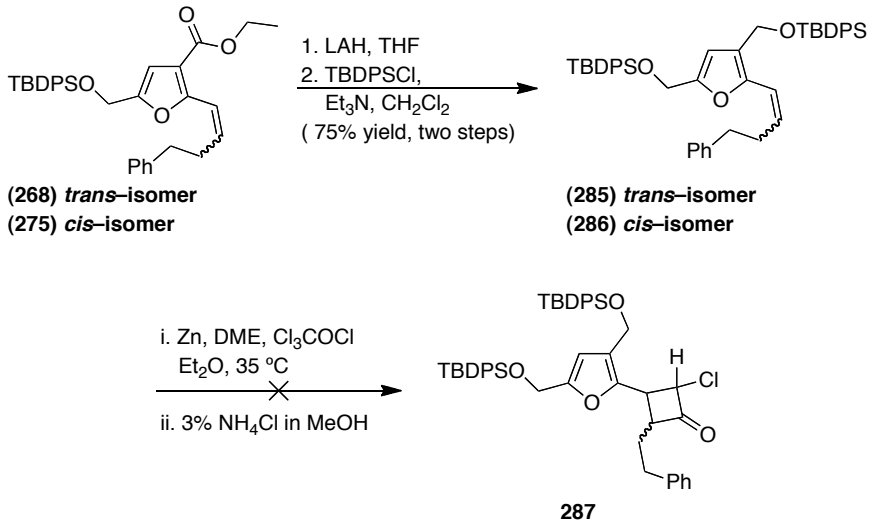
268 **284**

Given the success of our model [2 + 2] system (Section 2.2.2), we wondered what was preventing the [2 + 2] cycloaddition reaction of the fully functionalized furan **268/275** from taking place. One possible explanation was that the increase of steric bulk around the alkene is preventing the reaction. Another explanation was that the conjugated alkene was too electron deficient to undergo this transformation. It is known

that ketenes react with isolated-alkenes, dienes and activated alkenes such as vinyl ethers readily, however ketenes do not react with deactivated alkenes.[24]

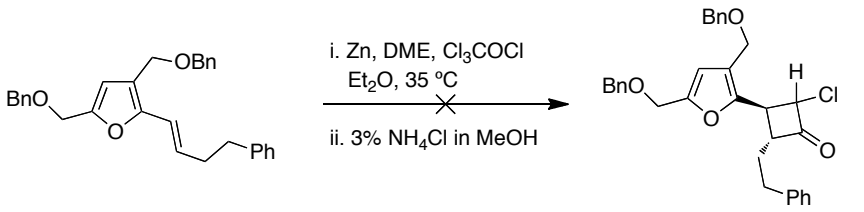
Therefore, we elected to alter the electronics of the olefin by reducing the ester on both the *cis*- and *trans*-substrates. The ester **268/275** was reduced with LAH and the resultant alcohol subsequently protected as its silyl ether **285/286**. Attempts to effect the [2 + 2] cycloaddition again failed, with cleavage of the silyl group being one of the competing pathways observed (Scheme 2.4.1.3).

Scheme 2.4.1.3 [2 + 2] Cycloaddition attempts on reduced furyl alkenes **285/286**

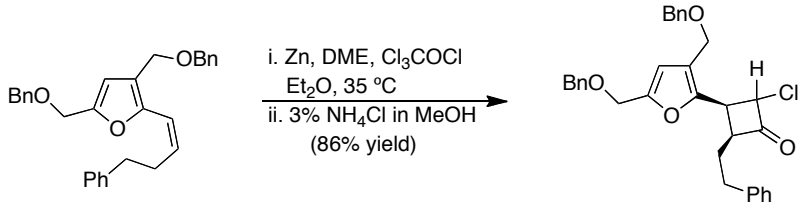


We decided to exchange the TBDPS-protecting groups for less labile benzyl-protecting groups. Even though the [2 + 2] cycloaddition did not occur with the *trans*-alkene **288**, we were pleased to discover that the [2 + 2] cycloaddition did occur when the *cis*-alkene **290** was employed, to provide the desired product **291** as a mixture of diastereomers (Scheme 2.4.1.4).

Scheme 2.4.1.4 [2 + 2] Cycloaddition attempts on furyl alkenes **288/290**



288 **289**



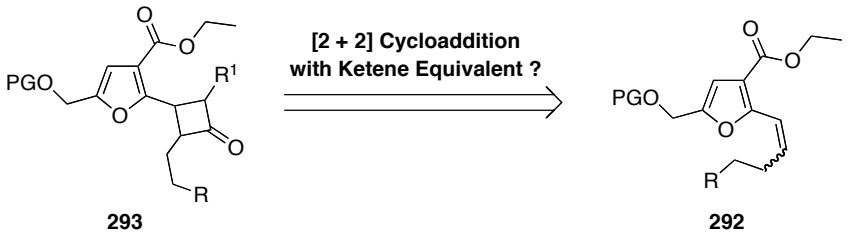
290 **291**

While we had at last obtained a functionalized furyl cyclobutanone **291**, we had several concerns about this approach. First, we noted the lack of stereocontrol in this approach. Second, there was the necessity to reduce the ester to the alcohol in order for the [2 + 2] cycloaddition to take place. Later in the synthesis the alcohol would need to be converted back to the ester, wherein oxidation of the furan was likely.

2.4.2 Ketene Equivalents in the [2 + 2] Cycloaddition

We postulated that it might be possible utilize an alkenyl furan with the ester intact, such as **268/275**, in a [2 + 2] cycloaddition if we employed ketene equivalents in place of dichloroketene (Scheme 2.4.2.1). Ketene equivalents are known to sometimes undergo [2 + 2] cycloadditions in reactions where ketenes have failed to give the desired products.[5] In a final attempt to convert a furyl alkene **292** into a furyl cyclobutanone **293** we investigated the use of ketene equivalents in the [2 + 2] cycloaddition.

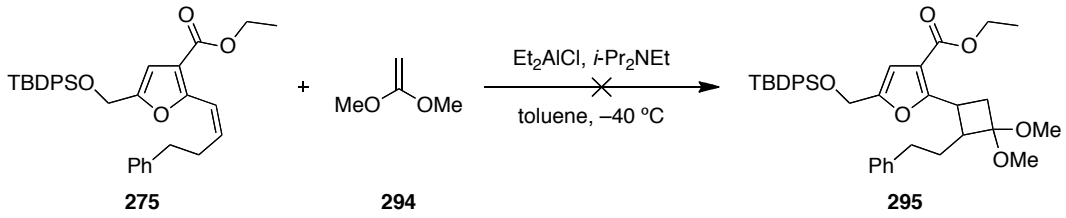
Scheme 2.4.2.1 [2 + 2] Cycloaddition with ketene or ketene equivalents



2.4.3 Ketene Dimethylacetal

While ketenes do not react with deactivated alkenes, ketene acetals participate in a formal [2 + 2] reaction with electron-deficient olefins under Lewis acid-mediated conditions. Using the previously described conditions (Section 1.4.1), we attempted to effect the [2 + 2] transformation with alkenyl furan **275** and ketene dimethyl acetal **294** (Scheme 2.4.3.1). Unfortunately no reaction took place and we recovered only starting material. Attempts to vary the reaction conditions failed to produce any desired product and again starting material was recovered.

Scheme 2.4.3.1 Attempted [2 + 2] cycloaddition with ketene dimethyl acetal

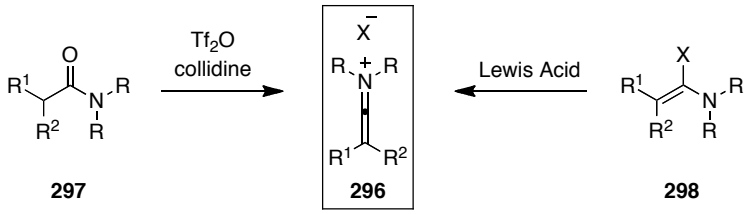


2.4.4 Keteniminium [2 + 2] Cycloadditions

Keteniminium salts **296** have been used as ketene equivalents in the synthesis of cyclobutanones from alkene substrates.[5, 25] In contrast to ketenes, theses salts do not undergo dimerization, and they react with a wider range of alkenes because they are more

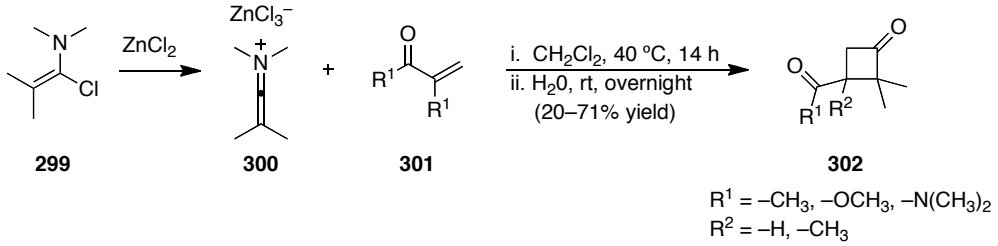
electrophilic than most ketenes. Importantly, keteniminium salts are readily prepared from amides **297** or α-halo enamines **298** (Scheme 2.4.4.1).

Scheme 2.4.4.1 Synthesis of keteniminium salts



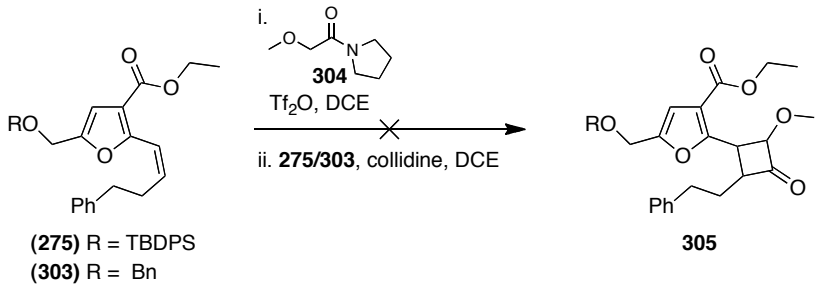
Amide substrates with a wide variety of substitution, both on the nitrogen and alpha to the carbonyl, have been successfully employed in the generation of keteniminium salts and their subsequent [2 + 2] cycloaddition. Both inter- and intramolecular variants of this reaction are known.[5] Literature precedent had shown that conjugated alkenes undergo [2 + 2] cycloaddition with keteniminium salts to yield cyclobutanones. Hartmann and Heine have shown that in situ generated tetramethylketeniminium ions **300** react with α,β-unsaturated ketones, esters, and amides **301** to give cyclobutanones **302** (Scheme 2.4.4.2).[26] We were hopeful that such an approach would result in the desired [2 + 2] cycloaddition on one of our furyl alkene substrates.

Scheme 2.4.4.2 [2 + 2] Cycloaddition of tetramethylketeniminium salts



We first prepared a simple amide substrate to test an intermolecular version of this type of reaction on our previously synthesized alkenyl furan **275** (Scheme 2.4.4.3). The amide **304** was cooled in DCE and treated with triflic anhydride. Then the alkene and collidine were added, and the reaction was warmed to room temperature. We observed no desired product and decomposition of the starting material. We subsequently elected to attempt this reaction with the benzyl-protected substrate **303**. The reaction failed to produce any cyclobutanone product, and no starting material was obtained, again due to decomposition under the reaction conditions. We also attempted the synthesis of other keteniminium precursors but were unsuccessful.

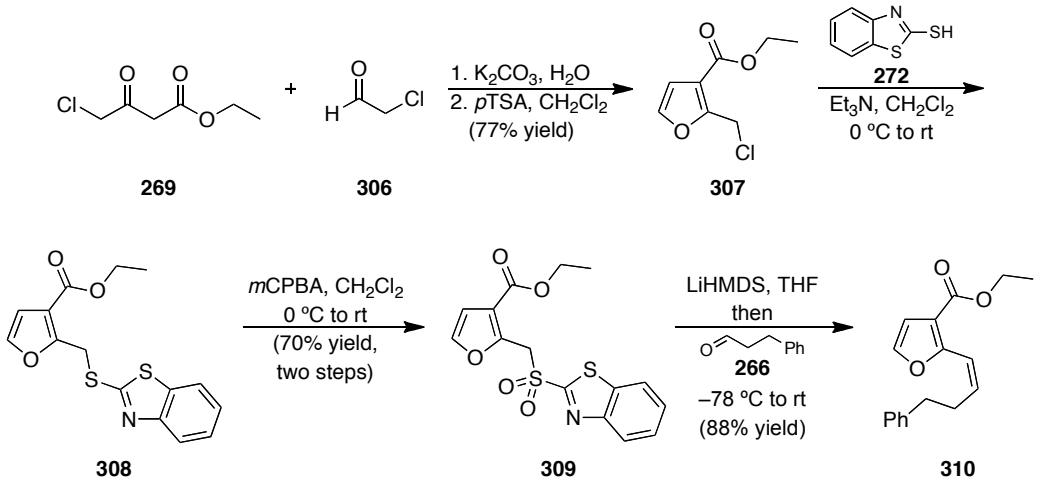
Scheme 2.4.4.3 Attempted intermolecular keteniminium [2 + 2] cycloaddition



As an alternative to the intermolecular approach, we attempted an intramolecular keteniminium cycloaddition reaction that we hoped would be more successful. A simplified alkenyl furan substrate **310** was prepared to test its reactivity in the proposed intramolecular keteniminium cycloaddition reaction (Scheme 2.4.4.4). Ethyl 4-chloroacetoacetate **269** and chloroacetaldehyde **306** underwent a Knoevenagal condensation aqueous, basic conditions to give an enone intermediate, which was directly treated with *p*TSA in dichloromethane overnight to induce cyclization to furan **307**. The chloride was displaced with benzothiazole **272** and subsequent oxidation furnished

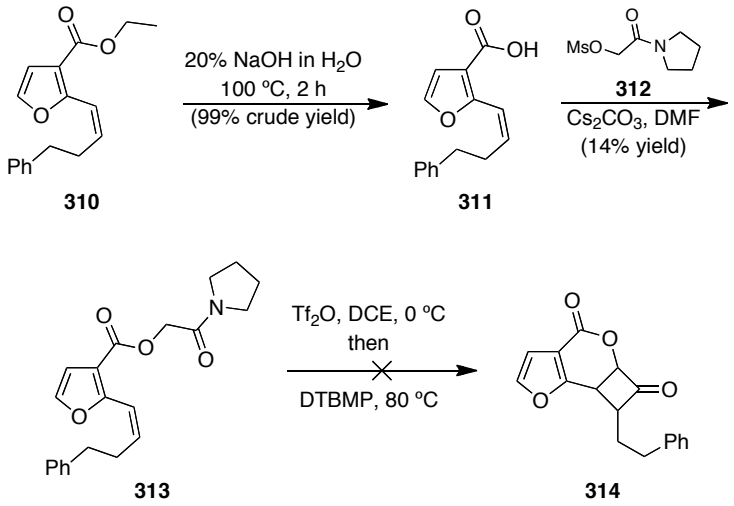
sulfone **309**. Deprotonation followed by treatment with hydrocinnamaldehyde **266** provided furyl alkene **310**.

Scheme 2.4.4.4 Synthesis of alkenyl furan **310**



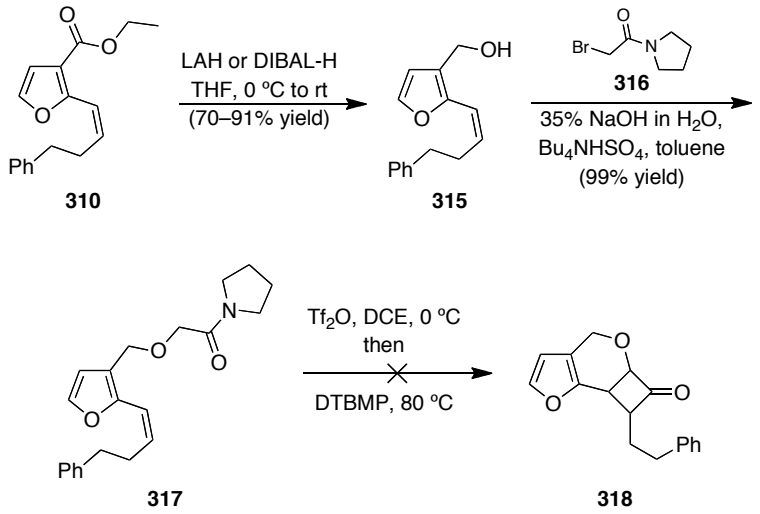
Our first attempt at intramolecular keteniminium cycloaddition was executed on ester substrate **313**. Ester **310** was saponified to carboxylic acid **311** and alkylated with amide **312** (Scheme 2.4.4.5). Exposure of amide **313** to triflic anhydride at 0 ºC, followed by treatment with DTBMP, and heating to 80 ºC only resulted in decomposition of the starting material. Attempts to confirm the formation of the keteniminium intermediate by trapping with methanol and cyclohexene failed.

Scheme 2.4.4.5 Attempted intramolecular keteniminium [2 + 2] cycloaddition



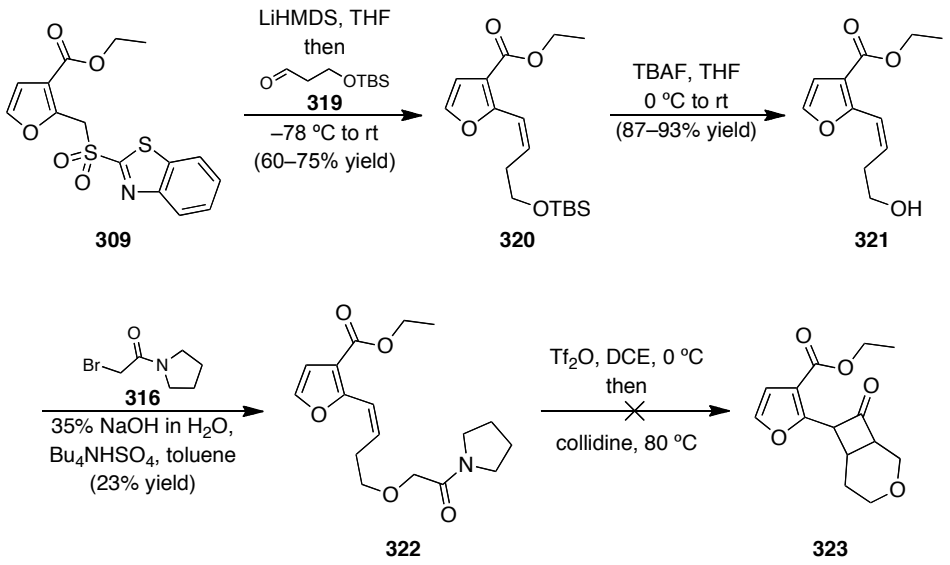
Concerned that the ester may be interfering with the formation of the iminium ketene we next attempted an intramolecular keteniminium cycloaddition on an ether substrate. Alkenyl furan **310** was reduced with lithium aluminum hydride to give alcohol **315** (Scheme 2.4.4.6). Alkylation of alcohol **315** with bromide **316**, in aqueous 35% NaOH solution, in the presence of a phase transfer catalyst tetrabutylammonium hydrogensulfate, furnished ether **317**. Unfortunately, treatment of the ether substrate **317** with triflic anhydride followed by either DTBMP or collidine failed to provide any cycloaddition products. We observed decomposition of the starting material under a variety of conditions. Using other common variations such as changing the solvent to benzene or adding 4Å molecular sieves did not improve the outcome of the reaction.

Scheme 2.4.4.6 Attempted intramolecular keteniminium [2 + 2] cycloaddition



Concurrently, we pursued an approach wherein the amide was tethered to the other side of the alkene. Deprotonation of sulfone **309** and subsequent treatment with aldehyde **319** furnished alkene **320** (Scheme 2.4.4.7). Deprotection and etherification with bromide **316** provided ether **322**. However, we also observed significant quantities of the elimination product that resulted in a diene, but enough of the desired product was isolated to attempt the cycloaddition. The use of sodium hydride as a base did not reduce the amount of elimination product observed. Treatment of amide **322** with triflic anhydride and subsequently collidine failed to produce any desired product. Some starting material was recovered but the remainder was lost due to decomposition.

Scheme 2.4.4.7 Attempted intramolecular keteniminium [2 + 2] cycloaddition



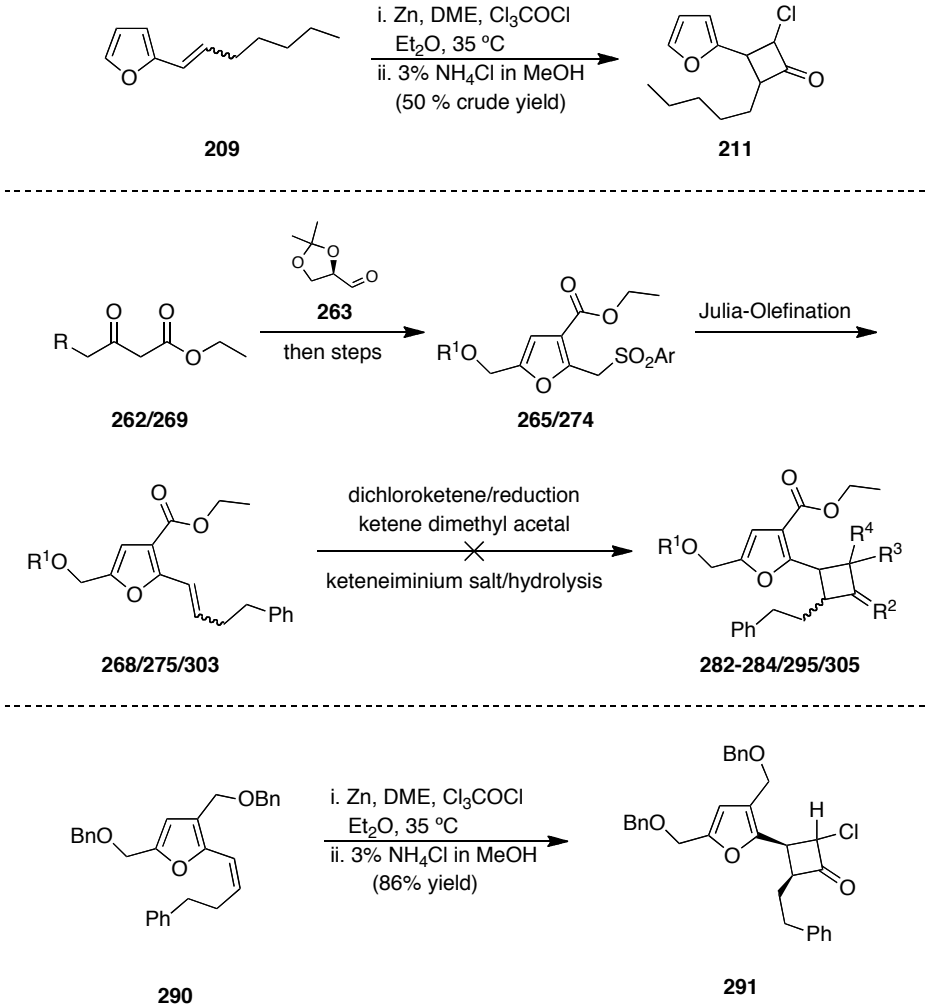
It became apparent that our substrates were ill disposed to undergo the keteniminium cycloaddition reactions. Even when the triflic anhydride was distilled before use, and excess of collidine or DTBMP and 4Å molecular sieves were used we still observed decomposition. Clearly a more effective approach would be needed.

2.5 Conclusions

This chapter covers the various approaches to the synthesis of cyclobutanes and our synthetic efforts towards the synthesis of a furyl cyclobutane en route to providencin (**1**). We have shown that it is possible to effect a [2 + 2] cycloaddition between an alkenyl furan and dichloroketene (Scheme 2.5.1). We have synthesized highly functionalized furan substrates **268/275/303** with appropriate functionalization for further elaboration. However, we found the [2 + 2] cycloaddition reaction does not proceed when there is an ester moiety at the 3-position of our furan substrates. The use of ketene equivalents on the ester substrates failed to produce any cyclobutanone products. The reaction was no more

successful when attempted intramolecularly. We have effected the [2 + 2] cycloaddition reaction on an alkenyl furan **290**, where the ester at the 3-position of the furan had been reduced to an alcohol. However, the requisite oxidation state changes were a concern. We have since decided to reevaluate our retrosynthetic approach and further efforts toward the synthesis of providencin (**1**) will be discussed in the following chapter.

Scheme 2.5.1 Chapter 2 summary



2.6 Experimental Procedures

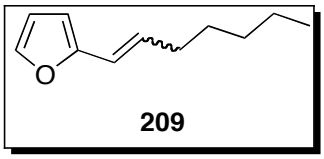
2.6.1 General Information

Unless otherwise stated, reactions were mechanically stirred in flame-dried glassware under an atmosphere of nitrogen. Tetrahydrofuran, benzene, toluene, dichloromethane and diethyl ether were dried using a solvent purification system manufactured by SG Water U.S.A., LLC. Commercially available reagents were obtained from Sigma-Aldrich, Strem, TCI-America or Alfa Aesar and were used as received. All known compounds were identified by comparison of NMR spectra to those reported in the literature.

Thin layer chromatography was performed using Silicycle glass-backed extra hard layer, 60 Å plates (indicator F-254, 250 μm). Developed plates were visualized using a 254 nm UV lamp and/or with the appropriate dip followed by heating. Typical dip solutions were ethanolic anisaldehyde, ceric ammonium molybdate and potassium permanganate. Flash chromatography was generally performed with Silicycle SiliaFlash® P60 (230-400 mesh) silica gel as the stationary phase. Infrared spectra were recorded on a Nicolet Avatar 320 FT-IR. Samples were analyzed as thin films on NaCl plates (sample dissolved in CH_2Cl_2) and the spectra are presented as transmittance vs. wavenumber (cm^{-1}). High-resolution mass spectrometry was conducted on an Agilent 6210 TOF LCMS. Proton (^1H) and carbon (^{13}C) NMR spectra were recorded on a Varian Inova 400 or 300 spectrometer. Spectra were obtained at 22 ºC in $CDCl_3$ unless otherwise noted. Chemical shifts (δ) are reported in parts per million (*ppm*) and are referenced to the residual solvent peak. Coupling constants (*J*) are reported in Hertz (Hz) and are rounded to the nearest 0.1 Hz. Multiplicities are defined as: s = singlet, d =

doublet, t = triplet, q = quartet, quint. = quintuplet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, dt = doublet of triplets, br = broad, app = apparent.

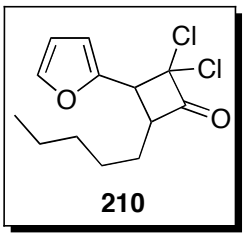
2.6.2 Preparative Procedures



209

Hexyltriphenylphosphonium bromide **207** (0.618 g, 1.44 mmol) was dissolved in THF (10 mL) and cooled to 0 ºC. 1M LiHMDS (1.8 mL, 1.8 mmol) was added dropwise and solution turned from pale yellow to bright orange. Furfural **208** (0.1 mL, 1.2 mmol) was added dropwise and the reaction was allowed to warm to room temperature. When TLC showed consumption of furfural the reaction was concentrated onto silica gel and purified by flash chromatography (hexanes). **209** was obtained as a mixture of olefin isomers in near quantitative yield.

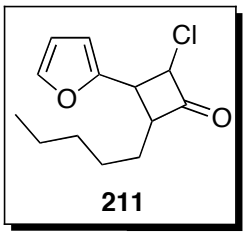
209: R_f = 0.6, hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J*=1.7 Hz, 0.2H), 7.30 (d, *J*=1.6 Hz, 0.8H), 6.39 (dd, *J*=3.3, 1.8 Hz, 0.2H), 6.34 (dd, *J*=3.3, 1.8 Hz, 0.8H), 6.25 (d, *J*=3.5 Hz, 0.2H), 6.20–6.17 (m, 1.8H), 6.12 (d, *J*=3.5 Hz, 0.8H), 5.56 (dt, *J*=11.8, 7.3 Hz, 0.2 H), 2.44 (app q, *J*=7.3 Hz, 0.4H), 2.17 (app q, *J*=7.2 Hz, 1.6H), 1.46–1.41 (m, 2H), 1.37–1.29 (m, 4H), 0.90 (app t, *J*=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *cis*–isomer δ 153.5, 141.3, 131.7, 117.3, 111.2, 108.8, 31.8, 29.4, 29.36, 22.7, 14.2 *trans*–isomer δ 153.61 141.,1 130.5, 118.7, 11.,3, 106.0, 33.0, 31.6, 29.1, 22.8, 14.3; IR (NaCl thin film): 2958(s), 2927(s), 2857(m), 1491(w), 1012(m), 959(m), 728(s); HRMS (ESI–APCI) *m*/*z* calcd. for $C_{11}H_{17}O$ $[M+H]^+$: 165.1274, found: 165.1275



210

To a solution of **209** (0.218 g, 1.33 mmol), zinc (0.435 g, 6.65 mmol) (activated by heating to 150 ºC for 3–18 h), DME (0.15 mL, 1.46 mmol) in diethyl ether (5 mL) at reflux was added trichloroacetyl chloride (0.16 mL, 1.46 mmol) in diethyl ether (3 mL) dropwise via a syringe pump. When TLC showed consumption of **209** the reaction was cooled and filtered through celite. The filtrate was washed 5x with dilute sodium bicarbonate solutions then dried over $MgSO_4$. Concentration *in vacuo* yielded a yellow oil, this product proved unstable to silica gel and alumina, resulting in a <10% yield, and was used without further purification.

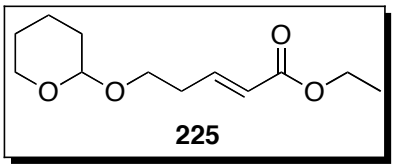
210: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 6.38 (m, 2H), 4.28 (d, *J*=11.25 Hz, 1H), 4.13 (dt, *J*=15.32, 11.25, 7.68 Hz, 1H), 1.91–1.82 (m, 1H), 1.6–1.5 (m, 1H), 1.36–1.13 (m, 6H), 0.83 (t, *J*=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.8, 148.6, 143.5, 111.9, 110.6, 87.0, 59.7, 49.5, 31.6, 27.5, 26.1, 22.4, 14.1; IR (NaCl thin film): 2957(m), 2930(m), 2860(m), 1807(s), 1150(w), 921(w), 738(w); HRMS (ESI–APCI) *m*/*z* calcd. for $C_{13}H_{15}Cl_2O_2$ $[M–H]^-$: 273.0455, found: 273.0451



211

To a solution of **210** (0.066 g, 0.4 mmol), zinc (0.262 g, 4 mmol) (activated by heating to 150 ºC for 3–18 h), DME (0.07 mL, 0.6 mmol) in diethyl ether (3 mL) at reflux was added trichloroacetyl chloride (0.07 mL, 0.6 mmol) in diethyl ether (1 mL) dropwise via a syringe pump. When TLC showed consumption of **211** a solution of 3% NH_4Cl in MeOH (0.5 mL) was added. After 20 min the reaction was cooled and filtered through celite. The filtrate was washed 5x with dilute sodium bicarbonate solutions then dried over $MgSO_4$. Concentration *in vacuo* yielded a crude yellow oil **211** in ~50% yield. This product proved unstable to silica gel and alumina and was used without further purification.

211: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.40 (m, 1H), 6.37 (dd, *J*=3.2, 1.9 Hz, 0.4H), 6.33 (dd, *J*=3.2, 1.9 Hz, 0.6H), 6.27–6.26 (m, 1H), 5.20 (dd, *J*=7.8, 2.8 Hz, 0.4H), 5.16 (dd, *J*=9.8, 2.8 Hz, 0.6H), 4.11 (t, *J*=10.0 Hz, 0.6H), 3.76 (dd, *J*=10.3, 7.8 Hz, 0.4 H), 3.61–3.52 (m, 1H), 1.71–1.07 (m, 8H), 0.80 (t, *J*=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5/200.8, 150.2/149.6, 142.5/142.7, 110.6/110.1, 108.5/110.4, 63.6/61.5, 61.4/59.6, 39.4/35.7, 31.4, 26.9/27.2, 27.0/25.1, 22.2, 13.9 ; IR (NaCl thin film): 2956(s), 2930(s), 2860(m), 1795(s), 735(m) ; HRMS (ESI–APCI) *m*/*z* calcd. for $C_{13}H_{19}O_2$ $[M+H]^+$: 207.138, found: 207.1384 (this is the mass for the over-reduced product)



225

3,4–dihydro–2*H*–pyran (50.4 mL, 556 mmol) in diethyl ether (250 mL) was cooled in an ice bath. Then *p*–toluenesulfonic acid (0.2 g, 1.1 mmol) and 3–butene–1–ol **223** (11.86 mL, 139 mmol) were added and reaction was allowed to warm to room

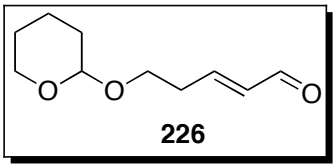
temperature and stir overnight. The reaction was quenched with NH_4OH (2 mL) in MeOH (20 mL) and concentrated. Ether was added to the residue and the ammonium *p*–toluenesulfate removed by filtration. The filtrate was concentrated and crude ^{1}H NMR of the alkene matched the published data.[27]

The crude alkene was dissolved in 1:1 MeOH:CH_2Cl_2 (1 L) with pyridine (1 mL) and the reaction cooled to –78 ºC. Ozone was bubbled through the reaction for 3 h until solution turned blue. Air was bubbled through the reaction until blue color dissipated and then dimethylsulfide (45 mL) was added and reaction was allowed to warm to room temperature. Water (500 mL) was added and layers were separated. The aqueous layer was extracted twice with dichloromethane (250 mL) and combined organics were dried over $MgSO_4$ and concentrated. Crude ^{1}H NMR of the aldehyde matched the published data.[28]

The crude aldehyde and ethyl (triphenylphosphoranylidene)acetate **224** (48.4 g, 139 mmol) in THF (250 mL) were heated to reflux for 12 h. Reaction was cooled and concentrated onto silica gel. Material was purified by flash chromatography (4:1 hexanes:EtOAc) to yield **225** in 71% yield over three steps.

225: R_f = 0.33, 4:1 hexanes:EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (dt, *J*=15.7, 8.8, 6.9 Hz, 1H), 5.90 (dt, *J*=15.7, 1.6 Hz, 1H), 4.59 (m, 1H), 4.18 (q, *J*=7.1 Hz, 2H), 3.88–3.81 (m, 2H), 3.54–3.48 (m, 2H), 2.49 (dddd, *J*=13.4, 6.7, 6.7, 1.6 Hz, 2H), 1.85–1.77 (m, 1H), 1.74–1.67 (m, 1H), 1.61–1.48 (m, 4H), 1.28 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 145.9, 123.1, 99.0, 65.8, 62.5, 60.4, 32.8, 30.8, 25.6, 19.7, 14.5; IR (NaCl thin film): 2941(s), 2871(s), 1722(s), 1657(m), 1262(m), 1218(s), 1033(s),

978(s); HRMS (ESI–APCI) *m/z* calcd. For $C_{12}H_{20}NaO_4$ $[M+Na]^+$: 251.1254, found: 251.1255

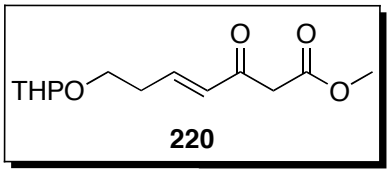


226

Ethyl ester **225** (6.2 g, 27 mmol) was stirred in THF (150 mL) and cooled to in an ice bath. 1M DIBAL-H in THF (68 mL, 68 mmol) was added dropwise via addition funnel. After addition the reaction was warmed to room temperature and stirred for 1 hour. When TLC showed a complete conversion, the reaction was cooled in an ice bath and carefully quenched with 0.5M Rochelle's salt solution. The layers were separated and the aqueous layer was extracted with three times with ether. The combined organics were washed with brine, dried over $MgSO_4$ and concentrated. Crude ^1H NMR of the alcohol matched the published data.[29]

Oxalyl chloride (2 mL, 22.5 mmol) was added to dichloromethane (100 mL) cooled to –78 ºC. Then dimethylsulfoxide (3.4 mL, 48 mmol) was added dropwise and the reaction was stirred at –78 ºC for 30 minutes. Then alcohol (2.8 g, 15 mmol) in dichloromethane (100 mL) was added dropwise and the reaction was stirred for 30 minutes at –78 ºC. Triethylamine (10.4 mL, 75 mmol) was added and the reaction was warmed to 0 ºC. The reaction was quenched with sodium bicarbonate solution. The layers were separated and the aqueous was extracted three times with ether. The combined organics were washed with sodium hydrogensulfate solution 1x, sodium bicarbonate solution 1x, and brine 1x, dried over $MgSO_4$ and concentrated. The crude material was flashed in 2:1 hexanes:EtOAc and aldehyde **226** was obtained in 73% yield over two steps.

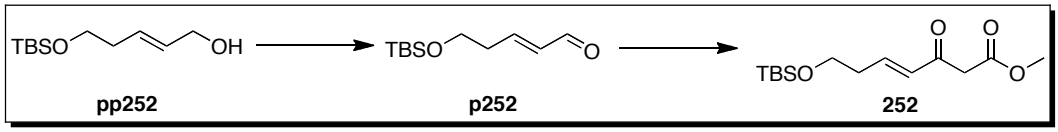
226: R_f = 0.37, 2:1 hexanes:EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (d, *J*=7.9 Hz, 1H), 6.87 (dt, *J*=15.8, 6.8 Hz, 1H), 6.18 (dd, *J*=15.7, 7.9 Hz, 1H), 4.59 (s, 1H), 3.92–3.79 (m, 2H), 3.58–3.47 (m, 2H), 2.61 (dddd, *J*=13.0, 6.6, 6.6, 1.3 Hz, 2H), 1.80–1.65 (m, 2H), 1.59–1.49 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.2, 155.5, 134.4, 99.2, 65.4, 62.7, 33.3, 30.8, 25.6, 19.7; IR (NaCl thin film): 2943(m), 2870(w), 1692(s), 1134(m), 1033(m); HRMS (ESI–APCI) *m*/*z* calcd. for $C_{10}H_{17}O_3$ $[M+H]^+$: 185.1172, found: 185.1167



220

The diisopropylamine (1.4 mL, 10.1 mmol) was stirred in THF (13 mL) at –78 ºC. Then 1.6 M *n*-BuLi (6.3 mL, 10.1 mmol) was added dropwise and the reaction was stirred at –78 ºC for 30 minutes. Methyl acetate (0.68 mL, 8.5 mmol) was added dropwise and the reaction was stirred for a further 30 minutes. Then aldehyde **226** (1.5g, 8.1 mmol) in THF was added and reaction was allowed to slowly warm to 0 ºC. TLC showed a complete reaction so reaction was quenched at 0 ºC with NH_4Cl solution. The layers were separated and the aqueous layer was extracted three times with ether. Combined organics were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was dissolved in CH_2Cl_2 and MnO_2 was added portionwise. The reaction was stirred overnight. When starting material remained we added additional MnO_2 at intervals until all starting material was consumed. Reaction was filtered through celite and concentrated. The crude material was flashed in 4:1 hexanes:EtOAc and the β-ketoester **220** was obtained in 25% yield over two steps. The enol form was also observed in the NMR.

220: R_f = 0.22, 4:1 hexanes:EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.79 (d, *J*=1.3 Hz, 0.3H), 6.93 (dt, *J*=16.0, 6.9 Hz, 0.7H), 6.68 (dt, *J*=15.6, 7.1 Hz, 0.3H), 6.24 (dt, *J*=16.0, 1.4 Hz, 0.7H), 5.89 (app dd, *J*=15.6, 1.4 Hz, 0.3H), 5.00 (s, 0.3H), 4.59 (m, 1H), 3.90–3.81 (m, 2H), 3.74 (m, 2.1H), 3.60 (s, 0.9H), 3.56–3.48 (m, 2H), 2.57–2.47 (m, 2H), 1.60–1.50 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) keto-form δ 192.1, 168.0, 146.9, 131.1, 99.1, 65.6, 62.6, 52.6, 46.8, 33.2, 30.8, 25.6, 19.7, enol-form δ 173.5, 169.5, 137.7, 126.1, 90.6, 66.2, 62.6, 51.4, 46.8, 33.2, 30.8, 25.6, 19.7; IR (NaCl thin film): 2947(m), 2870(w), 1746(m), 1240(s), 1033(s); HRMS (ESI–APCI) *m/z* calcd. for $C_{13}H_{20}NaO_5$ $[M+Na]^+$: 279.1203, found: 279.1205



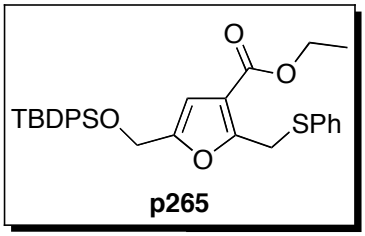
Oxalyl chloride (0.72 mL, 8.25 mmol) was added to dichloromethane (30 mL) cooled to –78 ºC. Then dimethylsulfoxide (1.25 mL, 17.6 mmol) in dichloromethane (30 mL) was added dropwise and the reaction was stirred at –78 ºC for 30 minutes. Then known alcohol **pp252**[31] (1.2 g, 5.5 mmol) in dichloromethane (10 mL) was added dropwise and the reaction was stirred for 30 minutes at –78 ºC. Triethylamine (3.8 mL, 27.5 mmol) was added and the reaction was warmed to 0 ºC. The reaction was quenched with sodium bicarbonate solution. The layers were separated and the aqueous was extracted three times with ether. The combined organics were washed with sodium hydrogensulfate solution 1x, sodium bicarbonate solution 1x, brine 1x, were dried over $MgSO_4$ and concentrated. The crude aldehyde **p252** was carried on directly.

p252: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (d, *J*=7.9 Hz, 1H), 6.88 (dt, *J*=15.7, 6.9 Hz, 1H), 6.17 (ddt, *J*=15.8, 7.8 Hz, 1H), 3.78 (t, *J*=6.2 Hz, 2H), 2.54 (m, 2H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.2, 155.7, 134.5, 61.4, 36.3, 26.1, 18.5, –5.1; IR (NaCl thin film): 2955(s), 2930(s), 2866(m), 1697(s), 1257(m), 1101(s), 836(s), 777(m); HRMS (ESI–APCI) *m*/*z* calcd. for $C_{11}H_{23}O_2Si$ $[M+H]^+$: 215.1462, found: 215.1461

The diisopropylamine (0.97 mL, 6.89 mmol) was stirred in THF (10 mL) at –78 ºC. Then 1.6 M *n*-BuLi (4.9 mL, 6.89 mmol) was added dropwise and the reaction was stirred at –78 ºC for 30 minutes. Methyl acetate (0.46 mL, 5.78 mmol) was added dropwise and the reaction was stirred for a further 30 minutes. Then aldehyde **p252** (5.5 mmol) in THF (2 mL) was added and reaction was allowed to slowly warm to 0 ºC. TLC showed a complete reaction so reaction was quenched at 0 ºC with NH_4Cl solution. The layers were separated and the aqueous layer was extracted three times with ether. Combined organics were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was dissolved in CH_2Cl_2 (125 mL) and MnO_2 (12 g, 137.5 mmol) was added portionwise. The reaction was stirred overnight. When starting material remained we added additional MnO_2 at intervals until all starting material was consumed. Reaction was filtered through celite and concentrated. The crude material was flashed in 10:1 hexanes:EtOAc and the β-ketoester **252** was obtained in 27% yield over three steps. The enol form was also observed in the NMR.

252: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.79 (d, *J*=1.4 Hz, 0.3H), 6.89 (dt, *J*=16.0, 7.0 Hz, 0.7H), 6.65 (dt, *J*=15.5, 6.6 Hz, 0.3H), 6.21 (dt, *J*=16.0, 1.5 Hz, 0.7H), 5.85 (app dd, *J*=15.5, 1.5 Hz, 0.3H), 5.00 (s, 0.3H), 3.76–3.70 (m, 5H), 3.59 (s, 1.4H), 2.48–2.37 (m,

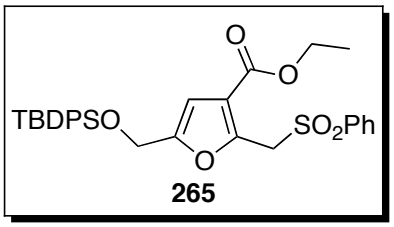
2H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) keto-form δ 192.1, 168.0, 147.1, 131.2, 61.5, 52.6, 46.7, 36.2, 26.1, 18.5, –5.1, enol-form δ 173.5, 169.6, 137.9, 126.2, 90.1, 62.2, 51.4, 46.7, 36.3, 26.1, 18.5, –5.1; IR (NaCl thin film): 2954(m), 2930(m), 2897(w), 2858(m), 1748(m), 1667(m), 1240(s), 1098(s), 837(s); HRMS (ESI–APCI) *m*/*z* calcd. for $C_{14}H_{27}O_4Si$ $[M+H]^+$: 287.1673, found: 287.1674



p265

Known alcohol **264**[20b] (0.5 g, 1.7 mmol) was dissolved in CH_2Cl_2 (10 mL) and a few crystals of DMAP were added followed by triethylamine (0.28 mL, 2.04 mmol) and TBDPSCl (0.49 mL, 1.9 mmol). The reaction was allowed to stir overnight. The reaction was diluted with ether and the organic layer was washed with H_2O 1x, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was flashed in 4:1 hexanes:EtOAc and furan **p265** was obtained in 91% yield.

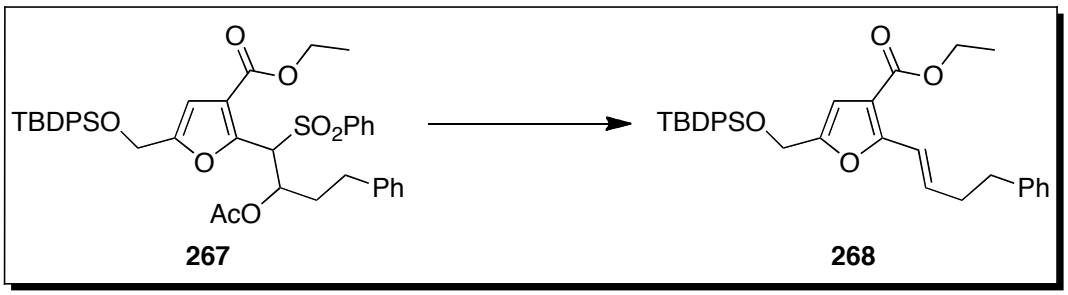
p265: R_f = 0.55, 4:1 hexanes:EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75–7.73 (m, 4H), 7.51–7.40 (m, 8H), 7.30–7.22 (m, 3H), 6.43 (s, 1H), 4.62 (s, 2H), 4.44 (s, 2H), 4.25 (q, *J*=7.1 Hz, 2H), 1.34 (t, *J*=7.1 Hz, 3H) , 1.11 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 156.9, 153.4, 135.8, 135.1, 133.3, 131.8, 130.0, 129.0, 128.0, 127.3, 115.9, 108.5, 60.5, 58.8, 31.1, 27.0, 19.5, 14.5; IR (NaCl thin film): 2930(w), 2857(w), 1716(s), 1427(w), 1208(m), 1062(s), 701(m); HRMS (ESI–APCI) *m*/*z* calcd. for $C_{31}H_{34}NaO_4SSi$ $[M+Na]^+$: 553.1839, found: 553.1843



265

The sulfide **p265** (0.168 g, 0.325 mmol) was dissolved in CH_2Cl_2 (2 mL) and the reaction was cooled to 0 ºC. Then *m*CPBA (0.142 g, 0.65 mmol) was added in one portion. The reaction was allowed to warm to room temperature and stir overnight. The reaction was concentrated and the residue was dissolved in EtOAc. The organic layer was washed with $Na_2S_2O_3$ 1x, $NaHCO_3$ 1x, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was clean by ^1H NMR and material was used directly.

265: R_f = 0.27, 4:1 hexanes:EtOAc; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71–7.67 (m, 6H), 7.56 (app t, *J*=7.5 Hz, 1H), 7.47–7.39 (m, 8H), 6.42 (s, 1H), 4.81 (s, 2H), 4.57 (s, 2H), 4.08 (q, *J*=7.1 Hz, 2H), 1.25 (t, *J*=7.1 Hz, 3H) , 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 155.7, 147.1, 138.5, 135.8, 134.0, 133.1, 130.1, 129.0, 128.8, 128.0, 119.5, 108.7, 60.8, 58.8, 55.2, 27.0, 19.4, 14.4; IR (NaCl thin film): 2930(w), 2857(w), 1717(s), 1327(s), 1222(m), 1065(s), 747(s); HRMS (ESI–APCI) *m*/*z* calcd. for $C_{31}H_{34}NaO_6SSi$ $[M+Na]^+$: 585.1738, found: 585.1737



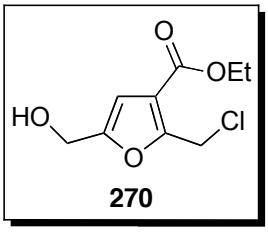
267 **268**

Sulfone **265** (3.38 g, 6 mmol) was dissolved in THF (20 mL) and cooled to –78 ºC. Then *n*-BuLi (4.4 mL, 6.6 mmol) was added and the reaction was stirred for 30 minutes at –78 ºC. The aldehyde **266** (0.83 mL, 6.3 mmol) was added and the reaction stirred at –78 ºC for a further three hours. Acetic anhydride (1.13 mL, 12 mmol) was

added and the reaction was allowed to warm to room temperature. The reaction was quenched with saturated NH_4Cl solution and the layers were separated. The aqueous layer was extracted with ether 2x. Combined organics were dried over $MgSO_4$ and concentrated *in vacuo* to give **267**. The crude material was carried on directly.

The acetate **267** was dissolved in THF (20 mL) and was then transferred to a flask containing SmI_2 (20 mmol) and HMPA (15 mL) in THF (200 mL) via syringe.[30] When starting material was consumed by TLC the reaction was diluted with ether and washed with 1 M HCl 1x, $NaHCO_3$ 1x, H_2O 1x, and brine 1x. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was flashed in 4:1 hexanes:EtOAc. The furyl alkene was isolated in 12% yield for two steps.

268: R_f = 0.28, 4:1 hexanes:EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.69 (m, 4H), 7.46–7.36 (m, 6H), 7.32–7.24 (m, 2H), 7.22–7.19 (m, 3H), 6.97 (app d, *J*=16.0 Hz, 1H), 6.49–6.41 (m, 2H), 4.61 (s, 2H), 4.28 (q, *J*=7.1 Hz, 2H), 2.83–2.79 (m, 2H), 2.61–2.53 (m, 2H), 1.35 (t, *J*=7.1 Hz, 3H) , 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 156.3, 152.4, 141.4, 135.6, 134.6, 133.2, 129.8, 128.4, 127.7, 126.0, 118.3, 113.3, 108.9, 60.2, 58.7, 35.4, 34.9, 26.8, 19.3, 14.4; IR (NaCl thin film): 3070(w), 3026(w), 2957(m), 2930(m), 2558(m), 1711(s), 1057(s), 701(s); HRMS (ESI–APCI) *m*/*z* calcd. for $C_{18}H_{19}O_3$ $[M–OTBDPS]^+$: 283.1329, found: 283.1332

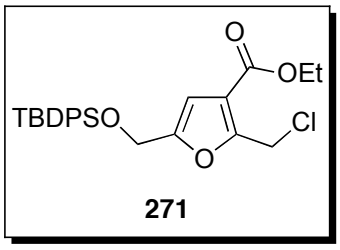


270

The bis-acetonide (5.25 g, 20 mmol) was stirred in (80 mL) of CH_2Cl_2 and cooled to 0 ºC and then sodium bicarbonate solution (1 mL, 1 mmol) was added. When the cleavage appeared to be complete $MgSO_4$ was added and reaction was stirred for a further

15 min. The reaction was filtered. Then β-ketoester **269** (2.7 mL, 20 mmol) and piperidine (0.2 mL, 2 mmol) were added to filtrate, which was then heated to reflux overnight. Then *p*TSA (0.76 g, 4 mmol) was added and the reaction, which was refluxed until reaction appeared to be complete by TLC. The reaction was cooled and quenched with H_2O and the aqueous layer was extracted with CH_2Cl_2. The combined organics were washed with H_2O 1x, brine 1x, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was flashed in 2:1 hexanes:EtOAc and furan **270** was isolated in 60% yield.

270: R_f = 0.09, 4:1 hexanes:EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.59 (s, 1H), 4.88 (s, 2H), 4.59 (s, 2H), 4.30 (q, *J*=7.1 Hz , 2H), 1.35 (t, *J*=7.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 155.0, 154.7, 117.3, 109.1, 61.1, 57.3, 35.8, 14.4; IR (NaCl thin film): 3425(w), 2983(w), 1717(s), 1228(m), 1077(s); HRMS (ESI–APCI) *m*/*z* calcd. for $C_9H_{11}ClO_4$ $[M–H]^-$: 217.0273, found: 217.0278

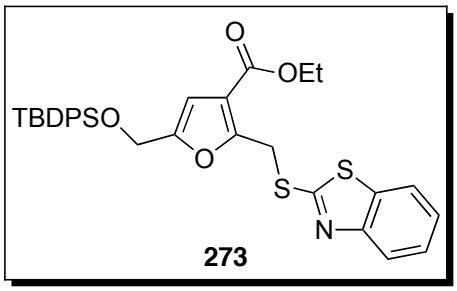


271

Alcohol **270** (85 mg, 0.39 mmol) was stirred in CH_2Cl_2 at room temperature. Then DMAP, Et_3N (0.065 mL, 0.47 mmol), and TBDPSCl (0.11 mL, 0.43 mmol) were added successively and the reaction was stirred overnight. The reaction was concentrated and the residue was dissolved in Et_2O and washed with H_2O 2x, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was flashed in 4:1 hexanes:EtOAc. The protected alcohol **271** was isolated in 80% yield.

271: R_f = 0.**59**, 4:1 hexanes:EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J*=6.9 Hz , 4H), 7.46–7.38 (m, 6H), 6.44 (s, 1H), 4.86 (s, 2H), 4.62 (s, 2H), 4.32 (q, *J*=7.5 Hz, 2H),

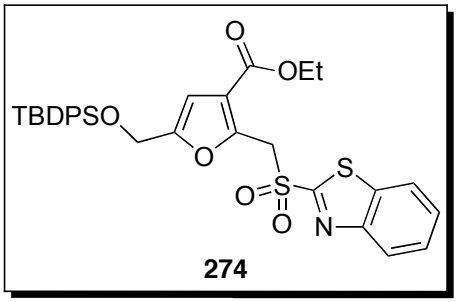
1.37 (t, *J*=7.5 Hz, 3H) , 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 154.7, 154.4, 135.8, 133.2, 130.1, 128.0, 117.2,108.7, 60.9, 58.8, 35.9, 27.0, 19.5, 14.5; IR (NaCl thin film): 2932(w), 2858(w), 1718(s), 1270(m), 1069(s), 702(s); HRMS (ESI–APCI) *m*/*z* calcd. for $C_{15}H_{14}O_3$ [M–OTBDPS]$^+$: 243.1016, found: 243.1022



273

Chloride **271** (2.19 g, 4.8 mmol) and 2-mercaptobenzothiazole (0.825 g, 4.9 mmol) were dissolved in CH_2Cl_2 (25 mL). Then Et_3N (0.7 mL, 5.0 mmol) was added and the reaction was heated to reflux overnight. The reaction was concentrated and the residue dissolved in EtOAc. The organic layer was washed with NaOH 1x, HCl 1x, and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was flashed in 20:1 – 4:1 hexanes:EtOAc. The sulfide **273** was isolated in >95% yield.

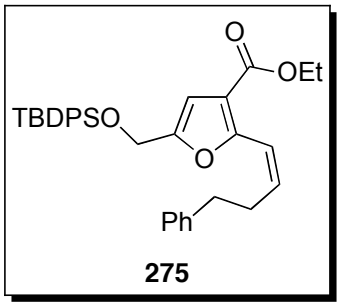
273: R_f = 0.41, 4:1 hexanes:EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J*=8.1 Hz, 1H), 7.75 (d, *J*=8.5 Hz, 1H), 7.67–7.64 (m, 4H), 7.44–7.26 (m, 8H), 6.44 (s, 1H), 4.96 (s, 2H), 4.57 (s, 2H), 4.30 (q, *J*=7.1 Hz, 2H), 1.34 (t, *J*=7.1 Hz, 3H) , 1.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 163.4, 154.9, 154.0, 153.4, 135.8, 133.2, 130.0, 128.0, 126.3, 124.6, 122.0, 121.2, 117.0, 108.7, 60.8, 58.8, 29.5, 26.9, 19.4, 15.4; IR (NaCl thin film): 2958(m), 2931(m), 2857(m), 1717(s), 1428(s), 1065(s), 702(s); HRMS (ESI–APCI) *m*/*z* calcd. for $C_{32}H_{34}NO_4S_2Si$ [M+H]$^+$: 588.1693, found: 588.1693



274

The sulfide **273** (4.8 mmol) was dissolved in CH_2Cl_2 (25 mL) and *m*CPBA (2.1 g, 9.6 mmol) was added. Reaction was allowed to stir overnight. The reaction was concentrated. The residue was dissolved in EtOAc and was washed with $Na_2S_2O_3$ 3x, $NaHCO_3$ 3x, dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was flashed in 20:1 – 4:1 hexanes:EtOAc. The sulfone **274** was isolated in about 70% yield.

274: R_f = 0.30, 4:1 hexanes:EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J*=8.0 Hz, 1H), 7.86 (d, *J*=8.1 Hz, 1H), 7.64–7.52 (m, 6H), 7.46–7.37 (m, 6H), 6.48 (s, 1H), 5.19 (s, 2H), 4.47 (s, 2H), 4.03 (q, *J*=7.1 Hz, 2H), 1.22 (t, *J*=7.1 Hz, 3H) , 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 162.3, 156.0, 152.7, 145.2, 137.3, 135.6, 132.9, 129.0, 128.1, 127.8, 127.6, 125.6, 122.3, 120.3, 108.7, 60.8, 58.5, 54.0, 26.7, 19.2, 14.1; IR (NaCl thin film): 2931(w), 2858(w), 1718(s), 1344(s), 1066(s), 703(s); HRMS (ESI–APCI) *m*/*z* calcd. for $C_{32}H_{34}NO_6S_2Si$ $[M+H]^+$: 620.1591, found: 620.1593

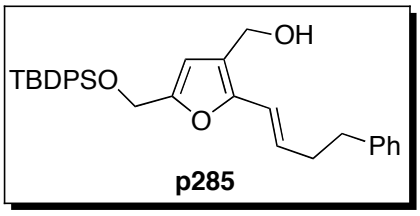


275

LiHMDS (2.85 mL, 3.05 mmol) was stirred in THF (20 mL) and cooled to –78 ºC. Then sulfone **274** (1.744 g, 2.9 mmol) in THF (25 mL) was added slowly and reaction was stirred for a further 30 min. Then aldehyde **266** (0.45 mL, 3.05 mmol) was added and reaction was allowed to slowly warm to room temperature. Reaction was quenched with H_2O and the aqueous layer was extracted with Et_2O 2x. The combined organics were washed with H_2O 2x, dried over $MgSO_4$ and concentrated *in*

vacuo. After flashing the crude material in 20:1 hexanes:EtOAc **275** was isolated in around 80% yield.

275: R_f = 0.5, 4:1 hexanes:EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.68 (m, 4H), 7.46–7.27 (m, 7H), 7.25–7.15 (m, 4H), 6.92 (dt, *J*=12.0, 1.6 Hz, 1H), 6.48 (s, 1H), 5.85 (dt, *J*=12.0, 7.3 Hz, 1H), 4.63 (s, 2H), 4.30 (q, *J*=7.1 Hz, 2H), 2.95–2.89 (m, 2H), 2.80 (dd, *J*=7.8 Hz, 2H), 1.36 (t, *J*=7.1 Hz, 3H) , 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 157.1, 152.8, 141.8, 135.8, 133.3, 130.0, 128.7, 128.6, 128.0, 126.1, 116.6, 115.4, 109.1, 60.5, 59.0, 35.9, 31.6, 27.0, 19.5, 14.6; IR (NaCl thin film): 2958(m), 2931(m), 2858(m), 1712(s), 1427(m), 1229(m), 1208(m), 1061(s), 700(s); HRMS (ESI–APCI) *m*/*z* calcd. for $C_{34}H_{38}NaO_4Si$ $[M+Na]^+$: 561.2432, found: 561.2436

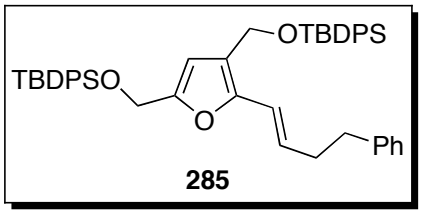


p285

Ester **268** (0.63 g, 1.17 mmol) was dissolved in THF (24 mL) and cooled to 0 ºC. Then LAH (0.093 g, 2.34 mmol) was added in one portion. When reaction appeared complete by TLC it was carefully quenched with saturated Na_2SO_4. The mixture was filtered, dried with Na_2SO_4 and concentrated *in vacuo*. The material was flashed in 2:1 hexanes:EtOAc. The purified alcohol **p285** was isolated in around 73% yield.

p285: R_f = 0.3, 2:1 hexanes:EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.68 (m, 4H), 7.45–7.35 (m, 6H), 7.32–7.28 (m, 2H), 7.23–7.18 (m, 3H), 6.29–6.14 (m, 3H), 4.62 (s, 2H), 4.46 (d, *J*=5.7 Hz, 2H), 2.79 (app t, *J*=8.2, 7.4 Hz, 2H), 2.52 (app q, *J*=7.7, 7.1 Hz , 2H), 1.22 (t, *J*=5.7 Hz, 1H) , 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 149.1, 141.6, 135.6, 134.8, 133.4, 129.7, 129.5, 128.4, 127.7, 125.9, 120.6, 116.8, 109.5, 59.0,

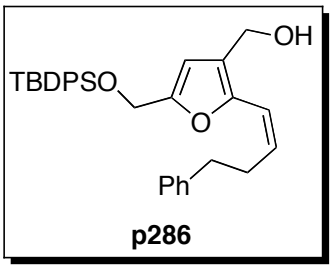
56.3, 35.8, 34.9, 26.8, 19.3; IR (NaCl thin film): 3341(w), 3070(w), 3026(w), 2930(m), 2557(m), 1112(s), 1069(m), 701(s); HRMS (ESI–APCI) *m/z* calcd. for $C_{16}H_{17}O_2$ [M–OTBDPS]$^+$: 241.1223, found: 241.122



285

Alcohol **p285** (60 mg, 0.12 mmol) was stirred in CH_2Cl_2 (8 mL) at room temperature. Then DMAP, Et_3N (0.02 mL, 0.144 mmol), and TBDPSCl (0.034 mL, 0.132 mmol) were added successively and the reaction was stirred overnight. The reaction was concentrated and the residue was dissolved in Et_2O and washed with H_2O 2x, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was flashed in 4:1 hexanes:EtOAc. The protected alcohol **285** was isolated in 85% yield.

285: R_f = 0.41, 20:1 hexanes:EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73–7.65 (m, 8H), 7.45–7.32 (m, 12H), 7.30–7.18 (m, 5H), 6.20–6.03 (m, 3H), 4.60 (s, 2H), 4.53 (s, 2H), 2.74–2.68 (m, 2H), 2.45–2.38 (m, 2H), 1.06 (s, 9H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4, 148.2, 141.8, 135.4, 133.7, 133.6, 130.1, 130.0, 129.6, 128.5, 128.4, 127.8, 126.0, 121.0, 117.6, 109.7, 59.2, 57.9, 36.0, 35.0, 27.0, 19.4; IR (NaCl thin film): 3307(w), 2929(m), 2856(m), 1112(s), 1053(m), 700(s); HRMS (ESI–APCI) *m/z* calcd. for $C_{32}H_{35}O_2Si$ [M–OTBDPS]$^+$: 479.2401, found: 479.2409

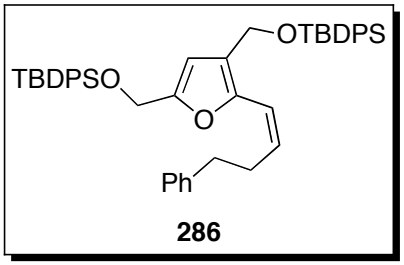


p286

Ester **275** (0.119 g, 0.22 mmol) was dissolved in THF (5 mL) and cooled to 0 ºC. Then LAH (0.0175 g, 0.44 mmol) was added in one portion. When reaction appeared complete by TLC it was carefully quenched with saturated Na_2SO_4. The mixture was filtered, dried with Na_2SO_4 and concentrated *in vacuo*. The

material was flashed in 2:1 hexanes:EtOAc. The purified alcohol **p286** was isolated in around 90% yield.

p286: R_f = 0.3, 2:1 hexanes:EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.68 (m, 4H), 7.44–7.28 (m, 7H), 7.25–7.17 (m, 4H), 6.19–6.16 (m, 2H), 6.00 (dt, *J*=11.8, 7.4, 7.1 Hz, 1H), 4.64 (s, 2H), 4.48 (s, 2H), 2.92–2.86 (m, 2H), 2.80–2.76 (m, 2H), 1.29 (s, 1H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 149.8, 142.0, 135.8, 133.5, 130.6, 129.9, 128.57, 128.5, 127.9, 126.0, 123.1, 114.9, 109.3, 59.2, 56.6, 36.1, 31.1, 26.9, 19.4; IR (NaCl thin film): 3307(w), 3026(w), 2929(m), 2856(m), 1427(m), 1112(s), 700(s); HRMS (ESI–APCI) *m/z* calcd. for $C_{32}H_{36}NaO_3Si$ $[M+Na]^+$: 519.2326, found: 519.2327

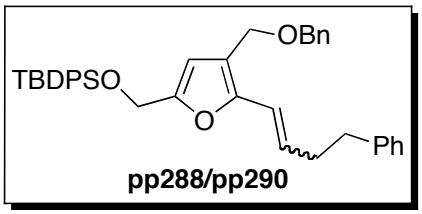


286

Alcohol **p286** (49 mg, 0.1 mmol) was stirred in CH_2Cl_2 (2 mL) at room temperature. Then DMAP, Et_3N (0.02 mL, 0.17 mmol), and TBDPSCl (0.04 mL, 0.15 mmol) were added successively and the reaction was stirred overnight. The reaction was concentrated and the residue was dissolved in Et_2O and washed with H_2O 2x, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was flashed in 4:1 hexanes:EtOAc. The protected alcohol **286** was isolated in 67% yield.

286: R_f = 0.41, 20:1 hexanes:EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73–7.67 (m, 8H), 7.44–7.33 (m, 12H), 7.24–7.14 (m, 5H), 6.20 (s, 1H), 5.95 (dt, *J*=11.8, 1.5, 1.3 Hz, 1H), 5.44 (dt, *J*=11.8, 7.3 Hz, 1H), 4.64 (s, 2H), 4.55 (s, 2H), 2.87–2.81 (m, 2H), 2.77–2.70 (m, 2H), 1.06 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 148.8, 142.2, 135.8, 133.8, 133.6, 129.9, 129.4, 128.8, 128.5, 127.9, 125.9, 123.5, 115.5, 109.5, 59.3, 58.0, 36.2, 31.1, 26.9, 19.4; IR (NaCl thin film): 3307(w), 2929(m), 2856(m), 1112(s), 1053(m),

700(s); HRMS (ESI–APCI) *m*/*z* calcd. for $C_{32}H_{35}O_2Si$ [M–OTBDPS]$^+$: 479.2401, found: 479.2409



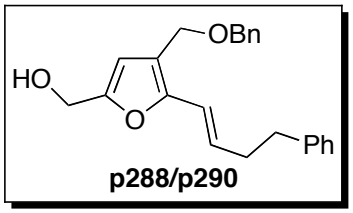
pp288/pp290

The same method was used on both the *cis*- and *trans*-isomers. The alcohol **p285/p286** (0.065 g, 0.13 mmol) and benzyl bromide (0.017 mL, 0.14 mmol) were dissolved in THF (6 mL) and cooled to 0 ºC. NaH (0.006 g, 0.14 mmol) was added and reaction was allowed to warm to room temperature and stirred overnight. The reaction was quenched with H_2O and the aqueous layer was extracted with Et_2O 2x. The combined organics were washed with H_2O, brine, dried over $MgSO_4$ and concentrated *in vacuo*. The material was flashed in 50:1 – 20:1 hexanes:EtOAc and **p288/p290** were isolated in 70–80% yield.

pp288: R_f = 0.75, 4:1 hexanes:EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.69 (m, 4H), 7.44–7.28 (m, 12H), 7.23–7.18 (m, 4H), 6.23–6.11 (m, 3H), 4.62 (s, 2H), 4.45 (s, 2H), 4.34 (s, 2H), 2.79–2.75 (m, 2H), 2.53–2.48 (m, 2H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 150.1, 141.9, 138.5, 135.9, 133.6, 129.9, 129.5, 128.8, 128.6, 128.1, 127.9, 126.1, 118.1, 117.3, 110.3, 71.6, 63.0, 59.2, 36.0, 35.1, 27.0, 19.5; IR (NaCl thin film): 3068(w), 3027(w), 2926(m), 2855(m), 1452(s), 1428(m), 699(s); HRMS (ESI–APCI) *m*/*z* calcd. for $C_{23}H_{23}O_2$ [M–OTBDPS]$^+$: 331.1693, found: 331.1688

pp290: R_f = 0.75, 4:1 hexanes:EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.68 (m, 4H), 7.43–7.28 (m, 12H), 7.23–7.15 (m, 4H), 6.20 (s, 1H), 6.11 (d, *J*=11.8 Hz, 1H), 5.55 (dt, *J*=11.8, 7.4, 7.2 Hz, 1H), 4.64 (s, 2H), 4.46 (s, 2H), 4.36 (s, 2H), 2.91–2.86 (m, 2H), 2.79–2.76 (m, 2H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 150.6, 142.1,

138.4, 135.8, 133.5, 130.3, 130.0, 128.7, 128.6, 128.5, 128.1, 127.9, 127.8, 126.0, 120.5, 115.2, 109.9, 71.8, 63.2, 59.3, 36.2, 31.1, 26.9, 19.4; IR (NaCl thin film): 3027(w), 2927(m), 2856(m), 1112(m), 1064(m), 700(s); HRMS (ESI–APCI) *m*/*z* calcd. for $C_{23}H_{23}O_2$ $[M–OTBDPS]^+$: 331.1693, found: 331.1698



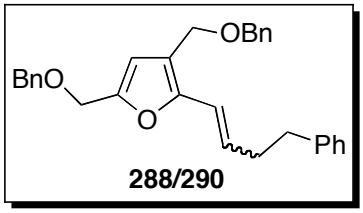
p288/p290

The same method was used on both the *cis*- and *trans*-isomers. Silyl ethers **pp288/pp290** (0.525 g, 0.9 mmol) were dissolved in THF (24 mL) and cooled to 0 ºC. Then TBAF (1.8 mL, 1.8 mmol) was added and reaction was allowed to stir for 30 min. Additional TBAF was added until all starting material was consumed by TLC. The reaction was quenched with H_2O and the aqueous layer was extracted with Et_2O 2x. The combined organics were washed with H_2O, brine, dried over $MgSO_4$ and concentrated *in vacuo*. The material was flashed in 2:1 – 1:1 hexanes:EtOAc and alcohols **p288/p290** were obtained in 50–80% yield.

p288: R_f = 0.09, 4:1 hexanes:EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.28 (m, 7H), 7.22–7.18 (m, 3H), 6.36–6.19 (m, 3H), 4.58 (d, *J*=5.4 Hz, 2H), 4.49 (s, 2H), 4.36 (s, 2H), 2.77 (app t, *J*=8.0, 7.6 Hz, 2H), 2.54–2.48 (m, 2H), 1.65 (t, *J*=6.0 Hz 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 150.6, 141.8, 138.4, 130.3, 128.6, 128.1, 127.9, 126.1, 118.3, 117.1, 110.8, 71.9, 63.0, 57.9, 35.9, 35.1; IR (NaCl thin film): 3420(w), 3026(w), 2923(m), 2853(m), 1066(m), 698(s); HRMS (ESI–APCI) *m*/*z* calcd. for $C_{23}H_{28}NO_3$ $[M+NH_4]^+$: 366.2064, found: 366.2058

p290: R_f = 0.09, 4:1 hexanes:EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.27 (m, 8H), 7.24–7.17 (m, 2H), 6.35 (s, 1H), 6.12 (d, *J*=11.8 Hz, 1H), 5.61 (dt, *J*=11.8, 7.4, 7.1 Hz,

1H), 4.60 (s, 2H), 4.50 (s, 2H), 4.37 (s, 2H), 2.91–2.85 (m, 2H), 2.81–2.77 (m, 2H), 1.61 (t, *J*=5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 150.9, 142.1, 138.3, 130.9, 128.6, 128.5, 128.4, 128.0, 127.8, 126.0, 120.6, 115.1, 110.3, 71.9, 63.1, 57.9, 36.0, 31.2; IR (NaCl thin film): 3423(w), 3062(w), 3026(w), 2924(m), 2854(m), 1452(s), 1065(m), 698(s); HRMS (ESI–APCI) *m*/*z* calcd. for $C_{23}H_{23}O_2$ $[M–OH]^+$: 331.1693, found: 331.1695

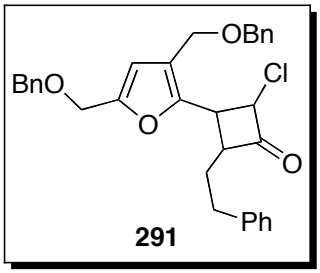


288/290

The alcohol **p290** (78 mg, 0.22 mmol), BnBr (0.03 mL, 0.25 mmol), and NaI were stirred in THF (5 mL) and cooled to 0 ºC. NaH (10 mg, 0.25 mmol) was added and reaction was allowed to warm to room temperature and stir overnight. The reaction was quenched with H_2O and the aqueous layer was extracted with Et_2O 2x. The combined organics were washed with H_2O, brine, dried over $MgSO_4$ and concentrated *in vacuo*. The material was flashed in 50:1 – 20:1 hexanes:EtOAc and **288/290** was isolated as a mixture in 70–80% yield.

288/290: R_f = 0.6, hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.27 (m, 11H), 7.26–7.16 (m, 4H), 6.40 (s, 0.4H), 6.36 (s, 0.6H), 6.33–6.20 (m, 1.2H), 6.14 (dt, *J*=11.8, 1.5 Hz, 0.4H), 5.62 (dt, *J*=11.8, 7.5, 7.3 Hz, 0.4 H), 4.58 (s, 0.8H), 4.58 (s, 1.2H), 4.50 (s, 0.8H), 4.49 (s, 2H), 4.46 (s, 1.2H), 4.39 (s, 0.8H), 4.38 (s, 1.2H), 2.95–2.89 (m, 0.8H), 2.82–2.76 (m, 2H), 2.54–2.49 (m, 1.2H); ^{13}C NMR (100 MHz, $CDCl_3$) *cis*–isomer δ 151.2, 150.5, 142.1, 138.1, 131.0, 128.7, 128.6, 128.5, 128.1, 128.0, 127.9, 126.0, 120.5, 115.1, 111.9, 72.1, 71.9, 64.2, 63.1, 36.0, 31.2 *trans*–isomer δ 151.0, 150.8, 141.8, 138.4, 130.3, 128.7, 128.6, 128.5, 128.1, 128.0, 127.9, 126.1, 118.2, 117.1, 112.4, 72.0,

71.7, 64.1, 62.9, 35.8, 35.0; IR (NaCl thin film): 3026(w), 2852(m), 1452(m), 1063(s), 734(m), 696(s); HRMS (ESI–APCI) *m/z* calcd. for $C_{23}H_{23}O_2$ $[M–OBn]^+$: 331.1693, found: 331.1697

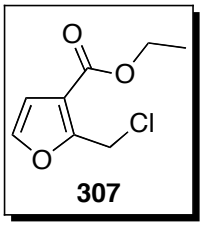


291

To a solution of **288/290** (0.037 g, 0.084 mmol), zinc (0.055 g, 0.84 mmol) (activated by heating to 150 ºC for 3–18h), DME (0.03 mL, 0.25 mmol) in diethyl ether (3 mL) at reflux was added trichloroacetyl chloride (0.03 mL, 0.25 mmol) in diethyl ether (1 mL) dropwise via a syringe pump. When TLC showed consumption of **288/290** a solution of 3% NH_4Cl in MeOH (0.5 mL) was added. After 20 min the reaction was cooled and filtered through celite. The filtrate was washed repeatedly (5x) with dilute sodium bicarbonate solutions then dried over $MgSO_4$. Concentration *in vacuo* yielded **291** in 86% crude yield.

291: R_f = 0.6, hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ diastereomers a, b: 7.36–7.28 (m, 10H), 7.22–7.12 (m, 3H), 7.07–6.97 (m, 2H), 6.39 (s, 0.7H), 6.37 (s, 0.3H), 5.40 (dd, *J*=10.4, 2.8 Hz, 0.7H), 5.05 (dd, *J*=9.2, 2.7 Hz, 0.3H), 4.57–4.35 (m, 8H), 3.81 (dd, *J*=10.5, 7.6 Hz, 0.7H), 3.33 (dd, *J*=9.2, 8.5 Hz, 0.3H), 2.68–2.60 (m, 0.6H), 2.55–2.42 (m, 1.4H), 2.15–1.69 (m, 2H); diastereomer c: 7.36–7.28 (m, 5H), 7.26 (s, 5H), 7.22–7.13 (m, 3H), 7.02 (d, *J*=7.8 Hz, 2H), 6.36 (s, 1H), 5.10 (d, *J*=9.7 Hz, 1H), 4.53 (s, 4H), 4.49–4.35 (m, 4H), 4.10–4.05 (m, 1H), 3.52–3.45 (m, 1H), 2.58–2.54 (m, 2H), 2.18–2.09 (m, 1H), 1.82–1.73 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ diastereomers a, b: 202.6, 151.5, 147.7, 140.5, 137.9, 128.5, 127.9, 126.2, 121.1, 111.9, 72.2, 72.1, 63.9, 63.5, 63.0, 60.6, 37.8, 33.1, 28.7; δ diastereomer c: 200.5, 152.5, 147.5, 140.8, 138.1, 128.5, 127.9, 126.2,

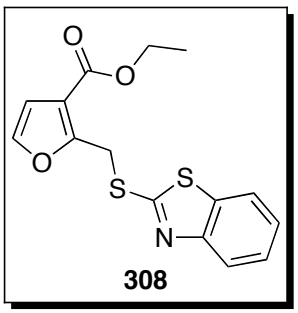
122.9, 110.9, 71.8, 63.7, 63.0, 61.9, 58.1, 33.7, 33.4, 27.1; IR (NaCl thin film): 3086(w), 3062(w), 3028(m), 2922(s), 2855(s), 1794(s), 1453(m), 1066(s), 697(s); HRMS (ESI–APCI) *m*/*z* calcd. for $C_{32}H_{35}ClNO_4$ $[M+NH_4]^+$: 532.2249, found: 532.2254



307

The β-ketoester **269** (16.1 mL, 100 mmol) was stirred in 250 mL of H_2O, K_2CO_3 (15.2 g, 110 mmol) was added and reaction was stirred for 5 min before addition of chloroacetaldehyde **306** (25.8 mL, 200 mmol). The aqueous solution was extracted with CH_2Cl_2 and *p*TSA (3.8 g, 20 mmol) was added and reaction was stirred overnight. The organic layer was washed with H_2O and dried over $MgSO_4$. Concentration *in vacuo* yielded **307** in 77% crude yield.

307: R_f = 0.48, 4:1 hexanes:EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J*=1.9 Hz, 1H), 6.70 (d, *J*=1.9 Hz, 1H), 4.91 (s, 2H), 4.32 (q, *J*=7.1 Hz, 2H), 1.36 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 155.0, 142.8, 116.6, 111.3, 60.9, 35.6, 14.3; IR (NaCl thin film): 2983(w), 1719(s), 1308(s), 1061(s), 750(m); HRMS (ESI–APCI) *m*/*z* calcd. for $C_8H_{10}ClO_3$ $[M+H]^+$: 189.0313, found: 189.0312

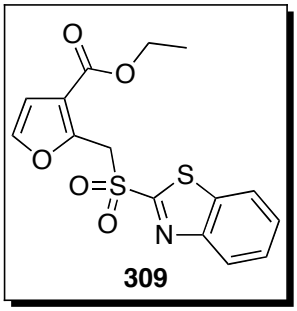


308

Chloride **307** (0.988 g, 5.24mmol), DMAP and 2-mercaptobenzothiazole (0.902 g, 5.4 mmol) were dissolved in CH_2Cl_2 (25 mL). Then Et_3N (0.76 mL, 5.5 mmol) was added and the reaction was stirred overnight. The reaction was concentrated and the residue dissolved in EtOAc. The organic

layer was washed with NaOH 1x, HCl 1x, and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was flashed in 10:1 hexanes:EtOAc. The sulfide **308** was isolated in 91% yield.

308: R_f = 0.37, 4:1 hexanes:EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J*=8.1 Hz, 1H), 7.77 (d, *J*=8.5 Hz, 1H), 7.46–7.41 (m, 1H), 7.33–7.27 (m, 1H), 6.71 (d, *J*=2.0 Hz, 1H), 5.01 (s, 2H), 4.32 (q, *J*=7.1 Hz, 2H), 1.36 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 163.2, 155.6, 153.2, 142.2, 135.7, 126.2, 124.5, 121.9, 121.1, 116.1, 111.2, 60.8, 29.2, 14.4; IR (NaCl thin film): 3126(w), 3060(w), 2979(w), 1712(s), 1601(w), 1427(s), 1304(s), 1174(m), 993(m), 726(m); HRMS (ESI–APCI) *m*/*z* calcd. for $C_{15}H_{14}NO_3S_2$ $[M+H]^+$: 320.0410, found: 320.0413

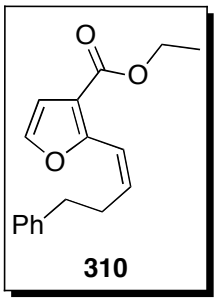


309

The sulfide **308** (2.34 g, 8.92 mmol) was dissolved in CH_2Cl_2 (50 mL) and *m*CPBA (3.89 g, 17.84 mmol) was added. Reaction was allowed to stir overnight. The reaction was concentrated. The residue was dissolved in EtOAc and was washed with $Na_2S_2O_3$ 3x, $NaHCO_3$ 3x, dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was flashed in 20:1 – 4:1 hexanes:EtOAc. The sulfone **309** was isolated in about 76% yield.

309: R_f = 0.18, 4:1 hexanes:EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (app d, *J*=8.8 Hz, 1H), 7.99 (d, *J*=8.8 Hz, 1H), 7.66–7.57 (m, 2H), 7.37 (d, *J*=1.9 Hz, 1H), 6.70 (d, *J*=1.9 Hz, 1H), 5.25 (s, 2H), 4.01 (q, *J*=7.1 Hz, 2H), 1.20 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 162.4, 152.8, 146.2, 144.3, 137.5, 128.3, 127.8, 125.8, 122.4, 119.9, 111.7, 61.0, 53.9, 14.2; IR (NaCl thin film): 3146(w), 3124(w), 2986(w), 2922(w),

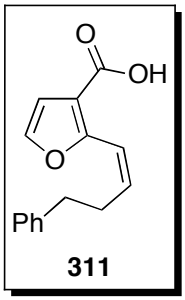
1712(s), 1333(s), 1314(s), 1200(s), 1119(s), 765(s); HRMS (ESI–APCI) *m*/*z* calcd. for $C_{15}H_{14}NO_5S_2$ $[M+H]^+$: 352.0308, found: 352.0307



310

LiHMDS (0.61 mL, 0.657 mmol) was stirred in THF (5 mL) and cooled to –78 ºC. Then sulfone **309** (0.22 g, 0.626 mmol) in THF (5 mL) was added slowly and reaction was stirred for a further 30 min. Then aldehyde **266** (0.1 mL, 0.657 mmol) was added and reaction was allowed to slowly warm to room temperature. Reaction was quenched with H_2O and the aqueous layer was extracted with Et_2O 2x. The combined organics were washed with H_2O 2x, dried over $MgSO_4$ and concentrated *in vacuo*. After flashing the crude material in 20:1 hexanes:EtOAc **275** was isolated in around 88% yield.

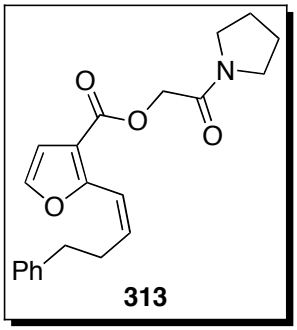
310: R_f = 0.63, 4:1 hexanes:EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J*=1.9 Hz, 1H), 7.32–7.28 (m, 2H), 7.26–7.18 (m, 3H), 6.94 (dt, *J*=12.0, 1.6 Hz, 1H), 6.73 (d, *J*=1.9 Hz, 1H), 5.88 (dt, *J*=12.0, 7.4, 7.3 Hz, 1H), 4.31 (q, *J*=7.1 Hz, 2H), 2.96–2.90 (m, 2H), 2.83–2.79 (m, 2H), 1.36 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 157.4, 141.8, 141.0, 135.7, 128.5, 128.4, 126.0, 116.4, 114.8, 111.5, 60.4, 35.8, 31.5, 14.5; IR (NaCl thin film): 3085(w), 3027(w), 2987(w), 2931(w), 2858(w), 1712(s), 1298(s), 1276(s), 1182(s), 737(m); HRMS (ESI–APCI) *m*/*z* calcd. for $C_{17}H_{19}O_3$ $[M+H]^+$: 271.1329, found: 271.1331



311

The ester **310** (0.055 g, 0.2 mmol) was refluxed in 5 mL of 20% NaOH solution for 2 h. The reaction was cooled and carefully quenched with 1M HCl until acidic. The aqueous layer was extracted with EtOAc 3x. The combined organics were dried over $MgSO_4$ and concentrated *in vacuo* to give **311** in <95% yield. The material was clean by ^{1}H NMR and was carried on crude.

311: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J*=1.9 Hz, 1H), 7.33–7.28 (m, 2H), 7.25–7.18 (m, 3H), 6.95 (dt, *J*=12.0, 1.5 Hz, 1H), 6.77 (d, *J*=1.9 Hz, 1H), 5.93 (dt, *J*=12.0, 7.4, 7.3 Hz, 1H), 2.97–2.91 (m, 2H), 2.84–2.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 158.8, 141.7, 141.3, 136.9, 128.5, 126.1, 116.3, 113.9 111.6, 35.8, 31.6; IR (NaCl thin film): 3156(w), 3061(w), 3026(w), 2923(w), 2665(w), 2567(w), 1677(s), 1560(m), 1303(m), 737(m); HRMS (ESI–APCI) *m*/*z* calcd. for $C_{15}H_{13}O_3$ $[M–H]^–$: 241.0870, found: 241.0868

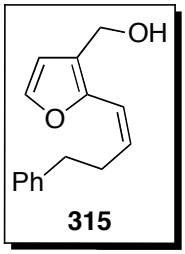


313

Mesylate **312** (0.28 g, 1.35 mmol), acid **311** (0.28 g, 1.17 mmol), and Cs_2CO_3 (0.42 g, 1.29 mmol), were stirred in DMF (5 mL) overnight. The reaction was diluted with CH_2Cl_2 and washed with H_2O. The combined organics were dried with $MgSO_4$ and concentrated *in vacuo*. The crude material was flashed in 1:1 hexanes:EtOAc and **313** was obtained in 14% yield.

313: R_f = 0.73, EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J*=1.8 Hz, 1H), 7.31–7.27 (m, 2H), 7.24–7.17 (m, 3H), 6.98 (app d, *J*=11.8 Hz, 1H), 6.79 (d, *J*=1.9 Hz, 1H), 5.88

(dt, *J*=12.0, 7.4, 7.2 Hz, 1H), 4.79 (s, 2H), 3.52 (t, *J*=6.9 Hz, 2H), 3.44 (t, *J*=6.8 Hz, 2H), 2.94–2.88 (m, 2H), 2.81–2.77 (m, 2H), 2.00 (quint., *J*=6.8, 6.7 Hz, 2H), (1.87 (quint., *J*=6.8, 6.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 165.1, 163.0, 158.2, 141.8, 141.1, 136.2, 128.5, 128.4, 126.0, 116.5, 113.9, 111.6, 62.0, 46.1, 45.4, 35.8, 31.6, 26.3, 24.0; IR (NaCl thin film): 2924(w), 2874(w), 1716(m), 1668(s), 1447(m), 1297(m), 1275(m), 1169(m); HRMS (ESI–APCI) *m*/*z* calcd. for $C_{21}H_{24}NO_4$ $[M+H]^+$: 354.17, found: 354.1703

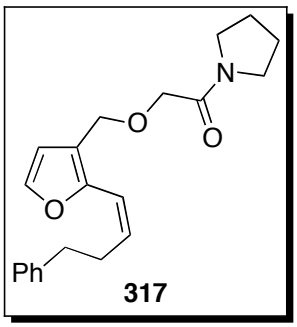


315

Ester **310** (0.709 g, 2.62 mmol) was dissolved in THF (20 mL) and cooled to 0 ºC. Then DIBAL-H (5.25 g, 5.25 mmol) was added until TLC showed consumption of **310**. The reaction was carefully quenched with Rochelle's salt solution and the mixture was stirred overnight. The aqueous layer was extracted with Et_2O 2x. The combined organics were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was flashed in 4:1 – 2:1 – 1:1 hexanes:EtOAc and **315** was isolated in 91% yield.

315: R_f = 0.16, 4:1 hexanes:EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J*=1.7 Hz, 1H), 7.33–7.19 (m, 5H), 6.46 (d, *J*=1.7 Hz, 0.8H), 6.43 (d, *J*=1.7 Hz, 0.2H), 6.35–6.23 (m, 0.4H), 6.22 (app d, *J*=11.8 Hz, 0.8), 5.63 (dt, *J*=11.8, 7.4, 7.2 Hz, 0.8H), 4.54 (s, 2H), 3.69 (t, *J*=6.4 Hz, 0.2H), 2.94–2.87 (m, 1.6H), 2.82–2.75 (m, 1.6H), 2.75–2.71 (m, 0.2H), 2.58–2.52 (m, 0.4H), 1.95–1.88 (m, 0.2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ *cis*-isomer: 150.2, 142.0, 141.6, 130.8, 128.6, 128.4, 125.9, 122.3, 114.8, 111.5, 56.5, 36.0, 31.1; *trans*–isomer: 149.7, 141.6, 141.3, 130.0, 128.6, 128.4, 126.0, 120.1, 117.0, 111.9, 56.3, 35.8, 35.0; IR (NaCl thin film): 3377(m), 3026(m), 2925(m), 2859(m), 1496(m),

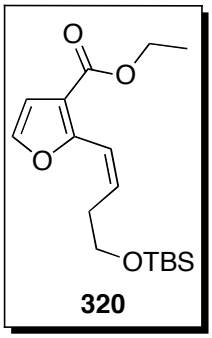
1454(m), 998(s), 735(s), 699(s); HRMS (ESI–APCI) *m*/*z* calcd. for $C_{15}H_{15}O$ $[M–OH]^-$: 211.1117, found: 211.1119



317

Alcohol **315** (0.274 g, 1.2 mmol) and bromide **316** (0.192 g, 1 mmol) were stirred in toluene (10 mL). Then a 35% NaOH solution (10 mL) and tetrabutylammonium hydrogensulfate (0.068 g, 0.2 mmol) were added and reaction was stirred for 3–5 h. The reaction was diluted with H_2O and the aqueous layer was extracted with Et_2O 2x. The combined organics were washed with saturated NH_4Cl solution 1x, dried over $MgSO_4$ and concentrated. The crude material was flashed in 1:1 – 1:2 – 0:1 hexanes:EtOAc and **317** was obtained in >95% yield.

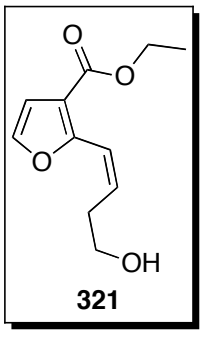
317: R_f = 0.58, EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J*=1.87 Hz, 1H), 7.32–7.18 (m, 5H), 6.46 (d, *J*=1.8 Hz, 1H), 6.24 (app d, *J*=11.8 Hz, 1H), 5.64 (dt, *J*=11.8, 7.4, 7.2 Hz, 1H), 4.53 (s, 2H), 4.04 (s, 2H), 3.51 (t, *J*=6.8 Hz, 2H), 3.35 (t, *J*=6.7 Hz, 2H), 2.94–2.88 (m, 2H), 2.81–2.77 (m, 2H), 1.92 (quint., *J*=6.6 Hz, 2H), 1.80 (quint., *J*=6.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 151.3, 141.9, 141.4, 130.7, 128.4, 128.3, 125.8, 118.9, 114.7, 112.1, 68.7, 63.8, 45.8, 45.6, 35.9, 30.9, 26.1, 23.9; IR (NaCl thin film): 3025(w), 2949(m), 2873(m), 1450(s), 1128(m), 735(m), 700(m); HRMS (ESI–APCI) *m*/*z* calcd. for $C_{21}H_{25}NNaO_3$ $[M+Na]^+$: 362.1727, found: 362.1725



320

Sulfone **309** (0.583 g, 1.66 mmol) was stirred in THF (15 mL) and cooled to –78 ºC. Then LiHMDS (1.75 g, 1.75 mmol) was added slowly and reaction was stirred for a further 30 min. Then aldehyde **319** (0.39 g, 2.07 mmol) was added and reaction was allowed to slowly warm to room temperature. Reaction was quenched with H_2O and the aqueous layer was extracted with Et_2O 2x. The combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. After flashing the crude material in 20:1 hexanes:EtOAc **320** was isolated in around 75% yield.

320: R_f = 0.66, 4:1 hexanes:EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J*=1.9 Hz, 1H), 6.96 (dt, *J*=12.0, 1.7 Hz, 1H), 6.72 (d, *J*=1.9 Hz, 1H), 5.88 (dt, *J*=12.0, 7.5 Hz, 1H), 4.30 (q, *J*=7.1 Hz, 2H), 3.74 (t, *J*=7.1 Hz, 2H), 2.84–2.79 (m, 2H), 1.35 (t, *J*=7.1 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 157.4, 140.9, 132.9, 117.2, 114.8, 111.4, 62.7, 60.4, 33.5, 26.0, 18.4, 14.4, –5.2; IR (NaCl thin film): 2956(m), 2930(m), 2857(m), 1716(s), 1297(m), 1100(m), 836(m), 776(m), 738(m); HRMS (ESI–APCI) *m/z* calcd. for $C_{17}H_{29}O_4Si$ $[M+H]^+$: 325.183, found: 325.183

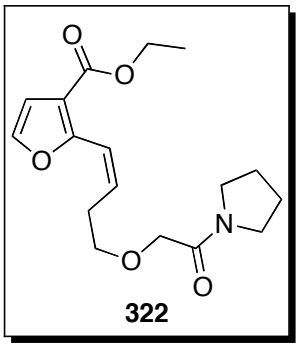


321

Silyl ether **320** (0.408 g, 1.26 mmol) was dissolved in THF (10 mL) and cooled to 0 ºC. Then TBAF (5 mL, 5.03 mmol) was added and reaction was allowed to stir for 30 min. Additional TBAF was added until all starting material was consumed by TLC. The reaction was quenched with H_2O and the aqueous layer was extracted with Et_2O 2x.

The combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. The material was flashed in 2:1 – 1:1 hexanes:EtOAc and alcohol **321** was obtained in 93% yield.

321: R_f = 0.1, 4:1 hexanes:EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J*=1.9 Hz, 1H), 7.01 (dt, *J*=12.0, 1.7 Hz, 1H), 6.72 (d, *J*=1.9 Hz, 1H), 5.86 (dt, *J*=12.0, 7.6 Hz, 1H), 4.29 (q, *J*=7.1 Hz, 2H), 3.78 (t, *J*=6.5 Hz, 2H), 2.89–2.84 (m, 2H), 1.84 (s, 1H), 1.34 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 157.1, 141.1, 132.2, 118.1, 115.1, 111.5, 62.4, 60.5, 33.3, 14.4; IR (NaCl thin film): 3409(m), 2982(m), 2934(m), 1712(s), 1300(s), 1182(s), 1050(s), 1036(s), 740(m); HRMS (ESI–APCI) *m*/*z* calcd. for $C_{11}H_{15}O_4$ $[M+H]^+$: 211.0965, found: 211.0967



322

Alcohol **321** (0.186 g, 0.88 mmol) and bromide **316** (0.142 g, 0.74 mmol) were stirred in toluene (10 mL). Then a 35% NaOH solution (10 mL) and tetrabutylammonium hydrogensulfate (0.061 g, 0.2 mmol) were added and reaction was stirred for 2 h. The reaction was diluted with H_2O and the aqueous layer was extracted with Et_2O 2x. The combined organics were washed with saturated NH_4Cl solution 1x, dried over $MgSO_4$ and concentrated. The crude material was flashed in 1:1 – 1:2 – 0:1 hexanes:EtOAc and **322** was obtained in 22% yield as a mixture of alkenes. There were also considerable amounts of the elimination product observed.

322: R_f = 0.36, 4:1 hexanes:EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J*=1.8 Hz, 0.8H), 7.23 (d, *J*=1.8 Hz, 0.2H), 7.04–6.97 (m, 1H), 6.72 (d, *J*=1.8 Hz, 0.8H), 6.67 (d, *J*=1.8 Hz, 0.2H), 6.50 (dt, *J*=16.0, 8.6, 7.2 Hz, 0.2H), 5.89 (dt, *J*=12.0, 7.3 Hz, 0.8H), 4.29 (q, *J*=7.1 Hz, 2H), 4.10 (s, 2H), 3.68 (t, *J*=6.6 Hz, 2H), 3.49 (t, *J*=6.9 Hz, 2H), 3.43 (t, *J*=6.7 Hz, 2H), 2.96–2.90 (m, 2H), 2.61–2.56 (m, 2H), 1.97–1.87 (m, 2H), 1.82–1.81 (m, 2H), 1.35 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ *cis*-isomer: 167.9, 163.5, 157.2, 141.1, 132.4, 117.5, 115.0, 111.1, 71.0, 70.8, 60.4, 45.9, 45.8, 30.7, 26.3, 24.0; *trans*-isomer: 167.9, 163.5, 157.2, 140.9, 131.9, 119.6, 115.0, 111.6, 70.9, 70.6, 60.4, 45.9, 45.8, 33.5, 26.3, 24.0; IR (NaCl thin film): 3394(m), 2975(w), 2929(w), 2872(w), 1710(m), 1646(m), 1136(s); HRMS (ESI–APCI) *m/z* calcd. for $C_{17}H_{24}NO_5$ $[M+H]^+$: 322.1649, found: 322.1651

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Appendix A2: Spectral Data Relevant to Chapter 2

Figure A2.1 1H NMR spectrum (400MHz, CDCl3) of compound **209**

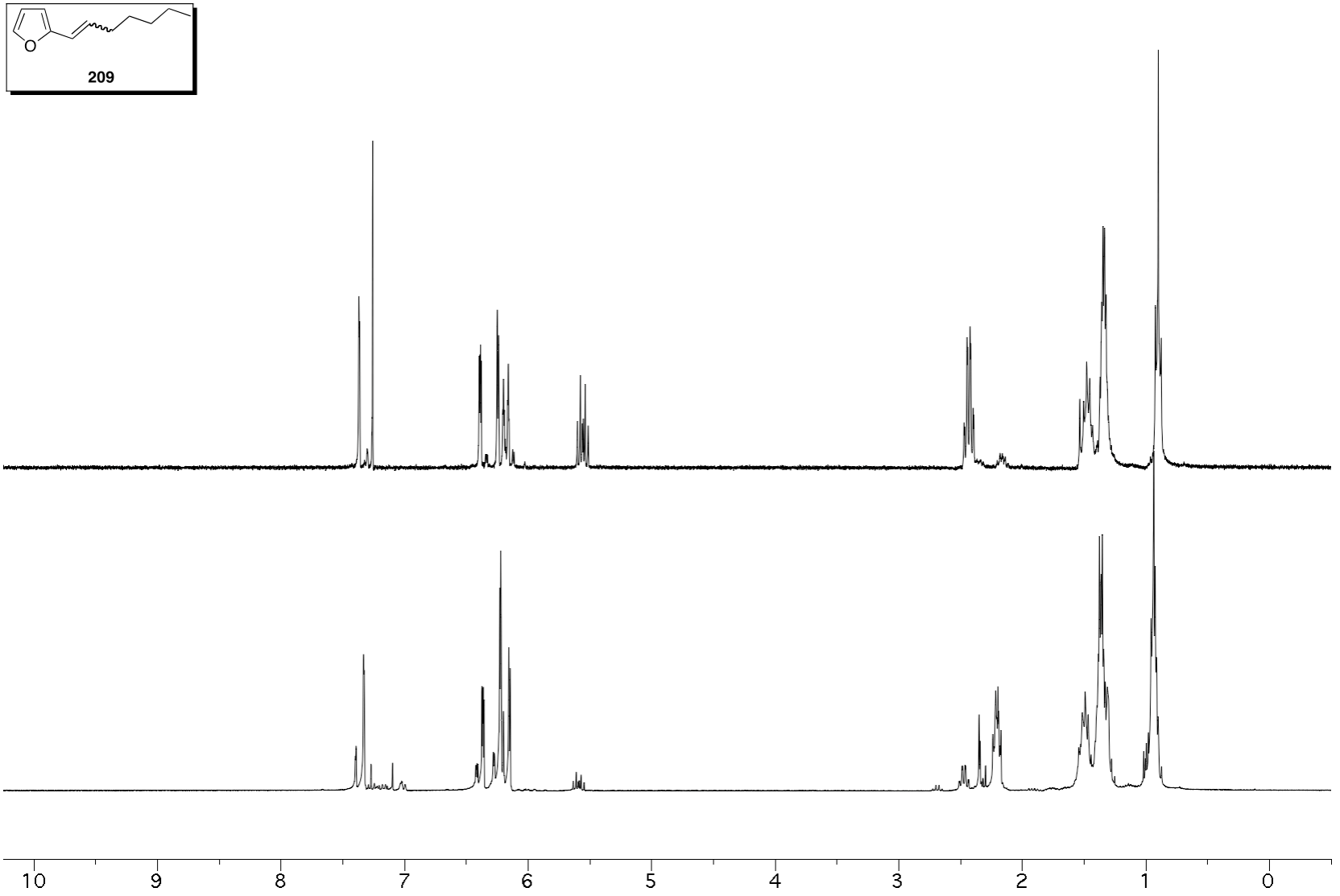


Figure A2.2 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **209**

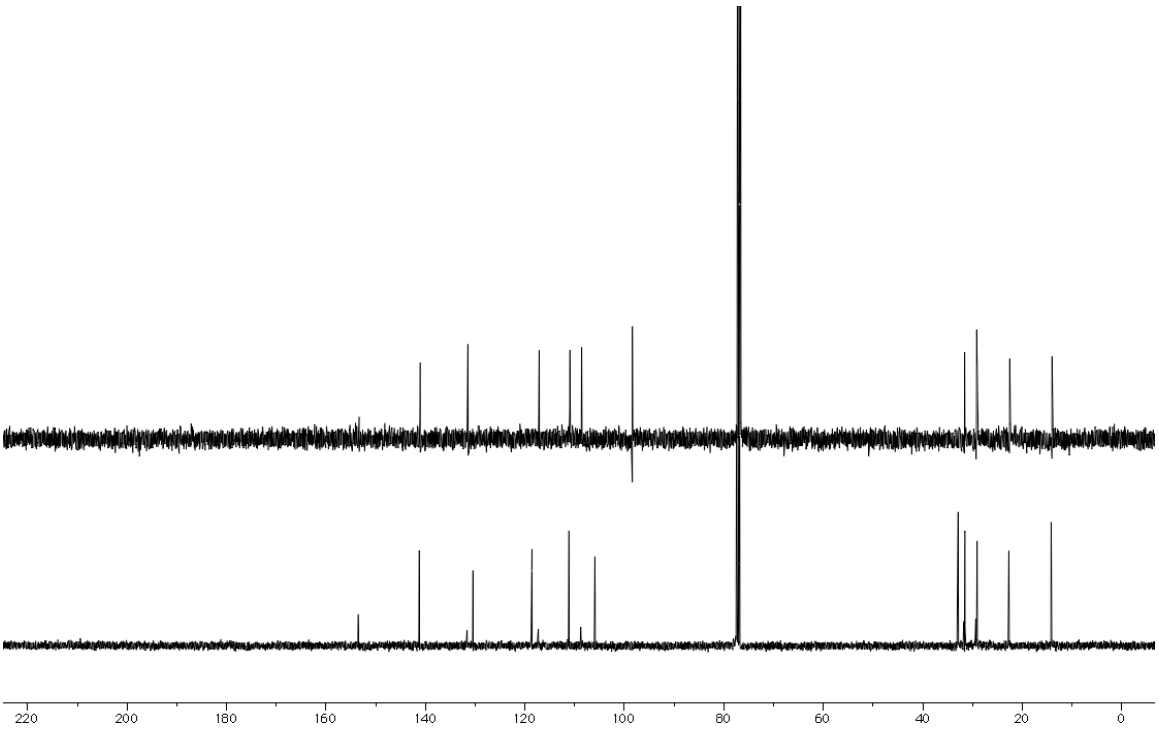


Figure A2.3 IR spectrum (thin film, NaCl) of compound **209**

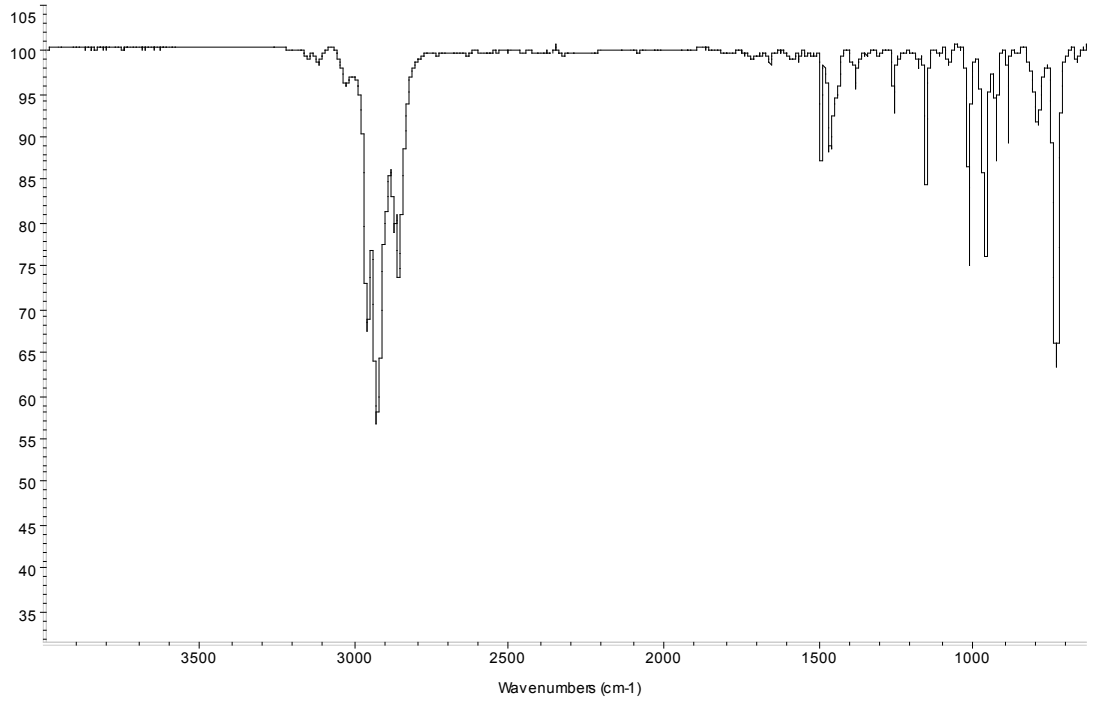
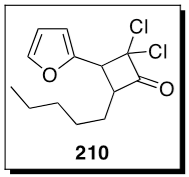


Figure A2.4 1H NMR spectrum (400MHz, CDCl3) of compound **210**



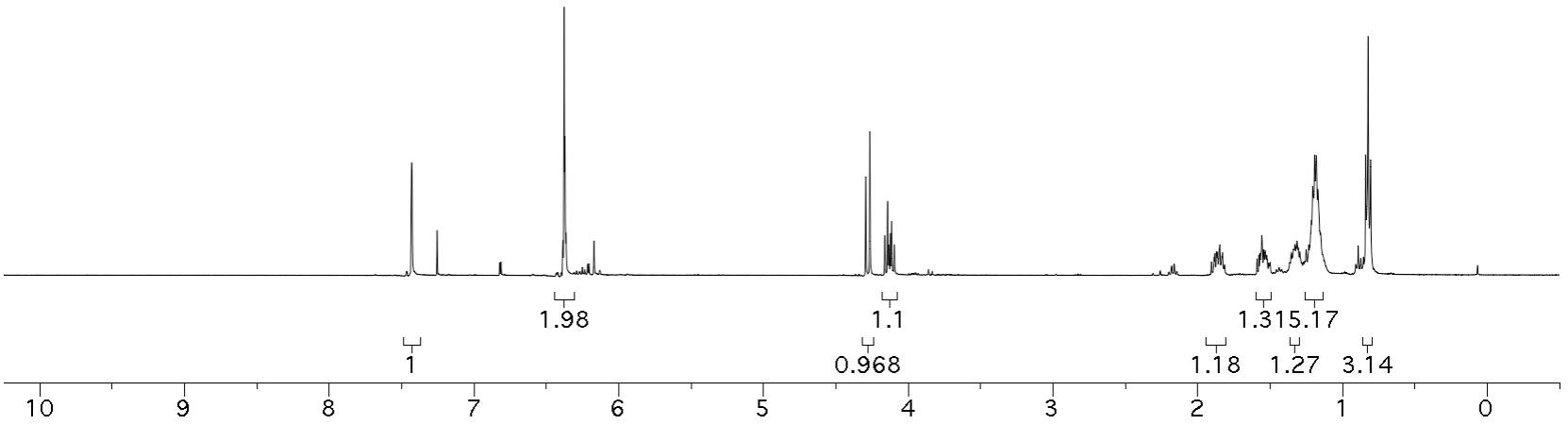


Figure A2.5 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **210**

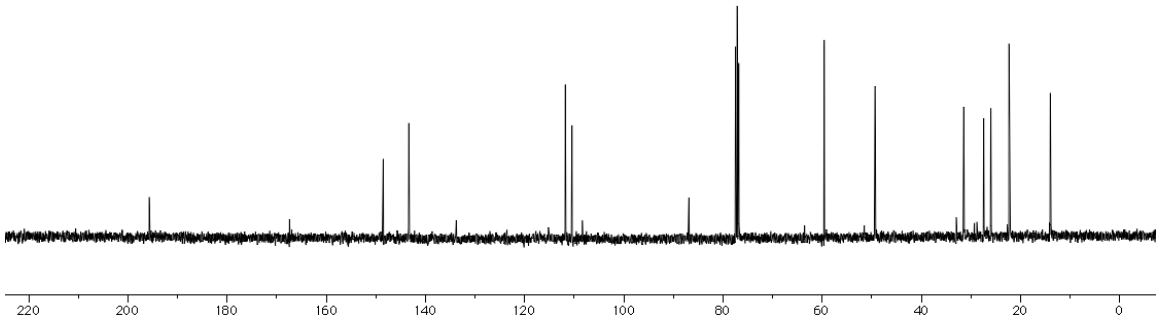


Figure A2.6 IR spectrum (thin film, NaCl) of compound **210**

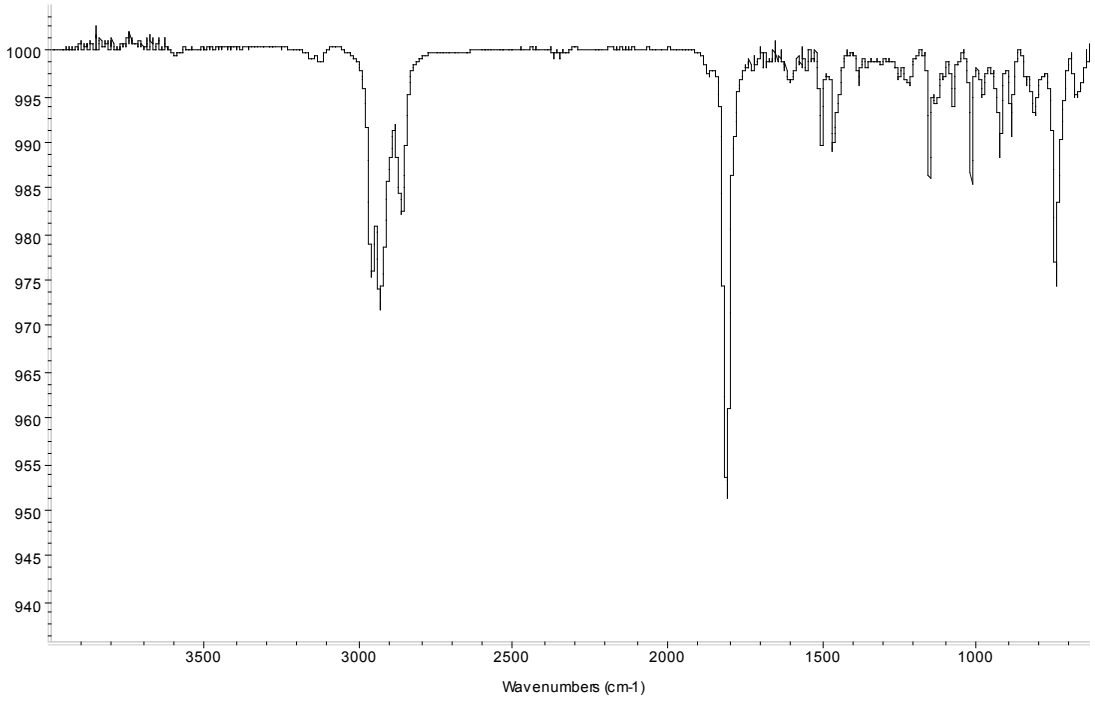
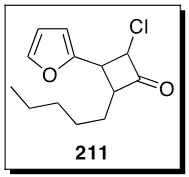


Figure A2.7 1H NMR spectrum (400MHz, CDCl3) of compound **211**



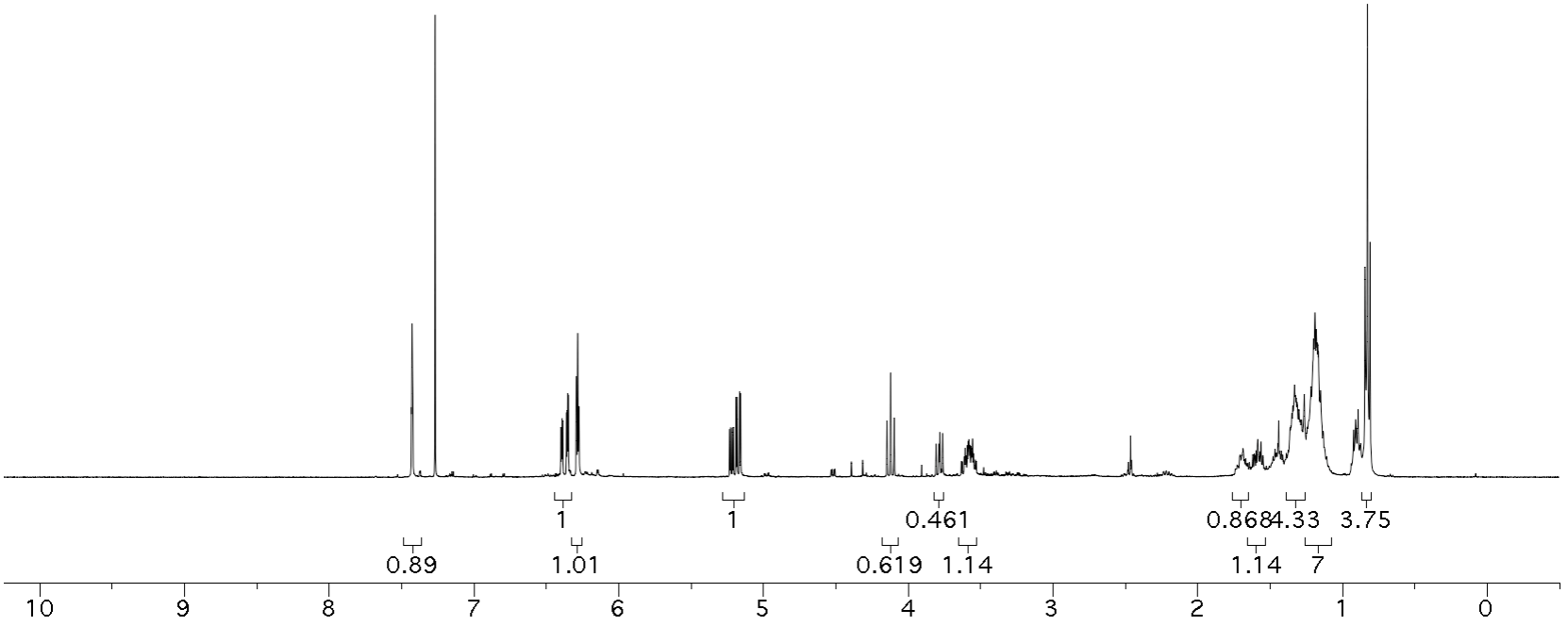


Figure A2.8 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **211**

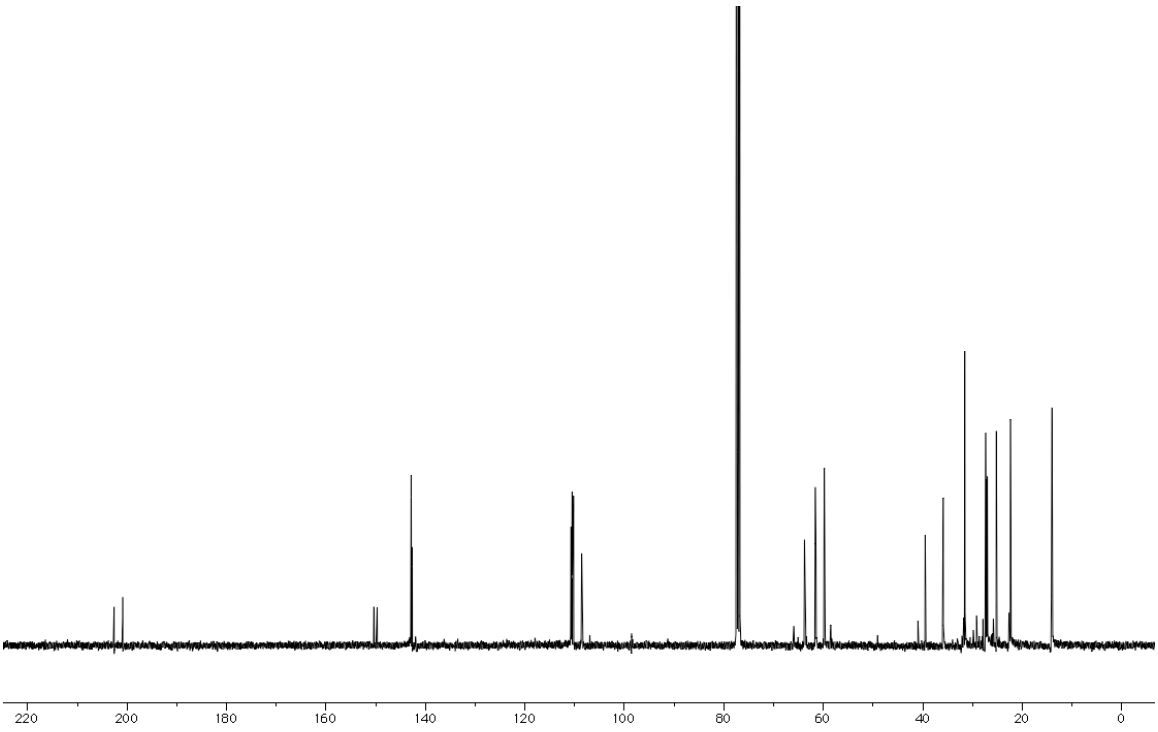


Figure A2.9 IR spectrum (thin film, NaCl) of compound **211**

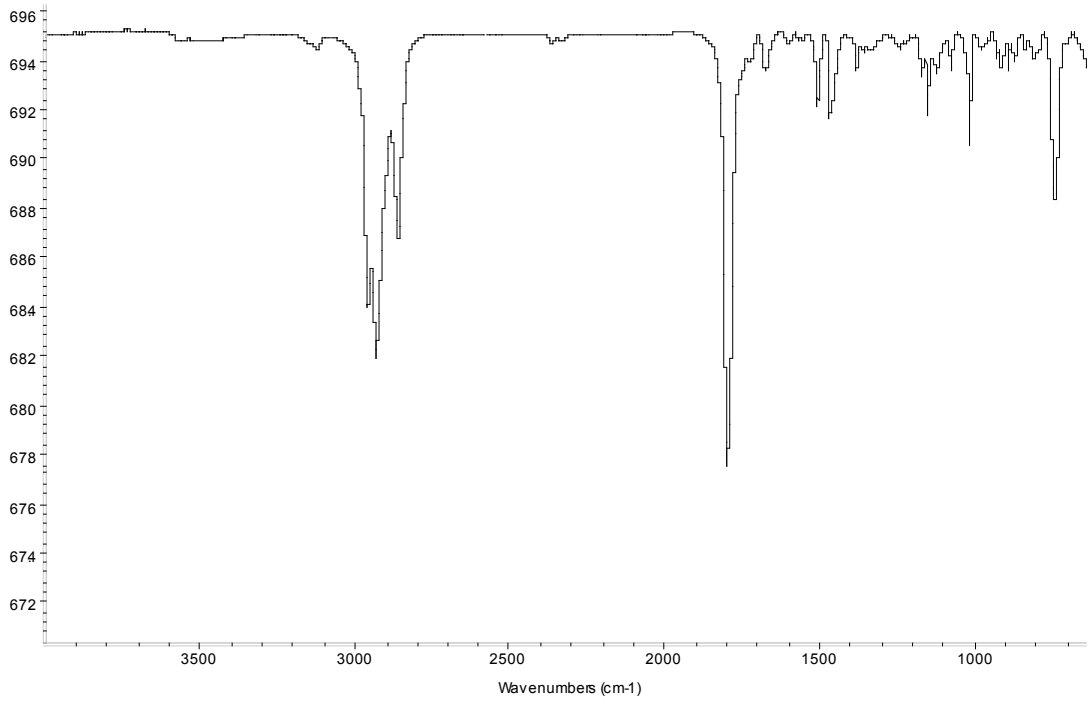
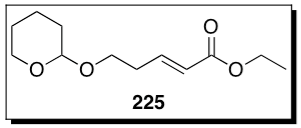


Figure A2.10 1H NMR spectrum (400MHz, CDCl3) of compound **225**



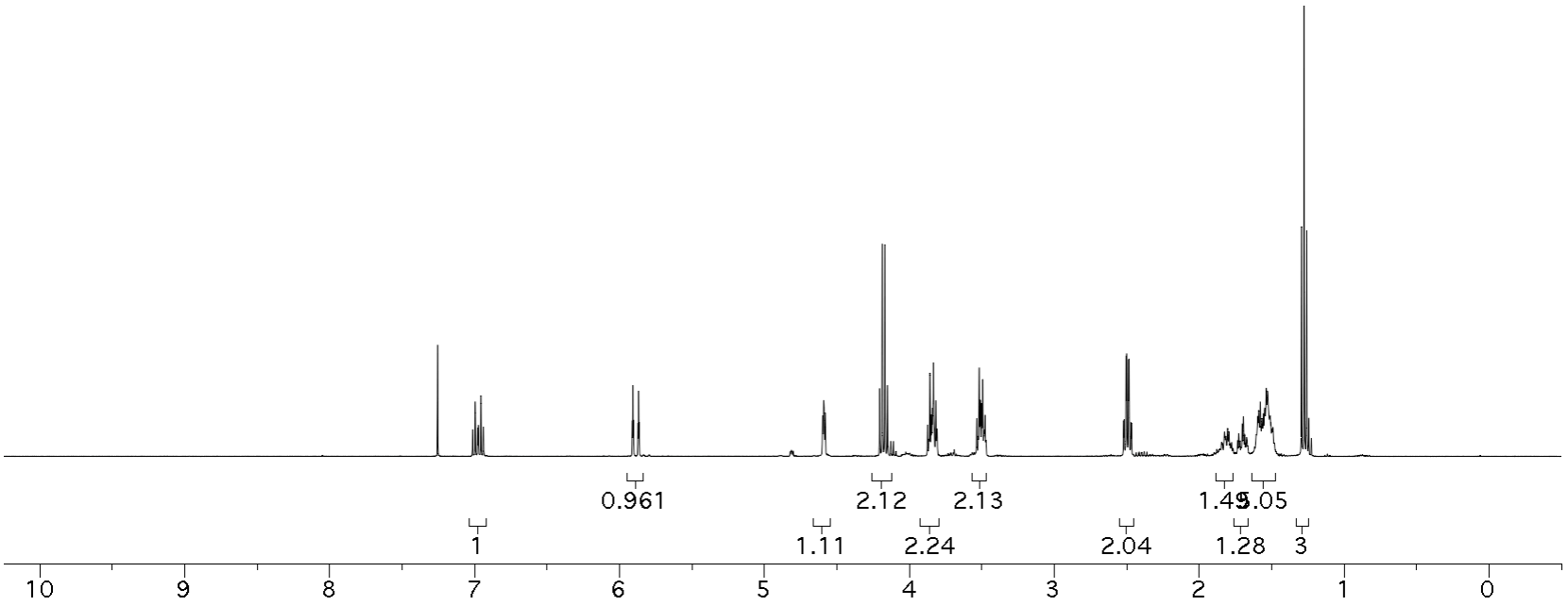


Figure A2.11 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **225**

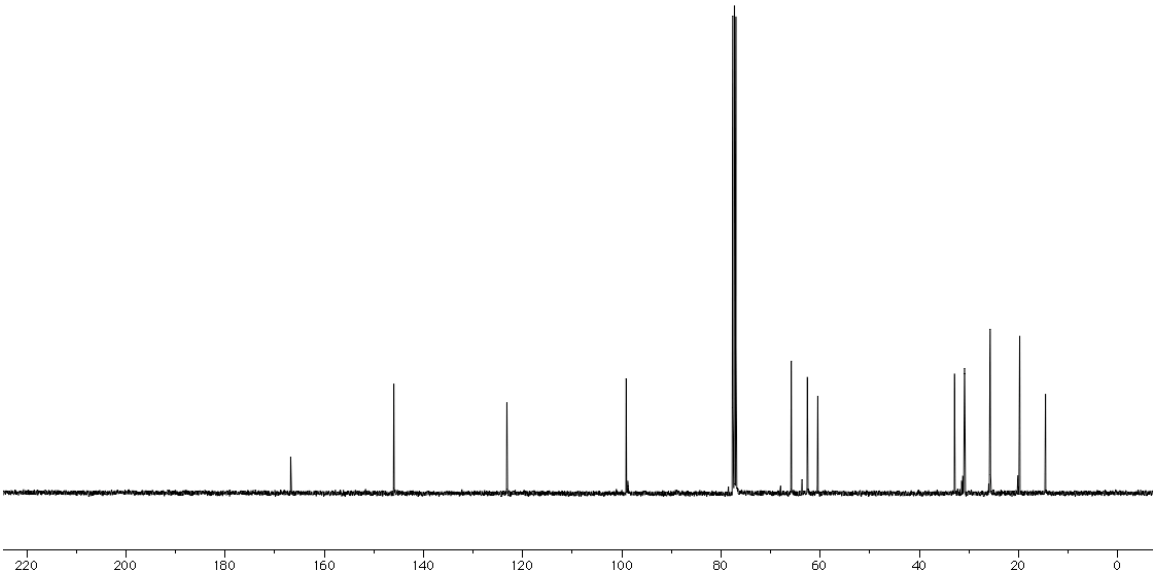


Figure A2.12 IR spectrum (thin film, NaCl) of compound **225**

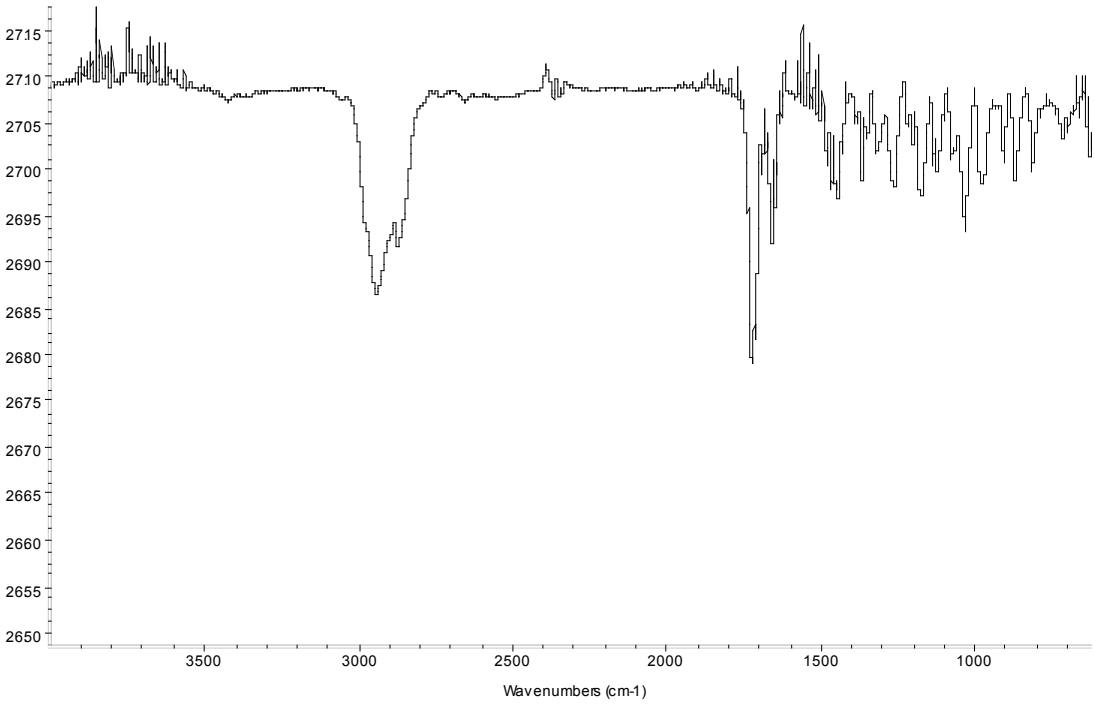
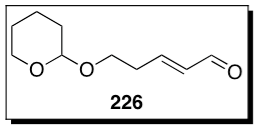


Figure A2.13 1H NMR spectrum (400MHz, CDCl3) of compound **226**



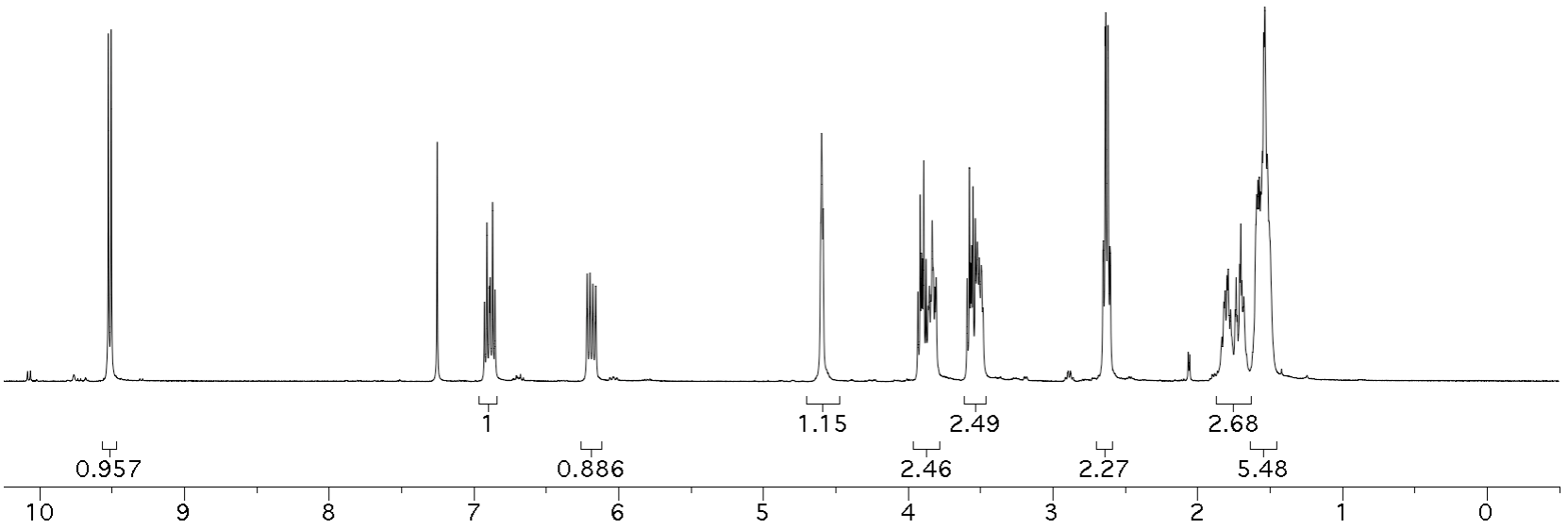


Figure A2.14 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **226**

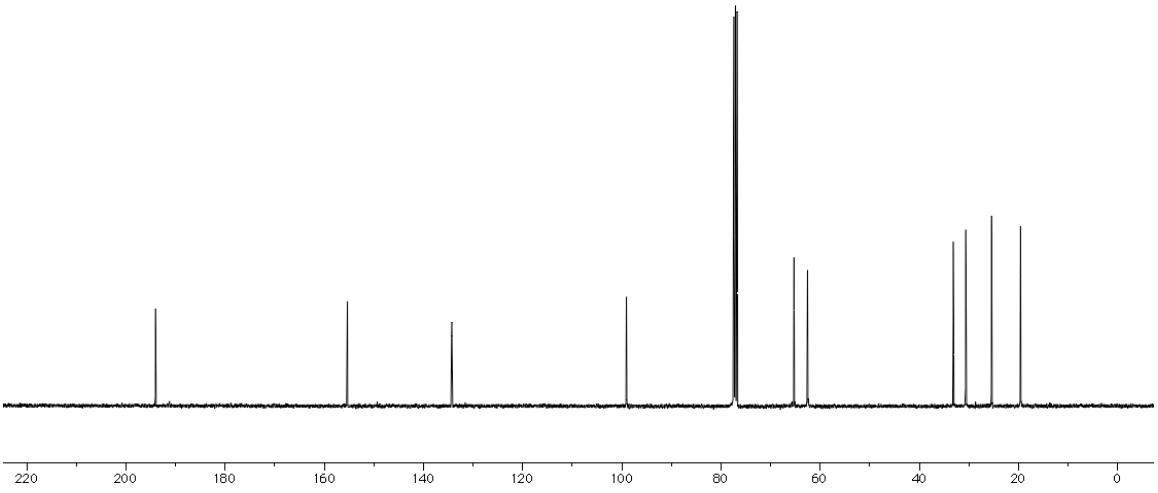


Figure A2.15 IR spectrum (thin film, NaCl) of compound **226**

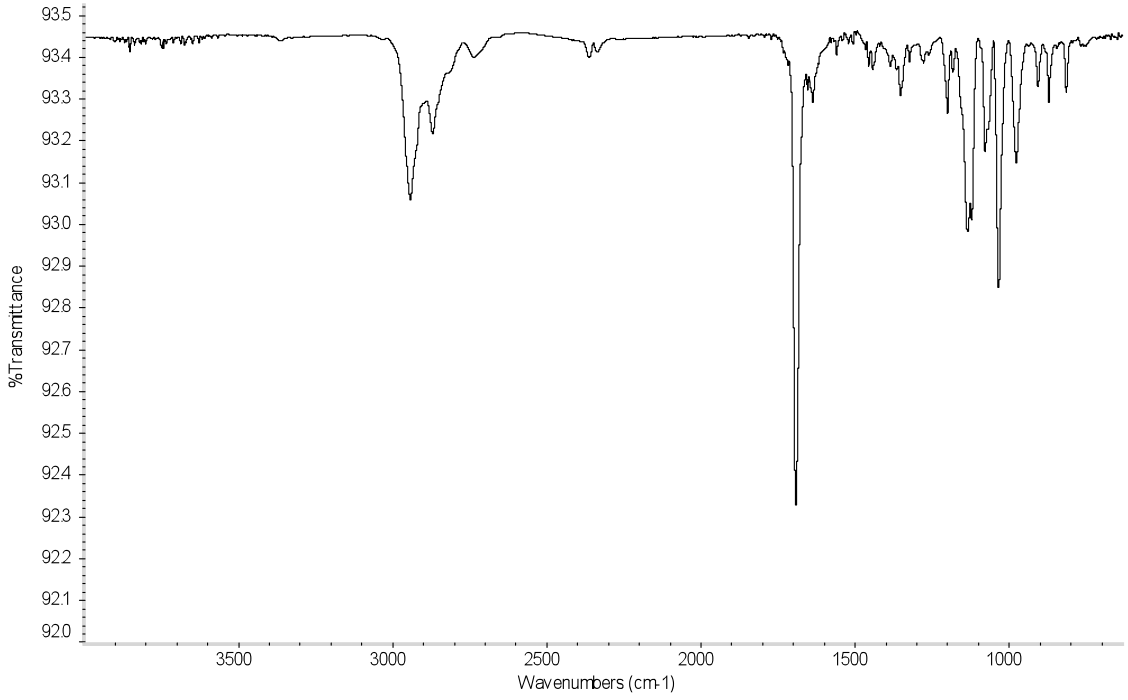


Figure A2.16 1H NMR spectrum (400MHz, CDCl3) of compound **220**

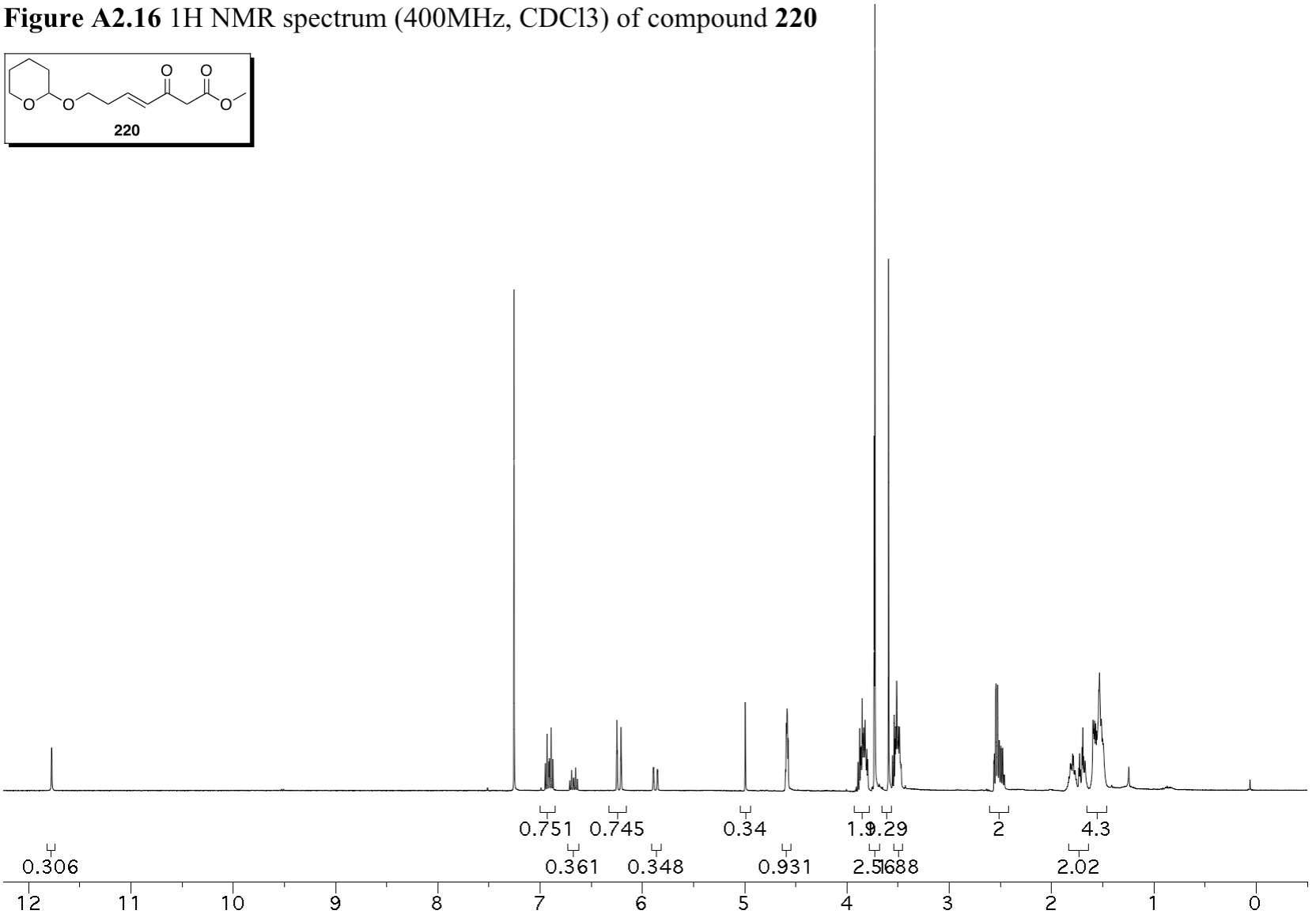


Figure A2.17 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **220**

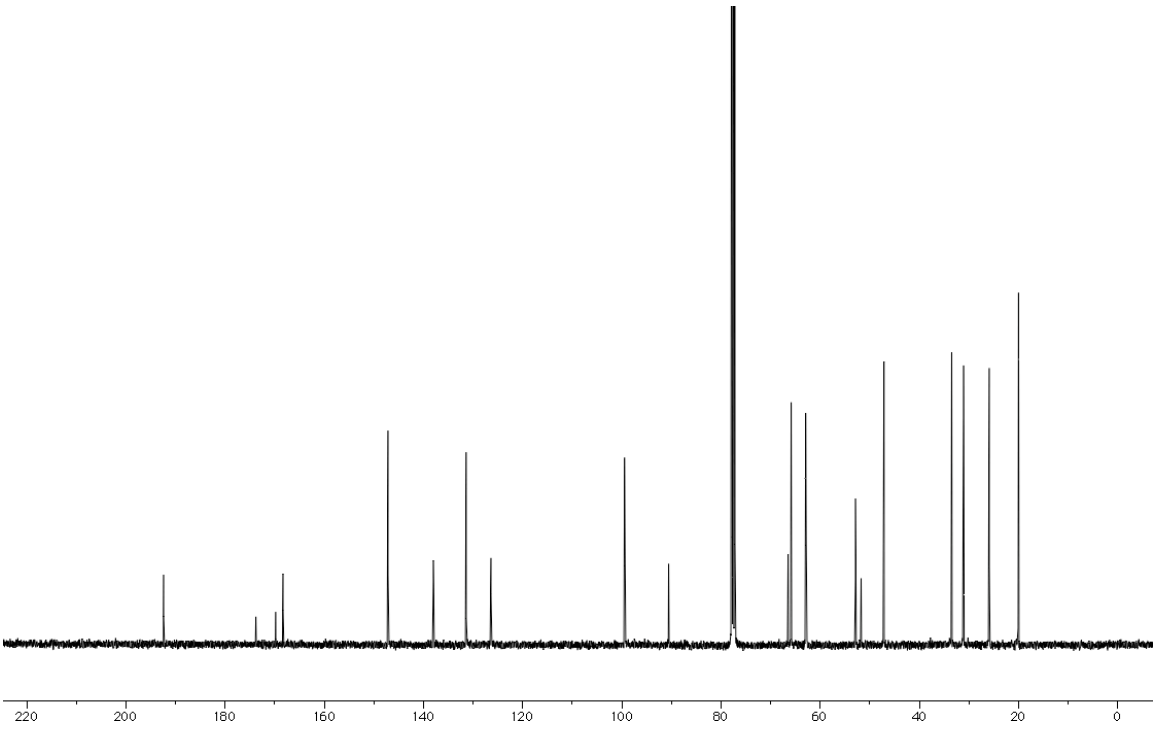


Figure A2.18 IR spectrum (thin film, NaCl) of compound **220**

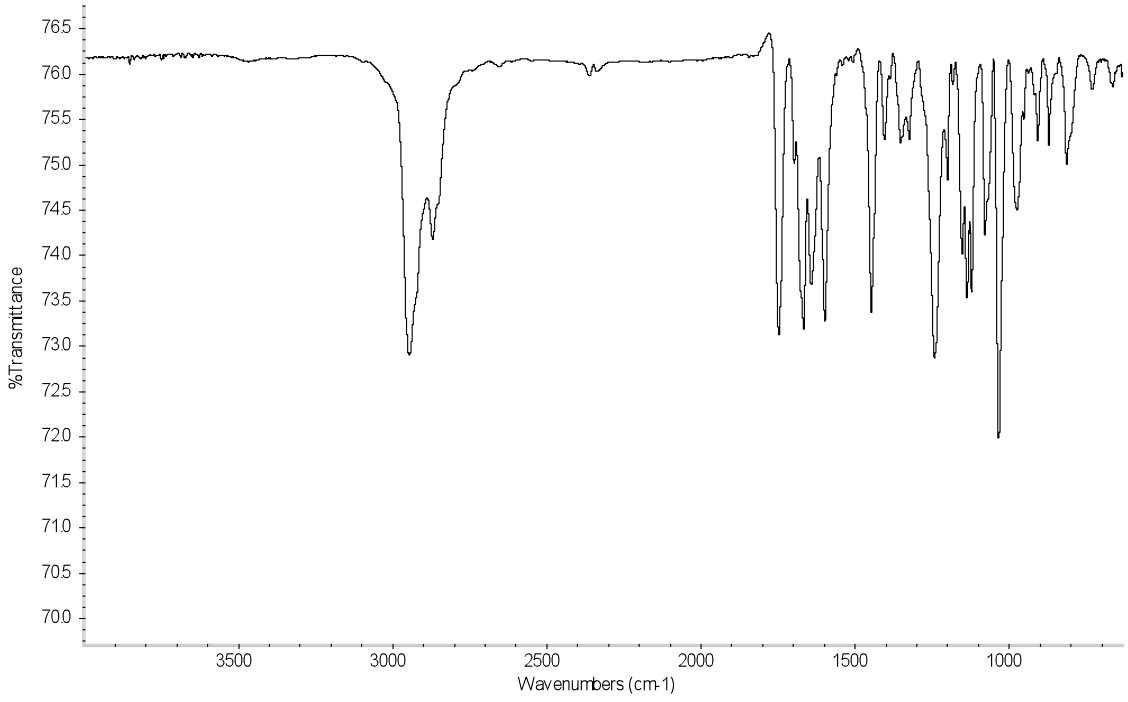


Figure A2.19 1H NMR spectrum (400MHz, CDCl3) of compound **p252**

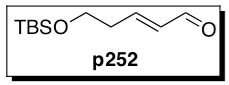


Figure A2.20 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **p252**

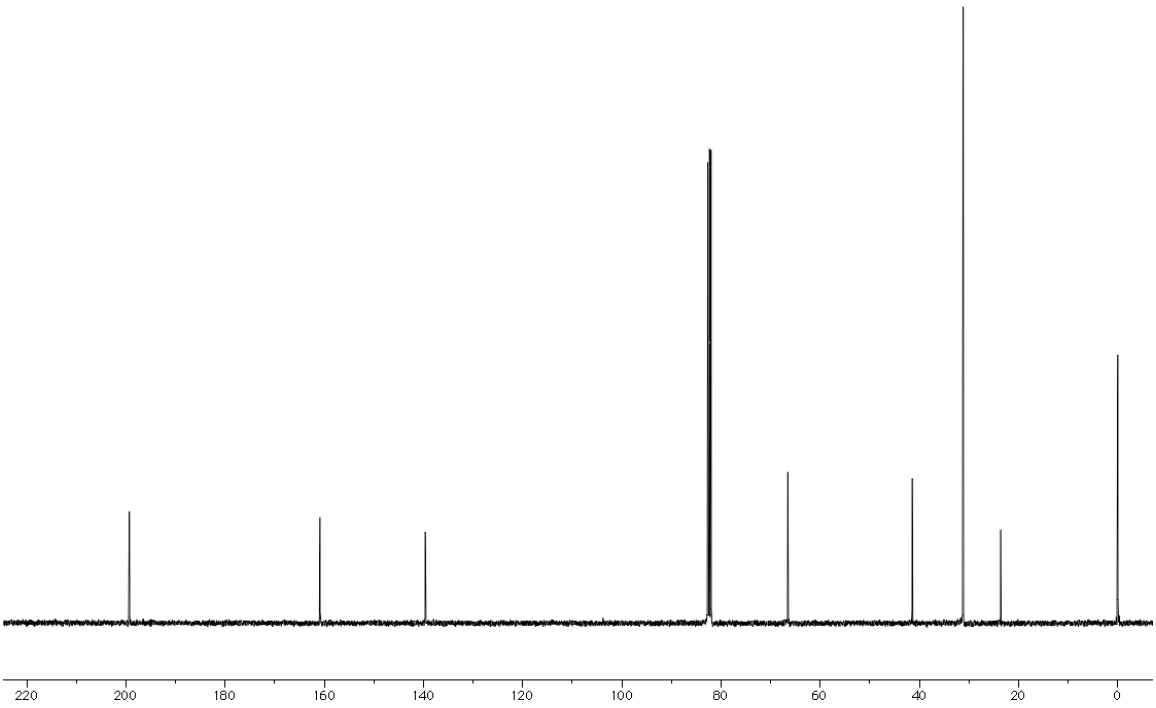


Figure A2.21 IR spectrum (thin film, NaCl) of compound **p252**

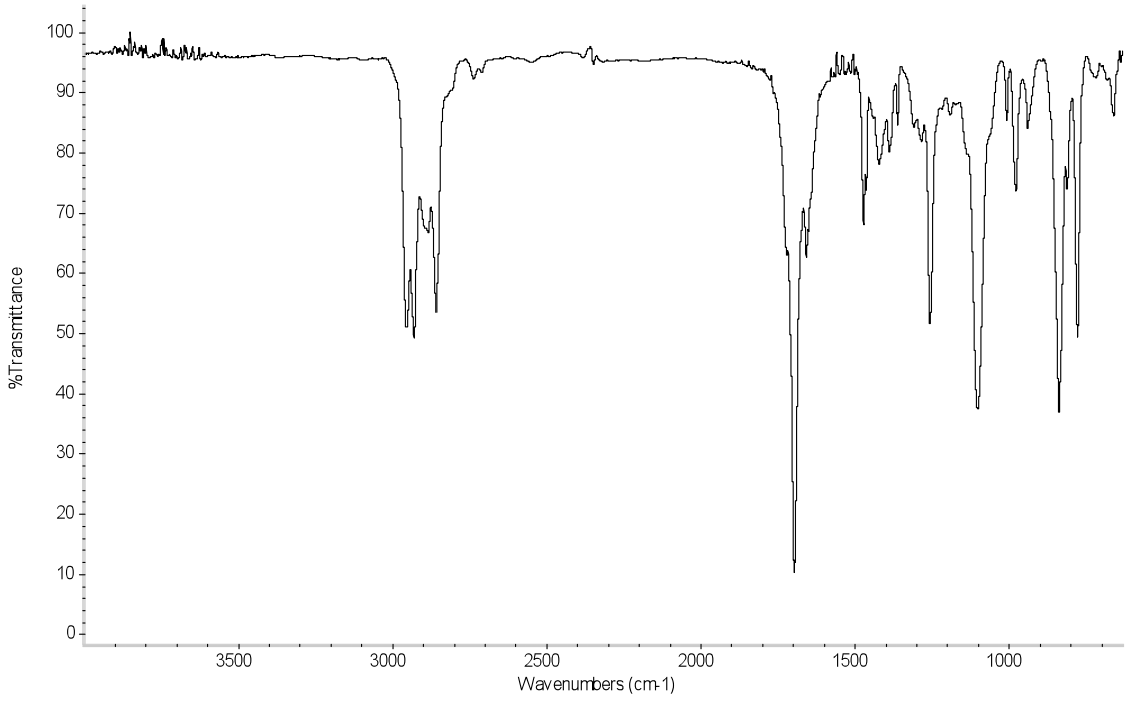


Figure A2.22 1H NMR spectrum (400MHz, CDCl3) of compound **252**

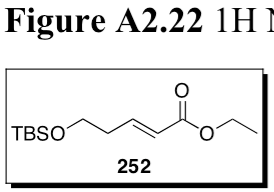


Figure A2.23 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **252**

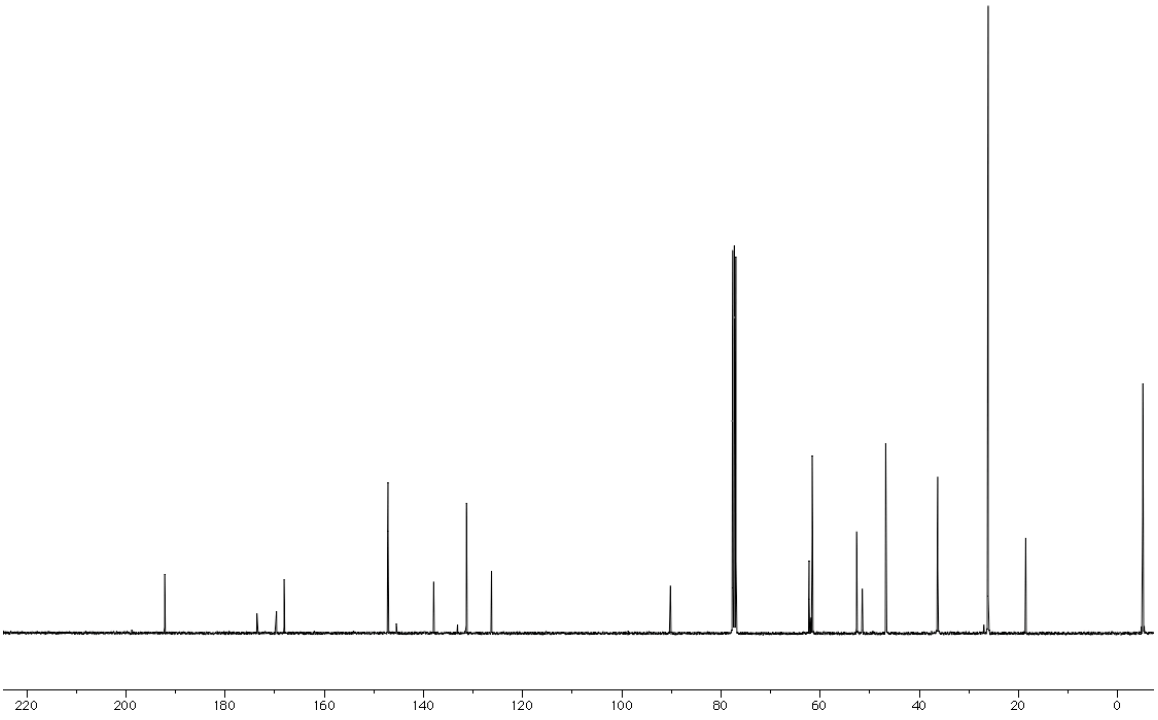


Figure A2.24 IR spectrum (thin film, NaCl) of compound **252**

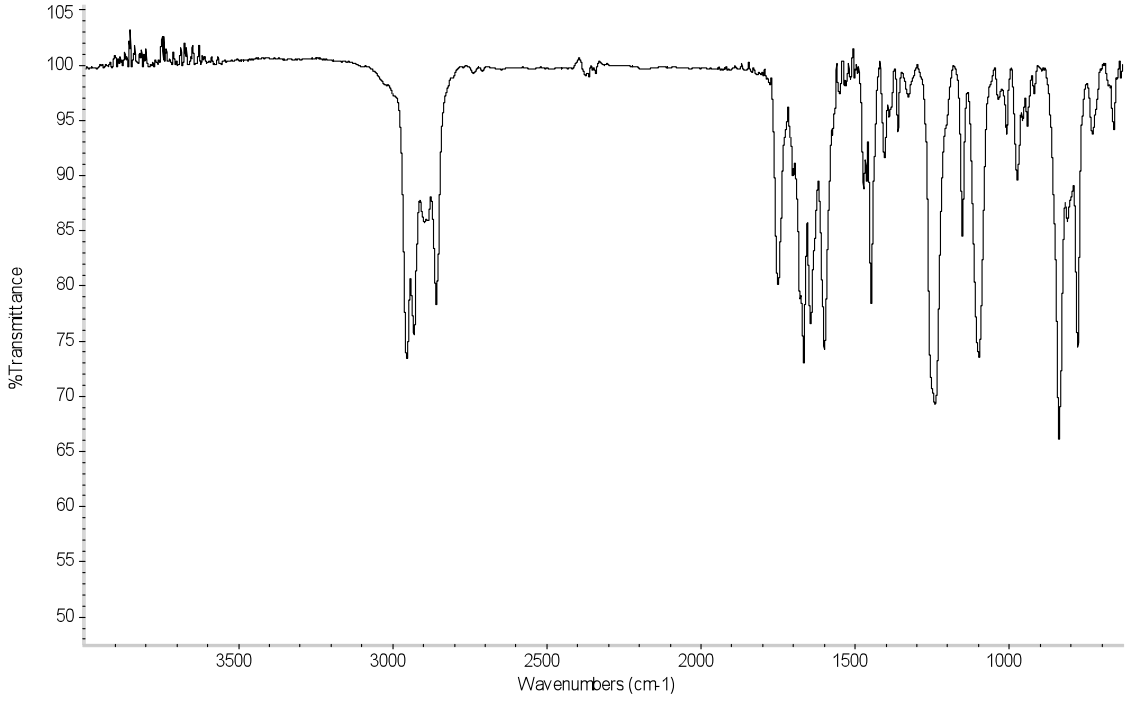


Figure A2.25 1H NMR spectrum (400MHz, CDCl3) of compound **p265**

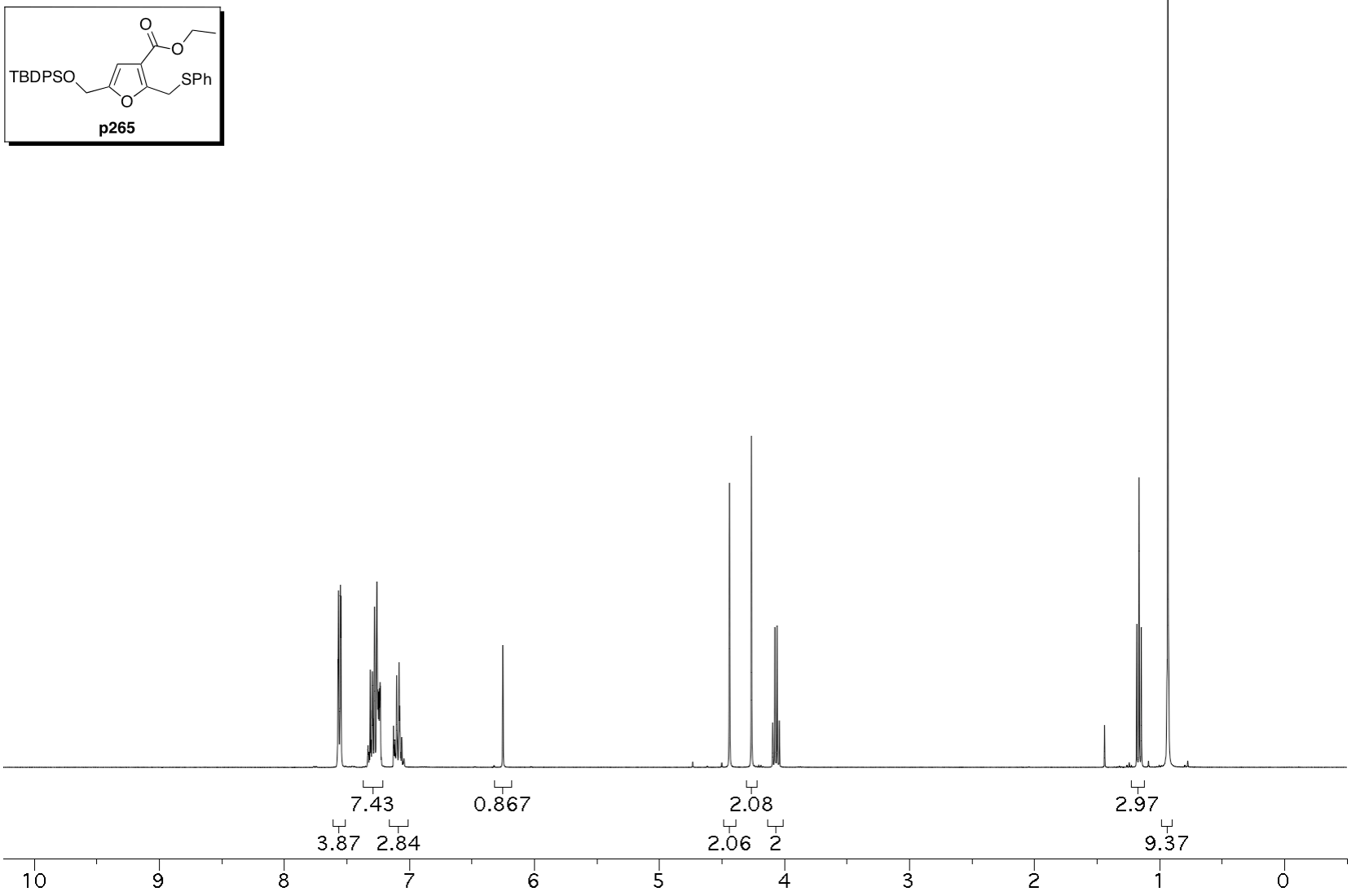


Figure A2.26 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **p265**

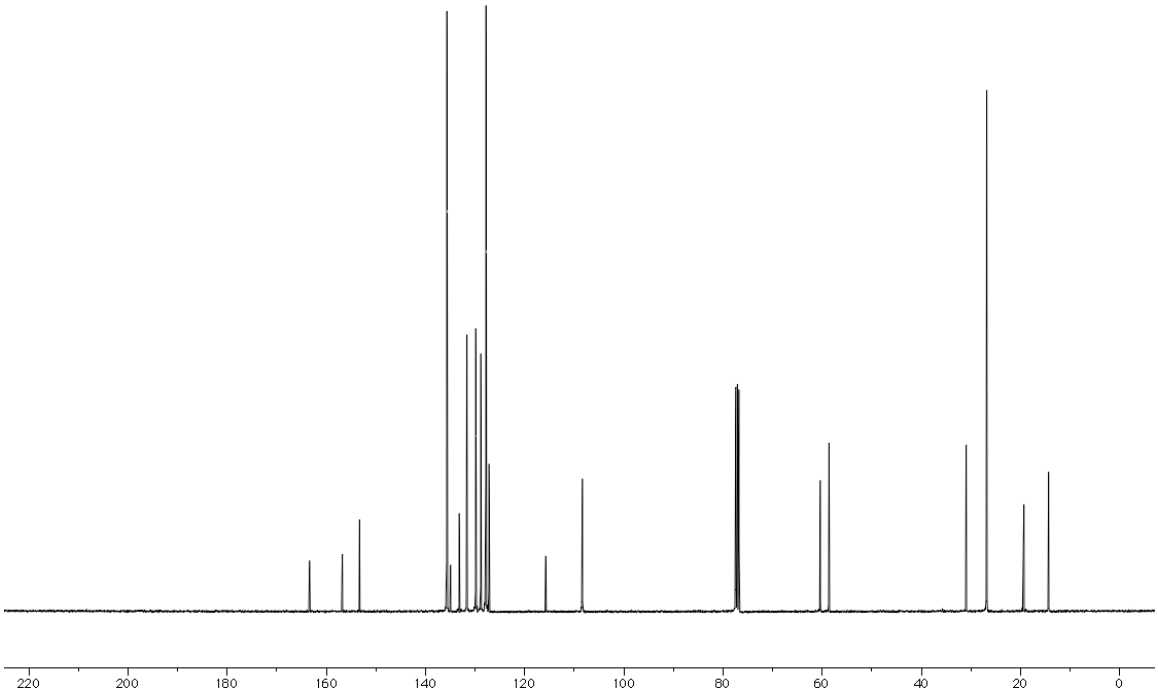


Figure A2.27 IR spectrum (thin film, NaCl) of compound **p265**

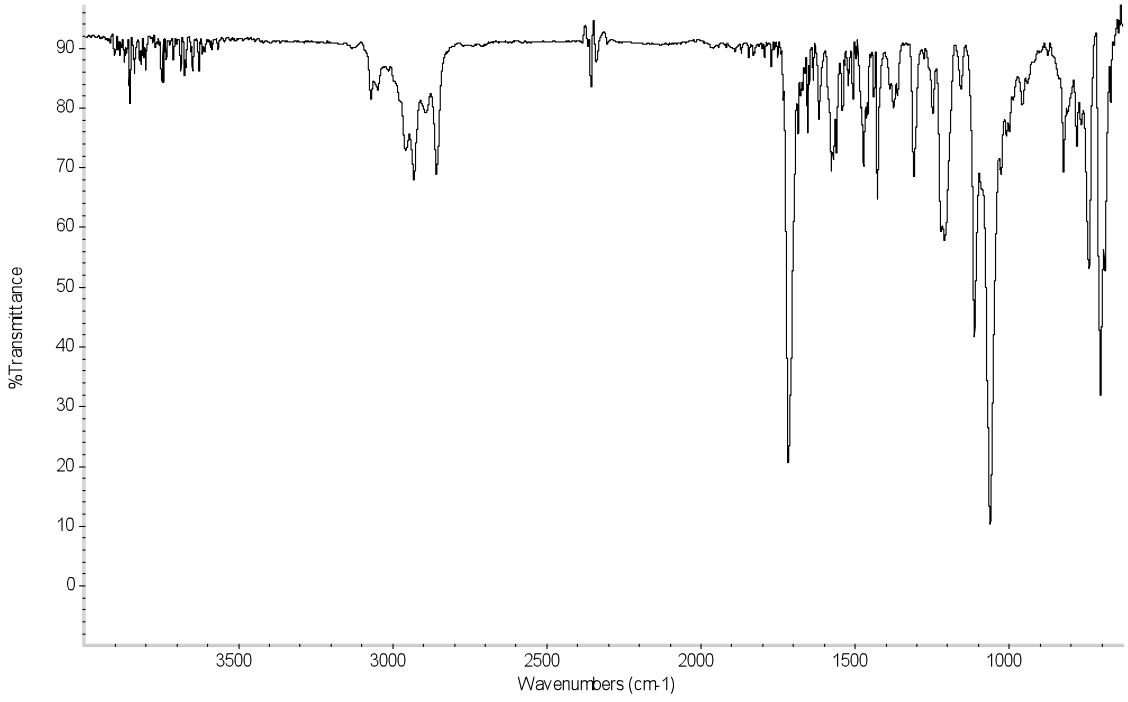


Figure A2.28 1H NMR spectrum (400MHz, CDCl3) of compound **265**

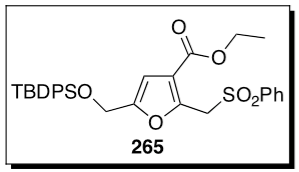


Figure A2.29 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **265**

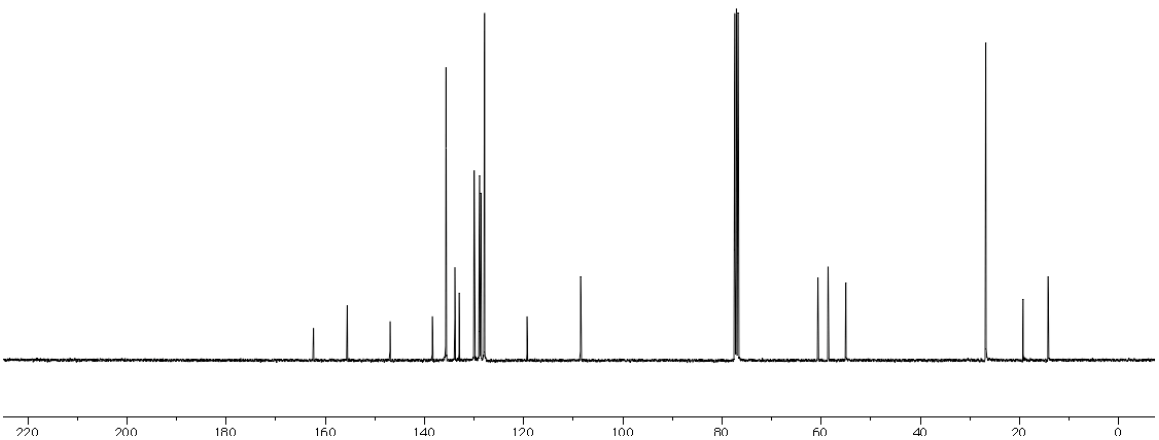


Figure A2.30 IR spectrum (thin film, NaCl) of compound **265**

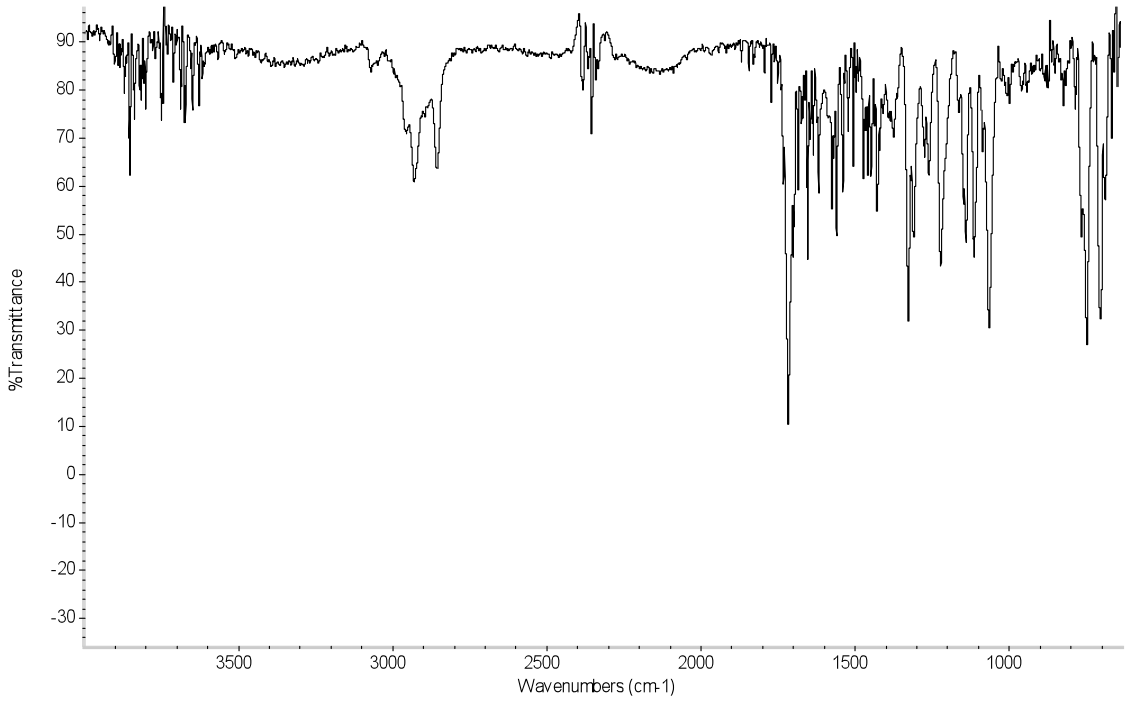


Figure A2.31 1H NMR spectrum (400MHz, CDCl3) of compound **268**

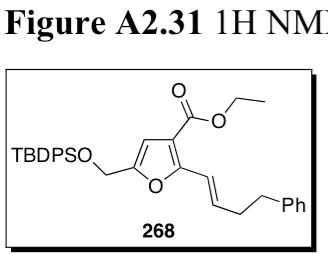


Figure A2.32 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **268**

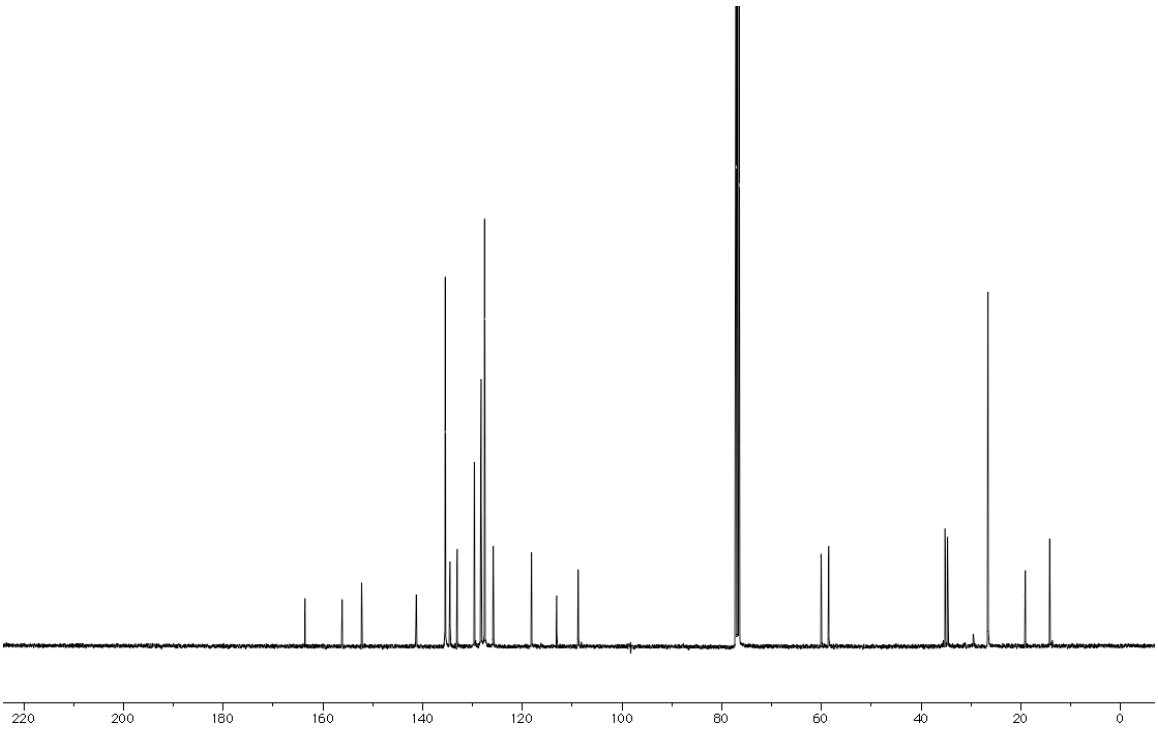


Figure A2.33 IR spectrum (thin film, NaCl) of compound **268**

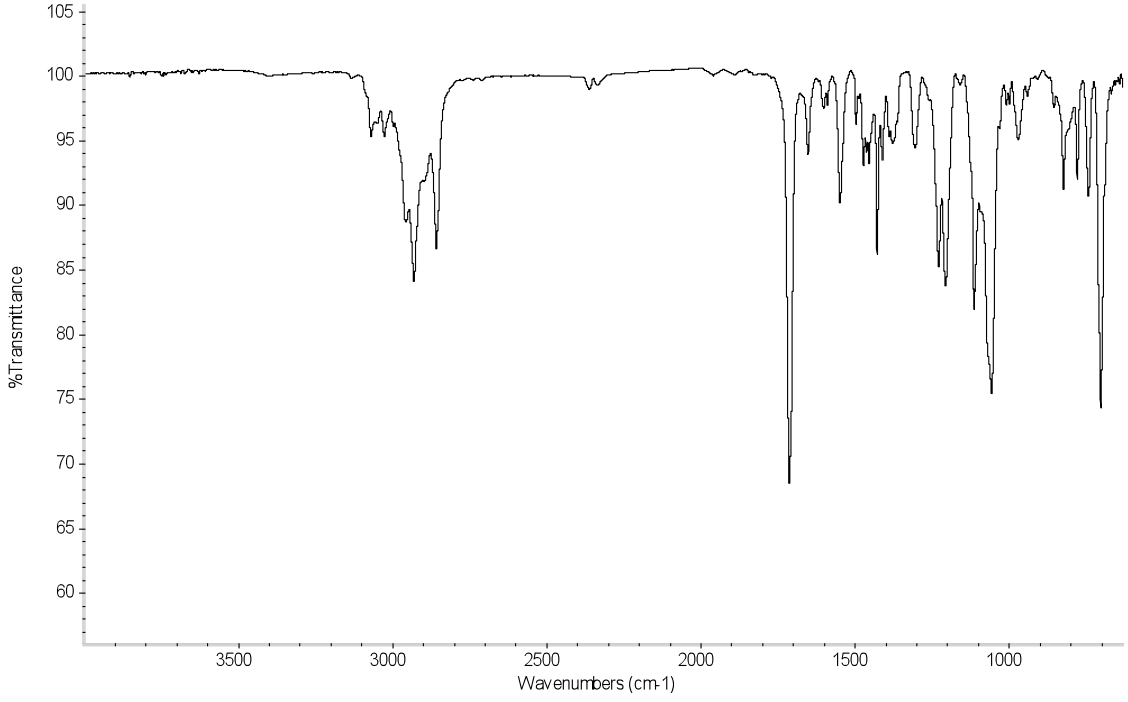


Figure A2.34 1H NMR spectrum (400MHz, CDCl3) of compound **270**

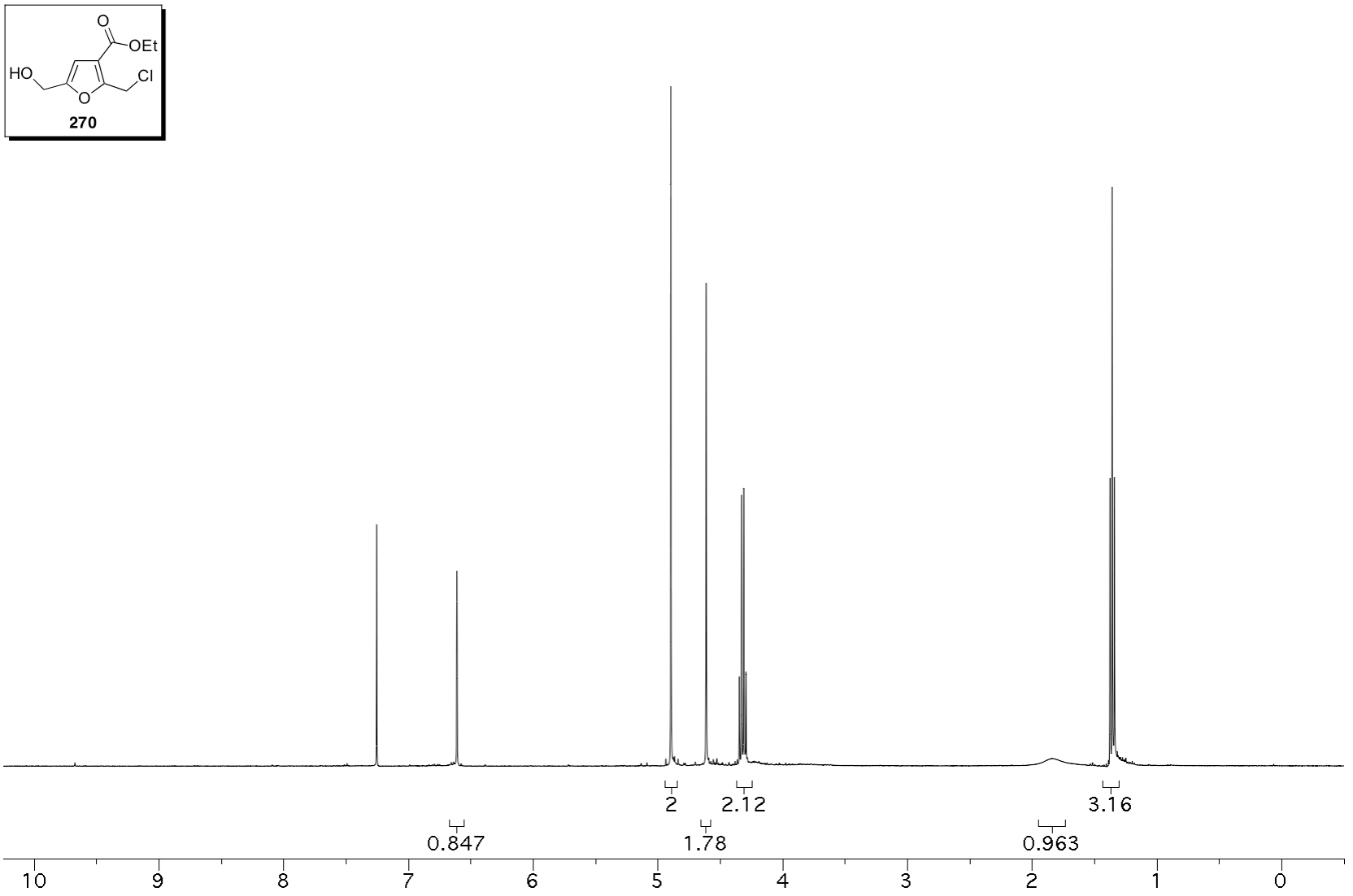


Figure A2.35 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **270**

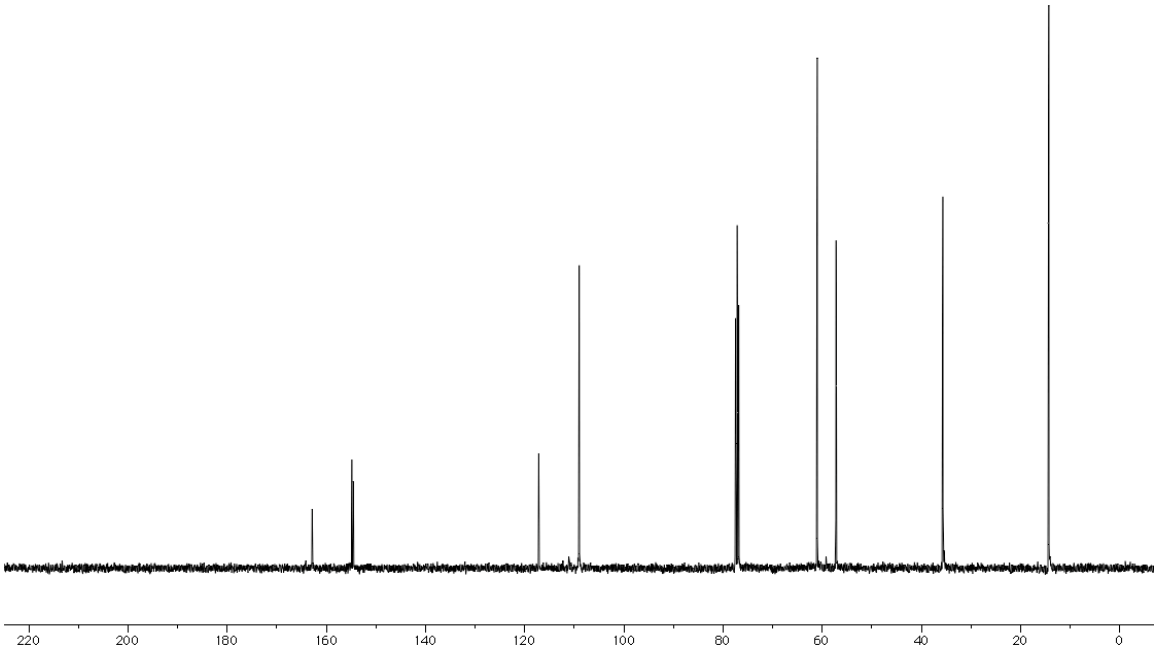


Figure A2.36 IR spectrum (thin film, NaCl) of compound **270**

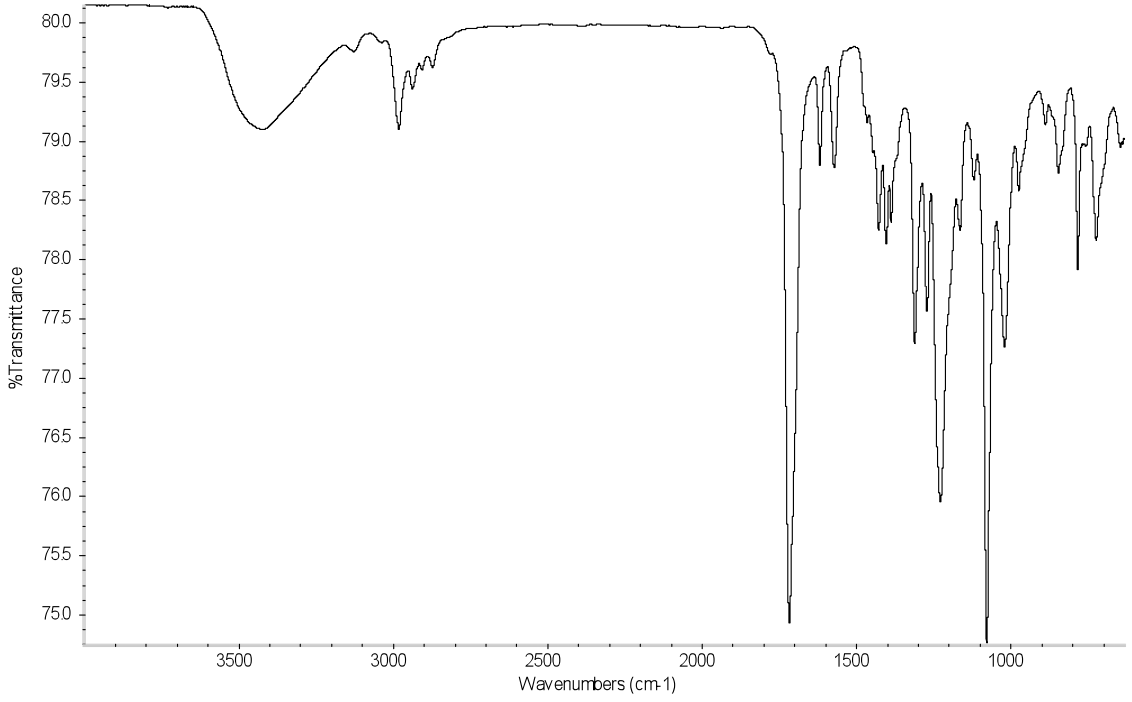


Figure A2.37 1H NMR spectrum (400MHz, CDCl3) of compound **271**

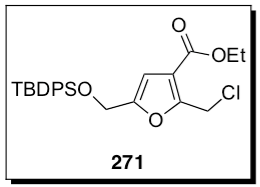


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Figure A2.38 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **271**

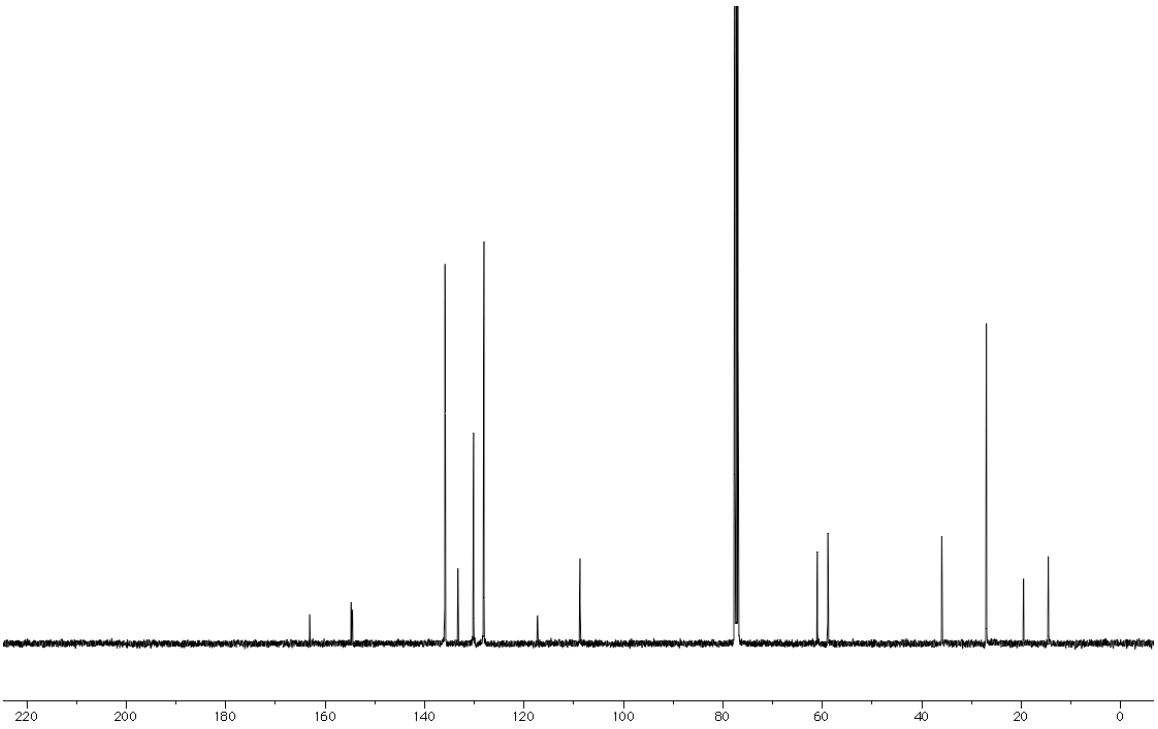


Figure A2.39 IR spectrum (thin film, NaCl) of compound **271**

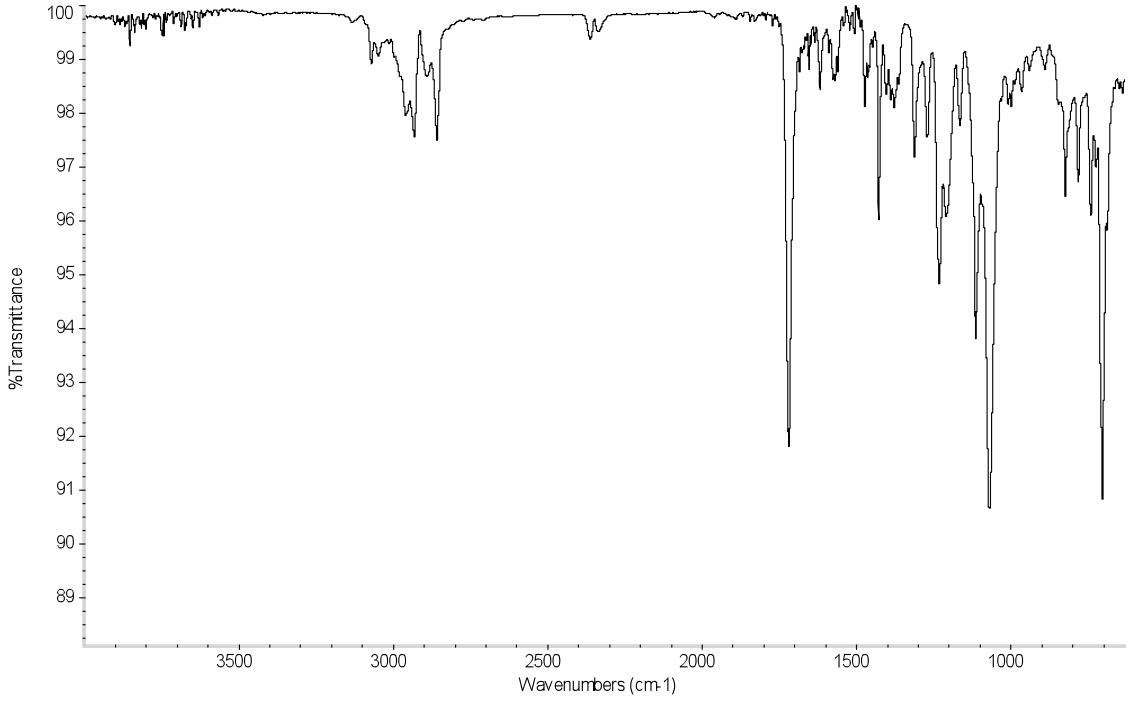
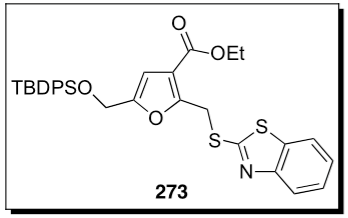


Figure A2.40 1H NMR spectrum (400MHz, CDCl3) of compound **273**



273

Figure A2.41 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **273**

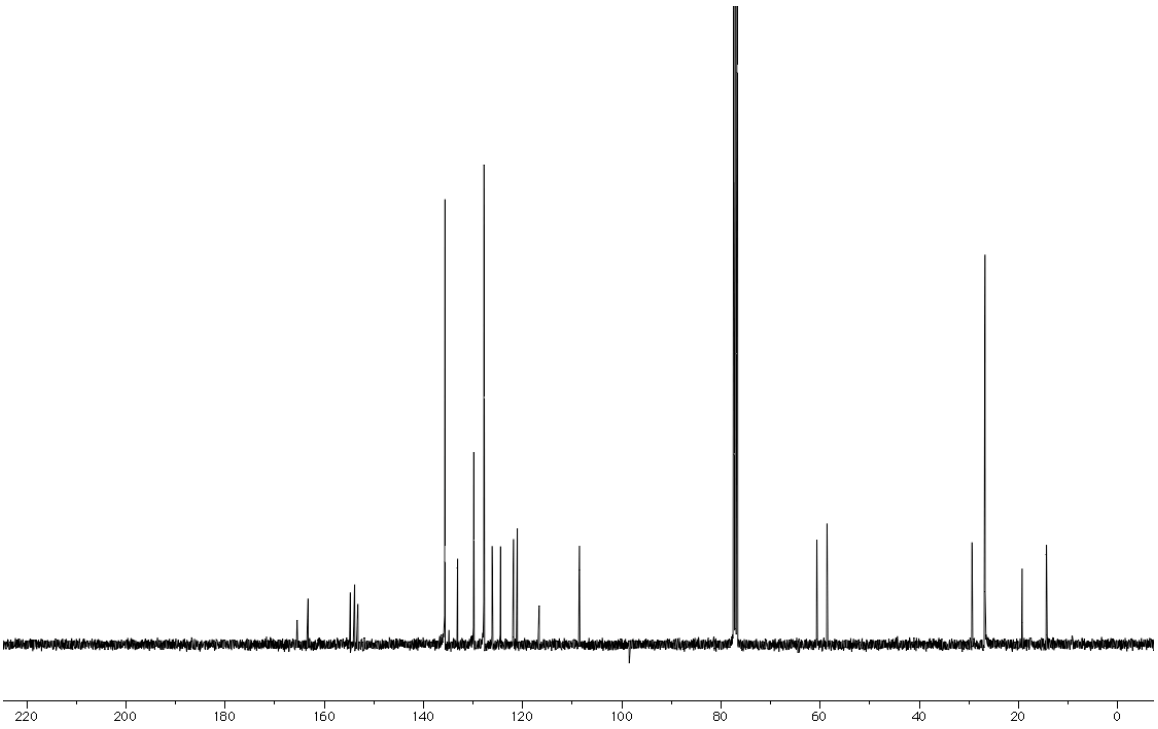


Figure A2.42 IR spectrum (thin film, NaCl) of compound **273**

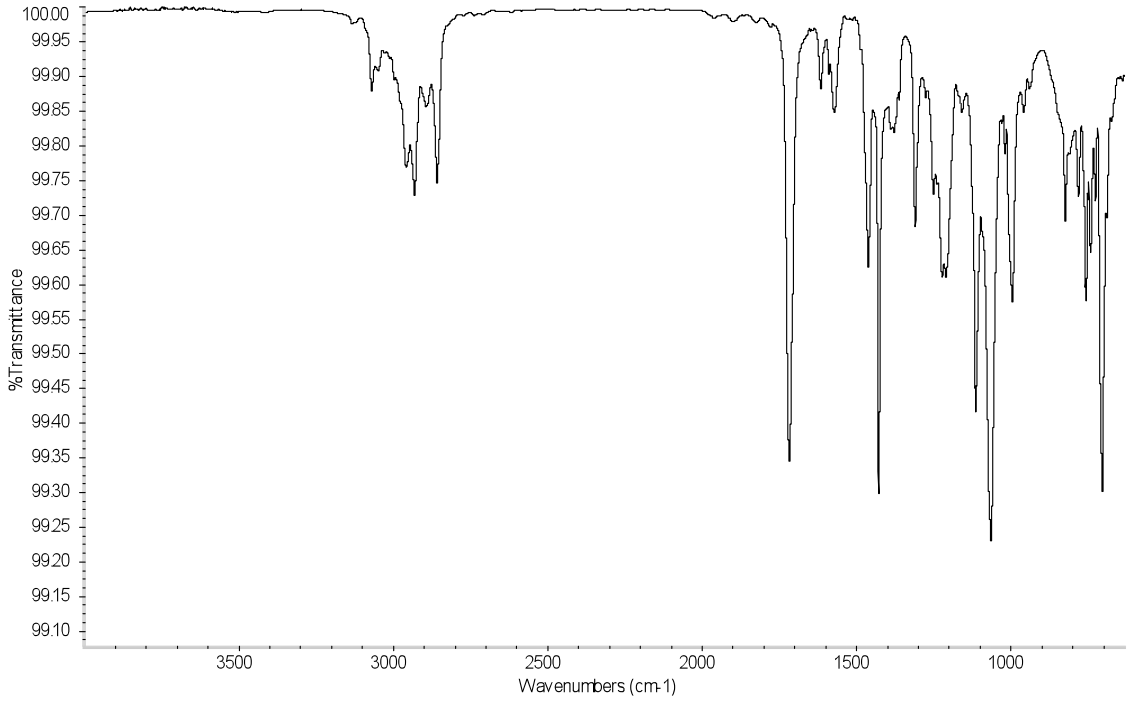


Figure A2.43 1H NMR spectrum (400MHz, CDCl3) of compound **274**

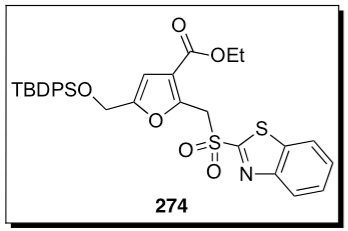


Figure A2.44 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **274**

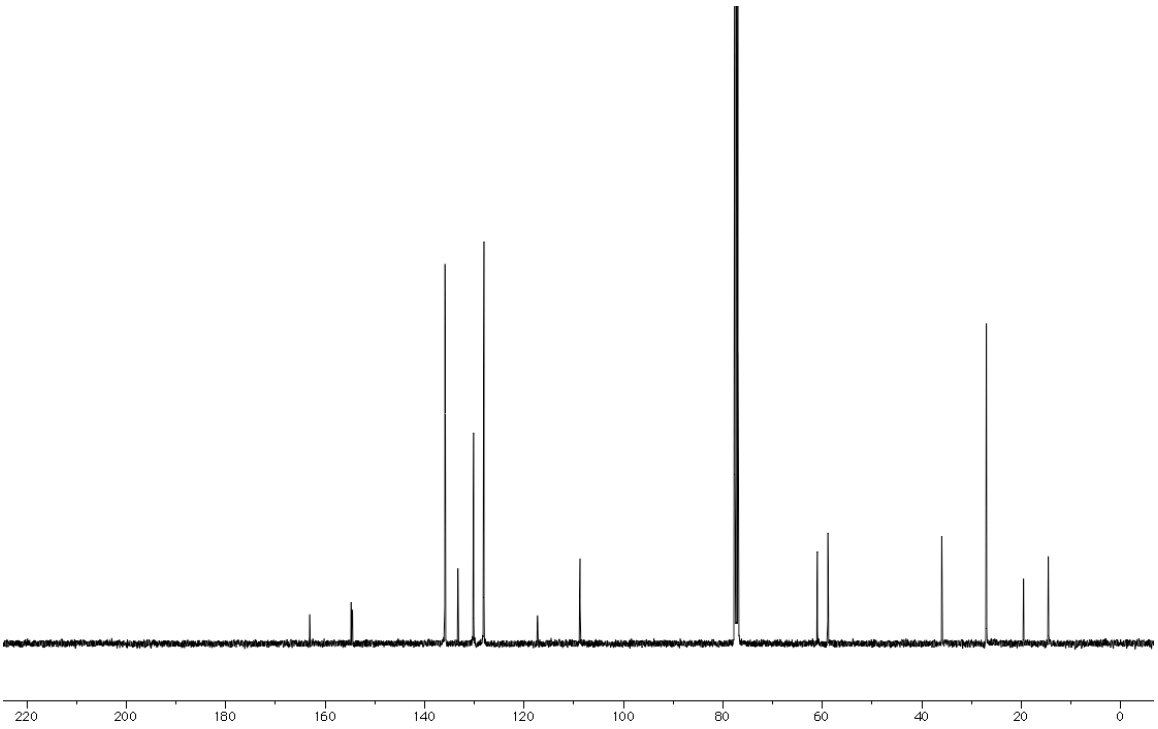


Figure A2.45 IR spectrum (thin film, NaCl) of compound **274**

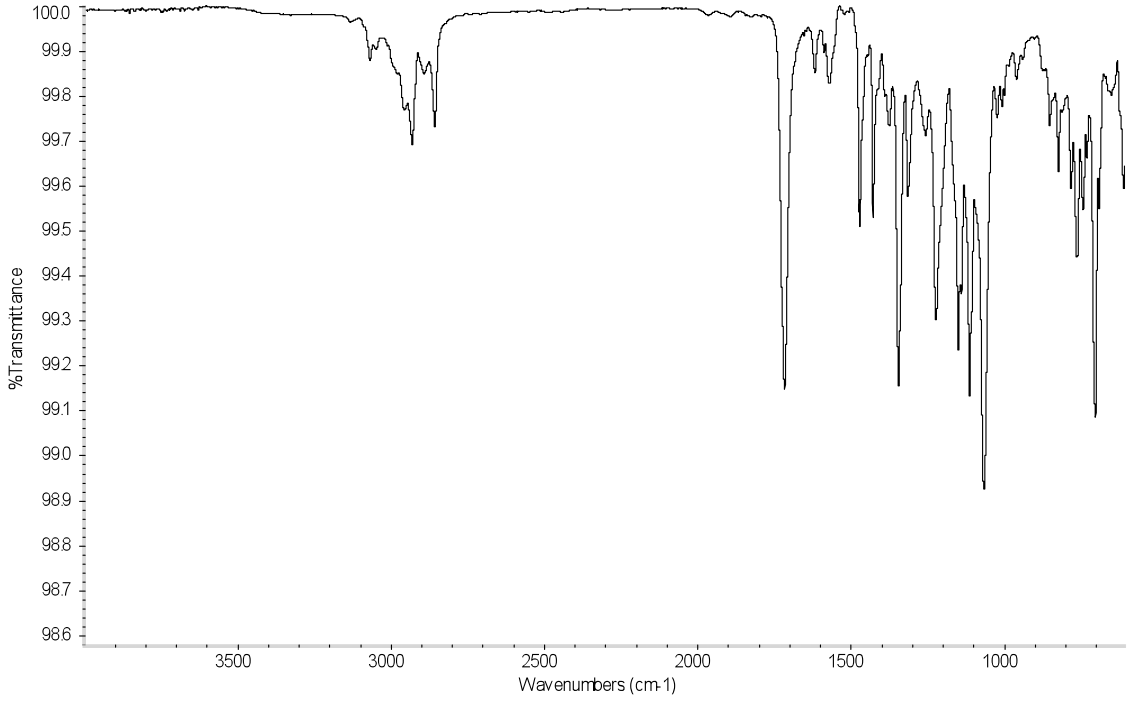
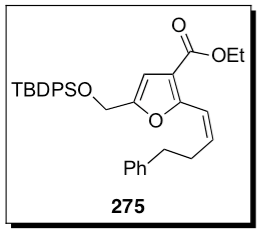


Figure A2.46 1H NMR spectrum (400MHz, CDCl3) of compound **275**



275

Figure A2.47 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **275**

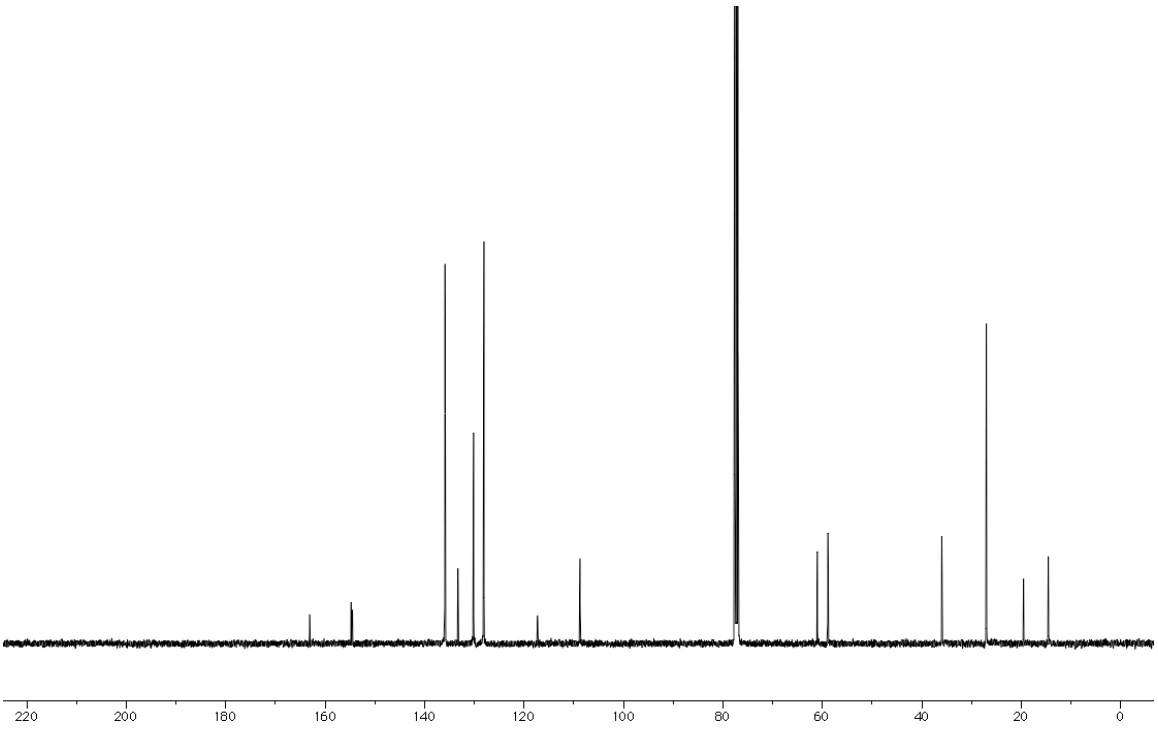


Figure A2.48 IR spectrum (thin film, NaCl) of compound **275**

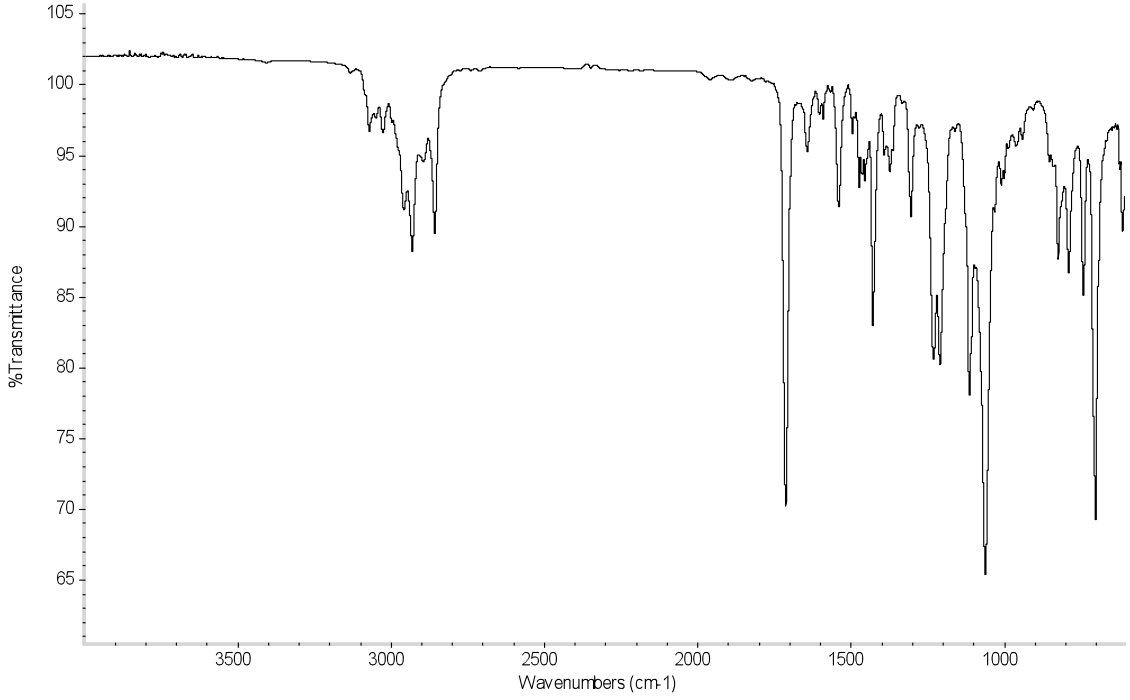


Figure A2.49 1H NMR spectrum (400MHz, CDCl3) of compound **p285**

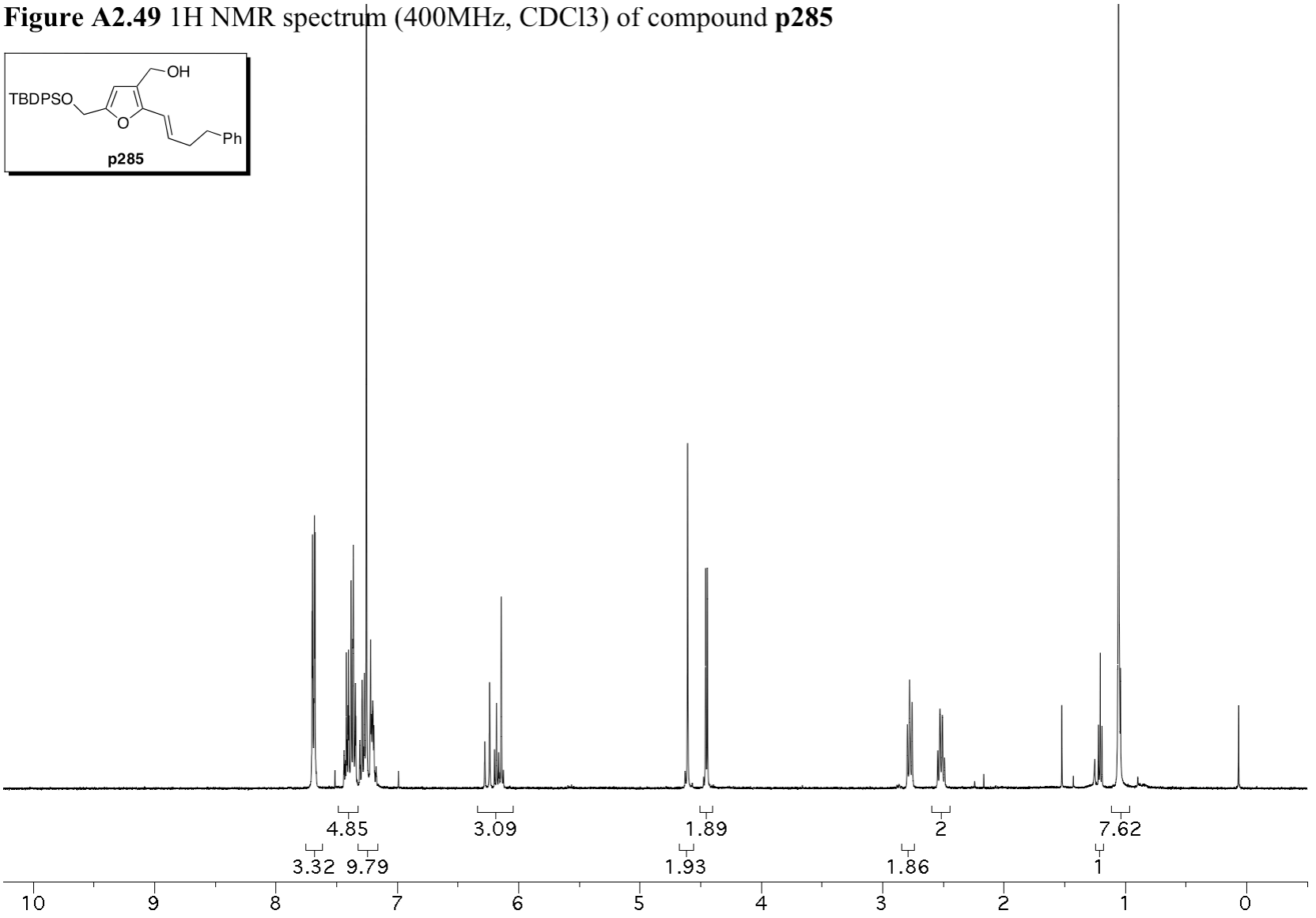


Figure A2.50 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **p285**

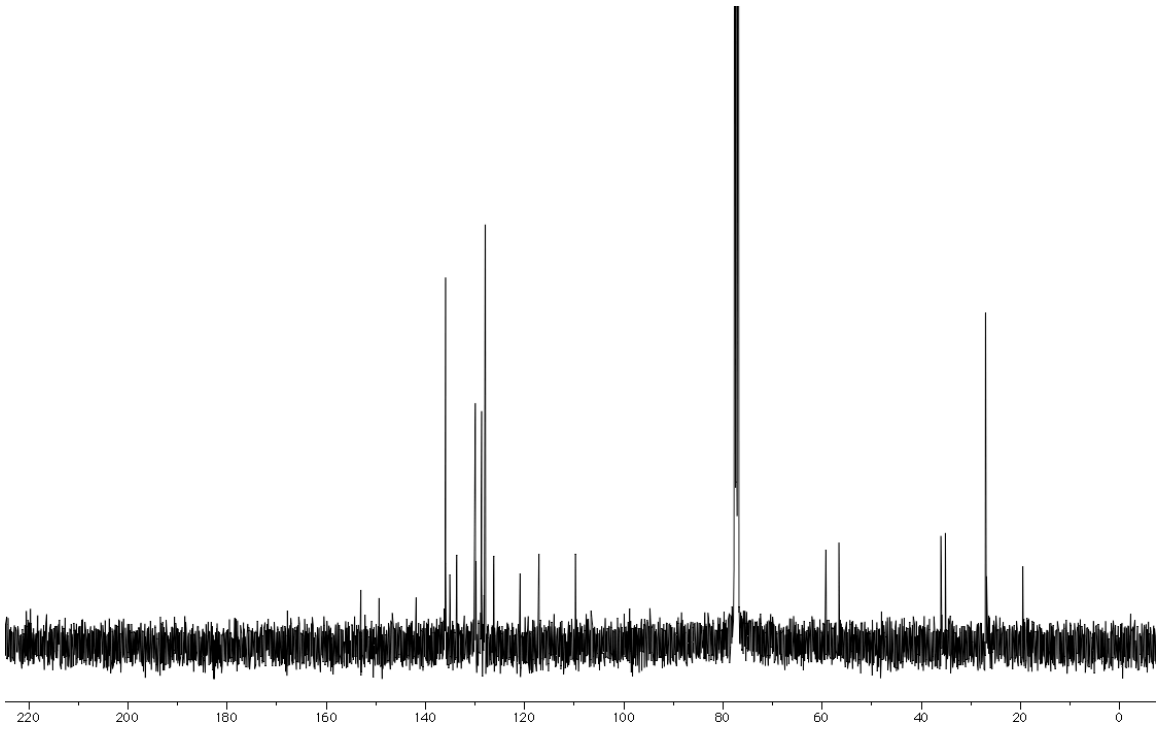


Figure A2.51 IR spectrum (thin film, NaCl) of compound **p285**

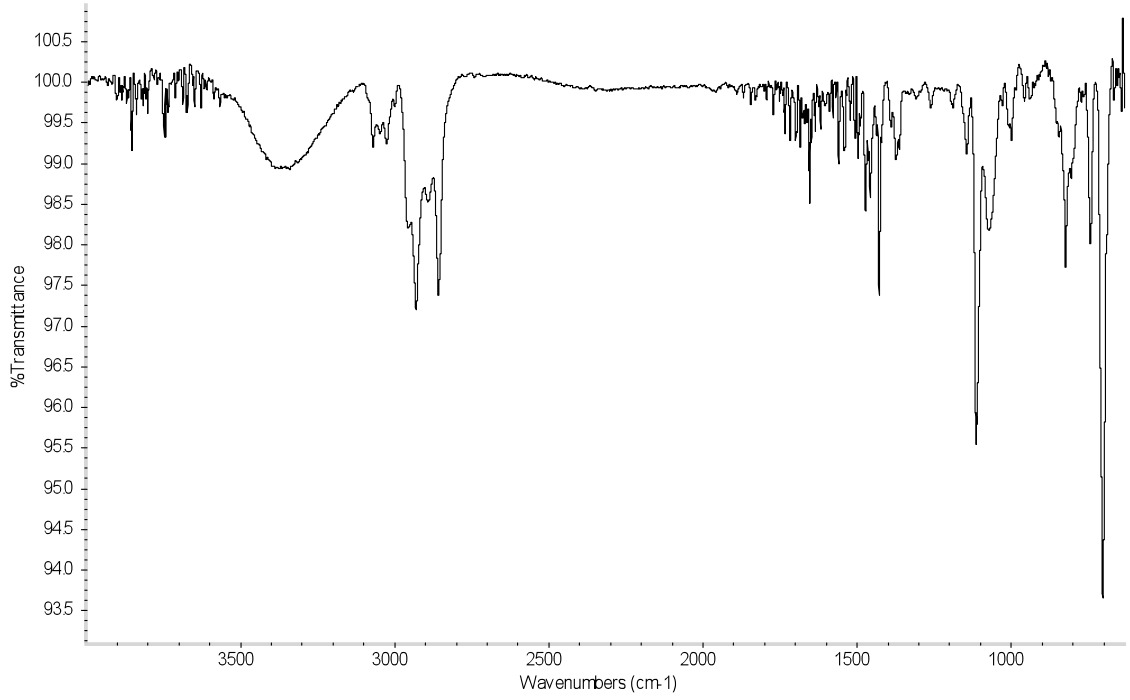


Figure A2.52 1H NMR spectrum (400MHz, CDCl3) of compound **p286**

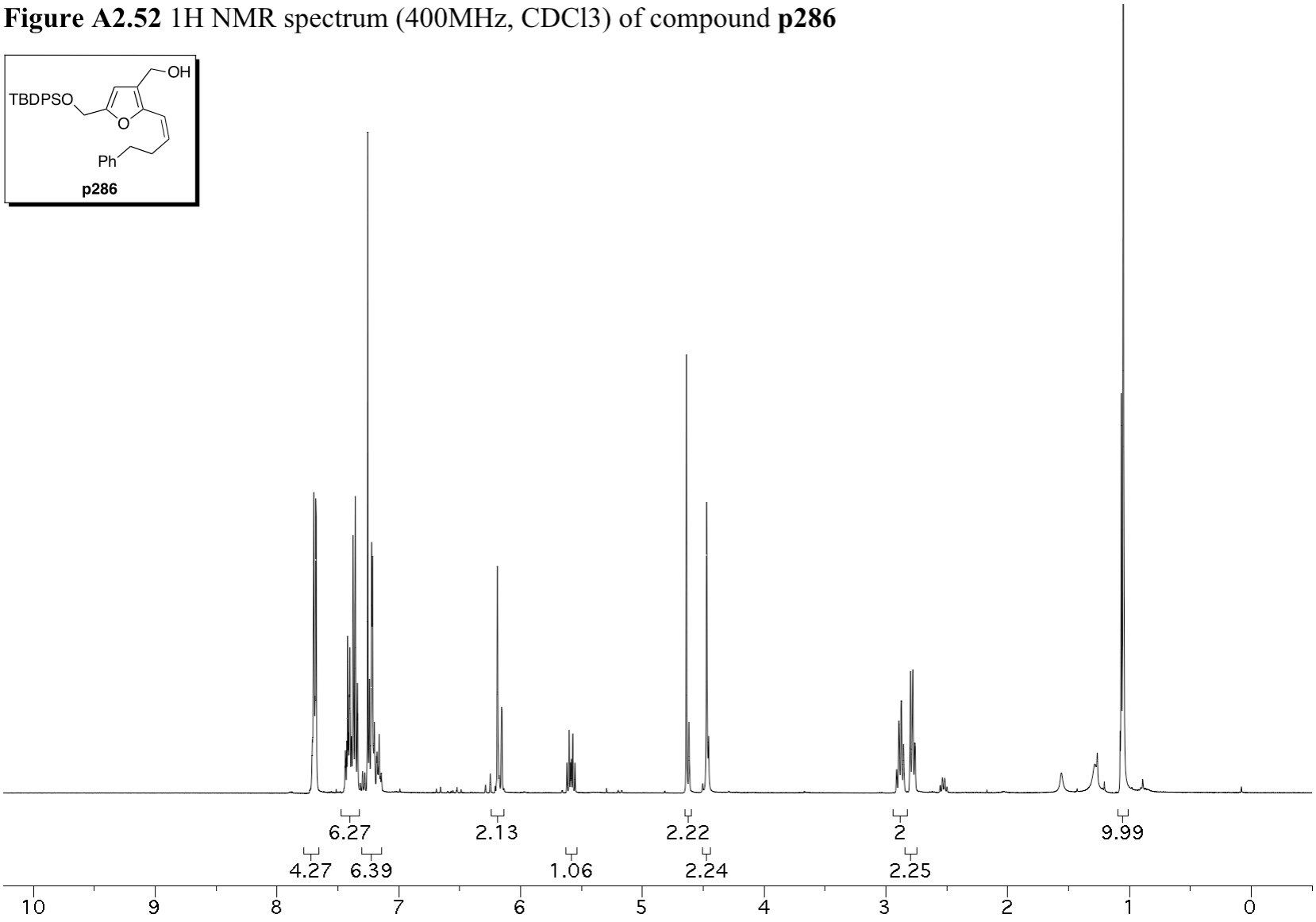


Figure A2.53 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **p286**

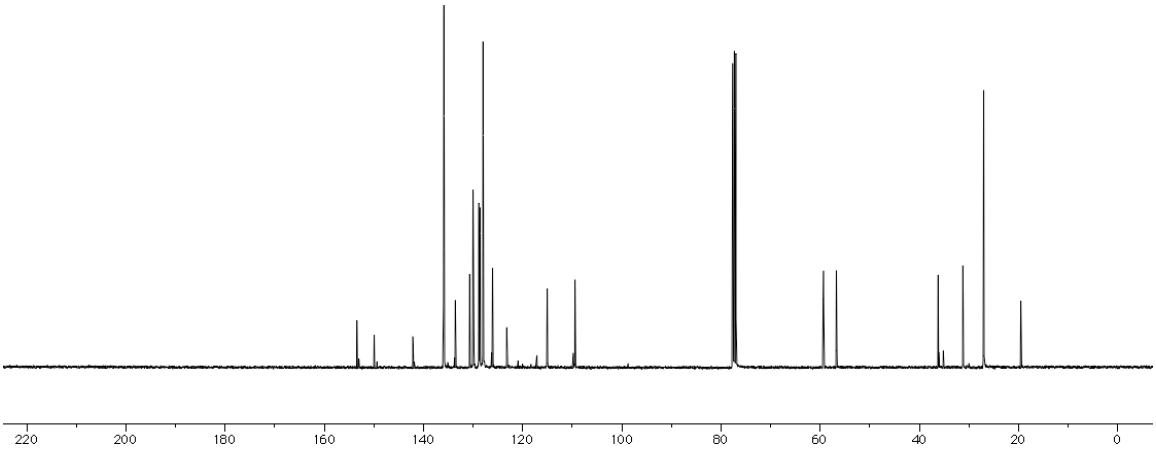


Figure A2.54 IR spectrum (thin film, NaCl) of compound **p286**

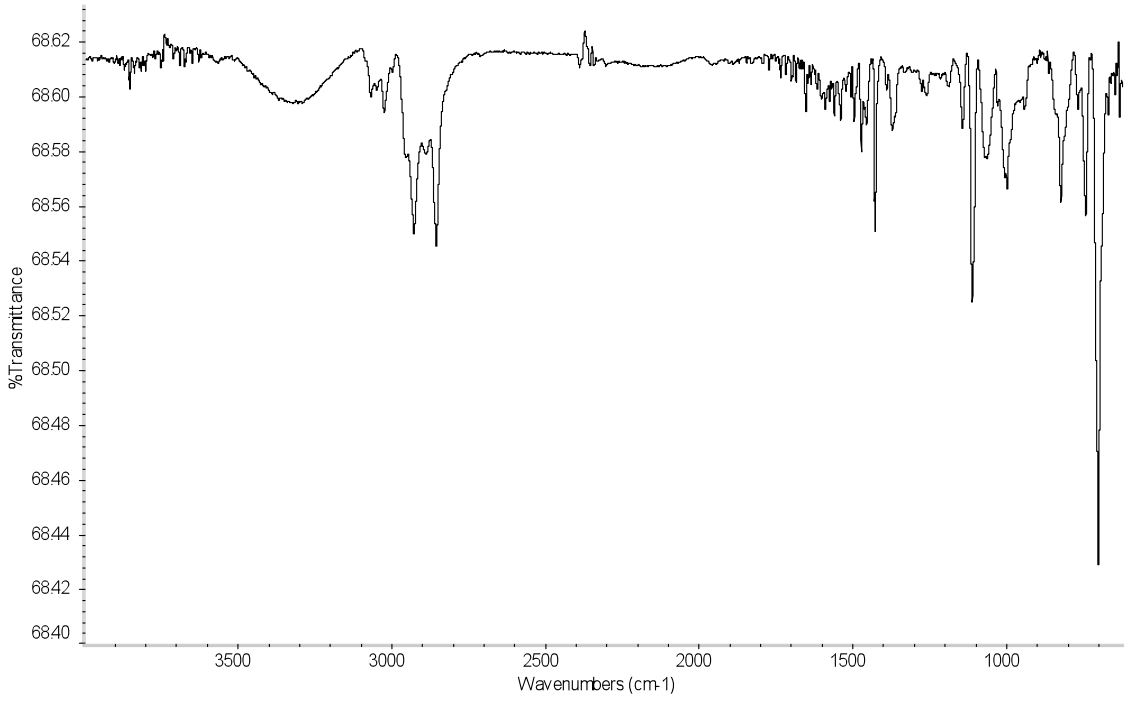


Figure A2.55 1H NMR spectrum (400MHz, CDCl3) of compound **285/286**

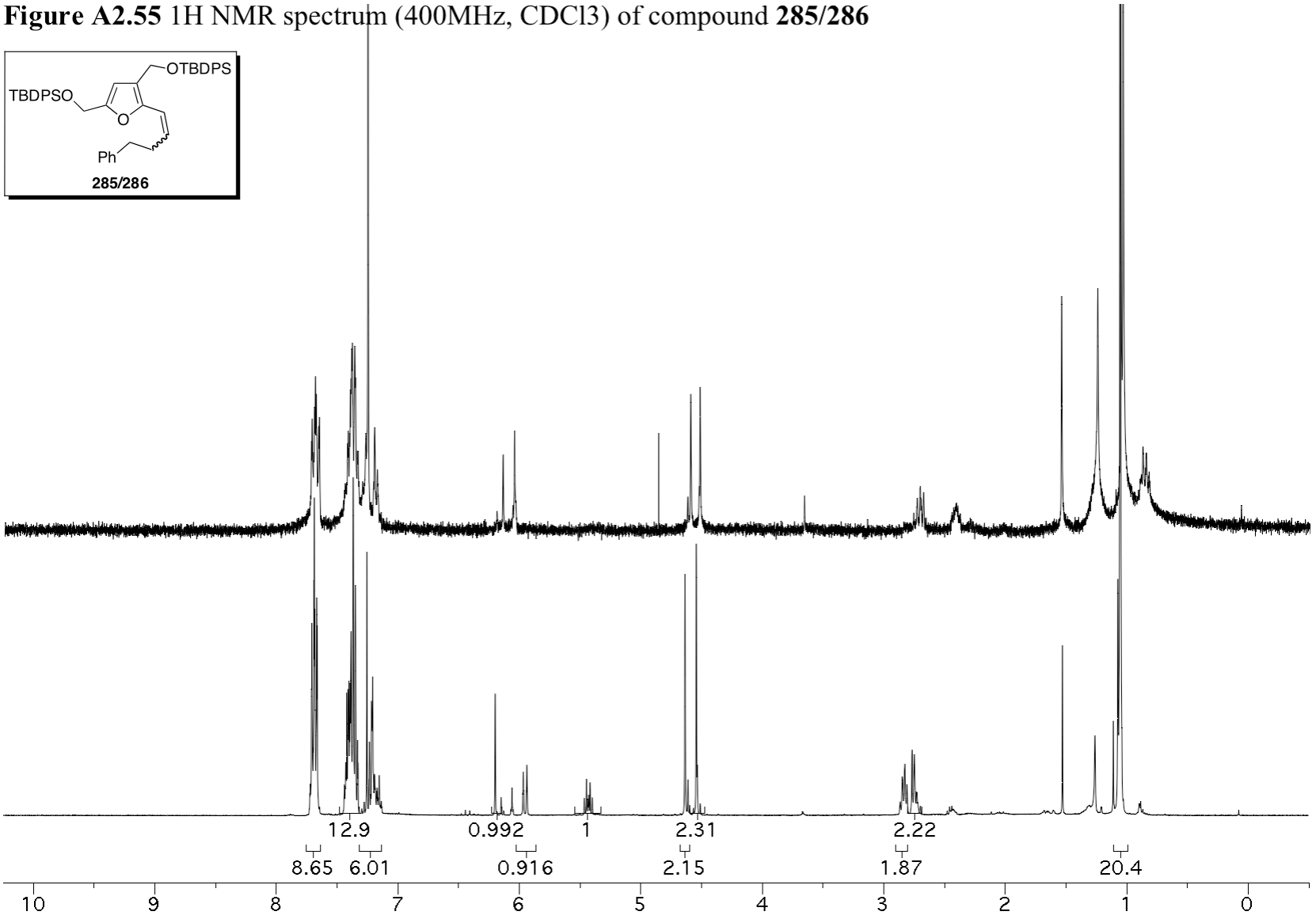


Figure A2.56 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **285/286**

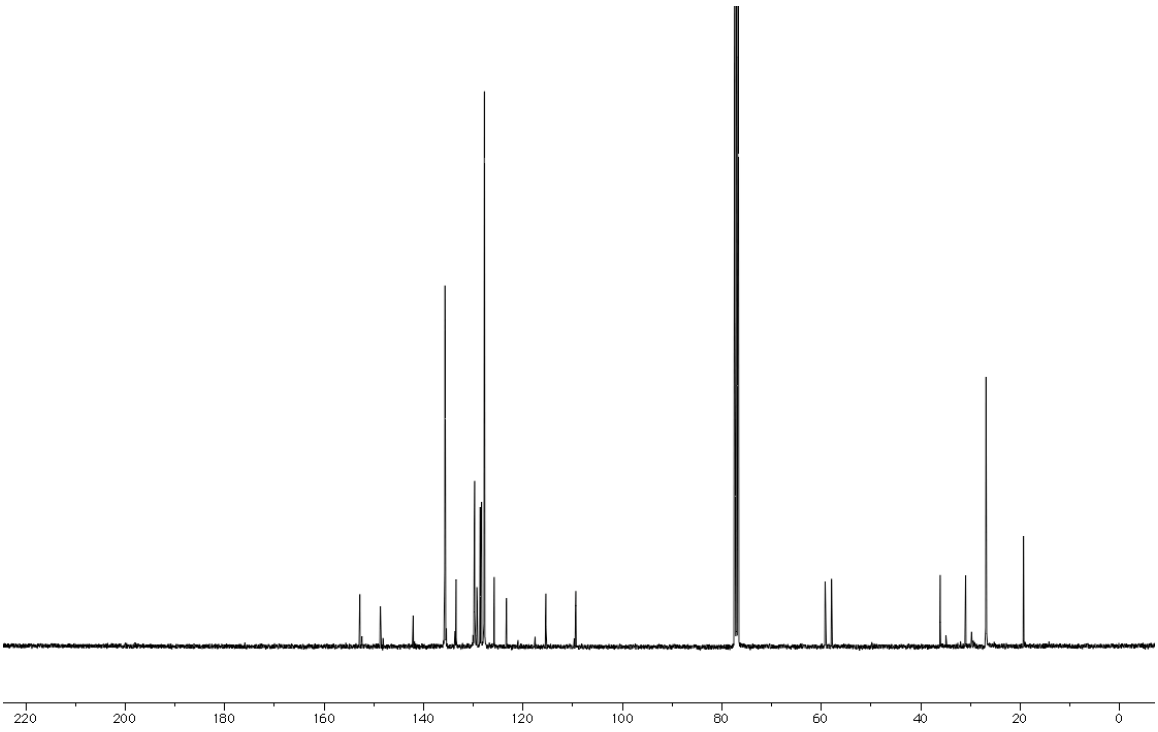


Figure A2.57 IR spectrum (thin film, NaCl) of compound **285/286**

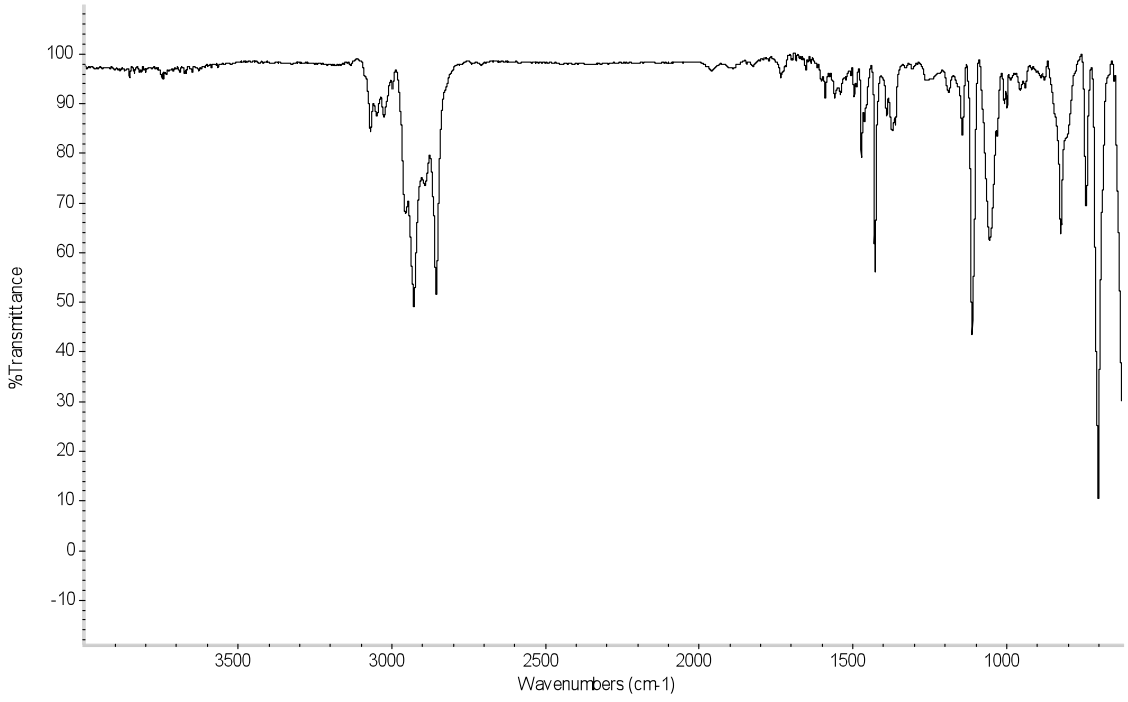


Figure A2.58 1H NMR spectrum (400MHz, CDCl3) of compound **pp288**

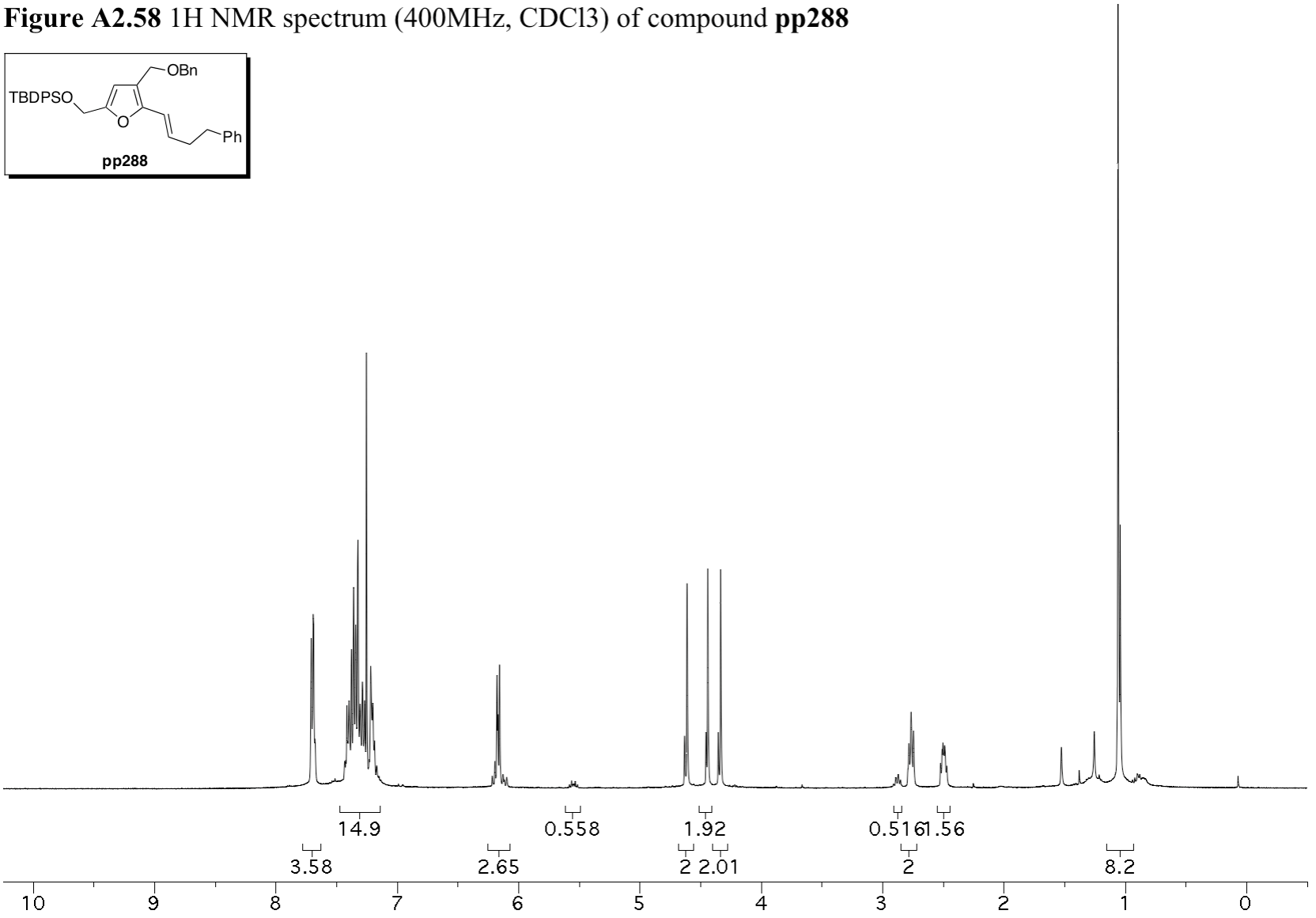


Figure A2.59 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **pp288**

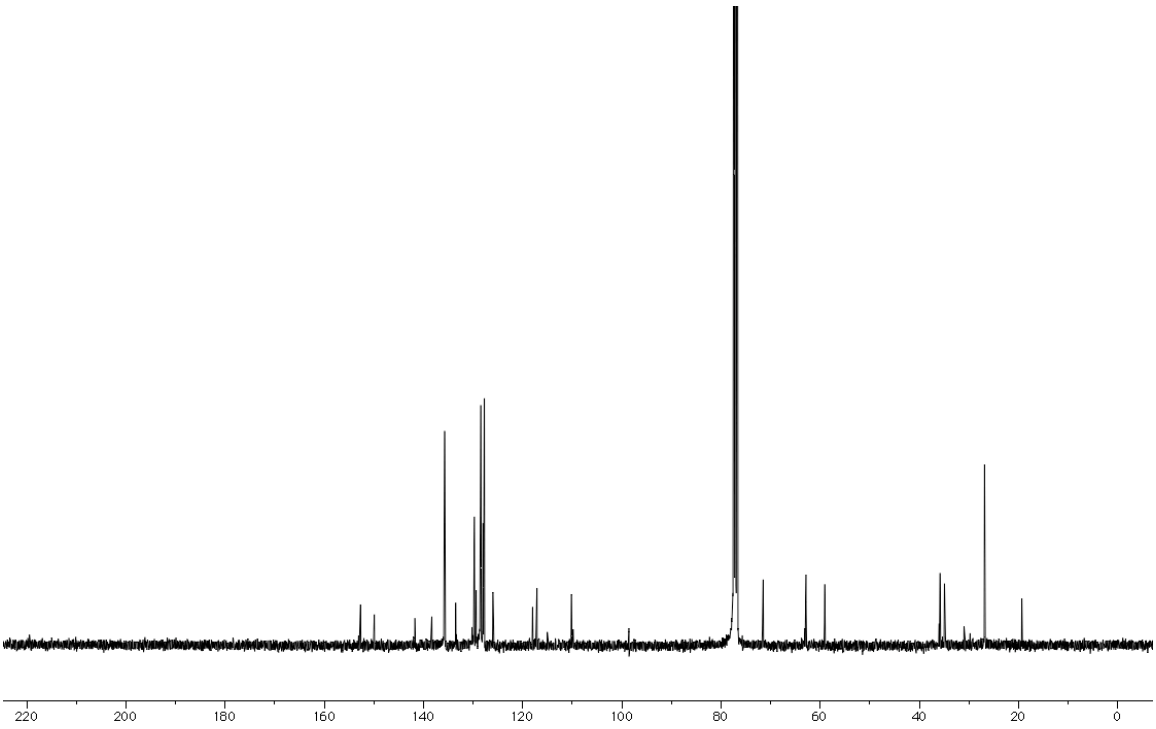


Figure A2.60 IR spectrum (thin film, NaCl) of compound **pp288**

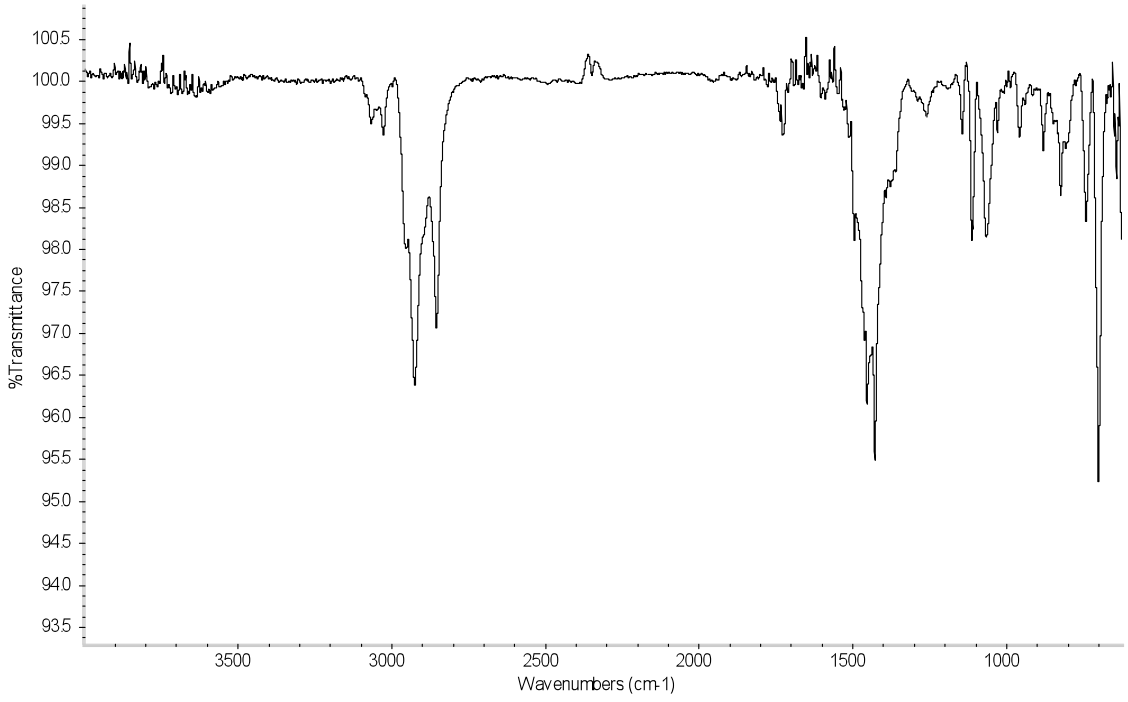
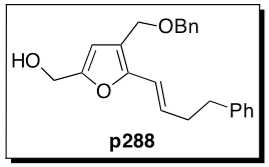


Figure A2.61 1H NMR spectrum (400MHz, CDCl3) of compound **p288**



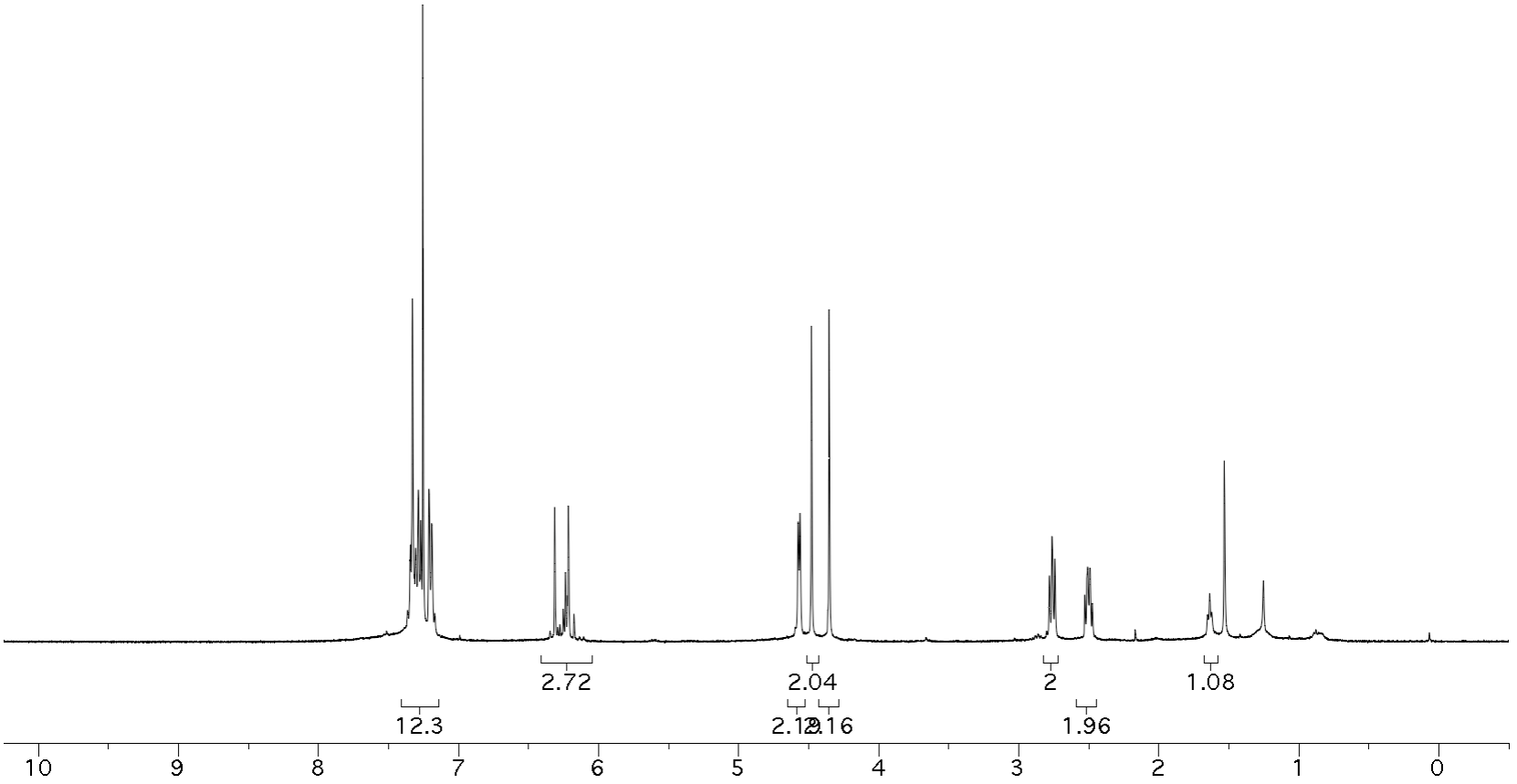


Figure A2.62 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **p288**

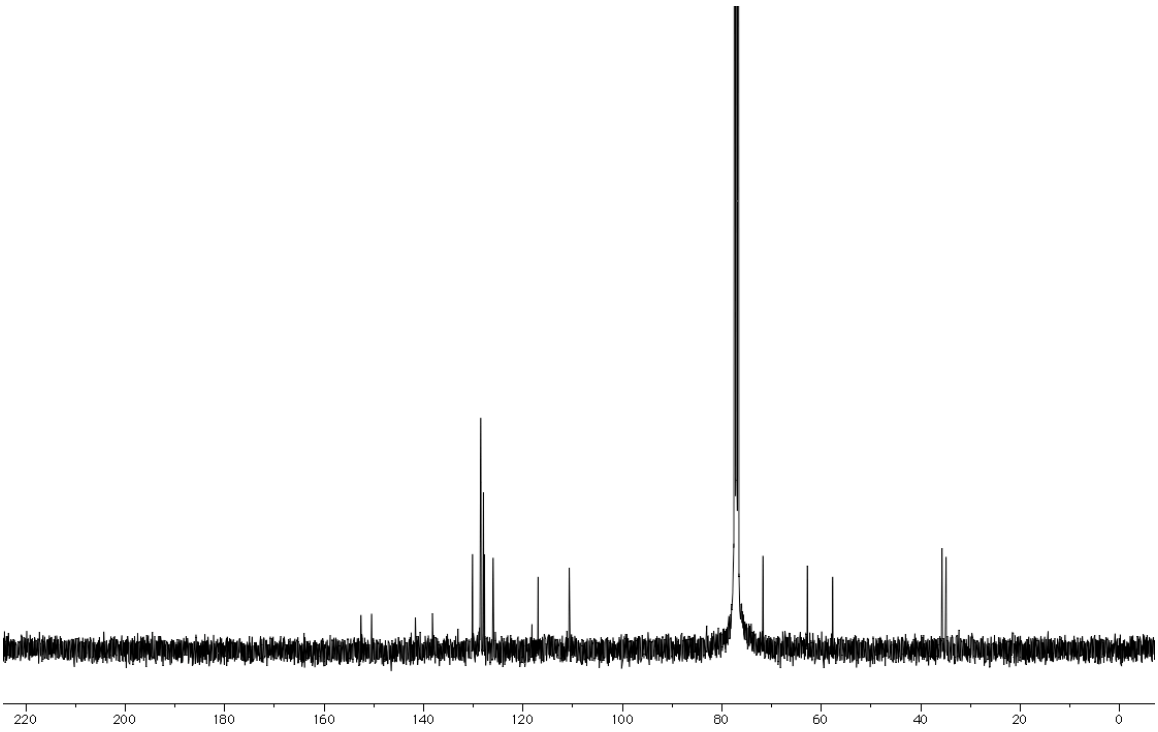


Figure A2.63 IR spectrum (thin film, NaCl) of compound **p288**

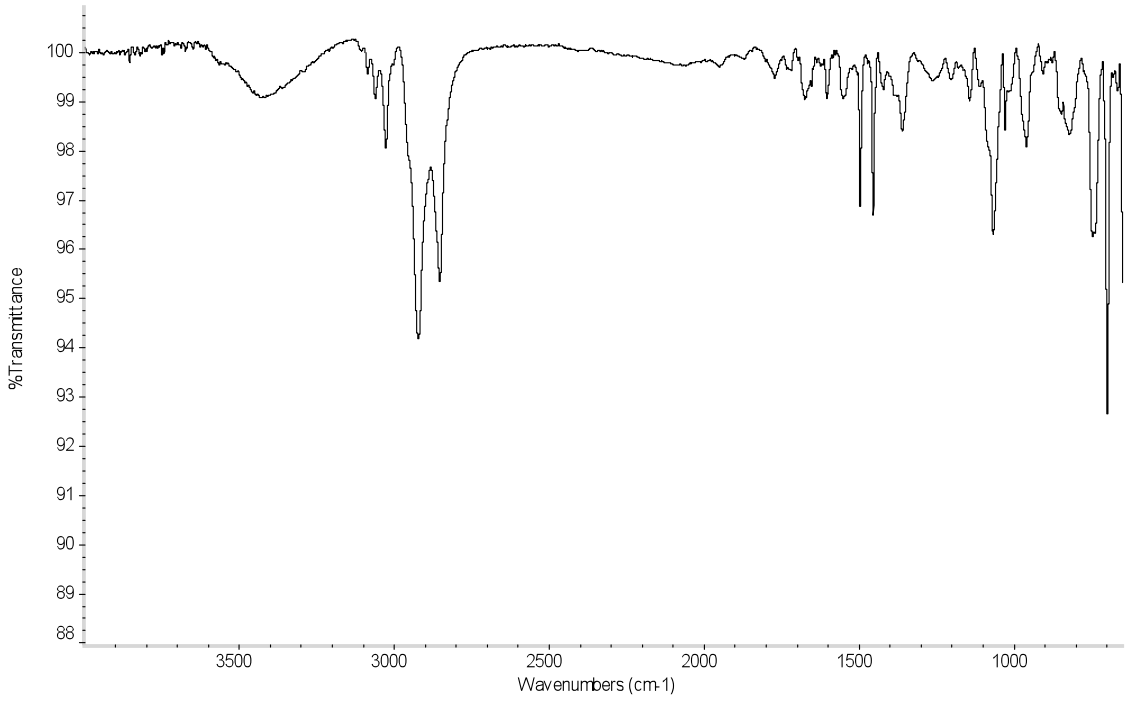
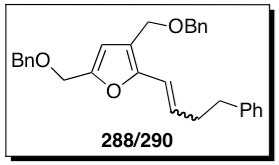


Figure A2.64 1H NMR spectrum (400MHz, CDCl3) of compound **288/290**



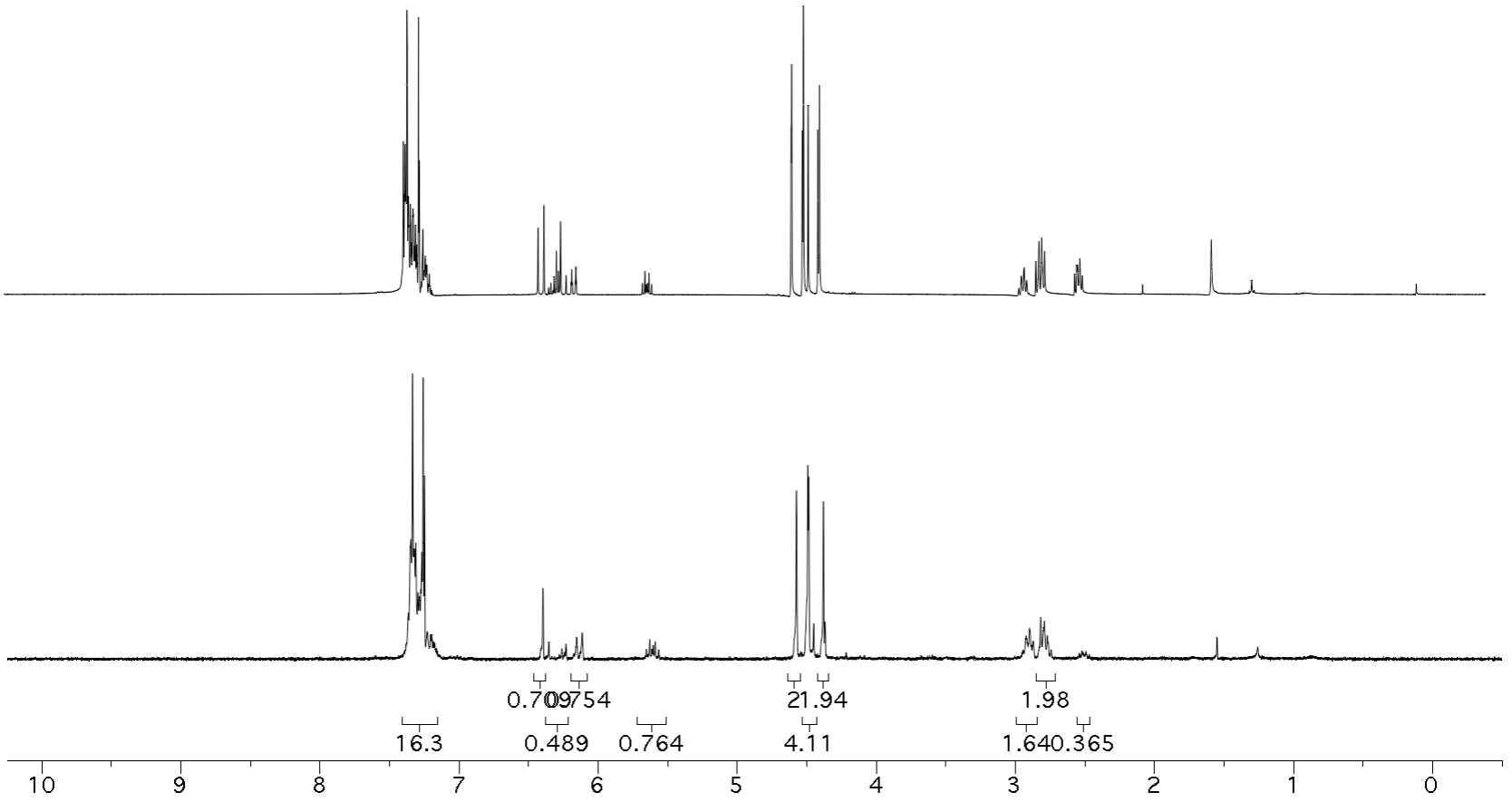


Figure A2.65 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **288/290**

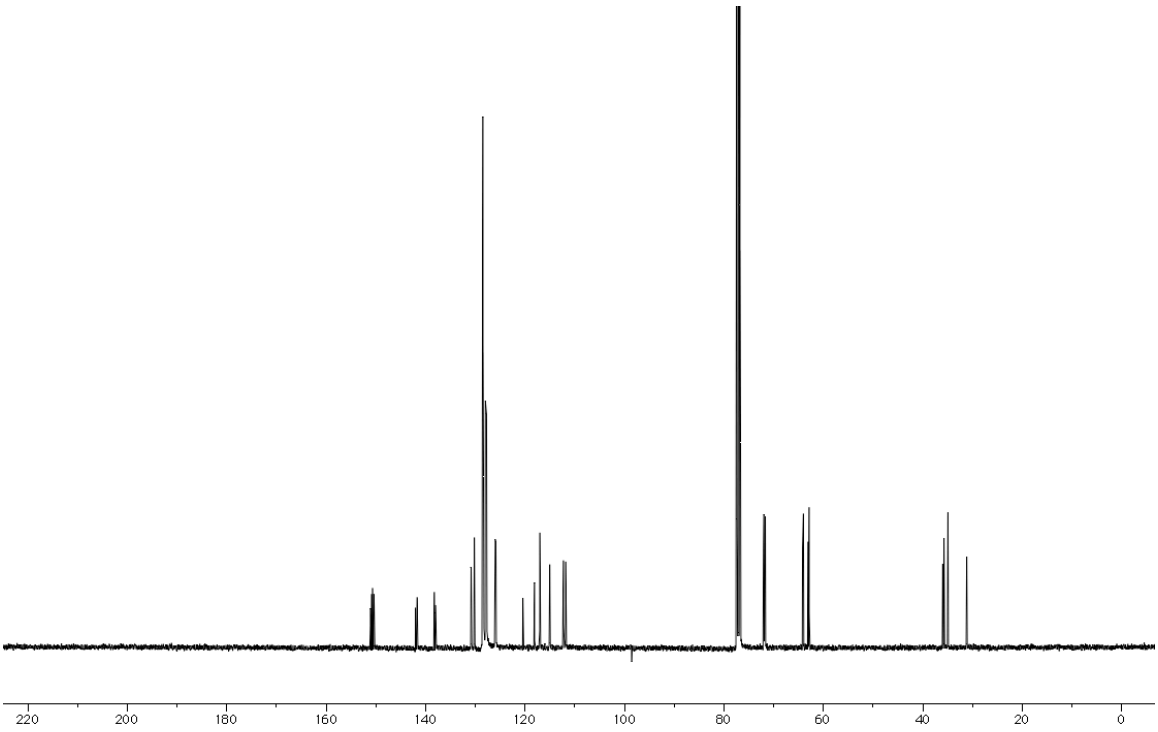


Figure A2.66 IR spectrum (thin film, NaCl) of compound **288/290**

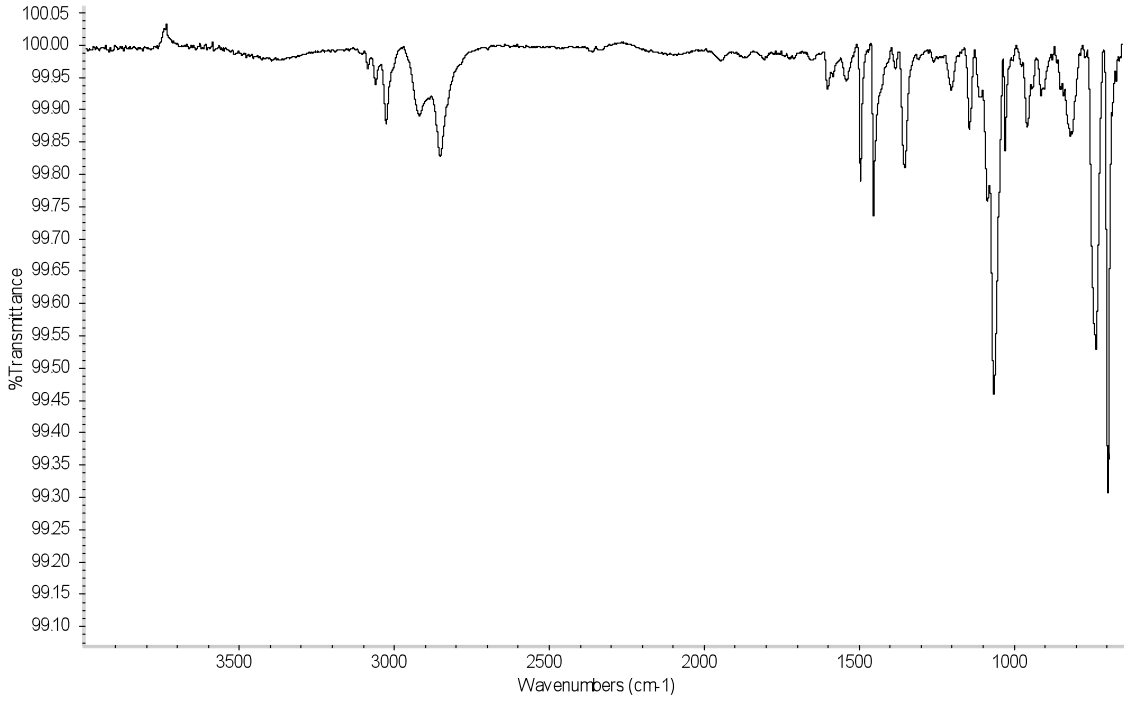


Figure A2.67 1H NMR spectrum (400MHz, CDCl3) of compound **pp290**

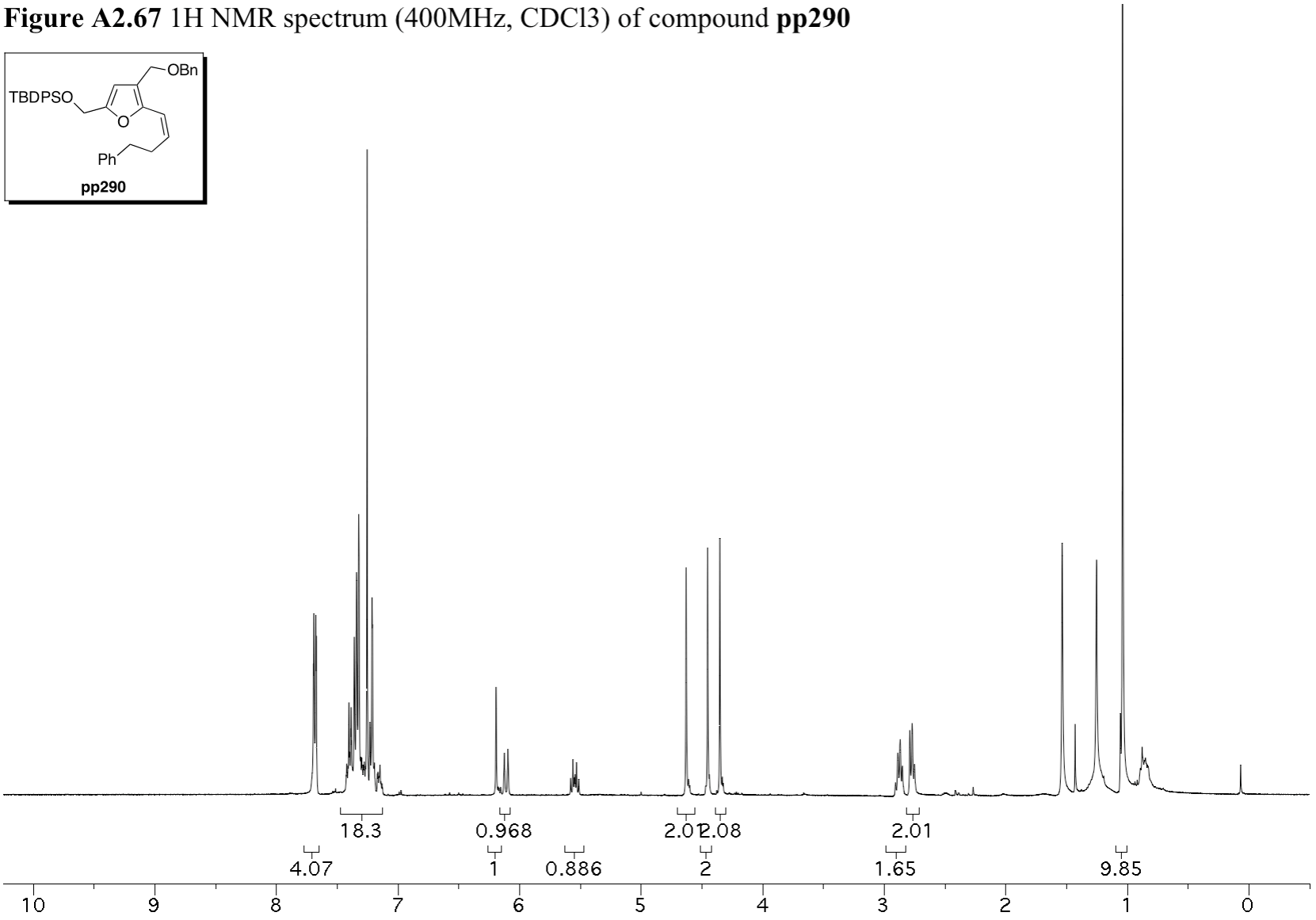


Figure A2.68 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **pp290**

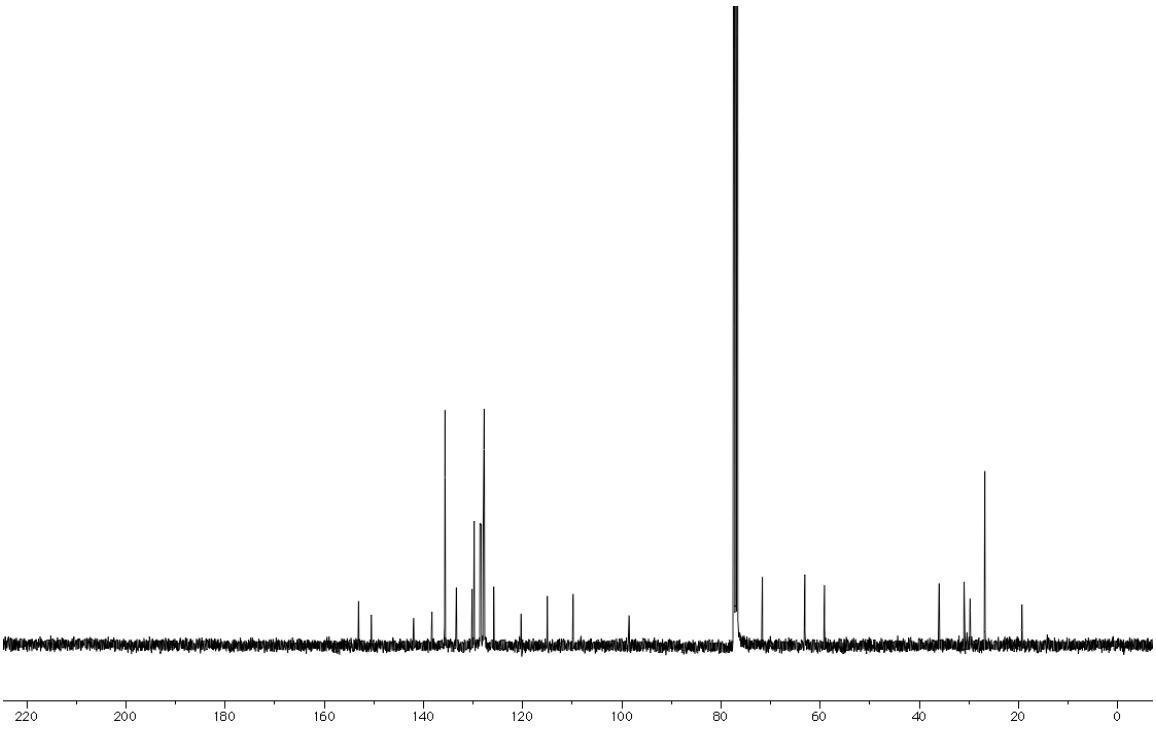


Figure A2.69 IR spectrum (thin film, NaCl) of compound **pp290**

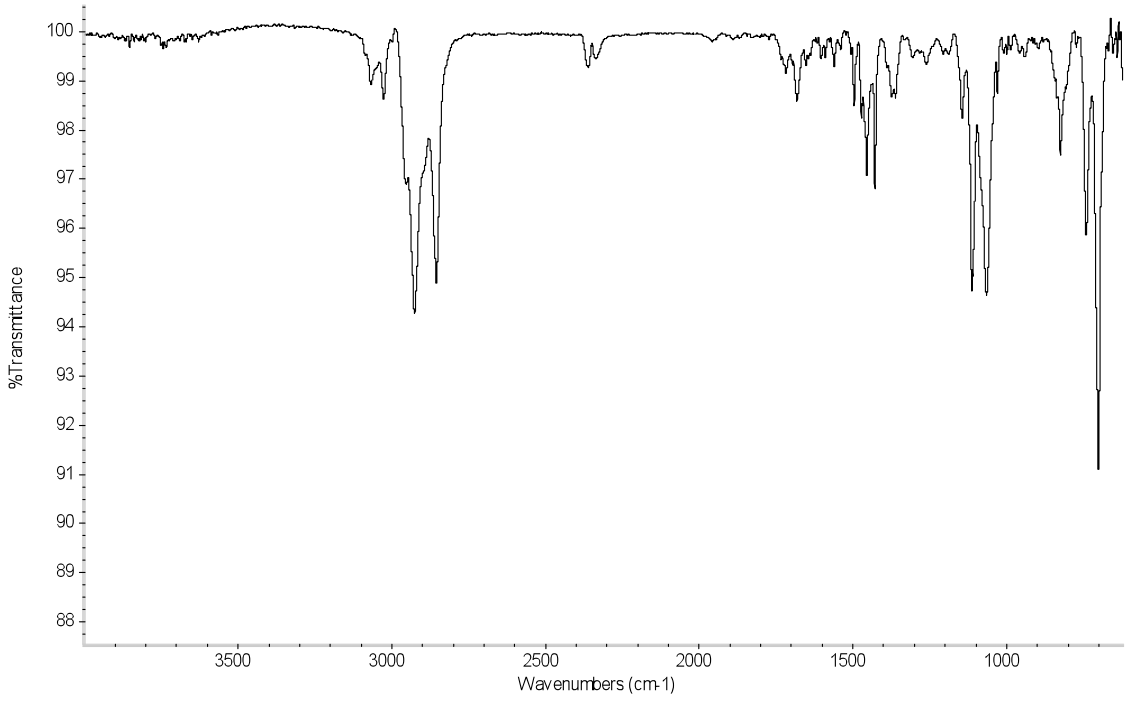


Figure A2.70 1H NMR spectrum (400MHz, CDCl3) of compound **p290**

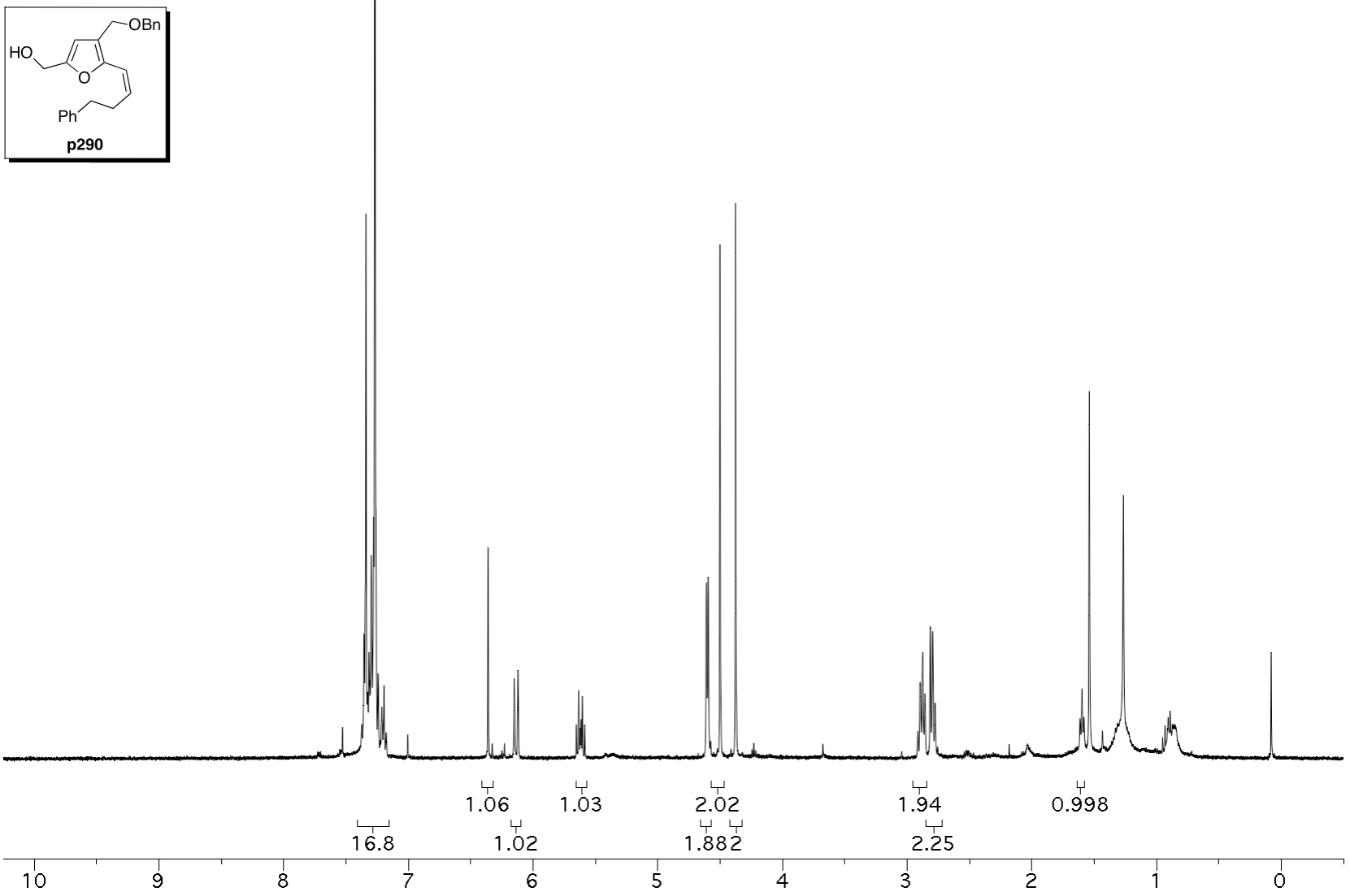


Figure A2.71 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **p290**

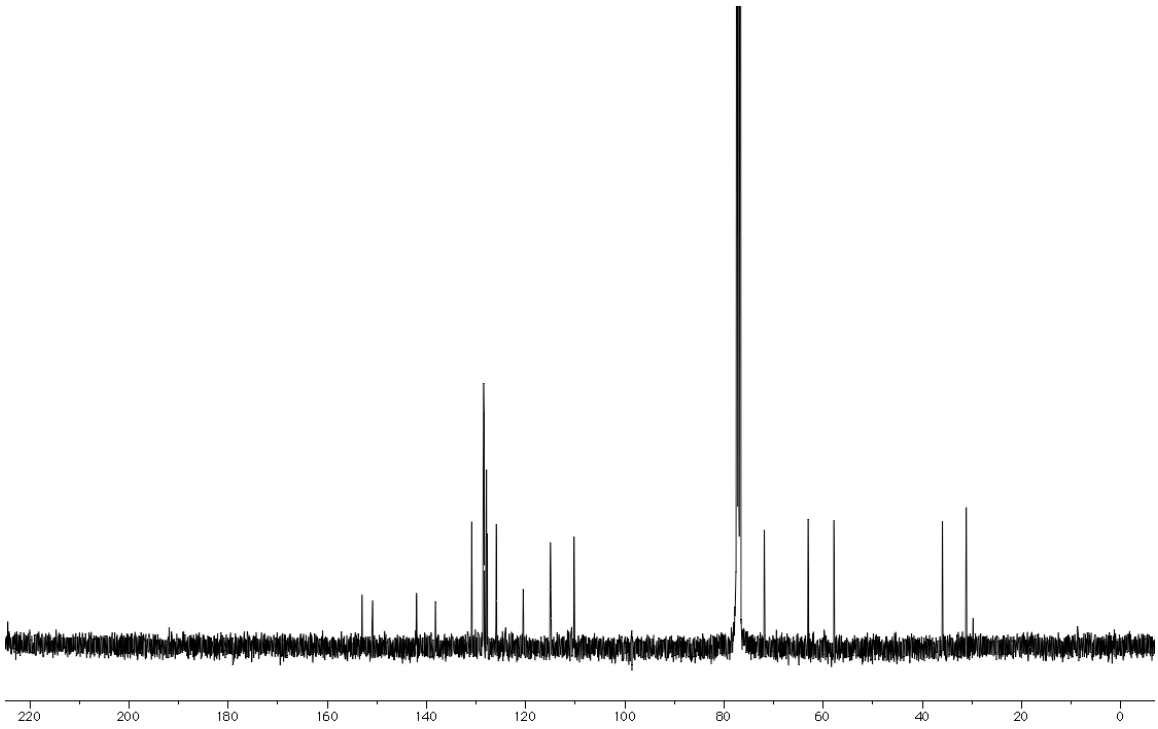


Figure A2.72 IR spectrum (thin film, NaCl) of compound **p290**

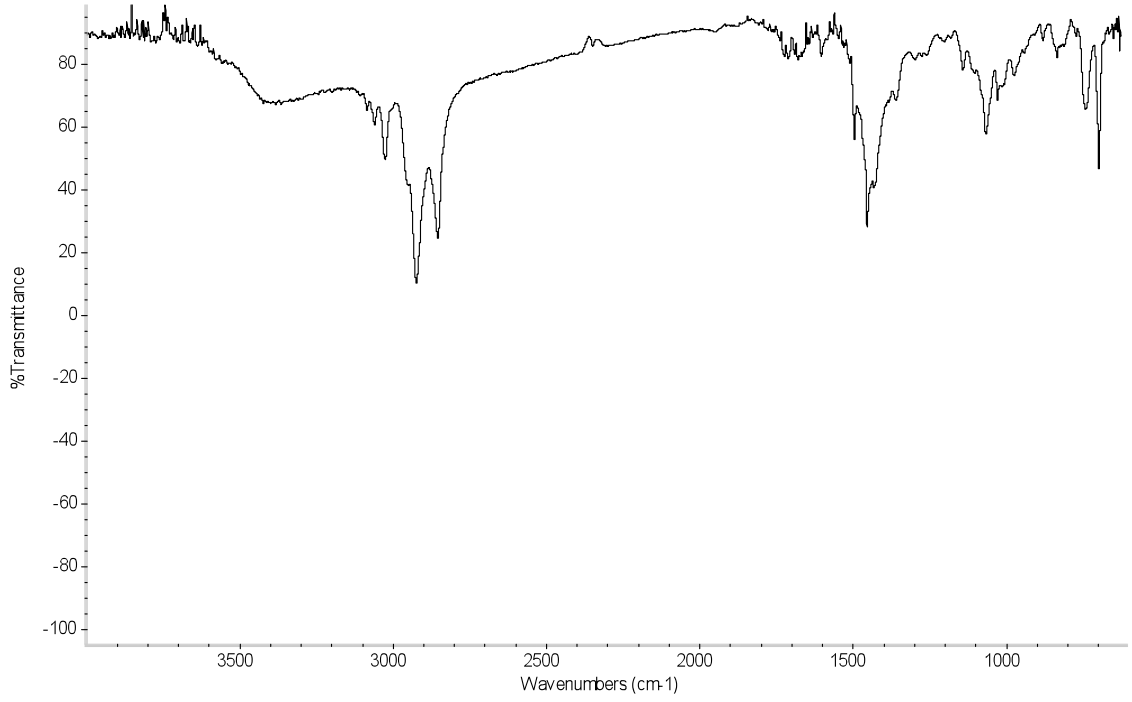


Figure A2.73 1H NMR spectrum (400MHz, CDCl3) of compound **291**

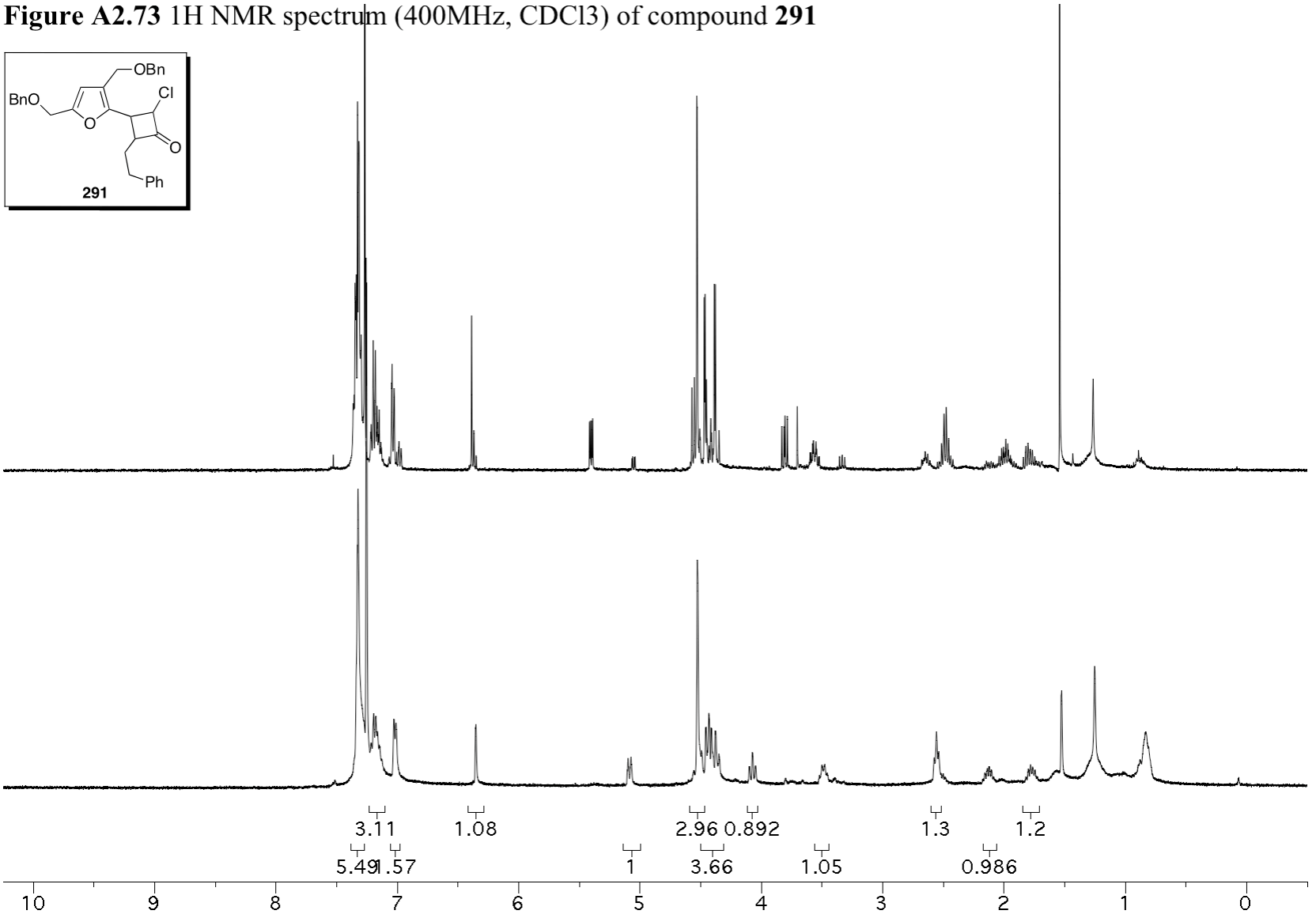


Figure A2.74 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **291**

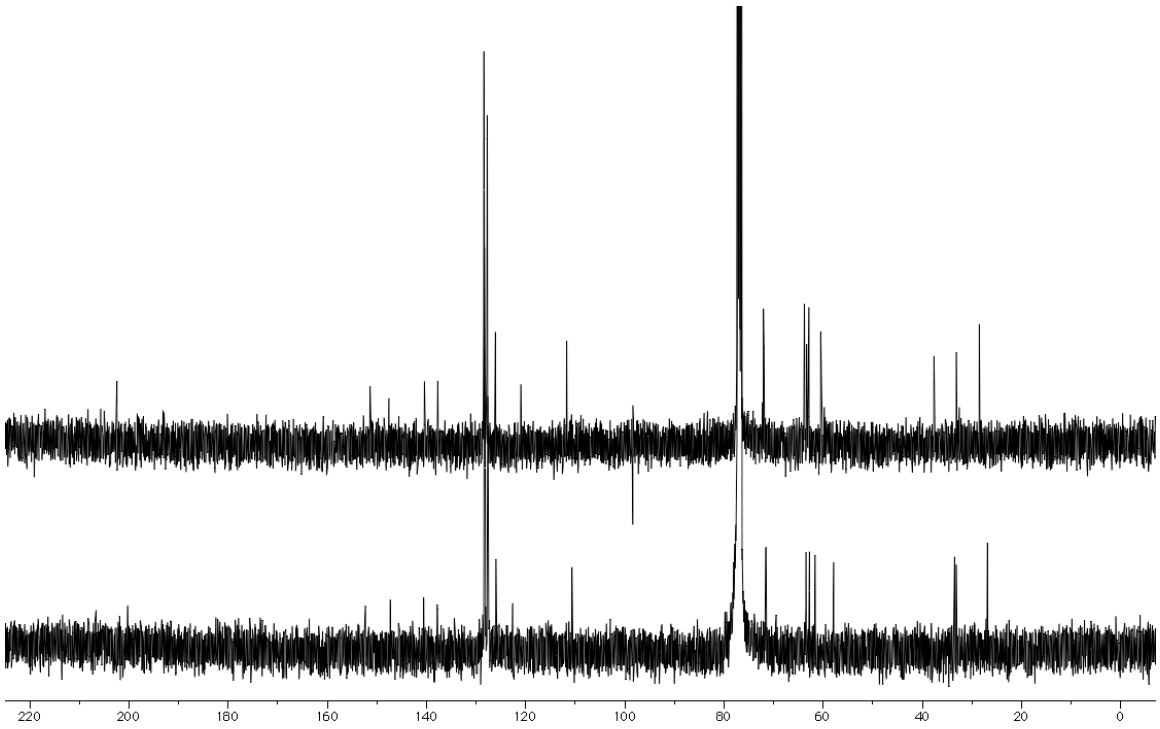


Figure A2.75 IR spectrum (thin film, NaCl) of compound **291**

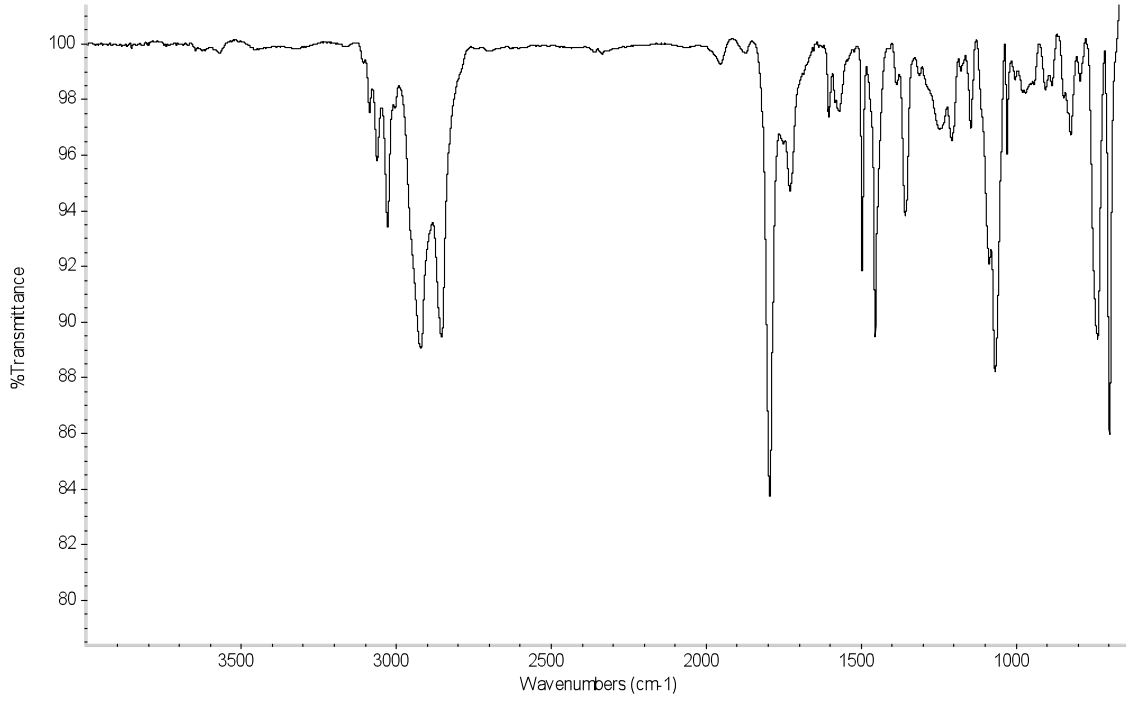


Figure A2.76 1H NMR spectrum (400MHz, CDCl3) of compound **307**

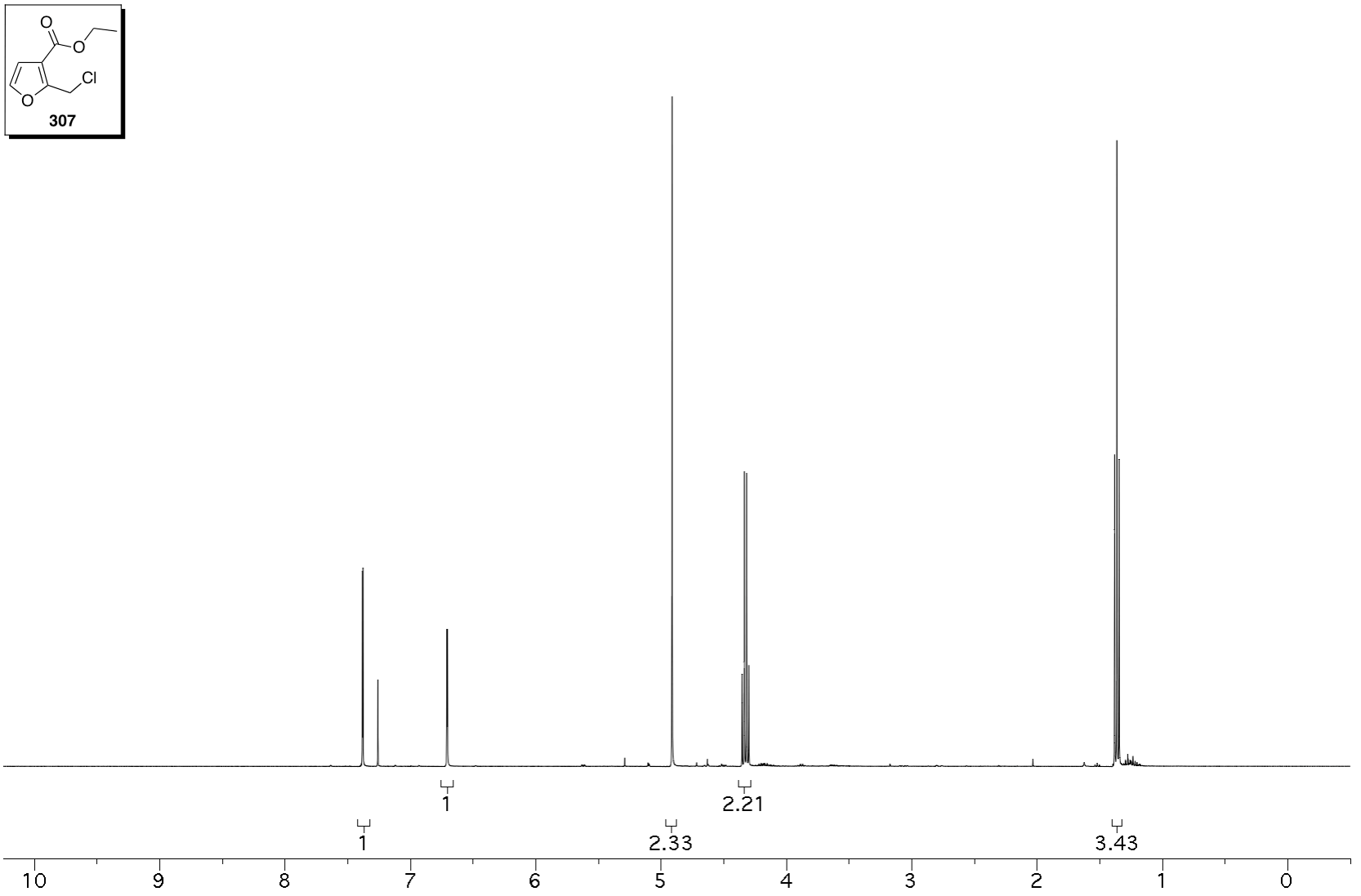


Figure A2.77 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **307**

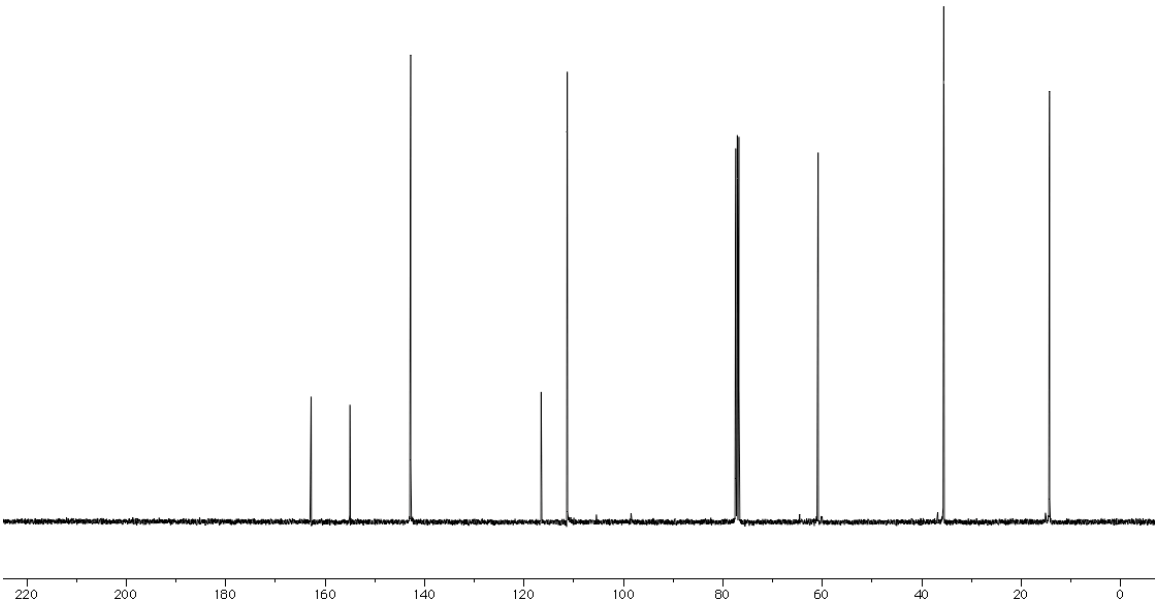


Figure A2.78 IR spectrum (thin film, NaCl) of compound **307**

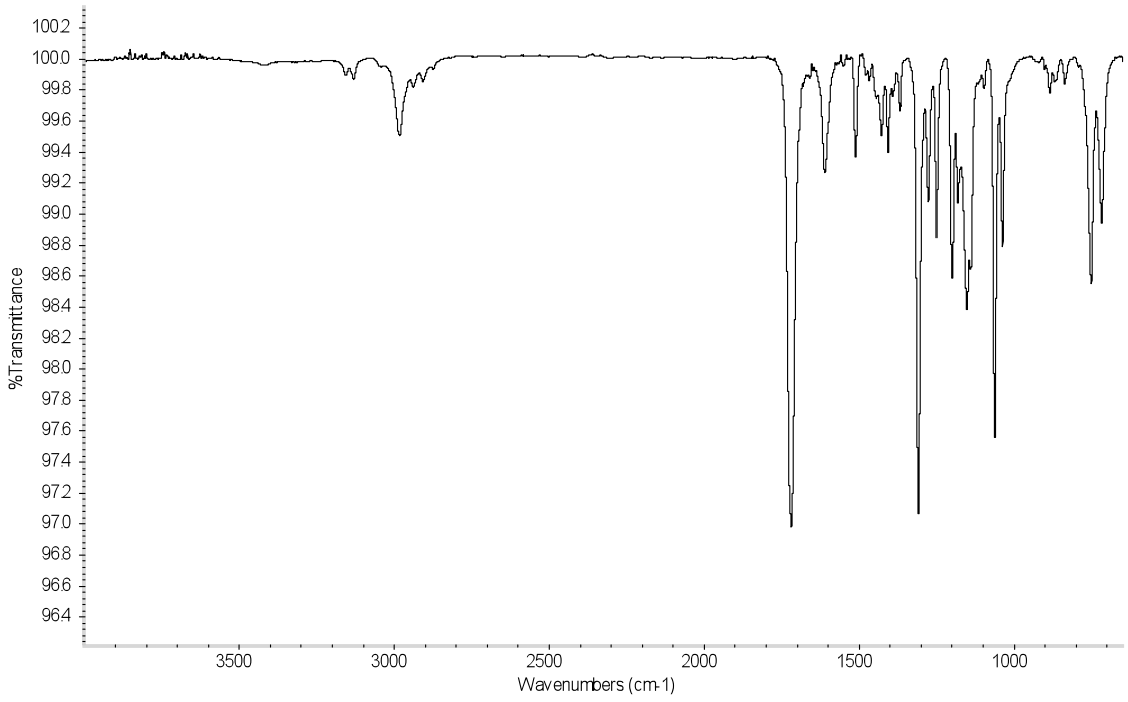
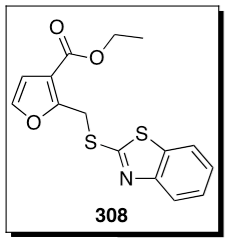


Figure A2.79 1H NMR spectrum (400MHz, CDCl3) of compound **308**



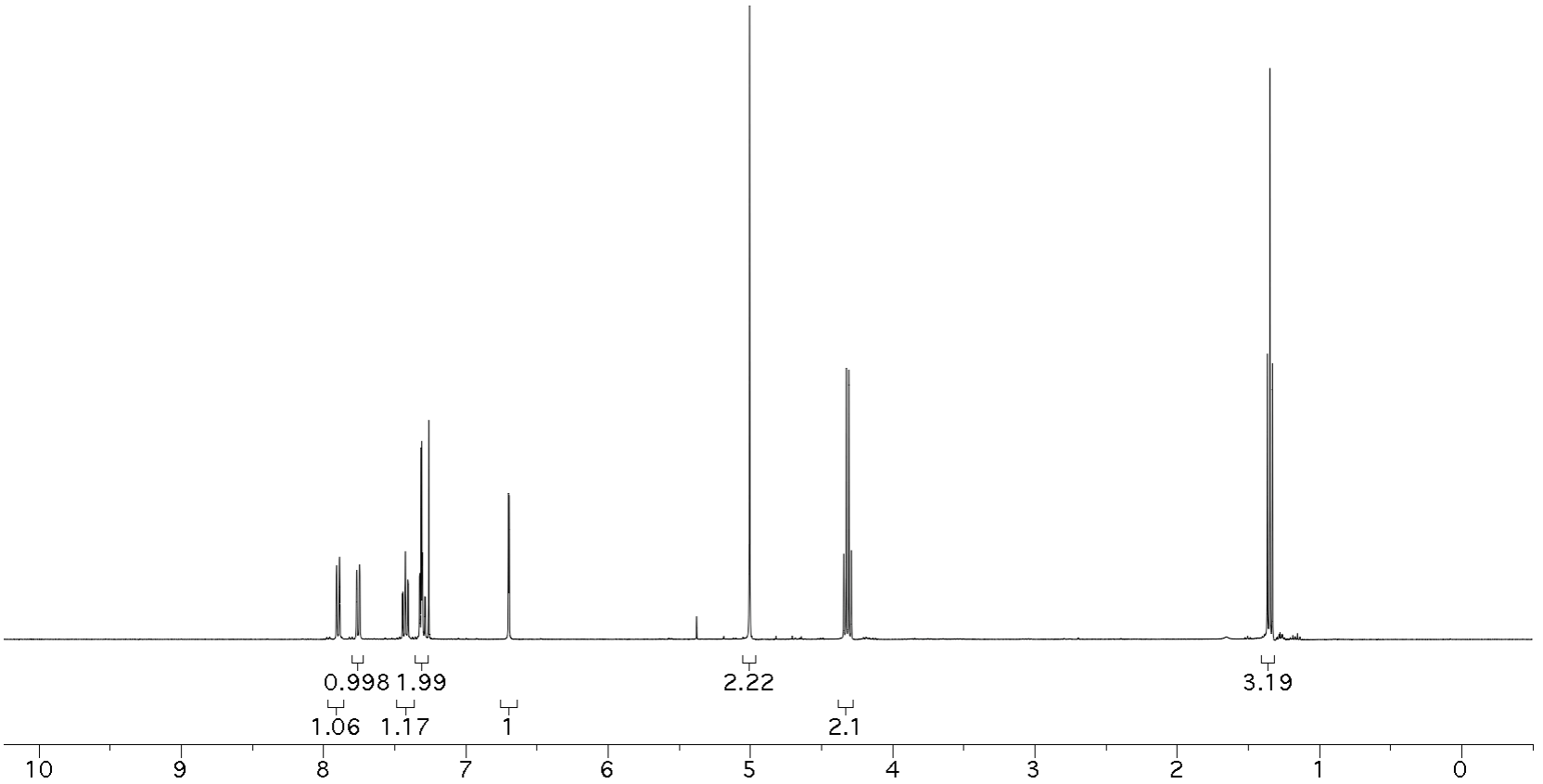


Figure A2.80 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **308**

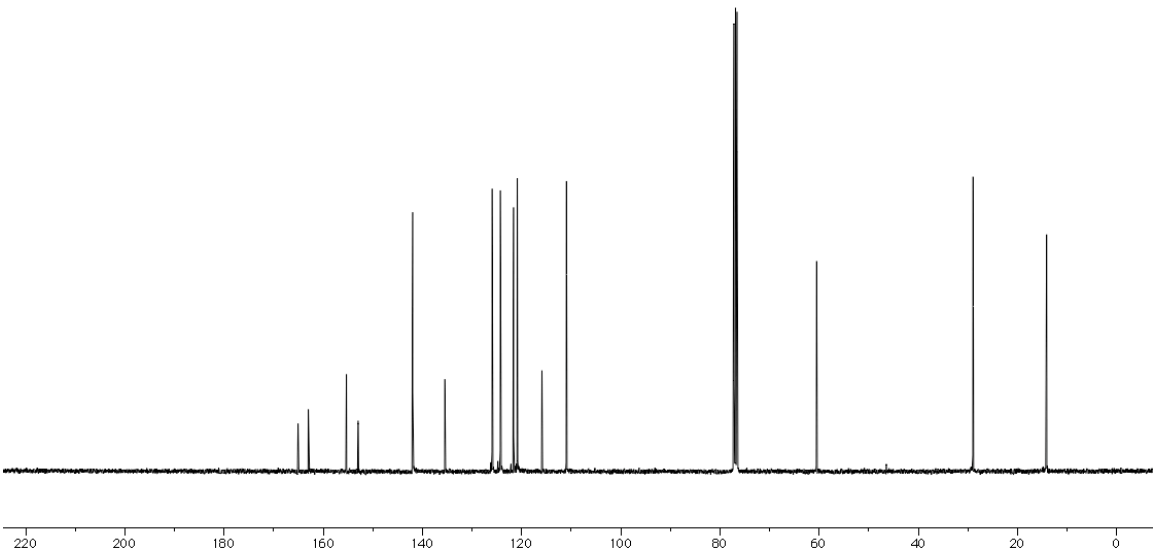


Figure A2.81 IR spectrum (thin film, NaCl) of compound **308**

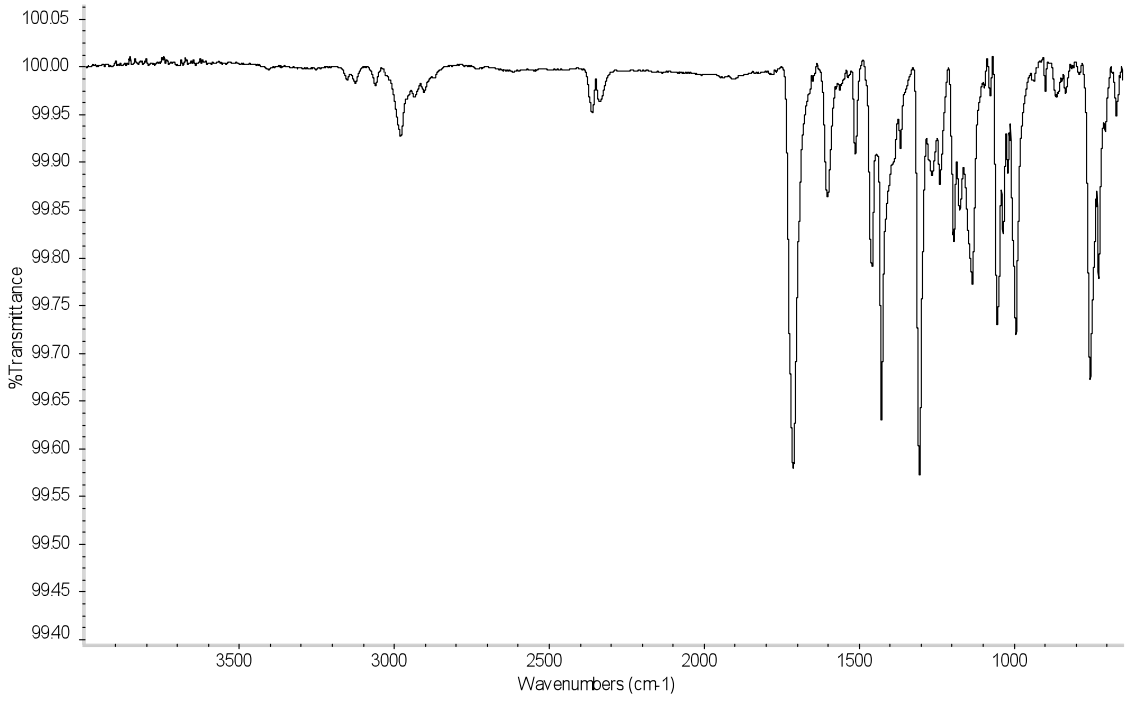


Figure A2.82 1H NMR spectrum (400MHz, CDCl3) of compound **309**

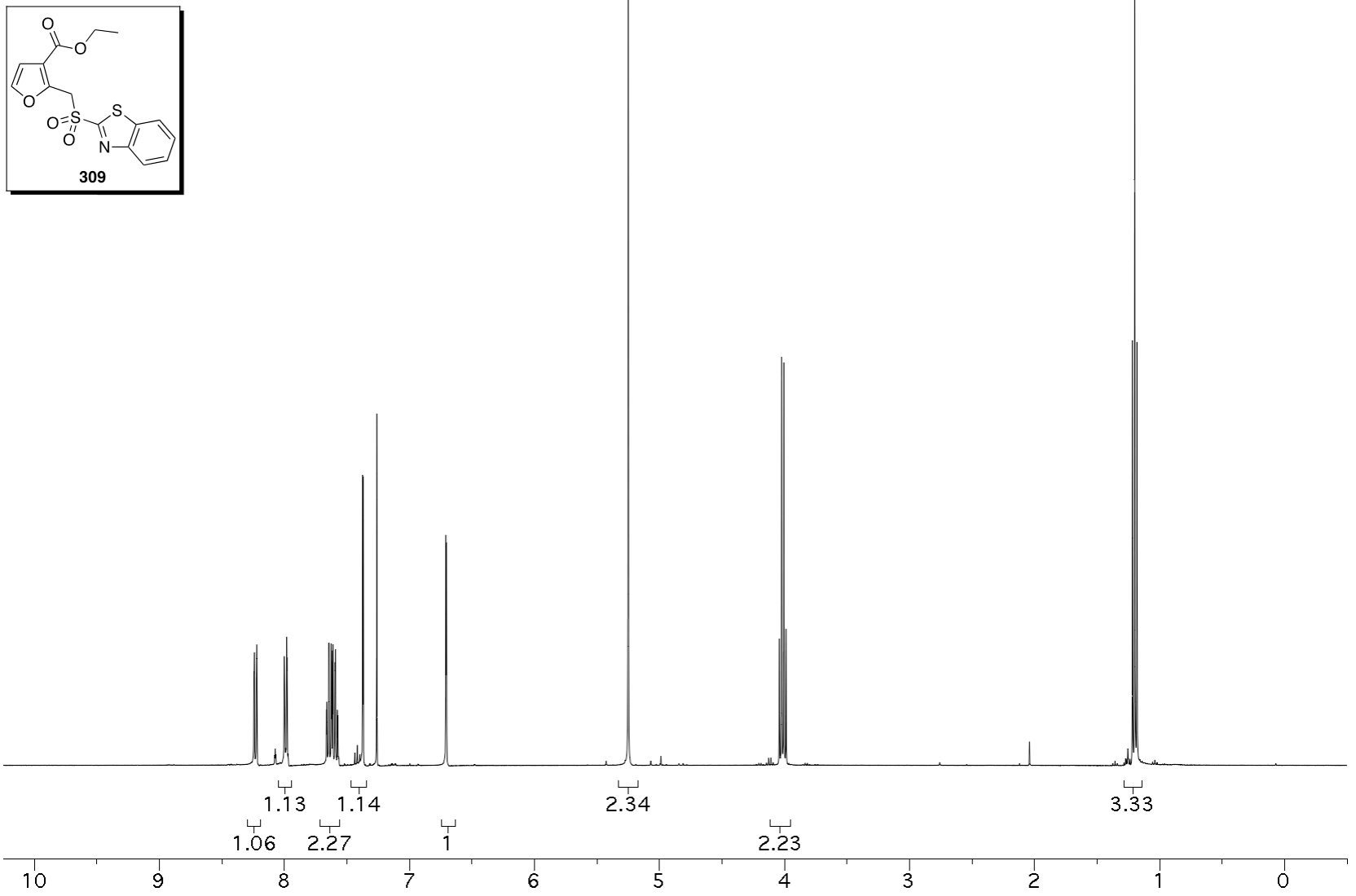


Figure A2.83 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **309**

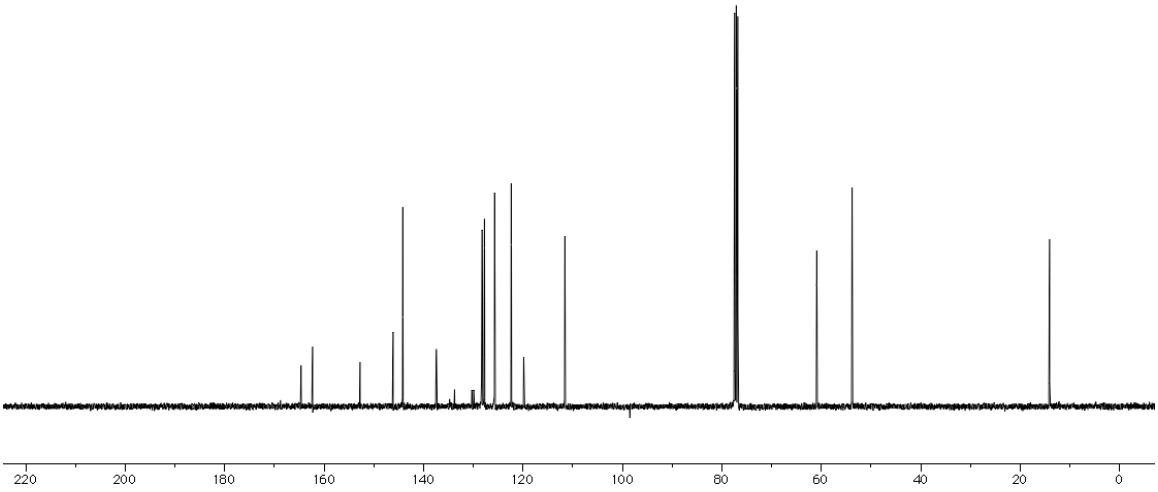


Figure A2.84 IR spectrum (thin film, NaCl) of compound **309**

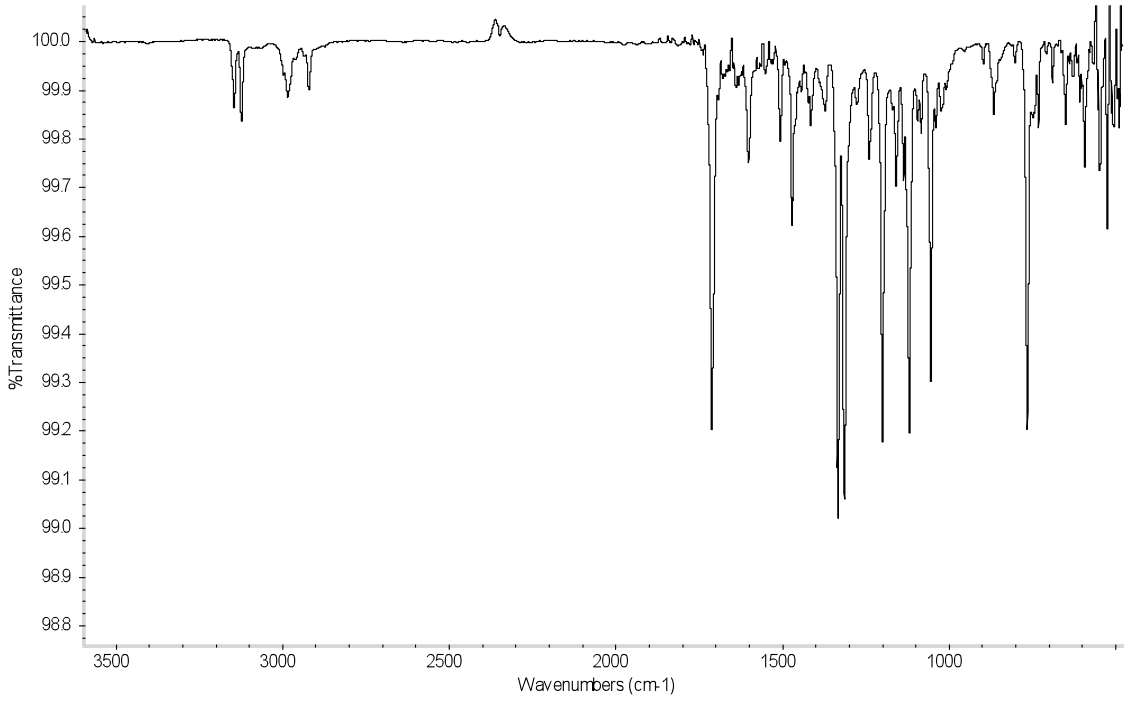


Figure A2.85 1H NMR spectrum (400MHz, CDCl3) of compound **310**

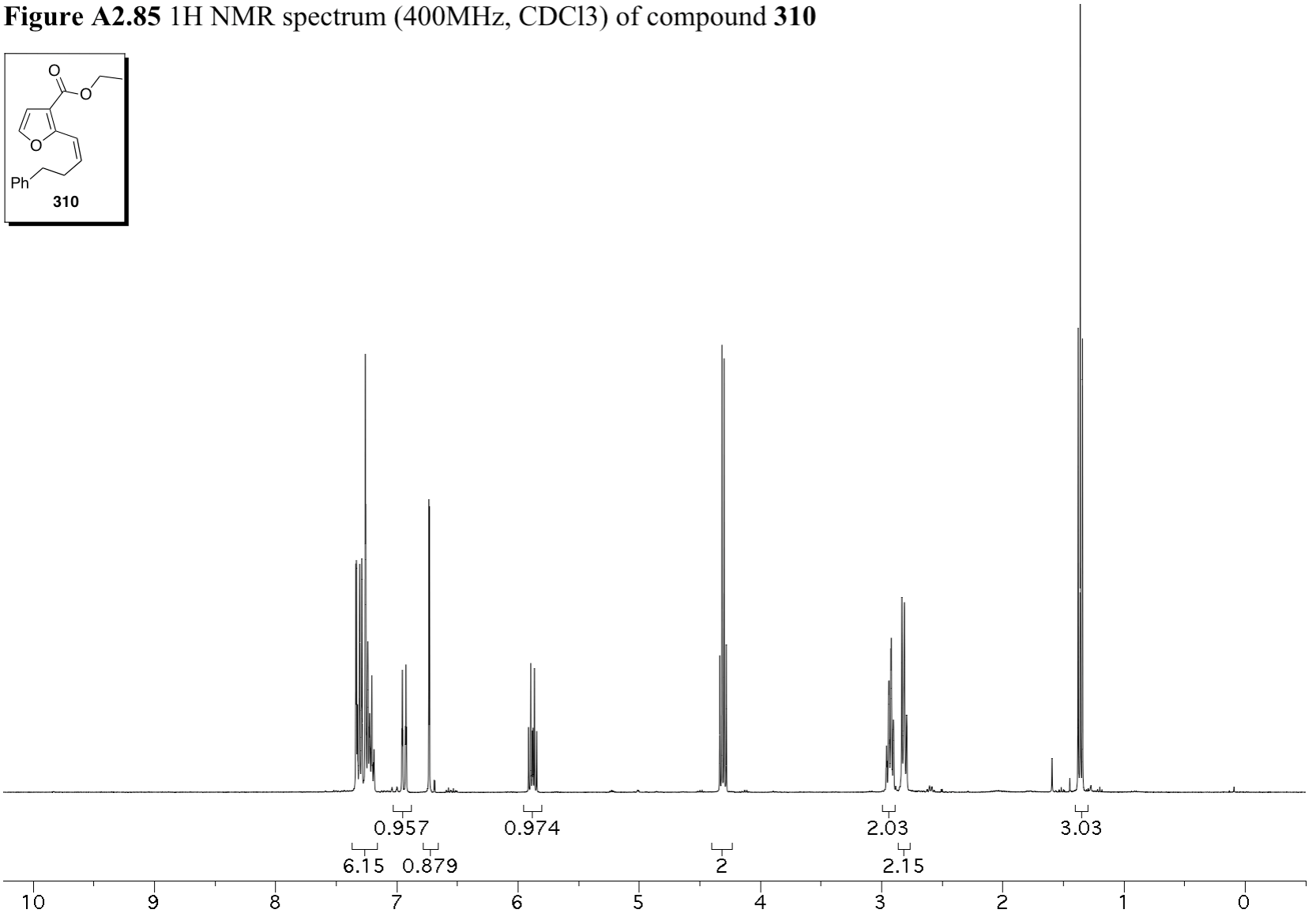


Figure A2.86 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **310**

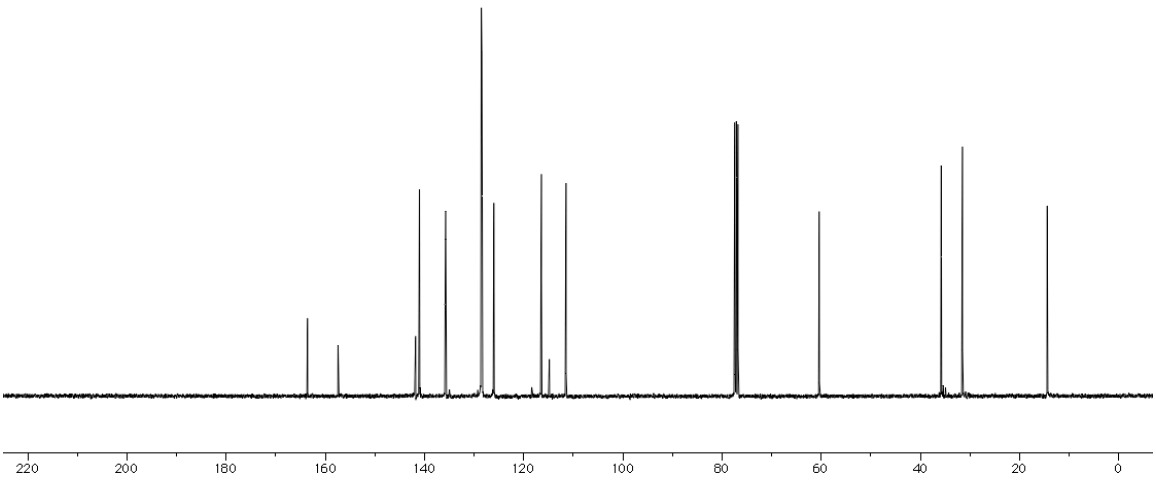


Figure A2.87 IR spectrum (thin film, NaCl) of compound **310**

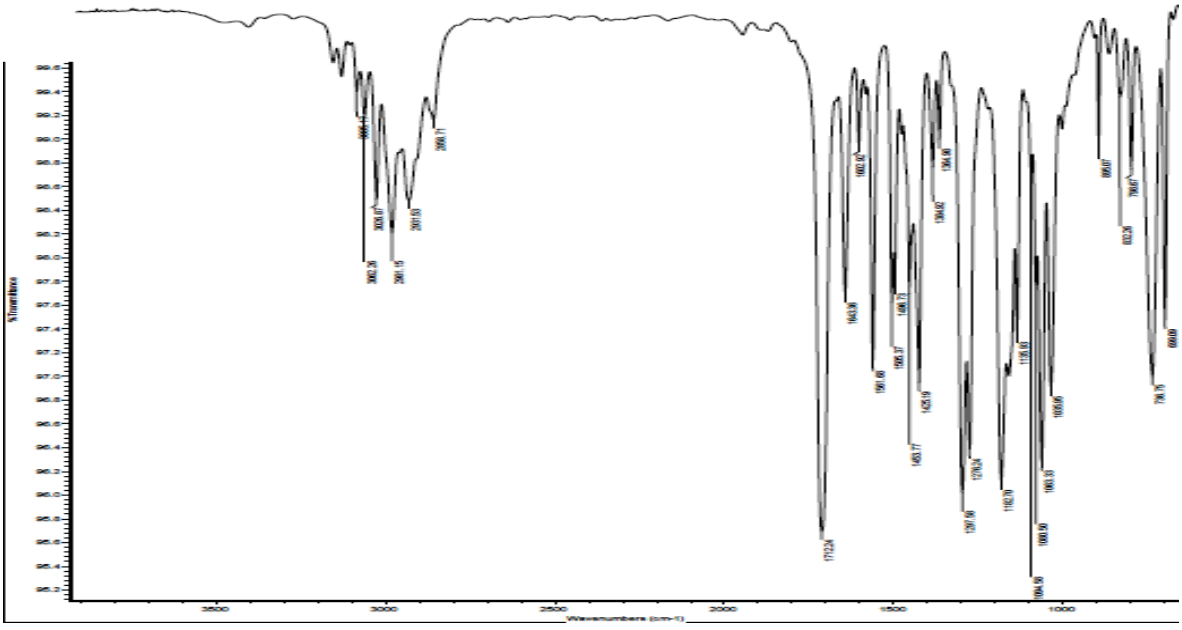
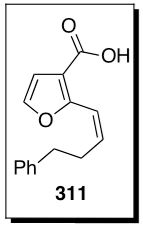


Figure A2.88 1H NMR spectrum (400MHz, CDCl3) of compound **311**



311

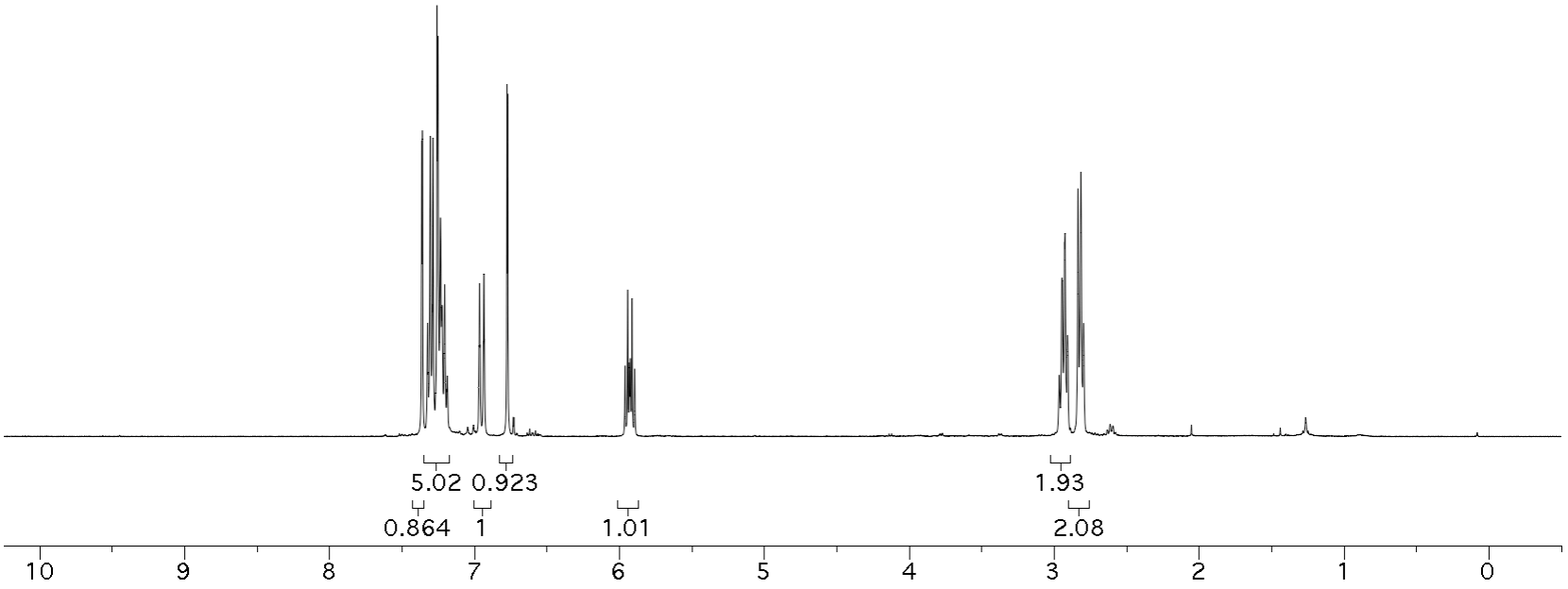


Figure A2.89 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **311**

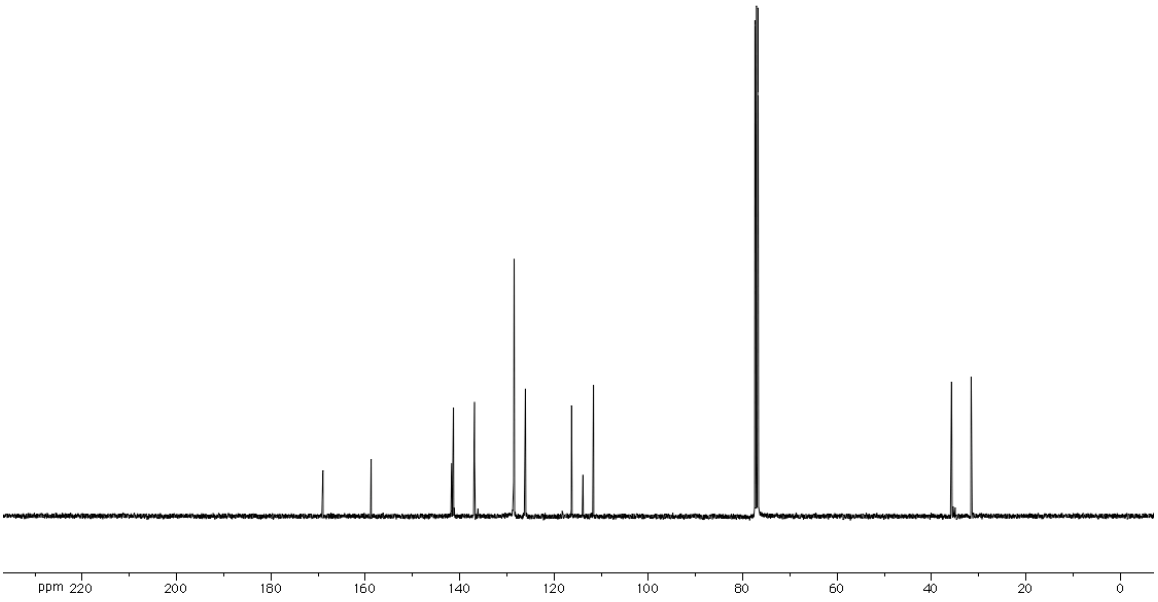


Figure A2.90 IR spectrum (thin film, NaCl) of compound **311**

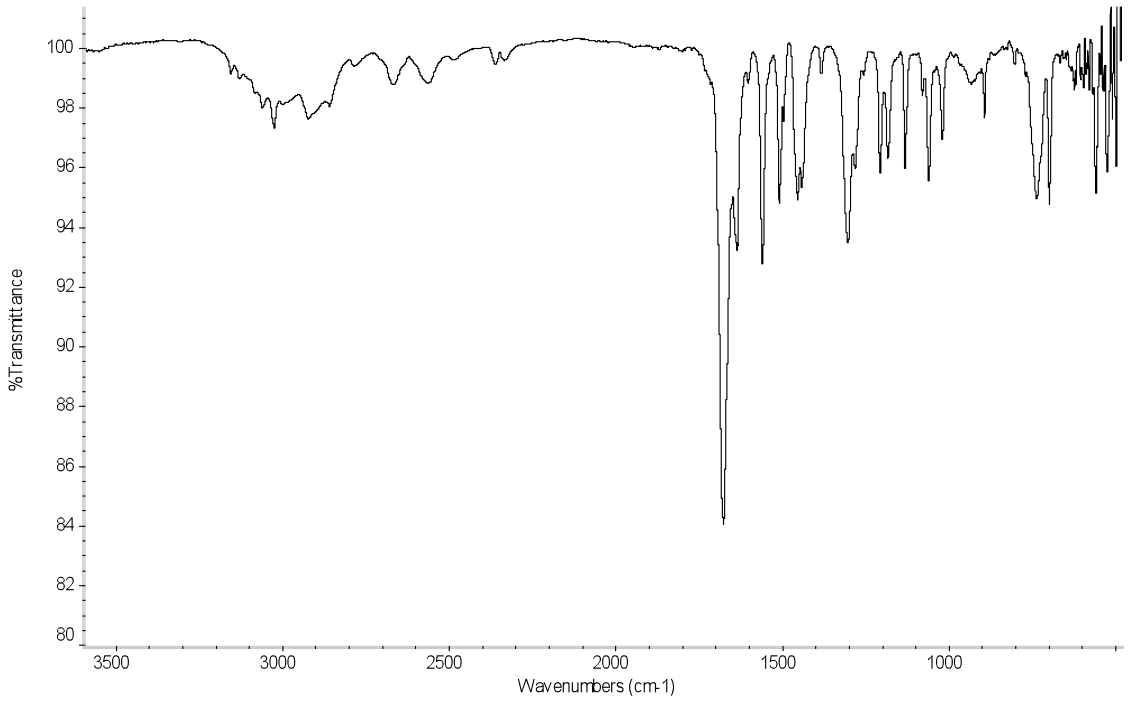


Figure A2.91 1H NMR spectrum (400MHz, CDCl3) of compound **313**

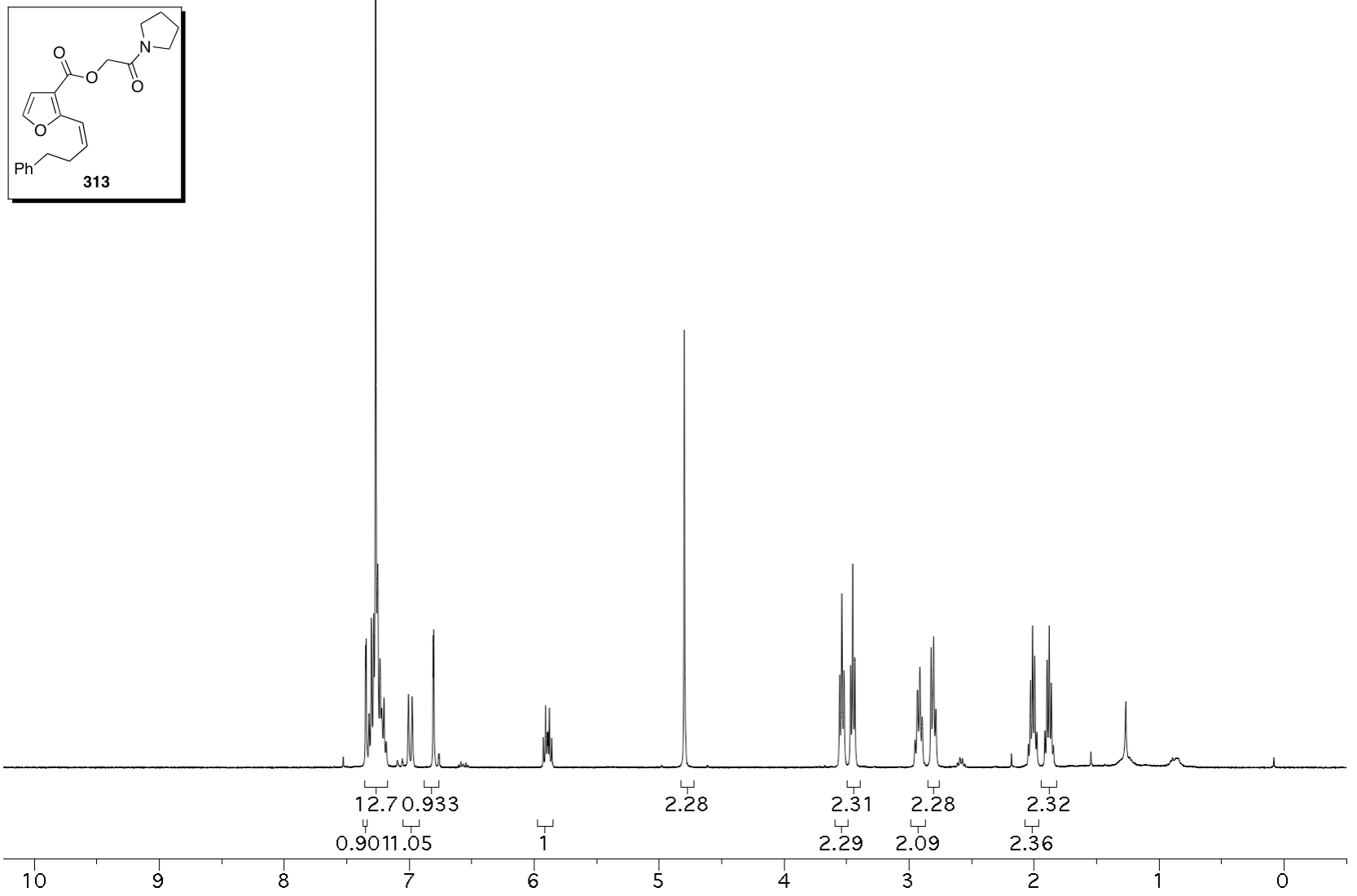


Figure A2.92 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **313**

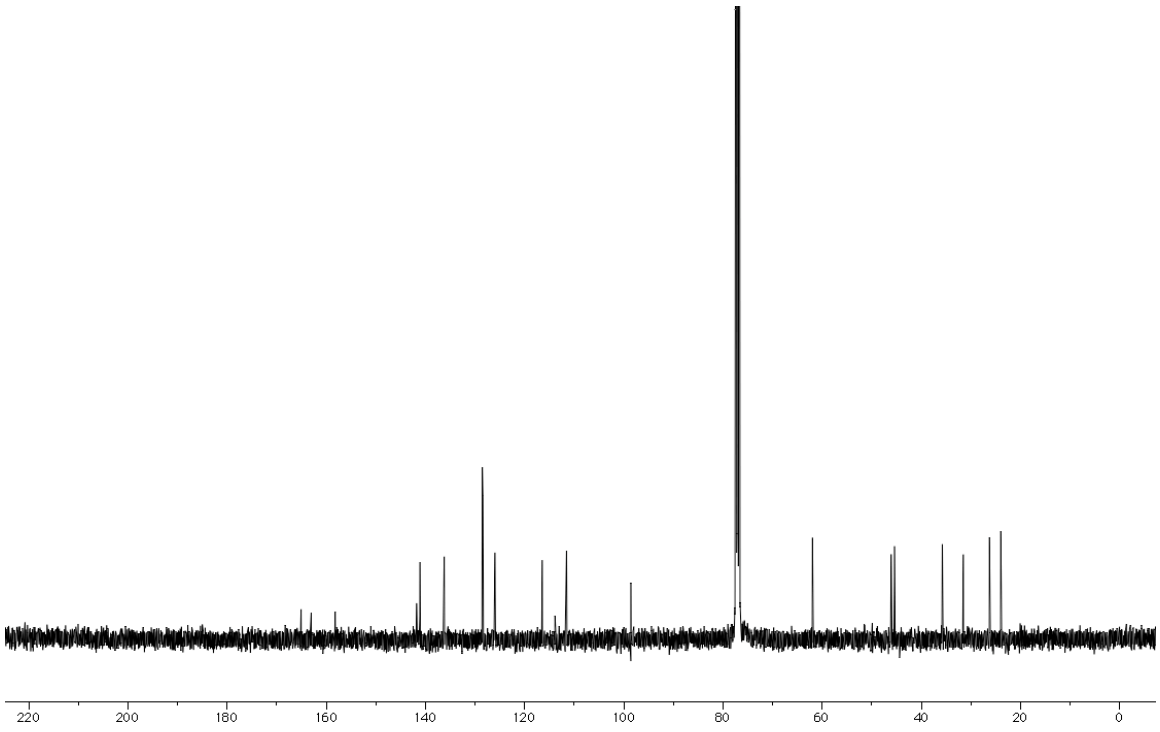


Figure A2.93 IR spectrum (thin film, NaCl) of compound **313**

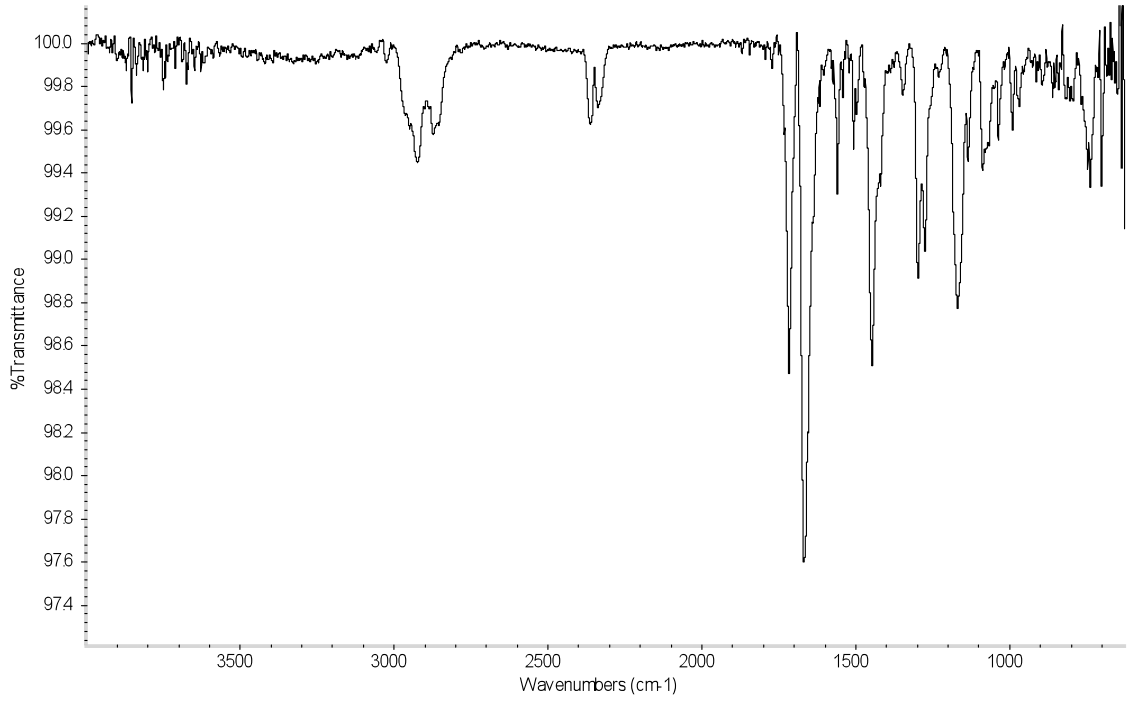


Figure A2.94 1H NMR spectrum (400MHz, CDCl3) of compound **315**

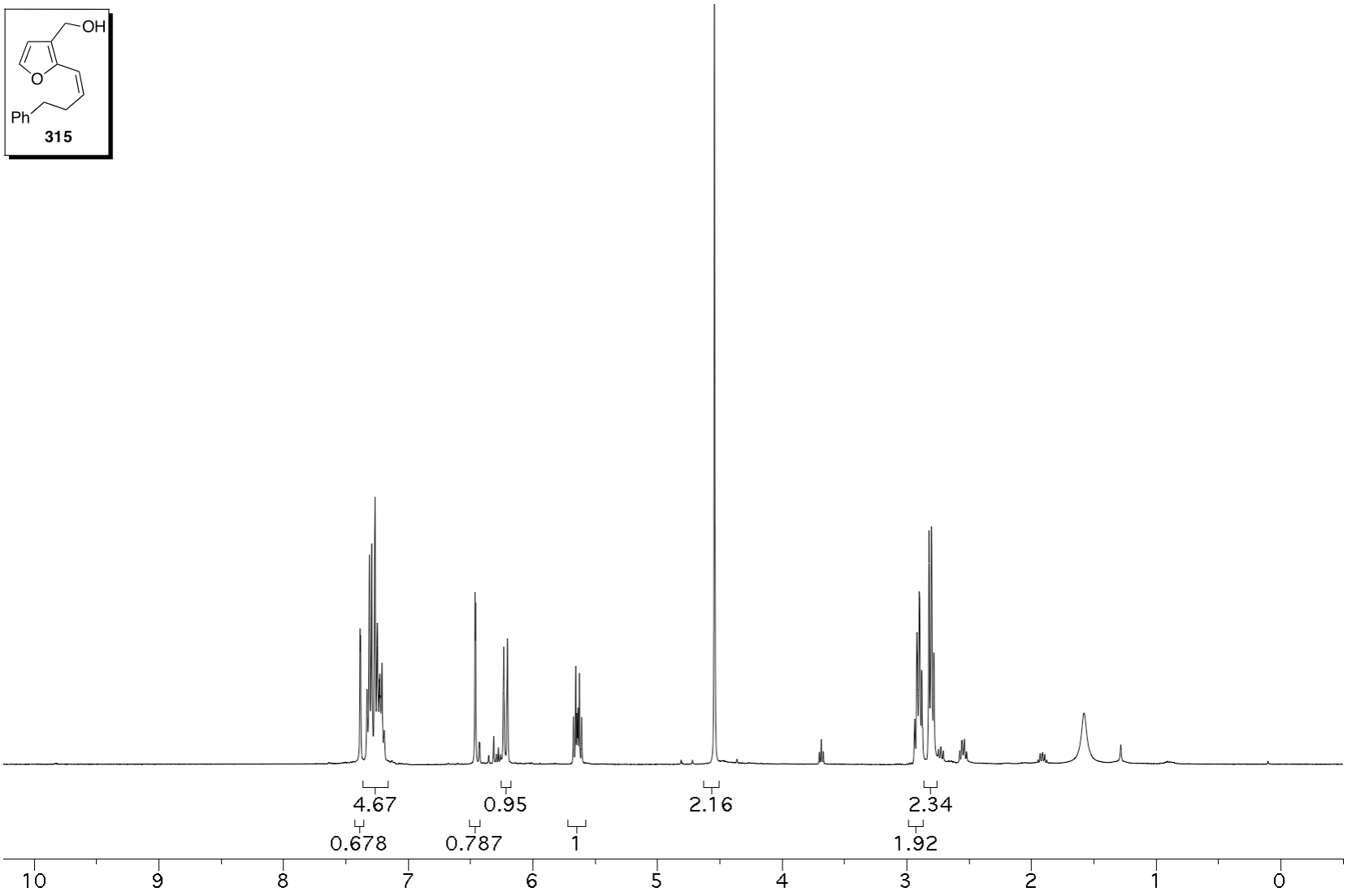


Figure A2.95 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **315**

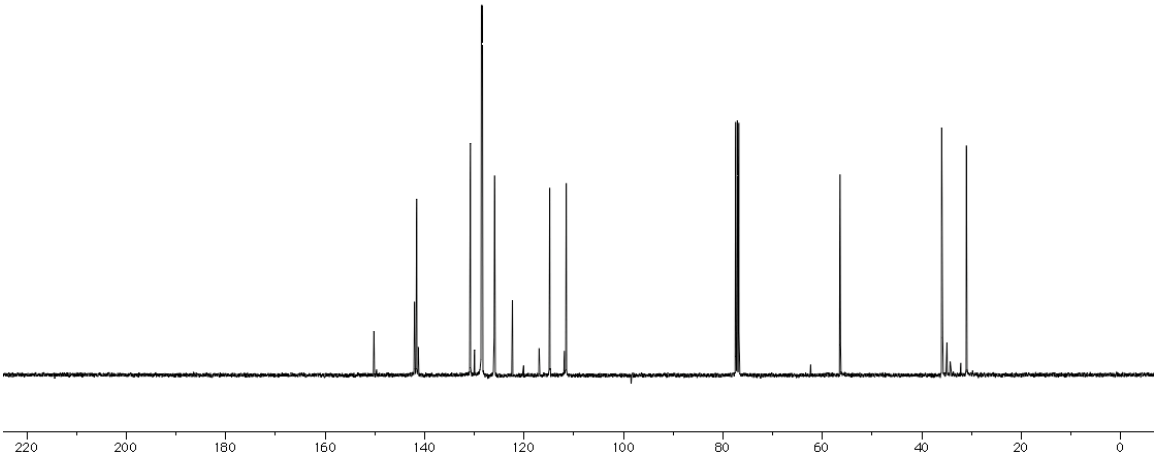


Figure A2.96 IR spectrum (thin film, NaCl) of compound **315**

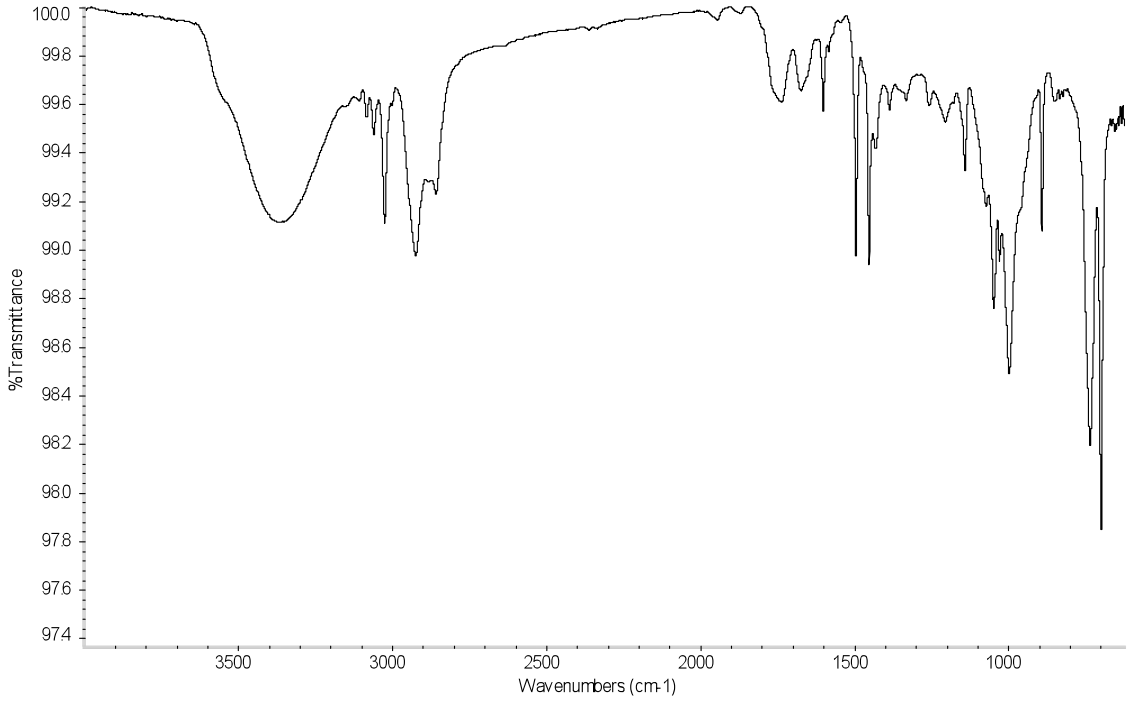
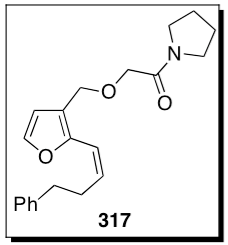


Figure A2.97 1H NMR spectrum (400MHz, CDCl3) of compound **317**



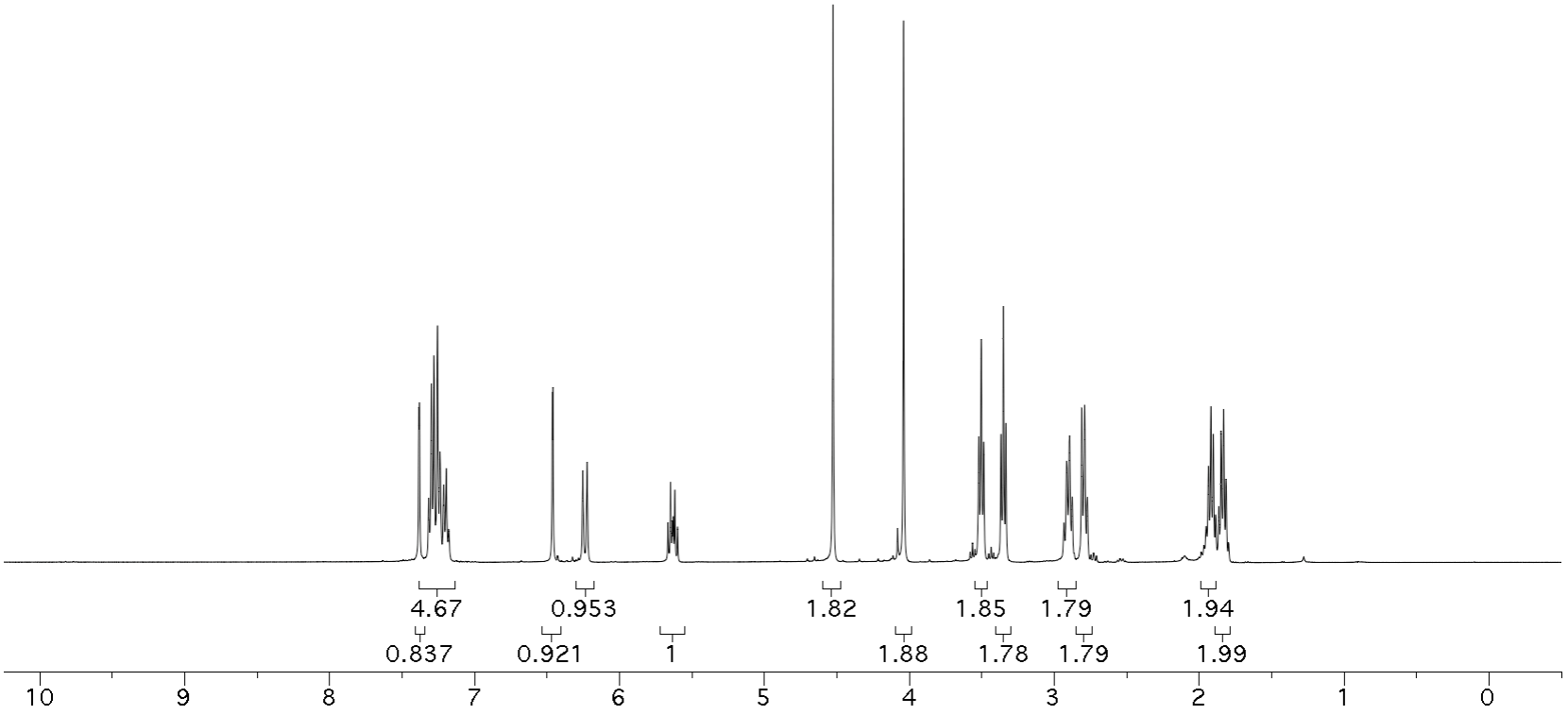


Figure A2.98 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **317**

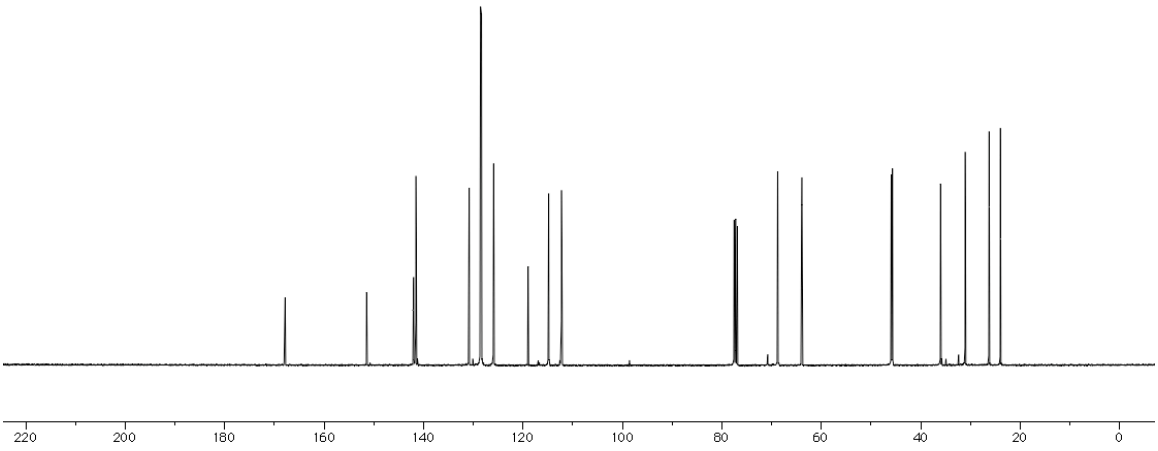


Figure A2.99 IR spectrum (thin film, NaCl) of compound **317**

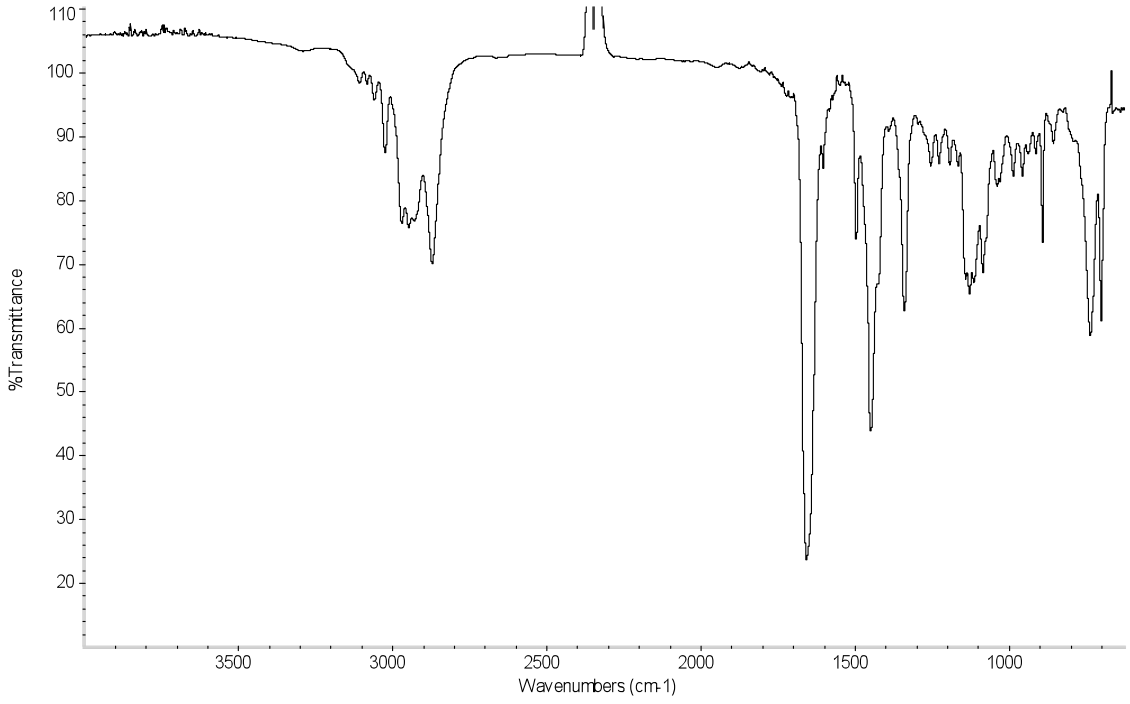


Figure A2.100 1H NMR spectrum (400MHz, CDCl3) of compound **320**

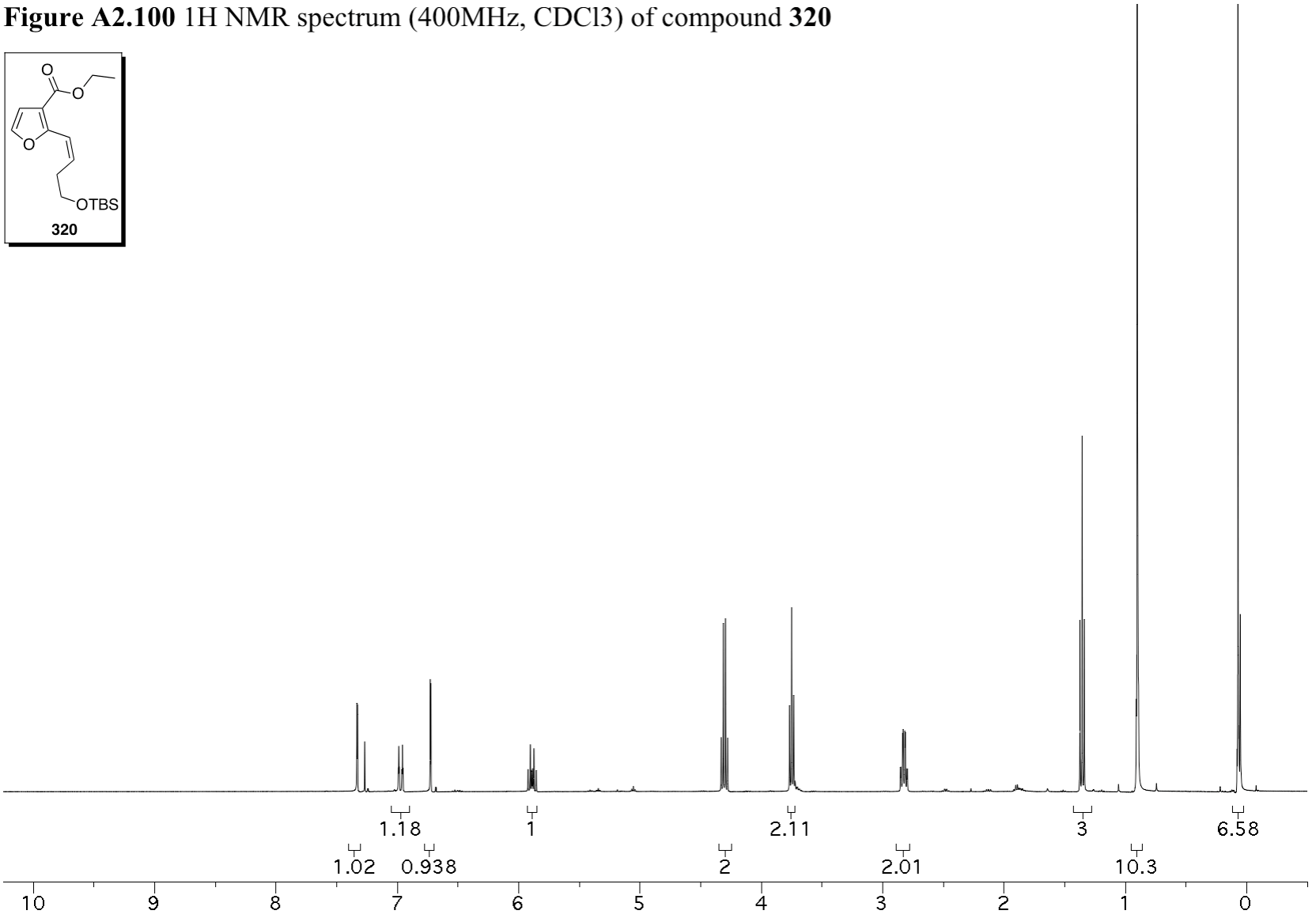


Figure A2.101 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **320**

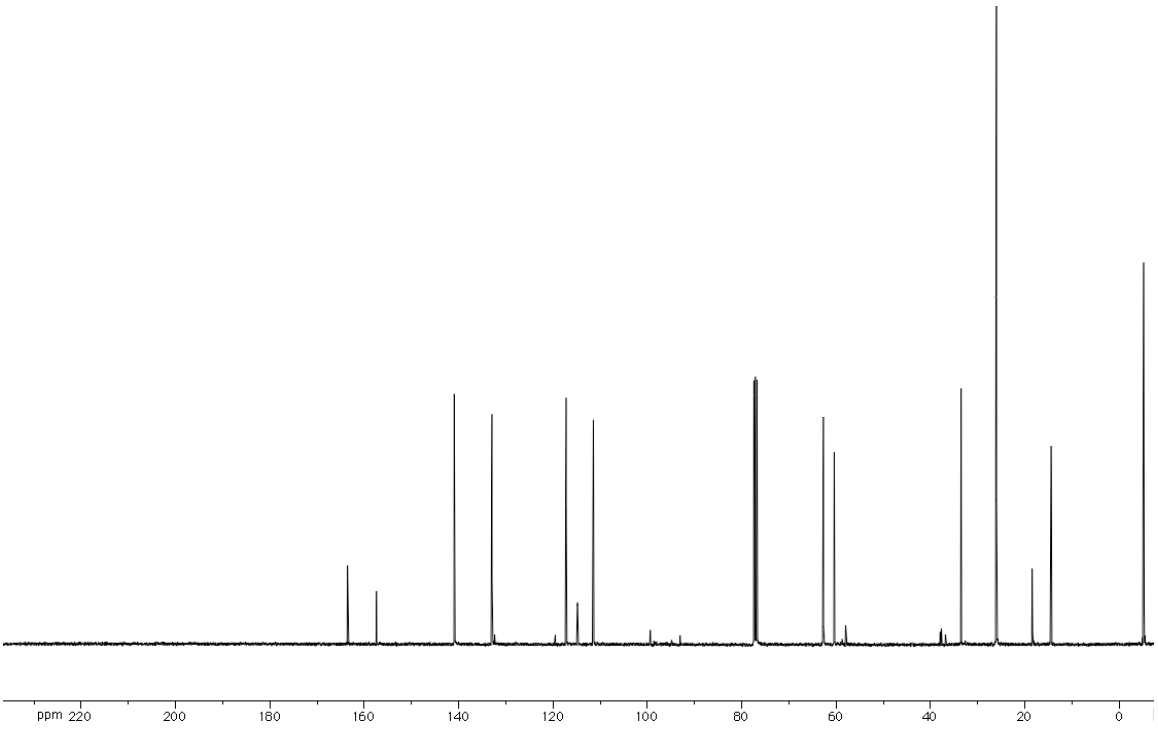


Figure A2.102 IR spectrum (thin film, NaCl) of compound **320**

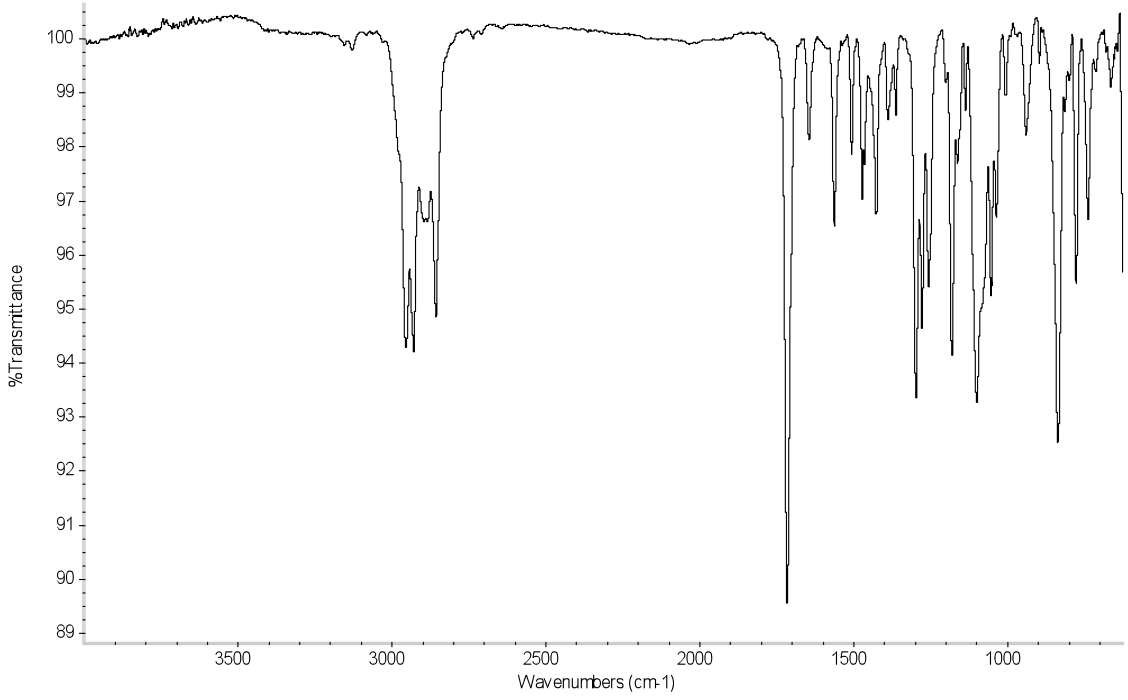
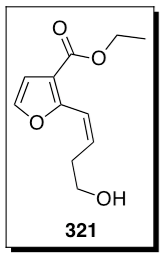


Figure A2.103 1H NMR spectrum (400MHz, CDCl3) of compound **321**



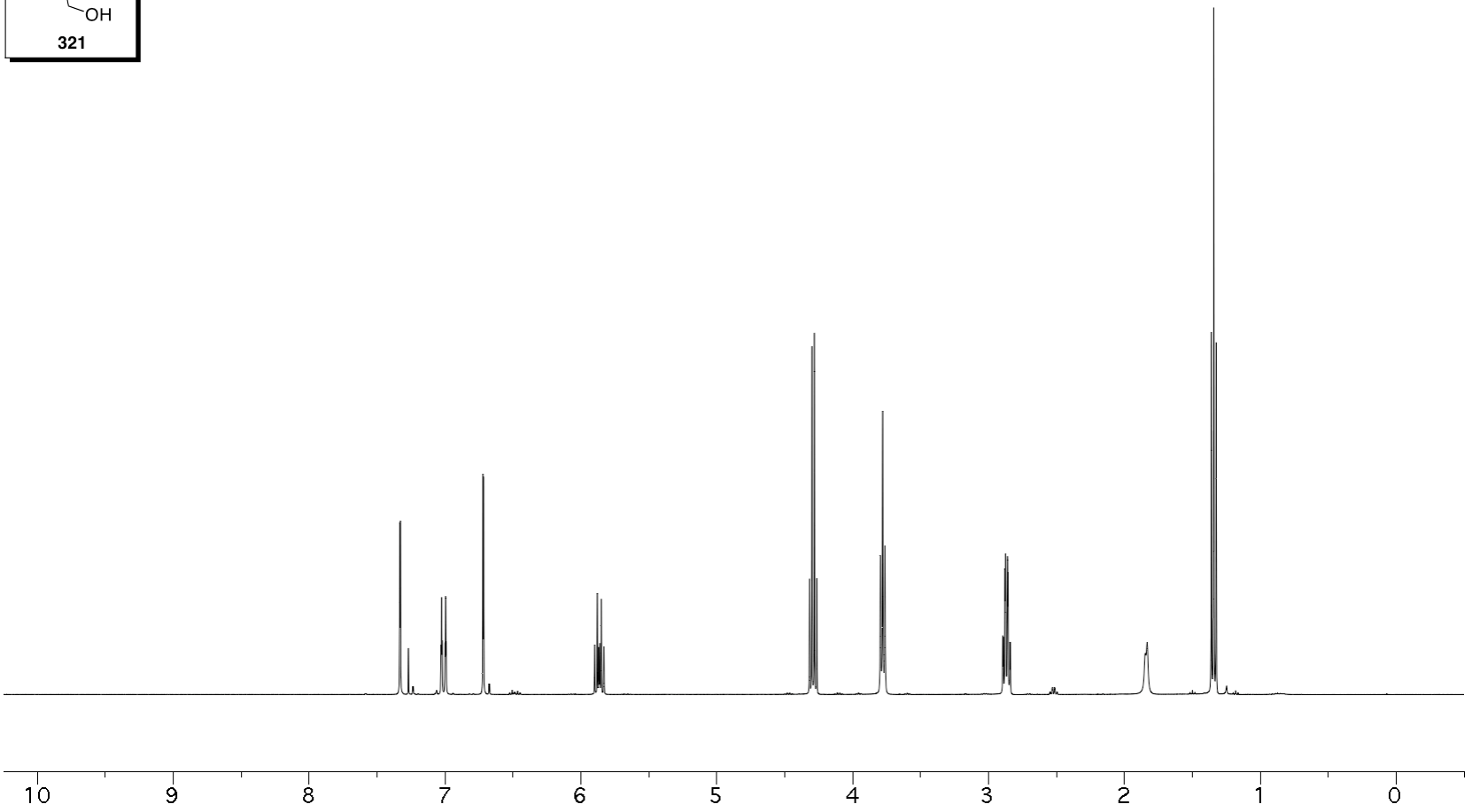


Figure A2.104 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **321**

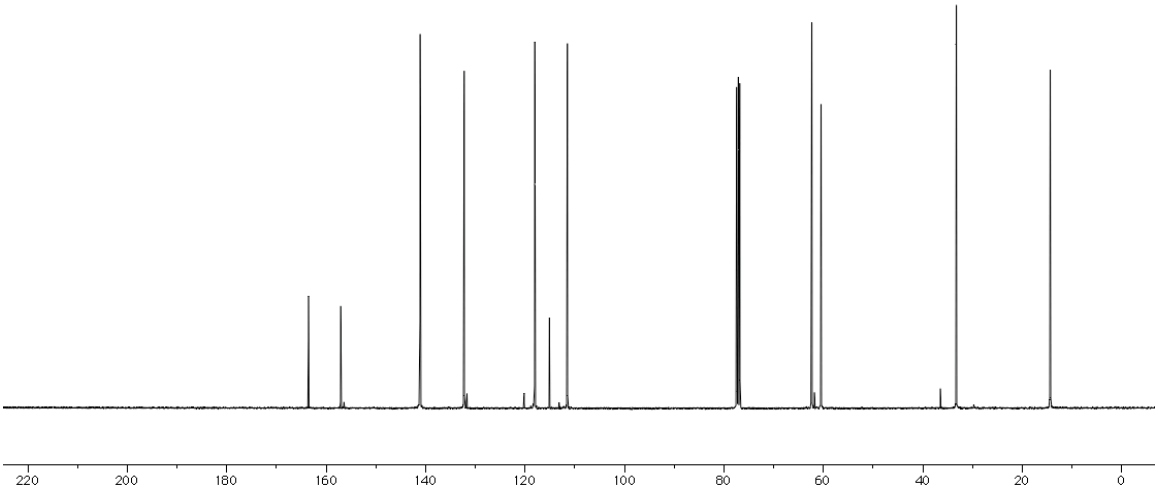


Figure A2.105 IR spectrum (thin film, NaCl) of compound **321**

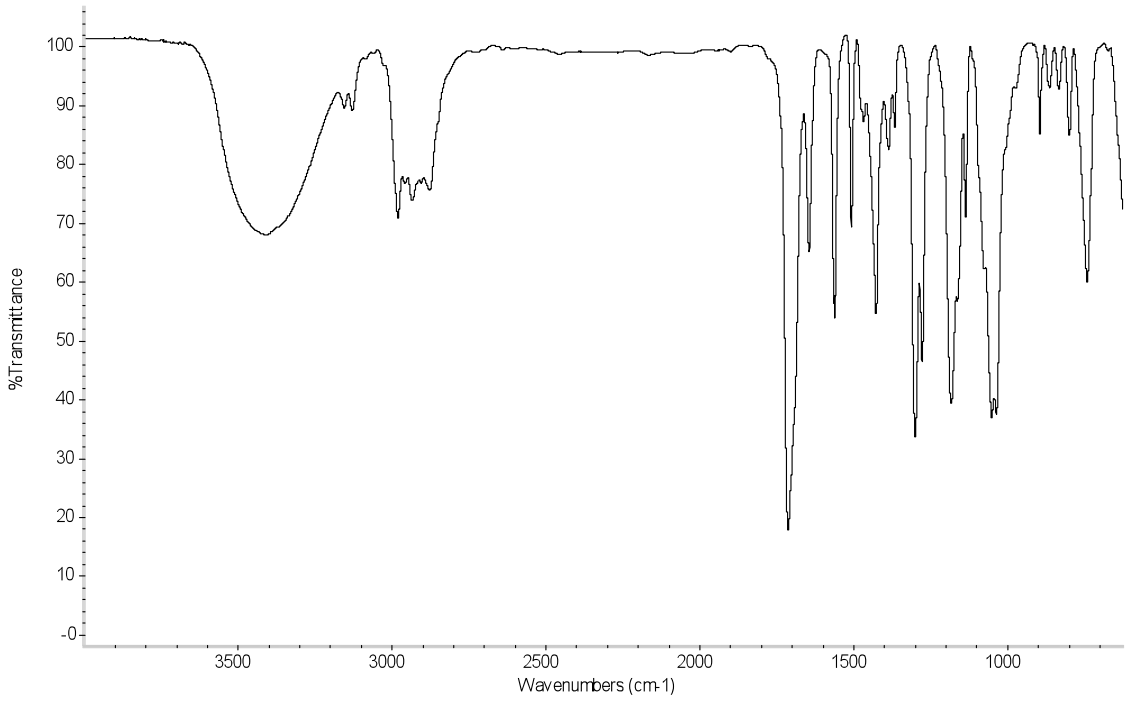
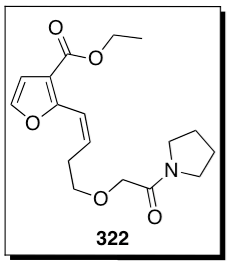


Figure A2.106 1H NMR spectrum (400MHz, CDCl3) of compound **322**



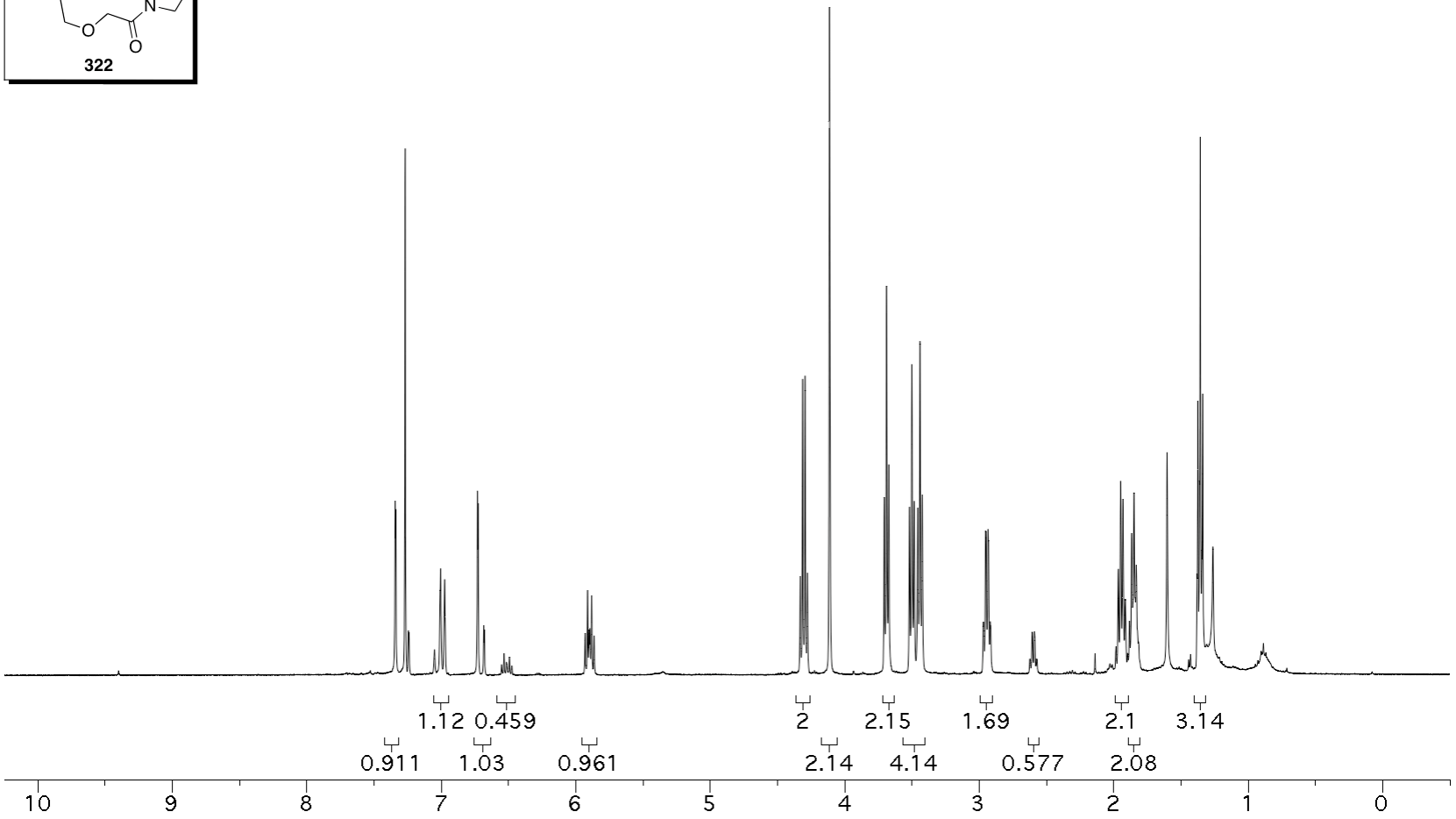


Figure A2.107 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **322**

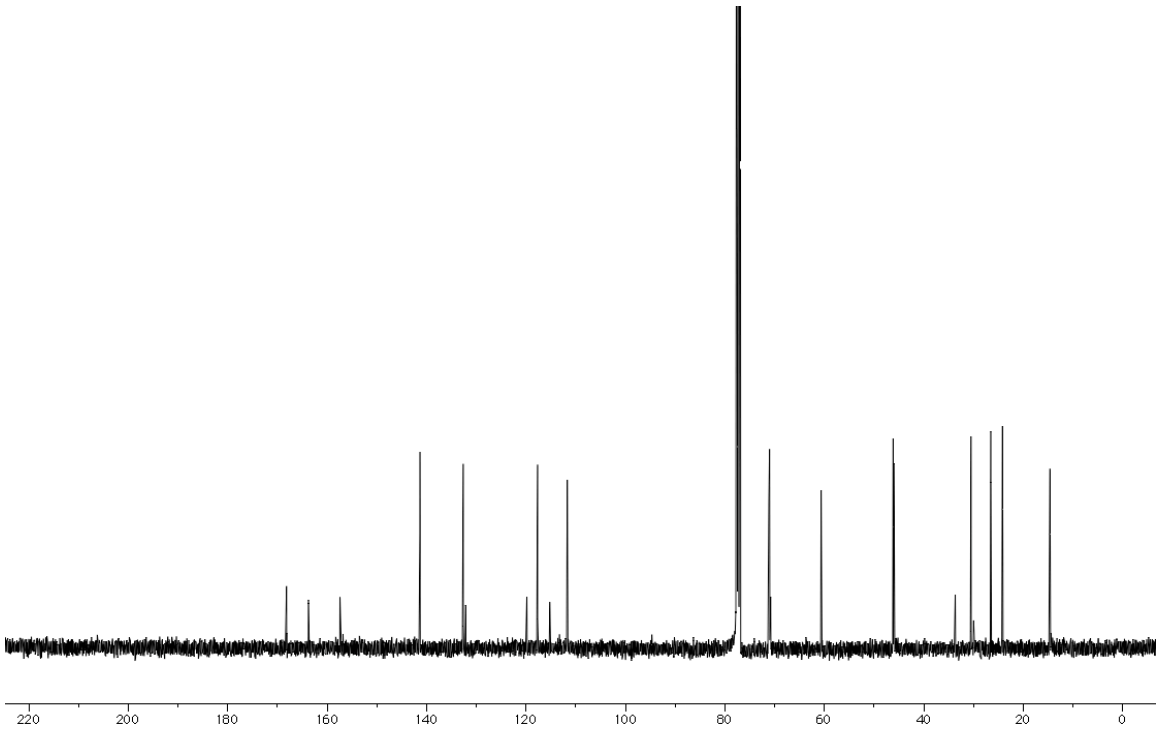
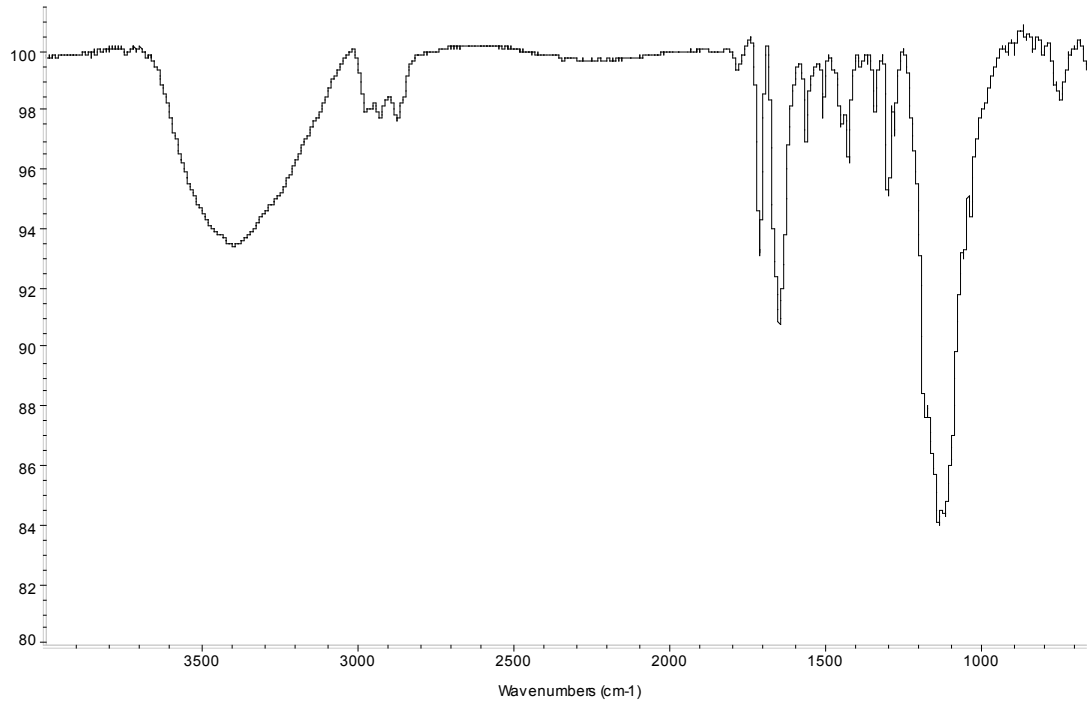


Figure A2.108 IR spectrum (thin film, NaCl) of compound **322**



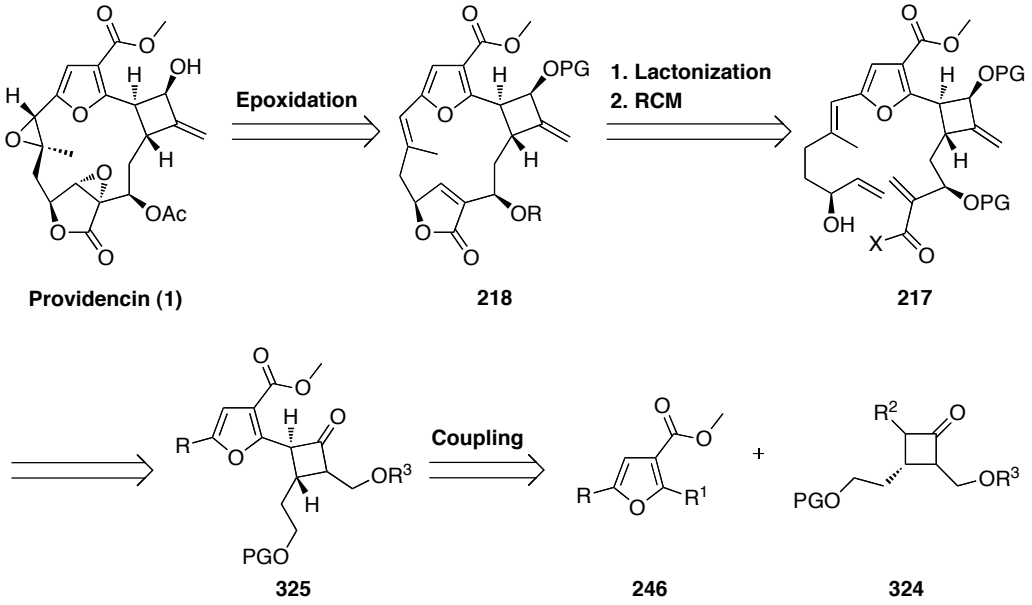
Chapter 3

A Revised Approach and Future Work Towards Providencin

3.1 A More Convergent Approach to the Furyl Cyclobutane

In our work towards providencin (**1**) thus far, we had encountered several pitfalls in our synthesis of the furyl cyclobutanone portion. The sequence employed to access the furyl cyclobutanone became lengthy and, due in part to its linear nature, low yielding. Therefore, a revised approach was needed, one in which a more convergent route was taken. To this end, we envisioned a retrosynthesis in which a late stage epoxidation and deprotection would provide **1** (Scheme 3.1.1). Butenolide **218** would arise from a macrolactonization/RCM sequence performed on diene **217**, which in turn, would derive from furyl cyclobutanone **325**. A coupling reaction between a functionalized furan **246** and a functionalized cyclobutane **324** would provide this furyl cyclobutanone **325** in a convergent fashion.

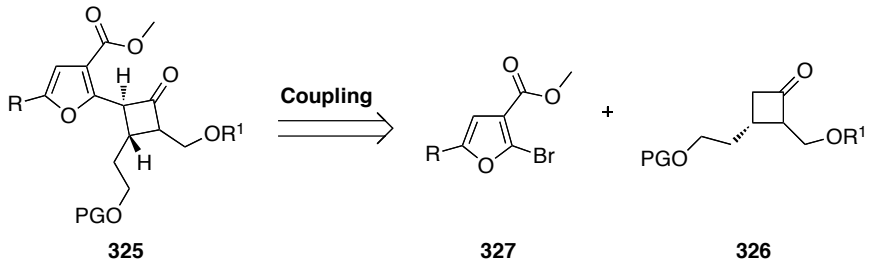
Scheme 3.1.1 A new retrosynthetic approach to Providencin (**1**)



3.1.1 Buchwald / Hartwig Type α-Arylation of Ketones

We elected to investigate Buchwald, Hartwig and Miura type α-arylations of ketones for the coupling of the two functionalized substrates.[1] In particular, an α-arylation of a cyclobutanone **326** with a 2-bromofuran **327** would yield a highly functionalized furyl cyclobutanone **325** in short order (Scheme 3.1.1.1).

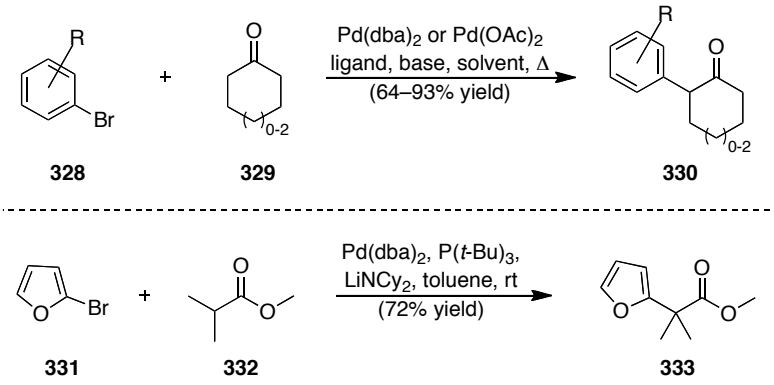
Scheme 3.1.1.1 Buchwald/Hartwig retrosynthetic approach to furyl cyclobutanone



These reactions are compatible with a wide variety of aryl halides (e.g., **328**), including those with electron withdrawing groups. [1] Hartwig et al. have demonstrated that

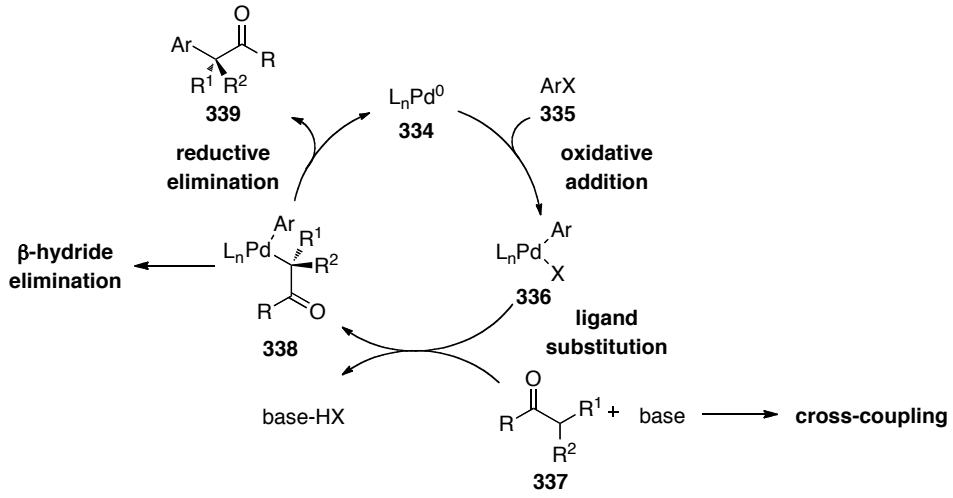
α,α-disubstituted esters (e.g., **332**) undergo arylation with 2-bromofuran **331** (Scheme 3.1.1.2).[2] Although the corresponding coupling of halo furans and ketones has not been reported, a number of cyclic ketones **329** do participate in the palladium-catalyzed coupling reaction. However, among the latter there are no examples of α-arylation of cyclobutanones; thus, addressing the synthesis of **1** via the coupling of a cyclobutanone and a halo furan advances the forefront of this powerful coupling method (Scheme 3.1.1.2).

Scheme 3.1.1.2 Examples of α-arylations



Mechanistically these transformations begin with the oxidative addition of an aryl halide **335** to a Pd(0) complex **334** (Scheme 3.1.1.3). Ligand exchange with an enolate of ketone **337** gives a palladium enolate complex **338** that subsequently undergoes reductive elimination to provide an α-aryl ketone **339**.[3] In general these reactions proceed with good regioselectivity and functional group tolerance. However, complications involving uncatalyzed cross-coupling between ketone substrates **337** and β-hydride elimination of the palladium complex **338** have been observed.

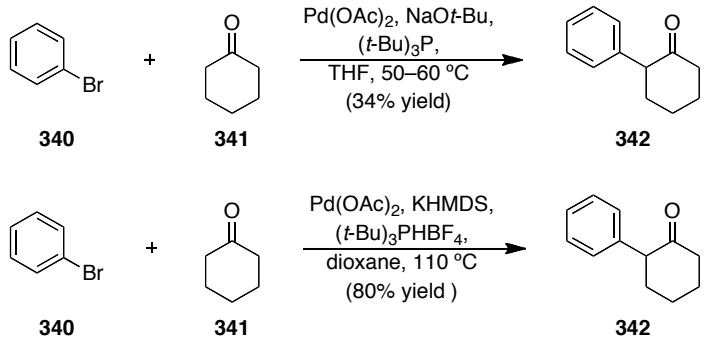
Scheme 3.1.1.3 Mechanism for α-arylations



3.1.2 Investigations into the α-Arylation Chemistry

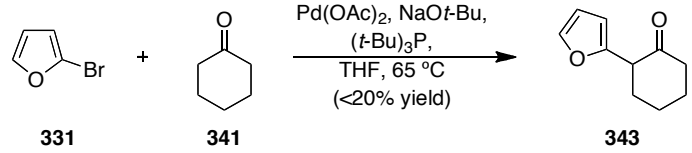
At the outset our efforts focused on identifying optimal reaction conditions for preparing a simple, known α-arylation product, 2-phenylcyclohexanone **342**. The use of sodium *tert*-butoxide, palladium(II) acetate, and *tri*-(*tert*-butyl)phosphine provided effective cross-coupling of cyclohexanone **341** and bromobenzene **340** (Scheme 3.1.2.1). These conditions furnished the mono-arylation product (**342**) in 34% yield following separation from a small amount of the corresponding bis-arylation product. Subsequent efforts revealed that the *tri*-(*tert*-butyl)phosphine could be replaced with the air-stable *tri*-(*tert*-butyl)phosphonium tetrafluoroborate salt, allowing for the assembly of reactions outside a glovebox.[4]

Scheme 3.1.2.1 Cyclohexanone α-arylation



Next, in an effort to establish whether 2-bromofurans would participate in the α-arylation of ketones, we subjected 2-bromofuran **331** and cyclohexanone **341** to our established conditions (Scheme 3.1.2.2).[5] Although we were gratified to find that these conditions furnished the known 2-furan-2-ylcyclohexanone product **343**, the yield was disappointing.[6] We anticipated the yields could be improved with further optimization.

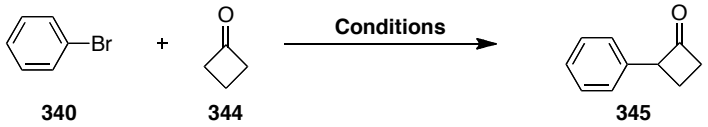
Scheme 3.1.2.2 α-Arylation of cyclohexanone with 2-bromofuran



Having established the viability of a furan/ketone coupling, we next explored the α-arylation of cyclobutanone **344** with bromobenzene **340**. Unfortunately, initial attempts using our established conditions were unsuccessful and a subsequent screen of additional reaction conditions was met with limited success (Scheme 3.1.2.3). When LiHMDS was utilized small amounts of a tentative product **345** were observed by NMR and GC/MS; however, the material proved unisolable.[7] When KHMDS was employed and the reaction was allowed to stir at room temperature for two hours prior to heating, a

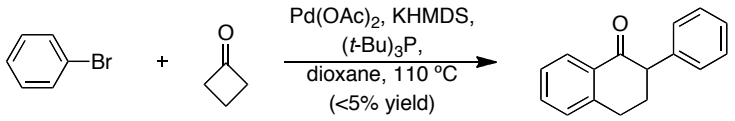
low yield of the known aryl tetralone **346** was obtained as the only isolable product. This compound presumably arises from an arylation/rearrangement sequence.[8]

Scheme 3.1.2.3 α-Arylation of cyclobutanone



340 **344** **345**

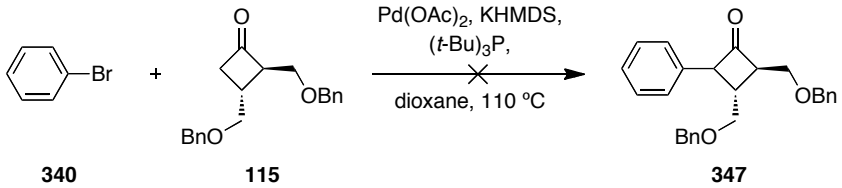
Catalyst	Base	Ligand	Solvent	Temperature	Result
$Pd(dba)_2$	LiHMDS	$(t\text{-Bu})_3P$	THF	65 °C	no reaction
$Pd(OAc)_2$	NaO*t*-Bu	$(t\text{-Bu})_3P$	THF	60–90 °C	no reaction
$Pd(OAc)_2$	LiHMDS	$(t\text{-Bu})_3P$	THF	65 °C	<5% desired product
$Pd(OAc)_2$	LiHMDS	$(t\text{-Bu})_3P$	dioxane	110 °C	no reaction
$Pd(OAc)_2$	KHMDS	$(t\text{-Bu})_3P$	dioxane	110 °C	no reaction
$Pd(OAc)_2$	KHMDS	$(t\text{-Bu})_3PHBF_4$	dioxane	110 °C	no reaction
$Pd(OAc)_2$	KHMDS	$(t\text{-Bu})_3P$	dioxane	110 °C	<5% bis-arylation/ rearrangement



340 **344** **346**

Concerned that low yields in the coupling of **345** may have been the result of cross-coupling of cyclobutanone with itself, we attempted to couple a more elaborate cyclobutanone **115** with bromobenzene **340**. The attempted α-arylation of cyclobutanone **115** resulted only in decomposition of the ketone (Scheme 3.1.2.4). Further experimentation revealed that functionalized cyclobutanones like **115** are not stable to deprotonation at room temperature, let alone at elevated temperatures. Thus, decomposition of the deprotonated cyclobutanones superceded the desired cross-coupling reaction.

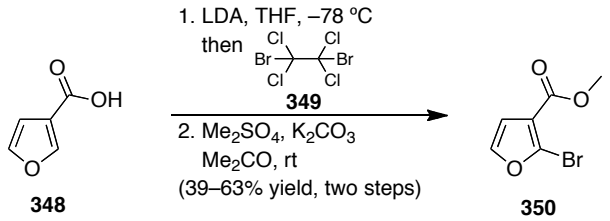
Scheme 3.1.2.4 Attempted α-arylation of cyclobutanone **115**



340 **115** **347**

Concurrently, investigation into the use of the more elaborate methyl 2-bromofuran-3-carboxylate **350** was underway (Scheme 3.1.2.5).[9] The furan **350** had been prepared by reacting the dianion of 3-furoic acid (**348**) with 1,2-dibromo-1,1,2,2-tetrachloroethane **349** followed by esterification of the resultant acid using dimethyl sulfate. Alternative brominating reagents were tested but proved inferior to **349**.

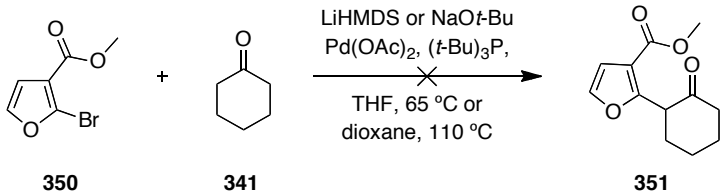
Scheme 3.1.2.5 Synthesis of bromo-cyclobutanone **350**



348 **350**

Unfortunately, the α-arylation of cyclohexanone (**341**) with methyl 2-bromofuran-3-carboxylate (**350**) was unsuccessful (Scheme 3.1.2.6). The observation of starting material, debrominated furan and several cyclohexanone condensation products led us to conclude that the rate of the desired cross-coupling was not competitive.

Scheme 3.1.2.6 Attempted α-arylation of cyclohexanone with **350**



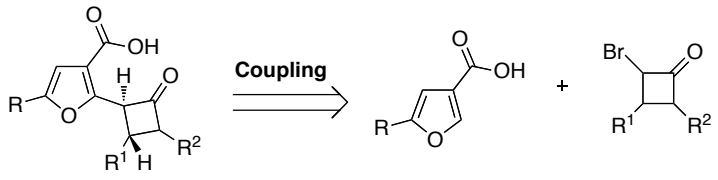
350 **341** **351**

We have demonstrated the successful α-arylation of cyclohexanone **341** with 2-bromofuran **350**. However, the instability of substituted cyclobutanones **115** under the reaction conditions and slow reactivity of methyl 2-bromofuran-3-carboxylate **350** led us to conclude that this was not a viable approach toward the synthesis of **1**. Thus, we began to investigate alternative coupling chemistries.

3.1.3 Bromide Displacement on Cyclobutanone Substrates

Having successfully trapped the carbanion of 3-furoic acid **348** with electrophilic bromine, we postulated that it might be possible to alkylate 3-furoic acid **348** with a halo-cyclobutane. With this plan in mind we set out to prepare an α-bromo cyclobutanone **352** (Scheme 3.1.3.1).

Scheme 3.1.3.1 A revised retrosynthesis for a furyl cyclobutanone **354**

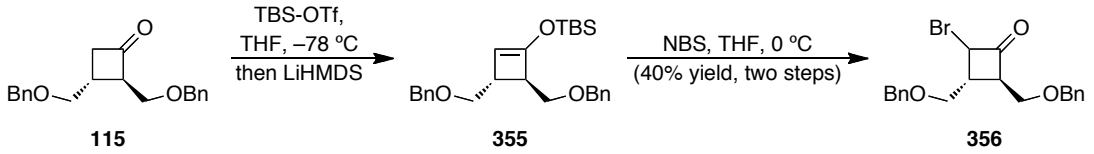


354 **353** **352**

Zard and co-workers have shown that the silyl-enol ethers of cyclobutanones can be generated and subsequently treated with NBS to furnish the corresponding α-bromo derivatives.[10] Initial attempts to utilize this reaction on cyclobutanone **115** resulted in only recovery of starting material. Mulzer et al. have shown that silyl-enol ethers of cyclobutanones can be generated using LiHMDS as a base.[11] We were pleased to find that treatment of cyclobutanone **115** with TBS-OTf followed by LiHMDS provided silyl-enol ether **355** (Scheme 3.1.3.2). Treatment of silyl-enol ether **355** with NBS

subsequently provided the desired mono-brominated cyclobutanone **356**, albeit in modest yields.

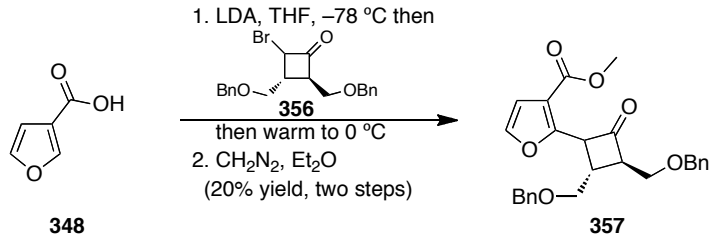
Scheme 3.1.3.2 Synthesis of α-bromocyclobutanone **356**

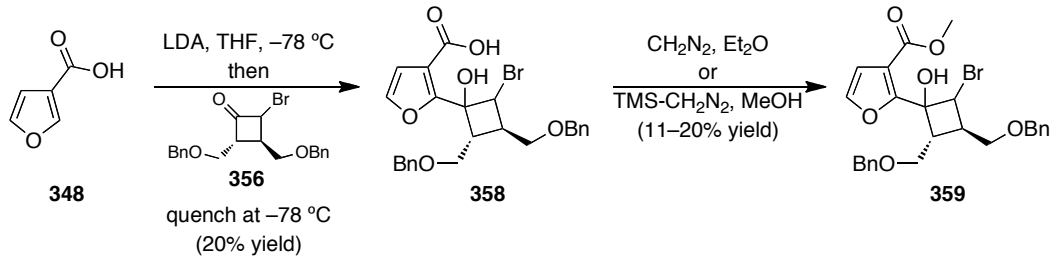


115 **355** **356**

The dianion of 3-furoic acid **348**, generated by treatment with LDA, was exposed to cyclobutanone **356** at low temperature and allowed to slowly warm to room temperature before being quenched (Scheme 3.1.3.3). Direct conversion to the methyl ester provided a small amount of furyl cyclobutanone **357**; however, the yield was low, multiple other products were present and some starting material **356** remained. In an effort to optimize the reaction, it was repeated but quenched at –78 ºC. Under these conditions a new product was observed which, upon treatment with diazomethane, was converted to a methyl ester. Detailed spectroscopic analysis of this ester provided data that was consistent with cyclobutanol **359**; thus, rather than undergoing nucleophilic displacement of the bromide, the dianion derived from **348** adds preferentially to the carbonyl and furnishes cyclobutanol **358**.

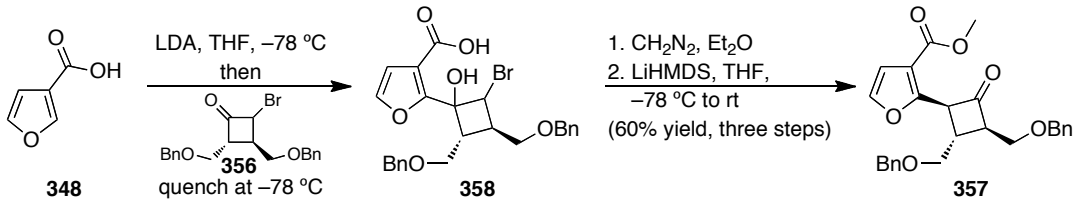
Scheme 3.1.3.3 Coupling of 3-furoic acid (**348**) and bromocyclobutanone **356**





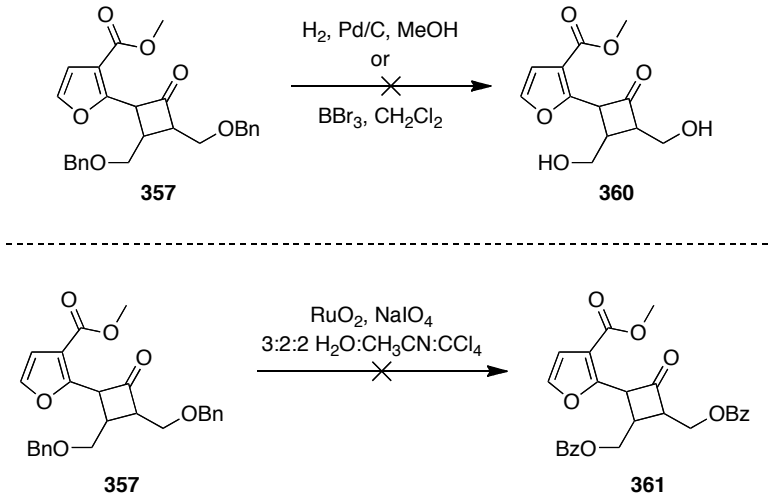
Further investigations revealed that treatment of the 1,2-adduct, cyclobutanol **359**, with LiHMDS at low temperature followed by warming induces a rearrangement reaction that furnishes the desired cyclobutanone **357**. Optimization studies revealed that the best yields of cyclobutanone **357** are obtained when substrates **358** and **359** are carried forward without purification (Scheme 3.1.3.4). This approach successfully provides cyclobutanone **357** in 60% isolated yield over three steps. Cyclobutanone **357** was isolated as a single diastereomer, and 1D nOe experiments confirmed the illustrated *trans*-*trans*-relationship between substituents.

Scheme 3.1.3.4 Synthesis of furyl cyclobutanone **357**



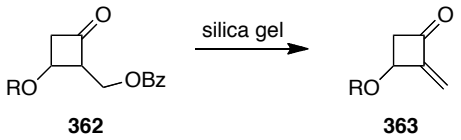
With cyclobutanone **357** in hand we sought to access diol **360**, via removal of the benzyl protecting groups (Scheme 3.1.3.5). Traditional conditions employing either hydrogenation or boron tribromide resulted in the degradation of starting material **357**. Attempts to oxidize the benzyl groups to benzoyl groups led to decomposition of the starting material **357**. Given these difficulties we elected to use different protecting groups from the outset.

Scheme 3.1.3.5 Attempted removal of benzyl protecting groups



In considering the nature of alternative protecting groups we noted the work of Poisson who has demonstrated that cyclobutanones such as **362** undergo silica-gel mediated elimination during purification to give exo-methylene cyclobutanones **363** (Scheme 3.1.3.6). Such a transformation would be ideal in the synthesis of the exo-methylene cyclobutanol moiety in **1**. [12] Thus synthesis of bis-benzoyl protected diol **361** began.

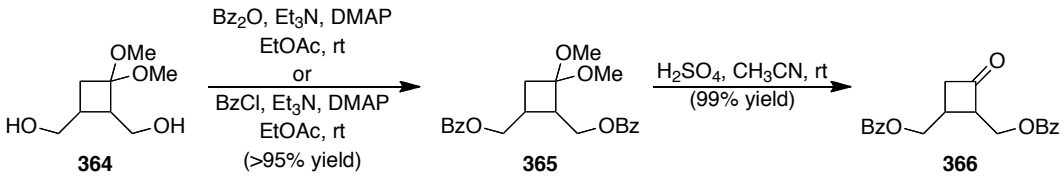
Scheme 3.1.3.6 Poisson's synthesis of exo-methylene cyclobutanones



362 **363**

Treatment of known diol **364** with either benzoic anhydride or benzoyl chloride and triethylamine provided the bis-protected diol **365** (Scheme 3.1.3.7). Subsequent cleavage of the acetal provided cyclobutanone **366** in near quantitative yields.

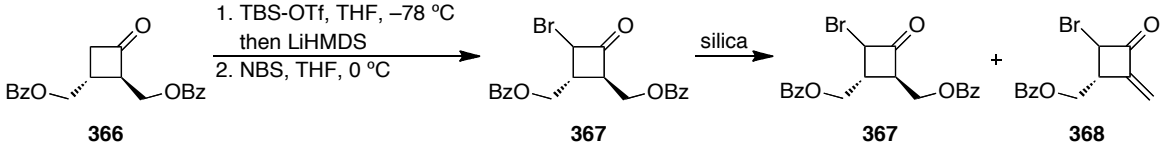
Scheme 3.1.3.7 Synthesis of bis-benzoyl protected cyclobutanone **366**



364 **365** **366**

Bromination alpha to the carbonyl in **366** resulted in the desired bromo-cyclobutanone **367**. Unfortunately, attempted purification led to mixtures of the desired product **367** and the exo-methylene cyclobutanone **368** (Scheme 3.1.3.8). Pre-treating the silica with triethylamine or utilizing basic alumina resulted in decomposition of the products. Attempts to convert the mixture entirely to methylene cyclobutanone **368** by stirring with silica gel were not successful.

Scheme 3.1.3.8 Bromination of cyclobutanone **366**

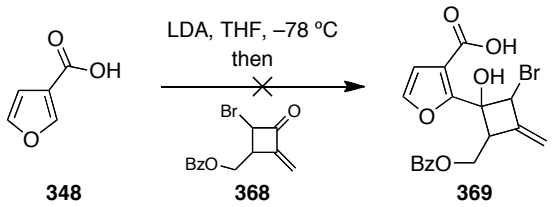


366 **367** **367** **368**

In an effort to determine the utility of methylene cyclobutanone **368** we exposed this material to the dianion derived from **348** under conditions that had proven effective

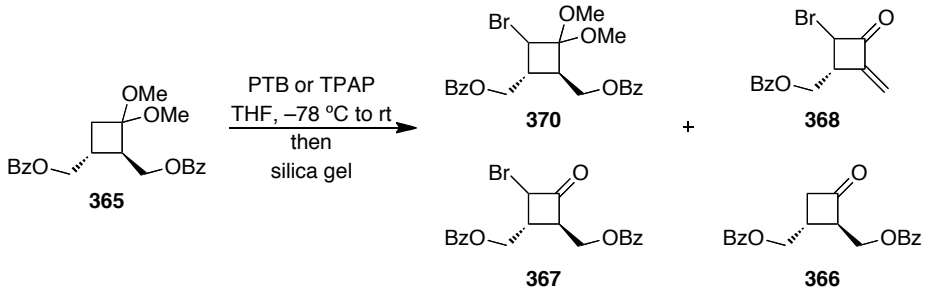
in the coupling of **356** (*vide supra*, Scheme 3.1.3.4). Unfortunately, the addition was unsuccessful and only decomposition was observed (Scheme 3.1.3.9).

Scheme 3.1.3.9 Attempted coupling of 3-furoic acid (**348**) and **368**



Although this initial negative result was discouraging we continued our investigations by attempting to develop a more robust approach to bromo-cyclobutanone **367**. To this end, efforts to brominate acetal **365** via addition of pyridinium tribromide or phenyltrimethyl ammonium tribromide did provide some brominated material. Unfortunately, the latter reactions were not clean and attempts to separate the derived complex mixtures of four compounds were unsuccessful (Scheme 3.1.3.10).

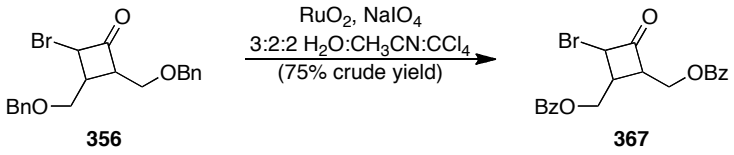
Scheme 3.1.3.10 Bromination of cyclobutyl acetal **365**



Given past success with the ruthenium oxide oxidation of benzyl groups to benzoyl groups on cyclobutanone substrate **117** (Scheme 1.4.1.3) we endeavored to effect this transformation on bromo-cyclobutanone **356**. Although the benzyl-protected cyclobutanone **356** was smoothly converted to the benzoyl-protected cyclobutanone **367**,

this material could not be purified due to a facile elimination that furnishes the corresponding exomethylene **368** (Scheme 3.1.3.11).

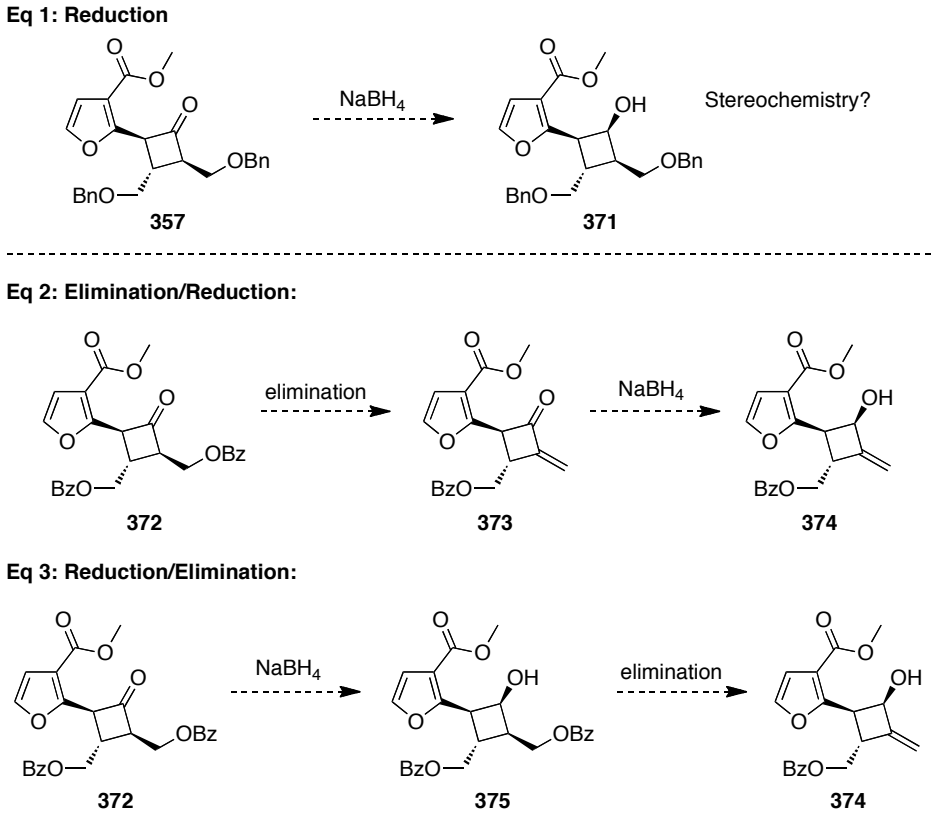
Scheme 3.1.3.11 RuO_2 oxidation of bis-benzyl protected cyclobutanone **356**



3.1.4 Future work on Furyl-Cyclobutanone Chemistry

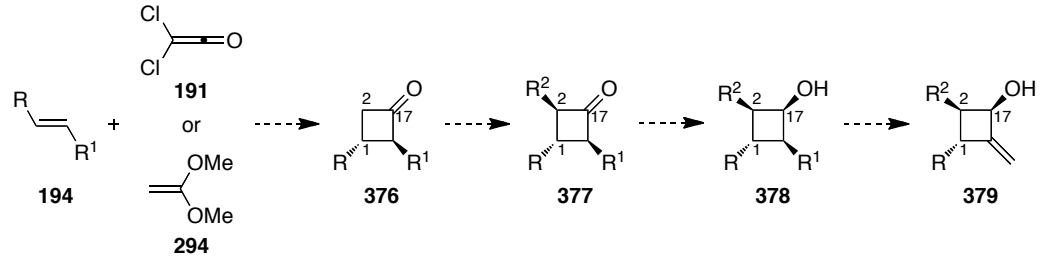
We have alkylated 3-furoic acid with bromo-cyclobutanone **356** and this has provided us with a furyl cyclobutanone **357** which possesses a relative stereochemistry configuration appropriate for conversion to **1**; however, to complete the synthesis, this intermediate (or one analogous to it) will have to undergo stereoselective reduction and conversion to the corresponding exomethylene. The feasibility and order of these latter two events remain to be addressed. In the event, we will first determine the stereochemical outcome upon reduction of cyclobutanone **357** using bulky hydride reagents; we anticipate sterics will aid in delivering the desired *cis*-relationship between the alcohol and furan substituents. We will also determine if there is any advantage in carrying out this reduction subsequent to introduction of the exo-methylene **373** (cf., eq. 2 and 3 in Scheme 3.1.4.1).

Scheme 3.1.4.1 Proposed reductions and elimination sequence



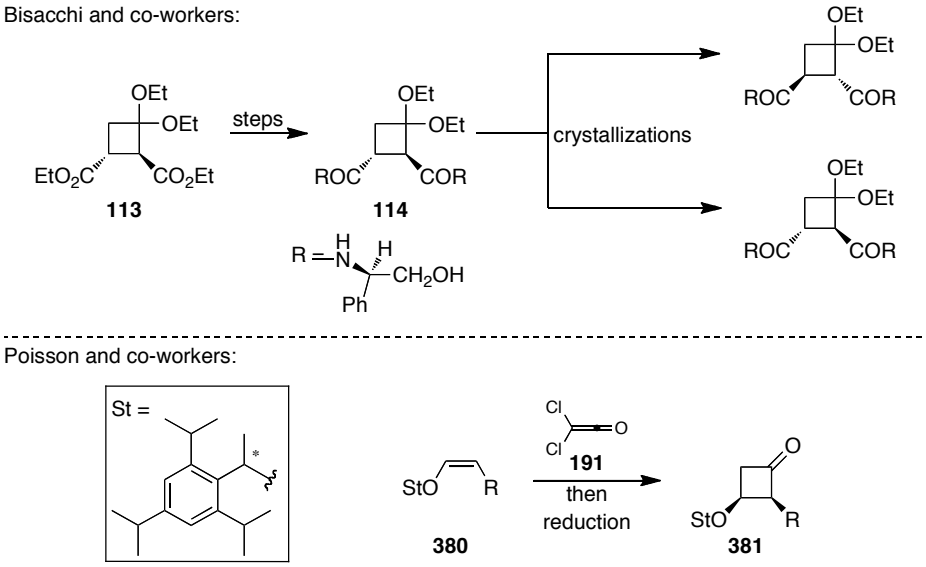
Another major concern for synthesis of **1** is the preparation of a cyclobutanone coupling partner possessing the necessary absolute stereochemistry. We plan to address this issue by employing a method in which the stereochemistry at C1 is set early. Based on previous observation, setting the stereochemistry at C1 will provide the necessary stereocontrol to access the desired stereochemistry at C2 and C17 (Scheme 3.1.4.2).

Scheme 3.1.4.2 Proposed stereoselective synthesis of exo-methylene cyclobutanones



Of particular use will be the method developed by Bisacchi and co-workers (*vide supra*, Section 1.4.1), where the bis-amide derivatives of cyclobutanone **113** are separated via crystallization to provide enantiopure cyclobutanone **114** (Scheme 3.1.4.3).[13] A second approach would involve the use of chemistry developed by Poisson et al., which demonstrated that chiral enol ethers **380** can be used in the asymmetric synthesis of cyclobutanones **381** via a [2 + 2] cycloaddition with dichloroketene **191**.[12] Utilization of either method should allow access to a functionalized cyclobutane with the desired chemistry at the C1 position.

Scheme 3.1.4.3 Proposed synthesis of cyclobutanones with desired C1 stereochemistry



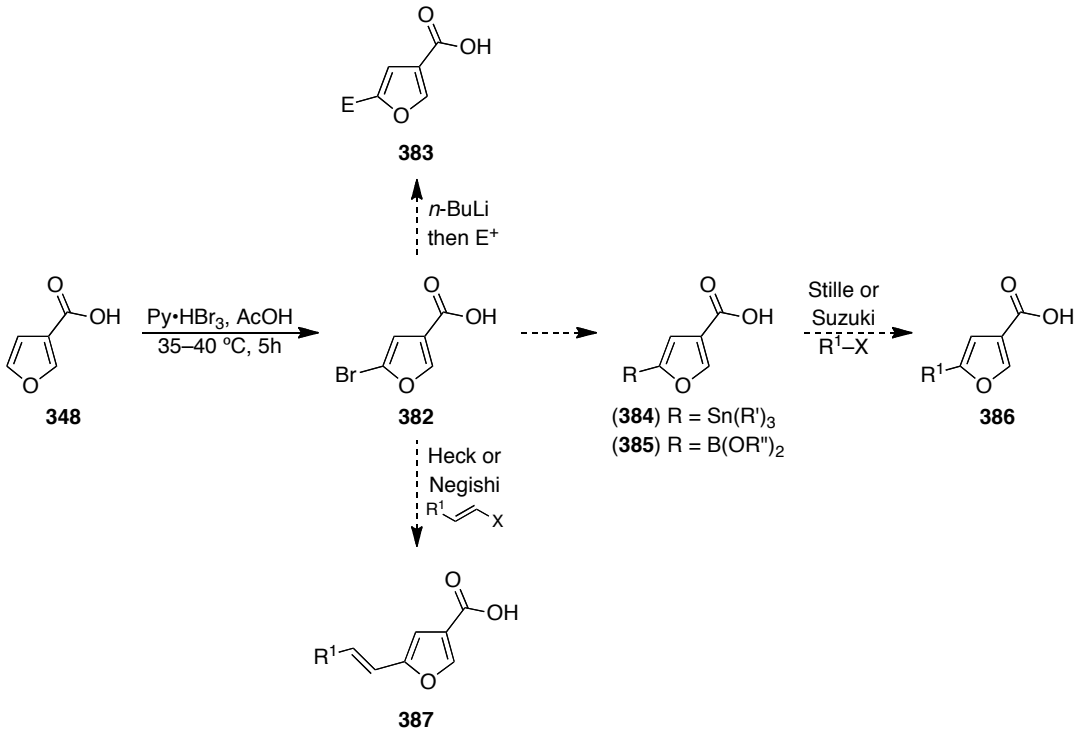
3.2 Consideration of the Western Portion of Providencin

3.2.1 A Functionalized Furan Coupling Partner

For a truly convergent approach it is necessary to prepare a furan coupling partner which contains all the functionality for conversion to **1**. We postulated that the commercially available 5-bromo-3-furoic acid **382** would be an ideal starting point for

the synthesis of a functionalized furan.[14] Several pathways for further elaboration from furan **382** seem plausible (Scheme 3.2.1.1). Lithium-halogen exchange and subsequent treatment with an electrophile could provide homologated furan **383**. Conversion of bromide **382** to furylstannane **384**, followed by a Stille cross-coupling would furnish furan **386**. Alternatively, furan **386** could also be accessed through a Suzuki cross-coupling. Access to alkenyl furan **387** could be gained through either a Heck reaction or via a Negishi cross-coupling.

Scheme 3.2.1.1 Proposed homologation of 3-furoic acid derivatives

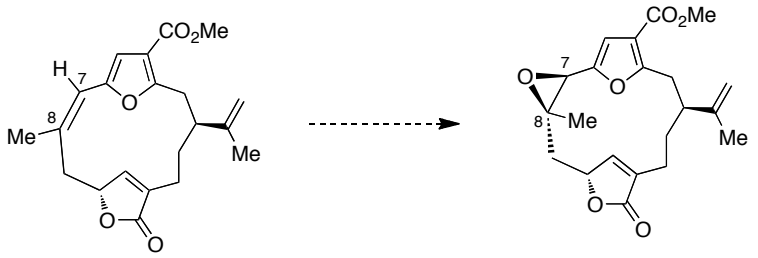


3.2.2 The C7–C8 Epoxide

Our current approach employs a late stage introduction of the two epoxides, however, this may prove problematic. To date no synthesis of an epoxide-containing

furanocembrane has been completed via a late stage epoxidation (Scheme 3.2.2.1). Indeed no synthesis of any C7–C8 epoxy furanocembrane has been achieved.

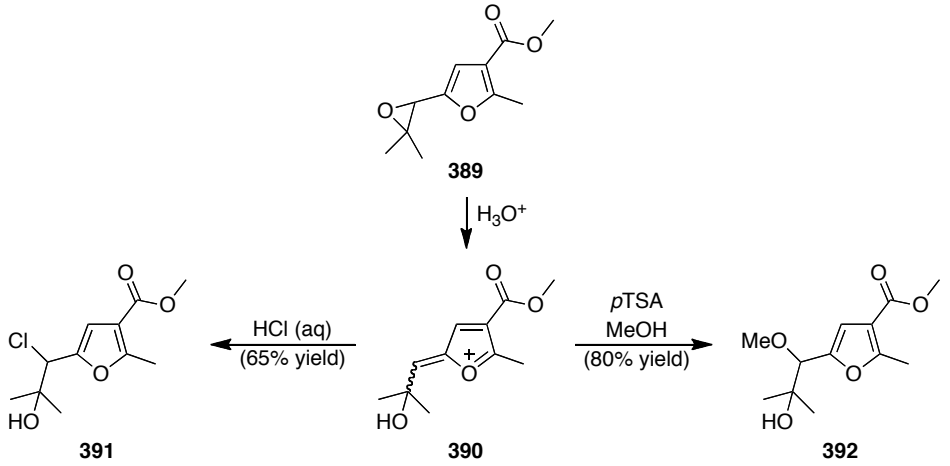
Scheme 3.2.2.1 Proposed late stage epoxidation of furanocembranes



(–)-Deoxypukalide (20) **(–)-pukalide (388)**

Pattenden and co-workers specifically discuss the need for further innovation in the synthesis of furanocembranes, especially when it comes to incorporating epoxides into these molecules.[15] One issue with the synthesis of these epoxides may be their sensitivity to acidic conditions. Recently, Pattenden has reported that treatment of epoxyfuran **389** with either aqueous acid or *p*TSA in methanol results in the opening of the epoxide via intermediate **390** (Scheme 3.2.2.2).[16] It is clear that epoxide opening is a potential issue in these substrates and due care must be taken when considering the purification and further elaboration of these epoxide substrates.

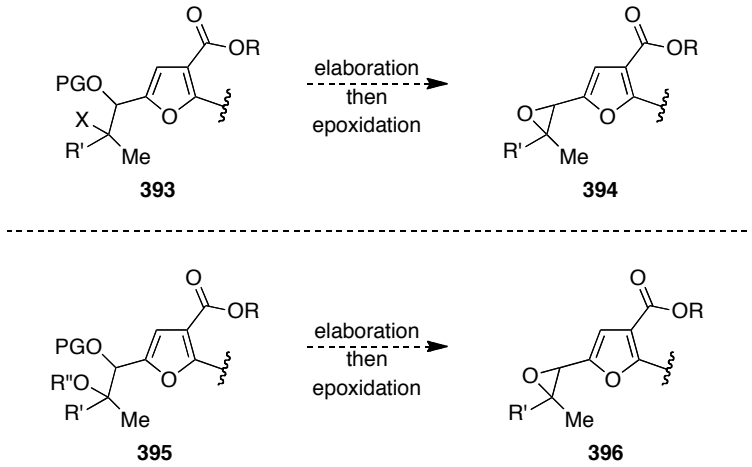
Scheme 3.2.2.2 Acid-promoted epoxide opening



3.2.3 Possible Methods of Epoxide Synthesis

An ideal scenario for access to an epoxy furan would involve the synthesis of halohydrin **393** wherein a masked epoxide exists prior to macrocyclization (Scheme 3.2.3.1). Thus the alcohol could remain protected until introduction of the epoxide **394** was desired. A similar approach would involve synthesis of diol **395** and subsequent conversion to the epoxide **394**.

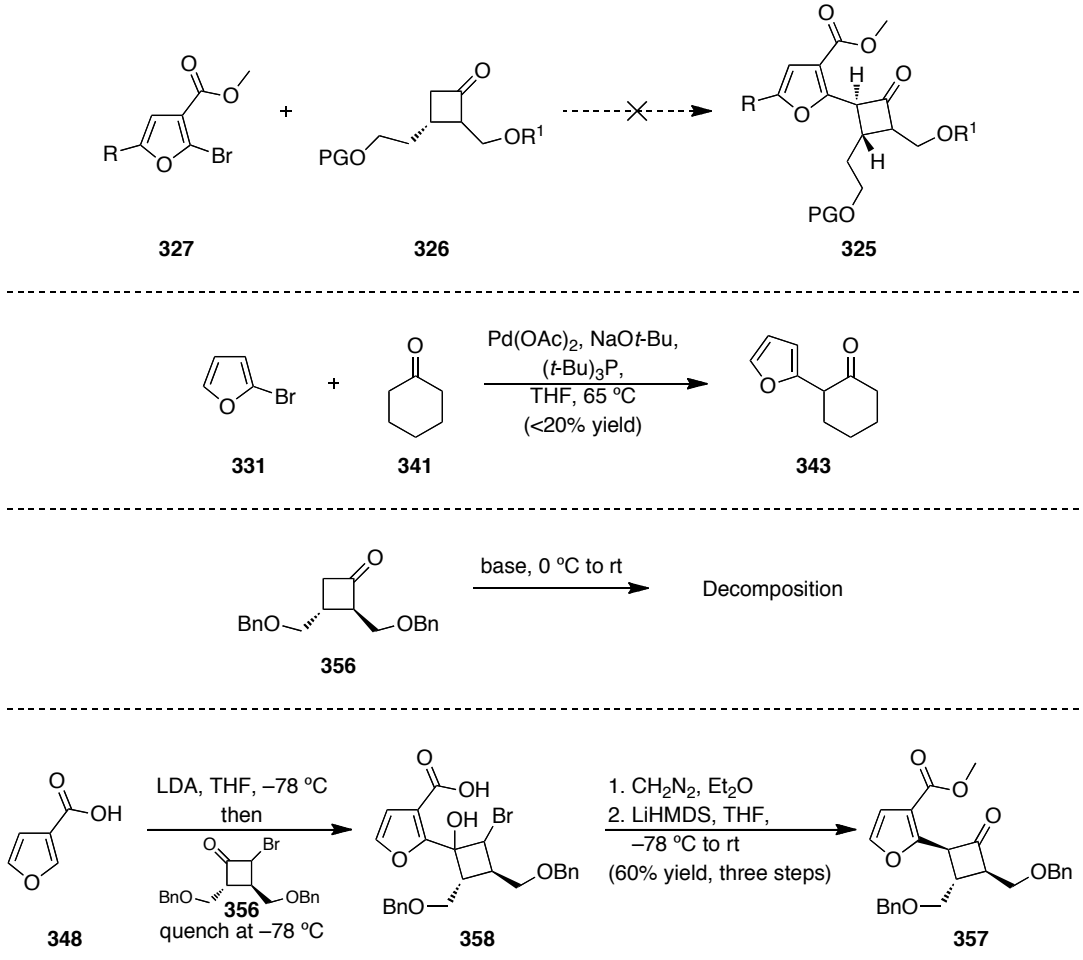
Scheme 3.2.3.1 Proposed introduction of furyl epoxides



3.3 Conclusions

Although we have found that the Buchwald–Hartwig type α-arylations of ketones is not an efficient method to couple bromofuran and cyclobutanone substrates, we did establish that ketones can undergo α-arylations with 2-bromofurans (Scheme 3.3.1). We established that enolates derived from our substituted cyclobutanone intermediates are unstable above –78 ºC, which led us to pursue an alkylation approach. We have successfully demonstrated the coupling of 3-furoic acid and a functionalized α-bromocyclobutanone via addition of the furan to the cyclobutanone. Further elaboration should provide a substrate well suited for advancement towards providencin (**1**).

Scheme 3.3.1 Chapter 3 summary



3.4 Experimental Procedures

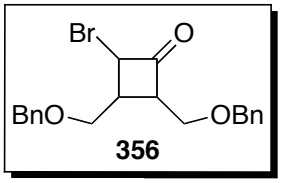
3.4.1 General Information

Unless otherwise stated, reactions were mechanically stirred in flame-dried glassware under an atmosphere of nitrogen. Tetrahydrofuran and diethyl ether were dried using a solvent purification system manufactured by SG Water U.S.A., LLC. Commercially available reagents were obtained from Sigma-Aldrich, Strem, TCI-America or Alfa Aesar and were used as received. All known compounds were identified by comparison of NMR spectra to those reported in the literature.

Thin layer chromatography was performed using Silicycle glass-backed extra hard layer, 60 Å plates (indicator F-254, 250 μm). Developed plates were visualized using a 254 nm UV lamp and/or with the appropriate dip followed by heating. Typical dip solutions were ethanolic anisaldehyde and potassium permanganate. Flash chromatography was generally performed with Silicycle SiliaFlash® P60 (230-400 mesh) silica gel as the stationary phase. Infrared spectra were recorded on a Nicolet Avatar 320 FT-IR. Samples were analyzed as thin films on NaCl plates (sample dissolved in CH_2Cl_2) and the spectra are presented as transmittance vs. wavenumber (cm^{-1}). High-resolution mass spectrometry was conducted on an Agilent 6210 TOF LCMS. Proton (^1H) and carbon (^{13}C) NMR spectra were recorded on a Varian Inova 400 or 300 spectrometer. Spectra were obtained at 22 ºC in $CDCl_3$ unless otherwise noted. Chemical shifts (δ) are reported in parts per million (*ppm*) and are referenced to the residual solvent peak. Coupling constants (*J*) are reported in Hertz (Hz) and are rounded to the nearest 0.1 Hz. Multiplicities are defined as: s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintuplet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets,

dddd = doublet of doublet of doublet of doublets, br = broad, app = apparent.

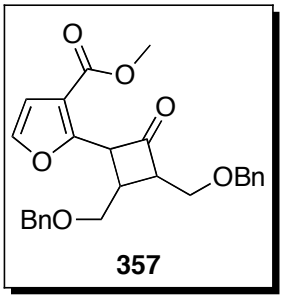
3.4.2 Preparative Procedures



356

Cyclobutanone **115** [17] (0.134 g, 0.43 mmol) was dissolved in THF (10 mL) and cooled to –78 ºC and TBS-OTf (0.29 mL, 1.29 mmol) was added slowly. Then 1M LiHMDS (2.2 mL, 2.15 mmol) was added rapidly down the side of the flask. After 1 h the reaction was carefully quenched with saturated NH_4Cl solution. The aqueous layer was extracted with Et_2O 2x. The combined organics were washed with H_2O and dried over $MgSO_4$ and then concentrated *in vacuo*. The crude material was dissolved in THF (10 mL) and cooled to 0 ºC. NBS (0.084 g, 0.47 mmol) was added in one portion and reaction was allowed to warm to room temperature and stir for 1 h. The reaction was quenched with H_2O and the aqueous layer was extracted with Et_2O 2x. The combined organics were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was flashed in 10:1 hexanes:EtOAc. Bromocyclobutanone **356** was isolated in 40% yield for two steps.

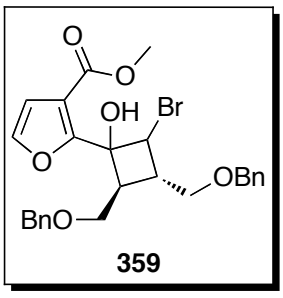
356: R_f = 0.28, 4:1 hexanes:EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.29 (m, 10H), 4.99 (dd, *J*=7.7, 2.4 Hz, 1H), 4.64–4.56 (m, 2H), 4.56–4.50 (m, 2H), 3.83 (dt, *J*=9.9, 3.9 Hz, 1H), 3.78–3.70 (m, 2H), 3.65–3.56 (m, 2H), 2.87–2.81 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.3, 137.9, 137.8, 128.6, 128.5, 128.0, 127.8, 127.7, 127.6, 73.3, 73.2, 67.9, 66.2, 58.4, 48.3, 41.0 IR (NaCl thin film): 3030(w), 2857(w), 1792(s), 1113(m), 737(m), 697(m); HRMS (ESI–APCI) *m*/*z* calcd. for $C_{20}H_{25}BrNO_3$ $[M+NH_4]^+$: 406.1012, found: 406.1011



357

To 3-furoic acid **348** (0.028 g, 0.249 mmol) in THF (3 mL) at –78 ºC, was added 0.5M LDA (1 mL, 0.497 mmol). The reaction was stirred for 30 min at –78 ºC and then bromocyclobutanone **356** (0.088 g, 0.226 mmol) in THF (1 mL) was added. When starting material was consumed by TLC the reaction was quenched with saturated NH_4Cl solution. The aqueous layer was extracted with Et_2O 2x. The combined organics were washed with H_2O and dried over $MgSO_4$ and then concentrated *in vacuo*. The crude material was stirred in Et_2O at room temperature and excess diazomethane was added. The reaction was filtered through $MgSO_4$ and then concentrated *in vacuo*. The crude material was flashed in 4:1 – 2:1 hexanes:EtOAc. Cyclobutanone **357** was isolated in 60% yield over 2 steps.

357: R_f = 0.17, 4:1 hexanes:EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J*=0.9 Hz, 1H), 7.38–7.17 (m, 10H), 6.83 (d, *J*=0.9 Hz, 1H), 4.55 (s, 2H), 4.40 (s, 2H), 3.90 (s, 3H), 3.86 (dd, *J*=19.0, 5.5 Hz, 1H), 3.59 (dd, *J*=16.3, 5.8 Hz, 1H), 3.54–3.49 (m, 2H), 3.03 (dd, *J*=14.1, 5.1 Hz, 1H), 2.23 (quint., *J*=5.9 Hz, 1H), 2.04–1.96 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.5, 163.3, 152.2, 144.2, 138.4, 138.3, 128.5, 128.4, 127.8, 127.6, 121.7, 113.6, 72.9, 72.8, 70.8, 66.7, 52.5, 30.6, 28.3, 26.7; IR (NaCl thin film): 3030(w), 2924(m), 2857(m), 1732(s), 1485(m), 1306(m), 1094(s), 738(m), 698(m); HRMS (ESI–APCI) *m*/*z* calcd. for $C_{26}H_{26}NaO_6$ $[M+Na]^+$: 457.1622, found: 457.1625

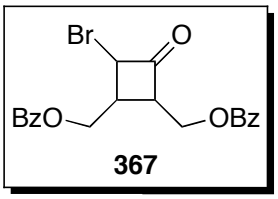


359

To 3-furoic acid **348** (0.123 g, 1.1 mmol) in THF (10 mL) at –78 ºC, was added 0.5M LDA (4.4 mL, 2.2 mmol). The reaction was stirred for 30 min at –78 ºC and then bromocyclobutanone **356**

(0.383 g, 1 mmol) in THF (1 mL) was added and reaction was stirred at –78 ºC. When starting material was consumed by TLC the reaction was quenched with saturated NH_4Cl solution. The aqueous layer was extracted with Et_2O 2x. The combined organics were washed with H_2O and dried over $MgSO_4$ and then concentrated *in vacuo*. The crude material was dissolved in Et_2O and treated with excess diazomethane at room temperature. The reaction was concentrated *in vacuo*. The crude material was flashed in 20:1 – 10:1 – 4:1 hexanes:EtOAc and **359** was obtained in around 20% yield.

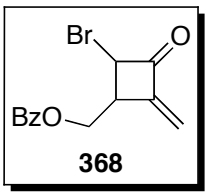
359: R_f = 0.31, 4:1 hexanes:EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.21 (m, 8H), 7.10–7.08 (m, 2H), 6.66 (d, *J*=1.9 Hz, 1H), 6.13 (d, *J*=0.7 Hz, 1H), 5.49 (d, *J*=8.9 Hz, 1H), 4.58 (s, 2H), 4.14 (dd, *J*=11.7, 8.7 Hz, 2H), 3.89 (d, *J*=6.8 Hz, 2H), 3.78 (s, 3H), 3.35–3.28 (m, 2H), 2.95 (q, *J*=4.8 Hz, 1H), 2.83–2.76 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 160.2, 140.9, 138.2, 138.0, 128.5, 128.3, 128.0, 127.7, 127.5, 114.6, 111.5, 75.2, 73.5, 73.2, 72.3, 68.8, 52.3, 51.0, 49.0, 38.7; IR (NaCl thin film): 3301(w), 3030(w), 2950(w), 2857(m), 1725(m), 1693(s), 1312(s), 1209(s), 1073(s), 740(s), 698(s); HRMS (ESI–APCI) *m/z* calcd. for $C_{26}H_{28}BrO_6$ $[M+H]^+$: 515.1064, found: 515.105



367

Known cyclobutanone **366** [18] (0.108 g, 0.35 mmol) was dissolved in THF (5 mL) and cooled to –78 º C. and TBS-OTf (0.24 mL, 1.05 mmol) was added slowly. Then 1M LiHMDS (1.75 mL, 1.75 mmol) was added rapidly down the side of the flask. After 1 h the reaction was carefully quenched with saturated NH_4Cl solution. The aqueous layer was extracted with Et_2O 2x. The combined organics were washed with H_2O and dried over $MgSO_4$ and then concentrated *in vacuo*. The crude material was dissolved in THF (10 mL) and cooled to 0 ºC. NBS (0.068 g, 0.38 mmol) was added in one portion and reaction was allowed to

warm to room temperature and stir for 1 h. The reaction was quenched with H_2O and the aqueous layer was extracted with Et_2O 2x. The combined organics were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Attempts to flash the crude material resulted in mixtures of the desired product **367** and the elimination product **368**.



368

367: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05–7.97 (m, 4H), 7.63–7.57 (m, 2H), 7.51–7.43 (m, 4H), 5.01 (dd, *J*=10.1, 2.4 Hz, 1H), 4.75–4.55 (m, 4H), 3.76–3.71 (m, 1H), 3.15–3.08 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.7, 166.3, 166.2, 133.6, 133.5, 130.3, 129.8, 129.3,128.6, 63.8, 60.6, 58.5, 48.8, 40.6; IR (NaCl thin film): 3064(w), 2952(w), 1797(m), 1722(s), 1270(s), 1115(m), 710(m); HRMS (ESI–APCI) *m*/*z* calcd. for $C_{20}H_{21}BrNO_5$ $[M+NH_4]^+$: 434.0598, found: 434.0591

368: ^{1}H NMR (400 MHz, $CDCl_3$) d 8.04–8.01 (m, 2H), 7.61–7.57 (m, 1H), 7.46 (app t, *J*=7.8, 7.5 Hz, 2H), 6.09–6.06 (m, 1H), 5.48–5.46 (m, 1H), 5.15 (d, *J*=8.8 Hz, 0.25H), 4.83 (d, *J*=5.8 Hz, 0.75H), 4.75–4.55 (m, 2H), 3.74–3.69(m, 0.25H), 3.63–3.57 (m, 0.75H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6, 166.2, 150.7, 133.6, 129.7, 128.7, 128.6, 118.2, 64.2, 49.4, 47.4; IR (NaCl thin film): 3064(w), 2954(w), 2851(w), 1772(s), 1719(s), 1271(s), 710(m); HRMS (ESI–APCI) *m*/*z* calcd. for $C_{13}H_{12}BrO_3$ $[M+H]^+$: 294.9964, found: 294.995

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Appendix A3: Spectral Data Relevant to Chapter 3

Figure A3.1 ^{1}H NMR spectrum (400MHz, CDCl3) of compound **356**

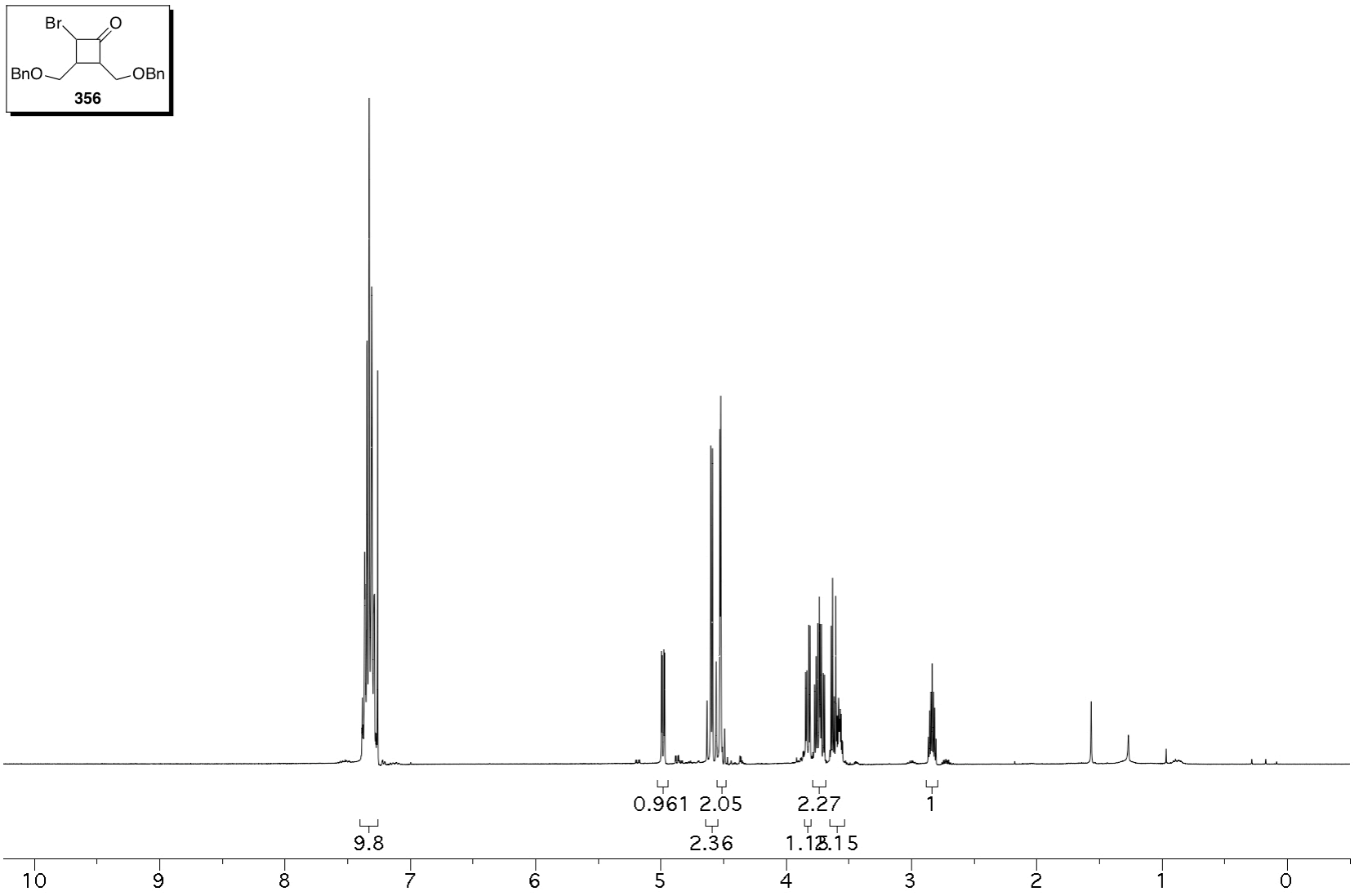


Figure A3.2 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **356**

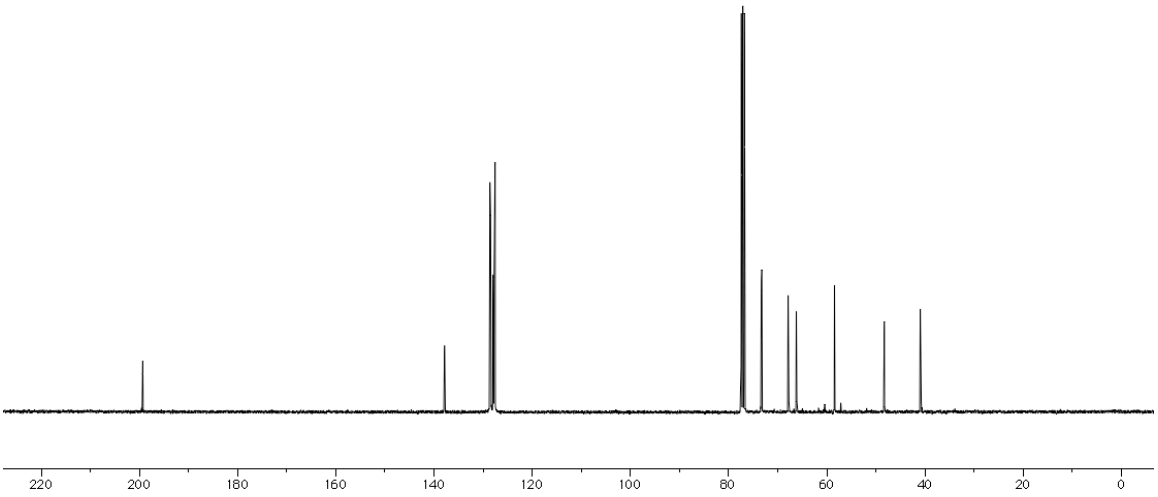


Figure A3.3 IR spectrum (thin film, NaCl) of compound **356**

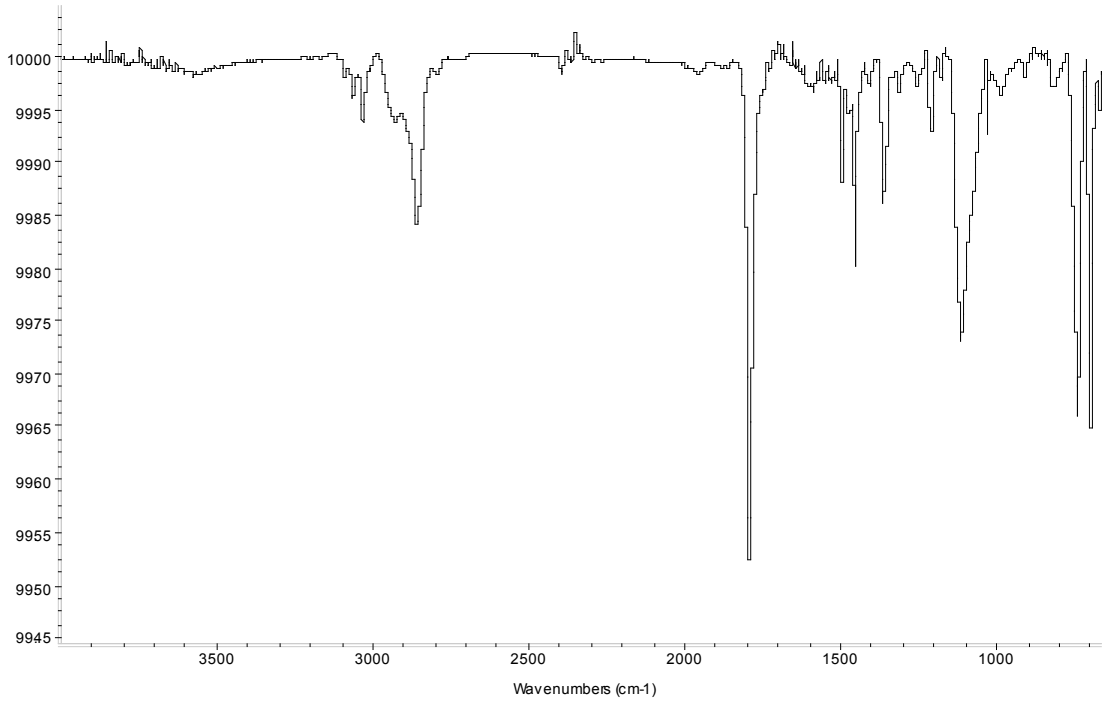
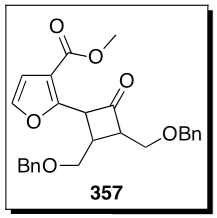


Figure A3.4 [1]H NMR spectrum (400MHz, CDCl3) of compound **357**



357

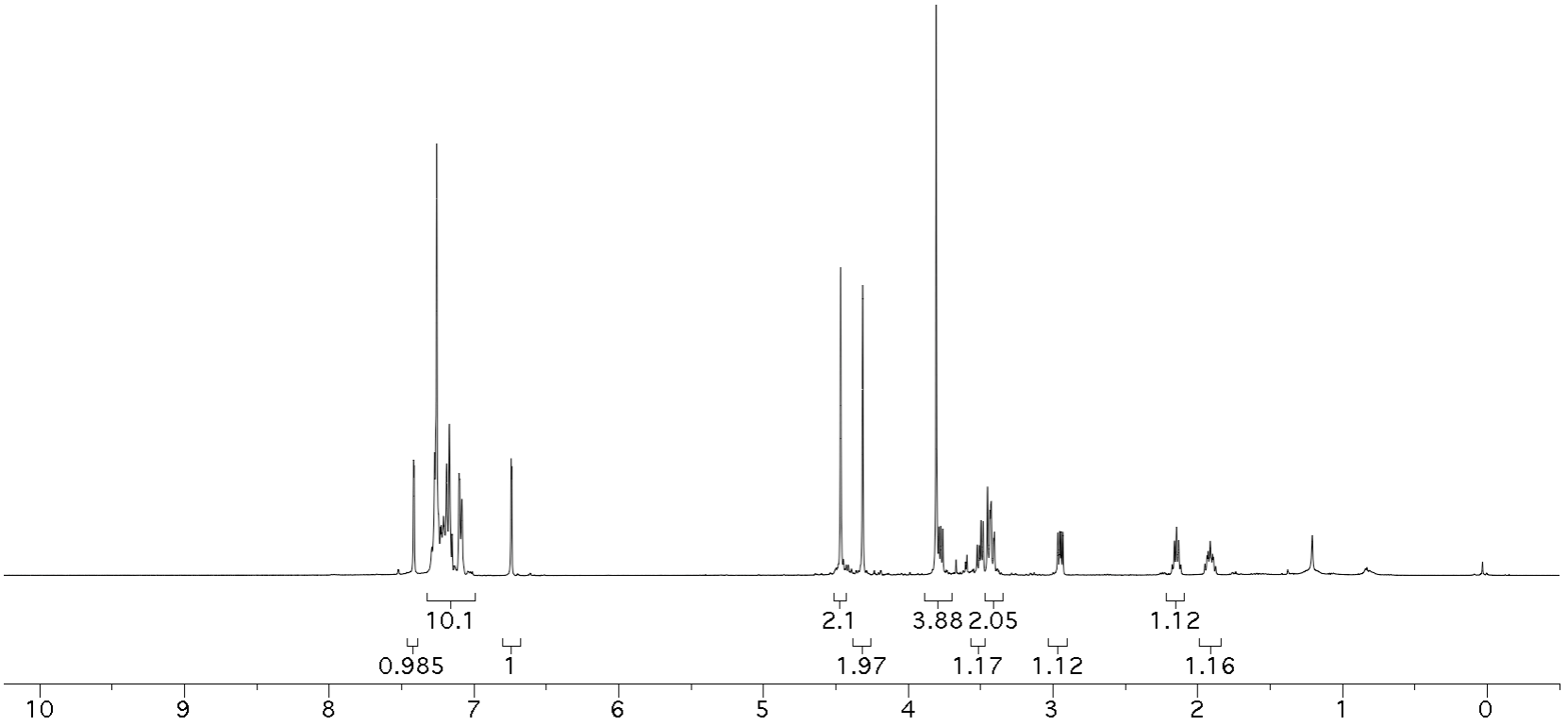


Figure A3.5 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **357**

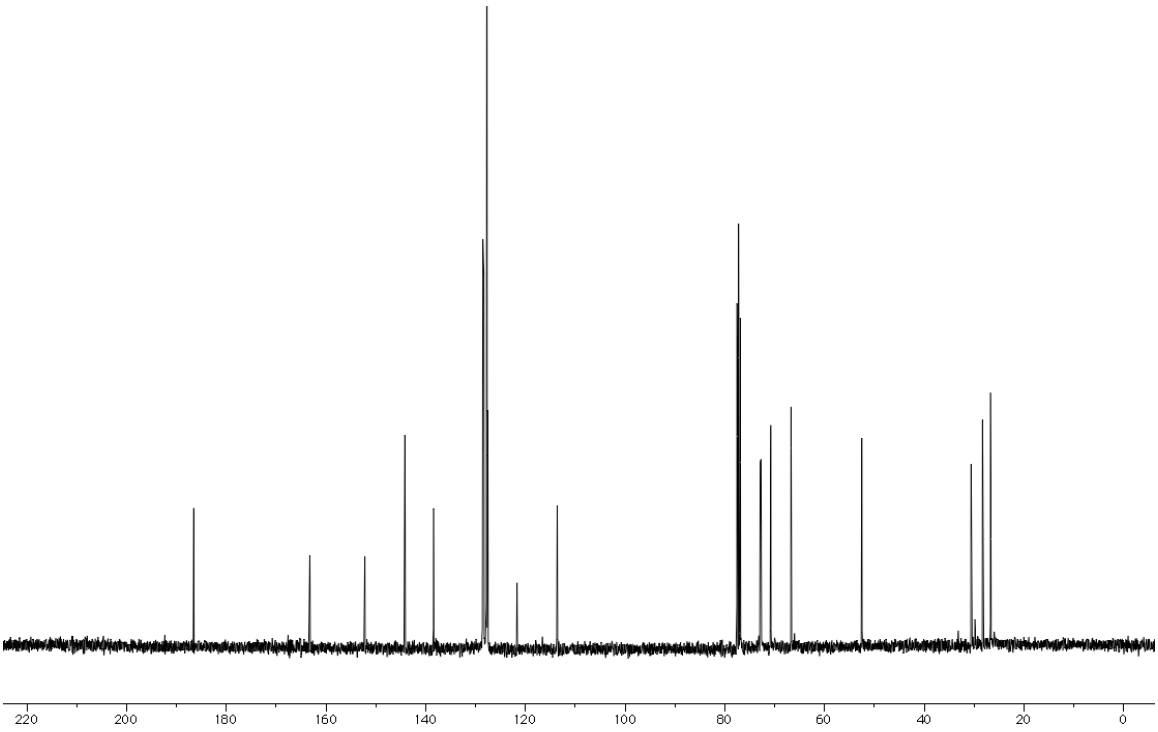


Figure A3.6 IR spectrum (thin film, NaCl) of compound **357**

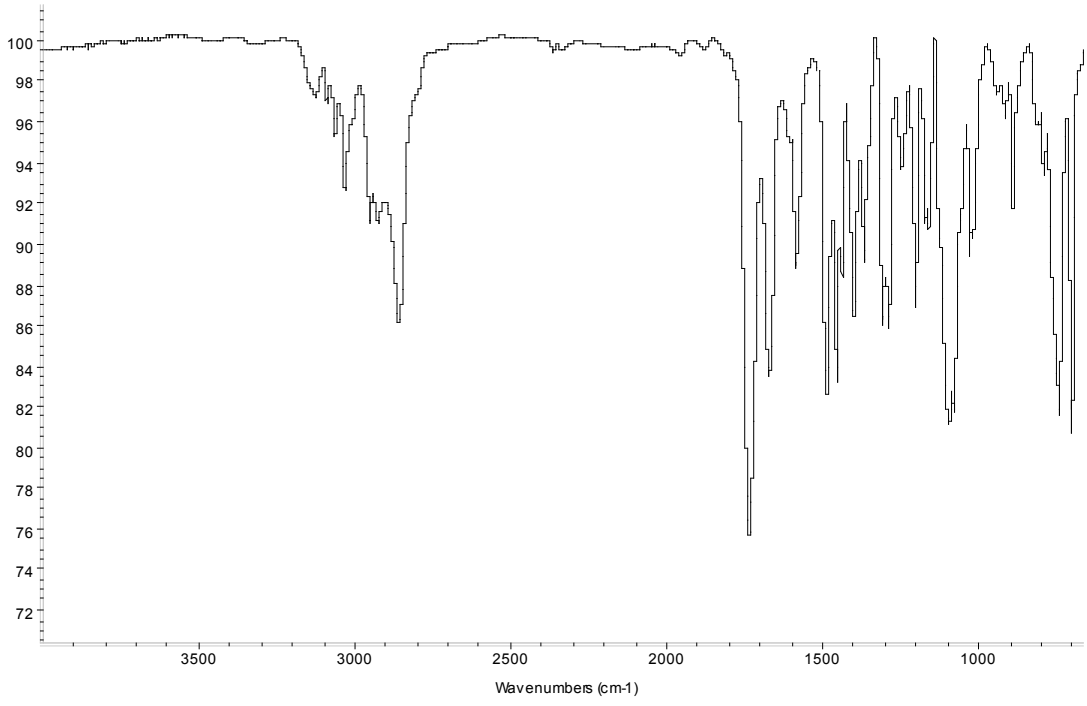


Figure A3.7 [1]H NMR spectrum (400MHz, CDCl3) of compound **359**

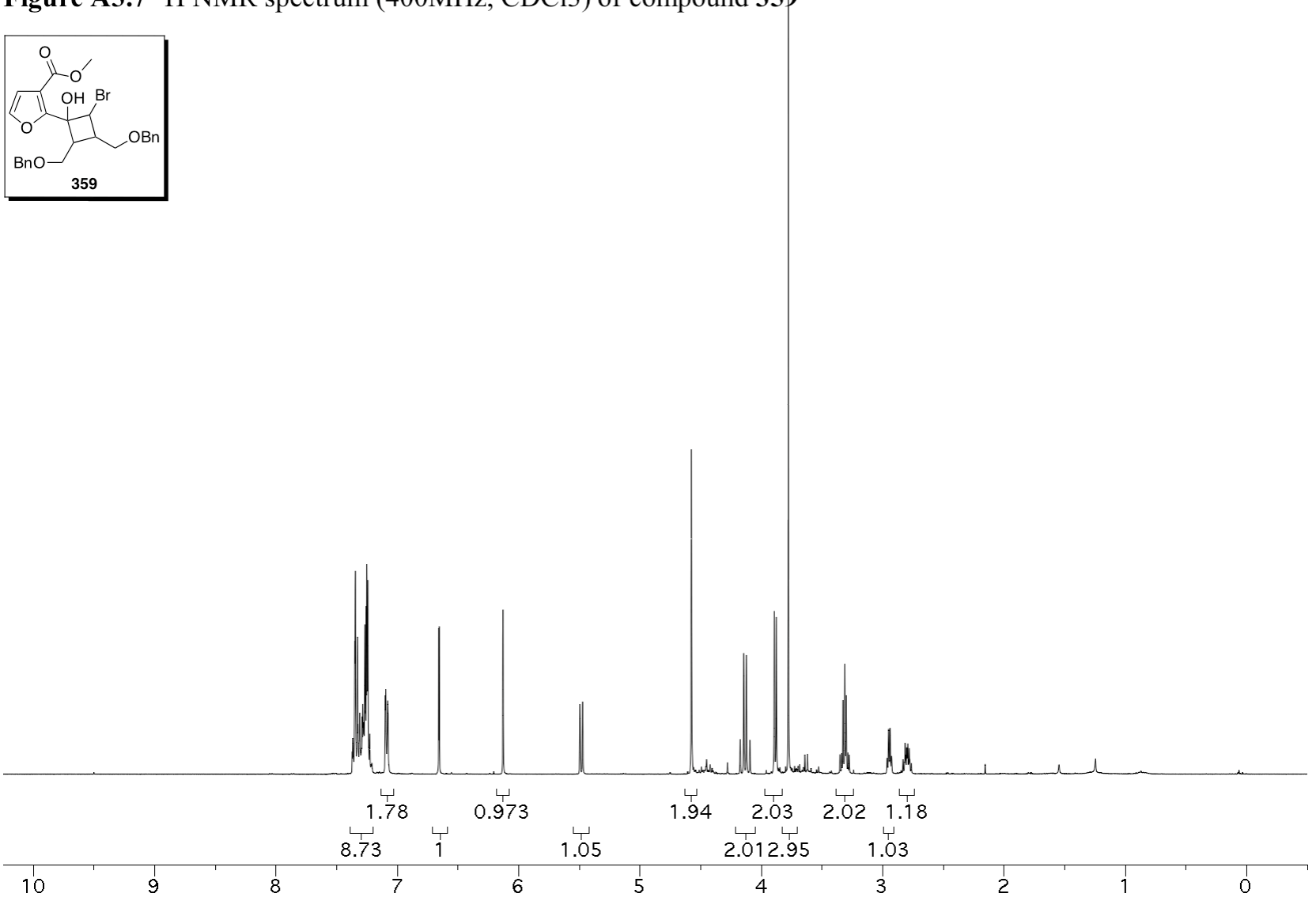


Figure A3.8 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **359**

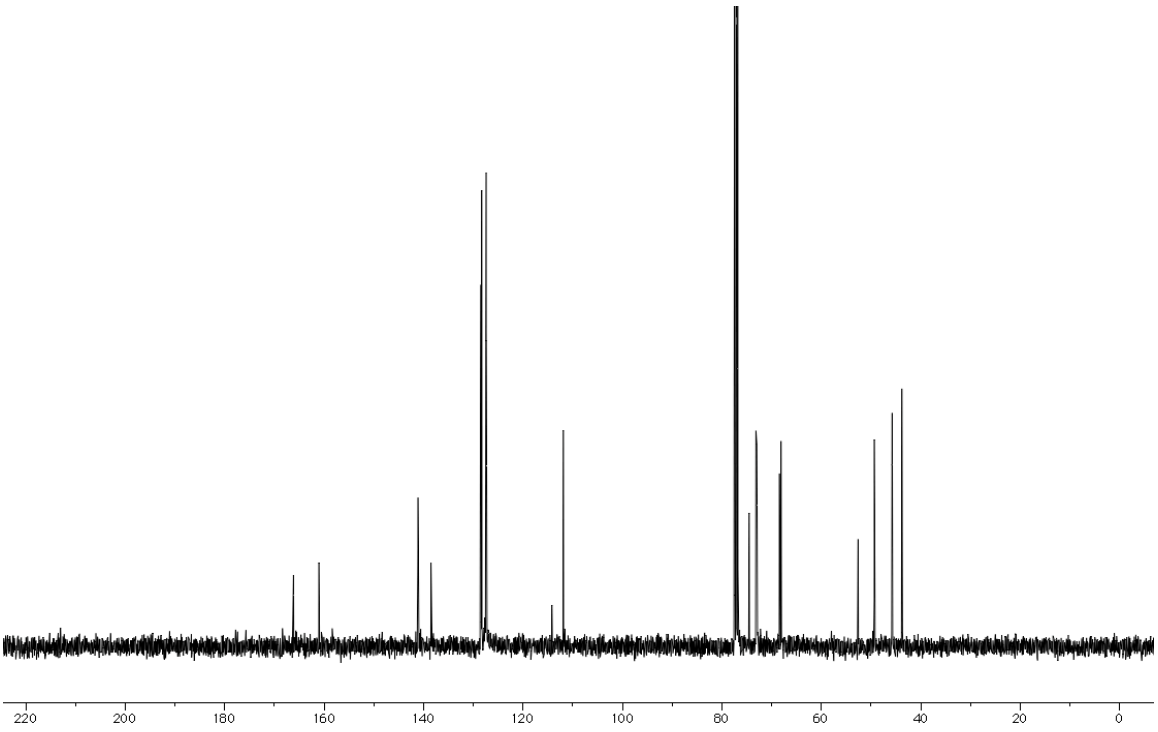


Figure A3.9 IR spectrum (thin film, NaCl) of compound **359**

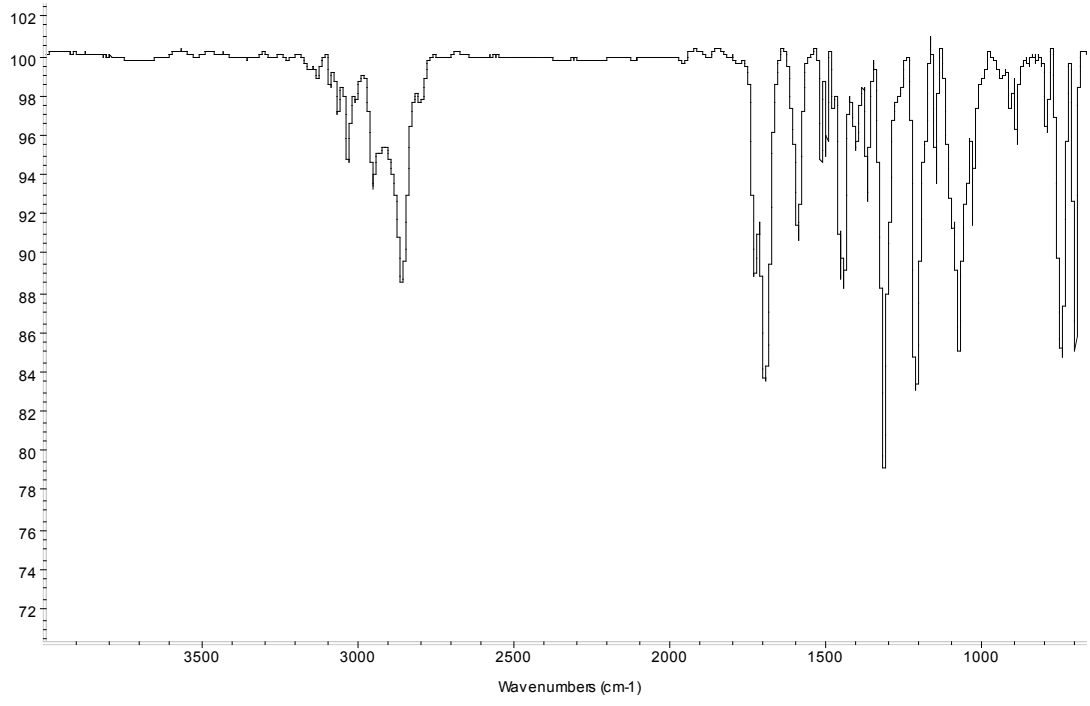
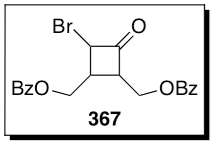


Figure A3.10 [1]H NMR spectrum (400MHz, CDCl3) of compound **367**



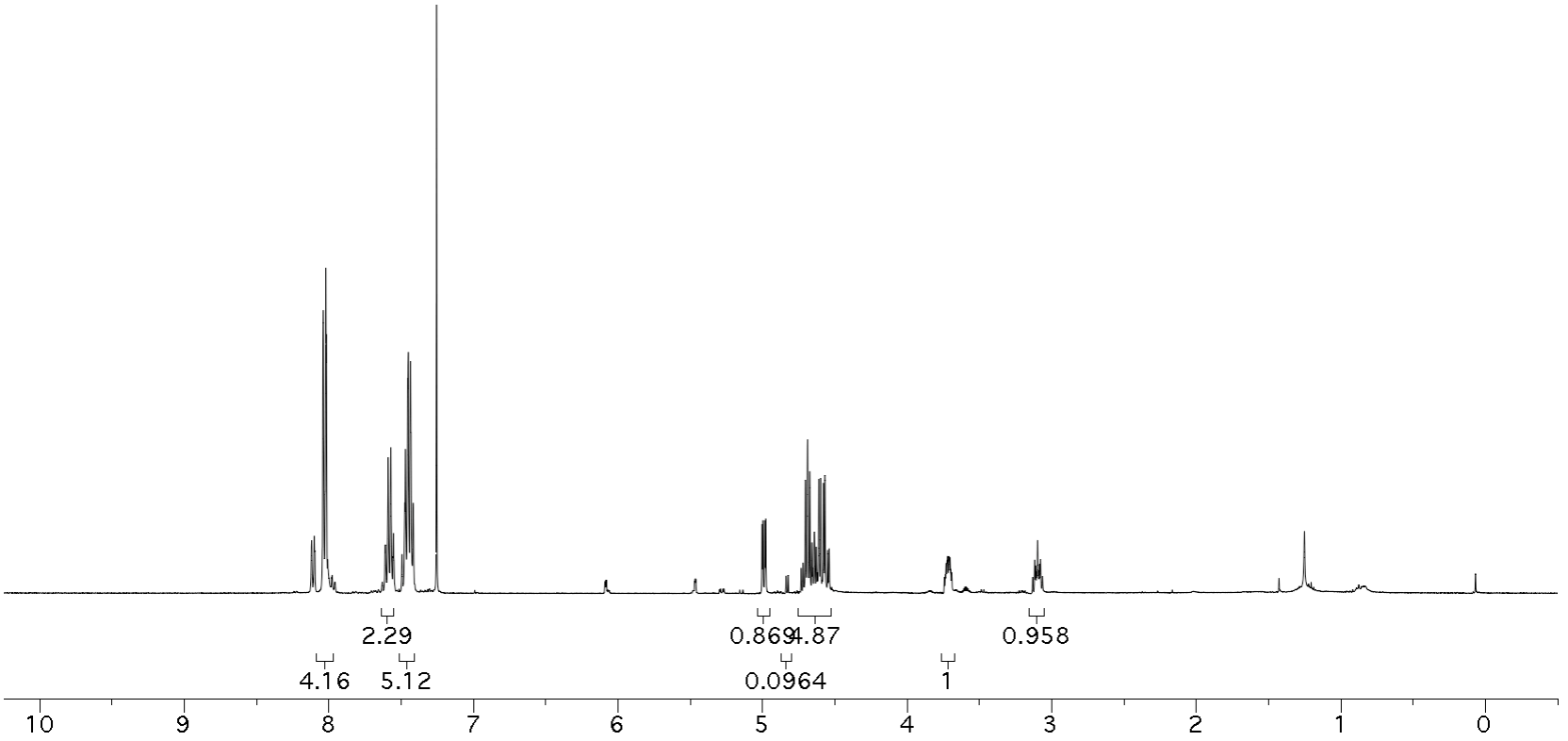


Figure A3.11 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **367**

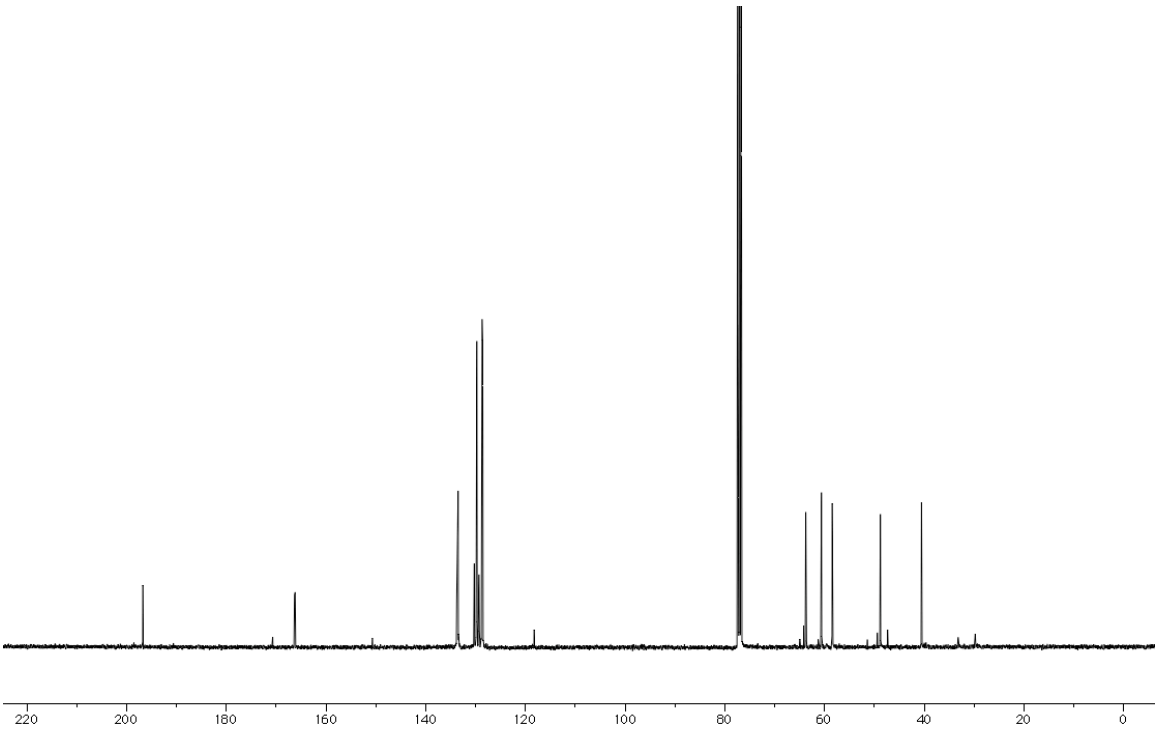


Figure A3.12 IR spectrum (thin film, NaCl) of compound **367**

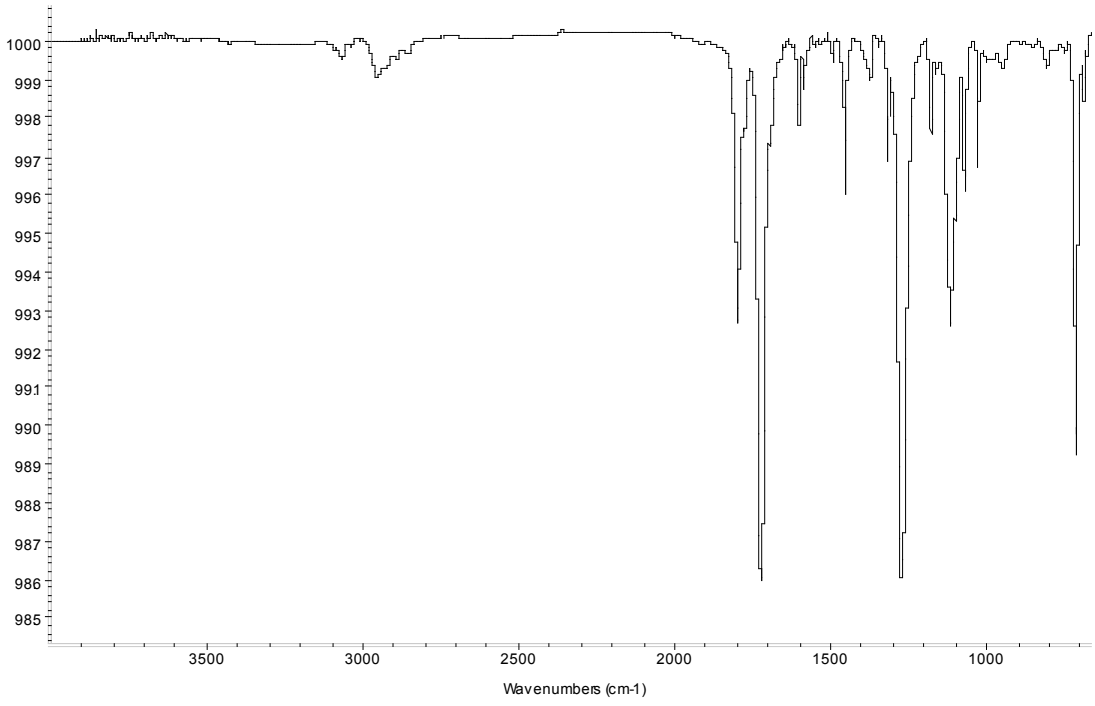
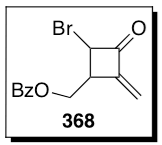


Figure A3.13 [1]H NMR spectrum (400MHz, CDCl3) of compound **368**



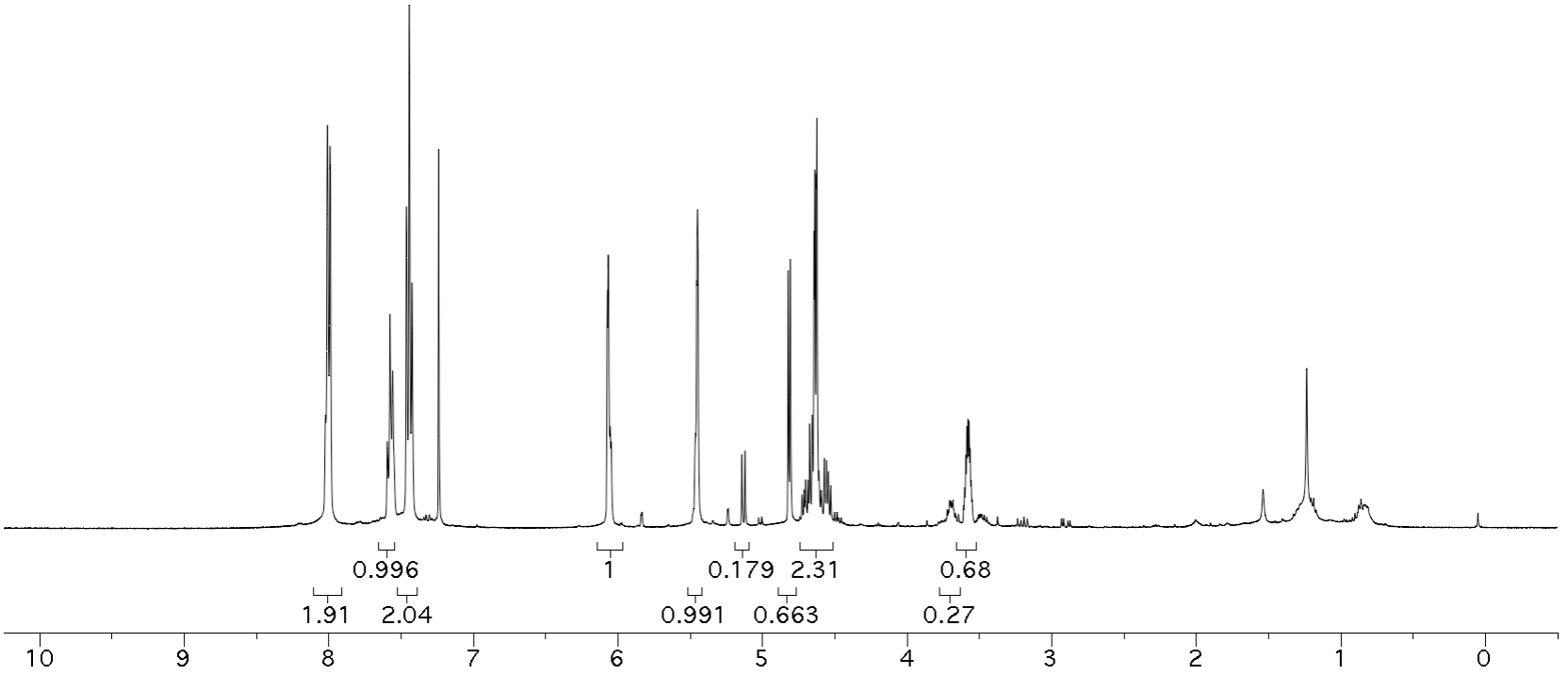


Figure A3.14 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **368**

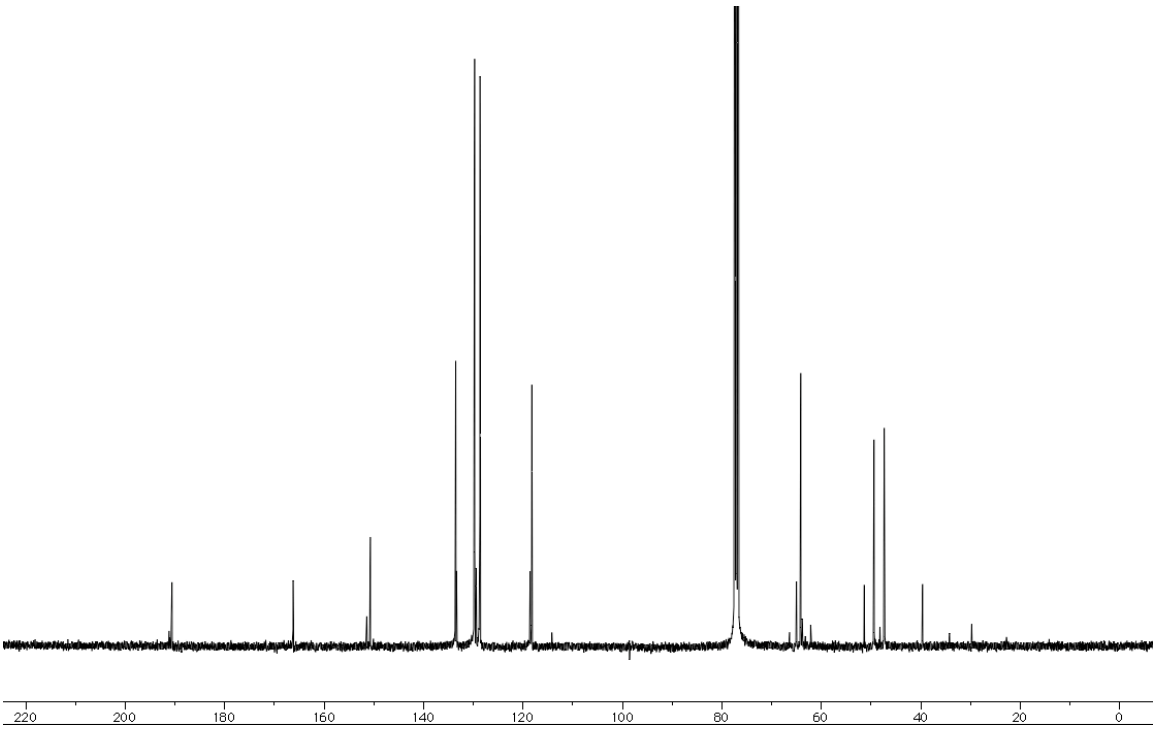
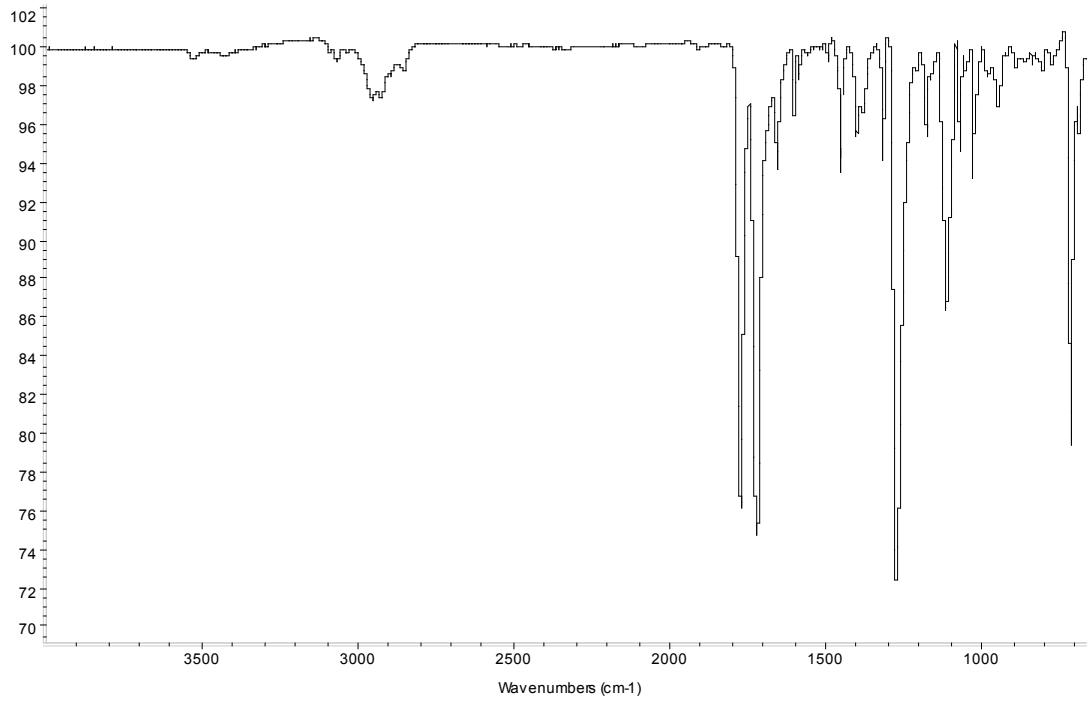


Figure A3.15 IR spectrum (thin film, NaCl) of compound **368**



Appendix A4: Notebook Cross-Reference