DISSERTATION

PROGRESS TOWARDS THE TOTAL SYNTHESIS OF DEBROMOPHYCOLIDE

Submitted by

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ABSTRACT

PROGRESS TOWARDS THE TOTAL SYNTHESIS OF DEBROMOPHYCOLIDE

The structure of debromophycolide provides a novel synthetic target that could provide synthetic insight into several other members of the bromophycolide family. Our synthetic efforts toward the total synthesis of debromophycolide are described. The discussion begins with the description of a planned convergent approach to the total synthesis of debromophycolide. Key disconnections dissect the molecule into four distinct fragments that can be joined in multiple ways to incorporate flexibility to the synthesis. Our approach begins with the construction of a benzyl-cyclopentenyl fragment utilizing a transition metal cross-coupling reaction. Then focus shifts towards a functionalized aliphatic fragment, which incorporates a conjugate addition reaction to link the two fragments. Efforts to implement this plan are then described.

Acknowledgements

Everything happens for a reason. I apply this thought to everyday life, as well as my research. "What has lead us into the field we are in," and "What direction we take once we get there," all has a reason. There is always something to learn from each and every reaction we run, whether the results are positive or negative, and it takes a patient and knowledgeable mind to understand and translate the outcome. This type of understanding has become an integral part of my understanding of science, and has been the philosophy taught to me from my graduate advisor, John L. Wood. I begin by expressing my appreciation for his knowledge and leadership that has allowed me to learn in an environment that has been created to advance the learning experience.

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To My Friends and Family

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List of Abbreviations

18-c-6	18-crown-6
AD-mix α	reagent for Sharpless Asymmetric Dihydroxylation
AIBN	2,2' Azodiisobutyronitrile
aq	aqueous
Boc_2O	di-tert-butyl dicarbonate
*n*BuLi	*n*-butyllithium
t$BuNH_2$	tert-butyl amine
tBu_4NI	tert-butyl ammonium iodide
*t*BuOH	tert-butyl alcohol
*t*BuOK	potassium tert-butoxide
C	carbon
°C	degrees celcius
$CDCl_3$	chloroform-*d*
$CeCl_3$	cerium trichloride
CuCN	copper (I) cyanide
CuI	copper (I) iodide
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DMAP	4-(dimethylamino)pyridine
DMF	dimethyl formamide
DNA	deoxyribonucleic acid
e.g.	*exempli gratia*, for example
eq	equation
Et_3N	triethyl amine
EtOAc	ethyl acetate
EtOH	ethanol
FT-IR (IR)	Fourier transform infrared spectroscopy
g	gram(s)
H	hydrogen
h	hour(s)
HCl	hydrochloric acid
HFIP	1,1,1,3,3,3-hexafluoro 2-propanol
HIV	human immunodeficiency syndrome
H_2O_2	hydrogen peroxide
HRMS	high-resolution mass spectrum
HWE	Horner-Wadsworth-Emmons
Hz	hertz
IC_{50}	half maximum inhibitory concentration
i.e.	*id est*, in other words
J	coupling constant
KHF_2	potassium hydrogen difluoride
KHMDS	potassium bis(trimethylsilyl)amide
KI	potassium iodide

L	liter(s)
LiBr	lithium bromide
LiHMDS	lithium bis(trimethylsilyl)amide
LiI	lithium iodide
LiOH	lithium hydroxide
MeLi	methyl lithium
MeOH	methanol
MgBr	magnesium bromide
mg/L	milligrams/liter
$MgSO_4$	magnesium sulfate
MHz	megahertz
Min	minute(s)
µM	micromolar
m/z	mass to charge ratio
NaCl	sodium chloride
NaO*t*Bu	sodium tert-butoxide
NaH	sodium hydride
$NaBH_4$	sodium borohydride
$NaHCO_3$	sodium bicarbonate
NaOH	sodium hydroxide
$NaSO_{3(aq)}$	sodium sulfite
NBS	*N*-bromosuccinimde
NH_4Cl	ammonium chloride
NH_4OH	ammonium hydroxide
NIS	*N*-iodosuccinimde
NMR	nuclear magnetic resonance
$Pd(cod)Cl_2$	(1,5) cyclooctadiene palldaium(II) dichloride
$Pd_2(dba)_3 \bullet CHCl_3$	tris(dibenzylideneacetate)dipalladium(II) chloroform adduct
$Pd(P(Ph)_3)_2Cl_2$	bis(triphenylphosphine)palladium (II) chloride
$Pd(P(o\text{-tolyl})_3)_2Cl_2$	bis(tri-*o*-toluenephosphine)palladium (II) chloride
ppm	parts per million
iPr_2NEt	N,N-diisopropylethylamine
rt	room temperature
S_N2	bimolecular nucleophilic substitution
TBAF	tetra-butylammonium fluoride
TBSCl	tert-butyldimethylsilyl chloride
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMEDA	tetra-methylethylenediamine
TMSCl	trimethylsilyl chloride
$TMSCH_2MgBr$	trimethylsilyl methylmagnesium bromide
TOF LCMS	time of flight liquid chromatography mass spectrometry
UV	ultra violet

Chapter 1

The Bromophycolide Family of Natural Products

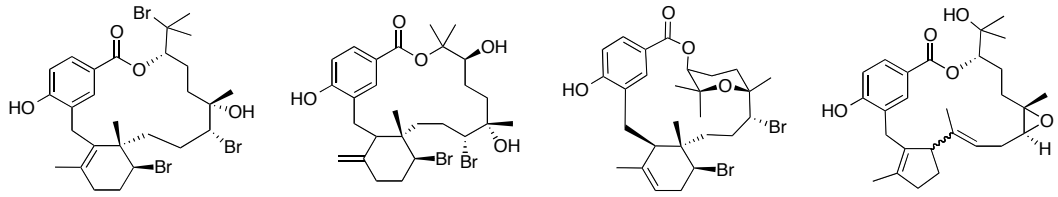
1.1 – Introduction and Background

1.1.1 – Isolation

Bromine can be found in concentrations of up to 65 mg/L in the ocean, which is significantly higher than what can be found in the earth's crust, ~2 ppm.[1] This abundance of bromine has led to the significant incorporation of elemental bromine into the organic metabolites of marine plants and animals. These organisms, which have produced over 1600 bromine-containing natural products, have piqued the interest of medicinal and synthetic communities alike.[1]

One marine species well documented in producing brominated metabolites is the red macroalgea *Callophycus serratus*. First harvested off the coast of Fiji by Kubanek and co-workers in 2005, *Callophycus serratus* was extracted and purified with reverse- and normal-phase HPLC to yield a number of related structures named the bromophycolides (Figure 1).[2-5] Due to their impressive biological activity and the scarce isolation yields (0.0007 – 0.80 % of the total dry mass) we began a project focused on the synthesis of debromophycolide, a member of the bromophycolide family which we envisioned to be a suitable synthetic intermediate for accessing a number of other bromophycolide congeners.

Figure 1 – Diverse Structures of the Bromophycolide Family

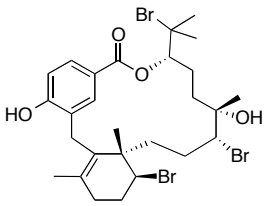


1.1.2 – Biological Activity

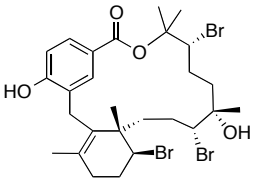
The bromophycolides exhibit widespread cytotoxicity including antibacterial, anticancer, antimalarial, antiviral and antifungal activities (Table 1).[2-5] As a sample, bromophycolides A, B, Q, and U display activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecium* (VREF), with IC_{50} values of 5.9 μM and 5.9 μM, 5.9 μM and 3.0 μM, 1.8 μM and 5.8 μM, and 0.9 μM and 0.9 μM, respectively. When tested against various cancer cell lines (e.g., ovarian, breast, prostate, lung and colon) bromophycolides A, B, Q, and U had mean IC_{50} values of 6.7 μM, 27.7 μM, 2.0 μM, and 16 μM, respectively. Bromophycolides A, B, Q, and U showed activity against the human malarial parasite *Plasmodium falciparum* with IC_{50} values of 0.9 μM, 4.8 μM, 1.4 μM , 2.1 μM, respectively. Bromophycolide A displayed activity against HIV-1 viral strains 96USHIPS7 and UG/92/029 (IC_{50} = 9.8 μM, 9.1 μM, respectively) as well as cytotoxicity against the amphotericin B-resistant fungus *Candida albicans* (IC_{50} = 0.9 μM). Bromophycolides Q and U displayed activity against *Mycobacterium tuberculosis* with an IC_{50} value of 22 μM each (bromophycolides A and B were not tested). Debromophycolide appears to be inactive with reported activity against cancer cell lines (IC_{50} > 76 μM) and the human malarial parasite *Plasmodium falciparum* (IC_{50} > 100

μM). Although, when tested in house against *Mycobacterial tuberculosis*, debromophycolide had an MIC value of 12.5 μg/mL.[6]

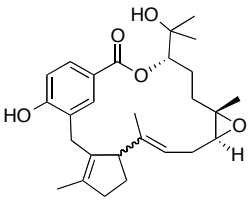
Table 1 – Biological Activity for Selected Bromophycolides. Reported IC_{50} in μM



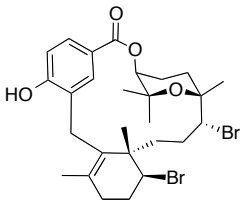
bromophycolide **A**



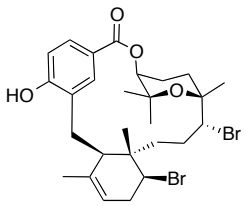
bromophycolide **B**



debromophycolide (**1**)



bromophycolide **Q**



bromophycolide **U**

	Antibacterial activity*		Anticancer activity*	Antimalarial*	Antiviral*	Antifungal*
compound	MRSA	VREF		P. falciparum	anti-HIV	C. albicans
A	5.9	5.9	6.7	0.9	9.8	49
B	5.9	3.0	27.7	4.8	NT	49
1	NT	NT	>76.0	>100	NT	NSA
Q	1.8	5.8	5.5	1.4	NT	>90
U	0.9	0.9	3.1	2.1	NT	>15

1.2 – Structural Characteristics of the Bromophycolides

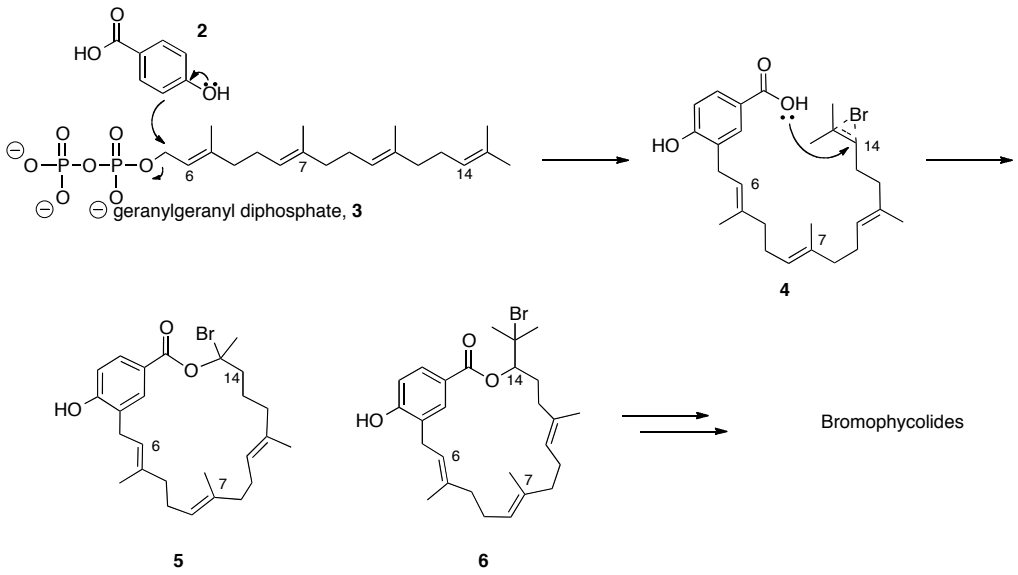
In addition to their interesting biological profile, the bromophycolides are defined by a benzoate-diterpene macrocyclic backbone, which possesses a number of different functionalities and structural variances to constitute a family of 21 known congeners.[2-5] Structural commonalities inherent to the members of the bromophycolide family include: a trisubstituted aryl ring, a tetrasubstituted cyclohexane (with the exception of

debromophycolide **1**, which contains a trisubstituted cyclopentene), and varying sites of oxidation which incorporate either C-O or C-Br bonds.

1.2.1 – Formation of Common Biosynthetic Intermediates

Kubanek has proposed a biosynthetic pathway by which the bromophycolides are synthesized in nature. To begin, an electrophilic aromatic substitution of benzoic acid **2** with geranylgeranyl diphosphate **3** delivers polyene **4** (Scheme 1).[2] Activation of the C14/C15 trisubstituted olefin with an electrophilic bromine source, likely from vanadium bromoperoxidase, would promote lactonization to deliver either a 19 or 20 membered macrocycle (**5** or **6**).[7] Biosynthetic intermediates **5** or **6** would then undergo a number of additional transformations at the sites of unsaturation, leading to the various members of the bromophycolide family.

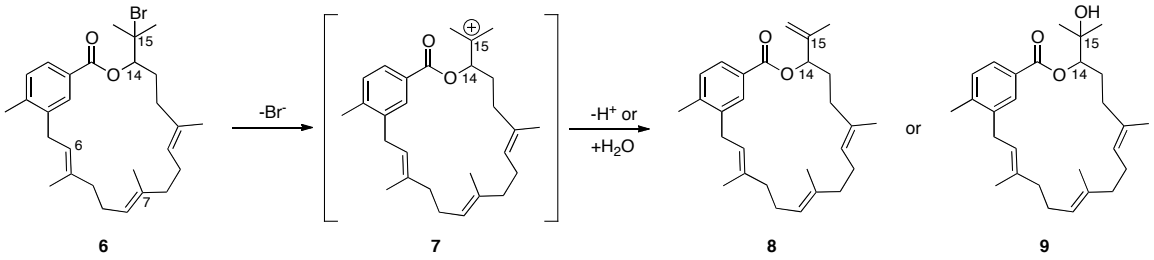
Scheme 1 – Biosynthesis of Macrocycles 5 and 6



1.2.2 – Variation of the C14 Isopropyl Unit

The second site of structural divergence, the C14 isopropyl unit, can undergo additional transformations to provide either an isoprene or a tertiary alcohol moiety. The tertiary bromide motif (observed in bromophycolides **A, D, J, O** and **S**) resulting from the macrocyclization event (Scheme 1), could undergo a loss of bromide to form carbocation **7** (Scheme 2). Intermediate **7** could then undergo deprotonation to yield isoprene **8**. Alternatively, nucleophilic attack by water would deliver tertiary alcohol **9**.

Scheme 2 – Variation of the C14 Isopropyl Bromide



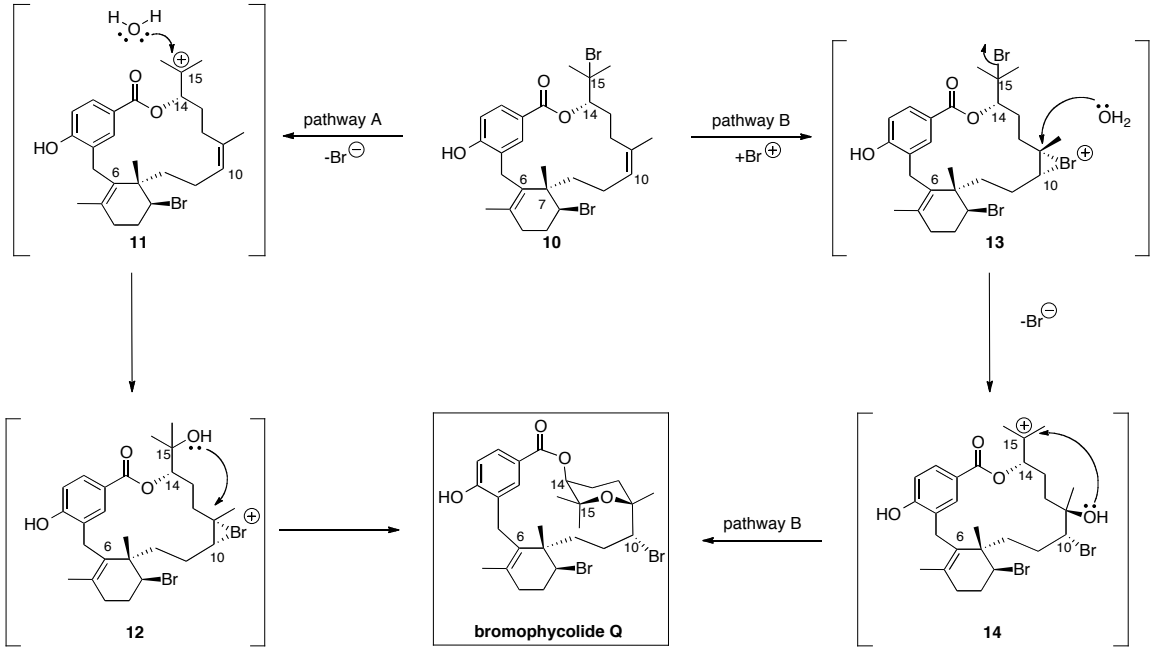
6 **7** **8** **9**

1.2.3 – Formation of the Tetrahydropyran Motif

In 2009 Kubanek reported the isolation of bromophycolides J-Q, two of which, bromophycolides P and Q, possess a tetrahydropyran ring.[4] The biosynthesis of this heterocycle is proposed to arise via one of two mechanistic pathways (Scheme 3). Starting with intermediate **10**, pathway **A** proceeds through the formation of a carbocation at C15 via loss of bromide, which is then quenched with a water molecule. Activation of the C10/C11 olefin of macrocycle **12** with an electrophilic bromine source results in formation of the tetrahydropyran of bromophycolide **Q** via attack of the C15 tertiary alcohol to open bromonium intermediate **12**. Alternatively, pathway **B** involves

the formation of bromohydrin **14** by a two-step process. First, activation of the olefin C10/C11 results in bromonium species **13**, which could be opened by water at C11 to produce bromohydrin **14**. Subsequent cyclization of the C11 tertiary alcohol onto the C15 carbocation would afford the THP. Based on the isolation data to date, the prevalence of the bromohydrin moiety found in the bromophycolide congeners indicates that the second pathway (**B**) dominates the THP-forming pathway (**A**).

Scheme 3 – Biosynthesis of the Tetrahydropyran Moiety

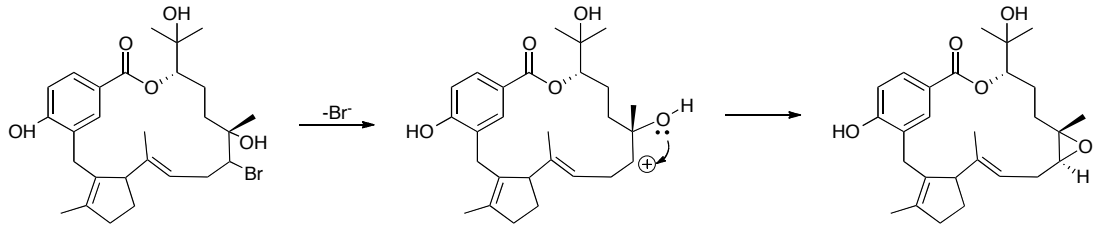


1.2.4 – Formation of the Trisubstituted Epoxide Moiety

The C10/C11 epoxide observed in bromophycolides D, R, S and the C11/C12 epoxide in debromophycolide could result from the loss of bromide from bromohydrin **14** followed by attack of the vicinal tertiary alcohol. It was initially proposed that the *trans*–oxirane was an artifact of bromohydrin degradation during isolation.[4] However,

subsequent studies, indicated that the epoxide-containing molecules were indeed metabolites of the red algae. Thus, temperatures above 50 °C or exposure to basic conditions were found to be required to effect conversion of the bromohydrin to an epoxide. Conditions which are in sharp contrast to 25 °C, pH neutral conditions used in the isloation.[5]

Scheme 4 – C11/C12 Epoxide Formation of Debromophycolide (1)

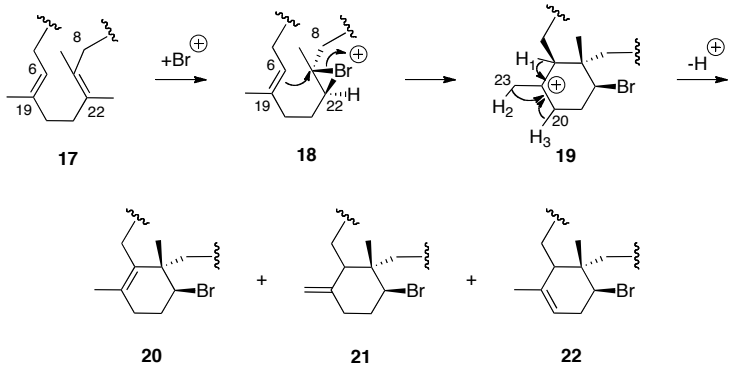


1.2.5 – Carbocycle of Bromophycolides

1.2.5.1 – C6/C7 Carbocycle Formation

Activation of the C8/C22 olefin in **17** with an electrophilic source of bromine could result in bromonium **18**. This could undergo cyclization with the C6/C19 olefin to provide cyclic carbocation **19**, wherein several deprotonation pathways are possible.[2] Deprotonation at C6 would result in the formation of cyclohexene **20**, deprotonation of C23 would lead to the formation of cyclohexene **21**, while deprotonation of C20 would yield cyclohexene **22**.

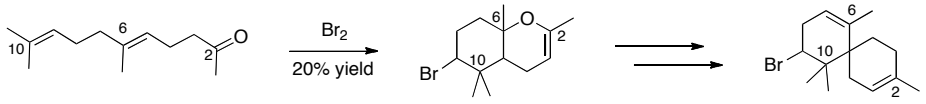
Scheme 5 – Carbocycle Formation



17 18 19 20 21 22

Feasibility of this six-membered ring forming paradigm is supported by the work of Faulkner (Scheme 6).[8] In these studies it was demonstrated that geranylacetone (**23**) spontaneously cyclizes upon bromine activation of the C9/C10 olefin to produce the fused bicyclic ring system **24**.

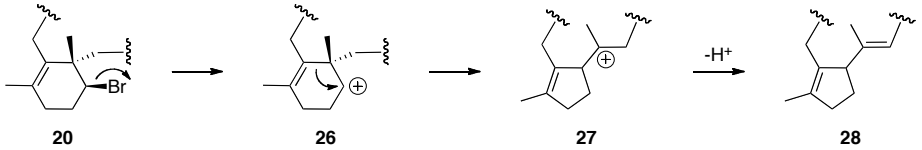
Scheme 6 – Bromine Induced Cyclization



23 24 25

Starting from carbocycle **20**, one can also envision a path for the formation of the debromophycolide cyclopentene moiety. Loss of bromide, resulting in carbocation **26**, could promote ring contraction of **27** which after deprotonation, would afford cyclopentene **28** as seen in debromophycolide **1** (scheme 7).[2]

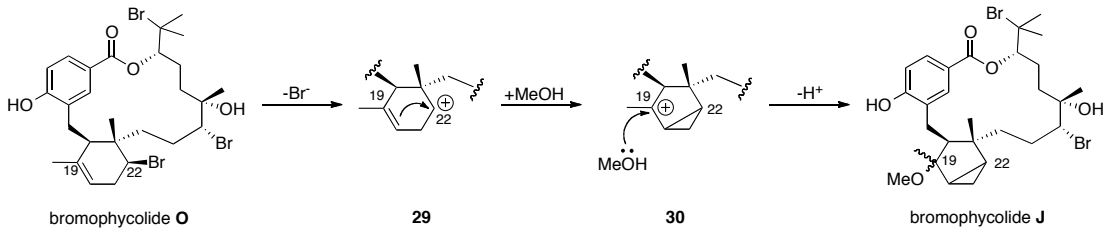
Scheme 7 – Ring Contraction to Deliver the Five-Membered Ring of Debromophycolide



1.2.5.2 – A Structural Anomaly Within the Bromophycolide Family

Bromophycolide J contains a fused [3.1.0] bicycle and a C19 methoxy group that are not observed in any other members of the bromophycolide family.[4] This functionality could arise from loss of the C22 bromide of bromophycolide O, followed by intramolecular nucleophilic attack by the C19-C20 olefin of carbocation **29**, and subsequent addition of methanol to **30**. It is also possible that this structural anomaly is an artifact of isolation. This hypothesis has not been investigated.

Scheme 8 – Formation of Bicyclo [3.1.0]

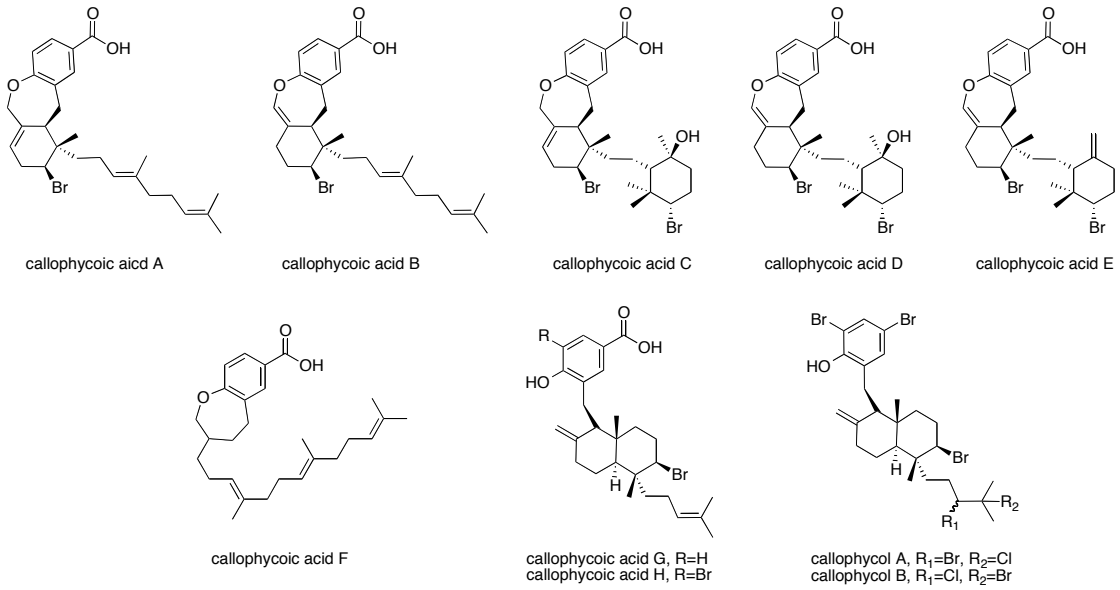


1.3 – Related Metabolites, Isolated from *Callophycus serratus*

Callophycus serratus has also been found to produce a family of closely related metabolites. The callophycoic acids were isolated from *C. serratus*, originating from a different location off the coast of Fiji (Figure 2).[9] Based on the presence of the benzoic

acid moiety, it is hypothesized that the biosynthesis of the callophycoic acids follows the initial steps of the biosynthesis of the bromophycolides then diverges to provide a second structurally related family of brominated metabolites.

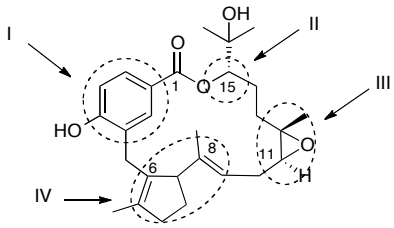
Figure 2 – Callophycoic Acids and Related Derivatives



1.4 –Structural Features of Debromophycolide: A Synthetic Perspective

Intrigued by the impressive biological profile and structural diversity of the bromophycolide family, we hoped to develop a synthesis that would provide access to multiple bromophycolide congeners. Specifically, we began with efforts towards the construction of the simplest family member, debromophycolide (**1** in Figure 3), a 16-membered macrolide whose key characteristics include: I) a tri-substituted aryl ring, II) stereocenter at C15, part of a vicinal diol, III) a *trans*-epoxide and, IV) a skipped diene containing a tetrasubstituted olefin and undetermined stereocenter at C7.

Figure 3 – Structural Characteristics of Debromophycolide



1.5 – References

1. Gibble, G. W. *Chem. Soc. Rev.* **1999**, *28*, 335.
2. Kubanek, J.; Prusak, A. C.; Snell, T. W.; Giese, R. A.; Hardcastle, K. I.; Fairchild, C. R. Aalbersberg, W.; Raventos-Suarez, M. E. *Org. Lett.* **2005**, *7,* 5261.
3. Kubanek, J.; Prusak, A. C.; Snell, T. W.; Giese, R. A.; Fairchild, C. R.; Aalberberg, W.; Hay, M. E. *J. Nat. Prod.* **2006**, *69*, 731.
4. Lane, A. L.; Stout, E. P.; Lin, A.-S.; Prudhomme, J.; Roch, K. L.; Fairchild, C. R.; Franzblau, S. G.; Hay, M. E.; Aalbersberg, W.; Kubanek, J. *J. Org. Chem.* **2009**, *74*, 2736.
5. Lin, A.-S.; Stout, E. P.; Prudhomme, J.; Le Roch, K.; Fairchild, C. R.; Franzblau, S. G.; Aalbersberg, W.; Hay, M. E.; Kubanek, J. *J. Nat. Prod.* **2010**, *73*, 275.
6. CSU Infectious Disease SuperCluster Report, private communication.
7. a) Carter- Franklin, J.N.; Parrish, J. D.; Tschirret-Guth, R. A.; Little, R.D.; Butler, A. *J. Am. Chem. Soc.* **2003**, *125*, 3688. b) Kato, T.; Ichinose, I.; Kamoshido, A.; Kitahara, Y. *J. Chem. Soc., Chem. Comm*. **1976**, 518. c) Kato, T.; Ishii, K.; Ichinose, I.; Nakai, Y.; Kumagai, T. *J. Chem. Soc., Chem. Comm*. **1980** 1106. d) Shieh, H.-M.; Preswich, G.D.; *Tetrahedron Lett.* **1982**, *23*, 4643.

8. Faulkner, D. J. *Pure Appl. Chem.* **1976**, *48*, 25. For the first reported cyclization with an electrophilic bromine source, see: van Tamelen, E.; Hessler, E. J. *Chem. Commun.* **1966**, 411.

9. Lane, A. L.; Stout, E. P.; Hay, M. E.; Prusak, A. C.; Hardcastle, K.; Fairchild, C. R.; Franzblau, S. G.; Roch, K. L.; Prudhomme, J.; Aalbersberg, W.; Kubanek, J. *J. Org. Chem.* **2007**, *72*, 7343.

Chapter 2

Synthesis of the C1-C8 Fragment of Debromophycolide

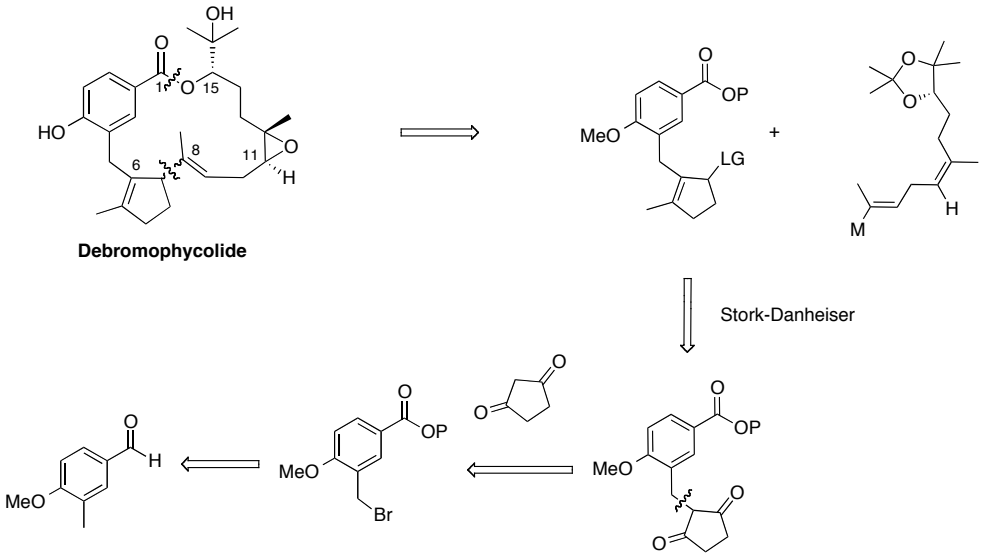
2.1 – Synthetic Efforts Towards Coupled Material Utilizing a β-diketone

2.1.1 –Retrosynthetic Analysis

From a retrosynthetic perspective, we envisioned closing the macrolide of debromophycolide via a macrolactonization reaction (Scheme 1). Several well-developed methods for this bond formation have been reported and tolerate a wide range of functionality.[1] Further disconnection of the C7-C8 bond would afford two major fragments, benzoate **31** and acetonide **32**, which could be linked via a transition metal mediated coupling reaction to form the desired bond and install all carbon atoms present in the natural product.

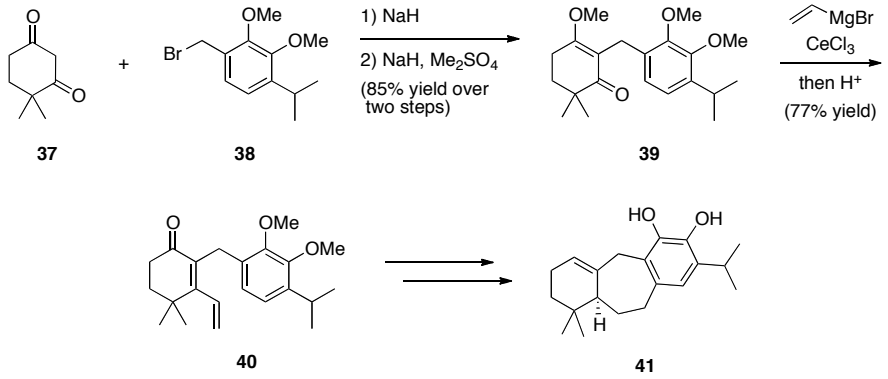
We chose to first pursue the complex aryl fragment **31**, which could arise from the desymmetrization of diketone **33** utilizing a Stork-Danheiser protocol.[2] Diketone **33** could be generated from an S_N2 reaction between benzyl bromide **35** and 1,3-cyclopentanedione **34**. Benzyl bromide **35** could be accessed from commercially available starting material **36** through a short sequence of synthetic manipulations.

Scheme 1 – Retrosynthetic Analysis for Debromophycolide



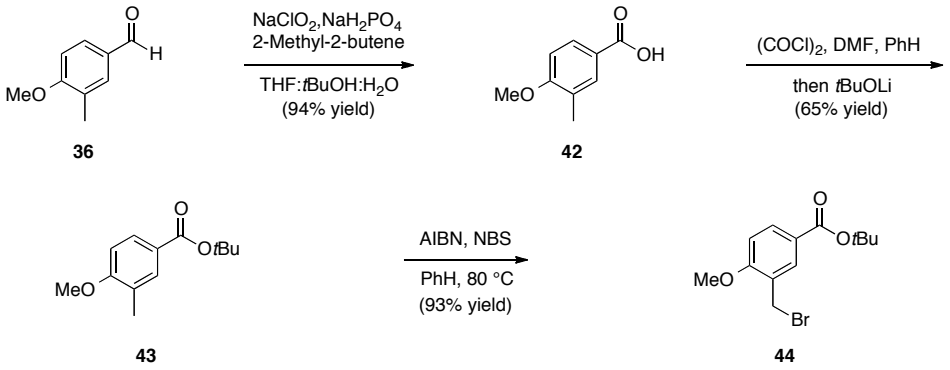
The total synthesis of (–)-barbatusol (**41**), reported by Majetich, provided the inspiration for a coupling of **34** and **35**.[3] As illustrated in Scheme 2, Majetich exposed benzyl bromide **38** to the sodium enolate of diketone **37**, and methylated the resultant vinylogous acid to afforded the desired coupled product **39**. Subsequent vinylation and acidification yielded unsaturated ketone **40**.

Scheme 2 – Majetich's Utilization of the Stork-Danheiser Protocol Towards the Total Synthesis of (–)-Barbatusol



Turning to our effort, synthesis of the desired benzyl bromide **44** began with oxidation of 4-methoxy-3-methyl-benzaldehyde (**36**) under Pinnick conditions (Scheme 3).[4] Conversion of carboxylic acid **42** to the acid chloride followed by exposure to lithiated *t*BuOH afforded *t*butyl ester **43**. Formation of benzyl bromide **44** was achieved by exposure of **43** to AIBN and NBS.[5]

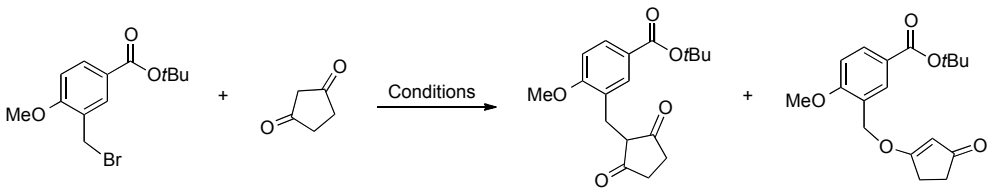
Scheme 3 – Synthesis of Benzyl Bromide 44



2.1.2 – Coupling Attempts

With the synthesis of benzyl bromide **44** complete, we investigated its coupling to 1,3-cyclopentatedione **34** (Table 1). Our initial approach involved treatment of diketone **34** with aqueous K_2CO_3 followed by the addition of benzyl bromide **44** and KI. Unfortunately no desired product was observed (Entry 1).[3b] We then continued by exploring various bases beginning with NaH. Again, we observed no reaction (Entry 2), and attempts at *in situ* generation of the benzyl-iodide though the use of Bu_4NI merely resulted in a 30% yield of *O*-alkylation product **46** (Entry 3). The use of Et_3N showed similar results (Entries 4 and 5). While K_2CO_3 (Entry 6) or NaOH (Entry 7) in the presence of Bu_4NI resulted only in degradation.[6] Not surprisingly, the use of Bu_4NI in the absence of a base also failed to promote any reaction (Entry8).

Table 1 – Coupling Attempts to Form Compound 45

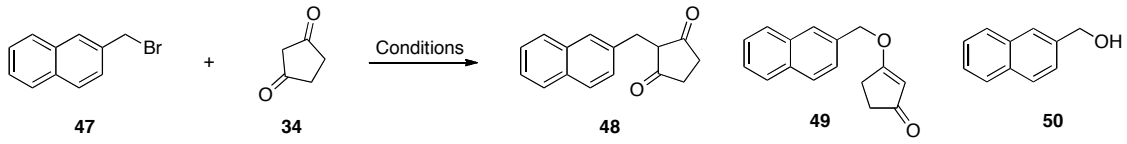


44 **34** **45** **46**

entry	Base	Additive	Solvent	result
1	K_2CO_3	KI	H_2O	NR
2	NaH	---	DMF	NR
3	NaH	$(Bu)_4NI$	THF	30% of **46**
4	Et_3N	---	THF	NR
5	Et_3N	$(Bu)_4NI$	THF	56% of **46**
6	K_2CO_3	$(Bu)_4NI$	H_2O	degradation
7	NaOH	$(Bu)_4NI$	H_2O	degradation
8	---	$(Bu)_4NI$	THF	NR

In a search for alternative conditions, we were encouraged by a patent that detailed the *C*-alkylation of 1,3-cyclopentanone with 2-(bromomethyl)-naphthalene **47**. As a prelude to investigating these conditions on our system, we attempted to reproduce the work found in the patent.[7] The conditions employed for the coupling was aqueous KOH in dioxane at reflux. Unfortunately, under the conditions reported by Malamas we were only able to isolate commercially available alcohol **50** (Entry 1, Table 2). The use of LiOH in the presence of Bu_4NI also resulted in alcohol **50** (Entry 2). LiHMDS (Entry 3) and Et_3N (Entry 4) in the absence of an additive resulted in the recovery of starting material. Efforts to employ conditions wherein K_2CO_3 serves as base along with KI in an H_2O/*t*BuOH (1:1) solvent system, provided 9% of the desired *C*-alkylated product **48** and 56% of the *O*-alkylated material **49** (Entry 5).[3] When similar conditions were employed using 100% *t*BuOH as the solvent, we observed 9% of the desired alkylated diketone **48** along with recovered starting material (Entry 6). Alcoholic solvents seemed to promote the desired reaction; both NaH in *t*BuOH (Entry 7) and K_2CO_3 in EtOH (Entry 8) resulted in the desired *C*-alkylated 1,3-diketone, albeit in low yield. We also discovered that DBU in THF in the presence of LiI resulted in 15% of the desired product **48** (Entry 9).[8] With a small amount of the desired alkylated 1,3-diketone we decided to investigate the Stork-Danheiser protocol.[2]

Table 2 – Model System Coupling Attempts



47 34 48 49 50

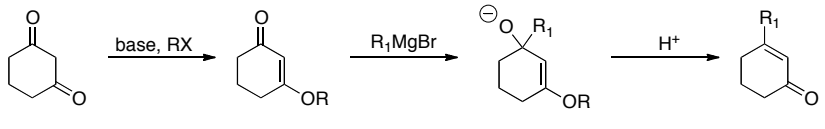
Entry	Base	Additive	Solvent	Result
1	$KOH_{(aq)}$	---	Dioxane	**50***
2	$LiOH_{(aq)}$	$(Bu)_4NI$	Dioxane	**50***
3	LiHMDS	---	THF	NR
4	Et_3N	---	MeCN	NR
5	K_2CO_3	KI	H_2O:*t*BuOH	9% of **48**, 56% of **49**
6	K_2CO_3	LiI	*t*BuOH	9% of **48**
7	NaH	---	*t*BuOH	9% of **48**
8	K_2CO_3	LiBr	EtOH	10% of **48**
9	DBU	LiI	THF	15% of **48**

*- yield not determined

2.1.3 – Stork-Danheiser Protocol

In 1973, Stork and Danheiser developed a method for the synthesis of β-substituted enones where a symmetrical diketone, such as **51**, is first converted to the corresponding vinylogous ester (i.e., **52**, Scheme 4**)**.[2] Subsequent 1,2-addition to the carbonyl, followed by acid promoted dehydration yields the alkylated enone (e.g., **54**).

Scheme 4 – General Conversion of a β-Diketone to an Enone Using the Stork-Danheiser Protocol

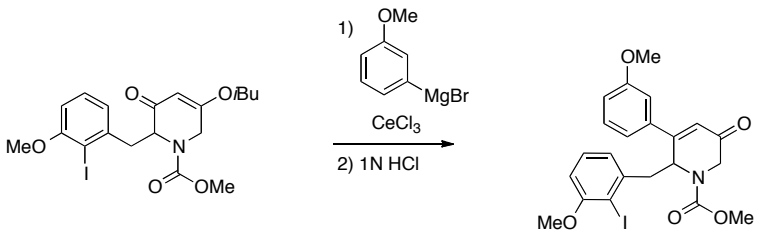


51 52 53 54

A relevant example of this protocol was reported by Trauner and coworkers in their total synthesis of Haouamine (Scheme 5).[9] In this work vinylogous ester **55** was

exposed to an aryl Grignard reagent, in the presence of $CeCl_3$, to effect 1, 2-addition.[9b] This was followed by acidification with 1N HCl to produce enone **56**.

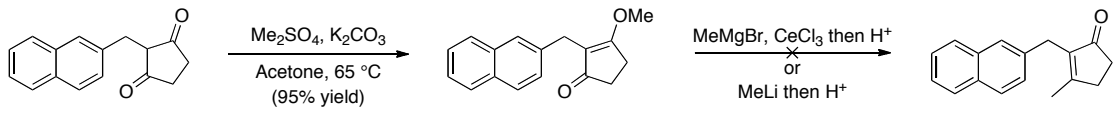
Scheme 5 – Trauner's Use of Stork-Danheiser Conditions



55 **56**

We intended to use a similar strategy to access the model enone **58** (Scheme 6).[7] First, diketone **48** was converted to the vinylogous methyl ester **57** with sodium hydride and dimethylsulfate. Next, vinylogous ester **57** was treated with methylmagnesium bromide with or without dried $CeCl_3$, followed by acidification.[10] These conditions resulted in recovered starting material and decomposition. Methyllithium was also tested for 1,2-addition, however, no desired product was observed.

Scheme 6 – Formation of Enone from Implementation of Stork-Danheiser Conditions

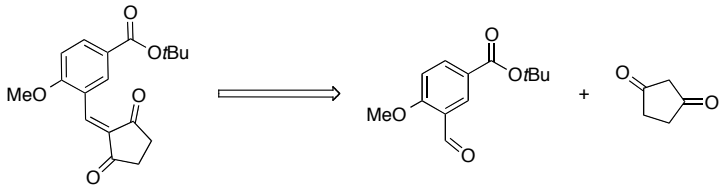


48 **57** **58**

2.1.4 – Other Attempts to Access Stork-Danheiser Precursor

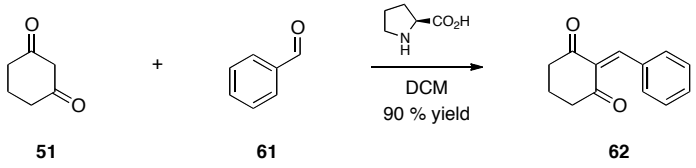
To enable a more comprehensive investigation of the Stork-Danheiser procedure we began to consider alternatives for the diketone alkylation. To this end we recognized that Knoevenagel's method for condensing aldehydes with β-diketones might be useful.[11] Using this approach, benzylidene **59** would be generated from condensation of aldehyde **60** with β-diketone **34** (Scheme 7).

Scheme 7 – Benzylidene Synthesis



Indeed, Ramachary has described the relevant condensation of 1, 3 cyclohexadione **51** onto benzaldehyde **61** in the presence of L-proline (Scheme 8).[12]

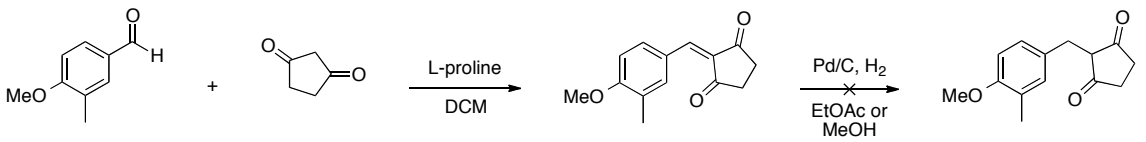
Scheme 8 – Ramachary Method for a Knoevonagel Condensation



Using a model system, we investigated the use of this chemistry for our purposes (Scheme 9). To our satisfaction, condensation of 1,3-diketone **34** in the presence of L-proline and benzaldehyde **36** afforded benzylidene **63**. Unfortunately, attempts to reduce

the enone via a palladium catalyzed hydrogenation in ethyl acetate or methanol did not result in diketone **64**.[12b]

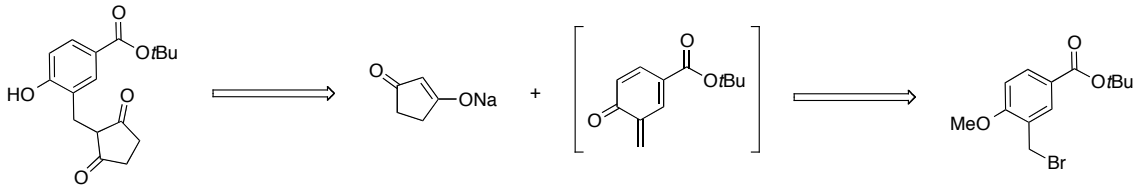
Scheme 9 – Knoevenagel Attempts Towards Coupled Diketone



2.2 – Ortho-Quinone Methide

In considering other electrophilic partners that could be employed in the diketone coupling we recognized the potential utility of ortho-quinone methide **66**. Generation of this intermediate requires an ortho-substituted benzyl bromide (e.g., **44**) as illustrated in the revised retrosynthesis (Scheme 10).

Scheme 10 – Nucleophilic Addition into a Michael Acceptor

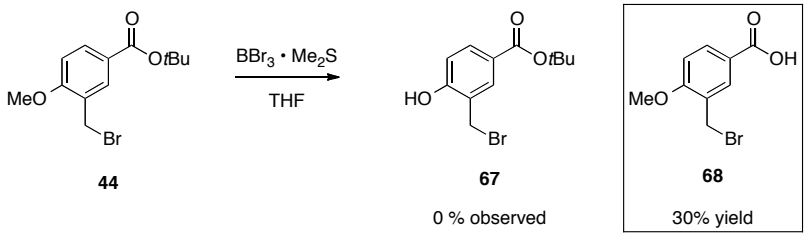


65 **34** **66** **44**

2.2.1 – Development of Benzyl Bromide

Our efforts to this point had utilized a benzyl bromide substrate wherein a methyl ether protects the phenol. Although in the previous route we anticipated removing the methyl ether at a later stage, on intermediates capable of withstanding the required strong Lewis acid; early removal, as called for in this route, was not possible. As illustrated in Scheme 11, exposure of **44** to Lewis acids boron trichloride or boron tribromide dimethyl sulfide, resulted only in removal of the *t*butyl ester.[13] This latter result was anticipated and thus alternate protecting groups were evaluated.

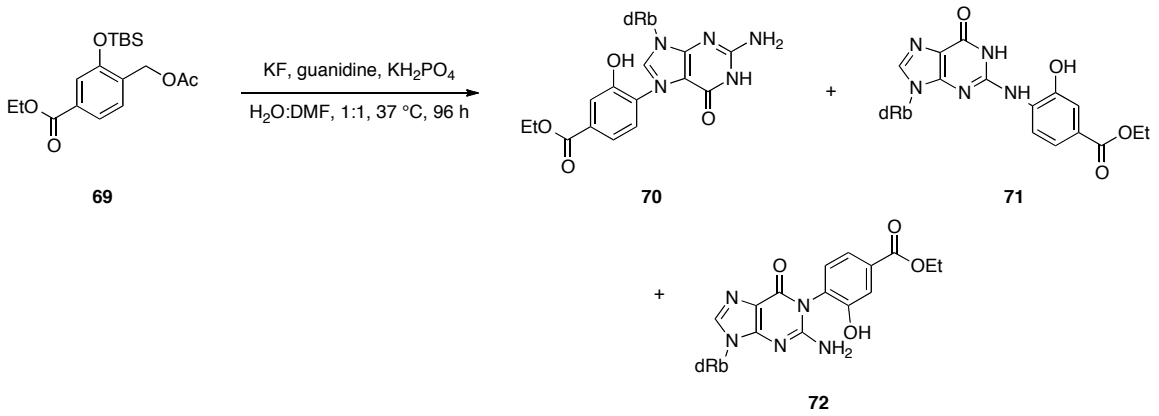
Scheme 11 – Attempted Methyl Group Removal



44 **67** 0 % observed **68** 30% yield

In further consideration of the quinone methide approach we were intrigued by a report from Zeng and Rokita wherein treatment of *o-tert*-butyldimethylsilyl-2-aceto-benzoic acid ethyl ester **69** with a fluoride source generates an electrophilic ortho-quinone methide *in situ*. When generated in the presence of guanidine, this reactive intermediate produced three intermediates (**70-72**, Scheme 12).[14]

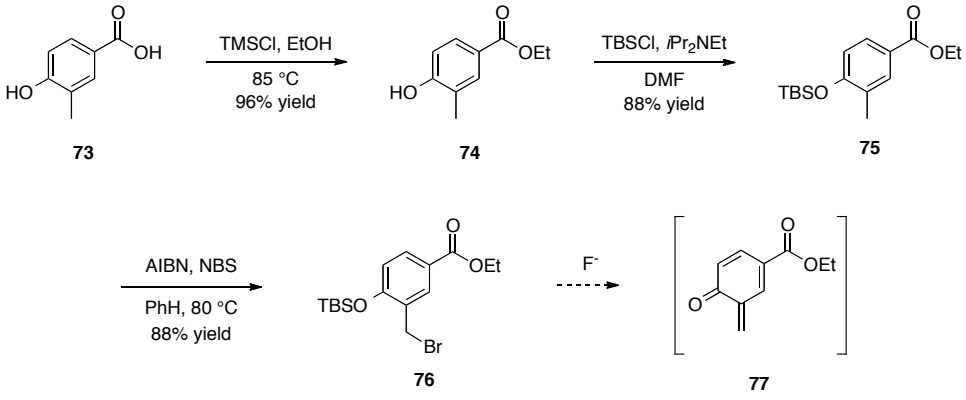
Scheme 12 – Cross Linked DNA via Ortho-Quinone Methide Intermediate



69 **70** **71** **72**

Hoping to generate an ortho-quinone methide in a fashion similar to Zeng and Rokita we set out to prepare silyl ether **76** as a suitable precursor to **77** (Scheme 13). To this end, commercially available benzoic acid **73** was esterified with ethanol and HCl, generated *in situ*, to afford phenol **74**. Treatment of **74** with TBSCl and Hunig's base, followed by bromination afforded benzyl bromide **76**, the precursor to ortho-quinone methide **77**.[15]

Scheme 13 – Ortho-Quinone Methide Generation

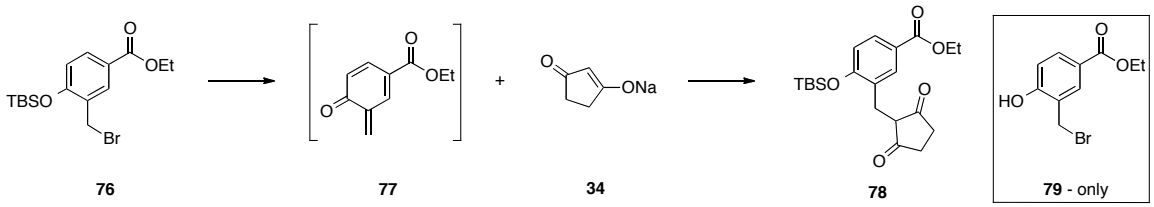


73 **74** **75** **76** **77**

2.2.2 – Attempts to Implement the Ortho-Quinone Methide

With silyl ether **76** in hand, treatment with TBAF would effect formation of ortho-quinone methide **77** (Scheme 14). However, subsequent addition of the sodium enolate of 1,3- cyclopentanone (**34**) did not provide any of the alkylated product **78**, only known free phenol **79**.[16] It seems likely that the ester functionality stabilizes the phenoxide anion that results from the silyl ether cleavage, preventing displacement of the bromide and formation of the ortho-quinone methide.

Scheme 14 – Addition of Nucleophile into Ortho-Quinone Methide

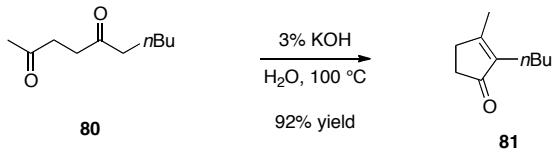


2.3 – New Approach to the Synthesis of C1-C8

2.3.1 – Linear Approach to Prepare Cyclic Diketone

Although efforts thus far had called for incorporating an intact cyclopentyl moiety, we recognized that ring closure also represents a viable alternative strategy. In 1942 Hunsdiecker reported that base catalyzed cyclizations of 1,4-diketones can furnish the corresponding cyclic enone.[17] As shown in Scheme 15, treatment of γ-diketone **80** with aqueous KOH at reflux results in the formation of β-substituted cyclic enone **81**.

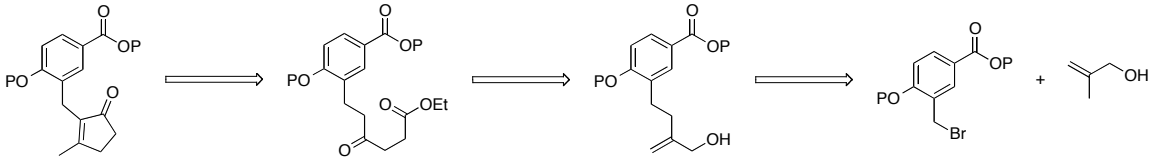
Scheme 15 – Formation of a Cylcopent-2-en-1-one from a β-Diketone



80 **81**

Based on the work of Hunsdiecker, we proposed that enone **82** could be accessed from γ-ketoester **83** (Scheme 16). In turn, γ-ketoester **83** was envisioned to arise from allylic alcohol **84** via a Johnson-Claisen rearrangement. Allylic alcohol **84** could be generated from an S_N2 reaction between benzyl bromide **85** and methallyl alcohol **86**.

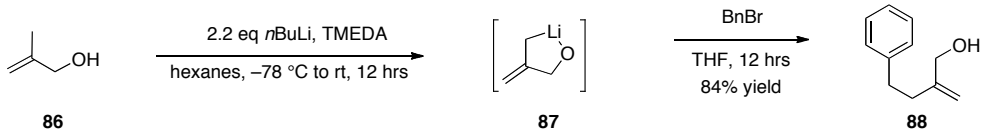
Scheme 16 – Retrosynthetic Approach from a γ-Dicarbonyl



82 **83** **84** **85** **86**

During synthetic studies towards C-4 alkylated dideoxyribosides, Lipshutz demonstrated that methallyl alcohol **86** can be metallated with *n*butyllithium in the presence of TMEDA and subsequently alkylated with benzyl bromide to provide **88** (Scheme 17).[18] No *O*-alkylated material was observed.

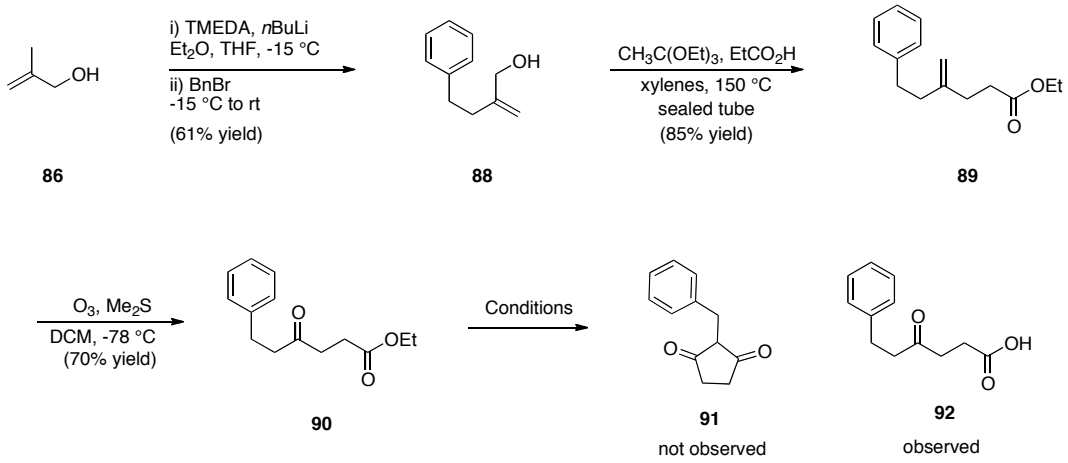
Scheme 17 – Formation of *C*-alkylated Allylic Alcohol



86 **87** **88**

To confirm our ability to generate the required anion we first sought to employ these conditions to access allylic alcohol **88** (Scheme 18). To this end, methallyl alcohol **86** was treated with *n*butyllithium and subsequently with benzyl bromide to produce alcohol **88**. To further explore the proposed Hunsdiecker sequence, alcohol **88** was transformed into ester **89** via Johnson-Claisen rearrangement. The resulting exomethylene (**89**) was then subjected to ozonolysis conditions to produce known γ-ketoester **90**.[19-21] Cyclization attempts in the presence of sodium hydroxide failed to produce diketone **91** and instead produced known carboxylic acid byproduct **92**.[21] A screen of alternate bases including NaH in MeOH and KHMDS resulted only in recovered starting material **90**.

Scheme 18 – Attempted Cyclization to form a β-Diketone

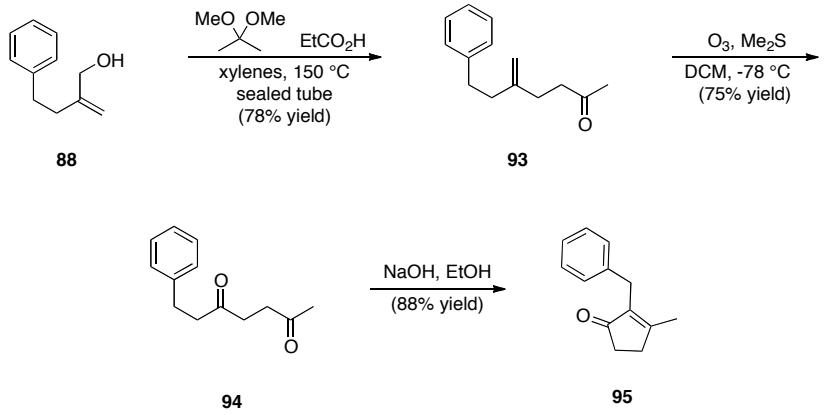


2.3.2 – Linear Approach to Cyclic Enone: Use of a Diketone

Unable to obtain the cyclized intermediate **91** through the Hunsdiecker cyclization, we next investigated the analogous methyl ketone. Allylic alcohol **88** was

subjected to Claisen rearrangement conditions to deliver methyl ketone **93** (Scheme 19).[23] Ozonolysis converted exomethylene **93** to known γ-diketone **94**.[24] Gratifyingly, treatment of γ-diketone **94** with NaOH in refluxing EtOH afforded the desired cyclopentenone **95** in high yield.[22]

Scheme 19 – Formation of Enone from Cyclization of γ-diketone

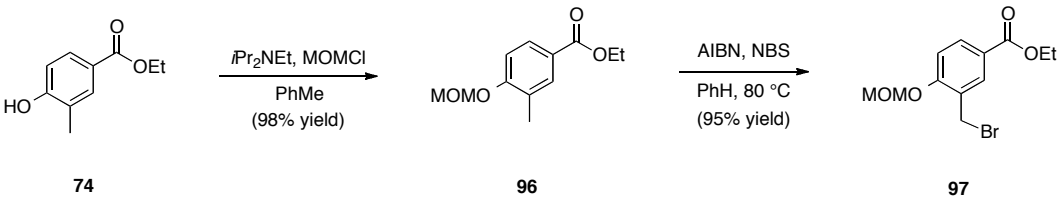


88 **93** **94** **95**

2.4 – Benzyl Bromide Revisited

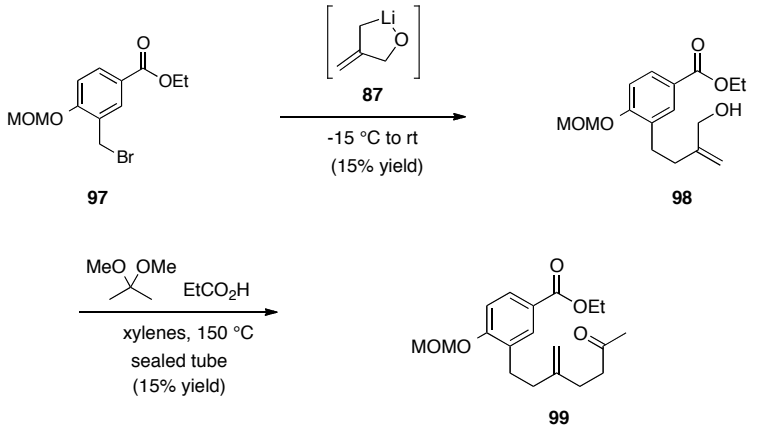
Having established an effective strategy for the incorporation of the cyclopentene moiety, we sought to access an appropriately functionalized aryl component wherein the substituent would be both poised for advancement in the synthesis and tolerant of the conditions needed to construct the cyclopentenone (Scheme 20). Towards this end, previously prepared benzoate **74** (Scheme 13) was protected as methoxymethyl ether **96**, which was acid sensitive and required the use of silica pretreated with Et_3N for purification.[23] Bromination of **96** proceeded smoothly to produce benzyl bromide **97**.[5]

Scheme 20 – Re-examined Synthesis of Benzyl Bromide



We then subjected benzyl bromide **97** to the alkylation sequence described above (Scheme 21). In the event, **97** was exposed to the dianion of methallyl alcohol **87** to afford allylic alcohol **98**. Exposure of allylic alcohol **98** to Claisen rearrangement conditions resulted in the desired keto-olefin **99**, but in low yield.[25] Although studies along this route continued, they were eventually abandoned in favor of a more promising metal-catalyzed coupling approach that was being pursued in parallel.

Scheme 21 – Decomposition of Substituted Benzyl Bromide in Claisen Rearrangement

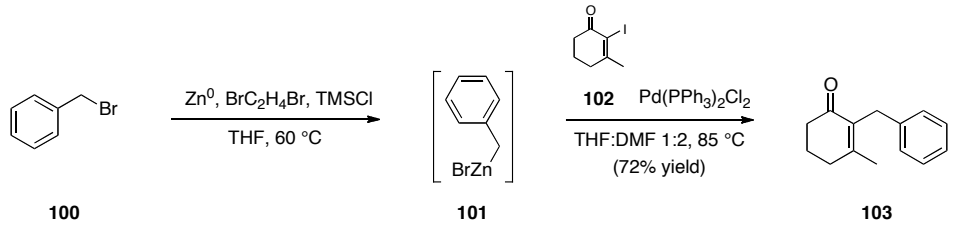


2.5 – Metal Catalyzed Coupling Reaction

2.5.1 – Negishi Protocol

In the 1970's, Negishi reported the coupling of α-halo enones with benzylzinc bromides.[25] As shown in Scheme 22, α-iodoenone **102** was coupled to benzylzinc bromide **101** in the presence of a palladium catalyst to afford alkylated enone **103**.

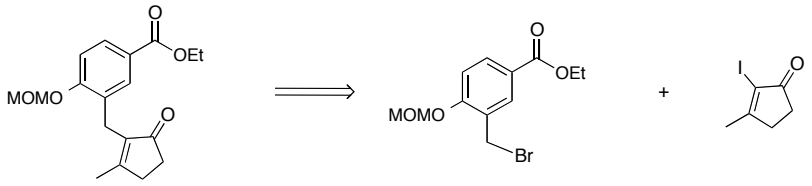
Scheme 22 – Negishi Coupling of Benzyl Bromide to an α-Iodo-Enone



100 101 103

Inspired by Negishi's work, we proposed the formation of the C5-C6 with a similar palladium mediated coupling (Scheme 23). The coupling between a benzyl bromide **97** and α-iodo enone **105** should provide access to the advanced coupled product **104**.

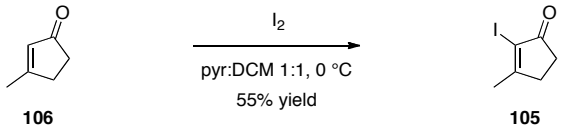
Scheme 23 – Disconnection via Negishi Coupling



104 97 105

Importantly, benzyl bromide **97** was already in hand from our ongoing efforts; to investigate this route we needed only to prepare iodo enone **105**. To this end, 3-Methyl cyclopentenone **106** was treated with iodine in the presence of pyridine to successfully deliver the desired coupling partner **105** (Scheme 24).[25]

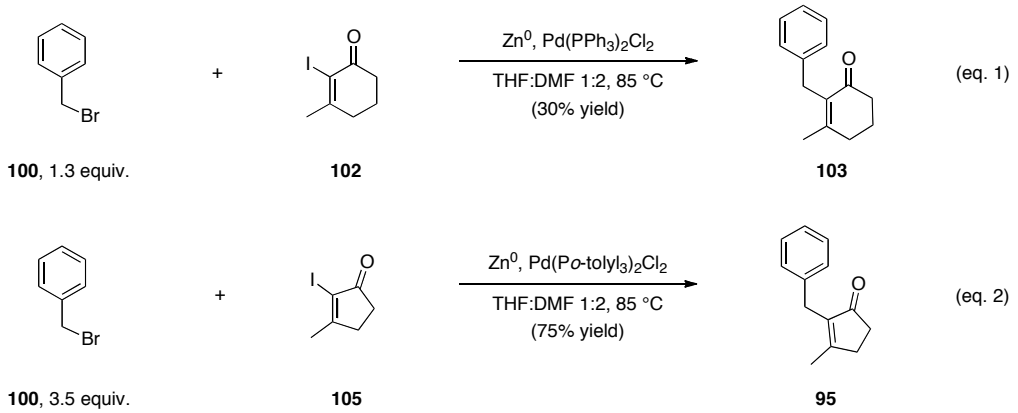
Scheme 24 – Halogenation of Cyclopent-2-en-1-one



106 **105**

Our first attempt to apply Negishi's chemistry was performed in a known system involving 2-iodo-2-cyclohexen-1-one **102** and benzyl bromide **100** (Scheme 25, eq. **1**). It was determined that proper activation of the zinc was essential to the formation of coupled product **103**. Using these optimized reaction conditions for the coupling of benzyl bromide **100** and α-iodo enone **105** resulted in the formation of product **95** in good yield (Scheme 25, eq. **2**).

Scheme 25 – Negishi Coupling Results. First Pass and Optimized Conditions.



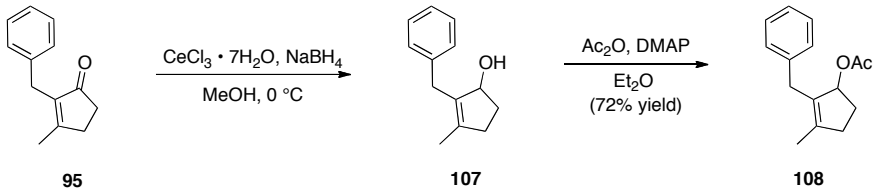
100, 1.3 equiv. **102** **103**

100, 3.5 equiv. **105** **95**

2.5.2 – Formation of Allylic Acetate

Given that our synthetic plan calls for the eventful preparation of a π-allyl intermediate from the enone, we explored the conversion of **95** to the corresponding allylic acetate (Scheme 26). Toward this end, enone **95** was subjected to Luche reduction conditions to affect a 1,2-reduction of the enone.[26] Acetylation of the resultant alcohol with acetic anhydride and DMAP produced the desired allylic acetate **108** in good yield.

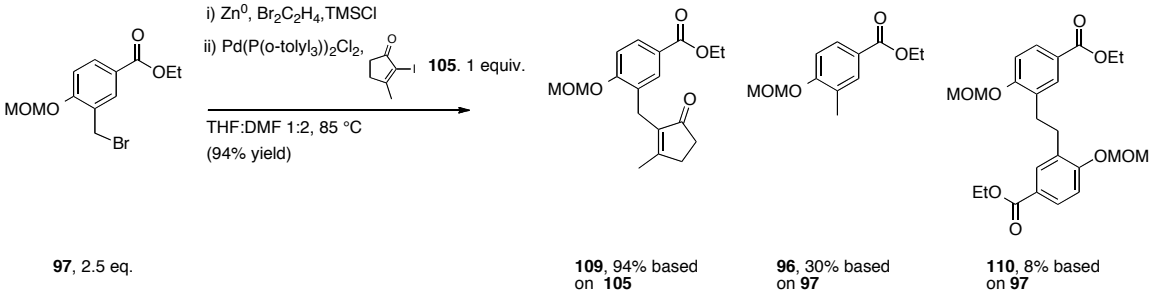
Scheme 26 – Reduction of Enone 95



95 **107** **108**

Next, the conditions optimized in the model system were applied to the more functionalized bromide (Scheme 27). Pretreatment of benzyl bromide **97** with activated zinc dust, (1,2-dibromoethane, then TMSCl) followed by addition to α-iodo enone **105** and $Pd(P(o\text{-tolyl})_3)_2Cl_2$ in a THF:DMF (1:2) solvent system at 85 °C, resulted in formation of the desired coupled product **109**. Debrominated compound **96** and dimer **110** were also observed in 30% and 8% isolated yield, respectively.

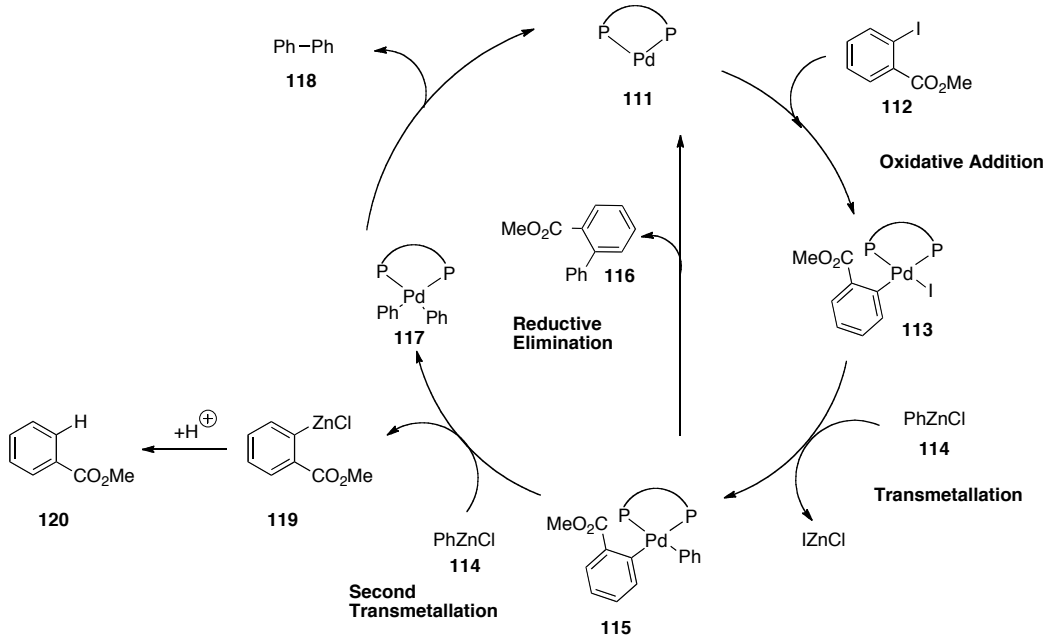
Scheme 27 – Negishi Coupling on Advanced Material: Optimized Conditions



2.5.3 – Negishi Mechanism: An Explanation of Side Product Formation

The byproducts observed under the Negishi reaction conditions are consistent with mechanistic studies reported by Lui and co-workers who concluded that two competing pathways occur during the Negishi coupling reaction. These two pathways are described in Scheme 28.[27] In an attempted coupling reaction of aryl iodide **112**, Lui isolated a homocoupled product **118** as well as dehalogenated material **120** in equal amounts. Based on these observations a mechanism was proposed wherein oxidative addition of the catalyst (**111**) into the aryl-halogen bond of **112** is followed by transmetallation with organozinc reagent **114**, intermediate **115** can follow one of two different mechanistic pathways. Reductive elimination of **115** produces product **116** and regenerates the active catalyst **111**. Alternatively, intermediate **115** could undergo a second transmetallation step with a second equivalent of benzyl zinc chloride **114** resulting in intermediate **117** and arylzinc bromide **119**. Reductive elimination of intermediate **117** would generate the homocoupled byproduct **118** and regenerate the catalyst **111**. Hydrolysis of the arylzinc halide **119** would result in dehalogenated side product **120**.

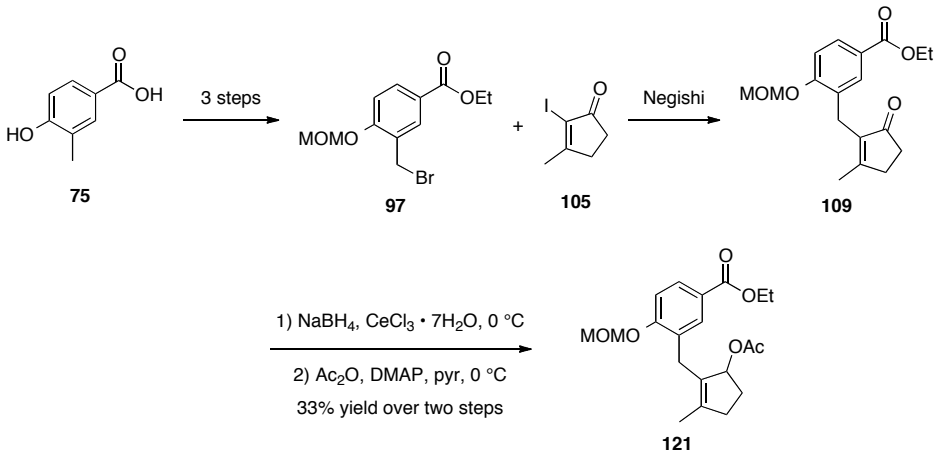
Scheme 28 – Proposed Mechanism for Second Transmetallation Step During the Negishi Coupling



2.6 - Summary

In summary, we have been successful in preparing several benzyl bromide fragments, which have allowed for the investigation of various alkylation strategies. A number of approaches for the incorporation of the cyclopentene moiety were explored, and it was ultimately determined that the use of a Negishi coupling reaction was most effective. The palladium mediated coupling of benzyl bromide **97** with α-iodo enone **105** resulted in complex intermediate **109**. Reduction of the enone and conversion to the allylic acetate would deliver the desired C1-C7 coupling partner **121** (Scheme 29).

Scheme 29 – Formation of Allylic Acetate



2.7 – Experimental

2.7.1 – Materials and Methods

General – Unless otherwise stated, all reactions were mechanically stirred in flame-dried glassware under an atmosphere of nitrogen. Diethyl ether, tetrahydrofuran, dichloromethane, benzene, and toluene were dried using a solvent purification system manufactured by SG Water U.S.A., LLC using technology based upon that originally described by Grubb's *et al*.[28] Anhydrous *N,N*-dimethylformamide was purchased from Sigma-Aldrich and stored under a nitrogen atmosphere. Methanol was dried over magnesium and triethylamine and *t*butyl alcohol were dried using calcium hydride and under stored a under nitrogen atmosphere.[29] Commercially available reagents were purchased from Sigma-Aldrich, Fluka, TCI, or Alfa Aesar and were used as received. *N*-Bromosuccinimide was recrystallized using a known procedure.[30] All known compounds were identified by comparison of NMR spectra with that found in the literature.

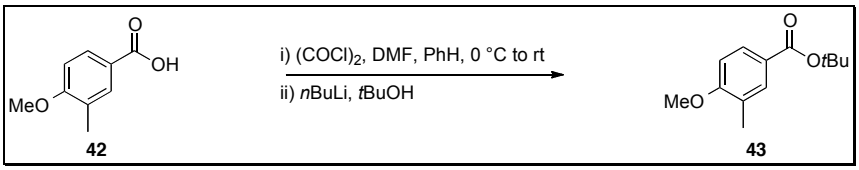
Thin layer chromatography was performed using Silicycle glass-backed extra hard layer, 60 Å plates (indicator F-245, 250 μm). Developed plates were visualized

using a 254 nm UV lamp and/or with the appropriate dip followed by heating. Anisaldehyde and potassium permanganate were prepared by known recipes.[31] Flash chromatography was generally performed according to the protocol described by Still *et al*.,[32] with Silicycle Siliaflash® P60 (230-400 mesh) silica get as the stationary phase. Melting points were obtained using a Gallenkamp melting point apparatus and are uncorrected.

Infrared spectra were recorded on a Nicolet Magna-IR 760 Spectrometer E.S.P. Samples were analyzed as thin films on NaCl plates (samples dissolved in dichloromethane) and the spectra are presented as transmittance vs. wavenumber (cm^{-1}). High-resolution mass spectrometry was conducted on an Agilent 6210 TOF LCMS. Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Varian Inova 400 or 300 spectrometer. Spectra were obtained at 22 °C in $CDCl_3$ unless otherwise noted. Chemical shifts are reported in parts per million (*ppm*) and are referenced to the residual solvent peak. Coupling constants (*J*) are reported in Hertz (*H*) and are rounded to the nearest 0.1 Hz. Multiplicities are defined as: s = singlet, d = doublet, dd = doublet of doublets, ddd= doublet of doublet of doublets, t = triplet, q = quartet, m = multiplet.

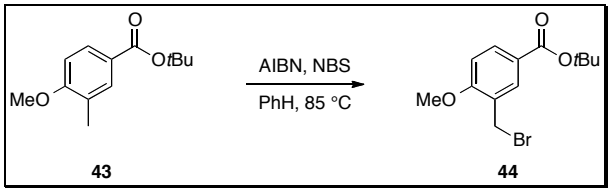
2.7.2 – Preparative Procedures

Preparation of *t*BuEster 43.



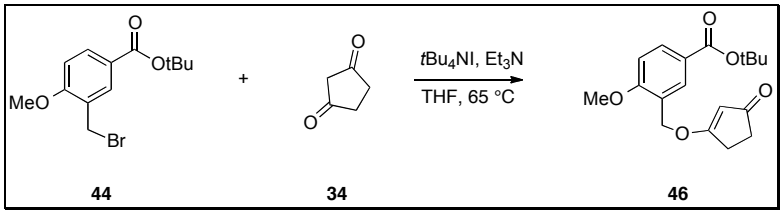
To a solution of compound **42** (250 mg, 1.51 mmol) in benzene (4 mL) oxalyl chloride (394 μL, 1.46 mmol) was slowly added at 0 °C. A pipette tip of DMF was added and the reaction was allowed to warm to rt and maintained at this temperature for 2.5 h. The reaction was monitored via TLC by quenching a small aliquot with MeOH. In a separate flask, *n*BuLi (0.991 mL, 1.59 mmol at 1.6M) was added slowly to *t*BuOH (4 mL) and allowed to stir. Once the initial reaction was complete, it was concentrated under reduced pressure, then slurried in *t*BuOH (4mL). The reaction was stirred for 3 h and quenched with water (8 mL), extracted with ether (3 x 10 mL), dried over $MgSO_4$, and concentrated. The residue was purified via column chromatography (hexane/EtOAc, 95:5) to afford **43** as a yellow oil (218 mg, 65 % yield). R_f=0.78, 95:5 EtOAc/hexane. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.84 (s, 1H), δ 7.82 (s, 1H), δ 7.76 (s, 1H), δ 6.81(d, *J*= 8.5Hz, 1H), δ 3.87 (s, 3H), δ 2.23 (s, 3H), δ 1.56 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) 166.1, 161.3, 132.0, 129.3, 126.5, 124.0, 123.5, 109.2, 80.5, 55.6, 28.5, 16.4; IR (thin film, NaCl) 2976, 2931, 1708, 1608, 1300, 1266, 1167, 1129; HRMS (ESI-APCI) *m/z* calcd. for $C_{13}H_{19}0_3$ $[M+H]^+$ 223.1329, found 223.1325.

Preparation of Benzyl Bromide 44.



Compound **43** (171.2 mg, 0.771 mmol) was dissolved in benzene (7 mL) followed by the addition of NBS (137.2 mg, 0.771 mmol) and AIBN (6.3 mg, 0.039 mmol) and refluxed for 8 h. The reaction was cooled to rt, then washed with a saturated solution of $NaHCO_3$ (4 mL) and extracted with ether (2 x 5 mL). The organic layer was dried over $MgSO_4$, and solvent removed under reduced pressure. The residue was purified via column chromatography (hexane/ether, 97:3) to afford **44** (213.5 mg, 92% yield) as an orange solid, melting point = 84 °C. R_f= 0.65 in hexane/EtOAc, 19:1. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.96-7.92 (m, *J*= 2.2 Hz, 2H), δ 6.87 (d, *J*= 9.2 Hz), δ 4.54 (s, 2H), δ 3.94 (s, 2H), δ 1.58 (s, 9H); ^{13}C NMR (100 MHz) 165.3, 160.9, 132.4, 132.3, 126.0, 124.6, 110.5, 81.0, 56.1, 28.5, 28.4: IR (thin film, NaCl) 2977, 1699, 1608, 1502, 1496, 1458, 1445, 1425, 1391, 1369, 1361, 1302, 1263, 1221, 1167, 1141, 1123, 1092, 1019, 944, 880, 845: HRMS (ESI-APCI) *m/z* calcd. for $C_{13}H_{21}BrNO_3$ $[M+NH_4]^+$: 318.0699, found 318.0694.

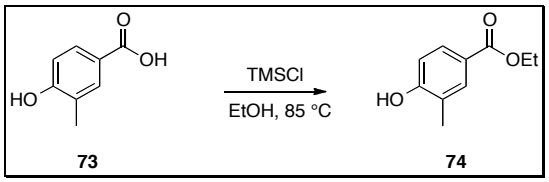
Preparation of 46.



To a solution of benzyl bromide **44** (50 mg, 0.167 mmol) in THF (2mL) was added *t*Bu_4NI (31 mg, 0.084 mmol) and the reaction was heated to 65 °C for 5 min. Dione **34**

(21 mg, 0.217 mmol) was added followed by Et_3N (70 μL, 0.50 mmol) and the reaction was monitored via TLC. After 10 h, a 20% HCl solution (0.5 mL) was added followed by water (4 mL), which was then extracted with ether (3 x 5 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified via column chromatography (MeOH/DCM, 1:99) afforded the product **46** (29.7 mg, 56% yield) as a yellow solid. R_f= 0.57 MeOH/DCM (1:99), ^1H NMR ($CDCl_3$, 300 MHz) δ 7.99-7.95 (m, 2H), δ 6.89 (d, *J*= 9.2 Hz, 1H), δ 5.41 (s, 1H), δ 5.04 (s, 2H), δ 3.88 (s, 3H), δ 2.67-2.63 (m, 2H), δ 2.45-2.42 (m, 2H), δ 1.56 (s, 9H): ^{13}C NMR (100 MHz) 190.2, 160.6, 132.3, 131.1, 124.8, 123.0, 110.1, 105.6, 81.1, 68.6, 56.0, 34.4, 28.8, 28.5: IR (thin film, NaCl) 2975, 2931, 2842, 1713, 1586, 1502, 1458, 1440, 1413, 1392, 1368, 1344, 1303, 1275, 1162, 1127, 1025, 959, 918: HRMS (ESI-ACPI) *m/z* calcd. for $C_{18}H_{22}NaO_5$ 341.1359, found 341.1356.

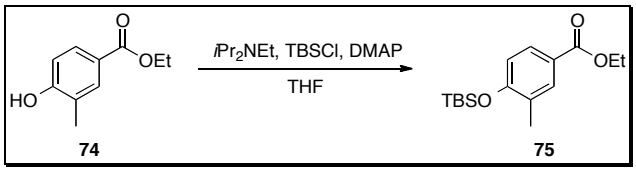
Preparation of Ethyl Ester 74.



To a solution of compound **73** (10.12 g, 66.5 mmol) in ethanol (70 mL) was added trimethylsilyl chloride (19.76 mL, 156 mmol) and the reaction was refluxed 6 h. After all the starting material had been consumed, the solvent was removed and the residue was treated with water (50 mL) and $NaHCO_3$ (50 mL), and extracted with ether (3 x 50 mL). The organic layer was dried over $MgSO_4$ and purified via column chromatography (EtOAc/hexane, 1:4) to afford compound **74** as a white solid (11.46 g, 96% yield, melting

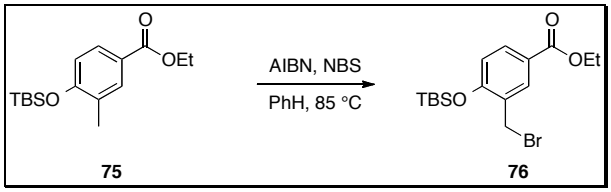
point = 78 °C). R_f= 0.47 in 1:4 EtOAc/hexane. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (s, 1H), δ 7.65 (d, *J*= 8.3 Hz, 1H), δ 7.66 (d, *J*= 8.3 Hz, 1H), δ 4.24 (q, *J*= 7.1 Hz, 2H), δ 2.16 (s, 3H), δ 1.31 (t, *J*= 7.1 Hz, 3H): ^{13}C NMR (100 MHz) 167.3, 160.3, 132.2, 128.9, 124.5, 121.0, 113.9, 60.4, 14.9, 13.5: IR (thin film, NaCl) 3301, 2933, 1680, 1602, 1512, 1396, 1368, 1283, 1225, 1184, 1143, 1116, 1024: HRMS (ESI-ACPI) *m/z* calcd. for $C_{10}H_{13}O_3$ $[M+H]^+$: 181.0859, found 181.0860.

Preparation of Silylated Phenol 75.



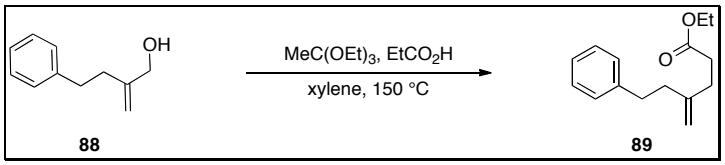
To a solution of phenol **74** (1.01 g, 5.59 mmol) in anhydrous DMF (50 mL) was added TBSCl (1.26 g, 8.38 mmol) over 10 min, followed by dropwise addition of *i*Pr_2NEt (1.70 mL, 9.78 mmol). After 8 h, saturated $NaHCO_{3(aq)}$ (25 mL) was added along with water (25 mL) and the mixture was extracted with ether (3 x 50 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified via column chromatography provided 1.45 g (88% yield) of silyl ether **75** as an oil. R_f= 0.68 in EtOAc/Hexane/Et_3N (3:96:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.85 (s, 1H), δ 7.79 (d, *J*= 8.4 Hz, 1H), δ 6.78 (d, *J*= 8.4 Hz, 1H), δ 4.33 (q, *J*= 7.1 Hz, 2H), δ 2.23 (s, 3H), δ 1.37 (t, *J*= 7.1 Hz, 3H), δ 1.02 (s, 9H), δ 0.24 (s, 6H): ^{13}C NMR (100 MHz) 166.8, 158.4, 132.7, 129.0, 123.3, 118.2, 60.8, 28.6, 25.9, 18.5, 17.0, 14.6, -4.0: IR (thin film, NaCl) 2957, 2931, 2859, 1716, 1606, 1499, 1472, 128, 1258, 1182, 1122, 1103, 942, 898: HRMS (ESI-ACPI) *m/z* calcd. for $C_{16}H_{27}O_3Si$ $[M+H]^+$: 295.1724, found 295.1727.

Preparation of Benzyl Bromide 76.



Compound **75** (2.47 mg, 8.4 mmol) was dissolved in benzene (15 mL) followed by the addition of NBS (1.57 g, 8.81 mmol) and AIBN (69.0 mg, 0.42 mmol) and refluxed for 8 h. The reaction was cooled to rt, then washed with a saturated solution of $NaHCO_3$ (10 mL) and extracted with ether (2 x 15 mL). The organic layer was dried over $MgSO_4$, and solvent removed under reduced pressure. The residue was purified via column chromatography (hexane/ether, 97:3) to afford **76** (2.84 g, 91% yield). Isolated as an oil. R_f= 0.58 in EtOAc/Hexane (1:99). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.01 (s, 1H), δ 7.86 (d, *J*= 8.5 Hz, 1H), δ 6.80 (d, *J*= 8.4 Hz, 1H), δ 4.48 (s, 2H), δ 4.31 (q, *J*= 7.1 Hz, 2H), δ 1.34 (t, *J*= 7.1 Hz, 3H), δ 1.02 (s, 9H), δ 0.28 (s, 6H): ^{13}C NMR (75 MHz) 166.8, 158.4, 133.1, 131.1, 128.7, 123.6, 118.4, 61.0, 28.6, 25.9, 18.5, 14.6, -4.0: IR (thin film, NaCl) 2957, 2931, 2897, 2859, 1717, 1607, 1500, 1472, 1391, 1365, 1288, 1182, 1142, 1109, 942, 859, 824: HRMS (ESI-ACPI) *m/z* calcd. for $C_{16}H_{26}BrO_3Si$ $[M+H]^+$: 373.0829, found 373.0834.

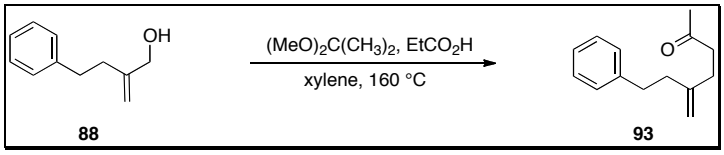
Preparation of Ester 89.



To a solution of compound **88** (148.3 mg, 0.92 mmol) in xylene (0.5 mL) was added triethyl orthoacetate (1.16 mL, 6.31 mmol) and propionic acid (5.0 μL, 0.062 mmol) in a

pressure tube which was sealed and heated to 150 °C for 10 h. Upon completion, the volatiles were removed under reduced pressure and the resulting oil was loaded onto silica gel. Column chromatography (EtOAc/hexane, 1:9) provided compound **89** as an oil (181 mg, 85% yield). R_f= 0.63 in EtOAc/Hexane, 1:9. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33-7.20 (m, 5H), δ 4.81 (d, *J*= 11.1 Hz, 2H), δ 4.16 (q, *J*= 7.14 Hz, 2H), δ 2.78 (t, *J*= 7.8 Hz, 2H), δ 2.53-2.33 (m, 6H), δ 1.28 (t, *J*= 7.14 Hz, 3H): ^{13}C NMR (75 MHz) 173.5, 147.7, 142.2, 128.6, 126.1, 110.0, 60.6, 38.3, 34.6, 33.0, 31.3, 14.5: IR (thin film, NaCl) 3084, 3063, 3027, 2981, 2936, 2859, 1736, 1646, 1496, 1453, 1370, 1251, 1162, 1030, 893: HRMS (ESI-ACPI) *m/z* calcd. for $C_{15}H_{21}O_2$ $[M+H]^+$: 233.1536, found 233.1540.

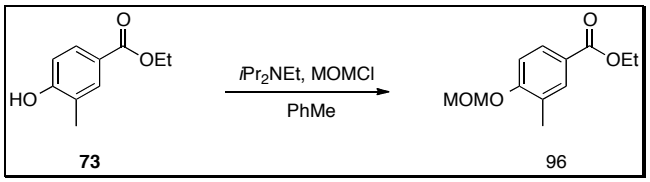
Preparation of Methyl Ketone 93.



To a solution of compound **88** (1.53 g, 9.42 mmol) in xylene (4 mL) was added dimethoxypropane (6.65 mL, 56.5 mmol) and propionic acid (71 μL, 0.94 mmol) in a pressure tube which was sealed and heated to 160 °C for 10 h. Upon completion, the volatiles were removed under reduced pressure and the resulting solution was loaded onto silica gel. Column chromatography (EtOAc/hexane, 1:9) provided compound **93** as an oil (1.5 g, 78% yield). R_f= 0.57 in EtOAc/Hexane, 1:9. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42 (m, 5H), δ 4.80 (s, 1H), δ 4.74 (s, 1H), δ 2.76 (t, *J*= 7.8 Hz, 2H), 2.60 (t, *J*= 8.2 Hz, 2H), δ 2.34 (t, *J*= 7.9 Hz, 4H), 2.16 (s, 3H): ^{13}C NMR (75 MHz) 208.5, 148.0, 142.2, 128.5, 126.1, 109.8, 42.1, 38.4, 34.6, 30.1: IR (thin film, NaCl) 3083, 3026, 2925, 2858,

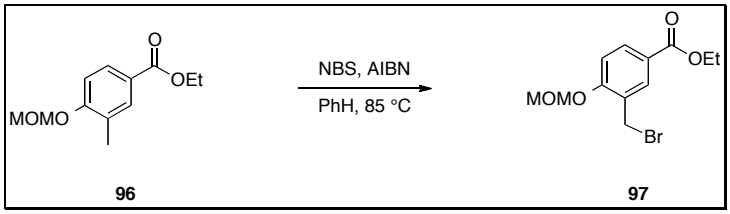
2362, 2338, 1717, 1645, 1496, 1357, 1160, 890: HRMS (ESI-ACPI) *m/z* calcd. for $C_{14}H_{19}O$ $[M+H]^+$: 203.1430, found 203.1434.

Preparation of Methoxymethylether 96.



To a solution of methyl chloromethyl ether (7.25 mL, 95.4 mmol) in toluene (100 mL) was added compound **73** (11.46 g, 63.6 mmol) in toluene (10 mL) at 0 °C, followed by diisopropylamine (13.86 mL, 79.5 mmol) in toluene (20 mL). The reaction was warmed to rt, then maintained for 12 h. Upon completion, the reaction was quenched with a saturated solution of $NH_4Cl_{(aq)}$ (50 mL) and stirred for an additional 5 min. The mixture was extract with ether (2 x 50 mL), dried over $MgSO_4$ and purified by column chromatography using EtOAc/hexane/Et_3N (1:19:0.5) to provided **96** as a white solid (14 g, 98% yield). R_f=0.8 in EtOAc/hexane, 1:19. (This reaction is also successful replacing diisopropylamine with NaH (1.2 equivalents). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.85 (m, 2H), δ 7.05 (d, *J*= 9.2 Hz, 1H), δ 5.25 (s, 2H), δ 4.34 (q, *J*= 7.1 Hz, 2H), δ 3.48 (s, 3H), δ 2.27 (s, 3H), 1.38 (t, *J*= 7.1 Hz, 3H): ^{13}C NMR (100 MHz) 166.7, 159.2, 132.4, 129.2, 127.3, 123.6, 112.8, 94.3, 60.8, 56.3, 16.4, 14.6: IR (thin film, NaCl) 3460, 2979, 2955, 2904, 2827, 1714, 1607, 1498, 1456, 1419, 1391, 1366, 1320, 1293, 1158, 1125, 1104, 1078, 1025, 991, 922, 769: HRMS (ESI-ACPI) *m/z* calcd. for $C_{12}H_{17}O_4$ $[M+H]^+$: 225.1121, found 225.1125.

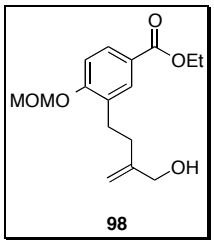
Preparation of Benzyl Bromide 97.



96 97

Compound **96** (16.3 g, 64.6 mmol) was dissolved in benzene (75 mL) followed by the addition of NBS (13.3 g, 80.8 mmol) and AIBN (1.15 g, 6.46 mmol) and refluxed for 8 h. The reaction was cooled to rt, then washed with a saturated solution of $NaHCO_3$ (30 mL) and extracted with ether (2 x 40 mL). The organic layer was dried over $MgSO_4$, and solvent removed under reduced pressure. The residue was purified via column chromatography (hexane/ether, 97:3) to afford **76** (18.6 g, 95% yield) as an oil. R_f= 0.65 in hexane/ether, 97:3. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.01 (d, *J*= 2.2 Hz, 1H), δ 7.96 (dd, *J*= 2.2 Hz, 8.7 Hz, 1H), δ 7.10 (d, *J*= 8.7 Hz, 1H), δ 5.30 (s, 2H), δ 4.54 (s, 2H), δ 4.33 (q, *J*= 7.1 Hz, 2H), δ 3.50 (s, 3H), 1.36 (t, *J*= 7.13 Hz, 3H): ^{13}C NMR (100 MHz) 166.0, 159.0, 132.6, 132.2, 126.8, 124.0, 113.7, 94.2, 61.1, 56.7, 28.4, 14.6: IR (thin film, NaCl) 2977, 2951, 1695, 1608, 1500, 1464, 1441, 1299, 1276, 1247, 1203, 1153, 1079, 1023, 982, 950, 925, 769: HRMS (ESI-ACPI) *m/z* calcd. for $C_{12}H_{16}BrO_4$ $[M+H]^+$: 303.0227, found 303.0225.

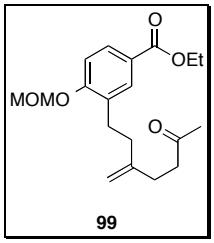
Preparation of Allyl Alcohol 98.



98

To a solution of TMEDA (4.28 g, 36.8 mmol) and methylallyl alcohol (857 mg, 11.9 mmol) in Et_2O (20 mL) was treated with *n*BuLi (22.1 mL, 1.19 M) over ten minutes at -15 °C. Stir for ten minutes then THF (5 mL) was added dropwise. Allow to warm to rt and maintained at this temperature for 6 h. where an orange gummy material started to stick to the walls of the round bottom flask. The mixture was recooled to -15 °C and treated with benzyl bromide **97** (3.53 g, 10.7 mmol) in THF (5 mL) added over the course of 25 min and the cooling bath was removed. The reaction was monitored via TLC and quenched with water (10 mL) and extracted with ether (2 x 40 mL). The organic layer was dried over $MgSO_4$, and solvent removed under reduced pressure. The residue was purified via column chromatography (hexane/ether, 9:1) to afford **98** (54.1 g, 15% yield) as an oil. R_f= 0.3 in hexane:EtOAc, 9:1. 1H NMR ($CDCl_3$, 300 MHz) δ 7.80 (d, *J*= 9.6 Hz, 1H), δ 7.78 (s, 1H), δ 7.05 (d, *J*= 9.1 Hz), δ 5.24 (s, 2h), δ 4.98 (d, *J*= 47.7 Hz, 2H), δ 4.13 (s, 2H), δ 3.48 (s, 3H), δ 2.82 (t, *J*= 7.7 Hz, *J*= 8.2 Hz, 2H), δ 2.36 (t, *J*= 8.6 Hz, *J*= 7.5 Hz, 2H), δ 1.57 (2, 9H): ^{13}C NMR (75 MHz) 166.0, 159.0, 148.8, 131.2, 130.7, 129.4, 125.4, 113.0, 110.0, 94.4, 80.8, 66.2, 56.5, 33.3, 29.0, 28.5: IR (thin film, NaCl) 3449, 2976, 2931, 1708, 1606, 1497, 1476, 1455, 1368, 1302, 1270, 1255, 1159, 1131, 1079, 994, 922: HRMS (ESI-APCI) *m/z* calcd. for $C_{18}H_{26}NaO_5$ $[M+Na]^+$: 345.1672, found 345.1675.[19]

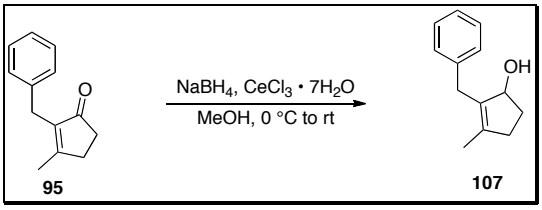
Preparation of Methyl Ketone 99.



99

To a solution of compound **98** (634.0 mg, 2.16 mmol) in xylene (5 mL) was added 2,2 dimethoxy propane (1.12 mL, 10.8 mmol) and propionic acid (11.0 μL, 0.15 mmol) in a pressure tube which was sealed and heated to 150 °C for 10 h. Upon completion, the volatiles were removed under reduced pressure and the resulting oil was loaded onto silica gel. Column chromatography (EtOAc/hexane, 1:9) provided compound **99** as an oil (108 mg, 15% yield). R_f= 0.3 in EtOAc/Hexane, 1:9. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.88 (m, 2H), δ 7.09 (d, *J*= 8.4 Hz, 1H), δ 5.25 (s, 2H), δ 4.79-4.73 (d, *J*= 20.0 Hz, 2H), δ 4.32 (q, *J*= 7.1 Hz, 2H), δ 3.48 (s, 3H), δ 2.78 (t, *J*= 8.3 Hz, 2H), δ 2.63 (t, *J*= 8.2 Hz, 2H), δ 2.38-2.28 (m, 4H), δ 2.16 (s, 3H), δ 1.38 (t, *J*= 7.1 Hz, 3H): ^{13}C NMR (75 MHz) 208.7, 166.9, 158.9, 148.1, 131.6, 131.0, 129.6, 123.8, 113.1, 109.8, 94.3, 60.9, 56.5, 51.4, 42.1, 36.6, 30.2, 29.1, 14.6: IR (thin film, NaCl) 2932, 1714, 1606, 1497, 1366, 1293, 1263, 1182, 1156, 1120, 1079, 1025, 991: HRMS (ESI-ACPI) *m/z* calcd. for $C_{19}H_{26}NaO_5$ $[M+Na]^+$: 357.1672, found 357.1676.

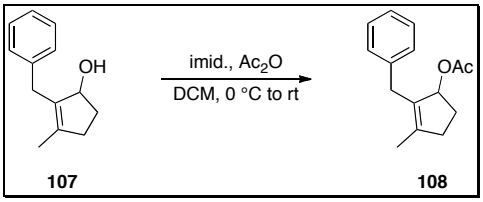
Preparation of Allylic Alcohol 107.



To a solution of cerium trichloride heptahydrate (178.3 mg, 0.479 mmol) in MeOH (2 mL) was added compound **95** (81 mg, 0.435 mmol). The solution was cooled to 0 °C and $NaBH_4$ (17.3 mg, 0.457 mmol) were subsequently added in small portions. The mixture was allowed to stir for 1h. Acetone (1 mL) was then added and the reaction was allowed to stir for an additional 15 min. The solvent was removed under reduced pressure then

dissolved in ether (15 mL) and washed with brine (5 mL), then water (5 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue is purified via column chromatography using EtOAc/hexane/Et_3N (2:18:1) to provide compound **107** (81.8 mg, 80% yield) as a mixture of enantiomers. R_f= 0.75 in EtOAc/hexane, 1:9 (stains blue with anisaldehyde stain), starting material, R_f= 0.69 in EtOAc/hexane, 1:9 stains yellow in same stain. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30-7.17 (m, 5H), δ 4.58 (bs, 1H), δ 3.48 (dd, *J*= 14.8 Hz, 2H), δ 2.52-2.38 (m, 1H), δ 2.27-2.08 (m, 2H), δ 1.80 (s, 3H), δ 1.70-1.59 (m, 1H), δ 1.35-1.29 (m, 1H): ^{13}C NMR (75 MHz) ^{13}C NMR (75 MHz) 140.4, 137.7, 136.6, 128.8, 126.2, 79.3, 77.7, 77.3, 76.7, 35.7, 32.7, 32.0, 14.7: IR (thin film, NaCl), 3334 (bs) 3026, 2961, 2914, 2846, 1494, 1452, 1064, 1029, 992: HRMS (ESI-APCI) calcd. for $C_{13}H_{15}$ $[M\text{-}OH]^+$: 171.1168, found 171.1164.

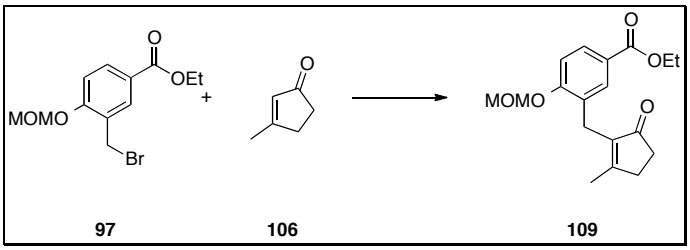
Preparation of Allylic Acetate 108.



To a solution of compound **107** (47.6 mg, 0.253 mmol) in DCM (2 mL) and was added imidazole (19 mg, 0.278 mmol) at 0 °C. Acetic anhydride (26.3 µL, 0.278 mmol) was added dropwise and the solution was allowed to warm to rt. After 8 h, the reaction was diluted with ether (5 mL) and washed with a 20% HCl solution (2 mL) followed by saturated $NaHCO_{3(aq)}$ (5 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was purified via column chromatography using EtOAc/hexane, 2:18:1, to afford compound **108** (27 mg, 77% yield). R_f= 0.69 in

EtOAc/hexane, 3:17. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29-7.11 (m, 5H), δ 5.61 (s, 1H), δ 3.50 (d, *J*= 14.9 Hz, 1H), δ 3.32 (d, *J*= 15.1 Hz), δ 2.57-2.46 (m, 1H), δ 2.32-2.18 (m, 2H), δ 1.90 (s, 3H), δ 1.84 (s, 3H), δ 1.74-1.67 (m, 1H): ^{13}C NMR (75 MHz) 171.3, 141.0, 140.0, 132.8, 128.7, 126.1, 82.4, 36.2, 32.3, 29.7, 21.4, 14.8 : IR (thin film, NaCl) 2915, 1731, 1494, 1453, 1370, 1242, 1031, 1014: NRMS (ESI-APCI) calcd. for [M-$C_2H_3O_2$]$^{+}$: 171.1168, found 171.1172.

Preparation of Substituted Enone 109.

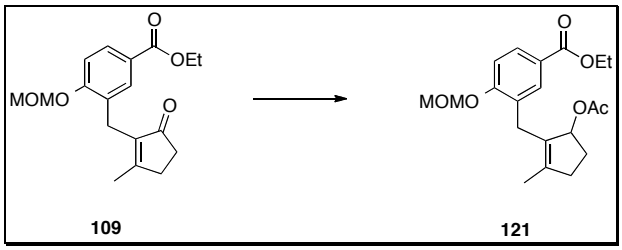


General Procedure for Cross Coupling

Zinc (600 mg, 2.87 mmol) was added to a round bottom flask and flame dried. Upon cooling, the flask was charged with THF (5 mL) and 1,2 dibromoethane (25 µL, 0.0029 mmol) and the mixture was heated to 60 °C for 10 min then cooled to rt. TMSCl (15 µL, 0.0012 mmol) was then added followed by cooling to 0 °C. A solution of compound **97** (2.17 g, 7.19 mmol) in THF (5 mL) was added dropwise under vigorous stirring, and the reaction remained at 0°C for 2 h. The solution was then degassed using the freeze-pump-thaw method, 3 times, and excess zinc was allowed to settle at the bottom of the flask. In a separate round bottom, α-halo-enone **106** (500 mg, 2.87 mmol) in DMF (20 mL) and dichlorobis(tri-*o*-tolylphosphine) palladium (II) (113 mg, 0.144 mmol) are combined and degassed. The benzyl zinc bromide solution was transferred via cannula and stirred at rt for 5 min, then at 85 °C for 3 h. Once the reaction is complete via TLC, a saturated

solution of NH_4Cl (5 mL) was added and the mixture was extracted with ether (3 x 15 mL). Addition of a few drops of 5 % solution of HCl was periodically necessary to help dissolve emulsions. The organic layer is dried over $MgSO_4$ and concentrated under reduced pressure. The residue is purified via column chromatography (acetone:hexane, 3:97) to provide coupled material **109** (616 mg, 94% yield) as an oil. R_f=0.2 (3% acetone in hexane), ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.84 (d, *J*= 8.6 Hz, 1H), δ 7.75 (s, 1H), δ 7.06 (d, *J*= 8.6 Hz, 1H), δ 5.25 (s, 2H), δ 4.31 (q, *J*= 7.1 Hz, 2H), δ 3.56 (s, 2H), δ 3.47 (s, 3H), δ 2.54 (bs, 2H), δ 2.42 (bs, 2H), δ 2.04 (s, 3H), δ 1.36 (t, *J*= 7.1 Hz, 3H): ^{13}C NMR (75 MHz) 209.1, 172.1, 166.7, 158.7, 138.5, 131.4, 129.6, 128.0, 123.7, 113.0, 94.3, 60.8, 56.4, 34.5, 32.0, 17.8, 14.6: IR (thin film, NaCl) 2979, 2911, 1711, 1646, 1606, 1499, 1291, 1264, 1175, 1156, 1121, 1079, 1023, 990: HRMS (ESI-ACIP) *m/z* calcd. for $C_{18}H_{22}O_5$ $[M+H]^+$: 319.1540, found 319.1540.

Preparation of Allylic Acetate 121



To a solution of **109** (116 mg, 0.365 mmol) in MeOH (5 mL) was added $CeCl_3 \cdot 7H_2O$ (136 mg, 0.365 mmol) and the mixture was stirred until homogenous. The solution was then cooled to 0 °C and $NaBH_4$ (13.8 mg, 0.365 mmol) was added portion wise. The bath was removed and allowed to stir for 1 h. where acetone was then added to quench the reaction. This reaction was be monitored via TLC (hexane:EtOAc, 4:1) with anisaldehyde stain. The solvent was removed under reduced pressure. The crude

mixture was then dissolved in DCM (2 mL) and treated with Ac_2O (47 µL, 0.58 mmol), pyridine (138 µL, 1.46 mmol), and DMAP (one crystal) at 0 °C. Upon warming to rt, the reaction was allowed to stir for 4 h. The reaction was quenched with HCl (0.5 mL, 20 % solution in H_2O) and extracted with ether (2 x 5 mL). The organic layer was then washed with $NaHCO_3$ and purified via column chromatography using a gradient system of hexane:EtOAc, 9:1 then 4:1, to provide compound **121** in 33 % yield over two steps (44 mg). R_f= 0.43 (hexane:EtOAc, 4:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.84 (d, *J*= 8.6 Hz, 1H), δ 7.76 (s, 1H), δ 7.04 (d, *J*= 8.6 Hz, 1H), δ 5.51 (d, *J*= 6.2 Hz, 1H), δ 4.31 (q, *J*= 7.1 Hz, 2H), δ 3.50-3.36 (m, 2H), δ 3.44 (s, 3H), δ 2.54 (bs, 1H), δ 2.25-2.22 (bs, 2H), δ 2.04 (s, 3H), δ 1.81 (s, 3H), δ 1.70-1.64 (m, 1H), δ 1.35 (t, *J*= 7.1 Hz, 3H): ^{13}C NMR (100 MHz) 193.5, 170.9, 166.4, 158.7, 141.2, 131.6, 129.3, 128.4, 123.5, 112.8, 94.1, 82.4, 60.6, 56.1, 346.0, 29.6, 26.4, 21.1, 14.5: IR (thin film, NaCl) 2934, 2850, 1713, 1606, 1498, 1444, 1368, 1291, 1265, 1246, 1179, 1157, 1119, 1079, 990, 923: HRMS (ESI-ACIP) *m/z* calcd. for $C_{20}H_{30}NO_6$ $[M+NH_4]^+$: 380.2068, found 380.2053.

2.8 – References and Notes

1. Campagne, J.-M.; Porenty, A.; Moreau, A.; Chemier, X. *Chem. Rev.* **2006**, *106*, 911.
2. Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775.
3. a) Majetich, G.; Hicks, R.; Zhang, Y.; Tian, X.; Feltman, T. L.; Fang, J.; Duncan Jr., S. *J. Org. Chem.* **1996**, *16*, 8169; b) Majetich, G.; Zhang, Y.; Feltman, T. L.; Duncan Jr., S. *Tetrahedron Lett.* **1993**, *34*, 445.

4. a) Bal, B. S.; Childers, W. E.; Pinnick Jr., H. W. *Tetrahedron*, **1981**, *37*, 2091; b) Schow, S. R.; Bloom, J. D.; Thompson, A. S.; Winzenberg, K. N.; Smith III, A. B. *J. Am. Chem. Soc.* **1986**, *108*, 2662; c) for compound **42** see Li, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 3987.
5. Djessari C. *Chem. Rev.* **1948**, *43*, 271.
6. Choudhary, A.; Baumstark, A. L. *Synthesis*, **1989**, *9*, 688.
7. US Patent # 5,444,086 Michael S. Malamas, **1995.**
8. Bedekar, A. V.; Watanabe, T.; Tanaka, K.; Fuji, K. *Synthesis*, **1995**, *9*, 1069.
9. Grundl, M. A.; Trauner, D. *Org. Lett.* **2006**, *8*, 23.
10. a) Inamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392; b) Conlon, D. A.; Kumke, D.; Moeder, C.; Hardiman, M.; Hutson, G.; Sailer, L. *Adv. Synth. Catal.* **2004**, *346*, 1307.
11. a) Knoevenagel, E. *Ber.* **1896**, *29*, 172; b) Miki, T.; Hiraga, K.; Asako, T.; Mosuya, H. *Chem. Pharm. Bull.* **1967**, *15*, 670.
12. Ramachary, D. B.; Kisher, M. *J. Org. Chem.* **2007**, *72*, 5056.
13. Willard, P. G.; Fryhle, C. B. *Tetrahedron Lett.* **1980**, *21*, 3731.
14. Zeng, Q.; Rokita, S. E. *J. Org. Chem.* **1996**, *61*, 9080.
15. Rokita, S. E.; Yang, J.; Pande, P.; Greenberg, W. H. *J. Org. Chem.* **1997**, *62*, 3010
16. Patent # 2137538 Kasztreiner, E.; Vargha, L.; Huszti, Z.; Bursy, J.; Szilagyi, G.; Judit, E.; Elek, S.; Polgari, S. **1972.**
17. Van De Water, R.; Pettus, T. R. R. *Tetrahedron* **2002**, *58*, 5367.
18. Hunsdiecker, H. *Ber.* **1942**, *75*, 460.
19. Lipshutz, B. H.; Sharma, S.; Dimock, S. H.; Behlig, J. R. *Synthesis* **1992**, 191.

20. Johnson, W. S.; Werthman, L.; Barlett, W. R.; Li, T.-T.; Faulkner, D. J.; Peterson, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.

21. Xue, S.; Liu, Y.-K.; Li, L.-Z.; Guo, Q.-X. *J. Org. Chem.* **2005**, *70*, 8245.

22. Büchi, G.; Wüest, H. *J. Org. Chem.* **1966**, *31*, 977.

23. Miyamoto, H.; Iwamoto, M.; Nakada, M. *Heterocycles* **2005**, *66,* 61.

24. Katritsky, A. R.; Zhang, G.; Jiang, J. *J. Org. Chem.* **1995**, *60*, 7605.

25. Negishi, E.-I. *Tetrahedron*, **2000**, *56*, 10197.

26. Luche, J. L. *J. Am. Chem. Soc.* **1978**, 100, 2226.

27. Liu, Q.; Lan, Y.; Liu, J.; Li, G.; Wu, Y.-D.; Lei, A. *J. Am. Chem. Soc.* **2009**, *131*, 10201.

28. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics*, **1996**, *15*, 1518.

29. Methanol, triethylamine, and were collected from a still, refluxing with calcium hydride, under an atmosphere of nitrogen.

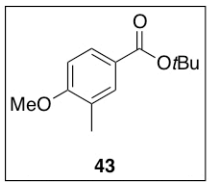
30. Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals*, 5^{th} ed. Elsevier Science: Burlinton, MA., 2003, p142.

31. Potassium Permanganate solution preparation – 3g of $KMnO_4$, 20g of K_2CO_3, 5 mL 5% $NaOH_{(aq)}$, and 300 mL of H_2O.

Anisladehyde solution preparation – 9.2 mL p-anisaldehyde, 3.75 mL AcOH, 338 mL 95% EtOH, and 12.5 mL H_2SO_4.

32. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

Appendix A1: Characterization Spectra Relevant to Chapter Two



43

Figure A.2.1 1H NMR (400MHz, $CDCl_3$) of compound 43

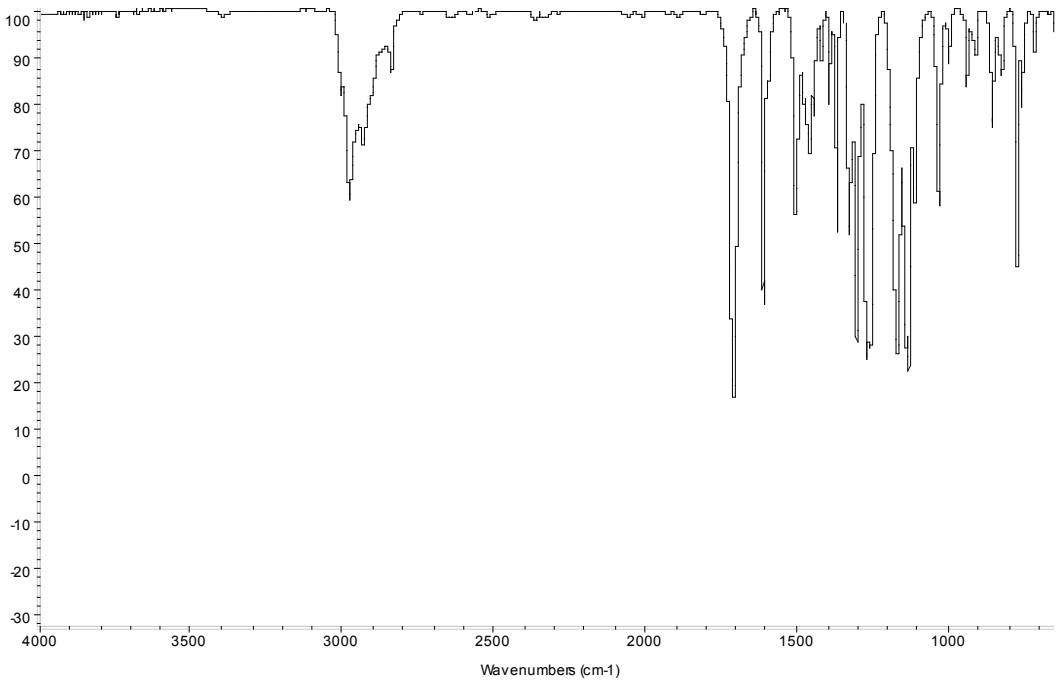


Figure A.2.2 Infrared Spectrum (thin film/NaCl) of compound **43**

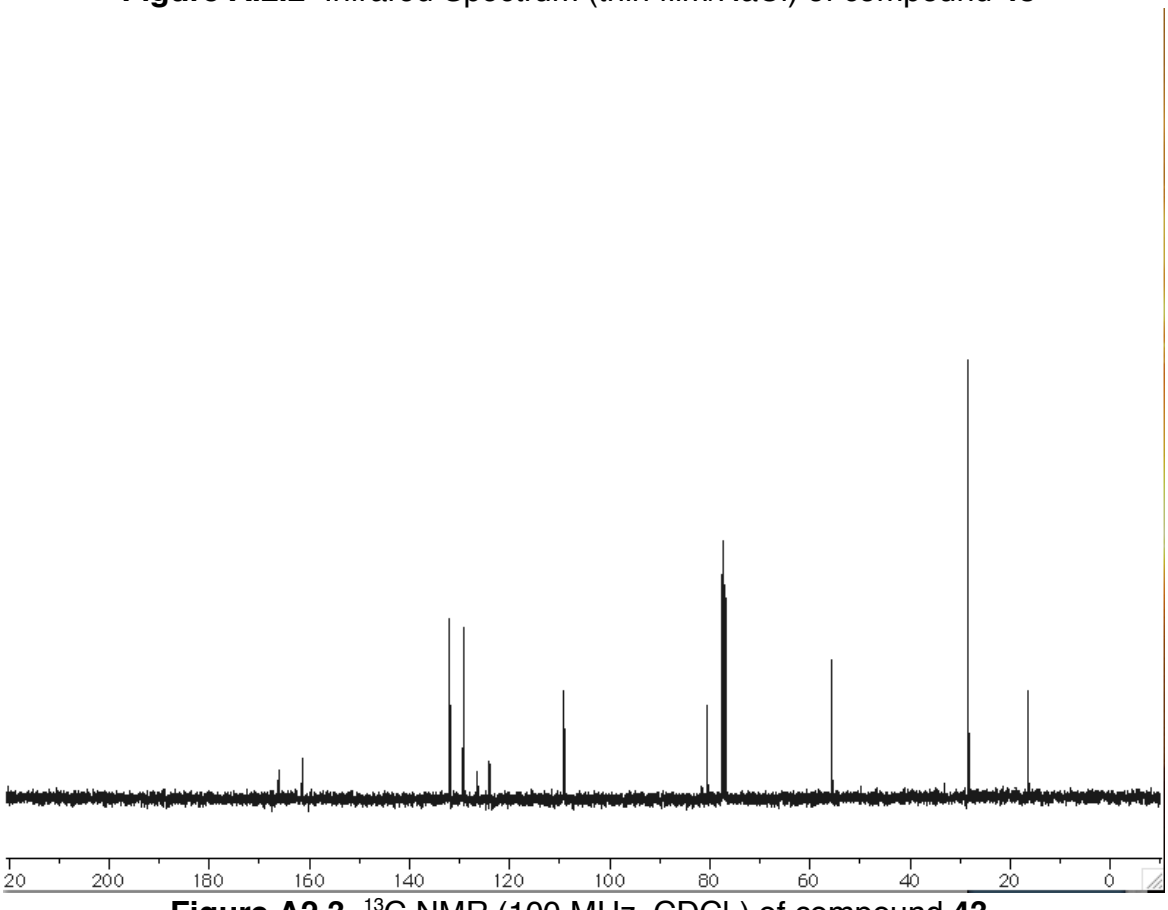


Figure A2.3 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **43**

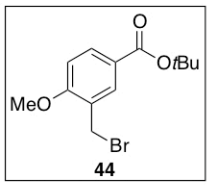


Figure A.2.4 1H NMR (400MHz, $CDCl_3$) of compound 44

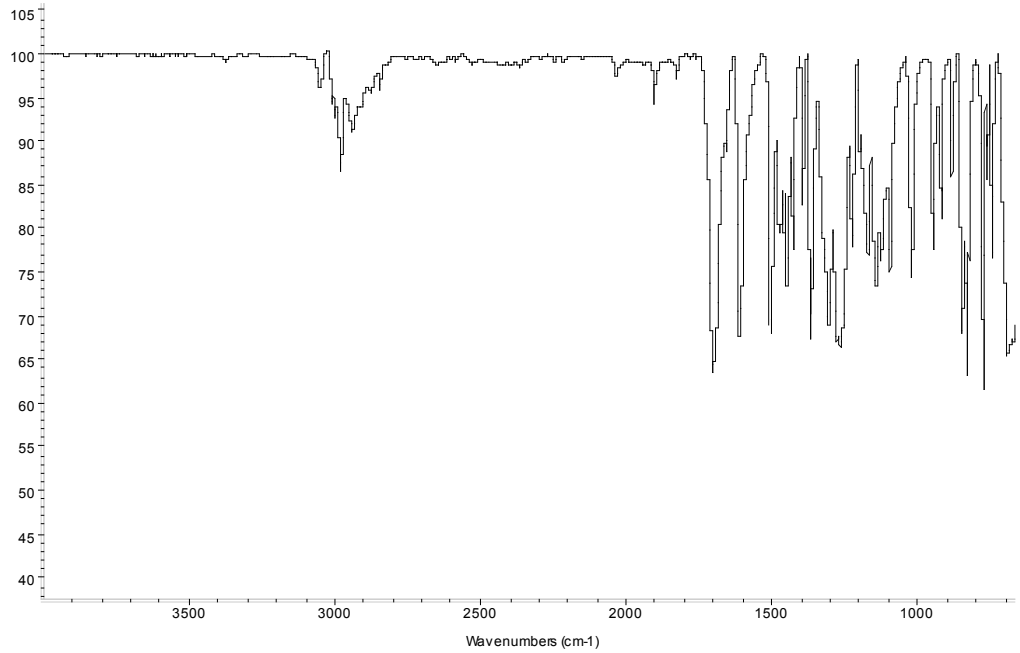


Figure A2.5 Infrared Spectrum (thin film/NaCl) of compound **44**

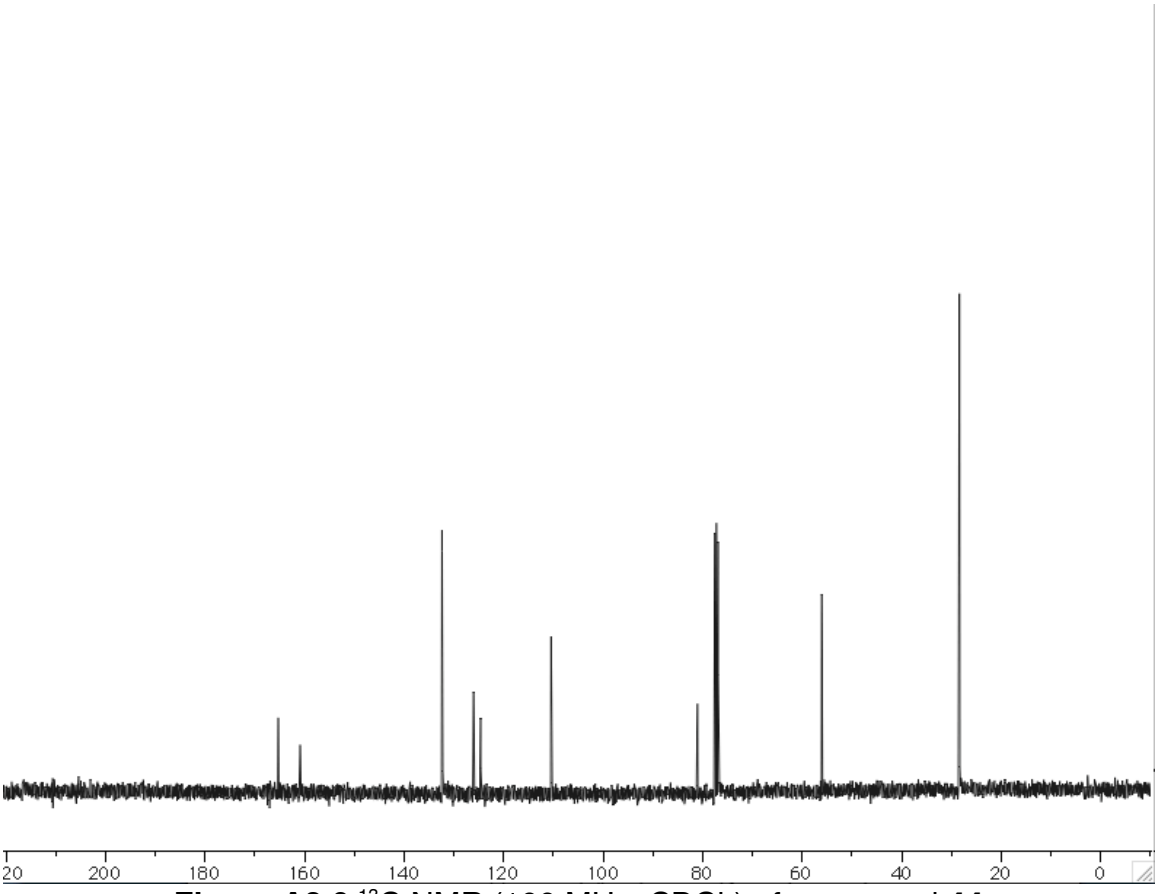


Figure A2.6 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **44**

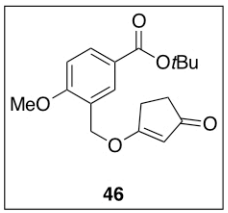


Figure A.2.7 1H NMR (400MHz, $CDCl_3$) of compound 46

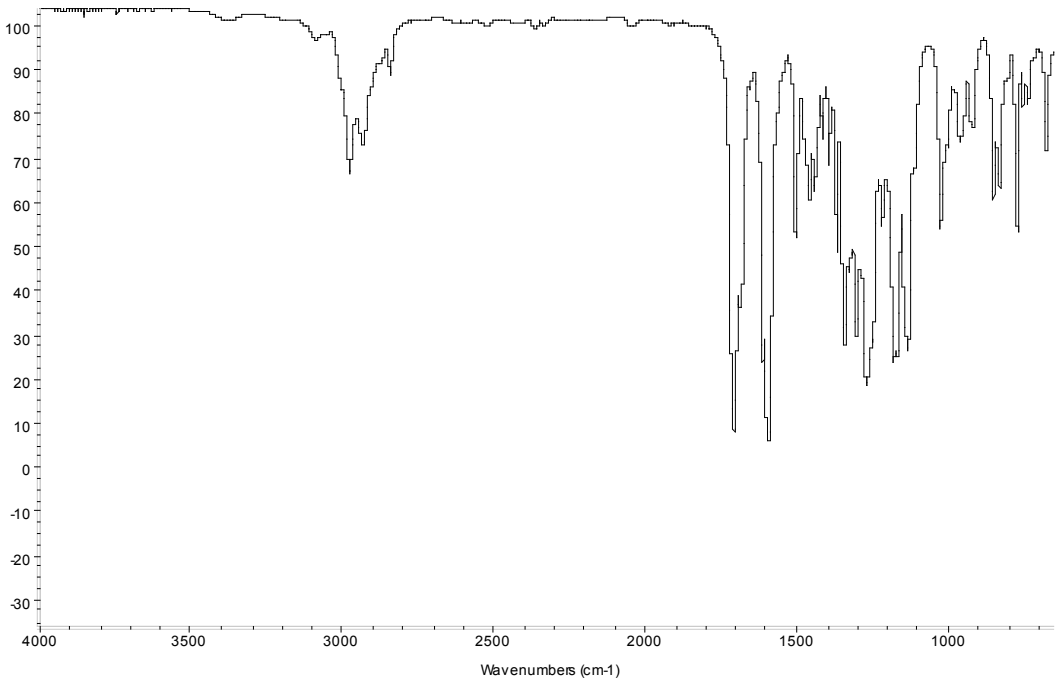


Figure A2.8 Infrared Spectrum (thin film/NaCl) of compound **46**

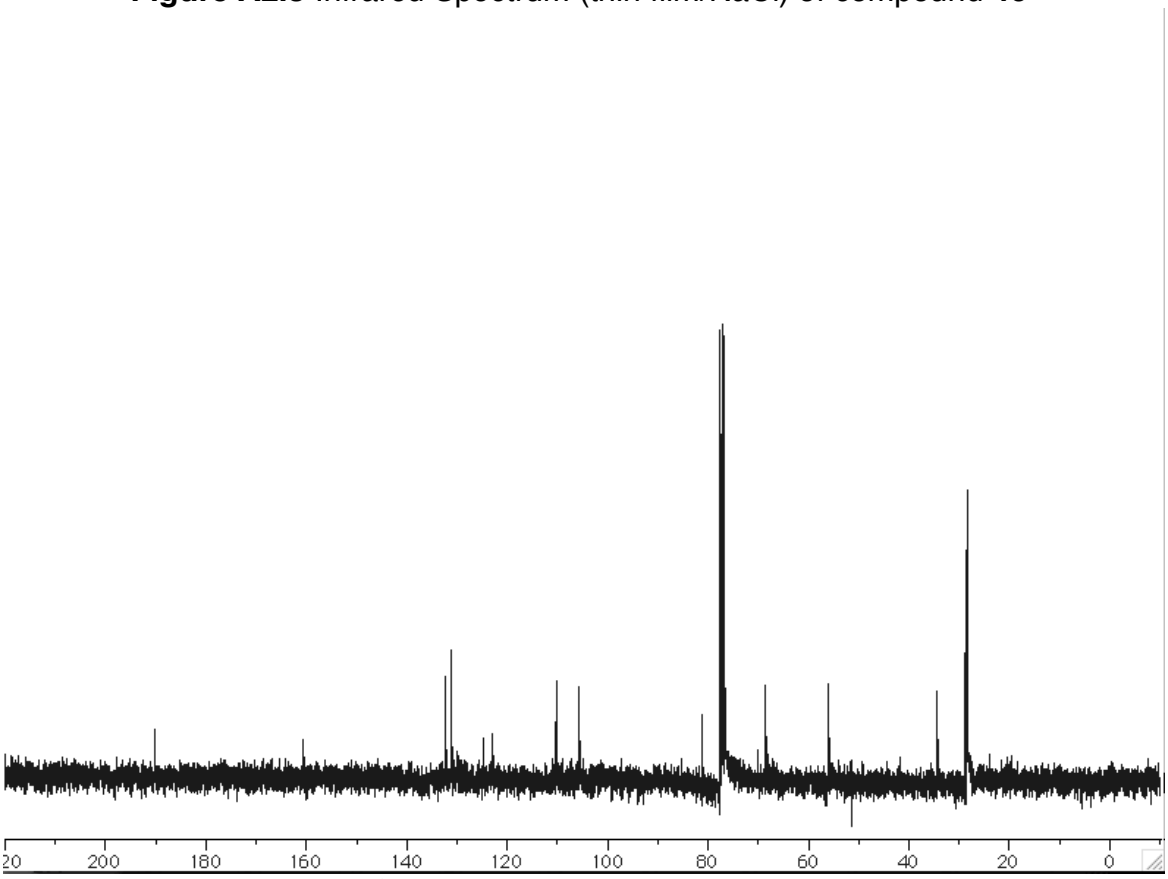
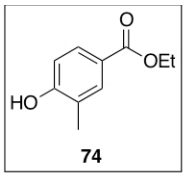


Figure A2.9 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **46**



74

Figure A.2.10 1H NMR (400MHz, $CDCl_3$) of compound 74

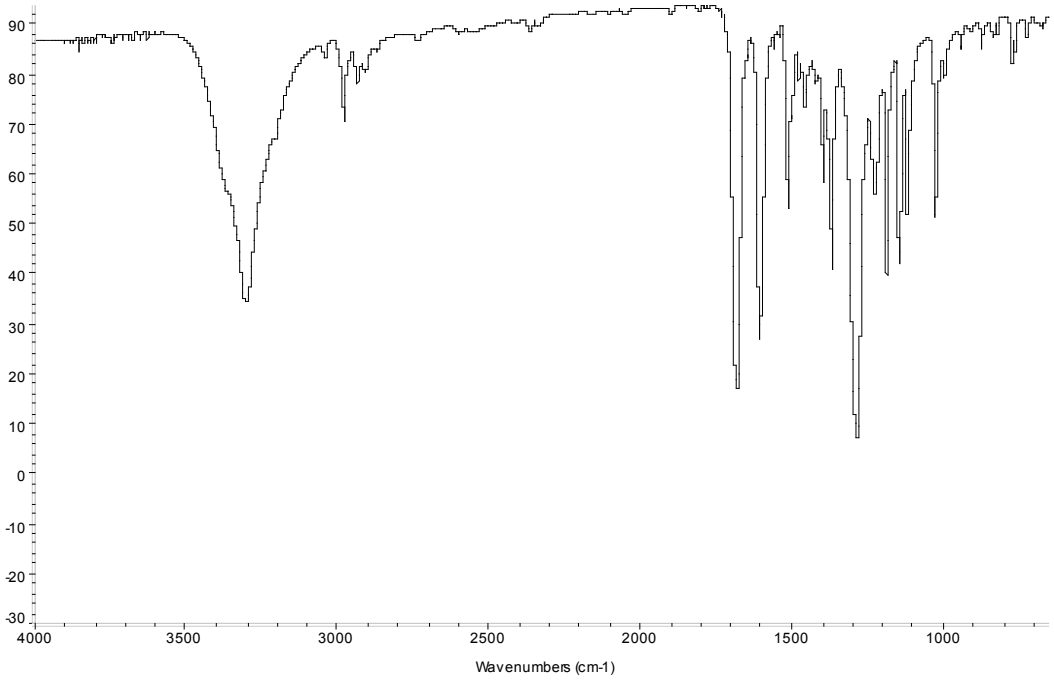


Figure A2.11 Infrared Spectrum (thin film/NaCl) of compound **74**

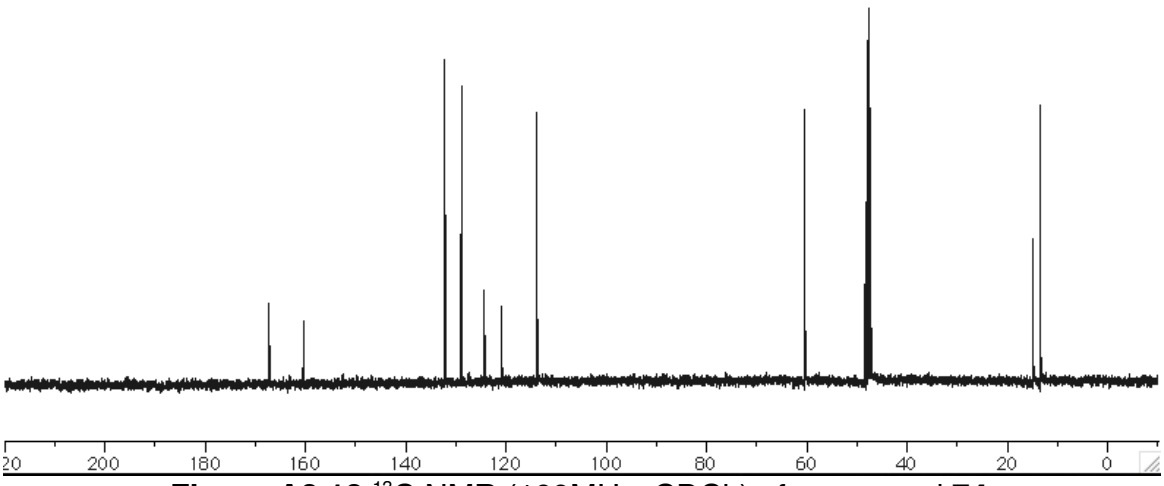
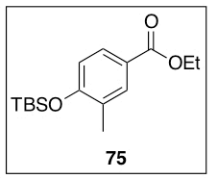


Figure A2.12 ^{13}C NMR (100MHz, $CDCl_3$) of compound **74**



75

Figure A.2.13 1H NMR (300MHz, $CDCl_3$) of compound 75

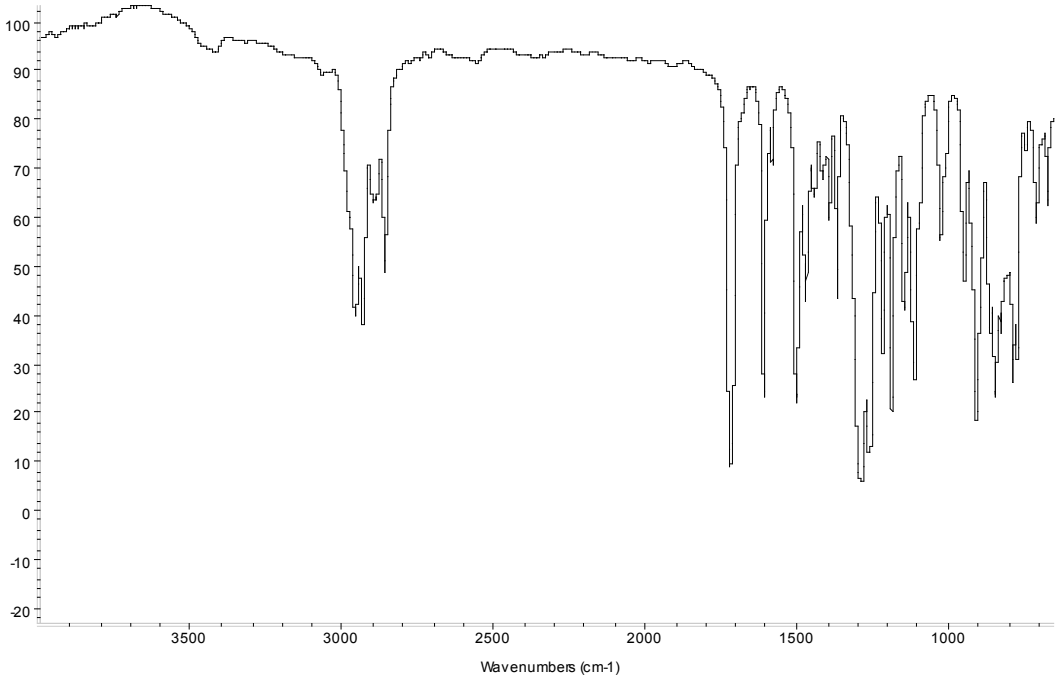


Figure A2.14 Infrared Spectrum (thin film/NaCl) of compound **75**

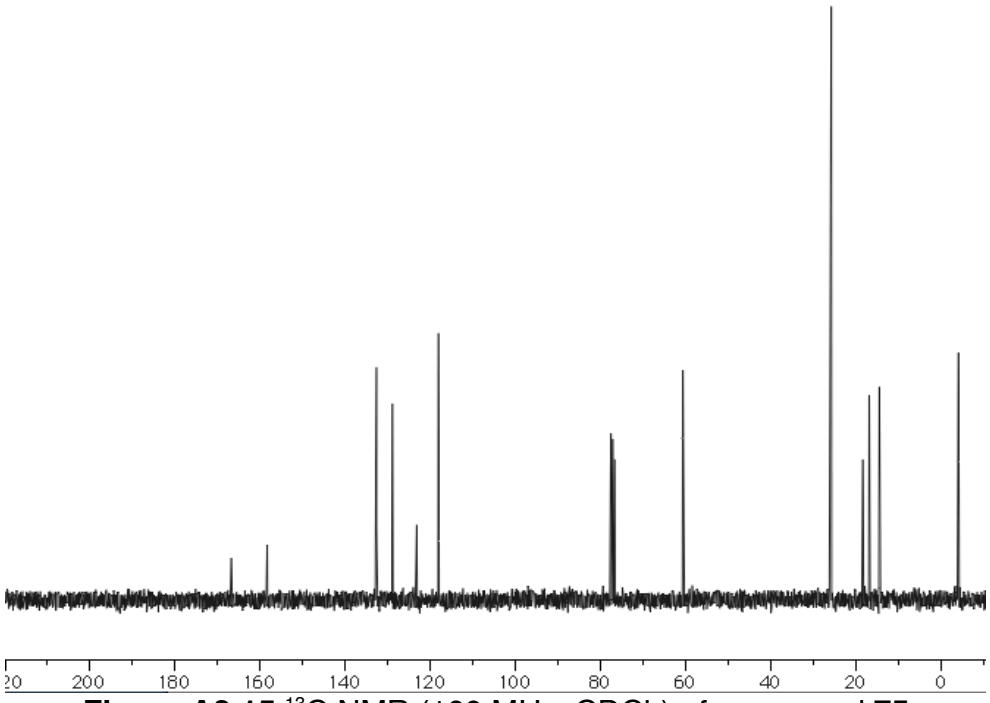


Figure A2.15 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **75**

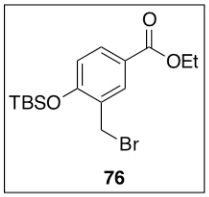


Figure A.2.16 1H NMR (400MHz, $CDCl_3$) of compound 76

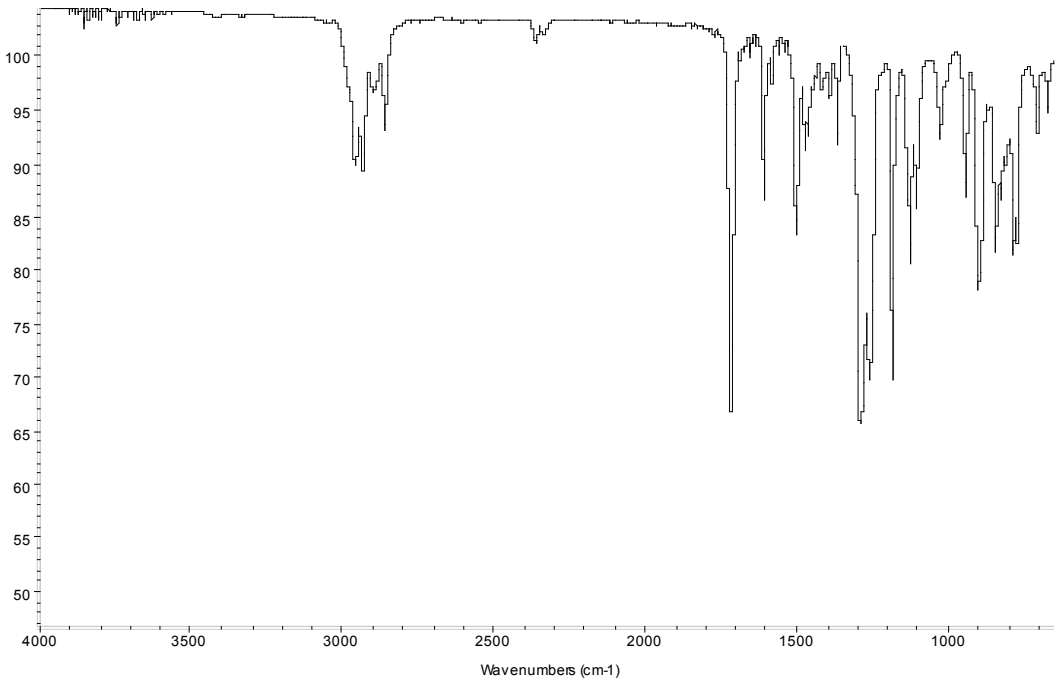


Figure A2.17 Infrared Spectrum (thin film/NaCl) of compound **76**

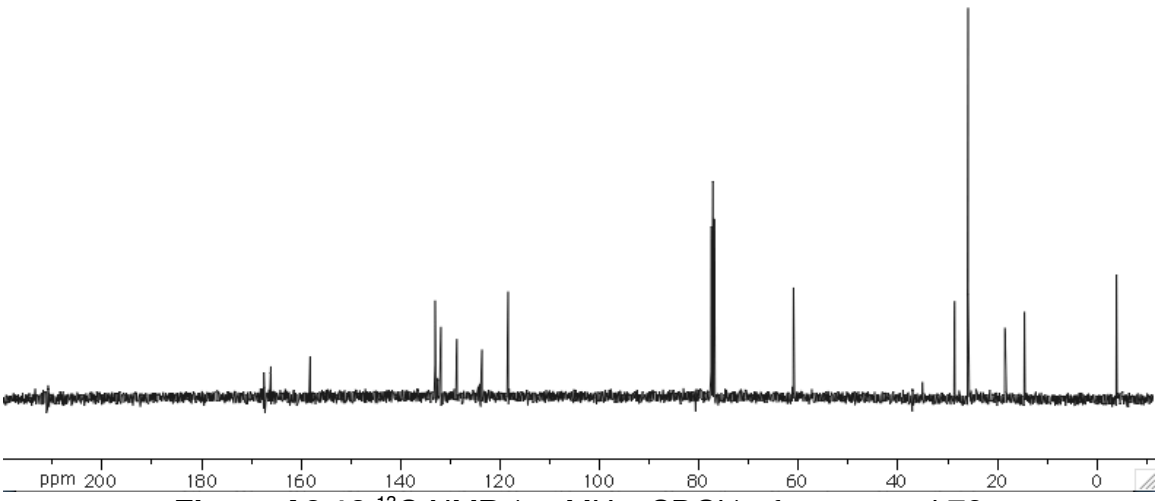
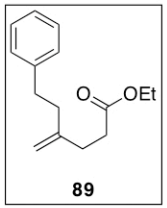
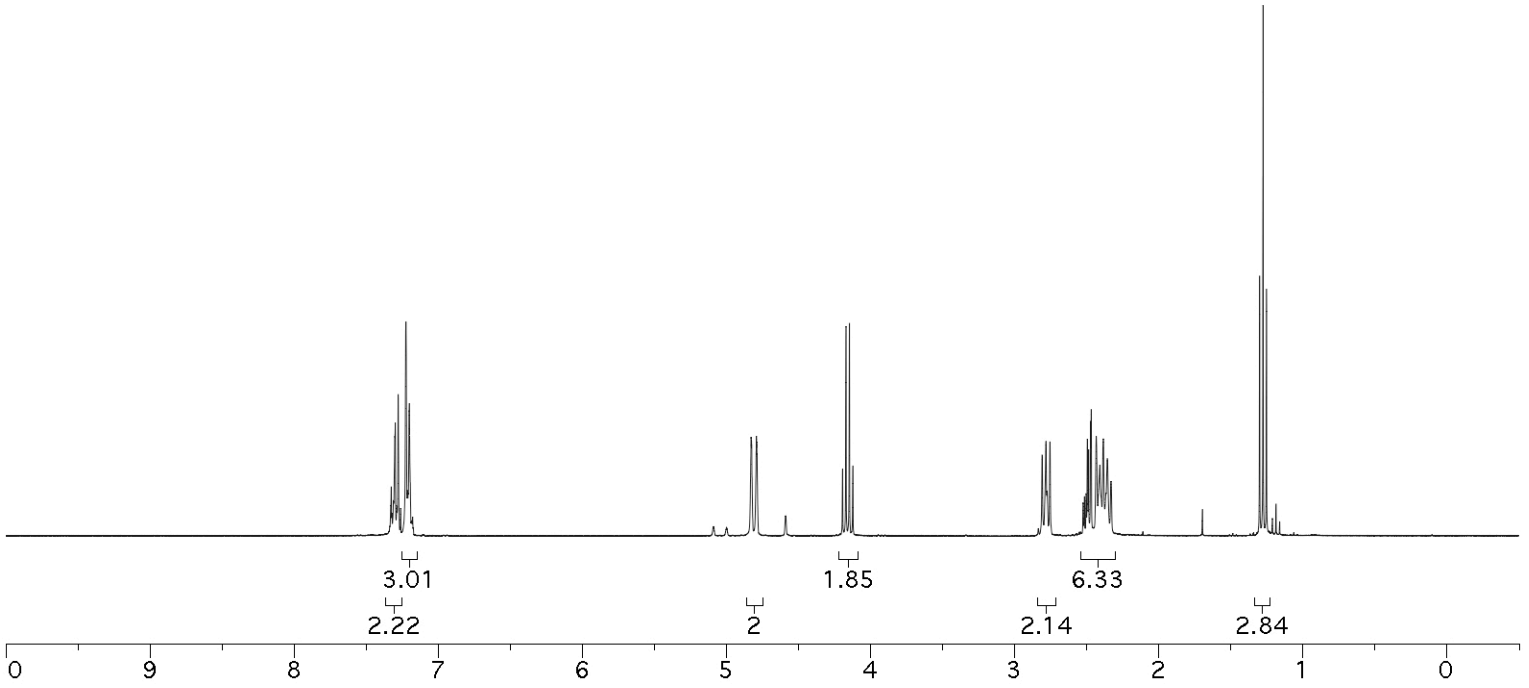


Figure A2.18 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **76**



89

Figure A.2.19 1H NMR (300MHz, $CDCl_3$) of compound 89



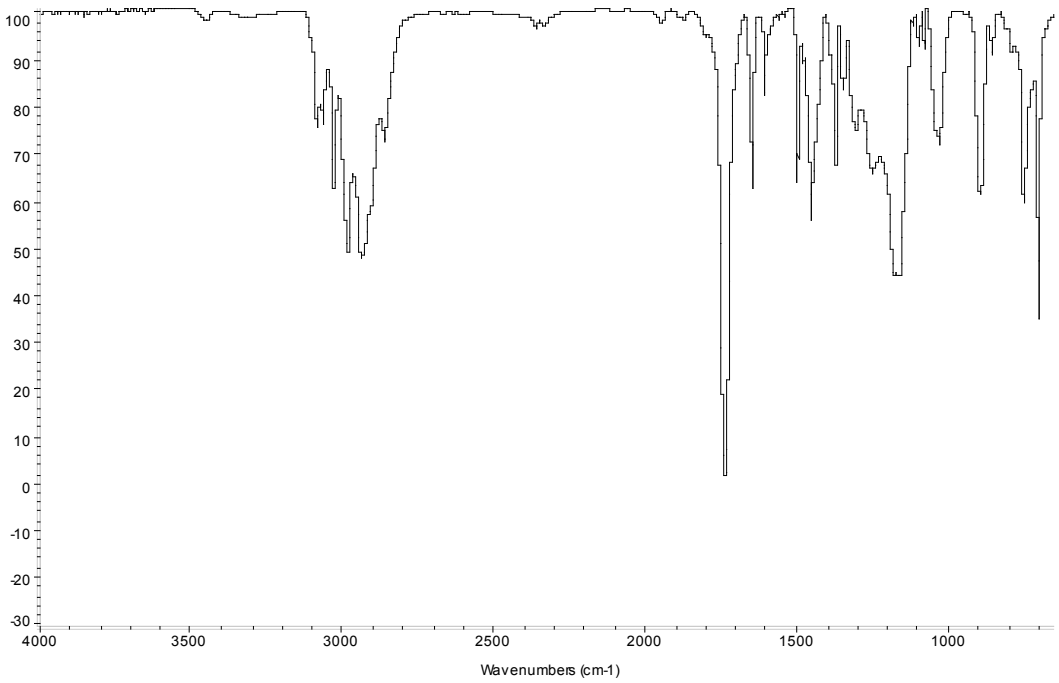


Figure A2.20 Infrared Spectrum (thin film/NaCl) of compound **89**

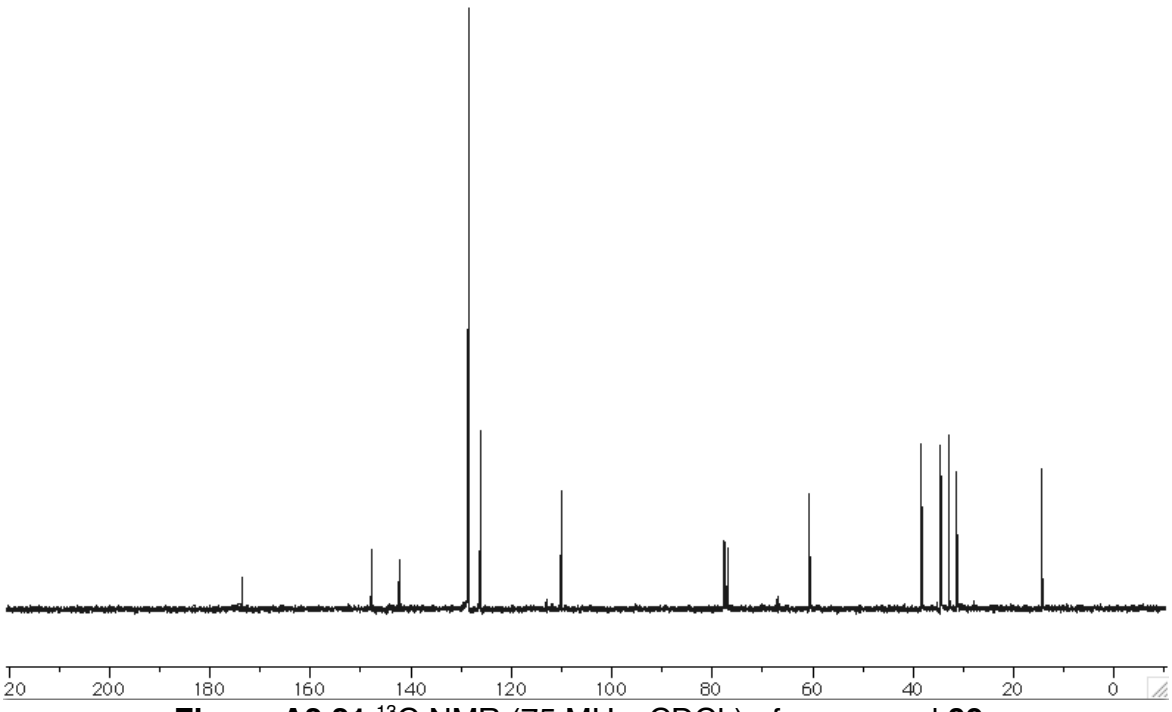


Figure A2.21 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **89**

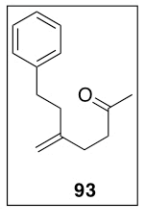
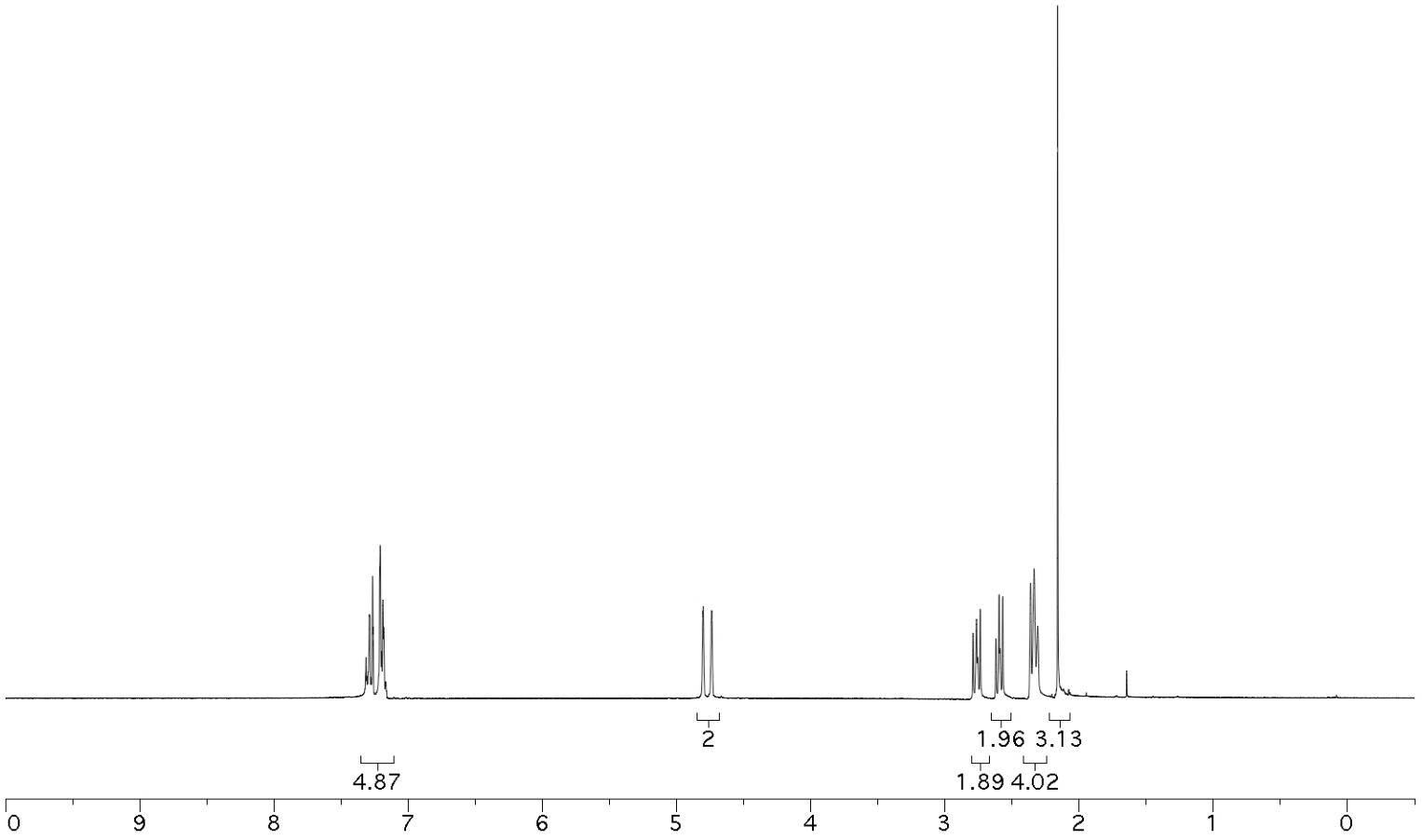


Figure A.2.22 1H NMR (300MHz, $CDCl_3$) of compound 93



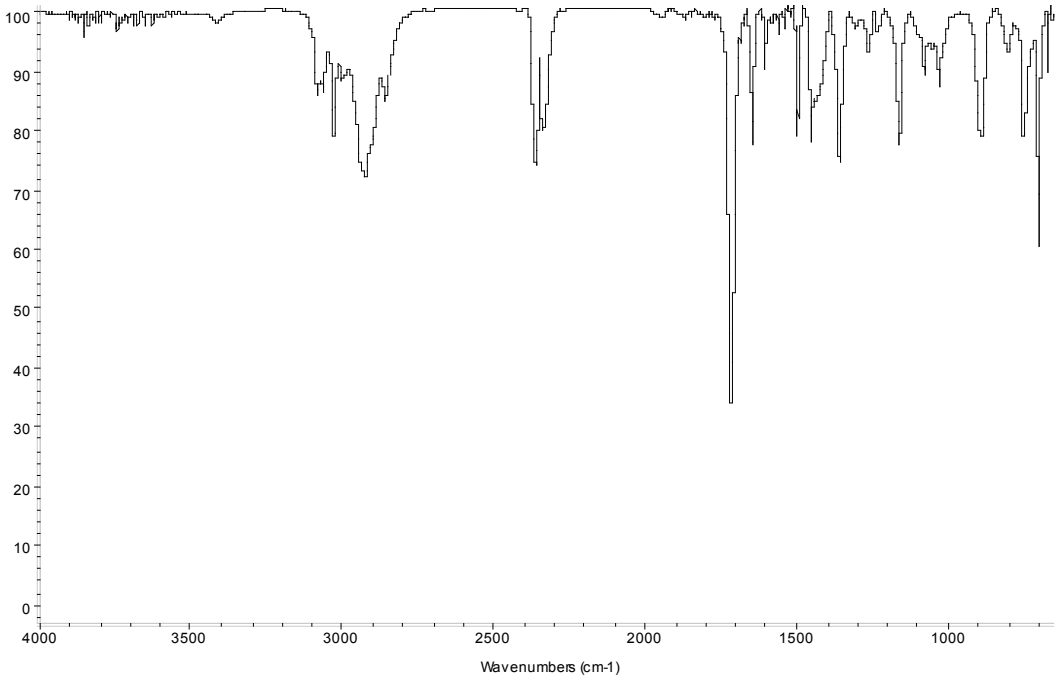


Figure A2.23 Infrared Spectrum (thin film/NaCl) of compound **93**

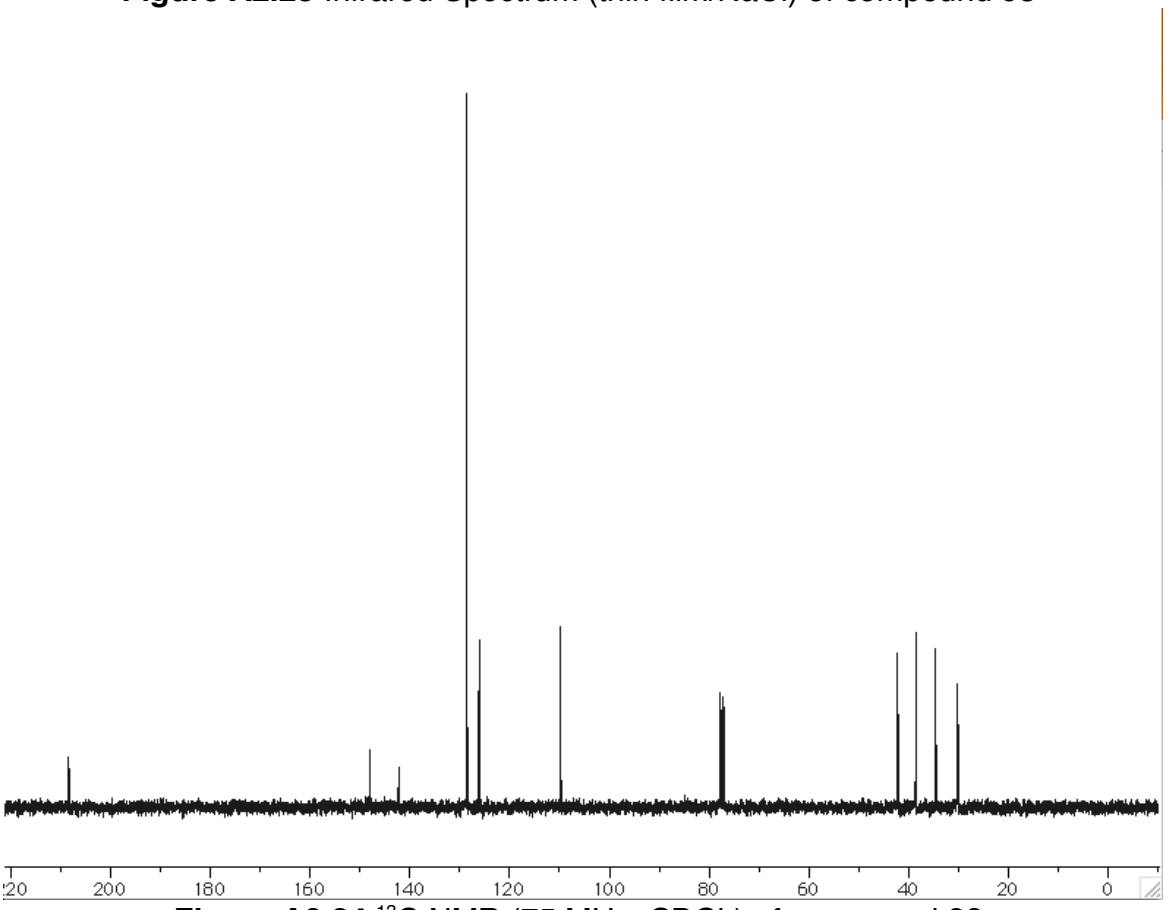
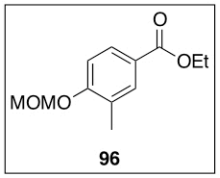
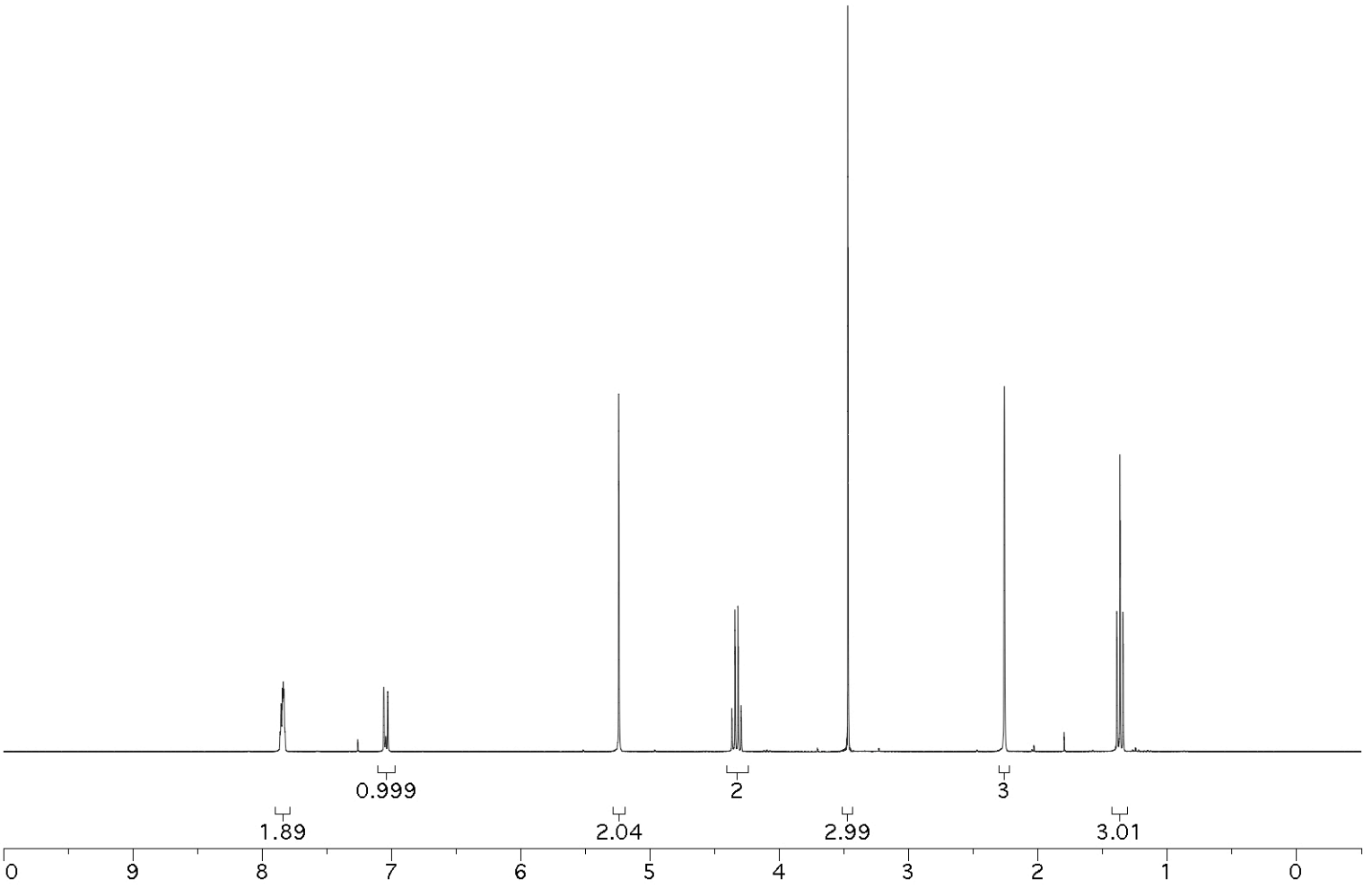


Figure A2.24 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **93**



96

Figure A.2.25 1H NMR (300MHz, $CDCl_3$) of compound 96



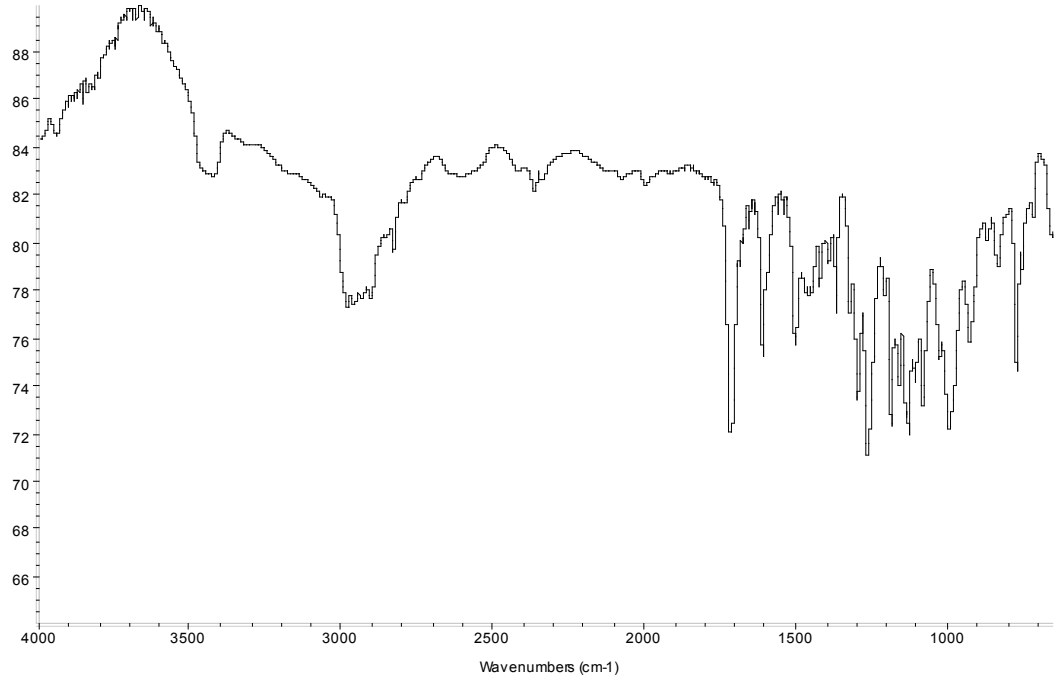


Figure A2.26 Infrared Spectrum (thin film/NaCl) of compound **96**

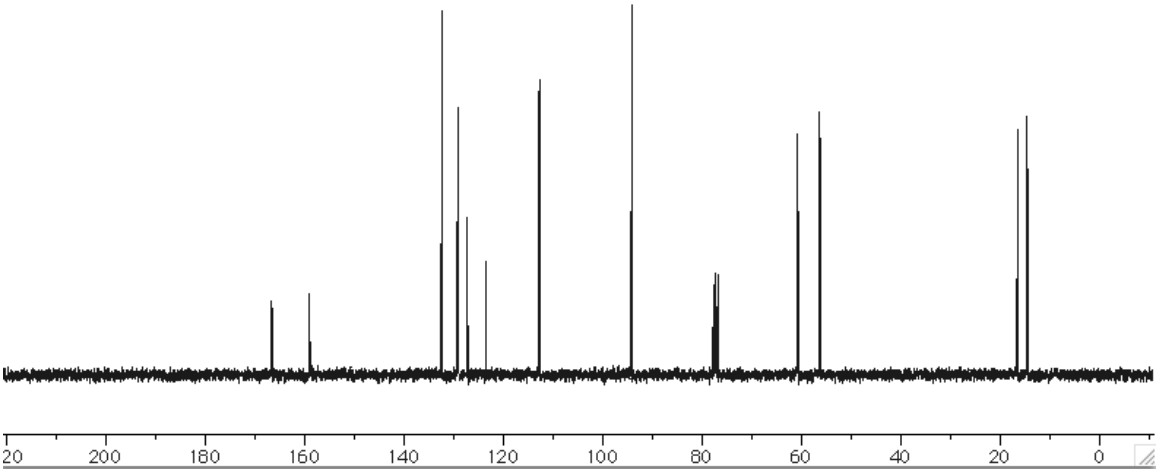
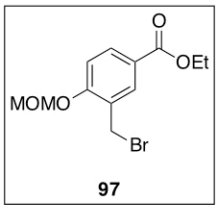
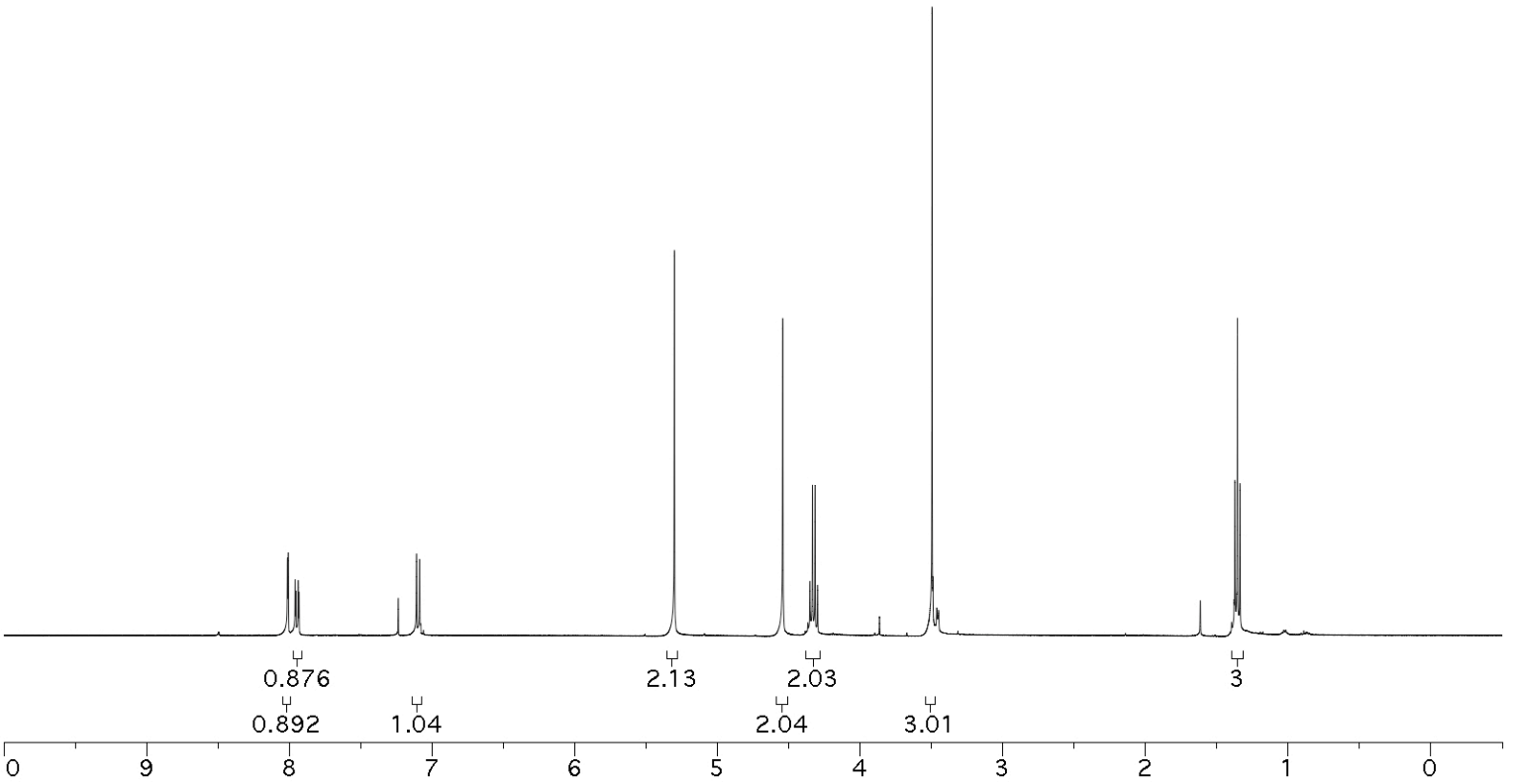


Figure A2.27 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **96**



97

Figure A.2.28 1H NMR (400MHz, $CDCl_3$) of compound 97



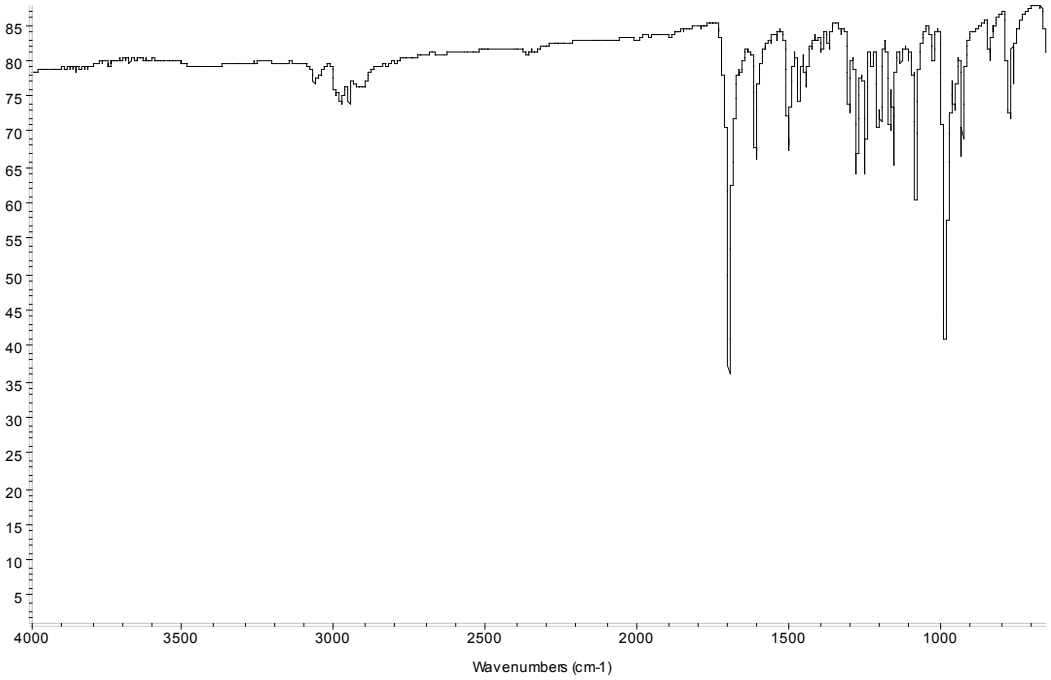


Figure A2.29 Infrared Spectrum (thin film/NaCl) of compound **97**

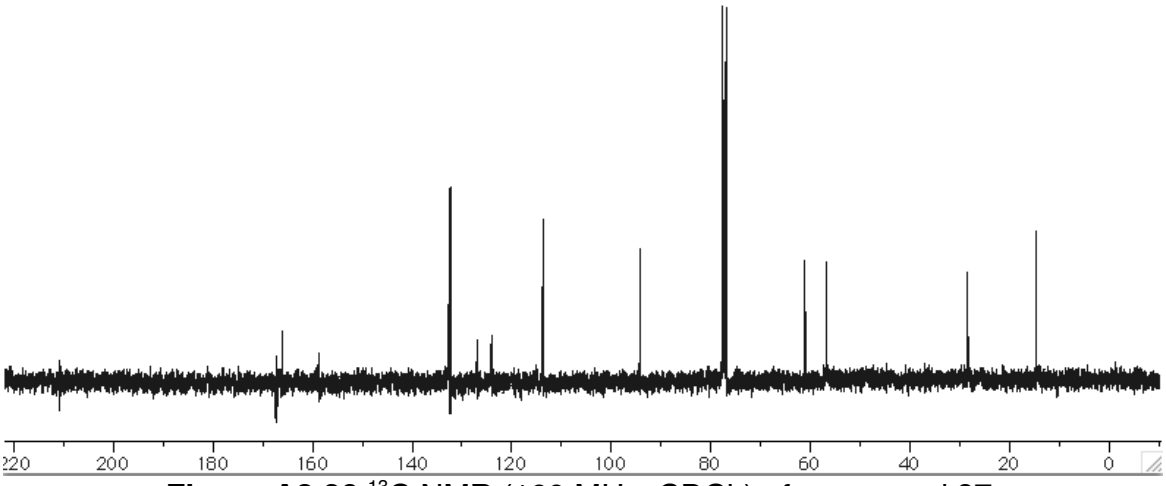
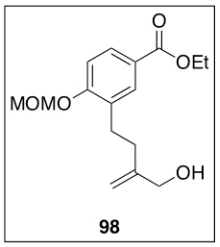


Figure A2.30 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **97**



98

Figure A.2.31 1H NMR (300MHz, $CDCl_3$) of compound 98

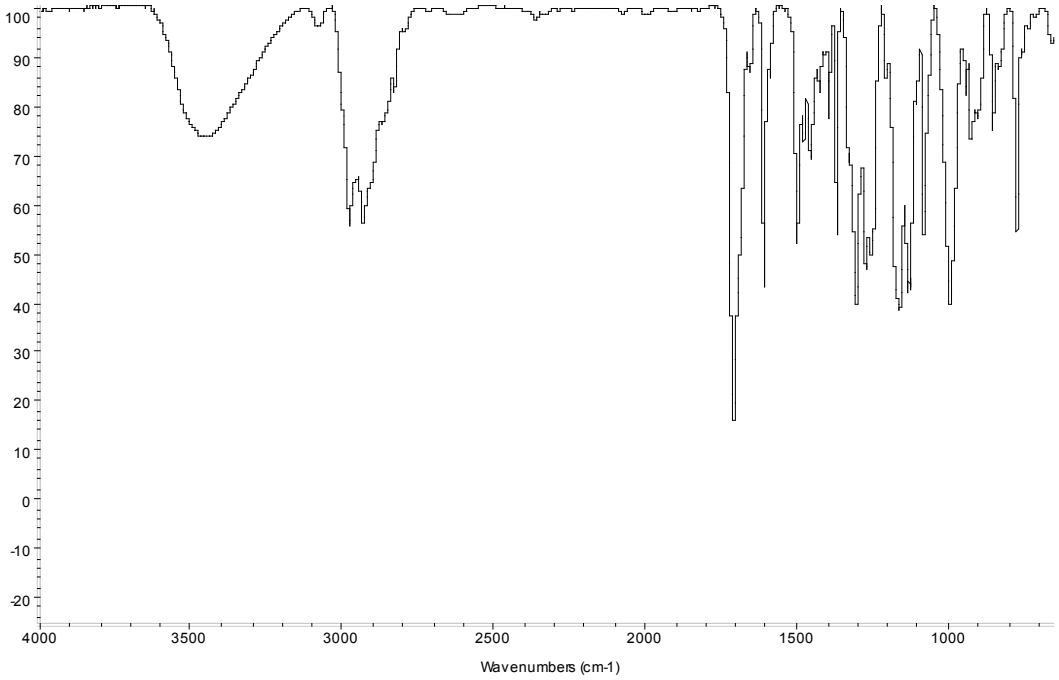


Figure A2.32 Infrared Spectrum (thin film/NaCl) of compound **98**

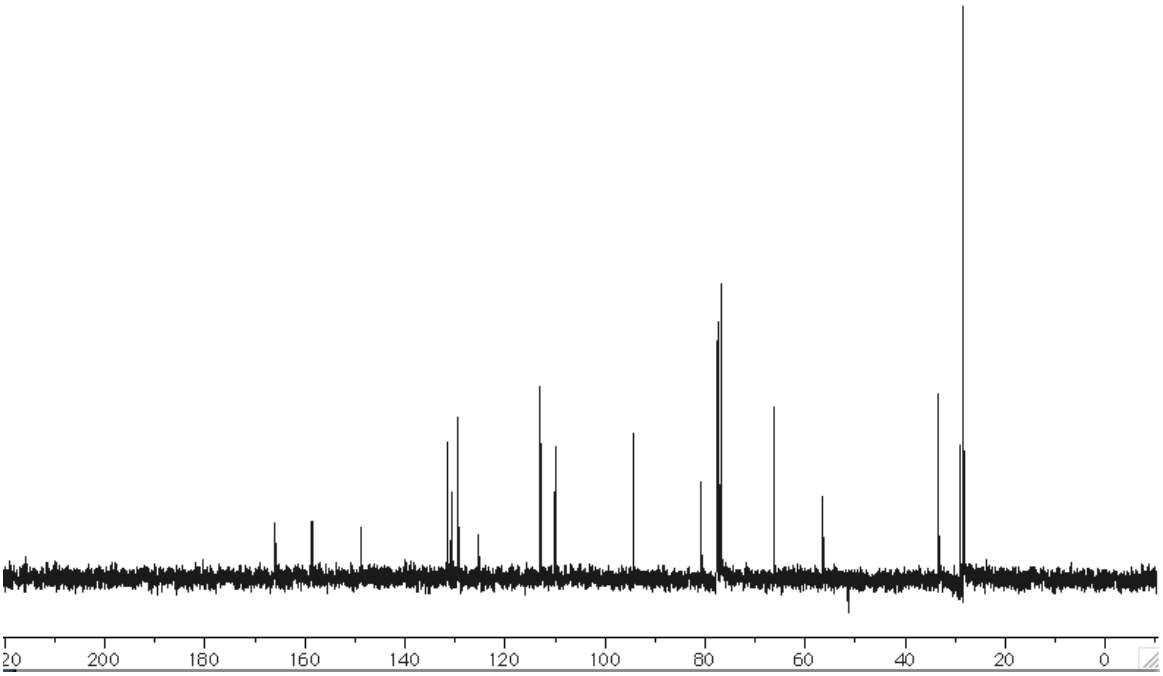
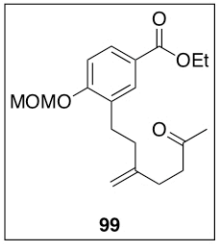
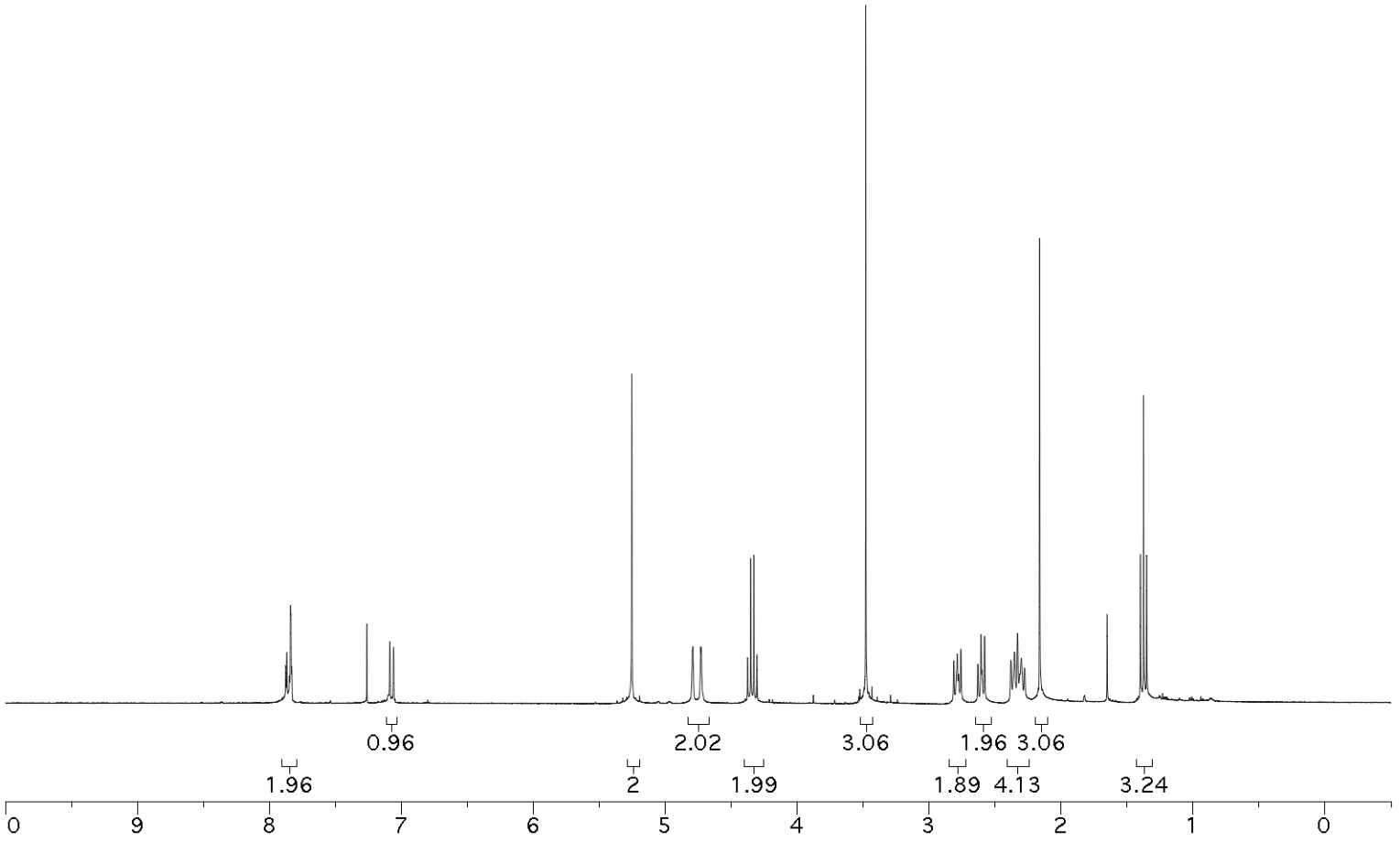


Figure A2.33 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **98**



99

Figure A.2.34 1H NMR (300MHz, $CDCl_3$) of compound 99



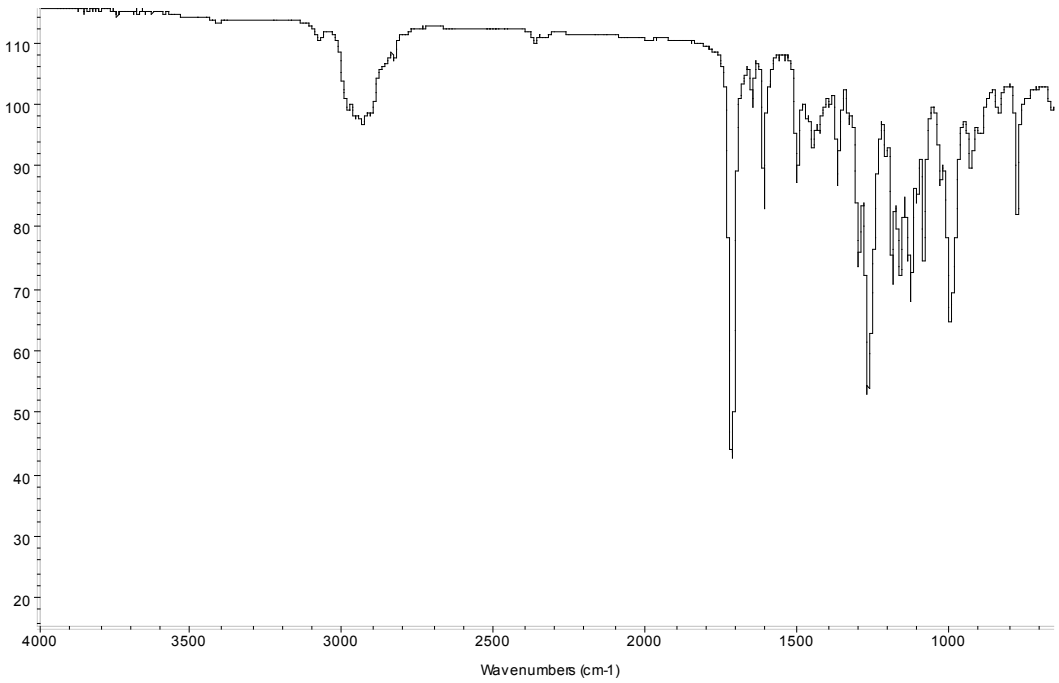


Figure A2.35 Infrared Spectrum (thin film/NaCl) of compound **99**

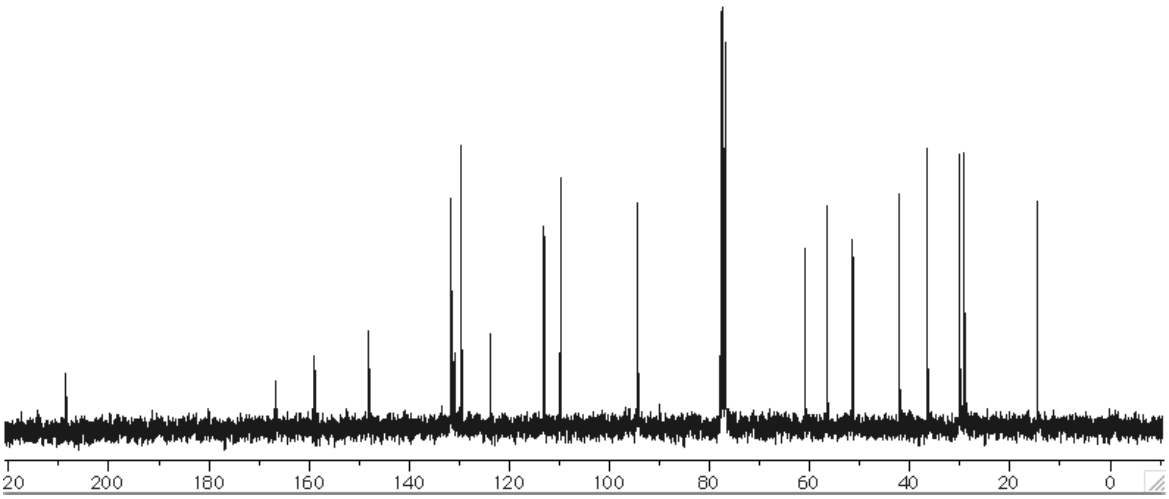
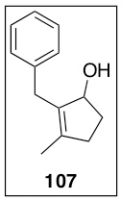
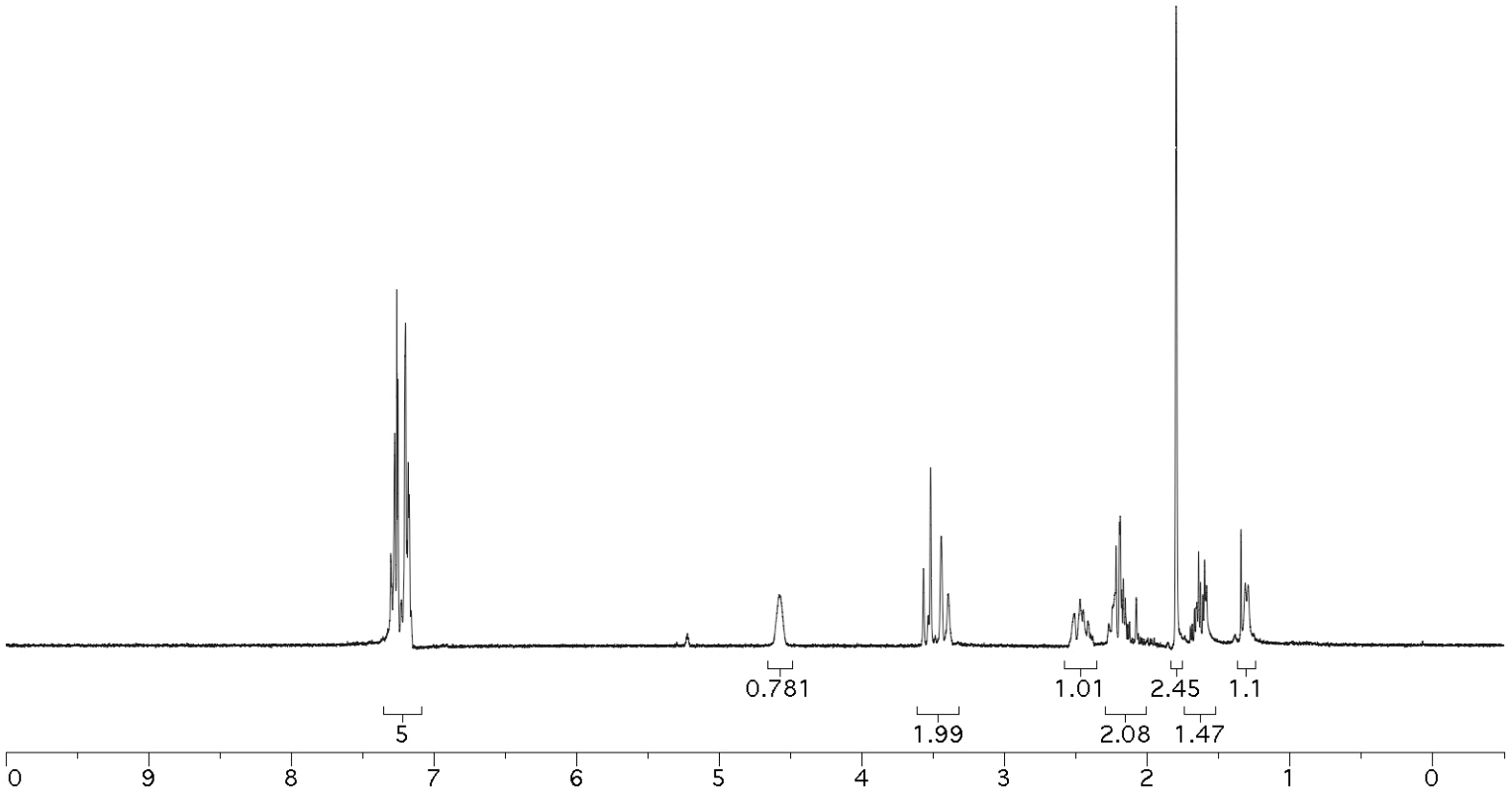


Figure A2.36 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **99**



107

Figure A.2.37 1H NMR (300MHz, $CDCl_3$) of compound 107



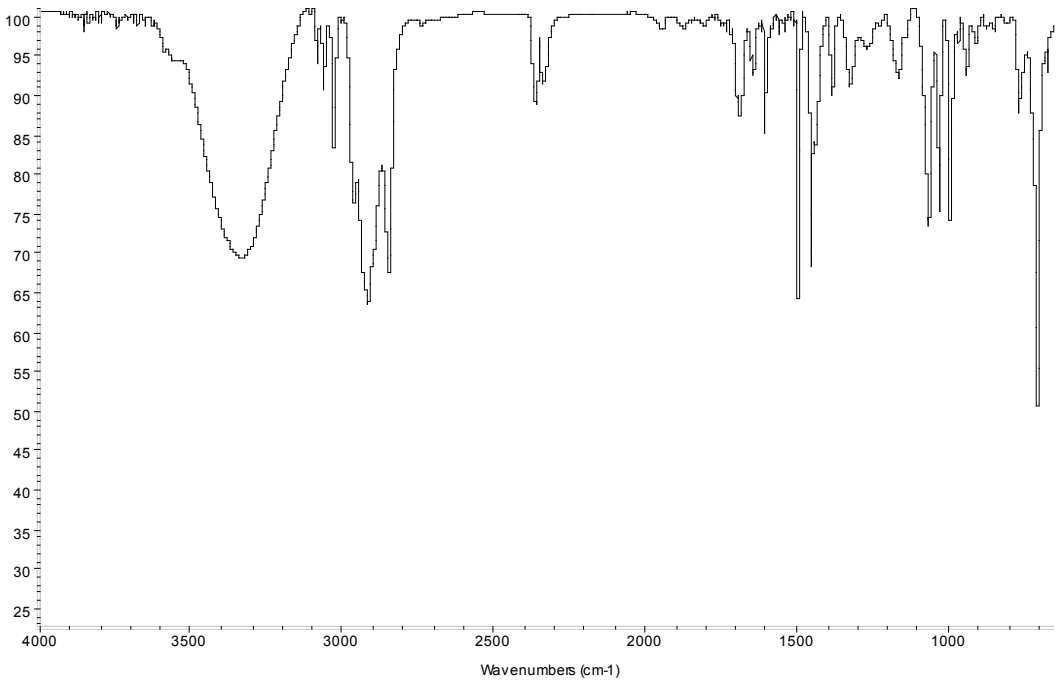


Figure A2.38 Infrared Spectrum (thin film/NaCl) of compound **107**

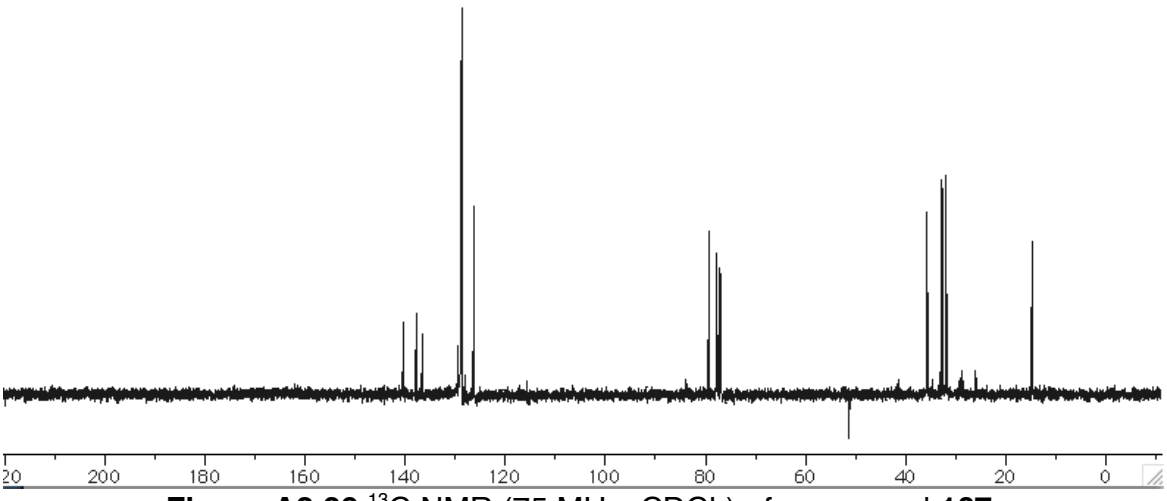
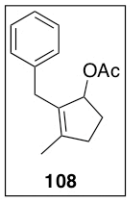


Figure A2.39 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **107**



108

Figure A.2.40 1H NMR (300MHz, $CDCl_3$) of compound 108

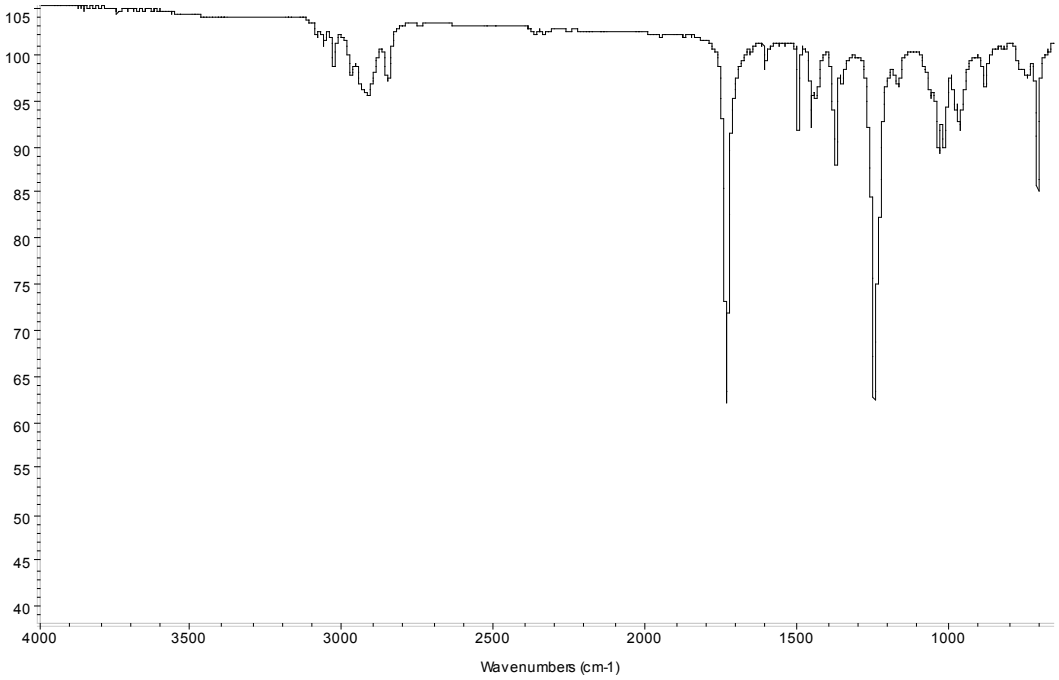


Figure A2.41 Infrared Spectrum (thin film/NaCl) of compound **108**

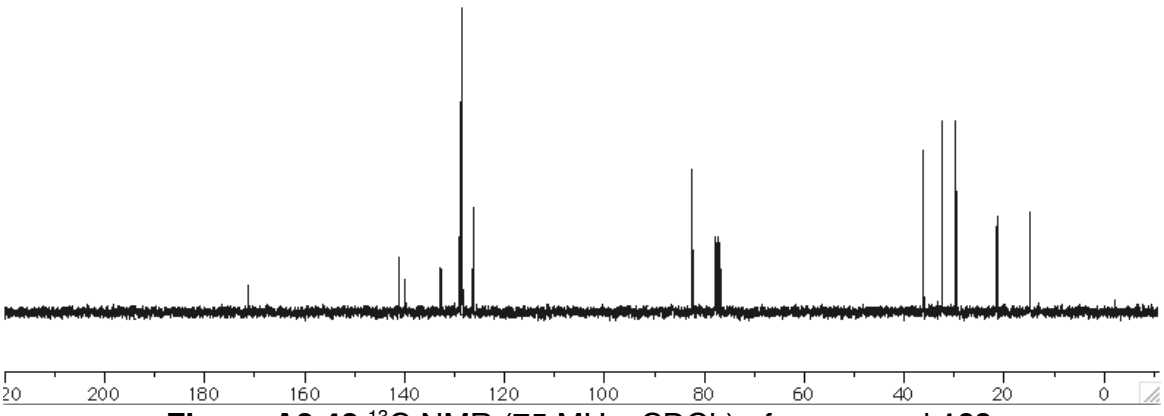
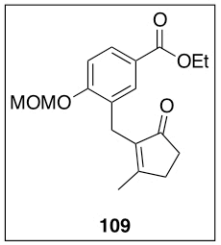
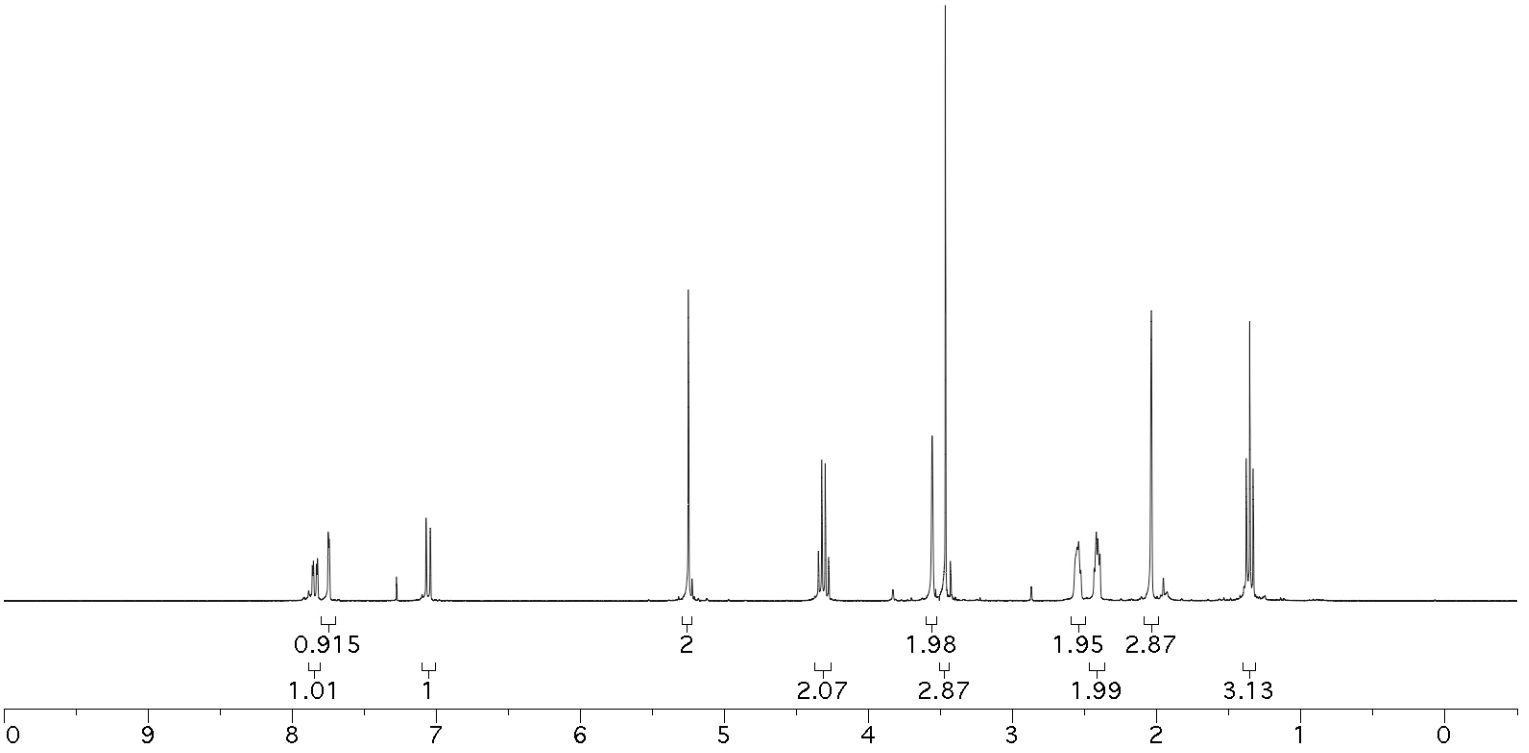


Figure A2.42 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **108**



109

Figure A.2.43 1H NMR (300MHz, $CDCl_3$) of compound 109



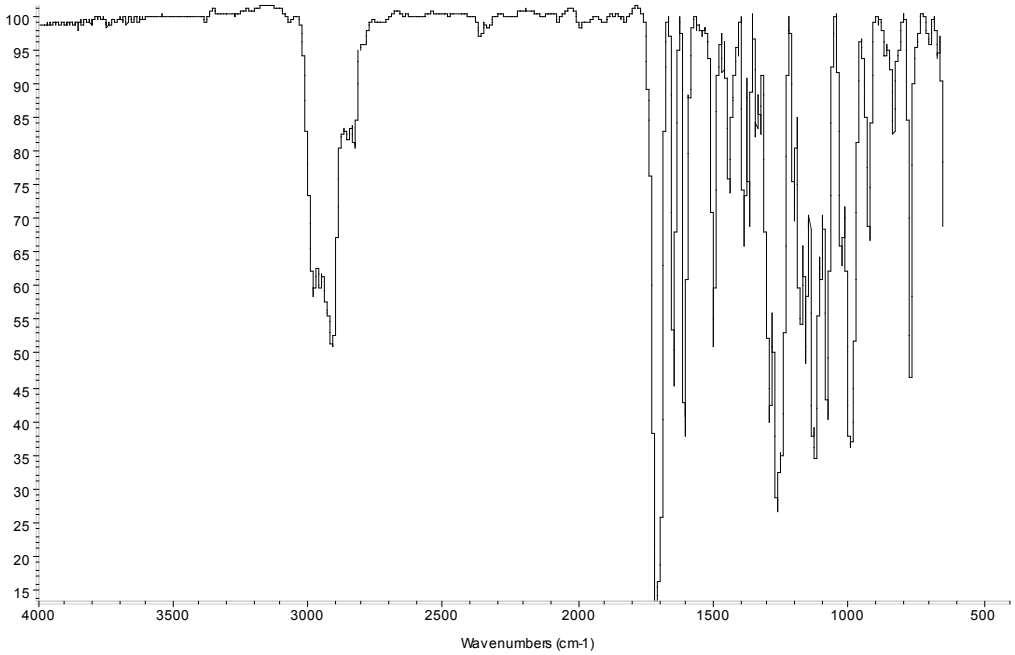


Figure A2.44 Infrared Spectrum (thin film/NaCl) of compound **109**

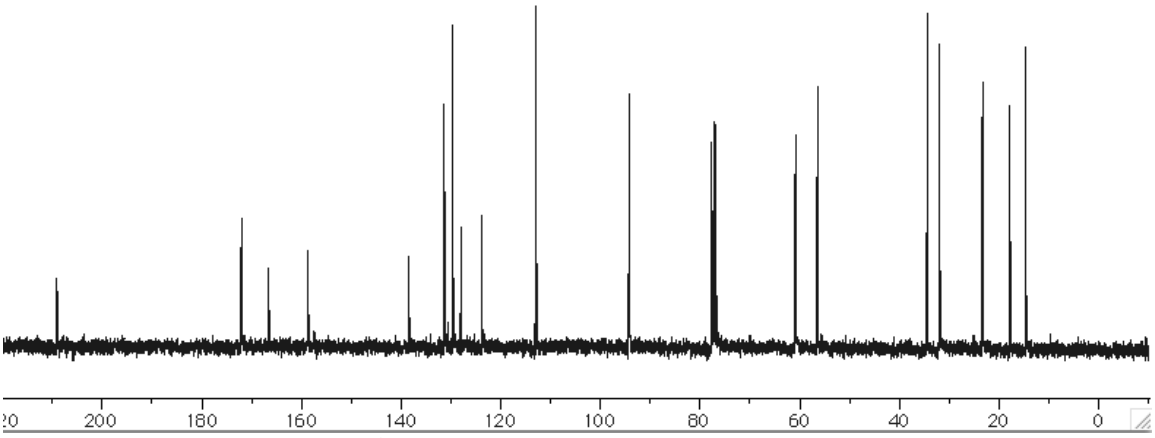
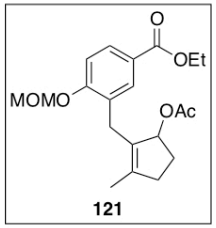
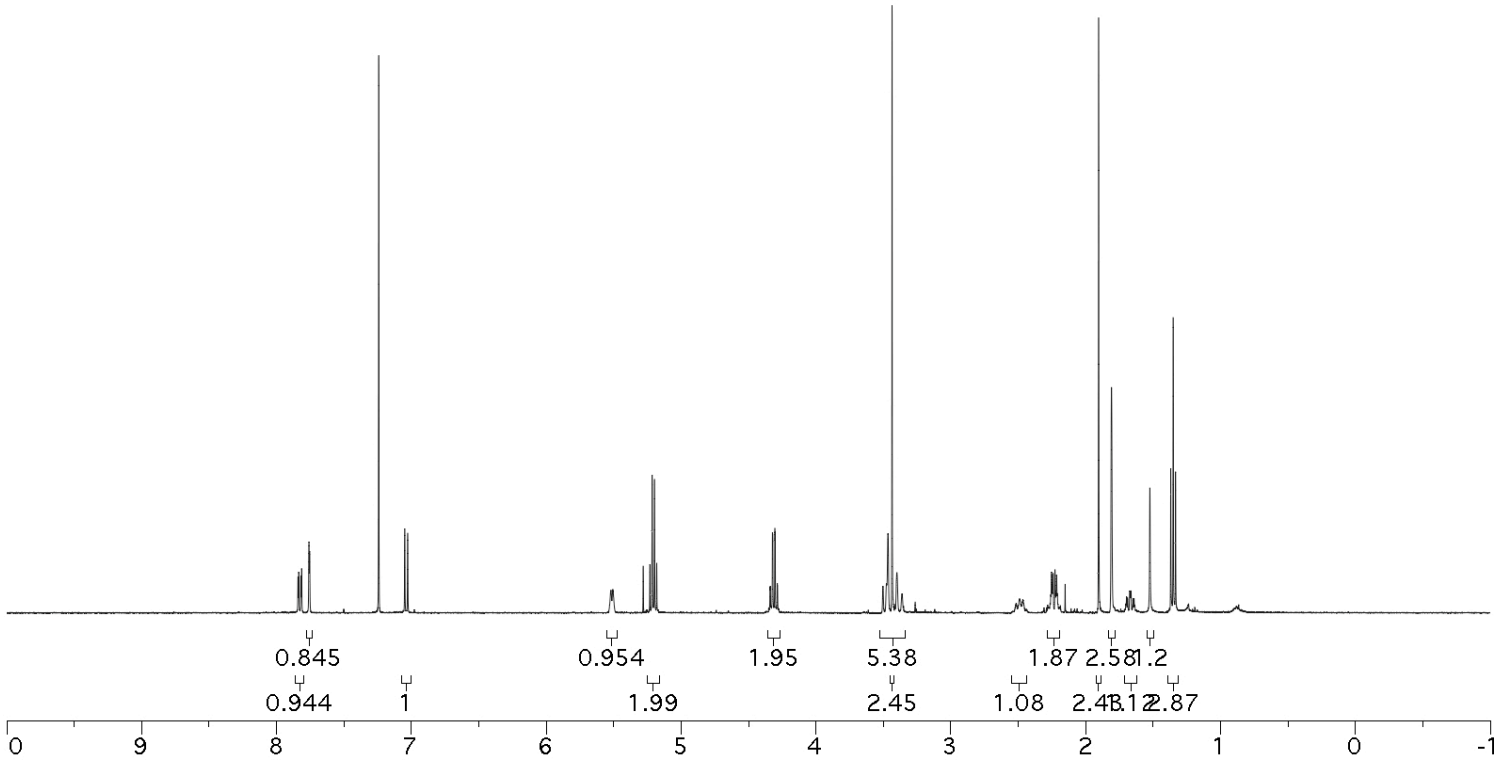


Figure A2.45 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **109**



121

Figure A.2.46 1H NMR (400MHz, $CDCl_3$) of compound 121



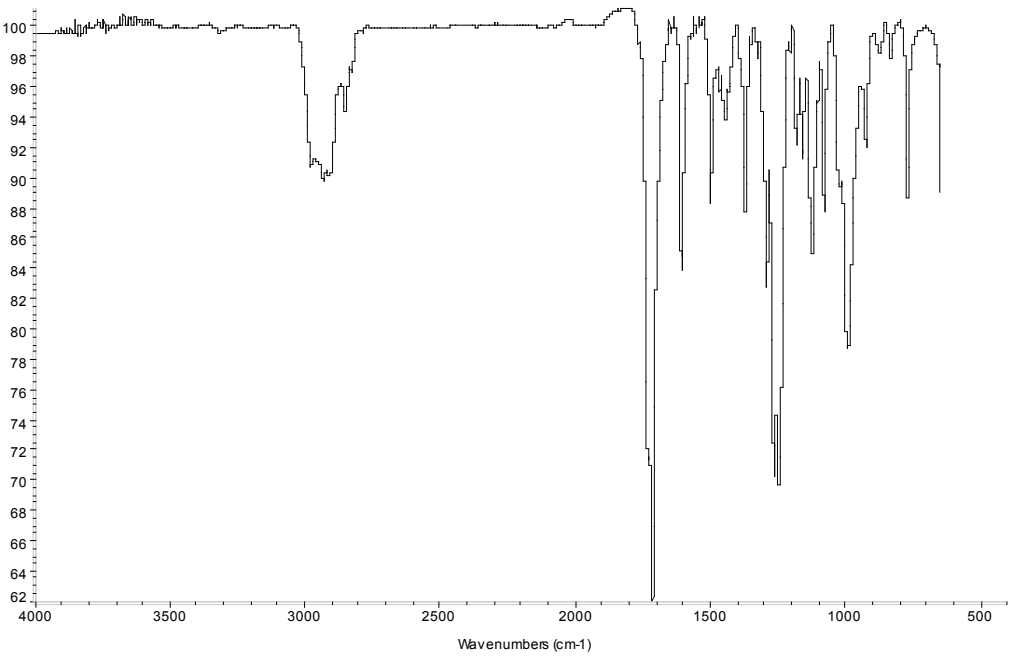


Figure A2.47 Infrared Spectrum (thin film/NaCl) of compound **121**

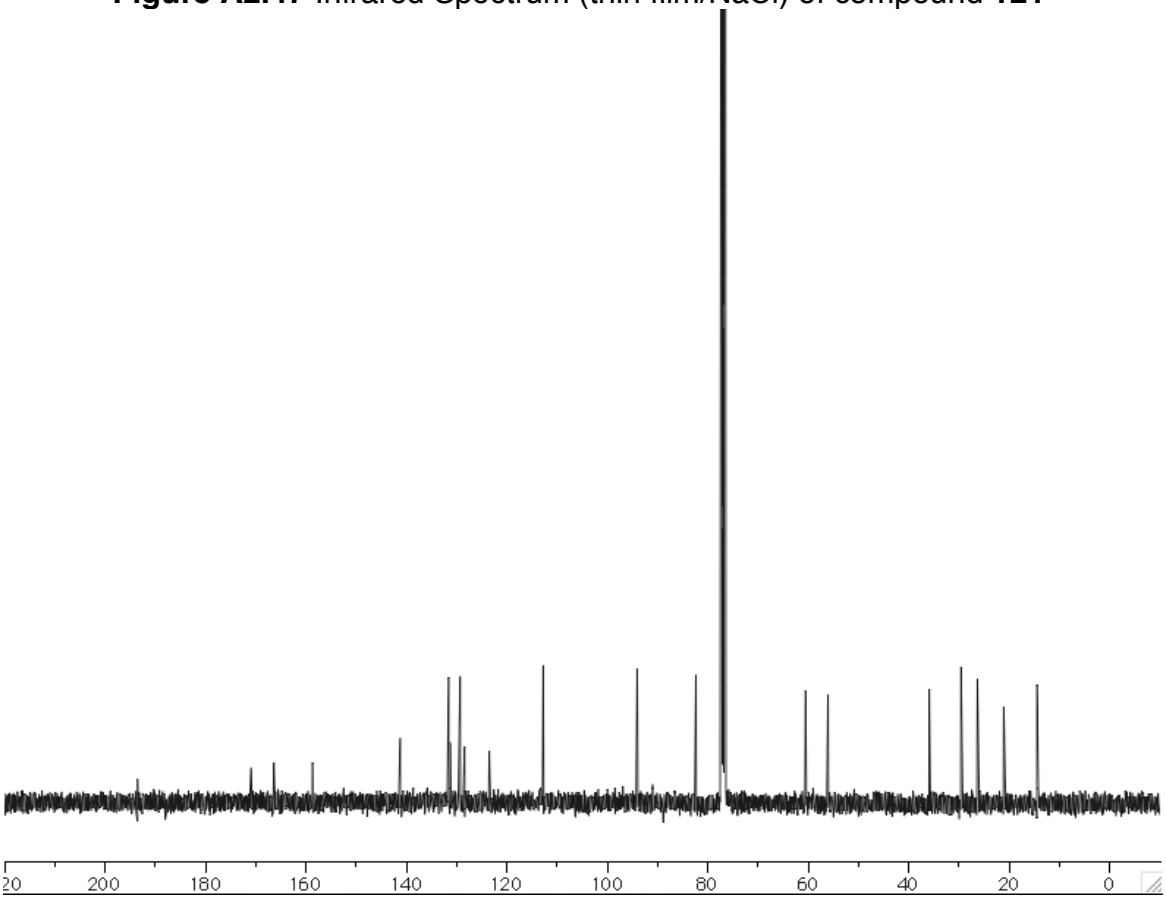


Figure A2.48 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **121**

Chapter 3

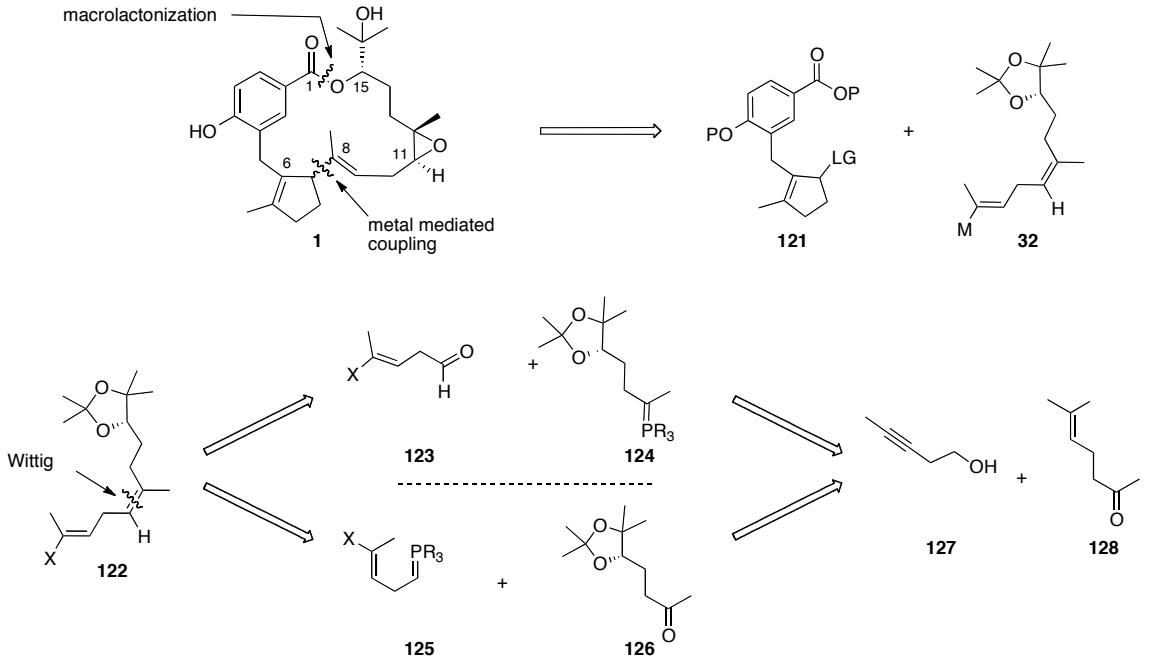
Synthetic Efforts Towards the C8-C14 Portion of Debromophycolide

3.1 – Heptane Functionalization

As detailed in Chapter 2, we envisioned constructing debromophycolide from benzoate **121** and organometallic species **32** via transition metal mediated coupling and macrolactonization (Scheme 1). This chapter describes progress towards **32**/**122**.

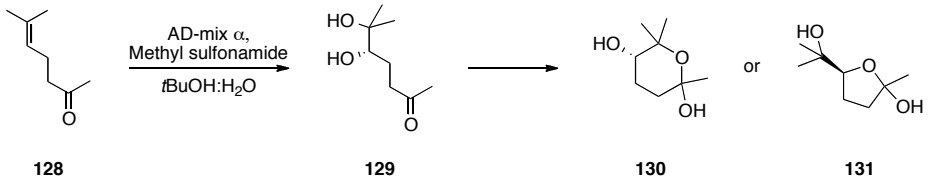
As illustrated, **122** was expected to derive from a Wittig reaction via one of two possible pathways.[1] Although, *E*/*Z*-olefin selectivity is an issue, the olefin geometry is ultimately manifest in the stereochemistry of a derived epoxide and given the potential of accessing the desired epoxide stereochemistry from either olefin isomer, we delayed concern over this issue. Compounds **123** and **125** were projected to arise from homopropargylic alcohol **127**, and intermediates **124** and **126** were seen as accessible from heptenone **128**.

Scheme 1 - Retrosynthetic Analysis for Debromophycolide



Our efforts towards the C8-C14 fragment focused initially on assembling acetonide **126** via the construction of vicinal diol **129**. To this end, trisubstituted olefin **128** was successfully subjected to Sharpless Asymmetric Dihydroxylation conditions;[2] however, the resultant diol **129** spontaneously cyclized to afford the two hemi-acetals **130** and **131** an equilibrating mixture (Scheme 2).[3]

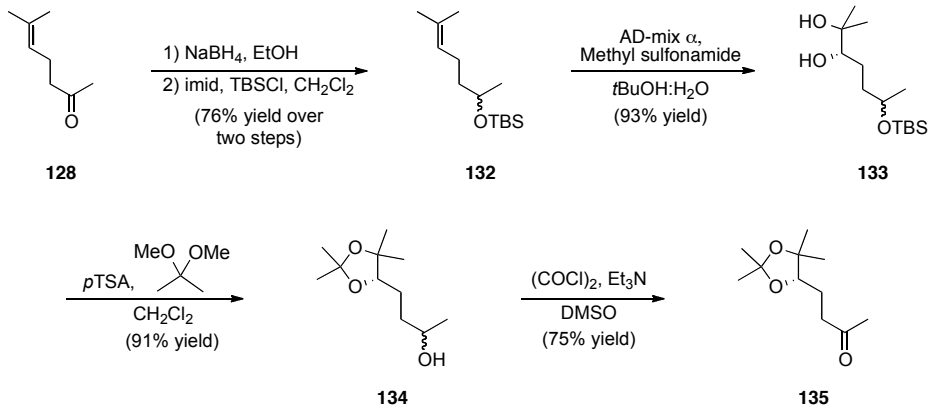
Scheme 2 – Attempted Dihydroxylation to Access Vicinal Diol 129



To avoid hemi-acetal formation, carbonyl protection was required. In this regard, one possibility would be reduction of the carbonyl and protection of the resultant alcohol

(Scheme 3). Toward this end, heptenone **128** was reduced with sodium borohydride and protected as the known TBS ether **132**.[4] A Sharpless Asymmetric Dihydroxylation reaction of the derived racemic mixture (**132**) was successful in delivering vicinal diol **133**,[2] which in turn was protected to furnish an inseparable mixture of diastereomeric acetonides, which due to concomitant cleavage of the silyl ether under the acidic conditions were isolated as the corresponding alcohol **134**. Swern oxidation[5] conditions were then utilized to oxidize alcohol **134** to known ketone **135**.[6]

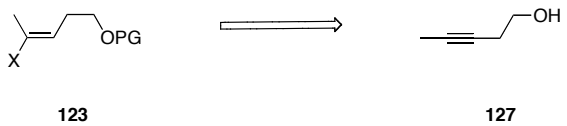
Scheme 3 – Functionalization of Hepten-one



3.2 – Synthetic Efforts Towards Organometallic Species

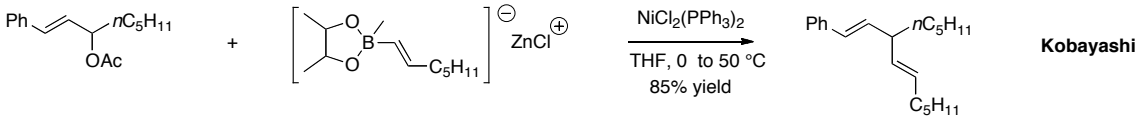
At this time our focus shifted to the synthesis of a vinyl organometallic species such as **123** for coupling to the C1/C7 fragment (Scheme 4).

Scheme 4 – Retrosynthetic Analysis: Organometallic Development



In accord with the retrosynthetic analysis illustrated in Scheme 1 (*vide supra*), this organometallic species was envisioned as the substrate in a transition metal mediated π-allyl coupling reaction. Inspiration for the formation of the C7/C8 bond via this type of allylic substitution came from a report by Kobayashi wherein the alkylation of allylic acetate **136** with zinc borate **137** was effected using nickel catalysis (Scheme 5).[7]

Scheme 5 – Kobayashi's Approach to a 1,4-Diene

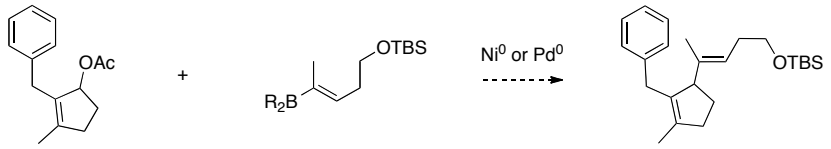


136 **137** **138**

3.2.1 – Attempted Hydroboration

In order to parallel Kobayashi's precedent for generating skipped dienes, we decided to explore a similar cross coupling reaction between allylic acetate **108** and vinyl borane **139** as a model of the actual system (cf., **121**/**32** Scheme 1 to **108**/**139** Scheme 6).[7]

Scheme 6 – Skipped Diene Coupling Reaction Model

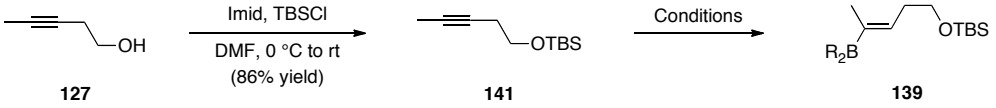


108 **139** **149**

Preparation of the substrates for the model reaction began with protection of homopropargylic alcohol **127** as TBS ether **141**. However, attempts to access the vinyl

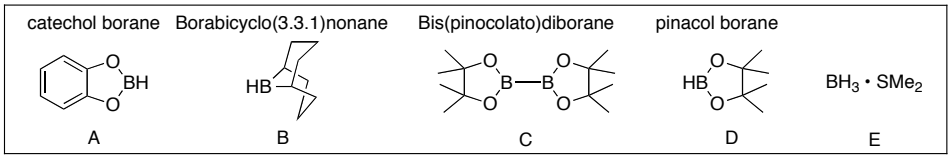
borane met with some difficulty; thus, hydroboration via exposure of alkyne **141** to catecholborane alone at 70 °C or in the presence of KHF_2 at room temperature only resulted in the recovery of starting material (Entries 1 and 2, Table 1).[8] Catecholborane with a catalytic amount of borabicyclo(3.3.1)nonane was also heated to 70 °C without observing any vinyl borane (Entry 3).[9] An Effort to effect a diboration by exposing **141** to bis(pinocolato)diborane treated with CuCl and NaO*t*Bu was also unsuccessful (Entry 4).[10] Pinacol borane was examined in the presence of Schwartz reagent; this also resulted only in recovery of starting material (Entry 5).[11] Heating **141** to 80 °C in the presence of pinacol borane resulted in decomposition along with a small amount of recollected alkyne (Entry 6).[12] The first success towards alkyne functionalization came with the use of triphenylphosphine rhodium (I) chloride or carbonyl triphenylphosphine rhodium(I) hydride and pinacol borane. Both conditions yielded vinyl borane products (e.g., **139**); however, the production of multiple regioisomers made purification difficult (Entry 7 and 8).[13] Borane dimethyl sulfide was also examined without success (Entry 9).[14] Thus, due to the inability to convert alkyne **141** efficiently to the desired hydroboration product, alternate strategies were explored.

Table 1 – Attempted Hydroboration Conditions



127 **141** **139**

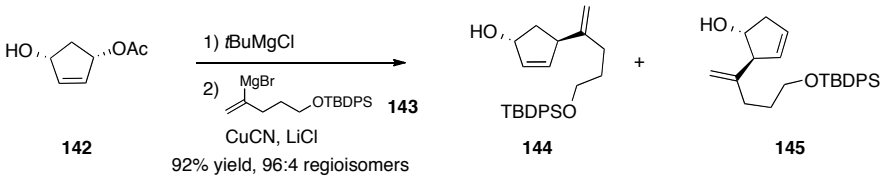
Entry	Borane	Catalyst	Additives	Solvent	Result
1	A	-----	-----	neat, 70 °C	SM
2	A	-----	$KHF_{2(aq)}$	neat	SM
3	A, B_{cat}	-----	-----	neat, 70 °C	SM
4	C	CuCl	NaO*t*Bu, MeOH	THF	SM
5	D	$ZrCp_2ClH$	-----	DCM, 0 to 30 °C	SM
6	D	-----	-----	THF, 80 °C	degradation
7	D	$Rh(PPh_3)(CO)H$	-----	DCM	complex mixture
8	D	$Rh(PPH_3)_3Cl$	-----	DCM	complex mixture
9	E	-----	$KHF_{2(aq)}$	DCM	SM



3.2.2 – Vinyl Halide

In addition to nickel mediated protocols, Kobayashi has demonstrated the substitution of allylic acetates with Grignard reagents in the presence of CuCN (Scheme 7). A relevant example demonstrates the coupling of allylic alcohol **142** with vinyl magnesium bromide **143** in the presence of a CuCN and LiCl to furnish the desired cross-coupled material **144** accompanied by a small amount of regioisomer **145** (Scheme 7).[15]

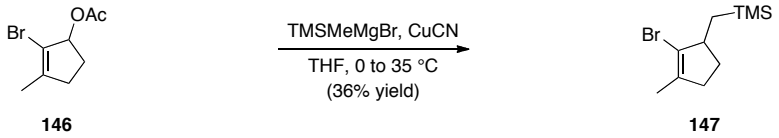
Scheme 7 – Kobayashi's Allylic Acetate Displacement Reaction



142 **144** **145**

With this reactivity in mind, we explored the coupling of cyclopentenyl acetate **146** with $TMSCH_2MgBr$ in the presence of CuCN and LiCl (Scheme 8). Under these conditions cross-coupling resulted in the formation of cyclopentene **147**, albeit in somewhat low yield.

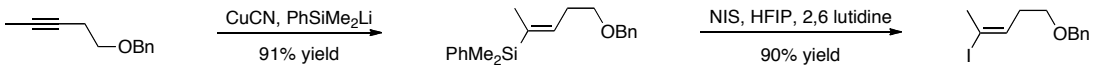
Scheme 8 – Allylic Acetate Displacement Model



146 **147**

Having established our ability to effect the substitution of an allylic acetate, we turned next to the preparation of an appropriate vinyl iodide and corresponding Grignard reagent. To this end, we followed a method described by Zakarian, wherein alkyne **148** was hydrosilylated to produce vinyl silane **149** (scheme 9). Vinyl silane **149** was then converted to vinyl iodide **150** by exposure to NIS in the presence of 2,6-lutidene in HFIP.[16]

Scheme 9 – Formation of Vinyl Iodide from Alkyne 148

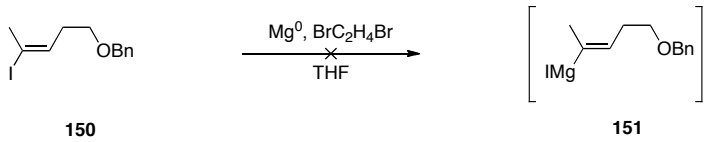


148 **149** **150**

With iodide **150** in hand, we investigated the formation of vinyl magnesium iodide **151** (Scheme 10). Unfortunately, all attempts were unsuccessful. This result, coupled with the low yield of the substitution reaction in the model system, encouraged

us to search for an alternate coupling partner for the formation of the skipped diene functionality.

Scheme 10 – Preparation of Vinyl Magnesium Iodide Intermediate

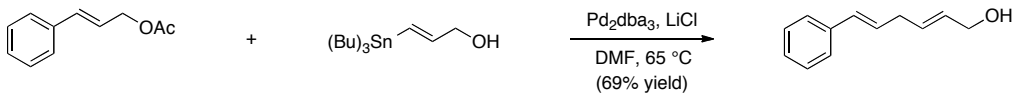


150 **151**

3.2.3 – Vinyl Stannane

The utility of palladium catalysts to form π-allyl complexes with allylic acetates is well documented.[17-19] As substitution generally occurs at the less hindered terminus of the π-allyl species, this method seemed ideal for our system. In an example from the Hegedus group, the coupling of allylic acetate **152** with vinyl stannane **153**, mediated by a palladium(0) catalyst and LiCl, afforded skipped diene **154** in good yield (Scheme 11).[17]

Scheme 11 – A Relevant Stille Coupling

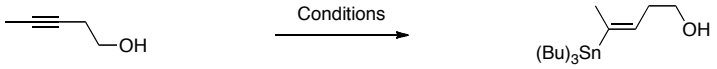


152 **153** **154**

To apply this chemistry to our system we pursued the construction of a suitable vinyl stannane. A study reported by Pancrazzi inspired us to investigate the hydrostannylation of alkyne **127** (Table 2).[20] Our initial attempt to produce known vinyl stannane **155**[21] from homopropargylic alcohol **127** utilizing Wilkinson's catalyst and

tributyltin hydride resulted in a low yield of the desired product (Entry 1). The use of a palladium(II) catalyst with tributyltin hydride gave moderate yields of hydrostannylation products as a 1:1 mixture of regioisomers, which proved difficult to separate (Entry 2). Higher order cuprates in conjunction with tributyltin hydride (Entries 3 and 4) or bis(tributyltin) (Entry 5) were screened with the latter providing vinyl stannane in acceptable yields.

Table 2 – Hydrostannylation Conditions

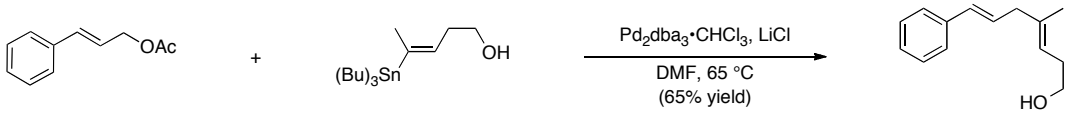


127 **155**

Entry	Additive	Tin Source	Solvent	Result
1	$Rh(P(Ph)_3)_3Cl$	Bu_3SnH	neat	7%
2	$Pd(P(Ph)_3)_2Cl_2$	Bu_3SnH	THF	55%, 1:1 regioisomers
3	CuCN, *n*BuLi, MeOH	Bu_3SnH	THF	10%
4	CuCN, MeLi, MeOH	Bu_3SnH	THF	11%
5	CuCN, *n*BuLi, MeOH	$(Bu_3Sn)_2$	THF	61%

To test the reactivity of the vinyl stannane **155**, we examined coupling reactions with cinnamyl acetate **152** as a model (Scheme 12). Gratifyingly, the reaction between vinyl stannane **155** and allylic acetate **152** with $Pd_2(dba)_3 \bullet CHCl_3$ in the presence of LiCl successfully afforded skipped diene **156**.[17]

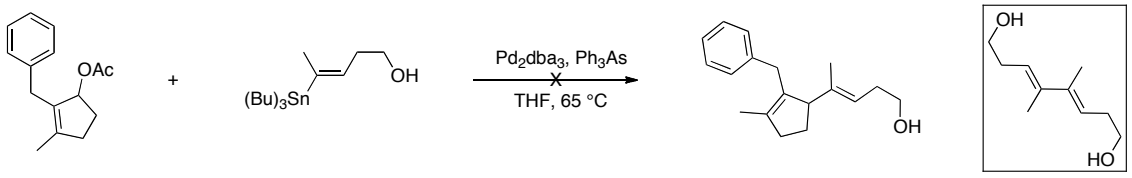
Scheme 12 – Stille Coupling



152 **155** **156**

Unfortunately, when applied to the coupling of allylic acetate **108** and vinyl stannane **155**, product **157** was not observed. Only homodimer **158** and unreacted allylic acetate **108** were isolated (Scheme 13). When the reaction conditions were repeated at 110 °C, allylic acetate **108** decomposed and no desired product was observed. Apparently oxidative addition of palladium into allylic acetate **108** is not favorable; thus, subsequent investigations focused on intermediates known to be more reactive than allylic acetates.

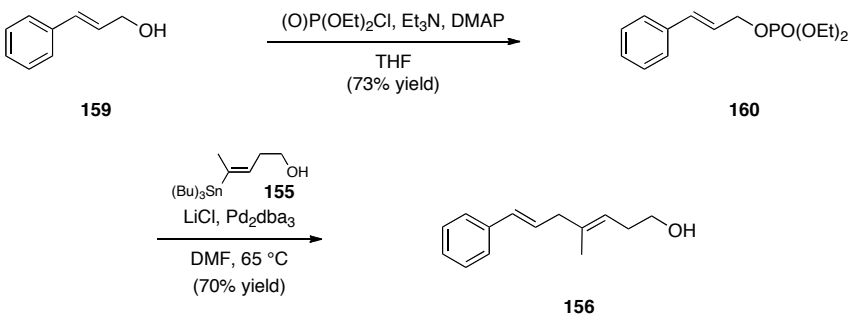
Scheme 13 – Results from Stille Coupling Reaction



108 **155** **157** **158**

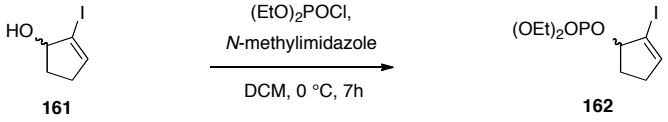
Both allylic carbonates and phosphonates have been reported to undergo metal catalyzed alkylations via π-allyl intermediates that form more readily in comparison to their acetate analogs.[22] As before, initial studies were performed with allylic alcohol **159** which was treated with diethyl chlorophosphite to produce model coupling partner **160** (Scheme 14).[23] Exposure of allylic phosphonate **160** to vinyl stannane **155** in the presence of $Pd_2(dba)_3$ and LiCl resulted in skipped diene **156** in good yield.

Scheme 14 – Allylic Phosphonate Stille Reaction



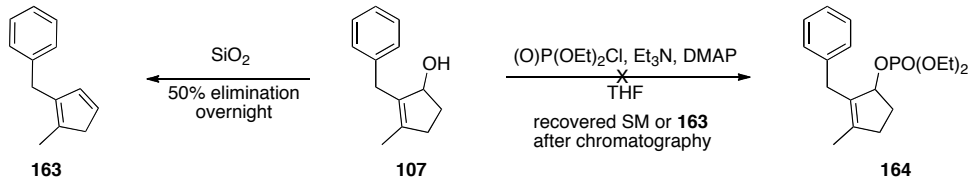
In turning to the preparation of a phosphonate more suited to the synthesis we were encouraged by a report from Knochel wherein cyclic allylic phosphate **162** was prepared in 76% yield from allylic alcohol **161** (Scheme 15).[24]

Scheme 15 – Knochel's Preparation of Allylic Cyclopentene Phosphonate



As illustrated in Scheme 16, attempts to repeat Knochel's chemistry on allylic alcohol **107** proved unsuccessful and the formation of diene **163** was observed.[25] Clearly the derived phosphonate is prone to elimination and attempts to isolate the phosphonate, under either neutral or basic conditions, resulted only in isolation of diene **163**. Additionally, efforts to carry the crude reaction mixture forward also failed to produce any desired product.

Scheme 16 – Formation of Diene Through an Elimination Pathway

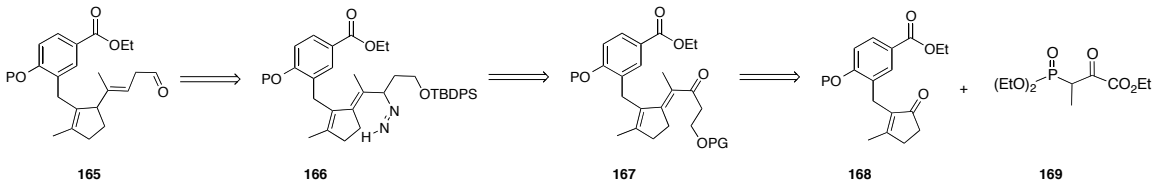


Although we could successfully couple vinyl stannane **155** to a model allylic acetate, the low reactivity of our desired allylic acetate and the instability of the allylic phosphonate prompted the exploration of a new synthetic route to form the skipped diene.

3.3 – Allylic Diazene Rearrangement

In considering other methods that have been reported for the preparation of skipped dienes we turned to an allylic diazene rearrangement.[26] As illustrated in Scheme 17, rearrangement of allylic diazene **166** would deliver aldehyde **165**. Diazene **166** was envisioned as being accessed from dienone **167**, which, in turn would result from a Horner-Wadsworth-Emmons reaction between cyclic enone **168** and phosphonopropionate **169**.

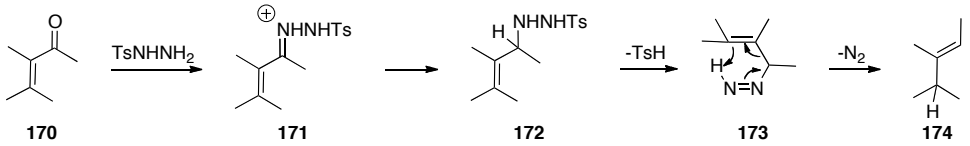
Scheme 17 – Retrosynthetic Analysis to Include a Diazene Rearrangement



Given a driving force that includes loss of nitrogen (Scheme 18), allylic diazene rearrangements have been used to a) obtain exocyclic double bonds from endocyclic

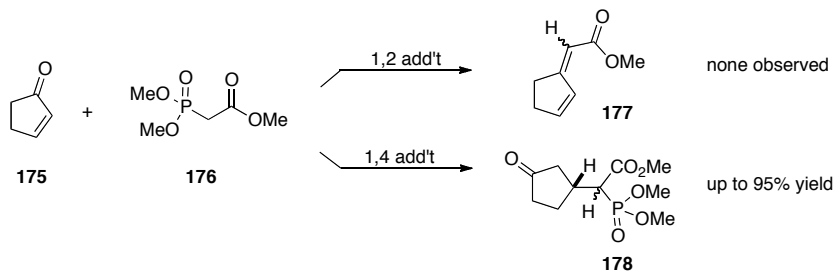
olefins, b) move conjugated systems out of conjugation, and c) construct *E*-alkenes.[26] The stage for these rearrangements is typically set by condensation of a sulfonylhydrazine with an α,β-unsaturated carbonyl (e.g., **170)** to produce a hydrazone (e.g., **171)**. Reduction with a hydride source (e.g., sodium cyanoborohydride) is coupled with loss of the sulfonyl moiety to furnish the allylic diazene (e.g., **173**). Once formed, the allylic diazene undergoes [1,5] sigmatropic rearrangement expelling nitrogen and effecting bond migration to the corresponding product (e.g., **174).**

Scheme 18 – Mechanism of Allylic Diazene Rearrangement



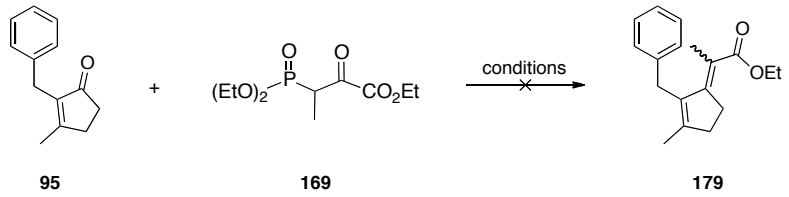
As illustrated in Scheme 19, our current retrosynthetic analysis calls for conversion of an α,β-unsaturated ketone the corresponding dienone via Wittig-type homologation. Although studies by Sasai on the addition of phosphonates to unhindered enones such as **175** show that the Michael type product **178** is favored over the 1,2 addition product **177**, the potential influence of the γ-methyl substituent in enone **95** (Scheme 20) on the regiochemistry of this addition led us to explore this addition experimentally (Scheme 19).[27]

Scheme 19 – Two Pathways for Addition of the Phosphonate Anion into Cyclopentenone



With the previously prepared substrate **95** in hand (Scheme 19, Chapter 2), the HWE reaction was explored using bases, including: NaH, KHMDS with 18-c-6, *n*BuLi with LiBr, NaH in MeOH, and LiBr with Et_3N, however, in all cases only starting material was recovered (Scheme 20).

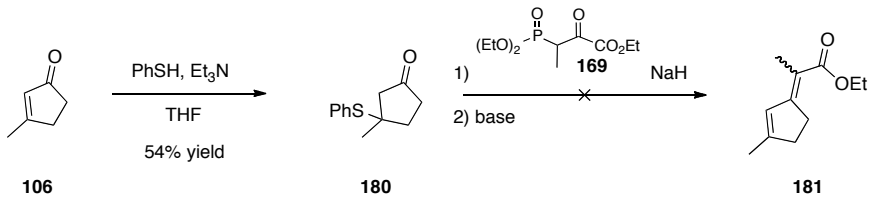
Scheme 20 – Attempts at 1,2 Phosphonate Addition



Speculating that our inability to effect the Wittig chemistry was the result of deleterious enolization we next investigated a substrate wherein the enone was masked via the addition of a thiol. It was speculated that the resultant thioether **180** might be less prone to enolization and were it to survive the reaction conditions would render the regioselectivity concerns of 1,2- vs. 1,4-addition, moot (Scheme 21).[28] Moreover, elimination of the thiol group could restore the olefin following a Horner-Wadsworth-

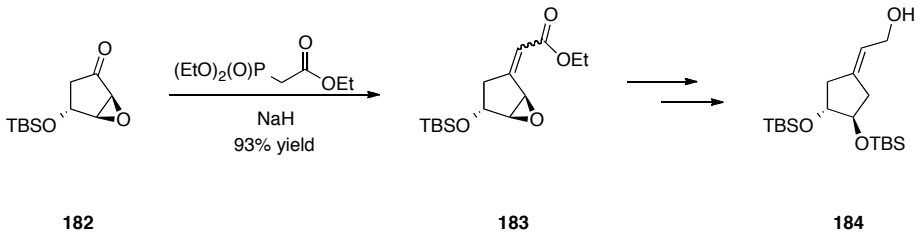
Emmons reaction. Unfortunately, **180** proved to be unstable and this notion was abandoned.

Scheme 21 – 1,4 Nucleophilic Addition into an Enone



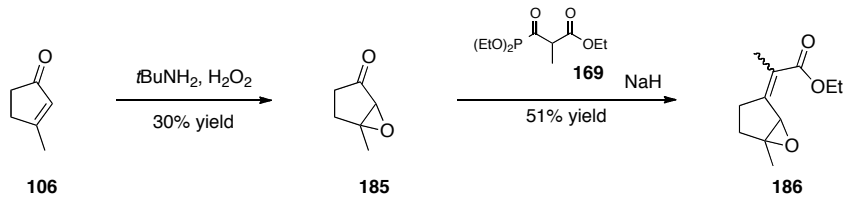
As an alternative to thiol protection of the enone, inspiration was drawn from a report by Posner which described the Wittig homologation of epoxy carbonyl **182** to yield epoxy enone **183** (Scheme 22).[29]

Scheme 22 – Epoxy Ketone Formation En Route to Epoxy Enone Formation



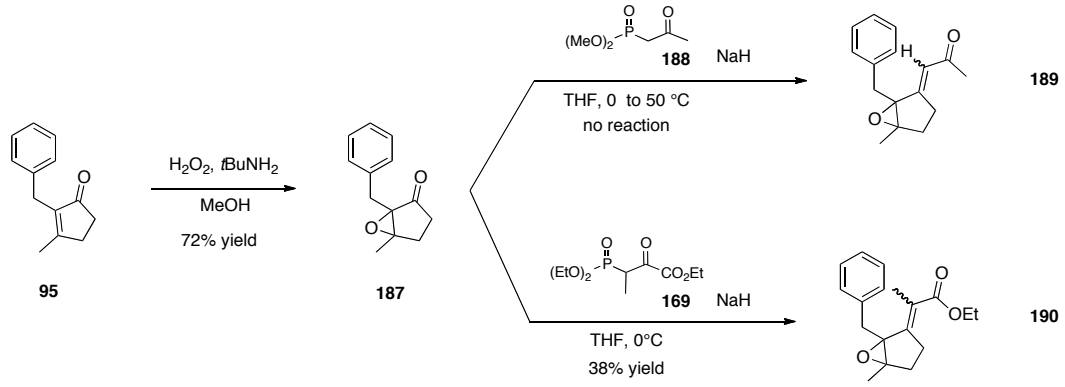
Towards our synthesis, enone **106** was subjected to epoxidation conditions with hydrogen peroxide and *t*butyl amine to produced epoxy ketone **185** (Scheme 23).[30] Exposure of epoxy ketone **185** to triethyl 2-phosphonopropionate **169**, pretreated with NaH, produced enoate **186** in reasonable yield. Given success in this model system, we pursued the olefination on a more advanced substrate.

Scheme 23 – A Model System For Formation of Epoxy Enone



Epoxidation of enone **95** afforded HWE precursor **187** (Scheme 24). Unfortunately, HWE reaction with phosphonate **188** failed to produce any of the desired enone **189**. Interestingly the corresponding phosphonopropionate did react to form enoate **190**, albeit in low yield. This led us to conclude that epoxy enone was not reactive enough for the olefination with dimethyl acetonylphosphonate.

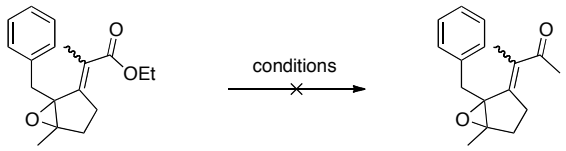
Scheme 24 – Horner-Wadsworth-Emmons Reaction of Epoxy Ketones



In an effort to convert **190** to **191**, we investigated the conversion of the ester to the methyl ketone via a Weinreb amide intermediate (Scheme 25).[31] Unfortunately, only starting material was observed. Other reactions attempted on **190** included saponification with lithium or sodium hydroxide, addition of vinyl magnesium bromide, as well as addition of a methyl nucleophile. Again, starting material was recollected in all cases.

Although disappointed by these failures we were still intrigued about pursuing an allylic diazene rearrangement and thus began to consider alternative approaches to preparing an α,β,γ,δ-unsaturated ketone substrate (e.g., **167** in Scheme 17).

Scheme 25 – Attempts to Access Methyl Ketone 191 from Ester 190

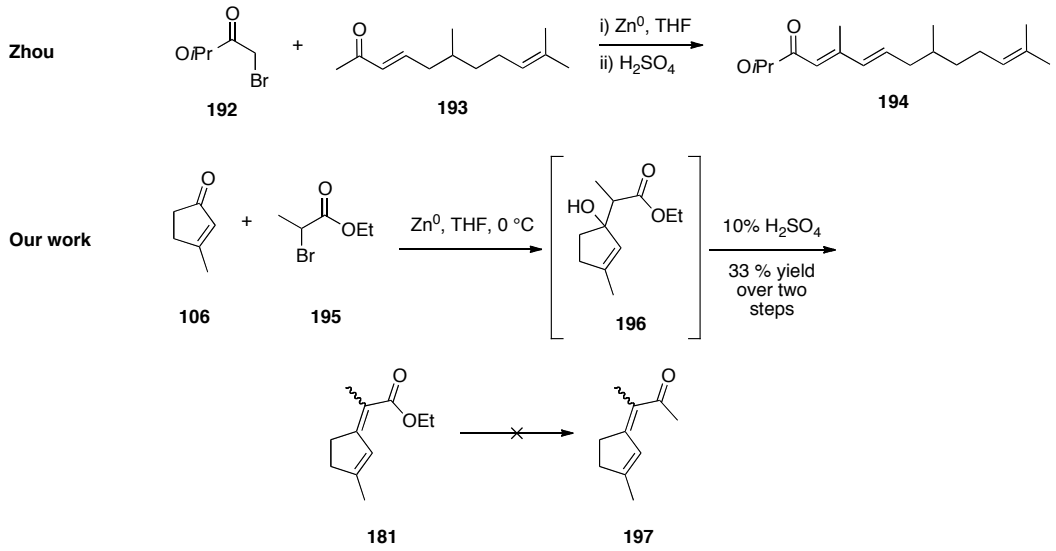


190 **191**

3.4 – Nucleophilic Addition into the Carbonyl of Enone 106

Turning to the literature one can find numerous examples of α,β,γ,δ-unsaturated carbonyls, Scheme 26 illustrates a precedent wherein a dienoate (i.e., **194)**[32] is prepared by addition of an α-halo-ester-derived nucleophile to an enone electrophile (i.e., **193**, Scheme 26).[33] To apply this Reformatsky-type addition/dehydration sequence to a system more similar to that found in the bromophycolides, we envisioned coupling **106** with **195** to furnish **196** which, upon dehydration of the alcohol, would result in dienoate **181**. In the event, zinc promoted coupling of cyclopentenone **106** and bromide **195** followed by treatment of the intermediate β-hydroxy ketone (**196**) with strong acid delivered enone **181**. Unfortunately, in reactivity similar to that observed for **190**, attempts to convert enoate **181** to methyl ketone **197** were unsuccessful.

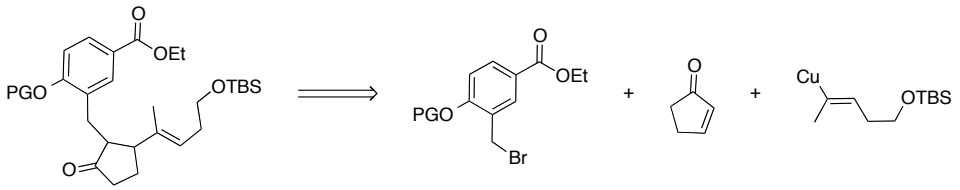
Scheme 26 – Reformatsky Conditions to Effect Dienone Formation



3.5 – Cuprate Assisted Conjugate Addition

Due to the difficulty experienced in our attempts to access a suitable diazene rearrangement precursor, it was decided to explore yet another strategy for the incorporation of the 1,4-skipped diene. After considering numerous alternatives we recognized the possibility of introducing the cyclopentenyl olefin at a later stage from an intermediate ketone. The envisioned intermediate (**198**) would potentially be accessible via a three component coupling strategy wherein 1,4-conjugate addition of organocuprate **199** to cyclopentenone (**175**) would form the desired C7-C8 bond and alkylation of the intermediate enolate with **97** would afford **198**.[34]

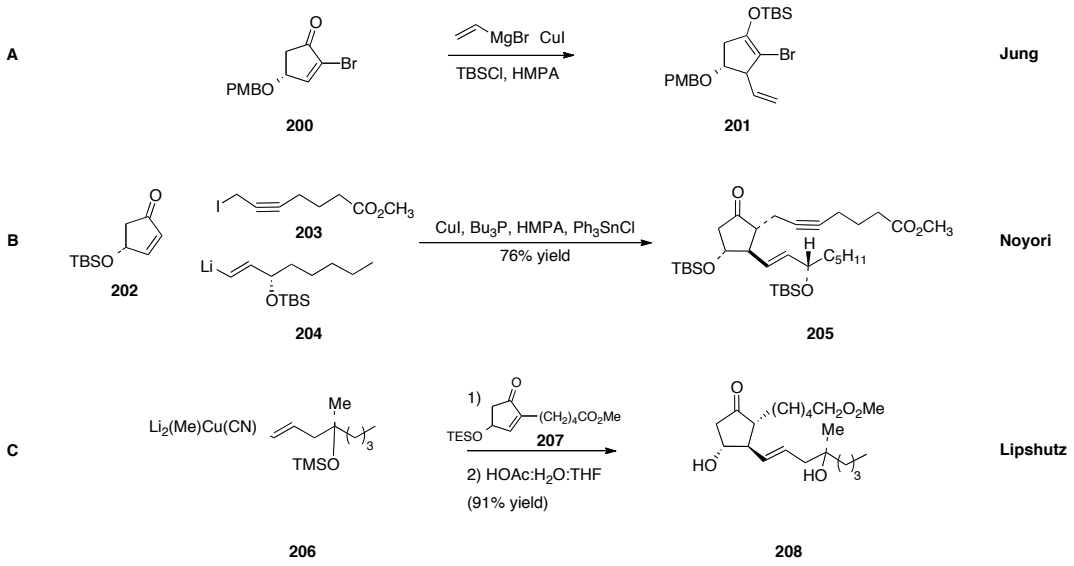
Scheme 27 – Revised Retrosynthetic Analysis of Debromophycolide



198 **97** **175** **199**

Numerous organocuprates and electrophiles have proven effective in these types of the three component coupling reactions and Scheme 28 highlights three examples. The first example, reported by Jung and co-workers, utilizes a five membered enone with a vinyl organocuprate and demonstrates the ability to capture the intermediate enolate as the corresponding silyl enol ether **201** (Equation **A**).[35] Noyori demonstrated that 1,4-addition of an organocuprate to enone **202**, followed by alkylation of propargylic iodide **203** smoothly affords the enyne **205** (Equation **B**).[36] Lipshutz and coworkers have reported efforts towards the synthesis of the prostaglandins which detail the elegant use of higher order cuprates to effect the 1,4-addition of vinyl cuprate **206** to enone **207** to produce cyclopentanone **208** (Equation **C**).[37]

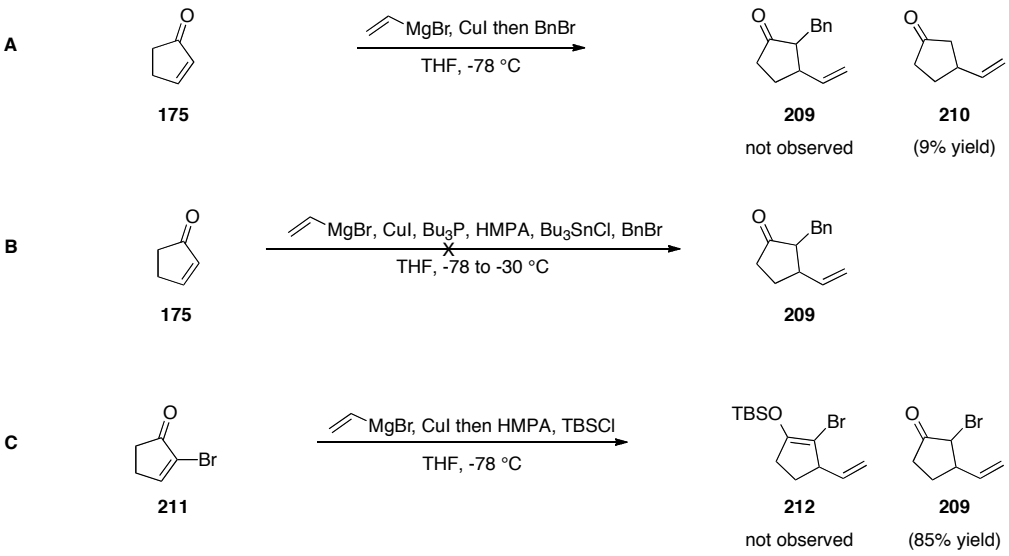
Scheme 28 – Examples of Copper Assisted Conjugate Addition



Beginning with the simplest system following the example by Jung, we sought to convert enone **175** to pentanone **209** (Scheme 29).[35] In the event, CuI and vinyl magnesium bromide were used to effect 1,4-addition followed by the addition of benzyl bromide.[34] Unfortunately, we observed only the 1,4-addition product **210** and none of the desired 2,3-disubstituted cyclopentanone **209** (Equation **A**). Transmetallation of the magnesium enolate to tin has been reported to improve subsequent coupling reactions by prolonging the life of the enolate (Equation **B**).[36] With our substrates, attempts to employ the corresponding tin enolate resulted in recovery of starting material; interestingly, Lipshutz has noted similar difficulties when using benzyl bromide as the electrophile.[38] This prompted us to investigate conjugate addition to α-bromo enone **211** and subsequent trapping of the enolate with TBSCl (Equation **C**); importantly, if successful this transformation would deliver a vinyl bromide product that we envisioned would be a good coupling partner in subsequent C-C bond forming steps. Unfortunately,

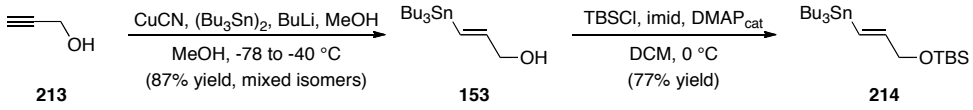
in our hands we were unable to capture the intermediate enolate upon vinyl cuprate addition to **211** and observed only 1,4-addition product **209**.

Scheme 29 – Results of Conjugate Addition with Vinyl Magnesium Bromide



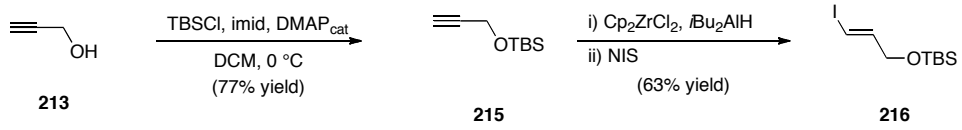
Further investigation into the conjugate addition chemistry of **175** led us to screen several higher order cuprates. To set the stage for preparing these cuprates we prepared known vinyl stannane **214** (Scheme 30).[39] In the event, hydrostannylation of propargyl alcohol **213** produced vinyl stannane **153** as a mixture of isomers which, upon conversion to the corresponding silyl ether could be separated to deliver the desired vinyl stannane **214** in good yield.

Scheme 30 – Model Organometallic for Conjugate Addition



An additional cuprate precursor, vinyl iodide **216**,[40] was efficiently accessed from propargyl alcohol as outlined in Scheme 31. Thus, protection of **213** as the corresponding TBS ether (**215**) was followed by treatment with the Schwartz reagent[8] and NIS to afford vinyl iodide **216**.[16]

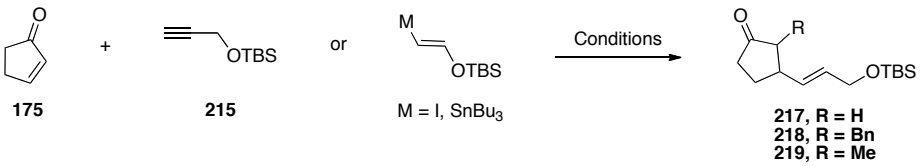
Scheme 31 – Zirconium Mediated Iodination



In our initial attempts to implement the three component coupling we established our ability to work with these reagents by utilizing conditions developed by Lipshutz for the 1,4-addition of organocuprate species derived from organometallics **214**/**216** or alkyne **215** into enone **175**.[37] With our substrates we initially explored conditions that called for generating an organocuprate from the hydrozirconation product derived by treating alkyne **215** with Schwartz's reagent[8] followed by transmetallation with methyllithium. However, decomposed material was observed (Entry 1, Table 3). In the next attempt, **216** was converted to the corresponding cuprate upon treatment with methyllithium and CuCN; subsequent conjugate addition to enone **175** furnished **217** in 11% yield (Entry 2). All subsequent attempts utilized the more efficiently accessed vinyl stannane **214** and the first of these employed the organocuprate derived from transmetallation of **214** with *n*butyllithium in the presence of CuCN; a 38% yield of ketone **217** was the result (Entry 3). Conjugate additions have also been performed wherein dimethylzinc is employed to generate the corresponding vinyl zinc species; use

of these conditions in our system produced a 56% isolated yield of product **217** (Entry 4).[36,41] Unfortunately, attempts to capture the intermediate enolate in these reactions with either methyl- or benzyl-iodide failed (Entries 5 and 6).

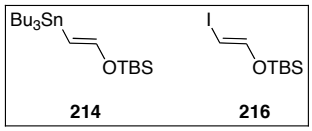
Table 3 – Result of Conjugate Addition and Trapping on a Model System



175 **215** M = I, $SnBu_3$ **217, R = H**
218, R = Bn
219, R = Me

Entry	alkene/ alkyne	Catalyst	Base	Additives	Solvent	% yield
1	**215**	CuCN	MeLi	Cp_2ZrClH^*	THF, -78 °C	R=H, degradation
2	**216**	CuCN	MeLi	-----	THF, -78 °C	R=H, 11% **217**
3	**214**	CuCN	*n*BuLi	-----	THF, -78 °C	R=H, 38% **217**
4	**214**	Me_2Zn	*n*BuLi	-----	THF, -78 °C	R=H, 56% **217**
5	**214**	Me_2Zn	*n*BuLi	HMPA, BnI	THF, -78 °C	R=Bn, NR **218**
6	**214**	CuCN	MeLi	HMPA, MeI	THF, -78 °C	R=Me, NR **219**

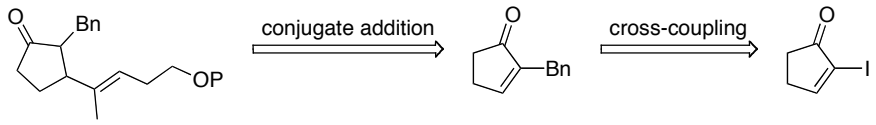
* - Involved reduciton of zirconecene dichloride with iBu_2AlH



214 **216**

Given success in functionalizing the beta position and failure of the subsequent *in situ* alpha alkylation we turned to a two-step process that called for introduction of the alpha substituent prior to conjugate addition. Specifically we hoped to employ a metal mediated cross coupling of an alpha-vinyl halide (e.g., **222**) with an appropriate benzyl halide (e.g., **97**) to deliver the requisite conjugate addition substrate (Scheme 32).

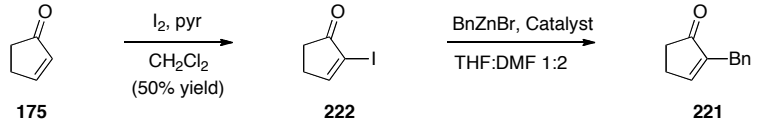
Scheme 32 – Retrosynthetic Analysis Involving a Two Step Process



220 **221** **222**

Investigation of the two-step protocol began with halogenation of enone **175** to provide vinyl iodide **222**. With our coupling partner in hand, initial attempts to convert this enone to the alkylated product (**221**) were unsuccessful (Entry 1, scheme 33).[42] However, we eventually discovered that temperature is a critical variable and that the reaction can be successfully performed using a variety of palladium catalysts to afford the desired coupled product **221** (Entries 2-4).

Scheme 33 – Cross Coupling Results



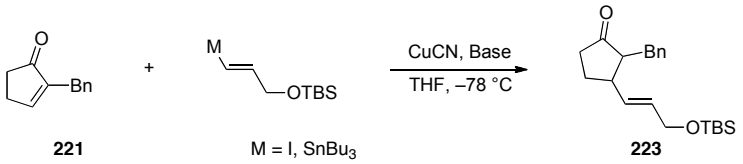
175 **222** **221**

Entry	Temperature	Catalyst	Yield
1	85 °C	$Pd(PPh_3)_2Cl_2$	0
2	40 °C	$Pd(cod)Cl_2$	30%
3	40 °C	$Pd(PPh_3)_2Cl_2$	52%
4	40 °C	$Pd(dppf)Cl_2$	48%

We next examined 1,4-addition by enone **221** utilizing the organocuprates generated from two precursors, vinyl stannane **214** and vinyl iodide **216** (Scheme 34). In the event, vinyl iodide **216** was transmetallated with either methyllithium or *n*-butyllithium to afford an intermediate vinyllithium that, in the presence of CuCN,

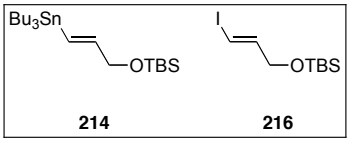
participates in the 1,4-addition and provides α,β-disubstituted ketone **223**, albeit in low yields. Gratifyingly, when organotin species **214** was subjected to similar conditions, an even greater yield of the cross-coupled product was obtained. However in this example, the use *n*butyllithium for transmetallation of the stannane resulted only in recovered starting material.

Scheme 34 – Study of 1,4 Addition Utilizing Various Vinyl Metal Species



221 M = I, $SnBu_3$ **223**

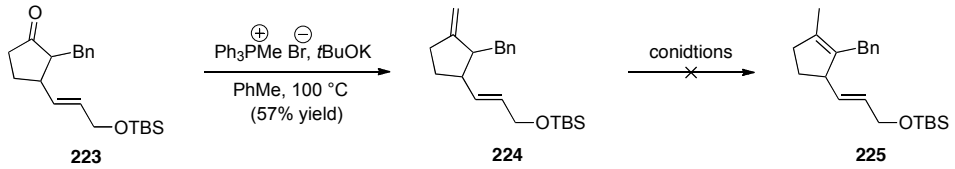
Entry	Precursor	Base	Result
1	**216**	MeLi	22%
2	**216**	*n*BuLi	18%
3	**214**	MeLi	46%
4	**214**	*n*BuLi	NR



214 **216**

As a first attempt toward introduction of the methyl group, cyclopentanone **223** was subjected to Wittig olefination conditions to afford the olefination product **224** (Scheme 35).[43] Isomerization of **224** to the internal tetrasubstituted olefin **225**, would provide a cyclopentene resembling that found in debromophycolide. We recognized that further isomerization could produce a conjugated 1,3-diene; however, our ability to control this deleterious event would have to be determined experimentally. To date, attempts to isomerize the double bond have only resulted in the recovery of starting material.

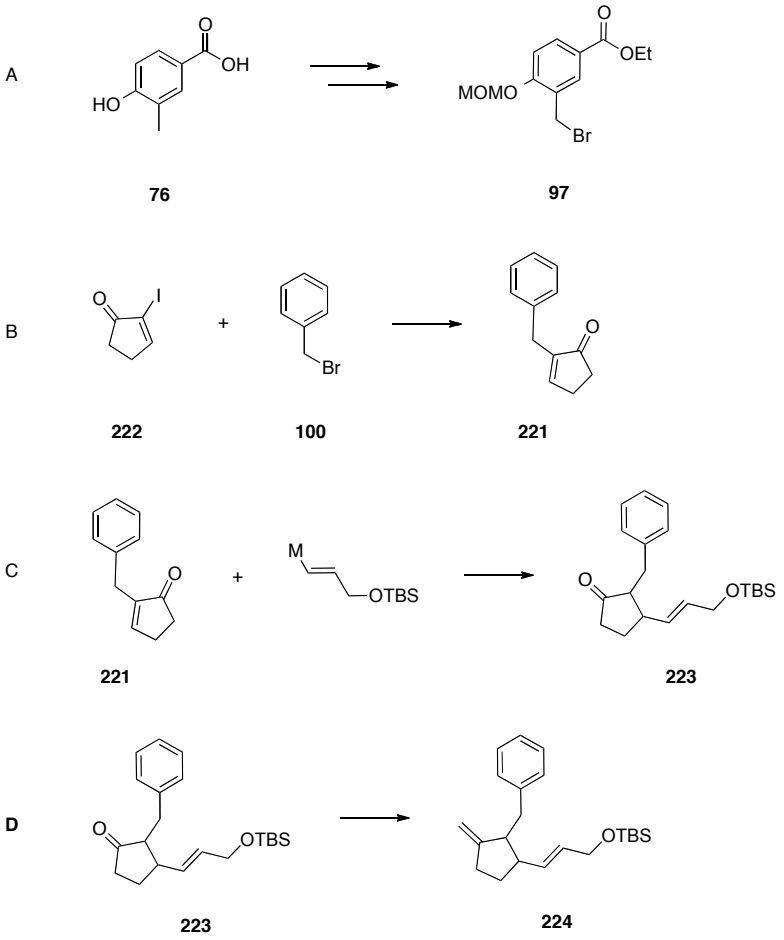
Scheme 35 – Attempts to Produce 1,4-Diene 225



3.6 – Conclusion

In conclusion, we have explored a number of approaches for assembling the C1-C7 fragment of debromophycolide (**1**, Scheme 36). Key elements of these studies include: A) the development of an efficient approach to benzyl bromide **97** from commercially available acid **76**; B) the development of coupling conditions for accessing α-benzyl cyclopentenones (e.g., **221**) from benzyl halide precursors; C) the development of copper-mediated conditions for the conjugate addition of vinyl organometallics to α-benzyl cyclopentenones (see, **221** to **223** in Scheme 36), and D) methylenation via Wittig reaction (see, **223** to **224**, Scheme 36). Importantly, C-D represent the steps needed to introduce the requisite C-C bonds present in the cyclopentene unit of debromophycolide.

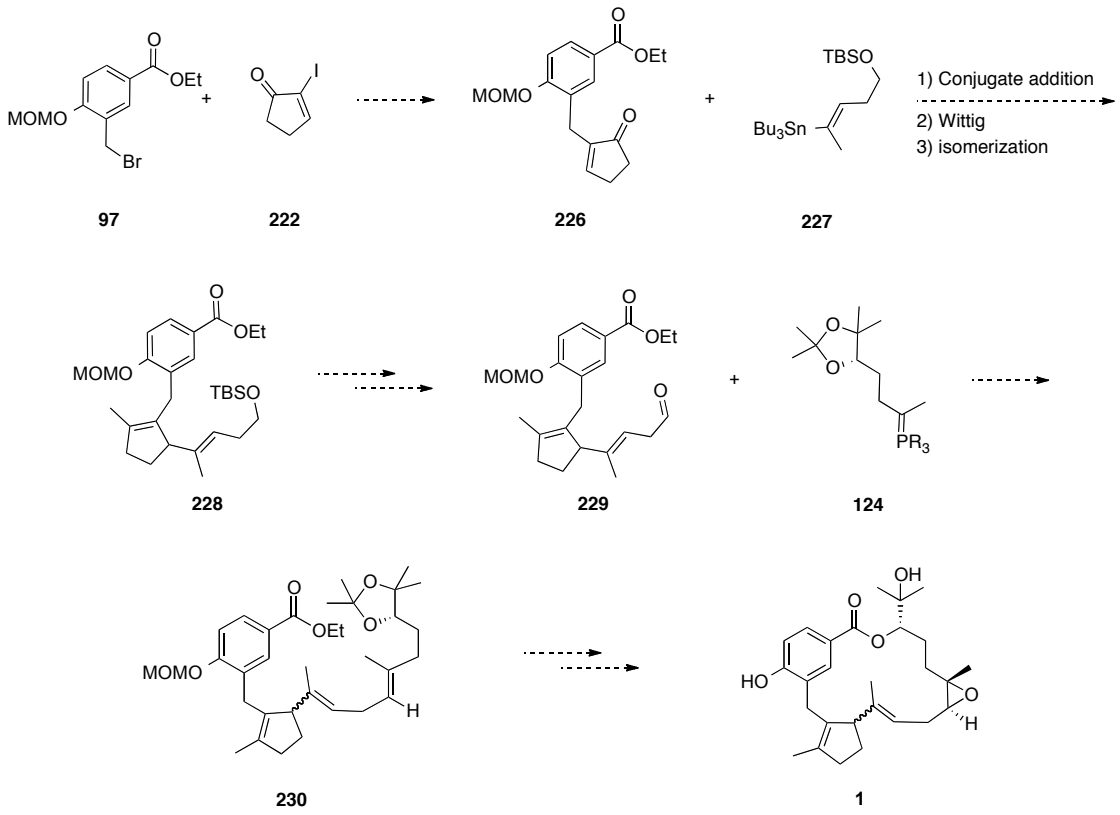
Scheme 36 – Summary



3.7 – Future Work

Based on our work, future efforts towards the completion of debromophycolide (**1**) would include: A) a cross-coupling between benzyl bromide **97** and vinyl iodide **222** to afford α-alkylated enone **226** (Scheme 37); B) conjugate addition, Wittig olefination, and isomerization of the exomethylene would then afford skipped diene **228**; C) a deprotection/oxidation sequence followed by Wittig olefination with ylide **124**. This sequence would install all the carbon atoms found in the debromophycolide. Finally, epoxidation and macrolactonization would afford the natural product.

Scheme 37 – Future Advancement of Material



3.8 – Experimental

3.8.1 – Materials and Methods

General – Unless otherwise stated, all reactions were mechanically stirred in flame-dried glassware under an atmosphere of nitrogen. Diethyl ether, tetrahydrofuran, dichloromethane, benzene, and toluene were dried using a solvent purification system manufactured by SG Water U.S.A., LLC using technology based upon that originally described by Grubb's *et al*.[44] Anhydrous *N,N*-dimethylformamide was purchased from Sigma-Aldrich and stored under a nitrogen atmosphere. Methanol was dried over magnesium and triethylamine and *t*-butyl alcohol were dried using calcium hydride and

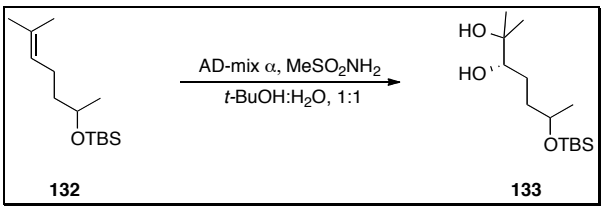
under stored a under nitrogen atmosphere.[45] Commercially available reagents were purchased from Sigma-Aldrich, Fluka, TCI, or Alfa Aesar and were used as received. *N*-Bromosuccinimde was recrystallized using a known procedure.[46] All known compounds were identified by comparison of NMR spectra with that found in the literature.

Thin layer chromatography was performed using Silicycle glass-backed extra hard layer, 60 Å plates (indicator F-245, 250 μm). Developed plates were visualized using a 254 nm UV lamp and/or with the appropriate dip followed by heating. Anisaldehyde and potassium permanganate were prepared by known recipes.[47] Flash chromatography was generally performed according to the protocol described by Still *et al*.,[48] with Silicycle Siliaflash® P60 (230-400 mesh) silica get as the stationary phase. Melting points were obtained using a Gallenkamp melting point apparatus and are uncorrected.

Infrared spectra were recorded on a Nicolet Magna-IR 760 Spectrometer E.S.P. Samples were analyzed as thin films on NaCl plates (samples dissolved in dichloromethane) and the spectra are presented as transmittance s. wavenumber (cm^{-1}). High-resolution mass spectrometry was conducted on an Agilent 6210 TOF LCMS. Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Varian Inova 400 or 300 spectrometer. Spectra were obtained at 22 °C in $CDCl_3$ unless otherwise noted. Chemical shifts are reported in parts per million (*ppm*) and are referenced to the residual solvent peak. Coupling constants (*J*) are reported in Hertz (*H*) and are rounded to the nearest 0.1 Hz. Multiplicities are defined as: s = singlet, d = doublet, dd = doublet of doublets, ddd= doublet of doublet of doublets, t = triplet, q = quartet, m = multiplet.

3.8.2 – Preparative Procedures

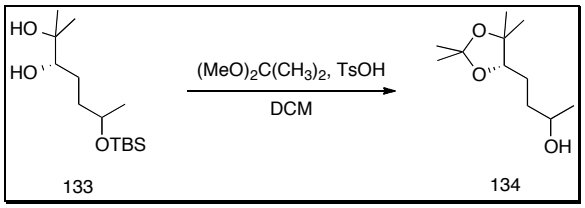
Preparation of Vicinal Diol 133.



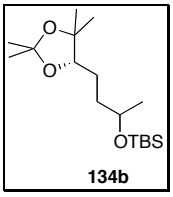
AD-mix α (134.12 g, 1.4 g per mmol of substrate used) was added portion wise to a mixture of *t*BuOH and water (1:1, 300 mL), followed by the addition of methyl sulfonamide (9.11 g, 95.8 mmol) and the reaction was stirred 15 min. Compound **132** (23.2 g, 95.8 mmol) was added dropwise via addition funnel at 0 °C with vigorously stirring. The reaction was then allowed to warm to rt and maintained for 12 h. In this time, a color change was observed, going from a heterogeneous dark orange to a light, more homogenous orange/yellow. The reaction was diluted with EtOAc (500 mL) followed by the addition of saturated $NaSO_{3(aq)}$ (500 mL). The aqueous layer extracted with EtOAc (2x100 mL), washed with 1N NaOH (300 mL), then brine (300 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified via column chromatography first using hexane/DCM (1:1), then a second purification with MeOH/DCM (10:90). Compound **133** is UV active and resulted in a clear oil (24.5 g, 93% yield) as a mixture of diastereomers (~1:1.3). R_f=0.25 in 3:97, MeOH/DCM. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.96-3.82 (m, 1H), δ 3.38-3.28 (m, 1H), δ 2.70-2.69 (d, *J*=10.4, 1.5H), δ 2.34 (s, .05H), δ 2.19 (2, 0.5H), δ 1.79-1.32 (m, 4H), δ 1.32-1.14 (m, 9H), δ 0.885 (s, 9H), δ 0.064 (s, 6H): ^{13}C NMR (75 MHz) 79.1, 78.7, 73.2, 69.0, 68.8, 37.0, 36.4, 27.9, 27.3, 26.7, 26.0, 23.9, 23.5, 23.4, 18.3, -4.1: IR (thin film,

NaCl) 3407, 2958, 2929, 1472, 1375, 1254, 1137, 1049, 1005, 834: HRMS (ESI-APCI) *m/z* calcd. for $C_{14}H_{31}O_3Si$ $[M-H]^-$: 275.2048, found 275.2054

Preparation of Acetonide 134.



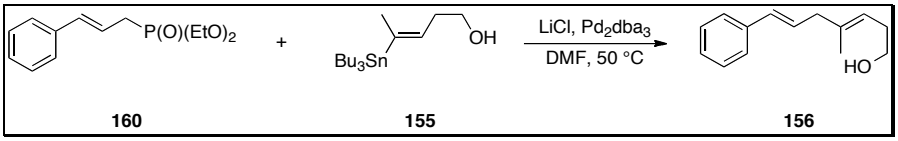
To a solution of diol **133** (153 mL, 0.554 mmol) in DCM (4 mL) was added *p*-toluenesulfonic acid (5.3 mg, 0.028 mmol) and 2,2-dimethoxypropane (188 µL, 1.53 mmol). The reaction was maintained at rt until complete via TLC. The solution was loaded onto silica and was purified with hexane:DCM, 1:1, then MeOH:DCM, 3:97. Compound **134** was isolated as a clear oil (106.4 mg, 94%) along with OTBS protected alcohol **134b** (4 mg, 4.2% yield) both as a mixture of diastereomers. R_f=0.39 in (3:97, MeOH/DCM) ^{1}H NMR($CDCl_3$, 400 MHz) δ 3.92-3.80 (m, 1H), δ 3.72-3.65 (m, 1H), δ 2.15 (s, 1H), δ 1.71-1.47 (m, 4H), δ 1.41 (s, 3H), δ 1.33 (s, 3H), δ 1.24 (s, 3H), δ 1.22-1.19 (dd, *J*=6.20 Hz, 3H), δ 1.19 (s, 3H), δ 1.10 (s, 3H): ^{13}C NMR ($CDCl_3$, 100MHz) 208.3, 167.5, 106.9, 82.7, 80.4, 41.1, 30.2, 28.7, 27.1, 26.1, 23.4: IR (thin film, NaCl) 3420, 2976, 2934, 2867, 1457, 1370, 1274, 1235, 1217, 1197, 1115, 1013, 912: HRMS (ESI-APCI) *m/z* calcd. for $C_8H_{15}O$ $[M-C_3H_7O_2]^+$: 127.1116, found 127.1117.



134b

^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.85-3.75 (m, 1H), δ 3.64-3.59 (m, 1H), δ 1.65-1.41 (m, 3H), δ 1.38 (s, 3H), δ 1.29 (s, 3H), δ 1.21 (s, 3H), δ 1.11 (d, *J*= 6.0 Hz, 3H), δ 1.01 (s, 3H), δ 0.849 (s, 9H), δ 0.017 (s, 6H): ^{13}C NMR ($CDCl_3$, 100MHz) 106.6, 83.9, 83.6, 80.4, 68.8, 68.2, 37.4, 36.7, 28.8, 27.1, 26.4, 26.1, 25.2, 24.3, 23.8, 23.1, 18.3, -4.1: IR (thin film, NaCl) 2957, 2931, 2858, 1472, 1463, 1376, 1369, 1255, 1236, 1216, 1199, 1118, 1049, 1016, 1001, 834: HRMS (ESI-APCI) *m/z* calcd. for $C_{14}H_{30}O_2Si$ $[M-C_3H_5O]^+$: 259.2088, found 259.2089.

Preparation of Diene 156.

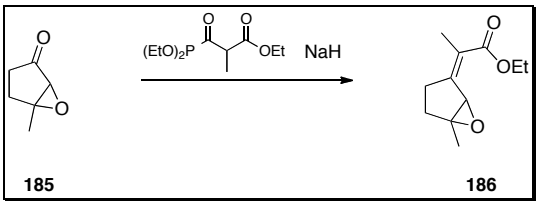


160 155 156

LiCl (14.6 mg, 0.345 mmol) was flame dried under reduced pressure. Once cool DMF (1 mL), compound **160** (30.9 mg, 0.115 mmol) and compound **155** (49.8 mg, 0.138 mmol) were added. After the LiCl fully dissolved the solution was added to tris(dibenzylideneacetone)dipalladium (0) which was stirred for 5 min at rt then 50 °C. After 2.5 h the solution had turned yellow-green and was quenched with NH_4Cl (2 mL). The mixture was extracted with ether (2 x 4 mL). The organic fractions were combined and washed with brine (4 mL) then dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was purified via column chromatography using (EtOAc/hexane, 1:4) to afford compound **156** (23.2 mg, 70.2 % yield). ^{1}H NMR ($CDCl_3$,

300MHz) δ7.57-7.2 (m, 5H), δ 6.41(d, *J*=15.9 Hz, 1H), δ 6.22 (ddd, *J*= 7 Hz, 1H), δ 5.24 (t, *J*= 7.4 Hz, 1H) δ 3.65 (dd, *J*=6.3 Hz, 2H), δ 2.91 (d, *J*= 7.0 Hz, 2H), δ 2.33 (q, *J*=7.3, 2H), δ 1.69 (s, 3H), δ 1.39-1.28 (m, 2H), 0.93 (t, *J*= 7.3 Hz, 1H): ^{13}C NMR (100 MHz) 137.6, 137.3, 131.2, 128.5, 128.4, 127.0, 126.0, 121.0, 62.4, 43.2, 31.6: IR (thin film, NaCl) 3353 (bs), 3025, 2955, 2920, 2881, 1448, 1047, 965: HRMS (ESI-APCI) *m/z* calcd. $C_{14}H_{19}O$ $[M+H]^+$: 203.1430, found 203.1429.

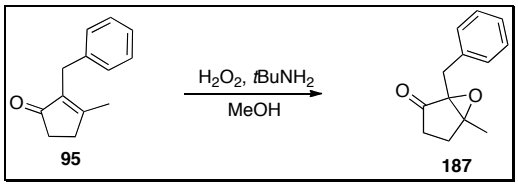
Preparation of Epoxy Enone 186.



To a suspension of NaH (62 mg, 1.6 mmol) in ether (2.5 mL) was added triethyl 2-phosphonoproprionate (0.395 mL, 1.8 mmol) dropwise at 0 °C. After 1 h, epoxy ketone **185** (145 mg, 1.3 mmol) in ether (2.5 mL) was added dropwise. The reaction was monitored via TLC (3:20, EtOAc:Hex) and when complete, quenched with the addition of water (5 mL) and extracted with ether (2x5 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was purified via column chromatography (1:10, EtOAc:Hex) to produced a mixture of diastereomers, **186** as an oil (127 mg, 51% yield). R_f= 0.55 (3:20, EtOAc:Hex), ^{1}H NMR ($CDCl_3$,300 MHz) δ 4.47 (s, 0.5H), δ 4.25-4.13 (m, 2H), δ 3.71 (s, 0.5), δ 2.98 (q, *J*= 9.5 Hz, 0.5H), δ 2.46-2.03 (m, 4H), δ 1.85 (s, 1H), δ 1.79-1.68 (m, 1H), δ 1.51 (s, 3H), δ 1.33-1.24 (m, 3H): ^{13}C NMR (75 MHz) 168.0, 152.4, 125.7, 124.5, 68.3(67.5), 63.8(63.0), 60.7(60.5), 31.4(30.3), 28.5(28.2), 18.3, 16.5(15.9), 14.5: IR (thin film, NaCl) 2981, 2931, 1710,

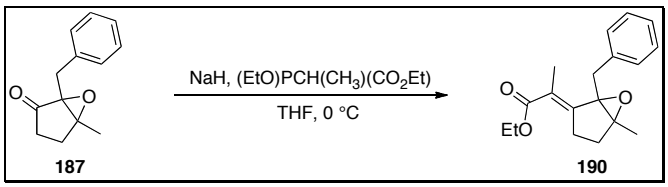
1653, 1447, 1408, 1367, 1324, 1294, 1279, 1258, 1214, 1187, 1167, 1104, 1040, 820: HRMS (ESI-APCI) *m/z* calcd. for $C_{11}H_{17}O_3$ $[M+H]^+$: 197.1172, found 197.1173.

Preparation of Epoxide 187.



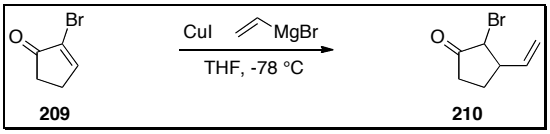
To a solution of compound **95** (156 mg, 0.838 mmol) in MeOH (1.5 mL) was added H_2O_2 (513 µL, 5.03 mmol) dropwise. The internal temperature was maintained below 25 °C. *t*$BuNH_2$ (132 µL, 0.696 mmol) was then added and the reaction was allowed to stir for 4 h. Brine (3 mL) was added and the mixture was extracted with EtOAc (2 x 5 mL). The organic layers were combined and dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified via column chromatography (EtOAc/hexane, 1:19) to produce mixture of diastereomers, **187** (123 mg, 72.4 % yield). The product stained red with anisaldehyde stain and the starting material stains yellow. R_f= 0.47 in EtOAc/hexane, 1:19. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27 (m, 5H), δ 3.28 (d, *J*=14.8 Hz, 1H), δ 2.97 (d, *J*=14.8 Hz, 1H), δ 2.42-1.85 (m, 4H), δ 1.60 (s, 3H): ^{13}C NMR (75 MHz) 211.5, 136.1, 129.7, 128.7, 126.8, 70.2, 67.5, 32.1, 30.1, 27.8, 17.2: IR (thin film, NaCl) 3031, 2964, 2931, 1742, 1496, 1454, 1407, 1080, 1057, 762: HRMS (ESI-APCI) *m/z* calcd. for $C_{13}H_{15}O_2$ $[M+H]^+$: 203.1067, found 203.1071.

Preparation of Epoxy Enone 190.



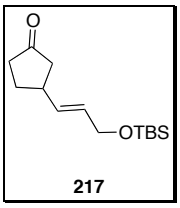
To a suspension of sodium hydride (44 mg, 1.09 mmol) in THF (0.5 mL) was added triethyl 2-phosphonopropionate (237 μL, 1.09 mmol) in THF (0.5 mL) at 0 °C. The reaction was stirred 30 min after effervescence had subsided, then cooled to 0 °C. Compound **187** (200 mg, 0.99 mmol) in THF (0.5 mL) was added dropwise and the reaction was then heated to 50 °C for 2 h. Upon cooling to rt, water (2 mL) was added and the mixture was extracted with EtOAc (2 x 3 mL). The organic fractions were combined and dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/hexane, 1:9) to produce a mixture of diastereomers, **190** (108 mg, 38% yield). R_f= 0.5 in EtOAc/hexane, 1:9. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24-7.12 (m, 5H), δ 7.05 (d, *J*= 7.4Hz, 2H), δ 4.06 (t, *J*=7.4 Hz, 2H), δ 3.69 (d, *J*=17.4 Hz, 1H), δ 3.20 (d, *J*= 14.8 Hz, 0.5H), δ 2.92 (d, *J*= 16.9 Hz, 1.3H), δ 2.78-2.71 (m, 1H), δ 2.47-1.96 (m, 3H), δ 1.79 (s, 3H), δ 1.50 (s, 2H), δ 1.40 (s, 2H), δ 1.18 (t, *J*=7.1 Hz, 3H): ^{13}C NMR (100 MHz) 169.4, 148.9, 136.7, 129.4, 128.4, 126.5, 126.3, 125.3, 72.4, 69.1, 60.3, 35.6, 31.1, 29.8, 27.6, 16.9, 14.9, 14.2: IR (thin film, NaCl) 2932, 1743, 1711, 1496, 1453, 1249, 1196, 1126, 705: HRMS (ESI-APCI) calcd. for $C_{18}H_{23}O_3$ $[M+H]^+$: 287.1642, found 287, 1644.

Preparation of Homoallylic Bromide 210.



To a suspension of CuI (202 mg, 1.06 mmol) in THF (10 mL) was added vinyl MgBr (2.54 mL, 0.82 M) at -78 °C. The reaction was warmed to –20 °C and held for 20 min before cooling to -78 °C and enone **209** (85 mg, 0.53 mmol) in THF (5 mL) was added dropwise. After 15 min, the reaction was quenched with a buffer pH 7 solution (4 mL), allowed to warm to rt, and extracted with ether (3x 8 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was purified via column chromatography (ether/hexane, 3:97). Compound **210** was isolated as an oil (85 mg, 85 % yield). R_f= 0.3 in 3:97 ether/hexane. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.91-5.80 (m, 1H), δ 5.11-5.02 (m, 2H), δ 2.91-2.78 (m, 1H), δ 2.44-1.63 (m, 5H): ^{13}C NMR (100 MHz) 210.1, 166.6, 137.0, 117.5, 54.0, 50.0, 45.9, 35.1, 26.7, 25.6: IR (thin film) 2924, 2361, 2336, 1756, 1652: HRMS (ESI-APCI) *m/z* calcd. for C_7H_9O $[M+H]^+$: 109.0648, found 109.0647.

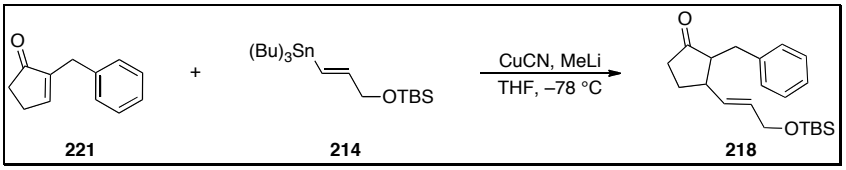
Preparation of β-substituted cyclopentanone 217.



To a solution of vinyl stannane **214** (116 mg, 0.251 mmol) in THF (0.2 mL) was added nBuLi (95 μL, 2.34M) at a quick dropwise pace, at –78 °C. After 1h, a solution of Me_2Zn (0.252 μL, 1.0M) was added and the reaction was warmed to 0 °C and maintained

for 15 min. At this time, the reaction was cooled back to –78 °C and cyclopent-2-en-1-one (10 μL, 0.126 mmol) in ether (0.2 mL) was added slowly. After 15 min, the reaction was quenched with NH_4Cl (1 mL) and extracted with ether (2 x 3 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was purified via column chromatography (ether/hexane, 3:97) to produce **217** as an oil (18 mg, 56 % yield). R_f= 0.3 in 3:97 ether/hexane. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.72-5.55 (m, 2H), δ 4.15 (d, *J*= 4.4 Hz, 2H), δ 2.91-2.79 (m, 1H), δ 2.44-1.96 (m, 5H), δ 1.76-1.64 (m, 1H), δ 0.90 (s, 9H), δ 0.062 (s, 6H): ^{13}C NMR (100 MHz) 219.1, 132.5, 129.6, 63.7, 44.9, 39.6, 38.4, 29.9, 26.2, 18.7, -4.9: IR (thin film NaCl) 2956, 2929, 2885, 2857, 1745, 1472, 1254, 1123, 1063, 971: HRMS (ESI-APCI) calcd. for $C_{14}H_{27}O_2Si$ $[M+H]^+$: 255.1775, found 255.1777.

Preparation of α,β-substituted cyclopentanone 218.



General Procedure for Conjugate Addition

All glassware was flame dried, CuCN was dried with a heat gun under reduced pressure and compounds **221** and **214** were azeotroped with anhydrous benzene twice.

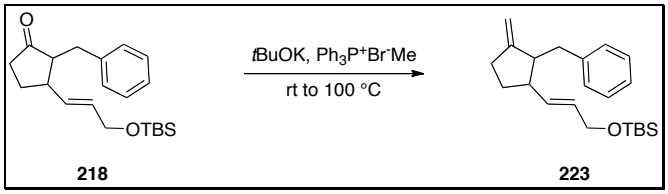
To a suspension of copper cyanide (25.5 mg, 0.284 mmol) in THF (3 mL) was added MeLi (438 μL, 0.609 mmol, 1.39 M) over 5 min at 0 °C. Compound **214** (141 mg, 0.305 mmol) in THF (1 mL) was added and the mixture was allowed to warm to rt and maintained for 30 min. The solution was then cooled to –78 °C and compound **221** (35 mg, 0.203 mmol) in THF (1 mL) was added over five min. The reaction remained at this

temperature 2 h before warming slightly and quenching with an NH_4Cl/NH_4OH solution (3 mL, 9:1) where the color of the solution changed from yellow to a dark blue color, then clear. The mixture was washed with brine (3 mL) and extracted with ether (2 x 5 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was purified via column chromatography (EtOAc/hexane, 1:19) to produce compound **218** (69.9 mg, 46 % yield) as an yellow oil. R_f= 0.61 in EtOAc/hexane, 1:19, stained with anisaldehyde (red spot).

*care must be taken to ensure the aqueous layer remains basic.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26-7.12 (m, 5H), δ 5.57 (t, 2H), δ 4.12 (d, *J*= 4.3Hz, 2H), δ 3.03 (ddd, *J*= 4.8 Hz, *J*=13.9 Hz, 1H), δ 2.86 (ddd, *J*=5.7Hz, *J*= 13.9Hz, 1H), δ 2.44-1.90 (m, 5H), δ 1.66-1.54 (m, 1H), δ 0.92 (s, 9H), δ 0.079 (s, 6H): ^{13}CNMR ($CDCl_3$) 219.2, 139.2, 132.2, 130.8, 130.0, 128.5, 126.4, 63.8, 56.4, 43.9, 38.2, 33.1, 27.9, 18.7, -4.9: IR (thin film, NaCl) 2955, 2929, 2884, 2856, 1742, 1471, 1254, 1128, 1098, 1058, 972, 837: HRMS (ESI-APCI) *m/z* calcd. for $C_{21}H_{36}NO_2Si$ $[M+NH_4]^+$: 362.2510, found 362.2507.

Preparation of Exomethylene 223.

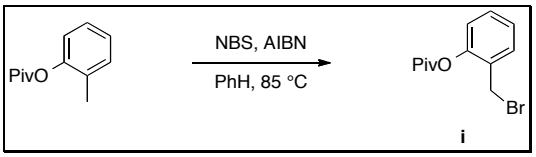


218 **223**

To a solution of methyl triphenylphosphonium bromide (149 mg, 0.417 mmol) in toluene (2 mL) was added *t*BuOK (44.7 mg, 0.398 mmol) and stirred for 45 min. Compound **218** (68 mg, 0.20 mmol) in toluene (1 mL) was added dropwise over 5 min. The solution

turned orange and was then heated to 100 °C for 3 hr. Upon cooling to rt, a saturated solution of NH_4Cl (3 mL) was added and the mixture was extracted with ether (2 x 5 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was purified via column chromatography (ether/hexane, 1:19) to provide compound **223** as a mixture of diastereomers as an oil (38.8 mg, 57 % yield). R_f= 0.48, ether/hexane, 1:19, anisaldehyde stain. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28-7.14 (m, 5H), δ 5.49-5.47 (m, 2H), δ 4.89 (bs, 1H), δ 4.71 (bs, 1H), δ 4.07-4.06 (m, 2H), δ 3.49 (d, *J*= 5.7Hz, 0.5H), δ 2.91-2.70 (dd, *J*= 5.7Hz, 2.5H), δ 2.51-2.18 (m, 1H), δ 1.89-1.79 (m, 4H), δ 1.50-1.36 (m, 1H), δ 1.26 (s, 1H), δ 0.91 (s, 9H), δ 0.61 (s, 6H): ^{13}C NMR ($CDCl_3$) 155.4, 140.9, 134.2, 129.7, 128.2, 126.0, 106.2, 64.2, 50.6, 48.4, 39.1, 32.7, 31.7, 26.2, -4.8: IR (thin film, NaCl) 2953, 2928, 2985, 2856, 1471, 1254, 1061, 970, 836: HRMS (ESI-APCI) *m/z* calcd. for $C_{22}H_{35}OSi$ $[M+H]^+$: 343.2452, found 343.2444.

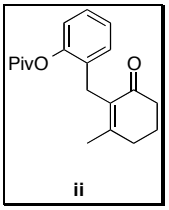
Preparation of Benzyl Bromide i.



Known compound 2-methyl-phenol[49] protected as the *t*butyl ester (268.6 mg, 1.4 mmol) was dissolved in benzene (3 mL) followed by the addition of NBS (275.5 mg, 1.68 mmol) and AIBN (25 mg, 0.14 mmol) and refluxed for 8 hrs. The reaction was cooled to rt, then washed with a saturated solution of $NaHCO_3$ (4 mL) and extracted with ether (2 x 5 mL). The organic layer was dried over $MgSO_4$, and solvent removed under reduced pressure. The residue was purified via column chromatography (hexane/ether, 97:3) to afford **i** (302.4 mg, 80% yield) as an oil. R_f= 0.65 in hexane/EtOAc, 19:1. 1HNMR

($CDCl_3$, 400 MHz) δ 7.41 (d, *J*=7.6 Hz, 1H) δ 7.35 (t, *J*=87.6 Hz, *J*=8.0 Hz, 1H) δ 7.21 (t, *J*=8.3 Hz, *J*=7.5 Hz, 1H), δ 7.09 (d, *J*=8.1Hz, 1H), 4.40 Hz (s, 2H), δ 1.43 Hz (s, 9H): ^{13}CNMR (100 MHz) 167.0, 131.0, 130.1, 126.3, 123.1, 39.6, 36.7, 27.4: HRMS (ESI-APCI) *m/z* calcd. for $C_{12}H_{19}BrNO_2$ $[M+H]^+$: 288.0594, found 288.0595.

Preparation of α-substituted enone ii.

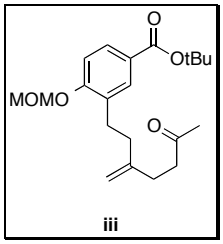


ii

Zinc (52 mg, 0.81 mmol) was added to a round bottom flask and flame dried. Upon cooling, the flask was charged with THF (0.6 mL) and 1,2 dibromoethane (15 μL, 0.00017 mmol) and the mixture was heated to 60 °C for 10 min then cooled to rt. TMSCl (10 μL, 0.000079 mmol) was then added followed by cooling to 0 °C. A solution of compound **i** (175 mg, 0.648 mmol) in THF (0.5 mL) was added dropwise under vigorous stirring, and the reaction remained at 0°C for 2 h. The solution was then degassed using the freeze-pump-thaw method, 3 times, and excess zinc was allowed to settle at the bottom of the flask. In a separate round bottom, α-halo-enone **102** (38 mg, 0.162 mmol) in DMF (1 mL) and dichlorobis(tri-*o*-tolylphosphine) palladium(II) (6.0 mg, 0.0081 mmol) are combined and degassed. The benzyl zinc bromide solution was transferred via cannula and stirred at rt for 5 min, then at 85 °C for 3 h. Once the reaction is complete via TLC, a saturated solution of NH_4Cl (1 mL) was added and the mixture was extracted with ether (3 x 4 mL). Addition of a few drops of 5 % solution of HCl was periodically necessary to help dissolve emulsions. The organic layer is dried over $MgSO_4$ and

concentrated under reduced pressure. The residue is purified via column chromatography (acetone:hexane, 3:97) to provide compound **ii**[50] as an oil (86% yield) R_f= 0.2 (1:10, EtOAc, Hex) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.17 (t, *J*=7.8 Hz, 1H), δ 7.07 (t, *J*=7.6 Hz, 1H), δ 6.96 (d, *J*= 7.9 Hz, 1H), δ 6.88 (d, *J*=7.5 Hz, 1H) δ 3.55 (s, 2H), δ 2.49-2.41 (m, 4H), δ 2.02 (m, 2H), δ 1.85 (s, 3H), δ 1.40 (s, 9H): ^{13}C NMR (75 MHz) 198.6, 177.1, 159.0, 149.2, 133.4, 132.3, 128.2, 127.0, 126.0, 122.1, 39.5, 37.9, 33.2, 27.5, 24.1, 22.5, 22.0: IR (thin film, NaCl) 2975, 2934, 2873, 1752, 1479, 1456, 1397, 1276, 1217, 1180, 1109, 1028, 754: HRMS (ESI-APCI) *m/z* calcd. for $C_{19}H_{25}O_3$ $[M+H]^+$: 301.1798, found 301.1804.

Preparation of Methyl Ketone iii.

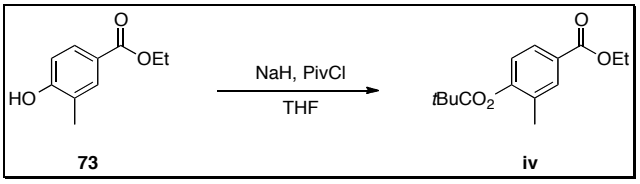


iii

To a solution of benzyl allyl alcohol (225.0 mg, 0.698 mmol) in xylene (2 mL) was added 2,2 dimethoxy propane (4.0 mL, 0.0325 mmol) and propionic acid (4 drop) in a pressure tube which was sealed and heated to 170 °C for 10 h. Upon completion, the volatiles were removed under reduced pressure and the resulting oil was loaded onto silica gel. Column chromatography (EtOAc/hexane, 1:9) provided compound **iii** as an oil (40 mg, 15% yield). R_f= 0.3 in EtOAc/Hexane, 1:9. Found as an oil (15% yield) R_f= 0.29 in 1:5 (EtOAc:Hex), ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.81 (d, *J*= 8.32 Hz, 2H), δ 7.07 (d, *J*=8.2 Hz, 1H), δ 5.25 (s, 2H), δ 4.80-4.73 (d, *J*=20.8 Hz, 2H), δ 3.47 (s, 3H), δ 2.78 (t, *J*=8.1 Hz, 2H), δ 2.63 (t, *J*= 7.2 Hz, 2H), δ 2.35 (m, 4H), δ 2.16 (s, 3H), δ 1.58 (s, 9H): ^{13}C

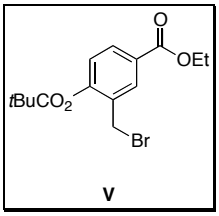
NMR (75 MHz) 208.6, 166.0, 158.6, 148.2, 131.4, 130.8, 129.3, 125.3, 113.0, 109.7, 94.3, 80.8, 56.4, 42.2, 36.6, 30.1, 29.1, 28.5: IR (thin film, NaCl) 2976, 2931, 1709, 1606, 1367, 1300, 1269, 1256, 1161, 1131, 1120, 1079, 993: HRMS (ESI-ACPI) *m/z* calcd. for $C_{21}H_{30}NaO_5$ $[M+Na]^+$: 385.1985, found 385.1996.

Preparation of *t*Butyl Ester iv.



To a suspension of NaH (0.56 mg, 13.9 mmol) in THF (24 mL) was added compound **73** (2.0g, 11.1 mmol) in THF (24 mL) to 0 °C. The reaction was stirred 30 min after effervescence had subsided. Trimethylacetyl chloride (1.40 mL, 11.4 mmol) was then slowly added and the reaction was followed by TLC. After 2 hr the reaction was quenched with $NaHCO_{3(aq)}$ (10 mL) and extracted with ether (2 x 30 mL). The organic layer was dried over $MgSO_4$, and solvent removed under reduced pressure. The residue was purified via column chromatography (hexane/DCM, 1:1) to afford **iv** (2.59 g, 88% yield) as an oil. R_f= 0.70 in hexane/DCM, 1:1. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.11 (d, *J*= 2.1, 1H), δ 8.03 (dd, *J*=2.1 Hz, 8.48 Hz, 1H), δ 7.18 (d, *J*= 8.5 Hz, 1H), δ 4.38 (m, *J*= 7.1 Hz, 4H), δ 2.20 (s, 3H), δ 1.43 (s, 9H): ^{13}C NMR (100 MHz) 176.4, 166.3, 153.5, 132.7, 130.6, 128.7, 128.2, 122.1, 61.2, 39.5, 27.4, 16.3, 14.5: IR (thin film, NaCl) 2978, 2936, 2907, 2873, 1759, 1720, 1592, 1496, 1479, 1463, 1414, 1396, 1367, 1296, 1260, 1217, 1174, 1096, 1027, 1027, 909: HRMS (ESI-ACPI) *m/z* calcd. for $C_{15}H_{21}O_4$ $[M+H]^+$: 265.1434, found 265.1435.

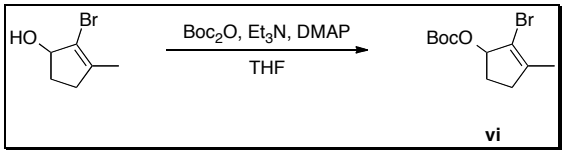
Preparation of Benzyl Bromide v.



v

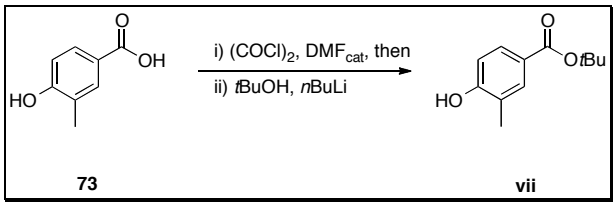
Compound **iv** (1.45 g, 4.93 mmol) was dissolved in benzene (20 mL) followed by the addition of NBS (1.10 g, 6.16 mmol) and AIBN (81.0 mg, 0.49 mmol) and refluxed for 8 h. The reaction was cooled to rt, then washed with a saturated solution of $NaHCO_3$ (10 mL) and extracted with ether (2 x 15 mL). The organic layer was dried over $MgSO_4$, and solvent removed under reduced pressure. The residue was purified via column chromatography (hexane/ether, 97:3) to afford **v** (1.48 g, 81% yield) as a orange solid, melting point = 84 °C. R_f= 0.65 in hexane/EtOAc, 19:1. **v** (86 % yield) as an oil. R_f= 0.70 in hexane/DCM, 1:1. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.11 (d, *J*=2.03, 1H), δ 8.02 (dd, *J*=2.1 Hz, 8.5 Hz, 1H), δ 7.18 (d, *J*=8.5 Hz, 1H), δ 4.41 (s, 4.38), δ 4.37 (q, *J*=7.14 Hz, 4H), δ 1.43 (s, 9H): ^{13}C NMR (100 MHz) 176.4, 166.3, 153.1, 132.7, 131.4, 130.2, 128.7, 123.2, 61.5, 39.7, 27.3, 14.5: IR (thin film, NaCl) 2978, 2936, 2907, 2873, 1759, 1720, 1610, 1496, 1479, 1463, 1445, 1396, 1367, 1296, 1263, 1220, 1179, 1139, 1102, 1027, 896: HRMS (ESI-ACPI) *m/z* calcd. for $C_{15}H_{20}BrO_4$ $[M+H]^+$: 343.0539, found 343.0551.

Preparation of Carbonate vi.



To a solution of known allylic alcohol[51] (482.6 mg, 2.74 mmol) in THF (10 mL) was added Boc_2O (718.2 mg, 3.29 mmol) and Et_3N (0.573 mL, 4.11 mmol) followed by dimethylaminopyridine (40 mg, 0.330 mmol). The reaction was maintained at rt for 10 h, then washed with water (15 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography using EtOAc/hexane, 3:97 to afford carbonate **vi** as an oil (512 mg, 68 % yield). R_f=0.70 in 3:97 EtOAc/hexane. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.55 (s, 1H), δ 2.52-2.20 (m, 3H), δ 2.00-1.90 (m, 1H), δ 1.90 (s, 3H), δ 1.79 (s, 3H), δ 1.49 (s, 9H): ^{13}C NMR ($CDCl_3$, 75 MHz) 168.2, 153.3, 145.6, 114.6, 84.9, 82.4, 34.7, 29.4, 28.0, 16.2: IR (thin film, NaCl) 2980, 2935, 1738, 1457, 1393, 1369, 1316, 1277, 1158, 1123, 1083, 1039, 989, 855: HRMS (ESI-ACPI) *m/z* calcd. for C_6H_8Br $[M\text{-}C_5H_9O_3]^+$: 158.9804, found 158.9803.

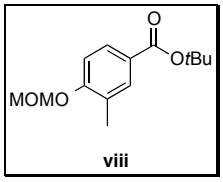
Preparation of *t*Butyl Ester vii.



To a solution of compound **73** (40 mg, 0.263 mmol) in benzene (2 mL), was slowly added oxalyl chloride (69 μL, 0.79 mmol) at 0 °C. A pipette tip of DMF was added and the reaction was allowed to warm to rt and maintained at this temperature for 2.5 h. The reaction was monitored via TLC by quenching a small aliquot with MeOH. In a separate

flask, *n*BuLi (177 µL, 1.56M) was added slowly to *t*BuOH (4 mL) and allowed to stir. Once the initial reaction was complete, it was concentrated under reduced pressure, then slurried in *t*BuOH (4 mL). The reaction was stirred for 3 hrs and quenched with brine (4 mL), extracted with ether (3 x 5 mL), dried over $MgSO_4$, and then concentrated. The residue was purified via column chromatography (MeOH/DCM (1:99) to afford the **vii** as a yellow tinted oil (49.7 mg, 91% yield). R_f= 0.63 in 1:99 Methanol/DCM. This compound was partially characterized. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.77 (s, 1H), δ 7.72 (d, *J*=8.35 Hz, 1H), δ 6.90 (s, 1H), δ 6.81 (d, *J*= 8.4 Hz, 1H), δ 2.27 (s, 3H), δ 1.59 (s, 9H): HRMS (ESI-APCI) *m/z* calcd. for $C_{12}H_{15}O_3$ $[M-H]^-$: 207.1027, found 207.1025.

Preparation of Methyl-methyoxy Ether viii.

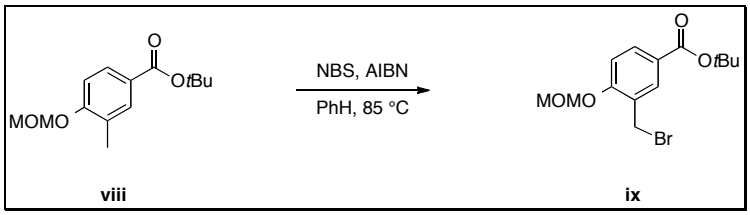


viii

To a solution of sodium hydride (191 mg, 4.77 mmol) in THF (5 mL) was added compound **vii** (928 mg, 4.46 mmol) in THF (3 mL) at 0 °C. Methyl chloromethyl ether (372 µL, 4.91 mmol) in THF (5 mL) was added 30 min later followed by stirring for 1h. Upon completion, the reaction was quenched with H_2O (5 mL) and extract with ether (2 x 5 mL), dried over $MgSO_4$ and purified by column chromatography using EtOAc/hexane/Et_3N (1:19:0.5) to provided **viii** as a white solid (14 g, 98% yield). R_f=0.8 in EtOAc/hexane, 1:19, melting point = 78 °C. Column chromatography using EtOAc/hexane, 6:94 provided the product as a white solid (900 mg, 81% yield). R_f=0.8 in EtOAc/hexane/Et_3N, 1:19:0.5. (This reaction is also successful replacing *i*Pr_2NEt base with NaH). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.76 (d, 1H), δ 7.79 (s, 1H), δ 7.03 (d, *J*=8.2

Hz, 1H), δ 5.24 (s, 2H), δ 3.47 (s, 3H), δ 2.26 (s, 3H), 1.57 (s, 9H): HRMS (ESI-ACPI) *m/z* calcd. for $C_{10}H_{12}O_4$ $[M\text{-}t\text{Bu}]^+$: 197.0808, found 197.0810.

Preparation of Benzyl Bromide ix.



viii **ix**

Compound **viii** (3.47 g, 13.8 mmol) was dissolved in benzene (15 mL) followed by the addition of NBS (2.72 g, 16.5 mmol) and AIBN (1.22 g, 6.88 mmol) and refluxed for 8 h. The reaction was cooled to rt, then washed with a saturated solution of $NaHCO_3$ (7 mL) and extracted with ether (2 x 15 mL). The organic layer was dried over $MgSO_4$, and solvent removed under reduced pressure. The residue was purified via column chromatography (hexane/ether, 97:3) to afford **ix** (4.24 g, 93% yield) as a orange solid, melting point = 84 °C. R_f= 0.65 in hexane/EtOAc, 19:1. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.96-7.92 (m, *J*= 2.21 Hz, 2H), δ 6.87 (d, *J*= 9.21 Hz), δ 4.54 (s, 2H), δ 3.94 (s, 2H), δ 1.58 (s, 9H): HRMS (ESI-APCI) *m/z* calcd. for $C_{13}H_{21}BrNO_3$ $[M+NH_4]^+$: 318.0699, found 318.0694.

3.9 – References and Notes

1. Wittig, G.; Geissler, G. *Ann*. **1953**, *580*, 44.
2. Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263.
3. Brimble, M. A.; Rowan, D. D.; Spicer, J. A. *Synthesis* **1995**, 1263.
4. Sugai, T.; Katch, O.; Ohta, H. *Tetrahedron* **1995**, *51*, 11987.

5. Omura, K; Sharma, A.K.; Swern, D. *J. Am. Chem. Soc.* **1976**, *41*, 957.
6. Terashima, S.; Tseng, C. C.; Hayshi, M.; Koga, K. *Chem. Bull. Pharm.* **1979**, *27*, 758.
7. a) Kobayashi, Y.; Tokoro, Y.; Watatani, K. *Eur. J. Org. Chem.* **2000**, 3825; Miyura, N.; b) Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972; c) Kobayshi, Y.; Mizojiri, R.; Ikeda, E. *J. Org. Chem.*, **1996**, *61*, 5391
8. a) Petasis, N. A.; Yudin, A. K.; Zavialov, I. A.; Prakash, G. K. S.; Olah, G. A. *Synlett* **1997**, 606; b) Rodriguez, J. E.; Adlington, R. M.; Baldwin, J. E.; Moses, J. E. *Tetrahedron* **2007**, *63*, 4500.
9. Nicolaou, K. C.; Fylaktakidov, K. C.; Monenschein, H.; Li, Y.; Wegershawsen, B.; Mitchell, H. J.; Wei, H.-X.; Guntupalli, P.; Hepworth, D.; Sugita, K. *J. Am. Chem. Soc.* **2003**, *125*, 15433.
10. Mun, S.; Lee, J.-E.; Yun, J. *Org. Lett.* **2006**, *8*, 4887.
11. a) Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc* **1974**, *96*, 8115; b) Huang, Z.; Negishi, E.-I. *Org. Lett.* **2006**, *8*, 3675.
12. Tucker, C. E.; Davison, J.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 3482.
13. Pereira, S.; Srebnik, M. *Tetrahedron Lett.* **1996**, *37*, 3283.
14. Molander, G. A.; Berani, C. R. *J. Org. Chem.* **2002**, *67*, 8424.
15. Kobayashi, Y; Nakata, K.; Ainai, T. *Org. Lett.* **2005**, *7*, 183.
16. Llardi, E. A.; Stivala, C. E.; Zakarian, A., *Org. Lett.* **2008**, *10*, 1727.
17. Sebahar, H. L.; Yoshida, K.; Hegedus, L. S. *J. Org. Chem.* **2002**, *67*, 3788.
18. a) Del Valle, L. Stille, J. K. Hegedus, L. S. *J. Org. Chem.* **1990**, *55*, 3019; Shipe, W. D.; b) Sorensen, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 7025.
19. Snyder, S. A.; Corey, E. J. *J. Am. Chem. Soc.* **2006,** *128,* 740.

20. Betzer, J.-F.; Delaloge, F.; Muller, B.; Pancrazi, A.; Prunet, J. *J. Org. Chem.* **1997**, *62,* 7768.

21. Taber, D. F.; Christos, T. E.; Rheingold, A. L.; Guzei, T. D. *J. Am. Chem. Soc.* **1999**, *121*, 5589.

22. a) Castaño, A. M.; Echavarren, A. M. *Tetrahedron Lett.* **1996**, *37*, 6587; b) Yasui, K.; Fugami, K.; Tamaru, Y. *J. Org. Chem.* **1995**, *60,* 1365; c) Murahashi, S.-I.; Imada, Y.; Taniguchi, Y.; Higashirua, S. *J. Org. Chem.* **1993**, *58*, 1538.

23. Murchashi, S.-I.; Taniguchu, Y.; Imada, Y.; Tanigawa, Y. *J. Org. Chem.* **1989**, *54,* 3293.

24. Calaza, M. I.; Hupe, E.; Knochel, P. *Org. Lett.* **2003**, *5*, 1059.

25. Carrillo-Marquez, T.; Caggiano, L.; Jackson, R. F. W.; Grabowska, U.; Rae, A.; Tozer, M. *J. Org. Biomol. Chem*. **2005**, *3*, 4117.

26. Hutchins, R. O.; Kacher, M.; Rua, L. *J. Org. Chem*. **1975**, *40*, 923.

27. Sasai, H.; Arai, T.; Watanabe, S.; Shibasaki, M. *Catalysis Today*, **2000**, *62*, 17.

28. Mudryk, B.; Cohen, T. *J. Am. Chem. Soc.* **1993**, *115*, 3855.

29. Posner, G. H.; Lee, S. H. T.; Kim, H. J.; Peleg, S.; Dolan, P.; Kensler, T. W. *Bioorg & Med Chem* **2005**, *13*, 2959.

30. Ouyang, X.-Y.; Jiang, H.-F.; Huang, J.-M. *Chinese J. Chem.* **2006**, *24*, 1480.

31. a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815; b) He, W.; Huang, J.; Sun, X.; Frontier, A. J. *J. Am. Chem. Soc.* **2007**, *129*, 498; c) Nicolaou, K. C.; Lim, Y.-H.; Becker, J. *Angew*. *Chem. Int. Ed.* **2009**, *48*, 3444.

32. Zhou, R. Liu, T.-F.; Su, L.-X.; Yang, H.-W.; Yin, D.-H. *Youji Huaxue*, **2008**, *28*, 436.

33. Reformatsky, S. *Ber*. **1887**, *20*, 1210.

34. a) Gilman, H.; Straley, J. M. *Red. Trav. Chim. Pays-Bas* **1936**, *55*, 821; b) Jung, M. E.; Berliner, J. A.; Koroniak, L.; Gugia, B. G.; Watson, A. D. *Org. Lett.* **2008**, *10*, 4207.

35. Jung, M. E.; Berliner, J. A.; Angst, D.; Yue, D.; Koroniak, L.; Watson, A. D.; Li, R. *Org. Lett.* **2005**, *7*, 3933.

36. a) Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1985**, *107*, 3348; b) Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 4718; c) Nishiyama, H.; Sakuta, K.; Itoh, K. *Tetrahedron Lett.* **1984**, *25*, 223.

37. a) Behling, J. R.; Babiak, K. A.; Ng, J. S.; Campbell, A. L.; Moretti, R.; Koerner, M.; Lipshutz, B. H. *J. Am. Chem. Soc* 1988, 110, 2641; b) Piers, E.; Gavai, A. V. *J. Org. Chem*. **1990**, *55*, 2380.

38. Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *J. Org. Chem*. **1984**, *49*, 3938.

39. Darwish, A.; Lang, A.; Kim, T.; Chang, J.-M. *Org. Lett.* **2008**, *10*, 861.

40. Hogenauer, K.; Mulzer, J. *Org. Lett.* **2001**, *3*, 1495.

41. Takahashi, T.; Nakazawa, M.; Kanoh, M.; Yamamoto, K. *Tetrahedron Lett.* **1990**, *31*, 7349.

42. Negishi, E.-I. *Tetrahedron*, **2000**, *56*, 10197.

43. Chandler, C. L.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 6737.

44. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics*, **1996**, *15*, 1518.

45. Methanol, triethylamine, and were collected from a still, refluxing with calcium hydride, under an atmosphere of nitrogen.

46. Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals*, 5^{th} ed. Elsevier Science: Burlinton, MA., 2003, p142.

47. Potassium Permanganate solution preparation – 3g of $KMnO_4$, 20g of K_2CO_3, 5 mL 5% $NaOH_{(aq)}$, and 300 mL of H_2O.

Anisladehyde solution preparation – 9.2 mL *p*-anisaldehyde, 3.75 mL AcOH, 338 mL 95% EtOH, and 12.5 mL H_2SO_4.

48. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

49. Gary, N. K.; Quasdorf, K. W.; Tian, X. *J. Am. Chem. Soc.* **2008**, *130*, 14422.

50. Negishi, E.-I. *Tetrahedron* **2000**, *56*, 10197.

51. Kim, J.; Bruning, J.; Park, K. E.; Lee, D. J.; Singaram, B. *Org. Lett.* **2009**, *11*, 4358.

Appendix A2: Characterization Spectra Relevant to Chapter Three

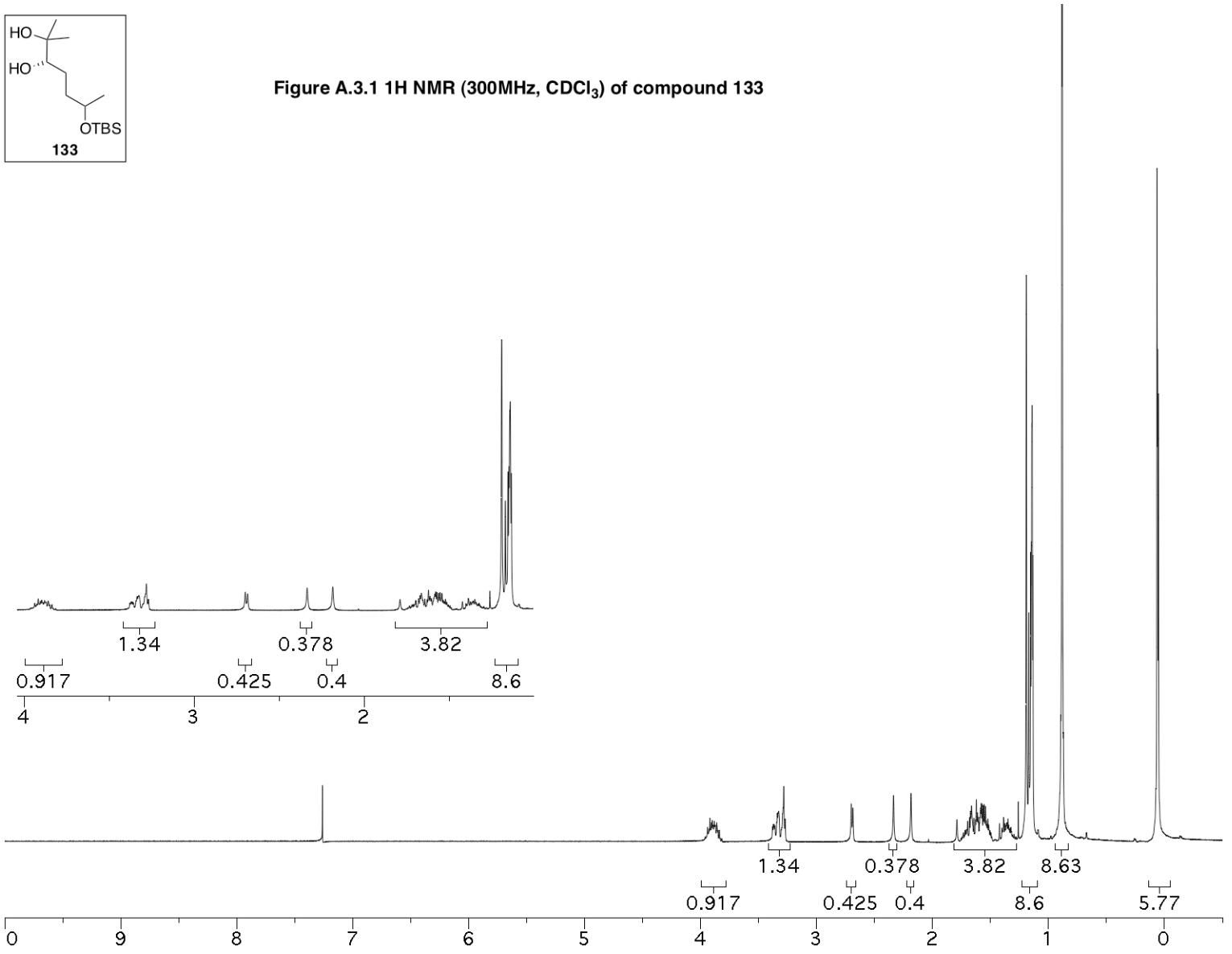


Figure A.3.1 1H NMR (300MHz, $CDCl_3$) of compound 133

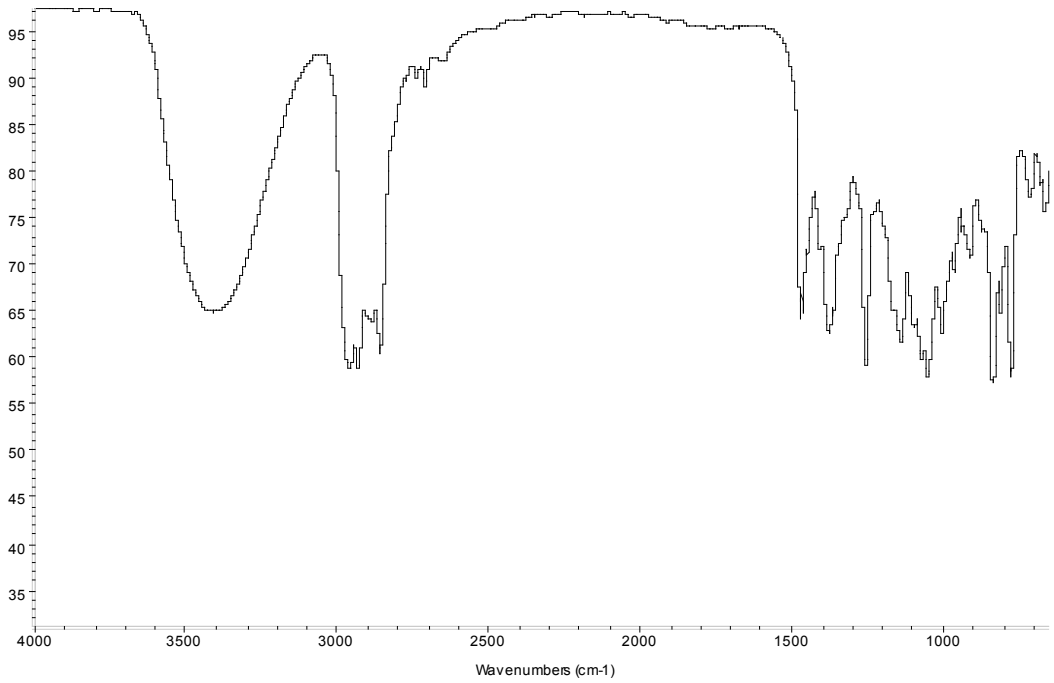


Figure A3.2 Infrared Spectrum (thin film/NaCl) of compound **133**

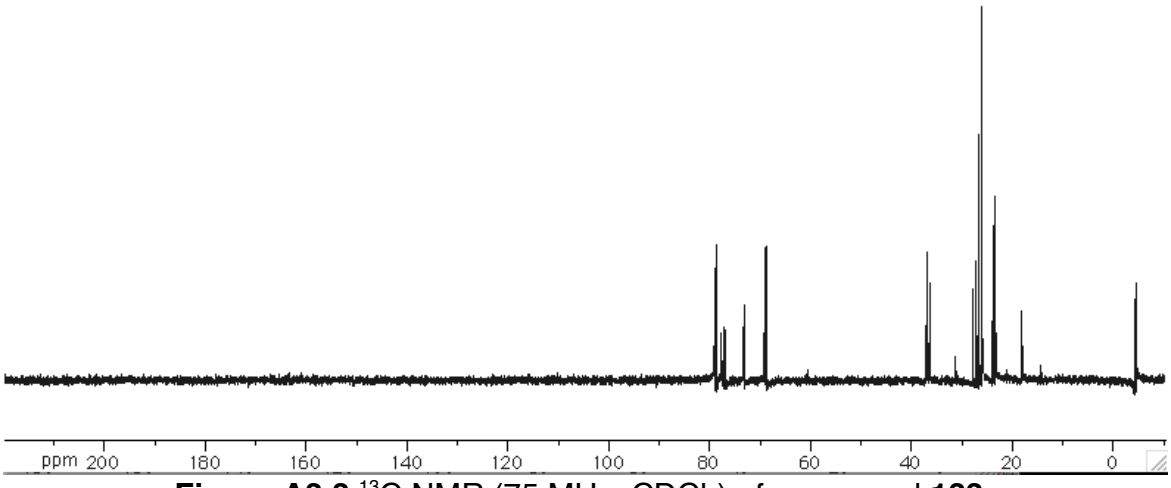


Figure A3.3 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **133**

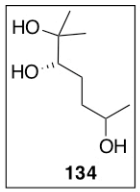


Figure A.3.4 1H NMR (300MHz, $CDCl_3$) of compound 134

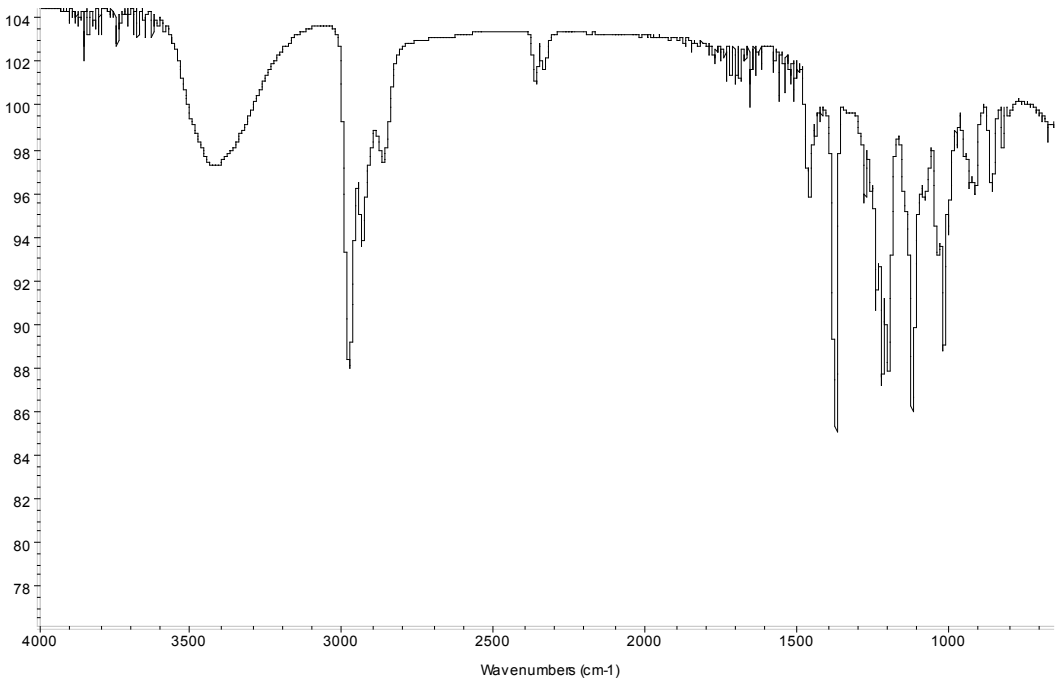


Figure A3.5 Infrared Spectrum (thin film/NaCl) of compound **134**

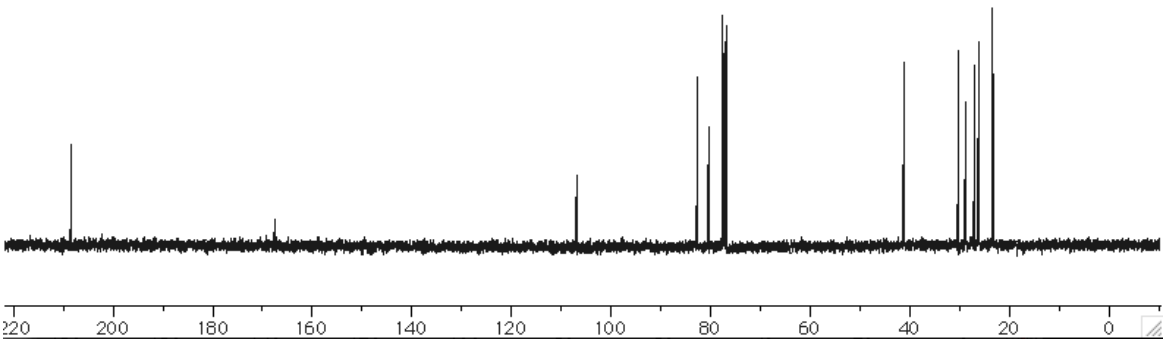


Figure A3.6 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **134**

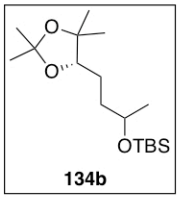


Figure A.2.52 1H NMR (400MHz, $CDCl_3$) of compound 134b

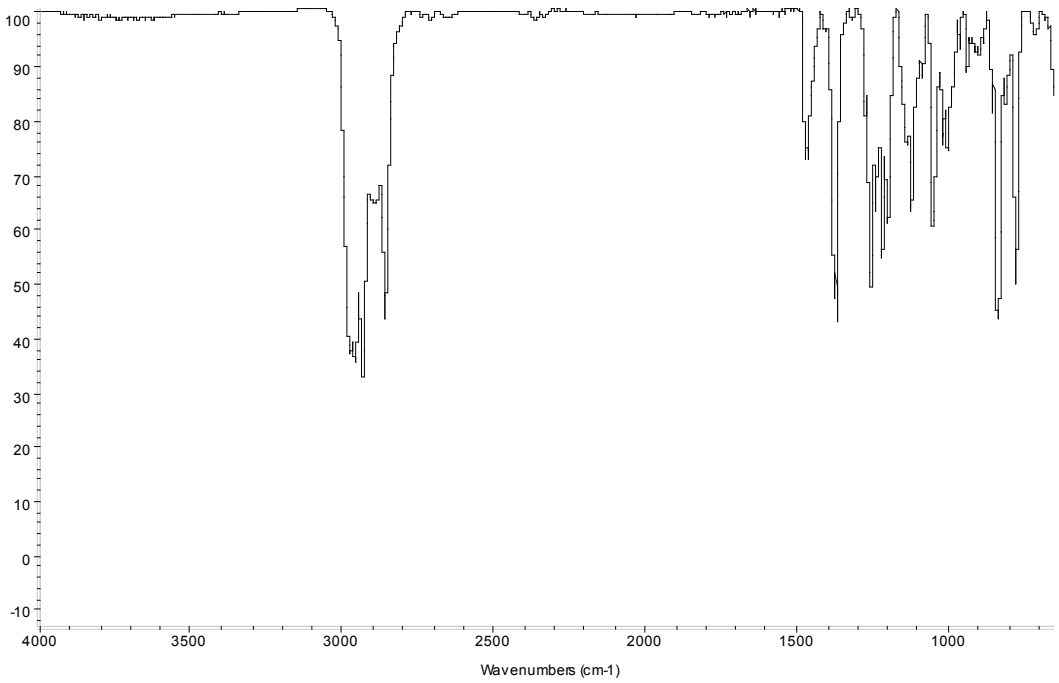


Figure A3.8 Infrared Spectrum (thin film/NaCl) of compound**134b**

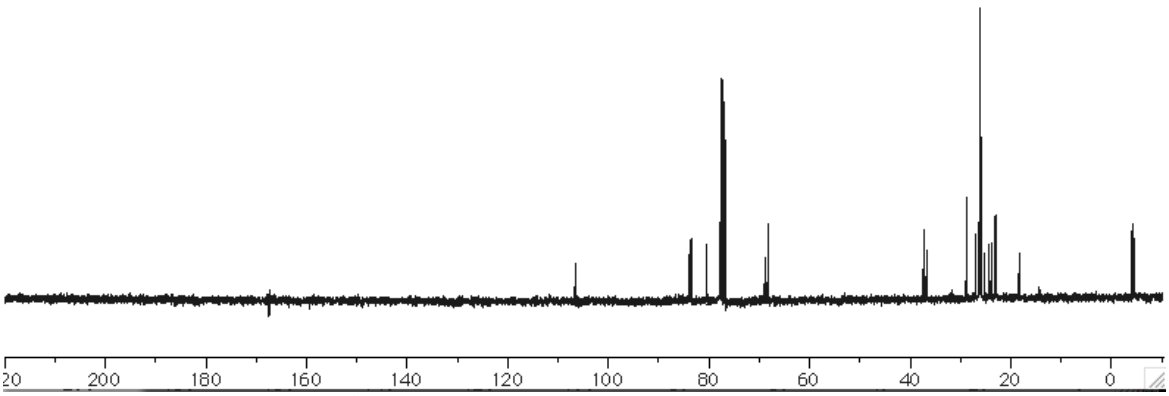


Figure A3.9 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **134b**

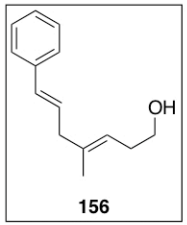
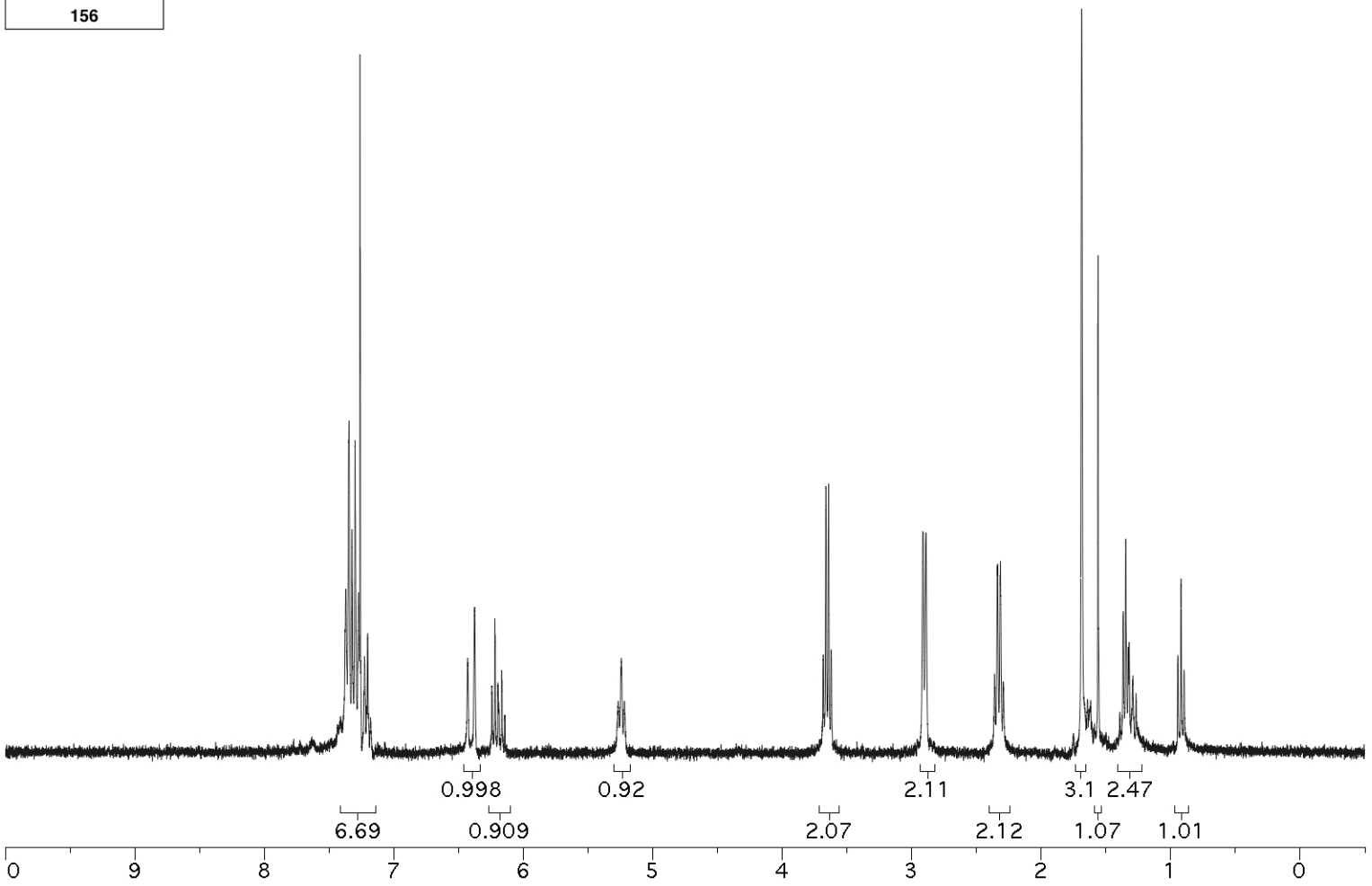


Figure A.3.10 1H NMR (300MHz, $CDCl_3$) of compound 156



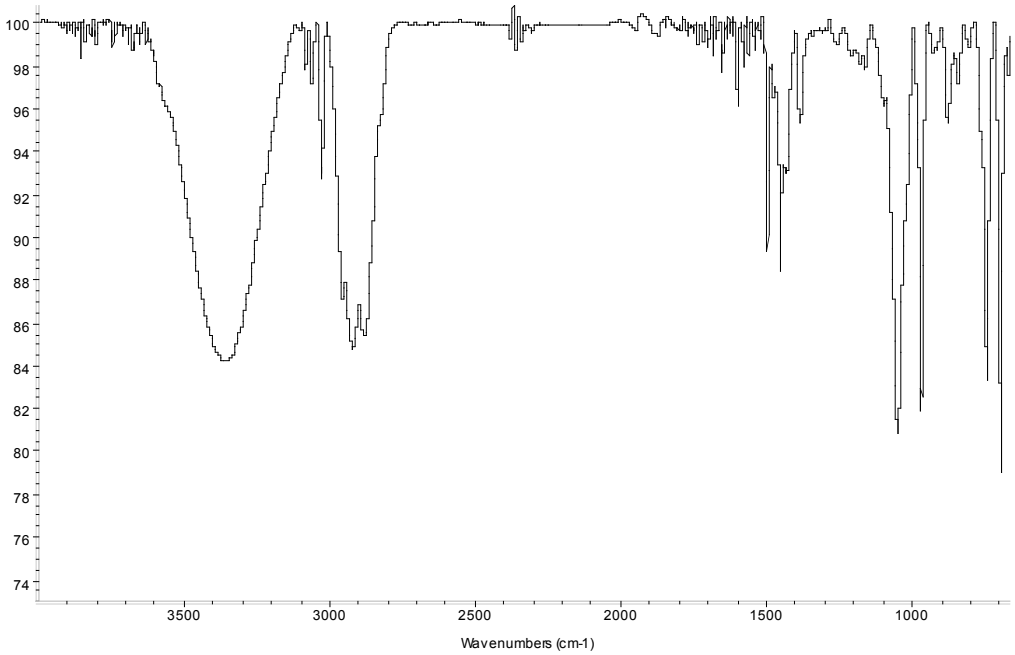


Figure A3.11 Infrared Spectrum (thin film/NaCl) of compound **156**

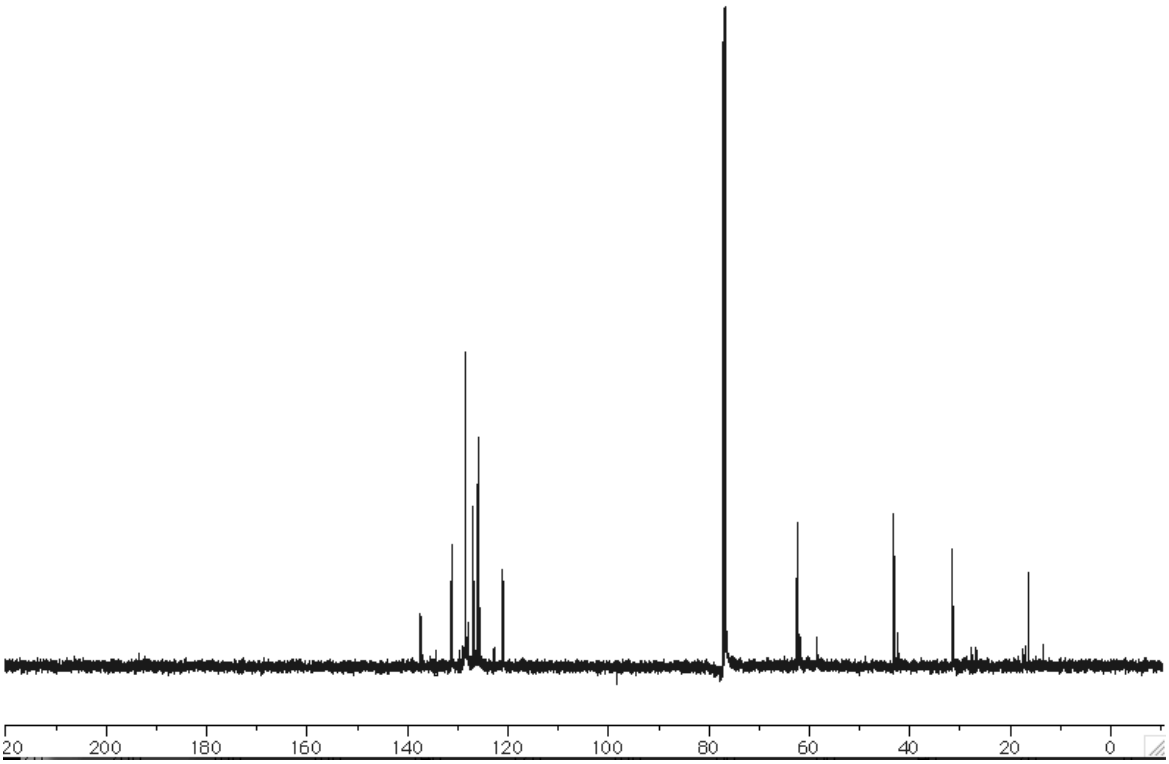
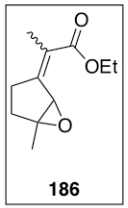
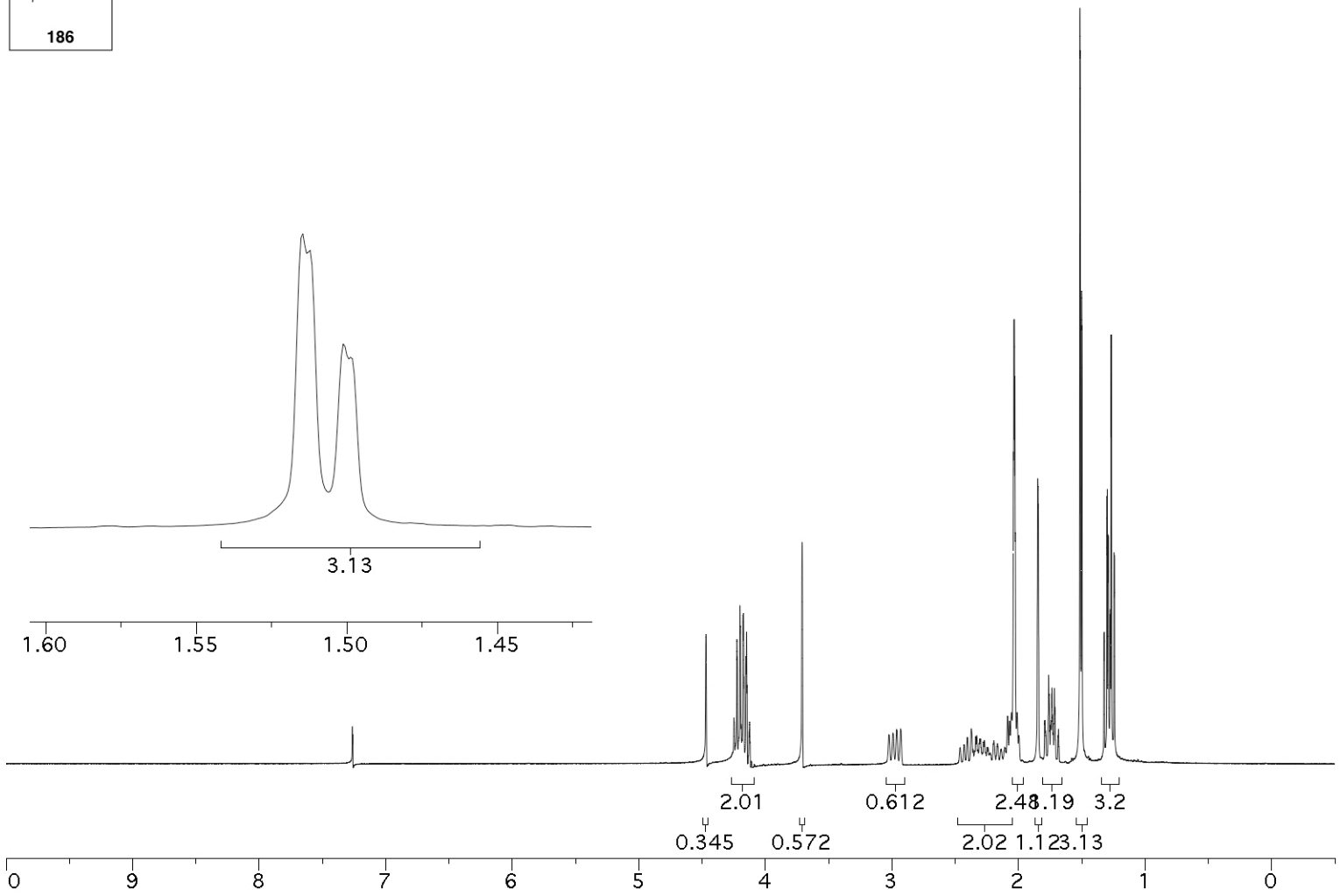


Figure A3.12 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **156**



186

Figure A.3.13 1H NMR (300MHz, $CDCl_3$) of compound 186



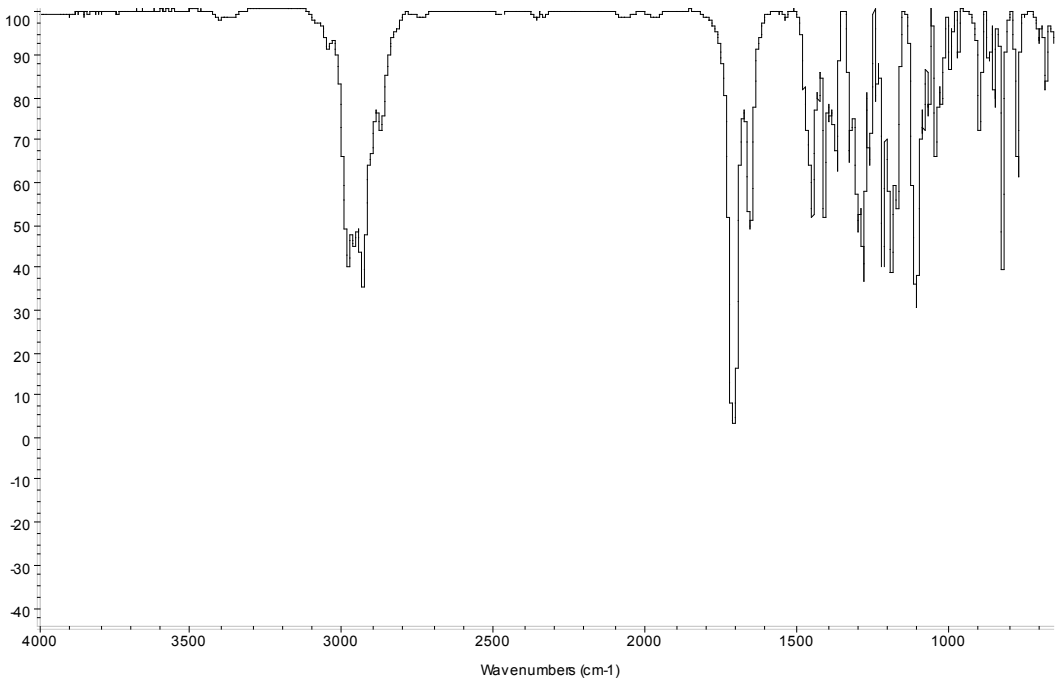


Figure A3.14 Infrared Spectrum (thin film/NaCl) of compound **186**

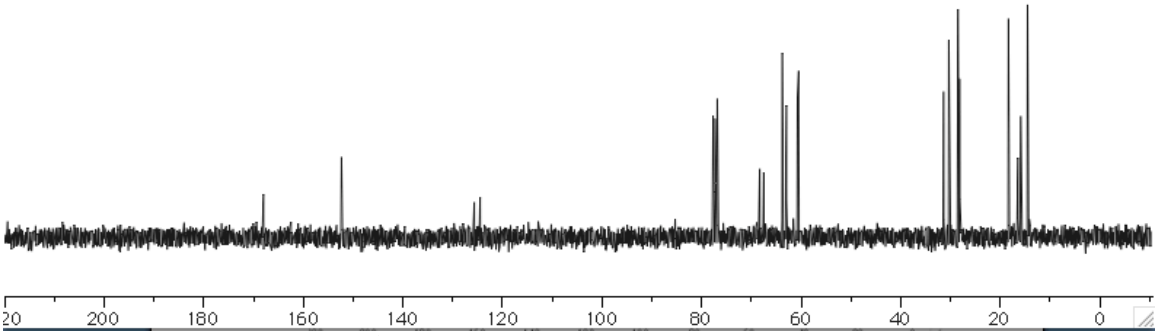


Figure A3.15 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **186**.

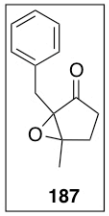
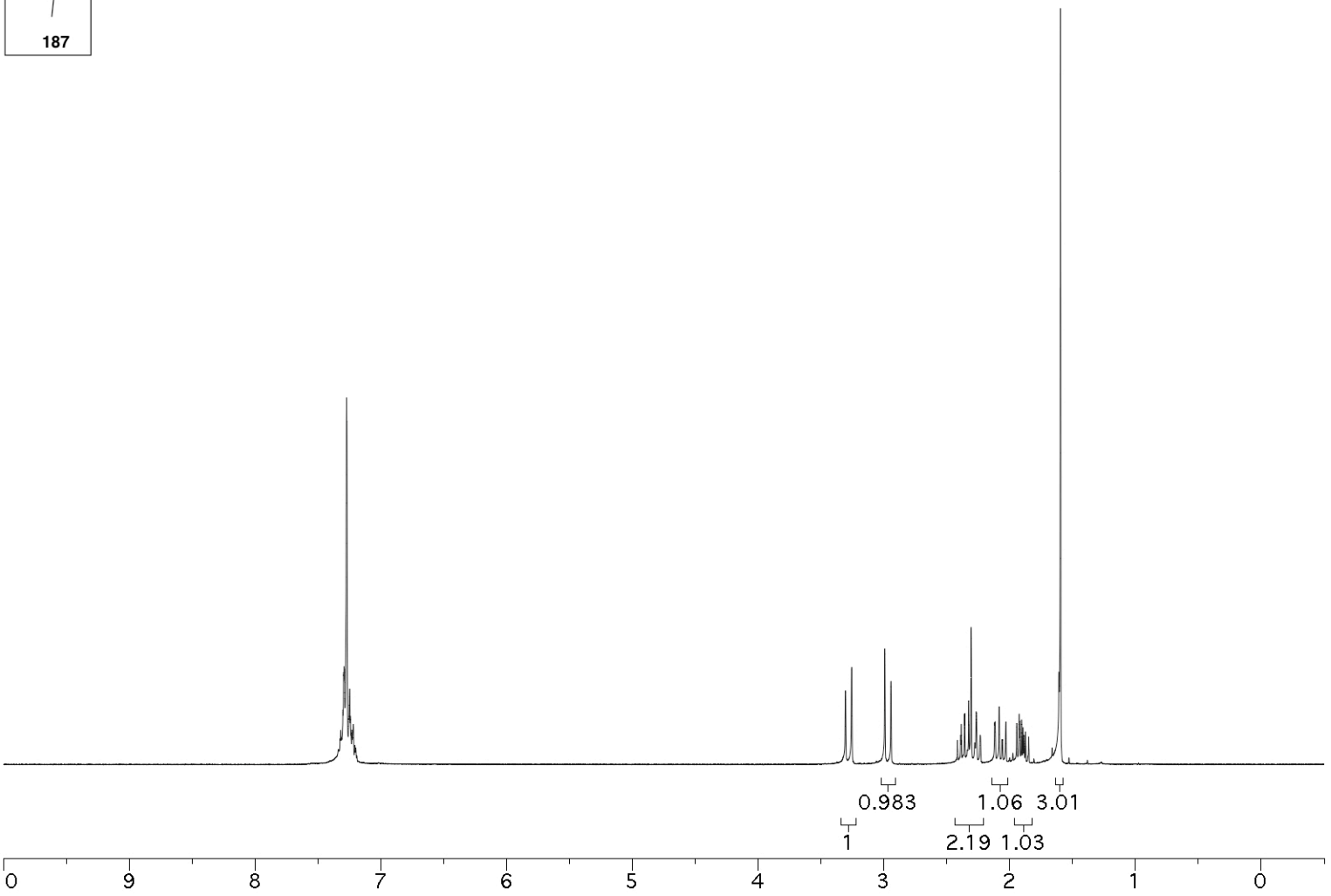


Figure A.3.16 1H NMR (300MHz, $CDCl_3$) of compound 187



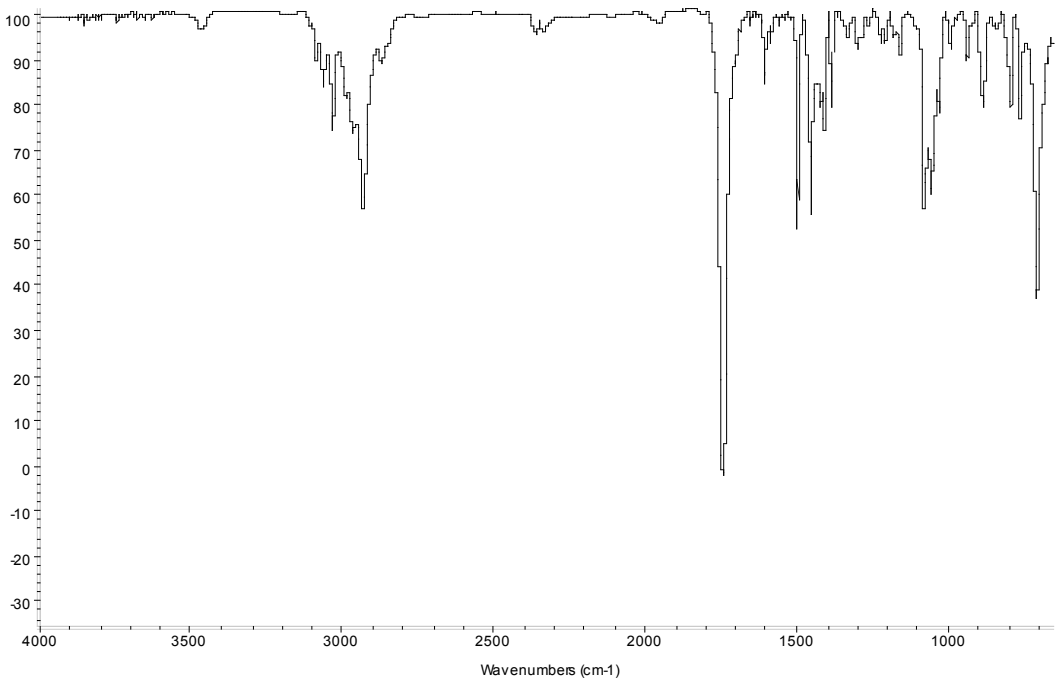


Figure A3.17 Infrared Spectrum (thin film/NaCl) of compound **187**

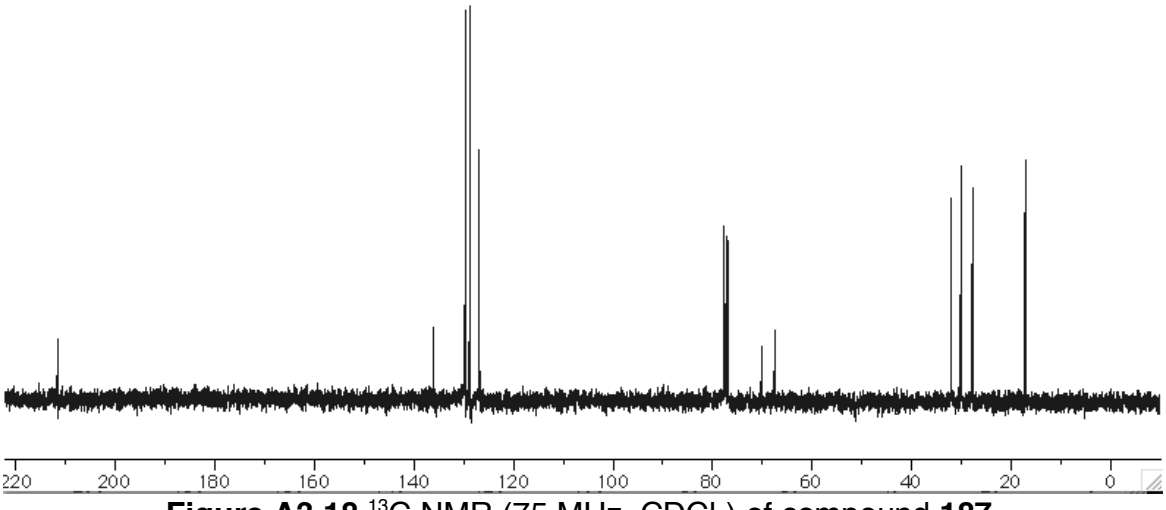
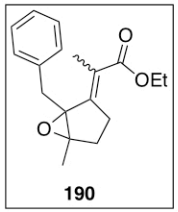


Figure A3.18 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **187**



190

Figure A.3.19 1H NMR (400MHz, $CDCl_3$) of compound 190

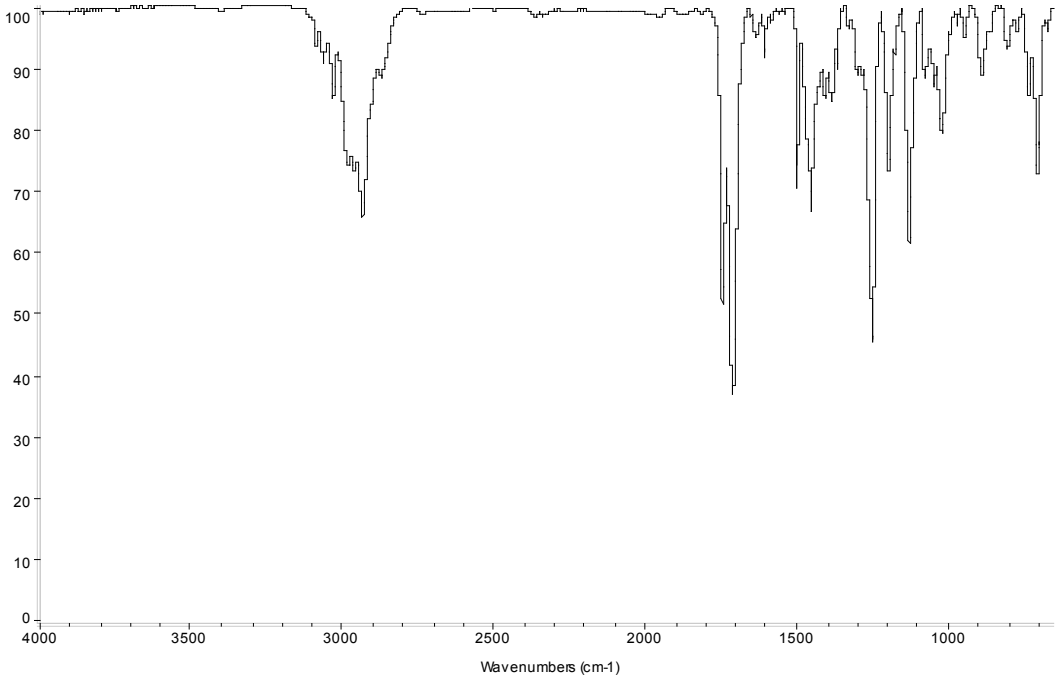


Figure A3.20 Infrared Spectrum (thin film/NaCl) of compound **190**

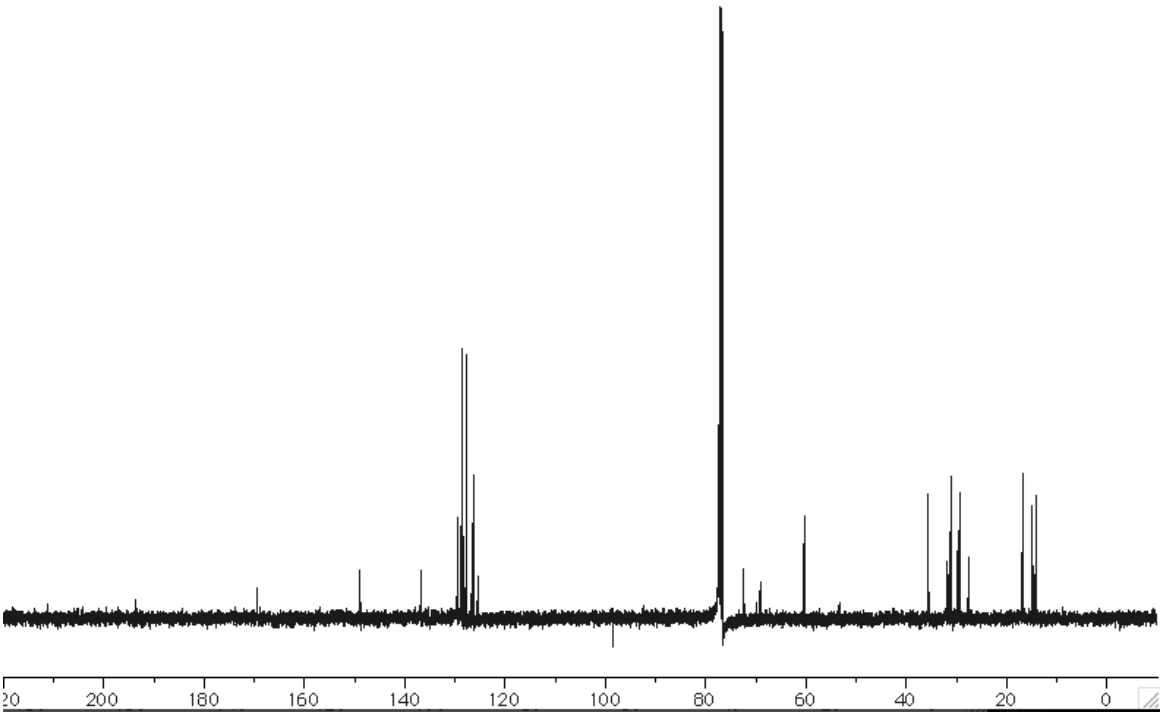
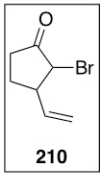
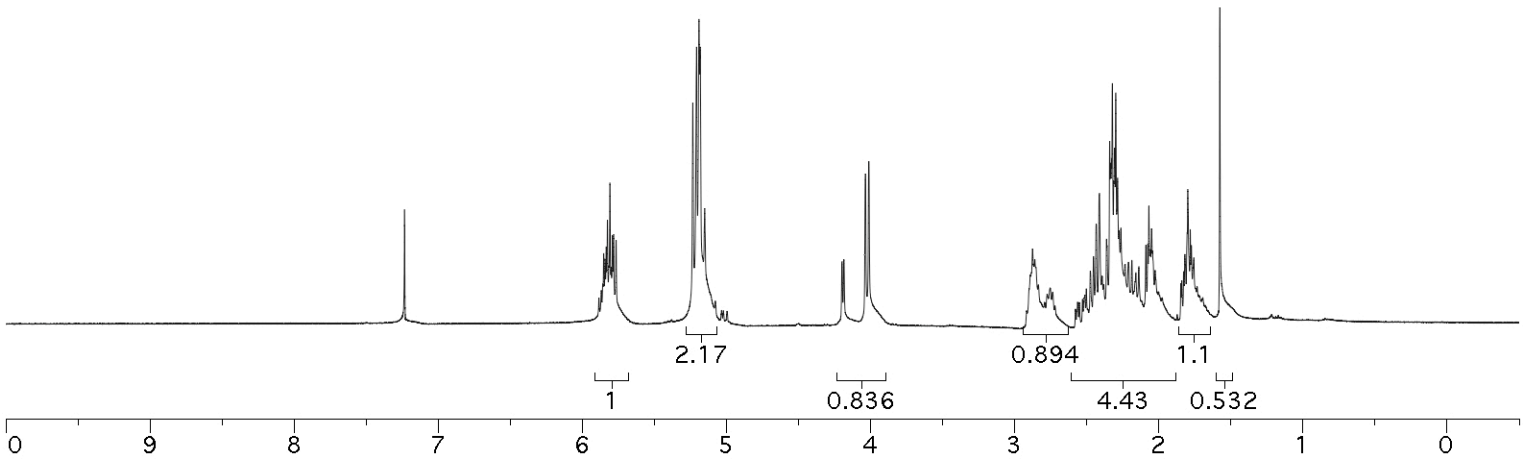


Figure A3.21 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **190**



210

Figure A.3.22 1H NMR (400MHz, $CDCl_3$) of compound 210



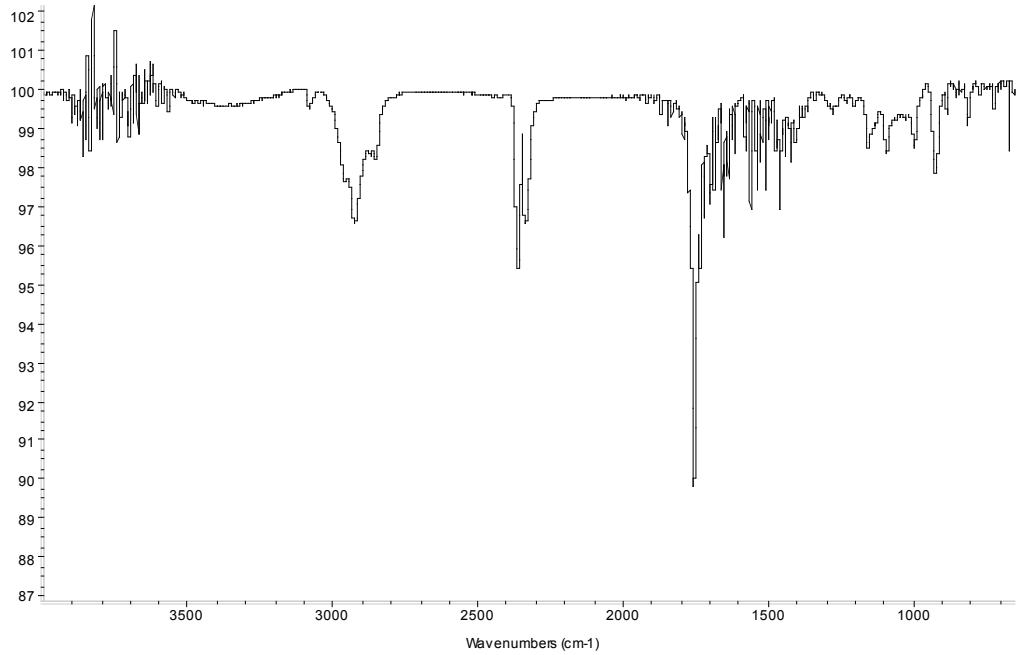


Figure A3.23 Infrared Spectrum (thin film/NaCl) of compound **210**

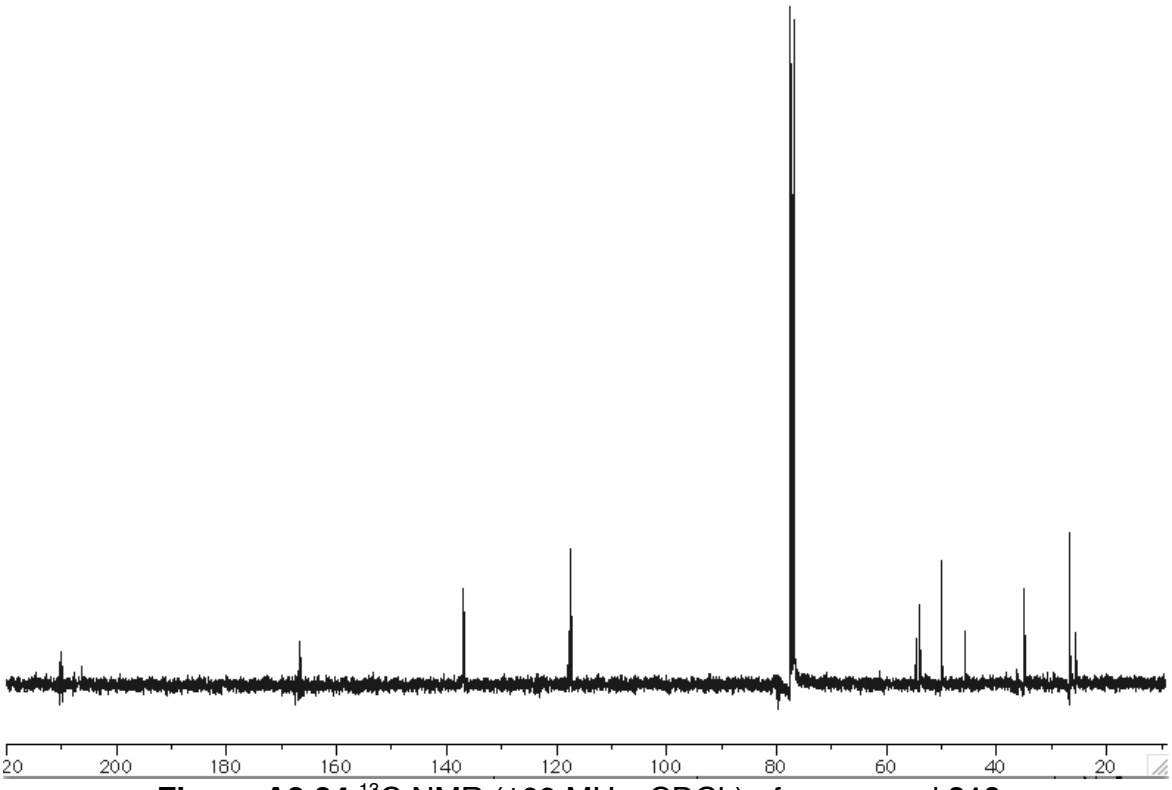


Figure A3.24 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **210**

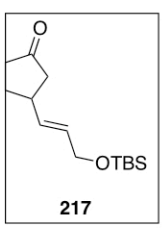


Figure A.3.25 1H NMR (300MHz, $CDCl_3$) of compound 217

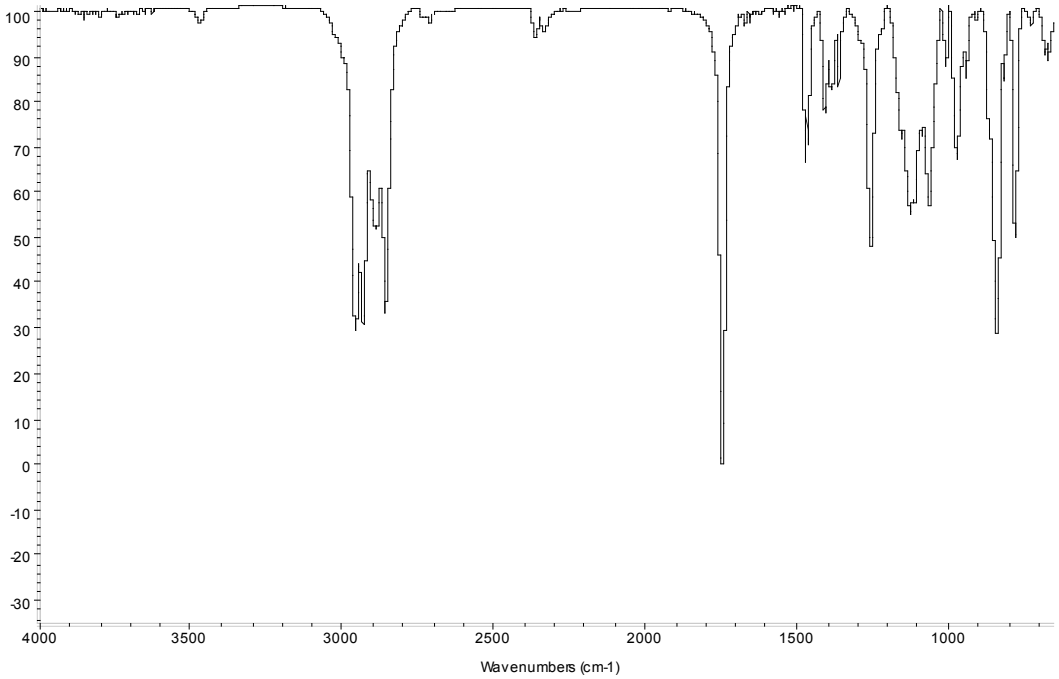


Figure A3.26 Infrared Spectrum (thin film/NaCl) of compound **217**

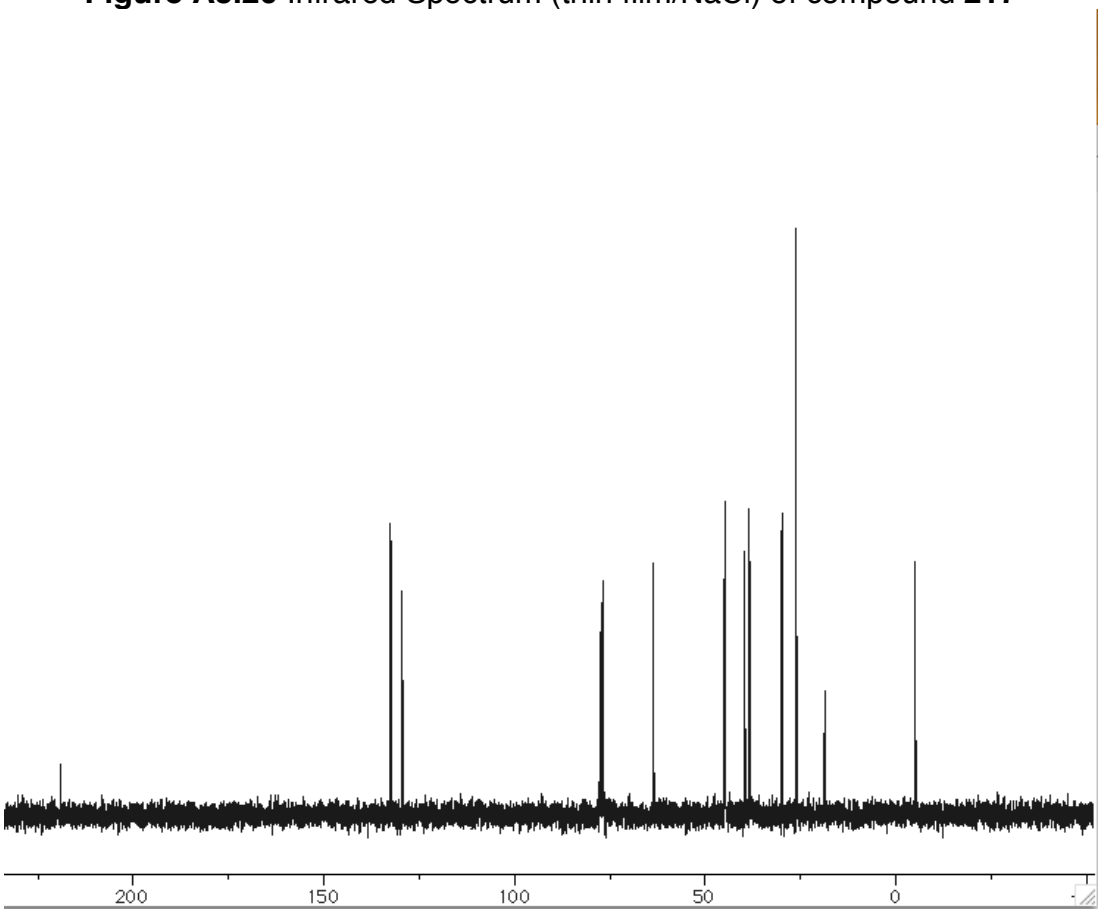
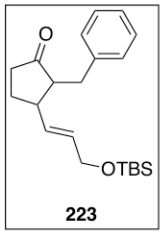


Figure A3.27 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **217**



223

Figure A.3.28 1H NMR (300MHz, $CDCl_3$) of compound 223

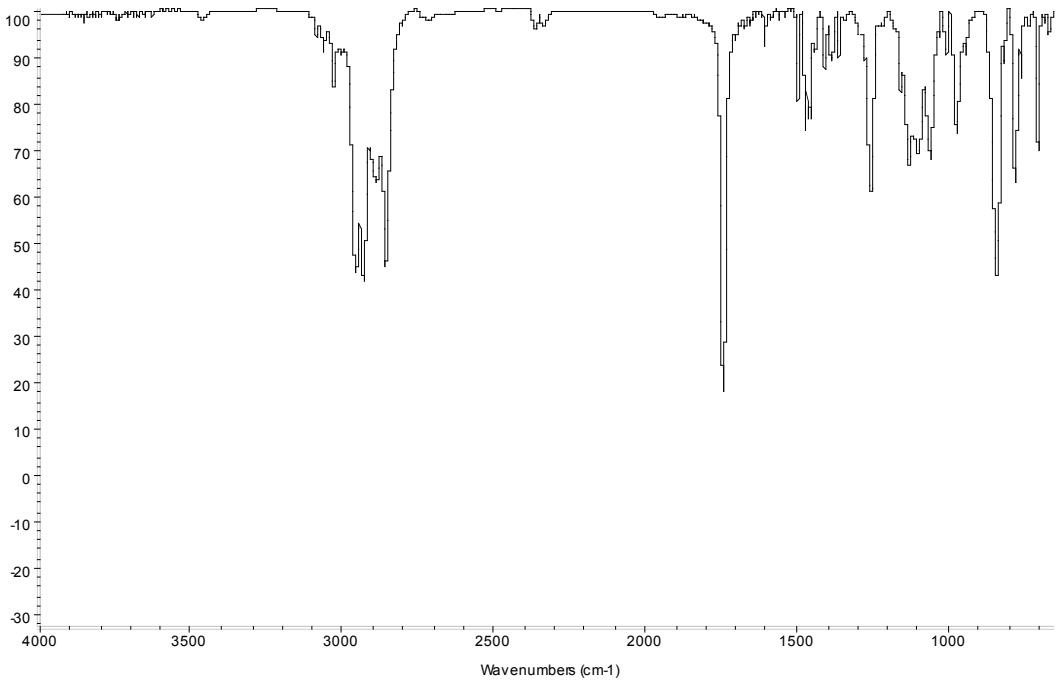


Figure A3.29 Infrared Spectrum (thin film/NaCl) of compound **223**

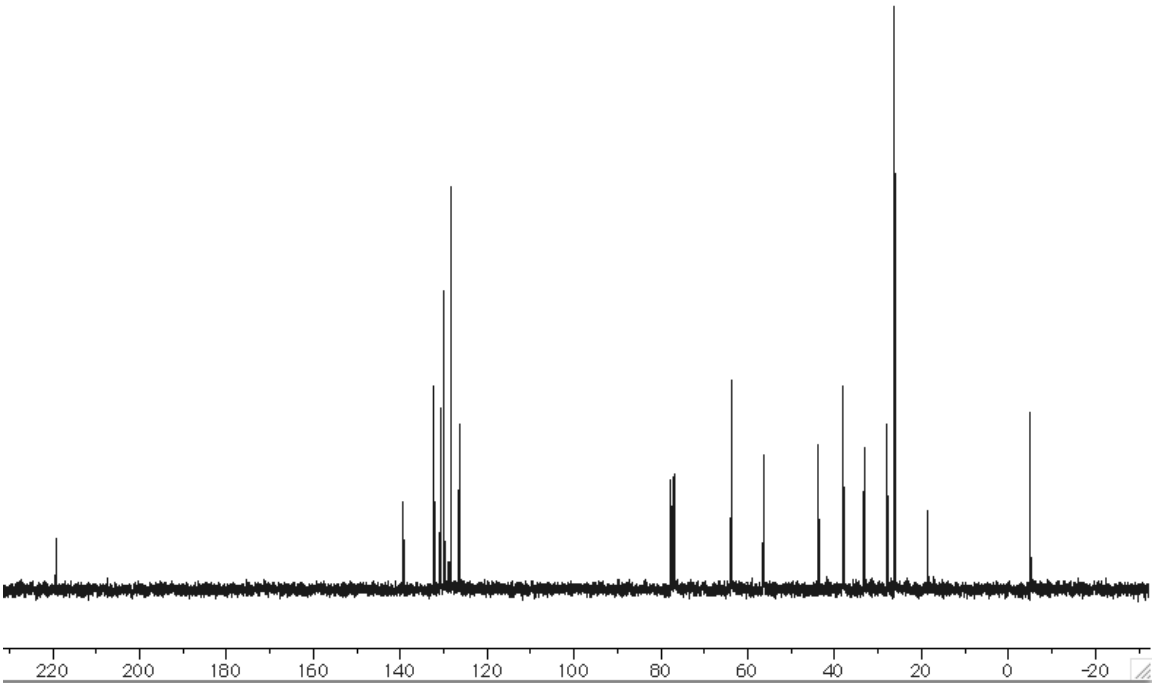


Figure A3.30 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **223**

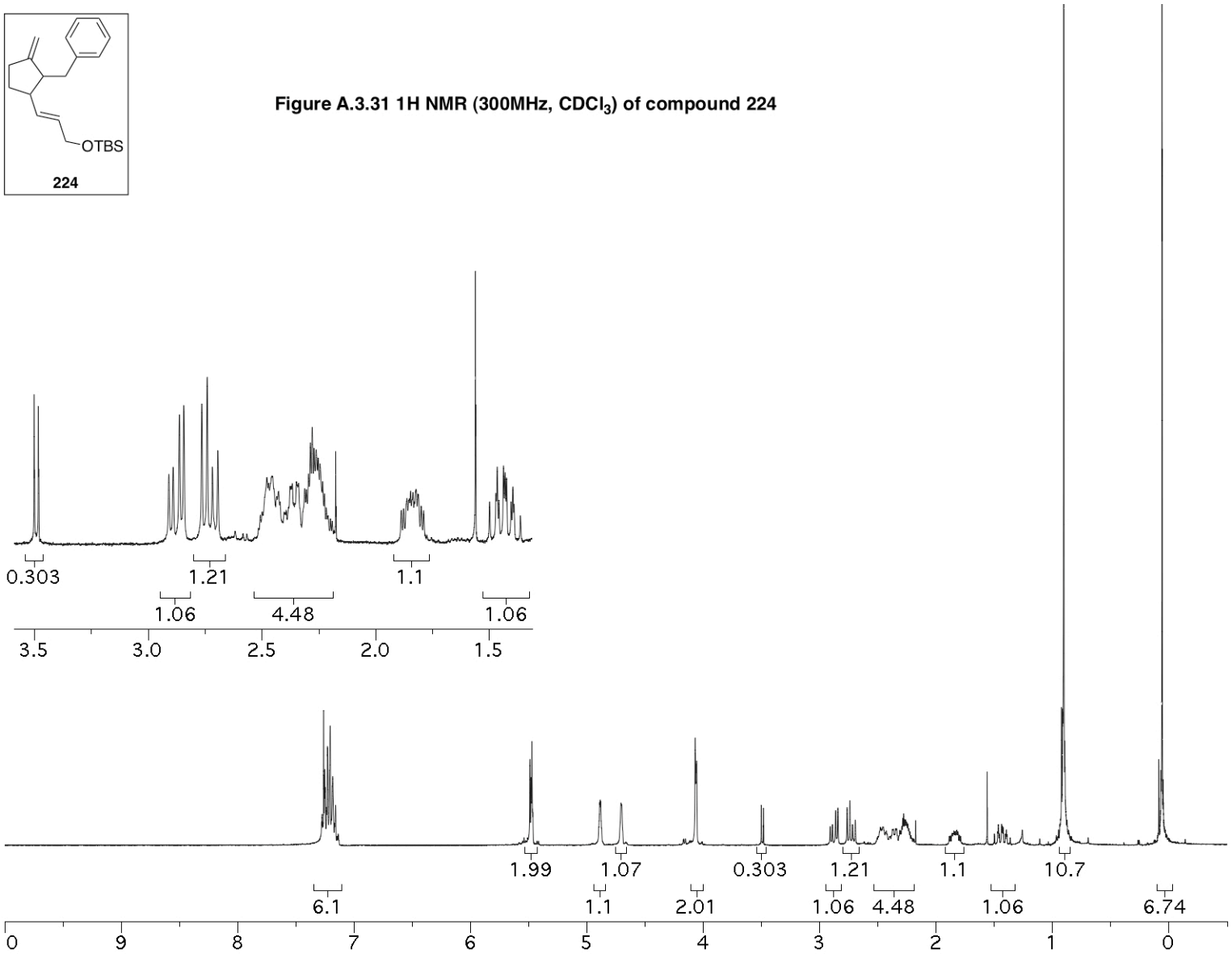


Figure A.3.31 1H NMR (300MHz, $CDCl_3$) of compound 224

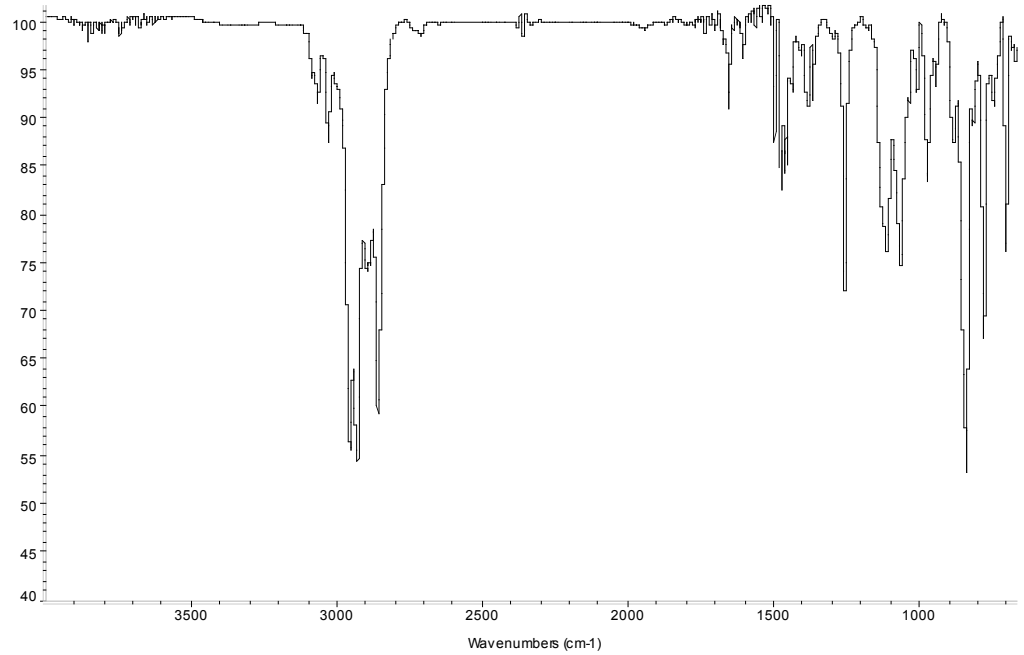


Figure A3.32 Infrared Spectrum (thin film/NaCl) of compound **224**

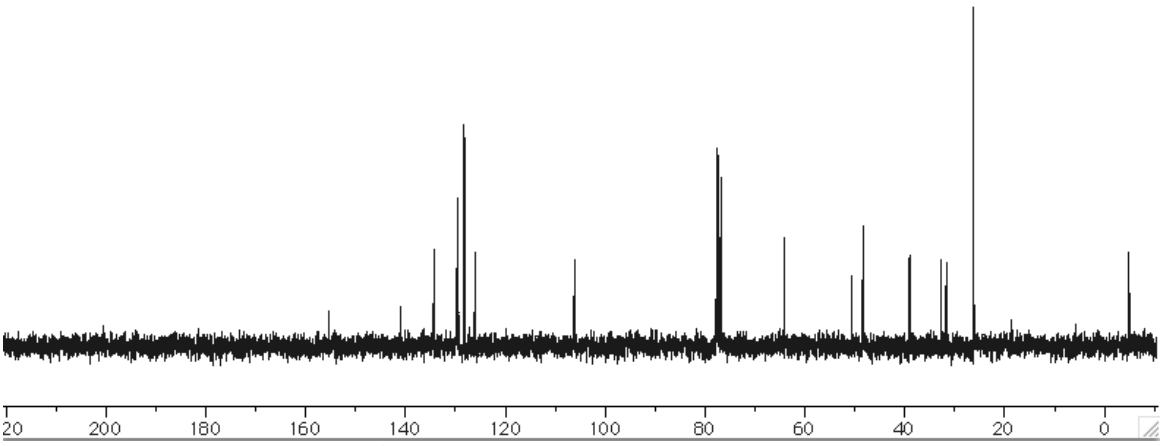


Figure A3.33 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **224**

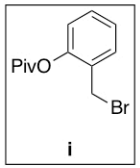


Figure A.3.34 1H NMR (400MHz, $CDCl_3$) of compound i

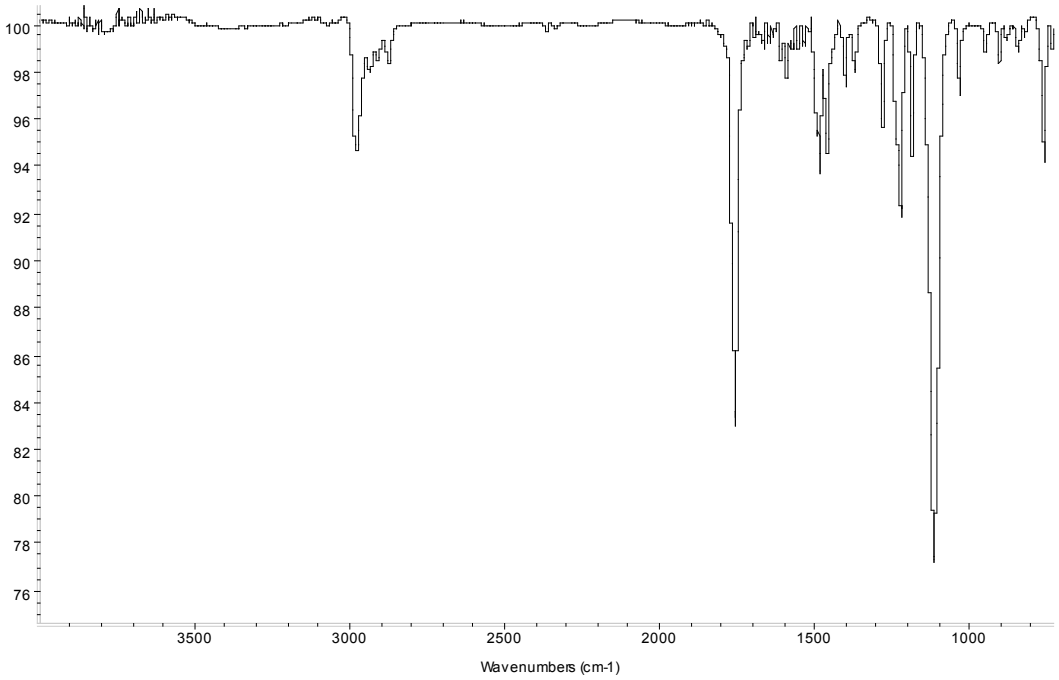


Figure A3.35 Infrared Spectrum (thin film/NaCl) of compound **i**

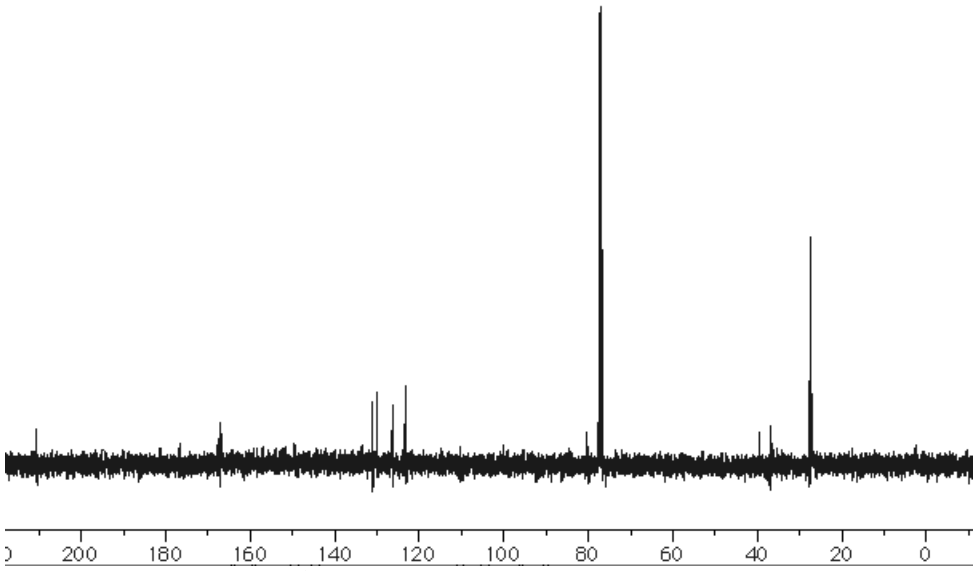
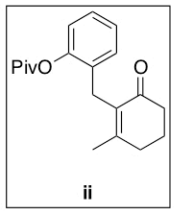


Figure A3.36 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **i**



ii

Figure A.3.37 1H NMR (300MHz, $CDCl_3$) of compound ii

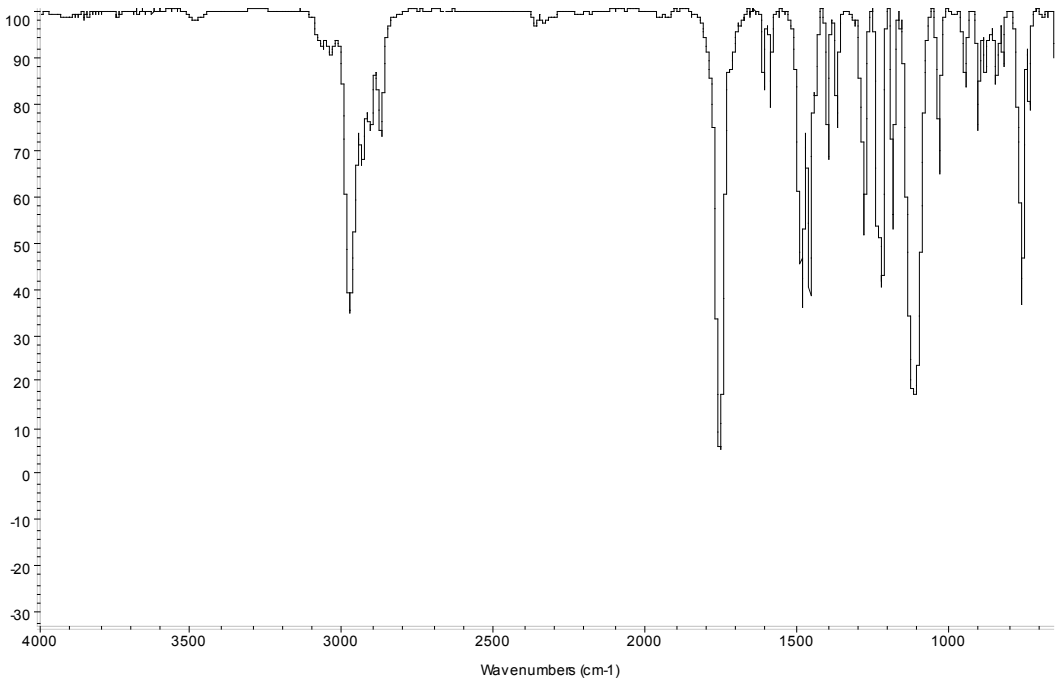


Figure A3.38 Infrared Spectrum (thin film/NaCl) of compound **ii**

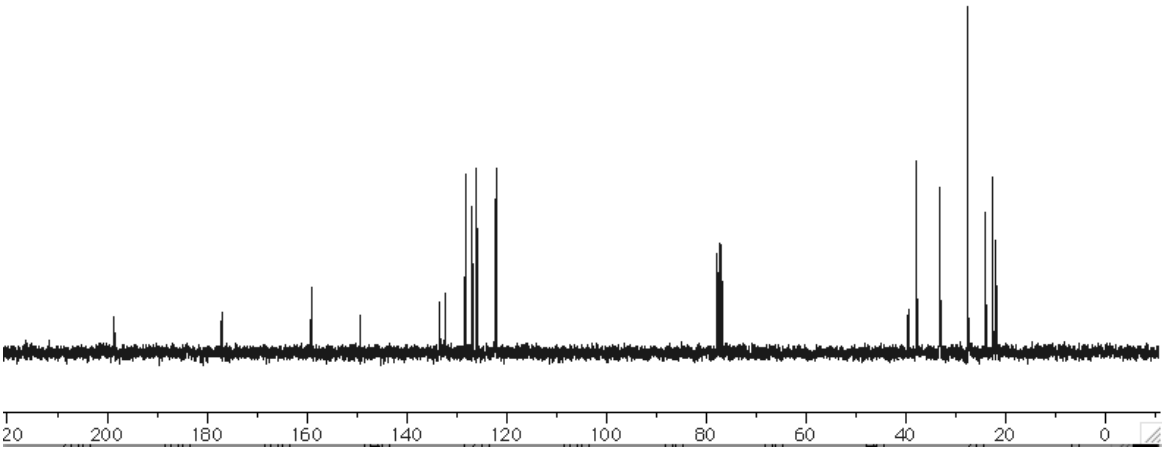
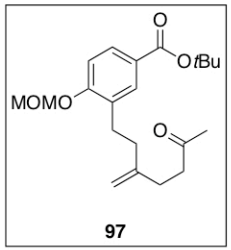


Figure A3.39 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **ii**



97

Figure A.3.40 1H NMR (300MHz, $CDCl_3$) of compound iii

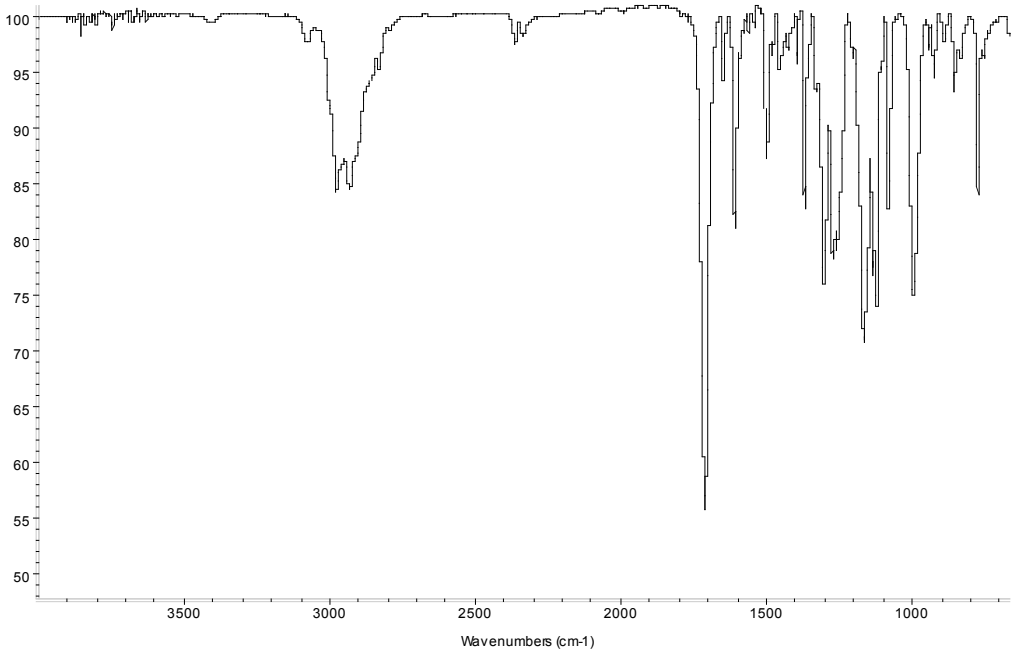


Figure A3.41 Infrared Spectrum (thin film/NaCl) of compound **iii**

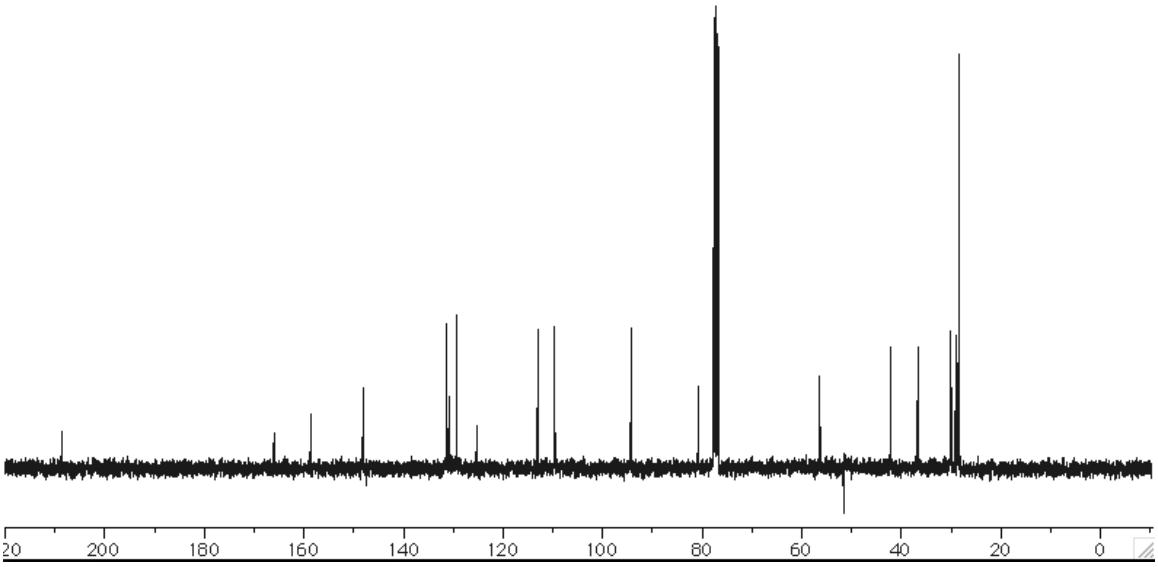
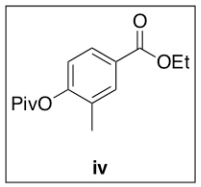


Figure A3.42 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **iii**



iv

Figure A.3.43 1H NMR (300MHz, $CDCl_3$) of compound iv

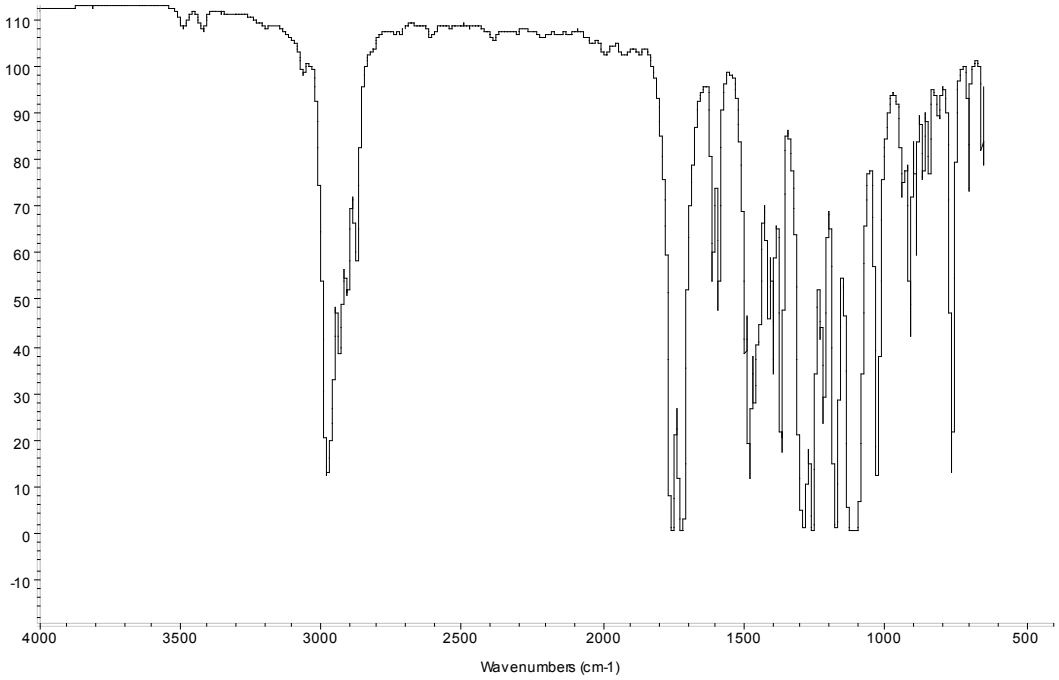


Figure A3.44 Infrared Spectrum (thin film/NaCl) of compound **iv**

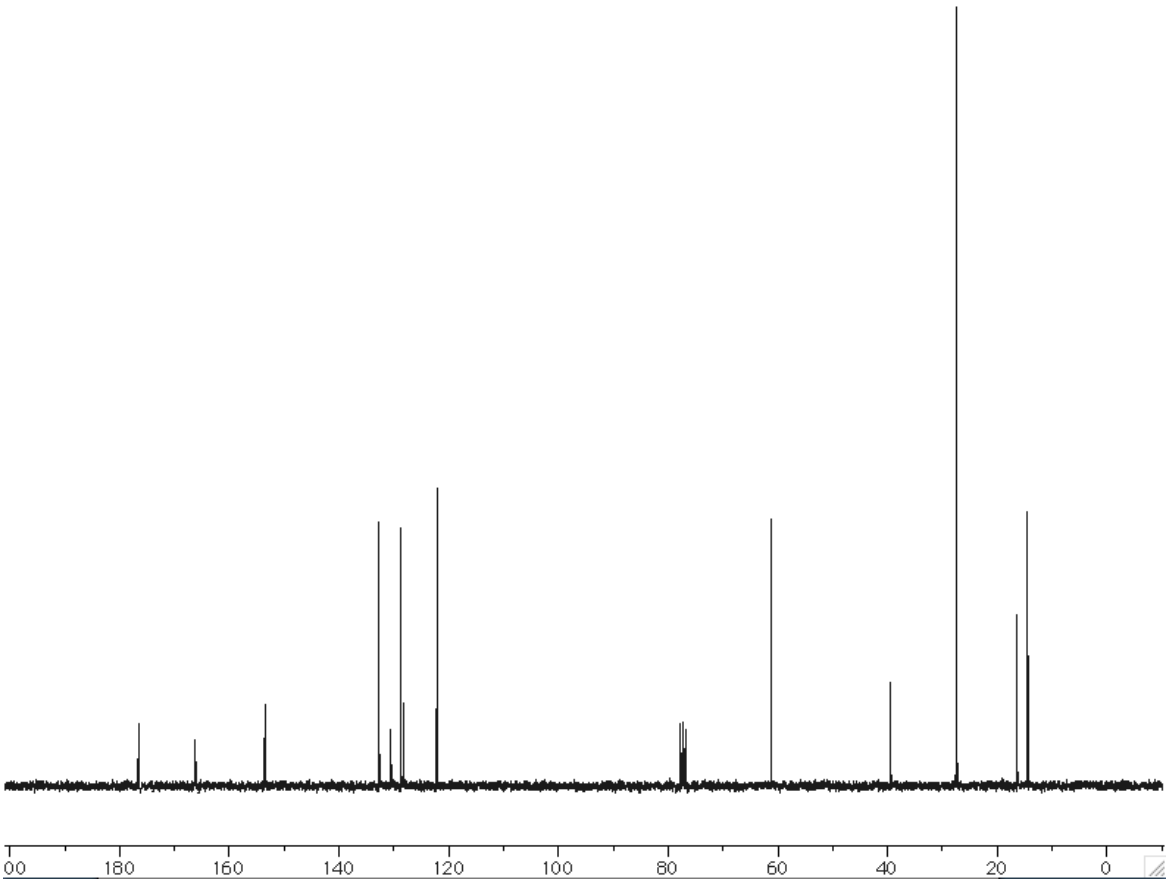
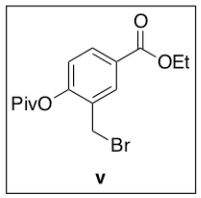


Figure A3.45 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **iv**



v

Figure A.3.46 1H NMR (300MHz, $CDCl_3$) of compound v

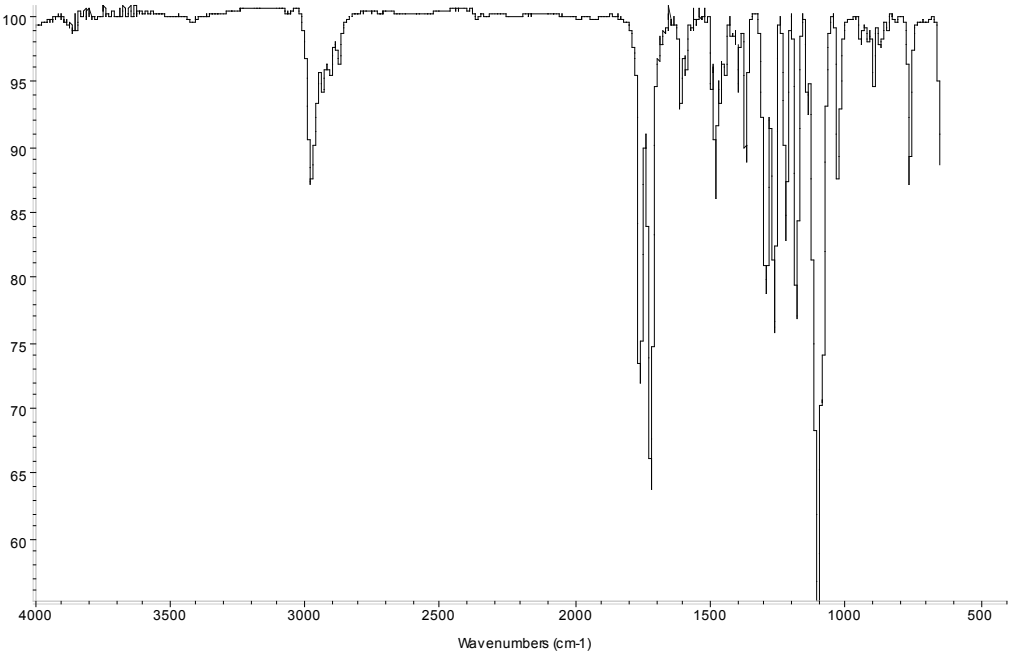


Figure A3.47 Infrared Spectrum (thin film/NaCl) of compound **v**

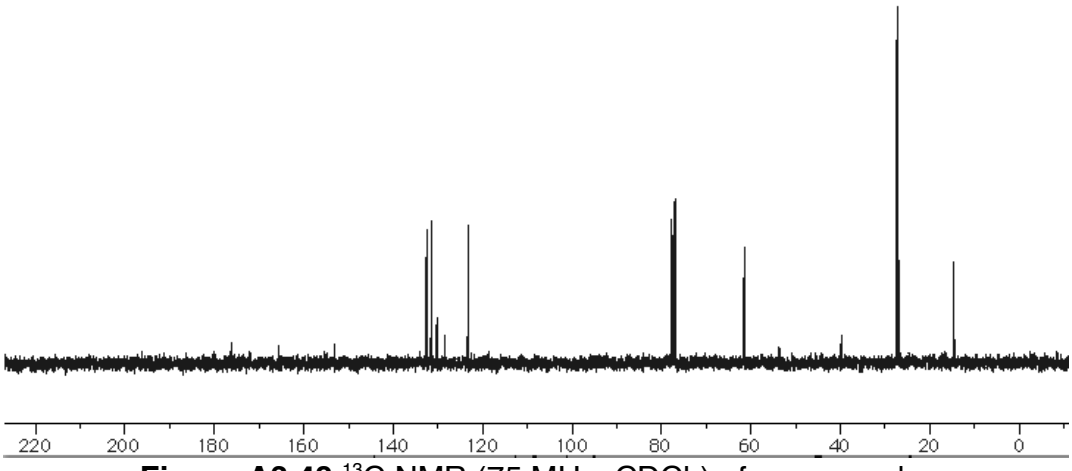
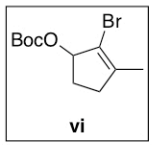


Figure A3.48 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **v**



vi

Figure A.3.49 1H NMR (300MHz, $CDCl_3$) of compound vi

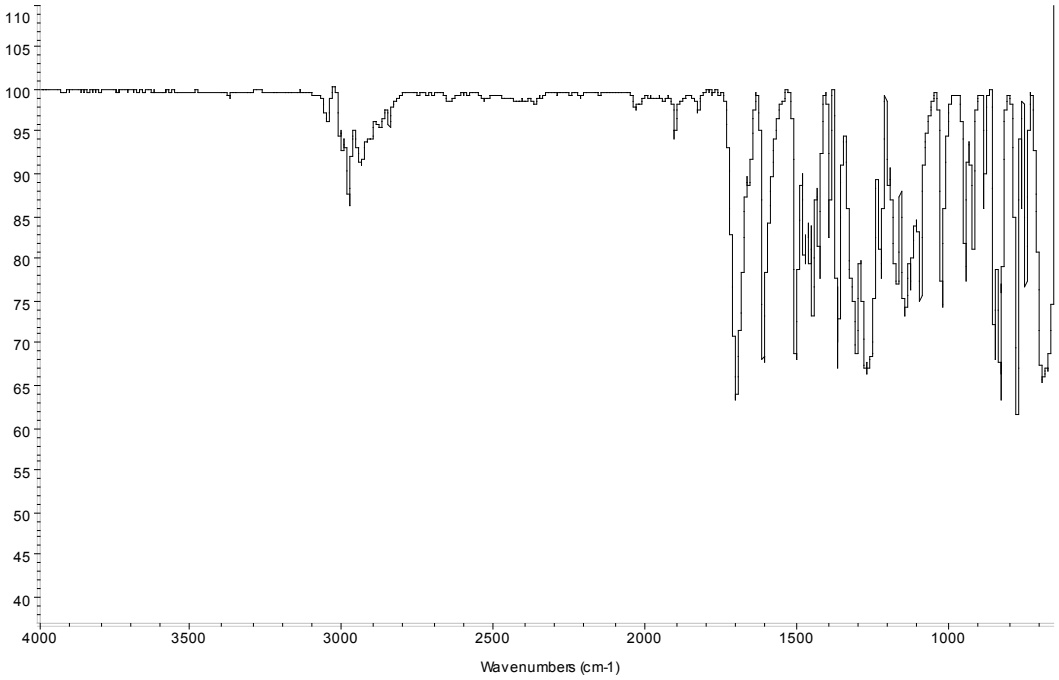


Figure A3.50 Infrared Spectrum (thin film/NaCl) of compound **vi**

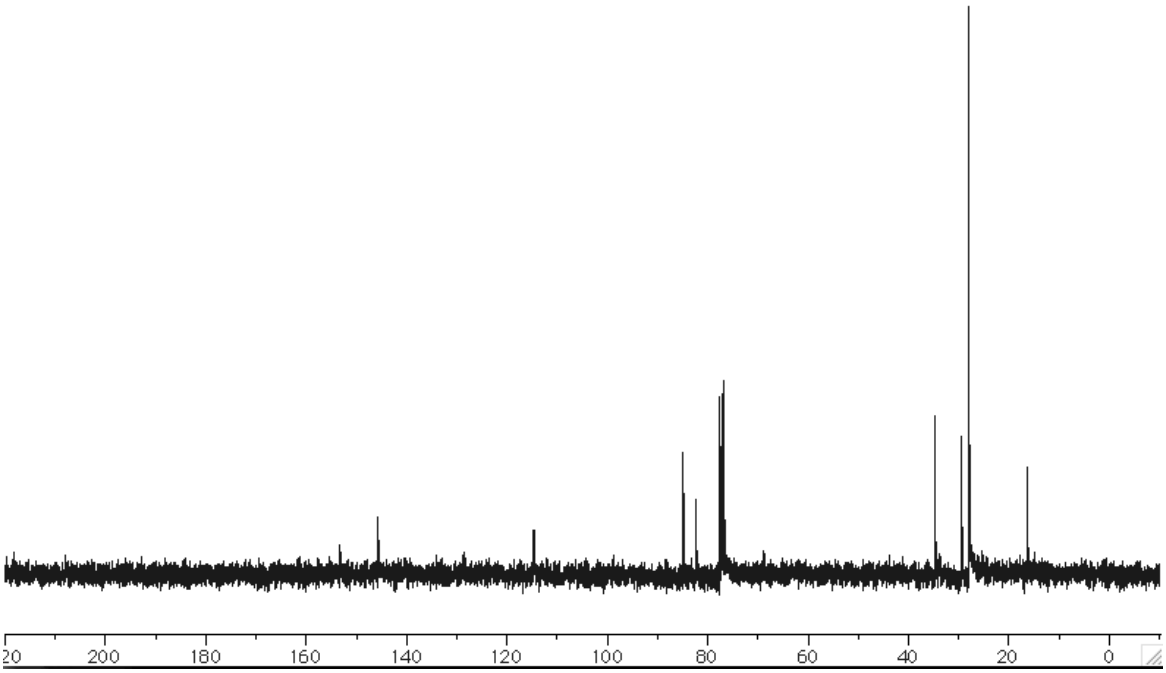
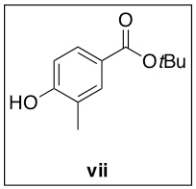
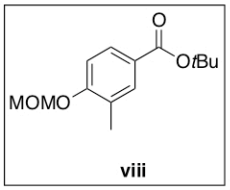


Figure A3.51 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **vi**



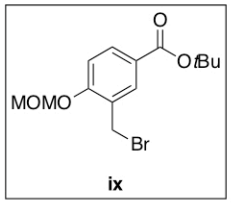
vii

Figure A.3.52 1H NMR (300MHz, $CDCl_3$) of compound vii



viii

Figure A.3.53 1H NMR (300MHz, $CDCl_3$) of compound viii



ix

Figure A.3.54 1H NMR (300MHz, $CDCl_3$) of compound ix

Appendix 3 – Notebook Cross-Reference

The following notebook cross-reference is included to facilitate access to the original spectroscopic data for compounds present in this dissertation. For each compound a book and page number are given which corresponds to an original notebook reference. BJP refers to Brett Joseph Prigaro's notebooks.

Compound	Notebook.Page	Compound	Notebook.Page
43	BJPI.60	108	BJPIII.19
44	BJPI.67	109	BJPIV.15
46	BJPI.121	121	BJPIV.18
74	BJPII.17	133	BJPI.103
75	BJPII.19	134	BJPI.93
76	BJPII.21	134b	BJPI.93
89	BJPII.296	156	BJPIV.106
93	BJPIII.27	186	BJPIV.271
96	BJPIII.12	190	BJPIV.303
97	BJPIII.14	210	BJPV.51
98	BJPIII.21	217	BJPV.106
99	BJPII.283	218	BJPV.174
107	BJPIII.280	219	BJPV.196

Bibliography

Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals*, 5th ed. Elsevier Science: Burlinton, MA., 2003, p142

Bal, B. S.; Childers, W. E.; Pinnick Jr., H. W. *Tetrahedron*, **1981**, *37*, 2091

Bedekar, A. V.; Watanabe, T.; Tanaka, K.; Fuji, K. *Synthesis*, **1995**, *9*, 1069

Behling, J. R.; Babiak, K. A.; Ng, J. S.; Campbell, A. L.; Moretti, R.; Koerner, M.; Piers, E.; Gavai, A. V. *J. Org. Chem*. **1990**, *55*, 2380

Betzer, J.-F.; Delaloge, F.; Muller, B.; Pancrazi, A.; Prunet, J. *J. Org. Chem.* **1997**, *62,* 7768

Brimble, M. A.; Rowan, D. D.; Spicer, J. A. *Synthesis* **1995**, 1263.

Büchi, G.; Wüest, H. *J. Org. Chem.* **1966**, *31*, 977

Calaza, M. I.; Hupe, E.; Knochel, P. *Org. Lett.* **2003**, *5*, 1059

Campagne, J.-M.; Porenty, A.; Moreau, A.; Chemier, X. *Chem. Rev.* **2006**, *106*, 911

Carrillo-Marquez, T.; Caggiano, L.; Jackson, R. F. W.; Grabowska, U.; Rae, A.; Tozer, M. *J. Org. Biomol. Chem*. **2005**, *3*, 4117

Carter- Franklin, J.N.; Parrish, J. D.; Tschirret-Guth, R. A.; Little, R.D.; Butler, A. *J. Am. Chem. Soc.* **2003**, *125*, 3688.

Castaño, A. M.; Echavarren, A. M. *Tetrahedron Lett.* **1996**, *37*, 6587

Chandler, C. L.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 6737

Choudhary, A.; Baumstark, A. L. *Synthesis*, **1989**, *9*, 688

Conlon, D. A.; Kumke, D.; Moeder, C.; Hardiman, M.; Hutson, G.; Sailer, L. *Adv. Synth. Catal.* **2004**, *346*, 1307

Darwish, A.; Lang, A.; Kim, T.; Chang, J.-M. *Org. Lett.* **2008**, *10*, 861

Del Valle, L. Stille, J. K. Hegedus, L. S. *J. Org. Chem.* **1990**, *55*, 3019

Djessari C. *Chem. Rev.* **1948**, *43*, 271

Faulkner, D. J. *Pure Appl. Chem.* **1976**, *48*, 25.

Franzblau, S. G.; Roch, K. L.; Prudhomme, J.; Aalbersberg, W.; Kubanek, J. *J. Org. Chem.* **2007**, *72*, 7343.

Gary, N. K.; Quasdorf, K. W.; Tian, X. *J. Am. Chem. Soc.*, **2008**, *130*, 14422

Gibble, G. W. *Chem. Soc. Rev.* **1999**, *28*, 335

Grundl, M. A.; Trauner, D. *Org. Lett.* **2006**, *8*, 23

Hart, D. W.;Schwartz, J. *J. Am. Chem. Soc* **1974**, *96*, 8115

He, W.; Huang, J.; Sun, X.; Frontier, A. J. *J. Am. Chem. Soc.* **2007**, *129*, 498

Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263.

Hogenauer, K.; Mulzer, J. *Org. Lett.* **2001**, *3*, 1495

Huang, Z.; Negishi, E.-I. *Org. Lett.* **2006**, *8*, 3675

Hunsdiecker, H. *Ber.* **1942**, *75*, 460Gilman, H.; Straley, J. M. *Red. Trav. Chim. Pays-Bas* **1936**, *55*, 821

Hutchins, R. O.; Kacher, M.; Rua, L. *J. Org. Chem*. **1975**, *40*, 923

Inamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392

Johnson, W. S.; Werthman, L.; Barlett, W. R.; Li, T.-T.; Faulkner, D. J.; Peterson, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741

Jung, M. E.; Berliner, J. A.; Angst, D.; Yue, D.; Koroniak, L.; Watson, A. D.; Li, R. *Org. Lett.* **2005**, *7*, 3933

Jung, M. E.; Berliner, J. A.; Koroniak, L.; Gugia, B. G.; Watson, A. D. *Org. Lett.* **2008**, *10*, 4207

Kasztreiner, E.; Vargha, L.; Huszti, Z.; Bursy, J.; Szilagyi, G.; Judit, E.; Elek, S.; Polgari, S. Patent # 2137538, **1972**

Kato, T.; Ishii, K.; Ichinose, I.; Nakai, Y.; Kumagai, T. *J. Chem. Soc., Chem. Comm*. **1980** 1106.

Katritsky, A. R.; Zhang, G.; Jiang, J. *J. Org. Chem.* **1995**, *60*, 7605

Kim, J.; Bruning, J.; Park, K. E.; Lee, D. J.; Singaram, B. *Org. Lett.* **2009**, *11*, 4358.

Knoevenagel, E. *Ber.* **1896**, *29*, 172

Kobayshi, Y.; Mizojiri, R.; Ikeda, E. *J. Org. Chem.*, **1996**, *61*, 5391

Kobayashi, Y; Nakata, K.; Ainai, T. *Org. Lett*. **2005**, *7*, 183

Kobayashi, Y.; Tokoro, Y.; Watatani, K. *Eur. J. Org. Chem.* **2000**, 3825

Kubanek, J.; Prusak, A. C.; Snell, T. W.; Giese, R. A.; Hardcastle, K. I.; Fairchild, C. R. Aalbersberg, W.; Raventos-Suarez, M. E. *Org. Lett.* **2005**, *7,* 5261

Kubanek, J.; Prusak, A. C.; Snell, T. W.; Giese, R. A.; Fairchild, C. R.; Aalberberg, W.; Hay, M. E. *J. Nat. Prod.* **2006**, *69*, 731.

Lane, A. L.; Stout, E. P.; Lin, A.-S.; Prudhomme, J.; Roch, K. L.; Fairchild, C. R.; Franzblau, S. G.; Hay, M. E.; Aalbersberg, W.; Kubanek, J. *J. Org. Chem.* **2009**, *74*, 2736.

Li, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 3987

Lin, A.-S.; Stout, E. P.; Prudhomme, J.; Le Roch, K.; Fairchild, C. R.; Franzblau, S. G.; Aalbersberg, W.; Hay, M. E.; Kubanek, J. *J. Nat. Prod.* **2010**, *73*, 275.

Kato, T.; Ichinose, I.; Kamoshido, A.; Kitahara, Y. *J. Chem. Soc., Chem. Comm*. **1976**, 518.

Lipshutz, B. H. *J. Am. Chem. Soc* 1988, 110, 2641

Lipshutz, B. H.; Sharma, S.; Dimock, S. H.; Behlig, J. R. *Synthesis*, **1992**, 191

Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *J. Org. Chem*. **1984**, *49*, 3938

Liu, Q.; Lan, Y.; Liu, J.; Li, G.; Wu, Y.-D.; Lei, A. *J. Am. Chem. Soc.* **2009**, *131*, 10201

Llardi, E. A.; Stivala, C. E.; Zakarian, A., *Org. Lett.* **2008**, *10*, 1727

Luche, J. L. *J. Am. Chem. Soc.* **1978**, 100, 2226

Majetich, G.; Hicks, R.; Zhang, Y.; Tian, X.; Feltman, T. L.; Fang, J.; Duncan Jr., S. *J. Org. Chem.* **1996**, *16*, 8169

Majetich, G.; Zhang, Y.; Feltman, T. L.; Duncan Jr., S. *Tetrahedron Lett.* **1993**, *34*, 445

Malamas, M. S., US Patent # 5,444,086 **1995**

Miki, T.; Hiraga, K.; Asako, T.; Mosuya, H. *Chem. Pharm. Bull.* **1967**, *15*, 670

Miyamoto, H.; Iwamoto, M.; Nakada, M. *Heterocycles* **2005**, *66,* 61

Miyura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972

Molander, G. A.; Berani, C. R. *J. Org. Chem.* **2002**, *67*, 8424

Mudryk, B.; Cohen, T. *J. Am. Chem. Soc.* **1993**, *115*, 3855

Mun, S.; Lee, J.-E.; Yun, J. *Org. Lett.* **2006**, *8*, 4887

Murahashi, S.-I.; Imada, Y.; Taniguchi, Y.; Higashirua, S. *J. Org. Chem.* **1993**, *58*, 1538

Murchashi, S.-I.; Taniguchu, Y.; Imada, Y.; Tanigawa, Y. *J. Org. Chem.* **1989**, *54,* 3293

Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815

Negishi, E.-I. *Tetrahedron*, **2000**, *56*, 10197

Nicolaou, K. C.; Fylaktakidov, K. C.; Monenschein, H.; Li, Y.; Wegershawsen, B.; Mitchell, H. J.; Wei, H.-X. Guntupalli, P.; Hepworth, D.; Sugita, K. *J. Am. Chem. Soc.* **2003**, *125*, 15433

Nicolaou, K. C.; Lim, Y.-H.; Becker, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 3444

Nishiyama, H.; Sakuta, K.; Itoh, K. *Tetrahedron Lett.* **1984**, *25*, 223

Omura, K; Sharma, A.K.; Swern, D. *J. Am. Chem. Soc.* **1976**, *41*, 957

Ouyang, X.-Y.; Jiang, H.-F.; Huang, J.-M. *Chinese J. Chem.* **2006**, *24*, 1480

Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics*, **1996**, *15*, 1518

Pereira, S.; Srebnik, M. *Tetrahedron Lett.* **1996**, *37*, 3283

Petasis, N. A.; Yudin, A. K.; Zavialov, I. A.; Prakash, G. K. S.; Olah, G. A. *Synlett* **1997**, 606

Posner, G. H.; Lee, S. H. T.; Kim, H. J.; Peleg, S.; Dolan, P.; Kensler, T. W. *Bioorg & Med Chem* **2005**, *13*, 2959

Ramachary, D. B.; Kisher, M. *J. Org. Chem.* **2007**, *72*, 5056

Reformatsky, S. *Ber*. **1887**, *20*, 1210

Rodriguez, J. E.; Adlington, R. M.; Baldwin, J. E.; Moses, J. E. *Tetrahedron* **2007**, *63*, 4500

Rokita, S. E.; Yang, J.; Pande, P.; Greenberg, W. H. *J. Org. Chem.* **1997**, *62*, 3010

Sasai, H.; Arai, T.; Watanabe, S.; Shibasaki, M. *Catalysis Today*, **2000**, *62*, 17

Schow, S. R.; Bloom, J. D.; Thompson, A. S.; Winzenberg, K. N.; Smith III, A. B. *J. Am. Chem. Soc.* **1986**, *108*, 2662

Sebahar, H. L.; Yoshida, K.; Hegedus, L. S. *J. Org. Chem.* **2002**, *67*, 3788

Shieh, H.-M.; Preswich, G.D.; *Tetrahedron Lett.* **1982**, *23*, 4643.

Shipe, W. D. Sorensen, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 7025

Snyder, S. A.; Corey, E. J. *J. Am. Chem. Soc.* **2006,** *128,* 740

Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923

Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775

Sugai, T.; Katch, O.; Ohta, H. *Tetrahedron* **1995**, *51*, 11987

Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1985**, *107*, 3348

Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 4718

Taber, D. F.; Christos, T. E.; Rheingold, A. L.; Guzei, T. D. *J. Am. Chem. Soc.* **1999**, *121*, 5589

Takahashi, T.; Nakazawa, M.; Kanoh, M.; Yamamoto, K. *Tetrahedron Lett.* **1990**, *31*, 7349

Terashima, S.; Tseng, C. C.; Hayshi, M.; Koga, K. *Chem. Bull. Pharm.* **1979**, *27*, 758

Tucker, C. E.; Davison, J.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 3482

Van De Water, R.; Pettus, T. R. R. *Tetrahedron* **2002**, *58*, 5367

van Tamelen, E.; Hessler, E. J. *Chem. Commun.* **1966**, 411.

Willard, P. G.; Fryhle, C. B. *Tetrahedron Lett.* **1980**, *21*, 3731

Wittig, G.; Geissler, G. *Ann*. **1953**, *580*, 44

Xue, S.; Liu, Y.-K.; Li, L.-Z.; Guo, Q.-X. *J. Org. Chem.* **2005**, *70*, 8245

Yasui, K.; Fugami, K.; Tamaru, Y. *J. Org. Chem.* **1995**, *60,* 1365

Zeng, Q.; Rokita, S. E. *J. Org. Chem.* **1996**, *61*, 9080

Zhou, R. Liu, T.-F.; Su, L.-X.; Yang, H.-W.; Yin, D.-H. *Youji Huaxue*, **2008**, *28*, 436

ABOUT THE AUTHOR

Brett Joseph Prigaro was born April 13, 1975 at General Hospital in Passaic NJ to Valerie and Joseph Prigaro. He has two younger siblings, Jennifer the middle sister and Craig the youngest brother. Jennifer is married to Karl and has taken is last name, Megules, and Craig wife's name is Andrea. His immediate family moved to Massachusetts in 1997, where they currently reside in the West Port area. He plans to get engaged to his girlfriend, Pamela Lynne Eagleberger in 2011.

He spent his life in Wayne, NJ where he participated in many outdoor activities, one of which he still enjoys today, and that is soccer. He attended John F. Kennedy Elementary School, followed by Schuyler Colfax Junior High School then Wayne Valley High School. First attending William Paterson University in 1993, one class stood out that changed his out look life: the assignment was to visit the same location, every week, and note how it has changed over the course of the semester. He chose to hike to the tallest peak in Wayne, at 800 ft above sea level, that offered a view of the New York City skyline. The result was the effect man had on his environment and how it has changed to fit his liking. This idea reflected in Brett's decision to transfer to Rutgers University, Cook College, in New Brunswick, NJ where he majored in Environmental Science and Chemistry and graduated with a Bachelor of Science in January of 1998.

Looking for direction in Chemistry, he held multiple positions in various fields of Chemistry that included precious metal analysis, preparation of organometallic catalysts, which he developed Schlenk line techniques, before moving to the Pharmaceutical industry. Johnson & Johnson in Raritan, NJ gave him his first experience in drug discovery, before moving to California, worked for three years at Valeant Pharmaceuticals where he developed the tools necessary for Organic synthesis. He eventually decided to pursue a deeper understanding of Organic Chemistry to utilize in the development of drugs. On the advice from a co-worker, he was accepted to the graduate program at Colorado State University, and began his graduate career path in 2005. He was part of the first class to begin Professor John L. Wood's tenure at CSU, where the Natural Product debromophycolide was used to direct his graduate studies in total synthesis. In July 2010, he accepted a post-doctoral position in the laboratory of Dr. Webb of St. Jude Children's Research Hospital.