Synthetic Studies on Hemiketal E_2 and 5-Hydroxy Prostaglandin E_2 Novel Arachidonic Acid Metabolites

By

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The Power of can’t

The word "can't" makes strong people weak, blinds people who can see, saddens happy people, turns brave people into cowards, robs a genius of their brilliance, causes rich people to think poorly, and limits the achievements of that great person living inside us all.”

Robert T. Kiyosaki

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List of Abbreviations:

AA	Arachidonic Acid
Ac	Acetyl
Ac_2O	Acetic Anhydride
App	Apparent
AIBN	azobisisobutyronitirile
BINAL-H	Binaphthylithium aluminum hydride
Bn	Benzyl
BOM	Benzyloxymethyl
br	Broad
Bu	Butyl
Bz	Benzoyl
°C	degrees Celsius
CBS	Corey Bakshi Shibata Catalyst
$(CH_2O)_n$	Paraformaldehyde
COX	Cyclooxygenase
Cp	Cyclopentadienyl
$cPLA_2$	Cytosolic phospholipase A_2
Δ	Reflux
δ	Chemical Shift in ppm
d	doublet
DCM	Dichloromethane

DHA	docosahexaenoic acid
DIBAL	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DME	1,2-dimethoxyethane
DMF	dimethyl formamide
DMP	Dess-Martin periodinane
2,2 DMP	2,2 dimethoxy propane
DMSO	dimethyl sulfoxide
Ee	Enantiomeric excess
Et	Ethyl
Et_2O	Diethyl Ether
EtOH	Ethanol
g	Gram
GPCR	G-protein coupled receptor
HETE	hydroxyicosatetraenoic acid
HMDS	hexamethydisilazide
HMPA	hexamethylphosphorictriamide
HPETE	hydroperoxyeicosatetraenoic acid
HRMS	high resolution mass spectrometry
Hz	Hertz
IBX	2-iodoxybenzoic acid
Im	Imidazole
IR	Infrared spectroscopy
IsoF	Isofuran
IsoP	Isoprostane
J	Coupling constant
L	Liter
LA	Lineoleic Acid
LDA	Lithium diisopropylamide

LOX	Lipoxygenase
LT	Leukotriene
M	Molar Concentration
m	milli, multiplate
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	Methyl
MeOH	Methanol
Mol	Mole
Ms	Methanesulfonate
MS	Molecular Sieves
NBS	N-bromosuccinimide
nBuLi	n-Butyl Lithium
NMO	N-methylmorpholine-N-oxide
Nuc	Nucleophile
PCC	pyridinium chlorochromate
PDC	Pyridinium dichromate
PPh_3	Triphenyl phosphine
PG	Prostaglandin
Ph	phenyl
PhMe	Toluene
PMB	*para* methoxybenzyl
ppm	parts per million
PPTS	pyridinium *para* toluenesulfonate
Py	pyridine
q	quartet
rt	room temperature
s	singlet
t	triplet
TEA	Triethyl amine
tBuLi	t butyl Lithium

TBAF	Tetrabutyl ammonium fluoride
TBDPS	*tert* butyl diphenylsilyl
TBDPSCl	*tert* butyl diphenylsilyl chloride
TBS	*tert* butyldimethylsilyl
TBSCl	*tert* butyldimethylsilyl chloride
THF	tetrahydrofuran
TMS	Trimethylsilyl
TMSCl	Trimethylsilyl chloride

Chapter 1: Physiology of Arachidonic Acid

1.1 The Inflammatory pathway

Inflammation is the body's natural defense against foreign pathogens and other harmful insults. It removes deleterious pathogens, harmful stimuli and subsequently initiates the body's natural recovery process.[1–3] At a basic level the inflammatory process is made up of three key components; recognition, activation and resolution. In recognition, pattern receptors identify some type of detrimental pathogen, such as bacteria, viruses, or a non-infectious ailment such as a cut, bruise or burn. Activation, the inflammatory pathway is activated resulting in the release of inflammatory cells and mediators. Finally resolution, results in the release of anti-inflammatory mediators allowing the cell to return to normal homeostasis.[3]

The first step in the inflammatory pathway is the recognition of some type of foreign pathogen or maligned cellular structure. This takes place through pattern recognition receptor activation also referred to as pathogen associated molecular patterns or PAMPS, which trigger the inflammatory pathway, through activation of pattern recognition receptors. [3,4] Some of the pattern recognition receptors can also recognize endogenous signals that will trigger the inflammatory pathway, primarily signals that are released during tissue or cellular damage.[3]

After recognition of damage, for example identification of foreign material or non-infections damage, the inflammatory pathway is activated. Stimuli activate a wide array of secondary metabolites and intracellular pathways that promote the activation of inflammatory mediators. Some of these include interleukins such as IL-1β and IL-6 as

well as tumor necrosis factor-α.[3,5] As a result of activation, a wide array of intracellular signaling pathways are activated and elicit their downstream effects within the cell.[3] Some of these specific intra-cellular signaling pathways are the NF-kB, MAPK, and JAK-STAT pathways, all that have a variety of different cellular functions.[3]

The NF-kB pathway results in the production and recruitment of pro-inflammatory cytokine and inflammatory cells. The MAPK pathway uses a series of serine/threonine protein kinases that are activated in response to a variety of different environmental factors including, but not limited to, heat shock, mitogens, and inflammatory cytokines. These kinases regulate cell survival, proliferation, differentiation and apoptosis.[5,6] Activation of MAPK results in the phosphorylation and activation of p38 transcription factors, which subsequently initiates the inflammatory pathway.[3,5,6]

The JAK-STAT pathway is highly conserved and contains a vast array of different cytokines as well as interferons, related molecules, and is an intracellular signaling pathway that allows for the control for gene expression.[7] The JAK-STAT pathway allows for the direct translation of an extracellular signal into a transcriptional response.[3] Dysregulation of these three signaling pathways is associated with a variety of diseases. Specifically, chronic inflammation which is associated with diseases such as cancer, diabetes, arthritis, autoimmune disorders, and some metabolic diseases.[3,8]

The inflammatory pathway further employs a highly coordinated network of different types of cells. Macrophages, monocytes and other cells mediate local responses to stress and tissue damage. At sites of injury, endothelial and epithelial cells release factors activating the inflammatory cascade. This, in conjunction with chemokines and growth factors, trigger the recruitment of neutrophils and monocytes. The first cells at the

site of aggravation are neutrophils, followed by monocytes, which differentiate into macrophages and dendritic cells. These are brought to the site of inflammation via chemotaxies.[3,9]

As noted, many diseases are associated with chronic inflammation. Neutrophils and macrophages are key components of the inflammatory pathway. Neutrophils program antigen presenting cells to activate T cells and subsequently release localized factors to attract monocytes and dendritic cells.[3,10] Macrophages are critical in the initiation phase of the inflammatory pathway. They present antigens, undergo phagocytosis, and modulate the immune response by producing cytokines and growth factors.[3] Mast cells which rest in the epithelial surfaces initiate a variety of inflammatory mediators, including both prostaglandins and leukotrienes.[3]

The final stage of the inflammatory pathway is the resolution phase. Chronic inflammation is a byproduct of a variety of different diseases, and has been shown to be very detrimental to cells.[3] Resolution results in a return to normal cell homeostasis. Constant inflammation can lead to tissue and cellular damage. Inflammation resolution is controlled by the production of anti-inflammatory mediators, which cause the cytokine gradient to be slowly diluted over time. White blood cells that are circulating in the blood no longer sense the cytokines, and are no longer recruited to the previous site of injury.[3,11,12] Chronic inflammation occurs when acute inflammatory mechanisms fail to eliminate the reason for activation or when the body is unable to resolve its own inflammatory pathway and return to normal homeostasis. This can lead to a number of different diseases such as atherosclerosis, diabetes, arthritis and potentially even cancer.[3] It is for these reasons, that truly understanding the intricate mechanisms of the

inflammatory pathway is of the utmost importance. By understanding the inflammatory pathway, we can accurately try and 1) resolve issues where the inflammatory pathway is not properly working in filtering out the body's toxins and other threatening pathogens, and 2) make sure that resolution properly takes place, returning the body to normal homeostasis.

1.2 Prostaglandin nomenclature

In terms of nomenclature, a balance needs to be maintained between ease of communication and accuracy of description. The chemical abstracts and IUPAC naming system is effective for referencing the prostaglandins; however, it is too difficult for day-to-day oral communication. A semi systematic approach to naming prostaglandins has evolved based on functionalization of the ring structure, side chain functionalization and degree of unsaturation.[13]

Prostaglandins may be regarded as derivatives of prostanoic acid. By convention the numbering system of prostaglandins denotes the carboxylic acid as carbon number one. The side chain with the carboxylic acid is referred to as the alpha (α) side chain, while the side chain with the n-pentyl substituent is referred to as the omega (Ω) side chain.[13,14]

Substitution and functionalization of the cyclopentane ring common to prostaglandins has been subdivided into ten families designated as prostaglandins A-J (Figure 1.1). The F family is further subdivided by the stereochemical configuration of the C9 alcohol as either α or β. Hence, a prostaglandin with the A ring structure would be

named PGA. Furthermore, prostaglandins G, H and R all have the same ring structure but have differences within the side chains of their respective prostaglandins.

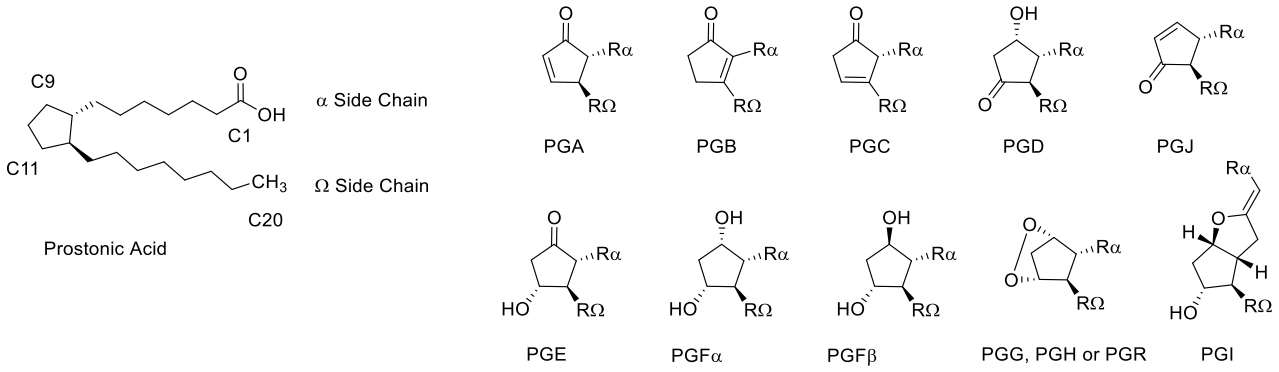


Figure 1.1 Prostaglandins nomenclature and numbering system.

1.3 Biosynthesis of lipid metabolites

The secondary metabolites of arachidonic acid have been the subject of study for the better part of 60 years. This has progressed both chemical methodology as well as understanding of human biology and physiology. There is a need to understand the physiological role of the lipid mediators of arachidonic acid to better understand the inflammatory pathway and subsequently their modulation. The inflammatory pathway when regulated properly is the body's natural defense against foreign pathogens, as well as resolution to physical injury. However, when regulated poorly the inflammatory pathway can lead to a variety of different deleterious effects such as tissue damage. Furthermore, many diseases are in a constant inflamed state such as Crohn's, diabetes,

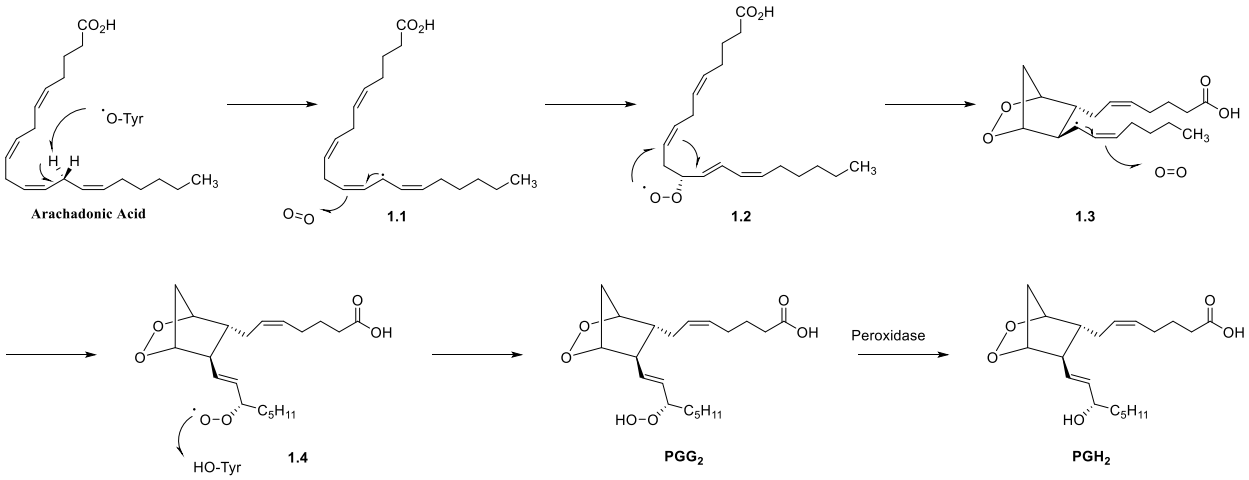
and cancer.[3,15–17] A better understanding of the inflammatory pathway could shed light on possible therapeutics for some of these diseases.

Secondary metabolites of arachidonic acid are generated through either enzymatic or non-enzymatic reactions. These biosynthetic pathways start with the liberation of arachidonic acid from the phospholipid bilayer through the activation of cytosolic phospholipase A_2, activated by intracellular calcium. These secondary metabolites are prostaglandins, leukotrienes, thromboxanes, isoprostanes, isofurans and others.[15–17] Many of the secondary metabolites have been shown to display a wide array of activity in the inflammatory pathway. Improper regulation of the inflammatory pathway has led to a variety of diseases, and many diseases are in a constant inflamed state such as: IBS, Crohn's, diabetes, and cancer as examples. It is critical that an intimate understanding of the inflammatory pathway is understood. With an intimate understanding, we will be able to treat some these diseases more effectively, as well as opening the door for new and improved therapeutics.

1.3.1 Cyclooxygenase generation of PGH_2

Prostaglandins such as PGE_2 and PGD_2 are generated from the synthetase enzymes, PGES and PGDS, from the common intermediate PGH_2. PGH_2 is enzymatically produced by oxidation of arachidonic acid by the cyclooxygenase enzymes (COX-1/2). The enzymatic production of PGH_2 starts by the tyrosine radical located in the active site of COX-2 abstracting the 13-pro-S hydrogen of arachidonic acid generating a bis-allylic radical, **1.1** (Scheme 1.3.1). This captures a unit of oxygen at the C-11 position, generating radical intermediate **1.2.** Intermediate **1.2** undergoes a 5-exo-trig cyclization

followed by a second 5-exo-trig closure resulting in formation of a C-C bond between the C-8 and C-12 carbons. The resulting allylic radical (**1.3**) captures a second unit of oxygen at the C15 position, furnishing peroxide radical **1.4**. This radical is subsequently quenched by hydrogen transfer from tyrosine to complete the first step of the COX enzymatic pathway, yielding PGG_2 and regenerating the active site of the COX enzyme. PGG_2 is then reduced to the alcohol by the reductase activity of COX furnishing PGH_2. [18]



Scheme 1.3.1 Biosynthetic pathway leading to PGH_2.

The endoperoxide PGH_2 is the precursor to all prostaglandins (Figure 1.2)**.** PGH_2 is enzymatically converted into a variety of different secondary metabolites based on what types of synthetases are available at a given time in the cell.[19] Different synthetases are expressed in quantities reflective of physiological needs. Some of the most notable secondary metabolites from PGH_2 are PGE_2 PGD_2, $PGF_{2\alpha}$, PGI_2 and Thromboxane A_2 (TXA_2). These secondary metabolites bind G protein coupled receptors, which then elicit a variety of different downstream cellular effects. [19]

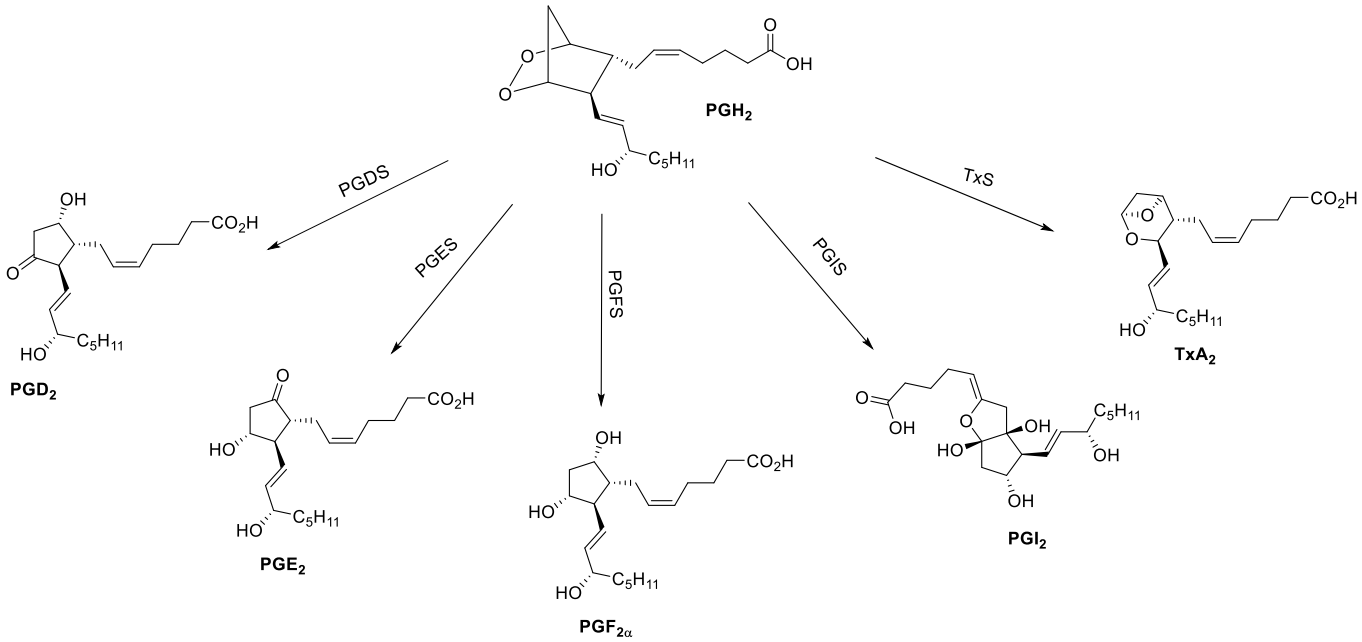
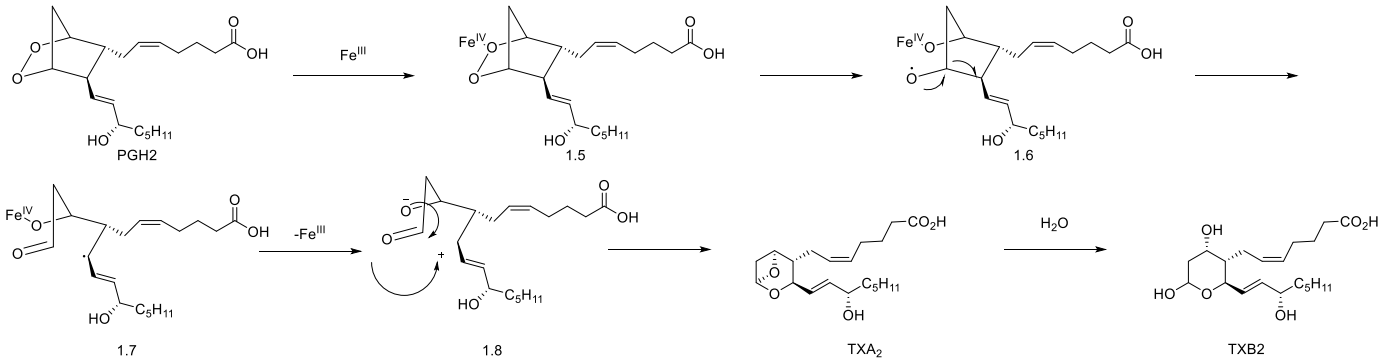


Figure 1.2 Conversion of PGH_2 to secondary metabolites

1.3.2 Conversion of PGH_2 to thromboxanes

Thromboxanes are generated from PGH_2 through the enzyme TxS, a cytochrome p450, and act on the receptor TP.[19] Thromboxanes are a potent mediator of hemodynamics, cardiovascular function, platelet shape and aggregation.[19] One accepted mechanism of the synthesis of thromboxane A_2 and B_2 starts with the binding of Iron(III) from the active site of Thromboxane synthase binding the C9 oxygen of PGH_2 resulting in intermediate complex **1.5** (Scheme 1.3.2). This coordination leads to homolytic cleavage of the endoperoxide, generating alkoxy radical **1.6**. Radical **1.6**, undergoes β scission of the C11-C12 bond, generating allylic radical **1.7.** Proposed intermediate radical **1.7** reduces iron(IV) to iron(III) and results in the allylic cation **1.8.** The latter

subsequently undergoes cyclization to furnish the six membered ring of Thromboxane A_2, which is immediately hydrolyzed to Thromboxane B_2, which is not bioactive.[20]

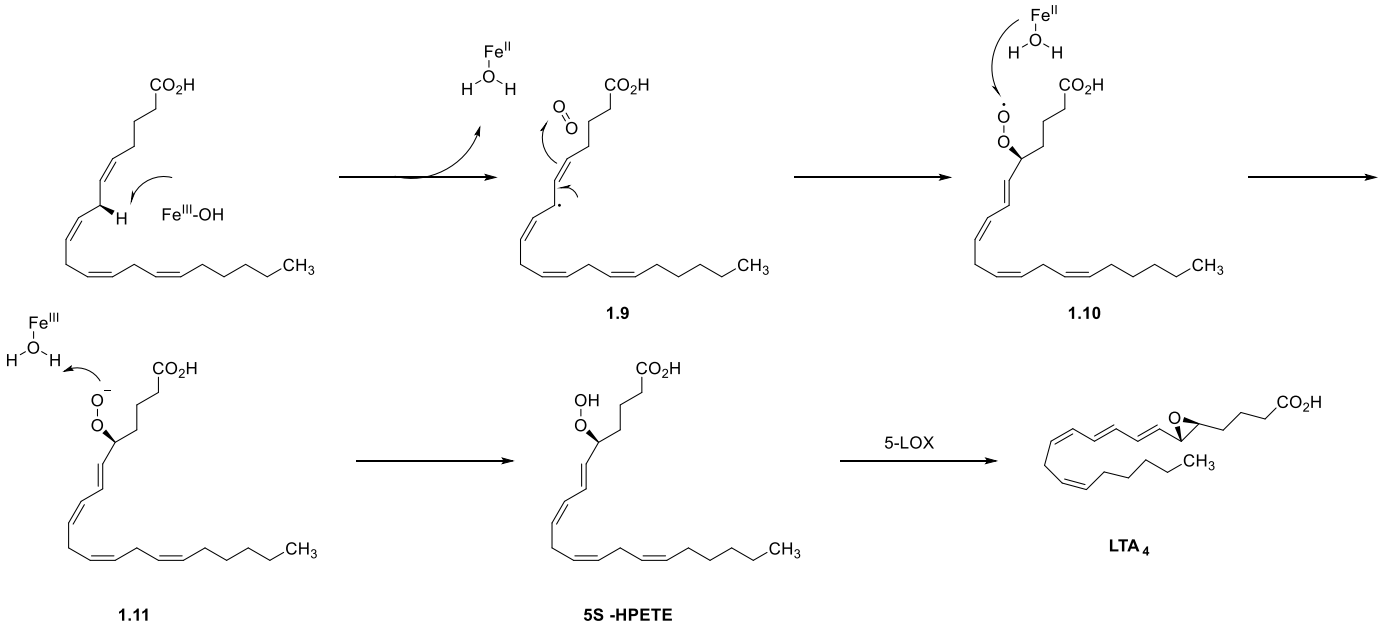


Scheme 1.3.2 Biosynthetic pathway leading to Thromboxanes

1.3.3 Lipoxygenases biosynthesis to LTA_4

Leukotrienes (LT's) are also derived from arachidonic acid. The triene in LT, refers to the conjugated triene within the respective molecules. Leukotrienes are derived from the common precursor LTA_4, which is enzymatically generated from arachidonic acid by the function of the enzyme 5-lipoxygenase (5-LOX).[18,21] The Iron(II) species in the active site of 5-LOX abstracts the 7 pro-S hydrogen from arachidonic acid, generating bis-allylic radical **1.9** (Scheme 1.3.3)**.** Radical **1.9** captures molecular oxygen at the 5-position resulting in radical **1.10**. Peroxy radical then oxidizes the active site of 5-LOX to iron(III), generating peroxide anion **1.11**, which then abstracts a proton to become 5S-hydroperoxyeicosatetraenoic acid (5S-HPETE). Subsequent abstraction of the C10

hydrogen results in eventual formation of epoxide LTA_4.[16,21] 5S-HPETE can also be reduced to the alcohol 5S-Hydroeicosatetraenoic acid (5S-HETE), which was historically thought to be an unreactive byproduct of the 5-LOX enzymatic pathway.



Scheme 1.3.3 Biosynthesis of leukotriene A_4 (LTA_4).

LTA_4 is the precursor to all leukotrienes, primarily LTB_4, LTC_4 and LTD_4 (Figure 1.3, LTD_4 through conversion to LTC_4).[16,21] Similar to prostaglandins, the LTs are involved in the inflammatory pathway, primarily responsible for recruiting neutrophils to sites of inflammation. Primarily LTD_4 is involved in the trigging of the smooth muscle contractions in the bronchioles. Furthermore, their overproduction is a cause of severe inflammation in asthma patients. [22]

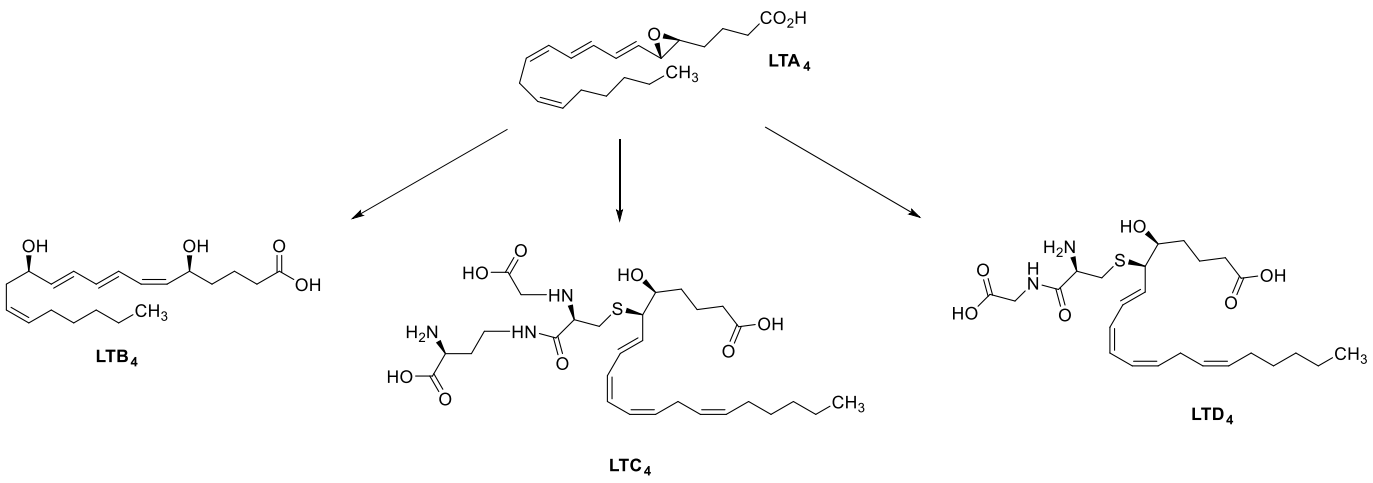


Figure 1.3 Conversion of LTA_4 to leukotrienes.

1.3.4 Free-radical generation of Isoprostanes

Isoprostanes were discovered in 1990, and following extensive structure elucidation determined to possess a prostaglandin F type ring.[13,23,24] Isoprostanes are produced non-enzymatically through free radical oxygenation. There are 4 common series for isoprostanes, designated as 5, 8, 12 and 15 series. The series are named based on where the allylic alcohol is located using standard prostaglandin numbering. Hence, the 15 series isoprostane has an allylic alcohol at carbon 15 (Figure 1.4).

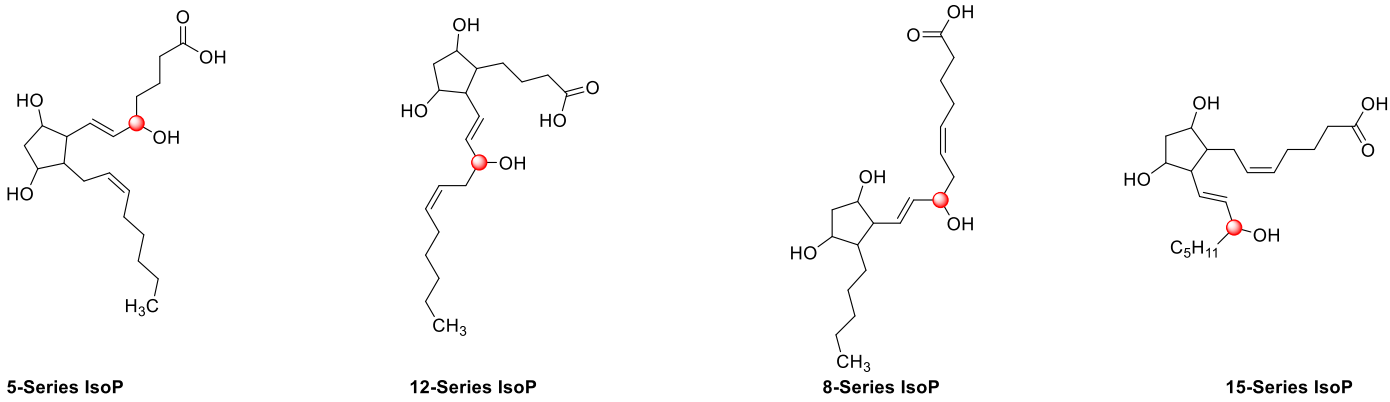
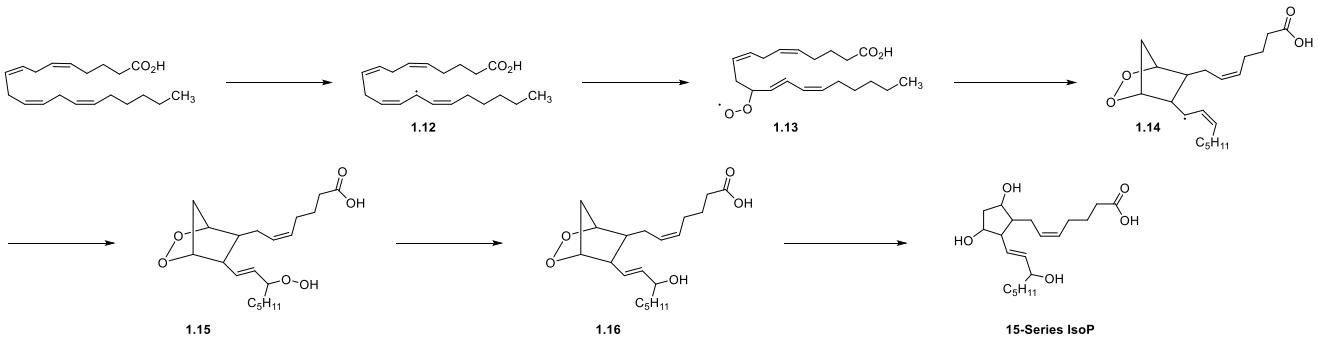


Figure 1.4 Illustrative structure of isoprostanes.

Like the isoprostanes, it was later determined *racemic* prostaglandins can be formed by non-enzymatic free radical oxygenation. The difference between prostaglandins formed from free radical oxygenation and COX is that free radical oxygenation results in a racemic mixture of products, while prostaglandins from COX are enantiopure.[23] Furthermore, Isoprostanes are generated while still located in the phospholipid bilayer. [25]

The mechanism for the creation of the 15-IsoP series begins with radical abstraction of a hydrogen at the C13 position resulting in bis-allylic radical **1.12** (**Scheme 1.3.4**). Radical **1.12** captures a unit of oxygen at position C11 resulting in the peroxy radical **1.13.** That radical then undergoes a 5-exo trig cyclization resulting in endoperoxide **1.14.** Allylic radical **1.14** then captures a second unit of oxygen at the 15-position resulting in allylic peroxide **1.15** after quenching of the generated radical. Subsequent reduction results in racemic PGH_2 **1.16**. [24] Endoperoxide **1.16** is then cleaved into the skeleton of the 15-isoprostane series. Isoprostanes have been shown to be potent vasoconstrictors, as well as inhibitors of platelet aggregation. Finally, they are the quintessential molecules to use to measure the oxidative stress of cells in-vivo. [23–25]



Scheme 1.3.4 Biosynthesis of 15 series isoprostanes.

1.3.5 Reactive oxygen species generation of Isofurans

The isofurans, like the isoprostanes, are produced non-enzymatically through reactive oxygen species.[26] The isofurans were determined to contain a tetrahyrofuran moiety as the central ring. Furthermore, there are 8 isofuran constitutional isomers proposed to be produced from two distinct mechanistic pathways, the epoxide hydrolysis pathway and the peroxide cleavage pathway (Figure 1.6).[25] Four of the constitutional isomers are only generated from the epoxide hydrolase mechanism, while the other 4 constitutional isomers are generated from both mechanisms. [25]

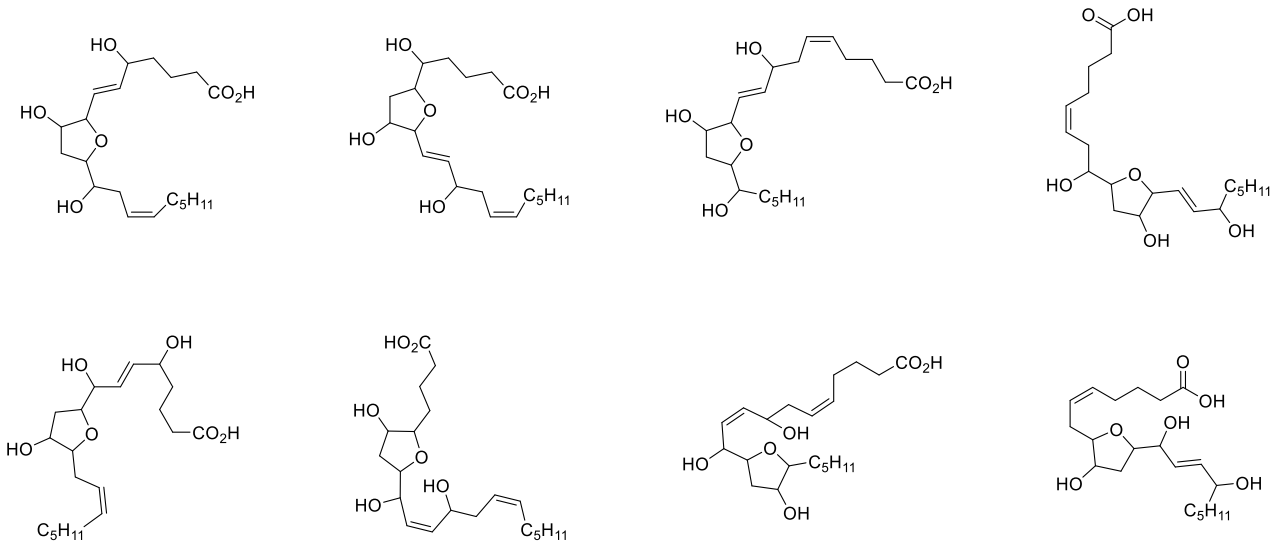
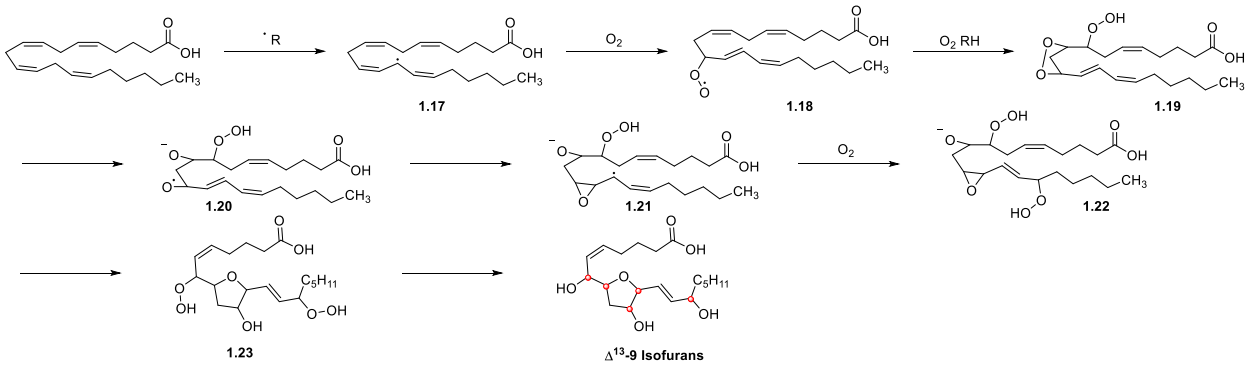


Figure 1.5 Eight isofuran constitutional isomers.

Each constitutional isomer incorporates 5 stereocenters, meaning that each constitutional isomer is a set of 32 diastereomers or 16 racemic diastereomers. This yields 256 possible isofurans from the two pathways. [25,26] Like the isoprostanes, the isofurans are a good way of measuring cellular oxidative stress within the cell. The ratio

of isoprostanes and isofurans generated from reactive oxygen species is related to the relative oxygen concentration of a given cell, as oxygen tension increases the production of isofurans increases. [26]

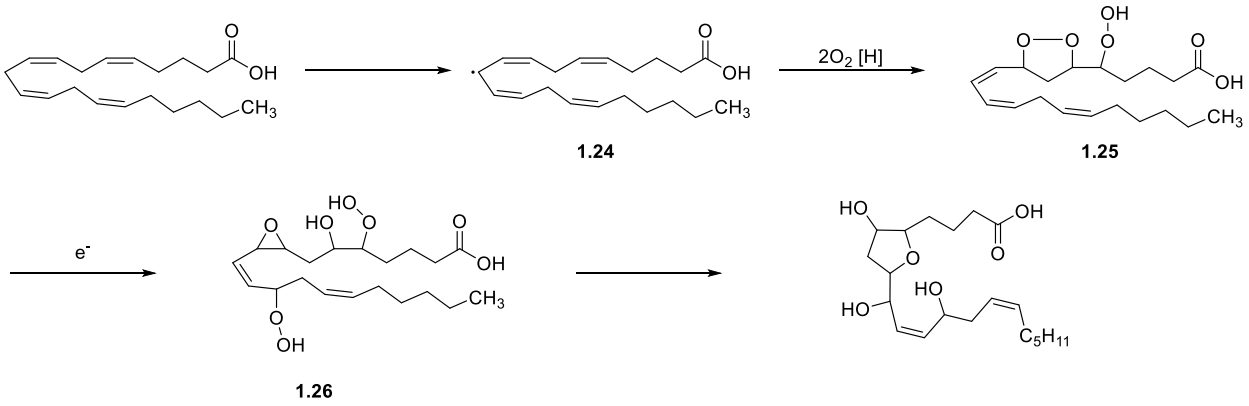
The epoxide hydrolyase mechanism (Scheme 1.3.5) of the formation of the Δ^{13}-9 isofurans starts with hydrogen abstraction at the C-13 position, followed by oxygen capture to furnish radical **1.17.** This undergoes a 5-exo trig cyclization with subsequent capture of a unit of oxygen to furnish peroxide **1.19.** The endoperoxide is cleaved via addition of an electron resulting in anion, and alkoxy radical **1.20**, that undergoes epoxidation and oxygen capture at the C-15 position yielding epoxide, **1.22.**[25] **1.22** is opened up by nucleophilic addition of the C9 alcohol resulting in furan **1.23.** The subsequent peroxides are reduced resulting in the constitutional Δ^{13}-9 isofuran skeleton. [25]



Scheme 1.3.5 Epoxide hydrolyase mechanism of Isofurans

The mechanism for the cyclic peroxide cleavage pathway (Scheme 1.3.6) starts with the abstraction of the C-10 hydrogen resulting in bisallylic radical **1.24.** This captures a unit of oxygen at the C8 position and cyclizes onto the 6 position, finally capturing a

second unit of oxygen at the C5 position resulting in peroxide **1.25.** The peroxide is cleaved via single electron addition generating epoxide **1.26.** The peroxide is cleaved and cyclization results in the isofuran skeleton.[25]



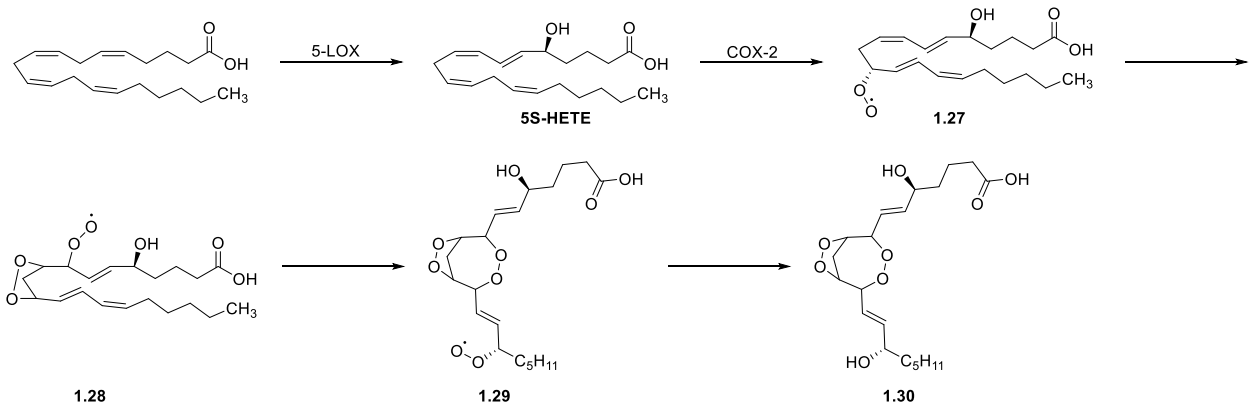
Scheme 1.3.6 Peroxide cleavage mechanism

1.3.6 Cross-over enzymatic pathway

Historically the initial oxidation of arachidonic acid was thought to determine its secondary metabolite fate. Conversion into PGH_2 via COX and subsequent enzymatic reactions into prostaglandins, or conversion into LTA_4 via 5-LOX and subsequently into leukotrienes.[27] A cross-over enzymatic pathway between these two enzymes had never been studied, as it would intuitively make sense the two pathways were committed. There is substantial opportunity for interactions between COX and LOX enzymes. First, they are both expressed in a variety of different cells, tissues, and disease. Both are primarily localized at the nuclear envelope of activated cells.[27,28] During times of inflammation, it could be inferred that the two enzymes would interact. Most importantly, 5S-HETE has double bonds at the structurally required positions for COX oxidation, the C-8,11, and 14

positions.[27,28] Initial studies in the Schneider group sought to oxidize 5S-HETE with both COX-1 and COX-2, however oxidation only successfully took place with COX-2. [27] Further, studies demonstrated that 5S-HETE was successfully oxidized by COX-2 but not COX-1. 5R-HETE, however, was poorly oxidized by both. Reactions followed by LC/MS showed an increase of 80 mass units, which would correspond to 5 units of oxygen. This could be explained by capture of 3 units of molecular oxygen followed by the reductase activity of COX-2 converting a peroxide into an alcohol. [29] After extensive NMR experiments it was determined that the structure formed was bis-endoperoxide **1.30** (Scheme 1.3.7).

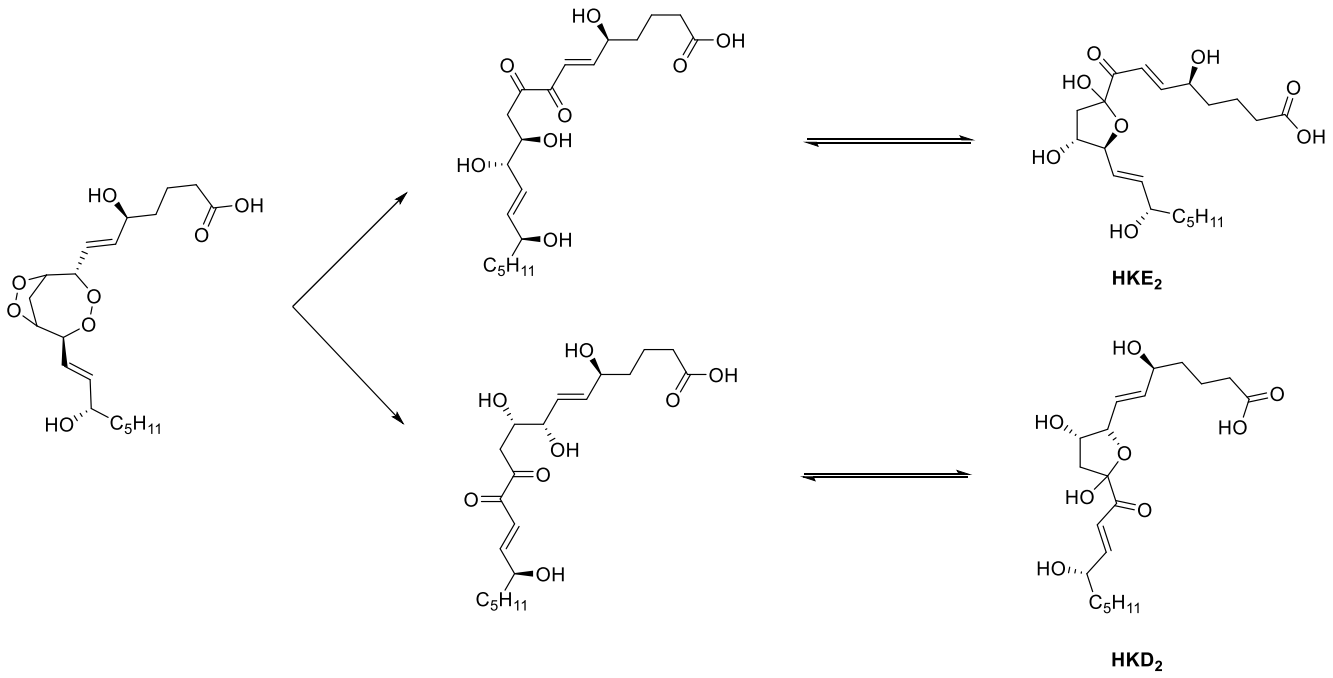
The proposed mechanism commences with the 5-LOX oxidation of arachidonic acid generating 5S-HETE. 5S-HETE is then oxidized by COX-2 resulting in the abstraction of the Pro 13-S hydrogen, and capture of a unit of oxygen yielding **1.27**. Radical **1.27,** undergoes a 5-exo trig cyclization capturing a second unit of oxygen at the C8 position resulting in peroxy radical **1.28**. This undergoes a cyclization reaction resulting in formation of bis-endoperoxide and capture of a third unit of oxygen at the C-15 position. Reduction of the peroxide into the alcohol completes the synthesis of bis-endoperoxide **1.30.** [29]



Scheme 1.3.7 Cross-over enzymatic pathway leading to bis-endoperoxide 1.3.31

Bis-endoperoxide **1.30,** can be thought of as analogous to PGH_2. Intuitively, one would think that **1.30** could collapse into a variety of different novel arachidonic acid secondary metabolites comparably to how PGH_2 is converted into a variety of different secondary metabolties.[17,18] When the previous reaction was run again, after 30 minutes HPLC analysis showed the disappearance of the bis-endoperoxide peak, and formation of two more polar peaks.[27,30] After isolation and extensive NMR studies it was believed that the bis-endoperoxide was collapsing into two unique hemiketals. The hemiketals were named HKE_2 and HKD_2 for their similarity in biosynthetic pathway to the formation of PGE_2 and PGD_2 (Scheme 1.3.8). Both hemiketals contain a 1,2 diketone, as well as a 1,2 diol on a specific side with respect to carboxylic acid and n-pentyl side chains.[31] Furthermore, since most secondary metabolites of arachidonic acid play some type of vital role in the inflammatory pathway, it was postulated that these novel metabolites also played a potential role in the inflammatory pathway. Mouse pulmonary endothelial cells were treated with the hemiketals, and a dose dependent amount of capillary like growths were observed. This implies a role in angiogenesis or the inflammatory cascade. Moreover, the hemiketals were isolated from human leukocytes, after COX-2 was activated with lipopolysacaride and calcium ionophore to stimulate 5-LOX. This suggests that these metabolites could be involved in the resolution phase of the inflammatory cascade. It is also possible that these could lead to tissue growth during chronic inflamed states. The discovery of these novel arachidonic acid metabolites has prompted the need to further elucidate their biological function. However, only nanograms of the hemiketals

are able to be bioenzymatically prepared. This necessitates the need for a total synthesis to be able to probe the biological function of the hemiketals.[29,31,32]



Scheme 1.3.8 Conversion of bis-endoperoxide into hemiketals E_2 and D_2

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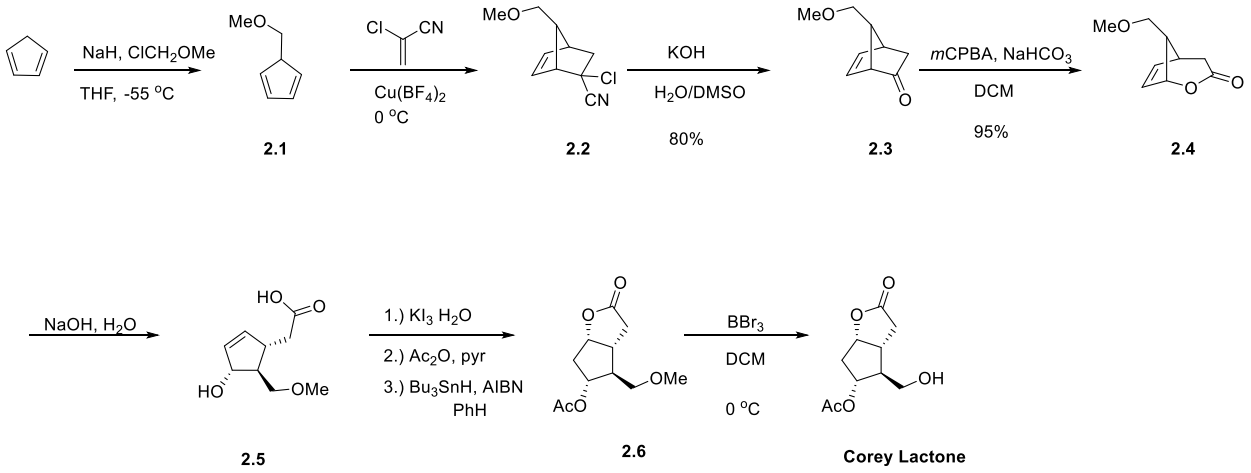
Chapter 2: Previous Syntheses of Prostaglandsins, Isoprostanes and Isofurans

The chemical synthesis of secondary metabolites of arachidonic acid has been an active area of research for the last 60 years, due in part to their scarcity in nature and associated with their central roles in human physiology. Cumulative, these synthetic studies have led to the development of a vast array of chemical methodology, as well as enabling and furthering biological research.

2.1 Corey Synthesis of $PGF_{2\alpha}$ and PGE_2

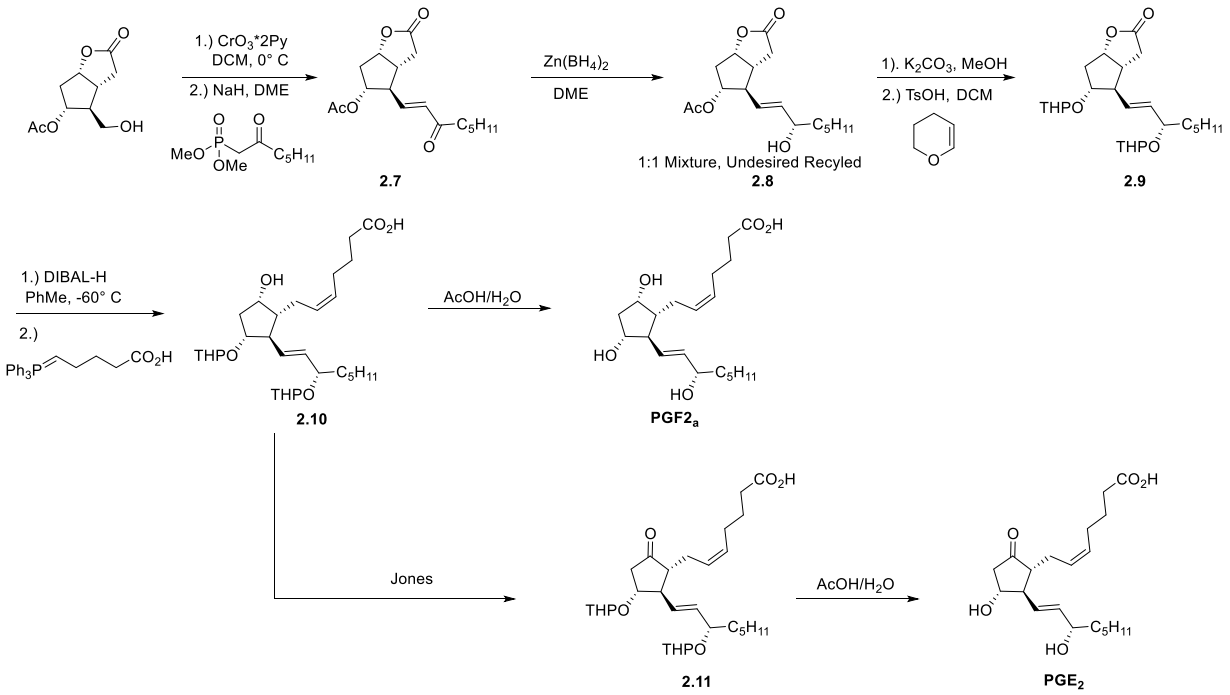
The seminal synthesis of PGE_2 was completed in 1969 by Corey. His groundbreaking synthesis started off with the deprotonation of cyclopentadiene, followed by alkylation with chloromethyl ether furnishing compound **2.1** (Scheme 2.1.1). Diels-Alder cycloaddition with 2-chloroacrylonitrile (a ketene dienophile equivalent) furnished an inconsequential mixture of endo and exo bicycle products **2.2.** Treatment of the latter with potassium hydroxide in aqueous DMSO generates ketone **2.3**. Baeyer-Villiger oxidation of ketone **2.3** afforded lactone **2.4**, and followed by basic hydrolysis yielded carboxylic acid **2.5.** Iodo lactonization, acetylation, and radical mediated dehalogenation generate bicycle **2.6.** Finally, deprotection of the methyl ether with BBr_3 completed the synthesis of the late stage intermediate that has become known as the Corey lactone.[33] Notably, a variety of methods to resolve Corey lactone into single enantiomeric products

have been developed in order to access the natural enantiomer series of prostaglandins and analogs.[34,35]



Scheme 2.1.1: Synthesis of Corey lactone

The Corey lactone undergoes a two-step oxidation-olefination sequence to yield enone **2.7** (Scheme 2.1.2). Reduction with zinc borohydride generates a 1:1 mixture of allylic alcohols **2.8**, which are separated. Undesired allylic alcohol, can be recycled through an oxidation-reduction sequence, while desired allylic alcohol, **2.8**¸ is deacetylated and diols protected as THP ethers to afford lactone **2.9.** DIBAL-H reduction of the latter followed by Wittig olefination generates the desired Z-olefin, **2.10**. Treatment with acetic acid in water removes the THP ethers, finishing the synthesis of $PGF_{2\alpha}$. Prostaglandin E_2 (PGE_2) is derived from secondary alcohol **2.10**, starting with oxidation to ketone **2.11**, followed by removal of THP ethers using aqueous acetic acid.[33]

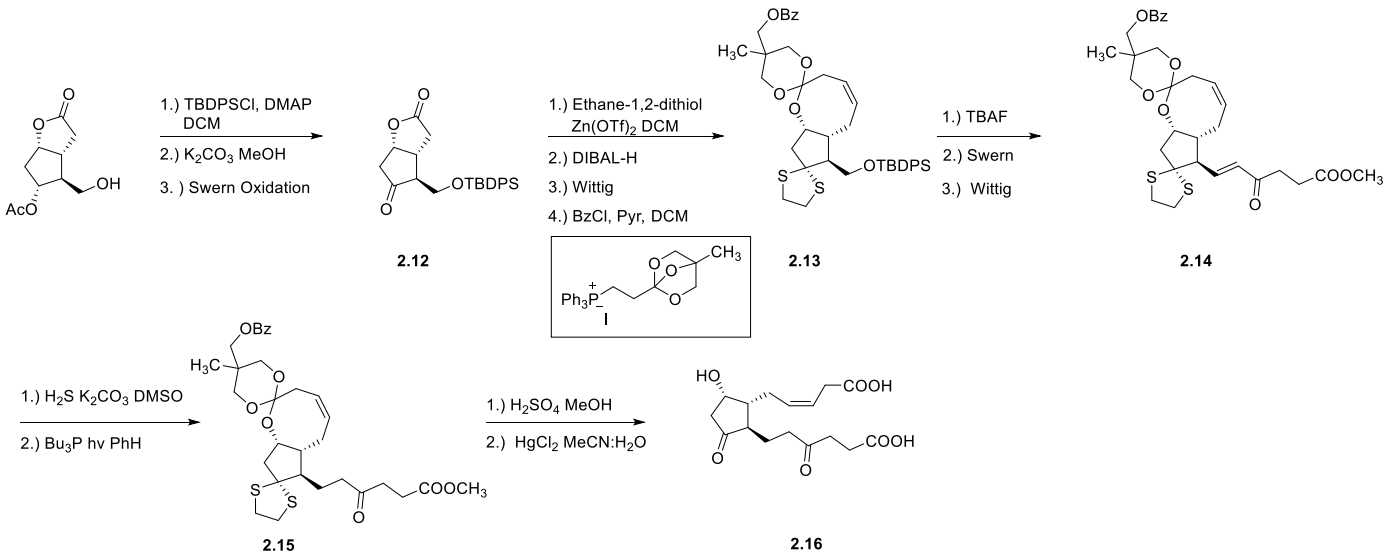


Scheme 2.1.2: Completion of $PGF_{2\alpha}$ and PGE_2

2.2 Corey Synthesis of PGD_2 Metabolite

One of the main metabolites of PGD_2 is the diacid 13,14-dihydro-15-keto PGD **2.16** (Scheme 2.2.1), identified as a human urinary metabolite. The first total synthesis of 13,14-dihydro-15-keto PGD was completed by Corey in 1983.[36] The synthesis started with silyl (TBDPS) protection of Corey lactone (Scheme 2.2.1), deacetylation and oxidation to afford lactone, **2.12.** New methodology was required for the selective protection of the keto group using 1,2-ethanedithiol and zinc triflate to give thioketal **2.13**. Semi-reduction of the lactone group with DIBAL followed by Wittig olefination and cyclization furnished bicycle **2.13.**[36] Silyl deprotection, oxidation and olefination generated enone **2.14,** completing the carbon framework of the PGD_2 metabolite. A novel two-step

reduction of enone **2.14** to ketone **2.15** was developed starting with Michael addition of hydrogen sulfide followed by reduction with tributyl phosphine and light**.** Global deprotection of intermediate **2.15** completes the synthesis of the PGD_2 metabolite.[36]

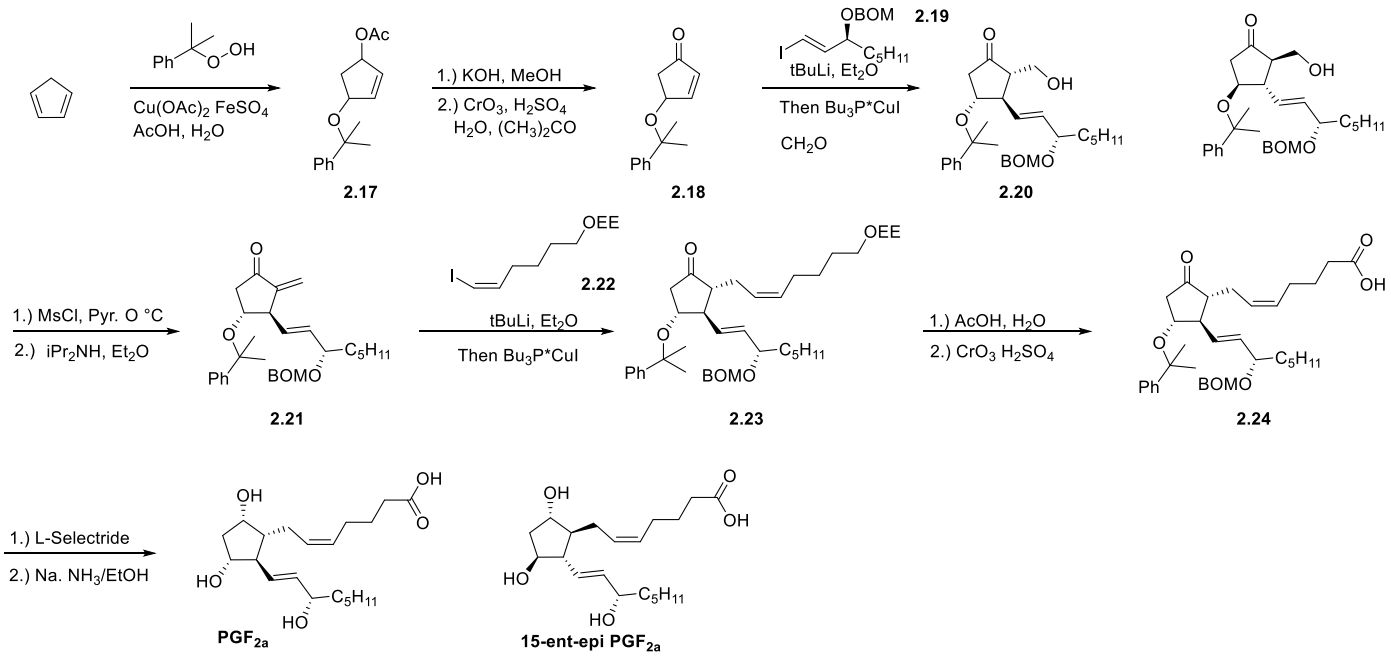


Scheme 2.2.1: Corey's synthesis of PGD_2 Metabolite

2.3 Stork Synthesis of $PGF_{2\alpha}$

While Corey developed a strategy to access prostaglandins and associated metabolites from the Corey lactone Stork pioneered what has become known as the three component couplings in his synthesis of $PGF_{2\alpha}$. Stork's synthesis commences with the treatment of cyclopentadiene with cumene hydroperoxide, copper acetate, and iron sulfate in acetic acid and water to generate allylic acetate **2.17** (Scheme 2.3.1). A two-step deprotection, oxidation sequence yields cyclopentenone **2.18**. Generation of the desired cuprate from vinyl iodide **2.19,** via lithium halogen exchange with tBuLi, followed by transmetallation with CuI, smoothly led to a 1,4 addition cuprate addition to enone

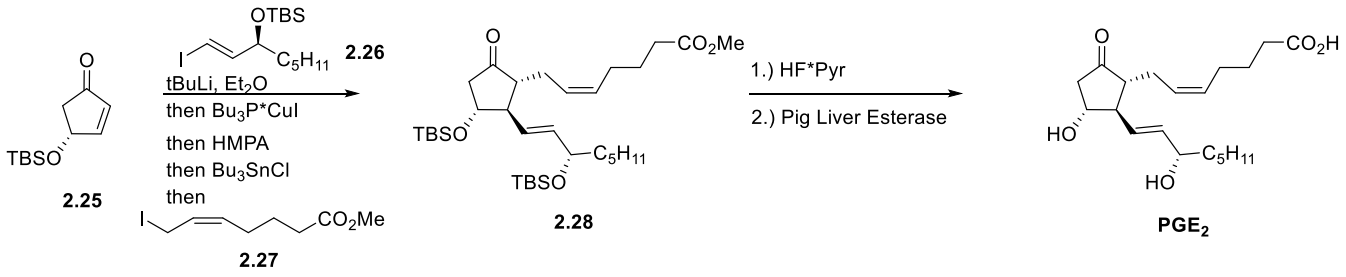
2.18. The intermediate cuprate enolate is treated with formaldehyde to yield primary alcohol **2.20**, in this case as a racemate. Mesylation of the primary alcohol followed by beta elimination furnishes enone **2.21,** setting the stage for a second cuprate mediated conjugate addition with vinyl iodide **2.22** to give ketone **2.23**, completing the carbon framework of $PGF_{2\alpha}$. Deprotection, and Jones oxidation generates carboxylic acid **2.24.** L-selectride reduction of ketone **2.24** and Birch mediated deprotection of benzyl ethers complete the synthesis of $PGF_{2\alpha}$ and the diastereomer 15-ent epi $PGF_{2\alpha}$. Stork's synthesis highlights the utility in using a three component coupling to quickly generate prostanoid carbon framework from key building blocks and remains one of the workhorse approaches to prostaglandins to this day.[37,38]



Scheme 2.3.1: Stork's synthesis of $PGF_{2\alpha}$

2.4 Noyori's Synthesis of PGE_2 and PGD_2

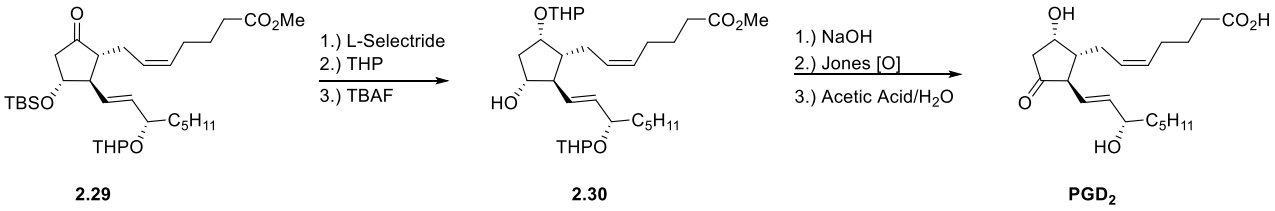
In the mid to late 80's Noyori expanded upon Stork's three-component coupling and solved some of the undesired side-reactions of the coupling, specifically enolate isomerization leading to β elimination of the silyl ether group. Noyori's synthesis started from 4-siloxycyclopentenone, **2.25** (Scheme 2.4.1). As in Stork's work the three component cuprate coupling starts with the generation of the cuprate form vinyl iodide **2.26,** with tBuLi, however the copper(I) source in this case was Bu_3P•CuI complex (a white crystalline solid). A further modification in the conjugate addition conditions**,** was addition of HMPA and Bu_3SnCl presumed to transmetallate the enolate to the corresponding tin enolate. The tin enolate suppresses isomerization and cleanly reacted with allylic iodide **2.27** to yield **2.28.** This reaction cleanly generates the entire carbon framework of the given prostaglandin from three key building blocks, in one high yielding step. Following this silyl deprotection using HF*Pyridine, followed by enzymatic hydrolysis, completes the synthesis of PGE_2. [39]



Scheme 2.4.1: Noyori's synthesis of PGE_2

Noyori also completed one of the first total syntheses of prostaglandin D_2 (Scheme 2.4.1). In this case, the same three component coupling was utilized but employed

orthogonal protecting groups in the side chain and core allowing for transposition of the C9 and C11 oxidation states (Scheme 2.4.2). Starting from the carbon framework of PGE_2, **2.29**, with a TBS group in the cyclopentenone core, and THP protected n-pentyl side chain, selective L-selectride reduction followed by THP protection and silyl deprotection generates secondary alcohol **2.30.** Saponification liberates the acid from the ester, followed by Jones oxidation of the C11 alcohol and deprotection of the THP group completes the synthesis of PGD_2. The saponification needs to take place before the oxidation of the C11 alcohol due to the base instability of the cyclopentenone core. Furthermore, cuprate chemistry nicely sets the 2,3-trans and 3,4-trans stereochemistry of the PGE_2 cyclopentanone core. Establishment of 2,3-trans and 3,4-cis relationship in the PGD_2 series remains problematic and most D series syntheses still rely on the inversion of the C9 and C11 oxidation states.[39]

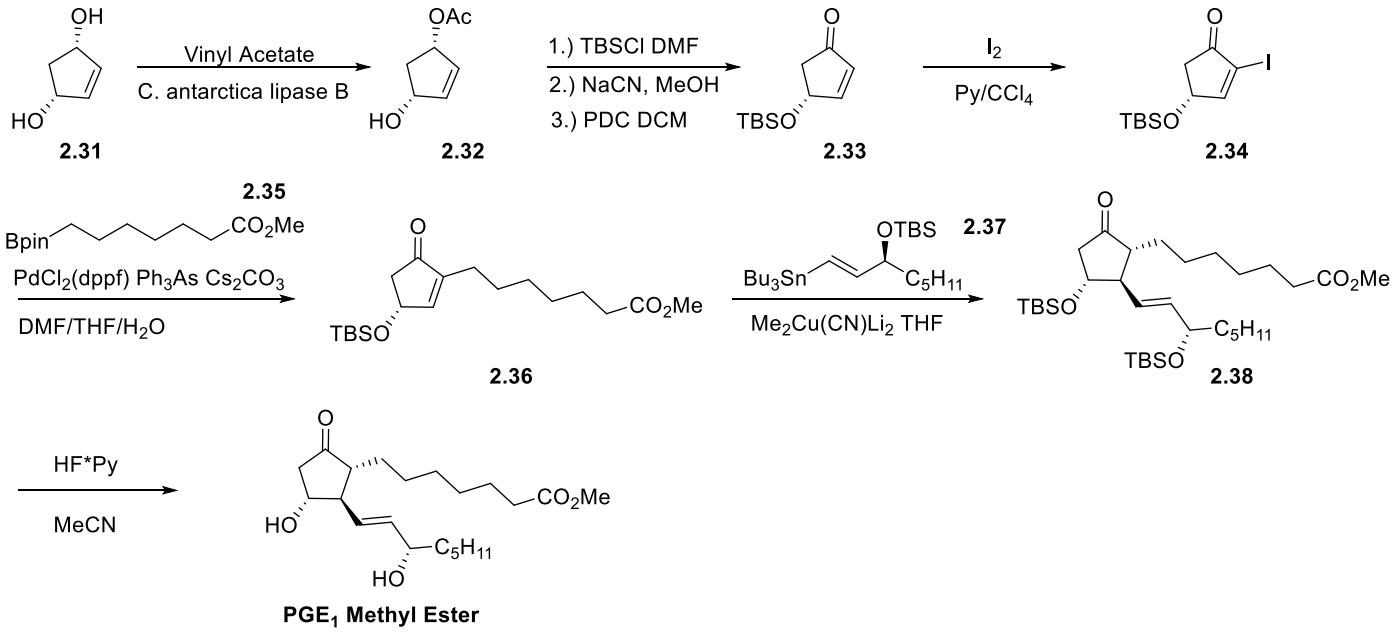


Scheme 2.4.2: Noyori's synthesis of PGE_2

2.5 Johnson Synthesis of PGE_1 Methyl Ester

Noyori's three-component coupling was synthetically very impressive and elegant, however, it required intense technical set ups and high synthetic skill. These two factors presented a large barrier to general utility of this methodology and limited its application

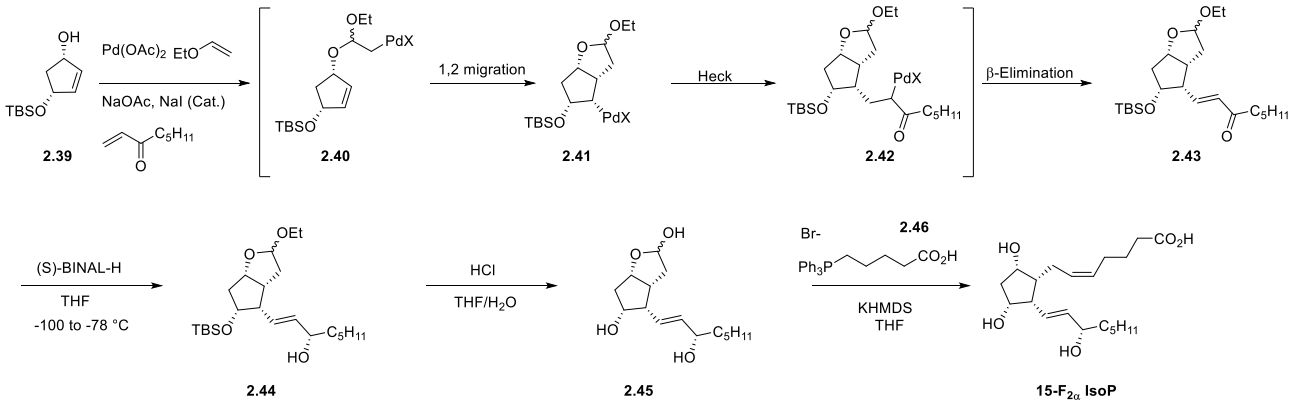
to other analogs of prostaglandins. Johnson and co-workers have developed a more general solution to “the enolate” problem. One strategy employed a Suzuki cross coupling enabling a two-component cuprate coupling (Scheme 2.5.1). Starting from meso diol **2.31**, enzymatic desymmetrization provides acetate **2.32** in high optical purity. Protection with TBSCl followed by deacetylation and oxidation generates valuable enone **2.33.** Iodination of enone **2.33** furnishes α-Iodoenone **2.34.** Suzuki cross coupling of the latter with B-alkyl reagent **2.35** installs the carboxylic acid side-chain in the form of enone **2.36.** Finally, generation of the necessary cuprate from vinyl tin **2.37,** elicits the necessary 1,4 addition, generating **2.38**. Global deprotection completes the synthesis of PGE_1 methyl ester. [40]



Scheme 2.5.1: Johnson’s synthesis of PGE_1 Methyl Ester

2.6 LaRock's Synthesis of 15-$F_{2\alpha}$ Isoprostane

LaRock's synthesis of 15-$F_2\alpha$ Isoprostane started with TBS protected allylic alcohol **2.39** (Scheme 2.6.1). A palladium mediated three-component coupling reaction starts with oxypallidation with ethyl vinyl ether to give intermediate **2.40** followed by a 1,2 migration of the double bond affording **2.41** which undergoes a Heck reaction with ocetenone, and yields acetal **2.43**. Enone **2.43,** is asymmetrically reduced using Noyori's (S)-BINAL-H reduction, to generate allylic alcohol **2.44.** Acid catalyzed deprotection of the acetal, furnishes lactol **2.45** which upon treatment with the ylide derived from phosphonium salt **2.46,** completes the synthesis of 15-$F_{2\alpha}$ IsoP. [41]

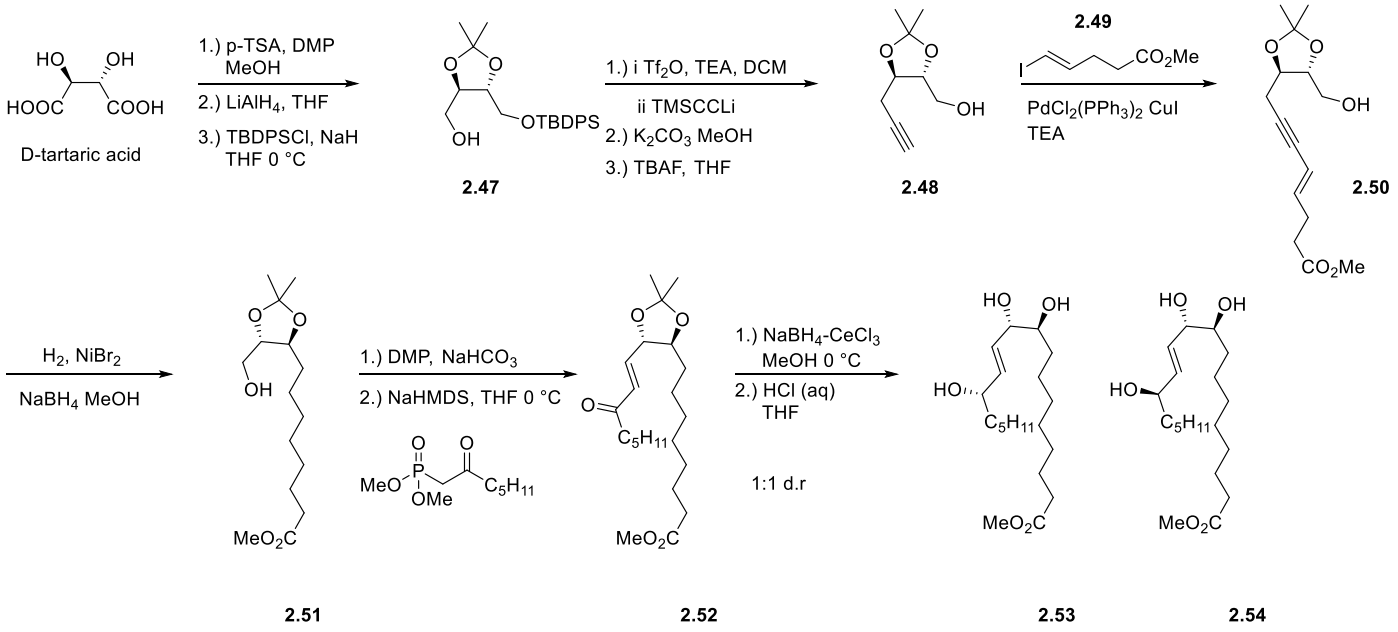


Scheme 2.6.1: LaRock's synthesis of 15-$F_{2\alpha}$ IsoP

2.7 Sulikowski Synthesis of 4 Linoleate Triols

The convergent synthesis of the four lineoleate triols began by reaching into the chiral pool, setting the 1,2 diol stereochemistry present in all of the triols. The synthesis begin with either D-tartaric acid or 2 deoxy-L-ribose. The tartaric acid route began with acetonide formation, Fischer esterification, LAH reduction and finally silyl protection to

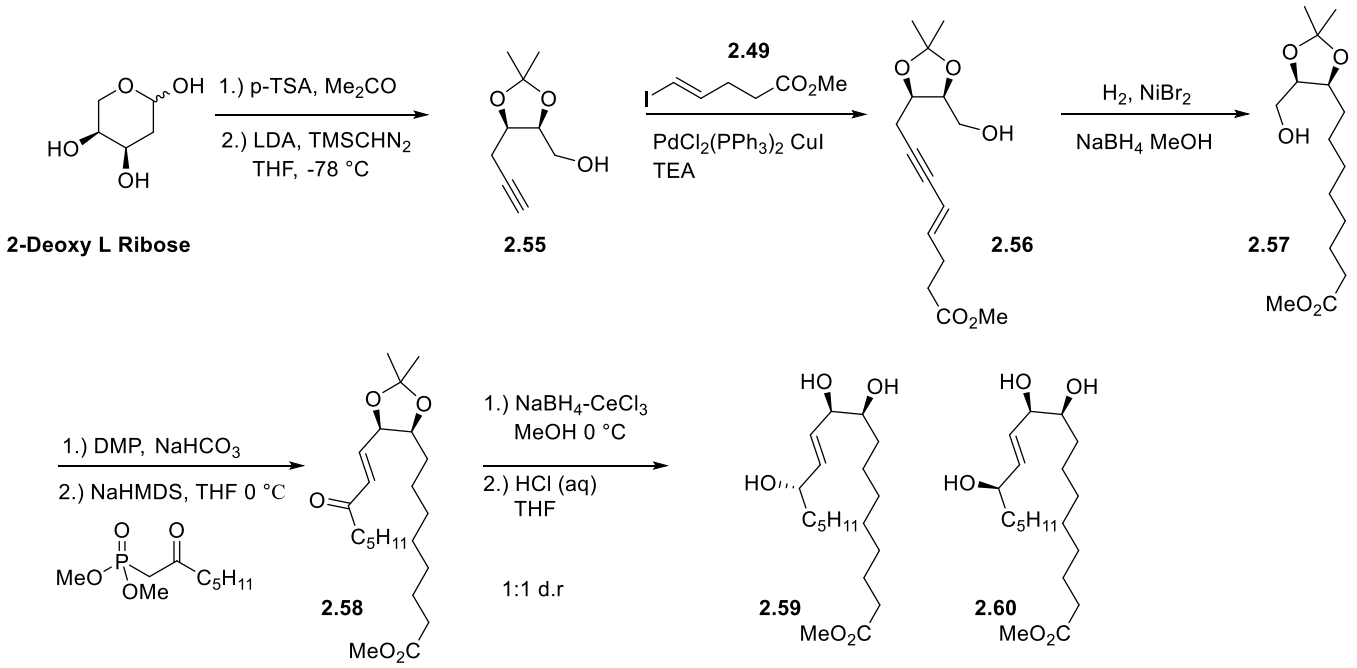
generate acetonide **2.47** (Scheme 2.7.1). Conversion of the primary alcohol into the desired alkyne took place in a two-step sequence commencing with triflation, then nucleophilic displacement with deprotonation of TMS acetylene. Protecting group manipulations furnishes alkynol **2.48.** Sonogashira cross-coupling with vinyl iodide **2.49** yields enyne **2.50,** followed by reduction using nickel catalyst and subsequent oxidation olefination sequence generates enone **2.52.** Luche reduction yields a mixture of allylic alcohols, which are separated, and finally acid catalyzed acetonide deprotection completes the synthesis of the first two triols, **2.53** and **2.54.**[42]



Scheme 2.7.1: Sulikowski D Tartaric acid synthesis of linoelic triols

The Sulikowski route starting from 2-deoxy-L-ribose, route begins with acetonide protection followed by Kolvin alkynylation to furnish alkynol **2.55** (Scheme 2.7.2). Sonogashira cross coupling with vinyl iodide **2.49,** yields enyne **2.56,** followed by

reduction using earlier described conditions, generate alkane **2.57.** Oxidation olefination sequence yields enone, **2.58,** followed by Luche reduction yielding a mixture of allylic alcohols which are separated and finally acid catalyzed acetonide deprotection completes the synthesis of the two Linoleate triols **2.59** and **2.60.** [42]

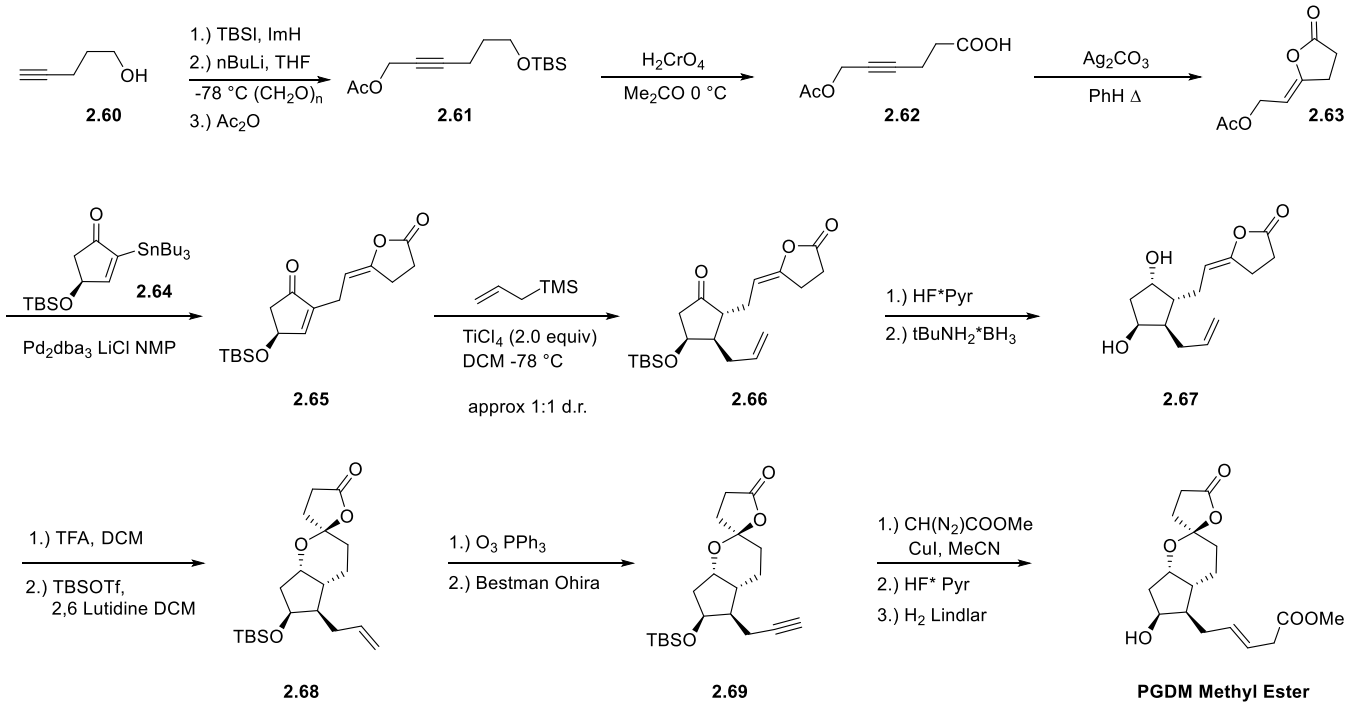


Scheme 2.7.2: Sulikowski 2 deoxy l Ribose synthesis of linoelic triols

2.8 Sulikowski Synthesis of PGDM methyl ester

The Sulikowski synthesis of prostaglandin D_2 metabolite known as PGDM methyl ester began with the synthesis of gamma lactone **2.63,** (Scheme 2.8.1). Silyl protection of pentynol followed by hydroxy methylation and acetylation generates **2.61.** One pot deprotection, Jones oxidation furnishes carboxylic acid **2.62.** Silver mediated

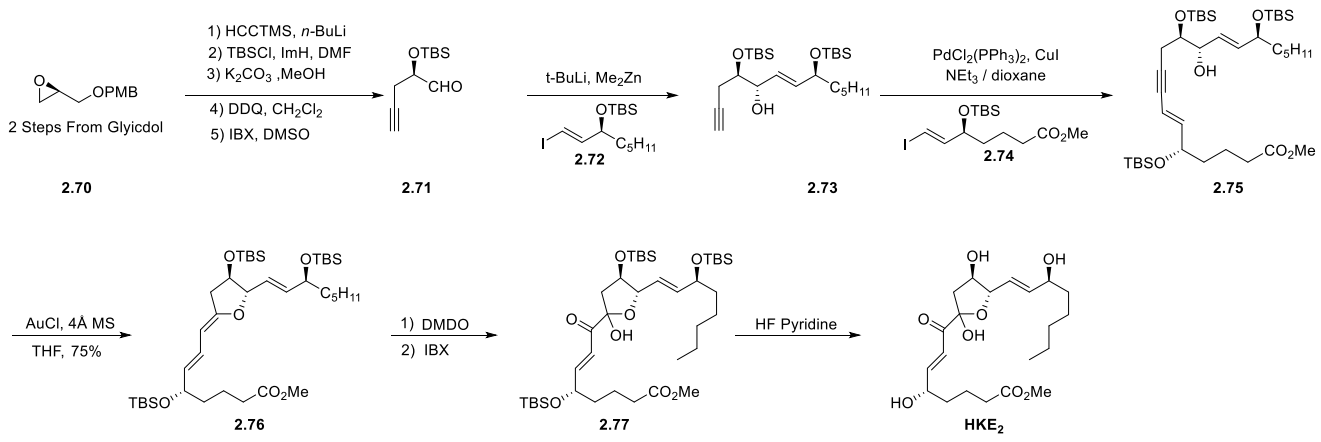
cycloisomerization furnishes gamma lactone **2.63.** Stille cross-coupling with vinyl tin **2.64** (derived from the iodoenone **2.34**) yields enone **2.65.** Treatment of **2.65,** with titanium tetrachloride and allyltrimethylsilane resulted in approximately a 1:1 mixture of diastereomers, **2.66,** that were separated via column chromatography. Deprotection followed by hydroxyl directed reduction with $tBuNH_2*BH_3$ yields diol **2.67.** Acid catalyzed cyclization followed by silylation furnishes tricycle, **2.68.** Ozonylsis, followed by Bestman-Ohira alkynylation converts the terminal alkene into desired alkyne **2.69.** Copper mediated coupling with methyl diazoacetate completed the carbon framework of PGDM methyl ester. Global deprotection and semi reduction completed the synthesis of tricyclic PGDM methyl ester.[43]



Scheme 2.8.1: Sulikowski synthesis of PGDM methyl ester

2.9 Sulikowski Synthesis of HKE_2

The Sulikowski synthesis of the novel arachidonic acid metabolite hemiketal E_2 began with epoxide **2.70** (Scheme 2.9.1). Treatment with the lithiate of TMS acetylene results in epoxide opening, followed by silyl protection of the derived secondary alcohol, PMB deprotection, TMS deprotection and oxidation of the primary alcohol furnishing aldehyde **2.71.** Lithium halogen exchange of vinyl iodide, **2.72**, followed by transmetallation with dimethyl zinc leads to Felkin-Ahn predicted addition into aldehyde **2.71** to afford anti diol, **2.73** as a single isomer**.** Sonogashira cross coupling with vinyl iodide, **2.74,** generates enyne, **2.75.** Gold(I) catalyzed cycloisomerization reaction generates labile enol ether **2.76,** which due to its unstable nature is rapidly oxidized by DMDO then IBX to furnish the keto hemiketal moiety of HKE_2. Global deprotection with HF pyridine completes the first total synthesis of HKE_2.[44]



Scheme 2.9.1: Sulikowski synthesis of HKE_2

Statement of Dissertation:

The work presented herein involves the attempted synthesis of hemiketal E_2 and the total synthesis of 5-hydroxy prostaglandin E_2. Both compounds are enzymatically derived from a crossover enzymatic pathway of 5-LOX and COX-2 which were historically thought to be independent enzymatic pathways. The hemiketals have been shown to stimulate capillary like growth of pulmonary endothelial cells, while the target and biological function of 5-hydroxy PGE_2 remains unknown. HKE_2 has been made by preparative biosynthesis as well as total synthesis, however both have resulted in limited material. The 5-hydroxy prostaglandins have been made from functionalization of prostaglandins. The metabolites of Arachidonic Acid have been the subject of countless total syntheses furthering understanding of human physiology as well as chemical synthesis. To truly elucidate their biological function and relation to human health a reproducible and robust total synthesis is required to generate material on scale.

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Chapter 3

Progress towards synthesis of HKE_2

While the discovery of the novel arachidonic acid metabolites the hemiketals was very exciting, studying their biological function has been hampered by their limited availability. Currently, hemiketals are produced enzymatically from 5S-HETE and COX-2 but yields only nanograms of products. As described in Chapter 2 the Sulikowski route produced milligrams of only HKE_2 (not HKD_2) and was plagued with scalability and reproducibility issues. The majority of my graduate career has been dedicated to developing a reproducible and robust route towards the synthesis of hemiketals E_2 and D_2 to enable their biological study.

3.1 Retrosynthetic analysis of HKE_2 and HKD_2

At the outset our aim was to develop a robust and reproducible route to both hemiketals building on our earlier route to HKE_2 as well as our work on the linoleic triols. Another major problem of the Sulikowski route was the inability to reach HKD_2. The original route was unable to generate the necessary 1,2 syn diol stereochemistry by way of a chelation controled addition to an alpha oxygenated aldehyde (cf. Felkin-Anh addition to aldehyde 2.9.2, Scheme 2.9.1).[44] Furthermore, we wished to avoid the key gold catalyzed cyclisomerization reaction present in the original Sulikowski route due to the inability to conduct the reaction on a scale greater than 20-50 mg, reproducibility issues and the inherent instability of the product enol ether and gold(I) chloride.[44]

The main differences between the hemiketals D_2 and E_2 is two-fold, first the relative stereochemistry of the vicinal stereocenters in the hemiketal ring. In HKE_2 the C11 and C12 positions possess a trans relative stereochemical relationship, and in HKD_2 the C8 C9 positions possess a cis relative stereochemical relationship. (Figure 3.1)The second difference is the relationship of the side chains. In HKE_2 the carboxylic acid side chain resides adjacent to the enone, while in HKD_2 the carboxylic acid side chain resides opposite the enone.

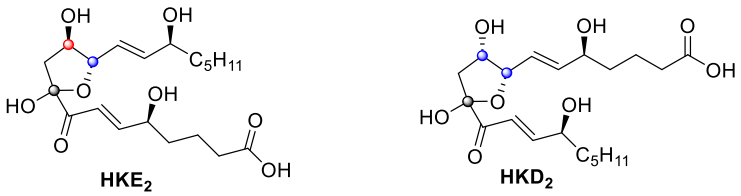


Figure 3.1: HKE_2 and HKD_2

As our earlier route's inaccessibility to hemiketal D_2 was largely related to our inability to effect a chelation controlled aldehyde addition to establish the correct relative stereochemistry we elected to start from one of two optically pure cis (for HKE_2) or trans (for HKD_2) acetonides as described in our route to the lineoates (cf. Scheme 2.7.1 and 2.7.2). This strategy is illustrated in Figure 3.2 starting from earlier described acetonide 3.1.4. Thus, retrosynthetic analysis of HKE_2 begins with disconnection between the keto group and the alkene in the carboxylic acid side chain. We envisioned this transformation from a cross coupling with vinyl metal **3.2** and **3.1** (Figure 3.2), followed by necessary oxidations to install the keto hemiketal functionality**.** The neccessary 1,1-dihalide **3.1** would be formally derived through a cycloisomerization-halogenation sequence starting

from alkyne **3.3.** The enone present in **3.3** can be disconnected to required aldehyde **3.4** and phosphonate, **3.5** for a Horner Wadsworth Emmons olefination.

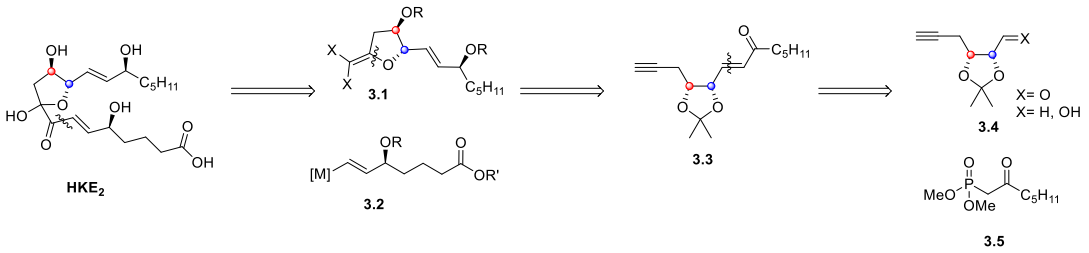


Figure 3.2: Retrosynthetic analysis of HKE_2

Importantly, the synthetic route would provide access to HKD_2 starting from trans acetonide 3.1.9 (Figure 3.3). A second required modification would be side-chain installation where the carboxylic acid containing side-chain is installed early by way of a Horner-Emmons olefination and n-pentyl side-chain by late-stage cross-coupling (Figure 3.3). Trans- and cis-acetonides would be obtained starting from D-tartaric acid and 2-deoxy-L-ribose, respectively. [42]

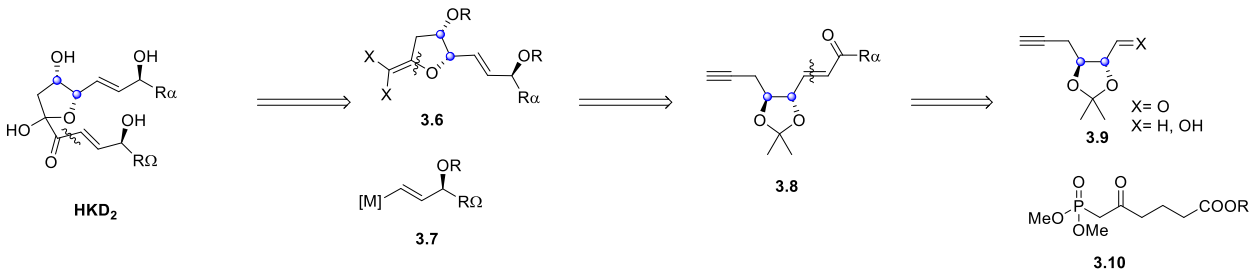


Figure 3.3: Retrosynthetic analysis of HKD

Finally, we required four different side chains for the synthesis of both HKE_2 and HKD_2 shown below (Figure 3.4). There are multiple published routes to these common prostaglandin like side-chains. Application and/or modification of theses syntheses are described in the next section.

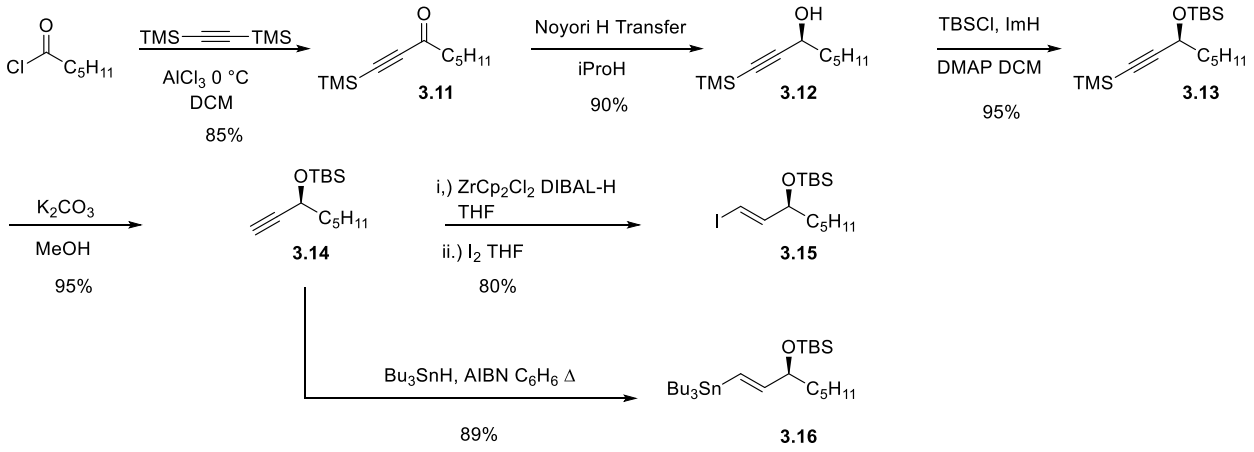
M= X, Bpin, Bu_3Sn

Figure 3.4: Necessary side chains for hemiketals

3.2 Synthesis of required side chains

3.2.1: Synthesis of n-pentyl containing (omega) side chain

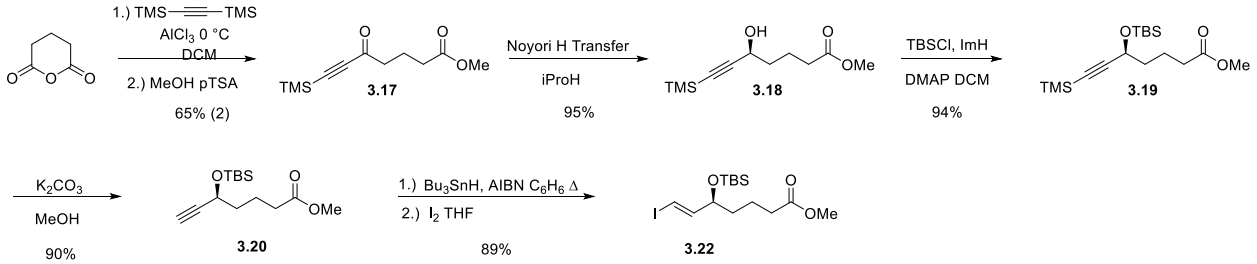
Synthesis of the n-pentyl containing side chain began with treatment of hexanoic acid with thionyl chloride to generate the corresponding acid chloride that engaged in a Friedel-Crafts like reaction with bis-trimethlsilylacetylene and aluminum trichloride to furnish desired alkynone **3.11** (Scheme 3.2.1)**.**[45] Asymmetric Noyori hydrogen transfer furnishes desired propargylic alcohol **3.12** in high optical purity (>95% ee)**.**[46] Protection of the secondary alcohol as a TBS ether and selective TMS removal generated terminal alkyne **3.14.** Alkyne **3.14** can be hydrometallated by a variety of methods to furnish either the corresponding vinyl halide or vinyl metal. We elected to access vinyl iodide **3.15** by a standard hydrozinconation-iodine quench**.** Vinyl stannane **3.16** was accessed as a single geometric isomer using Bu_3SnH and AIBN as a radical initiator.[47–51]



Scheme 3.2.1: synthesis of n-pentyl (omega) side chain

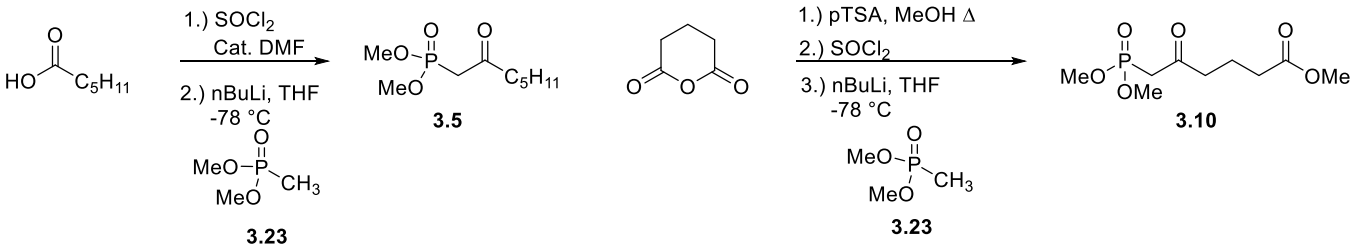
3.2.2: Synthesis of carboxylic acid containing (alpha) side chain

The synthesis of the carboxylic acid containing (alpha) side chain began with Friedel Crafts reaction between glutaric anhydride and bis-trimethylsilylacetylene and aluminum trichloride.[45] The derived carboxylic acid was subjected to a Fischer esterification, to yield methyl ester **3.17** (Scheme 3.2.2). Enantioselective reduction of the alkynone was again accomplished using Noyori hydrogen transfer.[46] Again, protection of the derived secondary alcohol was followed by selective TMS removal to give alkyne **3.20.** Radical mediated hydrostannylation followed by tin-iodide exchange furnishes vinyl iodide **3.22.**[45,50–53]



Scheme 3.2.2: Synthetsis of α side chain

3.2.3: Synthesis of phosphonate side chains



Scheme 3.2.3: Synthesis of phosphonate side chains

Having established access to either carboxylic acid or n-pentyl side-chains with terminal alkenyl stannanes for late stage cross-coupling (cf. Figures 3.2 and 3.3) we turned our attention to accessing the corresponding phosphonates required for early stage HWE olefinations. The synthesis of either n-pentyl (**3.5**) or carboxylate (**3.10**) phosphonate side chains has been published and follow similar routes of assembly using classical Claisen reactions (Scheme 3.2.3)[54,55] To this end, deprotonation of methyl phosphonate **3.23** (Scheme 3.2.3), followed by treatment with an acid chloride either derived from hexanoic acid or glutaric anhydride furnished phosphonates **3.5** and **3.10**, respectively**.**

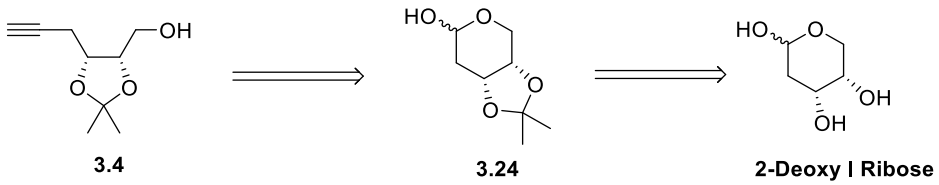
3.3 Synthesis of 1,2-oxygenated core alkyne

We selected hemiketal E_2 (HKE_2) as our primary synthetic target as this would enable direct comparison of efficiency and reproducibility to our groups first-generation synthesis of HKE_2. As discussed above our first-generation synthesis required a Felkin-

Anh addition to an alpha-oxygenated aldehyde. In contrast, our current route aims to establish the 1,2-oxyganation by starting from cis-acetonide **3.4,** (Figure 3.2). Synthesis and reaction optimization of our synthesis of cis-acetonide **3.4** starting from 2-deoxy-L-ribose is described in the following sections.

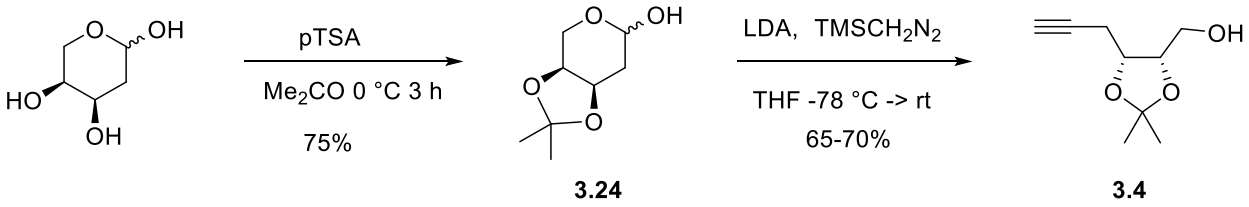
3.3.1: Kolvin alkynylation

A report by Chen describes access to alkyne by alkynylation of lactol **3.24** (Figure 3.5)[56]. Lactol 3.24 is derived from 2-deoxy-L-ribose as described by Chen. Thus synthesis commenced with acetonide protection of 2-deoxy-L-ribose, which after reaction optimization was achieved with pTSA in acetone at 0 °C for 3 hours (Table 3.1). Alkynylation was achieved using Kolvin conditions starting with treatment of trimethylsilyldiazomethane with LDA, followed by addition of **3.24** Under these conditions the alkynylated product **3.4** was produced in 45% from commercial ribose (Scheme 3.3.1).[56]

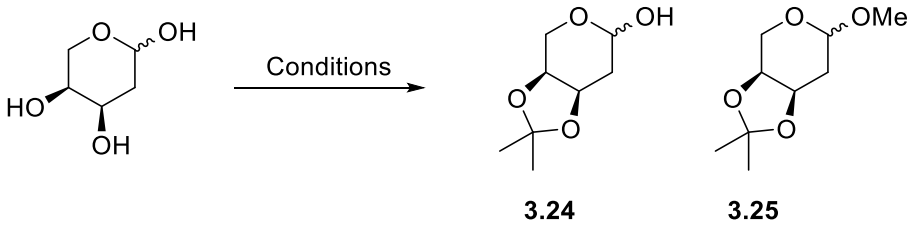


3.4 **3.24** **2-Deoxy l Ribose**

Figure 3.5: Retrosynthetic analysis of Alkynol



Scheme 3.3.1: Synthesis of alkynol 3.4



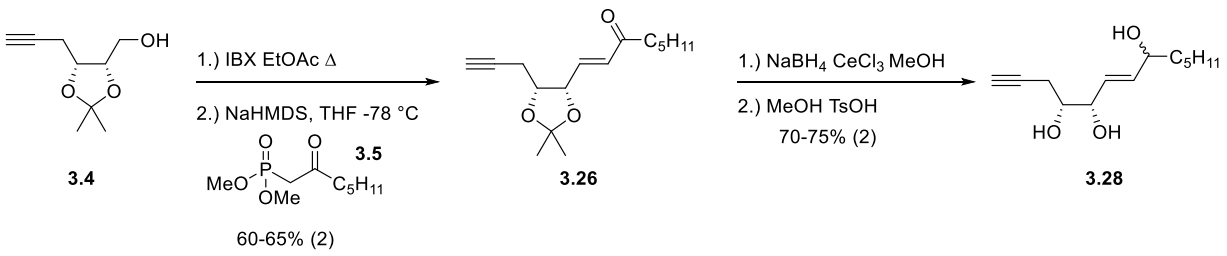
Entry	Reagents	Solvent	Temperature	Time	Result
1	pTSA, DMP	Acetone	Reflux	2 h	**3.25** 65%
2	pTSA, DCM	Acetone	Reflux	12 h	RSM
3	2-Methoxypropene	EtOAc	-10 °C	12 h	**3.25** 50%
4	pTSA	Acetone	0 °C	2 h	**3.24** 55%
5	pTSA	Acetone	0 °C	3 h	**3.24** 75%

Table 3.1: Acetonide protection optimization

3.3.2 Triol synthesis and incorporation of n-pentyl side-chain

With two required side-chains and the central deoxygenated core in hand, our assembly of hemiketal-E_2 started with oxidation of alcohol **3.4** to the corresponding aldehyde in preparation for HWE reaction. A series of alcohol oxidations were examined which included Swern, DMP and Parikh-Von Doering conditions. However, best results were obtained using IBX in EtOAc at reflux for 7 hours providing the highest yields and greatest reproducibility**.** Horner Wadsworth Emmons olefination proceeded smoothly with

the crude aldehyde upon treatment of phosphonate, **3.5 (Scheme 3.3.2)** and NaHMDS at -78 ° C in THF. This two-step oxidation-alkenylation reproducibly provided enone **3.26** in 60% overall yield. Luche reduction of the atter, yielded approximately a 1:1 mixture of diastereomers, which proved inseparable. In principle, a CBS asymmetric reduction could be employed to obtain the natural S-isomer, but we elected to move forward with an isomeric mixture for process development. Our next objective was to reveal the corresponding 1,2-diol by acetonide removal. To that end, treatment with pTSA in methanol yielded triol **3.28**. The stage was now set to examine metal catalyzed cycloisomerizations and establish the HKE_2 core ring structure.



Scheme 3.3.2: Synthesis of triol 3.28

3.3.3: Metal catalyzed cycloisomerizations

Furans and pyrans are common ring structures among a variety of natural products. This commonality has led to the development of numerous types of methodologies aimed at incorporating these modalities within complex molecules. One set of methodologies rely on metal-promoted cycloisomerization reactions using alkynols as reaction substrates. These are commonly accomplished via a wide variety of metals

such as gold, molybdenum, palladium, mercury, and silver to name a few. In general terms these isomerization reactions are initiated though electrophilic coordination of metals to electron rich alkynes (Figure 3.6). This coordination serves to activate the alkyne towards nucleophilic attack of the pended alcohol functionality. Cyclization has been reported to take place by either a 5-exo-dig or 6-endo-dig fashion to furnish furan and pyran rings, respectively. From the 5-exo-dig as illustrated in Figure 3.6 provides a vinyl metal species which can be subjected to several reaction paths. First, protodemetallation could occur as shown yielding a furan ring and regeneration of the metal catalyst.[57–66] A second possibility (not shown) is the intermediate vinyl metal can engage in a cross-coupling reaction, installing the remaining side-chain functionality. Finally, the vinyl metal intermediate can be quenched with a source of electrophilic halide to give the corresponding alkenyl halide.

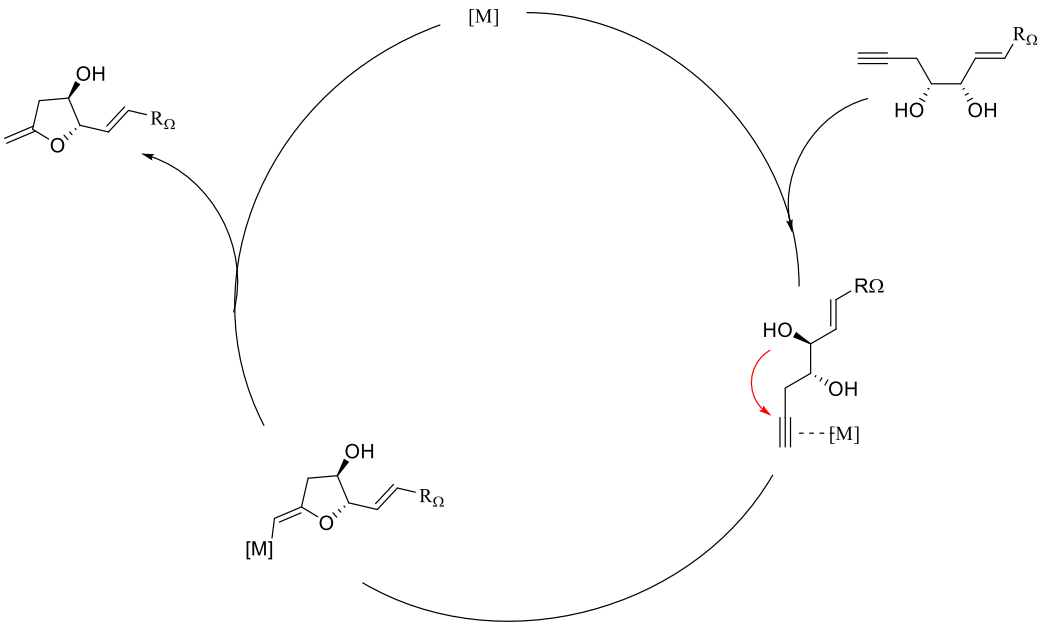
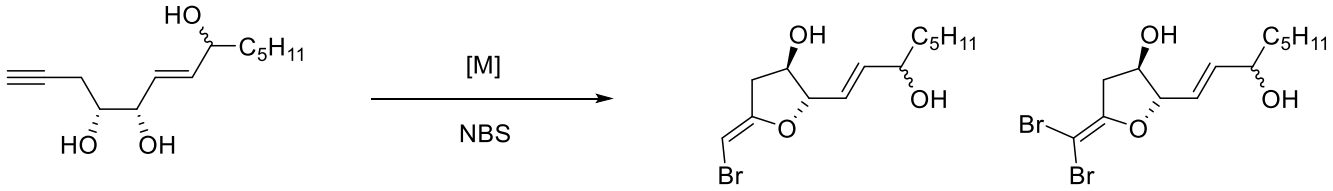


Figure 3.6: General 5-exo dig cycloisomerization mechanism

Based on the mechanistic rational described we examined a series of reaction conditions aimed at demonstrating ring closure and possible halogen incorporation (Table 3.2). Much to our disappointment no productive conditions were identified, with decomposition the most common result. It was believed that the product was inherently unstable and was decomposing upon purification on silica gel. Following this, great pains were taken to both make sure the reaction was purified on buffered silica, either with 1% TEA or on pH 7 buffered silica. Reactions were resulting in a complex mixture of products that were not isolable, decomposition, or a recovery of starting triol. The only conditions that showed any promise was $AgNO_3$ and NBS, which resulted in the isolation of geminal 1,1 dibromo vinyl ether **3.30**, shown in Table 3.2 (entry 8)**.**



3.28 **3.29** **3.30**

Entry	Catalyst	Reagents	Solvent	Result
1	$AgNO_3$	-	MeCN	Mixture
2	AgF	-	MeCN	Decomp
3	$PdCl_2$	DMAP	MeCN	Decomp
4	$HgCl_2$	DMAP	MeCN	Decomp
5	Ag_2CO_3	-	Benzene	Decomp
6	-	-	THF	RSM
7	Ag_2CO_3	-	DCM	RSM
8	$AgNO_3$	DMAP	MeCN	**3.30**, 5%

Table 3.2: Screening of metal catalyzed cycloisomerizations

The proposed mechanism of the 1,1 dibromo compound is shown in Figure 3.7. Silver abstracts the alkyne proton resulting in subsequent alkyne bromination. Silver then coordinates with the alkyne promoting the 5-exo dig cyclization yielding intermediate **3.34** Finally, halogenation at the vinyl metal species results in the 1,1 dibromo compound **3.30.** Following this result, we elected to halogenate the terminal alkyne prior to screening conditions to affect the desired cycloisomerization.

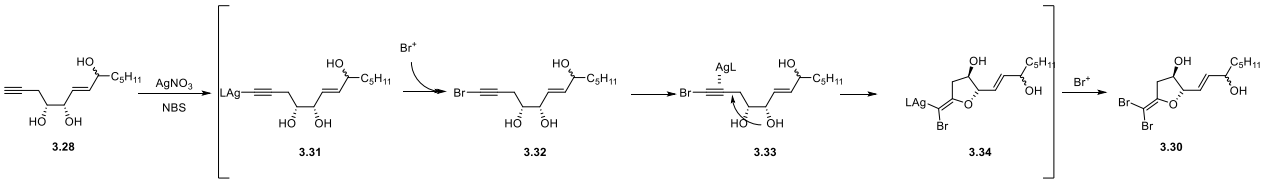
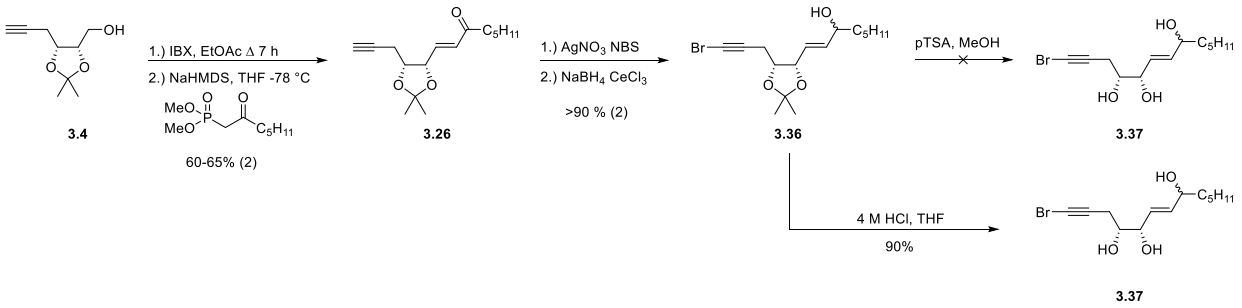


Figure 3.7: Proposed mechanism of 1,1 dibromo compound

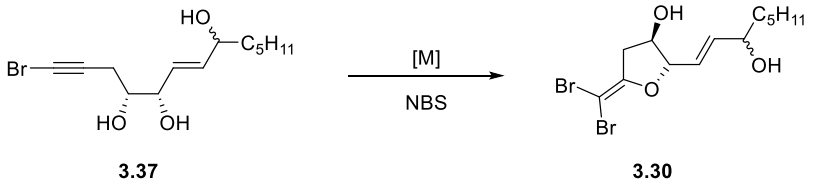
3.3.4 Synthesis of bromo alkyne triol

Oxidation, olefination of alkynol **3.4,** furnishes enone **3.26** (Scheme 3.3.3). Treatment with silver nitrate and NBS cleanly yields bromo alkyne**.** Which was subjected to Luche reduction to afford alcohol **3.36,** as a mixture of diastereomers. Unfortunately, previously optimized acetonide deprotection conditions (pTSA in MeOH) were now unsuccessful resulting in decomposition. However, treatment of acetonide with 4M HCl in THF, successfully generated triol **3.37**.



Scheme 3.3.3: Synthesis of triol **3.37**

The results of the cycloisomerization reactions with the terminal bromide were more favorable than with the naked alkyne. Cycloisomerization studies are summarized in Table 3.3**.** These reactions worked well with a variety of different metal sources such as palladium(II), silver(I) and mercury(II). The best obtained conditions were silver carbonate, summarized in entry 2 of table 3.3**.**



Entry	Catalyst	Reagents	Solvent	Result
1	$HgCl_2$	DMAP	MeCN	35%
2	Ag_2CO_3	DMAP	MeCN	58%
3	$PdCl_2(MeCN)_2$	DMAP	MeCN	Decomp
4	$PdCl_2$	DMAP	MeCN	10%
5	$PdCl_2$	Benzoquinone	THF	40%

Table 3.3: Bromo alkyne cycloisomerization conditions

3.3.5 Attempted cross couplings and tandem cycloisomerizations

At this stage we had established the central core structure of HKE_2, one side chain and a handle to install the remaining side-chain by a cross-coupling reaction (cf. 3.3.8, Figure 3.8). Our remaining requirements were side-chain installation and oxidation to reach hemiketal oxidation state. At this point we were anticipating the higher oxidation state of the vinyl halide would abate the need for the double oxidation in the original Sulikowski route.[44]

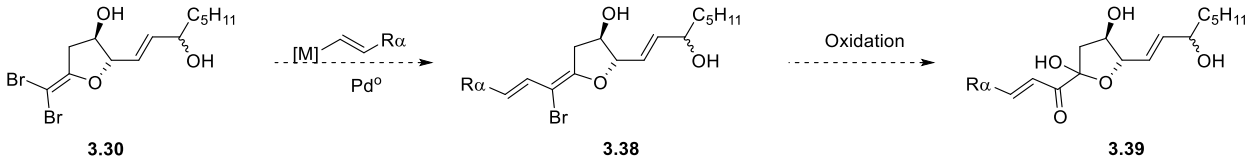
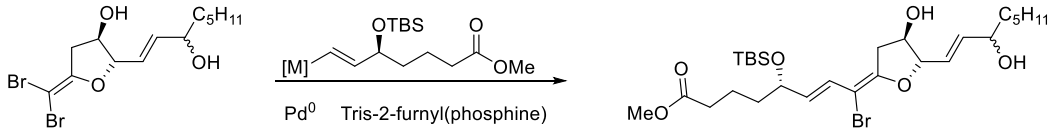


Figure 3.8: Synthetic strategy from 1,1 dibromo compound

The results of cross coupling to furnish the fully elaborated carbon framework are summarized in Table 3.4**.** Unfortunately, the desired carbon-carbon bond was never formed. Attempted cross couplings began with attempted Stille cross couplings.[67] However, after altering time, temperature and heating type the results were all consistently poor with complex reaction mixtures that did not provide any useful information. Suzuki cross couplings were next attempted, with initial results being very promising. Initial attempts showed reduction of the 1,1-dibromo compound to the mono vinyl halide **3.29** (entry 5 Table 3.4). This would imply that oxidative addition was taking place, but transmetallation was the rate limiting step. A common solution to this problem is the Kishi-Roush modification of Suzuki cross couplings which relies upon using thallium(I) bases such as thallium ethoxide or thallium hydroxide. The thallium bases generate the boronate complex quicker, speeding up the rate of transmetallation in cross

couplings. Following this Suzuki couplings were attempted using Thallaium ethoxide as a base, however what was observed was dimerization of the vinyl boronate side chains, and desired carbon-carbon bond was never isolated.



Entry	Metal	Catalyst	Base	Solvent	Temperature	Time	Result
1	Bu_3Sn	$Pd_2(dba)_3$	-	PhMe	140 °C	45 min/Mw	Mixture
2	Bu_3Sn	$Pd_2(dba)_3$	-	PhMe	80 °C	1h	Mixture
3	Bu_3Sn	$Pd_2(dba)_3$	-	PhMe	140 °C	10 min/Mw	RSM
4	Bu_3Sn	$Pd_2(dba)_3$	-	PhMe	80 °C	30 min	Mixture
5	Bpin	$PCl_2(PPh_3)_2$	K_2CO_3	DME	85 °C	2 h	**3.29**
6	Bpin	$Pd(PPh_3)_4$	Tl(OEt)	THF/H_2O	0 °C	30 min	RSM
7	Bpin	$Pd(PPh_3)_4$	Tl(OEt)	THF/H_2O	0 °C	2 h	Decomp

Table 3.4: Attempted Cross coupling reactions

Previous work out of the Larock and Fujino groups showed precedence for tandem cyclization cross coupling reactions.[41,68] This would be an attractive idea, in theory solving the two major reactions that had cause problems, the cycloisomerization and cross coupling reactions. The proposed mechanism is shown in Figure 3.9, starting with oxidative addition of the palladium(0) with vinyl iodide **3.15,** resulting in generation of the palladium(II) species. Coordination with the free alcohol, followed by cyclization results in

the vinyl palladium (II) compound. This intermediate undergoes reductive elimination generating the desired carbon-carbon bond, and, regenerating the palladium(0) species, subsequently re starting the catalytic cycle.

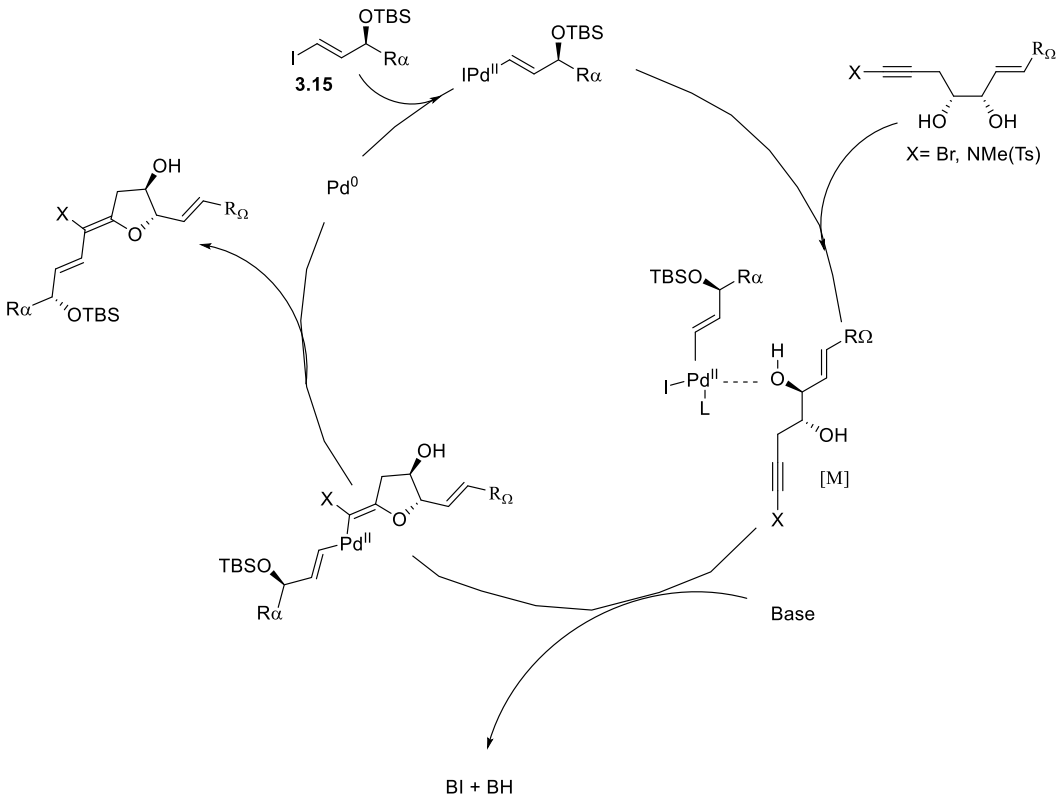
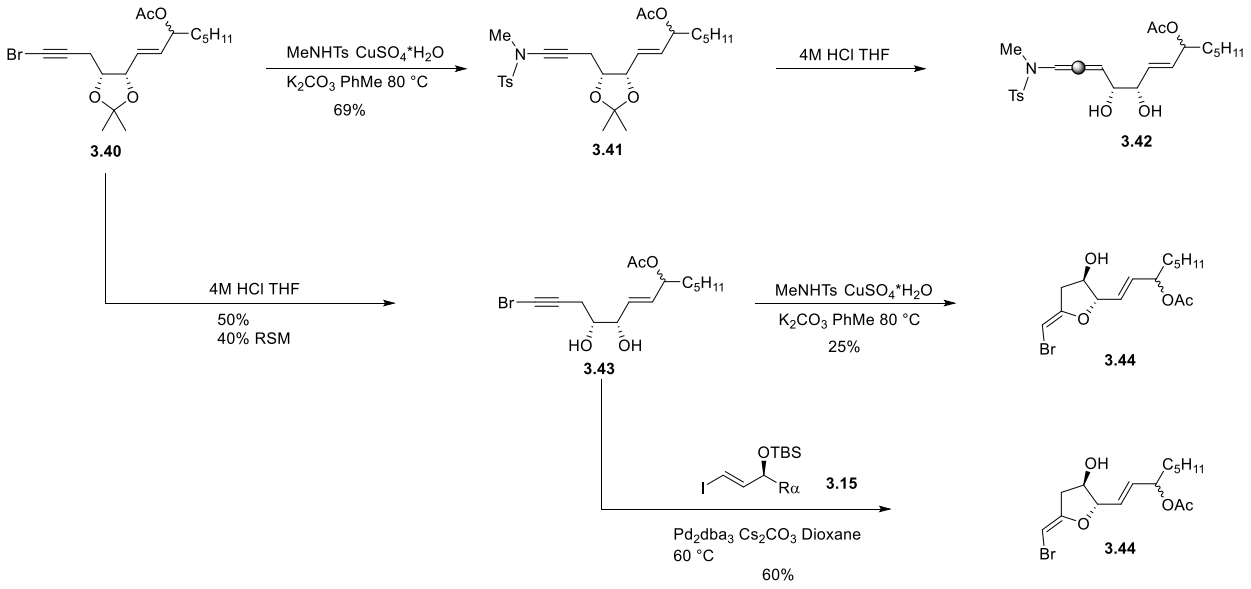


Figure 3.9: Proposed mechanism of tandem cycloisomerization cross coupling

Starting from allylic acetate **3.40** (Scheme 3.3.4), conversion to the ynamide, through copper mediated cross coupling cleanly generated **3.41.** Unfortunately, acetonide deprotection conditions resulted in allene **3.42.** At this point we opted to deprotect the acetonide before conversion to the ynamide generating diol **3.43**, which when subjected to copper cross coupling conditions, underwent a cycloisomerization reaction resulting in mono vinyl halide **3.44.** Tandem cycloisomerization, cross coupling reaction was tried

between diol **3.43** and vinyl iodide **3.44**, however the only product ever isolated was cycloisomerization product **3.44**.

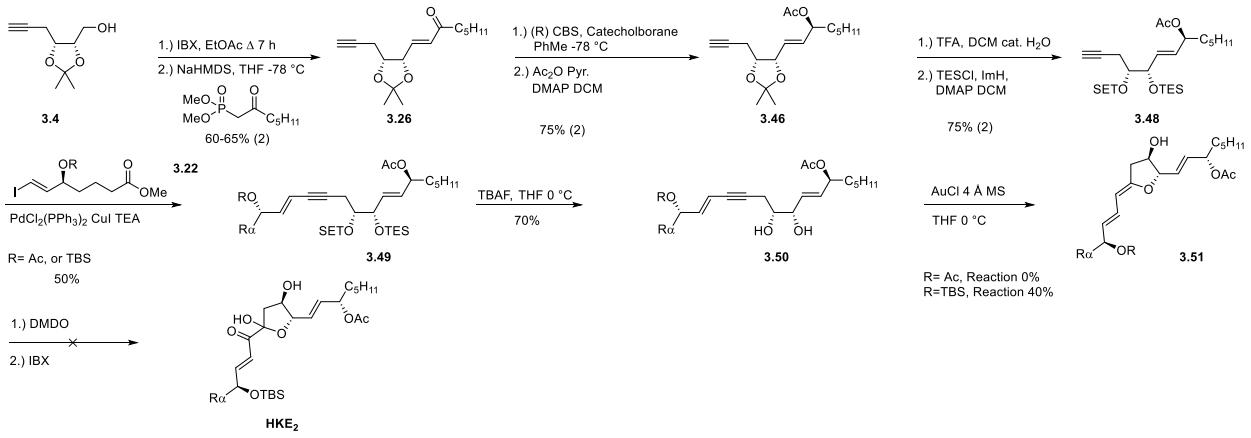


Scheme 3.3.4: Tandem cycloisomerization cross coupling route

3.3.6 Convergence with Boer-Sulikowski route

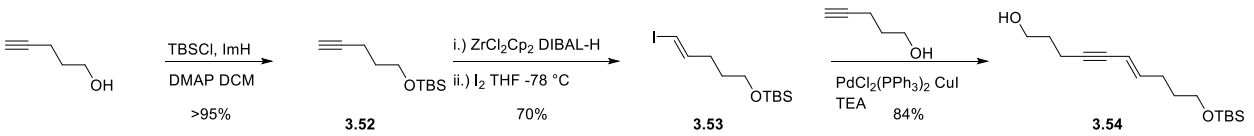
It was determined at this point that convergence with the original Sulikowski route may facilitate development of HKE_2. While we would unfortunately not get away from the unstable vinyl ether diene, we would still enable a successful route to HKD_2 through the cis acetonide built from tartaric acid. This sequence commenced with alkynol **3.4** (Scheme 3.3.5), following the same two step oxidation, HWE olefination sequence resulting in enone **3.26.** This was asymmetrically reduced using the (R)-CBS catalyst and catechol borane, resulting in approximately a 9:1 diastereomeric ratio by NMR.[69] Acetylation, followed by protecting group manipulations resulted in the TES protected silyl

ether, **3.48.** Sonogashira cross coupling with vinyl iodide, **3.22**, furnishes the entire carbon framework of HKE_2, **3.49.** Selective deprotection of the TES groups proceeded smoothly to yield diol **3.50,** setting the stage for cycloisomerization. Attempts at following the original Sulikowski procedure resulted in a complex mixture of products. However, after lowering the temperature to 0 °C, we were successfully able to obtain desired vinyl ether diene, **3.51.** Subsequent oxidations were attempted to generate the keto hemiketal moiety, however all were unsuccessful.



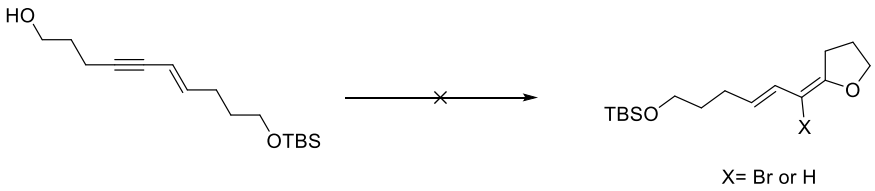
Scheme 3.3.5: Convergence with Sulikwoski route

A model system was developed and different cycloisomerization reactions were attempted. It was believed that the free alcohol present in our route was interfering in the oxidation. We looked to use a model system to optimize cycloisomerization, and oxidation conditions that could be transferred into the real system. Development of the model system began with protection of 4-pentynol as the TBS silyl ether, **3.52** (Scheme 3.3.6). Hydrozirconation, and iodination generated vinyl iodide **3.53.** Model system was completed via Sonogashira cross coupling with 4-penynol to furnish desired enyne, **3.54.**



Scheme 3.3.6: Synthesis of model system 3.54

Unfortunately, under a variety of different metal catalysts such as palladium, mercury, and gold, desired cyclisomerization product was never obtained, resulting in a complex mixture of products or a recovery of starting material as summarized in table 3.6. Further attempts at trapping the potential vinyl metal with an electrophile were also unsuccessful. Following these shortcomings this route was abandoned.



Entry	Catalyst	Electrophile	Solvent	Temperature	Result
1	$PdCl_2(CH_3CN)_2$	NH_4HCO_2	MeOH	-78 °C	Mixture
2	$Hg(OTf)_2$	-	MeOH	-78 °C	Mixture
3	$PdCl_2$	NH_4HCO_2	THF	Rt	RSM
4	$HgCl_2$	NBS	MeCN	Rt	RSM
5	AuCl	-	THF	0 °C	Mixture

Table 3.5: Attempted model cycloisomerizations

3.3.7 D-GluconoLactone

After the failure of the model cycloisomerizations, we came across an interesting reaction reported by the Fernandes group (Figure 3.10).[70] Heating a solution of D-gluconolactone in 30% hydrobromic acid in acetic acid , followed by addition of activated zinc afforded gamma-lactone **3.55** (Figure 3.10). Comparison of lactone **3.55** to HKE_2 core structure reveals the functionality and stereochemistry align between the two oxygenated ring structures.

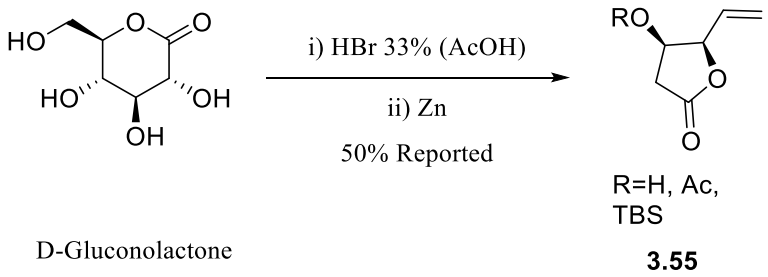


Figure 3.10: gamma-lactone 3.55

From comparison to HKE_2 it is easy to see how gamma-lactone **3.55** would nicely map onto HKE_2 (Figure 3.11). The terminal olefin of gamma-Lactone **3.55,** could be envisioned as a handle for a cross methasis reaction to incorporate the n-pentyl side chain for HKE_2. Furthermore, the 1,2 diol of HKE_2 is nicely set in the gamma-lactone, requiring an isomerization to set the necessary 1,2 trans diol stereochemistry. Finally, the lactone could be envisioned as an electrophilic handle for incorporation of the carboxylic acid side chain.

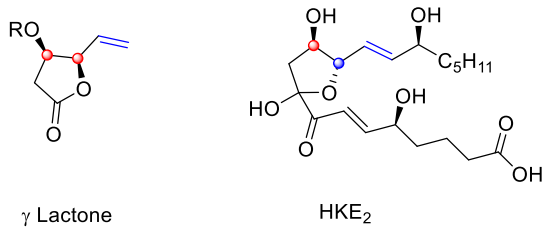


Figure 3.11: Comparison of γ lactone 3.55 with HKE_2

From a retrosynthetic standpoint of hemiketal E_2 we can envision disconnecting at the lactone from the carboxylic acid side chain, with an equivalent of carbon monoxide and a vinyl halide or metal species that are brought together in a cross-coupling reaction (Figure 3.12). The internal olefin can be disconnected through a cross-methasis reaction to install n-pentyl side chain. Gamma-lactone **3.55** can be reached from a known isomerization reaction.[69]

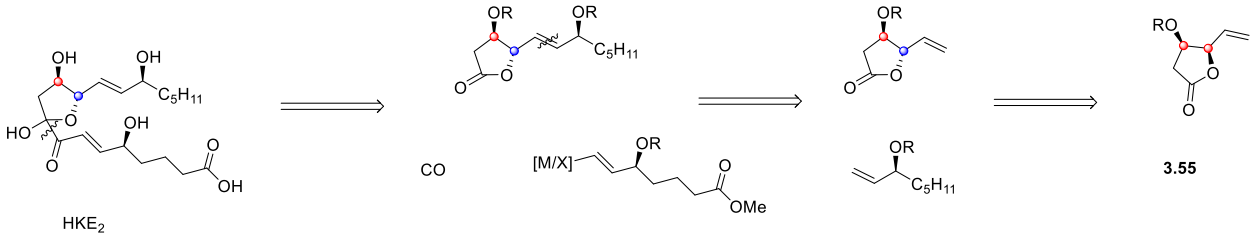


Figure 3.12: New retrosynthetic analysis of HKE_2

Furthermore, looking at the reaction of the enantiomer, L-gluconolactone, treatment with HBr in AcOH followed by treatment with activated zinc would furnish the enantiomer of gamma-lactone **3.55**. This lactone would have the correct 1,2 cis diol stereochemistry required for HKD_2. (Figure 3.13). The same analysis for the synthesis would apply as before, however the incorporation of the side chains would be reversed.

The n-pentyl side chain would be brought in through functionalization of the lactone, while the carboxylic acid side chain would be incorporated through a cross methasis reaction with the terminal olefin.

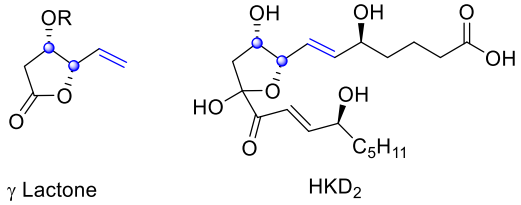
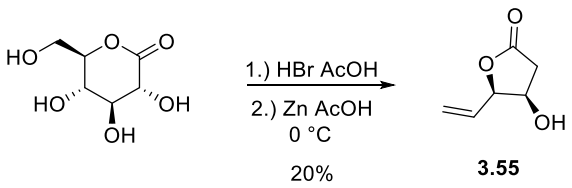


Figure 3.13: Comparision of γ lactone with HKD_2

The initial report of the construction of gamma Lactone **3.55**, from D-gluconolactone was reported by Hollingsworth in 2001, reporting a 58% yield over two steps.[71] The Fernandes group upon attempted replication of their work were unsuccessful. However, they eventually reported a 51% yield after optimization.[70] Upon attempts at both procedures the best yield ever obtained was 10%. After optimization of conditions, the best achieved result was treatment of D-gluconolactone with HBr in AcOH overnight, followed by addition of activated zinc generating gamma lactone **3.55**, in 20% yield over 2 steps (Scheme 3.3.7). While not an ideal yield, this reaction was scalable, and it was possible to produce multi gram quantities of gamma-lactone **3.55**.



Scheme 3.3.7: Synthesis of **3.55**

With gamma Lactone in hand we looked to convert the gamma-lactone to the correct 1,2 diol stereochemistry for HKE_2. (Figure 3.14).[69] Following, this conversion into vinyl triflate for incorporation of the carboxylic acid side chain through a cross coupling reaction. The keto hemiketal moiety could be achieved through a Mukaiyama hydration reaction.[72]

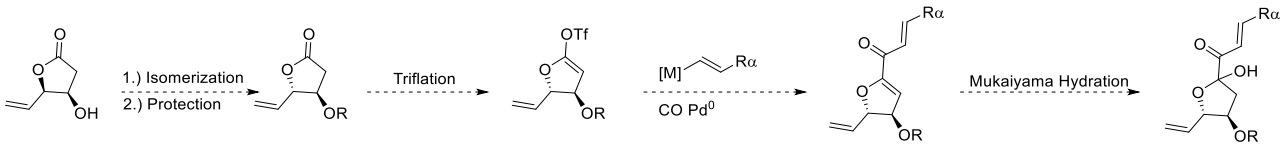
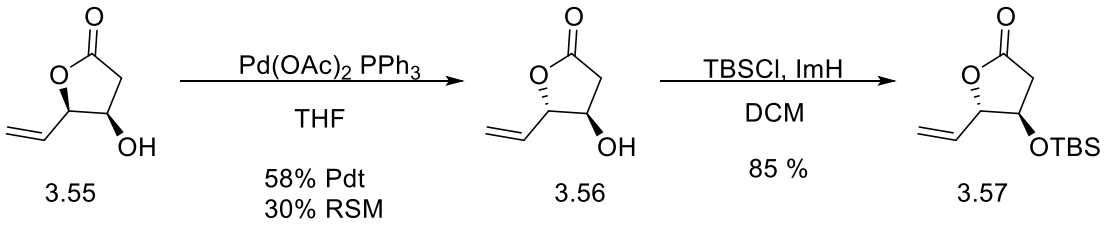


Figure 3.14: Synthetic Strategy for HKE_2

Starting from gamma-Lactone, **3.55** Tsuji Trost like reaction isomerizes lactone **3.55** to the 1,2 trans stereochemistry of **3.56.** This is followed by silyl protection generating desired gamma- Lactone **3.57** (Scheme 3.3.8).[69]



Scheme 3.3.8: Synthesis of lactone 3.57

Isomerization reaction commences with the reduction of the palladium (II) source to palladium (0). Coordination of palladium (0) to the terminal olefin of the gamma-lactone**,**

results in intermediate **1,** Figure 3.15. Oxidative addition results in the generation of the η-3 complex, intermediate **2,** which is subjected to backside nucleophilic attack of the resulting carboxylate resulting in intermediate **3**, with inversion of stereochemistry. Finally, decomplexation results in desired isomerized gamma-lactone **3.56**, and palladium (0), restarting the cycle.[73,74]

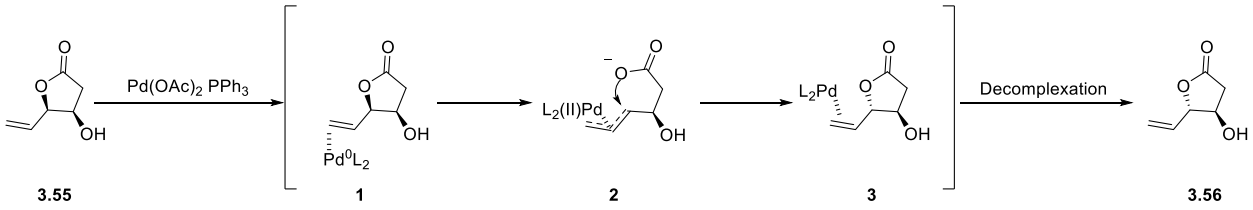
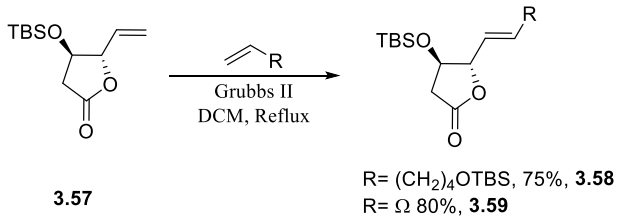


Figure 3.15: Proposed mechanism of isomerization reaction

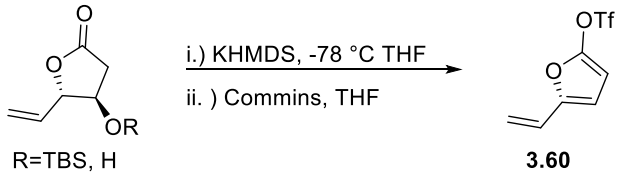
With the gamma-lactone in hand test reactions were run to verify incorporation of the n-pentyl side chain through cross methasis (Scheme 3.3.9). Based on the work from the Fernandes lab, Grubbs II catalyzed reactions with both TBS protected hexenol, and the elaborated n-pentyl side chain worked well to provide cross products **3.58**, and **3.59** in 75 and 80% yields respectively**.**[69,70,75]



Scheme 3.3.8: Cross methasis reactions

With verification that we could successfully incorporate the n-pentyl side chain, we next sought out to functionalize the lactone for incorporation of the carboxylic acid side chain. Attempted reactions sought to convert lactone **3.57** into a vinyl triflate.

Unfortunately, all attempted conditions either resulted in a recovery of starting material, a complex mixture of products, or generation of undesired furan **3.60** (Scheme 3.3.9). With the destruction of the stereocenters this route was abandoned.



Scheme 3.3.9: Generation of undesired furan **3.60**

3.3.8 New synthetic strategy

With the inability to form the vinyl triflate, we looked to move towards an anionic approach. Principally, either direct nucleophilic addition into the lactone, or opening of the lactone up to the Weinreb amide, followed by nucleophilic addition (Figure 3.16). Due to the possibility for over addition of nucleophiles into lactones, we opted to moved towards opening of lactone **3.57**, into the Weinreb amide and attempt umpolung nucleophilic additions to generate the 1,2 diketone of HKE_2.[33,36]

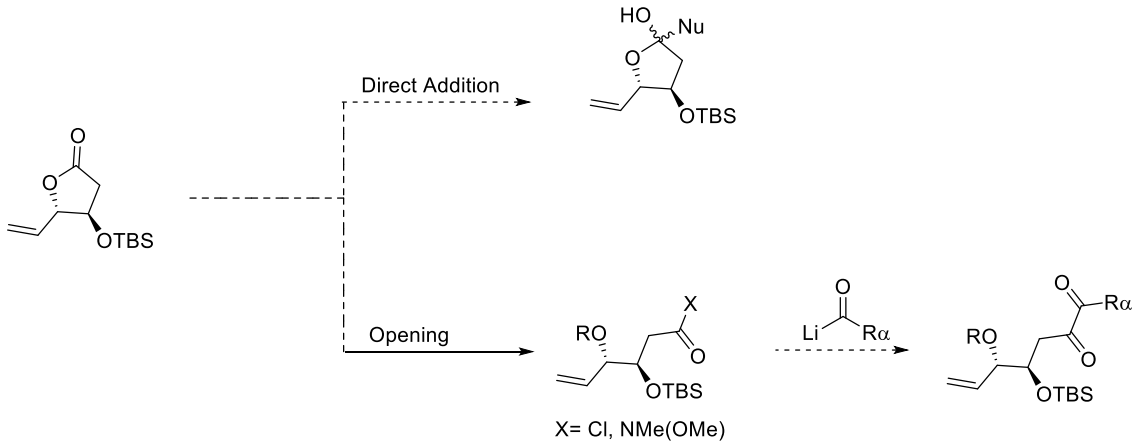
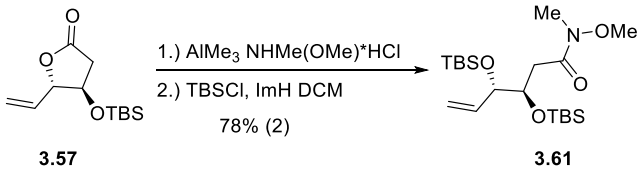


Figure 3.16: New synthetic plan for HKE_2

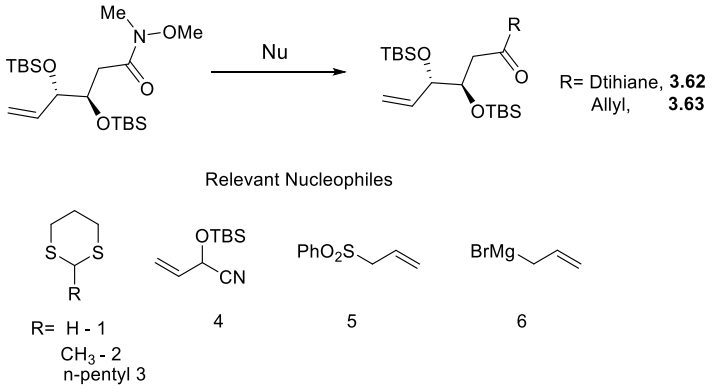
Synthesis of the Weinreb amide commenced by addition of lactone **3.57** (Scheme 3.3.10)**,** into a stirred solution of Weinreb salt in DCM with $AlMe_3$ at -78 °C, generating desired Weinreb amide, which was subsequently silyl protected to furnish **3.61.**



Scheme 3.3.10: Synthesis of Weinreb Amide 3.61

With Weinreb amide **3.61** in hand we looked to incorporate the carboxylic acid side chain, through a variety of different nucleophilic additions. A summary of attempted nucleophiles is highlighted in Table 3.6**.** To abate the need for unnecessary oxidations, initial attempts started with dithianes, either as 1,3 dithiane, methylated 1,3 dithiane or the dithiane of the fully elaborated carboxylic acid side chain. Initial results were promising, with 1,3 dithiane, adding into the amide in a 40% yield, however, the methylated dithiane resulted in a complex mixture, and the dithiane of the fully elaborated carboxylic acid led to decomposition of the side chain. Focus was then shifted to

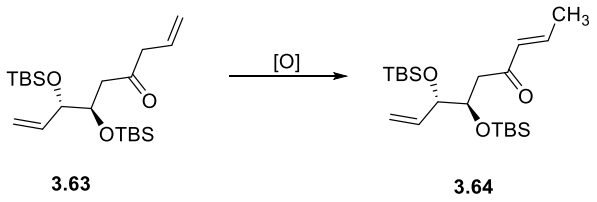
cyanohydrins which lead to complex mixture of products, and allyl sulphone which appeared to be unreactive towards the amide. However, allyl Grignard cleanly added into Weinreb amide in an 80% yield (Table 3.6, Entry 6).



Entry	Nucleophile	Base	Solvent	Temperature	Result
1	1	nBuLi	THF	-78 °C	**3.62** 40%
2	2	nBuLi	THF	-78 °C	Mixture
3	3	nBuLi	THF	-78 °C	Decomp
4	4	nBuLi	THF	-78 °C	Mixture
5	5	nBuLi	THF	78 °C	RSM
6	6	-	THF	-78 °C	**3.63** 80%

Table 3.6 attempted nucleophilic additions

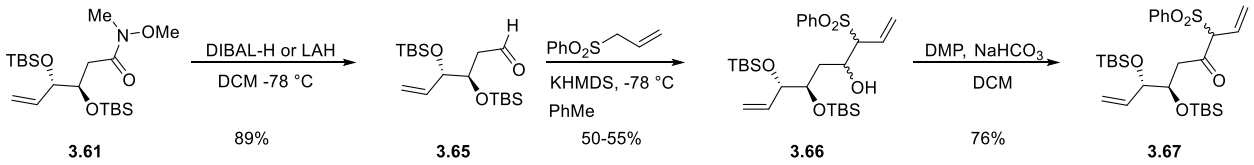
While the allyl Grignard addition into the Weinreb amide was a promising lead, it would require two oxidations of the allylic carbon to get to the necessary 1,2 diketone of HKE_2. Unfortunately, under a variety of different conditions, attempts to oxidize or halogenate the allylic carbon were all unsuccessful resulting in either isomerization into enone **3.64** (Figure 3.17), or a complex mixture of products.



3.63 **3.64**

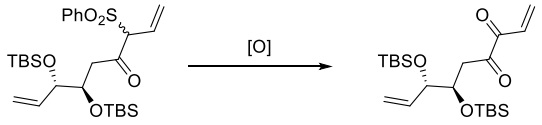
Figure 3.17: Isomerization to enone **3.64**

After the failure to furnish the desired oxidation to the 1,2 diketone, it was decided to try and incorporate a higher oxidation state compound, which would potentially ease the conversion into the 1,2 diketone. Williams had shown the elimination of α-keto sulfones into unsymmetric 1,2 diketones, and this was an attractive idea to follow.[76] However, previous work had shown that the desired allyl sulfone, was unreactive towards Weinreb amide, **3.61**, (Table 3.6, entry 5). This problem was solved by moving to a more reactive electrophile. Reduction of amide **3.61** with DIBAL-H or LAH furnished aldehyde **3.65** (Scheme 3.3.11) which undergoes addition of allyl sulfone resulting in **3.66** as a mixture of inseparable diastereomers. This inseparable mixture was oxidized by DMP to α keto sulfone, **3.67.** It was believed that having the higher oxidation state carbon would help facilitate the transformation into the desired 1,2 diketone.[76]



Scheme 3.3.11: Synthesis of α keto sulfone 3.67

Attempts at converting α keto sulfone **3.67** into the desired 1,2 diketone are summarized in Table 3.7**.** Unfortunately, after extensive trials of oxidation and halogenation, product was never obtained. These reactions resulted in a complex mixture of products, believed to be a combination of gamma alkylation and isomerization into the internal enone. Following these failures, we opted to move towards a different nucleophile.



Entry	Base	Reagents	Oxidant	Solvent	Temperature	Result
1	KOtBu	-	Davis Oxaziradine	THF	-78 °C	Decomp
2	KHMDS	-	Davis Oxaziradine	THF	-78 °C	Decomp
3	-	NaI	TBHP	DMF	60 °C	RSM
4	-	AIBN	NBS	DCM	80 °C	Mixture
5	KHMDS	TMSCl	*m*CPBA	DCM	-78 °C	Mixture

Table 3.7 attempted oxidations

3.3.9 Synthetic strategy towards hemiketals E_2 and D_2

Retrospectively, the key remaining obstacle to an efficient route towards hemiketal E_2 remains introduction of the central 1,2-dicarbonyl functionality. The optically active side-chains **3.71** and **3.72** (Figure 3.18) should be introduced by selective cross-metathesis reactions. As described earlier, optically active aldehydes **3.68** and **3.69** are readily derived from D- and L-gluconolactone and lead to hemiketals E_2 and D_2, respectively. While anion additions to the corresponding Weinreb amide varied in success, we anticipate addition of dithiane alkyne **3.70** to either aldehyde **3.68** or **3.69** to be successful. Dithiane **3.70** has been described by Andersen and Jacobsen, and we anticipate will furnish secondary alcohols **3.73** (Figure 3.19) and **3.77** (Figure 3.20)**.**[77,78] Dithiane **3.70** can be made in 2 steps from TMS acetylene according to Sharpless.[79,80] In practice, this approach should be first examined towards hemiketal E_2 as the n-pentyl containing side-chain should pose little obstacle when compared to carboxylate containing side-chain that would be necessary for a synthesis towards hemiketal D_2. For the latter, we will delay cross-metathesis, if necessary, by one of several routes as described in Figure 3.20.

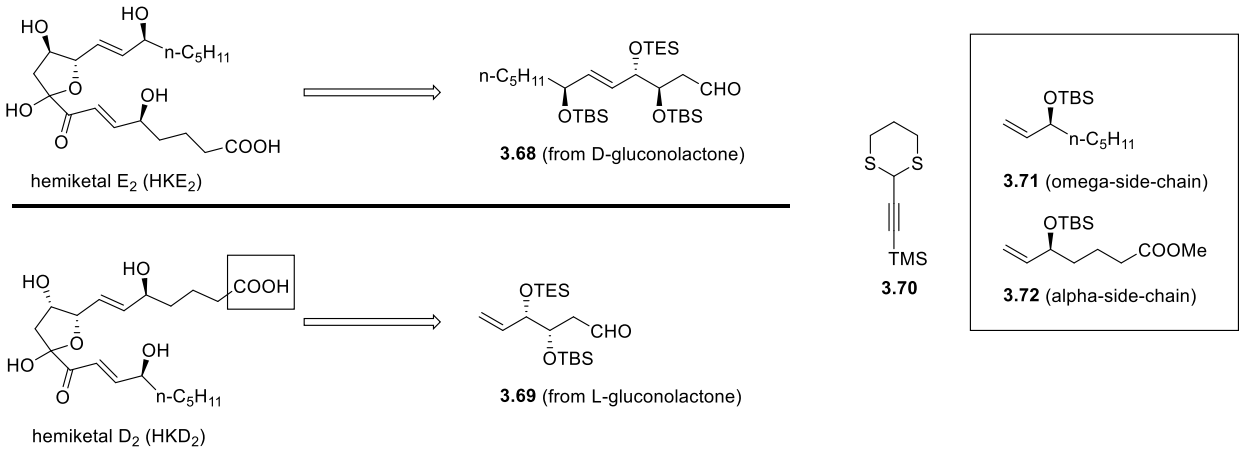


Figure 3.18: Overview of synthetic strategy directed towards HKE_2 and HKD_2.

Following generation of secondary alcohol, **3.73** (Figure 3.19), a combination of hydrolysis, oxidation and selective TES deprotection could furnish hemiketal **3.74.** Removal of the TMS group, followed by semi reduction would yield enone, **3.75,** setting the stage for selective cross metathesis with optically active carboxylic acid side chain **3.72**, completing the carbon framework of HKE_2. Silyl deprotection and saponification would finish the synthesis of HKE_2.

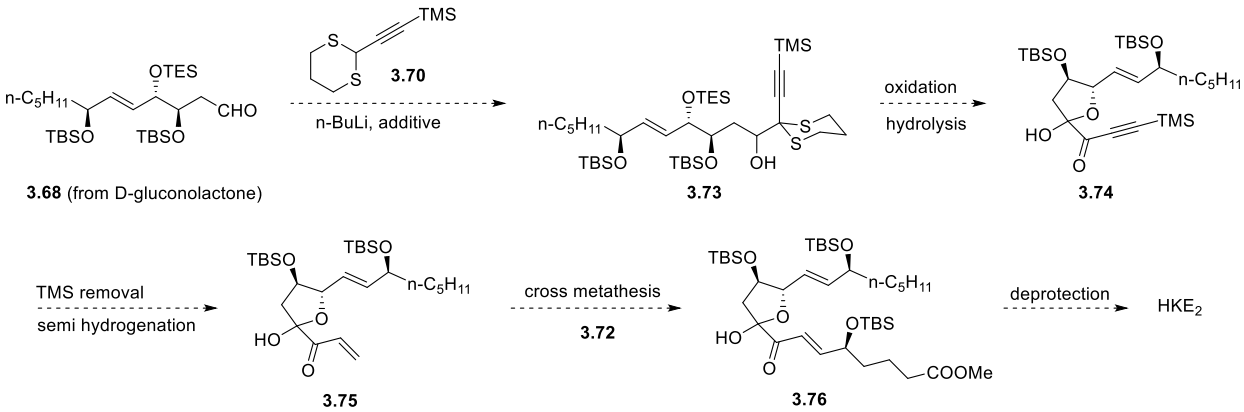


Figure 3.19 Proposed synthesis of HKE_2.

Synthesis of HKD_2 could commence with addition of dithiane **3.70** to optically active aldehyde **3.69** generating secondary alcohol **3.77** (Figure 3.20). At this stage a vast optionality exists, with conversion of **3.77** to **3.78**-**3.81** through a number of reaction combinations consisting of hydrolysis of the dithiane, oxidation of the secondary alcohol, selective TES deprotection, TMS deprotection and semi reduction. According to Grubbs, the terminal olefins highlighted in the boxes should selectively undergo a cross metathesis reaction with carboxylic acid side chain **3.72**, over any other olefin or alkyne present within the respective molecule.[75] Subsequently, the key remaining transformation for HKD_2 is incorporation of the n-pentyl side chain **3.71** through a second selective cross metathesis reaction furnishing the entire carbon framework of HKD_2. The synthesis could be completed with silyl deprotections and saponification.[44]

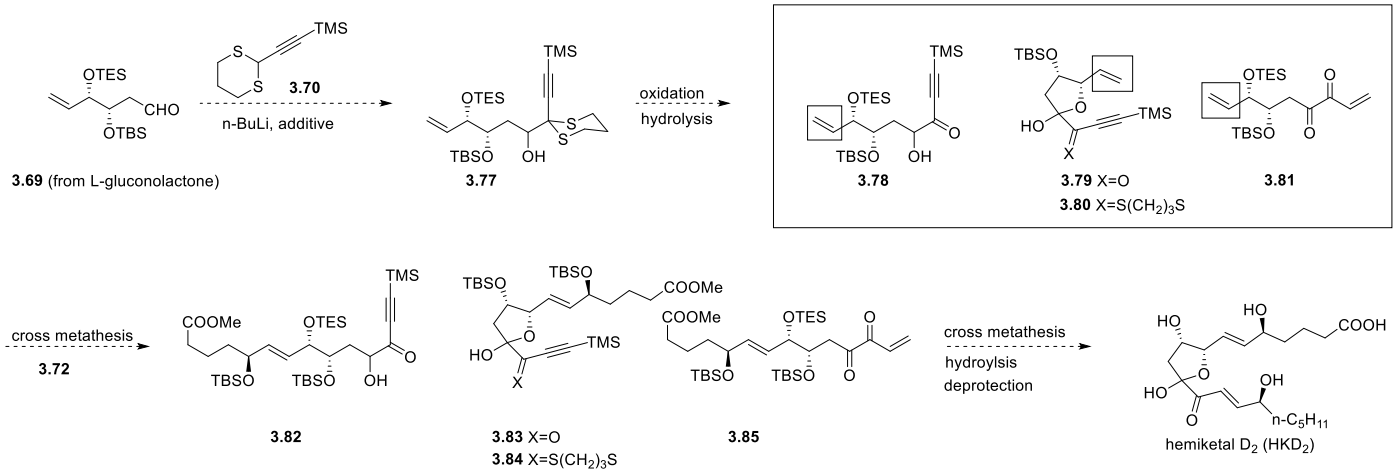


Figure 3.20 Proposed synthesis of HKD2.

1. General Procedure: All non-aqueous reactions were performed in flame-dried or oven dried round-bottomed flasks under an atmosphere of argon. Stainless steel syringes or cannula were used to transfer air- and moisture-sensitive liquids. Reaction temperatures were controlled using a thermocouple thermometer and analog hotplate stirrer and monitored using liquid-in-glass thermometers. Reactions were conducted at room temperature (approximately 21-23 °C) unless otherwise noted. Flash column chromatography was conducted using silica gel 230-400 mesh. Reactions were monitored by analytical thin-layer chromatography, using EMD Silica Gel 60 F254 glass-backed pre-coated silica gel plates. The plates were visualized with UV light (254 nm) and stained with potassium permanganate or *p*- anisaldehyde-sulfuric acid followed by charring. Yields were reported as isolated, spectroscopically pure compounds.

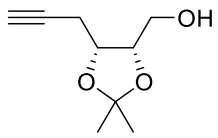
2. Materials: Solvents and chemicals were purchased from Sigma-Aldrich, Acros Organics, TCI and/or Alfa Aesar and used without further purification. Solvents were

purchased from Fisher Scientific. Dry dichloromethane (CH_2Cl_2) was collected from an MBraun MB-SPS solvent system. Dichloroethane (DCE) was distilled from calcium hydride and stored over 4 Å molecular sieves. Triethylamine, N,N-dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) were used as received in a bottle with a Sure/Seal. N,N-diisopropylethylamine was distilled from calcium hydride and stored over KOH. $BF_3 \cdot Et_2O$ was distilled prior to use from calcium hydride. Deuterated solvents were purchased from Cambridge Isotope Laboratories.

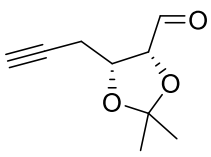
3. Instrumentation: ^1H NMR spectra were recorded on Bruker 400 or 600 MHz spectrometers and are reported relative to internal chloroform (^1H, δ 7.26), methanol (^1H, δ 3.31), and DMSO (^1H, δ 2.50). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublet, ddd = doublet of doublet of doublet, m = multiplet, br=broad), coupling constants (Hz), and integration. ^{13}C NMR were recorded on Bruker 100 MHz spectrometers and are reported relative to internal chloroform (^{13}C, δ 77.1), methanol (^{13}C, δ 49.2), and DMSO (^{13}C, δ 40.3). Low-resolution mass spectra were acquired on an Agilent Technologies Series 1200 single quad ChemStation autosampler system using electrospray ionization (ESI) in positive mode. High-resolution mass spectra (HRMS) were obtained from the Department of Chemistry and Biochemistry, University of Notre Dame Mass Spectrometry Center or the Mass Spectrometry Research Center at Vanderbilt University.

Experimental Methods:

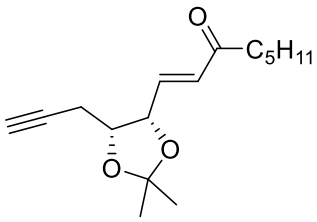
vinyl stannanes 3.16, 3.21 and vinyl iodides 3.15, 3.22 where prepared as previously described [1]



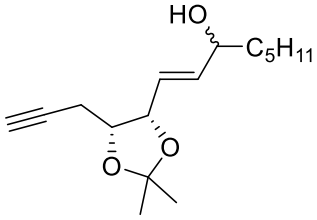
Alkynol 3.4: To a solution of diisopropylamine (5.5 mL, 40 mmol) in THF (20 mL) at -78 °C was added n-buLi (15.8 mL of 2.5 M in hexanes, 40 mmol), the mixture was maintained at -78 °C for 20 min and warmed to 0 °C. To the solution of LDA at 0 °C was added $TMSCHN_2$ solution (11.2 mL of 2M in ether), stirring continued for 20 min, the mixture was cooled to -78 °C and a solution of **3.3.1** (3.00 g, 17.2 mmol) in THF (8 mL) added slowly over 20 min. The reaction mixture was allowed to warm to room temperature and after 3 h judged complete by TLC analysis (40% EtOAc in Hexanes). The reaction mixture was quenched with *saturated. aqueous* NH_4Cl (15 mL), extracted with EtOAc (3 x 40 mL), the combined extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a brown oil. The oil was dissolved in MeOH (15 mL), an aqueous solution of K_2CO_3 (40 mg in 10 mL of water) added and the reaction mixture allowed to stir for 30 min. The reaction was neutralized to pH 6 by the portion wise addition of 1M HCl. The mixture was extracted with EtOAc (3 x 40 mL), the combined extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford an orange oil. The residue was purified by flash chromatography (silica gel, gradient elution 0%-30% EtOAc in Hexanes) to provide **3.4**, 2.12 g, (72%) as a yellow oil. The spectral data matched reported values. [59]



Aldehyde 3.25: To a solution of alcohol, **3.**, (1.5 g, 11.8 mmol) in EtOAc (30 mL, 0.4M) was added IBX (0.98 g, 35 mmol) and heated to reflux and stirred for 7 hours cooled to 0 °C and stirred for 20 min, a white precipitate appears and is filtered through celite and washed with EtOAc(3 x 10 mL). Solvent is concentrated *in vacuo* and crude oil is used without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ 9.64(d, J = 2.2 Hz, 1H), 4.42 (m, 1H), 4.30 (m, 1H), 2.34 (m, 2H), 1.98(m, 1H), 1.48 (s, 3H), 1.26(s, 3H).

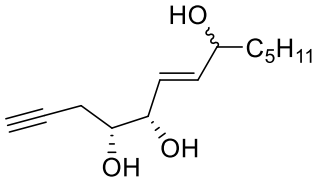


Enone 3.26: To a solution of phosphonate, **3.5** (1.98 g, 8.92 mmol) in THF (60 mL, 0.15 M) at 0 °C is added NaHMDS (4.46 mL, 2M in THF) dropwise and stirred for 10 minutes. Aldehyde, **3.25**, (1.5 g, 8.92 mmole) as a solution of THF (12 mL, 0.8 M) is added dropwise over 20 minutes at 0 °C. Reaction is stirred for 12 hours then diluted with water (40 mL), and extracted with EtOAc (3 x 50 mL). Combined organics are washed with brine (40 mL), dried ($MgSO_4$), filtered concentrated *in vacuo* and purified by column chromatography (Silica gel, gradient elution 0%-20% EtOAc in Hexanes) to provide enone **3.26**, 1.2 g, (60% over 2) as a pale oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.40 (dd, *J* = 5.4, 15.8 Hz, 1H), 6.2 (d, *J* = 15.8 Hz, 1H), 4.64 (m, 1H), 4.24 (q, *J* = 7.8 Hz*, 1H),* (4.30 (m, 1H), 2.38 (t, *J* = 7.32 Hz, 2H), 2.21-2.09(m, 2H), 1.91 (t, *J* = 2.68 Hz, 1H), 1.45-1.41 (m, 2H), 1.32 (s, 3H), 1.19 (s, 3H), 1.15-1.09 (m, 4H), 0.70 (t, *J* = 6.8 Hz, 3H).

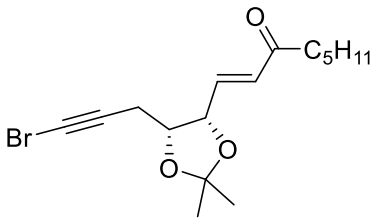


Allylic Alcohol 3.27: To a solution of enone, **3.26**, (0.5 g, 1.9 mmol) in DCM (6 mL) and MeOH (6 mL) was added $CeCl_3$ (0.634 g, 2.3 mmol) stirred for 10 min then $NaBH_4$ (75 mg, 1.9 mmol) was added and stirred for 2 h, reaction is quenched by addition of aqueous Rochelle salts (20 mL) and extracted with DCM (3 x 20 mL). Combined organics are dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by column chromatography (silica gel, gradient elution 0%-20%-100% EtOAc in Hexanes) to provide allylic alcohols **3.27,** 0.46 g, (92%) as a pale oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.88 (dd, *J* = 6.4, 15.6 Hz, 1H), 5.72 (ddd, *J* = 0.8, 7.2, 15.6 Hz, 1H), 4.65 (t, *J* = 6.8 Hz, 1H) 4.32 (q, *J* = 6.4 Hz, 1H), 2.44-2.27 (m, 2H), 2.00 (t, *J* = 4 Hz, 1H), 1.55-

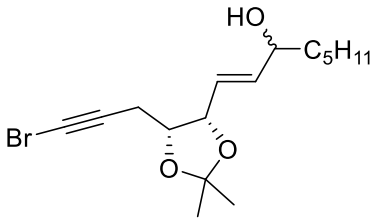
1.24 (m, 8H), 0.90-0.85(m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.8, 125.0, 108.7, 80.4, 78.1, 72.1, 70.0, 60.2, 36.8, 31.6, 27.8, 25.3, 24.9, 22.4, 22.1 21.1, 20.8, 14.0.



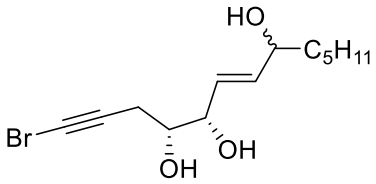
Triol 3.28: To a solution of Allylic alcohol, **3.27** (0.46 g, 1.75 mmol) in MeOH (12 mL, 0.15 M) is added a catalytic amount of p-TSA (33 mg, 0.17 mmol) and reaction is stirred for 48 hours quenched by addition of TEA (1 mL), concentrated *in vacuo* and purified by column chromatography (silica gel, gradient elution 0%- 20%- 40% -100% EtOAc in Hexanes) to provide triol **3.28**, 0.31 g, (79%) as a clear oil. ^{1}H NMR (400 MHz, MeOD) δ: 5.75(m, 2H), 4.11-4.06(m, 2H), 3.69-3.66(m, 1H) 2.39-2.38(m, 2H), 2.28-2.27(m, 1H), 1.56-1.500 (m, 8H), 0.93(t, *J* =4 Hz, 3H). ^{13}C NMR (100 MHz, MeOD) δ: 135.6, 135.5, , 128.8, 128.7, 80.6, 80.5, , 73.6, 72.8, 72.7, 71.7, 71.6, 69.6, 69.6, 36.8 (2), 31, 24.8, 24.7, 22.2, 13.0.



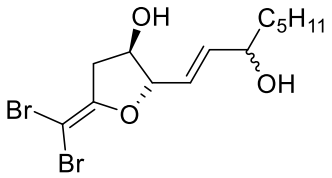
Bromo Alkyne 3.35: To a solution of Enone, **3.26, (**1.11 g, 4.23 mmol) in MeCN (40 mL, 0.1 M) was added $AgNO_3$ (0.79 g, 4.65 mmol), NBS (0.83 g, 4.65 mmol), and stirred for 5 h diluted with water (40 mL) and extracted with EtOAc (3 x 40 mL). Combined organics are washed with brine (40 mL), dried ($MgSO_4$) filtered, concentrated *in vacuo* and purified by flash column chromatography (silica gel, gradient elution 0%-20%-100% EtOAc in Hexanes) to afford **3.35**, 1.27 g, (>95%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ : 6.62 (dd, *J* = 5.48, 15.88 Hz, 1H), 6.23 (d, *J* = 15.88 Hz, 1H), 4.68-4.65 (m, 1H), 4.27-4.23 (m, 1H), 2.42 (t, *J* = 7.4 Hz, 2H), 2.23-2.16(m, 2H), 1.48-1.45(m, 2H), 1.34 (s, 3H), 1.21(s, 3H), 1.18-1.13(m, 4H), 0.74(t, *J* = 8Hz, 3H).



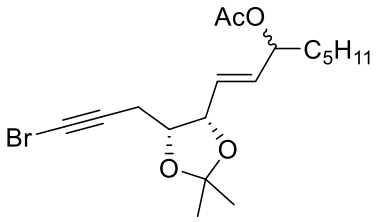
Allylic Alcohol 3.36: To a solution of **3.35**, (1.27 g, 4.2 mmol) in DCM (15 mL) and MeOH (15 mL) was added $CeCl_3$ (1.92 g, 5.01 mmol) and stirred for 10 min then $NaBH_4$ (0.15 g, 4.2 mmol) stirred for 2 h, quenched by addition of *saturated aqueous* Rochelle salts (20 mL) and extracted with DCM (3 x 20 mL). Combined organics are washed with brine (20 mL), dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography (silica gel, gradient elution, 0% -20% EtOAc in Hexanes) to provide allylic alcohols **3.36,** 1.29 g, (89%) as a pale oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.93-5.85 (m, 1H) 5.76-5.68 (m, 1H), 4.69 (q, *J* = 6.32 Hz, 1H), 4.31 (q, *J* = 8 Hz, 1H), 4.18-4.11 (m, 1H), 2.47-2.33 (m, 2H), 1.57-1.55(m, 2H), 1.51 (s, 3H), 1.39 (s, 3H), 1.33-1.30 (m, 6H), 0.91 (t, *J* = 6.72 Hz, 3H) ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.1, 137.9,124.8, 124.5, 108.7, 108.4, 78.1, 78.0, 76.7, 76.4, 72.0, 71.7, 39.9, 39.8, 36.9 (2), 31.6, 27.8(2), 25.3(2), 24.9, 22.3, 22.2, 20.8, 14.0.



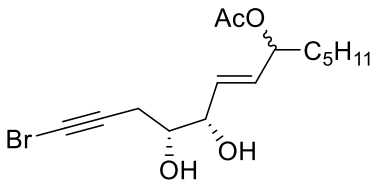
Triol 3.37: To a solution of Acetonide **3.36**, (0.40 g, 1.16 mmol) in THF (36 mL) was added 4M HCl (24 mL), stirred for 1 h at which point *saturated aqueous* $NaHCO_3$ (24 mL) was added, and extracted with EtOAc (3 x 30 mL). Combined organics washed with brine (40 mL) , dried ($MgSO_4$), filtered, concentrated *in vacuo* and run through a celite plug, washed with EtOAc (3 x 10 mL), and concentrated *in vacuo* providing triol **3.37** 0.34 g, (95%) as an oil used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.78-5.61 (m, 2H), 4.15-4.13(m, 1H), 4.08-4.034 (m, 1H), 3.78-3.74 (m, 1H), 2.41-2.25 (m, 2H), 1.46-1.45(m, 2H), 1.23-1.22 (m, 2H), 0.82(t, *J* = 6.64 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 136.9, 127.6, 127.2, 73.9, 73.7, 72.3, 72.2, 71.7, 40.2, 40.2, 37.0, 36.9, 31.6 (2), 25.1, 25.0, 22.5, 13.9.



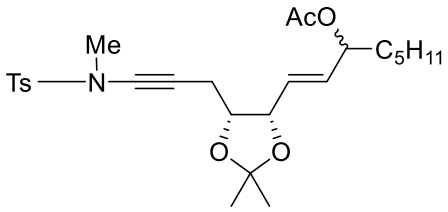
1,1 Dibromo 3.30: To a solution of triol, **3.37** (20 mg, 0.06 mmol) in MeCN (2 mL, 0.003 M) was added DMAP (crystal), $HgCl_2$ (20 mg, 0.07 mmol) and NBS (13 mg, 0.07 mmol), stirred for 2 h concentrated *in vacuo* and purified by column chromatography (pH = 7 buffered silica gel, gradient elution, 0% -40% EtOAc in Hexanes) to afford **3.30,** 8 mg (35%) as an oil. ^{1}H NMR (400 MHz, C_6D_6) δ: 5.65 (dd, *J* = 1.28, 5.44 Hz, 1H), 5.34-5.28 (m, 1H), 4.44-4.41 (m, 1H), 3.76 (bs, 1H), 3.59-3.57 (m, 1H), 2.54-2.46(m, 1H), 2.33-2.26(m, 1H), 1.29-1.16(m, 8H), 0.93-0.86(m, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ : 155.6, 137.0, 136.9, 125.1, 124.9, 90.2(2), 74.1(2), 71.4, 71.0, 61.7, 41.6 39.1(2), 37.0, 36.9, 31.6, 29.7, 28.7, 24.9(2), 22.5, 20.1, 17.5, 13.7.



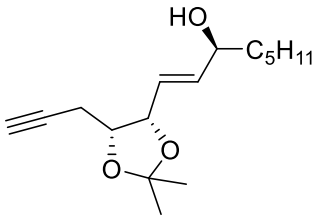
Acetate 3.40: To a solution of allylic alcohol **3.36,** (0.15 g, .43 mmol) in DCM (5 mL, 0.09 M) was added pyridine (0.17 mL), acetic anhydride (0.2 mL) and DMAP (Catalytic), stirred for 2 h, diluted with DCM (10 mL) and washed with $CuSO_4$ (5 mL), then *saturated aqueous* $NaHCO_3$ (5 mL). Aqueous layer was extracted with DCM (3 x 10 mL) and combined organics washed with brine (10 mL) dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by column chromatography (silica gel, gradient elution 0% -10% EtOAc in Hexanes) to afford acetate, **3.40,** 0.13 g, (86%) as a clear oil.. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.77-5.71(m, 2H), 5.27-5.25 (m, 1H), 4.68-4.63(m, 1H), 4.29-4.26(m, 1H), 2.38-2.31(m, 2H), 2.04 (s, 3H), 1.69-1.54 (m, 2H), 1.47 (s, 3H), 1.34 (s, 3H), 1.32-1.28(m, 6H), 1.24 (s, 3H), 0.86 (t, *J* = 3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ :169.8, 169.7 132.4, 134.1, 127.4, 126.8, 108.5 (2), 77.6, 77.5, 76.1 (2), 73.6, 73.3, 39.7, 39.6, 33.9, 31.3 (2), 27.5 (2), 25.1 (2), 24.5 (2), 22.2, 22.1, 22.0, 20.8 (2), 20.6, 13.9.



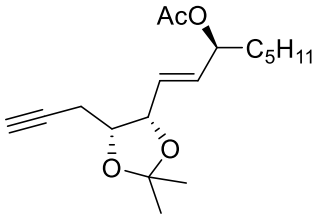
Diol 3.43: To a solution of Acetonide **3.40**, (0.13 g, 0.35 mmol) in THF (10 mL) was added 4M HCl (6.6 mL), reaction stirred for 1 h, quenched by addition of *saturated aqueous* $NaHCO_3$ (10 mL), extracted with EtOAc (3 x 10 mL). Combined organics are washed with brine (20 mL), dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography (silica gel, gradient elution, 0% -100% EtOAc in Hexanes) providing diol **3.43,** 60 mg, (54%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.73 (t, *J* = 4Hz, 2H), 5.22-5.21(m, 1H), 4.25-4.24 (m, 1H), 3.81 (t, *J* = 2.52 Hz, 1H), 2.50- 2.44 (m, 2H), 2.06 (s, 3H), 1.64-1.57 (m, 2H), 1.39-1.21 (m, 6H), 0.88 (t, *J* = 2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.9, 170.8, 131.8, 129.7, 129.4, 77.3, 77.0, 76.7, 76.6, 76.5, 74.5, 74.2, 73.6 (2), 73.6 (2), 72.1, 39.9 (2), 34.1 (2), 31.3, 24.6, 23.2, 23.1, 22.3, 22.1 (2), 20.8, 20.5, 14.0.



Ynamide 3.41: To a solution of bromo alkyne **3.40** (0.1 g, 0.26 mmole) in PhMe (3 mL, 0.3M) is added dimethyl benzenesulfonamide (50 mg, 0.28 mmol), potassium carbonate (70 mg, 0.5 mmol), 1, 10 phenanthroline (10 mg, 0.05 mmol) and Copper sulfate (7 mg, 0.03 mmol), heated to 80 °C and stirred for 48 h. Reaction was cooled to room temperature, filtered through celite, washed with EtOAc (3 x 10 mL), concentrated *in vacuo* and purified by flash column chromatography (silica gel, gradient elution, 0% -10% -20% -100% EtOAc in Hexanes) to afford **3.41,** 87 mg, (69%) as an oil. .^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.80 (d, *J* = 8.12 Hz, 2H), 7.37 (d, *J* = 7.92 Hz, 2H), 5.75-5.70 (m, 2H), 5.27-5.24 (m, 1H), 4.60 (t, *J* = 6.4 Hz, 1H), 4.26 (q, *J* = 6.4 Hz, 1H), 3.01 (s, 3H), 2.49-2.43 (m, 4H), 2.34 (dd, *J* = 7.32, 16.56 Hz, 1H), 2.04 (d, *J* = 7.64 Hz, 1H), 1.63-1.58 (m, 2H), 1.48 (s, 3H), 1.37 (s, 3H), 1.26-1.21 (m, 6H), 0.86 (t, *J* = 8.28 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.2, 170.1, 144.5, 144.4, 133.2, 132.5, 132.3, 129.6, 127.8, 127.7, 127.1, 108.7, 77.9, 73.8, 73.6, 64.5 (2), 39.0, 34.1, 31.4, 27.8, 25.4, 24.7, 24.6, 21.5, 21.1(2), 20.8, 13.8.

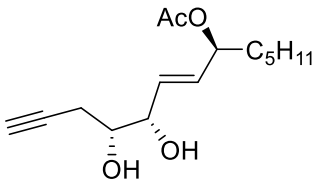


Allylic Alcohol 3.45: To a solution of enone **3.26,** (100 mg, 0.38 mmol) and (R) CBS catalyst (52 mg, 0.19 mmol) in Toluene (1.5 mL, 0.25M) at -78 °C was stirred for 30 minutes followed by addition of Catecholborane (0.18 g, 0.16 mL, .152 mmol) dropwise and stirred for 12 hours. Reaction was quenched by addition of MeOH (2 mL) and diluted with EtOAc (5 mL) washed with 1M NaOH (5 mL), 1M HCl (10 mL), brine (10 mL), dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography (silica gel, gradient elution, 0% -100% EtOAc in Hexanes) to afford allylic alcohol **3.45** 82mg, (81%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.82 (dd, *J* = 5.84, 15.56 Hz, 1H), 5.69-5.63 (m, 1H), 4.59 (t, *J* = 6.52 Hz, 1H), 4.26 (q, *J* = 6.68 Hz, 1H), 4.11-4.09 (m, 1H), 2.37-2.21 (m, 2H), 1.92 (t, *J* = 2.68 Hz, 1H) 1.51-1.45 (m, 2H), 1.44 (s, 3H), 1.31 (s, 3H), 1.23-1.19(m, 6H), 0.82 (t, *J* = 6.64 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.8, 124.9, 108.7, 80.5, 78.0, 76.6, 71.9, 70.0 36.9, 31.6, 27.8, 25.3, 24.9, 22.5, 21.2, 13.9.

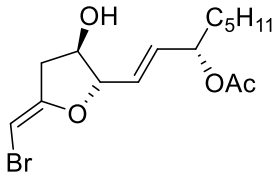


Acetate 3.46: To a solution of alcohol **3.45** (0.26 g, 1 mmol) in DCM (10 mL, 0.1 M) was added pyridine (0.16 mL, 2 mmol), DMAP (Crystal) and acetic anhydride (0.18 mL, 2 mmol) and stirred for 2 h at which point reaction was quenched with *saturated aqueous* $NaHCO_3$ (20 mL) extracted with DCM (3 x 10 mL), combined organics washed with brine (20 mL), dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography (silica gel, gradient elution 0% EtOAc -10% EtOAc in Hexanes) to afford acetate **3.46** (0.28 g, 95%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.77-5.76 (m, 2H), 5.32-5.27(m, 1H), 4.68-4.65(m, 1H), 4.37-4.29(m,

1H), 2.45-2.26 (m, 2H), 2.07 (s, 3H), 1.68-1.62 (m, 2H), 1.59 (s, 3H), 1.39 (s, 3H),1.38-1.31 (m, 6H), 0.90 (t, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.2, 132.4, 127.6, 108.8, 80.3, 77.8, 76.6, 73.8, 69.9, 34.1, 31.4, 27.8, 25.3, 24.6, 22.4, 21.1(2), 13.9.

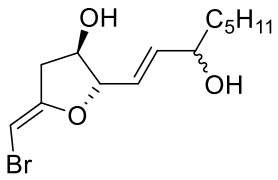


Diol 3.47: To a solution of Acetate, **3.46** (0.13 g, 0.42 mmol) in DCM (1.5 mL, 0.3M) was added TFA (0.06 mL, 0.84 mmol) followed by water (Catalytic), stirred for 2 hours quenched by addition of *saturated aqueous* $NaHCO_3$ (5 mL) and extracted with EtOAC (3 x 5 mL). Combined organics are washed with brine (10 mL), dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography (silica gel, gradient elution, 0% -10% MeOH in DCM) to afford diol **3.47** 92 mg, (82%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.73 (t, *J* = 2.4 Hz, 2H), 5.25-5.20 (m, 1H), 4.26 (bs, 1H), 3.79 (d, *J* = 2.8 Hz, 1H), 2.46-2.31 (m, 2H), 2.05 (s, 3H), 1.65-1.57 (m, 2H), 1.29-1.24 (m, 6H), 0.88 (t, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.5, 131.8, 129.7, 80.5, 74.0, 73.5, 72.0, 70.6, 34.1, 31.4, 24.6, 22.3, 22.1, 21.1, 13.8.

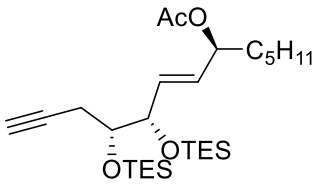


Vinyl Halide 3.44: To a solution of diol **3.43** (20 mg, 0.06 mmol) in Dioxane (1 mL) was added methyl acrylate (10 mg, 0.12 mmol), Cesium Carbonate (37 mg, 0.12 mmol), XPhos (6 mg, 0.01 mmol), and $PdCl_2$ (1 mg , 0.01 mmol) heated to 60 °C stirred for 2 h then quenched by addition of Water (5 mL) and extracted with EtOAc(3 x 5 mL). Combined organics washed with brine (5 mL), dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography (silica gel, gradient elution, 0% -20% EtOAc in Hexanes) yielding vinyl halide **3.44,** 12 mg, (60%) as an oil. ^{1}H NMR (400 MHz, C_6D_6) δ: 5.51-5.47 (m, 1H), 5.26-5.08 (m, 2H), 4.48 (s, 1H), 4.41 (d, *J* = 4.4 Hz, 1H),

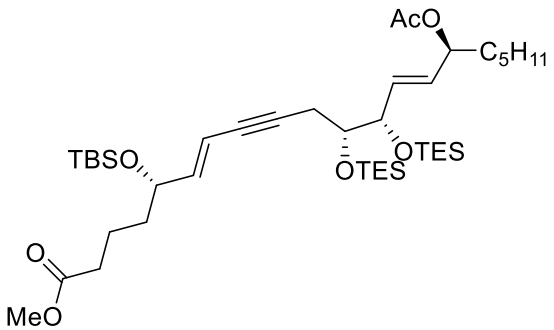
3.35 (bs, 1H), 2.04-1.96 (m, 1H), 1.76 (dd, *J* = 4 Hz, 16 Hz, 1H), 1.48 (s, 3H), 1.45-1.40 (m, 2H), 1.04-0.96 (m, 6H), 0.66 (t, *J* = 6.8 Hz, 3H).



Vinyl Halide 3.29: ^{1}H NMR (400 MHz, C_6D_6) δ: 5.73-5.68 (m, 1H), 5.44-5.35 (m, 1H), 4.71 (s, 1H), 4.45 -4.41 (m, 1H), 3.82-3.67 (m, 2H), 2.35-2.27 (m, 1H), 2.09 (tdd, *J* = 1.2 Hz, 4.8 Hz, 15.6 Hz, 1H), 1.30-1.18 (m, 8H), 0.88 (t, *J* = 6.4 Hz, 3H).

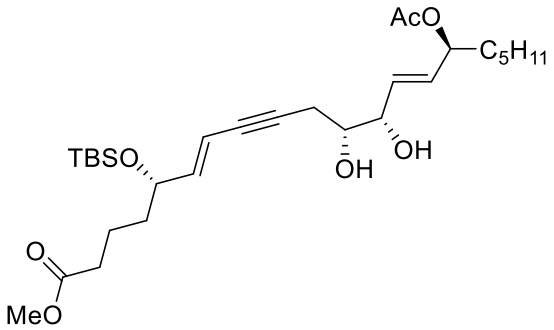


Silyl Ether 3.48: To a solution of alcohol **3.47** (0.15 g, 0.56 mmol) in DMF (2 mL, 0.28 M) was added Imidazole (0.11 g, 1.68 mmol), DMAP (Crystal) and TESCl (0.20 mL, 1.23 mmol) heated to 40 °C stirred for 3 hours, then quenched by addition of *saturated aqueous* NH_4Cl (5 mL) extracted with EtOAc (3 x 10 mL). Combined organics are washed with brine (10 mL), dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography (silica gel, gradient elution 0% -30% EtOAc -EtOAc in Hexanes) to afford **3.47**, 0.27 g, (95%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.0, 133.2, 130.2, 81.4, 75.0, 74.7, 73.7, 69.9, 34.2 31.4, 24.7, 23.7, 22.4, 21.0, 13.8, 6.7 (2), 4.8 (2).

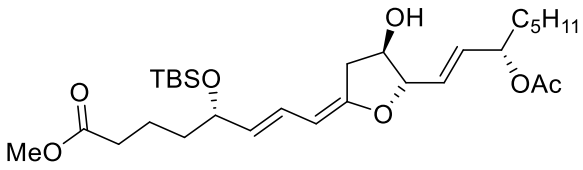


Enyne 3.49: To a solution of **3.48** (50 mg, 0.1 mmol) and vinyl iodide, **3.22,** (44 mg, 0.11 mmol) in TEA (1 mL) was added CuI (6 mg, 0.03 mmol) and $PdCl_2(PPh_3)_4$ (7 mg, 0.01 mmol) stirred for 4 hours concentrated *in vacuo* and purified by column chromatography (silica gel, gradient elution, 0% -5% -10% -100% EtOAc in Hexanes) to afford eneyne **3.3.20** 35 mg, (47%) as an oil. 20 mg (40%) of **3.48** was recovered. ^{1}H NMR (400 MHz,

$CDCl_3$) δ: 5.97 (dd, *J* = 5.6, 15.6 Hz, 1H), 5.73- 5.55 (m, 3H), 5.27-5.21 (m, 1H), 4.14-4.07 (m, 2H), 3.72-3.67 (m, 1H), 3.63 (s, 3H), 2.41-2.37 (m, 2H), 2.27 (t, *J* = 7.6 Hz, 2H), 2.00 (s, 3H), 1.65-1.44 (m, 6H), 1.25 (bs, 6H), 0.94-0.86 (m, 30 H), 0.61-0.52 (12H), 0.01 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.8, 170.1, 144.4, 132.2, 130.1, 109.5, 87.9, 80.0, 75.2, 73.7, 72.2, 51.3, 37.1, 34.2 ,33.9, 31.5, 31.4, 25.7, 24.7, 22.4, 21.0, 20.3, 18.0, 13.8, 6.8, 6.2, 4.9, 4.8, -4.5, -4.9.

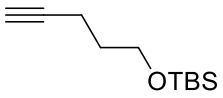


Diol 3.50: To a solution of **3.49** (34 mg, 0.04 mmol) in THF (1 mL) at 0 °C was added TBAF (0.09 mL, 0.09 mmol) dropwise, and reaction is monitored by TLC. After 30 min reaction is quenched by addition of *saturated aqueous* NH_4Cl (5 mL) and extracted with EtOAc (3 x 5 mL). Combined organics were washed with brine (10 mL), dried ($MgSO_4$) filtered, concentrated *in vacuo* and purified by flash column chromatography (silica gel, gradient elution 0% -100% EtOAc in Hexanes) to afford diol **3.50** 16 mg, (70%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.08 (dd, *J* = 5.2, 15.6 Hz, 1H), 5.77-5.76 (m, 2H), 5.65 (d, *J* = 15.6 Hz, 1H), 5.26 (d, *J* = 5.2 Hz, 1H), 4.30 (bs, 1H), 4.23-4.21 (m, 1H), 3.82 (bs, 1H), 2.62-2.56 (m, 3H), 2.49 (t, *J* = 2.8 Hz, 3H), 2.06 (s, 3H), 1.69-1.51 (m, 6H), 1.30-1.24 (m, 6H), 0.91 (bs, 12 H), 0.06 (s, 3H), 0.04(s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.8, 171.2, 145.5, 135.1, 134.2, 132.0, 131.9, 131.7, 130.1, 129.8, 128.4, 108.8, 85.9, 81.0, 74.1, 74.0, 73.5, 72.2, 72.0, 60.3, 37.0, 34.2, 34.1, 31.4, 29.6, 25.7, 24.6, 23.0, 22.3, 21.1, 20.9, 20.3, 20.2, 18.0, 14.1, 14.0, 13.8, -4.5, -4.9.

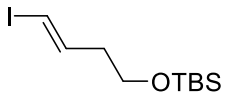


Diene 3.51: To a stirring solution of AuCl (Crystal) in THF(1 mL) with 4 Å MS at 0 °C was added diol, **3.50**, (20 mg, 0.04 mmol) as a solution of THF (1 mL). Reaction is kept at 0 °C, and stirred for 1 h, quenched by addition of *saturated aqueous.*

$NaHCO_3$ (5 mL), and extracted with EtOAc (3 x 5 mL). Combined organics are washed with brine (5 mL), dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography (pH = 7 buffered silica gel, gradient elution, 0% -20% -40% -100% EtOAc in Hexanes) to afford diene **3.51** 8 mg, (40%) plus recovered diol **3.50** (5 mg, 25%). ^{1}H NMR (400 MHz, C_6D_6) δ: 6.72 (dd, *J* = 10.8 Hz, 14.8 Hz, 1H), 5.62-5.54 (m, 1H), 5.41-5.20 (m, 2H), 5.23-5.21 (m, 1H), 4.85 (d, *J* = 10.8 Hz, 1H), 4.20 (t, *J* = 4.8 Hz, 1H), 4.00 (q, *J* = 6 Hz, 1H), 3.44 (bs, 1H), 3.17 (s, 3H), 2.31-2.23 (m, 1H), 1.98 (t, *J* = 7.6 Hz, 3H), 1.6-1.18 (m, 11H), 0.87 (s, 9H), 0.75 (t, *J* = 6.4 Hz, 3H), 0.00 (s, 3H), -0.04 (s, 3H).

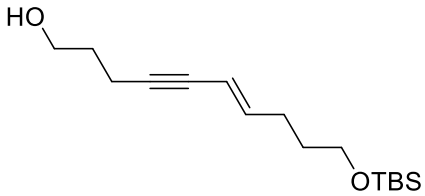


Silyl Ether 3.52: To a solution of pentynol (1g, 11.9 mmol) in DMF (24 mL, 0.5 M) was added imidazole (1.6 g, 23.8 mmol), DMAP (0.15 g, 1.19 mmol) and TBSCl (2.6 g, 17.8 mmol) stirred for 2 hours diluted with water (20 mL) and extracted with EtOAc (3 x 30 mL). Combined organics are washed with brine (40 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* affording silyl ether, **3.52** 2.2 g, (>95%) used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.65 (t, *J* = 6 Hz, 2H), 2.19 (td, *J* = 2.4, 6.8 Hz, 2H), 1.83 (t, *J* = 2.4 Hz, 1H), 1.676-1.611 (m, 2H), 0.84 (s, 9H), 0.00 (s, 6H).

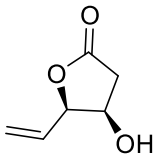


Vinyl Iodide 3.53: To a solution of zirconencence dichloride (1.97 g, 6.7 mmol) in THF (15 mL, 0.4M) at 0 °C was added DIBAL-H (6.7 mL, 1M in THF) dropwise and stirred for 30 minutes. Silyl Ether **3.52** (1.2 g, 6.2 mmol), as a solution of THF (15 mL) was added dropwise to the solution at 0 °C and stirred for 1 h. Reaction mixture is cooled to -78 °C and iodide (2.0 g, 8.0 mmol) was added dropwise as a solution of THF(16 mL). Reaction is stirred for 30 minutes then quenched by slow addition of 1M HCl (20 mL), extracted with EtOAc (3 x 20 mL). Combined organics are washed with *saturated aqueous* Na_2SO_3 (20 mL), brine (20

mL), dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography (silica gel, gradient elution 0%-5% -10% -100% EtOAc in Hexanes) to afford vinyl iodide, **3.53** 1.4 g, (70%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.51-6.44 (m, 1H), 5.92 (td, *J* = 1.6, 14.4 Hz, 1H), 3.56 (t, *J* = 6 Hz, 2H), 2.09 (q, *J* = 1.2 Hz, 2H), 1.57 (q, *J* = 1.2 Hz, 2H), 0.84 (s, 9H), 0.00 (s, 6H).

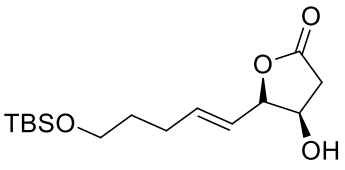


Eneyne 3.54: To a solution of vinyl iodide **3.53** (1.4 g, 4.3 mmol) and propargylic alcohol (0.43 g, 5.15 mmol) in MeCN (9 mL) and TEA (6 mL) was added CuI (0.32 g, 1.7 mmol) and $Pd(PPh_3)_4$ (0.5 g, 0.43 mmol) and stirred for 12 hours then concentrated *in vacuo* and purified by flash column chromatography (silica gel, gradient elution, 0% -20% -40% -100% EtOAc in Hexanes) to afford title eneyne **3.54** 1.5 g, (83 %) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ:6.10-6.02 (m, 1H), 5.47 (dt, *J* = 1.6 Hz, 16 Hz, 1H), 3.76 (t, *J* = 6 Hz, 2H), 3.61 (t, *J* = 6.4 Hz, 2H), 2.31 (td, *J* =*1.6*, 7.2 Hz, 2H), 2.07 (q, *J* = 7.2 Hz, 2H), 1.70-1.63 (m, 2H), 1.54-1.47 (m, 2H), 0.81 (s, 9H), -0.03 (s, 6H).

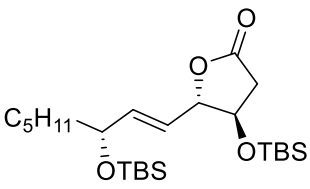


gamma Lactone 3.55: To D-gluconolactone (4.0 g, 22.45 mmol) was added Hydrogen bromide in acetic acid (HBA, 33%, 16 mL) and the reaction mixture was stirred at 50 °C for 1 h. The mixture was cooled to room temperature and excess HBA was removed *in vacuo*. The resultant oil was dissolved in 50% aqueous acetic acid (40 mL), cooled to -10 °C and zinc powder (8.07 g, 123.49 mmol) was added in portions over 1 h. The mixture was warmed to room temperature stirred for 2 h, then heated to 60 °C for 1 h. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was dissolved in water (30 mL),

cooled to 0 °C, and the pH adjusted to 10 by slow addition of KOH pellets followed by filtration. The basic filtrate was acidified to pH 5 with concentrated hydrochloric acid at 0 °C. Water was removed *in vacuo* and the residue was dissolved in cold ethanol. Precipitated potassium chloride was removed by filtration and the filtrate was concentrated *in vacuo*, and purified by flash column chromatography (silica gel, gradient elution, 0% -50% -100% EtOAc in Hexanes) to afford γ lactone **3.55** 0.570 g (20%) as a colorless oil. Spectra matched reported values.[73]

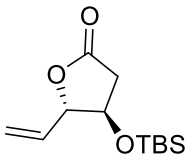


Cross Product **3.58**: To a solution of lactone **3.55** (40 mg, 0.3 mmol) in degassed DCM (3 mL, 0.1M) was added Grubbs II catalyst (20 mg, 0.03 mmol) and TBS protected hexenol (0.15 g, 1.2 mmol) heated to reflux and stirred for 12 hours. Reaction is concentrated *in vacuo* and purified by flash column chromatography (silica gel, gradient elution, 0% -50% -100% EtOAc in Hexanes) to afford desired cross product **3.58** 75 mg, (80%) as an oil. ^{1}H NMR (400 MHz, CDCl3): δ=:5.77-5.74 (m, 1H), 5.55-5.51(m, 1H), 5.19-5.15(m, 1H), 4.47 (s, 1H), 3.60-3.57 (m, 2H), 2.74 (dd, *J* = 5.6, 17.6 Hz, 1H), 2.58 (dd, *J* = 1.6 Hz, 17.6 Hz, 1H), 2.18-2.15 (m, 2H), 1.60-1.53 (m, 2H), 0.83 (s, 9H), 0.0 (s, 3H), -0.06 (s, 3H). ^{13}CNMR (100 MHz, $CDCl_3$) δ: 175.1, 136.5, 122.7, 80.6, 69.5, 61.7, 38.0, 31.8, 25.8, 24.6, 18.2, 0.0, -5.3(2).

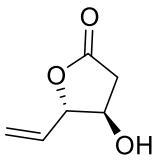


Cross Product **3.59**: ^{1}H NMR (400 MHz, CDCl3): δ 5.79 (dd, *J* = 4.4, 15.2 Hz, 1H), 5.53 (dd, *J* = 6, 15.2 Hz, 1H), 4.65 (bs, 1H), 4.13 (t, *J* = 2.8 Hz, 1H), 4.12-4.00 (m, 1H), 2.65 (dd, *J* = 6.4 Hz,

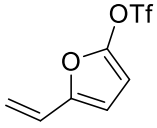
17.2 Hz, 1H), 2.37 (dd, *J* = 4, 17.6 Hz, 1H), 1.48-1.24 (m, 8H), 0.81-0.80 (m, 21H), 0.00 (s, 3H), 0.003 (s, 3H), -0.03 (s, 3H), -0.06 (s, 3H).



Silyl Ether **3.57:** To a solution of **3.56** (1.9g, 14.8 mmol) in DMF (14.8 mL, 1M) was added imidazole (2.012g, 29.6 mmol), DMAP (200mg, 1.48 mmol) and TBSCl (3.33g, 22.2 mmol), stirred for 1 hour then diluted with water (20 mL) and extracted with EtOAc (3 x 20 mL). Combined organics were washed with brine (50 mL), dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography (silica gel, gradient elution 0% -10% EtOAc in Hexanes) affording silyl ether **3.57** 3.0 g, (85%) as a yellow oil. Spectra matched reported values.[72]

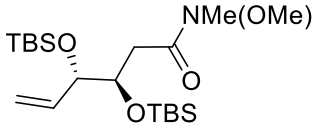


Lactone 3.56: To a solution of **3.55** (4g, 16.5 mmol) in THF (16.5 mL, 1M) was added PPh_3 (866 mg, 3.3 mmol) and $Pd(OAc)_2$ (370 mg, 1.65 mmol) and stirred for 12 h, absorbed onto silica gel, and purified by flash column chromatography (silica gel, gradient elution, 0% -10% -20% -50%-100% EtOAc in Hexanes) affording silyl ether **3.56** 2.3 g, (58%) and recovered starting material, **3.355** 1.3 g, (32%) as clear oils. Spectra matched reported values. [72]



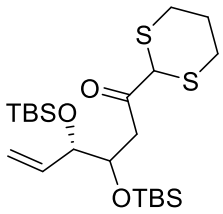
Furan 3.60: To a solution of Lactone **3.55 (**50 mg, 0.2 mmol) in THF (1 mL) at -78 °C was added KHMDS (0.23 mL, 1M soln. in THF) dropwise, and stirred for 1 h. Commins reagent (97 mg, 0.25 mmol) was added as a solution of

THF (1 mL) and stirred for 30 minutes, quenched by addition of TEA (1 mL), diluted with water (10 mL) extracted with EtOAc (3 x 5 mL). Combined organics are washed with brine (10 mL), dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography (silica gel, gradient elution, 0% -5% -10% -100% EtOAc in Hexanes) to afford furan-1 30 mg, (60%) as an oil. ^{1}H NMR (400 MHz, CDCl3): δ 6.30 (dd, *J* = 11.2 Hz, 17.2 Hz, 1H), 6.06 (d, *J* = 3.2 Hz, 1H), 5.40 (dd, *J* = 0.8 Hz, 17.2 Hz, 1H), 4.94 (dd, *J* = 1.2 Hz, 11.6 Hz, 1H). ^{13}C NMR (100 MHz, CDCl3): δ: 150, 140, 124, 110, 107, 85.

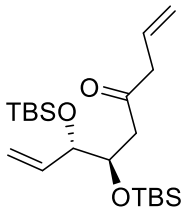


Weinreb Amide 3.61: To a solution of Weinreb salt (5g, 51.5 mmol) in DCM (50 mL, 1M) at -78 °C was added $AlMe_3$ (2M in toluene, 25.75 mL, 51.5 mmol) dropwise over 30 min. Reaction was allowed to warm to rt and stir for 2 h then was cooled to 0 °C, where a solution of **3.57** (5.2g, 21.5 mmol) in DCM (21.5 mL, 1M) was added dropwise. Reaction was stirred for 2 h, quenched by slow addition of *saturated aqueous.* Rochelle's salts (30 mL) and stirred for 12 hours. Aqueous layer was extracted with DCM (3 x 50 mL). Combined organics were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Crude Oil was dissolved in DMF (18 mL, 1M) and Imidazole (2.52 g, 37 mmol), DMAP (300 mg, 1.8 mmol) and TBSCl (3.62 g, 24.15 mmol) were added. Reaction was stirred at room temperature for 1 h, diluted with water (50 mL) and extracted with EtOAc (3 x 50 mL). Combined organics were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* then purified by flash column chromatography (silica gel, gradient

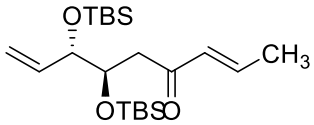
elution, 0% -20% -100% in Hexanes) to afford Weinreb amide, **3.61** 7 g, (78% over 2) as an oil. ^{1}H NMR (400 MHz, CDCl3): δ= 5.795.71(m, 1H), 5.11(d, J= 16 Hz, 1H), 5.06(d, J= 12 Hz, 1H), 4.15 (t, J= 4 Hz, 1H), 4.02(d, J= 4 Hz, 1H), 3.59(s, 3H), 3.077(s, 3H), 2.68-2.62(m, 1H), 2.34-2.29 (m, 1H), 0.82(s, 9H), 0.78(s, 9H), 0.01(s, 3H), 0.0(s, 3H), -0.03(s, 3H), -0.04(s, 3H); ^{13}C NMR (100 MHz, CDCl3): δ= 171.8, 136.2, 115.0, 74.3, 71.9, 61.0, 60.1, 33.4, 31.8, 31.3, 29.5, 25.6 (2), 18.0, 17.7, -4.3, -4.2, -4.7, -4.9.



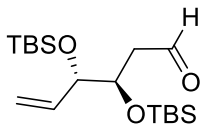
Dithiane **3.62**: To a solution of 1,3 dithiane (13 mg, 0.1 mmol) in THF (1 mL, 0.1 M) at -78 °C was added nBuLi (0.04 mL, 2.5 M soln. in THF) dropwise, and stirred for 1 h. Weinreb Amide **3.61** (43 mg, 0.1 mmol) as a solution of THF (1 mL) is added dropwise, warmed to room temperature and stirred for 3 h, quenched by addition of *saturated aqueous* NH_4Cl (5 mL) and extracted with EtOAc (3 x 10 mL). Combined organics are washed with brine (10 mL), dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography (silica gel, gradient elution 0% -5% -100% EtOAc in Hexanes) to afford dithiane **3.62** 24 mg, (48%) as an oil. ^{1}H NMR (400 MHz, CDCl3): δ 6.02-5.95 (m, 1H), 5.33 (d, *J* = 1.6 Hz, 1H), 5.21 (d, *J* = 1.6 Hz, 1H), 4.22-4.20 (m, 3H), 3.23-3.12 (m, 2H), 2.98-2.95 (m, 1H), 2.68-2.53 (m 3H), 2.10-1.95 (m, 2H), 0.90 (s, 9H), 0.87 (s, 9H), 0.12 (s, 3H), 0.07 (s, 6H), 0.06 (s, 3H). ^{13}C NMR (100 MHz, CDCl3): 201.5, 135.9, 115.4, 74.0, 71.7, 42.0, 30.8, 26.3 (2), 25.7 (2), 25.2, 18.1, -4.6, -4.8, -4.9, -5.



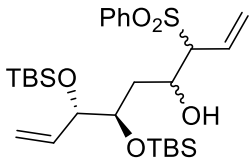
Allyl **3.63:** To a solution Weinreb Amide **3.61** (0.26 g, 0.62 mmol) in THF (3 mL) at -78 °C was added a solution of allyl Magnesium bromide (1.24 mL, 1M soln in THF) dropwise stirred for 1 h then quenched by addition of *saturated aqueous* NH_4Cl (10 mL) and extracted with EtOAc (3 x 10 mL).Combined organics are washed with brine (10 mL), dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography (silica gel, gradient elution 0% -5% EtOAc -10% EtOAc in Hexanes) to afford Allyl **3.63** 0.21 g, (84%) as an oil. ^{1}H NMR (400 MHz, CDCl3) δ: 5.92-5.66 (m, 2H), 5.13-4.99 (m, 4H), 4.16-4.08 (m, 1H), 3.97-3.95 (m, 1H), 3.08 (d, *J* = 6 Hz, 2H), 2.56-2.44 (m, 2H), 0.82 (s, 9H), 0.81 (s, 9H), 0.00 (s, 3H), -0.01 (s, 3H), -0.02 (s, 3H), -0.04 (s, 3H).



Enone **3.64**: To a solution of **3.64** (50 mg, 0.12 mmol) in DCM (1 mL), was added NBS (27 mg, 0.15 mmol), and AIBN (2 mg, 0.01 mmol) heated to reflux and stirred for 1.5 h, cooled to room temperature and quenched by addition of *saturated aqueous* $NaHCO_3$ (5 mL), extracted with DCM (3 x 5 mL). Combined organics washed with brine (10 mL), dried ($MgSO_4$), filtered, concentrated *in vacuo*, and purified by flash column chromatography (silica gel, gradient elution, 0% -20% EtOAc in Hexanes), affording **3.64** 45 mg, (90%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ:6.77-6.70 (m, 1H), 6.05 (dd, = 1.6 Hz, 6 Hz, 1H), 5.78-5.69 (m, 1H), 5.11 (t, *J* = 11.2 Hz, 2H), (m, 4H), 4.16-4.08 (m, 1H), 3.97-3.95 (m, 1H), 3.08, 2.67 (dd, *J* = 7.2 Hz, 16 Hz, 1H), 2.58-2.43 (m, 1H), 1.81 (t, *J* = 7.2 Hz, 3H), 0.83 (s, 9H), 0.77 (s, 9H), 0.01—0.08 (m, 12H).

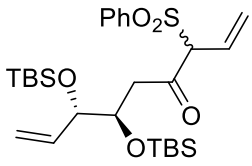


Aldehyde **3.65:** To a solution of LAH (50 mg, 1.26 mmol) in THF (4mL, 0.32 M) at 0 °C was added a solution of **3.61** (400mg, .96 mmol) in THF (4mL, .24M). After 2 h reaction was quenched by addition of *saturated aqueous* $NaHSO_4$ (2 mL), and stirred until a clear solution persisted, reaction was diluted water (10 mL) and extracted with EtOAc (3x10 mL), combined organics were washed with brine (20mL) dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography (silica gel, gradient elution, 0% -10% -20% EtOAc in Hexanes) affording aldehyde **3.65** 305 mg, (89%) as a clear oil. 1H NMR (400 MHz, CDCl3): δ= 9.76(dd. J= 2 Hz, 3Hz, 1H), 5.74-5.66(m,1H), 5.18(d, J= 1.2 Hz, 1H), 5.11 (d, J= 1.2 Hz, 1H), 4.07-3.99(m, 1H), 2.53(ddq, J = 3.2 Hz, 5.2 Hz, 16 Hz, 2H), 0.82(s, 9H), 0.80(s, 9H), 0.02(s, 3H), 0.0(s, 6H), -0.04(s, 3H).

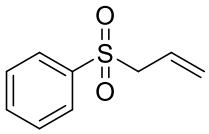


β hydroxy sulfone 3.66: To a solution of (allylsulfonyl)benzene, (390 mg, 2.12 mmol) in THF (2.12 mL, 1M) at -78 °C was added NaHMDS (1M in THF, 1.94 mL, 1.94 mmol) and stirred for 30 min. A solution of **3.65** (380 mg, 1.06 mmol) in THF (1.06 mL, 1M) was added dropwise, and reaction was stirred for 5 h, quenched by addition of *saturated aq*ueous NH_4Cl (2 mL) diluted with water (5 mL), extracted with EtOAc (3x10 mL). Combined organics were washed with brine (20 mL), dried, ($MgSO_4$) filtered, concentrated *in vacuo* and purified by flash column chromatography (silica gel, gradient elution 0%- 20% EtOAc in Hexanes) affording **3.66** 290 mg (55%) as a complex mixture of inseparable diastereomers. ^{1}H NMR (400 MHz, CDCl3) δ:7.85-7.82(m, 2H), 7.61-7.59(m, 1H), 7.49(q, J= 8Hz, 2H), 6.02-5.90 (m, 1H), 5.79-5.67 (m, 1H), 5.40 (t, J= 1.2 Hz, 1H), 5.15-

5.01 (m, 3H), 4.694.64 (m, 1H), 3.98-3.97 (m, .5H), 3.88-3.85 (m, .5H), 3.77-3.74 (m, .5H), 3.62-3.61 (d, J= 1.6 Hz, .5H), 3.66 (d, J= 3Hz, 1H), 1.73-1.57 (m, 2H), 0.87-0.83 (m, 18H), 0.09-0.00 (m, 12H); ^{13}C NMR (100 MHz, CDCl3) δ: 138.4, 138.2, 138.1, 133.8, 133.7, 133.6, 133.5, 129.4, 129.2, 129.1, 128.9, 128.8, 128.6, 128.5, 127.7, 127.4, 125.9, 125.5, 125.3, 124.6, 124.1, 116.5, 116.3, 116.1, 115.9, 78.5, 78.2, 78.0, 75.9, 75.2, 74.9, 74.5, 73.8, 73.6, 72.9, 72.4, 65.6, 65.4, 65.8, 37.8, 37.5, 37.4, 37.2, 26.1, 26.0, 25.9, 25.88, 25.84, 25.7, 25.0, 18.2, 18.1, -4.2, -4.3, -4.4, -4.6, -4.7, -4.8.



α Keto Sulfone 3.67: To a solution of **3.66** (290 mg, 0.54 mmol) in DCM (2 mL, .25 M) was added Dess-Martin periodinane (570 mg, 1.35 mmol), reaction was stirred for 3 h then quenched by addition of *saturated aqueous* $NaHCO_3$(2 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL), and stirred until a clear solution persisted. Aqueous layer was extracted with DCM (3x10 mL), combined organics were washed with brine (20 mL), dried ($MgSO_4$), filtered, concentrated *in vacuo* then purified by flash column chromatography(silica gel, gradient elution 0% -10% -20% EtOAc in Hexanes) affording **3.67** 220 mg, (76%) as a mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.82-7.80 (m, 2H), 7.90 (t, J= 1.2 Hz, 1H), 7.55 (t, J= 8 Hz, 2H), 5.92-5.71 (m, 1H), 5.41 (dd, J= 7, 10 Hz, 1H), 5.28-5.11(m, 3H), 4.67(d, J= 8 Hz, 1H), 4.214.05(m, 2H), 3.00(dt, J= 4 Hz, 20 Hz, 1H), 2.86(t, J= 7 Hz, 1H), 0.94-0.88(m, 18H), 0.1-0.9(m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 198.1, 197.8,144.5, 144.3, 137.8, 137.7, 137.6, 134, 133.4, 129.6, 129.5, 129.0, 128.7, 128.6, 127.9, 126, 124.9, 124.8, 116.7, 116.2, 80.0, 79.8, 71.8, 71.7, 71.1, 48.2, 47.8, 25.9, 18.2,18.02,18.0,17.9,-4.2,-4.26,-4.3,-4.37,-4.4,-4.43,-4.7,4.9.



Allyl Sulfone-1: To a solution of benzene sulfinate (1 g, 6.1 mmol) in EtOH (6.1 mL, 1M) was added allyl bromide (0.5 mL, 6.1 mL) dropwise heated to reflux and stirred for 4 h at which point the reaction mixture is concentrated *in vacuo* and purified by flash column chromatography (silica gel, gradient elution, 0% - 100% EtOAc in Hexanes) to afford allyl sulfone **1** (1.0 g, 95%). ^{1}H NMR (400 MHz, CDCl3) δ: 7.91 (d, *J* = 8 Hz, 2H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 2H), 5.87-5.76 (m, 1H), 5.37 (d, *J* = 10 Hz, 1H), 5.19 (d, *J* = 10 Hz, 1H), 3.83 (d, *J* = 7.2 Hz, 2H).

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Appendix A.4

Spectra Relevant to Chapter 3

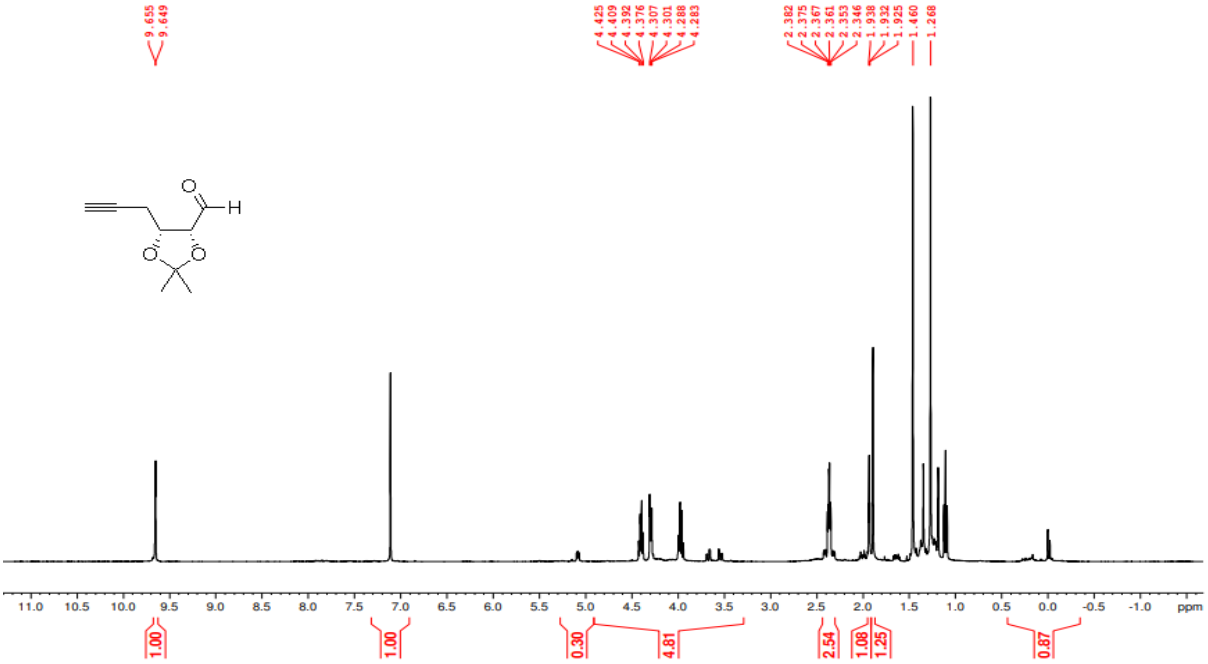


Figure A.3.20: ^{1}HNMR (400 MHz $CDCl_3$) of **3.25**

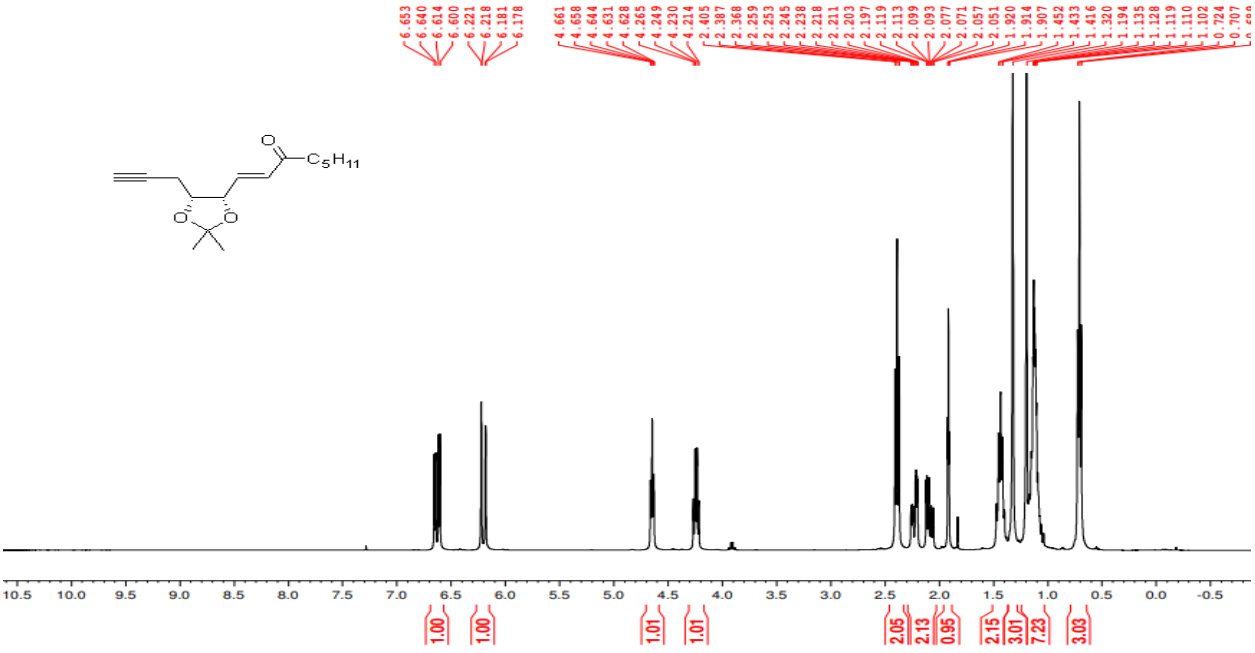


Figure A.3.21 ^{1}HNMR (400 MHz $CDCl_3$) of **3.26**

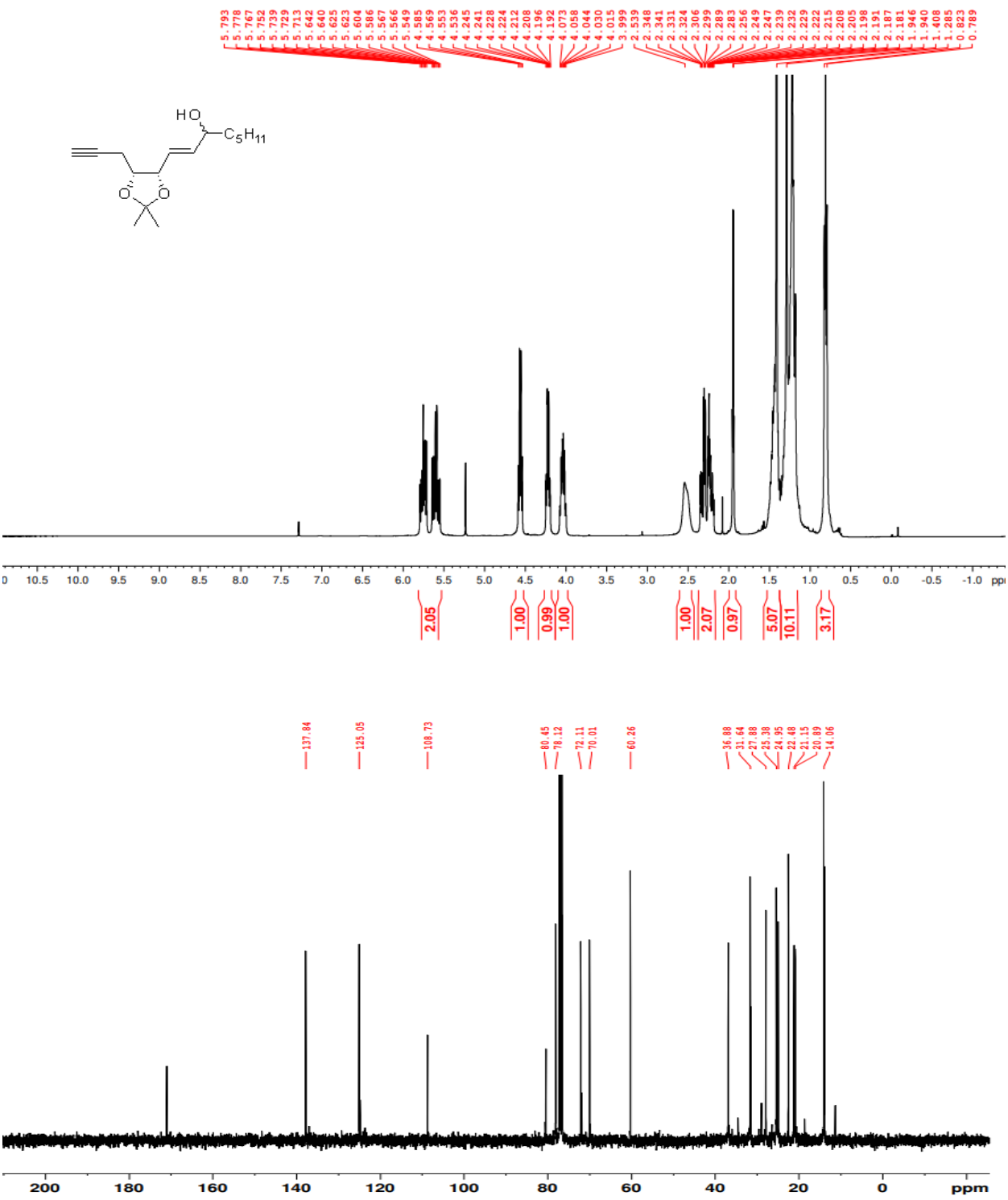


Figure A.3.22: ^{1}HNMR (400 MHz $CDCl_3$), and ^{13}CNMR (100 MHz, $CDCl_3$), of 3.27

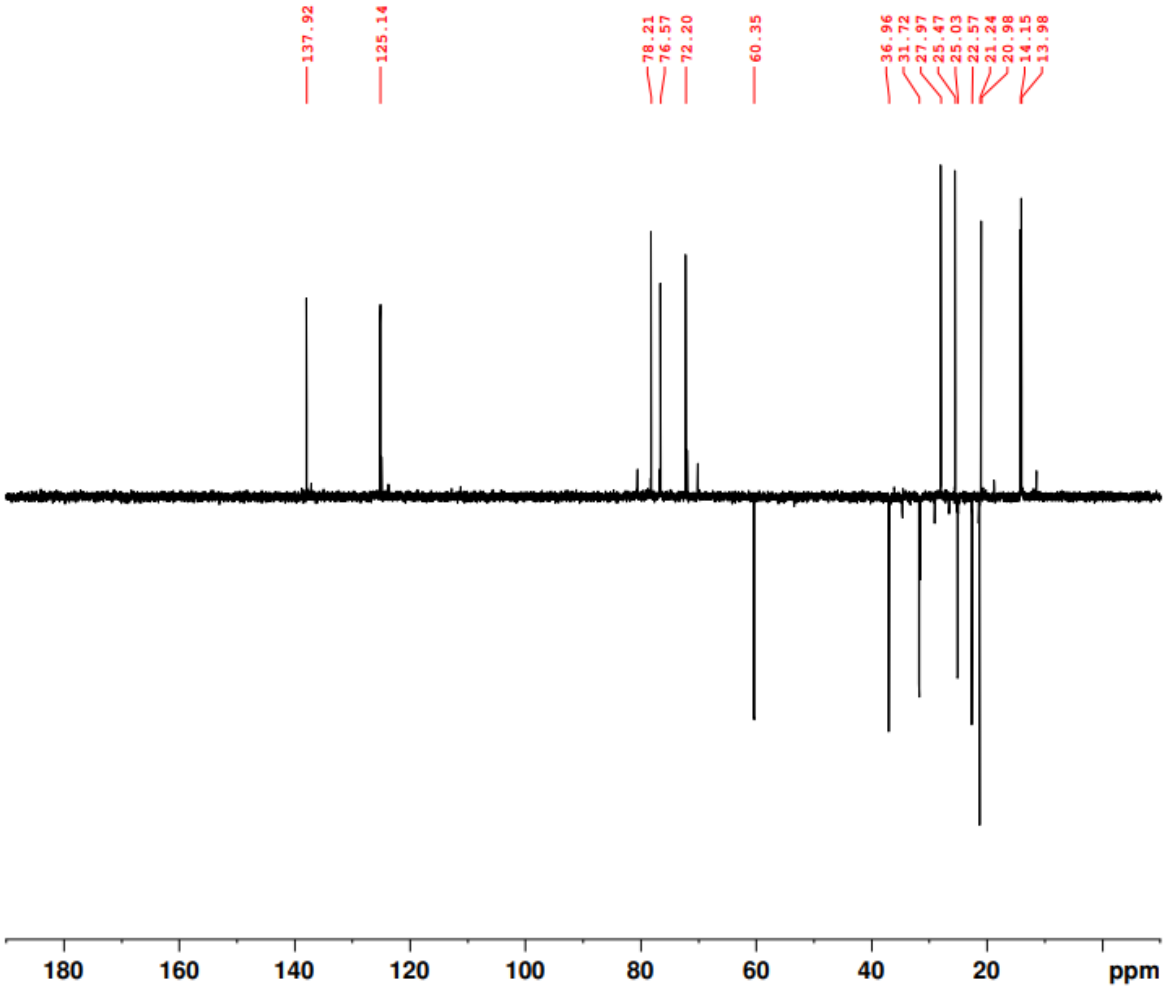


Figure A.3.23: DEPT 135 of 3.27

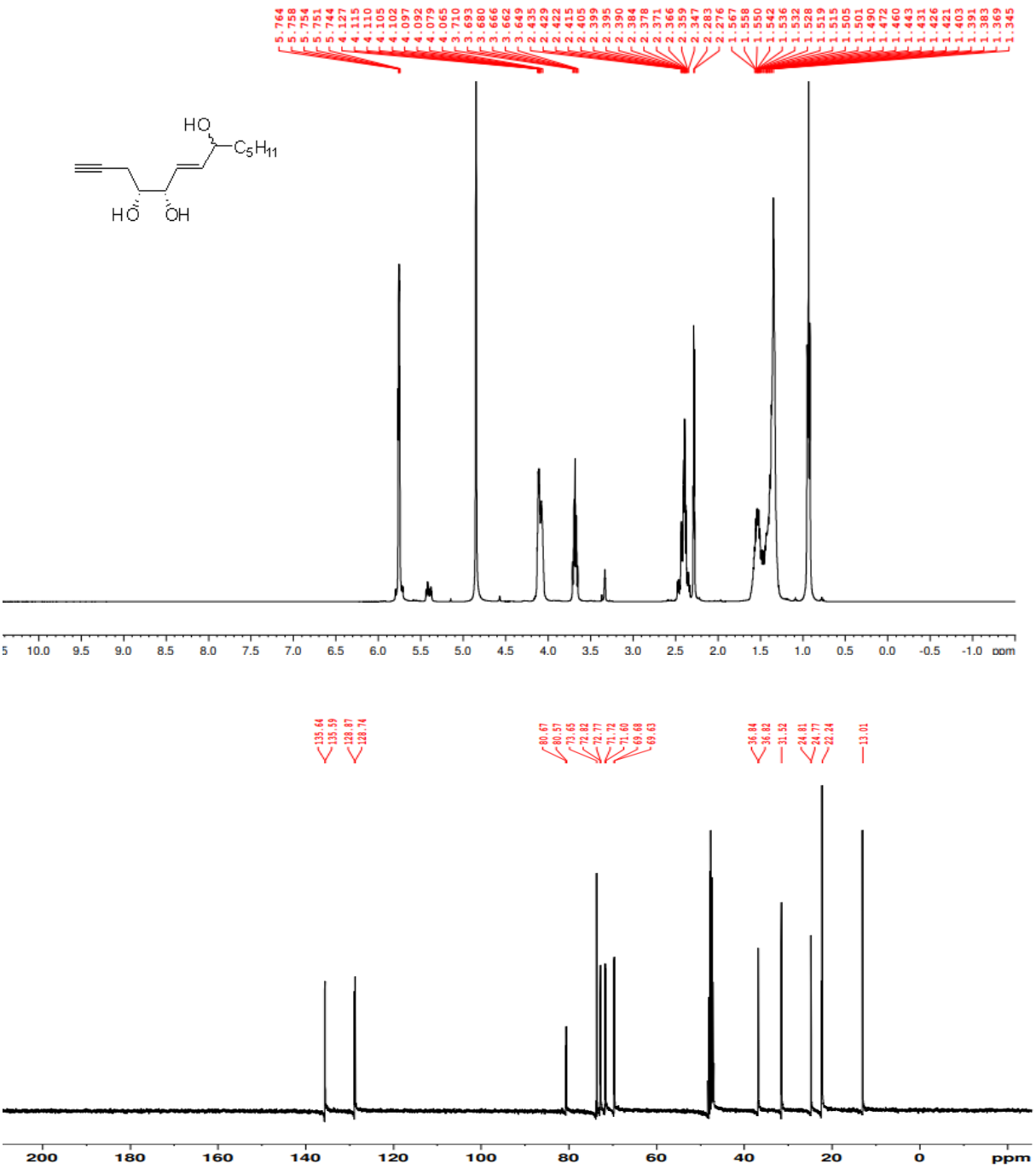


Figure A.3.24: ^{1}HNMR (400 MHz $CDCl_3$) and ^{13}CNMR (100 MHz, $CDCl_3$) of 3.28

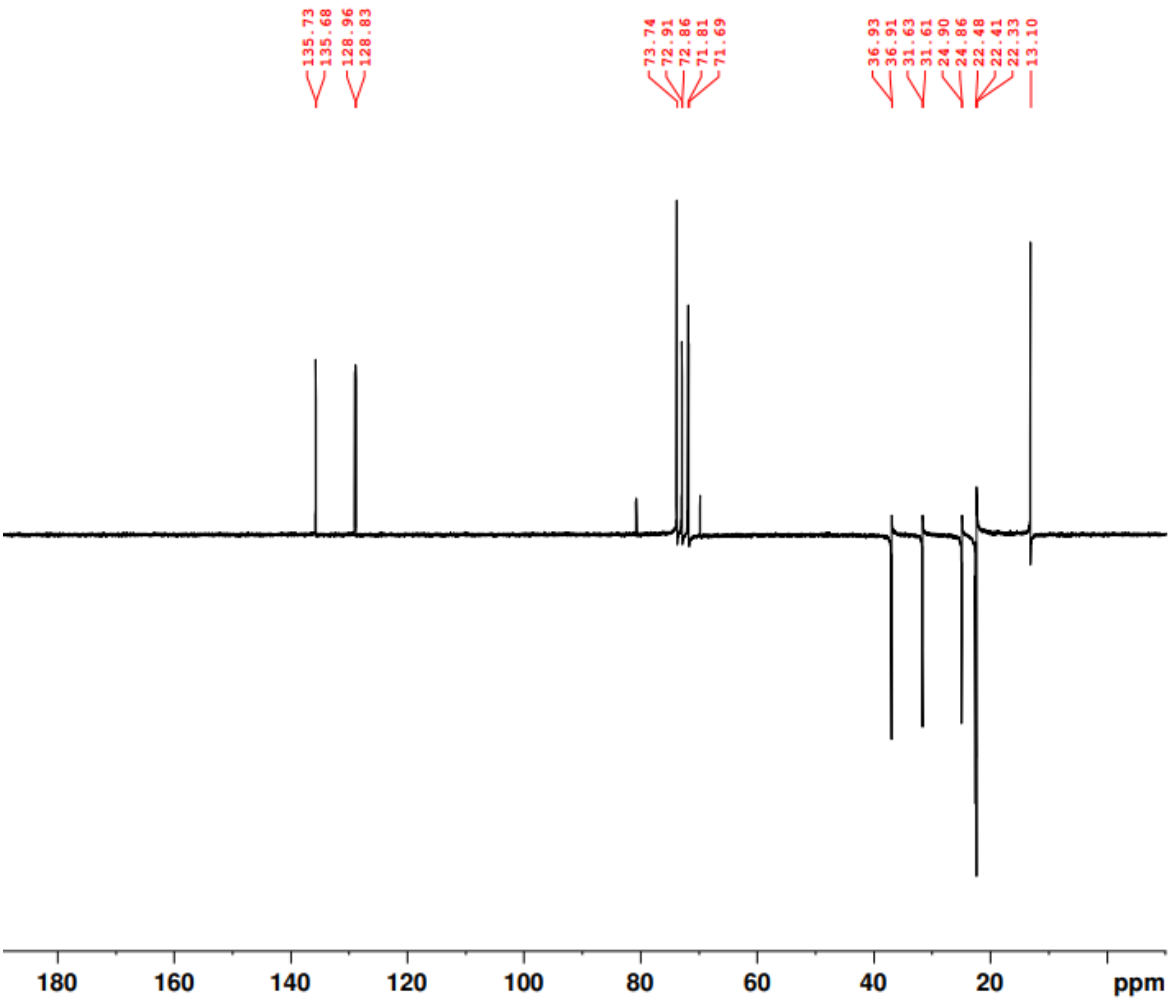


Figure A.3.25: DEPT-135 NMR (400 MHz $CDCl_3$) of 3.28

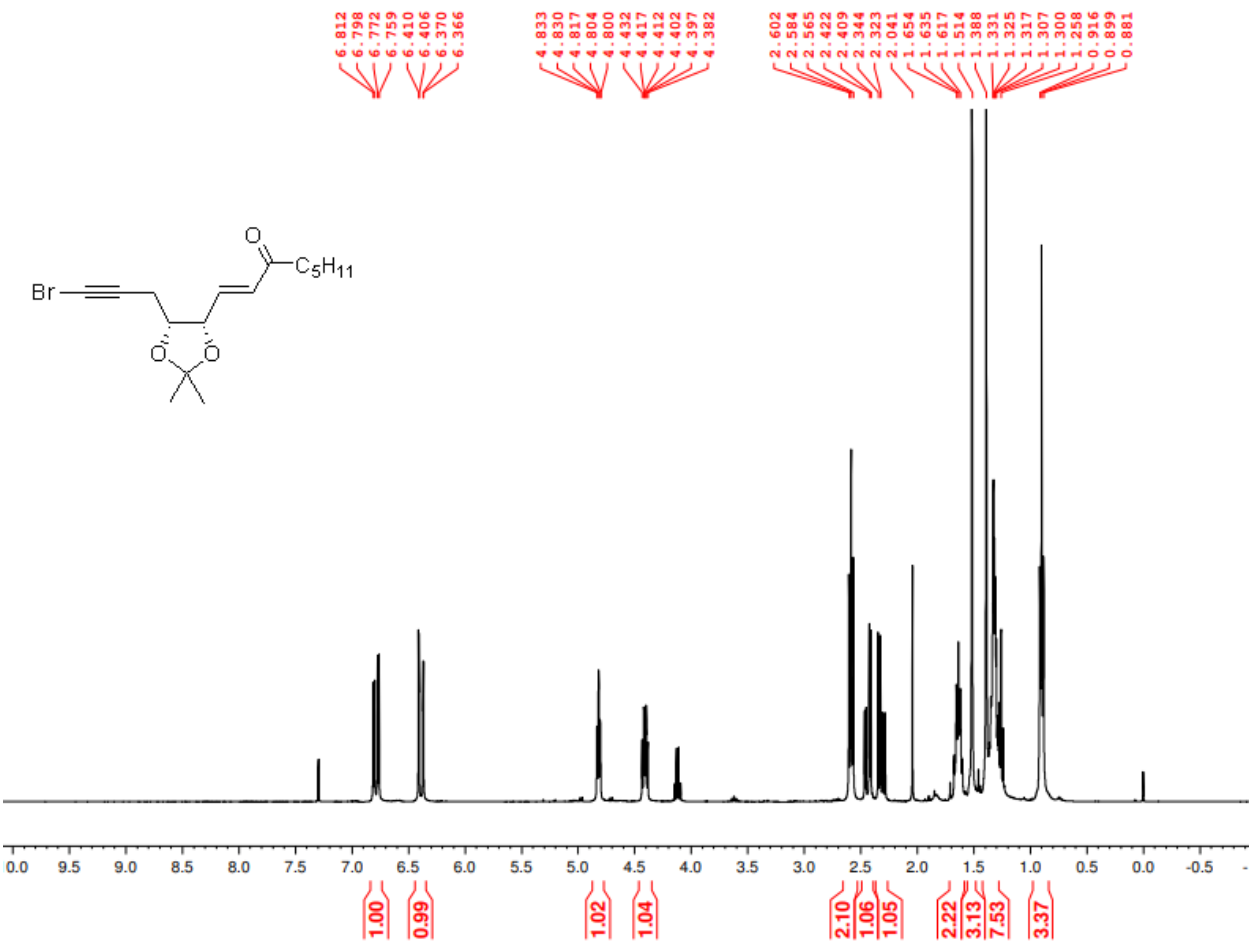


Figure A.3.26: ^{1}HNMR (400 MHz $CDCl_3$) of 3.35

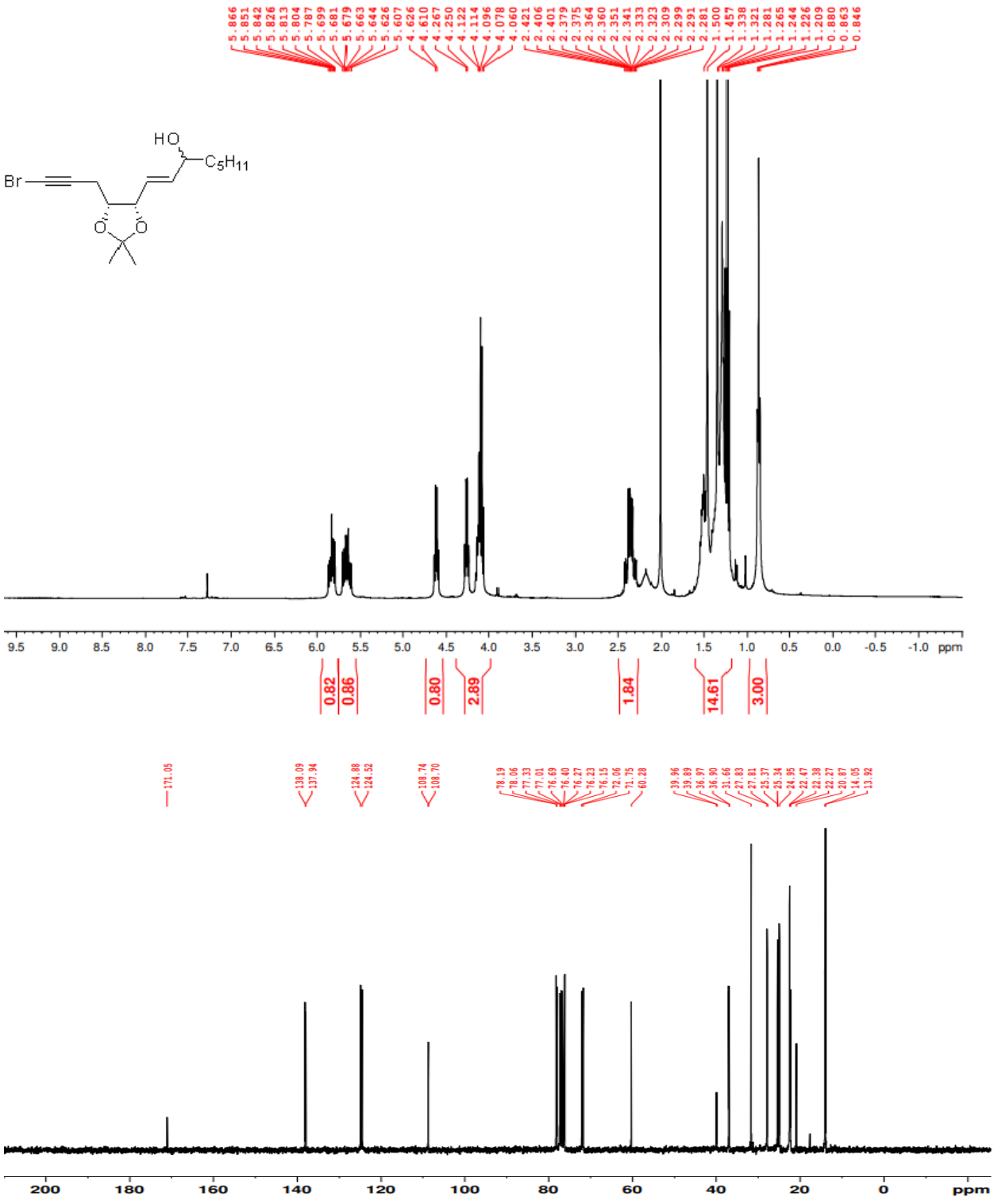


Figure A.3.27: ^{1}HNMR (400 MHz $CDCl_3$) and ^{13}CNMR (100 MHz, $CDCl_3$) of 3.36

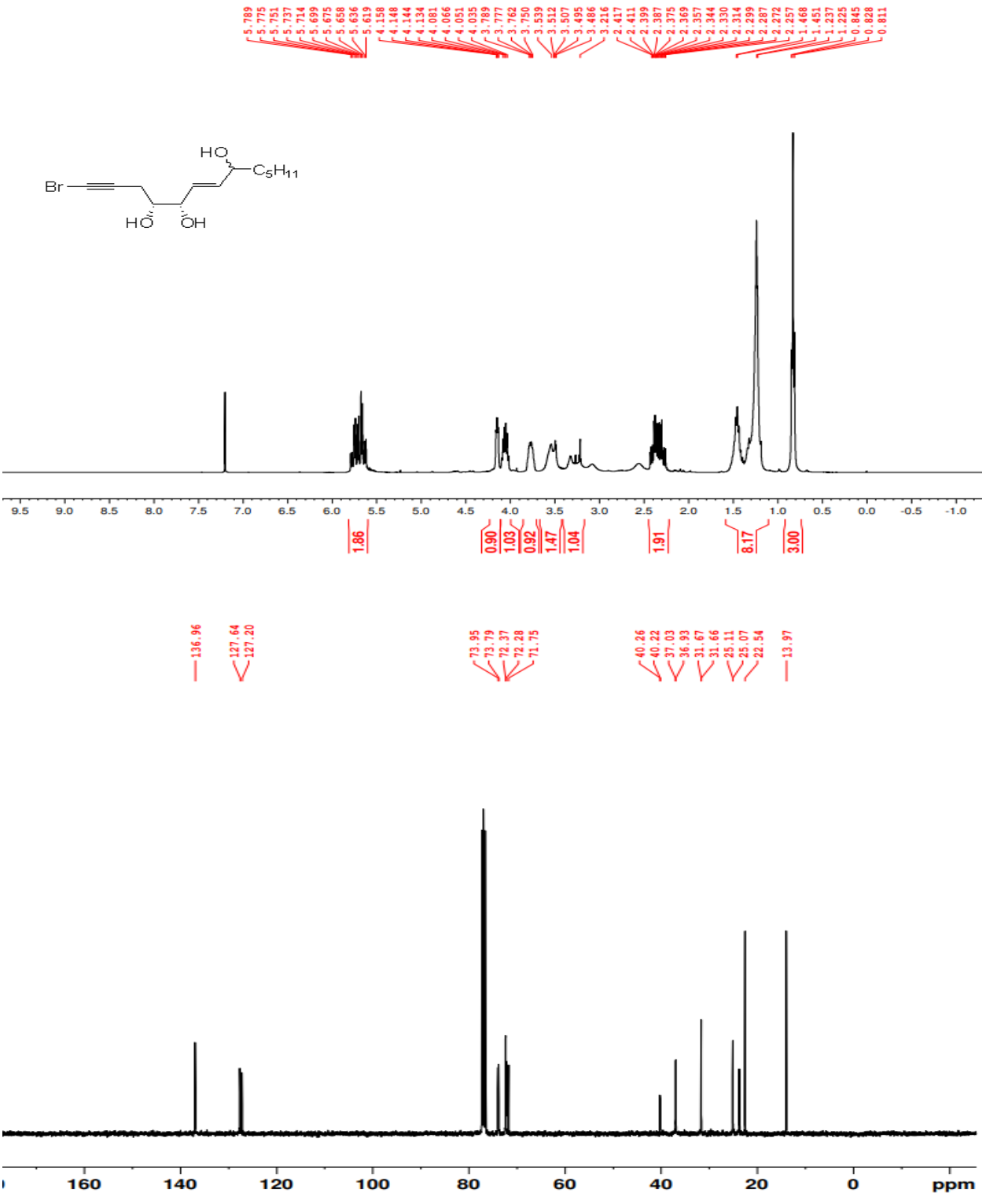


Figure A.3.28: ^{1}HNMR (400 MHz $CDCl_3$) and ^{13}CNMR (100 MHz, $CDCl_3$) of 3.37

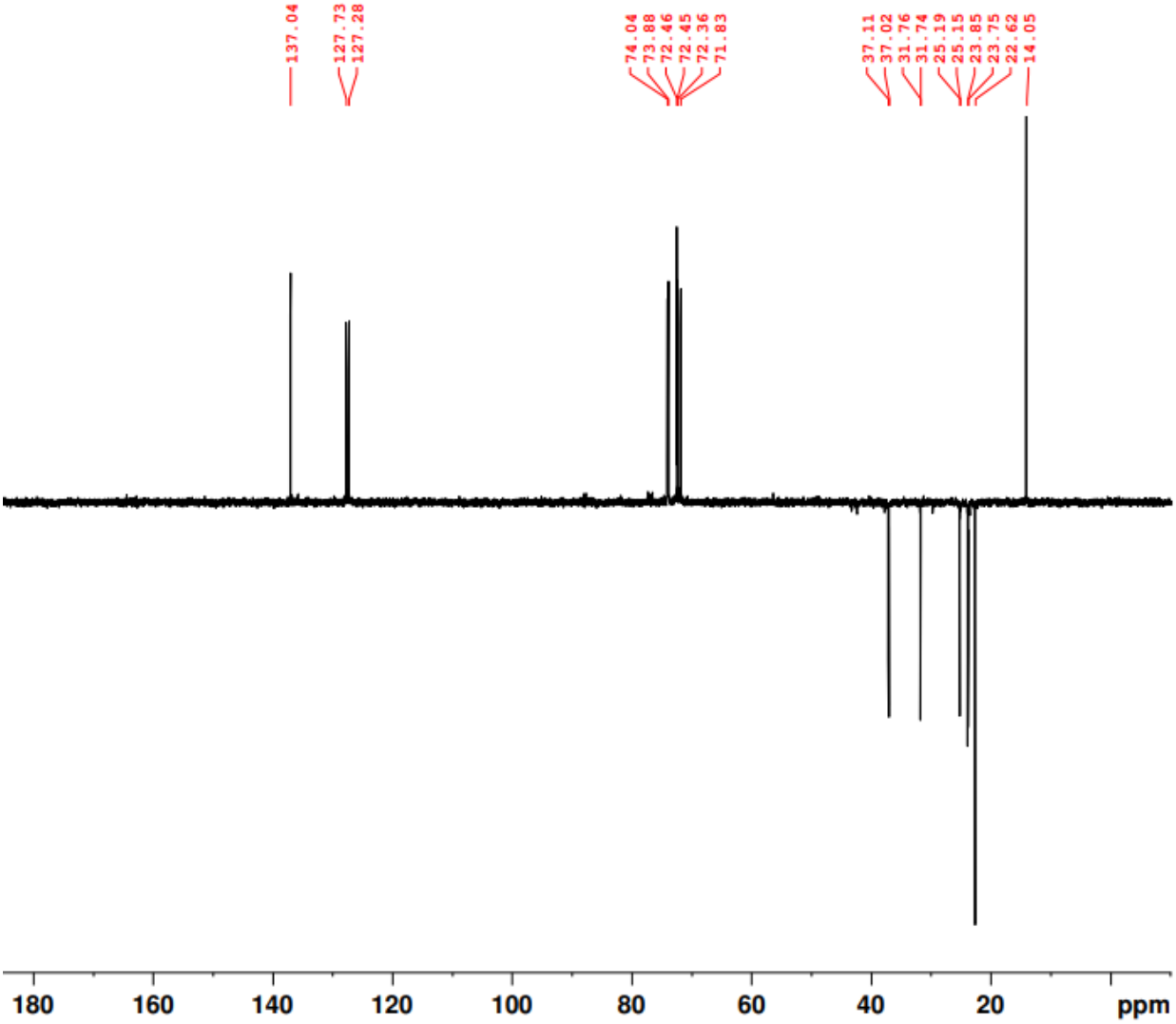


Figure A.3.29: DEPT 135 NMR (400 MHz $CDCl_3$) of 3.37

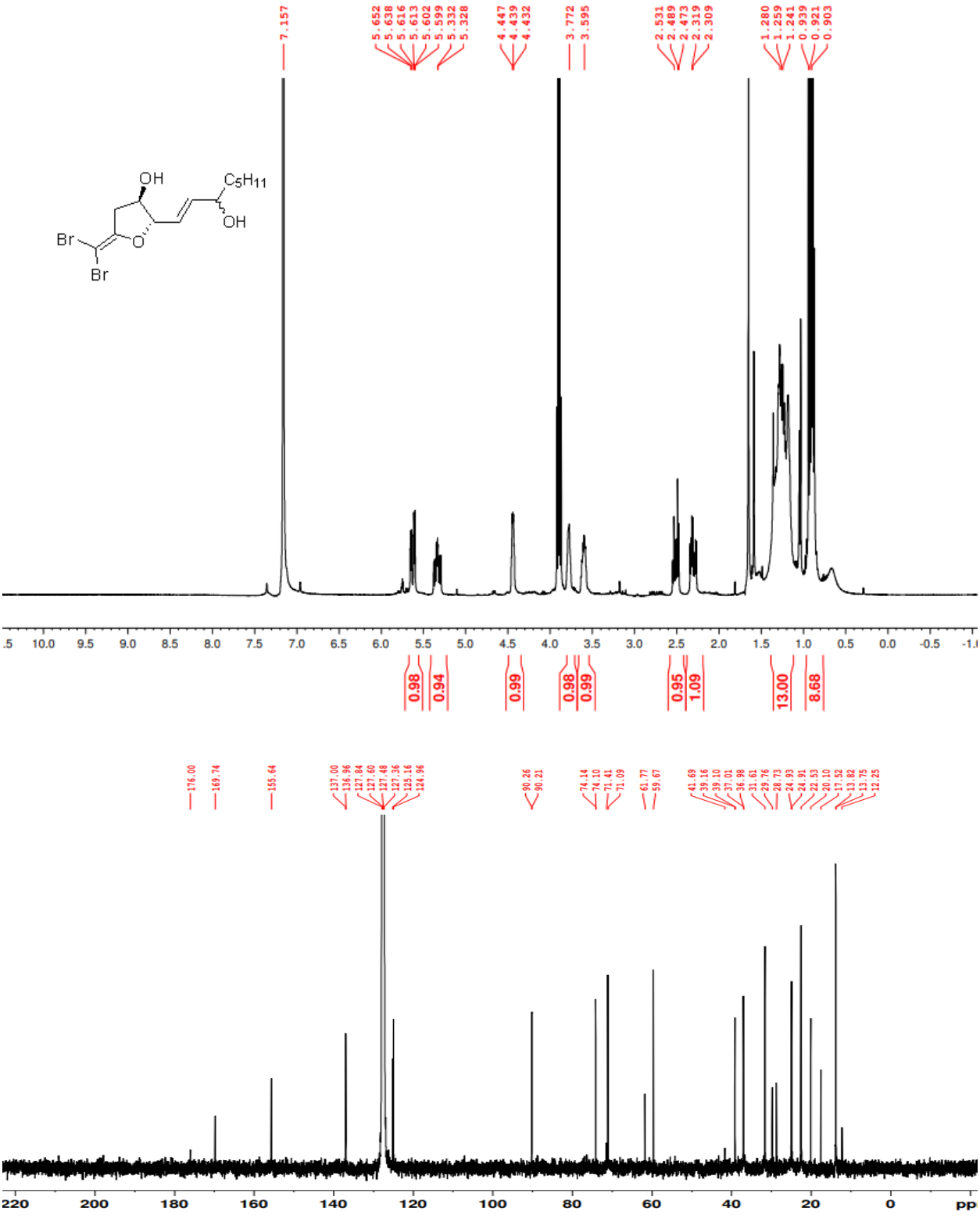


Figure A.30: ^{1}HNMR (400 MHz C_6D_6) and ^{13}CNMR (100 MHz, C_6D_6) of 3.30

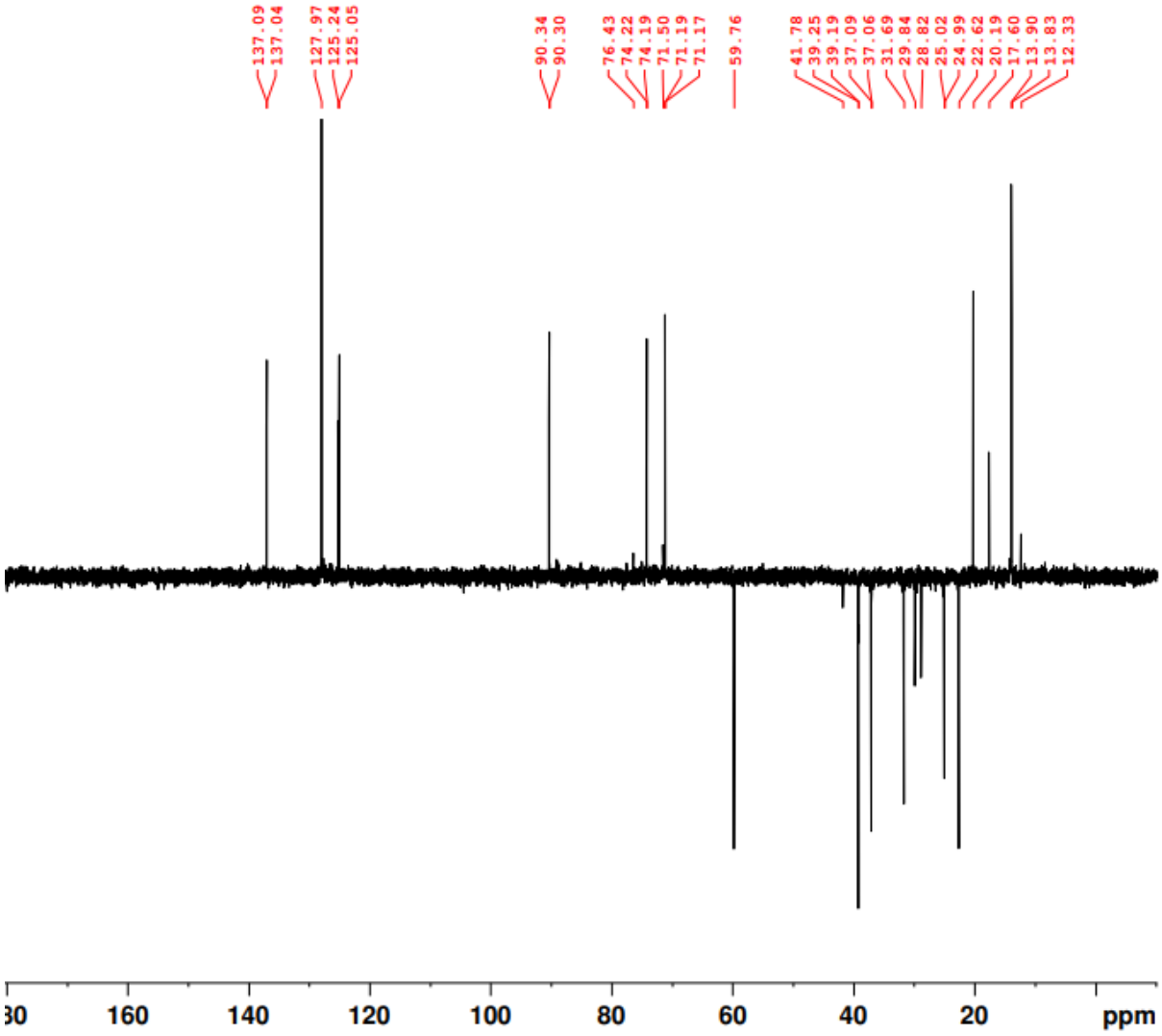


Figure A.3.31: DEPT 135 NMR (400 MHz, C_6D_6) of 3.30

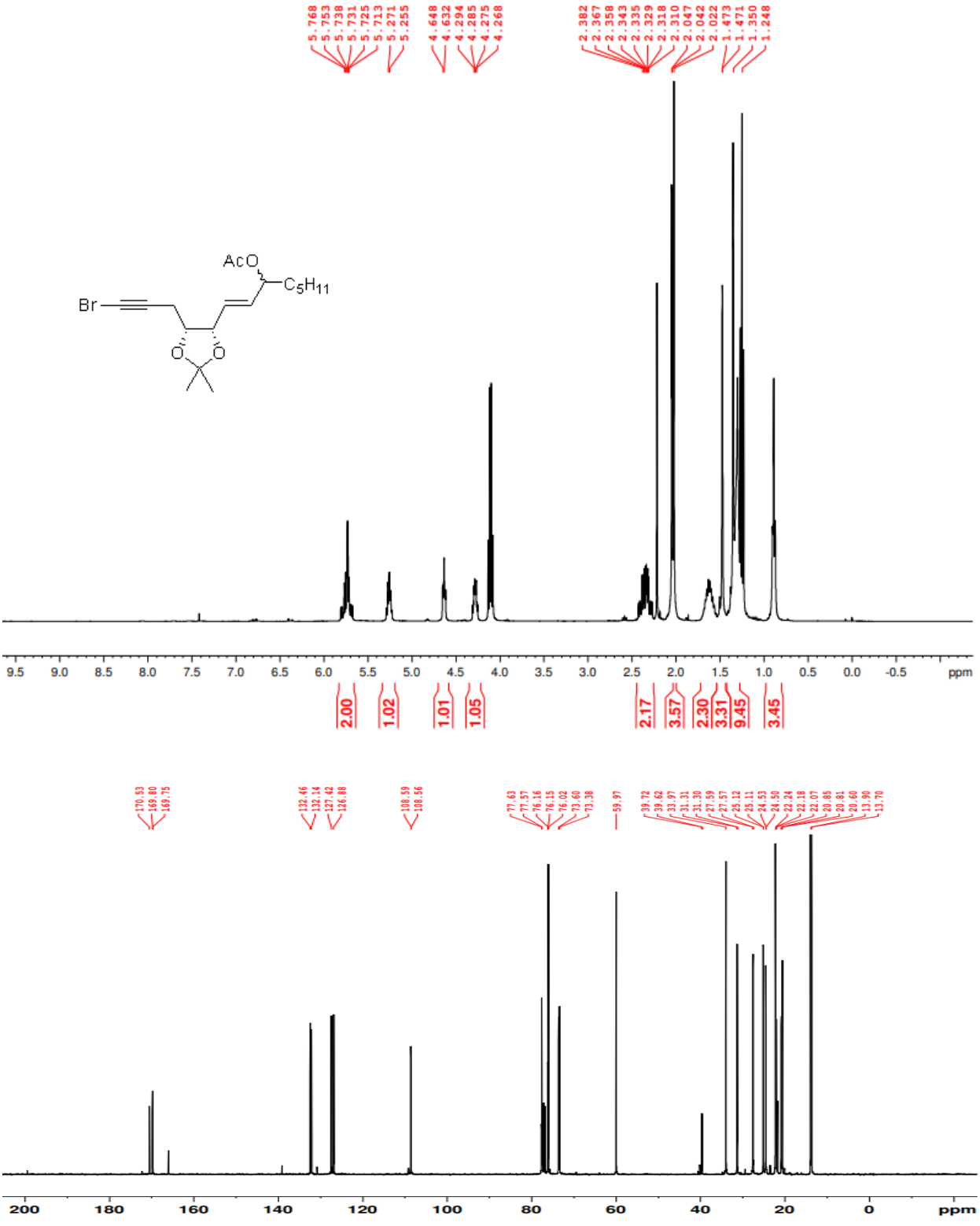


Figure A.3.32: ^{1}HNMR (400 MHz $CDCl_3$) and ^{13}CNMR (100 MHz, $CDCl_3$) of 3.40

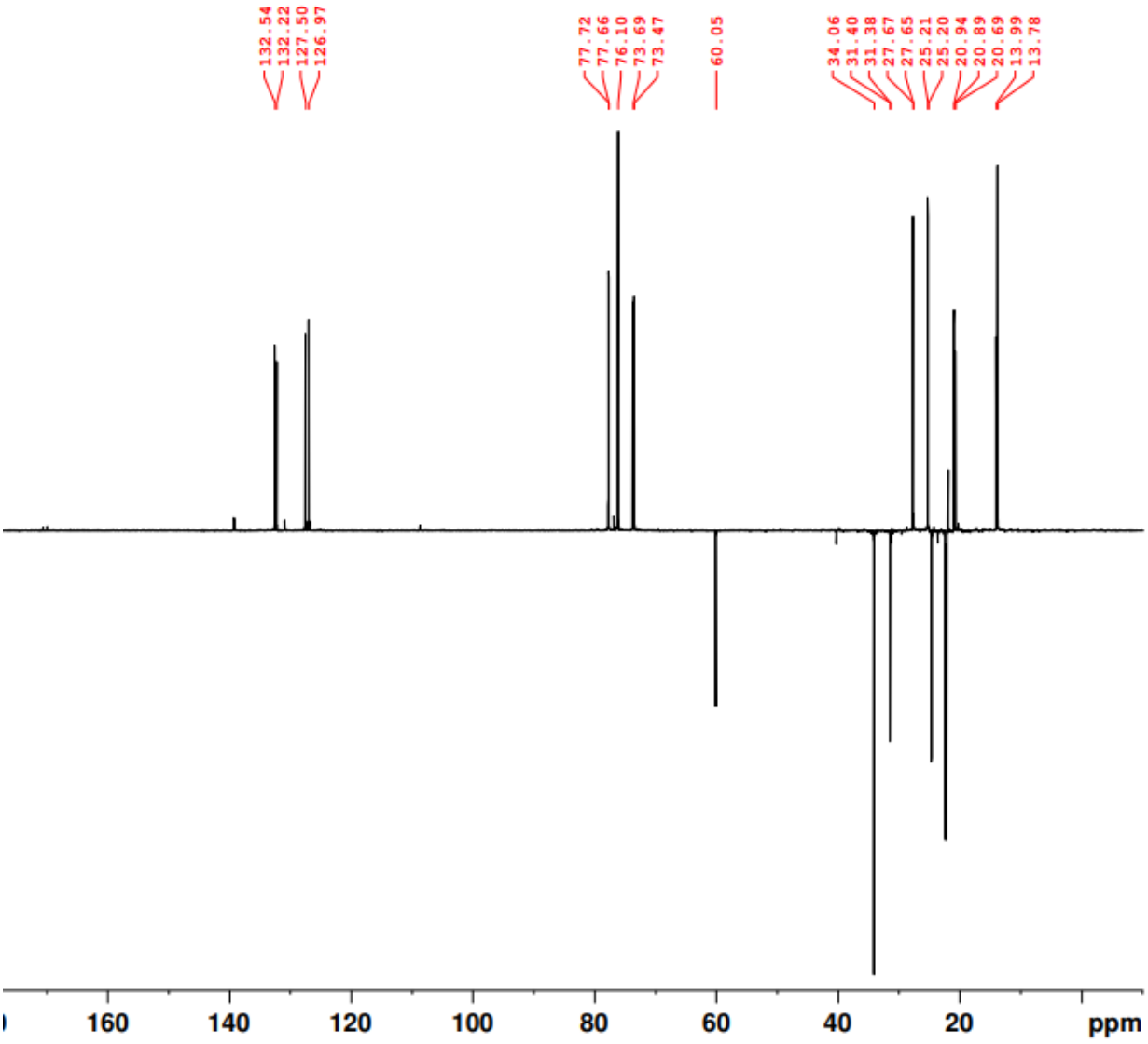


Figure A.3.33: DEPT 135 NMR (400 MHz $CDCl_3$) of 3.40

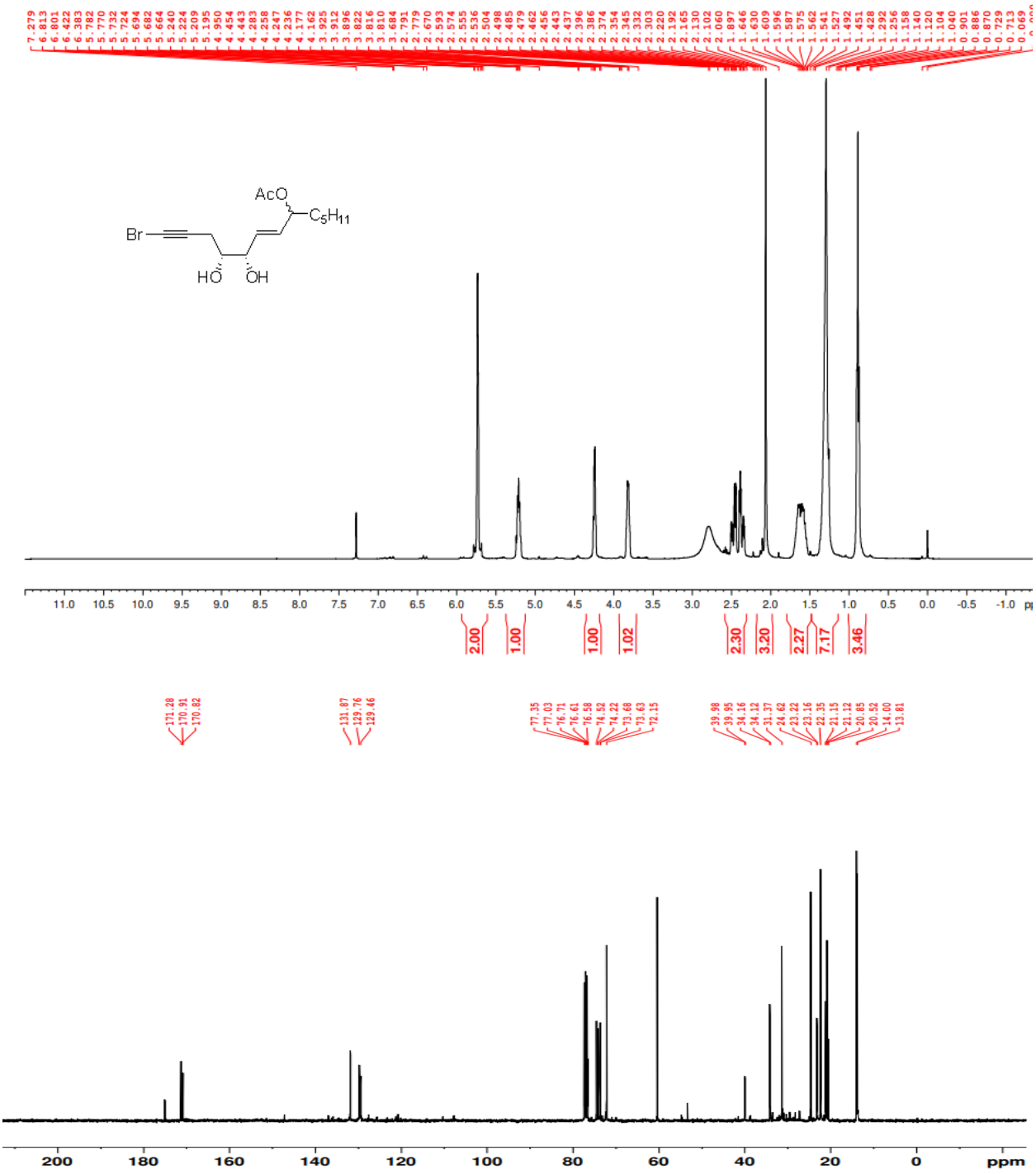


Figure A.3.34: ^{1}HNMR (400 MHz $CDCl_3$) and ^{13}CNMR (100 MHz, $CDCl_3$) of 3.43

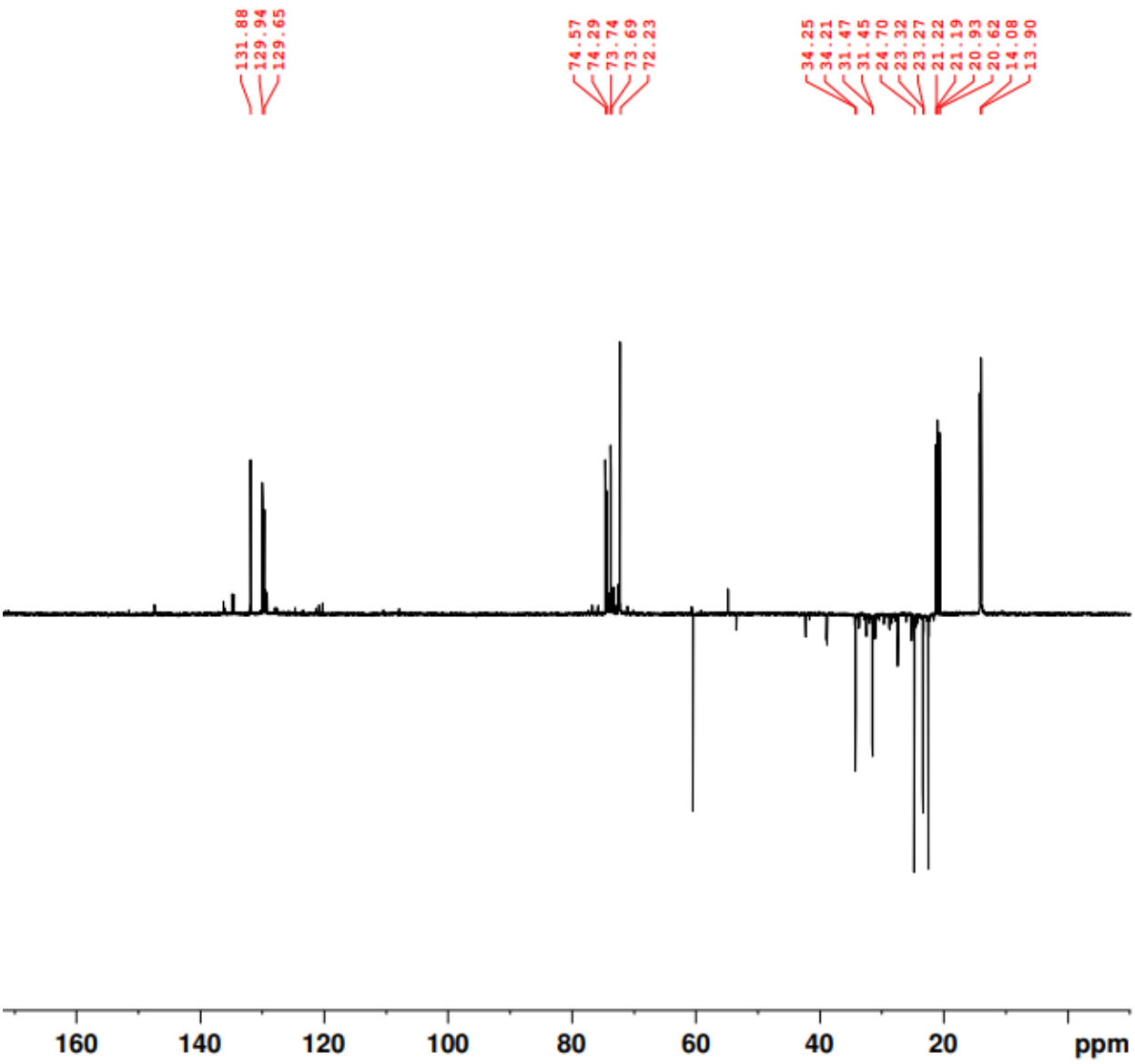


Figure A.3.35: DEPT 135 NMR (400 MHz $CDCl_3$) of 3.43

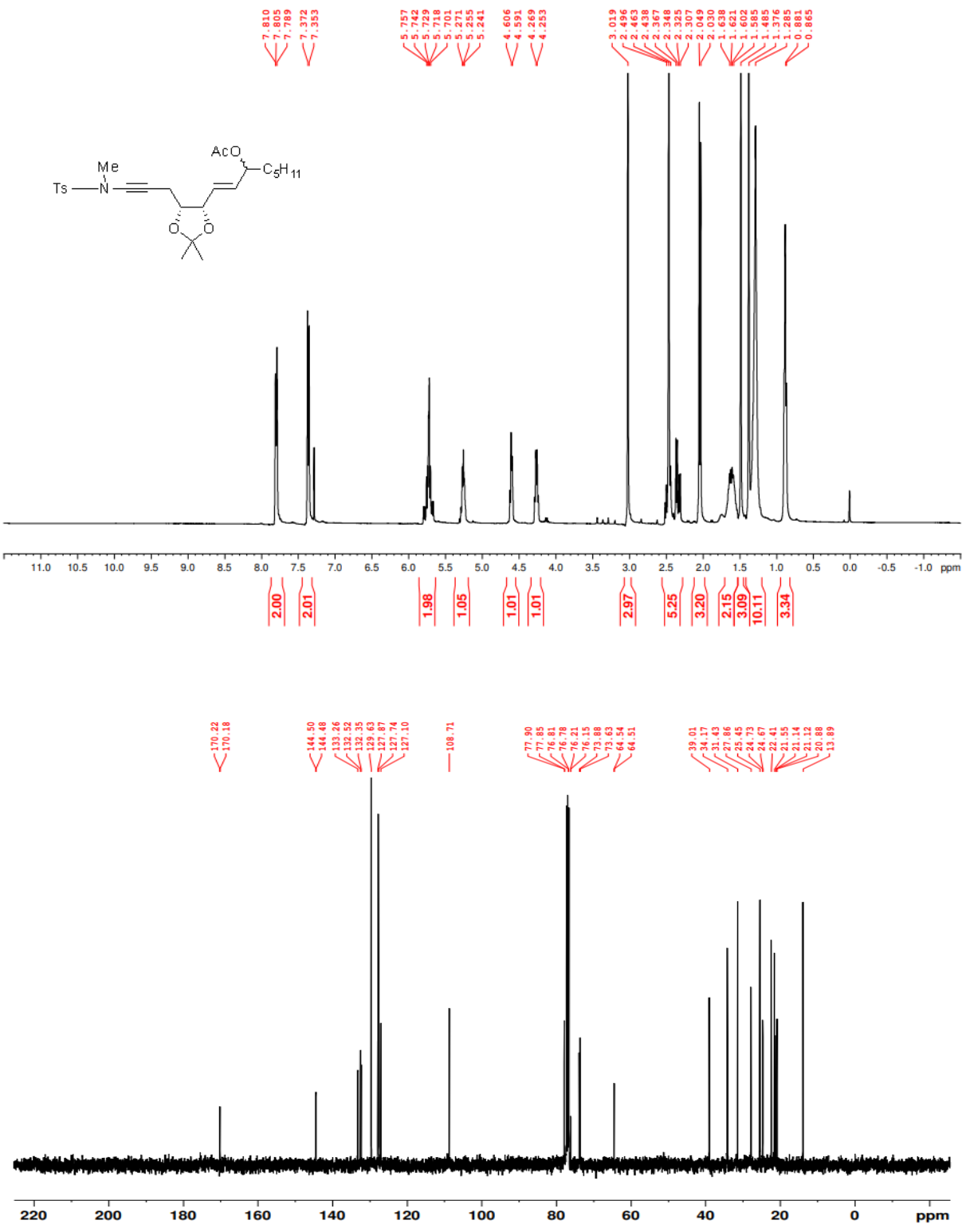


Figure A. 3.36: ^{1}HNMR (400 MHz $CDCl_3$) and ^{13}CNMR (100 MHz, $CDCl_3$) of 3.41

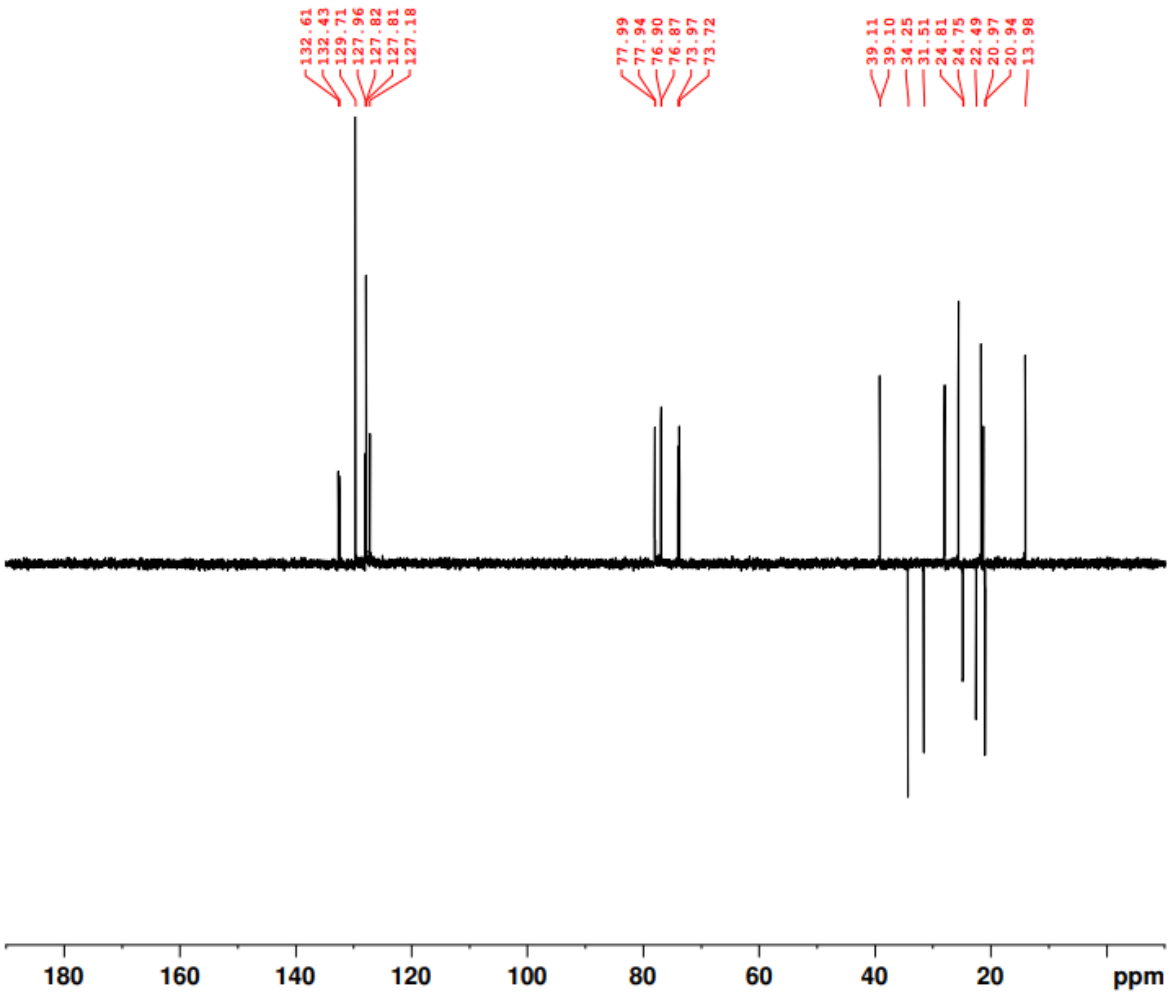


Figure A. 3.37: DEPT 135 NMR (400 MHz $CDCl_3$)) of 3.41

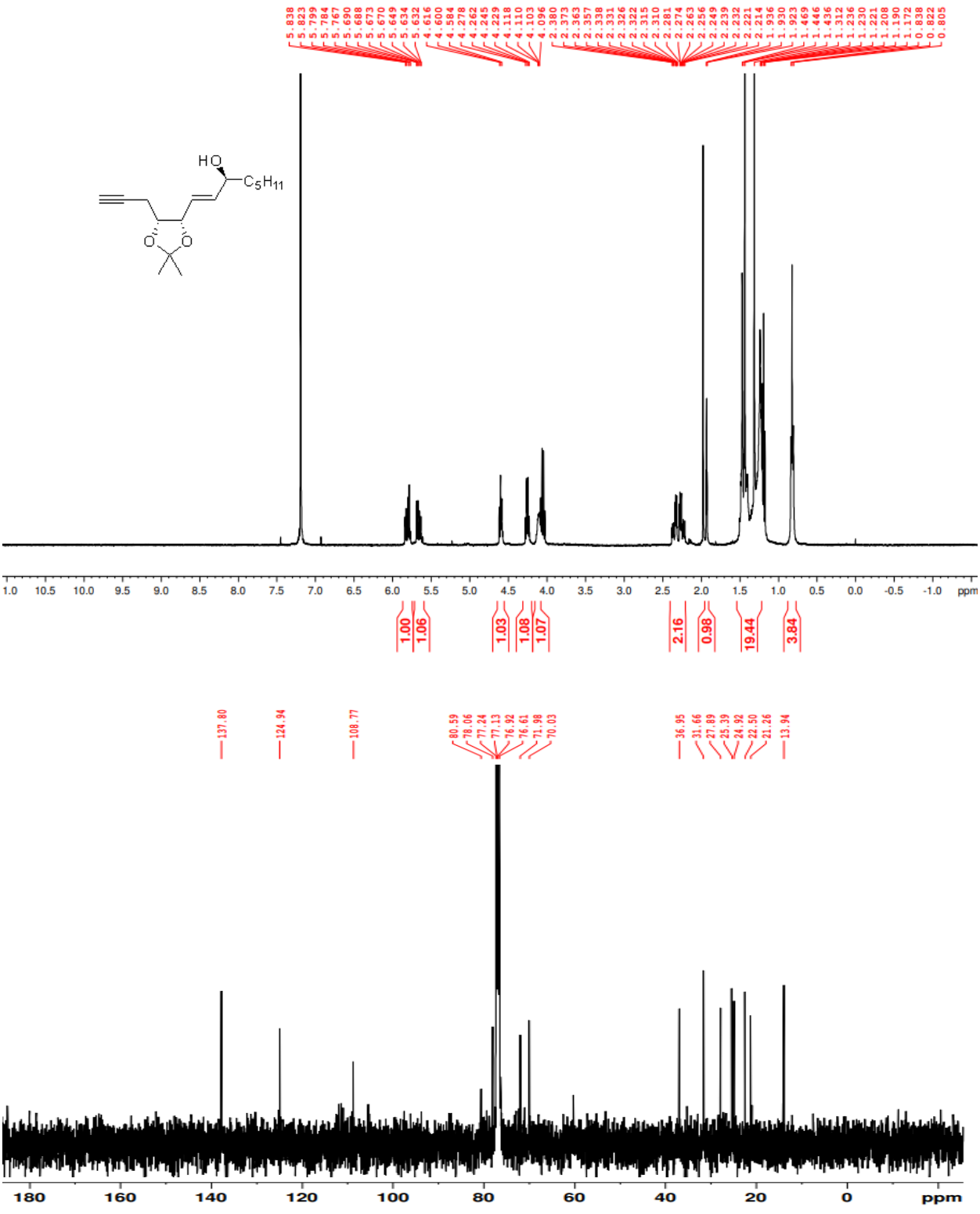


Figure A.3.38: ^{1}HNMR (400 MHz $CDCl_3$) and ^{13}CNMR (100 MHz, $CDCl_3$) of 3.45

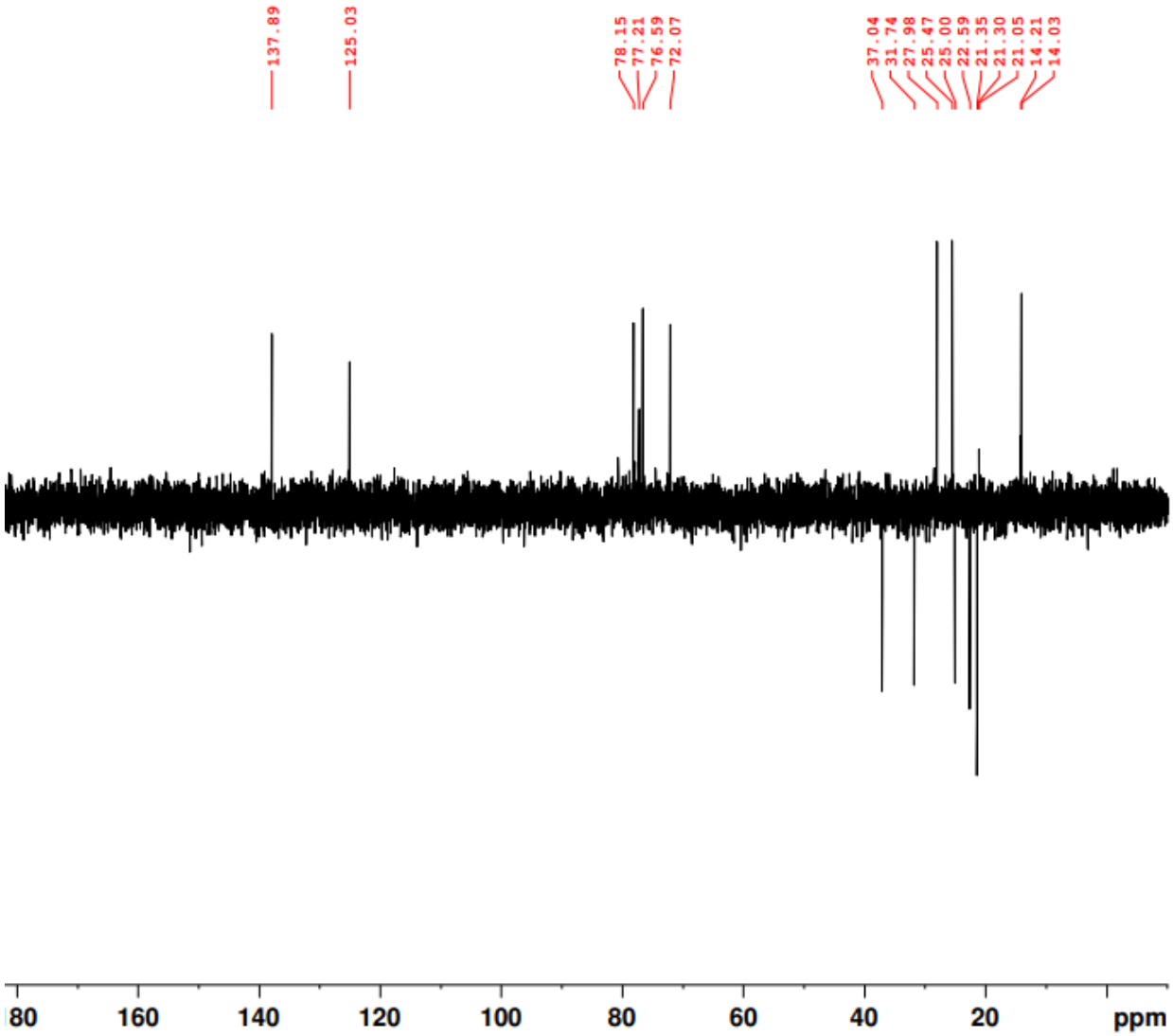


Figure A.3.39: DEPT 135 NMR (400 MHz $CDCl_3$) of 3.45

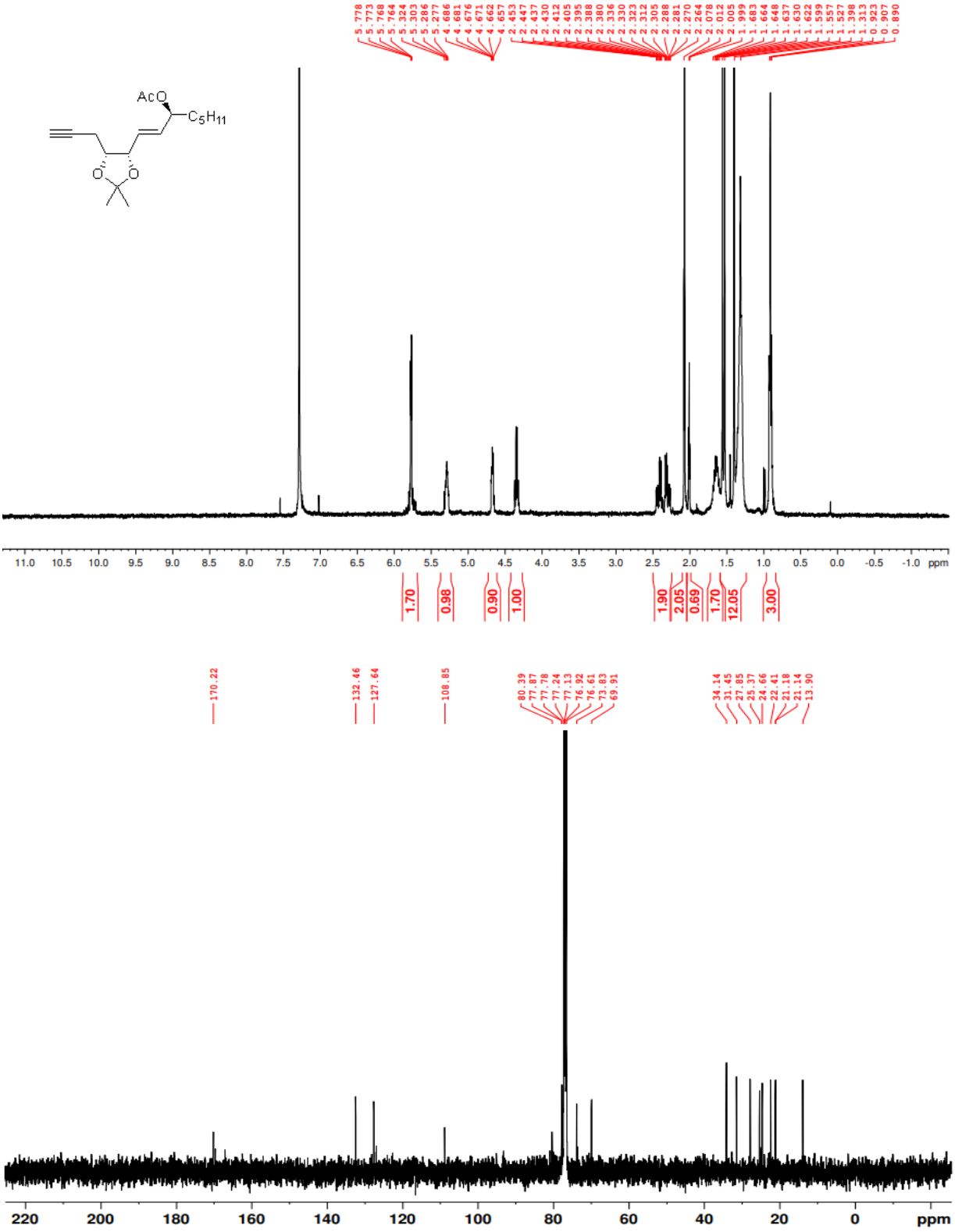


Figure A.3.40: ^{1}HNMR (400 MHz $CDCl_3$) and ^{13}CNMR (100 MHz, $CDCl_3$) of 3.46

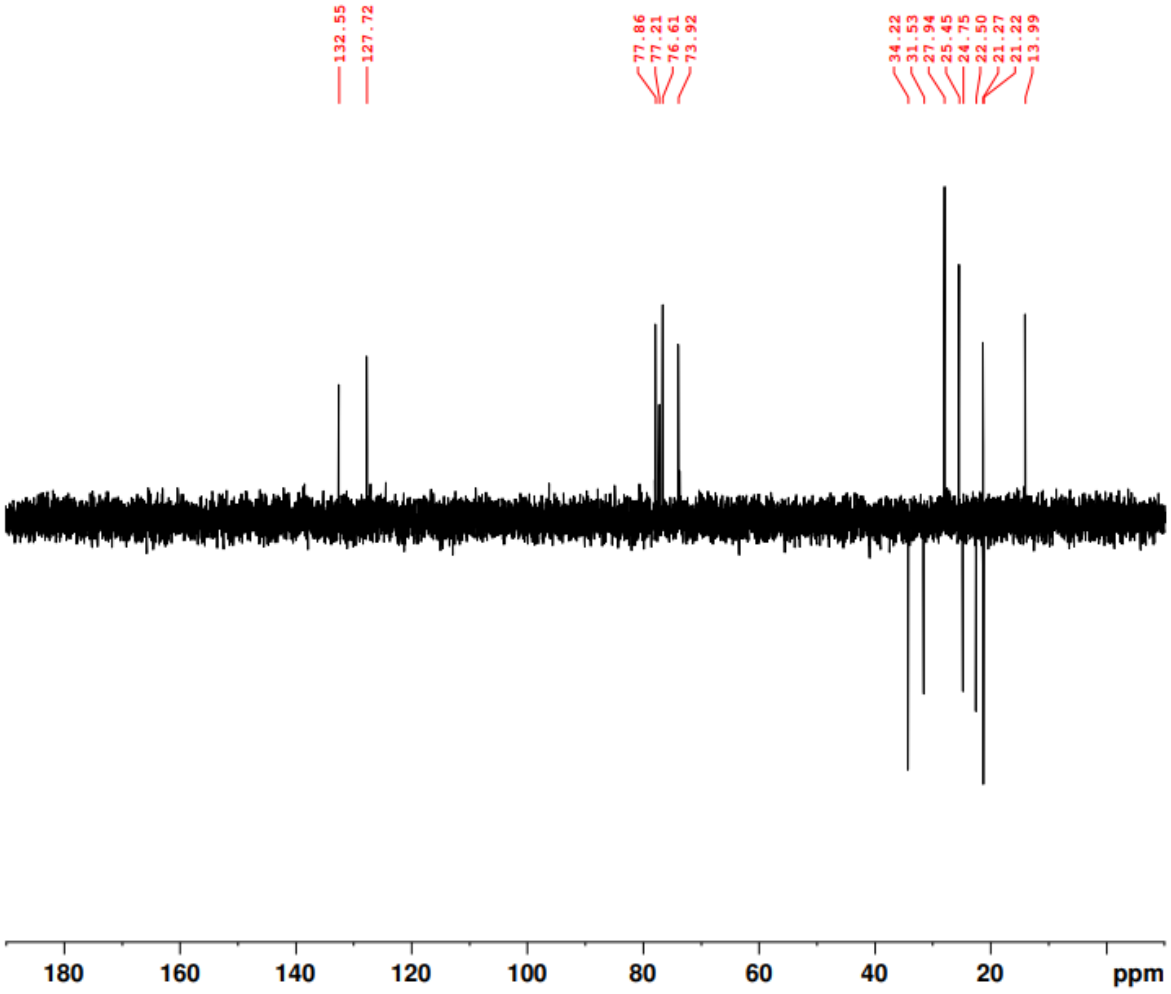


Figure A.3.41: DEPT 135 NMR (400 MHz $CDCl_3$ of 3.46

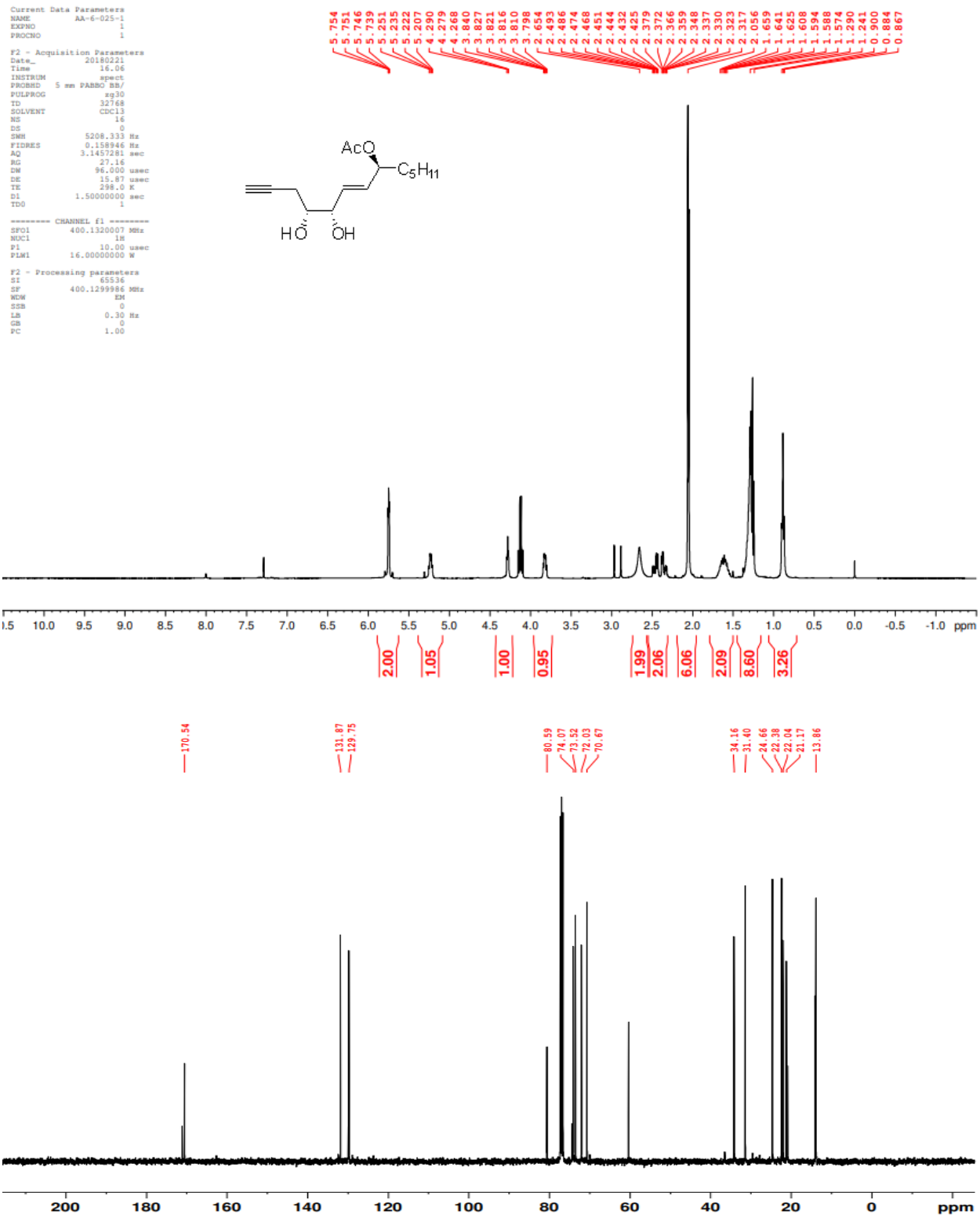


Figure A.3.42: ^{1}HNMR (400 MHz $CDCl_3$) and ^{13}CNMR (100 MHz, $CDCl_3$) of 3.47

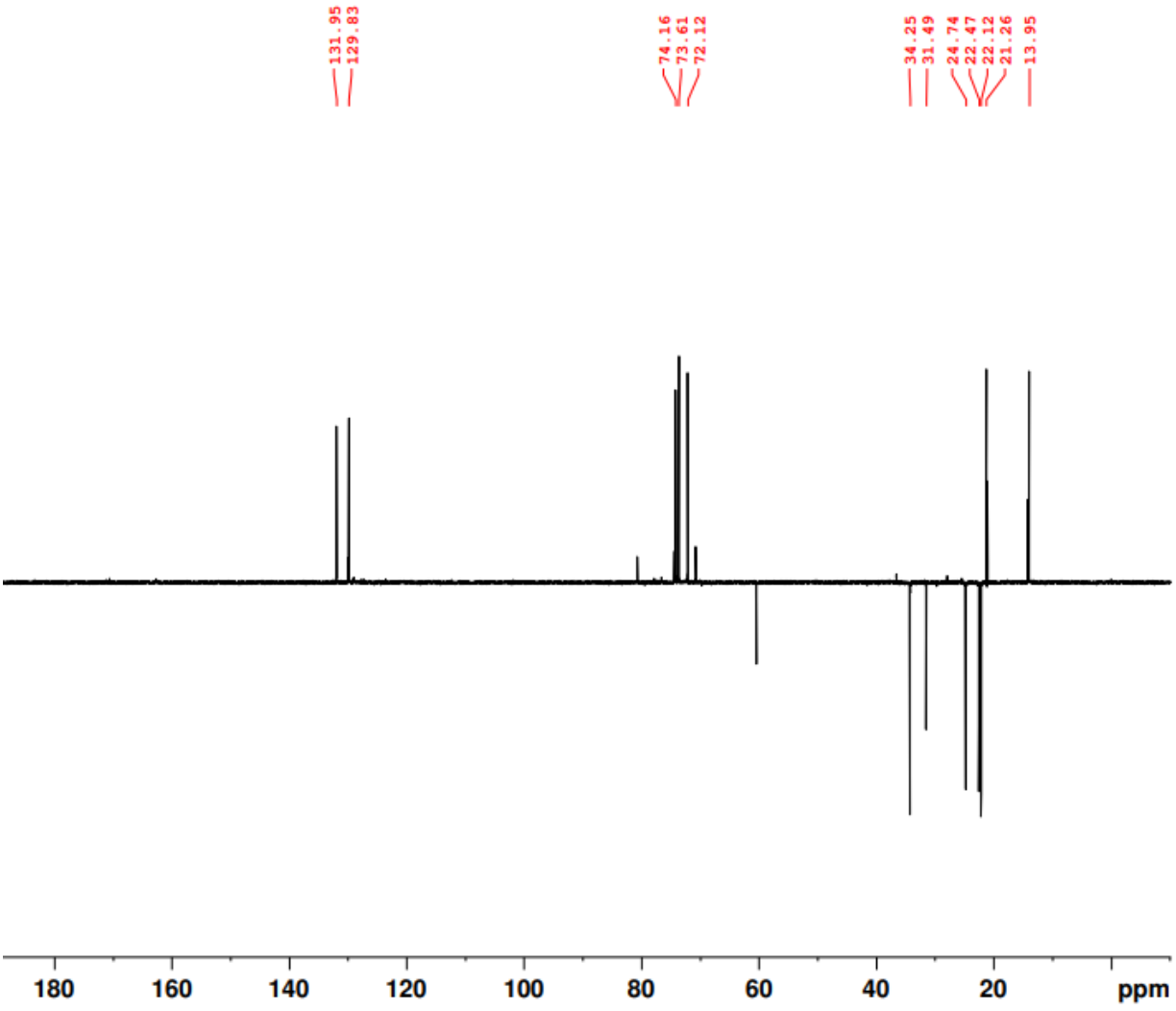


Figure A.3.43: DEPT 135 NMR (400 MHz $CDCl_3$) of 3.47

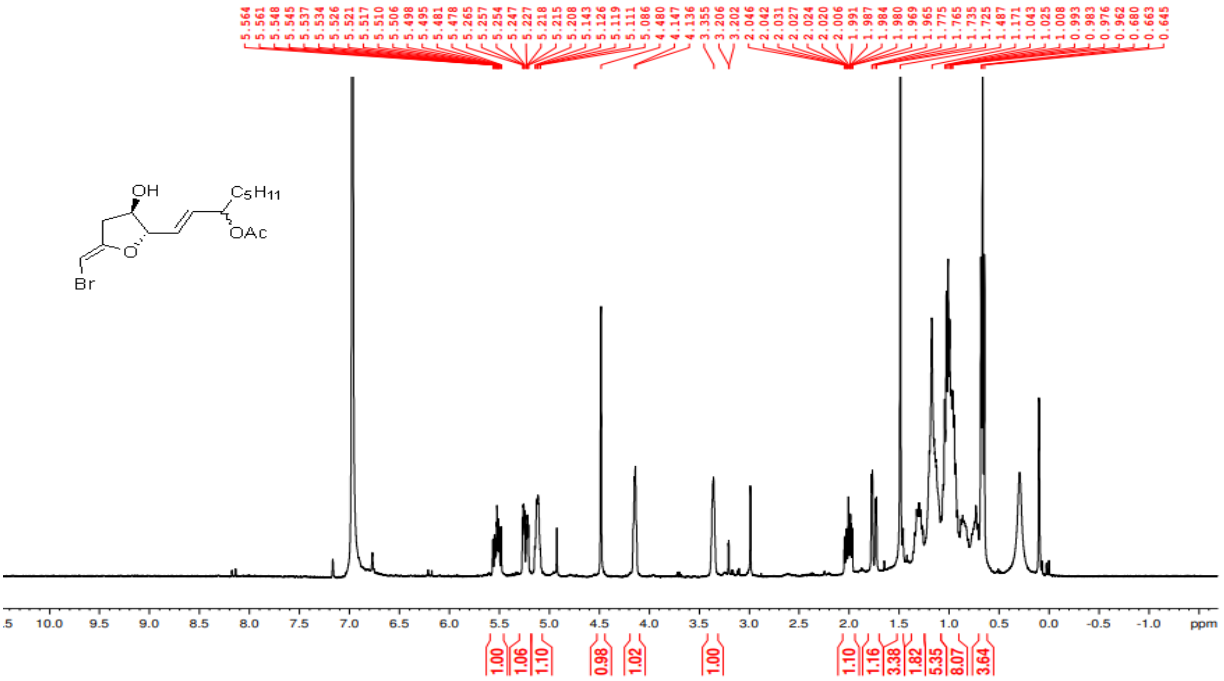


Figure A.3.44: ^{1}HNMR (400 MHz $CDCl_3$) of 3.44

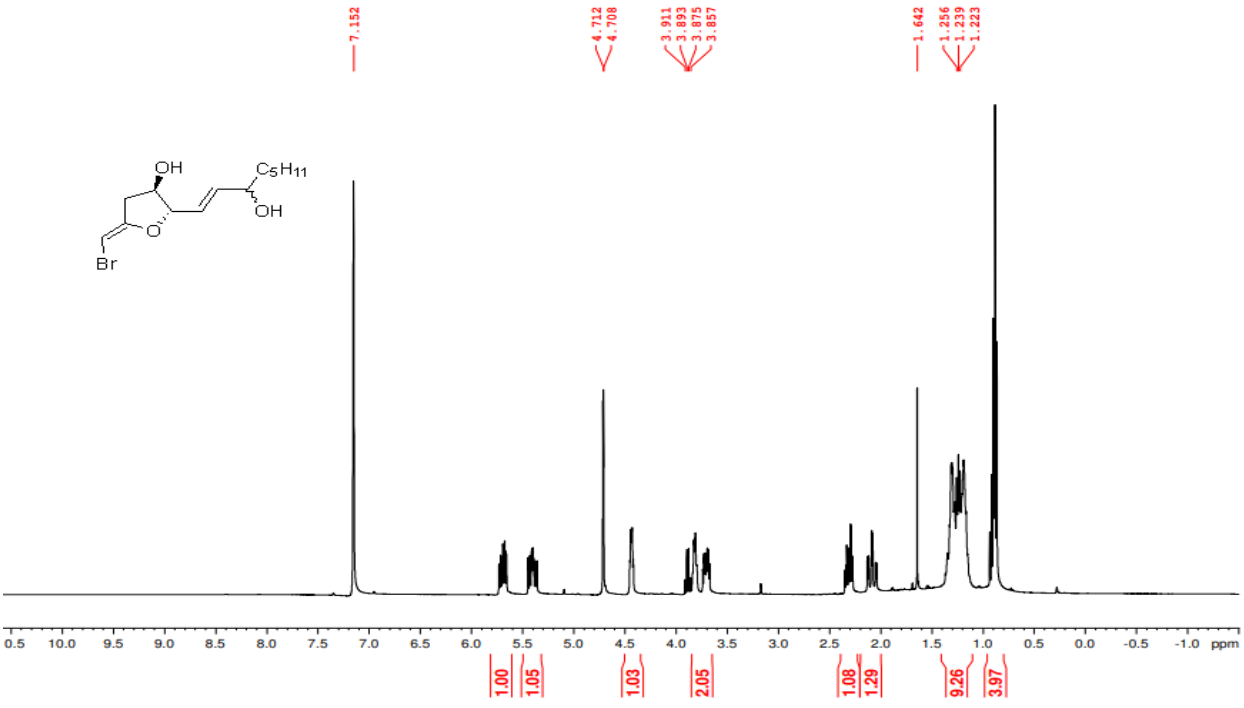


Figure A.3.45: ^{1}HNMR (400 MHz $CDCl_3$)

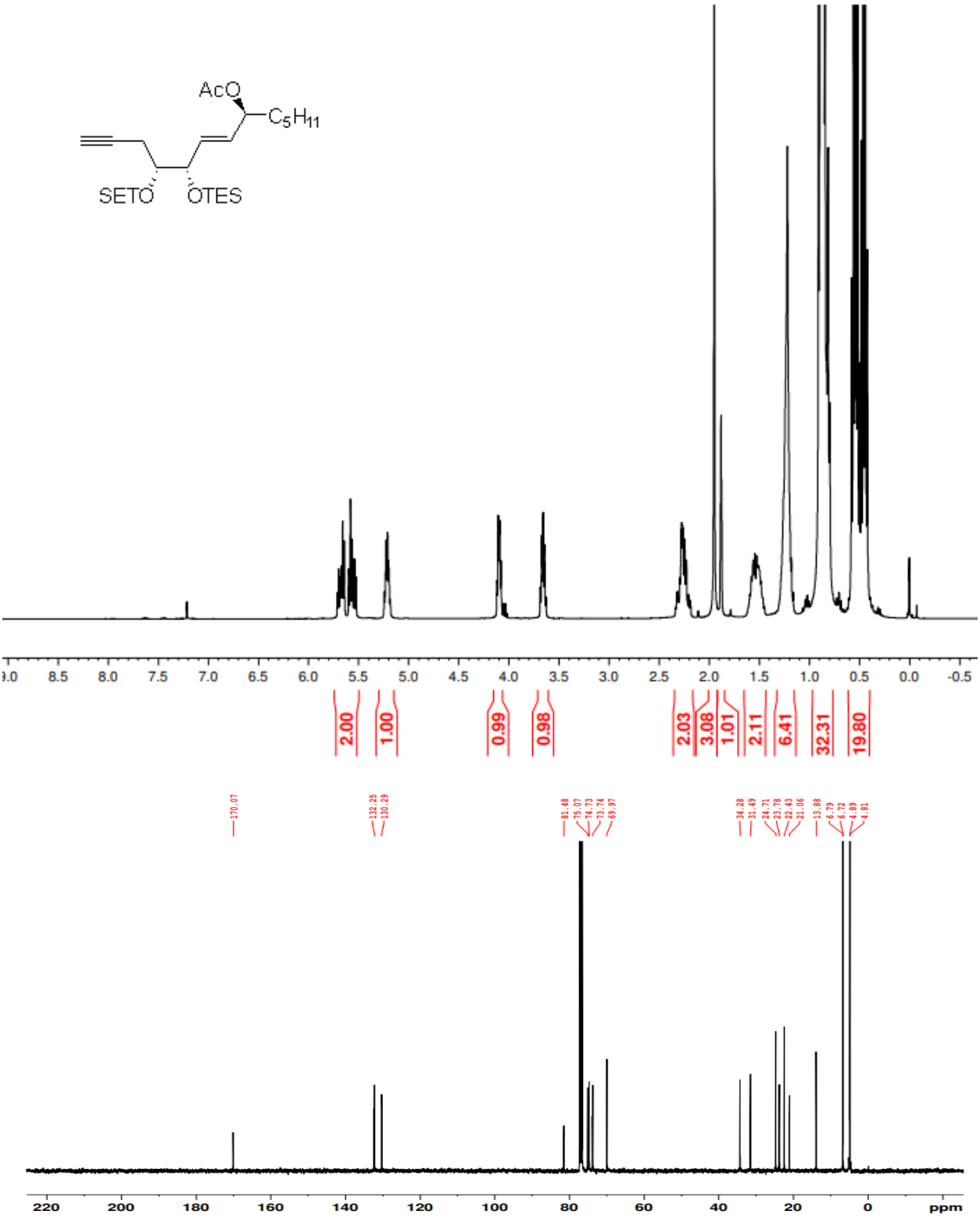


Figure A.3.46: ^{1}HNMR (400 MHz $CDCl_3$) and ^{13}CNMR (100 MHz, $CDCl_3$) of 3.48

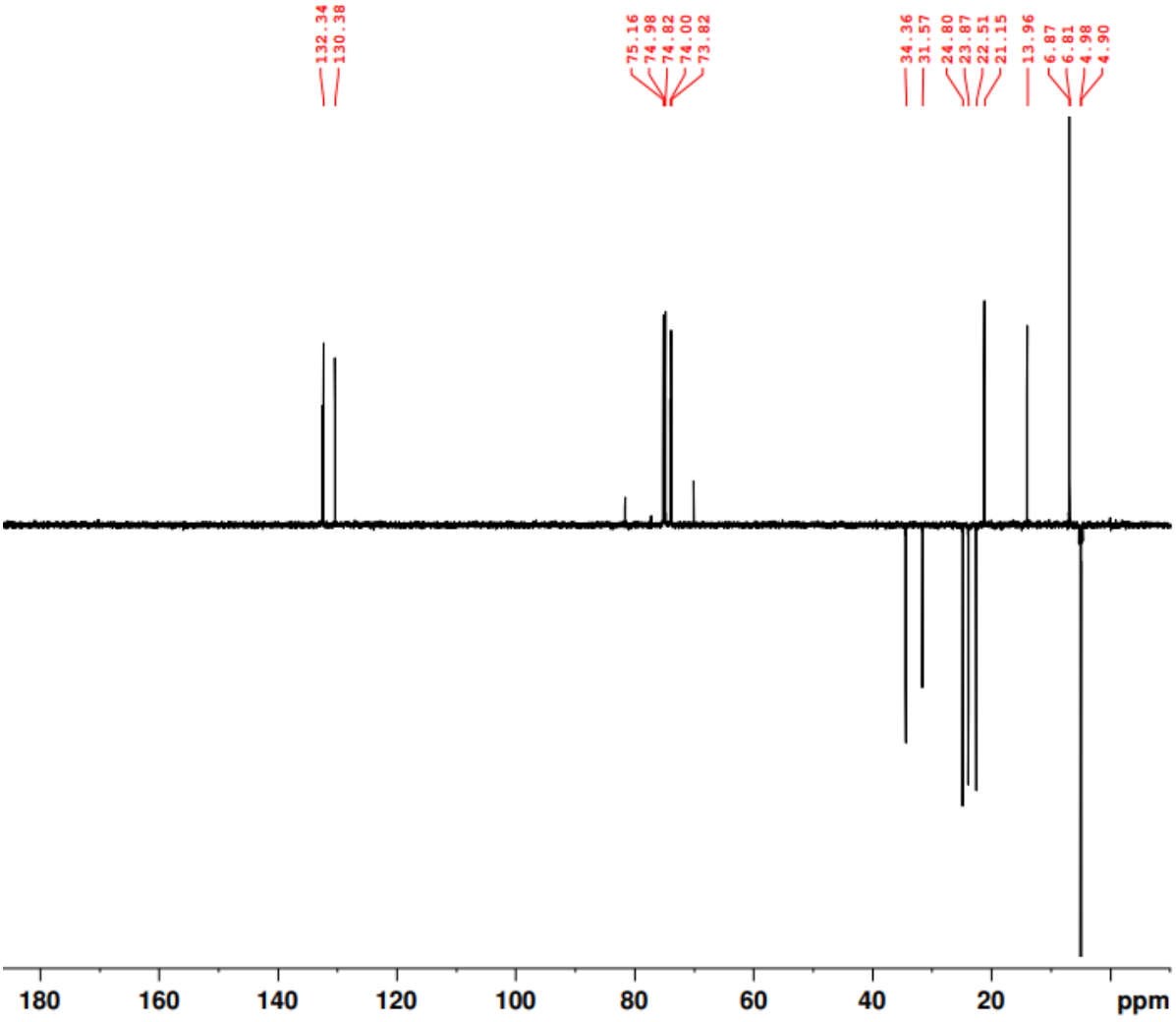


Figure A.3.47:DEPT 135 NMR (400 MHz $CDCl_3$) of 3.48

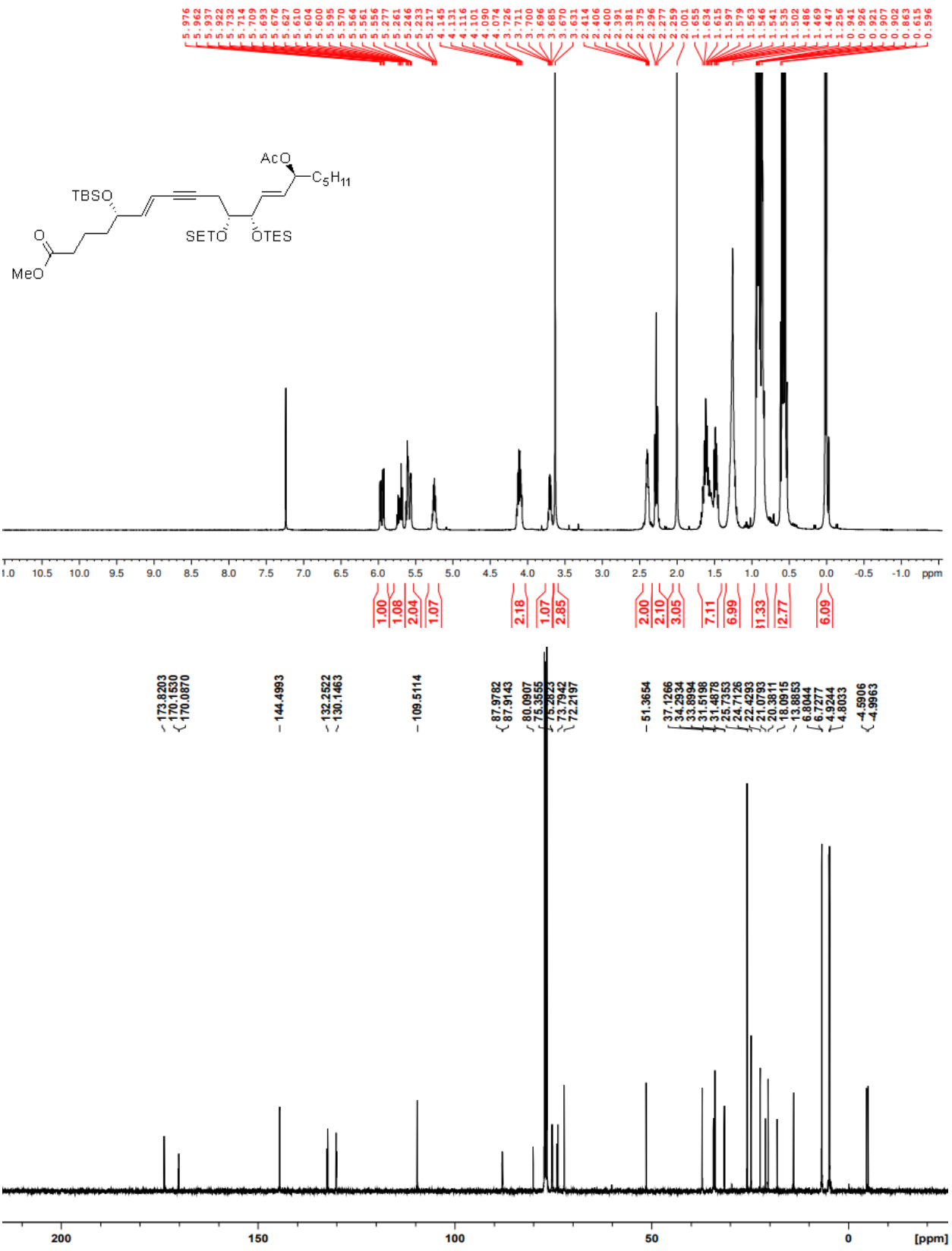


Figure A.3.48: ^{1}HNMR (400 MHz $CDCl_3$) and ^{13}CNMR (100 MHz, $CDCl_3$) of 3.49

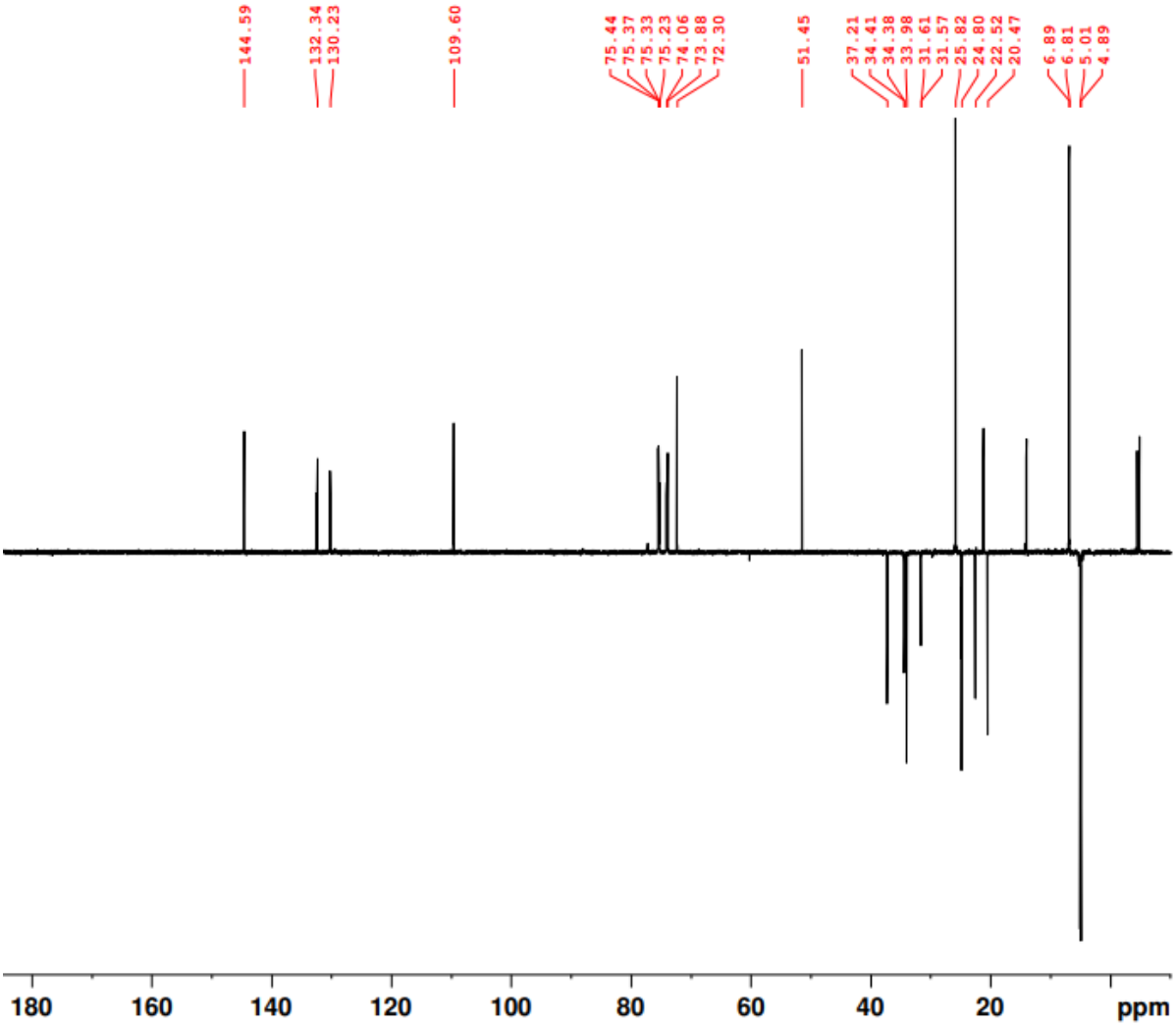


Figure A.3.49: DEPT 135 NMR (400 MHz $CDCl_3$) of 3.49

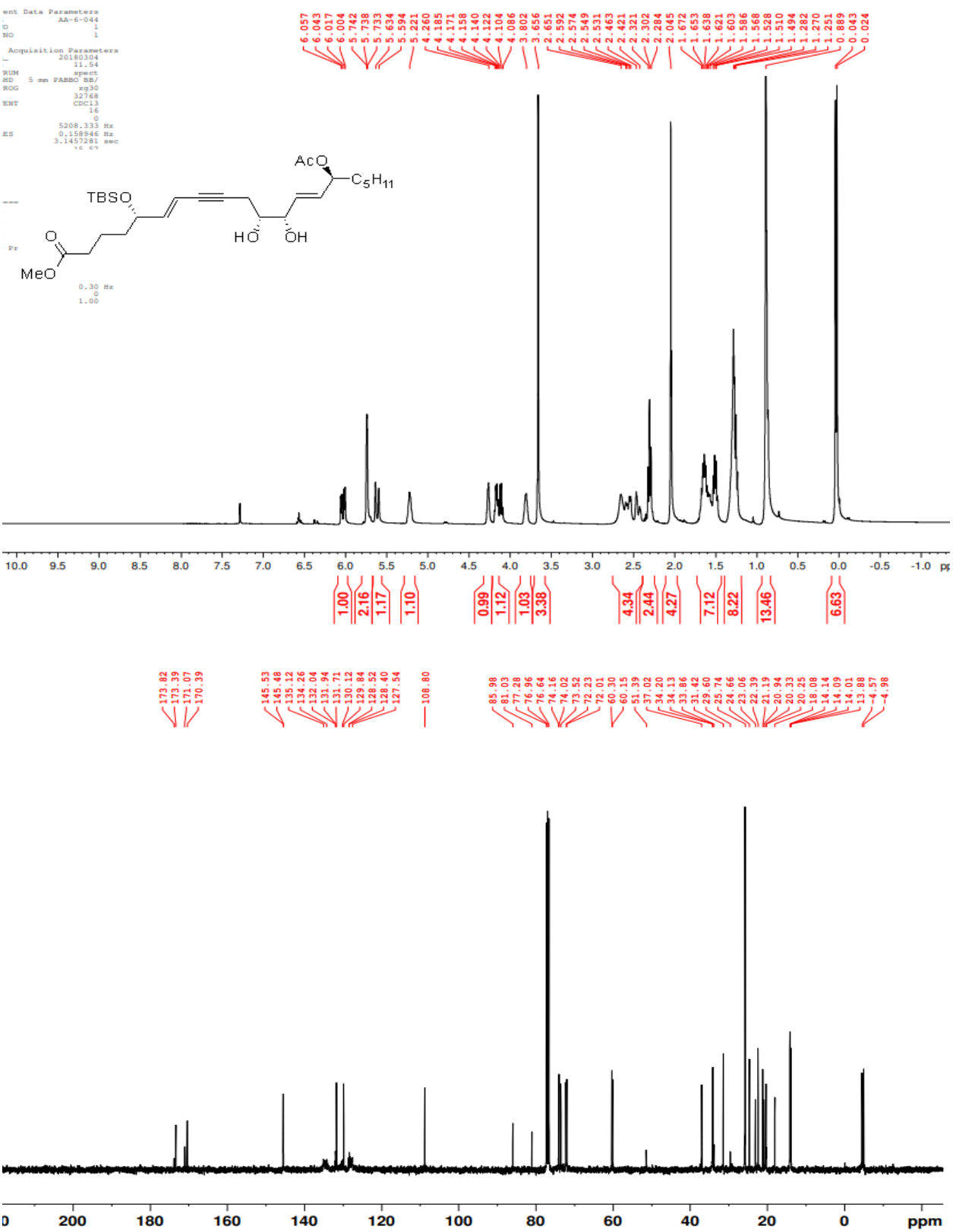


Figure A.3.50: ^{1}HNMR (400 MHz $CDCl_3$) and ^{13}CNMR (100 MHz, $CDCl_3$) of 3.50

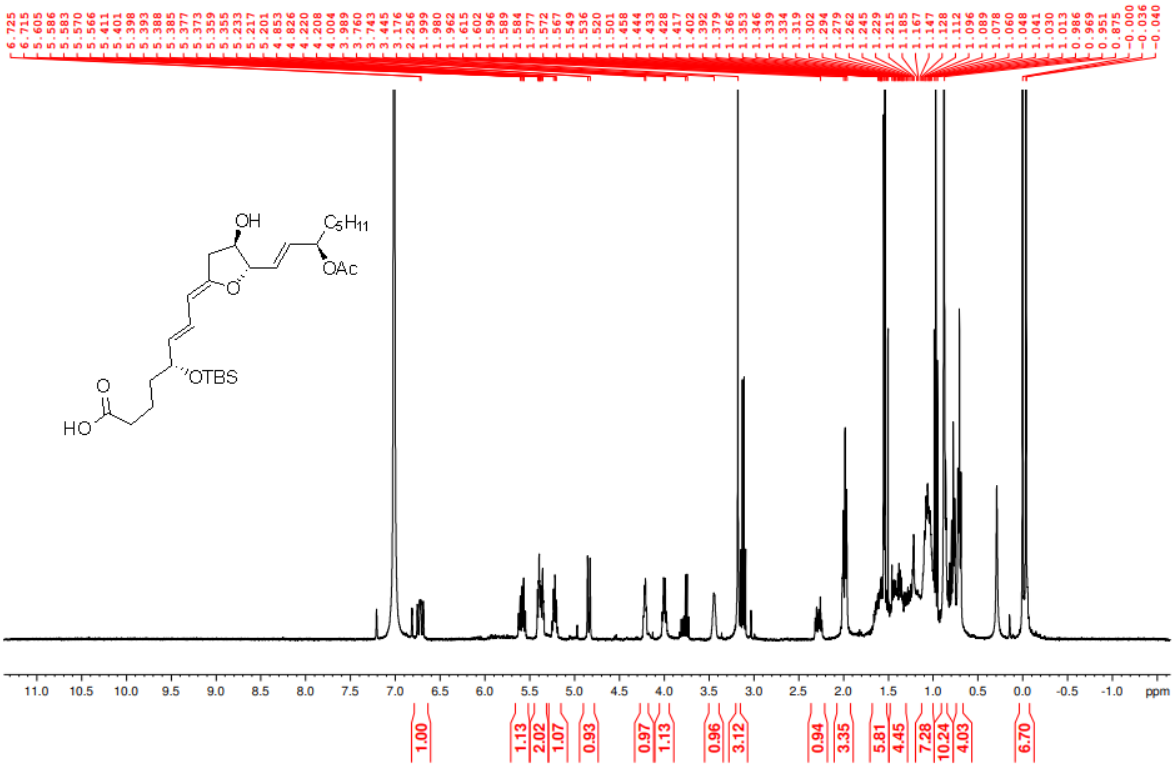


Figure A.3.51: ^{1}HNMR (400 MHz $CDCl_3$) of 3.51

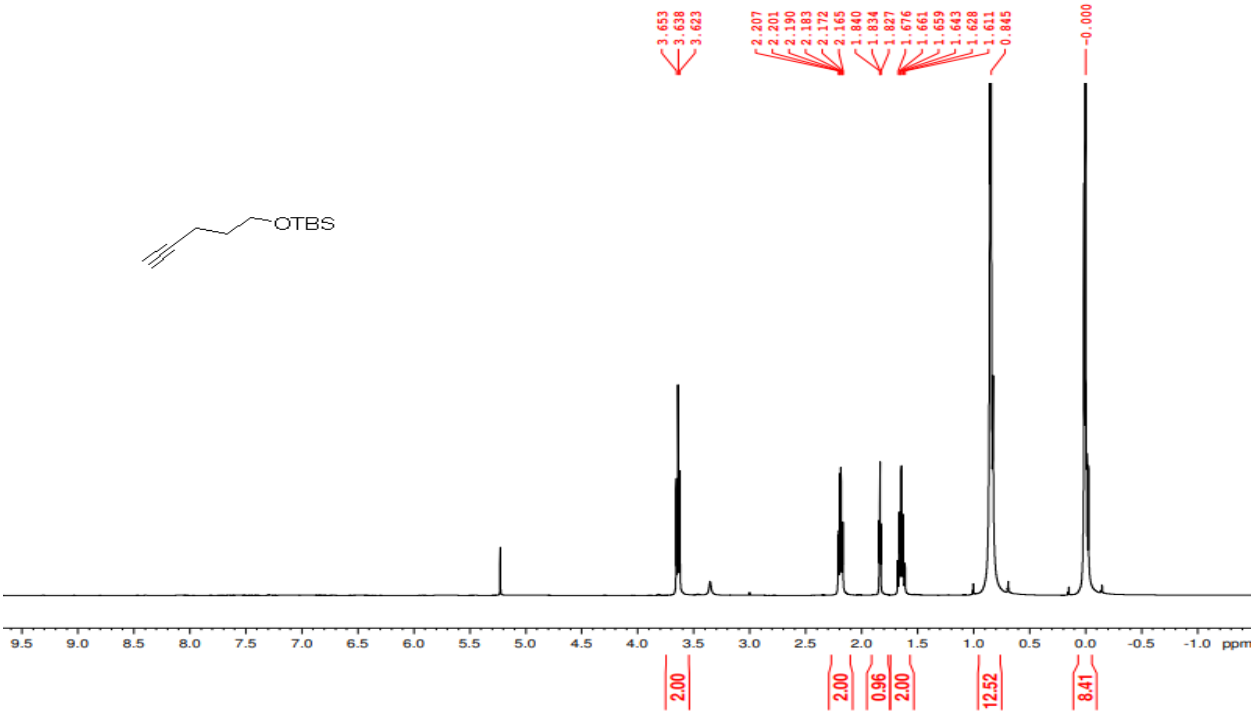


FIGURE A.3.52: ^{1}HNMR (400 MHZ $CDCL_3$) OF 3.52

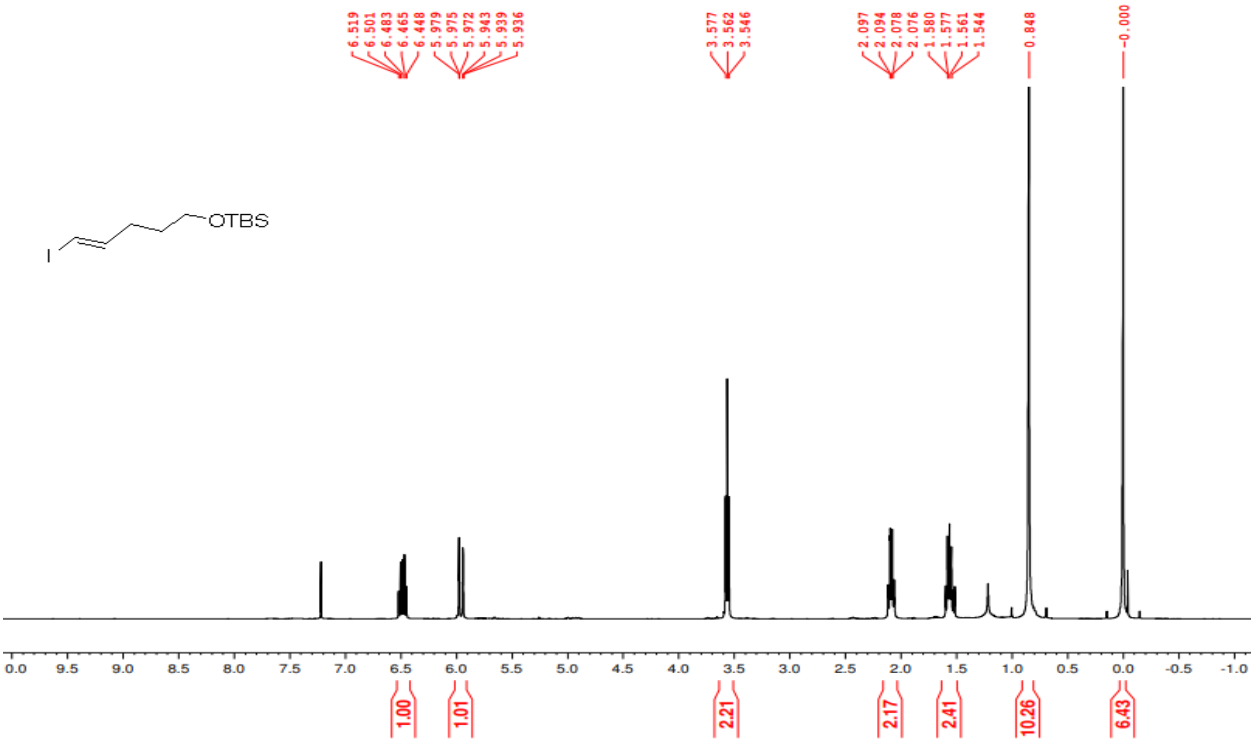


Figure A.3.53: ^{1}HNMR (400 MHz $CDCl_3$) of 3.53

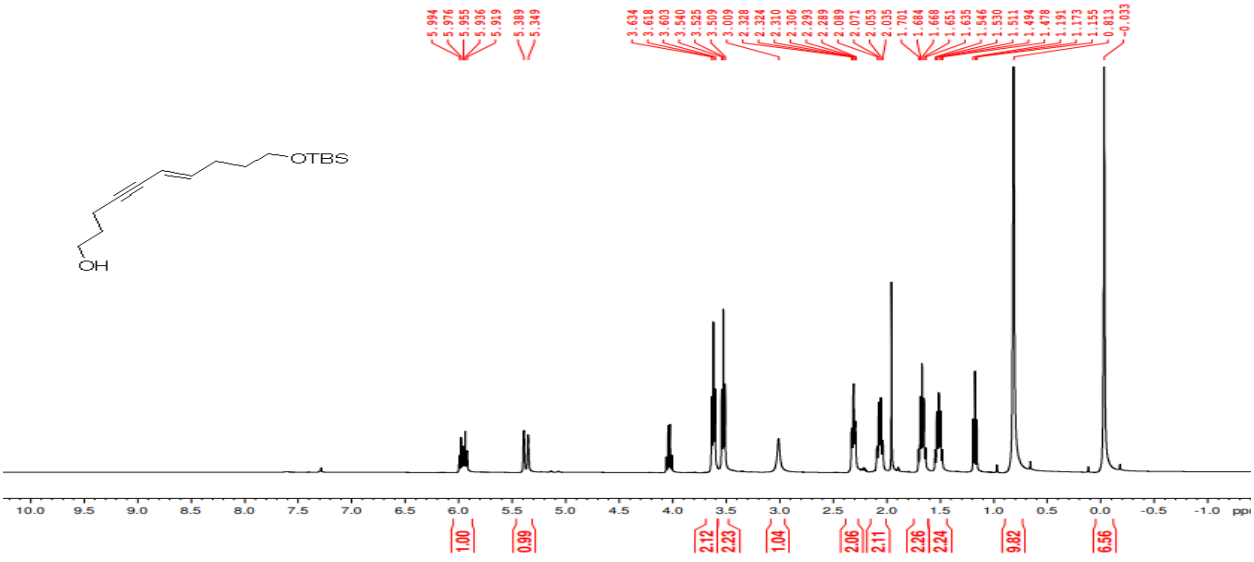


Figure A.3.54: ^{1}HNMR (400 MHz $CDCl_3$) of 3.54

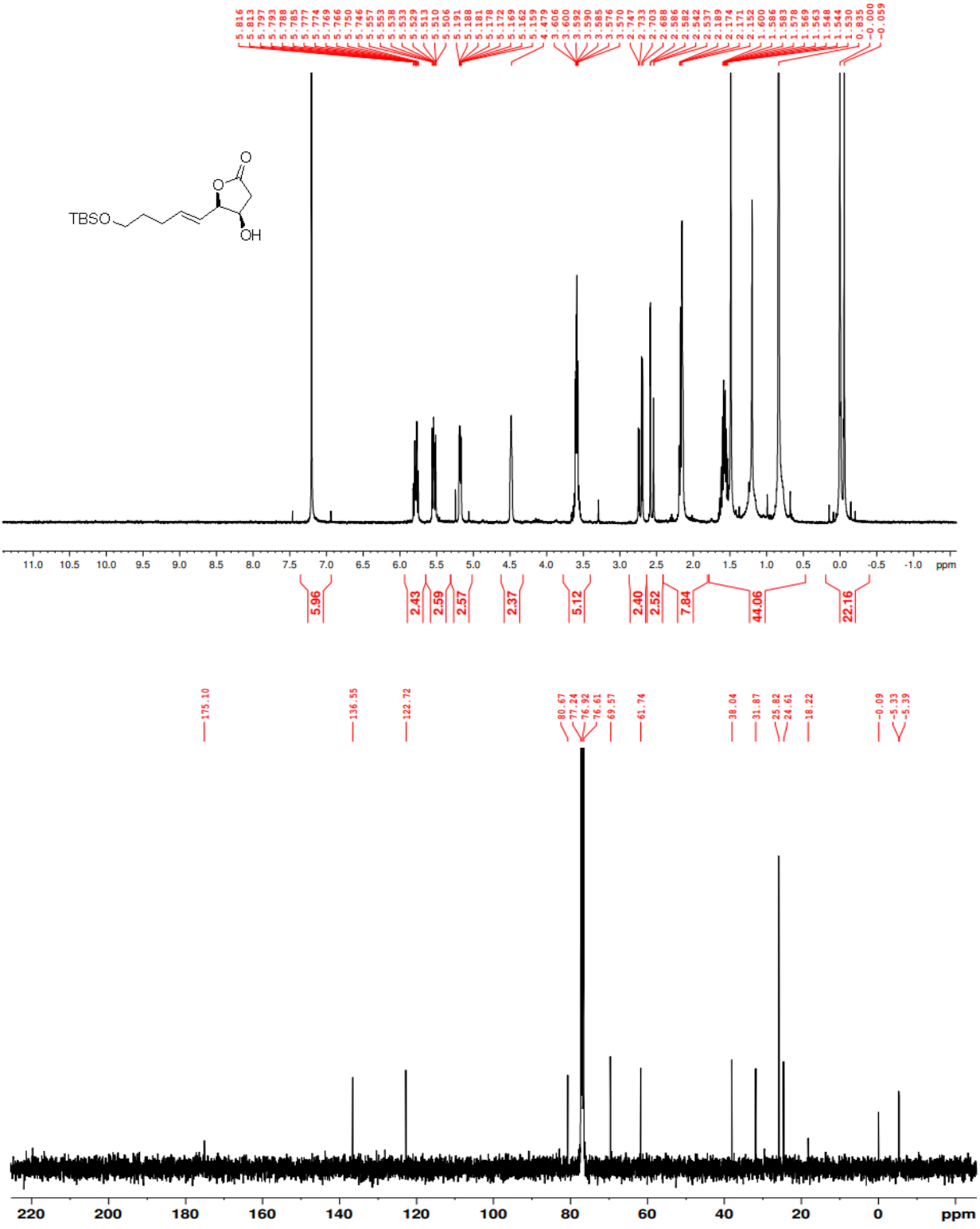


Figure A.3.55: ^{1}HNMR (400 MHz $CDCl_3$) and ^{13}CNMR (100 MHz, $CDCl_3$) of 3.59

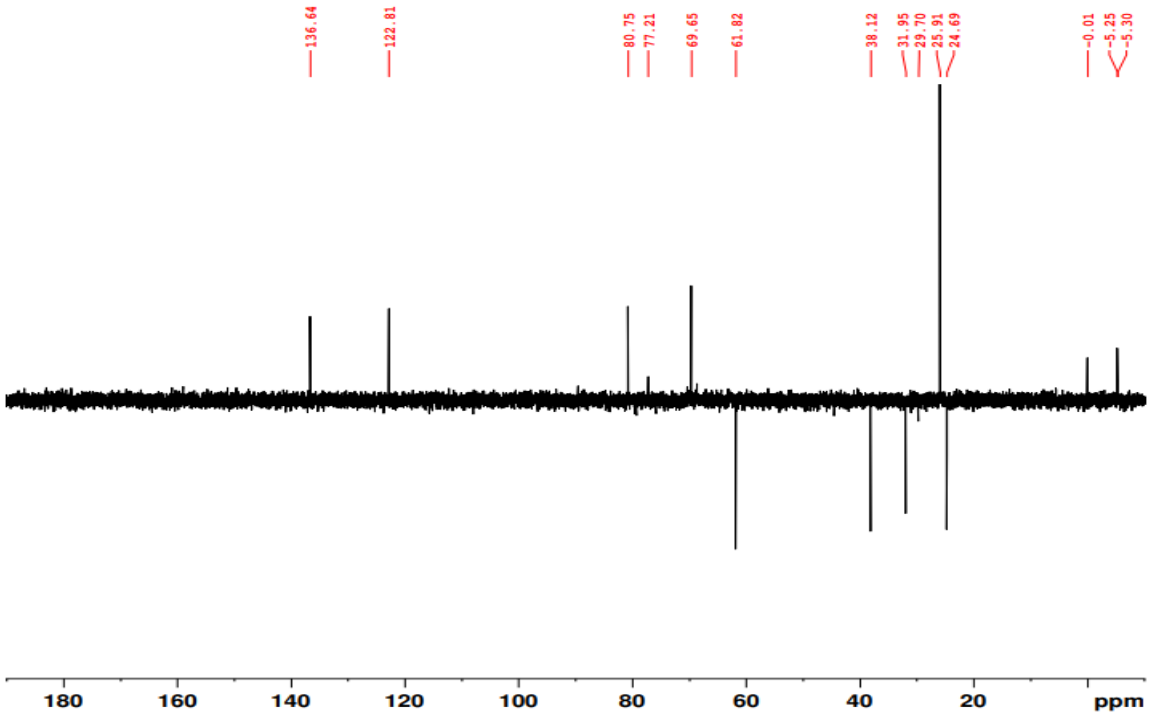


Figure A.3.56:DEPT 135 NMR (400 MHz $CDCl_3$) of 3.59

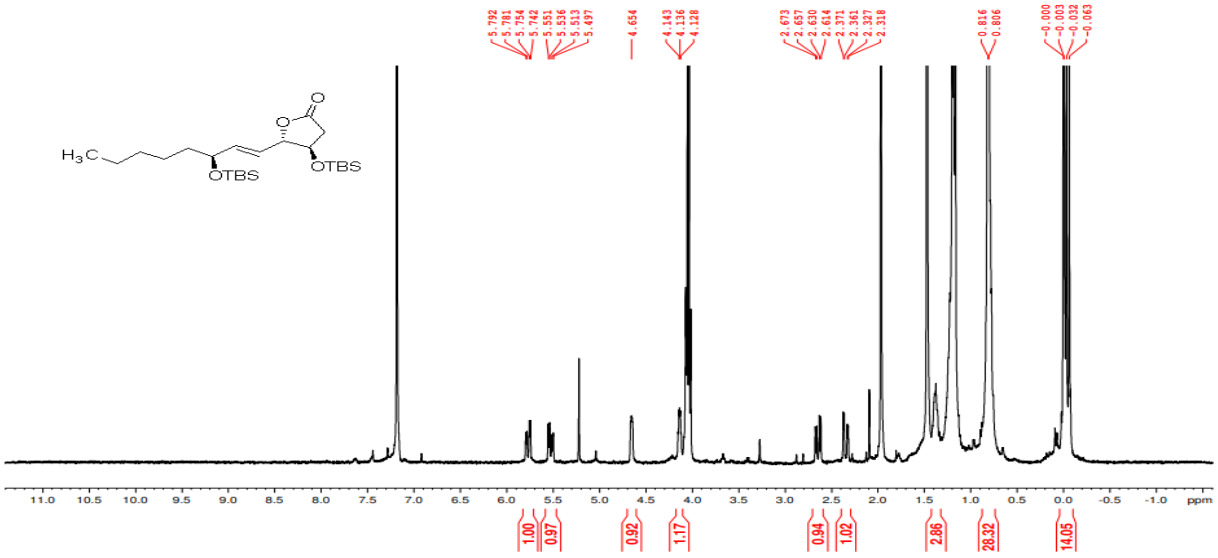


Figure A.3.57: ^{1}HNMR (400 MHz $CDCl_3$) of 3.58

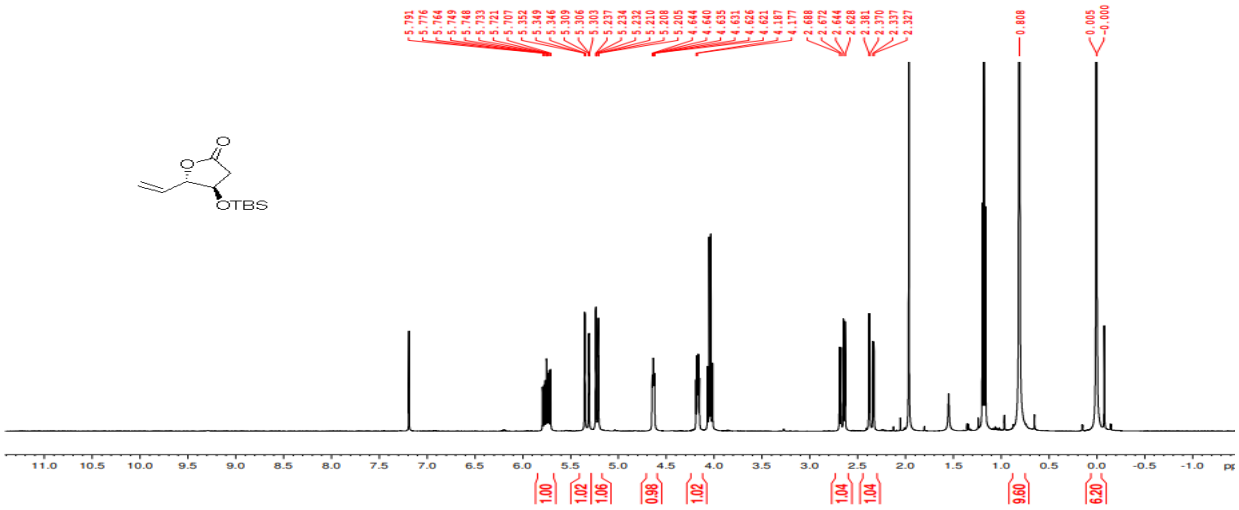


Figure A.3.58: ^{1}HNMR (400 MHz $CDCl_3$) of 3.57

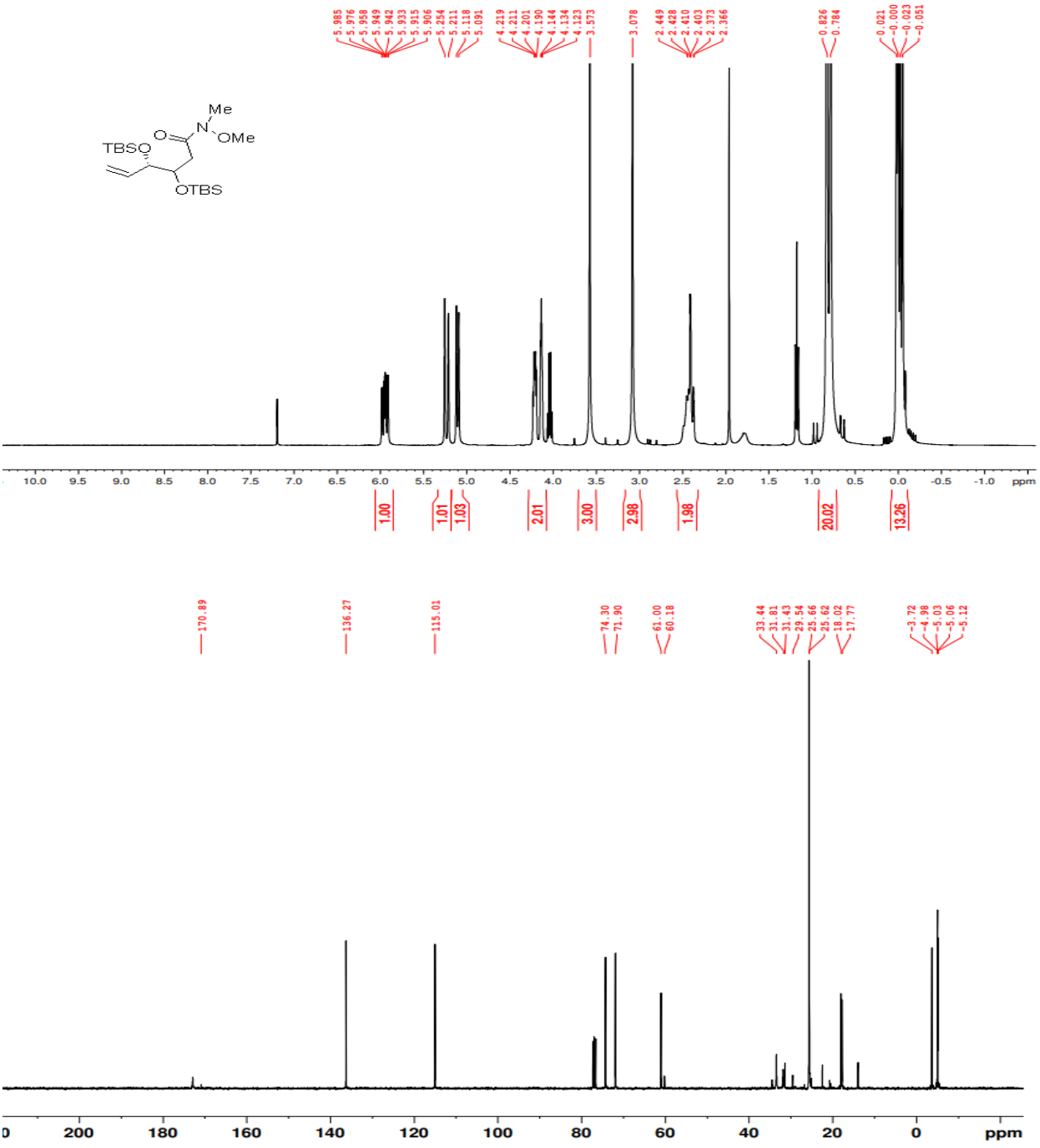


Figure A.3.59: ^{1}HNMR (400 MHz $CDCl_3$) and ^{13}CNMR (100 MHz, $CDCl_3$) of 3.61

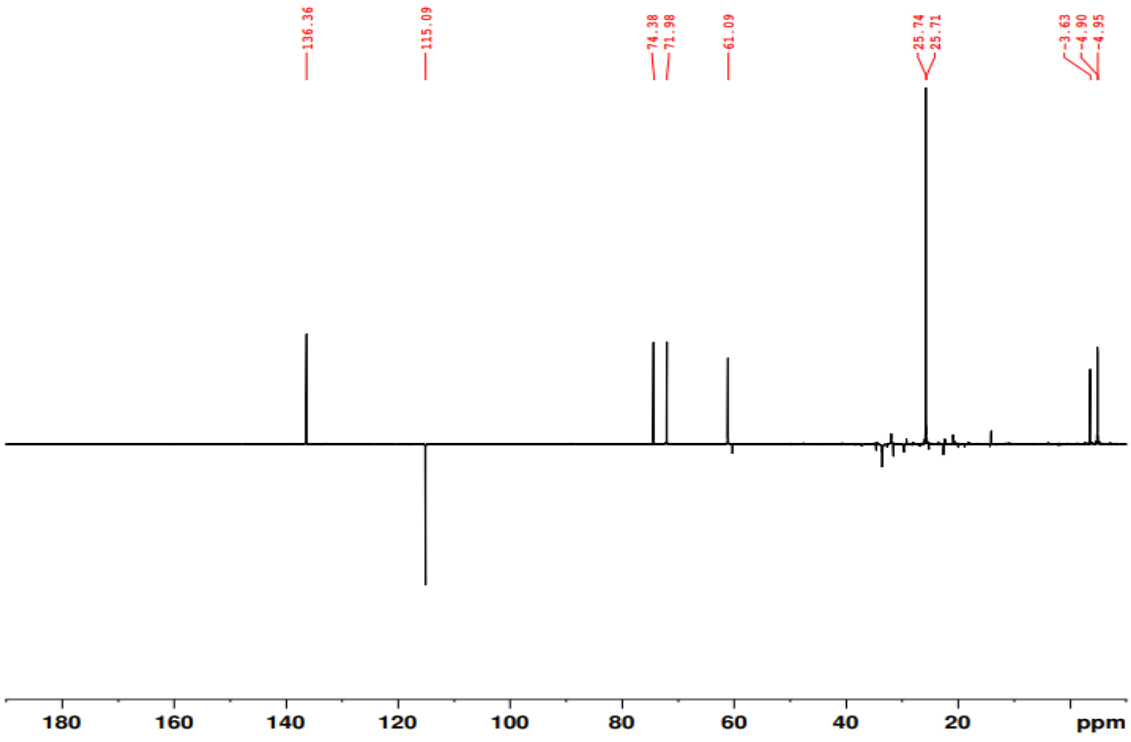


Figure A.3.60:DEPT 135 NMR (400 MHz $CDCl_3$) of 3.61

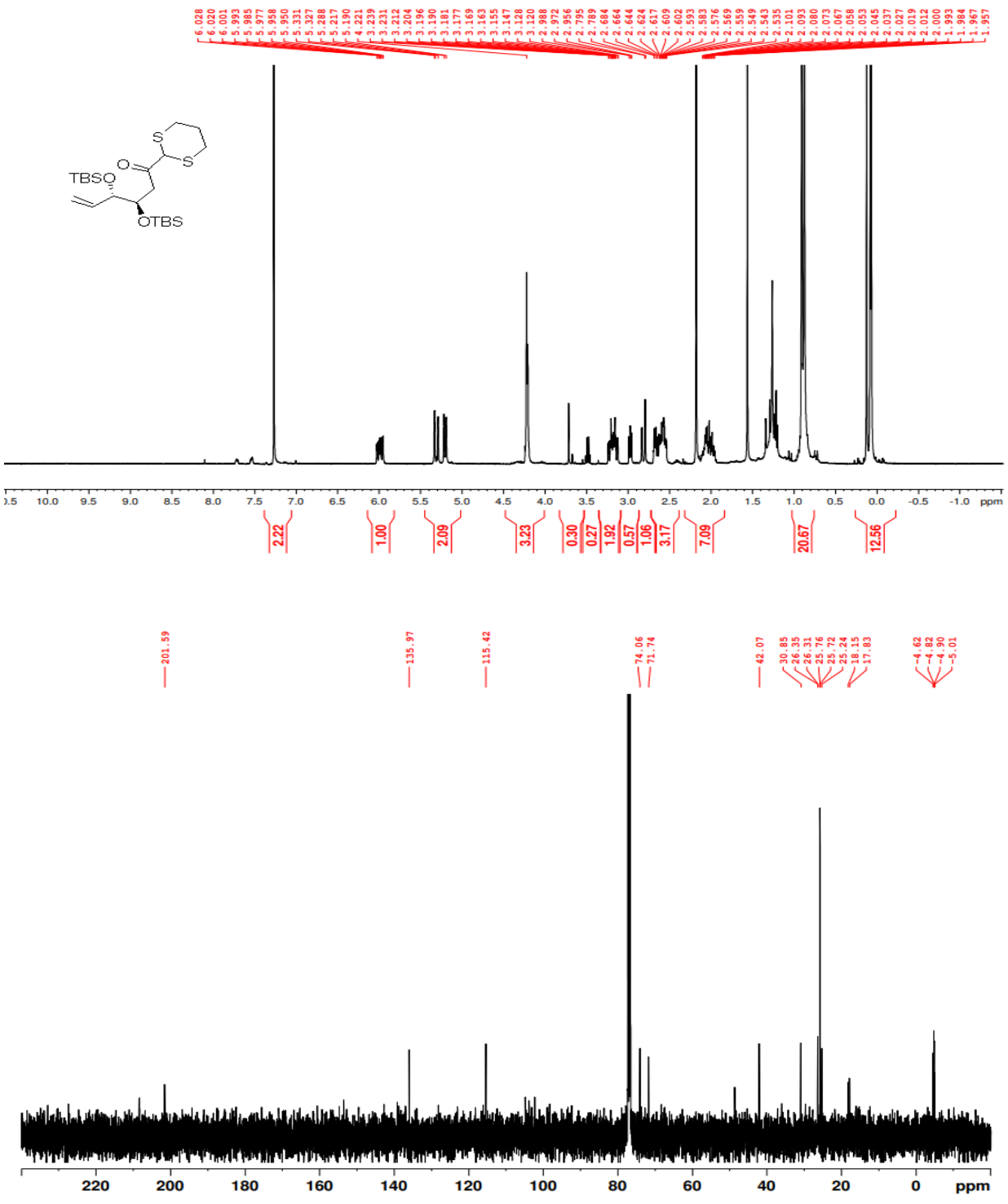


Figure A.3.61: ^{1}HNMR (400 MHz $CDCl_3$) and ^{13}CNMR (100 MHz, $CDCl_3$) of 3.62

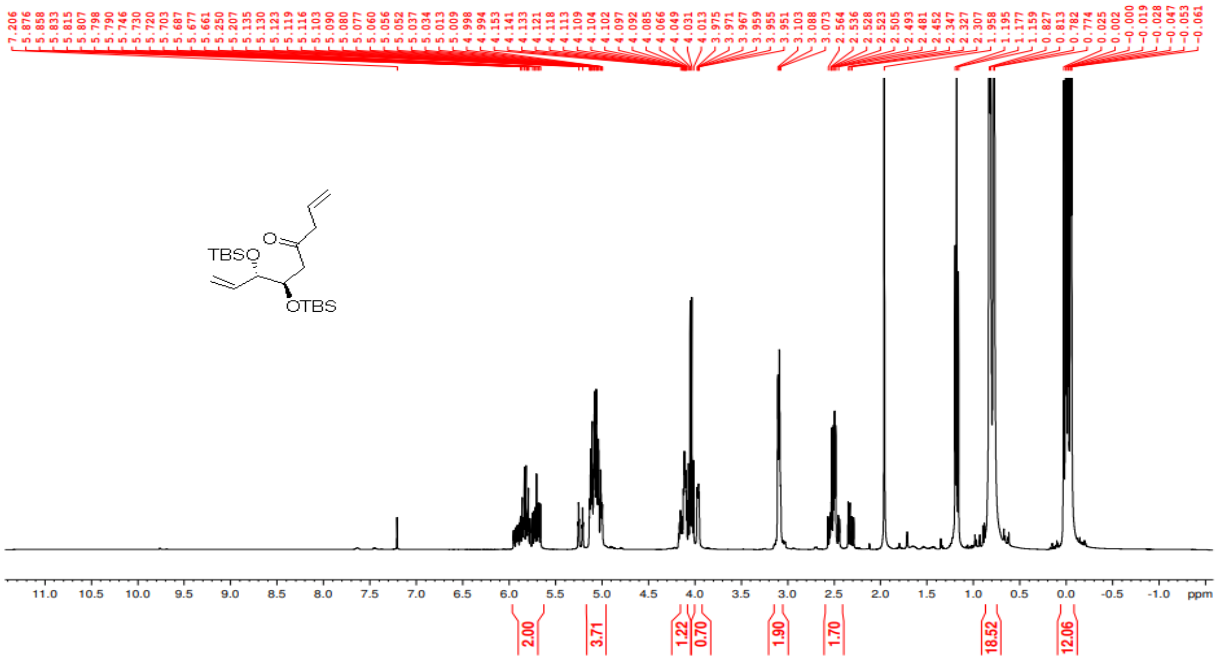


Figure A.3.62: ^{1}HNMR (400 MHz $CDCl_3$) of 3.63

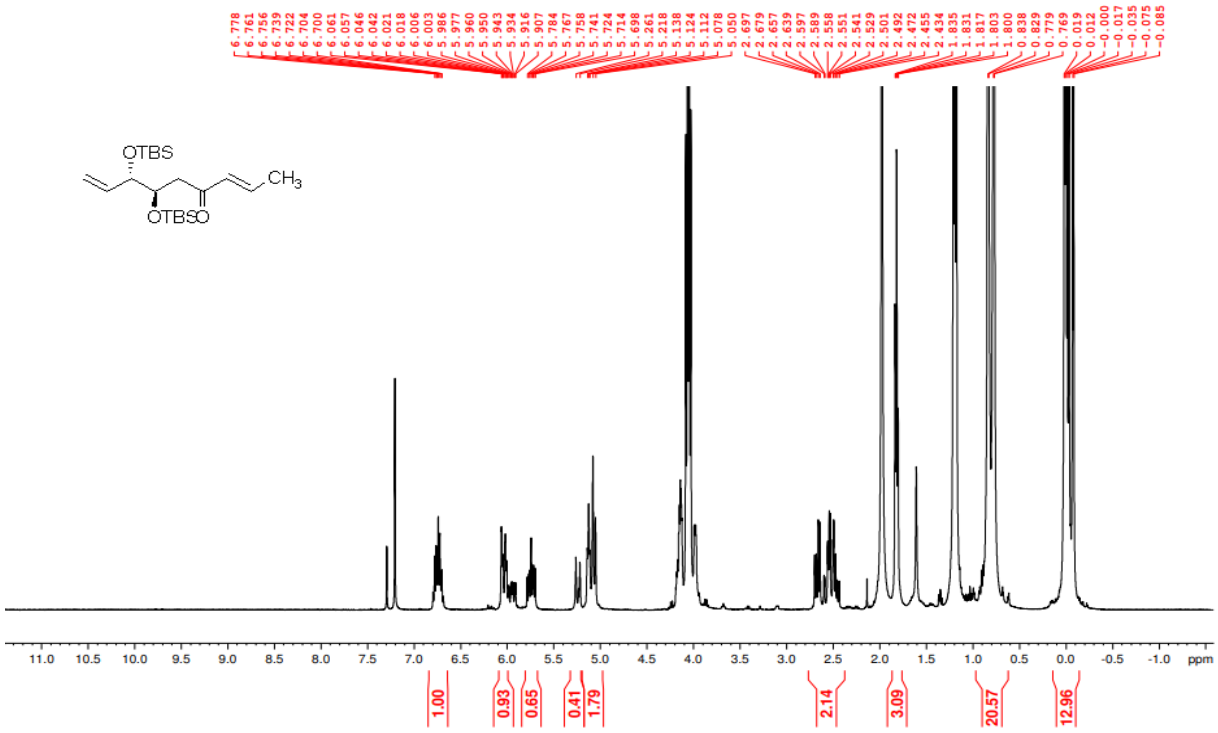


Figure A.3.63: ^{1}HNMR (400 MHz $CDCl_3$) of Enone 3.64

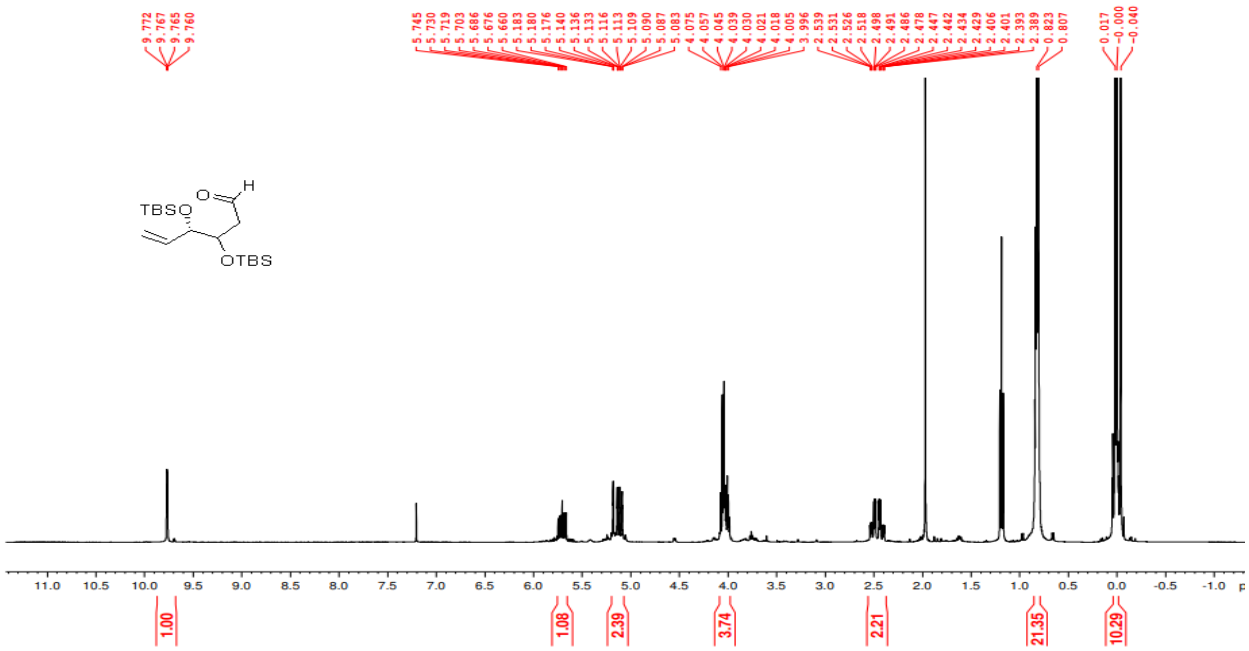


Figure A.3.64: ^{1}HNMR (400 MHz $CDCl_3$) of 3.65

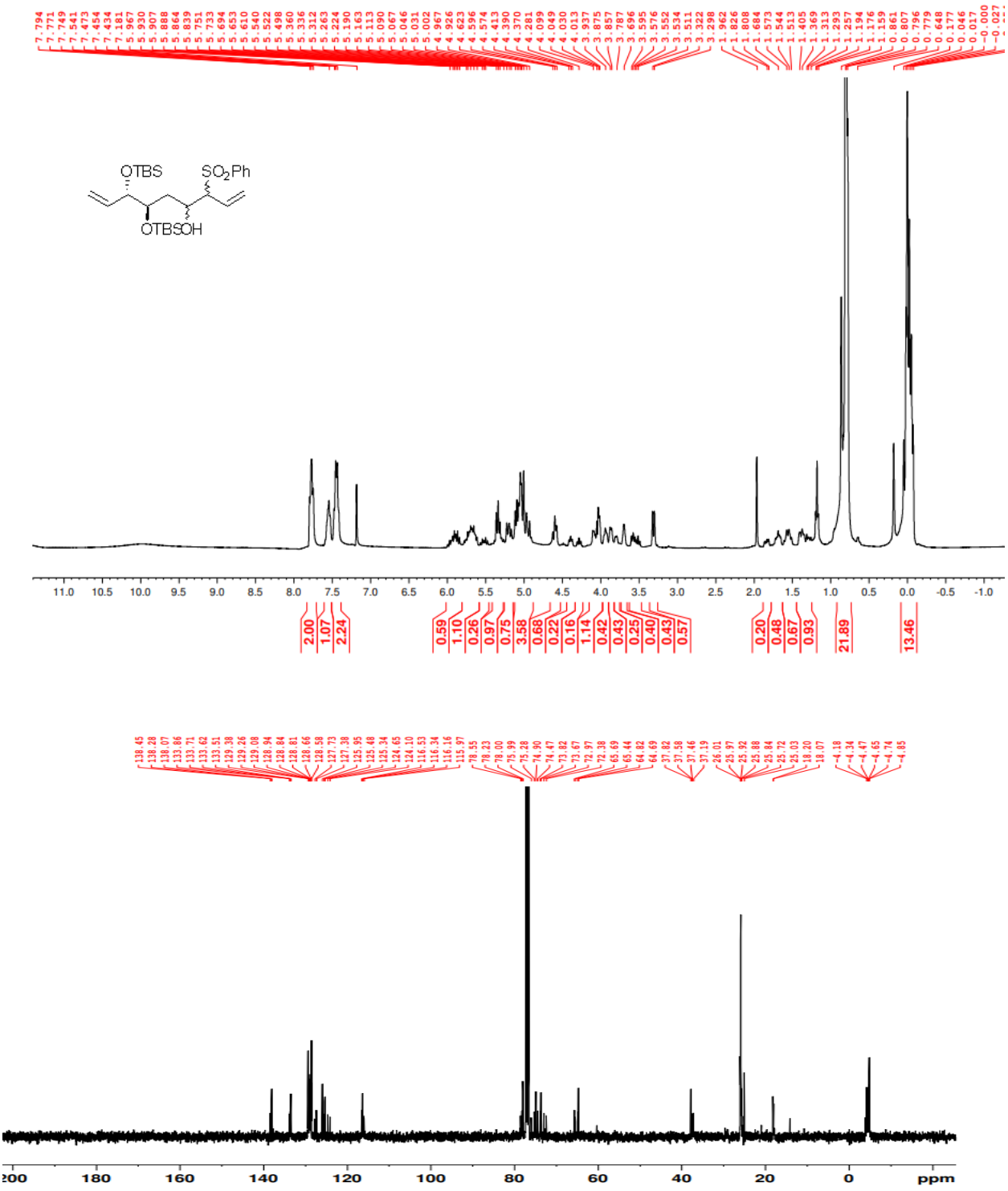


Figure A.3.65: ^{1}HNMR (400 MHz $CDCl_3$) and ^{13}CNMR (100 MHz, $CDCl_3$) of 3.66

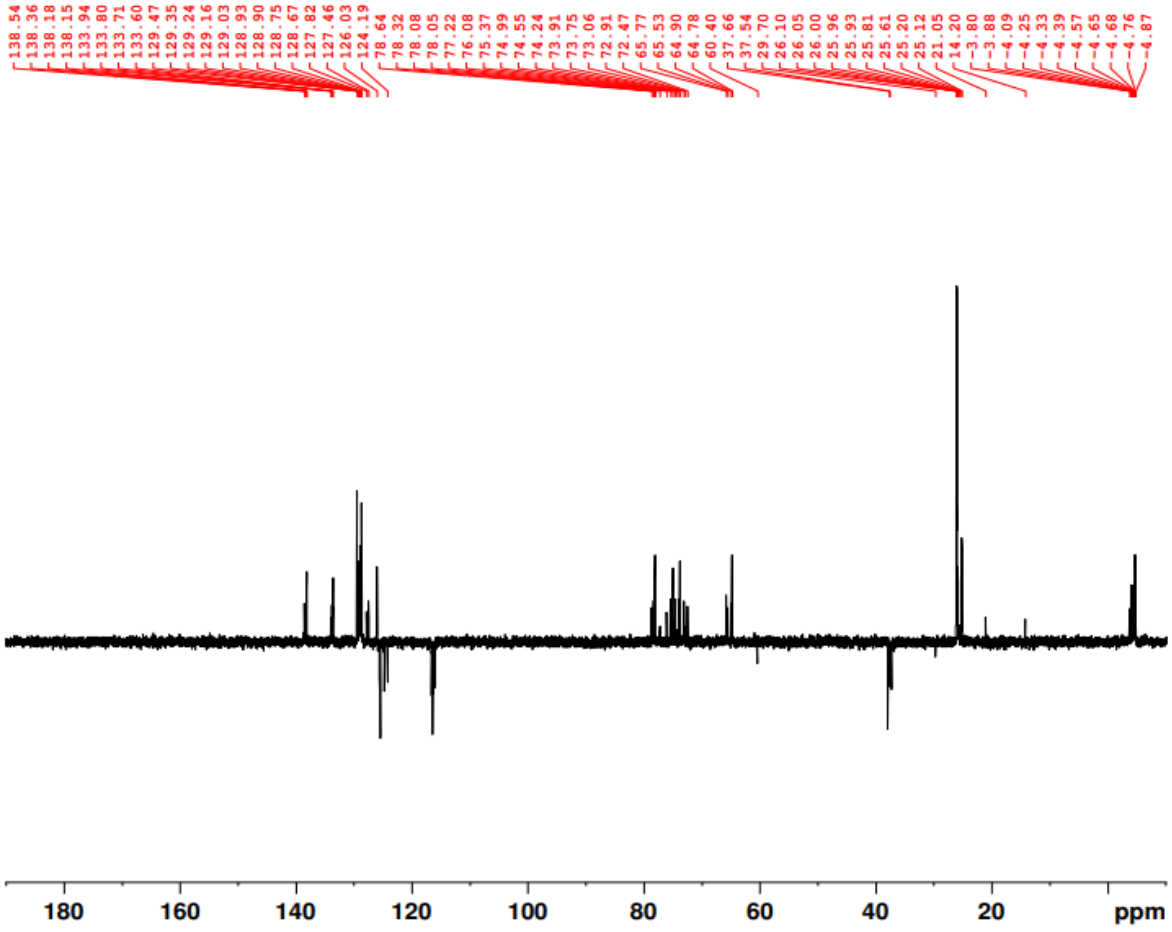


Figure A.3.66: DEPT 135 NMR (400 MHz $CDCl_3$) of 3.66

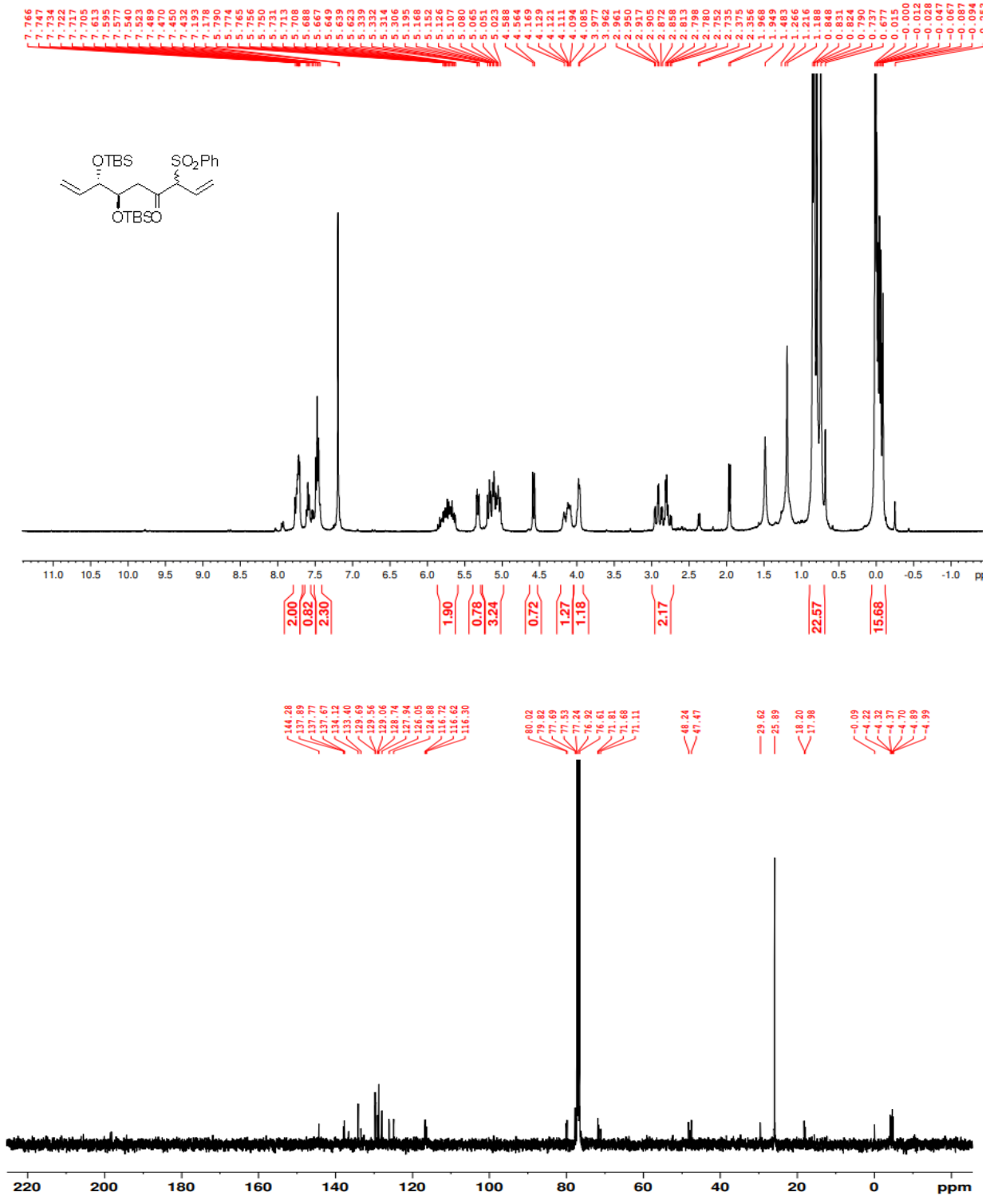


Figure A.3.67: ^{1}HNMR (400 MHz $CDCl_3$) and ^{13}CNMR (100 MHz, $CDCl_3$) of 3.67

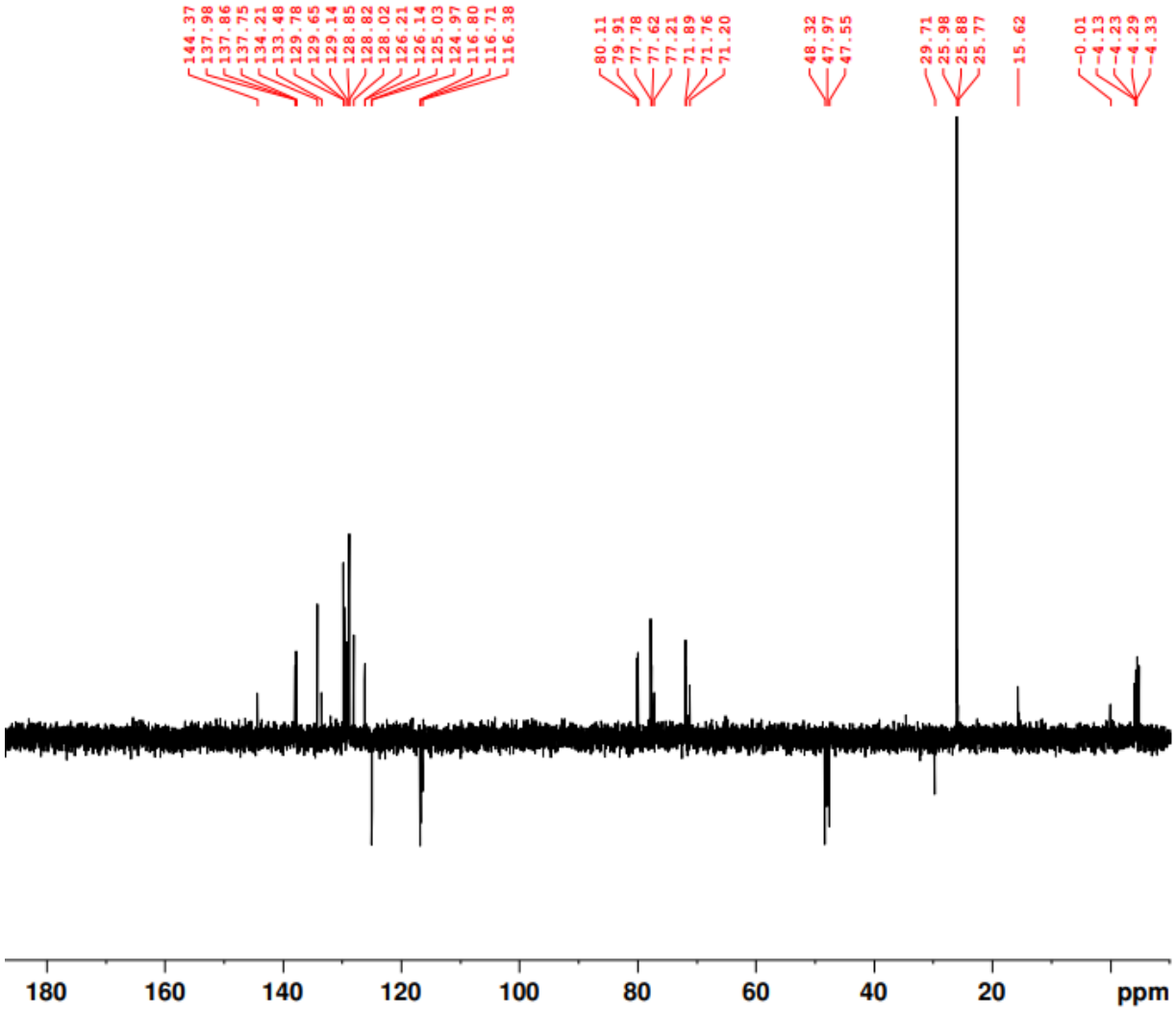


Figure A.3.68: DEPT 135 NMR (400 MHz $CDCl_3$) of 3.67

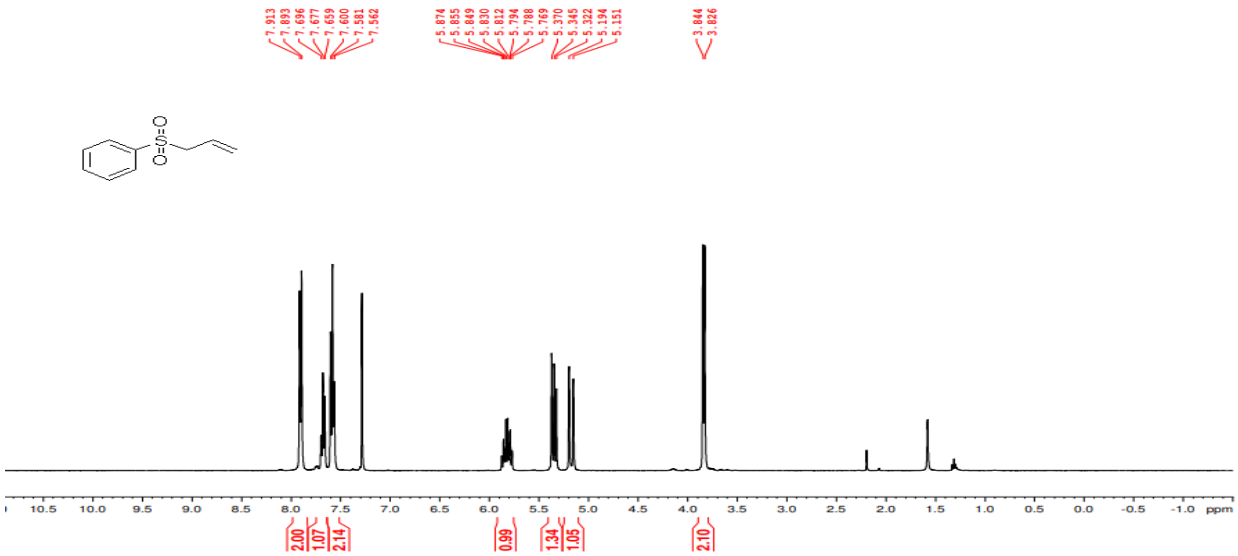


Figure A.3.69: ^{1}HNMR (400 MHz $CDCl_3$) of Allyl Sulfone

Chapter 4: 5-Hydroxy Prostaglandins

4.1: Biosynthesis of 5-Hydroxy Prostaglandins

Upon examination of the crossover enzymatic pathway that produces hemiketals D_2 and E_2 a key unique feature, compared to prostaglandins D_2/E_2 is capture of an additional unit of oxygen. Intuitively the enzymatic pathway that would make sense would be for 5S-HETE as a substrate of COX-2 to yield 5-hydroxylated prostaglandin D_2 and E_2.

The biosynthetic pathways of COX and the cross over enzymatic pathway have previously been shown in Chapter 1, and are reshown here for ease of comparison as Figures 4.1 and Figure 4.2. Figure 4.3, shows the simplified enzymatic pathway, that does not capture the second unit of oxygen. Starting with the same initial oxidation by 5-LOX generating 5S-HETE, COX-2 abstracts the 13-pro-S hydrogen, and captures a unit of molecular oxygen resulting in radical, **4.1.** This radical undergoes 5-exo trig cyclization, followed by a second 5-exo trig closure resulting in the C-C bond between the C8 and C12 positions. Oxygen capture at the C15 position, and subsequent conversion of the peroxide into the alcohol results in the generation of 5-hydroxy PGH_2. Like PGH_2, 5-OH PGH_2 could be enzymatically converted into a variety of novel secondary metabolites, such as the 5-hydroxy prostaglandins. [17,27,81–85] Furthermore, like the hemiketals, human leukocytes activated by treatment of lipopolysaccharide, and calcium ionophore have been shown to produce the 5-hydroxy prostaglandins.[85]

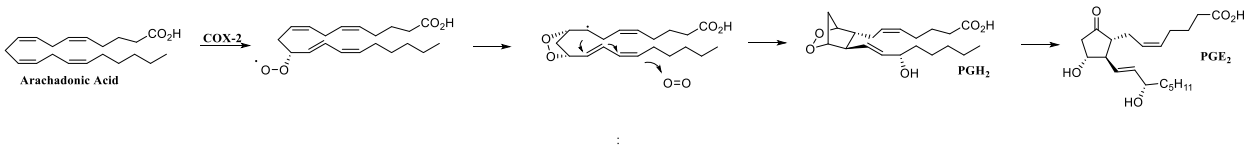


Figure 4.1 COX enzymatic pathway

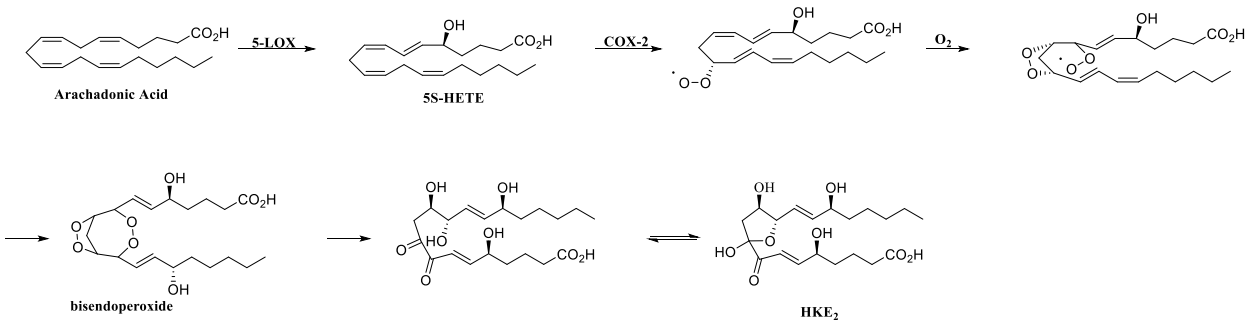


Figure 4.2: Crossover enzymatic pathway

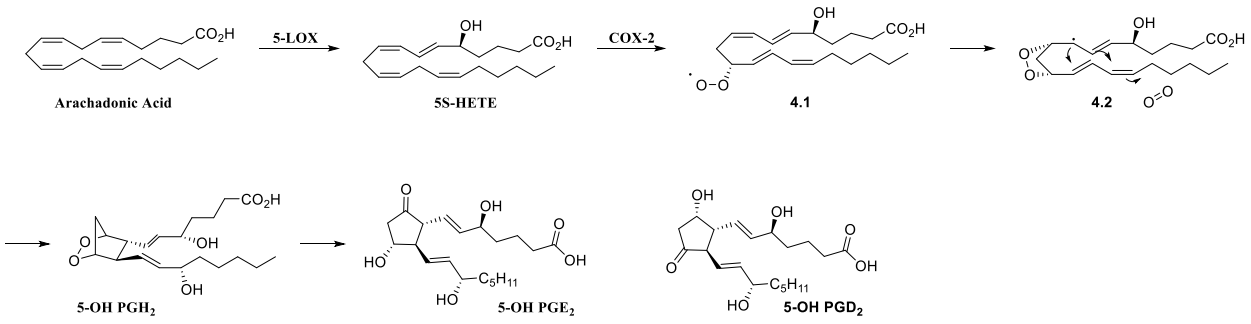
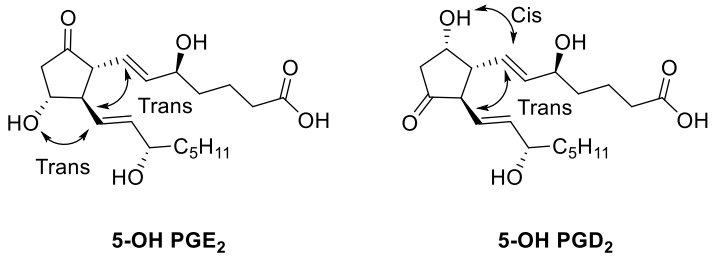


Figure 4.3: Biosynthesis of 5 hydroxy prostaglandins

4.2 Retrosynthetic Analysis of 5-OH Prostaglandins

The differences between 5-hydroxy PGE_2 and PGD_2 is the relationship around the cyclopentenone ring, and the oxidation states of the C9 and C11 carbons. 5-Hydroxy PGE_2 has a trans, trans, relationship while 5 Hydroxy PGD_2 has a cis trans relationship (Figure 4.4). Historically, trans, trans relative stereochemistry is well studied and can be set through implementation of cuprate chemistry (as summarized in Chapter 2).[39,86] Methodology to generate the cis, trans relationship of 5-OH PGD_2 is still not well developed, and PGD_2 syntheses usually rely on selective reduction of the C9 carbonyl to set this cis trans stereochemical relationship.[39] Further, differences would be the oxidation state at the C-9 and C-11 carbons which are inverted in the respective prostanoids.



5-OH PGE_2 **5-OH PGD_2**

Figure 4.4: Comparision between 5-hydroxy PGE_2 and PGD_2

Starting from 5-OH PGE_2 we opted to take an approach similar to that of Johnson's synthesis of PGE_1 methyl ester, as a two component coupling reaction (Figure 4.5).[40] Initial disconnection from the n-pentyl side-chain, utilizing a cuprate reaction generates necessary pieces, **4.3** and vinyl halide, **4.4**. **4.3**, could be disconnected at the diene resulting in α iodo cyclopentenone and vinyl metal **4.4** furnished through a cross coupling

(Stille or Suzuki). Finally, α Iodo compound can be made in 6 steps from cyclopentadiene.[37,40,43,87]

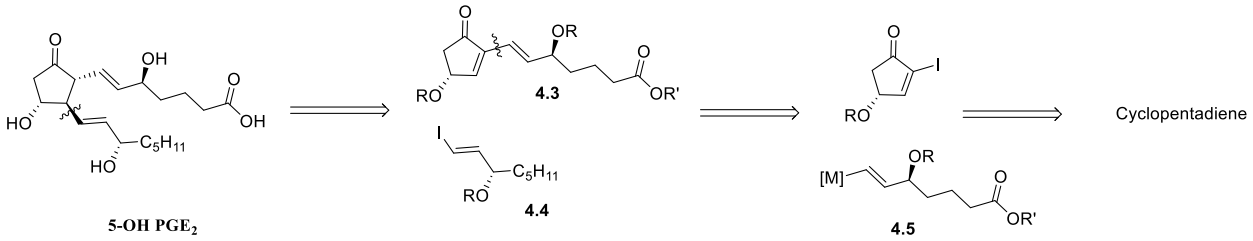


Figure 4.5: Retrosynthetic analysis of 5-OH PGE_2

Following Noyori's work, 5-OH PGD_2 can be mapped back to protected 5-OH PGE_2 as a series of functional group manipulations (Figure 4.6).[39] At this late stage intermediate previous logic prevails and we can disconnect to the three main building blocks, vinyl halide **4.44,** vinyl metal **4.5**, and α iodo compound.

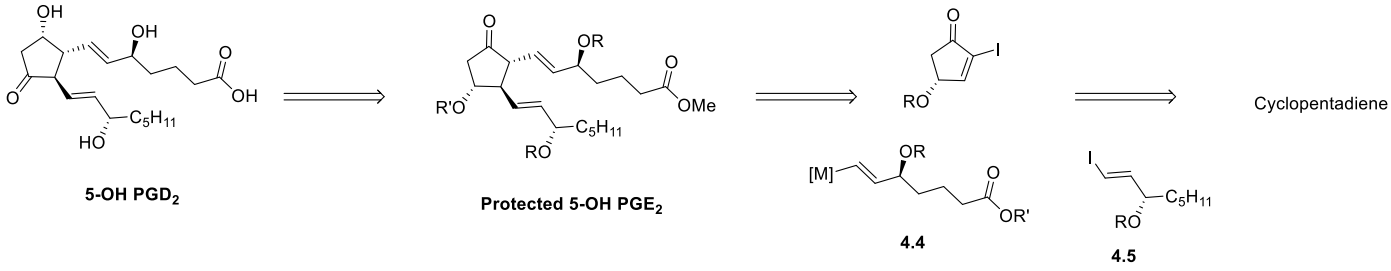
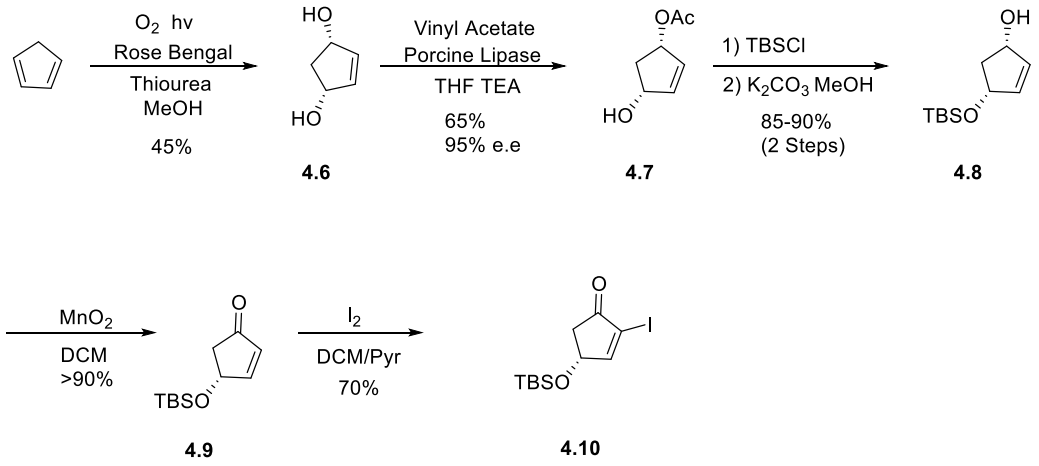


Figure 4.6: Retrosynthetic analysis of 5-OH PGD_2

4.3 Synthesis of 5-Hydroxy Prostaglandin E_2

The synthesis of 5-hydroxy PGE_2 started by the building of the α-Iodo cyclopenteneone **4.10** (Scheme 4.3.1). Starting from cyclopentadiene, Diels Alder

cycloaddition with singlet oxygen produces cis diol **4.6.** This can be enzymatically de-symmetrized using porcine lipase and vinyl acetate resulting in enantioenriched monoacetate, **4.7.** Protecting group manipulation furnishes allylic alcohol **4.8.** Oxidation of the allylic alcohol via MnO_2 yields enone **4.9,** which is α iodoinated to generate the desired α-iodo cyclopentenone **4.10.** [40,43,88]



Scheme 4.3.1: Synthesis of α-Iodo cyclopentenone **4.10**

4.3.1 Protecting group determination for α-Side Chain

From a historical standpoint the carboxylic acid side chain in prostanoid syntheses is usually protected as a methyl ester. This requires deprotection through an enzymatic hydrolysis, strong basic conditions, or most simply, kept as the methyl ester.[33,39,40] The PGE and PGD cores are base sensitive, and prone to β-elimination of the C9 or C11 alcohol into the PGA or PGJ cores respectively, making these late stage deprotections very challenging.[39,85] (Figure 4.7)

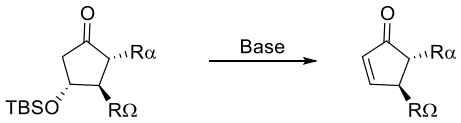
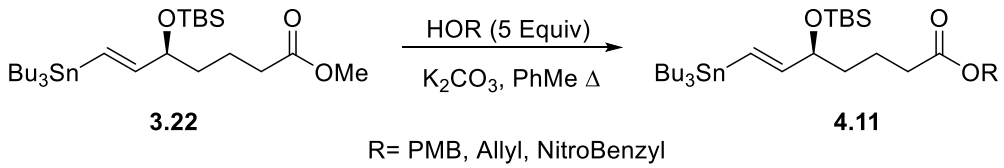


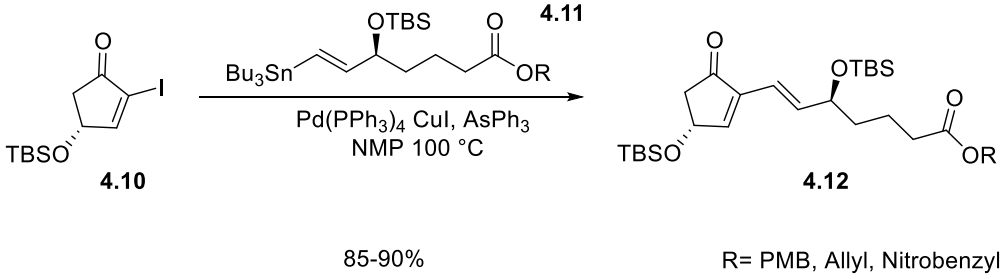
Figure 4.7: β-Elimination of PG Core

With this in mind a non-base labile ester protecting group would be ideal to circumvent potential β-Elimination. Initial screening of protecting groups focused on PMB, allyl, and Nitro Benzyl esters, which could be removed through oxidative deprotections, palladium mediated deprotections or photolysis respectively. These side chains were made from the previously reported synthesis of the carboxylic acid side chain, followed by Fischer esterification with the requisite alcohol to generate protected esters **4.11** (Scheme 4.3.2).



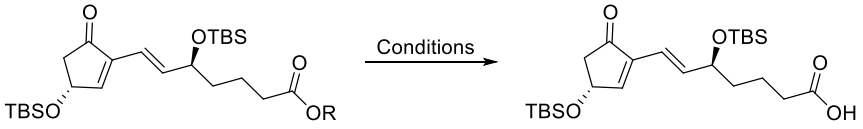
Scheme 4.3.2: Synthesis of esters **4.11**

Stille cross coupling worked well, after it was determined that NMP had to be freeze pump thawed after distillation for serviceable yields (Scheme 4.3.3). Screening of deprotection conditions were run on the diene, fully elaborated carbon framework, and the alkyne.



Scheme 4.3.3: Synthesis of diene **4.12**

Table 4.1, summarizes the attempted deprotections of esters to the acid at the diene stage. As the results from table 4.1 highlight the best result for deprotection was photolyzing the nitro benzyl ester.[89]



R= PMB, Ally, Nitrobenzyl **4.13**

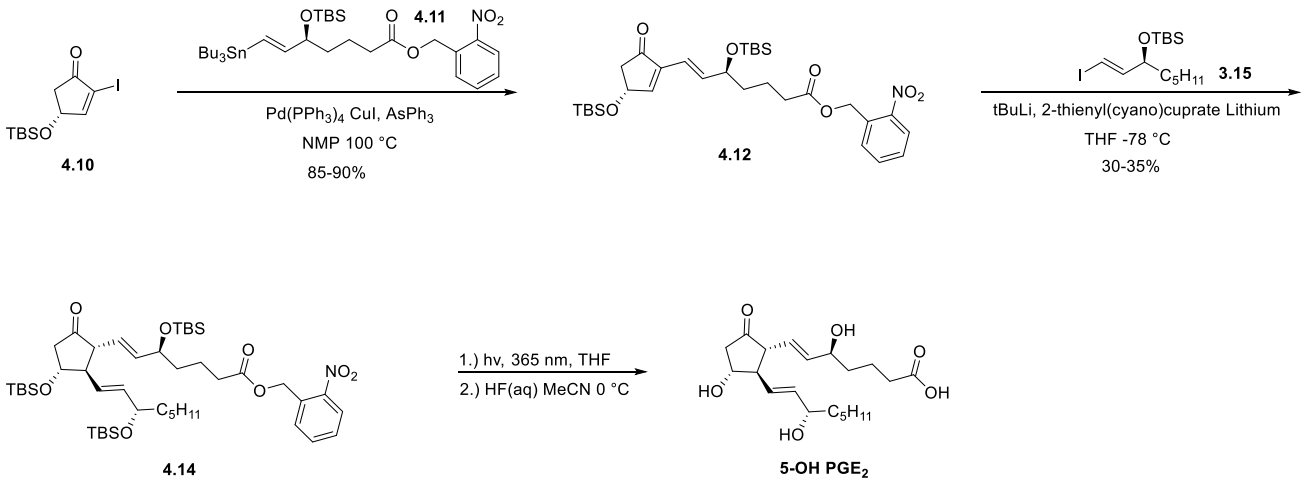
Entry	R	Reagents	Solvent	Result
1	Allyl	$Pd(OAc)_2$ PPh_3 Dimedone	THF/H_2O	Mixture
2	Allyl	$Pd(PPh_3)_4$	THF	Mixture
3	PMB	DDQ	DCM/H_2O	Mixture
4	PMB	TFA	PhMe	Silyl deprotection
5	PMB	TFA, Anisole 0 °C	DCM	RSM
6	NB	365 hv, 8 h	THF	**4.13**, 30%
7	NB	365 hv, 24 h	THF	**4.13**, 50%

Table 4.1: Optimization of ester deprotection

4.3.2: Completion of 5-OH PGE_2

With acid deprotection conditions in hand we set about completing the synthesis of 5-OH PGE_2. Stille cross coupling of α-iodo compound, **4.10** and nitrobenzyl ester, **4.11,** cleanly generated diene **4.12** (Scheme 4.3.4). Cuprate was generated, from treatment of vinyl iodide, **3.15** with tBuLi followed by transmetallation with 2-

Thienyl(cyano)cuprate and subsequent 1,4 addition,[43] yielding **4.14,** completing the entire carbon framework of 5 OH PGE_2 in a moderate yield. Photocleavable deprotection using 365 nm light, furnished desired acid, and global deprotections using aqueous HF in MeCN, at 0 °C completed the synthesis of 5-OH PGE_2.



Scheme 4.3.4: Completion of 5-OH PGE_2

4.4 Progress towards 5-OH PGD_2

The initial synthetic strategy for 5-OH PGD_2 was predicated on building a cyclopentenone core, with a protected alcohol orthogonal to silyl deprotections (Figure 4.8). The 5-OH PGE_2 carbon framework would be built through previously employed chemistry, cross coupling to install the carboxylic acid side chain, and cuprate addition to bring in the n-pentyl side chain. Orthogonal protecting group on the C11 position, would enable inversion of the C9 and C11 oxidation states through functional group

manipulation. At this point global deprotections would complete the synthesis of 5-OH PGD_2. [39]

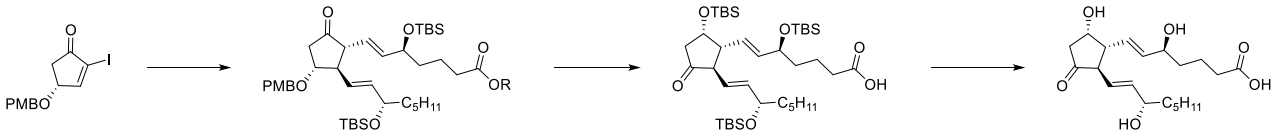
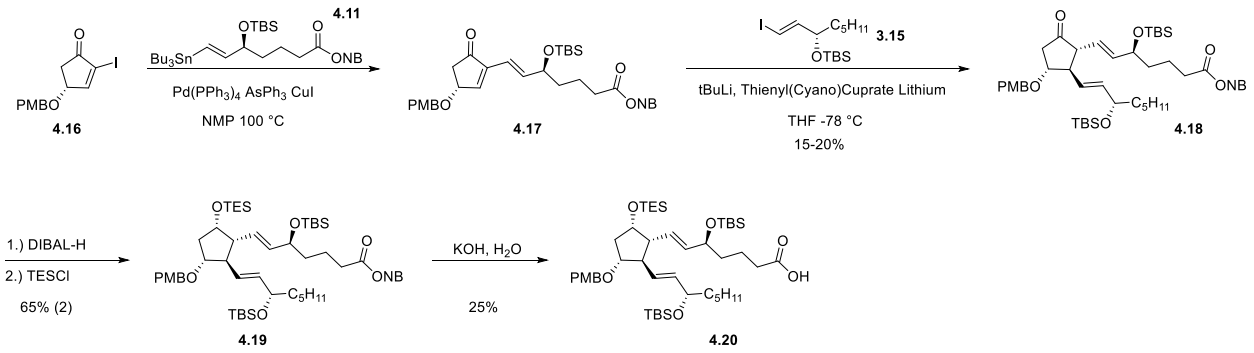


Figure 4.8: 5-OH PGD_2 synthethic strategy

Initial attempts at the synthesis of 5-OH PGD_2 began with a PMB protecting group for the alcohol within the ring, **4.16** (Scheme 4.4.1). Stille coupling with vinyl tin **4.11** was employed to successfully yield diene **4.17** in good yield. 1,4 cuprate addition, using vinyl iodide **3.15**, while successful in obtaining **4.18**, resulted in a precipitous drop in yield from previous results, dropping from 35-40% to 15-20%. This material was pushed forward with DIBAL-H reduction of the C9 carbonyl, followed by TES protection to generate **4.19,** in good yield, setting the stage to invert the oxidation states of the C9 and C11 positions.[39] Hydrolysis at this stage furnished acid, **4.20.** This route allowed for the use of strong base in converting the ester into the acid since after reduction of the C9 carbonyl, β-elimination is not a problem. Unfortunately, only 2 mg of this late-stage intermediate was obtained. After trying a variety of different cuprate conditions, and protecting groups, yields for this cuprate reaction were never high enough to enable the completion of the synthesis of 5-OH PGD_2.

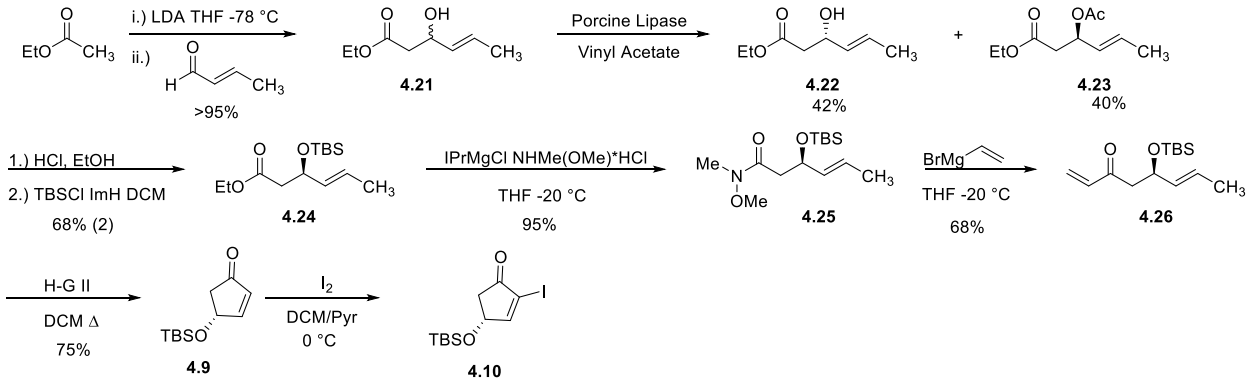


Scheme 4.4.1: Synthesis of acid **4.20**

4.4.1 New Synthesis of Cyclopentenone Core

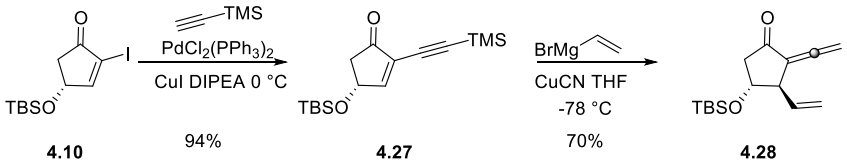
Of the three building blocks, the cyclopentenone core, the carboxylic acid and n-pentyl side chains, the cyclopentenone core was the hardest to make on large scale. The major issue with this route was the Diels Alder cycloaddition reaction. This reaction could only be run on 1.5 g of cyclopentadiene, due to the size of the photoreactor. This roughly translated to 500 mg – 1 g of final α iodo compound, **4.10.** A more scalable route to α-Iodo compound, **4.10** would be advantageous. Scheme 4.4.2 shows the new route, which starts with an aldol of ethyl acetate and crotenaldyde, easily run on over 100 mmoles, resulting in racemic allylic alcohol **4.21.** This racemate can be enzymatically resolved using porcine lipase run in vinyl acetate for 2 days resulting in undesired allylic alcohol **4.22,** and desired allylic acetate **4.23.** The undesired alcohol, **4.22** can be recycled through a two-step oxidation, reduction sequence. Allylic acetate, **4.23** undergoes protecting group manipulation to furnish, silyl ether **4.24.** Conversion of the ethyl ester into the Weinreb amide is achieved using iPrMgCl and Weinreb's salt, furnishing **4.25**. Grignard addition with vinyl magnesium bromide, generated terminal enone **4.26.** Ring

closing metathesis using Hoveyda Grubbs II yielded enone **4.9**, Which was iodinated to complete the new synthesis of α Iodo enone **4.10.**[88,90] This new procedure resulted in roughly 3-4 g of final α iodo enone, compared to that of 500 mg-1g from the singlet oxygen route.



Scheme 4.4.2: New synthesis of α Iodo cyclopentenone **4.10**

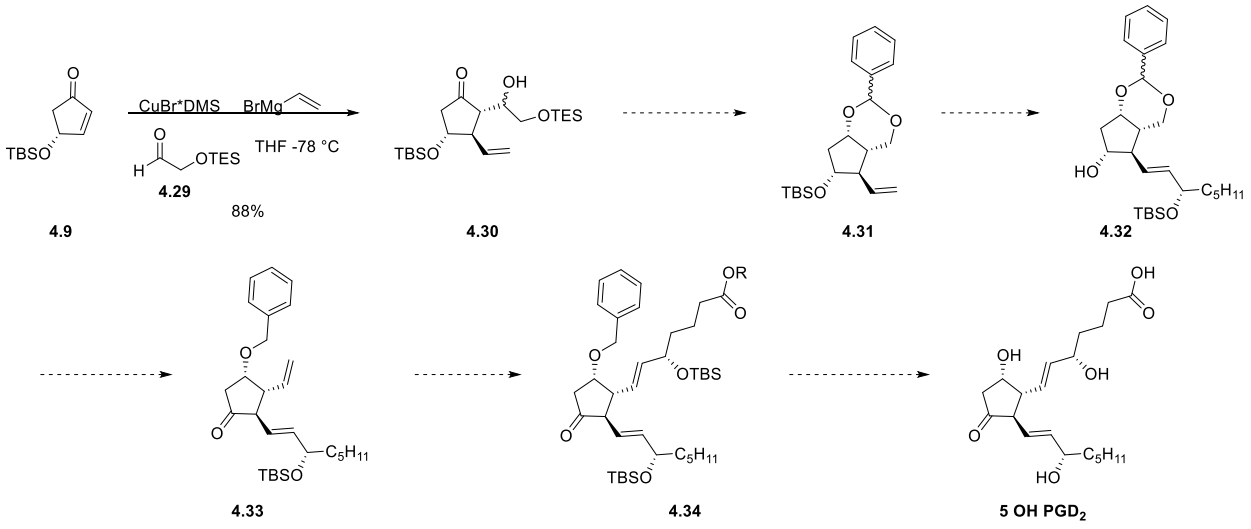
Sonogashira cross coupling of α iodo enone **4.10,** with TMS acetylene generates enyne **4.27** (Scheme 4.4.3) in great yield. At this point attempted cuprate addition with vinyl magnesium bromide looked to provide a handle for a cross metathesis with the n-pentyl side chain. Unfortunately, cuprate addition resulted in the formation of allene **4.28.** With the destruction of that stereocenter this route was abandoned.



Scheme 4.4.3: Synthesis of allene **4.28**

4.4.2: 3 Component coupling and proposed synthesis of 5-OH PGD_2

After failure of the TMS acetylene pathway, we opted to go towards a more historical three component coupling reaction. From enone, **4.9** (Scheme 4.4.4) three component coupling with aldehyde, **4.29,** generates 1,2 diol **4.30.**[90] To finish the synthesis of 5-OH PGD_2 a silyl deprotection, oxidative cleavage, selective reduction and subsequent treatment with benzaldehyde to furnish benzylidene **4.31.** The C11 silyl ether could be deprotected, followed by cross metathesis to incorporate the n-pentyl side chain, yielding **4.32.** Benzylidene deprotection with DIBAL-H, generates the primary alcohol, followed by oxidation and olefination to furnish, **4.33**. Second cross metathesis completes the entire carbon frame work of 5-OH PGD_2. Finally, global deprotection can complete the synthesis of 5-OH PGD_2.



Scheme 4.4.4: Proposed synthesis of 5-OH PGD_2

1. General Procedure: All non-aqueous reactions were performed in flame-dried or oven dried round-bottomed flasks under an atmosphere of argon. Stainless steel syringes or cannula were used to transfer air- and moisture-sensitive liquids. Reaction temperatures were controlled using a thermocouple thermometer and analog hotplate stirrer and monitored using liquid-in-glass thermometers. Reactions were conducted at room temperature (approximately 21-23 °C) unless otherwise noted. Flash column chromatography was conducted using silica gel 230-400 mesh. Reactions were monitored by analytical thin-layer chromatography, using EMD Silica Gel 60 F254 glass-backed pre-coated silica gel plates. The plates were visualized with UV light (254 nm) and stained with potassium permanganate or *p*- anisaldehyde-sulfuric acid followed by charring. Yields were reported as isolated, spectroscopically pure compounds.

2. Materials: Solvents and chemicals were purchased from Sigma-Aldrich, Acros Organics, TCI and/or Alfa Aesar and used without further purification. Solvents were purchased from Fisher Scientific. Dry dichloromethane (CH_2Cl_2) was collected from an MBraun MB-SPS solvent system. Dichloroethane (DCE) was distilled from calcium hydride and stored over 4 Å molecular sieves. Triethylamine, N,N-dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) were used as received in a bottle with a Sure/Seal. N,N-diisopropylethylamine was distilled from calcium hydride and stored over KOH. $BF_3{\cdot}Et_2O$ was distilled prior to use from calcium hydride. Deuterated solvents were purchased from Cambridge Isotope Laboratories.

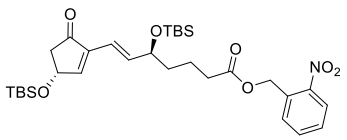
3. Instrumentation: Preparative reverse phase HPLC (Gilson) was performed using a Phenomenex Gemini column (5 micron, 110 Å, 50 x 21.20 mm, flow rate 30 mL/min) with

UV/Vis detection. ^{1}H NMR spectra were recorded on Bruker 400 or 600 MHz spectrometers and are reported relative to internal chloroform (^{1}H, δ 7.26), methanol (^{1}H, δ 3.31), and DMSO (^{1}H, δ 2.50). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublet, ddd = doublet of doublet of doublet, m = multiplet, br=broad), coupling constants (Hz), and integration. ^{13}C NMR were recorded on Bruker 100 MHz spectrometers and are reported relative to internal chloroform (^{13}C, δ 77.1), methanol (^{13}C, δ 49.2), and DMSO (^{13}C, δ 40.3). Low-resolution mass spectra were acquired on an Agilent Technologies Series 1200 single quad ChemStation autosampler system using electrospray ionization (ESI) in positive mode. High-resolution mass spectra (HRMS) were obtained from the Department of Chemistry and Biochemistry, University of Notre Dame Mass Spectrometry Center or the Mass Spectrometry Research Center at Vanderbilt University.

Experimental Methods:

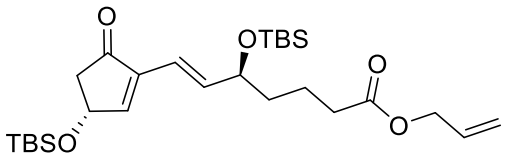
Experimental Methods:

α Iodo enone **4.10** was prepared as previously described [43]

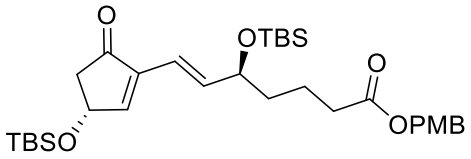


Enone 4.12.A: To a solution of vinyl iodide **4.10** (0.226 g, 0.67 mmol), CuI (32 mg, 0.17 mmol), Ph_3As (52 mg, 0.17 mmol), and $Pd(PPh_3)_4$ (50 mg, 0.04 mmol) in freshly distilled and degassed (Freeze pump thaw) NMP(2.5 mL) was lowered into an oil bath at 100 ˚C and a solution of vinylstannane **4.11** (0.550 g, 0.80 mmol) in degassed NMP (2.5 mL) was added dropwise. The reaction

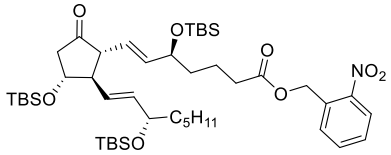
mixture was maintained for 2 h, quenched by the addition of *saturated aqueous* KF (20 mL), and extracted with EtOAc (3 x 20 mL). The organic extracts were combined, washed with *saturated aqueous* KF (20 mL), brine (20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel/10% K_2CO_3, gradient elution: 0% -10% -20% -100% EtOAc in Hexanes) to yield enone **4.12.A**, 0.35 g, (87%) as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.4 Hz, 1H), 7.51 (app t, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.34 (app t, *J* = 7.6 Hz, 1H), 7.02 (s, 1H), 6.59-6.52 (m, 1H), 6.07 (d, *J* = 16 Hz, 1H), 5.37 (s, 2H), 4.78 (t, *J* = 3.2 Hz, 1H), 4.11 (app q, *J* = 5.6 Hz, 1H), 2.66 (dd, *J* = 6, 18.4 Hz, 1H), 2.28 (app t, *J* = 7.6 Hz, 2H), 2.20 (dd, *J* = 2.4, 18.4 Hz, 1H), 1.61-1.42 (m, 4H), 0.78 (s, 9H), 0.76 (s, 9H), 0.00 (s, 3H), -0.01 (s, 3H), -0.08 (s, 3H), -0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.3, 172.6, 156.4, 147.4, 140.5, 139.6, 133.6, 132.2, 128.8, 128.6, 124.9, 118.0, 72.5, 68.5, 62.6, 46.4, 37.1, 34.0, 25.7, 25.7, 18.1, 14.1, -4.4, -4.7, -4.9.



Enone 4.12.B: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.01 (d, *J* = 2.4 Hz, 1H), 6.59-6.51 (m, 1H), 6.08 (d, *J* = 16 Hz, 1H), 5.82-5.72 (m, 1H), 5.18 (dd, *J* = 1.2 , 17.2 Hz, 1H), 5.09 (dd, *J* = 1.2 , 10.4 Hz, 1H), 4.78-4.77 (m, 1H), 4.37 (d, *J* = 6 Hz, 2H), 4.10 (q, *J* = 5.6 Hz, 1H), 2.69 (dd, *J* = 6 , 18 Hz, 1H), 2.23-2.17 (m, 3H), 1.60-138 (m, 6H), 0.78-0.74 (m, 18H), 0.00 (s, 3H), -0.01 (s, 3H)-0.08 (s, 3H), -0.1 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ:204.2, 173.0, 156.4, 156.3, 140.6, 139.7, 132.2, 118.0, 117.9, 72.5 (2), 68.5, 68.4, 64.8, 46.4, 37.1, 34.0,31.4, 25.7, 25.6, 22.5, 20.4, 18.1, -4.4, -4.7, -4.8, -4.9.

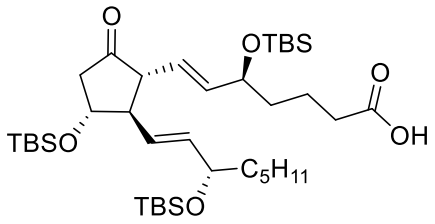


Enone 4.12.C: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27 (d, *J* = 12 Hz, 2H), 7.12 (s, 1H), 6.81 (d, *J* = 8.4 Hz, 2H), 6.57-6.6.40 (m, 1H), 6.07 (d, *J* = 16 Hz, 1H), 4.90 (s, 2H), 4.78-4.76 (m, 1H), 4.07 (d, *J* = 5.6 Hz, 1H), 3.66 (s, 3H), 2.69 (dd, *J* = 6 , 18.4 Hz, 1H), 2.34-2.16 (m, 3H), 1.55-1.36 (m, 4H), 0.78 (s, 9H), 0.75 (s, 9H), 0.00--.16 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 204.3, 173.3, 159.5, 156.4, 156.3, 140.6, 139.7, 129.9, 128.1, 117.9 (2), 113.8, 72.6, 68.5, 65.8, 55.1, 46.4, 37.1, 34.1, 25.8, 25.7, 20.4, 18.1, 18.0, -4.4, -4.7, -4.9.

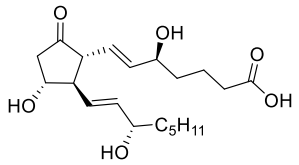


Cyclopentanone **4.14:** To a solution of vinyl iodide **3.15** (0.397 g, 1.07 mmol) in THF (2.5 mL) at -78 °C was added a solution a solution of t-BuLi (1.26 mL, 2.14 mmol, 1.7 *M* in pentane) dropwise. The reaction mixture was maintained for 30 min, and a solution of lithium 2-thienylcyanocuprate in THF (4.5 mL, 1.12 mmol, 0.25 *M* in THF) was added dropwise and the yellow solution was allowed to warm to 0 °C and stirred for 10 min. The red solution was then cooled to -78 °C and a solution of enone **4.12**, (0.310 g, 0.51 mmol) in THF (2.5 mL) was added dropwise and the reaction mixture maintained at -78 °C for 3 h. The reaction was then, quenched by the addition of *saturated aqueous* NH_4Cl (2 mL), extracted with EtOAc (3 x 10 mL), the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, gradient elution: 0%-25%-100% EtOAc in Hexanes) to afford **4.14,** 0.145 g, (35%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.4 Hz, 1H), 7.61 (app t, *J* = 8 Hz, 1H), 7.55 (app d, *J* = 7.6 Hz, 1H), 7.44 (app t, *J* =

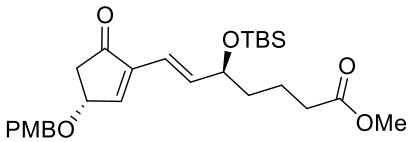
7.6 Hz, 1H), 5.57-5.44 (m, 6H), 4.11-3.95 (m, 3H), 2.654-2.50 (m, 3H), 2.38 (app t, *J* = 7.6 Hz, 2H), 2.24-2.17 (m, 1H), 1.74-1.59 (m, 2H), 1.48-1.24 (m. 10H), 0.85-0.83 (m, 30H), 0.03 (s, 3H), 0.01 (s, 3H), 0.0 (s, 3H), -0.01 (s, 3H), -0.3 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.7, 172.7, 137.2, 136.4, 133.6, 132.3, 128.8, 128.5, 127.8, 124.9, 124.6, 124.4, 72.8, 72.4, 72.3, 62.6, 57.2, 54.2, 47.1, 38.4, 38.2, 37.5, 37.4, 34.0, 31.7, 25.8, 25.7, 24.9, 22.5, 20.6, 18.1, 17.9, 13.9, -4.20 (2), -4.5,-4.6,-4.7,-4.8.



Acid **4.15**: In a scintillation flask, a solution of ester **4.14** (100 mg, 0.12 mmol) in THF (3 mL) was irradiated at 365 nm, with Spectroline Minimax 4 Watt lamp for 16 h. The reaction was concentrated *in vacuo* and the residue purified by flash chromatography (silica gel, Gradient elution: 0%- 30%- 50% EtOAc in Hexanes) to yield acid **4.15,** 43 mg (50%) as a colorless oil and recovered **4.14,** 37 mg (37%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57-5.43 (m, 4H), 4.07-4.03 (m, 3H), 2.65-2.50 (m, 3H), 2.30 (app t, *J* = 7.2 Hz, 2H), 2.20 (dd, *J* = 9.6, 18.4 Hz, 1H), 1.67-1.57 (m, 2H), 1.49-1.35 (m, 2H), 1.24-1.21 (m, 8H), 0.85-0.84 (m, 30H), 0.03 (s, 3H), 0.01 (s, 3H), 0.0 (s, 3H), -0.01 (s, 3H), -0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 212.9, 137.3, 136.4, 127.8, 124.3, 72.8, 72.4, 72.4, 57.3, 54.2, 47.1, 38.3, 37.2, 33.5, 31.7, 25.84, 25.81, 25.7, 24.9, 24.7, 22.5, 20.3, 18.1, 17.9, 13.9, -4.3, -4.6, -4.7, -4.8, -5.0.

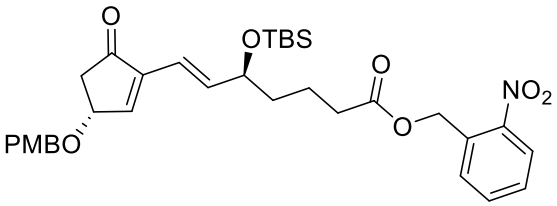


5-Hydroxy PGE$_2$: To a solution of acid, **4.15,** (10 mg, 0.01 mmol) in MeCN (3 mL) at 0 °C was added aqueous HF (49%, 25 mg, 0.05 mL). The reaction mixture was maintained at 0 °C for 2 h, concentrated and purified by HPLC (20 min Isocratic Elution, 70:30:0.01, H_2O:MeCN:AcOH), to yield **5-Hydroxy PGE$_2$** , 1.4 mg, (27%) as a colorless oil ^{1}HNMR (400 MHz, CD_3CN) δ= 8.85 (bs, 1H), 5.50-5.37 (m, 4H), 3.96-3.389 (m, 3H), 2.68 (bs, 1H), 2.63-2.61 (m, 1H), 2.55 (dd, *J* = 0.8, 8 Hz, 1H),2.36-2.32 (m, 1H), 2.18 (t, *J* = 2.4 Hz, 2H), 1.54-1.19 (m, 12H), 0.80 (t, *J* = 2.8 Hz, 3H); ^{13}C NMR (150 MHz, CD_3CN)δ 138.2, 137.2, 130.2, 125.6, 72.6, 72.1, 70.7, 58.2, 54.7, 46.3, 37.8, 37.0, 33.8, 32.1, 25.6, 23.0, 21.3, 14.0. ; MS (ESI) calc'd for $C_{20}H_{32}O_6$ [M-H]: 367.27, [M-18]: 349.14 [M-36] 331.16.

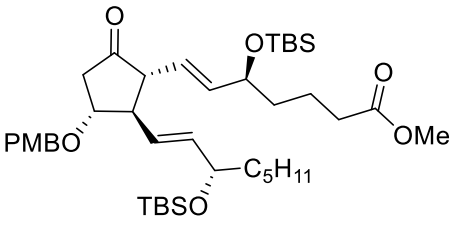


Enone 4.17.1: To a solution of vinyl iodide **4.16** (0.10 g, 0.3 mmol), CuI (11 mg, 0.06 mmol), Ph_3As (18 mg, 0.06 mmol), and $Pd(PPh_3)_4$ (17 mg, 0.015 mmol) in freshly distilled and degassed(Freeze pump thaw) NMP (2.5 mL) The reaction mixture was then lowered into an oil bath at 100 °C and a solution of vinylstannane **3.21** (0.18 g, 0.32 mmol) in degassed NMP (2.5 mL) was added dropwise. The reaction mixture was maintained for 2 h, quenched by the addition of *saturated aqueous* KF (5 mL), and extracted with EtOAc (3 x 10 mL) and the organic extracts were combined, washed with *saturated aqueous* KF (20 mL), brine (20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, gradient elution: 0% -10% - 20% EtOAc in Hexanes) to yield desired enone, **4.17** 80 mg, (60%) as an orange oil ^{1}H NMR (400 MHz, $CDCl_3$) δ

: 7.54 (dd, *J* = 2.4 , 5.6 Hz, 1H), 7.25-7.22 (m, 3H), 6.86-6.84 (m, 3H), 6.20 (dd, *J* = 1.6 , 6 Hz, 1H), 4.72-4.69 (m, 1H), 4.56 (q, *J* = 7.2 Hz, 2H), 3.76 (s, 6H), ^{13}C NMR (100 MHz, $CDCl_3$) δ : 204.0, 173.8, 159.4, 153.6, 141.6, 140.0, 129.6, 129.4, 117.9, 113.9, 74.1, 72.6, 71.3, 55.2, 51.3, 43.2, 37.1, 33.9, 25.7, 20.4, 19.1, 18.0, 13.7, -4.4, -4.9.

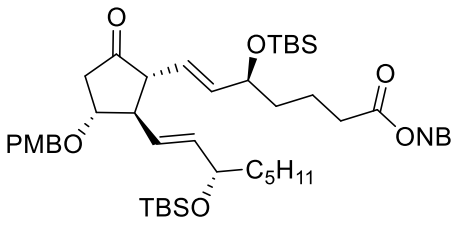


Enone 4.17: ^{1}H NMR (400 MHz, $CDCl_3$) δ : 8.02 (d, *J* = 8 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 6.68-6.62 (m, 1H), 6.19 (d, *J* = 15.6 Hz, 1H), 5.48 (s, 2H), 4.62 (t, *J* = 3.2 Hz, 1H), 4.50-4.49 (m, 2H), 4.19 (t, *J* = 5.6 Hz, 1H), 3.74 (s, 3H), 2.71 (dd, *J* = 6 Hz, 1H), 2.40-2.35 (m, 3H), 1.66-1.54 (m, 4H), 0.84 (s, 9H), 0.0 (s, 3H), -0.03 (s, 3H).



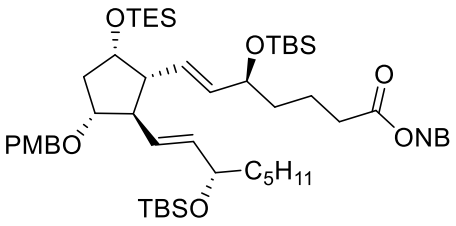
Cyclopentanone **4.18.1:** To a solution of CuCN (10 mg, 0.10 mmol) in THF (1 mL) at 0 °C was added a solution a solution of MeLi (0.19 mL, 0.22 mmol, 1.16 *M* in pentane) dropwise. The reaction mixture was warmed to room temperature and stirred until the cloudy solution became homogenous, then vinyl stannane **3.16** (65 mg, 0.12 mmol) in THF (1 mL) was added and allowed to

stir for 1.5 h. The reaction was then cooled to -78 °C, and a solution of enone **4.17.1** (37 mg, 0.075 mmol) in THF (1 mL) was added rapidly via cannula. After 10 minutes the reaction was quenched by pouring into a solution of 10% NH_4Cl/NH_4OH, and extracted with EtOAc (3 x 10 mL), the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, gradient elution: 0% - 25% EtOAc in Hexanes) to yield cyclopentanone, **4.18.1,** 30 mg (20%) as a pale yellow oil ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.22 (d, *J* = 2.4 Hz, 2H), 6.86 (d, *J* = 8 Hz, 2H), 6.65 (dd, *J* = 5.2 , 16 Hz, 1H), 4.62 (s, 1H), 4.53-4.47 (m, 2H), 4.18 (d, *J* = 5.2 Hz, 1H), 3.76 (s, 3H), 3.61 (s, 3H), 2.74 (dd, *J* = 5.6 , 18 Hz, 1H), 2.42 (d, *J* = 18.4 Hz, 1H), 2.27-2.24 (m, 2H), 1.62-1.21 (m, 4H), 0.85 (s, 9H), 0.00 (s, 3H), -0.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ:212.3, 173.3, 159.2,137.6, 136.5, 129.2, 124.0, 113.7, 78.3, 72.4, 72.0, 57.3, 55.1, 51.9, 44.1, 38.3, 37.4, 33.8, 31.7, 25.8, 24.8, 22.5, 20.6, 18.1 (2), 13.9, -4.2, -4.3, -4.8, -4.9.



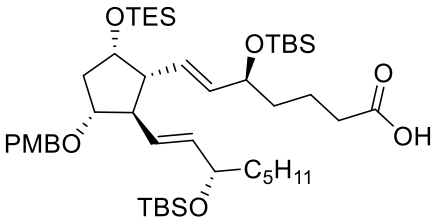
Cyclopentenone **4.18:** ^{1}H NMR (400 MHz, $CDCl_3$) δ:8.09 (d, *J* = 8 Hz, 1H), 7.64-7.56 (m, 2H), 7.46 (t, *J* = 7.2 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 5.58-5.46 (m, 6H), 4.52-4.45 (m, 2H), 4.11-4.08 (m, 2H), 3.88 (q, *J* = 8.4 Hz, 1H), 3.78 (s, 3H), 2.72-2.60 (m, 2H), 2.41-2.37 (m, 3H), 2.25 (dd, *J* = 8.8 Hz, 18.4 Hz, 1H), 1.76-1.60 (m, 2H), 1.47-140 (m, 4H), 1.35-1.29 (m, 6H), 0.87-0.844 (m, 21 H), 0.02 (s, 3H), 0.00 (s, 6H), -0.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 212.3, 172.7, 159.2, 147.4, 138.9, 137.4, 136.7, 133.6, 132.3, 129.8, 129.5, 128.8, 128.5, 128.3, 124.9, 124.0,

113.7, 78.3, 72.8, 72.3, 72.0, 62.6, 57.3, 55.1, 51.9, 44.1, 38.3, 37.3, 34.0, 31.7, 25.8 (2), 24.5, 22.5, 20.6, 18.1 (2), 13.9, -4.2, -4.3, -4.8, -4.9.



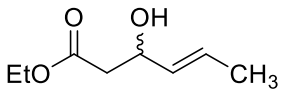
Silyl Ether **4.19:** To a solution of carbonyl **4.18** (20 mg, 0.02 mmol) in THF (1 mL) at -78 °C is added L-selectride (0.03 mL, 0.03 mmol) dropwise. Reaction is monitored by TLC, and after 30 minutes reaction is quenched by addition of 30% H_2O_2 (1 mL), and reaction is warmed to room temperature and stirred for 10 minutes. Following this reaction is diluted with water (10 mL) and EtOAc (10 mL) and layers are separated. Aqueous layer is washed with EtOAc (3 x 5 mL), combined organics are washed with brine (5 mL), dried ($MgSO_4$), filtered, concentrated *in vacuo* and used without further purification. To a solution of crude alcohol (6 mg, 0.007 mmol) in DCM (1 mL) is added imidazole (1 mg, 0.014 mmol), DMAP (1 mg) and TESCl (0.01 mL, 0.008 mmol) and reaction is allowed to stir overnight. Reaction is diluted by addition of water (5 mL) and extracted with DCM (3 x 5 mL), and combined organics are washed with brine (5 mL), dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography (silica gel, gradient elution: 0%-15% -30% EtOAc in Hexanes) to afford silyl ether **4.19,** 6 mg, (85%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.08 (dd, *J* = 0.8 , 8 Hz, 1H), 7.64 (t, *J* = 8.4 Hz, 1H), 7.59 (d, *J* = 6.8 Hz, 1H), 7.41 (t, *J* = 3.6 Hz, 1H), 7.22 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 11.6 Hz, 2H), 5.67 (dd, *J* = 8.4 Hz, 15.6

Hz, 1H), 5.44 (s, 2H), 5.38 (dd, *J* = 5.2 Hz, 15.2 Hz, 2H), 5.30 (dd, *J* = 5.6 , 10.4 Hz, 1H), 4.57-4.39 (m, 2H), 4.08-4.05 (m, 2H), 4.00 (q, *J* = 6 Hz, 1H), 3.76 (s, 3H), 3.73-3.68 (m, 1H), 2.35 (t, *J* = 7.2 Hz, 2H), 2.17-2.13(m, 1H), 2.02-1.97 (m, 1H), 1.72-1.64(m, 2H), 1.47-1.37 (m, 4H), 1.30-1.21 (m, 6H), 0.94 (t, *J* = 4.8 Hz, 9H), 0.88 (s, 9H), 0.84 (s, 9H), 0.52 (q, *J* = 10 Hz, 6H), 0.01—0.02 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ : 172.7, 135.0, 134.6, 133.5, 130.6, 129.0, 128.7, 128.5, 128.2, 124.9, 113.5, 83.3, 73.4, 72.5, 70.9, 62.6, 55.1, 53.9, 51.8, 38.5, 34.1, 31.8, 25.8 (2), 24.9, 22.6, 20.7, 18.1 (2), 14.0, 6.8, 4.8, -4.1, -4.2, -4.8, -4.9.

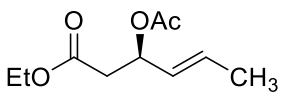


Acid 4.20: To a solution of silyl ether **4.19** (5 mg, 0.005 mmol) in THF (1 mL), is added 1M LiOH (1 mL) and stirred for 24 hours, then quenched by slow addition of of 1M HCl (1 mL), and extracted with EtOAc (3 x 5 mL). Combined organics are washed with brine (5 mL), dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography (silica gel, 50% EtOAc in Hexanes) to afford acid **4.20** 1 mg, (25%) and recovered starting material **4.19** 3 mg, (60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.23 (d, *J* = 5.6 Hz, 2H), 6.83 (d, *J* = 5.6 Hz, 2H), 5.68 (dd, *J* = 6 , 10 Hz, 1H), 5.44 (dd, *J* = 3.6 , 10 Hz, 1H), 5.37(dd, *J* = 5.2 , 10 Hz, 1H), 5.30 (dd, *J* = 3.6 , 10.4 Hz, 1H), 4.41 (d, *J* = 2.4 Hz, 2H), 4.09-4.08 (m, 2H), 4.02 (q, *J* = 4 Hz, 1H), 3.78 (s, 3H), 3.74-3.70 (m, 1H), 2.72-2.67 (m, 1H), 2.32 (t, *J* = 5.2 Hz, 2H), 2.19-2.14 (m, 1H), 2.03-1.97 (m, 1H), 1.73-1.64 (m, 6H),1.48-1.34 (m, 6H), 0.91 (t, *J* = 5.6 Hz, 9H), 0.88 (s, 9H), 0.84 (s, 9H), 0.55 (q, *J* = 5.2 Hz, 6H), 0.02 (s, 3H), 0.01 (s, 3H), 0.00 (s, 3H), -

0.02 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) DEPT 135 δ: 135.0, 134.7, 130.7, 129.1, 128.3, 113.6, 83.4, 74.2, 73.5, 72.6, 71.0, 55.2, 54.0, 51.8, 41.5, 38.6, 37.8, 33.3, 31.9, 29.7, 25.9 (2), 22.7, 20.5, 14.1, 6.9, 4.9.

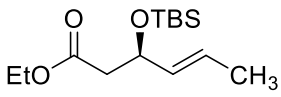


Allylic Alcohol 4.21: To a solution of freshly distilled diisopropylamine (8.8 mL, 63 mmole) in THF (60 mL) is added nBuLi (30 mL, 1.96 M in THF) dropwise at -78 °C over 30 minutes via addition funnel. Reaction is stirred for 10 minutes then distilled Ethyl Acetate (5.5 mL, 57 mmole) is added dropwise. Reaction is kept at -78 °C for 1 h at which point crotenaldehyde (6.9 mL, 85 mmole) is added dropwise stirred for 20 minutes then quenched by addition of *Saturated aqueous* NH_4Cl (100 mL) and extracted with ethyl acetate (3 x 50 mL). Combined organics are washed with brine (50 mL), dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography (silica gel, 20% EtOAc in Hexanes) to afford allylic alcohol **4.21** 8.97 g, (>95%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ*:* 5.81-5.72 (m, 1H), 5.56-5.50 (m, 1H), 4.50 (bs, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 2.55 (dd, *J* = 1.6, 5.2 Hz, 2H), 1.72 (d, *J* = 6.8 Hz, 3H), 1.29 (q, *J* = 7.2 Hz, 3H).



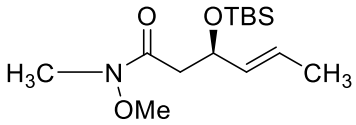
Allylic Acetate 4.23: To a solution of allylic alcohol **4.21 (**8.95 g, 56.8 mmol) in Vinyl Acetate (5.35 mL, 1 equiv) is added

pancreatin lipase (1 g), and reaction is stirred for 48 h then filtered and washed with EtOAc (50 mL x 3) concentrated *in vacuo* and purified by flash column chromatography (silic gel, gradient elution 0 % to 10% EtOAc to 100% EtOAc in Hexanes) to afford desired allylic acetate, **4.23** , 4.5 g (40 %), and allylic alcohol **4.22** , 3.5 g, (42%) as oils. ^{1}H NMR (400 MHz, $CDCl_3$) δ*:* 5.86-5.78 (m, 1H), 5.61 (q, *J* = 8 Hz, 1H), 5.51-5.45 (m, 1H), 4.16 (q, *J* = 6.8 Hz, 2H), 2.70 (dd, *J* = 7.6 , 15.2 Hz, 1H), 2.59 (dd, *J* = 5.6 , 15.2 Hz, 1H), 2.04 (s, 3H), 1.72 (dd, *J* = 1.2 , 6.4 Hz, 3H), 1.26 (t, *J* = 6.8 Hz, 3H).

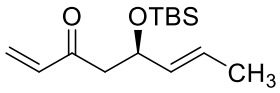


Silyl Alcohol 4.24: To a solution of allylic acetate **4.23, (**2.0 g, 10 mmol) in EtOH (40 mL, 0.25M) is added 12 M HCl (0.2 mL) and heated to reflux for 24 h. Reaction is cooled to room temperature and quenched by slow addition of *Saturated aqueous* $NaHCO_3$ (20 mL), and extracted with EtOAc (3 x 40 mL), combined organics are washed with brine (20 mL), dried ($MgSO_4$) filtered, concentrated *in vacuo* and purified by flash column chromatography (silica gel, 10% EtOAc in Hexanes) to afford allylic alcohol 1.2 g, (80 %) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ*:* 5.81-5.72 (m, 1H), 5.56-5.50 (m, 1H), 4.50 (bs, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 2.55 (dd, *J* = 1.6Hz, 5.2 Hz, 2H), 1.72 (d, *J* = 6.8 Hz, 3H), 1.29 (q, *J* = 7.2 Hz, 3H). To a solution of allylic alchol (7.9 g, 50 mmol) in DCM (50 mL, 1M) was added Imiadazole (6.8 g, 100 mmole), DMAP (1 g, 5 mmol) and TBSCl (8.2 g, 55 mmol) was stirred for 30 minutes then quenched with water (50 mL) and extracted with DCM (3 x 25 mL) , combined organics are washed with brine (50 mL), dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography (silica gel 10% EtOAc in Hexanes) to afford **4.24** 9.0g, (85%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ*:* 5.63-5.56 (m, 1H), 5.41 (dd, *J* = 5.6 , 15.2 Hz, 1H), 4.51

(q, *J* = 6.8 Hz, 1H), 4.12-4.060 (m, 2H), 2.40 (dddd, *J* = 8 , 14.4 , 46.4 , 60.8, 2H), 1.65 (d, *J* = 6.4 Hz, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 0.83 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H).

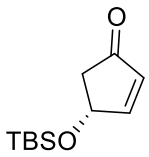


Weinreb Amide 4.25: To a solution of **4.24,** (4.0 g, 14.7 mmol) in THF (30 mL, 0.5 M) is added N,O hydroxylamine hydrochloride (2.16 g, 22.0 mmol) at -20 °C and stirred for 20 minutes. Following this isopropyl magnesium chloride (22.0 mL, 3 equiv, 2M) is added dropwise at – 20 °C and stirred for 20 minutes, quenched by slow addition of *saturated aqueous* NH_4Cl (50 mL), extracted with EtOAc (3 x 50 mL), combined organics are washed with brine (40 mL), dried ($MgSO_4$) filtered, concentrated *in vacuo* and purified flash column chromatography (silica gel, gradient elution: 0% -20% EtOAc in Hexanes) to afford desired Weinreb Amide **4.4.10,** 4.0 g, (95%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ*:* 5.64-5.57 (m, 1H), 5.48 (dddd, *J* = 1.6 , 6.4 , 15.2 , 22 , 1H), 4.61 (q, *J* = 6.4 Hz, 1H), 3.65 (s, 3H), 3.14 (s, 3H), 2.77 (q, *J* = 8.4 Hz, 1H), 2.37 (dd, *J* = 4.8 Hz, 14.4 Hz, 1H), 1.64 (dd, *J* = *0.8 ,* 6.4 Hz, 3H), 0.82 (s, 3H), 0.07 (s, 3H), 0.00 (s, 3H).

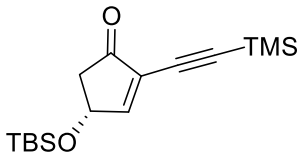


Enone 4.26: To a solution of Weinreb aminde **4.25** (1.5 g, 5.22 mmol) , in THF (17 mL, 0.3 M) at -20 °C is added vinyl magnesium grinard (16 mL, 1M, 3 equiv) dropwise over 10 minutes. Reaction is allowed to warm to room temperature and stirred for 1 h, where reaction is quenched by slow addition of *saturated aqueous* NH_4Cl (30 mL) and extracted with EtOAc (3 x 30 mL), combined organics are washed with brine (40 mL), dried ($MgSO_4$) filtered, concentrated *in vacuo*

and purified by flash column chromatography (silica gel, gradient elution: 0% -10% -20% EtOAc in Hexanes) to afford desired enone **4.26**, 0.9 g, (68%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ*:* 6.35 (dd, *J* = 10.8 , 17.6 Hz, 1H), 6.20 (d, *J* = 17.6 Hz, 1H), 5.81 (d, *J* = 10.4 Hz, 1H), 5.64-5.57 (m, 1H), 5.44 (dddd, *J* = 1.2 , 6.8 , 15.2 , 22 Hz, 1H), 4.60 (q, *J* = 6.8 Hz, 1H), 2.88 (dd, *J* = 8 , 14.8 Hz, 1H), 2.53(dd, *J* = 4.8 , 14.8 Hz, 1H), 1.65 (d, *J* = 6.8 Hz, 3H), 0.83 (s, 9H), 0.00 (s, 6H).

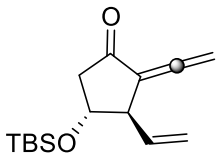


Cyclopentenone 4.9: To a stirred solution of enone **4.26** (0.9 g, 3.54 mmol) , in DCM (7 mL, 0.5 M) was added second generation Hoveyda-Grubbs Catalyst (10 mg) and heated to reflux and stirred for 48 h, then concentrated *in vacuo* and purified by Flash Column chromatography (silica gel, 20% EtOAc in Hexanes) to afford desired cyclopentenone, **4.9,** 0.6 g, (75 %). Spectral data matched previous compound [43]

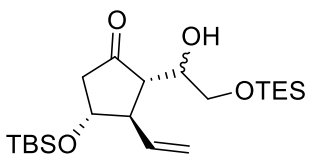


Enyne 4.27: To a solution of α-Iodo, **4.10** (0.75 g, 2.18 mmol) in THF (5 mL, 0.5 M) at 0 °C was added TMS acetylene (0.77 mL, Diisopropyl amine (0.92 mL, 6.54 mmol), CuI (38 mg, 0.2 mmol) and $PdCl_2(PPh_3)_4$ (0.14 g, 0.2 mmol) stirred for 1 h. Reaction is quenched by addition of 1M HCl (5 mL) and extracted with EtOAc (3 x 5 mL), combined organics are washed with brine (20 mL), dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography (silica gel, gradient elution: 0% -10% EtOAc in Hexanes) to afford desired enyne **4.27**, 0.65 g, (94%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ*:*

7.27 (d, *J* = 2.4 Hz, 1H), 4.74 (t, *J* = 3.2 Hz, 1H), 2.57 (dd, *J* = 6 , 18.4 Hz, 1H), 2.08 (dd, *J* = 2 ,18.4 Hz, 1H), 9.36 (s, 9H), 0.00 (s, 9H), -0.09 (s, 3H), -0.10 (s, 3H).

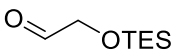


Allene 4.28: To a solution of CuCN (89 mg, 0.5 mmol) in THF (5 mL, 0.1 M) cooled to -78 °C was added vinyl magnesium bromide (2 mL, 1 M in THF) dropwise and stirred for 15 minutes. The cuprate solution is added to a solution of Enyne **4.27** (0.15 g, 0.5 mmol) in THF (1 mL) via cannula, at -78 °C and stirred for 2 h, then poured into a solution of 10% NH_4Cl/NH_4OH (10 mL), and extracted with EtOAc (3 x 10 mL), combined organics are washed with brine (10 mL), dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography (silica gel, 20% EtOAc in Hexanes) to afford allene 0.12 g, (70%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ*:* 5.74-5.65 (m, 1H), 5.23 (d, *J* = 5.2 Hz, 2H), 5.17 (d, *J* = 9.6 Hz, 1H), 4.09 (q, *J* = 6.4 Hz, 1H), 3.39 (t, *J* = 6.4 Hz, 1H), 2.60 (dd, *J* = 6 , 17.6 Hz, 1H), 2.32 (dd, *J* = 6.8 Hz, 17.6 Hz, 1H), 0.82 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 208.4, 202.7, 136.1, 117.6, 105.8, 81.1, 72.9, 54.2, 47.0, 25.6, 17.9, -4.7.



Terminal Olefin 4.30: To a stirred solution of CuBr*DMS complex (33 mg , 0.3 mmole) in THF (5 mL) was added vinyl magnesium bromide (1.1 mL, 1M solution in THF) dropwise and freshly distilled HMPA (0.04 mL, 0.27 mmole) at -78 °C and stirred for 15 minutes.

Cyclopentenone **4.10 (**0.12 g, 0.55 mmol) was added as a solution of THF (1 mL) followed by Aldehdye **4.29 (**0.12 g**,** 0.71 mL) as a solution of THF (1 mL) and stirred for 3 h, then quenched by addition of *saturated aqueous* NH_4Cl (5 mL) and extracted with EtOAc (3 x 5 mL), combined organics are washed with brine (10 mL), dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified flash column chromotagraphy (silica gel, gradient elution: 0 % -20% - 100% EtOAc in Hexanes) to afford a 1:1 mixture of **4.30** 0.2 g, (88 %) as a clear oil. . ^{1}H NMR (400 MHz, $CDCl_3$) δ*:* 5.74-5.65 (m, 1H), 5.13 (t, *J* = 18.4 Hz, 2H), 3.98 (q, *J* = 7.6 Hz, 1H), 3.82-3.78(m, 1H), 3.67-3.59 (m, 2H), 2.81 (q, *J* = 8 Hz, 1H), 2.56 (dd, *J* = 6.8 , 18 Hz, 1H), 2.28-2.18 (m, 2H), 0.92-0.83 (m, 18 H), 0.57 (q, *J* = 8 H, 6H), 0.01 (s, 3H), 0.00 (s, 3H).



Aldehyde 4.4.15: To a solution of Cis 1,4 butene-diol (0.88 g, 10 mmole) in DCM (10 mL) was added TESCl (3.5 mL, 21 mmole), imidazole (2.72 g, 40 mmole) and DMAP(0.24 g, 2 mmole) stirred for 12 h, quenched with water (10 mL), extracted with DCM (3 x 20 mL), combined organics are washed with brine (20 mL), dried ($MgSO_4$) filter, and concentrated *in vacuo*. Crude filtrate is then used without further purification. Filtrate is dissolved in DCM (30 mL) and ozone is bubbled through the reaction mixture for 2 h, which shows the appearance of a light blue color. Triphenylphosphine (2.82 g, 11 mmole) was added, and the reaction is stirred overnight. The next day, the reaction is concentrated *in vacuo*, and the desired aldehyde is distilled from the remaining filtrate (80-85 °C) to afford aldehyde **4.29** 2.0 g, (65% over 2) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.73 (s, 1H), 4.22 (d, *J* = 0.8 Hz, 2H), 1.0 (t, *J* = 8Hz, 9 H), 0.68 (q, *J* = 7.6 Hz, 6H).

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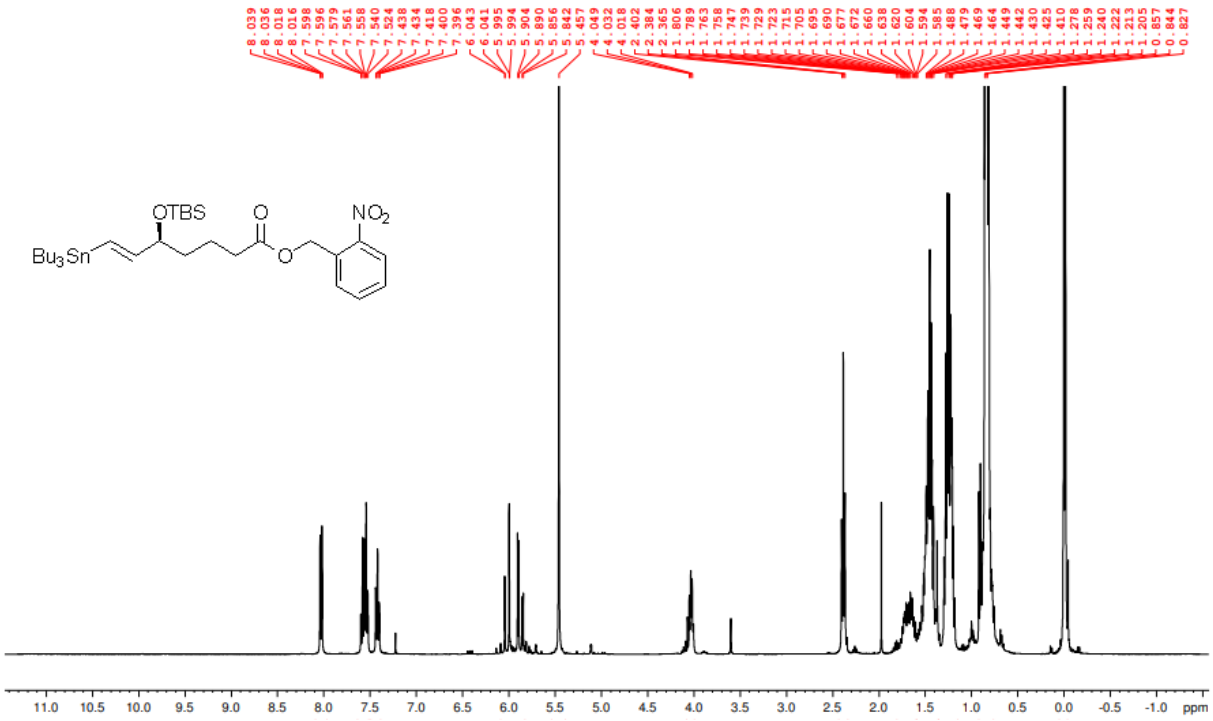
Appendix to Chapter 4

Relevant spectra



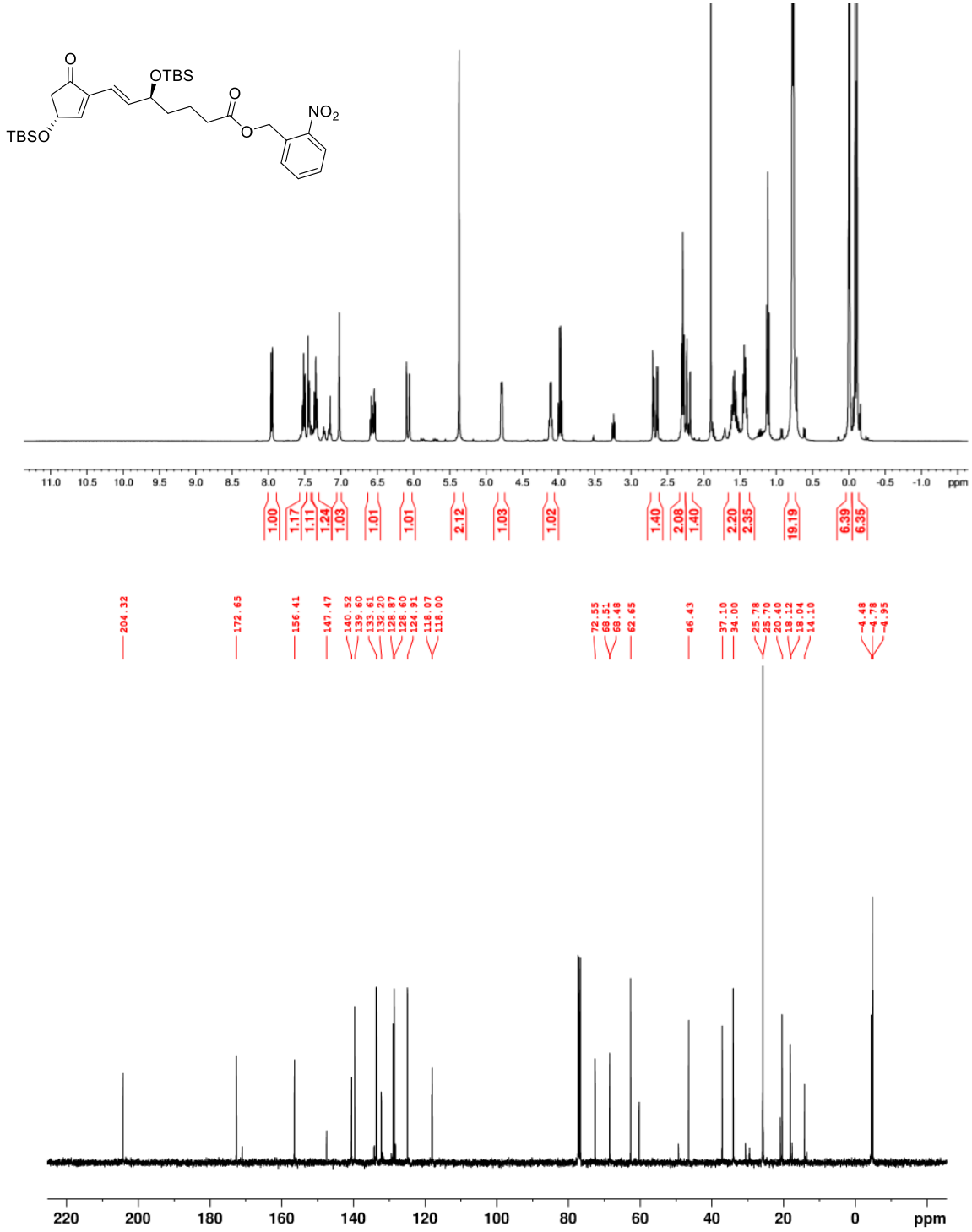


Figure A.4.10: ^{1}HNMR (400 MHz $CDCl_3$) and ^{13}CNMR (100 MHz,$CDCl_3$) of 4.12.A

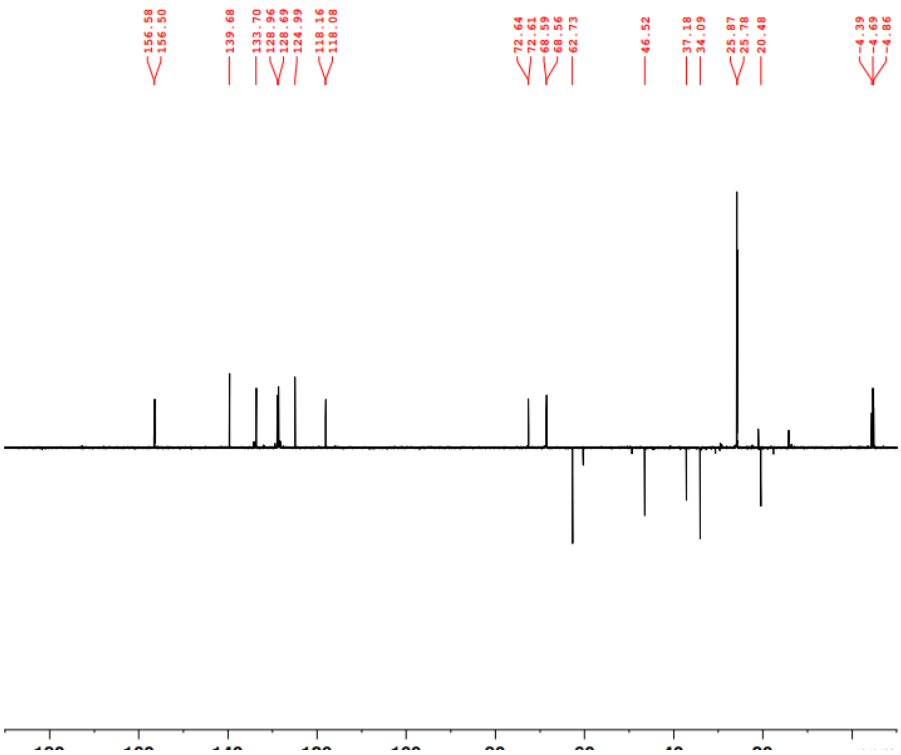


Figure A.4.11: DEPT 135 NMR (400 MHz $CDCl_3$) of 4.12.A

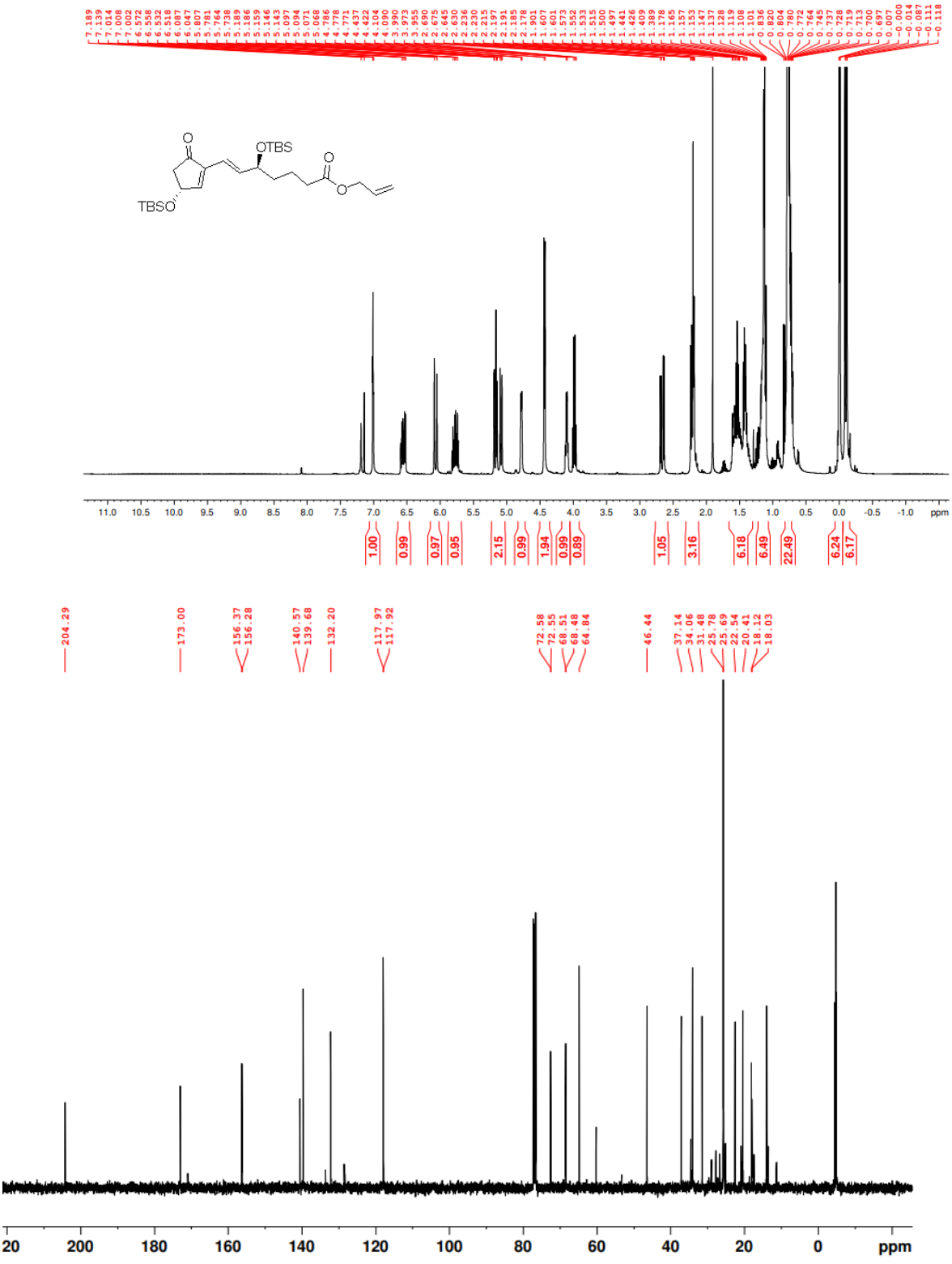


Figure A.4.12: ^{1}HNMR(400 MHz $CDCl_3$) and ^{13}CNMR(100 MHz,$CDCl_3$) of 4.12.B

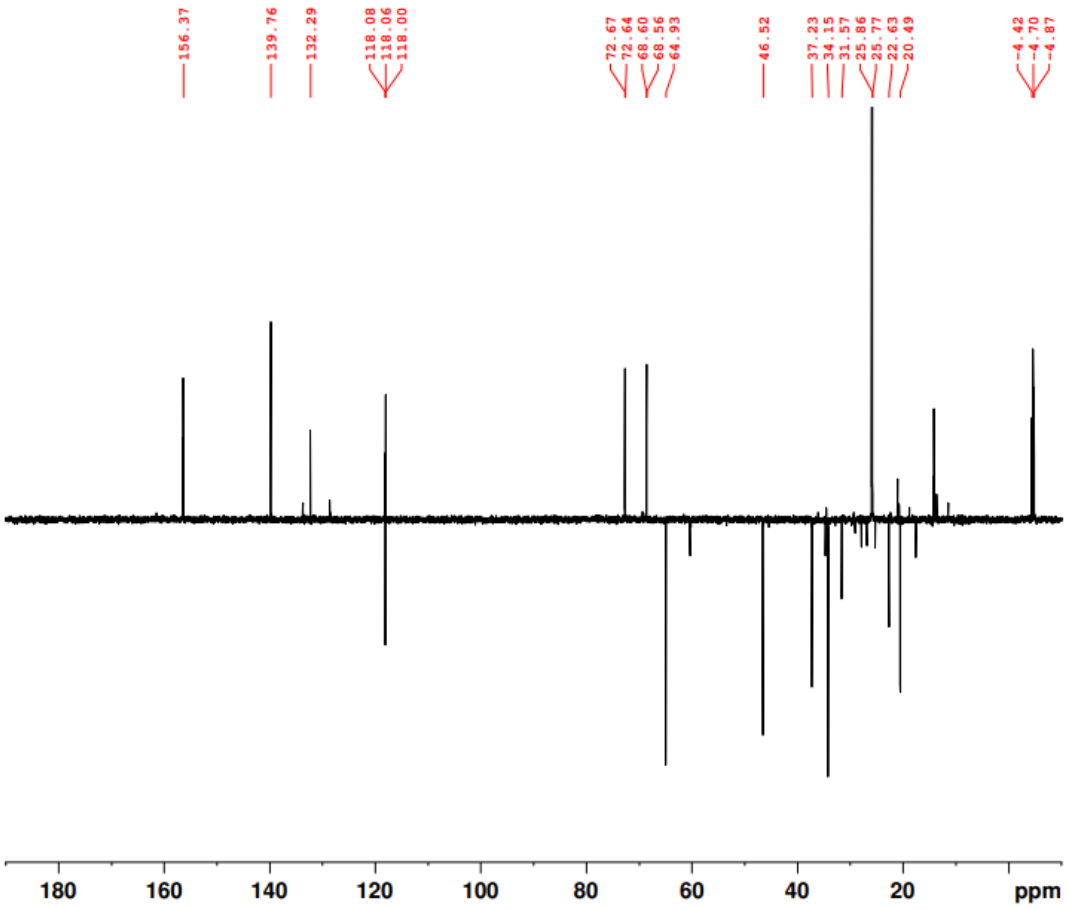


Figure A.4.13: DEPT 135 (400 MHz $CDCl_3$) of 4.12.B

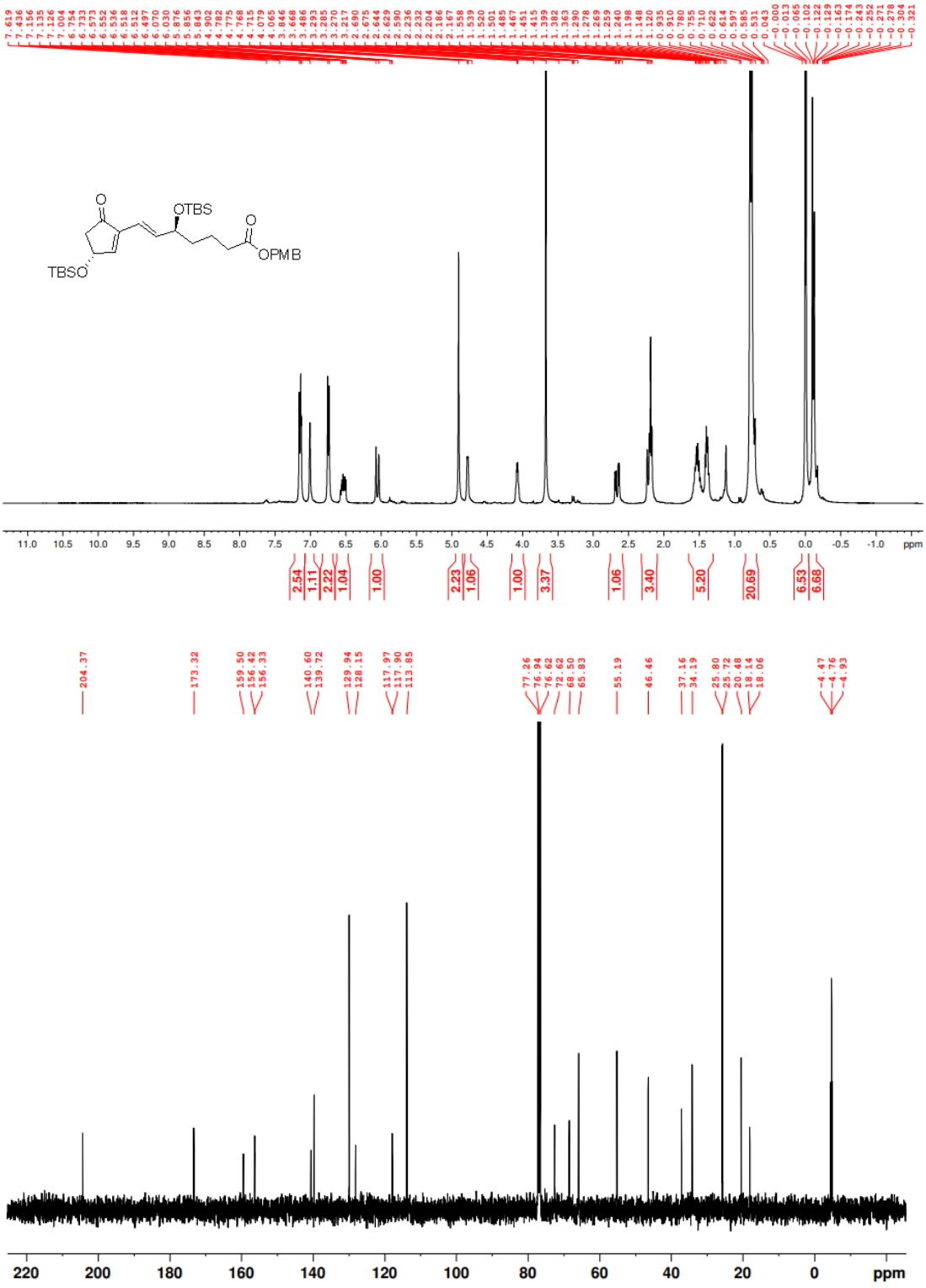


Figure A.4.14: ^{1}HNMR (400 MHz $CDCl_3$) and ^{13}CNMR (100 MHz, $CDCl_3$) of 4.12.C

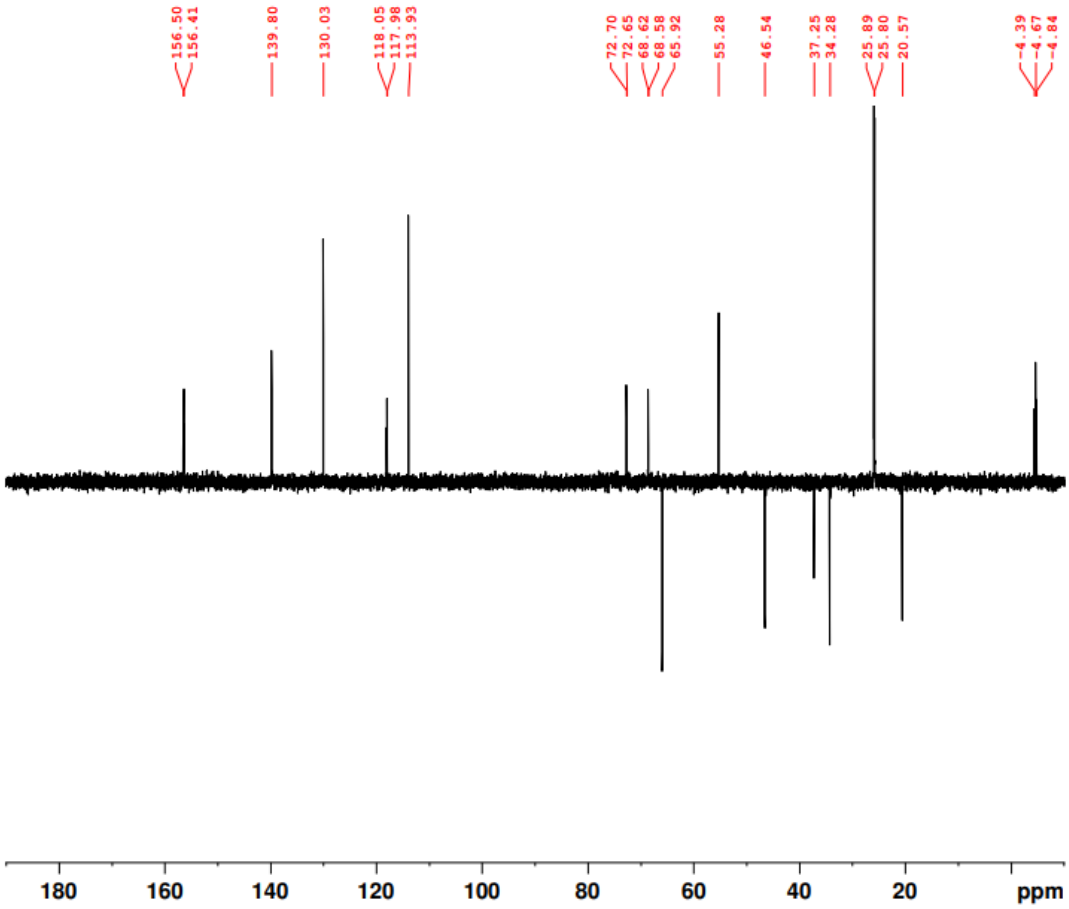


Figure A.4.15: DEPT 135 (400 MHz $CDCl_3$) of 4.12.C

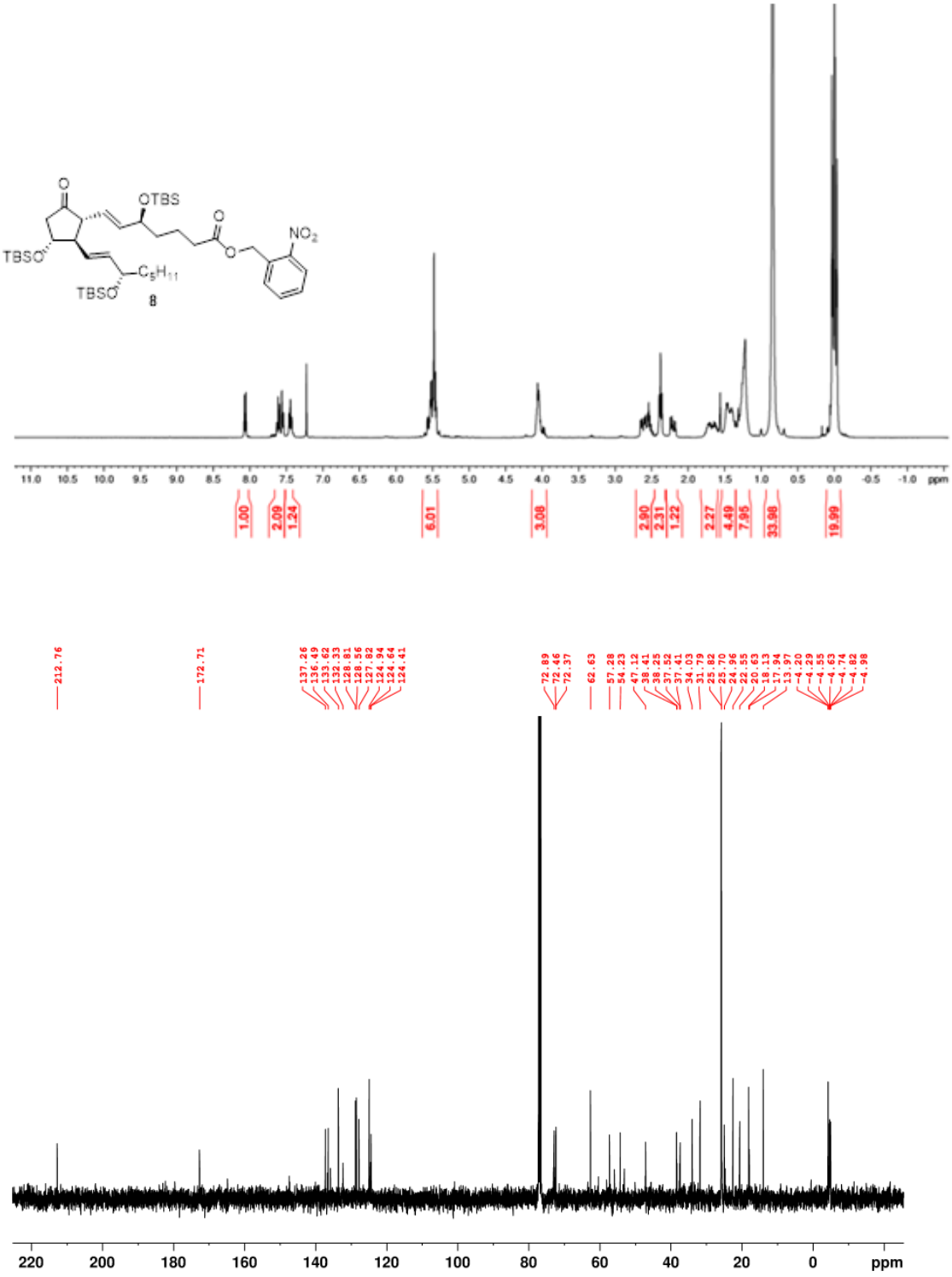


Figure A.4.16: ^{1}HNMR (400 MHz $CDCl_3$) and ^{13}CNMR (100 MHz, $CDCl_3$) of 4.14

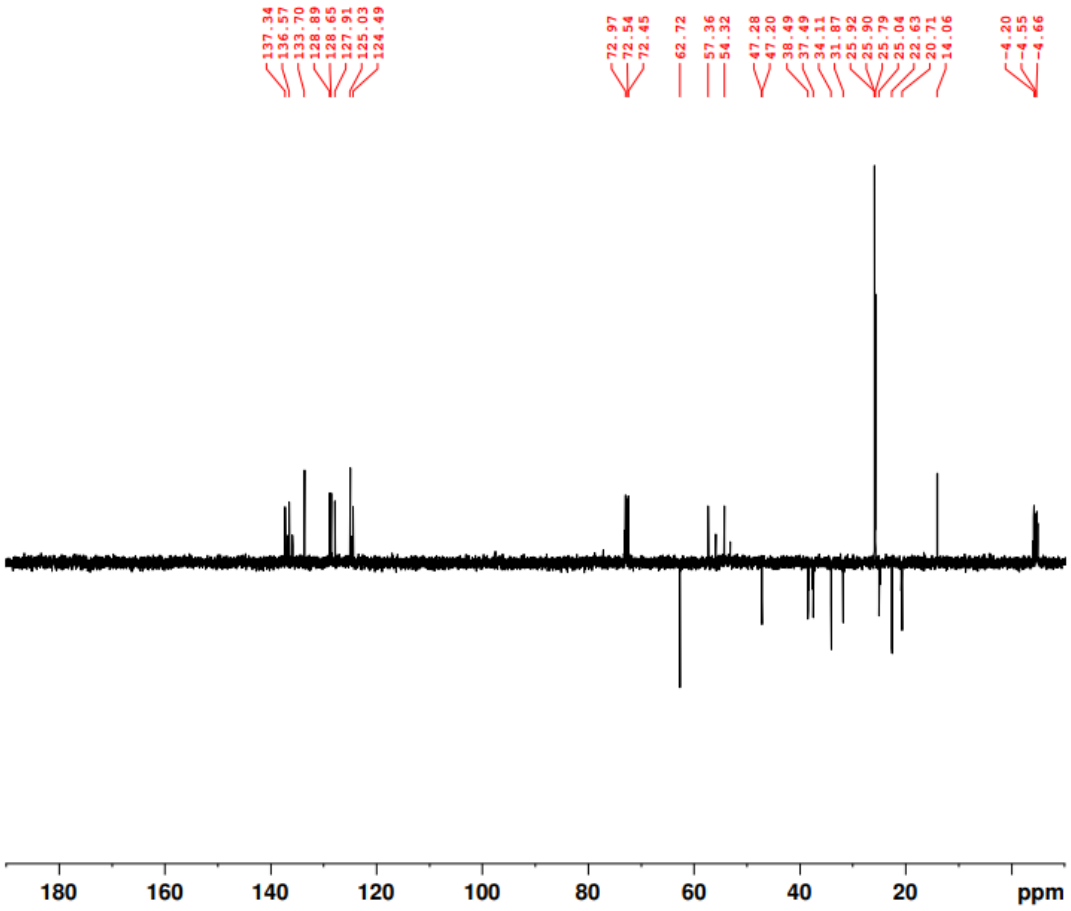


Figure A.4.17: DEPT 135 NMR (100 MHz, $CDCl_3$) of 4.14

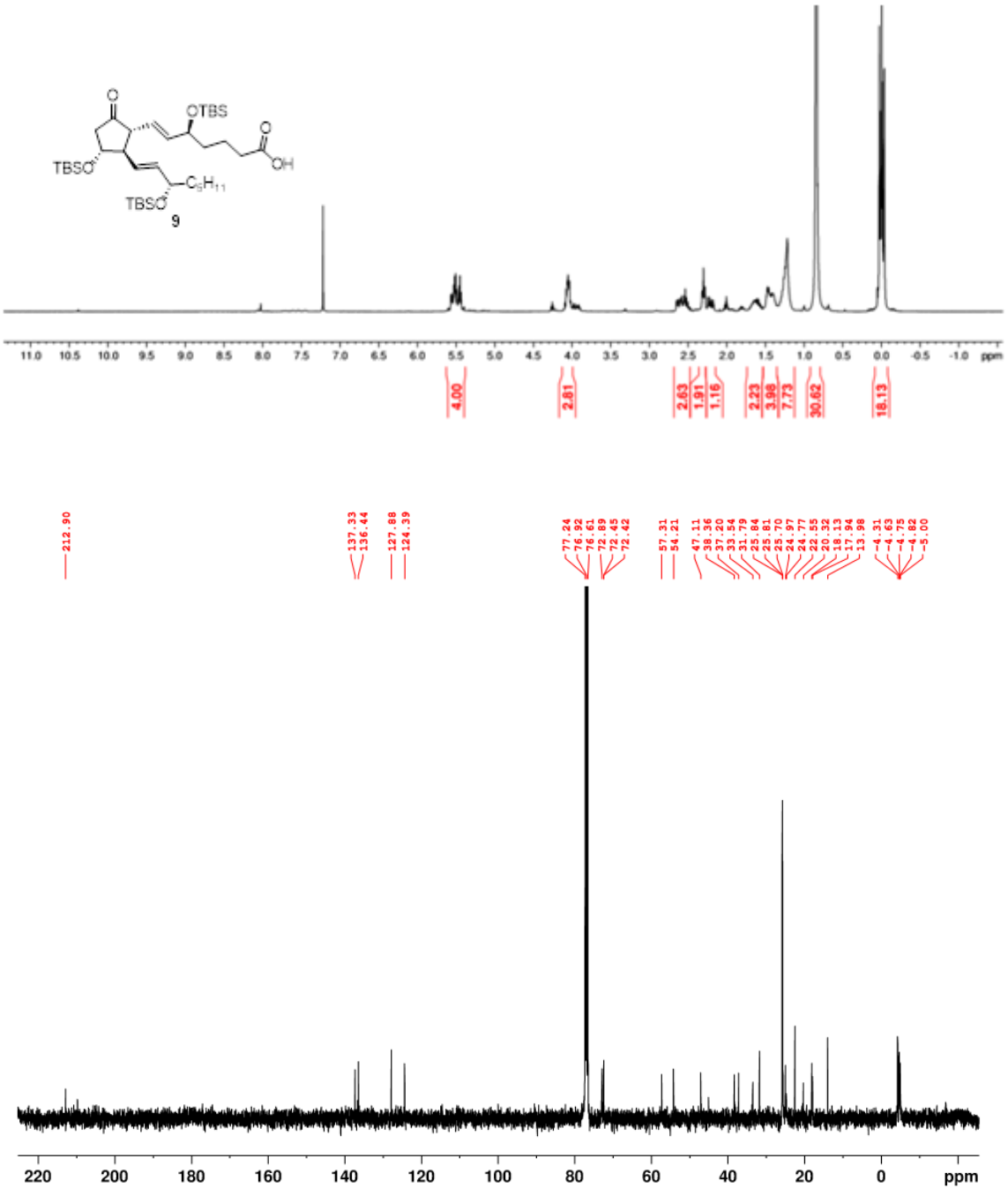


Figure A.4.18: ^{1}HNMR (400 MHz $CDCl_3$) and ^{13}CNMR (100 MHz, $CDCl_3$) of 4.15

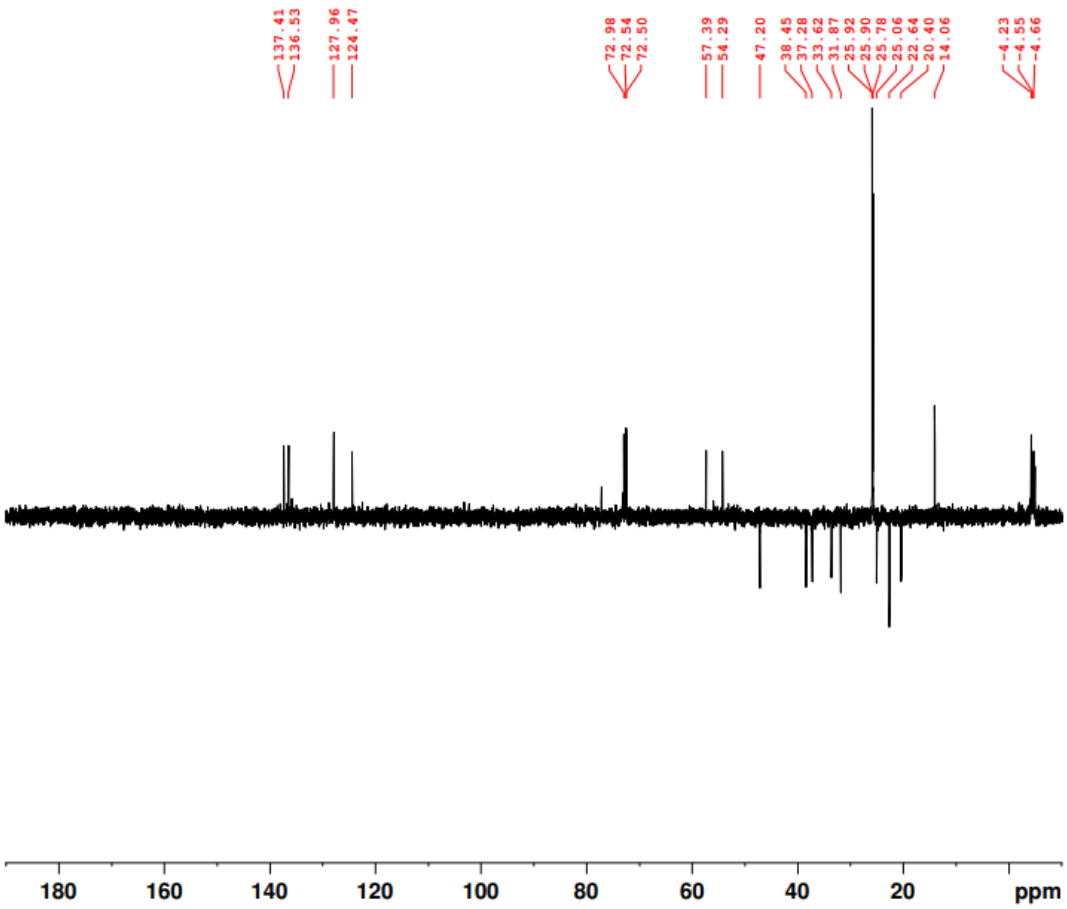


Figure A.4.19: DEPT 135 NMR (100 MHz, $CDCl_3$) of 4.15

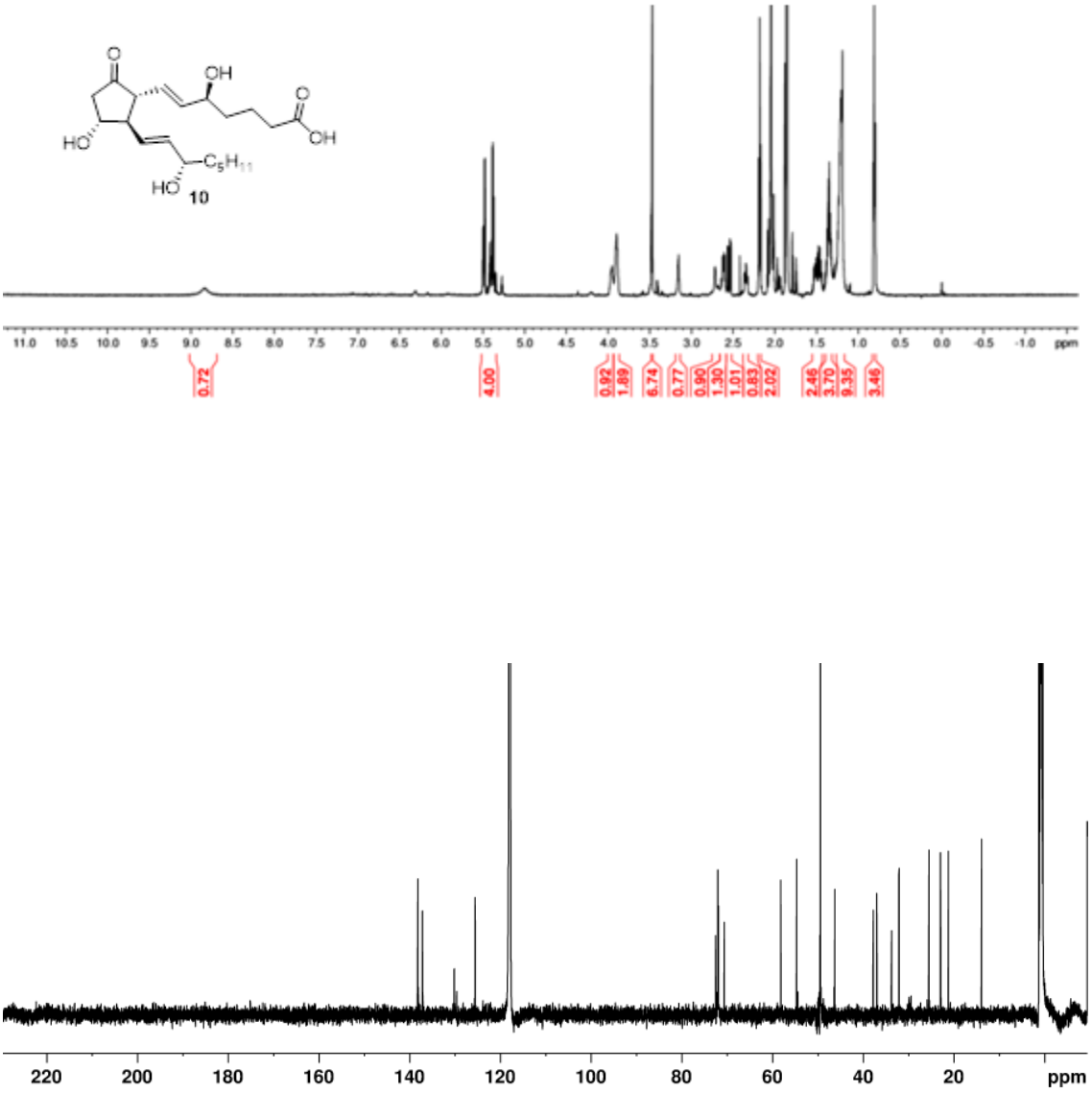


Figure A.4.20: ^{1}HNMR (600 MHz CD_3CN) and ^{13}CNMR (150 MHz, CD_3CN) of 5-OH PGE_2

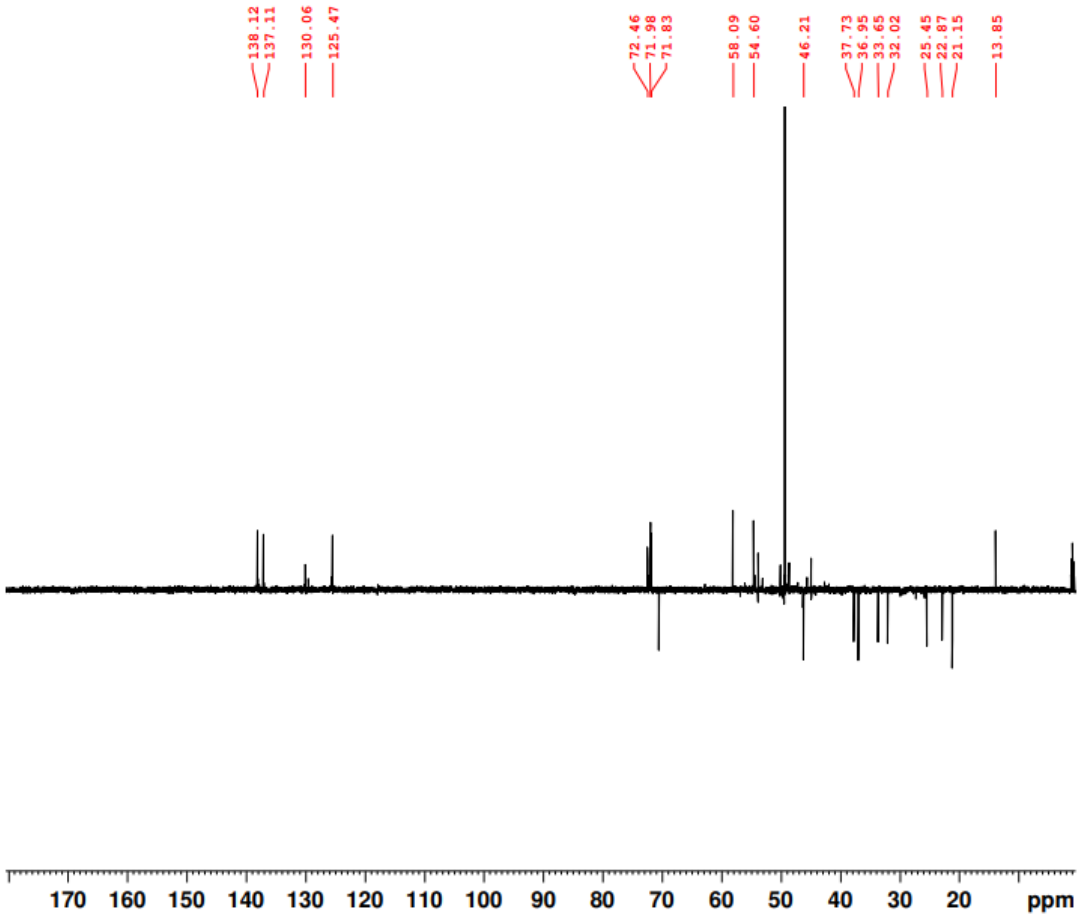


Figure A.4.21: DEPT 135 NMR (100 MHz, CD_3CN) of 5-OH PGE_2

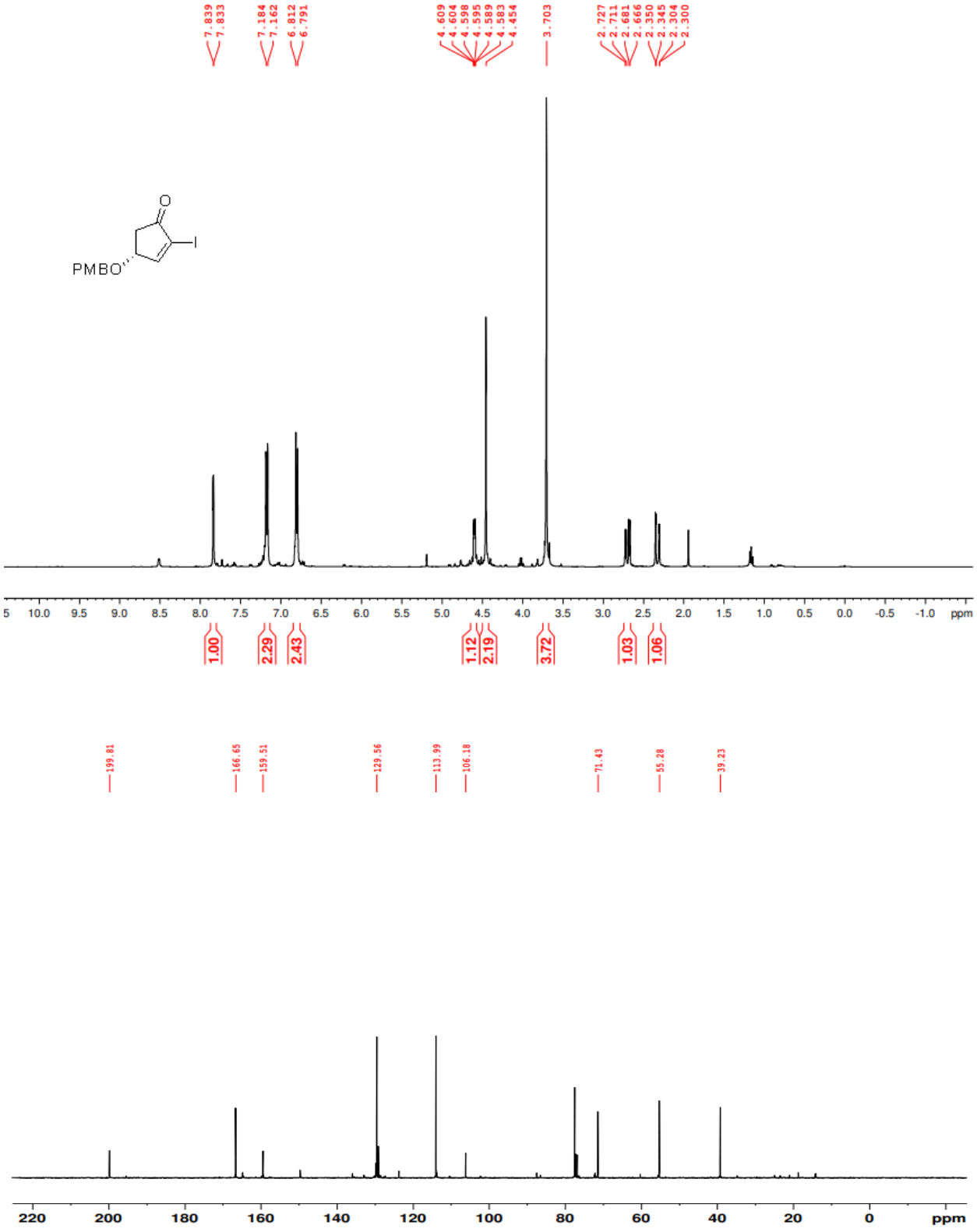


Figure A.4.22: ^{1}HNMR (400 MHz $CDCl_3$) and ^{13}CNMR (100 MHz, $CDCl_3$) of 4.16

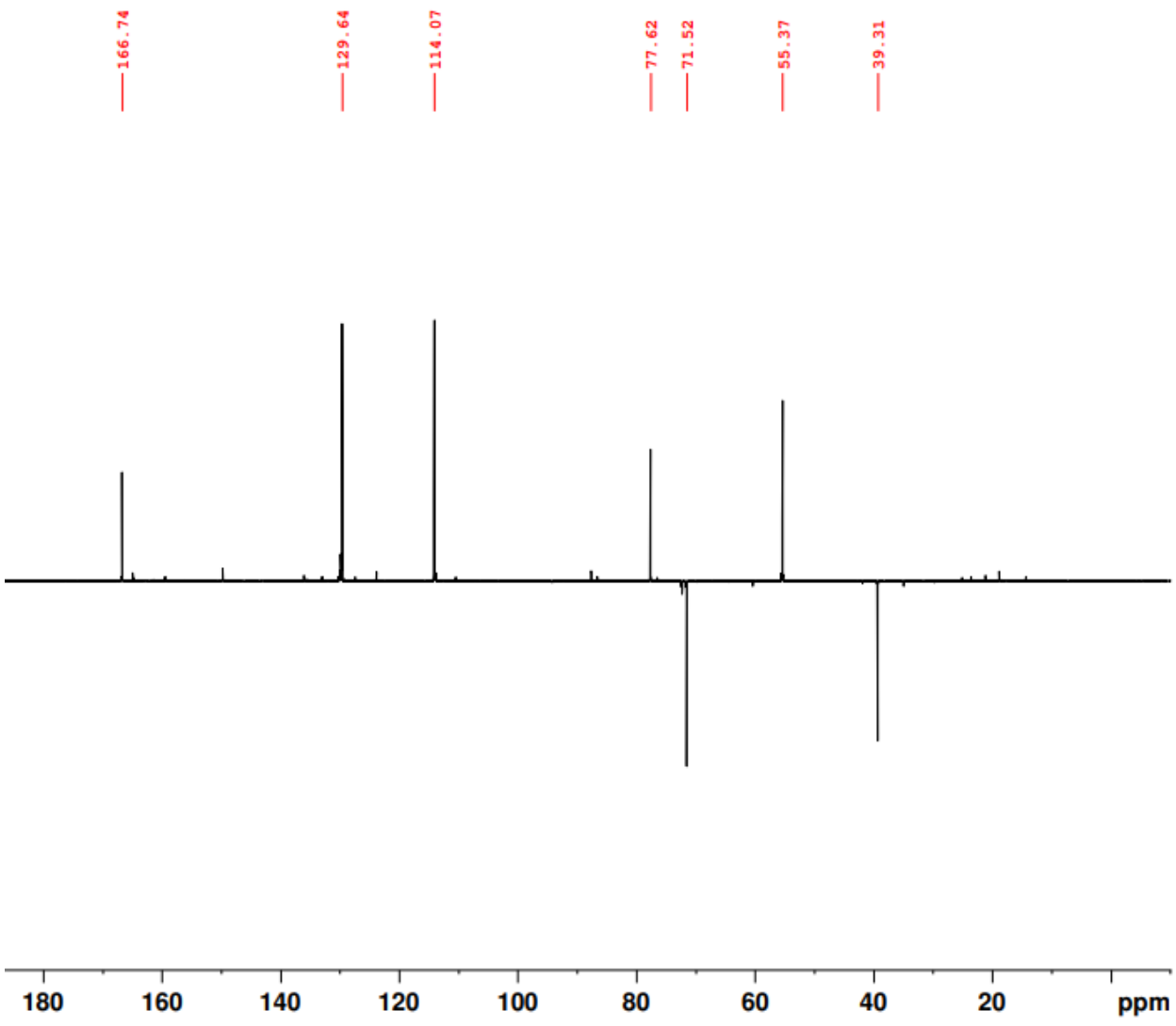


Figure A.4.23:DEPT 135 NMR (100 MHz, $CDCl_3$) of 4.16

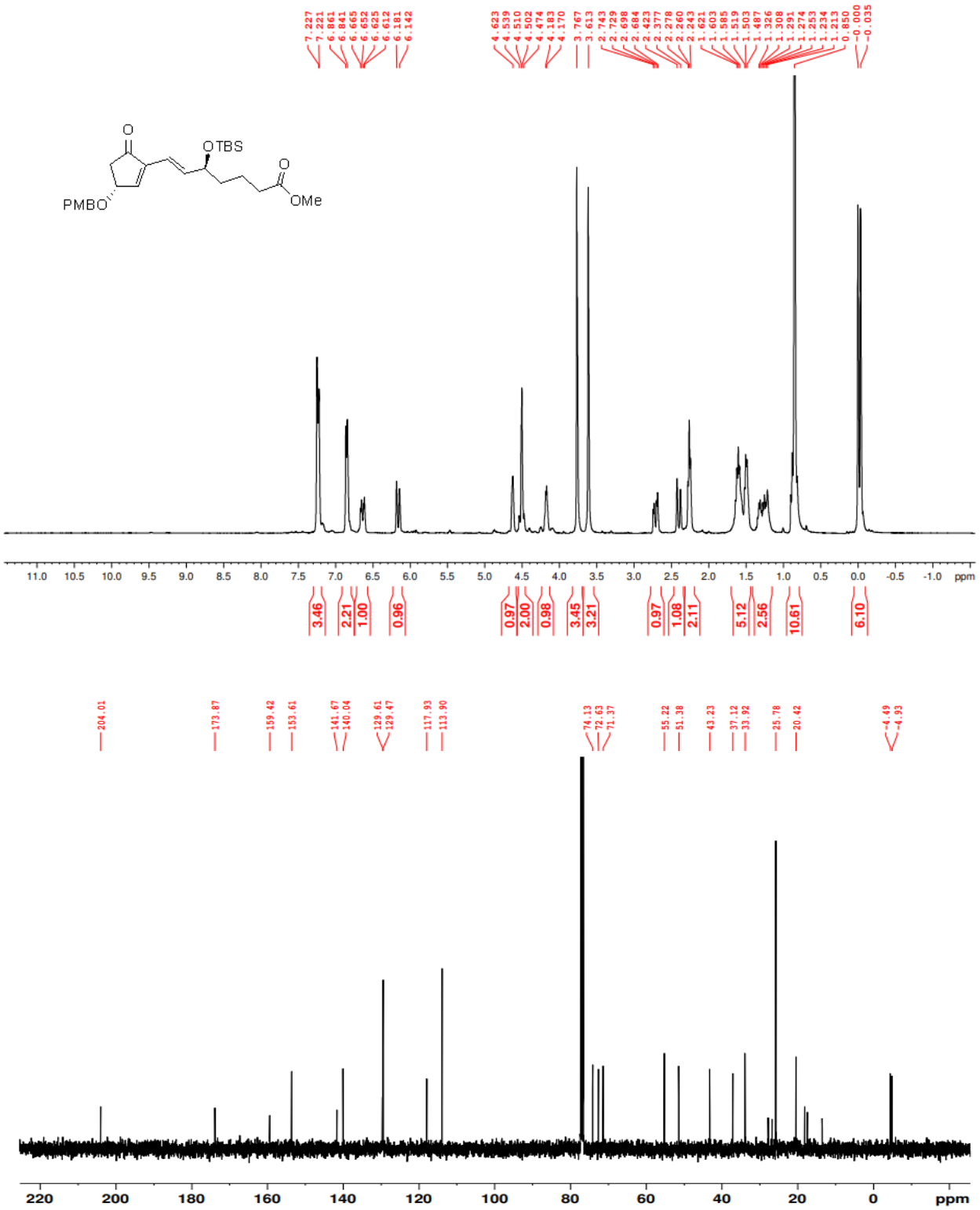


Figure A.4.24: ^{1}HNMR (400 MHz $CDCl_3$) and ^{13}CNMR (100 MHz, $CDCl_3$) of 4.17.A

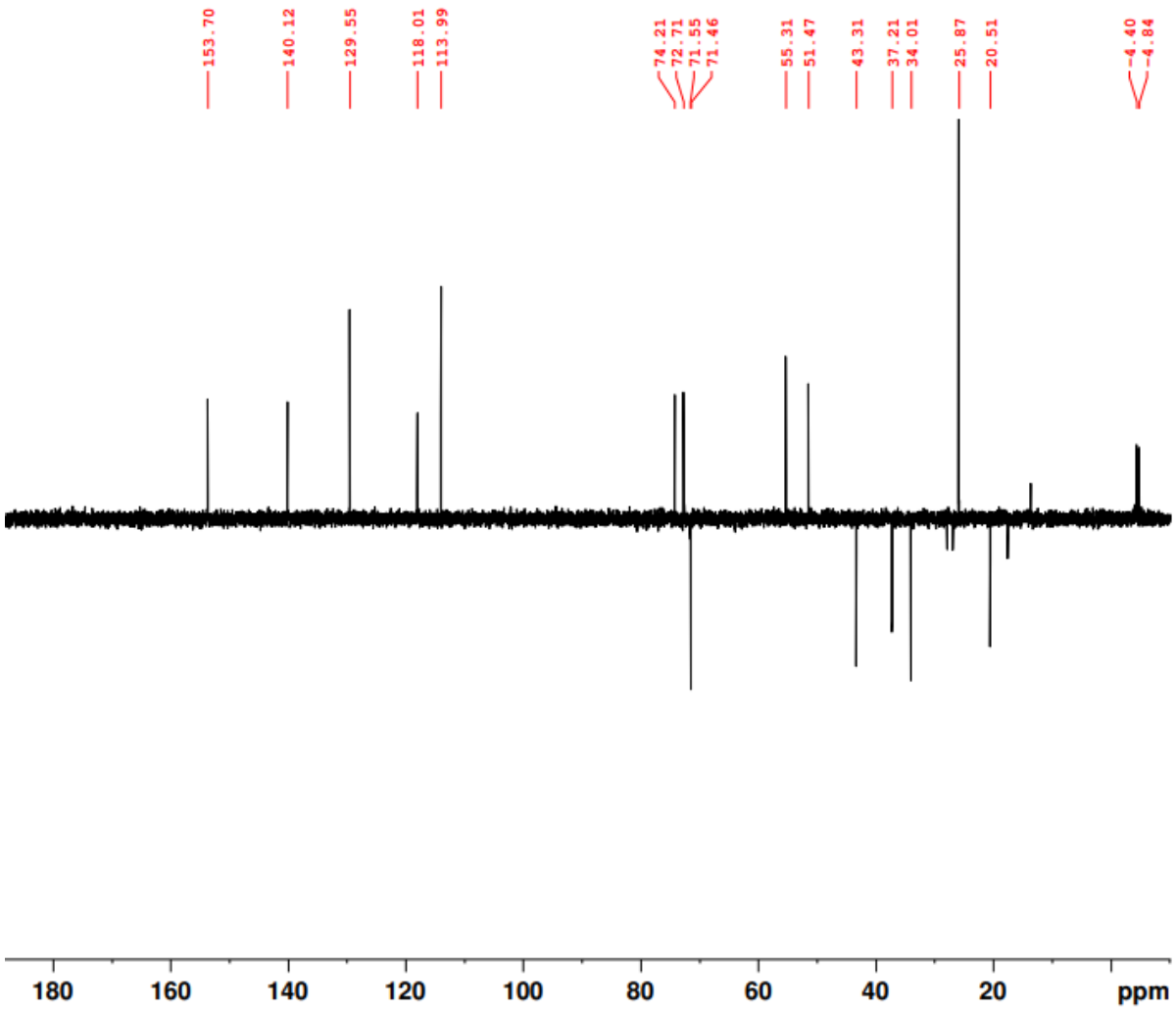


Figure A.4.25: DEPT 135 NMR (100 MHz, $CDCl_3$) of 4.17.A

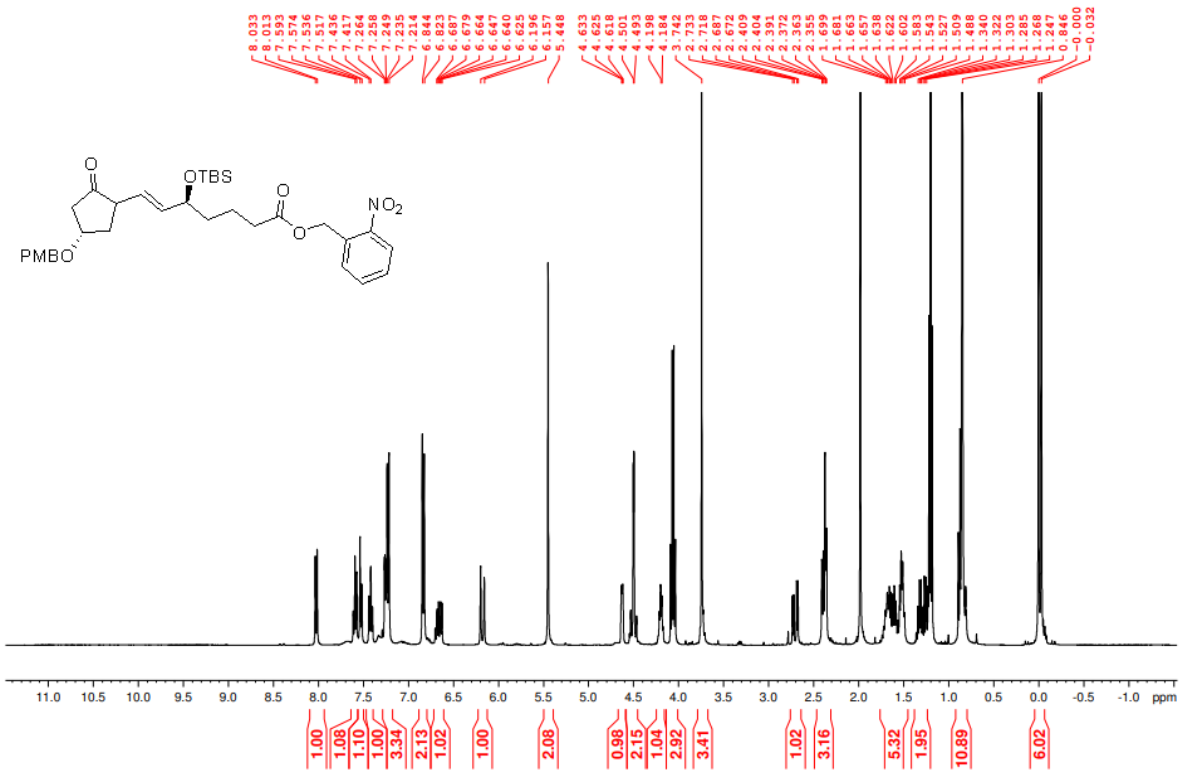


Figure A.4.26: ^{1}HNMR (400 MHz $CDCl_3$) 4.17

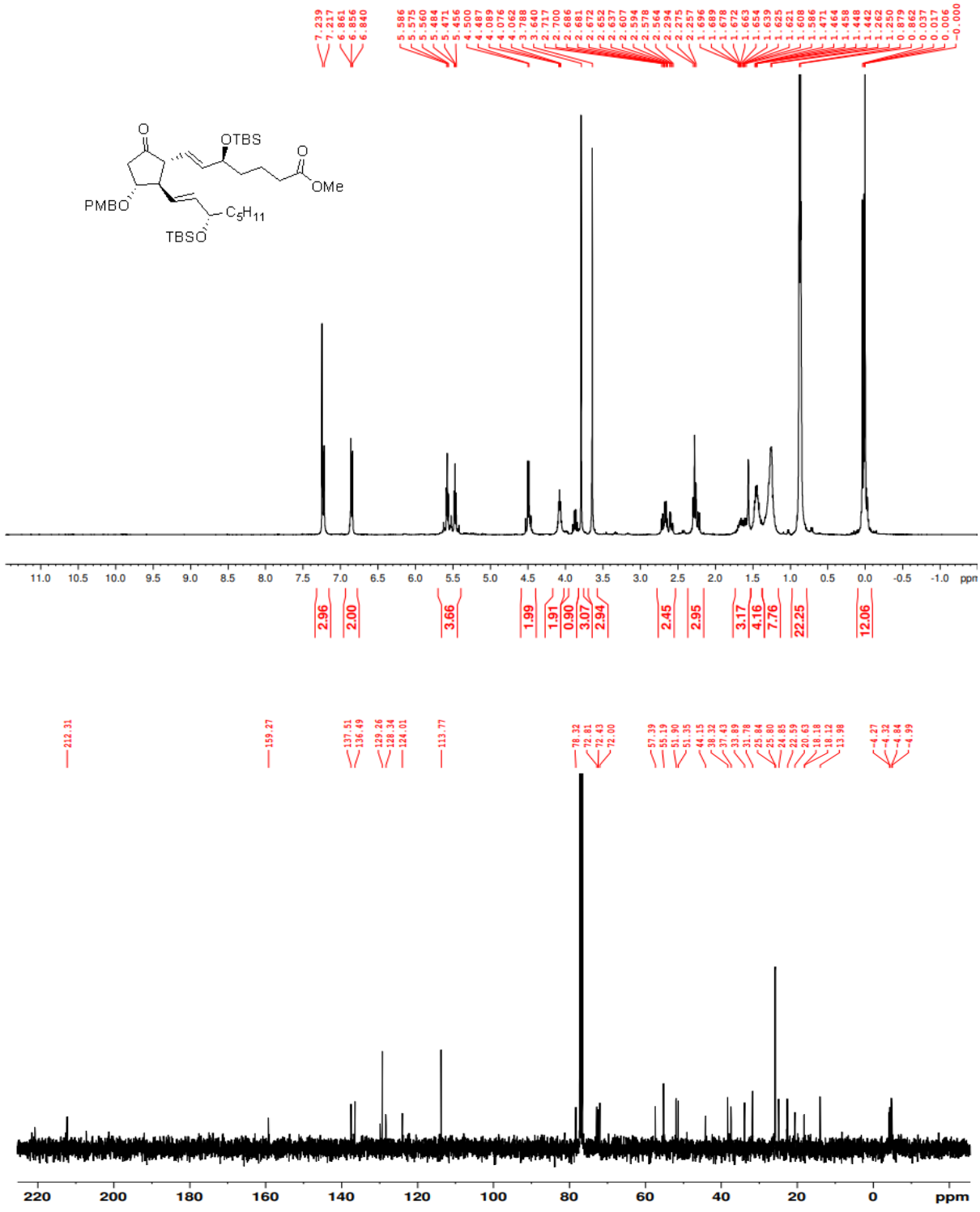


Figure A.4.27: ^{1}HNMR (400 MHz $CDCl_3$) and ^{13}CNMR (100 MHz, $CDCl_3$) of 4.18.A

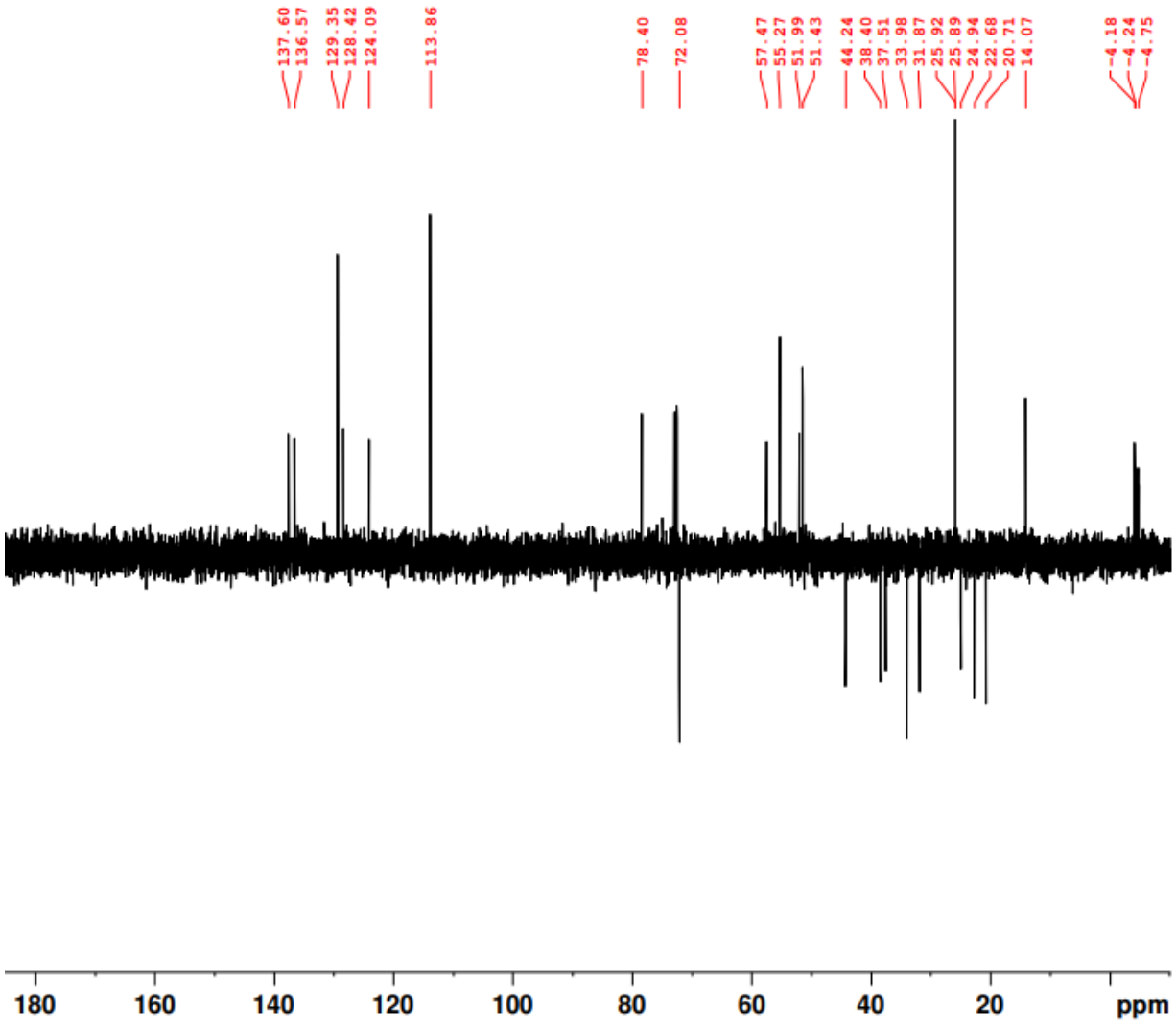


Figure A.4.28: DEPT 135 NMR (100 MHz, $CDCl_3$) of 4.18.A

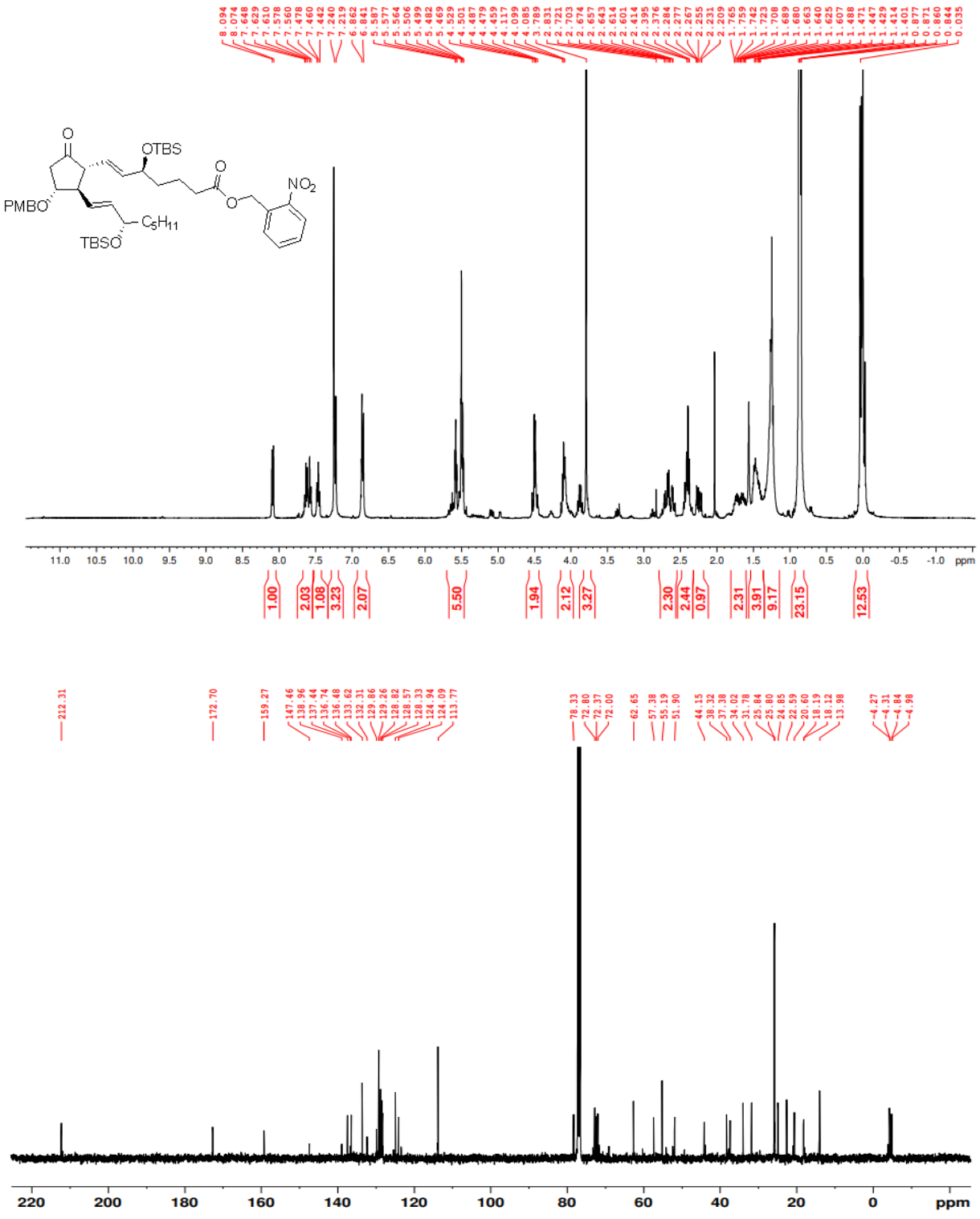


Figure A.4.29: ^{1}HNMR (400 MHz $CDCl_3$) and ^{13}CNMR (100 MHz, $CDCl_3$) of 4.18

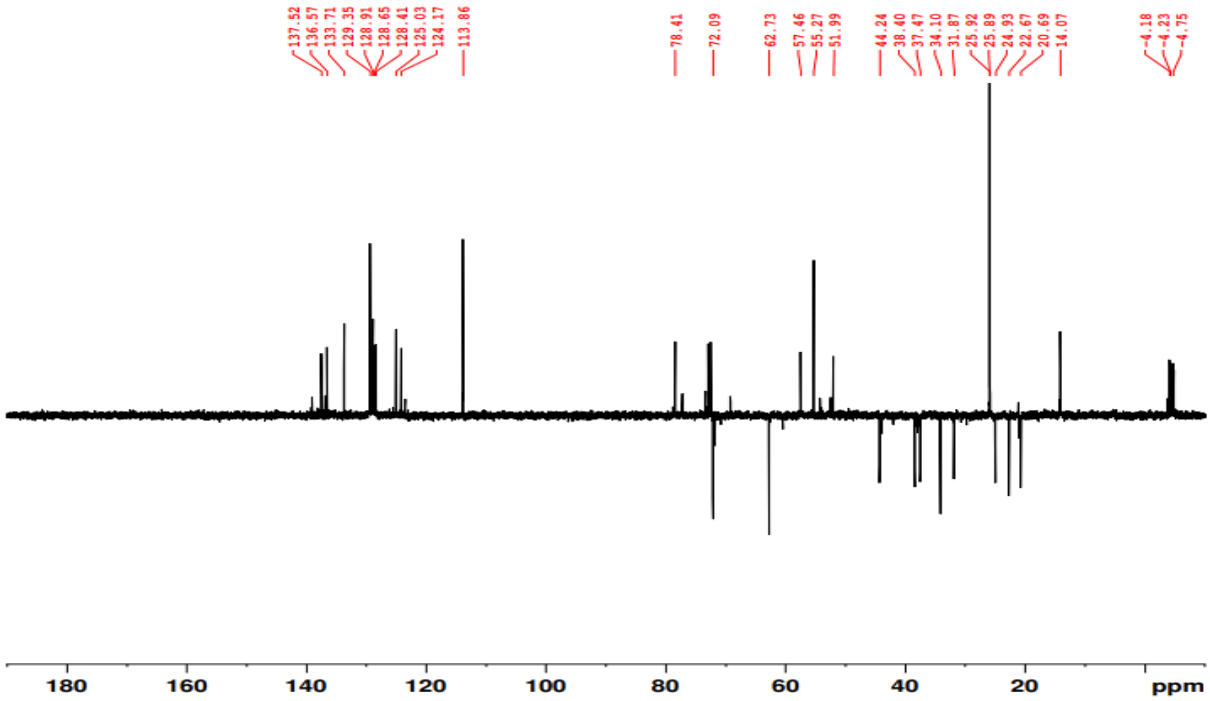


Figure A.4.30: DEPT 135 NMR (100 MHz, $CDCl_3$) of 4.18

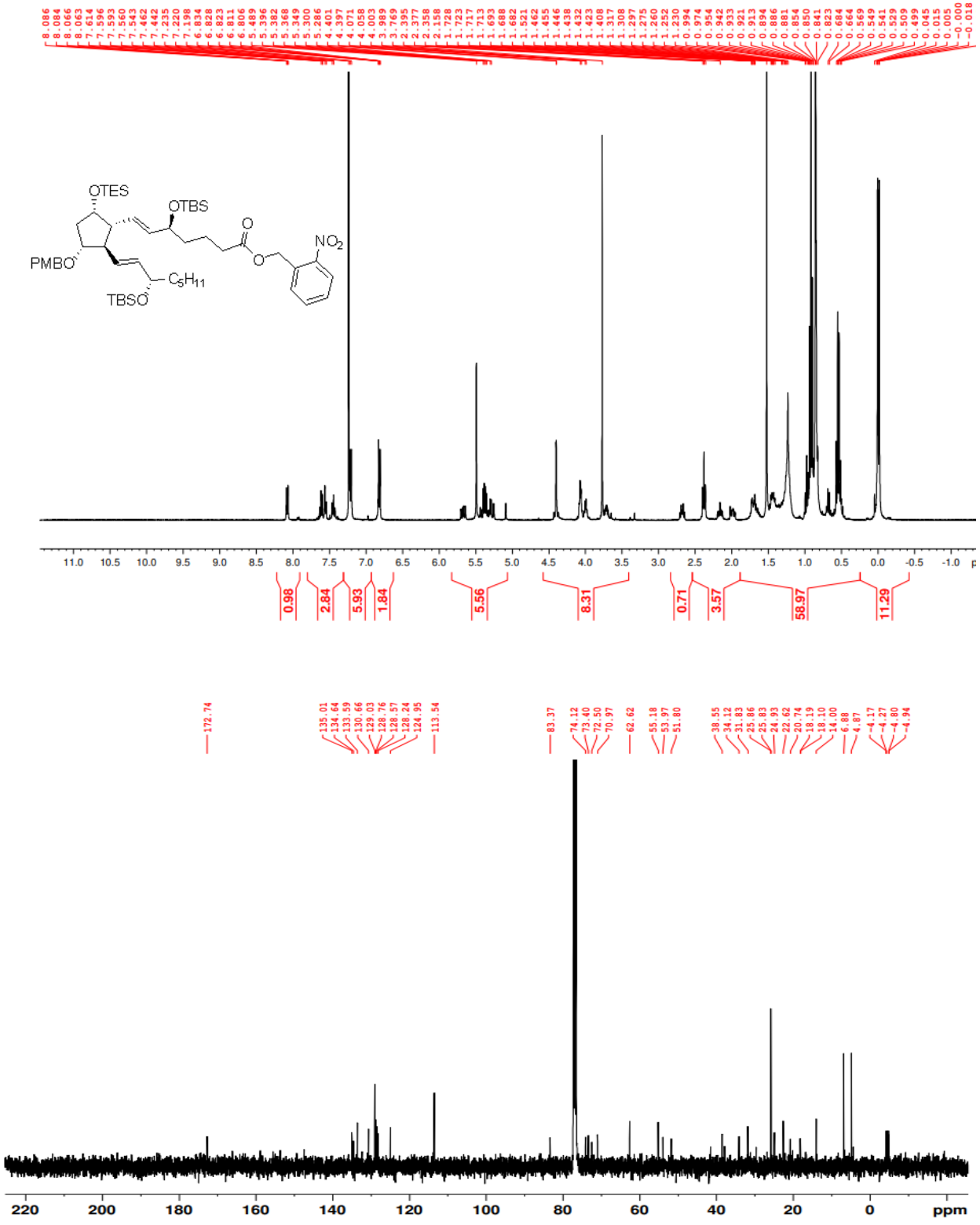


Figure A.4.31: ^{1}HNMR (400 MHz $CDCl_3$) and ^{13}CNMR (100 MHz, $CDCl_3$) of 4.19

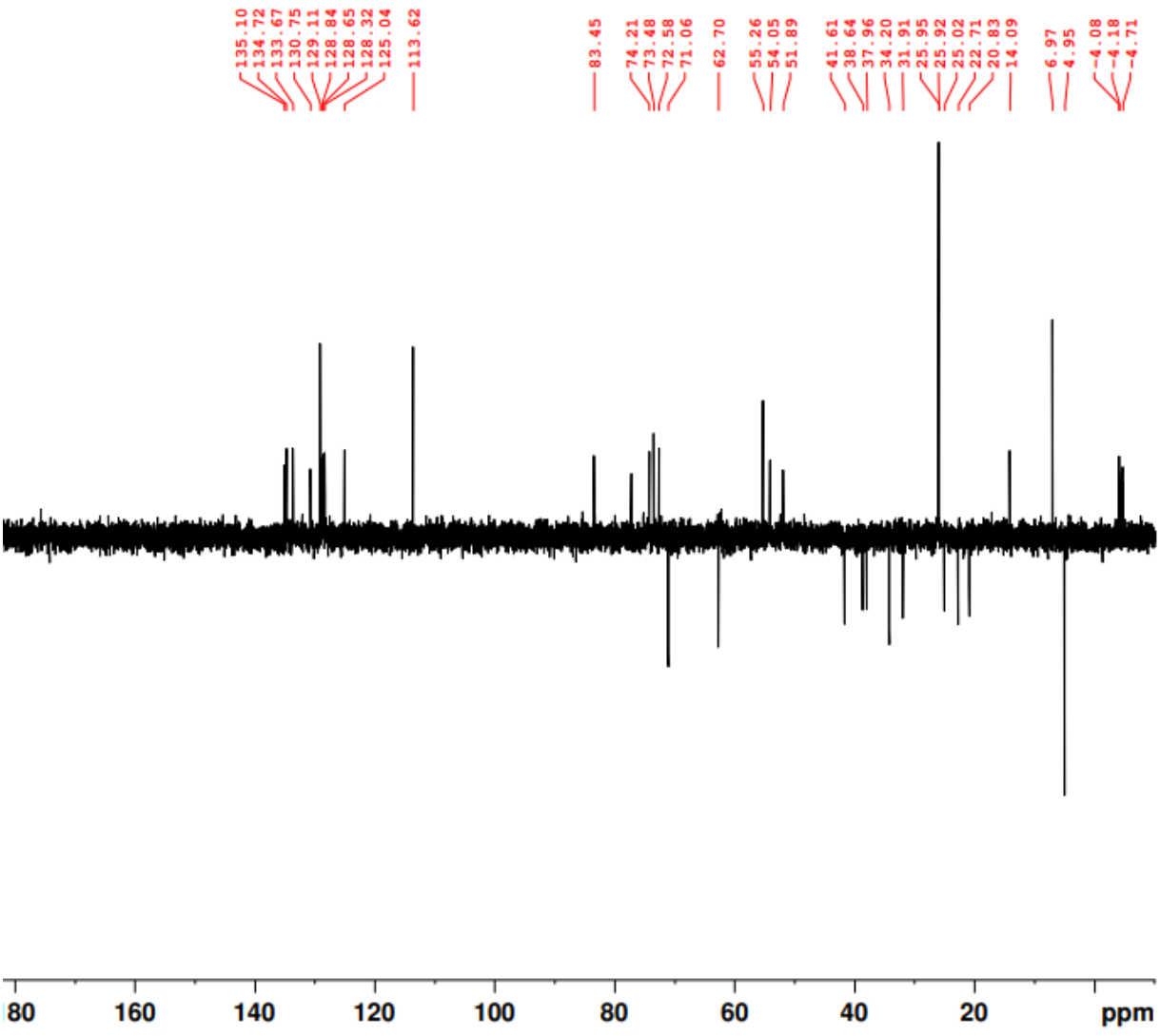


Figure A.4.32:DEPT 135 NMR (100 MHz, $CDCl_3$) of 4.19

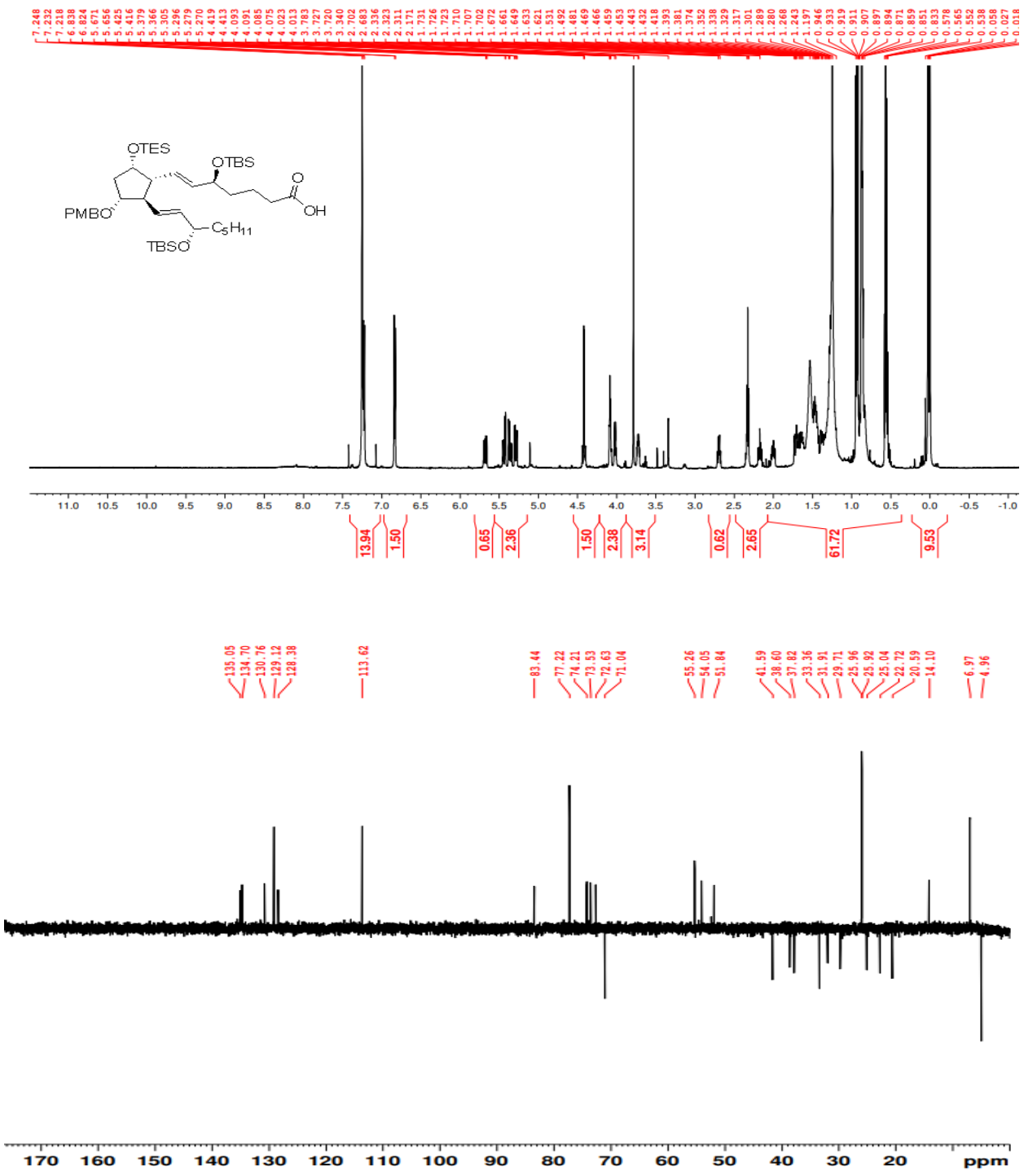


Figure A.4.33: ^{1}HNMR (400 MHz $CDCl_3$) and DEPT 135 NMR (100 MHz, $CDCl_3$) of 4.20

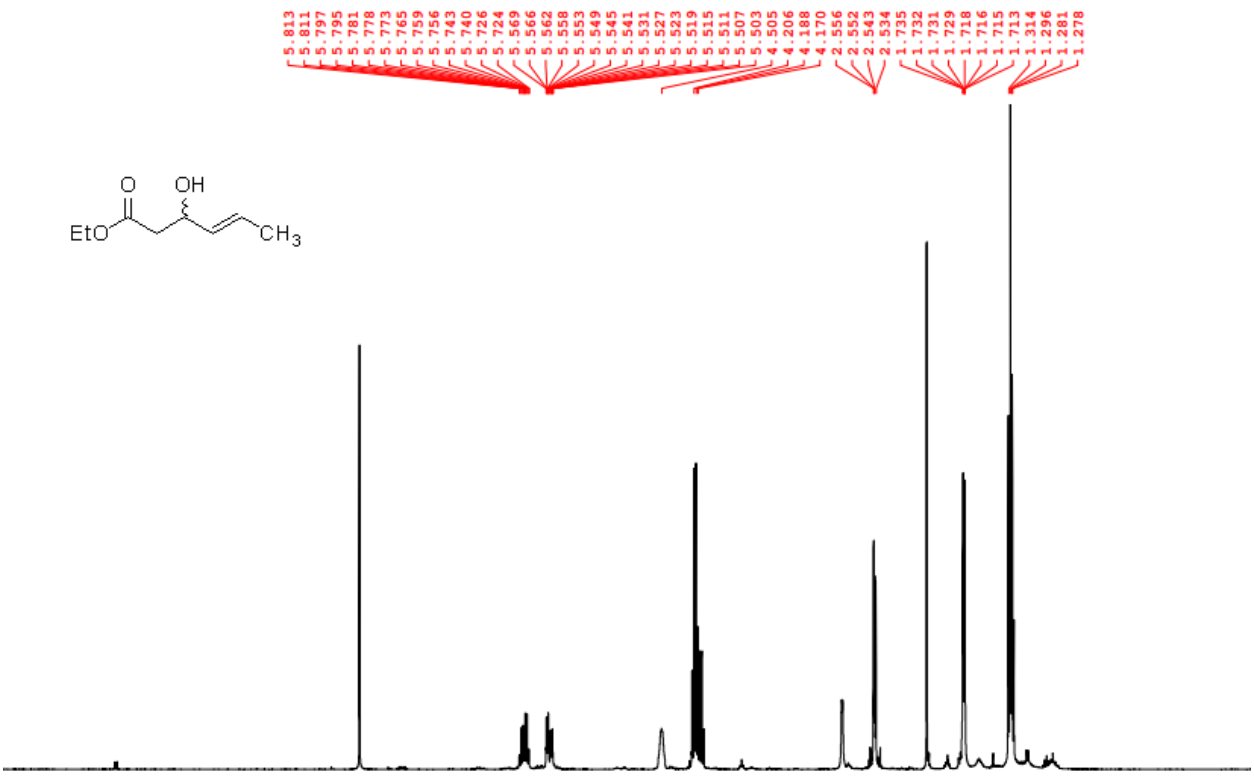


Figure A.4.34: ^{1}HNMR (400 MHz $CDCl_3$) of 4.22

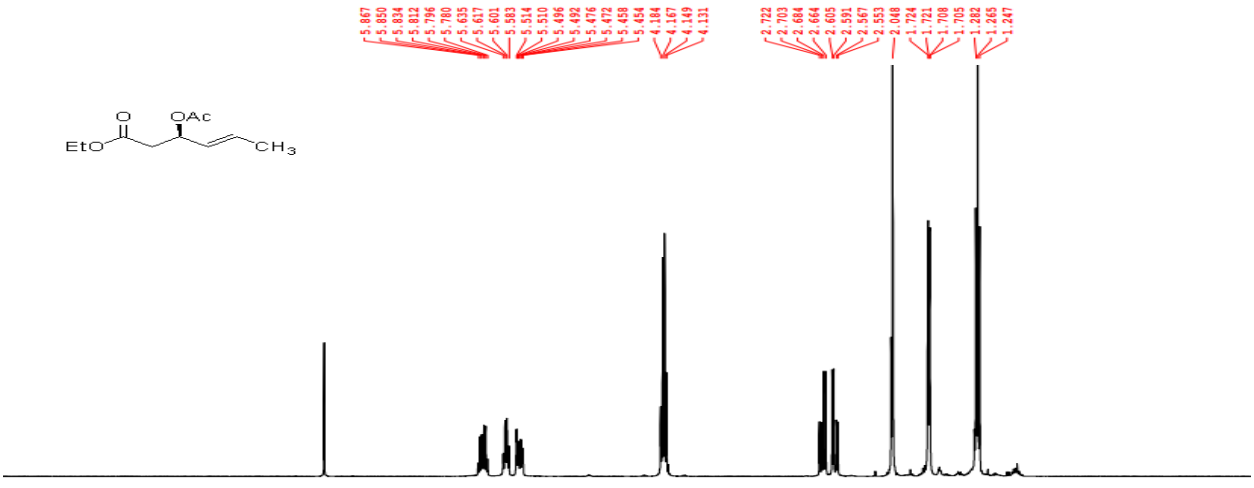


Figure A.4.35: ^{1}HNMR (400 MHz $CDCl_3$) of 4.23

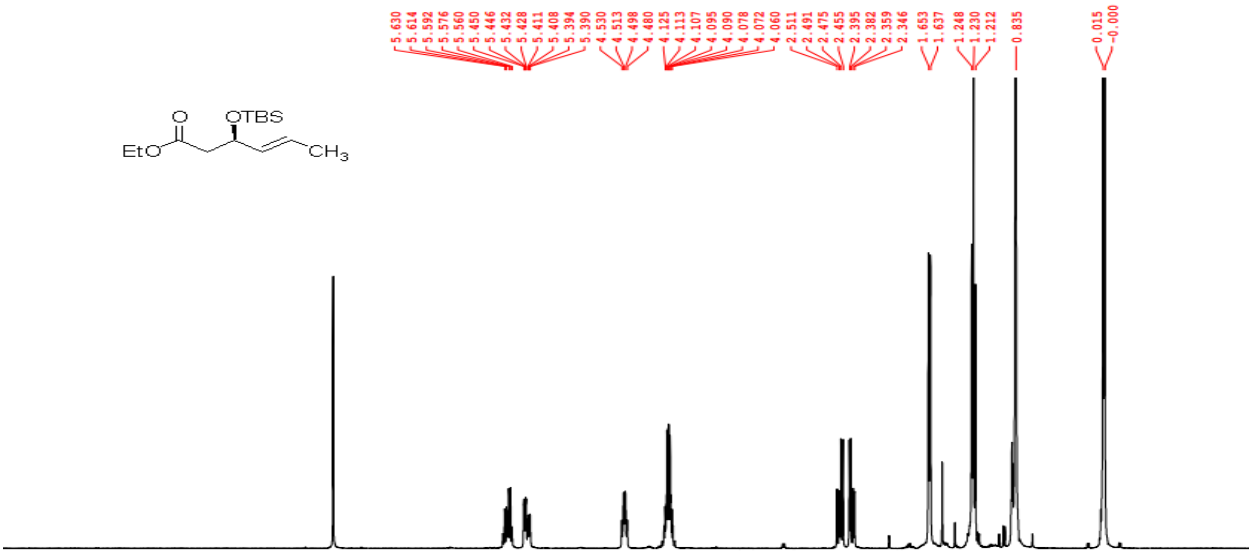


Figure A.4.36: ^{1}HNMR (400 MHz $CDCl_3$) of 4.24

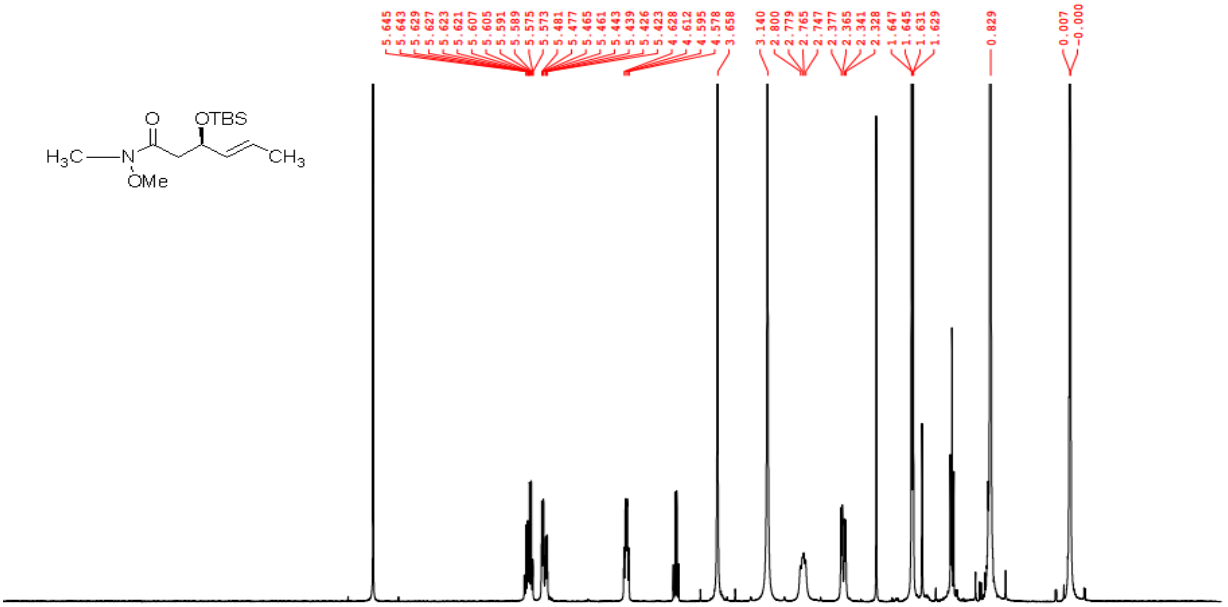


Figure A.4.37: ^{1}HNMR (400 MHz $CDCl_3$) of 4.25

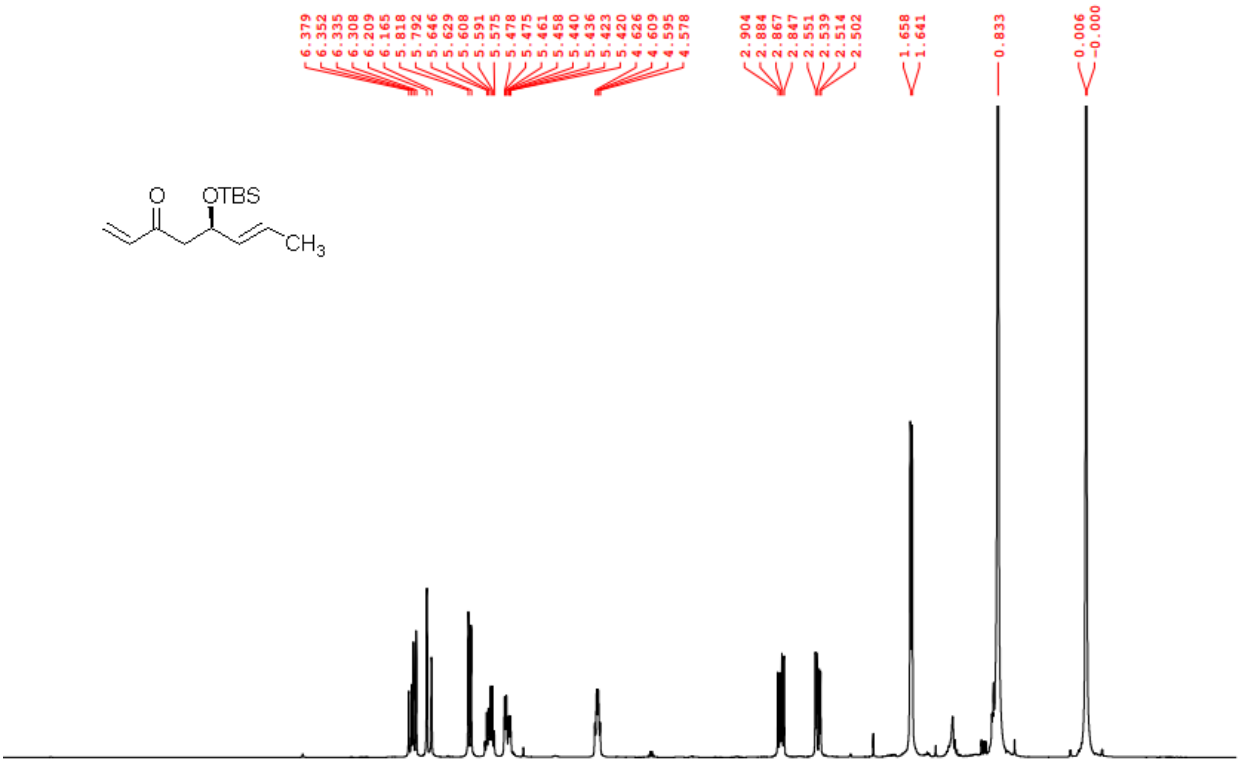


Figure A.4.38: ^{1}HNMR (400 MHz $CDCl_3$) of 4.26

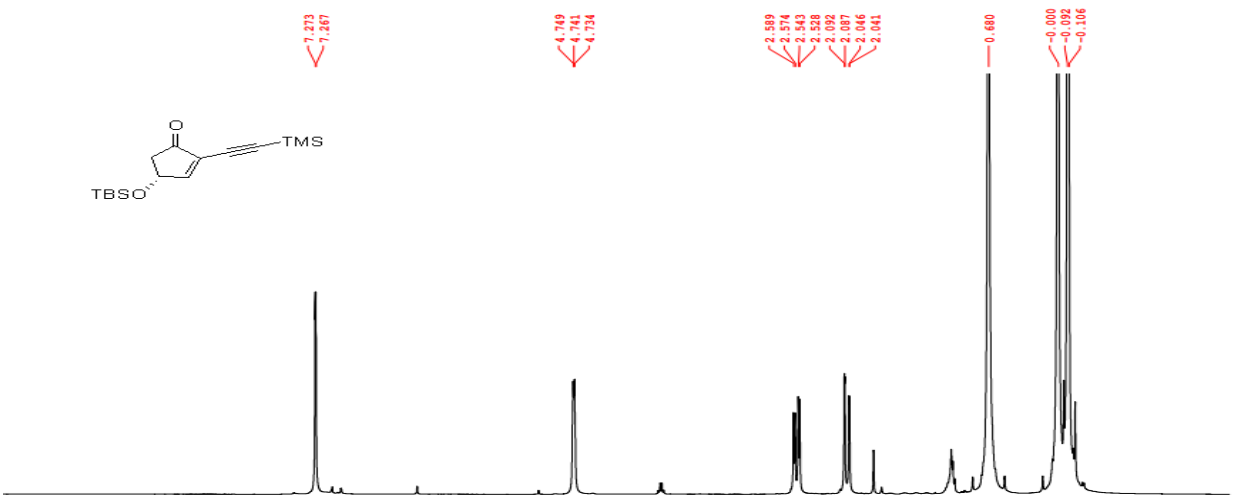


Figure A.4.39: ^{1}HNMR (400 MHz $CDCl_3$) of 4.27

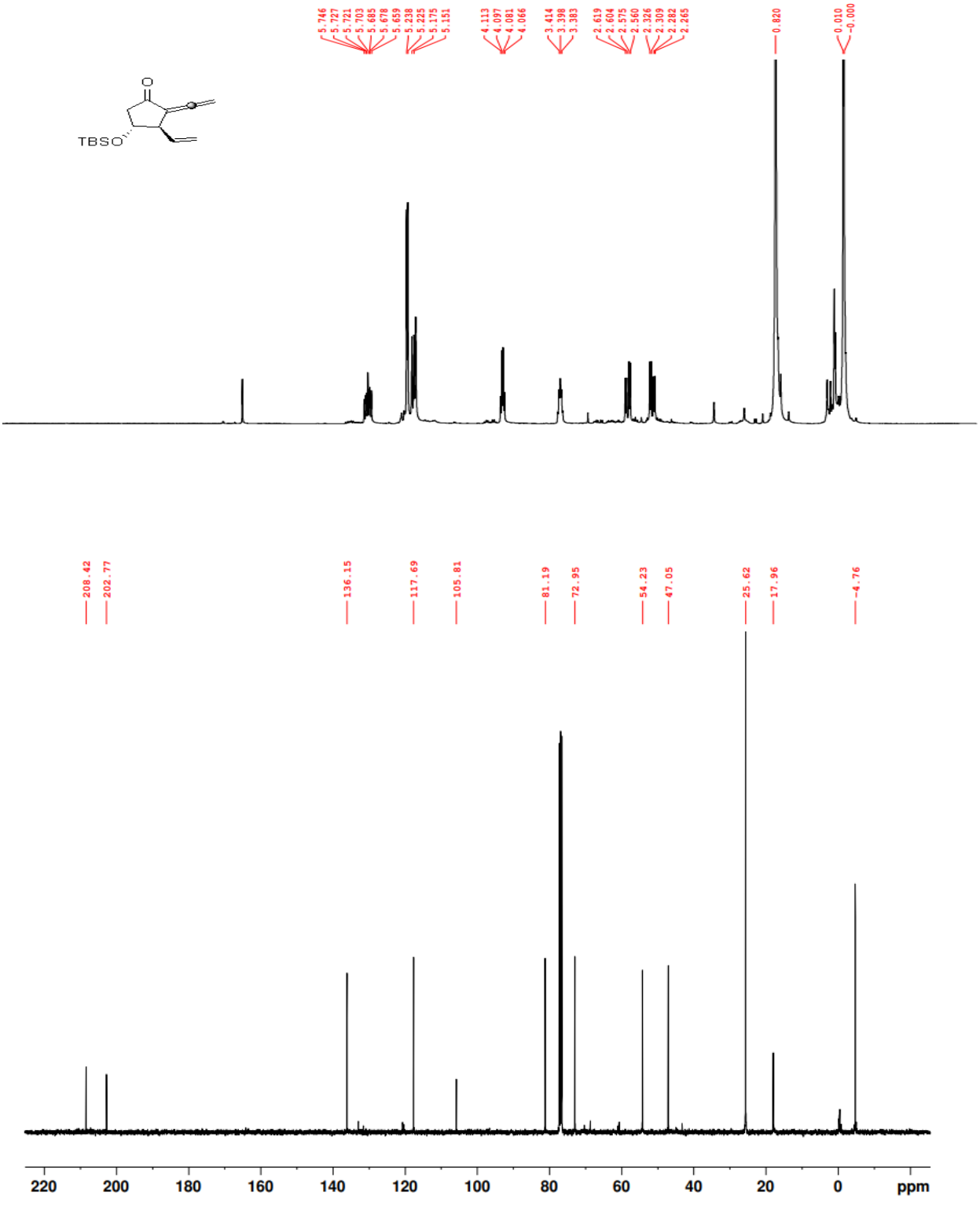


Figure A.4.40: ^{1}HNMR (400 MHz $CDCl_3$) and ^{13}CNMR (100 MHz, $CDCl_3$) of 4.28

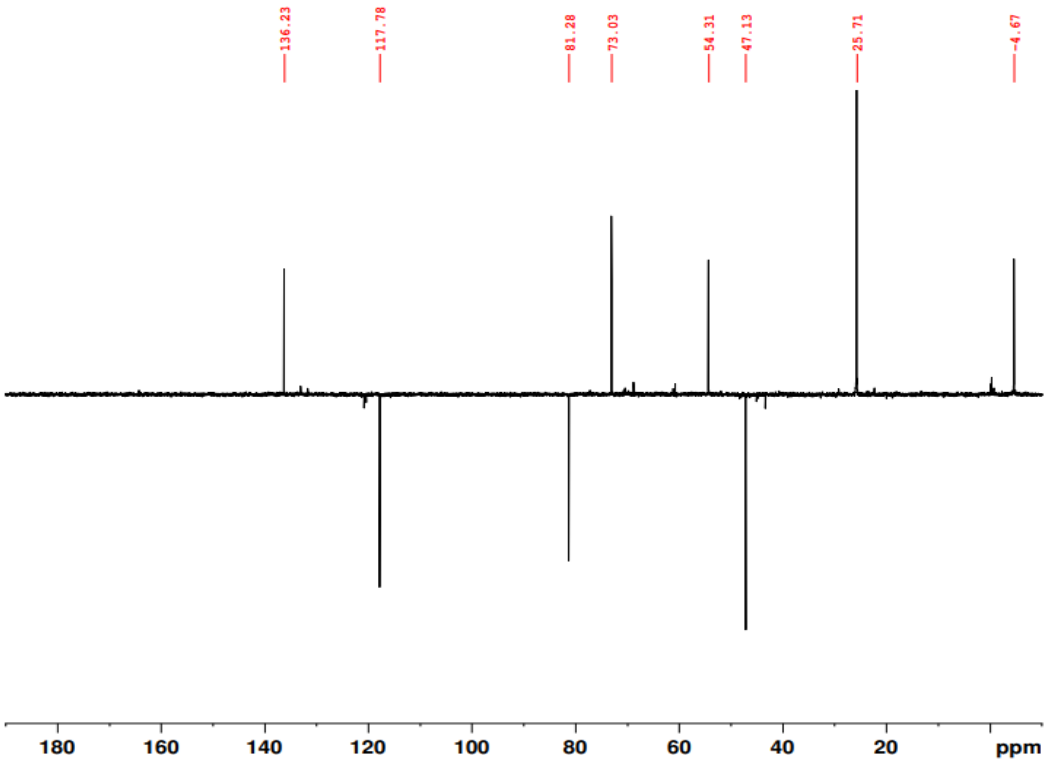


Figure A.4.41: DEPT 135 NMR (100 MHz $CDCl_3$) of 4.28

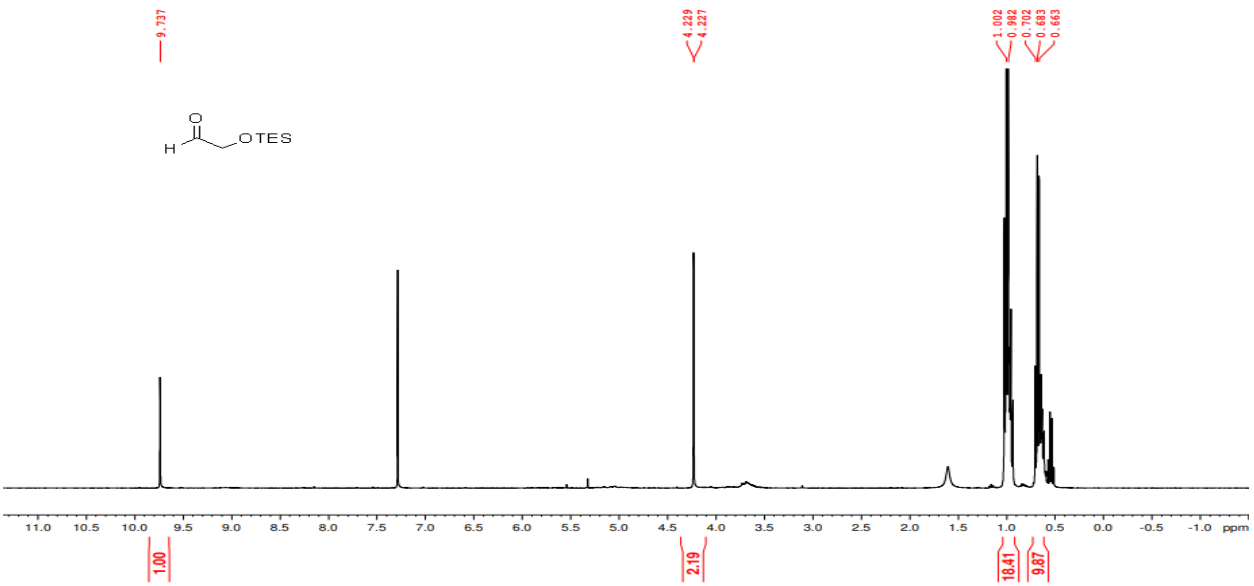


Figure A.4.42: ^{1}HNMR (400 MHz $CDCl_3$) of 4.29

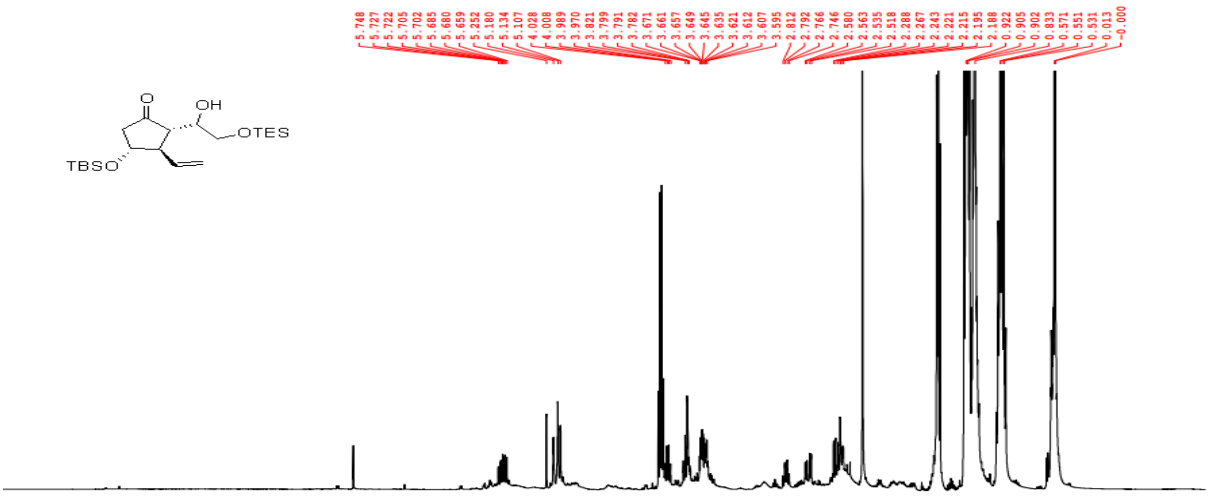


Figure A.4.43: ^{1}HNMR (400 MHz $CDCl_3$) of 4.30