APPROACHES TOWARD THE CHEMICAL SYNTHESIS OF NOVEL ARACHIDONIC ACID METABOLITES HEMIKETAL D_2 AND HEMIKETAL E_2

By

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For Mom and Dad

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AA	arachidonic acid
Ac	acetyl
Ac_2O	acetic anhydride
acac	acetylacetone
app	apparent
AIBN	azobisisobutyronitrile
BBN	borabicyclo[3.3.1]nonane
BHT	butylated hydroxy toluene (2,6-di-t-butyl-4-methylphenol)
BINAL	lithium 2,2'-dihydroxy-1,1'-binaphthylethoxyaluminum hydride
Bn	benzyl
BOM	benzyloxymethyl
br	broad
Bs	p-bromobenzenesulfonate
Bu	butyl
Bz	benzoyl
°C	degrees Celsius
CBS	Corey Bakshi Shibata catalyst
$(CH_2O)_n$	paraformaldehyde
COSY	correlation spectroscopy
COX	cyclooxygenase
Cp	cyclopentadienyl
$cPLA_2$	cytosolic phospholipase A_2
Δ	reflux
δ	chemical shift in ppm
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexyl carbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
DHA	docosahexaenoic acid
DIBAL	diisobutylaluminum hydride
DIPCl	B-chlorodiisopinocampheylborane
DIPT	diisopropyl tartrate
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DME	1,2-dimethoxyethane
DMF	dimethyl formamide

DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dppf	1,1'-bis(diphenylphosphanyl)ferrocene
ee	enantiomeric excess
EHA	eicosapentaenoic acid
Et	ethyl
g	gram
GPCR	G-protein coupled receptor
HETE	hydroxyicosatetraenoic acid
HMBC	heteronuclear multiple bond correlation spectroscopy
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphorictriamide
HPETE	hydroperoxyeicosatetraenoic acid
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence spectroscopy
Hz	hertz
*i*Bu	isobutyl
IBX	2-iodoxybenzoic acid
Im	imidazole
*i*Pr	isopropyl
IR	infrared spectroscopy
isoF	isofuran
isoP	isoprostane
J	coupling constant
L	liter
LA	linoleic acid
LDA	lithium diisopropylamide
LOX	lipoxygenase
LT	leukotriene
LX	lipoxin
M	molar concentration, mega
μ	micro
m	milli, multiplet
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
mol	mole
Ms	methanesulfonate
MS	molecular sieves
N	normal concentration
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NOE	nuclear Overhauser effect

NOESY	nuclear Overhauser effect spectroscopy
Nuc	nucleophile
OAc	acetoxy
p	pentet
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PG	prostaglandin
Ph	phenyl
Piv	pivaloate
PMB	*para*-methoxybenzyl
PMBCl	*para*-methoxybenzylchloride
ppm	parts per million
PPTS	pyridinium *para*-toluenesulofnate
Py	pyridine
q	quartet
rt	room temperature
s	singlet
sBu	*sec*-butyl
Sia_2BH	disiamylborane
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBDPSCl	*tert*-butyldiphenylsilyl chloride
TBS	*tert*-butyldimethylsilyl
TBSCl	*tert*-butyldimethylsilyl chloride
TBSOTf	*tert*-butyldimethylsilyl trifluromethanesulfonate
*t*Bu	*tert*-butyl
TDMPP	tris(2,6-dimethoxyphenyl)phosphine
TEMPO	(2,2,6,6-tetramethyl-piperidin-1-yl)oxyl
TES	triethylsilyl
TESCl	triethylsilyl chloride
THF	tetrahydrofuran
THP	tetrahydropyran
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
TPAP	tetra-*n*-propylammonium perruthenate
Ts	para-toluenesulfonate

CHAPTER 1

LIPID MEDIATORS AND THE INFLAMMATORY PATHWAY

The Inflammatory Pathway

Inflammation is an important biological process through which the body can defend itself from infection and injury. When encountering pathogens, tissue injury, or tissue malfunction, the body uses the this tightly regulated process to clear foreign organisms, initiate tissue repair, or adapt to stress and restore homeostasis.[1] When controlled properly, this response is beneficial for restoration of normal tissue function; however, when dysregulated, this pathway can become harmful, leading to a number of pathological consequences, including inflammatory tissue damage, fibrosis, tumor growth, and autoinflammatory diseases.[1] Furthermore, chronic inflammation occurs in a number of disease states, such as atherosclerosis, diabetes, cancer, neurodegenerative disease, and cancer.[2] Therefore, understanding the complex and multi-faceted inflammatory response and finding novel methods to control this process offers a potential for treatment of a wide variety of diseases.

The inflammatory response is initiated by infection or injury to tissue. Macrophages and mast cells at the site of injury or infection will recognize pathogens or tissue damage and, in response, generate an array of chemical mediators, including vasoactive amines, cytokines, chemokines, eicosanoids, and adhesion molecules.[1] These mediators cause vasodilation of blood vessels, resulting in increased blood flow and delivery of plasma proteins and neutrophils from blood vessels to the site of injury via postcapillary venules.[3,4] Additionally, the increased

presence of adhesion molecules brings circulating leukocytes to the vascular endothelium and, due to the increased permeability of the vasculature, allows migration to the injury site.[3] This movement gives rise to the key signs of inflammation, namely redness, heat, swelling, and pain. Once arriving, the neutrophils attempt to kill the invading organism by releasing reactive oxygen species, proteases, and reactive nitrogen species and engulfing the resulting debris via phagocytosis.[1] The clearance of the invading substances initiates the resolution phase in order to restore normal tissue structure and function. During this phase, lipid mediators switch from pro-inflammatory to anti-inflammatory activities; furthermore, these signaling molecules inhibit neutrophil migration and cause the neutrophils at the former injurious site to undergo apoptosis, the remnants of which are cleared through the action of macrophages.[1] Finally, these anti-inflammatory mediators, in conjunction with growth factors, will initiate tissue repair, completing the resolution phase and restoring tissue homeostasis.

Biosynthesis of Lipid Mediators

For over half a century, lipid mediators have been the focus of much research attention, leading to a deeper understanding of the mechanisms of the inflammatory response. These mediators are generated as needed from precursor membrane phospholipids.[5] Intracellular calcium ions activate cytosolic phospholipase A_2 ($cPLA_2$), which release polyunsaturated fatty acids such as arachidonic acid, linoleic acid, eicosapentaenoic acid (EHA), and docosahexaenoic acid (DHA) that can be converted, either enzymatically or non-enzymatically, into lipid mediators, such as prostaglandins, leukotrienes, lipoxins, resolvins, protectins, isoprostanes, and isofurans, that exert their effects through binding to G-protein coupled receptors.[1,5] While these

mediators are critical to the inflammatory response, they also play vital roles in regulating cell proliferation and differentiation and the regulation of reproductive and gastrointestinal systems.[5]

The prostaglandins are a class of lipid mediators that are generated from arachidonic acid. Representative prostaglandins (PGs) are shown in Figure 1.1. This class of molecules contains twenty carbons, incorporating a five-membered ring with trans alkyl chains (α chain and ω chain).[6] Furthermore, the letter following the letters PG refers to the substitution and structure of the five-membered ring and the subscript denotes the degrees of unsaturation present in the side chains. The carboxylate carbon is termed C1 and the carbon at the terminus of the aliphatic side chain is termed C20.

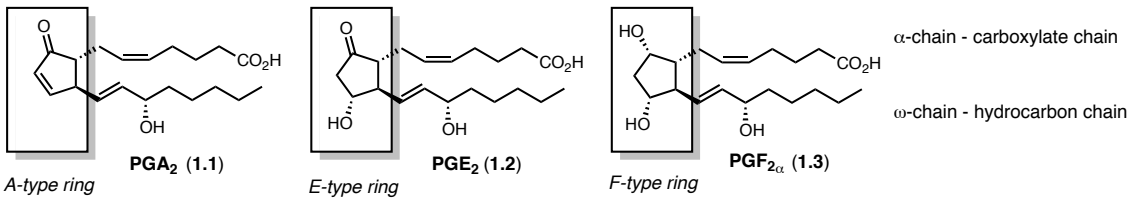
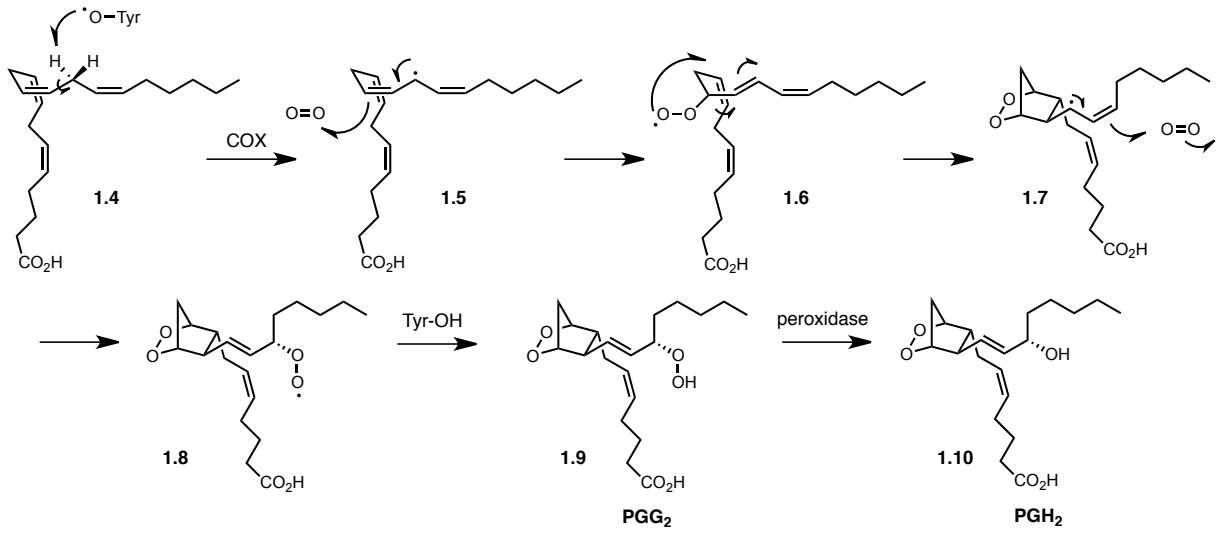


Figure 1.1: Examples of Prostaglandins

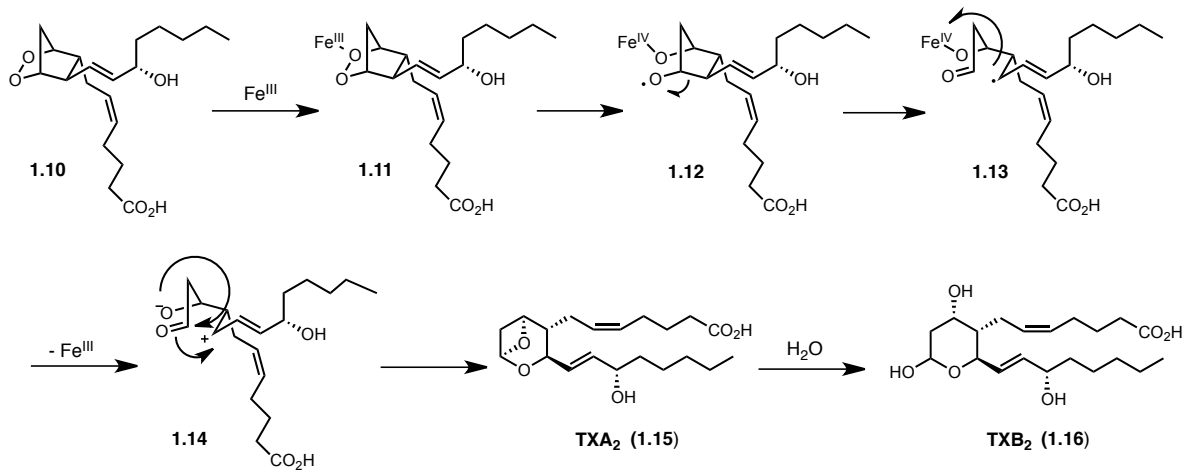
The prostaglandins are generated biosynthetically by action of cyclooxygenase (COX) enzymes upon arachidonic acid (**1.4**) (Scheme 1.1). A tyrosine radical from the COX active site abstracts the 13-*pro-S* hydrogen to generate a pentadienyl radical **1.5** which captures oxygen at C11 to produce peroxyl radical **1.6**.[7] This intermediate will then undergo a 5-*exo-trig* cyclization to produce an intermediate peroxide and radical at C8. This radical then undergoes another 5-*exo-trig* cyclization to provide bicyclic peroxide **1.7** and an allylic radical, which is subsequently trapped by a second molecule of oxygen to provide peroxyl radical **1.8**, which is reduced to produce hydroperoxide PGG_2 (**1.9**). The peroxidase activity of COX then reduces this peroxide

to PGH_2 (**1.10**), which is the precursor for all prostaglandins. Broadly, these compounds control changes in blood flow leading to a variety of effects during inflammation.[4]



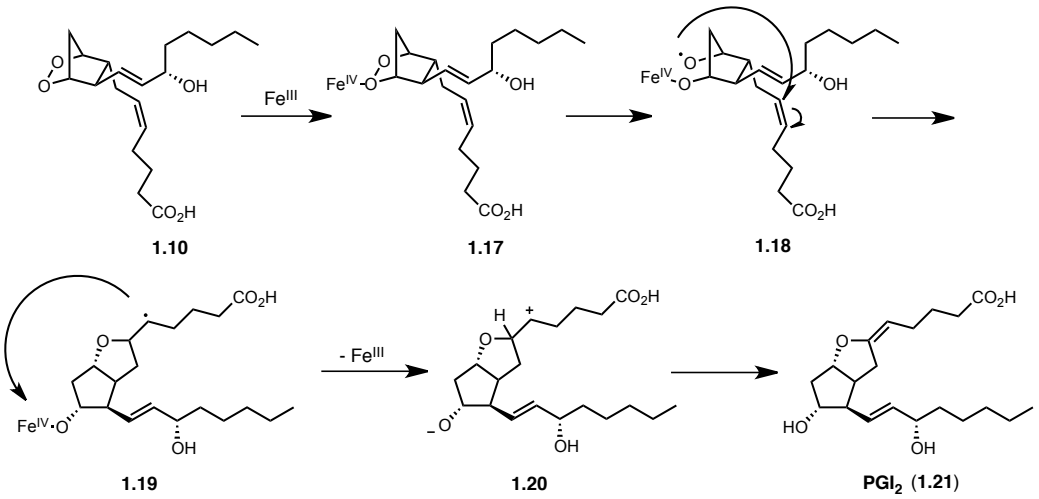
Scheme 1.1: Biosynthesis of Prostaglandins

Thromboxanes are closely related compounds that are generated downstream of PGH_2 (Scheme 1.2). Thromboxanes are recognized by the presence of a tetrahydropyran ring in place of the typical five-membered ring. One mechanism proposed for the biosynthesis of TXA_2 (**1.15**) suggests that PGH_2 binds through its C9 oxygen to the active site heme iron of thromboxane synthase, whereupon homolytic cleavage of the endoperoxide bond provides alkoxy radical **1.12**.[8] Next, β-scission of the C11-C12 bond provides allylic radical **1.13** and iron oxidation provides intermediate **1.14**, which undergoes ring closure to form **1.15**. TXA_2 is a vasoconstrictor and promotes platelet aggregation. Furthermore, this highly unstable lipid mediator has a half-life of approximately thirty seconds and is rapidly hydrolyzed to the inactive TXB_2 (**1.16**).[9]



Scheme 1.2: Biosynthesis of Thromboxanes

Prostacyclin, also known as PGI_2, is another lipid mediator generated downstream of PGH_2 (Scheme 1.3). When PGH_2 encounters prostacyclin synthase, the active site heme coordinates to the C11 oxygen and the endoperoxide bond undergoes homolytic cleavage to provide alkoxy radical **1.18**.[8] Next, 5-*exo-trig* cyclization with the C5-C6 olefin provides carbon radial **1.19** and, after Fe(IV) oxidation and removal of the C6 hydrogen, provides the identifying bicycle of PGI_2 (**1.21**). This mediator is responsible for vasodilation and inhibiting platelet aggreagation.[8]



Scheme 1.3: Biosynthesis of Prostacyclin (PGI_2)

Leukotrienes (LTs) are another class of lipid mediators derived from arachidonic acid. As with prostaglandins, these molecules contain twenty carbons and four double bonds, three of which, as the name suggests, are part of a conjugated triene (Figure 1.2).

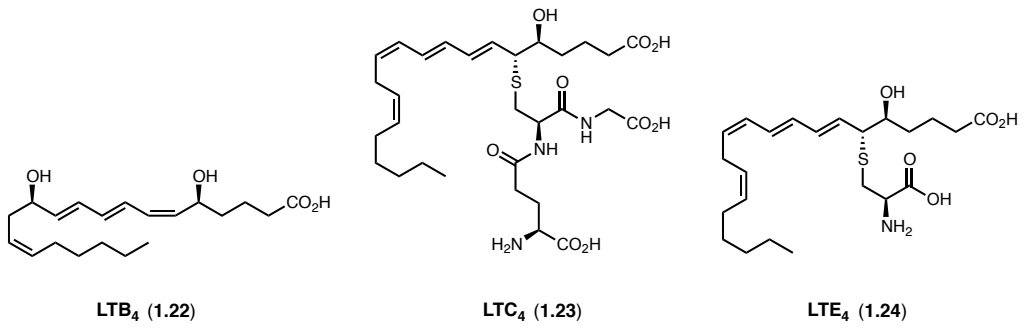
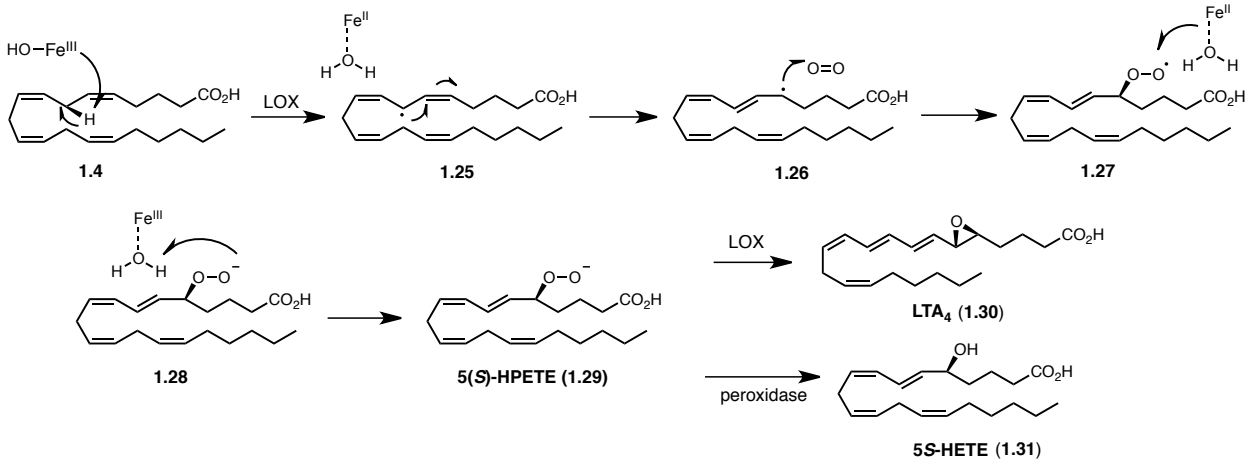


Figure 1.2: Examples of Leukotrienes

The leukotrienes are biosynthetically prepared by interaction of 5-lipoxygenase (5-LOX) and arachidonic acid (Scheme 1.4).[10] Fe^{III} in the active site of 5-LOX abstracts the 7-pro-*S* hydrogen to give carbon radical **1.25**, which captures oxygen at C5 to produce peroxyradical

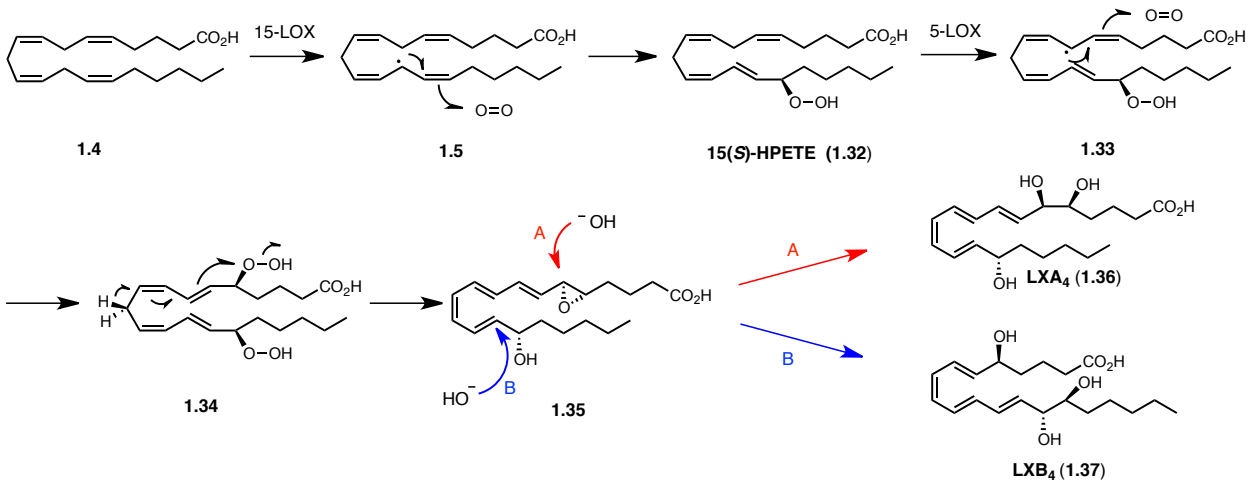
1.27. The peroxy radical can then oxidize the active site iron to provide Fe^{III} and peroxy anion **1.28** that becomes 5(*S*)-HPETE (**1.29**). This intermediate can then undergo further reaction with the 5-LOX active site to abstract the C10 hydrogen to provide a hexatrienyl radical that reacts with the peroxide oxygen to form the epoxide LTA_4 (**1.30**), the precursor for the entire family of leukotrienes. However, 5(S)-HPETE can also be reduced to provide 5S-HETE (**1.31**). These lipid mediators are responsible for neutrophil recruitment and vascular permeability.[4]



Scheme 1.4: Biosynthesis of Leukotrienes and 5(*S*)-HETE

The lipoxins are also arachidonic acid-derived lipid mediators that play a role not in the initiation but rather in the resolution of inflammation; their mechanism of formation is analogous to that of leukotrienes (Scheme 1.5). Reaction of arachidonic acid with 15-lipoxygenase generates 15(S)-HPETE (**1.32**), which then encounters 5-LOX to provide the bisperoxide **1.34** and subsequently transforms into 15(S)-hydroxy-5(6)-epoxy-ETE (**1.35**). This epoxide intermediate can react with hydroxide at C7 to afford LXA_4 (**1.36**) or at C14 to generate LXB_4 (**1.37**). These antiinflammatory mediators are responsible for reducing neutrophil migration to

the inflamed area and promote leukocyte apoptosis and the clearance of inflammatory cellular debris.[4]



Scheme 1.5: Biosynthesis of Lipoxins

Isoprostanes are a class of racemic lipid mediators that are generated from the autooxidation of arachidonic acid. Figure 1.3 shows the four different isomeric classes of isoprostanes. For example, 5-F_{2t}-isoP indicates that the side chain hydroxyl is at C5, the cyclopentane ring resembles the "F-series" ring (prostaglandin nomenclature), and the sidechains are oriented *trans* to the ring hydroxyl groups.[11] The initial hydrogen atom abstraction determines whether the 5-, 8-, 12-, or 15-series isoprostanes will be formed, and the ring can resemble the D, E, and F-type prostaglandins and are therefore referred to as D_2, E_2, or F_2-isoprostanes. The absolute configuration of the ring hydroxyls is determined to sit in the α configuration; therefore, should they reside in the β configuration, the prefix *ent-* would be added to the abbreviation. To indicate inversion of the side chain hydroxyl group or one of the side chains on the cyclopentane ring, the prefix *epi-* is used. Since these four regioisomers can

each be made up of eight different racemic diastereomers, 64 different isomers from each class can exist, giving way to a large number of possible isoprostane isomers.

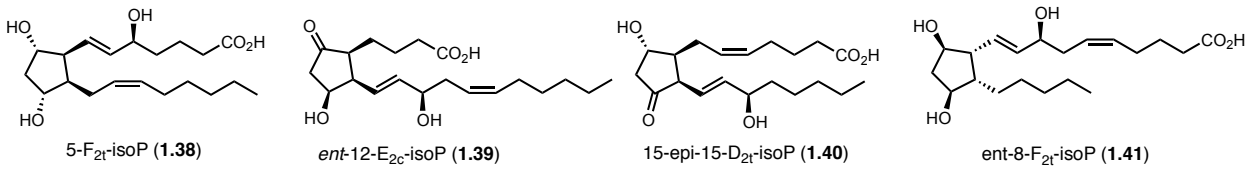
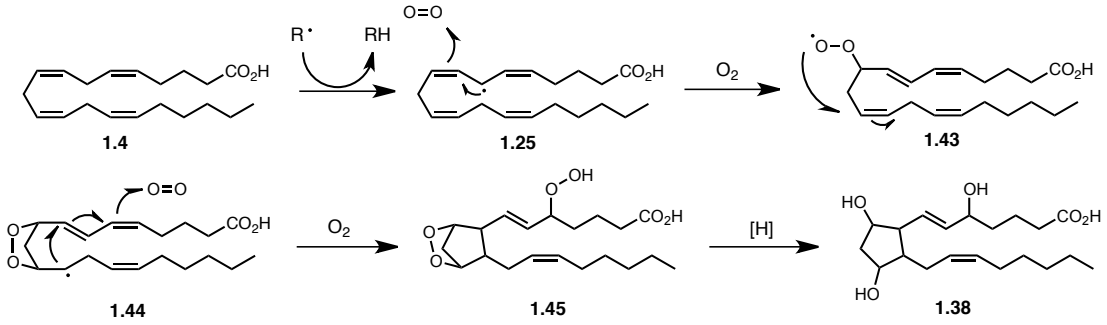


Figure 1.3: Examples of Isoprostanes

For simplicity, only the formation of the 5-F_2-isoprostanes is illustrated in Scheme 1.6. Thus, free radical abstraction of the C7 hydrogen and subsequent capture of oxygen at C9 provides peroxy radical **1.43**. Endoperoxide formation generates the C13 radical **1.44,** which then undergoes cyclization and, after capture of oxygen at C5, provides **1.45**. Reduction of both the endoperoxide and the peroxide at C5 provides 5-F_2-isoprostanes (**1.38**). These compounds are important biomarkers of endogenous oxidative stress, which plays a role in a number of disease states.[12]



Scheme 1.6: Biosynthesis of 5-F_2-Isoprostanes

The isofurans are another class of racemic lipid mediators that are derived from free radical oxidation of arachidonic acid. Eight possible regioisomers of the isofurans can be generated giving rise to a total of 256 possible isomers, two of which are indicated in Figure 1.4.[13] For example, in the diastereomer ST-D^{10}-5-IsoF, the "S" highlights the *syn* orientation of the two side chains of the tetrahydrofuran ring and the "T" indicates that the hydroxyl group on the ring is *trans* to its adjacent alkyl group. D^{10} indicates the position of the alkene of the allylic alcohol and 5 refers to the first carbon of the tetrahydrofuran ring. Furthermore, the default absolute configuration of the isofurans is as follows: the sidechain alcohols have an (*S*)-configuration, the isolated alkene has (*Z*) geometry, and the alkene of the allylic alcohols has (*E*) geometry. Therefore, any enantiomer will be denoted with *ent-* and any isofuran that is epimeric at either or both sidechain alcohols will be termed "epi." The isofurans exist as two major classes: the "alkenyl" isofurans (ex. **1.46**) and the "ene-diol" isofurans (ex. **1.47**).

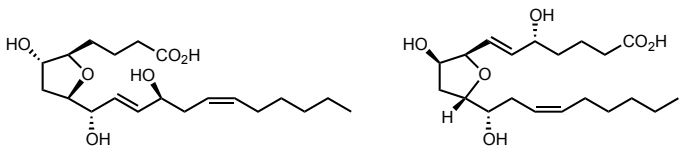
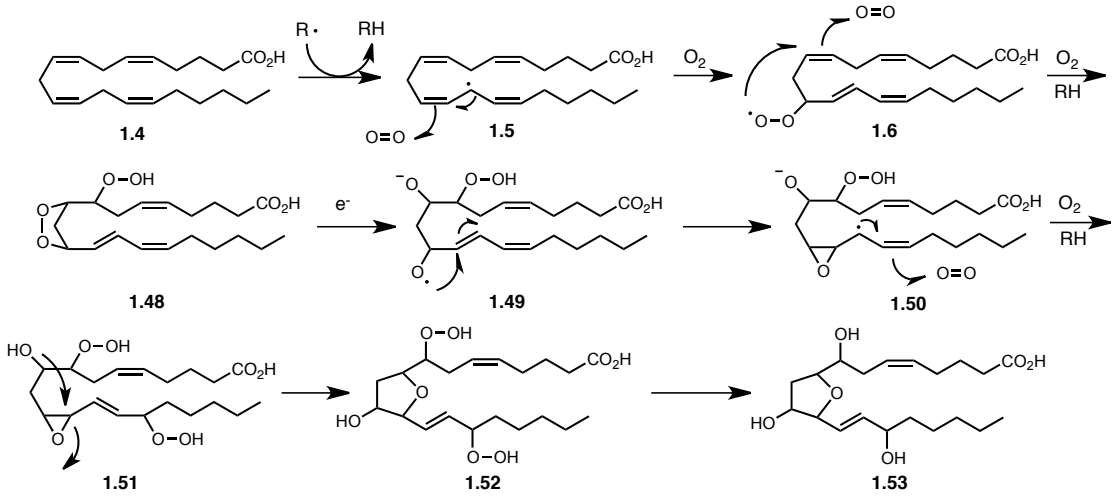


Figure 1.4: Examples of Isofurans

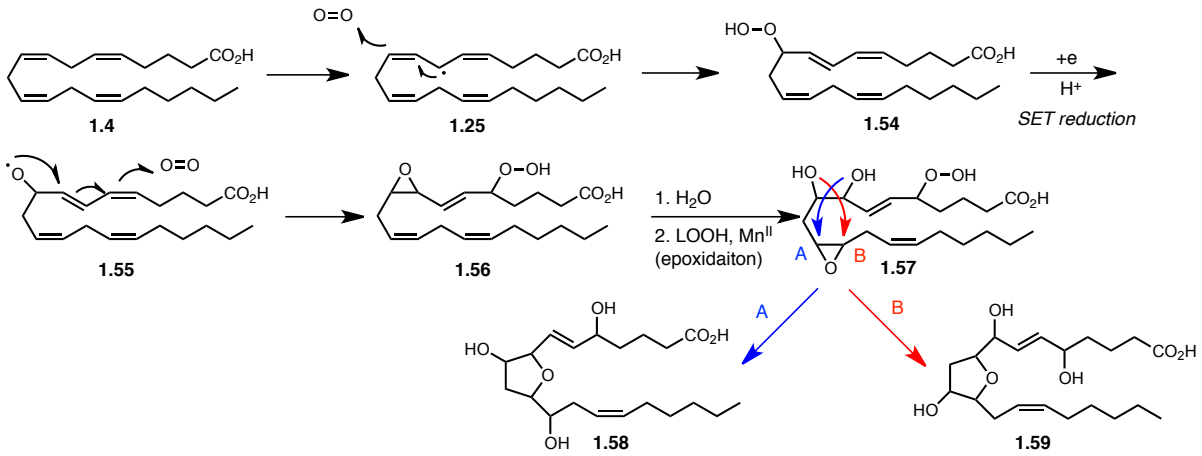
There are two proposed mechanisms for the formation of isofurans based upon $^{18}O_2$ and $H_2{}^{18}O$ labeling studies.[14] The first proposed mechanism is the "cyclic peroxide cleavage" mechanism, which is applicable mostly to the formation of the alkenyl isofurans (Scheme 1.7). Abstraction of the C13 hydrogen and subsequent capture of oxygen at C11 generates peroxy radical **1.6**. Formation of the endoperoxide is followed by trapping of a second molecule of

oxygen at C8 to provide peroxide **1.48**. Single electron reduction of the endoperoxide gives an alkoxy radical **1.49**, which can undergo a 3-*exo-dig* cyclization to provide epoxide **1.50**. Reaction with a third molecule of oxygen at C15 provides epoxy alcohol **1.51**, which can undergo a 5-*endo* cyclization and subsequent peroxide reductions to afford Δ^{13}-9-isofurans.



Scheme 1.7: "Cyclic Peroxide Cleavage" Mechanism for Δ^{13}-9-Isofuran Biosynthesis

The second proposed mechanism is the "epoxide hydrolysis" mechanism and is applicable to the ene-diol isofurans and certain alkenyl isofurans (Scheme 1.8).[14] Hydrogen atom abstraction at C7 and subsequent trapping of oxygen provides peroxide **1.54**. Single electron reduction generates alkoxy radical **1.55** that can then undergo 3-*exo-trig* cyclization and trapping of oxygen at C5 to provide the epoxyhydroperoxide **1.56**. Epoxide hydrolysis with water provides a diol and epoxidation of the C12-C13 olefin in the presence of Mn^{II} ions would provide epoxy diol **1.57**. Epoxide opening via pathway A provides the alkenyl isofuran **1.58**, whereas opening via pathway B generates the enediol isofuran **1.59**.



Scheme 1.8: "Epoxide Hydrolysis" Mechanism for Isofuran Biosynthesis

Synthetic Approaches toward Lipid Mediators

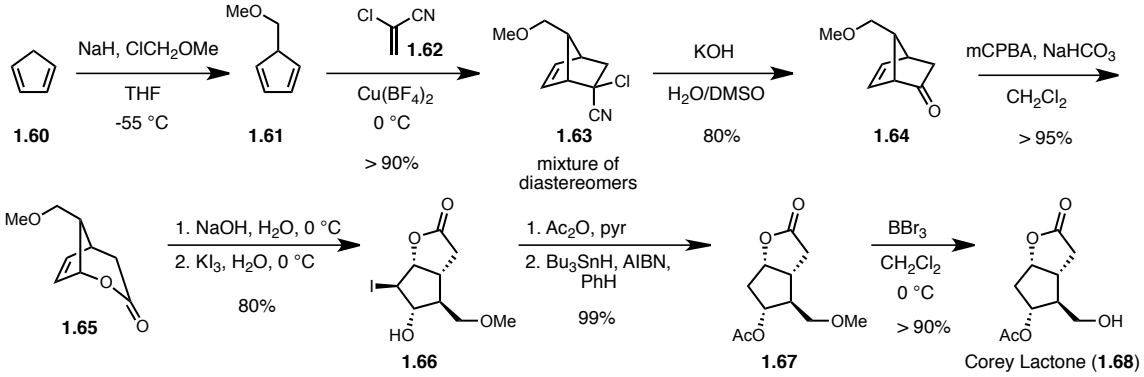
The chemical synthesis of lipid mediators was an active area of research for several decades, due to their interesting structural composition, biological activities, and scarcity. The many research programs aimed at synthesizing these molecules contributed significantly to synthetic chemistry by developing new methodologies for stereochemical control and new strategies for target-oriented synthesis.

Chemical Synthesis of Prostaglandins

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

The first prostaglandin synthesis was achieved by Corey in 1969 and is described in Scheme 1.9.[15] Starting from cyclopentadiene (**1.60**), alkylation with chloromethyl methyl ether

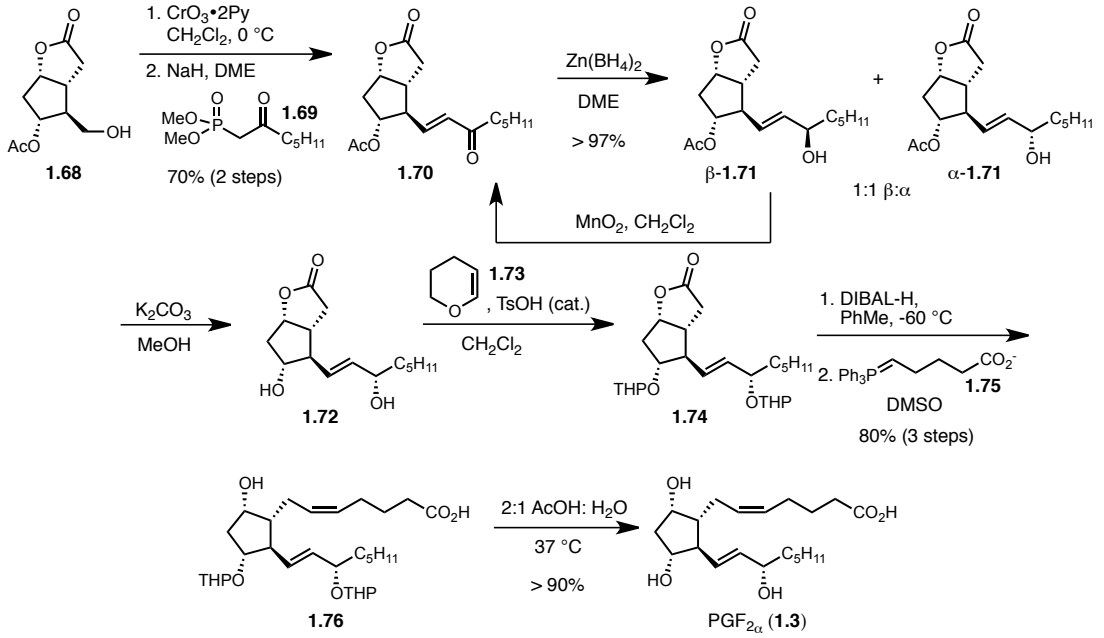
provides diene **1.61**, which underwent Diels-Alder cycloaddition with 2-chloroacrylonitrile (**1.62**) to provide bicycle **1.63** as a mixture of *endo*/*exo* isomers in excellent yield. Treatment of **1.63** with potassium hydroxide provided ketone **1.64**, which was converted in high yield to lactone **1.65** via Bayer-Villager oxidation with *m*CPBA. Saponification of the lactone and subsequent treatment with KI_3 led to formation of the iodo lactone **1.66**. Acetate protection of the secondary alcohol followed by reduction with Bu_3SnH provided methyl ether **1.67**, which was converted using BBr_3 to the primary alcohol **1.68** (the "Corey Lactone").



Scheme 1.9: Corey's Synthesis of $PGF_{2\alpha}$ - Synthesis of Corey Lactone

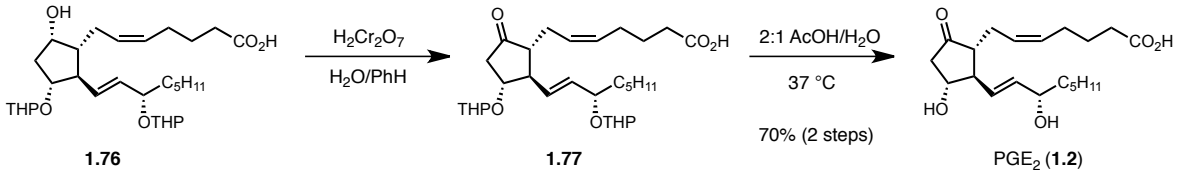
Oxidation of **1.68** to the aldehyde and olefination with phosphonate **1.69** provided *E*-enone **1.70** exclusively in good yield over two steps. Reduction with zinc borohydride provided a 1:1 mixture of alcohols **β-1.71** and **α-1.71** that were epimeric at C_{15}. However, the undesired β-isomer could be recycled to lactone **1.70** through allylic oxidation with MnO_2. The desired α-isomer was deacetylated to provide diol **1.72**, which was subsequently protected as the bis-THP ether **1.74**. Treatment with DIBAL-H provided the lactol, which then underwent Wittig

olefination with ylide **1.75** to provide alcohol **1.76**. Removal of the THP groups provided $PGF_{2\alpha}$ (**1.3**).



Scheme 1.10: Corey's Synthesis of $PGF_{2\alpha}$ - Completion of the Synthesis

Additionally, the flexibility of this route provided for the synthesis of PGE_2. Oxidation of intermediate **1.76** provided ketone **1.77** and, following THP removal, provided PGE_2 (**1.3**) in good yield over two steps.



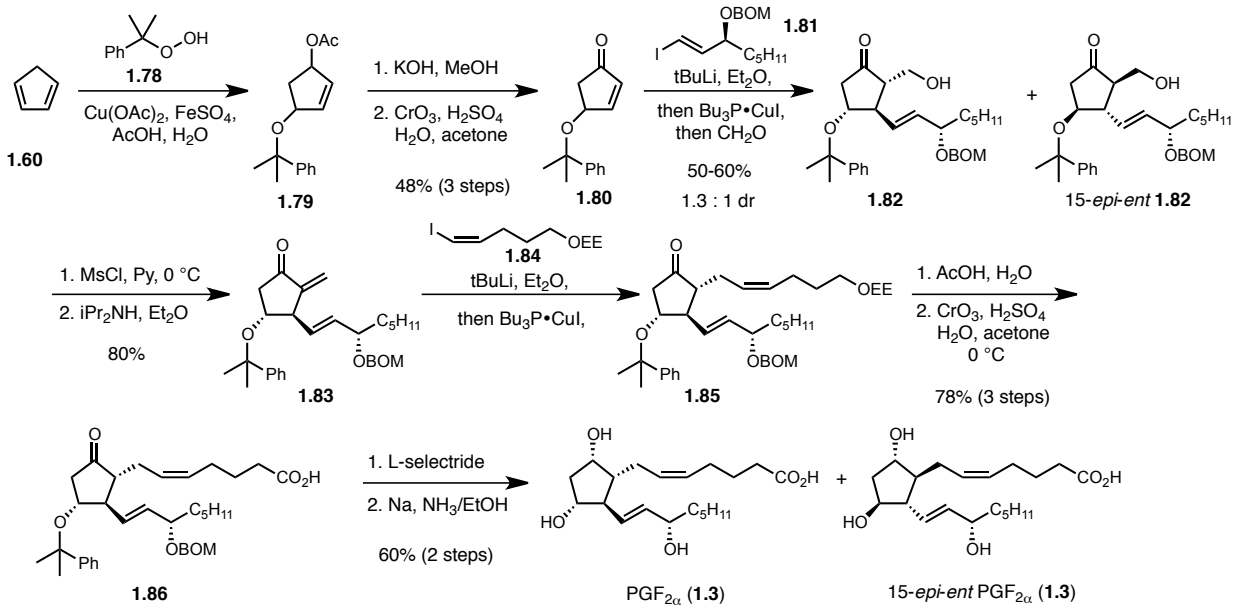
Scheme 1.11: Corey's Synthesis of PGE_2

Corey's route provided a flexible approach to access the many different prostaglandin family members and is also currently used in the manufacturing of prostaglandin analogues. Furthermore, subsequent work in Corey's group sought to overcome the limitations of the initial synthesis. The racemic Diels-Alder cycloaddition and the selectivity of the enone reduction were the two major limitations of the synthetic route, both of which were solved through the development of chiral auxiliary-based[16] and catalytic enantioselective[17] Diels-Alder reactions and the development of chiral oxazaborolidine catalysts [18], respectively.

Stork's Synthesis of $PGF_{2\alpha}$

Several years later, Stork developed a novel approach to access prostaglandins utilizing a three component coupling, whereby the aliphatic and carboxylate side chains could be appended to the cyclopentanone core via subsequent conjugate addition-alkylation sequences.[19, 20] Treatment of **1.60** with cumene hydroperoxide (**1.78**) and acetic acid in the presence of cupric acetate and iron sulfate provided allylic acetate **1.79** and, upon acetate cleavage and oxidation, provided cyclopentenone **1.80**. Conjugate addition of the vinyl cuprate derived from **1.81** and subsequent trapping of the enolate with formaldehyde provided a 1.3:1 mixture of cyclopentanones **1.82** and 15-*epi*-*ent*-**1.82**. This diastereomeric mixture underwent a mesylation/elimination sequence to provide enone **1.83**, which was subjected to a second conjugate addition with the vinyl cuprate derived from vinyl iodide **1.84** to afford the full carbon skeleton of $PGF_{2\alpha}$. Removal of the ethoxyethyl group and oxidation of the released alcohol to the carboxylic acid provided **1.86**. Reduction of the cyclopentanone with L-selectride followed by deprotection with sodium in ammonia provided **1.3** as well as its diastereomer 15-*epi*-*ent*-**1.3**,

which were converted to methyl esters and separated by chromatography. This approach highlights the utility of conjugate additions in rapidly generating the carbon scaffolds for prostaglandins.

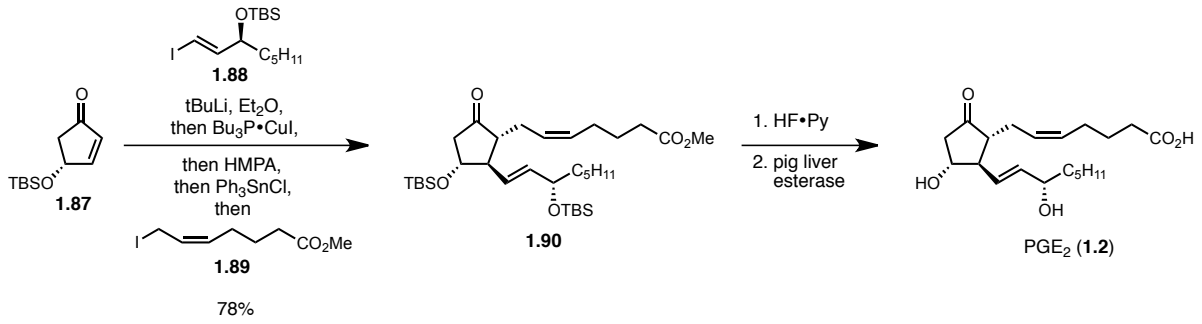


Scheme 1.12: Stork's Synthesis of $PGF_{2\alpha}$

Noyori's Synthesis of PGE_2 and $PGF_{2\alpha}$

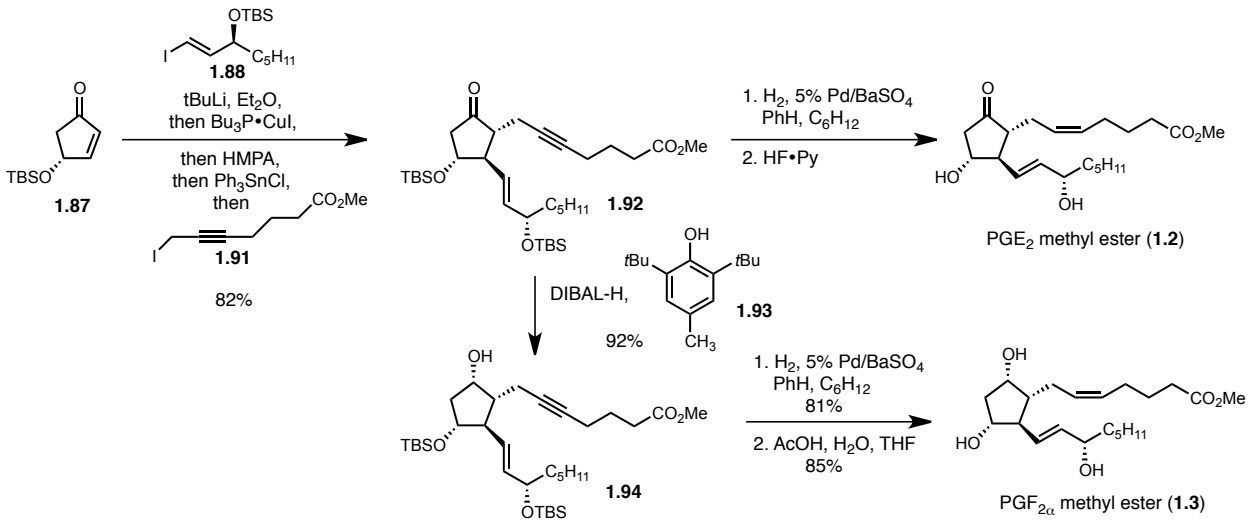
Noyori's approach to the synthesis of prostaglandins also employed a three-component coupling to achieve the requisite carbon skeleton.[21,22,23] However, he improved upon Stork's approach by developing conditions for a one-pot protocol to install both side chains. Starting from the optically active cyclopentenone **1.87**, conjugate addition with the cuprate derived from vinyl iodide **1.88** and subsequent transmetallation with Ph_3SnCl produces a tin enolate that can react with alkyl iodide **1.89** to generate cyclopentanone **1.90** in high yield and excellent

diastereoselectivity. Desilylation with HF•pyridine and enzymatic hydrolysis of the methyl ester provided PGE_2.



Scheme 1.13: Noyori's Synthesis of PGE_2

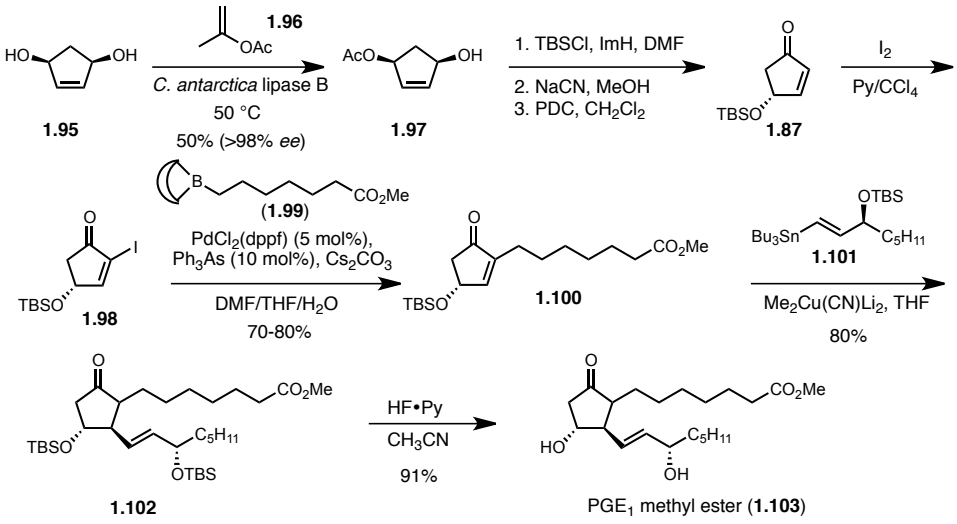
Additionally, Noyori also noted that using propargyl iodide **1.91** as the alkylating agent for the tin enolate allows for the generation of a common precursor to access multiple classes of prostaglandins. Highlighted in Scheme 1.13, the one pot, three-component coupling employing **1.91** provides alkyne **1.92** in high yield and high diastereoselectivity. Semihydrogenation of the alkyne with hydrogen gas and palladium over barium sulfate and subsequent desilylation produces PGE_2 methyl ester. Additionally, treatment of **1.92** with DIBAL-H and phenol **1.93** provides alkyne **1.94**, which can be subjected to the semihydrogenation and desilylation with acetic acid to provide $PGF_{2\alpha}$ methyl ester. Therefore, this alkyne precursor provides a divergent strategy to access multiple different prostaglandins.



Scheme 1.14: Noyori's Synthesis of PGE_2 and $PGF_{2\alpha}$ Methyl Esters

Johnson's Synthesis of PGE_1 Methyl Ester

Johnson's approach to prostaglandin synthesis involved use of a two-component conjugate addition that avoids enolate equilibration and β-elimination of the hydroxyl group.[24] Starting from optically active 1,4-cyclopentenediol (**1.95**), enzyme-mediated asymmetrization with isopropenyl acetate (**1.96**) provided cyclopentenol **1.97**. Silylation of the alcohol, acetate cleavage, and oxidation afforded optically active cyclopentenone **1.87**. α-Iodination generates the α-iodocyclopentenone **1.98**, which underwent cross coupling with boronate **1.99** to provide enone **1.100**. Conjugate addition of the cuprate derived from stannane **1.101** followed by desilylation with HF•pyridine provided PGE_1 methyl ester (**1.103**) in high yield and excellent stereocontrol.

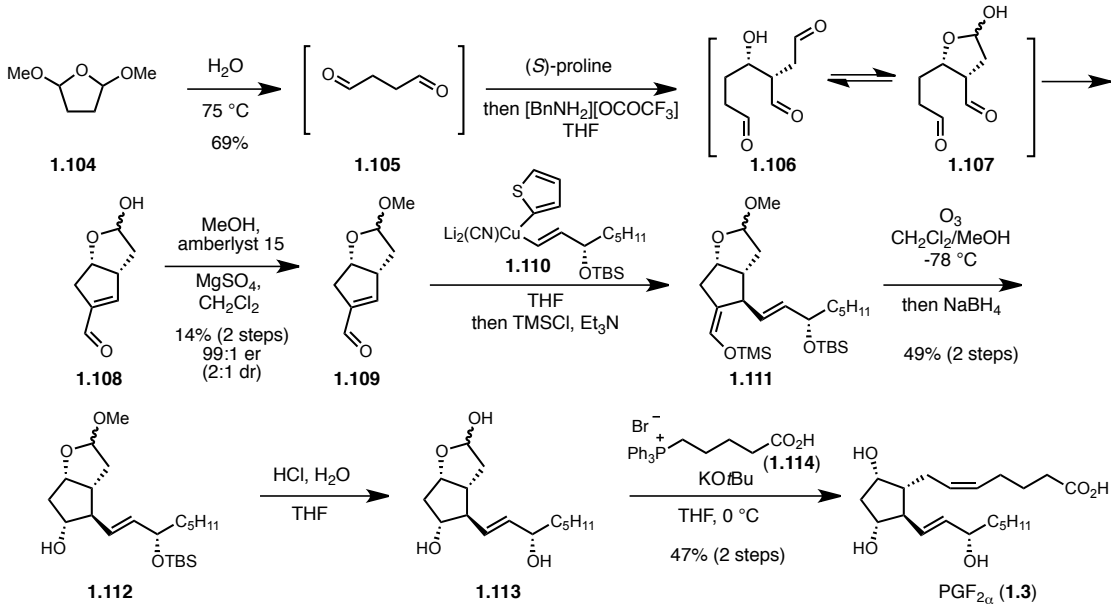


Scheme 1.15: Johnson's Synthesis of PGE_1 Methyl Ester

Aggarwal's Synthesis of $PGF_{2\alpha}$

Most recently, Aggarwal developed an impressive seven-step synthesis of $PGF_{2\alpha}$ utilizing an organocatalytic aldol dimerization of succinaldehyde (Scheme 1.15).[25] Heating 2,5-dimethoxy THF (**1.104**) in water provided succinaldehyde (**1.105**), which underwent self-aldol using catalytic (*S*)-proline and catalytic dibenzylammonium trifluoroacetate to generate the hemi-acetal **1.108** that was converted to an inconsequential mixture of methoxy acetals **1.109**. Although low yielding, this sequence provided access to enantioenriched enal **1.109** in just 3 steps and could be performed on large (> 200 g) scale. Next, conjugate addition of mixed vinyl cuprate **1.110** and trapping with TMSCl provided the silyl enol ether **1.111**. Selective ozonolysis and reduction of the resulting ketone provided alcohol **1.112**. These two steps occurred with excellent stereoselectivity and in modest yield. Concomitant desilylation and deprotection of the methoxy

acetal provided lactol **1.113**. Wittig reaction with phosphonium salt **1.114** then provided $PGF_{2\alpha}$. This short and flexible route provides rapid access to the family of prostaglandins.



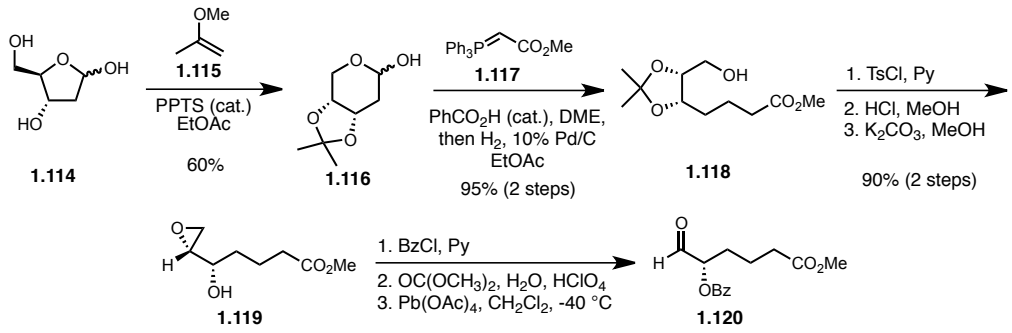
Scheme 1.16: Aggarwal's Synthesis of $PGF_{2\alpha}$

Chemical Synthesis of Leukotrienes

Corey's Synthesis of LTB_4

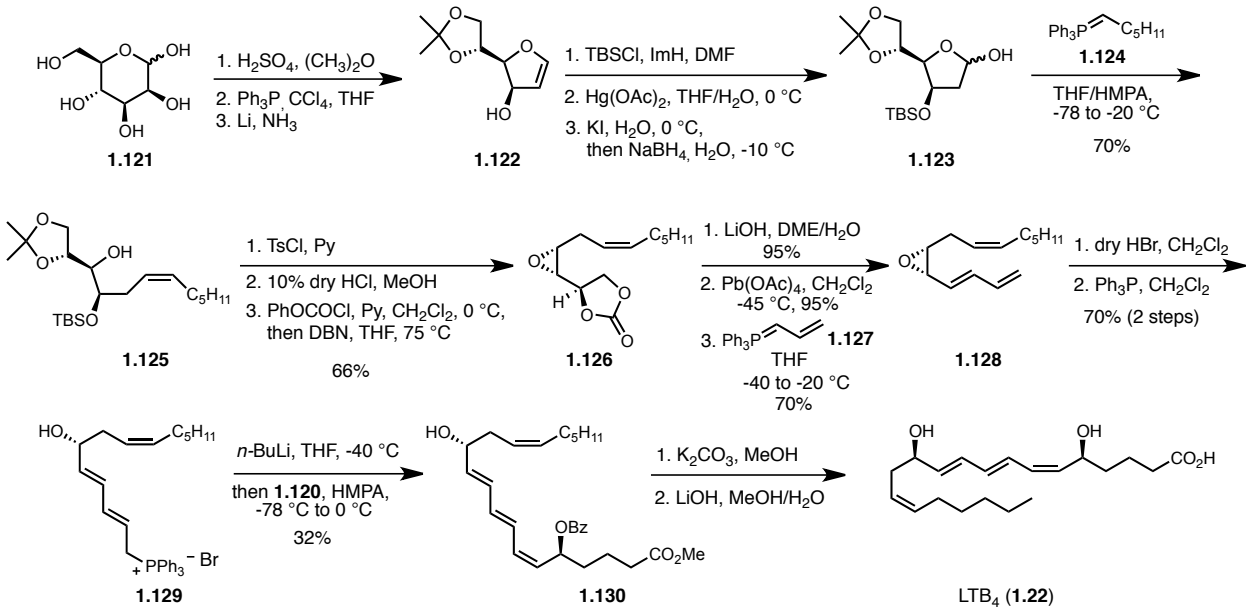
The first total synthesis of LTB_4 was achieved by Corey in 1980 and aided in its absolute stereochemical assignment.[26] Starting from 2-deoxyribose (**1.114**), formation of the acetonide with 2-methoxypropene was followed by Wittig reaction with phosphorane **1.117** and hydrogenation of the resulting alkene to afford alcohol **1.118** in high yield. Tosylation of the alcohol, acetonide hydrolysis, and base-induced epoxide formation provided **1.119**. Benzoylation

of the secondary alcohol and diol formation was followed by oxidative cleavage of the diol to generate aldehyde **1.120**.



Scheme 1.17: Corey's Synthesis of LTB_4 – Formation of Aldehyde 1.120

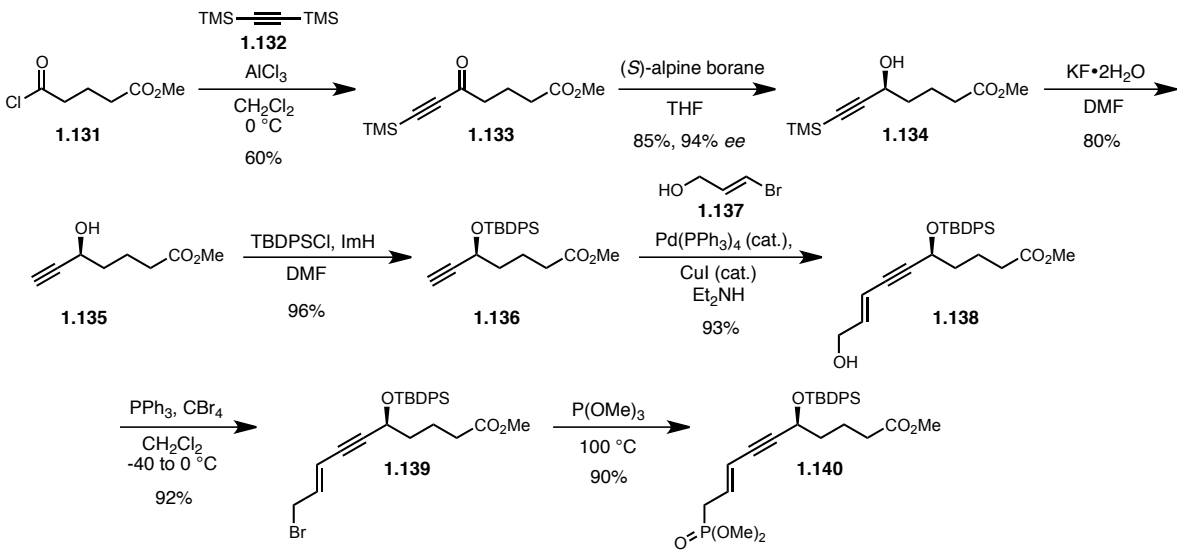
Next, D-Mannose (**1.121**) was treated with acetone and sulfuric acid to form a bisacetonide, which was converted to the glycal monoacetonide **1.122** via a two-step sequence. Silylation of the alcohol and oxymercuration of the alkene afforded acetal **1.123**. Wittig reaction with phosphorane **1.124** provided the *cis* alkene **1.125** exclusively. Tosylation of the alcohol and acetonide cleavage provided a triol that was treated with phenyl chloroformate and DBU to provide epoxide **1.126**. Carbonate hydrolysis and cleavage of the resulting diol, followed by Wittig reaction of the resultant aldehyde with phosphorane **1.127** provided epoxide **1.128**. Conversion to the bromo alcohol using HBr and treatment with triphenylphosphine produced phosphonium salt **1.129**. Generation of the ylide and addition of aldehyde **1.120** provided the carbon framework for LTB_4, which underwent removal of the benzoate group and basic hydrolysis of the methyl ester to provide LTB_4.



Scheme 1.18: Corey's Synthesis of LTB_4 - Completion of the Synthesis

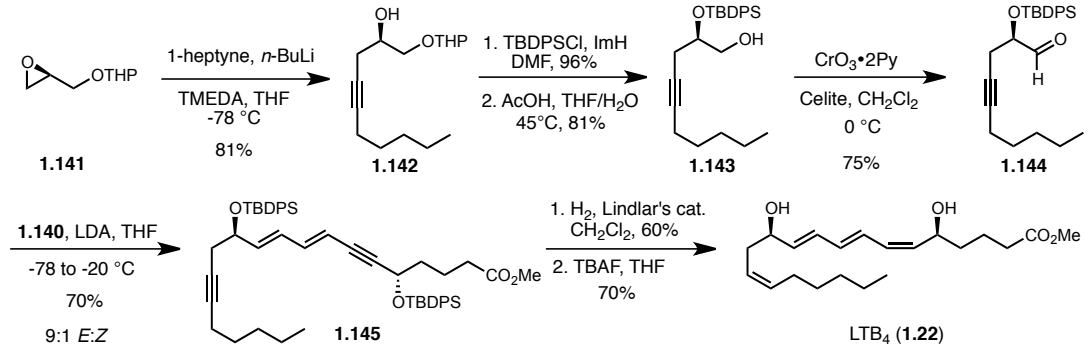
Nicolaou's Synthesis of LTB_4

Nicolaou's approach to leukotriene synthesis employed a highly convergent strategy that required the synthesis of two ten-carbon fragments.[27] Treatment of methyl 4-(chloroformyl)-butyrate (**1.131**) with bis(trimethylsilyl)acetylene (**1.132)** in the presence of aluminum trichloride provided alkynone **1.133**, which then underwent Midland reduction to afford propargyl alcohol **1.134** in high yield and enantioselectivity. Desilylation of the alkyne and subsequent protection of the alcohol as a *tert*-butyldiphenylsilyl either produced **1.136**. Sonogashira coupling with vinyl bromide **1.137** gave allylic alcohol **1.138**. Conversion to the alkyl bromide followed by Arbuzov reaction generated the requisite phosphonate **1.140**.



Scheme 1.19: Nicolaou's Synthesis of LTB_4 - Generation of Phosphonate 1.140

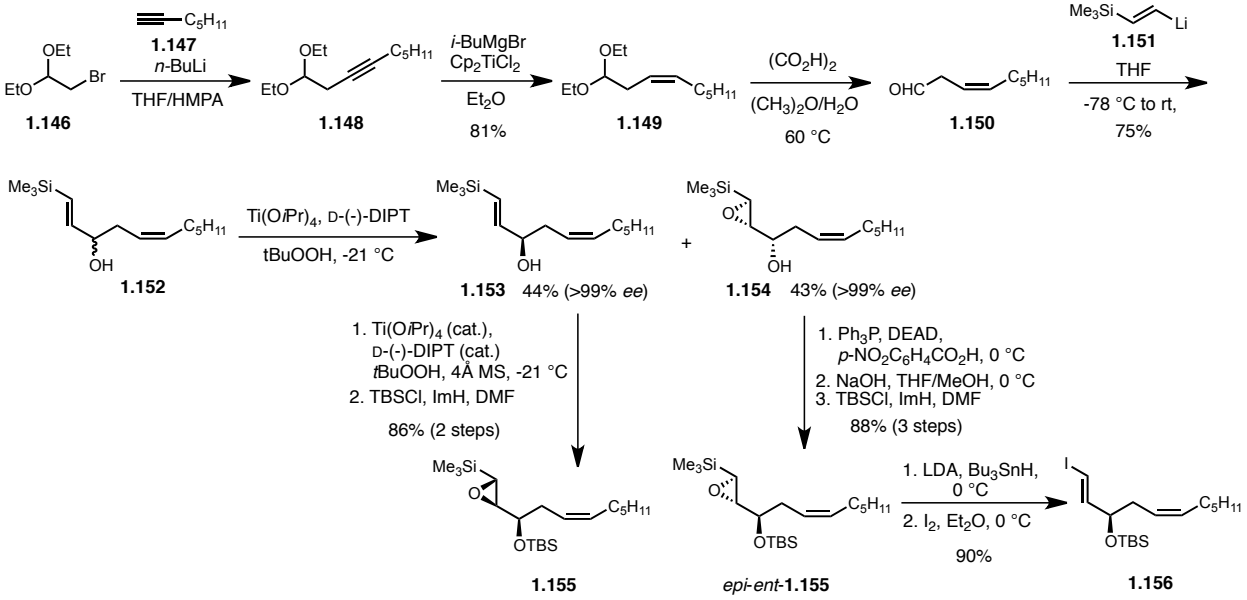
The synthesis of the second required fragment started from the THP ether **1.141**. Opening of the epoxide with 1-heptyne gave the secondary alcohol **1.142**. Protection as a TBDPS ether and THP cleavage provided primary alcohol **1.143**, which was oxidized to give aldehyde **1.144**. Coupling of **1.144** with the anion generated from phosphonate **1.140** provided diyne **1.145**. Semihydrogenation of both alkynes and desilylation completed the synthesis LTB_4.



Scheme 1.20: Nicolaou's Synthesis of LTB_4 - Completion of the Synthesis

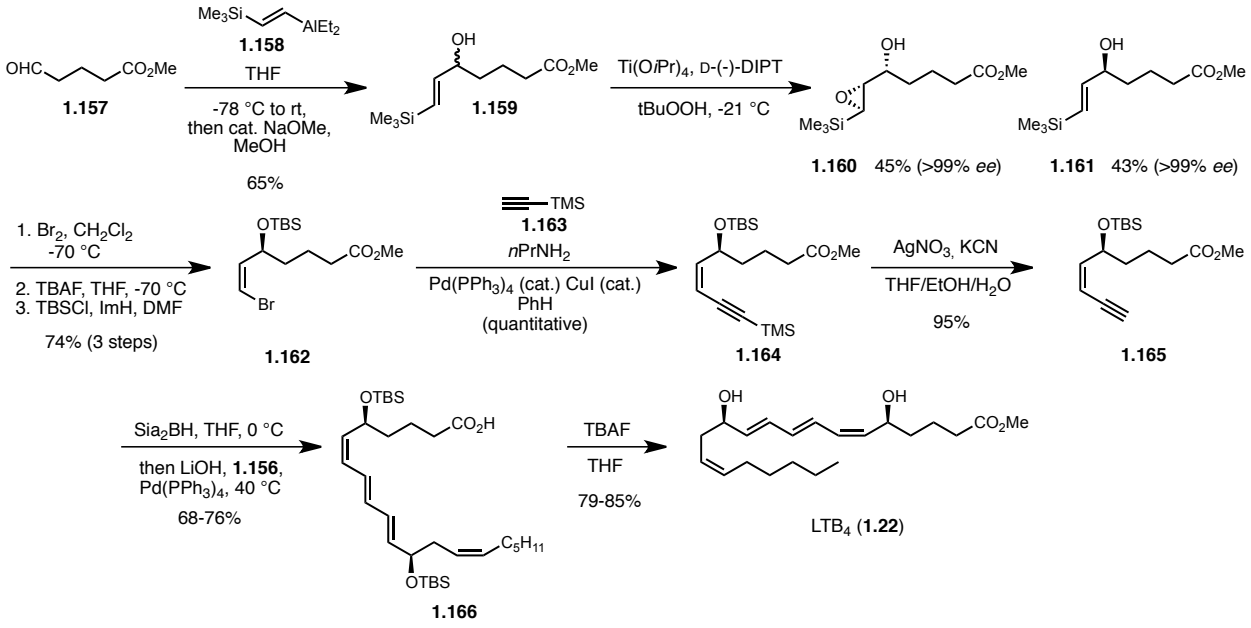
Kobayashi and Sato's Synthesis of LTB_4

Kobayashi and Sato also developed a convergent route to access LTB_4.[28] Addition of the lithiate of heptyne (**1.147**) to bromoacetaldehyde diethyl acetal (**1.146**) provided alkyne **1.148**, which underwent hydromagnesiation to selectively generate cis olefin **1.149**. Hydrolysis of the acetal and addition of vinyl lithiate **1.151** provided racemic **1.152**. Kinetic resolution afforded alcohol **1.153** and epoxide **1.154**, both in exceptional yield and enantiomeric excess. The alcohol was converted to epoxide **1.155** via regioselective Sharpless asymmetric epoxidation and subsequent protection of the alcohol as a TBS ether. The epoxy alcohol **1.154** was subjected to Mitsunobu inversion and protection as the TBS ether to provide *ent-epi*-**1.155**. Both epoxides were opened and subsequently transformed to vinyl stannanes via Peterson olefination. Tin-iodine exchange then provided vinyl iodide **1.156**.



Scheme 1.21: Kobayashi and Sato's Synthesis of LTB_4 - Synthesis of Vinyl Iodide 1.156

Next, addition of vinyl aluminate **1.158** to aldehyde **1.157** provided a racemic mixture of alcohol **1.159**. Kinetic resolution provided the desired alcohol enantiomer **1.160** in high yield and exceptional enantiomeric excess. Conversion to the *cis* vinyl bromide and silylation afforded bromide **1.162**. Sonogashira coupling with ethynyltrimethylsilane (**1.163**) and subsequent desilylation of the alkyne provided **1.165**. This alkyne was treated with disiamylborane to provide a vinyl boronate that was cross coupled with vinyl iodide **1.156** with concomitant methyl ester hydrolysis to provide **1.166**. Desilylation provided LTB_4 in good yield.

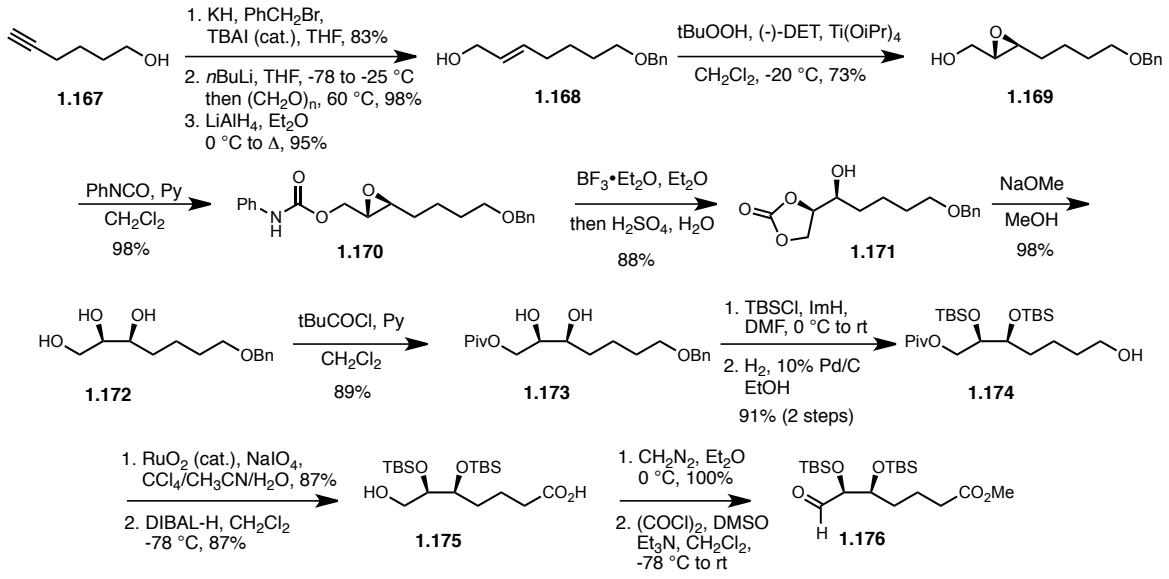


Scheme 1.22: Kobayashi and Sato's Synthesis of LTB_4 - Completion of the Synthesis

Chemical Synthesis of Lipoxins

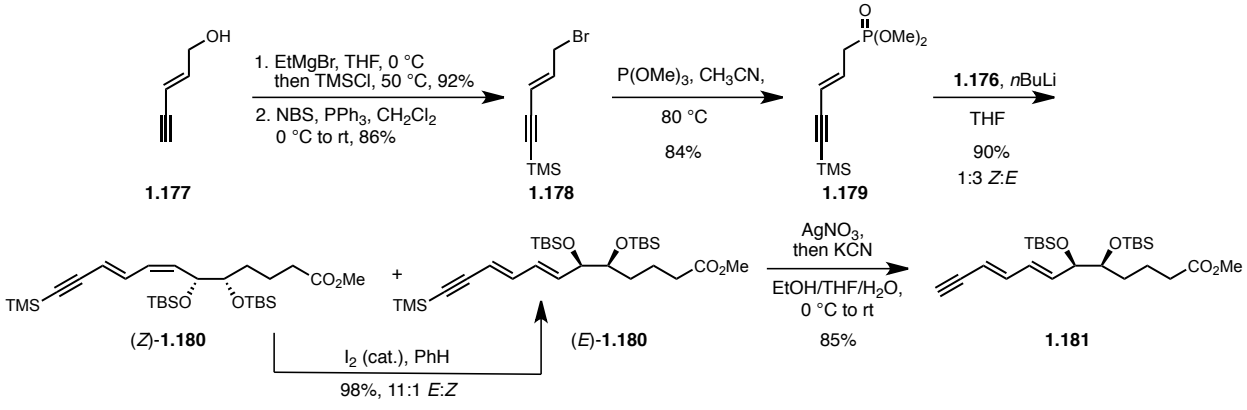
Nicolaou's Synthesis of LXA_4

Since the absolute stereochemistry of LXA_4 was not known at the outset of the synthesis, Nicolaou's strategy allowed for the flexibility to generate different lipoxin stereoisomers for comparison to the natural samples.[29] Starting from hexynol (**1.167**), protection of the alcohol as a benzyl ether, hydroxymethylation of the alkynyl lithiate, and reduction of the alkyne to the (*E*)-alkene with $LiAlH_4$ provided allylic alcohol **1.168**. Furthermore, the choice of reducing agent in the third step provides flexibility to produce either the *Z*- or *E*- alkene, aiding in the development of different lipoxin isomers. From **1.168**, Sharpless asymmetric epoxidation provided epoxide **1.169**. Additionally, this reaction also served as a point of divergence, as choice of tartrate salt could result in formation of other lipoxin stereoisomers. Treatment with phenylisocyanate formed carbamate **1.170**, which then underwent epoxide opening and subsequent hydrolysis to afford carbonate **1.171**. Carbonate methanolysis formed triol **1.172** and the primary hydroxyl was pivylated to afford **1.173**. The secondary alcohols were protected as TBS ethers and removal of the benzyl group provided **1.174**. Oxidation to the carboxylic acid provided and removal of the pivaloate provided **1.175**. Methyl ester formation with diazomethane and Swern oxidation provided aldehyde **1.176**.



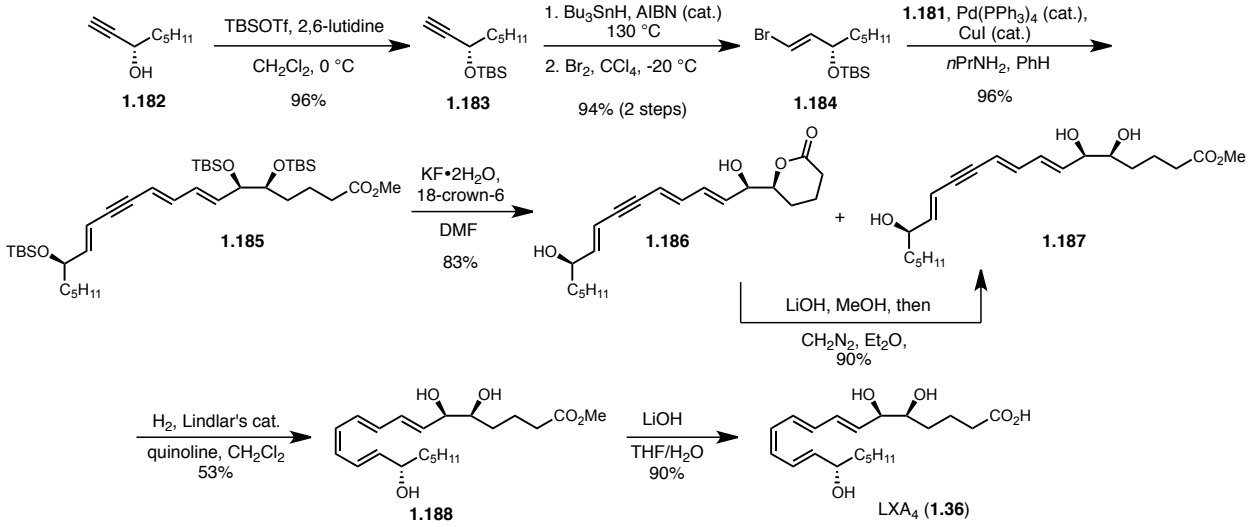
Scheme 1.23: Nicolaou's Synthesis of LXA_4 - Synthesis of Aldehyde 1.176

The second of three key fragments was initiated from alkyne **1.177**. Silylation of the alkyne and conversion of the alcohol to the bromide provided **1.178**. Arbuzov reaction provided phosphonate **1.179**, the anion of which was coupled with aldehyde **1.176** to form enyne **1.180** as a 3:1 mixture of *E*- and *Z*- alkenes. The *Z*-alkene could be isomerized upon treatment with catalytic iodine to afford an 11:1 *E*:*Z* isomers. Desilylation of the alkyne provided alkyne **1.181**.



Scheme 1.24: Nicolaou's Synthesis of LXA_4 - Generation of Alkyne 1.181

The final fragment began from commerical alkynol **1.182**. Silylation of the alcohol provided **1.183**, which underwent a hydrostannylation/bromination sequence to provide vinyl bromide **1.184** in high yield. Sonogashira coupling of the bromide with alkyne **1.181** provided the fully protected lipoxin **1.185**. Desilylation provided a 1:1 mixture of desired triol **1.187** and lactone **1.186**. However, the lactone could be converted to the desired triol upon treatment with LiOH and subsequent treatment with diazomethane. Semireduction of the alkyne provided the *Z*-alkene **1.188** and, upon basic hydrolysis of the methyl ester, provided LXA_4.

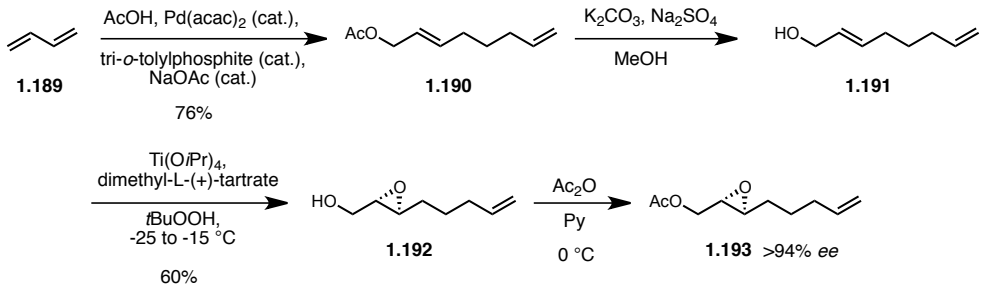


Scheme 1.25: Nicolaou's Synthesis of LXA_4 - Completion of the Synthesis

Spur's Synthesis of LXA_4 and LXB_4

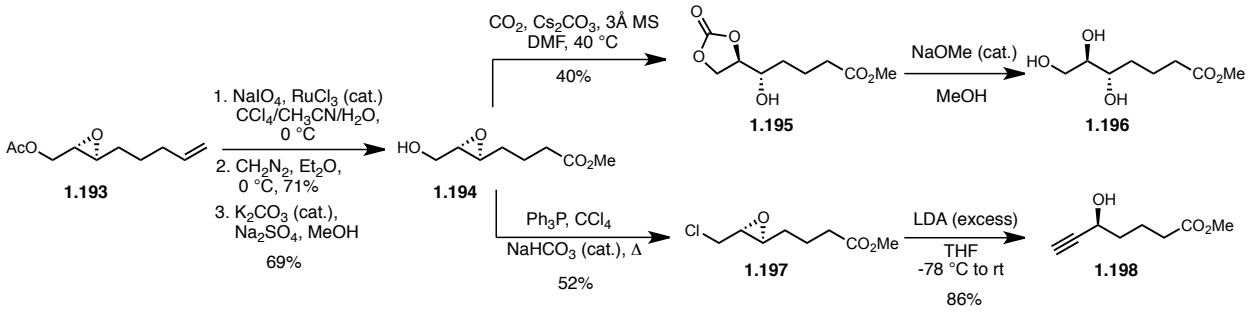
Spur developed an elegant strategy to access both LXA_4 and LXB_4.[30] Starting from butadiene (**1.189**), Pd-catalyzed dimerization in the presence of acetic acid formed allylic acetate **1.190** as the major product. Acetate removal provided the allylic alcohol **1.191**, which was

subjected to Sharpless asymmetric epoxidation to provide, upon acetate protection, epoxide **1.193** in high enantioselectivity.



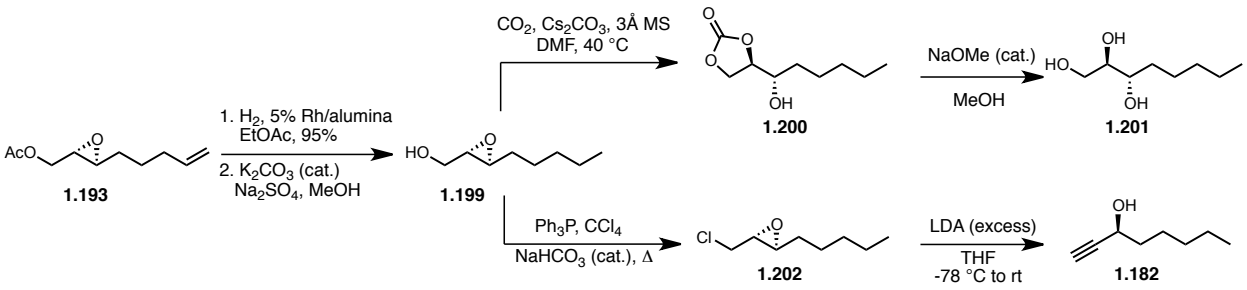
Scheme 1.26: Spur's Synthesis of Lipoxins - Generation of Epoxide 1.193

Furthermore, this epoxide served as the starting point for the synthesis of key fragments required for lipoxin synthesis. Ru-catalyzed oxidative cleavage of the terminal alkene, methylation of the resulting carboxylic acid, and acetate removal provided methyl ester **1.194**. From here, the epoxide could be converted to carbonate **1.195** upon treatment with CO_2. Hydrolysis of the carbonate provided triol **1.196**. Alternatively, **1.194** underwent Appel reaction to form chloro epoxide **1.197**, which was treated with LDA to generate alkynol **1.198**.



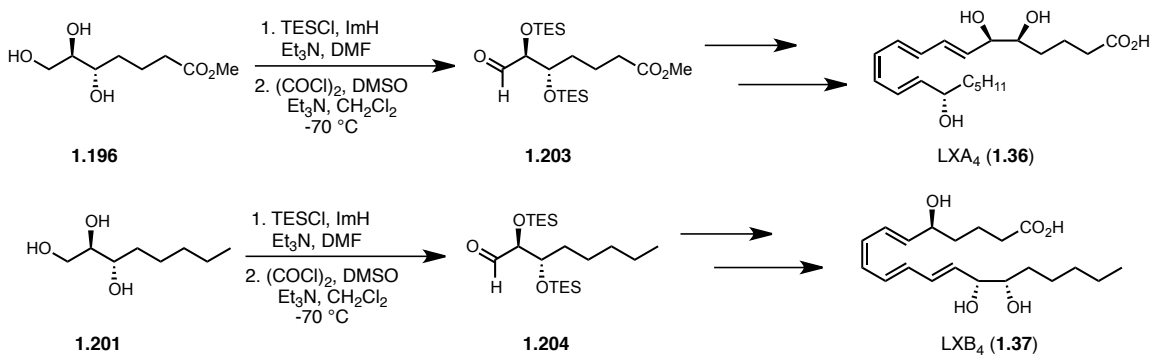
Scheme 1.27: Spur's Synthesis of Lipoxins - Synthesis of Requisite Ester Fragments

The same strategy could be used to generate the necessary aliphatic fragments for lipoxin synthesis. Starting again from **1.193**, hydrogenation of the alkene and acetate removal formed epoxide **1.199**. Treatment with CO_2 followed by carbonate hydrolysis provided triol **1.201**. Additionally, Appel reaction of **1.199** and elimination of the resulting chloride **1.202** provided alkynol **1.182**.



Scheme 1.28: Spur's Synthesis of Lipoxins - Synthesis of Requisite Aliphatic Fragments

From the triols **1.196** and **1.201**, persilylation of the triol allowed for the selective oxidation of the primary TES-ether under Swern conditions without affecting the secondary TES ethers.[31] The resulting aldehydes **1.203** and **1.204**, along with the alkynes **1.182** and **1.198**, respectively, were used following Nicolaou's route to furnish both LXA_4 and LXB_4. The use of a common intermediate to generate the key fragments made this route flexible and allowed for synthesis of multiple lipoxins.

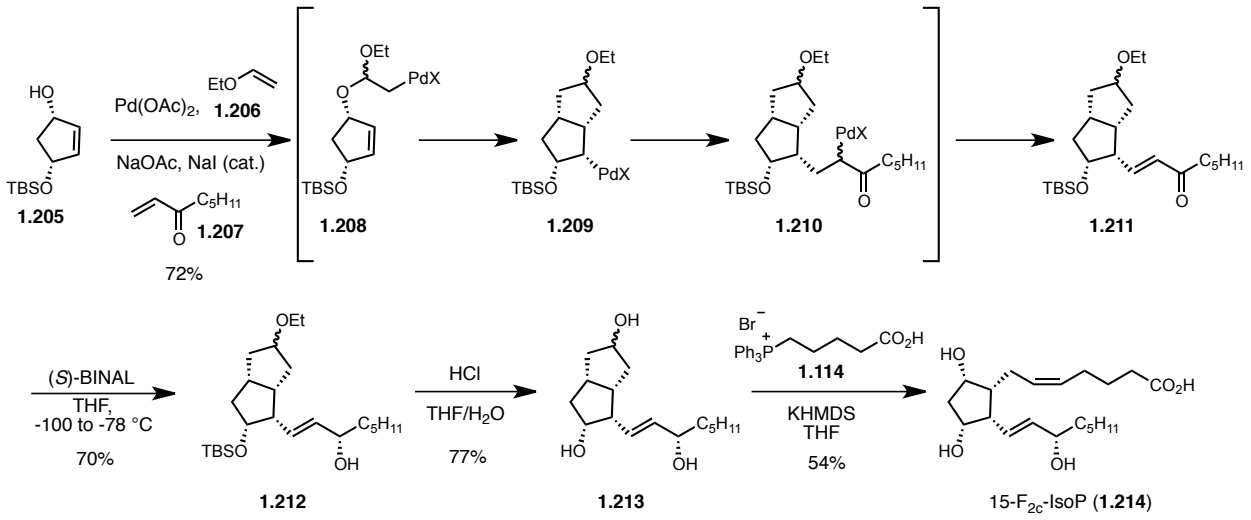


Scheme 1.29: Spur's Synthesis of Lipoxin A_4 and B_4

Chemical Synthesis of Isoprostanes

Larock's Synthesis of 15-F_{2c}-IsoP

Shortly after the discovery of isoprostanes, Larock had developed a route to access isoprostanes.[32] Starting from enantioenriched cyclopentene diol **1.205**, a one pot, three-component coupling provided bicycle **1.211**. The coupling is initiated by oxypalladation reaction with ethyl vinyl ether (**1.206**) to produce intermediate **1.208**, which undergoes alkene insertion from the cyclopentene to provide bicycle **1.209**. Carbopalladation of enone **1.207** to this intermediate provides **1.210** and β-elimination generates the bicyclic acetal **1.211** in high yield. Asymmetric reduction of the enone and deprotection of the acetal provides lactol **1.213**. Wittig reaction with phosphonium salt **1.114** completed the synthesis of 15-F_{2c}-IsoP in an impressively concise manner.

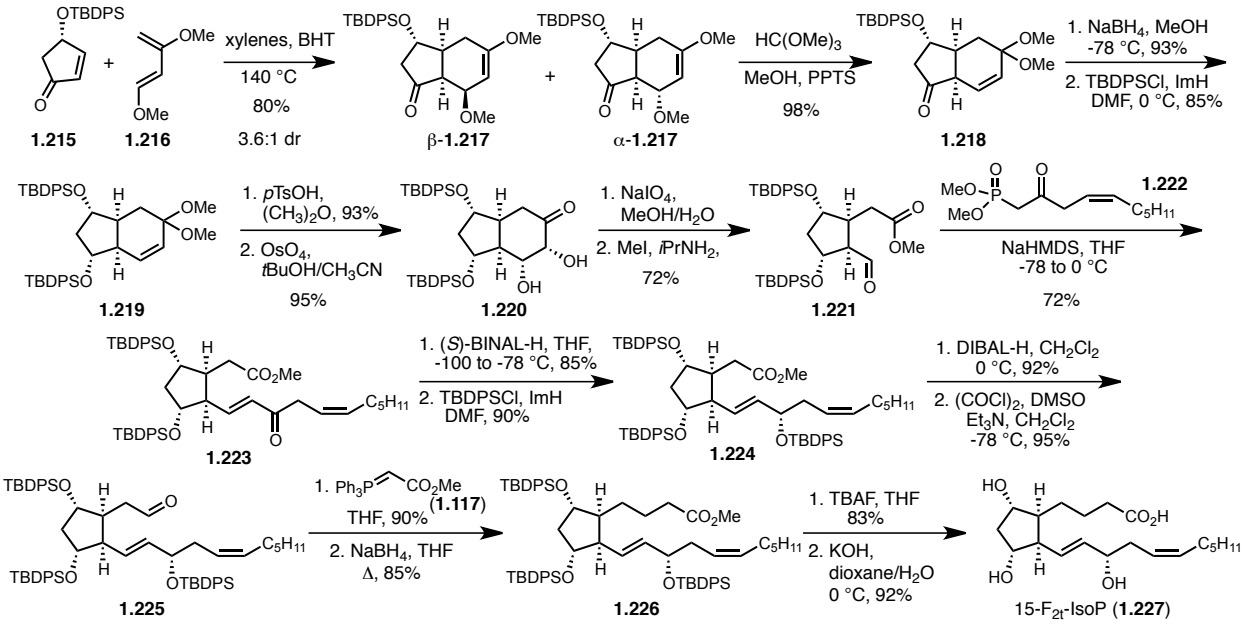


Scheme 1.30: Larock's Synthesis of 15-F_{2c}-IsoP

Rokach's Synthesis of 12-F_{2t}-IsoP

Rokach's strategy to access isoprostanes relied on Diels-Alder chemistry to set the desired *cis* orientation of the side chains.[33] Starting with enantiopure cyclopentenone **1.215**, Diels- Alder with diene **1.216** generated a 3.6:1 mixture of isomers **1.217**. This mixture was carried forward to dimethyl ketal **1.218** via allylic rearrangement with trimethyl orthoformate. Reduction of the ketone and protection of the resulting alcohol as the TBDPS ether provided **1.219**. Ketal hydrolysis was followed by dihydroxylation to generate diol **1.220**. Cleavage of the diol with sodium periodate and subsequent treatment with methyl iodide provided the methyl ester aldehyde **1.221**. Olefination with β-ketophosphonate **1.222** provided the *E*-alkene **1.223** exclusively. Enantioselective reduction with (*S*)-BINAL and protection of the resulting alcohol as a TBDPS ether afforded **1.224**. A reduction/oxidation sequence converted the methyl ester to aldehyde **1.225**, which was subjected to olefination with phosphorane **1.117** to provide an α,β-

unsaturated ester, the double bond of which was reduced with $NaBH_4$ to provide ester **1.226**. Desilylation and methyl ester hydrolysis provided the isoprostane **1.227**.

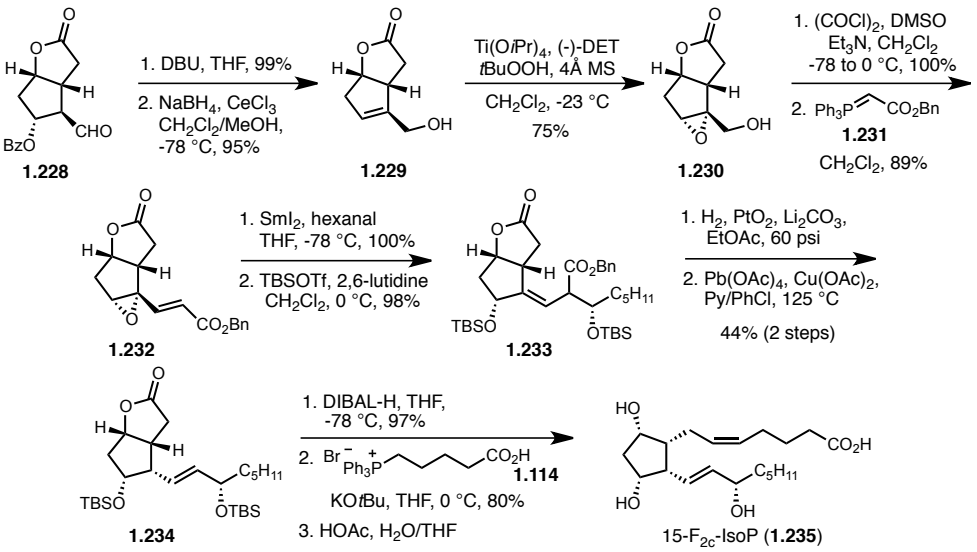


Scheme 1.31: Rokach's Synthesis of 12-F_{2t}-IsoP

Cha's Synthesis of 15-F_{2c}-IsoP

Cha's approach to isoprostane synthesis started from Corey lactone **1.228**.[34] Elimination of the benzoate and subsequent Luche reduction of the resultant α,β-unsaturated aldehyde provided allylic alcohol **1.229**. Sharpless asymmetric epoxidation gave epoxide **1.230** in good yield and high stereoselectivity. Swern oxidation and Wittig olefination with phosphorane **1.231** provided the α,β-unaturated ester **1.232**. Reductive epoxide opening with SmI_2 followed by addition of hexanal provided a mixture of C15 epimers that were silylated to provide **1.233**. Separation of the epimers was possible at this point and the desired epimer was treated with H_2 to

provide an intermediate carboxylic acid, which underwent oxidative decarboxylation to provide **1.234**. Reduction to the lactol, Wittig olefination with phosphonium salt **1.114**, and silyl group removal produced 15-F_{2c}-IsoP.

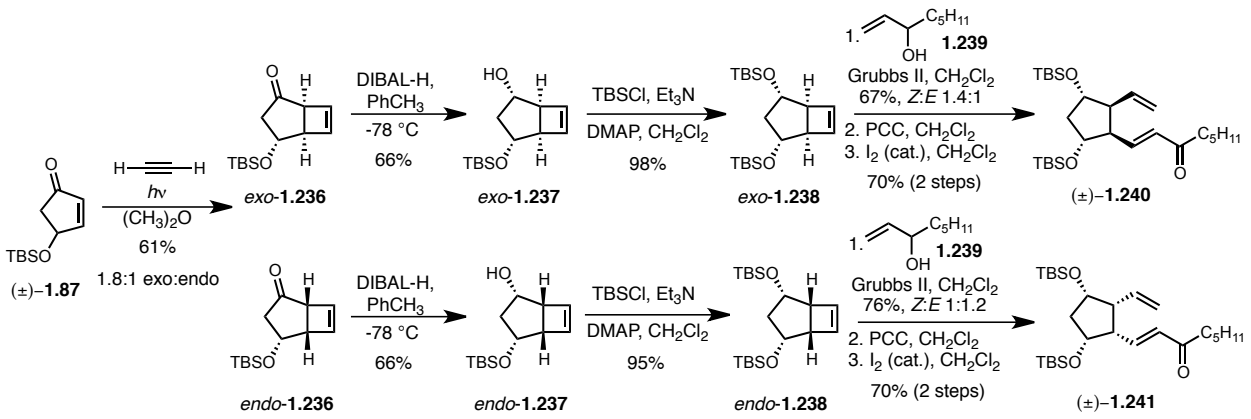


Scheme 1.32: Cha's Synthesis of 15-F_{2c}-IsoP

Snapper's Synthesis of 15-F_{2t}-IsoP Isomers

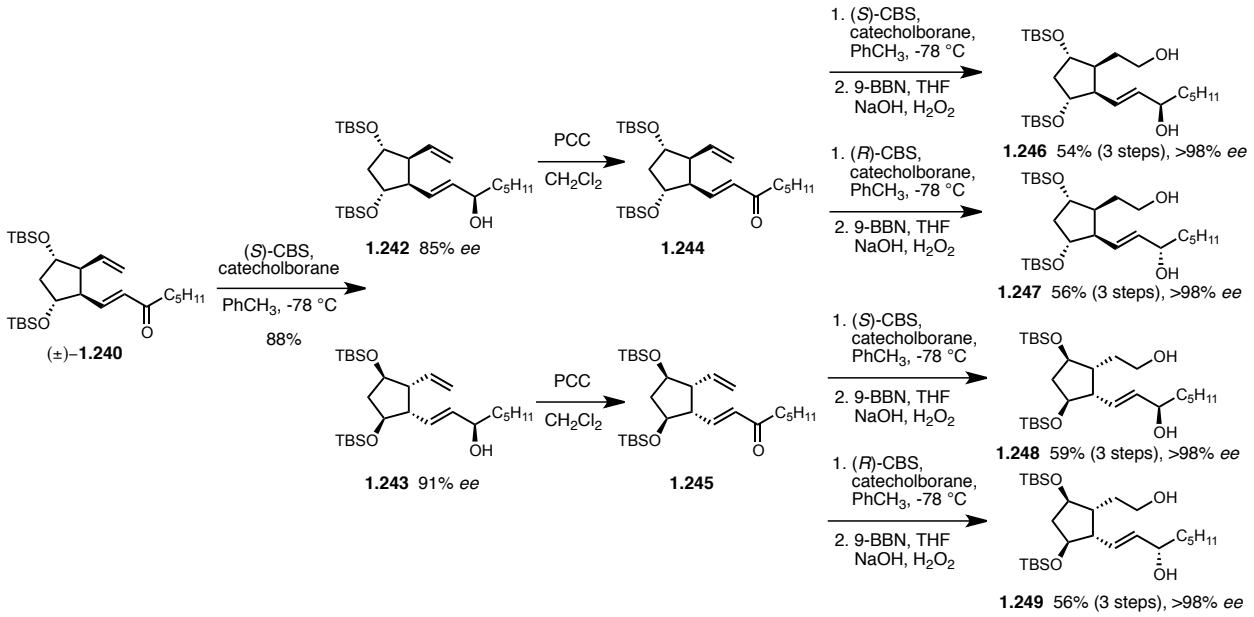
Snapper developed a highly stereodivergent strategy to access the multitude of isomers of isoprostanes from a common starting substrate.[35] Starting from racemic cyclopentenone **1.87**, photocycloaddition with acetylene provided an inseparable mixture of *endo*-**1.236** and *exo*-**1.236**. DIBAL-H reduction allowed for separation of the isomers, which were protected as TBS ethers to provide *meso*-cyclobutenes *exo*-**1.238** and *endo*-**1.238**. Ring opening cross-metathesis with racemic octen-3-ol (**1.239**) provided a mixture of *E*/*Z* isomers that, after PCC oxidation, were

treated with catalytic iodine to isomerize the undesired *Z*-olefin to achieve racemic *cis,trans* **1.240** and racemic all *cis*-**1.241** in high yields.



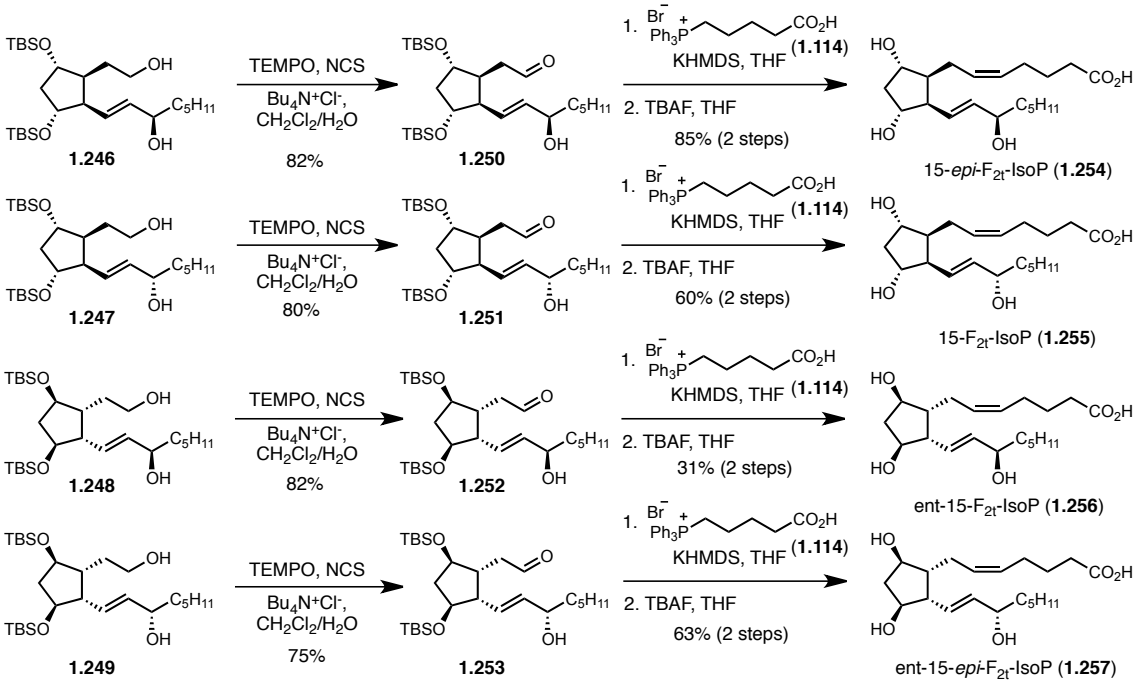
Scheme 1.33: Snapper's Synthesis of 15-F_{2t}-IsoPs - Formation of Cyclopentane Isomers

Enantiopure compounds were prepared from the *cis,trans*-isomer **1.240** as illustrated in Scheme 1.32. CBS-reduction of the enone provided diastereomeric alcohols **1.242** and **1.243** in great enantiomeric excess that could be separated at this stage. Oxidation with PCC and reduction with either (*R*)- or (*S*)- CBS catalysts followed by hydroboration/oxidation of the terminal alkene that results provided four enantiopure diastereomers (**1.246 – 1.249**) in exceptional enantiomeric excess.



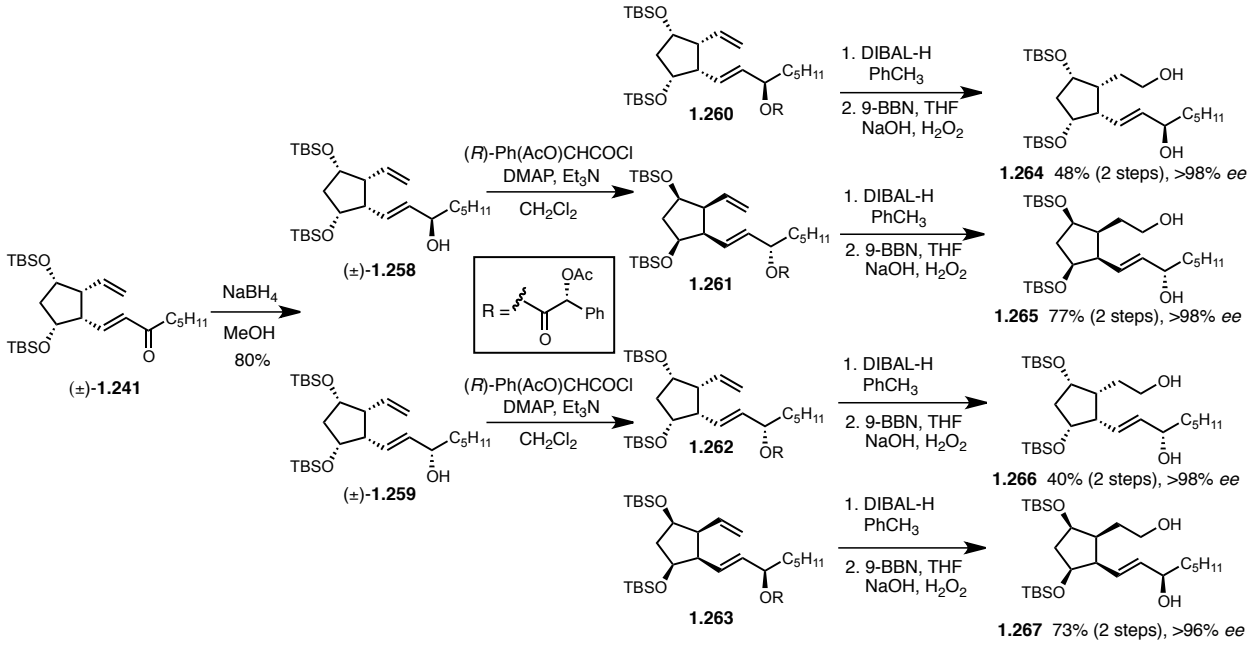
Scheme 1.34: Snapper's Synthesis of 15-F_{2t}-IsoP - Formation of Four Diastereomers from 1.240

To complete the synthesis of the diastereomers of 15-F_{2t}-isoprostanes, selective oxidation of the primary alcohol with TEMPO provided aldehydes **1.250**-**1.253**, which were subjected to Wittig olefination with phosphonium salt **1.114** and subsequently desilylated to provide four different isoprostane diastereomers **1.254**-**1.257**.



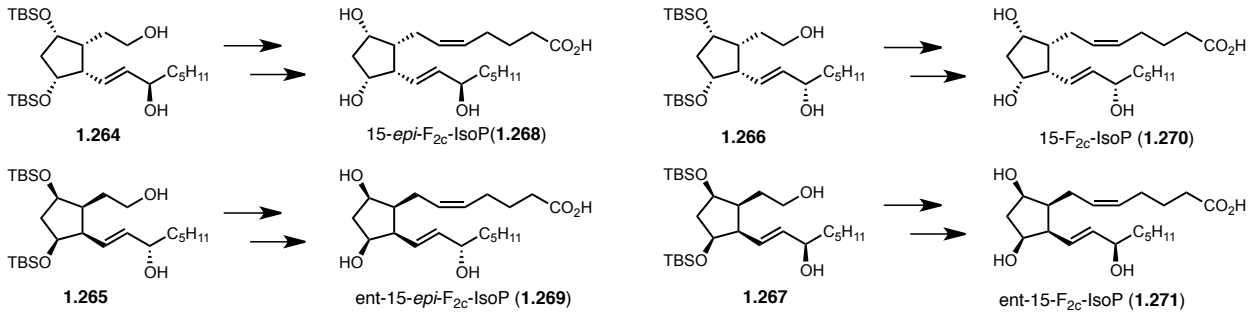
Scheme 1.35: Snapper's Synthesis of 15-F_{2t}-IsoP - Completion of the Synthesis of Four Diastereomers

From the all *cis*-racemic mixture **1.241**, the reduction of the enone was carried out using $NaBH_4$ to provide racemates **1.258** and **1.259**. Resolution of the alcohols using (*R*)-*O*-acetylmandelic acid chloride and separation of the resulting diastereomers provided **1.260** – **1.263**. Removal of the auxiliary with DIBAL-H and hydroboration/oxidation of the terminal olefin provided four isoprostane diastereomers **1.264** – **1.267** in excellent enantiomeric excess and moderate yields.



Scheme 1.36: Snapper's Synthesis of 15-F_{2c}-IsoP - Formation of Four Diastereomers from 1.241

To complete the synthesis of the isoprostanes, the same selective oxidation / Wittig olefination / desilylation sequence was employed (as in Scheme 1.33) to provide four diastereomerically pure 15-F_{2c}-isprostanes. This approach impressively utilizes asymmetric reductions to provide a multitude of isprostane isomers in rapid fashion.

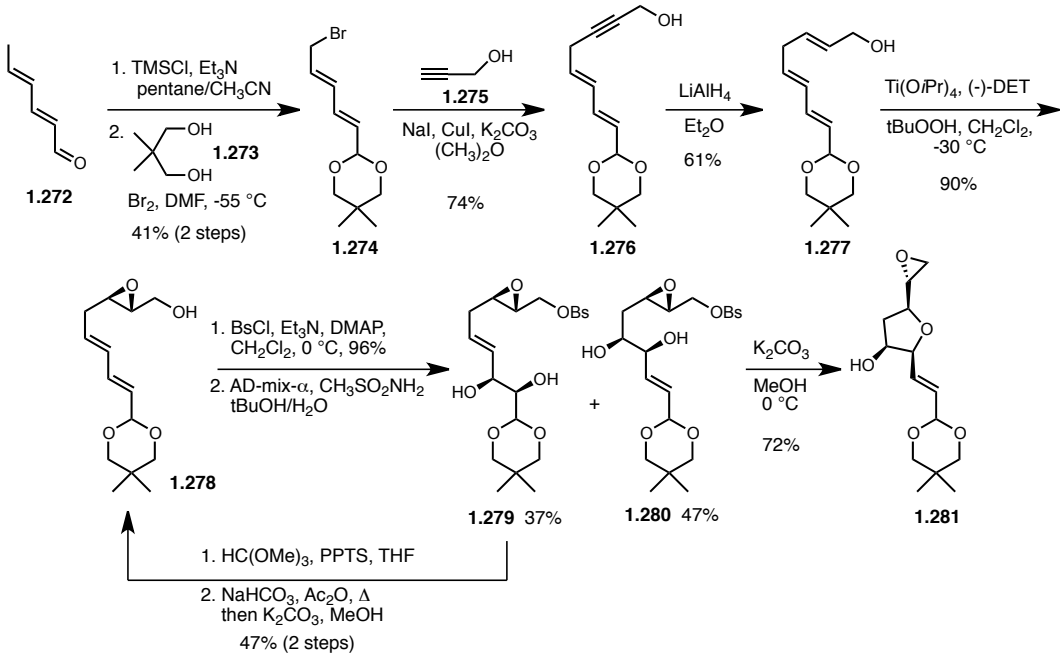


Scheme 1.37: Snapper's Synthesis of 15-F_{2c}-IsoP - Completion of the Synthesis of Four Diastereomers

Chemical Synthesis of Isofurans

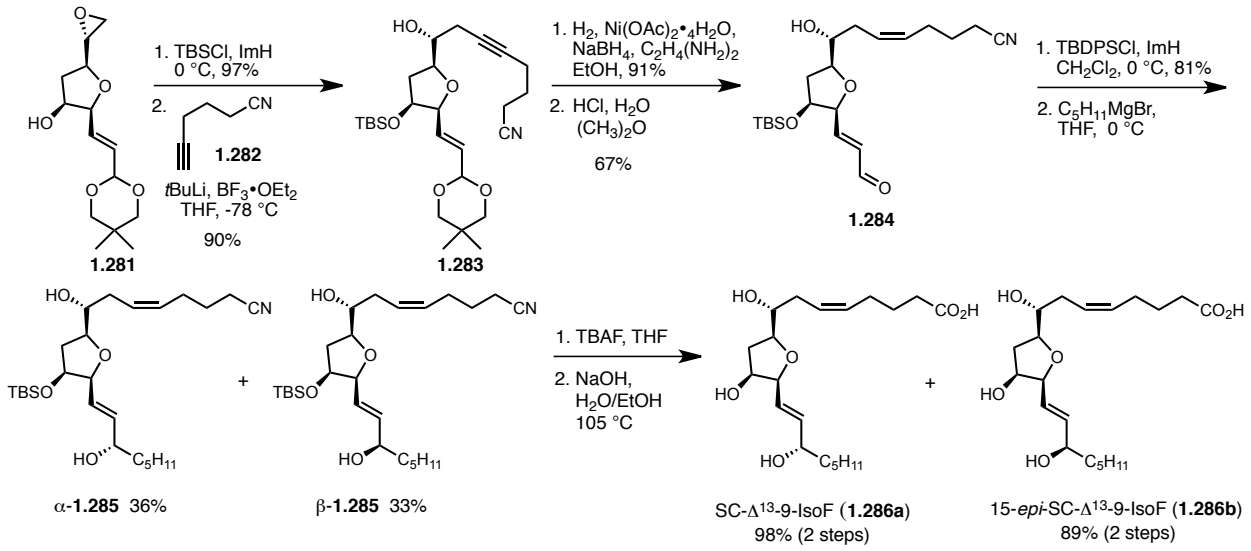
Taber's Synthesis of Alkenyl Isofurans

Taber's synthetic strategy for the alkenyl isofurans involved a flexible approach to several enantiomerically pure diastereomers.[36] Starting with sorbaldehyde (**1.272**), formation of the TMS enol ether followed by bromination of the enol ether and trapping with diol **1.273** provided the bromoacetal **1.274**. Sonogashira coupling with propargyl alcohol (**1.275**) provided alkynol **1.276**. Reduction of the alkyne with $LiAlH_4$ provided allylic alcohol **1.277**. Sharpless asymmetric epoxidation generated epoxy alcohol **1.278**, which was then converted to the benzene sulfonate and, after Sharpless asymmetric dihydroxylation, gave a mixture of regioisomeric diols **1.279** and **1.280**. The undesired diol **1.279** could be funneled back to epoxyalcohol **1.279** through a two-step process involving formation of a cyclic orthoester and subsequent thermal fragmentation. The desired diol **1.280** was subjected to base catalyzed 5-*exo*-*tet* cyclization followed by epoxide formation to provide **1.281**.



Scheme 1.38: Taber's Synthesis of Alkenyl Isofurans - Formation of Intermediate Epoxide 1.281

Protection of the secondary alcohol followed by addition of the lithiate of alkyne **1.282** to the epoxide formed alcohol **1.283**. Semihydrogenation of the alkyne and acetal hydrolysis provided aldehyde **1.284**. Protection of the alcohol as the TBDPS ether and pentylmagnesium bromide addition provided two easily separable alcohol diastereomers α-**1.285** and β-**1.285**. Desilylation with TBAF and hydrolysis of the cyanide provided SC-Δ^{13}-9-IsoF and 15-*epi*-SC-Δ^{13}-9-IsoF.

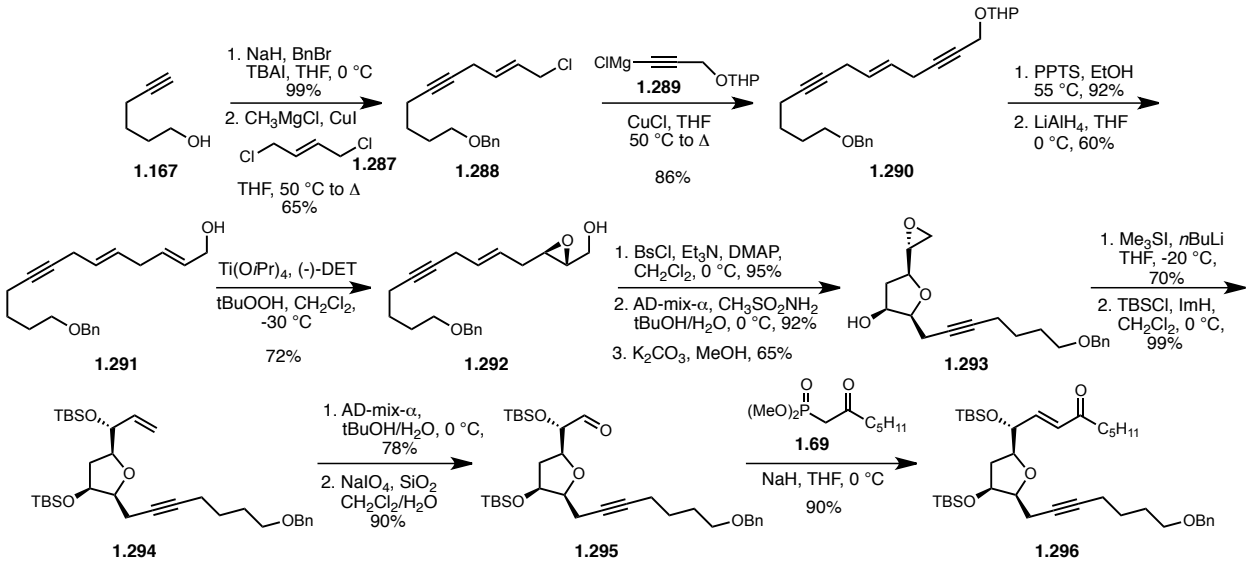


Scheme 1.39: Taber's Synthesis of Alkenyl Isofurans - Completion of the Synthesis

Taber's Synthesis of Enediol Isofurans

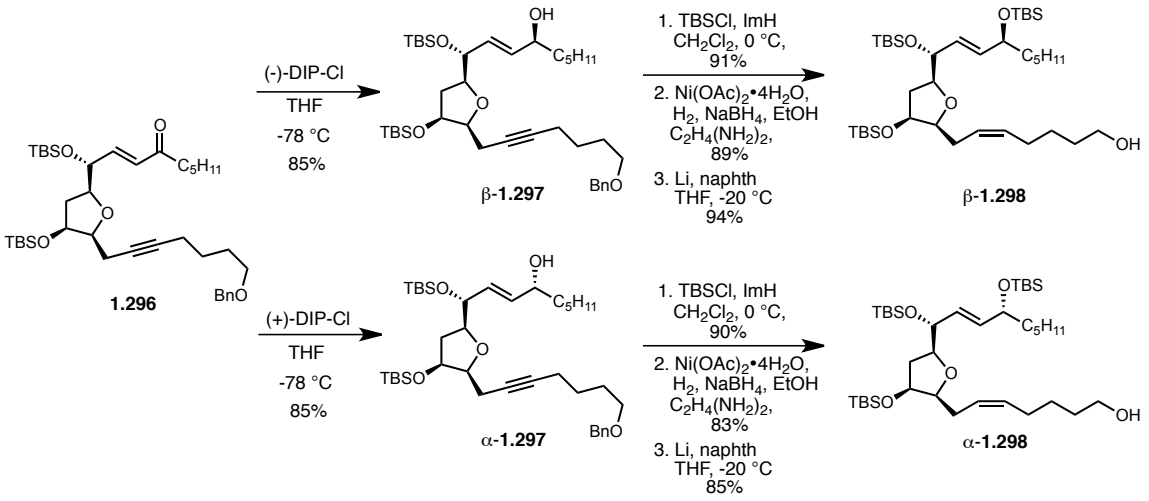
Taber's strategy to access the enediol isofurans utilized an approach highly similar to that used to generate the alkenyl isofurans.[37] Starting from hexynol (**1.167**), protection of the alcohol as a benzyl ether and reaction with *trans*-1,4-dichloro-2-butene (**1.287**) produced the alkylated product **1.288**. Copper-mediated coupling of alkynyl Grignard **1.289** and **1.288** provided diyne **1.290**. THP cleavage and hydroxyl-directed alkyne reduction with $LiAlH_4$ generated alkene **1.291**, which was transformed to epoxide **1.292** via Sharpless asymmetric epoxidation. Conversion to the benzene sulfonate, Sharpless asymmetric dihydroxylation, and base-catalyzed cyclization and formed the tetrahydrofuran epoxide **1.293** in a manner analogous to the alkenyl isofuran synthesis. Reaction with the sulfonium ylide generated from TMSI opened the epoxide to form a diol that is subsequently silylated to form **1.294**. Dihydroxylation and oxidative

cleavage of the diol provided aldehyde **1.295**. Coupling with the anion of β-ketophosphonate **1.69** provided enone **1.296**.



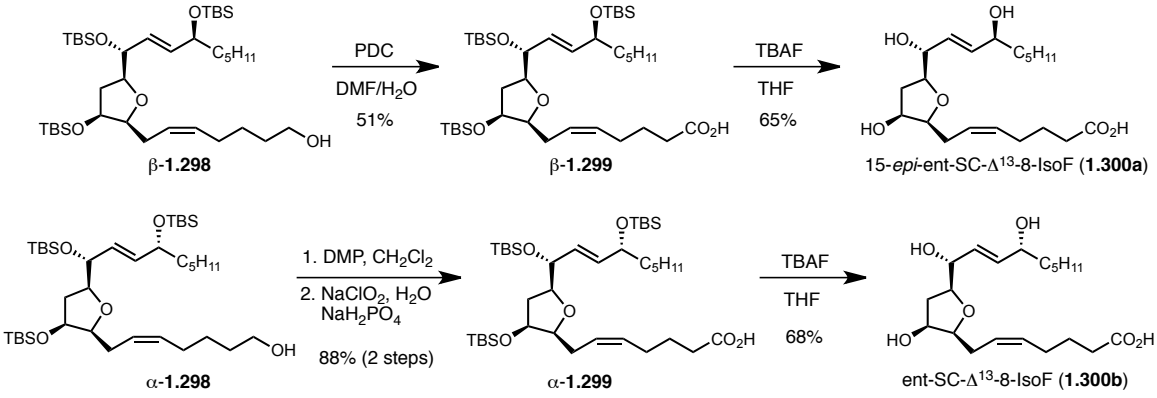
Scheme 1.40: Taber's Synthesis of Enediol Isofurans - Generation of Intermediate Enone 1.296

To generate the different isofuran isomers, the enone was subjected to asymmetric reduction with either enantiomer of DIP-Cl to make two separate diastereomers α-**1.297** and β-**1.297**. Silylation of the resulting alcohol, semihydrogenation of the alkyne to generate the *Z*-olefin, and removal of the benzyl group provided alcohols α-**1.298** and β-**1.298**.



Scheme 1.41: Taber's Synthesis of Enediol Isofurans - Formation of 2 IsoF Diastereomers

To achieve the synthesis of 15-*epi*-ent-SC-Δ^{13}-8-IsoF (**1.300a**), the primary alcohol of β-**1.298** was oxidized to the carboxylic acid with PDC and desilylated with TBAF. Furthermore, to generate the other isofuran diastereomer, a two-step oxidation was required to provide the carboxylic acid α-**1.299** and, after silyl group cleavage, made ent-SC-Δ^{13}-8-IsoF (**1.300b**).



Scheme 1.42: Taber's Synthesis of Enediol Isofurans - Completion of the Synthesis of Two IsoF Diastereomers

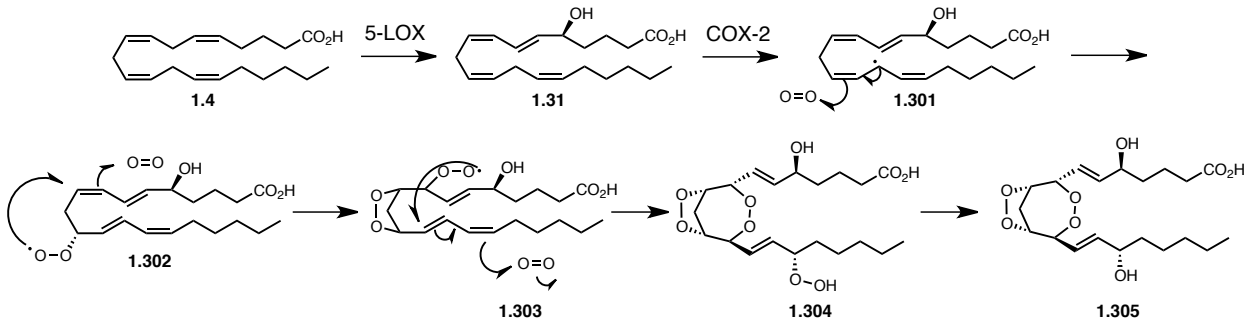
Isolation of Novel Lipid Mediators

Historically, the initial oxidation of arachidonic acid by COX-2 or 5-LOX was thought to determine its fate. Oxidation by COX-2 would lead to the formation of prostaglandins while oxidation by 5-LOX would produce leukotrienes. However, the idea that these two pathways could be operating together to form a novel class of lipid mediators had not been explored.

When thinking about the inflammatory cascade, it is not farfetched to hypothesize that some interaction between these two enzymatic pathways could exist. Both COX-2 and 5-LOX are coexpressed in a number of tissues and disease states, including breast, colon, and pancreatic cancer cells[38], atherosclerotic lesions[39], and asthmatic states[40]. Furthermore, both enzymes are localized at the nuclear envelope of activated cells[41,42,43]. COX-2 is prevalent in macrophages and neutrophils are a rich source of 5-LOX; both cell types are involved in the inflammatory response.

With these details in mind, Schneider and coworkers investigated the possibility of a COX-2/5-LOX crossover pathway that could produce a novel class of lipid mediators.[44] Noticing the similarities between the structure of arachidonic acid and 5(*S*)-HETE, they incubated radiolabelled ^{14}C-5(*S*)-HETE with recombinant COX-2 and saw formation of a single product. Additionally, it is worth noting that no reaction occurred with COX-1; therefore the ability of COX-2 alone to react with 5(*S*)-HETE might be relevant for this crossover pathway. LC-MS analysis showed an increase in molecular weight of 80 mass units, corresponding to the incorporation of 3 molecules of O_2 followed by removal of one oxygen atom through the peroxidase activity of COX-2. Based on extensive NMR analysis, they proposed that bisendoperoxide **1.305** was formed, the mechanism of which is shown in Scheme 1.43. COX-2

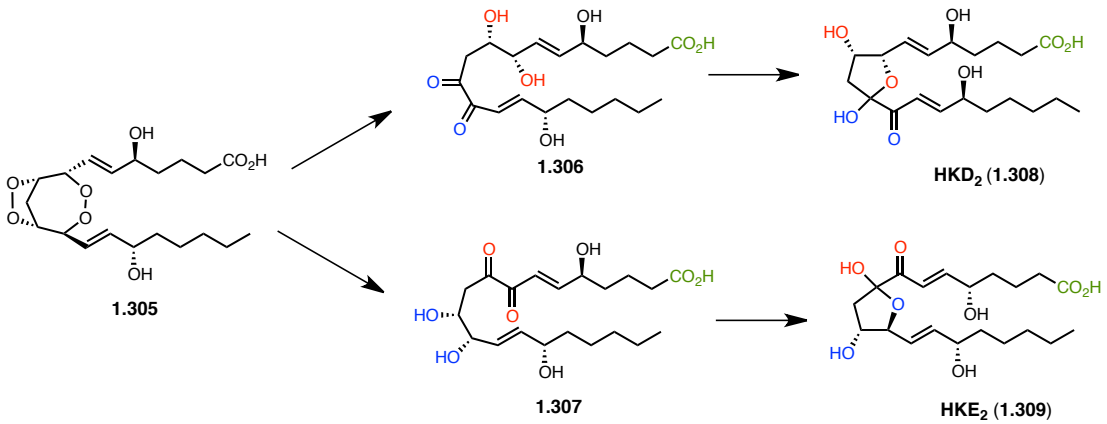
abstracts a hydrogen from C13 of 5(*S*)-HETE to form the bisallylic radical **1.301**, which captures molecular oxygen at C11 to provide peroxy radical **1.302**. This radical undergoes 5-*exo-trig* cyclization and subsequently captures a second molecule of oxygen at C8 to provide peroxy radical **1.303**. A second cyclization followed by capture of oxygen at C15 and reduction of the resulting peroxide via peroxidase activity of COX-2 provides bisendoperoxide **1.305**.



Scheme 1.43: Mechanism of Formation of Bisendoperoxide (1.305)

Furthermore, this same incubation was extracted 30 minutes after addition of 5(*S*)-HETE to COX-2. HPLC analysis showed disappearance of the peak corresponding to **1.305** and the appearance of two new peaks. Isolation of these two compounds followed by LC-MS and extensive NMR analysis suggested the formation of two hemiketals (**1.308** and **1.309**), which are believed to be rearrangement products of the bisendoperoxide analogous to the rearrangement of PGH_2 into prostaglandins. (Scheme 1.44).[45] The non-enzymatic opening of both endoperoxides can lead to two regioisomers containing a 1,2-diketone moiety and a 1,2-diol moiety. The first regioisomer places the diketone opposite the carboxylate side chain (**1.306**) whereas the second regioisomer places the diketone opposite the aliphatic side chain (**1.307**). 5-*exo* closure then

produces either hemiketal D_2 (**1.308**) or hemiketal E_2 (**1.309**). The letters D and E are to indicate the structural similarities to PGD_2 and PGE_2, respectively.



Scheme 1.44: Nonenzymatic Rearrangement of 1.305 into Hemiketals D_2 and E_2

Because both COX-2 and 5-LOX are involved in a number of cellular processes in the regulation of endothelial cell function, mouse pulmonary endothelial cells were treated with both hemiketals. The results indicated that both hemiketals could induce the formation of capillary-like structures and endothelial cell migration in a dose-dependent manner, implicating a role in angiogenesis and the inflammatory cascade. Furthermore, the hemiketals were detected in human leukocytes after activation of the cells with lipopolysaccharide to stimulate COX-2 expression and with calcium ionophore to stimulate 5-LOX activity. Thus, this finding suggests that hemiketals can be relevant to the resolution of inflammation as mediators of angiogenesis and tissue restoration. Alternatively, this same activity could be responsible for tumor cell growth in disease states where COX-2 and 5-LOX are coexpressed. Therefore, these compounds require further investigation in order to determine their functional relevance to the immune response and human health.

Statement of Dissertation

The work presented herein involves the synthesis of hemiketal D_2 (HKD_2) and hemiketal E_2 (HKE_2), two novel arachidonic acid metabolites. Structurally, these compounds contain a rather unique keto hemiketal moiety that poses an intriguing synthetic challenge and provides a pathway through which to unveil new chemical methods to access such scaffolds. Both compounds also demonstrated the ability to induce branching and sprouting of endothelial cells, indicating an important role in angiogenesis and tissue repair. Furthermore, the hemiketals were detected in human leukocytes after stimulation of COX-2 and 5-LOX with lipopolysaccharide and calcium ionophore, respectively. Given the rich history and important biological activities of related lipid mediators such as prostalgandins and leukotrienes, we believe these hemiketals are biologically relevant. Furthermore, due to the limited access to these compounds via preparative biosynthesis, chemical synthesis would allow for the generation of significant quantities of the hemiketals to evaluate their importance in human health.

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CHAPTER 2

INITIAL EFFORTS TOWARD THE SYNTHESIS OF HEMIKETAL E_2

While the isolation of hemiketals D_2 and E_2 is certainly exciting, the ability to further probe their biological properties is hindered by their low abundance. Accessing these compounds via preparative biosynthesis yields low microgram quantities that are insufficient for extensive investigations into their potential activities. Therefore, chemical synthesis provides a viable option for accessing multi-milligram quantities.

Keto Hemiketal Groups in Natural Products

The most intriguing structural feature of both HKD_2 and HKE_2 is the keto-hemiketal moiety. There are a handful of examples of keto-hemiketals in nature whose structures are illustrated in Figure 2.1. Both rapamycin (**2.1**) and FK-506 (**2.2**) contain a 6-membered hemiketal α-ketoamide group whereas polycavernoside A (**2.3**) possesses a 5-membered keto-hemiketal feature.[1,2,3] We believed the molecule's rather unique hemiketal moiety would present a synthetic challenge and would require the development of novel chemical methods for its construction.

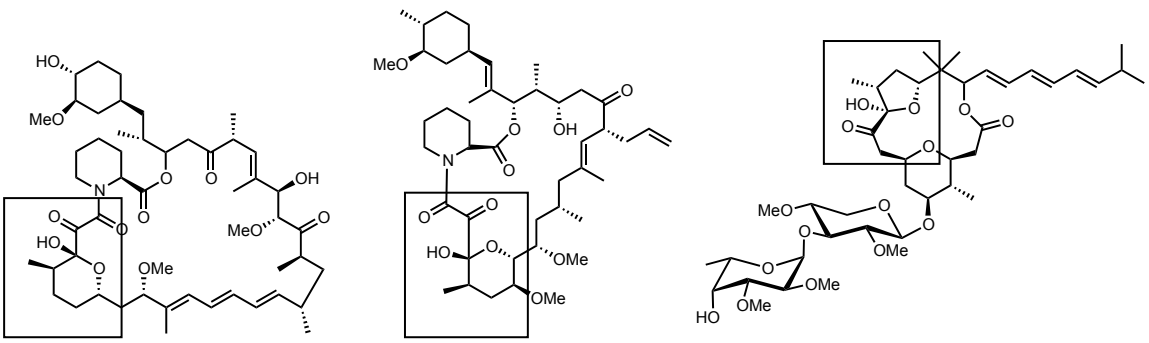


Figure 2.1: Natural Products Containing Keto Hemiketal Groups

Retrosynthetic Analysis for HKD_2 and HKE_2

When planning our strategy for the synthesis of these novel metabolites, we desired a route that would have a high degree of convergence and would incorporate flexibility so as to efficiently access both hemiketal D_2 and E_2. In examining their structures, the main differences lie in (1) the orientation of the aliphatic (pentyl) and carboxylate (propyl carboxylate) side chains and (2) the relative stereochemistry of the vicinal stereocenters located in the hemiketal ring. In HKD_2, the carboxylate side chain sits opposite the enone group and the C8-C9 bond of the furan ring possesses *cis* relative stereochemistry. For HKE_2, the carboxylate side chain resides adjacent to the enone group and the C11-C12 bond has *trans* relative stereochemistry.

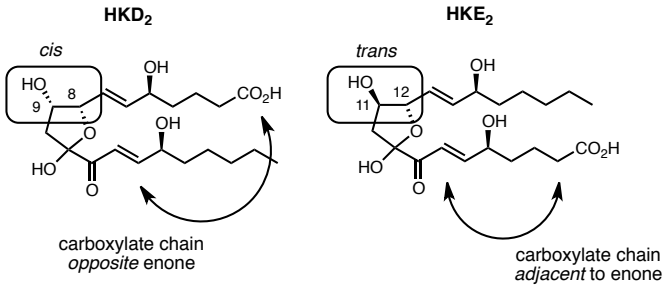
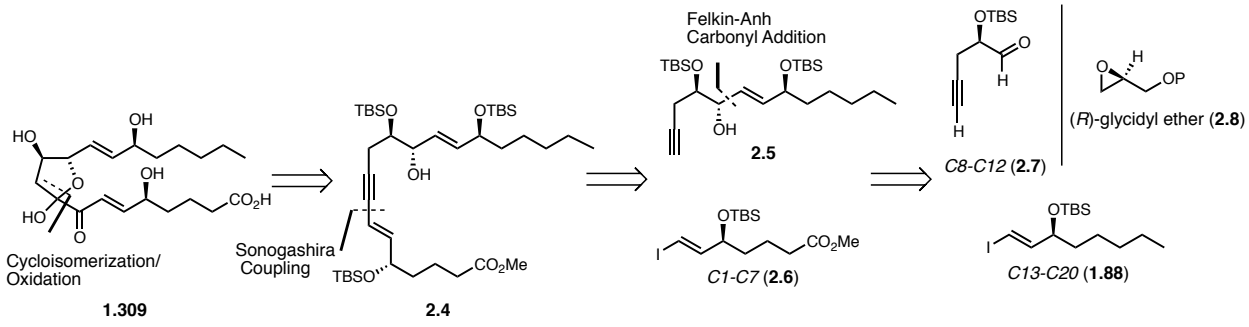


Figure 2.2: Structural Differences of HKD_2 and HKE_2

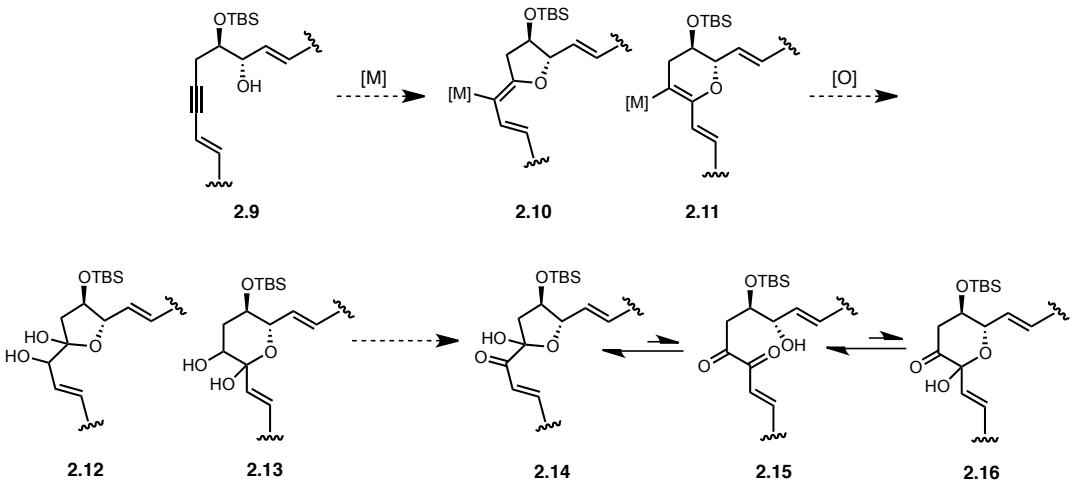
The retrosynthetic analysis of HKE_2 is shown in Scheme 2.1. We envisioned a cycloisomerization/oxidation sequence from alkynol **2.4** would produce the key keto hemiketal moiety (see Scheme 2.1). The required carbon framework **2.4** could be accessed from Sonogashira coupling between alkyne **2.5** and vinyl iodide **2.6**.[4] Furthermore, the relative *anti* stereochemistry about the diol group in alkyne **2.5** could be generated via Felkin-Anh controlled addition of a vinyl metal reagent derived from **1.88** to aldehyde **2.8**, which in turn could arise from an (*R*)-glycidyl ether **2.8**.[5,6,7]



Scheme 2.1: Retrosynthetic Analysis of HKE_2

Furthermore, we believed the implementation of a cycloisomerization/oxidation sequence would provide flexibility in our synthetic route. While we hoped that the choice of metal would

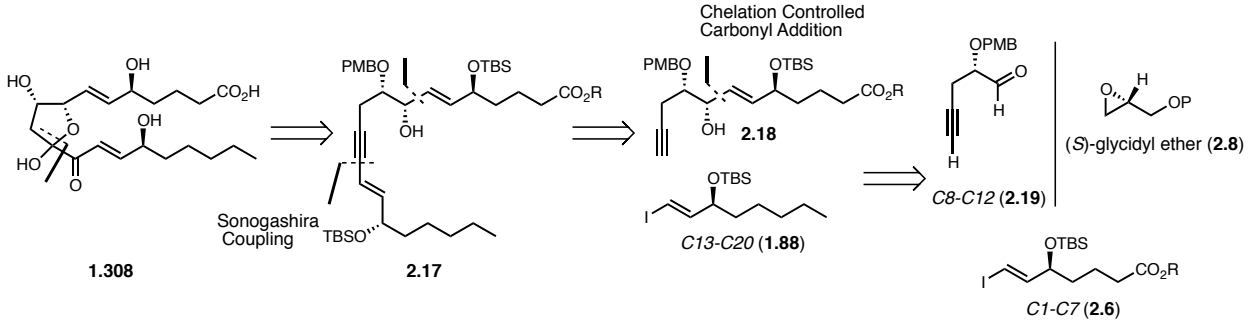
allow for selective formation of the 5-*exo* product, we noticed that the 6-*endo* product could also be converted to the desired keto-hemiketal. As illustrated in Scheme 2.2, we believed that, upon generation of the vinyl ethers **2.10** and **2.11**, oxidation to diols **2.12** and **2.13** and subsequent oxidation of the secondary alcohol would provide both keto hemiketals **2.14** and **2.16**. Furthermore, we postulated that the 6-*endo* product **2.16** could equilibrate via opening to the 1,2-diketone **2.15** to the 5-*exo* product **2.14**. This hypothesis was predicated on observations from the Schneider group that in different solvents, different ratios of hemiketal isomers were observed by NMR.[8]



Scheme 2.2: Proposed 5-*exo*/6-*endo* Equilibrium of Hemiketals

We hypothesized that we could access HKD_2 through a very similar approach (Scheme 2.3). Again, the keto-hemiketal moiety could arise from cycloisomerization/oxidation of alkynol **2.17**. This framework could arise from Sonogashira coupling of vinyl iodide **1.88** and alkyne **2.18**. In this instance, however, the requisite *syn* relative stereochemistry about the diol would be

generated from a chelation-controlled addition of **2.6** to aldehyde **2.19**, which would be prepared from the (*S*)-glycidyl ether **2.8**.[9]



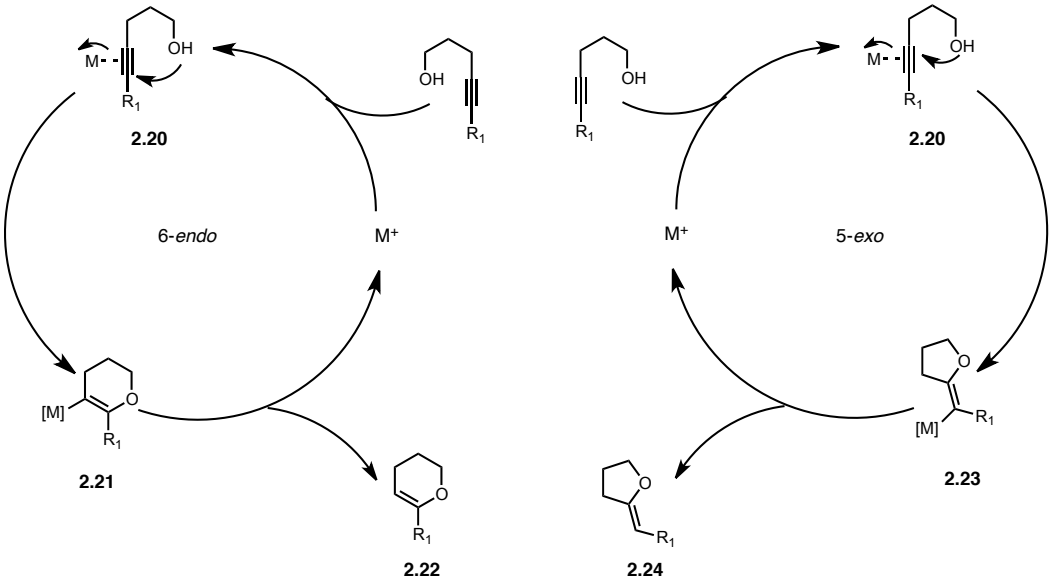
Scheme 2.3: Retrosynthetic Analysis for HKD_2

It is worth noting that both syntheses would make use of vinyl iodides **1.88** and **2.6**. Furthermore, enantioselective syntheses of both fragments are relatively well established from earlier eicosanoid syntheses. A simple switch of protecting groups on the aldehyde fragment will change the facial selectivity of the carbonyl addition from the Felkin-Anh control to the chelation-controlled reaction manifold. Additionally, enantiomers of the same glycidyl ether **2.8** would be used in each synthesis, making this approach highly convergent.

Metal-Catalyzed Cycloisomerizations and Applications to Total Synthesis

Tetrahydrofuran and pyran ring systems are ubiquitous in natural products.[10] As such, many methods have been developed to rapidly access these heterocycles.[11] One such method involves the metal-catalyzed cycloisomerization of acetylenic alcohols. As depicted in Scheme 2.4, these cyclizations most commonly occur either in a 5-*exo* or 6-*endo* fashion.[12] After

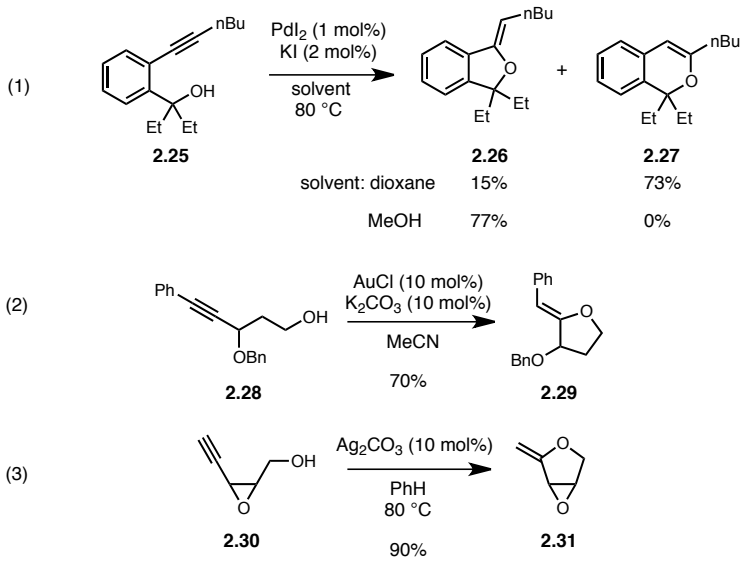
coordination of the metal to the alkyne (**2.20**), the alcohol can undergo a 5-*exo-dig* or 6-*endo-dig* cyclization to form a vinyl metal species **2.21** or **2.23**. After protodemetallation, the desired vinyl ethers **2.22** and **2.24** are generated and the metal can reenter the catalytic cycle. The most common transition metals used as catalysts in these transformations include palladium(II),[13] silver(I),[14] gold(I),[15] mercury(II),[16] molybdenum,[17] and iridium(I).[18] Furthermore, the choice of metal can have significant impact in determining the ring size of the product vinyl ether.



Scheme 2.4: 5-*exo* and 6-*endo* Cycloisomerization Pathways

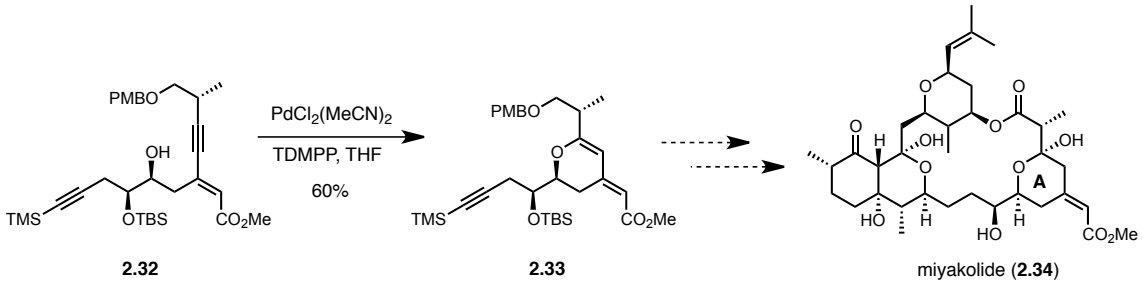
Select examples of metal-catalyzed cycloisomerizations are highlighted in Scheme 2.5. Gabriele and coworkers indicated that alkynylbenzyl alcohols (**2.25**) can be treated with palladium(II) catalysts to afford benzofurans **2.26** and **2.27** (equation 1, Scheme 2.5).[19] Furthermore, they determined that solvent influences the product distribution, as solvents such as dioxane favored a 6-*endo* pathway but more polar solvents, such as MeOH or DMA, led to

exclusive production of the 5-*exo* adduct. Pale and coworkers demonstrated that treatment of 3-benzyloxypentynol (**2.28**) could undergo exclusive 5-*exo* cyclization upon treatment with catalytic AuCl and K_2CO_3 to afford α-alkylidene **2.29** (equation 2, Scheme 2.5).[6] Furthermore, they note that only the *Z*-isomer of the product is detected. Pale also showed that silver-catalyzed cycloisomerization reaction of epoxy-substituted acetylenic alcohol **2.30** could be converted into epoxyoxolane **2.31** (equation 3, Scheme 2.5).[20]



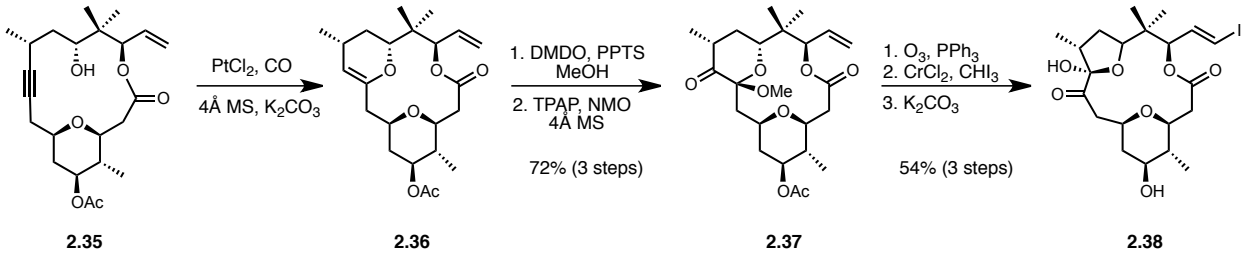
Scheme 2.5: Examples of Metal-Catalyzed Alkynol Cycloisomerizations

The cycloisomerization reaction has also been used in a number of total synthesis efforts as a way of generating furan or pyran rings from a complex, advanced intermediate acetylenic alcohols. Trost employed a Pd-catalyzed cycloisomerization of alkynol **2.32** for the construction of the A ring on miyakolide (Scheme 2.6).[21] Furthermore, the reaction is selective for the alkyne conjugated to the enoate and reaction with the silylated alkyne was not detected.



Scheme 2.6: Pd-catalyzed Cycloisomerization en Route to Miyakolide

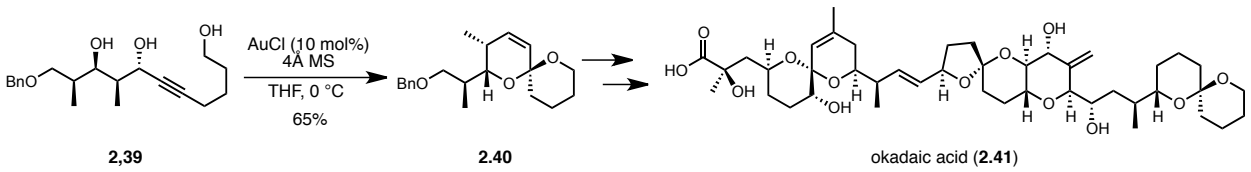
In his synthesis of polycavernoside A, Lee utilized a 6-*endo* cycliosomerization to generate the keto-hemiketal ring system.[22] Starting from macrocycle **2.35**, platinum(II) catalyzed cyclization afforded the 6-*endo* product **2.36**. Treatment with DMDO followed by addition of MeOH provided a hydroxyketal intermediate, which was subjected to Ley-Griffith oxidation to provide the keto ketal **2.37**.[23] Ozonolysis of the terminal olefin and Takai olefination installed the vinyl iodide moiety.[24] Interestingly, prolonged exposure to the Takai reaction conditions resulted in acetal hydrolysis and rearrangement to the 5-membered keto hemiketal. Basic hydrolysis of the acetate provided the aglycone of polycavernoside A (**2.38**).



Scheme 2.7: Lee's Synthesis of the Aglycone of Polycavernoside A

Forsyth used a gold-catalyzed spiroketalization of **2.39** to provide the terminal ring system **2.40** en route to the formal synthesis of okadaic acid (**2.36**).[25] Interestingly, the *anti*

stereochemistry about the 1,3-diol afforded the desired 6,6-spirocycle exclusively without any formation of the undesired 5,7-spirocycle.

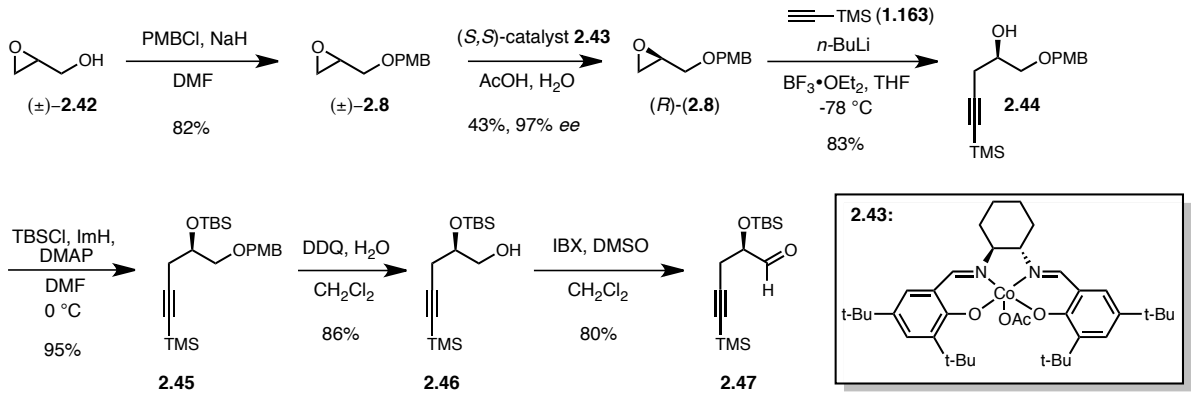


Scheme 2.8: Au-catalyzed Spiroketalization Applied to Okadaic Acid

Synthesis of Key Fragments Required for HKE_2

Synthesis of C8-C12 Aldehyde Fragment

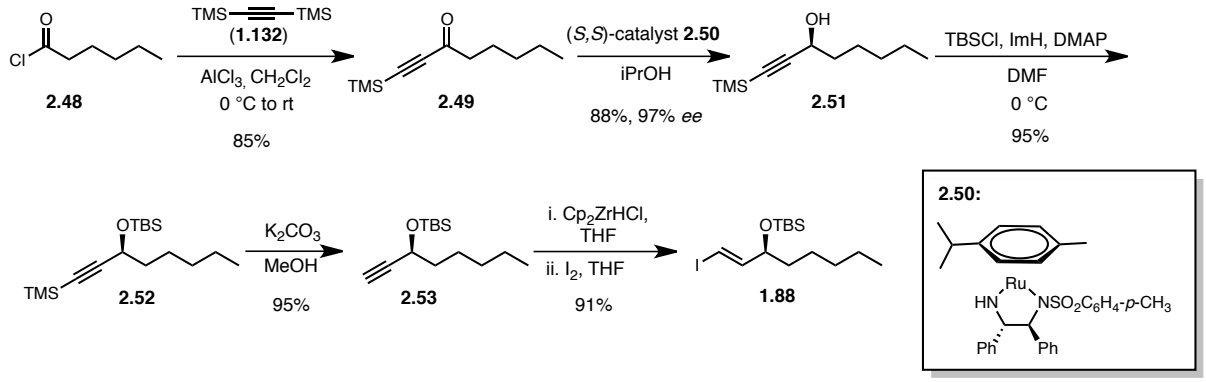
The synthesis of the C8-C12 aldehyde fragment (Scheme 2.9) started from racemic glycidol (**2.42**). Protection of the primary alcohol as a *p*-methoxybenzyl ether provided terminal epoxide (±)-**2.8**, which was subjected to Jacobsen's hydrolytic kinetic resolution using cobalt (salen) catalyst **2.43** to provide the resolved epoxide in high yield and excellent enantiomeric excess.[26] Opening of the epoxide with ethynyltrimethylsilane (**1.163)** provided alcohol **2.44** and subsequent protection as a TBS ether generated **2.45**. The choice of silyl protecting group at this stage was not arbitrary, as silyl ethers are known to influence Felkin-Anh control in nucleophilic additions to α-siloxy-substituted aldehydes.[27] Oxidative cleavage of the benzyl group with DDQ provided alcohol **2.46**, which upon oxidation with IBX provided the desired aldehyde **2.47** in high yield.



Scheme 2.9: Synthesis of C8-C12 Aldehyde Fragment

Synthesis of the C13-C20 Vinyl Iodide Fragment

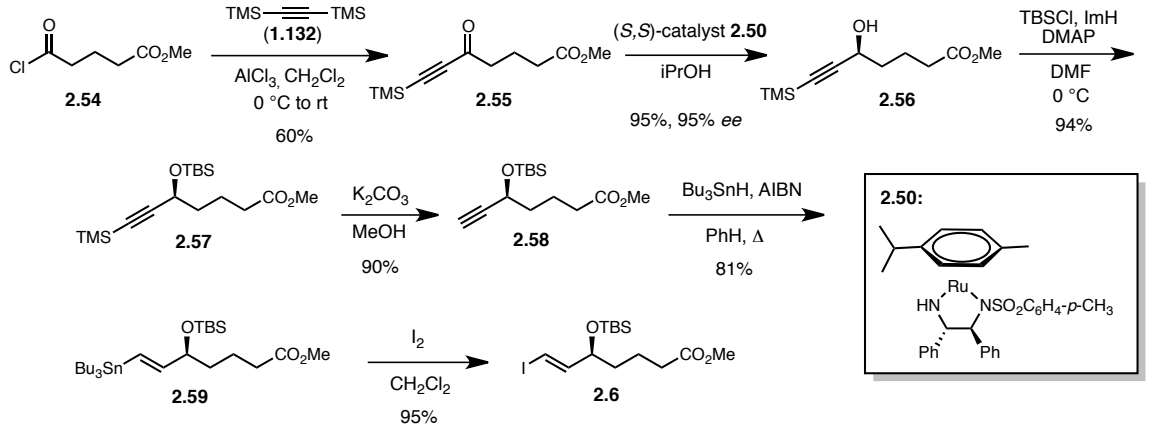
Access to the first of two vinyl iodide fragments is outlined in Scheme 2.10. Treatment of hexanoyl chloride (**2.48**) with bis(trimethylsilyl)acetylene (**1.132**) and $AlCl_3$ provided alkynone **2.49**. Noyori's asymmetric hydrogen transfer with ruthenium catalyst **2.50** gave propargyl alcohol **2.51** in high yield and high enantiomeric excess.[28] Silylation of the resultant alcohol followed by desilylation of the alkyne generated **2.53**, which was subjected to a one-pot hydrozirconation - iodination to provide vinyl iodide **1.88**.



Scheme 2.10: Synthesis of C13-C20 Fragment

Synthesis of the C1-C7 Vinyl Iodide Fragment

Utilizing an approach almost identical to that of the C13-C20 fragment **1.88** completed the synthesis of the last required vinyl iodide fragment **2.6**. Alkynone **2.55** was produced from bis(trimethylsilyl)acetylene (**1.132**) addition to methyl 4-(chloroformyl)butyrate (**2.54**), which can be accessed in two steps from glutaric anhydride.[29] Again, implementation of Noyori's asymmetric hydrogen transfer with the same Ru-catalyst **2.50** provided propargyl alcohol **2.56** in high yield and excellent enantiomeric excess. Protection of the alcohol as a TBS ether generated **2.57** and subsequent removal of the TMS group afforded alkyne **2.58**. Unfortunately, the hydrozirconation - iodination sequence was unsuccessful for this substrate. Therefore, hydrostannylation of the alkyne and subsequent tin/iodine of stannane **2.59** exchange provided the desired vinyl iodide **2.6** in high yield over two steps.



Scheme 2.11: Synthesis of C1-C7 Vinyl Iodide

Synthesis of Carbon Framework of HKE_2

With each of the three key fragments in hand, our attention was turned towards uniting these fragments to produce the carbon framework of HKE_2. As highlighted in Figure 2.3, we proposed that the use of a TBS protecting group would favor Felkin-Anh addition to provide *anti* relative stereochemistry about the diol of **2.60**.

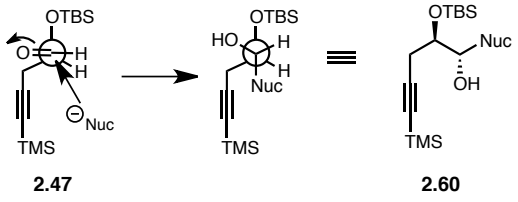
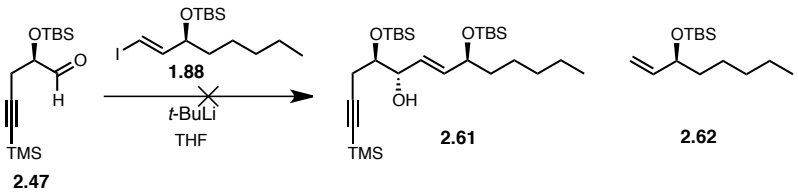


Figure 2.3: Felkin-Anh Model Predicts *Anti* Selectivity

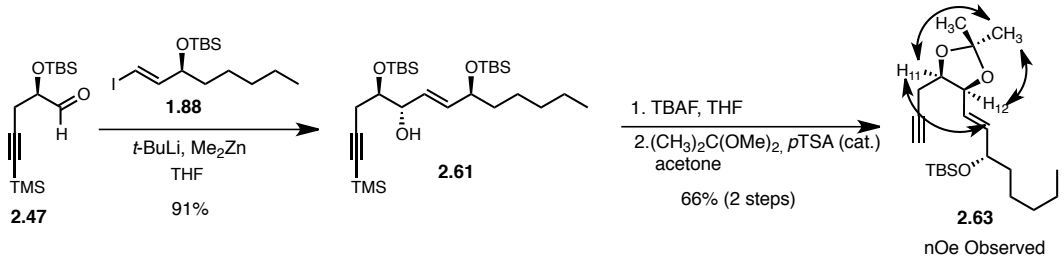
Thus, treatment of vinyl iodide **1.88** with *t*-butyllithium resulted in lithium-halogen exchange and generated a vinyl lithiate that was reacted with aldehyde **2.47**. Unfortunately,

under these conditions we observed no addition product and only isolated the quenched vinyl lithium reagent **2.62**. We believe that the basicity of the alkenyl lithium resulted in simple deprotonation alpha to the aldehyde, resulting solely in racemization of the aldehyde and production of alkene **2.62**.



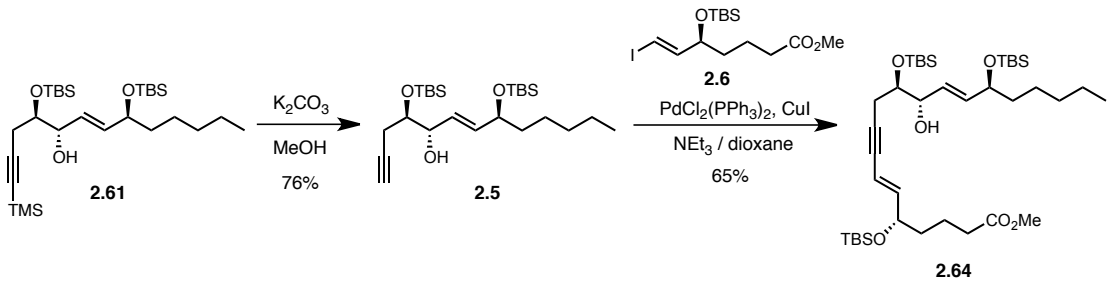
Scheme 2.12: Failed Lithiate Addition to Aldehyde 2.47

To circumvent this problem, generation of the vinyl lithiate was followed by transmetallation with Me_2Zn and, after addition of **2.47**, the desired allylic alcohol **2.61** was isolated in high yield as a single diastereomer.[30] In order to verify that the desired *anti* diastereomer had been produced, **2.61** was treated with TBAF to afford a diol that was subsequently treated with dimethoxypropane and catalytic *p*TSA to produce acetonide **2.63**. 2D NOESY experiments revealed a nOe correlation between H11 and H12, providing evidence in support of the *anti* diastereomer being formed.



Scheme 2.13: Successful Synthesis of Alkyne 2.61 and Verification of Diastereoselectivity

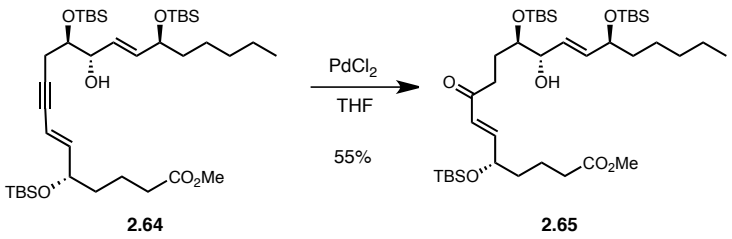
With the desired diastereomer in hand, deprotection of alkyne **2.61** with K_2CO_3 in methanol provided alkyne **2.5**. Sonogashira coupling with vinyl iodide **2.6** then generated the requisite carbon framework **2.64** in 65% yield.



Scheme 2.14: Synthesis of Alkynol 2.64

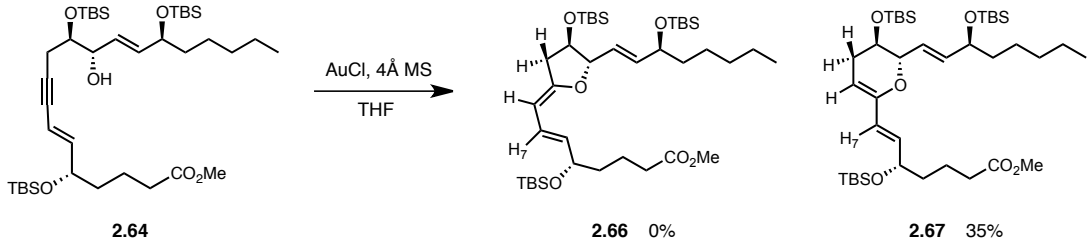
Cycloisomerization Attempts

Now that the necessary carbon skeleton of HKE_2 had been generated, we began our investigations into the cycloisomerization/oxidation sequence. When alkynol **2.64** was treated with $PdCl_2$, a new product was isolated. Extensive NMR analysis revealed that alkyne hydration had occurred to provide enone **2.65**. Furthermore, when molecular sieves were added to the reaction in the hopes of preventing hydration and favoring cyclization, only starting material was recovered.



Scheme 2.15: Pd-Catalysis Yields Undesired Alkyne Hydration

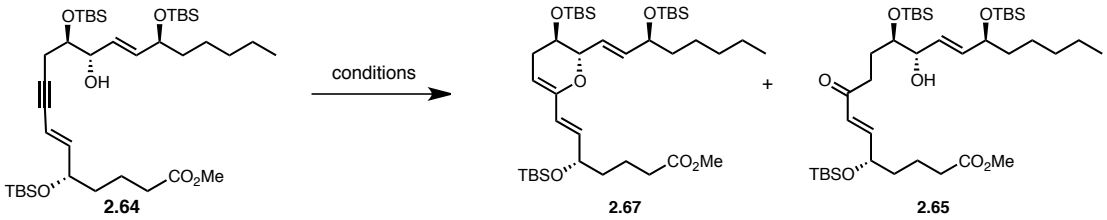
However, when the alkynol **2.64** was treated with AuCl in the presence of molecular sieves, a new, more non-polar product was generated. Based on NMR analysis, the product was tentatively assigned as the 6-*endo* product **2.67**. The hydrogen at C7 appears as a doublet in ^{1}H NMR as would be expected in the 6-*endo* product **2.67** and not as a doublet of doublets as would be expected for the 5-*exo* product **2.66**. Furthermore, 2D COSY analysis seemed to support the assignment of a 6-*endo* closure.



Scheme 2.16: Au-catalyzed Cycloisomerization Yields 6-*endo* Product 2.67

While excited by the isolation of a cyclized product, we were discouraged by the low yield and sought further evidence for our structural assignment. Therefore, we sought to investigate a variety of metal catalysts in the hopes of accessing **2.67** in higher yields. Furthermore, we were interested to see if changing the metal source would have an effect on the

5-*exo*/6-*endo* product distribution. Table 2.1 details the variety of metal catalysts that were screened. When $PdCl_2$ was used (entry 1), only alkyne hydration was observed; furthermore, the addition of molecular sieves precluded the undesired hydrated product but unfortunately returned only starting material (entry 2). Mercury (II) chloride, which has been shown to selectively generate 5-*exo*-dig cyclization of acetylenic alcohols,[16] was unreactive with our substrate and led to recovery of starting material (entry 4). Reaction with silver nitrate (entry 5), expected to lead to 5-*exo* cyclization, lead to hydration product **2.65**.[13] Use of $PdCl_2(CH_3CN)_2$, used successfully for 6-*endo* cyclization in Trost's efforts toward miyakolide, [20] was unproductive in our hands (entry 6), whereas use of a different palladium source ($Pd(OAc)_2$, entry 7) led to the desired 6-*endo* product **2.67**, albeit in low yield. Use of $PtCl_2$ (entry 8), which had been used in Lee's synthesis of polycavernoside A,[21] also produced the desired 6-*endo* product but in 28% yield. Attempts at utilizing alternative gold catalysts in order to increase the yield of the reaction (entries 9 and 10) unfortunately were unsuccessful and returned starting material or led to decomposition, respectively. Therefore, after a screen of several different catalysts, no improvement upon the original 30% yield was achieved.

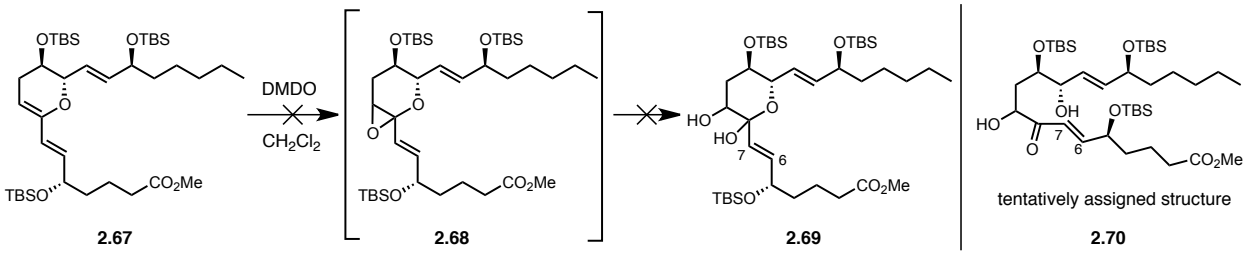


Entry	Conditions	Result
1	$PdCl_2$	**2.65** (55%)
2	$PdCl_2$, 4A MS	starting material
3	AuCl + 4A MS	**2.67** (35%)
4	$HgCl_2$	starting material
5	$AgNO_3$	**2.65** (47%)
6	$PdCl_2(CH_3CN)_2$, 4A MS	starting material
7	$Pd(OAc)_2$, 4A MS	**2.67** (30%) + starting material (55%)
8	$PtCl_2$ + 4A MS	**2.67** (28%)
9	Ph_3PAuCl, $AgBF_4$, 4A MS	starting material
10	Ph_3PAuCl, $AgSbF_6$, 4A MS	decomposition

Table 2.1: Metal Catalysts Screened for Cycloisomerization of 2.6

Despite the low yield of the cycloisomerization reaction, we decided to next test conditions for the oxidation to the keto hemiketal (Scheme 2.18). We hypothesized that reaction with dimethyldioxirane (DMDO) would form an intermediate epoxide that could be hydrolyzed to afford the diol. When **2.67** was treated with DMDO solution, a more polar product was formed and isolated. However, the presence of either the epoxide **2.68** or the desired diol **2.69** was not observed by NMR; however, an enone group was evident. We anticipated that the hemiketal carbon would resonate between 100 and 110 ppm in the ^{13}C NMR but did not observe any signals in that range. However, the presence of an enone was apparent as H6 and H7 appeared at 6.98 and 6.44 ppm, respectively, in the ^{1}H NMR and a peak at ~200 ppm was present in the ^{13}C NMR. Thus, we tentatively assigned **2.70** as the structure of the isolated compound. At

this point, we were uncertain of the structural assignment and our access to material was limited due to the low-yielding cyclization and the time required to generate single-enantiomer fragments. For these reasons, we looked toward repeating these studies using a simplified model system.



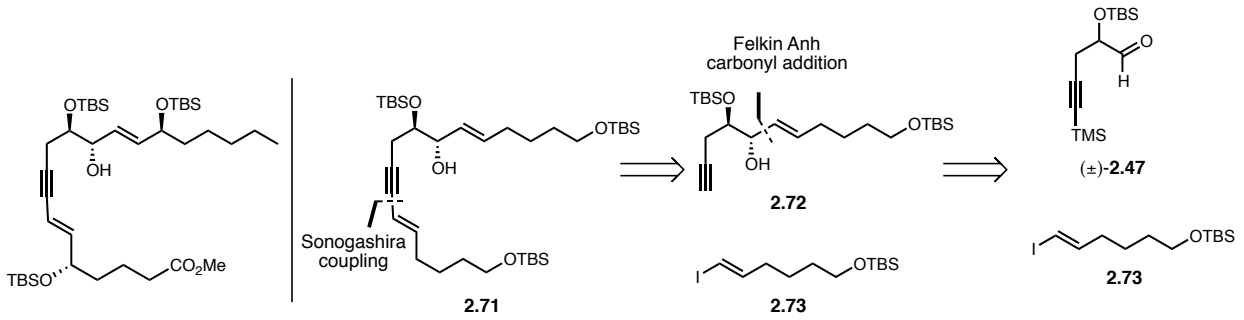
Scheme 2.17: Unsuccessful Oxidation Sequence toward Hemiketal Formation

Model System to Explore Cycloisomerization/Oxidation Sequence

The use of a model system would allow us the luxury of testing a large number of conditions in order to uncover the problematic points of this synthetic sequence. We envisioned a model that could be generated with few synthetic transformations but still maintained the key functional groups necessary for the desired transformation.

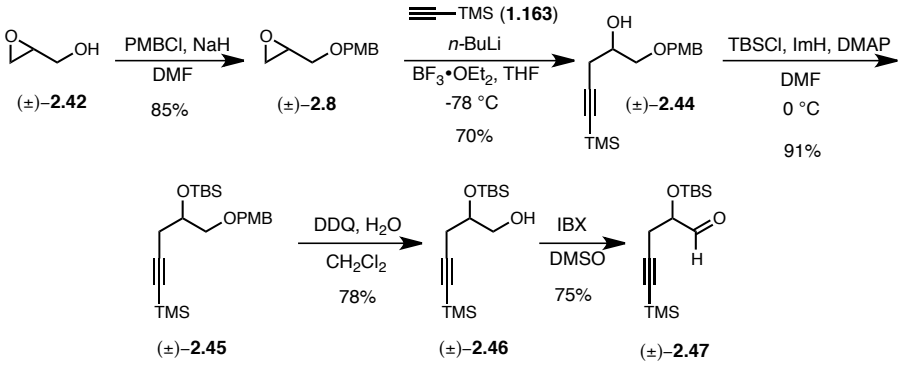
Thus, we decided upon alkynol **2.71** as a good model system for our purposes (Scheme 2.19). This model maintains the key acetylenic alcohol functionality present in the actual system. However, the side chains were simplified by removing the stereocenters adjacent to the olefins. Furthermore, the same side chain could be used on either side of the alkynol, thereby simplifying the assembly of the model system. So, we envisioned that our model could arise from Sonogashira coupling between alkyne **2.72** and vinyl iodide **2.73**. Further, the same vinyl iodide

could be used in a Felkin-Anh controlled carbonyl addition to aldehyde **2.47** to access **2.72**. The requisite aldehyde is the same one used to construct the carbon framework of HKE_2.



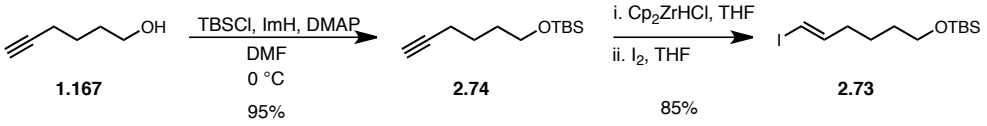
Scheme 2.18: Retrosynthetic Analysis of Model System

The synthesis of the model system began with (±)-glycidol (**2.42**). Protection of the alcohol as a PMB ether provided epoxide (±)-**2.8**, which was opened with ethnyltrimethylsilyl lithium to afford alcohol (±)-**2.44**. Silylation of the alcohol and cleavage of the benzyl ether provided (±)-**2.46**. Oxidation with IBX gave aldehyde (±)-**2.47**.



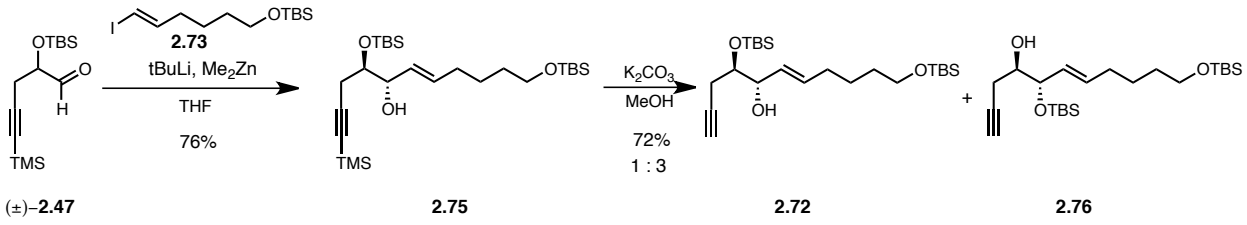
Scheme 2.19: Synthesis of Racemic C8-C12 Fragment

The side chain synthesis was completed in two steps. 5-Hexynol (**1.167**) was protected as a TBS ether to provide alkyne **2.74**. Hydrozirconation - iodination then provided the necessary vinyl iodide **2.73** in high yield.



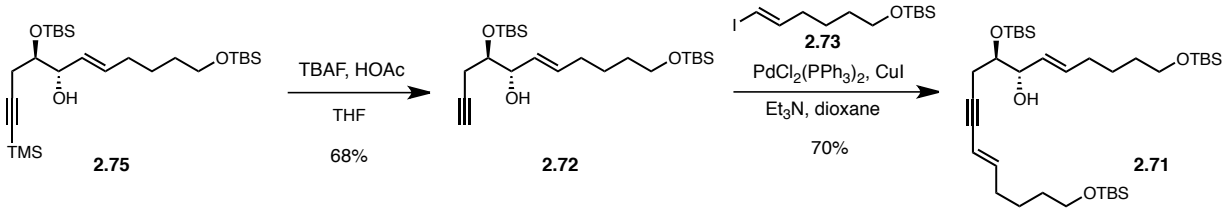
Scheme 2.20: Synthesis of Vinyl Iodide 2.69

Next, the assembly of the carbon framework was explored (Scheme 2.22). Lithium-halogen exchange of vinyl iodide **2.73** was carried out using *t*-BuLi and subsequently transmetallation with Me_2Zn followed by addition of aldehyde (±)-**2.47** provided allylic alcohol **2.75** in good yield. Additionally, only one diastereomer were observed by NMR and assigned as the *anti* (**2.75**) configuration. Next, desilylation of the alkyne was attempted using potassium carbonate in MeOH. To our surprise, two products were isolated. After separation by chromatography, NMR revealed a 1:3 mixture of desired desilylated alkyne **2.72** and an alkyne in which the TBS group had migrated to the adjacent free alcohol of the diol (**2.76**).



Scheme 2.21: Alkyne Desilylation Results in Silyl Migration

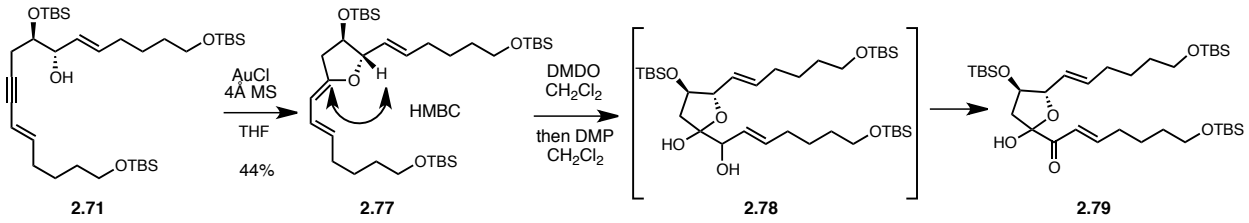
This type of silyl migration is not unprecedented, especially for TBS groups of 1,2-diols.[31] When the same TMS-alkyne **2.75** was treated with TBAF, a 1:4 ratio in favor of the undesired silyl migration product was observed. Gratifyingly, when **2.75** was treated with TBAF with an acetic acid buffer,[32] the desired alkyne **2.72** was the only product observed and was generated in good yield. Sonogashira coupling with vinyl iodide **2.73** produced the desired model alkynol **2.71**.



Scheme 2.22: Synthesis of the Model Alkynol 2.71

With the desired model system assembled, we could now investigate cycloisomerization conditions to improve upon the poor yield observed in earlier attempts. We started with AuCl, which had been our most successful catalyst, and surprisingly obtained a product with a completely different NMR spectrum. The splitting observed for the olefinic protons seemed to suggest the presence of the 5-*exo* product **2.77**. Furthermore, for the first time, we were able to observe a correlation between the hydrogen of the furan ring and the carbon of the vinyl ether. While not optimal, the 44% yield was improved relative to earlier cycloisomeration attempts. We next decided to test our oxidation sequence. Treatment of the vinyl ether **2.77** with DMDO generated a more polar product that could not be isolated. However, upon treatment with Dess-Martin periodinane, we were able to obtain the keto hemiketal **2.79** (via diol **2.78**). The strongest evidence to support formation of the hemiketal arose from ^{13}C NMR peaks that resonated at 195

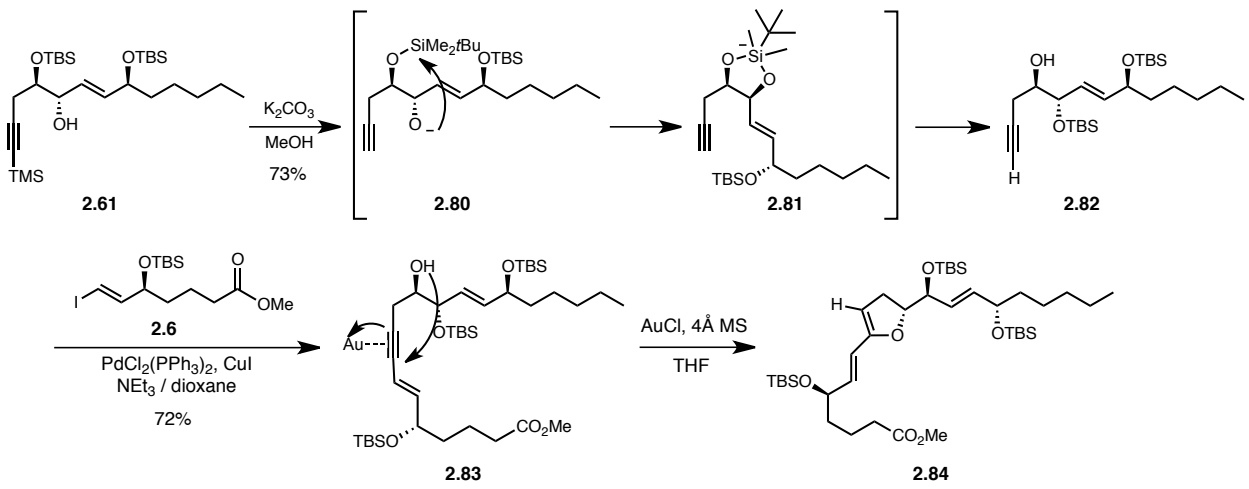
ppm and 105 ppm, corresponding to the enone carbonyl and the hemiketal carbon, respectively. Furthermore, both peaks disappeared in DEPT experiments as would be expected for quaternary carbons.



2.71 2.77 2.78 2.79

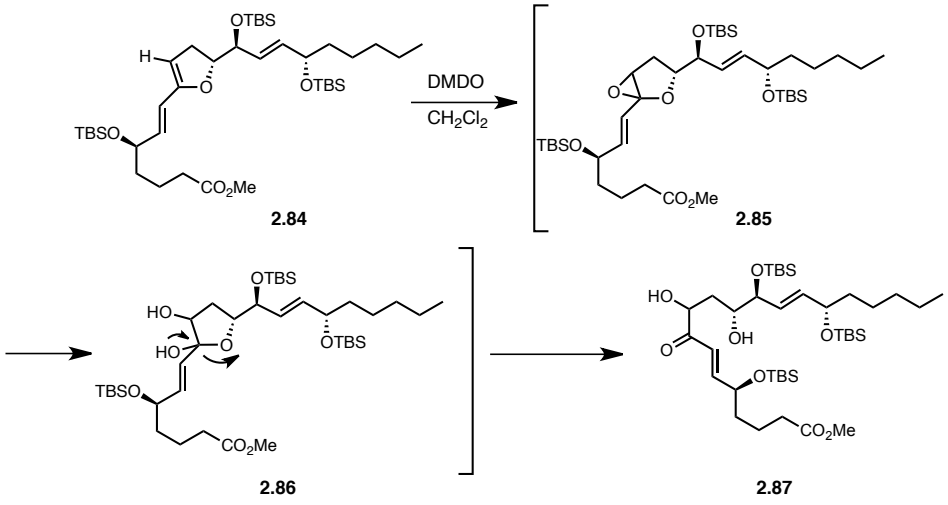
Scheme 2.23: Synthesis of Model Hemiketal 2.75

Based on these experiments, we determined that a silyl migration negatively affected the cycloisomerization sequence in the real system. Scheme 2.25 illustrates the implications of the silyl migration. After desilylation, excess base can deprotonate the free alcohol to provide alkoxide **2.80** which can then form a pentavalent silicon intermediate **2.81**. This intermediate can then transform into silyl migrated product **2.82**. Sonogashira coupling with vinyl iodide **2.6** forms alkynol **2.83** and treatment with AuCl induces a 5-*endo-dig* cyclization to provide dihydrofuran **2.84**. Reexamination of the NMR data supports this structural assignment.



Scheme 2.24: Silyl Migration Leads to Undesired 5-*endo* Product

Additionally, with this information in mind, we reinvestigated the results of the DMDO reaction. We propose that when the 5-*endo* product **2.84** is treated with DMDO, the resulting epoxide **2.85** is rapidly hydrolyzed into diol **2.86**, which can undergo ring-opening to form enone **2.87**. This structural assignment fits well with the NMR data previously discussed.



Scheme 2.25: DMDO Oxidation of 5-endo Product Produces Enone 2.87

Thus, the model system helped us uncover the silyl migration problem in the alkyne desilylation step that plagued our efforts towards the total synthesis of HKE_2. Furthermore, the model system demonstrated that the desired cycloisomerization/oxidation sequence was successful and provided hope that the same conditions could work on the correct substrate for HKE_2 synthesis.

Experimental Methods

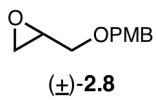
General Procedure: All non-aqueous reactions were performed in flame-dried or oven dried round-bottomed flasks under an atmosphere of argon. Stainless steel syringes or cannula were used to transfer air- and moisture-sensitive liquids. Reaction temperatures were controlled using a thermocouple thermometer and analog hotplate stirrer. Reactions were conducted at room temperature (rt, approximately 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 F_{254} glass-backed pre-coated silica gel plates. The plates were visualized with UV light (254 nm) and developed in an iodine chamber or stained with potassium permanganate or *p*-anisaldehyde-sulfuric acid followed by charring. Yields were reported as isolated, spectroscopically pure compounds.

Materials: Solvents were obtained from either an MBraun MB-SPS solvent system or freshly distilled (tetrahydrofuran was distilled from sodium-benzophenone; toluene was distilled from calcium hydride and used immediately; dimethyl sulfoxide was distilled from calcium hydride and stored over 4 Å molecular sieves). Unless indicated, all commercial reagents were used as

received without further purification. The (*S*,S)-Co(salen) catalyst was synthesized according to the procedure reported by Jacobsen.[33] Ru-(*S*,*S*)-TsDPEN catalyst was synthesized according to the procedure reported by Noyori.[34] The molarity of *n*-butyllithium solutions was determined by titration using diphenylacetic acid as an indicator (average of three determinations).

Instrumentation: ^{1}H NMR spectra were recorded on Bruker 400, 500, or 600 MHz spectrometers and are reported relative to deuterated solvent signals ($CDCl_3$: 7.26; C_6D_6: 7.16). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded on Bruker 100, 125, or 150 MHz spectrometers and are reported relative to deuterated solvent signals ($CDCl_3$: 130 77.0; C_6D_6: 128.1). IR Spectra were recorded on a Nicolet Avatar 360 spectrophotometer and values are reported in wavenumbers (cm^{-1}). Compounds were analyzed as neat films on a NaCl plate (transmission). Optical rotations were measured on a Perkin-Elmer 341 digital polarimeter at ambient temperature. High-resolution mass spectra were obtained from the Department of Chemistry and Biochemistry, University of Notre Dame.

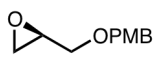
Preparative Procedures:



(±)-**2.8**

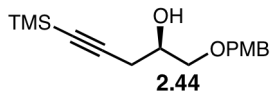
(±) Glycidyl ether 2.8: To a stirred suspension of NaH (60% dispersion in mineral oil, 4.75 g, 119 mmol) in dry DMF (250 mL) at 0 °C was added PMBCl (16.1 g, 119 mmol) dropwise. After 25 min, (±)-glycidol (**2.42**) (neat) (8.00 g, 108 mmol) was added dropwise *via* syringe pump over 45 min, at which point the reaction was allowed to warm to rt. After 20 h, the mixture was added to a separatory funnel containing sat.

aq. NH_4Cl (100 mL) and EtOAc (250 mL). The organic phase was washed with 10% aq. $NaHCO_3$ (100 mL) and H_2O (150 mL) and the combined aqueous phases were extracted with EtOAc (100 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to afford 17.1 g (82 %) of (±)-**2.8** as a colorless oil. The spectral data matched reported values.[35]



(*R*)-**2.8**

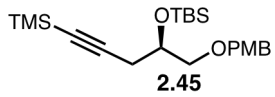
Glycidyl ether (*R*)-2.8: To a solution of (±)-glycidyl ether **2.8** (6.35 g, 32.7 mmol) in acetic acid (37.4 μL, 0.654 mmol) was added (*S*,*S*)-(+)-*N*,*N*-bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) (98.0 mg, 0.163 mmol). The mixture was stirred at rt for 20 min before being cooled to 0 °C. THF (300 μL) and H_2O (0.323 mL, 18.0 mmol) were added and the mixture was maintained at 0 °C for 1 h before being warmed to rt and stirred for 16 h. The mixture was distilled under reduced pressure to give 2.71 g (43 %) of (*R*)-**2.8** as a clear colorless oil. Enantiomeric excess was determined to be > 98% by Chiral HPLC analysis (Chiralpak® IA, 98:2 hexanes : iPrOH, 1 mL / min, λ = 254 nm, t_R(minor) = 15.807 min, t_R(major)= 18.523 min). The spectral data and optical rotation matched reported values.[36]



2.44

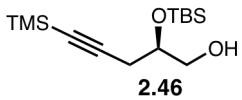
Alcohol 2.44: To a solution of ethynyltrimethylsilane (1.46 g, 14.8 mmol) in THF (30 mL) cooled to -78 °C was added *n*-BuLi (6.40 mL, 14.8 mmol, 2.3 *M* in hexanes) dropwise. The solution was stirred at -78 °C for 15 min, at which point a solution of epoxide (*R*)-**2.8** (2.40 g, 12.4 mmol) in THF (12 mL) was added dropwise, followed by addition of BF_3•OEt_2 (1.83 mL, 14.8 mmol). The reaction mixture was allowed to stir at -78 °C for 2 h, and reaction was quenched with sat. aq. NH_4Cl (20

mL). The aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to afford 3.00 g (83 %) of **2.44** as a colorless oil. The spectral data matched reported values.[37]



2.45

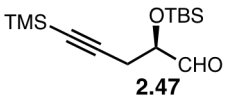
Silyl ether 2.45: To a solution of alcohol **2.44** (0.783 g, 2.68 mmol) in DMF (4.00 mL) at 0 °C was added TBSCl (0.806 g, 5.35 mmol), imidazole (0.547 g, 8.04 mmol), and DMAP (16.0 mg, 0.134 mmol). The reaction was allowed to stir at 0 °C for 2 h, quenched with H_2O (8 mL) and extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with H_2O (2 x 30 mL) and brine (30 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 2% EtOAc in hexanes) to afford 1.03 g (95 %) of **2.45** as a colorless oil: $[\alpha]_D^{20}$ = + 3.52° (*c* 3.5, $CHCl_3$); IR (neat) ν_{max} = 2856, 2178, 1613, 1514, 1466 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.6 Hz, 2 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 4.47 (s, 2 H), 3.92-3.98 (m, 1H), 3.80 (s, 3 H), 3.43 (app d, *J* = 5.4 Hz, 2 H), 2.51 (dd, *J* = 5.5, 16.9 Hz, 1 H), 2.35 (dd, *J* = 6.6, 16.9 Hz), 0.89 (s, 9 H), 0.13 (s, 9 H), 0.11 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 130.4, 129.1 (2 C), 113.7 (2 C), 104.3, 85.9, 73.5, 73.0, 70.5, 55.2, 26.2, 25.7 (3 C), 18.1, -0.02 (3 C), -4.63, -4.70; HRMS (ESI) calc'd for $C_{22}H_{38}O_3Si_2$ $[M+H]^+$: 406.2359; submitted.



2.46

Alcohol 2.46: To a solution of **2.45** (2.96 g, 7.28 mmol) in CH_2Cl_2 (70 mL) was added DDQ (1.82 g, 8.00 mmol) and H_2O (10 mL). The reaction was allowed to stir for 1.5 h at rt, during which time the color

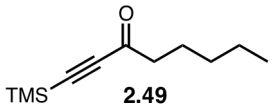
changed from dark green to red-orange. The reaction mixture was filtered through a pad of Celite and the resulting yellow mixture was washed with 10% aq. $NaHCO_3$ (70 mL) and H_2O (2 x 100 mL) and the organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to afford 1.79 g (86 %) of **2.46** as a colorless oil. $[\alpha]_D^{20}$ = - 5.89° (*c* 5.0, $CHCl_3$); IR (neat) ν_{max} = 3393, 2895, 2859, 2178, 1468 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.86 (apparent p, *J* = 5.5 Hz, 1 H), 3.63 (dd, *J* = 3.9, 11.1 Hz, 1 H), 3.54 (dd, *J* = 4.8, 11.2 Hz, 1 H), 2.43 (dd, J = 7.0, 16.8 Hz, 1 H), 2.36 (dd, *J* = 6.1, 17.0 Hz, 1 H), 2.00 (br s, 1 H), 0.88 (s, 9 H), 0.11 (s, 9 H), 0.10 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 103.2, 86.2, 71.4, 65.8, 25.7, 25.3 (3 C), 18.0, -0.09 (3 C), -4.60, -4.84; HRMS (ESI) calc'd for $C_{14}H_{30}O_2Si_2$ $[M+H]^+$: 287.1784; found: 287.1873.



2.47

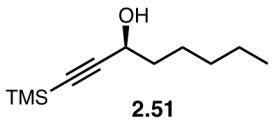
Aldehyde 2.47: To a solution of **2.46** (0.860 g, 3.00 mmol) in CH_2Cl_2 (30.0 mL) and DMSO (30.0 mL) at 0 °C was added IBX (1.68 g, 6.00 mmol). The solution was warmed to rt and stirred for 12 h. The reaction mixture was diluted with H_2O (50 mL) and CH_2Cl_2 (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with H_2O (3 x 100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 2% Et_2O in hexanes) to provide 0.680 g (89 %) of **2.47** as a light yellow oil: $[\alpha]_D^{20}$ = +35.7° (*c* 2.78, $CHCl_3$); IR (neat) ν_{max} = 2957, 2933, 2859, 2181, 1742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.63 (d, *J* = 1.2 Hz, 1 H), 4.12 (ddd, *J* = 1.2, 5.0, 7.8 Hz, 1 H), 2.65 (dd, *J* = 5.0, 17.0 Hz, 1 H), 2.48 (dd, J = 7.9, 17.0 Hz, 1 H), 0.94 (s, 9 H), 0.15 (s, 9 H), 0.15 (s, 3 H), 0.14 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0, 101.8, 87.3, 76.0, 25.6,

(3 C) 24.4, 18.1, -0.16 (3 C), -4.60, -4.84; HRMS (ESI) calc'd for $C_{14}H_{28}O_2Si_2$ $[M+H]^+$: 285.1628; found 285.1713.



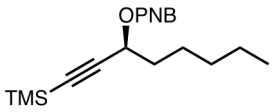
2.49

1-(trimethylsilyl)oct-1-yn-3-one (**2.49**): To a suspension of $AlCl_3$ (10.3 g, 77.2 mmol) in CH_2Cl_2 (120 mL) at 0 °C was added a solution of hexanoyl chloride (8.00 g, 59.4 mmol) and bistrimethylsilylacetylene (10.1 g, 59.4 mmol) in CH_2Cl_2 (100 mL) via cannula over a period of 10 min. The resulting yellow solution was allowed to warm to rt over 30 min, at which point the reaction was cooled to 0 °C and quenched by slow addition of 1*N* HCl (100 mL). The resulting solution was extracted with CH_2Cl_2 (2 x 100 mL) and the combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 5% EtOAc in hexanes) to afford 9.90 g (85 %) of alkynone **2.49** as a yellow oil. The spectral data matched reported values.[38]

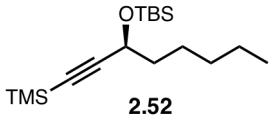


2.51

(*S*)-1-(trimethylsilyl)oct-1-yn-3-ol (**2.51**): A mixture of alkynone **2.49** (4.00 g, 20.4 mmol) and Ru[(1*S*, 2*S*)-p-$TsNCH(C_6H_5)CH(C_6H_5)NH](\eta^6$-p-cymene) (0.855 g, 1.43 mmol) in 2-propanol (200 mL) was stirred at rt for 16 h. The mixture was concentrated *in vacuo* and the resulting residue was purified by flash column chromatography (silica gel, 10 % EtOAc in hexanes) to provide 3.53 g (88 %) of **2.51** as a yellow oil. The spectral data and optical rotation matched reported values.[38]



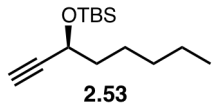
Enantiomeric excess analysis of 4-nitrobenzoate of 2.51: To a solution of alcohol **2.51** (0.068 g, 0.343 mmol) in CH_2Cl_2 (5 mL) was added triethylamine (0.144 mL, 1.03 mmol), PNBCl (0.127 g, 0.686 mmol), and DMAP (2.0 mg, 0.017 mmol). The reaction was allowed to stir at rt for 1 h, at which point the reaction was quenched with sat. aq. $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 5% EtOAc in hexanes) to provide 100 mg (85 %) of **PNB-2.51** as a dark yellow oil. The *ee* was determined to be 98% by Chiral SFC analysis (Lux Cellulose 2, 5% to 30% 2-propanol, 3.5 mL / min, λ = 254 nm, t_R(major) = 2.071 min, t_R(minor)= 2.462 min). $[\alpha]_D^{20}$ = -10.9° (*c* 2.50, $CHCl_3$); IR (neat) ν_{max} = 2958, 2863, 2180, 1730, 1607, 1531, 1463 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.9 Hz, 2H), 8.22 (d, *J* = 9.0 Hz, 2H), 5.63 (app t, *J* = 6.6 Hz, 1H), 1.86-1.93 (m, 2H), 1.47-1.54 (m, 2H), 1.31-1.36 (m, 4H), 0.89 (app t, *J* = 6.9 Hz, 3H), 0.17 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 150.7, 135.6, 131.0 (2 C), 123.6 (2 C), 102.1, 91.4, 66.2, 34.9, 31.3, 24.8, 22.5, 14.0, -0.140; HRMS (ESI) calc'd for $C_{18}H_{25}NNaO_4Si$ $[M+Na]^+$: 370.1451; found: 370.1478



2.52

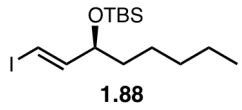
Silane 2.52: To a solution of **2.51** (1.76 g, 8.87 mmol) in DMF (8 mL) at 0 °C was added TBSCl (2.67 g, 17.7 mmol), imidazole (1.81 g, 26.6 mmol), and DMAP (0.050 g, 0.444 mmol). The reaction was allowed to stir at 0 °C for 2 h, at which point the reaction was quenched with H_2O (10 mL) and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was

purified by flash column chromatography (silica gel, 5% EtOAc in hexanes) to provide 2.60 g (95%) of **2.52** as a colorless oil: $[\alpha]_D^{20}$ = -45.2° (*c* 3.20, $CHCl_3$); IR (neat) ν_{max} = 2956, 2859, 2173, 1467, 1408 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.31 (dd, *J* = 6.1, 7.0 Hz, 1H), 1.57-1.71 (m, 2H), 1.32-1.49 (m, 2H), 1.24 – 1.37 (m, 4H), 0.90 (s, 9H), 0.89 (apparent t, 3H), 0.15 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 107.9, 88.1, 63.3, 38.4, 31.3, 25.7 (3 C), 24.8, 22.4, 18.2, 13.9, -0.255 (3 C), -4.56, -5.03; HRMS (ESI) calc'd for $C_{17}H_{36}NaOSi2$ $[M+Na]^+$: 335.2202; found: 335.2164



2.53

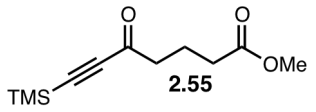
Alkyne 2.53: To a solution of silane **2.52** (2.60 g, 8.32 mmol) in MeOH (50 mL) was added K_2CO_3 (1.15 g, 8.32 mmol). The reaction was allowed to stir at rt for 1 h, at which point the MeOH was removed *in vacuo*. The resulting residue was taken up in H_2O (20 mL) and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 5% EtOAc in hexanes) to yield 1.88 g (95%) of alkyne **2.53** as a colorless oil. The spectral data matched reported values.[39]



1.88

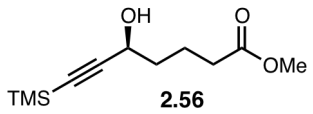
Vinyl iodide 1.88: To a solution of alkyne **2.53** (0.680 g, 2.83 mmol) in THF (30 mL) was added half the required amount of zirconecene hydrochloride (0.456 g, 1.76 mmol). The mixture was allowed to stir at rt for 20 min, over which time the reaction changed from cloudy to clear. At this point, additional zirconocene hydrochloride (0.456 g, 1.76 mmol) was added and the mixture was allowed to stir at rt for 20 min. Iodine (0.718 g, 2.83 mmol) was added and the mixture changed color from light yellow to

dark brown. The reaction was allowed to stir for 5 min, at which point the mixture was diluted with hexanes (10 mL) and filtered through a pad of Celite. The resulting solution was washed with sat. aq. $Na_2S_2O_3$ (2 x 15 mL) and brine (15 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, hexanes) to afford 0.948 g (91 %) of vinyl iodide **1.88** as a clear oil. $[\alpha]_D^{20}$ = -30.4° (*c* 2.35, $CHCl_3$); IR (neat) ν_{max} = 2931, 2858, 1607, 1466 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.51 (dd, J = 6.0, 14.3 Hz, 1H), 6.19 (dd, *J* = 1.1, 14.3 Hz, 1H), 4.07 (ddd, *J* = 1.2, 6.0, 12.1 Hz, 1H), 1.41-1.50 (m, 2H), 1.21-1.34 (m, 6H), 0.89 (s, 9H), 0.88, (apparent t, *J* = 6.9 Hz, 3H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 75.3, 75.1, 37.4, 31.7, 25.7, 24.4 (3 C), 22.5, 18.1, 14.0, -4.60, -4.96; HRMS (ESI) calc'd for $C_{14}H_{29}IOSi$ $[M+H]^+$: 368.1032; submitted.[40]



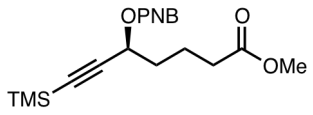
2.55

Alkynone 2.55 : To a suspension of $AlCl_3$ (12.6 g, 94.8 mmol) in CH_2Cl_2 (120 mL) at 0 °C was added a solution of methyl 4-(chloroformyl)butyrate (12.0 g, 72.9 mmol) and bistrimethylsilylacetylene (12.4 g, 72.9 mmol) in CH_2Cl_2 (90 mL) via cannula over a period of 10 min. The resulting yellow solution was allowed to warm to rt over 30 min, at which point the reaction was cooled to 0 °C and quenched by slow addition of 1*N* HCl (90 mL). The resulting solution was extracted with CH_2Cl_2 (2 x 100 mL) and the combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to afford 9.90 g (60 %) of **2.55** as a yellow oil. Spectral data matched reported values.[41]

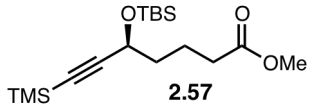


2.56

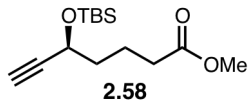
Alcohol 2.56: A mixture of alkynone **2.55** (3.00 g, 13.3 mmol) and Ru[(1*S*, 2*S*)-p-TsNCH(C_6H_5)CH(C_6H_5)NH](η^6-p-cymene) (0.398 g, 0.665 mmol) in 2-propanol (130 mL) was stirred at rt for 1 h. The mixture was concentrated *in vacuo* and the resulting residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to provide 2.87 g (95 %) of alcohol **2.56** as a yellow oil. The spectral data and optical rotation matched reported values.[42]



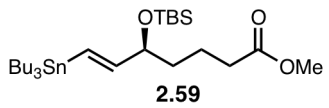
Enantiomeric excess analysis of 4-nitrobenzoate of 2.56: To a solution of alcohol **2.56** (0.050 g, 0.221 mmol) in CH_2Cl_2 (2.2 mL) was added triethylamine (0.300 mL, 2.21 mmol), PNBCl (0.205mg, 1.10 mmol), and DMAP (0.001 g, 0.008 mmol). The reaction was allowed to stir at rt for 1 h, at which point the reaction was quenched with sat. aq. $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic layers were dried (MgSO4), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to provide 0.068 g (82 %) of **PNB-2.56** as a dark yellow oil. The *ee* was determined to be 95% by Chiral SFC analysis (Lux Cellulose 2, 5% to 30% 2-propanol, 3.5 mL / min, λ = 254 nm, t_R(major) = 2.840 min, t_R(minor)= 3.139 min). $[\alpha]_D^{20}$ = -11.3° (*c* 2.10, $CHCl_3$); IR (neat) ν_{max} = 2957, 2179, 1734, 1606, 1531, 1442 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.9 Hz, 2H), 8.21 (d, J = 8.9 Hz, 2H), 5.64 (app t, *J* = 6.2 Hz, 1H) 3.65 (s, 3H), 2.40 (app t, *J* = 7.2 Hz, 2H), 1.91-1.98 (m, 2H), 1.80-1.88 (m, 2H), 0.16 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 163.4, 150.6, 135.2, 130.9 (2 C), 123.4 (2 C), 101.2, 91.7, 65.4, 51.5, 34.0, 33.2, 20.3, -0.383 (3 C); HRMS (ESI) calc'd for $C_{18}H_{23}NNaO_6Si$ $[M+Na]^+$: 400.1192; found: 400.1206.



Silyl ether 2.57: To a solution of alcohol **2.56** (2.87 g, 12.6 mmol) in DMF (15 mL) at 0 °C was added TBSCl (3.79 g, 25.1 mmol), imidazole (2.57 g, 37.7 mmol), and DMAP (0.077, 0.630 mmol). The reaction was allowed to stir at 0 °C for 2 h, at which point the reaction was quenched with H_2O (20 mL) and extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 5% EtOAc in hexanes) to provide 4.10 g (94%) of silyl ether **2.57** as a colorless oil: $[\alpha]_D^{20}$ = -42.2° (*c* 3.51, $CHCl_3$); IR (neat) ν_{max} = 2953, 2859, 2172, 1743, 1462 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.35 (app t, *J* = 6.1 Hz, 1H), 3.67 (s, 3H), 2.35 (app t, *J* = 7.2 Hz, 2H), 1.65-1.87 (m, 4H), 0.90 (s, 9H), 0.16 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 107.2, 86.7, 62.9, 51.3, 37.6, 33.5, 25.7 (3 C), 20.7, 18.1, -0.310 (3 C), -4.58, -5.08; HRMS (ESI) calc'd for $C_{17}H_{34}O_3Si_2$ $[M+H]^+$: 342.2046; submitted.[43]

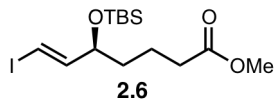


Alkyne 2.58: To a solution of silane **2.57** (0.770 g, 2.25 mmol) in MeOH (20 mL) was added K_2CO_3 (0. 311 g, 2.25 mmol). The reaction was allowed to stir at rt for 1h, at which point the MeOH was removed *in vacuo*. The resulting residue was taken up in H_2O (20 mL) and EtOAc (20 mL) and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 5% EtOAc in hexanes) to yield 547 mg (90%) of alkyne **2.58** as a colorless oil. The spectral data matched reported values.[44]



2.59

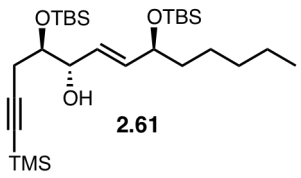
Vinyl stannane 2.59: To a solution of alkyne **2.58** (2.00 g, 7.39 mmol) in benzene (150 mL) was added Bu_3SnH (6.00 mL, 22.2 mmol) and AIBN (0.200 g, 1.48 mmol). The reaction was heated to 80 °C and stirred for 2 h. The mixture was then cooled to rt and the benzene was removed *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, gradient of 0% to 2% Et_2O/hexanes) to provide 3.35 g (81 %) of **2.59** as a clear, colorless oil: $[\alpha]_D^{20}$ = -12.2° (*c* 3.19, $CHCl_3$); IR (neat) ν_{max} = 2956, 2928, 2856, 1744, 1462 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.04 (dd, *J* = 0.8, 19.0 Hz, 1H), 5.89 (dd, *J* = 5.7, 19.0 Hz, 1H), 4.04 (ddd, *J* = 1.0, 5.7, 12.3 Hz, 1H), 3.65 (s, 3H), 2.31 (app t, *J* = 7.4 Hz, 2 H), 1.56-1.72 (m, 2H), 1.43-1.52 (m, 8H), 1.25-1.34 (m, 6H), 0.83-0.94 (m, 24H), 0.89 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 151.3, 126.9, 76.2, 51.3, 37.2, 34.0, 29.0 (3 C), 27.1 (3 C), 25.8 (3 C), 20.8, 18.2, 13.6 (3 C), 9.35 (3 C), -4.38, -4.91. HRMS (ESI) calc'd for $C_{26}H_{54}NaO_3SiSn$ $[M+Na]^+$: 585.2762; found: 585.2789.



2.6

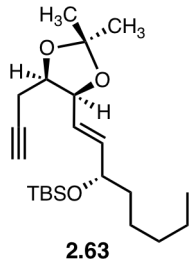
Vinyl iodide 2.6: To a solution of stannane **2.59** (0.300 g, 0.534 mmol) in CH_2Cl_2 (2 mL) was added a solution of I_2 (0.200 g, 0.801 mmol) in CH_2Cl_2 (3 mL) dropwise until the resulting solution maintained a light pink color. The reaction was allowed to stir for 10 min, at which point sat. aq. $Na_2S_2O_3$ (5 mL), H_2O (5 mL), and sat. aq. $NaHCO_3$ (5 mL) were added. The mixture stirred for an additional 5 min, at which time the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 5% Et_2O in hexanes) to provide 0.200 g (90 %) of **2.6** as a light yellow oil: $[\alpha]_D^{20}$ = -25.8° (*c* 1.70, $CHCl_3$); IR (neat) ν_{max} = 2952, 2856, 1739, 1607 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.50 (dd, *J* = 6.0, 14.4 Hz, 1H), 6.22 (dd, *J* = 1.1, 14.4 Hz, 1H), 4.10

(ddd, J = 1.3, 5.9, 11.8 Hz, 1H), 3.66 (s, 3H) 2.31 (app t, J = 7.3 Hz, 2H), 1.57-1.71 (m, 2H), 1.46-1.56 (m, 2H), 0.882 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 148.7, 75.9, 74.7, 51.4, 36.7, 33.8, 25.7 (3 C), 20.2, 18.1, -4.62, -5.00. HRMS (ESI) calc'd for $C_{14}H_{27}INaO_3Si$ $[M+Na]^+$: 421.0672; found: 421.0677.



Allylic alcohol 2.61: To a solution of vinyl iodide **1.88** (1.32 g, 3.60 mmol) in THF (7.2 mL) at -78 °C was added a solution of *t*-BuLi (4.50 mL, 7.20 mmol, 1.7 *M* in pentane) dropwise. The mixture was allowed to stir at -78 °C for 1.5 h, at which point a solution of Me_2Zn (2.16 mL, 2.16 mmol, 1.0 *M* in heptane) was added dropwise slowly. The reaction mixture was stirred at -78 °C for 15 min, at which point a solution of aldehyde **2.47** (410 mg, 1.44 mmol) in THF (6 mL) was added dropwise. The reaction stirred at -78 °C for 3 h and was subsequently quenched by addition of sat. aq. NH_4Cl (20 mL). The mixture was extracted with Et_2O (3 x 20 mL) and the combined extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, gradient of 2% to 10% Et_2O in hexanes) to provide 680 mg (91 %) of **2.61** as a light yellow oil. (Note: both the vinyl iodide and aldehyde were azeotroped with benzene (3 x 10 mL) prior to use.): $[\alpha]_D^{20}$ = - 24.3° (*c* 3.70, $CHCl_3$); IR (neat) ν_{max} = 3476, 2955, 2932, 2858, 2179, 1741, 1467 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (dd, J = 5.7, 15.5 Hz, 1H), 5.58 (dd, J = 6.5, 15.7 Hz, 1H), 4.19-4.24 (m, 1H), 4.12 (app q, J = 5.6 Hz, 1H), 3.89 (ddd, J = 3.1, 6.0, 7.2 Hz, 1H), 2.39 (dd, J = 7.2, 17.0 Hz, 1H), 2.29 (dd, J = 6.0, 17.0 Hz, 1H), 2.10 (d, J = 5.5 Hz, 1H), 1.41–1.50 (m, 2H), 1.23-1.35 (m, 6H), 0.91 (s, 9H), 0.89 (s, 9H), 0.13 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ136.9, 126.2, 104.0, 86.3, 74.4, 74.2, 72.7, 38.1, 31.8, 25.8 (3 C), 25.7 (3 C), 24.7, 24.0, 22.5,

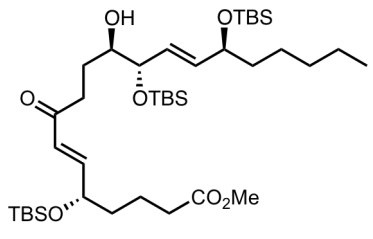
18.1, 18.0, 14.0, -0.0699 (3 C), -4.39 (2 C), -4.81, -4.84; HRMS (ESI) calc'd for $C_{28}H_{58}O_3Si_3$ $[M+H]^+$: 526.3694; submitted.



2.63

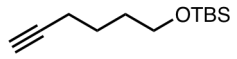
Acetonide 2.63: To a solution of **2.61** (0.100 g, 0.220 mmol) in THF (2 mL) at 0 °C was added a solution of TBAF (1.1 mL, 1.10 mmol, 1.0 *M* in THF). The reaction was allowed to stir at 0 °C for 2 h, at which point it was quenched with H_2O (5 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (10 mL) and H_2O (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The reaction product was not purified, but used directly in the next reaction.

To a solution of crude diol (70.0 mg, 0.205 mmol) in acetone (1 mL) was added 2,2-dimethoxypropane (0.163 mL, 1.33 mmol) and *p*TSA (1.0 mg, 1.06 μmol). The reaction was allowed to stir for 1 h, at which point the reaction was quenched with sat. aq. $NaHCO_3$ (5 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to afford 0.055 g (70%) of **2.63** as a yellow oil. $[\alpha]_D^{20}$ = -13.3° (*c* 1.16, $CHCl_3$); IR (neat) ν_{max} = 3313, 2985, 2930, 2123, 1732, 1462 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.79 (dd, J = 5.4, 15.4 Hz, 1H), 5.62 (dd, J = 7.4, 15.4 Hz, 1H), 2.41 (ddd, J = 2.7, 7.2, 16.6 Hz, 1H), 2.29 (ddd, J = 2.7, 6.4, 16.7 Hz, 1H), 1.99 (app t, J = 2.7 Hz, 1H), 1.50 (s, 3H), 1.41-1.48 (m, 2H), 1.38 (s, 3H), 1.26-1.32 (m, 6H), 0.90 (s, 9H), 0.88 (app t, J = 6.7, 3H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 123.6, 108.7, 80.5, 78.5, 76.6, 72.3, 69.8, 38.0, 31.8, 28.0, 25.8 (3C), 25.5, 24.6, 22.5, 21.1, 18.1, 13.9, -4.48, -4.88. HRMS (ESI) calc'd for $C_{22}H_{40}NaO_3Si$ $[M+Na]^+$: 403.2644; found: 403.2616.



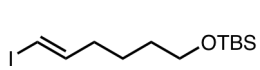
2.65

Enone 2.65: To a solution of **2.64** (0.050 g, 0.0689 mmol) in THF (2 mL) at rt was added $PdCl_2$ (1.2 mg, 0.00689 mmol). The reaction was allowed to stir at rt for 6 h and was concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, gradient elution 5% to 20% Et_2O in hexanes) to afford 0.054 g (55%) of enone **2.65** as a dark yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.76 (dd, J = 4.8, 15.8 Hz, 1H), 6.25 (dd, J = 1.4, 15.8 Hz, 1H), 5.66 (dd, J = 5.7, 15.6 Hz, 1H), 5.57 (dd, J = 6.6, 15.6 Hz, 1H) 4.33 (app q, J = 4.9 Hz, 1H), 4.12 (app q, J = 6.4 Hz, 1H), 4.05 (dd, J = 4.2, 6.5 Hz, 1H), 3.67 (s, 3H), 3.50-3.53 (m, 1 H), 2.68-2.82 (m, 2H), 2.31 (app t, J = 7.2 Hz, 2H), 1.77-1.85 (m, 2H), 1.62-1.70 (m, 2H), 1.54-1.62 (m, 4H), 1.26-1.34 (m, 8H), 0.91 (s, 9H), 0.90 (s, 9H), 0.89 (s, 9H), 0.86-0.89 (m, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.3, 173.7, 148.1, 136.7, 128.3, 127.6, 125.4, 76.5, 74.3, 72.7, 71.3, 51.4, 38.2, 37.0, 36.5, 33.8, 31.7, 30.2, 25.8 (3C), 25.7 (3C), 24.8 (3C), 22.5, 20.2, 18.1, 18.1, 18.0, 14.0, -4.31, -4.43, -4.63 (2C), -4.87 (2C).



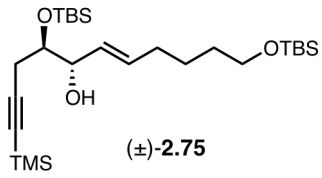
2.74

Alkyne 2.74: To a solution of 5-hexyn-1-ol (1.50 g, 15.3 mmol) in DMF (20 mL) at 0 °C was added TBSCl (4.60 g, 30.6 mmol), ImH (3.12 g, 45.9 mmol), and DMAP (93.0 mg, 0.765 mmol). The reaction was allowed to stir at 0 °C for 3 h. The reaction was quenched with H_2O (10 mL) and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 40 mL) and brine (40 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 2% EtOAc in hexanes) to afford 3.10 g (95%) of **2.74** as a clear, colorless oil. The spectral data matched reported values.[45]



2.73

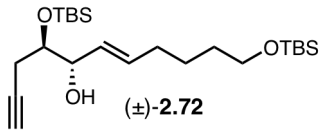
Vinyl iodide 2.73: To a solution of alkyne **2.74** (1.00 g, 4.71 mmol) in THF (50 mL) was added half the required amount of zirconecene hydrochloride (0.750 g, 2.94 mmol). The reaction was allowed to stir for 10 min, over which time the cloudy solution became clear. The remainder of the zirconecene hydrochloride (0.750 g, 2.94 mmol) was added and the reaction stirred for another 10 min, at which point I_2 (1.20 g, 4.71 mmol) was added in one portion. The reaction turned dark reddish-brown and was stirred for an additional 10 min. The reaction mixture was diluted with hexanes (50 mL) and filtered through Celite. The filtrate was washed with saturated aqueous $Na_2S_2O_3$ (50 mL) and brine (50 mL) and the organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 2% EtOAc in hexanes) to provide 1.35 g (85%) of **2.73** as a light yellow oil. Spectral data matched reported values.[45]



(±)-**2.75**

(±)-Allylic alcohol 2.75: To a solution of vinyl iodide **2.73** (1.94 g, 5.71 mmol) in THF (11.0 mL) at -78 °C was added *t*-BuLi (1.7 *M* in pentane, 6.70 mL, 11.4 mmol) dropwise slowly. The reaction stirred for 1.5 h at -78 °C, at which point Me_2Zn (1.0 *M* in THF, 3.42 mL, 3.42 mmol) was added dropwise. The solution stirred at -78 °C for 15 min, at which point a solution of (±) aldehyde **2.47** (0.650 g, 2.28 mmol) in THF (8.00 mL) was added dropwise. The reaction stirred at -78 °C for 3 h. The reaction was quenched by dropwise addition of sat. aq. NH_4Cl until bubbling ceased. The mixture was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude residue was

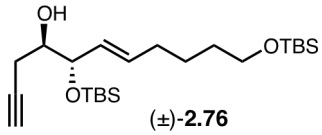
purified by flash column chromatography (silica gel, gradient elution 1% to 4 % EtOAc in hexanes) to afford 0.870 g (76%) of (±)-**2.75** as a clear, light yellow oil. IR (neat) ν_{max} = 3454, 2953, 2929, 2856, 2177, 1471 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.73 (dt, *J* = 14.3, 7.2 Hz, 1H), 5.43 (dd, *J* = 6.7, 15.5 Hz, 1H), 4.14-4.16 (m, 1H), 3.84 (ddd, *J* = 3.5, 5.7, 7.1 Hz, 1H), 3.61 (app t, *J* = 6.5 Hz, 2H), 2.40 (dd, *J* = 7.1, 17.0 Hz, 1H), 2.35 (dd, *J* = 5.7, 17.0 Hz, 1H), 2.14 (d, *J* = 4.6 Hz, 1H), 2.07 (app q, *J* = 7.0 Hz, 2H), 1.50-1.54 (m, 2H), 1.41-1.46 (m, 2H), 0.91 (s, 9H), 0.89 (s, 9H), 0.15 (s, 3H), 0.14 (s, 9H), 0.12 (s 3H), 0.05 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 134, 128, 105, 86.5, 75.4, 74.5, 63.2, 32.5, 32.4, 26.1 (3 C), 26.0 (3 C), 25.5, 24.0, 18.5, 18.2, 0.184 (3 C), -4.13, -4.53, -5.12 (2 C).



(±)-**2.72**

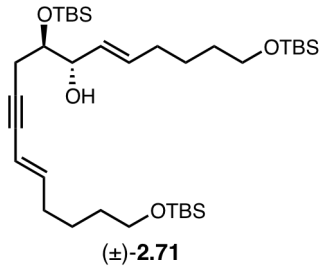
(±)-Alkyne 2.72: To a solution of (±)-**2.75** (0.820 g, 1.64 mmol) in THF (3.2 mL) at 0 °C was added AcOH (0.0940 mL, 1.64 mmol). The reaction stirred for 5 min, at which point TBAF (1.64 mL, 1.64 mmol, 1.0 *M* in THF) was added dropwise. The solution turned light brown and was stirred at 0 °C for 1.5 h. The reaction was quenched with H_2O (4 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with H_2O (2 x 10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 2% Et_2O in hexanes) to provide 0.485 g (68%) of (±)-**2.72** as a yellow oil. IR (neat) ν_{max} = 3466, 2929, 2857, 1470 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.75 (ddd, *J* = 7.3, 7.8, 15.1 Hz, 1H), 5.45 (dd, *J* = 7.1, 15.5 Hz, 1H), 4.17 (dt, *J* = 7.35, 3.68 Hz, 1H), 3.84 (ddd, *J* = 3.7, 6.3, 6.3 Hz, 1H), 3.61 (app t, *J* = 6.4 Hz, 2H), 2.37 (ddd, *J* = 2.7, 6.6, 16.9 Hz, 1H), 2.25 (ddd, *J* = 2.7, 6.0, 16.9 Hz, 1H), 2.27 (d, *J* = 3.6 Hz, 1H), 2.07 (app q, *J* = 7.0 Hz, 2H), 1.96 (app t, *J* = 2.7 Hz, 1H), 1.50-1.55 (m, 2H), 1.41-1.46 (m, 2H), 0.91 (s, 9H), 0.89 (s, 9H),

0.14 (s, 3H), 0.11 (s, 3H), 0.05 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135, 128, 81.8, 75.2, 74.3, 70.2, 63.2, 32.5, 32.4, 26.1 (3 C), 26.0 (3 C), 25.5, 24.0, 18.5, 18.2, 0.184 (3 C), -4.24, -4.53, -5.12 (2 C).



(±)-**2.76**

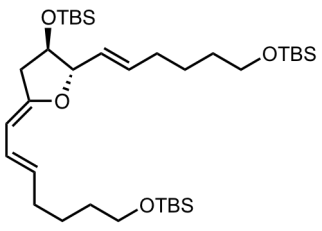
(±)-Alcohol 2.76: To a solution of (±)-**2.75** (0.555 g, 1.11 mmol) in MeOH (11.0 mL) was added K_2CO_3 (0.154 mg, 1.11 mmol). The reaction stirred for 3 h, at which point the MeOH was removed *in vacuo*. The resulting residue was taken up in H_2O (10 mL) and Et_2O (10 mL). The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 2% Et_2O in hexanes) to yield 0.417 g (88%) of a 3:1 mixture of (±)-**2.76** and (±)-**2.72** as a colorless oil. Data for (±)-**2.76**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (dd, *J* = 7.0, 14.3 Hz, 1H), 5.42 (dd, *J* = 7.5, 15.6 Hz, 1H), 4.13 (dd, *J* = 4.9, 7.6 Hz, 1H), 3.84 (ddd, *J* = 3.7, 6.3, 6.3 Hz, 1H), 3.65-3.71 (m, 1H), 3.65 (app t, *J* = 6.3 Hz, 2H), 2.42 (ddd, *J* = 2.7, 6.7, 16.8 Hz, 1H) 2.36 (ddd, *J* = 2.7, 6.0, 17.5 Hz, 1H), 2.27 (d, *J* = 3.6 Hz, 1H), 2.07 (app q, *J* = 7.1 Hz, 2H), 2.00 (app t, *J* = 2.7 Hz, 1H), 1.49-1.56 (m, 2H), 1.40-1.48 (m, 2H), 0.89 (s 9H), 0.88 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H), 0.04 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 134.6, 128.4, 80.9, 75.7, 72.9, 70.0, 62.8, 32.2, 32.0, 25.9 (3C), 25.7 (3C), 25.3, 22.1, 18.2, 18.0, -4.16, -4.95, -5.39 (2C).



(±)-**2.71**

(±)-**Alkynol 2.71**: To a solution of vinyl iodide **2.73** (0.132 g, 0.367 mmol) in Et_3N / dioxane (1:1, 0.350 mL) was added CuI (2.7 mg, 0.0140 mmol) and $PdCl_2(PPh_3)_2$ (5.0 mg, 0.00703 mmol). The

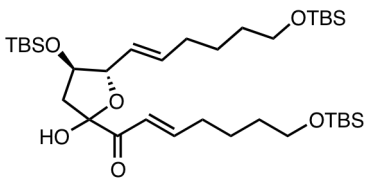
solution changed color to orange and the reaction stirred for 5 min, at which point a solution of alkyne **2.72** (0.150 mg, 0.351 mmol) in Et_3N / dioxane (1:1, 0.350 mL) was added dropwise. The reaction stirred at rt for 16 h. The reaction was concentrated and the resulting residue was taken up in H_2O (4 mL) and Et_2O (4 mL). The layers were separated and the aqueous layer extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 2% EtOAc in hexanes) to provide 0.158 g (70%) of **2.71** as a yellow oil. IR (neat) ν_{max} = 3443, 2952, 2893, 1729, 1471 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 6.15 (dt, *J* = 15.0, 7.5 Hz, 1H), 5.74 (dt, *J* = 7.2, 14.4 Hz, 1H), 5.55-5.58 (m, 2H), 4.24 (dd, *J* = 4.0, 6.0 Hz, 1H), 3.93 (ddd, *J* = 3.8, 5.7, 6.7 Hz, 1H), 3.53 (app t, *J* = 6.2 Hz, 2H), 3.45 (app t, *J* = 6.2 Hz, 2H), 2.65 (ddd, *J* = 2.1, 6.8, 17.0 Hz, 1H), 2.57 (ddd, *J* = 2.1, 5.6, 17.0 Hz, 1H), 1.99 (app q, *J* = 7.0 Hz, 2H), 1.90 (app q, *J* = 7.2 Hz, 2H), 1.47-1.52 (m, 2H), 1.38-1.44 (m, 4H), 1.31-1.35 (m, 2H), 1.00 (s, 9H), 0.99 (s, 9H), 0.98 (s, 9H), 0.18 (s, 3H), 0.13 (s, 3H), 0.08 (s, 6H), 0.05 (s, 6H); ^{13}C NMR (150 MHz, C_6D_6) δ 143, 133, 129, 111, 86.2, 81.2, 75.1, 75.0, 62.8, 62.7, 32.7, 32.4, 32.3, 32.2, 25.9 (6C), 25.8 (3C), 25.6, 25.2, 24.2, 18.2 (2C), 18.1, -4.57, -4.73, -5.42 (2C), -5.46 (2C).



(±)-**2.77**

(±)-**Vinyl ether 2.77**: To a solution of AuCl (1.0 mg, 3.91 μmol) and powdered 4Å molecular sieves in THF (2 mL) at rt was added a solution of alkynol **2.71** (25.0 mg, 0.0391 mmol) in THF (1 mL). The reaction was allowed to stir at room temperature for 30 min, over which time the solution turned purple. The solution was filtered to remove the molecular sieves and the sieves rinsed with Et_2O (2 x 10 mL). The filtrate was

washed with sat. aq. $NaHCO_3$ (10 mL) and the aqueous layer extracted with Et_2O (3 x 10 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (pH = 7 buffered silica gel, 2% EtOAc in hexanes) to provide 11.2 mg (44%) of **2.77** as a pale yellow oil: ^{1}H NMR (600 MHz, C_6D_6) δ 6.86 (dd, *J* = 10.7, 15.4 Hz, 1H), 5.75 (dt, *J* = 7.1, 14.2 Hz, 1H), 5.57 (dt, *J* = 14.7, 7.3 Hz, 1H), 5.39 (dd, *J* = 7.2, 15.4 Hz, 1H), 5.11 (d, *J* = 10.7 Hz, 1H), 4.47 (app t, *J* = 6.2 Hz, 1H), 3.89 (app q, *J* = 6.0 Hz, 1H), 3.51 (app t, *J* = 6.1 Hz, 4H), 2.58 (dd, *J* = 6.6, 15.8 Hz, 1H), 2.45 (dd, *J* = 6.4, 15.7 Hz, 1H), 2.12 (app q, *J* = 6.9 Hz, 2H), 1.95 (app q, *J* = 6.9 Hz, 2H), 1.42-1.55 (m, 8H), 1.32-1.40 (m, 4H), 1.00 (s, 9H), 0.99 (s, 9H), 0.91 (s, 9H), 0.07 (s, 6H), 0.06 (s, 6H), -0.02 (s, 3H), -0.03 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 153, 135, 128, 127, 125, 99.5, 88.3, 75.3, 62.9, 62.8, 38.4, 32.9, 32.5, 32.4, 32.1, 26.2, 25.9 (6 C), 25.6 (3C), 18.2 (2 C), 18.1, 17.9, -4.88, -4.90, -5.42 (2 C), -5.44 (2 C).

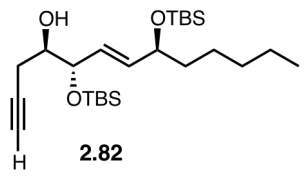


(±)-**2.79**

(±)-**Hemiketal 2.79** A solution of vinyl ether **2.77** (5.7 mg, 8.92 μmol) in CH_2Cl_2 (0.500 mL) was cooled to 0 °C. A solution of dimethyldioxirane (0.256 mL, 0.035 *M* solution in acetone, 8.92 μmol) was added dropwise. The reaction stirred for 2 min and was concentrated *in vacuo*. The reaction product was not purified, but used directly in the next reaction.

To a solution of crude diol (8.92 μmol) in CH_2Cl_2 (1.00 mL) was added DMP (4.0 mg, 8.92 μmol). The reaction stirred at rt for 3 h. The reaction was quenched by addition of 1:1 sat. aq. $NaHCO_3$: sat. aq. $Na_2S_2O_3$ (2 mL) The aqueous later was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The

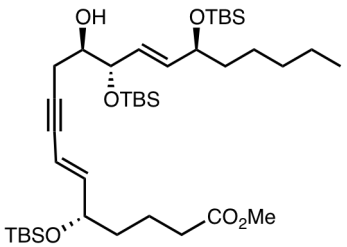
resulting residue was purified by flash column chromatography (silica gel, 2% EtOAc in hexanes) to yield a mixture of diastereomers of hemiketal **2.79** as a light yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.13-7.21 (m, 2H), 6.70 (d, *J* = 15.5 Hz, 1H), 6.58 (d, *J* = 15.7 Hz, 1H), 5.76-5.86 (m, 2H), 5.71 (ddd, *J* = 7.0, 7.3, 14.6 Hz, 1H), 5.55 (dd, *J* = 8.7, 15.7 Hz, 1H), 5.41 (dd, *J* = 6.9, 15.4 Hz, 1H), 5.31 (dd, *J* = 7.2, 15.3 Hz, 1H), 4.64 (dd, *J* = 4.3, 7.3 Hz, 1H) 4.58 (dd, *J* = 2.5, 7.2 Hz, 1H), 4.39 (app q, *J* = 6.3 Hz, 1H) 4.30 (dd, *J* = 5.4, 8.3 Hz, 1H), 4.21 (ddd, *J* = 4.0, 4.7, 6.5 Hz, 1H), 4.15 (app p, *J* = 2.9 Hz, 1H), 3.58-3.63 (m, 8H), 2.73 (dd, *J* = 6.5, 17.3 Hz, 1H), 2.55 (dd, *J* = 5.8, 13.8 Hz, 1H), 2.43 (dd, *J* = 4.8, 17.3 Hz, 1H), 2.27-2.30 (m, 4H), 2.26 (dd, *J* = 6.5, 13.2 Hz, 1H), 2.20 (dd, *J* = 7.1, 13.2 Hz, 1H), 2.07-2.11 (m, 4H), 1.97 (dd, *J* = 3.2, 14.0 Hz, 1H), 1.38-1.47 (m, 8H) 1.24-1.30 (m, 12H), 0.88-0.92 (m, 54H), 0.01-0.04 (m, 36H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.2, 193.0, 174.6, 152.0, 151.1, 136.1, 135.6, 134.5, 128.5, 126.9, 124.9, 123.3, 122.4, 104.9, 102.7, 89.0, 88.0, 87.8, 76.5, 73.0, 62.9, 62.8, 62.7, 62.6, 60.3, 44.7, 41.6, 37.7, 32.6, 32.5, 32.3, 32.2, 32.1, 32.0, 31.9, 31.5, 29.6, 25.9, 25.7, 25.6, 25.5, 25.2, 25.1, 25.0, 24.5, 24.3, 22.6, 18.3, 17.9, 17.8, 14.1, 14.0, -4.73, -4.87, -4.97, -5.37.



2.82

Alkyne 2.82: To a solution of alkyne **13** (1.17 g, 2.22 mmol) in MeOH (22 mL) was added K_2CO_3 (0.307 g, 2.22 mmol). The reaction was allowed to stir at rt for 1h, at which point the MeOH was removed *in vacuo*. The resulting residue was dissolved in H_2O (20 mL) and extracted with Et_2O (3 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 2% Et_2O in hexanes) to yield 0.727 g (72%) of **2.82** as a colorless oil: $[\alpha]_D^{20}$ = - 7.52° (*c* 3.95, $CHCl_3$); IR (neat) ν_{max} = 3575, 3311, 2936, 2860, 2121, 1466 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (dd, *J* = 5.7, 15.6 Hz, 1H), 5.56 (dd, *J* = 7.0, 15.5 Hz, 1H), 4.20 (dd, *J* = 4.5, 6.9 Hz, 1H),

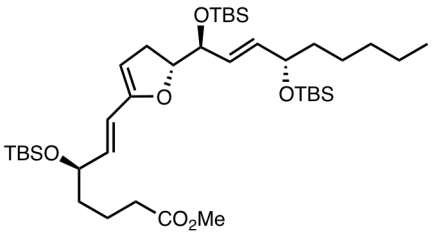
4.13 (ddd, J = 5.9, 5.9, 11.9 Hz, 1H), 3.67-3.72 (m, 1H), 2.43 (ddd, J = 2.7, 7.0, 16.8 Hz, 1H), 2.34 (ddd, J = 2.7, 5.9, 16.8 Hz, 1H), 2.27 (d, J = 3.8 Hz, 1H), 2.00 (app t, J = 2.7 Hz, 1H), 1.41-1.50 (m, 2H), 1.22-1.34 (m, 6H), 0.89 (s, 9H), 0.88 (s, 9H), 0.87 (app t, J = 6.9 Hz, 3H), 0.08 (s, 3H), 0.04 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.4, 127.0, 80.8, 75.1, 73.0, 72.5, 70.1, 38.2, 31.6, 25.8 (3 C), 25.7 (3 C), 24.7, 22.5, 22.0, 18.1, 18.0, 13.9, -4.34, -4.51, -4.87, -4.96; HRMS (ESI) calc'd for $C_{25}H_{50}O_3Si_2$ $[M+H]^+$: 454.3298; submitted.



2.83

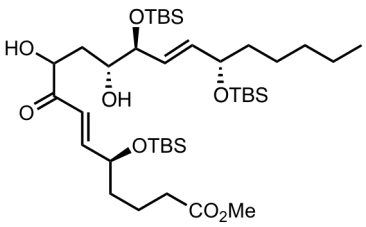
Alkynol 2.83: To a solution of vinyl iodide (0.530 g, 1.33 mmol) in 1:1 NEt_3/dioxane (4 mL) was added CuI (9.0 mg, 0.048 mmol) and $PdCl_2(PPh_3)_2$ (17.0 mg, 0.024 mmol). Alkyne **2.82** (0.550 g, 1.21 mmol) was added and the reaction was allowed to stir for 8 h. The solution was concentrated *in vacuo* and the resulting residue was taken up in H_2O (5 mL) and Et_2O (5 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 x 15 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 3% Et_2O in hexanes) to provide 0.440 g (50%) of **2.83** as a yellow oil. ^{1}H NMR (600 MHz, C_6D_6) δ 6.19 (dd, J = 5.8, 15.8 Hz, 1H), 5.87 (dd, J = 1.5, 15.8 Hz, 1H), 5.86 (dd, J = 5.9, 15.7 Hz, 1H), 5.80 (dd, J = 6.4, 15.7 Hz, 1H), 4.40 (dd, J = 4.7, 5.9 Hz, 1H), 4.19 (app q, J = 5.8 Hz, 1H), 4.06 (app q, J = 5.5 Hz, 1H), 3.87-3.89 (m, 1H), 3.43 (s, 3H), 2.83 (ddd, J = 1.9, 6.8, 16.9 Hz, 1H), 2.72 (ddd, J = 2.0, 5.8, 16.9 Hz, 1H), 2.26 (d, J = 3.0 Hz, 1H), 2.15 (app t, J = 7.4 Hz, 2H), 1.56-1.77 (m, 4H), 1.33-1.53 (m, 8H), 1.11 (s, 9H), 1.06 (s, 9H), 1.04 (s, 9H), 1.00 (app t, J = 7.2 Hz, 3H), 0.21 (s, 3H), 0.21 (s, 3H), 0.20 (s, 3H), 0.19 (s, 3H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 173.8, 145.0, 137.3, 127.2, 109.2, 86.6, 80.4, 75.2, 73.3, 72.6, 72.2, 65.8, 51.4, 38.2, 37.1, 33.9, 31.8,

25.78 (3C), 25.77 (3C), 25.76 (3C), 24.7, 23.1, 22.6, 20.4, 18.14, 18.11, 18.08, 15.2, 14.0, -4.33, -4.45, -4.52, -4.85, -4.92, -4.95.



2.84

Dihydrofuran 2.84: To a solution of AuCl (1.0 mg, 4.14 μmol) and 4Å MS in THF (2 mL) was added a solution of alkynol **2.83** (30.0 mg, 0.0414 mmol) in THF (1 mL). The reaction was stirred for 30 min over which time the solution changed color from light yellow to purple. The reaction mixture was filtered to remove the molecular sieves and the sieves were washed with Et_2O (5 mL). The filtrate was quenched with sat. aq. $NaHCO_3$ (3 mL) and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (pH = 7 buffered silica gel, 2% EtOAc in hexanes) to provide 13 mg (44%) of **2.84** as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.32 (dd, *J* = 5.8, 15.5 Hz, 1H), 6.19 (d, *J* = 15.6 Hz, 1H), 5.89 (dd, *J* = 5.4, 14.9 Hz, 1H), 5.64 (dd, *J* = 5.0, 15.4 Hz, 1H), 4.84 (app t, *J* = 2.2 Hz, 1H), 4.54-4.58 (m, 2H), 4.24 (app q, *J* = 5.8 Hz, 1H), 4.17 (app q, *J* = 5.8 Hz, 1H), 3.40 (s, 3H), 2.97 (ddd, *J* = 2.0, 8.2, 16.0 Hz, 1H), 2.51 (ddd, *J* = 2.4, 10.2, 16.0 Hz, 1H), 2.21 (app t, *J* = 7.3 Hz, 2H), 1.75-1.87 (m, 2H), 1.58-1.68 (m, 4H), 1.31-1.4 (m, 8H), 1.12 (s, 9H), 1.11 (s, 9H), 1.09 (s, 9H), 0.89-0.95 (m, 3H), 0.28 (s, 3H), 0.27 (s, 3H), 0.19 (s, 3H), 0.19 (s, 3H), 0.18 (s. 3H), 0.17 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.1, 153.1, 135.3, 134.5, 129.1, 119.1, 100.3, 84.6, 73.7, 73.2, 72.9, 50.9, 38.8, 38.1, 34.1, 32.3, 30.5, 30.2, 26.2 (9 C), 25.3, 23.1, 21.0, 18.6, 18.5 (2C), 14.3, -4.04, -4.15, -4.22, -4.24.



2.87

Enone 2.87: To a solution of vinyl ether **2.84** (20.0 mg, 0.0276 mmol) in CH_2Cl_2 (1 mL) at 0 °C was added a solution of dimethyldioxirane (0.459 mL, 0.060 *M* solution in acetone, 0.0276 mmol,). The reaction was stirred for 5 min and the solvent was removed *in vacuo*. The resulting residue was purified by flash column chromatography (pH = 7 buffered silica gel, 5% EtOAc in hexanes) to provide **2.87** as a colorless oil. ^{1}H NMR (600 MHz, C_6D_6) δ 6.99 (dd, *J* = 4.7, 15.5 Hz, 1H), 6.64 (d, *J* = 1.5, 15.5 Hz, 1H), 5.73 (m, 2H), 4.36-4.39 (m, 1H), 4.11-4.16 (m, 2H), 4.04-4.08 (m, 2H), 3.88-3.92 (m, 1H), 3.34 (s, 3H), 2.20 (ddd, *J* = 2.2, 4.0, 14.4 Hz, 1H), 2.06 (dt, *J* = 1.5, 7.3 Hz, 2H), 1.83 (ddd, *J* = 7.5, 9.8, 14.4 Hz, 1H), 1.54-1.62 (m, 4H), 1.22-1.36 (m, 12H), 1.06 (s, 9H), 0.99 (s, 9H), 0.97 (s, 9H), 0.84-0.93 (m, 6H), 0.18 (s, 3H), 0.15 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H), 0.03 (s. 3H), 0.02 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.0, 173.0, 150.0, 136.4, 129.0, 123.4, 76.8, 75.5, 73.5, 73.2, 71.9, 51.0, 38.8, 36.6, 36.0, 33.8, 32.3, 32.0, 26.2 (3C), 26.1 (3C), 26.0 (3C), 25.3, 23.1, 20.1, 18.5, 18.5, 18.4, 14.4, 14.3, 11.7, -3.92, -4.11, -4.40, -4.48, -4.53, -4.80.

References

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Appendix A1:

Spectra Relevant to Chapter 2

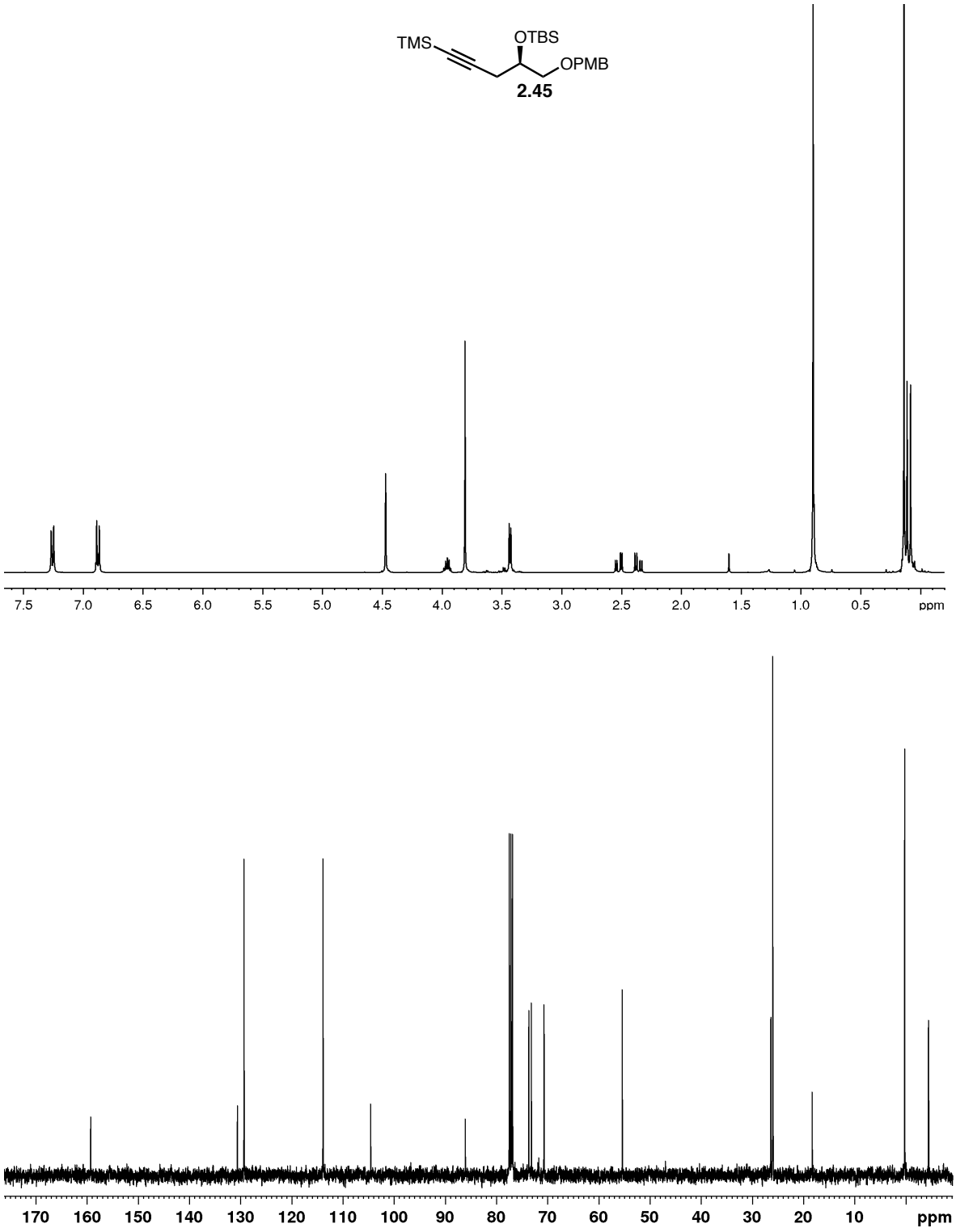


Figure A1.1: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of Compound 2.45

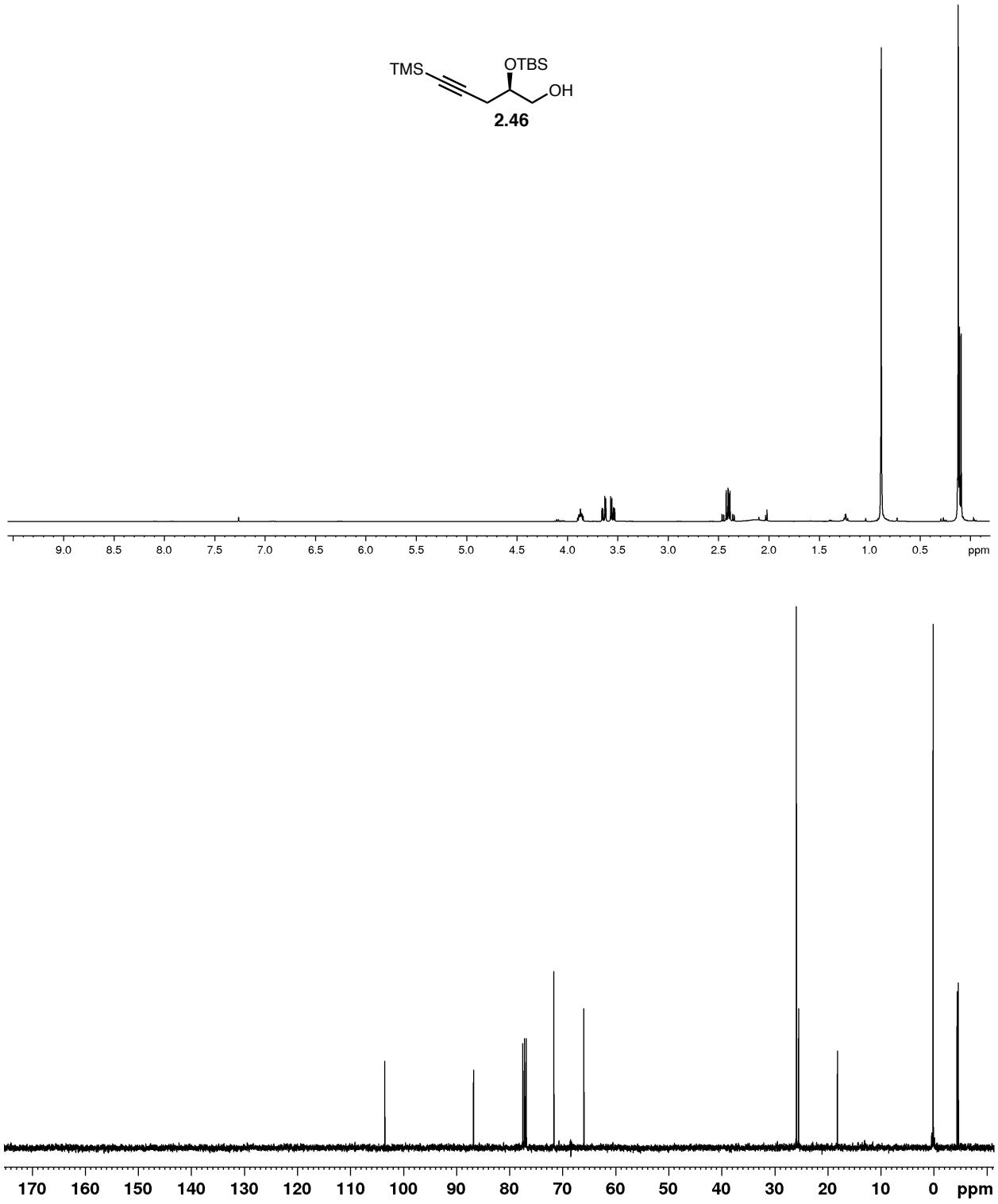


Figure A1.2: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of Compound 2.46

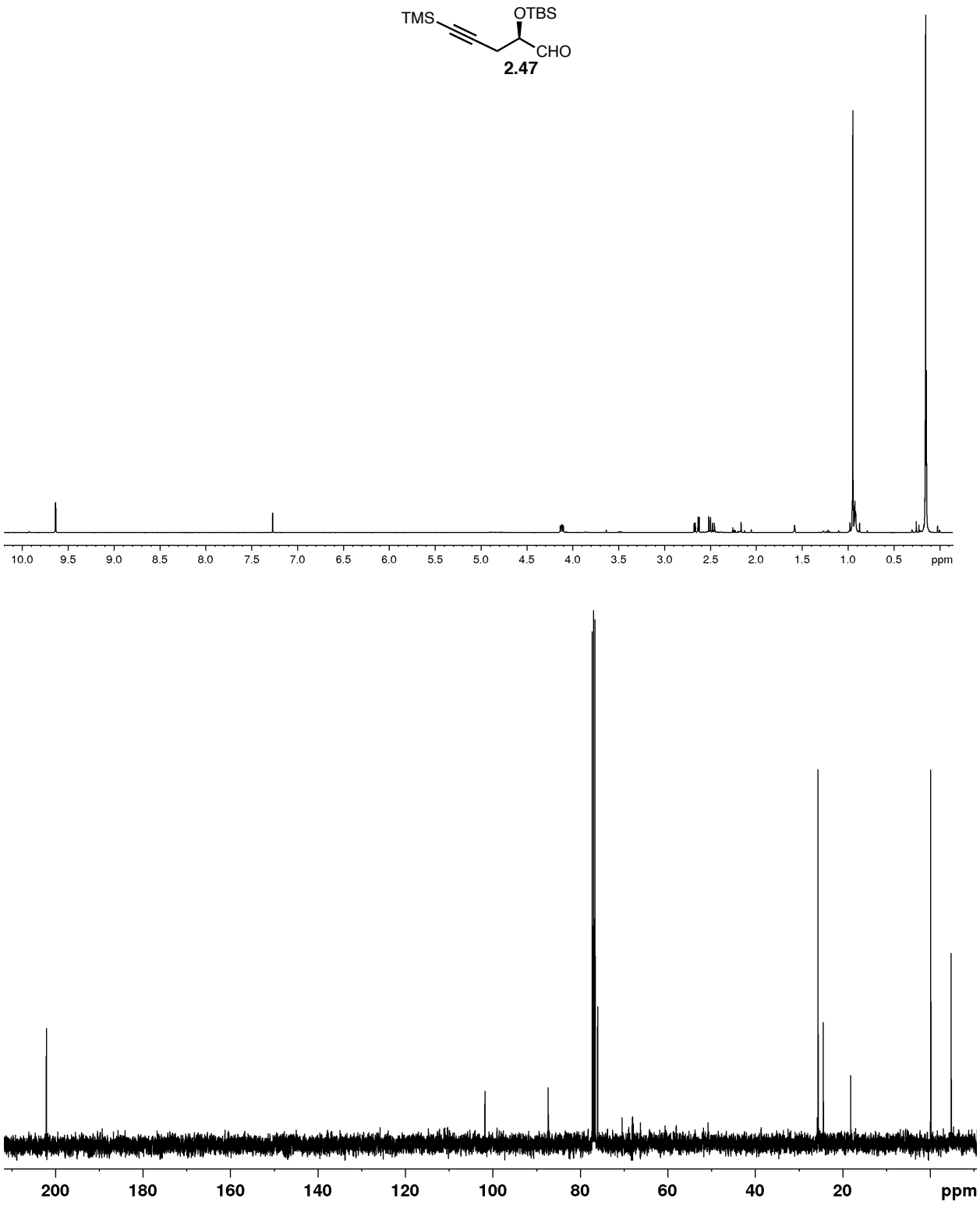


Figure A1.3: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of Compound 2.47

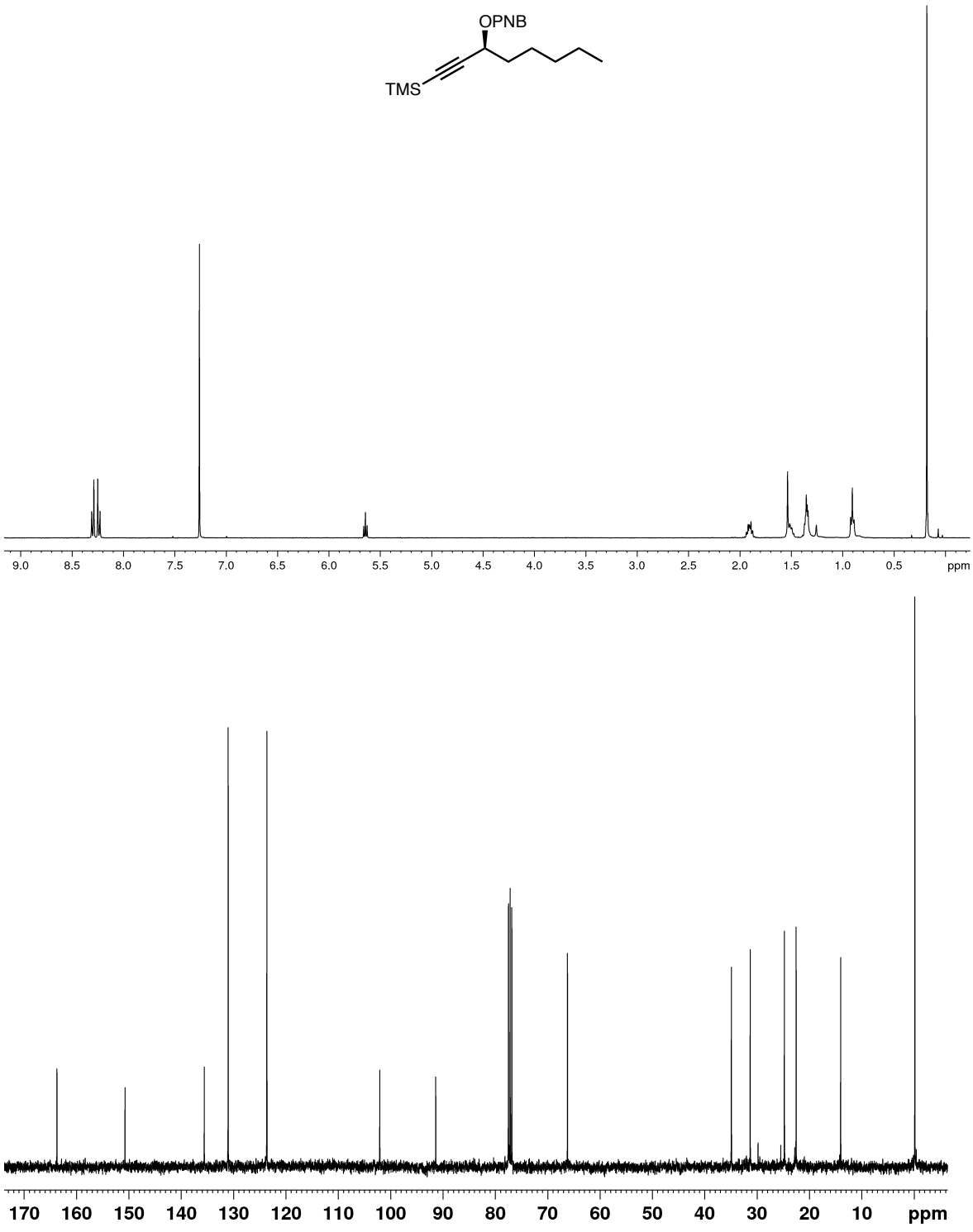


Figure A1.4: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of *p*-Nitrobenzoate of Compound 2.51

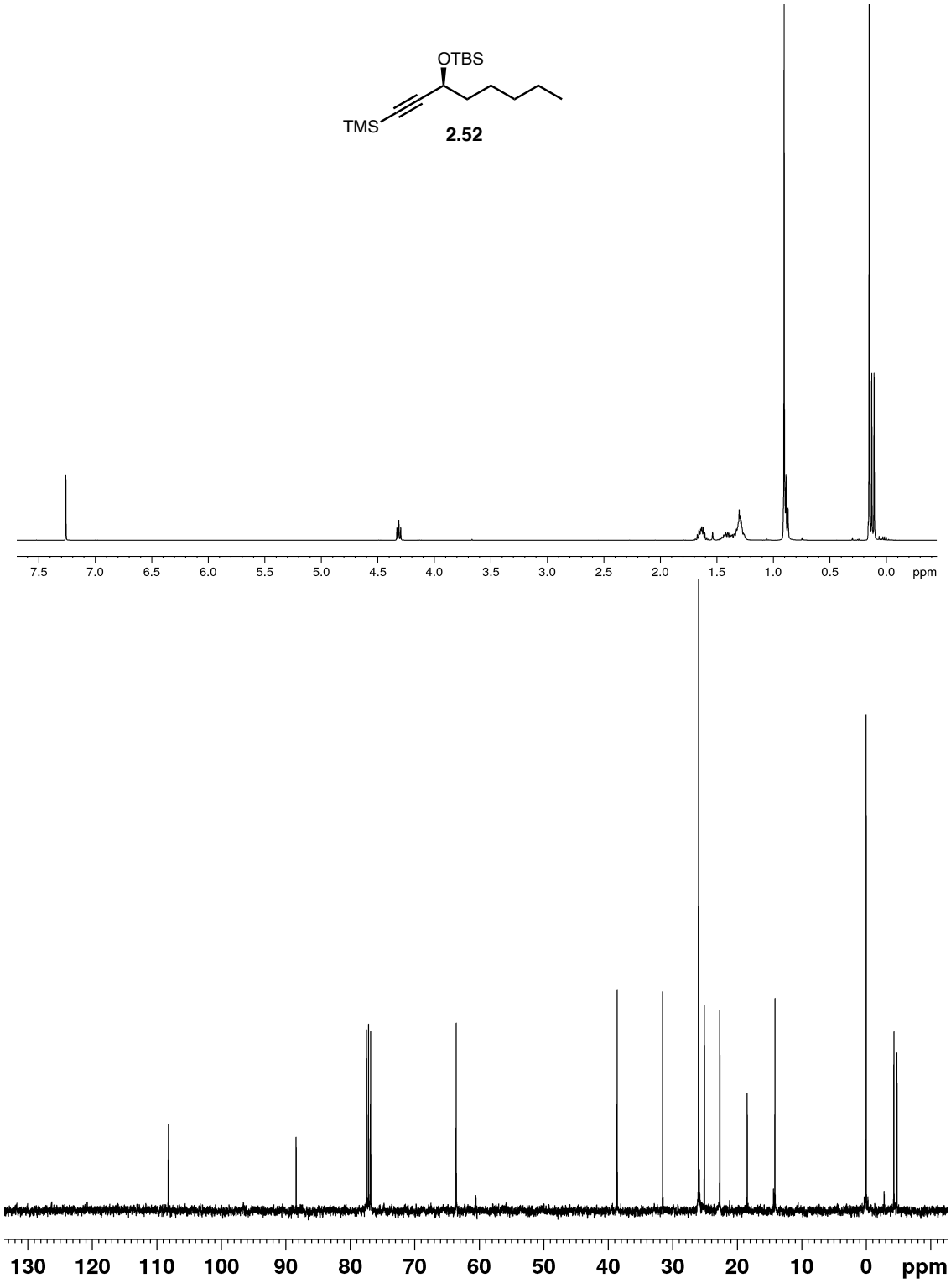


Figure A1.5: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of Compound 2.52

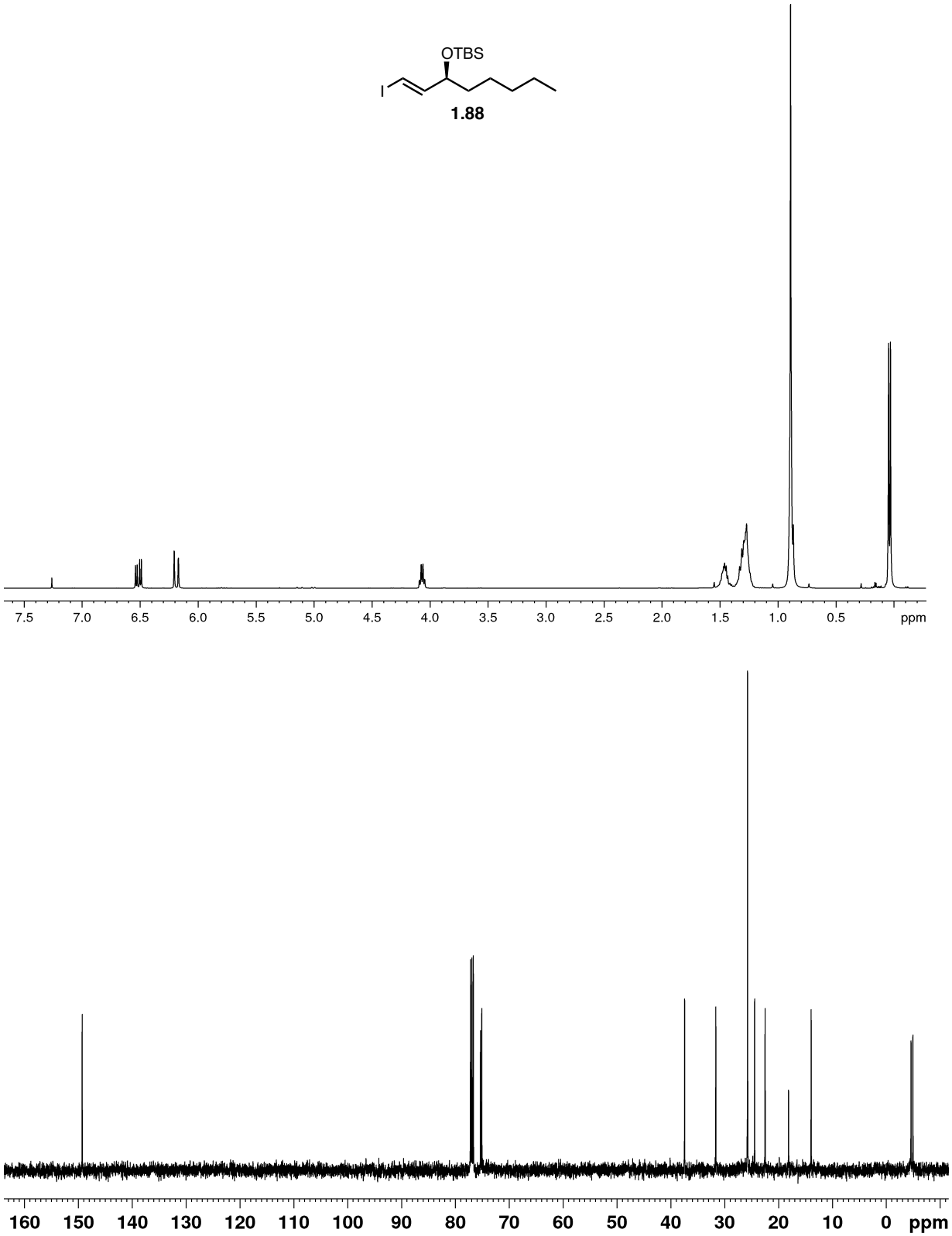


Figure A1.6:^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) of Compound 1.88

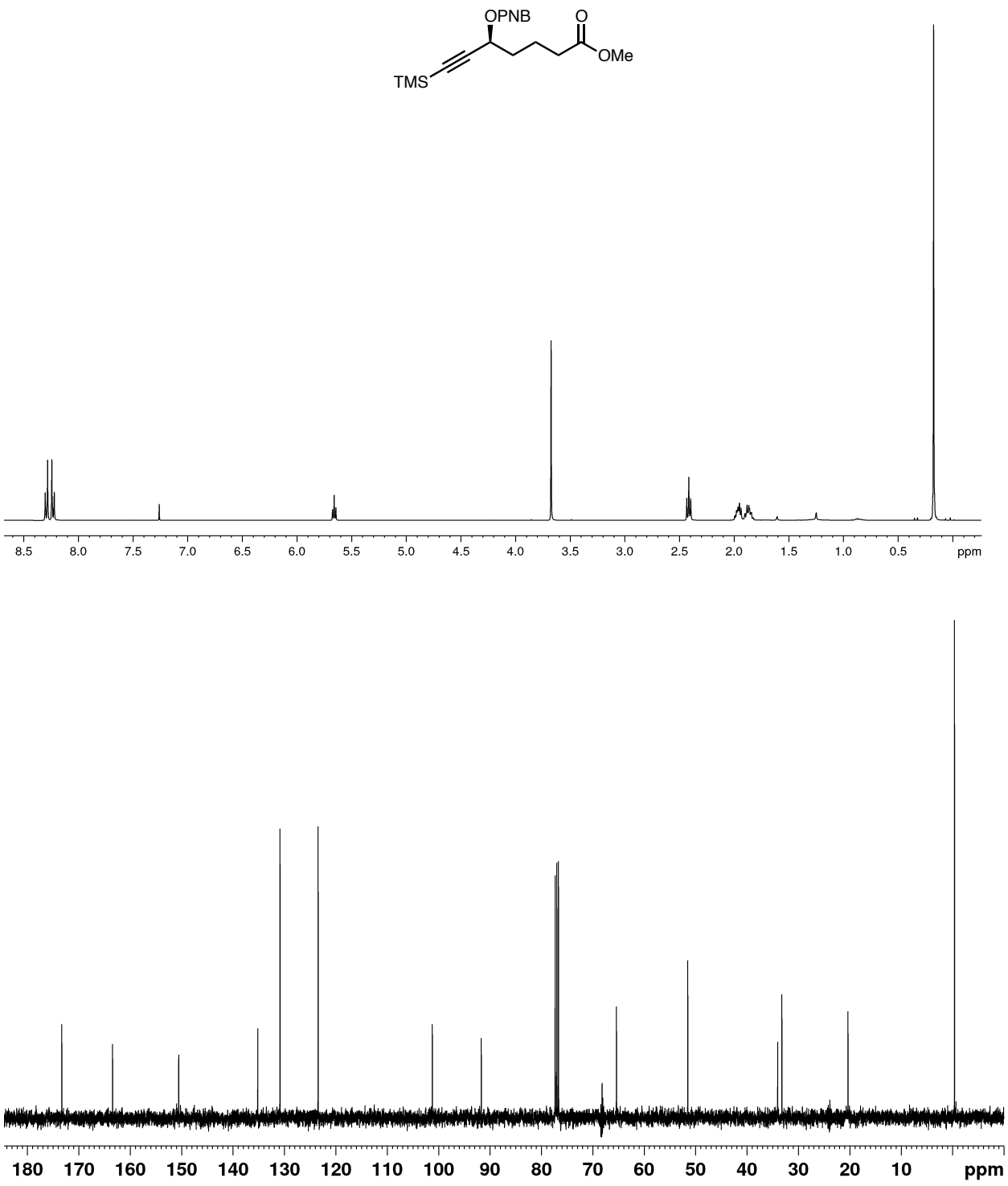


Figure A1.7: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of *p*-Nitrobenzoate of 2.56

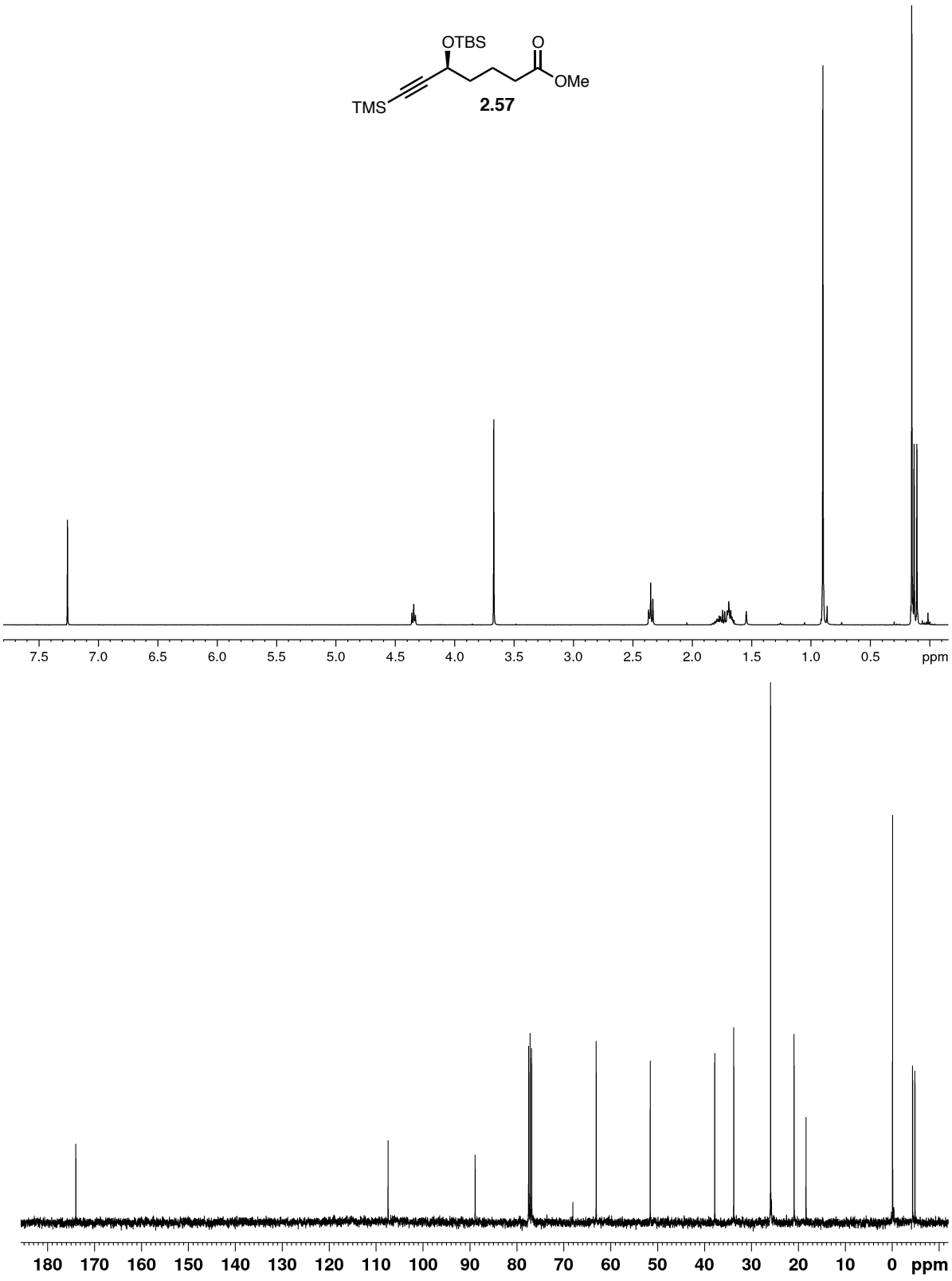


Figure A1.8: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of Compound 2.57

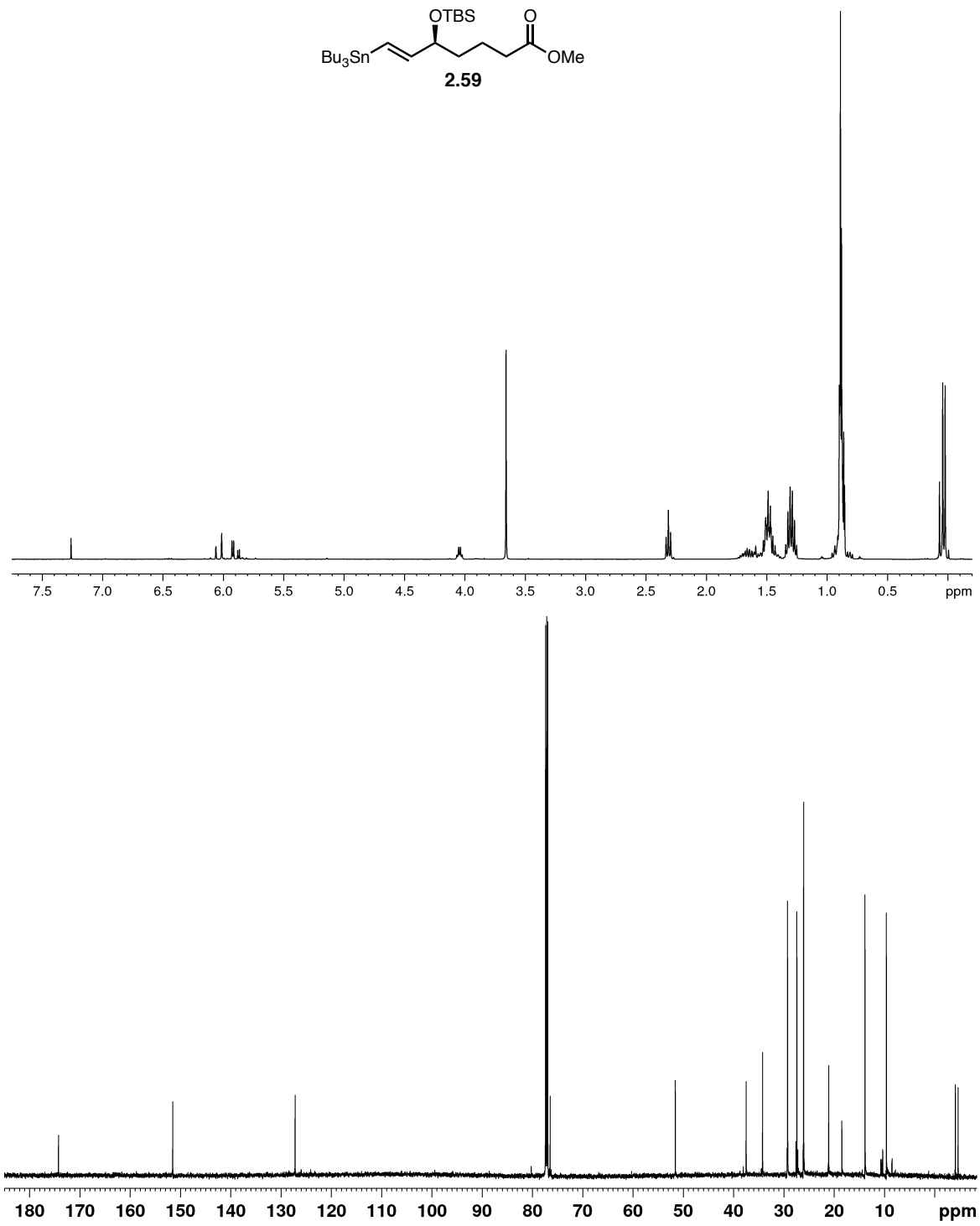


Figure A1.9: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of Compound 2.59

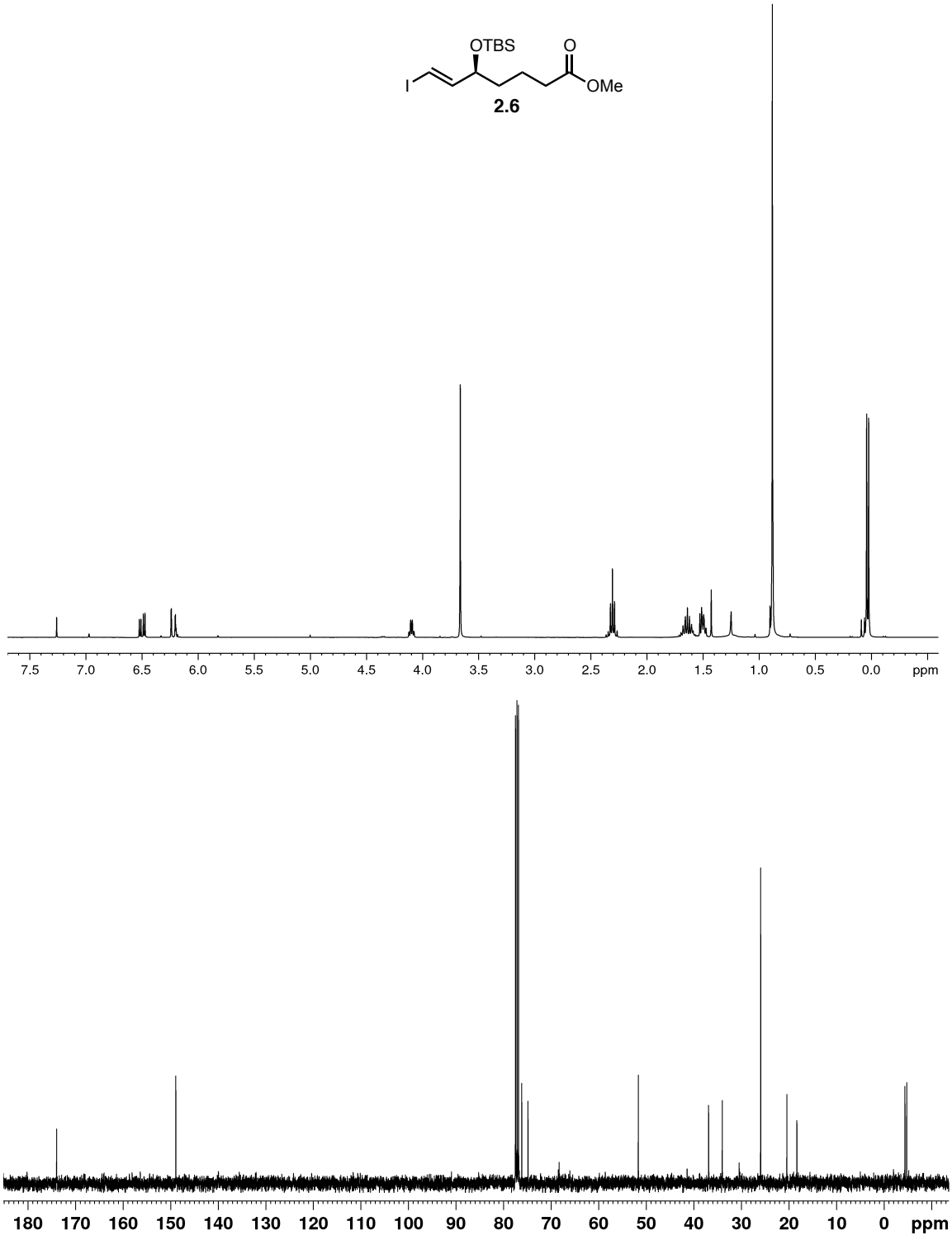


Figure A1.10: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of Compound 2.6

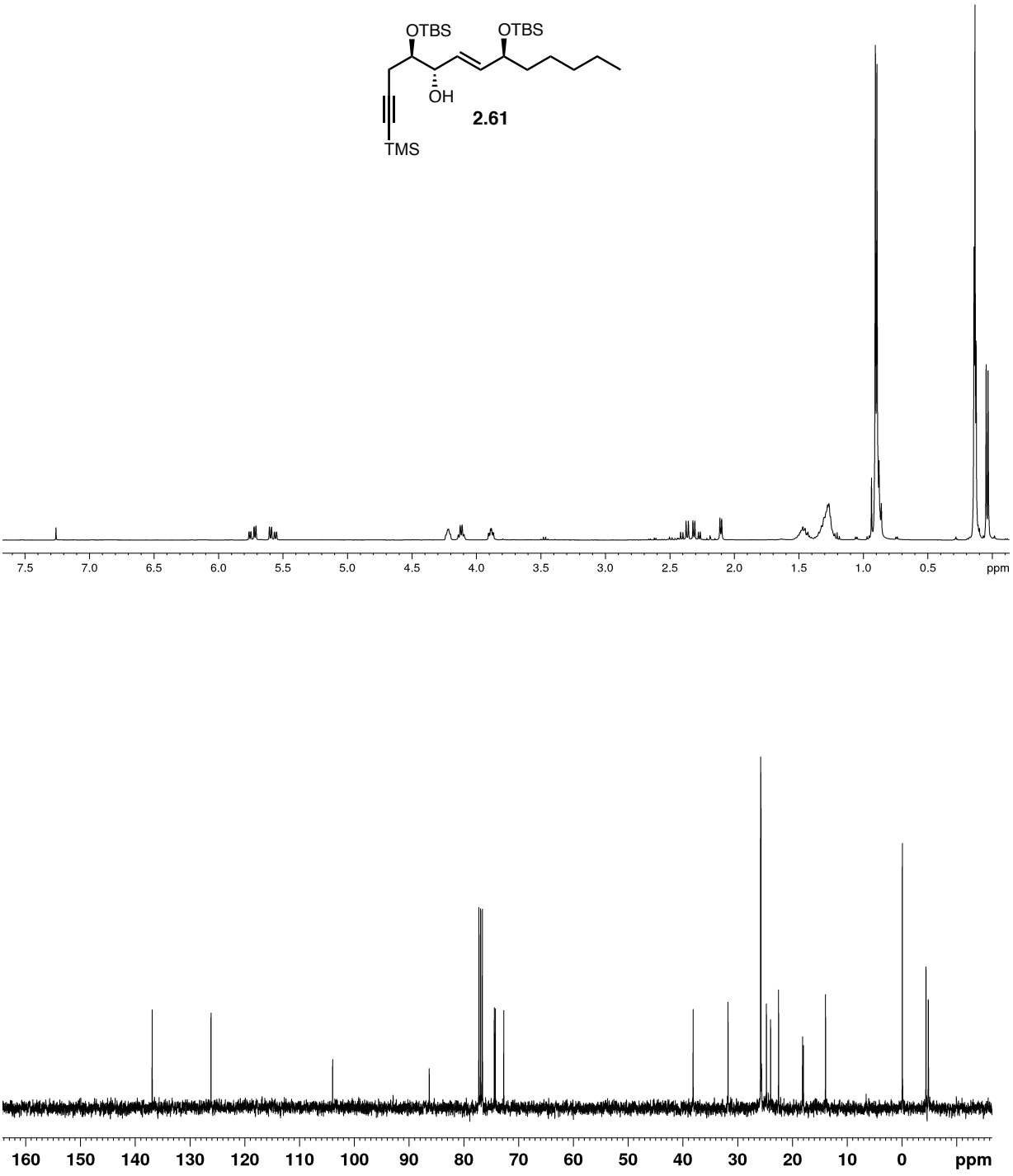


Figure A1.11: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of Compound 2.61

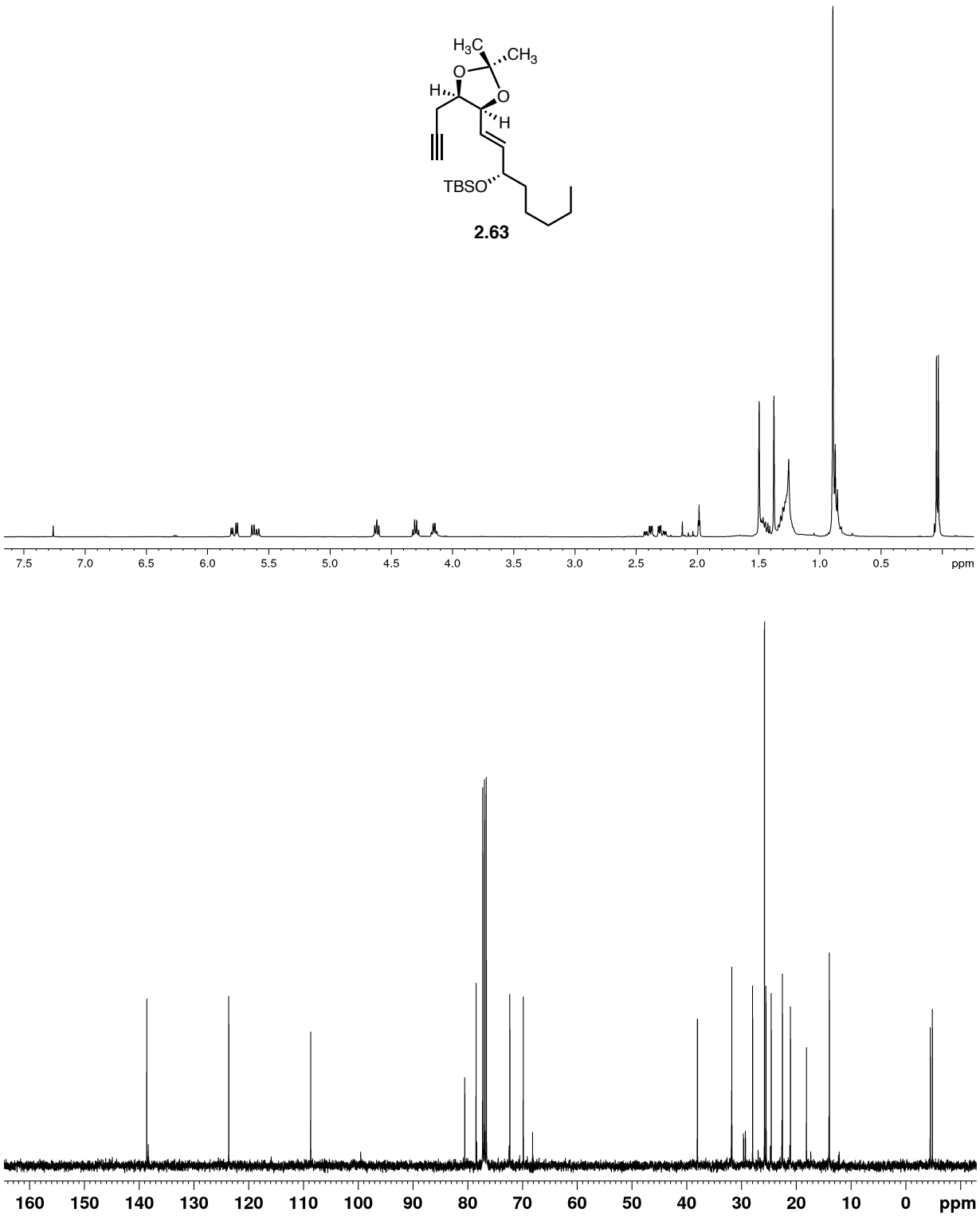


Figure A1.12: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of Compound 2.63

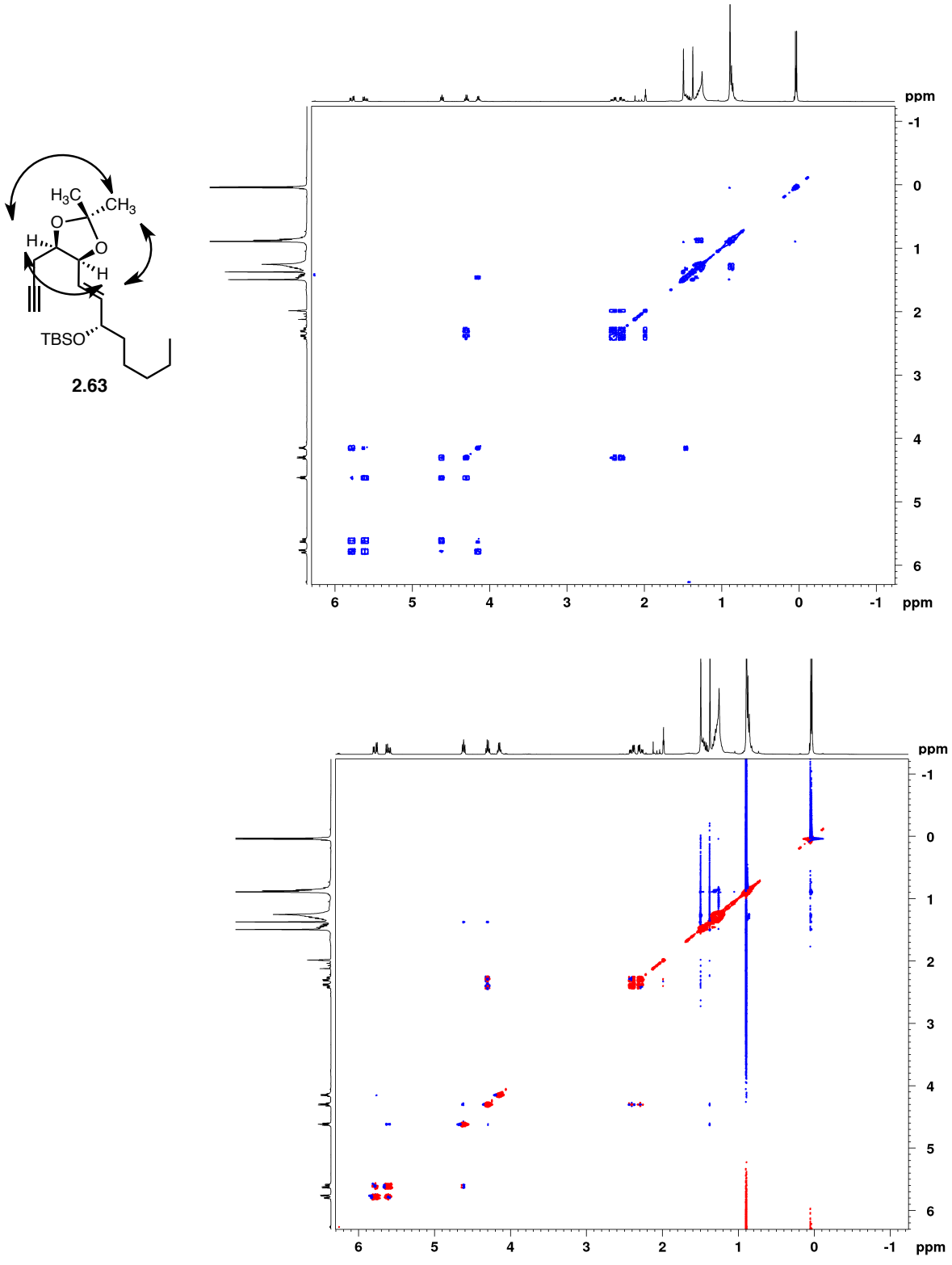


Figure A1.13: COSY Spectrum (400 MHz, $CDCl_3$) and NOESY Spectrum (400MHz, $CDCl_3$) of Compound 2.63

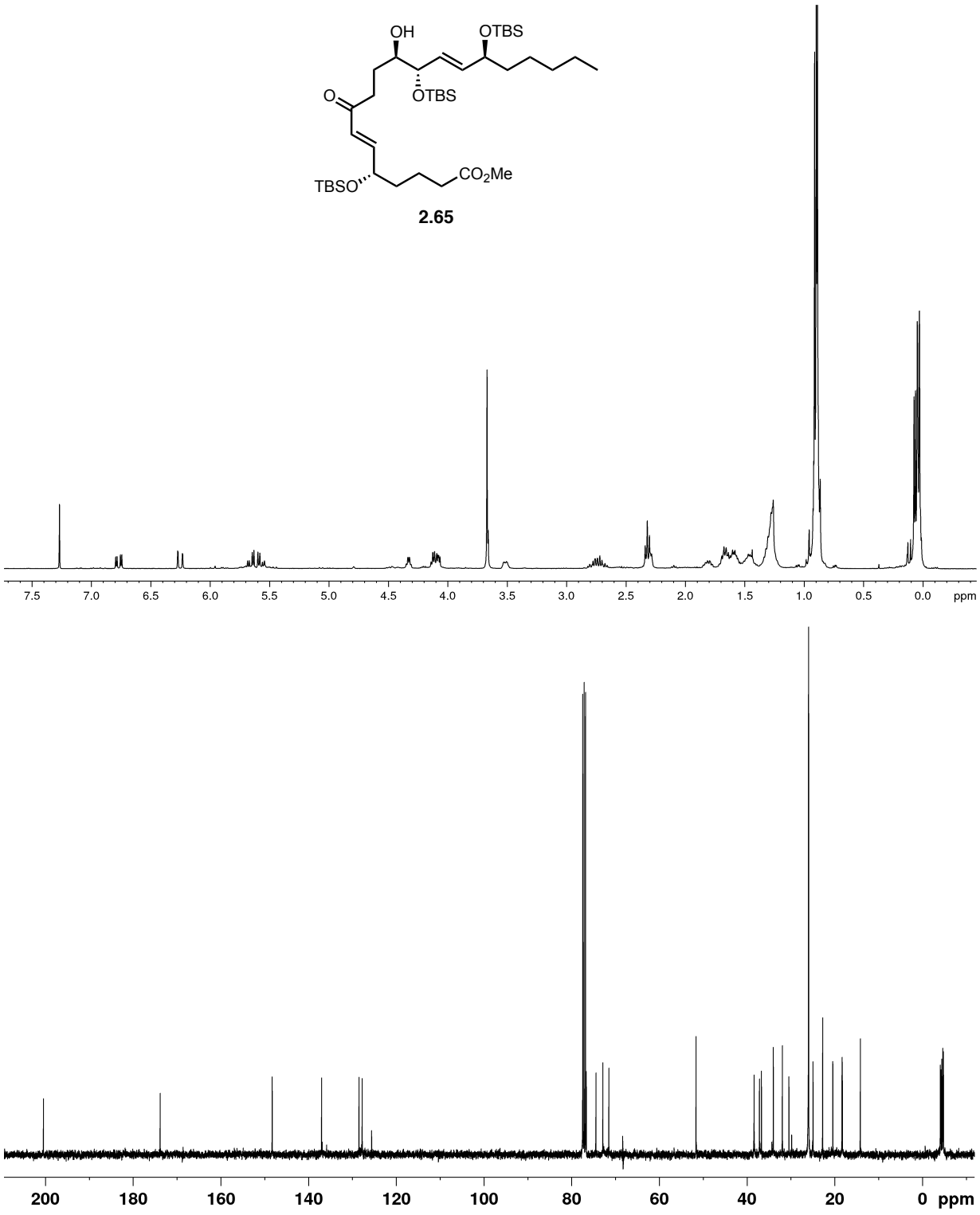


Figure A1.14: ^{1}H NMR (600MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of Compound 2.65

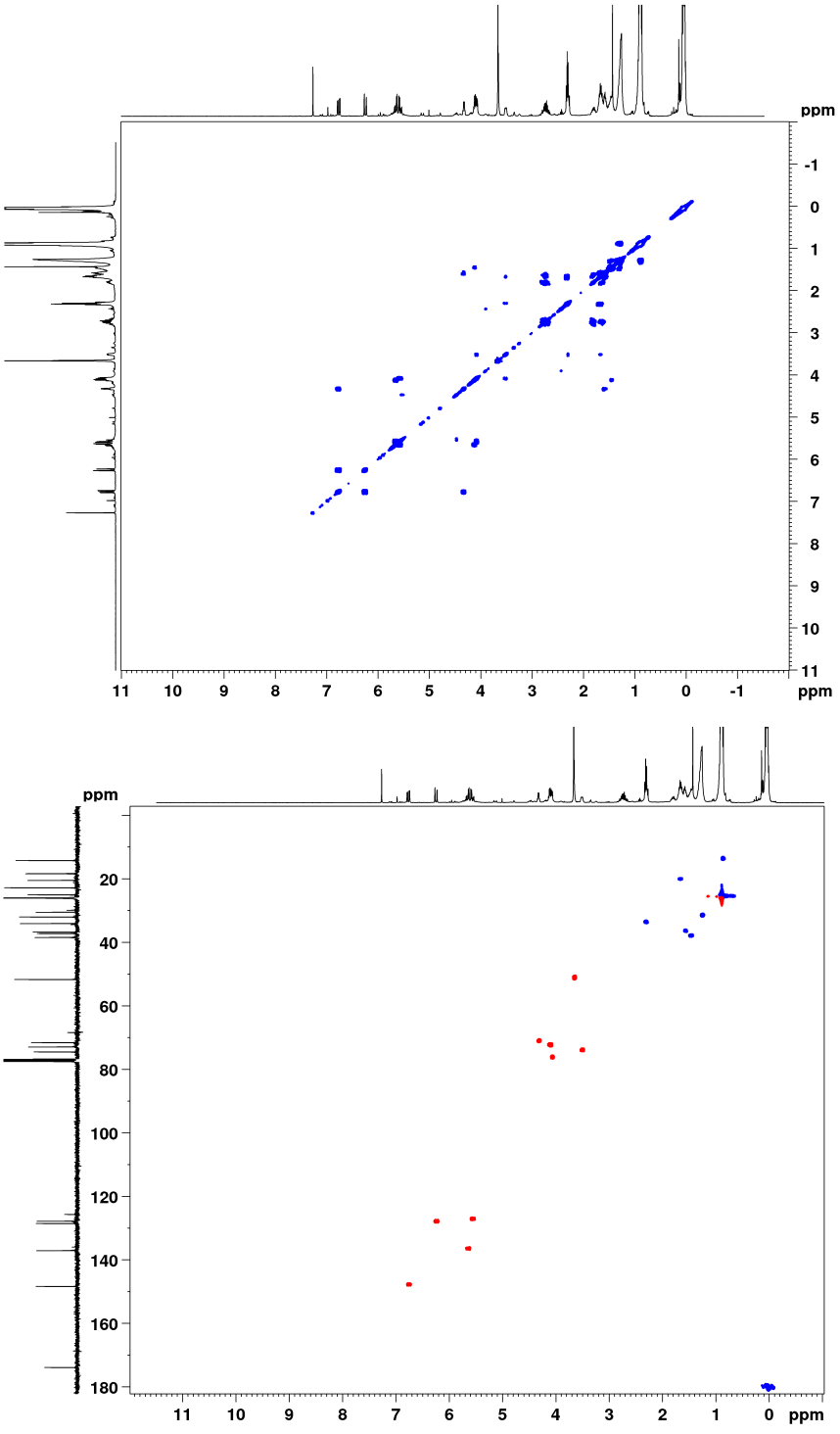


Figure A1.15: COSY Spectrum (600MHz, CDCl3) and HSQC Spectrum (600 MHz, $CDCl_3$) of Compound 2.65

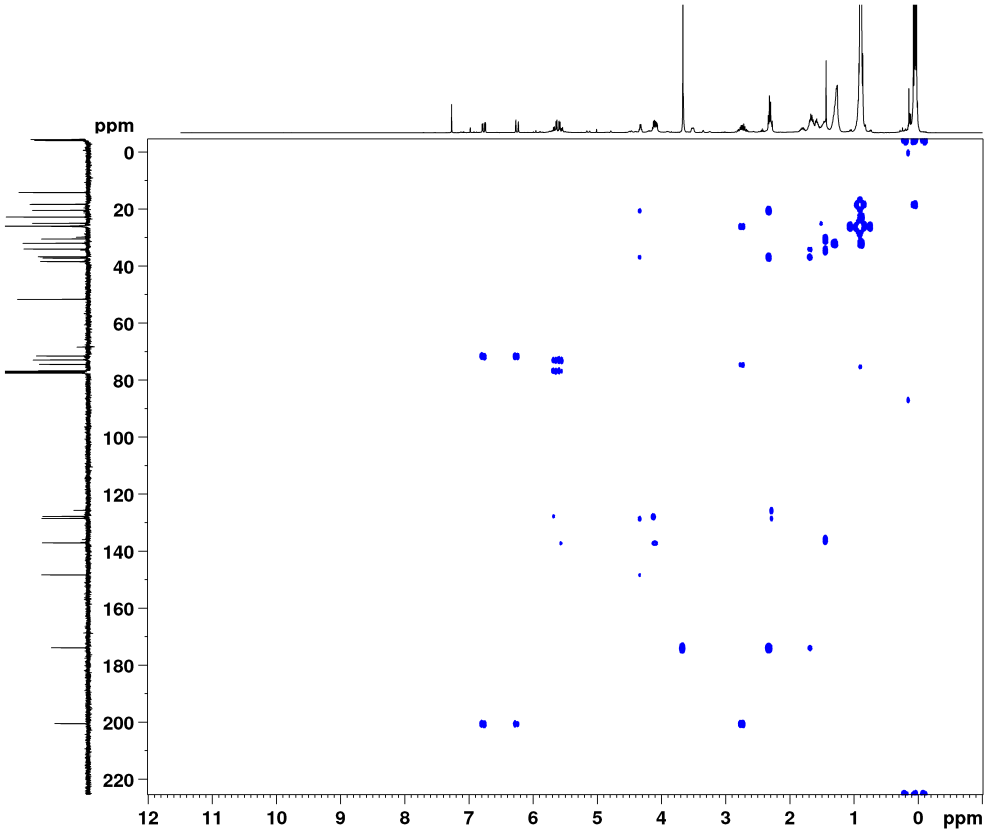


Figure A1.16: HMBC Spectrum (600 MHz, $CDCl_3$) of Compound 2.65

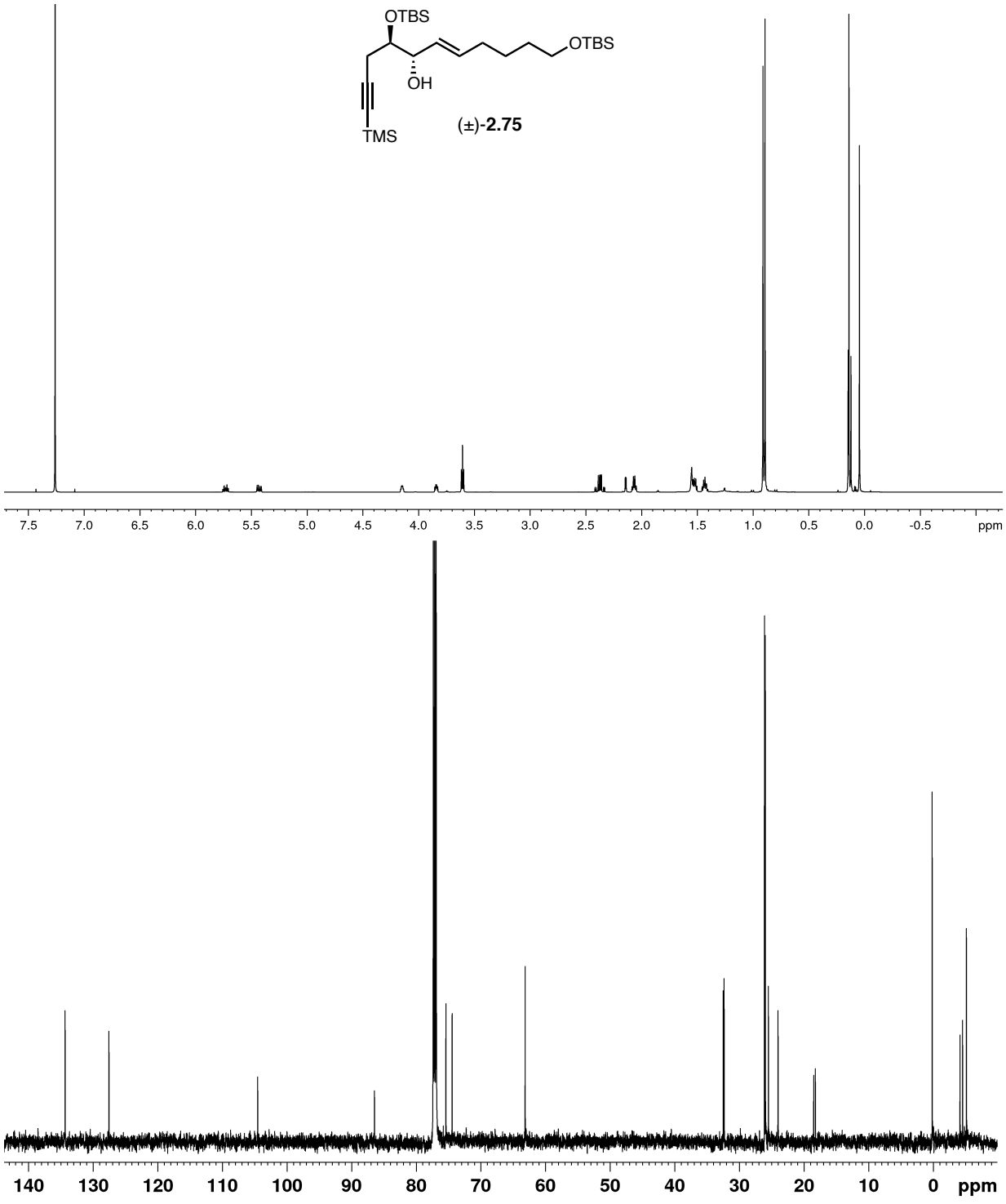


Figure A1.17: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of Compound 2.75

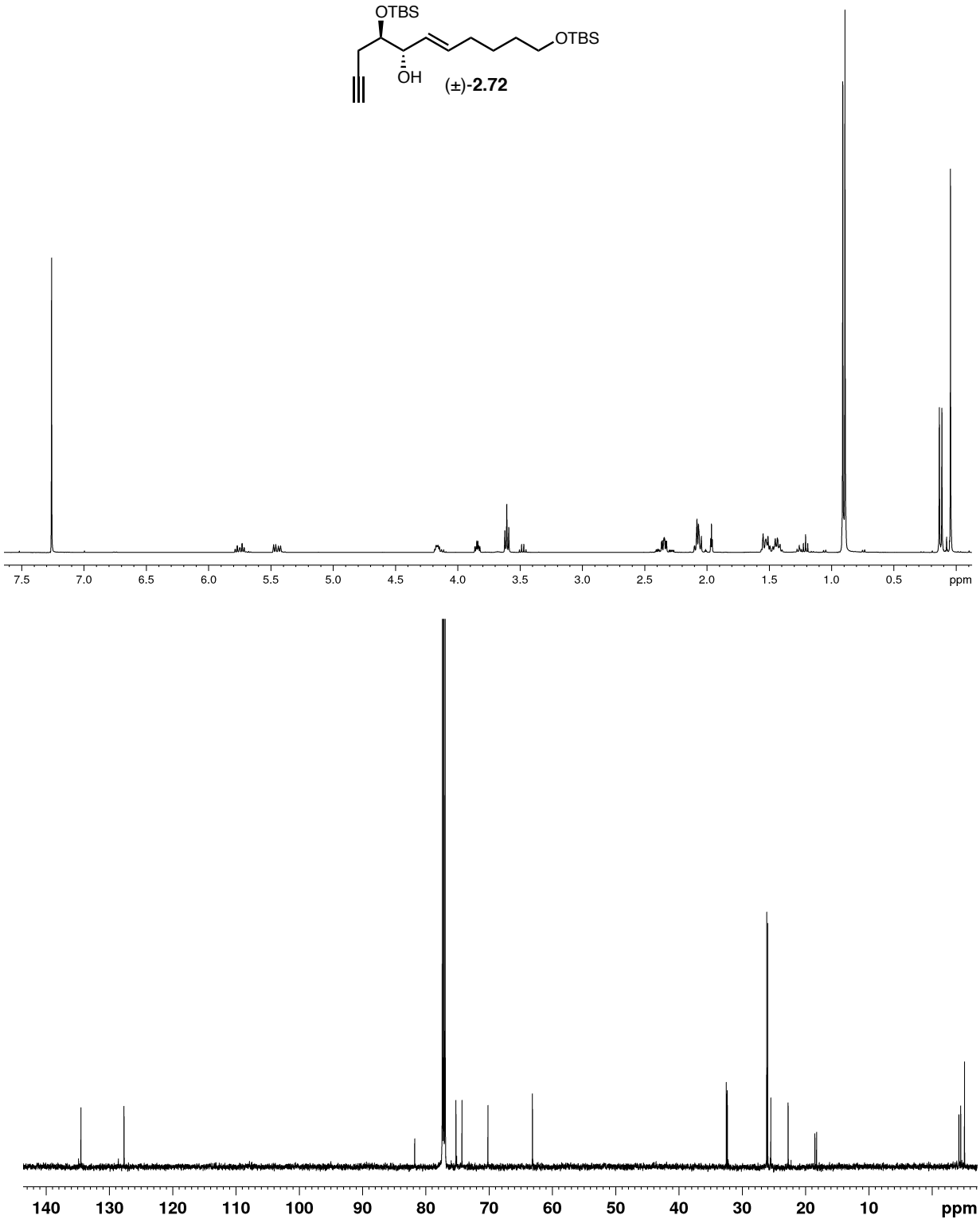


Figure A1.18: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of Compound 2.72

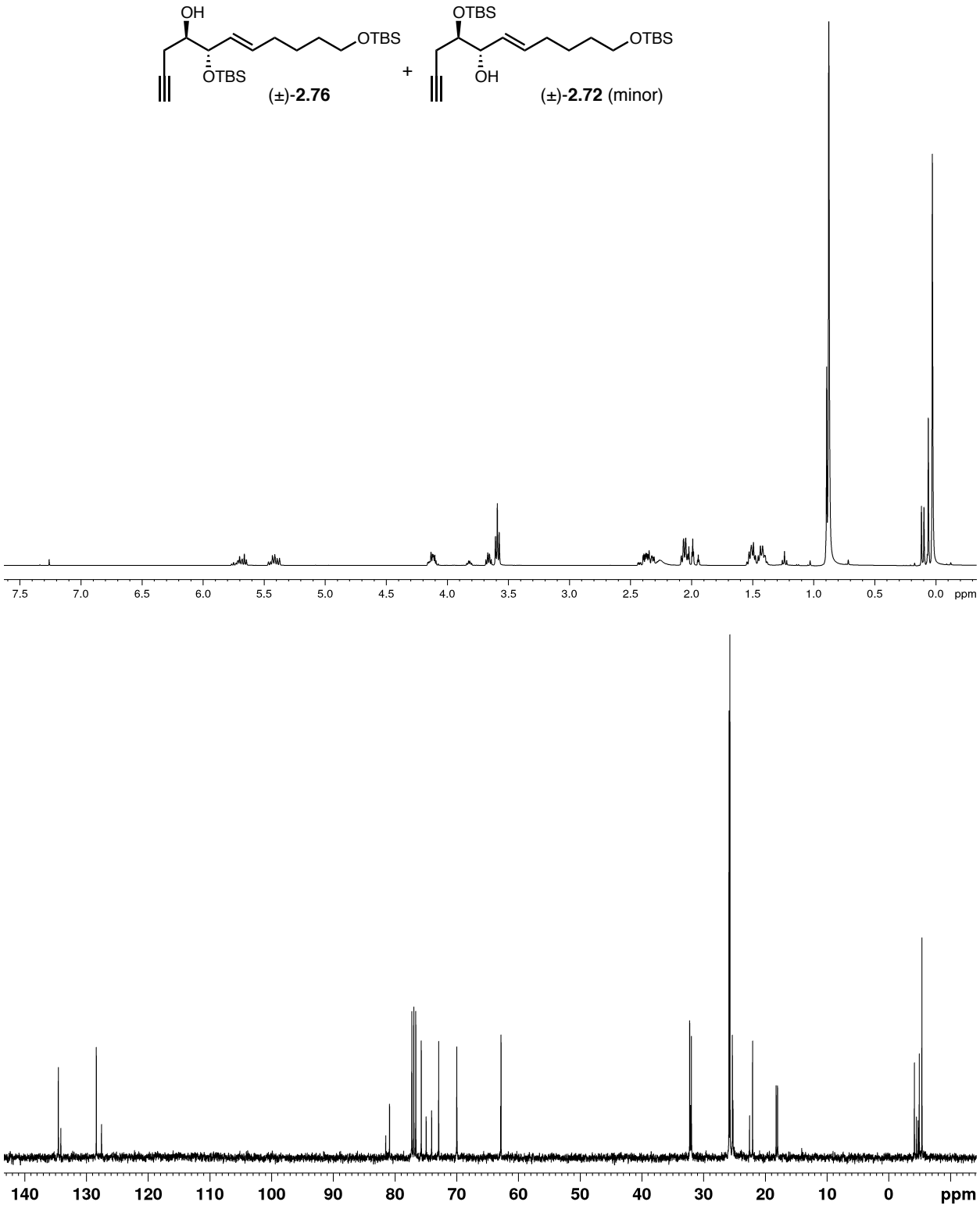


Figure A1.19: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of Compound 2.76 (with minor product 2.72)

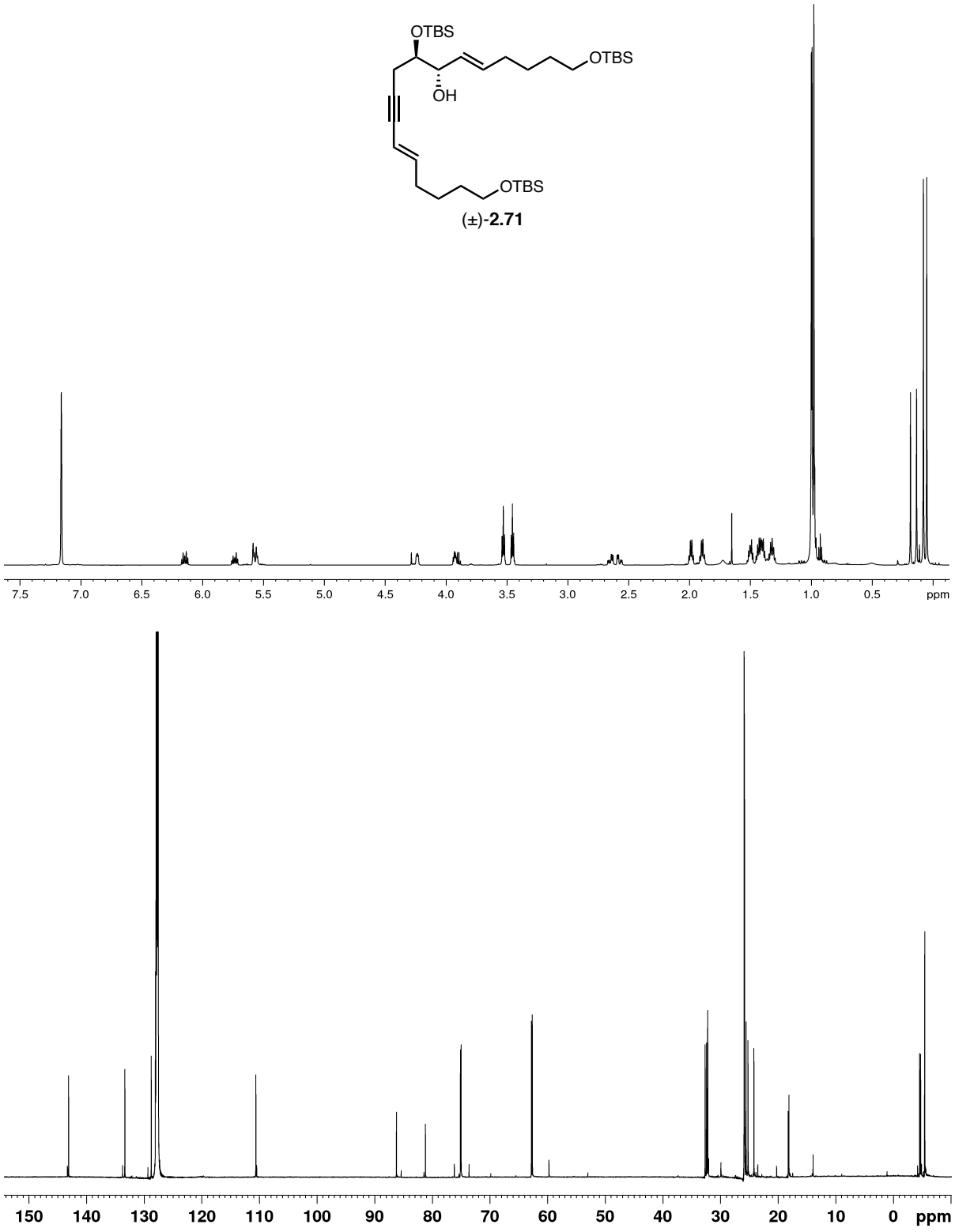


Figure A1.20: ^{1}H NMR (600MHz, C_6D_6) and ^{13}C NMR (150 MHz, C_6D_6) of Compound 2.71

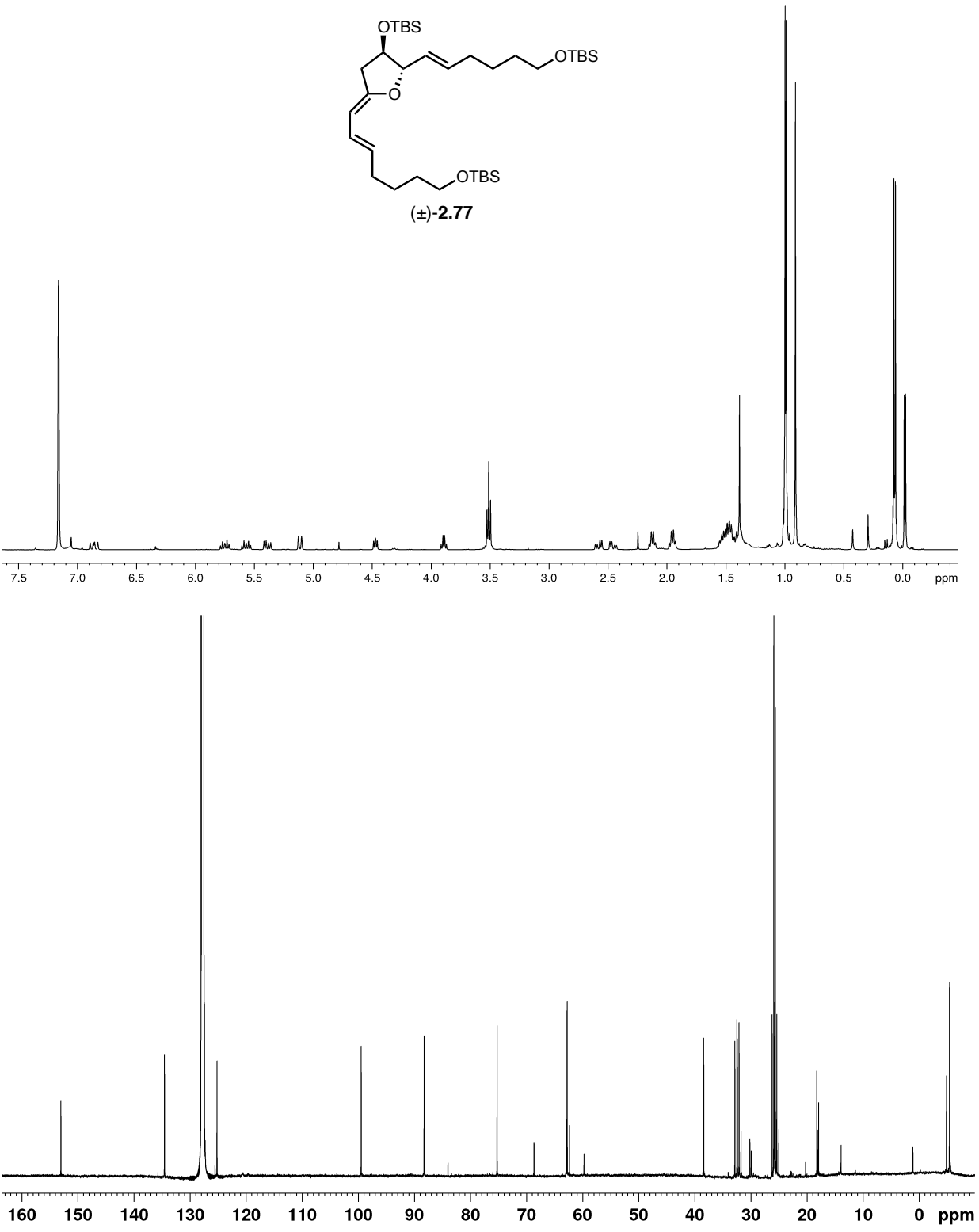


Figure A1.21: ^{1}H NMR (600 MHz, C_6D_6) and ^{13}C NMR (150 MHz, C_6D_6) of Compound 2.77

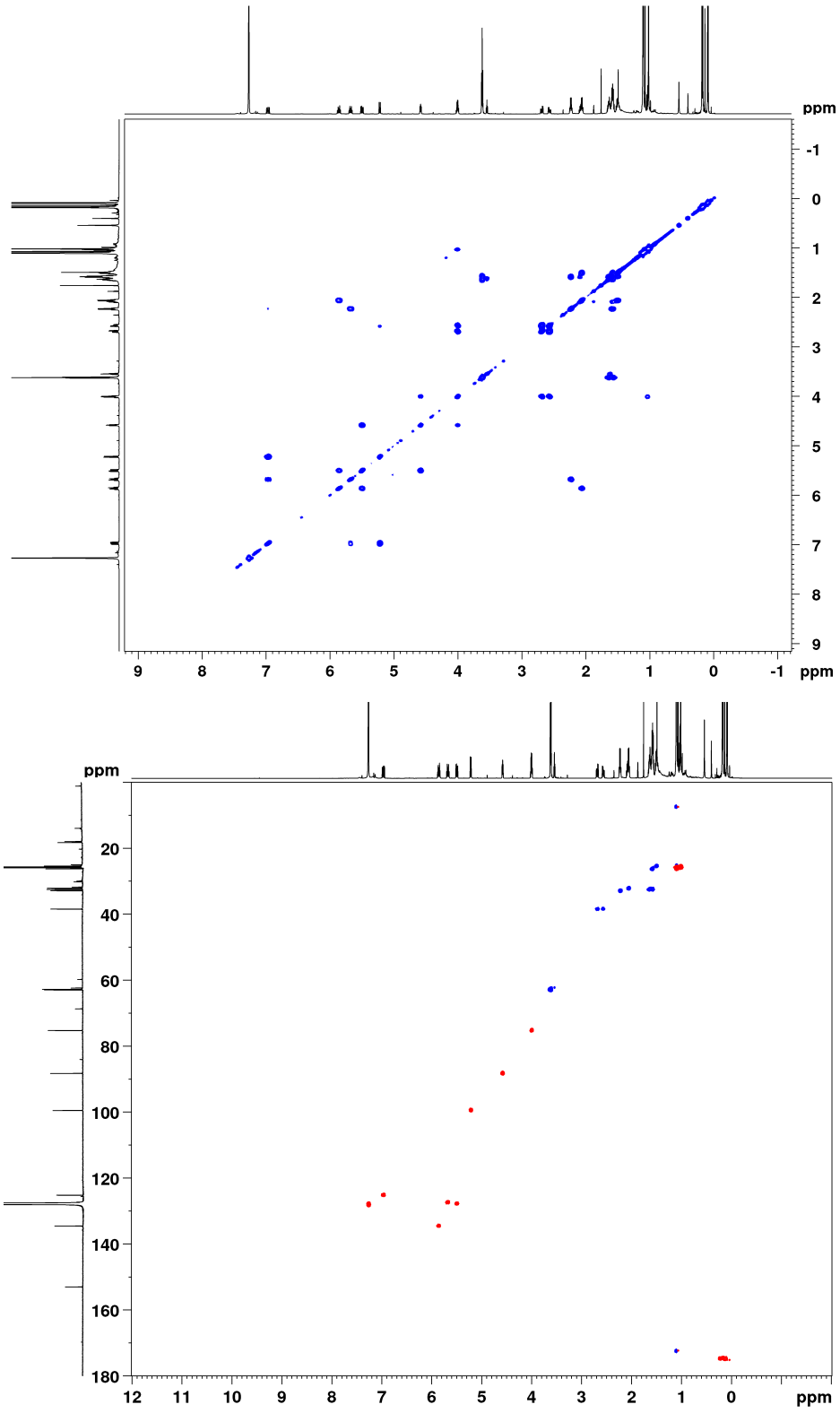


Figure A1.22: COSY Spectrum (600 MHz, C_6D_6) and HSQC Spectrum (600 MHz, C_6D_6) of Compound 2.77

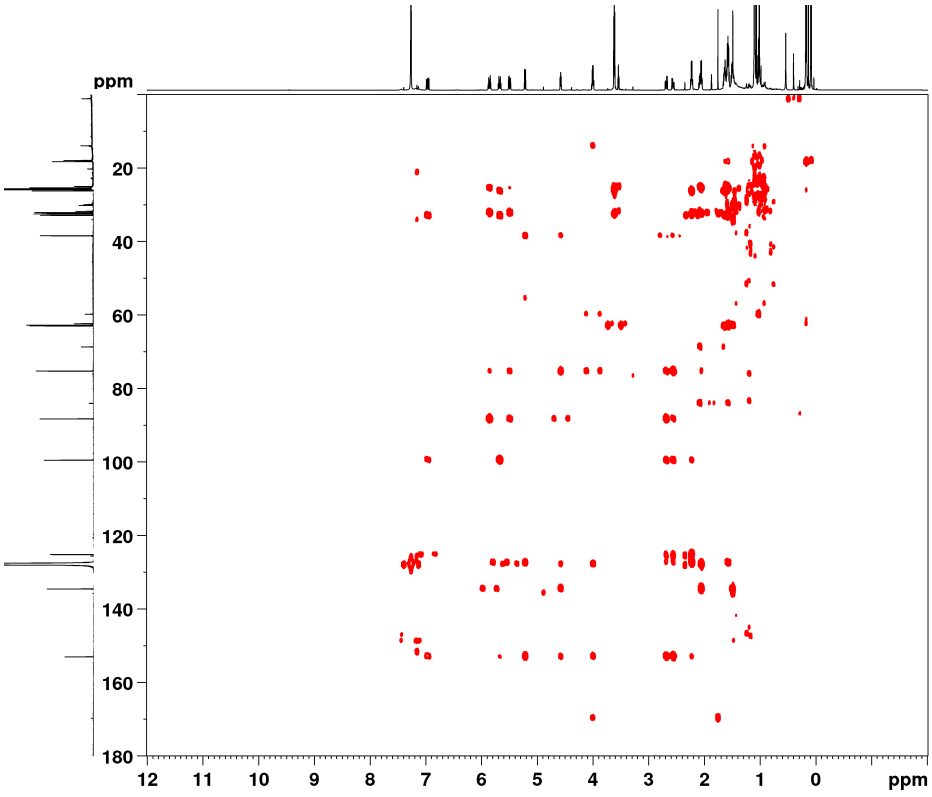


Figure A1.23: HMBC Spectrum (600 MHz, C_6D_6) of Compound 2.77

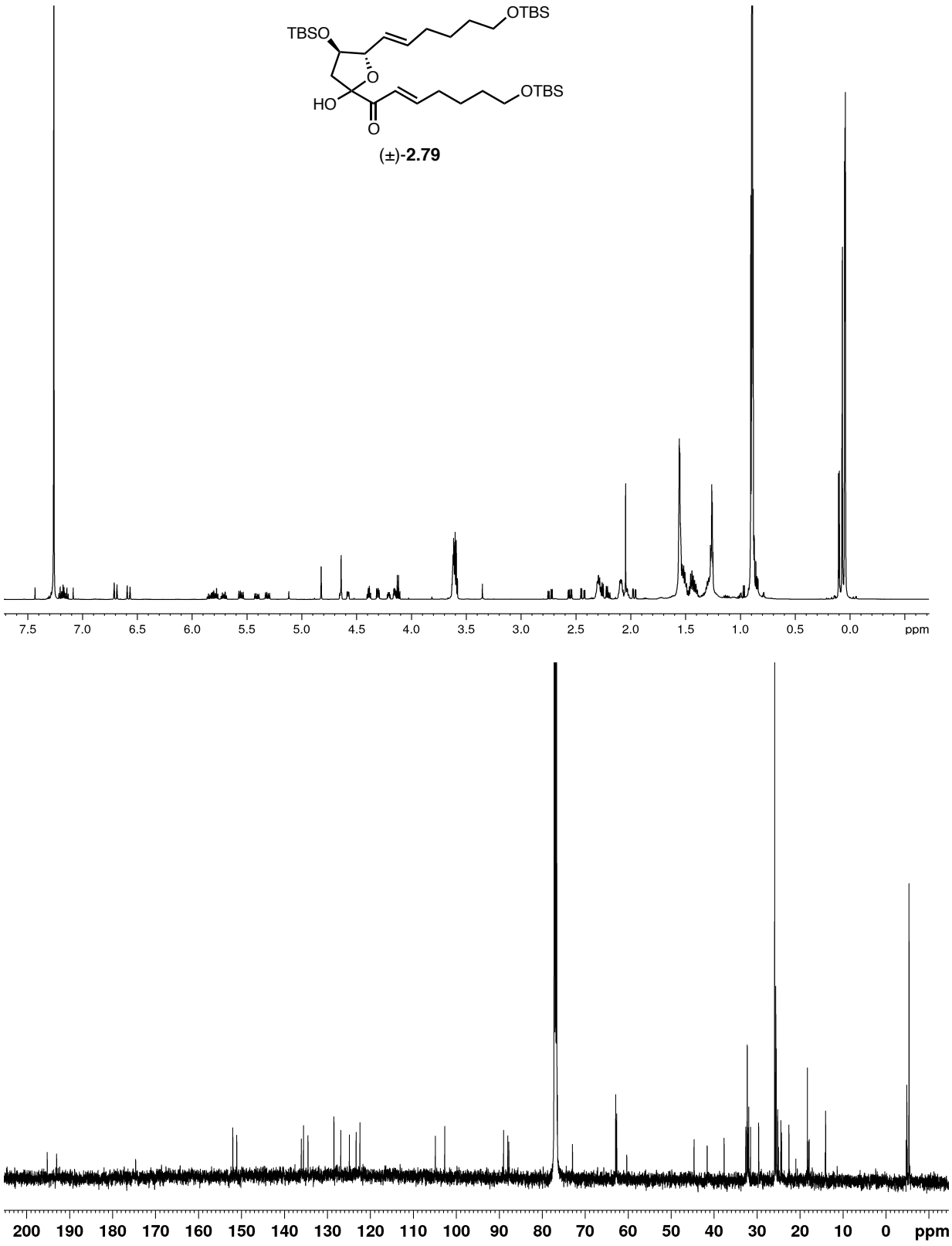


Figure A1.24: ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) of Compound 2.79

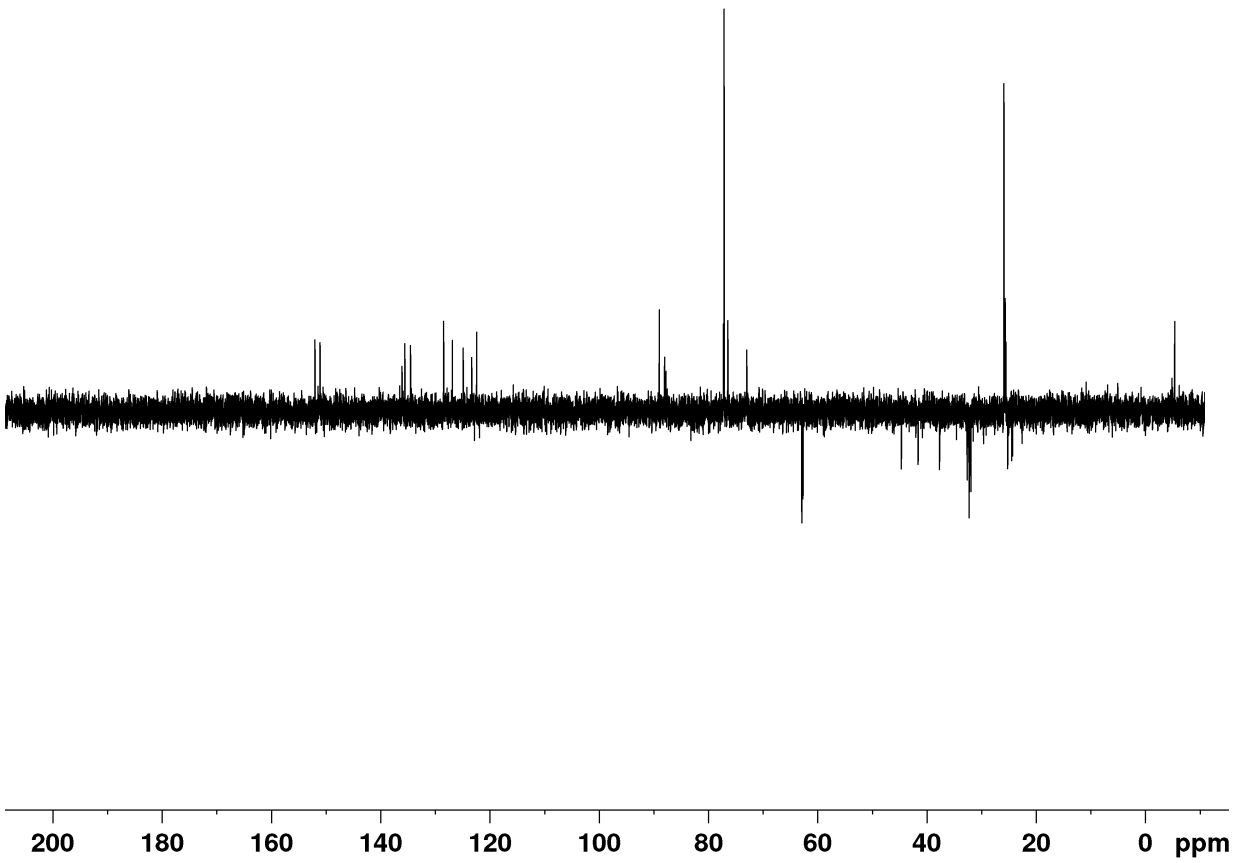


Figure A1.25: DEPT-135 NMR (125 MHz, $CDCl_3$) of Compound 2.79

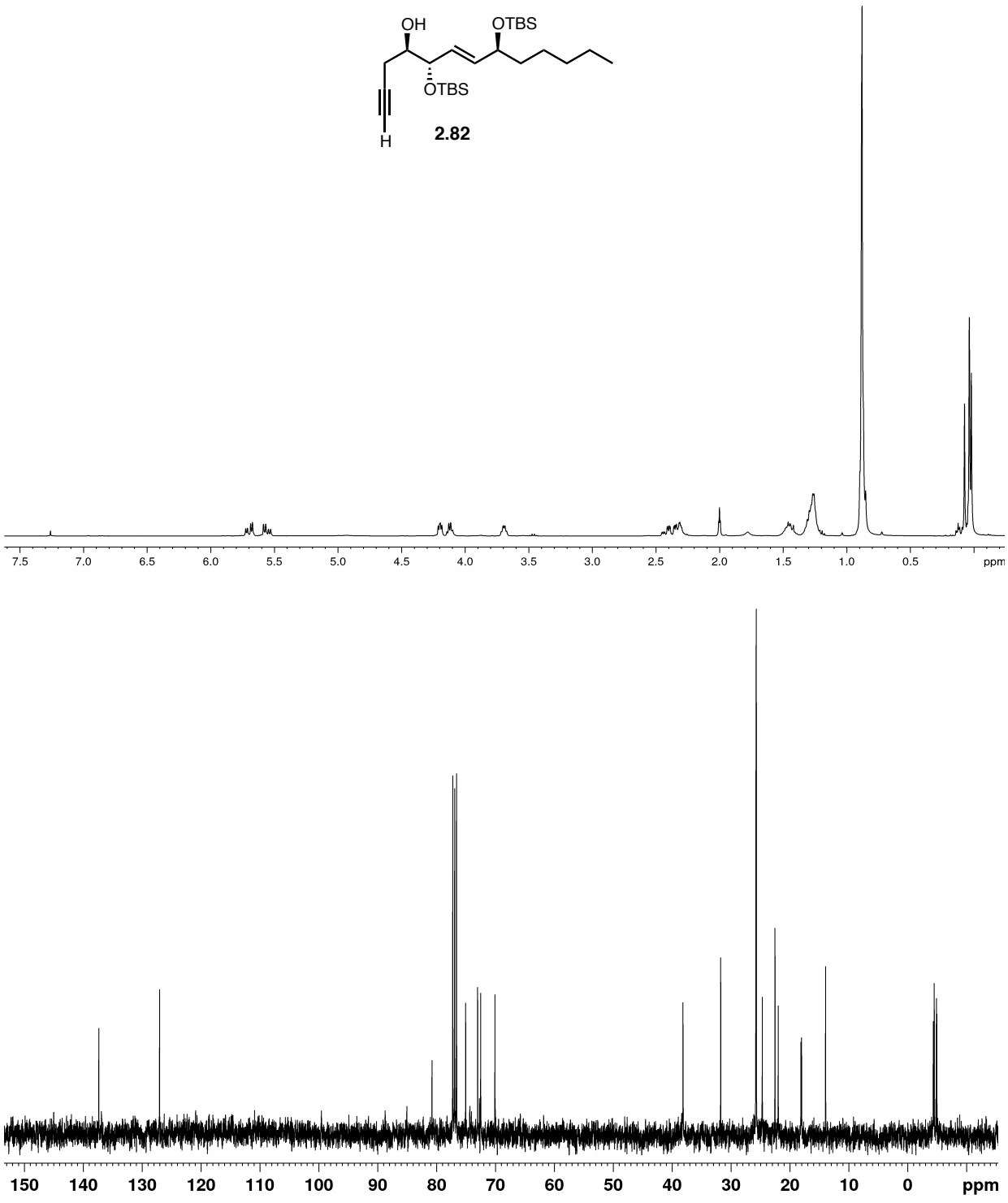


Figure A1.26: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of Compound 2.82

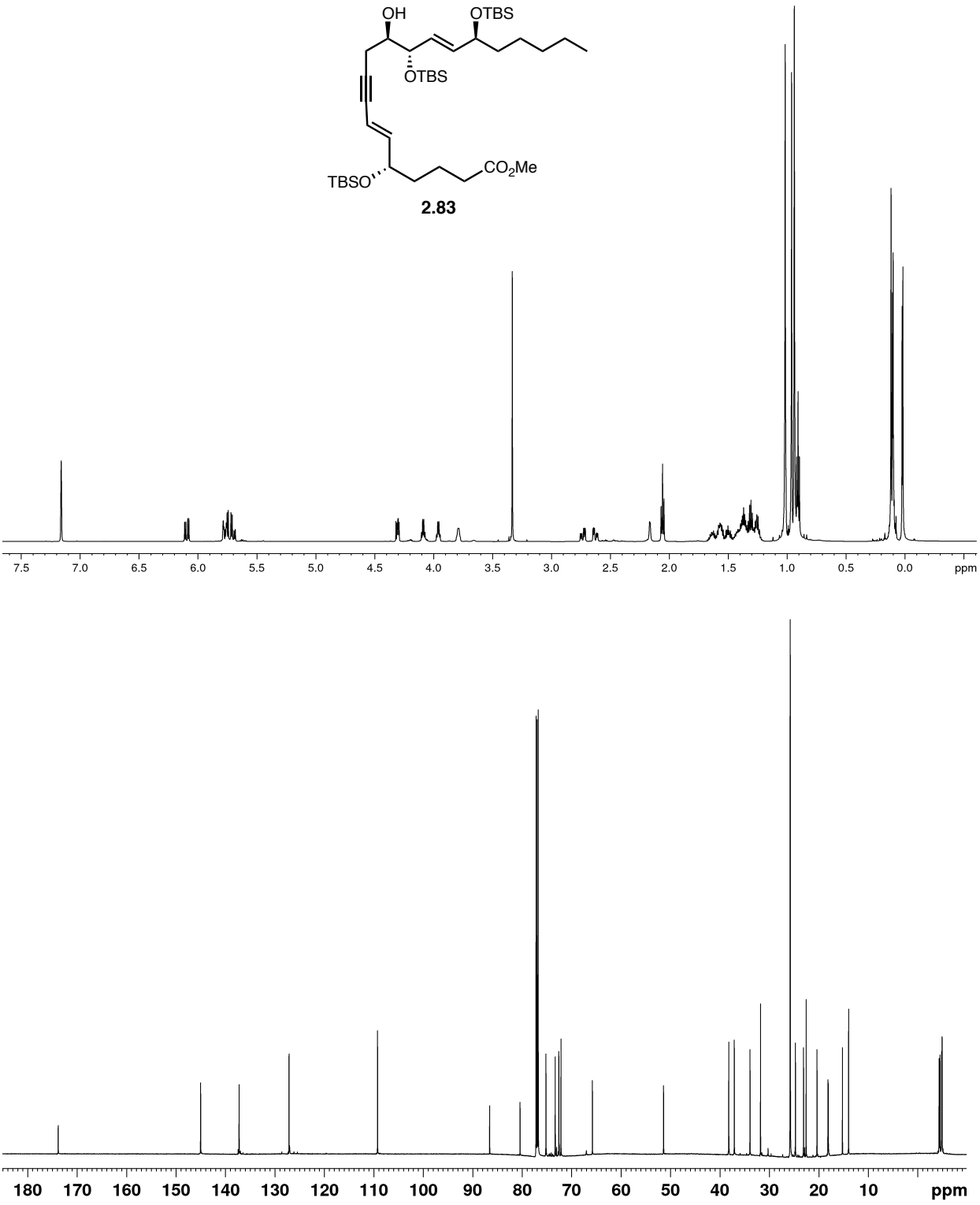


Figure A1.27: ^{1}H NMR (600 MHz, C_6D_6) and ^{13}C NMR (150 MHz, C_6D_6) of Compound 2.83

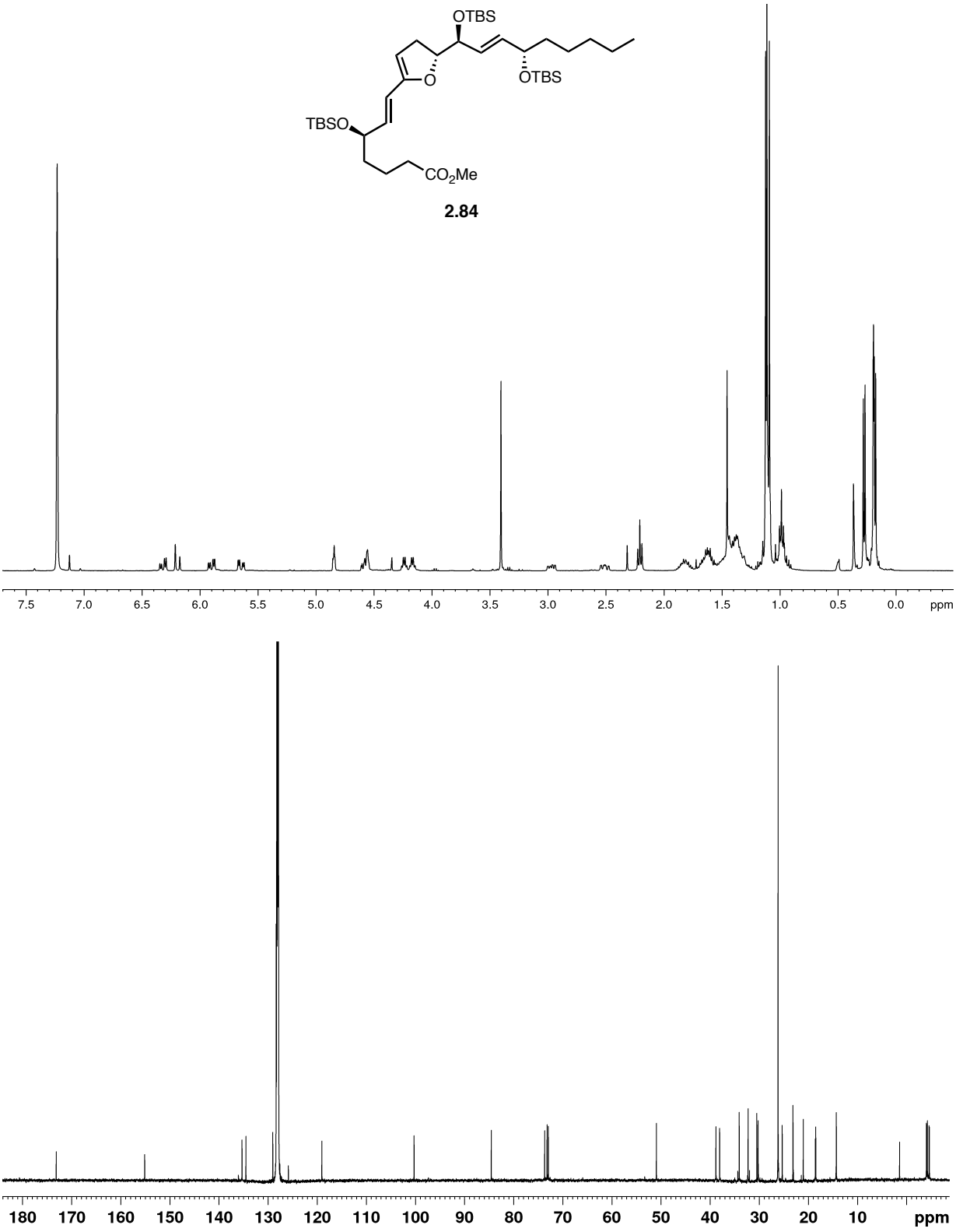


Figure A1.28: ^{1}H NMR (600 MHz, C_6D_6) and ^{13}C NMR (150 MHz, C_6D_6) of Compound 2.84

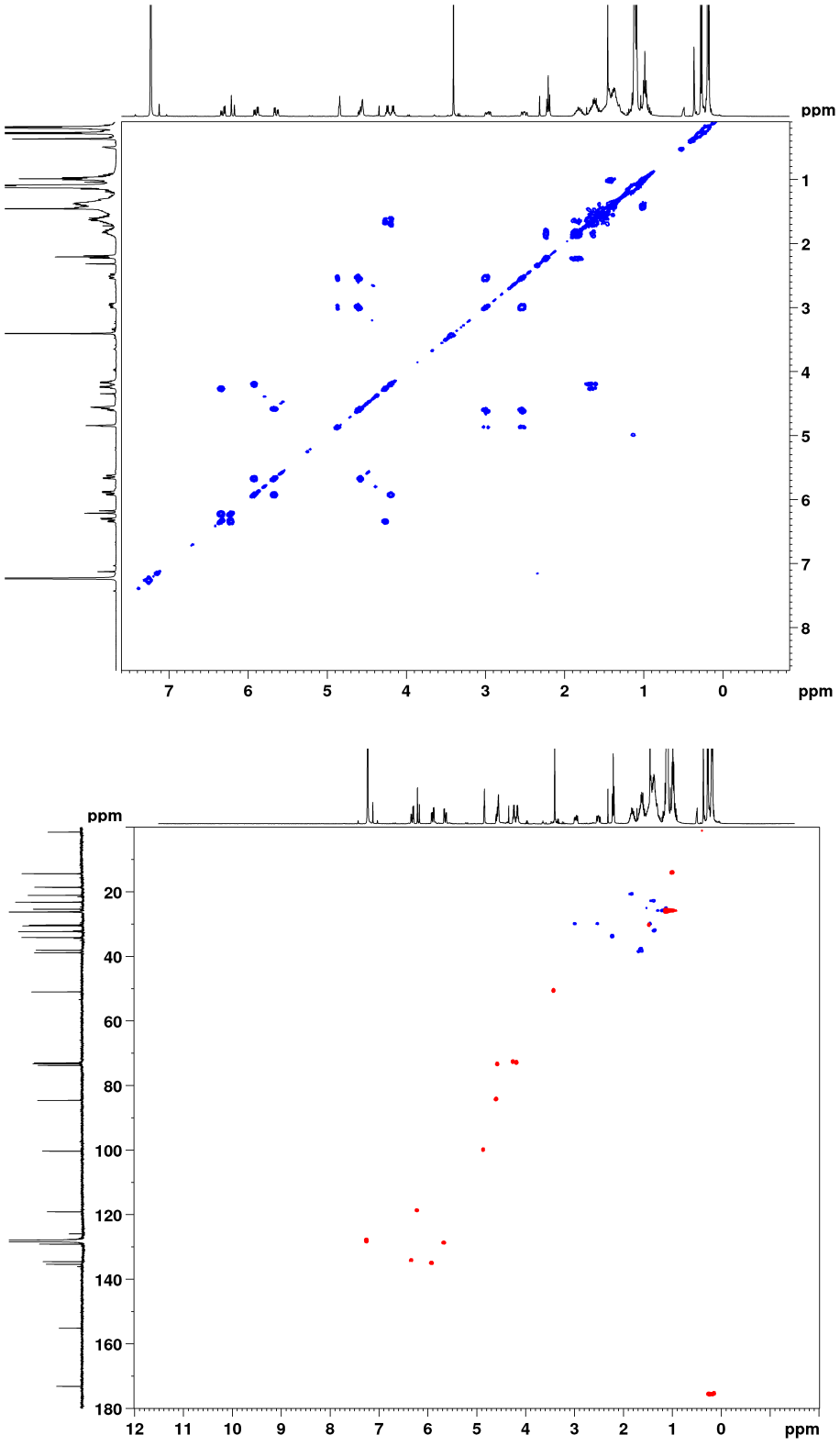


Figure A1.29: COSY Spectrum (600 MHz, C_6D_6) and HSQC Spectrum (600 MHz, C_6D_6) of Compound 2.84

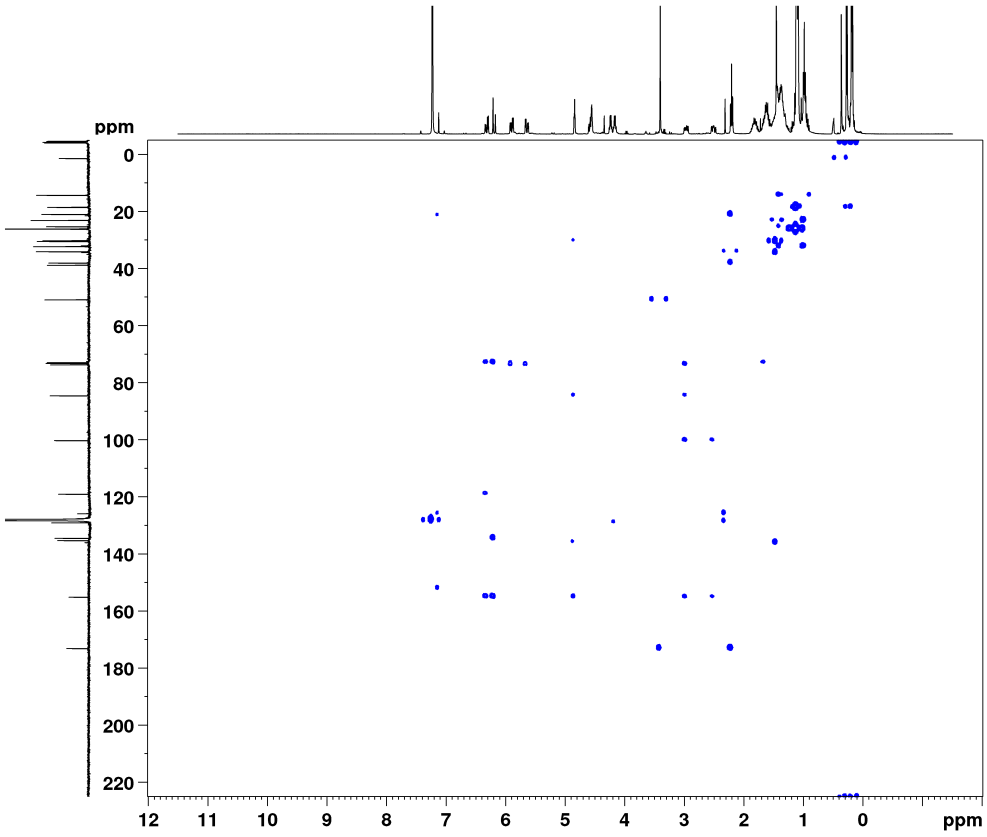


Figure A1.30: HMBC Spectrum (600 MHz, C_6D_6) of Compound 2.84

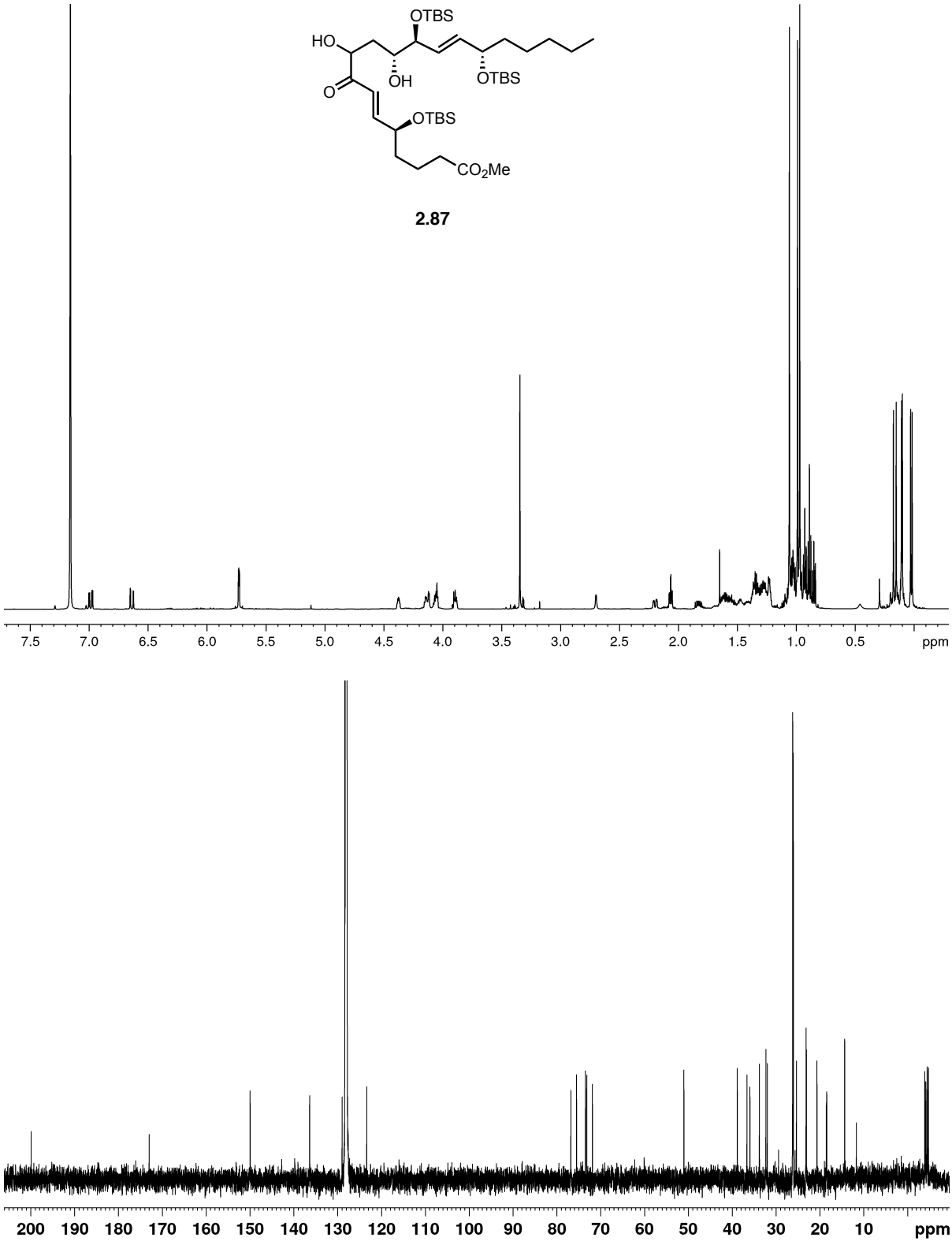


Figure A1.31: ^{1}H NMR (600 MHz, C_6D_6) and ^{13}C NMR (150 MHz, C_6D_6) of Compound 2.87

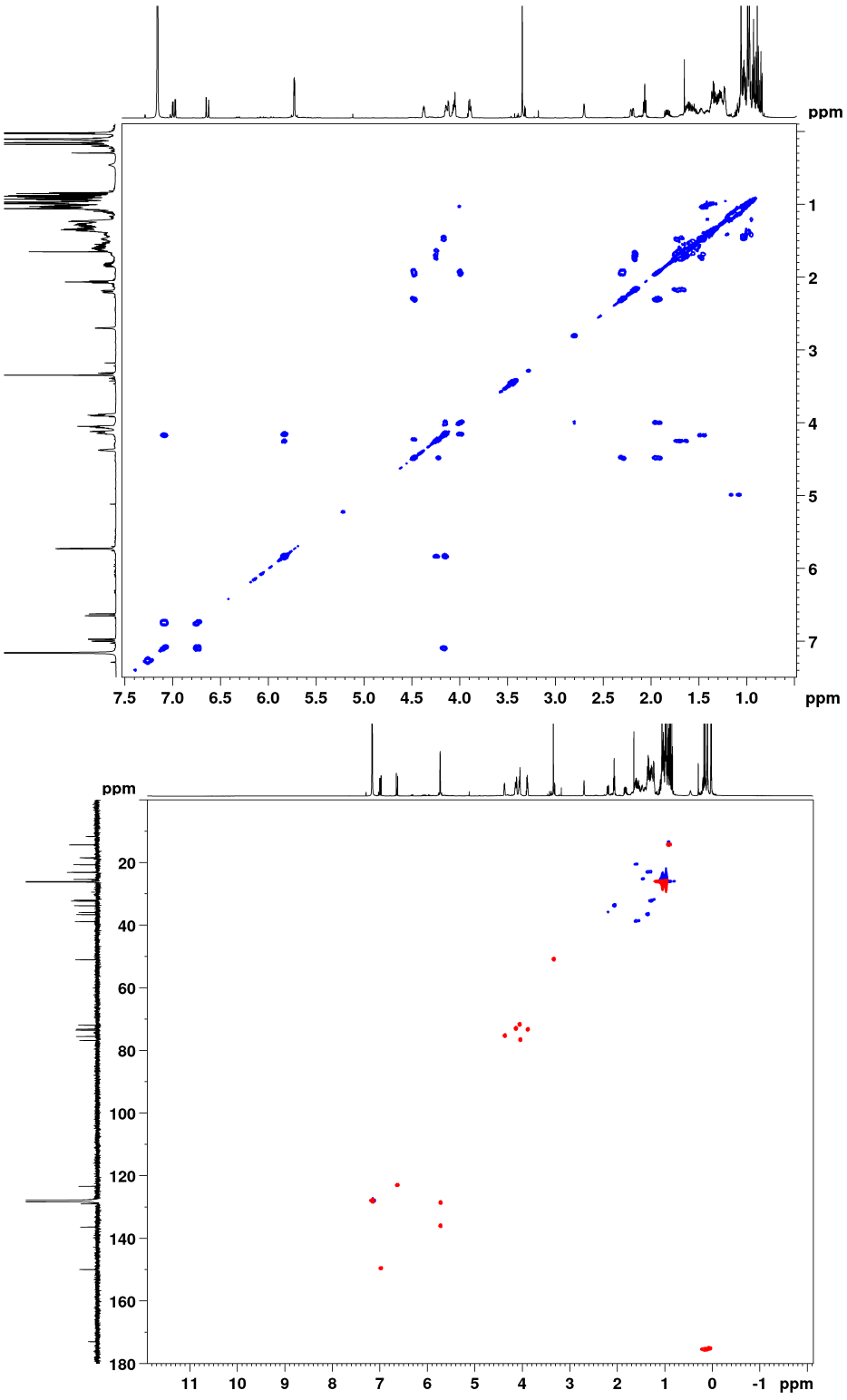


Figure A1.32: COSY Spectrum (600 MHz, C_6D_6) and HSQC Spectrum (600 MHz, C_6D_6) of Compound 2.87

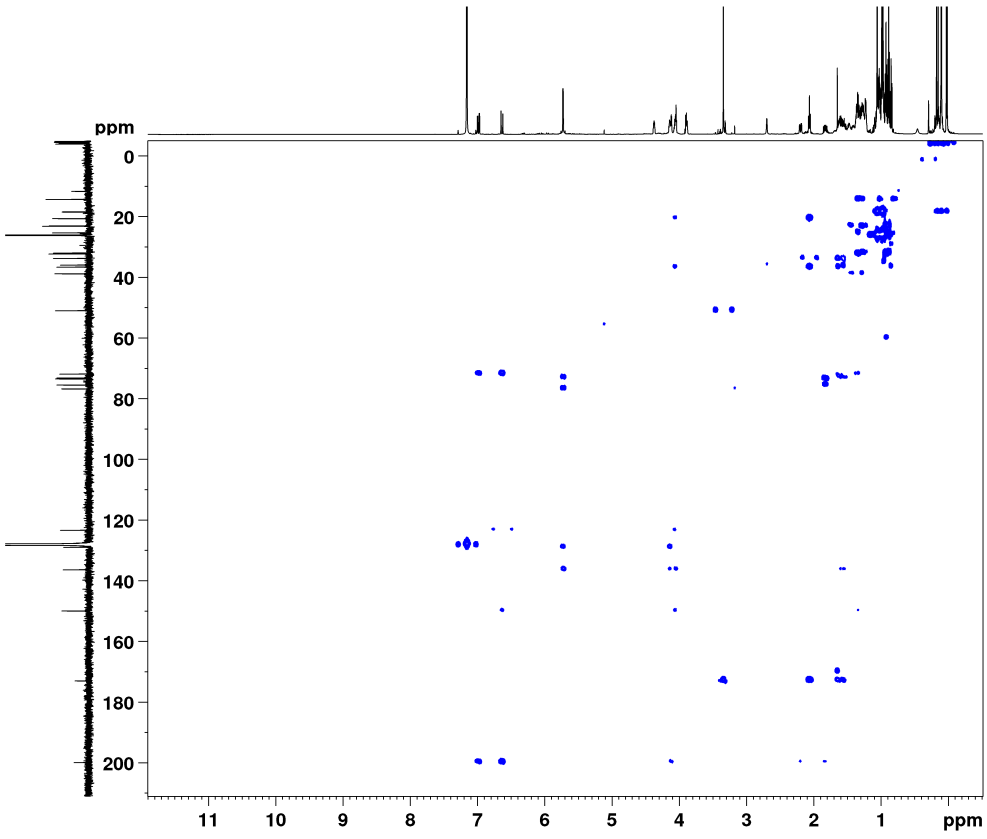


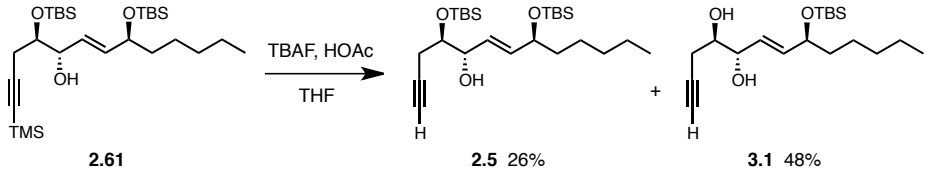
Figure A1.33: HMBC Spectrum (600 MHz, C_6D_6) of Compound 2.87

CHAPTER 3

THE CHEMICAL SYNTHESIS OF HKE_2 and d_{11}-HKE_2

Completion of HKE_2 Synthesis

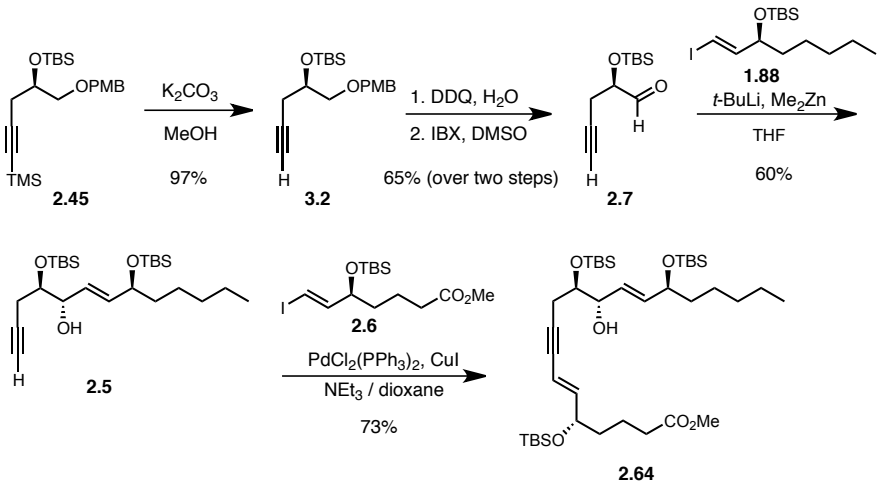
Following the success of the model system, we focused our efforts on resolving the silyl migration problem in the HKE_2 synthesis. Using the method we had employed for the model system, allylic alcohol **2.61** was subjected to acetic acid-buffered TBAF and, to our dismay, we were only able to arrive at the desired alkyne **2.5** in low yield. The major side product isolated from this reaction sequence was diol **3.1** as a result of desilylation of the TBS group at C11.



Scheme 3.1: AcOH-buffered TBAF Results in Loss of TBS Group

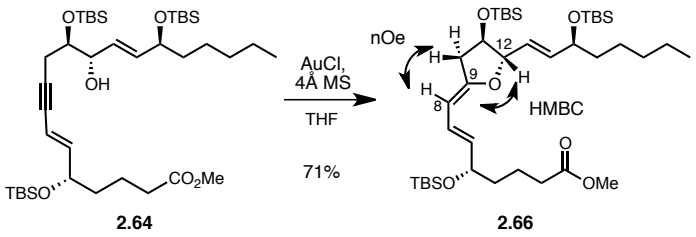
In order to optimize this reaction sequence, we determined that removal of the TMS group earlier in the synthesis would be beneficial, so as to avoid both the possibility of silyl migration and the low yield of desilylation. Therefore, starting from TMS alkyne **2.45**, basic removal of the TMS group afforded free alkyne **3.2**. Deprotection of the PMB ether with DDQ provided an intermediate alcohol that could not be separated from the byproducts by chromatography. Thus, the crude residue was oxidized with IBX to provide alkynyl aldehyde

2.7. Formation of the vinyl lithiate of **1.88**, followed by transmetallation with dimethyl zinc and addition of aldehyde **2.7** provided the desired allylic alcohol **2.5** as a single diastereomer. Although lower than the TMS-alkyne route, the yield was acceptable for our purposes and allowed us to circumvent the major issues we had previously observed. Sonogashira coupling with vinyl iodide **2.6** provided the desired carbon framework **2.64** in good yield.



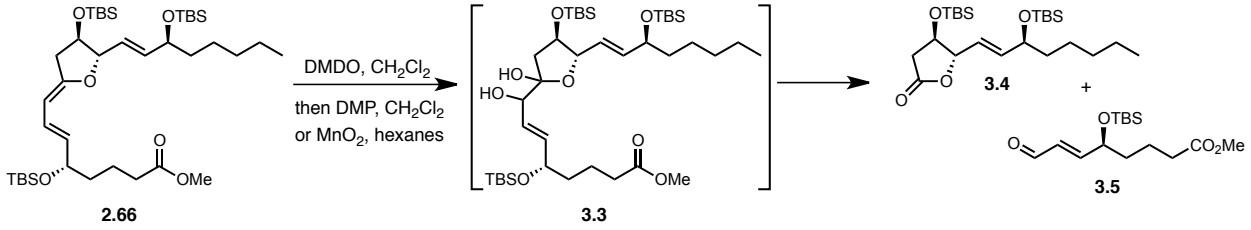
Scheme 3.2: Synthesis of Correct Alkynol 2.60

Next, we investigated whether alkynol **2.64** would undergo a 5-*exo* or 6-*endo* cyclization. Gratifyingly, when **2.64** was treated with AuCl, the 5-*exo* cyclizaton product **2.62** was observed in high yield. Furthermore, HMBC analysis indicated the expected cross peak between H12 and C9. Additionally, 1D NOE experiments showed correlation between H8 and the diastereotopic hydrogens of C10, suggesting that the olefin generated from the cyclization was in the *Z*-configuration.



Scheme 3.3: Au-catalyzed Cycloisomerization Yields 5-*exo* Product

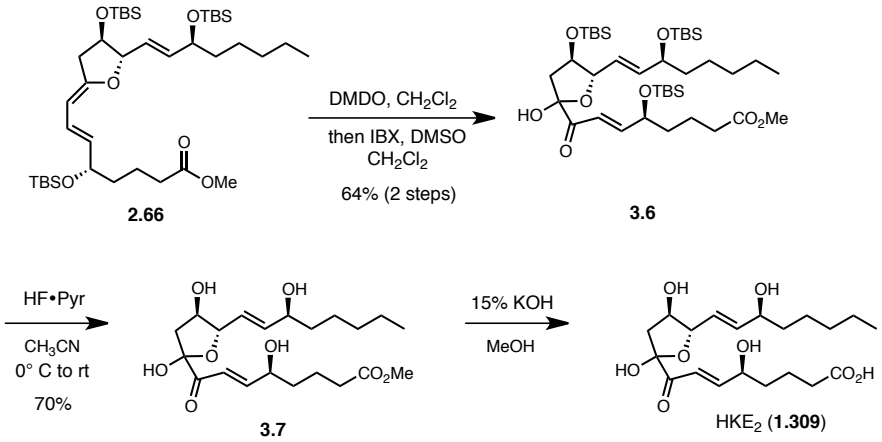
Next, we sought to see if model system conditions for the oxidation sequence would apply to the *5-exo* product **2.66**. Treatment of the vinyl ether **2.66** with DMDO affords a more polar product that, when oxidized with Dess-Mertin periodinane (DMP), led to the isolation of two products. Upon NMR analysis, it was obvious that the periodinane had induced diol cleavage to afford lactone **3.4** and aldehyde **3.5**.[1] Furthermore, the same cleavage was observed when MnO_2 was used as the oxidant.



Scheme 3.4: Dess-Martin Periodinane Causes Diol Cleavage

However, use of IBX as the oxidant resulted in the production of the keto hemiketal as **3.6** as a mixture of hemiketal diastereomers (Scheme 3.5). This observation is not surprising, as Schneider and coworkers observed two isomers of HKD_2 and HKE_2 during the initial isolation whose ratio was solvent dependent.[2] Interestingly, the vinyl ether **2.66** is rather sensitive and upon standing at room temperature for several hours in $CDCl_3$ will readily decompose.

Therefore, the entire sequence must be performed in rapid succession. Upon successfully producing fully protected HKE_2, attention was turned toward deprotection. After screening several conditions, desilylation was realized with HF pyridine complex to afford methyl ester **3.7**. Basic hydrolysis with KOH completed the first synthesis of HKE_2.



Scheme 3.5: Completion of the Total Synthesis of HKE_2

Comparison of the NMR spectra of synthetic HKE_2 and HKE_2 isolated from Schneider and coworkers is shown in Figure 3.1. The spectral data was in agreement with that published in the literature,[3] thereby confirming we had synthesized the desired hemiketal.

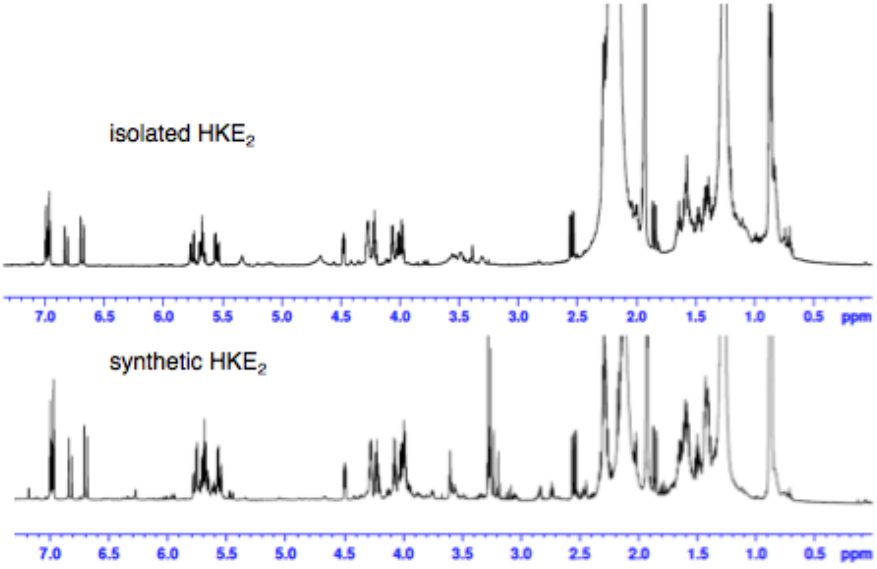
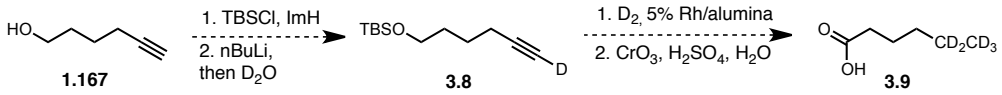


Figure 3.1: Comparison of Isolated and Synthetic HKE_2

Efforts toward the Synthesis of d_{11}-HKE_2

With the synthesis of HKE_2 complete, we hoped to apply this synthetic route toward the generation of analogs that would help uncover more information about the interesting biological properties of these molecules. Primarily, we were interested in accessing a polydeuterated version of HKE_2 that would allow for quantification of hemiketals in biological assays.[4]

Based upon Nicolaou's work toward the synthesis of pentadeuterated lipoxins, we attempted to synthesize d_5-heaxanoic acid en route to d_5-HKE_2.[4] While we could access the hexanoic acid derivative **3.9** in acceptable yield, MS analysis (Figure 3.2) revealed that the deuterium incorporation was insufficient for our purposes, as the hexanoic acid sample contained a mixture of d_0-d_5 isomers. Of these isomers, the most concerning was the d_0 isomer which would cause significant error in quantifying HKE_2.



Scheme 3.6: Synthetic Proposal for d_5-Hexanoic Acid

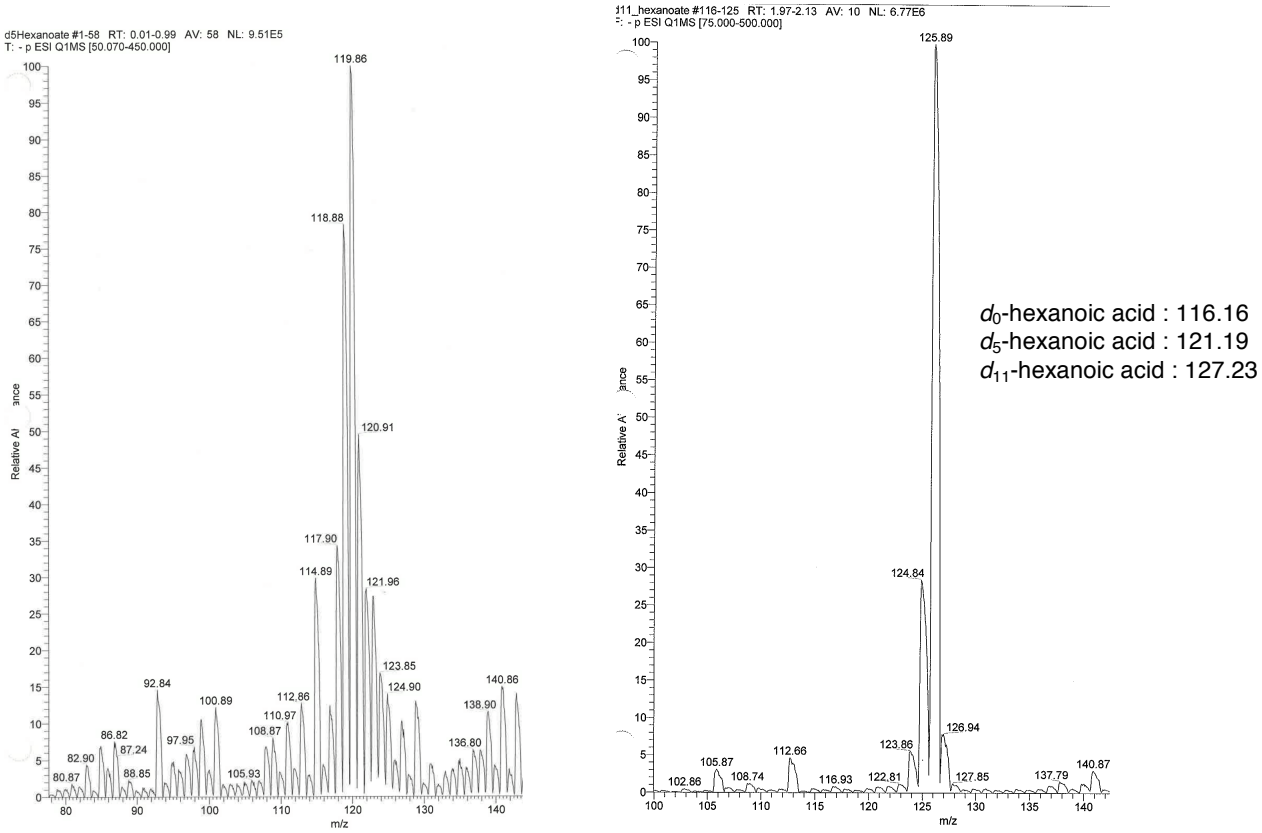
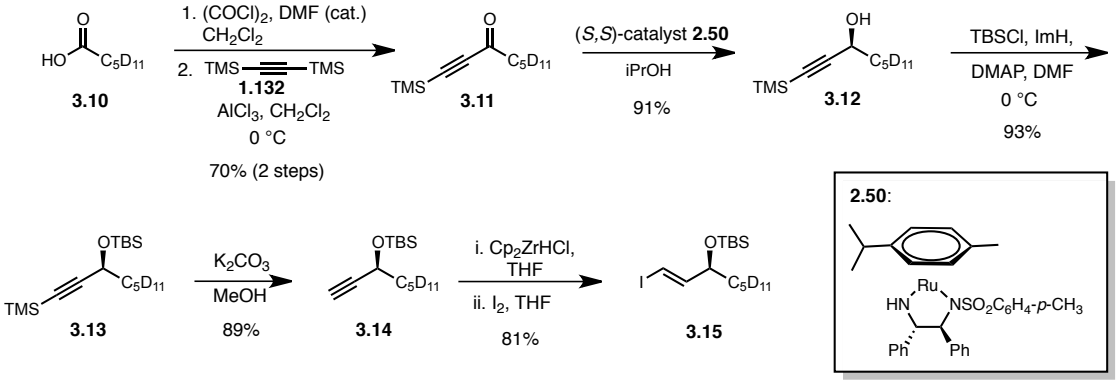


Figure 3.2: MS Analysis of d_5-Hexanoic Acid (left) and d_{11}-Hexanoic Acid (right)

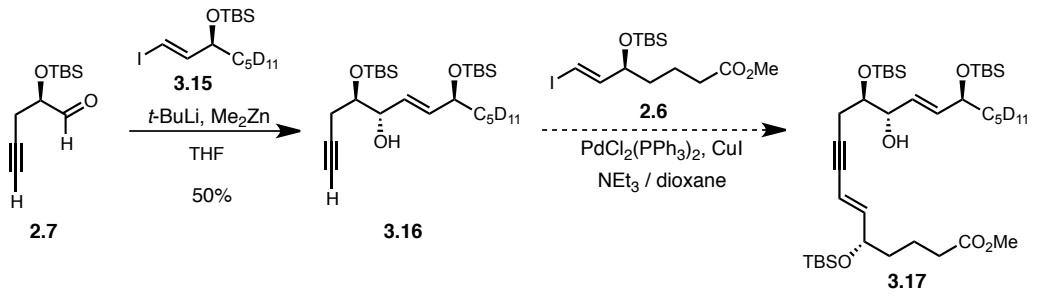
Therefore, we decided to start from commercially available d_{11}-hexanoic acid (**3.10**) (Scheme 3.7), the MS analysis of which showed no presence of d_0-hexanoic acid (Figure 3.2). Conversion to the acid chloride using oxalyl chloride and catalytic DMF was followed by

addition of bis(trimethylsilyl)acetylene (**1.132**) to the crude acid chloride to provide the desired alkynone **3.11** in good yield over two steps. Noyori's asymmetric hydrogen transfer using ruthenium catalyst **2.50** provided propargyl alcohol **3.12** in good yield. Silylation of the alcohol provided TMS alkyne **3.13**, which was desilylated to afford alkyne **3.14**. A hydrozirconation / iodination sequence then provided the required vinyl iodide **3.15** in good yield.



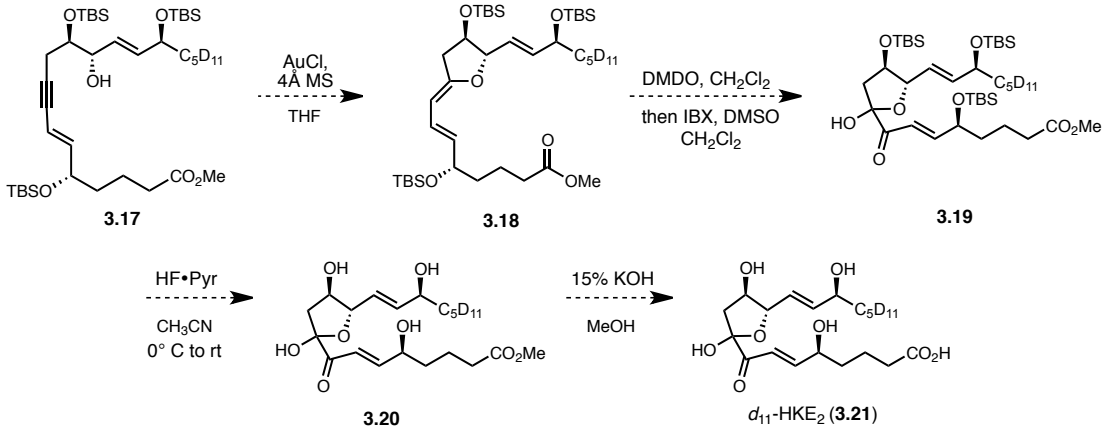
Scheme 3.7: Synthesis of d_{11}-C13-C20 Vinyl Iodide

With the vinyl iodide fragment complete, we now focused on generation of the d_{11}-carbon backbone of HKE_2. Felkin-Anh controlled carbonyl addition of the zincate of vinyl iodide **3.15** to aldehyde **2.5** (from the HKE_2 synthesis) provided allylic alcohol **3.16**, albeit in modest yield. Sonnogashira coupling with vinyl iodide **2.6** (also from the HKE_2 synthesis) would provide the carbon framework of d_{11}-HKE_2 (**3.17**).



Scheme 3.8: Synthesis of d_{11}-Alkynol 3.17

All that remains to complete the synthesis of d_{11}-HKE$_2$ is successful cycloisomerization / oxidation sequence followed by global deprotection. Treatment of alkynol **3.17** with AuCl will hopefully provide vinyl ether **3.18** and, after oxidation to the diol and subsequent oxidation to the enone, will produce keto hemiketal **3.19**. Desilylation with HF pyridine complex and basic hydrolysis of the ester should provide d_{11}-HKE$_2$ (**3.21**).



Scheme 3.9: Proposal for the Completion of d_{11}-HKE$_2$

Thus, the lessons learned from our model system studies have allowed us to achieve the first total synthesis of HKE$_2$. Furthermore, the flexibility of our synthetic approach and the broad

application of the reaction sequence has allowed us to make significant progress in the synthesis of a polydeuterated analog of HKE_2 that will aid in the biological studies of the hemiketal compounds.

Experimental Methods

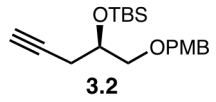
General Procedure: All non-aqueous reactions were performed in flame-dried or oven dried round-bottomed flasks under an atmosphere of argon. Stainless steel syringes or cannula were used to transfer air- and moisture-sensitive liquids. Reaction temperatures were controlled using a thermocouple thermometer and analog hotplate stirrer. Reactions were conducted at room temperature (rt, approximately 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 F_{254} glass-backed pre-coated silica gel plates. The plates were visualized with UV light (254 nm) and developed in an iodine chamber or stained with potassium permanganate or *p*-anisaldehyde-sulfuric acid followed by charring. Yields were reported as isolated, spectroscopically pure compounds.

Materials: Solvents were obtained from either an MBraun MB-SPS solvent system or freshly distilled (tetrahydrofuran was distilled from sodium-benzophenone; toluene was distilled from calcium hydride and used immediately; dimethyl sulfoxide was distilled from calcium hydride and stored over 4 Å molecular sieves). Unless indicated, all commercial reagents were used as received without further purification. The (*S*,S)-Co(salen) catalyst was synthesized according to the procedure reported by Jacobsen.[5] Ru-(*S*,*S*)-TsDPEN catalyst was synthesized according to

the procedure reported by Noyori.[6] The molarity of *n*-butyllithium solutions was determined by titration using diphenylacetic acid as an indicator (average of three determinations).

Instrumentation: ^{1}H NMR spectra were recorded on Bruker 400, 500, or 600 MHz spectrometers and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded on Bruker 100, 125, or 150 MHz spectrometers and are reported relative to deuterated solvent signals. IR Spectra were recorded on a Nicolet Avatar 360 spectrophotometer and values are reported in wavenumbers (cm^{-1}). Compounds were analyzed as neat films on a NaCl plate (transmission). Optical rotations were measured on a Perkin-Elmer 341 digital polarimeter at ambient temperature. High-resolution mass spectra were obtained from the Department of Chemistry and Biochemistry, University of Notre Dame.

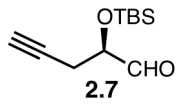
Compound preparation:



3.2

Alkyne 3.2: To a solution of silane **2.45** (1.00 g, 2.46 mmol) in MeOH (25 mL) was added K_2CO_3 (0.340 g, 2.46 mmol). The reaction was allowed to stir at room temp for 5 h. The MeOH was removed *in vacuo* and the resulting residue was dissolved in H_2O (10 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 2% EtOAc in hexanes) to yield 0.795 g (97%) of **5** as a colorless oil: $[\alpha]_D^{20}$ = + .707° (*c* 2.45, $CHCl_3$); IR (neat) ν_{max} = 3310, 3000, 2954, 2930, 2857, 2360, 2122, 1615, 1587, 1514 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.7 Hz, 2H), 6.87

(d, J = 8.7 Hz, 2H), 4.48 (s, 2H), 3.93-3.99 (m, 1H), 3.81 (s, 3H), 3.48 (dd, J = 5.4, 9.7 1H), 3.45 (dd, J = 5.4, 9.7 Hz, 1H), 2.47 (ddd, J = 2.7, 5.9, 16.7 Hz, 1H), 2.35 (ddd, J = 2.7, 6.0, 16.7 Hz, 1H), 1.95 (app t, J = 2.7 Hz, 1H), 0.89 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 130.4, 129.1 (2 C), 113.6 (2 C), 81.4, 73.2, 73.0, 70.2, 69.7, 55.2, 25.7 (3 C), 24.6, 18.1, -4.61, -4.70; HRMS (ESI) calc'd for $C_{19}H_{30}NaO_3Si$ $[M+Na]^+$: 357.1862; found: 357.1854.

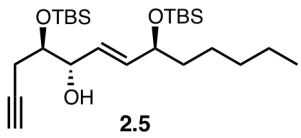


2.7

Aldehyde 2.7: To a solution of ether **3.2** (1.65 g, 4.90 mmol) in CH_2Cl_2 (50 mL) was added DDQ (1.22 g, 5.39 mmol) and H_2O (6 mL). The reaction was allowed to stir for 1.5 h at rt, during which time the color changed from dark green to red-orange. The reaction mixture was filtered through a pad of Celite and the resulting yellow mixture was washed with 10% aq. $NaHCO_3$ (50 mL) and H_2O (2 x 100 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The reaction product was not purified but used directly in the next reaction.

To a solution of crude alcohol **6** in CH_2Cl_2/DMSO (100 mL, 1:1) at 0 °C was added IBX (1.52 g, 5.42 mmol). The reaction stirred at 0 °C for 1 h, was subsequently allowed to warm to room temp, and stirred at that temperature for 16 h. The mixture was diluted with CH_2Cl_2/H_2O (100 mL) and the aqueous layer extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with H_2O (2 x 100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, gradient of 1-2% Et_2O in hexanes) to afford 0.830 g (78 % over two steps) of aldehyde **7** as a light yellow oil: $[\alpha]_D^{20}$ = +17.9 (*c* 1.28, $CHCl_3$); IR (neat) ν_{max} = 3313, 2955, 2930, 2898, 2858, 2180, 2124, 1740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (d, J = 1.2 Hz, 1H), 4.11 (ddd, J = 1.2, 5.7, 6.9 Hz,

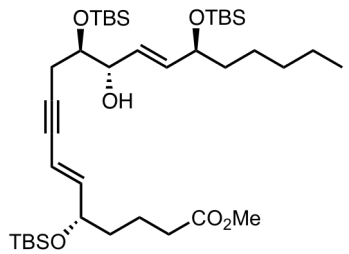
1H), 2.59 (ddd, *J* = 2.7, 5.7, 16.9 Hz, 1H), 2.48 (ddd, J = 2.7, 7.0, 16.9 Hz, 1H), 0.93 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 79.2, 75.7, 70.8, 25.6 (3 C), 23.0, 18.1, -4.85, -4.89; HRMS (ESI) calc'd for $C_{11}H_{20}NaO_2Si$ $[M+Na]^+$: 235.1131; found: 235.1112.



2.5

Alcohol 2.5: To a solution of vinyl iodide **1.88** (2.69 g, 7.30 mmol) in THF (14 mL) at -78°C was added a solution of *t*-BuLi (8.6 mL, 14.6 mmol, 1.7 *M* in pentane) dropwise. The mixture was allowed to stir at -78 °C for 1.5 h, at which point a solution of Me_2Zn (4.40 mL, 4.40 mmol, 1.0 *M* in heptane) was added dropwise. The reaction mixture was stirred at -78 °C for 15 min, at which point a solution of aldehyde **2.7** (0.620 g, 2.92 mmol) in THF (12 mL) was added dropwise. The reaction stirred at -78 °C for 3 h and was subsequently quenched by addition of sat. aq. NH_4Cl (10 mL). The mixture was extracted with Et_2O (3 x 15 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, gradient of 1-4% EtOAc in hexanes) to provide 0.806 g (61%) of alcohol **9** as a pale yellow oil. $[\alpha]_D^{20}$ = -8.49 (*c* 3.24, $CHCl_3$); IR (neat) ν_{max} = 3429, 2954, 2856, 1635, 1471 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (dd, *J* = 5.9, 15.5 Hz, 1H), 5.60 (dd, *J* = 6.5, 15.5 Hz, 1H), 4.22-4.26 (m, 1H), 4.12 (app q, *J* = 5.9 Hz, 1H), 3.89 (ddd, *J* = 3.2, 6.5, 6.5 Hz, 1H), 2.36 (ddd, *J* = 2.7, 6.8, 16.9 Hz, 1H), 2.28 (ddd, *J* = 2.7, 6.2, 16.9 Hz, 1H), 2.08 (d, *J* = 5.2 Hz, 1H), 1.96 (app t, *J* = 2.7 Hz, 1H), 1.42-1.52 (m, 2H) 1.23-1.36 (m, 6H), 0.91 (s, 9H), 0.90 (s, 9H), 0.88 (app t, *J* = 7.0 Hz, 3H), 0.14 (s, 3H), 0.12 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 126.5, 81.5, 74.6, 74.3, 73.0, 70.3, 38.5, 32.0, 26.0 (3

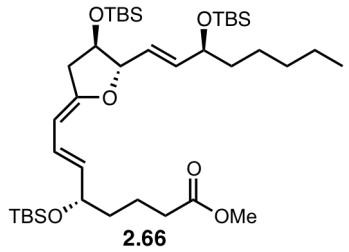
C), 25.9 (3 C), 25.0, 22.8 (2 C) 18.4, 18.2, 14.2, -4.16, -4.25, -4.56, -4.60. HRMS (ESI) calc'd for $C_{25}H_{50}NaO_3Si_2$ $[M+Na]^+$: 477.3196; found: 477.3221.



2.64

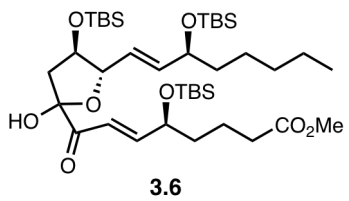
Enyne 2.64: To a solution of vinyl iodide (0.188 g, 0.472 mmol) in Et_3N/dioxane (1:1. 0.500 mL) was added $PdCl_2(PPh_3)_2$ (6.00 mg, 0.00858 mmol) and CuI (3.30 mg, 0.0172 mmol). The reaction stirred for 5 min at which point a solution of alkyne (0.195 g, 0.429 mmol) in Et_3N/dioxane (1:1. 0.500 mL) was added. The reaction stirred at rt for 12 h. The solvent was removed *in vacuo* and the resulting residue was taken up in Et_2O (5 mL) and H_2O (5 mL). The aqueous layer was extracted with Et_2O (2 x 5 mL) and the combined organic layers were washed with H_2O (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, gradient elution 0% to 5% Et_2O in hexanes) to afford 0.227 g (73%) of enyne **2.64** as a yellow oil. $[\alpha]_D^{20}$ = -25.0 (*c* 3.1, $CHCl_3$); IR (neat) ν_{max} = 3505, 2953, 2856, 2360, 2220, 1741 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 6.13 (dd, *J* = 5.8, 15.8 Hz, 1H), 5.89 (dd, *J* = 5.7, 15.4 Hz, 1H), 5.82 (dd, *J* = 1.4, 15.8 Hz, 1H), 5.80 (dd, *J* = 6.0, 15.6 Hz, 1H), 4.30-4.34 (m, 1H), 4.14 (app q, *J* = 5.8 Hz, 1H), 3.96-4.01 (m, 2H), 3.33 (s, 3H), 2.68 (ddd, *J* = 2.0, 7.3, 16.9 Hz, 1H), 2.58 (ddd, *J* = 1.9, 5.6, 16.9 Hz, 1H), 2.07 (app t, *J* = 7.3 Hz, 2H), 1.80 (d, *J* = 4.3 Hz, 1H), 1.56-1.70 (m, 4H), 1.36-1.49 (m, 2H), 1.22-1.35 (m, 6H), 1.04 (s, 9H), 0.99 (s, 9H), 0.96 (s, 9H), 0.91 (app t, *J* = 6.84 Hz, 3H), 0.16 (s, 3H), 0.14 (s, 3H), 0.14 (s, 3H), 0.12 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ173.1, 145.4, 136.9, 110.1, 88.5, 80.9, 75.3, 74.8, 73.4, 72.7, 60.0, 51.0, 38.8, 37.5, 33.9, 32.3, 26.2 (3C), 26.1 (3C), 26.0 (3C),

25.4, 24.4, 23.1, 20.9, 18.5 (2C), 18.4, 14.3, -3.93, -4.27, -4.30, -4.45, -4.52, -4.73. HRMS (ESI) calc'd for $C_{39}H_{76}NaO_6Si_3$ $[M+Na]^+$: 747.4847; found: 747.4828.



2.66

Vinyl Ether 2.66: To a solution of AuCl (0.64 mg, 0.00276 mmol) and powdered 4Å molecular sieves (150 mg) in THF (2.00 mL) was added a solution of alkyne **2.64** (20.0 mg, 0.0276 mmol) in THF (0.500 mL). The reaction stirred at rt for 30 min, over which time the solution changed color from light yellow to deep purple. The reaction was filtered to remove the molecular sieves and the sieves were washed with Et_2O (3 x 5 mL). The resulting filtrate was washed with sat. aq. $NaHCO_3$ (10 mL) and the aqueous layer extracted with Et_2O (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (pH = 7 buffered SiO_2, 50:1 hexanes: EtOAc) to provide 15.0 mg (75%) of furan **2.66** as a colorless oil. $[\alpha]_D^{20}$ = +3.44 (*c* 1.8, C_6D_6); IR (neat) ν_{max} = 2953, 2928, 2856, 1741, 1675 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 7.01 (dd, *J* = 10.9, 15.4 Hz, 1H), 5.98 (ddd, *J* = 1.0, 5.3, 15.4 Hz, 1H), 5.80 (ddd, *J* = 1.2, 6.4, 15.4 Hz, 1H), 5.66 (dd, *J* = 7.0, 15.5 Hz, 1H), 5.15 (d, *J* = 10.8 Hz, 1H), 4.68 (app t, *J* = 5.3 Hz, 1H), 4.26 (app q, *J* = 6.3 Hz, 1H), 4.20 (app q, *J* = 5.5 Hz, 1H), 4.10 (app q, *J* = 5.5, 1H), 3.44 (s, 3H), 2.70 (dd, *J* = 6.2, 16.1 Hz, 1H), 2.53 (dd, *J* = 5.4, 16.1 Hz, 1H), 2.24 (app t, *J* = 7.4 Hz, 2H), 1.69-1.77 (m, 2H), 1.46-1.65 (m, 6H), 1.26-1.42 (m, 9H), 1.15 (s, 9H), 1.13 (s, 9H), 1.01 (s, 9H), 0.27 (s, 3H), 0.22 (s, 3H), 0.22 (s, 3H), 0.21 (s, 3H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 173, 155, 137, 130, 126, 124, 98.8, 88.1, 75.2, 73.8, 72.4, 50.6, 38.5, 38.3, 38.2, 33.8, 31.9, 26.0, 25.9, 25.6, 24.9, 22.7, 21.1, 18.2, 18.1, 17.9, 14.0, -4.04, -4.31, -4.83, -4.86, -4.89, -4.94.

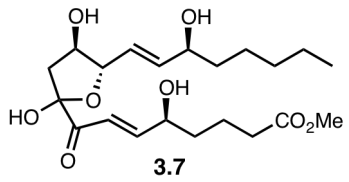


3.6

Hemiketal 3.6: A solution of vinyl ether **2.62** (21.0 mg, 0.0290 mmol) in CH_2Cl_2 (1.00 mL) was cooled to 0 °C. A solution of dimethyldioxirane (0.500 mL, 0.058 *M* solution in acetone, 0.0290 mmol,) was added dropwise. The reaction stirred for 2 min and was concentrated *in vacuo*. The reaction product was not purified but used directly in the next reaction.

The crude residue was taken up in CH_2Cl_2 (1.00 mL) and DMSO (1.00 mL) and cooled to 0 °C. IBX (16.0 mg, 0.0579 mmol) was added and the reaction was allowed to warm to rt and stirred for 6h. The reaction was diluted with CH_2Cl_2 and H_2O (1:1, 2 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with H_2O (3 x 5 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, gradient elution 2% to 5% EtOAc in hexanes) to yield 15.2 mg (70%) of an inseparable mixture of diastereomers of hemiketal **3.6** as a light yellow oil. $[\alpha]_D^{20}$ = -12.8 (*c* 2.3, $CHCl_3$); IR (neat) ν_{max} = 3482, 2955, 2858, 2360, 2340, 1741, 1704, 1635, 1471 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.12 (dd, *J* = 4.7, 15.5 Hz, 1H), 7.08 (dd, *J* = 4.8, 15.6 Hz, 1H), 6.85 (dd, *J* = 1.5, 15.5 Hz, 1H), 6.71 (dd, *J* = 1.5, 15.6 Hz, 1H), 5.76 (dd, *J* = 5.5, 15.4 Hz, 1H), 5.67-5.71 (m, 2H), 5.48 (ddd, *J* = 1.3, 6.5, 15.4 Hz, 1H), 4.63 (dd, *J* = 2.6, 6.4 Hz, 1H), 4.32-4.42 (m, 4H), 4.11-4.17 (m, 3H), 4.08 (app q, *J* = 5.7 Hz, 1H), 3.66 (s, 3H), 3.65 (s, 3H), 2.50 (dd, *J* = 5.9, 13.8 Hz, 1H), 2.32 (app t, *J* = 6.8 Hz, 4 H), 2.29 (dd, *J* = 6.9, 14.4 Hz, 1H), 2.19 (dd, *J* = 7.1, 13.2 Hz, 1H), 1.97 (dd, *J* = 2.9, 13.8 Hz, 1H) 1.64-1.72 (m, 4H), 1.56-1.62 (m, 4H), 1.40-1.50 (m, 4H), 1.24-1.29 (m, 12H), 0.92 (s, 9H), 0.91 (s, 9H), 0.90 (s, 9H), 0.89 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.07 (s, 6H), 0.06 (s, 3H), 0.04 (s, 3H), 0.03 (s, 6H), 0.03 (s, 3H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ

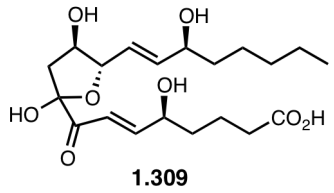
195.5, 193.3, 173.7, 173.6, 152.7, 151.9, 137.6, 136.7, 127.4, 125.8, 121.9, 120.9, 105.0, 103.0, 88.5, 87.3, 76.4, 72.4, 72.3, 71.6, 51.5, 51.4, 44.9, 41.8, 38.1, 38.0, 36.5, 36.4, 33.8, 31.8, 31.7, 26.1 (3C), 26.0 (3C), 25.9 (3C), 25.9 (3C), 25.8 (3C), 25.8 (3C), 24.9, 24.8, 22.7, 20.7, 20.6, 18.4 (2C), 18.3 (2C), 18.1, 18.0, 14.2, -4.12, -4.18, -4.34, -4.49, -4.51, -4.55, -4.61, -4.64, -4.66, -4.70, -4.72, -4.81.



3.7

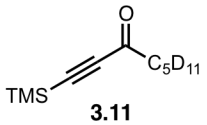
Methyl ester 3.7: To a solution of hemiketal **3.6** (21.0 mg, 0.0278 mmol) in CH_3CN (1.00 mL) at 0 °C was added HF•Pyr complex (0.020 mL) dropwise slowly. The reaction stirred at 0 °C for 3 h. The reaction was quenched with sat. aq. $NaHCO_3$ (2 mL) and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to yield. The resulting residue was purified by flash column chromatography (silica gel, gradient elution 0% to 6% MeOH in CH_2Cl_2) to provide 8.30 mg (72%) of an inseparable mixture of diastereomers of methyl ester **3.7** as a light yellow oil. When the NMR is recorded in $CDCl_3$, a 3:1 mixture of diastereomers is observed. When recorded in CD_3OD, a 1:1 mixture of diastereomers is observed. ^{1}H NMR (600 MHz, $CDCl_3$) δ major diastereomer 7.14 (dd, *J* = 3.6, 15.5 Hz, 1H), 6.79 (d, *J* = 15.4 Hz, 1H), 5-76-5.88 (m, 1H), 5.68 (dd, *J* = 5.5, 15.2 Hz, 1H), 4.82 (d, *J* = 3.9 Hz, 1H), 4.43-4.46 (m, 1H), 4.37-4.39 (m, 1H), 4.28-4.30 (m, 1H), 4.12-4.16 (m, 1H), 3.67 (s, 3H), 2.49 (dd, *J* = 5.5, 13.7 Hz, 1H), 2.37 (app t, *J* = 6.9 Hz, 2H), 2.07 (d, *J* = 13.6 Hz, 1H), 1.64-1.82 (m, 4H), 1.48-1.55 (m, 2H), 1.24-1.32 (m, 6H), 0.86-0.91 (m, 3H); δ minor diastereomer: 7.14 (dd, *J* = 3.6, 15.5 Hz, 1H), 6.96 (d, *J* = 15.6 Hz, 1H), 5-76-5.88 (m, 2H), 4.82 (d, *J* = 3.9 Hz, 1H), 4.43-4.46 (m, 1H), 4.37-4.39 (m, 1H), 4.28-4.30 (m, 1H), 4.12-4.16 (m, 1H), 3.67 (s, 3H), 2.37 (app t, *J* = 6.9 Hz, 2 H), 2.17-2.22 (m, 1H), 2.07 (d, *J* =

13.6 Hz, 1H), 1.64-1.82 (m, 4H), 1.48-1.55 (m, 2H), 1.24-1.32 (m, 6H), 0.86-0.91 (m, 3H); 1H NMR (600 MHz, CD_3OD) δ 7.01 (dd, *J* = 4.8, 15.7 Hz, 2H), 6.86 (dd, *J* = 1.5, 15.6 Hz, 1H), 6.80 (dd, *J* = 1.6, 15.7 Hz, 1H), 5.81 (dd, *J* = 6.0, 15.5 Hz, 1H), 5.76 (dd, *J* = 6.3, 17.8 Hz, 1H), 5.75 (dd, *J* = 6.4, 13.7 Hz, 1H), 5.64 (dd, *J* = 6.3, 15.5 Hz, 1H), 4.49 (app t, *J* = 5.8 Hz, 1H), 4.28-4.31 (m, 2H), 4.22-4.28 (m, 2H), 4.01-4.08 (m, 4H), 3.66 (s, 6H), 2.68 (dd, *J* = 7.2, 13.7 Hz, 1H), 2.37 (app t, *J* = 7.2 Hz, 2H), 2.37 (app t, *J* = 7.5 Hz, 2H), 2.33 (dd, *J* = 7.4, 13.2 Hz, 1H), 2.21 (dd, *J* = 6.4, 13.2 Hz, 2H), 1.93 (dd, *J* = 5.6, 13.7 Hz, 1H), 1.66-1.72 (m, 2H), 1.60-1.66 (m, 2H), 1.46-1.57 (m, 8H), 1.29-1.34 (m, 12H), 0.90-0.92 (m, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 195.5, 194.2, 174.4, 174.3, 152.4, 152.3, 137.2, 136.2, 129.0, 127.2, 121.0, 120.9, 104.6, 103.8, 88.6, 88.4, 76.4, 76.0, 72.2, 71.8, 70.9, 51.9, 43.5, 42.0, 37.2, 37.1, 36.9, 35.7, 35.6, 33.7, 33.6, 31.9, 29.9, 25.2, 22.8, 22.7, 20.7, 20.6, 14.3, 14.2.



1.309

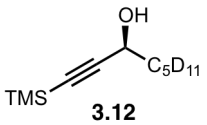
HKE_2 1.309: To a solution of methyl ester **3.7** (1.0 mg, 2.41 μmol) in MeOH (2 mL) was added 15 % KOH (2.0 mL, 5.2 mmol). The reaction stirred at rt for 2 min. The reaction was acidified to pH = 4 with 5 *N* HCl and the mixture was passed through a C18 cartridge. The cartridge was washed with H_2O and the desired acid was eluted with MeOH. The combined organic phases were concentrated. The resulting residue was purified by reverse phase HPLC (Symmetry C18, gradient elution, H_2O/Acetonitrile/Acetic Acid (80%/20%/0.01%) to (20%/80%/0.01%) over 25 minutes, 1 mL / min, $t_R(HKE_2)$ = 9.8 min) to afford **1.309**. The spectral data matched reported values.[3]



3.11

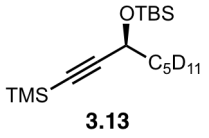
***d_{11}*-Alkyone 3.11**: To a solution of d_{11}-hexanoic acid (0.300 g, 2.36 mmol) in CH_2Cl_2 (5.00 mL) was added oxalyl chloride (0.222 mL, 2.59 mmol). DMF (0.001 mL, cat.) was added and gas evolution was observed. The reaction stirred for 30 min and was then concentrated *in vacuo*. The reaction product was not purified but used directly in the next reaction.

To a solution of $AlCl_3$ (0.408 g, 3.06 mmol) in CH_2Cl_2 (10.0 mL) at 0 °C was added a solution of crude acid chloride (0.343 g, 2.35 mmol) and bistrimethylsilylacetylene (0.400 g, 2.35 mmol) in CH_2Cl_2 (10.0 mL) via cannula over a period of 10 min. The resulting yellow solution was allowed to warm to rt over 30 min, at which point the reaction was cooled to 0 °C and quenched by slow addition of 1*N* HCl (10.0 mL). The resulting solution was extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, gradient elution, 1% to 5% EtOAc in hexanes) to afford 0.340 g (70 %) of alkynone **3.11** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.215 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.3, 102.2, 97.6, -0.066 (3C).



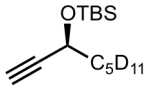
3.12

Alcohol 3.12: A mixture of alkynone **3.11** (0.335 g, 1.62 mmol) and Ru[(1*S*, 2*S*)-p-TsNCH(C_6H_5)CH(C_6H_5)NH](η^6-p-cymene) (0.068 g, 0.113 mmol) in 2-propanol (16.0 mL) was stirred at rt for 16 h. The mixture was concentrated *in vacuo* and the resulting residue was purified by flash column chromatography (silica gel, 2% EtOAc in hexanes) to provide 0.309 g (91 %) of alcohol **S2** as a faint yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (s, 1H), 2.03 (br s, 1H), 0.154 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 107.2, 89.3, 62.9, 0.00 (3C).



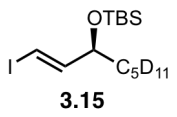
3.13

Silyl ether 3.13: To a solution of alcohol **3.12** (0.308 g, 1.47 mmol) in DMF (2 mL) at 0 °C was added TBSCl (0.443 g, 2.94 mmol), imidazole (0.300 g, 4.41 mmol), and DMAP (0.009 g, 0.0735 mmol). The reaction was allowed to stir at 0 °C for 2 h, at which point the reaction was quenched with H_2O (5 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 2% EtOAc in hexanes) to provide 0.444 g (93%) of silyl ether **3.13** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.30 (s, 1H), 0.906 (s, 9H), 0.152 (s, 9H), 0.131 (s, 3H), 0.109 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 108.2, 88.4, 63.5, 26.0 (3 C), 18.5, 13.9, 0.010 (3 C), -4.30, -4.76;



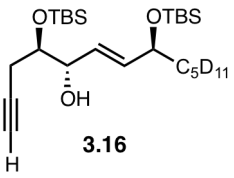
3.14

Alkyne 3.14: To a solution of silane **3.12** (0.440 g, 1.36 mmol) in MeOH (14.0 mL) was added K_2CO_3 (0.188 g, 1.36 mmol). The reaction was allowed to stir at rt for 1 h, at which point the MeOH was removed *in vacuo*. The resulting residue was taken up in H_2O (5 mL) and EtOAc (5 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 3% EtOAc in hexanes) to yield 0.305 g (89%) of alkyne **3.14** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (s, 1H), 2.36 (d, J = 2.08 Hz, 1H), 0.906 (s, 9H), 0.133 (s, 3H), 0.109 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 86.0, 72.0, 62.9, 26.0 (3C), 18.4, -4.44, -4.94.



3.15

Vinyl iodide 3.15: To a solution of alkyne **3.14** (0.250 g, 0.994 mmol) in CH_2Cl_2 (10.0 mL) was added zirconecene hydrochloride (0.513 g, 1.99 mmol) portion wise over 20 min. The mixture was allowed to stir at rt for 1 h, over which time the reaction changed from cloudy to clear. Iodine (0.278 g, 1.09 mmol) was added and the mixture changed color from light yellow to dark brown. The reaction was allowed to stir for 5 min, at which point the mixture was diluted with hexanes (10 mL) and filtered through a pad of Celite. The resulting solution was washed with sat. aq. $Na_2S_2O_3$ (2 x 15 mL) and brine (15 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, hexanes) to afford 0.306 g (81 %) of vinyl iodide **3.15** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (dd, *J* = 5.96, 14.4 Hz, 1H), 6.18 (dd, *J* = 1.10, 14.3 Hz, 1H), 4.05 (d, *J* = 5.76 Hz, 1H), 0.887 (s, 9H), 0.0420 (s, 3H), 0.0260 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 75.5, 75.2, 26.0 (3C), 18.4, -4.38, -4.73.



3.16

Alcohol 3.16: To a solution of vinyl iodide **3.15** (0.300 g, 0.791 mmol) in THF (2.00 mL) at -78 °C was added a solution of *t*-BuLi (1.30 mL, 1.58 mmol, 1.7 *M* in pentane) dropwise. The mixture was allowed to stir at -78 °C for 1.5 h, at which point a solution of Me_2Zn (0.400 mL, 0.400 mmol, 1.0 *M* in heptane) was added dropwise. The reaction mixture was stirred at -78 °C for 15 min, at which point a solution of aldehyde **2.7** (0.0670 g, 0.316 mmol) in THF (1.00 mL) was added dropwise. The reaction stirred at -78 °C for 3 h and was subsequently quenched by addition of sat. aq. NH_4Cl (5 mL). The mixture was extracted with Et_2O (3 x 10 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, gradient of 1-4% EtOAc in hexanes) to

provide 0.074 g (50%) of alcohol **3.16** as a clear, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (dd, *J* = 5.54, 15.6 Hz, 1 H), 5.60 (dd, *J* = 6.38, 15.5 Hz, 1 H), 4.21-4.26 (m, 1 H), 4.11 (app d, *J* = 5.44 Hz, 1 H), 3.89 (ddd, *J* = 3.17, 6.43, 6.43 Hz, 1 H), 2.36 (ddd, *J* = 2.64, 6.80, 16.8 Hz, 1 H), 2.28 (ddd, *J* = 2.64, 6.24, 16.8 Hz, 1 H), 2.08 (d, *J* = 4.59 Hz, 1 H), 1.96 (app t, *J* = 2.46 Hz, 1 H), 0.909 (s, 9 H), 0.895 (s 9 H), 0.136 (s, 3 H), 0.122 (s, 3 H), 0.0489 (s, 3 H), 0.0335 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 126.5, 81.5, 74.6, 74.3, 73.0, 70.3, 38.5, 32.0, 26.0 (3 C), 25.9 (3 C), 25.0, 22.8 (2 C) 18.4, 18.2, 14.2, -4.16, -4.25, -4.56, -4.60. HRMS (ESI) calc'd for $C_{25}H_{50}NaO_3Si_2$ $[M+Na]^+$: 477.3196; found: 477.3221.

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Appendix A2:

Spectra Relevant to Chapter 3

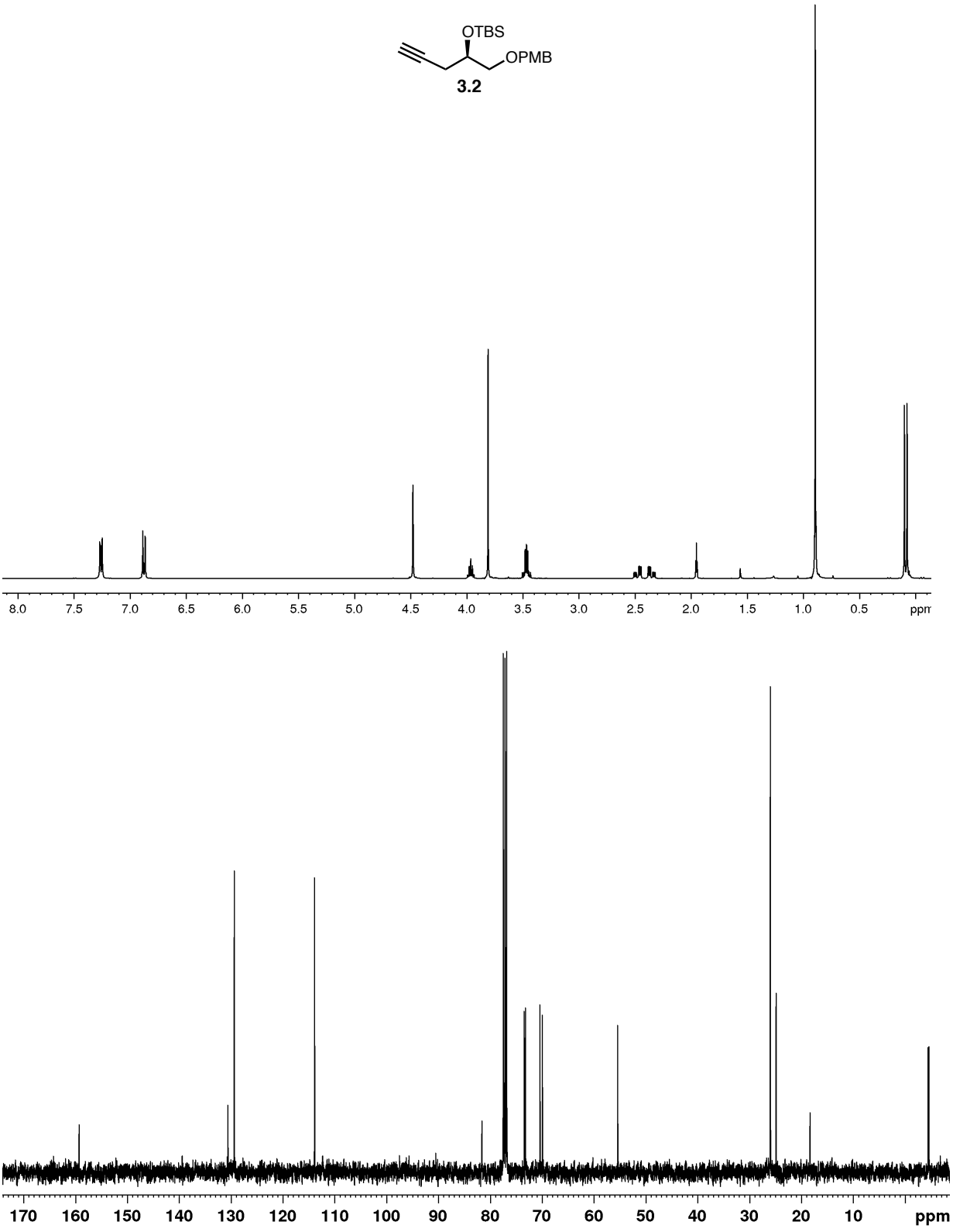


Figure A2.1: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of Compound 3.2

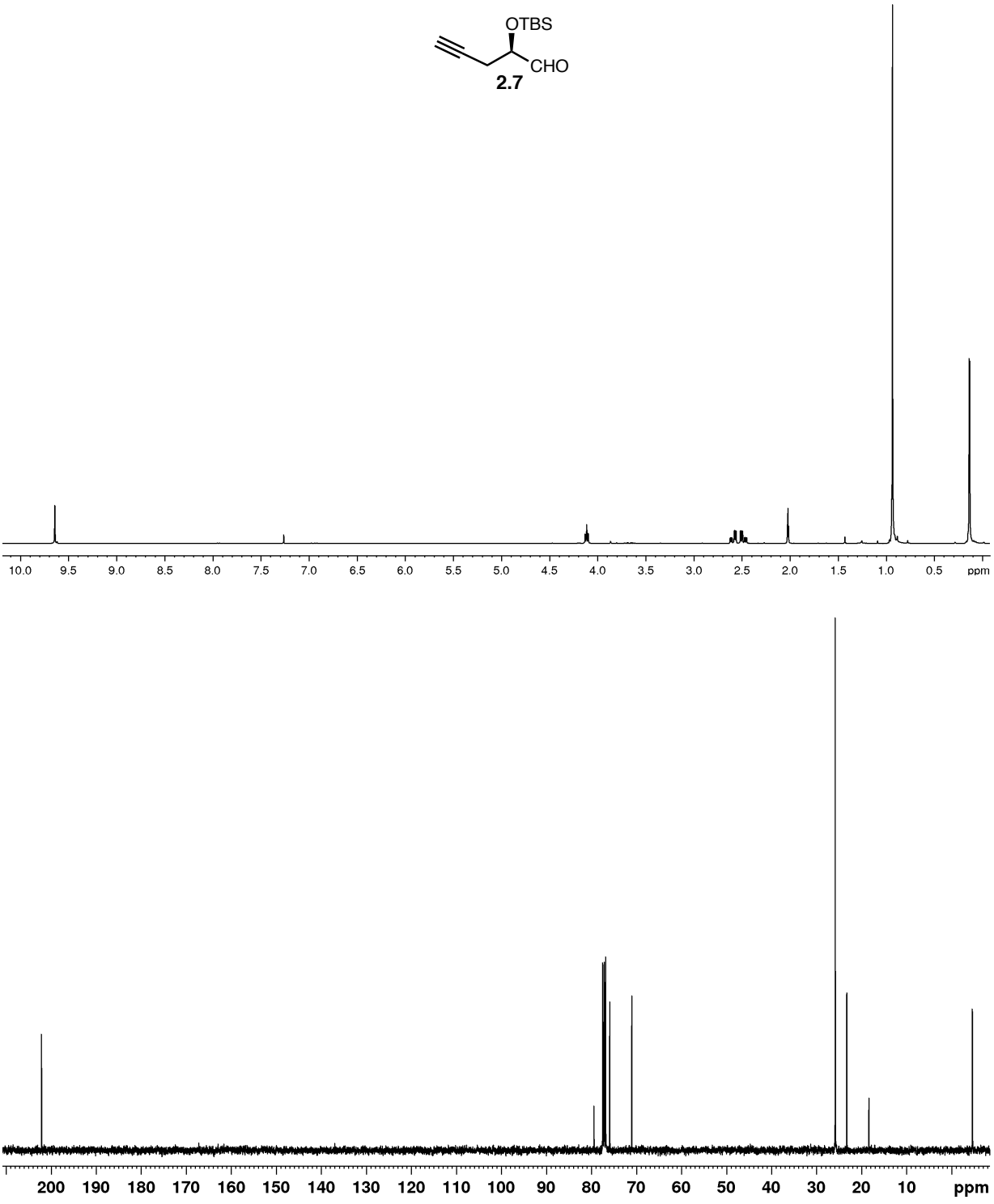


Figure A2.2: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of Compound 2.7

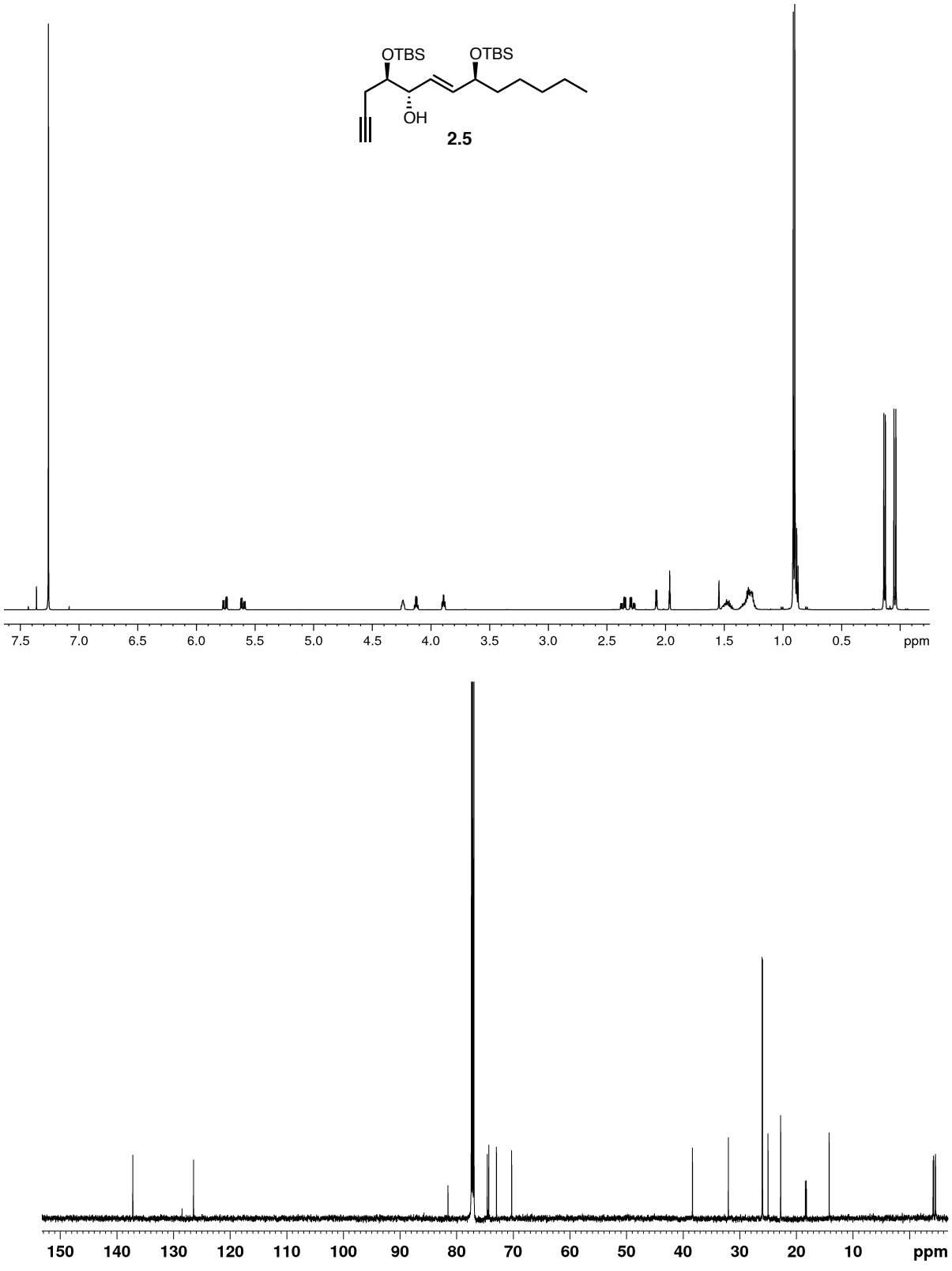


Figure A2.3: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of Compound 2.5

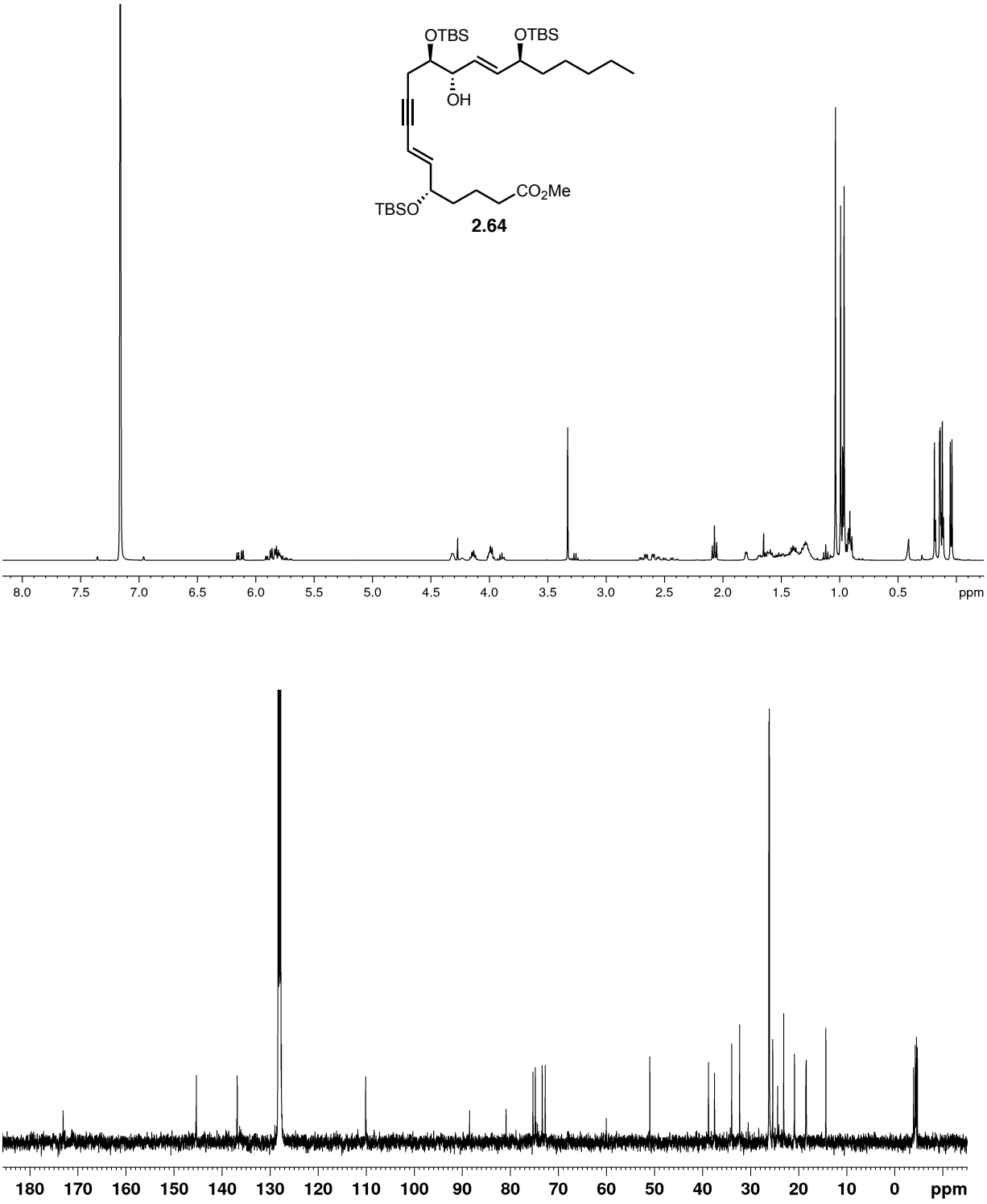


Figure A2.4: ^{1}H NMR (400 MHz, C_6D_6) and ^{13}C NMR (100 MHz, C_6D_6) of Compound 2.64

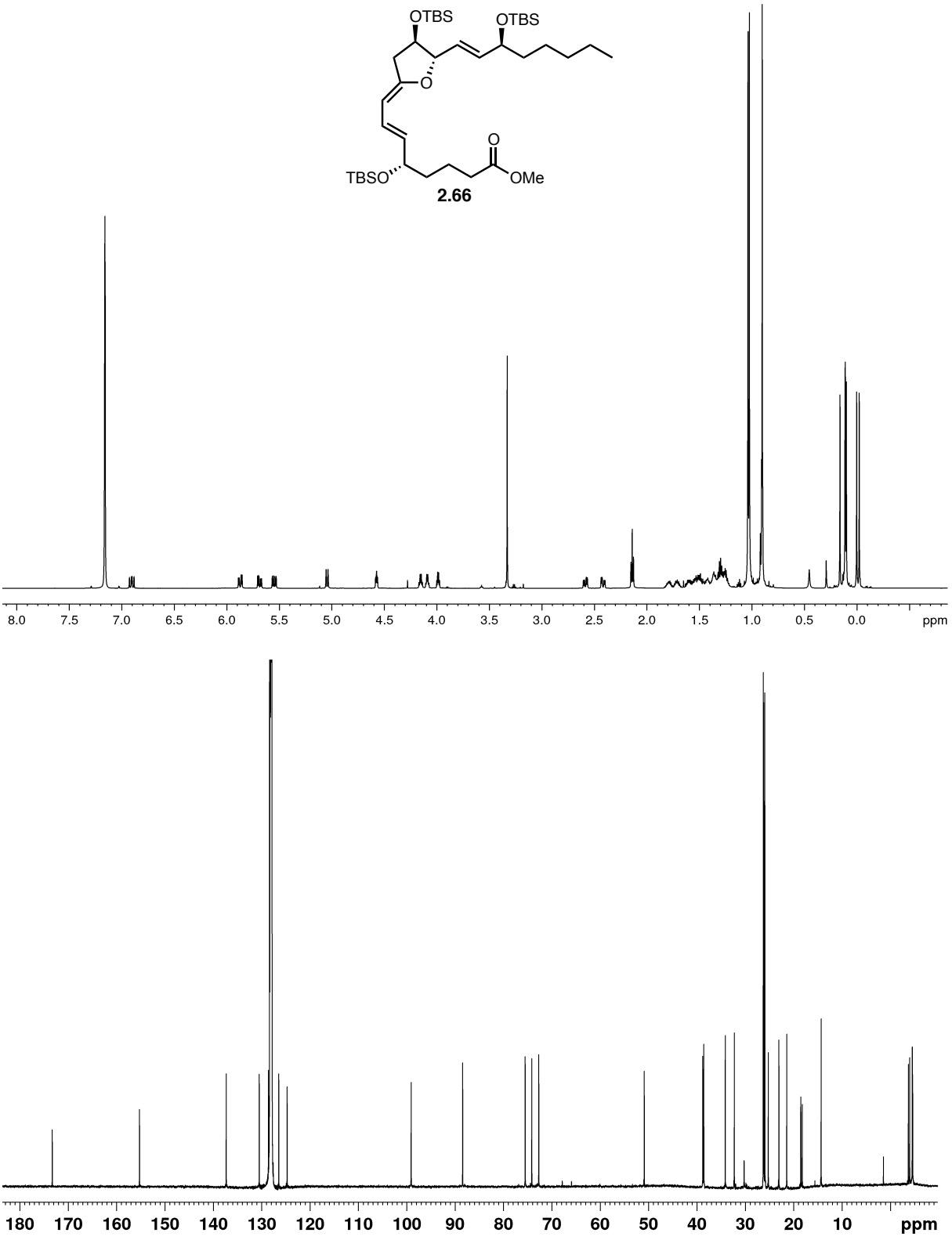


Figure A2.5: ^{1}H NMR (600 MHz, C_6D_6) and ^{13}C NMR (150 MHz, C_6D_6) of Compound 2.66

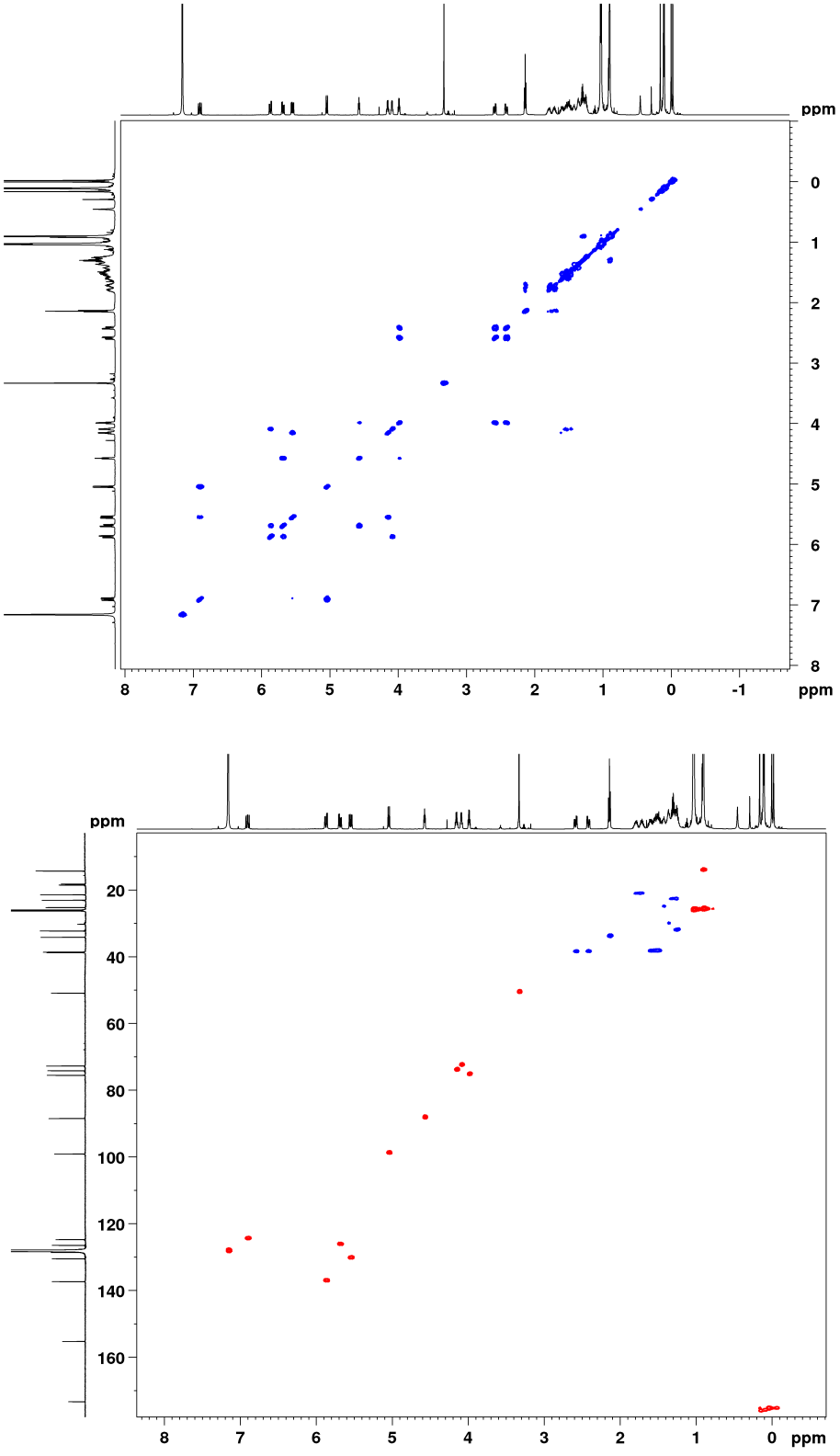


Figure A2.6: COSY Spectrum (600 MHz, C_6D_6) and HSQC Spectrum (600 MHz, C_6D_6) of Compound 2.66

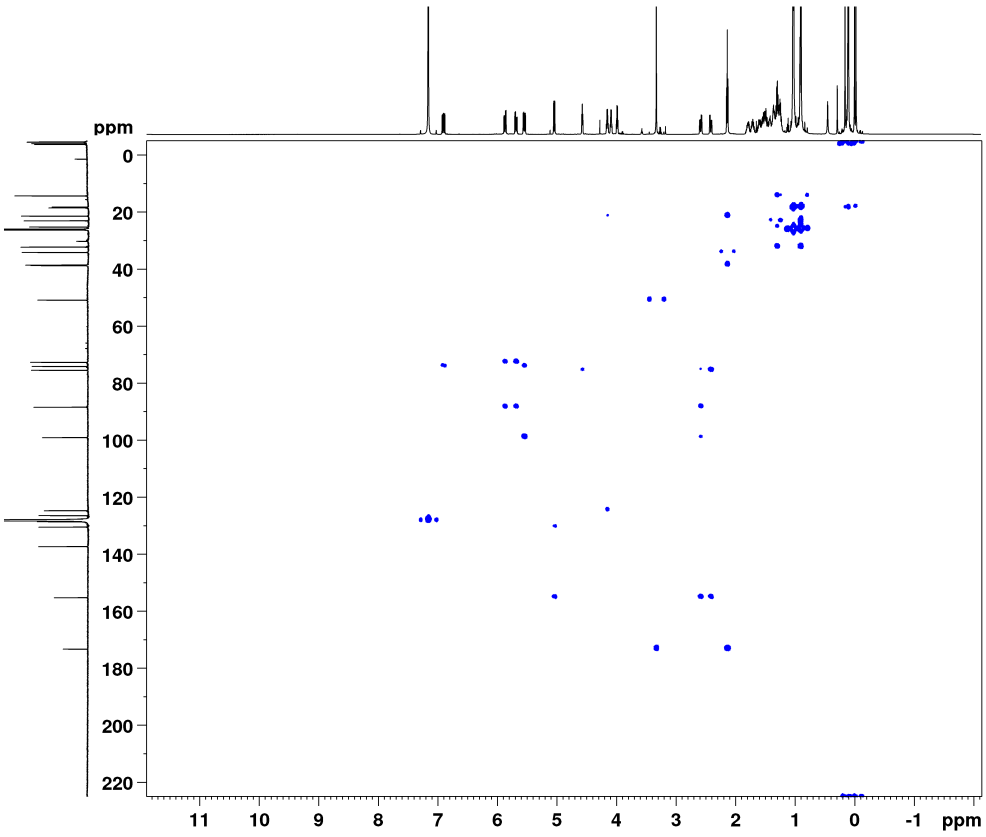


Figure A2.7: HMBC Spectrum (600 MHz, C_6D_6) of Compound 2.66

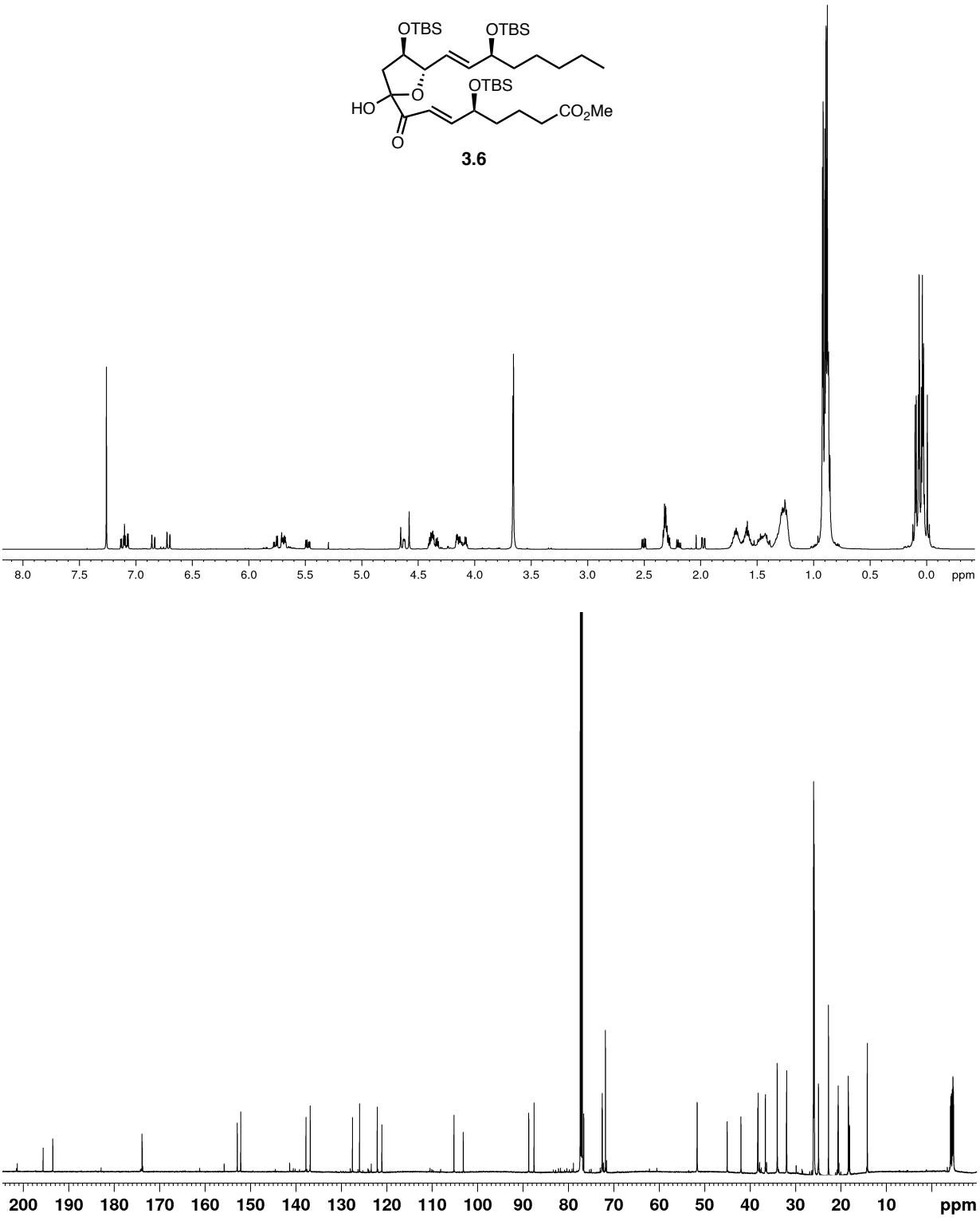


Figure A2.8: ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, CDCl3) of Compound 3.6

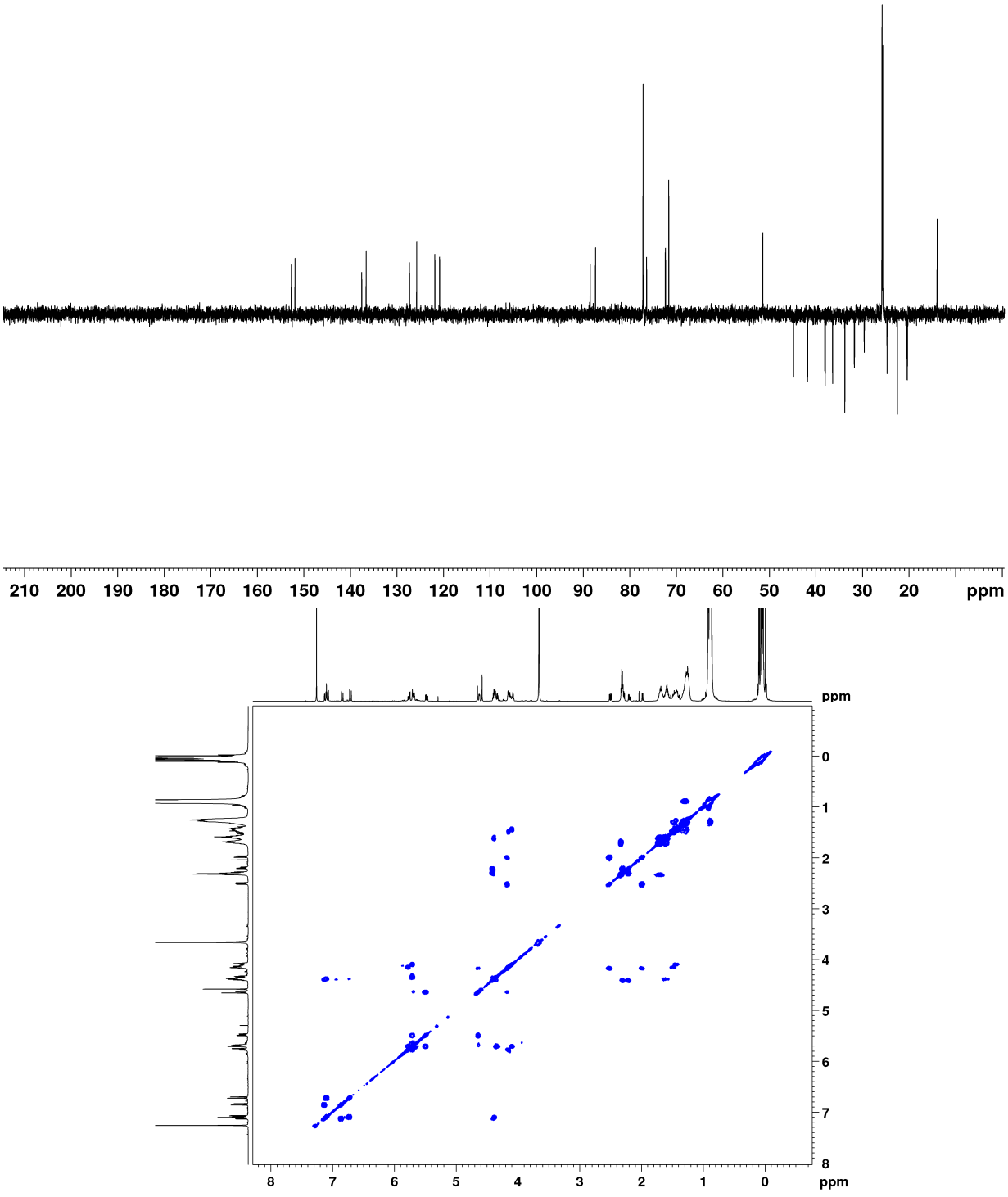


Figure A2.9: DEPT-135 NMR (150 MHz, $CDCl_3$) and COSY Spectrum (600 MHz, $CDCl_3$) of Compound 3.6

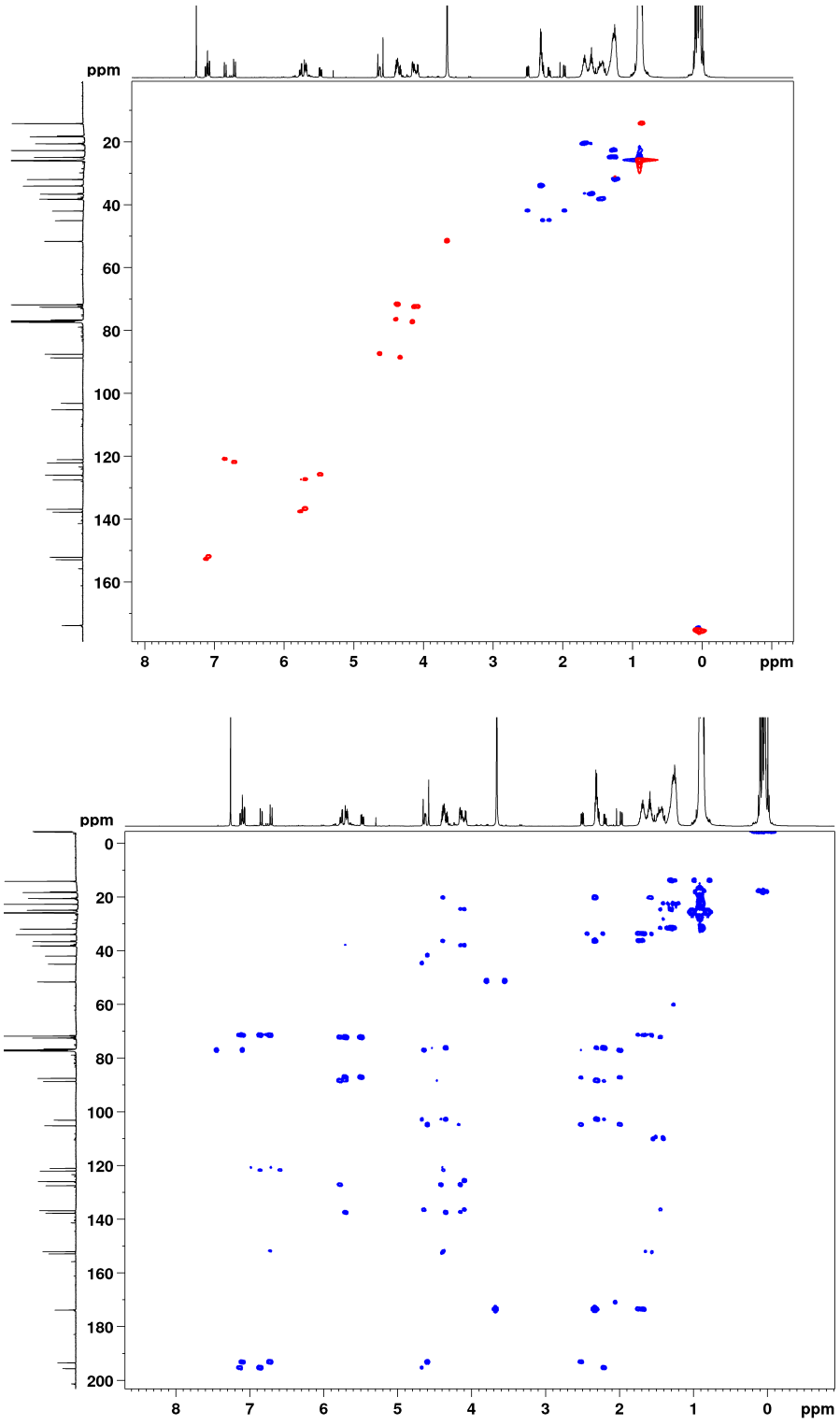


Figure A2.10: HSQC Spectrum (600 MHz, $CDCl_3$) and HMBC Spectrum (600 MHz, $CDCl_3$) of Compound 3.6

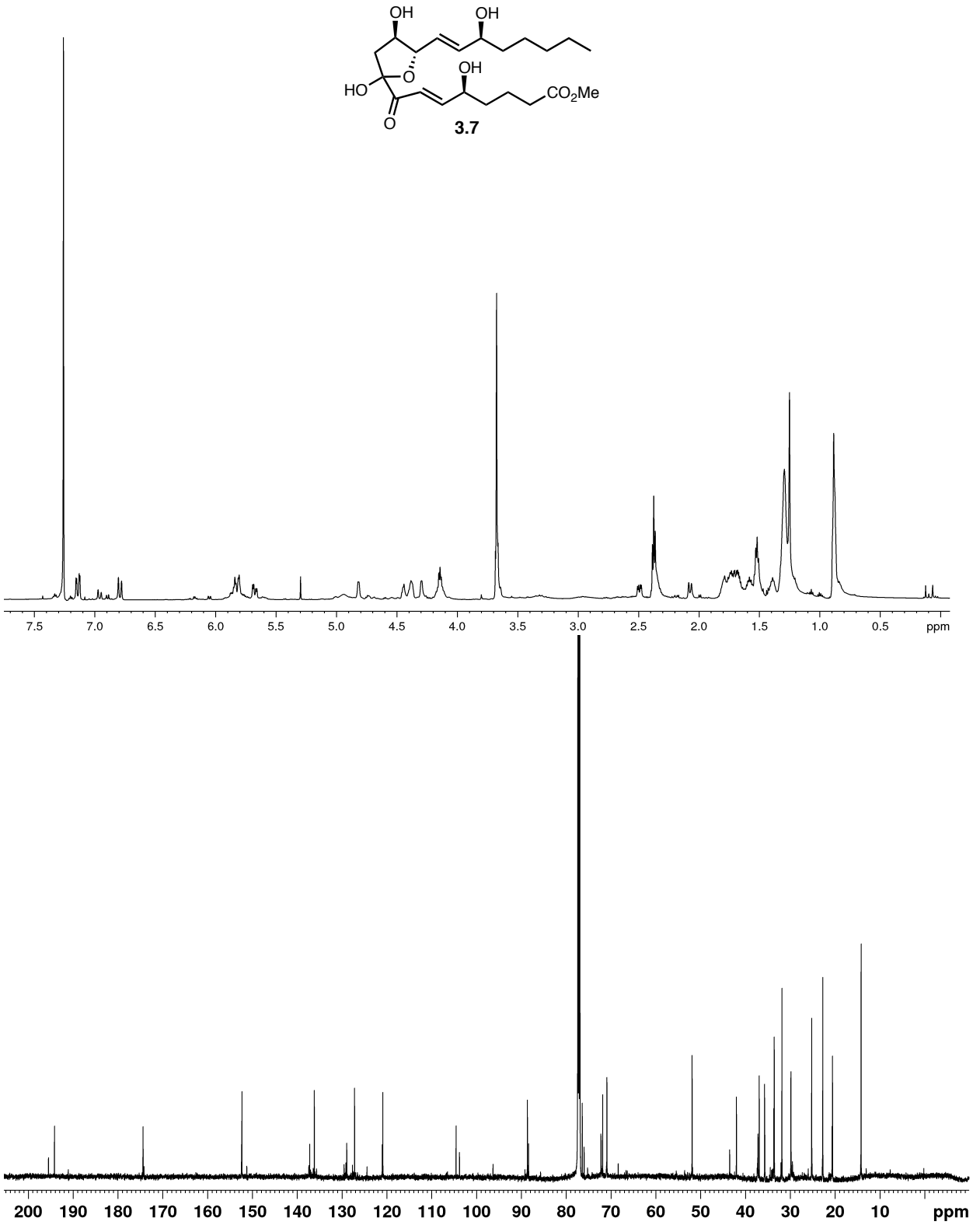


Figure A2.11: ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of Compound 3.7

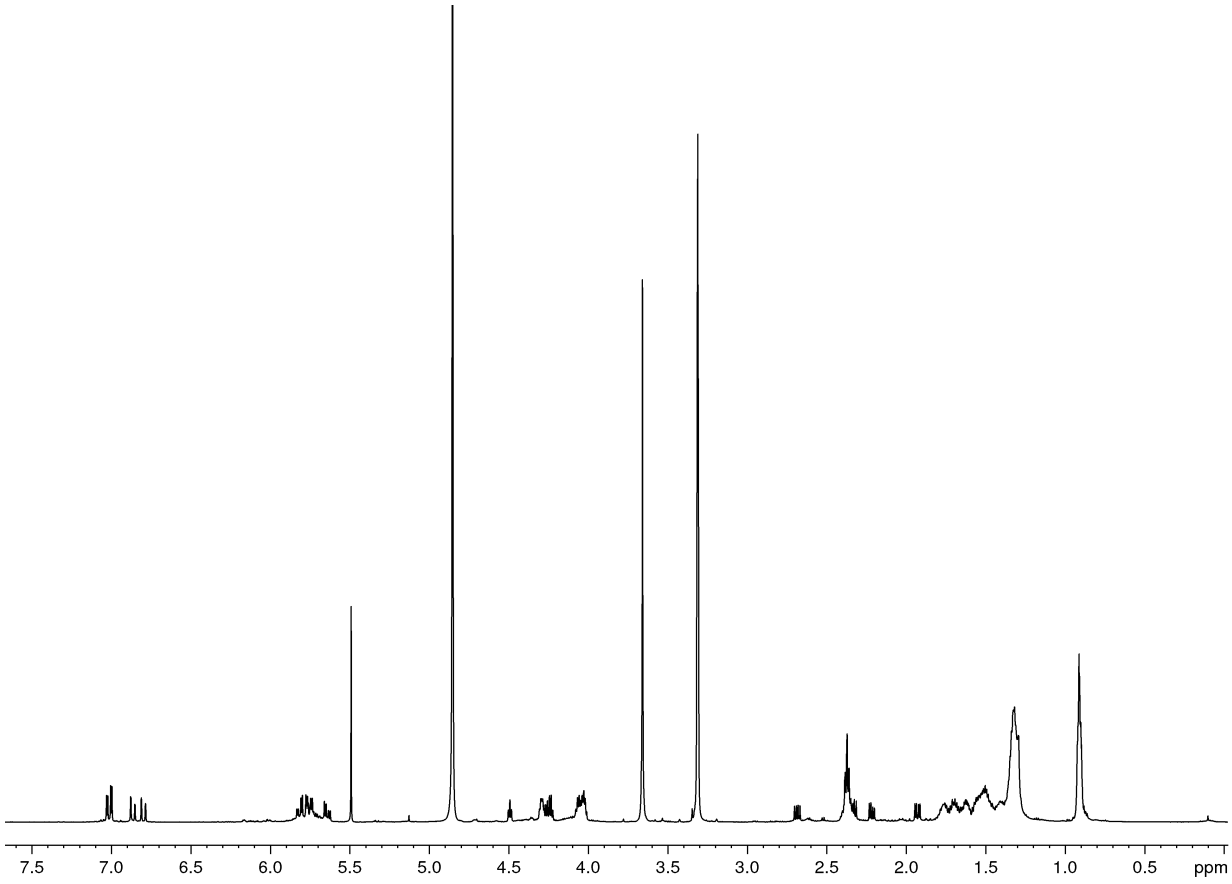


Figure A2.12: ^{1}H NMR (600 MHz, MeOD) of Compound 3.7

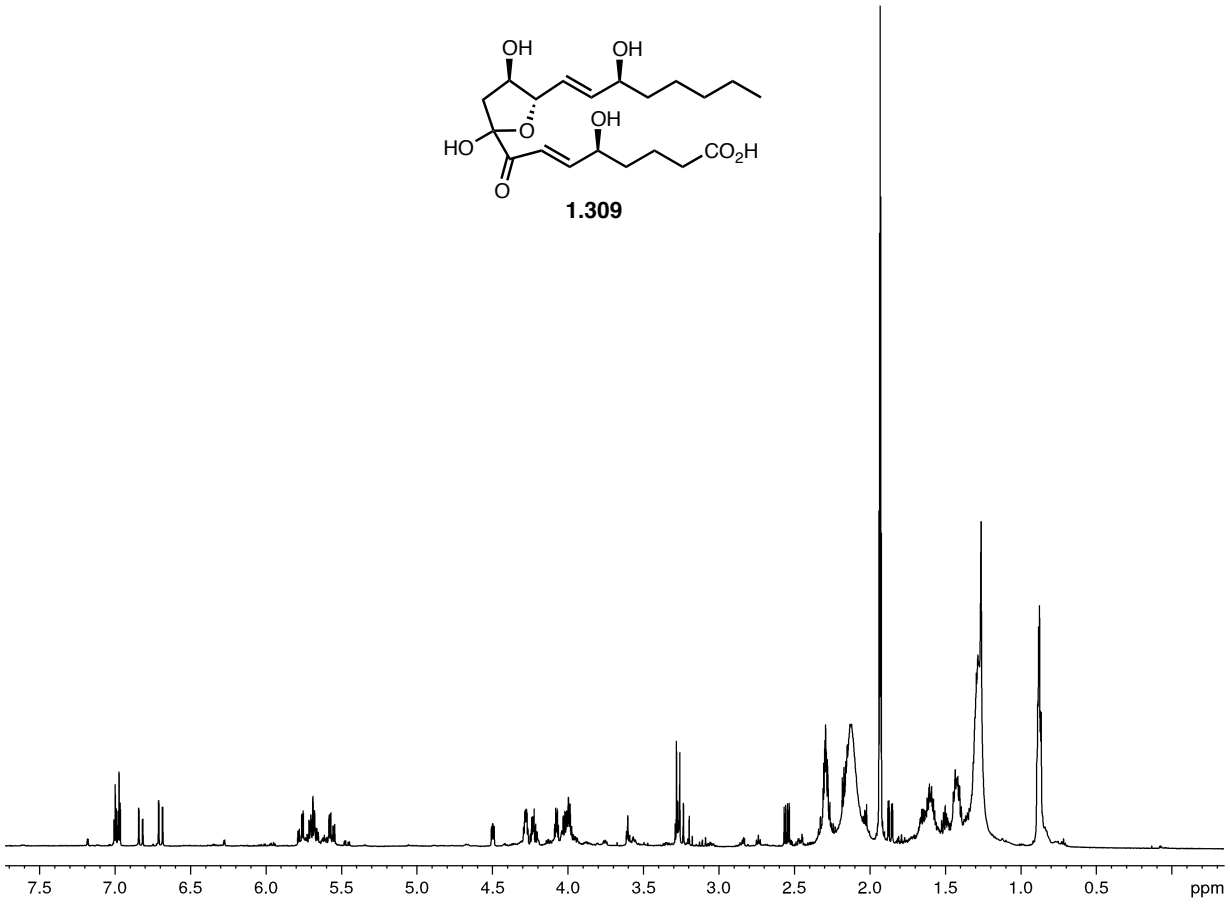


Figure A2.13: ^{1}H NMR (600 MHz, CD_3CN) of Compound 1.309

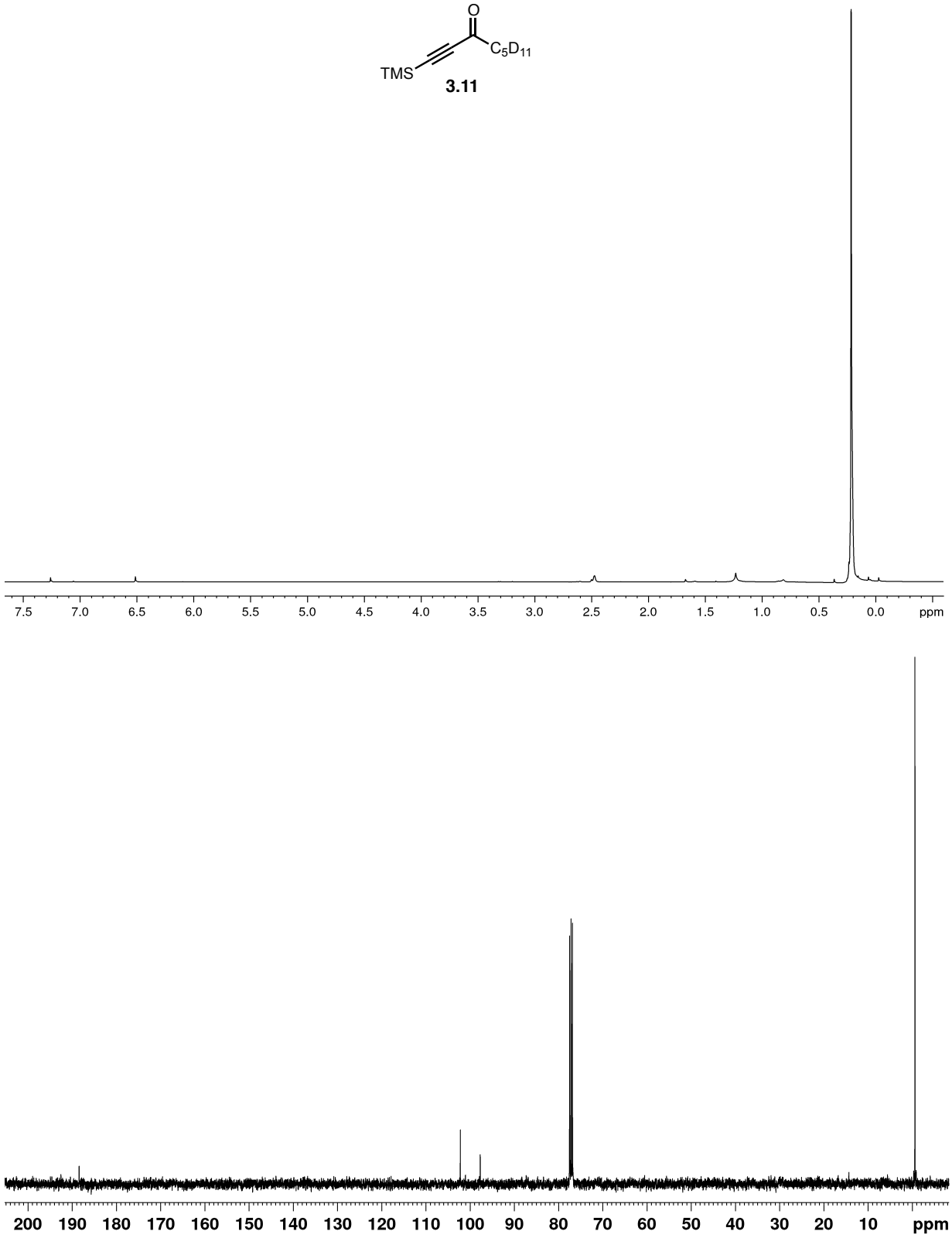


Figure A2.14: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of Compound 3.11

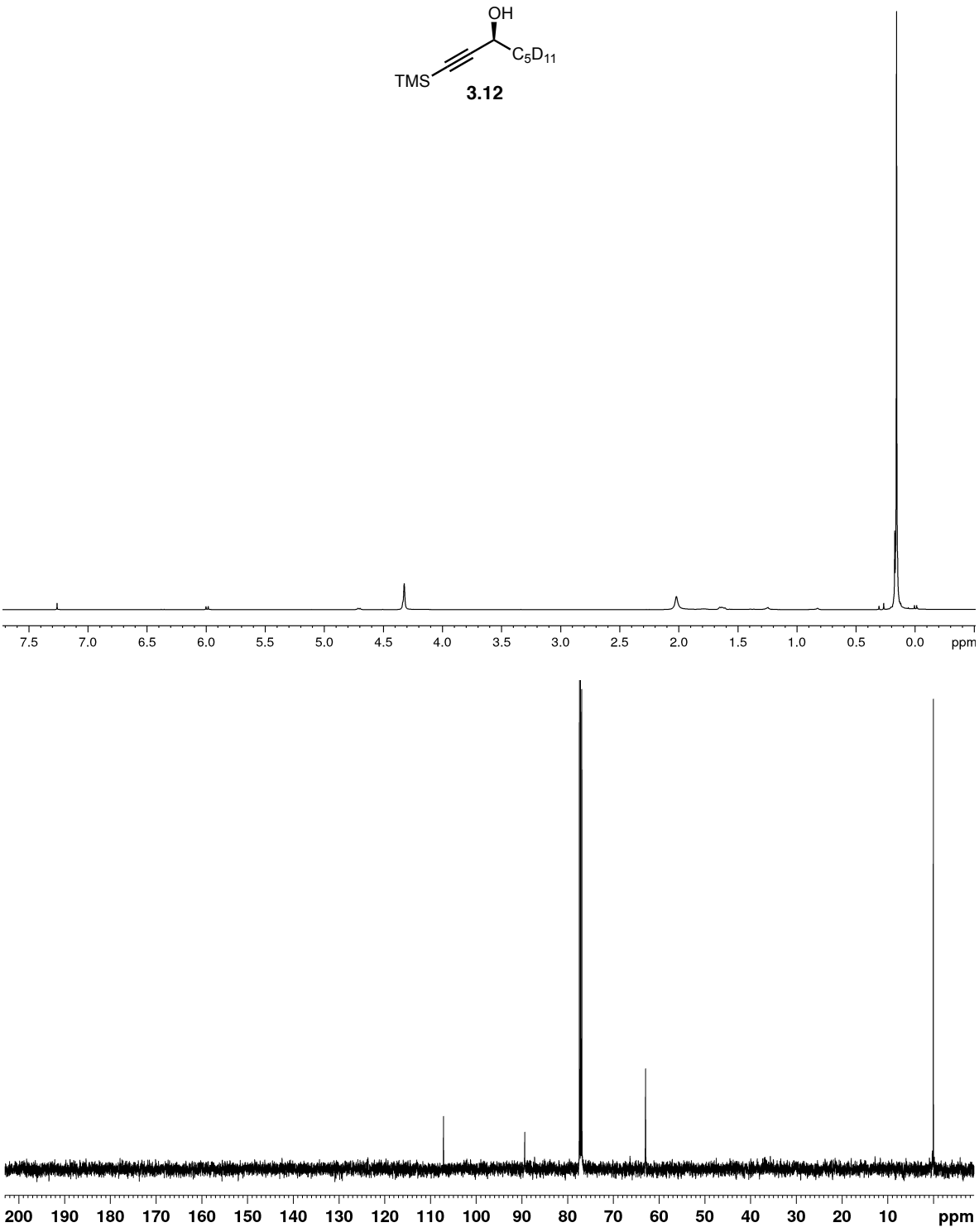


Figure A2.15: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of Compound 3.12

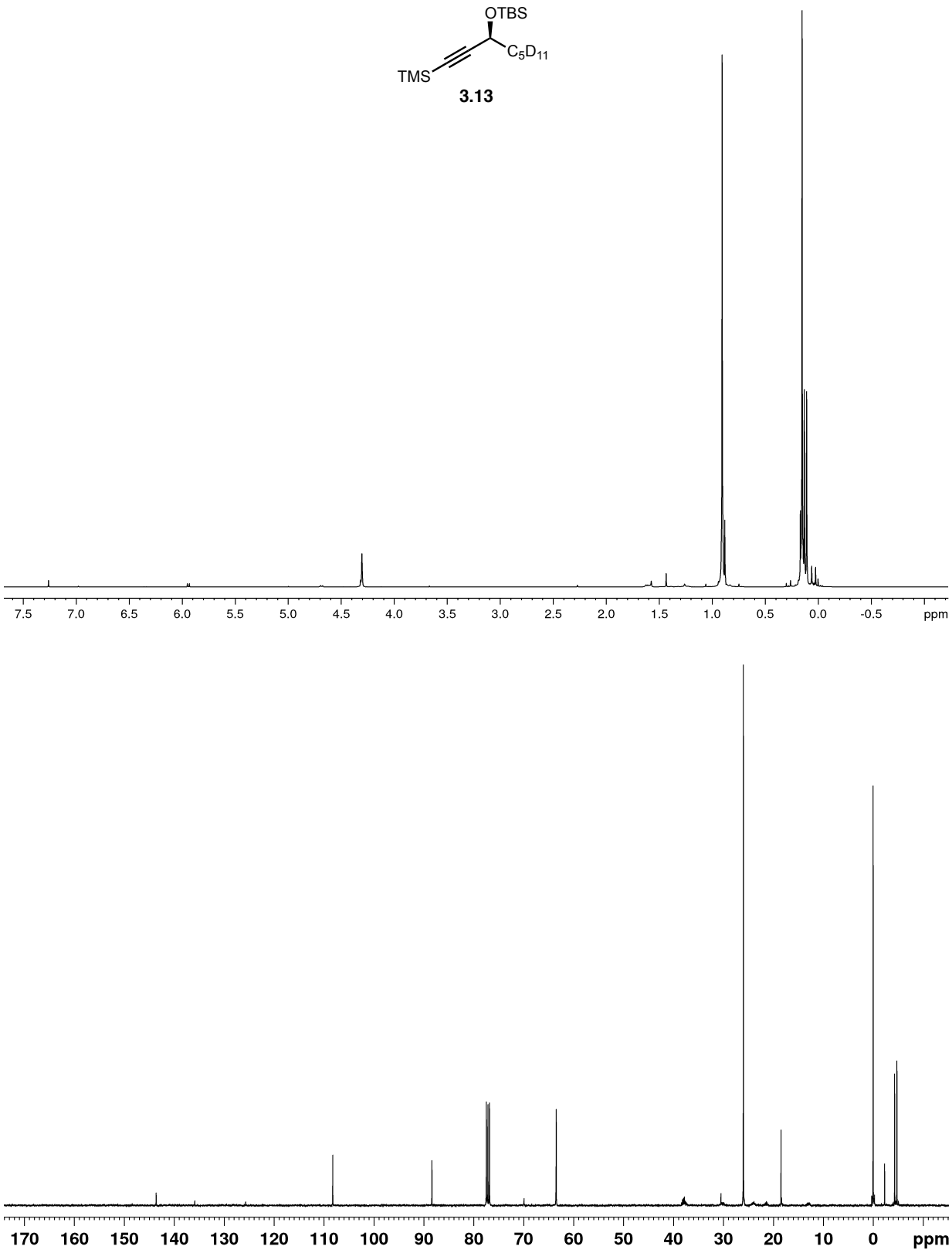


Figure A2.16: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of Compound 3.13

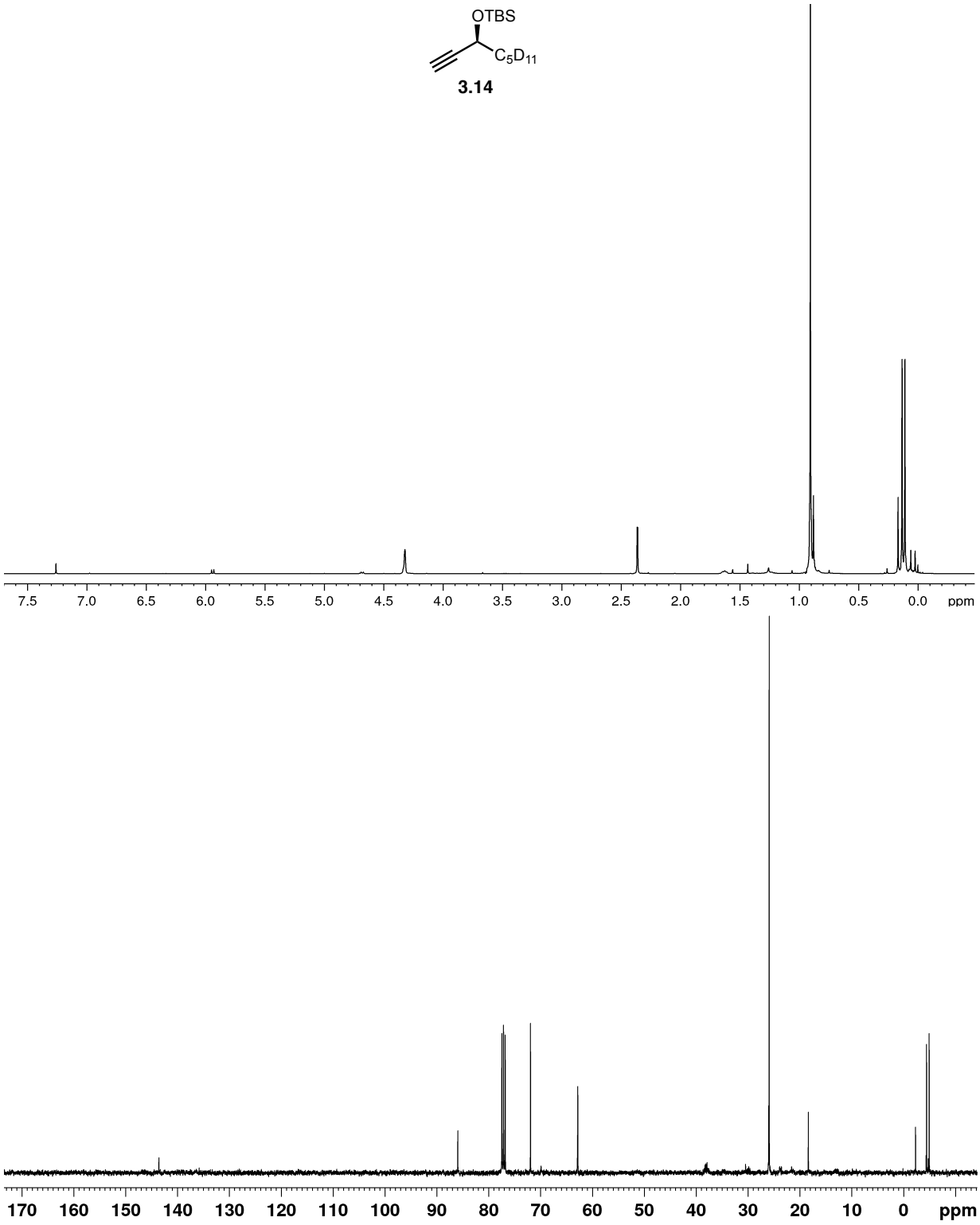


Figure A2.17: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of Compound 3.14

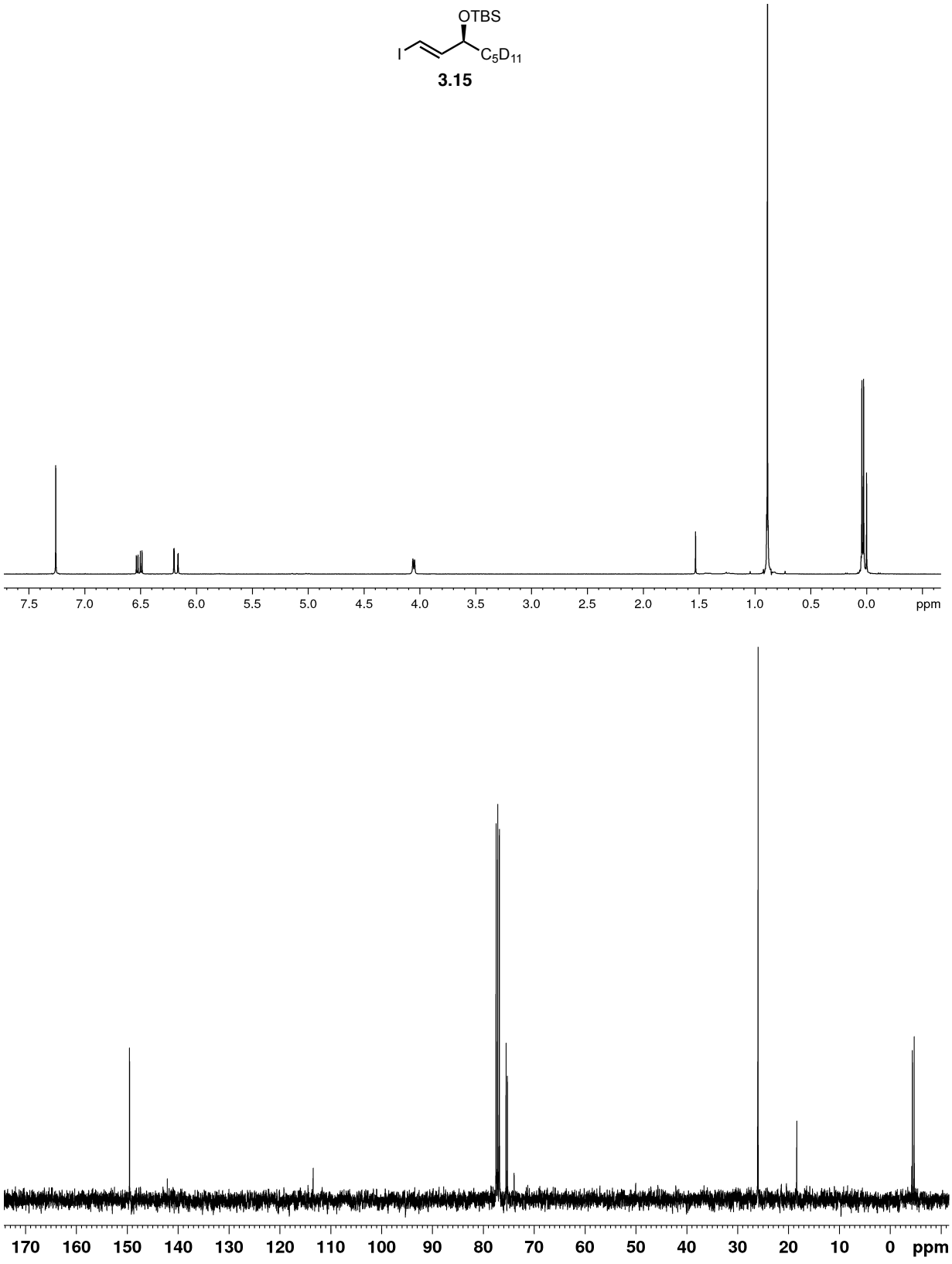


Figure A2.18: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of Compound 3.15

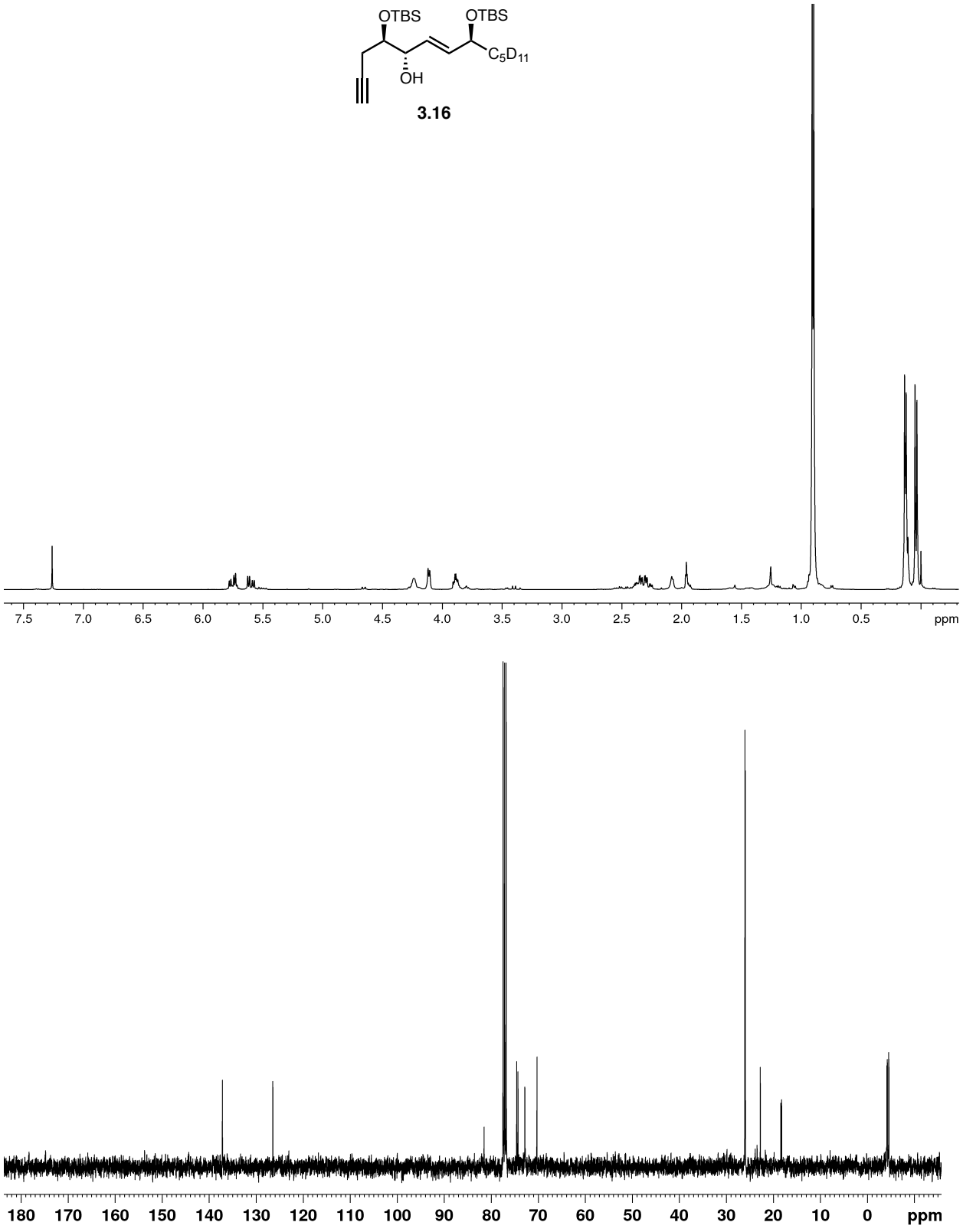


Figure A2.19: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of Compound 3.16

CHAPTER 4

PROGRESS TOWARD THE SYNTHESIS OF HEMIKETAL D_2

Key Considerations for Synthetic Approach

With the synthesis of HKE_2 completed, we focused our attention on employing the successful cycloisomerization/oxidation sequence to access the isomeric compound hemiketal D_2 (HKD_2). Though the strategy to access HKD_2 is comparable to our synthetic route for HKE_2, some key differences are important to highlight (Figure 4.1). First, the synthesis would start from (*R*)-glycidyl ether **2.8**, the enantiomer of the epoxide previously used. Secondly, we required a chelation-controlled carbonyl addition so as to achieve the desired *syn* relative stereochemistry about the C8-C9 bond. With this in mind, we selected a *p*-methoxybenzyl protecting group for the C8 alcohol.[1]

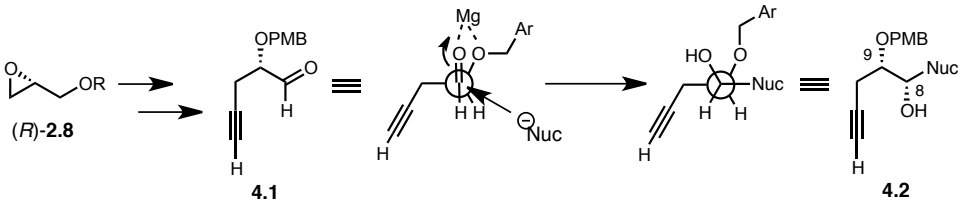
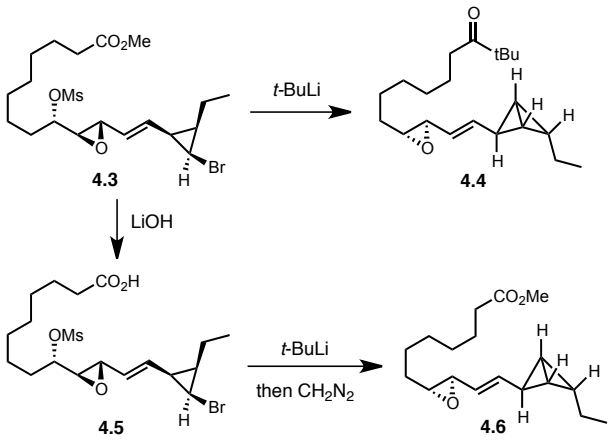


Figure 4.1: Synthetic Considerations for HKD_2

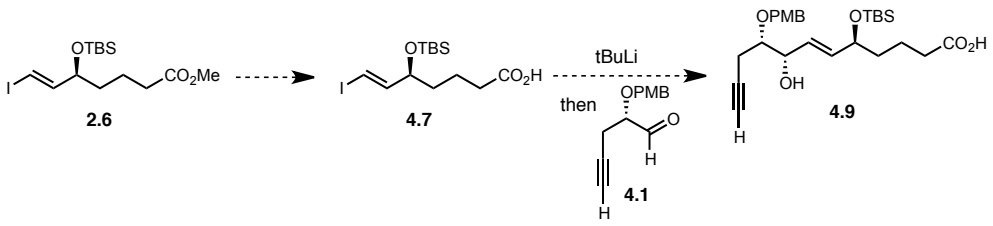
Lastly, we recognized the potential for the C1 carboxylate functional group could potentially be problematic for our proposed organometallic addition to the carbonyl group. Based on earlier work in our group en route to a bicyclobutane fatty acid (Scheme 4.1), we knew that methyl esters are sensitive to reactions requiring alkyllithiums.[2] The original proposal required

lithium halogen exchange of alkyl bromide **4.3** with *t*-BuLi, which would induce a cascade reaction to form the bicyclobutane moiety **4.6**. However, with the methyl ester present, only *t*-butyl ketone **4.4** was isolated. To solve this problem, the methyl ester was first hydrolyzed to carboxylic acid **4.5**. Then, excess *t*-BuLi was used to first deprotonate the acid and subsequently accomplish lithium-halogen exchange to induce the desired cascade reaction and form the bicyclobutane core **4.6**.



Scheme 4.1: Sulikowski's Synthesis of a Bicyclobutane Fatty Acid

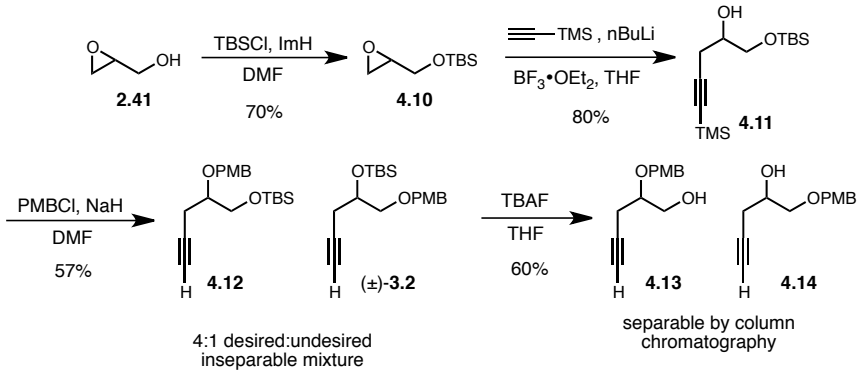
Therefore, from the outset, we planned to use carboxylic acid **4.7** in the key carbonyl addition reaction so as to avoid undesired side reactions (Scheme 4.2). Furthermore, the desired carboxylic acid could easily be accessed from vinyl iodide **2.6** in one step.



Scheme 4.2: Proposed Plan for Lithium-Halogen Exchange and Carbonyl Addition

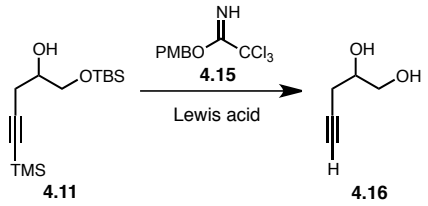
First Generation Approach to C8-C12 Aldehyde

In order to access the requisite aldehyde fragment **4.1**, we once again started from (±)-glycidol (Scheme 4.3). Protection of the alcohol as a TBS ether provided glycidyl ether (±)-**4.10**. Next, epoxide opening with ethynyltrimethylsilane provided alcohol **4.11** in good yield. However, protection of the alcohol under basic conditions using PMBCl and sodium hydride provided a 4:1 mixture of PMB ether regioisomers **4.12** and (±)-**3.2**, arising from silyl migration of the TBS group. Furthermore, this process was accompanied by loss of the silyl group on the alkyne. Desilylation of the alcohols then provided a separable mixture of alcohols **4.13** and **4.14** in modest yield.



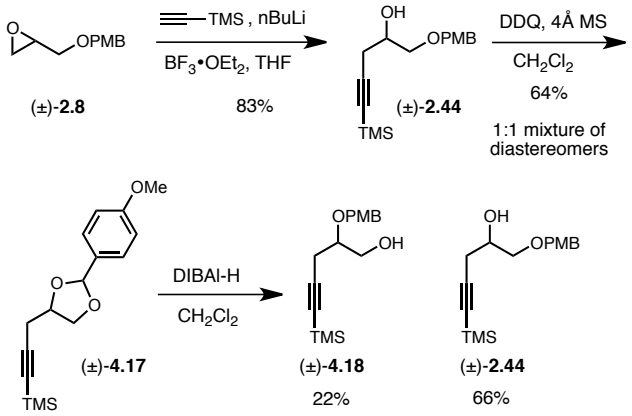
Scheme 4.3: First Approach to the Synthesis of the C8-C12 Fragment

Unfortunately, the yields of both the PMB protection step and desilylation step were modest at best, prompting us to search for a more efficient synthesis of the desired C8-C12 fragment. Therefore, we tried to employ trichloroacetimidate **4.15** as the PMB source. We anticipated the acidic conditions required to append the PMB group using this reagent would circumvent the silyl migration. Unfortunately, the Lewis acids tested, including PPTS, BF_3•OEt_2, and CSA, used in conjunction with **4.15** resulted primarily in cleavage of the TBS ether to provide diol **4.16**.



Scheme 4.4: PMB Protection with Trichloroacetimidate 4.15 Results in TBS Cleavage

Because the trichloroacetimidate approach proved unsuccessful with a primary TBS ether present, we searched for alternatives to the TBS glycidyl ether as the starting point for the synthesis. We next planned on employing a regioselective reductive opening of an anisylidene acetal to produce the desired benzyl ether.[3] Starting from PMB glycidyl ether (±)-**2.8**, which is the starting point for our HKE_2 synthesis, epoxide opening with ethynyltrimethylsilane afforded alcohol (±)-**2.44**. Next, treatment of the benzyl ether with DDQ in the presence of molecular sieves provided the anisylidene acetal (±)-**4.17** as a 1:1 inseparable mixture of diastereomers. Unfortunately, treatment of the acetal with DIBAL-H resulted in a 3:1 mixture of PMB ether regioisomers (±)-**4.18** and (±)-**2.44**, with the undesired primary PMB ether being the major isomer.

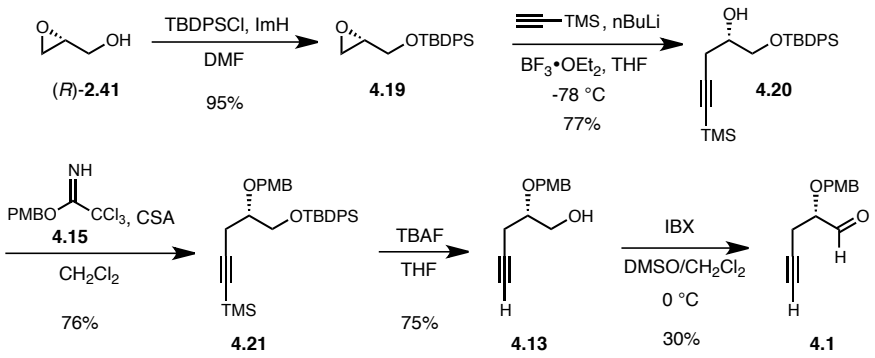


Scheme 4.5: Reductive Opening of Anisylidene Acetal Favors Undesired Regioisomer

Second Generation Approach to the C8-C12 Aldehyde

With the information learned from our unsuccessful attempts at generating the desired aldehyde, we decided that a more robust protecting group would be necessary. As such, we settled on using a TBDPS ether in place of the TBS ether, as this particular silyl group is stable to mildly acidic conditions. To see if this approach would be successful, (*R*)-glycidol was treated with TBDPSCl to provide the TBDPS glycidyl ether **4.19**. Epoxide opening provided alcohol **4.20**, which was then treated with trichloroacetimidate **4.15** in the presence of catalytic CSA to provide the desired PMB ether **4.21** in good yield. Concomitant desilylation of the TBDPS ether and the TMS alkyne with TBAF provided alcohol **4.13**, which was oxidized with IBX to provide aldehyde **4.1**, albeit in low yield. Thus, it appears that the choice of TBDPS group is successful in providing the desired PMB ether. While we started with the commercially available but expensive single-enantiomer material, we are currently investigating the possibility of a hydrolytic kinetic resolution of racemic **4.19** to afford optically enriched material. Furthermore, for the sake of saving the valuable enantiopure aldehyde, we opted to employ the racemic

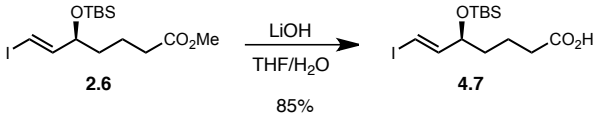
version of this route until conditions for the chelation-controlled carbonyl addition had been optimized.



Scheme 4.6: Synthesis of C8-C12 Aldehyde

Initial Attempts at Lithium-Halogen Exchange

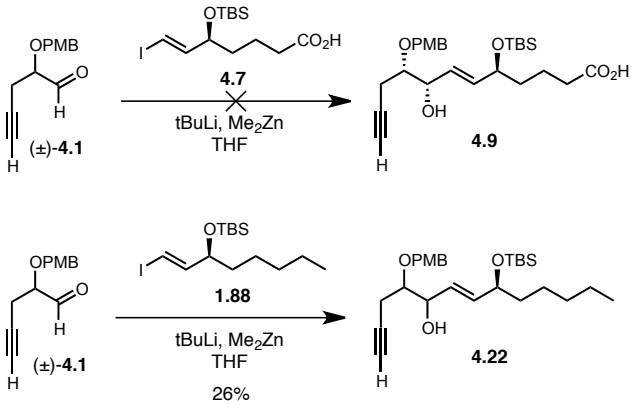
In order to investigate the carbonyl addition, we first needed to generate the desired vinyl iodide **4.7**. From methyl ester **2.6**, basic hydrolysis using LiOH provided the carboxylic acid **4.7** in good yield.



Scheme 4.7: Synthesis of Carboxylic Acid 4.7

Now, with both vinyl iodide **4.7** and aldehyde (±)-**4.1** in hand, we were well positioned to investigate the lithium-halogen exchange. Using the procedure optimized for HKE_2, vinyl iodide

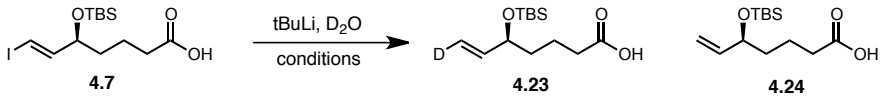
4.7 was treated with *t*-BuLi and subsequently transmetallated with dimethylzinc. Addition of the PMB aldehyde (±)-**4.1** to this vinyl zinc solution was met with no conversion to the desired allylic alcohol **4.9**. To probe whether or not the aldehyde was problematic in this step, we took vinyl iodide **1.88** that lacks the necessary carboxylate group and, after employing our lithium-halogen exchange conditions, saw reaction with PMB aldehyde to generate allylic alcohol **4.22** in poor yield.



Scheme 4.8: Initial Attempts at Lithium Halogen Exchange

We next focused out attention on verifying that lithium halogen exchange was indeed occurring with vinyl iodide **4.7**. Table 4.1 summarized our efforts to affect lithium-halogen exchange and quench the resulting lithiate with D_2O. When trying the conditions that were successful in HKE_2 synthesis (entry 1), no deuterium incorporation was observed, but the only product recovered was the quenched vinyl lithiate **4.24**. In an effort to see if reaction time had any effect on product distribution (entries 2 and 3), only alkene **4.24** was generated. A screen of temperatures was then attempted (entries 4 through 6). At -100 °C, again alkene 4.24 was the major product; however, lowering the reaction temperature to -196 °C returned starting material.

Exposure to the reaction conditions for 3 h at the same temperature, however, produced alkene **4.24**, again with no signs of deuterium incorporation. The lack of deuterium incorporation was puzzling, as each reaction was run with special care to ensure an inert atmosphere. Thus, we attempted to run the same reaction using freshly distilled Et_2O as the solvent. At -78 °C, only alkene **4.24** was isolated, whereas lowering the temperature only led to recovery of starting material. These results seem to indicate that the vinyl lithiate is being quenched before reaction with deuterium can occur. Therefore, we hypothesize that the lithum-halogen exchange is occurring at a faster rate than acid-base reaction between *t*-BuLi and the carboxylic acid. As a result, we believe the basicity of the resulting vinyl lithiate is deprotonating the carboxylic acid, leading to production of alkene **4.24**, preventing deuterium incorporation.

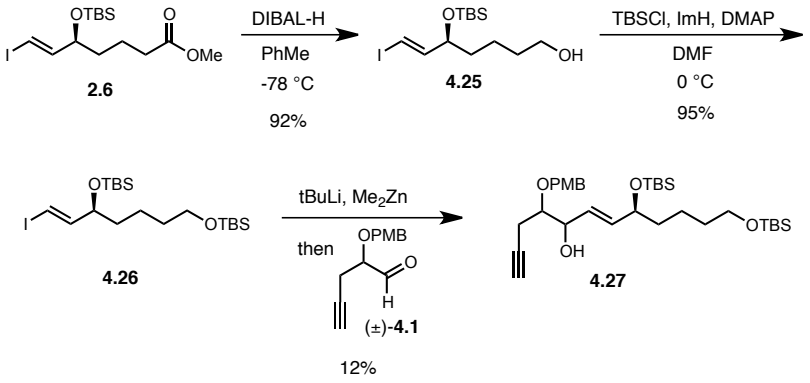


4.7 **4.23** **4.24**

Entry	Solvent	Temperature	Reaction Time	Result
1	THF	-78 °C	1.5 h	**4.24**
2	THF	-78 °C	5 min	**4.24**
3	THF	-78 °C	10 min	**4.24**
4	THF	-100 °C	1 h	**4.24**
5	THF	-196 °C	1 h	recovered **4.7**
6	THF	-196 °C	3 h	**4.24**
7	Et_2O	-78 °C	1 h	**4.24**
8	Et_2O	-196 °C	45 min	recovered **4.7**

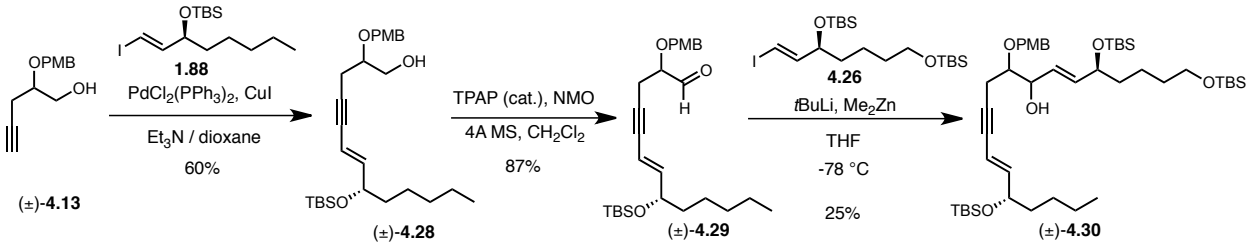
Table 4.1: Conditions Tested for Lithium-Halogen Exchange

To circumvent the problematic carboxylate functionality, we hoped that reduction to a primary alcohol would facilitate addition of the vinyl lithiate into aldehyde **4.1**. Starting with ester **2.6**, reduction with DIBAL-H provided the primary alcohol **4.25**, which upon protection as a TBS ether afforded vinyl iodide **4.26**. Subjection of this vinyl iodide to our lithium-halogen exchange conditions provided allylic alcohol **4.27** only in low yields.



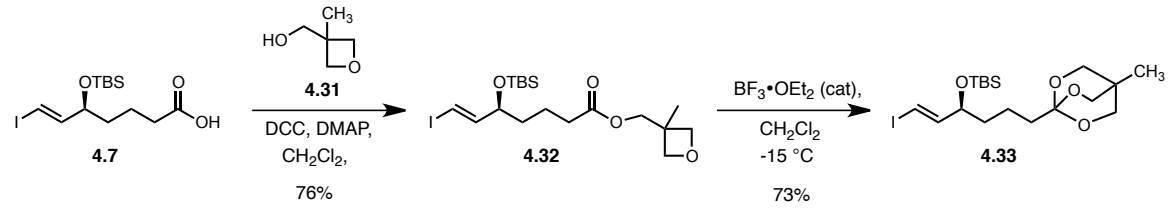
Scheme 4.9: Carbonyl Addition with Vinyl Iodide

At this point, we wondered whether or not aldehyde **4.1** could be responsible for the low yields of this reaction. Thus, we sought to introduce the aliphatic side chain first, which would allow the full carbon framework to be generated after carbonyl addition. Therefore, Sonogashira of alkyne (±)-**4.13** with vinyl iodide **1.88** provided alcohol **4.28** in good yield. Ley-Griffith oxidation proved to be the most successful set of oxidizing condition, providing aldehyde **4.29** in high yield. Lithium halogen exchange of vinyl iodide **4.26** followed by transmetallation with zinc and addition of aldehyde **4.29** then provided the desired allylic alcohol **4.30** with only a moderate increase in yield.



Scheme 4.10: Synthesis of Aldehyde 4.29 and Carbonyl Addition with 4.26

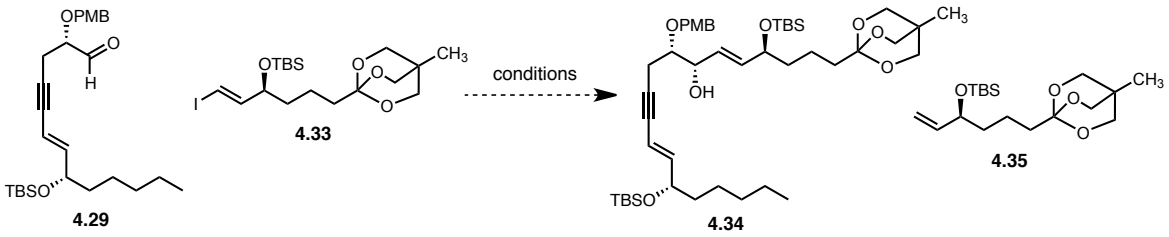
Due to the low yielding nature of this transformation and the required oxidation state manipulations, we sought alternatives to access the desired carbon framework of HKD_2. We next focused our attention on utilizing the 4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (OBO) group to mask the carboxylate functionality and facilitate lithium-halogen exchange and subsequent carbonyl addition to succeed.[4] Thus, using carboxylic acid **4.7** as the starting point, DCC coupling with oxetane alcohol **4.31** provided ester **4.32**. Treatment of the ester with catalytic BF_3•OEt_2 provided the desired orthoester **4.33** in good overall yield.



Scheme 4.11: Synthesis of OBO Orthoester 4.33

With the orthoester in hand, we were now set up to investigate lithium-halogen exchange conditions. We opted to use our enantiopure aldehyde **4.29** in these studies in an effort to simplify the analysis of any diastereomers that result from successful carbonyl addition. Gratifyingly, initial studies demonstrated that lithium-halogen exchange could be accomplished

with the use of *n*-BuLi. Table 4.2 shows our efforts to date in adding the vinyl iodide **4.33** to aldehyde **4.29** under a variety of conditions. Lithium-halogen exchange with *n*-BuLi and transmetallation with dimethyl zinc (as used in HKE_2) was able to produce the desired allylic alcohol **4.34**, but in low yield. Unfortunately, all efforts to reproduce this result were unsuccessful. Furthermore, varying the concentration of the reaction was unproductive and did not lead to formation of the desired product. We next attempted magnesium insertion into the alkenyl iodide through the use of Rieke magnesium and Knochel's Turbo Grignard.[5] In both cases, the desired magnesium-halogen exchange was unsuccessful and only starting vinyl iodide **4.33** was recovered. Transmetallation with $MgBr_2 \bullet OEt_2$, which has been utilized in a number of total synthesis endeavors, resulted only in recovery of aldehyde and alkene **4.35**.[6] $CeCl_3$, often used as a transmetallating agent to provide a less basic nucleophile, was also unsuccessful and lead to recovery of starting aldehyde and quenched vinyl lithiate.[7,8,9] Use of TMEDA as an additive to break up alkyl lithium aggregates was unsuccessful.[10] From these studies, we are confident that lithium-halogen exchange is occurring with *n*-BuLi; however, the transmetallation step seems to be problematic and further investigations to accomplish this transformation are necessary.



Entry	Reagent	Additive	Solvent	Concentration (**4.29**)	Result
1	*n*BuLi	Me_2Zn	THF	0.1 *M*	**4.34** (25%)
2	*n*BuLi	Me_2Zn	THF	0.05 *M*	**4.29** + **4.35**
3	*n*BuLi	Me_2Zn	THF	neat	**4.29** + **4.35**
4	*i*PrMgCl•LiCl	--	THF	--	**4.33**
5	Rieke Mg	--	THF	--	**4.33**
6	*n*BuLi	$MgBr_2$•OEt_2	Et_2O/CH_2Cl_2	0.1 *M*	**4.29** + **4.35**
7	*n*BuLi	$CeCl_3$	THF	0.1 *M*	**4.35**
8	*n*BuLi	TMEDA, Me_2Zn	THF	0.1 *M*	**4.29** + **4.35**

Table 4.2: Carbonyl Addition Attempts with Orthoester Vinyl Iodide 4.33

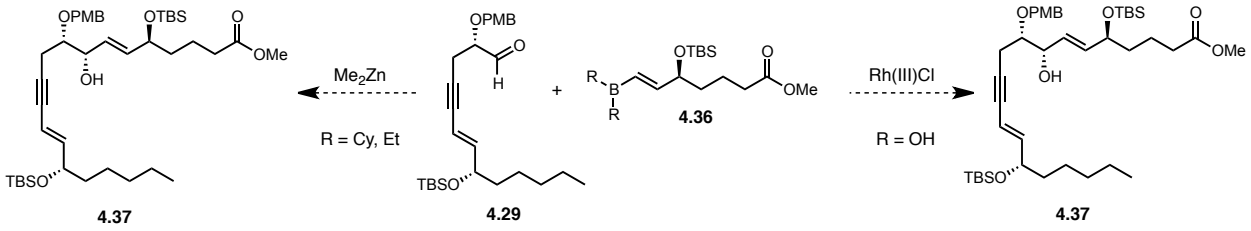
Future Directions

*Screening Conditions for Transmetallation of Vinyl Iodide **4.33***

While our initial screen of conditions for the lithium-halogen exchange with orthoester **4.33** was a good start, it is far from extensive. First, investigations into the effect of solvent on the reaction could be investigated, as almost all of the previous reactions have only been performed in THF. Secondly, we could explore a variety of zinc halides and alkylzinc reagents for transmetallation of the vinyl lithiate, as zinc was the sole source of success.

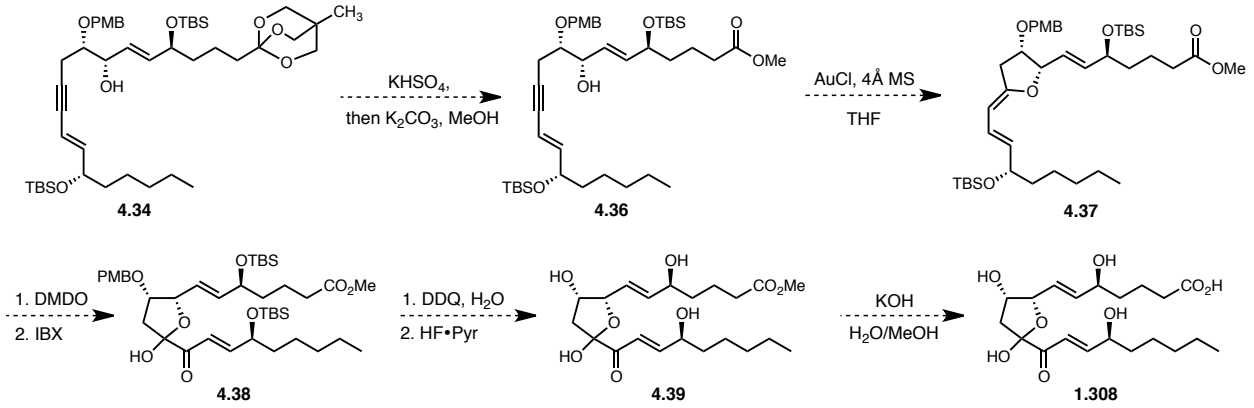
Alternative Approaches to C7-C8 Bond Formation

Should these conditions be unproductive, we are also investigating methods to afford coupling between aldehydes and vinyl iodides that will not affect the carboxylate functionality. One such example is Walsh's work utilizing the transmetallation of vinyl boronates with alkylzinc reagents to generate allylic alcohols.[11] A second example is found in Furstner's work with the rhodium(III)-catalyzed addition of boronic acids to aldehydes.[12] Furthermore, in both processes, diastereoselective additions to chiral aldehydes have been investigated and would allow us to still access the desired *syn* relative stereochemistry without added transformations.



Scheme 4.12: Approaches to Access Carbon Framework of HKD_2

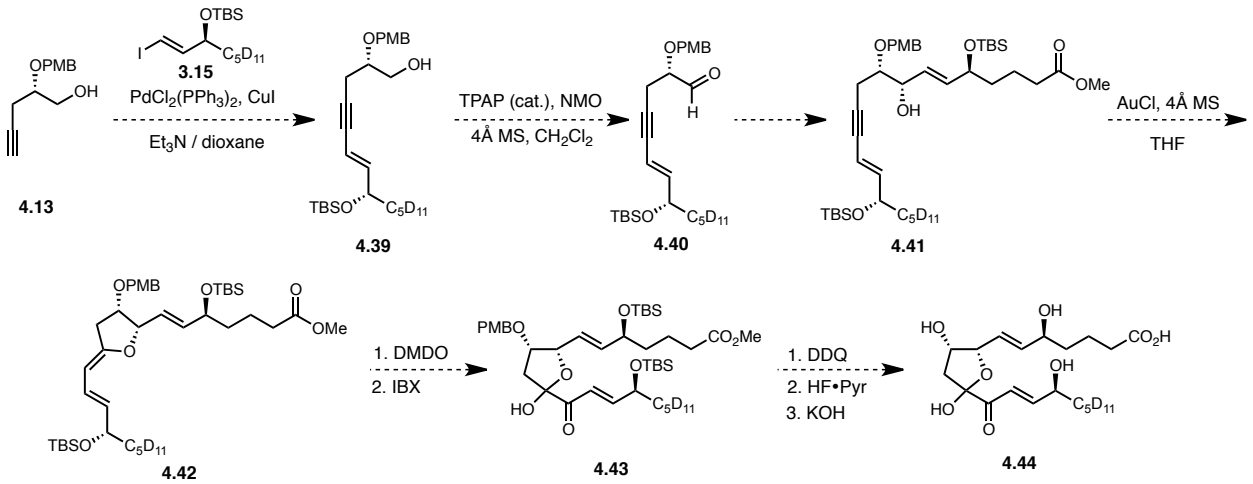
Upon realization of the key carbon-carbon bond forming event, attention can be applied toward completing the synthesis of HKD_2. Conversion of the orthoester to the methyl ester can be achieved in one step (ref). From here, cycloisomerization/oxidation sequence will hopefully provide the required hemiketal **4.38**. Deprotection of the benzyl ether and desilylation will then provide methyl ester **4.39**. Hydrolysis will then allow us to arrive at HKD_2.



Scheme 4.13: Proposal for the Completion of HKD_2

Synthesis of d_{11}-HKD_2

Additionally, once the synthesis of HKD_2 has been achieved, the route can be applied toward the synthesis of d_{11}-HKD_2. From alcohol **4.13**, Sonogashira coupling with d_{11}-vinyl iodide **3.15** (produced in the synthesis of d_{11}-HKE_2) would provide alcohol **4.39**. Oxidation with TPAP and NMO would provide the requisite d_{11}-aldehyde **4.40**. After completing the carbon framework, cycloisomerization/oxidation sequence will provide hemiketal **4.43**. Protecting group removal and methyl ester hydrolysis will then generate d_{11}-HKD_2 for use as an internal standard in biological studies.



Scheme 4.14: Proposed Synthesis of d_{11}-HKD$_2$

In conclusion, we believe our synthetic efforts will prove successful in the first synthesis of HKD$_2$. Furthermore, we hope that the approach detailed for HKD$_2$, in conjunction with our successful synthesis of HKE$_2$, will allow for relatively quick and efficient access to hemiketal analogues to help further probe the biological function of these intriguing natural products.

Experimental Methods

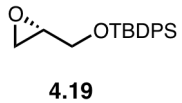
General Procedure: All non-aqueous reactions were performed in flame-dried or oven dried round-bottomed flasks under an atmosphere of argon. Stainless steel syringes or cannula were used to transfer air- and moisture-sensitive liquids. Reaction temperatures were controlled using a thermocouple thermometer and analog hotplate stirrer. Reactions were conducted at room temperature (rt, approximately 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 F_{254} glass-backed pre-coated silica gel plates. The

plates were visualized with UV light (254 nm) and developed in an iodine chamber or stained with potassium permanganate or *p*-anisaldehyde-sulfuric acid followed by charring. Yields were reported as isolated, spectroscopically pure compounds.

Materials: Solvents were obtained from either an MBraun MB-SPS solvent system or freshly distilled (tetrahydrofuran was distilled from sodium-benzophenone; toluene was distilled from calcium hydride and used immediately; dimethyl sulfoxide was distilled from calcium hydride and stored over 4 Å molecular sieves). Unless indicated, all commercial reagents were used as received without further purification. The (*S*,S)-Co(salen) catalyst was synthesized according to the procedure reported by Jacobsen.[13] Ru-(*S*,*S*)-TsDPEN catalyst was synthesized according to the procedure reported by Noyori.[14] The molarity of *n*-butyllithium solutions was determined by titration using diphenylacetic acid as an indicator (average of three determinations).

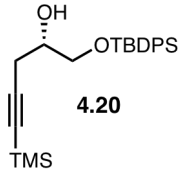
Instrumentation: ^{1}H NMR spectra were recorded on Bruker 400, 500, or 600 MHz spectrometers and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded on Bruker 100, 125, or 150 MHz spectrometers and are reported relative to deuterated solvent signals. IR Spectra were recorded on a Nicolet Avatar 360 spectrophotometer and values are reported in wavenumbers (cm^{-1}). Compounds were analyzed as neat films on a NaCl plate (transmission). Optical rotations were measured on a Perkin-Elmer 341 digital polarimeter at ambient temperature. High-resolution mass spectra were obtained from the Department of Chemistry and Biochemistry, University of Notre Dame.

Compound preparation:



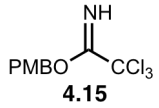
4.19

Glyidyl Ether 4.19: To a solution of (*R*)-glycidol (**2.41**) (1.00 g, 13.5 mmol) in CH_2Cl_2 (30.0 mL) was added Et_3N (3.00 mL, 21.6 mmol), DMAP (5.0 mg, 4.05 mmol), and TBDPSCl (4.08 g, 14.8 mmol). The reaction was allowed to stir at rt for 3 h. The reaction was quenched with 1 *N* HCl (30 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, gradient elution, 0% to 2% EtOAc in hexanes) to yield 3.68 g (87%) of **4.19** as a clear, colorless oil. The spectral data matched reported values.[15]



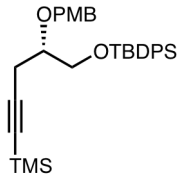
4.20

Alcohol 4.20: To a solution of ethynyltrimethylsilane (0.754 g, 7.68 mmol) in THF (15.0 mL) at -78 °C was added *n*-BuLi (3.48 mL, 2.21 *M* in hexanes, 7.68 mmol). The reaction stirred for 15 min, at which point a solution of glycidyl ether **4.19** (2.00 g, 6.40 mmol) in THF (7.00 mL) was added dropwise, followed by addition of BF_3•OEt_2 (0.950 mL, 7.68 mmol). The reaction stirred at -78 °C for 2.5 h. The reaction was quenched with sat. aq. NH_4Cl (20.0 mL) and the aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, gradient elution, 2% to 5% EtOAc in hexanes) to yield 2.17 g (82%) of **4.20** as a clear, colorless oil. The spectral data matched the reported values.[16]



4.15

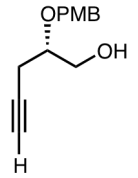
Trichloroacetimidate 4.15: A flame dried 100-mL round bottom flask was charged with a 60% dispersion of sodium hydride in mineral oil (0.320 g, 8.00 mmol). The sodium hydride was washed with hexanes (3 x 2.00 mL). Et_2O (25.0 mL) was added followed by 4-methoxybenzyl alcohol (10.0 mL, 80.0 mmol), which was added slowly over 15 min. The mixture was stirred at rt for 30 min after which it was cooled to 0 °C. Trichloroacetonitrile (8.85 mL, 8.80 mmol) was added dropwise over 20 min and after 1 h, the reaction was allowed to warm to rt and stirred for 45 min. The reaction was concentrated *in vacuo* to a dark orange oil. The crude residue was treated with a mixture of pentane and MeOH (85.0 mL, 275:1 pentane:MeOH) and stirred for 30 min. The heterogeneous mixture was filtered through a plug of Celite and the filtrate was concentrated *in vacuo* to afford 22.0 g (95%) of trichloroacetimidate **4.15** as an orange oil. The spectral data matched the reported values.[17]



4.21

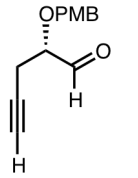
Benzyl ether 4.21: To a solution of alcohol **4.20** (3.56g, 8.67 mmol) in CH_2Cl_2 (25.0 mL) at 0 °C was added trichloroacetimidate **4.15** (4.90 g, 17.3 mmol). CSA (0.202 g, 0.867 mmol) was added and the reaction was allowed to warm to rt. The reaction stirred for 16 h and was concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, gradient elution, 3% to 10% EtOAc in hexanes) to yield 3.80 g (83%) of **4.21** as a faint yellow oil. $[\alpha]_D^{20}$ = - 11.0° (*c* 4.29, $CHCl_3$); IR (neat) ν_{max} = 3069, 2998, 2856, 2175, 1612, 1513, 1463 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69-7.72 (m, 4H), 7.36-7.46 (m, 6H), 7.29 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 1H), 4.61 (s, 2H), 3.81 (s, 3H), 3.79 (app d, *J* = 4.8 Hz, 2 H), 3.71 (app p, *J* = 5.6 Hz, 1H), 2.65 (dd, *J* = 6.1, 16.9 Hz, 1H), 2.54 (dd, *J* = 6.3, 16.9 Hz, 1H), 1.09 (s, 9H), 0.16 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 135.8 (2C), 135.7 (2C), 133.7, 133.6, 130.8 (2C), 129.8 (2C),

129.4 (2C), 127.8 (4C), 113.9 (2C), 104.2, 86.2, 77.9, 72.0, 65.2, 55.4, 27.0 (3C), 23.1, 19.4, 0.21 (3C).



4.13

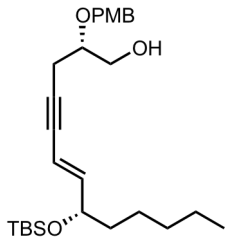
Alcohol 4.13: To a solution of silyl ether **4.21** (1.29 g, 2.43 mmol) in THF (2.50 mL) at 0 °C was added TBAF (7.29 mL, 1.0 *M* in THF) and the reaction stirred for 2 h. The reaction was quenched with H_2O (5 mL) and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with H_2O (30 mL) and brine (30 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, gradient elution, 10% to 50% EtOAc in hexanes) to yield 0.498 g (93%) of **4.13** as a yellow oil. $[\alpha]_D^{20}$ = + 29.4° (*c* 2.96, $CHCl_3$); IR (neat) ν_{max} = 3423, 3289, 2933, 2117, 1612, 1513 cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2CO$) δ 7.31 (d, *J* = 8.7 Hz, 1H), 6.98 (d, *J* = 8.7 Hz, 1H), 4.59 (ap q, *J* = 10.6 Hz, 2H), 3.78 (s, 3H), 3.65-3.71 (m, 1H), 3.58-3.64 (m, 2H), 2.50 (ddd, *J* = 2.7, 6.2, 16.9 Hz, 1H), 2.43 (ddd, *J* = 2.8, 5.3, 16.9 Hz, 1H), 2.36 (app t, *J* = 2.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 130.1, 129.6 (2C), 114.1 (2C), 80.6, 77.2, 71.7, 70.5, 63.9, 55.4, 20.8.



4.1

Aldehyde 4.1: To a solution of **4.13** (0.390 g, 1.77 mmol) in CH_2Cl_2 (5.00 mL) and DMSO (5.00 mL) at 0 °C was added IBX (0.744 g, 2.66 mmol). The solution was warmed to rt and stirred for 16 h. The reaction mixture was diluted with H_2O (5.00 mL) and CH_2Cl_2 (5.00 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with H_2O (3 x 20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, gradient eludtion 2% to 5% Et_2O in hexanes) to provide 0.104 g (30

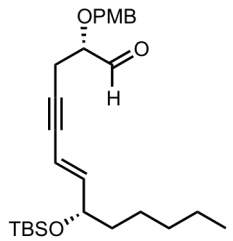
%) of **4.1** as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (d, *J* = 1.5 Hz, 1 H), 7.31 (d, *J* = 8.6 Hz, 2 H), 6.89 (d, *J* = 8.6 Hz, 2 H), 4.68 (d, *J* = 11.6 Hz, 1H), 4.64 (d, *J* = 13.5 Hz 1H), 3.89 (ddd, *J* = 1.5, 6.2, 6.2 Hz, 1H), 3.81 (s, 3H), 2.65 (ddd, J = 2.7, 6.0, 17.1 Hz, 1H), 2.58 (ddd, J = 2.7, 6.4, 17.1 Hz, 1H) 2.05 (app t, *J* = 2.7 Hz, 1H).



4.28

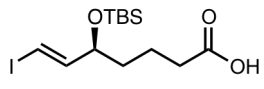
Alcohol 4.28: To a solution of vinyl iodide **1.88** (0.920 g, 2.50 mmol) in Et_3N / dioxane (1:1, 2.25 mL) was added CuI (17.0 mg, 0.0908 mmol) and $PdCl_2(PPh_3)_2$ (32.0 mg, 0.0454 mmol). The solution changed color to orange and the reaction stirred for 5 min, at which point a solution of alkyne **4.13** (0.500 mg, 2.27 mmol) in Et_3N / dioxane (1:1, 2.25 mL) was added dropwise. The reaction stirred at rt for 16 h. The reaction was concentrated and the resulting residue was taken up in H_2O (4 mL) and Et_2O (4 mL). The layers were separated and the aqueous layer extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, gradient elution, 10% to 25% EtOAc in hexanes) to provide 0.710 g (68%) of **4.28** as a yellow oil. $[\alpha]_D^{20}$ = -4.95° (*c* 0.62, $CHCl_3$); IR (neat) ν_{max} = 3428, 2953, 2857, 2358, 1716, 1605, 1513, 1462 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.6 Hz, 1H), 6.89 (d, *J* = 8.6 Hz, 1H) 6.04 (dd, *J* = 5.6, 15.8 Hz, 1H), 5.60 (dd, *J* = 1.6, 15.8 Hz, 1H), 4.65 (app d, *J* = 11.3 Hz, 1H), 4.51 (app d, *J* = 11.3 Hz, 1H), 4.13 (app q, *J* = 6.0 Hz, 1H), 3.81 (s, 3H), 3.76-3.80 (m, 1H), 3.63-3.70 (m, 2H), 2.63 (ddd, *J* = 2.1, 4.9, 17.0 Hz, 1H), 2.54 (ddd, *J* = 1.9, 7.2, 16.9 Hz, 1H), 1.43-1.49 (m, 2H), 1.24-1.32 (m, 6H), 0.89 (s, 9H), 0.88 (app t, *J* = 6.5 Hz, 3H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 146, 130, 129 (2C), 114 (2C), 108, 85.7, 77.6, 72.5, 71.5, 64.0, 55.2, 37.8, 31.7, 25.8 (3C), 24.6, 22.5, 21.6, 18.1, 14.0, -4.53, -4.93.



4.29

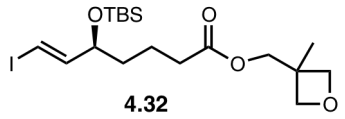
Aldehyde 4.29: To a solution of alcohol **4.28** (30.0 mg, 0.0651 mmol) and 4Å MS in CH_2Cl_2 (2.00 mL) NMO (15.3 mg, 0.130 mmol). The reaction stirred for 20 min, at which point TPAP (2.30 mg, 0.00651 mmol) was added. The reaction stirred at rt for 30 min. The reaction mixture was filtered through a plug of silica gel and the filtrate was concentrated *in vacuo* to provide 26.0 mg (87%) of **4.29** as a yellow oil. IR (neat) ν_{max} = 2955, 2858, 1737, 1613, 1514, 1464 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.66 Hz (d, *J* = 1.6 Hz, 1H), 7.31 (d, *J* = 8.7 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 1H) 6.06 (dd, *J* = 5.5, 15.8 Hz, 1H), 5.68 (dd, *J* = 1.6, 15.8 Hz, 1H), 4.66 (s, 2H), 4.13 (ddd, *J* = 1.3, 5.9, 11.9 Hz, 1H), 3.90 (ddd, *J* = 1.6, 6.5, 6.5 Hz, 1H), 3.81 (s, 3H), 3.77-3.79 (m, 1H), 2.77 (ddd, *J* = 2.1, 6.1, 17.1 Hz, 1H), 2.70 (ddd, *J* = 2.1, 6.7, 17.1 Hz, 1H), 1.43-1.50 (m, 2H), 1.23-1.33 (m, 6H), 0.90 (s, 9H), 0.89 (m, 3H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 1598, 146.7, 130.0 (2C), 129.1, 114.1 (2C), 108.4, 84.2, 81.4, 80.7, 72.7, 72.6, 55.4, 38.0, 32.0, 26.0 (3C), 24.8, 22.7, 21.6, 18.3, 14.2, -4.33, -4.71.



4.7

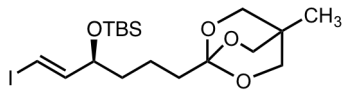
Carboxylic acid 4.7: To a solution of vinyl iodide **2.6** (1.98 g, 4.97 mmol) in THF (20.0 mL) was added a 1*N* LiOH (20.0 mL, 20.0 mmol). The reaction was allowed to stir at rt for 16 h. The reaction mixture was washed with 1*N* HCl (20 mL) and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, gradient elution

0% to 8% MeOH in CH_2Cl_2) to provide 1.70 g (89 %) of **4.7** as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.48 (dd, *J* = 6.0, 14.4 Hz, 1H), 6.20 (dd, *J* = 1.2, 14.4 Hz, 1H), 4.06-4.14 (m, 1H), 2.33 (app t, *J* = 7.3 Hz, 2H), 1.59-1.67 (m, 2H), 1.47-1.53 (m, 2H), 0.86 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 76.0, 74.6, 36.5, 33.7, 25.7 (3 C), 19.9, 18.1, -4.62, -5.00.



4.32

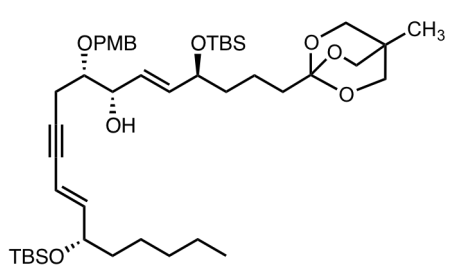
Ester 4.32: To a solution of acid **4.7** (2.00 g, 5.20 mmol) in CH_2Cl_2 (6.00 mL) was added alcohol **4.31** (0.584 g, 5.72 mmol), DMAP (0.191 g, 1.56 mmol) and DCC (1.29 g, 6.24 mmol). The reaction was allowed to stir at rt for 12 h, at which point the reaction mixture was filtered through Celite and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, gradient elution 5% to 20% EtOAc in hexanes) to provide 1.92 g (79 %) of **4.32** as a clear oil. $[\alpha]_D^{20}$ = -20.3° (*c* 3.1, $CHCl_3$); IR (neat) ν_{max} = 2955, 22858, 1739, 1462 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 (dd, *J* = 6.0, 14.4 Hz, 1H), 6.23 (dd, *J* = 1.1, 14.4 Hz, 1H), 4.51 (app d, *J* = 6.0 Hz, 2H), 4.38 (app d, *J* = 6.0 Hz, 2H), 4.17 (s, 2H), 4.10 (app q, *J* = 6.0 Hz, 1H), 2.36 (app t, *J* = 7.4 Hz, 2H), 1.60-1.74 (m, 2H), 1.48-1.56 (m, 2H), 1.33 (s, 3H), 0.88 (s, 9H), 0.04 (s, 3H) 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 148.7, 79.5 (2C), 76.0, 74.7, 39.0, 36.7, 34.0, 25.7 (3C), 21.1, 20.3, 18.1, -4.60, -5.00;



4.33

Orthoester 4.33: To a solution of ester **4.32** (1.92 g, 4.09 mmol) in CH_2Cl_2 (4.10 mL) at -15 °C was added BF_3•OEt_2 (0.145 g, 1.02 mmol). The reaction stirred at -15 °C for 30 min and was then warmed to rt and stirred for 2h. Et_3N (0.142 mL, 1.02 mmol) was added and the solution

was concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, gradient elution 5% to 10% EtOAc in hexanes with 1% Et_3N) to provide 1.40 g (73 %) of **4.33** as a white solid. $[\alpha]_D^{20}$ = -12.1° (*c* 1.8, $CHCl_3$); IR (neat) ν_{max} = 2954, 2874, 2359, 1732, 1606, 1470 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.51 (dd, *J* = 6.0, 14.4 Hz, 1H), 6.19 (dd, *J* = 1.2, 14.4 Hz, 1H), 4.06 (app q, *J* = 5.4 Hz, 1H), 3.88 (s, 6H), 1.65 (app t, *J* = 7.3 Hz, 2H), 1.47-1.50 (m, 4H), 0.88 (s, 9H), 0.79 (s, 3H) 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149, 109, 75.7, 75.0, 72.5 (3C), 37.3, 36.4, 30.2, 25.8 (3C), 18.5, 15.1, 14.5, -4.66, -4.95.



4.34

Allylic alcohol 4.34: To a solution of vinyl iodide **4.33** (55.0 mg, 0.114 mmol) in THF (1.00 mL) at -78 °C was added a solution of *n*-BuLi (0.100 mL, 2.21 *M* in hexanes, 0.228 mmol) dropwise. The mixture was allowed to stir at -78 °C for 30 min and was warmed to 0 °C and stirred for 2 h. A solution of Me_2Zn (0.228 mL, 0.228 mmol, 1.0 *M* in heptane) was added dropwise slowly. The reaction mixture was stirred at 0 °C for 15 min, at which point a solution of aldehyde **4.29** (35.0 mg, 0.0763 mmol) in THF (0.700 mL) was added dropwise. The reaction stirred at -78 °C for 1.5 h and was quenched by addition of sat. aq. NH_4Cl (5 mL). The mixture was extracted with Et_2O (3 x 10 mL) and the combined extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, gradient elution 5% to 30% EtOAc in hexanes) to provide 15.0 mg (25 %) of **4.34** as a clear oil. (Note: both the vinyl iodide and aldehyde were azeotroped with benzene (3 x 10 mL) prior to use.): ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.6 Hz, 2H), 6.87

(d, *J* = 8.6 Hz, 2H), 6.03 (dd, *J* = 5.6, 15.8 Hz, 1H), 5.72 (dd, *J* = 5.7, 15.8 Hz, 1H), 5.63 (dd, *J* = 6.7, 15.6 Hz, 1H), 5.61 (dd, *J* = 1.5, 15.8 Hz, 1H), 4.69 (app d, *J* = 11.3 Hz, 1H), 4.57 (app d, *J* = 11.2 Hz, 1H), 4.30 (app q, *J* = 5.3 Hz, 1H), 4.08-4.14 (m, 2H), 3.86 (s, 6H), 3.80 (s, 3H), 2.62 (ddd, *J* = 2.0, 7.1, 17.1 Hz, 1H), 2.46 (ddd, *J* = 1.9, 5.5, 17.1 Hz, 1H), 2.12 (d, *J* = 5.2 Hz, 1H), 1.65 (app t, *J* = 7.3 Hz, 2H), 1.43–1.50 (m, 6H), 1.25-1.31 (m, 9H), 0.90 (s, 9H), 0.88 (s, 9H), 0.86-0.89 (m, 3H), 0.77 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.01d (s, 3H);

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Appendix A3:

Spectra Relevant to Chapter 4

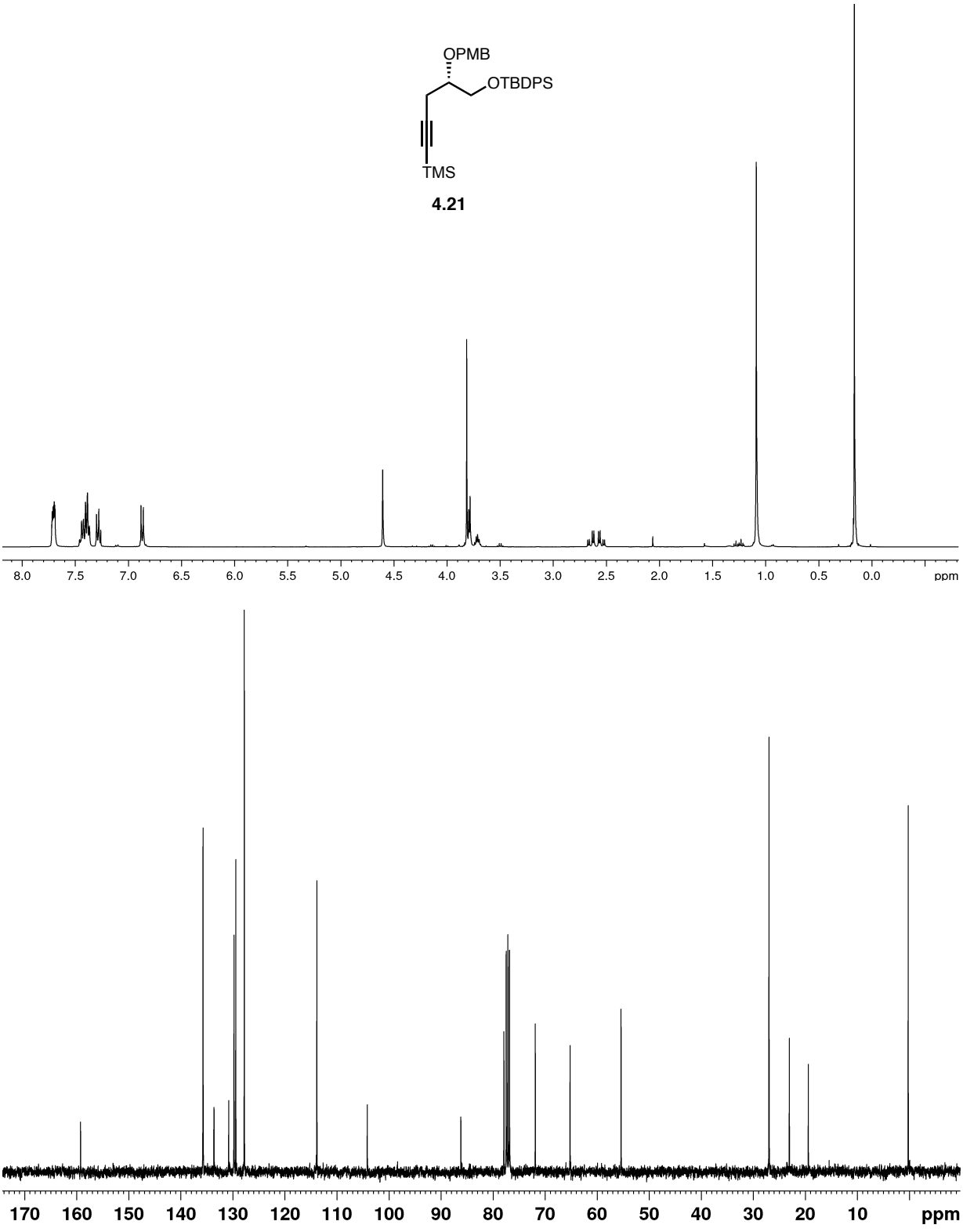

Figure A3.1: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of Compound 4.21

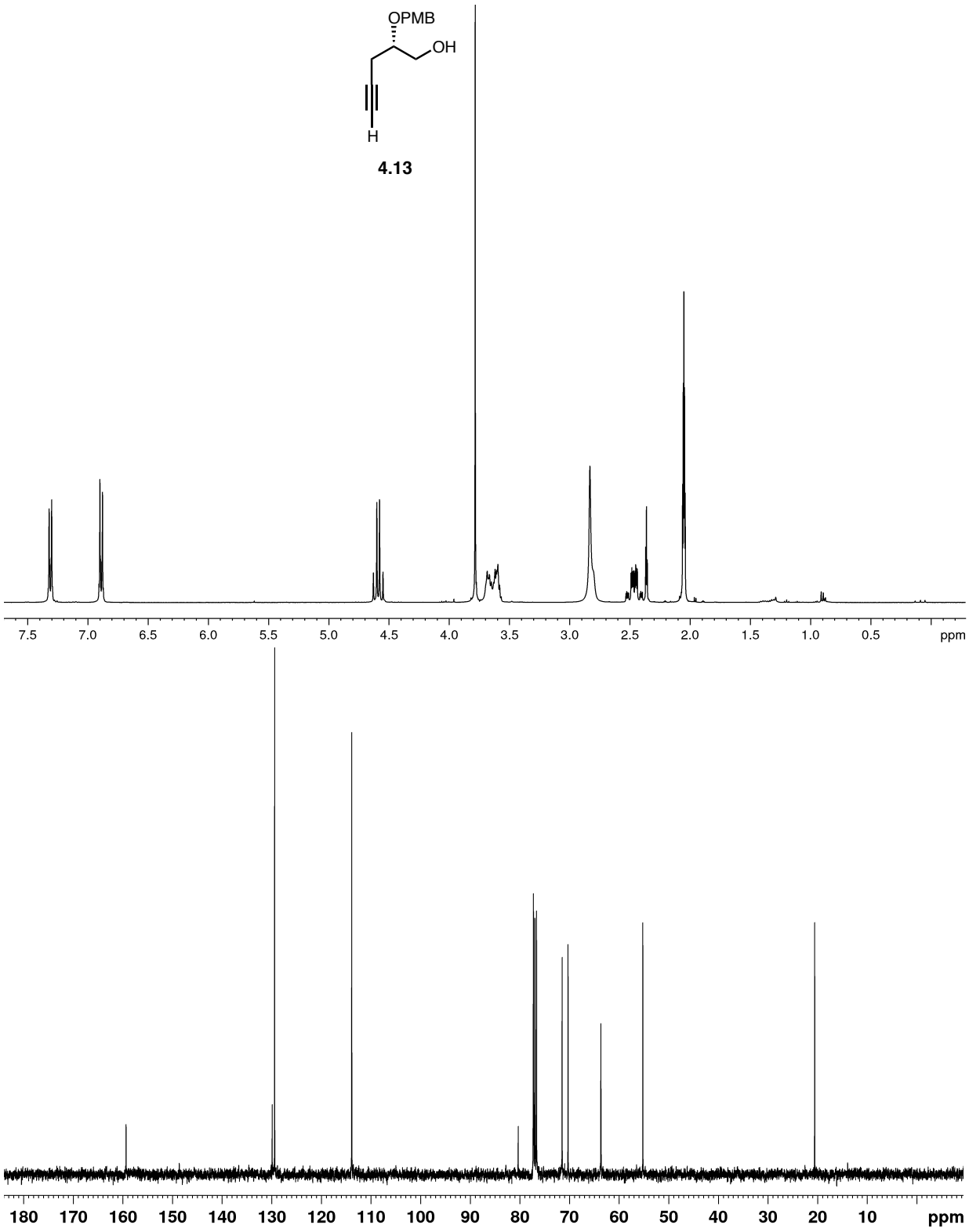

Figure A3.2: ^{1}H NMR (400 MHz, $(CD_3)_2O$) and ^{13}C NMR (100 MHz, $CDCl_3$) of Compound 4.13

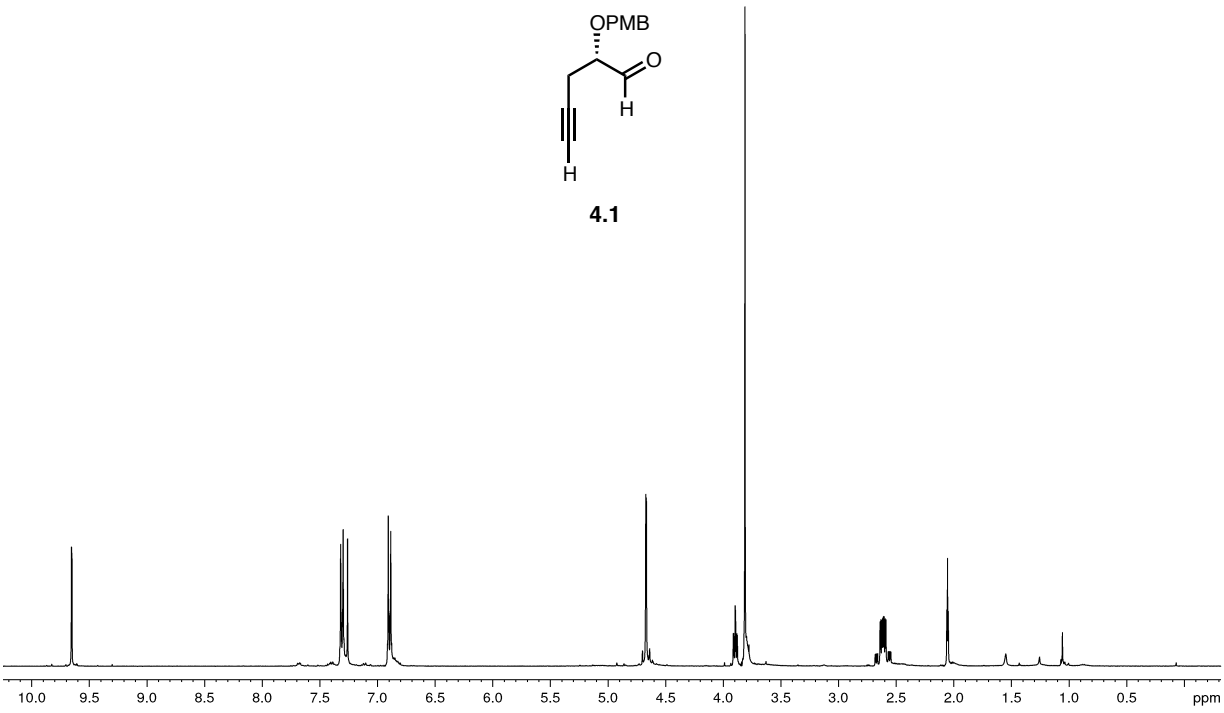

Figure A3.3: ^{1}H NMR (400 MHz, $CDCl_3$) of Compound 4.1

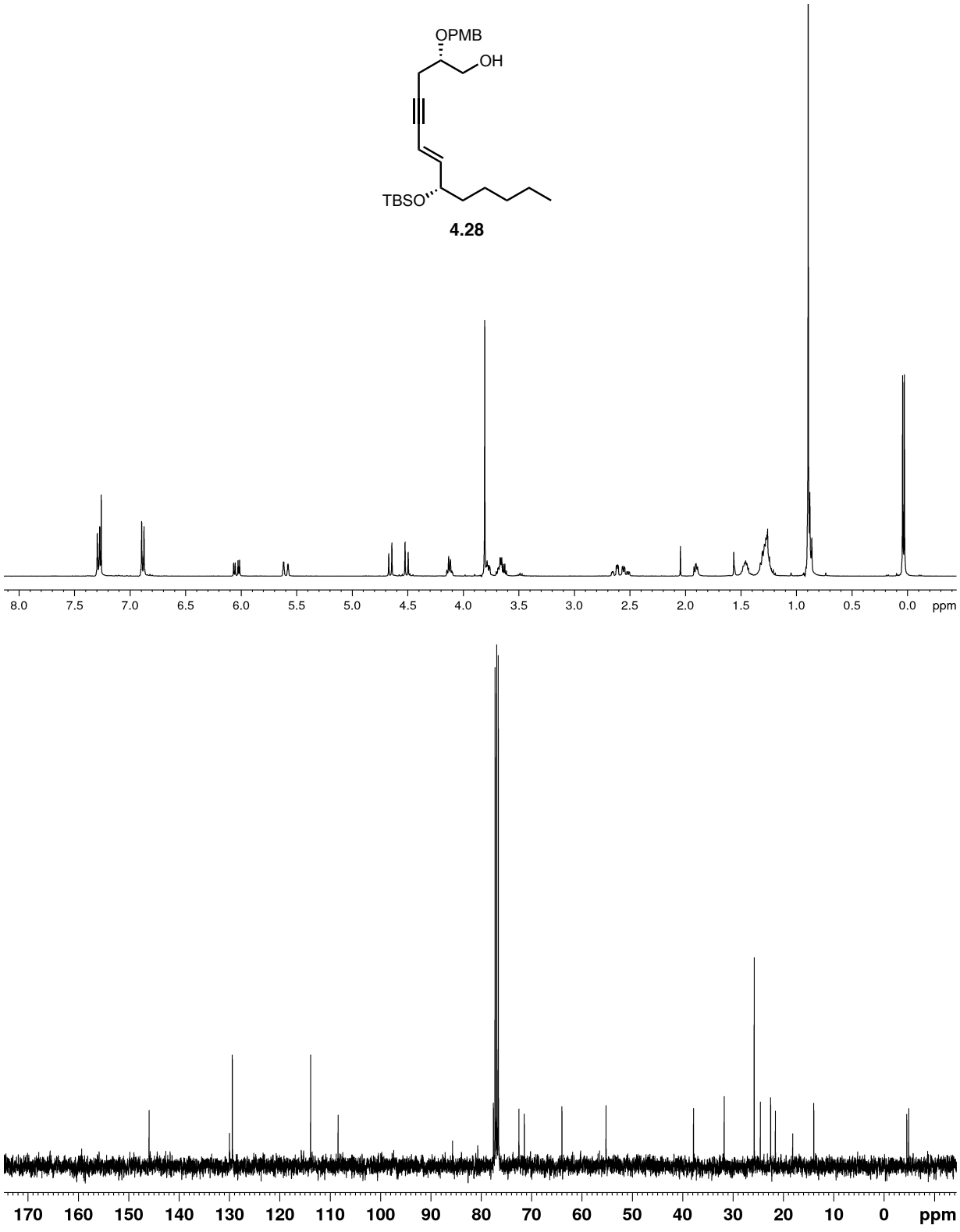

Figure A3.4: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of Compound 4.28

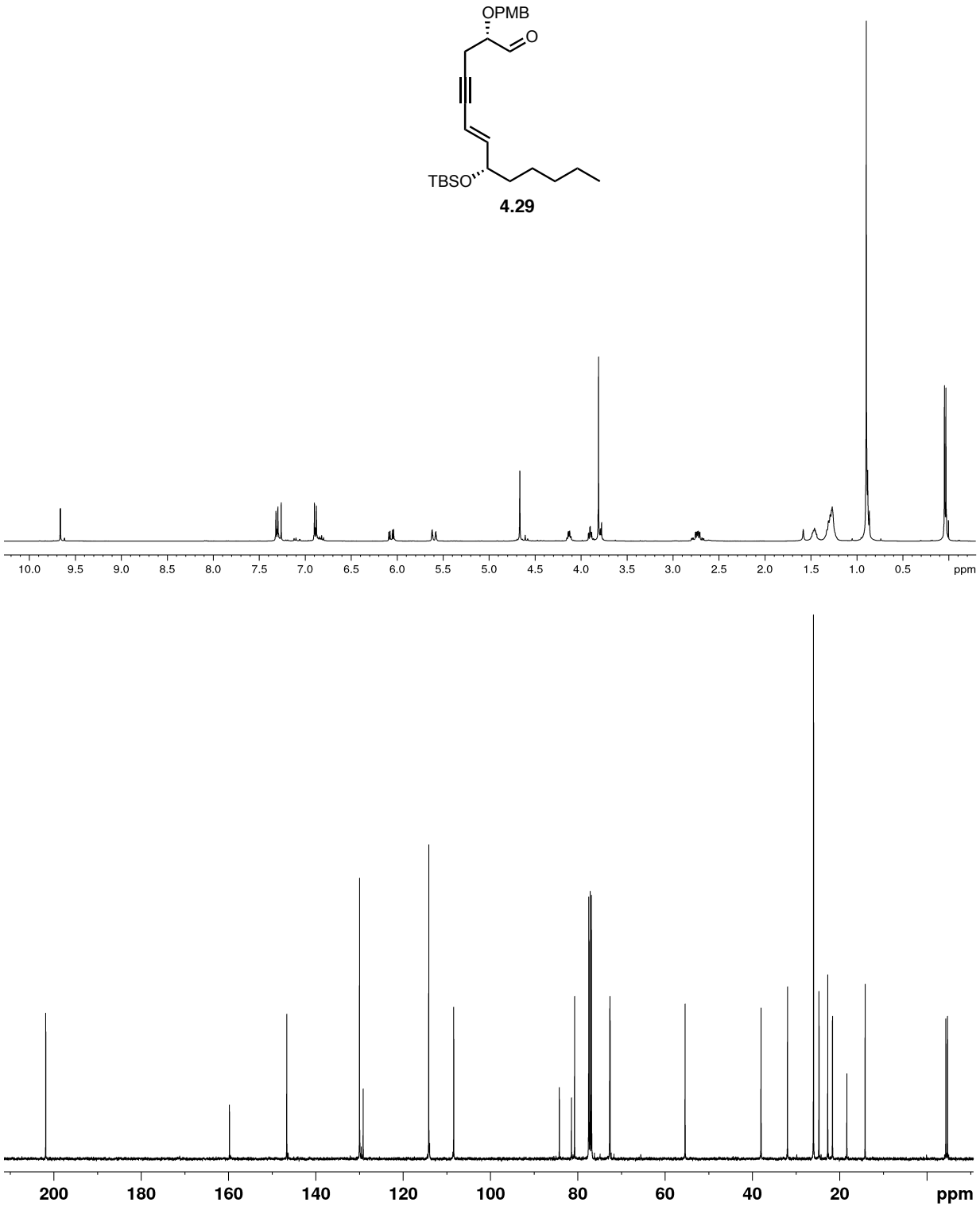

Figure A3.5: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of Compound 4.29

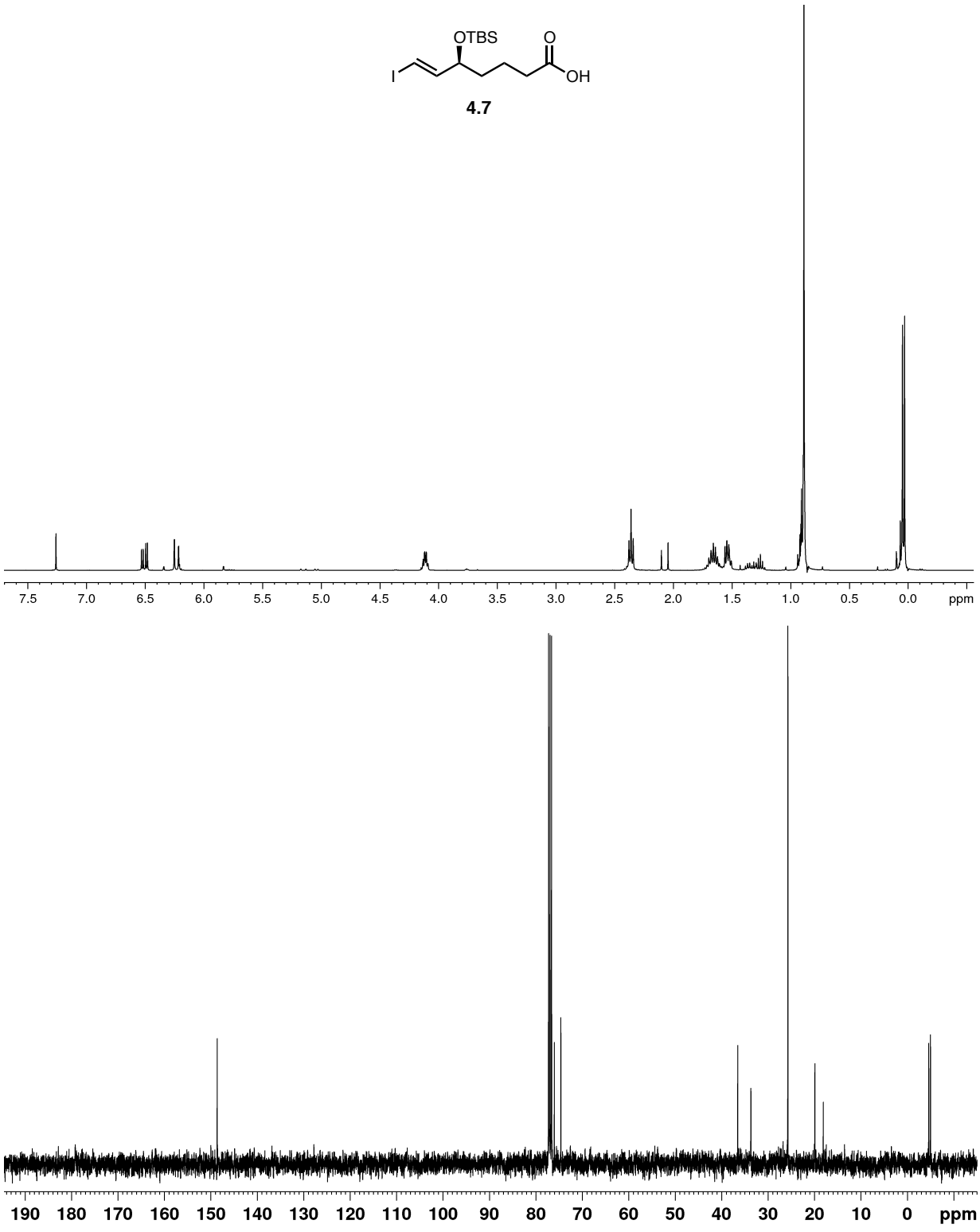

Figure A3.6: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of Compound 4.7

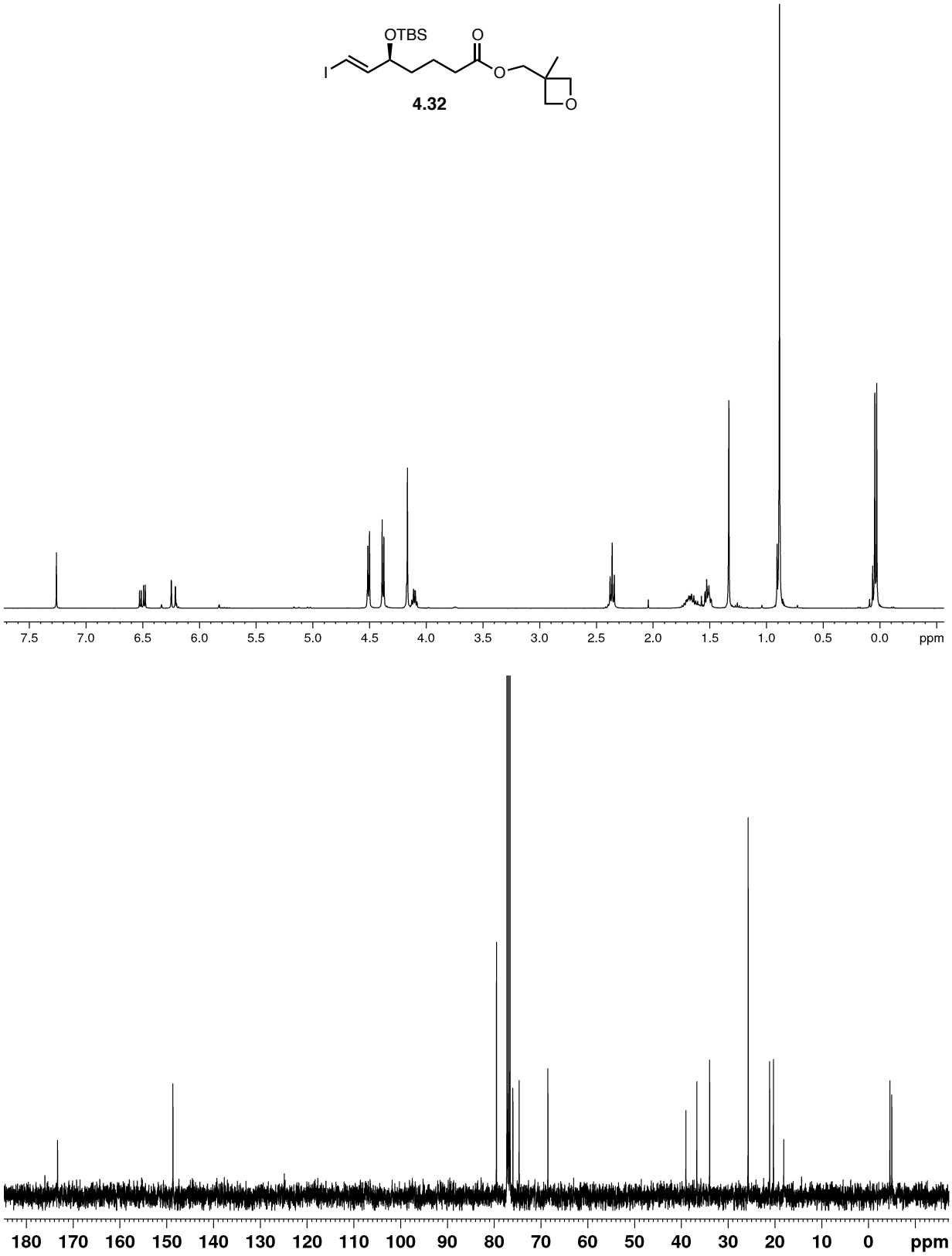

Figure A3.7: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of Compound 4.32

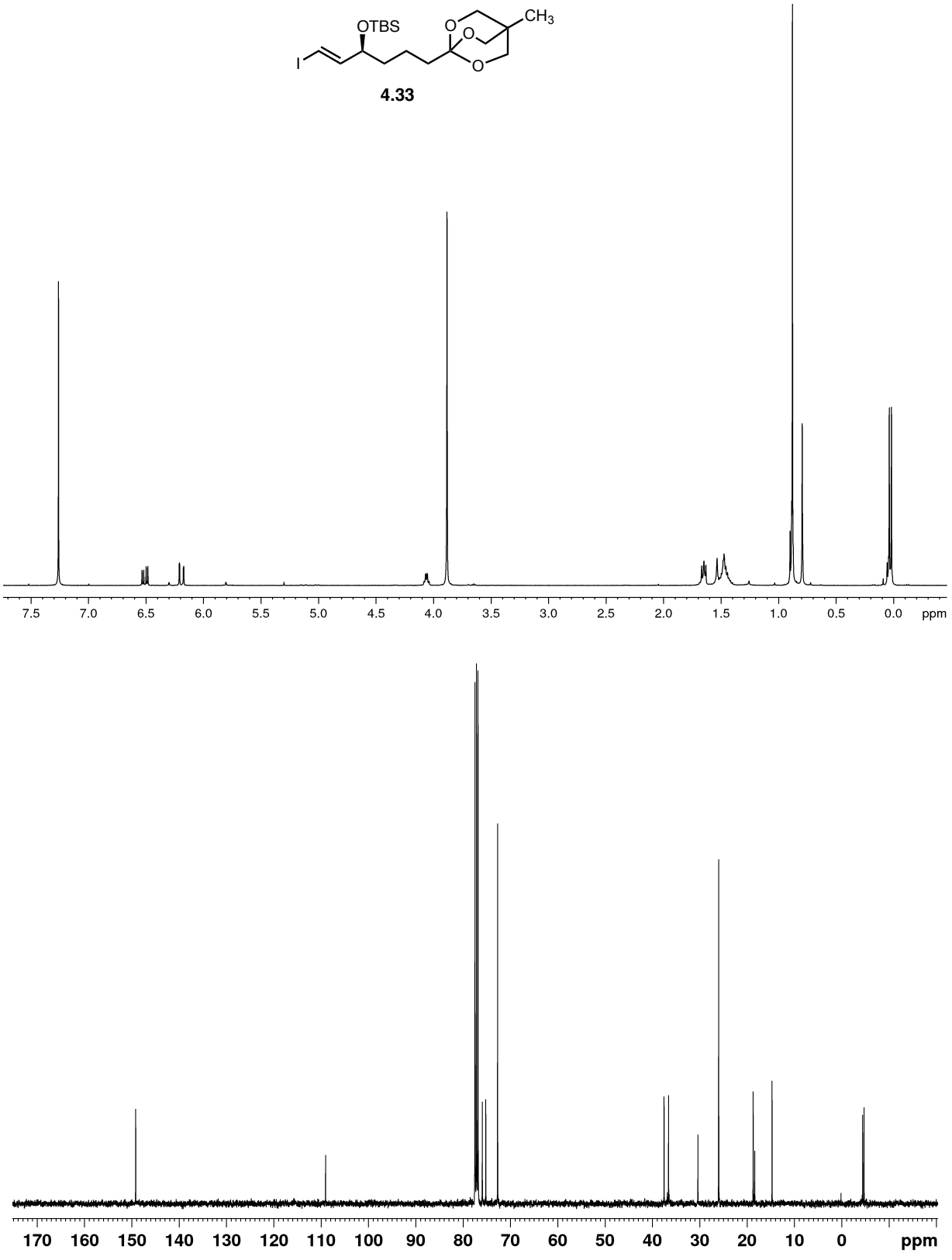

Figure A3.8: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of Compound 4.33

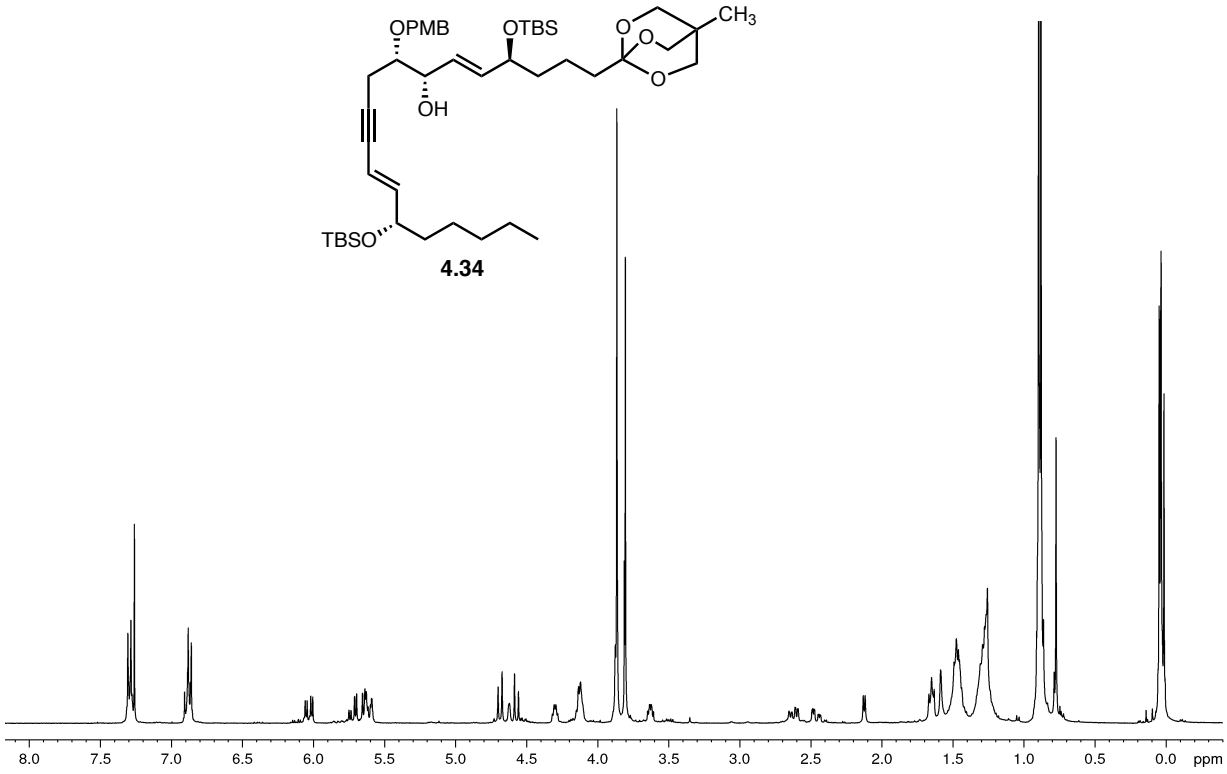

Figure A3.9: ^{1}H NMR (400 MHz, $CDCl_3$) of Compound 4.34