TOTAL SYNTHESIS AND BIOLOGICAL SIGNIFICANCE OF PROSTAGLANDIN D_2 AND E_2 METABOLITES

By

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“Remember, if you don’t hit the fairway on your drive, you can always one-putt.”

-my dad

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TABLE OF CONTENTS

Page

LIST OF FIGURES

LIST OF SCHEMES

LIST OF TABLES

Table Page

LIST OF ABBREVIATIONS

AA	arachidonic acid
Ac	acetyl
Ac_2O	acetic anhydride
AIBN	azobisisobutyronitrile
BBN	borabicyclo[3.3.1]nonane
Bn	benzyl
Bu	butyl
Bz	benzoyl
°C	degrees Celsius
COX	cyclooxygenase
Cp	cyclopentadienyl
$cPLA_2$	cytosolic phospholipase A_2
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
DIBAL	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	dimethyl formamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
Ee	enantiomeric excess
Et	ethyl
g	gram
GPCR	G-protein coupled receptor
HMDS	hexamethyldisilazide
HRMS	high resolution mass spectrometry
*i*Bu	isobutyl
ImH	imidazole
*i*Pr	isopropyl
IR	infrared spectroscopy
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
mol	mole
Ms	methanesulfonate
N	normal concentration
NBS	N-bromosuccinimide
NOESY	nuclear Overhauser effect spectroscopy Nuc nucleophile
OAc	acetoxy
p	pentet
PCC	pyridinium chlorochromate

PDC	pyridinium dichromate
PG	prostaglandin
Ph	phenyl
PMB	*para*-methoxybenzyl
PMBCl	*para*-methoxybenzylchloride
ppm	parts per million
PPTS	pyridinium *para*-toluenesulofnate
Pyr	pyridine
q	quartet
rt	room temperature
s	singlet
Sia_2BH	disiamylborane
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBDPSCl	*tert*-butyldiphenylsilyl chloride
TBP	tributylphosphine
TBS	*tert*-butyldimethylsilyl
TBSCl	*tert*-butyldimethylsilyl chloride
TBSOTf	*tert*-butyldimethylsilyl trifluromethanesulfonate
*t*Bu	*tert*-butyl
TES	triethylsilyl
TESCl	triethylsilyl chloride
THF	tetrahydrofuran
THP	tetrahydropyran
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
TPAP	tetra-*n*-propylammonium perruthenate
Ts	para-toluenesulfonate
TTIP	titanium tetraisopropoxide

CHAPTER 1

BIOSYNTHESIS, BIOLOGY, AND METABOLISM OF PROSTAGLANDINS

Inflammation and the Immune Response

The cellular and molecular mechanisms involved in inflammation is made up of an intricate cascade of events that regulate the pain response.[1] Cell surface receptors will first recognize and identify the harmful stimuli before activation of the inflammatory pathway occurs. This process involves the release of critical inflammatory markers from damaged tissues and cells and includes interleukins, growth factors, cytokines and prostaglandins.[2] These inflammatory markers will cause granulocytes (a type of white blood cell) and monocytes (another type of white blood cell that will proliferate into macrophages) to rapidly migrate to the affected area where repair of the damaged site can begin.[3] When controlled, the inflammatory pathway is beneficial and works as an adaptive response to restoring homeostasis.[2]

Biological Production of Prostaglandins

Prostaglandins are cyclic, bioactive molecules derived from arachidonic acid. While broadly involved in homeostasis and pathogenic mediation, they are widely studied for their involvement in the inflammatory response and modulate several physiological systems including the CNS, cardiovascular, gastrointestinal, genitourinary, endocrine, respiratory and immune systems.[4] Considering the vast array of physiological systems prostaglandins are involved in, it is unsurprising that their production has been implicated in cancer, inflammation, cardiovascular disease and hypertension.[4]

The formation of prostaglandins occurs via the arachidonic acid pathway through an enzymatic process. When acted upon by a physical or chemical stimuli, cytosolic phospholipase A_2 ($cPLA_2$) releases arachidonic acid from the membrane phospholipids. The cyclooxygenase (COX) enzyme then induces an oxidative cyclization of arachidonic acid **1.1** initiated via a Tyrosine-385 radical to generate bis-allylic radical **1.2** by abstraction of the pro-*S* hydrogen at C-13.[5] After the initial capture of oxygen to form the peroxyl radical species **1.3**, two subsequent *5-exo-trig* radical cyclizations yield bicyclic endoperoxide **1.4**. After capture of a second molecule of oxygen, the peroxyl radical **1.5** is reduced to form hydroperoxide prostaglandin G_2 (PGG_2) and further reduced by peroxidase to yield the gatekeeper endoperoxide PGH_2.

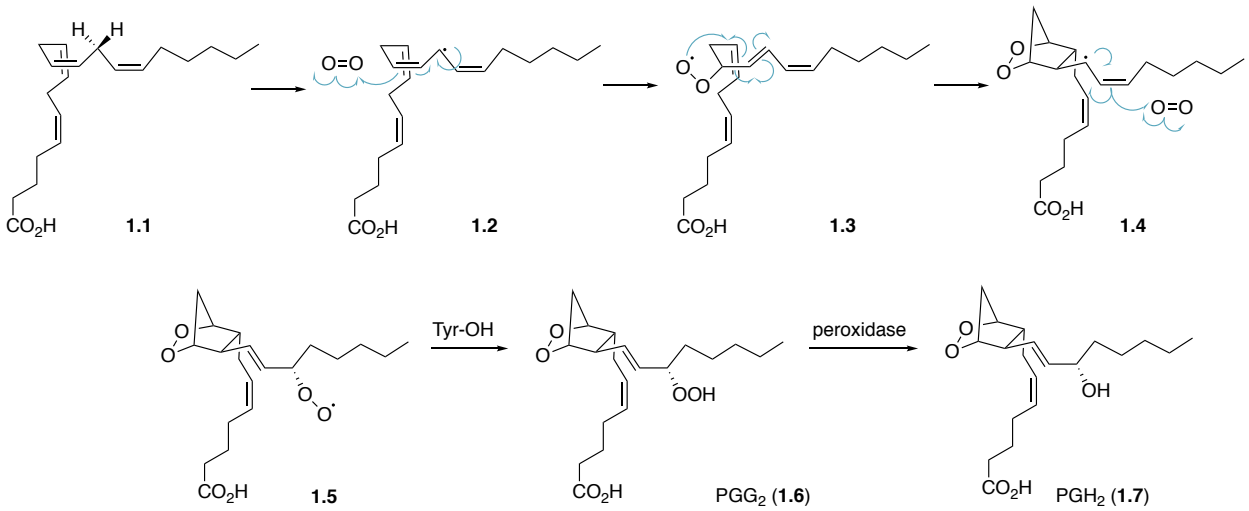


Figure 1.1: Biosynthesis of PGH_2 starting from arachidonic acid

PGH_2 is the precursor for a number of several metabolites including PGI_2, PGE_2, PGD_2, $PGF_{2\alpha}$, and thromboxanes (Figure 1.1). The formation of each of these molecules is dependent on the activity of the corresponding synthetases that are activated and production of each class of molecules is associated with different receptors that perform a wide range of functions. The effects of prostaglandins are mediated largely by nine different G-protein-coupled prostanoid receptors

(DP, EP1-4, FP, IP, TP and CRTH2) and these receptors elicit varying responses depending on the cell type and tissue.[4] The formation of PGD_2, for example, activates the DP1 receptor in lung and epithelial cells, which is associated with allergic asthma.[4]

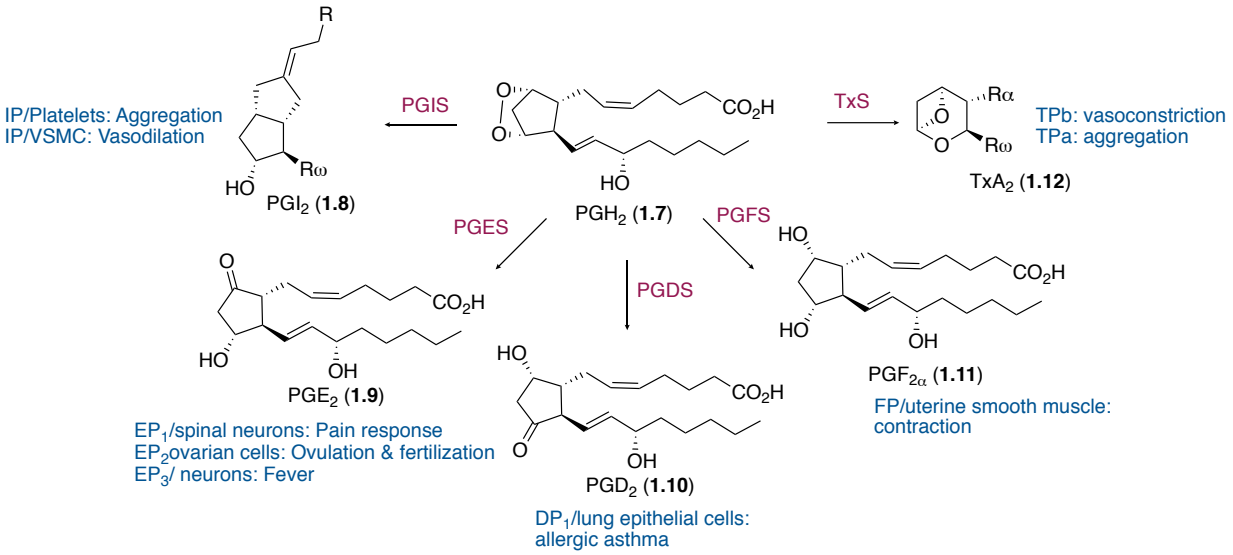


Figure 1.2: Biosynthesis of Prostaglandins

Upon production, prostaglandins are rapidly metabolized. Thus, in order to accurately assess formation of these biologically active molecules, the individual metabolites have been identified. Currently, the best method to evaluate prostaglandin formation *in vivo* is through the measurement of excreted urinary metabolites. This method is preferential to quantification of prostaglandins in blood due to the transient nature of the parent prostaglandins and because prostaglandins can be generated artifactually *ex vivo* by the blood drawing process.[6]

Prostaglandins are metabolized by multiple enzymatic pathways that involve dehydrogenation, β–oxidation, and ω-oxidation. β–oxidation is a process that occurs in the mitochondria of cells and shortens the carbon chain of lipids by two carbon units (Figure 1.3). The process begins when Acyl-CoA- dehydrogenase introduces an element of unsaturation before hydration of the olefin by Enoyl-CoA-hydrolase affords β-hydroxy thioester **1.15**.[7] The alcohol is

oxidized by hydroxyacyl-CoA-dehydrogenase to the β- keto thioester **1.16** before the thioester is cleaved by a thiolase to afford acetyl CoA **1.18** and an acyl-CoA **1.17** molecule that is shortened by two carbons. Acetyl-CoA can be used by cells in the TCA cycle or ketogenesis.[7]

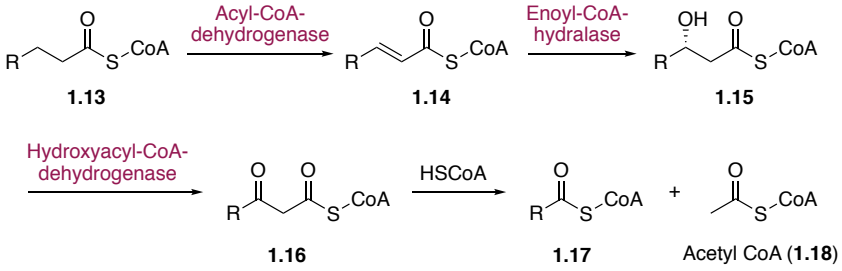


Figure 1.3: β–oxidation in lipid metabolism

Another key process in lipid metabolism is ω-oxidation (Figure 1.4). ω-oxidation occurs on the alphatic, ω-chain and begins with the oxidation of the terminal carbon to an alcohol by the action of a cytochrome P450 (CYP) enzyme.[8] Alcohol dehydrogenase oxidizes the alcohol to aldehyde **1.21** before action aldehyde dehydrogenase affords carboxylic acid **1.22**.

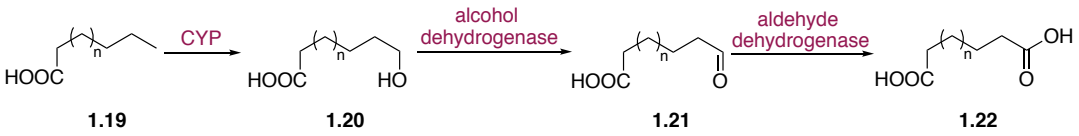


Figure 1.4: ω–oxidation in lipid metabolism

Prostaglandin Nomenclature

The nomenclature of prostaglandins and their metabolites is based around prostanoic acid (Figure 1.5). The letter following "PG" refers to the functionality and substitution pattern within the cyclopentane ring and the subscript numeral refers to the number of side-chain double bonds. The numbering system always begins on the sidechain bearing the carboxylic acid (the α–chain) and ends on the aliphatic sidechain (the ω–chain). The numbering of all prostaglandins is based

on the 20-carbon prostanoic acid structure and numbering of the individual carbons does not change, regardless of whether or not the carbon chain is cleaved during metabolism.

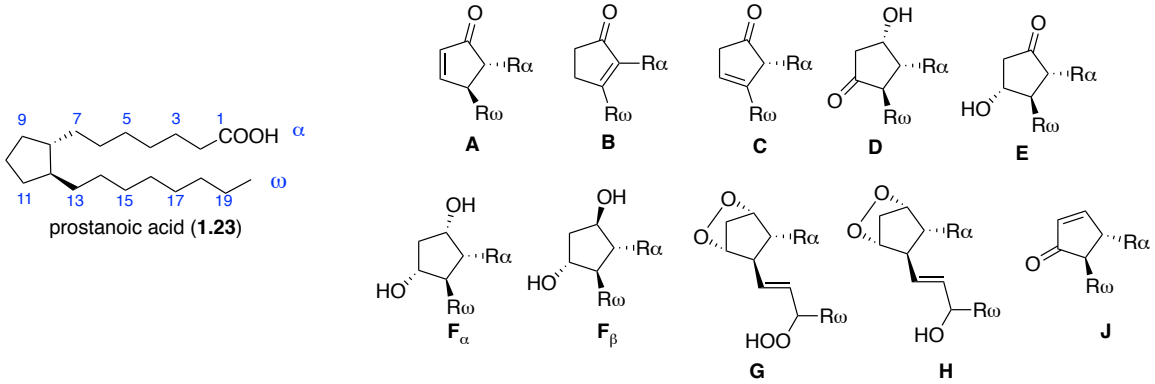


Figure 1.5: Prostaglandin ring structure nomenclature

Prostaglandin E_2 Metabolism

PGE_2 is metabolized to two important urinary metabolites: PGE-M and tetranor PGE_1. (Figure 1.6) PGE-M was identified as the major urinary metabolite of PGE_2 in humans in a landmark study conducted by Hamberg and Samuelsson.[9] Tetranor PGE_1 was later identified by Samuelsson in collaboration with Oates and co-workers as a minor metabolite.[10] Samuelsson, alongside Sune Bergström and John Vane, were awarded the 1982 Nobel Prize in Physiology or Medicin "for their discoveries concerning prostaglandins and related biologically active substances."

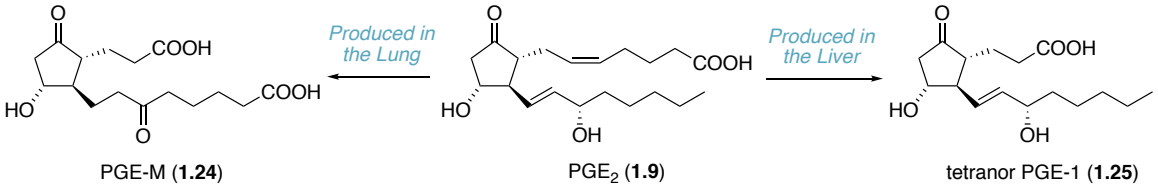
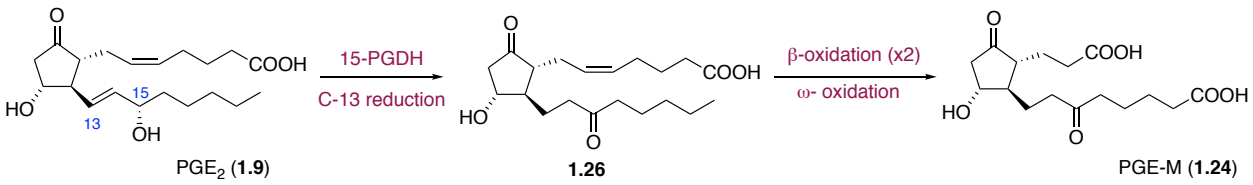


Figure 1.6: Prostaglandin E_2 Metabolism

PGE-M has been validated as the major urinary metabolite of PGE_2 and widely used as a biomarker to study PGE_2 metabolism in relation to a number of different diseases.[11, 12, 13] Tetranor PGE_1, however, has not been studied for decades following its initial discovery due to the lack of an available standard. The minor metabolite became of interest to Milne and coworkers when they hypothesized that tetranor PGE-1 could be a better biomarker in persons with a mutation in the gene that encodes for 15-prostaglandin dehydrogenase (15-PGDH), an enzyme required for the formation of PGE-M.

The metabolic pathway converting PGE_2 to PGE-M is proposed to initiate by C-15 hydroxyl oxidation by 15-PGDH to the corresponding enone.[14] Enzymatic reduction of the latter then affords **1.26** before two rounds of β-oxidation and a round of ω – oxidation result in diacid PGE-M (Figure 1.7). In certain types of cancer, such as colon cancer, 15-PGDH activity is decreased. Therefore, formation of **1.26** (and thus **1.24)** is greatly decreased leading to a buildup of PGE_2.



PGE$_2$ (**1.9**) **1.26** PGE-M (**1.24**)

Figure 1.7: PGE-M biosynthesis

The alternative pathway for PGE_2 metabolism that does not require 15-PGDH leads to formation of tetranor PGE_1 (Figure 1.8). Metabolism of PGE_2 **1.9** to tetranor PGE_1 **1.25** involves two rounds of β-oxidation to the 16-carbon metabolite tetranor PGE_1.[9] Formation of tetranor PGE_1 in human disease has not yet been evaluated.

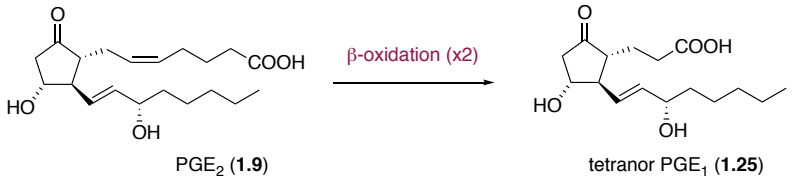


Figure 1.8: Tetranor PGE_1 formation

Prostaglandin D_2 Metabolism

Prostaglandin D_2 is metabolized to three major metabolites via three independent pathways.[6] Each pathway produces a metabolite with a different ring structure and differing functional groups. The existence of the three known metabolic pathways (Figure 1.9) and presence of intermediates preceding the terminal metabolite of each route makes the study and analysis of PGD_2 metabolism complex.

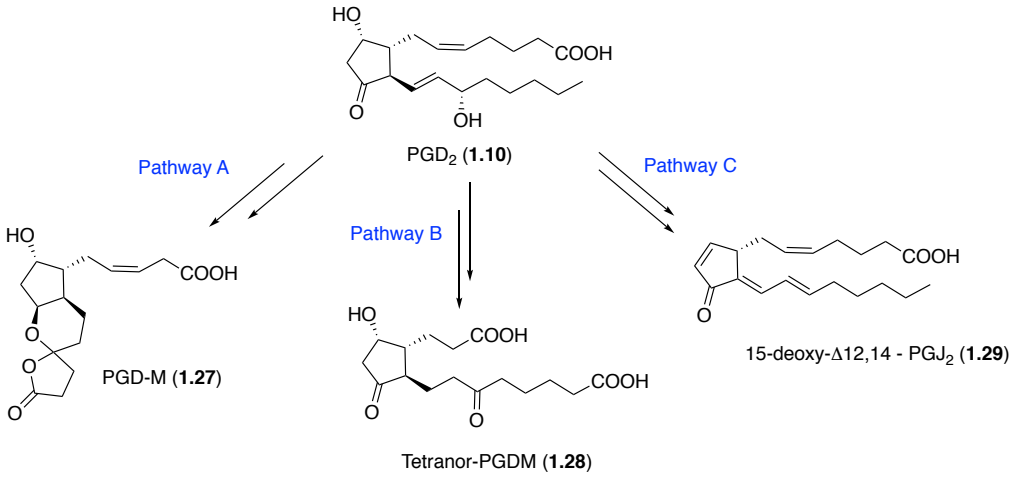


Figure 1.9: Prostaglandin D_2 Metabolism

In Pathway A, reduction of the keto group of PGD_2 via 11-ketoreductase leads to 9α, 11β – $PGF_{2\alpha}$ **1.30**. The ω–chain is first to undergo β–oxidation to yield the 18-carbon metabolite, 2,3-dinor -11β- $PGF_{2\alpha}$ **1.31**.[6] (Figure 1.10) Similar to E_2 metabolism, it is likely that the first manipulation of the α - chain includes action of 15-PGDH to oxidize the allylic alcohol

to the enone, followed by reduction of the Δ^{13} olefin to yield **1.32**. Lastly, ω–oxidation to the diacid **1.33**, followed by β–oxidation to cleave two carbons affords PGD-M. PGD-M exists in equilibrium as the open-chain diacid and the tricyclic form. The tricyclic form is resultant of the condensation of the C-11 hydroxyl onto the C-15 keto moiety which is able to undergo lactonization onto the carboxylic acid. PGD-M was identified by Roberts and Liston in 1985 as the major metabolite of PGD_2 after a human subject was injected with tritium labeled PGD_2. The urinary metabolites were isolated and characterized by gas chromatography- mass spectrometry.[15]

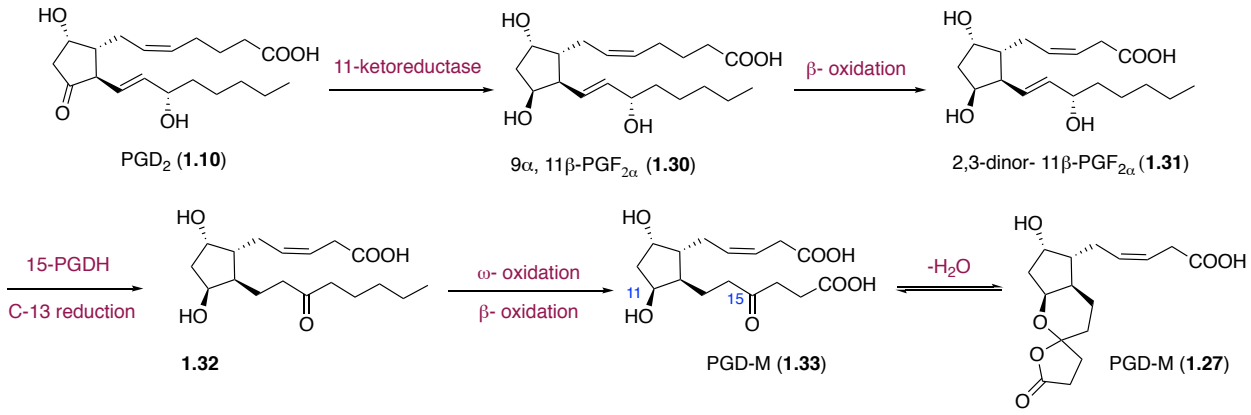


Figure 1.10: PGD-M formation (Pathway A of Figure 1.9)

In the second route of metabolism (Pathway B, Figure 1.9), PGD_2 is first acted upon by 15-PGDH. The reduction of the enone to a ketone occurs before two rounds of β-oxidation and a round of ω–oxidation yields tetranor PGDM (Figure 1.11). This diacid metabolite maintains the D-ring structure and was discovered serendipitously by Song and coworkers when they were studying tetranor PGEM, a structural isomer of tetranor PGDM.[16]

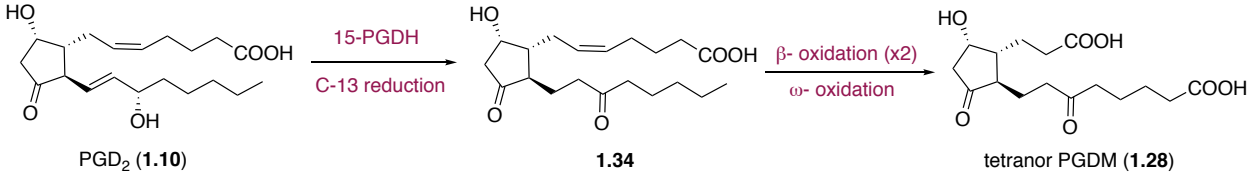
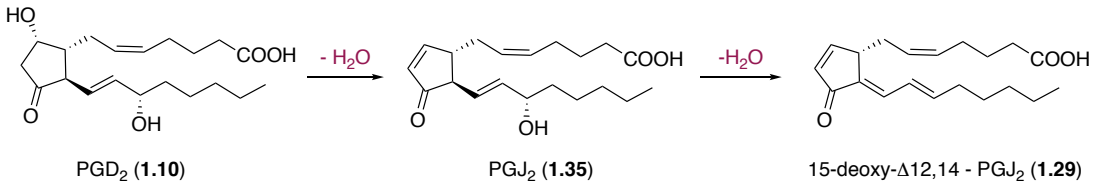


Figure 1.11: Formation of Tetranor PGDM

In the third route of metabolism (Pathway C, Figure 1.9), PGD_2 undergoes dehydration to yield the cyclopentenone PGJ_2 (**1.35**). A second dehydration yields 15-deoxy- $\Delta^{12,14}$-PGJ_2 ($15dPGJ_2$) (**1.29**).[17,18] The enone moiety makes PGJ_2 and $15dPGJ_2$ very reactive and susceptible to adduction by nucleophilic amino acids and small peptides, complicating analysis and quantification of the metabolite.[6] Caution must be exercised when handling biological samples for the quantification of PGD_2 as dehydration (and subsequent formation of PGJ_2 and $15dPGJ_2$) can occur *ex vivo*.



PGD$_2$ (**1.10**) PGJ$_2$ (**1.35**) 15-deoxy-Δ12,14 - PGJ$_2$ (**1.29**)

Figure 1.12: Formation of 15-deoxy- Δ12,14 -PGJ_2

Conclusion to Chapter One

Due to the complex and intriguing metabolic profile of PGD_2 and PGE_2, additional studies are required in order to gain a more complete understanding of arachidonic acid metabolism. These metabolites are broadly important for human health due to their use as clinical biomarkers for a wide range of diseased cell states. We saw a need to specifically investigate tetranor PGE_1 and PGD-M to gain a better understanding of their biological relevance and use as clinical biomarkers.

References

1. Chen, L.; Deng, H.; Cui, H.; Fang, J.; Zuo, Z.; Deng, J.; Li, Y.; Wang, X.; Zhao, L. "Inflammatory responses and inflammation-associated diseases in organs" *Oncotarget*. **2017**, *9*, 7204-7218.

2. Medzhitov, R. "Origin and physiological roles of inflammation" *Nature* **2008**, *454,* 428–435.

3. Ricciotti, E.; FitzGerald, G.A. "Prostaglandins and inflammation" *Arterioscler Thromb Vasc Biol.* **2011**, *31,* 986–1000.

4. Hata, A.N.; Breyer, R.M. "Pharmacology and signaling of prostaglandin receptors: multiple roles in inflammation and immune modulation" *Pharmacol. Ther.* **2004**, *103,* 147–166.

5. Rouzer, C. A.; Marnett, L.J. "Mechanism of Free Radical Oxygenation of Polyunsaturated Fatty Acids by Cyclooxygenases" *Chem. Rev.* **2003**, *103,* 2239−2304.

6. Milne, G.L. "Lipid Biomarkers of Inflammation" In Chronic inflammation: nutritional and therapeutic interventions; Roy, S.; Bagchi, D.; Raychaudhuri, S. P.; Eds.; Taylor & Francis: Boca Raton, **2013**; 275-285.

7. Houten, S. M.; Violante, S.; Ventura, F. V.; Wanders, R. J. A. "The Biochemistry and Physiology of Mitochondrial Fatty Acid β– Oxidation and Its Genetic Disorders" *Annu. Rev. Physiol.* **2016**, *78,* 23–44.

8. Miura, Y. "The biological significance of ω-oxidation of fatty acids" *Proc. Jpn. Acad.* **2013**, *89,* 370-382.

9. Hamberg, M.; Samuelsson, B. "On the metabolism of prostaglandins E1 and E2 in Man" *J. Biol. Chem.* **1971**, *246,* 6713-6721.

10. Oates, J. A.; Sweetnam, B. J.; Green, K.; Samuelsson, B. "Identification and assay of tetranor-prostaglandin E1 in human urine" *Anal. Biochem.* **1976**, *74,* 546-559.

11. Idborg, H.; Pawelzik, S.C.; Perez-Manso, M.; Björk, L.; Hamrin, J.; Herlenius, E. Jakobsson, P.J. "Evaluation of urinary prostaglandin E2 metabolite as a biomarker in infants with fever due to viral infection." *Prostaglandins Leukot. Essent. Fatty Acids.* **2014**, *91,* 269-75.

12. Kekatpure, V.D.; Boyle, J.O.; Zhou, X.K.; Duffield-Lillico, A.J.; Gross, N.D.; Lee, N.Y.; Subbaramaiah, K.; Morrow, J.D.; Milne, G.L.; Lippman, S.M.; Dannenberg, A. J. "Elevated levels of urinary prostaglandin E metabolite indicate a poor prognosis in ever smoker head and neck squamous cell carcinoma patients" *Cancer Prev. Res.* **2009**, *2,* 957-965.

13. Cai, Q.; Gao, Y.T.; Chow, W.H.; Shu, X.O.; Yang, G.; Ji, B.T.; Wen, W.; Rothman, N.; Li, H.L.; Morrow, J.D.; Zheng, W. "Prospective study of urinary prostaglandin E2 metabolite and colorectal cancer risk" *J. Clin. Oncol.* **2006**, *24,* 5010-5016.

14. Hamberg, M.; Samuelsson, B. "Metabolism of prostaglandin E2 in guinea pig liver. II. Pathways in the formation of the major metabolites." *J. Biol. Chem.* **1971**, *246,* 1073-1077.

15. Liston, T.E.; Roberts, L.J. "Metabolic Fate of Radiolabeled Prostaglandin D2 in a Normal Human Male Volunteer" *J. Biol. Chem.* **1985**, *260,* 13172.

16. Song, W.L.; Wang, M.; Ricciotti, E.; Fries, S.; Yu, Y.; Grosser, T.; Reilly, M.; Lawson, J. A.; FitzGerald, G.A. "Tetranor PGDM, an abundant urinary metabolite reflects biosynthesis of prostaglandin D2 in Mice and Humans." *J. Biol. Chem.* **2008**, *283,* 1179–1188.

17. Fitzpatrick, F.A.; Wynalda, M.A.; "Albumin-catalyzed metabolism of prostaglandin D2: identification of products formed in vitro." J. *Biol. Chem.* **1983**, *258,* 11713-11718.

18. Shibata, T., Kondo, M.; Osawa, T.; Shibata, N.; Kobayashi, M., Uchida, K. "15-deoxy-delta 12,14-prostaglandin J2. A prostaglandin D2 metabolite generated during inflammatory processes." *J. Biol. Chem.* **2002**, 10459-10466.

CHAPTER 2

TOTAL SYNTHESIS OF SELECT PROSTAGLANDINS

General Chemical Approaches Towards Prostaglandins

Prostaglandins have been compelling targets for total synthesis since the late 1960's.[1] Many of the earliest approaches were developed at Upjohn Pharmaceutical[2] and were semisynthetic, beginning from arachidonic acid metabolites isolated from biological samples. The total synthesis of prostaglandins and their metabolites synthesis started in the coming years and moved toward approaches that were scalable and amenable to analogue synthesis. The three primary strategies toward prostaglandins that emerged employed either 1) a two-component coupling[3], 2) Noyori's three-component coupling system[4,5] or 3) the Corey Lactone.[1] (Figure 2.1)

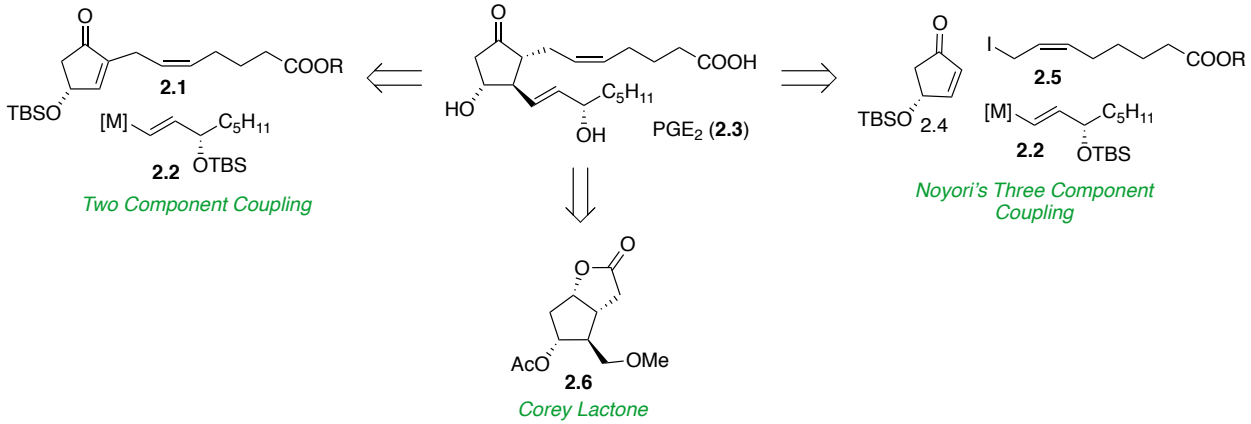


Figure 2.1: Strategies toward prostaglandin synthesis

In the two-component coupling approach, the α-substituted cyclopentenone was originally constructed by Sih and coworkers[3] by alkylating lithiated cyclopentadiene **2.7** and subsequently oxidizing diene **2.8** to a mixture of constitutional isomers, initially favoring undesired

β–substituted isomer **2.10**. The ratio could be improved upon by oxidation of the mixture to the 1,3-dione, followed by mild ketone reduction with sodium borohydride. This synthesis of the α-substituted cyclopentenone was significantly improved upon by Johnson and coworkers[6] in 1993 through the use of α-iodoenone **2.11**. B- alkyl Suzuki coupling of **2.11** with boronate **2.12** provided methyl ester **2.13** in good yield. Enones **2.9** and **2.13** and were intermediates in route to the synthesis of PGE_1.

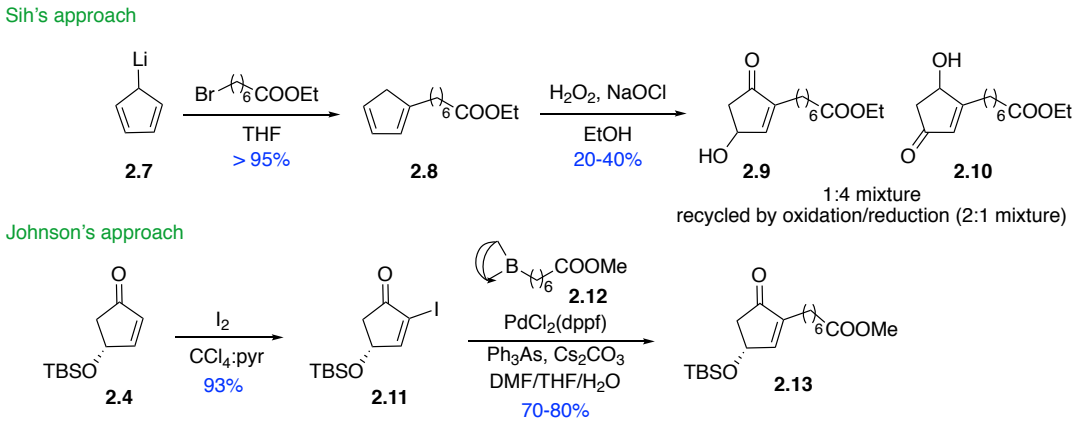


Figure 2.2 Two-component coupling α-substituted enone construction

The three-component coupling approach is chemically very similar to the two-component coupling approach, but achieves alkylation of α and β positions in a single step as opposed to two steps. Noyori's classic conditions[5] (Figure 2.3) allow for the critical *trans,trans* relationship of the α and β substituents present in PGE_2 and PGE_1 synthesis. This method has also been employed for the synthesis of $PGF_{2\alpha}$ and related analogues.

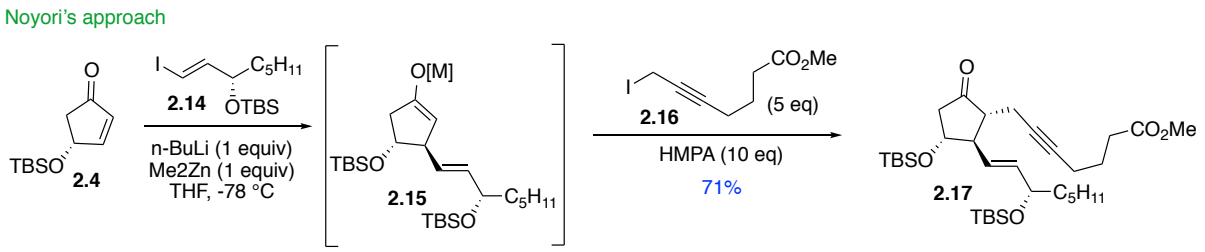
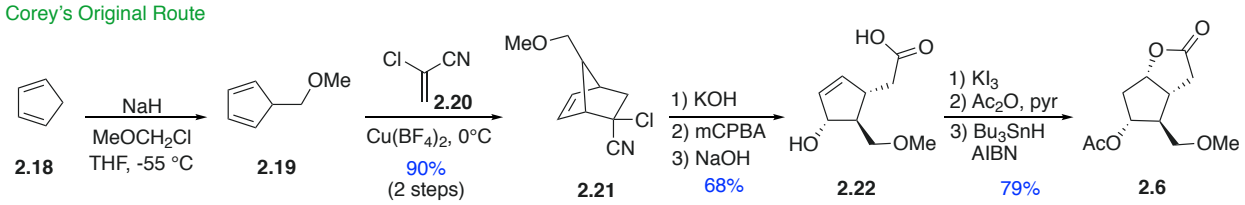


Figure 2.3 Three-component coupling system

Lastly, the Corey lactone[1] **2.6** offers a convenient solution to the main challenge in many prostaglandin syntheses: achieving the necessary stereochemistry around the central pentacyle. The Corey lactone (a compound with four contiguous stereocenters around the central pentacycle already installed) is a versatile intermediate that is amenable to many different prostaglandin frameworks and is now commercially available. In the original synthesis, alkylation of cyclopentadiene **2.18**, followed by Diels-Alder[7] with 2-chloroacrylonitrile (as a ketene equivalent) provided [2.2.1] bicycle **2.21**. Hydrolysis with KOH provides the corresponding ketone, followed by Bayer-Villager oxidation[8] and saponification afforded carboxylic acid **2.22**. Iodolactonization followed by acetylation of the free alcohol and reductive dehalogenation revealed Corey lactone **2.6**. Several different analogues of the Corey lactone are now available bearing different protecting groups at the primary and secondary alcohols in the southern region of the molecule and differing in the oxidation state of the primary alcohol.

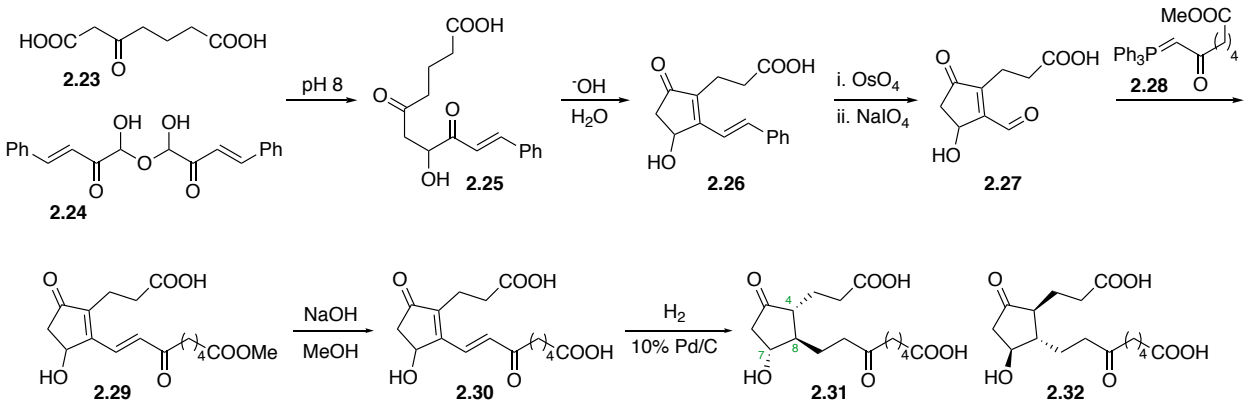


Scheme 2.1: Original synthesis of the Corey lactone

Chemical Approaches Towards PGE_2 Urinary Metabolites

Lilly's Synthesis of PGE-M (1974)

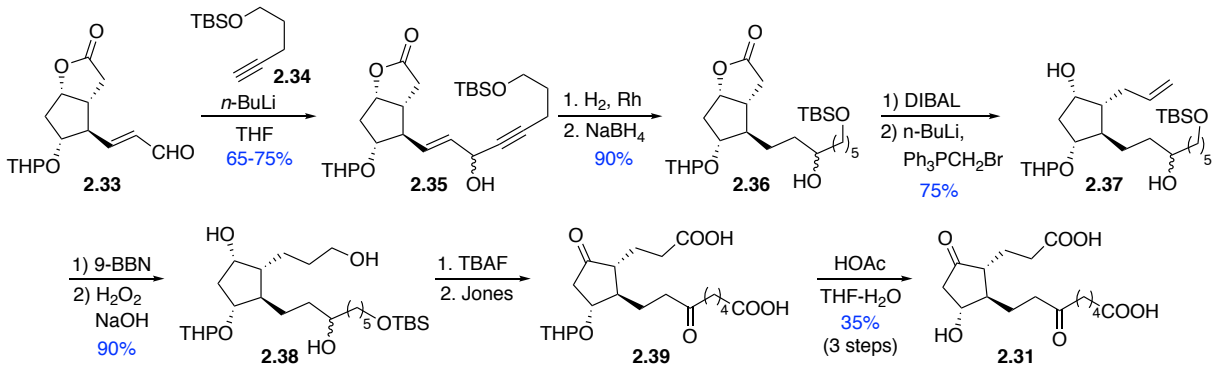
The major urinary metabolite of PGE_2, PGE-M was first prepared by Lilly in 1974[9] and yields were not disclosed for any step. The synthesis commenced with an aldol condensation of a solution of the hemihydrate of styrylglyoxal **2.23** and β- ketopimelic acid **2.24**. Treatment of diketone **2.25** with aqueous hydroxide afforded cyclopentenone condensation product **2.26**. Oxidative cleavage of the disubstituted alkene to unstable aldehyde **2.24**, followed by Wittig olefination[10] lead to the installation of the lower sidechain. After saponification of the methyl ester, the dienone underwent reduction with 10% Pd/C under H_2 to afford diacid **2.31** and **2.32** as racemates. It was reasoned that the stereochemistry around the cyclopentanone ring was *trans* in regard to the C-7 and C-8 positions based on the shift of the α-hydroxy proton (δ 4.2). The relationship of the C-4 and C-8 substituents was reasoned to also be *trans* after treatment of the compound with potassium acetate in ethanol did not epimerize the C-4 substituent. The route was also modified to produce enantiopure **2.31** and **2.32** by carrying out a resolution of the α–methyl benzylamine salt of **2.26** before oxidative cleavage.



Scheme 2.2 First Synthesis of PGE-M by Lilly

Upjohn's Synthesis of PGE-M (1975)

Upjohn began their synthesis from Corey lactone derivative **2.33**.[11] Addition of alkyne **2.34** to the aldehyde produced an inconsequential mixture of propargylic alcohols. Complete reduction of the internal alkene and alkyne to the alkane was achieved with an atmosphere of hydrogen with rhodium on alumina. $NaBH_4$ was employed in the next step to reduce any undesired ketone product back to an alcohol. Standard reduction of lactone **2.36** to the lactol and Wittig olefination of the masked aldehyde with methyltriphenylphosphonium bromide afforded the full carbon framework of the target metabolite. Hydroboration and oxidation of the terminal alkene was followed by deprotection of the TBS group. The tetraol was then fully oxidized to diacid **2.39**. Deprotection of the THP group under acidic conditions afforded the fully deprotected product. One major positive aspect of the synthesis is the amenability of the synthesis for deuterium or tritium incorporation, which could conceivably occur via the addition of isotopically labeled pentynol to the Corey lactone derivative in the first step.

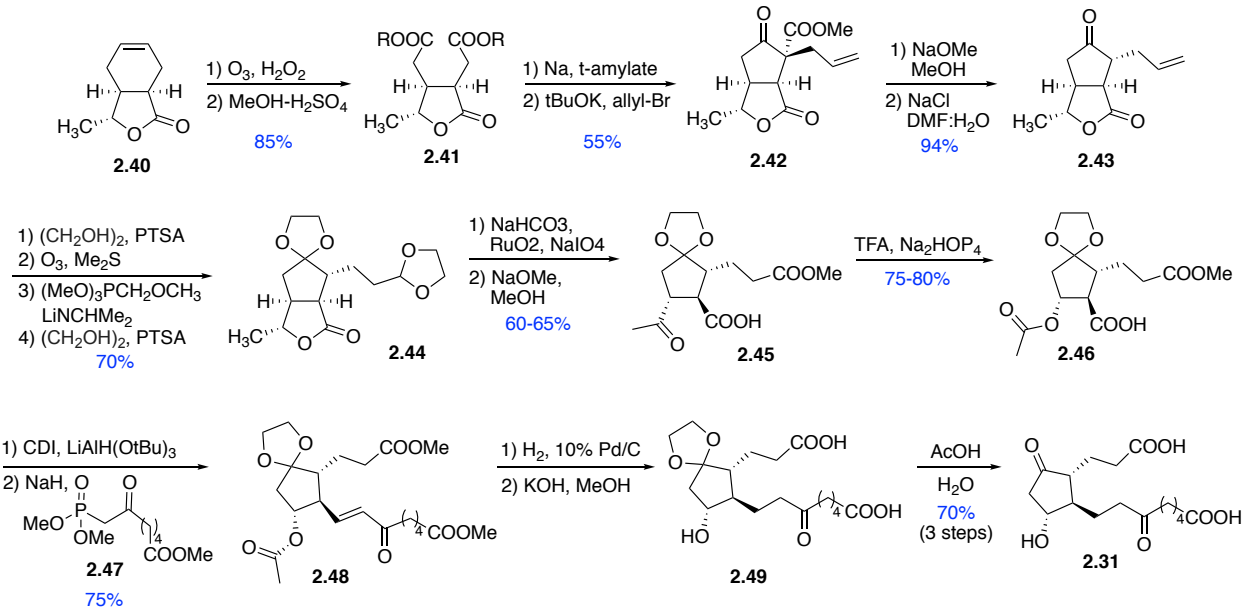


Scheme 2.3: Synthesis of PGE-M by Upjohn

Merck's Synthesis of PGE-M (1976)

Merck diverged from common prostaglandin synthetic strategies by relying on a condensation of angelica lactone and methyl 8,10-undecadienoate to initially introduce

stereochemistry in their synthesis of PGE-M.[12] From Diels Alder product **2.40**, ozonolysis and esterification provided dimethylester **2.41**. Dieckmann condensation[13] and allylation with allyl bromide and potassium *tert*-butoxide yielded β-keto ester **2.42**, which smoothly underwent decarboxymethylation and favorably epimerized the α-allyl group. Following protection of the ketone, ozonolysis safely afforded the terminal aldehyde required for one-carbon homologation via a Horner-Wadsworth-Emmons olefination.[14] Acetalization of the resultant aldehyde yielded diacetal **2.44**. Oxidation of the lactone and subsequent esterification provided **2.45** with the required *trans, trans* stereochemistry around the cyclopentane core, before Baeyer-Villager oxidation of the γ sidechain and elongation of the β sidechain resulted in the full carbon framework of the natural product. Reduction of the olefin, saponification of the esters, and removal of the ketal protecting group liberated PGE-M.

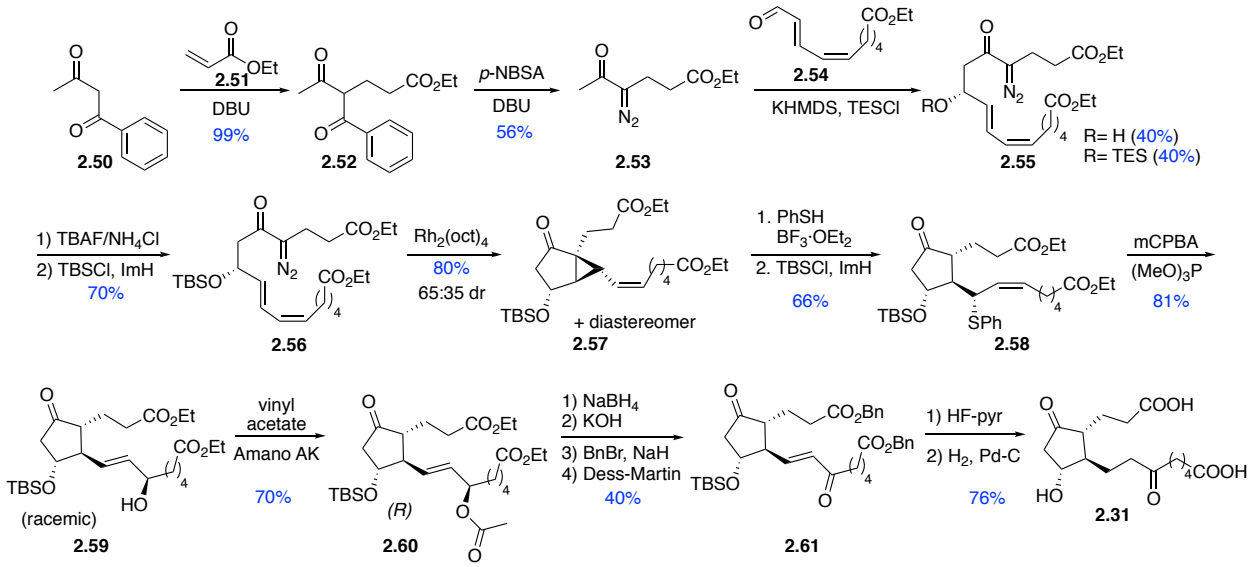


Scheme 2.4: Synthesis of PGE-M by Merck

Taber's Synthesis of PGE-M (2009)

PGE-M was most recently prepared by Taber[15] and utilized an intramolecular cyclopropanation to install the necessary stereochemistry around the cyclopentanone core. The

route commenced with a Michael addition of benzoyl acetone to ethyl acrylate and was followed by diazo transfer with *p*-nitrobenzenesulfonyl azide and DBU. Aldol reaction of the resultant diazoketone **2.53** with aldehyde **2.54** provided the entire carbon framework of the target molecule as a mixture of the free alcohol and TES-protected alcohol. After conversion of the mixture to TBS-ether **2.56**, the stage was set for the rhodium catalyzed cyclopropanation to provide **2.57**. Thiol opening of the cyclopropane ring with thiophenol and reprotection of the free alcohol resulted in a single diastereomer. Oxidation and Mislow-Evans[16,17] rearrangement then provided racemic allylic alcohol **2.59** before resolution with *R*- selective Amano lipase AK afforded pure *R* enantiomer **2.60**. In an effort to avoid β- elimination to the enone, ketone **2.60** was temporarily reduced to the alcohol prior to saponification and transesterification. Following oxidation to the ketone **2.61**, desilylation and treatment with Pd-C under an atmosphere of H_2 revealed diacid **2.31**.

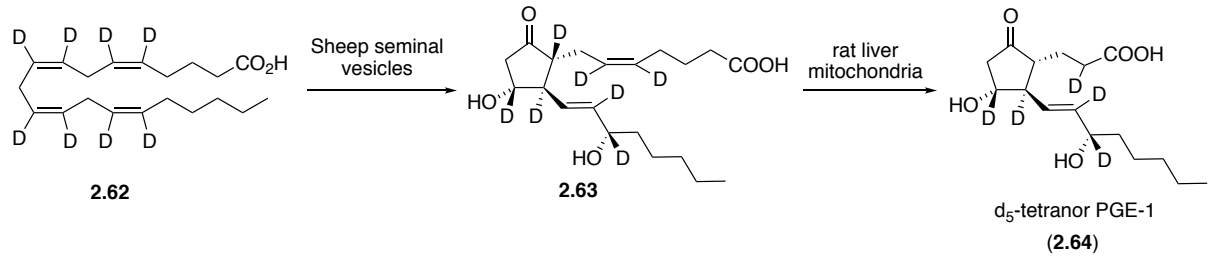


Scheme 2.5: Synthesis of PGE-M by Taber

Samuelsson's Synthesis of Tetranor PGE-1 (1976)

After identification of urinary metabolite Tetranor PGE-1[18], isotopically labeled tetranor PGE-1 was prepared from incubation of d_8-arachidonic acid in sheep seminal vesicle microsomes

and rat liver mitochondria. Carnitine (known to enhance fatty acid transport into the mitochondria) was added during incubation with rat liver mitochondria in order to increase β–oxidation product formation. During the incubation process with sheep vesicles, one of the deuteriums was lost, but this loss was consistent with the enzymatic mechanism for the transformation from arachidonic acid to PGE_2. Two additional deuterium labels were lost during incubation with rat liver mitochondria: one on the α-chain from β- oxidation and one α to the enolizable ketone. The d_5-Tetranor PGE-1 standard was used as an internal standard to determine normal Tetranor PGE-1 levels in human females and found to be 342 ng (± 116 ng).[18]



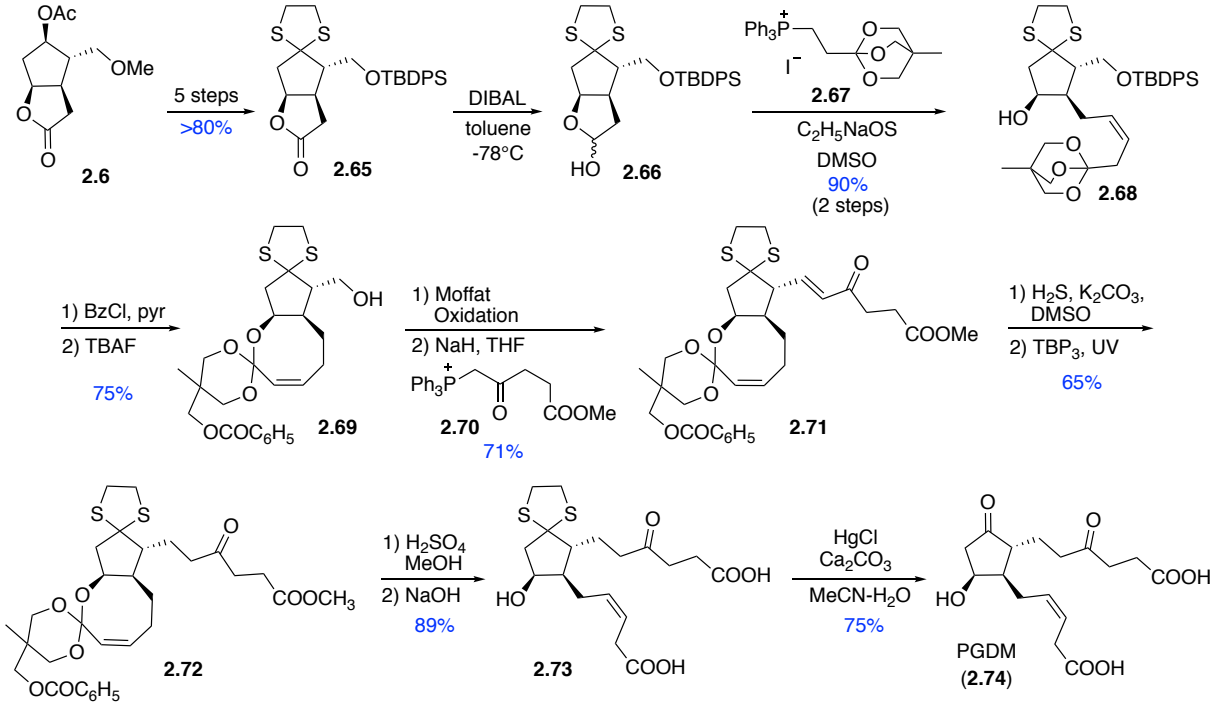
Scheme 2.6: Synthesis of d_5-tetranor PGE-1

Chemical Approaches Towards PGD_2 Urinary Metabolites

Corey's Synthesis of PGDM (1979)

In 1979, Sweetman and coworkers identified Tetranor PGD-M as the major D-ring metabolite isolated from a urinary sample of a monkey.[19] Because previous prostaglandin studies performed in humans and monkeys had shown strong similarities, it was hypothesized that the metabolite would be a useful biomarker for human studies. With this in mind, Corey and coworkers chemically synthesized Tetranor PGDM in 16 steps from the Corey lactone.[20] After smoothly converting the Corey lactone to thioacetal **2.65**, DIBAL reduction produced an inconsequential mixture of diastereomeric lactols. The Corey Shimoji reagent was employed for the olefination

with the masked aldehyde. Further treatment of the orthoester with benzoyl chloride and deprotection with TBAF yielded tetracycle **2.69**. Moffat oxidation[21] and Horner-Wadsworth-Emmons olefination completed the carbon framework. After selective reduction of the alkene over 2 steps, saponification of both esters liberated diacid **2.73**. Removal of the thioacetal resulted in target compound Tetranor PGDM.

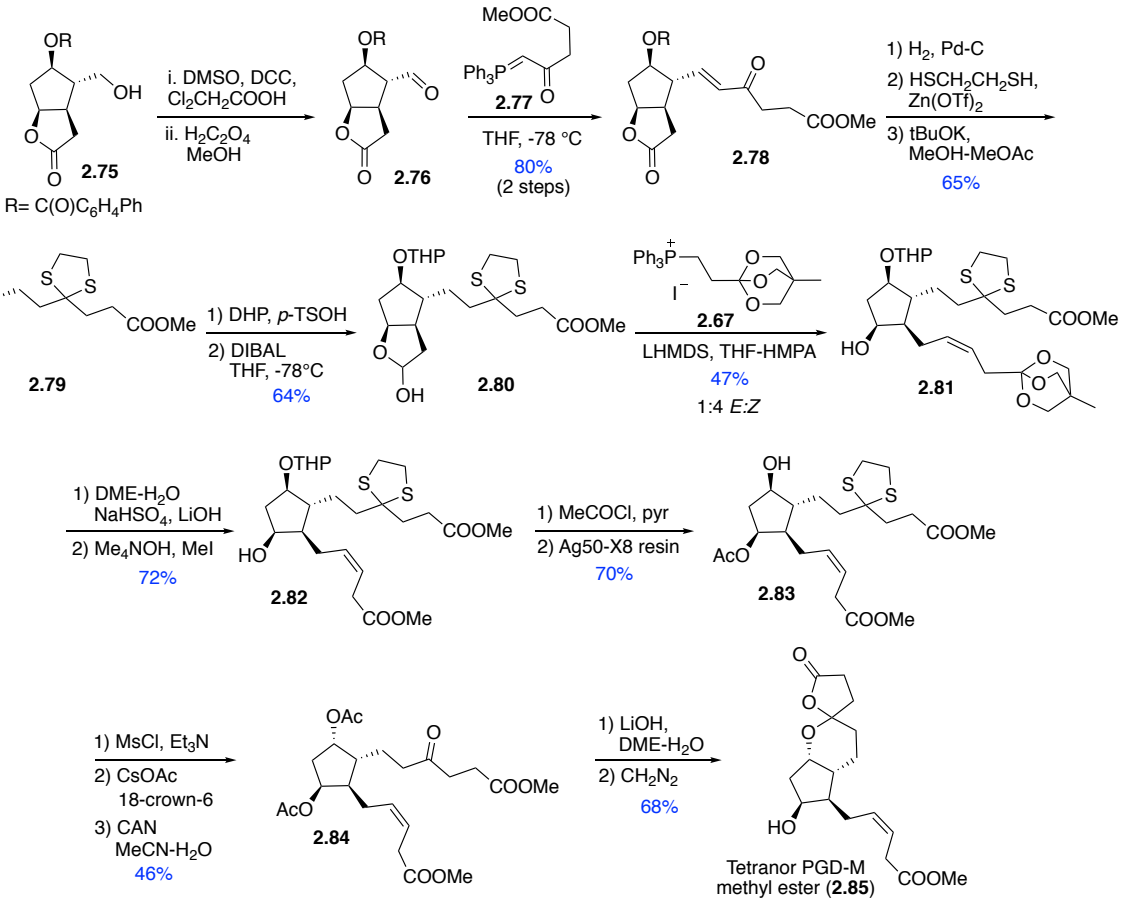


Scheme 2.7: Corey's Synthesis of PGDM

Taber's Synthesis of PGD-M (1984)

The first and only synthesis of PGD-M was achieved by Taber and coworkers in 1984.[22] Beginning from commercially available Corey lactone derivative **2.75**, the primary alcohol was oxidized under Moffatt conditions in preparation for a Horner-Wadsworth-Emmons olefination with phosphonate **2.77** to yield enone **2.78**. Hydrogenation, thioacetylization, and deprotection yielded free alcohol **2.79**, which was then immediately reprotected as an acetal before selective reduction with DIBAL revealed lactol **2.8**. *Z*-selective olefination with the Corey-Shimoji

reagent[20] rendered a 1:4 *E/Z* ratio of isomers in modest yield. Carrying forward exclusively with the *Z* isomer, the orthoester was converted to methyl ester **2.82** over 2 steps. Acetylation of the free alcohol, followed by deprotection of the THP group rendered the free alcohol. Activation of the alcohol with mesylchloride followed by substitution resulted the diacetate before CAN oxidation of the disulfide, followed by treatment of the ketone with LiOH to yield PGD-M. The target molecule was characterized as the methyl ester after treatment with diazomethane.

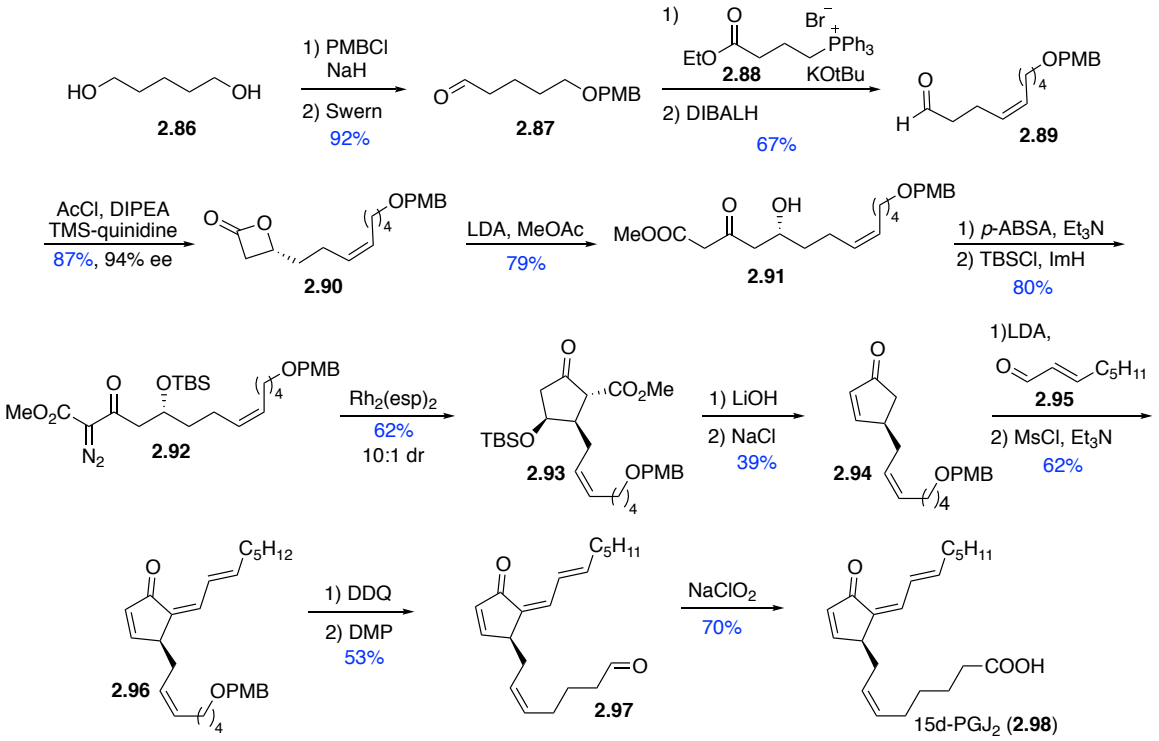


Scheme 2.8: Taber's Synthesis of PGD-M

Carriera's Synthesis of 15d-PGJ$_2$ (2015)

The synthesis of 15d- PGJ$_2$ commenced with the mono-protection of 1,5 pentanediol as the PMB ether.[23] Swern oxidation of the primary alcohol, followed by Wittig olefination and partial

reduction of the ethyl ester provided aldehyde **2.89**. [2+2] cyclization with ketene and TMS-quinidine allowed access to lactone **2.90** in 94% e.e. Opening of the β - lactone, followed by diazo transfer and protection of the secondary alcohol set the stage for the rhodium catalyzed, diastereoselective C-H insertion to form β- ketoester **2.93**. Decarboxylation of the methyl ester and β - elimination of the siloxy group afforded diene **2.94**. Introduction of the ω alkyl chain was achieved through acylation with enal, **2.95** before activation of the newly installed alcohol with MsCl resulted in tetraene **2.96**. Deprotection of the primary alcohol, followed by DMP and Pinnick oxidation[24], revealed 15d-PGJ$_2$.

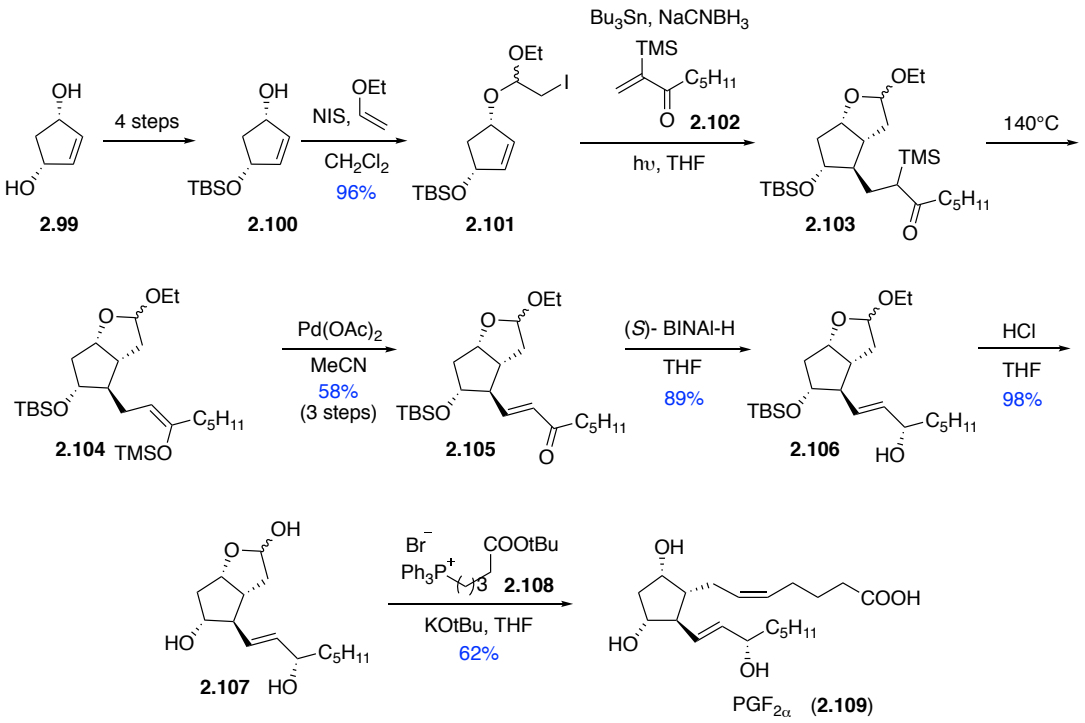


Scheme 2.9: Carriera's Synthesis of 15d-PGJ$_2$

Key Chemical Approach Towards $PGF_{2\alpha}$

Stork's Synthesis of $PGF_{2\alpha}$ (1986)

Though not a PGE_2 or PGD_2 urinary metabolite, Stork's synthesis of $PGF_{2\alpha}$[25] played a pivotal role in shaping a significant portion of this thesis work. Thus, discussion of the synthesis is warranted. Cyclopentenediol **2.99** (generated from photo-oxygenation-reduction of cyclopentadiene) was converted in 4 steps to enantiopure TBS-siloxy ether **2.100** in good yield. Haloetherification with NIS and ethyl vinyl ether resulted in a diastereomeric mixture of acetals. The key radical cyclization of the α-iodo acetal and trapping with enone **2.102** resulted in [3.3.0] bicycle **2.103**. After thermal rearrangement and oxidation by $Pd(OAc)_2$, the enone was obtained in good yields. Diastereoselective reduction of enone **2.105** to allylic alcohol **2.106** proceeded smoothly before silyl deprotection and Wittig homologation with phosphonium bromide **2.107** afforded $PGF_{2\alpha}$.



Scheme 2.10: Stork's synthesis of $PGF_{2\alpha}$

Statement of Dissertation

The work herein describes the synthesis of two prostaglandin metabolites: PGD-M and tetranor PGE_1. Prostaglandins and related metabolites have a rich history in total synthesis that dates back to the 1960's that helped to shape the synthetic routes outlined in this dissertation. The chemical synthesis of these metabolites is necessary due to the limited access of the compounds via preparative biosynthesis. We saw a need for direct chemical syntheses of tetranor PGE_1 and PGD-M that would allow for the incorporation of isotopes necessary for quantification in clinical samples which would contribute to our understanding of PGE_2 and PGD_2 metabolism in different diseased states.

References

1. Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. "Stereo-controlled synthesis of prostaglandins F2α and E2 (dl)" *J. Am. Chem. Soc.* **1969**, *91,* 5675-5677.

2. Schneider, W.P.; Axen, U.; Lincoln, F. H.; Pike, J. E.; Thompson, J. L. "The total synthesis of prostaglandins" *J. Am. Chem. Soc.* **1968**, *90,* 5895–5896.

3. Sih, C. J.; Salomon, R.G.; Price, P.; Peruzzoti, G.; Sood, R. "Total synthesis of (±) -15-Deoxyprostaglandin E1" *J. Chem. Soc. Chem. Comm*. **1972**, 240-241.

4. Suzuki, M.; Kawagishi, T.; Noyori, R. "A general synthesis of primary prostaglandins" *Tetrahedron Lett.* **1982**, *23,* 5563-5566.

5. Suzuki, M.; Kawagishi, T.; Suzuki, T.; Noyori, R. "A facile synthesis of (−)-prostaglandin E1 via a three-component coupling process" *Tetrahedron Lett.* **1982**, *23,* 4057-4060.

6. C. R. Johnson, M. P. Braun, "A two-step, three-component synthesis of PGE1: utilization of α-iodoenones in Pd(0)-catalyzed cross-couplings of organoboranes" *J. Am. Chem. Soc.* **1993**, *115,* 11014-11015.

7. Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. "The Diels-Alder reaction in total synthesis" *Angew. Chem. Int. Ed.* **2002**, *41,*1668–1698.

8. Renz, M.; Meunier, B. "100 years of Baeyer-Villiger oxidations" *Eur. J. Org. Chem.* **1999**, *4,* 737–750.

9. Boot, J. R.; Foulis, M. J.; Gutteridge, N. J. A; Smith, C.W. "Synthesis of two PGE2 human urinary metabolites" *Prostaglandins,* **1974**, *8,* 439- 446.

10. Wittig, G.; Schöllkopf, U. "Über Triphenyl-phosphin-methylene als olefinbildende reagenzien I" *Chemische Berichte* **1954**, *87,*1318- 1330.

11. Taub, D.; Zelawski, Z.S.; Wendler, N.L. "A Stereoselective total synthesis of 7□-hydroxy-5,11-diketotetranor-prostane-1,16-doic acid, the major human urinary metabolite of PGE1 and PGE2" *Tetrahedron Lett.* **1975**, *16,* 3667 -3670.

12. Lin, C.H. "Prostaglandin Metabolites. Synthesis of E and F Urinary Metabolites" *J. Org. Chem*. **1976**, *58,* 4045-4047.

13. Dieckmann, W. Ber. Dtsch. Chem. Ges. **1894**, *27,* 102–103.

14. Wadsworth, W. S.; Emmons, W. D. "The utility of phosphonate carbanions in olefin synthesis" *J. Am. Chem. Soc.* **1961**, *83,* 1733-1738.

15. Taber, D. F.; Gu, P. "Preparation of the major urinary metabolite of (-)-prostaglandin E2" *Tetrahedron* **2009**, 65, 5904-5907.

16. Bickart, P.; Carson, F. W.; Jacobus, J.; Miller, E. G.; Mislow, K. "Thermal racemization of allylic sulfoxides and interconversion of allylic sulfoxides and sulfenates. Mechanism and stereochemistry" *J. Am. Chem. Soc.* **1968**, *90,* 4869 -4876.

17. Evans, D. A.; Andrews, G. C.; Sims, C. L. "Reversible 1,3 transposition of sulfoxide and alcohol functions. Potential synthetic utility" *J. Am. Chem. Soc.* **1971**, *93,* 4956-4957.

18. Oates, J. A.; Sweetnam, B. J.; Green, K.; Samuelsson, B. "Identification and assay of tetranor-prostaglandin E1 in human urine" *Anal. Biochem.* **1976**, *74,* 546-559.

19. Ellis, C. K.; Smigel, M. D.; Oates, J. A.; Oelz, O.; Sweetnam, B. J. "Metabolism of prostaglandin D2 in the monkey" *J. Biol. Chem*. **1979**, *254,* 4152-4163.

20. Corey, E.J.; Shimoji, K. "Total synthesis of the major human urinary metabolite of prostaglandin D2, a key diagnostic indicator" *J. Am. Chem. Soc*. **1983**, *105,* 1662–1664.

21. Pfitzner, K.E.; Moffatt, J. G. "A new and selective oxidation of alcohols" *J. Am. Chem. Soc.* **1963**, *85,* 3027–3028.

22. Prakash, C.; Saleh, S.; Roberts, L. J.; Blair, I. A.; Taber, D. F. "Synthesis of the major urinary metabolite of prostaglandin D2" *J. Chem. Soc. Perk. Trans.* 1 **1988**, *10,* 2821-2826.

23. Egger, J.; Fischer, S.; Pretscher, P.; Freigang, S.; Kopf, M.; Carreira, E. M.; "Total Synthesis of prostaglandin 15d-PGJ2 and investigation of its effect on the Secretion of IL-6 and IL-12" *Org. Lett.* **2015**, *17,* 4340–4343.

24. Bal, B. S.; Childers, W. E.; Pinnick, H. W. "Oxidation of α,β-unsaturated aldehydes" *Tetrahedron* **1981**, *37,* 2091-2096.

25. Stork. G.; Sher, P.M.; Chen, H.L. "Radical cyclization-trapping in the synthesis of natural products. A simple, stereocontrolled route to prostaglandin F2α" *J. Am. Chem. Soc.* **1986**, *108, 6834-6385.*

CHAPTER 3

TOTAL SYNTHESIS OF TETRANOR PGE_1

Retrosynthetic Analysis

When planning the chemical synthesis of tetranor PGE_1 we envisioned a straightforward synthesis, utilizing the two-component coupling strategy. We anticipated that the primary synthetic challenge would be the construction of α-substituted enone **3.2.** Enone **3.4** and vinyl halide **3.3** are both known compounds that could be prepared in quantity to facilitate the investigation of the construction of enone **3.2** and the conjugate addition that was anticipated to establish the *trans,trans* relationship of the substituents 2,3,4- trisubstituted cyclopentanone.

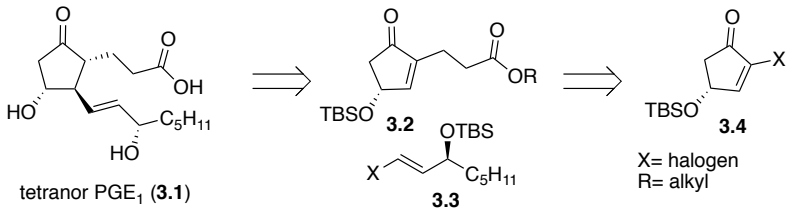


Figure 3.1 Retrosynthetic analysis

Literature Precedence for 4-siloxycyclopentenone

There are multiple approaches known for the synthesis of 4-siloxycyclopentenone, racemic and optically active, that were considered. The syntheses primarily begin from simple starting materials, such as cyclopentadiene,[1,2,3] furfuryl alcohol,[4] or tartaric acid.[5] Many utilize chiral starting materials, chirality inducing reagents or enzymatic desymmetrization of achiral intermediates to prepare either the pure *R* or *S* enantiomer of **3.4**. Although there are also short racemic syntheses. (Figure 3.2) the two-component coupling stragegy required us to use optically

pure enone as the ω-sidechain, introduced by a copper-mediated conjugate addition, incorporates the 10*S* alcohol.

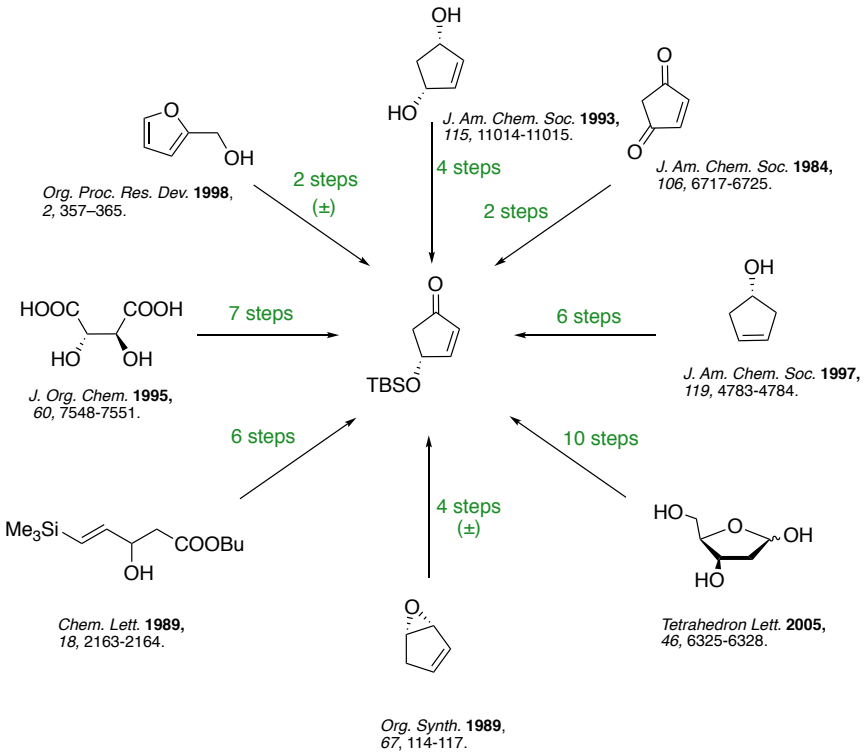
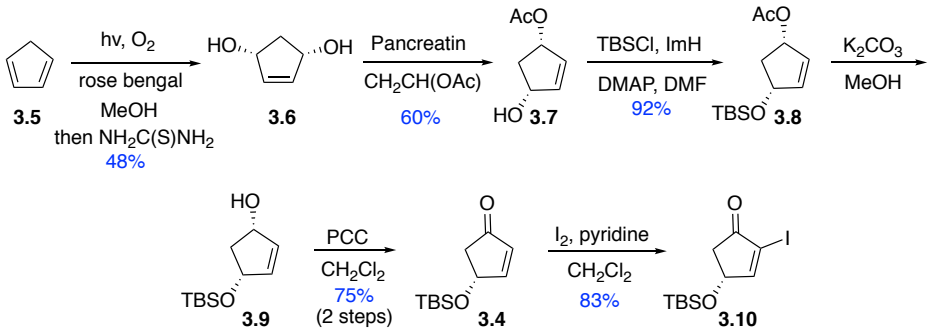


Figure 3.2 Synthetic Approaches for synthesis of 4-siloxycyclopentenone

Chemical Synthesis of Tetranor PGE-1

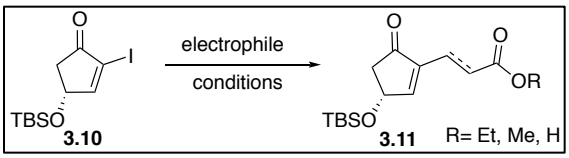
The synthesis commenced with the oxygenation of cyclopentadiene and the resultant *meso*-diol **3.6** was desymmetrised through the use of commercially available lipase, pancreatin.[6] Protection of allylic alcohol **3.7** as a TBS ether, followed by ester methanolysis and alcohol oxidation to the corresponding enone with pyridinium chlorochromate afforded *(R)*-4-((*tert*-butyldimethylsilyl)oxy)cyclopent-2-en-1-one. α-Iodination of the enone[7] provided **3.10** in favorable yields and set the stage for the key α-functionalization of enone **3.10**.



Scheme 3.1 Synthesis of α-substituted cyclopentenone

Screening conditions for α-alkylation of enone

The most challenging transformation in the synthesis proved to be the α–alkylation of enone **3.10**. We explored several different sets of conditions and our efforts are summarized in Table 3.1. Radical conditions[8] resulted in recovery of starting material and a variety of Pd-catalyzed cross coupling reactions[9] were equally unsuccessful. Our first set of successful conditions (Entry 4) employed a Heck coupling reaction with ethyl acrylate and afforded the desired dienone **3.16** but we were unable to chemoselectively reduce the enoate double bond. Based on a publication by Battistuzzi and co-workers[10], we did carry out a productive Heck coupling utilizing diethyl acetal **3.17** as the electrophilic component (Entry 5). These conditions provided desired ethyl ester **3.18**, albeit in modest yields. We screened one additional acetal, but observed none of the desired acid and instead observed diene **3.20**. Though we briefly considered isomerizing diene **3.20** to encourage liberation of the acid, we ultimately decided to move forward with the Heck coupling substrate and Jeffries conditions in Entry 5.



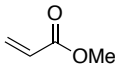
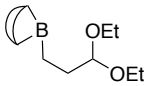
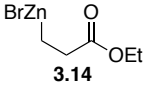
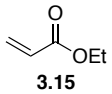
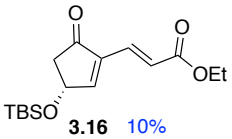
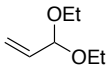
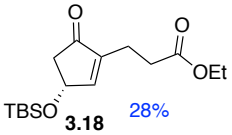
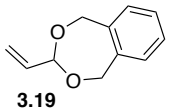
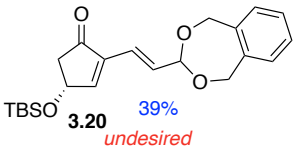
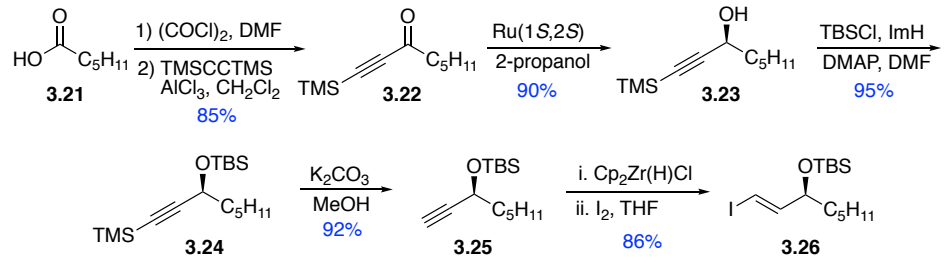
Entry	Electrophile	Conditions	Result
1.	 3.12	Bu_3SnH, AIBN benzene	recovered sm
2.	 3.13	$PdCl_2(dppf)_2$ THF, 75 °C	recovered sm
3.	 3.14	$Pd(dba)_2$, dppf THF, 60 °C	decomposition
4.	 3.15	$Pd(OAc)_2$, DIPEA DMF, 110°C	 3.16 10%
5.	 3.17	$Pd(OAc)_2$, TBACl Bu_3N, DMF, 90 °C	 3.18 28%
6.	 3.19	$Pd(OAc)_2$, Bu_3N TBACl DMF, 70 °C	 3.20 39% *undesired*

Table 3.1: Alkylation conditions

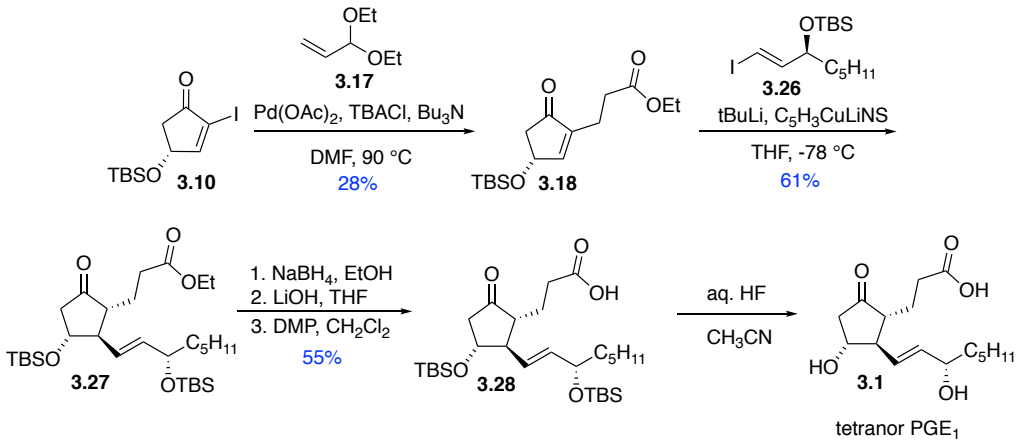
We next set out to make the required sidechain for the conjugate addition onto α-substituted enone **3.18** (Scheme 3.4). The vinyl iodide coupling partner was synthesized by utilizing the key enantioselective reduction developed by Noyori[11] starting with bis(trimethylsilyl)acetylene addition to the acid chloride derived from hexanoic acid **3.21** (Scheme 3.3). The acid chloride was generated *in situ*, and the alkynone product **3.22** which underwent

asymmetric reduction to propargylic alcohol **3.23**. After protection of the alcohol and removal of the terminal TMS group, reaction with the Schwartz reagent was used to generate an intermediate vinyl zirconate, which was quenched with iodine to arrive at vinyl **3.26** all in favorable yields.



Scheme 3.3 Synthesis of vinyl iodide coupling partner

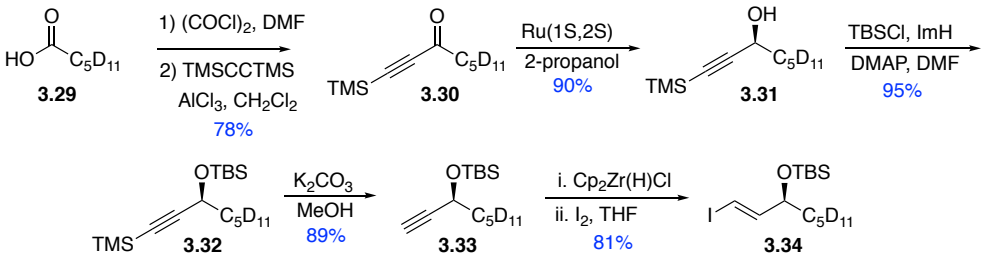
Ester **3.18** was carried through to a copper-mediated conjugate addition with vinyl iodide **3.26**. Unfortunately, saponification of the ethyl ester of **3.27** was accompanied by β–elimination of the C-7 siloxy group. To circumvent this result, cyclopentanone **3.27** was reduced to the alcohol with $NaBH_4$. Following saponification of the ester to the acid, oxidation with Dess-Martin periodinane resulted in ketone **3.28**.[12] Deprotection of ketone **3.28** with HF-pyridine provided the target molecule, tetranor PGE-1. Due to the tendency of tetranor PGE-1 to decompose at room temperature when concentrated, the final product was kept as a solution in ethyl acetate and analyzed by mass spectrometry.



Scheme 3.4 Synthesis of Tetranor PGE_1

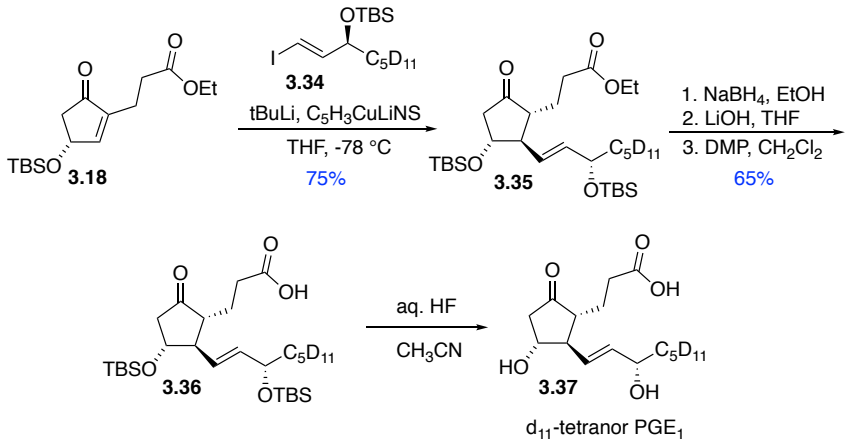
Chemical Synthesis of d_{11}- Tetranor PGE_1

Following completion of the synthesis of tetranor PGE_1, we next set out to synthesize an isotopically labeled analogue with the intention of using it as an internal standard for quantification of tetranor PGE_1 in clinical samples. Isotopic labels are typically introduced with ^{13}C or deuterium labels. We elected to use deuterium due to the commercial availability of d_{11}-hexynoic acid. Utilizing the same route as previously employed, we produced the deuterated vinyl iodide in 6 steps from d_{11}-hexynoic acid. Bis(trimethylsilyl)acetylene was added to the acyl chloride of **3.29** to afford TMS alkyne **3.30** before asymmetric reduction using Noyori's catalyst provided propargylic alcohol **3.31**. After protection of the alcohol and removal of the TMS group under mild conditions, the Schwartz reagent was once again used to generate the vinyl zirconicene, which was quenched with iodine to arrive at d_{11}-vinyl iodide **3.34**.



Scheme 3.5: Synthesis of d_{11}-vinyliodide

With deuterated coupling partner **3.34** in hand, we proceeded forward to the conjugate addition and obtained ethyl ester **3.35** in good yield. Selective reduction of the ketone with $NaBH_4$, saponification of the ethyl ester with LiOH and oxidation with Dess-Martin periodinane resulted in acid **3.36**. The final deuterated compound was kept as a solution in EtOAc to avoid decomposition and analyzed by mass spectrometry.



Scheme 3.6 Synthesis of d_{11}-tetranor PGE_1

Preliminary findings enabled by d_{11} -Tetranor PGE_1

Milne, Oates and coworkers have used d_{11}- Tetranor PGE_1 as an internal standard to define normal levels of tetranor PGE_1 in human males and females. The study involved 30 male

participants and 30 female participants and tetranor PGE_1 levels were and defined as 3.63 ± 3.90 ng/mg Cr and 1.55 ± 1.02 ng/mg Cr, respectively.[13] Comparatively, Samulesson's original establishment of tetranor PGE-1 levels was reported for only females and over a 24-hour period, not taking creatine levels into account.[14]

Additionally, the relationship between tetranor PGE_1 and PGE-M was examined in a family of people with a mutation for the gene that encodes for 15-PGDH. One of the male members of the family had colon cancer and his tetranor PGE_1 levels were measured as 52.8 ng/mg Cr. However, after 6 weeks of treatment with celecoxib and fish oil, levels of tetranor PGE-1 decreased by 64%.[13]

Conclusion to Chapter Three

We completed the total synthesis of Tetranor PGE_1 and d_{11}-Tetranor PGE_1 in twelve steps beginning from cyclopentadiene. One of the major benefits of our approach is amenability of the route for incorporation of isotopic labels and access to the perdeuterated analogue. The material produced from this this synthesis has enabled clinical studies that are ongoing, but the preliminary data suggest that Tetranor PGE_1 may be a better (or complimentary) biomarker for lung cancer in some patients.

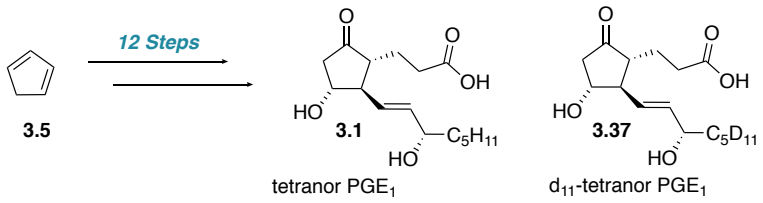


Figure 3.2 Summary of Chapter 3

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 (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 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, or Sure-Seal Sigma reagent bottles. Unless indicated, all commercial reagents were used as received without further purification. Ru-(*S,S*)-TsDPEN catalyst was synthesized according to the procedure reported by Noyori. The molarity of *n*-butyllithium solutions was determined by titration using *n*-benzylbenzamide as an indicator (average of three determinations).

Instrumentation: ^{1}H NMR spectra were recorded on Bruker 400 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), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded on Bruker 100 or 150 MHz spectrometers and are reported relative to deuterated solvent signals. 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 and the Eicosanoid Core at Vanderbilt University.

Compound Preparation

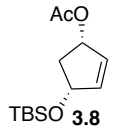
3.6

Diol 3.6: To a solution of fresh cyclopentadiene (1.54 g, 23.3 mmol) in MeOH (435 mL) in a photochemical reactor vessel was added Rose Bengal (50 mg) and thiourea (1.20 g, 15.8 mmol). Oxygen was bubbled through the solution for 5 min before the apparatus was irradiated with a 450 W mercury immersion lamp equipped with a Pyrex filter. After 2.5 h, bubbling of oxygen through the solution ceased and the reaction stirred overnight at room temperature in the dark. The resultant solution was concentrated *in vacuo*, the residue dissolved in water (50 mL) and washed with benzene (3 x 60 mL). The aqueous layer was then concentrated *in vacuo*. The resultant residue was purified by flash chromatography (silica gel, gradient, 1 to 10% MeOH-CH_2Cl_2) to yield 1.13 g (48%) of diol **3.6** as a white solid. Spectral data matched reported literature values.[15]

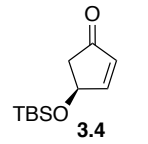
3.7

(1*S*,4*R*)-4-hydroxycyclopent-2-en-1-yl acetate [(-)-3.7]: To a solution of diol **3.6** (1.01 g, 10.1 mmol) in THF (20.0 mL) was added vinyl acetate (1.48 mL, 16.1 mmol), Et_3N (0.98 mL, 7.06 mmol) and Pancreatin (3.80 g). The reaction mixture was stirred overnight, filtered and concentrated *in vacuo*. The resultant brown residue was purified by flash chromatography (silica gel, gradient elution, 5% to 35% EtOAc-hexanes) to yield 863 mg (60%) of acetate (-)-**3.7** as a white solid. The *e.e.* was determined to be >95% by Mosher ester analysis.

The spectral data and optical rotation [Lit. $[\alpha]_D^{24}$ – 69.0° (*c* 1.00, $CHCl_3$); Obs. $[\alpha]_D^{24}$ – 66.2° (*c* 8.5, $CHCl_3$)] matched reported values.[6]

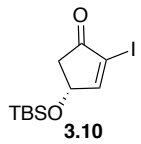


(*R*)-4-((*tert*-butyldimethylsilyl)oxy)-2-iodocyclopent-2-en-1-one (3.8): To a solution of acetate **3.7** (0.750 g, 5.28 mmol) in DMF (6.0 mL) was added TBSCl (1.19 g, 7.91 mmol), imidazole (1.08 g, 15.8 mmol) and DMAP (64 mg, 0.53 mmol). The solution was stirred for 3 h, quenched with water (5 mL) and extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with 1N HCl (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, 0 to 10% EtOAc-hexanes) to afford 1.24 g (92%) of **3.8** as a colorless oil. Spectral data matched reported literature values.[16]



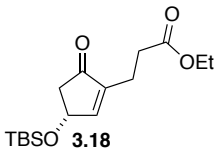
(*R*)-4-((*tert*-butyldimethylsilyl)oxy)cyclopent-2-en-1-one (3.9): To a solution of monoacetate **3.8** (685 mg, 2.67 mmol) in MeOH (12.0 mL) was added K_2CO_3 (738 mg, 5.34 mmol). The solution stirred overnight before being filtered and concentrated. The residue was dissolved in CH_2Cl_2 (20 mL), washed with H_2O (10 mL), and extracted from the aqueous layer with CH_2Cl_2 (3 x 20 mL). The combined extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. To the crude alcohol dissolved in CH_2Cl_2 (12 mL) cooled to 0 °C and PCC (802 mg, 3.72 mmol) and NaOAc (61 mg, 0.744 mmol) were added. The reaction was then allowed to warm to room temperature and stirred for 4 h. The reaction mixture was then diluted with Et_2O (20 mL) and filtered through a pad of Celite before being washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, gradient

elution, 10 to 20% Et_2O in hexanes) to afford 424 mg (75%) of cyclopentenone **3.4** as a white solid. Spectral data matched reported literature values.[16]



3.10

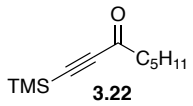
(*R*)-4-((*tert*-butyldimethylsilyl)oxy)-2-iodocyclopent-2-en-1-one (3.10): To a solution of cyclopentenone **3.4** (500 mg, 2.36 mmol) in CH_2Cl_2 (2.0 mL) and pyridine (2.0 mL) was added a solution of I_2 (1.02 g, 4.01 mmol) in CH_2Cl_2 (2.0 mL) and pyridine (2.0 mL) dropwise over 1 h at 0 °C. The mixture was then allowed to warm to room temperature, stirred for 2 h and 2 N HCl (10 mL) added slowly. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined extracts were washed with 2N HCl (2 x 20 mL), satd. aq. Na_2SO_3 (3 x 10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resultant residue was purified by flash chromatography (silica gel, 10% EtOAc in hexanes) to yield 707 mg (80%) of iodocyclopentenone **3.10** as a pale-yellow solid. Spectral data matched reported literature values.[7]



3.18

Ethyl (*R*)-3-(3-((*tert*-butyldimethylsilyl)oxy)-5-oxocyclopent-1-en-1-yl)propanoate (3.18): To a degassed solution of iodocyclopentenone **3.10** (665 mg, 1.96 mmol), acrolein diethylacetal (1.0 mL, 7.86 mmol), *tetra*-n-butylammonium chloride (653 mg, 2.35 mmol), *tri*-n-butylamine (0.94 mL, 3.94 mmol) in DMF (10.0 mL) was added $Pd(OAc)_2$ (44 mg, 0.196 mmol). The mixture was heated at 90 °C for 6 h before cooling to room temperature, quenched with saturated aqueous $NaHCO_3$ (5 mL), and extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with 10% aqueous $CuSO_4$ (2 x 25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, gradient elution, 0% - 25% EtOAc in hexanes) to

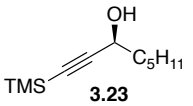
yield 174 mg (28%) of ethyl ester **3.18** as a yellow oil. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.08 (d, *J* = 2.4, 1H), 4.88 (d, *J* = 5.6, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 2.73 (dd, *J* = 6.0, 18.4 Hz), 2.52 (s, 4H), 2.26 (dd, *J* = 2.4, 18.4 Hz), 1.24 (t, *J* = 7.2 Hz, 3H), 0.90 (s, 9H), 0.11 (d, *J* = 4.0 Hz, 6H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 205.8, 172.7, 157.6, 145.4, 69.1, 60.7, 45.6, 32.1, 25.9, 20.3, 18.3, 14.4, -4.6.



3.22

1-(Trimethylsilyl)oct-1-yn-3-one (3.22): To a solution of hexanoic acid (300 mg, 2.58 mmol) in CH_2Cl_2 (25.0 mL) at room temperature was added oxalyl chloride (0.244 mL, 2.84 mmol) and DMF (1 drop). The solution stirred at room temperature for 30 min before it was concentrated *in vacuo*.

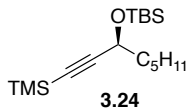
To a suspension of $AlCl_3$ (448 mg, 3.36 mmol) in CH_2Cl_2 (10.0 mL) at 0 °C was added a solution of the above prepared hexanoyl chloride and bistrimethylsilylacetylene (4480 mg, 2.58 mmol) in CH_2Cl_2 (10 mL) via syringe pump over 10 min. The resulting yellow solution was allowed to warm to room temperature over 1 h, at which point the reaction was cooled to 0 °C and quenched by slow addition of 2*N* HCl (20 mL). The resulting solution was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic layers were washed with 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 afford 376 mg (76%) of alkynone **3.22** as a yellow oil. The spectral data matched reported values.[17]



3.23

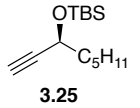
(*S*)-1-(trimethylsilyl)oct-1-yn-3-ol (3.23): To a solution of **3.22** (372 mg, 1.89 mmol) in 2- propanol (18.0 mL) was added Ru[(1*S*, 2*S*)-p-$TsNCH(C_6H_5)CH(C_6H_5)NH](\eta^6$-p-cymene) (68 mg, 0.113 mmol). The reaction stirred for 16 h before it was concentrated *in vacuo* and the resulting residue was purified by flash column

chromatography (silica gel, gradient elution, 5-10 % EtOAc in hexanes) to provide 348 mg (93%) of **3.23** as a light-yellow oil. The spectral data matched reported values.[18]



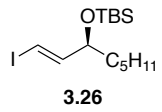
3.24

(*S*)-*tert*-butyldimethyl((1-(trimethylsilyl)oct-1-yn-3-yl)oxy)silane (3.24): To a solution of alcohol **3.23** (300 mg, 1.51 mmol) in DMF (1.5 mL) at 0 °C was added TBSCl (456 mg, 3.03 mmol), imidazole (309 mg, 4.54 mmol), and DMAP (9 mg, 0.076 mmol). The reaction was allowed to stir at 0 °C for 2 h, at which point the reaction was quenched with water (2 mL) and extracted with Et_2O (5 x 20 mL). The combined organic layers were washed with brine (3 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 452 mg (96%) of **3.24** as a colorless oil. The spectral data matched reported values.[18]



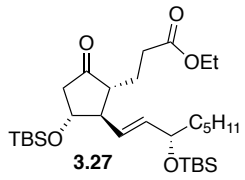
3.25

***(S)*-*tert*-butyldimethyl(oct-1-yn-3-yloxy)silane (3.25):** To a solution of silane **3.24** (452 mg, 1.45 mmol) in MeOH (9.0 mL) was added K_2CO_3 (200 mg, 1.45 mmol). The reaction was allowed to stir room temperature for 3 h, at which point the MeOH was removed *in vacuo*. The resulting residue was taken up in water (10 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (3 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- 5% EtOAc in hexanes) to yield 320 mg (92%) of alkyne **3.25** as a colorless oil. The spectral data matched reported values.[19]



3.26

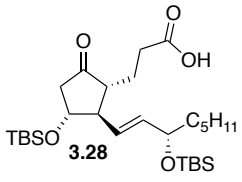
***(S,E)-tert*-butyl((1-iodooct-1-en-3-yl)oxy)dimethylsilane (3.26):** To a solution of alkyne **3.25** (100 mg, 0.416 mmol) in CH_2Cl_2 (4.2 mL) at room temperature was added the ziroconecene hydrochloride (268 mg, 1.04 mmol) and allowed to stir at room temperature was allowed to stir for 1.5 h. Iodine (127 mg, 0.500 mmol) was added and the mixture changed color from light yellow to dark brown. The reaction was allowed to stir for 10 min, at which point the mixture was diluted with hexanes (5 mL) and filtered through a pad of Celite. The resulting solution was washed with sat. aq. $Na_2S_2O_3$ (3 x 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, hexanes) to afford 0.131 g (86%) of vinyl iodide **3.26** as a colorless oil. The spectral data matched reported values.[20]



3.27

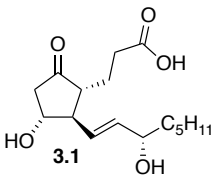
Ethyl 3-((2*R*,3*R*)-3-((*tert*-butyldimethylsilyl)oxy)-2-((*S*,*E*)-3-((*tert*-butyldimethylsilyl)oxy)oct-1-en-1-yl)-5-oxocyclopentyl)propanoate (3.27): To a solution of vinyl iodide **3.26** (116 mg. 0.314 mmol) in THF (3.0 mL) at -78 °C was added t-BuLi (0.38 mL, 0.656 mmol, 1.7 *M* in pentane) and the reaction stirred at -78 °C for 30 min. To the reaction was added Lithium 2-thienylcyanocuprate solution in THF (1.28 mL, 0.315 mmol, 0.25 *M* in THF) and mixture allowed to warm to 0 °C. After stirring for 10 min at 0 °C, the reaction was cooled to -78 °C before cyclopentenone **3.18** (76 mg, 0.243 mmol) in THF (3.0 mL) was added dropwise. The reaction mixture was maintained at -78 °C for 30 min, warmed to 0 °C, stirred for 50 min, and quenched with saturated aqueous NH_4Cl (10 mL). The reaction mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resultant residue was purified by ISCO flash chromatography (silica gel, gradient elution, 0% -25% EtOAc in hexanes) to yield 88 mg

(65%) of cyclopentanone **3.27** as a colorless oil. ^{1}HNMR (400 MHz, $CDCl_3$) δ 5.63 (dd, *J* = 5.2, 15.2, 1H), 5.51 (dd, *J* = 8.0, 15.2, 1H), 4.16-4.00 (m, 4H), 2.63 (dd, *J* = 7.2, 18.4, 1H), 2.56-2.30 (m, 3H), 2.18 (dd, *J* = 8.0, 18.4, 1H), 2.06-1.94 (m, 1H), 1.92-1.81 (m, 1H), 1.54-1.38 (m, 2H), 1.38-1.15 (m, 9H), 0.99-0.77 (21H), 0.11-(-0.06) (m, 12H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 215.5, 173.2, 137.0, 128.5, 73.2, 72.7, 60.4, 54.0, 52.8, 47.5, 38.6, 32.0, 31.8, 26.0, 25.9, 25.2, 23.5, 22.7, 18.4, 18.1, 14.4, 14.2, -4.1, -4.4, -4.5, -4.6.



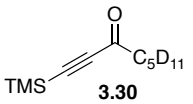
3-((2*R*,3*R*)-3-((*tert*-butyldimethylsilyl)oxy)-2-((*S*,*E*)-3-((*tert*-butyldimethylsilyl)oxy)oct-1-en-1-yl)-5-oxocyclopentyl)propanoic acid (3.28): To a stirred solution of ester **3.27** (88 mg, 0.158 mmol) in EtOH (1.5 mL) at 0 °C was added $NaBH_4$ (10 mg, 0.269 mmol). The reaction mixture was stirred for 45 min at 0 °C, quenched with water (1.5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude alcohol (78 mg, 0.140 mmol) was dissolved in THF (1.5 mL), LiOH (2.8 mL, 2.8 mmol, 1 *N* in water) was added and the reaction maintained for 3 h. The reaction was quenched with 1 *N* HCl (2.9 mL), and extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude carboxylic acid (72 mg, 0.136 mmol) was dissolved in CH_2Cl_2 (1.5 mL), cooled to 0 °C and Dess-Martin periodinane (115 mg, 0.272 mmol) was added. The reaction was stirred for 1 h, quenched with saturated aqueous $NaHCO_3$ (1.5 mL), and extracted with CH_2Cl_2 (3x 5 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resultant residue was purified by ISCO flash chromatography (silica gel, gradient elution, 0% - 25% EtOAc in hexanes) to yield 48 mg (58%) of carboxylic acid **3.28** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63 (dd, *J* = 4.9, 15.3 Hz, 1H), 5.51 (dd, *J* = 8.0,

16.0 Hz, 1H), 4.12-4.05 (m, 2H), 2.63 (*J* = 7.2, 18.4 Hz, 1H), 2.59-2.51 (m, 1H), 2.51-2.42, (m, 1 H), 2.42-2.33 (m, 1H), 2.19 (*J* = 8.1, 18.4 Hz, 1H), 2.05-1.96 (m, 1H), 1.91-1.79 (m, 2 H), 1.56-1.38 (m, 2H), 1.38-1.17 (m, 6H), 0.96-0.75 (m, 21H), 0.08-(-0.02) (m, 12H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 215.6, 178.9, 137.2, 128.3, 73.2, 72.6, 54.2, 52.7, 47.5, 38.6, 32.0, 31.4, 26.0, 25.9, 25.2, 23.2, 22.7, 18.4, 18.2, 14.2, -4.21, -4.48, -4.53, -4.60.



3.1
tetranor PGE_1

tetranor prostaglandin E_1: A solution of carboxylic acid **3.32** (18 mg, 0.034 mmol) in MeCN (1.5 mL) was cooled to 0 °C and 49% aqueous HF (55 µL, 1.36 mmol) dropwise. The reaction was stirred at 0 °C for 5 h, poured into a pH 7 buffered solution (20 mL) and extracted with EtOAc (3 x 6 mL). The combined organic extracts were washed with brine (15 mL), dried (Na_2SO_4), filtered and kept as a solution in EtOAc. HRMS (ESI) calc'd for $C_{16}H_{26}O_5$ $[M-H]^-$: 297.1708; found .

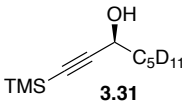


3.30

d_{11}-1-(Trimethylsilyl)oct-1-yn-3-one (30): To a solution of hexanoic acid (718 mg, 5.64 mmol) in CH_2Cl_2 (12.0 mL) at room temperature was added oxalyl chloride (0.533 mL, 6.21 mmol) and DMF (2 drops). The solution stirred at room temperature for 30 min before it was concentrated *in vacuo*.

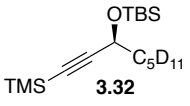
To a suspension of $AlCl_3$ (978 mg, 7.34 mmol) in CH_2Cl_2 (25.0 mL) at 0 °C was added a solution of the above prepared hexanoyl chloride and bistrimethylsilylacetylene (962 mg, 5.64 mmol) in CH_2Cl_2 (25 mL) via syringe pump over 10 min. The resulting yellow solution was allowed to warm to room temperature over 1 h, at which point the reaction was cooled to 0 °C and quenched by slow addition of 2*N* HCl (20 mL). The resulting solution was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic layers were washed with brine (50 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 917 mg (78%) of alkynone **3.30** as a yellow oil. The spectral data matched reported values.[21]



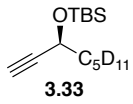
3.31

(*S*)-1-(trimethylsilyl)oct-1-yn-3-ol (31): To a solution of alkynone **3.30** (338 mg, 1.63 mmol) in 2- propanol (16.5 mL) was added Ru[(1*S*, 2*S*)-p-TsNCH(C_6H_5)CH(C_6H_5)NH](η^6-p-cymene) (77 mg, 0.128 mmol). The reaction stirred for 16 h before it was concentrated *in vacuo* and the resulting residue was purified by flash column chromatography (silica gel, gradient elution, 5-10 % EtOAc in hexanes) to provide 306 mg (90%) of **3.31** as a light-yellow oil. The spectral data matched reported values.[21]



3.32

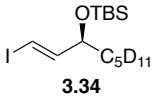
(*S*)-*tert*-butyldimethyl((1-(trimethylsilyl)oct-1-yn-3-yl)oxy)silane (3.32): To a solution of alcohol **3.31** (789 mg, 3.98 mmol) in DMF (5 mL) at room temperature was added TBSCl (1.20 g, 7.96 mmol), imidazole (813 mg, 11.94 mmol), and DMAP (24 mg, 0.20 mmol). The reaction was allowed to stir at room temperature for 2 h, at which point the reaction was quenched with water (5 mL) and extracted with Et_2O (5 x 20 mL). The combined organic layers were washed with 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 1.23 g (95%) of **3.32** as a colorless oil. The spectral data matched reported values.[21]



3.33

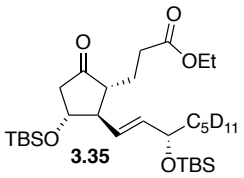
***(S)*-*tert*-butyldimethyl(oct-1-yn-3-yloxy)silane (33):** To a solution of silane **3.32** (1.22 g, 3.75 mmol) in MeOH (25 mL) was added K_2CO_3 (519 mg, 3.75 mmol). The reaction was allowed to stir room temperature for 16 h, at which point the MeOH was

removed *in vacuo*. The resulting residue was taken up in water (10 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL) and the combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, gradient elution, 1- 5% EtOAc in hexanes) to yield 837 mg (89%) of alkyne **3.33** as a colorless oil. The spectral data matched reported values.[20]



3.34

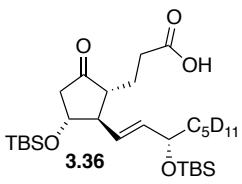
***(S,E)*-*tert*-butyl((1-iodooct-1-en-3-yl)oxy)dimethylsilane (3.34):** To a solution of alkyne **3.33** (200 mg, 0.795 mmol) in CH_2Cl_2 (8.5 mL) at room temperature was added the ziroconecene hydrochloride (513 mg, 1.99 mmol) and allowed to stir at room temperature was allowed to stir for 1.5 h. Iodine (242 mg, 0.954 mmol) was added and the mixture changed color from light yellow to dark brown. The reaction was allowed to stir for 30 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. $Na_2S_2O_3$ (3 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, hexanes) to afford 0.237 g (81%) of d_{11}-vinyl iodide **3.34** as a colorless oil. The spectral data matched reported values.[21]



3.35

d_{11}-Ethyl 3-((2*R*,3*R*)-3-((*tert*-butyldimethylsilyl)oxy)-2-((*S*,*E*)-3-((*tert*-butyldimethylsilyl)oxy)oct-1-en-1-yl)-5-oxocyclopentyl)propanoate (3.35): To a solution of vinyl iodide **3.34** (271 mg. 0.741 mmol) in THF (5.0 mL) at -78 °C was added 1.7 *M* tBuLi (0.88 mL,1.48 mmol) in hexanes and the reaction stirred at -78 °C for 30 min. To the reaction was added 0.25 *M* Lithium 2-thienylcyanocuprate solution in

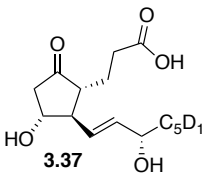
THF (2.63 mL, 0.660 mmol) and then warmed to 0 °C. After stirring for 10 min at 0 °C, the reaction was cooled to -78 °C before enone **3.18** (174 mg, 0.557 mmol) was added in THF (5.0 mL) and stirred for 30 min. The solution was then warmed to 0 °C and stirred for 50 min, before being quenched with saturated aqueous NH_4Cl (10 mL), extracted with EtOAc (3 x 10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resultant residue was purified by ISCO flash chromatography (silica gel, gradient elution, 0% -25% EtOAc in hexanes) to yield 237 mg (75%) of **3.35**. ^{1}HNMR (400 MHz, $CDCl_3$) δ 5.61 (dd, *J* = 5.2, 15.2 Hz, 1H), 5.50 (dd, *J* = 8.0, 15.2 Hz, 1H), 4.14-4.01 (m, 4H), 2.62 (dd, *J* = 7.2, 18.4, 1H), 2.54-2.28 (m, 4H), 2.17 (dd, *J* = 8.0, 18.4 Hz), 1.99 (p, *J* = 5.6 Hz, 1H), 1.91-1.79 (m, 2H), 1.22 (t, *J* = 7.2 Hz, 3H), 0.99-0.72 (m, 18H), 0.13-(-0.11) (m, 12H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 215.5, 173.2, 137.0, 128.4, 73.2, 72.6, 60.4, 54.0, 52.8, 47.5, 31.7, 26.0, 25.9, 23.4, 18.3, 18.1, 14.3, -4.2, -4.5, -4.6, -4.6.



3.36

d_{11}-3-((2*R*,3*R*)-3-((*tert*-butyldimethylsilyl)oxy)-2-((*S*,*E*)-3-((*tert*-butyldimethylsilyl)oxy)oct-1-en-1-yl)-5-oxocyclopentyl)propanoic acid (3.36): To a stirred solution of **3.35** (237 mg, 0.418 mmol) in EtOH (4.0 mL) at 0°C was added $NaBH_4$ (29 mg, 0.767 mmol). The solution stirred for 1 h at 0 °C before being quenched with H_2O (1.5 mL) and extracted with EtOAc (3 x 5 mL). The organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. To the crude resultant alcohol (207 mg, 0.365 mmol) in THF (4.0 mL) at room temperature was added 1 *N* LiOH (3.64 mL, 3.64 mmol) and stirred for 1.5 h. The reaction was quenched with 1 *N* HCl (4 mL), extracted with EtOAc (3 x 5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. To the crude resultant carboxylic acid (191 mg, 0.353 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C was added DMP (59 mg, 0.702 mmol). The solution stirred for 1 h before being quenched with saturated aqueous $NaHCO_3$ (4 mL), extracted

with CH_2Cl_2 (3x 5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resultant residue was purified by ISCO flash chromatography (silica gel, gradient elution, 0% - 25% EtOAc in hexanes) to yield 146 mg (65%) of **3.36**. ^{1}HNMR (400 MHz, $CDCl_3$) δ 5.63 (dd, *J* = 4.8, 15.2, 1H), 5.50 (dd, *J* = 8.0, 16.0 Hz, 1H), 4.15-4.05 (m, 2H), 2.64 (dd, *J* = 7.2, 18.4 Hz, 1 H), 2.60-2.50 (m, 1H), 2.50-2.42, (m, 1 H), 2.42-2.35 (m, 1H), 2.19 (dd, *J* = 8.4, 18.4 Hz, 1H), 2.01 (p, *J* = 5.2 Hz, 1H), 1.91-1.79 (m, 2 H), 0.89 (s, 9H), 0.87 (s, 9H), 0.20-(-0.18) (m, 12H); ^{13}CNMR (100 MHz, $CDCl_3$) 215.6, 179.0, 137.2, 128.3, 73.2, 72.5, 54.2, 52.7, 47.4, 31.3, 26.0, 25.9, 23.2, 18.4, 18.2, -4.2, -4.5, -4.5, -4.6.



3.37

d_{11}-tetranor PGE_1

d_{11}-tetranor prostaglandin E_1: A solution of carboxylic acid **3.36** (20 mg, 0.037 mmol) in MeCN (1.5 mL) was cooled to 0 °C and 49% aqueous HF (60 μL, 1.48 mmol) was added dropwise. The reaction was stirred at room temperature for 5 h, poured into a pH=7 buffered solution (20 mL) and extracted with EtOAc (4 x 6 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (20 mL), brine (20 mL), dried (Na_2SO_4), and kept as a solution in EtOAc. HRMS (ESI) calc'd for $C_{16}H_{14}D_{11}O_5$ $[M-H]^-$: 308.24; found 308.15.

References

1. C. R. Johnson, M. P. Braun, "A two-step, three-component synthesis of PGE1: utilization of α-iodoenones in Pd(0)-catalyzed cross-couplings of organoboranes" *J. Am. Chem. Soc.* **1993**, *115*, 11014-11015.

2. Just, G.; Simonovitch, C. "A Prostaglandin Synthesis" *Tetrahedron Lett.* **1967**, *22,* 2093-2097.

3. Iida, T.; Yamamoto, N.; Sasai, H.; Shibasaki, M. "New asymmetric reactions using a gallium complex: A highly enantioselective ring opening of epoxides with thiols catalyzed by a gallium-lithium-bis(binaphthoxide) complex" *J. Am. Chem. Soc.* **1997**, *119,* 4783-4784.

4. Watson, T. J.; Curran, T. T.; Hay, D. A.; Shah, R. S.; Wenstrup, D. L.; Webster, M. E. "Development of the carbocyclic nucleoside MDL 201449A: a tumor necrosis factor-a inhibitor" *Org. Proc. Res. Dev*. **1998**, *2,* 357–365.

5. Khanapure, S. P.; Najafi, N.; Manna, S.; Yang, J.J.; Rokach, J. "An efficient synthesis of 4(S)-hydroxycyclopent-2-enone" *J. Org. Chem.* **1995**, *60,* 7548–7551.

6. Tietze, L.F.; Stadler, C.; Böhnke N.; Brasche, N.; Grube, A. "Synthesis of enantiomerically pure cyclopentene building blocks" *Synlett.* **2007**, 485-487.

7. Myers, A. G.; Dragovich, P. S. "A reaction cascade leading to 1,6-didehydro[10]annulene to 1,5-dehydronaphthalene cyclization initiated by thiol addition" *J. Am. Chem. Soc.* **1993**, *115,* 7021–7022.

8. Liu, K. M.; Chau, C. M.; Sha, C.K. "Intermolecular radical addition reactions of α-iodo cycloalkenones and a synthetic study of the formal synthesis of enantiopure fawcettimine" *Chem. Comm.* **2008**, 91-93.

9. Nicolaou, K. C.; Jennings, M. P; Dagneau, P. "An expedient entry into the fused polycyclic skeleton of vannusal A" *Chem. Commun.* **2002**, 2480-2481.

10. Battistuzzi, G.; Cacchi, S.; Fabrizi, G.; Bernini, R. "3-Arylpropanoate Esters through the Palladium-Catalyzed Reaction of Aryl Halides with Acrolein Diethyl Acetal" *Synlett.* **2003**, 1133-1136.

11. Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. "Asymmetric transfer hydrogenation of α,β–acetylenic ketones" *J. Am. Chem. Soc.* **1997**, *119,* 8738-8739.

12. Taber, D. F.; Gu, P. "Preparation of the major urinary metabolite of (-)-prostaglandin E2" *Tetrahedron* **2009**, 65, 5904-5907.

13. Milne, G. L.; Oates, J. A.; Coffey, R. J.; Markowitz, S. unpublished results, **2019**.

14. Oates, J. A.; Sweetnam, B. J.; Green, K.; Samuelsson, B. "Identification and assay of tetranor-prostaglandin E1 in human urine" *Anal. Biochem.* **1976**, *74,* 546-559.

15. Kaneko, C.; Sugimoto, A.; Tanaka, S. "A facile one-step synthesis of cis-2-cyclopentene- and cis-2- cyclohexene- 1,4-diols from the corresponding cyclodienes" *Synthesis* **1974**, *12,* 876-877.

16. Basra, S.K.; Drew, M.G.B.; Mann, J.; Kane, P.; "A novel approach to bis-isoxazolines using a latent form of cyclopentadienone" *J. Chem. Soc., Perkin Trans. 1* **2000**, *21,* 3592-3598.

17. Mclaughlin, E. C; Doyle, M. P. "Propargylic Oxidations Catalyzed by Dirhodium Caprolactamate in Water: Efficient Access to α,β-Acetylenic Ketones" *J. Org. Chem*. **2008**, *73,* 4317.

18. Boer, R. E.; Gimeńez-Bastida, J. A.; Boutaud, O.; Jana, S.; Schneider, C.; Sulikowski, G. A. "Total Synthesis and Biological Activity of the Arachidonic Acid Metabolite Hemiketal E2" *Org. Lett.* **2018**, *20,* 4020-4022.

19. Nicolaou, K. C.; Veale, C. A.; Webber, S. E.; Katerinopoulos, H. "Stereocontrolled total synthesis of lipoxins A" *J. Am. Chem. Soc*. **1985**, *107,* 7515.

20. Chemin, D.; Linstrumelle, G. "An efficient stereocontrolled synthesis of methyl (9Z, 11E, 13S)- 13-hydroxyoctadeca-9,11-dienoate (methyl coriolate)" *Synthesis* **1993**, 377-379.

21. Boer, R. E. "Approaches toward the Chemical Synthesis of Novel Arachidonic Acid Metabolites Hemiketal D2 and Hemiketal E2" Doctoral Thesis, **2015**, Vanderbilt University, Nashville, TN.

Appendix A.3:

Spectra Relevant to Chapter 3

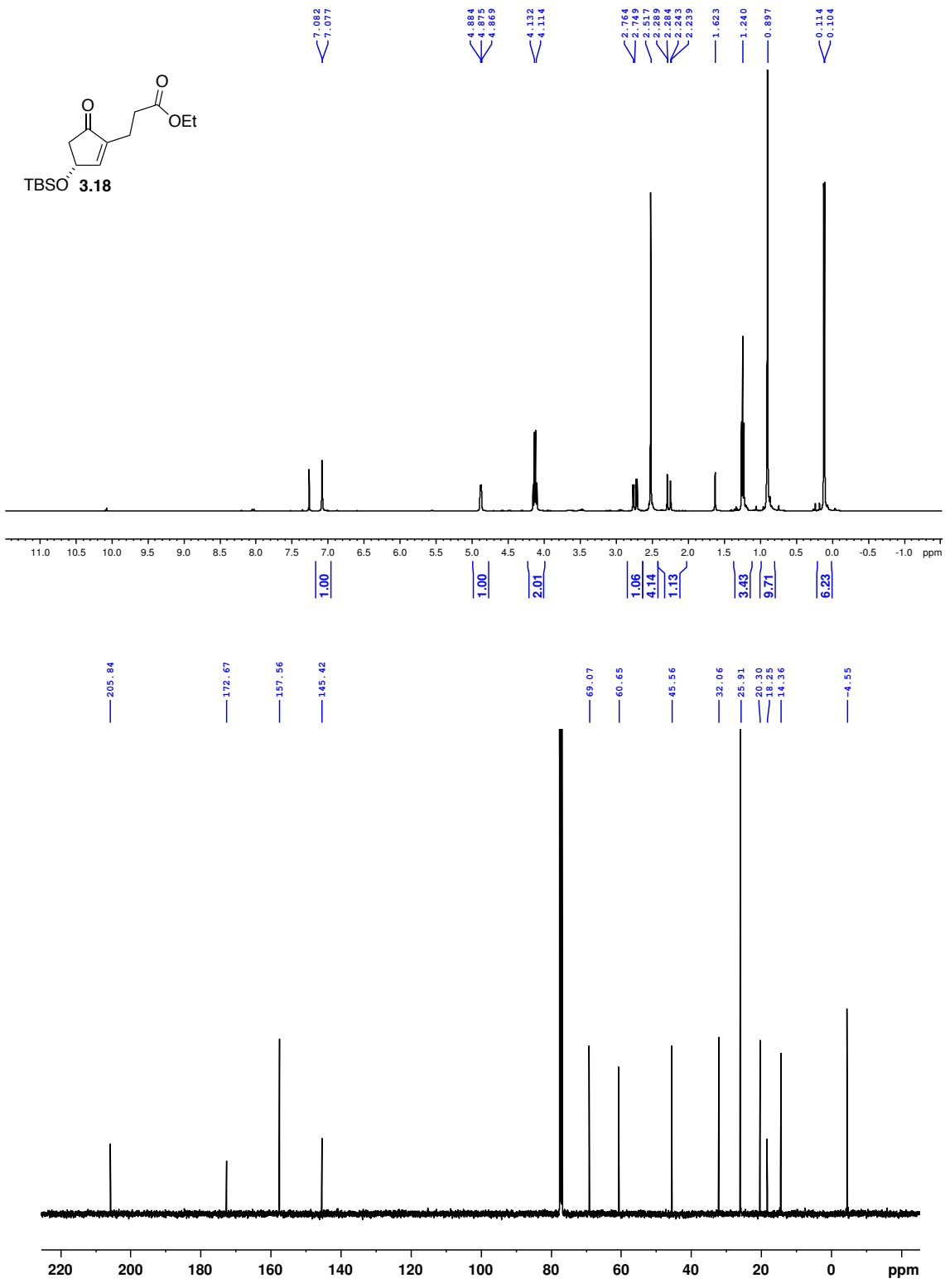


Figure A.3.1 1HNMR (400 MHz, CDCl3) and 13C NMR (100 MHz, CDCl3) of **3.18**

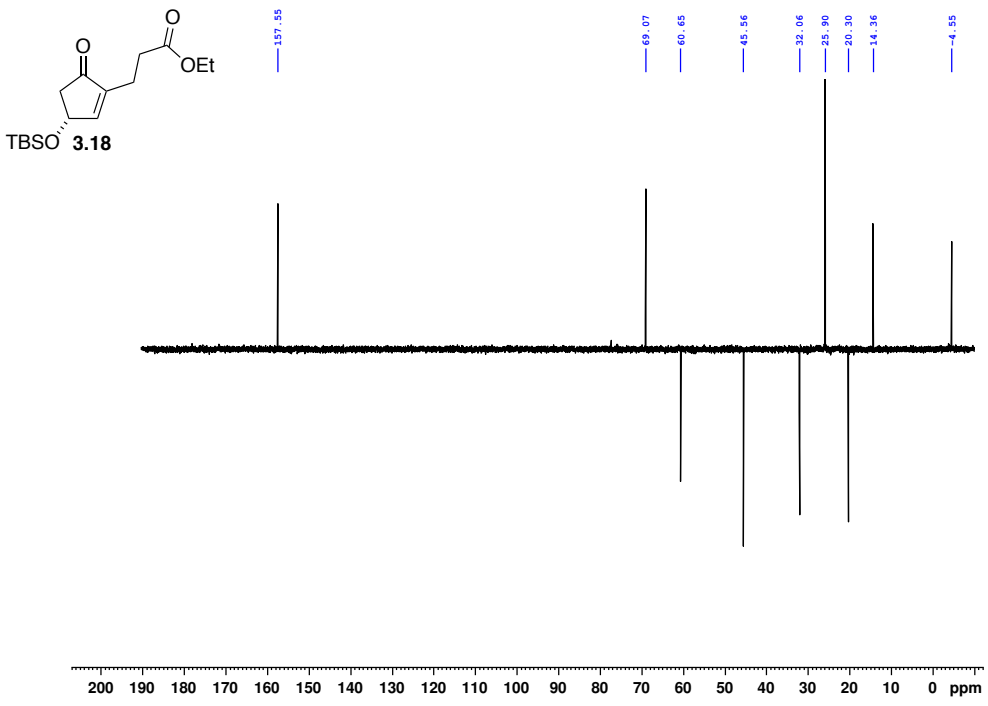


Figure A.3.2 DEPT-135 NMR (100 MHz, CDCl3) of **3.18**

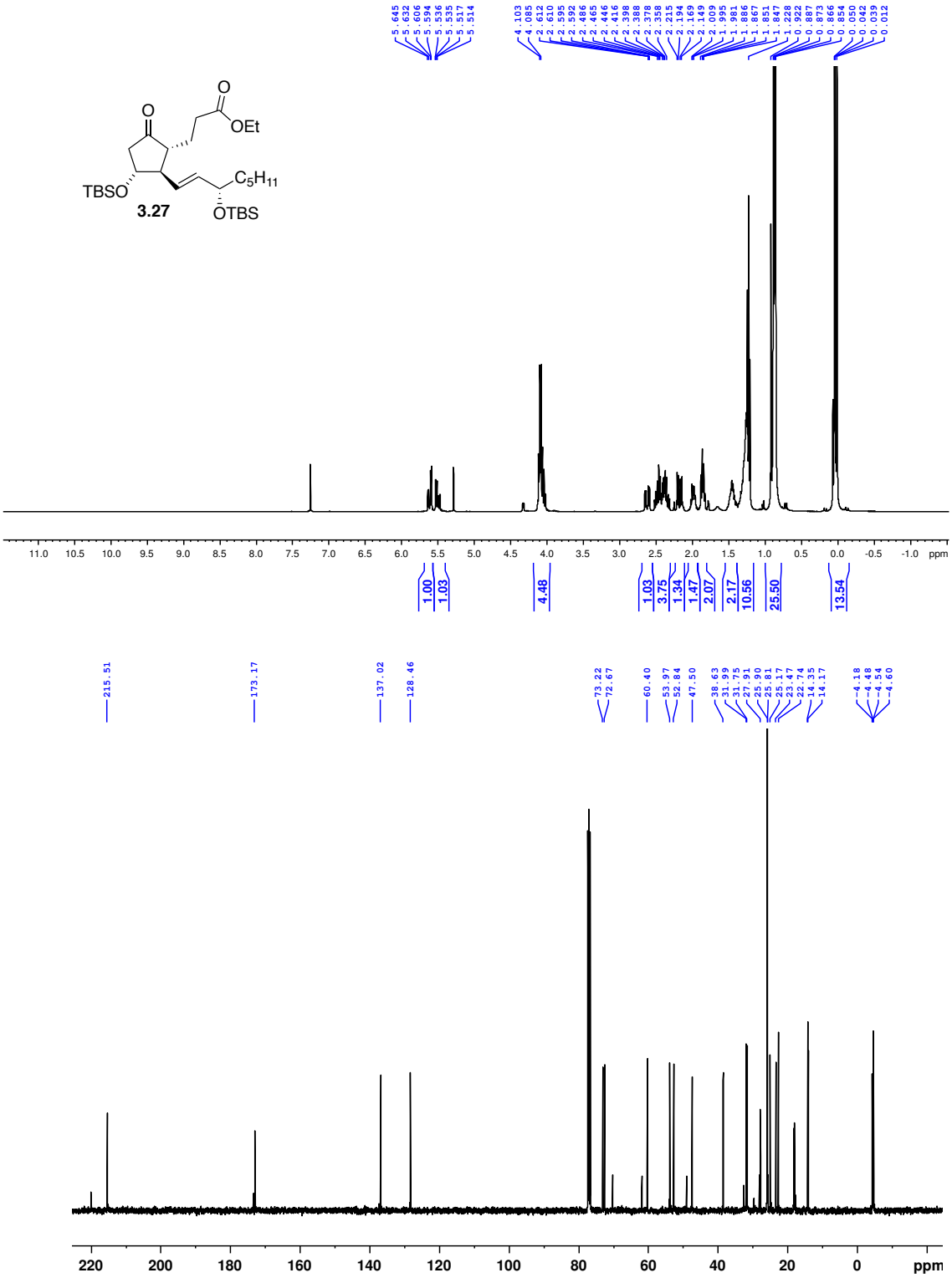


Figure A.3.3 ^{1}HNMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **3.27**

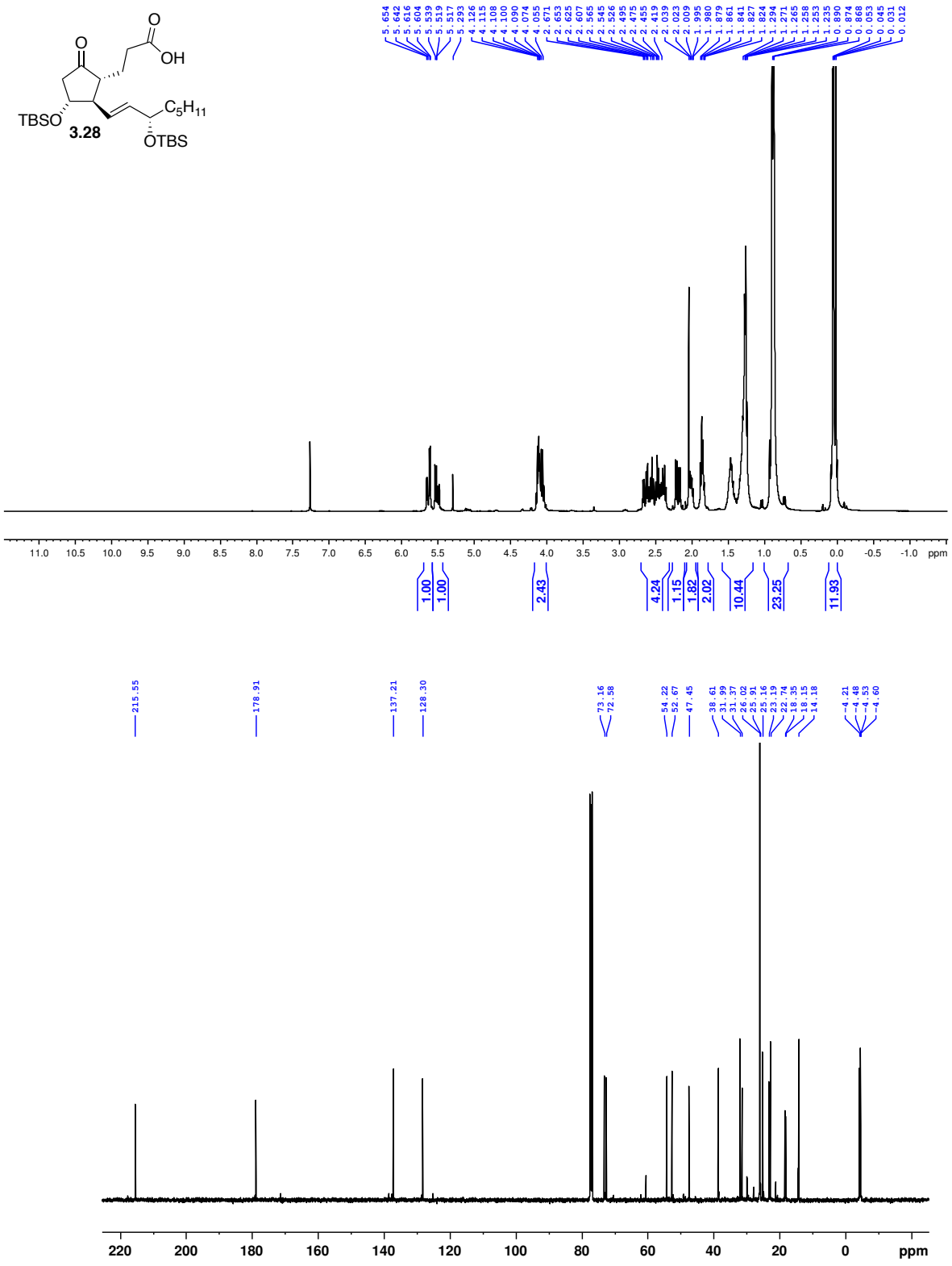


Figure A.3.4 1HNMR (400 MHz, CDCl3) and 13C NMR (100 MHz, CDCl3) of **3.28**

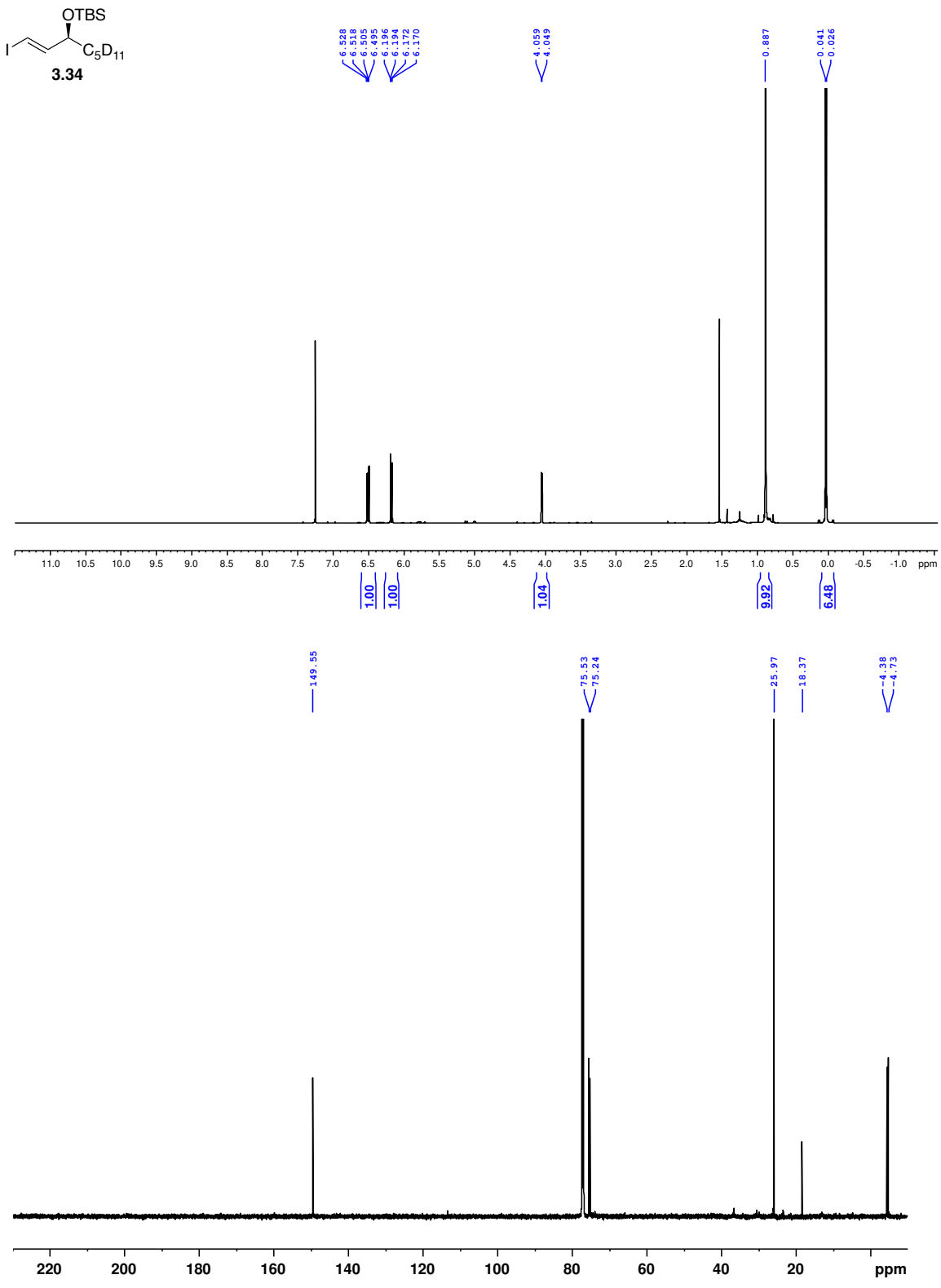


Figure A.3.5 1HNMR (600 MHz, CDCl3) and 13C NMR (150 MHz, CDCl3) of **3.34**

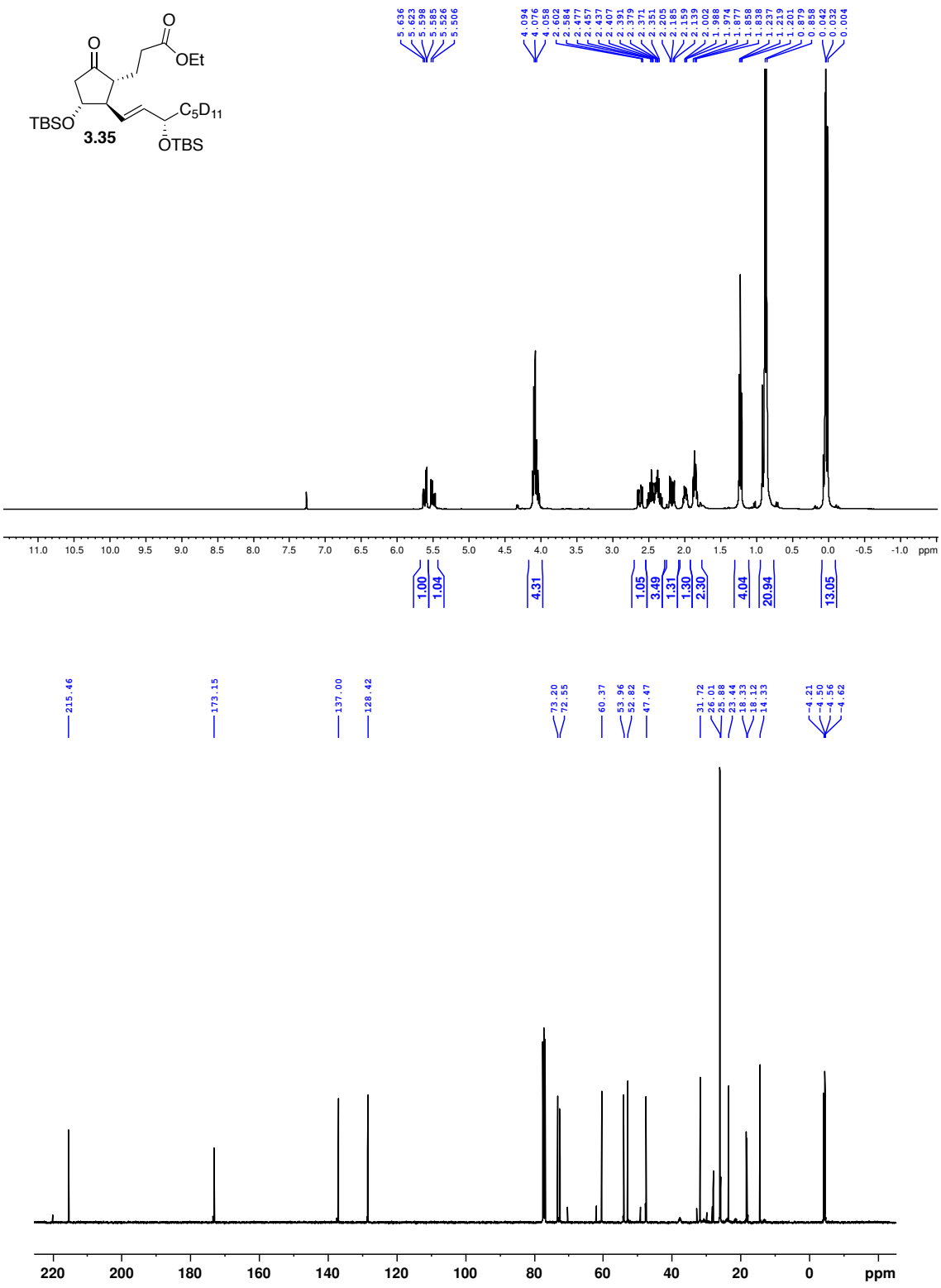


Figure A.3.6 ^{1}HNMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **3.35**

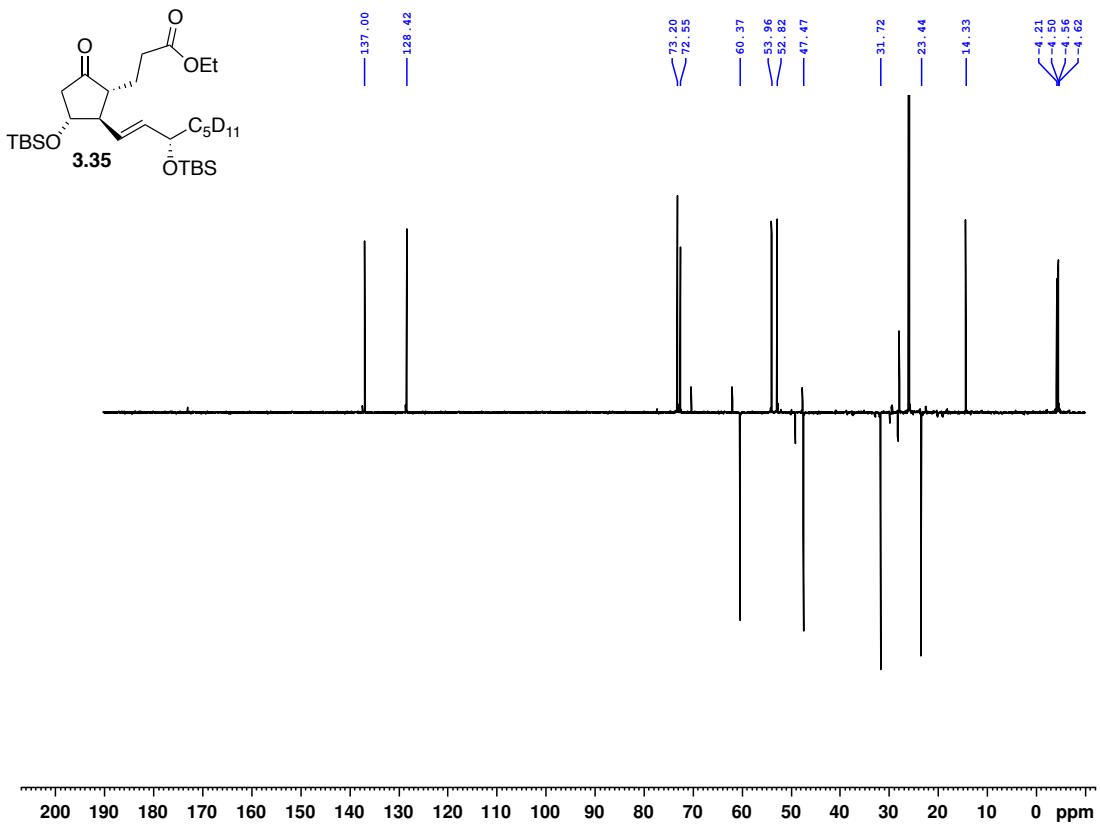


Figure A.3.7 DEPT-135 NMR (100 MHz, CDCl3) of **3.35**

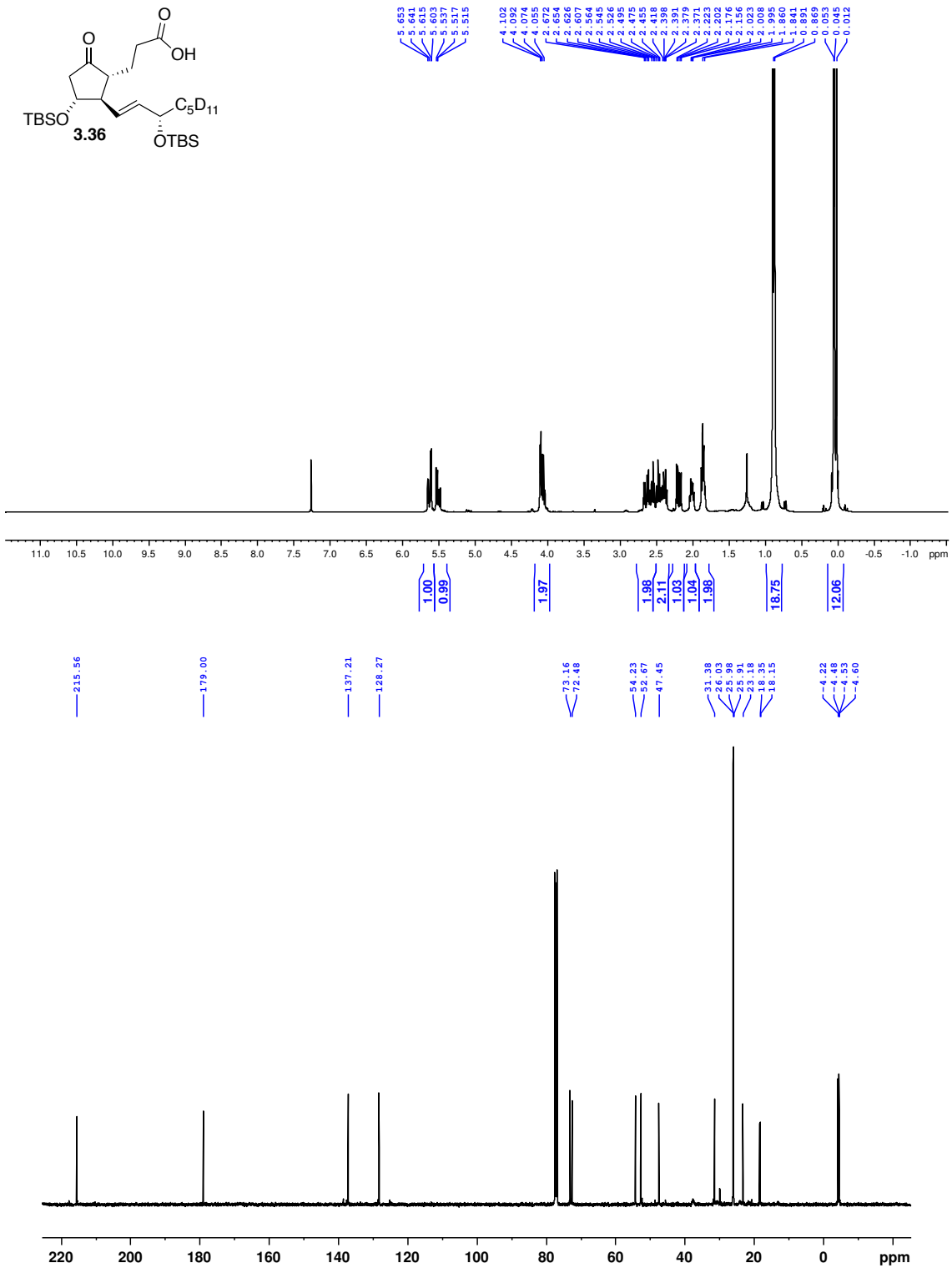


Figure A.3.8 DEPT-135 NMR (100 MHz, $CDCl_3$) of **3.36**

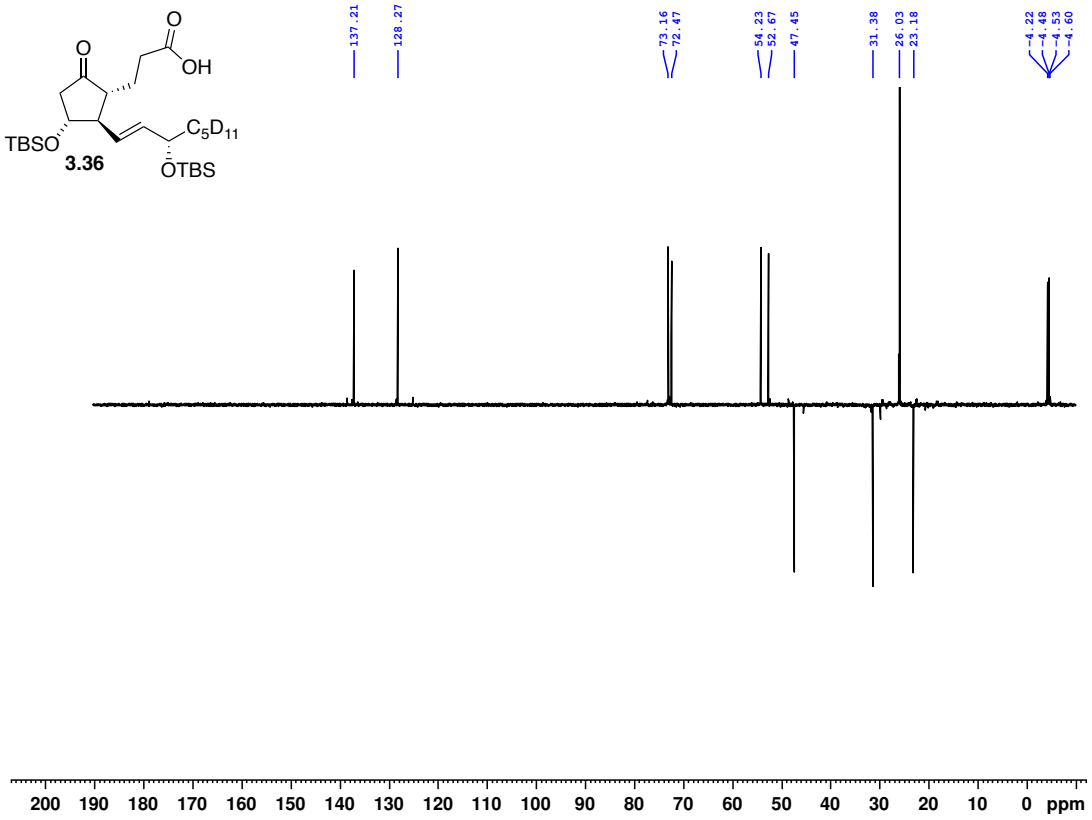


Figure A.3.9 DEPT-135 NMR (100 MHz, $CDCl_3$) of **3.36**

CHAPTER 4

THE TOTAL CHEMICAL SYNTHESIS OF PGD-M

Retrosynthetic Analysis and Preliminary Results

PGD-M contains several structural features that make it a challenging target for total synthesis: the four contiguous stereocenters surrounding the cyclopentane core, the *cis* relationship between the hydroxyl group of C-9 and the alkyl sidechain of C-8, and the β,γ-unsaturated carboxylic acid (Figure 4.1). We envisioned the core spirocyclic acetal of PGD-M to emerge from an acid-catalyzed cyclization of γ-alkylidene lactone **4.2** (X=α–OH, β–H). Anticipating difficulty in establishing the central four contiguous stereocenters within the cyclopentane core, we considered several synthetic routes to access **4.2**. The first route featured a contrasteric allyl-metal addition to enone **4.3** (Route A); the second showcased a *cis*-selective intramolecular C-H insertion followed by a Tsuji-Trost decarboxylative allylation[2] (**4.4**, Route B); and the final route featured an intramolecular Ueno-Stork radical cyclization[3] of **4.5**. (Route C) The successful strategy, Route A, will be discussed in this chapter, while results from Routes B and C will be discussed in Chapter Five.

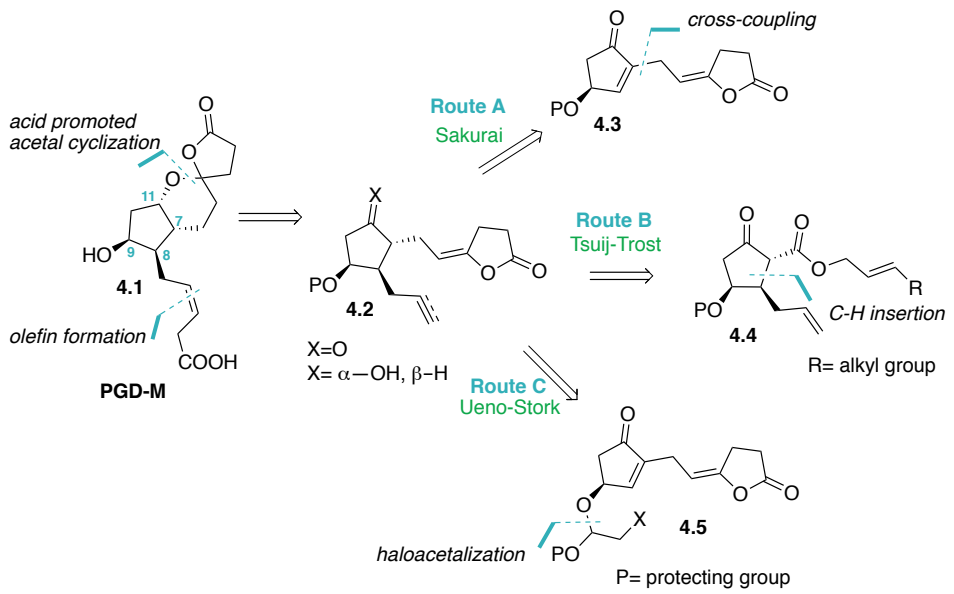


Figure 4.1: Overview of three synthetic strategies leading to PGD-M

Preliminary studies: Establishing stereoselectivity on cyclopentanone model system

As mentioned, the primary challenge of the synthesis of PGD-M is ring formation accompanied by establishment of stereochemistry of the four contiguous stereocenters, with the *cis* relationship being the most challenging. Danishefsky and coworkers reported a novel *cis* addition of an allylsilane to 4-*tert*-butyldimethylsiloxycyclopentenone, promoted by titanium tetrachloride.[4] This addition was intriguing because it afforded a disubstituted cyclopentanone core with the required *cis* stereochemistry, rather than the *trans* stereochemistry resultant of the standard cuprate addition[5] to the same cyclopentenone substrate. We prepared both the *cis* and *trans* allylation products, employing Lewis acid-promoted allylation and allyl cupration, respectively. As the relative stereochemistry of substituted cyclopentanones can be a challenge to assign, we noted the almost 0.4 ppm difference in ^{1}H NMR shift of H_a (Figure 4.2) in the two isomers. Moving forward, there were two pressing questions relating to the viability of this strategy: 1) would a substituent at the α-position affect the diastereoselectivity of the allylation

and 2) would there be preference for the α-substituent to be *cis* or *trans* to the alkyl substituent at C-3.

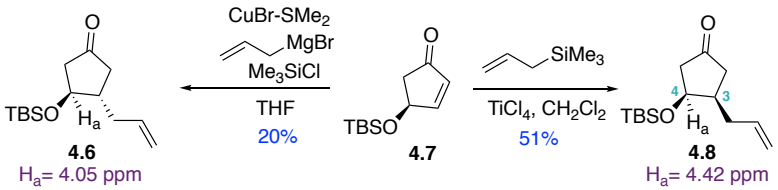


Figure 4.2: Allylation of 4-siloxy cyclopentenone and comparison of H_a chemical shifts

One theory originally suggested by Danishefsky to account for the unique *cis* selectivity of the allylation under Sakurai conditions is the Cieplak effect,[6] a stereoelectronic effect where the transition state leading to the higher energy product is stabilized by hyperconjugation. Specifically, Cieplak effect hypothesized that the emerging σ* orbital at C-3 is stabilized by electron donation from the high energy C-H σ bond at C-4. According to Cieplak, C-H bonds are better electron donors than C-C bonds and thus direct the incoming nucleophile to add *cis* to the sterically demanding -OTBS group.

Preliminary investigation Z olefin synthesis

Following the allylation, we would be left with the challenge of converting the terminal olefin to a β,γ-*cis*-enonate. We explored several different routes on a model system in order to establish this transformation while avoiding isomerization of the double bond. To this end, we examined a Wittig olefination,[7] two cross-couplings, and an alkyne C-H insertion followed by a semi-hydrogenation.[8] (Figure 4.3) We also considered, but did not ultimately pursue, a *Z*-selective cross-metathesis.[9] The eventual successful route to the *Z*-olefin utilized an alkyne C-H insertion followed by a Lindlar catalyzed semi-hydrogenation.

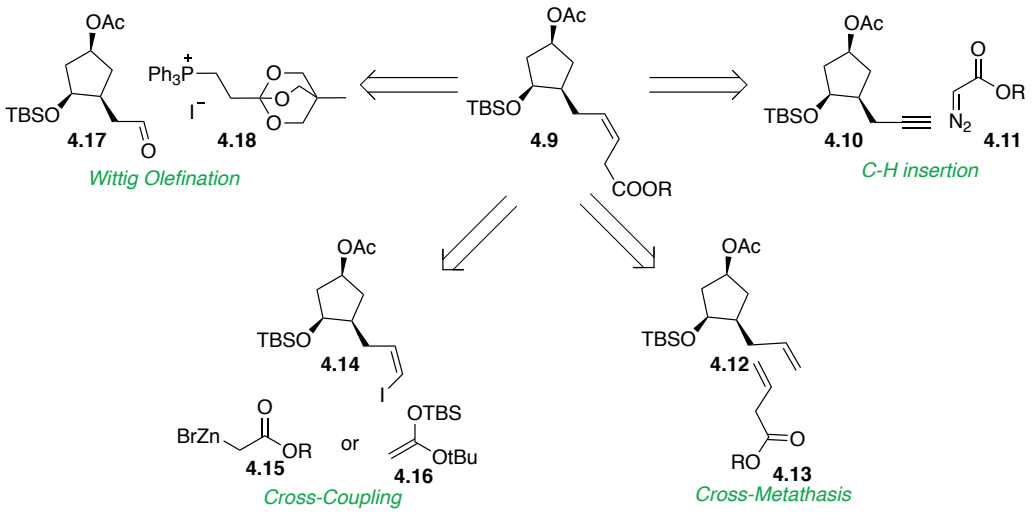
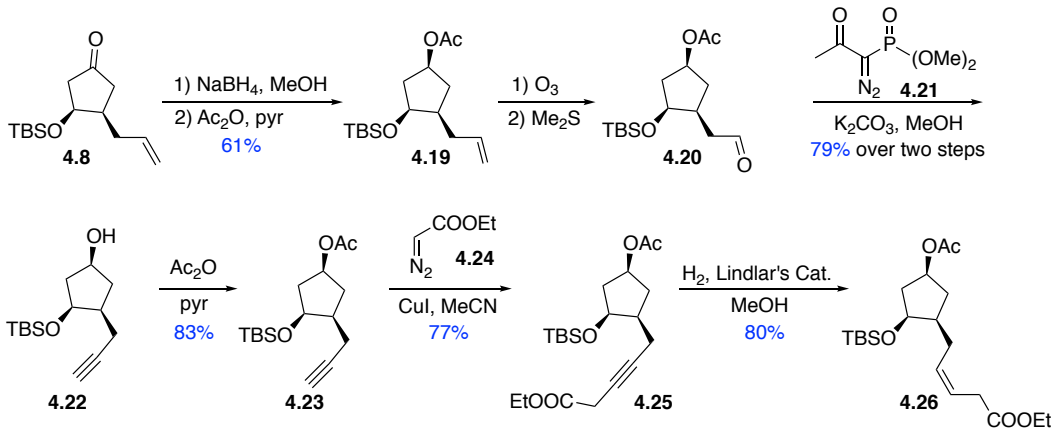


Figure 4.3: Possible routes to access the β,γ unsaturated ester

Formation of the β,γ unsaturated ester on a model system

Reduction of *cis* allylation product **4.8**, and subsequent acetylation, provided acetate **4.19** in favorable yields. Ozonolysis of the terminal olefin, followed by one-carbon homologation with the Bestmann-Ohira reagent[10] resulted in alkyne **4.22**. During the homologation, the acetate was inadvertently removed and was consequently reinstalled to arrive at **4.23**. Next, a C-H insertion was effected using ethyldiazoacetate as described by Fu and coworkers[8] to afford alkynoate **4.25** followed by semi-hydrogenation in the presence of Lindlar's catalyst[11] to provide **4.26** in good yield.



Scheme 4.1: Construction of the lower sidechain on a model system

Revisiting the retrosynthetic analysis

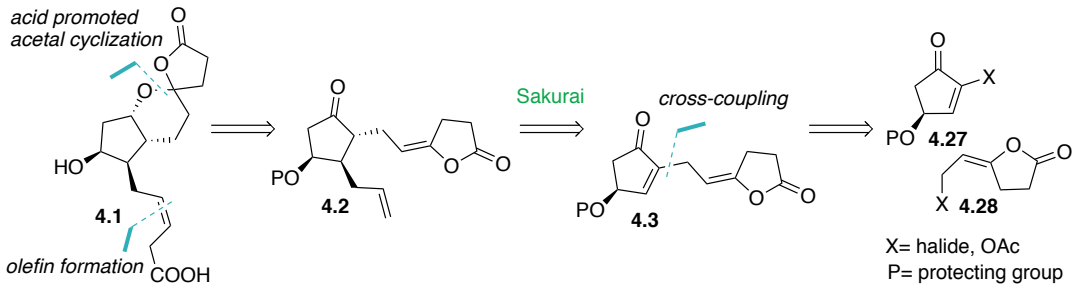


Figure 4.4: Retrosynthetic analysis of PGD-M

Our major concern with incorporating Danishefsky's *cis*-selective allylation into our synthetic plan was the possible effect an α-substituent would have upon diastereoselectivity and the lack of literature precedence as no reports on this unique stereoselective transformation with an α-substituted enone appeared in the literature. In order to investigate, we needed a reliable method for constructing enone **4.3**, which we had planned would be the result of a cross-coupling between cyclopentenone **4.27** and alkylidene lactone **4.28**. Traditionally, cross-couplings occur between sp^2-sp^2 hybridized carbons, which is why we were intrigued by the sp^2-sp^3 hybridized Stille coupling reported by Sorenson in his synthesis of guanacastepenes.[12] The coupling featured

α-stannenone **4.29** and allylic acetate **4.30** and we immediately noted the potential application of the reaction into our synthesis.

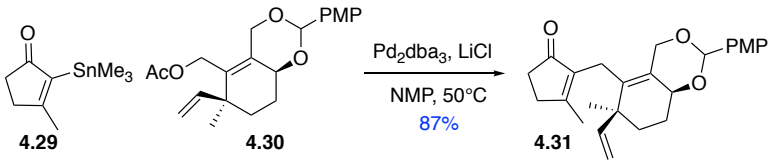
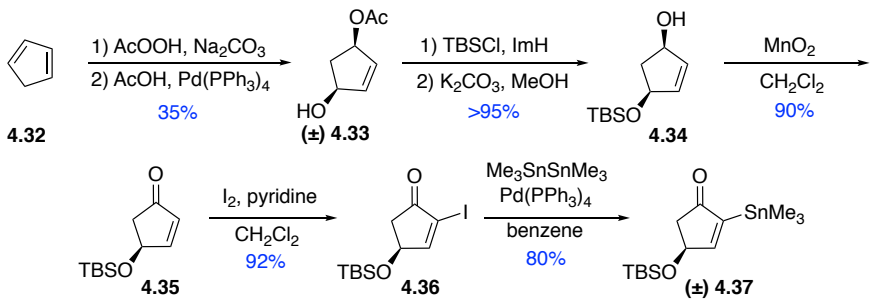


Figure 4.5: Stille Coupling by Sorenson and coworkers

Preparation and Results of Key Stille Coupling

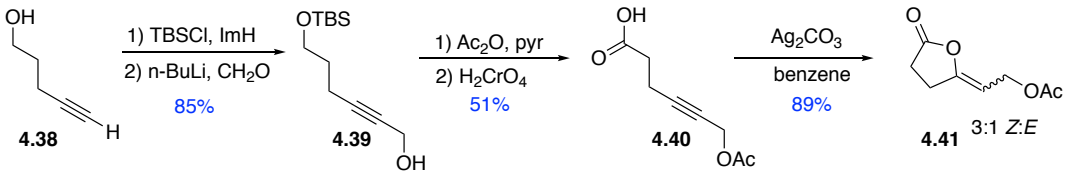
As our synthetic target PGD-M was to be used as analytic standard in GC analysis of patient samples, an optically active final product was not necessary. Thus, we amended the previous synthesis outlined in Chapter 3 of enantiopure **4.36** to a more scalable and more easily accessible route to racemic **4.35**. To this end, epoxidation of **4.32** and subsequent palladium-mediated, stereoselective opening by acetic acid afforded racemic monoacetate **4.33.** This sequence was performed on reaction scales up to 25-grams, in contrast to the photooxygenation of cyclopentadiene followed by enzymatic resolution to optically pure **4.33** that was limited to a 1-gram scale. Oxidation of allylic alcohol **4.34** was also modified from the previous route involving PCC to incorporate more environmentally-friendly MnO_2. Following α-iodination of enone **4.35**, Stille coupling with heximethylditin resulted in α–stannenone **4.37** in good yield following Sorenson's reaction conditions.



Scheme 4.2: Preparation of the α–stannenone

Synthesis of the allylic acetate coupling partner:

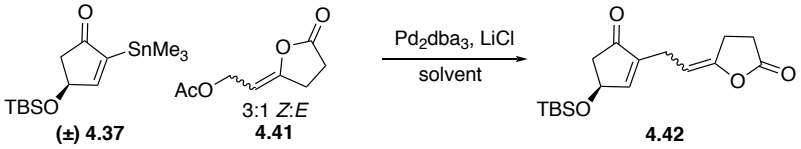
Simultaneously, γ-alkylidene lactone **4.41** was readily prepared was prepared in 5 steps (Scheme 4.3). The reaction sequence commence with silyl protection of 4-pentynol followed by alkyne hydroxymethylation to afford propargylic alcohol **4.39**. Acetylation and subsequent direct Jones oxidation provided carboxylic acid **4.40** before the *5-exo-dig*, silver-mediated cycloisomerization[13] afforded alkylidene lactone **4.41** as a 3:1 mixture of geometric isomers.



Scheme 4.3: Synthesis of allylic acetate coupling partner

With stannenone **4.37** and allylic acetate coupling partner **4.41** in hand, the stage was set for the Stille coupling. A modest solvent screen was conducted to identify the most favorable set of conditions for the coupling. Sorenson's original conditions with Pd_2dba_3 and LiCl in NMP proved optimal over MeCN and DMF. (Table 4.1) We were pleased to observe that enone **4.42**

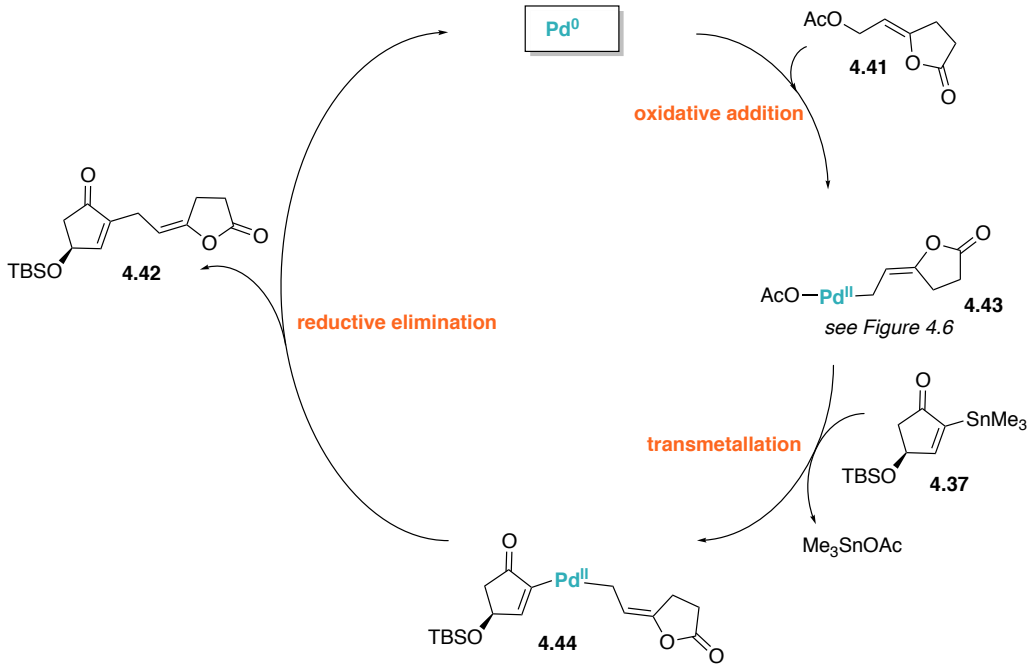
was produced in an optimized 94% yield as a 1:3 *Z*:*E* mixture of isomers, separable by flash chromatography.



Solvent	**Yield**	***Z*:*E* ratio**
DMF	82%	3:1
MeCN	50%	3:2
NMP	94%	3:1

Table 4.1: Stille coupling conditions

Interestingly, the double bond geometry of isomers **4.42** changed from favoring the *Z* geometry in **4.41** from the *5-exo-dig* cyclization, to the *E* geometry in **4.42** after the cross-coupling. Though rare, inversion of double bond geometry in a Stille coupling employing an allyic acetate coupling partner has previously been reported.[14] Outlined in Scheme 4.4 are the key steps of the cross-coupling reaction, starting with oxidative addition of Pd^0 to the allylic acetate 4.41. It is at this stage that the isomerization can occur via the η^3- η^1– η^3 mechanism known to occur with allylic acetates in the presence of palladium.[15] (Figure 4.6) When the complex is in the η^1 form, free rotation can occur about the sigma bond as shown and interconversion between the E and Z isomers is dependent on catalyst, solvent and ionic additives.[15] Transmetallation is the next step in the catalytic cycle, followed by reductive elimination to the desired enone **4.42**.



Scheme 4.4: Catalytic cycle of the Stille Coupling

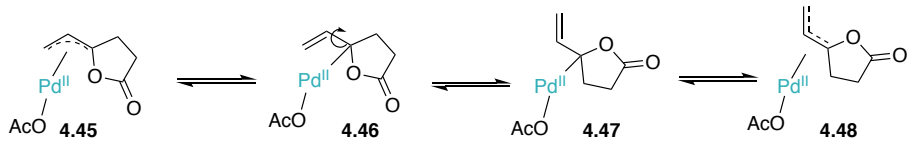


Figure 4.6: the η^3- η^1– η^3 isomerization

Completion of the Total Synthesis of PGD-M

Allylation of the E geometric isomer

With α-substituted enone in hand, the anticipated *cis*-selective allylation under Sakurai conditions was carried out. In order to simplify product analysis and minimize the formation of diastereomers, the *Z* and *E* isomers of enone **4.42** were separated and the isomers were individually subjected to the key allylation conditions. We first examined the major isomer *E* isomer of **4.42** and ultimately isolated two isomeric products and a third product that incorporated a trimethyl

silyl group. Although the stereochemistry of the products was not immediately apparent, it was eventually determined that the desired *trans, cis* cyclopentanone **4.49** was produced in 36% yield, while the undesired *cis,cis* cyclopentanone **4.50** was produced in 41% yield. The third product (**4.51**) proved to be the result of a [3+2] annulation and was produced in 3%. Products similar to the 3+2 annulation product have been previously reported by Danheiser. In an effort to improve the yield of the desired *cis*-isomer **4.49,** a variety of Lewis acids were screened. Examined Lewis acids included $Sc(OTf)_3$, $SnCl_4$, $Yb(OTf)_3$ Et_2AlCl, $BF_3{\cdot}OEt_2$ and TTIP. The only Lewis acid that produced any of the desired cyclopentanone **4.49** was $Sc(OTf)_3$ and in a modest 7% yield.

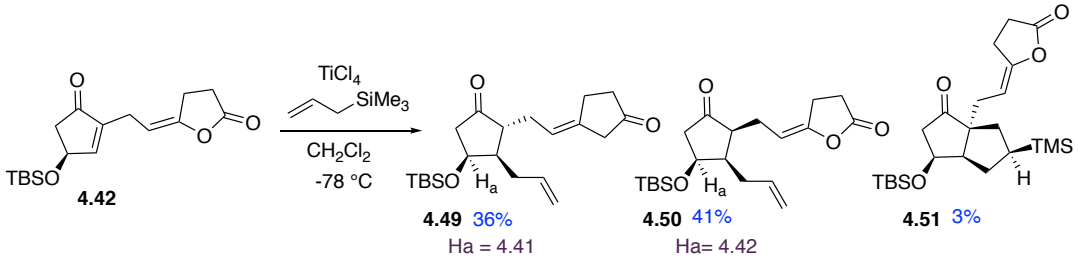
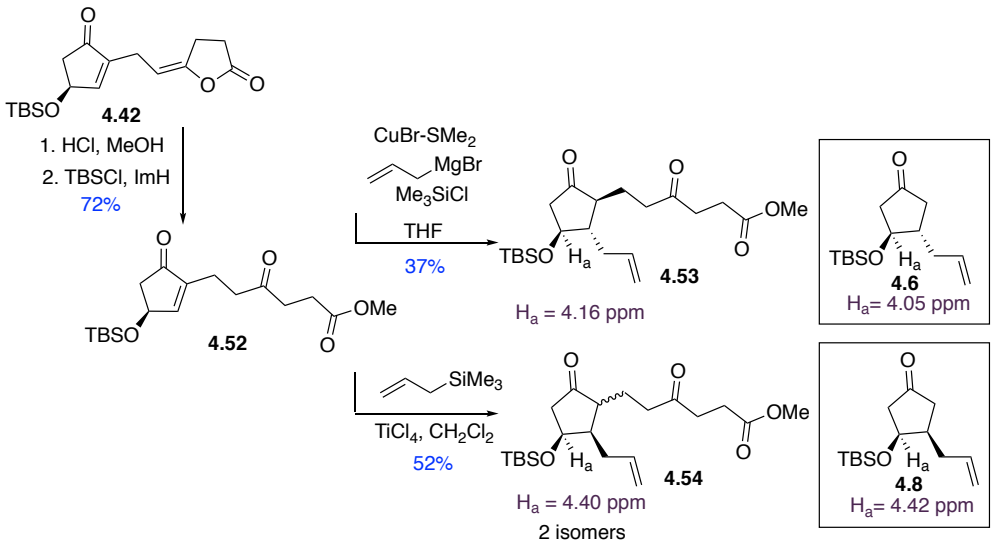


Figure 4.7: Allylation under Sakurai conditions

Assignment of product stereochemistry

Assignment of stereochemistry of isomeric products **4.49** and **4.50** proved challenging. When a series of NOE experiments and analysis of coupling constants proved inconclusive, we turned chemical correlation methods to determine the stereochemistry of **4.49** and **4.50.** Though cautiously optimistic that the structural isomers of the allylation had a *cis* relationship at the β and γ positions based on the proton shifts of H_a (4.41 ppm in **4.49** and 4.42 ppm in **4.50**) in relation to *cis* isomer **4.8** (4.42 ppm), we investigated the allylation on a model system bearing an α–alkyl substituent. (Scheme 4.5) We replicated the Sakurai conditions[4] of the allylation on the model system after opening the lactone of **4.42** to arrive at the diketone **4.52**. When diketone **4.52** was subjected to Sakurai conditions, an inseparable mixture of diastereomers resulted. In both

diastereomers, H_a appeared at 4.40 ppm. For comparison, the *trans,trans* allylation product was produced under standard cuprate conditions.[5] H_a appeared at 4.16 ppm, similar to what was observed on the unsubstituted *trans* cyclopentenone **4.6**



Scheme 4.5: Allylation of diketone 4.52

In an effort to correlate the two isomers isolated in the allylation of enone **4.42**, we attempted to open lactones **4.49** and **4.50** assuming the two products would match spectral data from **4.54**. While lactone **4.49** opened to diketone **4.54a** (with undesired enone **4.55** resulting from β-elimination as a minor sideproduct), cyclopentanone **4.50** produced none of the anticipated diketone and instead formed solely β-elimination product **4.55**. This observation led us to hypothesize that cyclopentanone **4.49** had the desired *trans, cis* stereochemistry and cyclopentanone **4.50** had the undesired *cis, cis* stereochemistry. The *cis,cis* product would likely experience significantly greater ring strain than the *trans, cis* cyclopentanone, thus making it more susceptibleto β - elimination. Our hypothesis regarding the stereochemistry of cyclopentanone **4.49** would later be confirmed by single-crystal X-ray analysis.

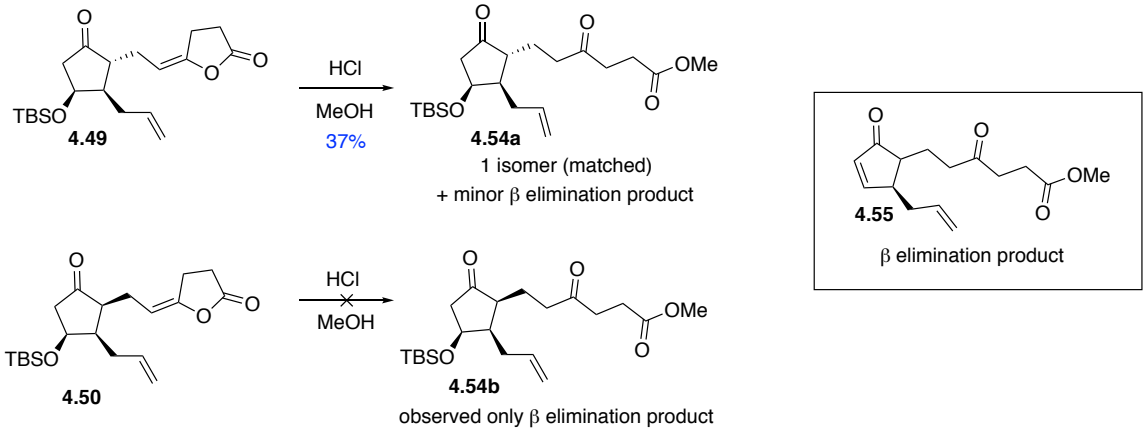


Figure 4.8: Chemical correlation experiments

Allylation of the Z geometric isomer

When the pure *Z* isomer of **4.42** was subjected to the same Sakurai allylation conditions as the *E* isomer, a 1:1 mixture of the *trans* and *cis* isomeric products was observed. Unfortunately, unlike the isomers produced from the *E* geometric isomer, the *cis* and *trans* products derived from the *Z* isomer were inseparable. Because we were unable to separate *trans* isomer **4.56** and *cis* isomer **4.57**, we continued in the route towards PGD-M exclusively with *E trans,cis* isomer **4.49.**

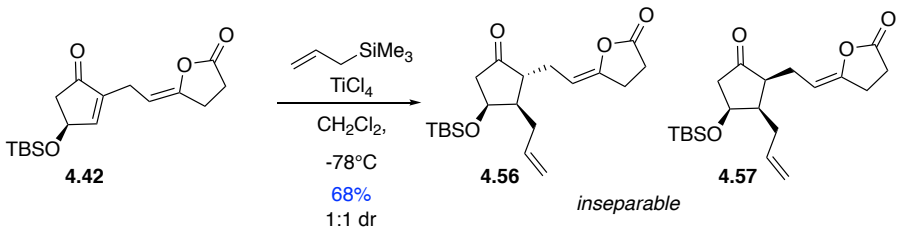


Figure 4.9: Allylation of 4.42b under Sakurai conditions

Chemoselective reduction and acid-promoted cyclization

Moving forward, we had several unsuccessful attempts to selectively reduce the ketone without disturbing the base-sensitive alkylidene lactone of **4.49**. For example, $NaBH_4$ in the presence of methanol reduced the desired ketone, but also opened the lactone and quickly began

reduced the newly formed ketone on the sidechain. However, treatment of cyclopentanone **4.49** with *tert*-butylamine-borane provided alcohol **4.58** as a 1:1 mixture of diastereomers. (Figure 4.10) We speculated that the bulky TBS group must be blocking the desired face for the hydride to approach from and decided to remove the protecting group in an effort to prevent the blocking interaction. Following deprotection with HF-pyridine, **4.59** was reduced using *tert*-butylamine-borane with a slight improvement in diastereoselectivity to 3:1, favoring the desired isomer. Other attempts to reduce the ketone with hydroxyl directed reducing agents failed to produce any of the desired product.

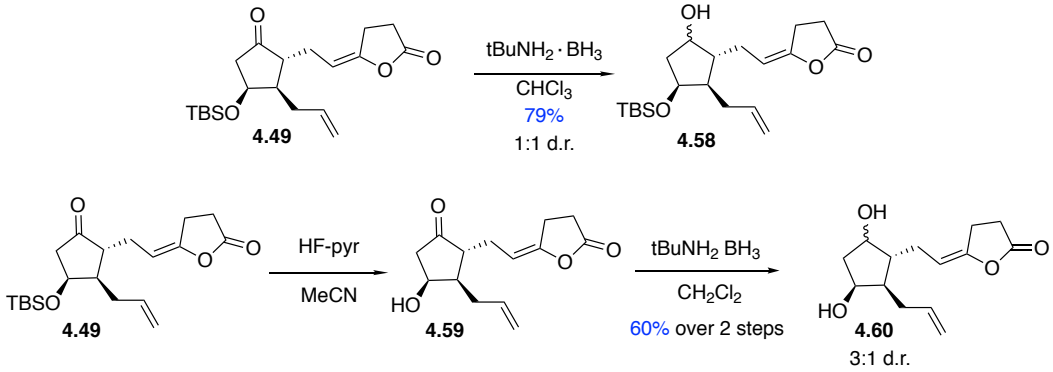


Figure 4.10: Reduction of 4-siloxy cyclopetnanone 4.49 vs. 4-hydroxy cyclopentanone **4.59**

Next, we set our sights on the anticipated acid promoted cyclization to introduce the spiroacetal of PGD-M. As we were unable to separate isomeric alcohols, we were forced to examine the cyclization of the mixture of alcohols **4.56.** Upon treatment with TFA, two spiroacetals were obtained out of a possibility of four isomers, thus we concluded each isomeric alcohol cyclized selectively and we tentatively assigned stereochemistry of **4.61** and **4.62**. Similarly, when inseparable diols **4.58** were treated with TFA, spiroacetals **4.63** and **4.**64 were formed with tentatively assigned stereochemistry. We were curious as to why the spirocyclization was selective for both substrates.

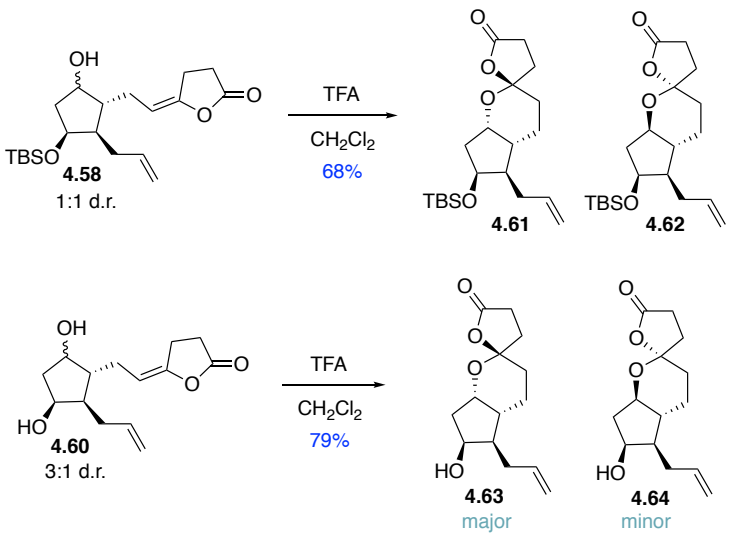


Figure 4.11: Formation of spirocycles 4.62-4.64

Fortunately, spirocycles **4.63** and **4.64** proved separable by flash chromatography and the major diastereomer (**4.63)** was derivatized to *para*-nitrobenzoate **4.65**, which proved crystalline. The major diastereomer could also be reprotected as the TBS ether albeit in low yield, converging with one of the diastereomers isolated during the spiroacetylization of compound **4.58**.

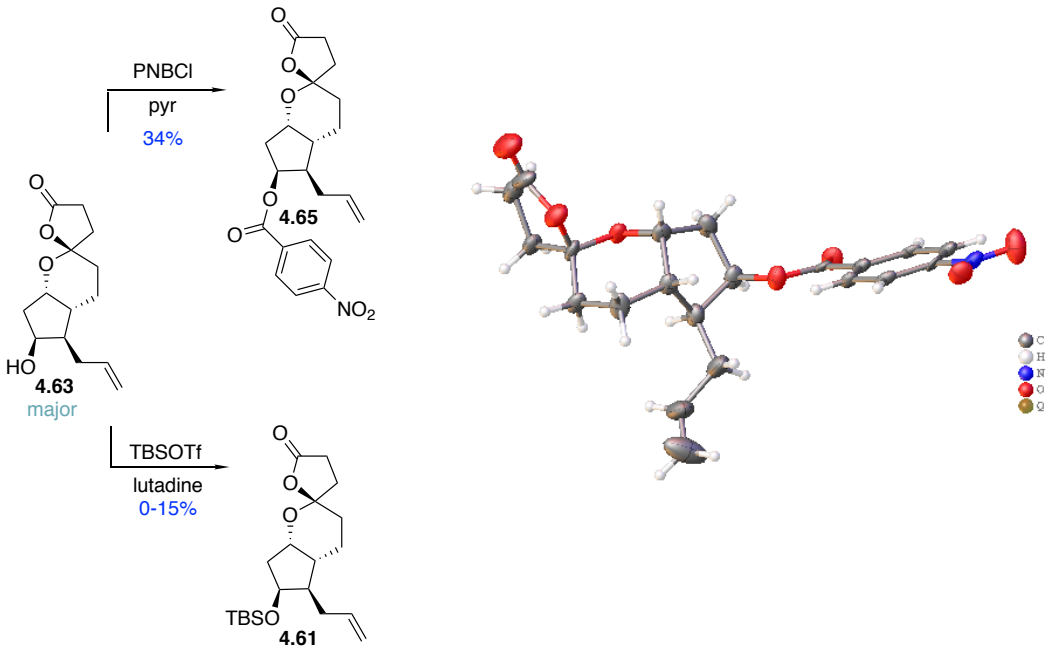


Figure 4.12: Crystal structure of PMB ester

Explanation of observed selectivity

The stereochemistry at the acetal carbon of the spirocycle is partially determined by the anomeric effect.[15] The anomeric effect is described as a preferred periplanar relationship of a σ* C-O orbital and neighboring lone pair. The optimal orientation results in the C-O bond occupying an axial orientation. The antiperiplanar configuration allows for sufficient orbital overlap for the axial lone pair on the cyclic oxygen atom to donate electron density into the σ* orbital of the forming C-O bond. The anomeric effect has been observed in natural products isolated in nature and has also been utilized in total syntheses of natural products, such as in Zammit's synthesis of Reveromycin B[16] and Nicolaou's synthesis of Azaspiracid-1.[17] (Figure 4.13)

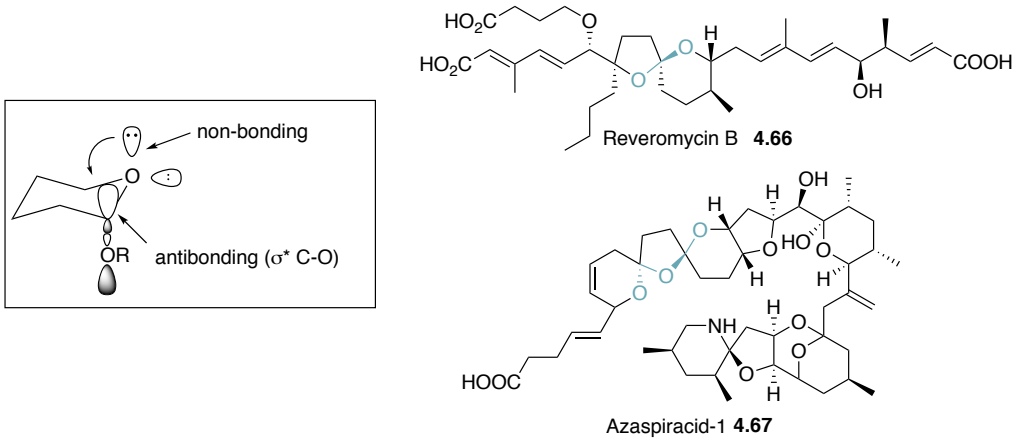


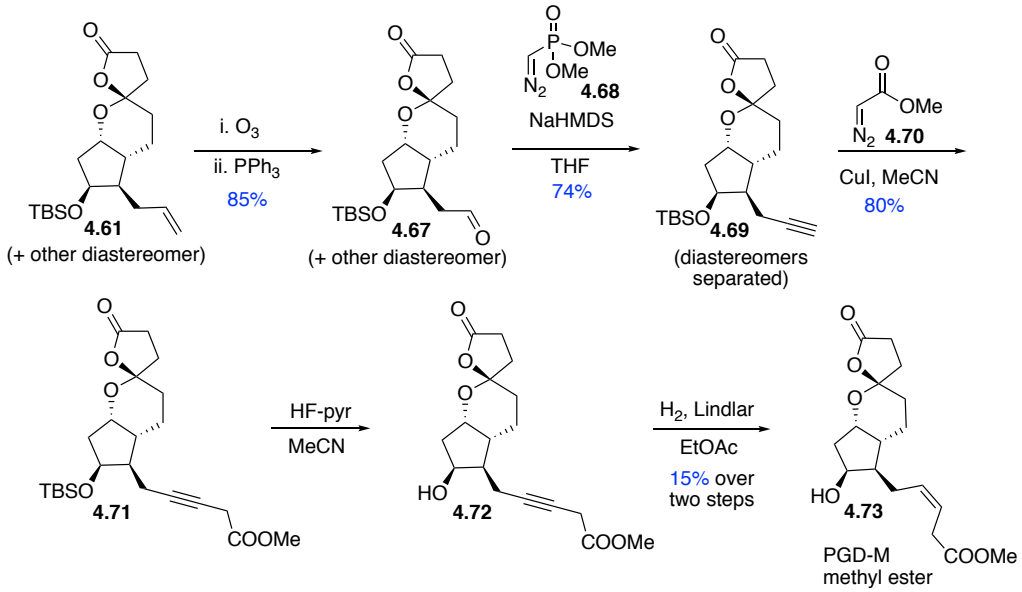
Figure 4.13: The anomeric effect in natural product total synthesis

Completion of the synthesis

Due to the low-yielding TBS protection of spiroacetal **4.63** and our ambition to avoid extra steps in the synthesis, we moved forward with the inseparable mixture of spiroacetal **4.61** and **4.62** resultant from the spiroacetalization of **4.58**. Ozonolysis and one carbon homologation with the Seyferth-Gilbert[18] reagent smoothly afforded terminal alkyne **4.69**. We were forced to pivot from the Bestmann-Ohira reagent to the Seyferth-Gilbert reagent due to the tendency of the spirocycle

to unravel when in the presence of a nucleophilic base. Though the Seyferth-Gilbert reagent is also typically used with the nucleophilic base sodium methoxide, there is precedence for its use with NaHMDS.[19]

The two diastereomers resultant from the reduction are able to be chromatographically separated after the introduction of the alkyne. The desired *cis,trans,cis* spirocycle **4.69** is taken forward and homologated using a Cu-mediated C-H insertion with to give alkynoate **4.71** in good yield. Following deprotection with HF-pyridine and semihydrogenation in the presence of Lindlar's catalyst in modest yield, we arrived at the methyl ester of the final compound, PGD-M.

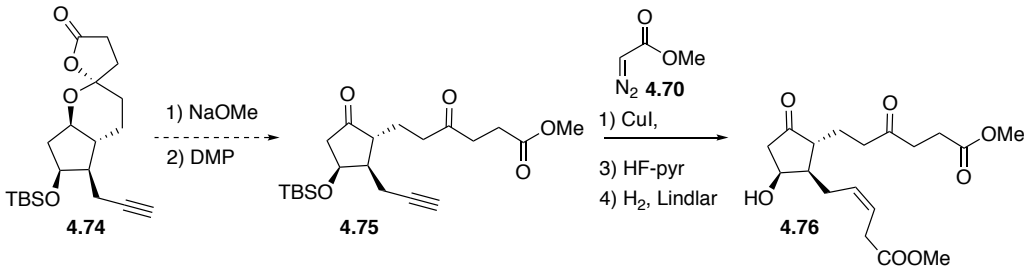


Scheme 4.6: Completion of the synthesis of the methyl ester of PGD-M

Ongoing Work

As mentioned, the undesired diastereomer resultant from the reduction of cyclopentanone **4.49** is carried forward with the correct isomer until formation of alkyne **4.69**, when the two are chromatographically separated. We propose to use spirocycle **4.74** to synthesize **4.76**, the diester

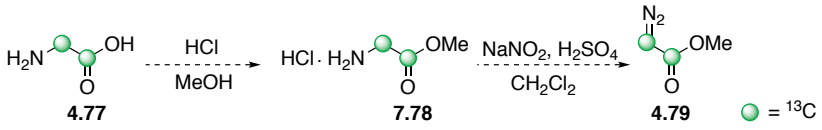
of another PGD_2 urinary metabolite that was previously made by Corey.[7] To achieve this, we will first unravel spirocycle **4.74** with NaOMe and subsequently oxidize the secondary alcohol with DMP to reveal diketone **4.75**. We will then perform the same C-H insertion, deprotection and semihydrogenation sequence that was utilized in the synthesis of PGD-M to arrive at target metabolite **4.76**.



Scheme 4.7: Proposed synthesis of metabolite 4.76

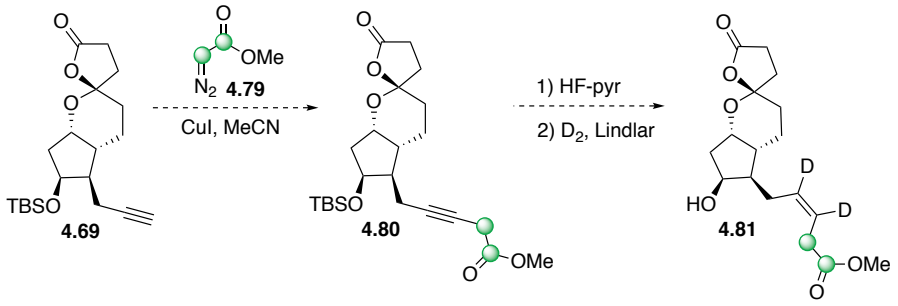
Proposed Introduction of Isotopic Labels

In order to use chemically synthesized PGD-M as an internal standard, the molecule must be isotopically labeled. We propose to incorporate ^{13}C by preparing ^{13}C-labeled methyldiazoacetate from Glycine-$^{13}C_2$.[20] (Scheme 4.9)



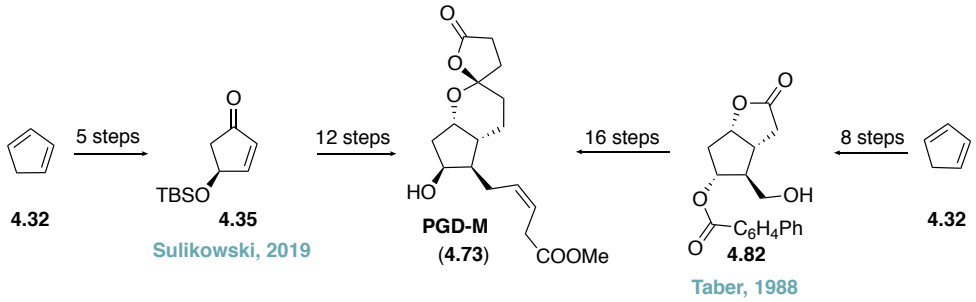
Scheme 4.9: Introduction of isotopic labels

With the ^{13}C labeled methyldiazoacetate **4.79** in hand, we will install the remaining carbon framework via copper-mediated C-H insertion to alkyne **4.80**. Following deprotection, the alkyne will be semi-reduced with deuterium gas to arrive at the $^{13}C_2$-D_2 labeled methyl ester of PGD-M (**4.81**) (Scheme 4.10).



Scheme 4.10: Introduction of isotopic labels

Conclusion to Chapter 4



Scheme 4.11: Comparison of routes to PGD-M

PGD-M, a urinary metabolite of PGD_2, has been prepared from cyclopentadiene in 17 linear steps (12 steps from 4-siloxycyclopentenone). This is an improvement in step count over the previous 24 step synthesis from cyclopentadiene (16 steps from Corey lactone derivative **4.82**) reported by Taber and coworkers. Our synthesis is easily amenable to isotope incorporation and will enable future quantification studies with clinical samples of PGD-M.

Experimental Methods

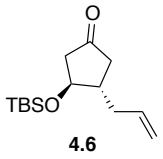
General Procedure: All non-aqueous reactions were performed in flame-dried or oven dried round-bottomed flasks under an atmosphere of argon. Stainless steel syringes or cannula were used to transfer air- and moisture-sensitive liquids. Reaction temperatures were controlled using a thermocouple thermometer and analog hotplate stirrer. Reactions were conducted at room temperature (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 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, or Sure-Seal Sigma reagent bottles. Unless indicated, all commercial reagents were used as received without further purification. The molarity of *n*-butyllithium solutions was determined by titration using *n*-benzylbenzamide 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), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded on Bruker 100 or 150 MHz spectrometers and are reported relative to deuterated solvent signals. Optical rotations were measured on a Perkin-Elmer 341 digital polarimeter at ambient temperature. High-

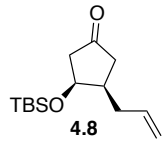
resolution mass spectra were obtained from the Department of Chemistry and Biochemistry, University of Notre Dame.

Compound Preparation



4.6

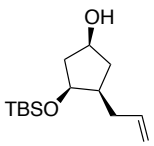
***Trans* cyclopentanone (4.6):** To a stirred solution of $CuBr \cdot SMe_2$ (162 mg, 0.790 mmol) and LiCl (33 mg, 0.768 mmol) in THF (1.5 mL) at -78 °C was added allyl magnesium bromide (1.0 M in Et_2O, 0.707 mL, 0.707 mmol), TMSCl (97 μL, 0.784 mmol) and a solution of enone **4.7** (75 mg, 0.354 mmol) in THF (1.0 mL). The solution stirred for 5 min at -78 °C, at which point it was quenched with a 1:9 solution of NH_4OH: sat. aq. NH_4Cl (3 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resultant residue was purified by flash chromatography (silica gel, 10% EtOAc in hexanes) to yield 18 mg (20%) of the trans-cyclopentanone **4.6** as a clear oil. Spectral data matched reported literature values.[5]



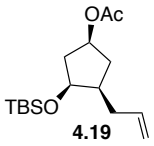
4.8

***Cis* cyclopentanone (4.8):** To a stirred solution of cyclopentenone **4.7** (500 mg, 2.36 mmol) in CH_2Cl_2 (20 mL) cooled to -78 °C was added $TiCl_4$ (1M solution in CH_2Cl_2) (2.36 mL, 2.36 mmol). After 5 min, allyl trimethylsilane (0.515 mL, 2.06 mmol) in CH_2Cl_2 (2.5 mL) was added dropwise. The dark purple mixture stirred at -78 °C for 2 h, at which point it was quenched with sat. aq. $NaHCO_3$ (15 mL) and allowed to warm to room temperature. The aqueous layer was extracted with Et_2O (3 x 15 mL) and the organic extracts were combined, washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resultant residue was purified by flash column chromatography (silica gel, gradient elution, 10 to

40% EtOAc in hexanes) to afford 305 mg (51%) of cyclopentanone **4.8** as a colorless oil. Spectral data matched reported literature values.[4]

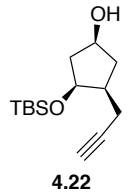


(1*S*,3*R*,4*S*)-3-allyl-4-((*tert*-butyldimethylsilyl)oxy)cyclopentan-1-ol: To a stirred solution of cyclopentanone **4.8** (0.265, 1.71 mmol) in MeOH (6.0 mL) at 0 °C was added $NaBH_4$ (15 mg, 0.40 mmol). The solution stirred at 0 °C for 3 h, at which point it was quenched with H_2O (5 mL) and extracted with EtOAc (3 x 5 mL). The organic extracts were washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resultant residue was purified by flash chromatography (silica gel, 5% EtOAc in hexanes) to yield 237 mg (89%) of the alcohol as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89-5.71 (m, 1H), 5.07 – 4.90 (m, 2H), 4.27- 4.12 (m, 2H), 2.70 (d, *J* = 10.3 Hz, 1H), 2.36-2.21 (m, 2H), 2.20-2.08 (m, 1H), 1.90-1.70 (m, 3H), 1.46 (t, *J* = 12.2, 1H), 0.89 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H).



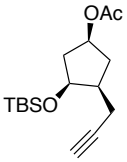
4.19

Acetate (4.19): To a solution of the alcohol (235 mg, 0.917 mmol) at room temperature in pyridine (6.0 mL) was added Ac_2O (0.173 mL, 1.83 mmol). The solution stirred at room temperature overnight, at which point it was diluted with EtOAc (20 mL) and washed with sat. aq. $CuSO_4$ (3 x 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resultant residue did not require further purification and was used crude in the next step. 190 mg (69%) of acetate **4.19** was isolated as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84-5.71 (m, 1H), 5.11-4.90 (m, 3H), 4.06 (s, 1H), 2.35-2.24 (m, 1H), 2.23-2.04 (m, 3H), 1.99 (s, 3H), 1.77-1.67 (m, 2H), 1.65-1.55 (m, 1H), 0.89 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 137.9, 115.3, 74.4, 73.2, 44.9, 42.3, 36.1, 33.7, 25.9, 21.3, 18.2, -4.3, -4.8.



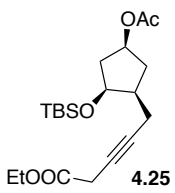
4.22

Terminal alkyne (4.22): To a solution of acetate **4.19** in CH_2Cl_2 (2.5 mL) at 0 °C was bubbled O_3 (excess) for 10 min. The solution was then purged with argon for 15 min, before Me_2S (0.06 mL, 0.087 mmol) was added and the solution stirred overnight at room temperature. It was then concentrated *in vacuo* and dissolved in MeOH (1.7 mL) at room temperature. The Bestmann Ohira reagent (50 mg, 0.261 mmol) and K_2CO_3 (48 mg, 0.348 mmol) were added and the reaction stirred at room temperature overnight. It was then diluted in CH_2Cl_2 (3 mL), washed with brine (3 mL), extracted with EtOAc (3 x 10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo.* The resultant residue was purified by flash chromatography (silica gel, 5% EtOAc in hexanes) to yield 35 mg (79%) of terminal alkyne **4.22** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.30-4.20 (m, 2H), 2.61 (d, *J* = 10.9 Hz, 1H), 2.44-2.24 (m, 3H), 2.06-1.95 (m, 1H), 1.93 (t, *J* = 2.7 Hz, 1H), 1.92–1.85 (m, 1H), 1.85-1.76 (m, 1 H), 1.49 (t, *J* = 11.8 Hz, 1 H), 0.92 (s, 9H), 0.13 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 84.3, 75.2, 73.5, 68.6, 44.9, 44.7, 40.7, 26.0, 19.4, 18.2, -4.4, -4.9.

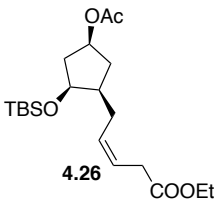


4.23

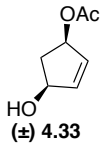
Acetate (4.23): To a solution of the alkyne **4.22** (35 mg, 0.138 mmol) in pyridine (1.5 mL) at room temperature was added Ac_2O (0.04 mL, 0.414 mmol). The solution stirred overnight at room temperature, at which point it was diluted in EtOAc (15 mL), washed with sat. aq. $CuSO_4$ (2 x 10 mL) and sat. aq. $NaHCO_3$ (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo.* The resultant residue did not require purification and was used crude in the next step. 34 mg (83%) of acetate **4.23** was isolated as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.13- 5.05 (m, 1H), 4.15 (td, *J* = 4.43 Hz, 2.07, 1H), 2.37 (ddd, *J* = 2.9, 7.8, 8.8 Hz, 1H), 2.31–2.20 (m, 2H), 2.19- 2.10 (m, 1H), 2.00 (s, 3H), 1.98 – 1.93 (m, 1H), 1.92 (t, *J* = 2.7 Hz, 1H), 1.73 (dt, *J* = 14.9, 2.3 Hz, 1 H), 1.70 – 1.61 (m, 1H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H).



Alkynoate (4.25): To a solution of terminal alkyne **4.23** (17 mg, 0.108 mmol) in MeCN (0.2 mL) at room temperature was added CuI (1 mg, 0.005 mmol), followed by ethyl diazoacetate (13% by wt in DCM) (7 μL, 0.108 mmol). The reaction stirred at room temperature for 24 h, at which point it was concentrated *in vacuo*. The resultant residue was purified by flash chromatography (silica gel, 3% EtOAc in hexanes) to yield 17 mg (77%) of the propargyl ester **4.25** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15-5.02 (m, 1H), 4.28–4.06 (m, 3H), 3.22 (t, *J* = 2.5 Hz, 2H), 2.43-2.32 (m, 1H), 2.31-2.21 (m, 2H), 2.19-2.08 (m, 1H), 1.99 (s, 3H), 1.97-1.88 (m, 1H), 1.72 (dt, *J* = 15.2, 2.3 Hz, 1H), 1.69-1.60 (m, 1H), 1.28 (t, *J* = 7.2 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 169.0, 83.2, 74.4, 72.9, 71.9, 61.6, 44.6, 42.2, 36.1, 26.2, 25.9, 21.4, 18.9, 18.2, 14.3, -4.5, -4.9.

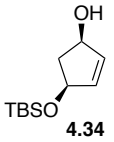


Alkenoate (4.26): To a solution of alkyne **4.25** (28 mg, 0.013 mmol) in MeOH (1.0 mL) was added Lindlar's catalyst (10 mg). The reaction vessel was purged with H_2 and stirred under H_2 for 8 h at which point it was filtered and concentrated. The resultant residue did not require further purification. 23 mg (80%) of the *Z* alkene **4.26** was isolated as a clear oil. ^{1}H NMR δ 5.61-5.53 (m, 1H), 5.12 -5.00 (m, 1H), 4.30-2.04 (m, 3H), 3.09 (d, *J* = 5.09 Hz, 2 H), 2.25-2.08 (m, 3H), 2.00 (s, 3H), 1.80-1.67 (2H), 1.36-1.28 (m, 1H), 1.26 (t, *J* = 7.2 Hz, 3H), 3.09 (d, *J* = 4.6 Hz, 2H), 0.90 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). δ ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 171.2, 132.1, 121.7, 74.3, 73.4, 60.8, 45.0, 42.2, 36.0, 33.2, 27.2, 25.9, 21.4, 18.2, 14.3, -4.3, -4.8.



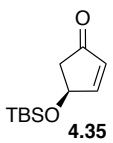
(±) 4.33

(±)-cis-4-Acetoxycyclopent-2-en-1-ol (4.33): To a solution of freshly distilled cyclopentadiene (15.0 g, 0.227 mol) in CH_2Cl_2 (140 mL) at 0 °C was added Na_2CO_3 (28.9 g, 0.272 mol). A mixture of NaOAc (558 mg, 0.007 mol) in 39% peracetic acid (9.2 mL, 0.227 mmol) was added. The internal temperature of the reaction was monitored and intermittent cooling ensured the reaction did not exceed 30 °C. The reaction then stirred at room temperature for 1 h before the crude epoxide was filtered through a fritted funnel. To a mixture of $Pd(PPh_3)_4$ (524 mg, 0.005 mmol) in THF (200 mL), cooled to 0°C was added AcOH (26 mL, 0.454 mol) and after 10 min the prepared solution of crude epoxide in CH_2Cl_2 was added. Upon completion of the addition, the reaction stirred at room temperature for 1 h before it was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resultant residue was purified by flash column chromatography (silica gel, gradient elution, 10% to 50% EtOAc-hexanes) to yield 10.3 g (32%) of monoacetate (±)-**4.33** as a yellow solid. The spectral data matched reported values.[22]



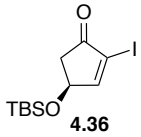
4.34

(1*R*,4*S*)-4-((*tert*-butyldimethylsilyl)oxy)cyclopent-2-en-1-ol (4.34): To a solution of acetate **4.33** (8.30 g, 58.4 mmol) in DMF (80 mL) at room temperature was added TBSCl (13.20 g, 87.6 mmol), imidazole (11.92 g, 0.175 mol) and DMAP (357 mg, 2.91 mmol). The solution was stirred overnight, quenched with water (50 mL) and extracted with Et_2O (5 x 75 mL). The combined organic extracts were washed with 1N HCl (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography. To a solution of the resultant TBS ether in MeOH (120 mL) was added K_2CO_3 (8.94g, 64.7 mmol). The solution stirred overnight before being filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, gradient elution, 5 to 20% EtOAc in hexanes) to afford 9.28 g (74%) of cyclopentenone **4.34** as a colorless oil. Spectral data matched reported literature values.[22]



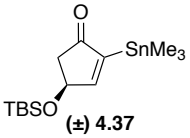
4.35

4-((*tert*-butyldimethylsilyl)oxy)cyclopent-2-en-1-one (4.35): To a solution of the allylic alcohol (9.28 g, 43.3 mmol) dissolved in CH_2Cl_2 (250 mL) at room temperature was added MnO_2 (90% by wt.)(41.86 g, 0.433 mol). The reaction was then allowed to stir at room temperature overnight, at which point additional MnO_2 (20.90 g, 0.216 mol) was added. The reaction mixture was then stirred for 2 h before it was filtered through a pad of Celite and concentrated *in vacuo.* The residue was purified by flash chromatography (silica gel, gradient elution, 5 to 20% Et_2O in hexanes) to afford 8.43 g (92%) of cyclopentenone **4.35** as a white solid. Spectral data matched reported literature values.[23]



4.36

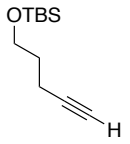
(*R*)- 4-((*tert*-butyldimethylsilyl)oxy)-2-iodocyclopent-2-en-1-one (4.36): To a solution of cyclopentenone **4.35** (2.04 g, 9.92 mmol) in CH_2Cl_2 (17.5 mL) and pyridine (17.5 mL) was added a solution of I_2 (4.15 g, 16.3 mmol) in CH_2Cl_2 (17.5 mL) and pyridine (17.5 mL) dropwise over 1 h at 0 °C via syringe pump. The mixture was then allowed to warm to room temperature and stirred for 30 min before 2 N HCl (30 mL) was added slowly. The organic layer was washed with satd. aq. Na_2SO_3 (2 x 50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resultant residue was purified by flash chromatography (silica gel, gradient elution, 0-10% EtOAc in hexanes) to yield 2.99 g (92%) of iodocyclopentenone **4.36** as a pale-yellow solid. Spectral data matched reported literature values.[24]



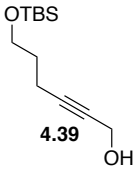
(±) 4.37

Stannenone (4.37): To a solution of the α-iodoenone **4.36** (342 mg, 1.01 mmol) in benzene (6.0 mL) was added $Me_3SnSnMe_3$ (0.42 mL, 2.02 mmol) and $Pd(PPh_3)_4$ (58 mg, 5.1 mmol). Argon was bubbled through the solution for 10 min and the mixture refluxed at 80°C for 16 h. It was then cooled to room temperature and diluted with

pentanes (10 mL) and sat. aq. KF (7 mL) was added. The tin salts were filtered off before the filtrate was washed with aq. sat. KF (10 mL) and H_2O (2 x 10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resultant residue was purified by flash chromatography (silica gel, gradient elution, 5 to 10% Et_2O in pentanes) to yield 305 mg (80%) of stannenone ±**4.37** as a clear oil. ^1H NMR (600 MHz, $CDCl_3$) δ 7.50 (d, J = 2.2 Hz, 1H), 4.97 (dt, J = 3.3, 6.1 Hz, 1H), 2.71-2.65 (dd, J = 17.9, 6.1 Hz, 1H), 2.24-2.19 (dd, J = 18.0, 2.6 Hz, 1H), 0.92 (s, 9H), 0.25 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 210.9, 172.4, 150.0, 73.3, 45.2, 26.0, 18.4, -4.50, 4.53, -9.60.

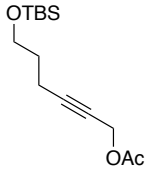


***tert*-butyldimethyl(pent-4-yn-1-yloxy)silane**: To a solution of pentynol (6.00 g, 71.3 mmol) in DMF (72 mL) at room temperature was added TBSCl (13.98 g, 92.7 mmol), ImH (9.70 g, 43 mmol) and DMAP (871 mg, 7.13 mmol). The solution stirred overnight at room temperature. The mixture was quenched with H_2O (100 mL), extracted with Et_2O (4 x 60 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resultant residue was purified by flash column chromatography (silica gel, gradient elution, 0-20% EtOAc in hexanes) to yield 13.92 g (>95%) of the alkyne as a colorless oil. Spectral data matched reported literature values.[25]

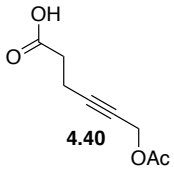


Propargyl alcohol (4.39): To a solution of the alkyne (5.93 g, 29.9 mmol) in THF (75 mL) at -78 °C was added *n*-BuLi (23.0 mL, 50.9 mmol, 2.21 M in hexanes) dropwise over 5 min. The solution stirred at -78 °C for 1 h, before paraformaldehyde (3.15 g, 0.11 mol) was added and the reaction slowly warmed to room temperature over 3.5 h. The mixture was quenched with sat. aq. NH_4Cl solution (100 mL), extracted with EtOAc (3 x 80 mL),

dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resultant residue was purified by flash column chromatography (silica gel, gradient elution, 5-40% EtOAc in hexanes) to yield 6.07 g (89%) of propargyl alcohol **4.39** as a colorless oil. Spectral data matched reported literature values.[26]

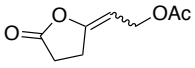


6-((*tert*-butyldimethylsilyl)oxy)hex-2-yn-1-yl acetate: To a solution of the propargyl alcohol **4.39** (6.04 g, 26.5 mmol) in pyridine (26.5 mL) was added Ac_2O (5.0 mL) at room temperature. The reaction stirred overnight before it was diluted in EtOAc (100 mL), washed with sat. aq. $CuSO_4$ (3 x 40 mL) and washed with sat. aq. $NaHCO_3$ (40 mL). The organic extract was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resultant residue was purified by flash column chromatography (silica gel, gradient elution, 0-10% Et_2O in hexanes) to yield 5.35 g (74%) of the propargyl acetate as a colorless oil. 1H NMR (600 MHz, $CDCl_3$) δ 4.66 (t, J = 2.0 Hz, 2H), 3.68, (t, J = 6.0 Hz, 2H), 2.31, (tt, J = 7.1, 2.1 Hz, 2H), 2.09 (s, 3H), 1.71 (p, J = 6.6 Hz, 2H), 0.89 (s, 9H), 0.05 (s, 6H).^{13}C NMR (150 MHz, $CDCl_3$) δ 170.4, 87.3, 74.0, 61.5, 52.8, 31.4, 25.9, 20.8, 18.3, 15.21, -5.36.



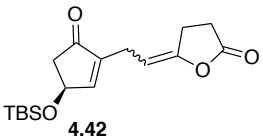
6-acetoxyhex-4-ynoic acid (4.40): The Jones reagent was freshly prepared by adding 0 °C H_2O (19 mL) to CrO_3 (5.93 g, 59.3 mmol) and H_2SO_4 (5.90 mL). The solution was cooled to 0 °C before a solution of the acetate (5.25 g, 19.8 mmol) in acetone (85 mL) was added dropwise via addition funnel over 15 min. The icebath was then removed and the reaction stirred at room temperature for 3 h. Isopropanol (90 mL) was then added and the mixture was filtered through Celite and partially concentrated *in vacuo*. The filtrate was then redissolved in EtOAc (50 mL) and washed with sat. aq. NH_4Cl (2 x 50 mL). The organic

extract was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resultant residue was purified by flash column chromatography (silica gel, gradient elution, 25-50% EtOAc in hexanes) to yield 2.30 g (68%) of carboxylic acid **4.40** as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.65 (t, *J* = 2.1, 2H) 2.58-2.63 (m, 2H), 2.53-2.58 (m, 2H), 2.09 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 170.5, 85.2, 75.1, 52.7, 33.0, 20.9, 14.6.



4.41

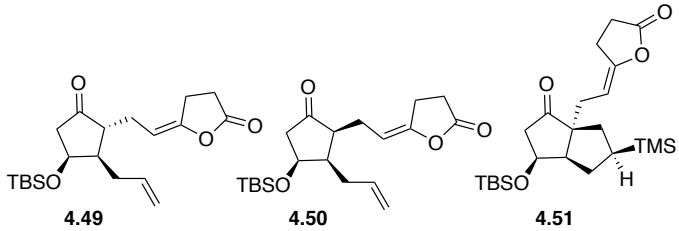
Allylic Acetate (4.41): To a solution of the propargyl acetate **4.40** (1.27 g, 7.47 mmol) in benzene (35 mL) at room temperature was added Ag_2CO_3 (206 mg, 0.747 mmol). The solution was heated to reflux and stirred for 8 h. The mixture was then filtered through Celite and concentrated *in vacuo* before the residue was purified by flash chromatography (silica gel, 0 to 50% EtOAc-hexanes) to afford 1.14 g (90%) of allylic acetate **4.41** as 3:1 *Z:E* ratio. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.39 (tt, 1H, *J*= 8.1, 2.2 Hz, 1H), 4.56 (d, *J*= 8.47 Hz, 2H)3.06-2.97 (m, 2H), 2.75-2.64 (m, 2H), 2.05, (s, 3H). 4.87 (dd, *J*= 1.6 , 7.5 Hz, 2H), 4.70 (d, *J*= 7.50, 2 H) 2.94-2.85 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 174.1, 171.0, 155.1, 152.4, 99.2, 99.1, 59.4, 58.7, 27.4, 27.3, 25.1, 22.9, 21.1.



4.42

Enone (4.42): To a mixture of LiCl (361 mg, 8.51 mmol) and Pd_2dba_3 (389 mg, 0.425 mmol) was added the allylic acetate **4.41** (434 mg, 2.55 mmol) in NMP (3.8 mL). The resultant solution stirred at room temperature for 15 min before stannenone **4.37** (800 mg, 2.13 mmol) in NMP (3.8 mL) was added. Argon was bubbled through the reaction mixture for 15 min before it was heated to 50 °C and stirred for 12 h. The solution was then cooled to room temperature, diluted with Et_2O (50 mL) and quenched with H_2O (30 mL). The aqueous layer was extracted with Et_2O (2 x 50 mL) and EtOAc (2 x 50

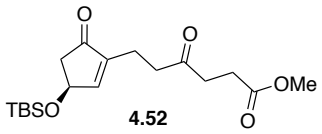
mL). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The resultant residue was purified by flash chromatography (silica gel, gradient elution, 5% to 100% Et_2O in hexanes) to yield 647 mg (94%) of enone **4.42** as a 3:1 *E*/*Z* mixture of diastereomers. The mixture could be separated with careful column chromatography. ***E* isomer:** ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.07 (d, *J* = 2.2 Hz, 1H), 5.25 (tt, *J* = 8.0, 2.2 Hz, 1H), 4.90 (dt, *J* = 2.0, 6.0 Hz, 1H), 2.90 (t, *J* = 8.8 Hz, 2H), 2.83 (d, *J* = 8.0 Hz, 2H), 2.76 (dd, *J* = 6.0, 18.2 Hz, 1H), 2.67-2.71 (m, 2H), 2.29 (dd, *J* = 2.0, 18.3 Hz, 1H), 0.91 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 205.7, 174.8, 157.3, 151.1, 145.1, 100.1, 69.1, 45.6, 27.6, 25.9, 22.7, 21.4, 18.3, -4.55. ***Z* isomer:** 1H NMR (600 MHz, $CDCl_3$) δ 7.05 (s, 1H), 4.87(tt, *J* = 5.8, 2.0 Hz, 1H), 4.72 (t, *J* = 7.5 Hz, 1H), 3.01 (d, *J* = 7.6 Hz, 2H), 2.84 (t, *J* = 8.8 Hz, 2H), 2.73 (dd, *J* = 5.8, 18.2 Hz, 1H), 2.61-2.68 (m, 2H), 2.26 (dd, *J* = 1.9, 18.2 Hz, 1H), 0.89 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 205.6, 174.8, 157.3, 149.5, 145.3, 100.1, 69.1, 45.6, 27.9, 25.9, 25.0, 21.2, 18.2, -4.58. HRMS (ESI) calc'd for $C_{15}H_{25}O_4Si[M+H]^+$: 323.1673; found: 323.1654.



4.49 **4.50** **4.51**

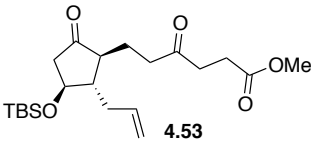
***Trans, cis* cyclopentanone (4.49); *cis, cis* cyclopentanone (4.50); silyl migration product (4.51):** To a solution of *E* enone **4.42** (272 mg, 0.844 mmol) dissolved in CH_2Cl_2 (7.0 mL) at -78 °C was added $TiCl_4$ (1 M solution in CH_2Cl_2) (0.850 mL, 0.850 mmol) dropwise. Allyltrimethylsilane (403 mL, 2.53 mmol) was then added dropwise in CH_2Cl_2 (1.5 mL) before additional $TiCl_4$ (1 M solution in CH_2Cl_2) (0.850 mL, 0.850 mmol) was added. After stirring for 1.5 h at -78 °C, to the solution was added 1:1 saturated aqueous $NaHCO_3$: CH_2Cl_2 (100 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 x 50

mL), EtOAc (1 x 50 mL) and Et_2O (1 x 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (0-40% EtOAc/hexanes) yielded the desired *trans, cis* isomer **4.49** as a clear oil (112 mg, 0.308 mmol, 36%), the undesired *cis, cis* isomer **4.50** as a clear oil (125 mg, 0.343 mmol, 41%), and undesired silyl migration **4.51** product as a white solid (9 mg, 0.021 mmol, 2%). ***Trans, cis* isomer 4.49:** ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.80-5.94 (m, 1H), 5.02-5.19 (m, 3H), 4.41 (t, *J* = 3.9 Hz, 1H), 2.77-3.00 (m, 2H), 2.65 (t, *J* = 8.6 Hz, 2H), 2.37-2.51 (m, 2H), 2.09-2.37 (m, 5H), 1.90-2.00 (m, 1H), 0.87 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 218.4, 175.0, 151.0, 136.5, 116.5, 100.4, 69.3, 50.4, 48.9, 46.2, 32.9, 27.7, 25.9, 23.3, 22.8, 18.1, -4.24, -4.81. HRMS (ESI) calc'd for $C_{20}H_{33}O_4Si[M+H]^+$: 365.2143; found: 365.2161. ***Cis, cis* isomer 4.50:** ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.77-5.91 (m, 1H), 5.30 (tt, *J* = 7.6, 2.2, 1H), 5.01-5.16 (m, 2H), 4.40- 4.44 (m, 1H), 2.77 (t, *J* = 8.0 Hz, 2H), 2.60- 2.68 (m, 2H), 2.44 (dd, *J* = 18.5, 5.4, 1H), 2.18-2.40 (7H), 0.89 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 218.2, 175.0, 149.5, 136.8, 116.4, 103.3, 71.5, 49.8, 48.3, 45.6, 30.1, 27.8, 25.9, 24.0, 22.8, 18.1, -4.37, -4.84. HRMS (ESI) calc'd for $C_{20}H_{33}O_4Si[M+H]^+$: 365.2143; found: 365.2141. **Silyl migration product 4.51:** ^{1}H NMR (400 MHz, $CDCl_3$) 5.06-5.15 (m, 1H), 4.44 (q, *J* = 7.5, 1H), 2.74- 2.88 (m, 2H), 2.65 (t, *J* = 8.4, 2H), 2.45-2.60 (m, 2H), 2.17- 2.39 (m, 3H), 1.94-2.08 (m, 2H), 1.40-1.55 (m, 1H), 1.18-1.37 (m, 2H), 0.91-1.03 (m, 1H), 0.89 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H), 0.05 (s, 9H), -0.05 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 222.4, 174.9, 151.4, 100.5, 69.6, 64.6, 51.9, 49.3, 40.9, 32.9, 29.2, 27.7, 27.5, 26.0, 22.8, 18.3, -2.96, -4.60, -4.71.



4.52

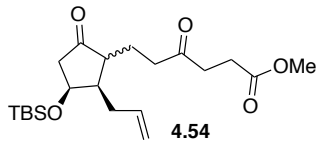
α–substituted enone (4.52): To a stirred solution of enone **4.42** (215 mg, 0.667 mmol) dissolved in methanol was added a 0.2 N solution of HCl (0.10 mL, 0.02 mmol) at room temperature. The reaction stirred at room temperature overnight before it was concentrated *in vacuo*. To the crude resultant methyl ester in DMF (2.5 mL) was added TBSCl (201 mg, 1.33 mmol), imidazole (136 mg, 2.00 mmol) and DMAP (8 mg, 0.067 mmol). The solution stirred at room temperature overnight before it was quenched with H_2O (2.0 mL) and extracted with Et_2O (6 x 10 mL). The organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resultant residue was purified by flash chromatography (silica gel, gradient elution, 5 to 15% EtOAc in hexanes) to yield 205 mg (87%) of methyl ester **4.52** as a clear oil. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.04 (t, *J* = 1.17 Hz, 1H), 4.84 (dd, *J* = 2.9, 2.2, 1H), 3.63 (s, 3H), 2.74-2.62 (m, 5H), 2.56 (t, *J* = 6.1, 2H), 2.45 (t, *J* = 7.2, 2H), 2.22 (dd, *J* = 2.1, 18.3, 1H), 0.87 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H). CNMR (100 MHz, $CDCl_3$) δ 207.5, 206.0, 173.2, 157.9, 145.4, 69.0, 51.8, 45.5, 40.1, 37.0, 27.8, 25.9, 19.0, 18.2, -4.63.



4.53

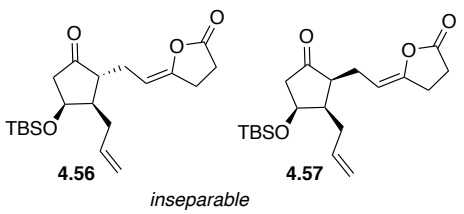
***Trans, trans* cyclopentanone (4.53):** To a stirred solution of $CuBr{\cdot}SMe_2$ (128 mg, 0.621 mmol) and LiCl (27 mg, 0.621 mmol) in THF (1.0 mL) at -78 °C was added allyl magnesium bromide (1.0 M in Et_2O, 564 μL, 0.564 mmol), TMSCl (79 μL, 0.621 mmol) and a solution of enone **4.52** (100 mg, 0.282 mmol) in THF (1.0 mL). The solution stirred for 15 min at -78 °C. To the reaction was added saturated NH_4Cl (3 mL) and the mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resultant residue was purified by flash chromatography (silica gel, gradient elution, 0% to 15% EtOAc in hexanes) to yield 58 mg (52%) of methyl ester **4.53** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$)

δ 5.85-5.75 (m, 1 H), 5.13- 5.06 (m, 2H), 4.04 (q, *J* = 6.5, 1H), 3.67 (s, 3H), 2.76-2.51 (m, 7H), 2.29 (s, 1H), 2.16 (dd, *J*= 6.5, 17.8, 1H), 1.96-1.87 (m, 2H), 1.84-1.76 (m, 1H), 0.88 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.4, 208.4, 173.4, 135.1, 117.9, 71.7, 51.9, 51.1, 49.1, 47.5, 39.8, 37.2, 35.0, 27.8, 25.9, 23.1, 18.0, -4.4, -4.7.

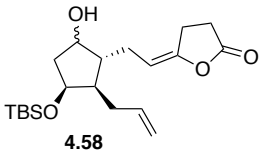


4.54

Cis* allylation product (4.54):** To a solution of the enone **4.52** (212 mg, 0.599 mmol) in CH_2Cl_2 (4.0 mL) cooled to -78 °C was added $TiCl_4$ (1.0 M in CH_2Cl_2, 600 μL, 0.600 mmol), followed by a solution of allyl TMS (285 μL, 1.80 mmol) in CH_2Cl_2 (1.0 mL) dropwise. After 1 h, additional $TiCl_4$ (1.0 M in CH_2Cl_2, 600 μL, 0.600 mmol) was added. The reaction continued to stir at -78° C for 1 h before sat. aq. $NaHCO_3$ (3.0 mL) was added slowly and the reaction was warmed to room temperature. The mixture was diluted with CH_2Cl_2 (20 mL), washed again with sat. aq. $NaHCO_3$ (3 x 10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo.* The resultant residue was purified by flash chromatography (silica gel, gradient elution, 5% to 20% EtOAc in hexanes) to yield 184 mg (78%) of ineseparable 1:1 mixture of diastereomers **4.54** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90-5.80 (m, 1H), 5.08 (dd, *J* = 17.7, 34.7 Hz), 4.39 (s, 1H), 3.67 (s, 3H), 2.82-2.49 (m, 7H), 2.43-2.33 (m, 1H), 2.29 (s, 2H), 2.27-2.21 (m, 1H), 2.10-2.04 (m, 1H), 1.97-1.80 (m, 2H), 1.70-1.63 (m, 1H), 0.86 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H). CNMR (100 MHz, $CDCl_3$) δ ***trans,cis: 219.2, 208.6, 173.4, 136.5, 116.4, 69.0, 51.9, 49.0, 48.7, 48.3, 39.8, 37.2, 32.5, 29.9, 27.8, 25.9, 22.2, 18.1, -4.2, -4.9. ***cis,cis;*** 219.8, 208.6, 173.4, 137.0, 116.2, 71.3, 51.9, 48.4, 48.3, 46.1, 40.3, 37.3, 32.5, 29.9, 27.8, 25.9, 21.0, 18.1, -4.4, -4.9.

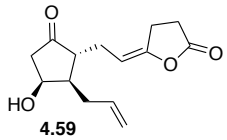


***Z* cyclopentanones (4.56) and (4.57):** To a solution of *Z* enone **4.42** (43mg, 0.133 mmol) dissolved in CH_2Cl_2 (1.25 mL) at -78 °C was added $TiCl_4$ (1 M solution in CH_2Cl_2) (0.267 mL, 0.267 mmol) dropwise. Allyltrimethylsilane (64 μL, 0.400 mmol) was then added dropwise in CH_2Cl_2 (0.25 mL). After stirring for 1.5 h, to the solution was added 1:1 sat. aq. $NaHCO_3$: CH_2Cl_2 (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL), EtOAc (1 x 5 mL) and Et_2O (1 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (0-40% EtOAc/hexanes) yielded 33 mg (68%) of the desired *trans, cis* isomer **4.56** and the *cis,cis* isomer **4.57** as an inseparable, 1:1 mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89–5.78 (m, 1H), 5.15- 5.01 (m, 2H), 4.81 (t, *J* = 7.8 Hz, 0.5H), 4.58 (t, *J* = 7.8 Hz, 0.5H), 4.42-4.38 (m, 1H), 2.87- 2.75 (m, 2H), 2.67- 2.59 (m, 2H), 2.53- 2.15 (m, 8H), 1.91-1.80 (m, 0.5 H), 0.89 (s, 4.5H), 0.85 (s, 4.5H), 0.07 (s, 1.5H), 0.06 (s, 1.5H), 0.05 (s, 1.5H), 0.04 (s, 1.5H). CNMR (100 MHz, $CDCl_3$) δ 218.9, 218.6 (isomers); 174.9, 174.8 (isomers); 149.3, 148.0 (isomers); 136.7, 136.44 (isomers); 116.2, 116.2 (isomers); 102.7, 101.1 (isomers); 71.2, 68.9 (isomers); 49.9, 49.6 (isomers), 48.7, 48.2 (isomers); 47.5, 45.8 (isomers); 32.3, 29.8 (isomers); 27.9, 27.9 (isomers); 25.75; 25.0; 23.6, 23.3 (isomers); 18.0, 17.9 (isomers); -4.3, -4.5, -.4.9, -5.0 (isomers).



Secondary Alcohols (4.58): To a solution of cyclopentanone **4.49** (37 mg, 0.10 mmol) in THF (2.0 mL) at room temperature was added *tert*-butylamine borane (40 mg, 0.46 mmol). The solution stirred at room temperature overnight before it was concentrated *in vacuo*. The resultant residue was purified by

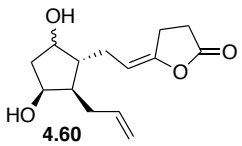
flash column chromatography (silica gel, gradient elution 5-30% EtOAc in hexanes) to yield 30 mg (81%) of a diastereomeric mixture of alcohols **4.58** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74-5.91 (m, 1H), 5.22–5.33 (m, 1H), 4.92-5.10 (m, 2H), 4.31 (q, *J* = 5.3 Hz, 1H), 4.24 (s), 3.77-3.86 (m) (isomers, 2H); 2.76-2.97 (m, 2H); 2.65 (t, *J* = 8.6, 2H), 1.70-2.40 (m), 1.40-1.49 (m) (isomers, 8H); 0.90, 0.87 (s, s, isomers, 9H); 0.10, 0.07 (s, s, isomers, 3H); 0.03, 0.02 (s, s, isomers, 3H). CNMR (100 MHz, $CDCl_3$) δ 175.2, 175.0 (isomers); 150.1, 149.5 (isomers); 138.2, 137.9 (isomers); 115.6, 115.2 (isomers); 103.7, 102.5 (isomers); 78.3, 75.9 (isomers); 72.7, 72.4 (isomers); 53.5, 50.5 (isomers); 47.5, 47.0 (isomers); 45.8, 43.2 (isomers); 33.8, 32.4 (isomers); 29.3; 27.9, 27.8 (isomers); 26.0; 24.4; 22.9, 22.8 (isomers); 18.2, 18.1 (isomers); -4.2, -4.2 (isomers); -4.8, -4.9 (isomers). HRMS (ESI) calc'd for $C_{20}H_{35}O_4Si[M+H]^+$: 367.2299; found: 367.2272.



4.59

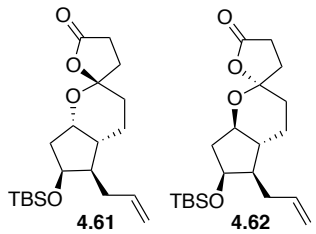
β–hydroxycyclopentanone (4.59): To a solution of cyclopentanone **4.49** (64 mg, 0.176 mmol) in MeCN (3.0 mL) at 0 °C was added 70% HF-pyridine (0.456 mL, 17.6 mmol) dropwise. The reaction stirred at 0 °C for 1 h before additional 70% HF-pyridine (0.456 mL, 1.76 mmol) was added. The reaction stirred at 0 °C for 2 h, at which point it was quenched slowly with aq. sat. $NaHCO_3$ (50 mL) and diluted with $CHCl_3$ (50 mL). The product was extracted from the aqueous layer with $CHCl_3$ (3 x 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* and purified by flash column chromatography (silica gel, gradient elution, 30-50% EtOAc in hexanes) to yield 33 mg (75%) of β–hydroxycyclopentenone **4.59** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98-5.80 (m, 1H), 5.31-5.05 (m, 3H), 4.67 (t, *J* = 4.1 Hz**,** 1H), 2.98- 2.76 (m, 2H); 2.64 (t, *J*=8.51 Hz), 2.49-

2.33 (m, 4H), 2.33-2.11 (m, 4H), 2.06- 1.96 (m, 2H). CNMR (100 MHz, $CDCl_3$) δ 218.1, 175.0, 151.1, 136.1, 117.1, 100.3, 68.5, 50.2, 48.0, 45.1, 33.1, 27.7, 23.2, 22.8.



4.60

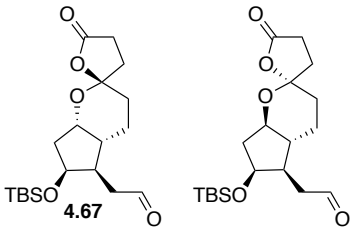
Diols (4.60): To a solution of cyclopentanone **4.59** (43 mg, 0.17 mmol) in THF (2.0 mL) at room temperature was added *tert*-butylamine borane (67 mg, 0.77 mmol). The solution stirred at room temperature overnight before it was concentrated *in vacuo*. The resultant residue was purified by flash column chromatography (silica gel, gradient elution 5-30% EtOAc in hexanes) to yield 35 mg (81%) of a 3:1 diastereomeric mixture of alcohols **4.60** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.00-5.76 (m, 1H), 5.32 -5.21 (m, 1H), 5.19-5.00 (m, 2H), 4.39 (q, *J*= 4.2 Hz, 0.75H), 4.32 (q, *J* = 3.4 Hz, 0.75H), 4.22 (m, 0.25H), 3.92 (m, 0.25H), 3.00- 2.74 (m, 2H), 2.66 (t, *J* = 8.6 Hz, 2H), 2.42-1.72 (m, 9H). CNMR (100 MHz, $CDCl_3$) δ 175.8, 174.9 (isomers); 150.2, 149.7 (isomers); 138.0, 137.6 (isomers); 116.0, 115.9 (isomers); 103.4, 102.3 (isomers); 78.2; 75.0; 72.5, 72.4 (isomers); 53.0, 50.1 (isomers); 47.4, 46.3 (isomers); 44.8, 42.5 (isomers); 39.9, 32.4 (isomers); 29.1, 27.8 (isomers); 27.8; 24.0; 22.9, 22.8 (isomers).



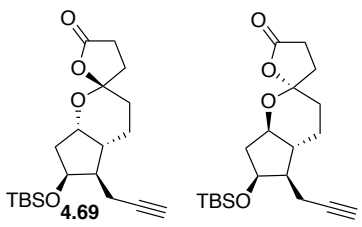
4.61 **4.62**

Spiroacetals (4.61) and (4.62): To a solution of the alcohols (29 mg, 0.080 mmol) in CH_2Cl_2 (1.0 mL) was added TFA (0.5M in CH_2Cl_2, 0.48 mL, 0.24 mmol) at rt. After 2 h, additional TFA (0.5 M in in CH_2Cl_2, 0.48 mL, 0.24 mmol) was added before the rxn was quenched with Et_3N (0.50 mL) after an additional 1 h and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, gradient elution 5-10% EtOAc in hexanes) to yield 22 mg (76%) of a diastereomeric mixture of spirocycles as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$)

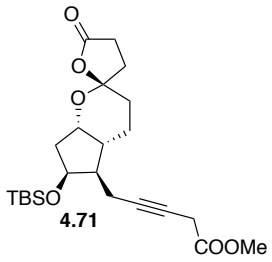
δ 5.94–5.78 (m, 1H), 5.10- 4.91 (m, 2H); 4.38- 4.28 (m, 1.5H); 4.24 (m, 0.25H), 3.61 (q, *J* = 9.8 Hz, 0.25H), 2.85-2.68 (m, 1H), 2.56-2.41 (m, 1H), 2.42-1.38 (m, 13H), 0.88 (s, 9H), 0.03 (s, 6H). CNMR (100 MHz, $CDCl_3$) δ 176.8; 138.3, 138.2 (isomers); 115.2, 115.1 (isomers); 109.2, 108.5 (isomers); 76.3, 74.9, 73.0, 70.6 (isomers); 45.9, 44.6 (isomers); 43.4, 40.8 (isomers); 40.1; 35.1, 34.4 (isomers); 32.0, 31.5 (isomers); 29.3; 28.6, 28.4 (isomers); 26.0; 19.3; 18.2; -4.1, -4.8, -5.0 (isomers). HRMS (ESI) calc'd for $C_{20}H_{35}O_4Si[M+H]^+$: 367.2299; found: 367.2289.



Aldehydes (4.67): To a mixture of the spirocycles (24 mg, 0.065 mmol) dissolved in CH_3Cl_3 (3.0 mL) and cooled to 0 °C was bubbled O_3 for ca. 3 min before triphenylphosphine (172 mg, 0.656 mmol) was added. The solution was allowed to warm to room temperature, stirred overnight, and concentrated *in vacuo*. The resultant residue was purified by flash column chromatography (silica gel, gradient elution 5-40% EtOAc in hexanes) to afford 20 mg (83%) of a diastereomeric mixture of aldehydes as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.9 (s, 0.5H), 9.81 (s, 0.5H), 4.41 (td, *J* = 6.6, 3.3 Hz, 0.5H), 4.43 (t, *J* = 5.3 Hz, 0.5H), 4.30 (td, *J* = 4.3, 3.3 Hz, 0.5H), 2.82, 2.70 (m, 2H), 2.56- 2.32 (m, 3H), 2.29- 1.90 (m, 4H), 1.88- 1.67 (3H), 1.60-1.41 (m, 2H), 0.86 (s, 4.5H), 0.85 (s, 4.5H), 0.01 (s, 3H), -0.03 (s, 3H). CNMR (100 MHz, $CDCl_3$) ***cis, trans, cis:*** δ 202.5, 176.7, 108.1, 74.7, 72.7, 43.6, 42.7, 40.0, 38.3, 34.9, 28.6, 28.4, 25.9, 18.8, 18.1, -4.3, -5.0. ***trans, trans ,cis*** δ 202.1, 176.6, 108.1, 75.9, 69.9, 43.9, 41.7, 40.7, 40.5, 34.3, 34.2, 28.3, 25.9, 24.2, 18.03, -4.3, -5.2. HRMS (ESI) calc'd for $C_{19}H_{33}O_5Si[M+H]^+$: 369.2092; found: 369.2105.

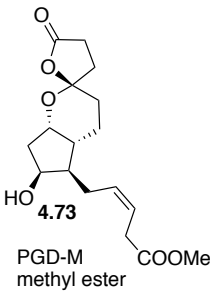


Terminal Alkynes (4.69): To the previously prepared Seyferth Gilbert reagent (48 mg 0.32 mmol) cooled to –78 °C in THF (4.0 mL) was added a solution of sodium bis(trimethylsilyl)amide (0.32 mL, 0. 321 mmol, 1.0 *M* in THF). The solution stirred at – 78 °C for 15 min before the dropwise addition of the aldehyde (78 mg, 0.212 mmol) in THF (2.0 mL). The solution stirred for 45 min at -78 °C for 45 min, at which point it was allowed to warm to rt, quenched with sat. aq. NH_4Cl (5 mL). The mixture was extracted from the aqueous layer with Et_2O (2 x 5 mL) and EtOAc (2 x 5 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* and purified by flash column chromatography (silica gel, gradient elution 5-30% EtOAc in hexanes) to yield 62 mg (80%) of a diastereomeric mixture of alkynes as a colorless oil. HNMR (400 MHz, $CDCl_3$) δ 4.33-4.41, 4.21-4.26, 3.59-3.68 (m, m, m, 2H); 2.68-2.82 (m, 1H); 2.43-2.53 (m, 1H); 2.30-2.43 (m, 1H); 1.68-2.69 (m, 12H), 0.89, 0.87 (s, s, isomers, 9H); 0.07, 0.05 (s, s, isomers, 6H). CNMR (100 MHz, $CDCl_3$) δ 177.8; 109.1, 108.3 (isomers); 84.5; 76.2; 75.0; 73.0; 68.9, 68.7 (isomers); 45.6, 44.3 (isomers); 44.0, 43.1 (isomers); 40.5, 40.1 (isomers); 35.0; 34.4, 34.3 (isomers); 29.1; 28.5, 28.0 (isomers); 26.0; 19.2, 18.5 (isomers); 17.2, 16.6 (isomers); -4.3, -4.9, -5.1 (isomers). HRMS (ESI) calc'd for $C_{20}H_{33}O_4Si[M+H]^+$: 365.2143; found: 365.2121.



Alkynoate (4.71): To a solution of the alkyne (49 mg, 0.135 mmol) in MeCN (1.5 mL) at rt was added CuI (3 mg, 0.013 mmol) and a solution of methyl diazoacetate (162 mg, 0.202 mmol, 12.5% by weight in CH_2Cl_2). The solution stirred at rt overnight at which point it was concentrated *in vacuo*. Purification by flash chromatography (silica gel, gradient elution 2-20% EtOAc in hexanes)

to yield 44 mg (75%) of methyl esters as a colorless oil. HNMR (400 MHz, $CDCl_3$) δ 4.38-4.32 (m, 2H), 3.73 (s, 3H), 3.24 (t, *J* = 2.5 Hz, 2H), 2.80- 2.69 (m, 1H), 2.47 (ddd, *J* = 2.7, 9.6 Hz, 1H), 2.35 (qt, *J* = 8.23, 2.7 Hz, 1H), 2.23- 1.93 (m, 6H), 1.93- 1.79 (m, 4H), 1.79-1.67 (m, 2H), 0.86 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H). 176.7, 169.4, 108.4, 83.6, 75.1, 73.1, 71.2, 52.6, 44.0, 43.1, 40.1, 35.0, 30.5, 29.1, 26.0, 25.9, 19.2, 18.1, 17.5, -4.4, -5.0. HRMS (ESI) calc'd for $C_{23}H_{37}O_6Si[M+H]^+$: 437.2354; found: 437.2348.



PGD-M methyl ester (4.73): To a solution of alkynoate **4.71** (9 mg, 0.021 mmol) in MeCN (1.0 mL) at 0 °C was added 70% HF-pyridine (13 μL, 0.52 mmol). The reaction was allowed to slowly warm to room temperature. After 2h, additional HF-pyridine (13 μL, 0.52 mmol) was added. The solution stirred at room termperature for 2 additional h, at which point it was quenched with sat. aq. $NaHCO_3$ (8 mL). The product was extracted from the aqueous layer with EtOAc (3 x 3 mL) and $CHCl_3$ (3 x 3 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo.* To a separate reaction flask was added Lindlar's catalyst (5 mg) and MeOH (0.5 mL) at room temperature. The vessel was purged with H_2 before the crude product was added in MeOH (0.5 mL). The reaction stirred overnight at room temperature at which point it was filtered through Celite and concentrated *in vacuo*. The resultant residue was purified by flash chromatography (silica gel, gradient elution 2-20% EtOAc in hexanes) to yield 1 mg (15%) of PGD-M methyl ester as a colorless oil. HNMR (600 MHz, $CDCl_3$) δ 5.68 (t, *J* = 5.68 Hz, 1H), 5.57 (q, *J* =6.8 Hz, 1H), 4.41(t, *J* = 4.7 Hz, 1H), 4.34- 4.29 (m, 1H), 3.70 (s, 3H), 3.29 (dd, *J* = 8.6, 14.7 Hz, 1H), 3.03 (dd, *J*= 6.2, 16.0 Hz, 1H), 2.76 (dt, *J*= 9.7, 17.9, 1H), 2.52- 2.43 (m, 2H), 2.37- 2.14 (m, 4H), 2.11- 1.91 (m, 6H), 1.91- 1.85 (m, 1H), 1.79 (td, *J* = 13.1, 5.0 Hz, 1H), 1.72 (dt, *J* = 4.24, 13.4 Hz, 1H), 1.68- 1.61 (m, 1H).

CNMR (150 MHz, $CDCl_3$) δ 176.7, 173.2, 133.1, 121.8, 108.2, 75.1, 72.0, 52.4, 43.8, 42.3, 39.5, 35.0, 33.1, 28.9, 28.5, 25.2, 18.5. HRMS (ESI) calc'd for $C_{17}H_{25}O_6[M+H]^+$: 325.1646; found: 325.1644.

References

1. Sakurai, H.; Hosomi, A. "Syntheses of γ,δ-unsaturated alcohols from allylsilanes and carbonyl compounds in the presence of titanium tetrachloride" *Tetrahedron Lett*. **1976**, *16*, 1295-1298.

2. Weaver, J. D.; Recio, A.; Grenning, A. J.; Tunge, J. A. "Transition metal-catalyzed decarboxylative allylation and benzylation reactions." *Chem. Rev.* **2011**, *111,* 1846-1913.

3. Salom-Roig, X. J.; Dénès, F.; Renaud, P. "Radical cyclization of haloacetals: the Ueno-Stork reaction." *Synthesis* **2004**, *12,* 1903-1928.

4. Jeroncic, L. O.; Cabal, M. P.; Danishefsky, S. J.; Shulte, G. M. "On the diastereofacial selectivity of lewis acid-catalyzed carbon-carbon bond forming reactions of conjugated cyclic enones bearing electron-withdrawing substituents at the gamma-position." *J. Org. Chem.* **1991**, *56,* 387–395.

5. Lipshutz, B. H.; Hackmann, C. "Conjugate addition reactions of allylic copper species derived from grignard reagents: synthetic and spectroscopic aspects." *J. Org. Chem.* **1994**, *59,* 7437–7444.

6. Cieplak, A. S. "Inductive and resonance effects of substituents on the π-face selection." *Chem. Rev.* **1999**, *99,* 1265-1336.

7. Corey, E.J.; Shimoji, K. "Total synthesis of the major human urinary metabolite of prostaglandin D2, a key diagnostic indicator." *J. Am. Chem. Soc.* **1983**, *105*, 1662–1664.

8. Suárez, A.; Fu, G. C. "A straightforward and mild synthesis of functionalized 3-alkynoates." *Angew. Chem. Int. Ed.,* **2004**, *43,* 3580–3582.

9. Li, J.; Ahmed, T. S.; Xu, C.; Stoltz, B. M.; Grubbs, R. E. "Concise syntheses of Δ^{12}-prostaglandin J natural products via stereoretentive metathesis." *J. Am. Chem. Soc.* **2019**, *141,* 154–158.

10. Müller; S.; B., Liepold, B.; Roth, G.; Bestmann, H. J. "An improved one-pot procedure for the synthesis of alkynes from aldehydes." *Synlett* **1996**, *6,* 521-522.

11. Lindlar, H. “Ein neuer katalysator für selektive hydrierungen.” *Helv. Chim. Acta.,* **1952**, *35,* 446.

12. Shipe, W.D.; Sorensen, E.J. “A convergent synthesis of the tricyclic architecture of the guanacastepenes featuring a selective ring fragmentation.” *Org. Lett.* **2002**, 2063-2066.

13. Pale, P.; Chuche, J. “Silver assisted heterocyclization of acetylenic compounds.” *Tetrahedron Lett.* **1987**, *28*, 6447–6448.

14. Vanderwal, C. D.; Vosburg, D. A.; Weiler, S.; Sorenson, E. J. “An enantioselective synthesis of FR182877 provides a chemical rationalization of its structure and affords multigram quantities of its direct precursor” *J. Am. Chem. Soc.* **2003**, *125,* 2593-5407.

15. Trost, B.M.; Van Vranken, D. L. “Asymmetric transition metal-catalyzed allylic alkylations.” *Chem. Rev.* **1996**, *96,* 395-422.

16. Box, V. G. “The role of lone pair interactions in the chemistry of the monosaccharides. The anomeric effects.” *Heterocycles* **1990**, *31,* 1157-1181.

17. Cuzzupe, A. N.; Hutton, C. A.; Lilly, M. J.; Mann, R. K.; Rizzacasa, M. A.; Zammit, S. C. “Total synthesis of (-)-reveromycin B.” *Org. Lett.* **2000**, *2,* 191-194.

18. Nicolaou, K. C.; Vyskocil, S.; Koftis, T. V.; Yamada, M. A. Y.; Ling, T.; Chen, D. Y.-K.; Tang, W.; Petrovic, G.; Frederick, M. O.; Li, Y.; Satake, M. “Total synthesis and structural elucidation of azaspiracid-1. Final assignment and total synthesis of the correct structure of azaspiracid-1.” *J. Am. Chem. Soc.* **2006**, *128,* 2859-2872.

19. Gilbert, J. C.; Weerasooriya, U. “Diazoethenes: their attempted synthesis from aldehydes and aromatic ketones by way of the Horner-Emmon modification fo the Wittig reaction. A facile synthesis of alkynes.” *J. Org. Chem.* **1982**, *47,* 1837-1845.

20. Trost, B. M.; Fleitz, F. J.; Watkins, W. J. “On Pd-catalyzed cycloisomerization versus cycloreduction. A general strategy for drimane synthesis and a short total synthesis of siccanin.” *J. Am. Chem. Soc.* **1996**, *118,* 5146-5147.

21. Myhre, P.C.; Maxey, C. T.; Bebout, D. C.; Swedberg, S. H.; Petersen, B. L. “Precursors to carbon-13-labeled reactive intermediates: preparation and NMR characterization of two doubly labeled isomers of methyl cyclopropane-3-carboxylate.” *J. Org. Chem.* **1990**, *55,*3417-3421.

22. Tietze, L.F.; Stadler, C.; Böhnke N.; Brasche, N.; Grube, A. “Synthesis of enantiomerically pure cyclopentene building blocks” *Synlett*. **2007**, 485-487.

23. Basra, S.K.; Drew, M.G.B.; Mann, J.; Kane, P.; “A novel approach to bis-isoxazolines using a latent form of cyclopentadienone” *J. Chem. Soc., Perkin Trans. 1* **2000**, *21,* 3592-3598.

24. Myers, A. G.; Dragovich, P. S. “A reaction cascade leading to 1,6-didehydro[10]annulene to 1,5-dehydronaphthalene cyclization initiated by thiol addition” *J. Am. Chem. Soc.* **1993**, *115,* 7021–7022.

25. Guo, H.; O’Doherty, G. A. “De novo asymmetric synthesis of daumone via a palladium-catalyzed glycosylation” *Org. Lett.* **2005**, *7*, 3921–3924.

26. Marshall, J. A.; Liao, J. “Stereoselective total synthesis of the pseudopterolide kallolide A” *J. Org. Chem.* **1998**, *63*, 5962–5970.

Appendix A.4:

Spectra Relevant to Chapter 4

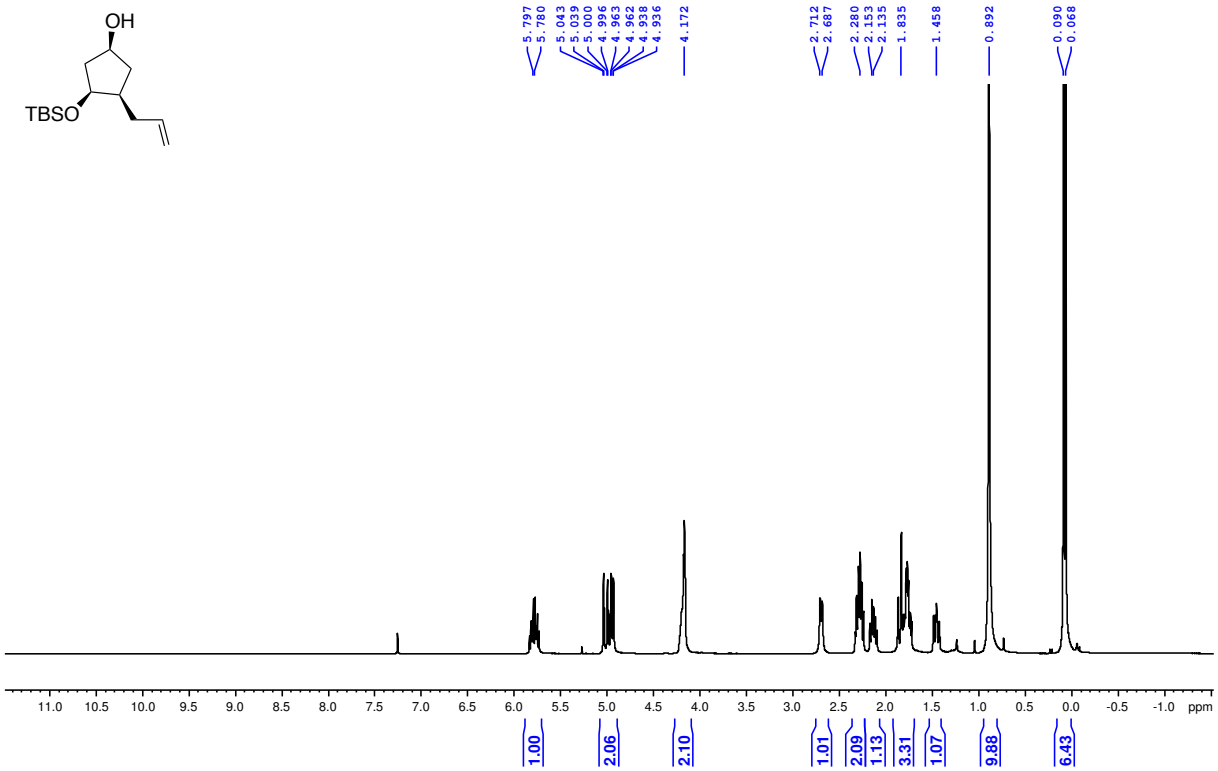


Figure A.4.1 ^{1}HNMR (400 MHz, $CDCl_3$) of *cis* alcohol

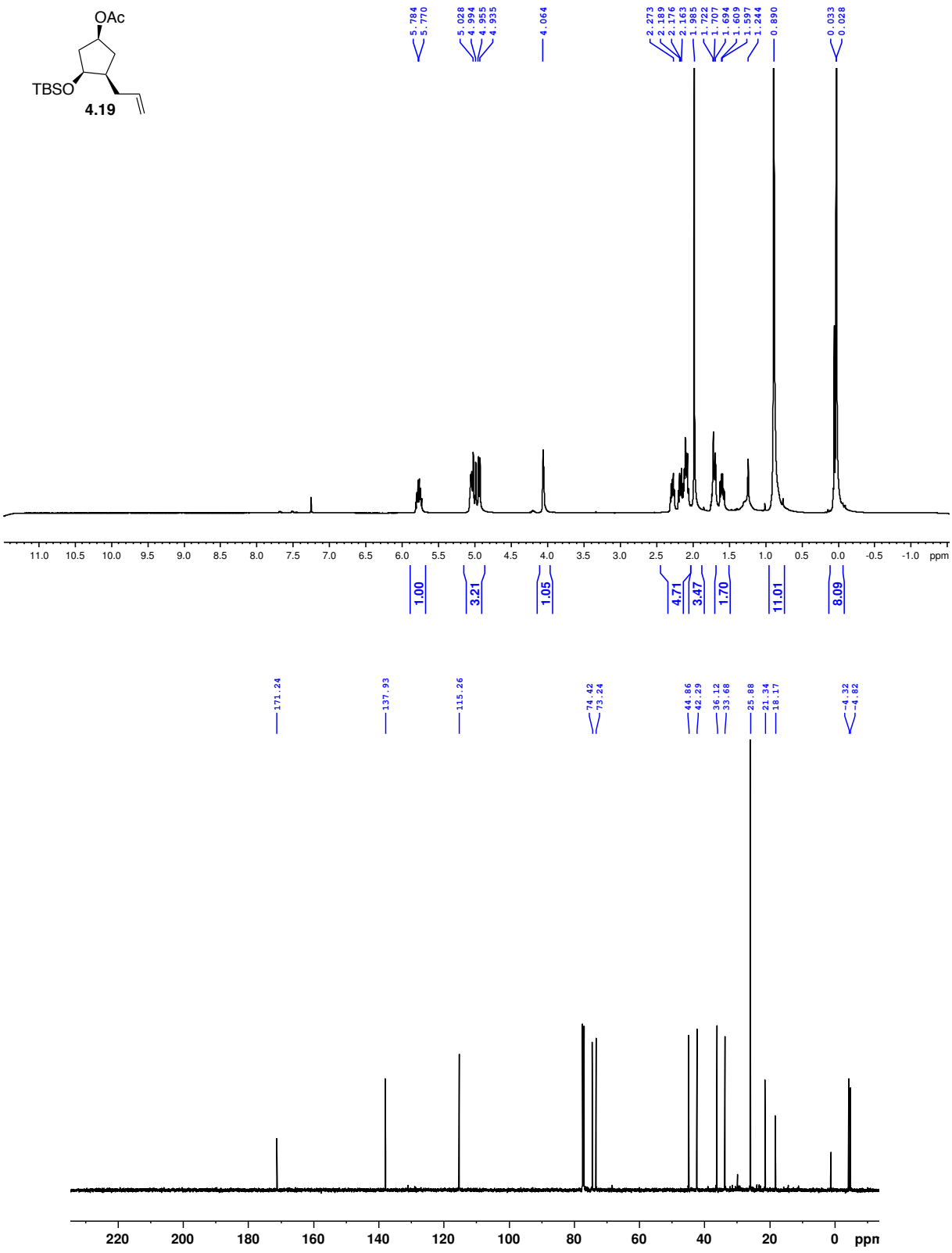


Figure A.4.2 ^{1}HNMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **4.19**

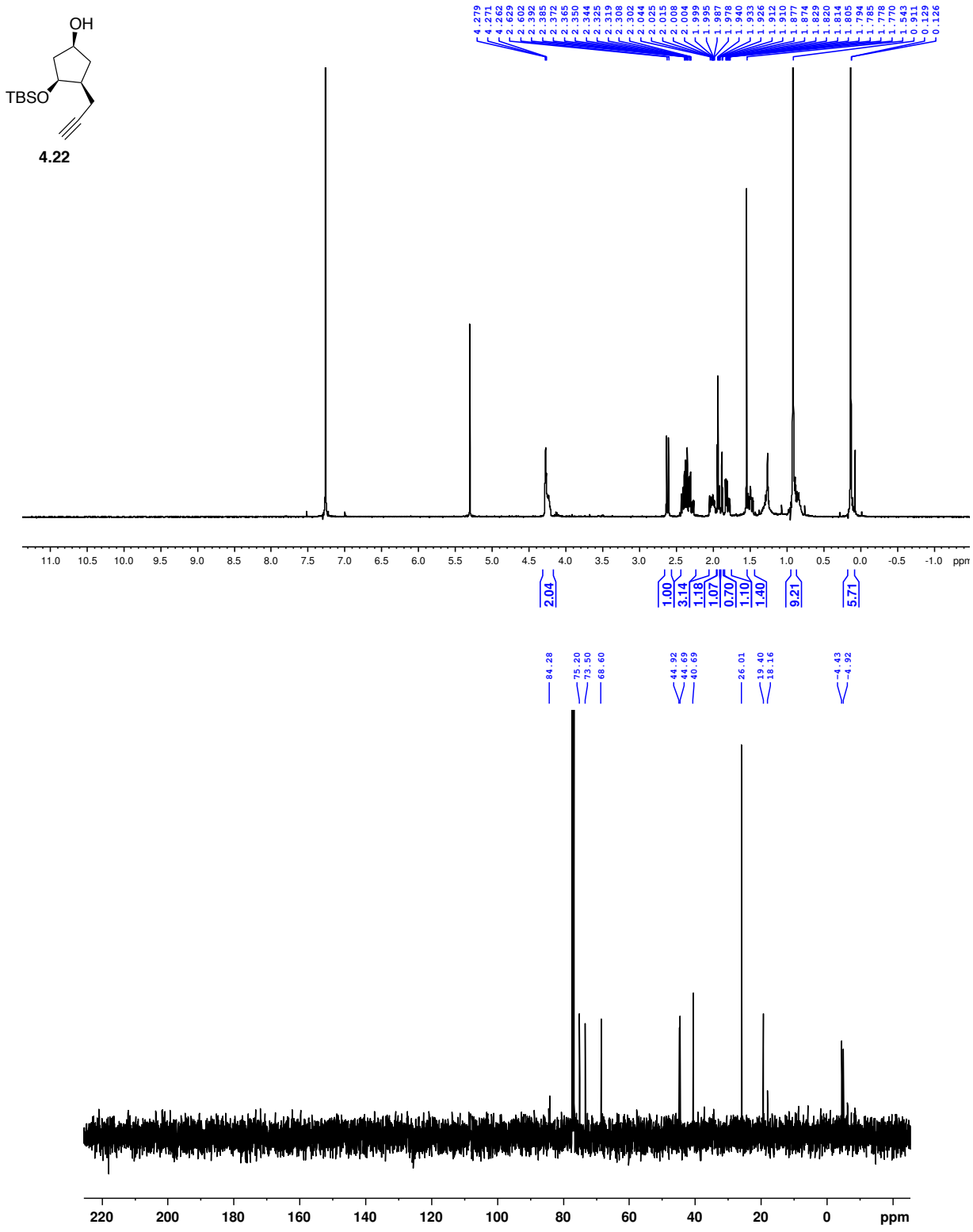


Figure A.4.3 ^{1}HNMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **4.22**

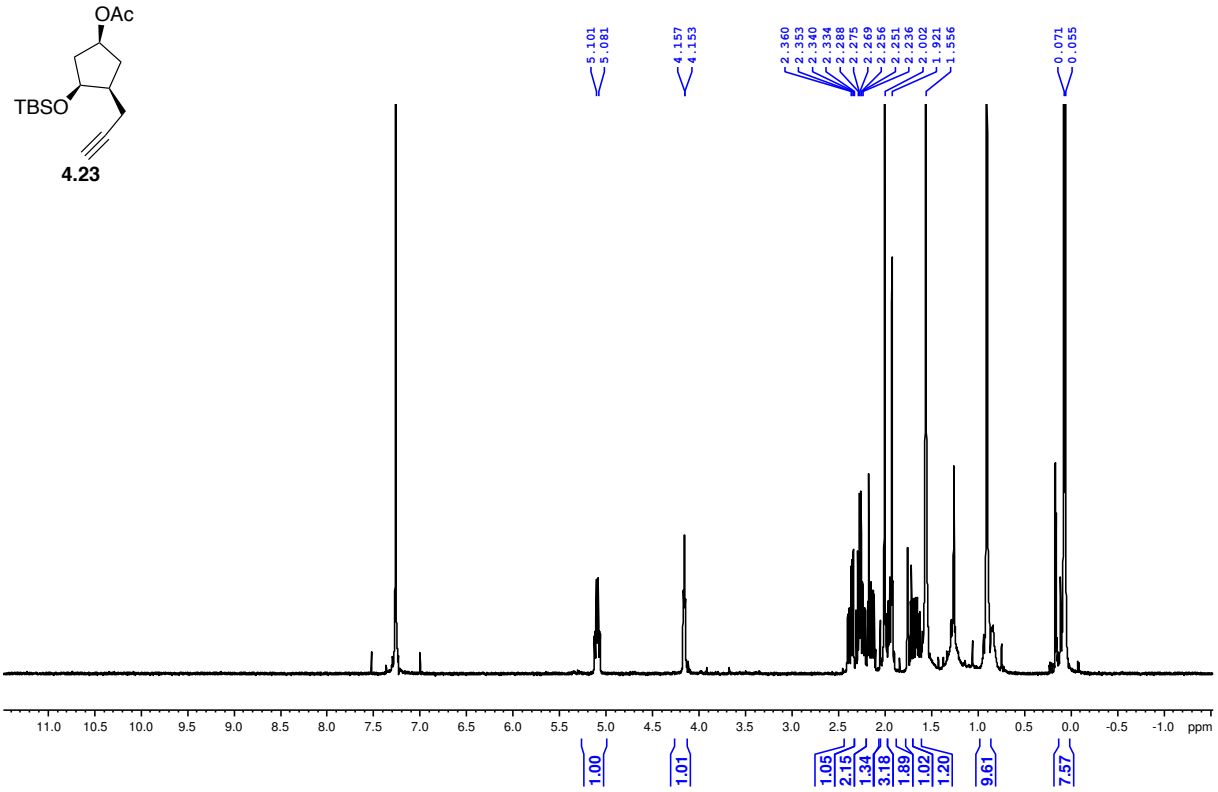


Figure A.4.4 ^{1}HNMR (400 MHz, $CDCl_3$) of **4.23**

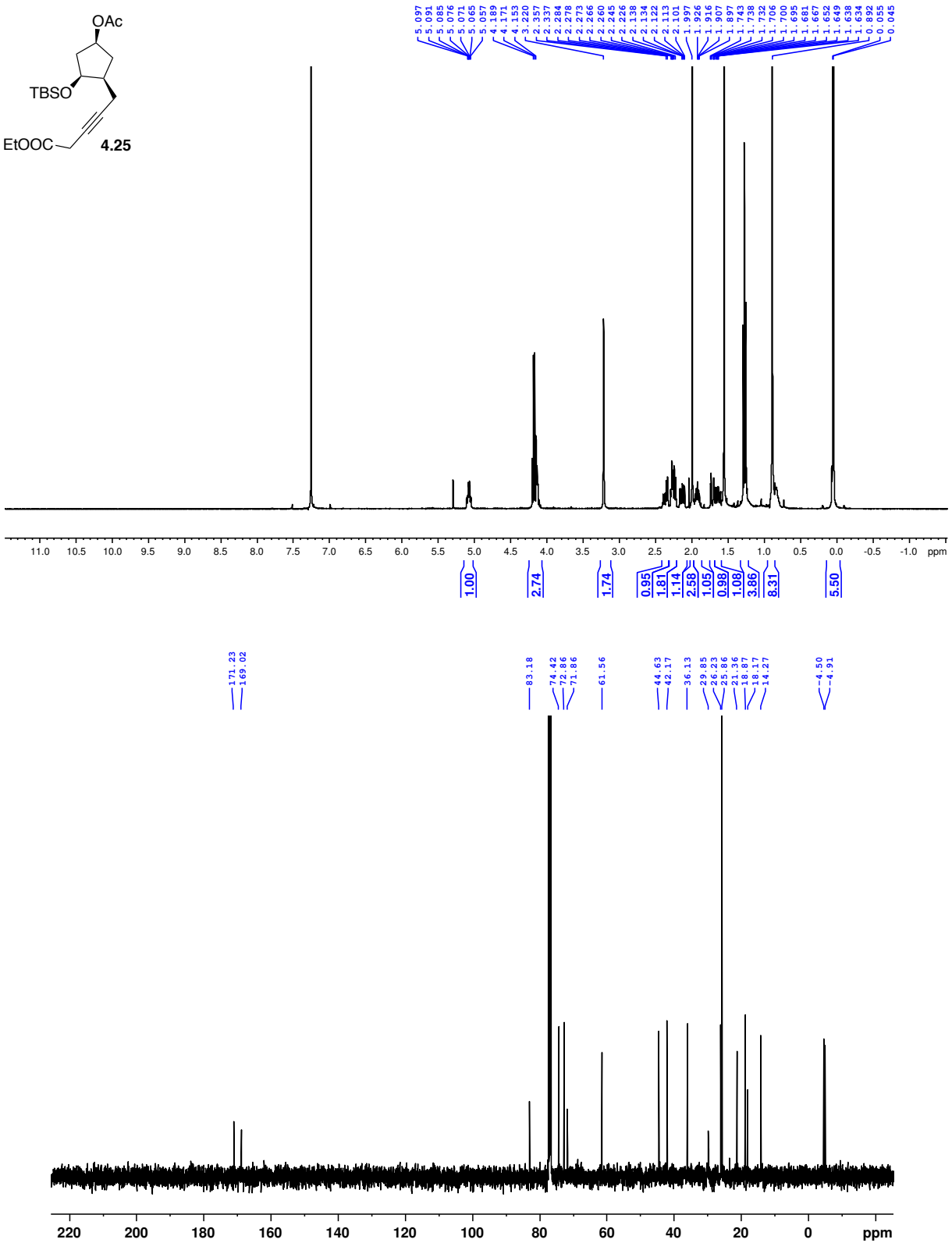


Figure A.4.5 ^{1}HNMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **4.25**

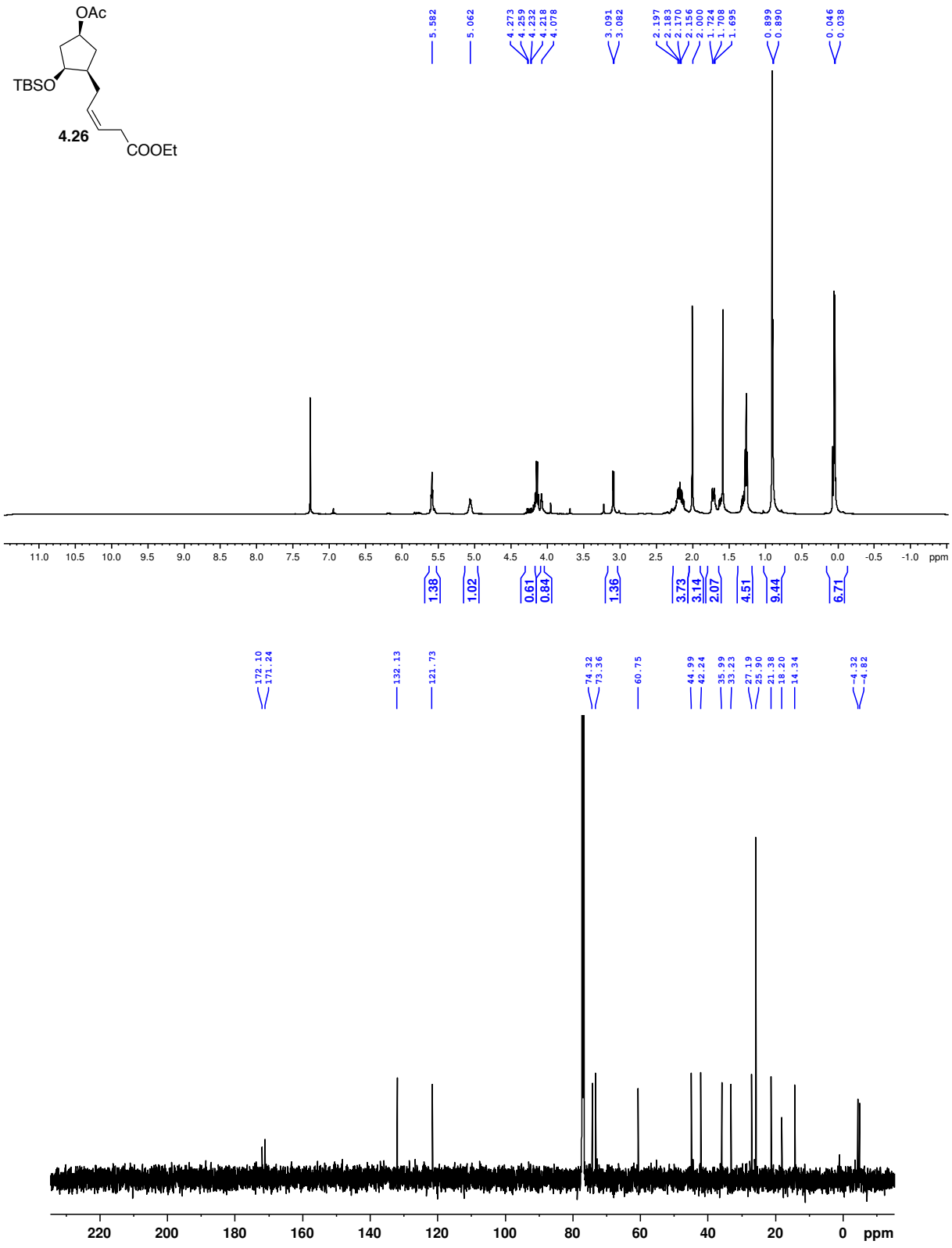


Figure A.4.6 ^{1}HNMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **4.26**

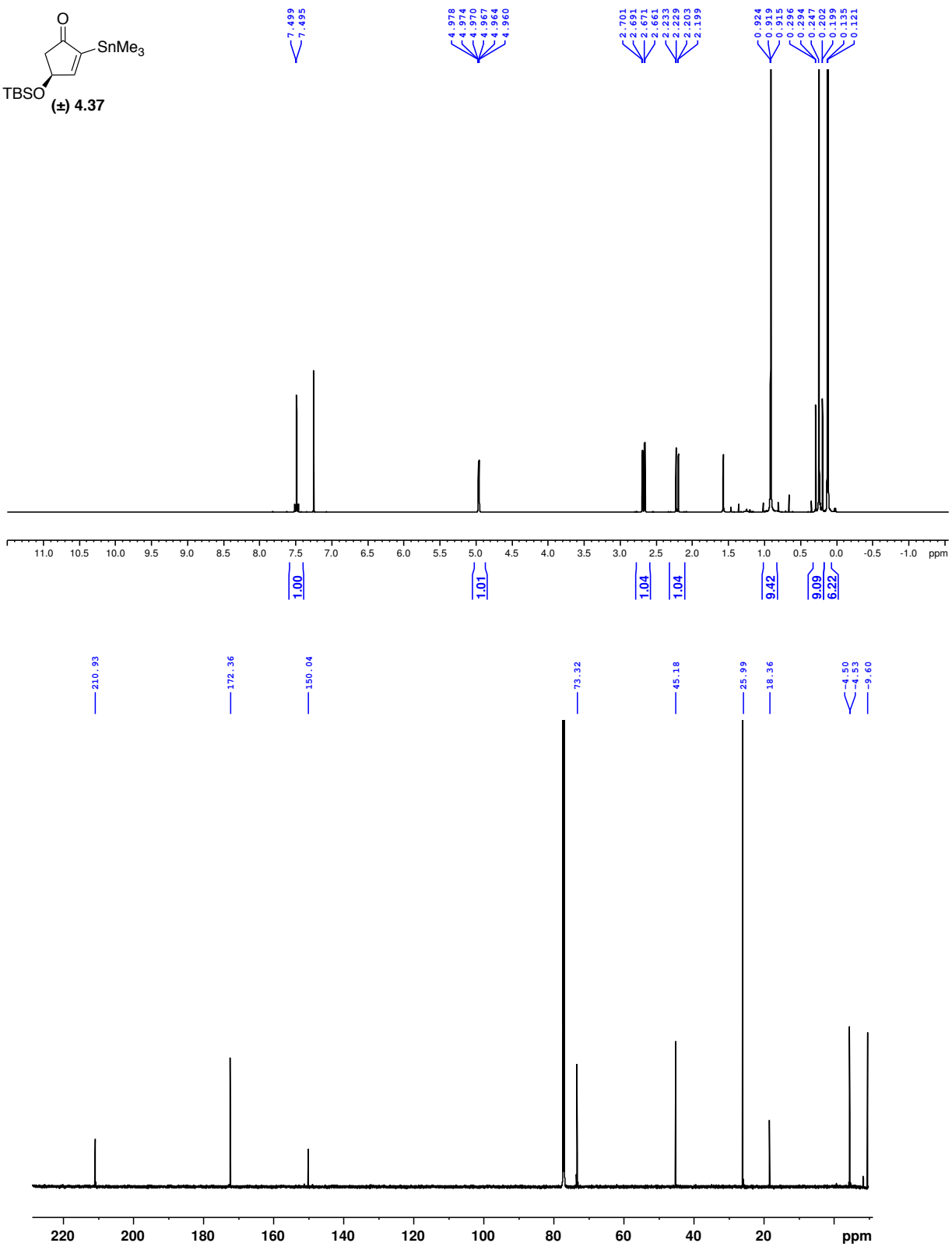


Figure A.4.7 ^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of **4.37**

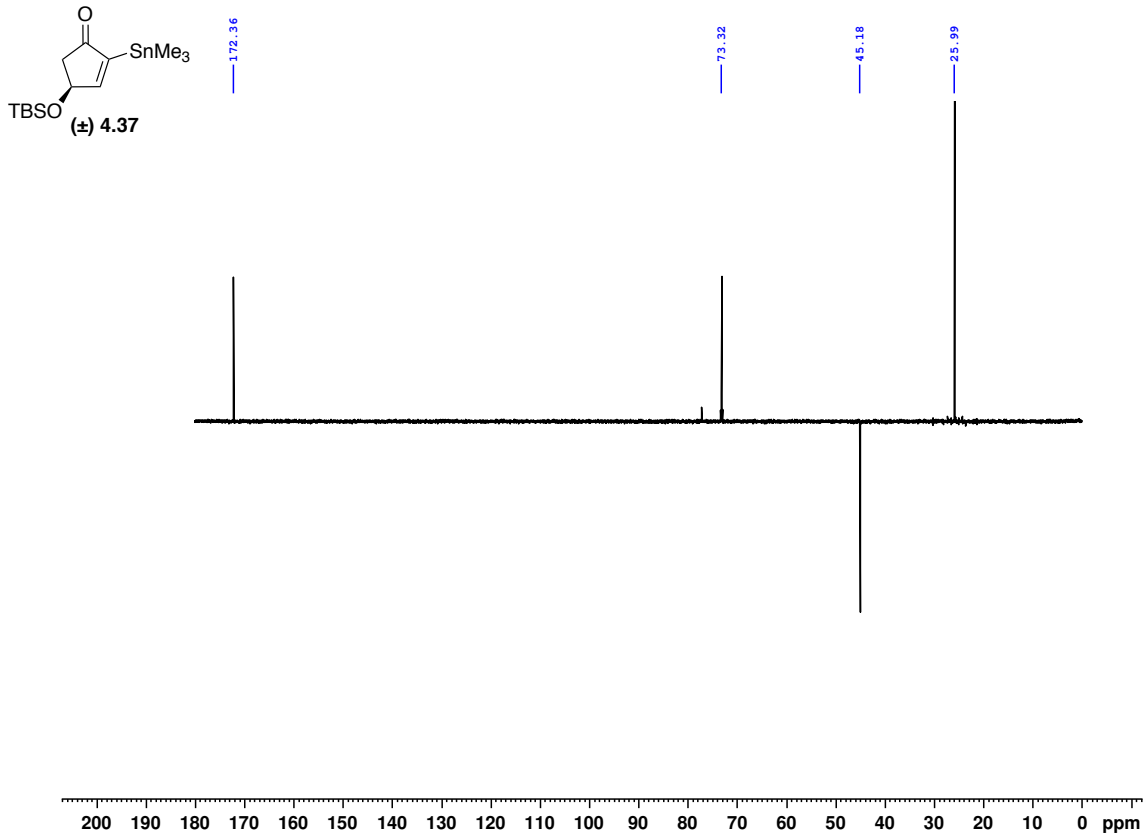


Figure A.4.8 DEPT-135 NMR (150 MHz, $CDCl_3$) of **4.37**

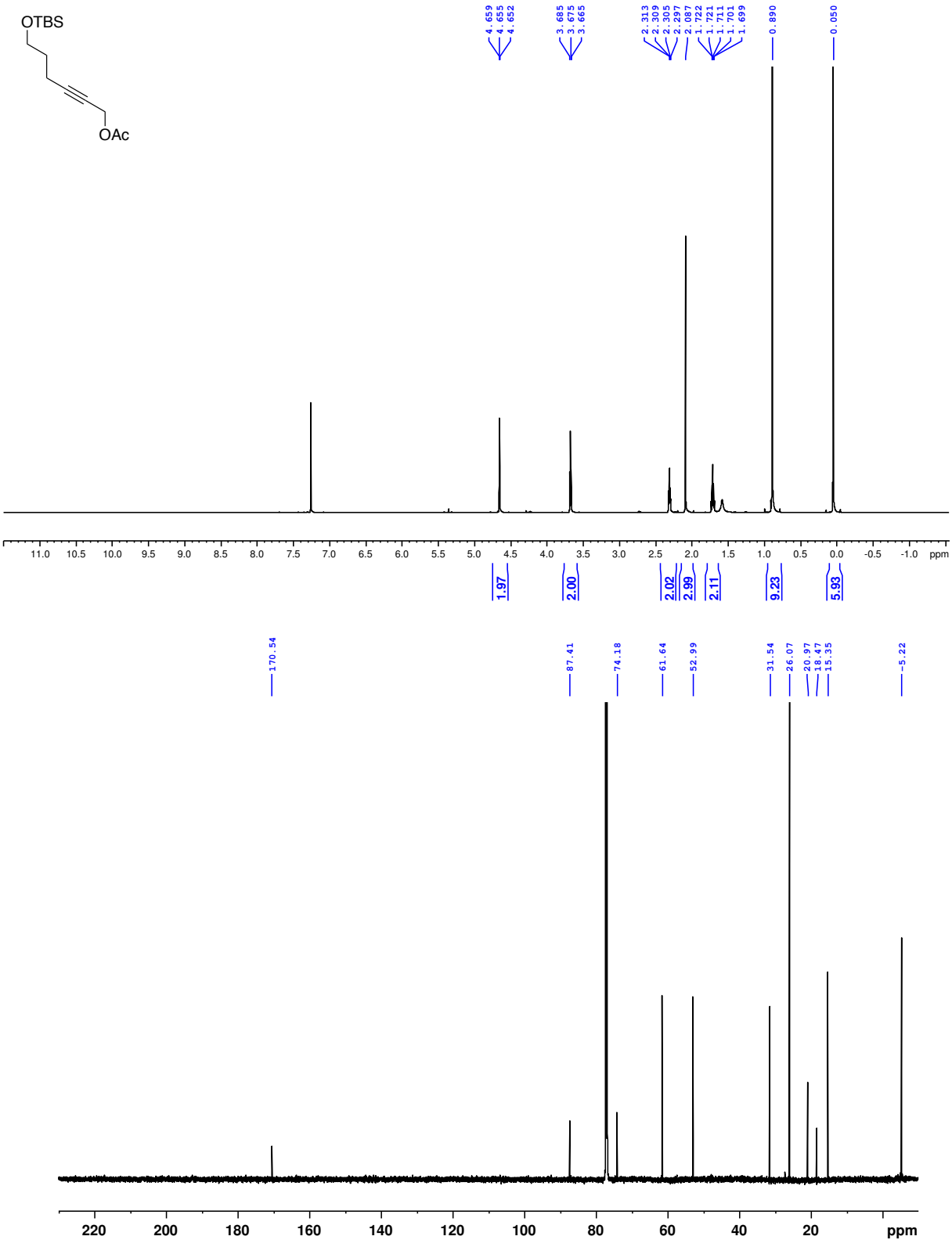


Figure A.4.9 ^{1}HNMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of acetate

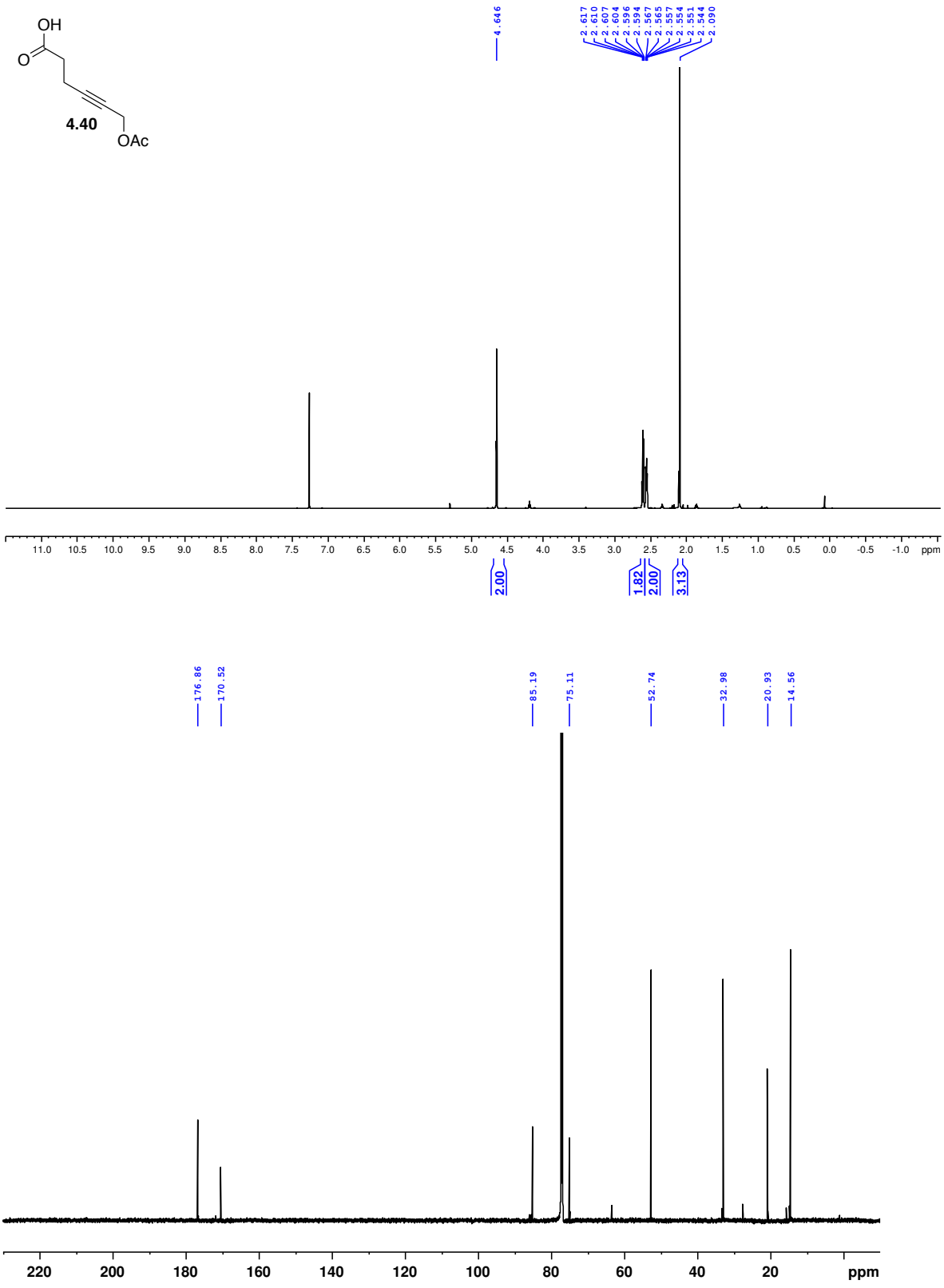


Figure A.4.10 ^{1}HNMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of acid **4.40**

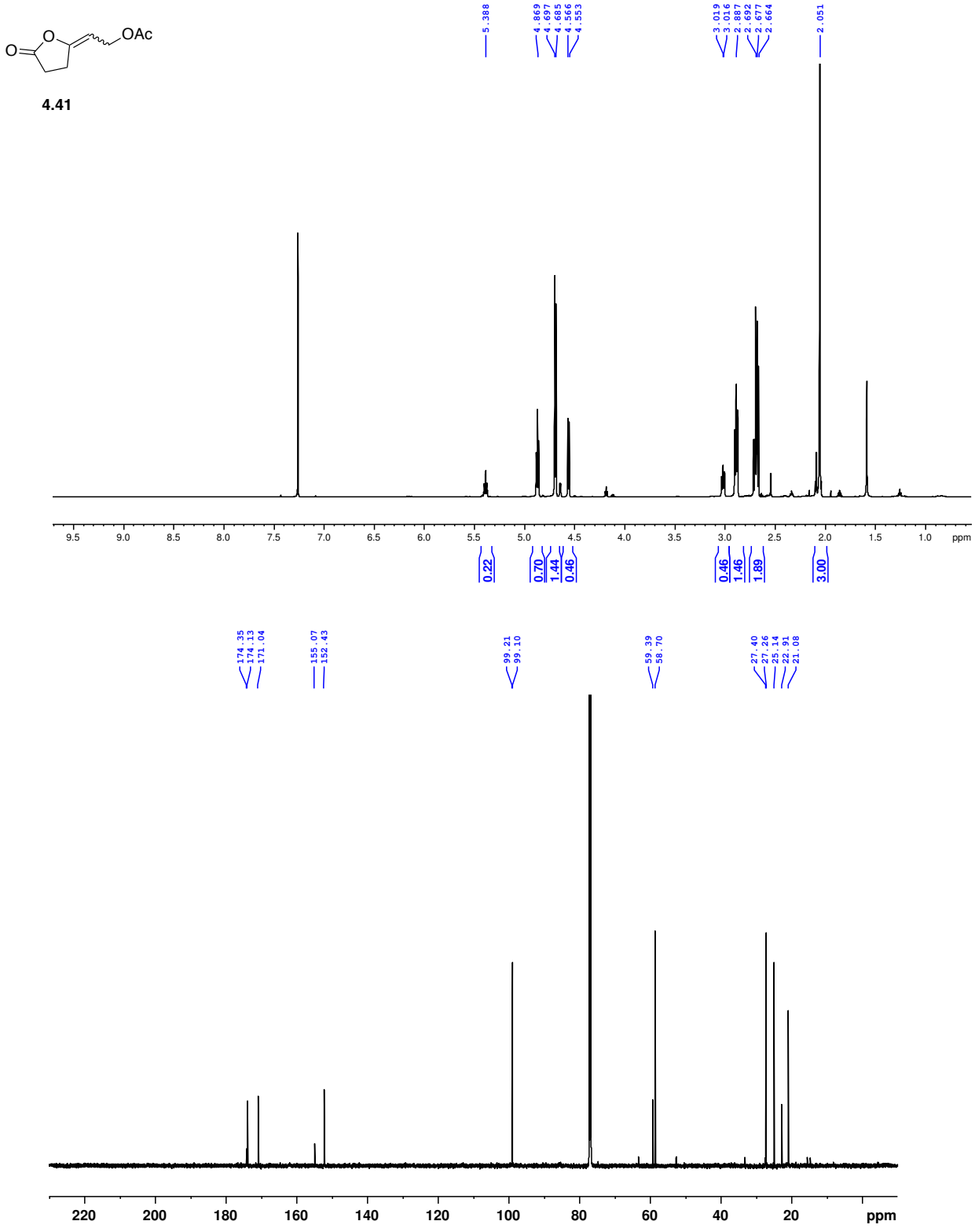


Figure A.4.11 ^{1}HNMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of acetate **4.41**

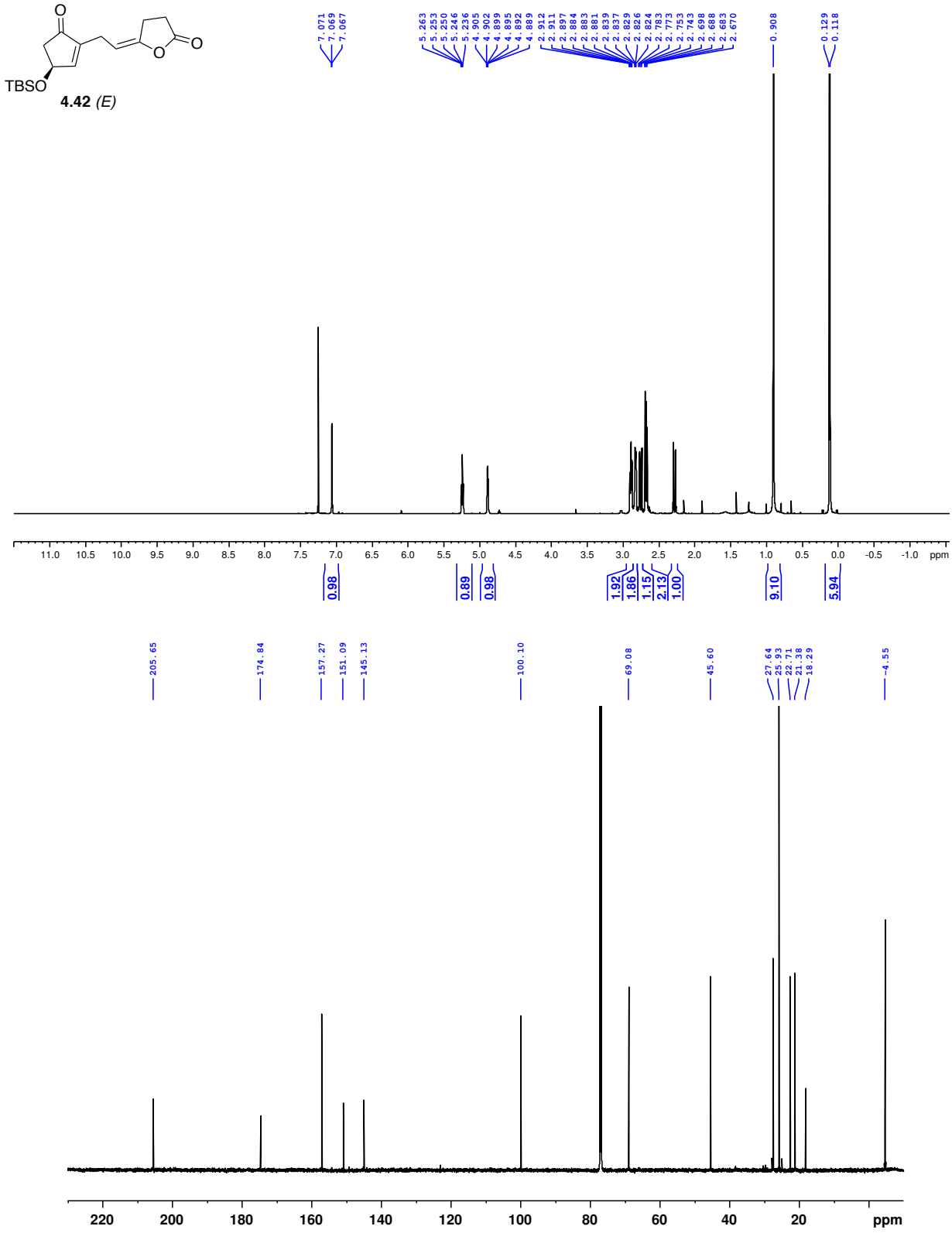


Figure A.4.12 ^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of *E* **4.42**

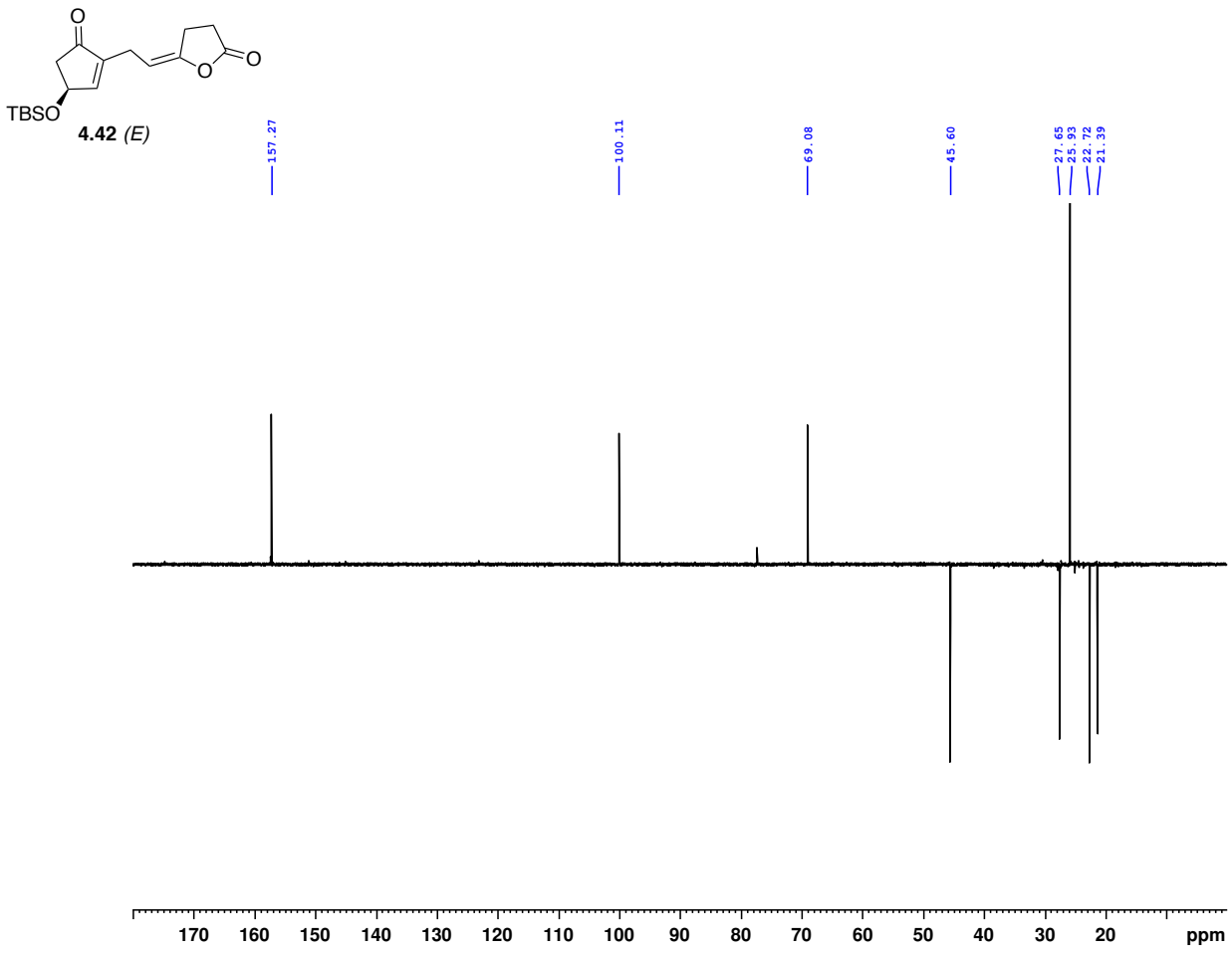


Figure A.4.13 DEPT-135 NMR (150 MHz, $CDCl_3$) of *E* **4.42**

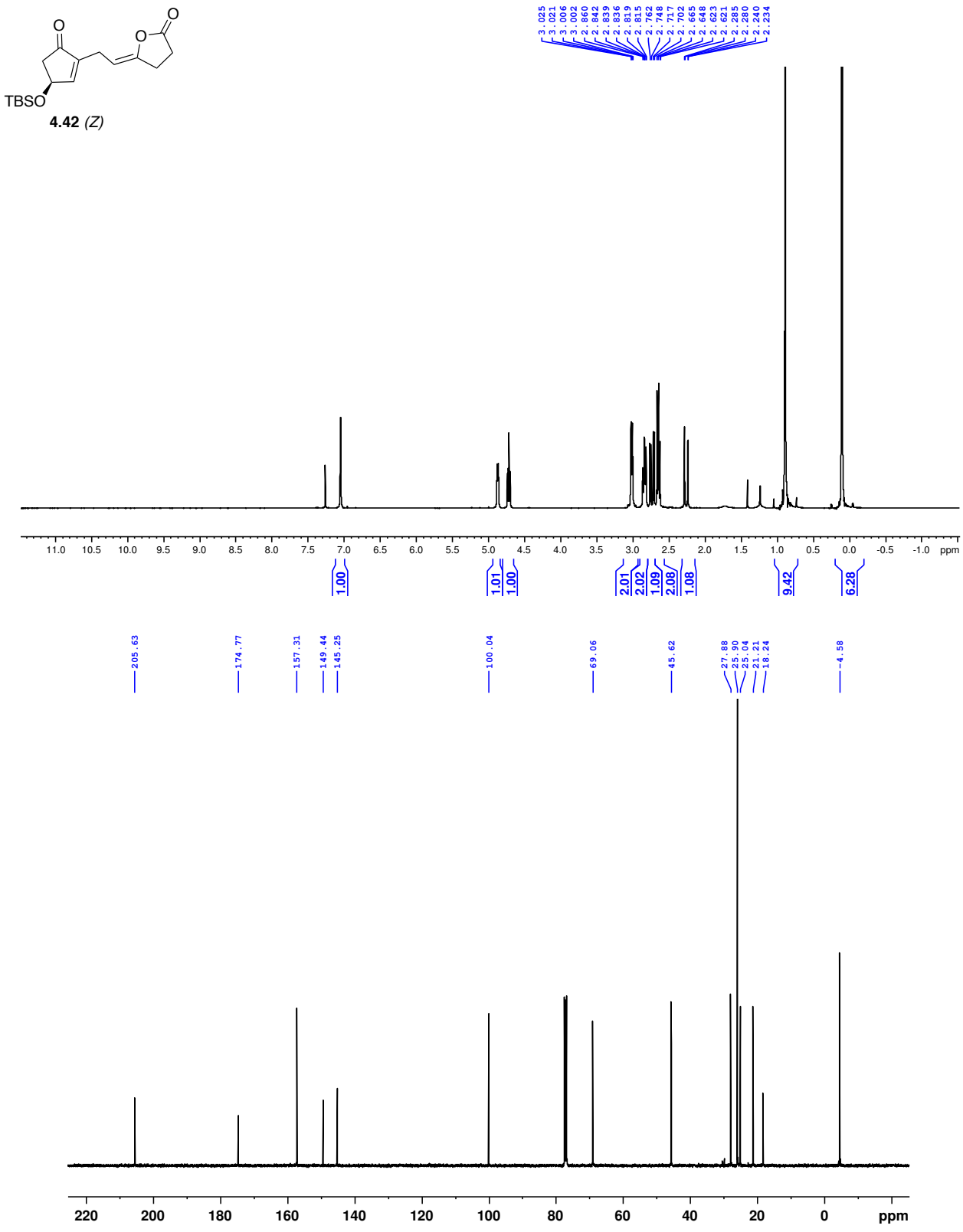


Figure A.4.14 ^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of *Z* **4.42**

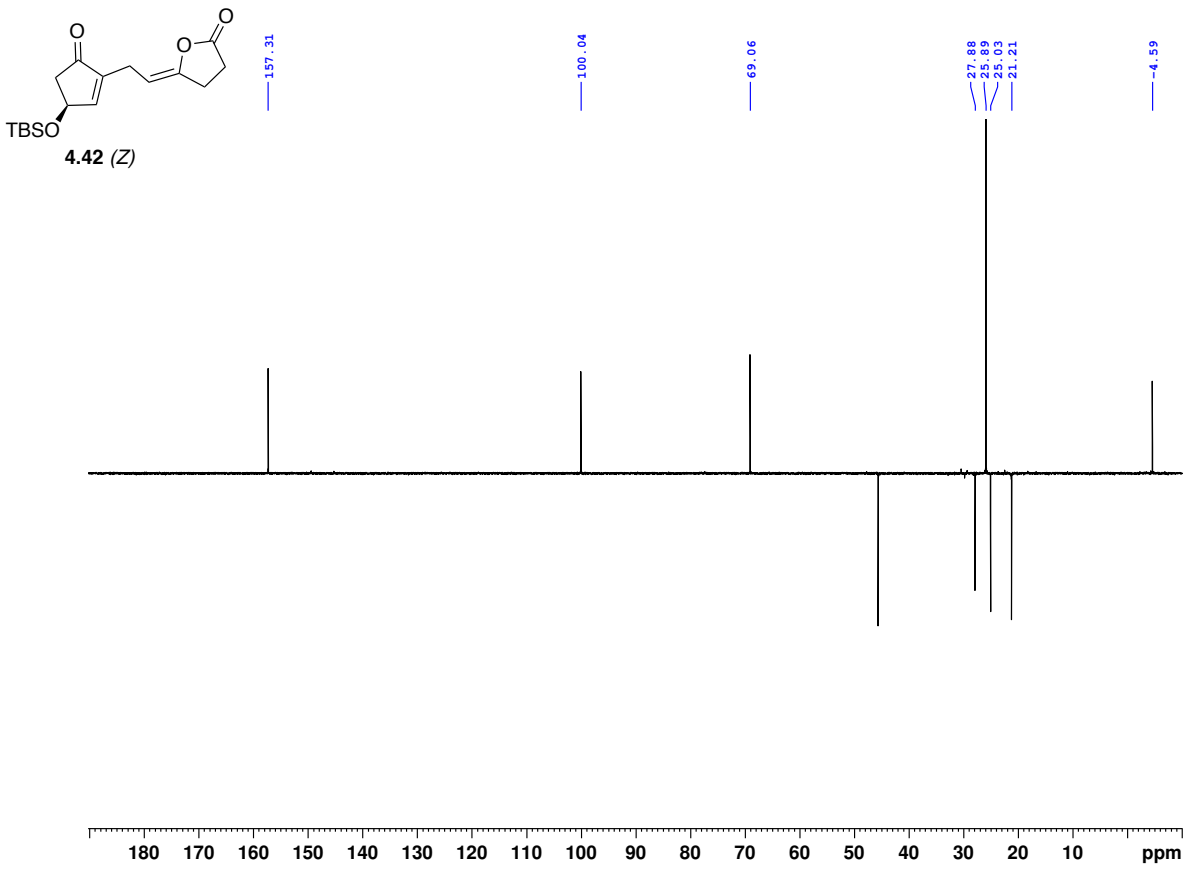


Figure A.4.15 DEPT-135 NMR (150 MHz, $CDCl_3$) of *Z* **4.42**

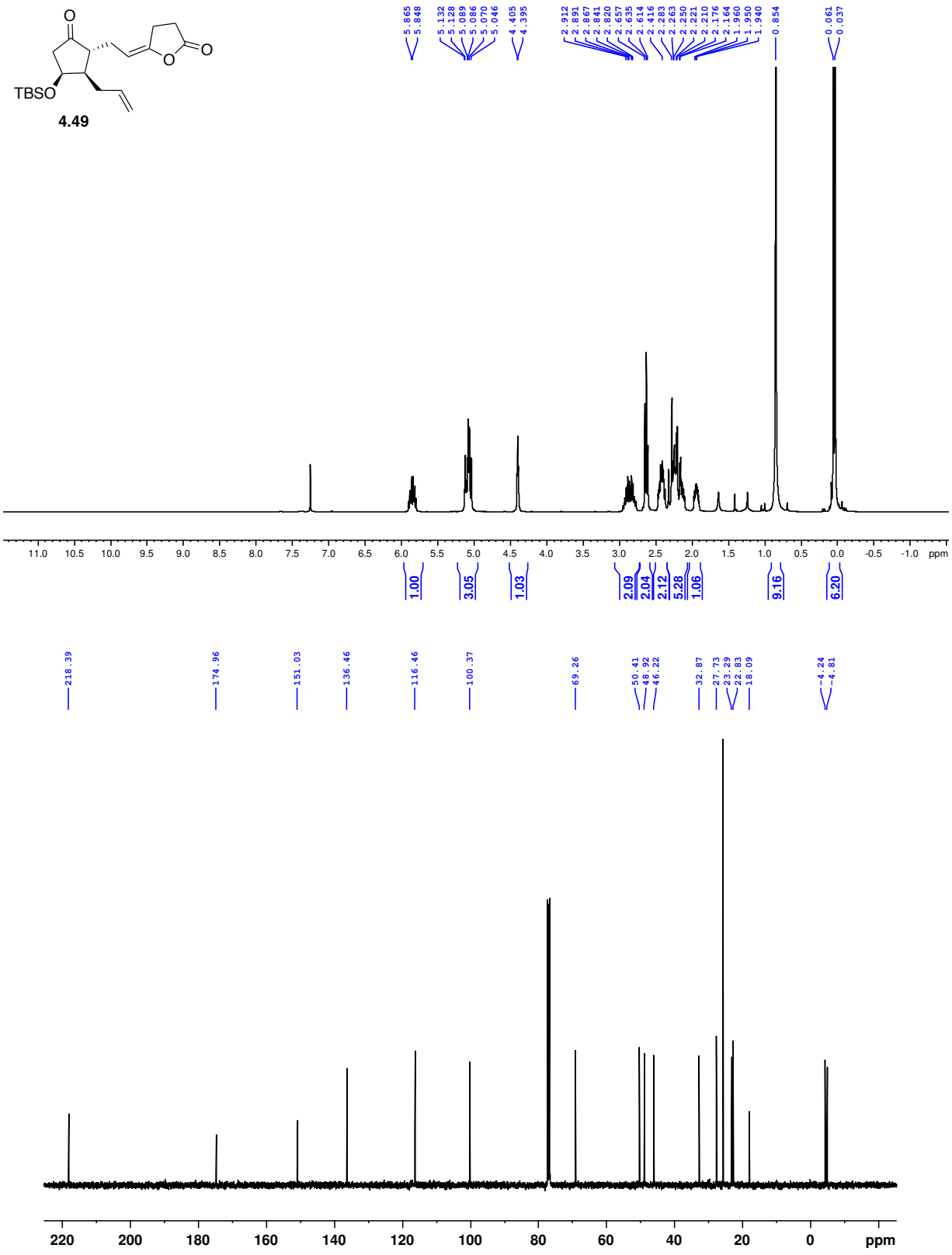


Figure A.4.16 ^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of **4.49**

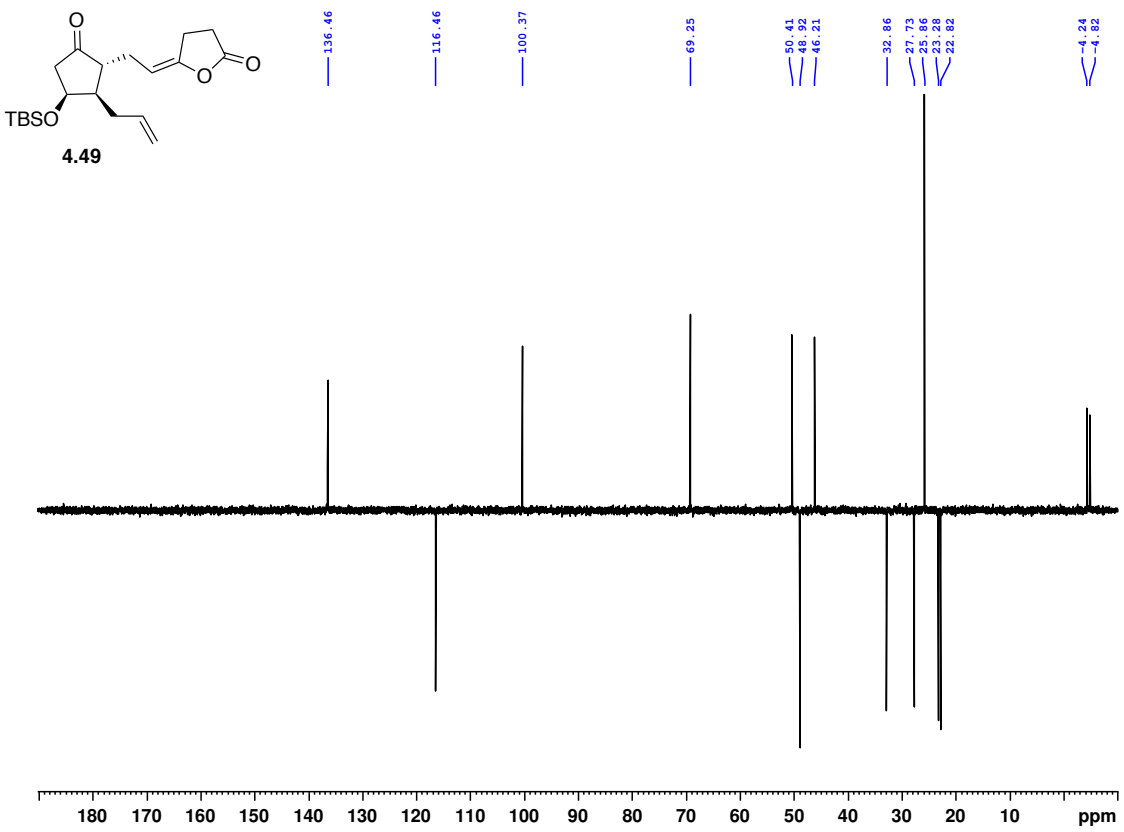


Figure A.4.17 DEPT-135 NMR (150 MHz, $CDCl_3$) of **4.49**

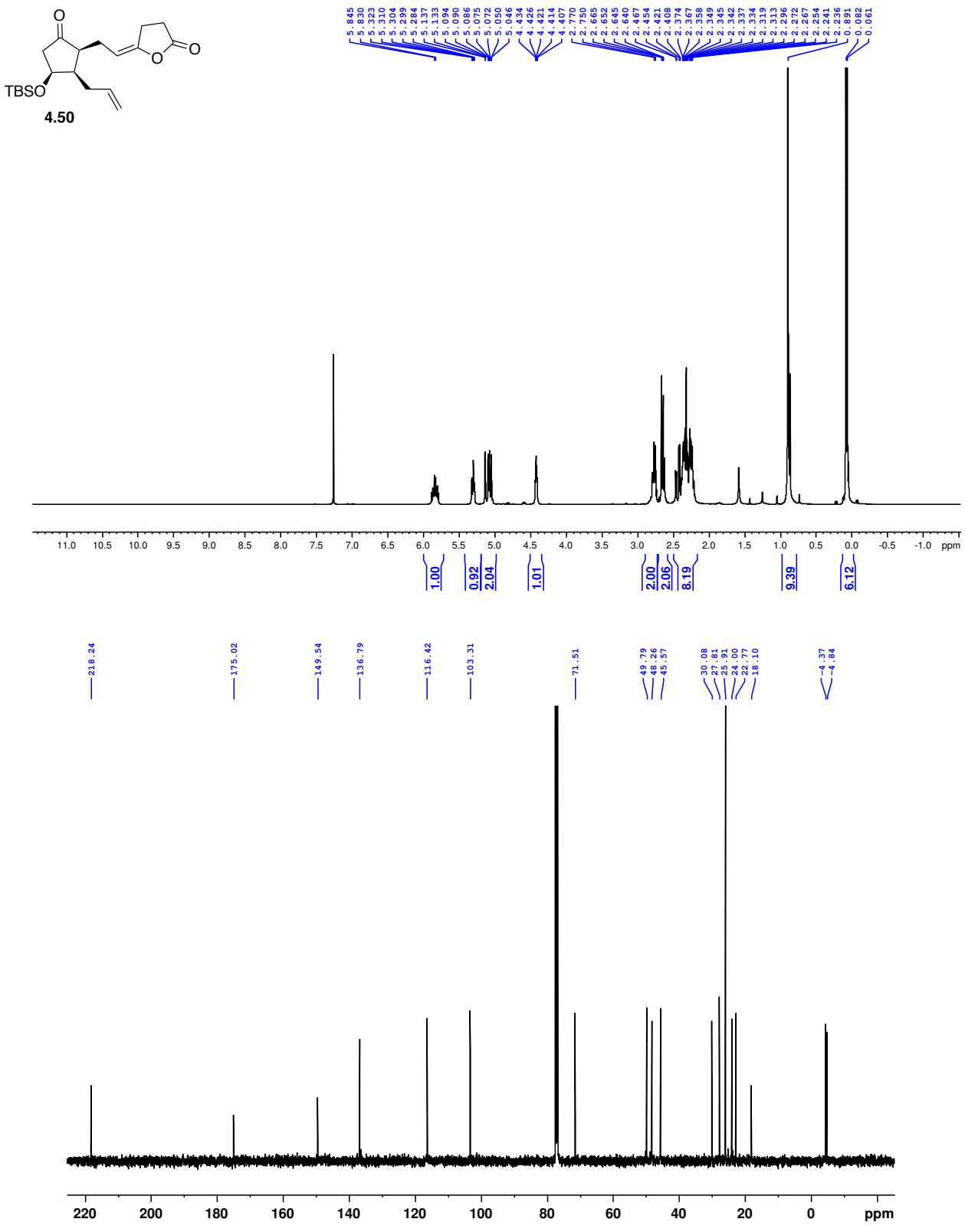


Figure A.4.18 ^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of **4.50**

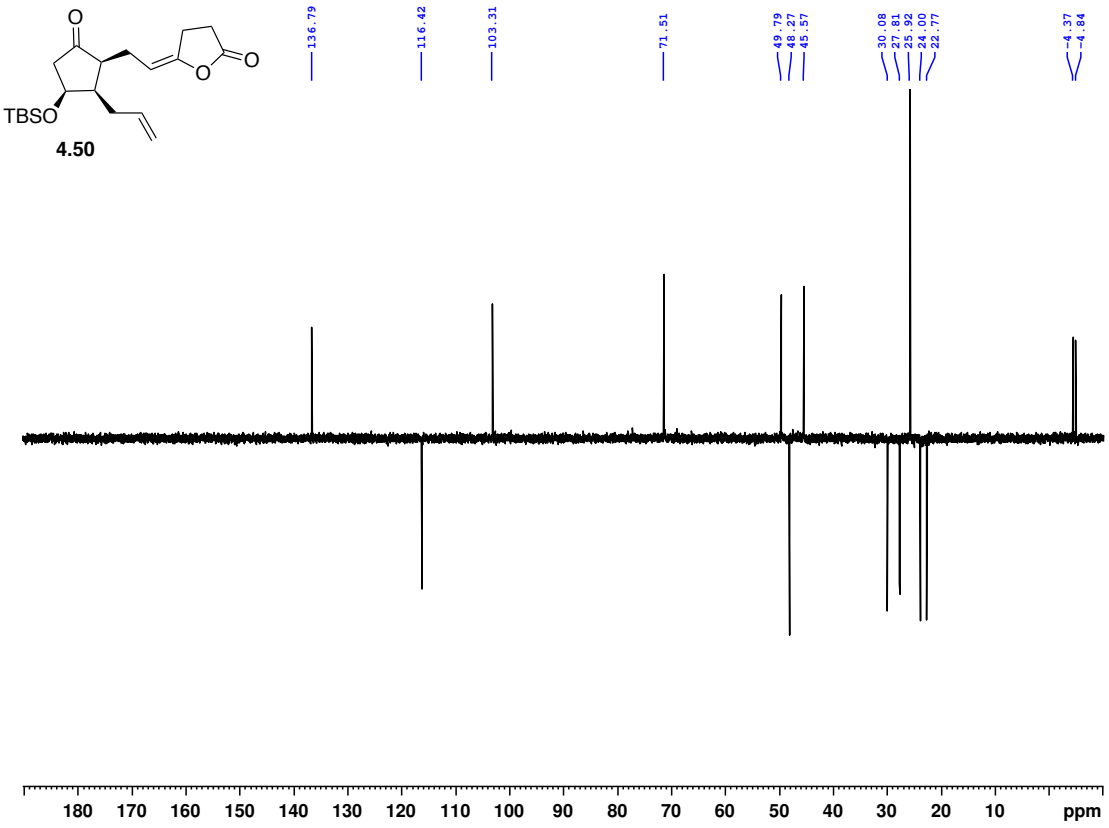


Figure A.4.19 DEPT-135 NMR (150 MHz, $CDCl_3$) of **4.50**

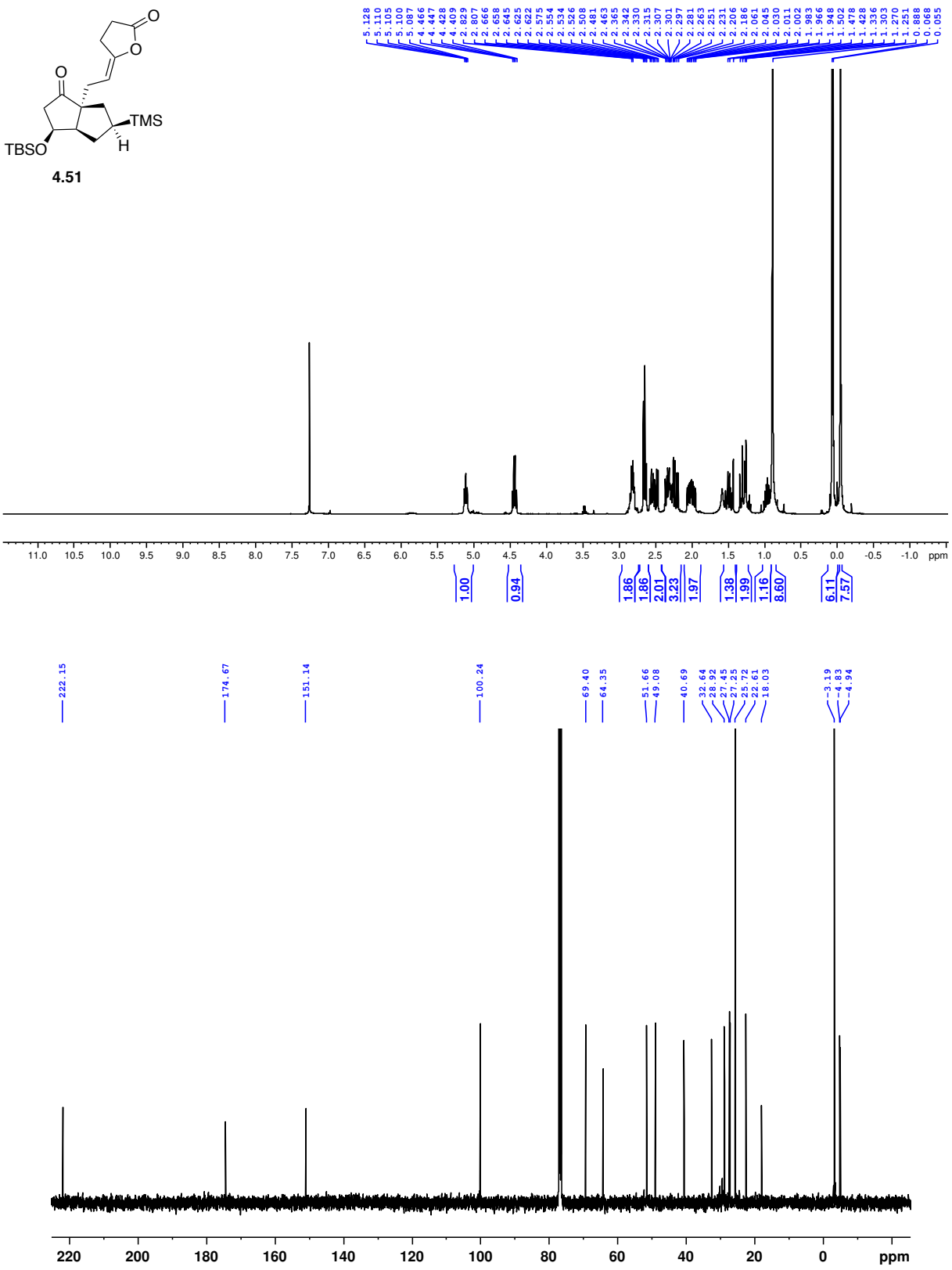


Figure A.4.20 ^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of **4.51**

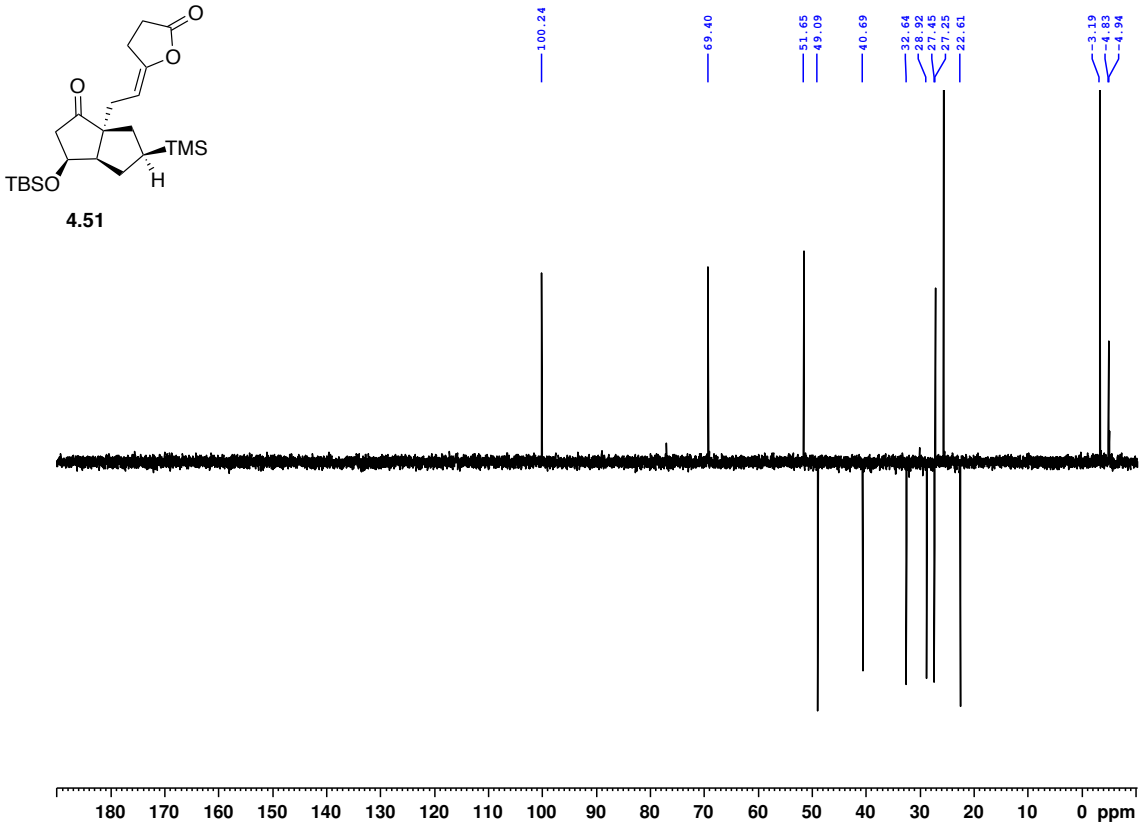


Figure A.4.21 DEPT-135 NMR (150 MHz, $CDCl_3$) of **4.51**

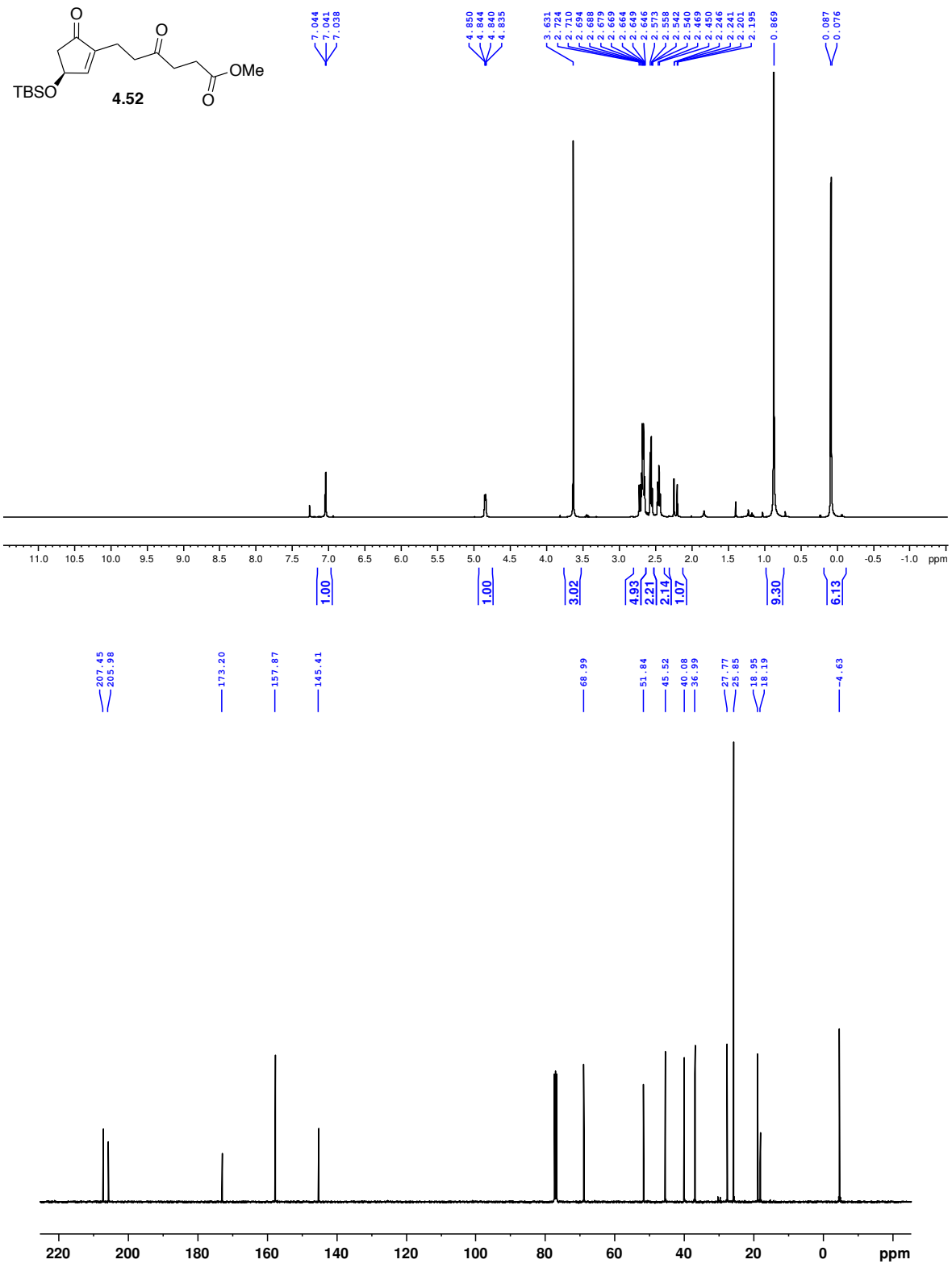


Figure A.4.22 ^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of **4.52**

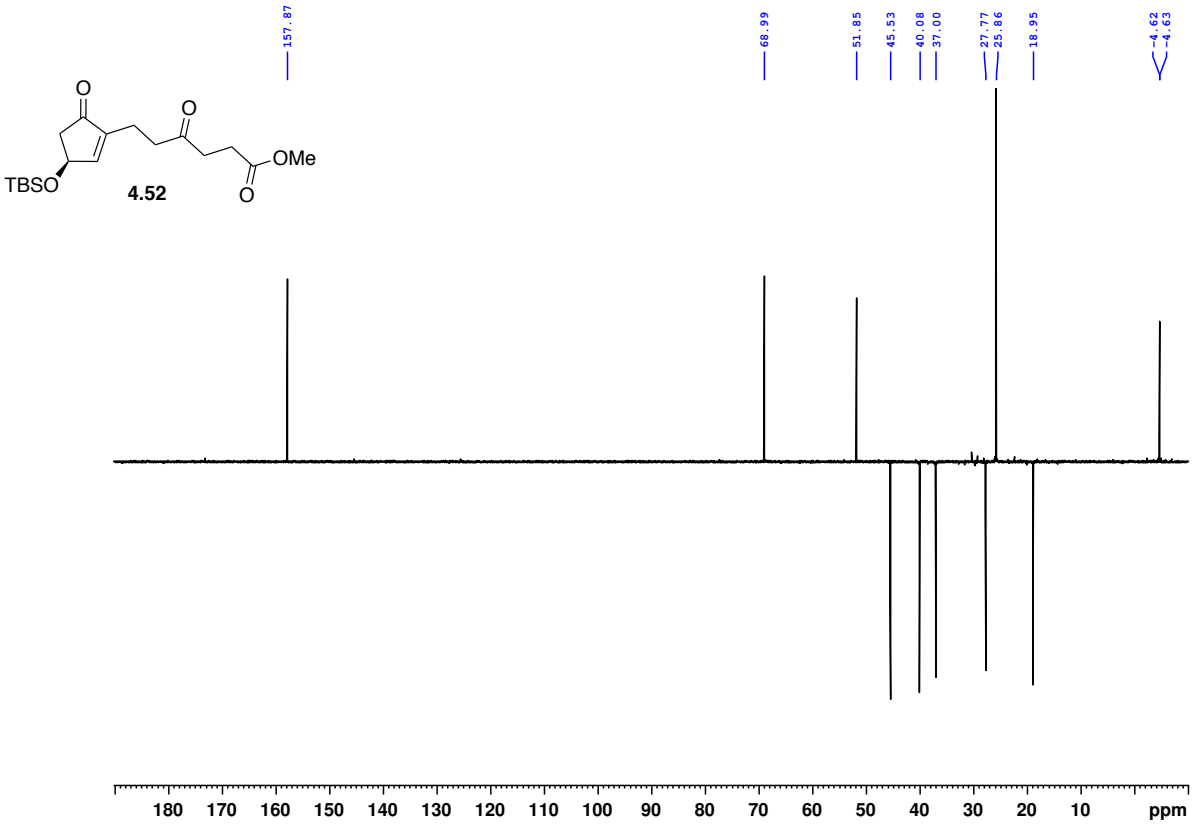


Figure A.4.23 DEPT-135 NMR (150 MHz, $CDCl_3$) of **4.52**

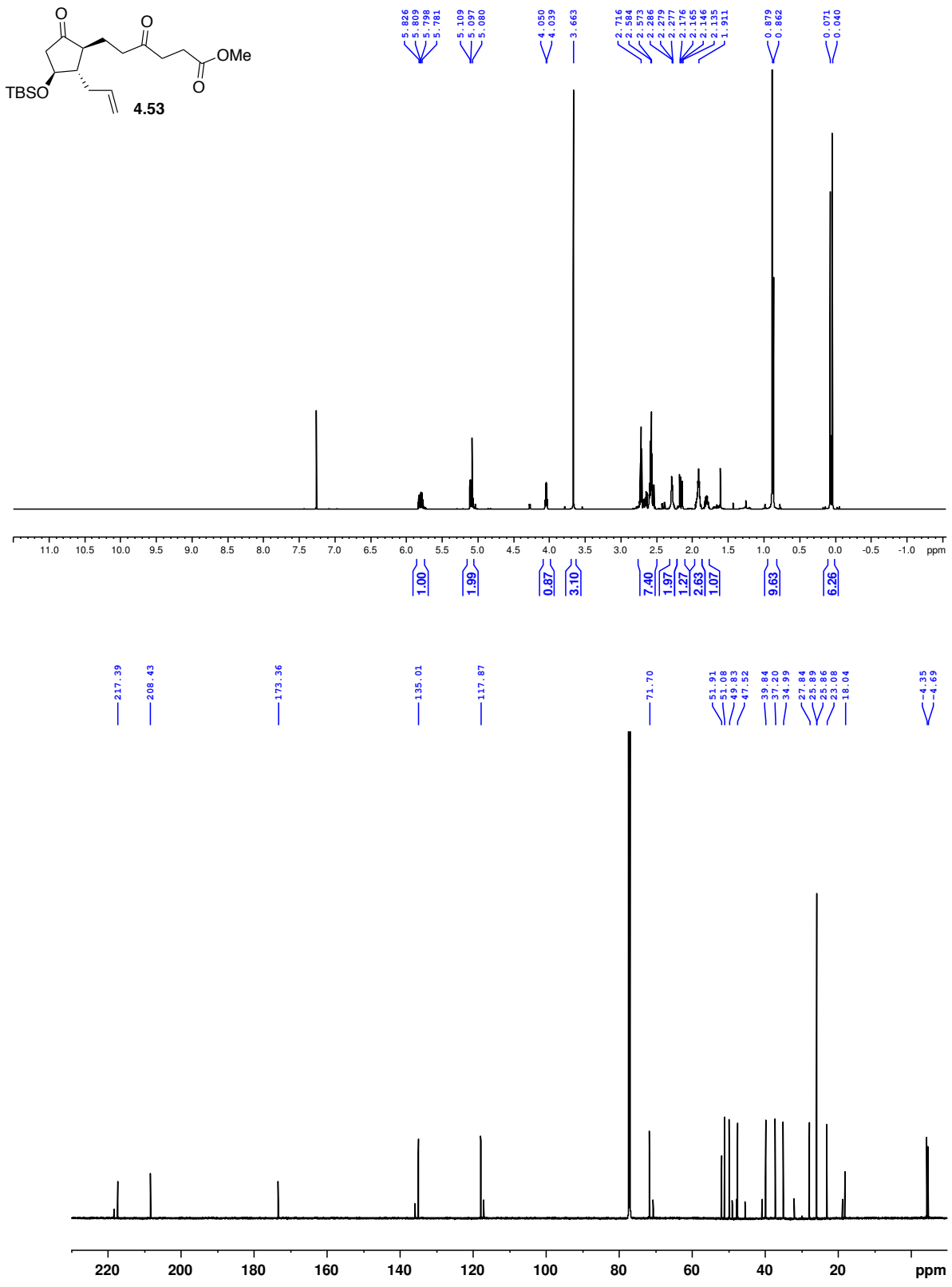


Figure A.4.24 ^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of **4.53**

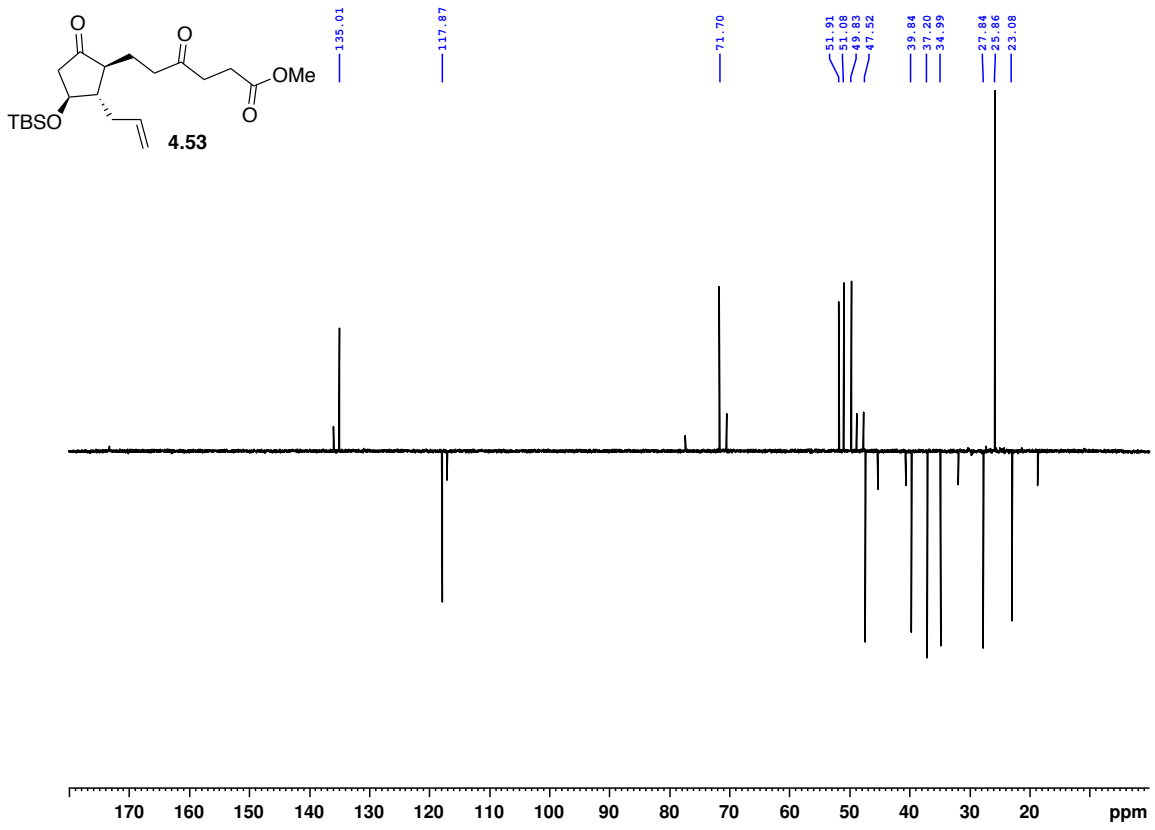


Figure A.4.25 DEPT-135 NMR (150 MHz, $CDCl_3$) of **4.53**

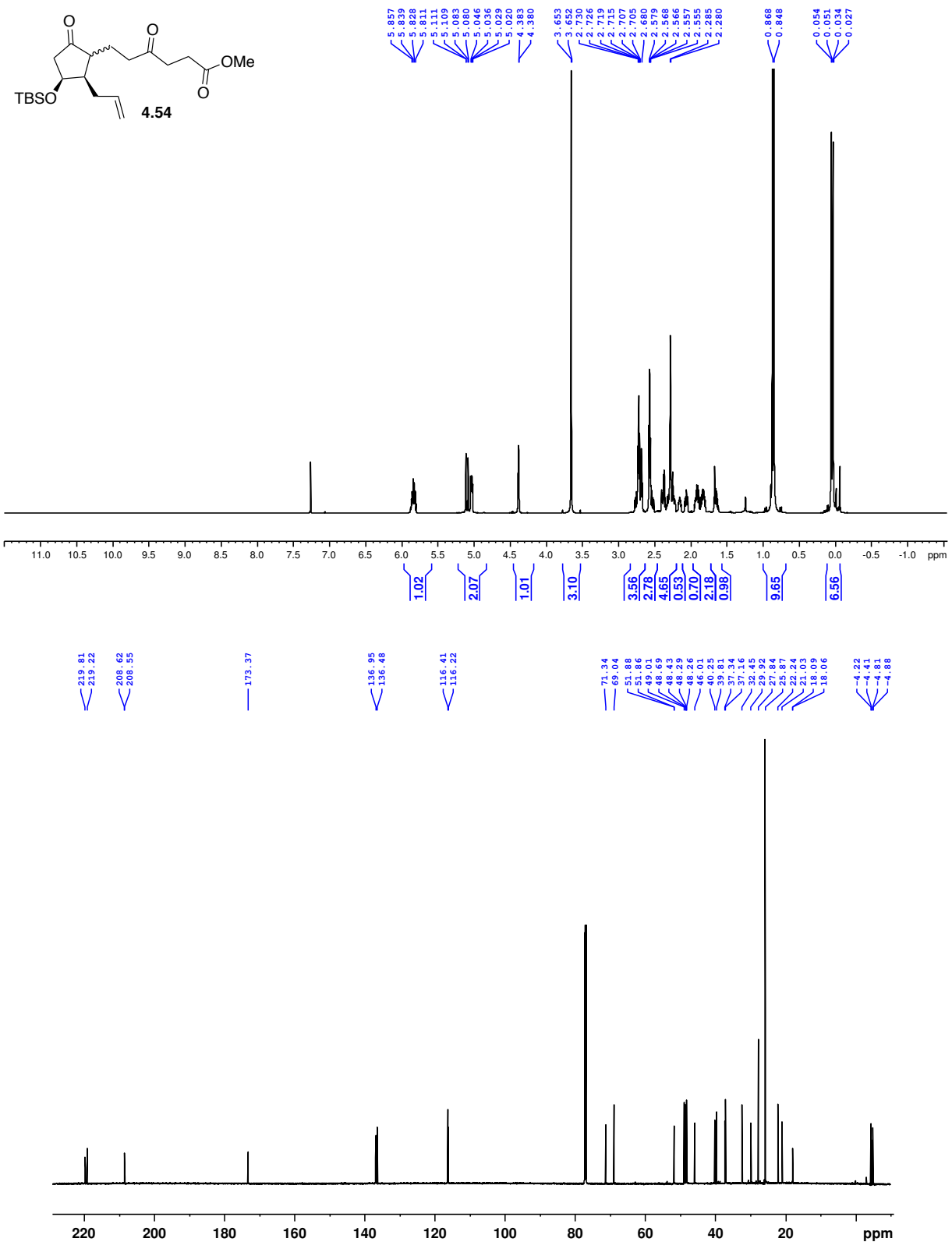


Figure A.4.26 ^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of **4.54**

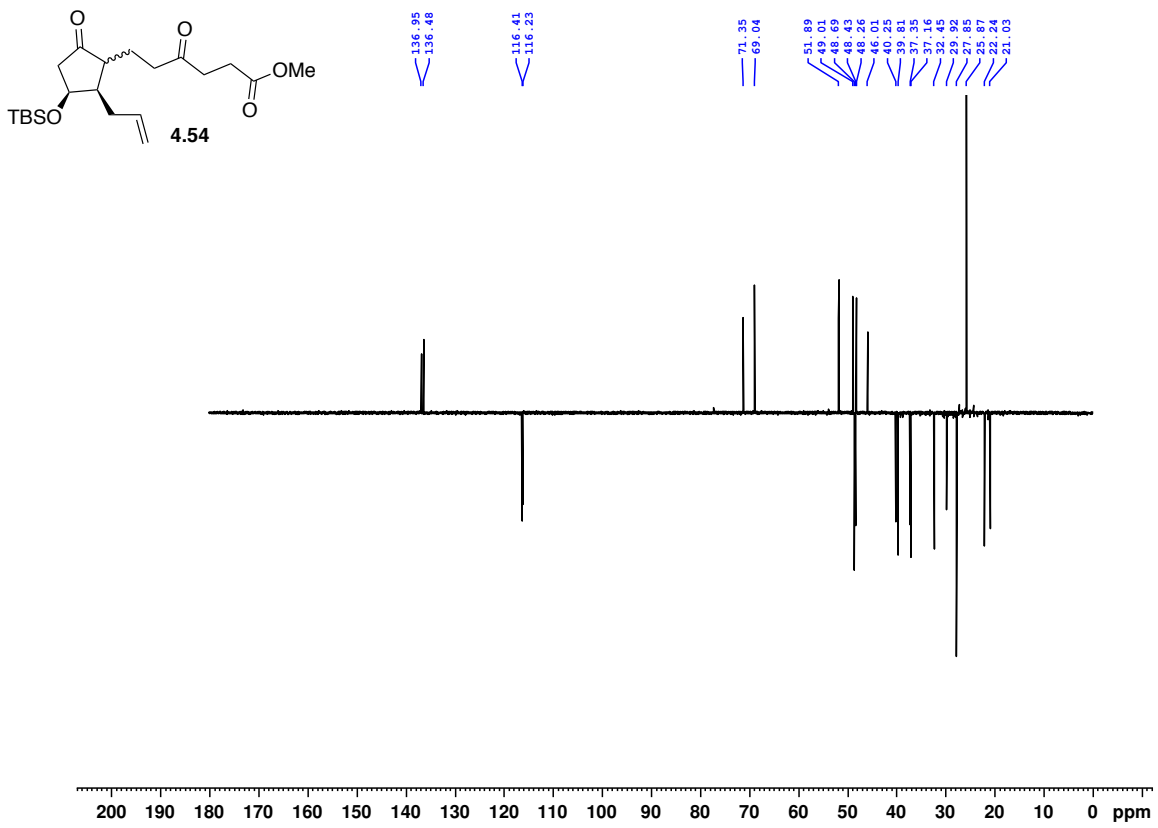


Figure A.4.27 DEPT-135 NMR (150 MHz, $CDCl_3$) of **4.54**

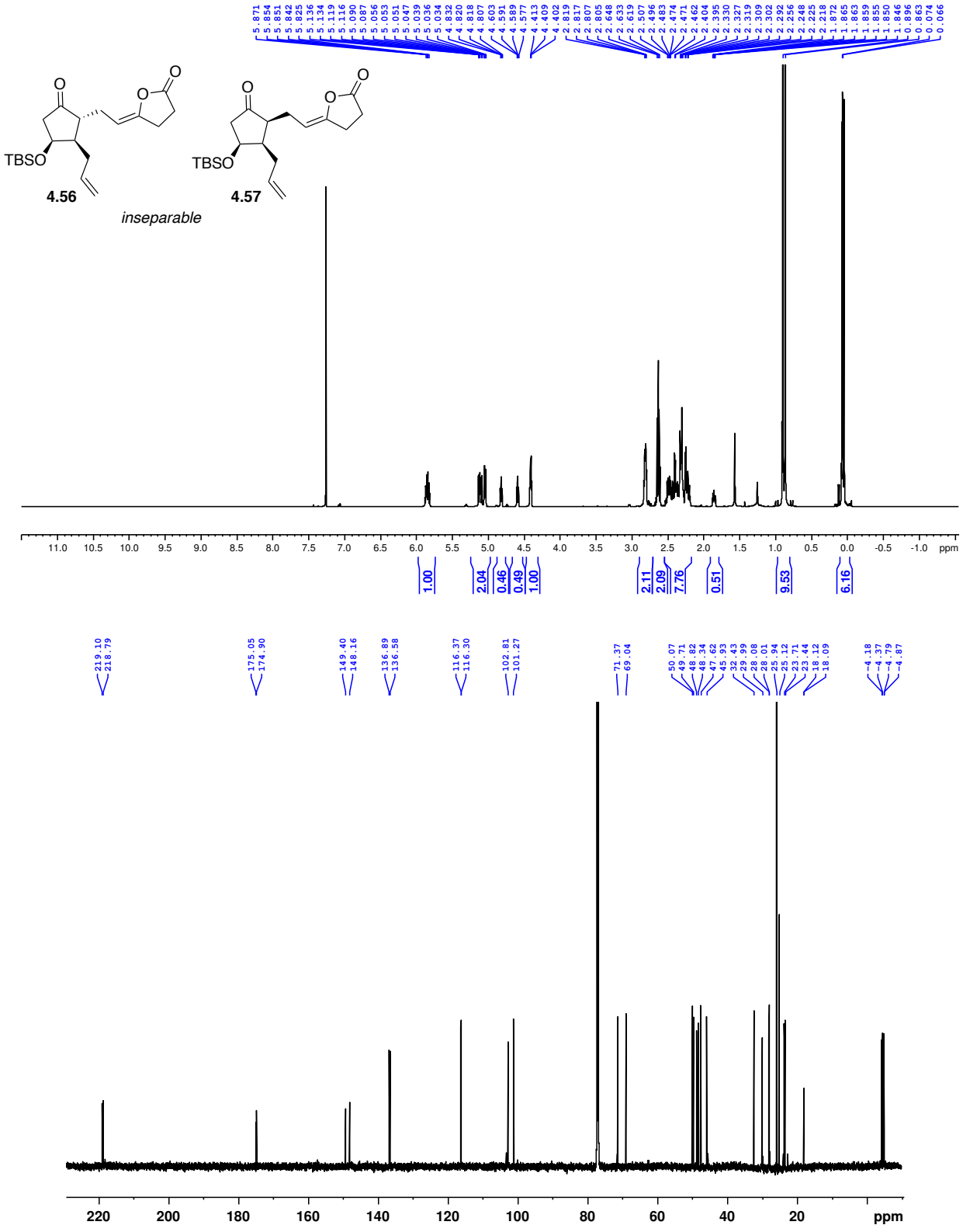


Figure A.4.26 ^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of **4.56** & **4.57**

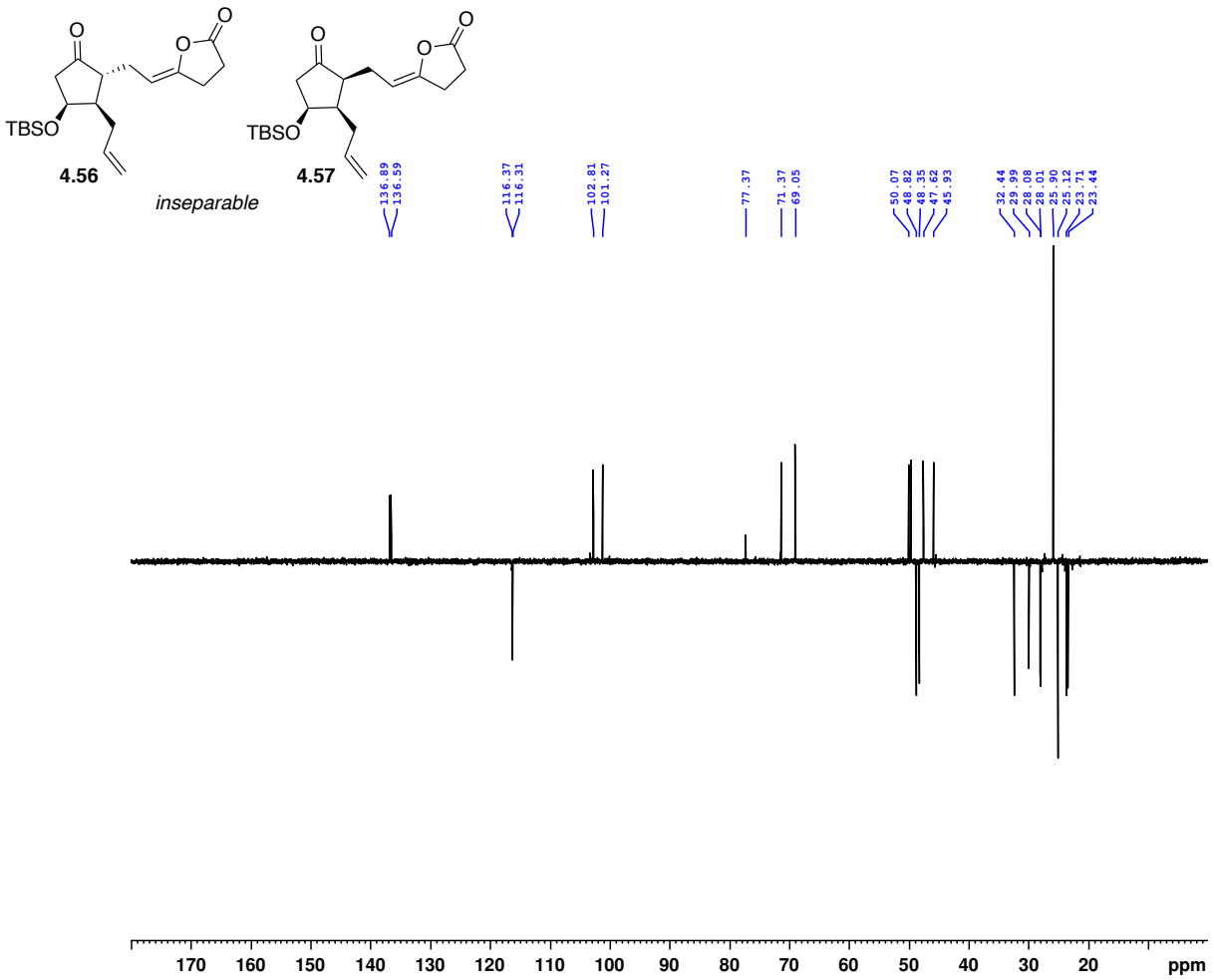


Figure A.4.29 DEPT-135 NMR (150 MHz, $CDCl_3$) of **4.56** & **4.57**

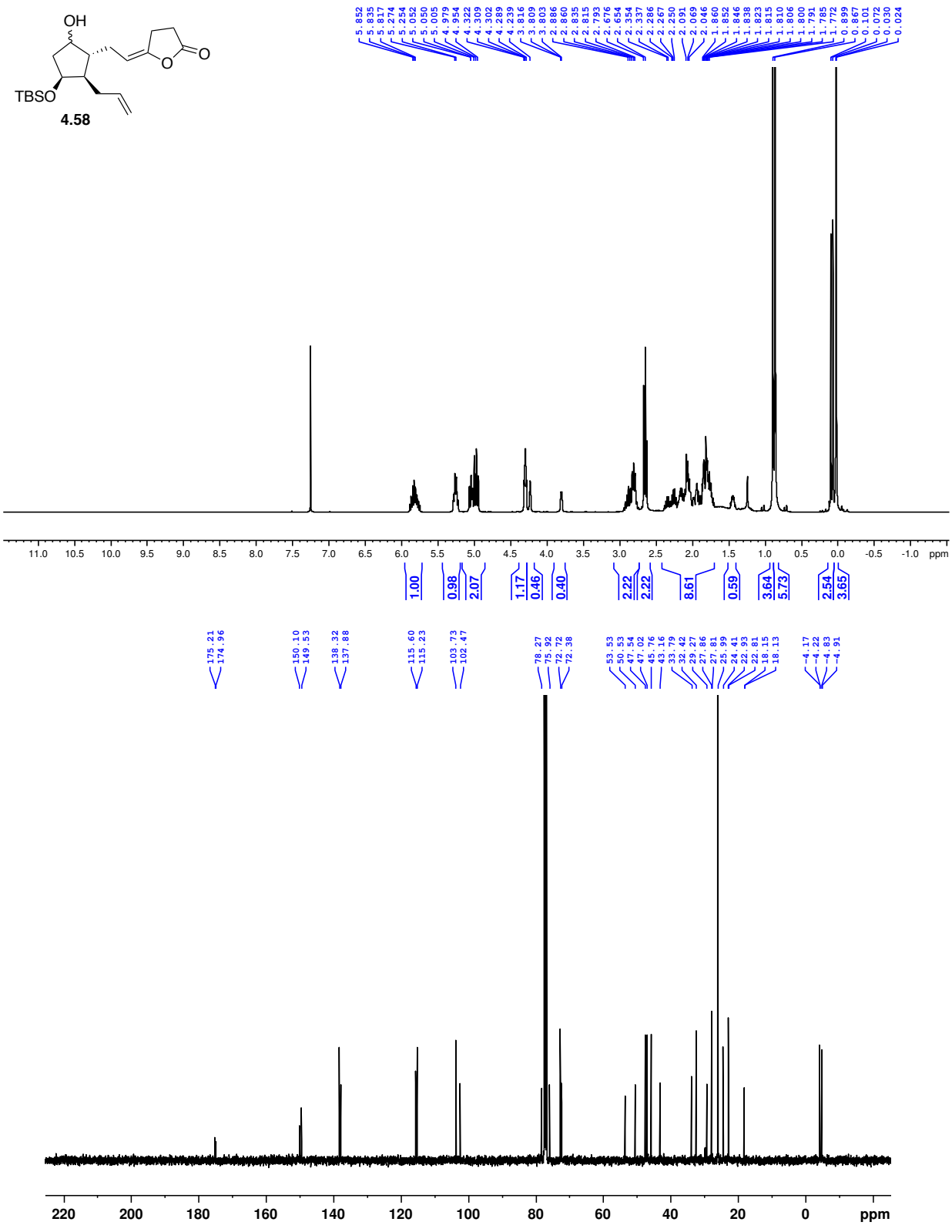


Figure A.4.30 ^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of **4.58**

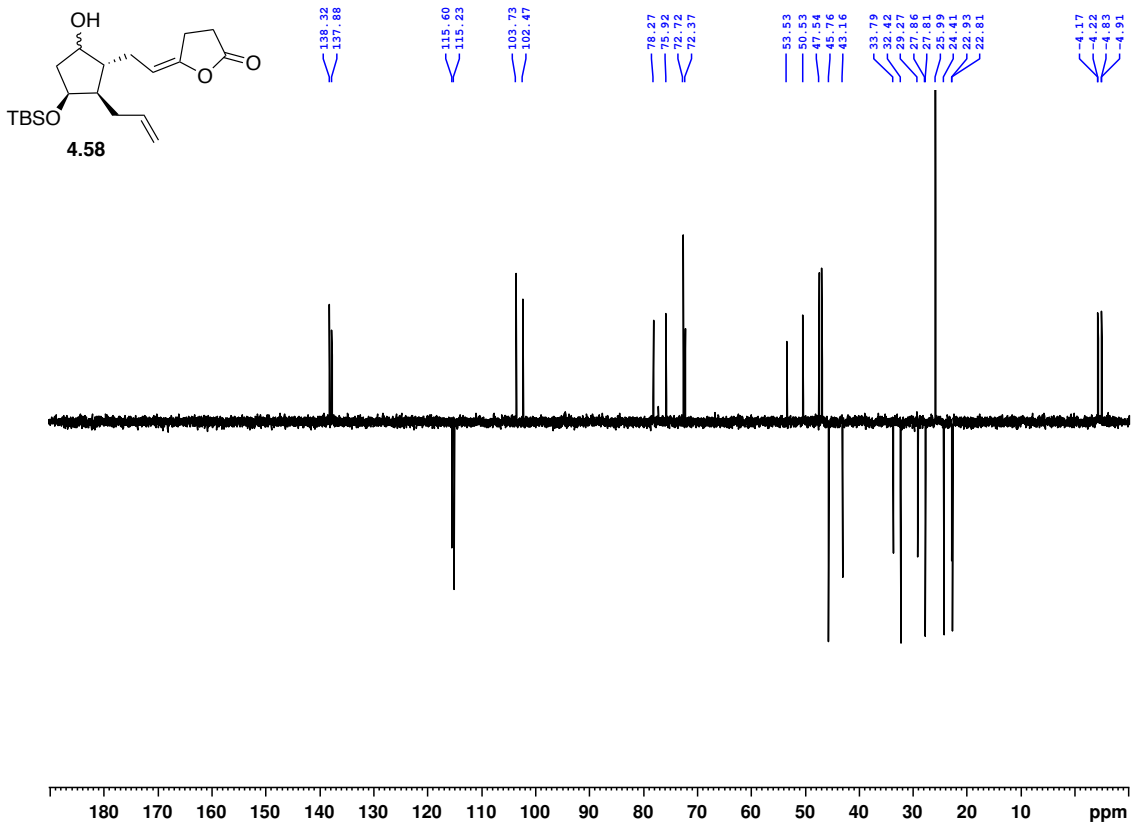


Figure A.4.31 DEPT-135 NMR (150 MHz, $CDCl_3$) of **4.58**

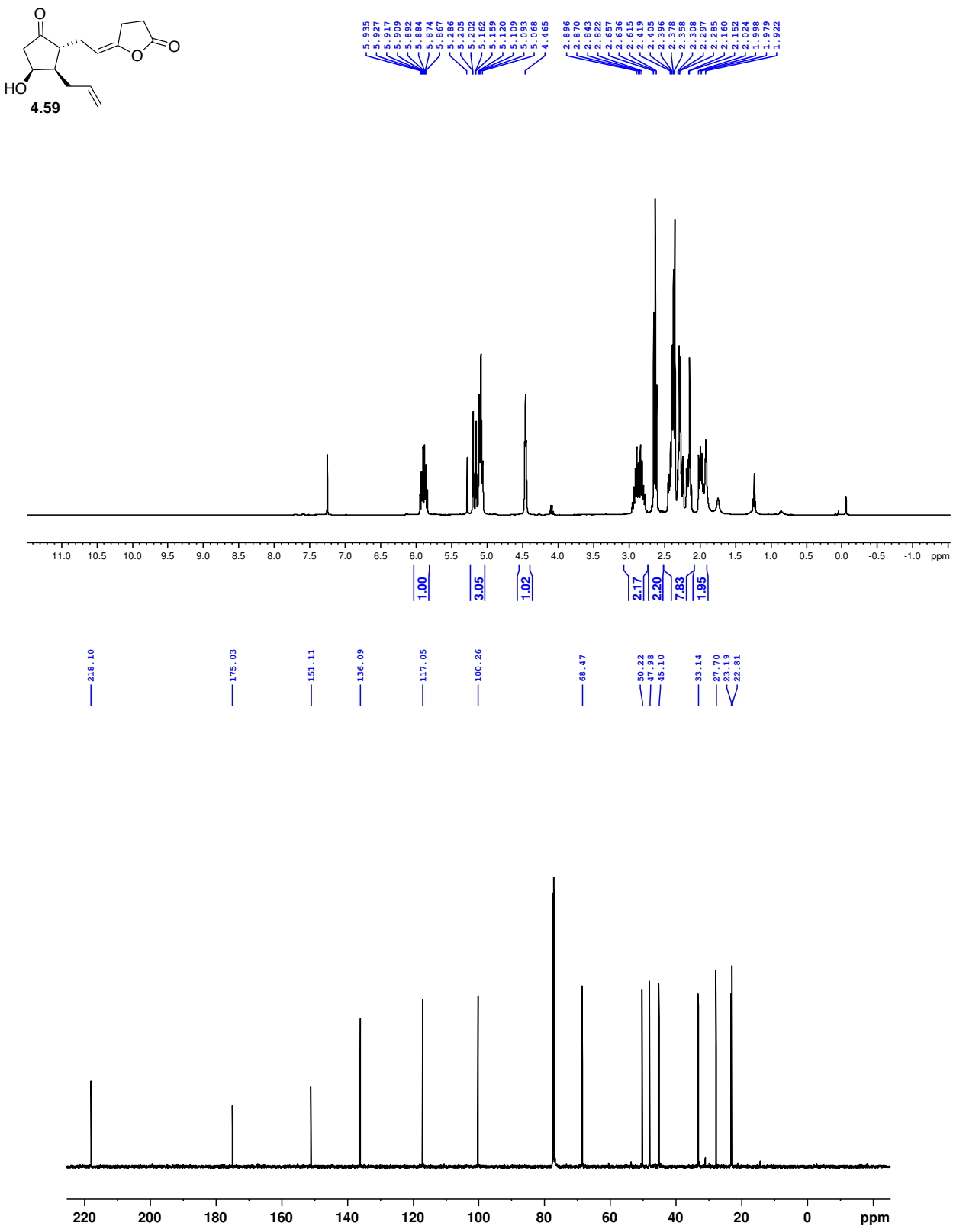


Figure A.4.32 ^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of **4.59**

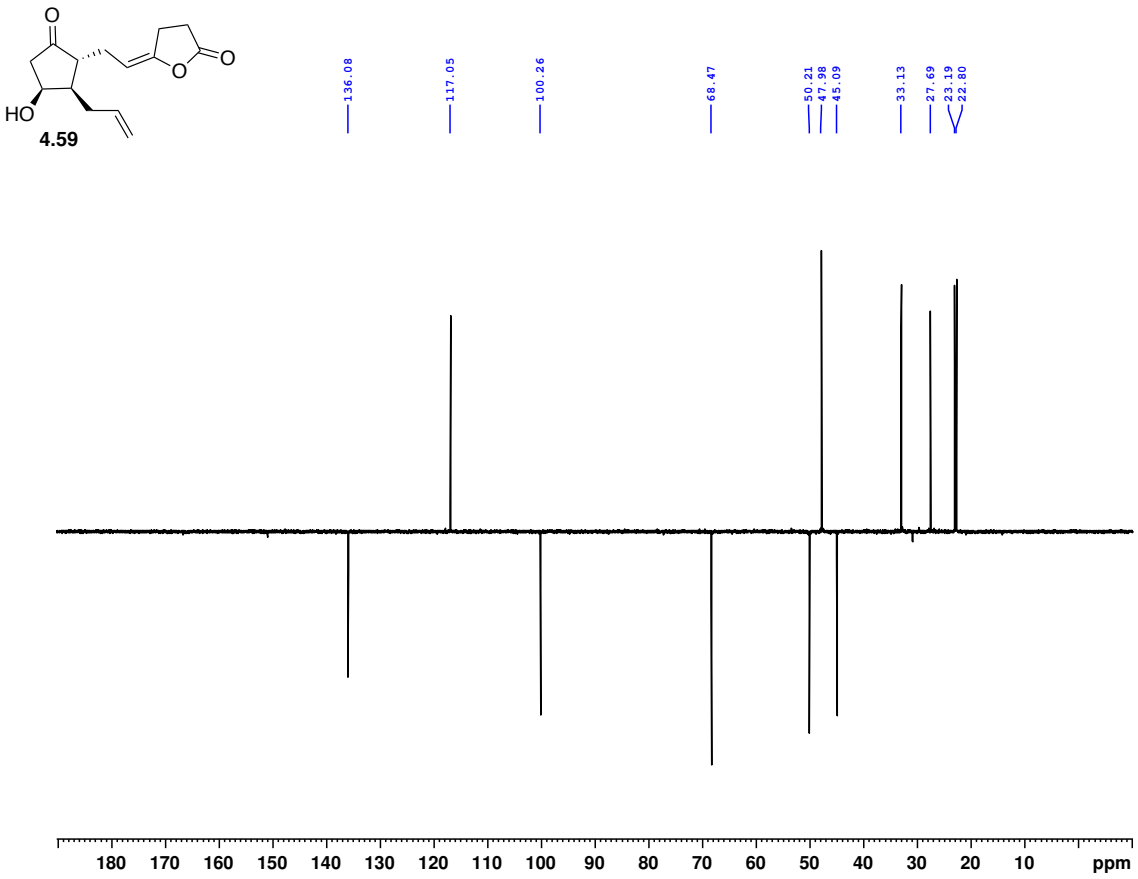


Figure A.4.33 DEPT-135 NMR (150 MHz, $CDCl_3$) of **4.59**

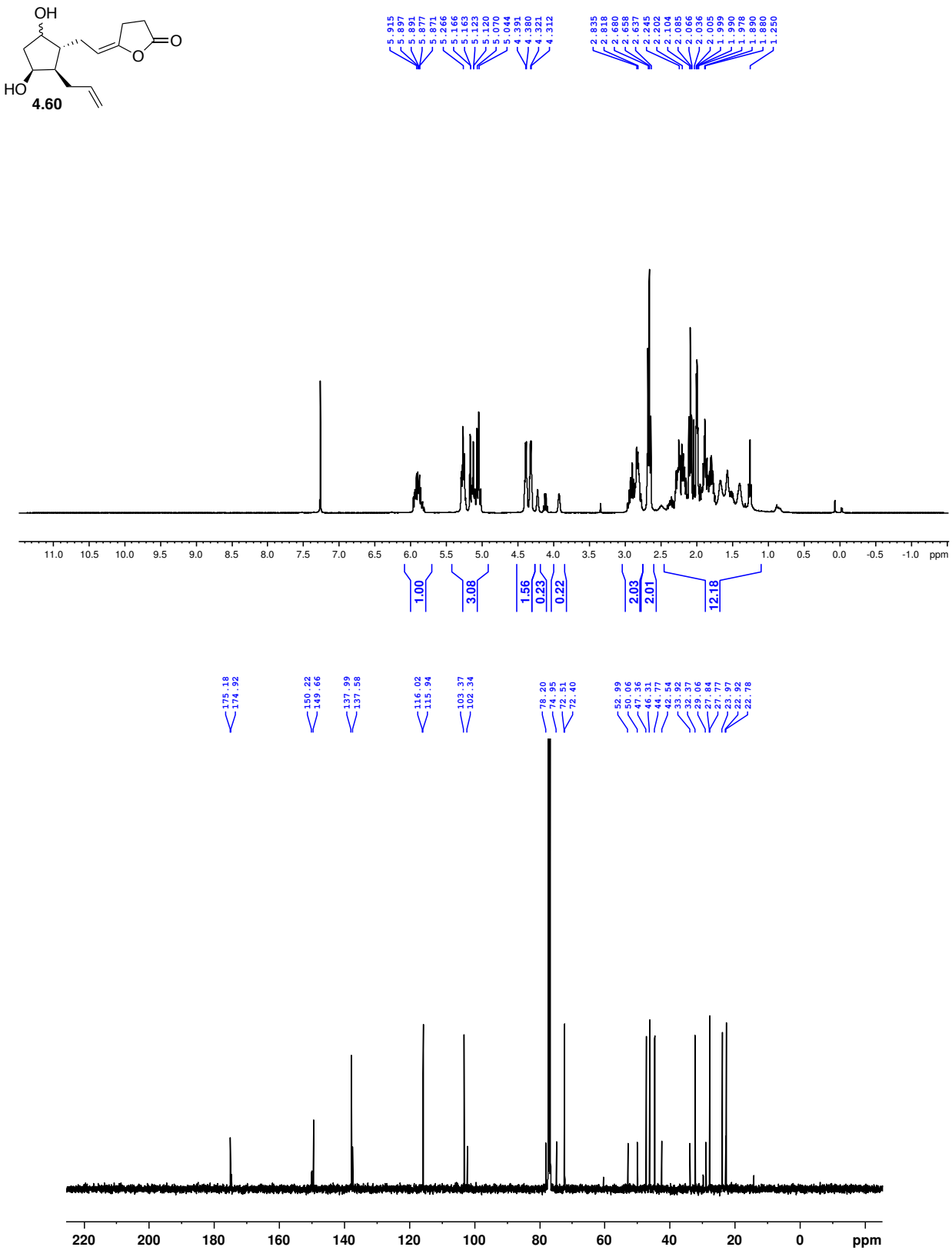


Figure A.4.34 ^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of **4.60**

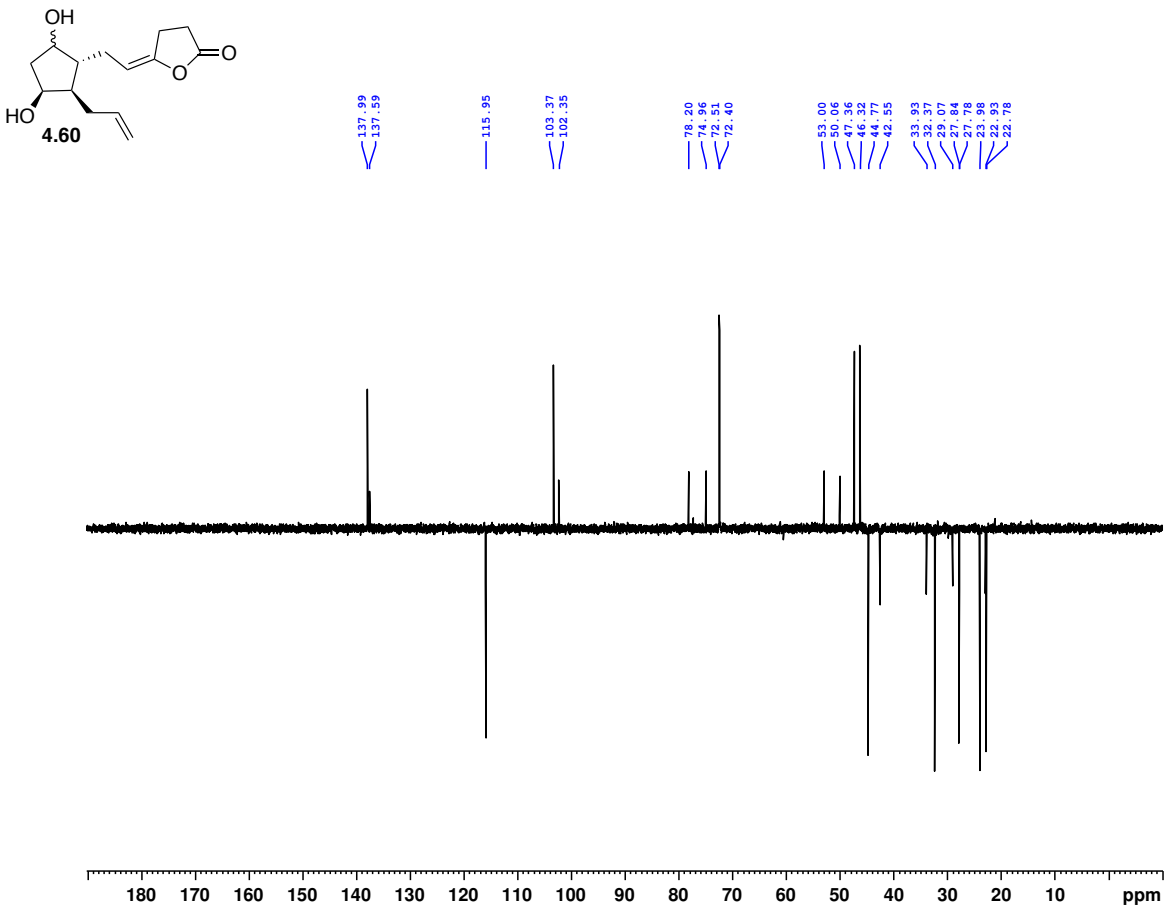


Figure A.4.35 DEPT-135 NMR (150 MHz, $CDCl_3$) of **4.60**

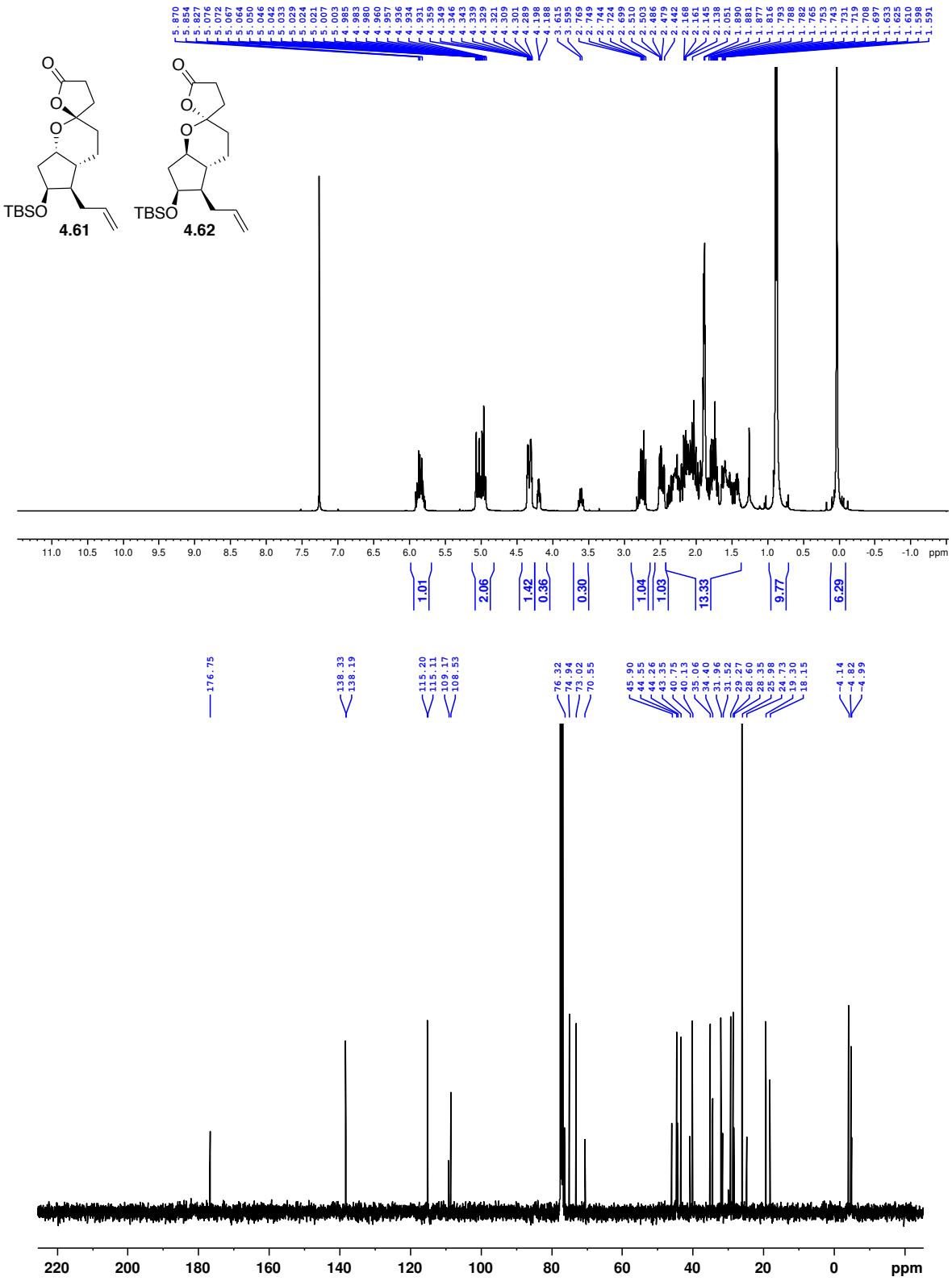


Figure A.4.36 ^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of **4.61** & **4.62**

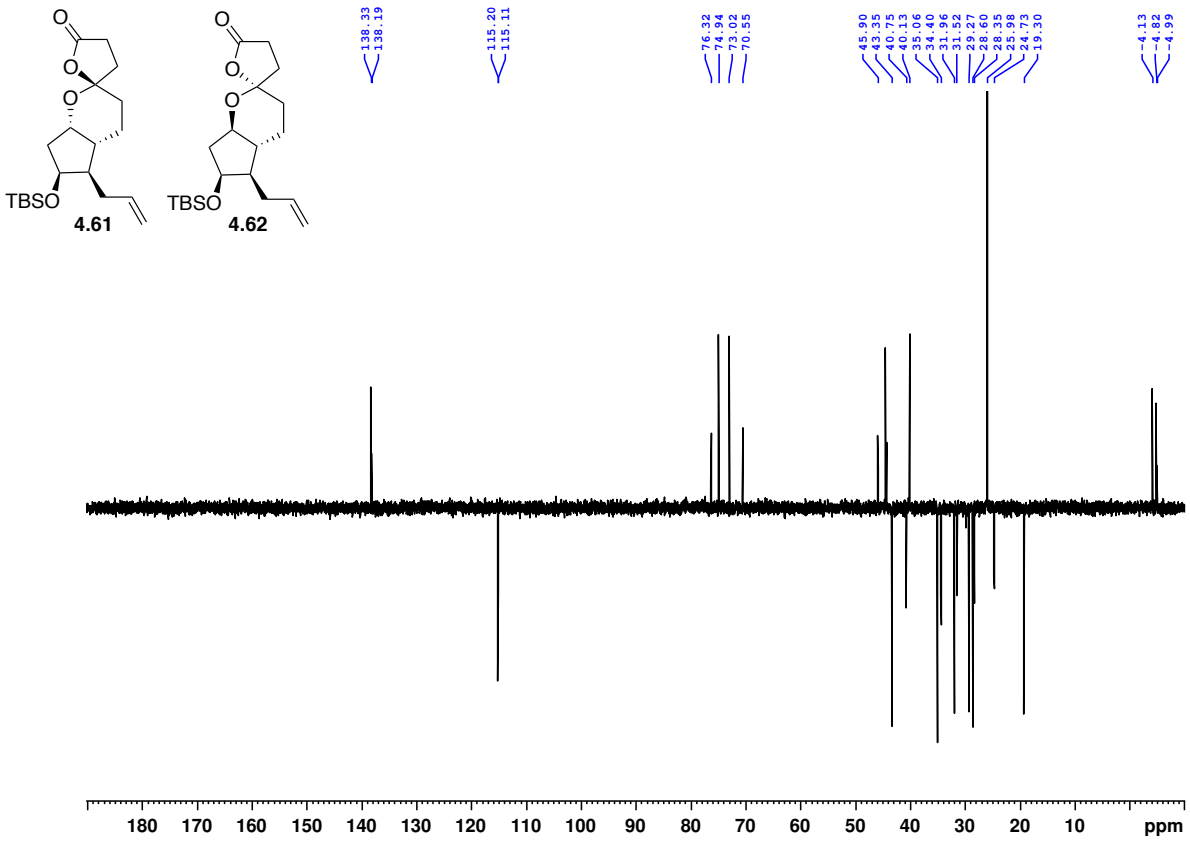


Figure A.4.37 DEPT-135 NMR (150 MHz, $CDCl_3$) of **4.61** and **4.62**

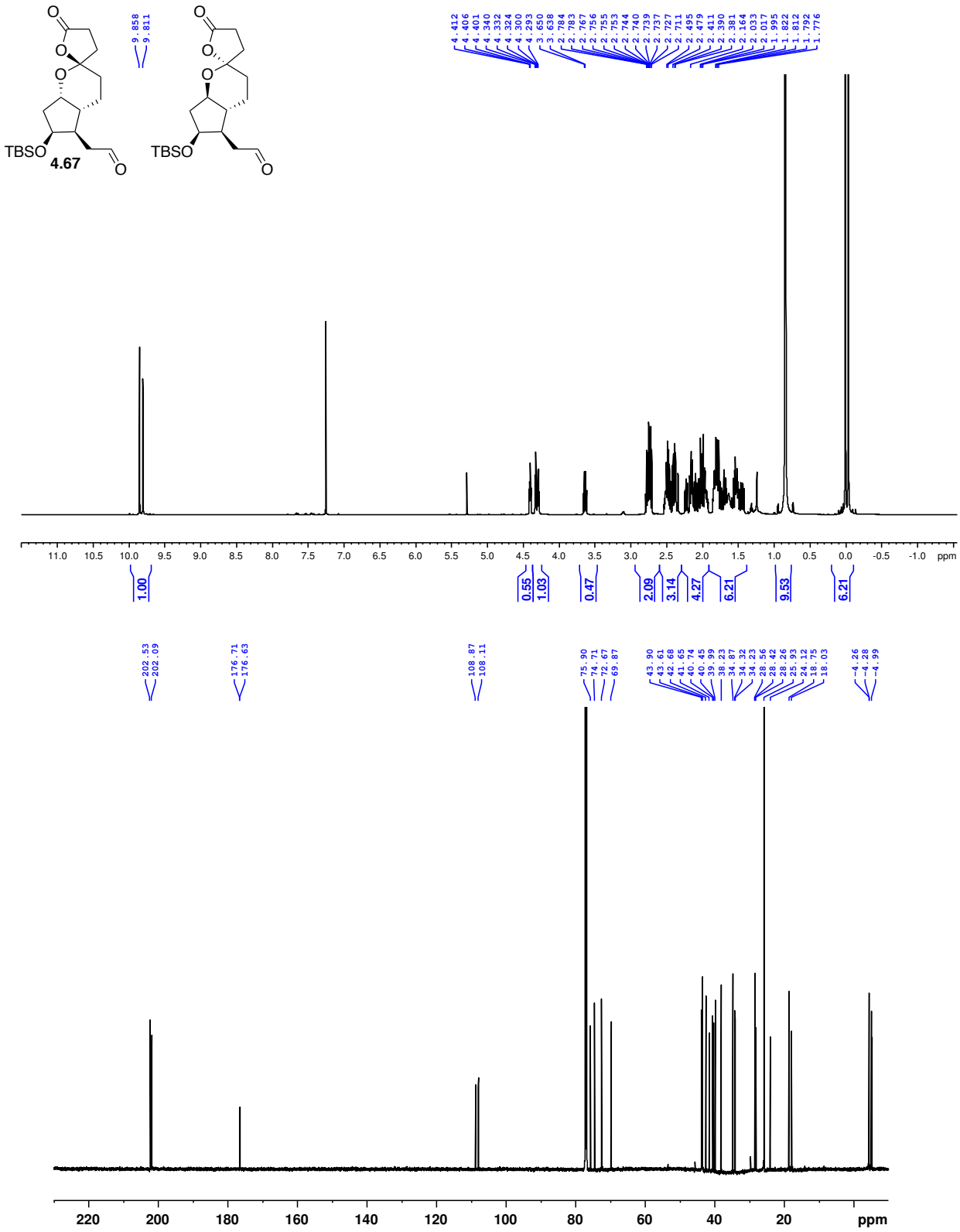


Figure A.4.38 ^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of **4.67**

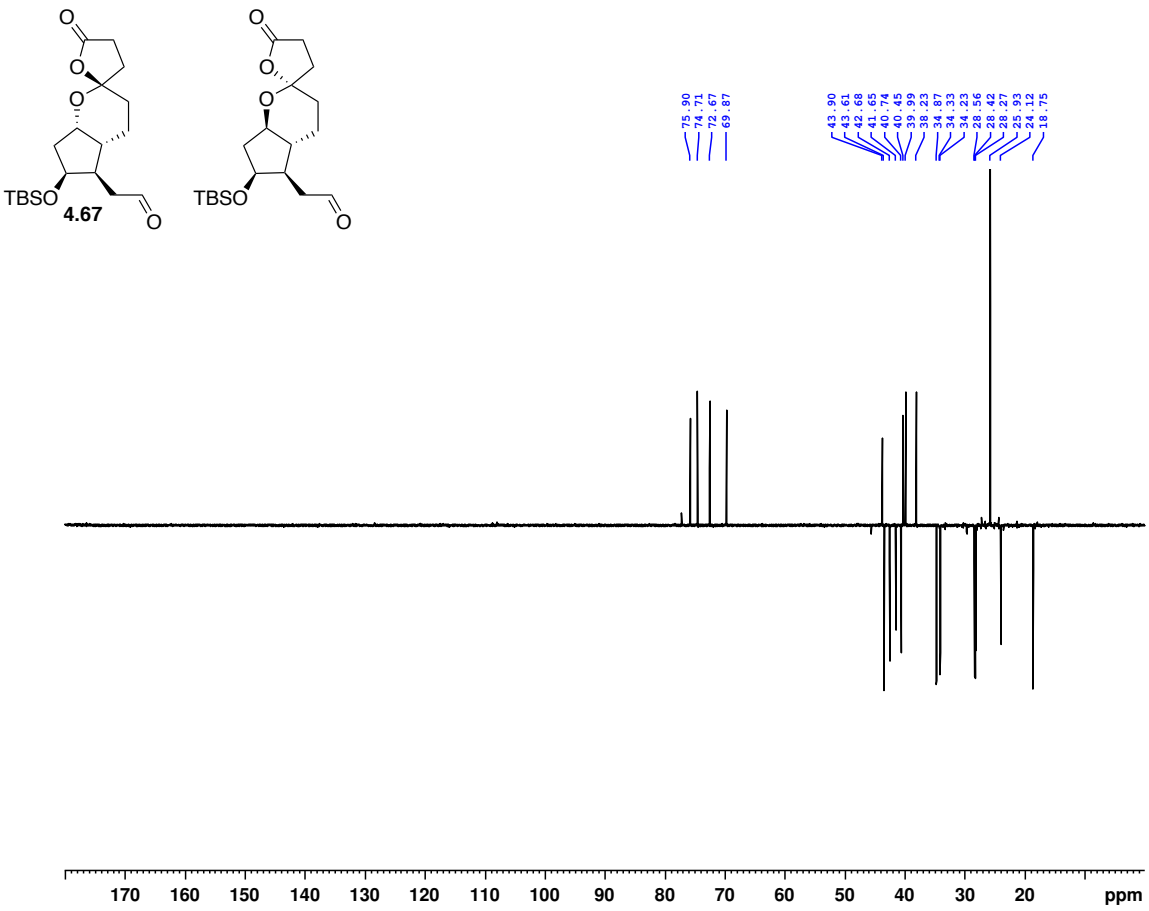


Figure A.4.39 DEPT-135 NMR (150 MHz, $CDCl_3$) of **4.67**

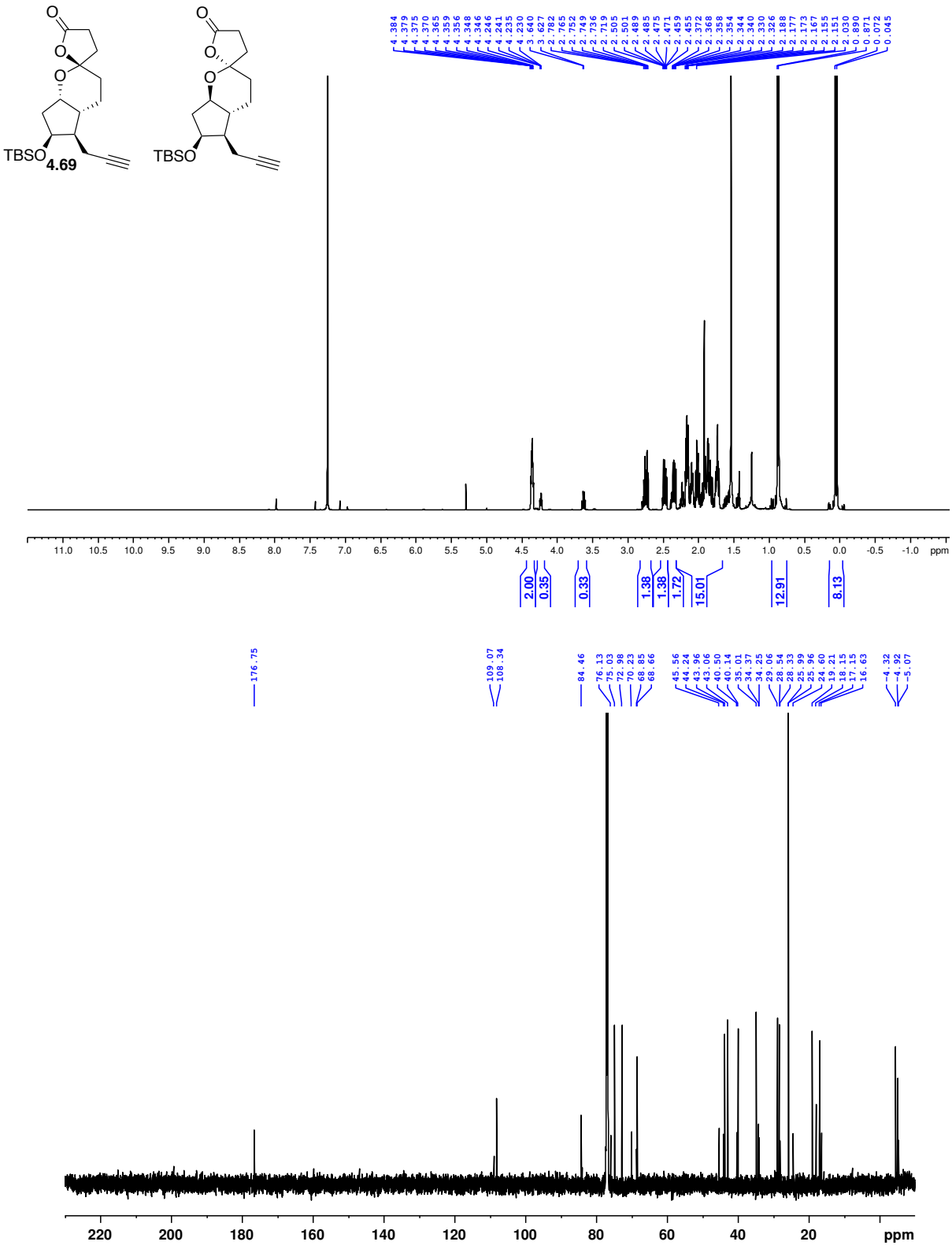


Figure A.4.40 ^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of **4.69**

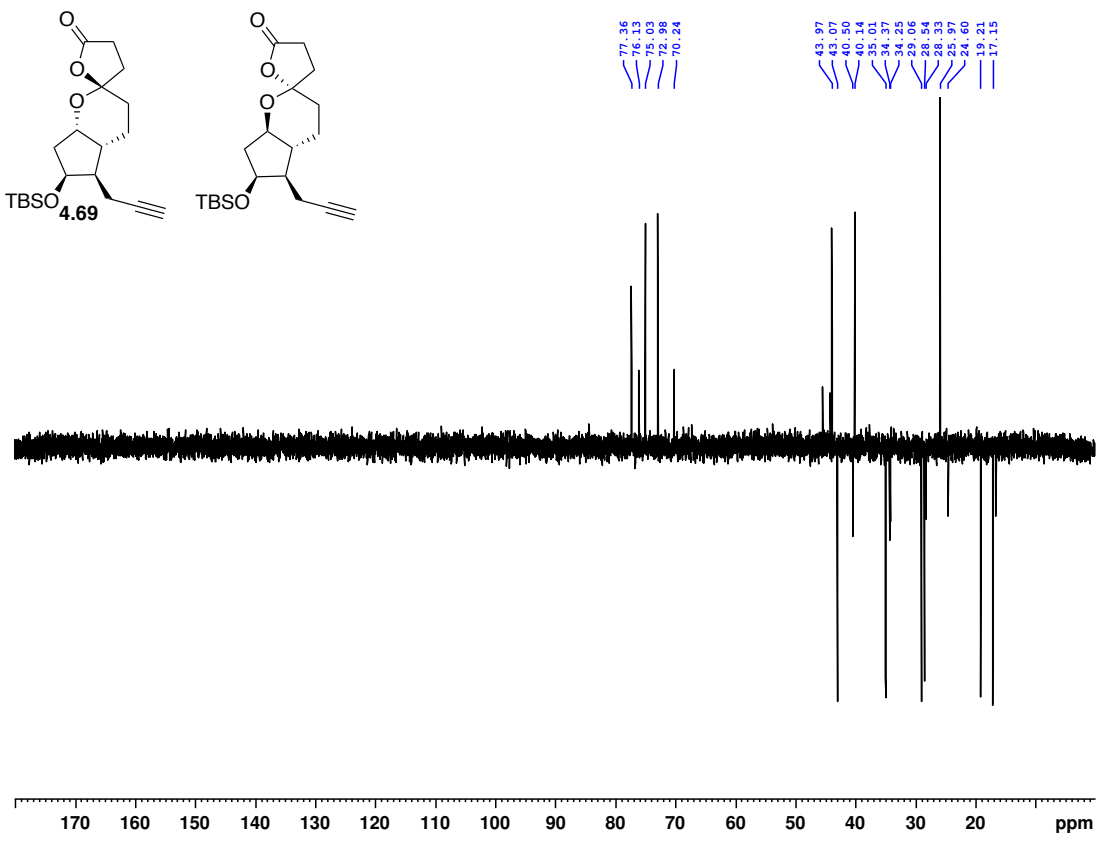


Figure A.4.41 DEPT-135 NMR (150 MHz, $CDCl_3$) of **4.69**

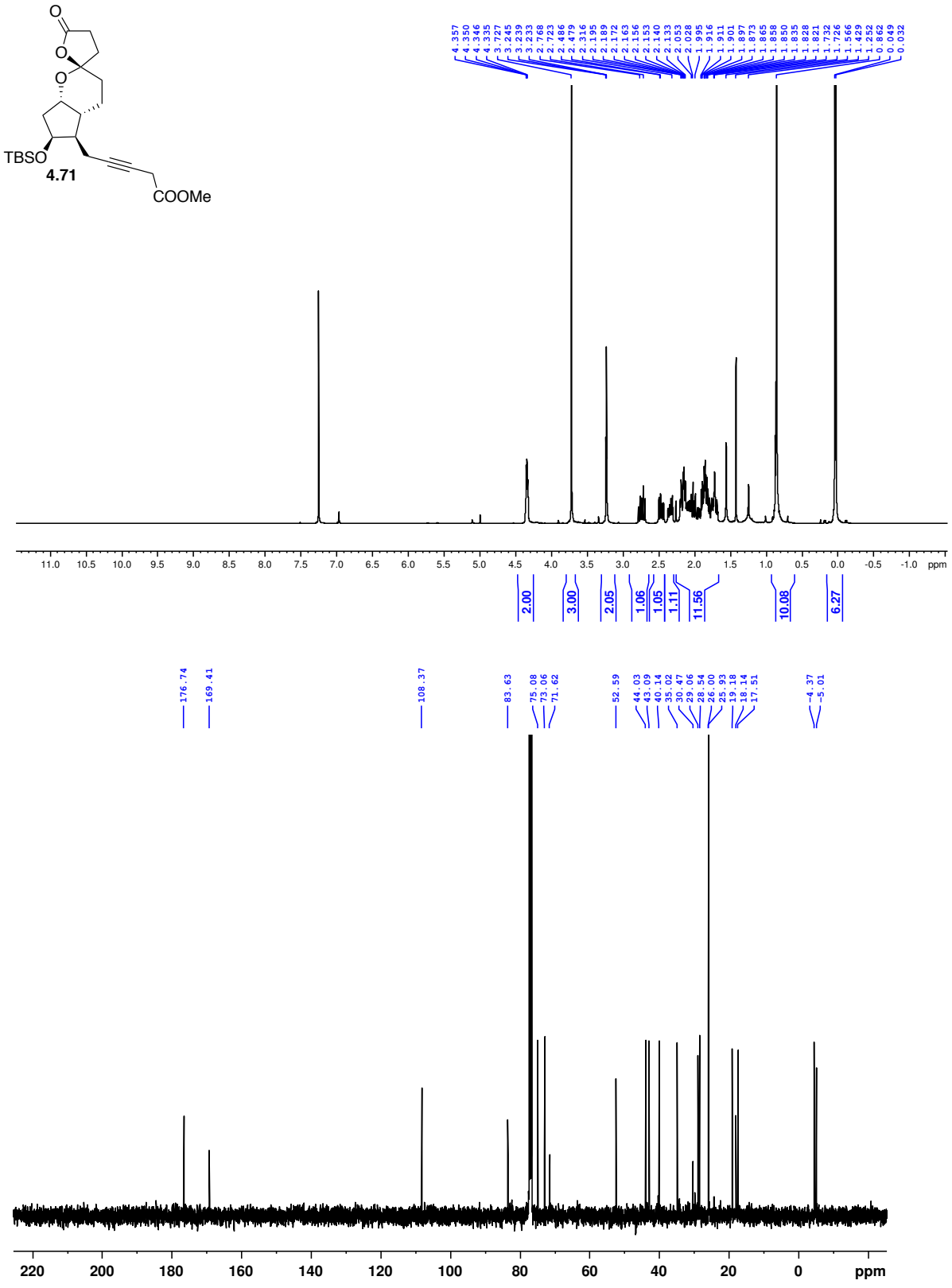


Figure A.4.42 ^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of **4.71**

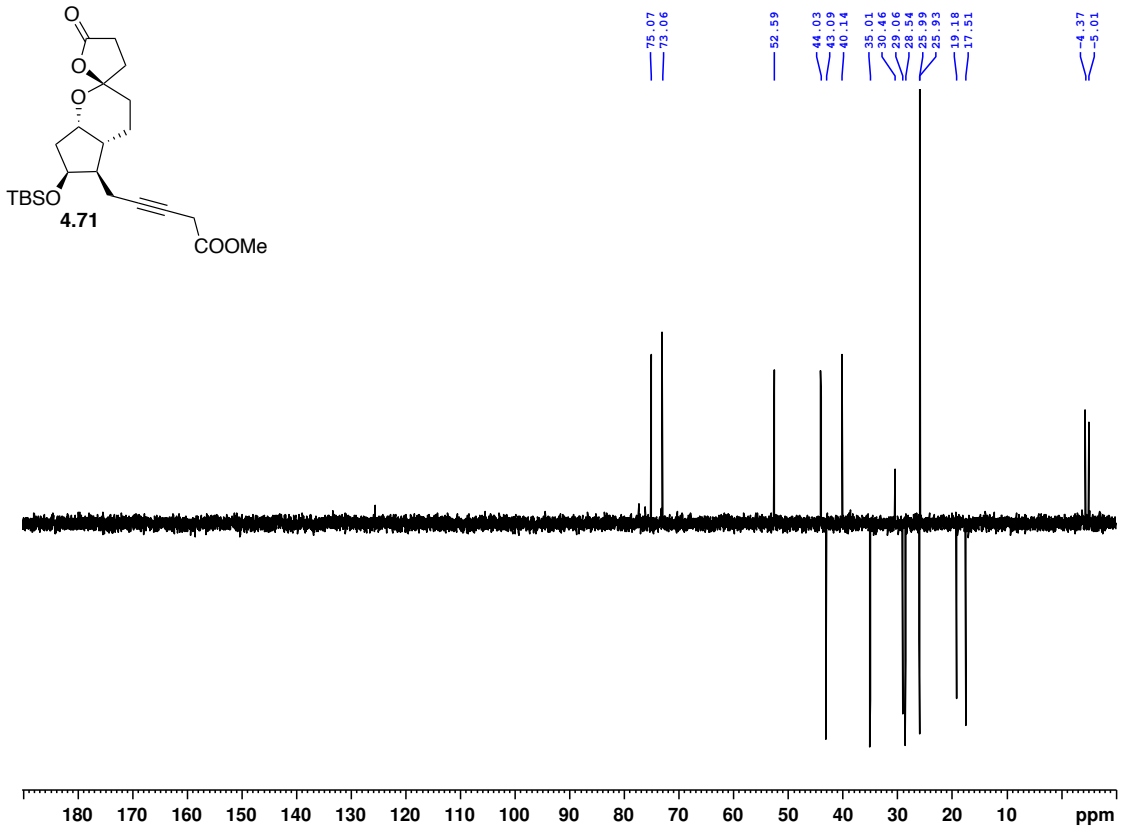


Figure A.4.43 DEPT-135 NMR (150 MHz, CDCl3) of **4.71**

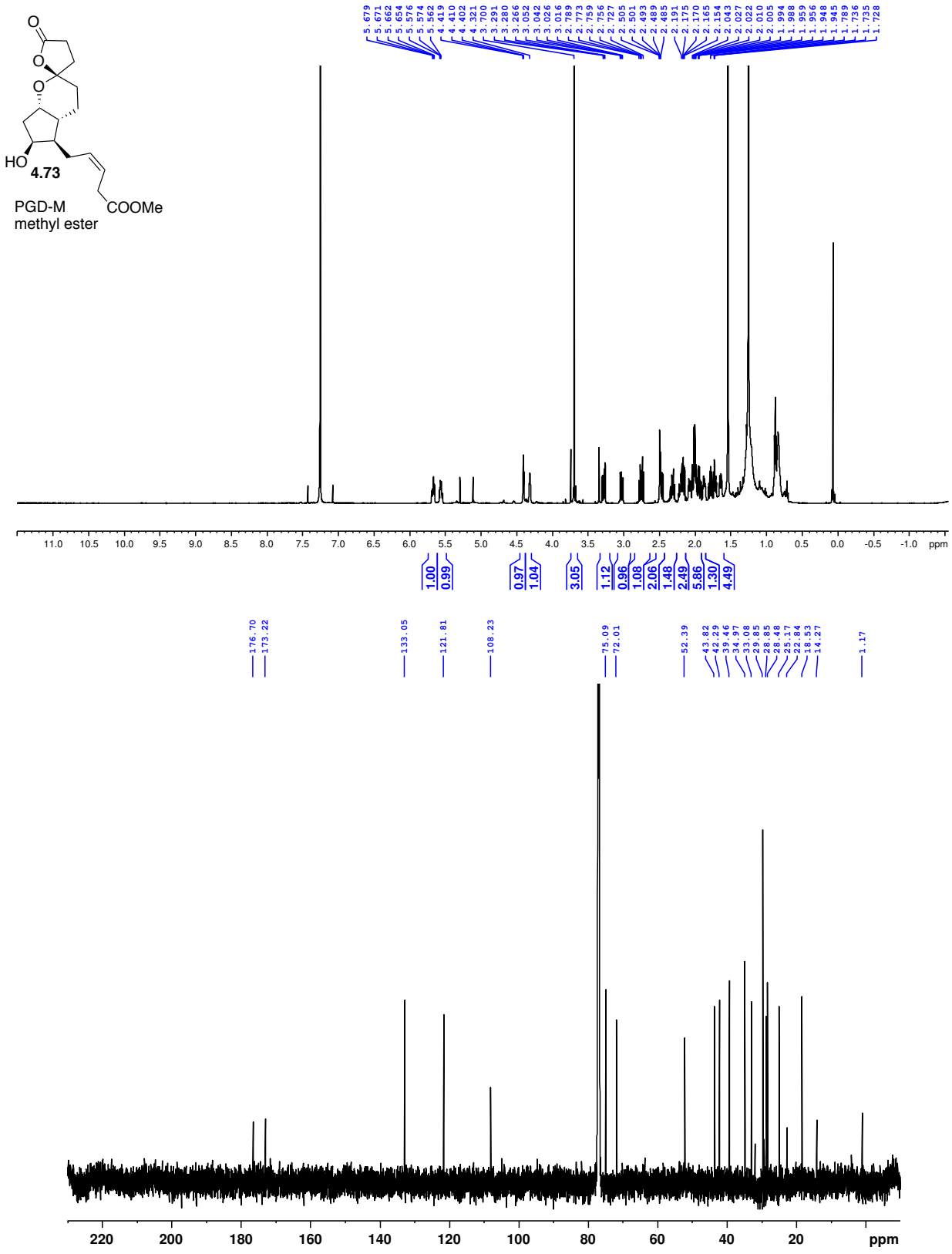


Figure A.4.44 ^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of **4.73**

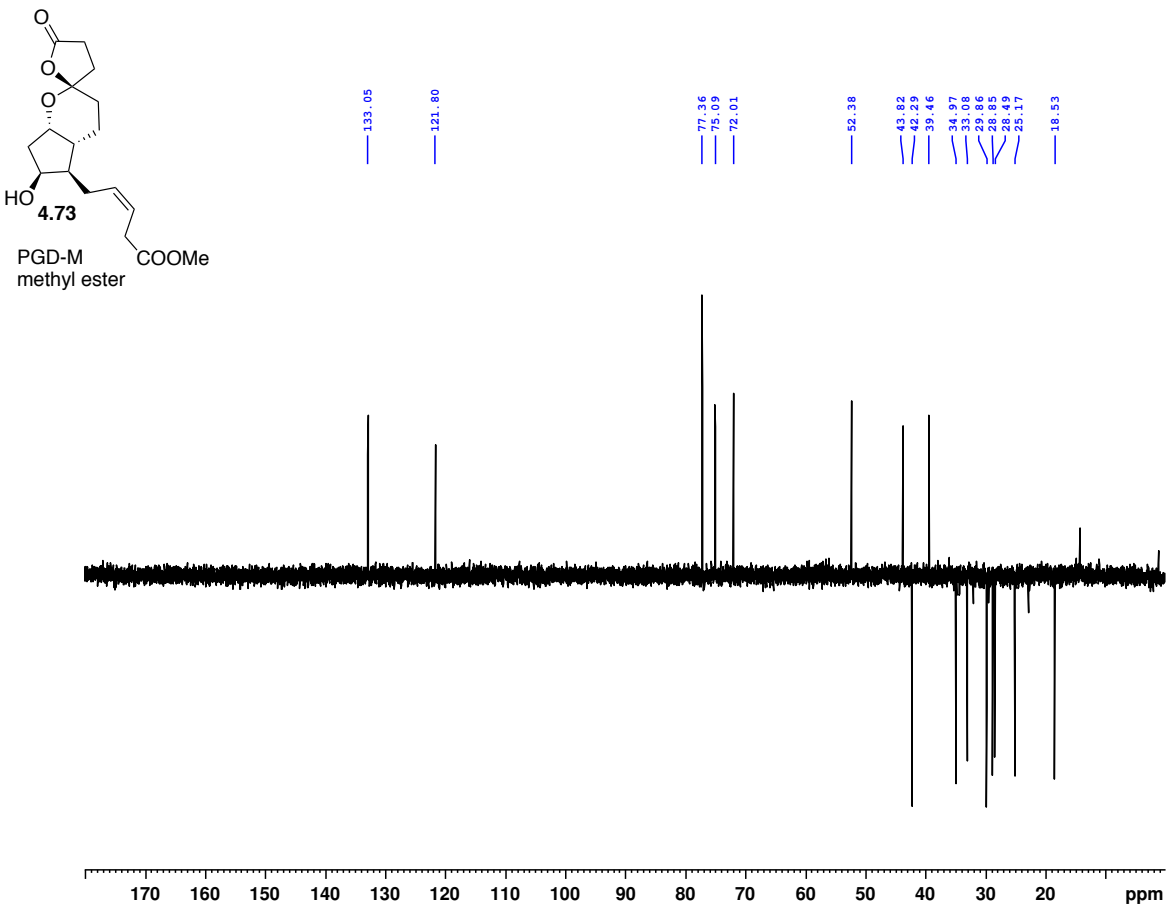


Figure A.4.45 DEPT-135 NMR (150 MHz, $CDCl_3$) of **4.73**

CHAPTER 5

EXPLORATIONS INTO ALTERNATIVE CHEMICAL ROUTES TO PGD-M

Introduction and Retrosynthetic Analysis

While we were pleased to obtain **5.2** with the desired *trans, cis* relationship via the key Sakurai allylation[1] employed in Route A, (Figure 5.1) we examined other approaches to installing the four contiguous stereocenters within the cyclopentanone core of PGD-M. We aimed to devise a new route that would allow for access to the desired *trans, cis* cyclopentanone **5.2** in higher yield without the production of the *cic, cis* cyclpentanone **5.3**, which accounted for 41% of the product yield.

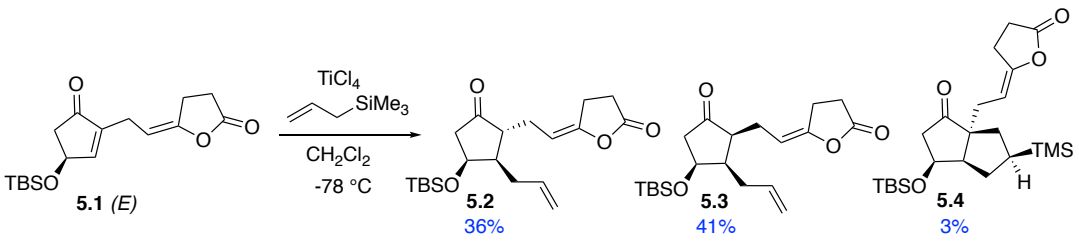


Figure 5.1: Allylation under Sakurai conditions

Rethinking the retrosynthetic analysis

As discussed in Chapter 4, we envisioned several routes to access *trans, cis* cyclopentanone **5.2**. Specifically, Route B, (Figure 5.2) which utilized a *cis*-selective intramolecular C-H insertion followed by a Tsuji-Trost decarboxylative-allylation of **5.6** and Route C, which featured an intramolecular Ueno-Stork radical cyclization[3] of **5.8**. (Route C) As both routes found ample literature precedent for establishing the C3-C4 *cis* relationship, we thought it prudent to examine what may prove to be more efficient access to cyclopentanone **5.2.**

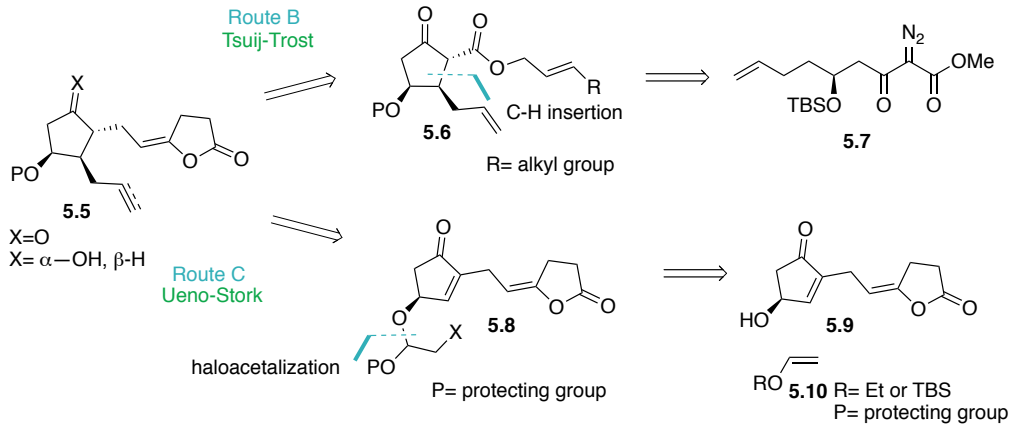


Figure 5.2: Retrosynthetic analysis

Progress Towards Cyclopentanone 5.2 Via Route B

Literature Precedence

Carriera recently disclosed a method to rapidly introduce *trans,cis* stereochemistry around a cyclopentanone core en route to the synthesis of PGJ_2. (Figure 5.3)[4] A truncated analogue of **5.10** bearing a terminal allyl group had also been previously prepared by Yakura and coworkers[5] and we recognized that this substrate would serve as a good model system for the challenging Tsuji-Trost decarboxylative allylation.

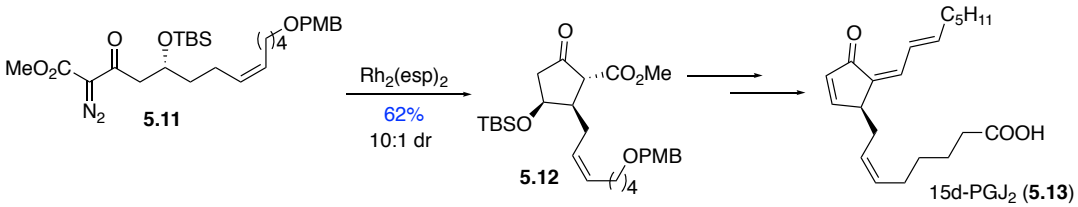
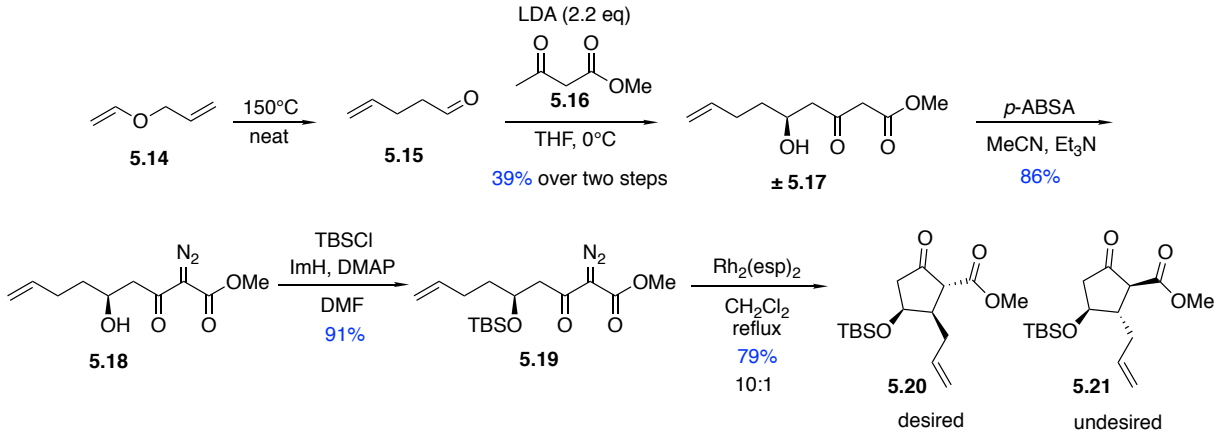


Figure 5.3: Carriera's route to 15-PGJ_2

Synthesis of β–ketoester 5.20

The synthesis of β–ketoester **5.20** commenced with the Claisen rearrangement of allyl vinyl ether to afford the aldehyde **5.15**. Addition of the aldehyde to the *in situ* generated Weiler dianion[6] of **5.16** rendered racemic aldol product **5.17**. Diazotransfer using *p*-ABSA and subsequent silyl protection of the derived alcohol provided the α–diazoester **5.18** required for the stereoselective, intramolecular C-H insertion with rhodium(II). The insertion reaction proceeded in good yield and diastereoselectivity with a 10:1 dr, favoring the desired *trans*, *cis* β–ketoester **5.20** over the *trans*, *trans* β–ketoester **5.21** and the two esters were chromatographically separable.



Scheme 5.1: Synthesis of β–ketoester 5.20

The *cis* diastereoselectivity has been proposed to be the result of the transition state shown in Figure 5.4.[7] One plausible explanation involves participation of the silicon in the pseudoaxial TBS ether participating in a weak Si-O interaction with the oxygen on the highlighted carbonyl. Literature precedence of siloxy groups in cyclohexanones preferring to be pseudoaxial support this proposal.[8]

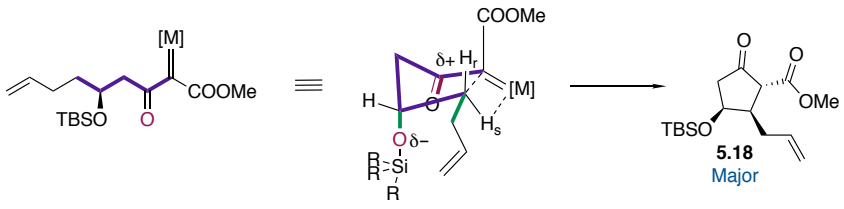
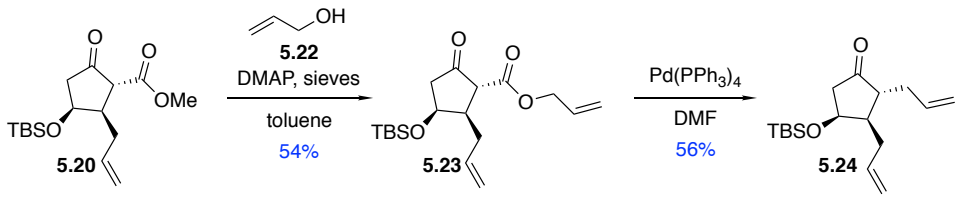


Figure 5.4: Transition state for diastereoselective cyclization

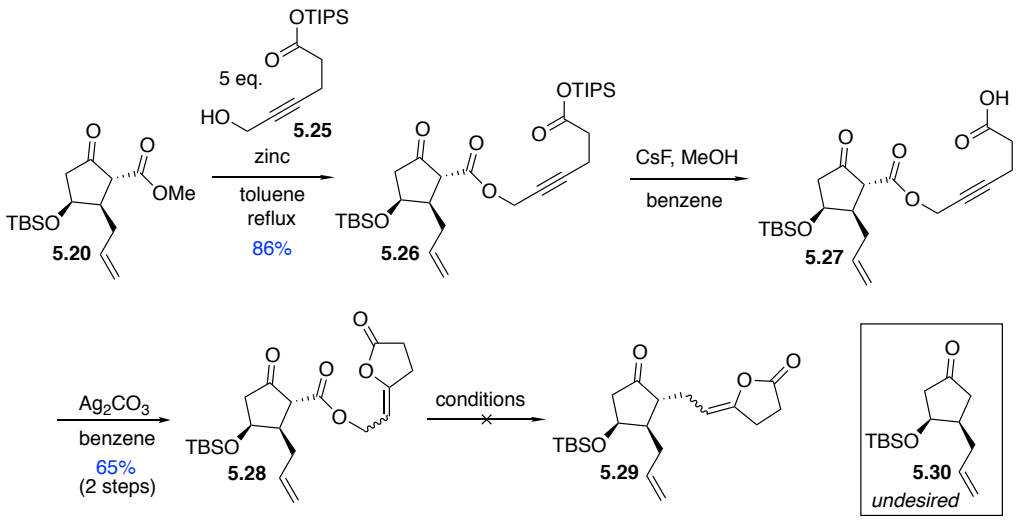
Tsuji-Trost Attempts

We first set out to explore the viability of the Tsuji-Trost with β-keto allyl ester **5.23**. Transesterification of methyl ester **5.20** occurred upon treatment with allyl alcohol **5.22** and DMAP.[9] Much to our satisfaction, the allyl ester product **5.23** readily underwent the desired decarboxylative allylation to afford the trisubstituted cyclopentanone **5.24** as a single isomer. The stereochemistry around the cyclopentane core was unconfirmed, but we tentatively assigned the stereochemistry as *trans, cis* due to the ring strain that would result from the *cis, cis* isomer.



Scheme 5.2: Decarboxylative allylation on a model system

Encouraged by these favorable results, we then set out to extend this reaction to a more complicated substrate incorporating the needed lactone. To this end, treatment of *trans*, *cis* β-keto ester **5.20** with propargyl alcohol **5.25** and zinc resulted in diester **5.26** (Scheme 5.3). Mild deprotection of the TIPS ester with CsF and subsequent silver mediated *5-exo-dig* cyclization provided the target framework for the anticipated decarboxylative allylation. Several reaction conditions were explored, but unfortunately, none proved to be successful. Every attempt resulted in either recovered starting material or decomposition of starting material except for Entry 5, which resulted in mostly decomposition and trace amounts of undesired decarboxylation product **5.30.**

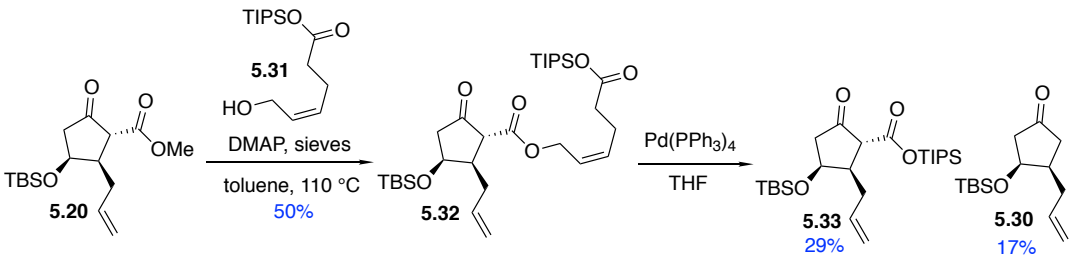


Scheme 5.3: Tsuji-Trost toward *trans,cis* cyclpentanone 5.29

Entry	Catalyst	Solvent	Temperature
1	$Pd(Ph_3)_4$	DMF	room temperature
2	$Pd(OAc)_2$, PPh_3	THF	65 °C
3	$Pd_2(dba)_3$	DMF	room temperature
4	$Mo(CO)_6$	toluene	110 °C
5	$Pd_2(dba)_3$	NMP	65 °C

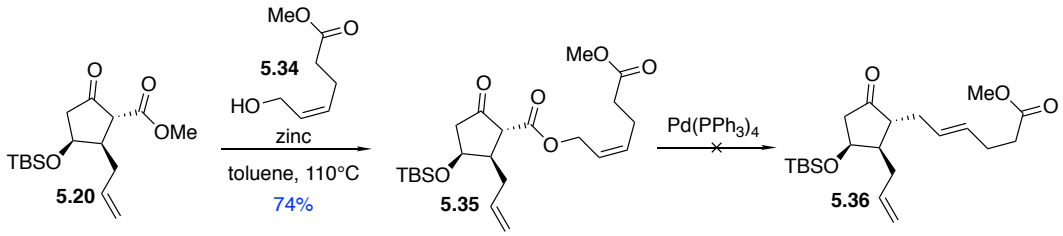
Table 5.1 Conditions for Tsuji-Trost

We hypothesized that we were unable to execute the more complex decarboxylative allylation due to the unfavorable electronics of the lactone moiety. With this in mind, we modified the substrate for the Tsuji-Trost and attempted the reaction on TIPS ester **5.32**. (Scheme 5.4) In this case, instead of desired allylation product, we observed TIPS ester **5.33** and decarboxylation product **5.30**.



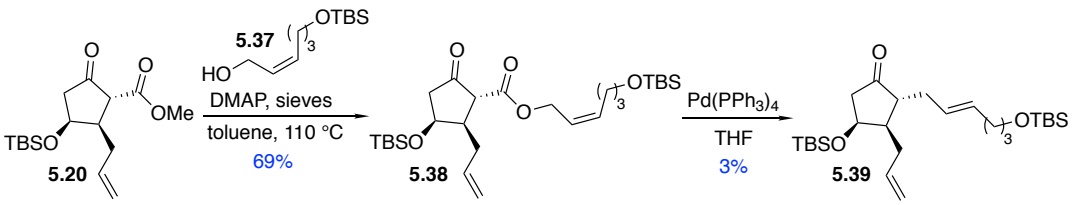
Scheme 5.4: Tsuji-Trost reaction with TIPS ester

Due to the undesired migration of the TIPS group, we then exchanged the TIPS ester for a methyl ester and prepared methyl ester **5.35** in acceptable yields. Unfortunately, treatment with $Pd(PPh_3)_4$ resulted in mostly recovery of starting material and decomposition.



Scheme 5.5: Tsuji Trost with methyl ester **5.20**

Simplifying the scaffold even further, when TBS ether **5.37** was prepared and subsequently treated with $Pd(PPh_3)_4$ we finally observed the desired product **5.38**, albeit in a very modest 3% yield (Scheme 5.6). As we considered trying to optimize this result, we began to recognize that transformation of **5.39** into the alkylidene lactone of **5.2**, or its equivalent, would require a series of nontrivial transformations. That realization, coupled with the 3% yield, led us to abandon the Tsuji-Trost route



Scheme 5.6: Tsuji Trost with TBS ether

Progress Towards Cyclopentanone 5.2 Via Route C

In another attempt to improve upon the key allylation of Route A, we explored options to introduce the β–substituent intramolecularly. The radical mediated *5-endo-trig* cyclization (Figure 5.5) onto a cyclopentene reported by Stork in his synthesis of PGF_{2a} (see Chapter 2)[10] exclusively provided **5.43** with a *cis* relationship of the substituents at the 1 and 2 positions. We sought to apply this methodology to our synthesis of PGD-M.

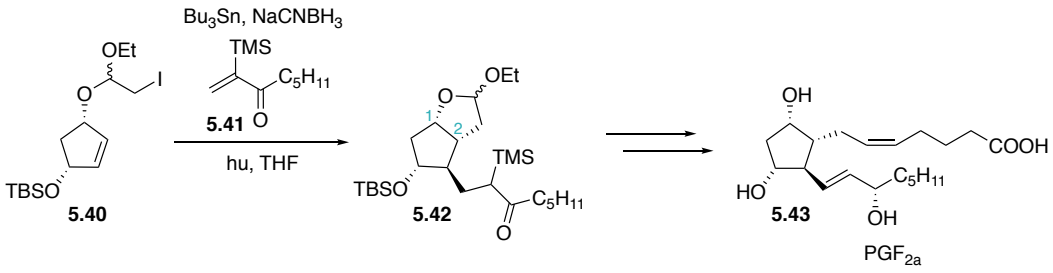
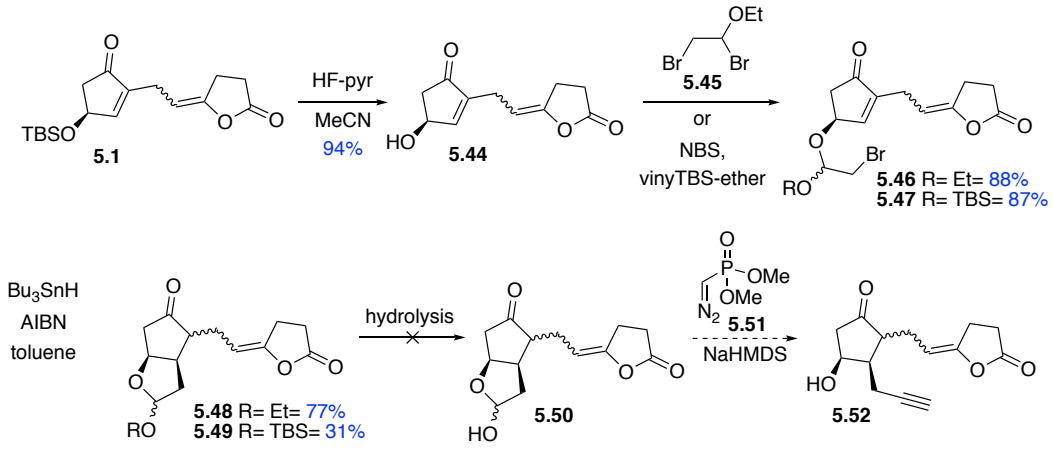


Figure 5.5: Stork's radical cyclization en route to PGF_{2a}

Investigation of the 5-endo-trig cyclization on varying substrates

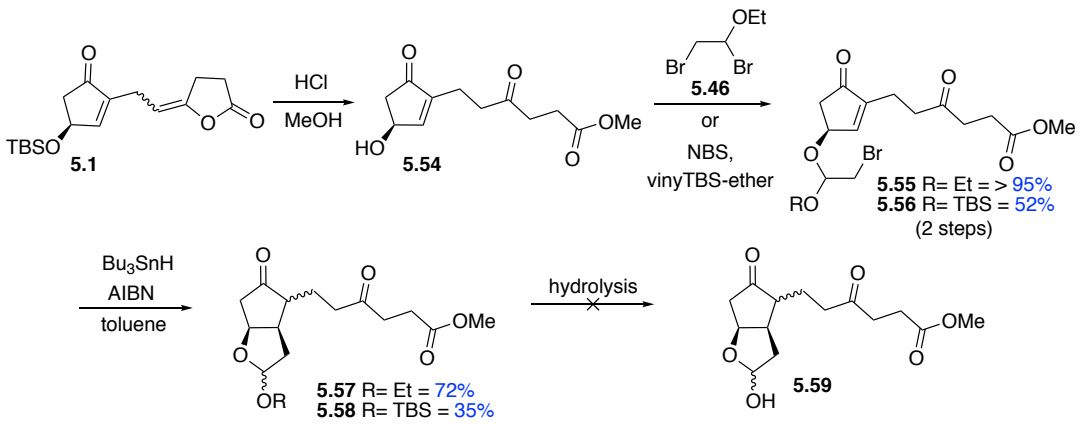
Beginning from γ-alkylidene lactone **5.1**, deprotection with HF pyridine provided the allylic alcohol **5.44** in good yield. Alkylation with dibromide **5.45** or haloetherification with TBS-vinyl ether afforded either ethyl acetal **5.46** or TBS acetal **5.47**, respectively. In each case, an inconsequential mixture of acetals was produced. *5-endo-trig* cyclization onto the enone provided a mixture of diastereoemers. We hoped to achieve a degree of selectivity at the α– position due to

the relationship of the β and γ substituents, but with a potential 8 diastereomers present in the cyclized product, spectral data was exceedingly difficult to discern. In each case, we combined all of the isomers and attempted to hydrolyze the acetal to the lactol which we could further manipulate to the alkyne via homologation with **5.51**, thus eliminating a stereocenter and deconvoluting the results. Unfortunately, efforts to hydrolyze the acetal and remove the TBS group proved unsuccessful and resulted in decomposition.



Scheme 5.7: First Generation Radical Cyclization Route

In an effort to simplify the analysis of the diastereomers, the lactone moiety was opened with acidic methanol (Scheme 5.8). Ethyl acetal **5.55** and TBS acetal **5.56** were both prepared in good yield, before *5-endo-trig* cyclization onto the enone produced [3.3.0] bicycles **5.57** and **5.58**. Disappointingly, the cyclization resulted in approximately a 1:1 mixture of diastereomers at the α-position. Still, we attempted to hydrolyze the ethyl acetal with acidic methanol and the TBS-acetal with TBAF and HF-pyridine. Unfortunately, all attempts resulted in either recovery of starting material or β-elimination.



Scheme 5.8: Second Generation Radical Cyclization Route

Conclusion of Routes B and C

Though neither of these routes were ultimately successful in accessing **5.2**, each route had minor successes and allowed for exploration of chemical methodology not previously encountered in Route A. Routes B and C both showed potential, but we conceded that Route A was clearly superior and consequently the allylation of enone **5.1** under Sakurai conditions was employed in our route towards PGD-M.

Experimental Methods

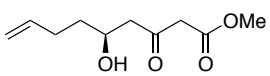
General Procedure: All non-aqueous reactions were performed in flame-dried or oven dried round-bottomed flasks under an atmosphere of argon. Stainless steel syringes or cannula were used to transfer air- and moisture-sensitive liquids. Reaction temperatures were controlled using a thermocouple thermometer and analog hotplate stirrer. Reactions were conducted at room temperature (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 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, or Sure-Seal Sigma reagent bottles. Unless indicated, all commercial reagents were used as received without further purification. The molarity of *n*-butyllithium solutions was determined by titration using *n*-benzylbenzamide 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), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded on Bruker 100 or 150 MHz spectrometers and are reported relative to deuterated solvent signals. Optical rotations were measured on a Perkin-Elmer 341 digital polarimeter at ambient temperature. High-

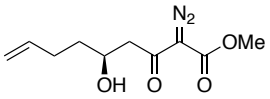
resolution mass spectra were obtained from the Department of Chemistry and Biochemistry, University of Notre Dame.

Compound Preparation



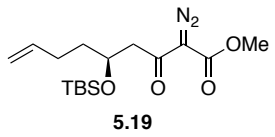
± 5.17

β-keto ester (5.17): To a solution of diisopropylamine (3.03 mL, 21.6 mmol) in THF (46 mL) at 0 °C was added nBuLi (1.90 M in hexanes)(11.89 mL, 22.6 mmol) dropwise. The solution stirred for 20 min at 0 °C before methyl acetoacetate (1.14 mL, 10.6 mmol) was added dropwise. The solution turned bright yellow and stirred at 0 °C for 20 min, before the aldehyde (1.15 mL, 11.6 mmol) was added dropwise and the solution stirred for an additional 20 min at which point the reaction was then quenched with sat. aq. NH_4Cl (30 mL), extracted with EtOAc (3 x 50 mL). The organic extracts were washed with brine (40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resultant residue was purified by flash column chromatography (silica gel, gradient elution, 35 to 50% EtOAc in hexanes) to yield 933 mg (40%) of the β-keto ester **5.17** as a colorless oil. Spectral data matched reported literature values.[5]



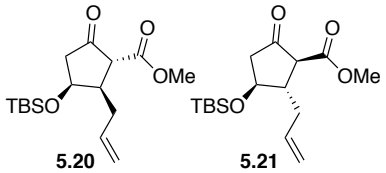
5.18

α-diazomethylester (5.18): To a solution of alcohol **5.17** (775 mg, 3.87 mmol) in MeCN (75 mL) at room temperature was added p-ABSA (1.39 g, 5.81 mmol) and Et_3N (1.08 mL, 7.74 mmol). The mixture stirred at room temperature for 4 h, at which point it was concentrated *in vacuo*, redissolved in CH_2Cl_2 (20 mL), filtered and concentrated *in vacuo*. The resultant residue was purified by flash column chromatography (silica gel, gradient elution, 15 to 25 % Et_2O in hexanes) to yield 746 mg (86%) of the α-diazomethylester **5.18** as a colorless oil. Spectral data matched reported literature values.[5]



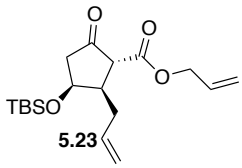
5.19

TBS protected diazoester (5.19): To a solution of α-diazomethylester **5.18** (492 mg, 2.20 mmol) in DMF (7.5 mL) at 0 °C was added TBSCl (397 mg, 2.60 mmol), ImH (219 mg, 4.40 mmol) and DMAP (13 mg, 0.110 mmol). The reaction was allowed to slowly warm to room temperature and stirred for 8 h at which point additional ImH (110 mg, 2.20 mmol) was added and the reaction stirred at room temperature overnight before it was quenched with H_2O (10 mL). The product was extracted from the aqueous layer with Et_2O (3 x 15 mL) and the combined extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resultant residue was purified by flash column chromatography (silica gel, 5% EtOAc in hexanes) to yield 670 mg (90%) of the TBS protected diazoester **5.19** a colorless oil. Spectral data matched reported literature values.[5]



5.20 5.21

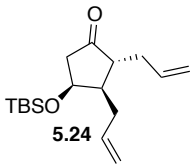
β- keto esters (5.20) (5.21): To a refluxing solution of Rh_2esp_2 (16 mg, 0.021 mmol) in CH_2Cl_2 was added diazoester **5.19** (0.700 mg, 2.06 mmol) in CH_2Cl_2 (30 mL) dropwise over 1 h before stirring at reflux for 1 h. It was then allowed to warm to room temperature and concentrated *in vacuo*. The resultant residue was purified by flash column chromatography (silica gel, gradient elution, 2 to 5% EtOAc in hexanes) to yield 542 mg (84%) of the β- keto esters **5.20** and **5.21** as a separable 10:1 mixture of diastereomers. Spectral data matched reported literature values.[5]



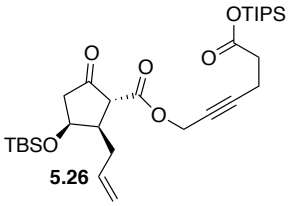
5.23

allyl ester (5.23): To a solution of β- keto ester **5.20** (121 mg, 0.360 mmol) in toluene (1.0 mL) at room temperature was added allyl alcohol (88 μL, 1.30 mmol) and zinc (7 mg, 0.104 mmol). The solution was heated to 100 °C for 7 h, at which point it was allowed to cool to room temperature before it was loaded directly onto

the flash column for purification (silica gel, 5% EtOAc in hexanes) to yield 71 mg (56 %) of the allyl ester **5.23** as a colorless oil. ^{1}HNMR (400 MHz, $CDCl_3$) 6.0- 5.89 (m, 1H), 5.87-5.74 (m, 1H), 5.32 (dd, *J* = 17.0, 60 Hz, 2H), 5.09 (dd, *J* = 17.3, 49.0), 4.70- 4.61 (m, 1H), 4.46 (t, *J* = 3.8, 1H) 3.20 (d, *J* = 11.8 Hz, 1H), 2.72- 2.64 (m, 1H), 2.53 (dd, *J*= 4.1, 18.1, 1H), 2.49- 2.21 (m, 4H), 0.89 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H). δ CNMR (100 MHz, $CDCl_3$) δ 209.8,169.4, 135.7, 131.9, 118.8, 117.1, 69.7, 66.1, 57.8, 49.3, 47.4, 33.7, 25.9, 25.9, 25.8, 18.1, -4.3, -4.8.

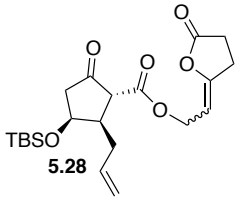


diene (5.24): To a solution of allyl ester **5.23** (51 mg, 0.151 mmol) in DMF (1.0 mL) at room temperature was added $Pd(PPh_3)_4$ (9 mg, 0.008 mmol). The reaction stirred at room temperature for 20 h, at which point it was diluted in EtOAc (5 mL), washed with brine (1 mL), dried ($MgSO_4$), filtered and concentrated. The resultant residue was purified by flash column chromatography (silica gel, gradient elution 0 to 10% EtOAc in hexanes) to yield 25 mg (56 %) of diene **5.24** as a colorless oil. ^{1}HNMR (400 MHz, $CDCl_3$) 6.0-5.72 (m, 2H), 5.22- 4.93 (m, 4H), 4.45- 4.39 (m, 1H), 2.55- 2.23 (m, 7H), 0.90 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H). CNMR (100 MHz, $CDCl_3$) δ 218.5, 137.4, 137.1, 116.2, 115.8, 71.4, 50.3, 48.0, 45.7, 31.9, 30.0 25.9, 18.1, -4.4, -4.9.



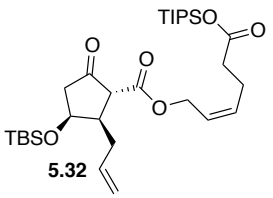
β- keto propargyl ester (5.26): To a solution of β- keto methylester **5.20** (103 mg, 0.331 mmol) in toluene (0.2 mL) was added the propargyl alcohol (471 mg, 1.66 mmol) in toluene (0.4 mL) and zinc (4 mg, 0.066 mmol). The solution was heated to reflux and heated for 6 h at which point it was allowed to cool to room temperature before it was loaded directly onto the flash column for purification (silica gel, gradient elution, 2 to 30% EtOAc in hexanes) to yield 186 mg (86%) of β- keto propargyl ester

5.26 as a colorless oil. ^{1}HNMR (400 MHz, $CDCl_3$) δ 5.90- 5.75 (m, 1H), 5.11 (dd, *J* = 16.8, 39.5, 2H), 4.78- 4.66 (m, 1H), 4.47 (t, *J* = 3.6 Hz, 1H), 3.24 (d, *J* = 12.1 Hz, 1H), 2.75- 2.09 (m, 9H), 1.38- 1.25 (m, 3H), 1.1 (t, *J = 7.1,* 18H), 0.91 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H). CNMR (100 MHz, $CDCl_3$) δ 209.3, 171.8, 169.1, 135.6, 117.0, 86.3, 74.3, 69.7, 57.6, 53.6, 49.3, 47.4, 34.9, 33.7, 25.8, 18.1, 17.8, 15.2, 12.0, -4.4, -4.9.

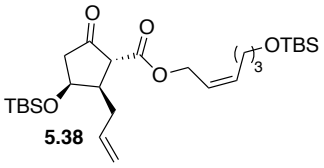


5.28

lactone (5.28): To a solution of the β- keto propargyl ester **5.26** (0.100 g, 0.177 mmol) in benzene (10.0 mL) at room temperature was added a solution of CsF (52 mg, 0.354 mmol) in MeOH (8.0 mL) dropwise. The reaction stirred at room temperature for 2 h, at which point additional CsF (52 mg, 0.354 mmol) was added. The reaction then stirred for 2 h before it was diluted in CH_2Cl_2 (40 mL), washed with sat. aq. KH_2PO_4 (20 mL), extracted with CH_2Cl_2 (3 x 20 mL), washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. To a solution of the resultant residue in benzene (3.0 mL) at room temperature was added Ag_2CO_3 (10 mg, 0.037 mmol). The reaction was heated to reflux and stirred for 10 h, at which point it was filtered through Celite and concentrated *in vacuo*. The resultant residue was purified by flash column chromatography (silica gel, gradient elution, 5 to 30% EtOAc in hexanes) to yield 47 mg (65%) of the lactone **5.28** as a 3:1 *Z:E* mixture of diastereomers. ^{1}HNMR (400 MHz, $CDCl_3$) δ 5.85 -5.71 (m, 1H), 5.40 (tt, *J* = 7.9, 2.1 Hz, 0.25H), 5.05 (dd, *J* = 18.4, 21.1 Hz, 2H), 4.87 (t, *J* = 7.5 Hz, 0.75H), 4.83- 4.69 (m, 2H), 4.43 (t, *J* = 3.4 Hz, 1H), 3.15 (d, *J* = 11.5 Hz, 1H), 3.06- 2.83 (m, 2H), 2.74- 2.59 (m, 3H), 2.51 (dd, *J* = 4.2,18.1 Hz, 1H), 2.44- 2.22 (m, 3H), 0.86 (s, 9H), 0.07 (s, 3H), 0.07 (s, 3H). CNMR (100 MHz, $CDCl_3$) δ 209.7, 174.1, 169.5, 152.5, 135.7, 98.9, 69.7, 59.6, 57.8, 49.3, 47.3, 33.8, 33.7, 27.4, 27.2, 25.8, 25.2, 22.9, 18.1, 1.2, -4.3, -4.8.

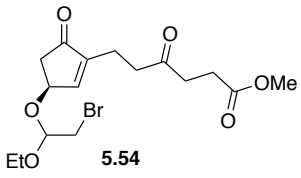


silyl ester (5.32): To a solution of β- keto methylester **5.20** (50 mg, 0.160 mmol) in toluene (0.5 mL) at room temperature was added molecular sieves (65 mg), a solution of the allylic alcohol (138 mg 0.480 mmol) and DMAP (29 mg, 0.240 mmol). The solution was heated to reflux and stirred for 3 h, at which point it was allowed to cool to room temperature. The solution was diluted in EtOAc (2 mL), quenched with 2N HCl (1 mL), extracted with EtOAc (3 x 5 mL), washed with brine (2 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resultant residue was purified by flash column chromatography (silica gel, gradient elution, 5 to 10% EtOAc in hexanes) to yield 45 mg (50%) of the silyl ester **5.32** as a colorless oil. ^{1}HNMR (400 MHz, $CDCl_3$) δ 5.83- 5.70 (m, 1H), 5.71- 5.61 (m, 1H), 5.61- 5.52 (m, 1H), 5.05 (dd, *J* = 17.5, 41.4 Hz, 2H), 4.70 (d, *J* = 6.7 Hz, 2H), 4.45- 4.40 (m, 1H), 3.15 (d, *J* = 12.6, 1H), 2.71- 2.59 (m, 1H), 2.55- 2.32 (7H), 2.31- 2.21 (m, 1H)1.33 – 1.23 (m, 3H), 1.96 (d, *J* = 7.7 Hz, 18H), 0.86 (s, 9H), 0.07 (s, 3H), 0.04 (3H). CNMR (100 MHz, $CDCl_3$) δ 209.8, 172.9, 169.5, 135.7,133.5, 124.5, 117.0, 69.7, 61.2, 57.8, 49.3, 47.4, 35.5, 33.8, 25.8,23.4, 17.9, 12.0, -4.4, -4.8.



allyl ester (5.38): To a solution of β- keto methylester **5.20** (50 mg, 0.160 mmol) in toluene (0.5 mL) at room temperature was added molecular sieves (70 mg), a solution of the allylic alcohol (130 mg 0.565 mmol) and DMAP (29 mg, 0.240 mmol). The solution was heated to reflux and stirred for 2 h, at which point it was allowed to cool to room temperature. The solution was diluted in EtOAc (2 mL), quenched with 2N HCl (1 mL), extracted with EtOAc (3 x 5 mL), washed with brine (2 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resultant residue was purified by flash column chromatography (silica gel, gradient elution, 2 to 5% EtOAc in hexanes) to yield 56

mg (69%) of allyl ester **5.38**. . ^{1}HNMR (400 MHz, $CDCl_3$) δ 5.84- 5.70 (m, 1H), 5.70-5.59 (m, 1H), 5.59-5.48 (m, 1H), 5.05 (dd, *J* = 16.2, 33.2 Hz, 2H), 4.68 (d, *J* = *6.6* Hz, 2H), 4.42 (t, *J* = 3.5 Hz, 1H), 3.60 (t, *J* = 6.3 Hz, 2H), 3.15 (d, *J* = 12.3 Hz, 1H), 2.70- 2.60 (m, 1H), 2.56- 2.32 (m, 3H), 2.32- 2.07 (m, 3H), 1.63- 1.54 (m, 2H), 0.88 (s, 9H), 0.86 (s, 9H), 0.07- 0.02 (m,12H). CNMR (100 MHz, $CDCl_3$) δ 209.3, 171.8, 169.1, 135.6, 117.0, 86.3, 74.3, 69.7, 57.6, 53.6, 49.3, 47.4, 34.9, 33.7, 25.8, 18.1, 17.8, 15.2, 12.0, -4.4, -4.9.

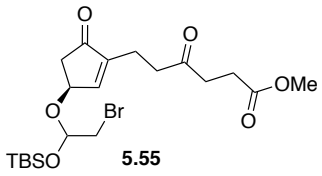


5.54

ethyl acetal (5.54): To a solution of enone **5.1** (95 mg, 0.295 mmol) in MeOH (30 mL) at 0 °C was added methanolic HCl (5 drops). The solution stirred at room temperature for 12 h, at which point additional methanolic HCl was added (30 drops) and the reaction stirred for 24 h at room temperature. It was then concentrated *in vacuo* and carried forward without purification.

To a solution of the resultant enone (71 mg, 0.296 mmol) in CH_2Cl_2 (1.8 mL) at room temperature was added the dibromide (47 μL, 0.355 mmol) and NEt_3 (62 μL, 0.444 mmol). The solution stirred at room temperature for 3 h, at which point additional dibromide (47 μL, 0.355 mmol) and NEt_3 (62 μL, 0.444 mmol) were added. After 10 min, the reaction was quenched with sat. aq. $NaHCO_3$ (2 mL), extracted with CH_2Cl_2 (2 x 3 mL) and Et_2O (2 x 3 mL). The organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resultant residue was purified by flash column chromatography (silica gel, gradient elution, 5 to 30% EtOAc in hexanes) to yield 113 mg (>95%) of ethyl acetal **5.54** as a colorless oil. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.22-7.18 (m, 1H), 4.90 – 4.86 (m, 0.5H), 4.84 (t, *J* = 4.84 Hz, 1H), 4.79 (t, *J* = 5.4 Hz, 0.5H), 3.83-3.55 (m, 4H), 3.45- 3.30 (m, 2H), 2.80 – 2.68 (m, 5 H), 2.60 (t, *J* = 6.6 Hz, 2H), 2.51 (t, *J*= 7.0 Hz, 2H), 2.48- 2.38 (m, 1H), 1.28 – 1.22 (m, 3H). CNMR (100 MHz, $CDCl_3$)

δ 207.4, 207.1 (isomers); 205.4, 205.2 (isomers), 173.3, 172.4 (isomers); 155.3, 154.8 (isomers); 147.1, 147.0 (isomers); 101.8, 101.4 (isomers); 96.; 72.8, 72.6 (isomers); 68.3; 62.7, 62.3; 52.0; 43.2, 42.5 (isomers); 40.1, 40.0 (isomers); 37.1, 36.9 (isomers); 31.8, 31.6 (isomers); 28.1, 27.9 (isomers); 19.1, 19.1 (isomers); 15.4, 15.3, 15.1 (isomers).



5.55

TBS acetal (5.55): To a solution of enone **5.1** (214 mg, 0.295 mmol) in MeOH (50 mL) at at room temperature was added methanolic HCl (30 drops) and stirred at room temperature for 3 d. It was then concentrated *in vacuo* and carried forward without purification. To a solution of the resultant enone (123 mg, 0.512 mmol) in CH_2Cl_2 (1.2 mL) at 0 °C was added NBS (274 mg, 1.54 mmol). The solution stirred at 0 °C for 3 h, at which point it was warmed to room temperature before it was loaded directly onto the flash column for purification (silica gel, gradient elution, 5 to 40% EtOAc in hexanes) to yield 126 mg (52%) of TBS acetal **5.55** as a colorless oil. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.20- 7.15 (m, 1H), 5.10 (q, *J* = 3.6 Hz, 0.5H), 5.01 (q, *J* = 3.6 Hz, 0.5H), 4.88- 4.83 (m, 0.5H), 4.82- 4.76 (m, 0.5H), 3.68 (s, 3H), 3.37- 3.26 (m, 2H), 2.78 -2.66 (5H), 2.60 (t, *J* = 5.9 Hz, 2H), 2.54- 2.42 (m, 3H), 0.93 (s, 4.5H), 0.92 (s, 4.5H), 0.18- 0.15 (m, 6H).

References

1. Sakurai, H.; Hosomi, A. "Syntheses of γ,δ-unsaturated alcohols from allylsilanes and carbonyl compounds in the presence of titanium tetrachloride" *Tetrahedron Lett*. **1976**, *16*, 1295-1298.

2. Weaver, J. D.; Recio, A.; Grenning, A. J.; Tunge, J. A. "Transition metal-catalyzed decarboxylative allylation and benzylation reactions." *Chem. Rev.* **2011**, *111,* 1846-1913.

3. Salom-Roig, X. J.; Dénès, F.; Renaud, P. "Radical cyclization of haloacetals: the Ueno-Stork reaction." *Synthesis* **2004**, *12,* 1903-1928.

4. Egger, J.; Fischer, S.; Bretscher, P.; Freigang, S.; Kopf, M.; Carreira, E. M. "Total synthesis of prostaglandin 15d-PGJ_2 and investigation of its effect on the secretion of IL-6 and IL-12." *Org. Lett.,* **2015**, *17,* 4340-4343.

5. Yakura, T.; Yamada, S.; Ueki, A.; Ikeda, M. "Stereoselective synthesis of 2,3-*cis*-2-Alkyl-5-oxo-3-silyloxycyclopentanecarboxylates using dirhodium(II)-catalyzed intramolecular C-H insertion reaction of 2-diazo-3-oxo-5-silyloxyalkanoates." *Synlett.* **1997**, *2,* 185–186.

6. Huckin, S. N.; Weiler, L. "Alkylation of dianions of beta-keto esters." *J. Am. Chem. Soc.* **1974**, *96,* 1082–1087.

7. Egger, J.; Bretscher, P.; Freigang, S.; Kopf, M.; Carreira, E. M. "Synthesis of epoxyisoprostanes: effects in reducing secretion of pro-inflammatory cytokines IL-6 and IL-12." *Angew. Chem. Int. Ed.* **2013**, *52,* 5382-5385.

8. Baghdasarian, G.; Woerpel, K. A. "Electrostatic Effects on the Reactions of Cyclohexanone Oxocarbenium Ions." *J. Org. Chem.*, **2006**, *71,* 6851–6858.

9. Boddaert, T.; Coquerel, Y.; Rodriguez, J. "Combination of rearrangement with metallic and organic catalyses – a step- and atom-economical approach to α-spiroactones and -lactams." *Euro. J. Org. Chem.* **2011**, 26*,* 5061–5070.

10. Stork, G.; Mook, R. Biller, S. A.; Rychnovsky, S.D. "Free-Radical Cyclization of Bromoacetals. Use in the construction of bicyclic acetals and lactones." *J. Am. Chem. Soc.* **1983**, *105,* 3741-3742.

Appendix A.5:

Spectra Relevant to Chapter 5

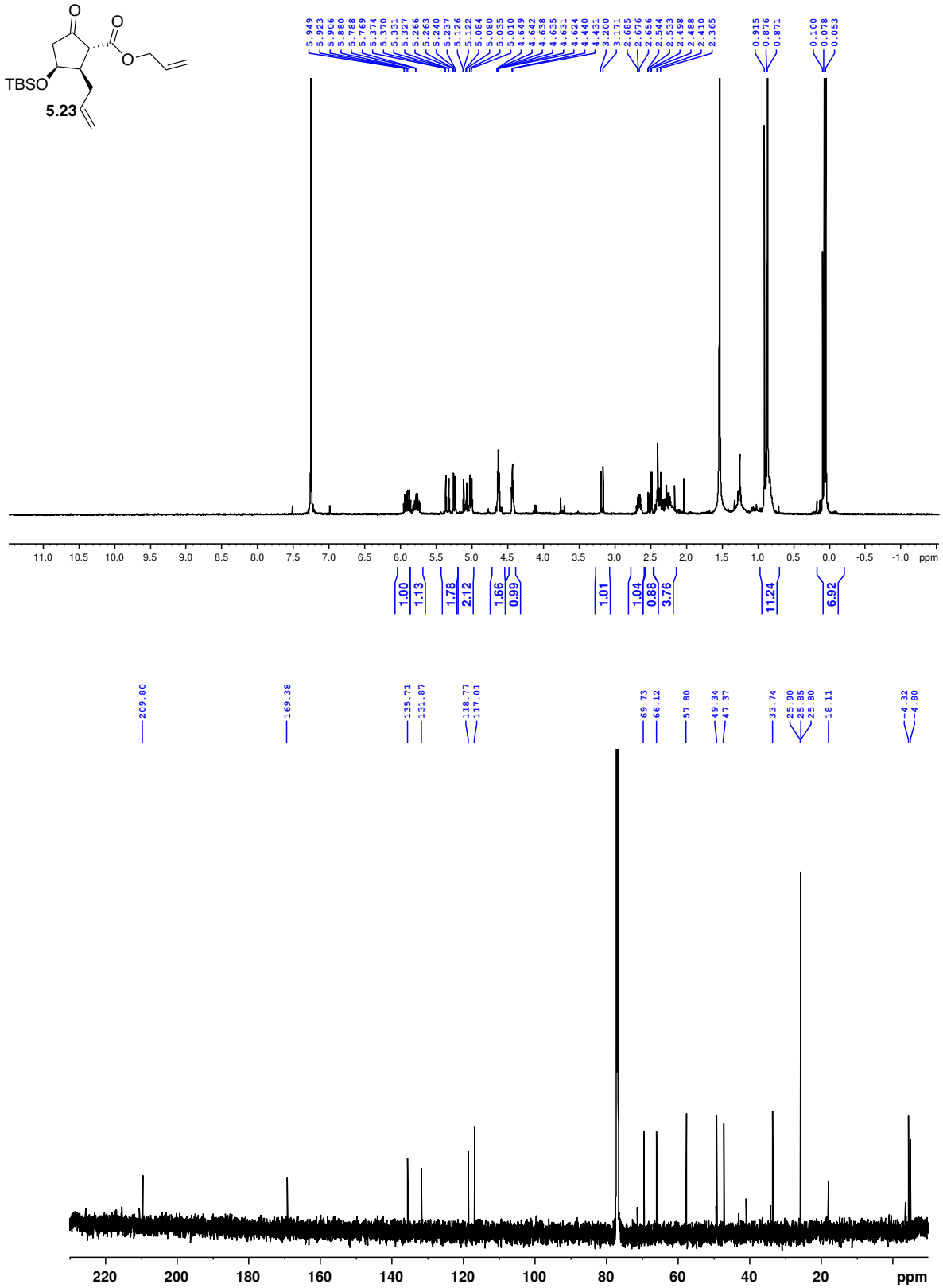


Figure A.5.1 ^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of **5.23**

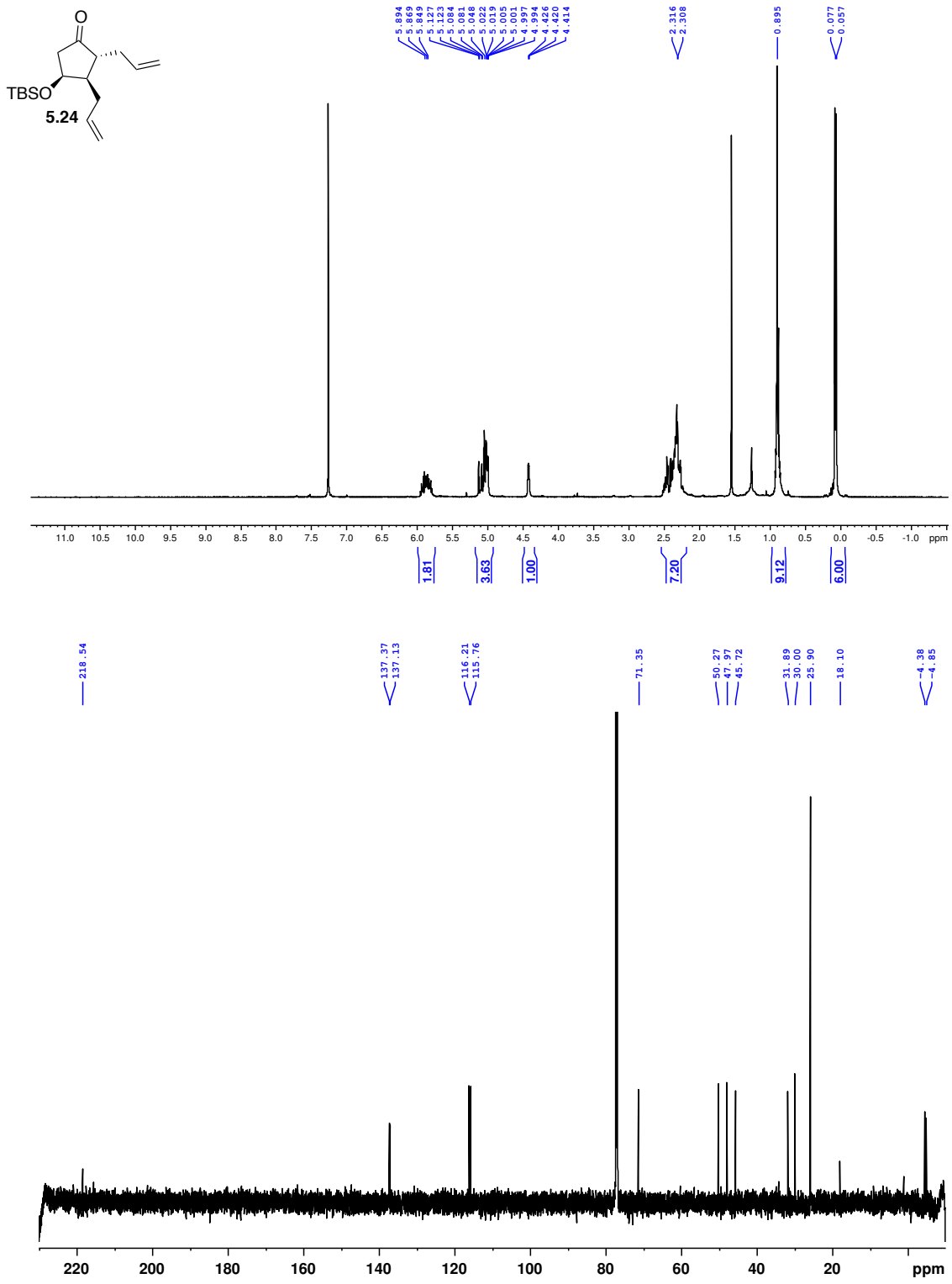


Figure A.5.2 ^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of **5.24**

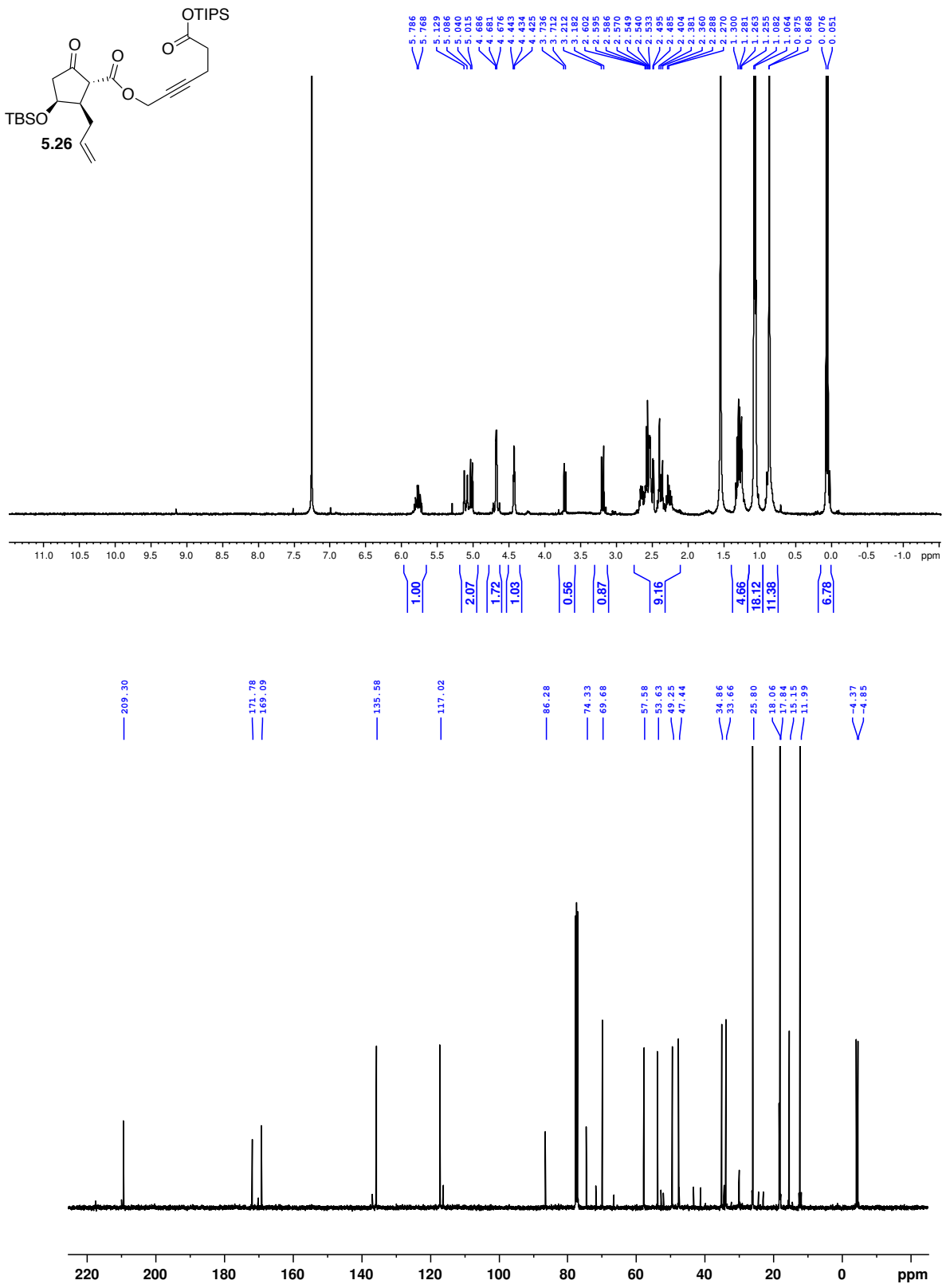


Figure A.5.3 ^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of **5.26**

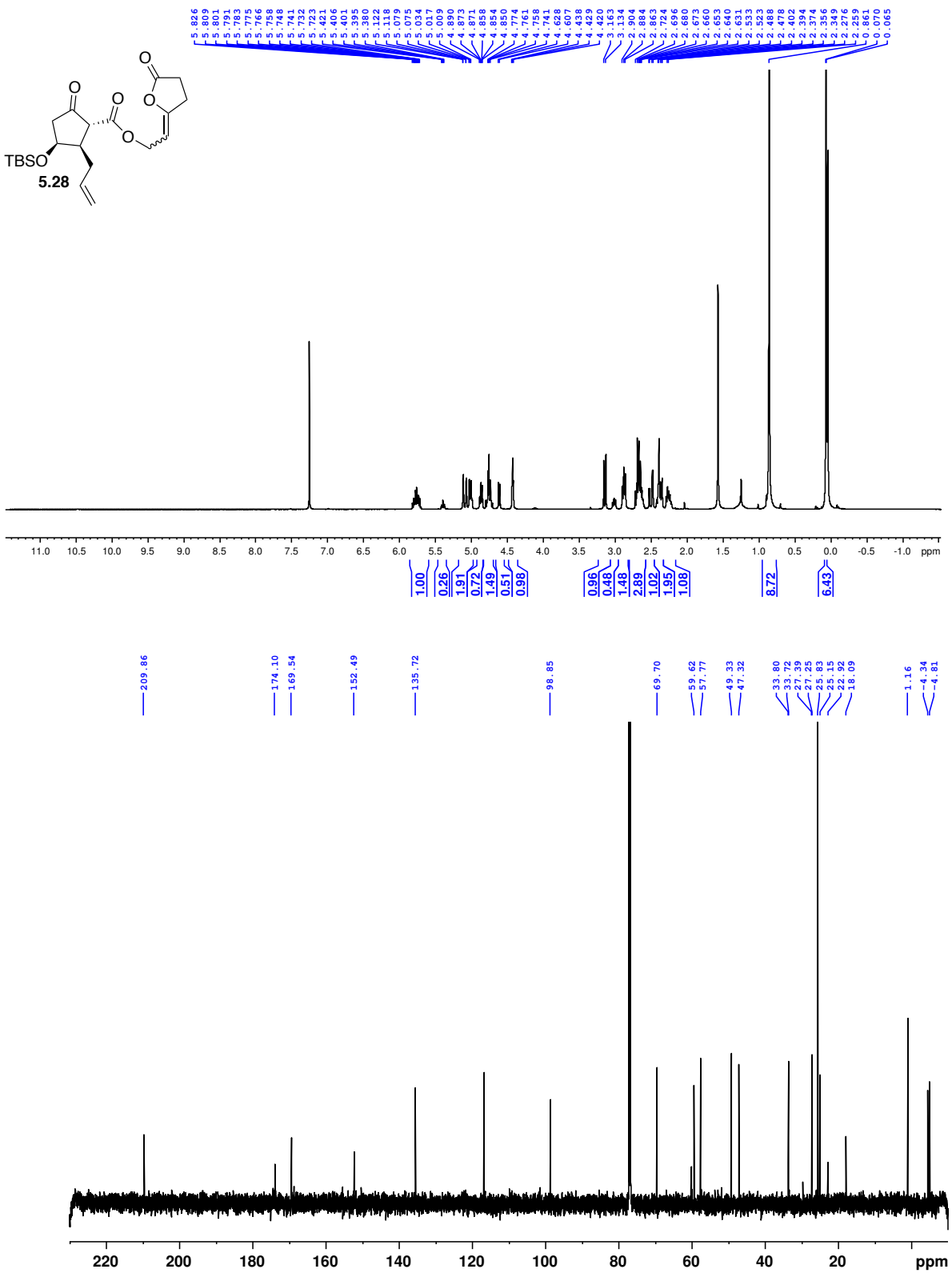


Figure A.5.4 ^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of **5.28**

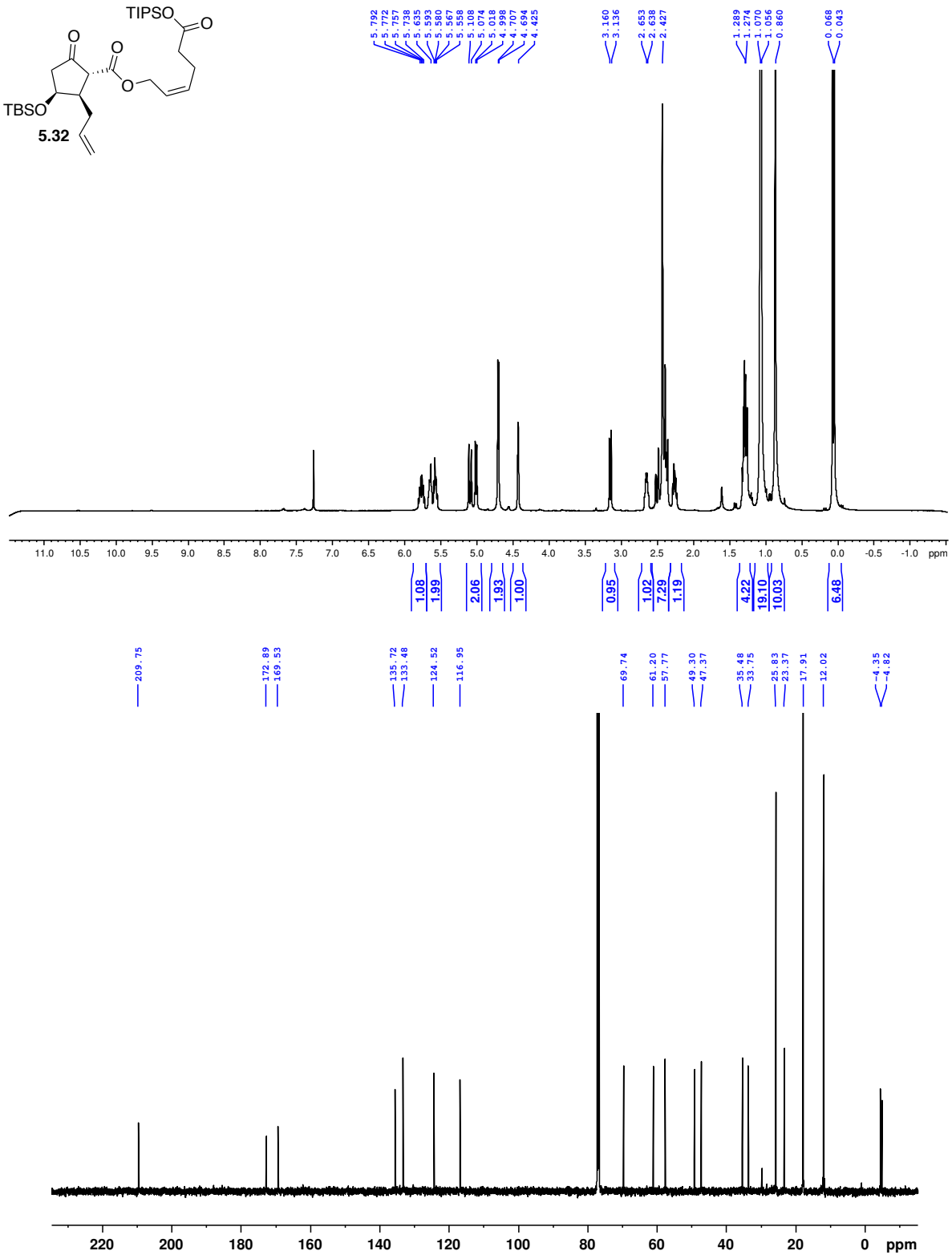


Figure A.5.5 ^{1}HNMR (400 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of **5.32**

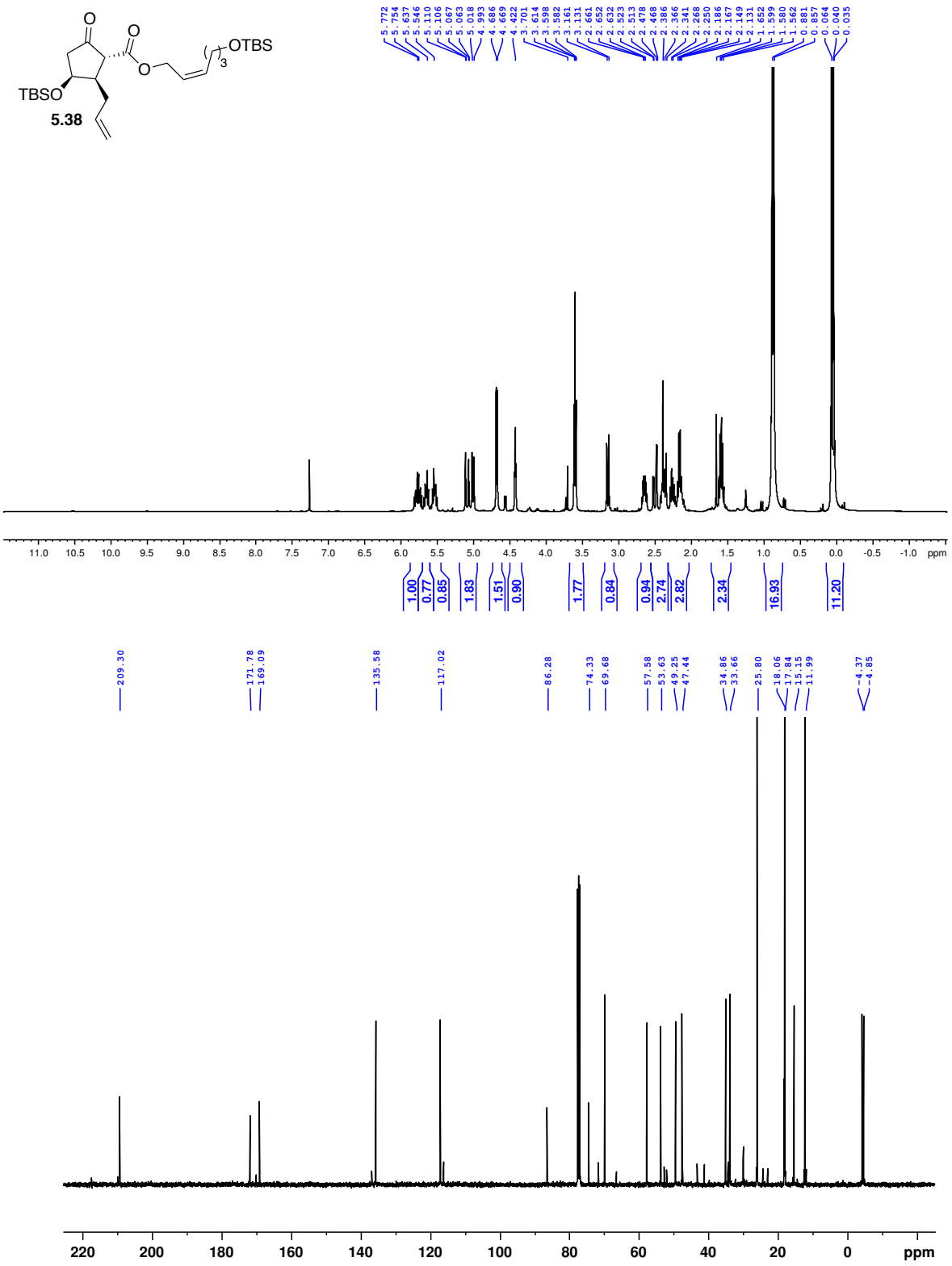


Figure A.5.6 ^{1}HNMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **5.38**

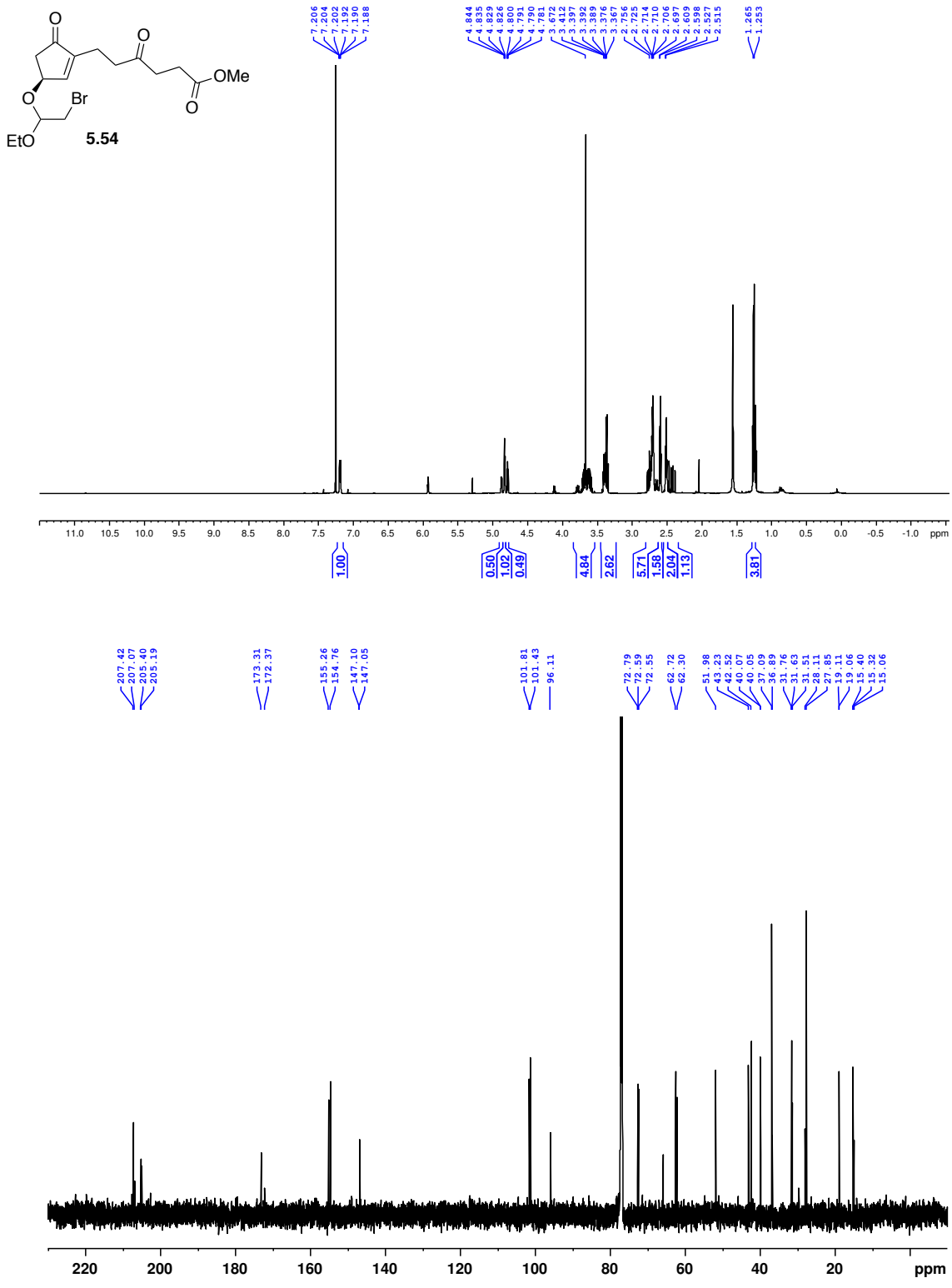


Figure A.5.7 ^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of **5.54**

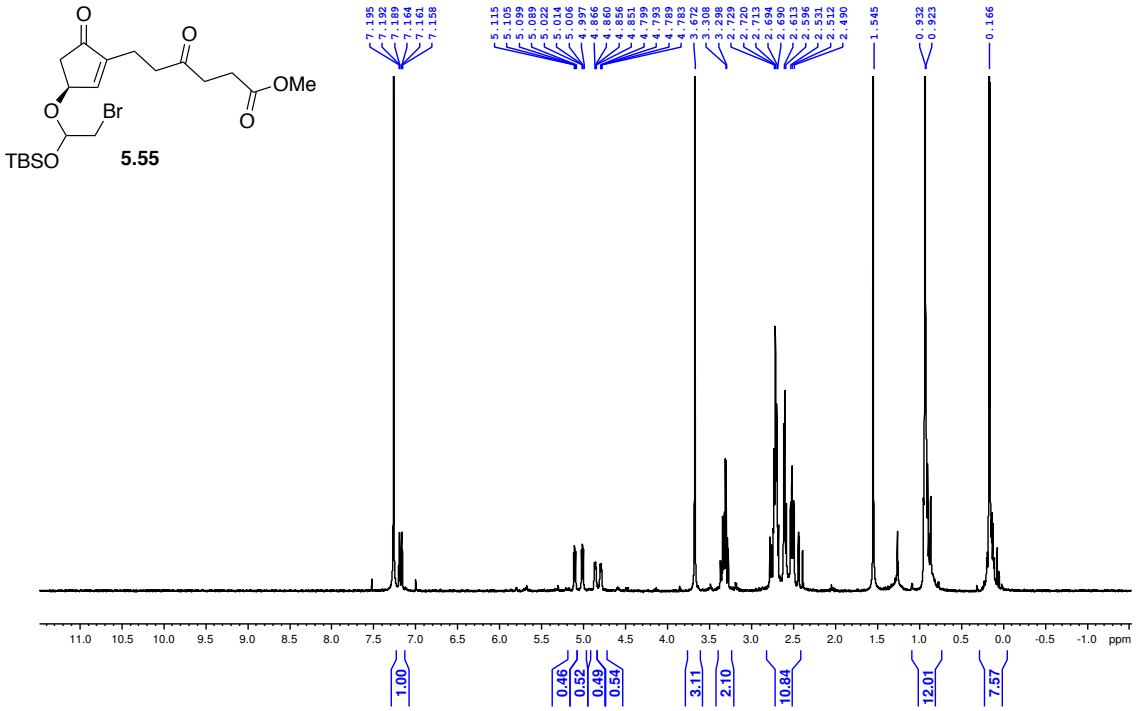


Figure A.5.8 ^{1}HNMR (400 MHz, $CDCl_3$) of **5.55**