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Part I: Total Synthesis of (−)-Azaspirene

Part II: Alkenylzincate and Disilylzinc Conjugate Additions Catalyzed by Copper(I) Iodide Dimethyl Sulfide Complex

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy

in

Chemistry

by

Timothy Robert Montgomery

Committee in Charge:

University of California, San Diego

Professor Thomas Hermann
Professor Stanley Opella

San Diego State University

Professor B. Mikael Bergdahl, Chair
Professor Jeffrey L. Gustafson
Professor Roland Wolkowicz

2016

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Chair

University of California, San Diego

San Diego State University

2016

DEDICATION

I want to dedicate this thesis to my wife and my family for all their love and support

TABLE OF CONTENTS

SIGNATURE PAGE iii

DEDICATION iv

TABLE OF CONTENTS v

LIST OF FIGURES ix

LIST OF SCHEMES x

LIST OF TABLES xii

LIST OF ABBREVIATIONS xiii

ACKNOWLEDGEMENTS xvi

VITA xviii

ABSTRACT OF THE DISSERTATION xx

Chapter 1 Introduction 1

Part I: Total Synthesis of (–)-Azaspirene 4

Chapter 2 Total Synthesis of Azaspirene 5

2.1 Introduction 5

2.2 Background of Angiogenesis 6

2.3 Biological Activity of Azaspirene 8

2.4 Biosynthetic Pathway to Azaspirene 11

2.5 Previous Syntheses of Azaspirene 12

2.5.1 The Osada Route to Azaspirene 13

2.5.2 The Tadano Route to Azaspirene 15

2.5.3 The Sugi Route to Azaspirene 18

2.6 First Proposed Route to Azaspirene 21

2.7 Final Route to Azaspirene 24

2.7.1 Building the Unsaturated Lactone 25

2.7.2 Installing the alcohols 28

2.7.3 Forming the spirocycle 38

2.7.4 Completion of Azaspirene 43

Part II: Alkenylzincate and Disilylzinc Conjugate Additions Catalyzed by Copper(I) Iodide Dimethyl Sulfide Complex 49

Chapter 3 Alkenylzincate Conjugate Additions Catalyzed by Copper(I) Iodide Dimethyl Sulfide Complex 50

3.1 Introduction 50

3.2 Utilizing Alkenylzincate Reagents in the Synthesis of Azaspirene 51

3.3 Building the Unsaturated Substrates 57

3.3.1 Synthesizing furanone derivative 3.2 57

3.3.2 Synthesizing the pyranone derivatives 3.3 and 3.4 58

3.3.3 Synthesizing the glucal derivative 3.5 59

Chapter 4 Disilylzinc Conjugate Additions Catalyzed by the Copper(I) Iodide Dimethyl Sulfide Complex 62

4.1 Introduction 62

4.2 Results and Discussion 63

4.3 Extending the silyl conjugate addition methodology 67

Chapter 5 Aqueous Conjugate Additions from Boronic Esters 71

5.1 Introduction 71

5.2 Aqueous silyl conjugate addition reactions to chiral imide enones 72

5.3 Aqueous vinyl conjugate addition reactions 75

Chapter 6 Future Work 77

6.1 Azaspirene 77
6.1.1 Adding a biomarker to Azaspirene 77
6.1.2 Milder Tamao oxidation of silyl group 79
6.2 Conjugate silyl addition methodology 80
6.2.1 Monosilylzinc chloride conjugate addition reactions 80
Chapter 7 Experimental Section 82
7.1 Instrumentation and Chemicals 82
7.2 General Experimental Procedures 83
7.2.1 General procedure for alkenylzirconocene additions 83
7.2.2 General procedure for alkenylzincate additions 83
7.2.3 General procedure for the disilylzinc reaction 84
7.2.4 General procedure for the disilylzinc to aldol reaction 85
7.2.5 General procedure for addition of silylboronic esters in water 86
7.2.6 General procedure for oxazolidinone coupling to acyl chlorides 87
7.3 Reagent Syntheses 87
7.3.1 Copper Iodine Dimethyl Sulfide (CuI·DMS) Complex Preparation 87
7.3.2 Preparation of Schwartz reagent, $Cp_2Zr(H)Cl$ 88
7.3.3 Silylboronic ester preparation 88
7.3.4 Dess-Martin Periodinane Preparation 89
7.3.5 Horner-Wadsworth Reagent Prep 90
7.3.6 (2*E*,4*E*) heptadienoic acid and ethyl ester prep 90
7.3.7 Dimethyldioxerane (DMDO) Prep 91
7.4 Experimental Procedures and Compound Characterization for Part I: Total Synthesis of Azaspirene 92

7.5 Experimental Procedures and Compound Characterization for Part II: Alkenylzincate and Disilylzinc Conjugate Additions Catalyzed by Copper(I) Iodide Dimethyl Sulfide Complex....123
Appendix....155
References....230

LIST OF FIGURES

Figure 2.1: Members of the pseurotin family of compounds.....5

Figure 2.2: Schematic depicting tumor-induced angiogenesis and choroidal neovascularization as manifested in wet AMD.....7

Figure 2.3: Commercial small molecule angiogenesis inhibitors.....8

Figure 2.4: Inhibition of tumor-related angiogenesis by azaspirene versus paclitaxel in a mouse model performed by the Osada group.....9

Figure 2.5: Inhibition of blood vessel growth by azaspirene in a CAM assay performed by the Osada group.....10

Figure 2.6: Mouse study data from the Emoto group for the (+) and (–) analog of azaspirene versus tumor volume and mouse body weight.....11

Figure 3.1: β-oxygenated enone test substrates.....52

Figure 3.2: Conformational differences between *s-cis* and *s-trans* enones.....55

Figure 4.1: Chelate versus no chelate control of reactive species.....65

Figure 4.2: Potential enone geometries for imide substrates under chelate control..65

Figure 4.3: The *threo* versus *erythro* orientation for aldol reaction products.....69

Figure 6.1: Simplified mechanistic route proposed by Oestreich.....80

Figure 6.2: Expanded mechanistic route to include the addition of the aldehyde.....81

LIST OF SCHEMES

Scheme 2.1: Biosynthetic Pathway to Azaspirene 12

Scheme 2.2: Osada's Total Synthesis of Azaspirene 14

Scheme 2.3: Tadano's Total Synthesis of Azaspirene 16

Scheme 2.4: Sugi total synthesis of Azaspirene 19

Scheme 2.5: First retrosynthetic route to Azaspirene 22

Scheme 2.6: First proposed route to Azaspirene 23

Scheme 2.7: Altered route to Azaspirene 24

Scheme 2.8: Retrosynthetic route to Azaspirene 25

Scheme 2.9: Building epoxide 2.4 26

Scheme 2.10: Oxidation of saturated lactone 2.5 with PhSeCl 27

Scheme 2.11: Completion of the unsaturated lactone 2.8 28

Scheme 2.12: Various silyl additions to unsaturated lactone 2.8 29

Scheme 2.13: Conjugate silyl to aldol reaction and incorporation of a tertiary alcohol 30

Scheme 2.14: Synthesis of test substarte for DMDO oxidation 31

Scheme 2.15: Fleming Oxidation of the silyl group 33

Scheme 2.16: Selective protection of diol 2.15 34

Scheme 2.17: Oxidation of alcohol 2.20 35

Scheme 2.18: Installing the tertiary alcohol 36

Scheme 2.19: "Margaretha" attempt at adding the "tail" of Azaspirene 38

Scheme 2.20: General method for adding the tail and forming the spirocycle 39

Scheme 2.21: Creation of the spirocycle 40

Scheme 2.22: Investigation into the scrambled stereocenter of 2.28a 42

Scheme 2.23: Formation of the lactam from the lactone spirocycle 44

Scheme 2.24 Finalized route to Azaspirene 47

Scheme 3.1: Alkenylzirconocene and alkenylalkylzincate additions utilizing CuI·DMS catalyst 51

Scheme 3.2: Implementation of copper chemistry in the Azaspirene synthesis 51

Scheme 3.3 Proposed ring opening of β-oxygenated enone substrates 52

Scheme 3.4: Synthesis of furanone 3.2 57

Scheme 3.5: Synthesis of pyranone 3.3 58

Scheme 3.6: Synthesis of chromone 3.4 58

Scheme 3.7: Synthesis of glucal derivative 3.5 60

Scheme 4.1: Electrophilic trapping of a silyl conjugate addition enolate 67

Scheme 5.1: Modified aqueous silyl conjugate addition reactions 72

Scheme 6.1: Proposed route for incorporation of a biotin tail onto Azaspirene 78

LIST OF TABLES

Table 3.1: Comparison of Methods A and B on addition product yield.....53

Table 3.2: Alkenylalkylzincate additions to various β-oxygenated enones.....54

Table 4.1: Silyl addition to various oxazolidinone substrates 64

Table 4.2: Results for the one-pot silyl aldol reactions 68

Table 5.1: Effects of the oxazolidinone chiral group on product d.r.....73

Table 5.2: Results from aqueous vinyl boronic ester additions 76

LIST OF ABBREVIATIONS

Ac	Acetate
acac	Acetylacetonate
ACN	Acetonitrile
aq	Aqueous
Bn	Benzyl
BSA	Bis(trimethylsilyl)acetamide
Bz	Benzoyl
cat	Catalytic
Cp	Cyclopentene
CSA	Camphorsulfonic acid
Cy	Cyclohexyl
d.r.	Diastereomeric ratio
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
DIPEA	Diisopropylethylamine
DMAP	4-*N,N*-dimethylaminopyridine
DMDO	Dimethyldioxirane
DMF	Dimethylformamide
DMP	Dess-Martin periodinane
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide

Et	Ethyl
HMDS	Hexamethyldisilizane
HMPA	Hexamethylphosphoramide
imid	Imidazole
*i*Pr	Isopropyl
LAH	Lithium aluminum hydride
LDA	Lithium diisopropyl amide
mCPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
MOM	Methoxymethyl
Ms	Methanesulfonyl
MTM	Methylthiomethyl
NIS	*N*-Iodosuccinamide
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Ph	Phenyl
pin	pinacol
PPTS	Pyridinium *para*-toluenesulfonate
Pyr	Pyridine
sat	Saturated
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl

*t*Bu	*tert*-Butyl
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Tr	Triphenylmethane or trityl
Ts	Toluenesulfonyl or tosyl

ACKNOWLEDGEMENTS

For starters, I would like to truly thank Dr. Mikael Bergdahl. He has been both a wonderful mentor and friend during my time in graduate school, which is something I will cherish for a lifetime. I also want to thank all of the Bergdahl lab members both past and present that helped make the many long hours in the lab an unforgettable and very enjoyable time. I especially want to thank Dave Schmit, Michael Kelly, Scott Burley, Lee Wang and Brent Banasik who were some of the core members of the lab for the majority of my time at SDSU and whom I have built lifelong friendships with. I would like to thank the other graduate students, faculty, and staff in both the San Diego State University and University of California San Diego chemistry departments for helping me obtain an education I am truly proud of. Thank you Dr. LeRoy Lafferty for all of your help and knowledge with obtaining my countless NMR spectra, and I want to thank the ARCS scholarship program for their support in my studies. I want to thank my family and friends for their help and support and I especially want to thank my wife Brianna, who first met me a month before I started graduate school, and who has been amazingly understanding, loving, and supportive of me on this wonderful journey.

Chapter 2 and Chapter 4 contain information that is being prepared for submission for publication. The following co-authors assisted in the work and should be commended: Michael Kelly, Jason Zbieg, and of course Dr. B. Mikael Bergdahl.

Montgomery, Timothy R.; Kelly, Michael J.; Bergdahl, Mikael. "An Efficient and Scalable Synthesis of the Angiogenesis Inhibitor Azaspirene" (Chapter 2).

Kelly, Michael J.; Montgomery, Timothy R.; Zbieg, Jason; Bergdahl, Mikael. “Conjugate Addition of Disilylzinc and Monosilylzincate Reagents; Efficiency of the Chiral *N*-Enoyl-2-oxazolidinones in the Preparation of Optically Active Acetate Aldol Products” (Chapter 4).

VITA

2016	Doctor of Philosophy, Chemistry, University of California, San Diego & San Diego State Univerisity Joint Doctoral Program, San Diego, CA
2015	Master of Arts, Chemistry, San Diego State University, San Diego, CA
2011 - 2016	Teaching Assistant, Department of Chemistry, San Diego State University, San Diego, CA
2006 - 2009	Research Associate, MediVas, LLC, San Diego, CA
2006	Research Chemist, CP Kelco, San Diego, CA
2005	Bachelor of Science, Chemistry, The College of William and Mary, Williamsburg, VA

Publications and Manuscripts in Progress:

Montgomery, Timothy R.; Kelly, Michael J.; Bergdahl, Mikael. "An Efficient and Scalable Synthesis of the Angiogenesis Inhibitor Azaspirene" (Manuscript in Progress).

Kelly, Michael J.; **Montgomery**, Timothy R.; Zbieg, Jason; Bergdahl, Mikael. "Conjugate Addition of Disilylzinc and Monosilylzincate Reagents; Efficiency of the Chiral *N*-Enoyl-2-oxazolidinones in the Preparation of Optically Active Acetate Aldol Products." (Manuscript in Progress)

Professional Presentations:

Montgomery *et. al*, 75th ACS San Diego Chapter Anniversary Symposium: "New methods towards the total synthesis of azaspirene: A potent angiogenisis inhibitor" San Diego, Ca; April **2016**.

Montgomery *et. al*, ARCS Scientist of the Year Dinner: "Total Synthesis of Azaspirene and its Analogs: Promising New Treatments for Cancer" San Diego, CA; April **2016**.

Montgomery *et.* al, 251st ACS National Meeting: "New methods towards the total synthesis of azaspirene: A potent angiogenisis inhibitor" San Diego, CA; March **2016**.

Montgomery *et. al*, ARCS Scientist of the Year Dinner: "Total Synthesis of Azaspirene and its Analogs: Promising New Treatments for Cancer" San Diego, CA; April **2015**.

Montgomery *et. al*, 45th ACS Western Regional Meeting: "Progressive new methods towards the total synthesis of azaspirene and its analogs: Promising new cancer treatments" San Marcos, CA; November **2015**.

Montgomery, *et. al*, CSUPERB Symposium: "Diversity Oriented Total Synthesis of Pseurotin Analogs: Powerful Inhibitors of Angiogenesis and Inflammation" Santa Clara, CA; **2012**

ABSTRACT OF THE DISSERTATION

Part I: Total Synthesis of (−)-Azaspirene

Part II: Alkenylzincate and Disilylzinc Conjugate Additions Catalyzed by Copper(I) Iodide Dimethyl Sulfide Complex

Timothy Robert Montgomery

Doctor of Philosophy in Chemistry

University of California, San Diego, 2016

San Diego State University, 2016

Professor B. Mikael Bergdahl, Chair

Angiogenesis inhibitors are being targeted for their potential as anti-tumor agents as well as theraputics to treat rhematoid arthritis and wet macular degeneration. The natural product azaspirene was shown to inhibit angiogenesis both *in vitro* and *in vivo* with low cyctotoxicity making it a compound of interest. Although three syntheses of azaspirene exist, they are lengthy (15 - 33 steps) and have low total yields (< 2%) making a reliable supply of the compound unavailable for further testing. Described in Part I of this thesis is the total synthesis of the natural

product azaspirene. The synthesis is the most direct and gives the highest total yield of the published syntheses of azaspirene to date. The synthesis consisted of 11 steps from a commercially available chiral unsaturated lactone in a 6% total yield. The route described can also be performed on the multi-gram scale allowing for an ample supply of azaspirene to continue biological testing. The continued testing will hopefully shed light on the mode of action of azaspirene and the binding site to allow for analogs to by synthesized. A key step in the synthesis utilized a novel one-pot silyl conjugate addition followed by an aldol reaction. Details of the methodology applied to the total synthesis is described in Part II of this thesis.

The silyl conjugate addition was catalyzed by the copper iodine dimethyl sulfide (CuI·DMS) complex, which allowed the presence of an aldehyde at the initiation of the conjugate addition reaction, and led to high yields of the β-silylated aldol product. Also described in Part II is the conjugate addition of vinyl groups catalyzed by the CuI·DMS complex and attempts towards an asymmetric conjugate addition of both silyl and vinyl groups in an aqueous environment.

Chapter 1 Introduction

The natural product azaspirene was isolated in 2002 from the soil fungus *Neosartorya sp*., and initial studies conducted by the Osada group[1,2] showed that azaspirene is a very promising inhibitor of angiogenesis. Since angiogenesis is the process by which new blood vessels form from pre-existing ones, it has been linked to the proliferation of diseases such as cancer and rheumatoid arthritis. The initial studies showed that azaspirene does not seem to affect normal cell function and has low cytotoxicity,[3] thus inhibitors of angiogenesis have the potential to provide a milder form of treatment for these kinds of diseases with less side effects.[4] Although various syntheses of azaspirene have been reported, they are not efficient enough to produce proper amounts of the compound to further test its therapeutic effects.[2,5,6] The research reported in Part I of this thesis was aimed at establishing an economic and efficient asymmetric synthetic route to azaspirene and its analogs allowing for an ample supply of compound to continue and assess biological testing. The synthetic route was initiated with the commercially available unsaturated benzyl lactone, which is also easily synthesized from L-phenylalanine. There were three instrumental steps in the proposed route in order to accomplish the synthesis of azaspirene. The first utilized novel methodology with a disilylzinc reagent along with catalytic amounts of copper iodide dimethyl sulfide (CuI•DMS) complex to foster a one-pot conjugate silyl addition-aldol reaction.[7] The second key reaction was a unique cyclization to form the bicyclic core of azaspirene based on the work of Margaretha[8] and finally an ammonolysis reaction converting the lactone to a lactam and finishing the synthesis.[5]

The final reported synthesis to azaspirene consisted of 11 steps from the unsaturated lactone with a 6% total yield.

Part II of the thesis describes the methodology for alkenylzincate and disilylzinc conjugate additions catalyzed by CuI•DMS. The ability to create new carbon-carbon bonds as well as carbon-oxygen bonds is important when synthesizing many natural products. Previous group members demonstrated that the use of the CuI•DMS catalyst facilitated the 1,4-addition of alkenylzincate reagents[9] as well as silylzincate reagents[7,10] to α,β-unsaturated ketones in high yields and with very little formation of the undesired 1,2-addition products. Chapter 3 describes the expansion of the vinylzincate methodology from simple substrates to also include β-oxygenated cyclic enones that mimicked the bicyclic core of azaspirene. The new methodology was developed to support a previous route to azaspirene that would allow for the attachment of the side chain to the bicyclic core of the target molecule.

The CuI•DMS catalyst was also employed in the asymmetric addition of disilylzinc reagents as described in Chapter 4. The addition of a bulky silyl group (i.e. phenyldimethylsilyl) has two advantages: 1) it can act as a bulky directing group for future reactions, and 2) the silyl group can also be readily oxidized using the Fleming-Tamao procedure with full retention of stereochemistry to give the corresponding β-hydroxyl carbonyl or aldol product.[11,12] A common reagent for these additions was the Gilman-type silylcuprates, however they require stoichiometric amounts of copper. The move towards using a catalytic amount of copper led to the use of silylzincates, however the silylzincates were conventionally synthesized using pyrophoric dialkyl zinc species. A newer disilylzinc[13] species can be made more safely starting from simple zinc chloride. The disilylzinc reagent is added in both high yields and high

diastereomeric ratios in the presence of the CuI•DMS catalyst to Evans-type unsaturated imides attached to chiral oxazolidinone auxiliaries.[7] In the proposed synthetic route to azaspirene, it was demonstrated that the additions were high yielding and highly stereocontrolled when added to chiral unsaturated lactones. It was also discovered that the disilylzinc reagent, with the CuI•DMS catalyst, is very useful in the presence of an aldehyde in a "one-pot" conjugate silyl addition aldol product trapping in near quantitative yields. Further exploration of this new methodology is currently underway.

Chapter 5 describes the attempts at a directed aqueous silyl conjugate addition from a silylboronic ester using copper (II) sulfate. The aqueous reaction was first demonstrated by Calderone and Santos with simple enones.[14] The work presented employed the aqueous addition methodology to investigate the directing ability of the unique Evans chiral auxiliary substrates.

Part I: Total Synthesis of (−)-Azaspirene

Chapter 2 Total Synthesis of Azaspirene

2.1 Introduction

Azaspirene, a member of the pseurotin family of compounds, has been shown to be a potent angiogenesis inhibitor.[2] The pseurotin compounds share the same 1-oxa-7-azaspiro-[4,4]non-2-ene-4,6-dione core however that possess different therapeutic applications.[15–18] Several compounds that are representative of the pseurotin family are shown in Figure 2.1. Each member has its unique side chain that is either a diene or an oxygenated version thereof. The pseurotin family members also possess tertiary methoxy and benzoyl groups where azaspirene has a tertiary alcohol and a benzyl group.

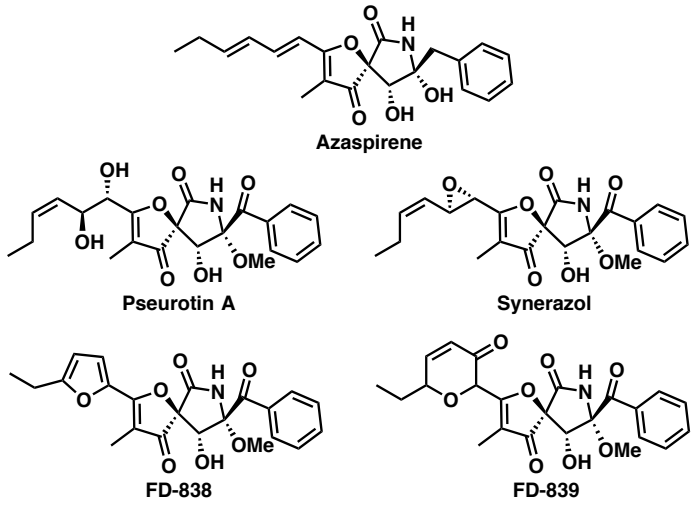


Figure 2.1: Members of the pseurotin family of compounds

Of the compounds within the pseurotin family, only azaspirene has been shown to inhibit angiogenesis. The initial testing of azaspirene showed *in vivo* inhibition of angiogenesis combined with a low cytotoxic profile making it a target of interest. Angiogenesis inhibitors are being considered a milder form of therapy for

diseases such as cancer, rheumatoid arthritis, and wet macular degeneration.[4,19,20] Although azaspirene was discovered in 2002, the details about the function of azaspirene as a drug such as the binding site and mode of action of azaspirene are unknown. These tests have been hampered due to the limited amount of natural sources of the compound as well as low yielding and lengthy syntheses. As a consequence, the goal was to design an efficient synthesis of azaspirene that is novel, scalable, and that would provide enough compound to continue testing of this unique and promising therapeutic.

2.2 Background of Angiogenesis

Angiogenesis is the process by which new blood vessels are formed from preexisting ones and is the normal function for cell growth and wound repair.[19,20] Angiogenesis works by the body releasing chemical signals such as vascular endothelial growth factors (VEGF). The VEGF bind to endothelial cells that line the inner walls of blood vessels and signal either the production of new blood vessels or the repair of old blood vessels. Several diseases such as rheumatoid arthritis, wet age-related macular degeneration (AMD), and cancer tumor cells also thrive from this process.[4,21–23] Tumor cells specifically use angiogenesis by releasing chemicals that mimic the natural VEGF signals. These signals stimulate blood vessel growth around the tumor allowing for rapid metastasis and growth as depicted in Figure 2.2[23] below.

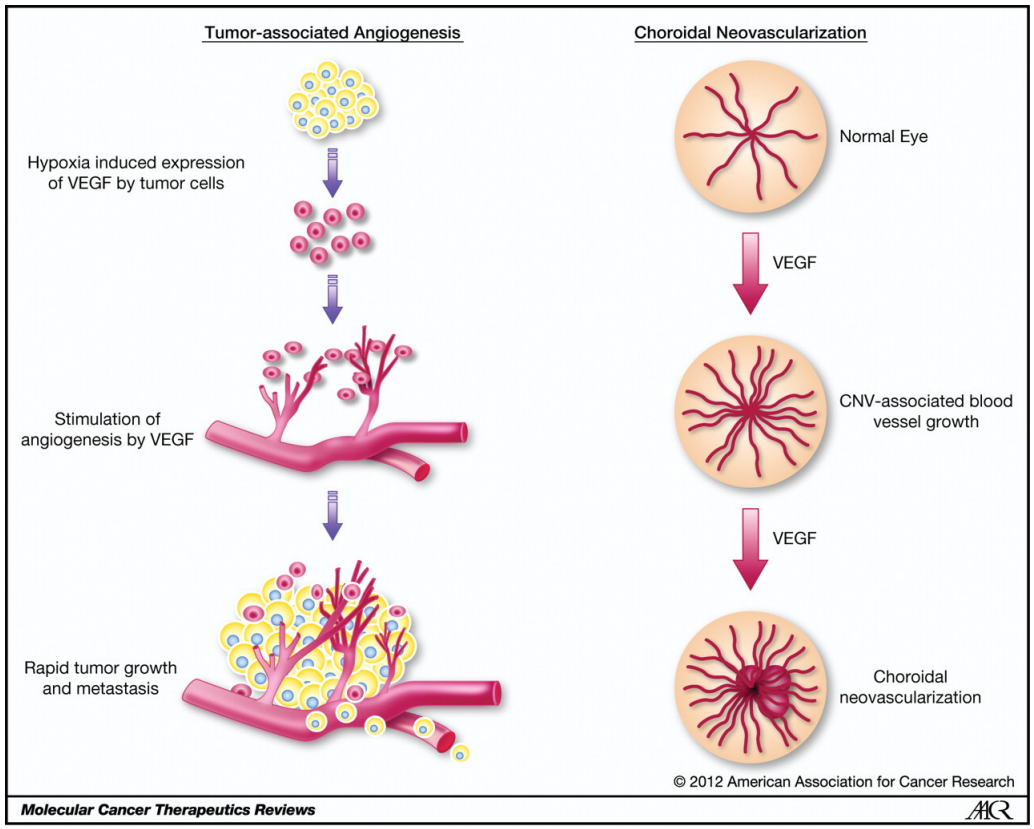


Figure 2.2: Schematic depicting tumor-induced angiogenesis and choroidal neovascularization as manifested in wet AMD

Without the excess blood vessels supplying a tumor cell, the tumor would not continue to grow. The ability of angiogenesis inhibitors to hinder tumor growth has made them a major target as a new type of cancer therapy. Angiogenesis inhibitors act by disrupting the chemical signals sent out by the tumor cells and blocking blood vessel growth. The ability to hinder tumor growth in this fashion makes angiogenesis inhibitors potential targets as future anti-cancer drugs.

Several anti-angiogenesis small molecule drug compounds that inhibit tyrosine kinases are commercially available but none share the unique structure of azaspirene as seen in Figure 2.3.

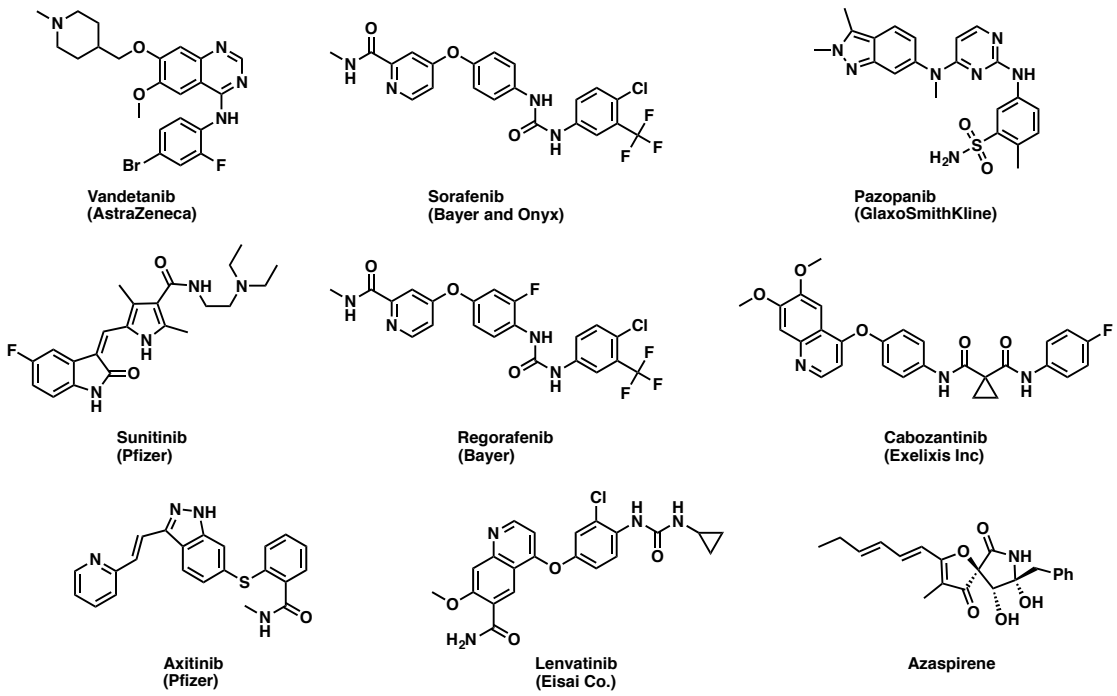


Figure 2.3: Commercial small molecule angiogenesis inhibitors

Due to limited supply of the compound either from natural sources or through synthetic routes to date, the mode of action for azaspirene is not completely understood. Judging by the structural differences of azaspirene with the other inhibitors, it is likely azaspirene acts in a completely different manner. Presented in this thesis is a novel and robust route for synthesizing azaspirene that could allow for the compound to be synthesized on the multi-gram scale.

2.3 Biological Activity of Azaspirene

Azaspirene was first isolated from the soil fungus *Neosartorya sp.* by the Osada group in 2002[1] while screening fungal metabolites for angiogenesis inhibitors. Through cultivation of *Neosartorya sp.* a total of 84 mg of azaspirene was isolated and used for *in vitro* and *in vivo* studies. The initial studies published by Osada tested azaspirene against a known angiogenesis inhibitor (SU5614) for azaspirene's

ability to inhibit VEGF-induced cell migration in human umbilical vein endothelial cells (HUVECs) at 3 mg/mL (8.1 μM), 10 mg/mL (27 μM), and 30 mg/mL (81.3 μM) concentrations. The results showed that azaspirene completely inhibited HUVEC migration at 27 μM without any significant cell toxicity inspiring more studies to be conducted by the Osada group.[1]

In 2008, the Osada group published the first *in vivo* results from testing azaspirene. It was tested in both a chicken chorioallantoic membrane (CAM) assay and a mouse model for tumor-induced angiogenesis. They also reported *in vitro* results aimed at determining azaspirene's mechanism of action.[3] The results of the mouse study conducted by Osada are shown in Figure 2.4.[3]

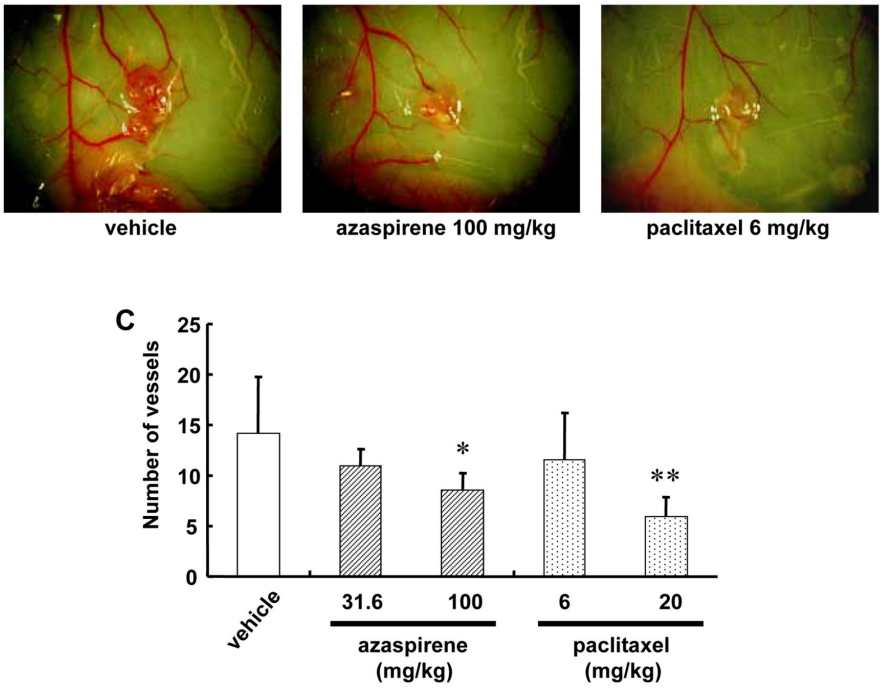


Figure 2.4: Inhibition of tumor-related angiogenesis by azaspirene versus paclitaxel in a mouse model performed by the Osada group

The visible reduction in tumor size for azaspirene at 100 mg/kg versus the control was evidence that azaspirene does inhibit tumor related angiogenesis. It was also

stated that the body weight of the mice that received azaspirene were not reduced indicating the low cytotoxicity of the compound.

The CAM assay also showed positive results that azaspirene exhibited anti-angiogenesis properties. A figure of the CAM assay results from the Osada study is shown below. There was a significant decrease in the number of blood vessels formed in the egg when azaspirene was administered at 30 μg per egg as seen in Figure 2.5.[3] The positive *in vivo* results of azaspirene acting as an angiogenesis inhibitor provided further support for the necessity of a scalable synthetic strategy to continue biological testing.

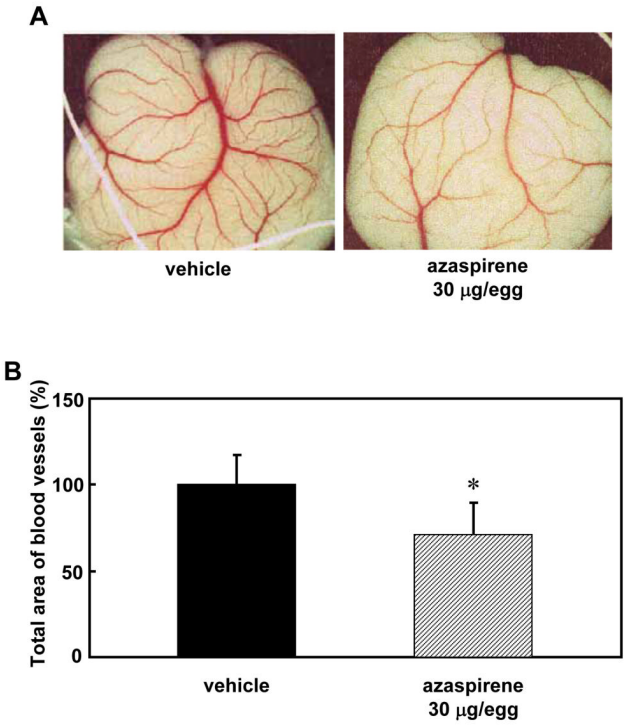


Figure 2.5: Inhibition of blood vessel growth by azaspirene in a CAM assay performed by the Osada group

The Osada group also performed further *in vitro* studies in an attempt to determine the mode of action for azaspirene. The results narrowed the binding site of azaspirene to be within the MAPK signaling pathway in HUVECs but the specific

molecular target was not determined. The results also indicated that azaspirene had a unique mode of action that differed from the current angiogenesis drugs on the market.[3]

Although no other testing has been performed with azaspirene, in 2015, Emoto *et. al* reported both *in vitro* and *in vivo* results from testing an analog of azaspirene modified by replacement of the diene with a shorter ethyl side chain.[24] It is interesting that this analog was reported to show similar inhibition of angiogenesis compared to azaspirene when tested against a highly metastasizing uterine carcinosarcoma (UCS) cell line as shown in Figure 2.6[24] below.

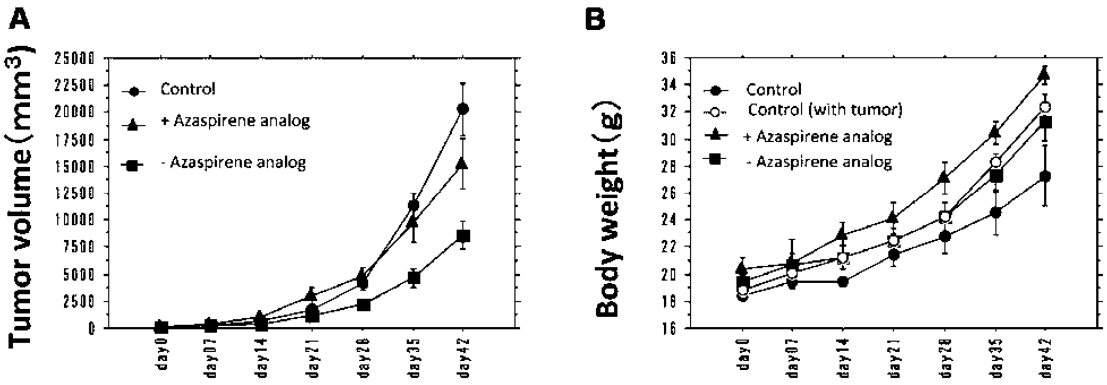


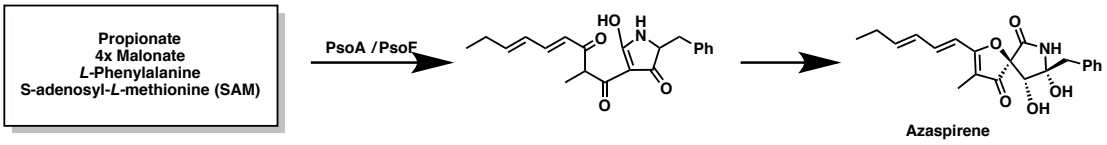
Figure 2.6: Mouse study data from the Emoto group for the (+) and (–) analog of azaspirene versus tumor volume and mouse body weight

Like azaspirene, the analog was reported to not cause any loss of weight to the mice treated with the analog. This supported the low cytotoxic profile of both azaspirene and potential analogs. The Emoto group's racemic synthesis of azaspirene and the analog has not to this date been published.

2.4 Biosynthetic Pathway to Azaspirene

In 2014, Watanabe *et. al* published the biosynthetic pathway of the pseurotin family members.[25] It was proposed that the main 1-oxa-7-azaspiro-[4,4]non-2-ene-

4,6-dione skeleton is biosynthesized by a hybrid gene of the polyketide synthase nonribosomal peptide synthase (PKS-NRPS) called *psoA*. The other major modification enzyme involved in the biosynthesis of azaspirene in the PsoF, which is a single polypeptide with two domains resembling a methyltransferase (MT) and an FAD-containing monooxygenase (FMO) respectively. It was also proposed that azaspirene is the core structure from which the other more oxidized members of the pseurotin family were derived. Thus azaspirene is originating from one unit of propionate, four units of malonate, a unit of *L*-phenylalanine, and a unit of *S*-adenosyl-*L*-methionine (SAM). The proposed biosynthetic pathway from this study is illustrated in Scheme 2.1 below.



Scheme 2.1: Biosynthetic Pathway to Azaspirene

The pathway shown above was similar to the biosynthetic pathway proposed by Osada upon first discovering azaspirene in 2002 based on earlier reports describing the proposed biosynthetic pathway of pseurotin A.[1,26]

2.5 Previous Syntheses of Azaspirene

Since its discovery, three syntheses of azaspirene have been published by Osada in 2002,[2] Tadano in 2004,[5] and relatively recently by Sugi in 2016,[6] however none of these syntheses seem capable of supplying enough material to continue the needed biological testing. The goal of this project was to create an economic, efficient, and scalable asymmetric route to azaspirene and potential analogs to allow for further biological testing. With ample amounts of material, more could be learned

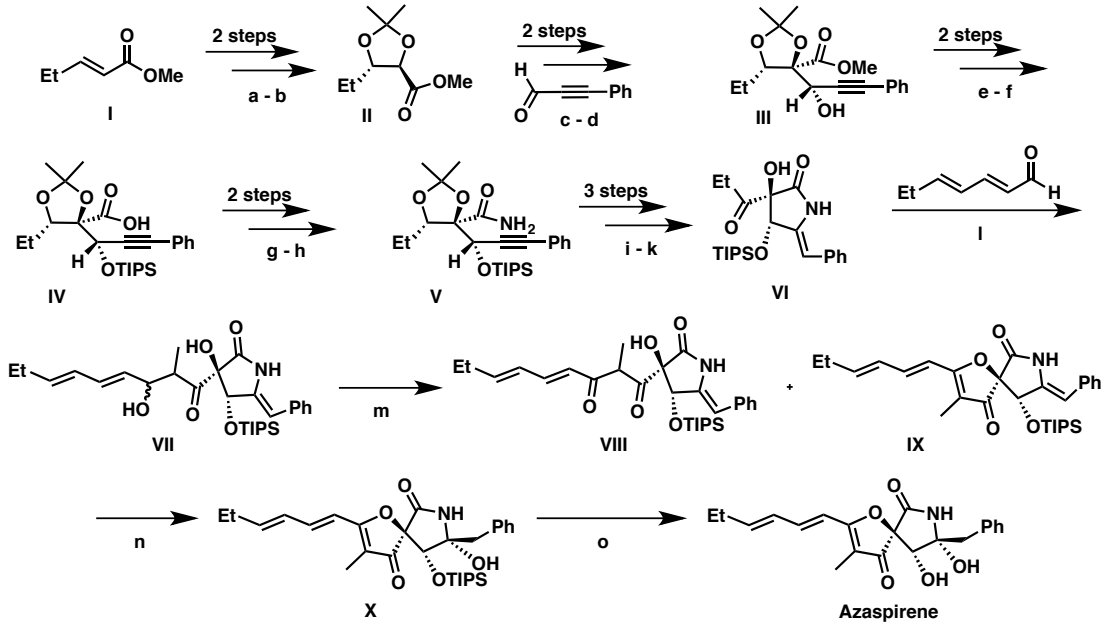
about the mode of action of azaspirene and structural activity relationship (SAR) studies could be undertaken to aid in the preparation of novel analogs also acting as potent angiogenesis inhibitors.

The three major challenges with synthesizing azaspirene were 1) forming the 1-oxa-7-azaspiro[4,4]non-2-ene-4,6-dione ring system, 2) installing the tertiary alcohols associated with the core, and 3) the addition of the unsaturated "tail" group to use as a point of future diversification and making analogs. The three previous syntheses of azaspirene as well as the synthesis herein all vary in those three aspects of the synthesis. The major goals for this synthesis were 1) create the first efficient and scalable route to azaspirene, 2) allow for late stage incorporation of the "tail" unit of azaspirene to use as a point of future diversification, and 3) incorporate novel copper catalyzed conjugate addition methodology. This approach of using CuI·DMS is discussed further in Chapter 4.

2.5.1 The Osada Route to Azaspirene

The Osada group was responsible for the discovery of azaspirene as well as the first total synthesis of the compound as shown in Scheme 2.2.[2] This route consisted of 15 steps starting from achiral (*E*)-methyl-2-pentenoate **I** and gave a total yield of 2%. The Osada group created the spirocycle carbon center very early in the synthesis which included one of the tertiary alcohol moieties to be incorporated into the keto side of the spirocycle followed by constructing each side of the spirocycle around that center. The second tertiary alcohol was then added in the final steps of the synthesis. The late stage addition of this tertiary alcohol eliminated the need for a protecting group. A potential problem with the tertiary alcohols is they have the possibility to eliminate once protected due to the stability of the tertiary carbocation

that would be formed. The “tail” of azaspirene was also added later in the synthesis modeled after the proposed biosynthesis of the Osada group.



Reagents: a) $(DHQ)_2PHAL$, $K_2OsO_4{\cdot}2H_2O$, $K_3Fe(CN)_6$, K_2CO_3, $CH_3SO_2NH_2$, t-BuOH:H_2O; b) $Me_2C(OCH_3)_2$, $TsOH{\cdot}H_2O$, CH_2Cl_2; c) LDA, TBSOTf, THF; d) $MgBr_2{\cdot}OEt_2$, phenypropargyl aldehyde, CH_2Cl_2; e) TIPSOTf, 2,6-leutidine, CH_2Cl_2; f) LiOH, t-BuOH; g) $(COCl)_2$, Et_3N, cat. DMF, CH_2Cl_2; h) liq. NH_3; i) NaH, DMF; j) TFA:MeOH - 10:1; k) DMP, H_2O, CH_2Cl_2; l) LDA, HMPA, (2*E*,4*E*)-hepta-2,4-dienal, THF; m) DMP, CH_2Cl_2; TLC; n) $TsOH{\cdot}H_2O$, CH_2Cl_2; o) NH_4F, MeOH

Scheme 2.2: Osada’s Total Synthesis of Azaspirene

The Osada synthesis started with (*E*)-methyl-2-pentenoate (**I**) which underwent a Sharpless asymmetric hydroxylation reaction followed by protection of the diol as an acetal group using dimethoxy propane in the presence of catalytic amounts of p-toluenesulfonic acid which gave compound **II** in a combined yield of 70%. In the next step, a Mukaiyama aldol reaction between compound **II** and phenylpropargyl aldehyde in the presence of magnesium bromide etherate acting as a Lewis acid gave compound **III** in a 69% purified yield of the correct diastereomer. The quaternary carbon stereocenter created in **III** establishes the spirocyclic center of azaspirene. The alcohol formed during the aldol condensation was protected as a TIPS ether using TIPSOTf and 2,6-lutidine prior to the hydrolysis of the methyl ester

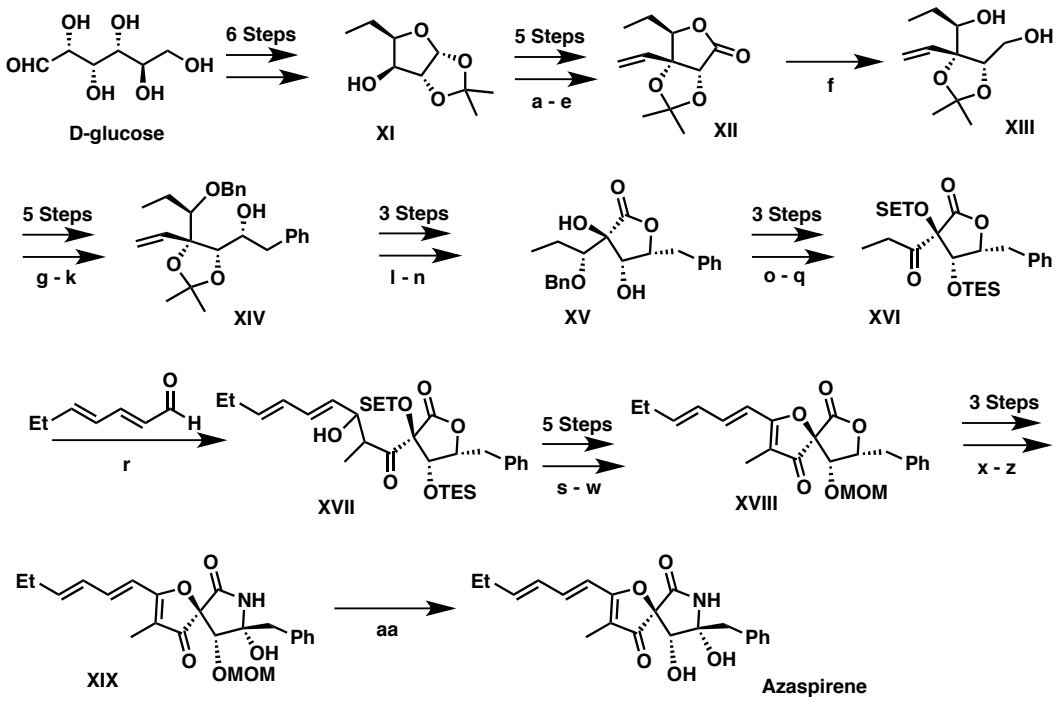
using LiOH and *t*- BuOH which gave carboxylic acid **IV**. The carboxylic acid was converted to an acyl chloride and then transformed into the corresponding amide using liquid ammonia that gave amide **V** in a combined 45% yield. Compound **V** then spontaneously cyclized upon amide deprotonation with sodium hydride to form the benzylidene lactam and the right half of the spirocycle. The acetal group was cleaved under acidic conditions followed by oxidation of the secondary alcohol with Dess-Martin periodinane (DMP) to give compound **VI** in a 69% yield over three steps. The "tail" of azaspirene was then incorporated by means of an aldol reaction between **VI** and (2*E*,4*E*)-heptadienal which gave compound **VII** in only 50% yield. The spirocycle **IX** was spontaneously created when the alcohol produced by the aldol reaction was oxidized using DMP (**VIII**). The tertiary alcohol of azaspirene was installed by hydrating the benzylidene with p-toluenesulfonic acid which provided compound **X** in 91% yield. The TIPS protecting group was then removed in the final step by using ammonium fluoride in methanol that provided azaspirene in a 35% yield.

Although this was a relatively short route, the low total yield and the small scale of most reactions being under 200 mg would make it difficult to produce large quantities of azaspirene to sustain continued biological testing.

2.5.2 The Tadano Route to Azaspirene

The next total synthesis of azaspirene was reported by Tadano *et. al* in 2004, which was accomplished in 33 steps starting from D-glucose with a total yield around 2%.[5] The Tadano route to azaspirene was adopted from their own routes to pseurotin A and synerazole,[27] and is illustrated in Scheme 2.3 below. The chiral information provided by glucose was taken advantage of as a starting point to direct

the chirality in the rest of azaspirene. Even though the Tadano synthesis is longer, there are several similarities between the Tadano and the Osada routes. The tertiary oxygen of the spirocycle was created similarly near the beginning of the synthesis. The unsaturated side chain was incorporated into the molecule following the same methodology as Osada. Moreover, the tertiary alcohol of azaspirene was created in the final steps eliminating the need for a protecting group. The unique features of the Tadano route are the use of a lactone within the synthesis to build up the spirocycle and then the use of an ammonolysis reaction that simultaneously converts the lactone to the corresponding lactam and provides the essential tertiary alcohol of azaspirene.



Reagents: a) PCC, 4A m.s., CH_2Cl_2; b) allyl-MgBr, THF; c) AcOH / H_2O; d) NIS, TBAI, CH_2Cl_2; e) $Me_2C(OMe)_2$, Me_2CO, CSA; f) $LiAlH_4$, THF; g) TrCl, DMAP, Pyr.; h) BnBr, NaH, DMF; i) CSA, MeOH, EtOAc; j) DMP, CH_2Cl_2; k) BnMgBr, CuBr, DMS, THF; l) O_3, Ph_3P, CH_2Cl_2; m) TFA, H_2O; n) NIS, TBAI,CH_2Cl_2; o) TESOTf, Pyr.; p) H_2, 10% Pd / C, EtOH; q) DMP, CH_2Cl_2; r) KHMDS, LiBr, THF; s) HF·Pyr., Pyr., THF; t) DMP, CH_2Cl_2; u) $SOCl_2$, Pyr.; v) HF·Pyr., Pyr., THF; w) $CH_2(OMe)_2$, P_2O_5, DCM; x) sat NH_3 in *i*-PrOH; y) DMP, CH_2Cl_2; z) sat. aq. Na_2CO_3; aa) 6M HCl, MeOH

Scheme 2.3: Tadano's Total Synthesis of Azaspirene

The Tadano route began with the preparation of 5,6-dideoxy-1,2-*O*-isopropylidene-α-*D*-*xylo*-hexofuranose (**XI**) from *D*-glucose in a six step synthesis from the literature.[28,29] The secondary alcohol of **XI** was oxidized to a ketone using pyridinium chlorochromate (PCC) in the presence of molecular sieves. This ketone was then reacted with a vinyl Grignard reagent under normal conditions that gave a single diastereomer in 83% yield. Acid hydrolysis of the acetal group allowed for a tetrabutylammonium iodide (TBAI) assisted *N*-iodosuccinimide (NIS) oxidation of the hemiacetal carbon that was accomplished in good overall yield. Acetal protection of the newly formed *cis*-diol using dimethoxy propane resulted in compound **XII**. Reduction of lactone **XII** with $LiAlH_4$ opened the ring and formed diol **XIII**. Selective protection of the primary alcohol of **XIII** with trityl chloride in the presence of DMAP in pyridine and subsequent protection of the secondary alcohol of **XIII** as the benzyl ether, using benzyl bromide and sodium hydride in DMF, made it easy for the selective deprotection of the trityl ether using camphorsulfonic acid (CSA). Subsequent oxidation of the primary alcohol using DMP gave the corresponding aldehyde in 96% yield. The benzyl group was introduced in a unique Grignard addition using benzyl-MgBr in the presence of CuBr·DMS which gave product **XIV** in an 89% yield. Ozonolysis of **XIV** followed by acid hydrolysis of the acetal group and chemoselective oxidation using *N*-iodosuccinimide (NIS) provided lactone **XV** in an 84% yield over three steps. Both alcohol groups of **XV** were protected as TES ethers using TESOTf in pyridine. Removal of the benzyl group by hydrogenation using hydrogen in the presence of 10% palladium on carbon followed by oxidation with DMP provided **XVI** in high yield. Similar to the Osada route, compound **XVI** set up an aldol reaction to connect what eventually became the “tail” of azaspirene. The aldol

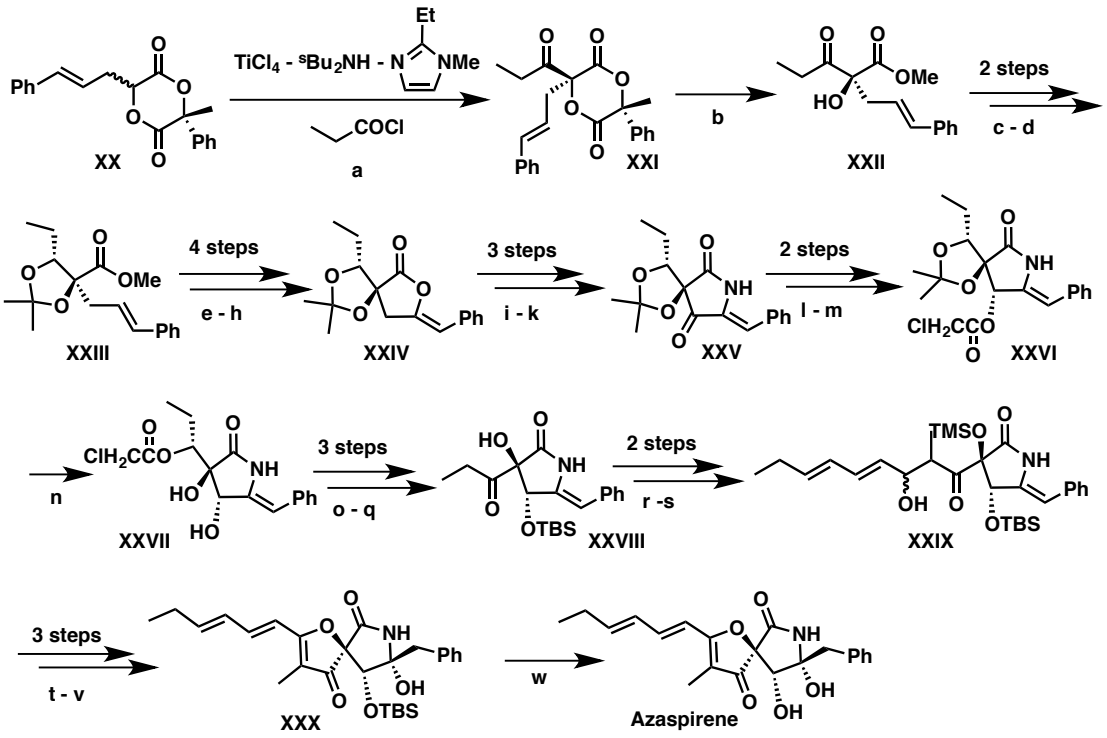
reaction between (2*E*,4*E*)-heptadienal and compound **XVI** using KHMDS in the presence of excess LiBr produced compound **XVII**. Selective deprotection of the tertiary TES ether was accomplished using a dilute HF·pyridine solution in a 59% yield over two steps. The alcohol formed from the aldol reaction was then oxidized using DMP which allowed for the cyclization and formation of the spirocycle in a two-step 42% overall yield. Protecting group manipulation from O-TES ether to the MOM ether gave compound **XVIII** in 72% yield. The lactone **XVIII** was then converted to lactam **XIX** over three steps in a combined 85% yield. First the lactone underwent a ring opening in an ammonolysis reaction using saturated ammonia in isopropanol. Oxidation of the resulting alcohol with DMP followed by treatment with saturated sodium carbonate then afforded the intramolecular attack of the amide-nitrogen to the carbonyl to produce hemi-aminal **XIX**. Finally, deprotection of the MOM ether using 6M hydrochloric acid in methanol gave the desired product azaspirene in a 51% isolated yield.

Although the reported Tadano route was impressive in terms of the high overall yield, the number of steps makes the route impractical for the preparation of large amounts of azaspirene for biological testing. Making use of a more reactive lactone for the majority of the synthesis and conversion into the lactam in the final steps while creating the final tertiary alcohol was a similar methodology adopted in the final route to azaspirene presented in this thesis.

2.5.3 The Sugi Route to Azaspirene

A recent route published in 2016 by Sugi *et. al*[6] achieved azaspirene from a chiral precursor in 23 steps with an overall yield of just under 2%. The route shared some similar intermediates with the Osada route but it took advantage of novel

titanium chemistry for some of the key transitions. Overall, the route was not an improvement on the efficiency or scalability over the other published routes to azaspirene. The Sugi synthesis is shown in Scheme 2.4 below.[6]



Reagents: a) DCM, -25 °C, 0.5 h; b) MeONa / MeOH, -50 °C, 5 h, 0 °C, 1 h; c) $NaBH_4$, $ZnCl_2$/THF; d) $Me_2C(OMe)_2$, CSA/acetone; e) 5 M aq. KOH / MeOH; f) I_2, $Et_3N^+BnCl^-$, sat. $NaHCO_3/CH_2Cl_2$; g) DBU, H_2O/DMF; h) Ac_2O; i) SeO_2/ dioxane; j) NH_3/iPrOH; k) cat. PPTS/benzene; l) $NaBH(OAc)_3$/THF/AcOH; m) $(ClCH_2CO)_2O$, cat. DMAP, Et_3N/CH_2Cl_2; n) TFA, H_2O/CH_2Cl_2; o) TBSOTf, 2,6-lutidine/CH_2Cl_2; p) 2-aminophenol, NaHMDS/THF; q) Dess-Martin periodinane, H_2O/CH_2Cl_2; r) BSA, $PyH^{+\cdot-}OTf$/THF; s) (2E,4E)-heptadienal, $TiCl_4$-Bu_3N/CH_2Cl_2; t) HF-pyridine; u) Dess-Martin periodinane/CH_2Cl_2; v) $TsOH{\cdot}H_2O$; w) $PhCO_2H$, TBAF/CH_2Cl_2

Scheme 2.4: Sugi total synthesis of Azaspirene

The route developed by Sugi *et. al* started with chiral precursor **XX** which was synthesized in six steps from *tert*-butyl acetoacetate, cinnamoyl chloride and (*R*)-atrolactic acid in a 39% combined yield.[6] Compound **XXI** was made via a titanium directed cross-Claisen reaction between an acyl chloride and the chiral moiety **XX** using titanium tetrachloride, di-*sec*-butylamine, and 2-ethyl-1-methylimidazole. The absolute stereochemistry of **XX** directed the asymmetric Claisen to occur in >95% d.r.

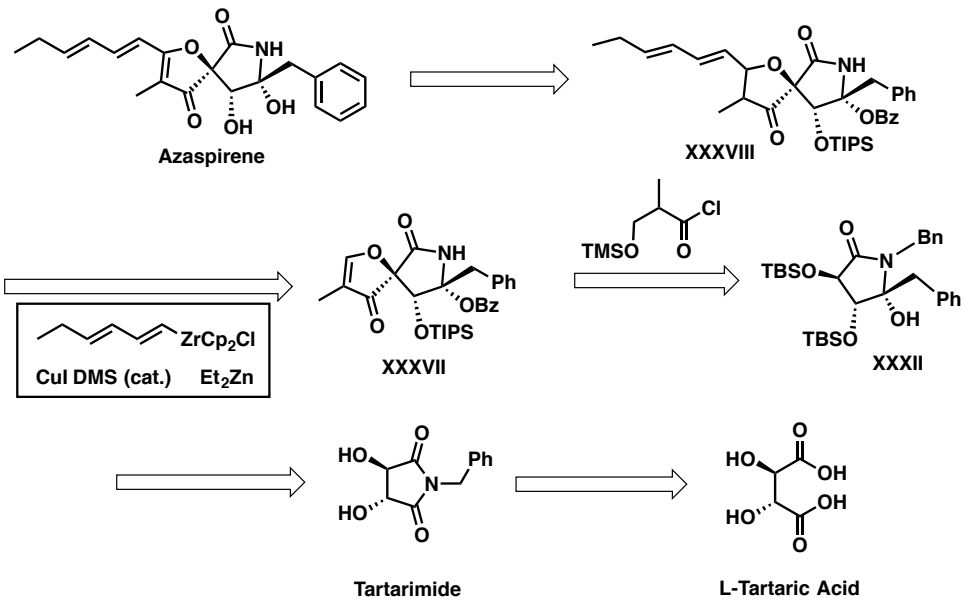
and 78% yield. The titanium mediated methodology employed by Sugi is one of two titanium catalyzed reactions that made this route unique. Compound **XXII** was formed by cleavage of the chiral group on **XXI** in an 86% yield. Compound **XXII** established the stereochemistry of the spirocenter of azaspirene with the formation of the tertiary alcohol. Selective reduction with $NaBH_4$ and protection of the resulting diol as the acetal using 2,2-dimethoxypropane gave compound **XXIII** in an 81% yield over two steps. Compound **XXIII** was hydrolyzed under basic conditions and then subjected to an iodolactonization using iodine, triethylaminobenzylchloride and saturated sodium bicarbonate as a base. The product was treated with DBU and water to provide a ketocarboxylic acid intermediate that cyclized into compound **XXIV** when treated with acetic anhydride. Lactone **XXIV** was subjected to selenium oxide which performed an allylic oxidation followed by ammonolysis and dehydration using pyridinium *para*-toluenesulfonate (PPTS) that resulted in spontaneous recyclization into lactam **XXV**. Asymmetric reduction using sodium triacetoxyborohydride followed by protection of the alcohol as the α-chloroacetate with $(ClCH_2CO)_2O$ gave **XXVI** in good yield. Cleavage of the acetal with TFA caused the migration of the chloroacetate group to the non-allylic secondary alcohol in **XXVII**. Reprotection of the allylic alcohol as a TBS ether using TBSOTf followed by deprotection of the chloroester using 2-aminophenol and NaHMDS and subsequent oxidation of the resulting alcohol with DMP led to compound **XXVIII**. Compound **XXVIII** now has the same core as the intermediate reported by the Osada group (Cmpd **VI**, Scheme 2.2) except for the TBS ether instead of a TIPS ether. The Osada group achieved their intermediate **VI** in 6 fewer steps than the Sugi group. The side chain of azaspirene was added by the Sugi group after a TMS protection of the tertiary alcohol using a

titanium-directed aldol reaction. The Sugi group reported the use of a titanium-directed aldol over the more traditional aldol reaction used by Osada or Tadano. Despite the reported robustness of the titanium-directed aldol methodology, the reported yield was slightly less than Osada's group. Deprotection of **XXIX** with HF·pyridine followed by oxidation using DMP then led to the spontaneous cyclization to the spirocycle, which is a similar transformation reported by Osada and Tadano. The final tertiary alcohol was then installed with p-toluenesulfonic acid which gave compound **XXX**. The final deprotection of the TBS ether with benzoic acid and TBAF gave azaspirene in a 70% purified yield.

Overall the Sugi route demonstrated a practical application of the titanium mediated cross-Claisen and aldol reactions, however the route is six steps longer than the Osada route to obtain the common intermediate **XXVIII**. Moreover, the overall yield of the Sugi route was the lowest of the reported routes found in the literature to date.

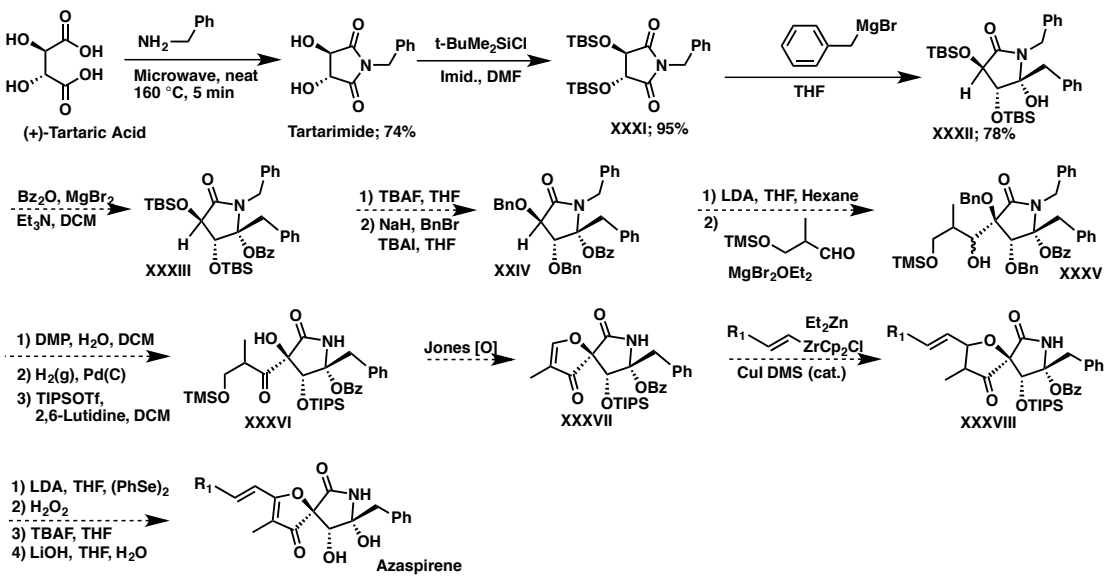
2.6 First Proposed Route to Azaspirene

The first route to azaspirene was built around the key intermediate **XXXVII** (Scheme 2.5). This intermediate would allow for late stage incorporation of the "tail" unit of azaspirene and highlight novel methodology that was being developed in the laboratory. Previous laboratory members had demonstrated the ability to add vinyl groups to simple α,β-unsaturated enone moieties using vinylzirconocene[30] and vinyl zincate[9] species catalyzed by CuI·DMS. An expansion of this methodology to allow vinyl groups to add to β-oxygenated enones similar to the left half of compound **XXXVII** is further discussed in Chapter 3.



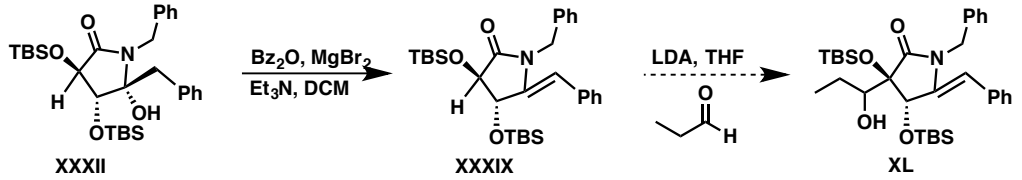
Scheme 2.5: First proposed retrosynthetic route to Azaspirene

The proposed route used *L*-tartaric acid as a chiral starting material because it is cheap, readily available and contained two of the three chiral centers found in azaspirene. The tartaric acid was converted to the subsequent tartarimide which was the basis for the amide half of the spirocycle backbone. The rest of the spirocycle would be built up from the Claisen condensation between **XXXII** and 2-methyl-3-((trimethylsilyl)-oxy)propanoyl chloride. Subsequent removal of the TMS group and oxidation of the alcohol would allow for the cyclization into key intermediate **XXXVII**. As mentioned previously, intermediate **XXXVII** would be a key point in diversifying azaspirene using the copper catalyzed vinyl zincate chemistry. After the "tail" was attached to give **XXXVIII**, oxidation followed by global deprotection would complete the synthesis of azaspirene.



Scheme 2.6: First proposed route to Azaspirene

The proposed route shown in Scheme 2.6 consisted of 17 steps from (+)-tartaric acid to azaspirene.[31] Tartaric acid was converted to the corresponding tartarimide using benzyl amine in a microwave reactor in a 74% yield. The two hydroxyl groups were then protected as their TBS ethers **XXXI** in a high 94% yield. The benzyl group of azaspirene was added by means of a Grignard reaction with benzyl-MgBr to produce the desired diastereomer **XXXII** in a 78% yield. The next step was to protect the tertiary alcohol of **XXXII** as a benzoyl ether however protection frequently led to elimination that produced the benzylidene lactam **XXXIX** (Scheme 2.7). Repeated attempts at protecting the tertiary alcohol continued to lead to the elimination product.[31] Although the hydroxyl group eliminated, it can potentially be reintroduced to the benzylidene lactam as reported by Osada *et. al.* The next steps of the route were modified as shown in Scheme 2.7 to make use of the benzylidene **XXXIX**. Unfortunately the aldol reaction to **XXXIX** was also unsuccessful in completing the synthesis of intermediate **XL**.



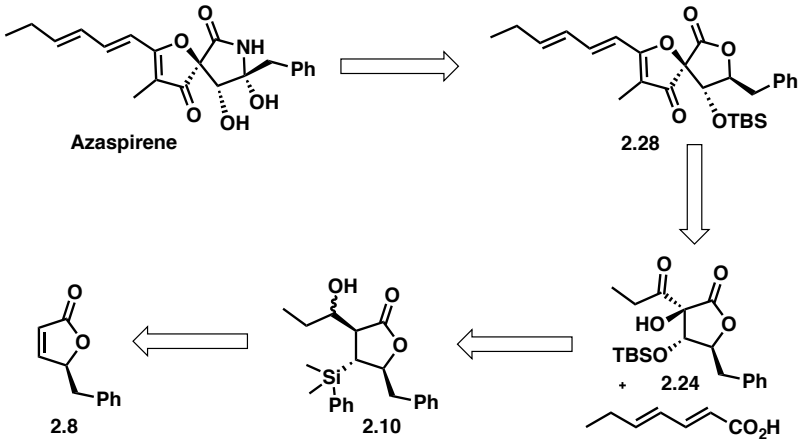
Scheme 2.7: Altered route to Azaspirene

Having a sterically demanding group in the *alpha* position of the lactam was believed to hinder the reaction. To circumvent this, a derivative of compound **XXXIX** was synthesized from malic acid which lacked the masked α-hydroxyl group. Unfortunately, the aldol addition to the malimide derivative was only accomplished in low yields (<40%).[31] Due to the low yielding aldol reactions, a new route that contained a more reactive lactone species was proposed. This new route would allow the incorporation of novel copper catalyzed silylzincate conjugate addition methodology.

2.7 Final Route to Azaspirene

With problems due to the reactivity of the lactam, the final route to azaspirene was modeled after using a more reactive lactone to construct the spirocycle. The plan was then to convert the lactone into the corresponding lactam following the Tadano route.[5] Although the new route did not incorporate the vinylzincate addition methodology, it did incorporate novel methodology for a silylzincate to aldol addition reaction also being developed in the laboratory. The silylzincate methodology will be discussed further in Chapter 4 of this thesis. The retrosynthetic route to azaspirene is shown in Scheme 2.8. The route began with the chiral unsaturated lactone **2.8** which could be built up from *L*-phenylalanine using published procedures[32–37] in good yields and on a multigram scale. The benzyl group offered a point of chirality from which to build up the other stereocenters of the spirocycle. Lactone **2.8** could then

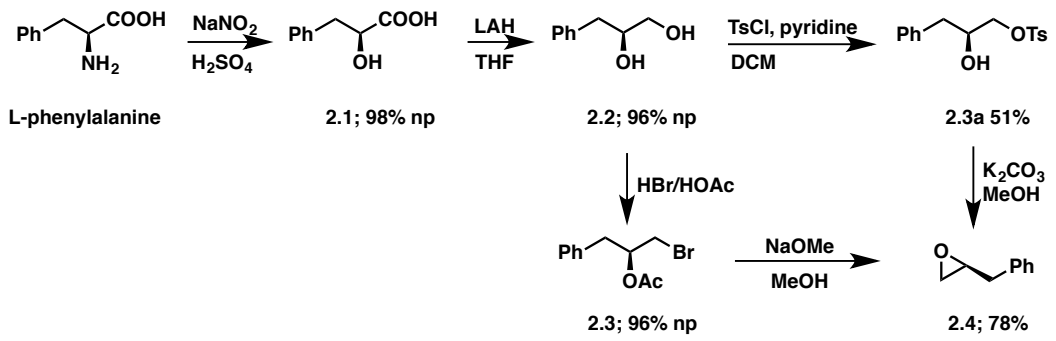
undergo a one-pot conjugate silyl addition to aldol trapping reaction to obtain compound **2.10**. The "tail" of azaspirene was added using a peptide coupling reaction between **2.24** and (*2E,4E*)-heptadienoic acid followed by an intramolecular aldol condensation to complete the spirocycle **2.28**. Ammonolysis of the lactone to the lactam and deprotection gave azaspirene in 11 steps with a 6% overall yield.



Scheme 2.8: Retrosynthetic route to Azaspirene

2.7.1 Building the Unsaturated Lactone

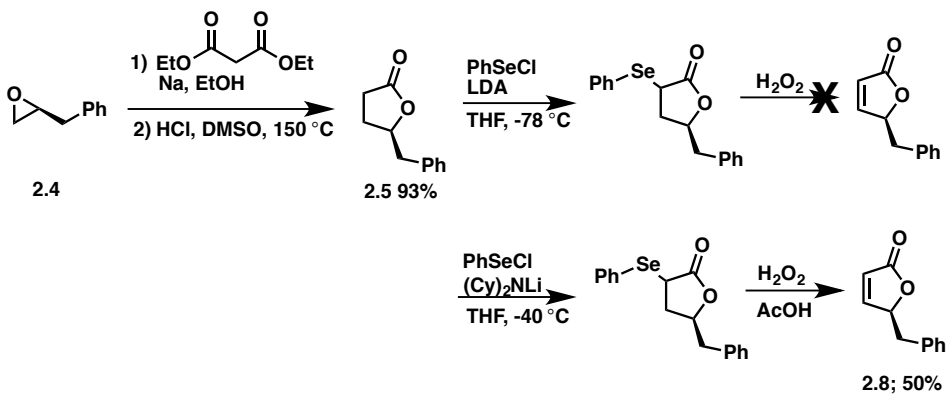
Although chiral unsaturated lactone **2.8** is commercially available, a synthesis was developed starting from *L*-phenylalanine that could provide the necessary chiral lactone on the multigram scale. An amino acid was chosen because it was cheap, readily available, and contained the needed chiral information. The point of chirality of the lactone enabled the spirocycle core of azaspirene to be built up in an asymmetric fashion. The first phase of the synthesis was building chiral unsaturated lactone **2.8**. *L*-phenylalanine was converted to the α-hydroxy acid **2.1** with retention of stereochemistry via a diazotization reaction[32] using sodium nitrate and sulfuric acid as shown in Scheme 2.9.



Scheme 2.9: Building epoxide 2.4

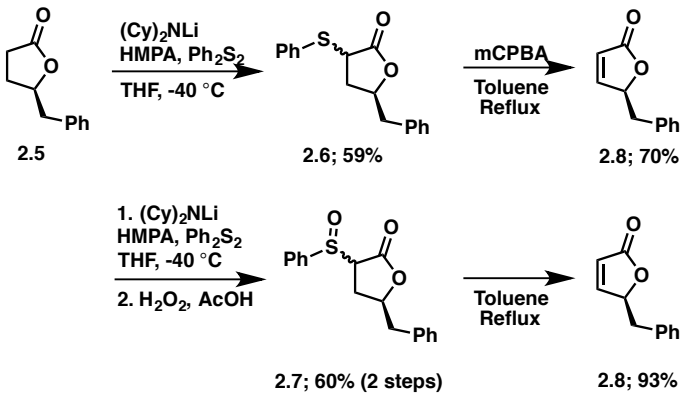
The desired α-hydroxy acid was obtained in 98% yield without the need for purification. Reduction of **2.1** with LAH gave the chiral diol **2.2** in a 96% crude yield also without the need for purification. The epoxide **2.4** could then be formed from an intramolecular attack of the secondary alcohol on the tosyl-protected primary alcohol **2.3a**. Attempts to tosylate the primary alcohol on **2.2**[38] failed to be selective for the primary alcohol over the secondary alcohol in more than a 51% yield. To optimize the formation of epoxide **2.4,** diol **2.2** was subjected to 33% hydrobromic acid in acetic acid which selectively acylated the secondary alcohol and introduced a bromine atom at the primary alcohol position to give acylbromide **2.3**.[33] Compound **2.3** was then subjected to sodium methoxide to give chiral epoxide **2.4** in a 78% purified yield from diol **2.2**.[39]

Epoxide **2.4** then underwent a ring expansion reaction involving diethyl malonate and sodium ethoxide to produce chiral lactone **2.5** in a 93% yield[35] (Scheme 2.10). Attempts were made to use phenyl selenium chloride and LDA followed by oxidation with hydrogen peroxide during the reaction workup[40] to convert **2.5** into the unsaturated lactone **2.8**.



Scheme 2.10: Oxidation of saturated lactone 2.5 with PhSeCl

The reaction with PhSeCl did not produce the desired unsaturated lactone **2.8** but produced instead a condensed ester side product. These results were confirmed when reviewing papers by Sharpless[41] and Rathke[42] which discussed the problem of ester enolates undergoing self-condensation reactions. Rathke discovered that the potential for ester self-condensation was dependent on the base used. According to the work of Rathke, *N*-isopropylcyclohexylamine did not allow for the ester self-condensation. The reaction was attempted with dicyclohexylamine which provided a 50% yield of the desired unsaturated lactone **2.6** with the remainder being the unreacted saturated lactone **2.5** (Scheme 2.10). A problem still remained however, because the unsaturated lactone product and saturated lactone starting material were inseparable on silica. To bypass this problem, diphenyl disulfide was used instead of phenyl selenium chloride because the diphenyl disulfide oxidation was a two-step process allowing the sulfonated compound to be separated from the starting material before it was eliminated to form unsaturated lactone **2.8**[36] (Scheme 2.11).



Scheme 2.11: Completion of the unsaturated lactone 2.8

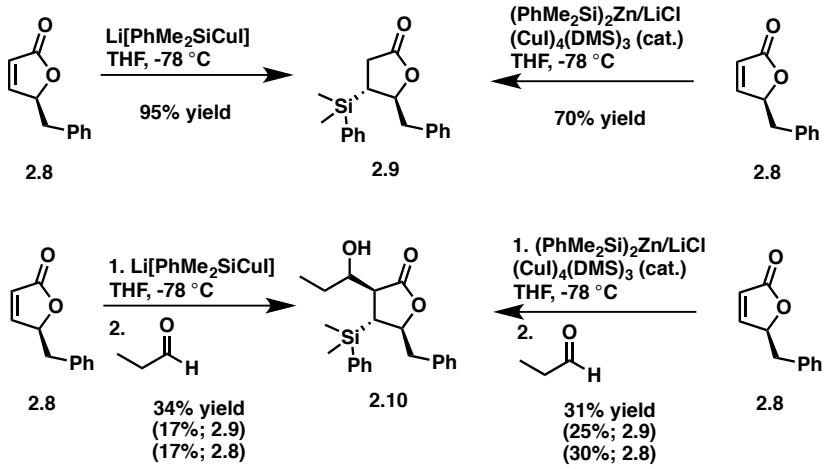
The use of lithium dicyclohexyl amine and diphenyl disulfide gave compound **2.6** in a 59% yield with a 35% recovery of the starting lactone. Purification was done on the sulfide followed by oxidation by *m*CPBA to provide a 70% yield of lactone **2.8** however the noxious odor of compound **2.6** led to bypassing the purification step. An excess of *m*CPBA used on crude **2.6** would lead to the overoxidation to the corresponding sulfone product. It was discovered that hydrogen peroxide with acetic acid was a milder oxidant which could be used in excess to form sulfoxide **2.7** without overoxidation to the corresponding sulfone.[37] Sulfoxide **2.7** was also successfully separated on silica from lactone **2.5**. An elimination reaction in refluxing toluene gave **2.8** in a 93% yield. Despite repeated attempts with different bases and additives, the yield of the conversion of **2.5** to **2.7** could not be increased but the use of lithium hexamethyldisilizane (LiHMDS) gave similar yields in the end.

2.7.2 Installing the alcohols

With an ample supply of chiral lactone **2.8**, the next steps in the synthesis of azaspirene could commence. A key intermediate of this route is α-hydroxy-lactone **2.24** which would allow for the side chain incorporation and spirocycle formation. The first step towards this lactone was to incorporate a phenyldimethylsilyl ($PhMe_2Si$)

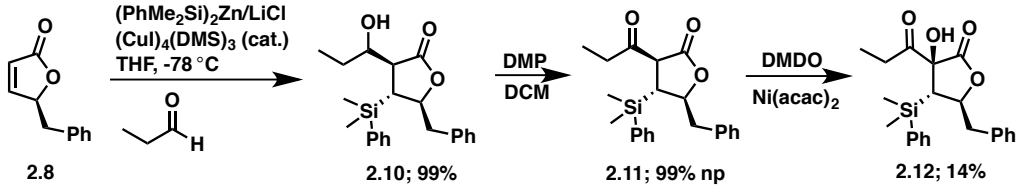
group in the *beta* position of the lactone ring. This silyl group was used for two reasons: First, it allowed for the incorporation of methodology involving a disilylzinc reagent[7,13] or silylcuprate reagent[10] in the presence of CuI·DMS developed by the Bergdahl group and will be discussed in more detail in Chapter 4 of this thesis. Second, the silyl group functioned as a masked hydroxyl group, or an aldol surrogate, that would undergo a Fleming oxidation to afford the free aldol-alcohol with retention of stereochemistry.[12]

The silyl addition was attempted using either the monosilylcopper reagent, Li[$PhMe_2SiCuI$], which gave the conjugate addition product **2.9** in a 95% yield or using the disilylzinc reagent, $(PhMe_2Si)_2Zn/LiCl$, in the presence of CuI·DMS which gave the same product **2.9** in a 70% yield. The subsequent step in the synthesis was to perform an aldol reaction between compound **2.9** and propionaldehyde. Due to the previous challenges when making the ester enolate of compound **2.7** (Scheme 2.10) and the difficulty of performing the aldol reaction step in the first proposed route, the trapping of the enolate produced in the conjugate addition step with an aldehyde to form compound **2.10** in a "one-pot" reaction was studied (Scheme 2.12).



Scheme 2.12: Various silyl additions to unsaturated lactone 2.8

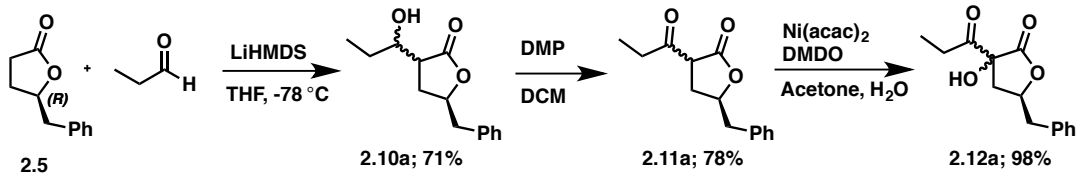
From Noyori's work in 1983[43] it was reported that enolates formed as a consequence of the silyl conjugate additions could be trapped with various activated electrophiles when the electrophile was added to the reaction mixture after the enolate had been formed. Initial attempts at subsequent enolate trapping by quenching the reaction with the aldehyde gave the desired product as well as just the 1,4-product and unreacted starting material (Scheme 2.12) for both reaction conditions. Since there are few reports of zinc enolates reacting with aldehydes,[44] it was exciting that the desired product was formed using the disilylzinc reagent. It was speculated that if the aldehyde was already present when the enolate was initially formed, the yield would increase. The electrophile was traditionally used as a second step to "quench" the enolate and avoid an unwanted reaction between the silyl group and the more reactive electrophile.[45] Previous methodology using the CuI·DMS complex had demonstrated that a 1,2-addition was not likely to occur with mild reagents such as the silylzincates. Thus, the silyl conjugate addition was repeated using the disilylzinc reagent with catalytic CuI·DMS and the substrate and propionaldehyde were added as a pre-mixed solution in THF. The result gave product **2.10** in an improved, outstanding 99% isolated yield as shown in Scheme 2.13.



Scheme 2.13: Conjugate silyl to aldol reaction and incorporation of a tertiary alcohol

The absolute stereochemistry of the silyl group was determined through *J*-couplings as *anti* to both the benzyl group of the ring and the aldol fragment in a >99%

diastereomeric ratio (d.r.). There is a d.r. of 86:14 with respect to the stereochemistry of the alcohol group within compound **2.10** with the major isomer being the alcohol group located *syn* to the silyl group. Compound **2.10** was oxidized using DMP to form diketone **2.11** in a 99% yield without the need for purification.[46] Obtaining a single isomer of **2.11** supported the fact that the stereocenters of the silyl group and aldol fragment in **2.10** were set and that the diastereomeric ratio arose solely from the alcohol group being *syn* or *anti* to the silyl group. The first of the tertiary alcohols was introduced by using dimethyldioxirane (DMDO) with catalytic $Ni(acac)_2$[47] however only starting material and a 14% yield of **2.12** was obtained. To study this reaction further, a test substrate **2.12a** lacking the β-silyl group was used to optimize the DMDO reaction conditions from the saturated lactone **2.5** as shown in Scheme 2.14



Scheme 2.14: Synthesis of a test substrate for DMDO oxidation

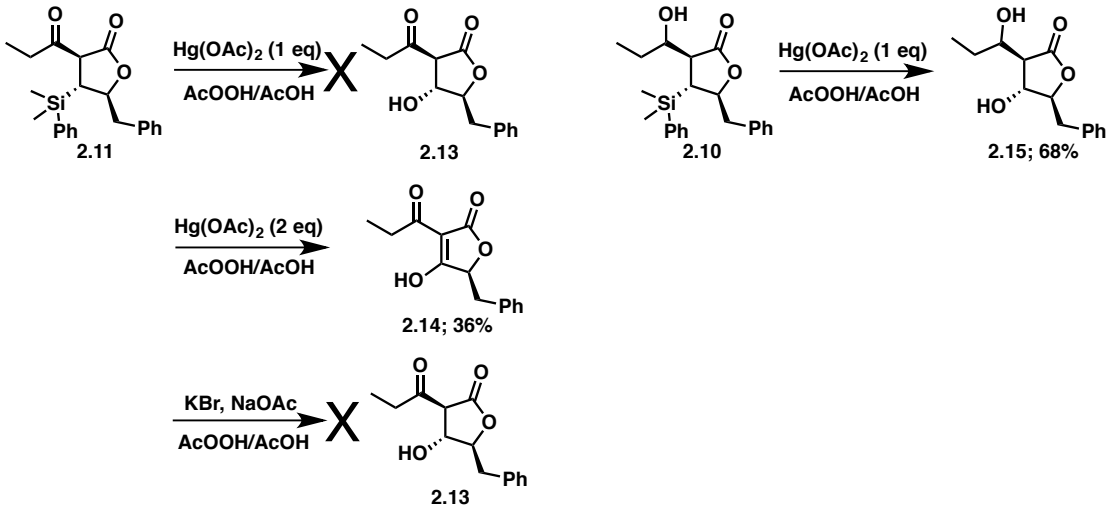
The aldol reaction between lactone **2.5** and propionaldehyde was accomplished using LiHMDS to obtain aldol product **2.10a** in a 71% yield.[48] Oxidation of compound **2.10a** with DMP gave **2.11a** in a 78% yield. Following the same procedure for the DMDO oxidation for compound **2.11**, hydroxylated compound **2.12a** was now produced in a 98% yield. The result showed that the DMDO reaction methodology worked but unfortunately not with the desired diketone **2.11**. Several other epoxidation reagents were used in an attempt to increase the yield of compound **2.12** including oxone in a water/acetonitrile mixture,[49] DMDO using a

palladium catalyst,[50] and *m*CPBA[51] however none of the other methods were able to incorporate the tertiary hydroxyl group. Only starting material was observed on the crude NMR spectra for the reactions. For some unknown reasons, having the silyl group present caused the inactivity of compound **2.11**. The presence of the silyl group was desired since it should direct the addition of the hydroxyl group to add with the correct stereochemistry and avoid the use of a chiral catalyst. It was rationalized that converting the silyl group to a bulky protected alcohol species might allow the hydroxylation to occur but still direct the reaction to form the correct diastereomer.

The Fleming oxidation typically uses mercury acetate with peracetic acid in acetic acid to achieve the desired oxidation product.[10,52] When 1 equiv. of mercury acetate was used to oxidize diketone **2.11** no reaction was observed (Scheme 2.15). When the amount of mercury acetate was drastically increased, the dehydrated compound **2.14** was observed in a 36% yield. The first equivalent of mercury acetate was believed to be chelating to the carbonyl groups therefore making it unavailable to oxidize the silyl group. When excess mercury acetate was used, the silyl oxidation proceeded, however the chelated mercury acetate with excess peracetic acid in the mixture led to the installation of the tertiary hydroxyl group which subsequently dehydrated due to the acidic reaction conditions and produced vinyl ether **2.14**.

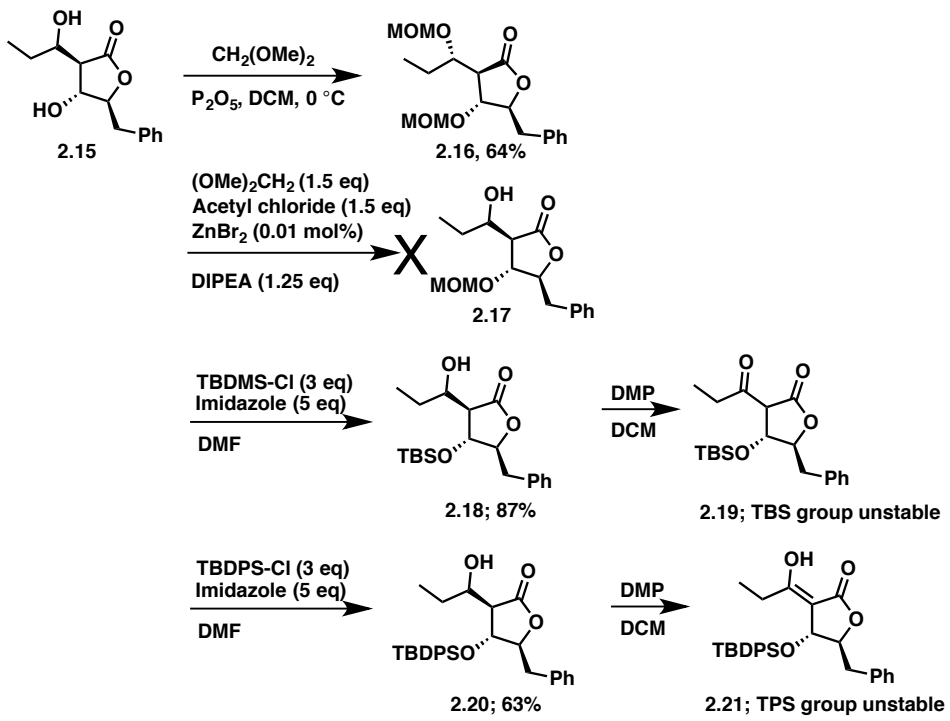
A variation of the Fleming oxidation procedure has been reported describing the use of potassium bromide and sodium acetate with peracetic acid in acetic acid.[53] The idea was that without a chelating metal, the hydroxylation reaction would not proceed. Unfortunately, there was no conversion of the silyl group under the alternate oxidation conditions. To eliminate the problem of the mercury chelating in **2.11**, the Fleming oxidation was performed instead on the silyl-aldol product **2.10**

which successfully produced the chiral diol **2.15** in a good 68% yield with a 30% recovery of the starting diol after 24 hr of mixing (Scheme 2.15). When the reaction was allowed to mix for longer periods of time, the starting material was eventually consumed however undesired side products were also formed.



Scheme 2.15: Fleming Oxidation of the silyl group

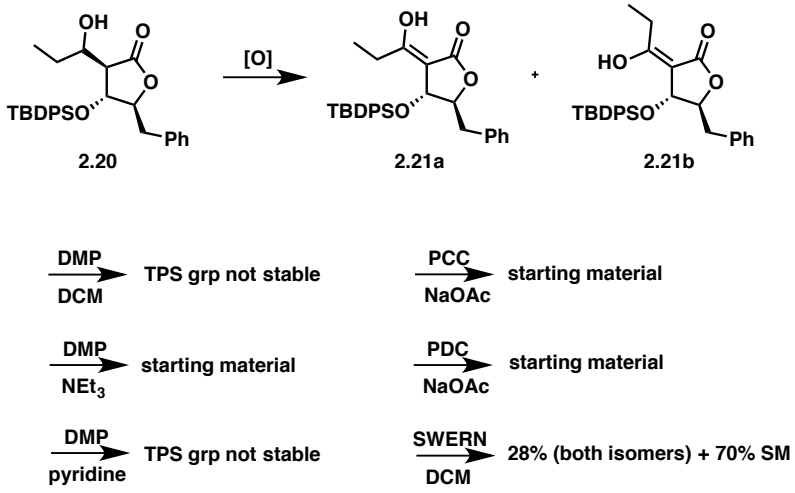
The next step in the revised synthetic route is the selective protection of the ring hydroxyl group over the hydroxyl group on the chain of **2.15**. The protection was attempted with a methoxyl methyl ether (MOM) group because it was known to be compatible with the ammonia hydrolysis conversion of the lactone to the corresponding lactam associated with the azaspirene core. Diol **2.15** was subjected to dimethoxymethane in the presence of phosphorous pentoxide[54] however only di-protected product **2.16** (64% yield) was observed as seen in Scheme 2.16.



Scheme 2.16: Selective protection of diol 2.15

The MOM protection was also attempted under basic conditions using dimethoxymethane with acetyl chloride, zinc bromide and DIPEA[55] however only starting material was observed in the crude NMR spectra. Thus the focus was switched to using a silyl ether as the protecting group. Proter *et. al* specifically described selective protection of a ring hydroxyl groups over a side chain hydroxyl group.[56] Tadano reported previously that the triethylsilyl (TES) ether was cleaved during the ammonolysis reaction so it was hopeful that the more robust silyl ether would be sufficient. Successful protection of diol **2.15** as the *tert*-butyldimethylsilyl (TBS) ether **2.18** was achieved in an 87% yield. The ring hydroxyl group was rationalized to be more reactive due to limited rotation and/or the inability to form a hydrogen bond with the carbonyl group on the ring.

The remaining alcohol group of **2.18** was then subjected to oxidation using DMP to form diol **2.19,** however the oxidation was unsuccessful due to the instability of the TBS group. Moreover, the instability of the TBS silyl ether was unexpected since DMP is often used in the presence of silyl ethers. The TBS silyl ether was replaced with an even more robust and bulkier *t*-butyldiphenylsilyl (TBDPS). The TBDPS silyl ether **2.20** was synthesized in a 63% yield however it was also unstable under the DMP oxidation conditions. Several milder oxidation conditions were attempted as shown in Scheme 2.17 including DMP with pyridine[57] and PCC with sodium acetate[58] but with no success. Finally successful oxidation was achieved using a SWERN oxidation[59] to give isomers **2.21a** and **2.21b** in a combined 28% yield with 70% unreacted starting material.

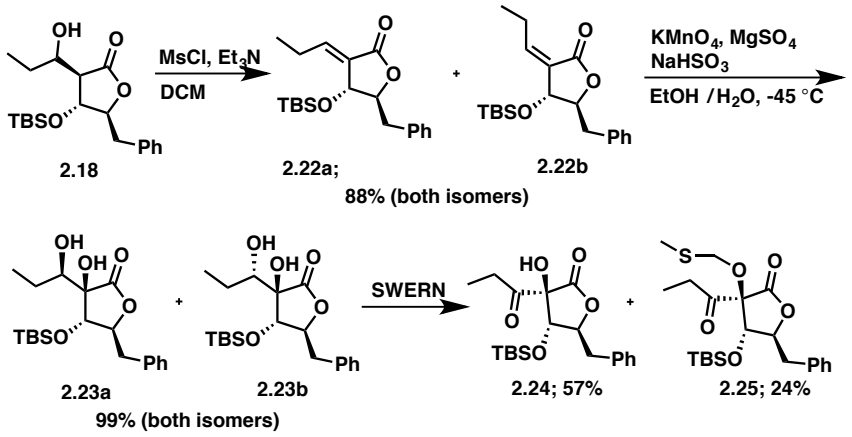


Scheme 2.17: Oxidation of alcohol 2.20

Unlike compound **2.11** that preferably existed as the diketone, product **2.21** preferred the keto-enol tautomerization which is the needed configuration for the DMDO epoxidation to occur. The keto-enol isomers **2.21a** and **2.21b** were subjected to the DMDO oxidation conditions, however all attempts were unsuccessful. It was hypothesized that the bulky nature of the TBDPS group could be hindering the

reaction, the SWERN oxidation was repeated on the TBS protected **2.18** but with similar failed results of adding the tertiary hydroxyl group.

With the DMDO addition unsuccessful, a new method for installing the tertiary alcohol was developed from the TBS protected alcohol **2.18** as shown in Scheme 2.18.



Scheme 2.18: Installing the tertiary alcohol

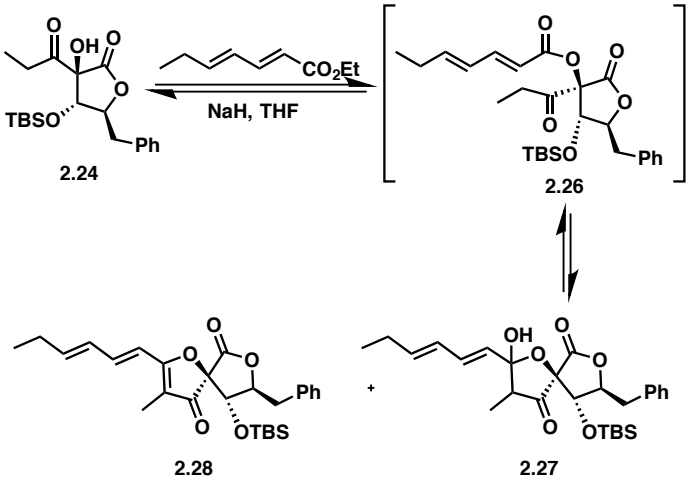
The oxidation of compound **2.18** was circumvented by dehydration using methanesulfonyl chloride (MsCl) in the presence of triethylamine[56] which gave the *E* and Z isomers of compounds **2.22a** and **2.22b** respectively in a 1:1 ratio and in a combined yield of 88%. Although the isomers were separable on silica gel, they were used together in the next step. The tertiary alcohol was installed in a dihydroxylation reaction using potassium permanganate in the presence of magnesium sulfate and sodium bisulfite.[60] Although the addition with potassium permanganate could not be directed as with the Sharpless dihydroxylation method,[61] it was attempted first to avoid the high toxicity of the osmium tetroxide used in the Sharpless method. The dihydroxylation reaction went in a combined 99% yield to give diols **2.23a** and **2.23b** in the same ratio as the starting alkenes. It was observed that the TBS ether successfully directed the dihydroxylation to occur from the

opposite desirable face. The required stereochemistry of the tertiary alcohol was also preserved in each diastereomer and the racemic secondary alcohol was successfully oxidized in the subsequent step.

A Swern oxidation was used next due to the previous issues of the instability of the silyl ether using other oxidizing agents (Scheme 2.17). Key intermediate diketone **2.24** was obtained in a 57% yield as well as the MTM protected product **2.25** in a 24% yield. The protection of a tertiary alcohol as an MTM ether under Swern conditions has been reported in literature as a common way of protecting tertiary alcohols[62] and resulted from the formation of methylene thiomethane as a side product during the oxidation. Quenching at reduced temperatures to avoid the unwanted protection as well as deprotection of the MTM group using either $HgCl_2$ or $AgNO_3$[63] failed. To circumvent the MTM protection, the oxidation was attempted with DMP with mixed results. Only the *syn* diol **2.23a** was oxidized by DMP to provide diketone **2.24**. Even after 7 days, none of the *anti* diol **2.23b** was converted to diketone **2.24**. The *syn* diol **2.23a**, resulted from the *E* alkene **2.22a** however all attempts at an *E* selective dehydration[56,64] of **2.18** were unsuccessful. A small amount of diketone **2.24** was observed when conducting the dihydroxylation step on a multigram scale therefore the use of excess potassium permanganate was investigated as well as running the reaction at elevated temperatures but only a 9 mol % conversion by crude ^{1}H NMR of the diol to the diketone was obtained. At this point, it was decided to move forward with the synthesis even with the lower yield using the Swern oxidation.

2.7.3 Forming the spirocycle

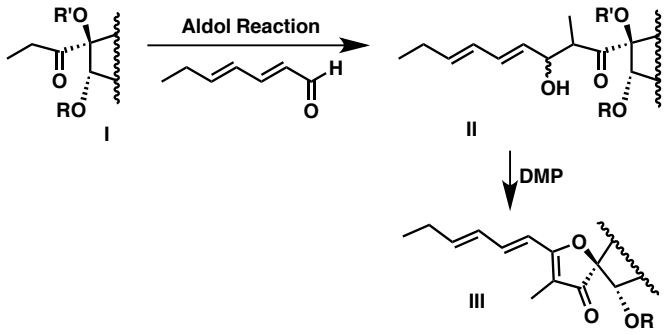
Diketone **2.24** is a key intermediate because, like the previous routes, the side chain of azaspirene would be incorporated allowing the spirocycle to be formed. A robust tail addition was desired because it would simplify the introduction of diversity when creating analogs of azaspirene. Attempts were made to add the tail and form the spirocycle in a one-pot reaction following the unique methodology reported by Margaretha[8] shown in Scheme 2.19 below. The Margaretha reaction was found in the literature when searching for a suitable synthesis to make β-oxygenated enones for the copper methodology projects discussed in later chapters of this thesis. In the original Margaretha paper, 3-hydroxy-3-methylbutanone and ethyl formate acted as the alcohol and ester species respectively.



Scheme 2.19: "Margaretha" attempt at adding the "tail" of Azaspirene

The proposed reaction mechanism would proceed from sodium hydride deprotonating the hydroxyl group on **2.24**. The tertiary alkoxide will then attack the ester to arrive at intermediate **2.26** and form an equivalent of the ethoxide, similar to an initial Claisen condensation. The ethoxide formed *in situ* could then act as the base for the intramolecular aldol reaction to produce hydrated compound **2.27** and

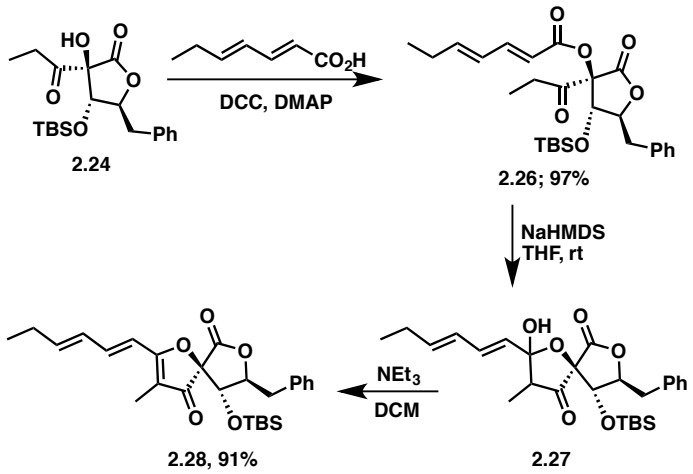
dehydrated compound **2.28**. Based on the literature,[2] the unsaturated spirocycle **2.28** should form upon exposure to silica gel. This methodology is interesting because unlike the previous syntheses, the C—O bond forms initially and then the C—C bond of the new ring. The previous syntheses all followed the opposite order of bond formation as shown in Scheme 2.20. As seen in Scheme 2.20 and discussed earlier in this chapter, the previous routes first added the side chain with an aldol reaction to form the C—C bond of **II** in varying yields. Subsequent oxidation with DMP and removal of the **R'** group allowed for cyclization by formation of the C—O bond.



Scheme 2.20: General method for adding the tail and forming the spirocycle

Initial attempts at utilizing the Margaretha methodology appeared very promising. When ethyl formate was substituted for ethyl (2*E*,4*E*)-heptadienoate, a 29% yield of the hydrated product was obtained. However, when the alcohol was replaced with the more complex alcohol **2.24**, the NaH reacted with the substrate and only the unsaturated ester was observed by NMR. When the base was changed to lithium diisopropyl amide (LDA), a conjugate addition of the amine base to the unsaturated ester was the observed major product. Ultimately, optimization to a high yielding reaction was unsuccessful despite attempting a broad spectrum of combinations of bases, esters, and alcohols.

To progress the synthesis using a unique cyclization route, the Margaretha reaction was simplified by dividing it into two parts. First, a Steglich esterification reaction was used with DCC and DMAP to secure the coupling of diketone **2.24** with (2*E*,4*E*)-heptadienoic acid to obtain compound **2.26** in a 97% yield (Scheme 2.21).[65]

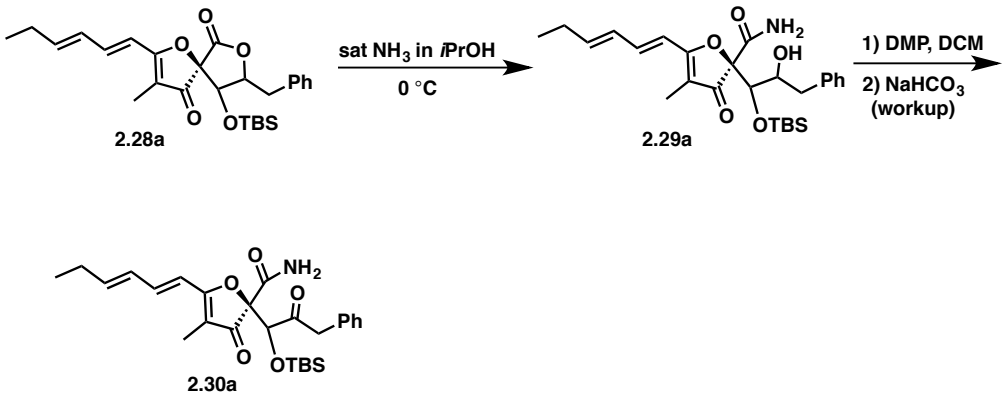


Scheme 2.21: Creation of the spirocycle

The intramolecular aldol/Claisen type reaction of **2.26** to complete the spirocycle was the next challenge. Initially sodium ethoxide in ethanol was employed to maintain the Margaretha methodology, however the ethoxide acted as a nucleophile and opened the lactone. Potassium *tert*-butoxide was also investigated but no reaction occurred. The use of LiHMDS made from *n*-butyl lithium and hexamethyldisilizane gave a 20% yield of a TBS eliminated product. Suspecting that wet HMDS was introduced and *in situ* formed hydroxide, the base was switched to NaHMDS purchased as a 1M solution. The reaction was run from -78 °C → room temperature with NaHMDS which afforded a 50:50 weight mixture of the desired dehydrated product **2.28** and a coupled side product post purification on a silica gel column. Variation of temperature and concentration in order to minimize the coupling product resulted in the ultimate reaction conditions employed as using 1 equiv. of

NaHMDS at room temperature for 1 hr to obtain hydrated **2.27** as the major product on crude ^{1}H NMR. A difficulty in optimization arose because purification of **2.27** on silica gel also gave dehydrated **2.28** and the previously observed coupled side product that resulted in half the mass recovered off the column. The hydrated product could not be purified on the column and the dehydrated product was not visible on the crude NMR. In order to dehydrate compound **2.27** in a more controlled fashion, it was subjected to the dehydration conditions of methanesulfonyl chloride (MsCl) and triethylamine (Et_3N) used previously in the synthesis.

Dehydration using MsCl led to a mix of diastereomers for compound **2.28**. Based on the ^{1}H NMR spectra, it appeared that the scrabbled stereocenter was part of the lactone due to those protons having the greatest difference in ppm shift. However, it was impossible to determine if the benzyl carbon or carbon with the silyl ether stereocenter was scrambling. It was postulated that the ring must have opened to incur racemization even though the previous use of MsCl with Et_3N did not affect the lactone. Repeated attempts at using MsCl to dehydrate **2.27** by varying the temperature and time of the reaction continued to give a mixture of diastereomers without a trend to the d.r. obtained. In the subsequent steps that convert the lactone to the lactam, the benzyl stereocenter is destroyed (Scheme 2.22). With the hopes that the scrambled stereocenter was indeed the benzyl carbon that would get oxidized anyway, the mixture was taken forward through the ammonolysis reaction.



Scheme 2.22: Investigation into the scrambled stereocenter of 2.28a

Mixture **2.28a** was subjected to anhydrous 2M ammonia in isopropanol at 0 °C for one hour[5] to obtain amide **2.29a** as a mixture of diastereomers. Oxidation using DMP was performed but to circumvent the subsequent cyclization, saturated sodium bicarbonate was used in the workup without prolonged mix times. The oxidized product **2.30a** also showed a mixture of diastereomers as products. This concluded that the carbon attached to the TBS ether or the spirocycle itself was isomerizing during the dehydration and therefore, a new method for dehydrating **2.27** was pursued.

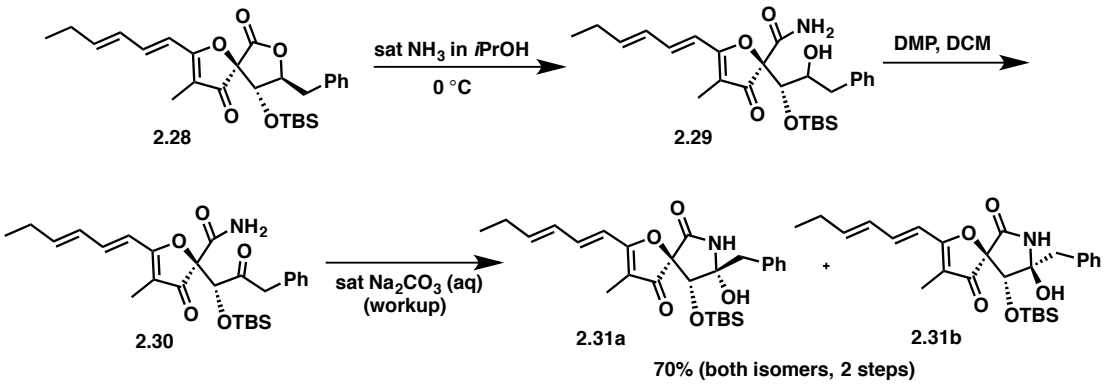
To investigate the origins of the isomerization during the dehydration step, the mixture of diastereomers **2.28a** were subjected to just Et_3N and DCM at room temperature overnight. Amazingly, the diastereomers converged to the desired isomer of compound **2.28**. To expand on that result, the coupled side product that was originally obtained from the silica gel column, when trying to purify hydrated **2.25**, also converged into the desired isomer of compound **2.28** when mixed with Et_3N overnight. The coupled product was suspected to be the result of the enolate of **2.25** performing a conjugate addition to a second molecule of **2.25**. Excited with an

apparent retro-aldol phenomenon, compound **2.25** was subjected to Et_3N in DCM overnight, however the intramolecular aldol condensation did not occur.

Ultimately, the dehydration step using Et_3N in DCM was incorporated into the workup of compound **2.27** that gave spirocycle **2.28** in a 91% yield from compound **2.26**. Even though the Margaretha methodology was broken down into two separate steps, the tail attachment and spirocycle formation were successfully completed in an 88% combined yield from key intermediate **2.24** (Scheme 2.21).

2.7.4 Completion of Azaspirene

With the desired isomer of lactone spirocycle **2.28** in hand, it was subjected to the ammonolysis conditions and compound **2.29** was seen as a single isomer plus some residual starting material. The reaction was allowed to mix for longer periods at 0 °C as well as at room temperature but the reaction was unable to reach 100% completion. The optimized conditions mixed **2.28** at 0 °C for 6 hr to obtain 90% conversion to amide **2.29**. The isopropanol was removed *in vacuo* with the aid of a hexanes azeotrope. The crude material was subjected to DMP in DCM at room temperature for 30 min to obtain oxidized ketone **2.30** as a single isomer. After mixing **2.30** in EtOAc and saturated Na_2CO_3 for 3 hr at room temperature, TBS protected azaspirene **2.31** was obtained as a near racemic mixture of diastereomers as outlined in Scheme 2.23. The diastereomeric ratio varied with the amount of mix time with the saturated Na_2CO_3 however complete convergence to a singe isomer was not observed. The diastereomers were separated on a silica gel column and attempts were made at deprotecting the TBS silyl ether.



Scheme 2.23: Formation of the lactam from the lactone spirocycle

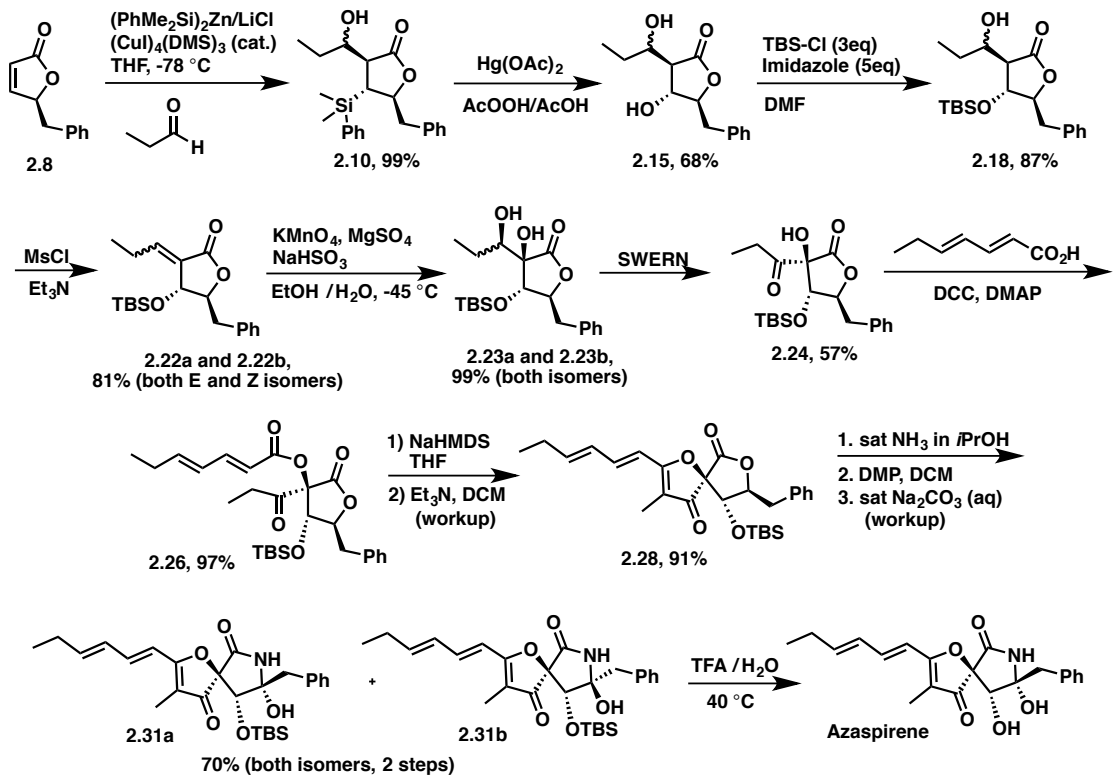
The initial attempt at removing the TBS group with TBAF[66] was however detrimental to the reaction. It immediately turned black and neither starting material or product could be recovered from the crude mixture. Continuing with the use of the traditional fluoride ion as the deprotection agent, aqueous HF[67] was attempted. Both isomers of protected azaspirene **2.31** were dissolved separately in acetonitrile and cooled to 0 °C before 49% HF(aq) was added to make a 10% solution in acetonitrile. The reaction was allowed to mix slowly up to room temperate. After workup, neither reaction showed the silyl-deprotected product however both crude ^{1}H NMRs were identical. The diastereomers converged into the suspected preferred isomer of **2.31a**. The reaction with HF was repeated but allowed to mix at room temperature overnight. With only starting material spots visible by TLC, the reaction was then heated at 40 °C for 4 hr. Unfortunately only starting material was again observed and therefore the reaction was heated to 80 °C overnight. After the reaction workup, no identifiable peaks were observed by NMR for either the starting material or product compounds. The final fluorine source attempted was fluourosilicic acid in acetonitrile[68] however after 4 days of mixing at room temperature only starting material was recovered.

Based on Tadano's method for the deprotection of the MOM ether using 5M HCl in MeOH and TBS silyl ethers being labile in an acidic environment, acids were studied next as deprotecting conditions. The idea was to start with a weak acid and then slowly increase the acidity of the reaction until the TBS was removed or the starting material was destroyed. A procedure reported by Corey was investigated describing the use of acetic acid in THF and water[66] but with no success. Next **2.31** was subjected to a 50:50 mixture of 1M HCl in MeOH overnight at room temperature without any visible deprotection. The strength of the hydrochloric acid was increased to 5M and the reaction was allowed to mix at ambient temperature. After 24 hr, the two diastereomers of **2.31** were observed to have converged into **2.31a** by TLC. After 48 hr of mixing at ambient temperature, a new spot on TLC was observed as well as still having a major starting material spot. The reaction was quenched and the ^{1}H NMR showed azaspirene and a diastereomer with almost identical peak shifts. A second reaction was attempted using a 1:3 mixture of concentrated HCl and MeOH which also appeared to converge the diastereomers of **2.31** and produced diastereomers of azaspirene however in a different ratio as the previous reaction employing 5M HCl. Although these conditions produced azaspirene it was lower yielding than desired and the acidic conditions led to some decomposition of the product. A number of acidic conditions were tried to achieve a cleaner and higher yielding reaction including TFA[69], formic acid[70], and acetyl chloride in MeOH.[71] The TFA reaction showed potential product peaks by NMR after 6 days of mixing at room temperature. Formic acid did not cleave the TBS silyl ether but did rather racemize the starting material into a new isomer. The use of acetyl chloride in methanol showed no reaction with small amounts of acetyl chloride however when a large

excess of acid was used neither starting material or desired product was seen in the crude ^{1}H NMR.

The TFA in water conditions also appeared promising, therefore the ratio was increased to 9:1 TFA in water and the reaction concentration was increased. After two days at ambient temperature, azaspirene along with 25 mol % unreacted starting material was observed by crude ^{1}H NMR. Heating the reaction from 35 °– 40 °C for 6 hr gave almost complete conversion of starting material to product.

Purification on silica following the reported syntheses all gave poor isolated yields of azaspirene (≤ 33%). Azaspirene appeared to be reacting or strongly interacting with the silica. Purification was attempted using 1% triethylamine spiked solvents however azaspirene reacted with the Et_3N and no compound was recovered off the column. Multiple attempts at washing the cleaved TBS away from azaspirene during the workup also failed. Purification with a biotage C-18 reverse phase column using an acetonitrile in water mobile phase gave a good mass balance of azaspirene off the column but an impurity that was separable on silica gel co-eluted with azaspirene in this method. Other purification techniques are being investigated to increase the disappointing final step isolated yield of 33%.



Scheme 2.24 Finalized route to Azaspirene

The final route to azaspirene shown in Scheme 2.24 consists of 11 steps with a total yield of 6% due to the low yielding final deprotection of azaspirene. Through the first 10 steps however, the total yield is 17%. With optimization of the final purification of azaspirene a 15% total yield is desired. The ^{1}H NMR spectra for azaspirene obtained matched closer to the natural product spectrum then the synthesized spectrum published by Osada[2] with respect to the amide proton shift and splitting pattern. The final spectra image of azaspirene was not published by either the Tadano or Sugi groups for comparison.

A sample of azaspirene was provided to the Klempke lab at UCSD to test for anti-angiogenetic properties in a zebra fish model.

Chapter 2 contained information being prepared for submission for publication where the dissertation author is a principle author on the manuscript. Special thanks to co-author Michael Kelly who gave written permission to use this information.

Part II: Alkenylzincate and Disilylzinc Conjugate Additions Catalyzed by Copper(I) Iodide Dimethyl Sulfide Complex

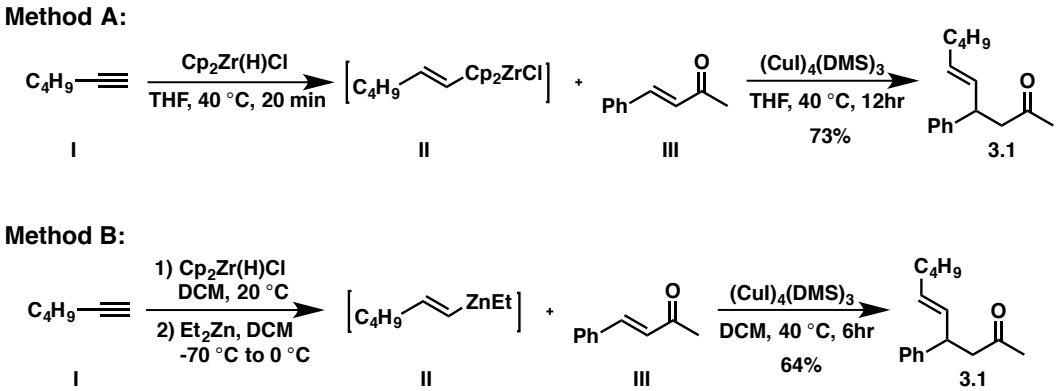
Chapter 3 Alkenylzincate Conjugate Additions Catalyzed by Copper(I) Iodide Dimethyl Sulfide Complex

3.1 Introduction

The ability to create carbon-carbon bonds is important in a plethora of chemical reactions. Organocopper reagents have been shown to be extremely versatile and useful for mediating 1,4-conjugate additions to α,β-unsaturated carbonyl compounds.[44,45] Bergdahl *et. al* has demonstrated that a CuI•DMS catalyst facilitated the 1,4-addition of alkenylzirconocene[30] and alkenylzincate[9] reagents to α,β-unsaturated ketones. The CuI•DMS catalyst facilitated these 1,4-additions in high yields and with very little formation of undesired 1,2-addition products. The research described in this chapter was focused on expanding the methodology of the CuI•DMS catalyst for addition of the alkenylalkylzincate reagents to α,β-unsaturated enone substrates containing a heteroatom attached to the β-carbon.

The Bergdahl group previously demonstrated that the CuI·DMS complex could catalyze the addition of vinyl groups from vinylzirconocene[30] and vinylzincate[9] reagents. The advantage of using one of these reagents instead of directly employing an organocopper reagent for the addition reaction is the ability to use a catalytic instead of stoichiometric amount of copper. The alkenylzirconocene reagents were formed from combining Schwartz's reagent with an alkyne. A transmetallation reaction involving diethylzinc would then afford the alkenylzincate

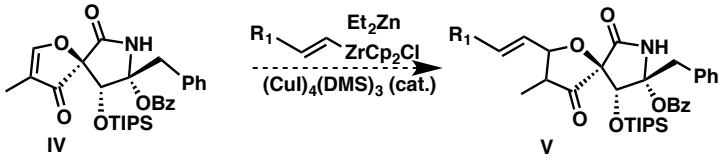
reagent. Initial tests were conducted using both the alkenylzirconocene reagent (Method A) and alkenylalkylzincate reagent (Method B) with hexyne **I** as the alkyne and benzalacetone **III** as the unsaturated carbonyl compound as shown in Scheme 3.1 below. Both methods provided the desired addition product **3.1** in modest yields.



Scheme 3.1: Alkenylzirconocene and alkenylalkylzincate additions utilizing CuI·DMS catalyst

3.2 Utilizing Alkenylzincate Reagents in the Synthesis of Azaspirene

With knowledge that the CuI·DMS complex would catalyze alkenylzirconocene and alkenylzincate reagents in conjugate addition reactions it was investigated if this technology could be used to add the unsaturated side chain to the spirocycle of azaspirene as highlighted in Scheme 3.2.



Scheme 3.2: Implementation of copper chemistry in the Azaspirene synthesis

The ability to add the side chain to azaspirene late in the synthesis was desired for the making of new derivatives of the title compound with variations within R_1 in compound **V**. Since the left half of the spirocycle **IV** contained a β-oxygenated

cyclic enone moiety, several test substrates were synthesized that shared the same β-oxygenated enone motif. The test substrates synthesized (Figure 3.1) were representative of furanone (**3.2**), pyranone (**3.3** and **3.4**), and glucal (**3.5**) derivatives.

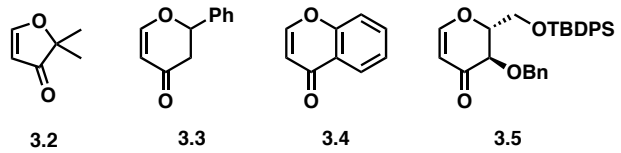
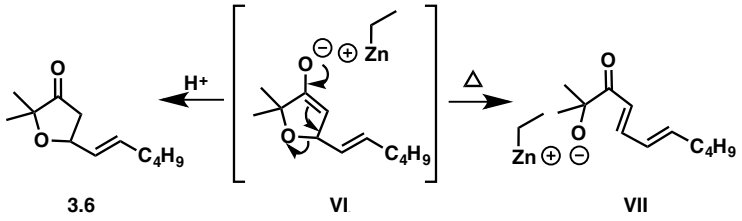


Figure 3.1: β-oxygenated enone test substrates

Due to the electron donating ability of the oxygen at the *beta* carbon, these substrates were hypothesized to be less reactive that the non-oxygen counterparts therefore, Method B using the more reactive alkenylalkylzincate was used in the preliminary studies. Performing the reaction using compound **3.2**, it was discovered that the oxygenated cyclic enones were more reactive than anticipated even though the oxygen is a good electron donor to the enone system. Prolonged reaction times at the elevated temperatures lead to a ring opening side reaction of the substrate. A schematic of the proposed ring opening reaction is highlighted in Scheme 3.3. Normally the enolate intermediate **VI** was quenched with a proton source to give the desired addition product **3.6** however the elevated temperatures appeared to push the reaction to the right leading to the ring opened, acyclic product **VII**.

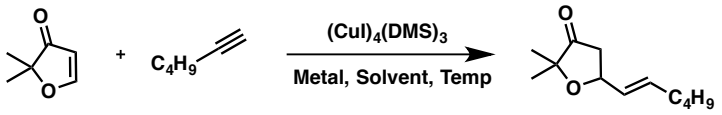


Scheme 3.3 Proposed ring opening of β-oxygenated enone substrates

Lowering the reaction temperature from 40 °C to room temperature was found to prevent the above ring opening from occurring. Considering the elevated reactivity

of enone **3.2**, the additions were also conducted with the less reactive and milder vinyl zirconocene reagents in THF at room temperature and at 40 °C. A comparison of reaction conditions is displayed in Table 3.1.

Table 3.1: Comparison of Methods A and B on addition product yield

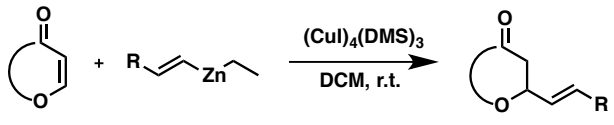


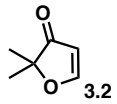
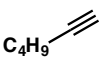
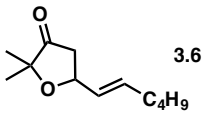
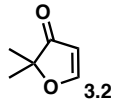
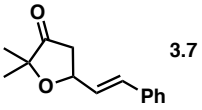
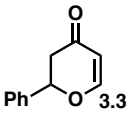
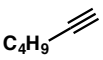
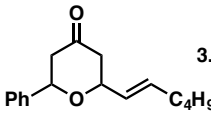
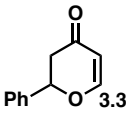
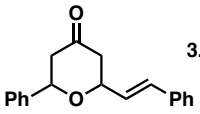
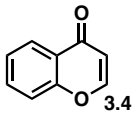
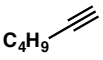
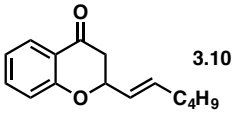
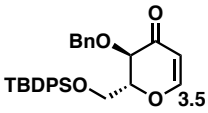
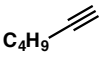
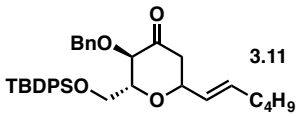
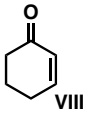
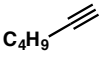
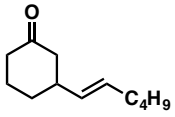
Entry	Metal	Solvent	Reaction Time	Temperature	Yield[a]
1	Et_2Zn	DCM	6 h	40 °C	4%
2	Et_2Zn	DCM	2 h	r.t.	60%
3	CpZr(H)Cl	THF	4 h	40 °C	48%
4	CpZr(H)Cl	THF	4 h	r.t.	40%

[a] Yields are representative of purified compound

The less reactive vinylzirconocene was able to produce the desired 1,4-addition product; however, the use of the vinylzincate reagent resulted in better yields and at a shorter reaction time. These results support the results of the original study with traditional enones describing that vinylzincate reagents reacted faster and provided greater yields.[9] The reaction conditions that produced the highest yield (Entry 2, Table 3.1) were adopted for the additions to other β-oxygenated cyclic enones, shown in Figure 3.1, as well as cyclohexenone as a control. The reaction times varied for each substrate based on the consumption of starting material by TLC. The results of these reactions were summarized in Table 3.2.

Table 3.2: Alkenylalkylzincate additions to various β-oxygenated enones



Entry	Substrate	Alkyne	Reaction Time	Product	Yield
1	 3.2		2 h	 3.6	60%
2	 3.2		1.5 h	 3.7	75%
3	 3.3		1 h	 3.8	51%
4	 3.3		3 h	 3.9	33%[a]
5	 3.4		1.5 h	 3.10	54%[b]
6	 3.5		18 h	 3.11	52%[c]
7	 VIII		0.5 h	 IX	65%

[a] estimated yields based on NMR. [b] done in the presence of TMSCl. [c] 1.0 eq of Cu complex used

The cyclohexenone **VIII** (Entry 7) reacted faster than the corresponding β-oxygenated enone as well as for the benzalacetone **III** which supports the previously published results that cyclic enones react faster than the acyclic analogs.[9] What was not expected was that most of the β-oxygenated substrates also reacted faster than the benzalacetone substrate. The increased reactivity suggested that the conformation of the alkene with respect to the carbonyl (*s-cis* or *s-trans)* had a greater

effect on reactivity than presumed. The cyclic enones are held in the *s-trans* conformation versus the acyclic enones, like benzalacetone, that can overcome a rotational barrier that allows for bond rotation between the *s-cis* and *s-trans* conformations as demonstrated in Figure 3.2.

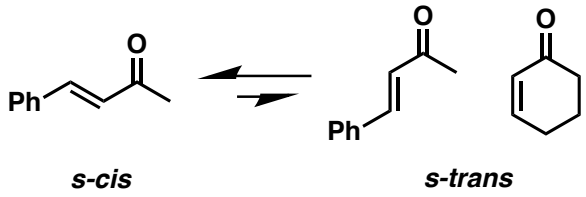


Figure 3.2: Conformational differences between *s-cis* and *s-trans* enones

Literature supports that acyclic enones favor the *s-cis* as the reactive conformation over the *s-trans* conformation.[72–74] The *s-cis* conformation is also more thermodynamically stable. The increased reactivity of the cyclic substrates must therefore be due to the limited rotation of the molecule even thought they exist only in the *s-trans* configuration.

Noticeable differences in reactivity between the types of β-oxygenated enones tested were observed. The pyranone derivatives **3.3** and **3.4** reacted the fastest (Entries 3 and 5, Table 3.2) followed by the furanone derivative **3.2** (Entry 1, Table 3.2) and then the glucal derivative **3.5** (Entry 6, Table 3.2) for the reaction conditions indicated. Chromone **3.4** (Entry 5, Table 3.2) was extremely reactive and favored the ring opening mechanism highlighted in Scheme 3.3 under the new reaction conditions. To achieve a successful vinyl addition to chromone **3.4**, several reaction parameters were changed. To hinder the ring opening side reaction, the reaction was cooled to 0 °C, run with the less reactive vinylzirconocene in THF, and by employing chlorotrimethylsilane (TMS-Cl) as an additive, the yield increased dramatically. The TMS-Cl appeared to aid the addition reaction by stabilizing the enolate intermediate

and not allowing for the ring opening side reaction. The use of silyl groups to trap enolates has been reported by Suzuki and Noyori.[45]

Since the use of TMS-Cl was incorporated into the reaction, efforts were made to isolate a silyl protected enolate species. The crude reaction ^{1}H NMR showed evidence of the trapped enolate species as the TMS ether, however attempts to isolate the silylenolether by silica gel column chromatography in the presence of a base such as triethylamine repeatedly led to deprotection and regeneration of the corresponding keto-1,4-addition product.

The glucal derivative **3.5** (Entry 6, Table 3.2) was found to be much less reactive among the enones tested. The reaction was allowed to run overnight with stoichiometric amounts of the CuI•DMS complex to afford the desired addition product in modest yield. The reason for the lack of reactivity of the glucal derivative was potentially the result of having steric bulk on both π-faces of the ring system and therefore hindering the addition. If the benzyl protecting group on glucal **3.5** was removed to reduce the steric bulk, no reaction was observed.

The effect of the starting alkyne on the product yields was also explored. The addition of phenyl acetylene instead of 1-hexyne increased the yield of addition product for the furanone derivative **3.2** (Entries 1 and 2, Table 3.2) but a purified product was not isolatable for pyranone **3.3** (Entry 4, Table 3.2). Further optimization was needed to increase the yields of the current 1,4-addition reactions; as well as, further expand on the use of the CuI•DMS complex towards other β-substituted cyclic enones. Incorporating more unsaturated substrates and alkynes would help determine trends for this new methodology. Having substrates with a nitrogen *beta* to the unsaturated site would also be interesting in showing how the electronics of the

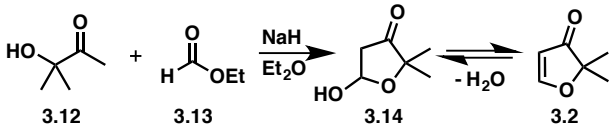
substrates drive the reactivity. The preliminary results were very promising for using this methodology towards the tail addition of azaspirene however the steps leading up to the needed intermediate (Compound **IV**, Scheme 3.2) were unsuccessful and the new route to azaspirene relied on the methodology described in Chapter 4.

3.3 Building the Unsaturated Substrates

All the β-oxygenated substrates for this study were synthesized in the laboratory. The lengthiest being the glucal derivate **3.5** which took 8 steps starting from D-glucose penta acetate. The synthesis of each of the substrates **3.2 – 3.5** will be discussed in this section.

3.3.1 Synthesizing furanone derivative 3.2

The furanone derivative was constructed following the methods described by Margaretha[8] and outlined in Scheme 3.4.



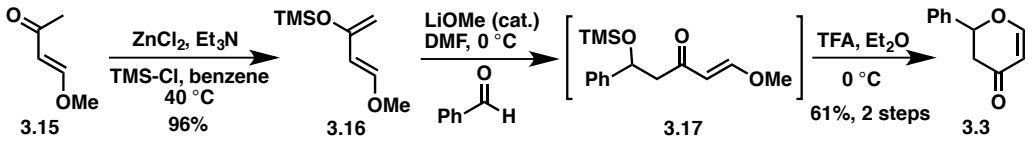
Scheme 3.4: Synthesis of furanone 3.2

The Margaretha reaction that made furanone **3.2** is quite a unique cyclization reaction. This reaction was the basis for the spirocycle formation in the route to azaspirene described in Chapter 2 of this thesis. The reaction gave a mixture of products **3.14** and **3.2** that were both in equilibrium. The original procedure used hydrochloric acid gas to dehydrate compound **3.14** into **3.2** and anhydrous $CuSO_4$ to act as a water trap. Although this method worked quite nicely, a milder alternative was desired for the dehydration reaction. Compound **3.14** was found to dehydrate to an extent under prolonged exposure to 10% aqueous hydrochloric acid or silica gel.

It was also difficult to purify compound **3.2** on silica gel. A Kuglerohr distillation was necessary to finally obtain pure compound resulting in a low purified yield. While all three methods successfully gave **3.2** as the main product, no method was able to produce an isolated yield above 40%.

3.3.2 Synthesizing the pyranone derivatives 3.3 and 3.4

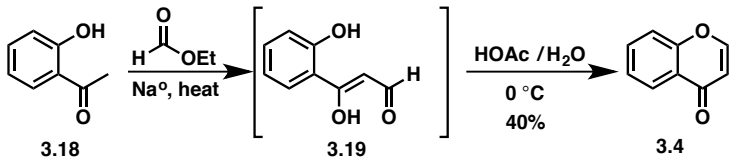
Pyranone **3.3** was synthesized using Danishefsky's diene **3.16** and benzaldehyde as shown in Scheme 3.5.



Scheme 3.5: Synthesis of pyranone 3.3

The first step in synthesizing compound **3.3** was the synthesis of Danishefsky's diene **3.16**. The diene was produced by trapping the enolate of methoxy butanone **3.15** as its trimethylsilylether. The enolate was formed using zinc chloride as a Lewis acid and triethylamine as the base.[75] The crude diene **3.16** was used immediately in the subsequent step where it was allowed to mix with benzaldehyde in the presence of catalytic lithium methoxide to give intermediate **3.17**. Exposure of the intermediate to trifluoroacetic acid allowed for the cyclization and elimination of methanol to give product **3.3** in a 61% purified yield.[76]

Chromone **3.4** was synthesized using *o*-hydroxyacetophenone **3.18** and ethyl formate shown in Scheme 3.6.[77,78]

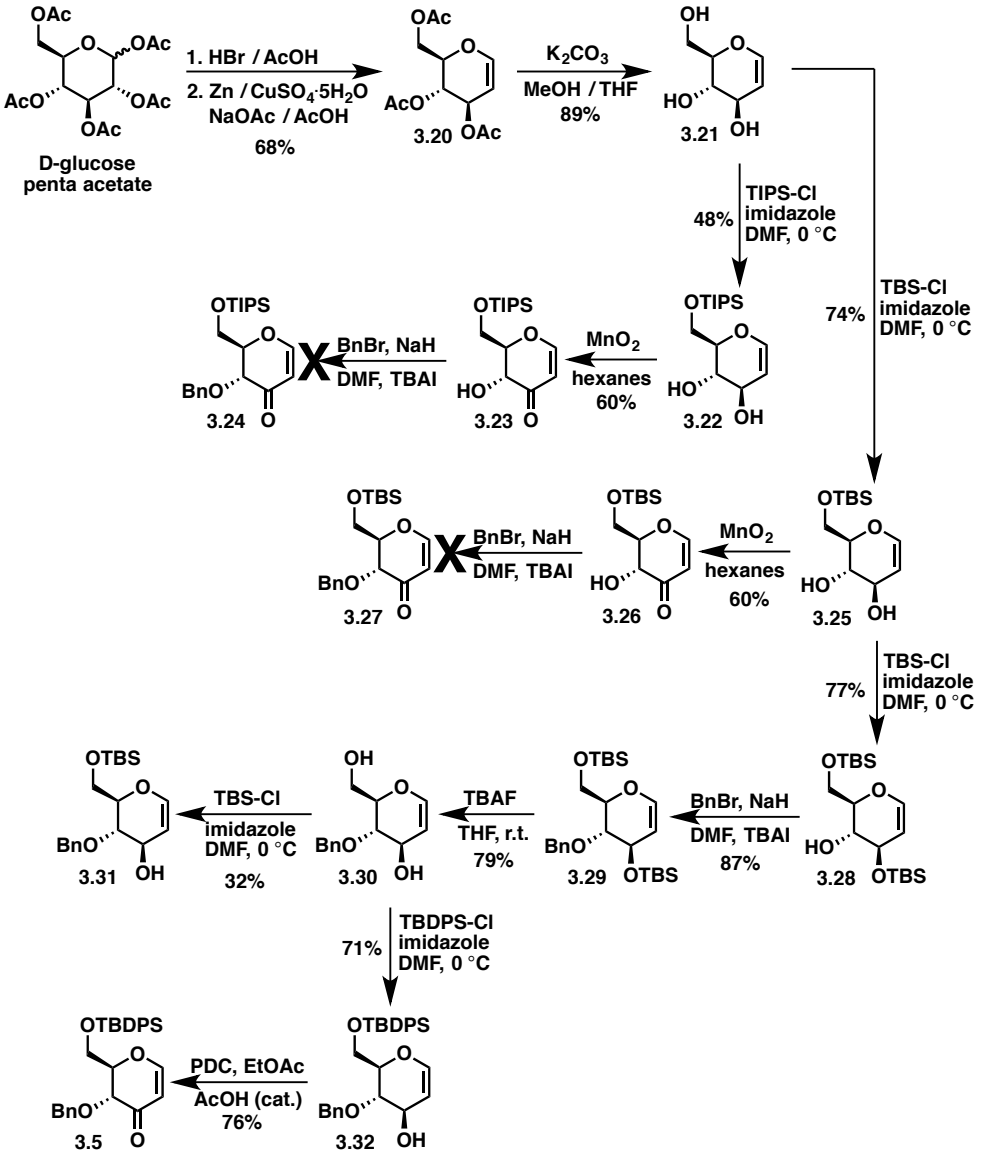


Scheme 3.6: Synthesis of chromone 3.4

This reaction required the use of “powdered” sodium which was attempted by heating sodium metal in xylenes until it was fully melted. Once melted, the stir plate was turned on high with a high sheer rate stir bar to disperse the sodium metal into small droplets. The flask was cooled while maintaining the high mixing however the sodium did not remain as individual small spheres. The xylenes were removed then a premixed solution of ethyl formate and compound **3.18** was added to get intermediate **3.19**. Upon acidifying intermediate **3.19** with acetic acid followed by cooling the reaction mixture, chromone **3.4** precipitated out as a white solid in a 40% overall yield.

3.3.3 Synthesizing the glucal derivative 3.5

The glucal derivate **3.5** was the most complex synthesis. It was synthesized starting from D-glucose pentaacetate following Scheme 3.7 below. The first step was a bromination reaction followed by reduction with Zn / $CuSO_4$ to give the unsaturated tri-o-acetyl glucal **3.20** in a 68% yield.[79] Potassium carbonate was then used to perform a global deacetylation to give triol **3.21** in a 89% yield.[80] The target molecule was compound **3.24** therefore a selective protection of the primary alcohol of **3.21** was performed with the bulky tri-isopropylsilyl chloride in the presence of imidazole to obtain a 48% yield on mono-protected **3.22**. A selective oxidation using MnO_2[81] of the allylic alcohol over the secondary alcohol was accomplished to give enone **3.23** in a 60% yield. The last step toward compound **3.24** was a benzyl protection using benzyl bromide with sodium hydride and tetrabutylammonium iodide (TBAI)[82] however no product was formed. The vinylzincate addition reaction was attempted with unprotected compound **3.23** however the unprotected alcohol was incompatible with the vinylzincate reagent.



Scheme 3.7: Synthesis of glucal derivative 3.5

With the consideration that the TIPS group was blocking the alcohol from being protected, it was replaced with the smaller TBS group. Protection of triol **3.21** with TBS gave monoprotected compound **3.25** in a 74% yield. Selective oxidation of **3.25** with MnO_2 gave compound **3.26** in a 60% yield however benzyl protection of the final alcohol to get compound **3.27** was still unsuccessful.

To accomplish orthogonally protected groups on the final glucal derivative, the order of reactions was changed to protect all the alcohols first and oxidize to the enone as the final step. Two equivalents of TBS-Cl with imidazole were added to triol **3.21** to obtain the diprotected compound **3.28** in a 77% yield. Compound **3.28** was successfully benzylated[82] at the secondary alcohol position provided compound **3.29** in 87% yield. Selective deprotection of the TBS groups using tetrabutyl ammonium fluoride (TBAF) gave diol **3.30** in a 79% yield. Selective protection of the primary alcohol on **3.30** with TBS was problematic due to di-protection therefore compound **3.31** was only isolated in a 32% yield. Using the bulkier *tert*-butyldiphenylsilyl chloride (TBDPS) group, monoprotection of **3.30** was accomplished in a 71% yield to give compound **3.32**. The final allylic oxidation to yield substrate **3.5** was very slow with MnO_2, but pyridinium dichromate (PDC) with catalytic acetic acid was used instead to obtain **3.5** in a 76% yield. The final synthesis of glucal **3.5** from D-glucose pentaacetate was 8 steps with a 17% overall yield.

Chapter 4 Disilylzinc Conjugate Additions Catalyzed by the Copper(I) Iodide Dimethyl Sulfide Complex

4.1 Introduction

Silyl groups have been used as masked hydroxyl groups[12] since Fleming demonstrated that they could be easily oxidized to a hydroxyl group with retention of stereochemistry.[83] The ability of adding a silyl group in an asymmetric conjugate addition reaction followed by oxidation allows for the construction of enantiomerically pure aldol type fragments. Organosilyl reagents have evolved over the years to limit heavy metal amounts, use less toxic reagents, and conserve the atom economy of the reactions.

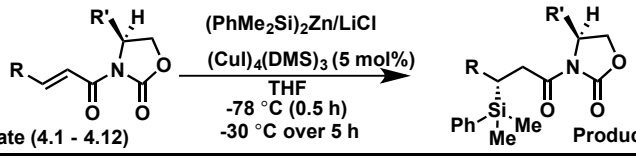
The first generation of silyl reagents heavily used in conjugate additions were the Gilman-type silylcuprates,[84] $(PhMe_2Si)_2CuLi/LiCN$, however these reagents required stoichiometric amounts of copper and two equivalents of the silyl reagent. The Bergdahl group published that a monosilyl cuprate,[10] $Li[PhMe_2SiCuI]$, could also be used in place of the disilylcuprates. The monosilyl cuprate improved the atom economy of the reaction but still required a stoichiometric amount of copper. The use of a dialkylsilylzincate,[85,86] $PhMe_2SiZnEt_2/LiCl$, was shown to add without the use of any copper however the dialkylzinc reagents are pyrophoric making them less ideal for large scale reactions. A fourth class of reagent first reported by Oestreich *et. al* was a disilylzinc,[13,87,88] $(PhMe_2Si)_2Zn/LiCl$, that was shown to add in good yields in the presence of catalytic copper and was produced using the easier to handle zinc

chloride reagent. This chapter will discuss the results from adding the disilylzinc species, $(PhMe_2Si)_2Zn/LiCl$ with catalytic amounts of CuI·DMS to chiral substrates.

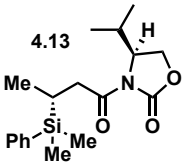
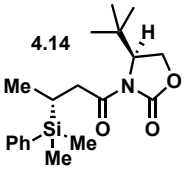
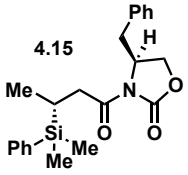
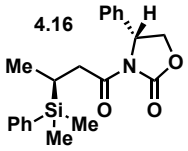
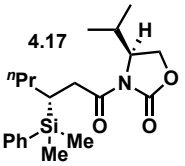
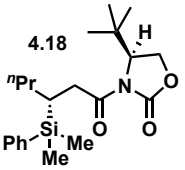
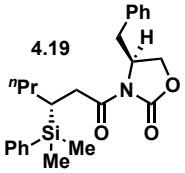
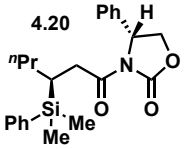
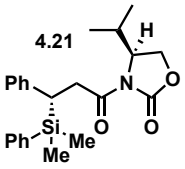
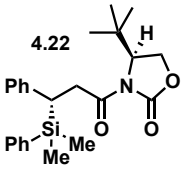
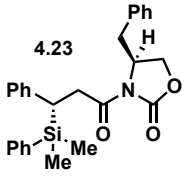
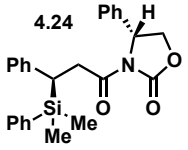
4.2 Results and Discussion

Disilylzinc reagents have been shown to undergo conjugate additions to α,β unsaturated carbonyl compounds,[13] however previous attempts at an asymmetric addition were unsuccessful.[87] The addition reactions using catalytic CuI·DMS and the disilylzinc reagent, $(PhMe_2Si)_2Zn/LiCl$, gave good yields with simple achiral substrates which supported the findings of Oestreich.[13] The versatility of the disilylzinc reagent catalyzed by CuI·DMS was examined using less reactive imide substrates containing an Evans type chiral auxiliary. Previously the Bergdahl lab showed successful asymmetric additions from the monosilylcuprate reagent, $Li[PhMe_2SiCuI]$, to this class of substrates.[10] The results of the disilylzinc additions to the chiral imides is shown in Table 4.1.

Table 4.1: Silyl addition to various oxazolidinone substrates



Substrate (4.1 - 4.12) Product (4.13 - 4.24)

Product[a] (4.13 - 4.24)	Yield[b]
4.13 	91%, dr = 87:13 88%, dr = 89:11[c] 58% (34%[e]), dr = 86:14[d]
4.14 	95%, dr = 95:5
4.15 	91%, dr = 92:8
4.16 	95%, dr = 95:5
4.17 	80%, dr = 87:13
4.18 	80%, dr = 97:3
4.19 	93%, dr = 91:9 72% (22%[e]), dr = 52:48[f]
4.20 	82%, dr = 98:2
4.21 	90%, dr = 87:13 81%, dr = 88:12[c] 24% (65%[e]), dr = 82:18[d]
4.22 	82%, dr = 96:4
4.23 	87%, dr = 84:16
4.24 	89%, dr = 97:3

[a] Characterized by NMR (^{1}H and ^{13}C), IR and MS. Diastereomeric ratios (dr) determined on the crude product ^{1}H-NMR (500 MHz). [b] Based on isolated and purified material. [c] Reactions were conducted in THF and Toluene (70:30) using purified CuI·0.75DMS complex. [d] Reactions done in THF in absence of Cu(I). [e] Calculated mole percent of starting material based on crude ^{1}H NMR. [f] Reaction warmed to 0°C for 5h instead of -30°C.

To evaluate the reactivity of the silyl species and the effectiveness of the auxiliary, four auxiliaries (*i*Pr, *t*Bu, Bn, and Ph) and three acyl chlorides (crotonyl, hexenoyl, and cinnamoyl) were chosen to create the 12 substrates (**4.1 – 4.12**) whose products (**4.13 – 4.24)** are shown in Table 4.1. Overall, good yields (all > 80%) and d.r.'s (all > 80:20) were obtained for all tested substrates. The silyl group was predicted to add *anti* to the π-face blocked by the chiral auxiliary of the substrate.

The stereochemistry of the major products suggested a chelation control of the reactive species as shown in Figure 4.1. Without a chelate to hold the carbonyls of the imide in place, rotation would occur and increase the formation of the minor product. The excess lithium used to create the initial silyl anion is presumed to be the metal responsible for the observed chelate control. The chelate control model was supported when additions to the same substrates in water resulted in a reversal of the observed major product. The water addition reactions will be discussed further in Chapter 5 of this thesis.

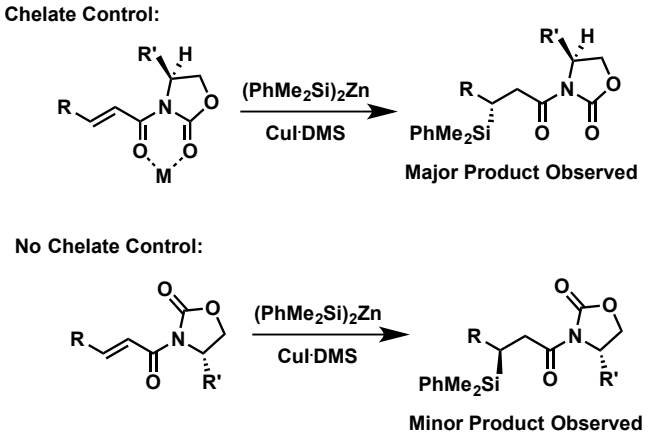


Figure 4.1: Chelate versus no chelate control of reactive species

As was previously mentioned, these acyclic enones preferred to react in the *s-cis* conformation. For these particular substrates, the *s-trans* conformation would be particularly unfavored due to the steric interaction between the alkene and the chiral auxiliary when the carbonyl groups where chelated as shown in Figure 4.2.

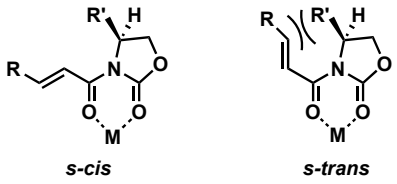


Figure 4.2: Potential enone geometries for imide substrates under chelate control

The observed diastereomeric ratios for all the products were similar with only small differences that trended more with the **R'** group on the auxiliary and appeared less dependent of the **R** group of the enone. Both the phenyl and *t*-butyl auxiliaries gave d.r.'s of >95:5 for all substrates tested. The isopropyl auxiliary gave the lowest d.r. and the benzyl auxiliary was in the middle. The yields were overall good for these reactions. The crotonyl substrates provided the least hindered enone and gave the highest yields. The electron rich cinnamoyl substrates were predicted to be the least reactive substrates in this study however, the yields for the hexenoyl substrates were lower than for the cinnamoyl substrates. The lower yields might suggest that the long alkyl chain could interfere with the attack of the silyl group.

The effect of removing the copper was also investigated since the silylalkylzincate species, $(PhMe_2Si)ZnEt_2$, has been shown to add without the use of copper. When the reactions were attempted without CuI·DMS, there was a major drop in yield however the d.r. was primarily unchanged. The drop in yield was accounted for as unreacted starting material indicating a slower reaction. It seemed that the copper was not needed for the reaction to occur, however the reaction times would need to be extended to allow full conversion of the starting materials. When the reaction was allowed to run at 0 °C, the d.r. dropped to almost a racemic mixture level of products. The yield also dropped presumably due to degradation of the disilylzinc reagent at the warmer temperature.

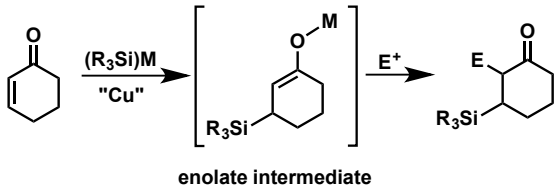
With the results from this study showing successful steric control of the silyl addition from the disilylzinc reagent catalyzed by CuI·DMS, the methodology was incorporated into the route to azaspirene discussed in Chapter 2. The reaction in the synthesis gave quantitative yield with a d.r. >99:1 by having the directing group closer

to the unsaturated bonds and the more reactive cyclic enone allowing the reaction to be conducted at lower temperatures.

During the course of this methodology a paper by Calderone and Santos[14] was published describing the conjugate addition of silylboronic esters in water catalyzed by copper sulfate pentahydrate to simple, achiral enones. The ability to add the silyl groups asymmetrically to the chiral imide substrates using the silylboronic esters in aqueous media is discussed in Chapter 5.

4.3 Extending the silyl conjugate addition methodology

Fleming and others had shown that the enolate formed during the silyl conjugate addition could be trapped with an electrophile in a step-wise manner[43–45,89] as demonstrated in Scheme 4.1. Traditionally the electrophile was added as the quenching step due to the ability of the silyl group to add directly to the electrophile as a competing reaction.



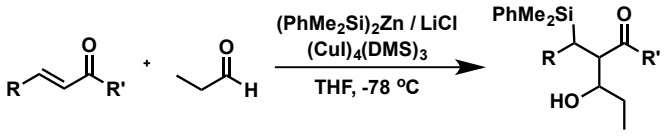
Scheme 4.1: Electrophilic trapping of a silyl conjugate addition enolate

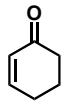
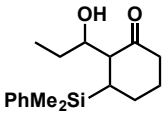
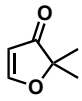
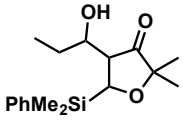
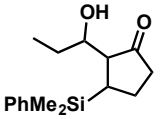
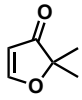
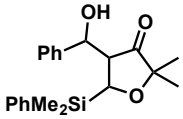
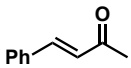
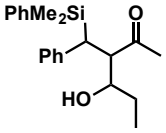
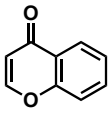
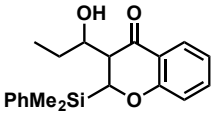
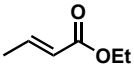
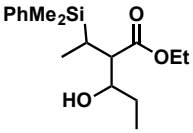
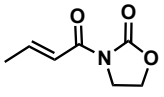
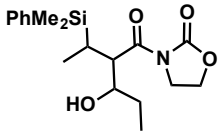
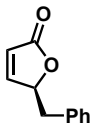
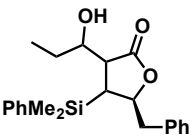
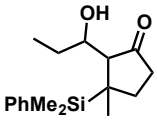
The possibility of trapping the enolate formed in the silyl addition with an aldehyde was investigated to aid in the synthesis of azaspirene. As mentioned in Chapter 2, there was difficultly with the formation and reactivity of the ester enolates. When the aldehyde was added as an enolate quenching reagent following Scheme 4.1, a mixture of the desired silyl addition and aldol product, only silyl addition product, and unreacted starting enone (Scheme 2.12) was observed. With the knowledge that the CuI·DMS complex did not favor 1,2-addition reactions, the aldehyde was added

as a premixed solution with the substrate. Having the aldehyde in the reaction mixture from the beginning led to an unprecedented formation of the product, which led to the one-pot reaction methodology described in this section.

Various classes of enones were tested using the disilylzinc reagent catalyzed by CuI·DMS and either propionaldehyde or benzaldehyde. The results that showed the versatility of this novel one-pot reaction are shown in Table 4.2 below.

Table 4.2: Results for the one-pot silyl aldol reactions

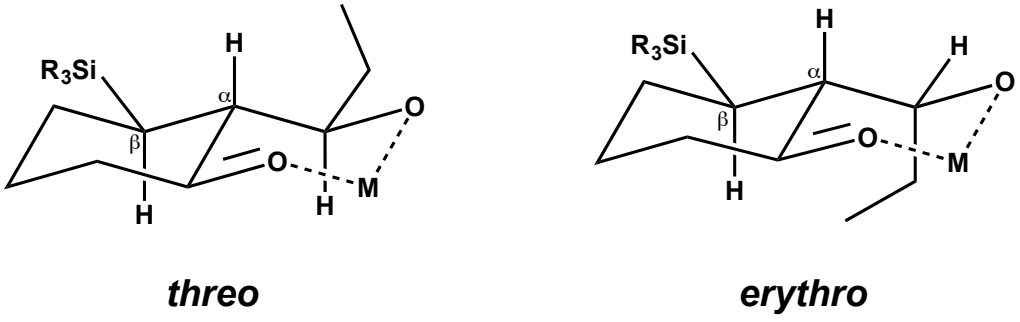


Entry	Substrate	Product	Yield[a]	Entry	Substrate	Product	Yield[a]
1			95%	6			99%
2			96%	7[b]			89%
3			92%	8			63%
4			39%[c]	9			77%
5			99%	10			NR[d]

[a] Yields representative of isolated product by ^{1}H NMR. [b] Reaction done with benzaldehyde. [c] The 1,4 addition product was recovered in 45% yield. [d] Reaction was attempted with DMS in place of THF, with 10 eq of aldehyde, and at -40 °C along with the above conditions

For this study, both acyclic and cyclic achiral substrates that represented various classes of enones were selected. The reactions proceeded in good to excellent yields for most of the substrates. The results showed that the CuI·DMS successfully hindered the 1,2-addition of the silyl group to the aldehyde, but only when the enone substrate was reactive enough for the initial silyl conjugate addition to occur. Thus, when the addition was attempted to the less reactive β-substituted cyclopentenone, only starting enone and the 1,2-addition product formed between the disilylzinc and aldehyde.

The ketones, esters, and β-oxygenated enones all reacted in good yields. Unfortunately, most of the product diastereomers were inseparable on silica making characterization of individual enantiomers more challenging. For all the substrates, no more than two diastereomers were formed. As with the chiral lactone, it appeared the silyl and aldol groups maintained the *anti* relationship and the d.r. observed arose from the relative positioning of the alcohol group. The stereochemistry of aldol reaction products specifically directed by zinc chelates have been studied.[90,91] The diastereomers of the alcohol group arose from the orientation of the aldehyde during the aldol reaction as illustrated in Figure 4.3.



threo ***erythro***

Figure 4.3: The *threo* versus *erythro* orientation for aldol reaction products

The more stable *threo* product arises from the R group of the aldehyde positioned equatorial in the 6-membered ring transition state and *erythro* when positioned axial. The major products observed in this study including the azaspirene chiral lactone substrate supported the predicted *threo* model. During this investigation questions arose about the active chelating metal associated with the various reactive intermediates as well as the ability of a monosilylzinc chloride species, $PhMe_2SiZnCl$, to be active. These will be discussed more in the future work section of this thesis.

Chapter 4 contained information that is being prepared for submission for publication where the dissertation author is a principle author on the manuscript. Special thanks to co-authors Michael Kelly and Jason Zbieg who gave written permission to use this information.

Chapter 5 Aqueous Conjugate Additions from Boronic Esters

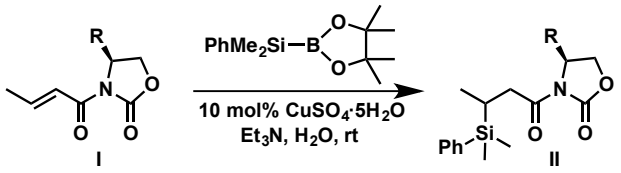
5.1 Introduction

While working on the asymmetric addition of the disilylzincs to chiral oxazolidinone moieties described in Chapter 4, an interesting paper was published by Calderone and Santos who described the conjugate addition of silyl groups in water from silylboronic esters.[14] The paper was interesting because the reaction was occurring on water and the reported catalyst was a copper (II) instead of a copper (I) species. Most of the traditional copper catalyzed conjugate addition reactions are performed using a copper (I) catalyst that is presumed to go through a Cu (III) intermediate during the addition. If the catalyst of these water addition reactions was truly a copper (II) species, a new mechanism could be driving the aqueous addition. The popular silylboronic ester species, $PhMe_2Si$-B(pin), used in the paper was made from coupling the silyl anion with pinacol borane following the procedures of Ito.[92] The silylboronic ester had previously been shown to perform conjugate additions with Cu(I) in organic substrates,[93,94] but not in water. The Santos group reported the conjugate additions in good yields to simple α,β-unsaturated ketones and esters, however the reactions were not under any stereocontrol. Under aprotic conditions with Cu(I), Hoveyda used *N*-heterocyclic carbenes[93] to direct the addition and Cordova used an iminium species[94] to impart an asymmetric addition. Since the imide enone species containing the Evans chiral auxiliary could perform asymmetric

silyl conjugate additions under organic conditions with CuI·DMS, their performance was tested in an aqueous environment using the methodology from Santos.

5.2 Aqueous silyl conjugate addition reactions to chiral imide enones

The initial tests followed the published reaction conditions that used 1 mol% copper and 5 mol% 4-picoline.[14] The amine was reported to serve as a ligand for the copper in these reactions. To accomplish better yields with the less reactive imide enones, the copper loading was increased to 10 mol% and the base to 20 mol%. It was determined that the base had little to no effect on the yield of the reaction compared to the report of Santos.[14] The amount of the silylboronic ester used was also increased from 1 to 2 equivalents. The general scheme for the aqueous silyl conjugate addition reactions explored is shown in Scheme 5.1 below.

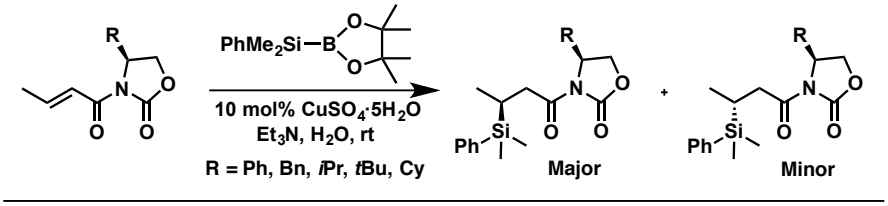


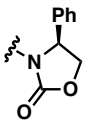
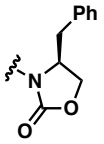
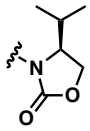
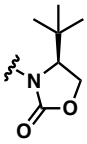
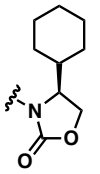
Scheme 5.1: Modified aqueous silyl conjugate addition reactions

The oxazolidinone substrate that gave the best d.r. under the chelate control model in organic solvents (Chapter 4) contained a phenyl group, and naturally it was examined first. The reaction was successful in making the desired product in an 83% yield however the products were in a 50:50 racemic mixture. Still, the result was rewarding since it supports the proposed chelate control model based on the absolute stereochemistry when conducting the reaction in THF. Furthermore, the result confirmed that under aqueous conditions, no such lithium chelate to the carbonyl compounds was able to form. Without the chelate control, the oxazolidinone group could freely rotate leading to the racemic mixture of products. The steric bulk of the

oxazolidinone group was then increased in an attempt to limit rotation of the substrates in solution. The oxazolidinones synthesized contained either a benzyl, isopropyl, *t*-butyl, or cyclohexyl **R** group. The results from changing the steric bulk of the chiral oxazolidinone group are shown in Table 5.1.

Table 5.1: Effects of the oxazolidinone chiral group on product d.r.



R					
Cmpd	5.1	5.2	5.3	5.4	5.5
Yield					
d.r. (major/minor)	50:50	53:47	67:33	53:47	57:43

The best d.r. achieved from using sterics to hinder rotation of the oxazolidinone group in aqueous conditions was a 2:1 ratio in favor of the minor product from the chelate control study. The most interesting result was that the best d.r. was not achieved by the *t*-butyl oxazolidinone, which is assumed to be the bulkiest group. Surprisingly, the best d.r. was achieved with the isopropyl oxazolidinone analog. With sterics not allowing for the desired asymmetric addition reaction to occur with good d.r., the focus moved to determine if any metal could potentially form a similar chelate to the carbonyl carbons in water as the lithium did under organic conditions. The phenyl oxazolidinone substrate was used to screen the metals because it would be easy to see a change from the 1:1 product ratios.

Although ultimately testing Li, Mg, Al, Ti(III), V(III), Fe(II), Fe(III), Pd(II), Ag(I), La(III), and Hg(II) as different water compatible metals, none showed any effect on the d.r. of the products. Considering the carbonyls to be too similar to a water oxygen for specific metal chelation, the final attempt at obtaining a chelate was to replace the carbonyl on the phenyl oxazolidinone with a sulfur group. The substitution from oxygen to sulfur of the oxazolidinone using Lawesson's reagent[95] was successful. The oxazolidethione was then coupled to the crotonyl chloride to obtain the desired substrate. When the reaction was run with the oxazolidethione substrate, no product was observed likely due to the sulfur chelating the copper catalyst out of the reaction. When an excess amount of copper was used, product was formed however the reaction did not proceed in an asymmetric stereocontrolled fashion.

Although high d.r. values were unable to be achieved using the chiral imide enones, good yields were produced with the lesser reactive substrates. A decent d.r. resulted when the silylboronic ester reacted with the chiral lactone from the azaspirene synthesis. The chiral lactone gave an 85:15 d.r. of the major product having the silyl group add *anti* to the benzyl group in a 78% combined yield and 22% recovery of starting material. The major difference between the chiral lactone and the chiral imides was the chiral directing group on the lactone, which lacked the freedom of rotation in this case.

The inability to obtain a high d.r. for the oxazolidinone substrates and a lower d.r. for the chiral lactone could be a result of the reaction temperature. The aqueous reactions to the oxazolidinones were run at room temperature compared to the disilylzinc reagents in organic solvents run at -78 °C. When the disilylzinc additions were conducted at 0 °C, the observed d.r. of the product dropped significantly.

Although the aqueous reactions cannot be conducted at the same low temperature as the organic reactions, lowering the temperature as much as possible would aid in hindering rotation within the substrate.

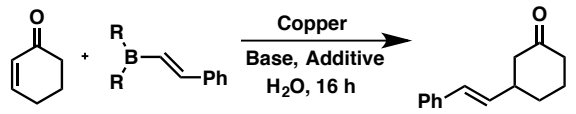
While working on using chiral substrates to afford the asymmetric additions, Kobayashi *et. al* published an asymmetric conjugate addition of a boronic ester from a dipinacolborane species, $B_2(pin)_2$, in water.[96] The catalyst used was Cu(II) hydroxide instead of the Cu(II) sulfate with a chiral bipyridine ligand to direct the addition to achiral substrates. The boronic esters, like the silyl groups, could be oxidized with retention of stereochemistry to form β-hydroxy aldol type scaffolds in high yields. More recently, the same group published the asymmetric addition of silylboronic esters in water using a Cu(II)(acac) chiral bipyridine catalyst.[97]

5.3 Aqueous vinyl conjugate addition reactions

The successful addition of silyl groups from silylboronic esters in aqueous media using a copper catalyst sparked investigation into the addition of vinyl groups from vinylboronic esters under similar conditions. Rhodium has been shown to catalyze the vinyl conjugate additions from vinyl-boronic esters,[98] boronic acids,[99] and fluoroborates[100] but not copper. Copper has only been shown to catalyze ether formation from alcohols and arylboronic acids[101] and vinyl or aryl fluoroborates.[102]

The optimized procedure for the silylboronic ester addition to cyclohexenone gave no reaction when using the vinylboronic ester (Entry 1, Table 5.2).

Table 5.2: Results from aqueous vinyl boronic ester additions



Entry	Borate	Copper	Base	Additive
1	(pin)B-	$CuSO_4$	4-picoline	---
2				K_2CO_3
3				KOH
4				KNO_3
5				KBr
6		CuOTf	4-picoline	---
7				K_2CO_3
8[a]		CuI·DMS	---	---
9	$(HO)_2B$-	$CuSO_4$	4-picoline	---
10	KF_3B-	$CuSO_4$	4-picoline	---
11		$Cu(OAc)_2$	DMAP	---
12[a]		CuI·DMS	---	---
13[a]			DMAP	---

[a] reactions done in DCM

Several attempts at using Lewis bases to weaken the C—B bond were also unsuccessful (Entries 2 - 5, Table 5.2). The addition was attempted using copper (I) sources however neither CuOTf in aqueous conditions (Entry 6, Table 5.2) or CuI·DMS in organic conditions (Entry 8, Table 5.2) were successful in adding the vinyl group. The more reactive potassium trifluoroborate species was also unsuccessful in providing a conjugate addition product under aqueous or organic conditions (Entries 10 - 13, Table 5.2). It was thought that increasing the electron withdrawing ability of the groups attached to boron would weaken the boron-carbon bond, however it was finally determined that copper was not favorable enough to disrupt the C—B bond and undergo the transmetallation reaction required for addition.

Chapter 6 Future Work

6.1 Azaspirene

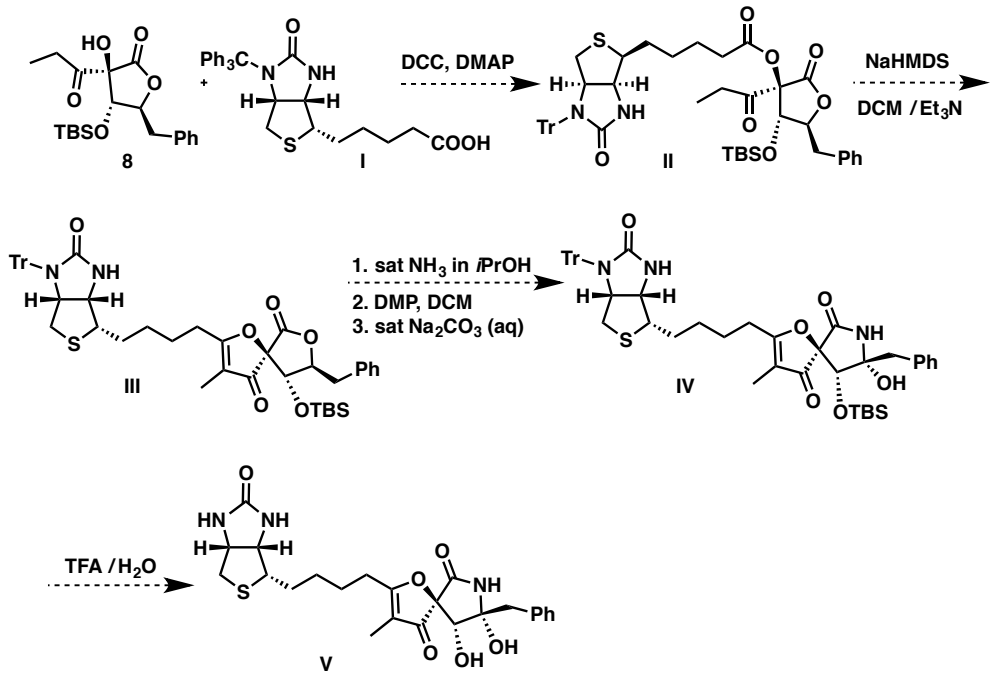
6.1.1 Adding a biomarker to Azaspirene

Azaspirene is a unique member of the pseurotin family for two reasons. Azaspirene is the only compound that showed anti-angiogenesis properties[1] and it is the only member with a slightly different spirocycle core. Originally it was believed that, because all of the other pseurotin compounds only differ in the side chain, azaspirene's unique function was also dependent on its specific side chain. The studies recently published by the Emoto group[24] with an azaspirene derivative showed that the replacement of the long unsaturated side chain of azaspirene with a short, saturated ethyl group still produced anti-angiogenesis properties both *in vitro* and *in vivo* with similar efficacy. These results suggest that the slight differences in the azaspirene core versus the other pseurotin compounds could be playing a bigger role than previously thought.

In comparison with the other pseurotins, azaspirene has a tertiary hydroxyl group instead of the methoxy group and a benzyl group instead of the benzoyl group, both attached to the same quaternary carbon. Based on the initial proposed route to synthesizing the backbone of azaspirene, this particular tertiary alcohol is quite labile and eliminates readily to form a quite stable carbocation. Contrary to that, the alcohol was shown to be stable in acidic conditions when deprotecting the silyl ether in our final step. Finding the binding site of azaspirene would give great insight into whether

azaspirene or dehydrated azaspirene is really the active and responsible molecule for the bioactivity.

If the side chain of azaspirene is less important than the core to function as an anti-angiogenesis agent, then it could be possible to add a biotin linker as the side chain. Since biotin has a carboxylic acid it could be incorporated into the synthetic route following Scheme 6.1 below.



Scheme 6.1: Proposed route for incorporation of a biotin tail onto Azaspirene

The urea functional group of biotin would have to be protected first to avoid deprotonation. One potential group is triphenylmethyl group (Tr) which would be cleaved using the same conditions the TBS ether is cleaved in the final step to azaspirene.[103]

Material was supplied to collaborators at UCSD to test the anti-angiogenesis properties of azaspirene in zebra fish. With the supply of azaspirene available from this route, new insight about the active binding site of azaspirene as well as the exact

mode of action could be possible. Once the binding site is accurately determined, a more definitive pathway for derivatization based on SAR assays could be established.

6.1.2 Milder Tamao oxidation of silyl group

The ability to add a silyl group in an asymmetric fashion was demonstrated in the finalized route to azaspirene as well as in the methodology described in Chapter 4. Although the $(PhMe_2Si)_2Zn/LiCl$ reagent has shown to be robust, the use of stoichiometric amounts of mercury acetate needed to oxidize the silyl group into the corresponding alcohol are both harsh and toxic. Tamao demonstrated that other silyl groups that contain a heteroatom can still be used to form silylcuprates but are oxidized under milder conditions.[104] One such group, $(Et_2N)Ph_2Si$, can be fluorinated with $BF_3{\cdot}Et_2O$ or KF then removed with hydrogen peroxide.[104]

For the current route to azaspirene, the oxidation of the silyl group using mercury acetate is not ideal for a scalable route. An aminosilylcuprate,[104] $(Et_2N)Ph_2SiCu(CN)Li$, and the aminosilylzincate reagent,[12] $(Et_2N)Ph_2SiZnEt_2/LiCl$, have been demonstrated to add in conjugate additions however the disilylzinc, $((Et_2N)Ph_2Si)_2Zn/LiCl$, has not been attempted. The ease of oxidation with the aminosilyl group has its disadvantages. The group has been reported as less reactive and more sensitive to temperature.[10,12]

The use of a more readily oxidized group was initially not explored because the silyl group was intended to be carried through multiple reactions, including two oxidation steps, before the transformation into the corresponding alcohol. With the final route, the silyl group is oxidized directly to the alcohol in the subsequent step, thus the more reactive aminosilyl group could be incorporated.

6.2 Conjugate silyl addition methodology

6.2.1 Monosilylzinc chloride conjugate addition reactions

To accompany the investigation into the di-addition reactions the use of a monosilylzinc chloride species, $PhMe_2SiZnCl$ should be explored. Previous reports claimed the monosilylzinc chloride species was unreactive or gave very low yields and that only a single silyl group would add from the disilylzinc reagent.[13] Preliminary tests indicate that the monosilylzinc chloride species, $PhMe_2SiZnCl$, catalyzed by the CuI·DMS complex is capable of performing the conjugate addition reactions in decent yields. The results prompted a more in depth study into the viability of this reagent and the potential of adding both silyl groups from the disilylzinc reagent.

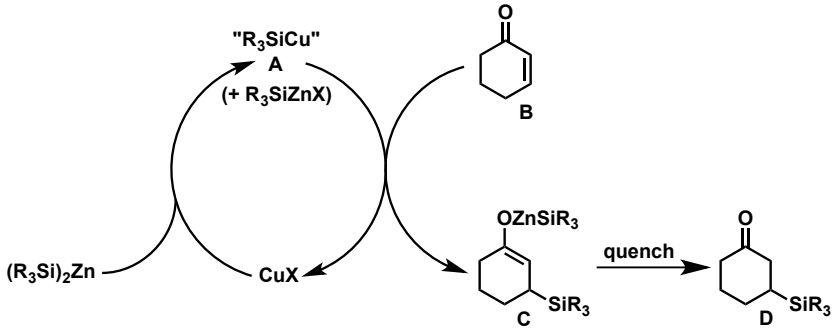


Figure 6.1: Simplified mechanistic route proposed by Oestreich

The simplified mechanistic route by Oestreich[13] (Figure 6.1) proposed a monosilylcuprate **A** as the active species adding the silyl group. The intermediate **A** was the product of a transmetallation between the disilylzinc and the copper catalyst. The addition of the silyl group from the copper would regenerate the catalyst and form zinc enolate **C**. A quenching step would lead to the conjugate product **D**. This mechanistic route would support the observation that only one of the silyl groups was

able to add from the zinc because the other silyl group remained on the zinc as part of the proposed enolate species formed.

A more suitable mechanistic route to include the addition of the aldehyde is shown in Figure 6.2 below. A current unknown in this new mechanistic route is whether lithium or zinc is the metal forming the chelate in compound **F**. If the metal is lithium, then a monosilylzinc chloride species is created that could be reincorporated into the catalytic cycle and add another silyl group.

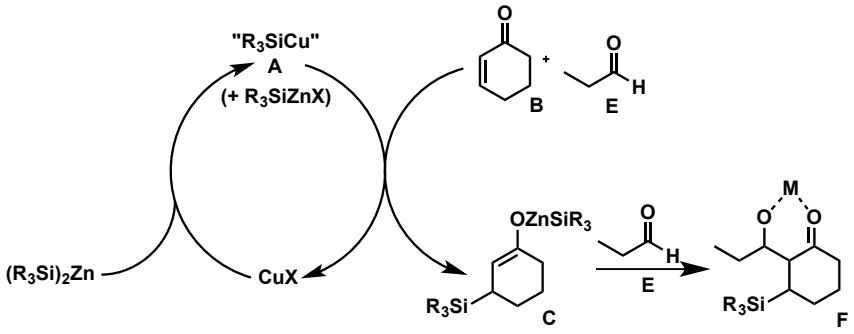


Figure 6.2: Expanded mechanistic route to include the addition of the aldehyde

Besides testing the monosilylzinc chloride reagent with and without the aldehyde present, using 0.5 mole equiv. of the disilylzinc species could show if the reagent would add the second silyl group after the enolate reacted with the aldehyde and probe which metal is incorporated into compound **F**. These control tests are currently underway.

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Chapter 7 Experimental Section

7.1 Instrumentation and Chemicals

General: All air and water sensitive reactions were conducted under an inert atmosphere of argon and in septum sealed oven-dried glassware. Chemical yields were based on purified material (>96% by ^{1}H NMR spectroscopy) unless otherwise specified. NMR spectra were recorded on a Varian 400 or 500-MHz (^{1}H NMR) and 150 MHz (^{13}C NMR) instrument using TMS as an internal standard (δ = 0.0 ppm). Coupling patterns for ^{1}H NMR are abbreviated as s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). In the cases of combined multiplicities, the multiplicity with the larger coupling constant is stated first. In some cases, *partially hidden* couplings refer to signals that overlapped but were definable. The peak shifts for ^{13}C NMR are given in ppm excluding the solvent and TMS peaks. Flash chromatography was conducted using a Biotage Isolera One instrument with self-packed Biotage snap columns filled with silica gel (Sorbent Technologies, 60Å, 230 – 400 mesh).

Materials: Tetrahydrofuran (THF) and diethylether (Et_2O) was distilled from sodium-benzophenone under argon prior to use. Dichloromethane (DCM) was distilled from calcium hydride. All other air and water sensitive reagents purchased were used as is from the manufacturer (Sigma-Aldrich) through sure-seal septa. Solvents used for extraction and purification were of technical grade and used as is from the manufacturer (Fisher Scientific). All other chemicals used for reactions were used as is from the manufacturer unless otherwise specified.

7.2 General Experimental Procedures

7.2.1 General procedure for alkenylzirconocene additions

An oven-dried 100 mL two-neck round-bottom flask equipped with a condenser and stir bar was purge under Ar(g). The alkyne (1.3 mmol, 1.5 eq) was added to the round bottom containing a suspension of Schwartz's reagent, ($Cp_2Zr(H)Cl$, 1.5 mmol, 1.7 eq) in anhydrous THF at room temperature. The reaction flask was immersed in an oil bath and heated to 40 °C while stirring for 20 min. The reaction temperature was cooled to 20 °C and the $(CuI)_4(DMS)_3$ complex (0.09 mmol, 0.1 eq) and desired enone (0.9 mmol, 1.0 eq) were added as solid or via micro syringe respectively. The reaction flask was reheated to 40 °C while stirring for 12 hr. The reaction mixture was then cooled to room temperature and quenched with Et_2O and H_2O. The reaction mixture was vacuum filtered through a Celite pad. The mixture was then transferred to a separatory funnel and the organic fraction washed with saturated $NaHCO_3$, brine (2x), and dried with anhydrous $MgSO_4$. Solvent was removed *in vacuo* and the crude product purified by flash-column chromatography on silica. [30]

7.2.2 General procedure for alkenylzincate additions

An oven-dried 25 mL two-neck round-bottom flask equipped with a stir bar was purged under argon gas. The alkyne (1.3 mmol, 1.5 eq) was added to the round bottom containing a suspension of Schwartz's reagent ($Cp_2Zr(H)Cl$, 1.5 mmol, 1.7 eq) in anhydrous dichloromethane at room temperature and stirred for 20 min. The reaction temperature was cooled to -78 °C and a solution of diethylzinc was added drop wise. The reaction temperature was increased to 0 °C and the $(CuI)_4(DMS)_3$

complex (0.09 mmol, 0.1 eq) and desired enone (0.9 mmol, 1.0 eq) were added as solid and via micro syringe respectively. The temperature of the reaction flask was then increased to room temperature while stirring. The reaction was monitored by TLC for completion and quenched with Et_2O and deionized water. The mixture was transferred to a separatory funnel and the organic fraction washed with saturated $NaHCO_3$, brine (2x), and dried over anhydrous $MgSO_4$. Solvent was removed *in vacuo* and the crude material purified by flash-column chromatography on silica. [9]

7.2.3 General procedure for the disilylzinc reaction

1M $LiSiMe_2Ph$ Preparation: In a 5 mL round bottom flask under Ar(g), Li^0 (65 mg, 9.38 mmol, 5 eq) was added to anhydrous THF (1.5 mL). The reaction mixture was cooled to 0 °C and the silyl chloride (315 μL, 1.875 mmol, 1 eq) was added. The resulting reaction mixture was stirred at 0 °C for 6 hr and then stored in the freezer under Ar(g) with a fresh septum until use in the next step.

$(PhMe_2Si)_2Zn/LiCl$ Preparation: In a 10 mL round bottom flask under Ar(g), anhydrous THF (2 mL) was added and cooled to -78 °C. A 0.5 M solution of $ZnCl_2$ (852 μL, 0.426 mmol, 1.25 eq) was added followed by the silyl anion (852 μL, 0.852 mmol, 2.5 eq). The reagent mixture was stirred at -78 °C for 20 min and the temperature increased to 0 °C just before transfer into the reaction mixture.

Reaction Setup: In a 25 mL round bottom flask under Ar(g), $(CuI)_4(DMS)_3$ (16 mg, 0.017 mmol, 0.05 eq) and the desired substrate (0.341 mmol, 1 eq) was added along with anhydrous THF (10 mL). The reaction flask was cooled to -78 °C and the entire silyl zincate solution made above was added to the reaction flask and allowed to mix at -78 °C for 2 hr. After 2 hr, the temperature of the reaction was increased to -30 °C

and the reaction stirred an additional 4 hr. The reaction was quenched with 10 mL sat. NH_4Cl/NH_3 pH 10 solution and allowed to equilibrate while mixing at room temperature until the aqueous layer turned a deep blue color. (The reaction can be allowed to equilibrate overnight). The reaction was diluted with 25 mL DI H_2O and 25 mL Et_2O. The aqueous layer was extracted with Et_2O (3 x 25 mL). The organic fractions were dried over anhydrous $MgSO_4$ and the solvents removed *in vacuo* to provide the crude product which was purified by flash-column chromatography on silica.

7.2.4 General procedure for the disilylzinc to aldol reaction

LiCl/Zn(SiMe$_2$Ph)$_2$ Preparation: In a 5 mL round bottom flask under Ar(g), Li^0 (50 mg, 7.20 mmol, 12.7 eq) was added followed by anhydrous THF (1 mL). The reaction mixture was cooled to 0 °C and the silyl chloride (250 μL, 1.49 mmol, 2.54 eq) was added. The resulting reaction mixture was stirred at 0 °C for 6 hr then stored in the freezer under Ar(g) with a fresh septum until use in the next step. In a 10 mL round bottom flask under Ar(g), anhydrous THF (2 mL) was added and the reaction flask cooled to -78 °C. A 0.5 M solution of $ZnCl_2$ (1.45 mL, 0.725 mmol, 1.25 eq) was added followed by the entire silyl anion from the freezer. The flask containing the silyl anion was then rinsed with anhydrous THF (1 mL) and the rinse added to the reaction mixture. The disilylzinc reagent was mixed at -78 °C for 20 min then the reaction temperature increased to 0 °C just before transfer into reaction mixture.

Reaction Setup: In a 25 mL round bottom flask under Ar(g), the $(CuI)_4(DMS)_3$ complex (28 mg, 0.029 mmol, 0.05 eq) was added and anhydrous THF (5 mL) before cooling the reaction flask to -78 °C. In a separate 5 mL round bottom flask under

Ar(g), the desired substrate (0.58 mmol, 1 eq) and freshly distilled propionaldehyde (83 μL, 1.16 mmol, 2 eq) was dissolved in anhydrous THF (2 mL). The entire disilylzinc solution was added to the reaction flask and the resulting reaction mixture stirred for 5 min at -78 °C. The substrate/aldehyde solution was then added to the reaction flask dropwise and the reaction allowed to mix for 4 hr at -78 °C. The reaction was quenched with 10 mL sat. NH_4Cl/NH_3 pH 10 solution and the resulting mixture allowed to equilibrate at room temperature until the aqueous layer turned a deep blue color. (The reaction can be allowed to equilibrate overnight). The reaction mixture was diluted with 25 mL DI H_2O and 25 mL EtOAc. The aqueous layer was extracted with EtOAc (3 x 25 mL). The organic fractions were washed with brine (25 mL) and dried over anhydrous Na_2SO_4. The solvents were removed *in vacuo* to give the crude product which was purified by flash-column chromatography on silica.

7.2.5 General procedure for addition of silylboronic esters in water

The desired enone (0.299 mmol, 1 eq) was weighed into an 8 mL glass vial equipped with a 1 cm stir bar. The silyl-boronic ester ($PhMe_2Si$-B(pin), 4.0 eq, 1.196 mmol, 327 μL) was added to the vial followed by Et_3N (0.20 eq, 0.060 mmol, 8.4 μL). Stirring was initiated creating a slurry. The $CuSO_4 \cdot 5H_2O$ solution (15.0 mM, 0.01 eq, 2 mL) was added as a bolus while stirring the slurry rapidly. The vial was capped and the reaction mixed at maximum stir plate speed overnight. The reaction was quenched with Et_2O and transferred to a separatory funnel. The reaction mixture was extracted with Et_2O (3 x 4 mL) then the organic fraction washed with DI H_2O (2 x 4

mL), dried over anhydrous $MgSO_4$, filtered, and the solvent removed *in vacuo* to provide the crude product. [14]

7.2.6 General procedure for oxazolidinone coupling to acyl chlorides

The oxazolidinone (10 mmol, 1 eq) was dissolved in anhydrous THF (10 mL) and the reaction flask cooled to -78 °C. A 2.5 M solution of *n*BuLi (4.4 mL, 11 mmol, 1.1 eq) was added slowly and the resulting reaction mixture was stirred for 30 min at -78 °C. The acyl chloride (10 mmol, 1 eq) was added dropwise as a solution in anhydrous THF and the reaction mixed for 30 min at -78 °C before the reaction temperature was increased to room temperature overnight (16 hr). The reaction was quenched with sat. NH_4Cl (10 mL) and extracted with Et_2O (3 x 25 mL). The organic fraction was washed with sat. $NaHCO_3$ (25 mL) and brine (25 mL) before being dried over anhydrous Na_2SO_4 and solvents removed *in vacuo* to give the crude product which was purified by flash-column chromatography on silica.

7.3 Reagent Syntheses

7.3.1 Copper Iodine Dimethyl Sulfide (CuI·DMS) Complex Preparation

In a 125 mL Erlenmeyer flask, CuI (26 mmol, 5.0 g) was dissolved in anhydrous Et_2O (15 mL) and mixed with DMS (380 mmol, 20 mL). The reaction mixture was filtered through a cotton plug to remove any heterogeneous material and the filtrate diluted with cold hexanes (50 mL). The crystals were allowed to form in the freezer overnight then collected by vacuum filtration and washed with cold

hexanes (3 x 50 mL). The white crystals were dried under reduced pressure using a high vacuum until constant mass was achieved (65%).[105]

7.3.2 Preparation of Schwartz reagent, $Cp_2Zr(H)Cl$

An oven-dried Schlank filter purged with Ar(g) was equipped with a two-neck 250 mL round-bottom flask for the reaction mixture and a 500 mL round bottom flask for wash collections. Cp_2ZrCl_2 (17 mmol, 5.0 g) was added to the reaction flask followed by anhydrous THF (35 mL). The reaction mixture was heated in an oil bath to 45 °C while mixing until homogeneous. LAH (1M in THF, 4.27 mL, 0.25 eq) was added dropwise to the reaction mixture and the reaction was mixed for 2 hr at 45 °C. The Schlank filter was then inverted and the product precipitate was filtered off under reduced pressure. The precipitate was washed with anhydrous THF (4 x 10 mL), anhydrous DCM (2 x 10 mL), and anhydrous Et_2O (3 x 10 mL) with agitation of the precipitate between each wash. The precipitate was allowed to dry under reduced pressure to yield a light orange powder (51%).[106]

7.3.3 Silylboronic ester preparation

In a round bottom flask under Ar(g), $PhMe_2SiCl$ (3.2 mL, 19.1 mmol, 1 eq) was added to a mixture of anhydrous THF (10 mL) and lithium (530 mg, 76.4 mmol, 4 eq) at 0 °C. The reaction was mixed at 0 °C overnight. In a separate flask, pinacol borane (5.5 mL, 37.9 mmol, 2 eq) was dissolved in hexanes (10 mL) and the resulting solution was cooled to 0 °C. The silyl anion was added dropwise to the pinacol borane solution and the anion flask was rinsed with anhydrous THF (5 mL) and the rinse also added to the reaction. The reaction was mixed at 0 °C for 5hr before the reaction temperature was increased to room temperature. The reaction was mixed

for a total of 3 days. The reaction was quenched by removing the solvents *in vacuo*. The crude material was redissolved in hexanes, filtered through a pad of Celite to remove insoluble particulates and the hexanes removed again *in vacuo* to give the desired silylpinacolborane ($PhMe_2Si$-B(pin), 4.45 g) as a yellow oil. Product NMR matched the literature.[92]

7.3.4 Dess-Martin Periodinane Preparation

IBX Prep:[107] In a 1 L flask, oxone (74.51 g, 0.121 mol, 3 eq) was dissolved in DI water (500 mL). 2-iodobenzoic acid (10 g, 40.32 mmol, 1 eq) was added and the temperature of the mixture was slowly increased to 70 °C for 2 hr. The reaction was allowed to cool to room temperature overnight before further cooling the reaction temperature to 0 °C and filtering off the precipitate that formed. The precipitate was washed with DI water (6 x 25 mL) and acetone (2 x 25 mL). Sodium sulfite (14 g) was added to the filtrate before it was neutralized to pH 7 with 1 M NaOH. The crystals formed upon neutralization were collected by vacuum filtration and dried in the vacuum desiccator to give white crystalline IBX (8.72 g, 77%).

DMP Prep:[46] The IBX from above (8.72 g, 31.14 mmol, 1 eq) was added to acetic acid (23 mL, 0.405 mol, 13 eq) and acetic anhydride (27 mL, 0.283 mol, 9.1). The resulting reaction mixture was heated to 85 °C for 1.5 hr. The reaction mixture was allowed to cool to room temperature and the reaction flask covered with foil and left undisturbed to allow for crystallization of the product. The product crystals were collected by vacuum filtration and washed with anhydrous Et_2O (5 x 15 mL) before being dried under reduced pressure to give DMP as a white crystalline solid (10.96 g, 83 %). Product NMR matched the literature.

7.3.5 Horner-Wadsworth Reagent Prep

Ethylbromoacetate (5.5 mL, 50 mmol, 1 eq) and triethyl phosphite (8.6 mL, 50 mmol, 1 eq) were added to a round bottom flask equipped with a short-path distillation apparatus. The reaction mixture was heated to 130 °C overnight in an oil bath under Ar(g) to give the desired triethyl phosphoroacetate (10.24 g, 91%) as a clear liquid. Product NMR matched the literature.[108]

7.3.6 (2*E*,4*E*) heptadienoic acid and ethyl ester prep

Ethyl (2*E*,4*E*) heptadienoate:[109] A mixture of 60% NaH in mineral oil (455 mg, 11.38 mmol, 1.75 eq) and anhydrous THF (10 mL) were cooled to -20 °C. Triethyl phosphoroacetate (2.28 mL, 11.38 mmol, 1.75 eq) was added slowly and the resulting reaction mixture was stirred for 20 min. Trans-pentenal (636 μL, 6.50 mmol, 1 eq) was added at -20 °C and the reaction allowed to mix while warming up to room temperature over 2 hr. The reaction was quenched with sat. NH_4Cl (10 mL) then extracted with Et_2O (3 x 25 mL). The organic fraction was washed with sat. Na_2CO_3 (2 x 25 mL) and brine (25 mL) before being dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo* to obtain a yellow liquid. The crude was run through a silica plug (10% EtOAc / Hex) to give the product as a clear liquid (983 mg, 98%). Product NMR matched the literature.

(2*E*,4*E*) heptadienoic acid:[25] Ethyl (2*E*,4*E*) heptadienoate (946 mg, 6.13 mmol, 1.1 eq) was dissolved in a 1:1 mixture of Et_2O / EtOH (10.2 mL). A 0.5 M solution of NaOH was added (11.1 mL, 5.58 mmol, 1 eq) and the resulting reaction mixture was stirred at room temp for 72 hr. The reaction was quenched by removing all solvents *in vacuo* and adjusting the pH of the reaction crude to pH 1 using 1M HCl. The crude

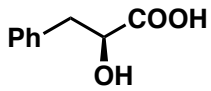
material was extracted with EtOAc (3 x 25 mL). The organic fraction was washed with brine (25 mL) and dried over anhydrous Na_2SO_4. The crude material was purified by flash-chromatography on silica (10 → 25% EtOAc / Hex) to give the product (621 mg, 88%) as a white crystalline solid. NOTE: the acid is heat / moisture sensitive therefore must be stored in the freezer under Ar(g). Product NMR matched the literature.

7.3.7 Dimethyldioxerane (DMDO) Prep

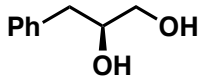
A 3-neck 3 L round bottom reaction flask was connected with a "U-tube" to a 3-neck 500 mL flask cooled to -78 °C. A mixture of sodium bicarbonate (58 g, 0.69 mol, 3.5 eq), DI water (254 mL, 14.1 mol, 72 eq) and acetone (192 mL, 2.61 mol, 13 eq) was cooled to 0 °C in the reaction flask. Oxone (K_2HSO_5, 120 g, 0.195 mol, 1 eq) was weighed into a beaker and added in 5 equal portions in 3 minute intervals to the reaction flask. Once all the oxone was added to the reaction flask, the ice bath was removed and the reaction distilled under reduced pressure (80 – 100 torr) for 35 min to give a 0.66 mM solution of DMDO in acetone. The DMDO solution collected was stored over 4Å molecular sieves in the freezer.[110]

DMDO Concentration Determination:[111] A 0.7 M solution of thioanisole (82 μL thioanisole, 918 μL acetone) was prepared in acetone-D_6. The thioanisole solution (100 μL) was added to an aliquot of DMDO solution (500 μL) and allowed to mix at 10 °C for 10 min before taking a ^1H NMR. The concentration was determined based on the ratio of sulfoxide peaks (δ 7.9 – 7.6) to sulfide peaks (δ 7.3 – 7.1).

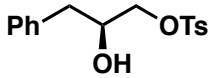
7.4 Experimental Procedures and Compound Characterization for Part I: Total Synthesis of Azaspirene



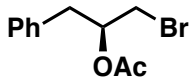
Diazotization of an amine,[32] **Compound 2.1,** *(S)-2-hydroxy-3-phenylpropanoic acid*: A solution of L-phenylalanine (20.0 g, 0.121 mol, 1 eq) in 2 M sulfuric acid (140 mL, 2.3 eq) was cooled to 0 °C in an ice bath. A 30% aqueous solution (wt/vol) of sodium nitrite (0.484 mol, 4 eq) was added dropwise to the reaction flask under a stream of air to remove the gas produced. The reaction was mixed for 6 hr at 0 °C before allowing the temperature to rise to ambient temperature over night. The reaction mixture was saturated with solid sodium chloride before being extracted with ethyl acetate (3 x 250 mL). The organic fraction was washed with brine (200 mL), dried over anhydrous sodium sulfate and the solvents were removed *in vacuo* to produce a light yellow fluffy solid (19.85 g, 98% yield) used without purification in the next step. **TLC** (50% EtOAc / Hex) R_f = 0.03. **MS** (ASAP): calcd for ([M+H], $C_9H_{11}O_3$)$^+$: 167.06, found 167.1. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 12.44 (bs, COO*H*, 1H), 7.33 - 7.14 (m, Ar*H*, 5H), 5.24 (bs, CHO*H*, 1H), 4.15 (dd, C*H*OH, *J* = 8.3, 4.5 Hz, 1H), 2.97 (dd, $C_6H_5CH_2$, *J* = 13.8, 4.5 Hz, 1H), 2.79 (dd, $C_6H_5CH_2$, *J* = 13.8, 8.3 Hz, 1H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 175.0, 138.1, 129.3, 127.9, 126.0, 71.0, 40.0. **$[\alpha]_D^{20}$** -28.8° (c = 1.03, DMF). *Lit.* **$[\alpha]_D^{20}$** +38.6° (c = 1.00, DMF, opposite enantiomer).[32]



Reduction with lithium aluminum hydride (LAH), Compound 2.2, *(S)-3-phenylpropane-1,2-diol*: A mixture of anhydrous THF (450 mL) and lithium aluminum hydride (20.4 g, 4 eq) was cooled to 0 °C in a 3-neck round bottom flask equipped with a condenser under Ar(g). Crude (S)-2-hydroxy-3-phenylpropanoic acid **2.1** (22.3 g, 0.131 mol, 1 eq) was added in small portions (~1 g) while keeping the reaction temperature cool. Once the addition was complete the reaction mixture was allowed to warm to room temperature before the temperature was increased to reflux for 16 hr. The reaction temperature was cooled to 0 °C and the reaction quenched with deionized water (20 mL), 15% NaOH (20 mL) and deionized water again (60 mL). The reaction was allowed to mix at room temperature for at least 1 hr. After the reaction color turned from grey to white, the reaction was filtered through Celite to remove the solids. The solids were washed with EtOAc (500 mL). The organic fraction was washed with brine (3 x 100 mL) and dried over anhydrous Na_2SO_4. Removal of solvents *in vacuo* gave a light brown solid (19.6 g, 96% yield) that was used in the next step without further purification. **TLC** (50% EtOAc / Hex) R_f = 0.19. **MS** (ASAP): calcd for ([M+H], $C_9H_{13}O_2)^+$: 153.08, found 153.2. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 - 7.29 (m, Ar*H*, 2H), 7.21 – 7.25 (m, Ar*H*, 3H), 3.95 (dddd, C*H*OH, *J* = 7.9, 7.0, 5.5, 2.5 Hz, 1H), 3.70 (dd, CH_2OH, *J* = 11.1, 2.5 Hz, 1H), 3.52 (dd, CH_2OH, *J* = 11.1, 7.0 Hz, 1H), 2.81 (dd, $C_6H_5CH_2$, *J* = 13.7, 5.5 Hz, 1H), 2.75 (dd, $C_6H_5CH_2$, *J* = 13.7, 7.9 Hz, 1H), 2.09 (bs, CHO*H*, 1H), 1.97 (bs, CH_2OH, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 137.8, 129.5, 128.8, 126.8, 73.2, 66.2, 40.0. **$[\alpha]_D^{20}$** -21.8° (c = 1.03, $CHCl_3$). *Lit.* **$[\alpha]_D^{27}$** -31.0° (c = 1.01, EtOH).[112]

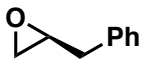


Tosylation of a primary alcohol,[38] **Compound 2.3a**, *(S)-2-hydroxy-3-phenylpropyl 4-methylbenzenesulfonate*: A solution of diol **2.2** (508 mg, 3.34 mmol, 1 eq) in anhydrous DCM (10 mL) under Ar(g) was cooled to 0 °C. Pyridine (410 μL, 5.09 mmol, 1.5 eq) was added to the reaction mixture followed by tosyl chloride (697 mg, 3.66 mmol, 1.1 eq). The reaction was allowed to mix from 0 °C to ambient temperature overnight. The reaction was quenched with 2M hydrochloric acid until acidic by pH paper. The reaction was diluted with DCM (25 mL), washed with brine (10 mL) and dried over anhydrous magnesium sulfate. Removal of solvents *in vacuo* gave a yellow oil. Purification by flash chromatography on silica (20% → 100% EtOAc / Hex) gave the product as a clear oil (519 mg, 51% yield). **TLC** (25% EtOAc / Hex) R_f = 0.21. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 (d, Ar*H*, *J* = 8.0 Hz, 2H), 7.35 (d, Ar*H*, *J* = 8.0 Hz, 2H), 7.32 - 7.11 (m, Ar*H*, 5H), 4.12 - 4.01 (m, C*H*OH, CH_2OTs, 2H), 3.95 (dd, CH_2OTs, *J* = 11.0, 7.2 Hz, 1H), 2.85 - 2.71 (m, CH_2Ph, 2H), 2.46 (s,TsCH_3, 3H).



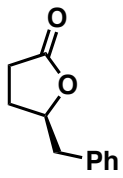
Conversion of a diol to bromo acetate,[33] **Compound 2.3**, *(S)-1-bromo-3-phenylpropan-2-yl acetate*: The crude diol **2.2** (19.0 g, 0.125 mol) was ground into a powder using a mortar and pestle and added to an Erlenmeyer flask submerged into an ice bath. Cold 33% hydrobromic acid in acetic acid (65.6 mL, 0.375 mol, 3 eq) was added to the flask and the reaction mixed for 5 min before the ice bath was removed and the reaction allowed to warm up to room temperature while mixing.

Mixing continued until all solids had dissolved (~2 hr total). The reaction was quenched by adding deionized water until the cloudy appearance persisted. The quenched reaction mixture was transferred to a 1 L Erlenmeyer flask and neutralized with solid sodium carbonate (approximately 1 g carbonate to 1 mL acid added). Diethyl ether (200 mL) was added and the mixture was allowed to equilibrate while mixing for 1 hr until both layers were translucent. The aqueous layer was further extracted with diethyl ether (3 x 100 mL) then the organic fraction was dried over anhydrous $MgSO_4$ and solvents removed *in vacuo* to produce a golden oil (30.85 g, 96% yield) used without further purification. **TLC** (5% EtOAc / Hex) R_f = 0.28. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 - 7.28 (m, Ar*H*, 2H), 7.27 - 7.21 (m, Ar*H*, 3H), 5.18 (tdd, C*H*OAc, *J* = 6.7, 5.0, 4.6 Hz, 1H), 3.49 (dd, CH_2Br, *J* = 10.9, 4.6 Hz, 1H), 3.37 (dd, CH_2Br, *J* = 10.9, 5.0 Hz, 1H), 3.01 (d, $C_6H_5CH_2$, *J* = 6.7 Hz, 2H), 2.06 (s, COCH_3, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.3, 136.3, 129.6, 128.8, 127.1, 73.1, 38.6, 33.5, 21.1.



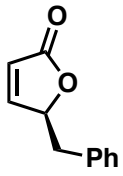
Acetal deprotection and epoxide formation,[39] **Compound 2.4**, *(S)-2-benzyloxirane*: A 1 M solution of NaOMe was prepared by adding anhydrous methanol (280 mL) to a flask under Ar(g) containing solid sodium (6.40 g, 0.279 mol, 2.6 eq) in an ice bath. A 1 L round bottom flask containing the crude bromoacetate compound **2.3** (27.22 g, 0.106 mol, 1 eq) was cooled to 0 °C in an ice bath. The freshly prepared sodium methoxide solution was added via cannula to the substrate flask at 0 °C. After addition of the sodium methoxide, the reaction was allowed to warm to room temperature then mixed for 1 hr checking for completion by thin layer

chromatography (TLC). Once complete, deionized water was added to the reaction until the cloudy appearance persisted. The crude was extracted with diethyl ether (3 x 200 mL). The organics were dried over anhydrous $MgSO_4$ and solvents removed *in vacuo* to produce a yellow liquid. The crude material was purified by flash-chromatography on silica (2% → 15% EtOAc / Hex) to afford a light yellow liquid **I** (11.05 g, 78% yield). **TLC** (5% EtOAc / Hex) R_f = 0.34. **MS** (ASAP): calcd for ([M+H], $C_9H_{11}O)^+$: 135.07, found 135.2. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 - 7.29 (m, Ar*H*, 2H), 7.27 - 7.22 (m, Ar*H*, 3H), 3.16 (dddd, C*H*, *J* = 5.6, 5.4, 3.9, 2.7 Hz, 1H), 2.93 (dd, $C_6H_5CH_2$, *J* = 14.6, 5.6 Hz, 1H), 2.85 - 2.77 (m, $C_6H_5CH_2$, CH_2O, 2H), 2.55 (dd, CH_2O, *J* = 5.0, 2.7 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 137.30, 129.14, 128.66, 126.79, 52.58, 47.02, 38.91. **$[\alpha]_D^{20}$** -0.9° (c = 1.77, $CHCl_3$). *Lit.* **$[\alpha]_D$** +17.6° (c = 1.9, $CHCl_3$).[38]



Ring expansion and decarboxylation of an epoxide,[35] **Compound 2.5**, *(R)-5-benzyldihydrofuran-2(3H)-one*: A 1.4 M solution of NaOEt was prepared by adding anhydrous ethanol (146 mL) to a flask containing solid sodium (4.72 g, 205 mmol, 2.5 eq) under Ar(g) in an ice bath. Once the sodium had fully dissolved, anhydrous THF (74 mL) was added to the flask followed by diethyl malonate (37.5 mL, 246 mmol, 3 eq) and the epoxide **2.4** (11.00 g, 82 mmol, 1 eq). The reaction mixture was slowly warmed from 0 °C up to ambient temperature while mixing overnight (16 hr). The now milky white reaction was quenched by the addition of 5 M hydrochloric acid (40 mL) to the reaction flask followed by the removal of all organic solvents *in vacuo*. The

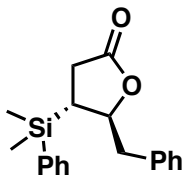
crude reaction mixture was suspended with DMSO (40 mL) and the reaction allowed to reflux until decarboxylation was complete as monitored by a bubbler (2 - 5 days). The reaction flask was cooled to room temperature then deionized water was added until the cloudy appearance persisted. The crude mixture was extracted with diethyl ether (3 x 100 mL). The organic fraction was washed with deionized water (3 x 100 mL) and dried over anhydrous magnesium sulfate. The solvents were removed *in vacuo* to give a light yellow oil which was purified by flash-column chromatography on silica (15% → 35% EtOAc / Hex) to produce a white crystalline solid **2.5** (12.4 g, 86% yield). **TLC** (25% EtOAc / Hex) R_f = 0.20. **MS** (ASAP): calcd for ([M+H], $C_{11}H_{13}O_2$)$^+$: 177.08, found 177.1. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.34 - 7.29 (m, Ar*H*, 2H), 7.28 - 7.21 (m, Ar*H*, 3H), 4.73 (dddd, C*H*, *J* = 7.5, 6.7, 6.3, 6.2 Hz, 1H), 3.07 (dd, $C_6H_5CH_2$, *J* = 14.0, 6.2 Hz, 1H), 2.93 (dd, $C_6H_5CH_2$, *J* = 14.0, 6.3 Hz, 1H), 2.46 (dt, $COCH_2$, *J* = 17.7, 9.4 Hz, 1H), 2.38 (ddd, $COCH_2$, *J* = 17.7, 9.4, 4.7 Hz, 1H), 2.25 (dddd, $CHCH_2$, *J* = 12.9, 9.4, 6.7, 4.7 Hz, 1H), 1.95 (dtd, $CHCH_2$, *J* = 12.9, 9.4, 7.5 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 177.11, 136.01, 129.57, 128.77, 127.10, 80.90, 41.46, 28.77, 27.26. **$[\alpha]_D^{20}$** -20.0° (c = 0.28, $CHCl_3$). *Lit.* **$[\alpha]_D^{26}$** -22.1° (c = 0.28, $CHCl_3$).[34]



Oxidation via phenyl sulfide,[36,37] **Compound 2.8**, *(S)-5-benzylfuran-2(5H)-one*: A solution of lithium hexamethyldisilizane (LiHMDS) was prepared by adding 2.5 M *n*BuLi (13.6 mL, 34.1 mmol, 1.2 eq) to a solution of HMDS (7.4 mL, 35.5 mmol, 1.25 eq) dropwise in anhydrous THF (100 mL) at 0 °C and under Ar(g). The resulting

solution was allowed to mix for 30 min at 0 °C before being cooled further to -78 °C. A solution of lactone **2.5** (5.00 g, 28.4 mmol, 1 eq) in anhydrous THF (10 mL) was added to the reaction mixture dropwise over 15 min and allowed to mix at -78 °C for 2 hr. A solution of Ph_2S_2 (8.05 g, 36.9 mmol, 1.3 eq) in anhydrous THF (15 mL) was added slowly dropwise to the reaction mixture and the reaction was allowed to mix an additional 5 hr at -78 °C. The reaction was quenched at -78 °C with sat. NH_4Cl (25 mL) and Et_2O (25 mL). The quenched reaction mixture was allowed to equilibrate and warm up to room temperature. The crude reaction mixture was extracted with Et_2O (3 x 200 mL). The organic fraction was washed with sat. NH_4Cl (3 x 100 mL) and dried over anhydrous $MgSO_4$ before removing the solvents *in vacuo* to obtain the crude sulfide **2.6**. The crude **2.6** was dissolved in glacial acetic acid (230 mL) then a 33% solution of hydrogen peroxide was added (84 mL, 0.738 mol, 10 eq based on amount of sulfur) and the reaction mixture stirred at room temperature for 2 hr before being quenched with deionized water (500 mL) and diluted with EtOAc (250 mL). The crude mixture was further extracted with EtOAc (3 x 400 mL). The organic fraction was neutralized with sat. $NaHCO_3$ (7 x 250 mL), washed with deionized water (250 mL) and brine (250 mL) before being dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo* and the crude material purified by flash-column chromatography on silica (20% → 40% EtOAc / Hex) to give 4.79 g of white solid sulfoxide **2.7** (56% yield, two steps) and 1.90 g (38 %) starting lactone **2.5**. The sulfoxide **2.7** was dissolved in toluene (200 mL) and refluxed for 30 min. The solvents were removed *in vacuo* and the crude material purified by flash-column chromatography on silica (20 → 40% EtOAc / Hex) to give a clear oil **2.8** (2.50 g, 92% yield) which crystallized upon storage in the freezer. **TLC** (25% EtOAc / Hex) R_f =

0.18. **MS** (ASAP): calcd for ([M+H], $C_{11}H_{11}O_2$)$^+$: 174.07, found 175.1. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 (dd, C*H*$^\beta$=CH$^\alpha$, *J* = 5.7, 1.5 Hz, 1H), 7.36 - 7.24 (m, Ar*H*, 3H), 7.24 - 7.18 (m, Ar*H*, 2H), 6.08 (dd, CH$^\beta$=C*H*$^\alpha$, *J* = 5.7, 2.0 Hz, 1H), 5.23 (dddd, C*H*, *J* = 7.1, 6.4, 2.0, 1.5 Hz, 1H), 3.16 (dd, $C_6H_5CH_2$, *J* = 13.8, 6.4 Hz, 1H), 2.96 (dd, $C_6H_5CH_2$, *J* = 13.8, 7.1 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 172.8, 155.7, 134.9, 129.5, 128.9, 127.4, 122.2, 83.5, 39.8. **IR** (Diamond-ATR, $CHCl_3$) ν_{max}: 3030, 1743, 1601, 1159, 810. **$[\alpha]_D^{20}$** +115.4° (c = 2.16, 1,4-dioxane). *Lit.* **$[\alpha]_D^{20}$** +117.8° (c = 2.19, 1,4-dioxane).[113]



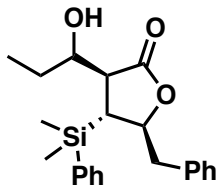
Conjugate silyl addition via Li[$PhMe_2SiCuI$][10] and $(PhMe_2Si)_2Zn$/LiCl, Compound 2.9, *(4R,5S)-5-benzyl-4-(dimethyl(phenyl)silyl)dihydrofuran-2(3H)-one*:

Method A, Li[$PhMe_2SiCuI$]: The silyl anion was prepared by adding $PhMe_2SiCl$ (245 μL, 1.46 mmol, 1.7 eq) to a mixture of lithium (50 mg, 7.2 mmol, 8.2 eq) in anhydrous THF (2 mL) at 0 °C. The anion was mixed for 5 hr at 0 °C then stored in the freezer under argon overnight. The reaction flask was charged with CuI·DMS (1.66 g, 1.75 mmol, 2 eq), anhydrous THF (8 mL) and cooled to -78 °C. The silyl anion was added to the reaction flask and allowed to mix for 20 minutes at -78 °C. The substrate (153 mg, 0.876 mmol, 1 eq) was added dropwise as a solution in anhydrous THF (5 mL). The reaction was allowed to mix at -78 °C for 5 hr then the temperature was increased to -40 °C for 2 hr. The reaction was quench with sat. NH_4Cl / NH_3 pH 10 (10 mL) and allowed to equilibrate while mixing at room temperature until the

aqueous layer turned a deep blue color. (The reaction can be allowed to equilibrate overnight). The crude was diluted with DI water (25 mL) and Et_2O (25 mL) and transferred to a separatory funnel. The crude was extracted with Et_2O (3 x 25 mL) and dried over anhydrous $MgSO_4$ before the solvents were removed *in vacuo*.

Method B, $(PhMe_2Si)_2Zn$/LiCl: See general procedure method for addition of disilylzinc reagents. Purification by flash column chromatography on silica (10 → 25% EtOAc/Hex) gave the product as a yellow oil (95% Method A, 70% Method B).

TLC (25% EtOAc / Hex) R_f = 0.28. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 - 7.37 (m, Ar*H*, 5H), 7.31 - 7.17 (m, Ar*H*, 3H), 7.12 - 7.04 (m, Ar*H*, 2H), 4.58 (ddd, C*H*CH_2Ph, *J* = 9.3, 7.2, 3.4 Hz, 1H), 2.84 (dd, C*H*$_2$Ph, *J* = 14.6, 3.4 Hz, 1H), 2.71 (dd, C*H*$_2$Ph, *J* = 14.6, 7.2 Hz, 1H), 2.50 (dd, COC*H*$_2$CH, *J* = 17.7, 9.8 Hz, 1H), 2.35 (dd, COC*H*$_2$CH, *J* = 17.7, 11.3 Hz, 1H), 1.72 (ddd, C*H*SiMe_2Ph, *J* = 11.3, 9.8, 9.3 Hz, 1H), 0.38 (s, 2 x SiC*H*$_3$, 6H).

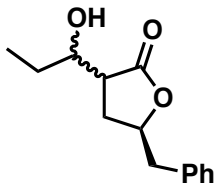


Conjugate silyl addition to aldol reaction,[7] Compound 2.10, *Synthesis of (3S,4R,5S)-5-benzyl-4-(dimethyl(phenyl)silyl)-3-((S)-1-hydroxypropyl)dihydrofuran-2(3H)-one*: **$(PhMe_2Si)_2Zn$ / LiCl Prep:** A suspension of lithium metal (1.27 g, 0.184 mmol, 12.8 eq) in anhydrous THF (20 mL) was cooled to 0 °C under Ar(g). Phenyldimethylsilyl chloride (6.1 mL, 36.5 mmol, 2.54 eq) was added dropwise and the resulting reaction allowed to mix for 5 hr at 0 °C and then stored in the freezer under Ar(g) with a fresh septum until use in the next step. In a separate flask, a

solution of $ZnCl_2$ (35.9 mL, 17.9 mmol, 1.25 eq) was added to anhydrous THF (20 mL) and cooled to -78 °C. The silyl anion from above was added and allowed to mix for 20 min at -78 °C. The reaction mixture was allowed to warm to 0 °C briefly prior to transferring to the main reaction.

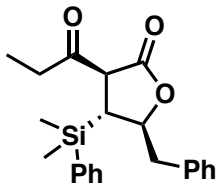
Reaction Method: A mixture of CuI·DMS complex (680 mg, 0.718 mmol, 0.05 eq) in anhydrous THF (50 mL) under Ar(g) was cooled to -78 °C. The solution of $(PhMe_2Si)_2Zn$ / LiCl in THF (1.25 eq) made above was added slowly to the reaction flask. In a separate flask, unsaturated lactone **2.8** (2.5 g, 14.4 mmol, 1 eq) and propionaldehyde (2.06 mL, 28.7 mmol, 2 eq) were dissolved in anhydrous THF (20 mL). The substrate/aldehyde solution was added dropwise to the reaction flask via a cannula and the resulting reaction mixture was stirred at -78 °C for 4 hr. The reaction was quenched with sat. NH_4Cl/NH_3 pH 10 (150 mL) and allowed to equilibrate while mixing at room temperature until the aqueous layer turned a deep blue color. (The reaction can be allowed to equilibrate overnight). The reaction was worked up by diluting with 150 mL DI water and 150 mL of EtOAc. The aqueous layer was extracted with EtOAc (3 x 150 mL). The organic fraction was dried over anhydrous Na_2SO_4 and the solvents removed *in vacuo*. Purification by flash-column chromatography on silica gel (10% → 30% EtOAc/Hex) gave 5.25 g (99% yield) of compound **2.10** as a clear oil with a d.r. of 85:15. **TLC** (25% EtOAc in hexanes): R_f = 0.28. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 - 7.44 (m, Ar*H*, 2H), 7.45 - 7.36 (m, Ar*H* 3H), 7.31 - 7.18 (m, Ar*H*, 3H), 7.10 - 7.04 (m, Ar*H,* 2H), 4.52 (ddd, C*H*CH_2Ph, *J* = 8.4, 7.2, 3.6 Hz, 1H), 3.15 (dddd, C*H*OH, *J* = 6.3, 5.8, 5.7, 4.1 Hz, 1H), 2.79 (dd, $C_6H_5CH_2$, *J* = 14.4, 3.6 Hz, 1H), 2.70 (dd, $C_6H_5CH_2$, *J* = 14.4, 7.2 Hz, 1H), 2.54 (dd, COC*H, J* = 9.7, 4.1 Hz, 1H), 2.15 (d, O*H*, *J* = 6.3 Hz, 1H), 1.73 (dd, $PhMe_2SiCH$, *J* = 9.7, 8.4 Hz, 1H),

1.59 – 1.48 (m, CH_2CH$_3$, 2H), 0.84 (t, CH$_2$CH_3, *J* = 7.4 Hz, 3H), 0.39 (s, SiCH_3, 3H), 0.36 (s, SiCH_3, 3H). **^{13}C NMR** (126 MHz, CDCl3) δ 177.7, 136.6, 135.5, 134.0, 130.2, 129.8, 128.6, 128.5, 127.0, 82.0, 73.9, 48.2, 42.8, 29.8, 28.1, 10.7, -4.1, -4.6. **IR** (Diamond-ATR, $CHCl_3$) ν_{max}: 3465, 2962, 1755, 1184, 816, 700. **MS** (ASAP): calcd for ([M+H], $C_{22}H_{29}O_3Si)^+$: 369.18, found 369.2. **$[\alpha]_D^{20}$** -3.1° (c = 1.27, $CHCl_3$, d.r 85:15).

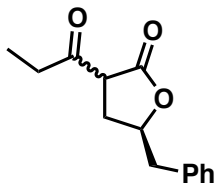


Aldol reaction using LiHMDS,[48] **Compound 2.10a**, *(5R)-5-benzyl-3-(1-hydroxypropyl)dihydrofuran-2(3H)-one*: A solution of LiHMDS was prepared by adding *n*BuLi (1.36 mL, 3.41 mmol, 1.2 eq) dropwise to a solution of HMDS (740 μL, 3.55 mmol, 1.25 eq) in anhydrous THF (10 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C before cooling further to -78 °C. A solution of saturated lactone **2.5** (500 mg, 2.84 mmol, 1 eq) in anhydrous THF (10 mL) was added to the reaction mixture dropwise and the resulting mixture stirred for 30 min at -78 °C before a solution of propionaldehyde (244 μL, 3.41 mmol, 1.2 eq) in anhydrous THF (2 mL) was added. The reaction mixed at -78 °C for 2.5 hr before being quenched with sat. NH_4Cl (10 mL) and warming the reaction to room temperature. The organics were extracted with Et_2O (3 x 25 mL) and dried briefly over anhydrous $MgSO_4$ before removing the solvents *in vacuo* to give a crude yellow oil. Purification by flash-chromatography on silica (1% → 25% EtOAc / DCM) gave compound **2.10a** as a mixture of diastereomers (472 mg, d.r. 68:32, 71% yield overall). **TLC** (25% EtOAc /

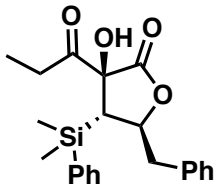
Hex) R_f = 0.16. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 - 7.18 (m, Ar*H*, 5H), 4.83 (dddd, C*H*CH_2Ph, *J* = 8.0, 6.2, 5.7, 4.1 Hz, 1H), 4.00 (dtd, C*H*OH, *J* = 7.9, 5.3, 2.4 Hz, 1H), 3.00 (dd, CH_2Ph, *J* = 14.0, 5.7 Hz, 1H), 2.94 (dd, CH_2Ph, *J* = 14.0, 6.2 Hz, 1H), 2.46 - 2.33 (m, CHCH_2CH, 2H), 2.01 - 1.91 (m, C*H*CO, 1H), 1.88 - 1.80 (m, O*H*, 1H), 1.54 - 1.34 (m, C$H_2$$CH_3$, 2H), 0.91 (t, CH_2CH_3, *J* = 7.4 Hz, 3H).



Dess-Martin periodinane (DMP) oxidation,[46] **Compound 2.11**, *(4R,5S)-5-benzyl-4-(dimethyl(phenyl)silyl)-3-propionyldihydrofuran-2(3H)-one*: To a flask containing compound **2.10** (92 mg, 0.250 mmol, 1 eq) in DCM (10 mL) was added DMP (119 mg, 0.280 mmol, 1.12 eq). The reaction was allowed to mix at room temperature. After 5 hr, no starting material was present by TLC. The reaction was quenched with sat. $Na_2S_2O_3$ (10 mL) and sat. $NaHCO_3$ (10 mL). The aqueous layer was extracted with DCM (3 x 20 mL) and the organic fraction dried over anhydrous $MgSO_4$. Removal of solvents *in vacuo* gave the product (86 mg, 93% yield) as an opaque oil without the need for further purification. **TLC** (10% EtOAc / Hex) R_f = 0.24. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.48 - 7.34 (m, Ar*H*, 5H), 7.32 - 7.17 (m, Ar*H*, 3H), 7.15 - 7.08 (m, Ar*H*, 2H), 4.54 (m, C*H*CH_2Ph, 1H), 3.50 (dd, COC*H*CO, *J* = 10.4, 1.3 Hz, 1H), 2.90 (*partially hidden* dq, C$H_2$$CH_3$, *J* = 19.0, 7.2 Hz, 1H), 2.85 (dd, CH_2Ph, *J* = 14.7, 7.3 Hz, 1H), 2.79 (dd, CH_2Ph, *J* = 14.7, 4.2 Hz, 1H), 2.45 (m, C*H*$SiMe_2$Ph, 1H), 2.23 (dq, C$H_2$$CH_3$, *J* = 19.0, 7.2 Hz, 1H), 0.98 (t, CH_2CH_3, *J* = 7.2 Hz, 3H), 0.32 (s, Si(CH_3)$_2$Ph, 3H), 0.27 (s, Si(CH_3)$_2$Ph, 3H).

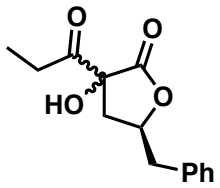


Dess-Martin periodinane (DMP) oxidation,[46] **Compound 2.11a***, (5R)-5-benzyl-3-propionyldihydrofuran-2(3H)-one*: To a flask containing compound **2.10a** (109 mg, 0.465 mmol, 1 eq) in DCM (11 mL) was added DMP (217 mg, 0.512 mmol, 1.1 eq). The reaction was allowed to mix at room temperature for 2 hr before being quenched with sat. $Na_2S_2O_3$ (7 mL) and sat. $NaHCO_3$ (7 mL). The resulting mixture was allowed to equilibrate until homogenous. The reaction was extracted with DCM (3 x 20 mL) and the organic fraction dried over anhydrous $MgSO_4$. Removal of the solvents *in vacuo* gave a yellow liquid which was purified by flash-chromatography on silica (15% → 35% EtOAc / Hex) to give a clear oil of the product as a racemic mixture (81 mg, 75% yield). **TLC** (25% EtOAc / Hex) R_f = 0.29.



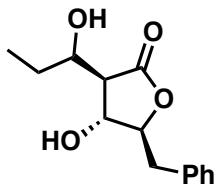
Dimethyldioxirane (DMDO) addition of tertiary alcohol,[47] **Compound 2.12**, *(3S,4S,5S)-5-benzyl-4-(dimethyl(phenyl)silyl)-3-hydroxy-3-propionyldihydrofuran-2(3H)-one*: To a flask containing substrate **2.11** (35 mg, 0.095 mmol, 1 eq) in DCM (2 mL) under Ar(g) was added a solution of $Ni(acac)_2$ (2.8 mg, 0.011 mmol, 0.12 eq) in DCM (1 mL). Next a solution of DMDO (4 mL, 0.109 mmol, 1.15 eq) was added and the reaction allowed to mix at room temperature. The reaction was monitored by TLC and quenched after 4 hr by removing all solvents *in vacuo*. The crude reaction

mixture was re-dissolved in DCM (20 mL) and washed with deionized water (3 x 10 mL). The organic fraction was dried over anhydrous $MgSO_4$. The solvent was removed again *in vacuo* to give a yellow oil. Purification by flash-chromatography on silica (10% → 25% EtOAc / Hex) gave the product **2.12** as a white solid (5 mg, 14% yield). **TLC** (25% EtOAc / Hex) R_f = 0.39. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 - 7.49 (m, Ar*H*, 2H), 7.47 - 7.36 (m, Ar*H*, 3H), 7.30 - 7.18 (m, Ar*H*, 3H), 7.08 - 7.00 (m, Ar*H*, 2H), 5.01 (ddd, C*H*CH_2Ph, *J* = 11.3, 8.2, 2.4 Hz, 1H), 3.45 (s, O*H*, 1H), 2.99 (dd, CH_2Ph, *J* = 14.9, 2.4 Hz, 1H), 2.65 (dd, CH_2Ph, *J* = 14.9, 8.2 Hz, 1H), 2.36 (qd, CH_2CH_3, *J* = 7.1, 1.5 Hz, 2H), 1.97 (d, C*H*$SiMe_2$Ph, *J* = 11.3 Hz, 1H), 0.88 (t, CH_2CH_3, *J* = 7.1 Hz, 3H), 0.48 (s, Si(CH_3)$_2$Ph, 3H), 0.44 (s, Si(CH_3)$_2$Ph, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.1, 174.7, 136.4, 136.2, 134.4, 130.0, 129.6, 128.6, 128.3, 127.1, 86.3, 83.3, 42.7, 41.6, 32.0, 7.0, -2.5 x 2.



Dimethyldioxirane (DMDO) addition of tertiary alcohol,[47] Compound 12a, *(5S)-5-benzyl-3-hydroxy-3-propionyldihydrofuran-2(3H)-one*: To a flask containing substrate **2.11a** (100 mg, 0.431 mmol, 1 eq) in acetone (4 mL) under Ar(g) was added a solution of Ni(acac)$_2$ (13.3 mg, 0.0517 mmol, 0.12 eq) in DI H_2O (2 mL). Next a solution of DMDO (7.5 mL, 0.0.495 mmol, 1.15 eq) was added and the reaction allowed to mix at room temperature. The reaction was monitored by TLC and quenched after 4 hr by removing all solvents *in vacuo*. The crude was re-dissolved in DCM (25 mL) and washed with deionized water (3 x 10 mL). The organic fraction

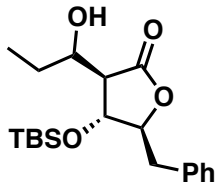
was dried over anhydrous $MgSO_4$. The solvent was removed again *in vacuo* to give **12a** as a clear oil without the need for further purification (106 mg, d.r. 77:23, 99% yield). **TLC** (25% EtOAc / Hex) R_f = 0.16. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45 - 7.14 (m, Ar*H*, 5H), 5.05 (dddd, C*H*CH_2Ph, *J* = 9.0, 5.9, 4.7, 4.6 Hz, 1H), 4.35 (s, O*H*, 1H), 3.15 (dd, C*H*$_2$Ph, *J* = 13.1, 4.7 Hz, 1H), 3.11 (dd, C*H*$_2$Ph, J = 13.1, 4.6 Hz, 1H), 2.41 - 2.20 (m, CHC*H*$_2$COH 4H), C*H*$_2$$CH_3$, 1.07 (t, CH_2C*H*$_3$, J = 7.2 Hz, 3H).



Fleming oxidation of phenyldimethylsilyl group,[10,52] **Compound 2.15**, *(3R,4R,5S)-5-benzyl-4-hydroxy-3-((S)-1-hydroxypropyl)dihydrofuran-2(3H)-one*:

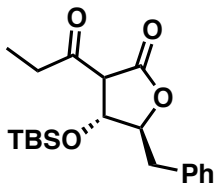
$Hg(OAc)_2$ (7.02 g, 22.0 mmol, 1.5 eq) was added to a solution of 32% wt AcOOH / AcOH (148 mL) and substrate **2.10** (5.41 g, 14.7 mmol, 1 eq). The resulting reaction mixture was stirred for 20 hr at room temperature. The reaction was quenched by the addition of 1.5 M $NaSO_3$ (100 mL) and EtOAc (100 mL). The reaction crude was filtered through a Celite pad to remove all precipitate. The reaction mixture was diluted in EtOAc (900 mL) and washed with sat. $NaHCO_3$ until basic (8 x 200 mL) and brine (200 mL). The organic fraction was dried over anhydrous Na_2SO_4 before the solvents were removed *in vacuo.* Purification by flash-column chromatography on silica gel (10% → 50% EtOAc/Hex) gave 2.36 g (64 %) of compound **2.15** as a white crystalline solid and 1.58 g (30 %) of starting compound **2.10**. **TLC** (50% EtOAc / Hex): R_f = 0.31. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 - 7.30 (m, Ar*H*, 2H), 7.30 - 7.23 (m, Ar*H*, 3H), 4.37 (ddd, C*H*CH_2Ph, *J* = 7.3, 6.9, 5.9 Hz, 1H), 4.15 (ddd, C*H*OH, *J* =

9.1, 7.3, 4.6 Hz, 1H), 3.76 (dddd, CH_3CH_2CH, *J* = 8.5, 6.1, 4.5, 4.4 Hz, 1H), 3.12 (dd, $C_6H_5CH_2$, *J* = 14.2, 6.9 Hz, 1H), 3.05 (dd, $C_6H_5CH_2$, *J* = 14.2, 5.9 Hz, 1H), 2.95 (d, O*H*, *J* = 4.4 Hz, 1H), 2.69 (dd, C*H*CO, *J* = 9.1, 6.1 Hz, 1H), 2.03 (d, O*H*, *J* = 4.6 Hz, 1H), 1.75 - 1.58 (m, CH_3CH_2, 2H), 0.99 (t, CH_3, *J* = 7.4 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.0, 135.6, 129.5, 129.07, 127.4, 83.9, 73.9, 71.7, 53.2, 38.9, 27.2, 9.9. **IR** (Diamond-ATR, $CHCl_3$) ν_{max}: 3374, 2969, 1764, 1158, 699. **MS** (ASAP): calcd for ([M+H], $C_{14}H_{19}O_4$)$^+$: 251.12, found 251.2. **$[\alpha]_D^{20}$** -16.4° (c = 0.73, $CHCl_3$).



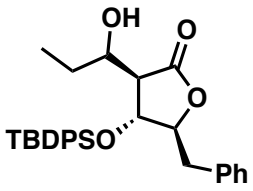
***tert*-butyldimethylsilyl (TBS) protection of an alcohol,[56] Compound 2.18**, *(3R,4R,5S)-5-benzyl-4-((tert-butyldimethylsilyl)oxy)-3-((S)-1-hydroxypropyl)dihydro-furan-2(3H)-one*: Imidazole (3.21 g, 47.1 mmol, 5 eq) was added to a solution of anhydrous DMF (24 mL) and substrate **2.15** (2.36 g, 9.43 mmol, 1 eq) at room temperature followed by addition of TBS-Cl (4.27 g, 28.3 mmol, 3 eq). The reaction was allowed to mix for 4 hr before quenching with sat. $NaHCO_3$ (25 mL) and diluted with EtOAc (25 mL). The aqueous layer was extracted with EtOAc (3 x 100 mL) then the organic fraction washed with DI water (4 x 100 mL), brine (100 mL), and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo* and the crude material purified by flash-column chromatography on silica gel (10% → 25% EtOAc/Hex) to afford 2.66 g (77 %) of compound **2.18** as a white crystalline solid. **TLC** (25% EtOAc / Hex): R_f = 0.48. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 - 7.29 (m, Ar*H*, 2H), 7.29 - 7.21 (m, Ar*H*, 3H), 4.39 (ddd, C*H*CH_2Ph, *J* = 8.2, 5.5, 4.4 Hz, 1H), 4.23 (dd, C*H*OTBS, *J* =

6.6, 5.5 Hz, 1H), 3.60 (dddd, C*H*OH, *J* = 7.5, 6.4, 5.8, 4.1 Hz, 1H), 3.11 (dd, $C_6H_5CH_2$, *J* = 14.4, 4.4 Hz, 1H), 2.92 (dd, $C_6H_5CH_2$, *J* = 14.4, 8.2 Hz, 1H), 2.61 (dd, COC*H*, *J* = 6.6, 4.1 Hz, 1H), 2.18 (d, O*H*, *J* = 6.4 Hz, 1H), 1.86 - 1.71 (m, CH_3CH_2, 2H), 0.99 (t, CH_3CH_2, *J* = 7.4 Hz, 3H), 0.88 (s, $(CH_3)_3CSi$, 9H), 0.07 (s, CH_3Si, 3H), 0.06 (s, CH_3Si, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.0, 136.4, 129.5, 128.8, 127.2, 86.1, 75.0, 71.5, 54.6, 39.0, 28.1, 25.8, 18.0, 10.4, -4.1. **MS** (ASAP): calcd for ([M+H], $C_{20}H_{33}O_4Si)^+$: 365.21, found 365.3. **IR** (Diamond-ATR, $CHCl_3$) ν_{max}: 3470, 2930, 1765, 1169, 837, 700. **$[\alpha]_D^{20}$** -22.2° (c = 1.27, $CHCl_3$).



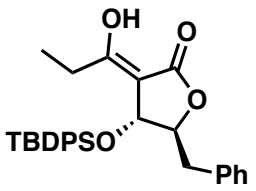
Dess-Martin periodinane (DMP) oxidation,[46] **Compound 2.19**, *(4R,5S)-5-benzyl-4-((tert-butyldimethylsilyl)oxy)-3-propionyl-dihydrofuran-2(3H)-one*: DMP (64 mg, 0.151 mmol, 1.1 eq) was added to a solution of DCM and substrate **2.18** (50 mg, 0.137 mmol, 1 eq) and allowed to mix at room temperature. After 2.5 hr, the reaction was incomplete by TLC therefore more DMP was added (29 mg, 0.5 eq). After another 1.5 hr, the reaction was complete by TLC and quenched with 4 mL each of sat. $NaHCO_3$ and sat. $Na_2S_2O_3$. The reaction was mixed at room temp until homogenous then extracted with DCM (3 x 10 mL). The organic fraction was dried over anhydrous Na_2SO_4. The solvents were removed *in vacuo* to give **2.19** as a white solid (48 mg) that was not purified due to instability on silica. **TLC** (25% EtOAc / Hex) R_f = 0.26. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 - 7.18 (m, Ar*H*, 5H), 4.73 (dd, C*H*OTBS, *J* = 5.1, 4.4 Hz, 1H), 4.45 (td, C*H*CH_2Ph, *J* = 6.9, 4.4 Hz, 1H), 3.67 (d, COC*H*CO, *J* = 5.1 Hz,

1H), 3.02 (dq, C*H*$_2$CH$_3$, *J* = 18.8, 7.2 Hz, 1H), 2.98 - 2.95 (m, C*H*$_2$Ph, 2H), 2.58 (dq, C*H*$_2$CH$_3$, *J* = 18.8, 7.2 Hz, 1H), 1.12 (t, CH$_2$C*H*$_3$, *J* = 7.2 Hz, 3H), 0.80 (s, SiC(C*H*$_3$)$_3$, 9H), -0.08 (s, SiC*H*$_3$, 3H), -0.12 (s, SiC*H*$_3$, 3H).



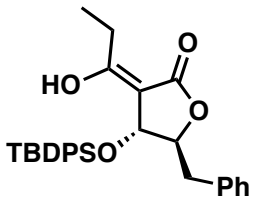
***tert*-butyldiphenylsilyl (TPS) protection of an alcohol,[56] Compound 2.20**, *(3R,4R,5S)-5-benzyl-4-((tert-butyldiphenylsilyl)oxy)-3-((S)-1-hydroxypropyl)dihydro-furan-2(3H)-one*: To a flask under Ar(g) containing substrate **2.15** (250 mg, 1.00 mmol, 1 eq) in anhydrous DMF (5 mL), was added imidazole (340 mg, 5.00 mmol, 5 eq) followed by the addition of *tert*-butyldiphenylsilyl chloride (TPSCl) (778 μL, 3.00 mmol, 3 eq) at room temperature. The reaction was allowed to mix at room temperature for 16 hr before being quenched with sat. $NaHCO_3$ (5 mL) and diluted with EtOAc (10 mL). The reaction crude was extracted with EtOAc (3 x 20 mL). The organic fraction was washed with deionized water (3 x 20 mL) and brine (3 x 20 mL) before being dried over anhydrous $MgSO_4$. Removal of solvents *in vacuo* gave a clear oil that was purified by flash-chromatography on silica (5% → 25% EtOAc / Hex) to give **2.20** as a clear oil (308 mg, 63% yield). **TLC** (25% EtOAc / Hex) R_f = 0.35. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.69 - 7.60 (m, Ar*H*, 4H), 7.54 - 7.37 (m, Ar*H*, 6H), 7.24 - 7.17 (m, Ar*H*, 3H), 6.99 - 6.92 (m, Ar*H*, 2H), 4.54 (dt, C*H*CH$_2$Ph, J = 8.4, 4.6, 4.0 Hz, 1H), 4.20 (dd, C*H*OTPS, J = 5.6, 4.6 Hz, 1H), 3.16 - 3.04 (m, C*H*OH, 1H), 2.77 (dd, C*H*$_2$Ph, J = 14.5, 4.0 Hz, 1H), 2.68 (dd, C*H*COO, J = 5.6, 4.0 Hz, 1H), 2.55 (dd,

C*H*$_2$Ph, J = 14.5, 8.4 Hz, 1H), 1.80 (d, O*H*, J = 6.0 Hz, 1H), 1.66 - 1.38 (m, C*H*$_2$CH$_3$, 2H), 1.05 (s, SiPh$_2$(C*H*$_3$)$_3$, 9H), 0.79 (t, CH$_2$C*H*$_3$, J = 7.4 Hz, 3H).

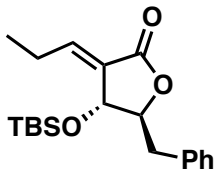


SWERN oxidation,[59] **Compound 2.21a**, *(4R,5S,Z)-5-benzyl-4-((tert-butyldiphenyl-silyl)oxy)-3-(1-hydroxypropylidene)dihydrofuran-2(3H)-one*: In a round bottom under Ar(g), added DCM (1.125 mL) and oxalyl chloride (45 μL, 0.522 mmol, 1.5 eq). The reaction flask was cooled to -78 °C then a mixture of DMSO (74 μL, 1.04 mmol, 3 eq) in DCM (225 μL) was added dropwise. The reaction was allowed to mix for 15 min at -78 °C before the addition of substrate **2.20** (170 mg, 0.348 mmol, 1 eq) in DCM (340 μL) dropwise. After 2 min of mixing at -78 °C, Et$_3$N (289 μL, 2.09 mmol, 6 eq) was added and the reaction was allowed to slowly warm from -78 °C to room temperature. Once at room temperature, the reaction mixture was quenched with DI water (5 mL) and diluted with DCM (5 mL). The reaction mixture was extracted with DCM (3 x 5 mL). The organic fraction was dried over anhydrous Na$_2$SO$_4$ before solvents were removed *in vacuo* to give an orange oil. Purification by flash-chromatography on silica (5% → 25% EtOAc / Hex) gave compounds **2.21a** and **2.21b** as a clear oil (37 mg, 60:40 d.r., 22% yield) as well as the starting compound **2.20** (42 mg, 25% recovery). **TLC** (25% EtOAc / Hex) R_f = 0.54. **^{1}H NMR** (500 MHz, CDCl$_3$) δ 7.83 - 7.66 (m, Ar*H*, 4H), 7.61 - 7.39 (m, Ar*H*, 6H), 7.19 - 7.11 (m, Ar*H*, 3H), 6.82 - 6.72 (m, Ar*H*, 2H), 4.68 (ddd, C*H*CH$_2$Ph, J = 9.9, 7.3, 2.2 Hz, 1H), 4.43 (d, C*H*OTPS, J = 7.3 Hz, 1H), 2.98 (q, C*H*$_2$CH$_3$, J = 7.1 Hz, 2H), 2.49 (dd, C*H*$_2$Ph, J = 14.7, 2.2 Hz, 1H),

2.09 (dd, CH_2Ph, J = 14.7, 9.9 Hz, 1H), 1.14 (t, CH_2CH$_3$, J = 7.1 Hz, 3H), 1.06 (s, SiPh$_2$(CH_3)$_3$, 9H).

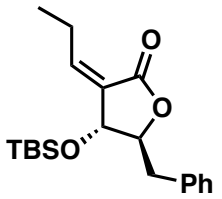


Compound 2.21b, *(4R,5S,E)-5-benzyl-4-((tert-butyldiphenylsilyl)oxy)-3-(1-hydroxy-propylidene)dihydrofuran-2(3H)-one*: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.83 - 6.93 (m, Ar*H*, 15H), 4.85 (d, C*H*OTPS, J = 7.7 Hz, 1H), 4.53 (ddd, C*H*CH$_2$Ph, J = 9.9, 7.7, 2.2 Hz, 1H), 2.87 - 2.76 (m, CH_2Ph, CH_2CH$_3$, 3H), 2.34 (dd, CH_2Ph, J = 14.8, 9.9 Hz, 1H), 1.09 (s, SiPh$_2$(CH_3)$_3$, 9H), 0.95 (t, CH$_2$CH_3, J = 7.0 Hz, 3H).

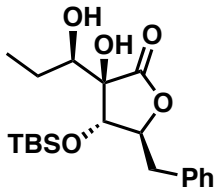


Mesylchloride (MsCl) dehydration,[56] **Compound 2.22a,** *(4R,5S,E)-5-benzyl-4-((tert-butyldimethylsilyl)oxy)-3-propylidenedihydrofuran-2(3H)-one*: A solution of anhydrous DCM (48 mL) and substrate **2.18** (1.6 g, 4.39 mmol, 1 eq) was cooled to -10 °C. Et_3N (9.13 mL, 65.8 mmol, 15 eq) was added followed by slow addition of MsCl (1.70 mL, 21.9 mmol, 5 eq). The resulting reaction mixture was stirred for 10 min at -10 °C before the reaction was warmed to room temperate over 2 hr. The reaction was quenched with sat. $NaHCO_3$ (25 mL). The aqueous phase was extracted with DCM (3 x 50 mL). The organic fraction was dried over anhydrous $MgSO_4$ and the solvents removed *in vacuo.* The crude material was purified by flash-

column chromatography on silica gel (2% → 15% EtOAc/Hex) to afford 1.48 g (97%) of products **2.22a** and **2.22b** in a 1:1 ratio. **TLC** (10% EtOAc / Hex): R_f = 0.34. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 - 7.23 (m, Ar*H*, 3H), 7.22 - 7.17 (m, Ar*H*, 2H), 6.81 (td, C*H*$^{\beta}$=CH$^{\alpha}$, *J* = 7.7, 1.5 Hz, 1H), 4.67 (m, C*H*OTBS, 1H), 4.52 (m, C*H*CH_2Ph, 1H), 2.96 (dd, $C_6H_5CH_2$, *J* = 14.0, 6.1 Hz, 1H), 2.74 (dd, $C_6H_5CH_2$, *J* = 14.0, 7.3 Hz, 1H), 2.37 - 2.14 (m, CH_3CH_2, 2H), 1.08 (t, CH_3CH_2, *J* = 7.6 Hz, 3H), 0.81 (s, $(CH_3)_3CSi$, 9H), -0.04 (s, CH_3Si, 3H), -0.11 (s, CH_3Si, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.1, 148.2, 135.4, 129.7, 128.9, 128.8, 127.3, 86.5, 69.7, 40.0, 25.7, 23.4, 17.9, 13.0, -4.2, -4.9. **MS** (ASAP): calcd for ([M+H], $(C_{20}H_{31}O_3Si)^+$: 347.20, found 347.3. **IR** (Diamond-ATR, $CHCl_3$) v_{max}: 2956, 1760, 1681, 1079, 838, 700. **$[\alpha]_D^{20}$** +74.9° (c = 1.27, $CHCl_3$).

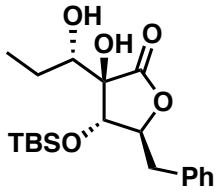


Compound 2.22b, *(4R,5S,Z)-5-benzyl-4-((tert-butyldimethylsilyl)oxy)-3-propylidene-dihydrofuran-2(3H)-one*: **TLC** (10% EtOAc / Hex): R_f = 0.24. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 - 7.28 (m, Ar*H*, 2H), 7.27 - 7.20 (m, Ar*H*, 3H), 6.28 (td, C*H*$^{\beta}$=CH$^{\alpha}$, *J* = 7.7, 1.4 Hz, 1H), 4.49 - 4.36 (m, C*H*OTBS, C*H*CH_2Ph, 2H), 2.95 (dd, $C_6H_5CH_2$, *J* = 14.2, 6.5 Hz, 1H), 2.87 (dd, $C_6H_5CH_2$, *J* = 14.2, 6.0 Hz, 1H), 2.80 - 2.61 (m, CH_3CH_2, 2H), 1.04 (t, CH_3CH_2, *J* = 7.5 Hz, 3H), 0.85 (s, $(CH_3)_3CSi$, 9H), 0.01 (s, CH_3Si, 3H), -0.03 (s, CH_3Si, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.4, 149.8, 135.9, 129.6, 128.8, 128.4, 127.2, 85.6, 73.8, 39.5, 25.8, 21.4, 18.0, 13.4, -4.1, -4.3. **MS** (ASAP): calcd for ([M+H], $(C_{20}H_{31}O_3Si)^+$: 347.20, found 347.2. **IR** (Diamond-ATR, $CHCl_3$) v_{max}: 2955, 1756, 1674, 1080, 836, 699. **$[\alpha]_D^{20}$** +28.7° (c = 3.36, $CHCl_3$).

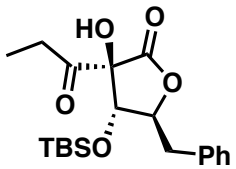


Dihydroxylation via $KMnO_4$,[60] **Compound 2.23a**, *(3R,4S,5S)-5-benzyl-4-((tert-butyldimethylsilyl)oxy)-3-hydroxy-3-((R)-1-hydroxypropyl)dihydrofuran-2(3H)-one*: A solution of anhydrous EtOH (43 mL) and a mixture of substrates **2.22a** and **2.22b** (1.48 g, 4.27 mmol, 1 eq) was cooled to -45 °C before adding an aqueous solution (26 mL) of $KMnO_4$ (658 mg, 4.16 mmol, 0.975 eq) and $MgSO_4$ (450 mg, 3.74 mmol, 0.875 eq) dropwise over 20 min. The reaction mixture was stirred at -45 °C for 40 min before adding a 40% solution of $NaHSO_3$ (8.5 mL) and allowing the reaction to warm up to room temp. The reaction was filtered through a Celite pad to remove precipitates before the solvents were removed *in vacuo*. The reaction crude was redissolved in EtOAc (200 mL) and the organic fraction washed with brine (200 mL) before being dried over anhydrous Na_2SO_4 and the solvents were removed *in vacuo*. The crude material was purified by flash-column chromatography on silica gel (15% → 30% EtOAc/Hex) to give 523 mg (32%) *syn* diol **2.23a** and 629 mg (39%) *anti* diol **2.23b**. **TLC** (25% EtOAc / Hex): R_f = 0.34. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 - 7.37 (m, Ar*H*, 2H), 7.37 - 7.30 (m, Ar*H*, 3H), 4.56 (ddd, C*H*CH_2Ph, *J* = 7.5, 6.7, 3.5 Hz, 1H), 4.22 (d, C*H*OTBS, *J* = 3.5 Hz, 1H), 3.96 (ddd, C*H*OH, *J* = 8.2, 4.7, 3.3 Hz, 1H), 3.33 (s, O*H*, 1H), 3.28 - 3.20 (m, $C_6H_5CH_2$, CHO*H*, 2H), 3.11 (dd, $C_6H_5CH_2$, *J* = 14.0, 7.5 Hz, 1H), 1.72 - 1.57 (m, CH_3CH_2, 2H), 1.10 (t, CH_3CH_2, *J* = 7.4 Hz, 3H), 0.94 (s, $(CH_3)_3$CSi, 9H), 0.07 (s, CH_3Si, 3H), 0.06 (s, CH_3Si, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 177.3, 136.2, 129.7, 128.9, 127.2, 86.5, 78.2, 78.0, 73.6, 39.2, 25.7, 22.8, 17.9, 10.5, -4.5, -4.9. **MS** (ASAP): calcd for ([M+H], $C_{20}H_{33}O_5Si)^+$: 381.20, found 381.2. **IR**

(Diamond-ATR, $CHCl_3$) ν_{max}: 3471, 2955, 1764, 1105, 839, 699. **$[\alpha]_D^{20}$** +26.7° (c = 1.09, $CHCl_3$).



Compound 2.23b, *(3R,4S,5S)-5-benzyl-4-((tert-butyldimethylsilyl)oxy)-3-hydroxy-3-((S)-1-hydroxypropyl)dihydrofuran-2(3H)-one*: **TLC** (25% EtOAc / Hex): R_f = 0.26. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 - 7.29 (m, Ar*H*, 2H), 7.29 - 7.23 (m, Ar*H*, 3H), 4.35 - 4.25 (m, C*H*CH_2Ph, C*H*OTBS, 2H), 3.81 (s, O*H*, 1H), 3.71 (ddd, C*H*OH, *J* = 11.1, 9.7, 2.3 Hz, 1H), 3.13 (dd, $C_6H_5CH_2$, *J* = 14.6, 2.3 Hz, 1H), 2.87 (dd, $C_6H_5CH_2$, *J* = 14.6, 8.4 Hz, 1H), 2.08 (d, CHO*H*, *J* = 9.7 Hz, 1H), 1.82 (ddq, CH_3CH_2 *J* = 14.8, 7.3, 2.3 Hz, 1H), 1.32 - 1.18 (m, CH_3CH_2, 1H), 1.04 (t, CH_3CH_2, *J* = 7.3 Hz, 3H), 0.94 (s, $(CH_3)_3$CSi, 9H), 0.19 (s, CH_3Si, 3H), 0.16 (s, CH_3Si, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.3, 136.2, 129.3, 128.7, 127.1, 83.3, 79.6, 78.7, 74.1, 39.6, 25.6, 24.7, 17.8, 10.3, -4.2, -5.0. **MS** (ASAP): calcd for ([M+H], $C_{20}H_{33}O_5Si)^+$: 381.20, found 381.2. **IR** (Diamond-ATR, $CHCl_3$) ν_{max}: 3453, 2954, 1777, 1107, 839, 699. **$[\alpha]_D^{20}$** -78.9° (c = 0.18, $CHCl_3$).



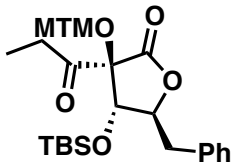
Oxidation of secondary alcohol, Compound 2.24, *(3S,4S,5S)-5-benzyl-4-((tert-butyldimethylsilyl)oxy)-3-hydroxy-3-propionyldihydrofuran-2(3H)-one*:

Dess-Martin periodinane (DMP) oxidation,[46] **Method A:** To a solution of *syn* diol **2.23a** (440 mg, 1.16 mmol, 1 eq) in DCM (45 mL) and was added DMP (981 mg, 2.31 mmol, 2 eq) at room temp and the reaction allowed to mix monitoring the reaction completion by TLC (24 hr). The reaction was quenched with sat. $Na_2S_2O_3$ (25 mL) and sat. $NaHCO_3$ (25 mL). The aqueous layer was extracted with DCM (3 x 25mL). The organic fraction was dried over anhydrous $MgSO_4$ and solvents removed *in vacuo*. The crude material was purified by flash chromatography (100% DCM) to give 348 mg (79%) of product **2.24** as a white crystallize solid.

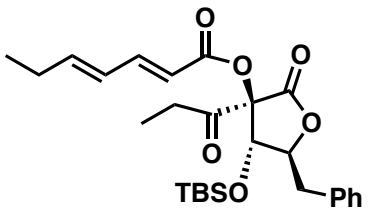
SWERN oxidation,[59] **Method B:** A solution of oxalyl chloride (648 μL, 7.55 mmol, 4.6 eq) in anhydrous DCM (16 mL) was cooled to -65 °C. A mixture of DMSO (1.07 mL, 15.1 mmol, 9.2 eq) in anhydrous DCM (3.25 mL) was added to the reaction flask slowly dropwise. After 10 min of mixing at -65 °C, the *anti* diol **2.23b** (625 mg, 1.64 mmol, 1 eq) in anhydrous DCM (6.6 mL) was added dropwise. After 5 min of mixing at -65 °C, anhydrous Et_3N (3.9 mL, 30.4 mmol, 18.5 eq) was added and the reaction allowed to mix at -65 °C for 45 min. The reaction mixture was quenched with DI water and allowed to warm to room temperature while mixing. The aqueous layer was extracted with DCM (3 x 50 mL). The organic fraction was washed with DI water (2 x 50 mL), sat NH_4Cl (2 x 50 mL), brine (2 x 50 mL) before being dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo* and the crude material purified by flash-column chromatography on silica gel (100% DCM) to afford 220 mg (54%) of **2.24** and 49 mg (10%) of MTM protected side product **2.25** and 64 mg (16%) starting diol.

TLC (25% EtOAc / Hex): R_f = 0.40. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 - 7.24 (m, Ar*H*, 5H), 4.65 (ddd, C*H*CH_2Ph, *J* = 8.7, 7.6, 3.0, 1H), 4.44 (s, O*H*, 1H), 4.28 (d, C*H*OTBS,

J = 7.6 Hz, 1H), 3.17 (dd, C*H*$_2$Ph, *J* = 14.7, 3.0 Hz, 1H), 2.94 (dd, C*H*$_2$Ph, *J* = 14.7, 8.7 Hz, 1H), 2.75 (dq, CH_3CH_2, *J* = 18.8, 7.1 Hz, 1H), 2.58 (dq, CH_3CH_2, *J* = 18.8, 7.1 Hz, 1H), 1.11 (t, C*H*$_3$CH$_2$, *J* = 7.1 Hz, 3H), 0.86 (s, (C*H*$_3$)$_3$CSi, 9H), 0.10 (s, C*H*$_3$Si, 3H), 0.06 (s, C*H*$_3$Si, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 203.2, 171.3, 135.8, 129.4, 128.7, 127.3, 85.5, 83.1, 81.2, 39.3, 32.9, 25.5, 17.7, 6.9, -4.3, -5.1. **MS** (ASAP): calcd for ([M+H], $C_{20}H_{31}O_5Si)^+$: 379.19, found 379.2. **HRMS** (ESI-TOF): calcd for ([M+Na], $C_{20}H_{30}O_5SiNa)^+$: 401.1755, found 401.1756. **IR** (Diamond-ATR, $CHCl_3$) ν_{max}: 3433, 2931, 1769, 1712, 1150, 840. **$[\alpha]_D^{20}$** -47.3° (c = 2.00, $CHCl_3$).

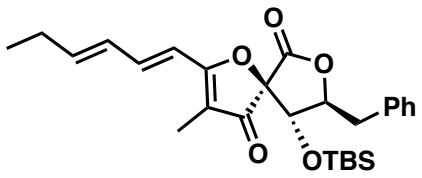


Compound 2.25, *(3S,4S,5S)-5-benzyl-4-((tert-butyldimethylsilyl)oxy)-3-((methylthio)-methoxy)-3-propionyldihydrofuran-2(3H)-one*: **TLC** (25% EtOAc / Hex) R_f = 0.53. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 - 7.20 (m, Ar*H*, 5H), 4.75 (d, OC*H*$_2$SCH$_3$, *J* = 11.1 Hz, 1H), 4.71 (d, OC*H*$_2$SCH$_3$, *J* = 11.1 Hz, 1H), 4.54 (ddd, C*H*CH$_2$Ph, *J* = 8.2, 6.5, 3.8 Hz, 1H), 4.43 (d, C*H*OTBS, *J* = 6.5 Hz, 1H), 3.15 (dd, C*H*$_2$Ph, *J* = 14.5, 3.8 Hz, 1H), 2.88 (dd, C*H*$_2$Ph, *J* = 14.5, 8.2 Hz, 1H), 2.69 (q, C*H*$_2$CH$_3$, *J* = 7.1 Hz, 2H), 2.25 (s, OCH$_2$SC*H*$_3$, 3H), 1.04 (t, CH$_2$C*H*$_3$, *J* = 7.1 Hz, 3H), 0.87 (s, SiC(C*H*$_3$)$_3$, 9H), 0.13 (s, SiC*H*$_3$, 3H), 0.09 (s, SiC*H*$_3$, 3H).



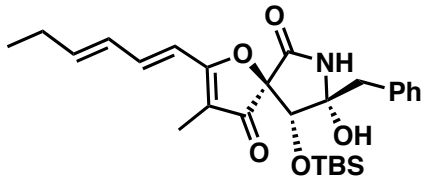
Steglich esterification coupling,[65] **Compound 2.26,** *(3S,4S,5S)-5-benzyl-4-((tert-butyldimethylsilyl)oxy)-2-oxo-3-propionyltetrahydrofuran-3-yl (2E,4E)-hepta-2,4-dien-oate:* A solution of (2*E*,4*E*)-hepta-2,4-dienoic acid (130 mg, 1.03 mmol, 1.3 eq) in anhydrous DCM (7.5 mL) was cooled to 0 °C. DMAP (155 mg, 1.27 mmol, 1.6 eq) was added followed by substrate **2.24** (300 mg, 0.793 mmol, 1eq) and then DCC (262 mg, 1.27 mmol, 1.6 eq). The reaction mixture was stirred at 0 °C for 5 min then allowed to warm up to room temperature while mixing overnight. The next day the reaction mixture was filtered through Celite to remove all solids and precipitate washed with DCM (100 mL). The organic fraction was washed with sat. NH_4Cl (2 x 50 mL), sat. $NaHCO_3$ (2 x 50 mL), and then dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo* and the crude material purified by flash-column chromatography on silica gel (5% → 15% EtOAc/Hex) to give 374 mg (97%) of **2.26** as a light yellow oil. **TLC** (25% EtOAc / Hex): R_f = 0.50. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 (dd, CH^{α}=C*H*$^{\beta}$-CH^{γ}=CH^{δ}, *J* = 15.3, 10.1 Hz, 1H), 7.35 - 7.22 (m, Ar*H*, 5H), 6.31 (dt, CH^{α}=CH^{β}-CH^{γ}=C*H*$^{\delta}$, *J* = 15.1, 5.8 Hz, 1H), 6.25 (dd, CH^{α}=CH^{β}-C*H*$^{\gamma}$=CH^{δ}, *J* = 15.1, 10.1 Hz, 1H), 5.91 (d, C*H*$^{\alpha}$=CH^{β}-CH^{γ}=CH^{δ}, *J* = 15.3 Hz, 1H), 4.88 (d, C*H*OTBS, *J* = 7.5 Hz, 1H), 4.64 (ddd, C*H*CH_2Ph, *J* = 9.8, 7.5, 2.8 Hz, 1H), 3.08 (dd, C*H*$_2$Ph, *J* = 14.7, 2.8 Hz, 1H), 3.00 (dd, C*H*$_2$Ph, *J* = 14.7, 9.8 Hz, 1H), 2.83 (dq, CH_3C*H*$_2$CO, *J* = 19.4, 7.1 Hz, 1H), 2.68 (dq, CH_3C*H*$_2$CO, *J* = 19.4, 7.1 Hz, 1H), 2.25 (qd, CH_3C*H*$_2$$CH^{\delta}$, *J* = 7.6, 5.8 Hz, 2H), 1.08 (overlapping t, C*H*$_3$$CH_2$CO, *J* = 7.1 Hz; C*H*$_3$$CH_2$CH, *J* = 7.6

Hz, 6H), 0.88 (s, $(CH_3)_3CSi$, 9H), 0.08 (s, CH_3Si x 2, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 202.0, 167.7, 165.3, 148.8, 148.5, 136.5, 129.2, 128.6, 127.1, 126.9, 116.7, 89.0, 82.7, 77.4, 39.0, 34.1, 26.2, 25.5, 17.7, 12.7, 6.6, -4.1, -4.8. **MS** (ASAP): calcd for ([M+H], $C_{27}H_{39}O_6Si)^+$: 487.24, found 487.3. **HRMS** (ESI-TOF): calcd for ([M+Na], $C_{27}H_{38}O_6SiNa)^+$: 509.2330, found 509.2329. **IR** (Diamond-ATR, $CHCl_3$) ν_{max}: 2931, 1800, 1721, 1639, 1114, 840. **$[\alpha]_D^{20}$** -50.5° (c = 1.36, $CHCl_3$).



Intramolecular aldol condensation, Compound 2.28, *(5S,8S,9S)-8-benzyl-9-((tert-butyldimethylsilyl)oxy)-2-((1E,3E)-hexa-1,3-dien-1-yl)-3-methyl-1,7-dioxaspiro[4.4]-non-2-ene-4,6-dione:* To a round bottom flask under Ar(g) containing anhydrous THF (50 mL) and 1 M NaHMDS (391 μL, 1.05 eq), a solution of the substrate **2.26** (181 mg, 0.372 mmol, 1 eq) in anhydrous THF (6 mL) was added slowly, dropwise via cannula. The reaction was allowed to mix at room temperature for 2 hr before quenching by the addition of sat. NH_4Cl (10 mL). The reaction was concentrated *in vacuo* and the crude material diluted with DCM (30 mL) and sat. NH_4Cl (30 mL). The aqueous layer was extracted with additional DCM (30 mL). Triethylamine (2 mL) was added to the organic fraction and allowed to mix overnight (16 hr) to afford dehydrated intermediate **2.27**. The reaction mixture was washed with sat. NH_4Cl (2 x 50 mL) and sat. $NaHCO_3$ (2 x 50 mL) before being dried over anhydrous $MgSO_4$ and the solvents removed *in vacuo* to give 158 mg (91% yield) of the crude product **2.28** as a yellow oil without the need for further purification. **TLC** (25% EtOAc / Hex): R_f = 0.43; (10%

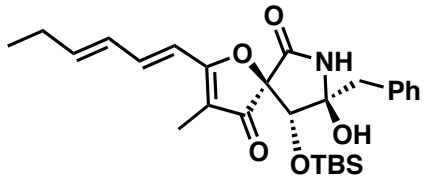
EtOAc / Hex): R_f = 0.24. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 - 7.25 (m, Ar*H*, 5H), 7.16 (ddd, CH^{γ}=C*H*$^{\delta}$-CH^{ε}=CH^{ζ}, *J* = 15.3, 8.8, 1.5 Hz, 1H), 6.32 - 6.21 (m, C*H*$^{\gamma}$=CH^{δ}-C*H*$^{\varepsilon}$=C*H*$^{\zeta}$, 3H), 5.18 (td, C*H*CH_2Ph, *J* = 8.4, 2.8 Hz, 1H), 4.47 (d, C*H*OTBS, *J* = 8.6 Hz, 1H), 3.23 (dd, C*H*$_2$Ph, *J* = 14.9, 2.8 Hz, 1H), 2.86 (dd, C*H*$_2$Ph, *J* = 14.9, 8.2 Hz, 1H), 2.24 (qd, CH_3C*H*$_2$CH$^{\zeta}$, *J* = 7.4, 4.9 Hz, 2H), 1.72 (s, C*H*$_3$, 3H), 1.08 (t, C*H*$_3$$CH_2CH^{\zeta}$, *J* = 7.4 Hz, 3H), 0.82 (s, (C*H*$_3$)$_3$CSi, 9H), 0.10 (s, C*H*$_3$Si, 3H), -0.07 (s, C*H*$_3$Si, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 194.2, 179.5, 166.6, 146.9, 140.0, 135.6, 129.6, 128.6, 128.5, 127.1, 114.8, 110.7, 89.9, 80.0, 76.9, 37.8, 26.2, 25.4, 17.7, 12.8, 5.5, -4.7, -4.8. **MS** (ASAP): calcd for ([M+H], $C_{27}H_{37}O_5Si)^+$: 469.23, found 469.3. **HRMS** (ESI-TOF): calcd for ([M+Na], $C_{27}H_{36}O_5SiNa)^+$: 491.2224, found 491.2225. **IR** (Diamond-ATR, $CHCl_3$) v_{max}: 2957, 1799, 1699, 1621, 1170, 840, 699. **$[\alpha]_D^{20}$** -145.3° (c = 0.46, $CHCl_3$).



Ammonolysis reaction followed by Dess-Martin periodinane oxidation and cyclization,[5] **Compound 2.31a**, *(5S,8R,9R)-8-benzyl-9-((tert-butyldimethylsilyl)oxy)-2-((1E,3E)-hexa-1,3-dien-1-yl)-8-hydroxy-3-methyl-1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione:* A round bottom flask containing substrate **2.28** (189 mg, 0.403 mmol, 1 eq) was cooled to 0 °C and a solution of 2M ammonia in isopropanol (22.2 mL, 110 eq) was added. The reaction mixture was stirred at 0 °C for 8 hr. The reaction was stopped by the removal of all solvents *in vacuo.* (NOTE: Due to the high boiling point of isopropanol, hexanes were added to the reaction to create an azeotrope which

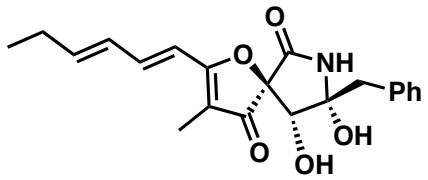
effectively removed the isopropanol.) Removal of the solvents gave the crude amide **2.29** as a yellow solid. The solid (0.403 mmol assumed) was dissolved in the same flask with anhydrous DCM (19 mL) and Dess-Martin periodinane (342 mg, 0.806 mmol, 2 eq) was added. The new reaction mixture was stirred for 30 min at room temperature. The reaction was quenched with sat. sodium thiosulfate (15 mL) and sat. Na_2CO_3 (15 mL) then diluted with EtOAc (25 mL) and allowed to mix until all solids were dissolved. The reaction mixture was transferred to a separatory funnel with additional sat. Na_2CO_3 (25 mL). The aqueous phase was extracted with EtOAc (3 x 50 mL). The organic fraction containing oxidized **2.30** was then mixed with sat. Na_2CO_3 (150 mL) at room temperature on max speed in an Erlenmeyer flask for 5 hr before the aqueous layer was removed and the organic fraction dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo* and the crude purified by flash-column chromatography on silica (20% → 40% EtOAc / Hex) to afford 130 mg (70% yield) of both isomers of protected azaspirene **2.31a** and **2.31b** with a 12% recovery of starting compound **2.28**. **TLC** (25% EtOAc / Hex): R_f = 0.23. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 - 7.27 (m, Ar*H*, CH^{γ}=C*H*$^{\delta}$-CH^{ε}=CH^{ζ}, 6H), 6.37 - 6.21 (m, N*H*, C*H*$^{\gamma}$=CH^{δ}-C*H*$^{\varepsilon}$=C*H*$^{\zeta}$, 4H), 6.08 (d, O*H*, *J* = 1.8 Hz, 1H), 4.51 (s, C*H*OTBS, 1H), 3.32 (d, C*H*$_2$Ph, *J* = 13.5 Hz, 1H), 2.77 (dd, C*H*$_2$Ph, *J* = 13.5, 1.8 Hz, 1H), 2.30 - 2.19 (m, C*H*$_2$$CH_3$, 2H), 1.74 (s, CC*H*$_3$, 3H), 1.08 (t, CH_2C*H*$_3$, *J* = 7.4 Hz, 3H), 0.86 (s, SiC(C*H*$_3$)$_3$, 9H), 0.16 (s, SiC*H*$_3$, 3H), -0.04 (s, SiC*H*$_3$, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 198.1, 181.6, 164.9, 147.5, 141.0, 134.6, 130.4, 128.7, 128.5, 127.5, 114.8, 111.1, 93.1, 84.8, 76.3, 44.1, 26.3, 25.4, 17.9, 12.8, 5.6, -4.6, -4.8. **MS** (ASAP): calcd for ([M+H-H_2O], $C_{27}H_{36}NO_4Si)^+$: 466.2, found 466.3. **HRMS** (ESI-TOF): calcd for ([M+Na], $C_{27}H_{37}NO_5SiNa)^+$: 506.2333, found 506.2333. **IR** (Diamond-ATR, $CHCl_3$) ν_{max}: 3277, 2929, 1731, 1677,

1611, 1412, 1172, 849. **$[\alpha]_D^{20}$** -253.3° (c = 2.09, $CHCl_3$). *Lit.* **$[\alpha]_D^{24}$** -217.2° (c = 1.02, $CHCl_3$).[6]



Compound 2.31b, *(5S,8S,9R)-8-benzyl-9-((tert-butyldimethylsilyl)oxy)-2-((1E,3E)-hexa-1,3-dien-1-yl)-8-hydroxy-3-methyl-1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione*:

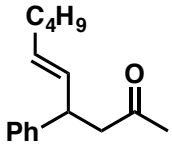
TLC (25% EtOAc / Hex): R_f = 0.13. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 - 7.27 (m, Ar*H*, 5H), 7.19 (dd, CH^{γ}=C*H*$^{\delta}$-CH^{ε}=CH^{ζ}, *J* = 15.3, 10.1 Hz, 1H), 6.32 (d, C*H*$^{\gamma}$=CH^{δ}-CH^{ε}=CH^{ζ}, *J* = 15.3 Hz, 1H), 6.28 - 6.12 (m, CH^{γ}=CH^{δ}-C*H*$^{\varepsilon}$=C*H*$^{\zeta}$, 2H), 5.92 (s, N*H*, 1H), 4.69 (s, C*H*OTBS, 1H), 3.95 (d, CH_2Ph, *J* = 14.0 Hz, 1H), 3.02 (d, CH_2Ph, *J* = 14.0 Hz, 1H), 2.80 (s, O*H*, 1H), 2.28 - 2.17 (m, C$H_2$$CH_3$, 2H), 1.75 (s, CC$H_3$, 3H), 1.07 (t, CH_2CH_3, *J* = 7.5 Hz, 3H), 0.85 (d, SiC(CH_3)$_3$, *J* = 1.6 Hz, 9H), 0.15 (s, SiCH_3, 3H), -0.00 (s, SiCH_3, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 196.3, 179.4, 164.8, 146.3, 139.6, 134.7, 130.7, 129.0, 128.5, 127.5, 115.1, 111.0, 91.7, 86.9, 82.1, 42.1, 26.2, 25.4, 17.9, 12.9, 5.6, -4.8, -5.2. **MS** (ASAP): calcd for ([M+H-H_2O], $C_{27}H_{36}NO_4Si$)$^+$: 466.2, found 466.3. **IR** (Diamond-ATR, $CHCl_3$) ν_{max}: 3350, 2929, 1721, 1698, 1622, 1406, 1170, 840. **$[\alpha]_D^{20}$** -9.6° (c = 1.55, $CHCl_3$).



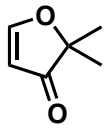
Deprotection of TBS ether,[69] **Azaspirene,** *(5S,8R,9R)-8-benzyl-2-((1E,3E)-hexa-1,3-dien-1-yl)-8,9-dihydroxy-3-methyl-1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione:* A mixture of protected azaspirene isomers (**2.31a** and **2.31b**) (20 mg) was dissolved at a concentration of 10 mg / mL in trifluoroacetic acid in a vial then diluted with DI water at a ratio of 9:1. The vial was tightly capped and the reaction was allowed to mix at room temperature for 48 hr or heated to 40 °C for 6 hr. The reaction was cooled in an ice bath before being diluted with DCM (2 mL) and quenched with sat. $NaHCO_3$ (2 mL). The reaction was transferred to a separatory funnel with DCM (25 mL) and sat. $NaHCO_3$ until neutral (~40 mL). The aqueous phase was extracted with DCM (2 x 25 mL). The organic fraction was dried over anhydrous Na_2SO_4 before the solvents were removed *in vacuo* to give crude azaspirene. Purification by flash-column chromatography on silica (30% → 60% EtOAc / Hex) gave 4 mg (33%) of azaspirene as a yellow solid. **TLC** (50% EtOAc / Hex) R_f = 0.50. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 - 7.24 (m, Ar*H*, CH^{γ}=C*H*$^{\delta}$-CH^{ε}=CH^{ζ}, 6H), 6.40 (bs, N*H*, 1H), 6.31 (d, C*H*$^{\gamma}$=CH^{δ}-CH^{ε}=CH^{ζ}, *J* = 15.3 Hz, 1H), 6.30 - 6.22 (m, CH^{γ}=CH^{δ}-C*H*$^{\varepsilon}$=C*H*$^{\zeta}$, 2H), 6.00 (d, CO*H*, *J* = 1.0 Hz, 1H), 4.50 (d, C*H*OH, *J* = 10.1 Hz, 1H), 3.27 (d, C*H*$_2$Ph, *J* = 13.9 Hz, 1H), 2.95 (dd, C*H*$_2$Ph, *J* = 13.9, 1.1 Hz, 1H), 2.92 (d, CHO*H*, *J* = 10.1 Hz, 1H), 2.24 (qd, C*H*$_2$$CH_3$, *J* = 7.4, 4.7 Hz, 2H), 1.76 (s, CC*H*$_3$, 3H), 1.07 (t, CH_2C*H*$_3$, *J* = 7.4 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 198.4, 183.3, 164.9, 148.3, 142.1, 134.2, 130.4, 128.8, 128.4, 127.7, 114.6, 110.6, 93.2, 84.5, 74.8, 42.9, 26.3, 12.8, 5.6. **HRMS** (ESI-TOF): calcd for ([M+Na], $C_{21}H_{23}NO_5Na)^+$: 392.1468, found 392.1472. **IR** (Diamond-ATR,

$CHCl_3$) ν_{max}: 3280, 2963, 1726, 1680, 1606, 1413, 1133, 700. **$[\alpha]_D^{20}$** -118° (c = 0.072, MeOH). *Lit.* **$[\alpha]_D^{25}$** -204.4° (c = 0.158, MeOH).[3]

7.5 Experimental Procedures and Compound Characterization for Part II: Alkenylzincate and Disilylzinc Conjugate Additions Catalyzed by Copper(I) Iodide Dimethyl Sulfide Complex

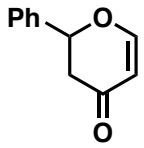


Compound 6.1, *(E)-4-phenyldec-5-en-2-one*: See general procedure for alkenylzincate additions. The crude compound was purified by flash-column chromatography on silica (2% → 10% EtOAc / Hex). **TLC** (10% EtOAc / Hex) R_f = 0.39. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.33 - 7.11 (m, Ar*H*, 5H), 5.52 (ddt, CH^{γ}=CH$^{\delta}$, *J* = 15.3, 7.4, 1.3 Hz, 1H), 5.38 (dtd, CH$^{\gamma}$=CH^{δ}, *J* = 15.3, 6.6, 1.0 Hz, 1H), 3.76 (dt, C*H*Ph, J = 7.4, 7.4 Hz, 1H), 2.82 (d, CH_2CO, *J* = 7.4 Hz, 2H), 2.03 (s, COCH_3, 3H), 1.98 - 1.89 (m, CH$^{\gamma}$=CH$^{\delta}$CH_2, 2H), 1.32 - 1.16 (m, CH_2CH_2CH$_3$, 4H), 0.83 (t, $CH_2CH_2CH_3$, *J* = 7.1 Hz, 3H).



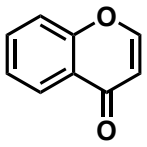
Compound 6.2[8], *2,2-dimethylfuran-3(2H)-one*: A suspension of 60% NaH in mineral oil (2.09g, 52.4 mmol, 1.78 eq) in anhydrous Et_2O (125mL) was cooled at 0 °C. 2-

hydroxy-methyl butanone (3.09 mL, 29.4 mmol, 1 eq) was added dropwise to the reaction followed by dropwise addition of ethyl formate (2.38 mL, 29.5 mmol, 1 eq). The reaction mixture was stirred overnight allowing the reaction to slowly warm from 0 °C to room temperature. The precipitate that formed was filtered off using a Schlank filter and washed with anhydrous Et_2O (2 x 20 mL) before being dissolved in 2% aqueous HCl. The aqueous solution was extracted with DCM (3 x 150 mL). The organic fraction was dried over anhydrous $MgSO_4$. Removal of the solvents *in vacuo* produced a light yellow liquid in a 3:1 ratio of hydrated-to-dehydrated products. The crude was loaded onto a silica plug (4 x 6 cm) and allowed to sit for 2 hr to dehydrate. Extracting with DCM gave 1.23 g (37% yield) of the unsaturated product as a clear liquid. **TLC** (50% EtOAc/Hex) R_f = 0.4. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.15 (d, CH^{α}=C*H*$^{\beta}$, *J* = 2.5 Hz, 1H), 5.61 (d, C*H*$^{\alpha}$=CH^{β}, *J* = 2.5 Hz, 1H), 1.39 (s, 2 x CH_3, 6H).



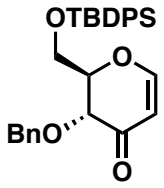
Compound 6.3[76], *2-phenyl-2,3-dihydro-4H-pyran-4-one*: A mixture of LiOMe (13.5 mg, 0.356 mmol, 0.11 eq) in anhydrous DMF (4 mL) was cooled to 0 °C. The substrate **6.16** (789 mg, 4.58 mmol, 1.46 eq) was added to the reaction flask followed by benzaldehyde (320 μL, 3.14 mmol, 1 eq). The reaction was diluted with another 4 mL of anhydrous DMF before mixing overnight and allowing the reaction to slowly warm from 0 °C slowly up to room temperature overnight. The reaction was quenched with sat. NH_4Cl (40 mL) and diluted with EtOAc (25 mL). The aqueous phase was extracted with additional EtOAc (3 x 25 mL). The organic fraction was

washed with DI water (25 mL) and brine (25 mL) before being dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo* then the crude washed with toluene (10 mL) which was also removed *in vacuo*. The crude was dissolved in anhydrous Et_2O (40 mL) and cooled to 0 °C. Trifluoroacetic acid (2.5 mL, 32.65 mmol, 10.4 eq) was added to the reaction and the reaction allowed to stir at 0 °C for 1 hr. The reaction mixture was quenched with sat. $NaHCO_3$ (25 mL). The aqueous phase was extracted with additional Et_2O (3 x 25 mL) and the organic fraction dried over anhydrous $MgSO_4$. Removal of solvents *in vacuo* followed by purification by flash-column chromatography on silica (15% → 35 % EtOAc in hexanes) gave 334 mg (61%) of **6.3** as a yellow liquid. **TLC** (25% EtOAc/Hex) R_f = 0.27. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 (dd, CH^{α}=C*H*$^{\beta}$, *J* = 6.0, 0.7 Hz, 1H), 7.46 - 7.35 (m, Ar*H*, 5H), 5.53 (dd, C*H*$^{\alpha}$=CH$^{\beta}$, *J* = 6.0, 1.3 Hz, 1H), 5.44 (dd, C*H*Ph, *J* = 14.4, 3.5 Hz, 1H), 2.92 (dd, C*H*$_2$CHPh, *J* = 16.9, 14.4 Hz, 1H), 2.67 (ddd, C*H*$_2$CHPh, *J* = 16.9, 3.5, 1.3 Hz, 1H).



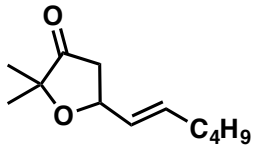
Compound 6.4[77,78], *4H-chromen-4-one*: In a round-bottom flask solid sodium (2.42 g, 105 mmol, 2.18 eq) was added followed by enough xylenes to fully submerge the sodium. The suspension was heated in an oil bath until the sodium melted (>110 °C). The heated Na / xylenes suspension was mixed on high to disperse sodium into a "powder" and cooled by quick removal of bath and continued mixing. (NOTE: This method did not work ideally but achieved some dispersion). The xylenes were removed via syringe and the dispersed sodium was washed with anhydrous Et_2O (20

mL). The Et_2O was also removed from the reaction flask via syringe. The flask containing the neat dispersion of sodium metal was cooled to 0 °C. The 2-hydroxyacetophenone (5.8 mL, 48.18 mmol, 1 eq) and ethyl formate (10.6 mL, 131.8 mmol, 2.74 eq) were premixed as a solution then added in 5 mL increments to the sodium metal keeping the reaction temperature cool. Anhydrous Et_2O (10 mL) was added post addition of the substrates and the reaction allowed to reflux until all the sodium had reacted. The reaction was quenched by cooling the reaction flask to 0 °C and slowly adding DI water (10 mL). The aqueous phase was extracted with Et_2O (3 x 25 mL). The aqueous phase was then acidified with glacial acetic acid and extracted with DCM (3 x 25 mL). The DCM fraction was dried over anhydrous $MgSO_4$ and solvents removed *in vacuo.* The crude material resulting from the DCM fraction was purified by flash column chromatography on silica (10% → 25% EtOAc in hexanes) to give 2.79 g (40%) product **6.4** as a white solid. **TLC** (25% EtOAc/Hex) R_f = 0.22. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.22 (ddd, Ar*H*, *J* = 8.1, 1.7, 0.6 Hz, 1H), 7.85 (dd, CH^{α}=C*H*$^{\beta}$, *J* = 6.1, 0.7 Hz, 1H), 7.67 (ddd, Ar*H*, *J* = 8.5, 7.1, 1.7 Hz, 1H), 7.46 (dt, Ar*H*, *J* = 8.5, 1.1, 0.6 Hz, 1H), 7.41 (ddd, Ar*H*, *J* = 8.1, 7.1, 1.1 Hz, 1H), 6.34 (dd, C*H*$^{\alpha}$=CH$^{\beta}$, *J* = 6.1, 0.7 Hz, 1H).

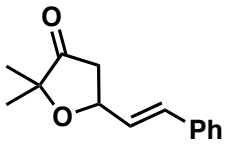


Pyridinium dichromate oxidation. Compound 6.5, *(2R,3R)-3-(benzyloxy)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-2,3-dihydro-4H-pyran-4-one*: A solution of substrate **6.32** (994 mg, 2.09 mmol, 1 eq) in EtOAc (2 mL) was fitted with a drying tube.

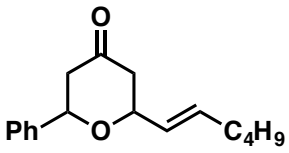
Pyridinium dichromate (PDC; 955 mg, 2.54 mmol, 1.21 eq) was added to the reaction followed by acetic acid (350 μL). The reaction was mixed at room temperature overnight. The crude mixture was filtered through a Celite pad to remove solid impurities and the solvents removed *in vacuo*. Purification through a silica plug with 10% EtOAc in hexanes gave 753 mg (76%) of compound **6.5** as a clear oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.69 - 7.62 (m, Ar*H*, 4H), 7.47 - 7.27 (m, Ar*H* (11H), CH^{α}=C*H*$^{\beta}$ (1H), 12H), 5.38 (dd, C*H*$^{\alpha}$=CH$^{\beta}$, J = 5.9 Hz, 1H), 5.14 (d, CH_2Ph, J = 10.9 Hz, 1H), 4.64 (d, CH_2Ph, J = 10.9 Hz, 1H), 4.38 - 4.36 (m, CH_2OTPS (1H), C*H*OBn (1H), 2H), 4.04 - 3.96 (m, CH_2OTPS (1H), C*H*CH_2OTPS (1H), 2H), 1.06 (s, SiC(CH_3)$_3$, 9H).



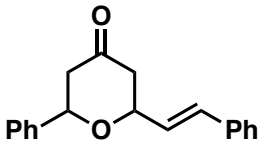
Compound 6.6, *(E)-5-(hex-1-en-1-yl)-2,2-dimethyldihydrofuran-3(2H)-one*: See general procedure for alkenylzincate additions. The crude was purified by flash column chromatography on silica (2% → 10% EtOAc/Hex). **TLC** (25% EtOAc / Hex) R_f = 0.60. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.83 (dtd, CH^{γ}=C*H*$^{\delta}$, *J* = 15.3, 6.8, 0.9 Hz, 1H), 5.54 (ddt, C*H*$^{\gamma}$=CH$^{\delta}$, *J* = 15.3, 7.4, 1.7 Hz, 1H), 4.58 (ddd, OC*H*, *J* = 10.0, 7.4, 5.9 Hz, 1H), 2.61 (ddd, COCH_2, *J* = 18.1, 5.9, 1.7 Hz, 1H), 2.36 (ddd, COCH_2, *J* = 18.1, 10.0, 1.7 Hz, 1H), 2.14 - 2.03 (m, CH^{γ}=CH^{δ}CH_2, 2H), 1.46 - 1.29 (m, CH_2C$H_2$$CH_3$, 4H), 1.30 (s, CCH_3, 3H), 1.23 (s, CCH_3, 3H), 0.90 (t, CH_2C$H_2$$CH_3$, J = 6.7 Hz, 3H).



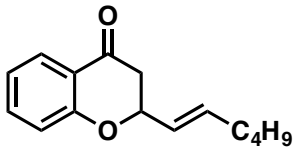
Compound 6.7, *(E)-2,2-dimethyl-5-styryldihydrofuran-3(2H)-one*: See general procedure for alkenylzincate additions. The crude was purified by flash column chromatography on silica (2% → 10% EtOAc/Hex). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 - 7.22 (m, Ar*H*, 5H), 6.72 (d, CH^{γ}=C*H*$^{\delta}$, *J* = 15.8 Hz, 1H), 6.28 (dd, C*H*$^{\gamma}$=CH^{δ}, *J* = 15.8, 7.0 Hz, 1H), 4.82 (dddd, OC*H*, *J* = 10.0, 7.0, 6.0, 1.1 Hz, 1H), 2.73 (dd, $COCH_2$, *J* = 18.1, 6.0 Hz, 1H), 2.48 (dd, $COCH_2$, *J* = 18.1, 10.0 Hz, 1H), 1.35 (s, CCH_3, 3H), 1.28 (s, CCH_3, 4H).



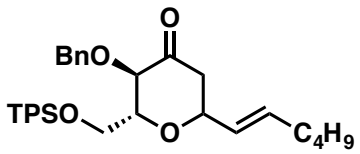
Compound 6.8, *(E)-2-(hex-1-en-1-yl)-6-phenyltetrahydro-4H-pyran-4-one*: See general procedure for alkenylzincate additions. The crude was purified by flash column chromatography on silica (2% → 10% EtOAc/Hex). **TLC** (10% EtOAc / Hex) R_f = 0.25. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 - 7.21 (m, Ar*H*, 5H), 5.52 - 5.20 (m, C*H*$^{\gamma}$=C*H*$^{\delta}$, 2H), 5.19 - 5.08 (m, C*H*Ph, 1H), 3.33 - 3.26 (m, OC*H*CH^{γ}=CH^{δ}, 1H), 3.18 - 3.08 (m, C*H*$_2$CHPh, 1H), 2.92 - 2.79 (m, C*H*$_2$CHPh, C*H*$_2$CHO, 2H), 2.47 - 2.25 (m, C*H*$_2$CHO, 1H), 2.04 - 1.92 (m, CH^{γ}=CH^{δ}C*H*$_2$, 2H), 1.47 - 1.11 (m, C*H*$_2$C*H*$_2$$CH_3$, 4H), 0.96 - 0.79 (m, CH_2CH_2C*H*$_3$, 3H).



Compound 6.9, *(E)-2-phenyl-6-styryltetrahydro-4H-pyran-4-one*: See general procedure for alkenylzincate additions. The crude was purified by flash column chromatography on silica (15% → 30% EtOAc/Hex). **TLC** (25% EtOAc / Hex) R_f = 0.32. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 - 7.11 (m, Ar*H*, 10H), 6.39 (dd, CH^{γ}=C*H*$^{\delta}$, *J* = 15.9, 4.2 Hz, 1H), 5.97 (ddd, C*H*$^{\gamma}$=CH^{δ}, *J* = 15.9, 8.7, 1.2 Hz, 1H), 5.13 (tdd, OC*H*CH^{γ}=CH^{δ}, *J* = 8.7, 4.2, 3.4 Hz, 1H), 3.26 (dd, CH_2CHPh, *J* = 10.9, 3.1 Hz, 1H), 3.14 (dd, C*H*Ph, *J* = 6.9, 3.1 Hz, 1H), 2.85 - 2.78 (m, CH_2CHPh, CH_2CHO, 2H), 2.57 - 2.50 (m, CH_2CHO, 1H).

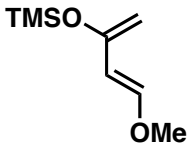


Compound 6.10, *(E)-2-(hex-1-en-1-yl)chroman-4-one*: See general procedure for alkenylzincate additions. The crude was purified by flash column chromatography on silica (2% → 10% EtOAc/Hex). **TLC** (10% EtOAc / Hex) R_f = 0.36. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 (ddd, Ar*H*, *J* = 7.7, 1.8, 0.8 Hz, 1H), 7.47 (ddd, Ar*H*, *J* = 8.0, 7.4, 1.8 Hz, 1H), 7.05 - 6.96 (m, Ar*H*, 2H), 5.89 (dtd, CH^{γ}=C*H*$^{\delta}$, *J* = 15.4, 6.7, 1.0 Hz, 1H), 5.68 (ddt, C*H*$^{\gamma}$=CH^{δ}, *J* = 15.4, 6.7, 1.5 Hz, 1H), 4.91 (dddd, OC*H*CH^{γ}=CH^{δ}, *J* = 11.3, 6.6, 3.9, 1.0 Hz, 1H), 2.82 (dd, CH_2CHO, *J* = 16.8, 11.3 Hz, 1H), 2.74 (dd, CH_2CHO, *J* = 16.8, 3.9 Hz, 1H), 2.15 - 2.05 (m, CH^{γ}=CH^{δ}CH_2, 2H), 1.47 - 1.18 (m, CH_2C$H_2$$CH_3$, 4H), 0.91 (t, $CH_2CH_2CH_3$, *J* = 7.2 Hz, 3H).



Compound 6.11, *(2R,3R)-3-(benzyloxy)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-6-((E)-hex-1-en-1-yl)tetrahydro-4H-pyran-4-one*: See general procedure for alkenylzincate additions. The crude was purified by flash column chromatography on silica (10% → 25% EtOAc/Hex). **TLC** (20% Et_2O / pentane) R_f = 0.36. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 - 7.56 (m, Ar*H*, 5H), 7.51 - 7.11 (m, Ar*H*, 10H), 5.54 - 5.10 (m, CH^{γ}=CH^{δ}, 2H), 4.58 - 4.48 (m, CH_2Ph, 1H), 4.45 - 4.31 (m, CH_2Ph, 1H), 4.03 - 3.85 (m, C*H*OBn, OC*H*CH$^{\gamma}$=CH$^{\delta}$, 2H), 3.83 - 3.76 (m, CH_2OTPS, 2H), 3.45 - 3.17 (m, C*H*CH_2OTPS, 1H), 2.63 - 2.40 (m, CH_2CHCH$^{\gamma}$=CH$^{\delta}$, 2H), 2.03 - 1.80 (m, CH$^{\gamma}$=CH$^{\delta}$CH_2, 2H), 1.45 - 1.13 (m, CH_2C$H_2$$CH_3$, 4H), 1.06 (s, SiC(C$H_3$)$_3$, 9H), 0.95 - 0.75 (m, CH_2CH_2CH_3, 3H).

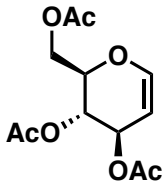
Compounds 6.12 – 6.15 were not synthesized or not isolated



Enolate trapping with TMS-Cl,[75] **Compound 6.16**, *(E)-((4-methoxybuta-1,3-dien-2-yl)oxy)trimethyl-silane, Danishefski's diene*: A solution of $ZnCl_2$ (0.5 M, 300 μL, 0.150 mmol, 0.03 eq) was added to Et_3N (1.5 mL) at room temperature to a round bottom flask under Ar(g). Benzene (2 mL) was added followed by methoxy butanone (510 μL, 5.00 mmol, 1 eq). Chlorotrimethyl silane (TMS-Cl) (1.27 mL, 10.00 mmol, 2 eq) was added last and the reaction mixture was heated to 40 °C and mixed for 16 hr. The

reaction was quenched by cooling the reaction flask to room temperature diluting the reaction with Et_2O (25 mL). The crude mixture was filtered through a Celite pad which was washed with more Et_2O (200 mL). The organic fraction was washed with sat. $NaHCO_3$ (3 x 25 mL) and dried over anhydrous Na_2SO_4. Removal of solvent *in vacuo* gave 789 mg (92%) of crude Danishefski's diene 6.16 that was used without further purification for the formation of compound **6.3**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.82 (d, CH=C*H*-OMe, J = 12.3 Hz, 1H), 5.36 (d, C*H*=CH-OMe, J = 12.3 Hz, 1H), 4.09 (d, CH_2=C, J = 16.3 Hz, 2H), 3.59 (s, OCH_3, 3H), 0.23 (s, Si(CH_3)$_3$, 9H).

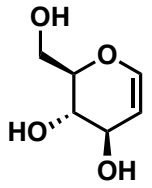
Compound 6.17 – 6.19 were not synthesized or not isolated



Bromination and reduction via Zn/$CuSO_4$,[79] **Compound 6.20**, *(2R,3S,4R)-2-(acetoxymethyl)-3,4-dihydro-2H-pyran-3,4-diyl diacetate*: **Solution A Prep**: A suspension of D-glucose pentaacetate (12.1 g, 31 mmol, 1 eq) and acetic anhydride (6 mL, 63.6 mmol, 2.05 eq) in glacial acetic acid (7.5 mL, 131 mmol, 4.23 eq) was cooled to 0 °C. A 33% solution of HBr in acetic acid (25 mL, 139 mmol, 4.5 eq) was added dropwise to the reaction using an addition funnel. The reaction was allowed to mix 0 °C slowly warming up to room temperature over 2 hr before using in the next step.

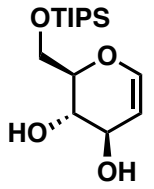
Reaction: A solution of sodium acetate (30.22 g, 368 mmol, 12 eq) in a 50:50 mixture of glacial acetic acid and DI water (80 mL) was cooled to -10 °C. Zinc

powder (21.4 g, 327 mmol, 10.6 eq) was added to the reaction followed by a solution of $CuSO_4 \cdot 5H_2O$ (2.1 g, 8.4 mmol, 0.27 eq) in DI water (10 mL). **Solution A** was then added to the reaction mixture dropwise through an addition funnel maintaining the reaction temperature at -10 °C. The reaction was allowed to mix for 2 hr and slowly warm up to 10 °C. The reaction was filtered through a Celite pad which was washed with cold 50% HOAc in DI water. The filtrate was diluted with crushed ice (200 g) and chloroform (200 mL) and allowed to mix until all ice melted. The aqueous phase was extracted with chloroform (2 x 100 mL). The organic fraction was washed with sat. $NaHCO_3$ (2 x 100 mL) and DI water (2 x 100 mL) then dried over anhydrous $MgSO_4$. The crude organic fraction was filtered again through Celite before solvents were removed *in vacuo*. Purification on silica column (25% EtOAc in hexanes) gave 5.34 g (64%) of product **6.20** as a clear, crystalline solid. **TLC** (25% EtOAc/Hex) R_f = 0.20. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.47 (dd, OC*H*=CH, J = 6.1, 1.4 Hz, 1H), 5.35 (ddd, OCH=CHC*H*OAc, J = 5.6, 3.3, 1.4 Hz, 1H), 5.23 (dd, OCHC*H*OAc, J = 7.6, 5.6 Hz, 1H), 4.85 (dd, OCH=C*H,* J = 6.1, 3.3 Hz, 1H), 4.40 (dd, CH_2OAc, J = 12.0, 5.6 Hz, 1H), 4.29 - 4.23 (m, C*H*CH_2OAc, 1H), 4.20 (dd, CH_2OAc, J = 12.0, 3.1 Hz, 1H), 2.10 (s, OCOCH_3, 3H), 2.08 (s, OCOCH_3, 3H), 2.05 (s, OCOCH_3, 3H).



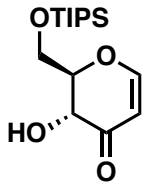
Deacetylation reaction,[80] **Compound 6.21**, *(2R,3S,4R)-2-(hydroxymethyl)-3,4-dihydro-2H-pyran-3,4-diol*: A flask containing a solution of triacetate **6.20** (5.25 g, 19.28 mmol, 1 eq) in 50% MeOH in THF (100 mL) was equipped with a drying tube.

Potassium carbonate (292 mg, 2.11 mmol, 0.1 eq) was added and the resulting reaction mixture was stirred at room temperature for 24 hr. The solvents were removed *in vacuo* and the crude material ran through a silica plug (10% MeOH in DCM) to give product **6.21** (2.49 g, 89%) as an off-white crystalline solid. **TLC** (25% EtOAc/Hex) R_f = 0.04. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 6.29 (dd, OC*H*=CH, *J* = 6.0, 1.7 Hz, 1H), 5.06 (d, O*H* *J* = 5.5 Hz, 1H), 4.83 (d, O*H*, *J* = 5.5 Hz, 1H), 4.57 (dd, OCH=C*H*, *J* = 6.0, 2.3 Hz, 1H), 4.54 (t, O*H*, *J* = 5.8 Hz, 1H), 3.93 (dddd, OCH=CHC*H*OH, *J* = 7.0, 5.5, 2.3, 1.7 Hz, 1H), 3.76 - 3.65 (m, OCHC*H*OH, 1H), 3.64 - 3.53 (m, CH_2OH, 2H), 3.42 - 3.33 (m, OC*H*CH_2OH, 1H).



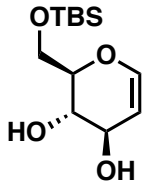
Protection with triisopropylsilyl chloride (TIPS-Cl).[114] **Compound 6.22**, *(2R,3S,4R)-2-(((triisopropylsilyl)oxy)methyl)-3,4-dihydro-2H-pyran-3,4-diol*: A solution of substrate **6.21** (600 mg, 4.1 mmol, 1 eq) in dry DMF (10 mL) was cooled to 0 °C. Imidazole (618 mg, 9.08 mmol, 2.2 eq) was added to the reaction flask followed by TIPS-Cl (920 μL, 4.3 mmol, 1.05 eq). The reaction was mixed for 2.5 h at 0 °C then allowed to warm up to room temperature overnight while mixing. The reaction was quenched by pouring the reaction mixture into a solution of 5% DI water in Et_2O (200 mL). The organic fraction was washed with DI water (5 x 25 mL) then dried over anhydrous $MgSO_4$ and solvents removed *in vacuo*. The crude was filtered through a silica plug (40% EtOAc in hexanes) to give the product **6.22** (597 mg, 48%) as a clear

oil. **TLC** (40% EtOAc/Hex) R_f = 0.18. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.30 (dd, OC*H*=CH, *J* = 6.0, 1.5 Hz, 1H), 4.74 (dd, OCH=C*H, J* = 6.0, 2.3 Hz, 1H), 4.33 – 4.24 (m, OCH=CHC*H*OH, 1H), 4.09 (dd, CH_2OTIPS, *J* = 10.6, 2.9 Hz, 1H), 3.99 (dd, CH_2OTIPS, *J* = 10.6, 4.6 Hz, 1H), 3.89 - 3.78 (m, OC*H*C*H*OH, 2H), 3.25 (d, O*H*, *J* = 1.8 Hz, 1H), 2.23 (d, O*H*, *J* = 5.4 Hz, 1H), 1.21 - 1.02 (m, OTIPS, 21H).

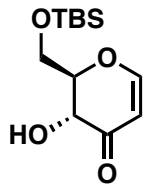


Manganese dioxide (MnO_2) oxidation.[81] **Compound 6.23**, *(2R,3R)-3-hydroxy-2-(((triisopropylsilyl)oxy)methyl)-2,3-dihydro-4H-pyran-4-one*: A solution of substrate **6.22** (597 mg, 1.97 mmol, 1 eq) in hexanes (30 mL) was added to a mixture of MnO_2 (4.31 g, 49.55 mmol, 25 eq) in hexanes (20 mL) at room temperature. A drying tube was attached to the reaction flask and the reaction mixture was stirred at room temperature for 4 hr. The reaction was filtered through a Celite pad to remove particulates before the solvents were removed *in vacuo*. The crude material was purified by flash-column chromatography on silica (10% → 40% EtOAc / Hex) to give product **6.23** (357 mg, 60%). **TLC** (20% EtOAc/Hex) R_f = 0.37. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 (d, CH^{α}=CH^{β}, *J* = 5.6 Hz, 1H), 5.45 (d, CH^{α}=CH^{β}, *J* = 5.6 Hz, 1H), 4.46 - 4.36 (m, C*H*OH, 1H), 4.22 - 4.06 (m, OC*H*CH_2, 3H), 3.52 - 3.45 (m, O*H*, 1H), 1.23 - 1.03 (m, OTIPS, 21H).

Compound 6.24 was not synthesized



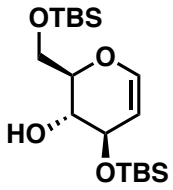
Selective *t*-butyldimethylsilyl chloride (TBS-Cl) protection,[114] **Compound 6.25**, *(2R,3S,4R)-2-(((tert-butyldimethylsilyl)oxy)methyl)-3,4-dihydro-2H-pyran-3,4-diol*: A solution of triol **6.21** (110 mg, 0.753 mmol, 1 eq) in DMF (5 mL) was cooled to 0 °C. Imidazole (132 mg, 1.939 mmol, 2.6 eq) was added followed by TBS-Cl (137 mg, 0.908 mmol, 1.2 eq) to the reaction flask. The reaction mixture was stirred at 0 °C for 4 hr. The reaction mixture was quenched with sat. $NaHCO_3$ (6 mL) and extracted with EtOAc (3 x 25 mL). The organic fraction was washed with DI water (3 x 25 mL) and dried over anhydrous Na_2SO_4 before solvents were removed *in vacuo*. The crude was purified by flash-column chromatography on silica (20% → 60% EtOAc/Hex) to give **6.25** (146 mg, 74%). **TLC** (40% EtOAc/Hex) R_f = 0.27. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.31 (dd, OC*H*=CH, *J* = 6.1, 1.7 Hz, 1H), 4.73 (dd, OCH=C*H*, *J* = 6.1, 2.3 Hz, 1H), 4.26 (dddd, OCH=CHC*H*, *J* = 7.4, 5.8, 2.3, 1.7 Hz, 1H), 4.00 (dd, CHCH_2, *J* = 11.1, 3.8 Hz, 1H), 3.91 (dd, CHCH_2, *J* = 11.1, 4.6 Hz, 1H), 3.83 - 3.77 (m, OC*H*C*H*OH, 2H), 3.00 (d, O*H*, *J* = 2.8 Hz, 1H), 2.29 (d, O*H*, *J* = 5.8 Hz, 1H), 0.91 (s, SiC(CH_3)$_3$, 9H), 0.11 (s, 2 x SiCH_3, 6H).



Manganese dioxide (MnO_2) oxidation.[81] **Compound 6.26**, *(2R,3R)-2-(((tert-butyldimethylsilyl)oxy)methyl)-3-hydroxy-2,3-dihydro-4H-pyran-4-one*: MnO_2 (756 mg,

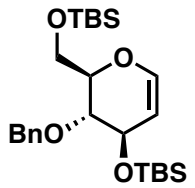
8.70 mmol, 25 eq) was added to a solution of diol **6.25** (90 mg, 0.346 mmol, 1 eq) in hexanes (10 mL). The reaction flask was fitting with a drying tube and the reaction mixture stirred at room temperature for 24 hr. The reaction was filtered though Celite to remove solids which was washed with DCM. The solvent was removed *in vacuo* to give product **6.26** (54 mg, 60%). **TLC** (20% EtOAc/Hex) R_f = 0.50. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 (d, CH^{α}=C*H*$^{\beta}$, *J* = 5.8 Hz, 1H), 5.45 (d, C*H*$^{\alpha}$=CH^{β}, *J* = 5.8 Hz, 1H), 4.35 (dd, C*H*OH, *J* = 13.2, 2.3 Hz, 1H), 4.18 - 4.10 (m, C*H*CH_2OTBS, 1H), 4.13 - 4.04 (m, C*H*$_2$OTBS, 1H), 4.06 - 3.45 (m, C*H*$_2$OTBS, 1H), 3.48 (d, O*H*, *J* = 2.3 Hz, 1H), 0.93 (s, SIC(C*H*$_3$)$_3$, 9H), 0.12 (s, 2 x SiC*H*$_3$, 6H).

Compound 6.27 was not synthesized



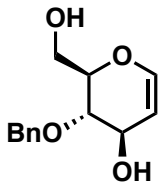
***t*-butyldimethylsilyl chloride (TBS-Cl) protection,**[66] **Compound 6.28**, *(2R,3R,4R)-4-((tert-butyldimethylsilyl)oxy)-2-(((tert-butyldimethylsilyl)oxy)methyl)-3,4-dihydro-2H-pyran-3-ol*: To a solution of triol **6.21** (250 mg, 1.7 mmol, 1.0 eq) in 10mL anhydrous DMF, imidazole (584 mg, 8.5 mmol, 5.0 eq) was added and the reaction flask cooled to 0 °C in an ice bath. The TBDMS-Cl (564 mg, 3.74 mmol, 2.2 eq) was added and the reaction mixture was stirred at 0 °C. The reaction was stirred overnight and the temperature allowed to warm up to ambient temperature. The reaction was quenched by adding 50 mL of a 1:9 solution of H_2O in EtOH. The organic fraction was washed with H_2O (5 x 25mL), dried over anhydrous $MgSO_4$, and filtered through

a Celite pad. Solvents were removed *in vacuo* and the sample purified by flash-column chromatography on silica (10% EtOAc/Hexanes) to give a whitish waxy solid (494 mg, 77%). **TLC** (10% EtOAc / Hex) R_f = 0.28. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.27 (dd, OC*H*=CH, *J* = 6.1, 1.6 Hz, 1H), 4.62 (dd, OCH=C*H*, *J* = 6.1, 2.4 Hz, 1H), 4.23 (ddd, C*H*OTBS, *J* = 6.4, 2.4, 1.6 Hz, 1H), 3.97 (dd, C*H*$_2$OTBS, *J* = 11.2, 4.8 Hz, 1H), 3.88 (dd, C*H*$_2$OTBS, *J* = 11.2, 3.8 Hz, 1H), 3.82 (ddd, C*H*CH$_2$OTBS, *J* = 8.8, 4.8, 3.8 Hz, 1H), 3.75 (ddd, C*H*OH, *J* = 8.8, 6.4, 3.6 Hz, 1H), 2.48 (d, O*H*, *J* = 3.6 Hz, 1H), 0.91 (s, 2 x SiC(C*H*$_3$)$_3$, 18H), 0.12 (s, SiC*H*$_3$, 6H), 0.09 (s, SiC*H*$_3$, 6H).



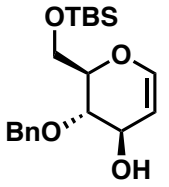
Benzyl protection of an alcohol,[82] **Compound 6.29**, *(((2R,3R,4R)-3-(benzyloxy)-2-(((tert-butyldimethylsilyl)oxy)methyl)-3,4-dihydro-2H-pyran-4-yl)oxy)(tert-butyl)di-methylsilane*: In an oven-dried 50 mL two-neck round-bottom flask under argon added alcohol **6.28** (254 mg, 0.68 mmol, 1.0 eq) and 10 mL anhydrous DMF. The reaction mixture was then cooled to 0 °C in an ice bath. A 60% suspension of NaH in mineral oil (40 mg, 1.0 mmol, 1.5 eq) was added and the reaction mixed for 20 - 30 min at 0 °C. BnBr (160 μL, 1.36 mmol, 2.0 eq) and TBAI (250 mg, 0.68 mmol, 1.0 eq) were added in succession and the reaction mixture was stirred overnight allowing the reaction flask to gradually warm up to room temperature. The reaction was quenched by adding saturated NH_4Cl. The reaction crude was transferred to a separatory funnel with 100mL 1:1 H_2O/Et_2O. The aqueous layer was washed with Et_2O (50 mL), the organic fraction washed with 1M $Na_2S_2O_3$ (50 mL) and H_2O (50 ml) then dried

over anhydrous $MgSO_4$. The sample was vacuum filtered through a Celite pad, solvents removed *in vacuo*, and purified by flash-chromatography on silica (5→10% EtOAc/Hexanes) yellow waxy solid (268 mg, 85%). **TLC** (10% EtOAc / Hex) R_f = 0.60. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 - 7.27 (m, Ar*H*, 5H), 6.30 (dd, OC*H*=CH, *J* = 6.1, 1.4 Hz, 1H), 4.82 (d, CH_2Ph, *J* = 11.3 Hz, 1H), 4.72 (d, CH_2Ph, *J* = 11.3 Hz, 1H), 4.63 (dd, OCH=C*H*, *J* = 6.1, 2.7 Hz, 1H), 4.34 (ddd, C*H*OTBS, *J* = 6.1, 2.7, 1.4 Hz, 1H), 3.95 (dd, CH_2OTBS, *J* = 11.2, 4.6 Hz, 1H), 3.90 (ddd, C*H*CH_2OTBS, *J* = 8.0, 4.6, 2.2 Hz, 1H), 3.83 (dd, CH_2OTBS, *J* = 11.2, 2.2 Hz, 1H), 3.64 (dd, C*H*OBn, *J* = 8.0, 6.1 Hz, 1H), 0.91 (s, SiC(CH_3)$_3$, 9H), 0.90 (s, SiC(CH_3)$_3$, 9H), 0.10 (s, SiCH_3, 3H), 0.08 (s, SiCH_3, 3H), 0.06 (s,2 x SiCH_3, 6H).



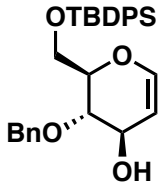
Deprotection of TBS ether with TBAF, Compound 6.30, *(2R,3S,4R)-3-(benzyloxy)-2-(hydroxymethyl)-3,4-dihydro-2H-pyran-4-ol*: Anhydrous THF (10 mL) was added to round-bottom flask containing **6.29** (248 mg, 0.53 mmol, 1.0 eq). A 1 M solution of TBAF in THF (1.6 mL, 1.6 mmol, 3.0 eq) was added to the reaction flask and allowed to stir at room temperature for 30 min. The reaction was quenched with 50mL 1:1 H_2O / Et_2O and transferred to a separatory funnel. The aqueous phase was extracted with Et_2O (3 x 25 mL). The organic fraction was dried over anhydrous $MgSO_4$, vacuum filtered through a Celite pad and solvents removed *in vacuo*. The sample was purified by flash-chromatography on silica (50% EtOAc / Hexanes) to give **6.30** as a white crystalline solid (90 mg, 77%). **TLC** (50% EtOAc / Hex) R_f = 0.15. **^{1}H**

NMR (400 MHz, $CDCl_3$) δ 7.41 - 7.28 (m, Ar*H*, 5H), 6.36 (dd, OC*H*=CH, *J* = 6.0, 1.7 Hz, 1H), 4.85 (d, CH_2Ph, *J* = 11.7 Hz, 1H), 4.81 (d, CH_2Ph, *J* = 11.7 Hz, 1H), 4.74 (dd, OCH=C*H*, *J* = 6.0, 2.5 Hz, 1H), 4.44 - 4.34 (m, C*H*OH, 1H), 4.00 - 3.82 (m, C*H*CH_2OH, 3H), 3.63 (dd, C*H*OBn, *J* = 9.1, 6.8 Hz, 1H), 1.86 (dd, CH_2O*H*, *J* = 7.9, 5.2 Hz, 1H), 1.77 (d, CHO*H*, *J* = 5.9 Hz, 1H).

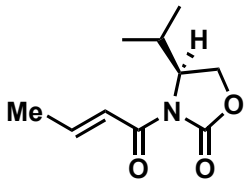


Selective *t*-butyldimethylsilyl chloride (TBS-Cl) protection,[114] **Compound 6.31**, *(2R,3S,4R)-3-(benzyloxy)-2-(((tert-butyldimethylsilyl)oxy)methyl)-3,4-dihydro-2H-pyran-4-ol*: In a round bottom flask under Ar(g), diol **6.30** (100 mg, 0.423 mmol, 1 eq) was dissolved in anhydrous DMF (10 mL). Imidazole (76 mg, 1.12 mmol, 2.6 eq) was added and the reaction flask cooled to 0 °C. TBS-Cl (68 mg, 0.451 mmol, 1.05 eq) was added and the reaction mixture was stirred for 24 hr allowing the reaction to warm up to room temperature. The reaction was quenched by adding 10% water in Et_2O (100 mL). The organic fraction was washed with DI water (5 x 25 mL) and dried over anhydrous $MgSO_4$. Removal of solvents *in vacuo* gave crude product that was purified by flash-chromatography on silica (20% EtOAc / Hex) to give **6.31** (115 mg, 60%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 - 7.28 (m, Ar*H*, 5H), 6.36 (dd, OC*H*=CH, *J* = 6.1, 1.4 Hz, 1H), 4.80 (d, CH_2Ph, *J* = 12.1 Hz, 1H), 4.78 (d, CH_2Ph, *J* = 12.1 Hz, 1H), 4.71 (dd, OCH=C*H*, *J* = 6.1, 2.8 Hz, 1H), 4.34 - 4.25 (m, C*H*OH, 1H), 3.98 - 3.94 (m,CH_2OTBS, 2H), 3.86 (dt, C*H*CH_2OTBS, *J* = 8.4, 2.8 Hz, 1H), 3.68 (dd, C*H*OBn, *J* =

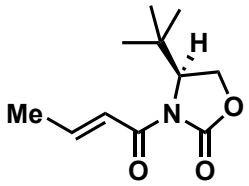
8.4, 6.2 Hz, 1H), 2.18 (d, O*H*, *J* = 6.2 Hz, 1H), 0.92 (s, SiC(C*H*$_3$)$_3$, 9H), 0.09 (s, 2 x SiC*H*$_3$, 6H).



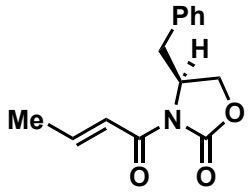
Selective *t*-butyldiphenylsilyl chloride (TPS-Cl) protection,[114] **Compound 6.32**, *(2R,3S,4R)-3-(benzyloxy)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-3,4-dihydro-2H-pyran-4-ol*: Diol **6.30** (1.54 g, 6.50 mmol, 1 eq) was dissolved in anhydrous DMF (24 mL) in a round bottom flask under Ar(g). Imidazole (1.01 g, 14.85 mmol, 2.3 eq) was added to the flask followed by TPS-Cl (2.6 mL,10 mmol, 1.54 eq) at room temperature. The reaction was mixed for 2 hr before being quenched with 10% water in Et_2O (500 mL). The organic fraction was washed with DI water (5 x 100 mL) and dried over anhydrous $MgSO_4$ before solvents were removed *in vacuo*. The crude material was purified by flash-chromatography on silica (20% EtOAc / Hex) to give product **6.32** (2.2 g, 71%) as a clear viscous liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 - 7.65 (m, Ar*H*, 4H), 7.48 - 7.23 (m, Ar*H*, 11H), 6.39 (dd, OC*H*=CH, *J* = 6.3, 1.9 Hz, 1H), 4.87 (d, C*H*$_2$Ph, *J* = 11.5 Hz, 1H), 4.80 (d, C*H*$_2$Ph, *J* = 11.5 Hz, 1H), 4.73 (dd, OCH=C*H*, *J* = 6.3, 2.7 Hz, 1H), 4.41 - 4.31 (m, C*H*OH, 1H), 4.03 (dd, C*H*$_2$OTPS, *J* = 11.4, 2.8 Hz, 1H), 3.99 (dd, C*H*$_2$OTPS, *J* = 11.4, 2.2 Hz, 1H), 3.91 - 3.79 (m, C*H*CH$_2$OTPS, C*H*OBn, 2H), 1.91 (d, O*H*, *J* = 5.9 Hz, 1H), 1.08 (s, SiC(C*H*$_3$)$_3$, 9H).



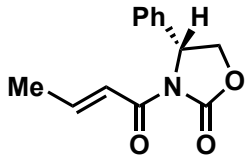
Compound 4.1, *(S,E)-3-(but-2-enoyl)-4-isopropyloxazolidin-2-one*: Obtained following the general procedure for oxazolidinone coupling to acyl chlorides. The crude material was purified by flash-column chromatography on silica (20% EtOAc / Hex). **TLC** (20% EtOAc / Hex) R_f = 0.30. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28 (dq, *partially hidden*, C*H*$^{\alpha}$=CH$^{\beta}$, *J* = 15.2, 1.5 Hz, 1H), 7.15 (dq, CH$^{\alpha}$=C*H*$^{\beta}$, *J* = 15.2, 6.7 Hz, 1H), 4.49 (ddd, NC*H*CH_2, *J* = 8.2, 4.0, 3.2 Hz, 1H), 4.27 (dd, NCHC*H*$_2$, *J* = 9.1, 8.2 Hz, 1H), 4.21 (dd, NCHC*H*$_2$, *J* = 9.1, 3.2 Hz, 1H), 2.41 (heptd, C*H*$(CH_3)_2$, *J* = 7.0, 4.0 Hz, 1H), 1.96 (dd, CH$^{\alpha}$=CH$^{\beta}$C*H*$_3$, *J* = 6.7, 1.5 Hz, 3H), 0.93 (d, CH(C*H*$_3)_2$, *J* = 7.0 Hz, 3H), 0.89 (d, CH(C*H*$_3)_2$, *J* = 7.0 Hz, 3H).



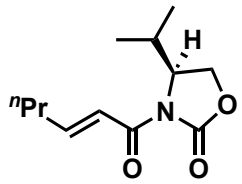
Compound 4.2, *(S,E)-3-(but-2-enoyl)-4-(tert-butyl)oxazolidin-2-one*: Obtained following the general procedure for oxazolidinone coupling to acyl chlorides. The crude material was purified by flash-column chromatography (10% → 25% EtOAc / Hex). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 (dq, *partially hidden*, C*H*$^{\alpha}$=CH$^{\beta}$, *J* = 15.2, 1.5 Hz, 1H), 7.15 (dq, CH$^{\alpha}$=C*H*$^{\beta}$, *J* = 15.2, 6.8 Hz, 1H), 4.51 (dd, NC*H*CH_2, *J* = 7.4, 1.9 Hz, 1H), 4.29 (dd, NCHC*H*$_2$, *J* = 9.2, 1.9 Hz, 1H), 4.24 (dd, NCHC*H*$_2$, *J* = 9.2, 7.4 Hz, 1H), 1.96 (dd, CH$^{\alpha}$=CH$^{\beta}$C*H*$_3$, *J* = 6.8, 1.5 Hz, 3H), 0.94 (s, C(C*H*$_3)_3$, 9H).



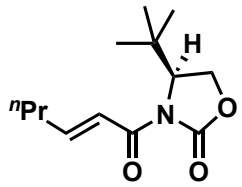
Compound 4.3, *(S,E)-4-benzyl-3-(but-2-enoyl)oxazolidin-2-one*: Obtained following the general procedure for oxazolidinone coupling to acyl chlorides. The crude material was purified by flash-column chromatography on silica (20% EtOAc / Hex). **TLC** (20% EtOAc / Hex) R_f = 0.27. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 - 7.17 (m, Ar*H*, C*H*$^{\alpha}$=C*H*$^{\beta}$, 7H), 4.78 - 4.69 (m, NC*H*CH_2, 1H), 4.26 - 4.17 (m, NCHC*H*$_2$, 1H), 4.17 (dd, NCHC*H*$_2$, *J* = 9.0, 3.1 Hz, 1H), 3.34 (dd, C*H*$_2$Ph, *J* = 13.4, 3.4 Hz, 1H), 2.81 (dd, C*H*$_2$Ph, *J* = 13.4, 9.5 Hz, 1H), 1.99 (d, CH^{α}=CH^{β}C*H*$_3$, *J* = 6.1 Hz, 3H).



Compound 4.4, *(R,E)-3-(but-2-enoyl)-4-phenyloxazolidin-2-one*: Obtained following the general procedure for oxazolidinone coupling to acyl chlorides. The crude material was purified through a silica plug (100% DCM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 - 7.28 (m, Ar*H*, C*H*$^{\alpha}$=CH^{β}, 6H), 7.09 (dq, CH^{α}=C*H*$^{\beta}$, *J* = 15.2, 6.8 Hz, 1H), 5.48 (dd, NC*H*CH_2, *J* = 8.7, 3.9 Hz, 1H), 4.69 (dd, NCHC*H*$_2$, *J* = 8.9, 8.7 Hz, 1H), 4.27 (dd, NCHC*H*$_2$, *J* = 8.9, 3.9 Hz, 1H), 1.93 (dd, CH^{α}=CH^{β}C*H*$_3$, *J* = 6.8, 1.6 Hz, 3H).

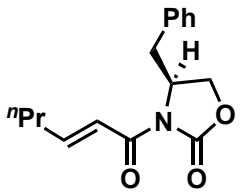


Compound 4.5, *N-(2'E-hexenoyl)-4S-isopropyl-1,3-oxazolidin-2-one:* Obtained following the general procedure for oxazolidinone coupling to acyl chlorides. The crude product was purified using flash chromatography (0 → 30% EtOAc in hexanes) $[\alpha]_D^{20}$ = +82.0° (c 1.0, $CHCl_3$). *Lit. value* $[\alpha]_D^{25}$ = +89.7° (c 1.0, $CHCl_3$).[115] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27 (dt, olefinic, CH_2CH=C*H*, *J* = 15.3, 1.4 Hz, 1H), 7.14 (dt, olefinic, CH_2C*H*=CH, *J* = 15.3, 6.9 Hz, 1H), 4.49 (m, OCH_2C*H*N, 1H), 4.27 (dd, O*C*H_2CHN, *J* = 9.1, 9.1 Hz, 1H), 4.21 (dd, O*C*H_2CHN, *J* = 9.1, 3.1 Hz, 1H), 2.41 (m, C*H*$(CH_3)_2$, 1H), 2.26 (ddd, CH_2C*H*$_2$CH=CH, *J* = 7.4, 6.9, 1.4 Hz, 2H), 1.53 (sext, CH_3C*H*$_2CH_2$, *J* = 7.4 Hz, 2H), 0.95 (t, *partly hidden*, C*H*$_3CH_2$, *J* = 7.3 Hz, 3H), 0.96-0.88 (2d, *partly hidden*, CHC*H*$_3$, *J* = 7.0 Hz, 3H each). **^{13}C NMR** (125.7 MHz, DMSO-d_6) δ 164.59, 154.42, 150.20, 121.08, 63.89, 58.52, 34.35, 28.72, 21.26, 17.97, 15.02, 13.92. **FTIR** (cm^{-1}) 1776, 1685, 1636, 1367, 1203, 712.

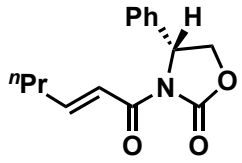


Compound 4.6, *N-(2'E-hexenoyl)-4S-tert-butyl-1,3-oxazolidin-2-one*: Obtained following the general procedure for oxazolidinone coupling to acyl chlorides. The crude product was purified using flash chromatography (0 → 30% EtOAc in hexanes). $[\alpha]_D^{20}$ = +88.0° (c 1.0, $CHCl_3$). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.17 (dt, olefinic, CH_2CH=C*H*, *J* = 15.2, 1.3 Hz, 1H), 6.98 (dt, olefinic, CH_2C*H*=CH, *J* = 15.2, 6.6 Hz,

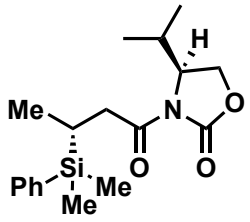
1H), 4.41-4.37 (m, OCH_2CHN and OCH_2CHN (1H), *partly hidden*, 2H), 4.33 (dd, ½OCH_2CHN, *J* = 9.1, 8.8 Hz, 1H), 2.22 (ddd, $CH_2CH_2CH{=}CH$, *J* = 7.1, 6.6, 1.3 Hz, 2H), 1.46 (sext, $CH_3CH_2CH_2$, *J* = 7.1 Hz, 2H), 0.91 (t, CH_3CH_2, *J* = 7.1 Hz, 3H), 0.85 (s, *tert*-Bu, 9H); **^{13}C NMR** (125.7 MHz, DMSO-d_6) δ 164.87, 155.08, 150.12, 121.18, 65.64, 60.94, 35.90, 34.37, 25.82, 21.27, 13.95. FTIR (cm^{-1}) 1777, 1689, 1657, 1340, 1186, 715.



Compound 4.7, *N-(2'E-hexenoyl)-4S-benzyl-1,3-oxazolidin-2-one*: Obtained following the general procedure for oxazolidinone coupling to acyl chlorides. The crude product was purified using flash chromatography (0 → 30% EtOAc in hexanes) **mp** 52.0 – 53.1 ºC, **$[\alpha]_D^{20}$** = +64.6º (c 1.1, $CHCl_3$). *Lit value* **$[\alpha]_D^{25}$** = +65.5º (c 1.1, $CHCl_3$)[116] **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.34-7.29 (m, Ph*H*, 2H), 7.28-7.23 (m, Ph*H*, 1H), 7.21-7.18 (m, Ph*H*, 2H), 7.14 (d, olefinic, $CH_2CH{=}CH$, *J* = 15.2 Hz, 1H), 7.06 (dt, olefinic, $CH_2CH{=}CH$, *J* = 15.2, 6.6 Hz, 1H), 4.74-4.68 (m, N*CH*, 1H), 4.35 (dd, OCH_2CHN, *J* = 8.6, 8.6 Hz, 1H), 4.19 (dd, OCH_2CHN, *J* = 8.6, 3.0 Hz, 1H), 3.05 (dd, $PhCH_2CH$, *J* = 13.3, 3.2 Hz, 1H), 2.96 (dd, $PhCH_2CH$, *J* = 13.3, 7.8 Hz, 1H), 2.25 (bq, $CH_2CH_2CH{=}CH$, *J* = 6.9 Hz, 2H), 1.46 (sext, $CH_3CH_2CH_2$, *J* = 7.0 Hz, 2H), 0.92 (t, CH_3CH_2, *J* = 7.0 Hz, 3H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 165.10, 153.41, 151.70, 135.41, 129.44, 128.92, 127.27, 120.47, 66.08, 55.31, 37.90, 34.68, 21.38, 13.70; FTIR (cm^{-1}) 1781, 1678, 1635, 1352, 1200, 705.

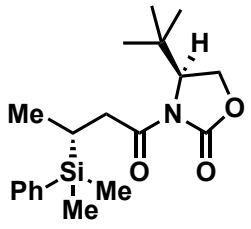


Compound 4.8, *N-(2'E-hexenoyl)-4R-phenyl-1,3-oxazolidin-2-one*: Obtained following the general procedure for oxazolidinone coupling to acyl chlorides. The crude product was purified using flash chromatography (0 → 30% EtOAc in hexanes) **mp** 76.0 – 77.2 ºC, **$[\alpha]_D^{20}$** = -101.1º (c 1.5, $CHCl_3$). *Lit value* $[a]_D^{25}$ = -95.0º (c 1.5, $CHCl_3$).[117] **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.41-7.36 (m, Ph*H*, 2H), 7.34-7.27 (m, Ph*H*, 3H), 7.17 (d, olefinic, CH_2CH=C*H*, *J* = 15.0 Hz, 1H), 6.92 (dt, olefinic, CH_2C*H*=CH, *J* = 15.0, 7.0 Hz, 1H), 5.50 (dd, NC*H*, *J* = 8.6, 3.3 Hz, 1H), 4.76 (dd, OCH_2CHN, *J* = 8.6, 8.6 Hz, 1H), 4.17 (dd, OCH_2CHN, *J* = 8.6, 3.3 Hz, 1H), 2.21 (bq, CH_2CH_2CH=CH, *J* = 6.9 Hz, 2H), 1.44 (sext, $CH_3CH_2CH_2$, *J* = 7.5 Hz, 2H), 0.92 (t, CH_3CH_2, *J* = 7.5 Hz, 3H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 164.69, 153.73, 151.99, 139.20, 129.18, 128.65, 125.97, 120.37, 69.94, 57.78, 34.69, 21.33, 13.68; **FTIR** (cm^{-1}) 1775, 1683, 1635, 1327, 1205, 707.



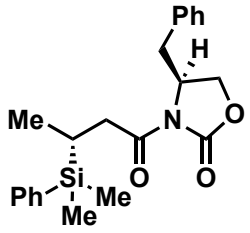
Compound 4.13, *N-(3'R-Dimethylphenylsilylbutanoyl)-4S-isopropyl-1,3-oxazolidin-2-one*: Obtained following the general procedure for the disilylzinc reaction. The crude product was purified using flash chromatography (0% → 20% EtOAc in hexane, R_f 0.40 in 10% EtOAc/Hex) and (100% DCM, R_f 0.90) to give 91% (91 mg, 87:13 d.r.) of

4.13 as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) d 7.53-7.50 (m, aromatic, 2H), 7.38-7.33 (m, aromatic, 3H), 4.39 (m, NC*H*CH_2O 1H), 4.26 (dd, NCHC*H*$_2$O, *J* = 9.2, 1.6 Hz, 1H), 4.20 (dd, NCHC*H*$_2$O, *J* = 9.2, 7.6 Hz, 1H), 3.10 (dd, COC*H*$_2$, *J* = 15.5, 3.5 Hz, 1H), 2.63 (dd, COC*H*$_2$, *J* = 15.5, 11.0 Hz, 1H), 2.33 (m, $(CH_3)_2$C*H*, 1H), 1.56 (m, SiC*H*, 1H), 0.97 (d, C*H*$_3$CH, *J* = 7.5, 3H), 0.90 (d, C*H*$_3$CH, *J* = 7.5, 3H), 0.85 (d, C*H*$_3$CH, *J* = 7.0, 3H), 0.34, 0.33 (2s, Si(C*H*$_3$)$_2$, 3H each); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 173.33, 153.94, 137.42, 134.02, 129.00, 127.73, 63.16, 58.30, 37.87, 28.31, 17.96, 15.78, 14.52, 14.28, −5.01, −5.09; **FTIR** (cm^{-1}) 1782, 1698; **HRMS** (ESI) calcd for $[C_{18}H_{27}NO_3SiNa]^+$ (MNa^+) 356.1657, found 356.1654.

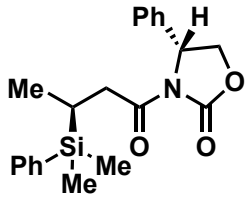


Compound 4.14, *N-(3′R-Dimethylphenylsilylbutanoyl)-4S-tert-butyl-1,3-oxazolidin-2-one*: Obtained following the general procedure for the disilylzinc reaction. The crude product was purified using flash chromatography (0% → 20% EtOAc in hexane, R_f 0.40 in 10% EtOAc/Hex) and (100% DCM, R_f 0.90) to give 95% (95 mg, 95:5 d.r.) of **4.14** as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.52 (m, Ar-*H*, 2H), 7.35 (m, Ar-*H*, 3H), 4.39 (dd, NC*H*, *J* = 7.6, 1.6 Hz, 1H), 4.24 (dd, OC*H*$_2$, *J* = 9.2, 1.6 Hz, 1H), 4.16 (dd, OC*H*$_2$, *J* = 9.2, 7.6 Hz, 1H), 3.02 (dd, COC*H*$_2$, *J* = 15.8, 3.2 Hz, 1H), 2.69 (dd, COC*H*$_2$, *J* = 15.8, 11.3 Hz, 1H), 1.57 (m, SiC*H*, 1H), 0.97 (d, C*H*$_3$CH, *J* = 7.5 Hz, 3H), 0.90 (s, *t*-Bu, 9H), 0.33, 0.32 (2s, Si(C*H*$_3$)$_2$, 3H each); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 173.47, 154.70, 137.49, 134.04, 129.05, 127.76, 65.33, 61.01, 37.60, 35.68, 25.71,

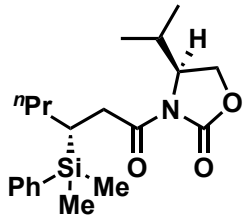
16.09, 14.41, –4.90, –5.08; **FTIR** (cm^{-1}) 1782, 1703; **HRMS** (EI, DCI/NH_3) calcd for $[C_{19}H_{30}NO_3Si]^+$ (MH^+) 348.1995, found 348.1985.



Compound 4.15, *N-(3′R-Dimethylphenylsilylbutanoyl)-4S-benzyl-1,3-oxazolidin-2-one*: Obtained following the general procedure for the disilylzinc reaction. The crude product was purified using flash chromatography (0% → 20% EtOAc in hexane, R_f 0.40 in 10% EtOAc/Hex) and (100% DCM, R_f 0.90) to give 91% (91 mg, 92:8 d.r.) of **4.15** as a white solid; mp 87-90 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.53-7.42 (m, aromatic, 2H), 7.38-7.23 (m, aromatic, 6H), 7.18 (m, aromatic, 2H), 4.59 (m, NC*H*, 1H), 4.14-4.08 (m, NHCH_2O, 2H), 3.25 (dd, PhCH_2, *J* = 13.3, 3.4 Hz, 1H), 3.03 (dd, NHCH_2O, *J*= 16.1, 3.8 Hz, 1H), 2.74 (dd, NHCH_2O, *J* = 16.1, 10.8 Hz, 1H), 2.66 (dd, PhCH_2, *J* = 13.3, 9.8 Hz, 1H), 1.60 (m, SiC*H*, 1H), 1.00 (d, CH_3CH, *J* = 7.3 Hz, 3H), 0.34, 0.33 (2s, Si(CH_3)$_2$, 3H each); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 173.30, 153.35, 137.46, 135.39, 134.03, 129.38, 129.06, 128.91, 127.76, 127.27, 66.13, 55.15, 37.97, 37.85, 15.50, 14.51, –4.96, –5.16; **FTIR** (cm^{-1}) 1790, 1697; **HRMS** (EI) calcd for $[C_{22}H_{27}NO_3Si]$ 381.1760, found 381.1756.

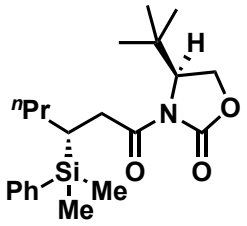


Compound 4.16, *N-(3′S-Dimethylphenylsilylbutanoyl)-4R-phenyl-1,3-oxazolidin-2-one*: Obtained following the general procedure for the disilylzinc reaction. The crude product was purified using flash chromatography (0% → 20% EtOAc in hexane, R_f 0.40 in 10% EtOAc/Hex) and (100% DCM, R_f 0.90) to give 95% (95 mg, 95:5 d.r.) of **4.16** as a white solid; mp 73-75 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.52 (m, Ar-*H*, 2H), 7.40-7.29 (m, Ar-*H*, 8H), 5.36 (dd, NC*H*, *J* = 8.7, 3.7 Hz, 1H), 4.64 (dd, OCH_2, *J* = 8.9, 8.7 Hz, 1H), 4.25 (dd, OCH_2, *J* = 8.9, 3.7 Hz, 1H), 3.05 (dd, COCH_2, *J* = 15.8, 3.7 Hz, 1H), 2.70 (dd, COCH_2, *J* = 15.8, 11.2 Hz, 1H), 1.54 (m, SiC*H*, 1H), 0.86 (d, CH_3CH, *J* = 7.3 Hz, 3H), 0.31, 0.30 (2s, SiCH_3, 3H each); **^{13}C NMR** (125.7 MHz, $CDCl_3$) *δ* 172.81, 153.56, 139.24, 137.34, 133.98, 129.07, 129.01, 128.61, 127.70, 125.96, 69.83, 57.51, 37.84, 15.59, 14.12, –5.11, –5.14; **FTIR** (cm^{-1}) 1785, 1703.



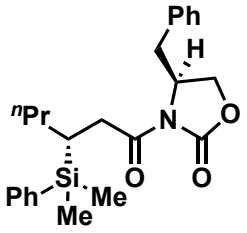
Compound 4.17, *N-(3′R-Dimethylphenylsilylhexanoyl)-4S-isopropyl-1,3-oxazolidin-2-one*: Obtained following the general procedure for the disilylzinc reaction. The crude product was purified using flash chromatography (0% → 20% EtOAc in hexane, R_f 0.40 in 10% EtOAc/Hex) and (100% DCM, R_f 0.90) to give 80% (80 mg, 87:13 d.r.) of **4.17** as a clear viscous oil. **^{1}H NMR** (500 MHz, $CDCl_3$) d 7.55-7.49 (m, aromatic, 2H),

7.36-7.31 (m, aromatic, 3H), 4.30 (ddd, NC*H*, *J* = 7.9, 3.5, 3.4 Hz, 1H), 4.17 (dd, NCHCH_2O, *J* = 9.1, 7.9 Hz, 1H), 4.14 (dd, NHCH_2O, *J* = 9.1, 3.4 Hz 1H), 3.00 (dd, COCH_2, *J* = 17.2, 5.9 Hz, 1H), 2.86 (dd, COCH_2, *J* = 17.2, 7.9 Hz, 1H), 2.33-2.20 (m, $(CH_3)_2$C*H*, 1H), 1.64-1.56 (m, SiC*H*, 1H), 1.49-1.39 (m, CH_2, 1H), 1.34-1.16 (m, CH_2, 3H), 0.87 (d, CH_3CH, *J* = 7.1 Hz, 3H), 0.81 (t, *partly hidden,* CH_3CH$_2$, *J* = 7.0 Hz, 3H), 0.80 (d, *partly hidden*, CH_3CH, *J* = 7.1 Hz, 3H), 0.31 (s, Si(CH_3)$_2$, 6H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 173.68, 154.11, 138.42, 134.10, 128.99, 127.79, 63.23, 58.55, 36.40, 32.78, 28.33, 22.29, 20.52, 18.12, 14.63, 14.39, -3.80, -4.00; **FTIR** 1778, 1700 (cm^{-1}).

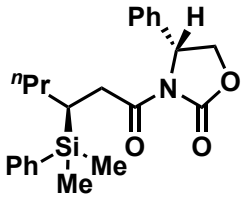


Compound 4.18, *N-(3′R-Dimethylphenylsilylhexanoyl)-4S-tert-butyl-1,3-oxazolidin-2-one*: Obtained following the general procedure for the disilylzinc reaction. The crude product was purified using flash chromatography (0% → 20% EtOAc in hexane, R_f 0.40 in 10% EtOAc/Hex) and (100% DCM, R_f 0.90) to give 80% (80 mg, 97:3 d.r.) of **4.18** as a clear viscous oil. **^{1}H NMR** (400 MHz, $CDCl_3$) d 7.56-7.49 (m, aromatic, 2H), 7.37-7.32 (m, aromatic, 3H), 4.35 (dd, NC*H*, *J* = 7.6, 1.6 Hz, 1H), 4.22 (dd, NCHCH_2O, *J* = 9.2, 1.6 Hz, 1H), 4.13 (NCHCH_2O, *J* = 9.2, 7.6 Hz, 1H), 2.94 (d, COCH_2, *J* = 6.5 Hz, 2H), 1.62 (m, SiC*H*, 1H), 1.50-1.39 (m, CH_2, 1H), 1.34-1.14 (m, CH_2, 3H), 0.87 (s, *tert*-Bu, 9H), 0.80 (t, CH_3CH$_2$, *J* = 7.1 Hz, 3H), 0.32 (2s, Si(CH_3)$_2$, 3H each); **^{13}C NMR**

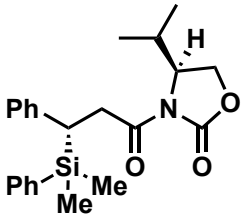
(125.7 MHz, $CDCl_3$) δ 173.79, 154.80, 138.49, 134.07, 129.00, 127.82, 65.36, 61.20, 36.14, 35.79, 32.90, 25.78, 22.34, 20.68, 14.38, -3.70, -3.90; **FTIR** (cm^{-1}) 1779, 1701.



Compound 4.19, *N-(3′R-Dimethylphenylsilylhexanoyl)-4S-benzyl-1,3-oxazolidin-2-one*: Obtained following the general procedure for the disilylzinc reaction. The crude product was purified using flash chromatography (0% → 20% EtOAc in hexane, R_f 0.40 in 10% EtOAc/Hex) and (100% DCM, R_f 0.90) to give 93% (93 mg, 91:9 d.r.) of **4.19** as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) d 7.57-7.50 (m, aromatic, 2H), 7.36-7.23 (m, aromatic, 6H), 7.17-7.13 (m, aromatic, 2H), 4.50 (m, NC*H*, 1H), 4.08 (d, NCHCH_2O, *J* = 5.0 Hz, 2H), 3.17 (dd, PhCH_2, *J* = 13.3, 3.3 Hz, 1H), 2.99 (dd, COCH_2, *J* = 17.3, 6.0 Hz, 1H), 2.90 (dd, COCH_2, *J* = 17.3, 7.6 Hz, 1H), 2.58 (dd, PhCH_2, *J* = 13.3, 9.9 Hz, 1H), 1.65 (m, SiC*H*, 1H), 1.53-1.44 (m, CH_2, 1H), 1.38-1.18 (m, CH_2, 3H), 0.84 (t, CH_3CH$_2$, *J* = 6.9 Hz, 3H), 0.34, 0.33 (2s, Si(CH_3)$_2$, 3H each); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 173.70, 153.50, 138.41, 135.55, 134.16, 129.48, 129.06, 129.04, 127.83, 127.38, 66.20, 55.36, 37.95, 36.36, 32.91, 22.31, 20.43, 14.42, -3.65, 4.23; **FTIR** (cm^{-1}) 1779, 1696.

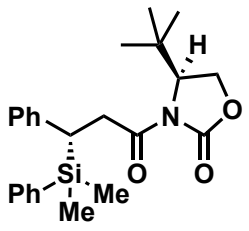


Compound 4.20, *N-(3′S-Dimethylphenylsilylhexanoyl)-4R-phenyl-1,3-oxazolidin-2-one*: Obtained following the general procedure for the disilylzinc reaction. The crude product was purified using flash chromatography (0% → 20% EtOAc in hexane, R_f 0.40 in 10% EtOAc/Hex) and (100% DCM, R_f 0.90) to give 82% (82 mg, 98:2 d.r.) of **4.20** as a clear viscous oil. **^{1}H NMR** (400 MHz, $CDCl_3$) d 7.49-7.45 (m, aromatic, 2H), 7.38-7.27 (m, aromatic, 6H), 7.26-7.22 (m, aromatic, 2H), 5.27 (dd, NC*H*, *J* = 8.8, 3.7 Hz, 1H), 4.58 (dd, NCHCH_2O, *J* = 8.8, 8.8 Hz, 1H), 4.22 (dd, NCHCH_2O, *J* = 8.8, 3.7 Hz, 1H), 2.94 (dd, COCH_2, *J* = 16.8, 5.8 Hz, 1H), 2.88 (dd, COCH_2, *J* = 16.8, 8.2 Hz, 1H), 1.54 (m, SiC*H*, 1H), 1.40-1.27 (m, CH_2, 1H), 1.22-1.06 (m, CH_2, 3H), 0.73 (t, CH_3CH$_2$, *J* = 6.9 Hz, 3H), 0.23, 0.22 (2s, Si(CH_3)$_2$, 3H each); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 173.24, 153.72, 139.25, 138.35, 134.06, 129.19, 128.99, 128.73, 127.80, 126.16, 69.97, 57.73, 36.59, 32.68, 22.25, 20.60, 14.35, -3.90, -4.08; **FTIR** (cm^{-1}) 1780, 1702.



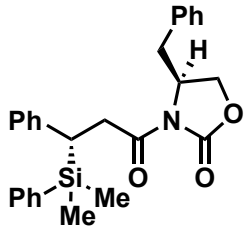
Compound 4.21, *N-(3′S-Dimethylphenylsilyl-3′-phenylpropanoyl)-4S-isopropyl-1,3-oxazolidin-2-one*: Obtained following the general procedure for the disilylzinc reaction. The crude product was purified using flash chromatography (0% → 20% EtOAc in

hexane, R_f 0.40 in 10% EtOAc/Hex) and (100% DCM, R_f 0.90) to give 90% (90 mg, 87:13 d.r.) of **4.21** as a clear viscous oil. **^{1}H NMR** (500 MHz, $CDCl_3$) d 7.31-7.45 (2m, aromatic, 5H), 7.19 (dd, aromatic, *J* = 7.5 Hz, 2H), 7.08 (dd, aromatic, *J* = 7.5 Hz, 1H), 6.97 (d, aromatic, *J* = 7.5 Hz, 2H), 4.18 (m, NC*H*OCH_2, 1H), 4.12-4.05 (dd, NCHOCH_2, partial overlap, 2H), 3.58 (dd, SiC*H*, *J* = 17.0, 12.0 Hz, 1H), 3.16 (dd, COCH_2, *J* = 17.0, 4.0 Hz, 1H), 3.01 (dd, COCH_2, *J* = 12.0, 4.0 Hz, 1H), 2.09 (m, $(CH_3)_2$C*H*, 1H), 0.79, 0.73 (2d, $(CH_3)_2$CH, *J* = 7.5, 3H each), 0.31, 0.26 (2s, Si$(CH_3)_2$, 3H each); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 172.49, 154.10, 141.59, 136.5, 134.18, 129.24, 128.01, 127.78, 127.68, 124.90, 63.31, 58.31, 35.67, 31.87, 28.26, 17.84, 14.58, -4.15, -5.27; **FTIR** (cm^{-1}) 1780, 1701; MS *m*/*z* 319 (M-C_6H_5, 23%), 135 ($C_8H_{10}Si$, 100%). **HRMS** (ESI) calcd for $[C_{23}H_{29}NO_3SiNa]^+$ (MNa^+) 418.1814, found 418.1811.

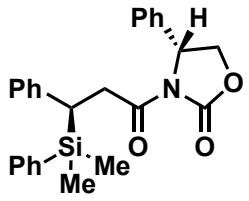


Compound 4.22, *N-(3′S-Dimethylphenylsilyl-3'-phenylpropanoyl)-4S-tert-butyl-1,3-oxazolidin-2-one*: Obtained following the general procedure for the disilylzinc reaction The crude product was purified using flash chromatography (0% → 20% EtOAc in hexane, R_f 0.40 in 10% EtOAc/Hex) and (100% DCM, R_f 0.90) to give 82% (82 mg, 96:4 d.r.) of **4.22** as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42-7.30 (m, aromatic, 5H), 7.15 (m, aromatic, 2H), 7.05 (m, aromatic, 1H), 6.94 (m, aromatic, 2H), 4.18 (dd, NC*H*, *J* = 7.8, 1.6 Hz, 1H), 4.14 (dd, OCH_2, *J* = 9.2, 1.6 Hz, 1H), 3.97 (dd,

OCH_2, *J* = 9.2, 7.8 Hz, 1H), 3.58 (dd, PhC*H*, *J* = 16.1, 12.2 Hz, 1H), 3.09 (dd, COCH_2, *J* = 16.1, 3.6 Hz, 1H), 3.05 (dd, COCH_2, *J* = 12.2, 3.6 Hz, 1H), 0.72 (s, *t*-Bu, 9H), 0.30, 0.24 (2s, Si(CH_3)$_2$, 3H each); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 173.00, 155.00, 141.62, 136.69, 134.42, 129.49, 128.29, 128.15, 127.92, 125.19, 65.53, 61.20, 35.75, 35.70, 32.69, 25.63, –3.97, –5.01; **FTIR** (film, cm^{-1}) 1774, 1701.



Compound 4.23, *N-(3′S-Dimethylphenylsilyl-3′-phenylpropanoyl)-4S-benzyl-1,3-oxazolidin-2-one*: Obtained following the general procedure for the disilylzinc reaction. The crude product was purified using flash chromatography (0% → 20% EtOAc in hexane, R_f 0.40 in 10% EtOAc/Hex) and (100% DCM, R_f 0.90) to give 87% (87 mg, 84:16 d.r.) of **4.23** as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.46-7.43 (m, aromatic, 2H), 7.38-7.31 (m, aromatic, 3H), 7.27-7.16 (m, aromatic, 5H), 7.09-7.04 (m, aromatic, 3H), 7.01-6.98 (m, aromatic, 2H), 4.41 (m, NC*H*, 1H), 4.02 (dd, OCH_2, *J* = 3.0, 9.0 Hz, 1H), 3.96 (dd, OCH_2, *J* = 8.0, 9.0 Hz, 1H), 3.60 (dd, SiC*H*, *J* = 17.0, 11.5 Hz, 1H), 3.12 (dd, COCH_2, *J* = 17.0, 4.0 Hz, 1H), 3.02 (dd, COCH_2, *J* = 11.5, 4.0 Hz, 1H), 3.02 (m, PhC*H*2, partial overlap, 1H), 2.48 (dd, PhCH_2, *J* = 13.5, 10.0 Hz, 1H), 0.31, 0.24 (2s, Si(CH_3)$_2$, 3H each); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 172.54, 153.49, 141.79, 136.59, 135.36, 134.2, 134.2, 129.30, 129.29, 128.84, 128.13, 127.76, 127.19, 125.00, 66.14, 55.08, 37.68, 35.82, 31.67, -4.04, -5.39; **FTIR** (cm^{-1}) 1778, 1701. **HRMS** (ESI) calcd for $[C_{27}H_{29}NO_3SiNa]^+$ (MNa^+) 466.1814, found 466.1806.



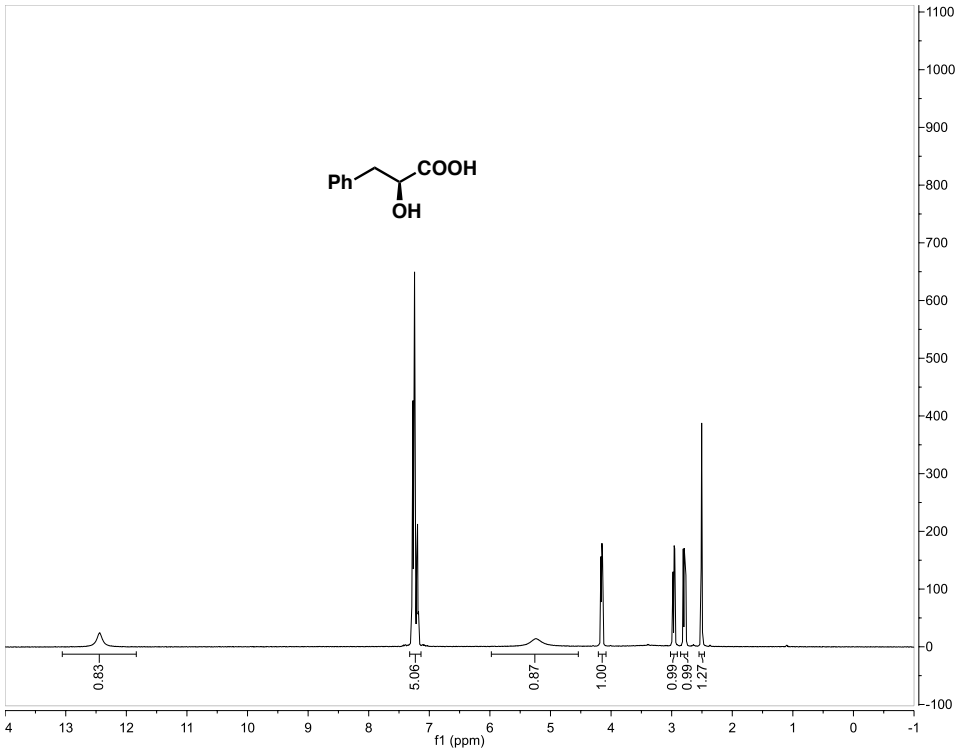
Compound 4.24, *N-(3′S-Dimethylphenylsilyl-3′-phenylpropanoyl)-4R-phenyl-1,3-oxazolidin-2-one*: Obtained following the general procedure for the disilylzinc reaction The crude product was purified using flash chromatography (0% → 20% EtOAc in hexane, R_f 0.40 in 10% EtOAc/Hex) and (100% DCM, R_f 0.90) to give 89% (89 mg, 97:3 d.r.) of **4.24** as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.43-7.26 (m, Ar-*H*, 8H), 7.21-7.07 (m, Ar-*H*, 5H), 6.97 (d, Ar-*H*, *J* = 7.5 Hz, 2H), 5.16 (dd, NC*H*, *J* = 8.5, 4.0 Hz, 1H), 4.47 (dd, OCH_2, *J* = 9.0, 8.5 Hz, 1H), 4.14 (dd, OCH_2, *J* = 9.0, 4.0 Hz, 1H), 3.73 (dd, PhC*H*, *J* = 17.0, 12.0 Hz, 1H), 3.09 (dd, COCH_2, *J* = 17.0, 4.0 Hz, 1H), 3.00 (dd, COCH_2, *J* = 12.0, 4.0 Hz, 1H), 0.31, 0.24 (2s, SiCH_3, 3H each); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 172.06, 153.79, 141.66, 138.84, 136.49, 134.16, 129.26, 129.03, 128.48, 128.07, 127.73, 127.70, 125.83, 124.91, 69.90, 57.54, 35.71, 31.50, -4.14, -5.29; **FTIR** (cm^{-1}) 1779, 1705; MS *m*/*z* 319 (35%), 265 (100%). **HRMS** (ESI) calcd for $[C_{26}H_{27}NO_3SiNa]^+$ (MNa^+) 452.1657, found 452.1652.

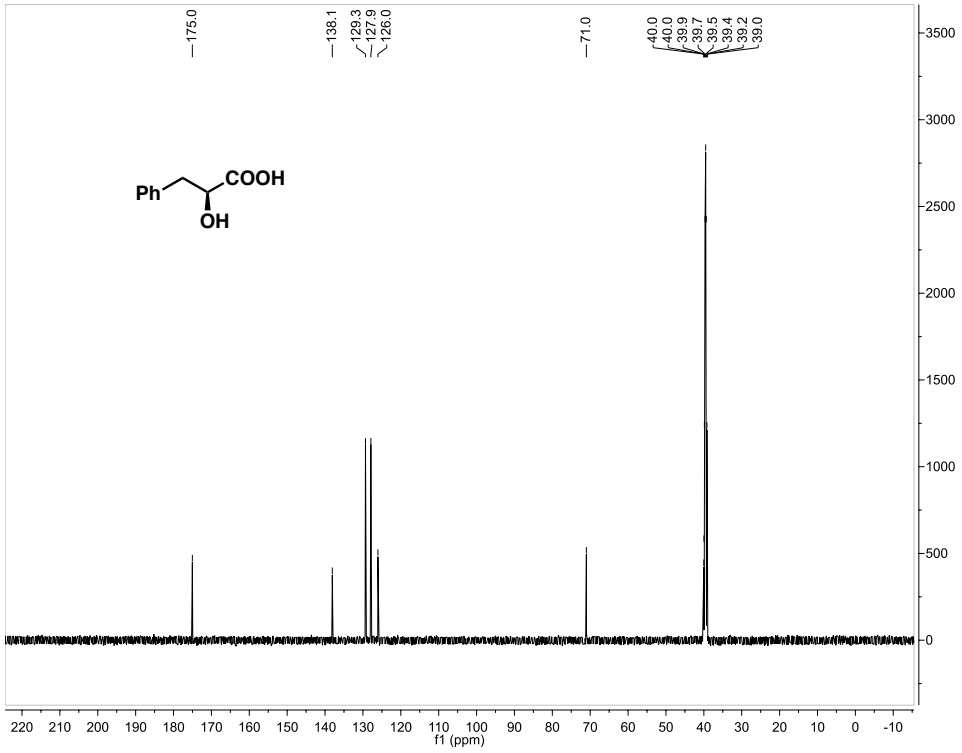
Appendix

^{1}H NMR

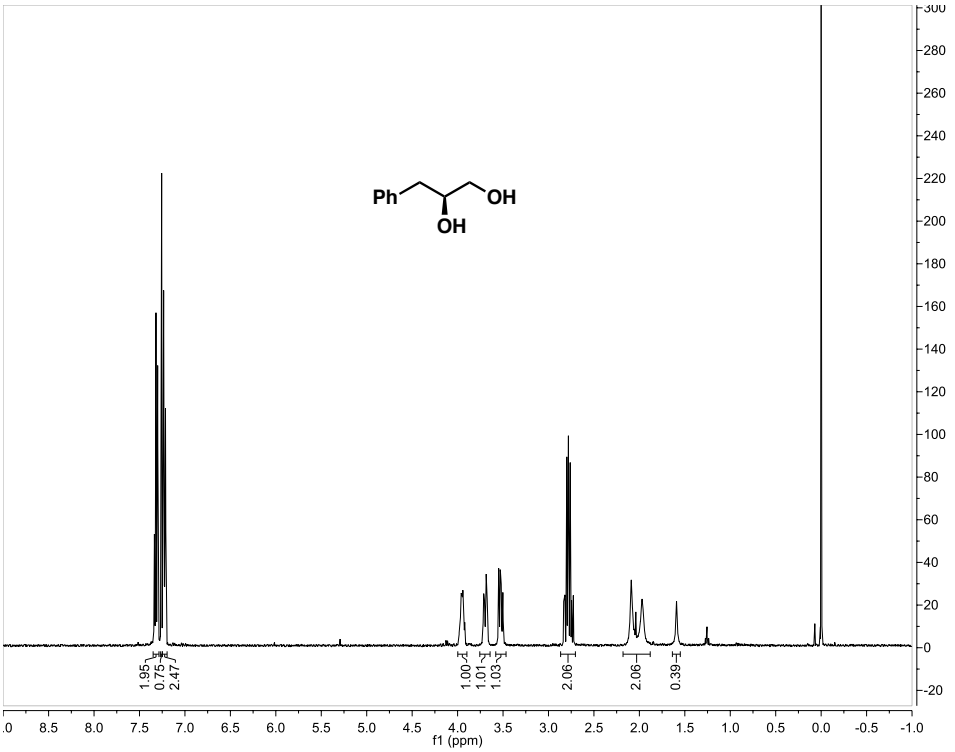
^{13}C NMR

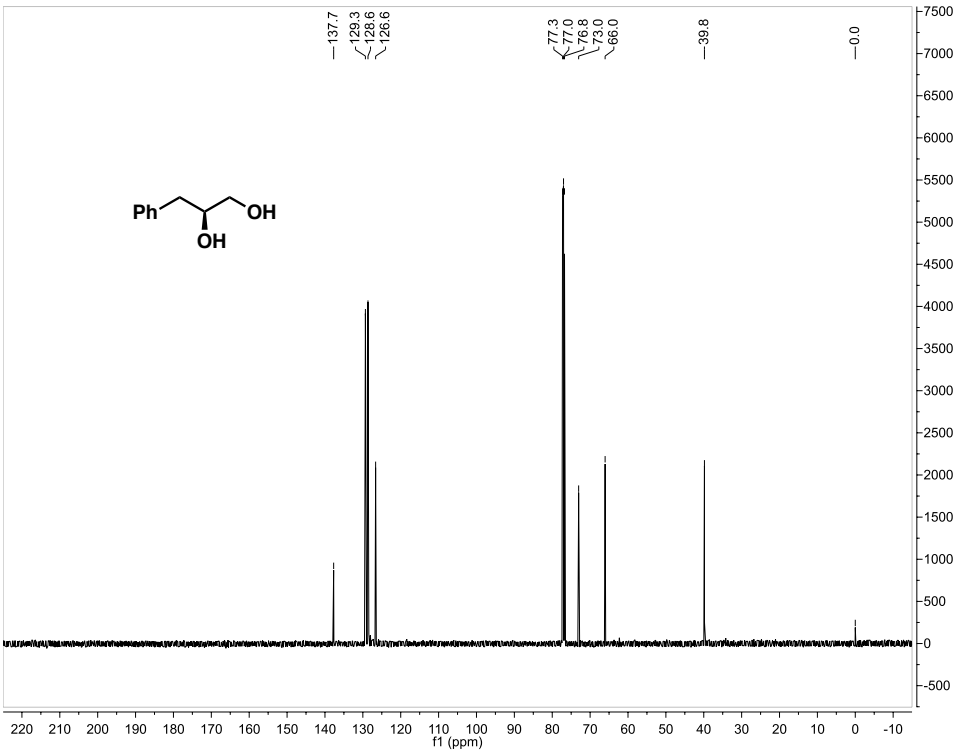
^{1}H and ^{13}C NMR for Compound 2.1



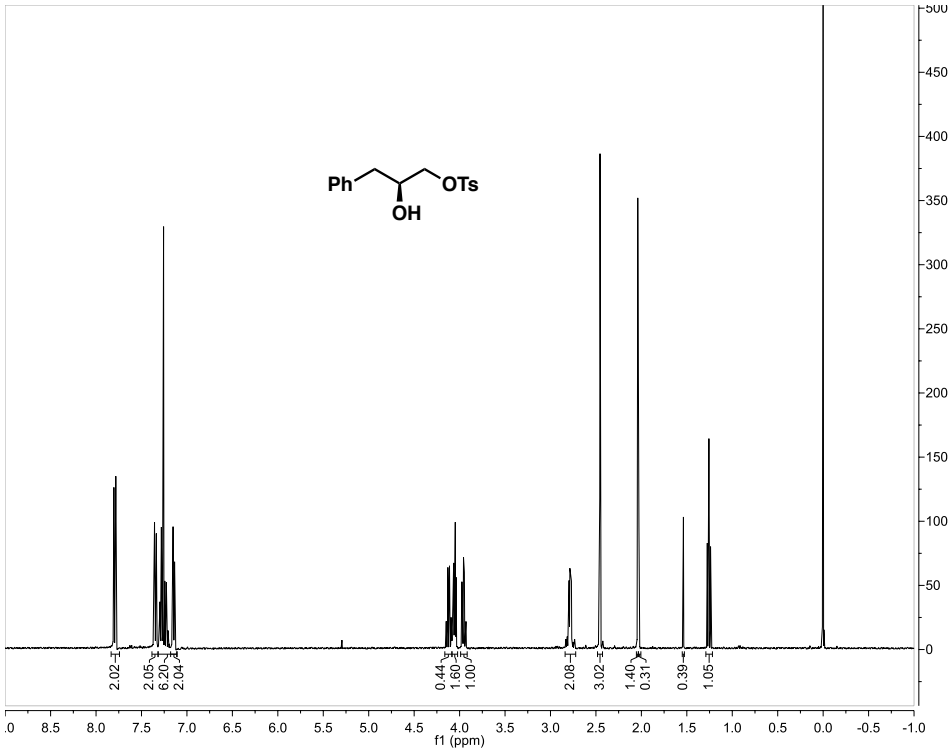


^{1}H and ^{13}C NMR for Compound 2.2

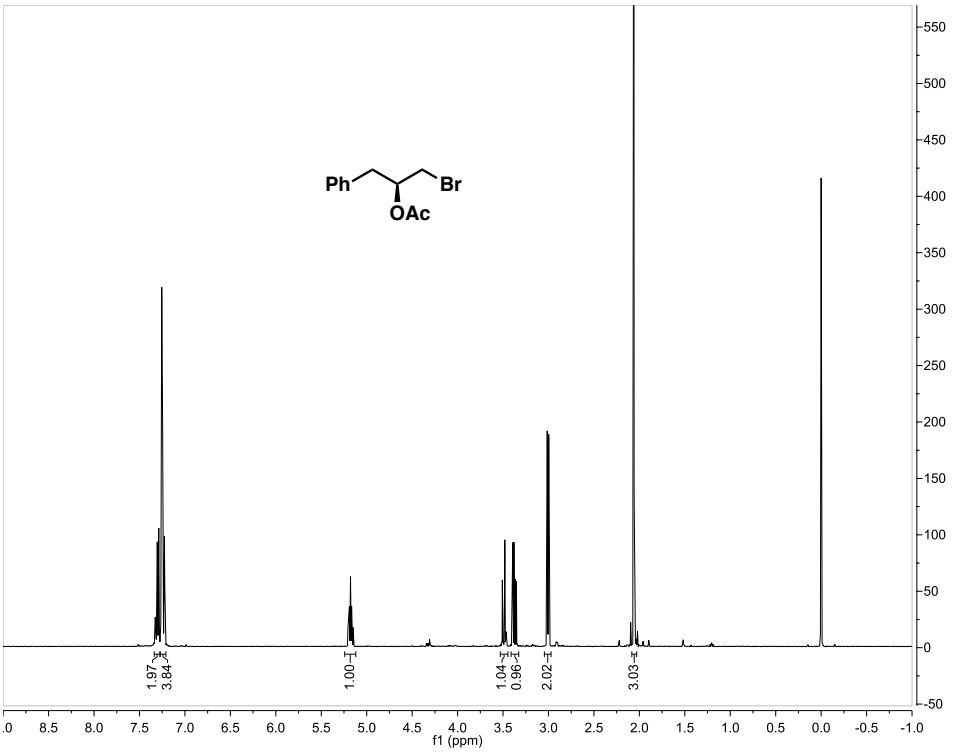


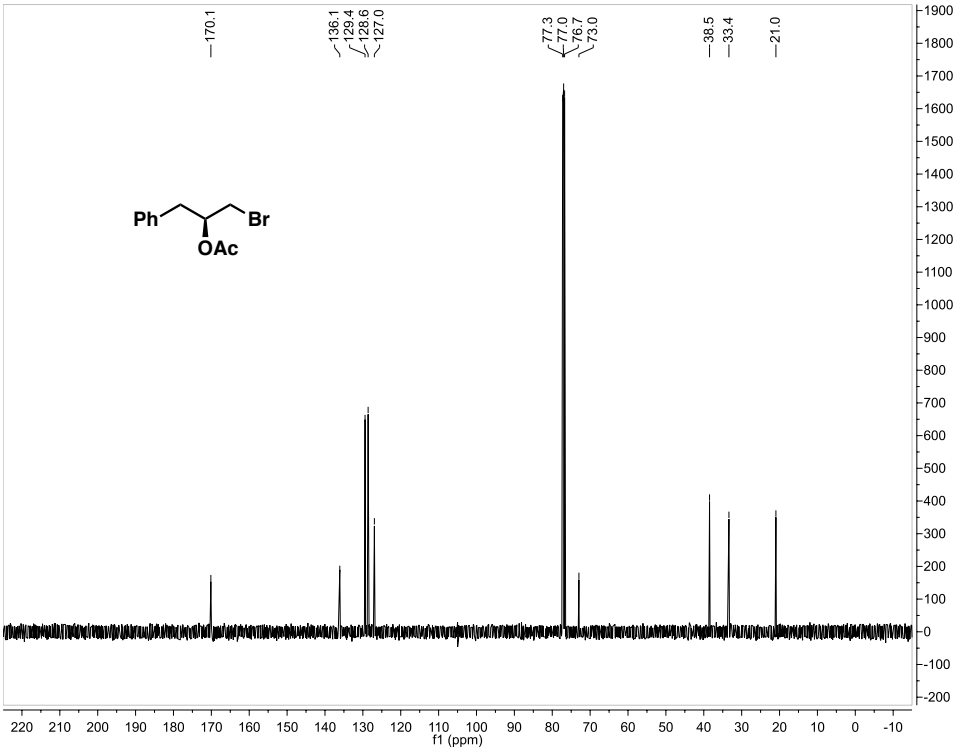


^{1}H NMR for Compound 2.3a

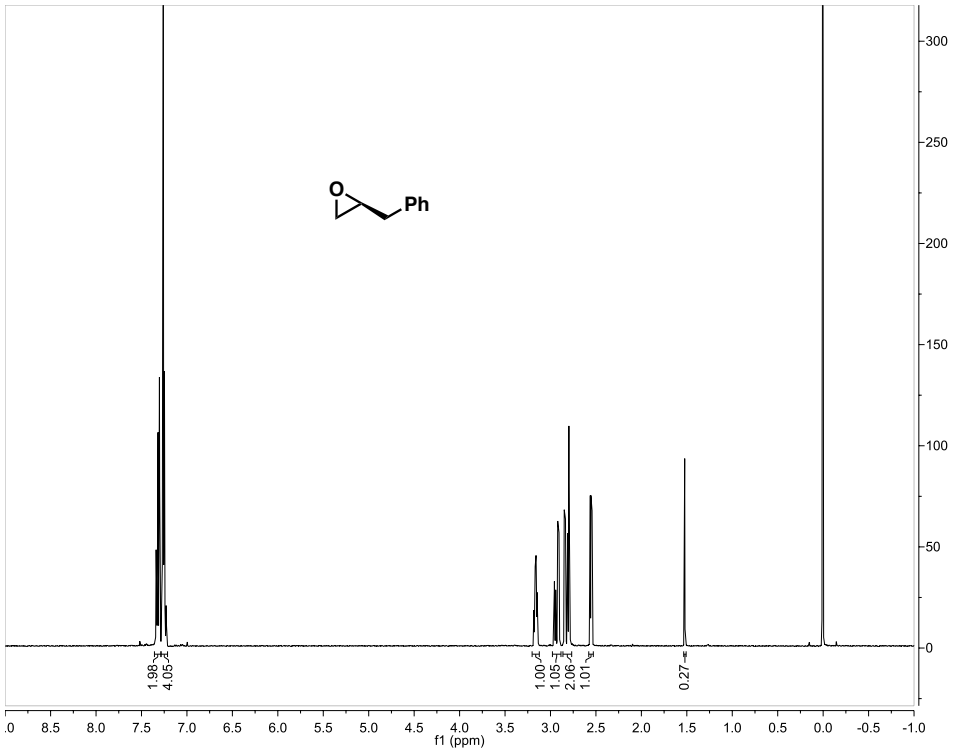


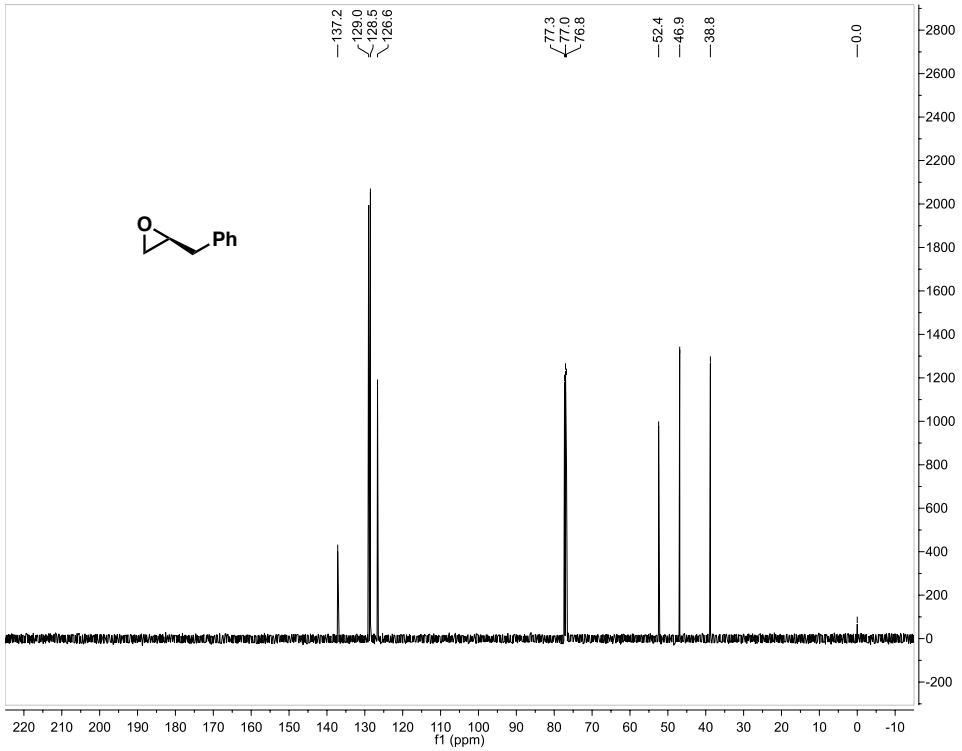
^{1}H and ^{13}C NMR for Compound 2.3



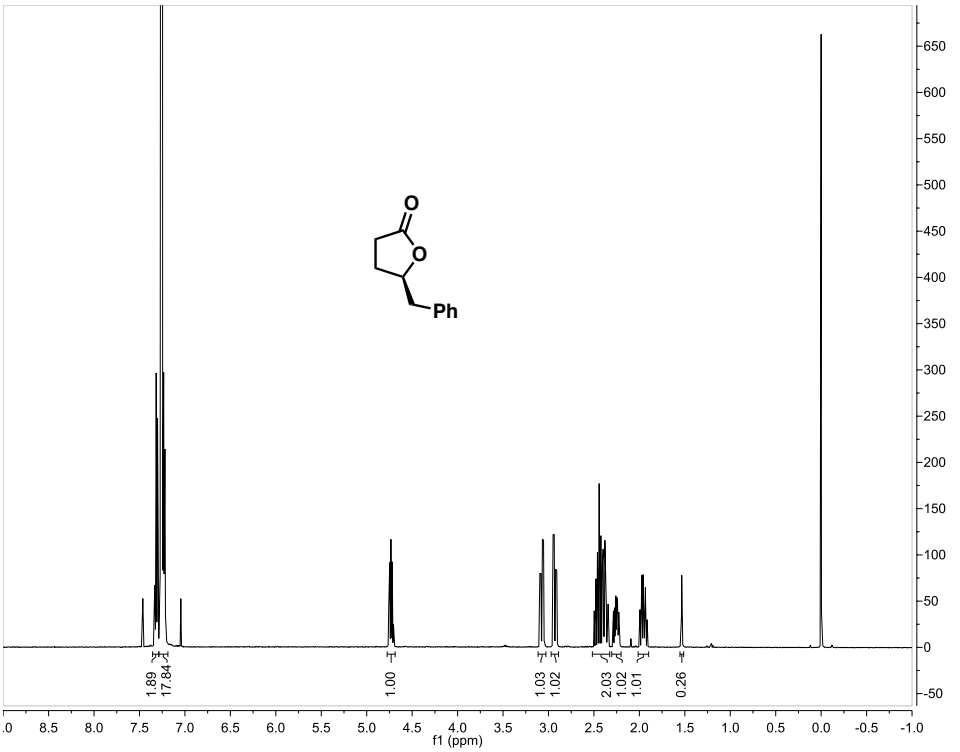


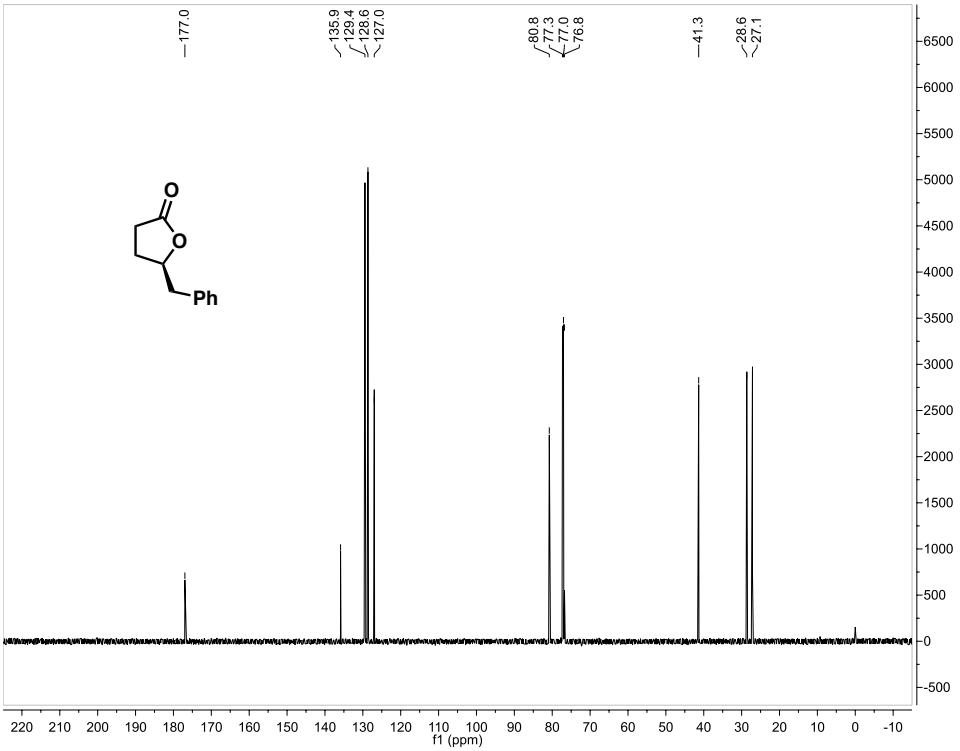
^{1}H and ^{13}C NMR for Compound 2.4



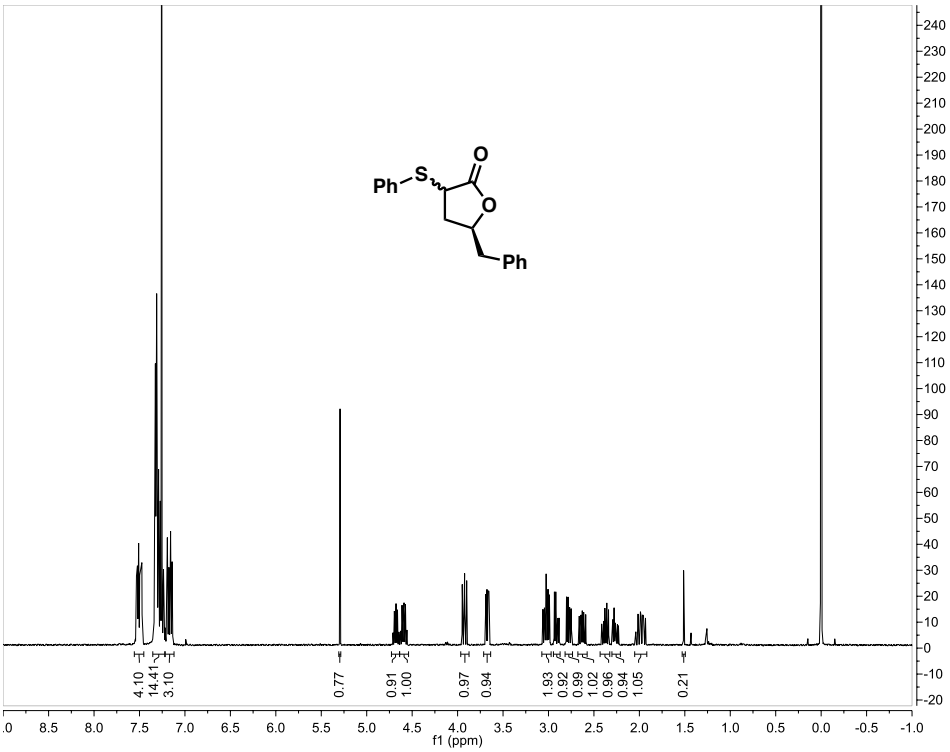


^{1}H and ^{13}C NMR for Compound 2.5

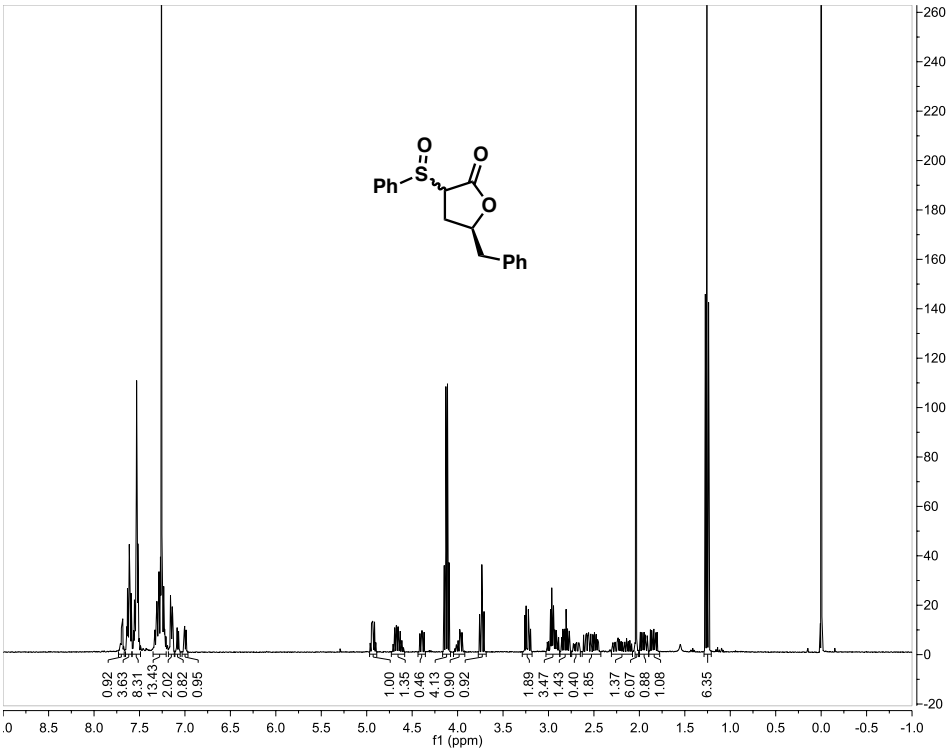




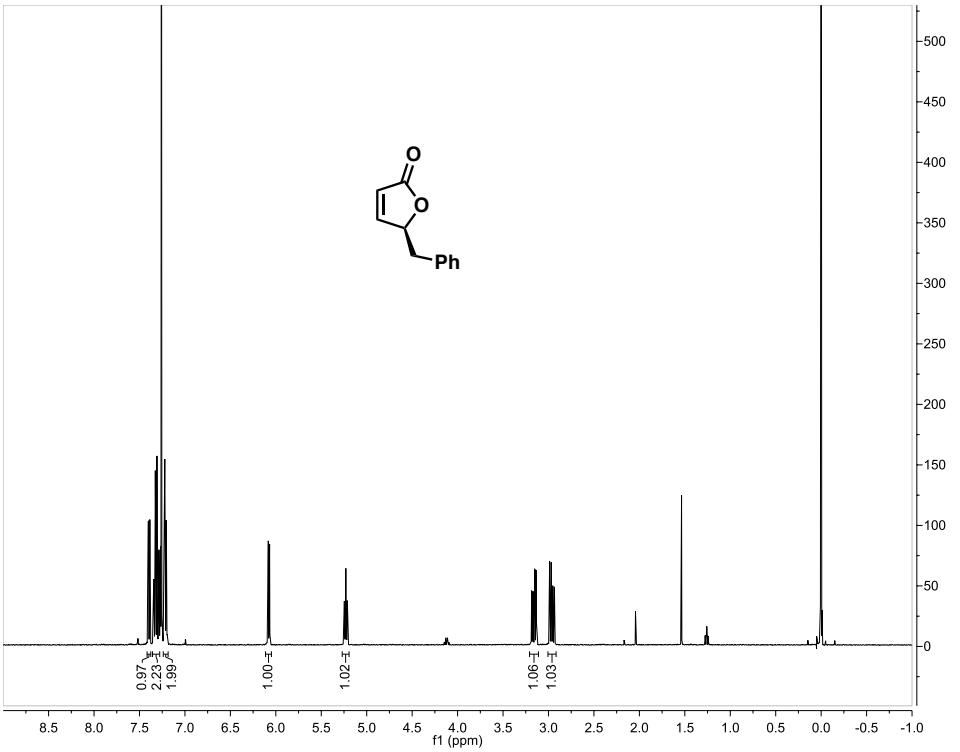
^{1}H NMR for Compound 2.6

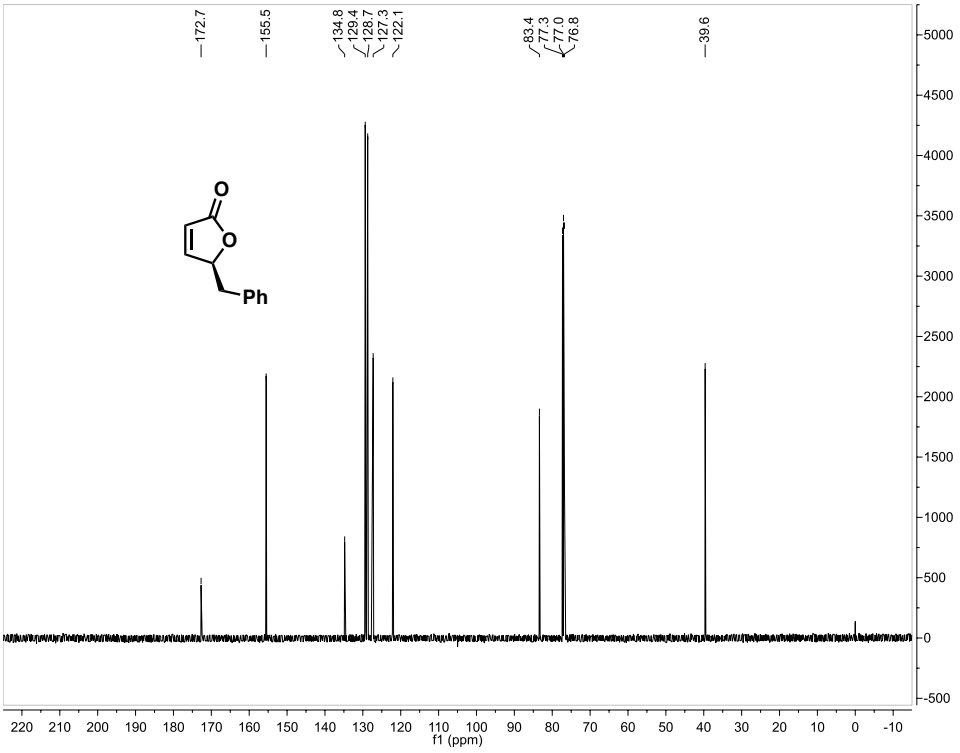


^{1}H NMR for Compound 2.7

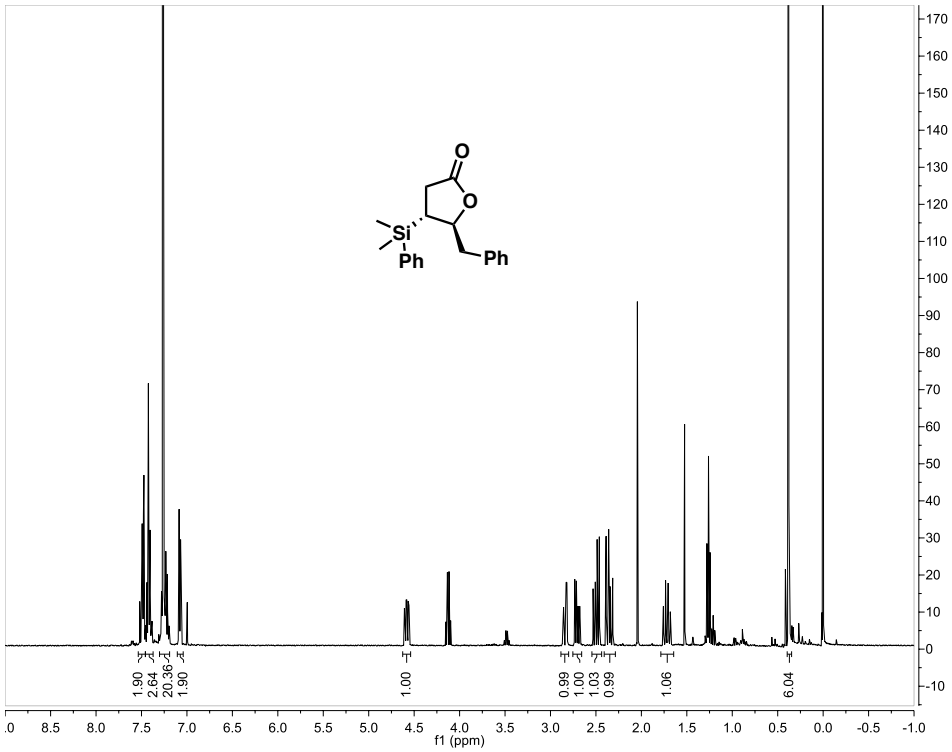


^{1}H and ^{13}C NMR for Compound 2.8

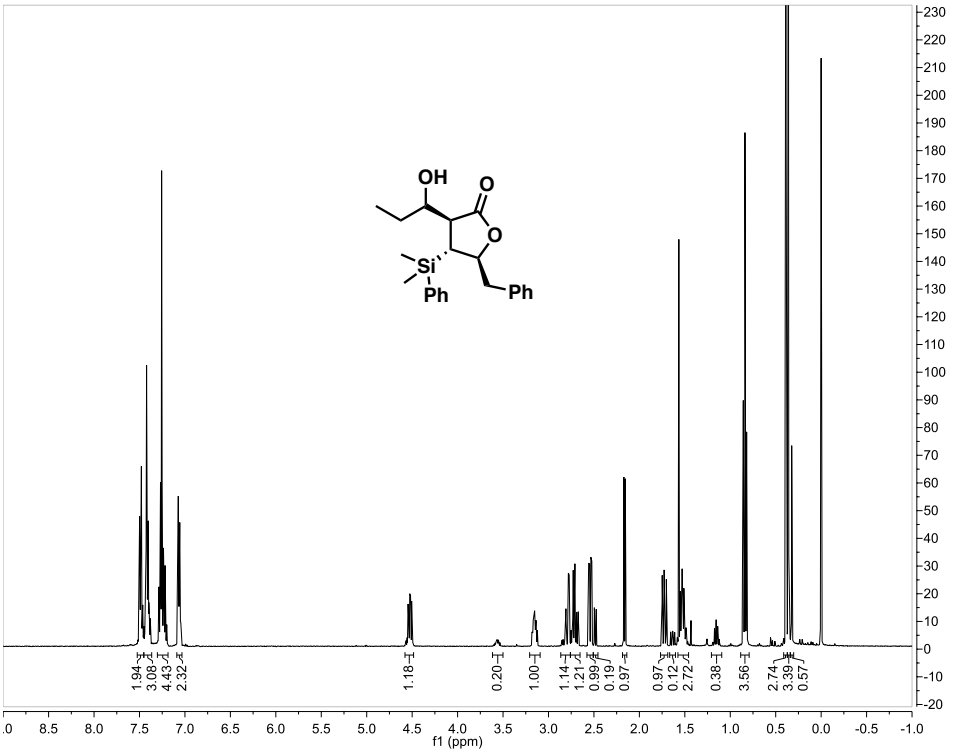


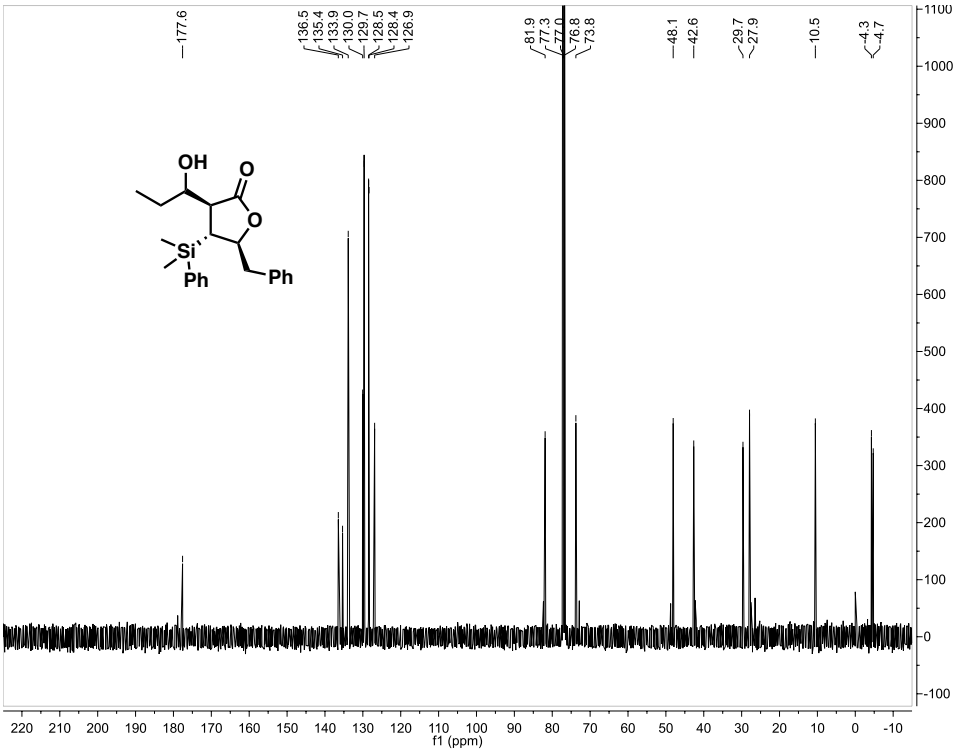


^{1}H NMR for Compound 2.9

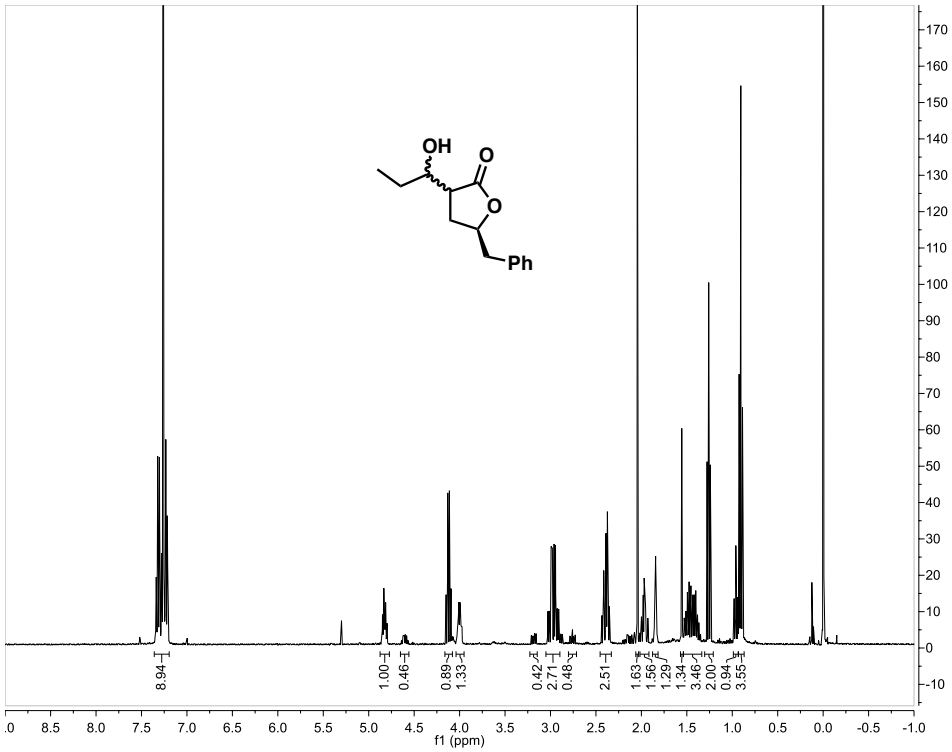


^{1}H and ^{13}C NMR for Compound 2.10

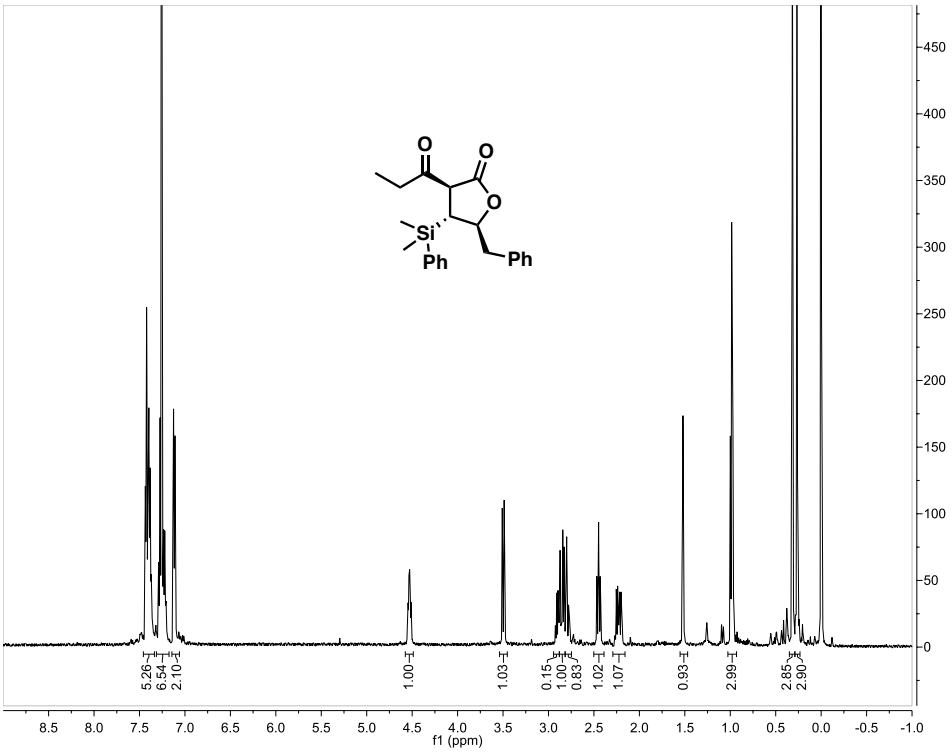




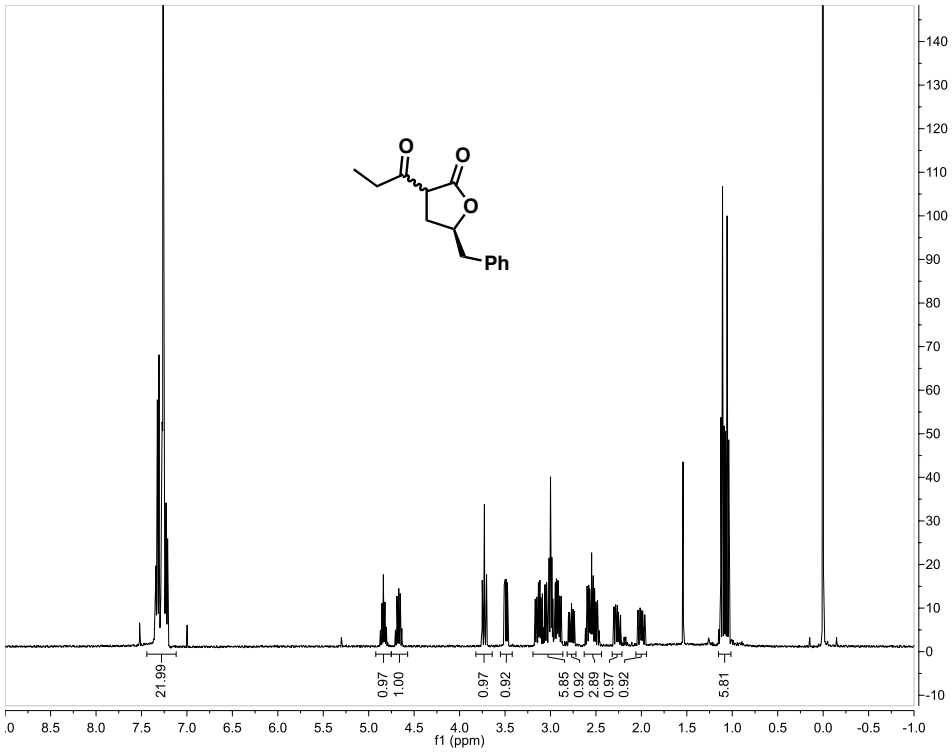
^{1}H NMR for Compound 2.10a



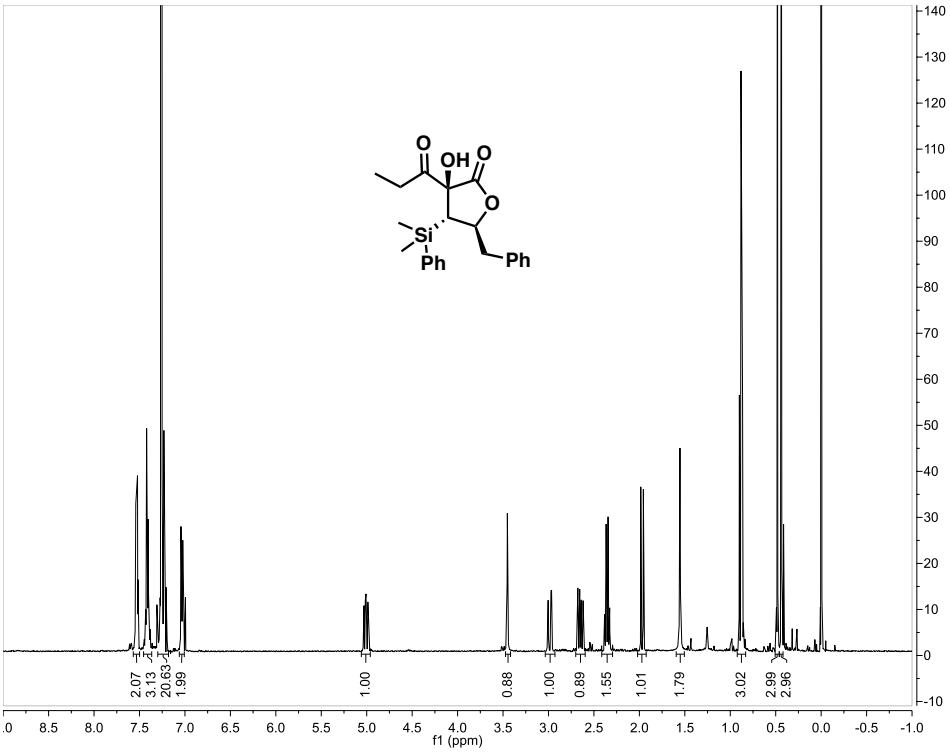
^{1}H NMR for Compound 2.11

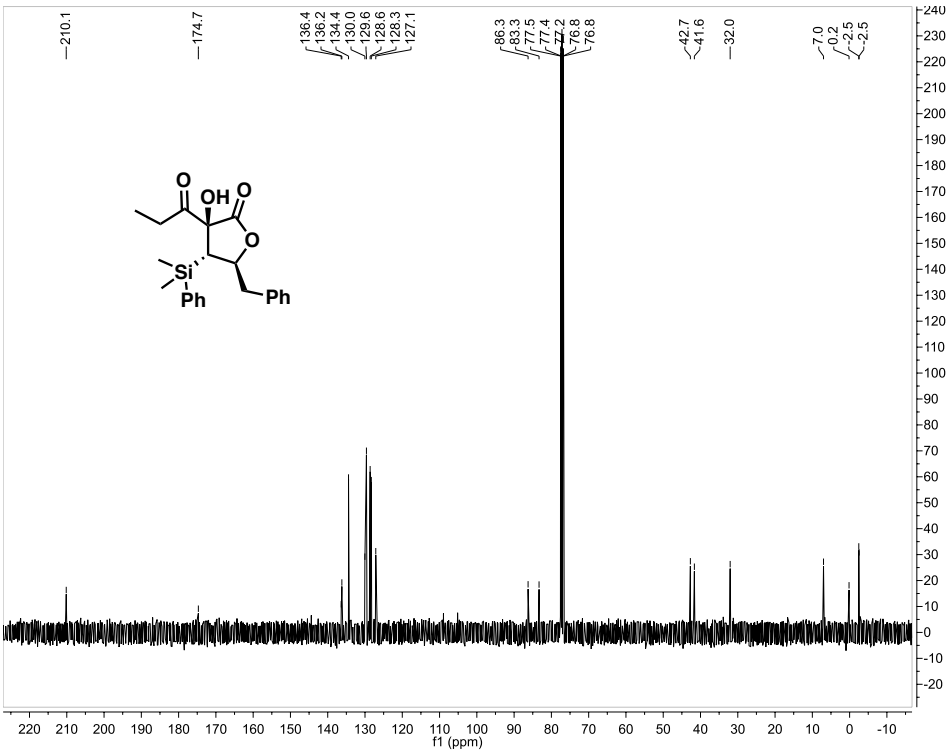


^{1}H NMR for Compound 2.11a

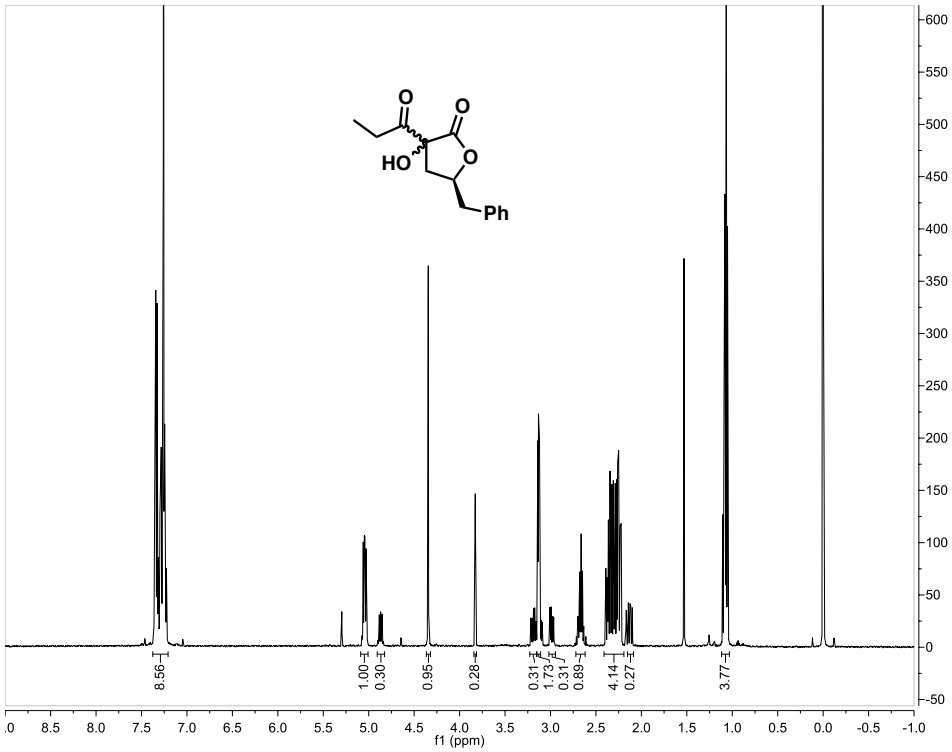


^{1}H and ^{13}C NMR for Compound 2.12

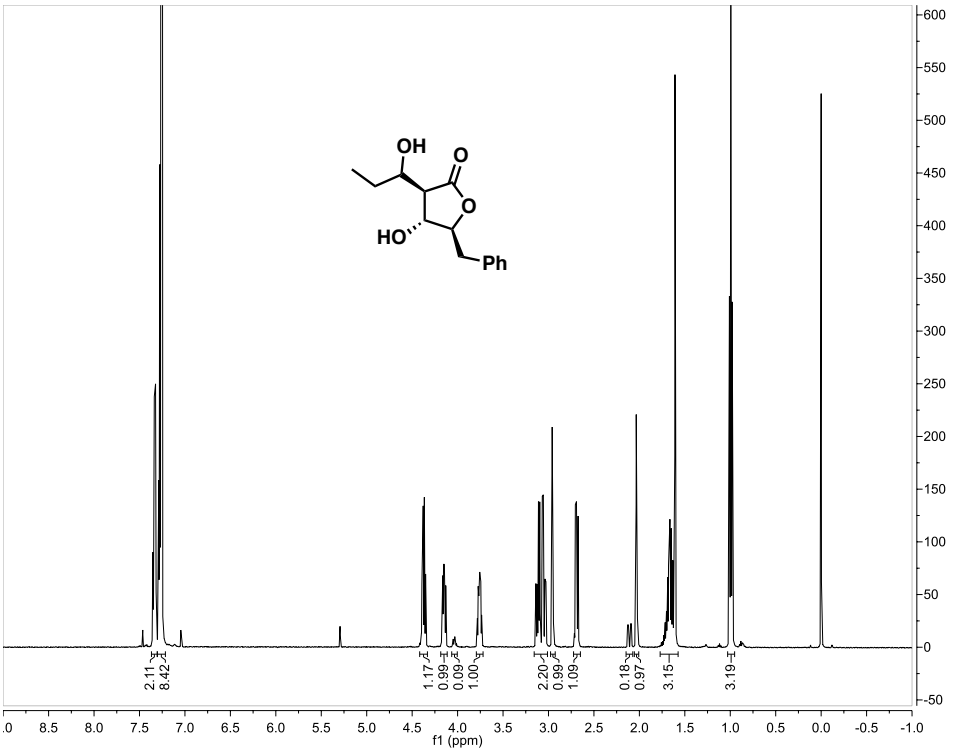


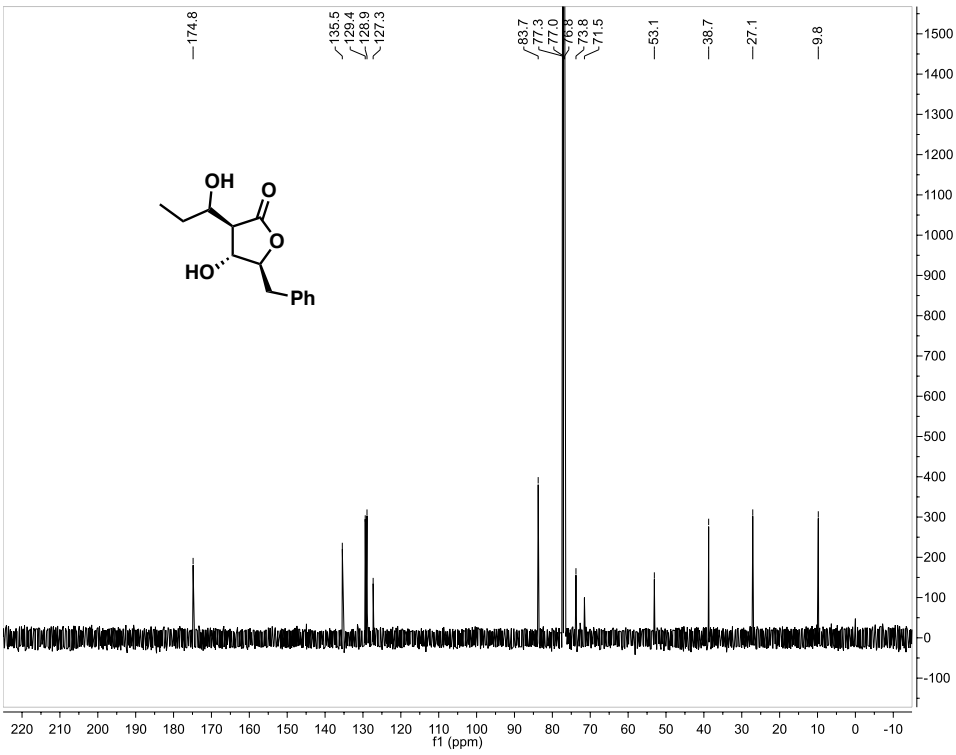


^{1}H NMR for Compound 2.12a

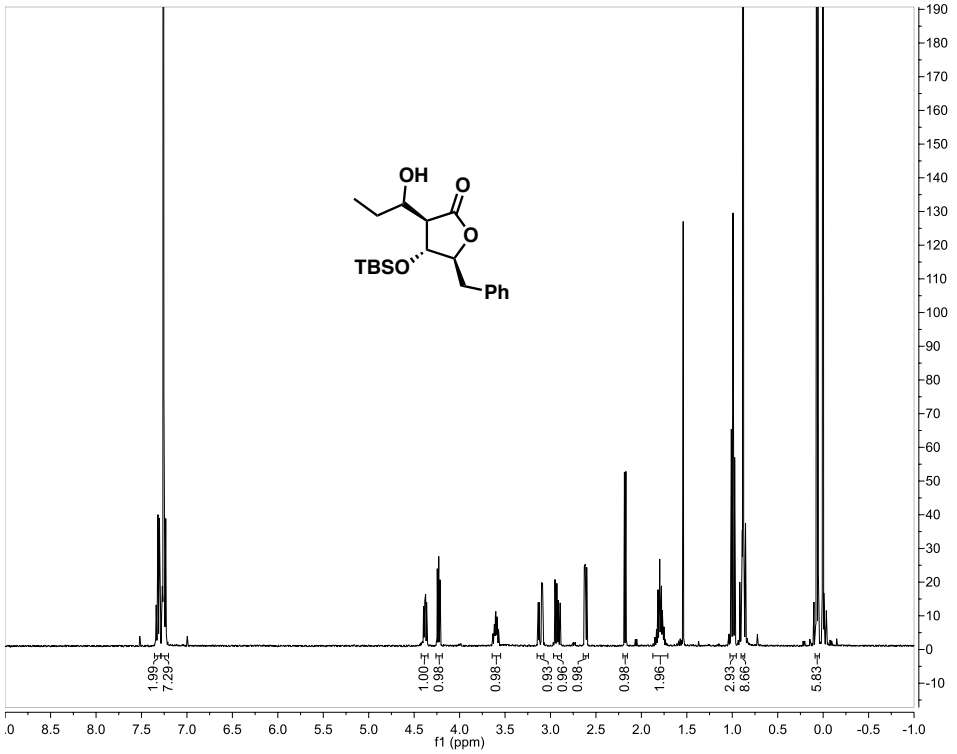


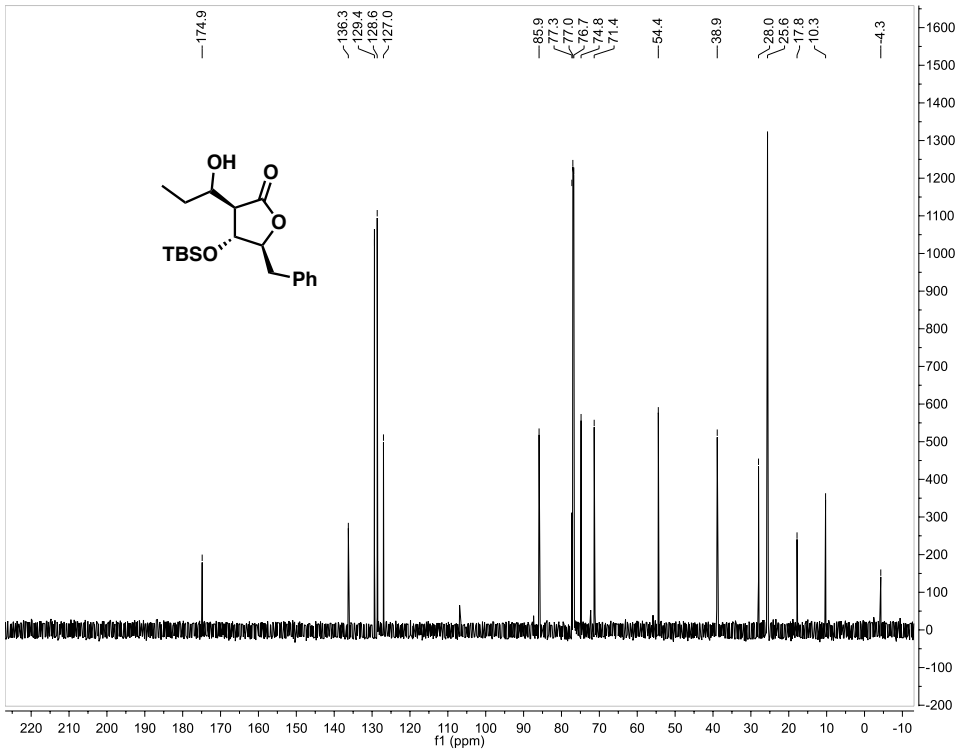
^{1}H and ^{13}C NMR for Compound 2.15



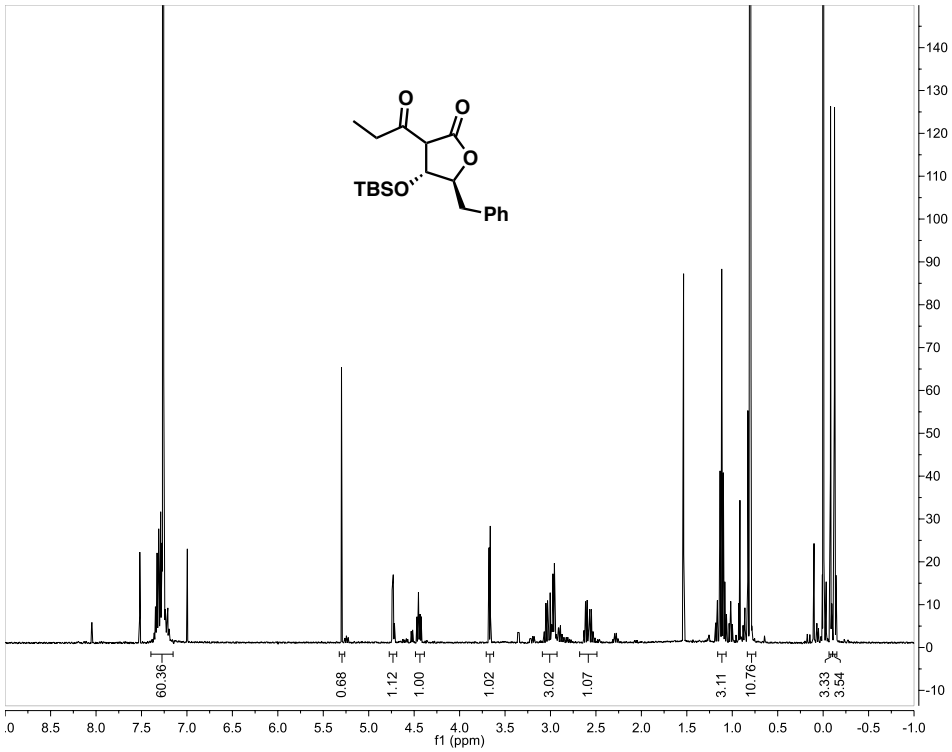


^{1}H and ^{13}C NMR for Compound 2.18

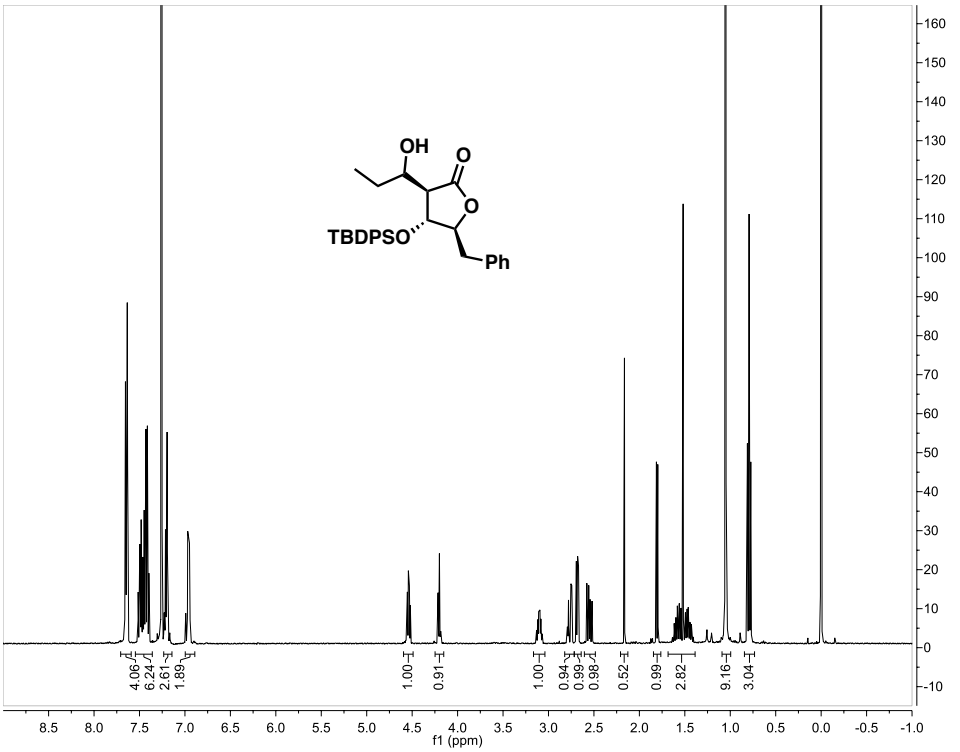


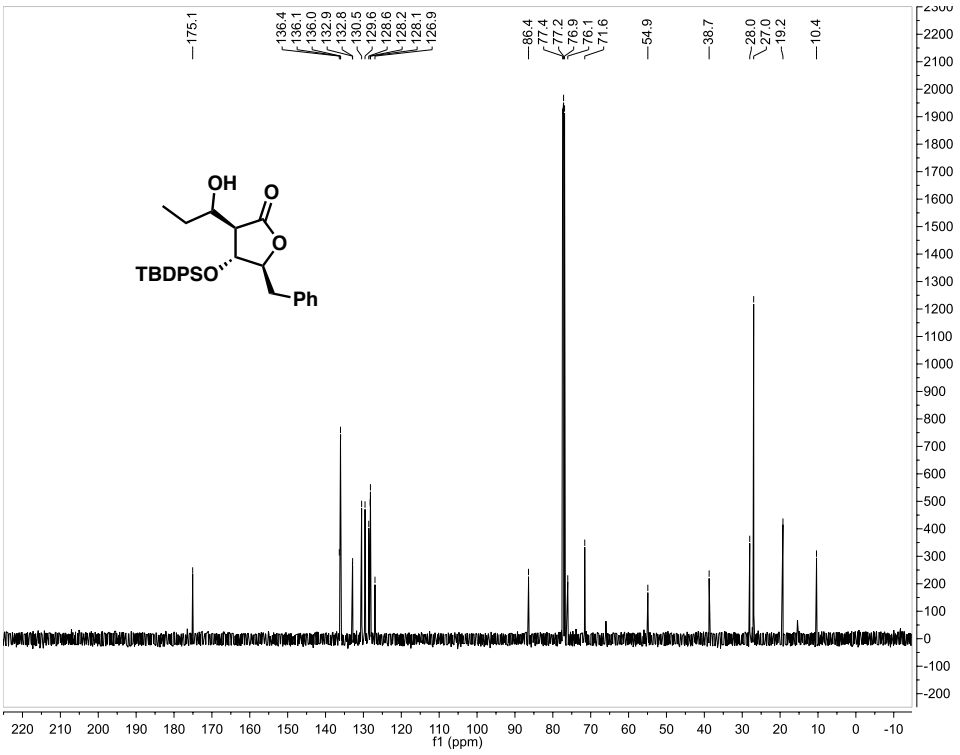


^{1}H NMR for Compound 2.19

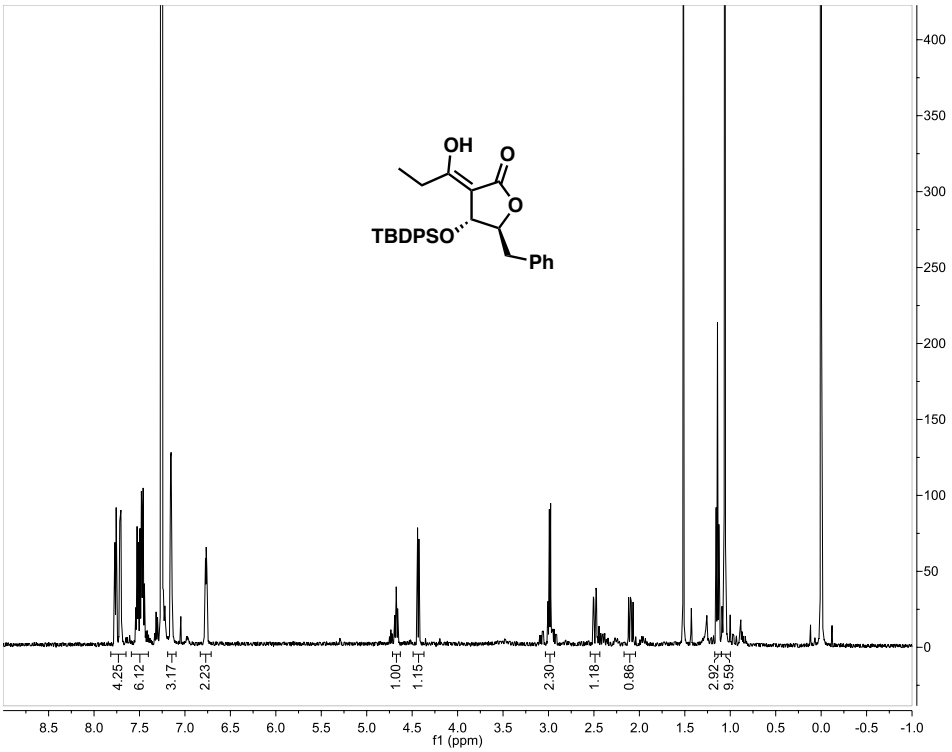


^{1}H and ^{13}C NMR for Compound 2.20

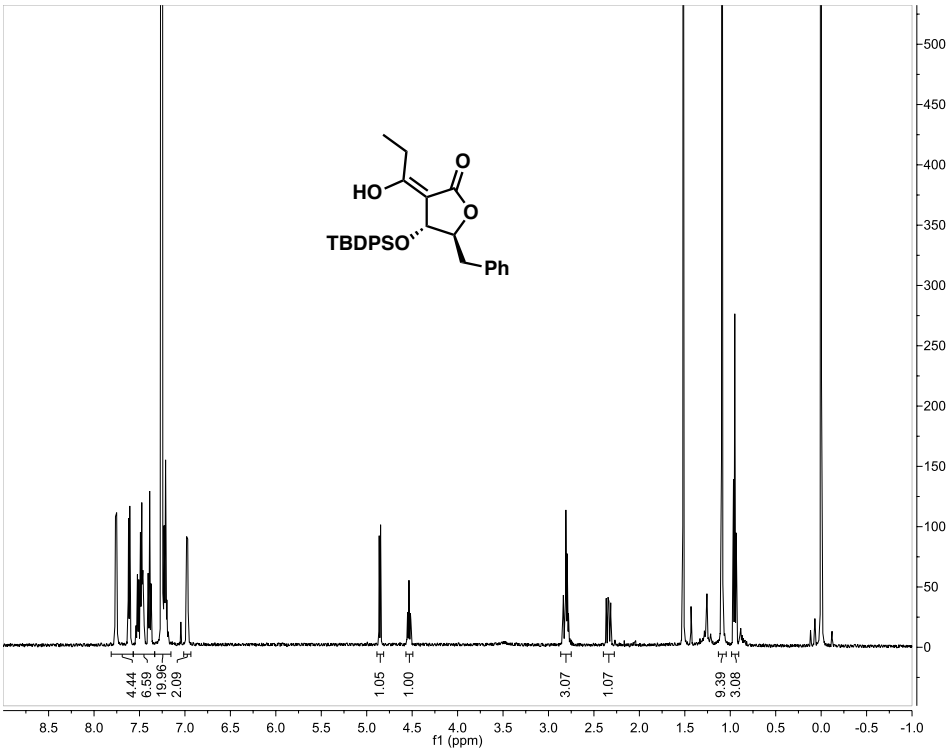




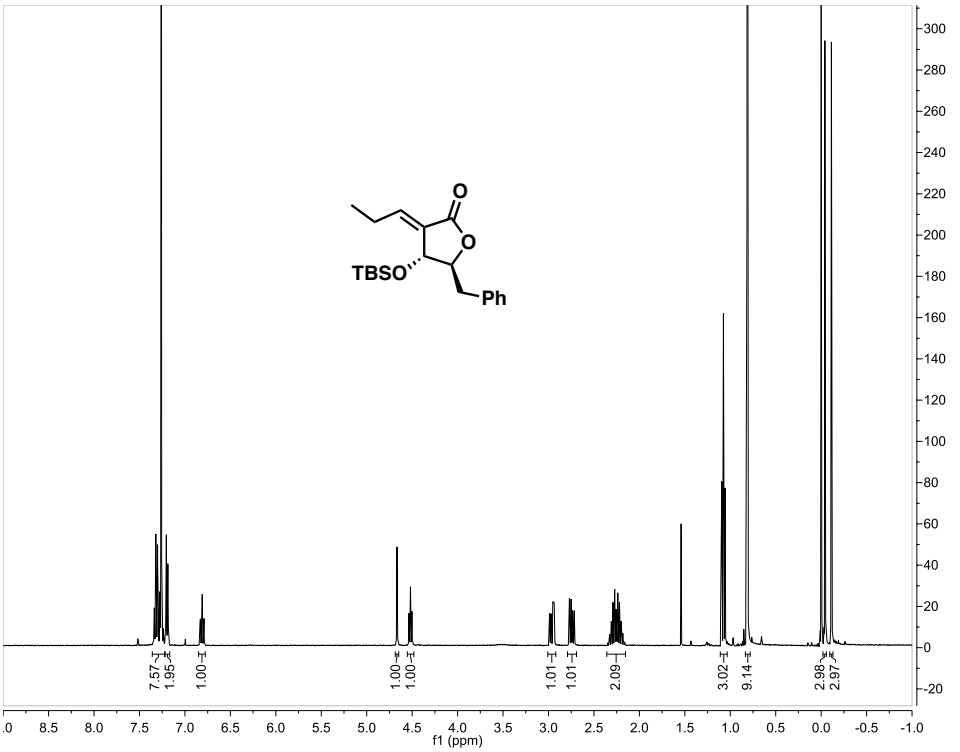
^{1}H NMR for Compound 2.21a

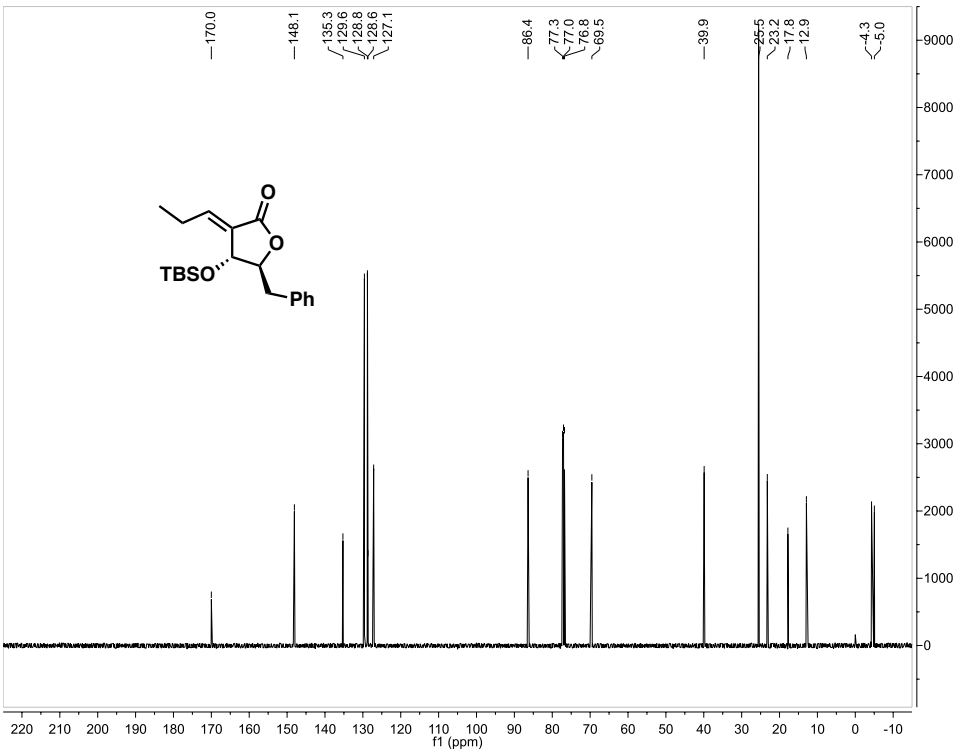


^{1}H NMR for Compound 2.21b



^{1}H and ^{13}C NMR for Compound 2.22a





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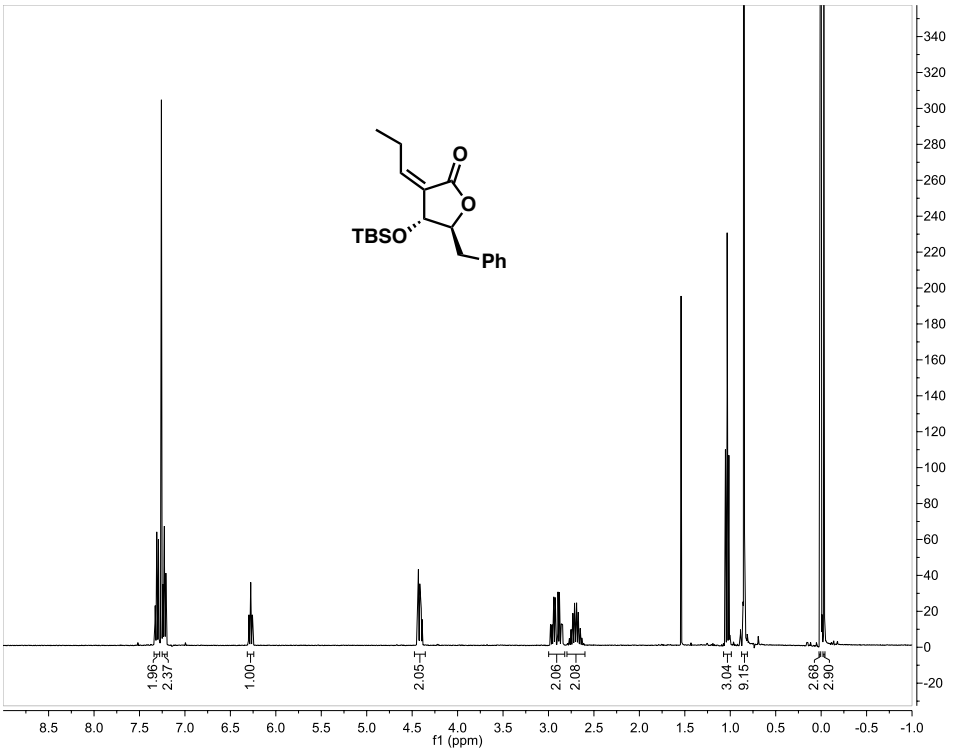
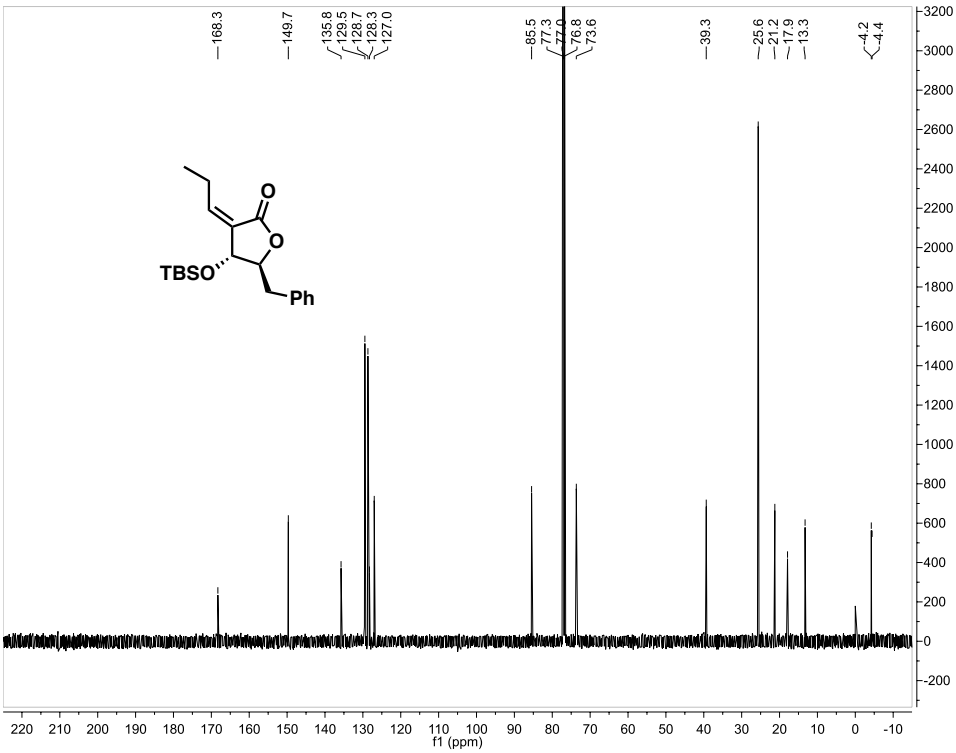
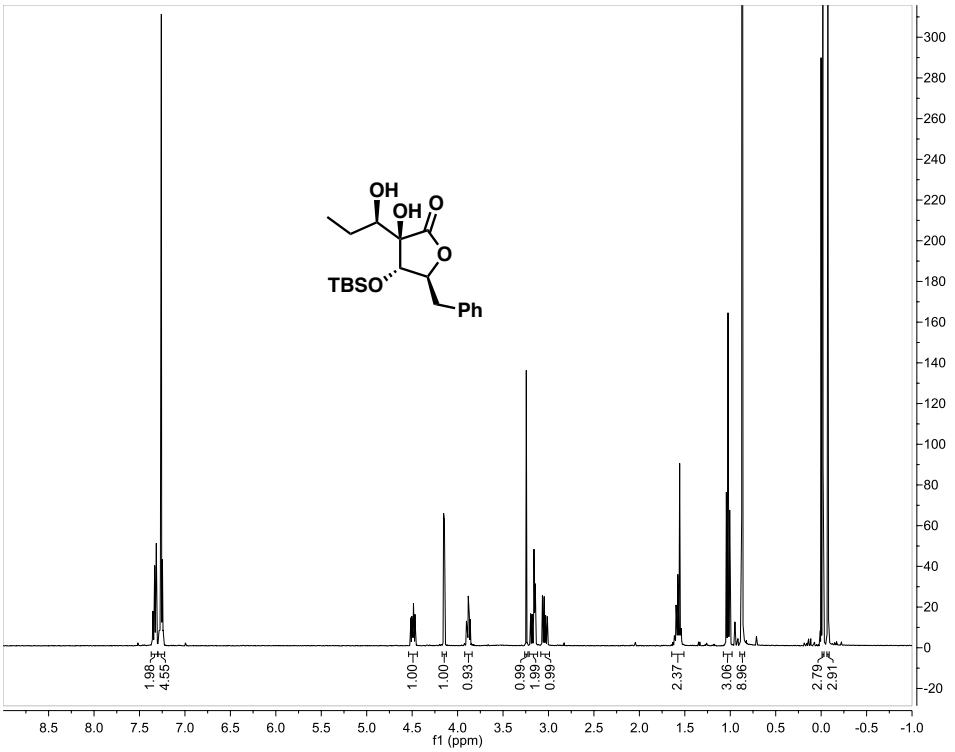
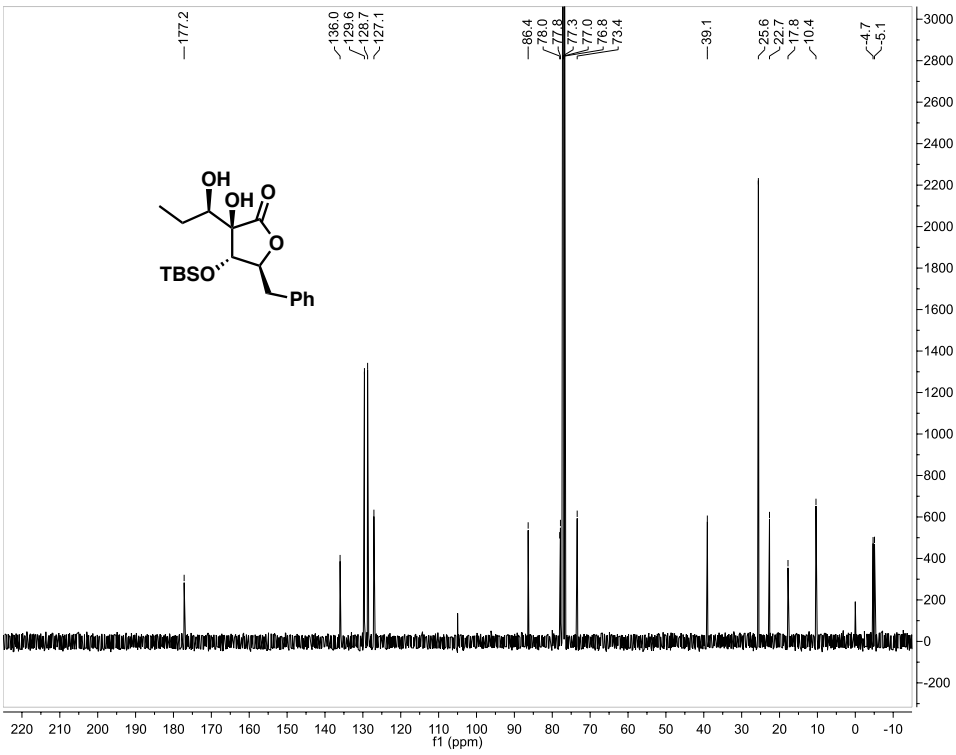




^{1}H and ^{13}C NMR for Compound 2.23a





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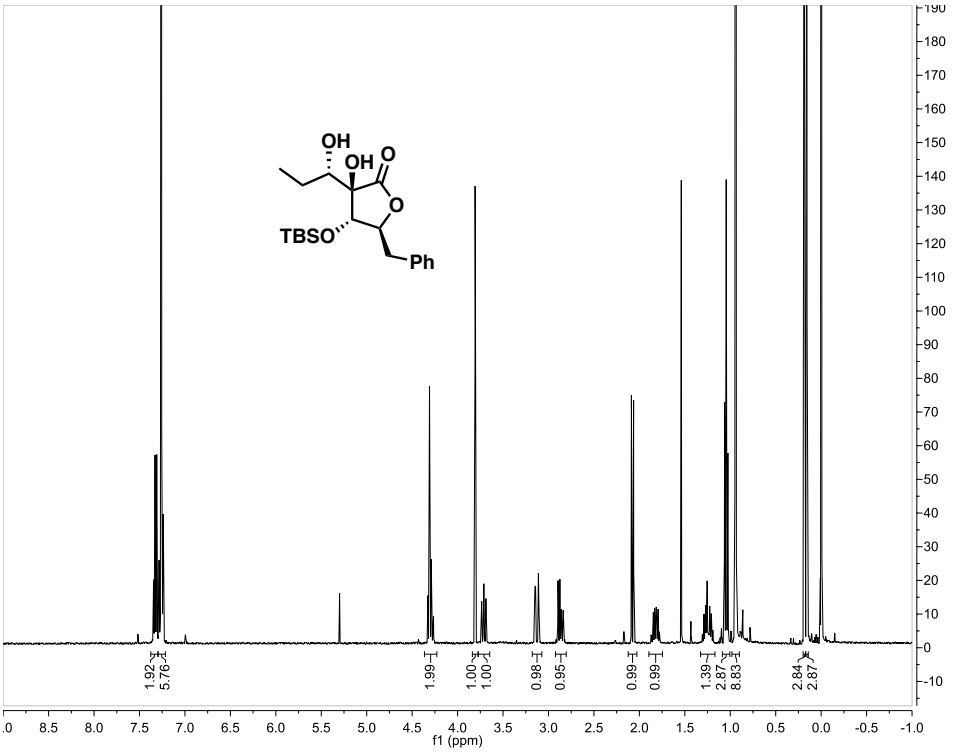
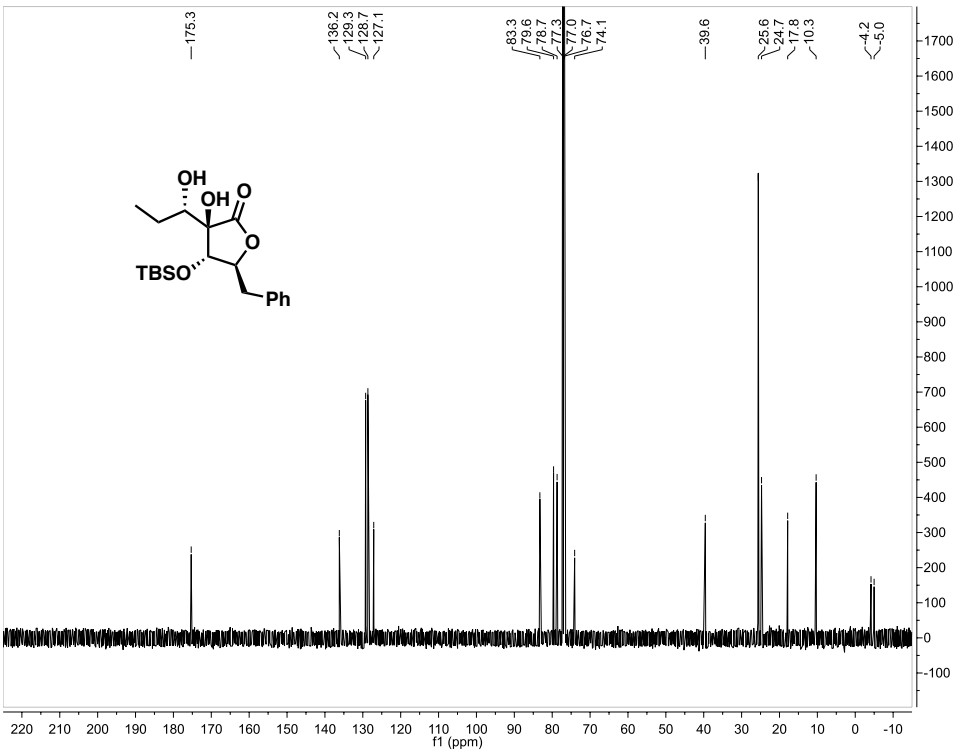
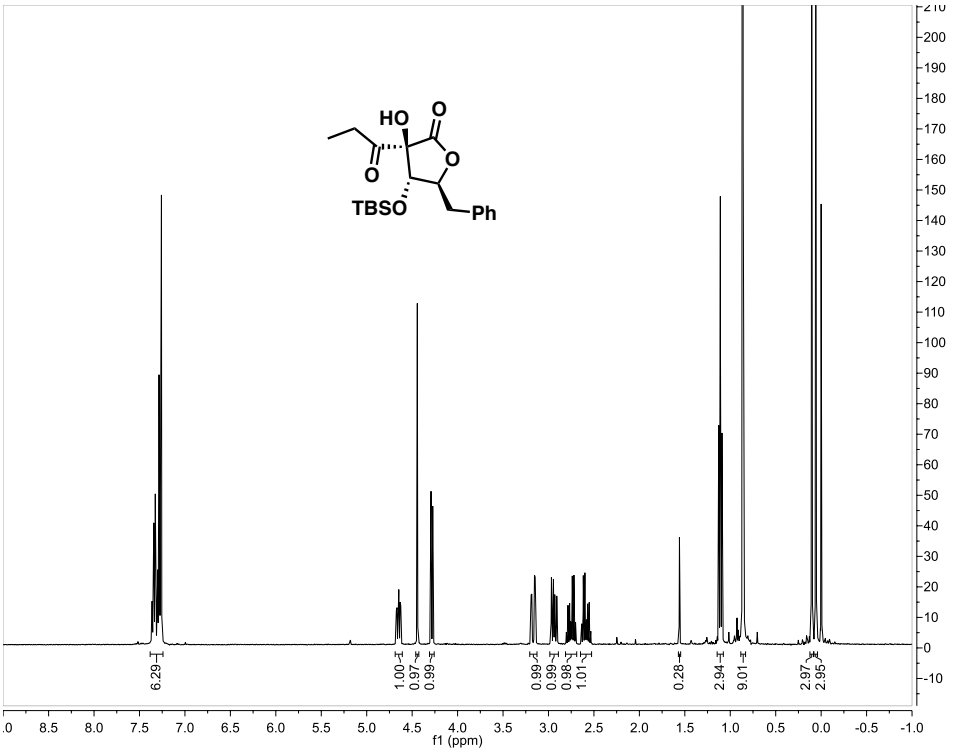
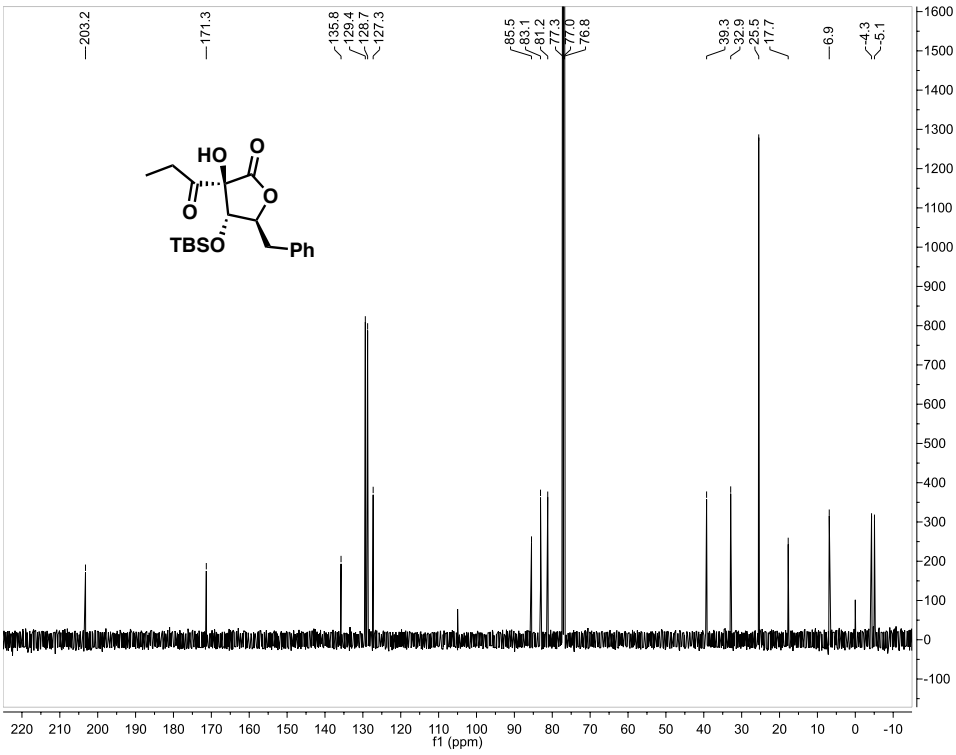


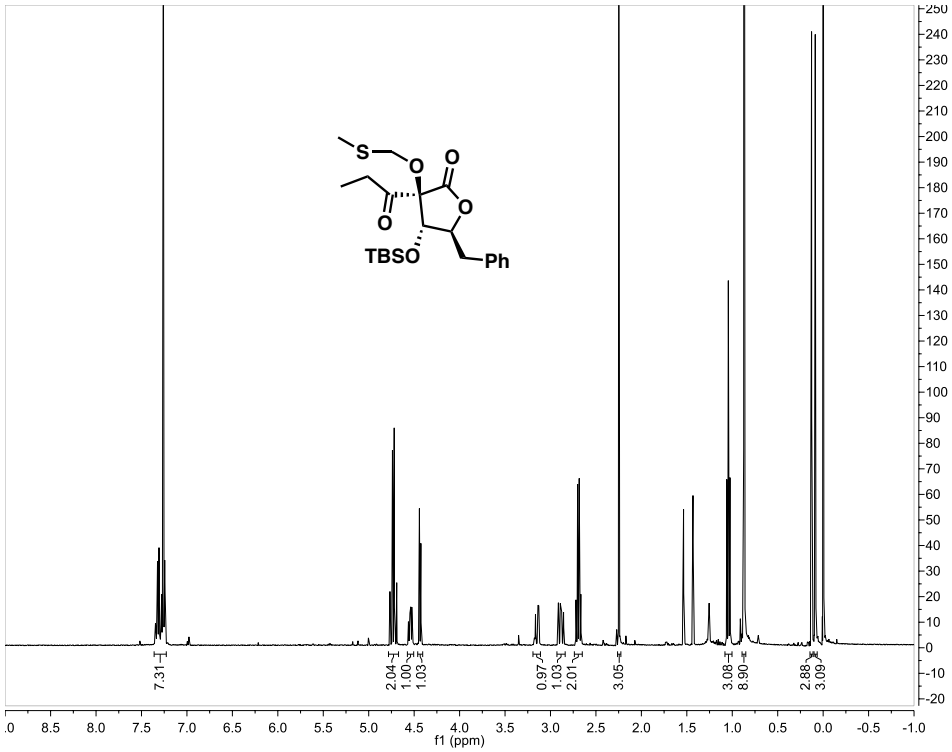


^{1}H and ^{13}C NMR for Compound 2.24

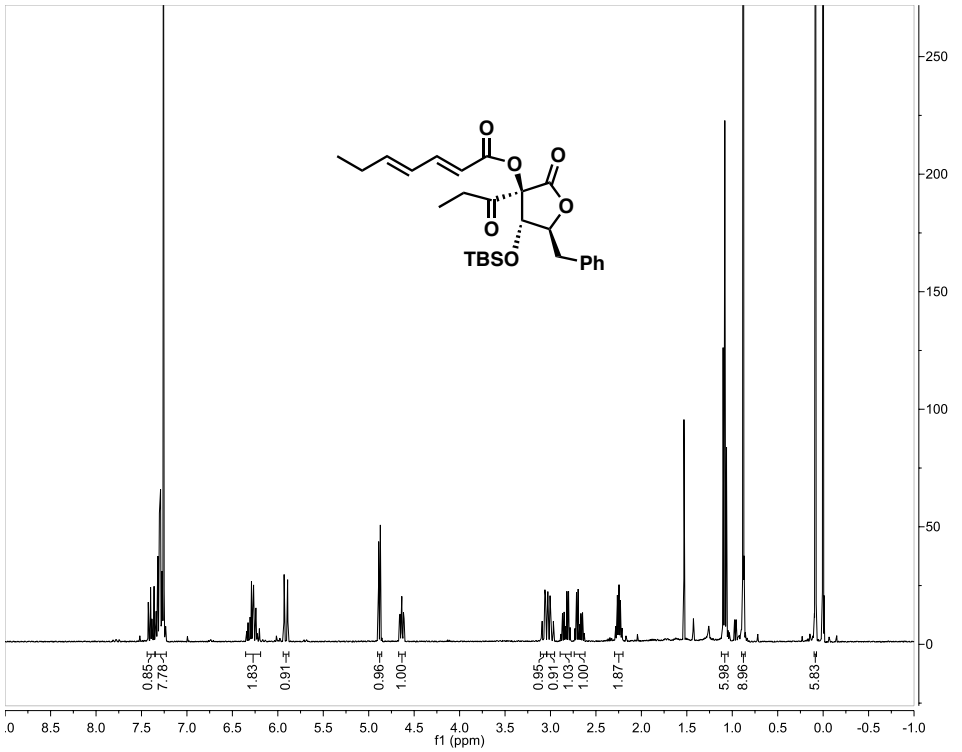


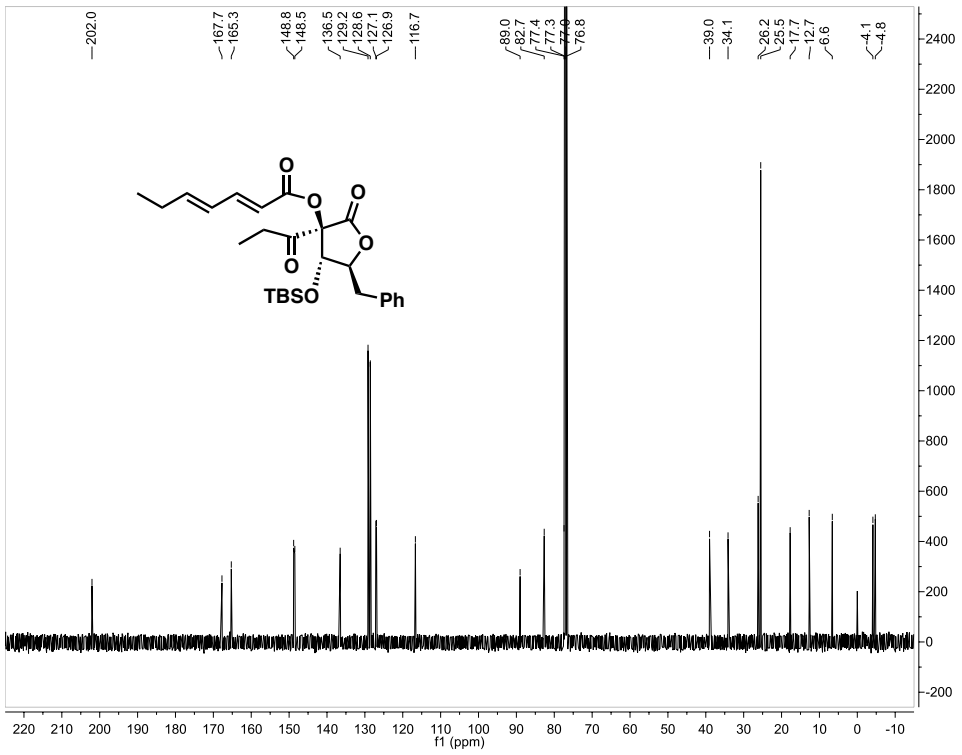


^{1}H NMR for Compound 2.25

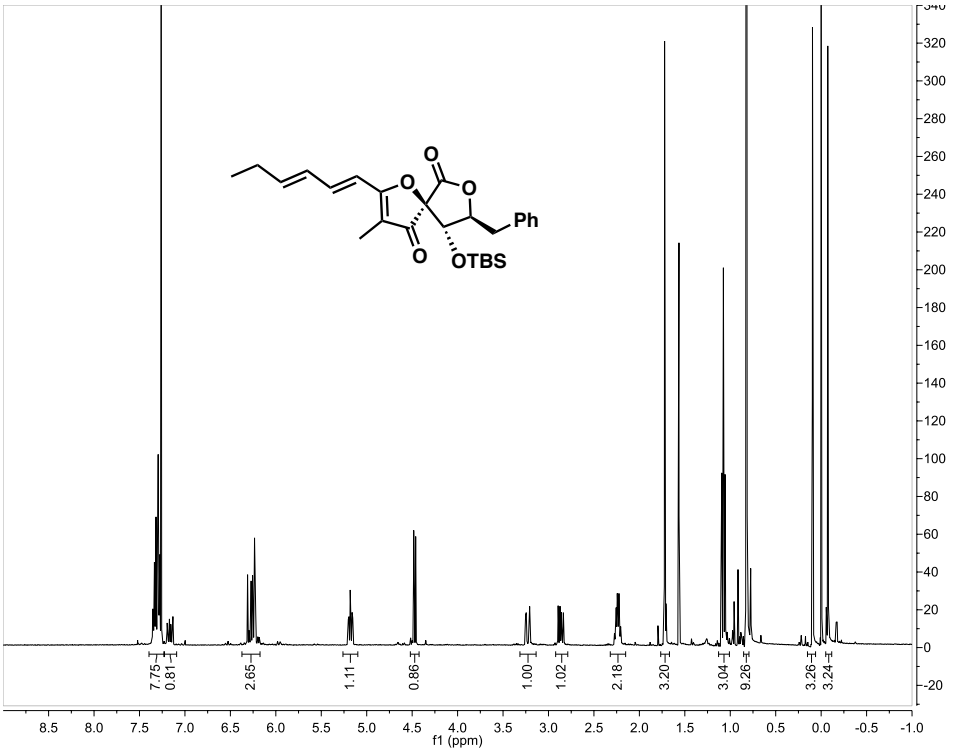


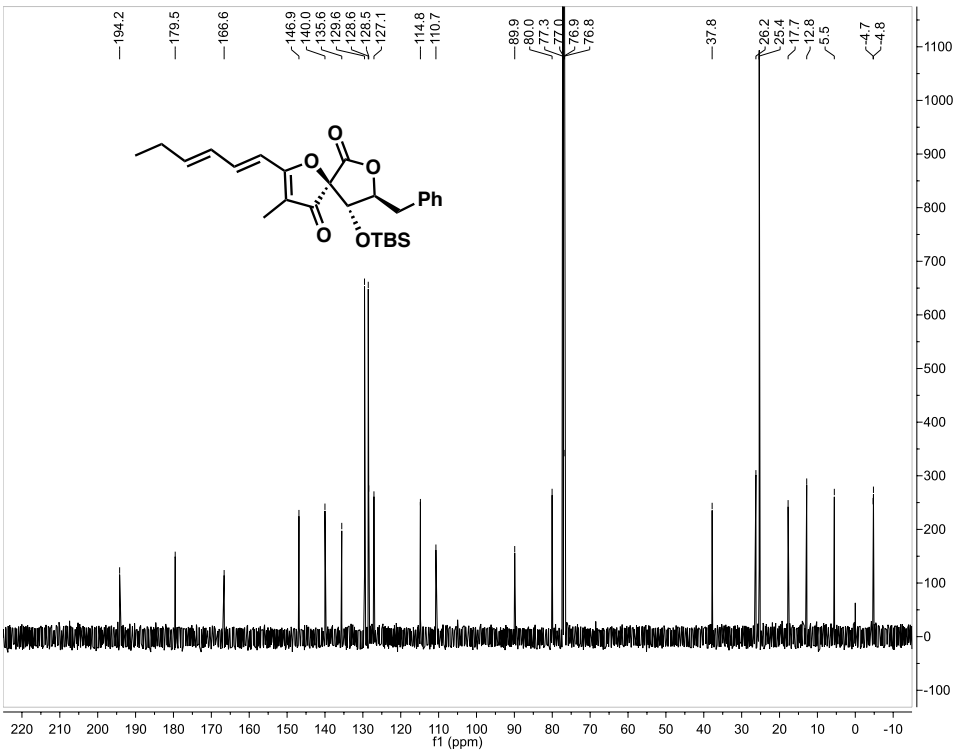
^{1}H and ^{13}C NMR for Compound 2.26



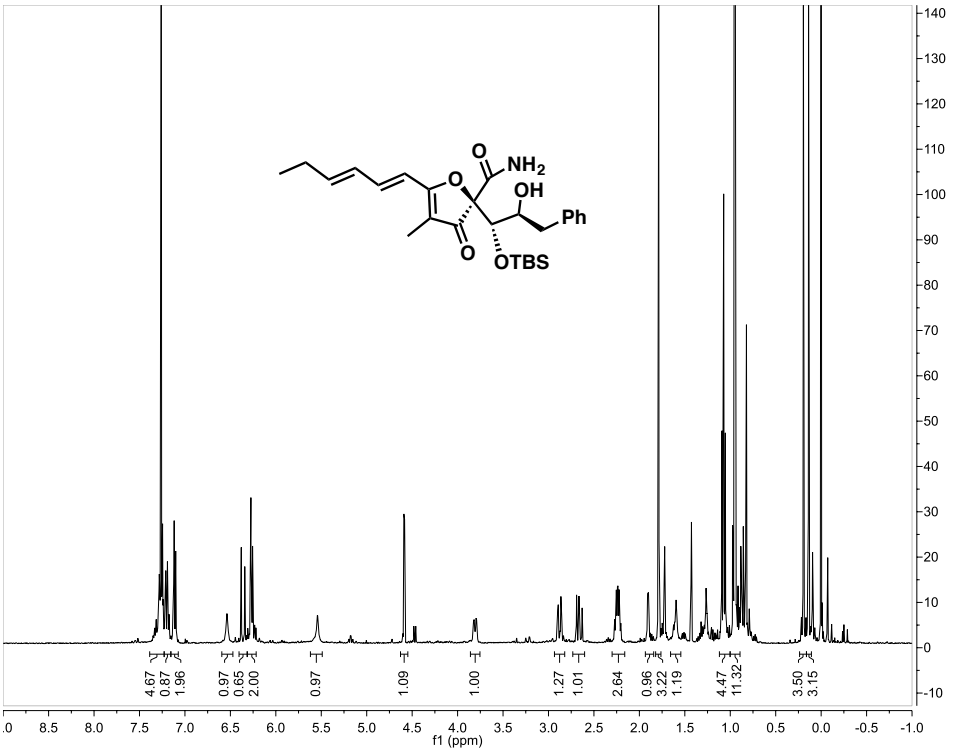


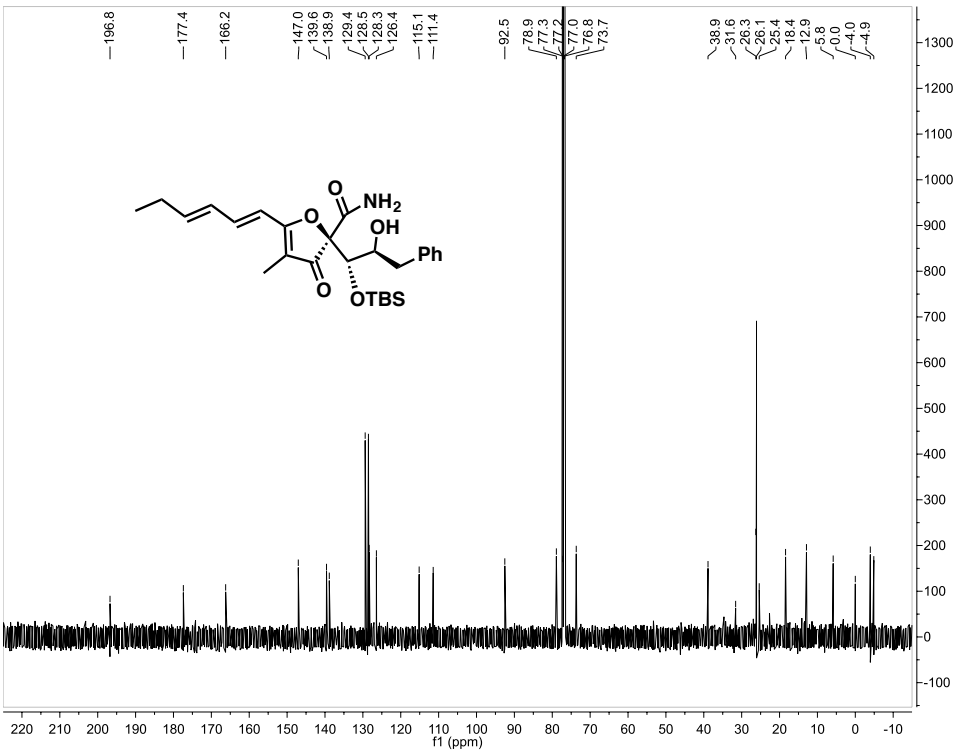
^{1}H and ^{13}C NMR for Compound 2.28



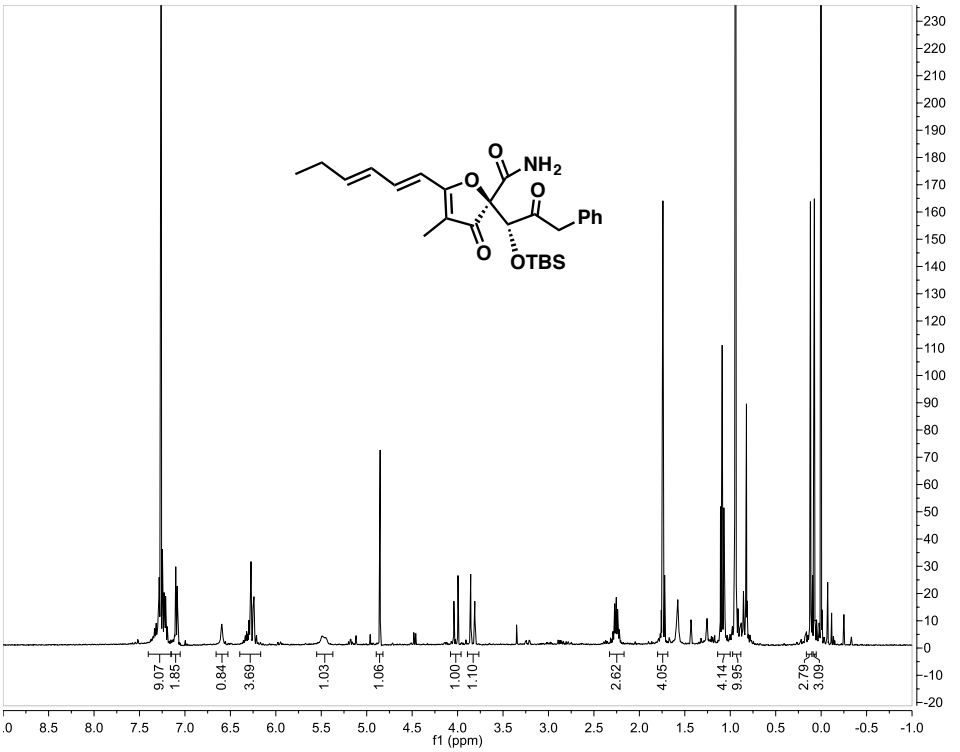


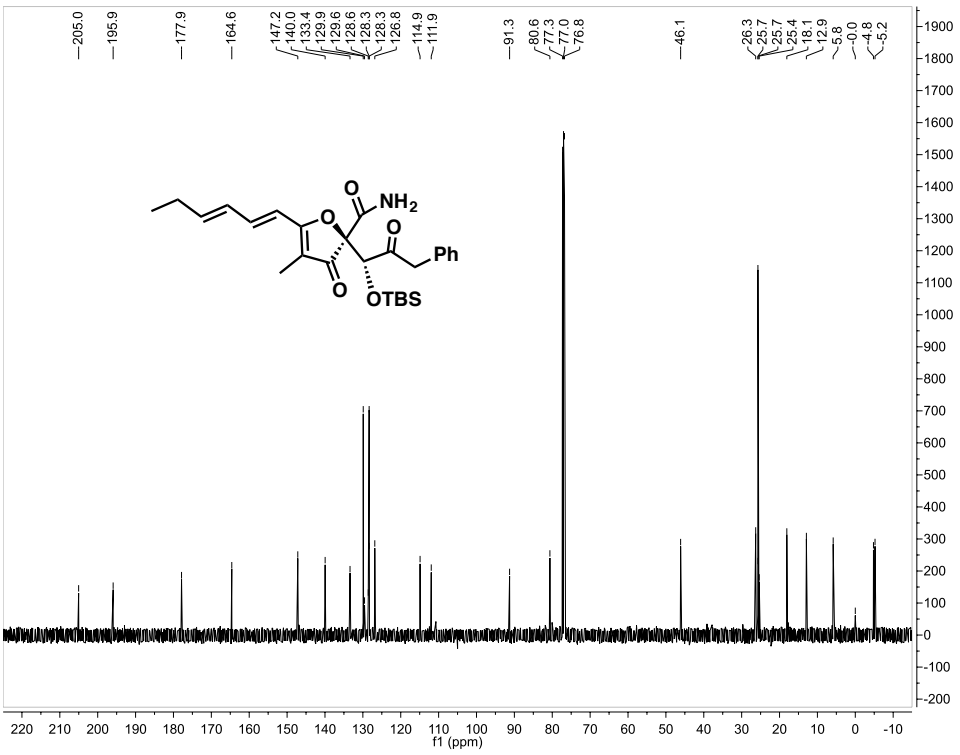
^{1}H and ^{13}C NMR for Compound 2.29



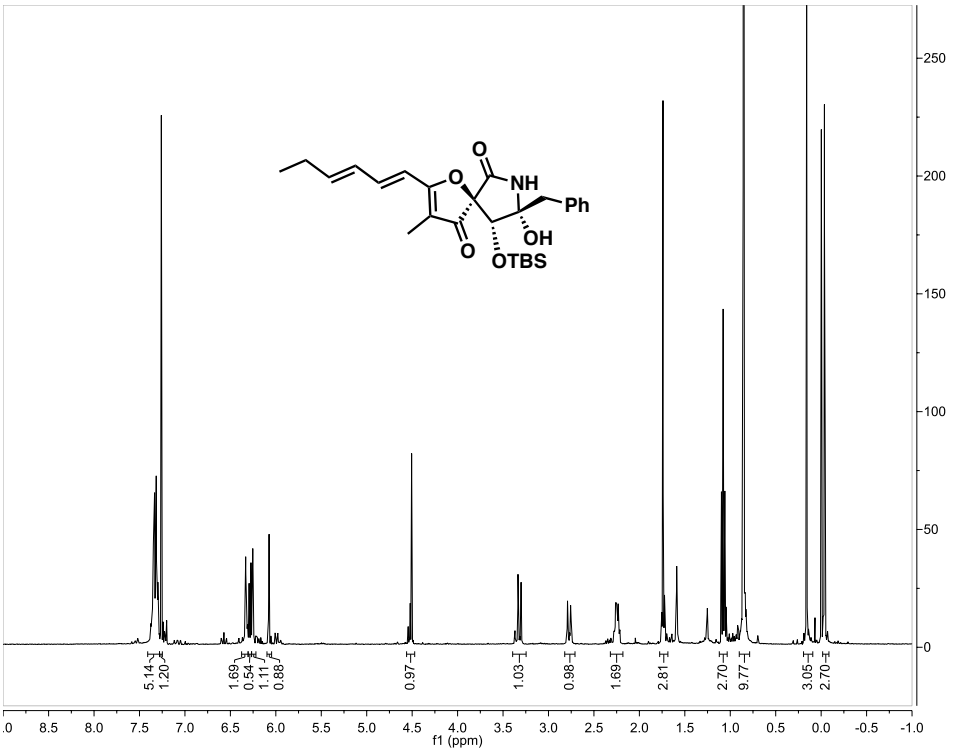


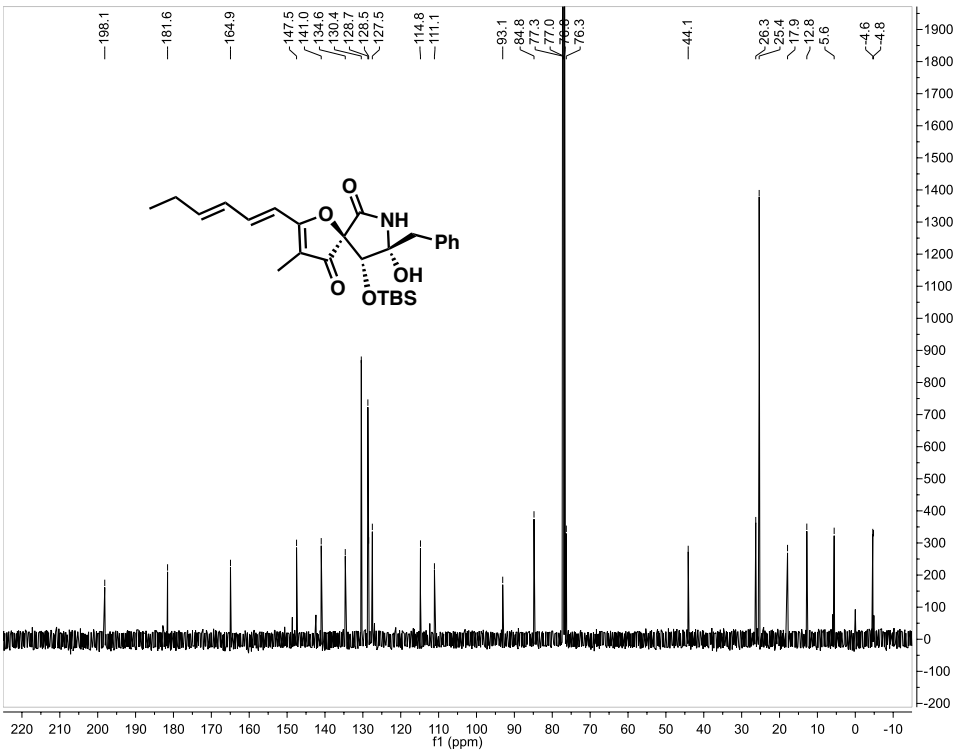
^{1}H and ^{13}C NMR for Compound 2.30



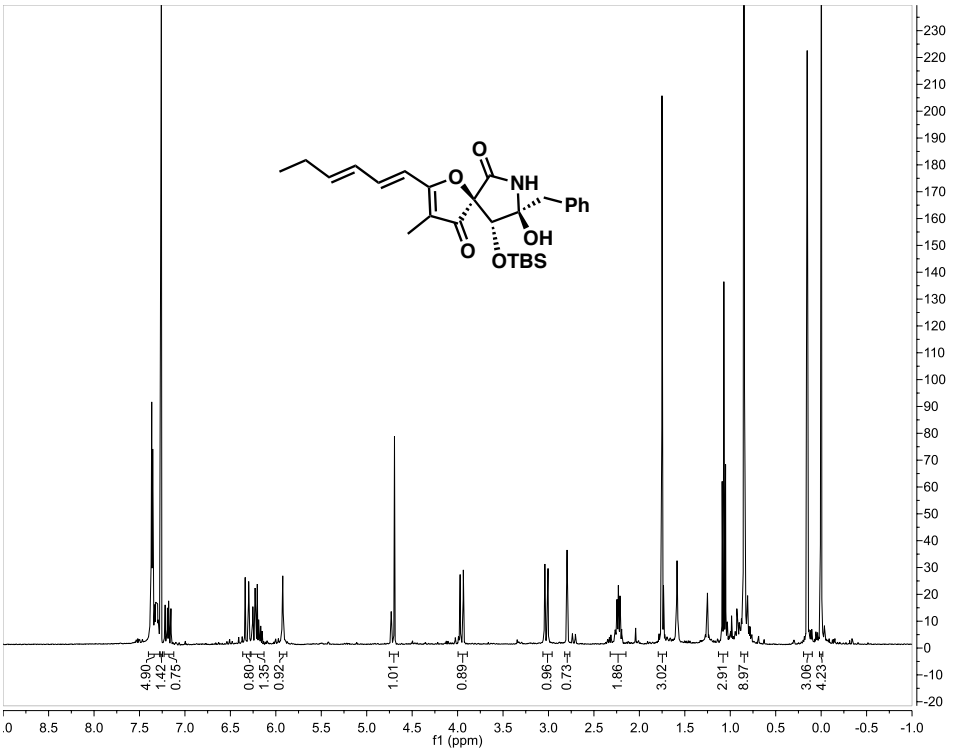


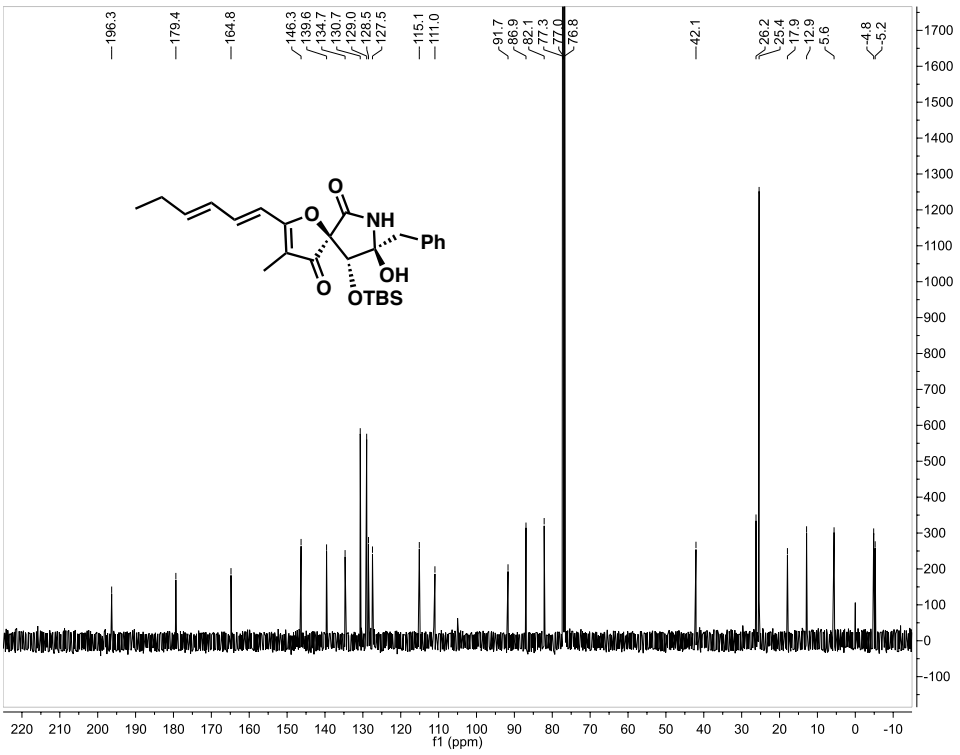
^{1}H and ^{13}C NMR for Compound 2.31a



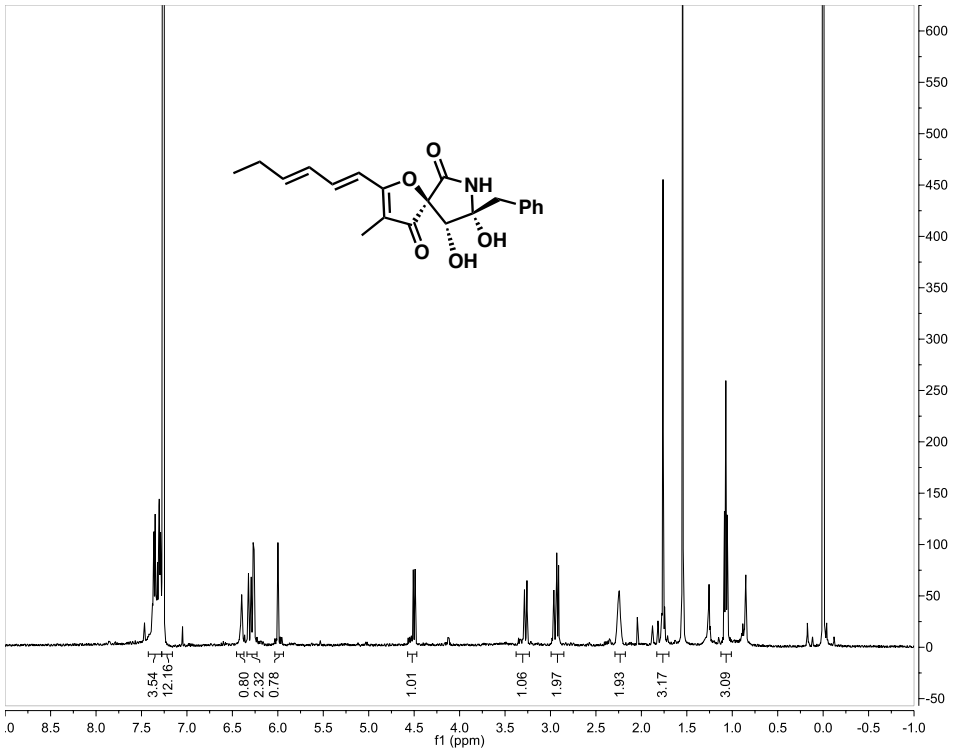


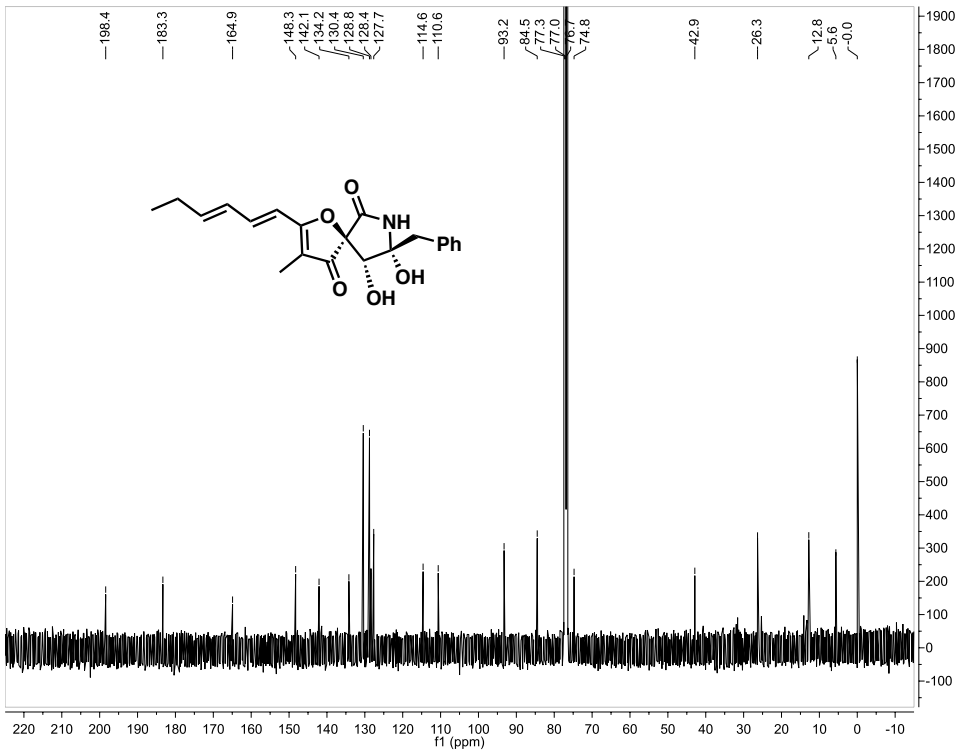
^{1}H and ^{13}C NMR for Compound 2.31b



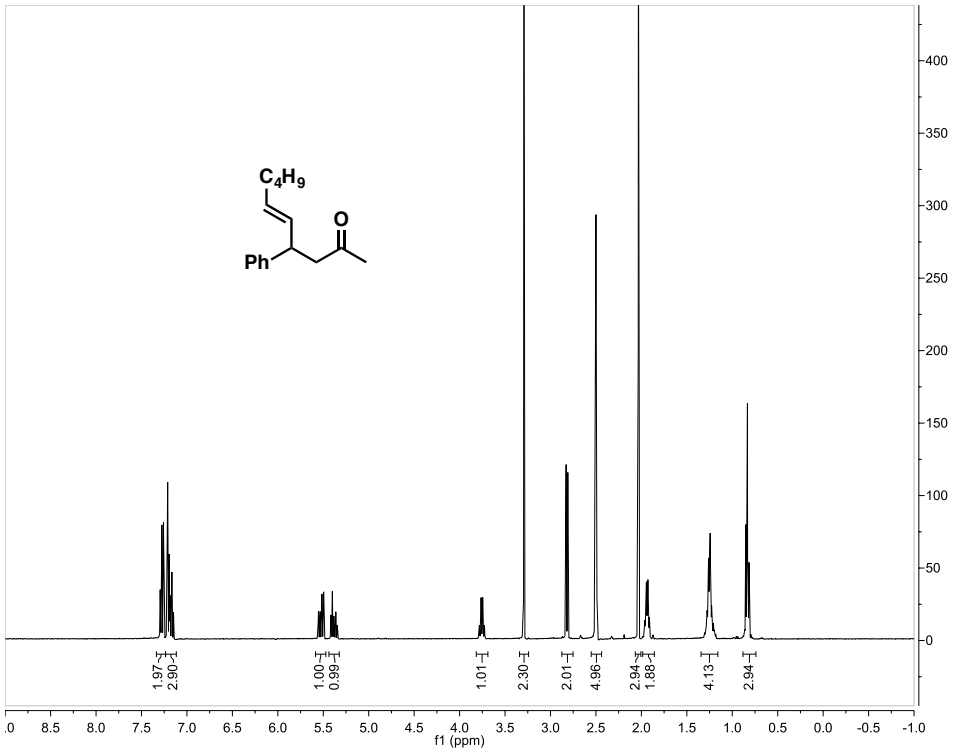


^{1}H and ^{13}C NMR for Azaspirene

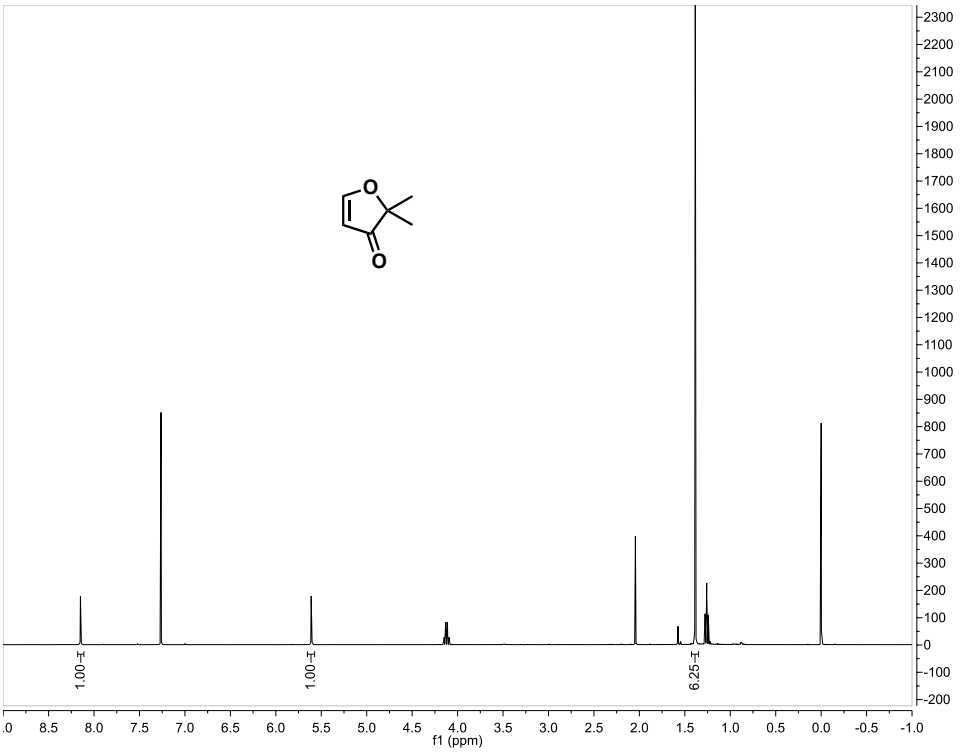




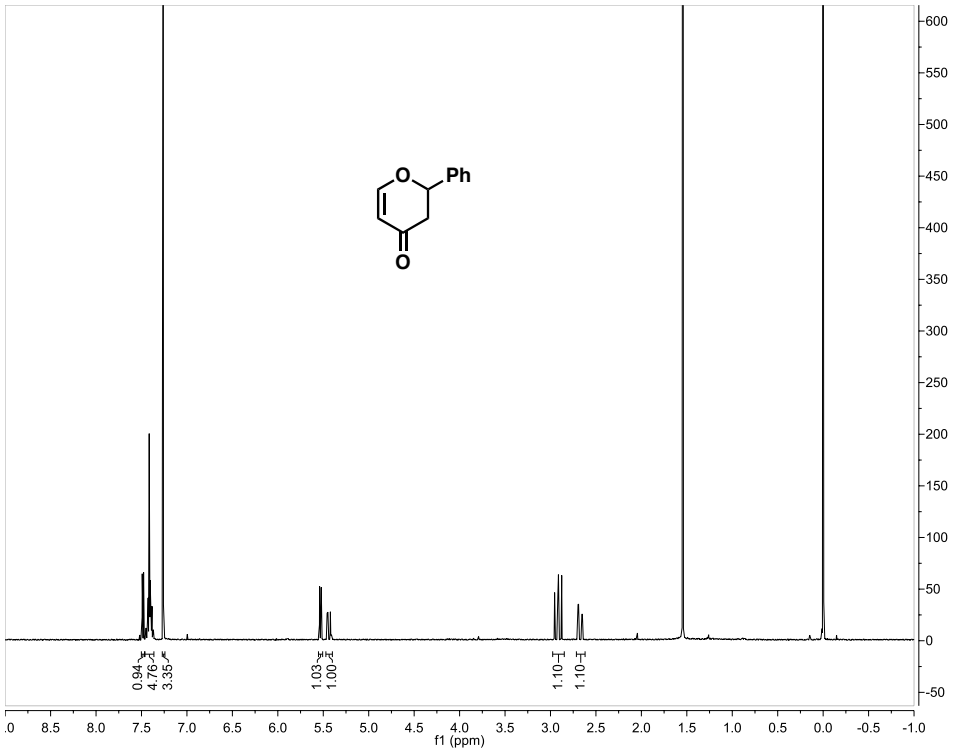
^{1}H NMR for Compound 3.1



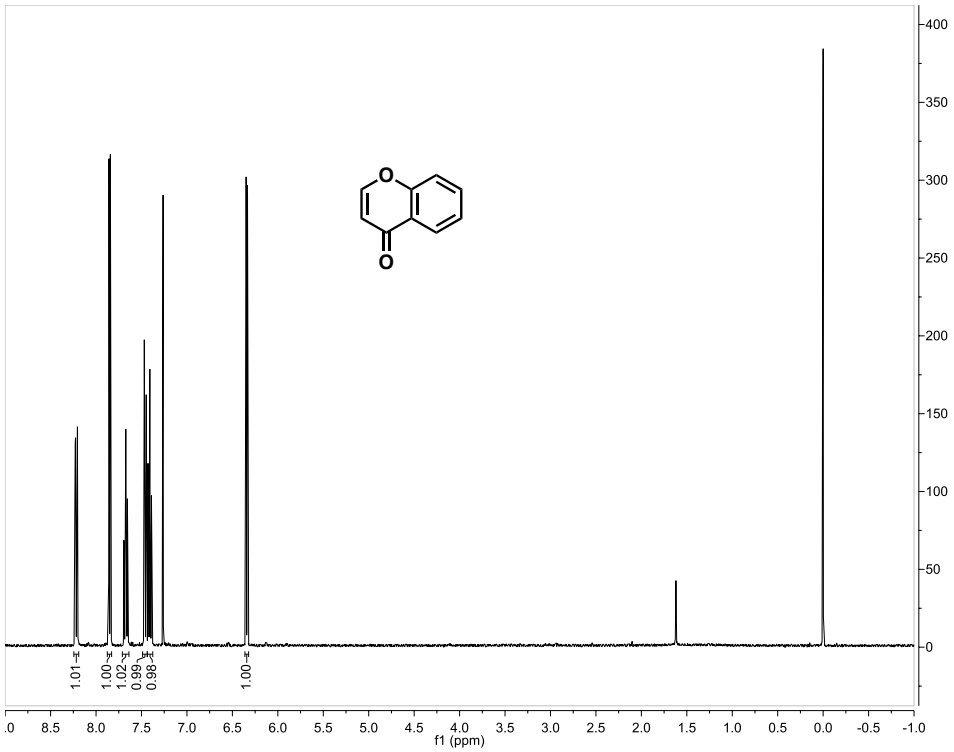
^{1}H NMR for Compound 3.2



^{1}H NMR for Compound 3.3



^{1}H NMR for Compound 3.4



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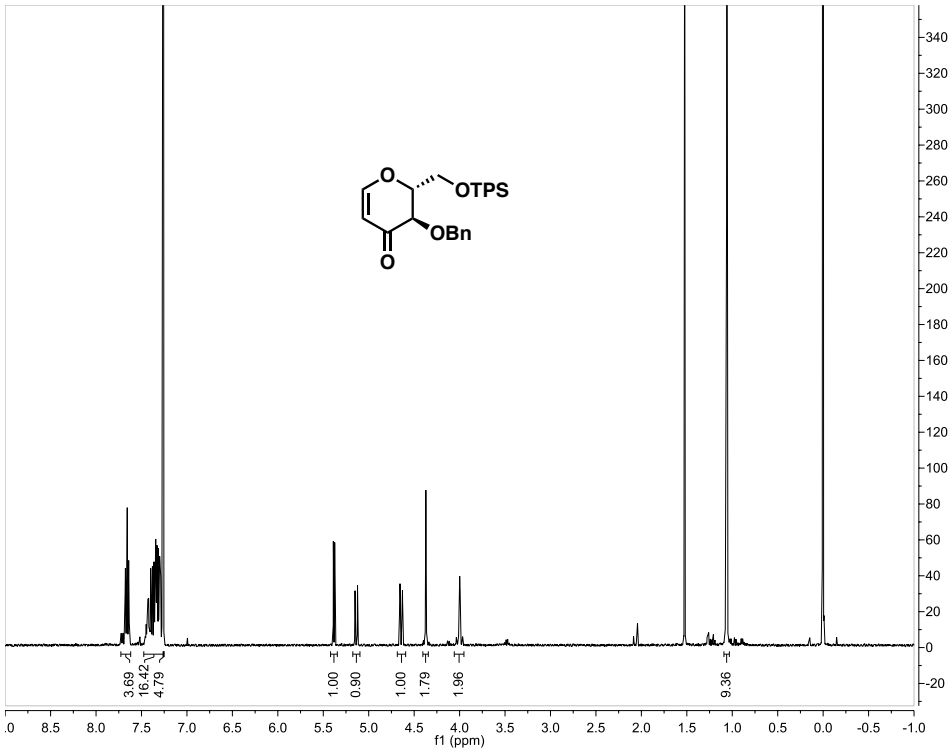

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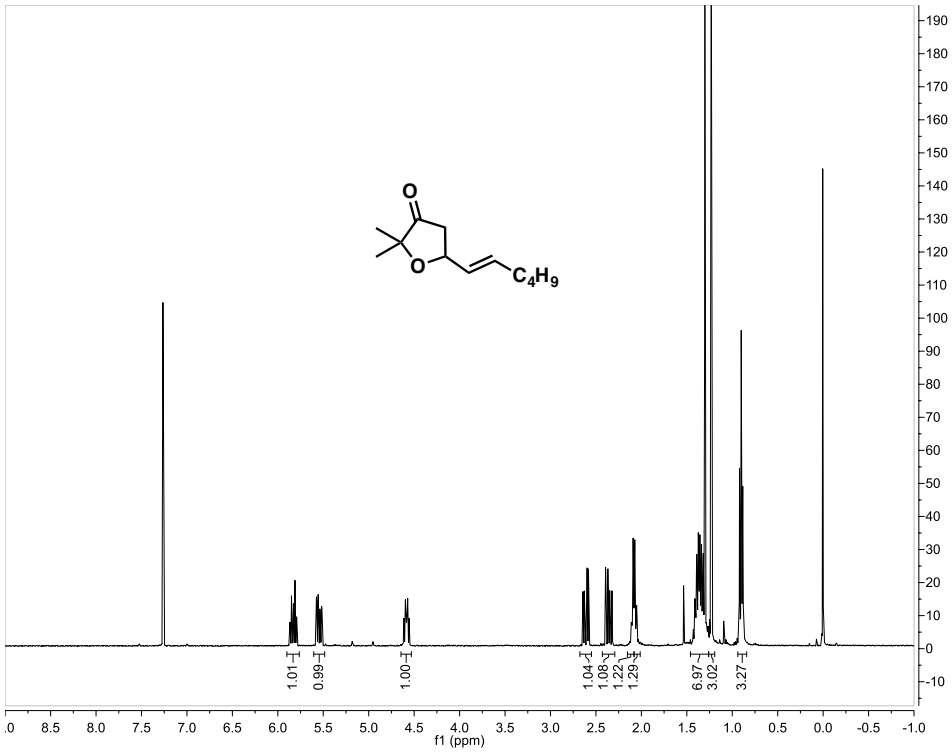

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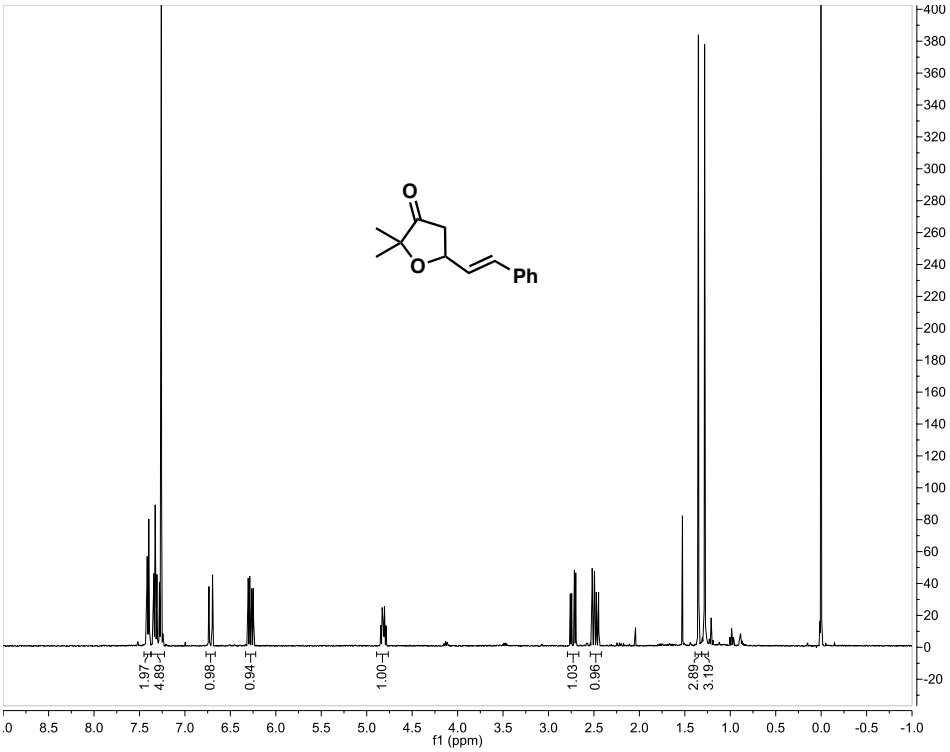

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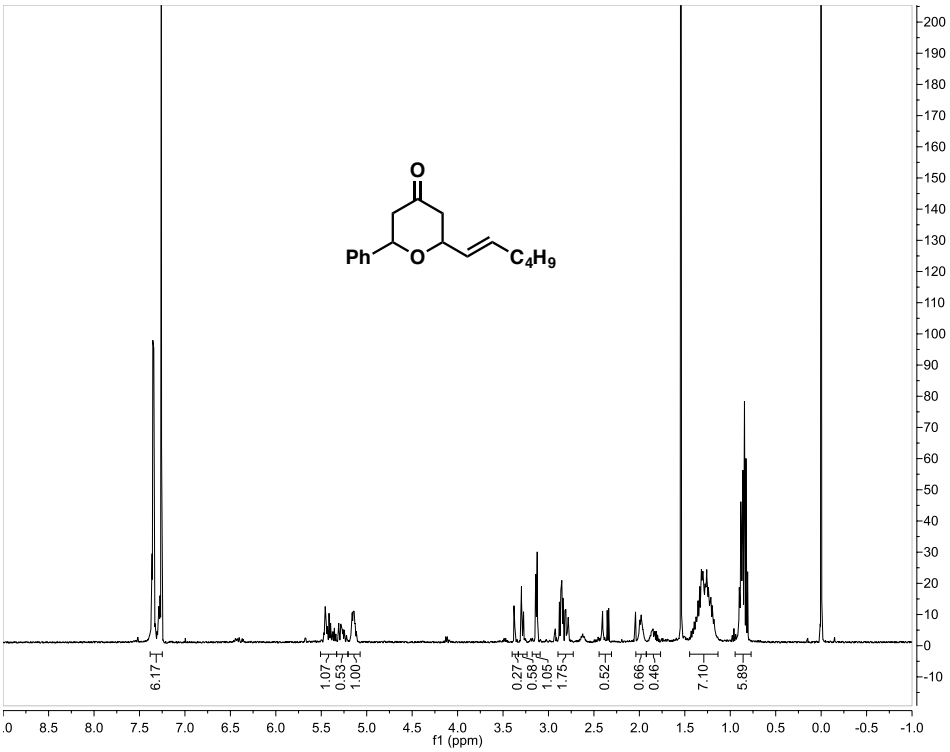
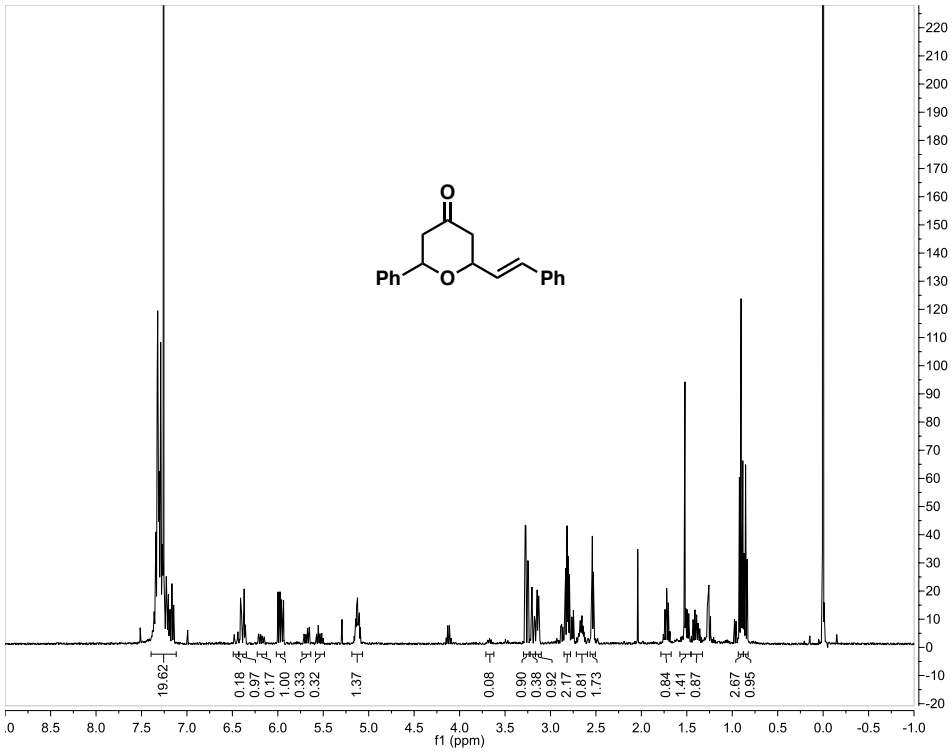


^{1}H NMR for Compound 3.9



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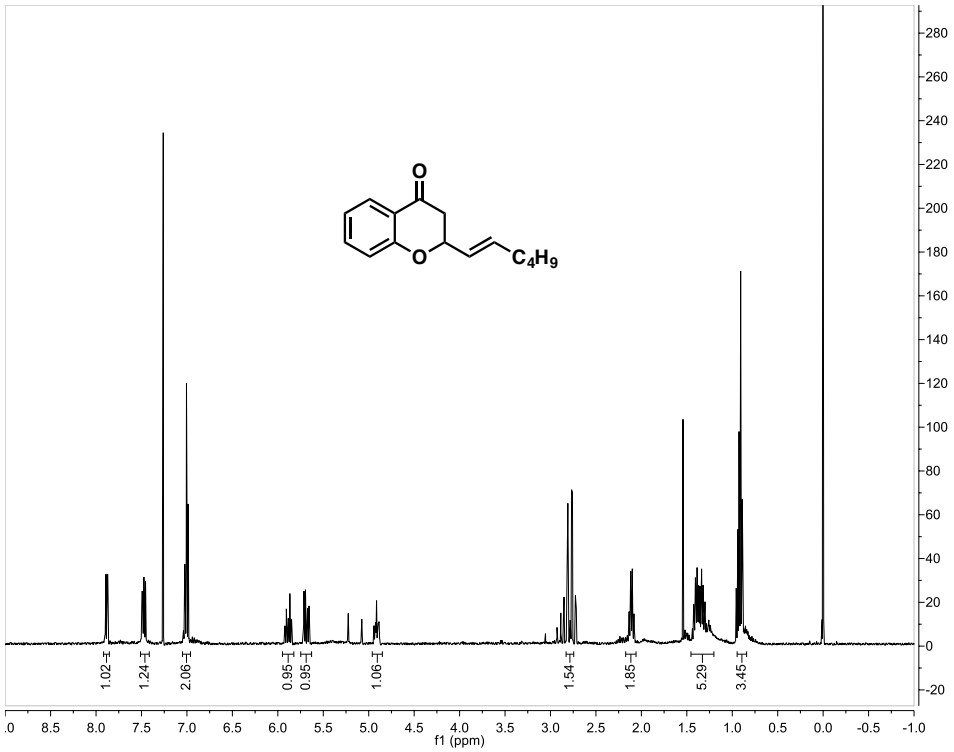
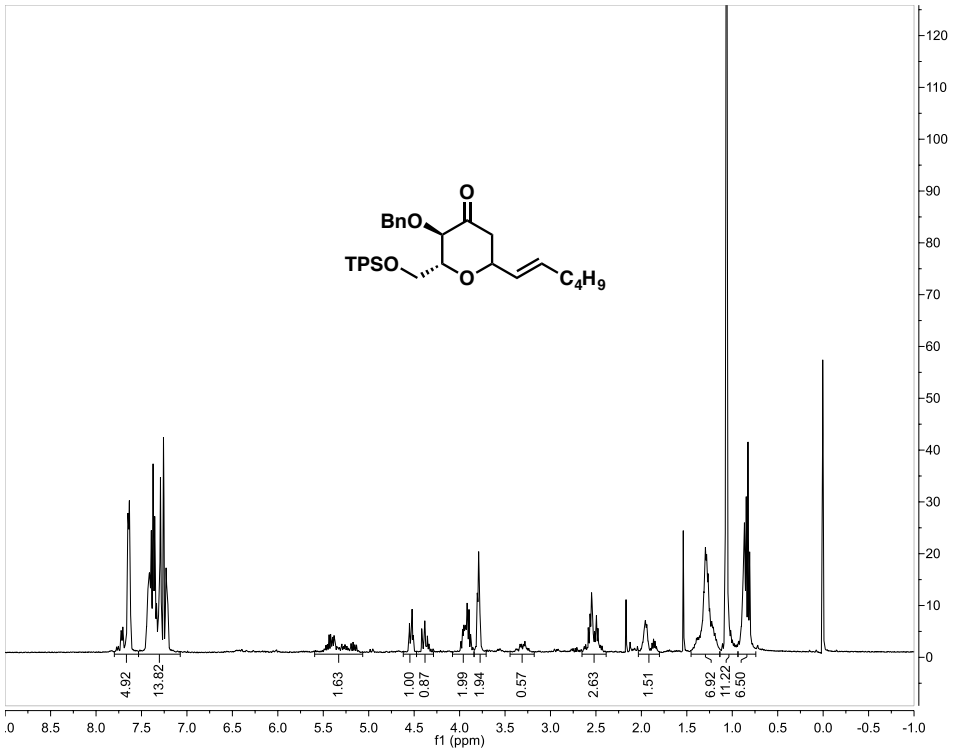


^{1}H NMR for Compound 3.11



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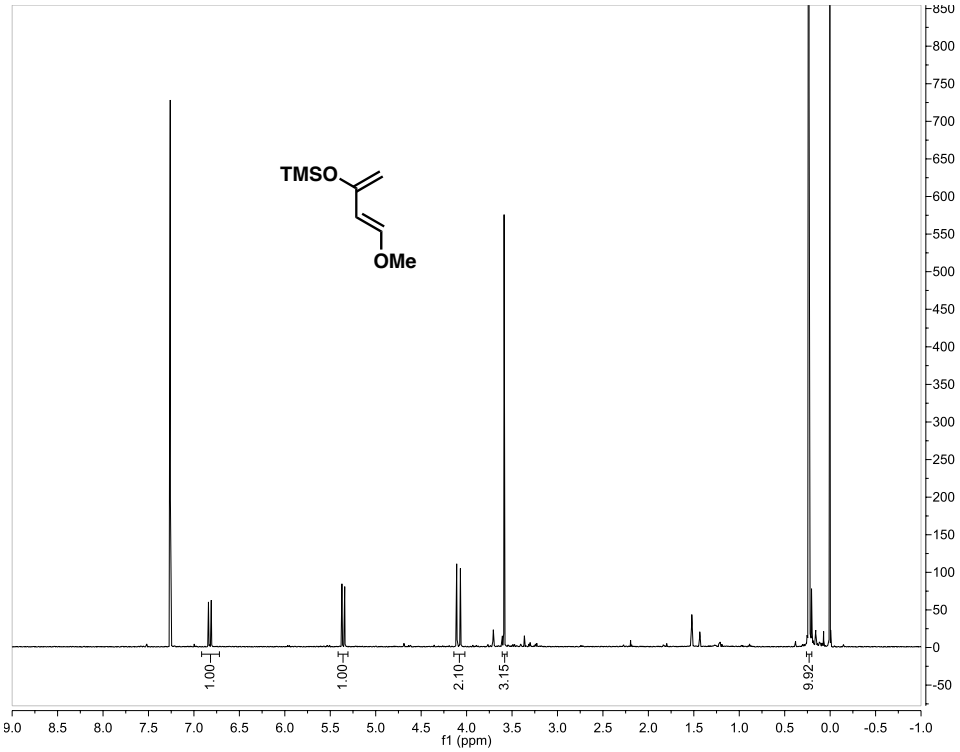

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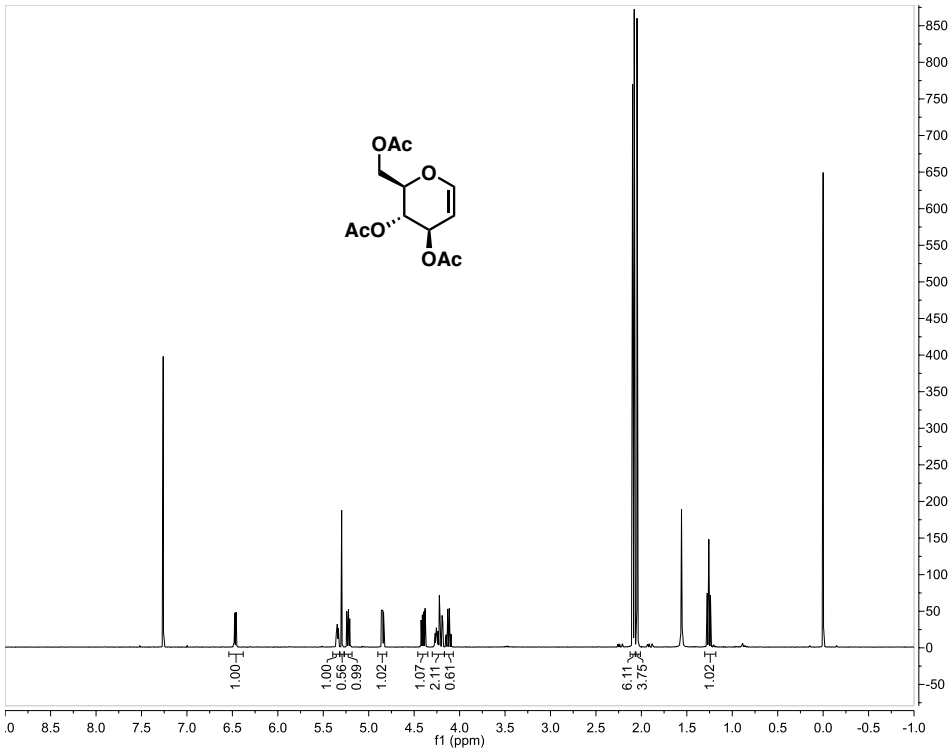

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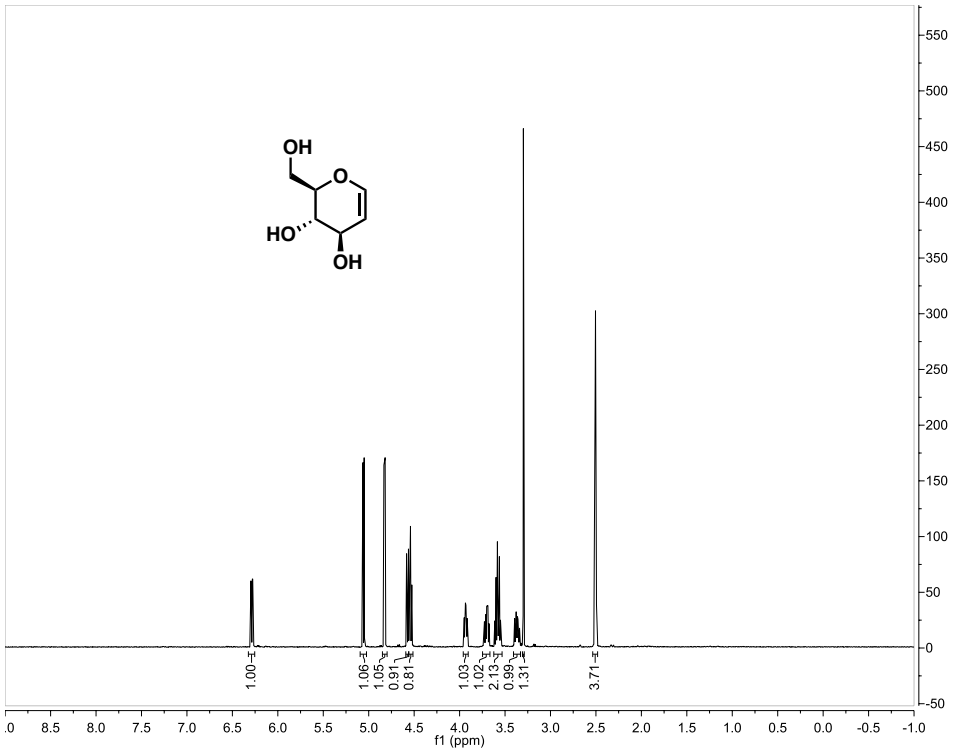

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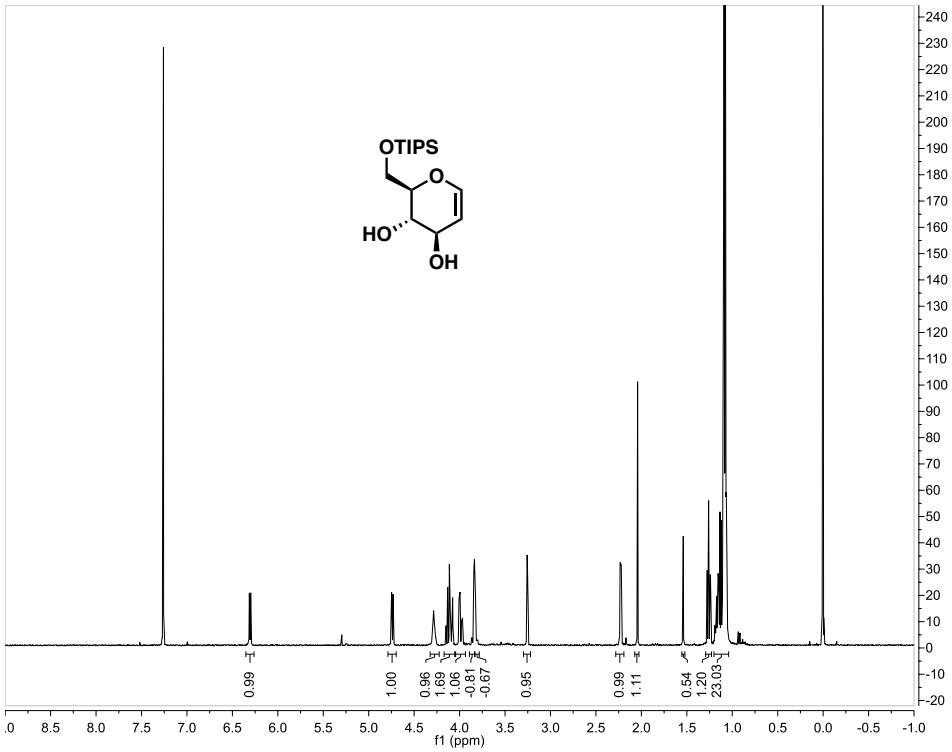
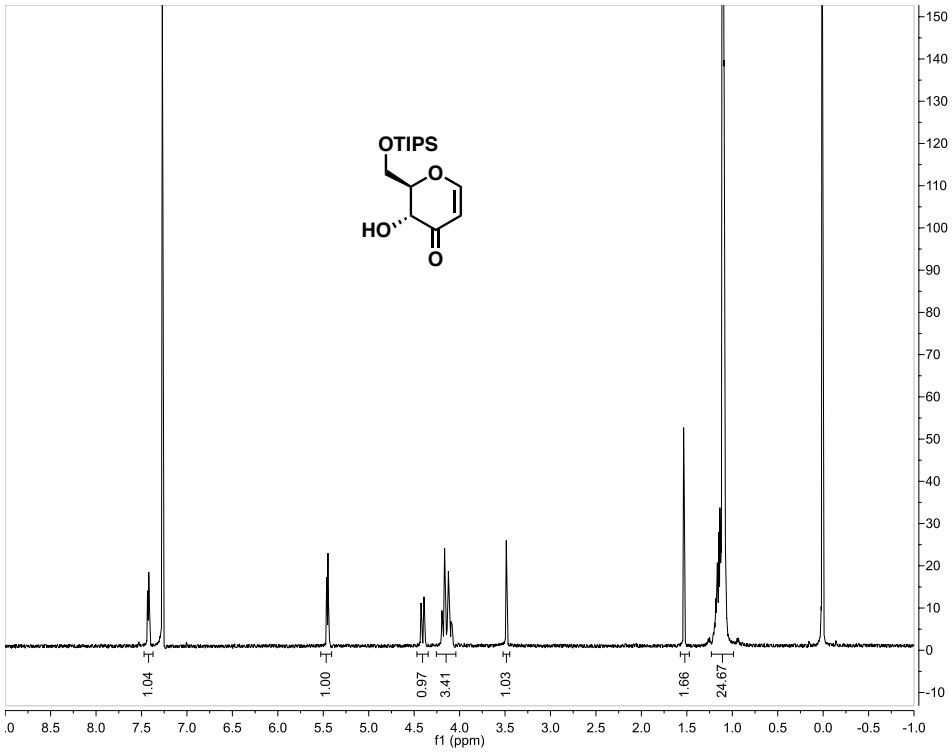


^{1}H NMR for Compound 3.23



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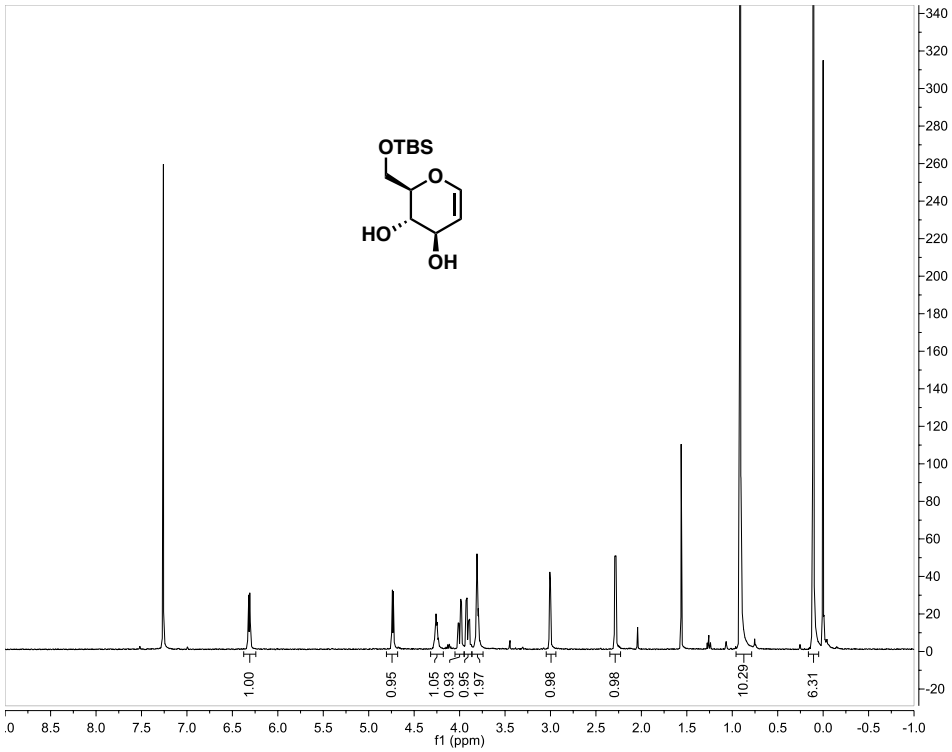

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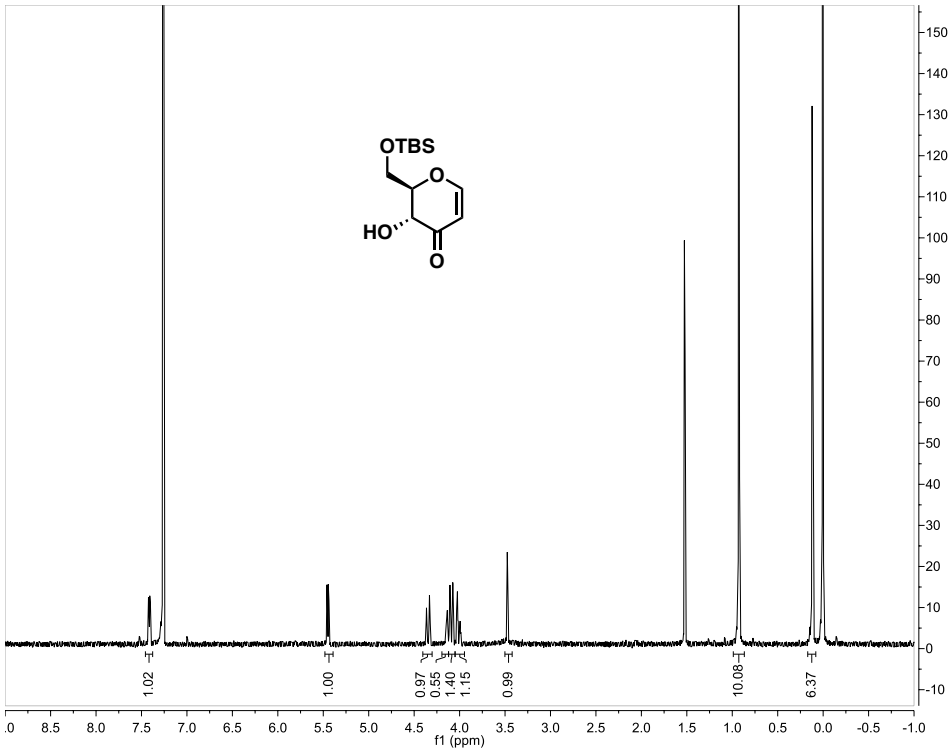

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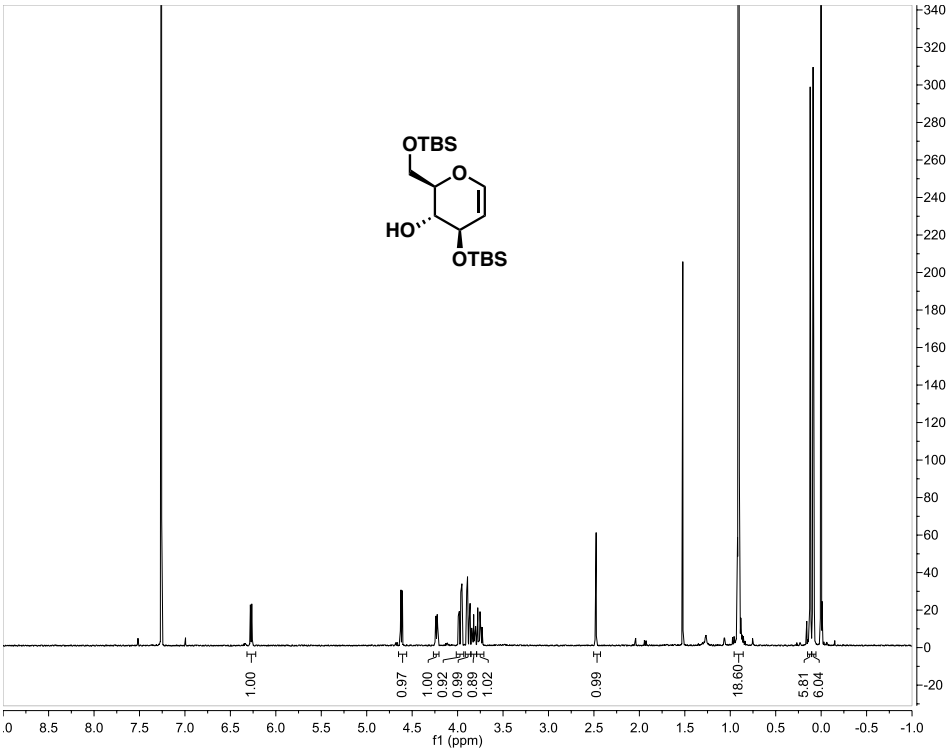

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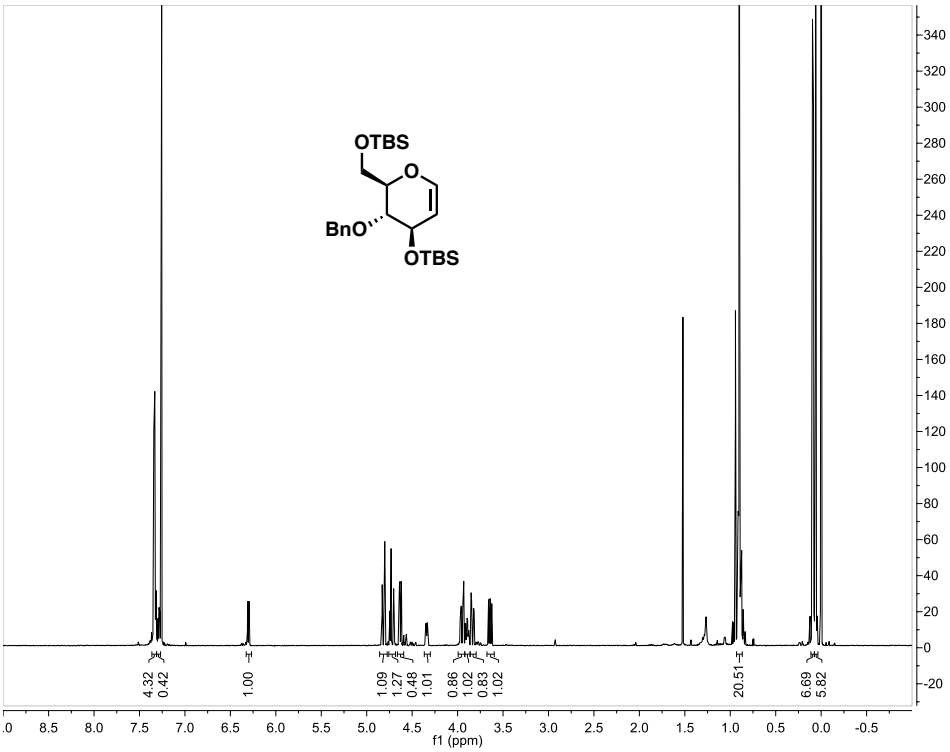

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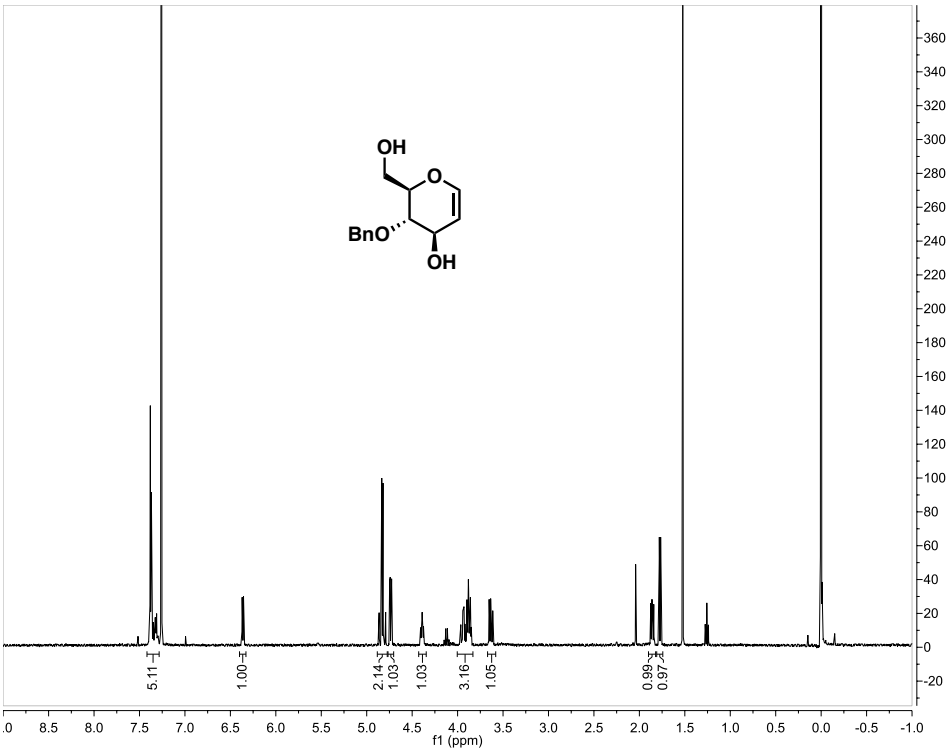

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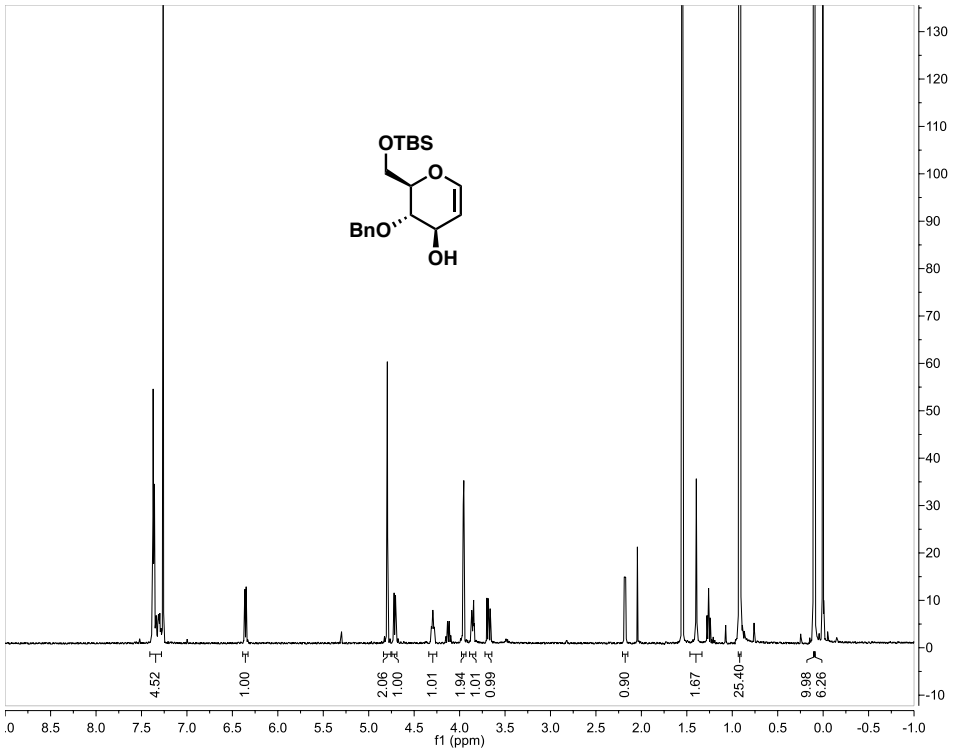
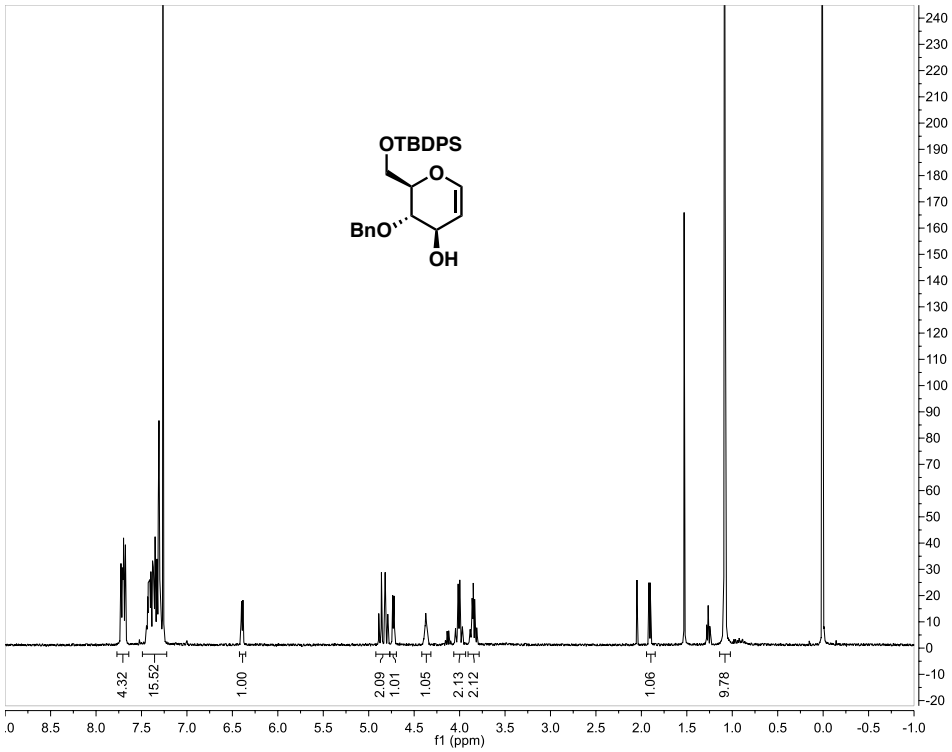
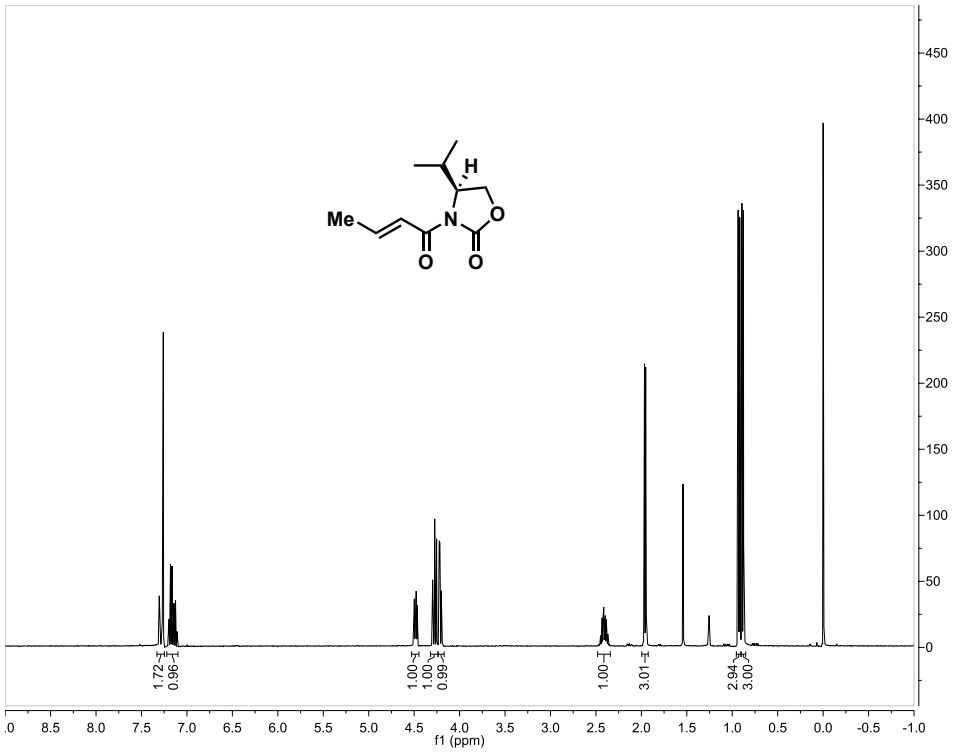


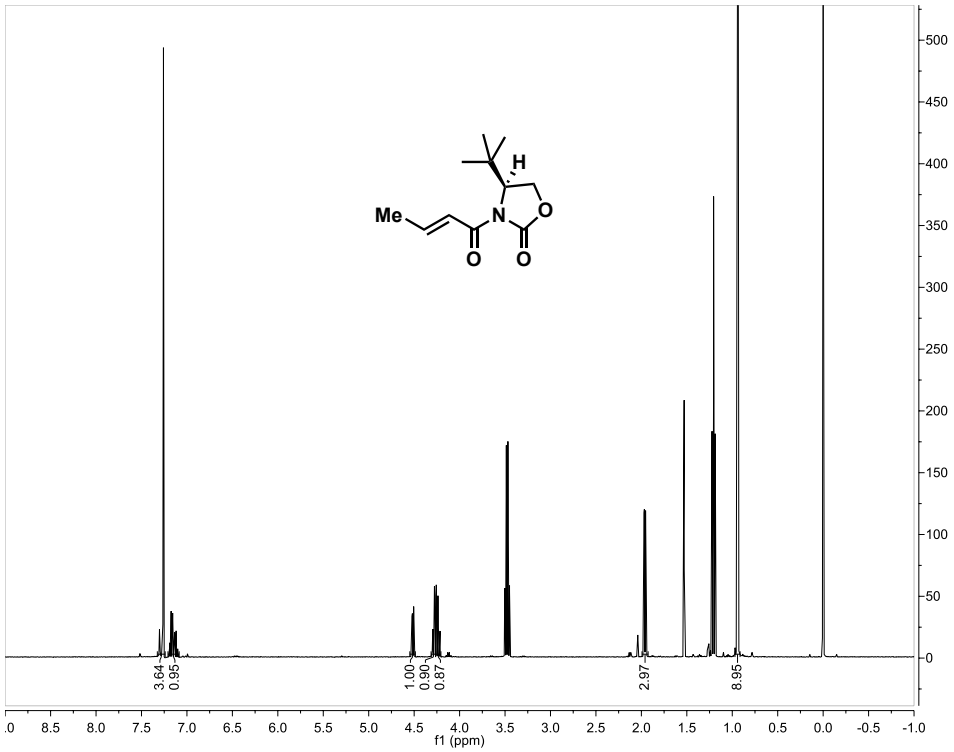
^{1}H NMR for Compound 3.32



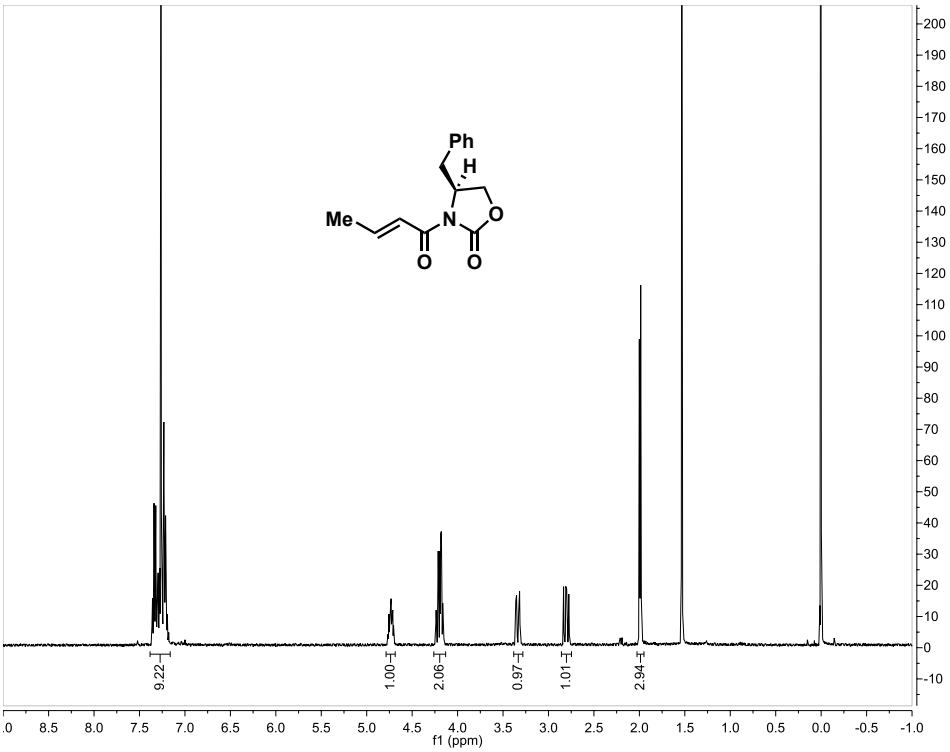
^{1}H NMR for Compound 4.1



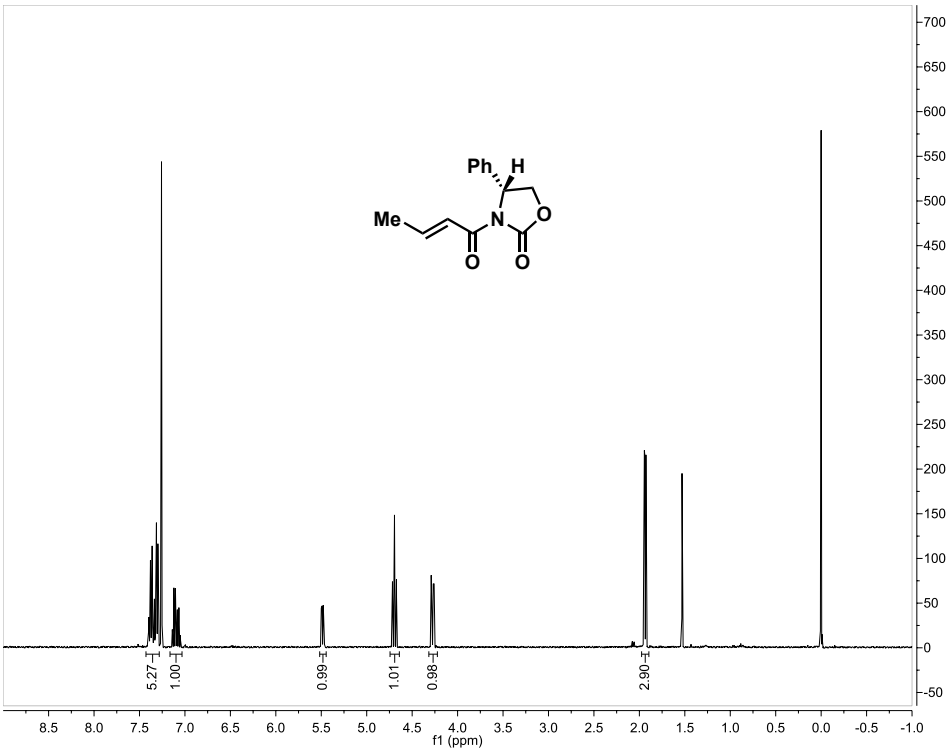
^{1}H NMR for Compound 4.2



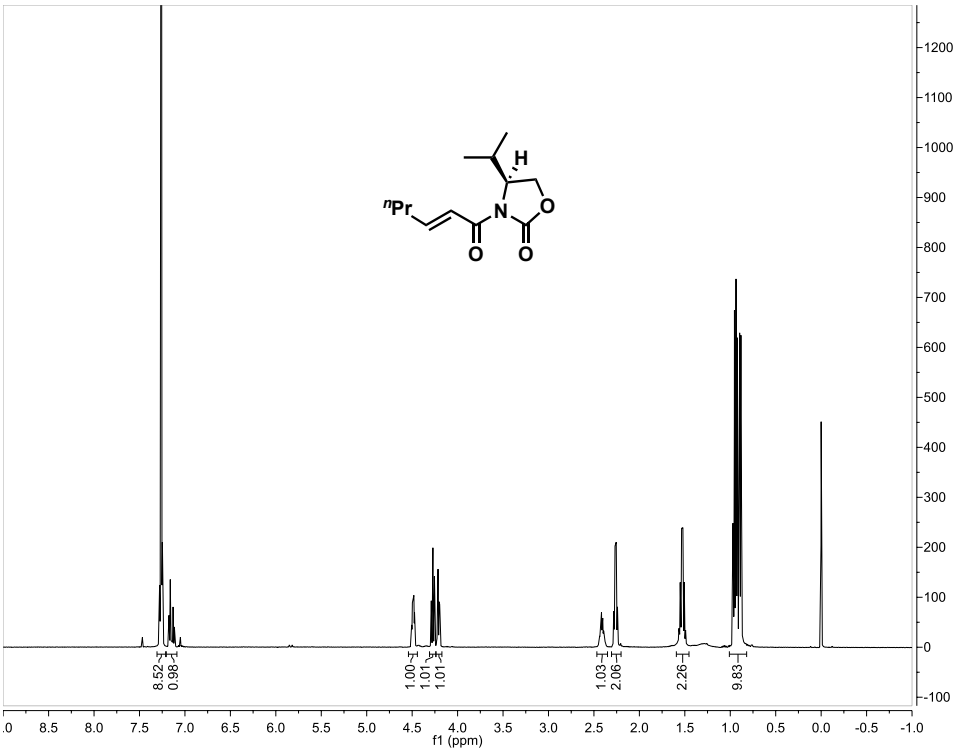
^{1}H NMR for Compound 4.3

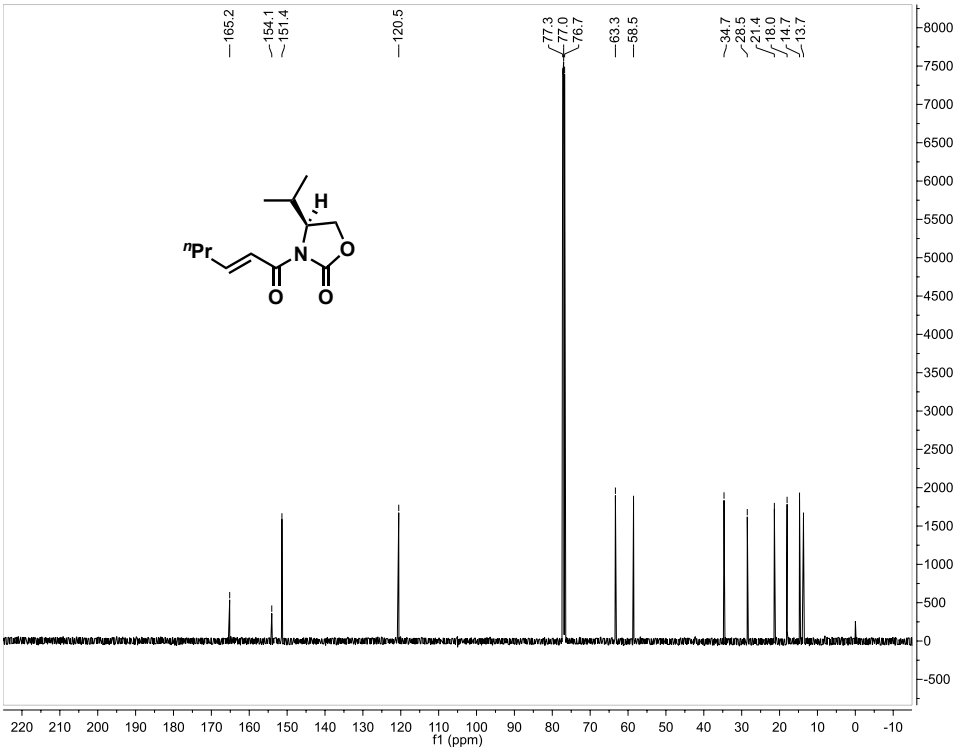


^{1}H NMR for Compound 4.4

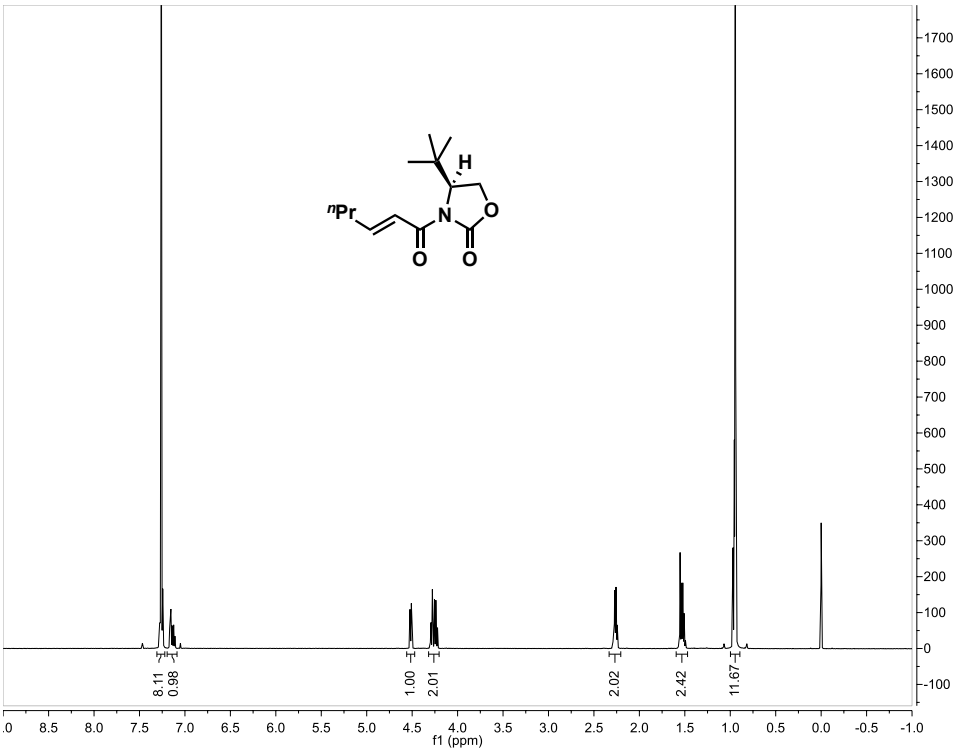


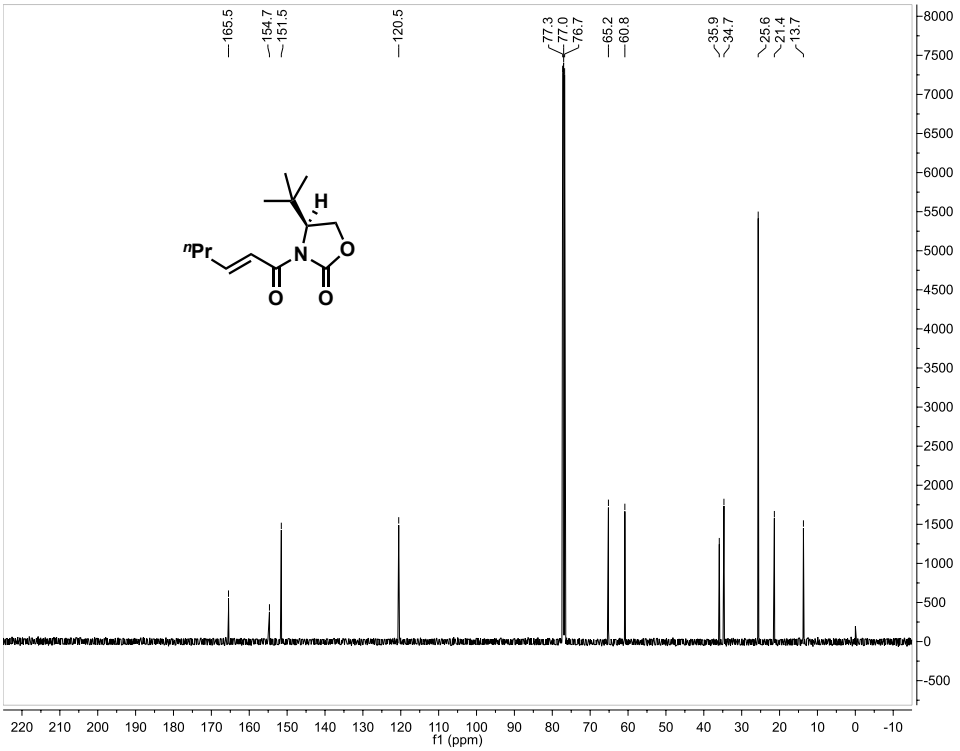
^{1}H and ^{13}C NMR for Compound 4.5



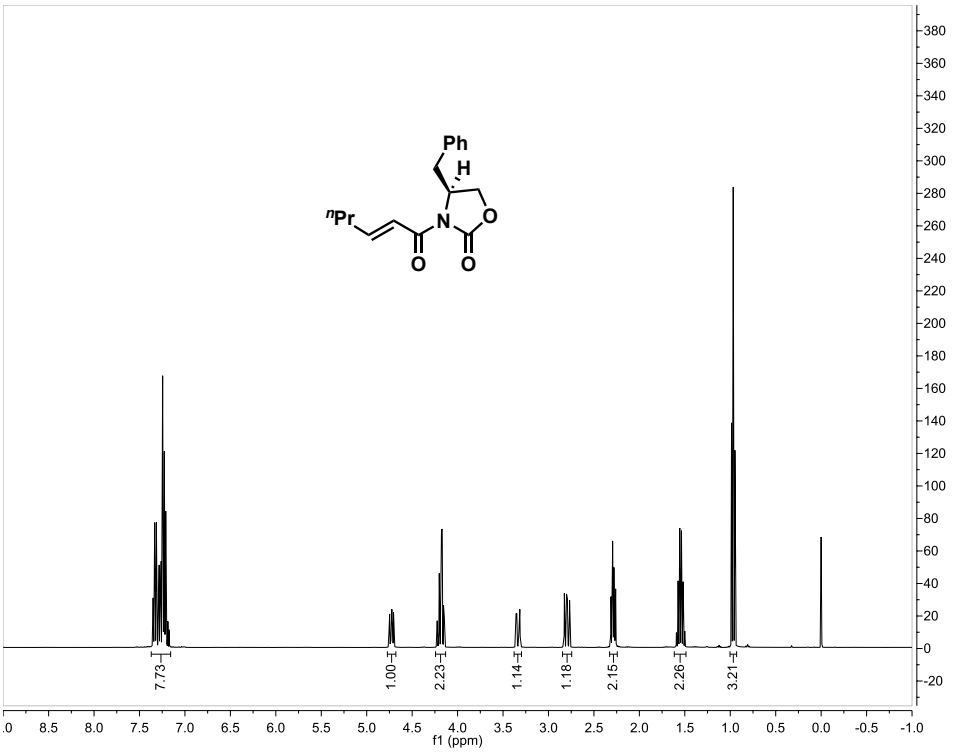


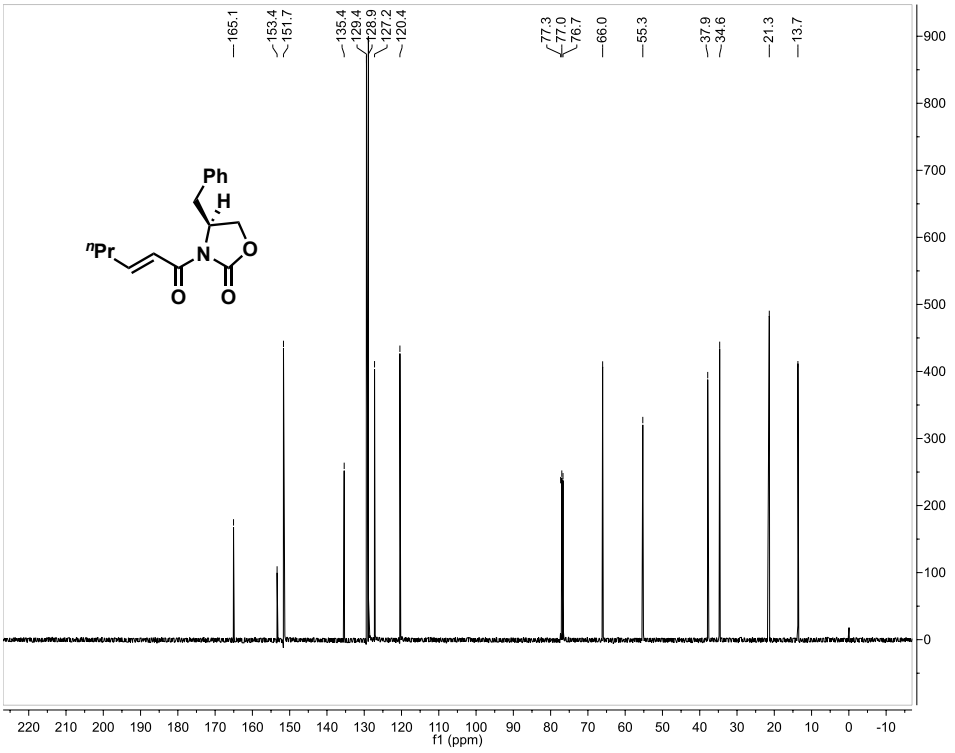
^{1}H and ^{13}C NMR for Compound 4.6



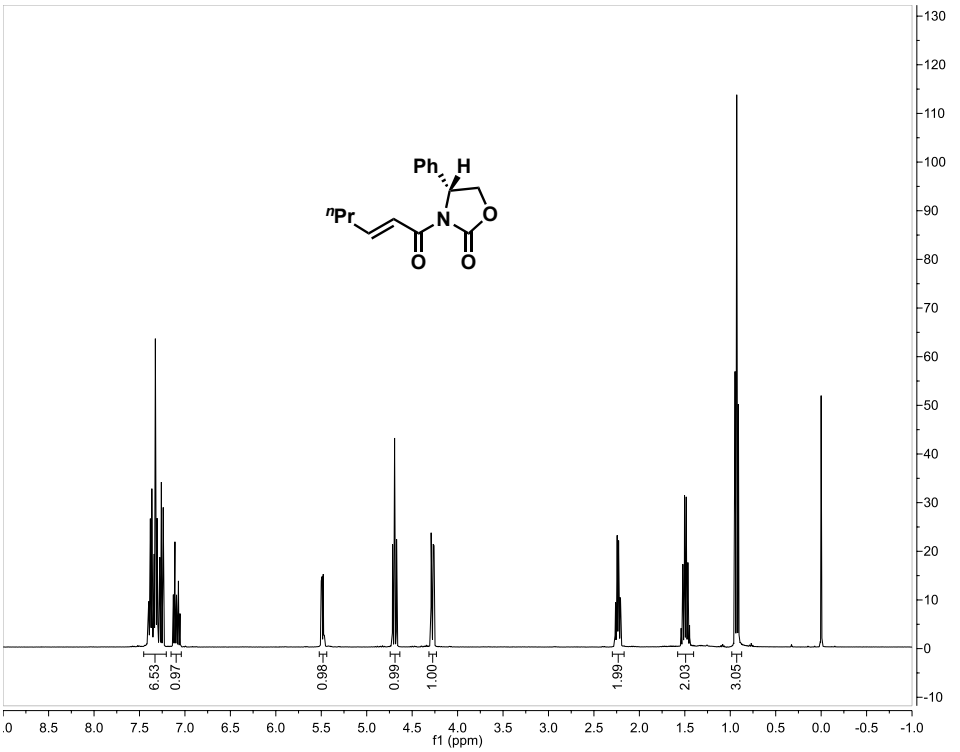


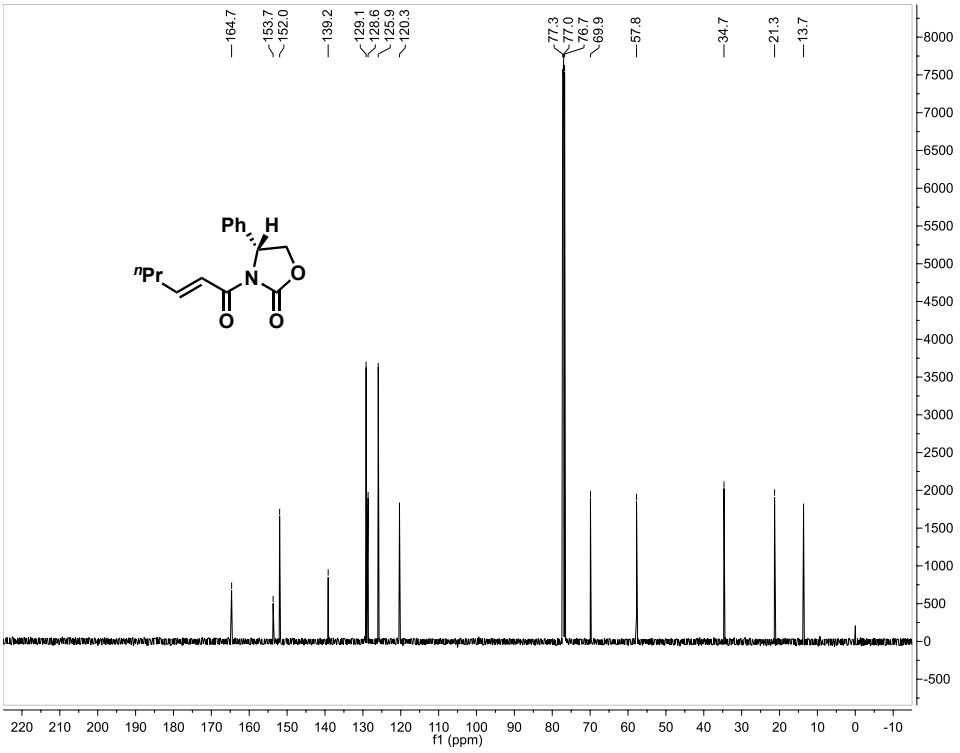
^{1}H and ^{13}C NMR for Compound 4.7



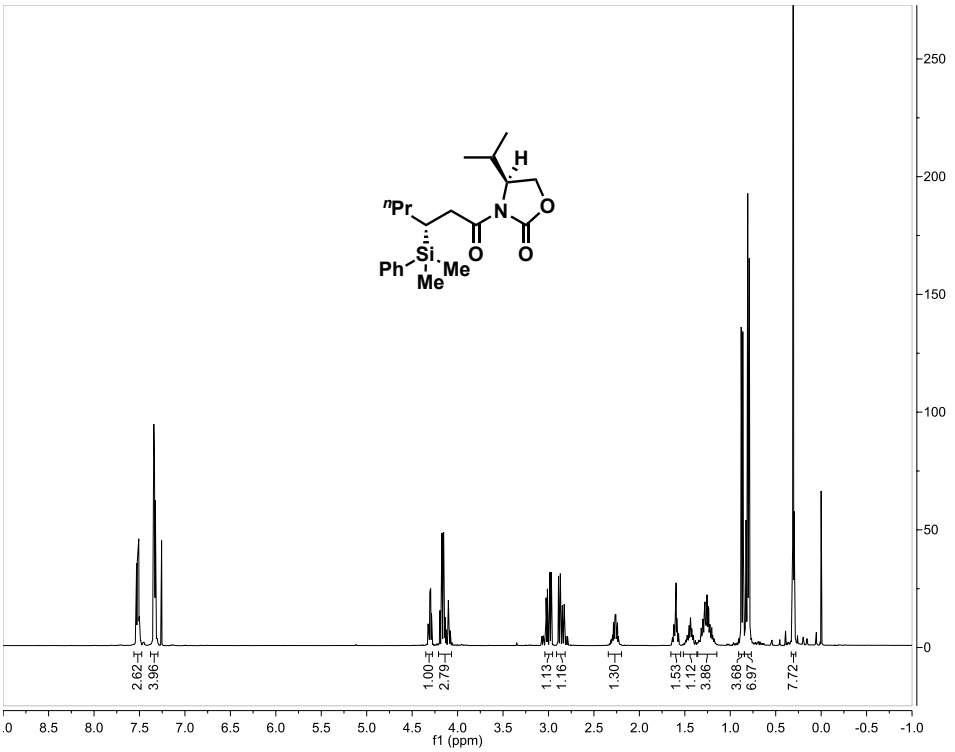


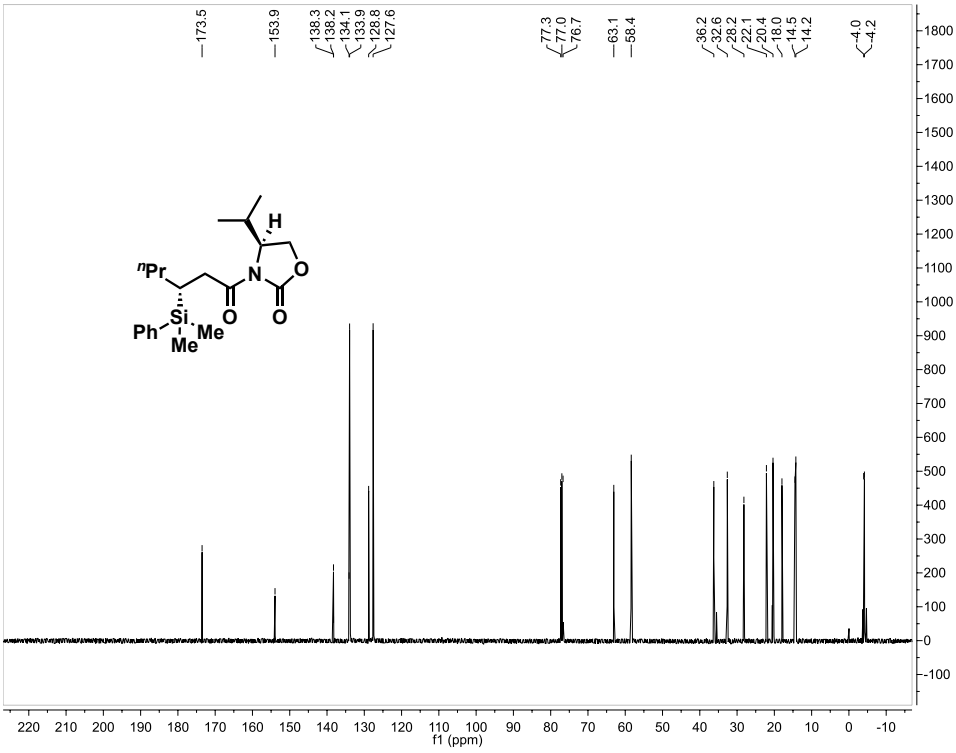
^{1}H and ^{13}C NMR for Compound 4.8



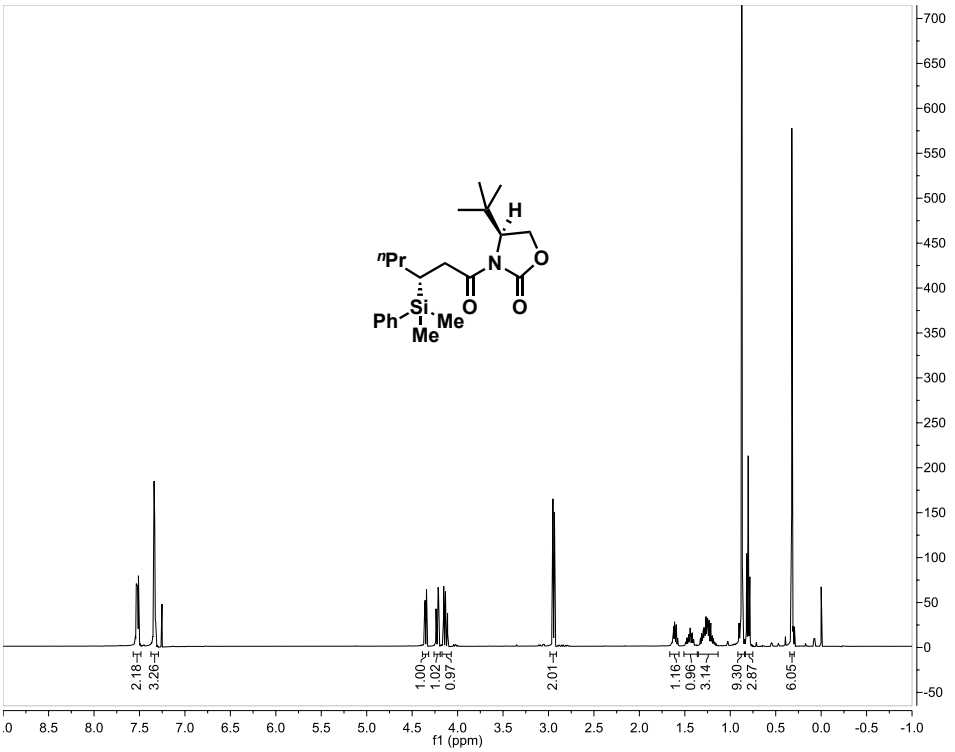


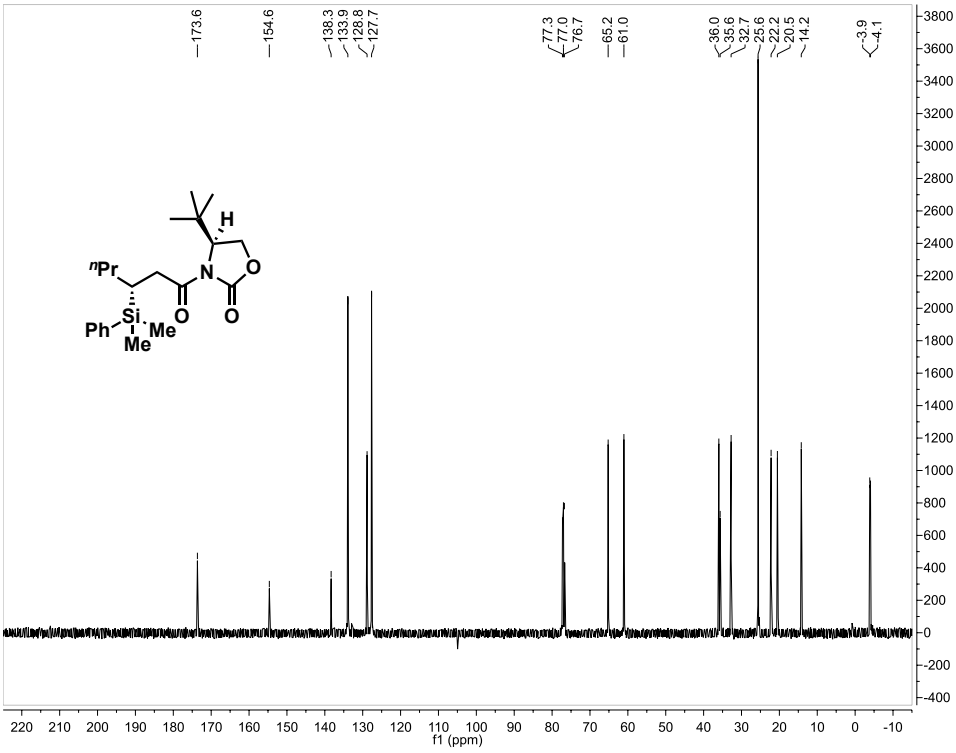
^{1}H and ^{13}C NMR for Compound 4.17



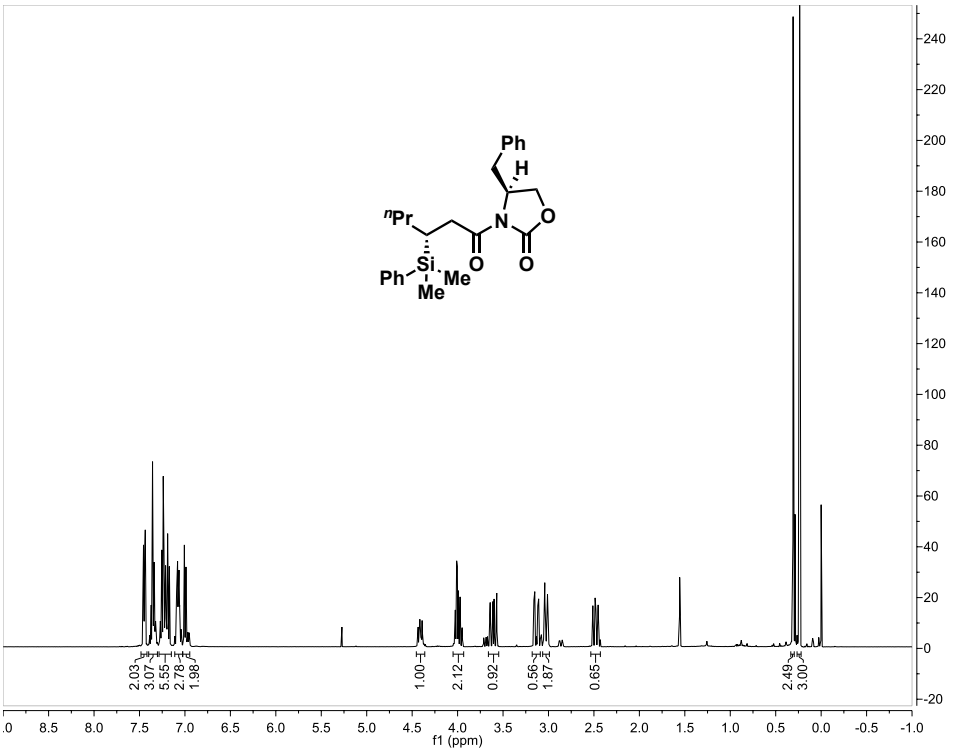


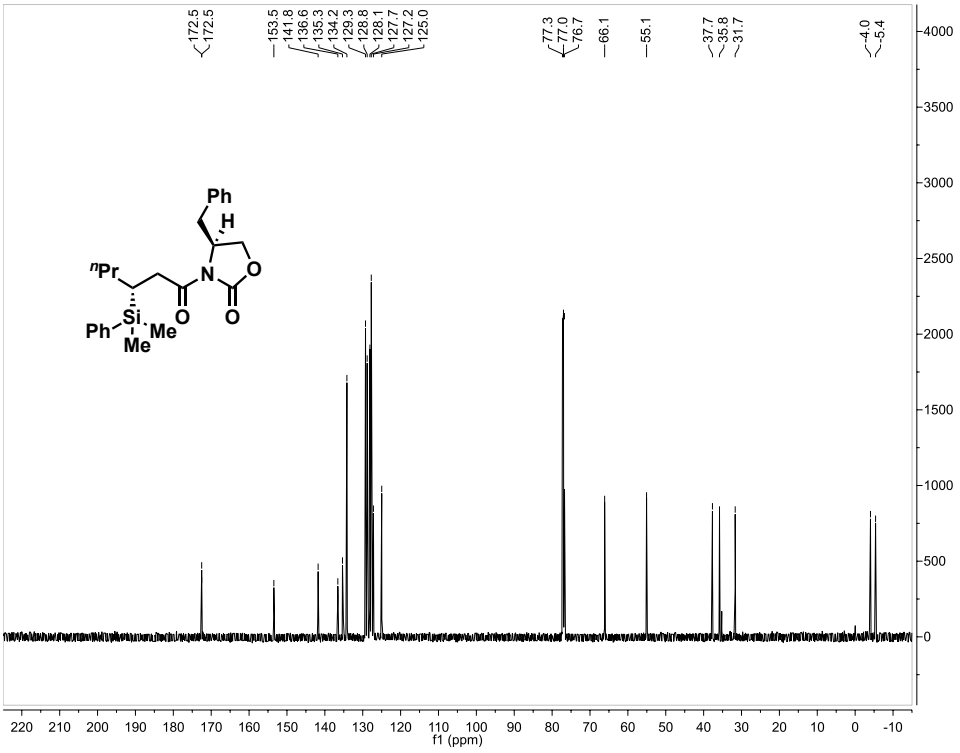
^{1}H and ^{13}C NMR for Compound 4.18



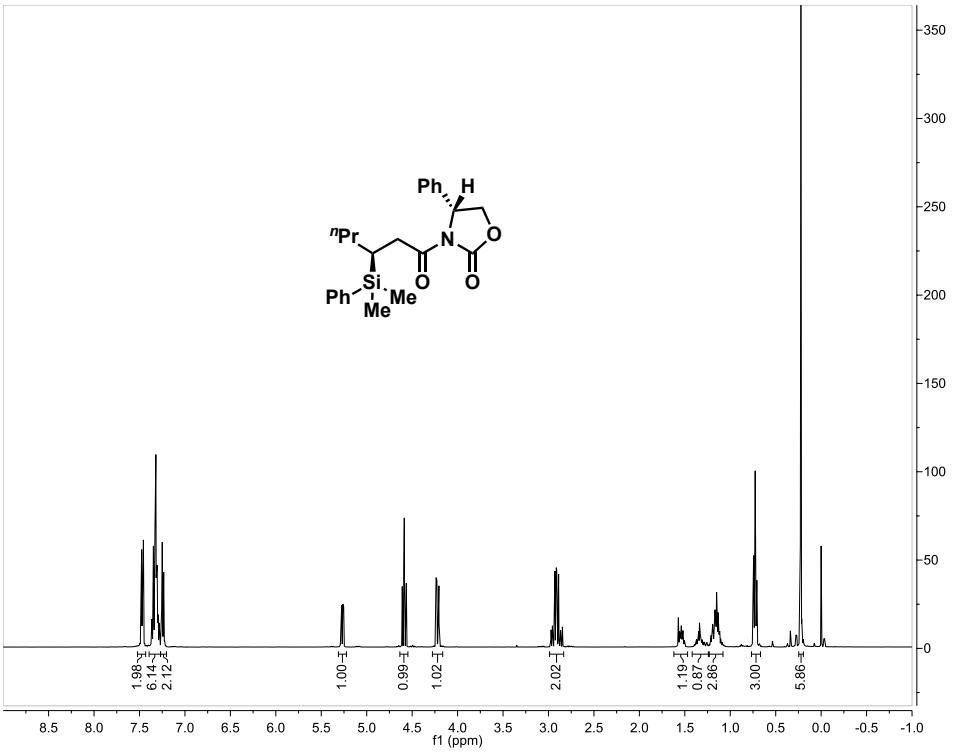


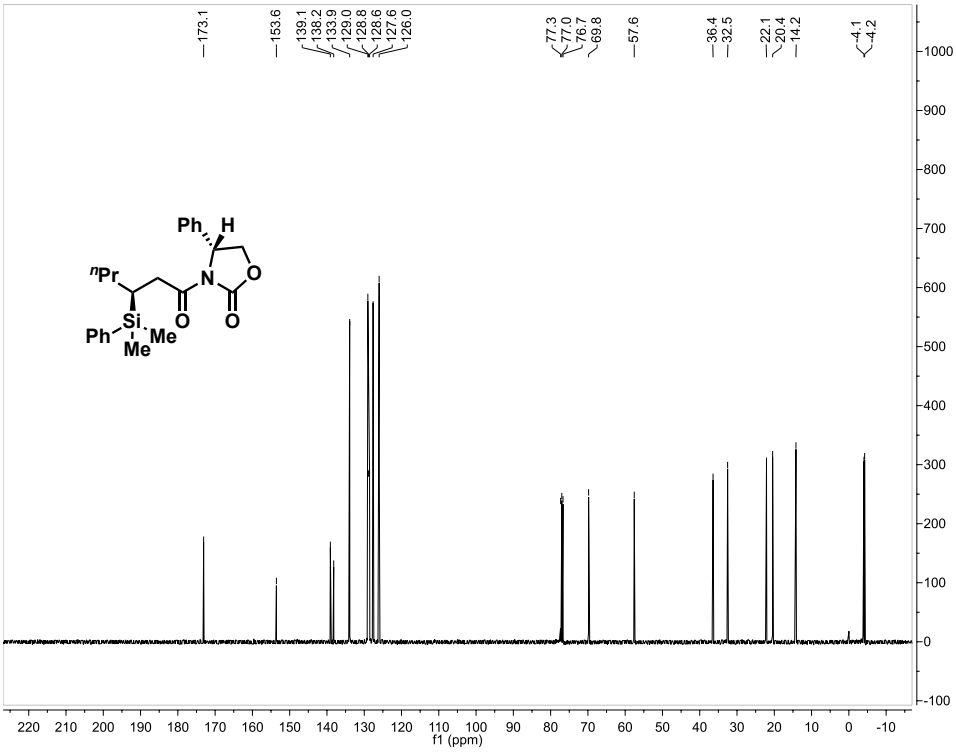
^{1}H and ^{13}C NMR for Compound 4.19



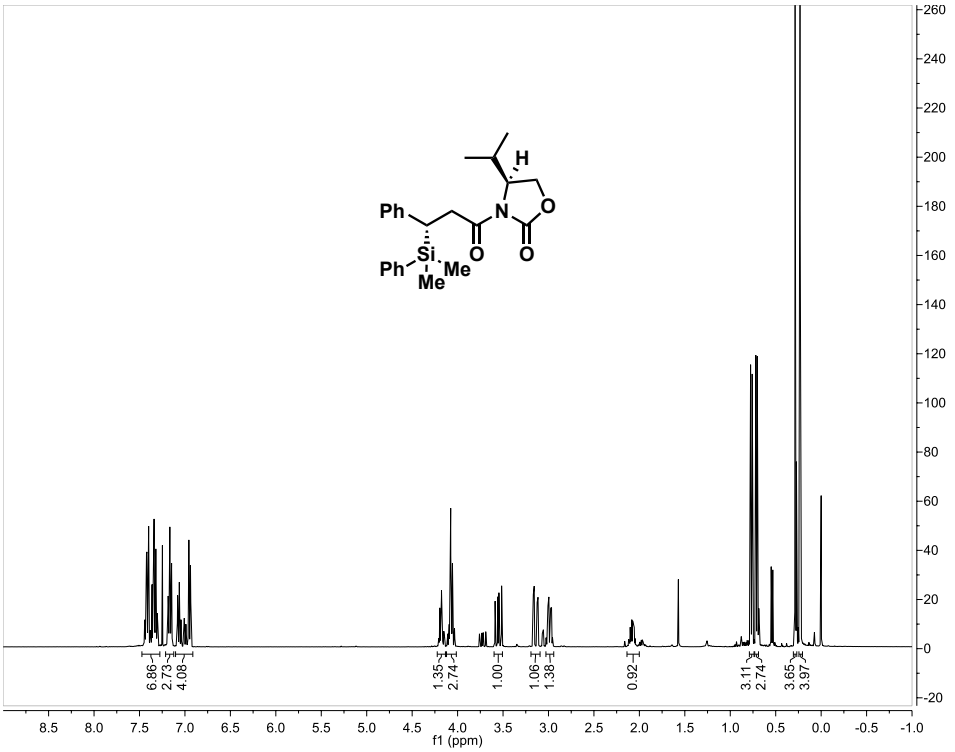


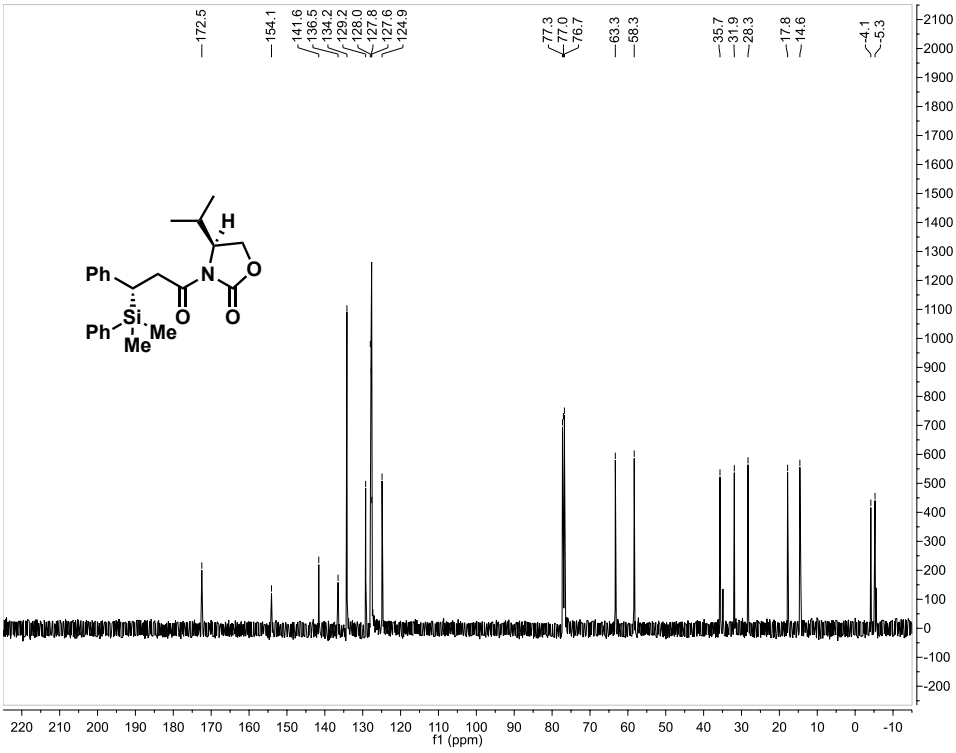
^{1}H and ^{13}C NMR for Compound 4.20



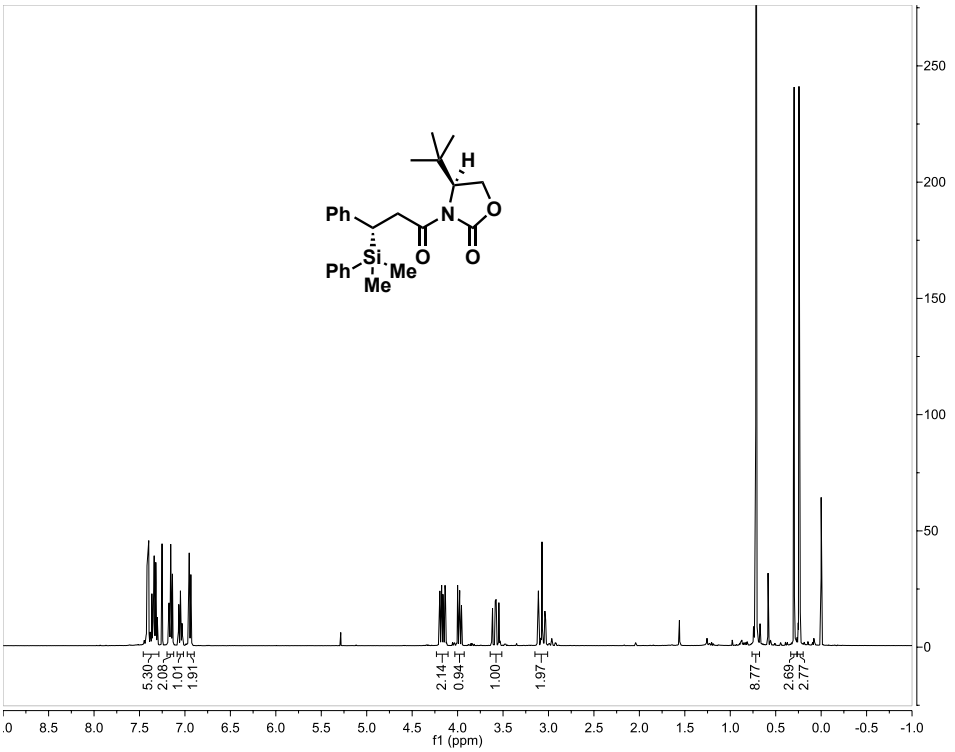


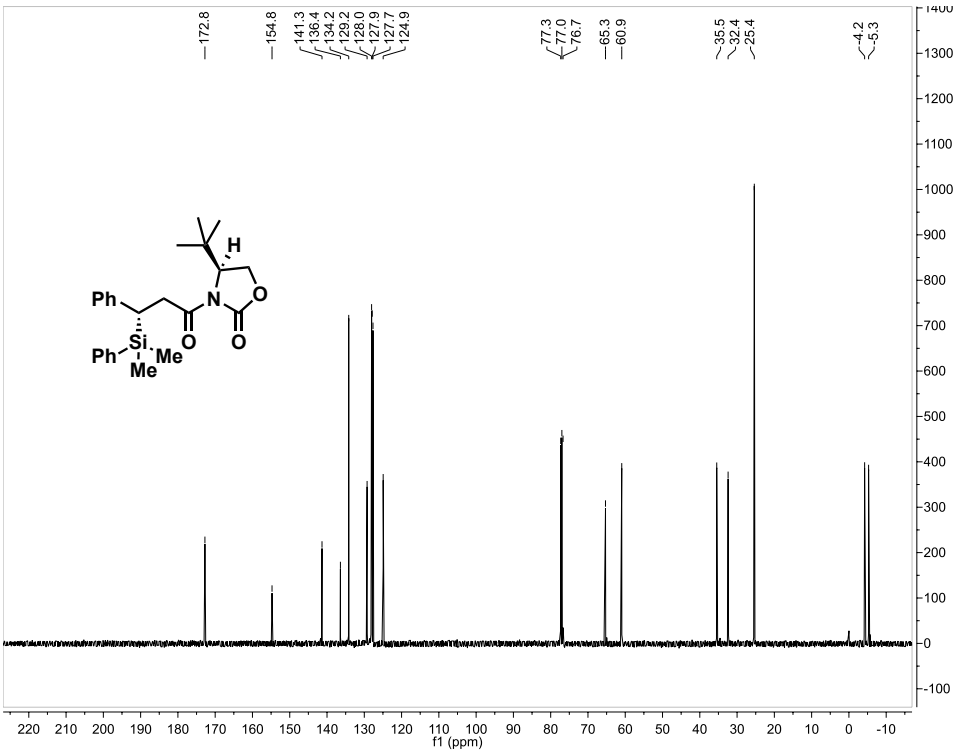
^{1}H and ^{13}C NMR for Compound 4.21



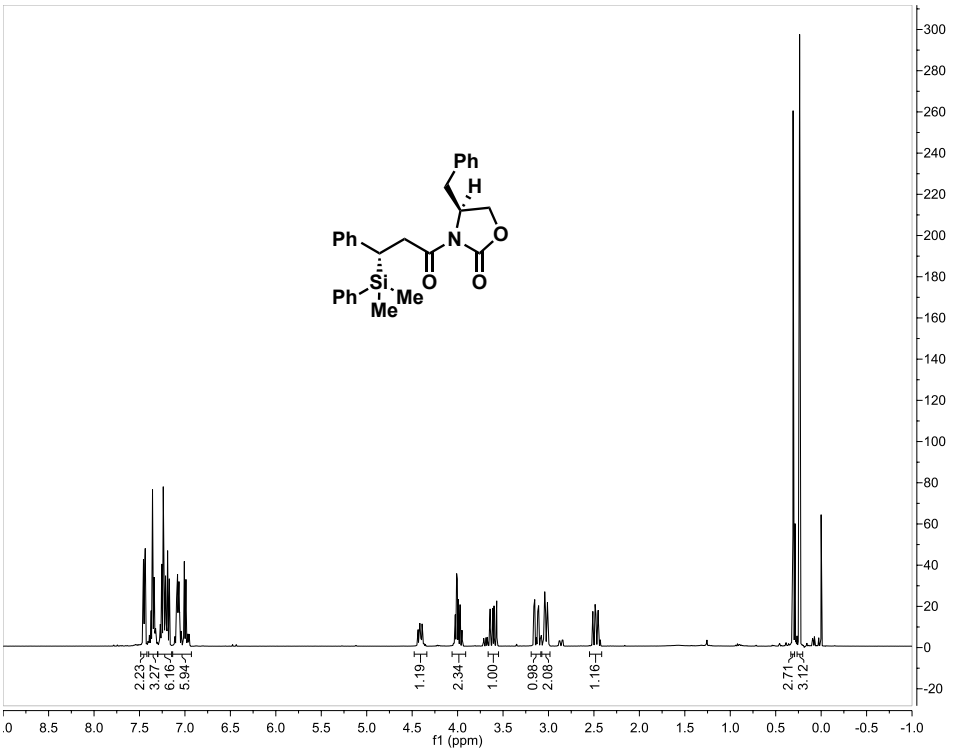


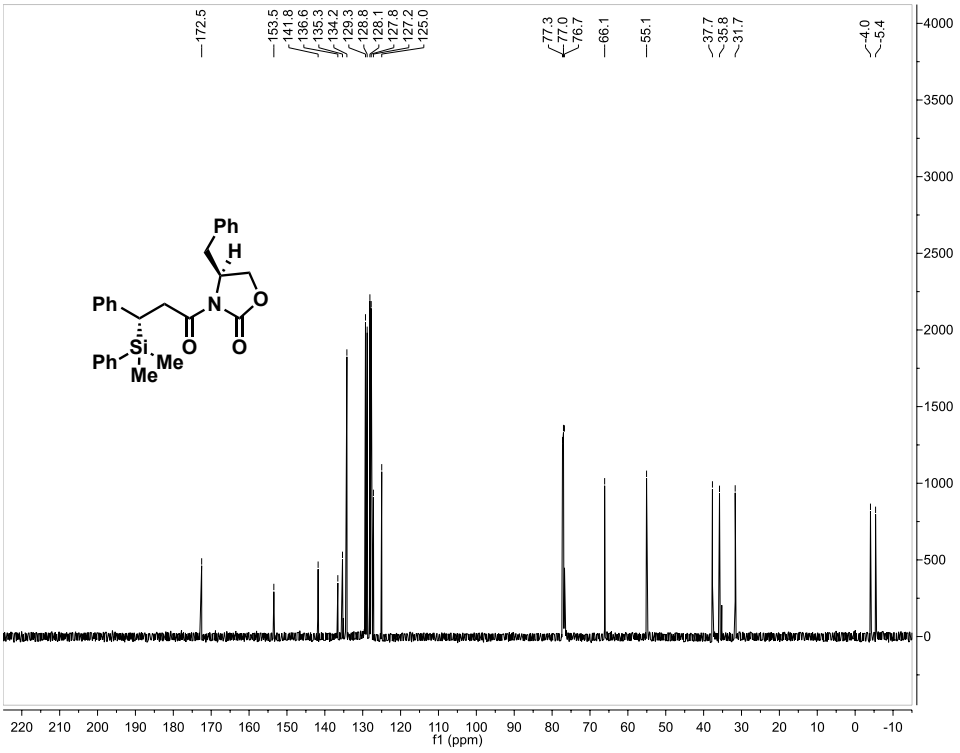
^{1}H and ^{13}C NMR for Compound 4.22



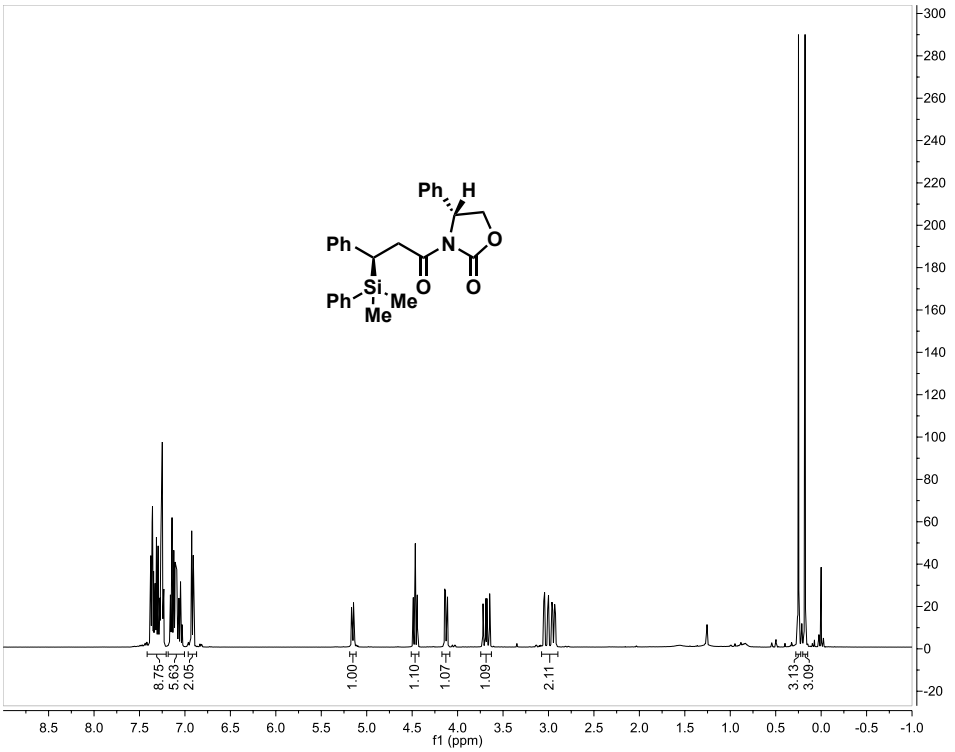


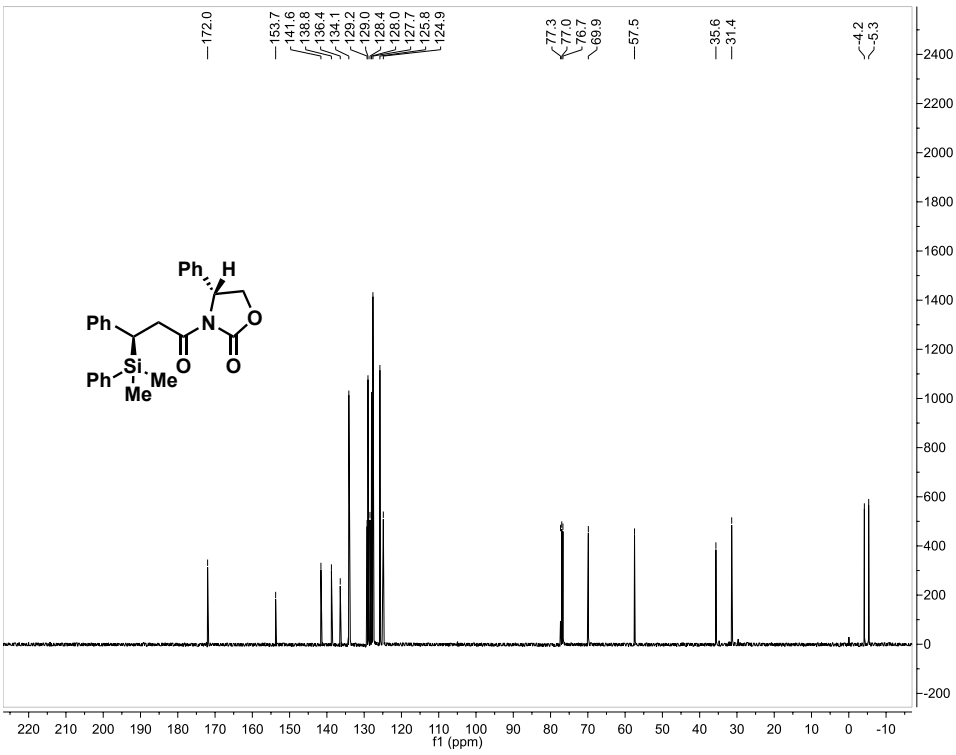
^{1}H and ^{13}C NMR for Compound 4.23





^{1}H and ^{13}C NMR for Compound 4.24





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