An Investigation in Oxidative Cation Formation: The Total Synthesis of Lactodehydrothyrsiferol and Synthetic Application for a Bimolecular Carbon–Carbon Bond Forming Reaction

by

Dane James Clausen

B.A., University of Colorado, 2007

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This dissertation was presented

by

Dane James Clausen

It was defended on

July 13, 2012

and approved by

Dr. Bill W. Day, Professor, Department of Pharmaceutical Sciences

Dr. Scott G. Nelson, Professor, Department of Chemistry

Dr. Peter Wipf, Professor, Department of Chemistry

Committee Chair: Paul E. Floreancig, Professor, Department of Chemistry

An Investigation in Oxidative Cation Formation: The Total Synthesis of Lactodehydrothyrsiferol and Synthetic Application for a Bimolecular Carbon–Carbon Bond Forming Reaction

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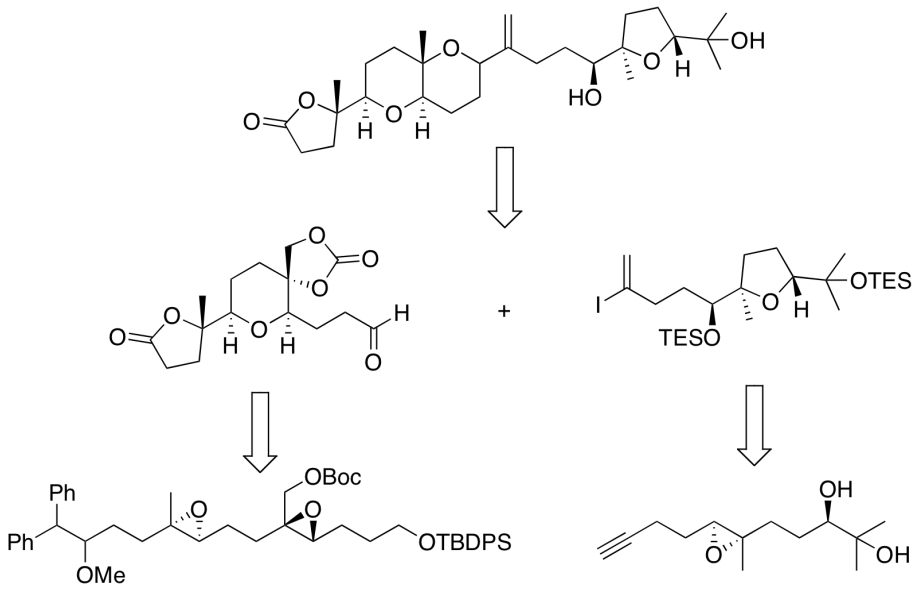
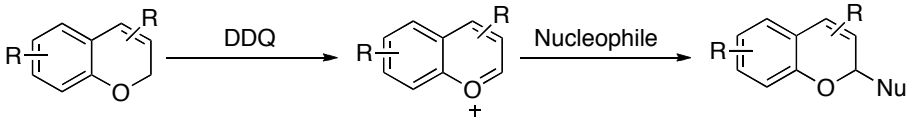
The first total synthesis of lactodehydrothyrsiferol, a selective inhibitor of protein phosphatase 2A, was accomplished through the application of our electron-transfer-initiated cyclization reaction. Other highlights of our synthetic strategy include a novel method for the formation of 1,1-disubstuted vinyl iodides from a terminal alkyne, a Suzuki-Miyaura cross coupling reaction on a iodinated allylic carbonate, a one pot diepoxidation of a diene to generate two epoxides with opposite stereochemical identities, an asymmetric Nozaki-Hiyama-Kishi reaction, and the selective deoxygenation of a triol. This document will focus on the key epoxide cascade and completion of the synthesis.



An oxidative method to form Carbon–Carbon bonds through Carbon–Hydrogen bond cleavage is described herein. Chromene and isochromene both form aromatically stabilized oxocarbenium ions in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). The reactivity of these cations was explored with a variety of nucleophiles. In addition, the electronic properties were altered on the benzopyran ring system to elucidate the substrate scope for this transformation.



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LIST OF ABBREVIATIONS

9-BBN	9-borabicyclo[3.3.1]nonane
BDE	bond dissociation energy
Boc	*tert*-butoxycarbonyl
C–C	Carbon–Carbon
C–H	Carbon–Hydrogen
CMMP	(cyanomethylene)trimethylphosphorane
CSA	camphorsulfonic acid
DCE	1,2-dichloroethene
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	diisobutylaluminium hydride
DMF	dimethylformamide
DMP	Dess–Martin periodinane
DMSO	dimethylsulfoxide
DNP	2,4-dinitrophenyl
E_{pa}	oxidation potential
ETIC	electron transfer initiation cyclization
IBX	2-iodoxybenzoic acid

IR	infrared
MPLC	medium pressure liquid chromatography
NHK	Nozaki-Hiyama-Kishi
NMQ	*N*-methylquinolinium
NMR	nuclear magnetic resonance
PK	protein kinase
PP	protein phosphatse
PPTS	pyridinium *para*-toluenesulfonate
rt	room temperature
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butydimethylsilyl
TES	triethylsilyl
THF	tetrahydrofuran
THP	tetrahydropyran
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl

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Next, I would like to express my thanks to group members past and present. Your patience in training me to become a laboratory scientist will never be forgotten. It was the fun and supportive environment that helped me achieve this academic goal. In addition, I want to sincerely thank all my friends in Chevron that provided me with constructive discussions and greatly appreciated laughs.

Finally, I would like to thank my totally rad wife, Dana. Your support over the last half-decade cannot be described. Your love and kindness provided me with the energy and desire to reach this milestone. I dedicate this document to you and hope to one day be able to repay you for all you have done for me.

1.0 OXIDATIVE CATION FORMATION

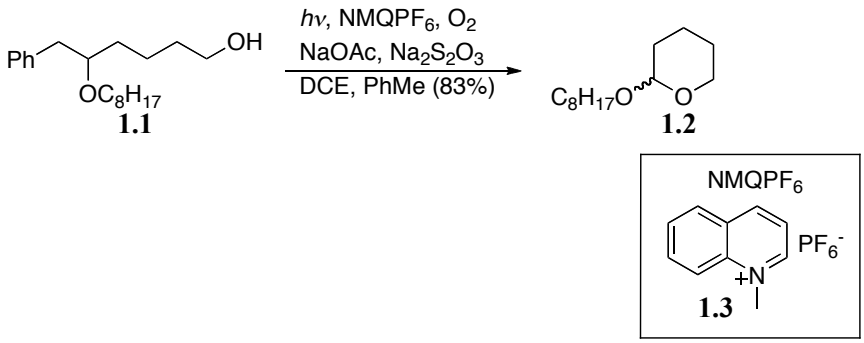
The chemical community has witnessed an increase in reaction methodologies devoted to functionalizing reactive cations obtained through oxidative protocols in the last few decades. These methods rely on designing cations that are stable yet sufficiently reactive enough to undergo a secondary transformation. Additionally, the oxidation procedure is generally mild and extremely chemoselective allowing for great functional group compatibility that makes these reactions useful for organic synthesis. This chapter describes oxidative cation formation through electron transfer to form radical cations and their cleavage and oxidizing activated carbon–hydrogen (C–H) bonds.

1.1 ELECTRON TRANSFER INITIATED CYCLIZATION

1.1.1 Radical Cation Cleavage

Radical cations were widely neglected as useful synthetic intermediates until a strong understanding of their reactivity patterns emerged within the chemical community.[1] This led to the development of a variety of methods to performing electron transfer chemistry to obtain radical cations. The Floreancig group has been active in this area by solving problematic synthetic transformations through the application of our electron transfer initiated cyclization

(ETIC) reaction (Scheme 1.1). The foundation for our research has been provided by Arnold and coworkers' early work on the oxidative cleavage of homobenzylic ethers to generate oxocarbenium ions and benzyl radicals.[2,3]



Scheme 1.1 Example of ETIC Reaction

Electron transfer provides requisite radical cation **1.4** that undergoes mesolytic cleavage to generate both a benzyl radical (**1.5**), which is converted into benzaldehyde,[4] and oxocarbenium ion **1.6** (Figure 1.1). The nucleophile that attacks the nascent electrophile is the tethered hydroxyl group to form tetrahydropyran lactol **1.2**. Our group has extended the ETIC

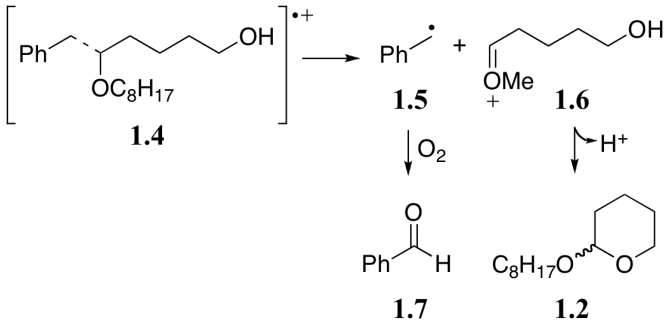


Figure 1.1 Radical Cation Fragmentation and Cyclization

reaction to form multiple heterocycles through thoughtful substrate design. By employing mild oxidation procedures on homobenzylic moieties to generate reactive cations our group has demonstrated the ability to form cyclic acetals,[5] cyclic acyl aminals,[6,7] and 2,6-disubsituted tetrahydropyrones.[8]

One current method for inducing ETIC reactions utilizes an aerobic, organocatalytic, photoinitiated procedure (Scheme 1.1).[9] These reactions are run in a photoreactor with a medium-pressure mercury lamp to cause the photoexcitation of the sensitizer *N*-methylquinolinium hexafluorophosphate ($NMQPF_6$) (**1.3**). Once the *N*-methylquinolinium ion (NMQ^+) (**1.8**) is excited, it performs a single electron oxidation on the cosensitizer toluene (**1.11**) (Figure 1.2). The newly formed radical-cation **1.10** is then free to remove an electron from the homobenzylic moiety present in **1.1** to generate reactive radical cation intermediate **1.4**. The NMQ radical (**1.9**) is oxidized backed to the active sensitizer NMQ^+ (**1.8**) using dioxygen that is gently bubbled through the reaction mixture. Dioxygen is reduced to form superoxide radical anion, and sodium thiosulfate is added to fully reduce superoxide to water. The 4Å molecular

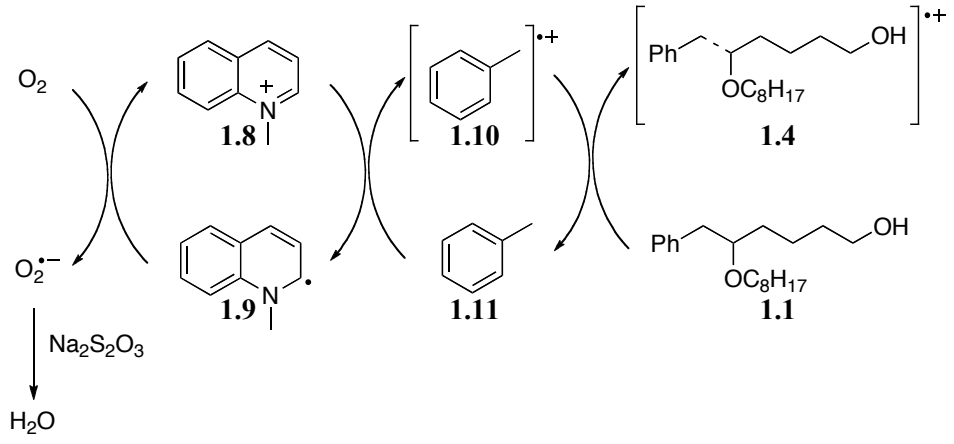
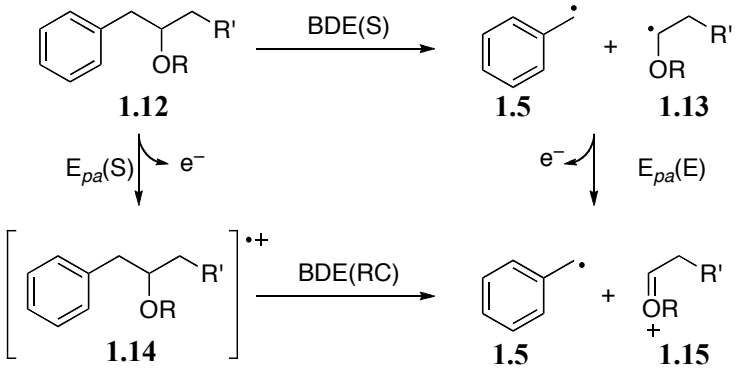


Figure 1.2 Formation of Radical Cation Using Current ETIC Conditions

sieves are added to sequester the water being formed and sodium acetate acts as a buffer to maintain mild conditions.

The cleavage of the radical cation to form a benzylic radical and an oxocarbenium ion warrants further discussion. It is necessary to design the homobenzylic ether with the correct functionality present to ensure that the bond dissociation energy (BDE) is sufficiently low enough that mesolytic cleavage is a favorable pathway.[3] Three factors have been elucidated for determining the BDE for the radical cation (BDE(RC)). These are the BDE for the benzylic bond in starting substrate **1.12** (BDE(S)), the oxidation potential of starting substrate **1.12** (E_{pa}(S)), and the oxidation potential of radical **1.13** (E_{pa}(E)) (Figure 1.3). Rearranging the chemical reaction and solving for BDE(RC) derived equation (1) (Figure 1.3). This equation can be used to aid in the design of substrates that readily undergo radical cation cleavage. Adding electron donating groups to the arene will lower E_{pa}(S) and result in no cation formation;[8] however the BDE(S) can be lowered through adhering stabilizing groups in the benzylic position to promote radical cation cleavage.

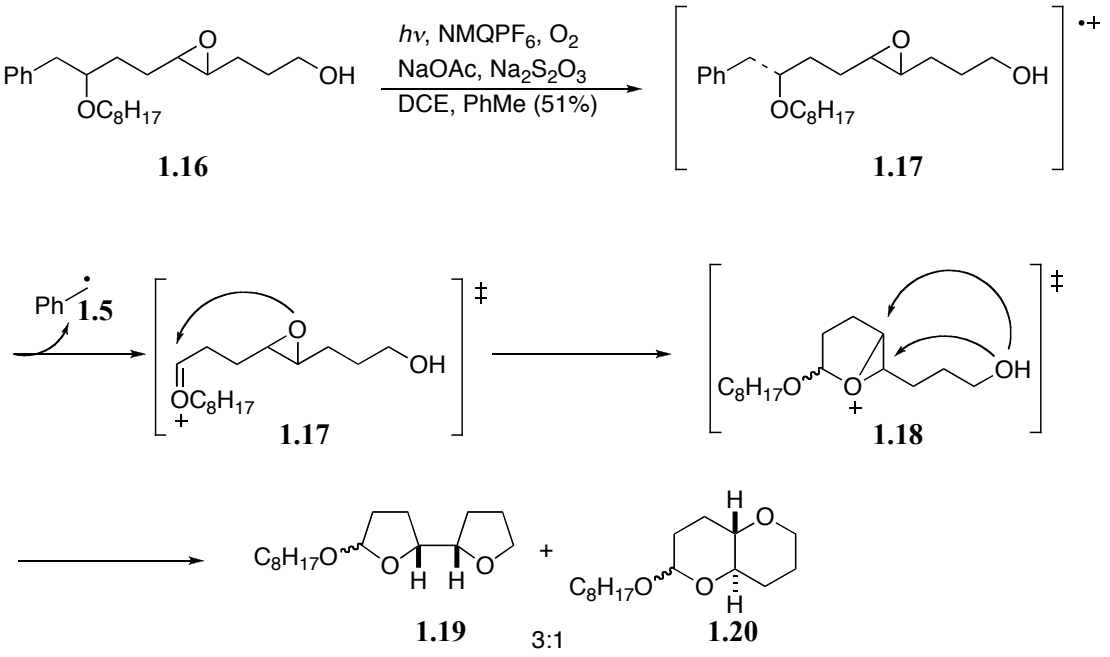


(1) $\quad BDE(RC) = BDE(S) - E_{pa}(S) + E_{pa}(E)$

Figure 1.3 Thermodynamics for Mesolytic Cleavage of Radical Cation

1.1.2 Epoxide Opening Cascade Reactions

The ability to generate complex organic scaffolds from relatively simple reactants under mild reaction conditions has been an area of high priority for the chemical community. These novel cascade reactions provide new options for reaching important chemical targets in a more direct and synthetically aesthetic manner than traditional methods.[10] Cascade reactions are defined as a series of sequential intramolecular transformations that occur in a single reaction. Epoxide opening cascades allow for the formation of polycyclic ether chemical scaffolds. Our mild ETIC procedure proved to be an efficient way of generating these domino reactions (Scheme 1.2).[11]



Scheme 1.2 Example of Epoxide Cascade Reaction

An in depth investigation on the transition states and reaction parameters for epoxide opening cascade reactions was performed to elucidate predictable regiochemical outcomes.

Intramolecular epoxonium ion opening is demonstrated in Figure 1.4. The general epoxonium ion **1.21** has a tethered nuclephile that has two available sites to attack on the neighboring epoxonium ion. Nucleophilic attack on C_1 causes the oxygen of the epoxide to lie outside the newly formed ring. This process is called an *exo* cyclization in accordance with Baldwin rules and the five-membered ring **1.22** is created. The six-membered ring **1.23** is generated from an *endo* cyclization resulting in the epoxide's oxygen placement on the newly formed ring after nucleophilic attack on C_2. Due to the potential for two separate reaction pathways resulting from the epoxonium-opening reactions Floreancig and coworkers set out to study and understand these processes in the context of cascade reactions.

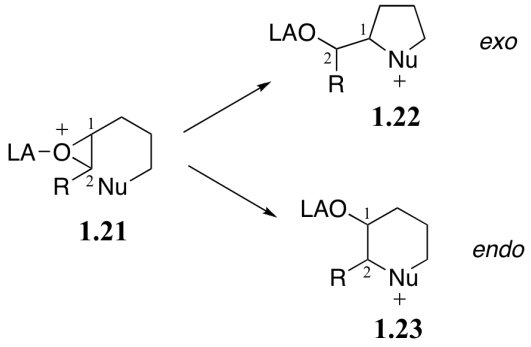


Figure 1.4 *Exo* versus *Endo* Cyclization of Epoxonium Ions

Efforts from both the Floreancig and Houk labs have aided in the understanding, both from a physical and mechanistic basis, in applying the oxidatively initiated epoxide cascade reaction to synthesis.[12] The regiochemical outcomes of the reactions based on epoxide substitution pattern (disubstituted versus trisubstituted), ring size of the bicyclic epoxonium ion ([3.1.0] versus [4.1.0]), and the Lewis acid used (oxocarbenium ions versus carbenium ions) were investigated.[13] The key variable in these transformations was revealed to be the ring size of

the bicyclic epoxonium ion. It was shown that bicyclo[4.1.0] epoxonium ions prefer *endo* cyclization (Figure 1.5). This stems from the dihedral angle of the *endo* attack being less distorted and lower in energy than the strained attack angle for the *exo* cyclization. Due to the larger ring size, the postulated transition state has more S_N1 character. This point is reinforced when one compares trisubstituted and disubstituted bicyclo[4.1.0] epoxonium ions. The trisubstituted compound undergoes exclusive *endo* cyclization because of the favored attack geometry and the stabilized, partially formed tertiary carbocation; however, the disubstituted compound shows no preference for *endo* or *exo* cyclization. The dihedral angle for *endo* cyclization of the disubstituted system is distorted significantly and the reaction pathway shows more S_N2 character. The increase in energy for the *endo* cyclization causes both outcomes to be observed.

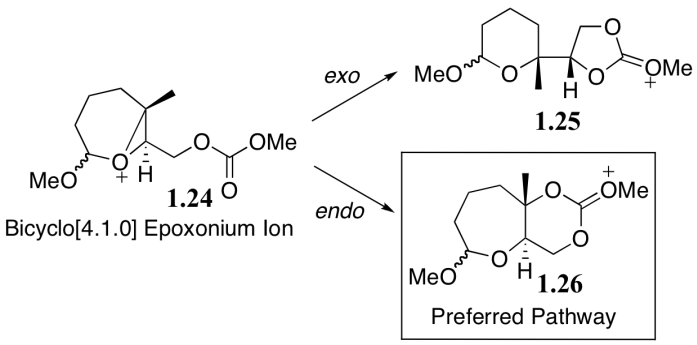


Figure 1.5 Opening of Bicyclo[4.1.0] Epoxonium Ions

The smaller bicyclo[3.1.0] epoxonium ion has a more distorted, higher energy *endo* cyclization transition state that forces it to undergo the lower energy *exo* cyclization (Figure 1.6). The Lewis acidity has a minor role in predicting the outcome for bicyclo[3.1.0] epoxonium ion. When an epoxide and a non-stabilized carbenium ion react, only *exo* cyclization is observed. However, the epoxonium ion formed from an oxocarbenium ion and an epoxide generally provides a decrease in *exo* selectivity. This observation stems from the lowering of the transition

state energy of the *endo* cyclization, due to the anomeric effect operating when the methoxy group adopts a pseudoaxial position off the ring.

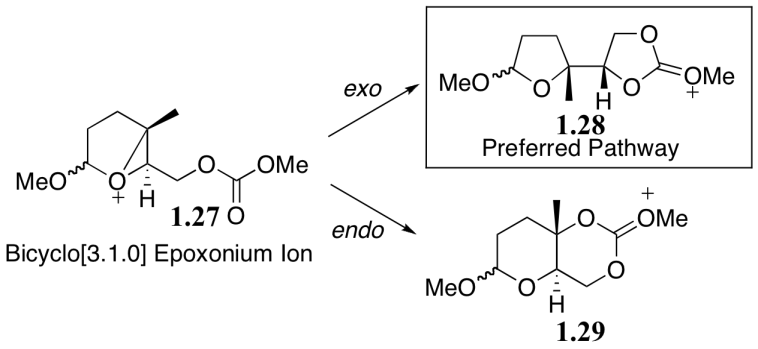


Figure 1.6 Opening of Bicyclo[3.1.0] Epoxonium Ions

1.2 CARBON–HYDROGEN BOND FUNCTIONALIZATION AND OXIDATIVE MEDIATED CROSS COUPLING REACTIONS

1.2.1 Introduction

The use of carbon-hydrogen (C–H) bond functionalization to furnish carbon–carbon (C–C) bonds has become an increasingly popular research focus over the past two decades.[14] These methods differ from traditional metal mediated cross-coupling reactions due to their ability to conduct this fundamental organic transformation without the need to convert unreactive starting materials into activated coupling partners (Figure 1.7).[15,16] Thus, C–H bond activation provides a practical way to achieve synthetic strategies that are both step[17] and atom economical.[18] Numerous total syntheses of biologically active molecules have been completed using this strategy.[19] Even though there are multiple ways to achieve C–H bond activation, this document

will be focused on the oxidative methods that utilized 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[20]

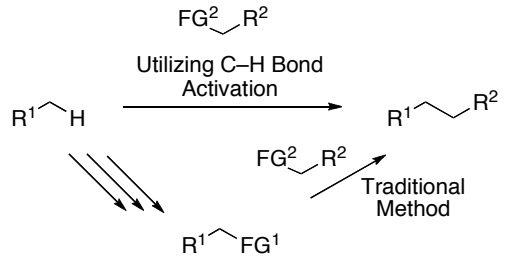
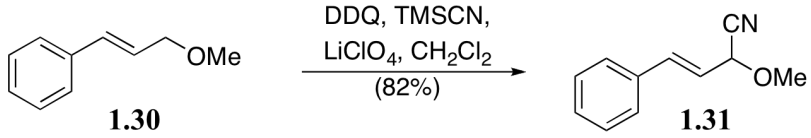


Figure 1.7 Benefits of Using C–H Bond Activation

1.2.2 DDQ Mediated Carbon–Hydrogen Bond Activation Functionalization

DDQ mediated C–H bond functionalization is most commonly seen during *para*-methoxybenzyl ether cleavage.[21] Successful C–H bond cleavage was achieved under this oxidative protocol due to the electron rich arene providing stabilization through its π-orbitals for the developing cation intermediate. In 1987, Mukaiyama and coworkers published their research showing a useful method for C–C bond formation using a similar oxidative C–H bond cleavage protocol (Scheme 1.3).[22] They were able to oxidize activated ethers with DDQ to form cation intermediates. Addition of $LiClO_4$ aided in disrupting the resulting DDQ adduct and forming an

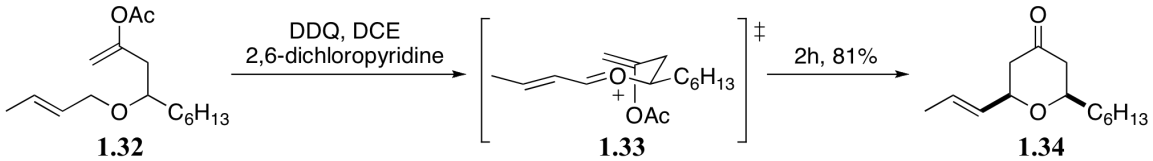


1.30 **1.31**

Scheme 1.3 Mukaiyama Oxidative Method to Form C–C Bonds

ion pair that would react with a selected number of nucleophiles.[23] Since their pivotal publication, numerous examples of C–H bond functionalization procedures have been reported using DDQ as the oxidant.

The Floreancig group's familiarity with oxidative cation formation provided them with the requisite skill set to provide novel methods in this field. They first expanded the substrate scope to include allylic ethers after successfully showing that benzyl ethers can undergo oxidation to react with tethered nucleophiles.[24] Allylic ether **1.32** underwent cyclization to yield tetrahydropyrone **1.34** with excellent diastereocontrol (Scheme 1.4). This stereochemical outcome is attributed to the reaction proceeding through a chair transition state. This observation was later used for the key transformation in the synthesis of the neopeltolide macrocycle.[25] The diastereoselectivity was shown to diminish when propargyl ethers were exposed to the reaction conditions.[26] This stems from alkynes being less sterically demanding than alkenes. The looser transition state was used advantageously to produce all four possible diastereomers of 2,6-substituted-tetrahydropyra-4-ols. We recently have reported the ability to oxidize and cyclize enamides, *N*-vinyl sulfonamides, and vinyl sulfides to form piperidines and sulfur containing heterocycles.[27,28]



1.32 **1.33** **1.34**

Scheme 1.4 DDQ Mediated Process to Form Tetrahydropyrones

A mechanistic study was needed in order to postulate the pathway for the DDQ mediated oxidation of activated ethers. Dr. Jung accomplished this by exploiting the kinetic isotope effect

(Figure 1.8).[29] The research revealed that an electron transfer occurs quickly between benzylic ether **1.35** and DDQ **(1.36**). This process provides radical cation **1.37** which undergoes either a hydrogen atom abstraction or a proton transfer followed by an electron transfer to generate oxocarbenium ion **1.39**. This mechanistic study also elucidated that the removal of hydrogen from the radical cation is the rate determining step. The mesolytic cleavage of the benzylic bond follows the thermodynamic trends previously derived in equation (1) (Figure 1.3). Therefore, it was showen clearly that these reactions follow an electron transfer mechanism versus a hydride transfer mechanism.

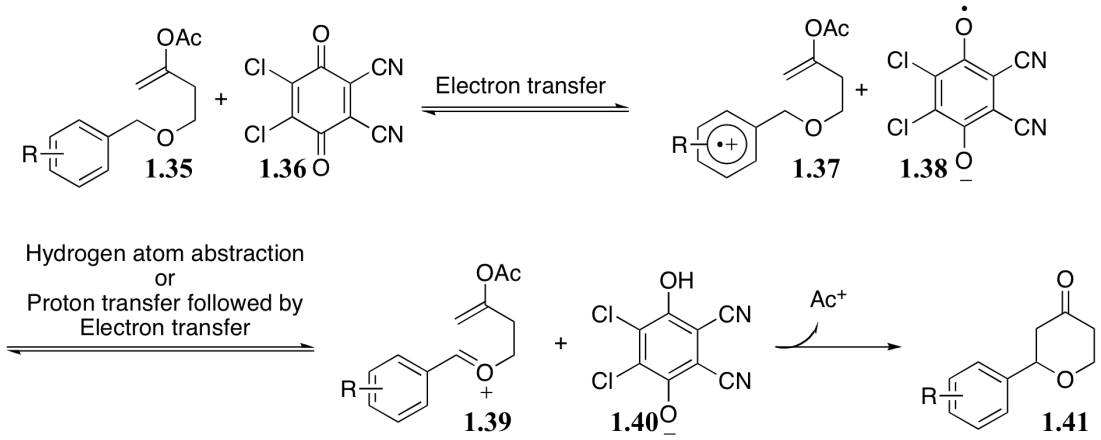


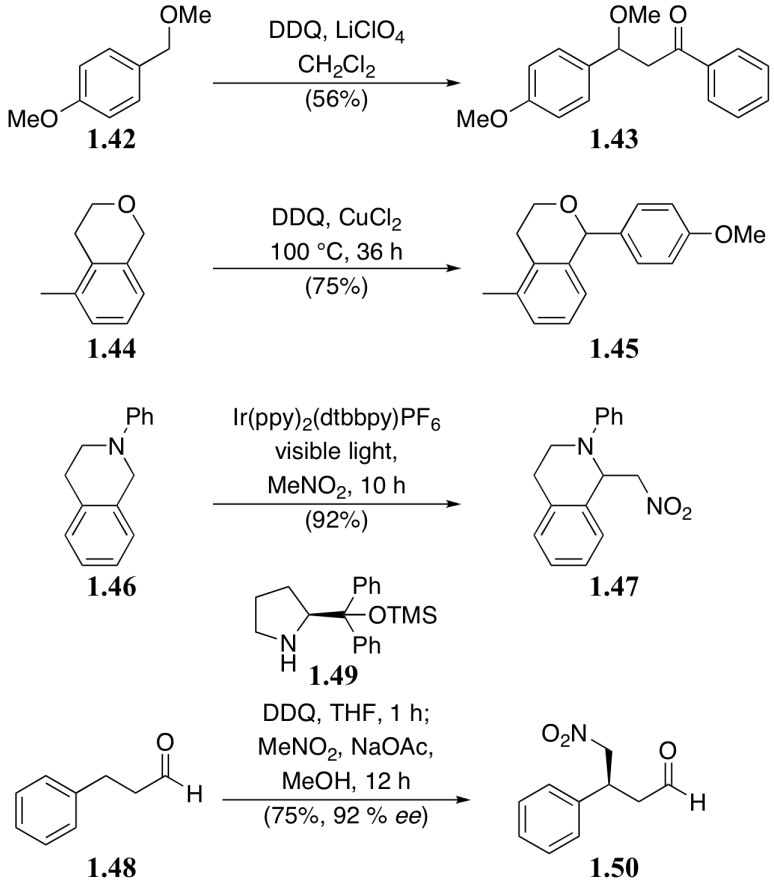
Figure 1.8 Proposed Mechanism for DDQ Oxidation

1.2.3 Oxidative Cross-Coupling Reactions

Bimolecular reactions are important for convergent syntheses and building diverse compound collections. An emerging class of cross-coupling reactions devoted to reacting cations achieved through oxidative C–H bond cleavage with a variety of nucleophiles has provided new options.[30] The underlying factor present in these oxidative coupling reactions has always been

creating a stable cation. These cations must be sufficiently reactive to undergo a bimolecular process and stable enough to avoid decomposition.

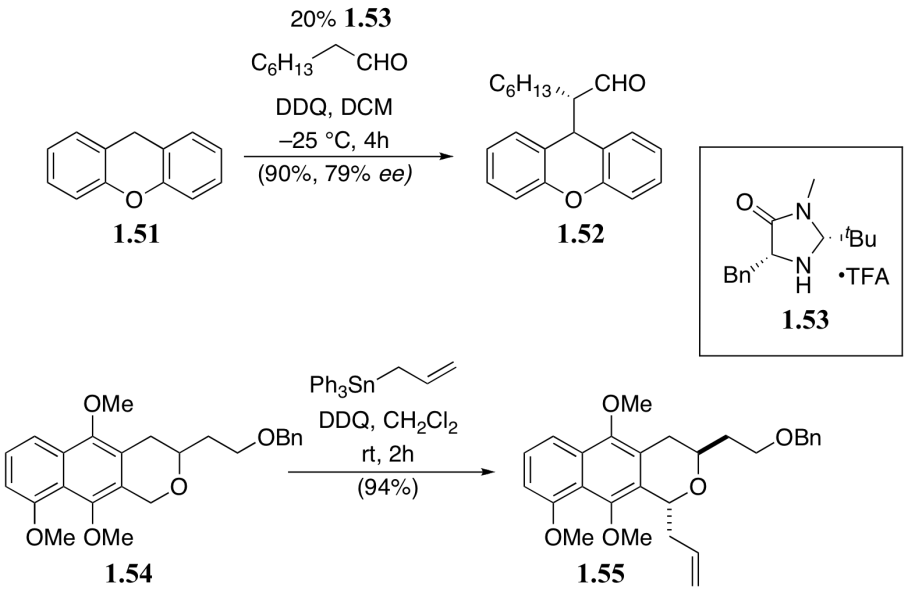
This was accomplished in many research laboratories by designing reactions around a specific substrate class (Scheme 1.5). Xu and coworkers extended Mukaiyama's procedure from electron rich alkenes to include activated benzylic ethers.[31] It is important to note that no product was formed in the absence of electron donating groups on the arene. The extension of theses methods to include heterocycles promises more alternatives to reach biologically active scaffolds. The oxidized version of isochroman was shown to undergo a Friedel–Crafts reaction with anisole to form coupling product **1.45**.[32] Stephenson and coworkers recently displayed their



Scheme 1.5 Selected Examples of Oxidative Cross-Coupling Reactions

ability to alkylate tetrahydroisoquinolines using a light induced iridium catalyzed oxidative procedure.[33] Additionally, Hayashi and coworkers created a method to perform an asymmetric variant.[34] This chemistry was performed using proline derived organocatalyst **1.49** to furnish a chiral enamine species. The enamine undergoes oxidation by DDQ to form an iminium ion that undergoes a stereospecific attack by nitromethane.

Cozzi and coworkers also provided the chemical community with an asymmetric version.[35] They use a chiral enamine, obtained through the dehydration of an aldehyde by organocatalyst **1.53**, to attack aromatically stabilized carbocations (Scheme 1.6). They were able to extend this chemistry to include a variety of aromatic substrates with good results. In addition, oxidative C–C bond forming protocols have been extended to total synthesis. Deoxyfrenolicin *trans*-geometry was achieved through the allylation of the DDQ oxidized version of naphthopyran **1.54**.[36]



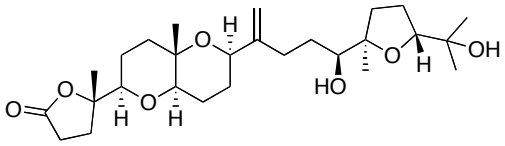
Scheme 1.6 More Examples of Oxidative Cross-Coupling Reactions

2.0 LACTODEHYDROTHYRSIFEROL

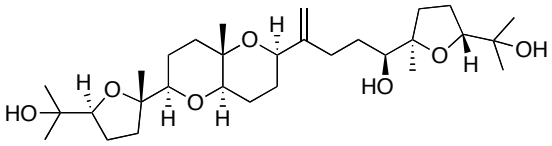
2.1 INTRODUCTION

2.1.1 Isolation of Natural Products from Marine Organisms

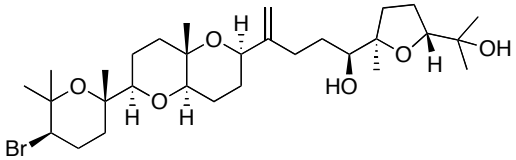
The red algae of the genus *Laurencia* produces a wide number of squalene derived secondary metabolites.[37-41] Fernández and coworkers have isolated many related polyether compounds from the red seaweed *Laurencia virdis* native to the Canary Islands (Figure 2.1).[41]



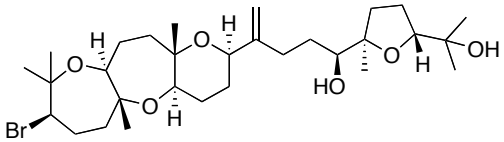
(**2.1**) Lactodehydrothyrsiferol



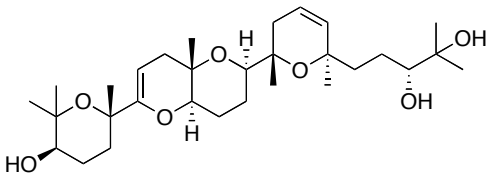
(**2.2**) Pseudodehydrothyrsiferol



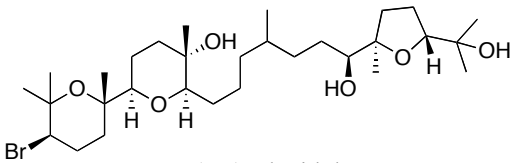
(**2.3**) Dehydrothyrsiferol



(**2.4**) Dioxepandehydothyrsiferol



(**2.5**) Martiriol



(**2.6**) Clavidol

Figure 2.1 A Selection of Polyethers Isolated from *Laurencia viridis*

This class of compounds has already received a great deal of attention in the chemical community, with the syntheses of pseudodehydrothyrsiferol (**2.2**) by Hioki and coworkers[42] and *ent*-dioxepandehydrothyrsifol (*ent*-**2.4**) by Jamison and coworkers.[43] The Floreancig group's interest in lactodehydrothyrsiferol (**2.1**) stems from our novel approach to constructing multicyclic polyethers through oxidatively initiated cascade reactions.[12]

2.1.2 Structure Determination of Lactodehydrothyrsiferol

Lactodehydrothyrsiferol (**2.1**) has many key structural components that make it an attractive and challenging target (Figure 2.2). The A ring was shown to be comprised of a γ-lactone moiety with an absorption at ν_{max} 1771 cm^{-1} in the IR region.[41] This 5-membered lactone is attached to a *trans*-fused pyranopyran ring system. This bicyclic ring motif is common in many of the compounds isolated from the genus *Laurencia*. Extensive NMR and X-ray analysis have concluded that the B-ring adopts the chair conformation. However, the C-ring prefers the twist boat conformation to avoid a 1,3-diaxial interaction.[37,40] The right side of the molecule contains a *trans*-fused tetrahydrofuran ring tethered by a short hydrocarbon chain to the pyranopyran ring through a vinyl linkage.

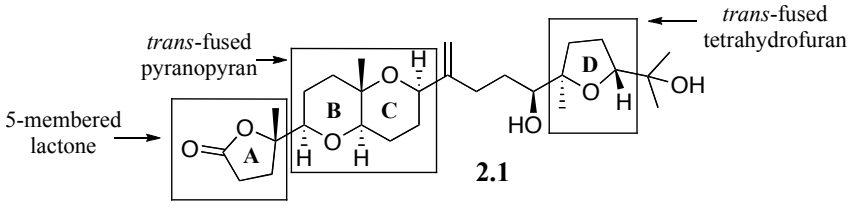


Figure 2.2 Polycyclic Ring System of Lactodehydrothyrsiferol

2.1.3 Biological Activity

The typical eukaryotic cell is able to regulate cellular activities through protein phosphorylation. This process takes place via protein kinases (PK), which attach phosphate groups to enzymes, and protein phosphatases (PP), which cleave phosphate groups from enzymes. These molecules allow the cell to control the timing of its life cycle and respond to extracellular signals.[44] By studying the role of specific PKs and PPs, one can achieve great insight into cellular pathways and function.

The class of compounds isolated by Fernández and coworkers (Figure 2.1) have been shown to be selective inhibitors of the serine/threonine protein phosphatase 2A (PP2A). They accomplish their inhibition while not interfering with other serine/threonine protein phosphatase (protein phosphatase 1 (PP1), 2B (PP2B), 2C (PP2C), and protein tyrosine phosphatase (PTP)). These compounds show modest inhibition on PP2A (Table 1), with **2.1** having a IC_{50} of 100 μm.[45] Compound **2.1** also exhibits non-linear inhibition of PP2A suggesting that it is a partial inhibitor. Previous work on the structurally similar compound thyrsiferyl 23-acetate (**2.8**) (Figure 2.3) has shown the same selective results with a more potent IC_{50} of 4-16 μm depending on enzyme concentration.[46]

Table 2.1 Inhibition Percentage on PP2A of Selected Compounds[45]

	Concentration			
Compound	1μM	10 μM	100μM	250μM
2.1	33.7	40.1	49.4	63.2
2.2	0	4.7	65.1	57.2
2.3	8.2	12.2	25.2	37.7
2.4	18.9	20.4	59.7	66.5
2.6	43.6	45.9	57.8	74.5

There have been reports of other natural products with more potent activity towards the inhibition of PP2A: including the polyketide calyculin A (**2.7**), the terpenoid cantharidin (**2.9**), and marine polyether okadaic acid (**2.10**) (See Figure 2.3).[47,48] The IC_{50} for these compounds are 0.1-1 nM, 40 nM, and 0.2 nM.[49] These compounds are dramatically more potent then **2.1** and **2.8**, however are lacking the selectivity that **2.1** and **2.8** exhibit for PP2A. Natural products **2.7**, **2.9**, and **2.10** all are potent towards the inhibition of PP1 and/or PP2B. The inability for these molecules (**2.7**, **2.9**, and **2.10**) to inhibit only one PP in the cell does not make them a good choice to study cellular pathways that involve a single phosphatase.

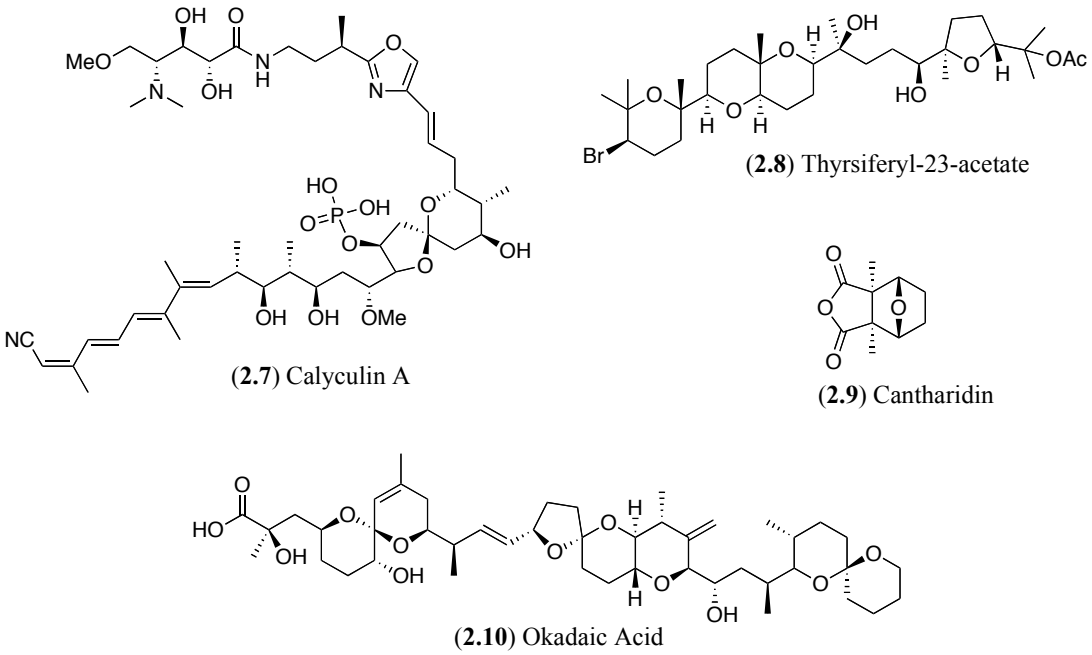


Figure 2.3 Selected Compounds that Inhibit PP2A

2.2 PREVIOUS SYNTHESIS OF RELATED COMPOUNDS

2.2.1 Forsyth's Total Synthesis of Thyrsiferyl 23-Acetate

Forsyth and coworkers reported the first total synthesis of thyrsiferyl 23-acetate (**2.8**) in the spring of 2000.[50] Their retrosynthetic analysis is displayed in Figure 2.4. They were able to design a convergent approach by performing multiple Nozaki-Hiyama-Kishi (NHK) cross-coupling reactions.[51-53] The first NHK disconnection of title compound **2.8** leads to the requisite coupling partners **2.11** and **2.12**. Aldehyde **2.11** can be formed through an additional NHK coupling of aldehyde **2.13** and halide **2.14**.

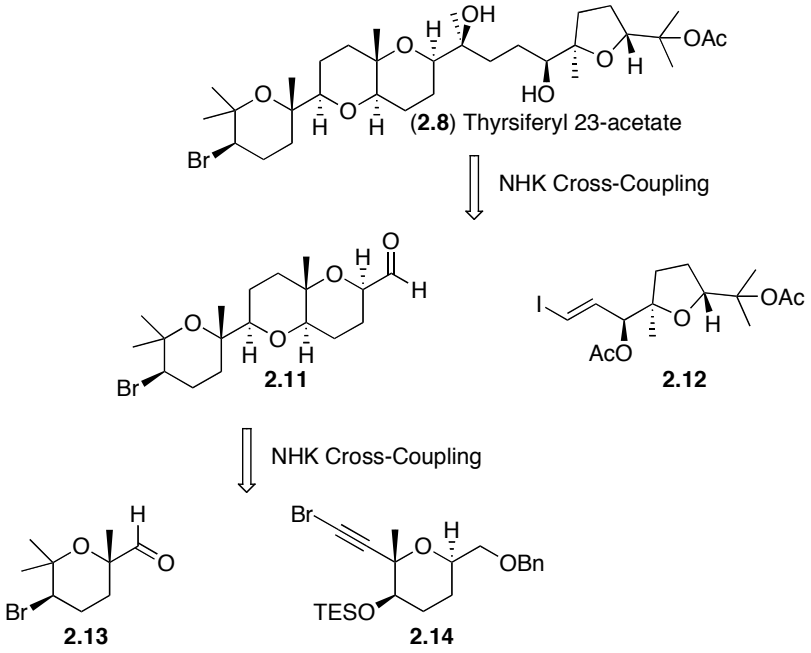
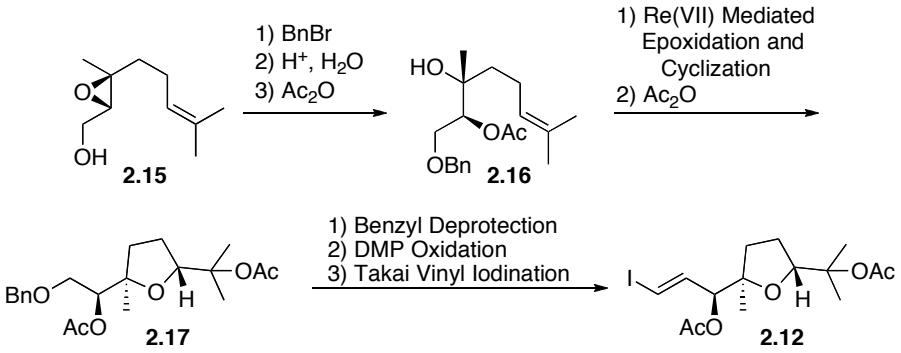


Figure 2.4 Retrosynthetic Analysis of Thyrsiferyl 23-Acetate

Vinyl iodide **2.12** was synthesized from known geraniol derived epoxide **2.15**. Tetrahydrofuran (THF) cyclization precursor **2.16** was furnished through the acid mediated

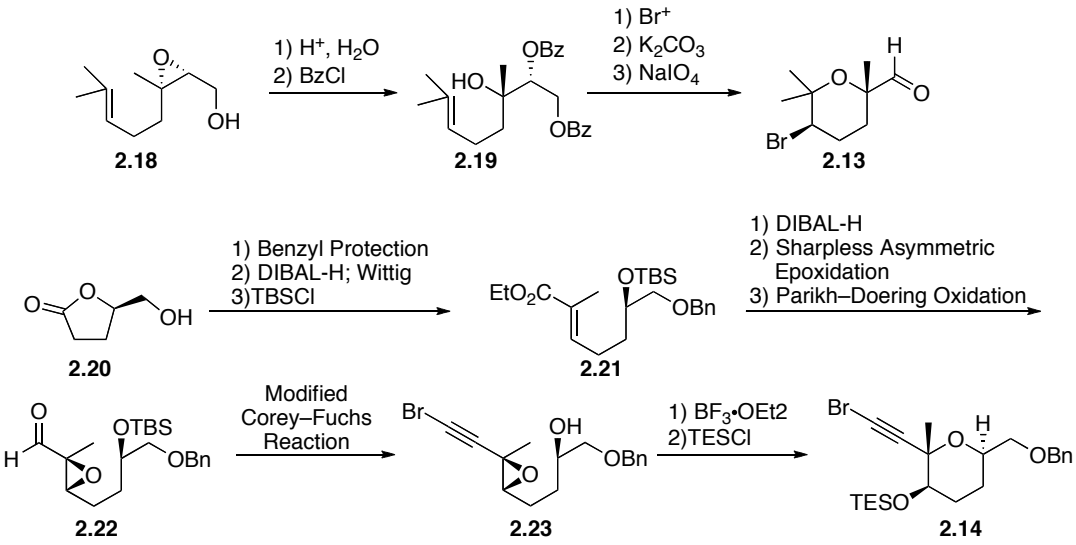
epoxide opening and after the necessary protecting group chemistry was performed on substrate **2.15**. A Re(VII) mediated epoxidation and cyclization afforded the desired *trans*-THF ring system.[54] THF **2.17** was converted to the NHK coupling partner **2.12** through protecting group manipulations, Dess-Martin periodinane oxidation,[55] and conversion of the aldehyde to a *trans*-substituted vinyl iodide using Takia's procedure.[56]



Scheme 2.1 Synthesis of Vinyl Iodide 2.12

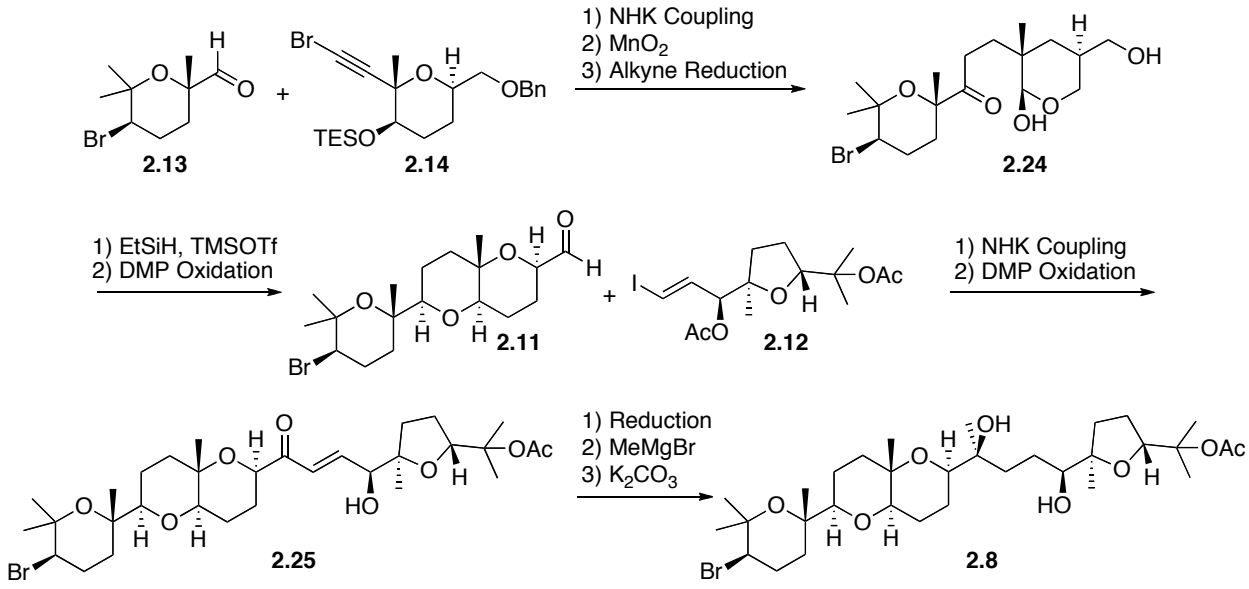
The synthetic schemes for the precursors of substrate **2.11** are shown in Scheme 2.2. Known epoxy-geraniol derivative **2.18** was converted to cyclization precursor **2.19** through acid mediated epoxide opening and protection. In the presence of a bromine cation, alkene **2.19** was cyclized into a mixture of separable haloalkanes. Tetrahydropyran (THP) **2.13** was furnished after benzoyl deprotection and sodium periodate oxidation. In contrast, THP **2.14** was formed starting with chiral lactone **2.20**. The α,β-unsaturated ester system present in substrate **2.21** was formed through the partial reduction of lactone **2.20** and Wittig homologation.[57] DIBAL-H reduction, Sharpless asymmetric epoxidation,[58] and Parikh-Doering oxidation provided substrate **2.22**.[59] A modified Corey-Fuchs reaction provided the requisite alkynyl bromide functionality in

substrate **2.23**.[60] The synthesis of **2.14** was completed after Lewis acid mediated THP formation and silyl protection.



Scheme 2.2 Synthesis of THP 2.13 and THP 2.12

The synthesis was completed after all the necessary coupling partners were formed. Aldehyde **2.13** and alkynyl bromide **2.14** were joined using the traditional NHK protocol (Scheme 2.3).[51-53] THP cyclization precursor **2.24** was yielded after allylic alcohol oxidation and alkyne reduction. The pyranopyran ring system present in **2.11** was created using triethylsilane and trimethylsilyl trifluoromethanesulfonate (TMSOTf) and the required aldehyde was generated through DMP oxidation.[55] Another NHK cross-coupling reaction was performed to join aldehyde **2.11** and vinyl iodide **2.12**. The total synthesis of thyrsiferyl 23-acetate (**2.8**) was completed after the allylic alcohol functionality was converted into the saturated tertiary alcohol and protecting group manipulation.



Scheme 2.3 Completion of Synthesis for Thyrsiferyl 23-Acetate

2.2.2 Hioki's Total Synthesis of Pseudodehydrothyrsiferol

Early in 2009, Hioki and coworkers reported the first total synthesis of the polyether pseudodehydrothyrsiferol (**2.2**).[42] By disconnecting fragment **2.26** from **2.27** through a Suzuki-Miyaura coupling the authors were able to take a convergent approach (Figure 2.5).[61-63] Vinyl bromide **2.27** was constructed from farnesol (**2.30**) via an acetyl protection followed by an oxidation and baker's yeast reduction to induce the correct stereochemistry of the newly formed diol on diene **2.31 (**Scheme 2.4).[64,65] Tetrahydrofuran **2.29** was formed via a Shi epoxidation on the central alkene, followed by cyclization.[66] After protecting group manipulation, oxidation of

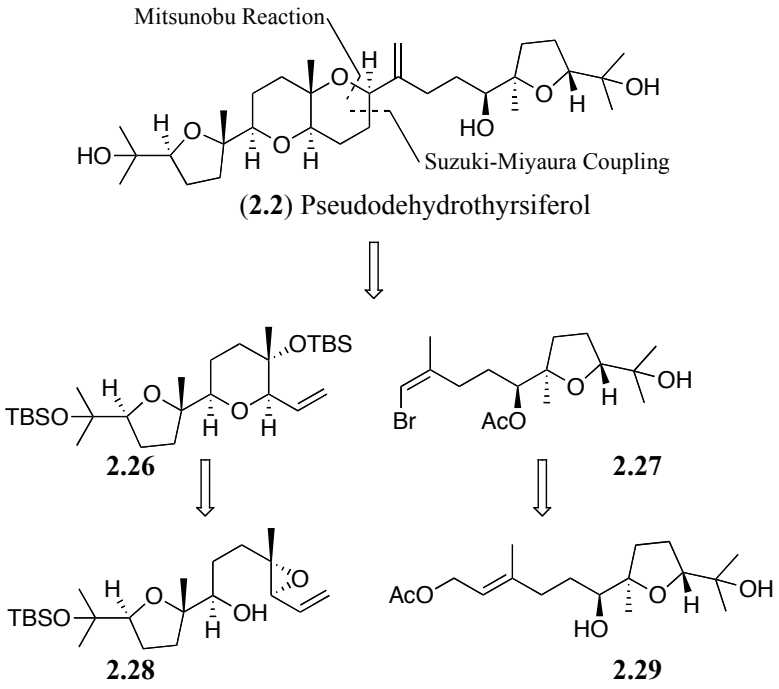
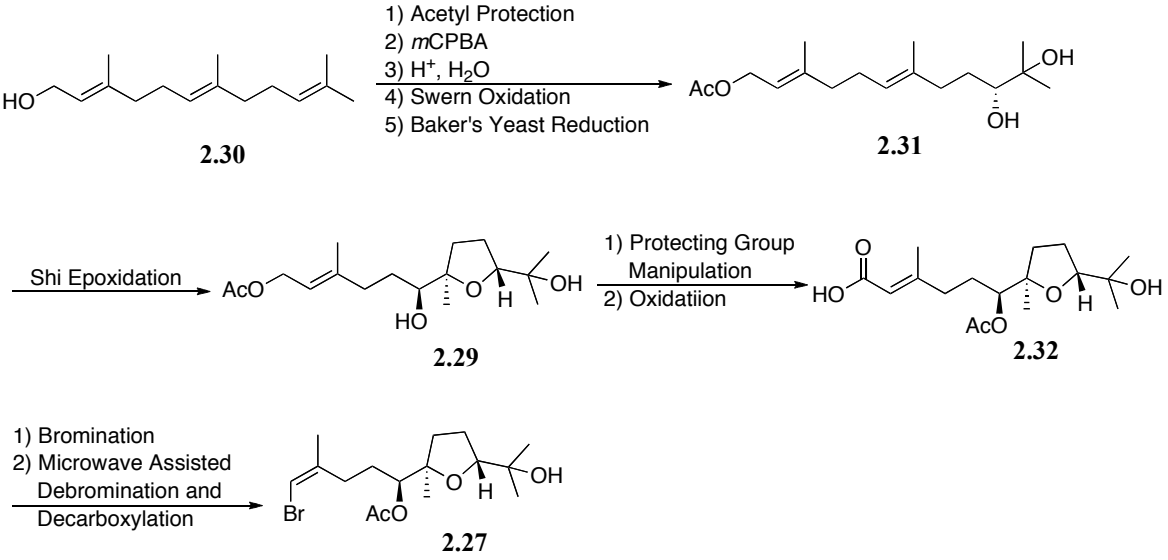


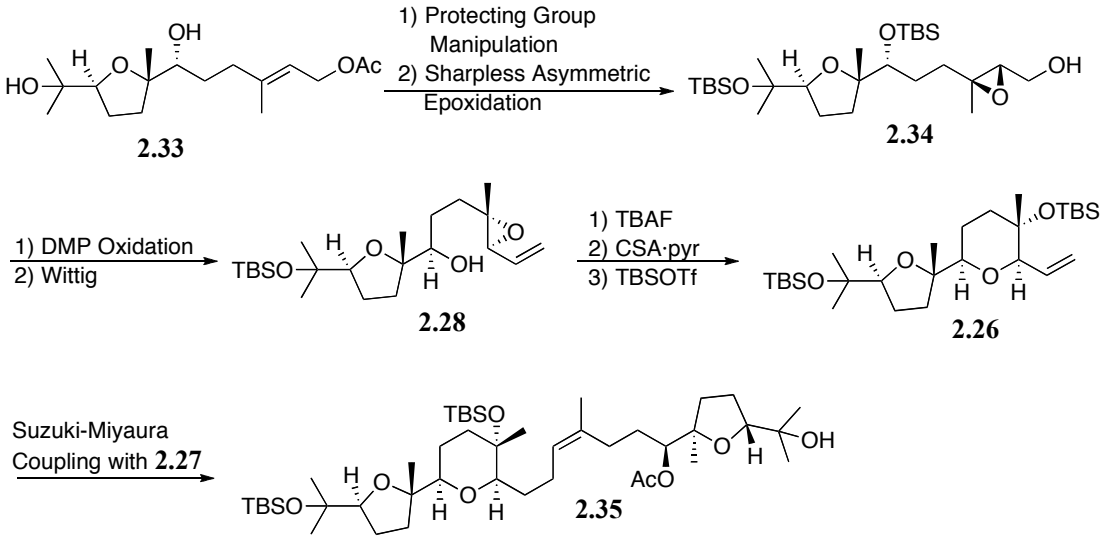
Figure 2.5 Retrosynthetic Analysis of Pseudodehydrothyrsiferol

the primary allylic alcohol afforded acid **2.32**. Bromination of the remaining alkene followed by a microwave assisted stereospecific reaction resulted in decarboxylation and debromination to give vinyl bromide **2.27**.[67]



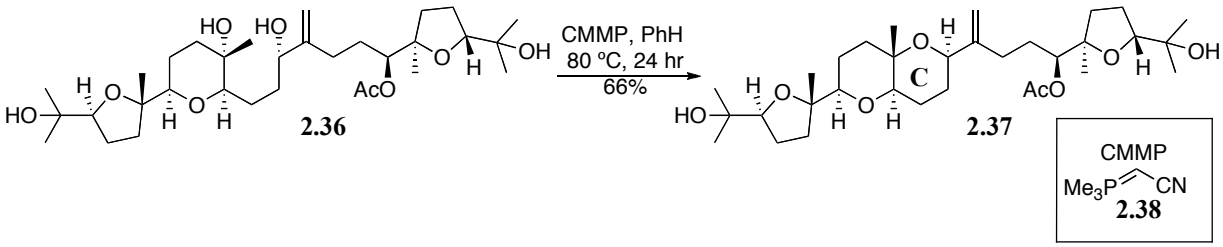
Scheme 2.4 Synthesis of Vinyl Bromide 2.27

Tetrahydrofuran **2.33** was constructed in a similar manner to tetrahydrofuran **2.29** (Scheme 2.5).[68] Epoxide **2.34** was synthesized through protecting group manipulation and the epoxide was introduced stereoselectively using Sharpless asymmetric epoxidation.[58] Oxidation of the primary alcohol to the aldehyde provided the needed functionality to perform a Wittig reaction to generate alkene **2.28**.[57] After mild acid promoted cyclization and silyl protection, alkene **2.26** was successfully coupled with vinyl bromide **2.27** to furnish the polyether **2.35**.



Scheme 2.5 Synthesis of Diene 2.26 and Suzuki-Miyaura Cross-Coupling

Instillation of an allylic secondary alcohol through epoxide formation, followed by an isomerization reaction, and protection group manipulation gave tetraol **2.36**. The Hioki group employed a modified Mitsunobu reaction[69] using the Tsunoda reagent,[70] CMMP (**2.38**), to achieve closure of the twist-boat C-ring (Scheme 2.6). This method proved to be effective and after deprotection of polycycle **2.37** the group successfully synthesized the natural product **2.2**.



Scheme 2.6 Formation of C-Ring System Using CMMP

2.2.3 Jamison's Total Synthesis of *ent*-Dioxepandehydrothyrsifol

Jamison and coworkers completed the total synthesis of *ent*-dioxepandehydrothyrsiferol (**2.4**) utilizing an epoxide-opening cascade sequence in mid 2009.[43] The first disconnection

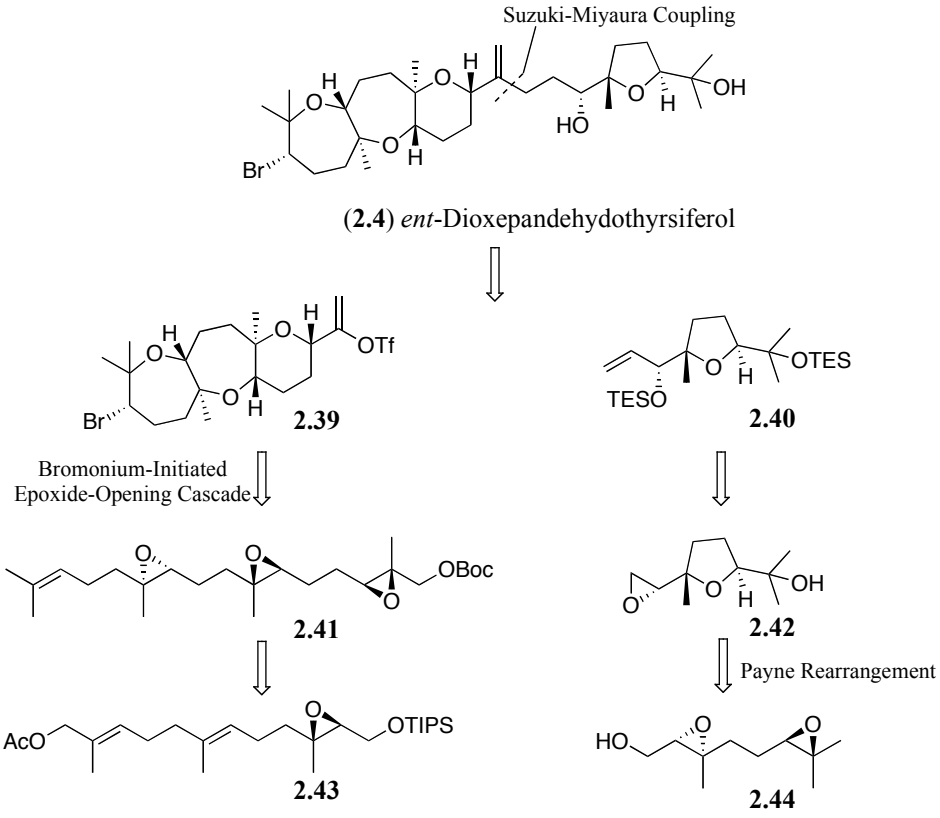
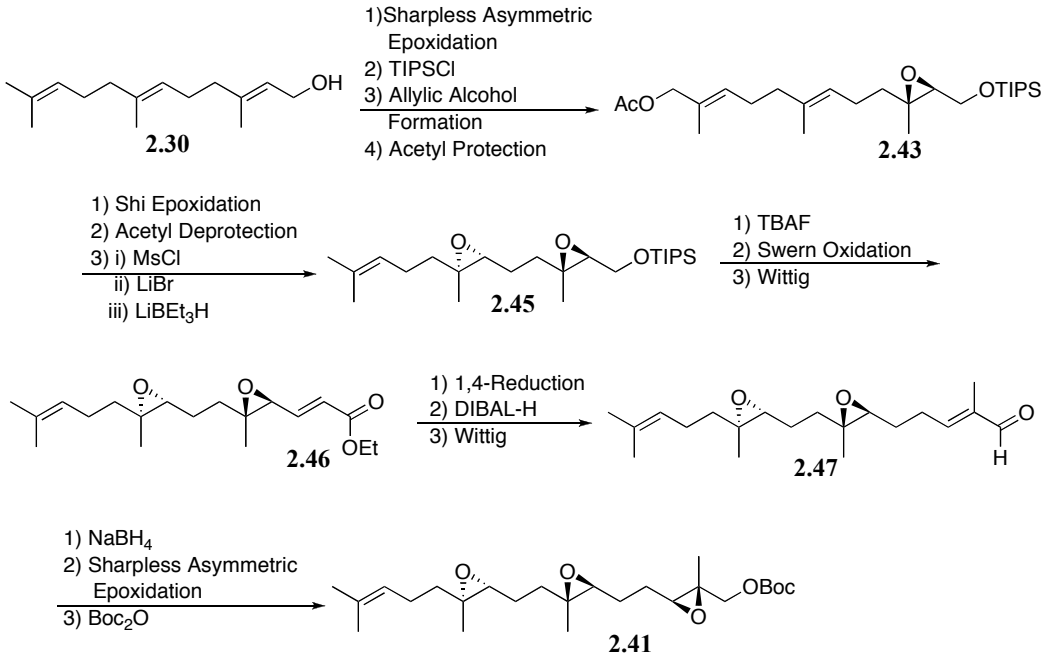


Figure 2.6 Retrosynthetic Analysis of *ent*-Dioxepandehydrothyrsifol

was to bisect the molecule into vinyl triflate **2.39** and alkene **2.40**, which could be joined together using a Suzuki-Miyaura coupling (Figure 2.6).[61-63] Known diepoxide **2.44**[71] was converted to tetrahydrofuran **2.42** through a Payne rearrangement.[72] Treatment of **2.42** with an ylide derived from trimethylsulfonium iodide[73] and silyl protection furnished the desired alkene **2.40**.

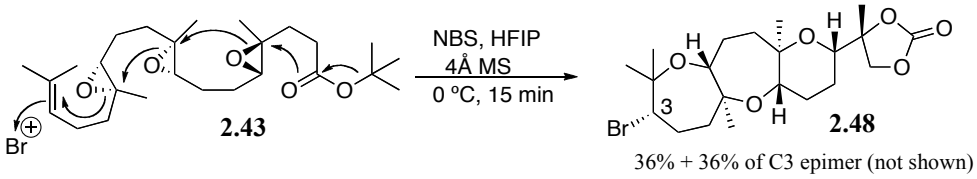
Sharpless asymmetric epoxidation[58] of farnesol (**2.30**) (Scheme 2.7) followed by formation of an allylic acetate and silyl protection provided epoxide **2.43**. Shi epoxidation[66] was performed prior to the allylic acetate being converted into an allylic alcohol to ensure selectivity between the two alkenes. The resulting allylic alcohol was transformed into the allylic bromide, which was reduced to afford a trisubsituted alkene moity in diepoxide **2.45**. Deprotection followed Swern oxidation[74] and a two-carbon Wittig[57] homologation resulted in allylic ester



Scheme 2.7 Synthesis of Triepoxy Carbonate 2.41 for Cascade Reaction

2.46. Using a copper mediated 1,4-reduction of the alkene and DIBAL-H reduction of the ester to an aldehyde provided the substrate necessary for the following Wittig reaction[57] to create allylic aldehyde **2.47**. Triepoxide **2.41** was ultimately accessed after reduction of the aldehyde to an allylic alcohol, Sharpless asymmetric epoxidation, and installation of a *tert*-butyl carbonate.

Triepoxide **2.43** underwent an epoxide-opening cascade via a bromine cation to generate carbonate **2.48** and its carbon three epimer in good yields. Carbonate **2.48** was converted to the needed coupling partner **2.39** via carbonate deprotection, oxidative cleavage, and vinyl triflate formation (Figure 2.6). Alkene **2.40** was then successfully coupled to vinyl triflate **2.39** using a Suzuki-Miyaura coupling.[61-63] Silyl deprotection generated the natural product **2.4**.



Scheme 2.8 Epoxide Cascade of Epoxy Carbonate 2.43 via a Bromonium Ion

2.3 PREVIOUS WORK ON THE TOTAL SYNTHESIS OF LACTODEHYDROTHYRSIFEROL

2.3.1 Retrosynthetic Analysis of Lactodehydrothyrsiferol

This work on the total synthesis of lactodehydrothyrsiferol (**2.1**) began with the retrosynthetic analysis presented in Scheme 2.7. Allylic alcohol **2.49** can be formed through a Nozaki-Hiyama-Kishi (NHK) reaction of coupling partners aldehyde **2.50** and vinyl iodide

2.51.[51-53] Aldehyde **2.50** will be obtained by performing the ETIC reaction on diepoxide **2.52**, derived from diene **2.54**. Vinyl iodide **2.51** will be accessed from epoxide **2.53**, generated from geraniol (**2.55**).

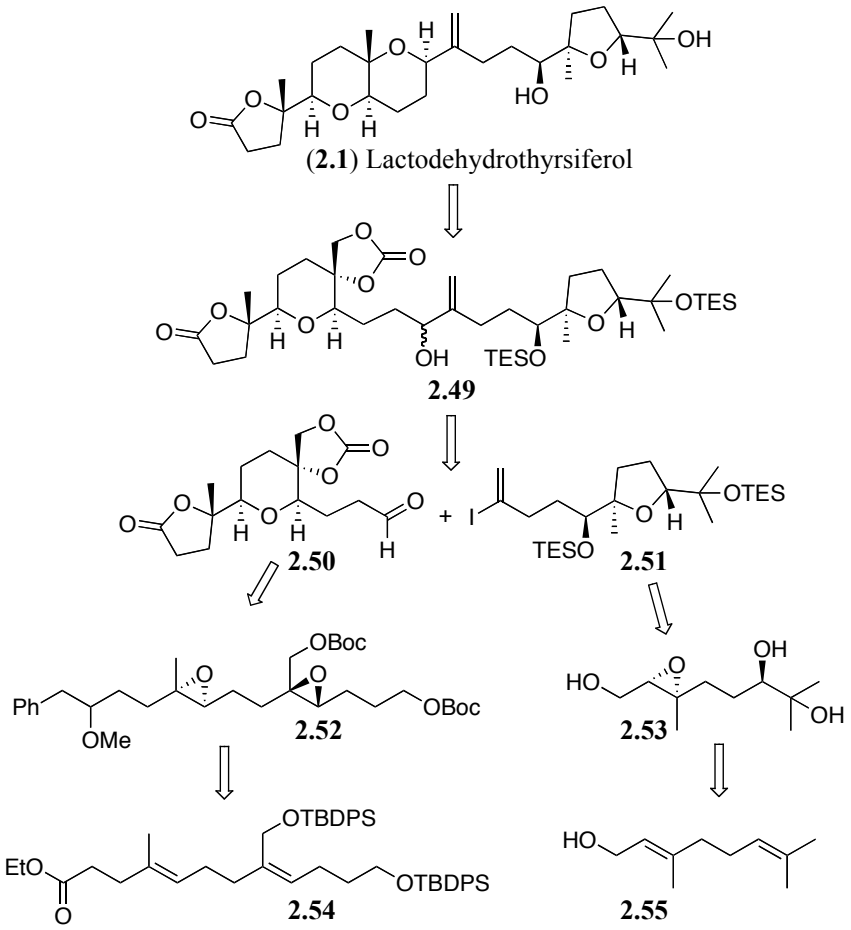
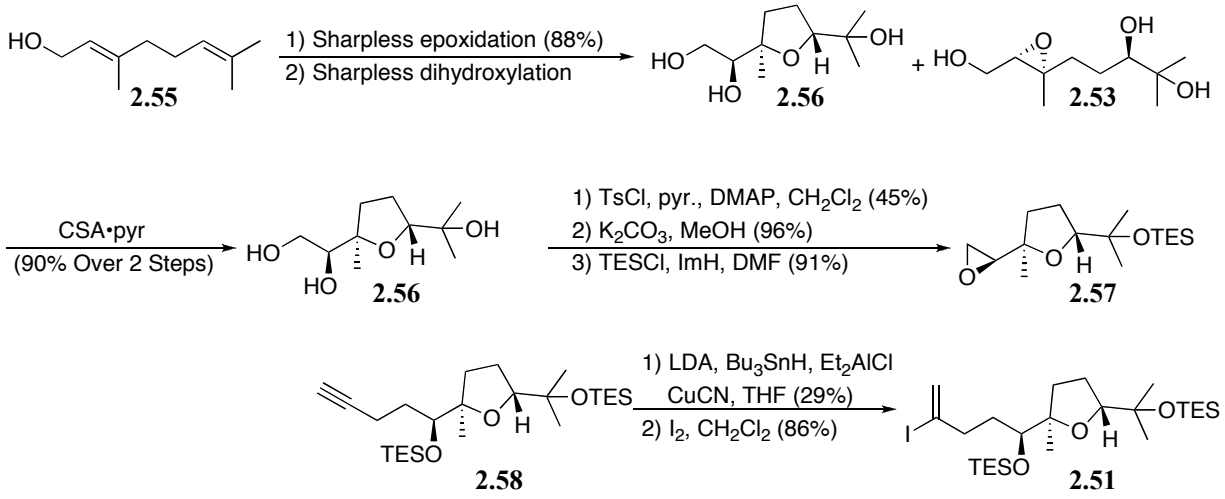


Figure 2.7 Retrosynthetic Analysis of Lactodehydrothyrsiferol

2.3.2 First Synthetic Route for Vinyl Iodide 2.51

Dr. Shuangyi Wan's initial work on the first generation route to vinyl iodide **2.51** was instrumental in directing our current research.[75] Geraniol (**2.55**) was converted to epoxide **2.53** utilizing Sharpless asymmetric epoxidation[58] followed by Sharpless asymmetric

dihydroxylation.[76] The formation of tetrahydrofuran **2.56** was seen immediately following the reaction and pushed to complete conversion using the mild acid pyridinium 10-camphorsulfonate (CSA·pyr). Monotosylation of the primary alcohol present on tetrahydrofuran **2.56** allowed for a displacement reaction to occur under basic conditions to afford the needed epoxide. Silyl protection of the tertiary alcohol went with an excellent yield to give epoxide **2.57**. The epoxide was opened using 1,3-dilithiopropyne[77] and the newly formed secondary alcohol was protected using chlorotriethylsilane (TESCl) to generate alkyne **2.58**. The vinyl iodide functional group was installed by performing a stannylalumination reaction using Bu_3Sn-$AlEt_2$ and CuCN followed by tin-iodide exchange.[78,79]

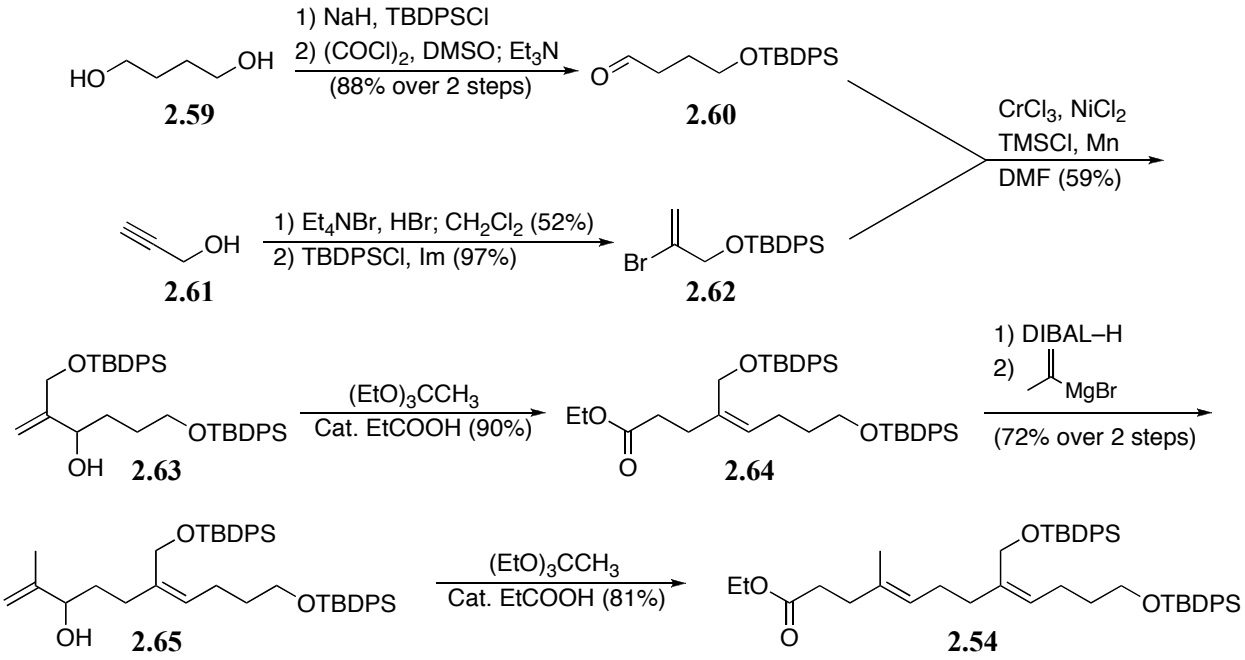


Scheme 2.9 First Synthetic Route for Vinyl Iodide 2.51

2.3.3 First Synthetic Route for Aldehyde *ent*-2.50

The first synthetic sequence leading to aldehyde **2.50** was a linear sequence of reactions that confirmed our predictions regarding the ETIC promoted epoxide-opening cascade.[75] The inexpensive starting material 1,4-butanediol (**2.59**) was readily converted to aldehyde **2.60**

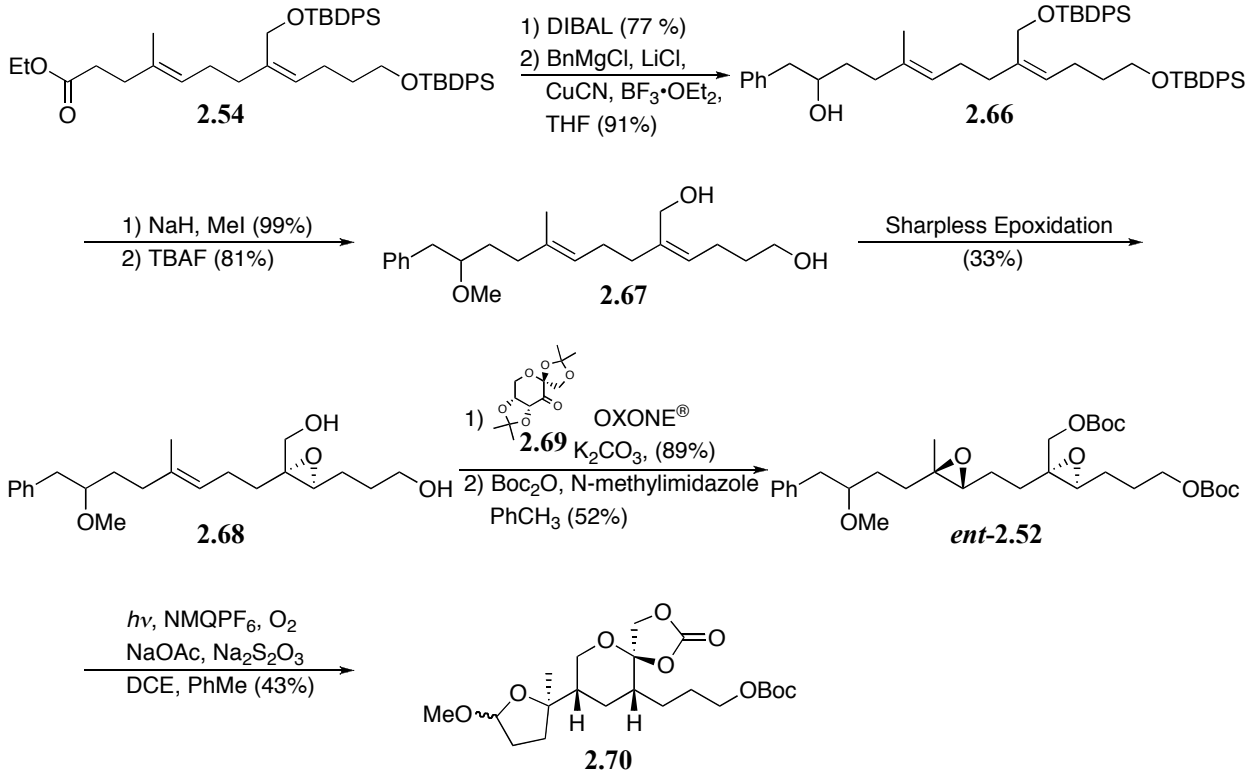
through monosilyl protection followed by Swern oxidation.[74] Propargyl alcohol (**2.61**) was converted into vinyl bromide **2.62**, the necessary coupling partner of **2.60**. The two were joined via Fürstner's-modified NHK conditions in moderate to good yields, generating allylic alcohol **2.63**.[80] Johnson-Claisen rearrangement provided a two carbon addition to give the ethyl ester **2.64**.[81] Another allylic alcohol moiety was installed from a DIBAL-H mediated reduction to the aldehyde followed by introduction of isopropenylmagnesium bromide. Johnson-Claisen rearrangement on allylic alcohol **2.65** gave ethyl ester **2.54**.



Scheme 2.10 Synthesis of Diene 2.54

Ethyl ester **2.54** underwent another DIBAL-H reduction to the aldehyde followed by the addition of benzylmagnesium chloride with CuCN to generate diene **2.66**.[82] Homobenzylic ether **2.67** was obtained from methylation of the secondary alcohol and silyl deprotection. The enantiomer of **2.52** (Figure 2.7) was synthesized due to readily available chiral reagents for

asymmetric epoxidation. Diepoxide ***ent*-2.52** was synthesized from Sharpless asymmetric epoxidation,[58] Shi epoxidation using the (D)-fructose derived Shi ketone **2.69**,[66] and protection using Boc-anhydride. When compound ***ent*-2.52** was exposed to the ETIC conditions it underwent the epoxide-opening cascaede reaction with a yield of 43%.



Scheme 2.11 Synthesis of Lactol 2.70

The epoxide cascade mechanism is shown in Figure 2.8. Radical cation formation was achieved using the previously mentioned aerobic, organocatalytic, photoinitiated procedure (Figure 1.1).[9] The radical-cation **2.71** undergos fragmentation, generating both a benzyl radical (**1.9**), which is converted into benzaldehyde,[4] and oxocarbenium ion **2.72**. The nucleophile that attacks the nascent electrophile is the proximal epoxide forming the bicyclo[3.1.0] epoxonium ion **2.73**. The distal epoxide then attacks the reactive center following the previously established

observation through an *exo* cyclization (Figure 1.6).[12] The *tert*-butyl carbonate subsequently attacks the proximal, tertiary carbon center preferentially to generate compound **2.75**. The formation of the 6-membered spiro ring product is generated by having the nucleophilic tether attached to C_{20} versus C_{16} (system described in Figure 2.8). Loss of the *tert*-butyl carbocation (**2.76**) furnishes the desired carbonate **2.70**.

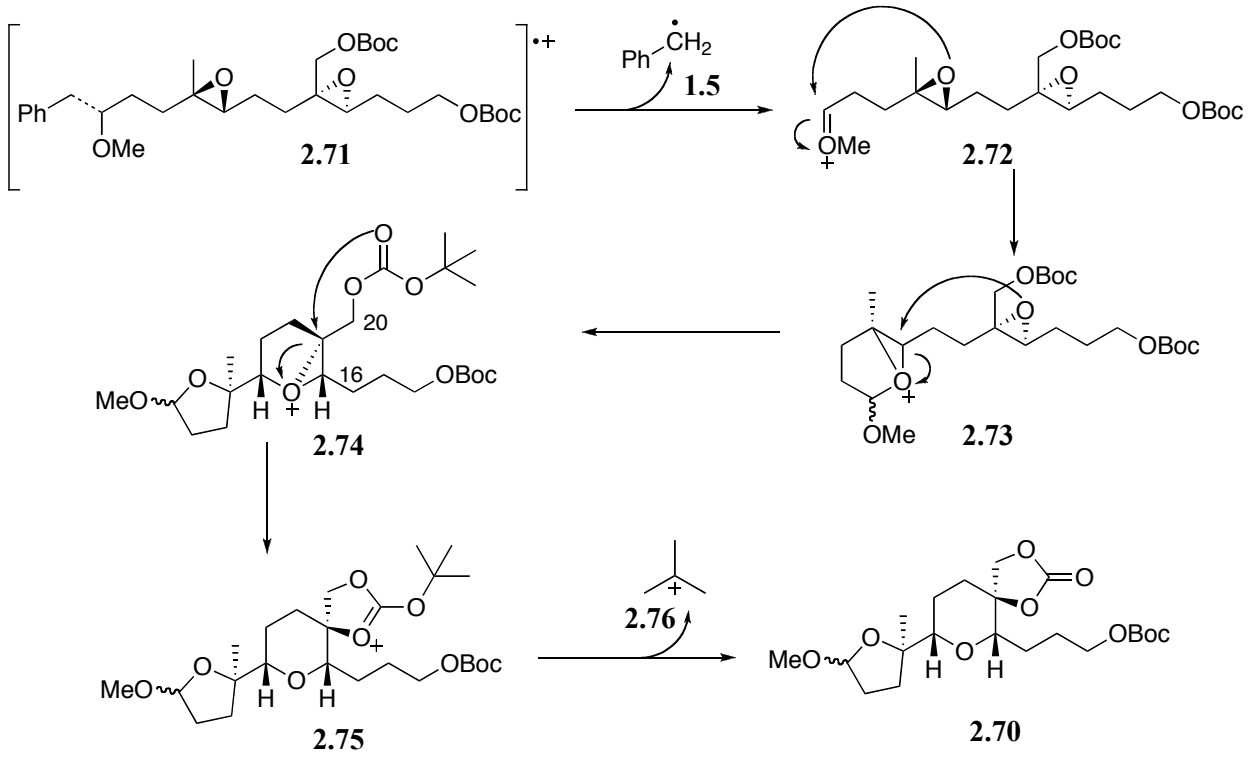
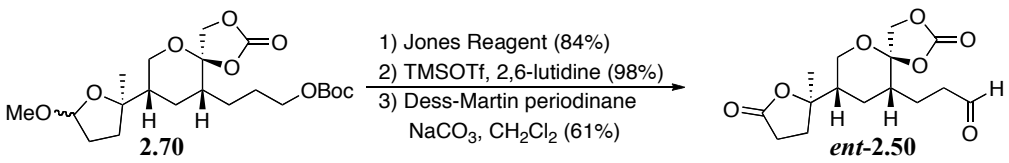


Figure 2.8 Proposed Epoxide Cascade Mechanism

Compound **2.70** was oxidized to a γ-lactone using Jones reagent with good yields.[83] Deprotection of the *tert*-butyl carbonate group revealed a primary alcohol that was oxidized to aldehyde ***ent*-2.50** using Dess-Martin periodinane.[55] Structure determination of aldehyde ***ent*-2.50** was performed using two-dimensional NMR experiments. This route clearly demonstrated that the ETIC chemistry could be used in the synthesis of the natural product **2.1**. However, due

to the linear nature of the described route the ability to generate a large amount of material was not practical.



Scheme 2.12 Synthesis of Aldehyde *ent*-2.50

2.3.4 Total Synthesis Objectives

The plan was to designing a modular synthesis of title compound **2.1** that showcases the oxidative epoxide cascade reaction. The goals include employing synthetic strategies that ensure a divergent approach by extending the utility of modern transition metal cross coupling procedures. Another goal of this total synthesis was to update certain transformations to a greener and laboratory practical option than commonly seen tradition practices. Hypotheses from the literature were used to develop novel methods to install two epoxides with opposite stereochemistry in succession. It was envisioned that the construction of natural product **2.1** would be both an accomplishment in synthetic chemistry and an opportunity to further key organic transformations.

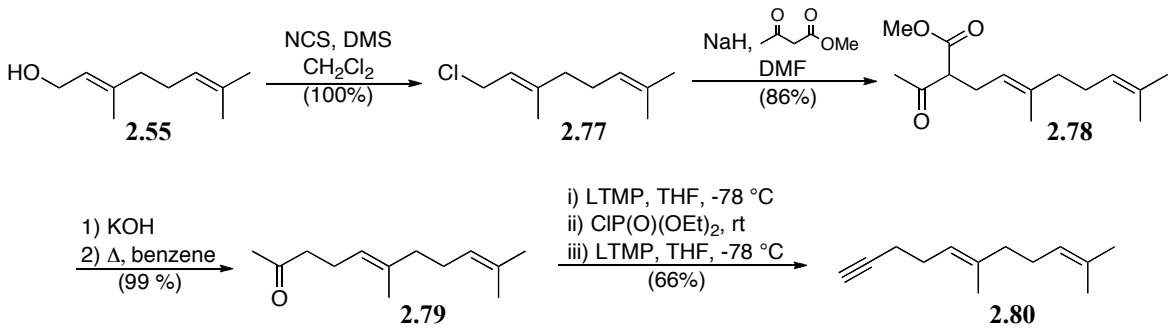
2.4 TOTAL SYNTHESIS OF LACTODEHYDROTHYSIFEROL

2.4.1 Optimized Route for Vinyl Iodide 2.51

Dr. Wan's successful synthesis of vinyl iodide **2.51** (Scheme 2.9) provided us with significant insight towards optimization.[75] It was hypothesized that changing the order of functional group installation would increase the efficiency of the synthesis. It was also desired an improved way of converting terminal alkynes into vinyl iodides. These goals were accomplished to arrive at the current synthesis of vinyl iodide **2.51**.

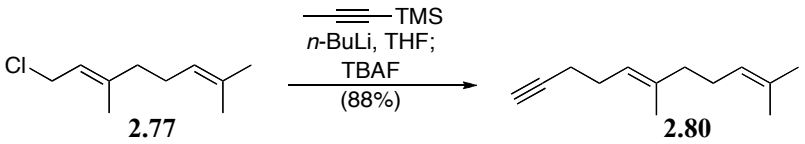
The first major change employed was the installation of the propargyl group prior to formation of the tetrahydrofuran core (Scheme 2.13). Once again, the synthesis started with geraniol (**2.54**) and performed a Corey-Kim oxidation in the absence of base to prevent aldehyde formation.[84] This lesser known transformation proceeds via the allylic alcohol reacting with the methyl sulfide/*N*-chlorosuccinimide complex to form a relatively unstable complex that decomposes into allyl chloride **2.77** and dimethylsulfoxide. Even though geranyl chloride (**2.77**) is commercially available, this method proved to be an economical and practical protocol for generating a large amount of the requisite starting material. Geranyl chloride (**2.77**) was converted into *β*-keto ester **2.78** via an acetoacetic ester synthesis with methyl acetoacetate and sodium hydride as the base. Ester **2.78** is easily saponified to the corresponding *β*-keto acid under basic, aqueous conditions using potassium hydroxide. The acid undergoes a decarboxylation in gently refluxing benzene to afford geranyl acetone (**2.79**). Negishi's protocol to convert methyl ketones into terminal acetylenes provided us with alkyne **2.80**.[85] This protocol calls for use of a large, bulky base, lithium 2,2,6,6-tetramethylpiperidine (LTMP), to ensure

enolization occurs at the less hindered carbon. Once the enol phosphate is formed, it is still essential to use LTMP to avoid allene formation.



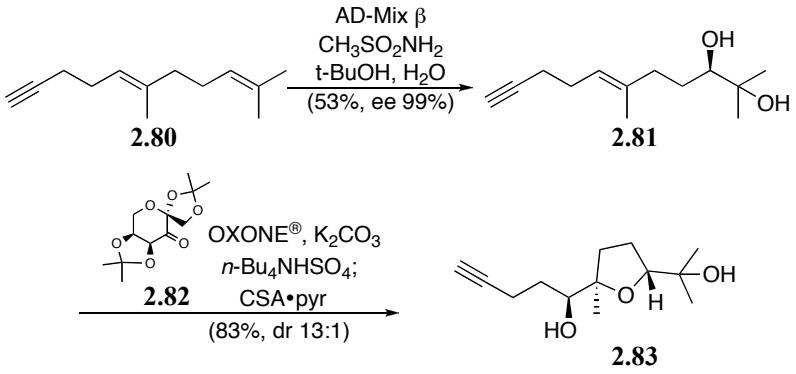
Scheme 2.13 Synthesis of Terminal Alkyne 2.80

A more efficient route for terminal alkyne **2.80** was needed due to the current scheme's length and overall yield. The fully optimized synthesis of alkyne **2.80** utilizes a lithium reagent to undergo an S_N2 reaction with geranyl chloride (**2.77**) (Scheme 2.14). The nucleophile for the reaction was generated by mixing 1-(trimethylsilyl)propyne and *n*-butyllithium in THF.[86] The newly formed propargylic lithium readily formed the TMS-protected alkyne when exposed to allyl chloride **2.77**. Terminal alkyne **2.80** was furnished in an 88% yield by quenching the reaction with TBAF.



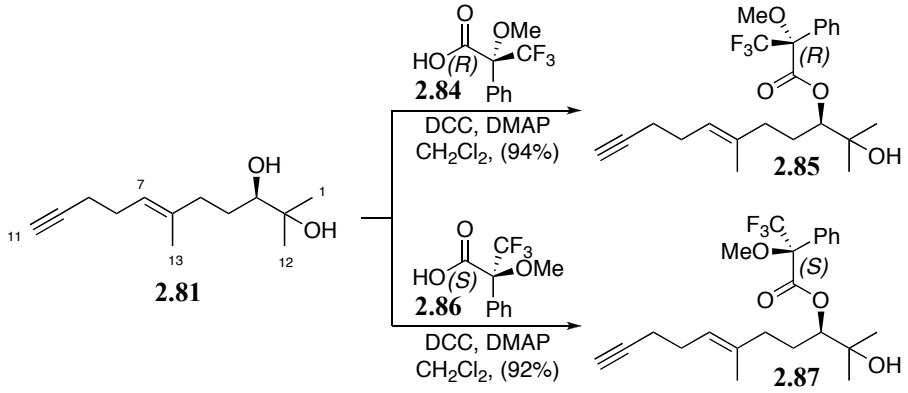
Scheme 2.14 Rapid Synthesis of Terminal Alkyne 2.80

The successful synthesis of terminal alkyne **2.80** allowed for construction of the tetrahydrofuran core via the route presented in Scheme 2.15. Sharpless asymmetric dihydroxylation allowed for a stereoselecive and mildly regioselective installation of a 1,2-diol across the desired alkene distal to the alkyne in compound **2.81**.[76] Despite the steric similarity of the two alkenes, the desired alkene was dihydroxylated with a slight preference to provide a 53% yield after purification with excellent stereocontrol. If necessary, the yield of this transformation could be improved if the Corey-Zhang catalyst were used.[87] This catalyst not only provides an asymmetric dihydroxylation, but is site-selective for the terminal isopropylidene group of polyisoprenoids. To install the required epoxide with the correct stereochemistry at the remaining trisubsituted alkene, a Shi epoxidation[66] was performed on alkene **2.81**. The unnatural (L)-fructose derived Shi ketone was used to generate the epoxy diol, which spontaneously underwent cyclization to form tetrahydrofuran **2.82**. Incomplete conversion to the tetrahydrofuran was observed without the use of the pyridinium 10-camphorsulfonate complex (CSA·pyr). Tetrahydrofuran **2.83** was formed in good yields with a 13:1 diastereomeric ratio (the diastereomers were readily separable using medium-pressure liquid chromatography (MPLC)).



Scheme 2.15 Synthesis of Tetrahydrofuran 2.83

A stereochemical analyses on diol **2.81** and tetrahydrofuran **2.83** were performed to ensure the correct orientation around each chiral center. The advantageous Mosher ester analysis was used to determine the absolute stereochemistry and enantiomeric purity of the secondary alcohol present on diol **2.81**.[88] Mosher esters **2.85** and **2.87** were created as diastereomeric pairs through the coupling of diol **2.81** to both enantiomers of the Mosher acid (**2.84** and **2.86**) (Scheme 2.16). These newly formed esters adopt an s-*trans* orientation across their O–CO bond and both the trifluoromethyl group and the methine proton of the secondary alcohol moiety align



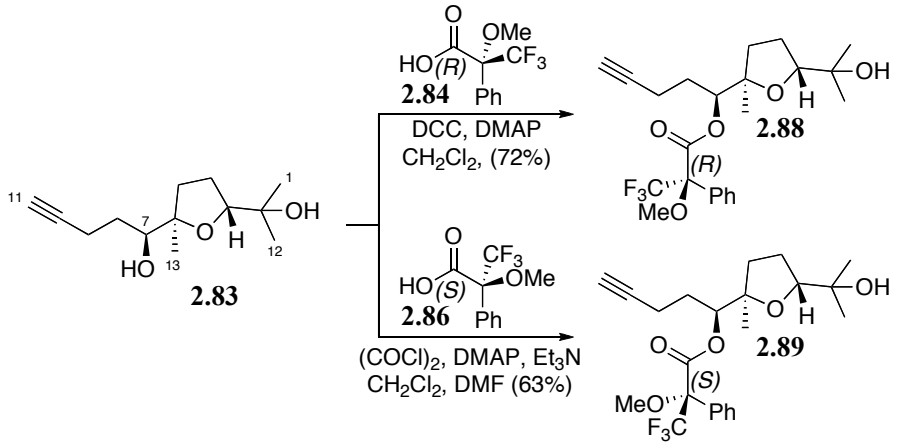
Scheme 2.16 Synthesis of Mosher Esters 2.85 and 2.87 for Stereochemical Analysis

themselves *syn*-coplanar with the carbonyl group.[89] This fixed arrangement of atoms can be exploited through nuclear magnetic resonance (NMR) experiments. The absolute stereochemistry at carbon three was determined to be the desired *R* conformation through comparing the proton shifts of both diastereomers (Table 2.2). The enantiomeric excess was determined to be 99% using ^{19}F NMR data on Mosher ester **2.85**.

Table 2.2 Chemical Shifts of Protons in Mosher Esters 2.85 and 2.87 and Application of the Advanced (δ_S-δ_R) Mosher Methods

H#	δ *(S)*-MTPA ester **2.87**	δ *(R)*-MTPA ester **2.85**	$\Delta\delta = \delta S - \delta R$
1	1.1455	1.1713	– 0.0258
12	1.1851	1.2346	– 0.0495
4	1.6934	1.6007	+ 0.0927
	1.8223	1.7260	+ 0.0963
13	1.6002	1.5560	+ 0.0442
7	5.1629	5.1111	+ 0.0518
11	1.9507	1.9491	+ 0.0016

The same analytical procedure was applied to tetrahydrofuran **2.83** to determine the stereochemistry of the newly formed secondary alcohol. Formation of the diastermeric Mosher ester pair is shown in Scheme 2.17. The absolute stereochemistry at C_7 was determined to be the desired *S* configuration through comparing the proton shifts of ester **2.88** and **2.89** (Table 2.3).



Scheme 2.17 Synthesis of Mosher Esters 2.88 and 2.89 for Stereochemical Analysis

Table 2.3 Chemical Shifts of Protons in Mosher Esters 2.88 and 2.89 and Application of the Advanced (δ_S-δ_R) Mosher Methods

H#	δ *(S)*-MTPA ester **2.89**	δ *(R)*-MTPA ester **2.88**	$\Delta\delta = \delta S - \delta R$
1	1.204	1.181	+ 0.023
12	1.200	1.164	+ 0.036
13	1.104	1.094	+ 0.010
8	2.214	2.262	– 0.048
	2.127	2.201	– 0.074

The last chiral center that needed to be checked was C_6 of tetrahydrofuran **2.83**. It was hypothesized that the THF ring system present in ester **2.89** (a derivative of tetrahydrofuran **2.83**) would adopt a fixed envelope conformation due to the unfavorable 1,3-diaxial interaction present if the substrate underwent a chair flip. This allowed for a two-dimensional NMR experiment to determine the stereochemistry at the remaining unknown center. We observed a strong NOE signal between the methine protons on C_3 and C_7 (Figure 2.9). This interaction confirms that the orientation around carbon six is the desired *R* configuration.

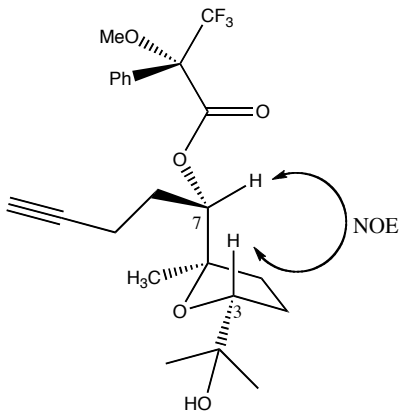
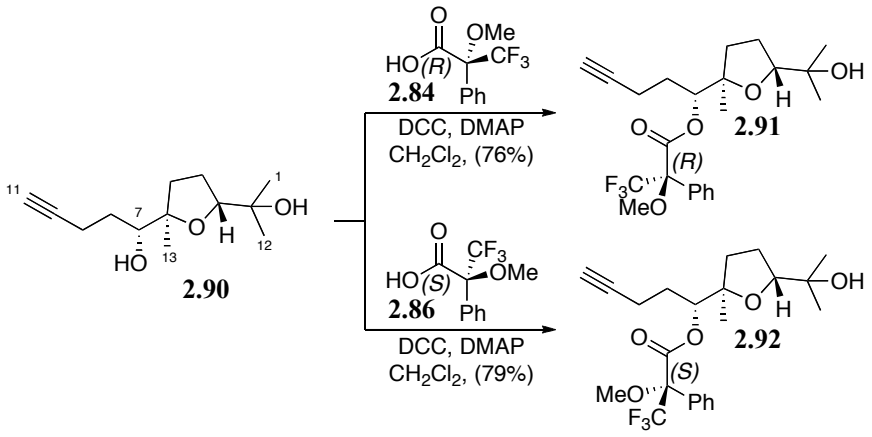


Figure 2.9 Key NOE Observed in NOESY Experiment of 2.89

The last stereochemical analysis we performed in route to vinyl iodide **2.51** was on the diastereomer that arose from the Shi epoxidation and cyclization step for tetrahydrofuran **2.83** (Scheme 2.15). The other diastereomer could be generated in two different manners. The first possibility would be if the Shi epoxidation proceeded without a high level of stereocontrol and the other option would be if the stereocenter at C_6 were scrambled due to opening the epoxide under acidic conditions. The Mosher ester analysis on tetrahydrofuran **2.90** elucidated an *R* configuration at C_7 (Scheme 2.18, Table 2.4). This indicates that complete inversion took place at C_6 during the cyclization reaction for tetrahydrofuran **2.83** and the other diastereomer is obtained from imperfect stereocontrol in the epoxide formation.

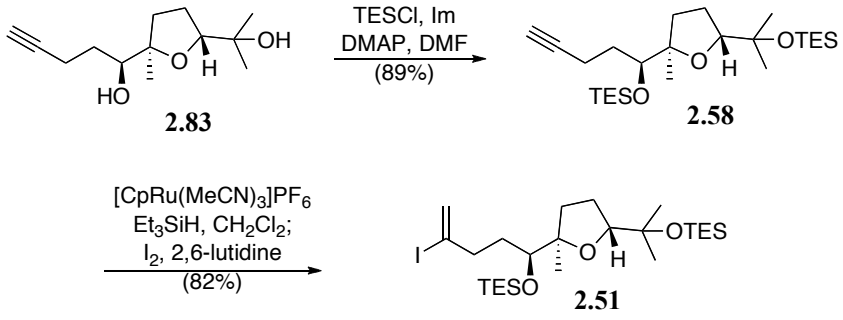


Scheme 2.18 Synthesis of Mosher Esters 2.91 and 2.92 for Stereochemical Analysis

Table 2.4 Chemical Shifts of Protons in Mosher Esters 2.91 and 2.92 and Application of the Advanced (δ_S-δ_R) Mosher Methods

H#	δ *(S)*-MTPA ester **2.92**	δ *(R)*-MTPA ester **2.91**	$\Delta\delta = \delta S - \delta R$
1	1.216	1.240	– 0.024
12	1.155	1.200	– 0.045
13	1.125	1.139	– 0.014
8	2.329	2.214	+ 0.115
	2.181	2.051	+ 0.130

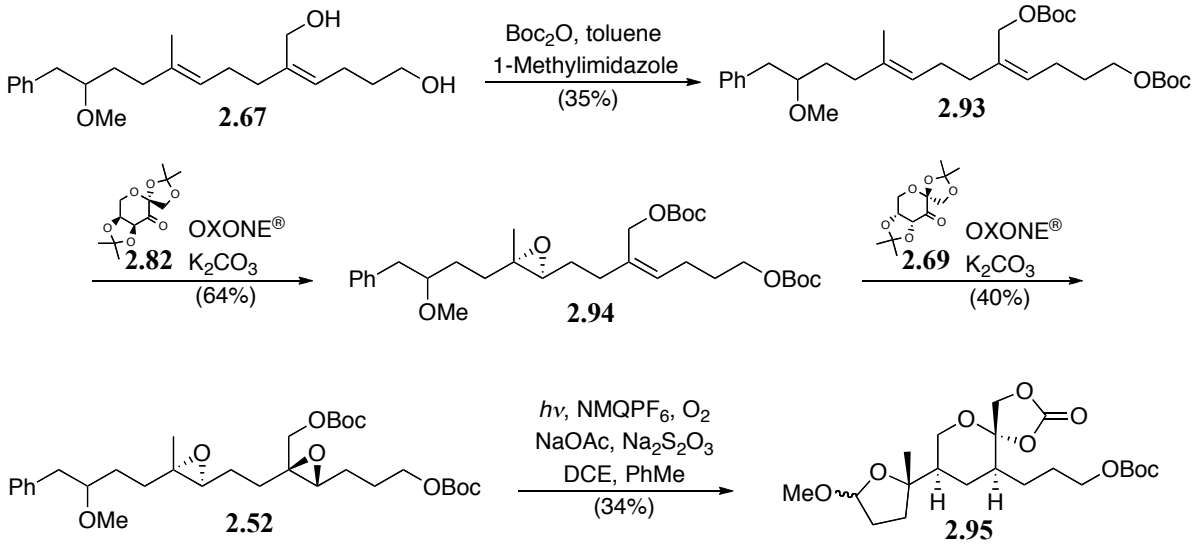
The formation of alkyne **2.83** leads to the final stages for synthesizing vinyl iodide **2.51**. The two hydroxy groups present in tetrahydrofuran **2.83** were protected using TESCl in an 89% yield. Next, we planned on optimizing the vinyl iodide formation reaction. Our standard method of generating 1,1-disubstituted vinyl iodides was to perform a stannylalumination reaction on an alkyne followed by a tin-iodide exchange.[78] This method, however, posed problems due to low yields and toxic reagents. To address the problem, a hydrosilylation reaction was performed across the alkyne with Markovnikov regioselectivity. The newly formed vinylsilane underwent a silyl-iodide exchange to arrive at the required 1,1-disubstituted vinyl iodide. This was accomplished by exposing alkyne **2.58** to Trost's procedure, which utilizes a catalytic cationic ruthenium complex ($[CpRu(MeCN)_3]PF_6$) and triethylsilane to perform the desired hydrosilylation reaction.[90] This method proved to be highly effective in generating the desired 1,1-disubstituted vinylsilane. Several silyl-iodine exchange procedures were unsuccessful. However, simple iodine addition under basic condition ensured no deprotection of the silyl ethers and excellent silyl-iodine exchange. Initially these reactions were run separately; however, after optimization the entire conversion of alkyne to vinyl iodide can be performed in one flask. In addition to being higher yielding and more operationally practical, the current protocol is dramatically less toxic for the environment than the originally proposed stannylalumination reaction.



Scheme 2.19 Optimized Route for Vinyl Iodide 2.51

2.4.2 First Improvements in the Route for Aldehyde 2.50

Dr. Shuangyi Wan's previous synthesis of aldehyde **2.50** exposed key spots in the route for optimization.[75] The first improvements addressed were the regioselective and stereoselective epoxidations and the timing of the *tert*-butyl carbonate installation (Scheme 2.20). Diol **2.67** was obtained through the route previously presented in Schemes 2.10 and 2.11. As shown previously, Sharpless asymmetric epoxidation of diene **2.67** was not efficient.[58] The tethered, free hydroxyl group present in compound **2.67** is positioned perfectly to undergo cyclization into the newly formed epoxide. Therefore, protection of the alcohol as the *tert*-butyl carbonate was performed prior to running iterative Shi epoxidations.[66] Unfortunately, low yields and incomplete conversion to diene **2.93** was observed when diol **2.67** was exposed to standard Boc-protection conditions, with a dimeric carbonate being a major byproduct. The dimerization of alcohols across a carbonate or anhydride linkage is a known byproduct when Boc-anhydride is used to generate *O*-Boc protected alcohols.[91]



Scheme 2.20 Improved Synthesis for Lactol 2.95

Following the *tert*-butyl carbonate installation, the more reactive alkene was epoxidized using the (L)-fructose derived Shi ketone (**2.82**) to generate epoxide **2.94** in moderate yields with no epoxidation occurring at the undesired alkene. The selectivity between the two alkenes present in diene **2.93** is primarily due to the electronics. The trisubsituted alkene present in the allylic *tert*-butyl carbonate moiety is significantly deactivated due to an inductive effect. Thus, the epoxidizing agent interacts with the desired electron rich alkene preferentially.

To perform the next epoxidation, the (D)-fructose derived Shi ketone (**2.69**) was used to generate the opposite stereochemical outcome at the remaining alkene in compound **2.94**. Extended reaction time and increased catalyst and oxidant loading provided the desired diepoxide **2.52**. The low conversion of starting material is due to the Baeyer-Villiger oxidation[92] of the Shi ketone becoming more favorable than epoxidation of the deactivated alkene.[93] Formation of lactol **2.95** was achieved when diepoxide **2.52** was exposed to the ETIC reaction conditions. The information gained from these preliminary reactions ultimately directed our synthesis towards its current iteration.

2.4.3 Retrosynthetic Analysis of Diepoxide 2.87

The retrosynthetic analysis of lactodehydrothyrsiferol (**2.1**) was redesigned to form a more practical route. The synthesis of diepoxide **2.96** was changed to a more convergent approach by bisecting the molecule into diene **2.97** and vinyl iodide **2.98** through a Suzuki-Miyaura coupling (Figure 2.10).[61-63] In addition to this redesign, the functionality present on diepoxide **2.96** was altered to aid in increasing the efficiency of certain transformations. The substrate was designed to be more reactive by adding a phenyl substituent in the benzylic position lowering the bond dissociation energy of the fragmenting bond in the ensuing ETIC

reaction.[8] In addition, a new protecting group scheme was proposed to allow for a higher conversion during installation of the requisite *tert*-butyl carbonate. Finally, a novel Shi epoxidation method was sought out by using newly designed Shi ketone analogs with heightened reactivity.[94,95]

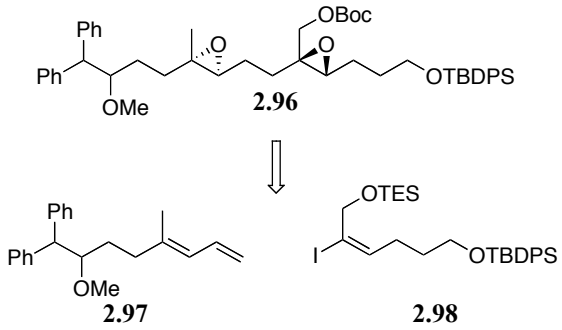
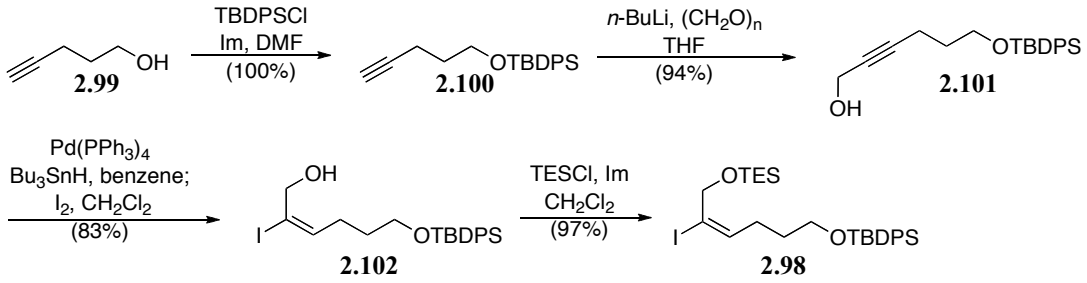


Figure 2.10 Retrosynthetic Analysis of Diepoxide 2.96

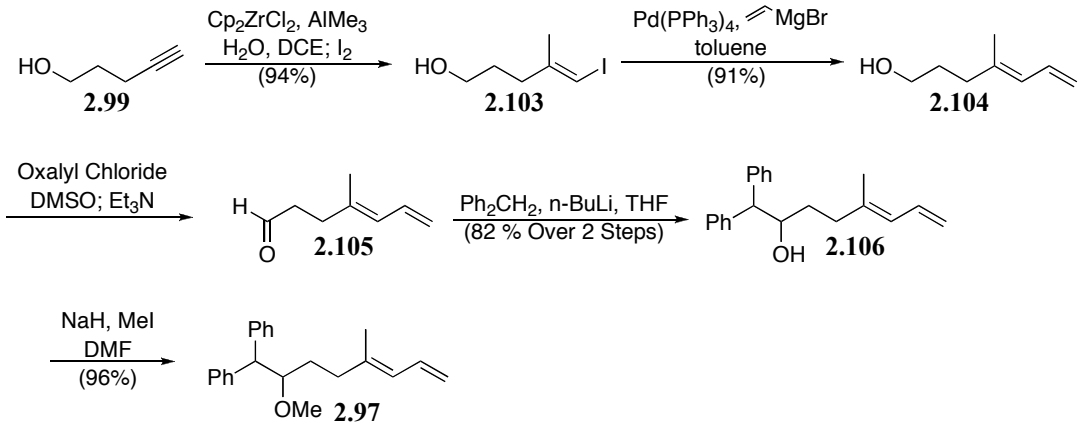
2.4.4 Synthetic Route for Suzuki-Miyaura Coupling Partners 2.97 and 2.98

Scheme 2.21 illustrates the synthesis of vinyl iodide **2.89** from alkynol **2.99**. The formation of silyl ether **2.100** was readily accomplished by treating 4-pentynol (**2.99**) with TBDPSCl and imidazole in DMF. Silyl ether **2.100** was converted into the propargylic alcohol **2.101** using *n*-butlylithium and paraformaldehyde. Tributyltin hydride and $Pd(PPh_3)_4$ induced a *cis* hydrostannylation across the alkyne present in compound **2.101**. The observed regioselectivity is provided by the heteroatom's ability to coordinate to the metal complex and direct its delivery.[96] A tin-iodide exchange rapidly took place upon adding iodine to the reaction mixture to produce vinyl iodide **2.102**. Vinyl iodide **2.98** was furnished in excellent yields after performing a TES protection on the remaining allylic alcohol.



Scheme 2.21 Synthesis of Vinyl Iodide 2.98

The construction of diene **2.97** was achieved using the route presented in Scheme 2.22. Starting with 4-pentynol (**2.99**), a carboalumination reaction was carried out according to Wipf's protocol.[97] The carboalumination intermediate was trapped with iodine to generate the trisubsituted vinyl iodide **2.103**. A Kumada cross-coupling between vinylmagnesium bromide and vinyl iodide **2.103** furnished diene **2.104** with excellent yields.[98] Attempts to perform this two-step protocol in one-pot using zinc chloride to facilitate a Negishi cross-coupling unfortunately provided a mixture of inseparable products. Primary alcohol **2.104** was converted to aldehyde **2.105** using a Swern oxidation.[74] Aldehyde **2.105** was taken directly to the next step

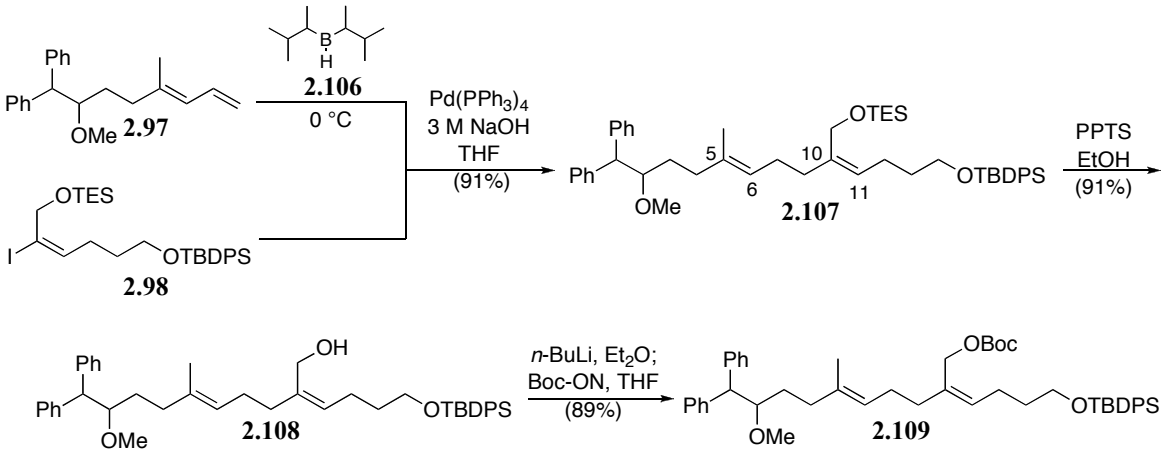


Scheme 2.22 Synthesis of Diene 2.97

without purification due to its volatility. Alcohol **2.106** was produced when aldehyde **2.105** was exposed to diphenylmethyl lithium. This provided the desired diphenylmethyl moiety that is necessary for the key ETIC reaction. Diene **2.97** was successfully obtained upon the methylation of the secondary alcohol present in compound **2.106**.

2.4.5 Suzuki-Miyaura Coupling of Diene 2.97 and Vinyl Iodide 2.98

The Suzuki-Miyaura coupling of diene **2.97** with vinyl iodide **2.98** was not a trivial undertaking.[61-63] Multiple reaction conditions were attempted to obtain the desired transformation (Scheme 2.23). The hydroboration of the terminal, monosubsituted alkene was achieved using freshly prepared disiamylborane (**2.106**). Low yields were a constant problem when the commercially purchased 1.0 M 9-borabicyclo[3.3.1]nonane (9-BBN) in THF solution was used. Tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) was chosen to be the optimal Pd^0 source after screening a wide variety of catalysts. The commonly utilized conditions employing [$PdCl_2$(dppf)], triphenylarsine, and cesium carbonate in DMF proved to be ineffective



Scheme 2.23 Suzuki-Miyaura Coupling and *tert*-Butyl Carbonate Instillation for Diene 2.109

in generating desired product. Coupling product **2.107** was obtainable however, by instead using 3.0 M NaOH in THF. The reaction reaches completion after stirring for two days at ambient temperature with a yield of 91%. Heating the reaction mixture to increase the rate unfortunately produces olefin isomers at alkene C_{10} in diene **2.107**.

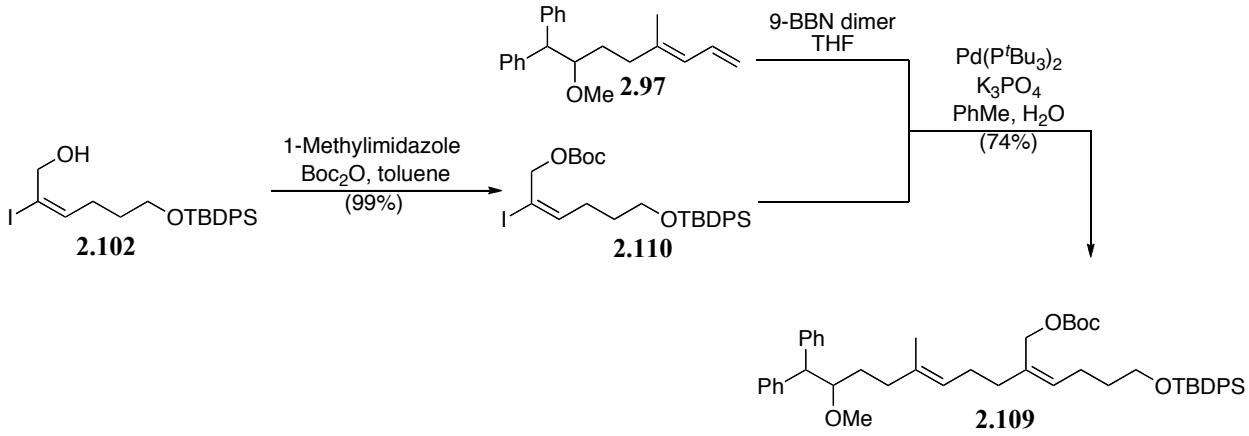
Installation of the *tert*-butyl carbonate was performed after generation of Suzuki-Miyaura coupling product **2.107**. Selective silyl deprotection was accomplished under mildly acidic conditions, using pyridinium *p*-toluenesulfonate (PPTS) to generate the allylic alcohol **2.108**. Boc-anhydride proved once again to be troublesome in generating the *O*-Boc protected alcohol, with dimerization being problematic when allylic alcohol **2.108** is exposed to the standard reaction conditions.[91] Ultimately, we were able to overcome the generation of the undesired dimer by using *n*-butyllithium and Boc-ON to obtain diene **2.109**.[99]

2.4.6 Optimized Suzuki-Miyaura Coupling with Direct Access to Diene 2.109

We desired to further optimize the Suzuki-Miyaura coupling reaction to remove the protecting group exchange plaguing our current route. A direct method to diene **2.109** would provide a synthetic strategy that is more step economical.[17] Kogen and coworkers have reported the Suzuki-Miyaura coupling of similar substrates where the allylic alcohol was uprotected.[100] However, the desired coupling product diene **2.108** (Scheme 2.23) was never generated when vinyl iodide **2.102** (Scheme 2.21) and diene **2.97** (Scheme 2.23) were exposed to their coupling conditions. Under their conditions, vinyl iodide **2.102** was converted into an unreactive coupling partner by the oxidation of the primary alcohol into the corresponding aldehyde and the reduction of the vinyl iodide into the disubsituted alkene. It was these observations that lead to the aforementioned optimized procedure.

We hypothesized that installation of the *tert*-butyl carbonate prior to coupling would allow for the direct conversion to diene **2.109**. Vinyl iodide **1.102** is readily converted into the *O*-Boc protcected alcohol **2.110** using Boc-anhydride with no dimerization being observed during this transformation (Scheme 2.24). Initially we used the Suzuki-Miyaura coupling conditions previously discussed in Scheme 2.23. We observed only partial conversion to the product with decomposition of vinyl iodide **2.110** through the loss of the carbonate functionality. This undesired pathway renders Boc-protection prior to coupling inefficient without further optimization.

The first improvement leading to higher reproducible yields was observed through exchanging the hydroboration reagent to commercially available 9-BBN dimer. Even though this led to more product formation, low yields and starting material degradation was still present while using $Pd(PPh_3)_4$ as the catalyst. We performed an exhaustive screen of Pd^0 sources and witnessed significant yield improvements with $Pd(P^tBu_3)_2$.[101,102] This catalyst generated the desired diene **2.109** without any observable vinyl iodide **2.110** decomposition. The reaction was



Scheme 2.24 Suzuki-Miyaura Coupling of Diene 2.97 and Vinyl Iodide 2.110

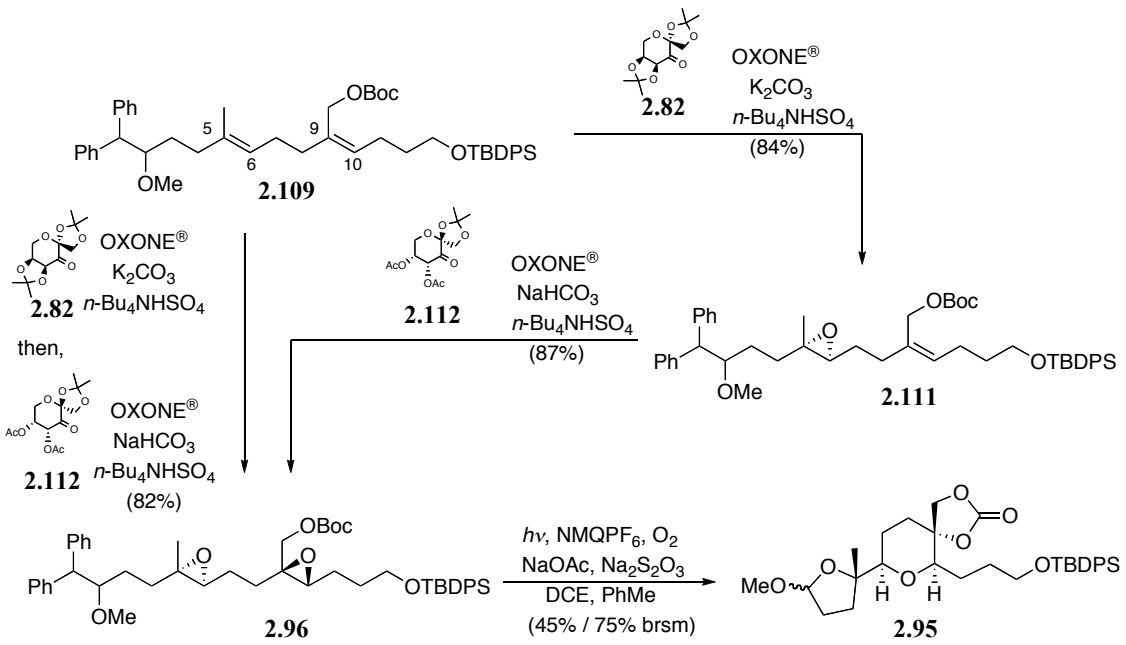
fully optimized after a solvent screen and base selection. This current route provided a practical method to generate a large amount of late stage intermediates.

2.4.7 Optimized Route to Aldehyde 2.50

The Suzuki-Miyaura coupling of compounds **2.97** with **2.110** provided the requisite diene **2.109** to undergo iterative Shi epoxidations.[66,95] It is important to reiterate that the epoxides being added across the two alkenes have opposite stereochemical orientations. Even though prior routes provided the desired outcome, the yields in both of the previous examples were not optimal (Scheme 2.11 and Scheme 2.20). The first epoxidation was performed using the (L)-fructose derived Shi ketone (**2.82**) to generate monoepoxide **2.111**. Once again, the electron rich alkene at C_5 interacted with the electron poor dioxirane preferentially to achieve a regioselective epoxidation (Scheme 2.25). Previous studies on a similar system (Scheme 2.20) revealed that the trisubsituted alkene between C_9 and C_{10} present in the allylic *tert*-butyl carbonate moiety is very deactivated. Thus, the epoxidation of the electron rich alkene at carbon five can be pushed towards completion by increasing the oxidant loading without the fear of forming the undesired diepoxide.

The next epoxidation called for a more robust and reactive catalyst that would favor epoxidation of the deactivated alkene at C_{10} over the competing Baeyer-Villiger oxidation pathway that renders the catalyst inactive.[92] To increase the reactivity of the Shi ketone, the electronic properties of the catalyst were altered by deprotecting one of the cyclic acetals to expose a 1,2-diol that was reprotected with acetyl groups.[94,95] Vidal-Ferran's practical synthesis of Shi ketone analog **2.112** was used to generate the (D)-fructose derived catalyst.[103] The

formation of diepoxide **2.96** occurred with an 87% yield when monoepoxide **2.111** was exposed to organocatalyst **2.112**.



Scheme 2.25 Diepoxidation of Diene 2.109 and ETIC

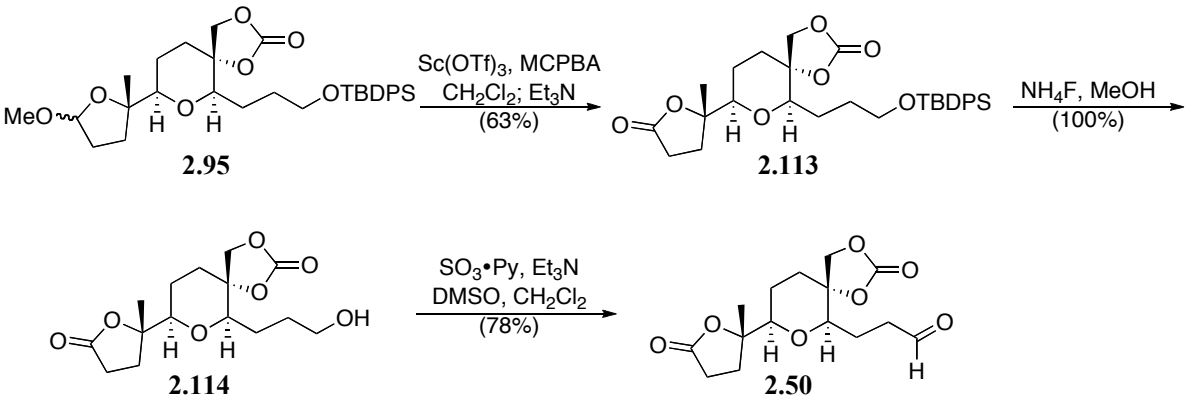
The Shi ketone anaolog **2.112** ultimately achieves its reactivity through its altered electronic character. The electron withdrawing effect provided by the two acetoxy groups present in the catalyst causes the Baeyer-Villiger oxidation pathway to be unfavorable. This alteration allows for the catalyst to be more robust and tolerate longer reaction times. In addition, the two acetoxy groups are able to pull electron density away from the dioxirane causing it to become more electrophilic. This effect increases the reactivity of catalyst **2.112** and allows for the deactivated alkene to undergo the desired transformation.

The large difference in reactivity of both the catalysts ((L)-fructose derived Shi ketone **2.82** vs. (D)-fructose derived Shi ketone analog **2.112**) and the two alkenes present on diene

2.109 provided the opportunity to attempt a one pot diepoxidation that is both stereoselective and regioselective. Diene **2.109** was exposed to the general Shi epoxidation procedure using (L)-fructose derived Shi ketone **2.82**. However, instead of quenching and working up the reaction mixture, the (D)-fructose derived Shi ketone analog **2.112** was added along with additional oxidant. Catalyst **2.82** undergoes the decomposition pathway before reacting with substrate **2.111**. This prevents the undesired diastereomers from being formed and produces diepoxide **2.96** in an 82% yield.

Finally, the ETIC reaction was performed on diepoxide **2.96** (Scheme 2.25) with improved results versus the 34% yield that was observed using diepoxide **2.52** (Scheme 2.20). The reaction now proceeded with an isolated yield of 45% (75% based on recovered starting materials). Thus, the previous observed reactivity enhancement for adding a phenyl substituent in the benzylic position to lower the bond dissociation energy of the fragmenting bond held true for substrate **2.96**.[8] Unfortunately, the reaction halts formation of product around ~55% conversion, and decompostion of lactol **2.95** was observed as reaction time is increased.

Our first improvements in obtaining aldehyde **2.50** are shown in Scheme 2.26. Oxidation of the lactol **2.95** to lactone **2.113** was achieved using Grieco's procedure.[104] Jones reagent was

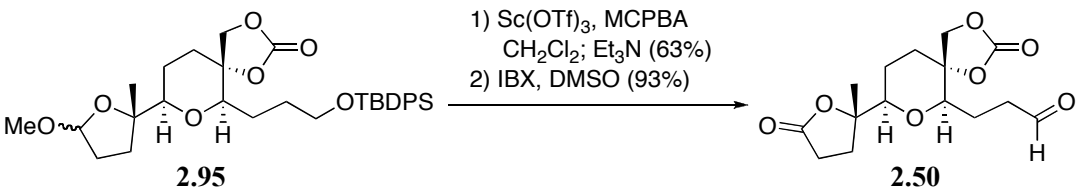


2.95 **2.113** **2.114** **2.50**

Scheme 2.26 First Improvements in Synthesis of Aldehyde 2.50

no longer a viable option due to excessive decompostion as the reaction was ran on a larger scale.[83] Silyl ether deprotection was accomplished in excellent yields under ammonium fluoride conditions. The commonly seen deprotection with TBAF proved to be too harsh and only gave fair yields. Formation of aldehyde **2.50** was completed through Parikh-Doering oxidation of alcohol **2.114**.[59]

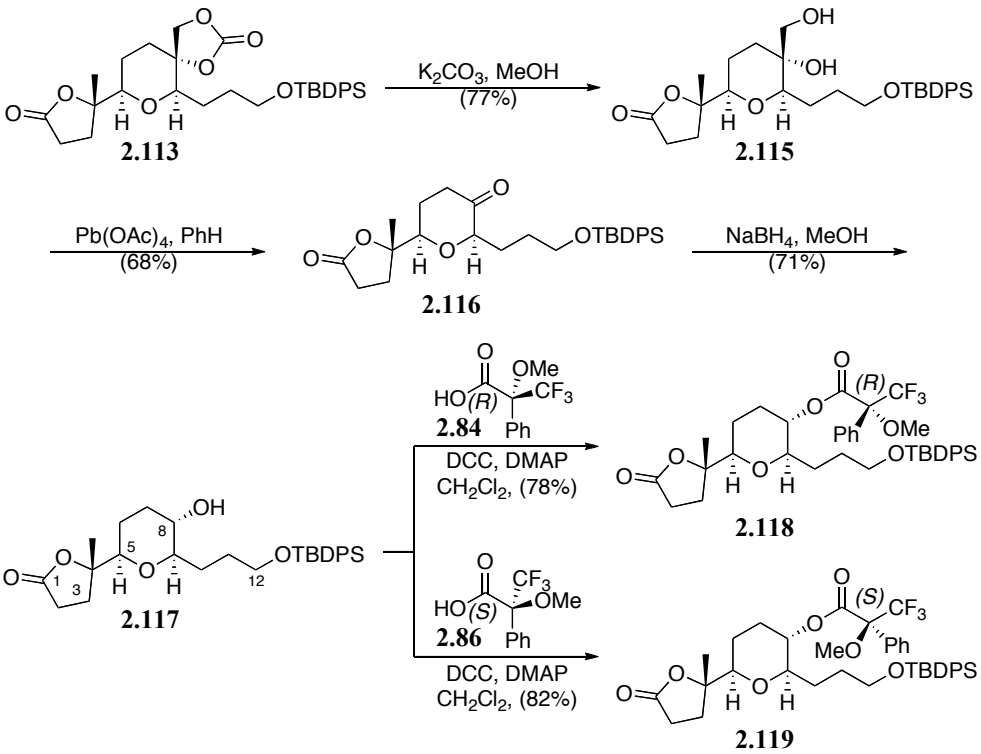
The current method for acquiring aldehyde **2.50** was generated from observing that Grieco's oxidation conditions caused silyl ether cleavage. Complete deprotection was achieved through stirring the reaction mixture overnight. We also desired a new oxidation procedure to create the requisite aldehyde functionality for the NHK coupling. Alcohol **2.114** was shown to be very polar and solubility issues caused the Parikh-Doering oxidation to result in varying yields. This problem was solved by running the reaction in DMSO with IBX to afford the desired transformation in a 93% yield.[105]



Scheme 2.27 Optimized Synthesis of Aldehyde 2.50

We performed another stereochemical analysis to ensure we proceeded onto the NHK coupling with the correct enantiomer of aldehyde **2.50**. Previous two-dimensional NMR experiments elucidated the correct diastereomer was achieved during the ETIC reaction.[75] We decided to derivatize carbonate **2.113** and perform a Mosher ester analysis on the newly formed secondary alcohol (Scheme 2.28).[88] The cyclic carbonate **2.113** was cleaved using potassium

carbonate in methanol to yield diol **2.115**. Ketone **2.116** was readily formed through the lead (IV) acetate mediated oxidation of the 1,2-diol present in compound **2.115**. Axial delivery of a hydride was accomplished using sodium borohydride to furnish secondary alcohol **2.117**. This was verified using Karplus's analysis for ^{3}J-coupling values.[106] Mosher esters **2.118** and **2.119** were created as diastereomeric pairs through the coupling of alcohol **2.117** to both enantiomers of the Mosher acid (**2.84** and **2.86**). The absolute stereochemistry at the recently formed secondary alcohol was determined to be the desired *S* orientation through comparing the ^{1}H shifts of both diastereomers (Table 2.5).



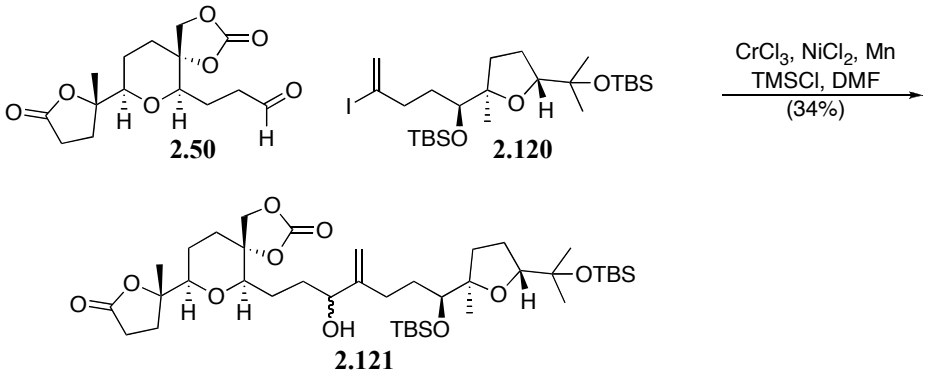
Scheme 2.28 Synthesis of Mosher Ester 2.118 and 2.119

Table 2.5 Chemical Shifts of Protons in Mosher Esters 2.118 and 2.119 and Application of the Advanced (δ_S-δ_R) Mosher Methods

H#	δ *(S)*-MTPA ester **2.119**	δ *(R)*-MTPA ester **2.118**	$\Delta\delta = \delta S - \delta R$
7	2.293	2.372	– 0.079
	2.278	2.291	– 0.013
12	3.617	3.519	+ 0.098

2.4.8 NHK Coupling of Vinyl Iodide 2.51 and Aldehyde 2.50

The successful formation of aldehyde **2.50** and vinyl iodide **2.51** allowed for another key coupling. The Nozaki-Hiyama-Kishi (NHK) reaction was chosen due to its high chemoselectivity in coupling aldehydes with vinyl halides via a well defined chromium mediated redox reaction.[51-53] The advantageous Fürstner procedure was employed to generate allylic alcohol **2.121**.[80] Unlike the original NHK coupling that uses multiple equivalents of toxic, air sensitive chromium (II) chloride, Fürstner's method is catalytic in air stable chromium (III) chloride. This is accomplished by using manganese metal to reduce the inactive chromium (III)



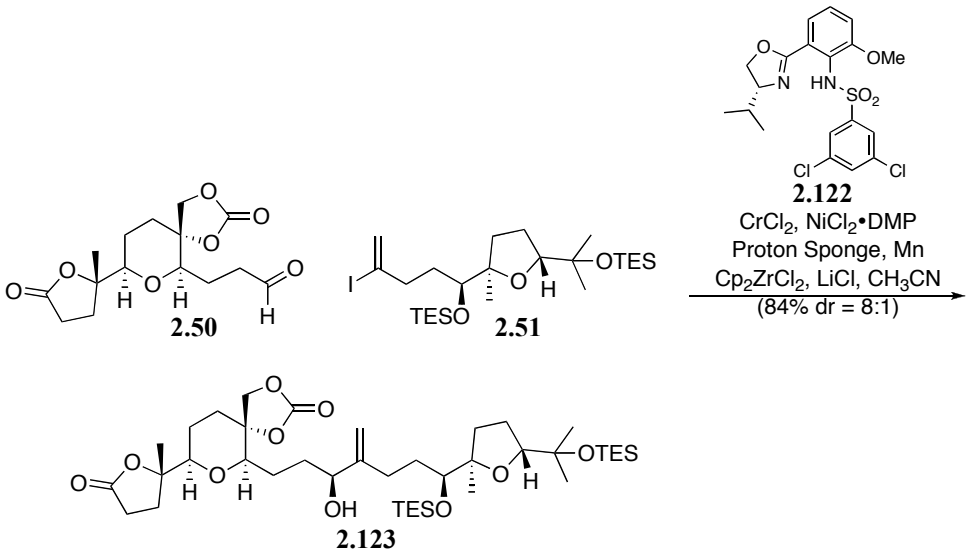
Scheme 2.29 Non-Asymmetric NHK Coupling of Vinyl Iodide 2.120 and Aldehyde 2.50

salt to the active chromium (II) salt, and by promoting catalyst turnover with the addition of TMSCl to cleave the chromium-oxygen bond formed during the reaction mechanism. These reaction conditions provided the formation of allylic alcohol **2.121** through the union of aldehyde **2.50** with vinyl iodide **2.120** (Scheme 2.29). The suboptimal yield was obtained in part due to the formation of complex salt mixtures that lead to difficult product isolation. In addition, these couplings are highly dependent on substrate concentration, making them technically challenging on small scale.

Originally we envisioned constructing the pyranopyran ring system in such a manner that the resulting mixture of diastereomers from the NHK cross coupling was not problematic. We planned on oxidizing the allylic alcohol to generate the corresponding ketone. Next the cyclic carbonate moiety was cleaved and the resulting lactol was exposed to reductive conditions. Unfortunately no desired product formation was seen. We next attempted to obtain diastereomericly pure product through oxidizing allylic alcohol **2.121** and performing a Corey-Bakshi-Shibata reduction.[107,108] Once again this synthetic strategy proved to be unfruitful.

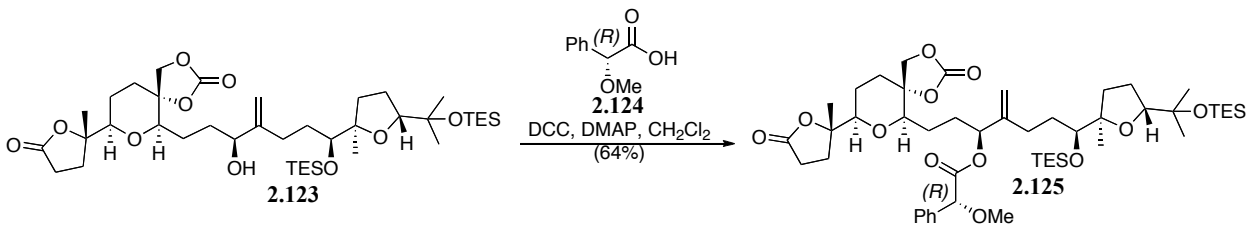
We decided to perform the more laboratory technical demanding asymmetric variant of the NHK cross coupling.[109-111] This reaction achieves its stereospecificity using chiral sulfonamide ligands that adhere to chromium. The sulfonamide ligands are accessed through enantio-pure amino acids. In addition, Kishi uses zirconcene dichloride to aid in catalyst turnover instead of the commonly seen TMSCl. This reagent switch helps improve the overall yield by removing the unproductive silyl enol ether formation pathway. We were hopeful in the application and results of this protocol, as the substrate scope reported by Kishi matches the substrates present in our route. It is important to mention that reagent purity is essential for obtaining reproducible yields. This entails recrystallizing all organometallics present in the

reaction mixture and activating the manganese prior to use. We selected sulfonamide **2.122** due to its reported ability to achieve a highly stereoselective transformation and the ease of its preparation (Scheme 2.30). The coupling proceeded with an excellent yield and a desirable diastereomer ratio of eight to one to give allylic alcohol **2.123**.



Scheme 2.30 Asymmetric NHK Coupling of Aldehyde 2.50 and Vinyl Iodide 2.51

We performed a stereochemical analysis on the diastereomeric mixture obtained from the asymmetric NHK reaction. Trost's chiral *O*-methylmandelate ester analysis was selected as our method to determine the absolute stereochemistry at the newly formed allylic alcohol.[112] The synthesis of the diastereomeric pair is shown in Scheme 2.31. These esters adopt a fixed orientation that allow for NMR studies to reveal the atoms orientation (Figure 2.11). The absolute stereochemistry at the major recently formed allylic alcohol was determined to be the desired *S* orientation through comparing the proton shifts of both diastereomers (Table 2.6).



Scheme 2.31 Stereochemical Analysis for Allylic Alcohol 2.123

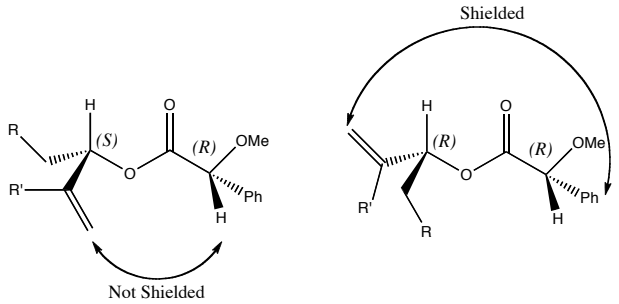


Figure 2.11 Shielding Effects Seen on 2.125 and 12-*epi*-2.125

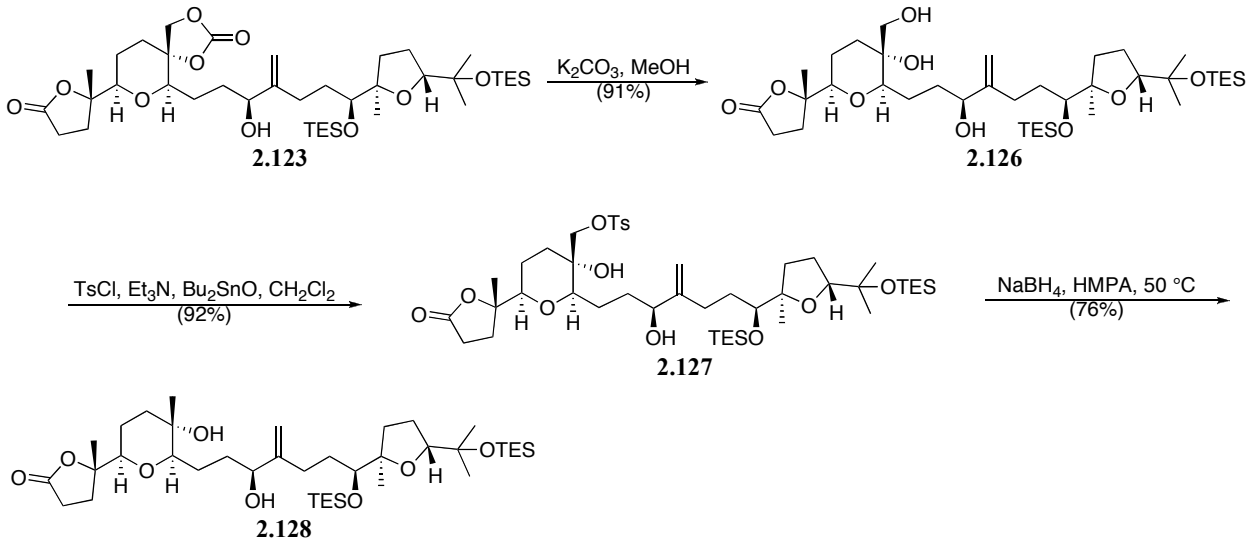
Table 2.6 Chemical Shifts and Abundance of Vinyl Protons in 2.125 and 12-*epi*-2.125

Substrate	δ Vinyl Protons	Relative Area of Peak
2.125	5.097	0.81
	4.988	0.82
12-*epi*-2.125	5.028	0.11
	4.965	0.13

2.4.9 Selective Deoxygenation of a Triol

The final functional group manipulations were performed with the generation of allylic alcohol **2.123** (Scheme 2.32). The 5-membered cyclic carbonate was deprotected to form the 1,2-diol (**2.126**) using potassium carbonate in methanol efficiently. Next, a selective tosylation of the primary alcohol in the presence of a secondary and tertiary alcohol needed to be performed. Unfortunately, a mixture of products was generated under standard tosylation procedures due to

the similarity of tosylation rates for the primary and secondary alcohol. Chemoselectivity was achieved by adding dibutyltin oxide into the reaction mixture to increase the rate for primary tosylate formation.[113] The 1,2-diol in compound **2.126** reacts with the dibutyltin oxide to form the five-membered chelate, which activates the primary position to attack tosyl chloride and generate tosylate **2.127**.



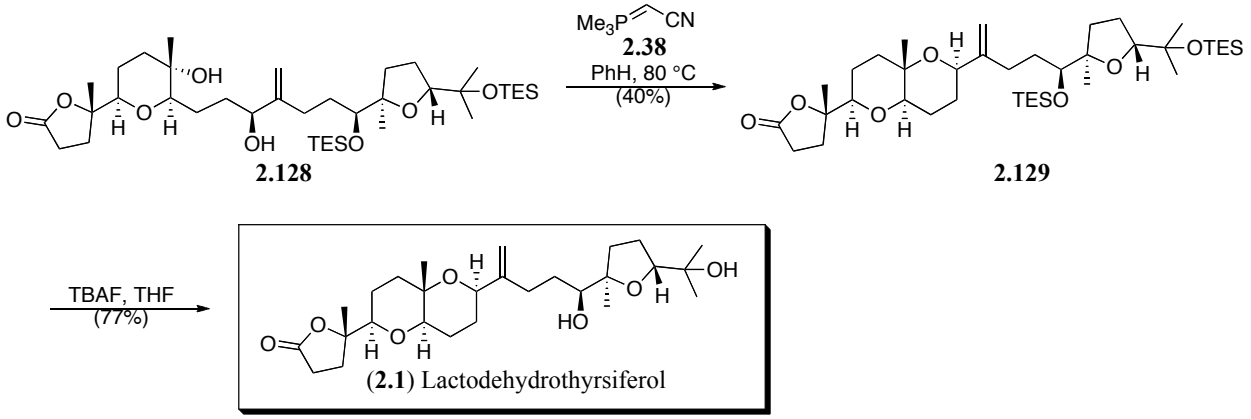
2.123 **2.126** **2.127** **2.128**

Scheme 2.32 Selective Deoxgenation of a Triol to Generate Diol 2.128

The necessary deoxygenation step was performed after the installation of the requisite tosylate functionality. Compound **2.127** was deoxygenated using $NaBH_4$ in the polar aprotic solvent HMPA.[114] At 50 °C, $NaBH_4$ successfully delivered a hydride to the substrate to furnish the desired methyl group. Originally, we tried to perform this transformation in less toxic solvents and with weaker hydride reagents, such as $NaCNBH_3$;[115] however, these conditions required an increase in temperature which ultimately lead to the tertiary alcohol displacing the tosylate to generate an epoxide. This three-step deoxygenation scheme readily delivered diol **2.128** from **2.125** with an overall yield of 64%.

2.4.10 Completion of Synthesis to Lactodehydrothyrsiferol

The final steps for the synthesis of lactodehydrothyrsiferol (**2.1**) included a cyclization to install the pyranopyran ring system followed by global deprotection. This was accomplished by exposing diol **2.128** to a modified Mitsunobu reaction[69] that utilizes the Tsunoda reagent,[70] CMMP (**2.38**), to facilitate the final ring closure. The reaction mechanism proceeded through activation of the secondary alcohol by CMMP to form a phosphonium ether and to liberate acetonitrile. This undergoes cyclization by the attack of tertiary alcohol to expel the stable trimethylphosphine oxide. Hoiki and coworkers already demonstrated the success of this cyclization during their synthesis of pseudodehydrothyrsiferol (**2**) (Scheme 2.6).[42] Finally, mild silyl ether cleaving conditions using TBAF granted access to the natural product **2.1**.



Scheme 2.33 Completion of Synthesis for Lactodehydrothyrsiferol (2.1)

Fernández and coworkers generously provided us with spectral data from their isolation of target **2.1**. We confirmed the structure proposed in the chemical literature to be correct through rigorous comparison of natural **2.1** versus synthetic **2.1**. This comparison is tabulated in Table 2.7, 2.8, and 2.9.

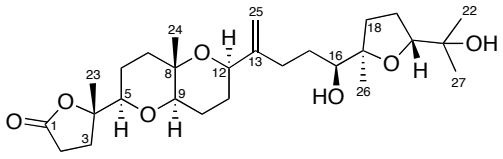


Figure 2.12 Carbon Numbering for Lactodehydrothyrsiferol (2.1)

Table 2.7 ^{1}H-NMR Comparison of Natural 2.1 versus Synthetic 2.1

Carbon	Natural (400 MHz, $CDCl_3$)	Synthetic (600 MHz, $CDCl_3$)
1		
2	2.50/2.68	2.44-2.53 (3H, m)/2.68 (ddd, *J* = 18.0, 9.6, 9.0 Hz)
3	1.75/2.46	1.81-1.90 (6H, m)/2.44-2.53 (3H, m)
4		
5	3.53 (dd, *J* = 11.8,1.7 Hz)	3.53-3.55 (2H, m)
6	1.49/1.67	1.45-1.50 (2H,m)/1.59-1.67 (5H, m)
7	1.63/1.87	1.59-1.67 (5H, m)/1.81-1.90 (6H, m)
8		
9	3.46 (dd, *J* = 11.7, 5.6 Hz)	3.47 (dd, *J* = 11.2, 5.2 Hz)
10	1.60/1.88	1.59-1.67 (5H, m)/1.81-1.90 (6H, m)
11	1.85/2.06	1.81-1.90 (6H, m)/2.06-2.21 (3H, m)
12	4.28	4.29 (dd, *J* = 7.2, 4.0 Hz)
13		
14	2.18/2.47	2.06-2.21 (3H, m)/2.44-2.53 (3H, m)
15	1.50/1.65	1.45-1.50 (2H,m)/1.59-1.67 (5H, m)
16	3.53 (dd, *J* = 11.7, 1.5 Hz)	3.53-3.55 (2H, m)
17		
18	1.60/2.13	1.59-1.67 (5H, m)/2.06-2.21 (3H, m)
19	1.87/1.87	1.81-1.90 (6H, m)/1.81-1.90 (6H, m)
20	3.76 (dd, *J* = 10.6, 6.6 Hz)	3.77 (dd, *J* = 10.3, 5.5 Hz)
21		
22	1.13 (s)	1.14 (s)
23	1.34 (s)	1.35 (s)
24	1.26 (s)	1.27 (s)
25	4.89/5.05 (bs, bs)	4.90 (s)/5.05 (s)
26	1.14 (s)	1.15 (s)
27	1.22 (s)	1.23 (s)

Table 2.8 ^{13}C-NMR Comparison of Natural 2.1 versus Synthetic 2.1

Carbon	Natural (400 MHz, $CDCl_3$)	Synthetic (600 MHz, $CDCl_3$)
1	177.4	177.3
2	29.7	29.7
3	29.1	29.2
4	87.1	87.2
5	82.7	82.7
6	24.3	24.2
7	38.3	38.3
8	72.2	72.2
9	78.8	78.8
10	21.6	21.6
11	26.2	26.1
12	72.7	72.6
13	151.1	151.1
14	29.3	29.4
15	29.8	29.8
16	76.2	76.1
17	86.1	86.1
18	31.6	31.5
19	26.6	26.6
20	87.7	87.6
21	70.5	70.4
22	24.0	23.9
23	23.3	23.3
24	19.5	19.5
25	110.0	110.0
26	23.8	23.8
27	27.7	27.7

Table 2.9 $[\alpha]_D$ Comparison of Natural 2.1 versus Synthetic 2.1

Natural	Synthetic
$[\alpha]_D$ = +4.3 (*c* = 0.21, CHCl3)	$[\alpha]_D$ = +5.1 (*c* = 0.68, CHCl3)

2.5 CONCLUSION

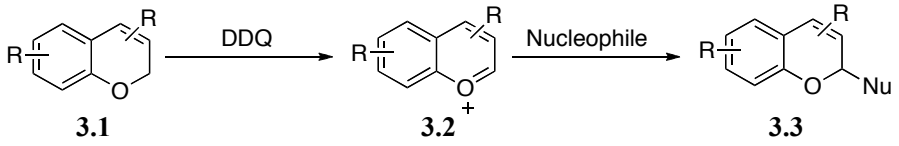
This is the first reported total synthesis of lactodehydrothyrsiferol, with a longest linear sequence of 16 steps. The synthesis showcased a variety of key transformations including an ETIC reaction on a diepoxide to generate a series of cyclic polyethers, a mild and envioromentally friendly procedure to generate 1,1-disubstuted alkenes from a terminal alkyne, a Suzuki cross coupling reaction on a iodinated allylic carbonate, a one pot diepoxidation of a diene to generate two epoxides with opposite stereochemical identities, an asymmetric NHK reaction, and the selective deoxygenation of a triol.

The convergent nature of this synthesis allows it to be a prime candidate to produce a variety of analogs. In addition, the stereocenters are formed using chiral reagents that are available in both enantiomers. This provides the ability to switch stereoisomers with ease. Future plans include constructing a library of analogs for biological testing against the serine/threonine protein phosphatase 2A.

3.0 OXIDATIVE BIMOLECULAR COUPLING REACTION

3.1 INTRODUCTION

Oxidative protocols to form C–C bonds through C–H bond cleavage are becoming an increasingly important transformation. The ability to extend these methods to include bimolecular cross-couplings is of high priority. The Floreancig group undertook this challenge due to its experience in C–H bond activation. They have previously shown that heterocycles can be formed through 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidation of allylic and benzylic ethers followed by sequential intramolecular attack of tethered nucleophiles (See Section 1.2).[24,26] It was hypothesized that this process could be extended to an intermolecular variant to form substituted benzopyran systems (Figure 3.1). The benzopyran subunit was selected for the chemical scaffold because it is common in many natural products and biologically active targets.[116]



3.1 **3.2** **3.3**

Figure 3.1 Proposed Oxidative Coupling Reaction

Previous research published on derivatizing 2*H*-chromene revealed that reactive intermediate 3.2 was stable and reactive enough to undergo the desired transformation (Figure 3.2).[117] This chemistry was performed by exposing the labile leaving group in benzopyran **3.4** to multiple equivalents of a Lewis acid. This process readily formed the aromatic stabilized oxocarbenium ion **3.2** that has been shown to react with π-nucleophiles. We planned on preparing the same reactive intermediate without the need for a leaving group through C–H bond activation. This would create a synthetic strategy that is more atom and step economical than current protocols.[17,18] In addition, the scope of the chromenes and nucleophiles that undergo these transformations will be expanded.

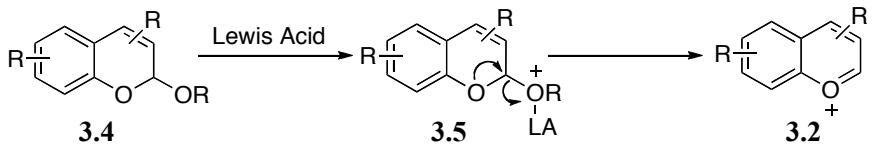
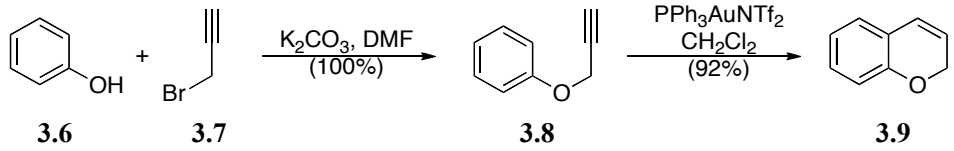


Figure 3.2 Current Method to Access Reactive Cation 3.2

3.2 OPTIMIZATION OF THE REACTION PROTOCOL

The goal was to optimize the conditions for the oxidative coupling procedure using 2*H*-chromene (**3.9**) as the substrate. Benzopyran **3.9** was easily accessed using a simple two-step method (Scheme 3.1). Phenol (**3.6**) undergoes a S_N2 reaction with propargyl bromide (**3.7**) in the presence of base to yield the requisite phenyl propargyl ether (**3.8**) needed for a gold catalyzed cyclization reaction. The cyclization was mediated using PPh_3AuNTf_2[118] under Stratakis' protocol.[119] These reactions are believed to proceed via gold coordination to the alkyne and

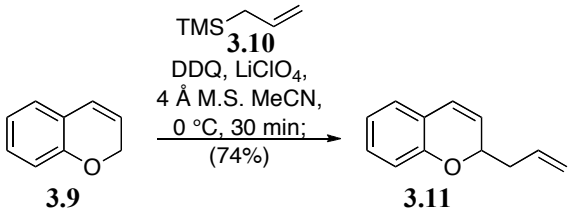
promoting a favorable 6-*endo-dig* cyclization.[120] This gold catalyst was far superior to the originally tested $PtCl_4$[121] method and provided a scalable reaction that produced high yields with short reaction times.



3.6 **3.7** **3.8** **3.9**

Scheme 3.1 Two-Step Protocol to Synthesize 2*H*-Chromene (3.9)

Multiple reaction parameters were screened on the recently furnished 2*H*-chromene (**3.9**) before we ultimately arrived at the optimized conditions displayed in Scheme 3.4 for C–H functionalization. It was discovered that the oxidation took place cleanly in 30 minutes with 1.3 equivalents of DDQ in acetonitrile. It was imperative to use freshly distilled acetonitrile and 4 Å molecular sieves to prevent water from quenching the reactive cation and forming unreactive hydroxylated and dimer byproducts. Acetonitrile was shown to be an effective solvent by its polar aprotic properties ability to stabilize the oxocarbenium ion intermediate. The reaction solvent can be changed to less polar solvents, such as 1,2-dichloroethane or toluene, with negligible effects on overall yield. The temperature of the reaction was lowered to 0 °C to prevent decomposition of the reactive cation (at lower temperatures the cation was too stable and did not react with nucleophiles). $LiClO_4$ (1.5 equivalents) was added to disrupt the DDQ adduct and form a stable ion pair with the oxocarbenium ion.[22,23] Failure to add $LiClO_4$ resulted in minimal product formation. Lastly, the reaction was shown to benefit from adding the nucleophile (2.0 equivalents) after the oxidation was complete.



Scheme 3.2 Optimized Reaction Conditions for 2*H*-Chromene (3.9)

The reaction was hypothesized to undergo the reaction mechanism presented in Figure 3.3. The oxidation of 2*H*-chromene (**3.9**) proceeded through an electron transfer to DDQ (**1.36**).[29] Radical cation **3.12** was furnished following either a hydrogen atom abstraction or proton transfer followed by electron transfer. DDQ adduct **3.14** was formed through the combination of oxocarbenium ion **3.13** and $DDQH^-$ (**1.40**). This unreactive intermediate was converted to reactive ion pair **3.15** in the presence of $LiClO_4$. The desired carbon–carbon bond formation was achieved after the addition of the π-nucloephile.

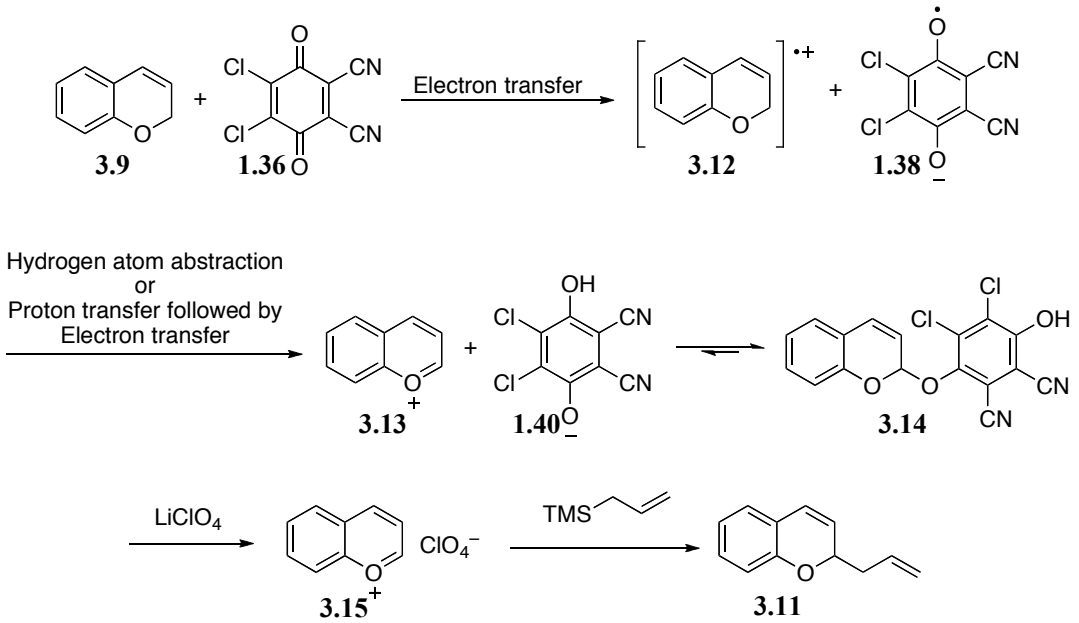
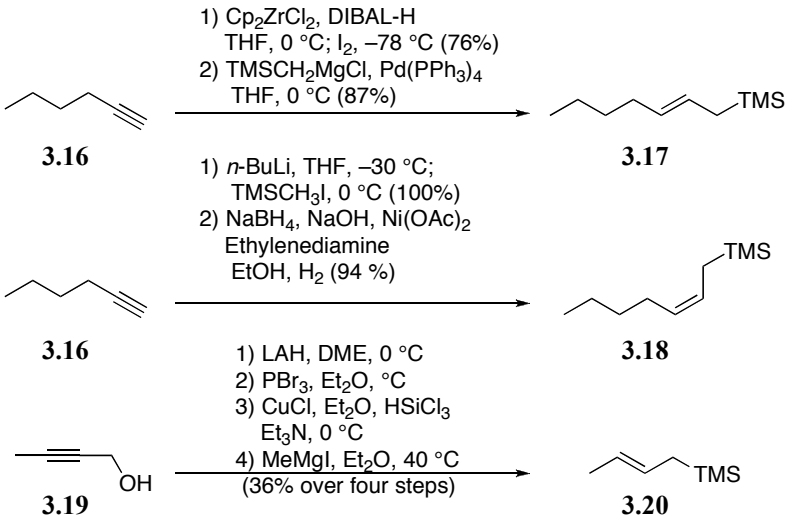


Figure 3.3 Proposed Mechanism for Oxidative Coupling Reaction

3.3 INVESTIGATION INTO NUCLEOPHILE SCOPE

3.3.1 Selection and Synthesis of Nucleophiles for Study

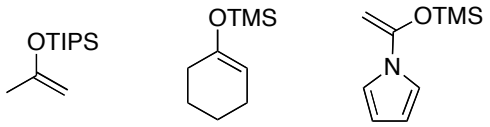
A representative class of π-nucleophiles was selected after optimizing our oxidative coupling reaction conditions. It was decided to synthesize a few allylic trimethylsilanes to test if there was a preferable transition state that would give rise to some level of diastereocontrol (Scheme 3.3). Olefin isomers **3.17** and **3.18** were both furnished from 1-hexyne (**3.16**). Alkyne **3.16** was reduced using Negishi's procedure for in situ Schwartz generation followed by quenching with iodine.[122] The *trans*-substituted olefin **3.17** was formed following a palladium mediated Kumada coupling with trimethylsilyl methyl Grignard.[98] In contrast, the *cis*-substituted olefin **3.18** was obtained following the P-2 nickel reduction of the propargylic alkyne formed through the union of hexyne (**3.16**) and iodomethyl trimethylsilane.[123] (*E*)-Crotyl trimethylsilane



Scheme 3.3 Synthesis of Allylic Trimethylsilanes

(**3.20**) was formed as a single olefin isomer through merging multiple protocols from the chemical literature.

The silyl enol ethers that were chosen for screening are displayed in Figure 3.4. Traditional silyl ether formation procedures provided access to acetone derived nucleophile **3.21** and *N*-acetyl pyrrole derived nucleophile **3.23**.[124] The commercially available cyclohexanone derived nucleophile **3.22** was exposed to the reaction conditions to determine the diastereocontrol for delivering the nucleophile to the reactive cation.

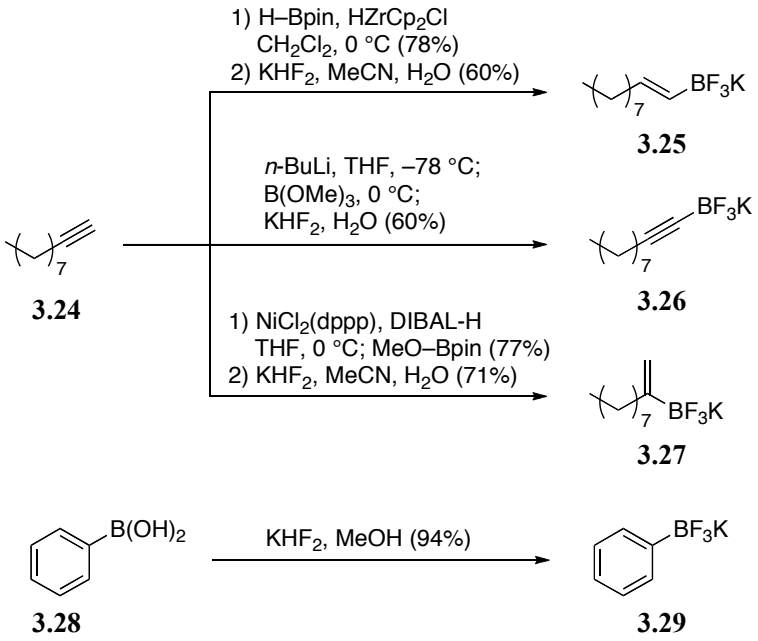


3.21 **3.22** **3.23**

Figure 3.4 Silyl Enol Ethers for Oxidative Coupling Reaction

The last class of nucleophiles selected were potassium organotrifluoroborates.[125] We felt confident that this emerging class of π-nucleophiles would cooperate with our electrophile due to the prior success demonstrated by MacMillan and coworkers with iminium ions[1126] and Bode and coworkers with activated acetals.[127] The majority of the organotrifluoroborates selected for testing were derived from 1-decyne (**3.24**) (Scheme 3.4). 1-Decyne (**3.24**) was reduced to a *trans*-1,2-disubstituted vinyl borane using pinnacolborane with a catalytic amount of Schwartz reagent.[128] The borane was converted to the desired vinyl organotrifluoroborate salt **3.25** using aqueous potassium bifluoride (KHF_2). Exposing the alkynyl anion to trimethyl borate and quenching with aqueous KHF_2 easily accessed alkynyl trifluoroborate **3.26**.[129] The 1,1-disubsituted functionality present in nucleophile **3.27** was achieved using Hoveyda and

coworkers' nickel mediated hydroboration procedure.[130] Potassium phenyl trifluoroborate (**3.29**) was synthesized by combining phenyl boronic acid (**3.28**) and KHF_2 in methanol.

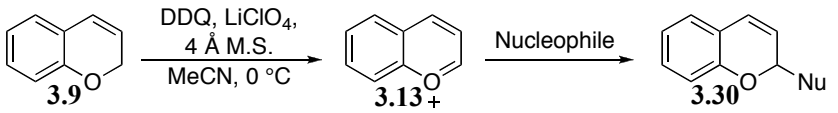


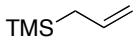
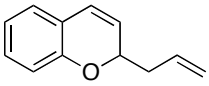
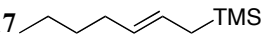
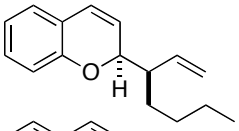
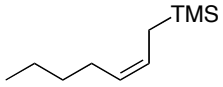
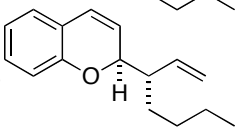
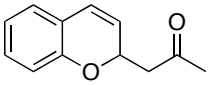
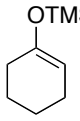
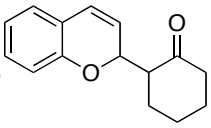
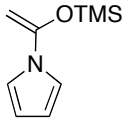
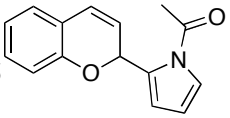
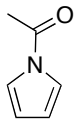
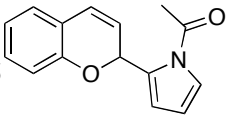
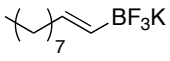
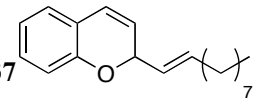
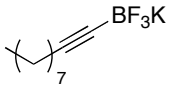
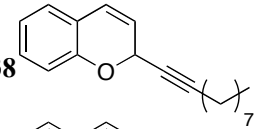
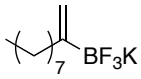
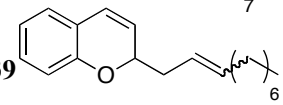
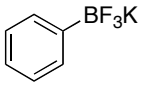
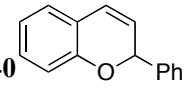
Scheme 3.4 Synthesis of Potassium Trifluoroborates

3.3.2 Nucleophile Scope for the Oxidative Coupling Reaction

The nucleophile scope for 2*H*-chromene is displayed in Table 3.1. The reactions were all run using the aforementioned optimized conditions for the oxidation segment of the reaction. The reaction times varied from 30 minutes to overnight depending on the nucleophile. All reactions underwent a basic workup before being purified using flash chromatography. The isolated yield of product was reported.

Table 3.1 Nucleophile Scope for Oxidative Coupling for 2*H*-Chromene (3.9)



Nucleophile	Product	Yield
3.10 	**3.11** 	74%
3.17 	**3.31** 	63%[a] dr 1:0
3.18 	**3.32** 	51%[a] dr 6:1
3.21 	**3.33** 	trace
3.22 	**3.34** 	71% dr 1:1.6
3.23 	**3.35** 	47%
3.36 	**3.35** 	33%[a]
3.25 	**3.37** 	65%
3.26 	**3.38** 	66%
3.27 	**3.39** 	66%
3.29 	**3.40** 	0%

All reactions were ran in MeCN at 0 °C with $LiClO_4$ (1.5 equiv.) and DDQ (1.3 equiv.). Reactions were stirred for 30 minutes prior to adding the nucleophile (2.0 equiv.). Reaction mixtures were quenched after stirring an additional 30 minutes. [a]Reactions were stirred overnight.

The first class of π-nucleophiles subjected to reactive cation **3.13** was the allylic trimethylsilanes. Allyltrimethylsilane (**3.10**) gave the best overall result of the nucleophiles screened with a yield of 74% within 30 minutes. Next, we tested the olefin isomer pair **3.17** and **3.18** to determine if any sort of diastereocontrol could be accomplished. The first observation seen using these bulkier nucleophiles was a significant decrease in reaction rate. The *trans*-olefin **3.17** proceeded to give only one diastereomer at the level of proton NMR detection. The product produced was the *syn*-isomer (stereochemistry was determined via x-ray crystallography of a derivative). The *cis*-olefin **3.18** produced the opposite *anti*-isomer but with less diastereocontrol giving a 6:1 mixture. The determination of product stereochemistry and an in depth analysis of transition states for these reactions is provided in Section 3.6.

The silyl enol ethers gave a few curious results. The addition of acetone derived nucleophile **3.21** seemed to proceed cleanly by TLC analysis, however product isolation was consistently minimal. We proposed that the product was unstable and readily undergoes a retro-aldol reaction. Addition of 2,6-dichloropyridine to the reaction mixture and keeping the reaction basic during purification proved to be unfruitful in increasing recovered product. Interestingly, cyclohexanone derived nucleophile **3.22** gave rise to stable coupling product **3.34** in a 71% yield. There was a minimal amount of diastereocontrol giving rise to a dr of 1:1.6. *N*-Acetyl pyrrole derived nucleophile **3.23** provided the electrophilic aromatic substitution product **3.35** versus the enol addition product. It was hypothesized this was due to the acidic properties of the reaction mixture, namely $DDQH^-$, destroying the silyl enol ether functionality before it could react with the electrophile. A non-nucleophilic base was added to buffer the reaction mixture to prevent silyl ether cleavage, however no enol addition product was isolated. *N*-Acetyl pyrrole (**3.36**) was subjected to the reaction conditions in order to gain insight into the transformation. The key

observation from this experiment was the significant rate decrease in forming arylation product **3.35**. Therefore, it was postulated that the electrophilic aromatic substitution reaction occurs preferentially and the silyl enol ether functionality allows for more electron density to reside on the aromatic ring system. This created more nucleophilic character for substrate **3.23** versus **3.36** and ultimately was the reason for the rate differences.

The final π-nucleophiles screened were the potassium organotrifluoroborates. Vinyl trifluoroborate **3.25** and alkynyl trifluoroborate **3.26** both reacted with cation **3.13** with good yields to give the predicted products; however, 1,1-disubstituted vinyl trifluoroborate **3.27** proceeded to undergo a rearrangement to form coupling product **3.39** (Figure 3.5). It was hypothesized this transformation occurred due to the relative stabilities of the possible zwitterions that may arise when nucleophile **3.27** reacts with electrophile **3.13**. The predicted mechanism for 1,1-disubstituted product formation includes highly unfavorable intermediate **3.45**, where an unstable primary cation was tethered to an electron deficient carbon. Therefore, nucleophile **3.41** was added into cation **3.13** to from zwitterion **3.42**. The resulting unfavorable

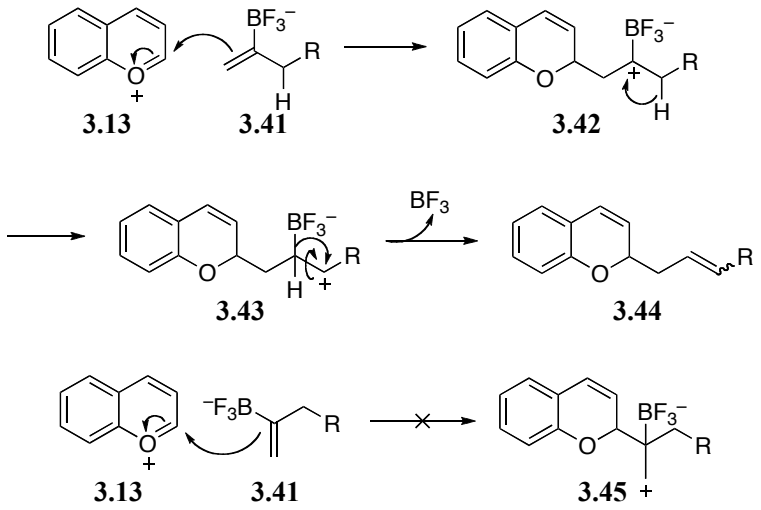


Figure 3.5 Rearrangement with 1,1-Disubstituted Vinyl Trifluoroborates

cation was relieved through a 1,2-hydride shift to form intermediate **3.43** that readily expelled trifluoroborane to give the isolated product. Unfortunately, potassium phenyl trifluoroborate was unreactive and provided no desired coupling product.

3.4 INVESTIGATION INTO BENZOPYRAN SCOPE

3.4.1 Selection and Synthesis of Benzopyrans for Study

The first class of benzopyrans selected for screening differed in electronic properties (Figure 3.6). All 2*H*-chromene derived substrates were synthesized using the previously mentioned two step protocol (Scheme 3.1).[119] We achieved substrates that were able to stabilize the oxocarbenium ion by placing electron donating groups in either the six (compound **3.47**) or eight (compound **3.48**) position of the chromene. In contrast, we destabilized the oxocarbenium ion by adhering an electron withdrawing group in the seven position (compound **3.49**). Chromene **3.46** was synthesized to create an electron rich system that neither aided nor hindered the electrophilic cation. We also wanted to expand the scope of our oxidative coupling to include isochromenes. Benzopyran **3.50** was furnished using Descotes protocol.[131]

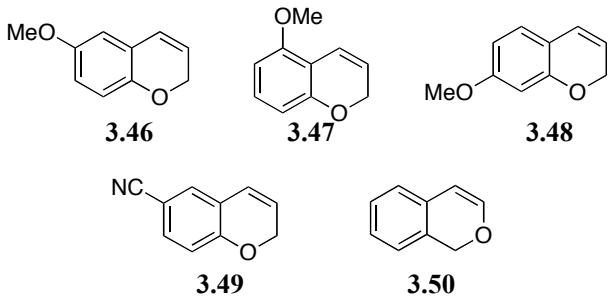
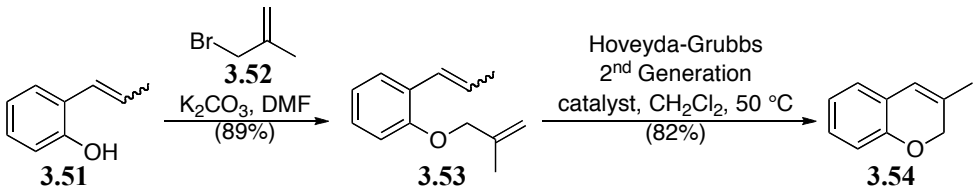


Figure 3.6 Selected Benzopyrans for Oxidative Coupling Reaction

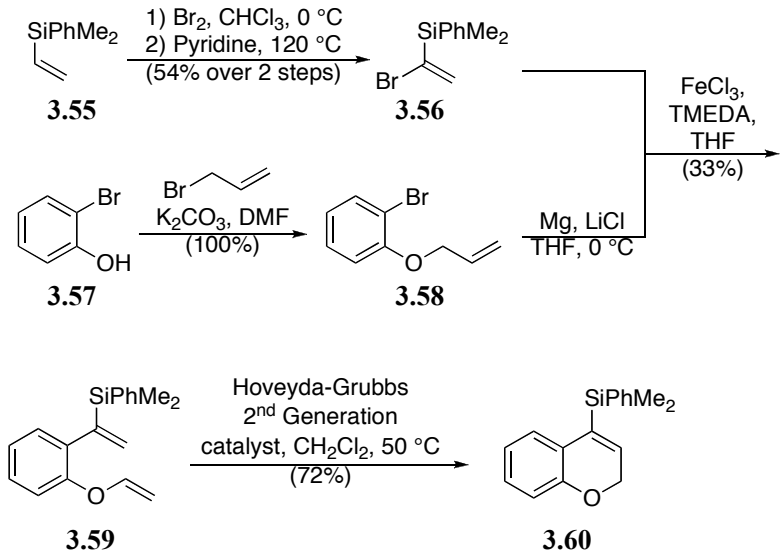
We wanted to elucidate the role of steric interactions in our bimolecular reaction. This was accomplished by adding a methyl group to the three position of chromene (Scheme 3.5). Substrate **3.54** was readily synthesized through a ring closing metathesis reaction from diene **3.53**.[9]



Scheme 3.5 Synthesis of Methyl Substituted Chromene 3.54

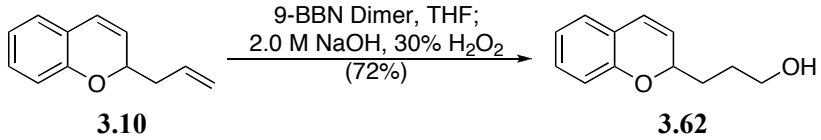
We also wanted to form a benzopyran with specific functionality present that provides access to more complex molecular scaffolds after our coupling was completed. We envisioned dimethylphenylsilyl substituted chromene **3.60** would achieve this goal. This vinyl silane moiety could be converted to a carbonyl under Fleming-Tamao oxidative conditions[132,133] or coupled with a variety of organohalides using Hiyama's palladium mediated cross-coupling reaction.[134] The synthesis of this unknown compound was not a trivial task and many synthetic routes were attempted before arriving at the strategy shown in Scheme 3.6. Vinyl silane **3.55** was converted into the requisite coupling partner **3.56** through a dibromination across the olefin followed by an elimination reaction.[135] Aryl bromide **3.58** was able to undergo an iron mediated coupling reaction with vinyl bromide **3.56** after being made into a Grignard reagent.[136] Attempts to optimized this reaction included using either palladium or nickel to achieve the Kumada coupling, but no desired product was isolated with the major byproduct pathway being

homocoupling.[98] Diene **3.59** was exposed to ring closing metathesis conditions to furnish the silyl derived benzopyran **3.60** with a 72% yield.[16]



Scheme 3.6 Synthesis of Silyl Substituted Chromene 3.60

Lastly, a substrate was designed with a tethered nucleophile that would give rise to a spiro product. This was easily achieved by performing a hydroboration oxidation on allyl substituted benzopyran **3.10**. Another goal was to reoxidize a few of the coupling products isolated during the nucleophile scope study and add another nucleophile into the newly formed oxocarbenium ion.



Scheme 3.7 Synthesis of Benzopyran 2.62

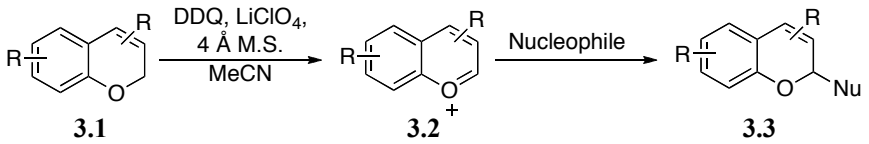
3.4.2 Benzopyran Scope for the Oxidative Coupling Reaction

The benzopyran scope for the oxidative coupling reaction is given in Table 3.2. The oxidation was performed prior to adding the nucleophile in all examples; however, cation formation differed between benzopyrans (see footnotes on Table 3.2 for reaction conditions). All reactions underwent a basic workup before purification using flash chromatography. The isolated yield of product was reported.

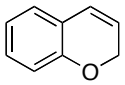
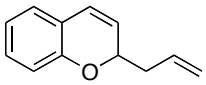
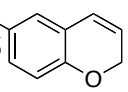
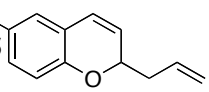
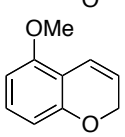
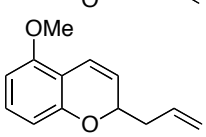
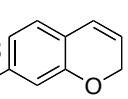
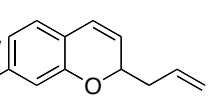
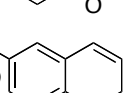
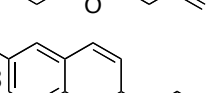
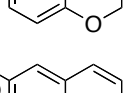
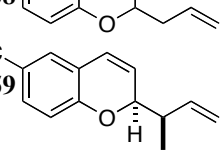
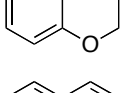
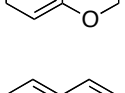
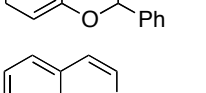
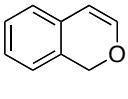
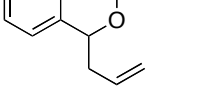
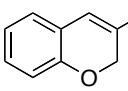
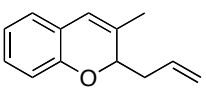
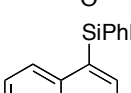
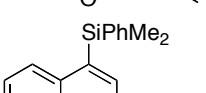
The role of electronic properties present in the benzopyran and their effect on the bimolecular carbon–carbon bond forming protocol was studied. Electron rich chromene **3.46** showed slightly less reactivity than unsubstituted 2*H*-chromene (**3.9**). Benzopyran **3.47** and **3.48** showed a remarkable decrease in yield. These substrates were easier to oxidize because of their ability to stabilize the oxocarbenium ion through resonance; however, this stabilization caused the electrophilicity of the cation to decrease and ultimately led to poor reactivity. In contrast, electron deficient benzopyran **3.49** gave excellent yields. The oxidation of substrate **3.49** required elevated temperature and increased reaction time. The poor stability of the resulting cation created a significant increase in electrophilicity. It was pleasing to discover that aryl trifluoroborate **3.29** showed reactivity towards the destabilized cation formed from benzopyran **3.49** even though it was unreactive with the oxidized version of 2*H*-chromene (**3.9**).

There was success in expanding the scope of the reaction to include isochromene **3.50**. It was observed that cation formation proceeded extremely quickly and once formed was highly unstable. Therefore the decision was made to run the reaction at lower temperatures and monitor

Table 3.2 Benzopyran Scope for Oxidative Coupling

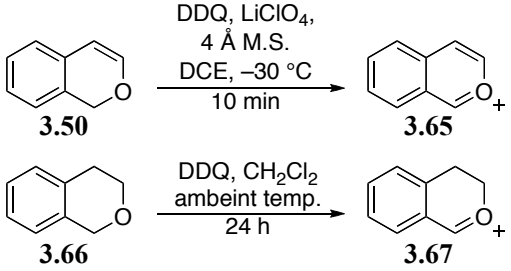


3.1 **3.2** **3.3**

Benzopyran	Nucleophile	Product	Yield
3.9 	TMS **3.10**	**3.11** 	74%
MeO **3.46** 	TMS **3.10**	MeO **3.55** 	64%
OMe **3.47** 	TMS **3.10**	OMe **3.56** 	46%
3.48 MeO 	TMS **3.10**	**3.57** MeO 	27%
NC **3.49** 	TMS **3.10**	NC **3.58** 	92%[a,b]
NC **3.49** 	TMS **3.20**	NC **3.59** 	74%[a,c] dr 1:0
NC **3.49** 	KF_3B Ph **3.29**	NC **3.60**	45%[a,d]
3.50 	$SnBu_3$ **3.54**	**3.61** 	79%[e]
3.51 	TMS **3.10**	**3.62** 	60%
$SiPhMe_2$ **3.52** 	TMS **3.10**	$SiPhMe_2$ **3.63** 	71%[f]
3.53 HO 	–	**3.64** 	93%[g]

Reactions were performed in MeCN at 0 °C with $LiClO_4$ (1.5 equiv.) and DDQ (1.3 equiv.). Reactions were stirred for 30 minutes prior to adding the nucleophile (2.0 equiv.). Reaction mixtures were quenched after stirring an additional 30 minutes. [a]Reactions were heated to reflux after DDQ addition for two hours then cooled to ambient temp before nucleophile was added. [b]Nucleophile addition took 15 min. [c]Nucleophile addition took 16 h. [d]Nucleophile addition went overnight at reflux. [e]Oxidation was performed in DCE at –30 °C and after ten minutes the nucleophile was added before warming to ambient temp. over 30 min. [f]Oxidation stirred for 2 h and nucleophile addition took 1 h to reach completion. [g]Reaction was complete 15 min after DDQ addition.

the progression of cation formation closely. It was postulated that increasing the nucleophilicity of the π-nucleophile would decrease the length of time the cation was present in the reaction mixture, ultimately giving it less time to degrade through unproductive pathways.[137] These measures allowed for the transformation to proceed with a 79% yield. It is important to highlight the extent of stabilization gained through aromaticity. This is clearly displayed through the comparison of our isochromene example with Li and coworkers with isochroman (Scheme 3.8).[138] Oxidation of isochromene (**3.50**) occurred within ten minutes at –30 °C, however isochroman (**3.66**) required a full twenty-four hours at ambient temperature to reach completion.



3.50 **3.65** **3.66** **3.67**

Scheme 3.8 Relative Rates of Cation Formation for Isochromene 3.50 versus Isochroman 3.66

Silyl derivative **3.52** reacted with similar yields as parent compound **3.9**. Coupling product **3.63** has the ability to undergo further modification through peroxide mediated oxidation[132,133] or palladium meditated cross-coupling at the four position.[134] We tried to apply our oxidative coupling procedure to other benzopyrans that can undergo secondary reactions. However, all attempts to oxidize benzopyrans substituted at the four position with silyl enol ethers or vinyl acetates unfortunately resulted in ene-one formation (Figure 3.7).

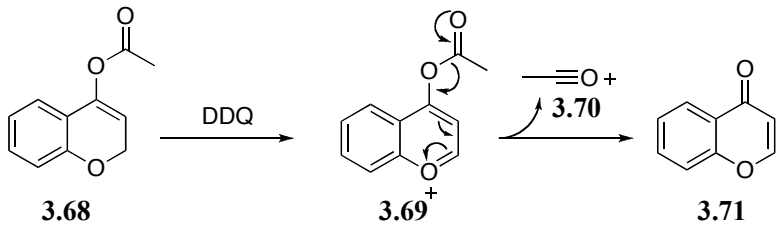


Figure 3.7 Ene-one Formation for DDQ Oxidation of Benzopyran 3.68

There was success in forming spiro compound **3.64** with a yield of 93% by exposing benzopyran **3.53** to the oxidative conditions. It was hypothesized that one could reoxidize a few of the compounds synthesized during the nucleophile scope investigation and perform another bimolecular bond forming reaction. Interestingly, no isolation of the desired product was seen when compound **3.11** was reoxidized and a nucleophile was introduced to the reaction mixture. The starting material possibly could decompose to form cation **3.13** and allyl radical **3.73** (Figure 3.8). Previous studies performed by Floreancig and coworkers concluded that DDQ removes an electron to form a radical cation before removing hydrogen.[29] Radical cation **3.72** has the option to fragment to create a stable cation and radical. This unproductive pathway rendered quaternary carbon formation unlikely without further optimization.

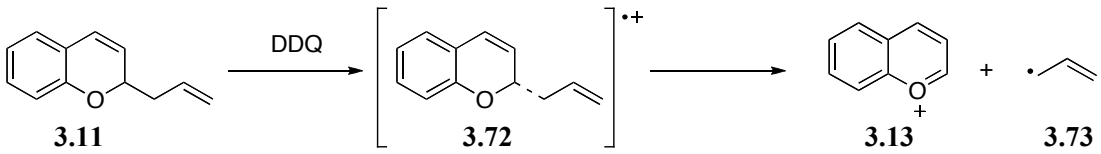
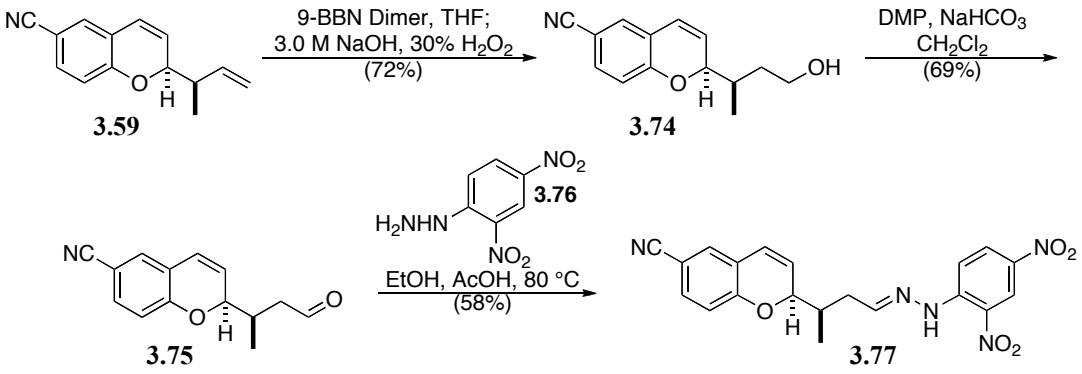


Figure 3.8 Unproductive Pathway During Reoxidation of Benzopyran 3.10

3.5 DETERMINATION OF STEREOCONTROL FOR PROCHIRAL NUCLEOPHILES

The stereochemical outcome observed when allylic silane **3.17** and **3.18** were added to reactive cation **3.11** deserves discussion (Table 3.1). The relative stereochemistry of oxidative coupling products **3.31** and **3.32** was determined through x-ray crystallography of a derivative. Cyano substituted benzopyran **3.49** was selected due to its strong preference to be a solid (Table 3.2). (*E*)-crotyl silane (**3.20**) was synthesized to remove the lengthy carbon chain that prevented solidification (Scheme 3.3). The synthesis of 2,4-dinitrophenylhydrazone (DNP-hydrazone) **3.77** was started by executing a hydroboration oxidation of alkene **3.59** (Scheme 3.9). The resulting alcohol was oxidized to the corresponding aldehyde **3.75** using DMP.[55] DNP-hydrazone **3.77** was synthesized through the combination of aldehyde **3.75** and hydrazine **3.76** using traditional acidic condensation protocols.



Scheme 3.9 Synthesis of Compound 3.77 for X-Ray Crystallography

X-ray crystallography revealed that the product received using (*E*)-crotyl silane was indeed the *syn*-isomer (Figure 3.9). This information allowed us to postulate the transition states

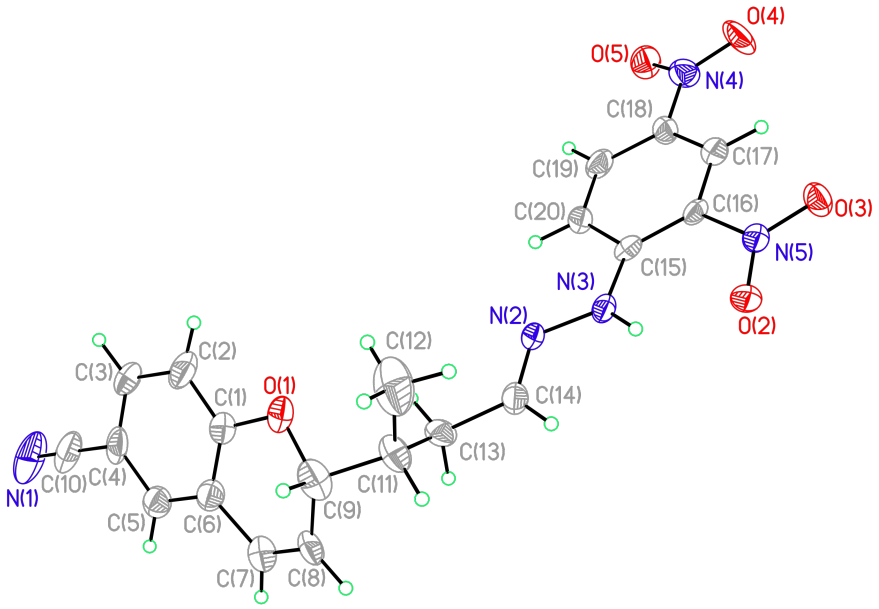


Figure 3.9 X-Ray Structure of Hydrazone 3.77

the reaction proceeded through when using prochiral allylic silanes. It was well established in the chemical literature that allylsilanes react with π-electrophiles in either an antiperiplanar or synclinal transition state.[139] This led to prediction of the two possible transition states for (*E*)-allylic silanes shown in Figure 3.10. It was positioned the hydrogen atom to lie above the reactive cation in both cases. The antiperiplanar arrangement in structure **3.79** has a steric interaction present from the overlapping methine and methylene moieties. This interaction is relieved through the synclinal arrangement shown in transition state **3.78**. This configuration allows for the larger substituent to be adjacent to the less stericly demanding oxygen atom. Thus, a single diastereomer was recovered from the bimolecular reaction.

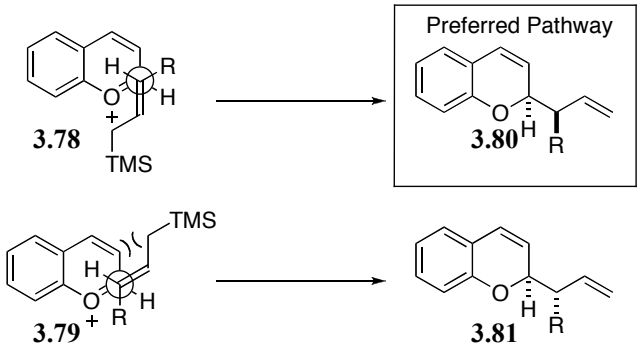


Figure 3.10 Proposed Transition State Using (*E*)-Allylic Silanes

Next, it was hypothesized about the transition states that arose when using (*Z*)-allylic silanes (Figure 3.11). NMR data from coupling products **3.31** and **3.32** clearly revealed that a different diastereomer was recovered when using the opposite olefin isomer. The two possible transition states were constructed with the hydrogen atom positioned above the aromatic ring system. Both synclinal arrangement **3.82** and antiperiplanar arrangement **3.83** were absent of any major steric interactions. Therefore it was postulated that there is a slight preference for the antiperiplanar orientation that gave rise to the six to one diastereomeric ratio seen.

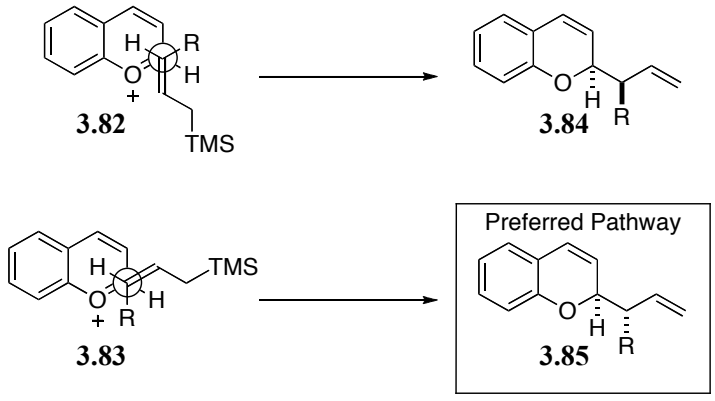


Figure 3.11 Proposed Transition State Using (*Z*)-Allylic Silanes

3.6 CONCLUSIONS

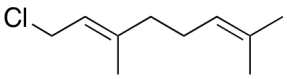
Herein was reported a novel method to form substituted benzopyrans using an oxidative coupling procedure. The substrates were easier to access compared to current methodology due to the utilization of C–H bond activation. The scope of nucleophiles and benzopyrans that underwent the desired transformation was investigated and research to expand it is occurring concurrently. The success of this research has lead to a wide variety of related projects. An asymmetric variant is being devoloped and the scope to include other oxidizable heterocycles is being explored. Additionally, future plans include showcasing the versatility of the reaction through the total synthesis of a natural product.

APPENDIX A

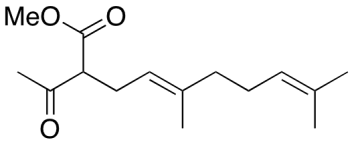
LACTODEHYDROTHYSIFEROL (SUPPORTING INFORMATION)

General Experimental Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on Bruker Avance 300 spectrometer at 300 MHz and 75 MHz, Bruker Avance 400 spectrometer at 400 MHz and 100 MHz, and Bruker Avance 600 spectrometer at 600 MHz and 150 MHz, respectively. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. The solvent peaks was used as a reference value, for ^{1}H NMR: $CDCl_3$ = 7.27 ppm, for ^{13}C NMR: $CDCl_3$ = 77.0. Some of the NMR spectra contain tetramethylsilane. Data are reported as follows: (s = singlet; d = doublet; t = triplet, q = quartet; dd = doublet of doublets; ddd = doublet of doublet of doublets; dt = doublet of triplet; br = broad; app = apparently). High resolution and low resolution mass spectra were recorded on a VG 7070 spectrometer using electron ionization (EI) or electron spray ionization (ESI). Infrared (IR) spectra were collected on a Mattson Cygnus 100 spectrometer. Samples for IR were prepared as a thin film on a NaCl plate by dissolving the compound in CH_2Cl_2 and then evaporating the CH_2Cl_2. Optical rotations were measured on a Perkin-Elmer 241 polarimeter with sodium lamp at ambient temperature as follows: $[a]_\lambda$ (*c*, g/100 mL). Tetrahydrofuran and diethyl ether were dried by passage through an activated alumina column under positive N_2 pressure. Methylene chloride, acetonitrile,

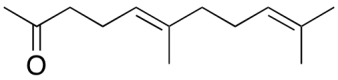
hexamethylphosphoramide, and benzene were distilled under N_2 from CaH_2. Analytical TLC was performed on E. Merck pre-coated (25 nm) silica gel 60F-254 plates. Visualization was done under UV light (254 nm). Flash chromatography was done using ICN SiliTech 32-63 60 Å silica gel. Reagent grade ethyl acetate, diethyl ether, pentane and hexanes (commercial mixture) were purchased from EM Science and used as is for chromatography. All reactions were performed in oven or flame-dried glassware under a positive pressure of N_2 with magnetic stirring unless otherwise noted. Alkyllithium reagents were titrated using menthol and the indicator 2,2-dipyridyl in THF prior to use.



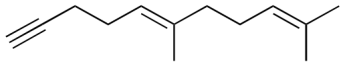
(*E*)-1-Chloro-3,7-dimethylocta-2,6-diene (2.77): To a solution of *N*-chlorosuccinimide (0.952 g, 7.13 mmol) in CH_2Cl_2 (31.0 mL) at –30 °C was added dimethyl sulfide (0.58 mL, 7.78 mmol) dropwise. The solution was warmed to 0 °C and continued to be stirred. After 10 min, the reaction was cooled to –40 °C and geraniol (**2.55)** (1.00 g, 6.48 mmol) in CH_2Cl_2 (3.40 mL) was added dropwise, and the solution was warmed to 0 °C. After 2 h, the reaction was warmed to room temperature and stirred for an additional 30 min. The solution was washed with brine (15 mL) and the resulting aqueous layer was extracted with pentane (2 x 10 mL). The combined organic layers were diluted with pentane (10 mL) and was added to the mixture. The mixture was washed with brine (2 x 10 mL) and then dried over $MgSO_4$. The solution was concentrated and placed under vacuum to yield a pale yellow liquid (1.12 g, 100%). The product was used without further purification: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.46 (td, J = 8.1, 1.2 Hz, 1H), 5.09 (m, 1H), 4.11 (d, J = 8.1 Hz, 2H), 2.04-2.14 (m, 4H), 1.74 (d, J = 0.9 Hz, 3H), 1.69 (s, 3H), 1.62 (s, 3H). *These data are consistent with literature values.*[140]



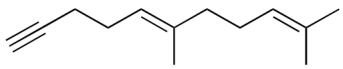
(*E*)-Methyl 2-acetyl-5,9-dimethyldeca-4,8-dienoate (2.78): To a suspension of NaH (3.57 g, 89.2 mmol) in DMF (84.5 mL) was added methyl acectoacetate (9.93 mL, 92.1 mmol) dropwise at ambient temperature. After stirring for 30 min, crude chloride **2.77** (5.13 g, 29.7 mmol) in DMF (5.12 mL) was added dropwise and the reaction continued to stir overnight. The reaction mixture was quenched with H_2O (125 mL) and extracted with ethyl acetate (3 x 200 mL). The organic layer was washed with H_2O (3 x 200 mL), dried over $MgSO_4$, and concentrated under vacuum. The mixture was purified using flash chromatography (4% to 10% ethyl acetate in hexanes) to obtain the desired *β*-keto-ester (6.41 g, 86%): ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.01-5.05 (m, 2H), 3.73 (s, 3H), 3.47 (t, *J* = 7.8 Hz, 1H), 2.57 (dd, *J* = 7.5, 7.5 Hz, 2H), 2.33 (s, 3H), 1.98-2.06 (m, 4H), 1.68 (s, 3H), 1.63 (s, 3H), 1.60 (s, 3H). *These data are consistent with literature values.*[141]



(*E*)-6,10-Dimethylundeca-5,9-dien-2-one (2.79): To a solution of 2.0 M KOH (527 mL) and ethanol (88.6 mL) at room temperature was added *β*-keto-esterate **2.78** (20.9 g, 82.8 mmol). The reaction stirred for 1.5 h and then was acidified using 5.0 M HCl. The reaction was extracted with diethyl ether (3 x 250 ml), dried over $MgSO_4$, and concentrated under vacuum. The crude mixture was taken up in benzene (200 mL) and heated to reflux for 2 h. The reaction was cooled and concentrated under vacuum before the mixture was purified using flash chromatography (4% to 8% ethyl acetate in hexanes) to isolate the methyl ketone (15.9 g, 99%): ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.06-5.10 (m, 2H), 2.47 (t, *J* = 7.2 Hz, 2H), 2.27 (q, *J* = 7.2 Hz, 2H), 2.15 (s, 3H), 1.96-2.08 (m, 4H), 1.68 (d, *J* = 0.9 Hz, 3H), 1.62 (s, 3H), 1.60 (s, 3H). *These data are consistent with literature values.*[142]

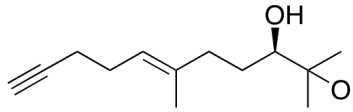


(*E*)-6,10-Dimethylundeca-5,9-dien-1-yne (2.80): To a solution of 2,2,6,6-tetramethylpiperidine (5.32 g, 31.5 mmol) in THF (57.5 mL) at –78 °C was added a solution of 1.6 M *n*-butyllithium in hexanes (19.3 mL, 30.9 mmol). The reaction was warmed to 0 °C and stirred for 30 min and then cooled back down to –78 °C. A solution of ketone **2.79** (5.57 g, 28.7 mmol) in THF (10.6 mL) was added dropwise to the mixture and continued to stir for 1 h. Chlorodiethylphosphate (4.55 mL, 31.5 mmol) was added and the reaction was warmed to ambient temperature. In a separate flask, a solution of 2,2,6,6-tetramethylpiperidine (10.1 g, 60.1 mmol) in THF (69.0 mL) at –78 °C was prepared. To this flask was added a solution of 1.6 M *n*-butyllithium in hexanes (37.3 mL, 59.6 mmol) and then warmed to 0 °C. After 30 min the flask was cooled back to –78 °C. The original mixture containing the enol phosphate was added dropwise to the second reaction flask via cannulation. The reaction warmed to ambient temperature slowly over the next 3 h. The solution was quenched with H_2O (300 mL) and 1.0 M HCl (48 mL). The aqueous layer was extracted with pentane (3 x 300 mL). The organic layer was washed with 1.0 M HCl (3 x 120 mL), H_2O (120 mL), a saturated solution of sodium bicarbonate (2 x 120 mL), and a saturated solution of sodium chloride (90 mL). The solution was dried over $MgSO_4$ and concentrated under vacuum. A silica plug was run (10% diether ethyl in pentane) to obtain the alkyne (3.30 g, 65%): ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.17-5.21 (m, 1H), 5.08-5.13 (s, 1H), 2.17-2.28 (m, 4H), 1.96-2.13 (m, 4H), 1.94 (t, J = 2.1 Hz, 1H), 1.69 (s, 3H), 1.63 (s, 3H), 1.61 (s, 3H). *These data are consistent with literature values.*[86]



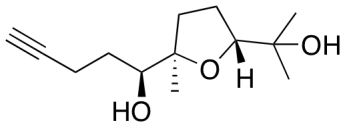
(*E*)-6,10-Dimethylundeca-5,9-dien-1-yne (2.80): To THF (106 mL) at 0 °C was added 1.31 M *n*-butyllithium in hexanes (17.6 mL, 23.1 mmol) followed by 1-TMS-propyne (3.00 g, 26.7 mmol). After stirring for 1.5 h the reaction was cooled to –78 °C. In

a separate flask, geranyl chloride (**2.77**) (3.08 g, 17.8 mmol) was disolved in THF (92 mL) and cooled to –78 °C. The geranyl chloride solution was added via cannulation dropwise to the flask containing the 1-TMS-propynyl lithium. After stirring for 2 h the reaction was quenched with 1.0 M TBAF in THF (26.7 mL, 26.7 mmol). The reaction was allowed to warm to rt, then was washed with H_2O (150 mL) and a saturated solution of NaCl (150 mL). The reaction mixture was concentrated dried using $MgSO_4$ and concentrated. The residue was purified by flash chromatography (2% ethyl ether in pentane) to obtain the terminal alkyne (2.76 g, 88%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.17-5.20 (m, 1H), 5.08-5.13 (s, 1H), 2.19-2.28 (m, 4H), 1.98-2.13 (m, 2H), 1.95 (t, J = 2.4 Hz, 1H), 1.69 (d, J = 0.9 Hz, 3H), 1.63 (s, 3H), 1.61 (s, 3H). *These data are consistent with literature values.*[86]



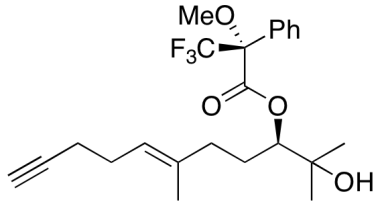
(*R*,*E*)-2,6-Dimethylundec-6-en-10-yne-2,3-diol (2.81): To a solution of H_2O (78 mL) and *tert*-butyl alcohol (78 mL) was added AD mix β (18.6 g) and $CH_3SO_2NH_2$ (1.27 g, 13.3 mmol) at rt. The mixture was stirred for 5 min and then was cooled to 0 °C. Diene **2.80** (2.34 g, 13.3 mmol) was added dropwise. The reaction stirred overnight and was quenched with sodium sulfite (9.36 g) in H_2O (93.6 mL). The mixture was stirred for 5 min and then was extracted with ethyl acetate (4 x 250 mL). The organic layer was dried over $MgSO_4$, concentrated, and purified by flash chromatography (30% to 50% ethyl acetate in hexanes) to yield the desired diol (1.48 g, 53%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.26 (m, 1H), 3.37 (d, J = 10.5 Hz, 1H), 2.20-2.31 (m, 4H), 2.06-2.15 (m, 2H), 1.95 (t, J = 2.4 Hz, 1H), 1.65 (s, 3H), 1.56-1.61 (m, 1H), 1.36-1.49 (m, 1H), 1.21 (s, 3H), 1.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.7, 123.2, 84.4, 78.1, 73.0, 68.3, 36.7, 29.5, 27.0, 26.4, 23.3, 18.8,

16.0; IR (neat): 3405, 3307, 2971, 2925, 2855, 1449, 1382, 1160, 1076 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{22}O_2Na$ $[M+Na]^+$ 233.1517, found 233.1497; $[\alpha]_D$ = +27.0 (*c* 1.05, $CHCl_3$).

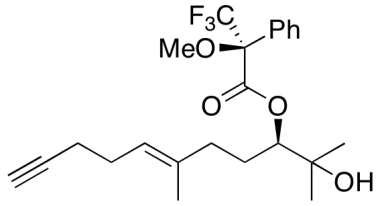


(*S*)-1-((2*R*,5*R*)-Tetrahydro-5-(2-hydroxypropan-2-yl)-2-methylfuran-2-yl)pent-4-yn-1-ol (2.83): To a solution of alkene **2.81** (1.47 g, 7.00 mmol) in acetonitrile/dimethoxymethane (102 mL, 1:2, v/v) at 0 °C was added Bu_4NHSO_4 (95 mg, 0.28 mmol), Shi ketone **2.82** (0.542 g, 2.10 mmol), and 0.500 M $Na_2B_4O_7$ in 0.4 mM Na_2(EDTA) (68.0 mL). Once the reaction mixture reached 0 °C (internal temperature), Oxone® (6.45 g, 10.5 mmol) in 0.4 mM Na_2(EDTA) (38.2 mL) and K_2CO_3 (6.35 g, 45.9 mmol) in H_2O (38.2 mL) were added simultaneously but separately via a syringe pump over 2 h. The reaction was quenched with H_2O (60 mL) and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude epoxy-alcohol was disolved in toluene (320 mL) and cooled to 0 °C. To the solution was added CSA•pyr (0.218 g, 0.700 mmol) and the reaction was allowed to stir for an additional 45 min. The reaction was quenched with triethylamine (15 mL) and concentrated under vacuum. Purification by flash chromatography (20% to 50% ethyl acetate in hexanes) provided the desired compound (1.31 g, 83%) with a slight impurity (13:1) being a diastereomer of the product. Final purification with an Analogix IntelliFlash 280 MPLC using an Analogix SF65-200g Sepra Si50 column and a flow rate of 100 mL/min and a gradient of 10% to 35% EtOAc in hexanes led to the isolation of pure **2.83**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.78 (dd, *J* = 10.2, 6.0 Hz, 1H), 3.69 (dt, *J* = 10.5, 4.2 Hz, 1H), 2.35-2.46 (m, 2H), 1.83-2.13 (m, 4H), 1.65-1.73 (m, 1H), 1.49-1.60 (m, 2H), 1.23 (s, 3H), 1.17 (s, 3H), 1.14 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 87.1, 85.4, 84.0, 74.7, 70.6, 68.3, 31.2, 30.3, 26.8, 26.5, 23.4, 23.3, 15.3; IR (neat) 3418, 3306, 2973, 2932, 2873, 1454, 1377, 1175,

1086, 942 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{12}H_{19}O_3$ $[M\text{-}CH_3]^+$ 211.1334, found 211.1330; $[\alpha]_D$ = –9.91 (*c* 1.07, $CHCl_3$).

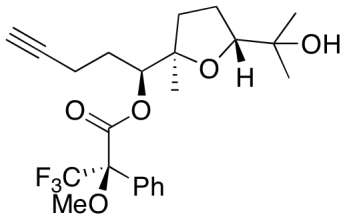


(*R*)-((*R*,*E*)-2-Hydroxy-2,6-dimethylundec-6-en-10-yn-3-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (2.85): A solution of diol **2.81** (3.3 mg, 15.7 μmol) and (*R*)-(+)-methoxy thrifluoromethyl phenylacetic acid (**2.84**) (11.0 mg, 47.1 μmol) in CH_2Cl_2 (0.3 mL) at 0 °C was treated with DCC (16.2 mg, 78.5 μmol) and DMAP (1.9 mg, 15.7 μmol). The mixture was stirred at room temperature for 3 h, and TLC showed the diol disappeared. The solvent was removed under reduced pressure. Crude material was used for ^{19}F NMR spectrum. ^{19}F NMR (376 MHz, $CDCl_3$) δ –70.59 (minor), –70.84 (major). After this, the ester was purified by preparative TLC, eluting with 25% ethyl acetate in hexanes to give (*R*)-MTPA ester (6.3 mg, 94%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.65-7.63 (m, 2H), 7.44-7.40 (m, 3H), 5.13-5.09 (m, 1H), 5.00 (dd, *J* = 10.0, 2.2 Hz, 1H), 3.58 (d, *J* = 1.2 Hz, 3H), 2.25-2.18 (m, 4H), 1.95 (app t, *J* = 2.3Hz, 1H), 1.91-1.87 (m, 2H), 1.72 (dddd, *J* = 14.2, 9.2, 7.1, 2.3 Hz, 1H), 1.65-1.57 (m, 1H), 1.55 (d, *J* = 0.6 Hz, 3H), 1.49 (s, 1H), 1.23 (s, 3H), 1.17 (s, 3H).

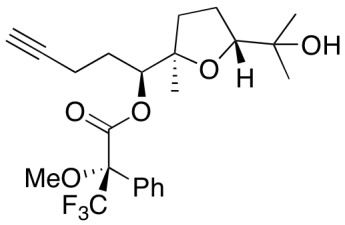


(*S*)-((*R*,*E*)-2-Hydroxy-2,6-dimethylundec-6-en-10-yn-3-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (2.87): A solution of diol **2.81** (3.3 mg, 15.7 μmol) and (*S*)-(–)-methoxy trifluoromethyl phenylacetic acid (**2.86**) (11.0 mg, 47.1 μmol) in CH_2Cl_2 (0.3 mL) at 0 °C was treated with DCC (16.2 mg, 78.5 μmol) and DMAP (1.9 mg, 15.7 μmol). The mixture was stirred at room temperature for 3 h, and TLC showed the diol disappeared. The solvent was

removed under reduced pressure. Crude material was used for ^{19}F NMR spectrum. ^{19}F NMR (376 MHz, $CDCl_3$) δ –70.56 (major), –70.82 (minor). After this, the ester was purified by preparative TLC, eluting with 25% ethyl acetate in hexanes to give (*S*)-MTPA ester (6.2 mg, 92%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.63-7.61 (m, 2H), 7.43-7.42 (m, 3H), 5.16 (t, *J* = 6.5 Hz, 1H), 5.01 (dd, *J* = 9.8, 2.2 Hz, 1H), 3.59 (s, 3H), 2.27-2.19 (m, 4H), 2.03-1.98 (m, 2H), 1.94 (app t, *J* = 2.0 Hz, 1H), 1.82 (dddd, *J* = 14.3, 9.4, 7.3, 2.2 Hz, 1H), 1.73-1.65 (m, 1H), 1.60 (s, 3H), 1.48 (s, 1H), 1.18 (s, 3H), 1.14 (s, 3H).

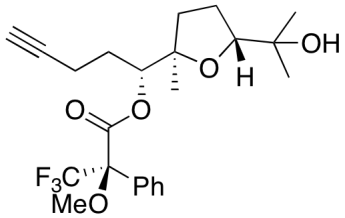


(*R*)-((*S*)-1-((2*R*,5*R*)-5-(2-Hydroxypropan-2-yl)-2-methyltetrahydrofuran-2-yl)pent-4-ynyl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (2.88): To a solution of diol **2.83** (10.0 mg, 0.044 mmol) in CH_2Cl_2 (0.40 mL) at ambient temperature was treated with (*R*)-(+)-methoxy trifluoromethyl phenylacetic acid (**2.84**) (31.0 mg, 0.133 mmol), DCC (45.4 mg, 0.220 mmol), and DMAP (5.3 mg, 0.044 mmol). After stirring for 1 h the reaction was at completion. The complete reaction mixture was purified using flash chromatography (10% to 30% ethyl acetate in hexanes) to yield the desired Mosher ester (14.0 mg, 72%): ^1H NMR ($CDCl_3$, 500 MHz) δ 7.56-7.58 (m, 2H), 7.42-7.44 (m, 3H), 5.21 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.71 (dd, *J* = 8.5, 6.0 Hz, 1H), 3.55 (d, *J* = 1.0 Hz, 3H), 2.16-2.29 (m, 2H), 2.04-2.10 (m, 1H), 2.00 (t, *J* = 2.5 Hz, 1H), 1.80-1.89 (m, 4H), 1.59-1.63 (m, 1H), 1.18 (s, 3H), 1.16 (s, 3H), 1.09 (s, 3H).

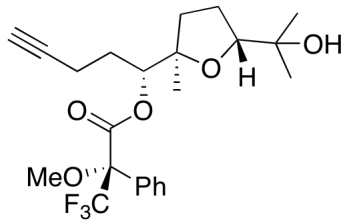


(*S*)-((*S*)-1-((2*R*,5*R*)-5-(2-Hydroxypropan-2-yl)-2-methyltetrahydrofuran-2-yl)pent-4-ynyl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (2.89): To a solution of (*S*)-(–)-

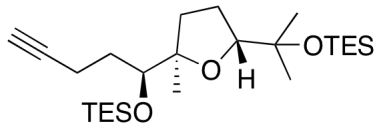
methoxy trifluoromethyl phenylacetic acid (**2.86**) (36.0 mg, 0.154 mmol) in CH_2Cl_2 (0.20 mL) was added oxalyl chloride (16.8 mg, 0.133 mmol) and one drop of DMF. The reaction stirred for one hour and then was added to a flask containing diol **2.83** (10.0 mg, 0.044 mmol), DMAP (cat.), triethylamine (44.5 mg, 0.440 mmol) in CH_2Cl_2 (0.20 mL). The reaction mixture stirred overnight and then was concentrated under vacuum. The residue was purified by flash chromatography to obtain the desired Mosher ester (12.3 mg, 63%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.56-7.58 (m, 2H), 7.42-7.44 (m, 3H), 5.25 (dd, *J* = 9.5, 3.0 Hz, 1H), 3.72 (dd, *J* = 9.5, 6.5 Hz, 1H), 3.54 (s, 3H), 2.19-2.24 (m, 1H), 2.09-2.16 (m, 1H), 2.01-2.05 (m, 1H), 1.99 (t, *J* = 2.0 Hz, 1H), 1.75-1.96 (m, 4H), 1.66 (ddd, *J* = 11.5, 7.0, 3.0 Hz, 1H), 1.20 (s, 3H), 1.20 (s, 3H), 1.10 (s, 3H).



(*R*)-((*R*)-1-((2*S*,5*R*)-5-(2-Hydroxypropan-2-yl)-2-methyltetrahydrofuran-2-yl)pent-4-ynyl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (2.91): A solution of the minor product **2.90** from the epoxidation/cyclization (8.5 mg, 0.038 mmol) in CH_2Cl_2 (0.20 mL) at ambient temperature was treated with (*R*)-(+)-methoxy trifluoromethyl phenylacetic acid (**2.84**) (26.4 mg, 0.113 mmol), DCC (39.2 mg, 0.190 mmol), and DMAP (4.6 mg, 0.038 mmol). After stirring for 1 h the reaction was at completion. The complete reaction mixture was purified using flash chromatography (10% to 30% ethyl acetate in hexanes) to yield the desired Mosher ester (12.8 mg, 76%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.56-7.58 (m, 2H), 7.42-7.44 (m, 3H), 5.24 (dd, *J* = 9.0, 2.5 Hz, 1H), 3.83 (dd, *J* = 8.0, 6.0 Hz, 1H), 3.55 (d, *J* = 1.0 Hz, 3H), 2.19-2.24 (m, 1H), 2.02-2.06 (m, 1H), 2.03 (t, *J* = 2.5 Hz, 1H), 2.01 (s, 1H) 1.76-1.97 (m, 5H), 1.61-1.66 (m, 1H), 1.24 (s, 3H), 1.20 (s, 3H), 1.14 (s, 3H).

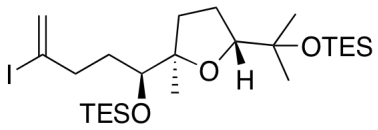


(*S*)-((*R*)-1-((2*S*,5*R*)-5-(2-Hydroxypropan-2-yl)-2-methyltetrahydrofuran-2-yl)pent-4-ynyl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (2.92): A solution of the minor product **2.60** from the epoxidation/cyclization (8.5 mg, 0.038 mmol) in CH_2Cl_2 (0.20 mL) at ambient temperature was treated with (*S*)-(–)-methoxy trifluoromethyl phenylacetic acid (**2.86**) (26.4 mg, 0.113 mmol), DCC (39.2 mg, 0.190 mmol), and DMAP (4.6 mg, 0.038 mmol). After stirring for 1 h the reaction was at completion. The complete reaction mixture was purified using flash chromatography (10% to 30% ethyl acetate in hexanes) to yield the desired Mosher ester (13.2 mg, 79%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.56-7.58 (m, 2H), 7.42-7.43 (m, 3H), 5.20 (dd, *J* = 9.0, 3.5 Hz, 1H), 3.81 (dd, *J* = 8.5, 6.0 Hz, 1H), 3.54 (d, *J* = 1.0 Hz, 3H), 2.30-2.36 (m, 1H), 2.08-2.22 (m, 2H), 2.05 (t, *J* = 2.5 Hz, 1H), 2.01 (s, 1H) 1.79-1.95 (m, 4H), 1.55-1.60 (m, 1H), 1.22 (s, 3H), 1.16 (s, 3H), 1.13 (s, 3H).



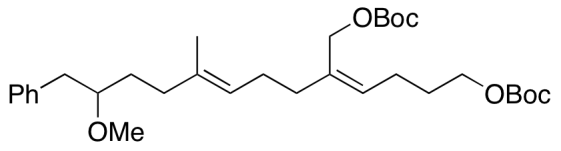
(1*S*)-1-((2*R*,5*R*)-5-(2-((Triethylsilyl)oxy)propan-2-yl)-2-methyloxolan-2-yl)-1-((triethylsilyl)oxy)pent-4-yne (2.58): To a solution of diol **2.83** (1.21 g, 5.35 mmol) in DMF (29.6 mL) at 0 °C was added imidazole (1.27 g, 18.7 mmol), TESCl (2.25 mL, 13.4 mmol), and DMAP (0.033 g, 0.268 mmol). The reaction was allowed to slowly warm to rt and continued stirring overnight. The mixture was cooled to 0 °C and quenched with H_2O (60 mL). The resulting solution was extracted with diethyl ether (3 x 60 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (2% ethyl acetate in hexanes) to yield the bis-silyl-protected alkyne (2.17 g, 89%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.66 (d, *J* = 8.8 Hz, 1H), 3.65 (dd, *J* = 8.8, 1.6 Hz, 1H),

2.34 (m, 1H), 2.25 (m, 1H), 1.75-1.99 (m, 4H), 1.94 (t, J = 2.8 Hz, 1H), 1.54 (m, 2H), 1.19 (s, 3H), 1.17 (s, 3H), 1.09 (s, 3H), 0.97 (t, J = 8.0 Hz, 9H), 0.96 (t, J = 8.0 Hz, 9H), 0.64 (q, J = 8.0 Hz, 6H), 0.56 (q, J = 8.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 87.1, 85.6, 84.4, 76.1, 74.0, 68.2, 34.3, 32.6, 27.9, 26.2, 25.5, 22.5, 15.6, 7.1, 7.1, 6.8, 5.4; IR (neat) 3313, 2956, 2911, 2876, 1460, 1238, 1101, 1040, 739 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{25}H_{50}O_3Si_2Na$ $[M+Na]^+$ 477.3196, found 477.3186; $[\alpha]_D$ = –4.10 (*c* 1.39, $CHCl_3$).

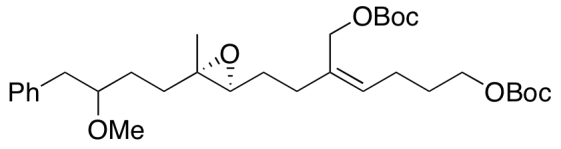


(1*S*)-1-((2*R*,5*R*)-5-(2-((Triethylsilyl)oxy)propan-2-yl)-2-methyloxolan-2-yl)-4-iodo-1-((triethylsilyl)oxy)pent-4-ene (2.51): To a solution of alkyne **2.58** (2.17 g, 4.76 mmol) and $[CpRu(MeCN)_3]PF_6$ (42 mg, 0.095 mmol) in CH_2Cl_2 (9.0 mL) at 0 °C was added triethylsilane (0.91 mL, 5.7 mmol). After stirring for 2 h the reaction mixture was concentrated and run through a small silica plug using hexanes as the eluent. The filtrate was concentrated and disolved in CH_2Cl_2 (9.0 mL). To the solution was added 2,6-lutidine (0.67 mL, 5.72 mmol) and I_2 (3.62 g, 14.3 mmol). After stirring for 1 h the reaction was quenched with triethylamine (3 mL) and a saturated solution of sodium thiosulfate (9 mL). After 20 min the reaction mixture was extracted with CH_2Cl_2 (3 x 15 mL), dried over $MgSO_4$, and concentrated. The mixture was purified by flash chromatography (1% to 3% ethyl acetate in hexanes) to obtain the desired vinyl iodide (2.29 g, 82%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.04 (d, J = 1.2 Hz, 1H), 5.69 (d, J = 1.2 Hz, 1H), 3.63 (dd, J = 9.2, 6.4 Hz, 1H), 3.54 (dd, J = 7.6, 4.4 Hz, 1H), 2.56 (m, 1H), 2.46 (m, 1H), 1.80-1.98 (m, 4H), 1.56 (m, 2H), 1.19 (s, 3H), 1.17 (s, 3H), 1.10 (s, 3H), 0.98 (t, J = 8.0 Hz, 9H), 0.96 (t, J = 8.0 Hz, 9H), 0.63 (q, J = 8.0 Hz, 6H), 0.58 (q, J = 8.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 125.0, 112.8, 87.2, 85.7, 76.5, 74.0, 42.6, 34.7, 33.7, 27.8, 26.3, 25.6, 22.4, 7.1, 7.1, 6.8, 5.5; IR (neat) 2956, 2911, 2876, 1460, 1238,

1100, 1040, 725 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{25}H_{51}O_3Si_2INa$ $[M+Na]^+$ 605.2319, found 605.2304; $[\alpha]_D$ = +1.78 (*c* 1.31, $CHCl_3$).

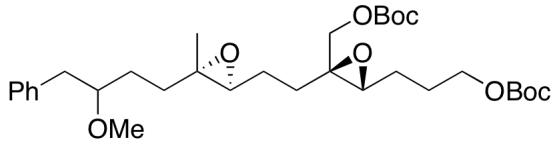


((5*E*,9*Z*)-13-(((*tert*-Butoxy)carbonyl)oxy)-9-((((*tert*-butoxy)carbonyl)oxy)methyl)-2-methoxy-5-methyltrideca-5,9-dien-1-yl]benzene (2.93): To a solution diol **2.67** (0.836 g, 2.41 mmol) in toluene (12.8 mL) at 0 °C was added 1-methylimidazole (.397 g, 4.83 mmol) and Boc_2O (2.11 g, 9.65 mmol). The reaction warmed to ambient temperature as it stirred overnight. The reaction was quenched with H_2O (25 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over $MgSO_4$ and then concentrated under vacuum. The mixture was purified using flash chromatography (5% to 12.5% ethyl acetate in hexanes) to obtain the bis-Boc protected diene (0.456 g, 35%): ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.18-7.32 (m, 5H), 5.38 (t, *J* = 7.5 Hz, 1H), 5.08 (m, 1H), 4.58 (s, 2H), 4.05 (t, *J* = 6.6 Hz, 2H), 3.34 (m, 1H), 3.31 (s, 3H), 2.85 (m, 1H), 2.71 (m, 1H), 1.99-2.23 (m, 6H), 2.09 (m, 3H), 1.66-1.76 (m, 4H), 1.51-1.59 (m, 2H), 1.49 (s, 18H).



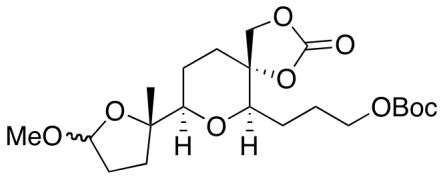
(2*S*,3*S*)-3-((3*Z*)-7-(((*tert*-Butoxy)carbonyl]oxy)-3-((((*tert*-butoxy)carbonyl]oxy)methyl)hept-3-en-1-yl)-2-(3-methoxy-4-phenylbutyl)-2-methyloxirane (2.94): To a solution of diene **2.93** (445 mg, 0.841 mmol) in acetonitrile/dimethoxymethane (11.9 mL, 1:2, v/v) at 0 °C was added Bu_4NHSO_4 (11.2 mg, 0.033 mmol), (L)-fructose derived Shi ketone (**2.82**) (63.0 mg, 0.244 mmol), and 0.500 M $Na_2B_4O_7$ in $4.00x10^{-4}$ M Na_2(EDTA) (7.91 mL). Oxone (601 mg, 0.977 mmol) in $4.00x10^{-4}$ M Na_2(EDTA) (4.45 mL) and K_2CO_3 (590 mg, 4.27 mmol) in H_2O (4.45

mL) were added simultaneously but separately via a syringe pump over 2 h. The reaction was stirred at 0 °C for an additional 1 h and then was diluted with H_2O (30 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The reaction mixture was purified using flash chromatography (0.5% triethylamine, 8% to 16% ethyl acetate in hexanes) to afford the desired monoepoxide (1:1 mixture of diastereomers) (293 mg, 64%): ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.19-7.32 (m, 5H), 5.43 (t, *J* = 7.2 Hz, 1H), 4.60 (s, 2H), 4.06 (t, *J* = 6.6 Hz, 2H), 3.35-3.39 (m, 1H), 3.31 (s, 3H), 2.82-2.88 (m, 1H), 2.66-2.72 (m, 2H), 2.17-2.26 (m, 4H), 1.41-1.78 (m, 8H), 1.49 (s, 18H), 1.20 (s, 3H).

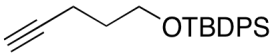


(3-((2*R*,3*S*)-3-((((*tert*-Butoxy)carbonyl)oxy)methyl)-3-(2-((2*S*,3*S*)-3-(3-methoxy-4-phenylbutyl)-3-methyloxiran-2-yl)ethyl)oxiran-2-yl)propyl) *tert*-butyl carbonate (2.52): To a solution of alkene **2.94** (285 mg, 0.506 mmol) in acetonitrile/dimethoxymethane (7.38 mL, 1:2, v/v) at 0 °C was added Bu_4NHSO_4 (6.8 mg, 0.020 mmol), (D)-fructose derived Shi ketone (**2.69**) (105 mg, 0.405 mmol), and 0.500 M $Na_2B_4O_7$ in $4.00x10^{-4}$ M Na_2(EDTA) (4.92 mL). Oxone (1.56 g, 2.53 mmol) in $4.00x10^{-4}$ M Na_2(EDTA) (4.28 mL) and K_2CO_3 (1.33 g, 9.61 mmol) in H_2O (4.28 mL) were added simultaneously but separately via a syringe pump over 2 h. The reaction was stirred at 0 °C for an additional 2 h and then was diluted with H_2O (25 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The reaction mixture was purified using flash chromatography (0.5% triethylamine, 8% to 20% ethyl acetate in hexanes) to afford the desired diepoxide (1:1 mixture of diastereomers) (118 mg, 40%): ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.18-

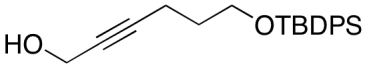
7.32 (m, 5H), 4.09-4.15 (m, 4H), 3.34-3.36 (m, 1H), 3.31 (s, 3H), 2.84-2.88 (m, 2H), 2.64-2.72 (m, 2H), 1.41-1.87 (m, 11H), 1.49 (s, 18H), 1.22-1.27 (m, 1H), 1.20 (s, 3H).



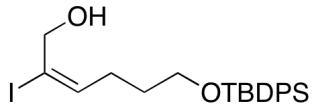
***tert*-Butyl (3-((5*R*,6*R*,8*R*)-8-((2*S*)-5-methoxy-2-methyloxolan-2-yl)-2-oxo-1,3,7-trioxaspiro[4.5]decan-6-yl)propyl) carbonate (2.95):** To a solution of diepoxide **2.52** (85.0 mg, 0.147 mmol) in dichloroethane/toluene (4.77 mL, 5:1, v/v) was added activated 4Å molecular sieves (170 mg), anhydrous sodium thiosulfate (170 mg), sodium acetate (170 mg), and *N*-methylquinolinium hexafluorophosphate (21.1 mg, 0.073 mmol) at room temperature in a borosilicate flask. The mixture was photoirradiated with gentle air bubbling for 5 h while stirring. The mixture was filtered through a small silica plug (100% ethyl acetate) to remove the insoluble inorganic material and the collected filtrate was concentrated under vacuum. The mixture was purified using flash chromatography (20% to 35% ethyl acetate in hexanes) to obtain the wanted lactol (1:1 mixture of diastereomers) (21.8 mg, 34%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.61-7.68 (m, 4H), 7.36-7.46 (m, 6H), 4.95 (m, 1/2 H), 4.92 (t, *J* = 2.7 Hz, 1/2 H), 4.51 (s, 1/2 H), 4.49 (s, 1/2 H), 4.07 (dd, *J* = 9.0, 3.3 Hz, 1H), 3.84-4.00 (m, 1H), 3.68 (t, *J* = 6.3 Hz, 2H), 3.41 (m, 1H), 3.32 (s, 1.5H), 3.30 (s, 1.5H), 1.57-2.16 (m, 10H), 1.26-1.48 (m, 2H), 1.24 (s, 1.5H), 1.09 (s, 1.5H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.1, 154.0, 135.4, 133.6, 133.6, 133.5, 129.5, 129.4, 127.5, 105.5, 105.4, 84.6, 84.4, 83.5, 82.4, 80.5, 80.4, 80.2, 80.0, 69.4, 63.1, 54.4, 54.0, 34.4, 34.3, 34.1, 32.8, 32.3, 31.9, 28.3, 26.7, 24.1, 24.1, 23.9, 23.5, 20.8, 19.1; IR (neat) 3070, 2933, 2858, 1809, 1460, 1335, 1209, 1066, 735 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{32}H_{44}O_7NaSi$ $[M+Na]^+$ 591.2754, found 591.2786; $[\alpha]_D$ = +4.45 (*c* 1.09, $CHCl_3$).



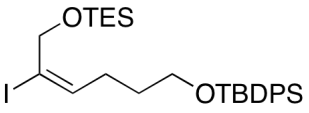
1-(*tert*-Butyldiphenylsiloxy)pent-4-yne (2.100): To a solution of pent-4-yn-1-ol (**2.99**) (2.50 g, 29.7 mmol) in CH_2Cl_2 (60 mL) at 0 °C was added imidazole (2.63 g, 38.6 mmol) followed by dropwise addition of TBDPSCl (8.21 mL, 32.1 mmol). After stirring for 1 h the reaction was quenched with H_2O (60 mL) and was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (2% to 10% ethyl acetate in hexanes) to yield the silyl ether (9.59 g, 100%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.67-7.69 (m, 4H), 7.36-7.44 (m, 6H), 3.76 (t, *J* = 6.0 Hz, 2H), 2.36 (td, *J* = 7.2, 2.7 Hz, 2H), 1.93 (t, *J* = 2.7 Hz, 1H), 1.79 (m, 2H), 1.06 (s, 9H). *These data are consistent with literature values.*[143]



6-(*tert*-Butyldiphenylsiloxy)hex-2-yn-1-ol (2.101): To a solution of alkyne **2.100** (9.58 g, 29.7 mmol) in THF (118 mL) at –78 °C was added a 1.6 M solution of *n*-butyllithium in hexanes (22.3 mL, 35.7 mmol) dropwise. After stirring for 1.5 h, paraformaldehyde (1.78 g, 59.4 mmol) was added and the reaction was warmed to rt. The reaction mixture was stirred overnight and then was quenched with a saturated solution of ammonium chloride (100 mL) and H_2O (100 mL). The mixture was extracted with diethyl ether (3 x 125 mL), dried over Na_2SO_4, and concentrated. The reaction was purified by flash chromatography (10% to 25% ethyl acetate in hexanes) to obtain the propargyl alcohol (9.89 g, 94%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.67-7.70 (m, 4H), 7.36-7.44 (m, 6H), 4.21 (dt, *J* = 6.0, 2.4 Hz, 2H), 3.75 (t, *J* = 6.0 Hz, 2H), 2.38 (tt, *J* = 7.2, 2.1 Hz, 2H), 1.77 (m, 2H), 1.39 (t, *J* = 6.0 Hz, 1H), 1.06 (s, 9H). *These data are consistent with literature values.*[144]

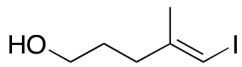


(*E*)-6-(*tert*-Butyldiphenylsiloxy)-2-iodohex-2-en-1-ol (2.102): To a solution of alkyne **2.101** (11.2 g, 31.9 mmol) and $Pd(PPh_3)_4$ (0.737 g, 0.638 mmol) in dry, degassed benzene (132 mL) at rt was added tributyltin hydride (8.45 mL, 31.9 mmol) dropwise. After 1 h the mixture was concentrated and run through a small silica plug using CH_2Cl_2. The filtrate was concentrated and dissolved in CH_2Cl_2 (300 mL). A solution of I_2 (8.90 g, 35.1 mmol) in CH_2Cl_2 (200 mL) was added via cannulation. After stirring for an additional 30 min, the reaction mixture was quenched with a saturated solution of sodium thiosulfate (300 mL) and was extracted with CH_2Cl_2 (3 x 200 mL). The combined organic layers were dried over Na_2SO_4, concentrated under vacuum, and purified by flash chromatography (5% to 15% ethyl acetate in hexanes) to yield the vinyl iodide (12.8 g, 83%): ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.68-7.73 (m, 4H), 7.40-7.50 (m, 6H), 6.34 (t, *J* = 7.8 Hz, 1H), 4.26 (d, *J* = 6.6 Hz, 2H), 3.71 (t, *J* = 6.0 Hz, 2H), 2.31 (q, *J* = 7.5 Hz, 2H), 2.20 (t, *J* = 6.6 Hz, 1H), 1.63 (m, 2H), 1.11 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.1, 135.7, 133.8, 129.9, 127.9, 103.1, 65.2, 62.7, 31.7, 27.5, 27.1, 19.3; IR (neat) 3391, 3070, 3048, 2931, 2858, 1470, 1427, 1389, 1109, 1045 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{22}H_{30}O_2SiI$ $[M+H]^+$ 481.1060, found 481.1051.



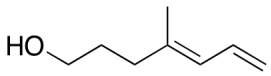
(*E*)-6-(*tert*-Butyldiphenylsiloxy)-1-(triethylsiloxy)-2-iodohex-2-ene (2.98): To a solution of alcohol **2.102** (10.9 g, 22.7 mmol) in CH_2Cl_2 (240 mL) at room temperature was added imidazole (2.56 g, 37.7 mmol). Once all solids were dissolved, TESCl (5.06 mL, 30.2 mmol) was added dropwise and the reaction was stirred for 1 h. The reaction was quenched with H_2O (200 mL), extracted with CH_2Cl_2 (3 x 150 mL), and dried over $MgSO_4$ and concentrated under vacuum. The mixture was purified using flash chromatography (1% to 5% ethyl acetate in hexanes) to generate the silyl protected alcohol (13.1

g, 97%): ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.68-7.71 (m, 4H), 7.39-7.49 (m, 6H), 6.32 (t, *J* = 7.8 Hz, 1H), 4.28 (s, 2H), 3.70 (t, *J* = 6.0 Hz, 2H), 2.31 (q, *J* = 7.5 Hz, 2H), 1.66 (m, 2H), 1.10 (s, 9H), 1.03 (m, 9H), 0.69 (q, *J* =7.5 Hz, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 142.4 135.7 134.0, 129.8, 127.9, 103.3, 65.0, 63.0, 32.1, 27.9, 27.1, 19.4, 7.1, 4.8; IR (neat) 3070, 3049, 2955, 2875, 1462, 1427, 1239, 1109; HRMS (EI): *m/z* calcd for $C_{26}H_{38}O_2Si_2I$ $[M\text{-}CH_2CH_3]^+$ 565.1455, found 565.1431.

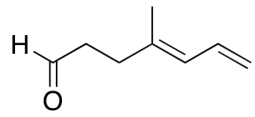


(*E*)-5-Iodo-4-methylpent-4-en-1-ol (2.103): To a solution of pent-4-yn-1-ol (**2.99**) (2.80 g, 33.3 mmol) in 1,2-dichloroethane (28 mL) at 0 °C was added a 2.0 M solution of trimethylaluminum in hexanes (5.7 mL, 11 mmol). The mixture was stirred for 20 min. In a separate flask containing zirconocene dichloride (3.89 g, 13.3 mmol) in 1,2-dichloroethane (106 mL) at –20 °C was added a 2.0 M solution of trimethylaluminum in hexanes (50 mL, 100 mmol) followed by a slow addition of H_2O (0.60 mL, 33 mmol). After stirring for 10 min the mixture containing the pent-4-yn-1-ol (**2.99**) was cannulated over and the mixture was warmed to room temperature and stirred for an additional 5 h. The reaction mixture was cooled to –30 °C and a solution of I_2 (12.7 g, 50.0 mmol) in THF (33.3 mL) was added dropwise. After stirring for 10 min the reaction mixture was warmed to rt and a saturated solution of K_2CO_3 (80 mL) was added slowly followed by a saturated solution of sodium tartrate (120 mL). The reaction mixture stirred for several hours and then was extracted with diethyl ether (3 x 125 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. Purification by flash chromatography (20% to 60% diethyl ether in hexanes) provided the desired vinyl iodide (7.08 g, 94%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.94 (q, *J* = 1.2 Hz, 1H), 3.65 (q, *J* = 5.1 Hz, 2H), 2.32 (td,

J = 7.5, 1.2 Hz, 2H), 1.86 (d, *J* = 1.2 Hz, 3H), 1.67-1.76 (m, 2H), 1.30 (t, *J* = 5.1 Hz, 1H). *These data are consistent with literature values.*[145]

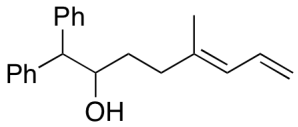


(*E*)-4-Methylhepta-4,6-dien-1-ol (2.104): To a flask containing $Pd(PPh_3)_4$ (1.80 g, 1.55 mmol) at 0 °C was added vinyl iodide **2.103** (7.02 g, 31.1 mmol) in dry, degassed toluene (225 mL). After stirring for 20 min, a 1.0 M solution of vinyl magnesium bromide in THF (93.3 mL, 93.3 mmol) was added dropwise. The solution was stirred for 1 h at 0 °C and then was warmed to rt where it stirred for an additional 30 min. The reaction was quenched with a saturated solution of ammonium chloride (125 mL) followed by the addition of H_2O (250 mL). The mixture was extracted with diethyl ether (3 x 150 mL), dried over $MgSO_4$, and concentrated. The mixture was run through a short silica plug (0% to 20% diethyl ether in hexanes). The filtrate was concentrated, and the residue was purified by flash chromatography (25% to 55% Et_2O in hexanes) to obtain diene (3.58 g, 91%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.58 (dt, *J* = 16.8, 10.5 Hz, 1H), 5.90 (d, *J* = 10.5 Hz, 1H), 5.11 (dd, *J* = 16.8, 1.8 Hz, 1H), 5.01 (dd, *J* = 10.2, 1.8 Hz, 1H), 3.66 (q, *J* = 6.3 Hz, 2H), 2.15 (t, *J* = 7.2 Hz, 2H), 1.79 (s, 3H), 1.68-1.78 (m, 2H), 1.33 (t, *J* = 4.8 Hz, 1H). *These data are consistent with literature values.*[146]



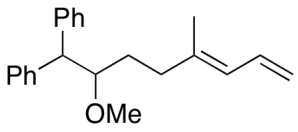
(*E*)-4-Methylhepta-4,6-dienal (2.105): To a solution of oxalyl chloride (3.98 mL, 45.7 mmol) in CH_2Cl_2 (144 mL) at –78 °C was added DMSO (6.49 mL, 91.4 mmol) in CH_2Cl_2 (10 mL) dropwise. The reaction was stirred for 10 min and then a solution of alcohol **2.104** (3.20 g, 25.4 mmol) in CH_2Cl_2 (18 mL) was added. After 30 min triethylamine (17.9 mL, 127 mmol) was added. The reaction continued to stir at –78 °C for 30

min and then was warmed to rt where it stirred for an addition 30 min. The reaction was quenched with H_2O (100 mL) and was then washed with 1.0 M HCl (2 x 75 mL), a saturated solution of sodium bicarbonate (75 mL), and a saturated solution of sodium chloride (75 mL). The reaction was dried over Na_2SO_4 and concentrated under vacuum at 0 °C. The crude aldehyde (3.15 g, 100%) carried to the next step without purification: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.79 (s, 1H), 6.56 (dt, *J* = 16.8, 10.5 Hz, 1H), 5.87 (d, *J* = 10.8 Hz, 1H), 5.13 (d, *J* = 16.8 Hz, 1H), 5.04 (d, *J* = 10.2 Hz, 1H), 2.57-2.63 (m, 2H), 2.40 (t, *J* = 7.2 Hz, 2H), 1.78 (s, 3H). *These data are consistent with literature values.*[147]

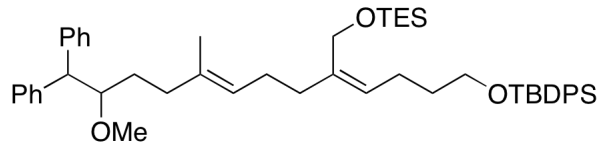


(*E*)-5-Methyl-1,1-diphenylocta-5,7-dien-2-ol (2.106): To a solution of diphenylmethane (45.4 g, 269 mmol) in THF (223 mL) at rt was added a solution of 1.6 M *n*-butyllithium in hexanes (169 mL, 269 mmol). The reaction mixture was gently refluxed for 1 h and then cooled to 0 °C. The crude aldehyde **2.105** (8.37 g, 67.4 mmol) in THF (20 mL) was added dropwise. After stirring for 1 h the reaction was quenched with a saturated solution of ammonium chloride (120 mL) and H_2O (1 L). The mixture was extracted with diethyl ether (3 x 1600 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated. The mixture was purified by flash chromatography (4% to 10% ethyl acetate in hexanes) to yield the desired alcohol (16.1 g, 82%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.18-7.50 (m, 10H), 6.61 (dt, *J* = 16.8, 10.5 Hz, 1H), 5.90 (d, *J* = 10.8 Hz, 1H), 5.14 (dd, *J* = 16.8, 1.8 Hz, 1H), 5.04 (d, *J* = 9.9 Hz, 1H), 4.37 (m, 1H), 3.94 (d, *J* =8.4 Hz, 1H), 2.17-2.40 (m, 2H), 1.73 (s, 3H), 1.15-1.64 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.4, 141.5, 139.2, 133.3, 128.9, 128.8, 128.7, 128.3 126.9, 126.6, 125.8, 114.9, 73.4, 58.9, 36.0, 33.0, 16.6; IR (neat) 3560, 3446, 3083,

3060, 3027, 2916, 1648, 1598, 1493, 1450, 1418, 1382 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{21}H_{24}O$ $[M]^+$ 292.1827, found 292.1825.

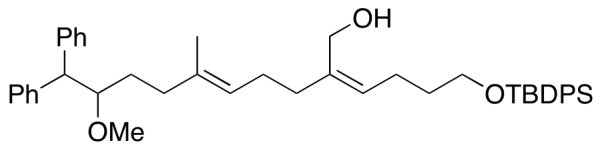


(*E*)-7-Methoxy-4-methyl-8,8-diphenylocta-1,3-diene (2.97): To a solution of alcohol **2.106** (5.25 g, 18.0 mmol) in DMF (108 mL) at 0 °C was added sodium hydride (1.80 g, 44.9 mmol) in portions over 10 min. After stirring for 30 min, iodomethane (3.35 mL, 53.9 mmol) was added and the reaction was warmed to rt where it was stirred for 16 h. The reaction was quenched with H_2O (100 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The mixture was purified by flash chromatography (1% to 5% ethyl acetate in hexanes) to obtain the desired diene (5.32 g, 96%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20-7.50 (m, 10H), 6.56 (dt, *J* = 16.8, 10.5 Hz, 1H), 5.93 (d, *J* = 10.8 Hz, 1H), 5.17 (dd, *J* = 16.8, 1.5 Hz, 1H), 5.08 (d, *J* = 10.2 Hz, 1H), 4.13 (d, *J* = 8.4 Hz, 1H), 3.99 (m, 1H), 3.24 (s, 3H), 2.51 (m, 2H), 1.62- 1.81 (m, 2H), 1.75 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.8, 142.4, 139.3, 133.4, 129.0, 128.6, 128.6, 128.4, 126.5, 126.4, 125.8, 83.2, 58.0, 56.3, 35.3, 30.4, 22.5, 16.7; IR (neat) 3084, 3060, 2928, 2826, 1649, 1598, 1493, 1451, 1105, 899 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{22}H_{26}O$ $[M]^+$ 306.1984, found 306.1970.



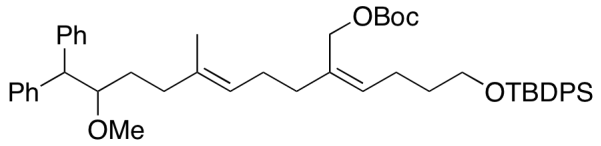
(2*Z*)-6-(*tert*-Butyldiphenylsiloxy)-1-(triethylsiloxy)-2-((*E*)-7-methoxy-4-methyl-8,8-diphenyloct-3-enyl)hex-2-ene (2.107): To a solution of 1.0 M BH_3·THF in THF (12.5 mL, 12.5 mmol) at –10 °C was added 2-methyl-2-butene (2.86 mL, 27.0 mmol). After stirring for 2 h, diene **2.97** (2.00 g, 6.53 mmol) in THF (6.44 mL) was added and the reaction was warmed to 0

°C. After 30 min the reaction was quenched with 5 drops of H_2O. To the reaction mixture was added 3.0 M NaOH (4.48 mL), a solution of vinyl iodide **2.98** (3.24 g, 5.44 mmol) in THF (4.20), and $Pd(PPh_3)_4$ (0.315 g, 0.272 mmol). The reaction was stirred at room temperature for 40 h and then was quenched with 3.0 M NaOH (5.6 mL) and 30% H_2O_2 (5.6 mL) at 0 °C. The reaction mixture continued to stir for 1 h and then was extracted with diethyl ether (3 x 40 mL). The organic layer was washed with a saturated solution of sodium bicarbonate (40 mL) and H_2O (40 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The mixture was purified using flash chromatography (1% to 5% ethyl acetate in hexanes) to yield the desired diene (3.86 g, 91%): ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.69-7.72 (m, 4H), 7.16-7.48 (m, 16H), 5.22 (t, *J* = 7.2 Hz, 1H), 5.14 (m, 1H), 4.19 (s, 2H), 4.04 (d, *J* = 8.1 Hz. 1H), 3.90 (m, 1H), 3.68 (t, *J* = 6.3 Hz, 2H), 3.17 (s, 3H), 1.99-2.21 (m, 8H), 1.49-1.66 (m, 4H), 1.56 (s, 3H), 1.09 (s, 9H), 0.98 (t, *J* = 7.8 Hz, 9H), 0.64 (q, *J* = 7.8 Hz, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 143.1, 142.6, 138.9, 135.8, 134.8, 134.3, 129.7, 129.1, 128.7, 128.6, 128.4, 127.8, 126.5, 126.4, 125.0, 83.4, 63.6, 60.2 58.1 56.3, 35.4, 34.8, 33.2, 30.8, 27.2, 27.1, 24.2, 19.4, 16.1, 7.1, 4.7; IR (neat): 3066, 3026, 2954, 2932, 2875, 1493, 1452, 1108, 823; HRMS (ESI): *m/z* calcd for $C_{50}H_{70}O_3Si_2Na$ $[M+Na]^+$ 797.4761, found 797.4812.



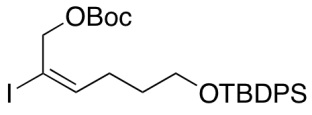
(2*Z*)-6-(*tert*-Butyldiphenylsiloxy)-2-((*E*)-7-methoxy-4-methyl-8,8-diphenyloct-3-enyl)hex-2-en-1-ol (2.108): To a solution of bis-silyl ether **2.107** (1.86 g, 2.40 mmol) in absolute ethanol (13.4 mL) at ambient temperature was added PPTS (0.181 g, 0.720 mmol). The reaction was stirred for 45 min and then was concentrated under vacuum. The reaction was purified using flash chromatography (5% to 15% ethyl acetate in hexanes) to obtain the wanted allylic alcohol

(1.44 g, 91%): ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.69-7.73 (m, 4H), 7.18-7.49 (m, 16H), 5.28 (t, *J* = 7.2 Hz, 1H), 5.14 (m, 1H), 4.14 (d, *J* = 6.0 Hz, 2H), 4.04 (d, *J* = 8.1 Hz, 1H), 3.91 (m, 1H), 3.70 (t, *J* = 6.3 Hz, 2H), 3.17 (s, 3H), 2.22 (q, *J* = 7.5 Hz, 2H), 2.06-2.19 (m, 6H), 1.49-1.66 (m, 4H), 1.53 (d, *J* = 0.6 Hz, 3H), 1.10 (s, 9H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 143.0, 142.5, 139.3, 135.8, 135.3, 134.1, 129.8, 129.1, 128.7, 128.6, 128.4, 128.2, 127.8, 126.5, 126.4, 124.6, 83.4, 63.1, 60.5, 58.1, 56.3, 35.6, 35.3, 32.7, 30.8, 27.1, 27.1, 23.9, 19.4, 16.1; IR (neat) 3441, 3068, 3027, 2931, 2858, 1493, 1451, 1109, 1006, 823; HRMS (EI): *m/z* calcd for $C_{44}H_{56}O_3Si$ $[M]^+$ 660.3999, found 660.4031.

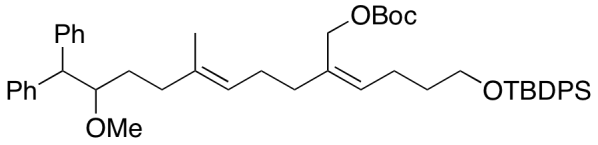


(2*Z*)-1-(*tert*-Butyloxycarbonyl)-6-(*tert*-butyldiphenylsiloxy)-2-((*E*)-7-methoxy-4-methyl-8,8-diphenyloct-3-enyl)hex-2-ene (2.109): To a solution of alcohol **2.108** (2.59 g, 3.92 mmol) in diethyl ether (24.8 mL) at –78 °C was added 1.6 M *n*-butyllithium in THF (2.69 mL, 4.32 mmol). After 30 min of stirring the solution was cannulated over to a separate flask containing BOC-ON (1.11 g, 4.51 mmol) in THF (9.93 mL) at –15 °C. The reaction was warmed to 0 °C and continued to stir for an additional 4 h. The reaction mixture was washed with 2.0 M NaOH solution (30 mL) and brine (30 mL). The combined aqueous layers were then extracted with diethyl ether (3 x 30mL) and then the combined organic layers were dried over Na_2SO_4. After concentrating under vacuum, the reaction was purified using flash chromatography (1% to 5% ethyl acetate in hexanes) to yield the desired carbonate (2.66 g, 89%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.69-7.72 (m, 4H), 7.18-7.47 (m, 16H), 5.40 (t, *J* = 7.5 Hz, 1H), 5.10 (br m, 1H), 4.62 (s, 2H), 4.03 (d, *J* = 8.1 Hz, 1H), 3.90 (m, 1H), 3.68 (t, *J* = 6.3 Hz, 2H), 3.17 (s, 3H), 2.22 (q, *J* = 7.2 Hz, 2H), 2.04-2.10 (m, 6H), 1.55-1.67 (m, 4H), 1.52 (s, 3H), 1.51 (s, 9H), 1.09 (s, 9H); ^{13}C NMR

($CDCl_3$, 75 MHz) δ 153.8, 142.9, 142.4, 135.6, 135.1, 134.1, 133.8, 130.8, 129.6, 129.0, 128.6, 128.5, 128.3, 127.7, 126.4, 126.3, 124.2, 83.3, 81.8, 64.3, 63.3, 58.0, 56.2, 35.2, 35.1, 32.8, 30.7, 27.9, 27.0, 26.8, 24.12, 19.3, 16.0; IR (neat) 3068, 3027, 2932, 2858, 1738, 1493, 1428, 1368, 1254, 1161, 1109 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{49}H_{64}O_5SiNa$ $[M+Na]^+$ 783.4421, found 783.4410.

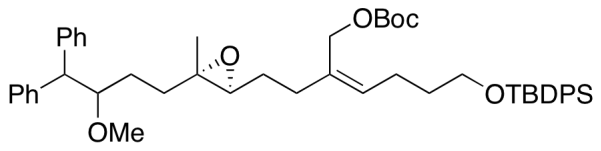


***tert*-Butyl (2*E*)-6-((*tert*-butyldiphenylsilyl)oxy)-2-iodohex-2-en-1-yl carbonate (2.110):** To a solution of alcohol **2.102** (380 mg, 0.791 mmol) in toluene (4.2 mL) at 0 °C was added 1-methylimidazole (65 mg, 0.79 mmol) and Boc_2O (345 mg, 1.58 mmol). The reaction was allowed to warm to rt as it was stirred overnight. The reaction was quenched with H_2O (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (5% to 10% ethyl acetate in hexanes) to provide the *O*-Boc protected vinyl iodide (454 mg, 99%): ^1H NMR ($CDCl_3$, 400 MHz) δ 7.65-7.67 (m, 4H), 7.38-7.47 (m, 6H), 6.44 (t, *J* = 7.6 Hz, 1H), 4.74 (s, 2H), 3.66 (t, *J* = 6.0 Hz, 2H), 2.30 (q, *J* = 7.6 Hz, 2H), 1.63 (p, *J* = 6.0 Hz, 2H), 1.51 (s, 9H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.9, 146.6, 135.5, 133.7, 129.6, 127.6, 93.0, 82.5, 68.0, 62.6, 31.6, 27.7, 27.7, 26.8, 19.1; IR (neat) 2932, 2858, 1743, 1471, 1369, 1254, 1107, 702 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{27}H_{37}O_4SiINa$ $[M+Na]^+$ 603.1404, found 603.1416.



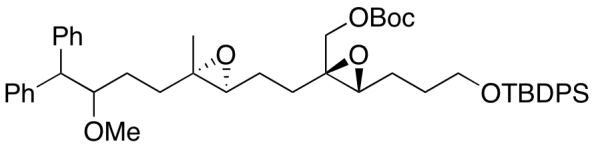
(2*Z*)-1-(*tert*-Butyloxycarbonyl)-6-(*tert*-butyldiphenylsiloxy)-2-((*E*)-7-methoxy-4-methyl-8,8-diphenyloct-3-enyl)hex-2-ene (2.109): To a solution of diene **2.97** (1.06 g, 3.45

mmol) in THF (5.2 mL) at rt was added 9-BBN dimer (0.441 g, 1.81 mmol). The reaction stirred for 2 h, then was quenched with 5 drops of H_2O. To the solution was added K_3PO_4 (0.730 g, 3.45 mmol) in H_2O (1.7 mL) and vinyl iodide **2.110** (1.00 g, 1.72 mmol) in THF (5.2 mL). $Pd(P^tBu_3)_2$ (0.132 g, 0.258 mmol) was added portion wise over 2 d and the reaction was allowed to stir for an additional day. The reaction was quenched with 3.0 M NaOH (2.8 mL) and 30% H_2O_2 (2.8 mL) at 0 °C. The reaction mixture continued to stir for 1 h and then was extracted with diethyl ether (3 x 40 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The mixture was purified by flash chromatography (1% to 7% ethyl acetate in hexanes) to yield the desired diene (0.963 g, 74%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.69-7.72 (m, 4H), 7.18-7.47 (m, 16H), 5.40 (t, *J* = 7.5 Hz, 1H), 5.10 (br m, 1H), 4.62 (s, 2H), 4.03 (d, *J* = 8.1 Hz, 1H), 3.90 (m, 1H), 3.68 (t, *J* = 6.3 Hz, 2H), 3.17 (s, 3H), 2.22 (q, *J* = 7.2 Hz, 2H), 2.04-2.10 (m, 6H), 1.55-1.67 (m, 4H), 1.52 (s, 3H), 1.51 (s, 9H), 1.09 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.8, 142.9, 142.4, 135.6, 135.1, 134.1, 133.8, 130.8, 129.6, 129.0, 128.6, 128.5, 128.3, 127.7, 126.4, 126.3, 124.2, 83.3, 81.8, 64.3, 63.3, 58.0, 56.2, 35.2, 35.1, 32.8, 30.7, 27.9, 27.0, 26.8, 24.12, 19.3, 16.0; IR (neat) 3068, 3027, 2932, 2858, 1738, 1493, 1428, 1368, 1254, 1161, 1109 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{49}H_{64}O_5SiNa$ $[M+Na]^+$ 783.4421, found 783.4410.



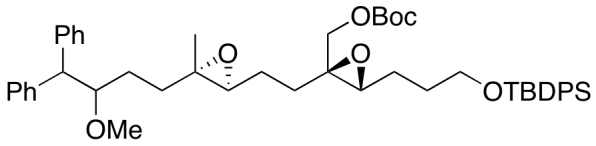
(2*Z*)-1-(*tert*-Butyloxycarbonyl)-6-(*tert*-butyldiphenylsiloxy)-2-((3*R*,4*S*)-epoxy-7-methoxy-4-methyl-8,8-diphenyloctanyl)hex-2-ene (2.111): To a solution of diene **2.109** (1.08 g, 1.42 mmol) in acetonitrile/dimethoxymethane (20.8 mL, 1:2, v/v) at 0 °C was added Bu_4NHSO_4 (0.024 g, 0.071 mmol), (L)-fructose derived Shi ketone (**2.82**) (0.147 g, 0.568 mmol), and 0.500 M $Na_2B_4O_7$ in 4.00x10^{-4} M Na_2(EDTA) (13.8 mL). Oxone (1.31 g, 2.13 mmol) in

$4.00x10^{-4}$ M $Na_2(EDTA)$ (7.75 mL) and K_2CO_3 (1.29 g, 9.31 mmol) in H_2O (7.75 mL) were added simultaneously but separately via a syringe pump over 2 h. The reaction was stirred at 0 °C overnight and then was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The reaction mixture was purified using flash chromatography (0.5% triethylamine, 5% to 10% ethyl acetate in hexanes) to afford the desired monoepoxide (1:1 mixture of diastereomers) (0.923 g, 84 %): ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.66-7.69 (m, 4H), 7.16-7.45 (m, 16H), 5.40 (t, *J* = 7.2 Hz, 1H), 4.60 (s, 2H), 3.90-4.00 (m, 2H), 3.66 (t, *J* = 6.3 Hz, 2H), 3.16 (s, 1.5H), 3.15 (s, 1.5H), 2.61 (t, *J* = 6.0 Hz, 1H), 2.20 (q, *J* = 7.2 Hz, 2H), 2.11-2.17 (m, 2H), 1.42-1.77 (m, 8H), 1.48 (s, 9H), 1.14 (s, 1.5H), 1.12 (s, 1.5H), 1.07 (s, 9H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 153.6, 142.5, 142.5, 142.2, 142.0, 135.5, 133.9, 132.9, 131.1, 129.5, 128.8, 128.7, 128.5, 128.5, 128.4, 128.2, 127.6, 126.4, 126.4, 126.2, 83.1, 83.1, 81.9, 64.0, 63.1, 63.1, 62.6, 60.7, 60.6, 57.9, 57.6, 56.1, 55.8, 33.8, 33.7, 32.6, 31.7, 27.8, 27.4, 27.1, 26.8, 24.0, 19.2, 16.6, 16.2; IR (neat): 3068, 3027, 2932, 2859, 1739, 1454, 1368, 1276, 1254, 1108, 702; HRMS (ESI): *m/z* calcd for $C_{49}H_{64}O_6SiNa$ $[M+Na]^+$ 799.4370, found 799.4410; $[\alpha]_D$ = –5.00 (*c* 1.06, $CHCl_3$).



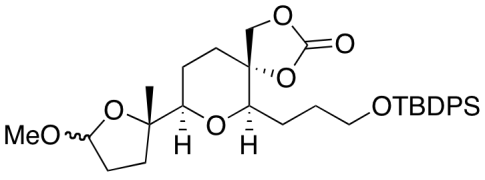
1-(*tert*-Butyloxycarbonyl)-6-(*tert*-butyldiphenylsiloxy)-(2*S*,3*S*)-epoxy-2-((3*R*,4*S*)-epoxy-7-methoxy-4-methyl-8,8-diphenyloctanyl)hexane (2.96): To a solution of alkene **2.111** (0.902 g, 1.16 mmol) and Bu_4NHSO_4 (0.024 g, 0.069 mmol) in acetonitrile (5.86 mL) and $4.00x10^{-4}$ M $Na_2(EDTA)$ (5.86 mL) at 0 °C was added a small portions of Oxone/$NaHCO_3$ until the pH was greater than 7. Then the (D)-fructose derived diacyl Shi ketone (**2.112**) (0.105 g, 0.348 mmol) in acetonitrile (2.93 mL) was added dropwise. Then a mixture of

Oxone (3.57 g, 5.80 mmol) and $NaHCO_3$ (1.51 g, 18.0 mmol) was added portion wise over the next 4 h. The reaction was stirred at 0 °C for an additional 6 h and then at room temperature overnight. The reaction was quenched with H_2O (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The mixture was purified using flash chromatography (0.5% triethylamine, 10% to 15% ethyl acetate in hexanes) to afford the desired diepoxide (1:1 mixture of diastereomers) (0.797 g, 87 %): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.68-7.72 (m, 4H), 7.18-7.48 (m, 16H), 4.16 (m, 2H), 3.92-4.03 (m, 2H), 3.74 (m, 2H), 3.18 (s, 1.5 H), 3.17 (s, 1.5H), 2.86 (m, 1H), 2.61 (t, *J* = 6.3 Hz, 1H), 1.43-1.83 (m, 12H), 1.51 (s, 9H), 1.17 (s, 1.5 H), 1.15 (s, 1.5 H), 1.09 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.2, 142.5, 142.5, 142.2, 142.0, 135.5, 133.7, 129.6, 128.7, 128.7, 128.5, 128.5, 128.4, 128.2, 127.6, 126.4, 126.4, 126.2, 83.1, 83.0, 82.4, 66.0, 63.2, 62,9, 62.9, 62.5, 60.8, 60.7, 60.3, 57.9, 57.6, 56.1, 55.8, 33.7, 33.6, 30.4, 29.5, 27.7, 27.4, 27.1, 26.8, 24.7, 23.9, 19.1 16.6, 16.2; IR (neat) 3068, 3026, 2932, 2859, 1742, 1454, 1369, 1277, 1104, 702 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{49}H_{64}O_7SiNa$ $[M+Na]^+$ 815.4319, found 815.4299; $[\alpha]_D$ = +0.50 (*c* 1.00, $CHCl_3$).



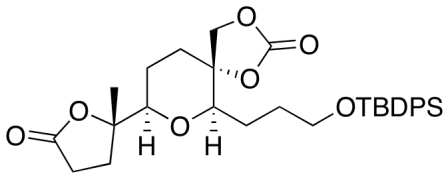
1-(*tert*-Butyloxycarbonyl)-6-(*tert*-butyldiphenylsiloxy)-(2*S*,3*S*)-epoxy-2-((3*R*,4*S*)-epoxy-7-methoxy-4-methyl-8,8-diphenyloctanyl)hexane (2.96): To a solution of diene **2.109** (2.50 g, 3.28 mmol) in acetonitrile/dimethoxymethane (49 mL, 1:2, v/v) at 0 °C was added Bu_4NHSO_4 (56 mg, 0.16 mmol), sorbose derived Shi ketone (**2.82**) (212 mg, 0.820 mmol), and 0.500 M $Na_2B_4O_7$ in 0.4 mM Na_2(EDTA) (31.7 mL). Oxone (3.02 g, 4.92 mmol) in 0.4.00 mM Na_2(EDTA) (18.1 mL) and K_2CO_3 (2.97 g, 21.5 mmol) in H_2O (18.1 mL) were added simultaneously but separately via a syringe pump over 1.5 h. The reaction was stirred for an

additional 1.5 h and then fructose derived diacyl Shi ketone **2.112** (496 mg, 1.64 mmol) in acetonitrile (3.0 mL) was added dropwise. Then a mixture of Oxone (10.1 g, 16.4 mmol) and $NaHCO_3$ (4.27 g, 50.8 mmol) was added portion wise over the next 2 h. The reaction stirred at 0 °C for 4 h and then at rt overnight. The mixture was diluted with H_2O (25 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried over Na_2SO_4, concentrated, and purified by flash chromatography (0.5% triethylamine, 5% to 15% ethyl acetate in hexanes) provide the desired diepoxide (1:1 mixture of diastereomers) (2.12 g, 82 %): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.68-7.72 (m, 4H), 7.18-7.48 (m, 16H), 4.16 (m, 2H), 3.92-4.03 (m, 2H), 3.74 (m, 2H), 3.18 (s, 1.5 H), 3.17 (s, 1.5H), 2.86 (m, 1H), 2.61 (t, *J* = 6.3 Hz, 1H), 1.43-1.83 (m, 12H), 1.51 (s, 9H), 1.17 (s, 1.5 H), 1.15 (s, 1.5 H), 1.09 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.2, 142.5, 142.5, 142.2, 142.0, 135.5, 133.7, 129.6, 128.7, 128.7, 128.5, 128.5, 128.4, 128.2, 127.6, 126.4, 126.4, 126.2, 83.1, 83.0, 82.4, 66.0, 63.2, 62,9, 62.9, 62.5, 60.8, 60.7, 60.3, 57.9, 57.6, 56.1, 55.8, 33.7, 33.6, 30.4, 29.5, 27.7, 27.4, 27.1, 26.8, 24.7, 23.9, 19.1 16.6, 16.2; IR (neat) 3068, 3026, 2932, 2859, 1742, 1454, 1369, 1277, 1104, 702 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{49}H_{64}O_7SiNa$ $[M+Na]^+$ 815.4319, found 815.4299; $[\alpha]_D$ = +0.50 (*c* 1.00, $CHCl_3$).



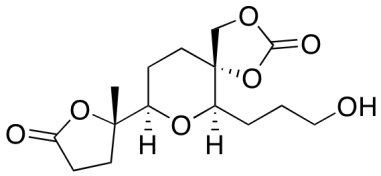
(5*R*,6*R*)-6-(3-((*tert*-butyldiphenylsilyl)oxy)propyl)-8-((2*S*)-5-methoxy-2-methyloxolan-2-yl)-1,3,7-trioxaspiro[4.5]decan-2-one (2.95): To a solution of diepoxide **2.96** (1.50 g, 1.89 mmol) in dichloroethane/toluene (64 mL, 5:1, v/v) was added activated 4Å molecular sieves (2.15 g), anhydrous sodium thiosulfate (2.15 g), sodium acetate (2.15 g), and *N*-methylquinolinium hexafluorophosphate (0.273 g, 0.945 mmol) at rt in a borosilicate flask. The mixture was photoirradiated (medium pressure mercury lamp) with gentle

air bubbling for 3 h while stirring. The mixture was filtered through a small silica plug using ethyl acetate to remove the insoluble inorganic material and the filtrate was concentrated. The residue was purified by flash chromatography (0.5% triethylamine, 10% to 30% ethyl acetate in hexanes) to obtain the tricycle (1:1 mixture of diastereomers) (0.473 g, 45%) and starting diepoxide (0.588 g, 75% based on recovered starting materials): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.61-7.68 (m, 4H), 7.36-7.46 (m, 6H), 4.95 (m, 1/2 H), 4.92 (t, *J* = 2.7 Hz, 1/2 H), 4.51 (s, 1/2 H), 4.49 (s, 1/2 H), 4.07 (dd, *J* = 9.0, 3.3 Hz, 1H), 3.84-4.00 (m, 1H), 3.68 (t, *J* = 6.3 Hz, 2H), 3.41 (m, 1H), 3.32 (s, 1.5H), 3.30 (s, 1.5H), 1.57-2.16 (m, 10H), 1.26-1.48 (m, 2H), 1.24 (s, 1.5H), 1.09 (s, 1.5H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.1, 154.0, 135.4, 133.6, 133.6, 133.5, 129.5, 129.4, 127.5, 105.5, 105.4, 84.6, 84.4, 83.5, 82.4, 80.5, 80.4, 80.2, 80.0, 69.4, 63.1, 54.4, 54.0, 34.4, 34.3, 34.1, 32.8, 32.3, 31.9, 28.3, 26.7, 24.1, 24.1, 23.9, 23.5, 20.8, 19.1; IR (neat) 3070, 2933, 2858, 1809, 1460, 1335, 1209, 1066, 735 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{32}H_{44}O_7NaSi$ $[M+Na]^+$ 591.2754, found 591.2786; $[\alpha]_D$ = +4.45 (*c* 1.09, $CHCl_3$).

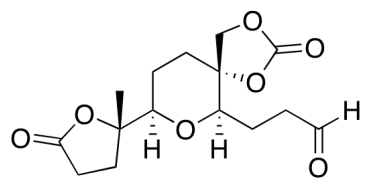


(5*R*,6*R*)-6-(3-((*tert*-Butyldiphenylsilyl)oxy]propyl)-8-((2S)-2-methyl-5-oxooxolan-2-yl)-1,3,7-trioxaspiro[4.5]decan-2-one (2.113): To a solution of lactol **2.95** (22.6 mg, 0.040 mmol) in CH_2Cl_2 (0.60 mL) was added scandium triflate (5.9 mg, 0.012 mmol) and *m*-CPBA (7.5 mg, 0.044 mmol) at 0 °C. After stirring for 3 h, triethylamine (20.1 mg, 0.198 mmol) was added and the reaction was stirred for an additional 30 min. The reaction mixture was concentrated under vacuum and purified using flash chromatography (20% to 60% ethyl acetate in hexanes) to afford the desired lactone (13.9 mg, 63%): ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.65-7.69 (m, 4H), 7.38-7.46 (m, 6H), 4.49 (d, *J* = 8.7 Hz, 1H), 4.09 (d, *J* = 9.0 Hz,

1H), 3.69 (t, *J* = 4.8 Hz, 2H), 3.46 (d, *J* = 9.6 Hz, 1H), 3.35 (dd, *J* = 11.7, 1.8 Hz, 1H), 2.51-2.60 (m, 2H), 1.99-2.22 (m, 3H), 1.72-1.92 (m, 4H), 1.35-1.65 (m, 3H), 1.31 (s, 3H), 1.06 (s, 9H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 176.3, 153.9, 135.5, 135.5, 133.7, 133.6, 129.5, 127.6, 85.9, 81.9, 80.1, 80.0, 69.3, 63.0, 34.0, 29.6, 29.1, 28.1, 26.8, 24.2, 23.5, 22.5, 19.2; IR (neat): 2932, 2858, 1807, 1773, 1427, 1208, 1142, 1087, 704; HRMS (ESI): *m/z* calcd for $C_{31}H_{40}O_7SiNa$ $[M+Na]^+$ 575.2441, found 575.2440; $[\alpha]_D$ = 9.99 (*c* 1.08, $CHCl_3$).

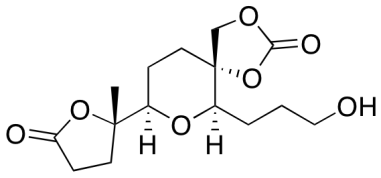


(5*R*,6*R*)-6-(3-Hydroxypropyl)-8-[(2*S*)-2-methyl-5-oxooxolan-2-yl]-1,3,7-trioxaspiro[4.5]decan-2-one (2.114): To a solution silyl ether **2.113** (190 mg, 0.344 mmol) in methanol (7.2 mL) was added NH_4F (145.1 mg, 3.92 mmol). The reaction was allowed to stir at room temperature for 48 h. The reaction mixture was concentrated under vacuum and purified using flash chromatography (50% to 100 % ethyl acetate in hexanes) was used to afford the desired alcohol (108 mg, 100%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.55 (d, *J* = 8.7 Hz, 1H), 4.11 (d, *J* = 8.7 Hz, 1H), 3.62-3.70 (m, 2H), 3.52 (td, *J* = 11.4, 1.8 Hz, 2H), 2.51-2.71 (m, 2H), 2.03-2.29 (m, 3H), 1.86-1.96 (m, 2H), 1.50-1.76 (m, 4H) 1.46 (t, *J* = 5.4 Hz, 1H), 1.37 (s, 3H), 1.26-1.31 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.1, 154.0, 86.5, 82.0, 80.3, 80.2, 69.4, 61.8, 34.0, 29.5, 29.0, 28.5, 24.2, 23.5, 22.8; IR (neat) 3415, 2951, 2873, 1801, 1765, 1383, 1263, 1211, 1065 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{15}H_{22}O_7$ $[M]^+$ 314.1366, found 314.1359; $[\alpha]_D$ = +10.5 (*c* 1.08, $CHCl_3$).



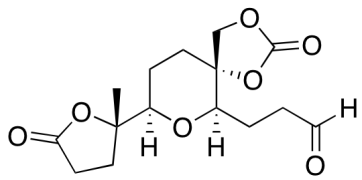
3-((5*R*,6*R*)-8-((2*S*)-2-Methyl-5-oxooxolan-2-yl)-2-oxo-1,3,7-trioxaspiro[4.5]decan-6-yl)propanal (2.50): To a solution of

alcohol **2.114** (108 mg, 0.344 mmol) in CH_2Cl_2 (0.30 mL) at 0 °C was added DMSO (0.41 mL), triethylamine (0.14 mL, 1.03 mmol), and $Py{\cdot}SO_3$ (82.0 mg, 0.515 mmol). The reaction was allowed to warm to room temperature slowly while it stirred overnight. The reaction was quenched with H_2O (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The reaction was dried over Na_2SO_4 and concentrated under vacuum. The reaction mixture was purified using flash chromatography (60% to 90% ethyl acetate in hexanes) to obtain the desired aldehyde (84.2 mg, 78%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.75 (s, 1H), 4.55 (d, *J* = 9.0 Hz, 1H), 4.13 (d, *J* = 9.0 Hz, 1H), 3.48 (td, *J* = 11.7, 2.1 Hz, 2H), 2.53-2.62 (m, 4H), 2.03-2.24 (m, 3H), 1.72-1.95 (m, 4H), 1.27-1.37 (m, 1H), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.8, 176.4, 153.7, 86.0, 82.3, 80.0, 79.6, 69.2, 39.4, 34.0, 29.2, 29.1, 23.5, 22.8, 20.2; IR (neat) 2934, 2851, 1805, 1768, 1721, 1457, 1383, 1264, 1165, 1066 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{20}O_7Na$ $[M+Na]^+$ 335.1107, found 335.1111; $[\alpha]_D$ = +18.1 (*c* 1.07, $CHCl_3$).

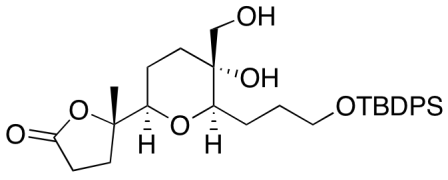


(5*R*,6*R*)-6-(3-Hydroxypropyl)-8-[(2*S*)-2-methyl-5-oxooxolan-2-yl]-1,3,7-trioxaspiro[4.5]decan-2-one (2.114): To a solution of lactol ether **2.95** (475 mg, 0.835 mmol) in CH_2Cl_2 (15 mL) was added $Sc(OTf)_3$ (164 mg, 0.334 mmol) and *m*-CPBA (159 mg, 0.919 mmol) at 0 °C. After stirring for 4 h the reaction was warmed to rt and stirred overnight. The reaction mixture was concentrated and purified by flash chromatography (20% to 100% ethyl acetate in hexanes) to afford the desired lactone (179 mg, 68%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.55 (d, *J* = 8.7 Hz, 1H), 4.11 (d, *J* = 8.7 Hz, 1H), 3.62-3.70 (m, 2H), 3.52 (td, *J* = 11.4, 1.8 Hz, 2H), 2.51-2.71 (m, 2H), 2.03-2.29 (m, 3H), 1.86-1.96 (m, 2H), 1.50-1.76 (m, 4H) 1.46 (t, *J* = 5.4 Hz, 1H), 1.37 (s, 3H), 1.26-1.31 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.1, 154.0, 86.5, 82.0, 80.3, 80.2, 69.4,

61.8, 34.0, 29.5, 29.0, 28.5, 24.2, 23.5, 22.8; IR (neat) 3415, 2951, 2873, 1801, 1765, 1383, 1263, 1211, 1065 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{15}H_{22}O_7$ $[M]^+$ 314.1366, found 314.1359; $[\alpha]_D$ = +10.5 (*c* 1.08, $CHCl_3$).

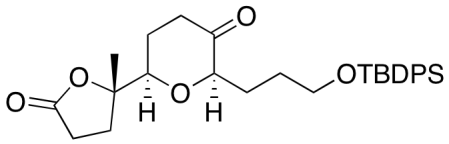


3-((5*R*,6*R*)-8-((2*S*)-2-Methyl-5-oxooxolan-2-yl)-2-oxo-1,3,7-trioxaspiro[4.5]decan-6-yl)propanal (2.50): To a solution of alcohol **2.114** (94 mg, 0.30 mmol) in DMSO (0.30 mL) at rt was added IBX (92 mg, 0.33 mmol). The reaction was stirred overnight, then was quenched with H_2O (1.0 mL) and extracted with ethyl acetate (3 x 3 mL). The reaction was dried over Na_2SO_4, concentrated, and purified by flash chromatography (50% to 100% ethyl acetate in hexanes) to obtain the desired aldehyde (87 mg, 93%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.75 (s, 1H), 4.55 (d, *J* = 9.0 Hz, 1H), 4.13 (d, *J* = 9.0 Hz, 1H), 3.48 (td, *J* = 11.7, 2.1 Hz, 2H), 2.53-2.62 (m, 4H), 2.03-2.24 (m, 3H), 1.72-1.95 (m, 4H), 1.27-1.37 (m, 1H), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.8, 176.4, 153.7, 86.0, 82.3, 80.0, 79.6, 69.2, 39.4, 34.0, 29.2, 29.1, 23.5, 22.8, 20.2; IR (neat) 2934, 2851, 1805, 1768, 1721, 1457, 1383, 1264, 1165, 1066 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{20}O_7Na$ $[M+Na]^+$ 335.1107, found 335.1111; $[\alpha]_D$ = +18.1 (*c* 1.07, $CHCl_3$).

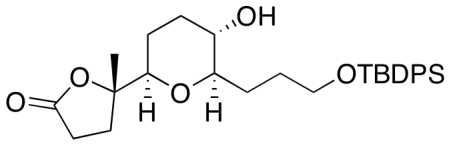


(*S*)-5-((2*R*,5*R*,6*R*)-6-(3-(*tert*-Butyldiphenylsilyloxy)propyl)-5-hydroxy-5-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)-5-methyldihydrofuran-2(3*H*)-one (2.115): To a solution of carbonate **2.113** (48.5 mg, 0.087 mmol) in methanol (2.00 mL) at ambient temperature was added K_2CO_3 (23.5 mg, 0.170 mmol). The reaction was stirred overnight and then quenched with H_2O (5 mL). The mixture was

extracted with ethyl acetate (3 x 5 mL), dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography (50% to 100% ethyl acetate in hexanes) to obtain the wanted diol (35.1 mg, 77%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.65-7.68 (m, 4H), 7.37-7.43 (m, 6H), 3.76 (d, *J* = 11.0 Hz, 1H), 3.63-3.70 (m, 3H), 3.39 (dd, *J* = 11.0, 2.0 Hz, 1H), 3.22 (dd, *J* = 10.5, 1.5 Hz, 1H), 2.60 (ddd, *J* = 18.0, 10.5, 8.0 Hz, 1H), 2.49 (ddd, *J* = 18.0, 10.5, 5.0 Hz, 1H), 2.24-2.30 (m, 1H), 1.40-1.91 (m, 9H), 1.33 (s, 3H), 1.05 (s, 9H).

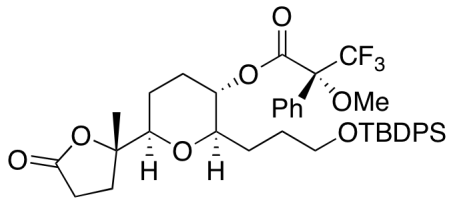


(2*R*,6*R*)-2-(3-(*tert*-Butyldiphenylsilyloxy)propyl)-6-((*S*)-2-methyl-5-oxotetrahydrofuran-2-yl)dihydro-2*H*-pyran-3(4*H*)-one (2.116): To a solution of diol **2.115** (35.0 mg, 0.066 mmol) in benzene (10.0 mL) at 0 °C was added $Pb(OAc)_4$ (39.0 mg, 0.088 mmol). After stirring for 5 min the reaction was quenched with a saturated solution of sodium bicarbonate (10.0 mL), extracted with diethyl ether (3 x 10 mL), dried over $MgSO_4$, and concentrated under vacuum. The mixture was purified by flash chromatography (10% ethyl acetate in hexanes) to yield the wanted ketone (22.0 mg, 68%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.65-7.68 (m, 4H), 7.37-7.45 (m, 6H), 3.80 (dd, *J* = 7.2, 4.0 Hz, 1H), 3.71 (dd, *J* = 11.2, 3.6 Hz, 1H), 3.69 (td, *J* = 6.4, 1.6 Hz, 2H), 2.32-2.67 (m, 5H), 1.85-2.12 (m, 4H), 1.59-1.69 (m, 3H), 1.39 (s, 3H), 1.05 (s, 9H).

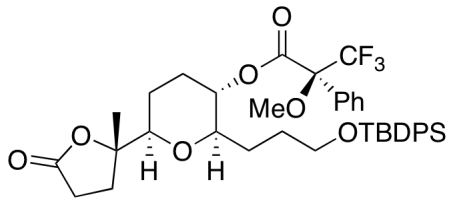


(*S*)-5-((2*R*,5*S*,6*R*)-6-(3-(*tert*-Butyldiphenylsilyloxy)propyl)-5-hydroxytetrahydro-2*H*-pyran-2-yl)-5-methyldihydrofuran-2(3*H*)-one (2.117): To a solution of ketone **2.116** (20.6 mg, 0.042 mmol) in methanol (2.00 mL) at ambient temperature was added $NaBH_4$ (1.6 mg, 0.042 mmol). After stirring for one h the reaction was quenched with a saturated solution of

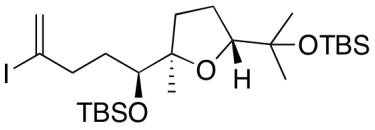
ammonium chloride (5.0 mL), extracted with CH_2Cl_2 (3 x 5 mL), dried over Na_2SO_4, and then concentrated under vacuum. The residue was purified by flash chromatography (10% to 35% ethyl acetate in hexanes) to obtain the wanted alcohol (14.7 mg, 71%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.66-7.69 (m, 4H), 7.37-7.44 (m, 6H), 3.70 (t, *J* = 6.0 Hz, 2H), 3.31 (dd, *J* = 11.0, 2.0 Hz, 1H), 3.24-3.27 (m, 1H), 3.04 (td, *J* = 9.0, 2.5 Hz, 1H), 2.60 (ddd, *J* = 18.0, 10.5, 8.5 Hz, 1H), 2.47 (ddd, *J* = 17.5, 10.0, 4.5 Hz, 1H), 2.29 (ddd, *J* = 15.0, 10.5, 5.0 Hz, 1H), 2.13-2.16 (m, 1H), 1.97 (ddd, *J* = 13.0, 6.0, 3.0 Hz, 1H), 1.72-1.83 (m, 3H), 1.57-1.61 (m, 1H), 1.40-1.50 (m, 4H), 1.32 (s, 3H), 1.06 (s, 9H).



(*R*)-((2*R*,3*S*,6*R*)-2-(3-(*tert*-Butyldiphenylsilyloxy)propyl)-6-((*S*)-2-methyl-5-oxotetrahydrofuran-2-yl)tetrahydro-2*H*-pyran-3-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (2.118): A solution of alcohol **2.117** (7.0 mg, 0.014 mmol) in CH_2Cl_2 (0.30 mL) at ambient temperature was treated with (*R*)-(+)-methoxy trifluormethyl phenylacetic acid (**2.84**) (9.8 mg, 0.042 mmol), DCC (14.4 mg, 0.070 mmol), and DMAP (1.7 mg, 0.014 mmol). After stirring for 1 h the reaction was at completion. The complete reaction mixture was purified using flash chromatography (10% to 30% ethyl acetate in hexanes) to yield the desired Mosher ester (7.8 mg, 78%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.63-7.66 (m, 4H), 7.48-7.50 (m, 2H), 7.37-7.44 (m, 6H), 7.31-7.33 (m, 3H), 4.68 (td, *J* = 10.0, 4.5 Hz, 1H), 3.49 (s, 3H), 3.51-3.55 (m, 2H), 3.36 (dd, *J* = 11.5, 2.0 Hz, 1H), 3.32 (td, *J* = 9.0, 2.5 Hz, 1H), 2.58 (ddd, *J* = 18.0, 10.5, 8.0 Hz, 1H), 2.48 (ddd, *J* = 18.0, 10.5, 5.0 Hz, 1H), 2.35-2.39 (m, 1H), 2.29 (ddd, *J* = 15.5, 10.5, 5.0 Hz, 1H), 1.79-1.85 (m, 2H), 1.42-1.73 (m, 6H), 1.33 (s, 3H), 1.03 (s, 9H).

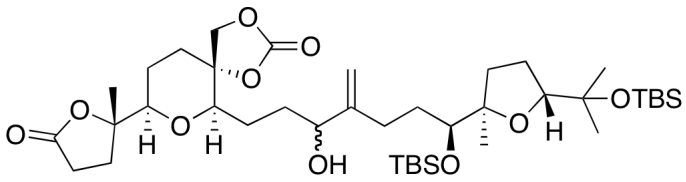


(*S*)-((2*R*,3*S*,6*R*)-2-(3-(*tert*-Butyldiphenylsilyloxy)propyl)-6-((*S*)-2-methyl-5-oxotetrahydrofuran-2-yl)tetrahydro-2*H*-pyran-3-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (2.119): A solution of alcohol **2.117** (7.0 mg, 0.014 mmol) in CH_2Cl_2 (0.30 mL) at ambient temperature was treated with (*S*)-(–)-methoxy trifluoromethyl phenylacetic acid (**2.86**) (9.8 mg, 0.042 mmol), DCC (14.4 mg, 0.070 mmol), and DMAP (1.7 mg, 0.014 mmol). After stirring for 1 h the reaction was at completion. The complete reaction mixture was purified using flash chromatography (10% to 30% ethyl acetate in hexanes) to yield the desired Mosher ester (8.2 mg, 82%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.63-7.65 (m, 4H), 7.48-7.49 (m, 2H), 7.34-7.44 (m, 9H), 4.65 (td, *J* = 10.5, 4.5 Hz, 1H), 3.62 (t, *J* = 6.0 Hz, 2H), 3.49 (d, *J* = 0.5 Hz, 3H), 3.30-3.33 (m, 2H), 2.58 (ddd, *J* = 18.0, 10.0, 8.0 Hz, 1H), 2.48 (ddd, *J* = 18.0, 10.5, 5.0 Hz, 1H), 2.26-2.31 (m, 2H), 1.69-1.84 (m, 4H), 1.40-1.56 (m, 4H), 1.32 (s, 3H), 1.04 (s, 9H).



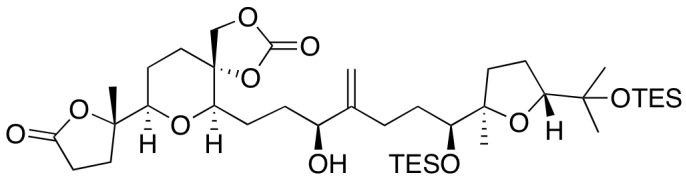
(1*S*)-1-((2*R*,5*R*)-5-(2-((*tert*-Butyldimethylsilyl)oxy)propan-2-yl)-2-methyloxolan-2-yl)-4-iodo-1-((tert-butyldimethylsilyl)oxy)pent-4-ene (2.120): To a solution of diol **2.83** (700 mg, 1.54 mmol) and $[CpRu(MeCN)_3]PF_6$ (33.4 mg, 0.077 mmol) in CH_2Cl_2 (3.00 mL) at 0 °C was added triethylsilane (215 mg, 1.85 mmol). After stirring for 2 h the reaction mixture was concentrated under vacuum and run through a small silica plug (hexanes). The filtrate was concentrated under vacuum and taken in CH_2Cl_2 (3.00 mL). To the solution was added 2,6-lutidine (198 mg, 1.85 mmol) and I_2 (937 mg, 3.69 mmol). After stirring for 1 h the reaction was quenched with triethylamine (1 mL) and a saturated solution of sodium thiosulfate (3 mL). After 20 min the

reaction mixture was extracted with CH_2Cl_2 (3 x 5 mL) and dried over $MgSO_4$. The mixture was purified using flash chromatography (1% to 3% ethyl acetate in hexanes) to obtain the desired vinyl iodide (676 mg, 75%): ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.03 (d, *J* = 1.5 Hz, 1H), 5.69 (d, *J* = 1.2 Hz, 1H), 3.64 (dd, *J* = 8.7, 6.3 Hz, 1H), 3.53 (dd, *J* = 6.3, 5.1 Hz, 1H), 2.49-2.56 (m, 2H), 1.79-1.97 (m, 4H), 1.55-1.63 (m, 2H), 1.19 (s, 6H), 1.12 (2, 3H), 0.91 (s, 9H), 0.87 (9H, s), 0.11 (s, 3H), 0.10 (s, 6H), 0.09 (s, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 124.9, 112.9, 87.0, 85.8, 76.3, 74.3, 42.6, 35.5, 33.9, 28.2, 26.4, 26.0, 25.9, 24.9, 22.3, 18.2, -2.0, -2.0, -3.7, -4.2; IR (neat): 2955, 2930, 2857, 1463, 1253, 1097, 1040, 834; HRMS (EI): *m/z* calc'd for $C_{24}H_{48}O_3Si_2I$ [M-CH_3]$^+$ 567.21868, found 567.22137; $[\alpha]_D$ = +7.70 (*c* 1.20, $CHCl_3$).



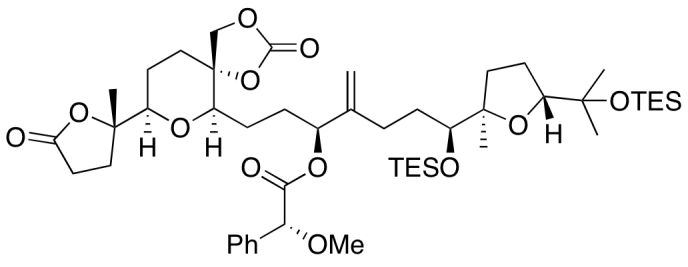
(5*R*,6*R*,8*R*)-6-((*S*)-7-(*tert*-Butyldimethylsilyloxy)-7-((2*R*,5*R*)-5-(2-(*tert*-butyldimethylsilyloxy)propan-2-yl)-2-methyltetrahydrofuran-2-yl)-3-hydroxy-4-methyleneheptyl)-8-((*S*)-2-methyl-5-oxotetrahydrofuran-2-yl)-1,3,7-trioxaspiro[4.5]decan-2-one (2.121): To a solution of aldehyde **2.50** (38.0 mg, 0.122 mmol) and vinyl iodide **2.120** (142 mg, 0.243 mmol) in DMF (0.20 mL) was added $CrCl_3$ (9.7 mg, 0.061 mmol), $NiCl_2$ (7.9 mg, 0.061 mmol), Mn^0 (33.5 mg, 0.610 mmol) and TMSCl (37.0 μL, 0.293 mmol) at ambient temperature. The reaction was allowed to stir overnight and was then quenched with H_2O (0.20 mL). Over the next 4 h 0.5 M HCl (2.0 mL) and ethyl acetate (2.0 mL) were added in portions. After concentrating under vacuum, the reaction mixture was extracted with ethyl acetate (3 x 5 mL), dried over Na_2SO_4, and filtered. The mixture was purified using flash chromatography (10% to 70% ethyl acetate in hexanes) to obtain the desired coupling product (1:1 mixture of diastereomers) (31.4 mg, 34%):

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.03 (s, 1H), 4.87 (s, 1H), 4.54 (d, *J* = 7.2 Hz, 0.5H), 4.51 (d, *J* = 7.2 Hz, 0.5H), 4.06-4.12 (m, 2H), 3.61-3.67 (m, 1H), 3.42-3.55 (m, 3H), 2.56-2.64 (m, 2H), 1.38-2.26 (m, 19H), 1.35 (s, 1.5H), 1.35 (s, 1.5H), 1.17 (s, 6H), 1.10 (s, 3H), 0.90 (s, 9H), 0.86 (s, 9H), 0.08 (s, 12H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 176.6, 176.4, 153.9, 153.8, 151.9, 151.8, 109.6, 109.4, 87.0, 86.1, 86.0, 86.0, 85.9, 82.1, 80.9, 80.8, 80.1, 80.1, 74.8, 74.3, 74.1, 69.4, 69.3, 35.2, 35.0, 34.3, 32.4, 32.3, 31.5, 31.4, 29.9, 29.8, 29.7, 29.3, 29.2, 28.9, 28.7, 28.3, 26.4, 26.4, 26.0, 26.0, 25.9, 24.8, 24.3, 23.9, 23.6, 22.5, 22.5, 22.4, 22.3, 18.1, -2.05, -3.6, -3.7, -4.1, -4.2; IR (neat): 2954, 2929, 2856, 1807, 1768, 1461, 1381, 1252, 1170, 1067; HRMS (ESI): *m/z* calcd for $C_{40}H_{72}O_{10}NaSi_2$ $[M+Na]^+$ 791.4562, found 791.4582; $[\alpha]_D$ = +6.91 (*c* 1.04, $CHCl_3$).



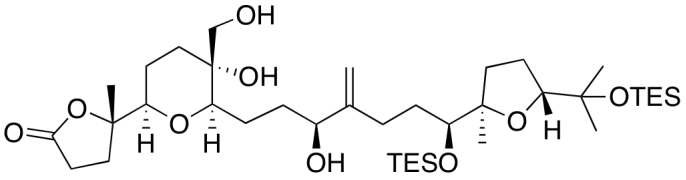
(5*R*,6*R*,8*R*)-6-((3*S*,7*S*)-3-Hydroxy-7-((2*R*,5*R*)-2-methyl-5-(2-(triethylsilyloxy)propan-2-yl)tetrahydrofuran-2-yl)-4-methylene-7-(triethylsilyloxy)heptyl)-8-((*S*)-2-methyl-5-oxotetrahydrofuran-2-yl)-1,3,7-trioxaspiro[4.5]decan-2-one (2.123): A vial containing sulfonamide **2.122** (106 mg, 0.240 mmol) and Proton Sponge (51 mg, 0.24 mmol) was transferred into an argon-filled glove box. $CrCl_2$ (29.5 mg, 0.240 mmol) was added to the vial under the inert atmosphere and sealed tightly before being removed from the glove box. The vial was placed under an N_2 atmosphere and freshly distilled and deoxygenated MeCN (0.30 mL) was added. The mixture stirred for 1 h to produce a deep green solution and then the vial was placed into an argon-filled glove bag. In a separate vial, aldehyde **2.50** (50 mg, 0.16 mmol), vinyl iodide **2.51** (140 mg, 0.240 mmol), anhydrous LiCl (14 mg, 0.32 mmol), freshly activated Mn (18 mg, 0.32 mmol), $NiCl_2$•DMP (16 mg, 0.048 mmol), and recrystallized $ZrCp_2Cl_2$ (56 mg,

0.19 mmol) were combined. After purging with argon the vial was transferred into the glove bag. A syringe was used to transfer the solution from the chromium-containing vial to the aldehyde-containing vial. The reaction was placed under an N_2 atmosphere and stirred for 2 h. Ethyl acetate (2 mL) and Florisil were added to the vial and the mixture was stirred vigorously for 30 minutes. The reaction mixture was filtered and concentrated under vacuum. The residue waspurified by flash chromatography (10% to 60% ethyl acetate in hexanes) to obtain the coupling product (103 mg, 84%, dr 8:1): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.03 (s, 1H), 4.87 (s, 1H), 4.52 (d, *J* = 8.8 Hz, 1H), 4.10 (m, 2H), 3.63 (dd, *J* = 8.8, 6.4 Hz, 1H), 3.53 (m, 2H), 3.46 (d, *J* = 10.0 Hz, 1H), 2.59 (m, 2H), 2.04-2.27 (m, 5H), 1.85-1.99 (m, 5H), 1.68-1.83 (m, 5H), 1.53-1.57 (m, 2H), 1.40-1.50 (m, 2H), 1.35 (s, 3H), 1.18 (s, 3H), 1.16 (s, 3H), 1.08 (s, 3H), 0.96 (t, *J* = 8.0 Hz, 9H), 0.94 (t, *J* = 8.0 Hz, 9H), 0.62 (q, *J* = 8.0 Hz, 6H), 0.57 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.6, 153.9, 151.8, 109.4, 87.1, 86.0, 85.8, 82.1, 80.9, 80.1, 77.7, 74.0, 74.0, 69.3, 34.2, 32.1, 31.4, 29.7, 29.2, 29.0, 27.8, 26.3, 25.5, 23.8, 23.5, 22.6, 22.5, 7.1, 7.1, 6.7, 5.5; IR (neat) 2955, 2875, 1807, 1773, 1459, 1239, 1173, 1067, 738 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{40}H_{72}O_{10}Si_2Na$ $[M+Na]^+$ 791.4562, found 791.4531; $[\alpha]_D$ = +3.60 (*c* 0.89, $CHCl_3$).



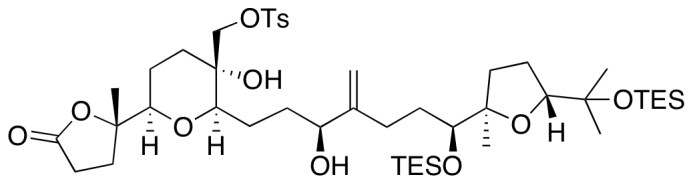
(*R*)-((3*S*,7*S*)-7-((2*R*,5*R*)-2-Methyl-5-(2-(triethylsilyloxy)propan-2-yl)tetrahydrofuran-2-yl)-1-((5*R*,6*R*,8*R*)-8-((*S*)-2-methyl-5-oxotetrahydrofuran-2-yl)-2-oxo-1,3,7-trioxaspiro[4.5]decan-6-yl)-4-methylene-7-(triethylsilyloxy)heptan-3-yl) 2-methoxy-2-phenylethanoate (2.125): To a solution of allylic

alcohol **2.123** and allylic alcohol **12-*epi*-2.123** (mixture of diastereomers 8:1) (8.3 mg, 0.011 mmol) in CH_2Cl_2 (0.20 mL) was added (*R*)-(–)-α-methoxyphenylacetic (**2.124**) (3.8 mg, 0.023 mmol), DMAP (0.1 mg, 0.001 mmol), and DCC (4.5 mg, 0.022 mmol). After stirring for 1 h the reaction was at completion. The complete reaction mixture was purified using flash chromatography (10% to 30% ethyl acetate in hexanes) to yield the desired mixture (6.4 mg, 64%). ^{1}H NMR (C_6D_6, 500 MHz) δ 7.58 (d, *J* = 7.5 Hz, 2H), 7.28-7.31 (m, 3H), 5.36 (dd, *J* = 8.5, 4.0 Hz, 1H), 5.10 (s, 0.89H), 5.03 (s, 0.11H), 4.99 (s, 0.89H), 4.97 (s, 0.11H), 4.75 (s, 1H), 3.84 (dd, *J* = 9.5, 6.0 Hz, 0.89H), 3.77 (dd, *J* = 8.0, 3.0 Hz, 0.89H), 3.69-3.82 (m, 0.33H), 3.62 (d, *J* = 9.0 Hz, 0.89H), 3.29 (s, 3H), 3.11-3.28 (m, 0.22H), 3.07 (d, *J* = 8.5 Hz, 0.89H), 2.89 (d, *J* = 10.0 Hz, 0.89H), 2.70-2.76 (m, 0.11H), 2.61 (d, *J* = 12.0 Hz, 0.89H), 1.38-2.43 (m, 20H), 1.35 (s, 3H), 1.29 (s, 3H), 1.25 (s, 6H), 1.04-1.12 (m, 18H), 0.73-0.79 (m, 6H), 0.63-0.69 (m, 6H).



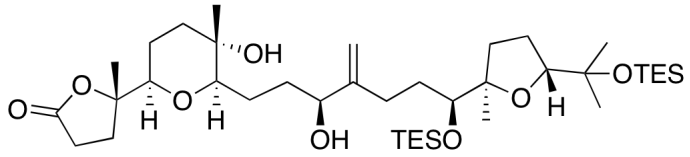
(*S*)-5-((2*R*,5*R*,6*R*)-5-Hydroxy-6-((3*S*,7*S*)-3-hydroxy-7-((2*R*,5*R*)-2-methyl-5-(2-(triethylsilyloxy)propan-2-yl)tetrahydrofuran-2-yl)-4-methylene-7-(triethylsilyloxy)heptyl)-5-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)-5-methyldihydrofuran-2(3*H*)-one (2.126): To a solution of carbonate **2.123** (65 mg, 0.085 mmol) in methanol (3.0 mL) at rt was added K_2CO_3 (23 mg, 0.16 mmol). The reaction was stirred overnight and then quenched with H_2O (5 mL). The mixture was extracted with ethyl acetate (3 x 5 mL), dried (Na_2SO_4), and concentrated. The resudue was purified by flash chromatography (50% ethyl acetate in hexanes to 100% ethyl acetate) to obtain the triol (57 mg, 91%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.04 (s, 1H), 4.86 (s, 1H), 4.11 (m, 1H), 3.81 (dd, *J* = 12.0, 7.6 Hz, 1H), 3.67 (dd, *J* = 11.6, 6.8 Hz, 1H), 3.64 (dd, *J* =

8.4, 6.0 Hz, 1H), 3.54 (dd, *J* = 8.0, 3.2 Hz, 1H), 3.47 (dd, *J* = 11.2, 2.0 Hz, 1H), 3.27 (dd, 10.4, 2.0 Hz, 1H), 2.69 (ddd, *J* = 18.0, 10.4, 8.0 Hz, 1H), 2.53 (ddd, *J* = 15.2, 10.4, 4.8 Hz, 1H), 2.27-2.36 (m, 2H), 2.07-2.15 (m, 2H), 1.85-1.98 (m, 4H), 1.66-1.82 (m, 7H), 1.39-1.57 (m, 4H), 1.36 (s, 3H), 1.19 (s, 3H), 1.17 (s, 3H), 1.09 (s, 3H), 0.97 (t, *J* = 8.0 Hz, 9H), 0.95 (t, *J* = 8.0 Hz, 9H), 0.63 (q, *J* = 8.0 Hz, 6H), 0.58 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.4, 152.1, 108.9, 87.1, 85.8, 84.4, 82.6, 77.7, 74.3, 74.0, 70.9, 62.5, 34.1, 33.3, 33.0, 32.1, 29.8, 29.5, 29.2, 27.9, 26.3, 25.5, 24.5, 24.0, 22.9, 22.7, 7.2, 7.1, 6.7, 5.5; IR (neat) 3395, 2955, 2877, 1773, 1458, 1239, 1100, 1067, 740 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{39}H_{74}O_9Si_2Na$ $[M+Na]^+$ 765.4769, found 765.4795; $[\alpha]_D$ = +1.14 (*c* 1.14, $CHCl_3$).



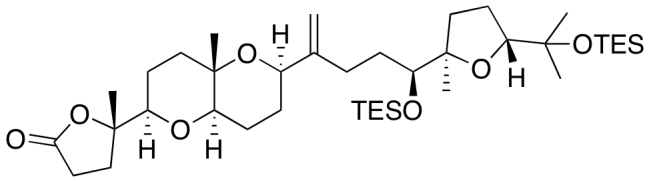
((2*R*,3*R*,6*R*)-3-Hydroxy-2-((3*S*,7*S*)-3-hydroxy-7-((2*R*,5*R*)-2-methyl-5-(2-(triethylsilyloxy)propan-2-yl)tetrahydrofuran-2-yl)-4-methylene-7-(triethylsilyloxy)heptyl)-6-((*S*)-2-methyl-5-oxotetrahydrofuran-2-yl)tetrahydro-2*H*-pyran-3-yl)methyl 4-methylbenzenesulfonate (2.127): To a solution of triol **2.126** (50 mg, 0.067 mmol) in CH_2Cl_2 (0.25 mL) at rt was added TsCl (13 mg, 0.067 mmol), triethylamine (9.3 μL, 0.067 mmol) and dibutyltin oxide (0.3 mg, 0.001 mmol). The reaction was stirred for 2 h, then the mixture was concentrated. The residue was purified by flash chromatography (10% to 40% ethyl acetate in hexanes) to provide the desired tosylate (57 mg, 94%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 5.01 (s, 1H), 4.85 (s, 1H), 4.25 (d, *J* = 10.8 Hz, 1H), 4.07 (m, 2H), 3.64 (dd, *J* = 9.2, 6.4 Hz, 1H), 3.53 (dd, *J* = 8.0, 2.8 Hz, 1H), 3.44 (dd, *J* = 11.6, 2.4 Hz, 1H), 3.25 (dd, 10.8, 1.6 Hz, 1H), 2.49-2.64 (m, 2H), 2.48 (s, 3H), 2.18-2.31 (m, 2H), 2.07-2.14 (m, 2H), 1.67-1.99

(m, 8H), 1.41-1.64 (m, 6H), 1.29 (s, 3H), 1.19 (s, 3H), 1.17 (s, 3H), 1.08 (s, 3H), 0.96 (t, J = 8.0 Hz, 9H), 0.95 (t, J = 8.0 Hz, 9H), 0.63 (q, J = 8.0 Hz, 6H), 0.58 (q, J = 8.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.1, 151.9, 145.3, 132.4, 130.0, 128.0, 108.9, 87.1, 86.7, 85.8, 83.8, 82.6, 77.7, 74.0, 74.0, 70.9, 70.2, 34.1, 32.9, 32.7, 32.0, 29.6, 29.5, 29.1, 27.9, 26.3, 25.5, 23.9, 23.5, 22.7, 22.7, 21.6, 7.1, 7.1, 6.7, 5.5; IR (neat) 3408, 2955, 2875, 1771, 1458, 1362, 1100, 740 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{46}H_{80}O_{11}SSi_2Na$ $[M+Na]^+$ 919.4858, found 919.4916; $[\alpha]_D$ = +6.10 (*c* 1.09, $CHCl_3$).



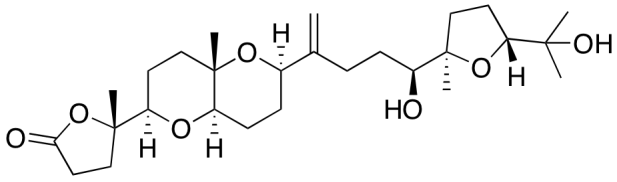
(*S*)-5-((2*R*,5*S*,6*R*)-5-Hydroxy-6-((3*S*,7*S*)-3-hydroxy-7-((2*R*,5*R*)-2-methyl-5-(2-(triethylsilyloxy)propan-2-yl)tetrahydrofuran-2-yl)-4-methylene-7-(triethylsilyloxy)heptyl)-5-methyltetrahydro-2*H*-pyran-2-yl)-5-methyldihydrofuran-2(3*H*)-one (2.128): To a solution of tosylate **2.127** (50 mg, 0.056 mmol) in HMPA (0.40 mL) was added $NaBH_4$ (5.5 mg, 0.17 mmol). The reaction was warmed to 50 °C and stirred for 3 h. The mixture was cooled to rt and quenched with aqueous NH_4Cl (2 mL). EtOAc (10 mL) was added and the mixture was washed with H_2O (3 x 10 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (20% to 70% ethyl acetate in hexanes) to obtain the diol (31 mg, 76%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.04 (s, 1H), 4.86 (s, 1H), 4.11 (m, 1H), 3.64 (dd, J = 8.0, 6.0 Hz, 1H), 3.55 (dd, J = 8.0, 2.8 Hz, 1H), 3.42 (dd, J = 11.2, 2.4 Hz, 1H), 3.11 (d, 8.8 Hz, 1H), 2.69 (ddd, J = 18.0, 10.4, 8.4 Hz, 1H), 2.52 (ddd, J = 15.2, 10.4, 4.8 Hz, 1H), 2.35 (ddd, J = 15.2, 10.4, 4.8 Hz, 1H), 2.10 (m, 1H), 1.60-2.00 (m, 12H), 1.43-1.54 (m, 4H), 1.36 (s, 3H), 1.19 (s, 3H), 1.19 (s, 3H), 1.17 (s, 3H), 1.09 (s, 3H), 0.97 (t, J = 8.0 Hz, 9H), 0.95 (t, J = 8.0 Hz, 9H),

0.63 (q, *J* = 8.0 Hz, 6H), 0.58 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.4, 152.1, 108.9, 87.1, 87.1, 85.8, 84.9, 82.4, 77.7, 74.3, 74.0, 69.4, 39.2, 34.2, 32.6, 32.1, 29.8, 29.7, 29.1, 27.9, 26.3, 25.5, 24.5, 24.5, 22.8, 22.7, 20.2, 7.1, 7.1, 6.7, 5.5; IR (neat): 3399, 2954, 2875, 1775, 1459, 1239, 1099, 1015, 740 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{39}H_{74}O_8Si_2Na$ $[M+Na]^+$ 749.4820, found 749.4899; $[\alpha]_D$ = +8.26 (*c* 1.00, $CHCl_3$).



(*S*)-5-Methyl-5-((2*R*,4a*S*,6*R*,8a*R*)-4a-methyl-6-((*S*)-5-((2*R*,5*R*)-2-methyl-5-(2-(triethylsilyloxy)propan-2-yl)tetrahydrofuran-2-yl)-5-(triethylsilyloxy)pent-1-en-2-yl)octahydropyrano[3,2-*b*]pyran-2-yl)dihydrofuran-2(3*H*)-one (2.129): Under an inert atmosphere, a solution of $Me_3PC(H)CN$ (**2.38**) (13.3 mg, 0.116 mmol) in benzene (1.5 mL) was added to a vial containing diol **2.128** (14 mg, 0.019 mmol). The vial was sealed and heated to 80 °C. The reaction mixture was stirred for 16 hours, then was cooled, concentrated, and purified by flash chromatography (5% to 30% ethyl acetate in hexanes) to yield the polyether (5.4 mg, 40%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 5.01 (s, 1H), 4.86 (s, 1H), 4.28 (dd, *J* = 7.8, 4.2 Hz, 1H), 3.63 (dd, *J* = 9.6, 6.6 Hz, 1H), 3.54 (m, 2H), 3.48 (dd, *J* = 11.4, 6.0 Hz, 1H), 2.68 (ddd, *J* = 18.0, 10.2, 8.4 Hz, 1H), 2.50 (ddd, *J* = 18.0, 10.2, 8.4 Hz, 1H), 2.38 (ddd, *J* = 13.2, 10.8, 4.8 Hz, 1H), 2.31 (m, 1H), 2.07 (m, 2H), 1.96 (m, 1H), 1.76-1.90 (m, 5H), 1.71 (m, 1H), 1.47-1.64 (m, 7H), 1.35 (s, 3H), 1.24 (s, 3H), 1.18 (s, 3H), 1.17 (s, 3H), 1.08 (s, 3H), 0.97 (t, *J* = 7.8 Hz, 9H), 0.95 (t, *J* = 7.8 Hz, 9H), 0.63 (q, *J* = 7.8 Hz, 6H), 0.58 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 177.3, 151.9, 109.3, 87.2, 87.1, 85.8, 82.7, 78.7, 77.9, 74.0, 72.7, 72.0, 38.3, 34.4, 32.3, 29.8, 29.6, 29.2, 27.9, 26.4, 26.2, 25.5, 24.3, 23.3, 22.6, 21.6, 19.6, 7.2, 7.1, 6.7, 5.5; IR (neat) 2954, 2875, 1778, 1460, 1239, 1099, 1041, 726

cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{39}H_{72}O_7Si_2Na$ $[M+Na]^+$ 731.4714, found 731.4771; $[\alpha]_D$ = –2.67 (*c* 0.50, $CHCl_3$).



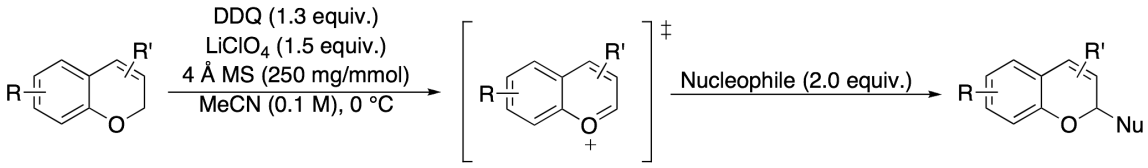
Lactodehydrothyrsiferol (2.1): To a solution of **1.129** (5.2 mg, 7.3 μmmol) in THF (0.1 mL) at rt was added 1.0 M TBAF in THF (18 μL, 18 μmol). The reaction stirred for 6 h, then was concentrated. The residue was purified by flash chromatography (10% to 80% ethyl acetate in hexanes) to obtain the natural product (2.7 mg, 77%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 5.06 (s, 1H), 4.90 (s, 1H), 4.29 (dd, *J* = 7.2, 4.0 Hz, 1H), 3.77 (dd, *J* = 10.3, 5.4 Hz, 1H), 3.53-3.55 (m, 2H), 3.47 (dd, *J* = 11.2, 5.2 Hz, 1H), 2.68 (ddd, *J* = 18.0, 9.6, 9.0 Hz, 1H), 2.44-2.53 (m, 3H), 2.38 (m, 2H), 2.06-2.21 (m, 3H), 1.81-1.90 (m, 6H), 1.59-1.67 (m, 5H), 1.45-1.50 (m, 2H), 1.35 (s, 3H), 1.27 (s, 3H), 1.23 (s, 3H), 1.15 (s, 3H), 1.14 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 177.3, 151.1, 110.0, 87.6, 87.2, 86.1, 82.7, 78.8, 76.1, 72.6, 72.2, 70.4, 38.3, 31.5, 29.8, 29.7, 29.4, 29.2, 27.7, 26.6, 26.1, 24.2, 24.0, 23.8, 23.3, 21.6, 19.5; IR (neat) 3438, 2925, 2854, 1770, 1454, 1378, 1152, 1096 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{27}H_{44}O_7Na$ $[M+Na]^+$ 503.2985, found 503.3026; $[\alpha]_D$ = 5.10 (*c* 0.68, $CHCl_3$).

APPENDIX B

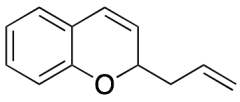
OXIDATIVE BIMOLECULAR COUPLING REACTION (SUPPORTING INFORMATION)

General Experimental Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on a Bruker Avance 300 spectrometer at 300 MHz and 75 MHz, a Bruker Avance 400 spectrometer at 400 MHz and 100 MHz, and a Bruker Avance 500 spectrometer at 500 MHz and 125 MHz, respectively. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. The solvent peaks was used as a reference value, for ^{1}H NMR: $CDCl_3$ = 7.27 ppm, for ^{13}C NMR: $CDCl_3$ = 77.0. Data are reported as follows: (s = singlet; d = doublet; t = triplet, q = quartet; dd = doublet of doublets; ddd = doublet of doublet of doublets; dt = doublet of triplet; br = broad; app = apparently). High resolution and low resolution mass spectra were recorded on a VG 7070 spectrometer using electron ionization (EI) or electron spray ionization (ESI). Infrared (IR) spectra were collected on a Mattson Cygnus 100 spectrometer. Samples for IR were prepared as a thin film on a NaCl plate by dissolving the compound in CH_2Cl_2 and then evaporating the CH_2Cl_2. Tetrahydrofuran and diethyl ether were dried by passage through an activated alumina column under positive N_2 pressure. Methylene chloride and acetonitrile and were distilled under N_2 from CaH_2. Analytical TLC was performed on E. Merck pre-coated (25

nm) silica gel 60F-254 plates. Visualization was done under UV light (254 nm). Flash chromatography was done using ICN SiliTech 32-63 60 Å silica gel. Reagent grade ethyl acetate, diethyl ether, pentane and hexanes (commercial mixture) were purchased from EM Science and used as is for chromatography. All reactions were performed in oven or flame-dried glassware under a positive pressure of N_2 with magnetic stirring unless otherwise noted.

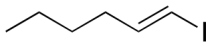


General Procedure for the Oxidative Coupling To a solution of benzopyran (1.0 equiv.) in freshly distilled acetonitrile (0.1 M) at 0 °C was added $LiClO_4$ (1.5 equiv.) and 4 Å MS (250 mg/mmol). After 5 min, DDQ (1.3 equiv.) was added to the reaction mixture and it was stirred until TLC analysis showed complete starting material consumption. The nucleophile (2.0 equiv.) was added and the reaction was stirred until completion (monitored via TLC analysis). The reaction was quenched with 10% aqueous $NaHCO_3$ solution (10 mL). The reaction mixture was extracted with diethyl ether (3 x 10 mL), dried over $MgSO_4$, and concentrated under vacuum. The crude mixture was purified by flash chromatography.



2-Allyl-2*H*-chromene (3.11): The general procedure for the oxidative coupling was followed using benzopyran **3.9**[119] (264 mg, 2.00 mmol), $LiClO_4$ (319 mg, 3.00 mmol), 4 Å MS (500 mg), DDQ (590 mg, 2.60 mmol), and acetonitrile (20 mL). After 30 min the oxidation was complete and allyl trimethylsilane (**3.10**) (457 mg, 4.00 mmol) was added. The reaction was complete after 30 min and was purified using flash

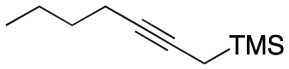
chromatography (1% to 5% ethyl acetate in hexanes) to yield the substituted benzopyran (254 mg, 74%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.02 (td, *J* = 7.6, 1.6 Hz, 1H), 6.88 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.76 (t, *J* = 7.6 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 6.33 (d, *J* = 9.6 Hz, 1H), 5.82 (ddt, *J* = 17.2, 10.4, 7.2 Hz, 1H), 5.61 (dd, *J* = 9.6, 3.2 Hz, 1H), 5.07 (d, *J* = 9.6 Hz, 1H), 5.04 (s, 1H), 4.82-4.85 (m, 1H), 2.46-2.53 (m, 1H), 2.34-2.41 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.3, 133.3, 129.1, 126.4,125.0,124.2, 121.8, 121.0, 117.8, 115.9, 74.7, 39.7; IR (neat) 3075, 2934, 1640, 1605, 1486, 1271, 1206, 1041, 754 cm^{-1}, HRMS (ESI) *m/z* calcd for $C_{12}H_{11}O$ $[M–H]^+$ 171.0810, found 171.0813.



(*E*)-1-Iodohex-1-ene (3.86): To a solution of zirconocene dichloride (13.7 g, 46.9 mmol) in THF (100 mL) at 0 °C was added a 1.0 M solution of DIBAL in hexanes (46.9 mL, 46.9 mmol) drop wise over 30 min. After stirring for an additional 30 min., 1-hexyne (**3.16**) (4.16 g, 50.6 mmol) was added and the reaction mixture was allowed to warm to rt and stirred for 1 h. The reaction was cooled to –78 °C and iodine (12.8 g, 50.6 mmol) was added to the mixture. After 30 min at this temperature, the reaction was warmed to rt and stirred for an additional 1.5 h. The resulting solution was cooled to 0 °C and quenched with H_2O (50 mL), a saturated solution of $NaHCO_3$ (100 mL), and a saturated solution of sodium potassium tartrate (100 mL). The biphasic mixture was stirred vigorously for 2 h and the layers were separated. The aqueous layer was extracted with hexanes (3 x 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The crude residue was purified using flash chromatography (100% hexanes) to yield the vinyl iodide (7.50 g, 76%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.52 (quin, *J* = 7.2 Hz, 1H), 5.98 (dt, *J* = 14.0, 1.2 Hz, 1H), 2.07 (qd, *J* = 7.2, 1.2 Hz,

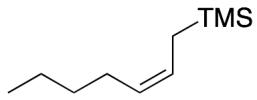
2H), 1.29-1.55 (m, 2H), 0.89 (t, *J* = 7.2 Hz, 3H). *These data are consistent with literature values.*[148]

(*E*)-1-(Trimethylsilyl)-hept-2-ene (3.17): To a flask containing vinyl iodide **3.86** (7.50 g, 35.7 mmol) in dry, degassed THF (100 mL) at 0 °C was added $Pd(PPh_3)_4$ (1.03 g, 0.893 mmol) and a 1.0 M solution of (trimethylsilyl)methylmagnesium chloride in diethyl ether (46.4 mL, 46.4 mmol). After 2 h, the reaction was quenched with H_2O (50 mL) and a saturated solution of NH_4Cl (50 mL). The aqueous layer was extracted with hexanes (3 x 50 mL), dried over $MgSO_4$, and concentrated under vacuum. The crude residue was purified using flash chromatography (100% hexanes) to yield the silane (5.28 g, 87%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.33-5.43 (m, 1H), 5.19-5.29 (m, 1H),1.98 (q, *J* = 8.8 Hz, 2H), 1.39 (d, *J* = 10.4 Hz, 2H), 1.28-1.32 (m, 4H), 0.89 (t, *J* = 8.8 Hz, 3H), –0.01 (s, 9H). *These data are consistent with literature values.*[149]

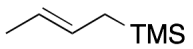


1-(Trimethylsilyl)-hept-2-yne (3.87): To a solution of 1-hexyne (2.87 g, 35.0 mmol) in THF (45 mL) at –30 °C was added a 1.6 M solution of *n*-butyllithium in hexanes (18.9 mL, 30.3 mmol) drop wise. The solution was warmed to 0 °C and stirred for 30 min. (Trimethylsilyl)methyl iodide (5.00 g, 23.3 mmol) was added and the reaction was warmed to rt over 30 min. The solution was refluxed at 60 °C for 16 h before cooling to rt and quenching with H_2O (50 mL). The aqueous layer was extracted with pentane (3 x 40 mL), dried over $MgSO_4$, and concentrated under vacuum. The crude residue was purified using flash chromatography (2% diethyl ether in hexanes) to yield the silane (3.32 g, 100%): ^{1}H NMR

($CDCl_3$, 400 MHz) δ 2.13-2.18 (m, 2H), 1.36-1.55 (m, 6H), 0.90 (t, *J* = 4.0 Hz, 3H), 0.10 (s, 9H). *These data are consistent with literature values.*[150]



(*Z*)-1-(Trimethylsilyl)-hept-2-ene (3.18): To a flask containing sodium borohydride (0.149 g, 3.93 mmol) in ethanol (4.75 mL) was added a 1.0 M aqueous solution of NaOH (0.25 mL). This solution was sonicated for 5 min and the remaining solids were filtered away. This $NaBH_4$ solution was then added to a flask containing $Ni(OAc)_2 \cdot 4H_2O$ (1.03 g, 4.15 mmol) in ethanol (300 mL). After stirring for 5 min, ethylenediamine (0.55 mL, 8.28 mmol) was added. After stirring for an additional 5 min, silane **3.87** (3.50 g, 20.7 mmol) was added and the N_2 atmosphere was replaced with an H_2 atmosphere using a balloon. The reaction mixture stirred vigorously for 3 h and was then quenched with H_2O (300 mL). The solution was extracted with hexanes (3 x 200 mL), dried over $MgSO_4$, and was concentrated under vacuum. The crude residue was purified using flash chromatography (2% diethyl ether in pentanes) to yield the silane (3.31 g, 94%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.36-5.42 (m, 1H), 5.24-5.30 (m, 1H), 1.97-2.01 (2H, m), 1.47 (dt, *J* = 8.5, 0.5 Hz, 2H), 1.27-1.36 (m, 2H), 0.89 (t, *J* = 7.0 Hz, 3H), 0.01 (s, 9H). *These data are consistent with literature values.*[149]



(*E*)-Crotyl trimethylsilane (3.20): To a suspension of LAH (6.51 g, 171 mmol) in dimethoxyethane (100 mL) at 0 °C was added 2-butyn-1-ol (**3.19**) (10.0 g, 142 mmol) via dimethoxyethane (25 mL) over 20 min. The reaction was warmed to rt and stirred for 48 h before cooling to 0 °C and quenching carefully with H_2O (6.5 mL), 15% aqueous NaOH (6.5 mL), and H_2O (19.5 mL). The remaining solids were filtered off using diethyl ether to wash the solid and

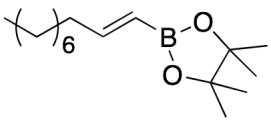
the solution was concentrated at 0 °C under minimal pressure to avoid loss desired product. The resulting oil was used in the next step without further purification.

To a solution of the crude (*E*)-crotyl alcohol (10.1 g, 140 mmol) in diethyl ether (150 mL) at 0 °C was added PBr_3 (7.98 mL, 84.0 mmol) drop wise. After 1 h, the reaction was quenched by pouring the solution into a beaker of iced H_2O. The resulting biphasic mixture was extracted with diethyl ether (3 x 150 mL) and dried over $MgSO_4$. The solution was concentrated at 0 °C under minimal pressure to avoid loss desired product. The resulting oil was used in the next step without further purification.

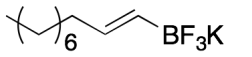
CuCl (0.354 g, 3.56 mmol) was placed into a flask under an inert atmosphere in a glove box. The flask was sealed and removed from the glove box where dry, degassed diethyl ether (75 mL) and triethylamine (26.3 mL, 190 mmol) added at 0 °C. The crude (*E*)- crotyl bromide (16.0 g, 119 mmol) was combined with $HSiCl_3$ (25.7 g, 190 mmol) and added over 20 min before stirring the reaction for 1 h at 0 °C and 1 h at rt. The resulting solids were removed by passing the solution through a pad of Celite via diethyl ether. The solution was concentrated at 0 °C under minimal pressure to avoid loss desired product. The resulting oil was used in the next step without further purification.

To a flask containing diethyl ether (100 mL) at 0 °C was added a 3.0 M solution methylmagnesium iodide in diethyl ether (130 mL, 389 mmol). The crude (*E*)-crotyl trichlorosilane (16.4 g, 86.5 mmol) was added drop wise over 30 min. The resulting solution was refluxed at 40 °C for 16 hours. The reaction was cooled to 0 °C and quenched carefully with a saturated solution of NH_4Cl (100 mL). The biphasic mixture was extracted with diethyl ether (3 x 50 mL) and dried over $MgSO_4$. . The solution was concentrated at 0 °C under minimal pressure to avoid loss desired product. The resulting oil was distilled (114 °C) to obtain pure (*E*)-crotyl

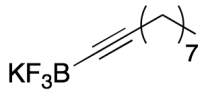
silane (6.62 g, 36% over 4 steps): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.35-5.46 (m, 1H), 5.20-5.32 (m, 1H), 1.65 (dd, *J* = 6.0, 1.2 Hz, 3H), 1.39 (dt, *J* = 7.5, 1.2 Hz, 2H), -0.01 (s, 9H). *These data are consistent with literature values.*[151]



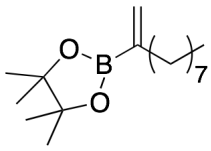
(*E*)-2-(Dec-1-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.88): To a solution on 1-decyne (**3.24**) (1.00 g, 7.39 mmol) in CH_2Cl_2 (3.6 mL) at 0 °C was added pinacolborane (0.972 g, 7.59 mmol) and $HZrCp_2Cl$ (0.093 g, 0.362 mmol). The solution was warmed to rt and stirred for 16 h. The reaction mixture was quenched with H_2O (10 mL) and extracted with diethyl ether (3 x 10 mL). The organic layer was dried over $MgSO_4$ and concentrated under vacuum. The crude residue was purified using flash chromatography (1% to 5% diethyl ether in hexanes) to yield the borane (1.50 g, 78%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.65 (dt, *J* = 18.0, 6.4 Hz, 1H), 5.43 (d, *J* = 18.0 Hz, 1H), 2.16 (q, *J* = 6.8 Hz, 2H), 1.34-1.43 (m, 2H), 1.27 (m, 22H), 0.89 (t, *J* = 6.8 Hz, 3H). *These data are consistent with literature values.*[152]



Potassium (*E*)-dec-1-enyltrifluoroborate (3.25): To a solution of borane **3.88** (1.50 g, 5.63 mmol) in acetonitrile (14 mL) was added KHF_2 (1.55 g, 19.9 mmol) and H_2O (4.6 mL). The solution was stirred for 2 h and was concentrated. The resulting solid was dissolved in hot acetone and filtered to remove undesired salts. The filtrate was concentrated and taken up in minimal volume of hot acetone to dissolve the solid completely. Adding diethyl ether to the solution solidified the desired product. The solid was collected by vacuum filtration to yield the trifluoroborate salt (0.831 g, 60%): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.44 (dt, *J* = 17.2, 6.0 Hz, 1H), 5.15-5.22 (m, 1H), 1.85 (q, *J* = 6.0 Hz, 2H), 1.21-1.29 (m, 12H), 0.85 (t, *J* = 6.8 Hz, 3H). *These data are consistent with literature values.*[153]

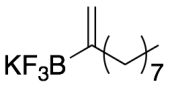


Potassium dec-1-ynyltrifluoroborate (3.26): To a solution of 1-decyne (**3.24**) (3.00 g, 21.6 mmol) in THF (45 mL) at –78 °C was added a 1.6 M solution of *n*-butyllithium in hexanes (13.6 mL, 21.6 mmol) drop wise. After 1 h, trimethyl borate (3.61 mL, 32.4 mmol) was added. The solution was stirred for 1 h at –78 °C and warmed to 0 °C where it was stirred for an additional hour. KHF_2 (10.1 g, 130 mmol) was added via H_2O (10 mL) slowly. The solution was stirred for 1 h at 0 °C and warmed to rt where it was stirred for an additional hour before being concentrated under reduced pressure. The crude solid was placed under high vacuum for 16 hours. The resulting solid was dissolved in hot acetone and filtered to remove undesired salts. The filtrate was concentrated and taken up in a minimal volume of hot acetone to dissolve the solid completely. Adding diethyl ether to the solution solidified the desired product. The solid was collected by vacuum filtration to yield the trifluoroborate salt (3.14 g, 60%): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.95 (t, J = 6.4 Hz, 2H), 1.23-1.31 (m, 12H), 0.84 (t, J = 6.8 Hz, 3H). *These data are consistent with literature values.*[154]

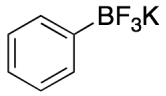


2-(Dec-1-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.89): To a solution of $NiCl_2$(dppp) (0.163 g, 0.300 mmol) in THF at 0 °C was added a 1.0 M solution of DIBAL in hexanes (13.0 mL, 13.0 mmol) drop wise. After stirring for 5 min, the reaction mixture was warmed to rt for 10 min and then cooled back to 0 °C. 1-Decyne (**3.24**) (1.38 g, 10.0 mmol) was added slowly and the reaction mixture was warmed to rt for 2 h. The reaction was cooled to 0 °C and 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.74 g, 30.0 mmol) was added. The solution was allowed to warm to rt and continued to be stirred for 16 h. The reaction mixture was quenched with H_2O (50 mL), extracted

with diethyl ether (3 x 50 mL), dried over $MgSO_4$, concentrated under reduced pressure. The crude residue was purified using flash chromatography (5% ethyl acetate in hexanes) to yield the borane (2.04 g, 77%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.75 (d, *J* = 3.2 Hz, 1H), 5.59 (s, 1H), 2.13 (t, *J* = 7.2 Hz, 2H), 1.36-1.42 (m, 2H), 1.20-1.27 (m, 22H), 0.88 (t, *J* = 6.8 Hz, 3H). *These data are consistent with literature values.*[152]

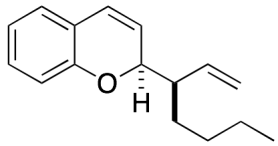


Potassium dec-1-en-2-yltrifluoroborate (3.27): To a solution of borane **3.89** (2.04 g, 7.68 mmol) in acetonitrile (15 mL) was added KHF_2 (1.80 g, 23.0 mmol) and H_2O (5.0 mL). The solution was stirred for 2 h and was concentrated. The resulting solid was dissolved in hot acetone and filtered to remove undesired salts. The filtrate was concentrated and dissolved in a minimal volume of hot acetone to dissolve the solid completely. Adding diethyl ether to the solution solidified the desired product. The solid was collected by vacuum filtration to yield the trifluoroborate salt (1.34 g, 71%): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.79 (d, *J* = 5.4 Hz, 1H), 4.69 (s, 1H), 1.88 (t, *J* = 6.9 Hz, 2H), 1.24-1.35 (m, 12H), 0.88 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 112.2, 112.2, 36.3, 31.5, 29.6, 29.3, 28.9, 28.5, 22.2,14.0; ^{11}B NMR (DMSO-d_6, 125 MHz) δ 2.62; ^{19}F NMR (DMSO-d_6, 376 MHz) δ -140.9; IR (neat) 2917, 2849, 1577, 1540, 1466, 1422, 1155, 1107; HRMS (ESI) *m/z* calcd for $C_{10}H_{19}BF_3K$ $[M]^+$ 246.1169, found 246.1148, mp > 245 °C..

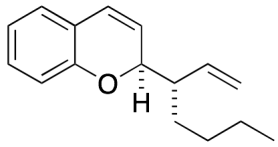


Potassium phenyltrifluoroborate (3.29): To a solution of phenylboronic acid (**3.28**) (3.00 g, 24.6 mmol) in methanol (7.5 mL) was added a 4.5 M aqueous solution of KHF_2 (18.8 mL, 81.9 mmol). After 30 min the reaction mixture was filtered and the solid was washed with cold acetonitrile. The collected solid was recrystallized from acetonitrile

to yield the trifluoroborate salt (4.25 g, 94%): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.38 (d, *J* = 5.6 Hz, 2H), 7.06-7.12 (m, 3H). *This data are consistent with literature values.*[155]

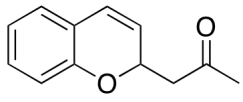


(±)-(*S*)-2-((*R*)-Hept-1-en-3-yl)-2*H*-chromene (3.31): The general procedure for the oxidative coupling was followed using benzopyran **3.9**[119] (132 mg, 1.00 mmol), $LiClO_4$ (160 mg, 1.50 mmol), 4 Å MS (250 mg), DDQ (295 mg, 1.30 mmol), and acetonitrile (10 mL). After 30 min the oxidation was complete and silane **3.17** (341 mg, 2.00 mmol) was added. The reaction was complete after 16 h and was purified using flash chromatography (1% to 5% ethyl acetate in hexanes) to yield the substituted benzopyran (144 mg, 63%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.09 (td, *J* = 7.6, 1.6 Hz, 1H), 6.94 (dd, *J* = 7.2, 1.2 Hz, 1H), 6.83 (td, *J* = 7.2, 0.8 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 6.42 (dd, *J* = 10.0, 1.2 Hz, 1H), 5.68-5.76 (m, 1H), 5.66 (dd, *J* = 10.0, 3.2 Hz, 1H), 5.11 (dd, *J* = 10.0, 1.6 Hz, 1H), 5.06 (dd, *J* = 16.8, 1.2 Hz, 1H), 4.85-4.87 (m, 1H), 2.37 (sep, *J* = 4.8 Hz, 1H), 1.59-1.68 (m, 1H), 1.41-1.51 (m, 1H), 1.19-1.37 (m, 4H), 0.90 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.9, 138.0, 129.0, 126.4, 124.4, 124.3, 121.9, 120.8, 116.9, 115.7, 77.8, 49.6, 29.5, 29.4, 22.7, 14.0; IR (neat) 3073, 2928, 2857, 1639, 1486, 1230, 1206, 1040, 915, 753; HRMS (ESI) *m/z* calcd for $C_{16}H_{21}O$ $[M+H]^+$ 229.1592, found 229.1594.

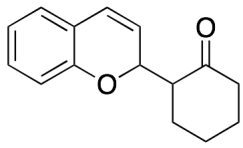


(±)-(*S*)-2-((*S*)-Hept-1-en-3-yl)-2*H*-chromene (3.32): The general procedure for the oxidative coupling was followed using benzopyran **3.9**[119] (132 mg, 1.00 mmol), $LiClO_4$ (160 mg, 1.50 mmol), 4 Å MS (250 mg), DDQ (295 mg, 1.30 mmol), and acetonitrile (10 mL). After 30 min the oxidation was complete and silane **3.18** (341 mg, 2.00 mmol) was added. The reaction was complete after 16 h and was purified using

flash chromatography (1% to 5% ethyl acetate in hexanes) to yield the substituted benzopyran (6:1 *anti*:*syn*) (117 mg, 51%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.09 (td, *J* = 8.0, 1.5 Hz, 1H), 6.95 (dd, *J* = 7.0, 1.5 Hz, 1H), 6.83 (td, *J* = 7.5, 1.0 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.41 (dd, *J* = 10.0, 1.0 Hz, 1H), 5.65-5.72 (m, 2H), 5.11 (dd, *J* = 10.5, 2.0 Hz, 1H), 5.07 (dd, *J* = 17.0, 1.0 Hz, 1H), 4.74-4.76 (m, 1H), 2.37-2.43 (m, 1H), 1.72-1.78 (m, 1H), 1.16-1.38 (m, 5H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.6, 138.1, 129.1, 126.4, 124.5, 124.2, 122.0, 120.8, 117.4, 115.8, 77.7, 49.6, 29.3, 29.1, 22.7, 14.0; IR (neat) 3073, 2919, 2852, 1638, 1485, 1229, 1038, 750; HRMS (ESI) *m/z* calcd for $C_{19}H_{21}O$ $[M+H]^+$ 229.1592, found 229.1586.

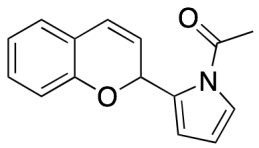


1-(2*H*-Chromen-2-yl)propan-2-one (3.33): The general procedure for the oxidative coupling was followed using benzopyran **3.9**[119] (132 mg, 1.00 mmol), $LiClO_4$ (160 mg, 1.50 mmol), 4 Å MS (250 mg), DDQ (295 mg, 1.30 mmol), and acetonitrile (10 mL). After 30 min the oxidation was complete and silyl enol ether **3.21** (429 mg, 2.00 mmol) was added. The reaction was complete after 30 min and was purified using flash chromatography (10% to 40% ethyl acetate in hexanes) to yield the substituted benzopyran (trace amounts): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.14 (td, *J* = 8.1, 1.2 Hz, 1H), 7.00 (d, *J* = 6.3 Hz, 1H), 6.90 (t, *J* = 7.2 Hz, 1H), 6.79 (d, *J* = 8.1 Hz, 1H), 6.45 (d, *J* = 9.9 Hz, 1H), 5.75 (dd, *J* = 9.6, 3.6 Hz, 1H), 5.36 (m, 1H), 3.07 (dd, *J* = 16.2, 7.8 Hz, 1H), 2.72 (dd, *J* = 15.9, 5.4 Hz, 1H), 2.24 (s, 3H).



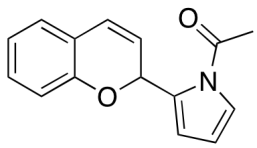
2-(2*H*-Chromen-2-yl)cyclohexanone (3.34): The general procedure for the oxidative coupling was followed using benzopyran **3.9**[119] (132 mg, 1.00 mmol), $LiClO_4$ (160 mg, 1.50 mmol), 4 Å MS (250 mg), DDQ (295 mg, 1.30 mmol), and

acetonitrile (10 mL). After 30 min the oxidation was complete and enol silane **3.22** (341 mg, 2.00 mmol) was added. The reaction was complete after 30 min and was purified using flash chromatography (5% to 15% ethyl acetate in hexanes) to yield the substituted benzopyran (dr 1:1.6) (162 mg, 71%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.03-7.12 (m, 1H), 6.92-6.97 (m, 1H), 6.83-6.86 (m, 1H), 6.78 (d, *J* = 8.4 Hz, 0.38H), 6.72 (d, *J* = 8.0 Hz, 0.62H), 6.39-6.45 (m, 1H), 5.86 (dd, *J* = 10.0, 3.6 Hz, 0.38H), 5.69 (dd, *J* = 10.0, 3.2 Hz, 0.62H), 5.47-5.50 (m, 0.62H), 5.17 (ddd, *J* = 7.6, 4.0, 1.2 Hz, 0.38H), 2.87-2.93 (m, 0.62H), 2.67-2.74 (m, 0.38H), 2.22-2.47 (m, 2.62H), 2.04-2.12 (m, 1H), 1.86-1.94 (m, 1.38H), 1.55-1.76 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 210.8, 210.6, 153.8, 152.9, 129.1, 126.4, 126.4, 125.4, 124.7, 123.8, 123.0, 121.8, 121.3, 121.1, 120.9, 115.9, 115.4, 73.8, 73.2, 55.7, 55.3, 42.6, 42.2, 29.6, 27.9, 27.6, 27.4, 24.5, 24.4; IR (neat) 3044, 2938, 2862, 1707, 1605, 1485, 1454, 1271, 1230, 1037, 778; HRMS (EI) *m/z* calcd for $C_{15}H_{16}O_2$ $[M]^+$ 228.1150, found 228.1173.

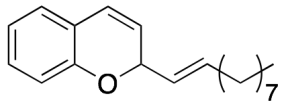


1-(2-(2*H*-Chromen-2-yl)-1*H*-pyrrol-1-yl)ethanone (3.35): The general procedure for the oxidative coupling was followed using benzopyran **3.9**[119] (26 mg, 0.20 mmol), $LiClO_4$ (32 mg, 0.30 mmol), 4 Å MS (50 mg), DDQ (59 mg, 0.26 mmol), and acetonitrile (2.0 mL). After 30 min the oxidation was complete and enol silane **3.23**[124] (72 mg, 0.400 mmol) was added. The reaction was complete after 30 min and was purified using flash chromatography (5% to 15% ethyl acetate in hexanes) to yield the substituted benzopyran (22 mg, 47%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.13 (dd, *J* = 3.0, 1.5 Hz, 1H), 7.10 (td, *J* = 7.5, 1.5 Hz, 1H), 7.00 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.85 (td, *J* = 7.5, 1.0 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 6.64 (d, *J* = 4.0 Hz, 1H), 6.52 (d, *J* = 10.0 Hz, 1H), 6.37-6.38 (m, 1H), 6.16 (t, *J* = 3.0 Hz, 1H), 5.93 (dd, *J* = 10.0, 4.0 Hz, 1H), 2.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.0, 153.0, 134.4,

129.2, 126.5, 124.1, 123.3, 122.1, 121.5, 121.1, 116.2, 115.0, 111.8, 69.8, 24.1; IR (neat) 3043, 2921, 1721, 1484, 1226, 1126, 1037, 939, 756; HRMS (ESI) *m/z* calcd for $C_{15}H_{13}NO_2Na$ $[M+Na]^+$ 262.0844, found 262.0851.

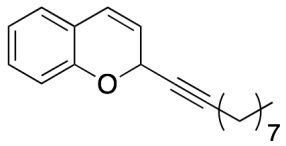


1-(2-(2*H*-Chromen-2-yl)-1*H*-pyrrol-1-yl)ethanone (3.35): The general procedure for the oxidative coupling was followed using benzopyran **3.9**[119] (132 mg, 1.00 mmol), $LiClO_4$ (160 mg, 1.50 mmol), 4 Å MS (250 mg), DDQ (295 mg, 1.30 mmol), and acetonitrile (10 mL). After 30 min the oxidation was complete and acetyl pyrrole **3.36** (72.5 mg, 0.400 mmol) was added. The reaction was at completion after 16 h and was purified using flash chromatography (5% to 15% ethyl acetate in hexanes) to yield the substituted benzopyran (78.0 mg, 33%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.13 (dd, *J* = 3.0, 1.5 Hz, 1H), 7.10 (td, *J* = 7.5, 1.5 Hz, 1H), 7.00 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.85 (td, *J* = 7.5, 1.0 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 6.64 (d, *J* = 4.0 Hz, 1H), 6.52 (d, *J* = 10.0 Hz, 1H), 6.37-6.38 (m, 1H), 6.16 (t, *J* = 3.0 Hz, 1H), 5.93 (dd, *J* = 10.0, 4.0 Hz, 1H), 2.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.0, 153.0, 134.4, 129.2, 126.5, 124.1, 123.3, 122.1, 121.5, 121.1, 116.2, 115.0, 111.8, 69.8, 24.1; IR (neat) 3043, 2921, 1721, 1484, 1226, 1126, 1037, 939, 756; HRMS (ESI) *m/z* calcd for $C_{15}H_{13}NO_2Na$ $[M+Na]^+$ 262.0844, found 262.0851.

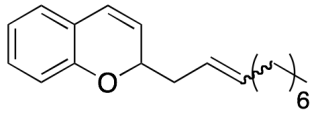


(*E*)-2-(Dec-1-enyl)-2*H*-chromene (3.37): The general procedure for the oxidative coupling was followed using benzopyran **3.9**[119] (132 mg, 1.00 mmol), $LiClO_4$ (160 mg, 1.50 mmol), 4 Å MS (250 mg), DDQ (295 mg, 1.30 mmol), and acetonitrile (10 mL). After 30 min the oxidation was complete and trifluoroborate **3.25** (492 mg, 2.00 mmol) was added. The reaction was complete after 30 min and was purified using flash

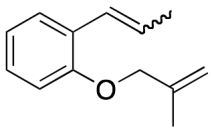
chromatography (1% to 5% ethyl acetate in hexanes) to yield the substituted benzopyran (176 mg, 65%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.12 (td, *J* = 7.2, 1.2 Hz, 1H), 6.98 (dd, *J* = 7.2, 0.8 Hz, 1H), 6.86 (t, *J* = 7.6 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.43 (d, *J* = 9.6 Hz, 1H), 5.81 (dt, *J* = 15.2, 6.8 Hz, 1H), 5.65-5.71 (m, 2H), 5.27-5.29 (m, 1H), 2.07 (q, *J* = 6.8 Hz, 2H), 1.28-1.40 (m, 12H), 0.91 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.2, 134.5, 129.1, 127.8, 126.4, 124.7, 123.7, 121.6, 120.9, 116.0, 75.8, 32.1, 31.8, 29.4, 29.2, 29.1, 28.9, 22.7, 14.1; IR (neat) 3042, 2924, 2853, 1638, 1485, 1456, 1227, 1036, 768; HRMS (ESI) *m/z* calcd for $C_{19}H_{25}O$ $[M–H]^+$ 269.1905, found 269.1899.



2-(Dec-1-ynyl)-2*H*-chromene (3.38): The general procedure for the oxidative coupling was followed using benzopyran **3.9**[119] (132 mg, 1.00 mmol), $LiClO_4$ (160 mg, 1.50 mmol), 4 Å MS (250 mg), DDQ (295 mg, 1.30 mmol), and acetonitrile (10 mL). After 30 min the oxidation was complete and trifluoroborate **3.26** (488 mg, 2.00 mmol) was added. The reaction was complete after 30 min and was purified using flash chromatography (1% to 5% ethyl acetate in hexanes) to yield the substituted benzopyran (176 mg, 66%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.15 (td, *J* = 7.8, 1.5 Hz, 1H), 7.02 (dd, *J* = 7.2, 1.2 Hz, 1H), 6.91 (t, *J* = 7.5 Hz, 1H) 6.88 (d, *J* = 8.1 Hz, 1H), 6.46 (d, *J* = 9.6 Hz, 1H), 5.76 (dd, *J* = 9.6, 3.9 Hz, 1H), 5.56 (q, *J* = 1.8 Hz, 1H), 2.21 (td, *J* = 6.9, 1.8 Hz, 2H), 1.49 (quin, *J* = 7.2 Hz, 2H), 1.26-1.34 (m, 10H), 0.90 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.6, 129.3, 126.6, 124.2, 123.0, 121.6, 121.5, 116.4, 87.1, 77.2, 64.9, 31.8, 29.1, 29.0, 28.8, 28.4, 22.6, 18.8, 14.1; IR (neat) 3045, 2925, 2854, 2277, 2219, 1606, 1485, 1293, 1198, 1111, 754; HRMS (EI) *m/z* calcd for $C_{19}H_{24}O$ $[M]^+$ 268.1827, found 268.1864.

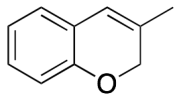


2-(Dec-2-enyl)-2*H*-chromene (3.39): The general procedure for the oxidative coupling was followed using benzopyran **3.9**[119] (132 mg, 1.00 mmol), $LiClO_4$ (160 mg, 1.50 mmol), 4 Å MS (250 mg), DDQ (295 mg, 1.30 mmol), and acetonitrile (10 mL). After 30 min the oxidation was complete and trifluoroborate **3.27** (492 mg, 2.00 mmol) was added. The reaction was complete after 30 min and was purified using flash chromatography (1% to 5% ethyl acetate in hexanes) to yield the substituted benzopyran (5:1 olefin mixture) (179 mg, 66%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.11 (td, *J* = 7.0, 0.8 Hz, 1H), 6.95-6.97 (m, 1H), 6.83-6.86 (m, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.40-6.42 (m, 1H), 5.70 (dd, *J* = 9.5, 3.0 Hz, 1H), 5.53-5.58 (m, 1H), 5.45-5.51 (m, 1H), 4.86-4.91 (m, 1H), 2.46-2.54 (m, 1.67H), 2.37-2.42 (m, 0.33H), 1.93-2.05 (m, 2H), 1.22-1.34 (m, 10H), 0.89 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.4, 153.4, 134.3, 133.2, 129.1, 129.0, 126.4, 126.3, 125.4, 125.3, 124.3, 124.1, 124.0, 123.5, 122.0, 121.8, 120.9, 120.9, 115.9, 74.9, 74.9, 38.7, 33.4, 32.6, 31.8, 29.5, 29.4, 29.2, 29.2, 29.2, 29.1, 27.4, 22.7, 14.1; IR (neat) 3011, 2925, 2853, 1638, 1468, 1457, 1230, 1112, 753; HRMS (ESI) *m/z* calcd for $C_{19}H_{27}O$ $[M+H]^+$ 271.2062, found 271. 2050.

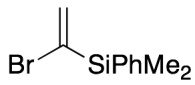


1-(2-Methylallyloxy)-2-(prop-1-enyl)benzene (3.53): To a solution of 2-(prop-1-enyl)phenol (**3.51**) (6:1 *E*:*Z* mixture) (1.40 g, 10.4 mmol) and K_2CO_3 (1.73 g, 12.5 mmol) in DMF (20 mL) at 0 ºC was added 3-bromo-2-methylprop-1-ene (**3.52**) (1.70 g, 12.5 mmol). The reaction was warmed to rt and was stirred for 16 hours. The reaction was quenched with H_2O (20 mL), extracted with diethyl ether (3 x 20 mL), dried over $MgSO_4$, and was concentrated under vacuum. The crude residue was purified using flash chromatography (5% ethyl acetate in hexanes) to yield the diene (6:1 *E*:*Z* mixture) (1.74 g, 89%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42 (dd, *J* = 7.6, 1.2 Hz, 0.83H), 7.29 (d, *J* = 7.2 Hz, 0.17H), 7.21 (t, *J* =

8.0 Hz, 0.17H), 7.16 (td, *J* = 8.4, 1.6 Hz, 0.83H), 6.83-6.96 (m, 2H), 6.78 (dd, *J* = 15.6, 1.2 Hz, 0.83H), 6.61 (d, *J* = 11.6 Hz, 0.17H), 6.25 (dq, *J* = 16.0, 6.8 Hz, 0.83H), 5.84 (dq, *J* = 11.6, 6.8 Hz, 0.17H), 5.12 (s, 1H), 5.01 (s, 0.83H), 4.99 (s, 0.17H), 4.47 (s, 2H), 1.91 (dd, *J* = 6.4, 1.6 Hz, 3H), 1.86 (s, 2.49H), 1.81 (s, 0.51H). *These data are consistent with literature values.*[156]

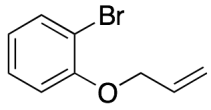


3-Methyl-2*H*-chromene (3.54): To a solution of diene **3.53** (3.12 g, 16.5 mmol) in CH_2Cl_2 (150 mL) was added Hoveyda-Grubbs 2nd generation catalyst (50 mg, 0.080 mmmol). The reaction mixture was heated to 50 ºC and stirred for 2 d. Add more Hoveyda-Grubbs 2nd generation catalyst (50 mg, 0.080 mmmol) and stir for an additional 2 d. The reaction mixture was cooled to rt and concentrated under vacuum. The crude residue was purified using flash chromatography (1% ethyl acetate in hexanes) to yield the benzopryran (1.97 g, 82%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.05 (td, *J* = 7.8, 1.8 Hz, 1H), 6.91 (dd, *J* = 7.2, 1.5 Hz, 1H), 6.84 (t, *J* = 7.2 Hz, 1H), 6.76 (d, *J* = 7.8 Hz, 1H), 6.16 (s, 1H), 4.69 (s, 2H), 1.80 (s, 3H). *These data are consistent with literature values.*[156]

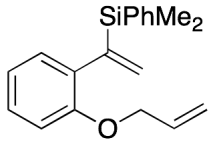


(1-Bromovinyl)dimethyl(phenyl)silane (3.56): To a solution of dimethylphenylvinylsilane (**3.55**) (5.84 g, 36.0 mmol) in $CHCl_3$ (30 mL) at 0 ºC was added Br_2 in $CHCl_3$ (10 mL) via cannulation. After 15 min, the reaction was quenched with a saturated solution of $NaHCO_3$ containing $NaHSO_3$ (50 mL). The mixture was washed with a saturated solution of $NaHCO_3$ containing $NaHSO_3$ (3 x 50 mL), a saturated solution of NaCl (50 mL), dried over $MgSO_4$, and concentrated under vacuum. The crude dibromo compound was dissolved in pyridine (50 mL) and refluxed at 120 ºC for 16 hours. The solution was cooled to rt and diluted with diethyl ether (50 mL) before washing with a saturated solution

of $CuSO_4$ (4 x 50 mL). The organic layer was dried over $MgSO_4$ and concentrated under vacuum. The crude residue was purified using flash chromatography (1% ethyl acetate in hexanes) to yield the vinyl bromide (4.69 g, 54%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.57-7.60 (m, 2H), 7.37-7.43 (m, 3H), 6.36 (d, *J* = 1.8 Hz, 1H), 6.18 (d, *J* = 1.5 Hz, 1H), 0.50 (s, 6H). *These data are consistent with literature values.*[157]

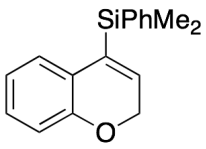


1-(Allyloxy)-2-bromobenzene (3.58): To a solution of 2-bromophenol (**3.57**) (3.00 g, 17.3 mmol) and K_2CO_3 (2.86 g, 20.8 mmol) in DMF (40 mL) at 0 ºC was added allyl bromide (3.15 g, 26.0 mmol). The reaction was allowed to warm to rt and was stirred for 16 hours. The reaction was quenched with H_2O (20 mL), extracted with diethyl ether (3 x 20 mL), dried over $MgSO_4$, and was concentrated under vacuum. The crude residue was purified using flash chromatography (5% ethyl acetate in hexanes) to yield the aryl bromide (3.68 g, 100%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.55 (d, *J* = 8.0 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.85 (t, *J* = 7.6 Hz, 1H), 6.08 (ddt, *J* = 16.0, 10.4, 5.2 Hz, 1H), 5.49 (d, *J* = 17.2 Hz, 1H), 5.32 (d, *J* = 11.2 Hz, 1H) 4.62 (d, *J* = 4.8 Hz, 2H). *These data are consistent with literature values.*[158]



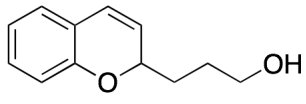
1-(Allyloxy)-2-(1-dimethylphenylsilylvinyl)benzene (3.59): To a solution of aryl bromide **3.58** (3.98 g, 18.6 mmol) in dry, degassed THF (35 mL) at 0 ºC was added magnesium ribbon (0.809 g, 33.3 mmol) and LiCl (0.926 g, 21.8 mmol). After stirring for 3 h, the Grignard reagent was cannulated off the excess magnesium ribbon into a different flask. $FeCl_3$ (0.084 g, 0.520 mmol) was added to a vial under an inert atmosphere in a glove box.

The vial was removed from the glove box and THF (2.0 mL) and TMEDA (0.242 g, 2.08 mmol) were added prior to cannulating the solution into the flask containing the Grignard reagent. Vinyl bromide **3.56** (2.50 g, 10.4 mmol) was added and the flask was stirred for 3 h. Another 1.00 equivalent of Grignard reagent was prepared in the same manner as described above and added to the solution via cannulation. After stirring for 16 hours, the reaction mixture was quenched with a saturated solution of $NaHCO_3$ (50 mL). The solution was extracted with diethyl ether (3 x 50 mL), dried over $MgSO_4$, and concentrated under vacuum. The crude residue was purified using MPLC (2% to 10% toluene in hexanes) to yield the diene (1.00 g, 33%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.52-7.55 (m, 2H), 7.30-7.35 (m, 3H), 7.16 (td, *J* = 8.0, 2.0 Hz, 1H), 7.00 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.89 (td, *J* = 7.5, 1.0 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 5.89 (d, *J* = 3.0 Hz, 1H), 5.86 (ddt, *J* = 17.0, 10.5, 5.0 Hz, 1H), 5.67 (d, *J* = 3.0 Hz, 1H), 5.28 (dq, *J* = 17.0, 1.5 Hz, 1H), 5.20 (dq, *J* = 10.5, 1.5 Hz, 1H), 4.34 (dt, *J* = 5.0, 1.5 Hz, 2H), 0.36 (s, 6H).

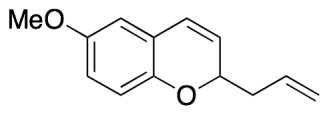


4-(Dimethylphenylsilyl)-2*H*-chromene (3.60): To a solution of diene **3.59** (107 mg, 0.363 mmol) in CH_2Cl_2 (5.0 mL) was added Hoveyda-Grubbs 2nd generation catalyst (2.3 mg, 0.004 mmmol). The reaction mixture was heated to 50 ºC and stirred for 6 h. The reaction mixture was cooled to rt and concentrated under vacuum. The crude residue was purified using flash chromatography (2% to 5% ethyl acetate in hexanes) to yield the benzopryran (69 mg, 72%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.56-7.59 (m, 2H), 7.35-7.38 (m, 3H), 7.07 (td, *J* = 7.6, 1.2 Hz, 1H), 7.01 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.82 (dd, *J* = 8.0, 0.8 Hz, 1H), 6.76 (td, *J* = 7.6, 0.8 Hz, 1H), 6.15 (t, *J* = 4.0 Hz, 1H), 4.73 (d, *J* = 3.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.6, 137.8, 134.0, 134.0, 133.7, 129.2, 128.6, 127.9, 127.5, 124.8, 121.1, 116.2, 65.2, –2.1; IR (neat) 3067, 2957, 2919, 1704, 1602, 1484, 1427,

1252, 1220, 1115, 1013, 912, 815, 777, 702; HRMS (ESI) *m/z* calcd for $C_{17}H_{17}OSi$ $[M–H]^+$ 265.1049, found 265.1049.

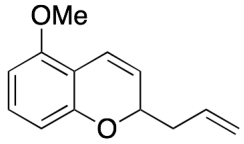


3-(2*H*-Chromen-2-yl)propan-1-ol (3.62): To a solution of terminal alkene **3.10** (130 mg, 0.75 mg) in THF (2.0 mL) was added 9-BBN dimer (124 mg, 0.52 mmol). After stirring for 1 h the reaction was cooled to 0 ºC. A solution of 2.0 M aqueous NaOH (0.75 mL) and 30% aqueous H_2O_2 (0.75 mL) was added and the reaction was warmed to rt. After 30 min, the mixture was extracted with CH_2Cl_2 (3 x 10 mL), dried over MgSO4, and concentrated under vacuum. The crude residue was purified using flash chromatography (2% to 25% ethyl acetate in hexanes) to yield the primary alcohol (92.0 mg, 65%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.11 (td, *J* = 7.6, 1.6 Hz, 1H), 6.97 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.85 (t, *J* = 7.6 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.41 (d, *J* = 10.0 Hz, 1H), 5.68 (dd, *J* = 9.6 3.2 Hz, 1H), 4.91-4.93 (m, 1H), 3.72 (t, *J* = 6.0 Hz, 2H), 1.76-2.06 (m, 4H); ^{3}C NMR ($CDCl_3$, 100 MHz) δ 153.1, 129.1, 126.4, 125.6, 124.0, 121.8, 121.0, 115.8, 74.9, 62.4, 31.6, 28.1; IR (neat) 3375, 3042, 2919, 1637, 1604, 1485, 1271, 1205, 1038, 932, 753; HRMS (ESI) *m/z* calcd for $C_{12}H_{14}O_2$ $[M]^+$ 190.0994, found 190.0975.

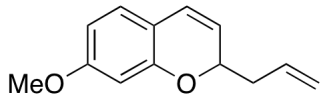


2-Allyl-6-methoxy-2*H*-chromene (3.55): The general procedure for the oxidative coupling was followed using benzopyran **3.46**[119] (162 mg, 1.00 mmol), $LiClO_4$ (160 mg, 1.50 mmol), 4 Å MS (250 mg), DDQ (295 mg, 1.30 mmol), and acetonitrile (10 mL). After 30 min the oxidation was complete and allyl trimethylsilane (**3.10**) (229 mg, 2.00 mmol) was added. The reaction was complete after 30 min and was purified using flash chromatography (1% to 10% ethyl acetate in hexanes) to yield the substituted

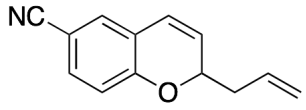
benzopyran (129 mg, 64%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.73 (d, *J* = 8.8 Hz, 1H), 6.67 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.55 (d, *J* = 2.8 Hz, 1H), 6.39 (d, *J* = 10.0 Hz, 1H), 5.90 (ddt, *J* = 17.2, 10.4, 7.2, 1H), 5.75 (dd, *J* = 9.6, 3.2 Hz, 1H), 5.15 (d, *J* = 8.8 Hz, 1H), 5.12 (s, 1H), 4.85 (m, 1H), 3.76 (s, 3H), 2.54-2.61 (m, 1H), 2.41-2.48 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.9, 147.1, 133.4, 126.1, 124.3, 122.5, 117.8, 116.5, 114.2, 111.6, 74.3, 55.6, 39.4; IR (neat) 3075, 2936, 2832, 1577, 1491, 1432, 1268, 1045, 920, 708; HRMS (ESI) *m/z* calcd for $C_{13}H_{15}O_2$ $[M+H]^+$ 203.1072, found 203.1069.



2-Allyl-5-methoxy-2*H*-chromene (3.56): The general procedure for the oxidative coupling was followed using benzopyran **3.47** (140 mg, 0.863 mmol), $LiClO_4$ (138 mg, 1.29 mmol), 4 Å MS (200 mg), DDQ (252 mg, 1.11 mmol), and acetonitrile (8.6 mL). After 30 min the oxidation was complete and allyl trimethylsilane (**3.10**) (197 mg, 1.72 mmol) was added. The reaction was complete after 30 min and was purified using flash chromatography (1% to 10% ethyl acetate in hexanes) to yield the substituted benzopyran (79.8 mg, 46%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.06 (t, *J* = 8.5 Hz, 1H), 6.76 (d, *J* = 10.0 Hz, 1H), 6.46 (d, *J* = 8.5 Hz, 1H), 6.43 (d, *J* = 8.0 Hz, 1H), 5.91 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H), 5.66 (dd, *J* = 10.0, 3.0 Hz, 1H), 5.15 (d, *J* = 17.0 Hz, 1H), 5.13 (d, *J* = 9.5 Hz, 1H), 4.85-4.87 (m, 1H), 3.83 (s, 3H), 2.56-2.61 (m, 1H), 2.43-2.48 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.2, 154.1, 133.4, 129.0, 123.2, 118.9, 117.8, 111.3, 109.1, 103.3, 74.1, 55.6, 39.5; IR (neat) 3074, 2934, 1634, 1580, 1310, 1101, 917, 749; HRMS (ESI) *m/z* calcd $C_{13}H_{13}O_2$ $[M–H]^+$ 201.0916, found 201. 0918.

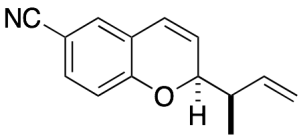


2-Allyl-7-methoxy-2*H*-chromene (3.57): The general procedure for the oxidative coupling was followed using benzopyran **3.48** (78.0 mg, 0.481 mmol), $LiClO_4$ (76.7 mg, 0.721 mmol), 4 Å MS (100 mg), DDQ (142 mg, 0.625 mmol), and acetonitrile (4.8 mL). After 30 min the oxidation was complete and allyl trimethylsilane (**3.10**) (110 mg, 0.962 mmol) was added. The reaction was at completion after 30 min and was purified using flash chromatography (1% to 10% ethyl acetate in hexanes) to yield the substituted benzopyran (26.2 mg, 27%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.88 (d, *J* = 8.5 Hz, 1H), 6.42 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.39 (s, 1H), 6.38 (dd, *J* = 8.5, 1.5 Hz, 1H), 5.91 (ddt, *J* = 17.5, 10.5, 7.0 Hz, 1H), 5.57 (dd, *J* = 9.5, 3.0 Hz, 1H), 5.15-5.18 (m, 1H), 5.12-5.15 (m, 1H), 4.88-4.92 (m, 1H), 3.78 (s, 3H), 2.55-2.61 (m, 1H), 2.43-2.49 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.6, 154.6, 133.4, 127.1, 123.8, 122.1, 117.9, 115.2, 106.8, 101.8, 74.7, 55.3, 39.8; IR (neat) 3075, 2934, 2836, 1615, 1504, 1274, 1156, 1032, 809; HRMS (ESI) *m/z* calcd for $C_{13}H_{15}O_2$ $[M+H]^+$ 203.1072, found 203.1052.

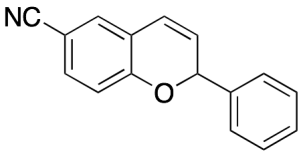


2-Allyl-2*H*-chromene-6-carbonitrile (3.58): To a solution of benzopyran **3.49**[119] (31 mg, 0.20 mmol) in freshly distilled acetonitrile (2.0 mL) at rt was added $LiClO_4$ (32 mg, 0.30 mmol) and 4 Å MS (50.0 mg). After 5 min, DDQ (59 mg, 0.260 mmol) was added the reaction was warmed to 75 °C for 2 h. The reaction was cooled to rt and allyl trimethylsilane (**3.10**) (46 mg, 0.40 mmol) was added and the reaction was stirred for 15 min. The solution was quenched with 10% aqueous $NaHCO_3$ solution (5 mL). The reaction mixture was extracted with diethyl ether (3 x 5 mL), dried over $MgSO_4$, and concentrated under vacuum. The crude residue was purified using flash chromatography (3% to 12% ethyl acetate in hexanes) to yield the substituted benzopyran (36 mg, 92%): ^{1}H NMR

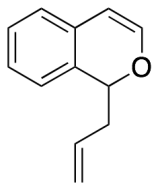
($CDCl_3$, 400 MHz) δ 7.38 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.23 (d, *J* = 1.2 Hz, 1H), 6.81 (d, *J* = 8.4 Hz, 1H), 6.38 (d, *J* = 10.0 Hz, 1H), 5.87 (ddt, *J* = 17.6, 10.8, 7.2 Hz, 1H), 5.78 (dd, *J* = 10.0, 3.2 Hz, 1H), 5.17 (d, *J* = 6.4 Hz, 1H), 5.14 (s, 1H), 5.06 (m, 1H), 2.47-2.61 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.1, 133.4, 132.3, 130.2, 126.6, 122.5, 122.2, 119.1, 118.7, 116.8, 104.1, 75.4, 40.1; IR (neat) 3078, 2926, 2225, 1640, 1488, 1251, 1130, 1021, 830, 715; HRMS (ESI) *m/z* calcd for $C_{13}H_{12}NO$ $[M+H]^+$ 198.0919, found 198.0917.



(±)-(*S*)-2-((*R*)-But-3-en-2-yl)-2*H*-chromene-6-carbonitrile (3.59): To a solution of benzopyran **3.49**[119] (314 mg, 2.00 mmol) in freshly distilled acetonitrile (20 mL) at rt was added $LiClO_4$ (319 mg, 3.00 mmol) and 4 Å MS (500 mg). After 5 min, DDQ (590 mg, 2.60 mmol) was added the reaction was warmed to 80 °C for 2 h. The reaction was cooled to rt and (*E*)-crotyl trimethylsilane (**3.20**) (513 mg, 4.00 mmol) was added and the reaction was stirred for 16 h. The solution was quenched with 10% aqueous $NaHCO_3$ solution (20 mL). The reaction mixture was extracted with diethyl ether (3 x 20 mL), dried over $MgSO_4$, and concentrated under vacuum. The crude residue was purified using flash chromatography (2% to 15% ethyl acetate in hexanes) to yield the substituted benzopyran (312 mg, 74%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.21 (d, *J* = 1.6 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.40 (d, *J* = 10.0 Hz, 1H), 5.78-5.87 (m, 1H), 5.73 (dd, *J* = 10.4, 3.2 Hz, 1H), 5.13 (d, *J* = 0.8 Hz, 1H), 5.09 (d, *J* = 7.2 Hz, 1H), 4.95-4.98 (m, 1H), 2.62 (sex, *J* = 6.8 Hz, 1H), 1.14 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.4, 137.8, 133.3, 129.9, 125.0, 122.9, 122.0, 118.9, 116.3, 116.1, 103.7, 79.3, 43.0, 14.2; IR (neat) 2971, 2868, 2224, 1640, 1573, 1488, 1251, 1232, 1012, 920; HRMS (ESI) *m/z* calcd for $C_{14}H_{14}NO$ $[M+H]^+$ 212.1075, found 212.1077.

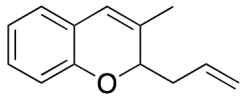


2-Phenyl-2*H*-chromene-6-carbonitrile (3.60): To a solution of benzopyran **3.49**[119] (157 mg, 1.00 mmol) in freshly distilled acetonitrile (10 mL) at rt was added $LiClO_4$ (160 mg, 1.50 mmol) and 4 Å MS (250 mg). After 5 min, DDQ (295 mg, 1.30 mmol) was added the reaction was warmed to 70 °C for 2 h. The reaction was cooled to rt and trifluoroborate **3.29** (368 mg, 2.00 mmol) was added and the reaction was warmed to 70 °C for 16 h. The solution was cooled to rt and quenched with 10% aqueous $NaHCO_3$ solution (10 mL). The reaction mixture was extracted with diethyl ether (3 x 10 mL), dried over $MgSO_4$, and concentrated under vacuum. The crude residue was purified using flash chromatography (2% to 10% ethyl acetate in hexanes) to yield the substituted benzopyran (104 mg, 45%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36-7.41 (m, 6H), 7.30 (s, 1H), 6.81 (d, *J* = 8.4 Hz, 1H), 6.53 (d, *J* = 10.0 Hz, 1H), 6.03 (m, 1H), 5.90 (dd, *J* = 10.0, 3.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.6, 139.6, 133.6, 130.2, 128.8, 128.8, 126.9, 126.2, 122.1, 121.6, 119.0, 116.8, 104.2, 77.9; IR (neat) 3061, 3032, 2221, 1649, 1602, 1488, 1251, 1128, 1026, 849, 718; HRMS (ESI) *m/z* calcd for $C_{16}H_{12}NO$ $[M+H]^+$ 234.0919, found 234.0927.

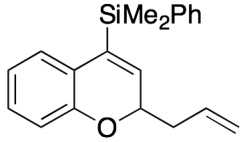


1-Allyl-1*H*-isochromene (3.61): To a solution of benzopyran **3.50**[131] (132 mg, 1.00 mmol) in freshly distilled CH_2Cl_2 (10 mL) at –35 °C was added $LiClO_4$ (160 mg, 1.50 mmol) and 4 Å MS (250 mg). After 5 min, DDQ (295 mg, 1.30 mmol) was added the reaction was warmed to –30 °C over 10 min. Allyl tributyltin (**3.54**) (662 mg, 2.00 mmol) was added and the reaction was warmed to rt over 30 min. The solution was quenched with 10% aqueous $NaHCO_3$ solution (5 mL). The reaction mixture was extracted with CH_2Cl_2 (3 x 5 mL), dried over $MgSO_4$, and concentrated under vacuum. The crude residue was

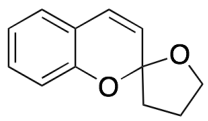
purified using flash chromatography (1% ethyl acetate in hexanes) to yield the substituted benzopyran (135 mg, 79%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.23 (td, *J* = 7.6, 1.2 Hz, 1H), 7.17 (td, *J* = 7.6, 1.2 Hz, 1H), 7.00 (d, *J* = 4.0 Hz, 1H), 6.98 (d, *J* = 3.6 Hz, 1H), 6.52 (d, *J* = 5.6 Hz, 1H), 5.93 (ddt, *J* = 17.2, 10.4, 6.8 Hz, 1H), 5.78 (d, *J* = 6.0 Hz, 1H), 5.16-5.21 (m, 2H), 5.14 (s, 1H), 2.79-2.86 (m, 1H), 2.51-2.57 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.1, 134.1, 130.7, 129.5, 127.9, 126.4, 124.2, 123.3, 117.6, 104.5, 76.9, 38.5; IR (neat) 3069, 2937, 2829, 1626, 1488, 1452, 1226, 1051, 917, 769; HRMS (EI) *m/z* calcd for $C_{12}H_{12}O$ $[M]^+$ 172.0888, found 172.0920.



2-Allyl-3-methyl-2*H*-chromene (2.62): The general procedure for the oxidative coupling was followed using benzopyran **3.51** (175 mg, 1.20 mmol), $LiClO_4$ (191 mg, 1.80 mmol), 4 Å MS (300 mg), DDQ (354 mg, 1.56 mmol), and acetonitrile (12 mL). After 30 min the oxidation was complete and allyl trimethylsilane (**3.10**) (274 mg, 2.40 mmol) was added. The reaction was complete after 30 min and was purified using flash chromatography (1% to 5% ethyl acetate in hexanes) to yield the substituted benzopyran (134 mg, 60%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.06 (td, *J* = 7.6, 1.6 Hz, 1H), 6.91 (dd, *J* = 7.2, 1.6 Hz, 1H), 6.84 (td, *J* = 7.2, 1.2 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.18 (s, 1H), 5.88-5.98 (m, 1H), 5.11-5.13 (m, 1H), 5.08 (t, *J* = 1.2 Hz, 1H), 4.71 (dd, *J* = 8.4, 3.6 Hz, 1H), 2.46-2.54 (m, 1H), 2.33-2.41 (m, 1H), 1.85 (d, *J* = 0.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.3, 134.0, 133.6, 128.2, 125.5, 122.6, 121.0, 119.6, 117.5, 115.9, 78.2, 37.2, 19.7; IR (neat) 3074, 2913, 1640, 1578, 1442, 1240, 1104, 916, 752; HRMS (ESI) *m/z* calcd for $C_{13}H_{13}O$ $[M–H]^+$ 185.0966, found 185.0962.

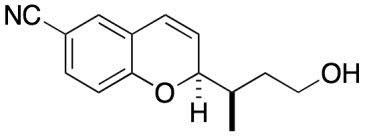


2-Allyl-4-(dimethylphenylsilyl)-2*H*-chromene (3.63): The general procedure for the oxidative coupling was followed using benzopyran **3.52** (266 mg, 1.00 mmol), $LiClO_4$ (160 mg, 1.50 mmol), 4 Å MS (250 mg), DDQ (295 mg, 1.30 mmol), and acetonitrile (10 mL). After 2 h the oxidation was complete and allyl trimethylsilane (**3.10**) (229 mg, 2.00 mmol) was added. The reaction was complete after 1 h and was purified using flash chromatography (1% to 5% ethyl acetate in hexanes) to yield the substituted benzopyran (216 mg, 71%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.55-7.58 (m, 2H), 7.34-7.41 (m, 3H), 7.06 (td, *J* = 8.0, 1.6 Hz, 1H), 7.00 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.82 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.74 (td, *J* = 7.2, 1.2 Hz, 1H), 6.05 (d, *J* = 3.6 Hz, 1H), 5.86-5.96 (m, 1H), 5.15-5.17 (m, 1H), 5.12 (t, *J* = 1.2 Hz, 1H), 4.80 (ddd, *J* = 6.8, 5.6, 3.2 Hz, 1H), 2.56-2.63 (m, 1H), 2.43-2.50 (m, 1H), 0.50 (s, 3H), 0.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 152.7, 137.8, 137.1, 134.0, 133.5, 133.0, 129.2, 128.6, 127.8, 127.4, 124.3, 120.9, 117.9, 116.6, 73.8, 39.0, –2.1, –2.1; IR (neat) 3068, 2956, 1641, 1595, 1482, 1450,1227, 1114, 814; HRMS (ESI) *m/z* calcd for $C_{20}H_{21}OSi$ $[M–H]^+$ 305.1362, found 305.1364.

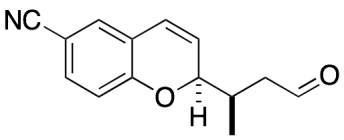


4',5'-Dihydro-3'*H*-spiro[chromene-2,2'-furan] (3.64): To a solution of benzopyran **3.53** (85 mg, 0.45 mmol) in freshly distilled acetonitrile (4.4 mL) at 0 °C was added $LiClO_4$ (71 mg, 0.67 mmol) and 4 Å MS (100 mg). After 5 min, DDQ (130 mg, 0.581 mmol) was added to the reaction mixture and it was stirred for 15 min before being quenched with 10% aqueous $NaHCO_3$ solution (5 mL). The reaction mixture was extracted with diethyl ether (3 x 5 mL), dried over $MgSO_4$, and concentrated under vacuum. The crude residue was purified using flash chromatography (5% to 10% ethyl acetate in hexanes) to yield the substituted benzopyran (77 mg, 93%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.19 (td, *J* = 7.5, 1.5 Hz,

1H), 7.14 (d, *J* = 7.2 Hz, 1H), 6.93 (t, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 7.8 Hz, 1H), 6.72 (d, *J* = 9.6 Hz, 1H), 5.76 (d, *J* = 9.6 Hz, 1H), 4.12-4.19 (m, 1H), 3.98 (q, *J* = 7.5 Hz, 1H), 2.32-2.44 (m, 2H), 1.96-2.14 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.7, 129.1, 126.8, 126.8, 122.5, 121.1, 120.3, 116.4, 105.2, 68.2, 39.1, 24.5; IR (neat) 3047, 2955, 1624, 1571, 1254, 1065, 1016, 988, 756; HRMS (EI) *m/z* calcd for $C_{12}H_{12}O_2$ $[M]^+$ 188.0837, found 188.0874.

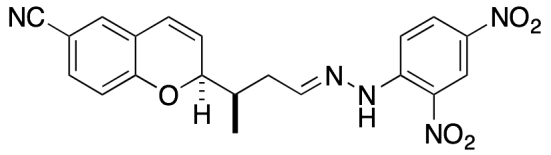


(±)-(*R*)-2-((*R*)-4-hydroxybutan-2-yl)-2*H*-chromene-6-carbonitrile (3.74): To a solution of terminal alkene **3.59** (312 mg, 1.48 mg) in THF (2.0 mL) was added 9-BBN dimer (285 mg, 1.03 mmol). After stirring for 1 h the reaction was cooled to 0 ºC. A solution of 3.0 M aqueous NaOH (1.5 mL) and 30% aqueous H_2O_2 (1.5 mL) was added and the reaction was warmed to rt. After 30 min, the mixture was extracted with CH_2Cl_2 (3 x 10 mL), dried over MgSO4, and concentrated under vacuum. The crude residue was purified using flash chromatography (2% to 25% ethyl acetate in hexanes) to yield the primary alcohol (242 mg, 72%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.21 (d, *J* = 2.0 Hz, 1H), 6.79 (d, *J* = 8.5 Hz, 1H), 6.42 (dd, *J* = 10.0, 2.0 Hz, 1H), 5.76 (dd, *J* = 10.0, 3.0 Hz, 1H), 4.94-4.96 (m, 1H), 3.75-3.79 (m, 1H), 3.68-3.73 (m, 1H), 2.04-2.09 (m, 1H), 1.88-1.92 (m, 1H), 1.45-1.51 (m, 1H), 1.06 (d, *J* = 7.0 Hz, 3H).



(±)-(*R*)-2-((*R*)-4-oxobutan-2-yl)-2*H*-chromene-6-carbonitrile (3.75): To a mixture of alcohol **3.74** (125 mg, 0.550 mmol) and $NaHCO_3$ (92.4 mg, 1.10 mmol) in CH_2Cl_2 (5.5 mL) was added Dess–Martin periodinane (350 mg, 0.825 mmol). After 1 h, the reaction was quenched with H_2O (5 mL), extracted with CH_2Cl_2 (3 x 5 mL), dried over $MgSO_4$, and concentrated under vacuum. The crude residue was purified

using flash chromatography (10% to 20% ethyl acetate in hexanes) to yield the aldehyde (85.7 mg, 69%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.79 (s, 1H), 7.39 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.24 (d, *J* = 1.6 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.44 (d, *J* = 10.4 Hz, 1H), 5.76 (dd, *J* = 10.0, 3.2 Hz, 1H), 4.88-4.89 (m, 1H), 2.74 (dd, *J* = 16.8, 3.6 Hz, 1H), 2.52 (quin, *J* = 6.4 Hz, 1H), 2.38 (ddd, *J* = 16.8, 8.0, 1.6 Hz, 1H), 1.11 (d, *J* = 6.8 Hz, 1H).

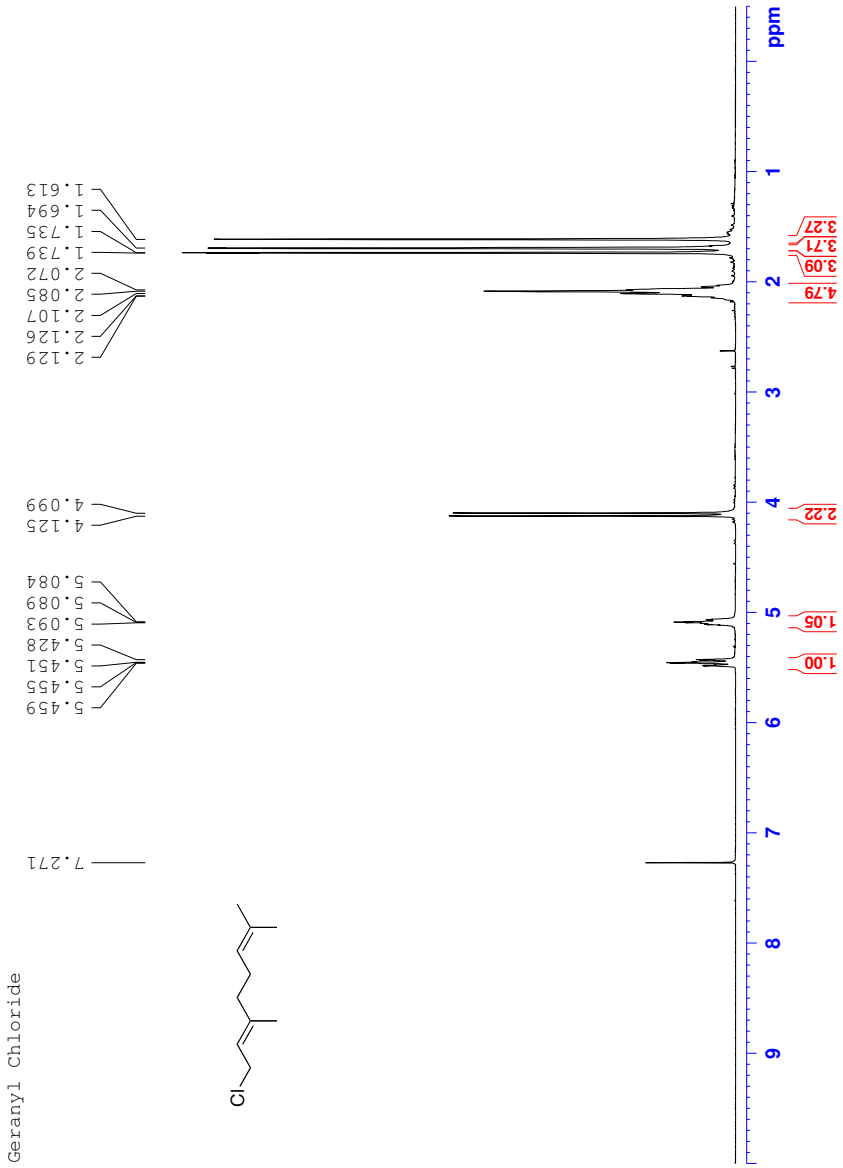


(±)-(*R*)-2-((*R*,*E*)-4-(2-(2,4-dinitrophenyl)hydrazono)butan-2-yl)-2*H*-chromene-6-carbonitrile (3.77): To a solution of aldehyde **3.75** (85.7 mg, 0.377 mmol) and 2,4-dinitrophenylhydrazine (107 mg, 0.377 mmol) in ethanol (3.0 mL) was added one drop of acetic acid. The resulting mixture was refluxed for 2 h and cooled back to rt. The resulting solid was collected via vacuum filtration. The crude solid was purified using flash chromatography (0.5% triethylamine, 10% to 40% ethyl acetate in hexanes) to yield pure hydrazine (*E/Z* Olefin Isomers 8:1). The solid was recrystallized using the 2-layer method with diethyl ether and hexanes. The crystals were characterized using X-ray diffraction. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.19 (s, 0.11H), 11.06 (s, 0.89H), 9.16 (m, 0.11H), 9.15 (d, *J* = 2.4 Hz, 0.89H), 8.36 (dd, *J* = 9.6, 2.0 Hz, 0.11H), 8.32 (dd, *J* = 9.6, 2.4 Hz, 0.89H), 7.96 (d, *J* = 9.6 Hz, 0.11H), 7.89 (d, *J* = 9.6 Hz), 7.56 (t, *J* = 5.6 Hz, 1H), 7.42 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.23 (d, *J* = 1.6 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 0.11H), 6.81 (d, *J* = 8.8 Hz, 0.89H), 6.52 (m, 0.11H) 6.49 (d, *J* = 10.0 Hz, 0.89H), 5.84 (m, 0.11H), 5.75 (dd, *J* = 9.6, 2.4 Hz, 0.89H), 4.95 (m, 0.89H), 4.92 (m, 0.11H), 2.67-2.79 (m, 1H), 2.36-2.44 (m, 1H), 2.26-2.32 (m, 1H), 1.18 (d, *J* = 6.8 Hz, 2.67H), 1.14 (d, *J* = 7.2 Hz, 0.33H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.1, 156.8, 150.6, 148.8, 145.1, 144.9, 138.3, 137.8, 133.7, 133.6, 130.3, 130.0, 129.9, 129.5, 128.7, 128.2,

125.0, 124.7, 123.7, 123.4, 123.3, 123.2, 121.9, 121.8, 118.8, 116.7, 116.5, 116.4, 104.4, 104.2, 79.6, 79.4, 37.2, 34.6, 15.9, 15.5; mp 138-141 °C.

APPENDIX C

LACTODEHYDROTHYSIFEROL (^{1}H-NMR AND ^{13}C-NMR FOR OPTIMIZED ROUTE)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2.072
1.739
1.735
1.694
1.613
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3.09
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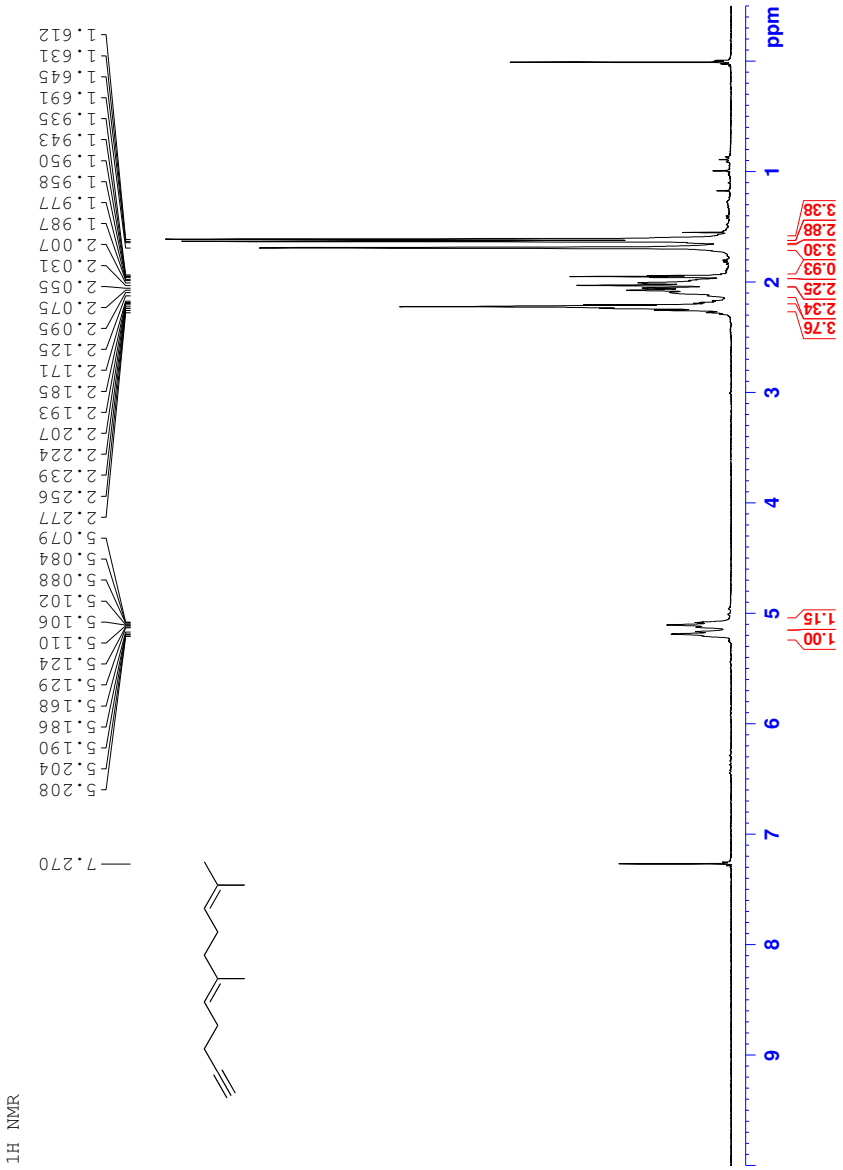
1.00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5.084
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2.239
2.224
2.207
2.193
2.185
2.171
2.125
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2.075
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1.977
1.958
1.950
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1.691
1.645
1.631
1.612
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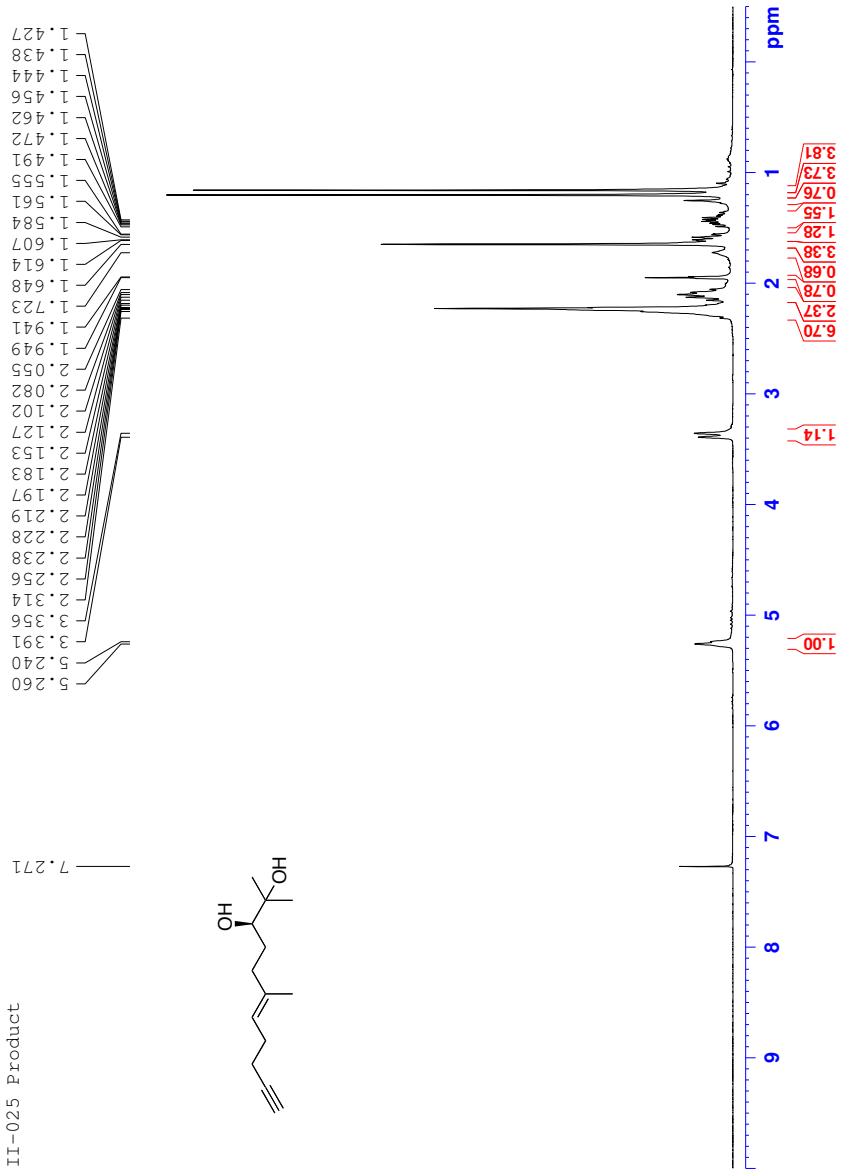
3.38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2.153
2.127
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2.082
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1.941
1.723
1.648
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1.561
1.555
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1.472
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1.456
1.444
1.438
1.427
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OH
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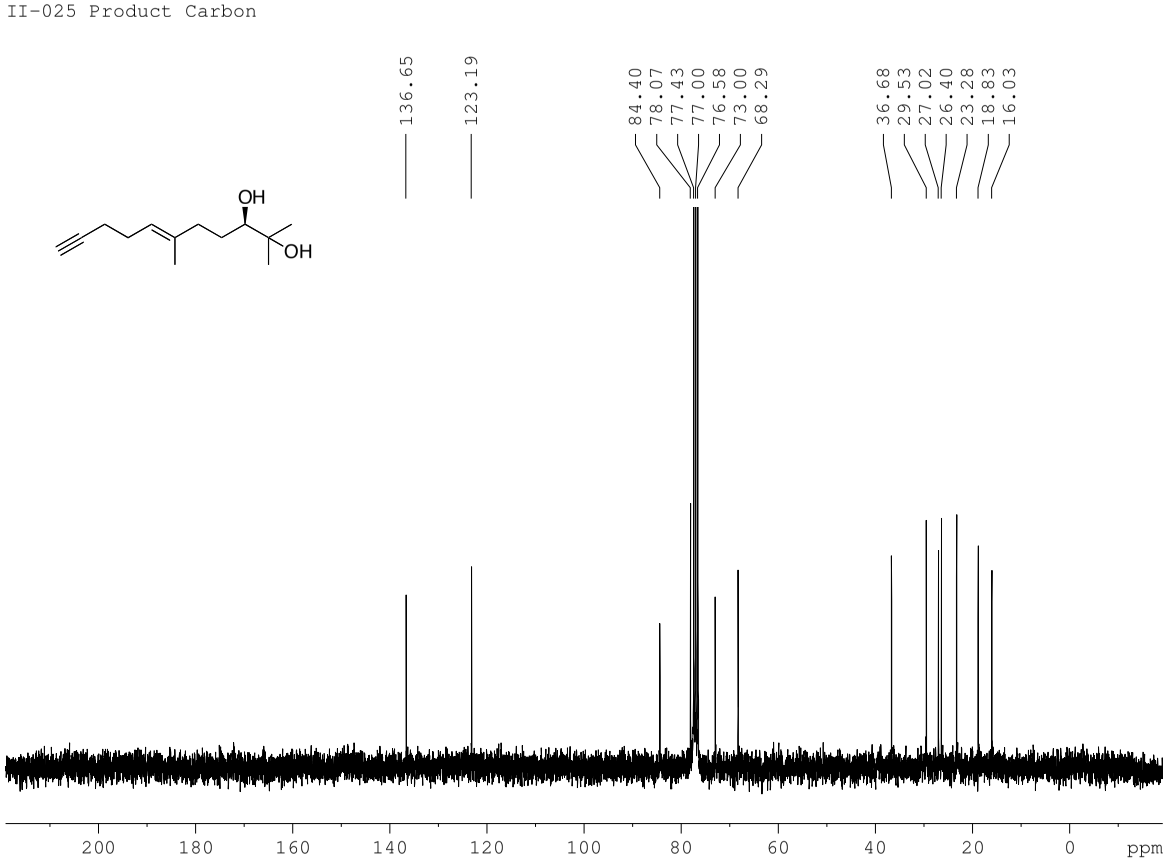
3.81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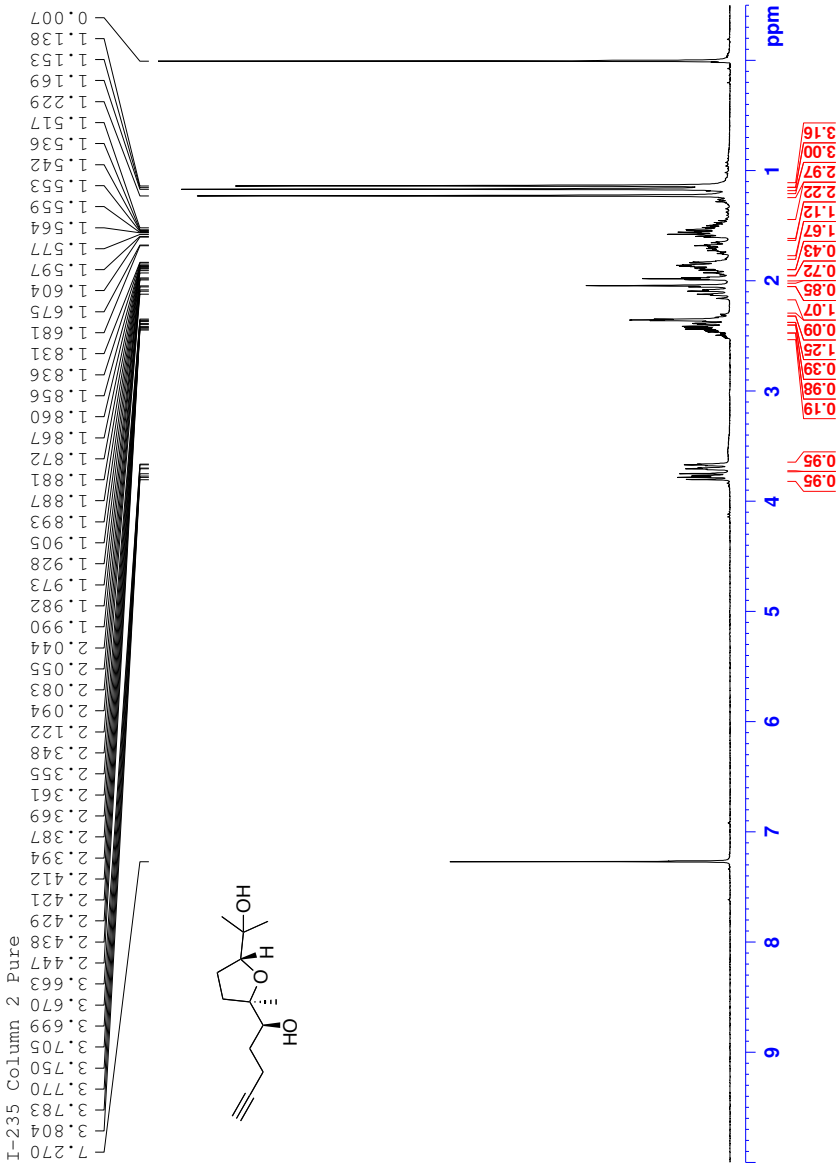
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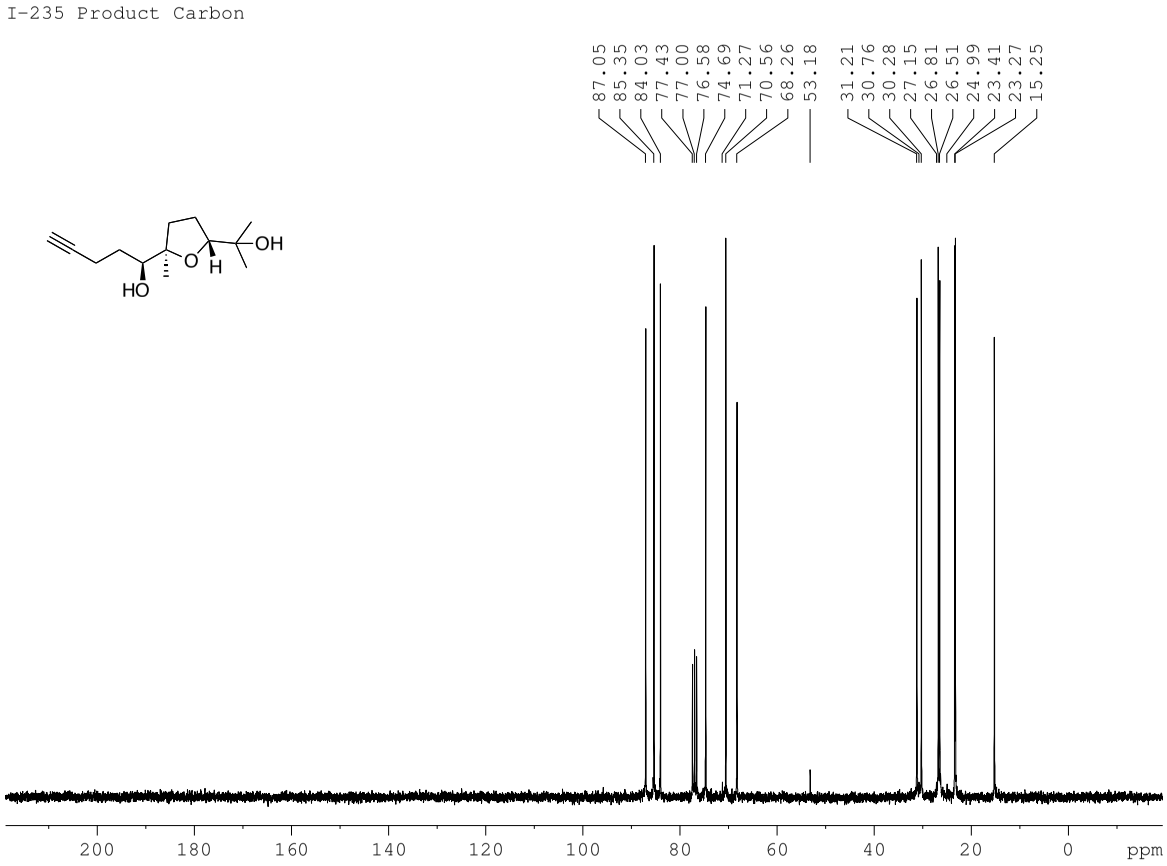
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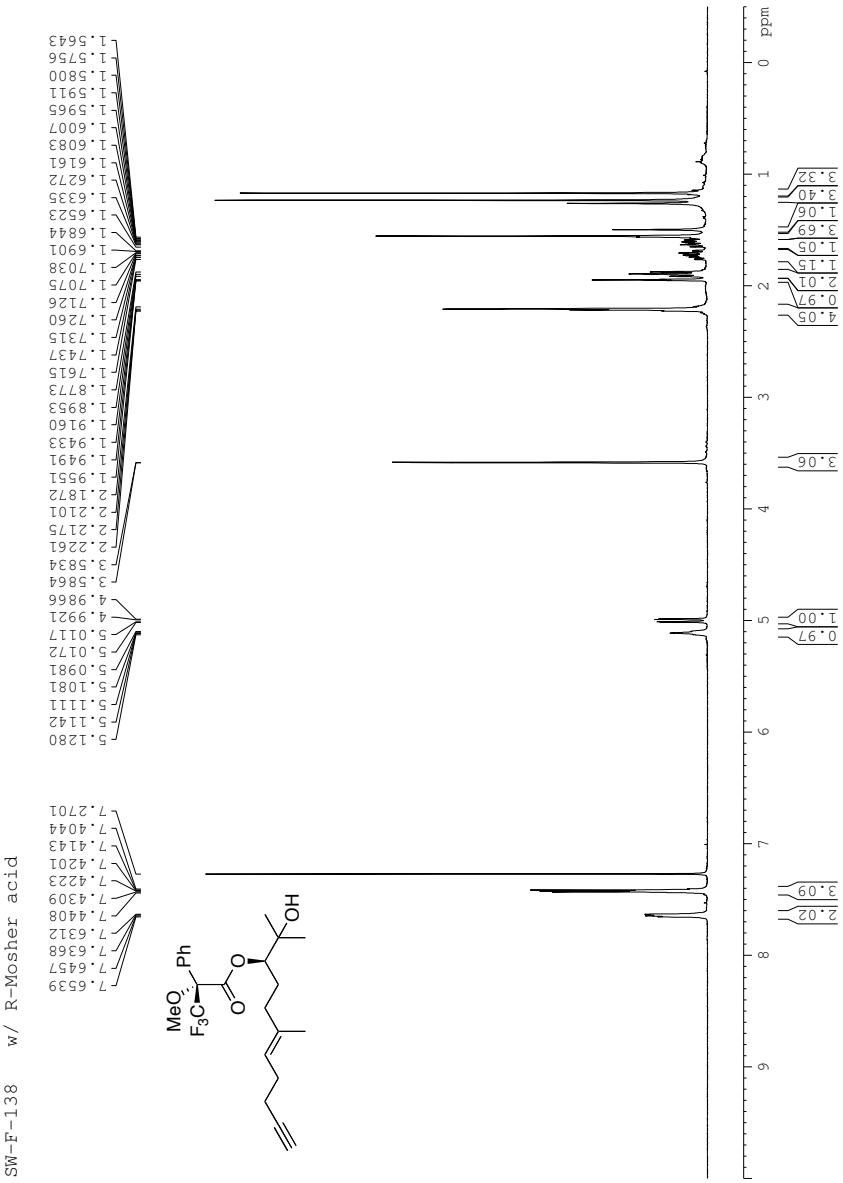
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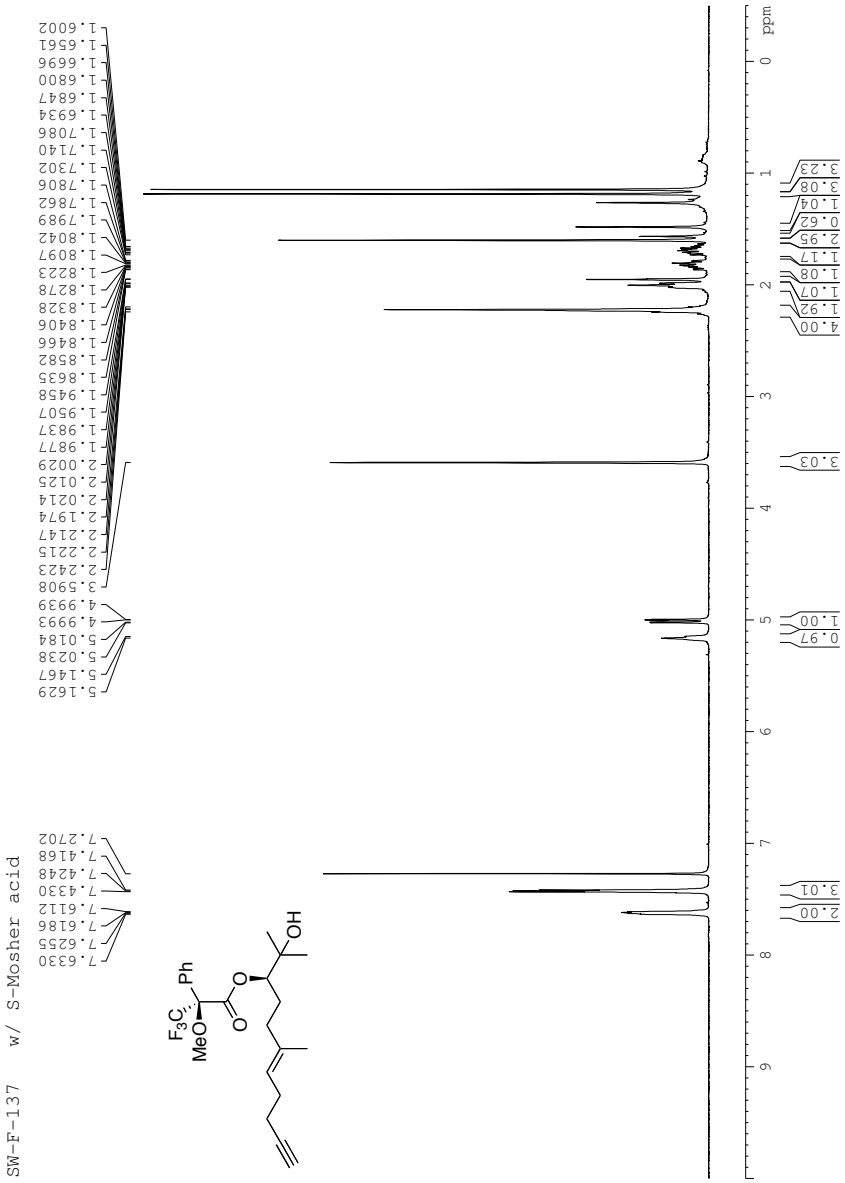
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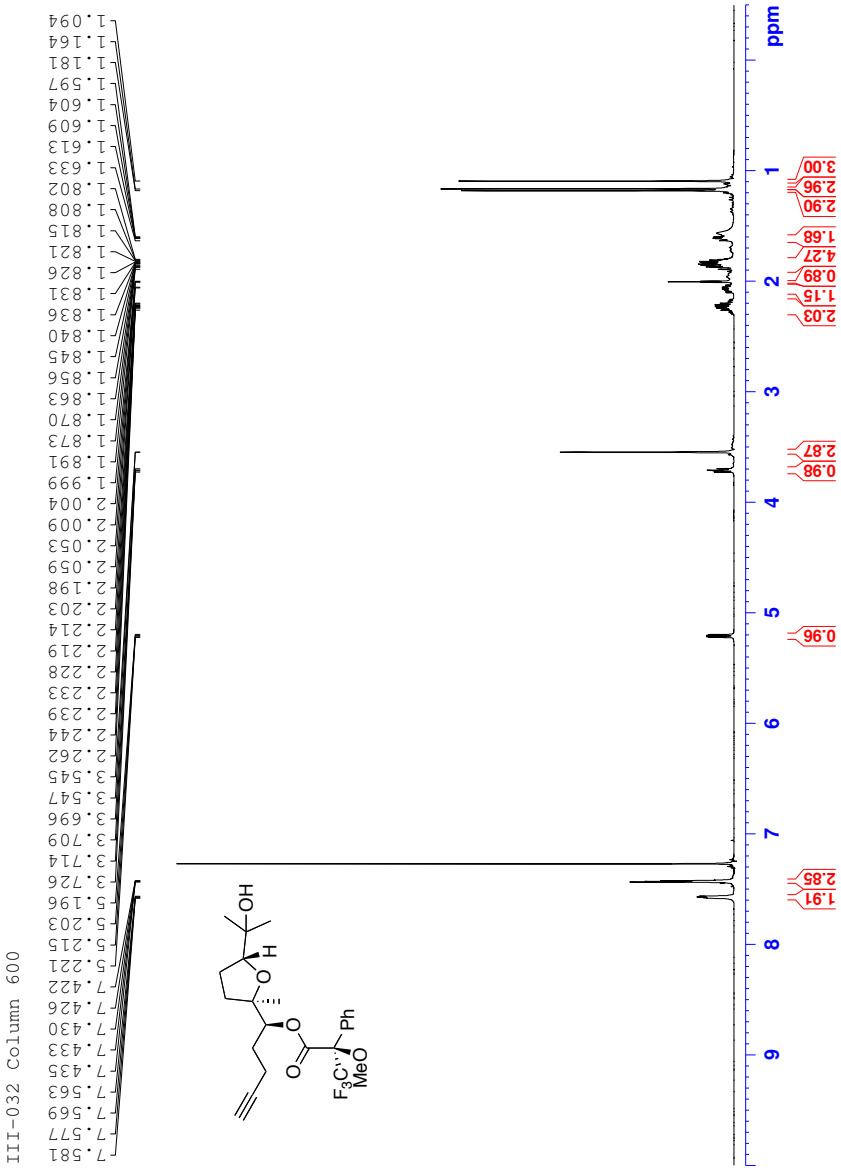
3.23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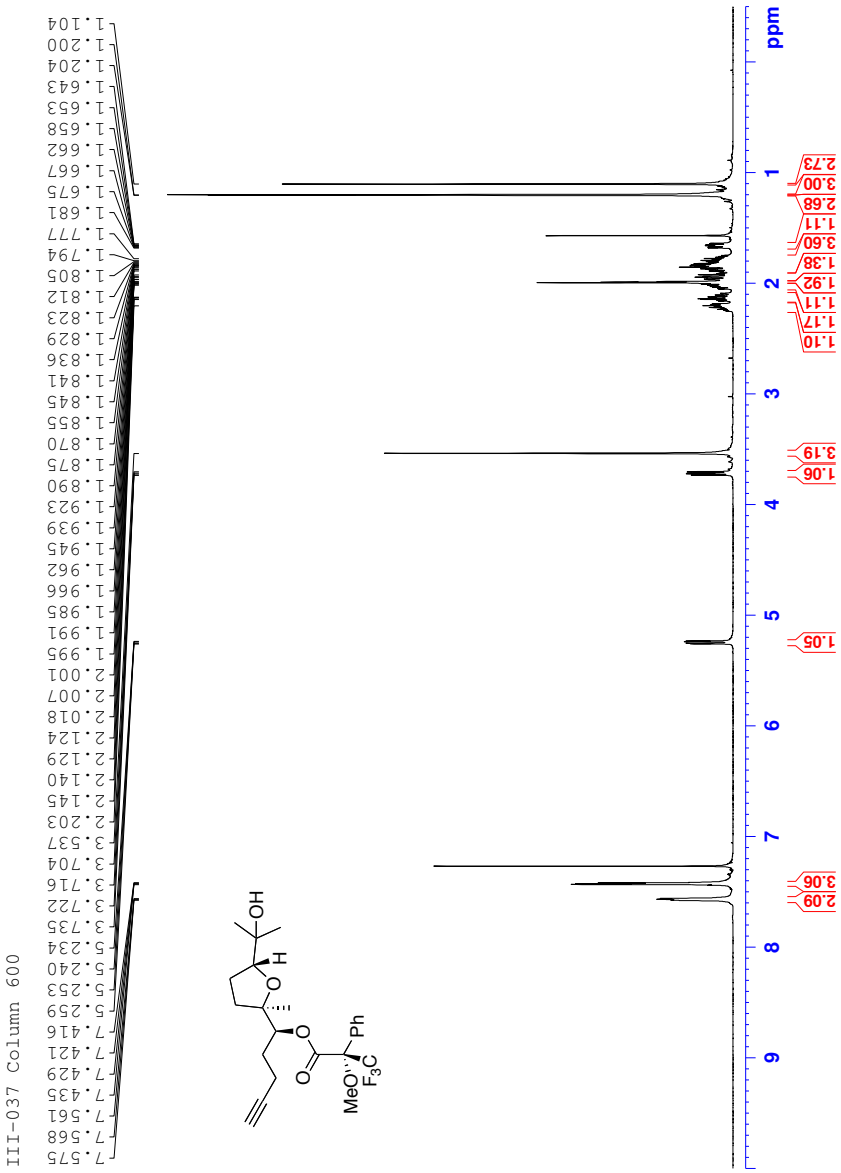
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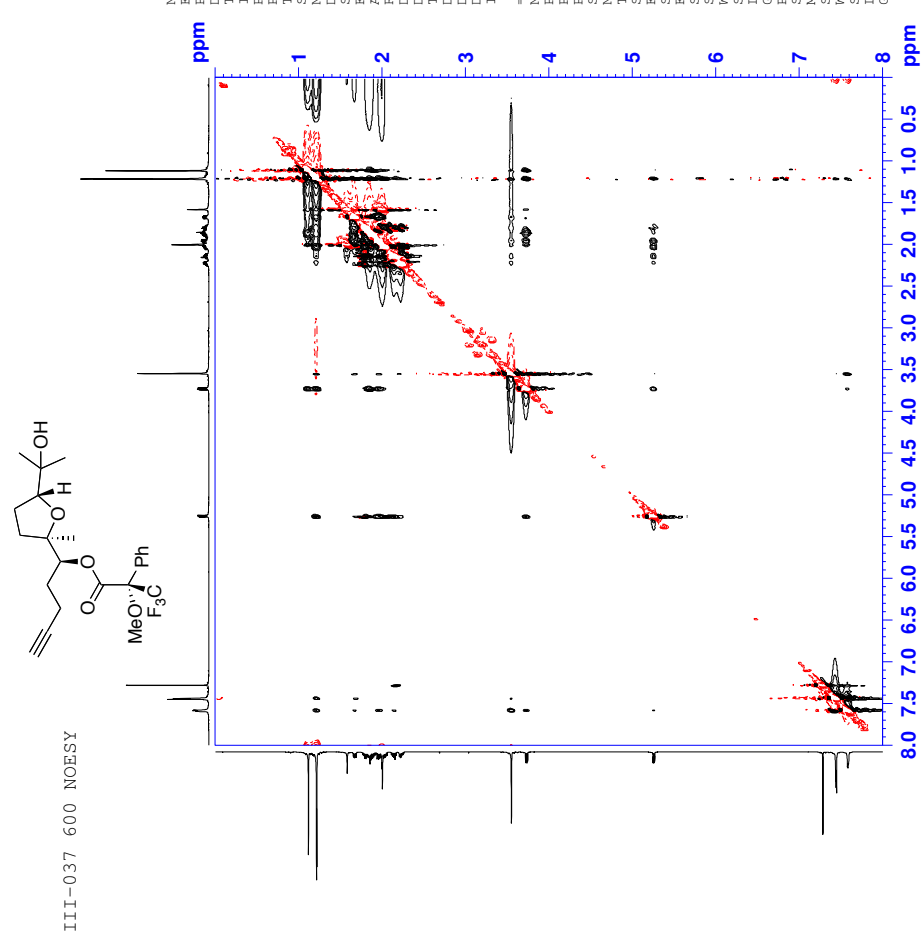
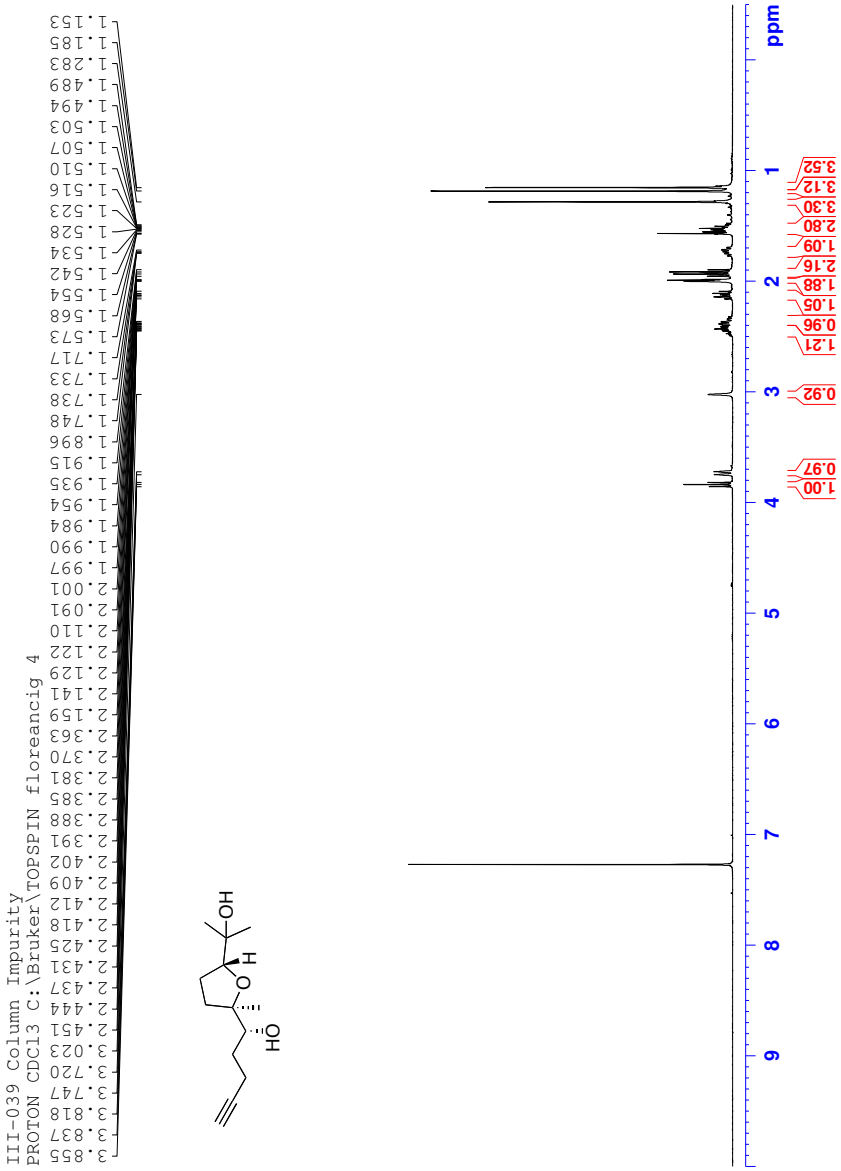
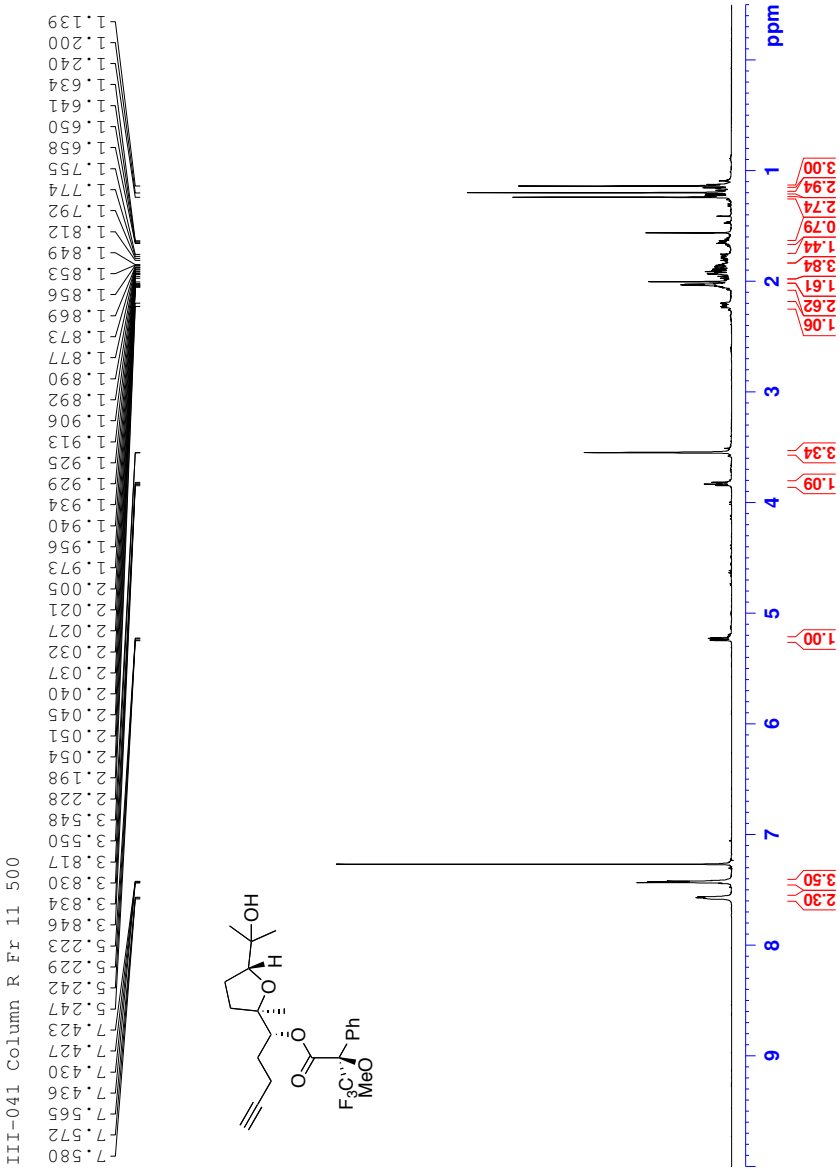
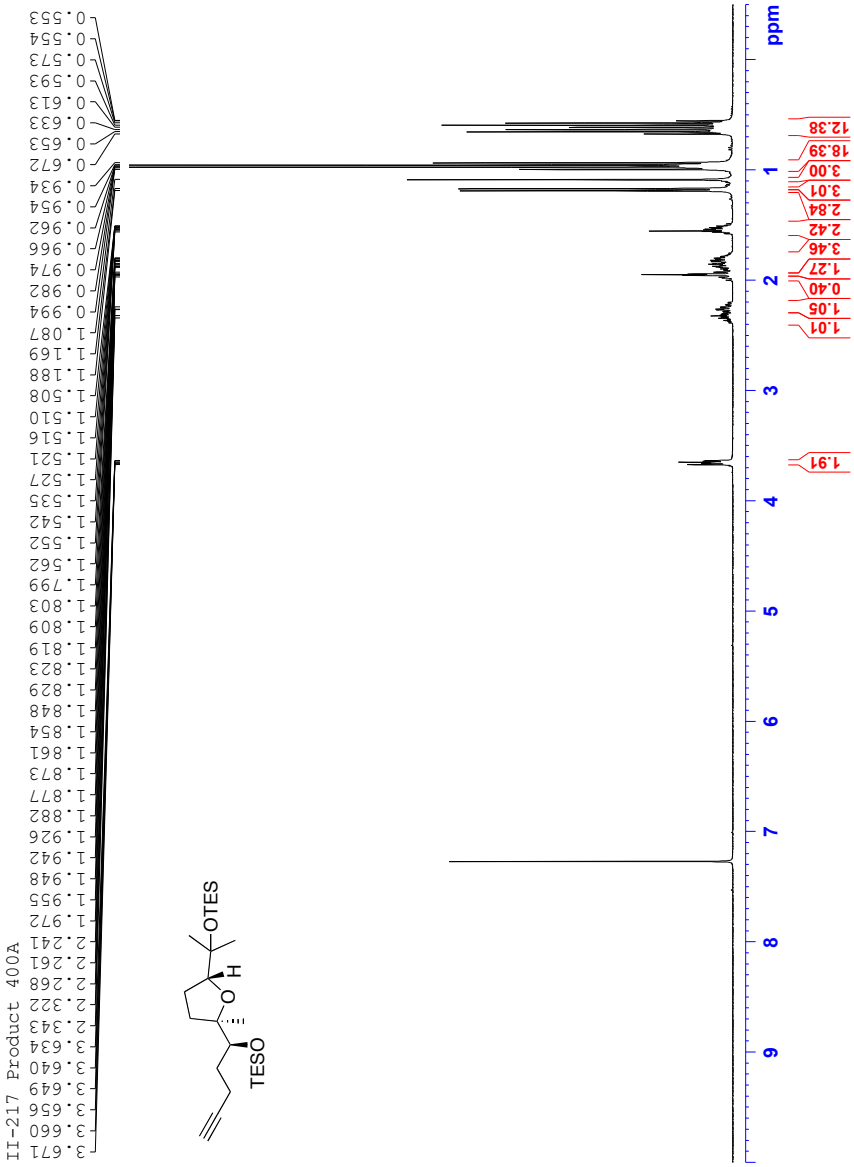
F3C

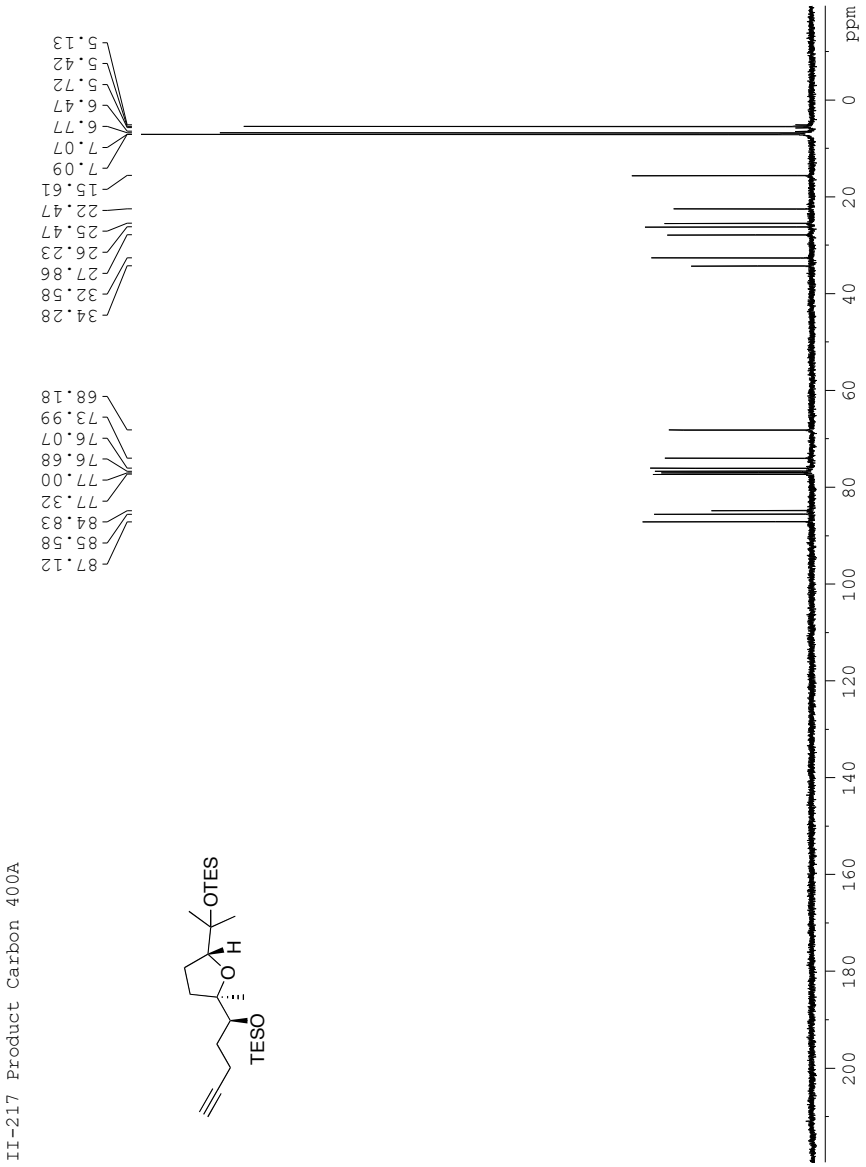

III-037 600 NOESY
OH
H
O
O
O
MeO
Ph
F3C
NAME III-037 600
EXPNO 2
PROCNO 1
Date_ 20110219
Time_ 13.47
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG noesyph
TD 2048
SOLVENT CDCl3
NS 222
DS 4
SWH 4807.692 Hz
FIDRES 2.347506 Hz
AQ 0.2130420 sec
RG 64
DW 104.000 usec
DE 6.50 usec
TE 296.2 K
D0 0.00009017 sec
D1 2.00000000 sec
D8 0.30000001 sec
INO 0.00020800 sec
======== CHANNEL f1 ========
NUC1 1H
P1 10.86 usec
PL1 -2.00 dB
PL1W 19.70630455 W
SFO1 600.8724034 MHz
NDO 1
TD 256
SFO1 600.8724 MHz
FIDRES 18.780079 Hz
SW 8.001 ppm
FnMODE States-TPPI
ST 1024
SF 600.8700000 MHz
WDW QSINE
SSB 2
LB 0.00 Hz
GB 0
PC 1.00
SI 1024
MC2 States-TPPI
SF 600.8700000 MHz
WDW QSINE
SSB 2
LB 0.00 Hz
GB 0
ppm
1
2
3
4
5
6
7
8
ppm
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5

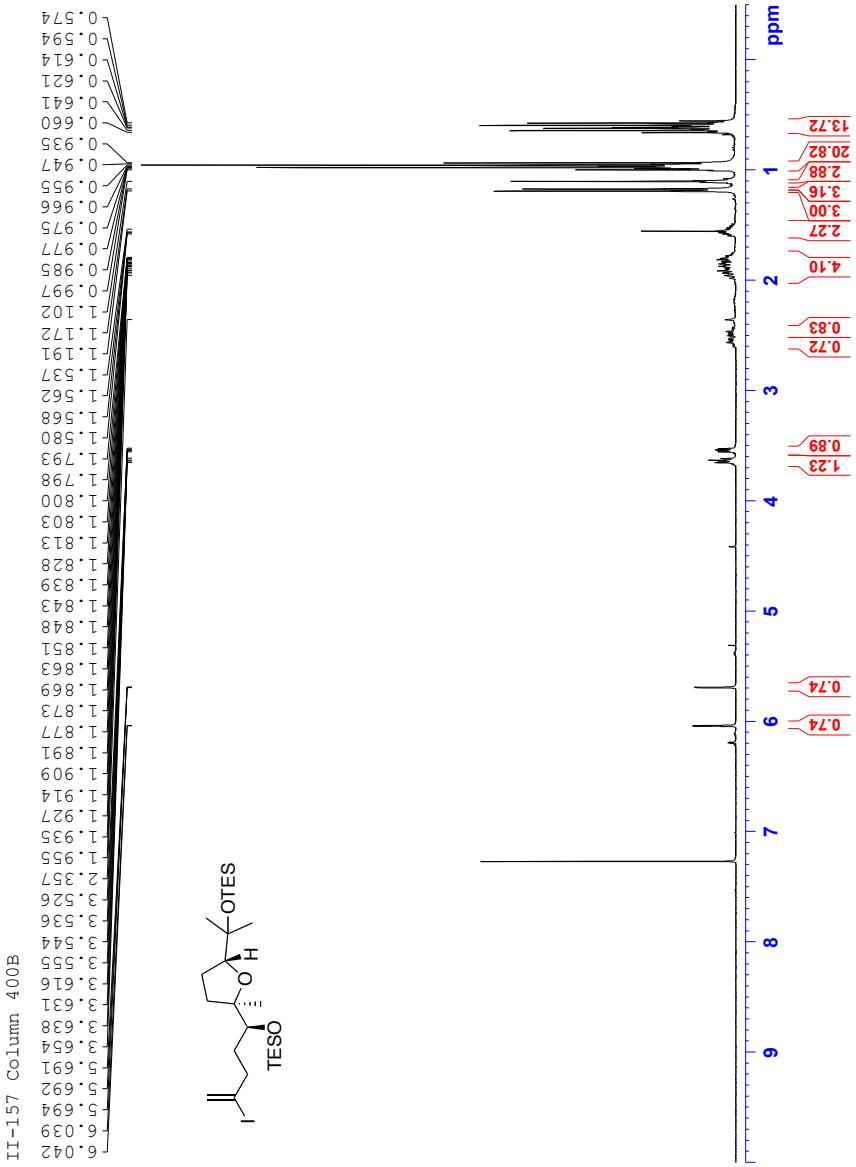

III-039 Column Impurity
PROTON CDCl3 C:\Bruker\TOPSPIN floreancig 4
3.855
3.837
3.818
3.747
3.720
3.023
2.451
2.444
2.437
2.431
2.425
2.418
2.412
2.409
2.402
2.391
2.388
2.385
2.381
2.370
2.363
2.159
2.141
2.129
2.122
2.110
2.091
2.001
1.997
1.990
1.984
1.954
1.935
1.915
1.896
1.748
1.738
1.733
1.717
1.573
1.568
1.554
1.542
1.534
1.528
1.523
1.516
1.510
1.507
1.503
1.494
1.489
1.283
1.185
1.153
OH
H
O
OH
ppm
1
2
3
4
5
6
7
8
9
3.52
3.12
3.30
2.80
1.09
2.16
1.88
1.05
0.96
1.21
0.92
1.00
0.97

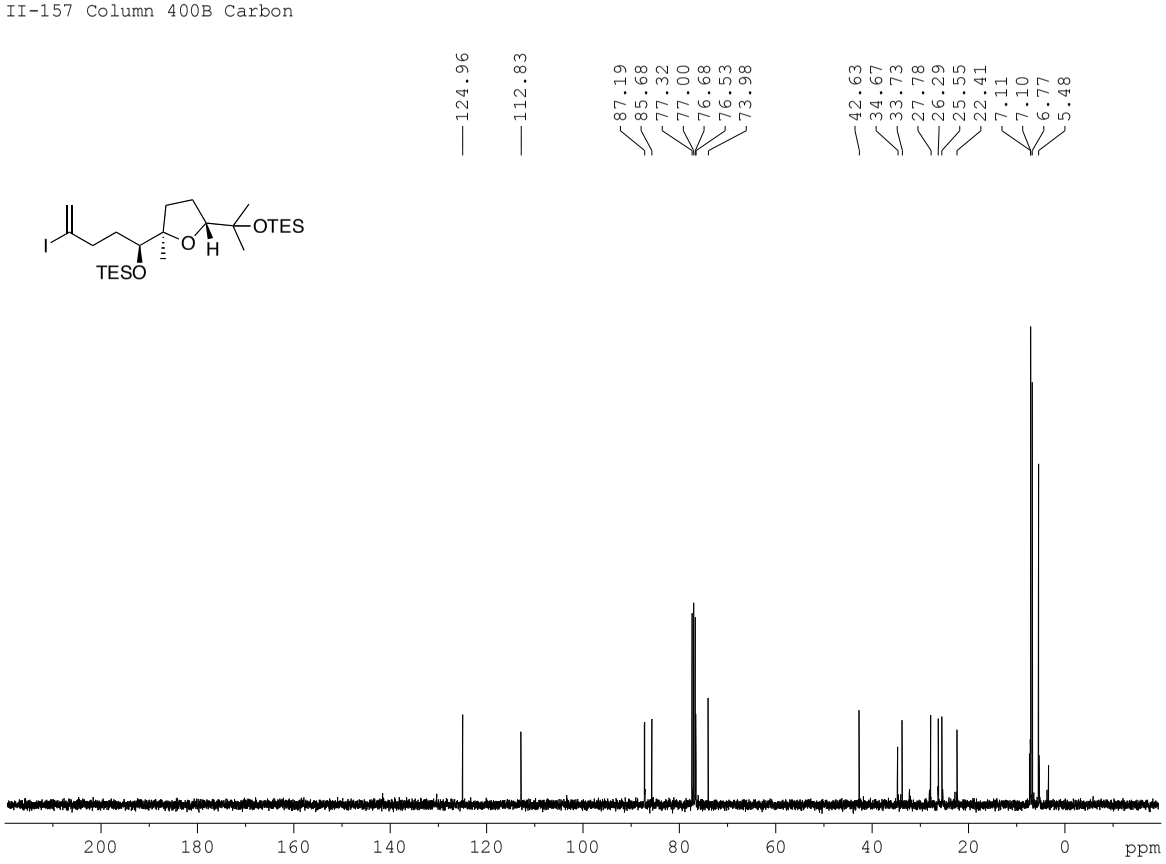

III-041 Column R Fr 11 500
7.580
7.572
7.565
7.436
7.430
7.427
7.423
5.247
5.242
5.229
5.223
3.846
3.834
3.830
3.817
3.550
3.548
2.228
2.198
2.054
2.051
2.045
2.040
2.037
2.032
2.027
2.021
2.005
1.973
1.956
1.940
1.934
1.929
1.925
1.913
1.906
1.892
1.890
1.877
1.873
1.869
1.856
1.853
1.849
1.812
1.792
1.774
1.755
1.658
1.650
1.641
1.634
1.240
1.200
1.139
OH
H
O
O
O
F3C
MeO
Ph
ppm
1
2
3
4
5
6
7
8
9
3.00
2.94
2.74
0.79
1.44
3.84
1.61
2.62
1.06
3.34
1.09
1.00
2.30
3.50

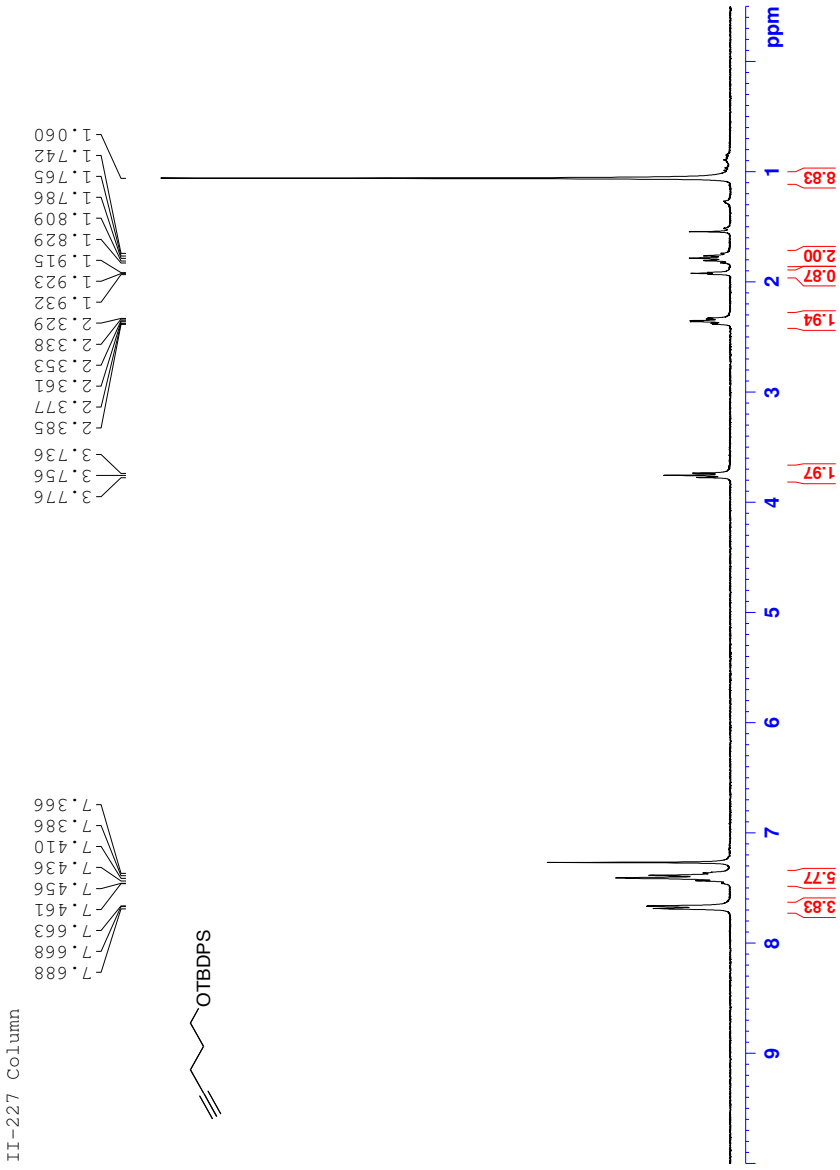
III-040 Column S
7.575
7.572
7.564
7.557
7.434
7.429
7.425
7.421
5.214
5.207
5.196
5.190
3.826
3.814
3.809
3.797
3.545
3.543
2.315
2.312
2.310
2.199
2.194
2.181
2.145
2.055
2.050
2.045
2.007
1.914
1.907
1.889
1.869
1.862
1.859
1.855
1.852
1.844
1.841
1.835
1.832
1.823
1.818
1.813
1.809
1.800
1.607
1.590
1.582
1.574
1.564
1.550
1.216
1.155
1.125
OH
H
O
O
O
MeO
Ph
F3C
ppm
2.08
3.20
0.94
0.93
2.69
0.97
1.14
0.84
0.77
0.75
1.53
2.97
0.91
2.72
2.75
3.00

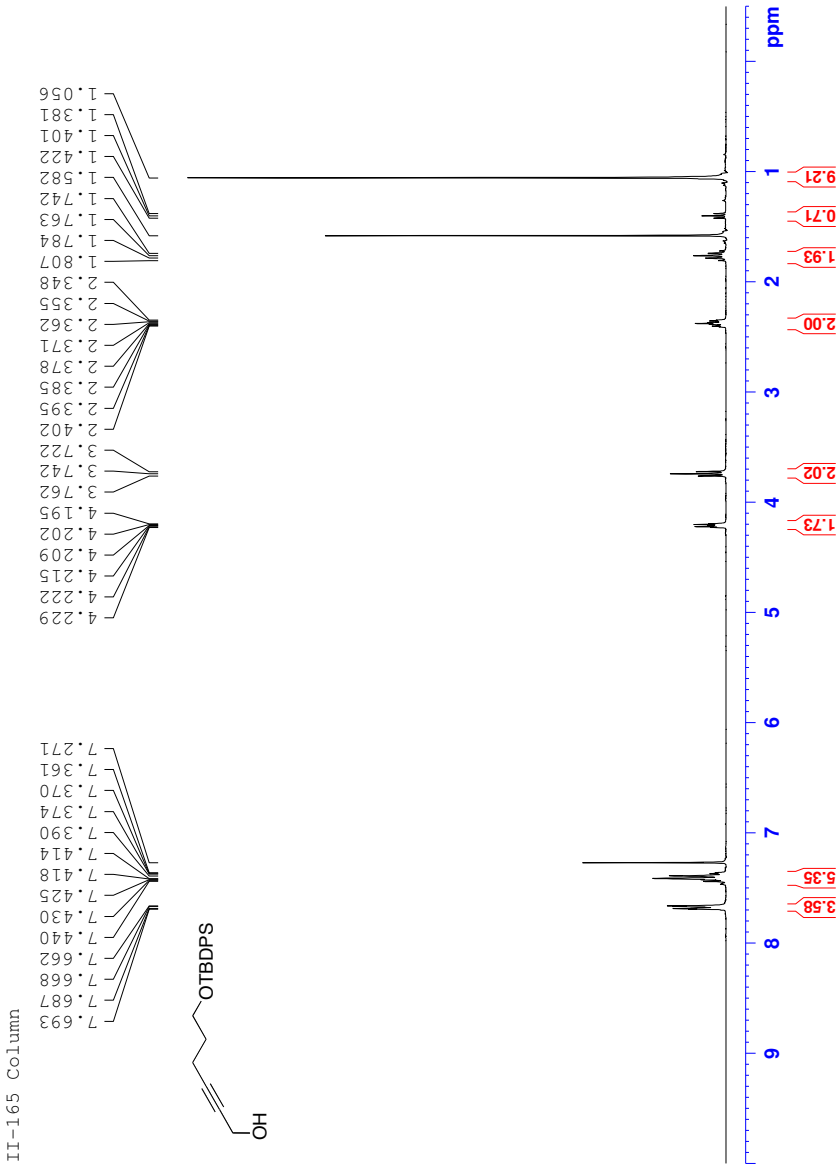

II-217 Product 400A
0.553
0.554
0.573
0.593
0.613
0.633
0.653
0.672
0.934
0.954
0.962
0.966
0.974
0.982
0.994
1.087
1.169
1.188
1.508
1.510
1.516
1.521
1.527
1.535
1.542
1.552
1.562
1.799
1.803
1.809
1.819
1.823
1.829
1.848
1.854
1.861
1.873
1.877
1.882
1.926
1.942
1.948
1.955
1.972
2.241
2.261
2.268
2.322
2.343
3.634
3.640
3.649
3.656
3.660
3.671
OTES
H
O
TESO
ppm
1
2
3
4
5
6
7
8
9
12.38
18.39
3.00
3.01
2.84
2.42
3.46
1.27
0.40
1.05
1.01
1.91


II-217 Product Carbon 400A
OTES
H
O
TESO
87.12
85.58
84.83
77.32
77.00
76.68
76.07
73.99
68.18
34.28
32.58
27.86
26.23
25.47
22.47
15.61
7.09
7.07
6.77
6.47
5.72
5.42
5.13
ppm
0
20
40
60
80
100
120
140
160
180
200

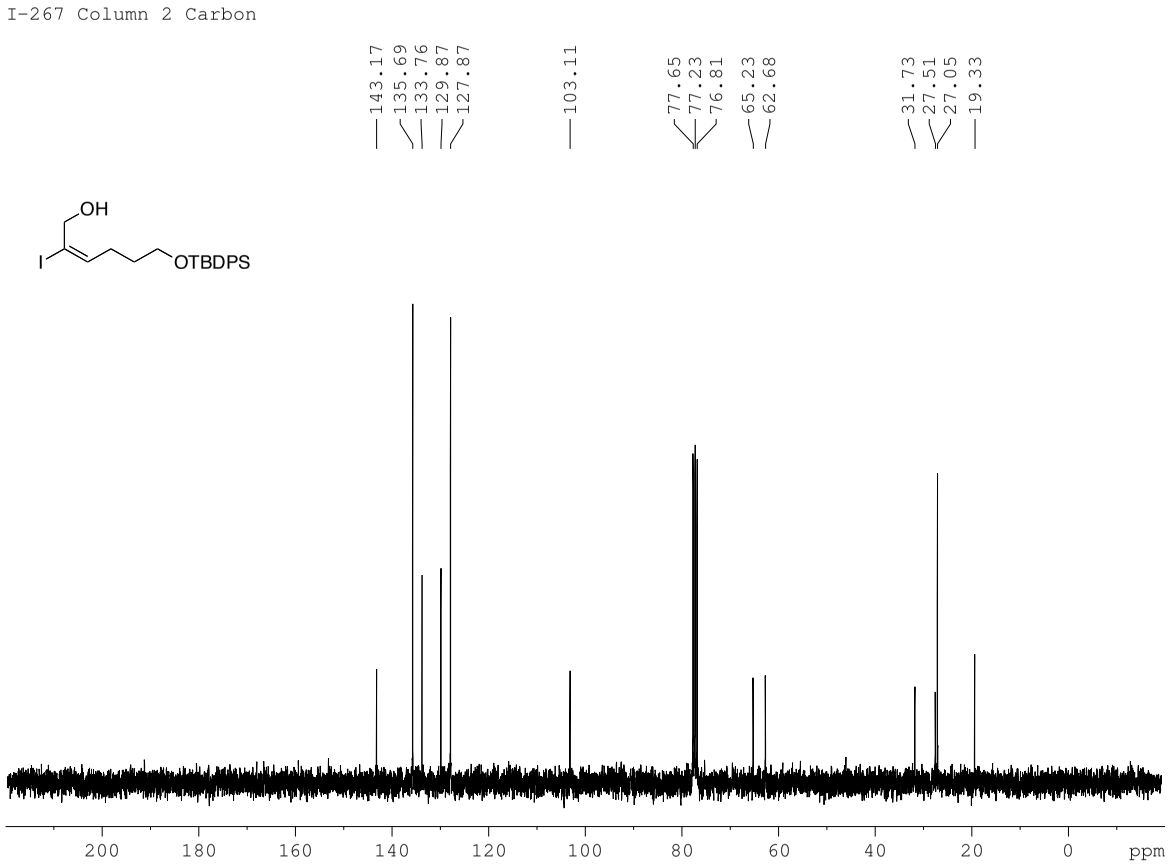

II-157 Column 400B
OTES
TESO
I
H
O
ppm
13.72
20.82
2.88
3.16
3.00
2.27
4.10
0.83
0.72
0.89
1.23
0.74
0.74

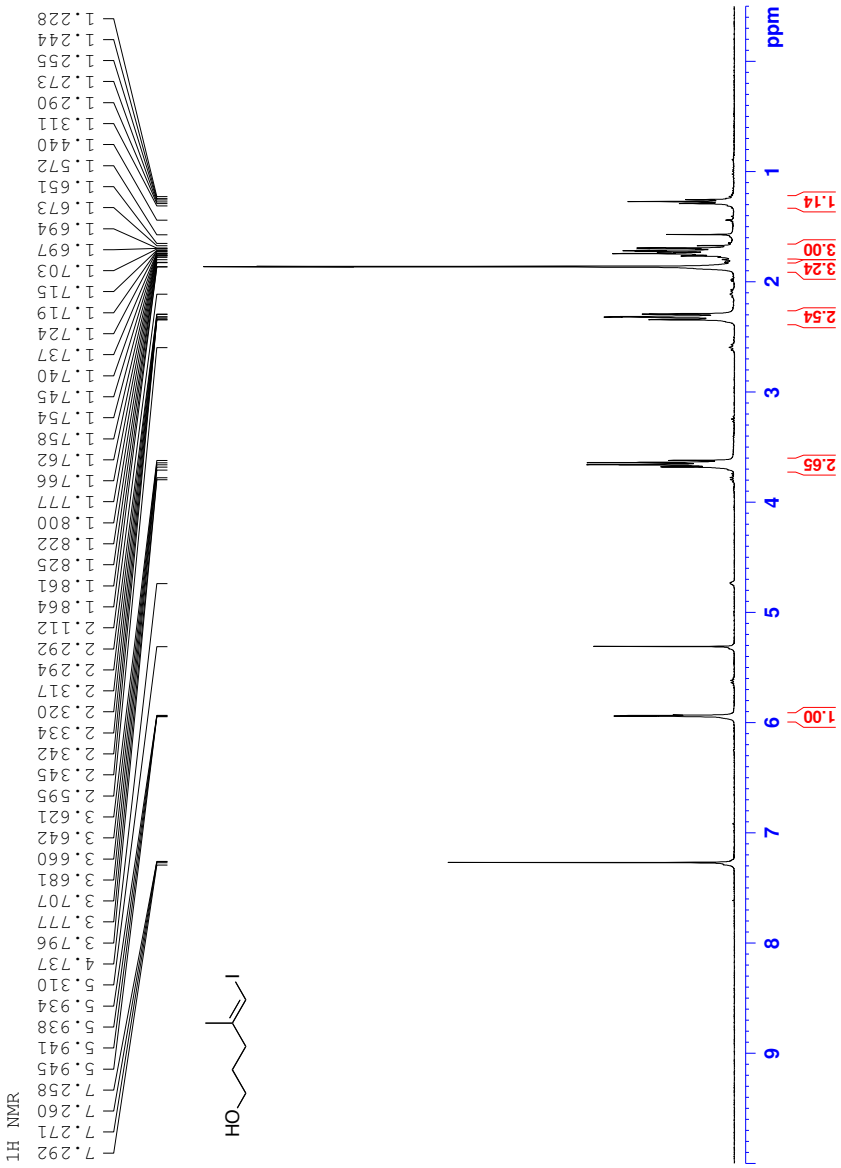

II-157 Column 400B Carbon
124.96
112.83
87.19
85.68
77.32
77.00
76.68
76.53
73.98
42.63
34.67
33.73
27.78
26.29
25.55
22.41
7.11
7.10
6.77
5.48
I
TESO
O
H
OTES
200
180
160
140
120
100
80
60
40
20
0
ppm

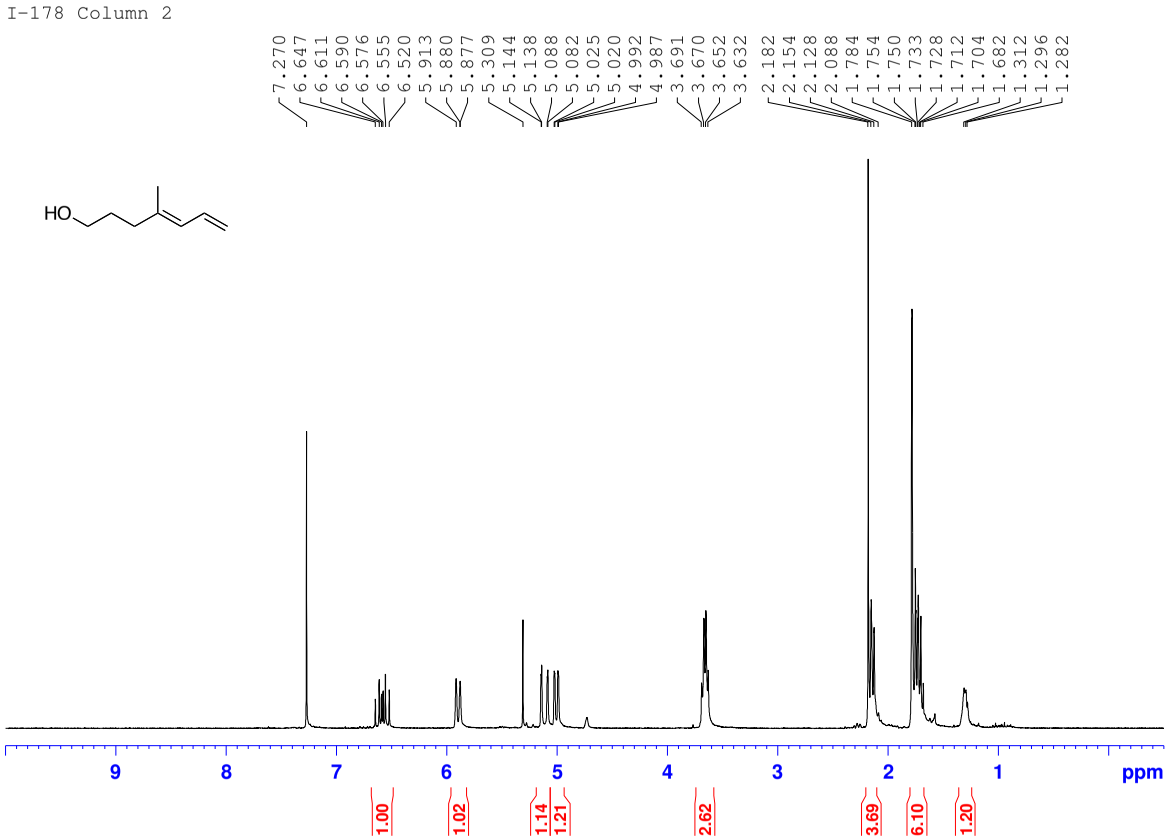

II-227 Column
OTBDPS
7.688
7.668
7.663
7.461
7.456
7.436
7.410
7.386
7.366
3.776
3.756
3.736
2.385
2.377
2.361
2.353
2.338
2.329
1.932
1.923
1.915
1.829
1.809
1.786
1.765
1.742
1.060
8.83
2.00
0.87
1.94
1.97
5.77
3.83
ppm


II-165 Column
7.693
7.687
7.668
7.662
7.440
7.430
7.425
7.418
7.414
7.390
7.374
7.370
7.361
7.271
4.229
4.222
4.215
4.209
4.202
4.195
3.762
3.742
3.722
2.402
2.395
2.385
2.378
2.371
2.362
2.355
2.348
1.807
1.784
1.763
1.742
1.582
1.422
1.401
1.381
1.056
OTBDPS
HO
ppm
9.21
0.71
1.93
2.00
2.02
1.73
3.58
5.35

1H NMR
OH
OTBDPS
I
ppm

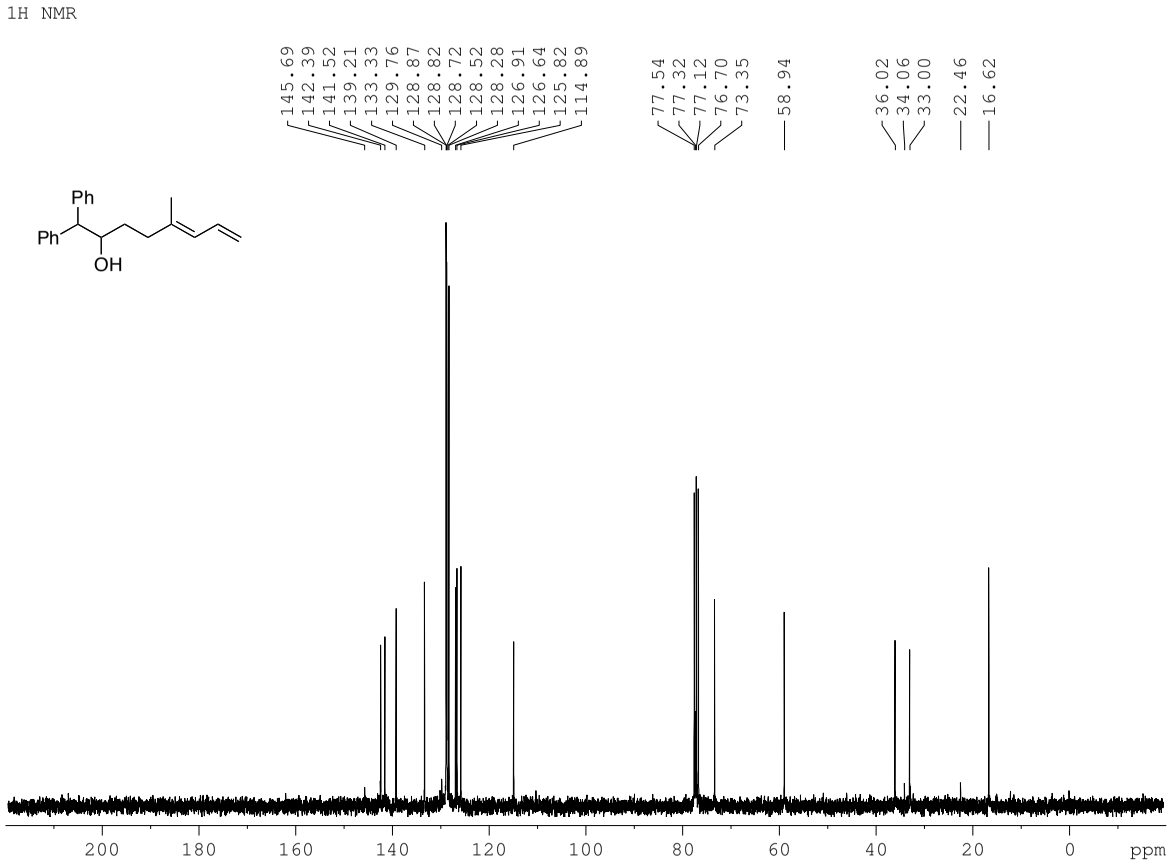

I-267 Column 2 Carbon
143.17
135.69
133.76
129.87
127.87
103.11
77.65
77.23
76.81
65.23
62.68
31.73
27.51
27.05
19.33
OH
I
OTBDPS
200
180
160
140
120
100
80
60
40
20
0
ppm


1H NMR
7.292
7.271
7.260
7.258
5.945
5.941
5.938
5.934
5.310
4.737
3.796
3.777
3.707
3.681
3.660
3.642
3.621
2.595
2.345
2.342
2.334
2.320
2.317
2.294
2.292
2.112
1.864
1.861
1.825
1.822
1.800
1.777
1.766
1.762
1.758
1.754
1.745
1.740
1.737
1.724
1.719
1.715
1.703
1.697
1.694
1.673
1.651
1.572
1.440
1.311
1.290
1.273
1.255
1.244
1.228
HO
I
ppm
1.14
3.00
3.24
2.54
2.65
1.00

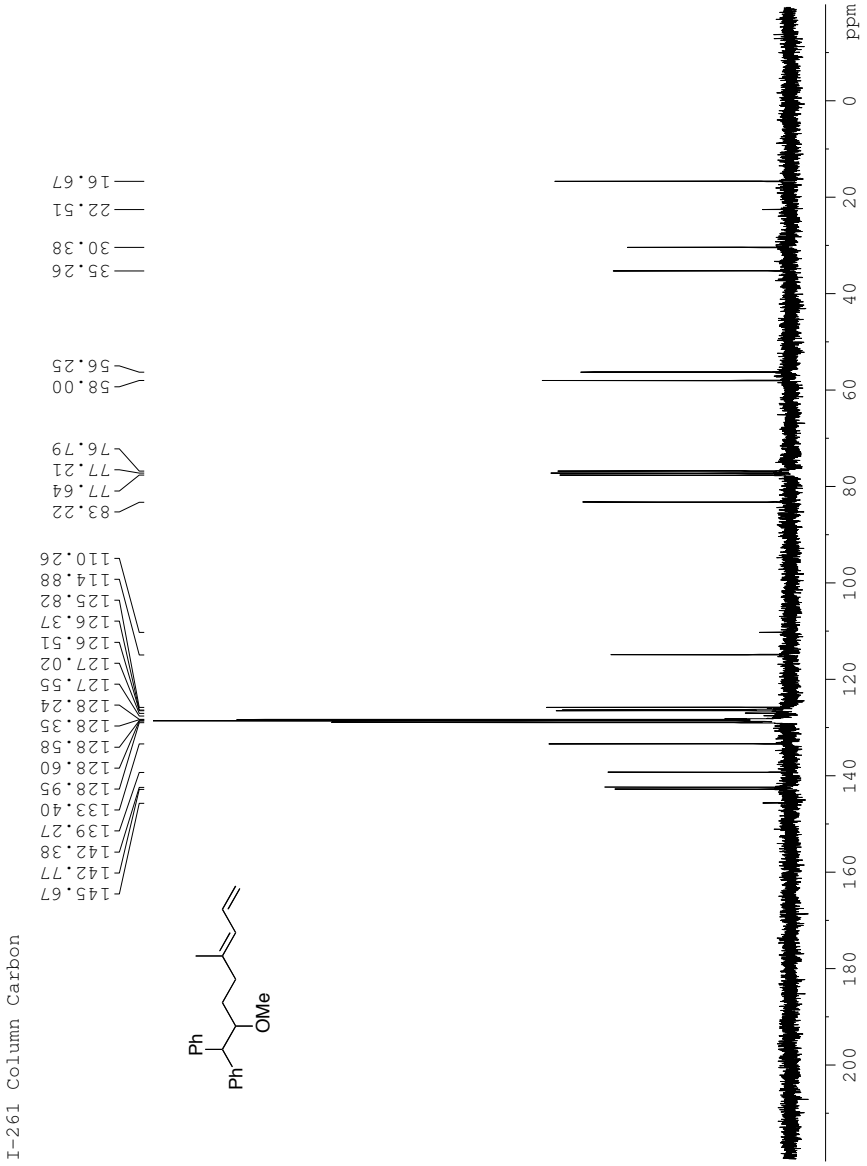

I-178 Column 2
7.270
6.647
6.611
6.590
6.576
6.555
6.520
5.913
5.880
5.877
5.309
5.144
5.138
5.088
5.082
5.025
5.020
4.992
4.987
3.691
3.670
3.652
3.632
2.182
2.154
2.128
2.088
1.784
1.754
1.750
1.733
1.728
1.712
1.704
1.682
1.312
1.296
1.282
HO
9
8
7
6
5
4
3
2
1
ppm
1.00
1.02
1.14
1.21
2.62
3.69
6.10
1.20

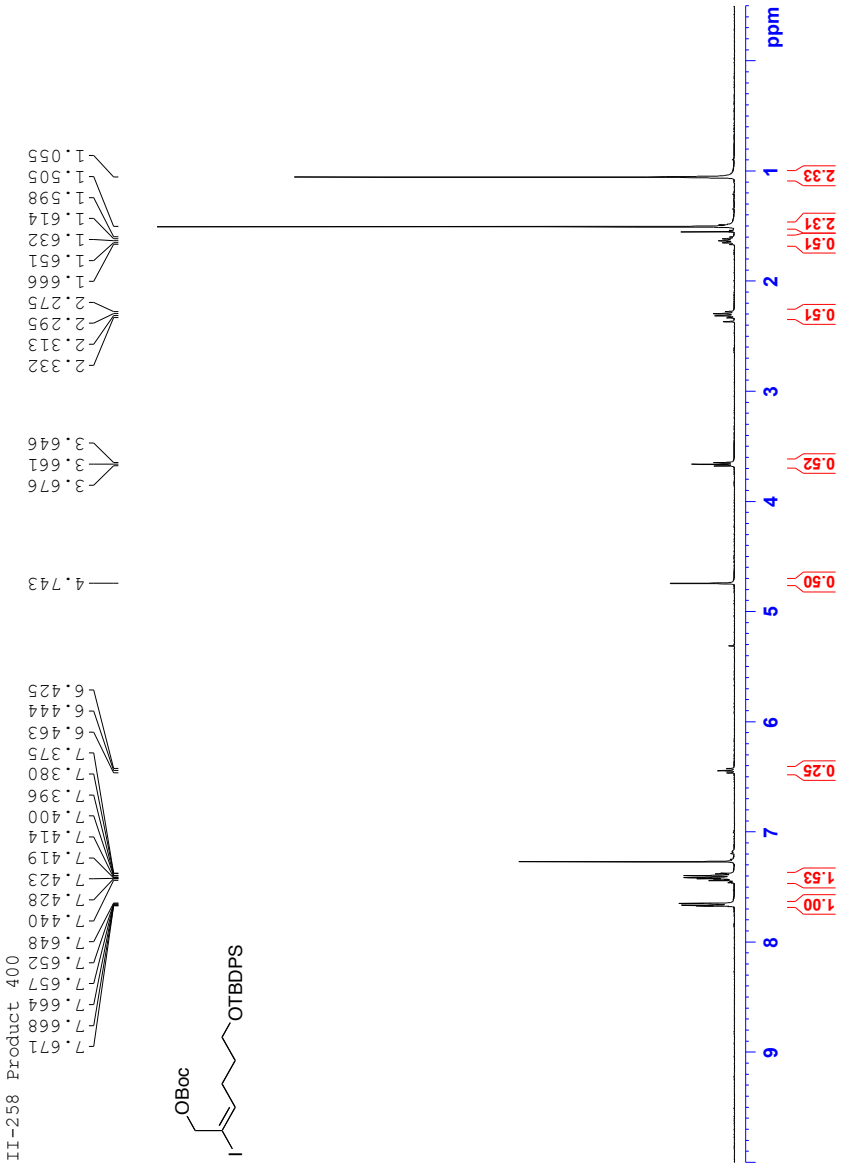
I-259 Aldehyde Check
9.795
9.790
7.270
7.256
6.625
6.590
6.569
6.555
6.534
6.499
5.894
5.858
5.310
5.163
5.106
5.059
5.025
4.726
4.698
2.663
2.649
2.621
2.617
2.612
2.595
2.590
2.585
2.577
2.568
2.565
2.483
2.451
2.431
2.406
2.382
2.361
2.314
2.260
2.055
1.786
1.762
1.558
0.019
0.008
O
H
ppm
1.00
0.99
0.98
1.10
1.12
2.15
1.99
2.86

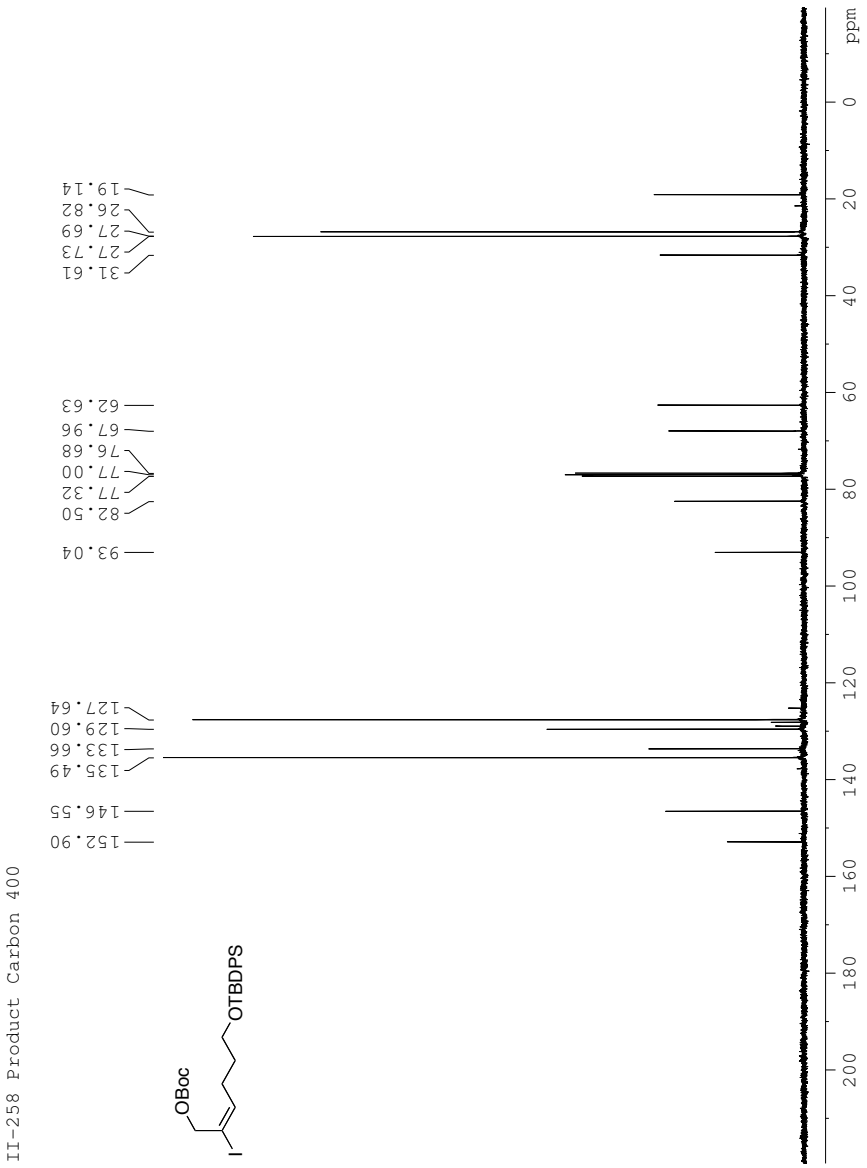
1H NMR
7.45
7.44
7.42
7.40
7.39
7.38
7.36
7.36
7.34
7.33
7.31
7.30
7.30
7.29
7.29
7.28
7.27
7.26
7.25
7.23
7.22
7.21
6.64
6.62
6.60
6.58
5.92
5.88
5.17
5.16
5.11
5.11
5.05
5.02
4.38
4.37
4.36
3.96
3.93
2.35
2.24
2.21
1.73
1.71
1.69
1.67
1.66
1.62
1.60
1.59
1.58
1.56
1.30
Ph
Ph
OH
0.70
1.51
0.80
1.25
2.06
2.34
0.30
0.66
1.08
1.04
0.90
0.90
0.96
0.98
1.00
1.00
1.00
1.19
4.79
1.61
0 ppm


1H NMR
145.69
142.39
141.52
139.21
133.33
129.76
128.87
128.82
128.72
128.52
128.28
126.91
126.64
125.82
114.89
77.54
77.32
77.12
76.70
73.35
58.94
36.02
34.06
33.00
22.46
16.62
Ph
Ph
OH
200
180
160
140
120
100
80
60
40
20
0
ppm

1H NMR
7.50
7.47
7.45
7.40
7.39
7.38
7.37
7.36
7.35
7.33
7.29
7.29
7.28
7.27
7.26
7.26
7.25
7.23
6.68
6.66
6.65
6.62
5.95
5.92
5.21
5.16
5.15
5.10
5.06
4.14
4.11
4.02
4.01
4.00
3.99
3.98
3.47
3.27
3.24
3.23
2.27
2.25
2.22
1.80
1.77
1.75
1.73
1.72
1.70
1.69
1.68
1.67
1.65
1.64
1.62
Ph
Ph
OMe
ppm
0
1
2
3
4
5
6
7
8
9
2.01
6.57
2.96
0.83
0.81
0.88
0.92
0.92
1.00
2.74
1.98
5.38

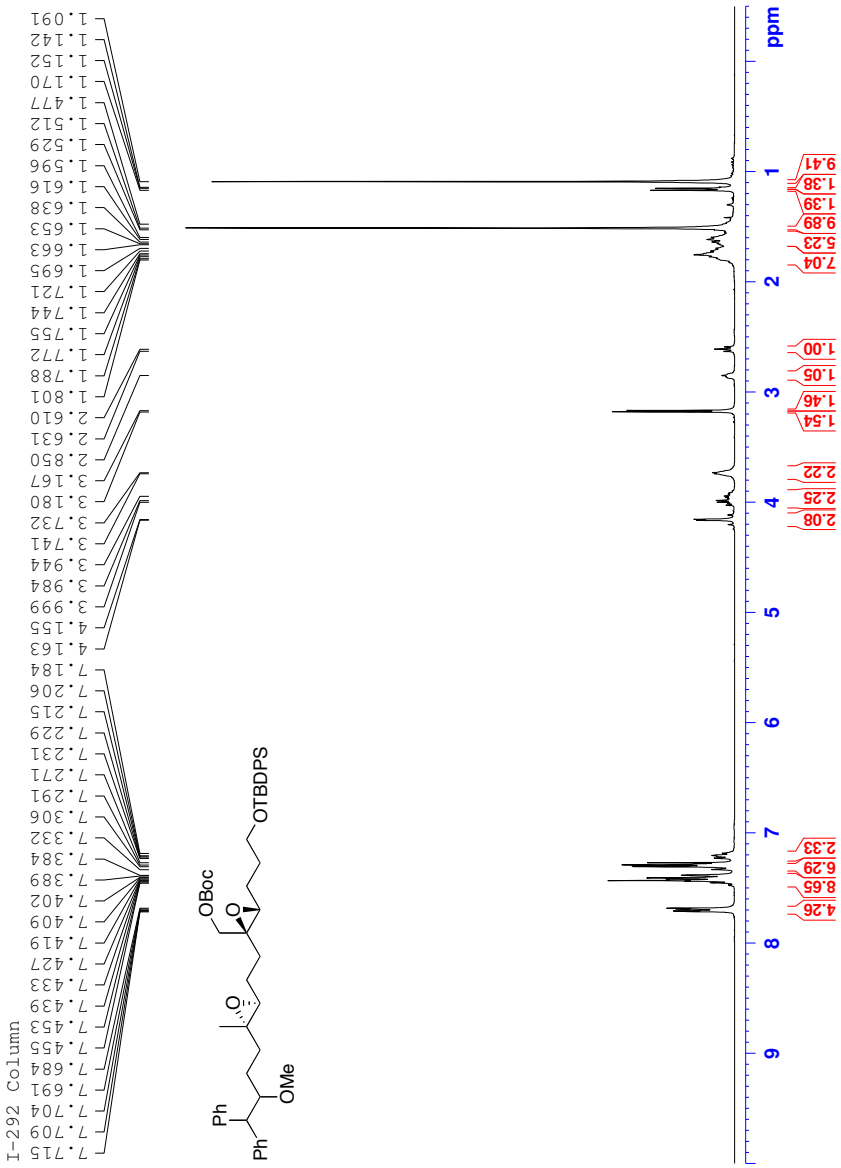

I-261 Column Carbon
145.67
142.77
142.38
139.27
133.40
128.95
128.60
128.58
128.35
128.24
127.55
127.02
126.51
126.37
125.82
114.88
110.26
83.22
77.64
77.21
76.79
58.00
56.25
35.26
30.38
22.51
16.67
Ph
Ph
OMe
ppm
0
20
40
60
80
100
120
140
160
180
200

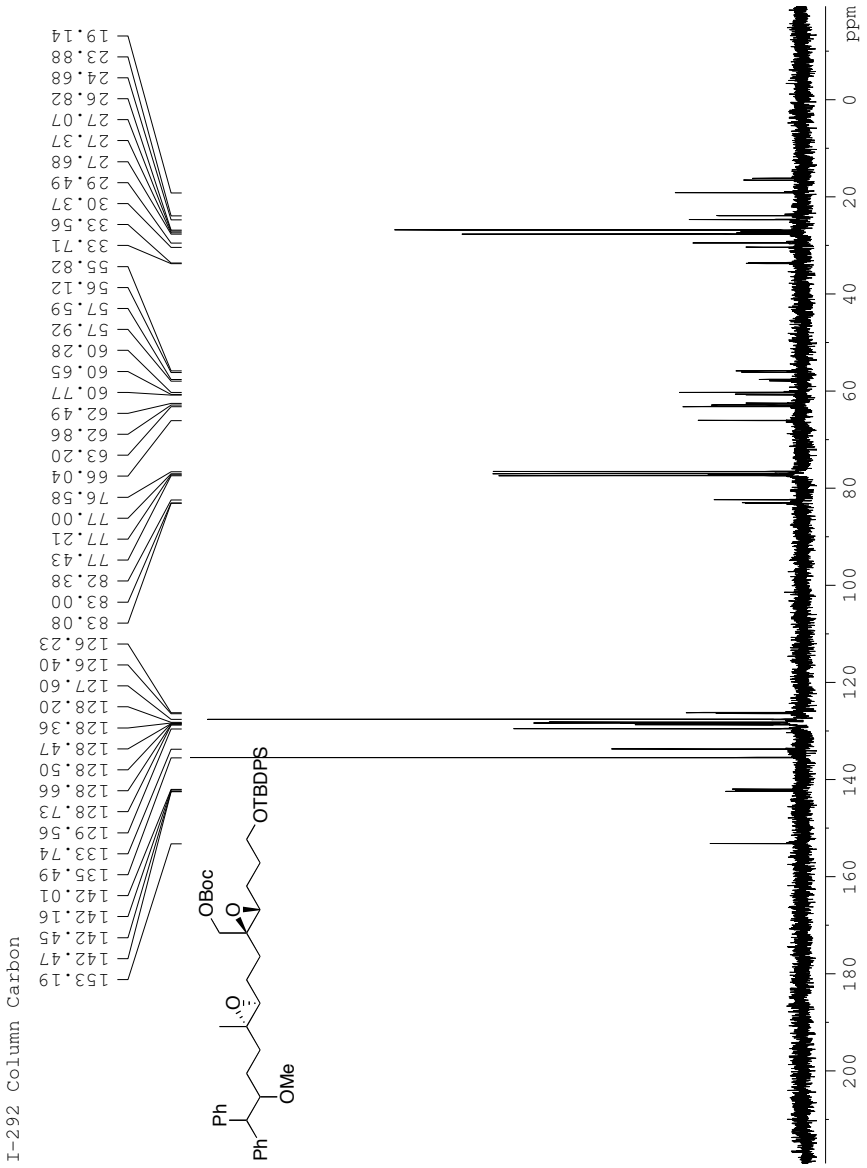

II-258 Product 400
7.671
7.668
7.664
7.657
7.652
7.648
7.440
7.428
7.423
7.419
7.414
7.400
7.396
7.380
7.375
6.463
6.444
6.425
4.743
3.676
3.661
3.646
2.332
2.313
2.295
2.275
1.666
1.651
1.632
1.614
1.598
1.505
1.055
OBoc
OTBDPS
I
ppm
1
2
3
4
5
6
7
8
9
2.33
2.31
0.51
0.51
0.52
0.50
0.25
1.53
1.00

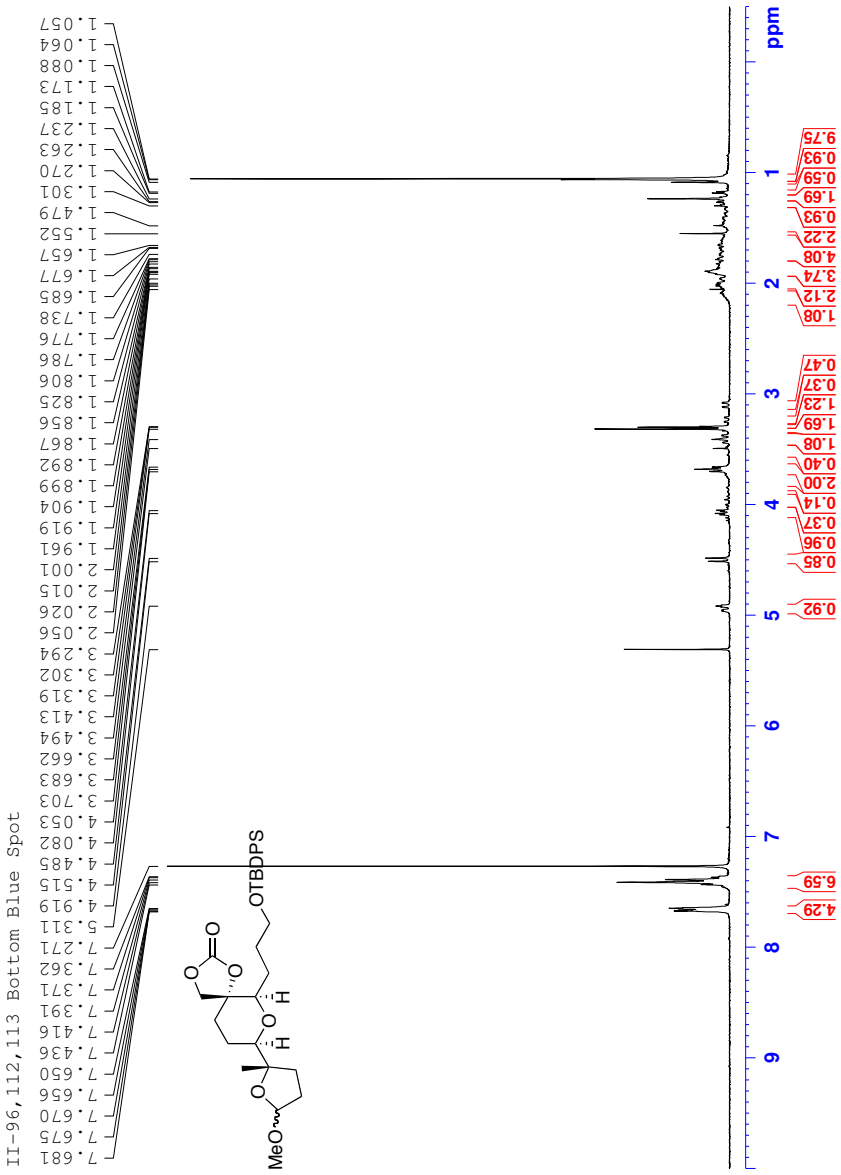

II-258 Product Carbon 400
OBoc
OTBDPS
152.90
146.55
135.49
133.66
129.60
127.64
93.04
82.50
77.32
77.00
76.68
67.96
62.63
31.61
27.73
27.69
26.82
19.14
200
180
160
140
120
100
80
60
40
20
0
ppm

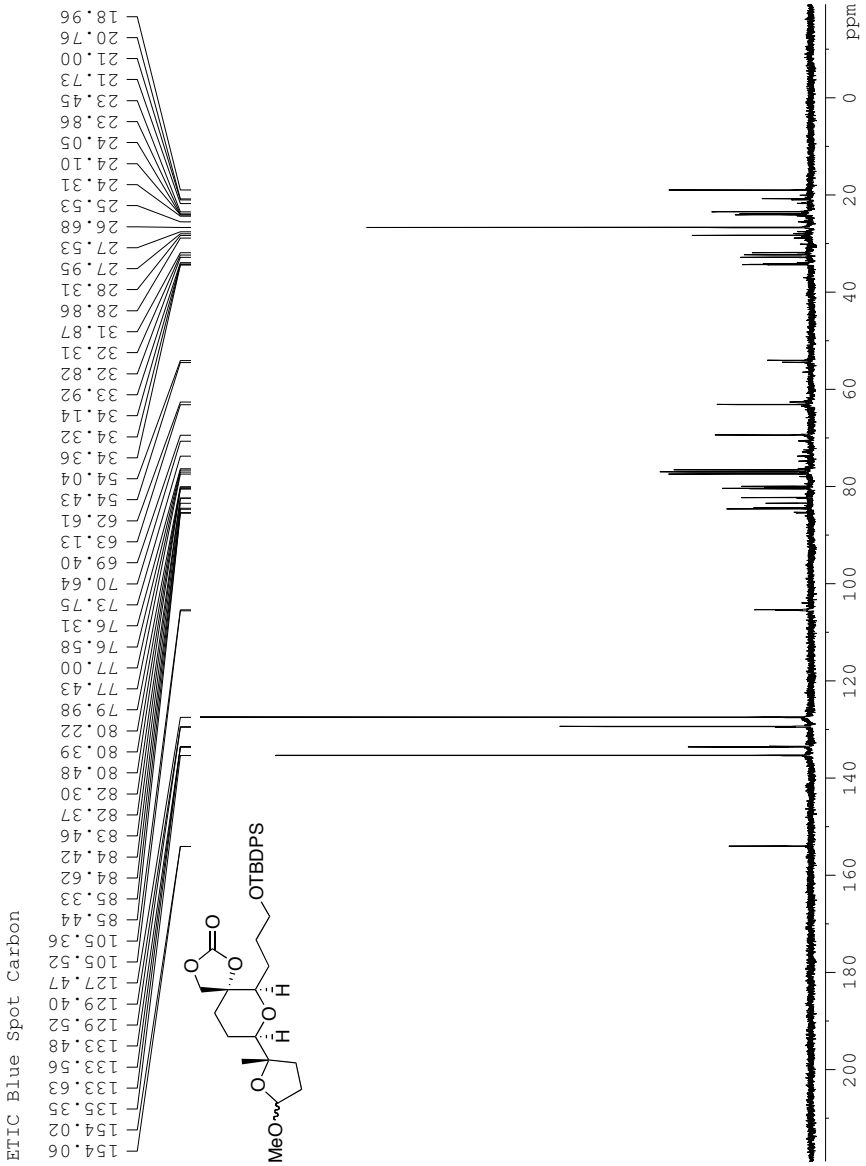
1H NMR
OBoc
OTBDPS
Ph
Ph
OMe
ppm

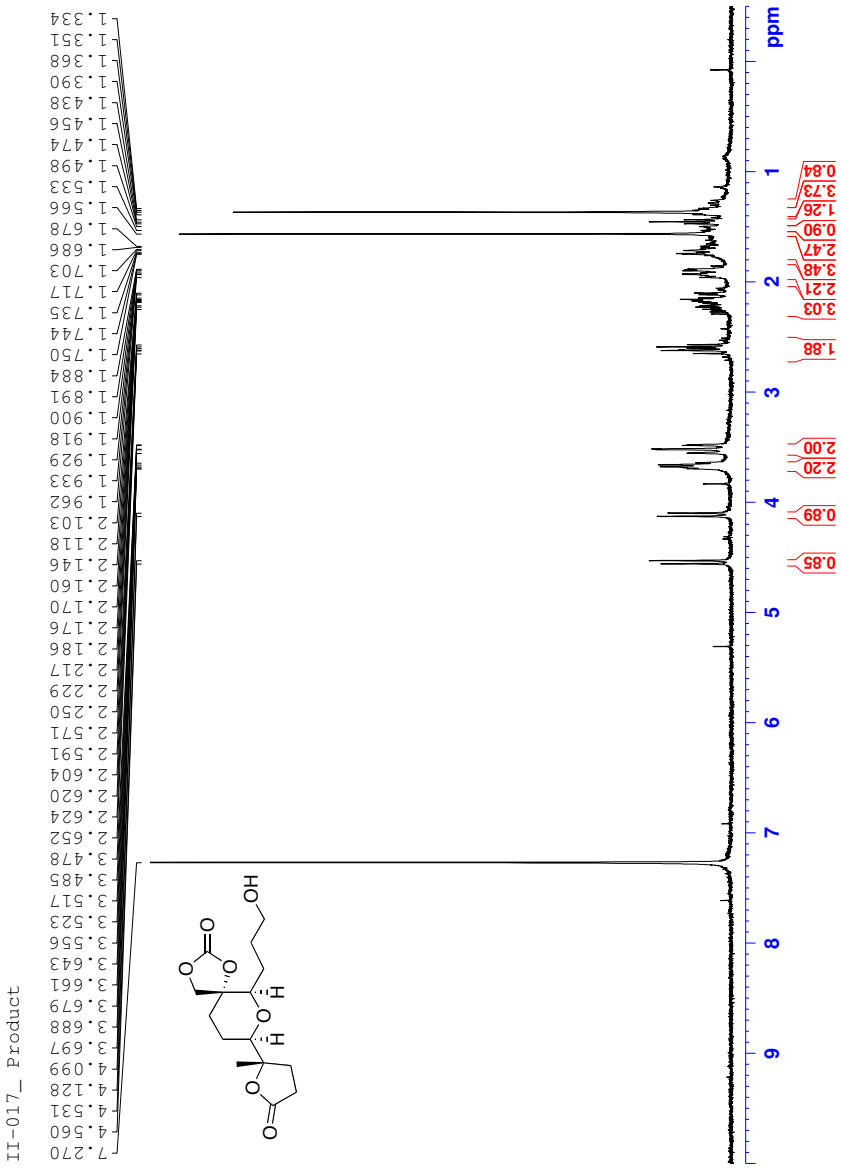
I-279_Column Carbon
153.80
142.89
142.39
135.64
135.14
134.05
133.75
130.84
129.62
129.30
128.98
128.57
128.51
128.26
127.70
126.38
126.27
124.24
83.26
81.83
77.57
77.35
77.14
76.72
64.29
63.26
57.96
56.15
35.17
35.07
32.79
30.65
27.88
27.70
26.97
26.76
24.12
19.28
15.98
OBoc
OTBDPS
Ph
Ph
OMe
ppm
0
20
40
60
80
100
120
140
160
180
200

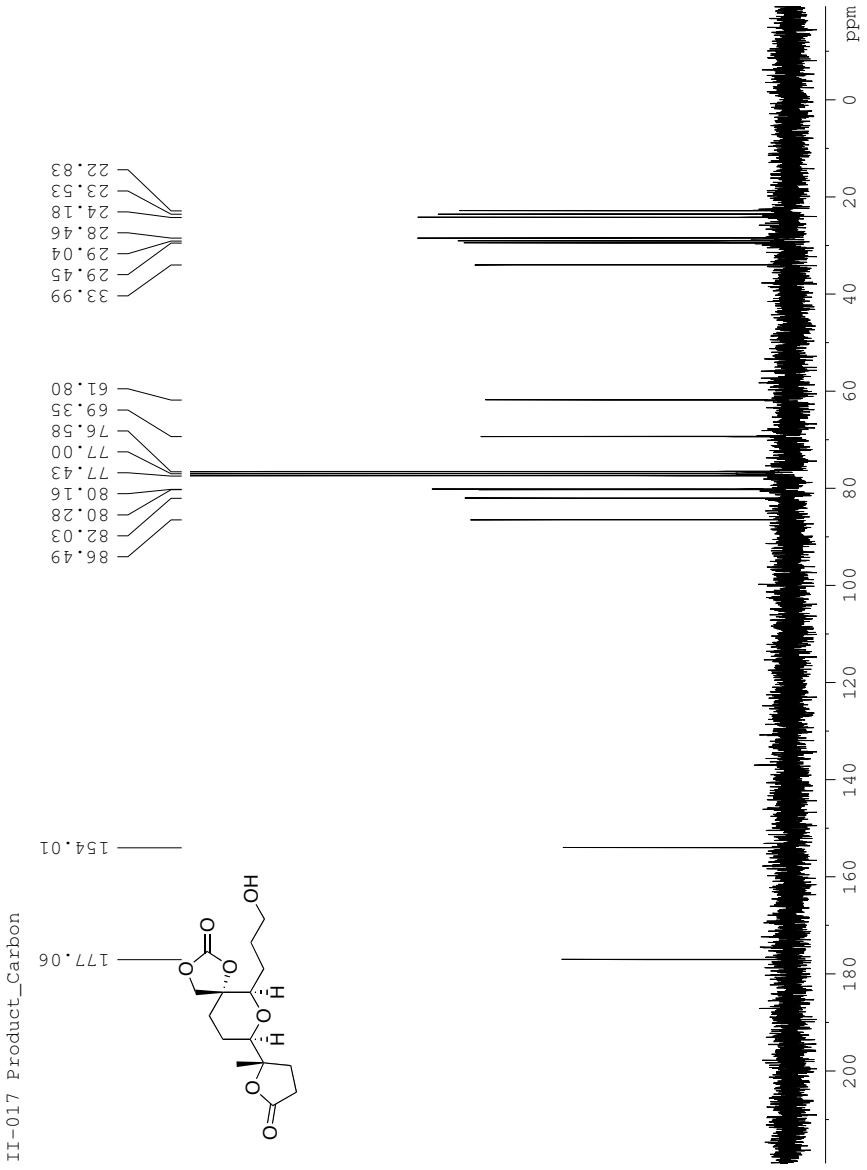

I-292 Column
7.715
7.709
7.704
7.691
7.684
7.455
7.453
7.439
7.433
7.427
7.419
7.409
7.402
7.389
7.384
7.332
7.306
7.291
7.271
7.231
7.229
7.215
7.206
7.184
4.163
4.155
3.999
3.984
3.944
3.741
3.732
3.180
3.167
2.850
2.631
2.610
1.801
1.788
1.772
1.755
1.744
1.721
1.695
1.663
1.653
1.638
1.616
1.596
1.529
1.512
1.477
1.170
1.152
1.142
1.091
OBoc
OTBDPS
Ph
OMe
Ph
ppm
9.41
1.38
1.39
9.89
5.23
7.04
1.00
1.05
1.46
1.54
2.22
2.25
2.08
2.33
6.29
8.65
4.26

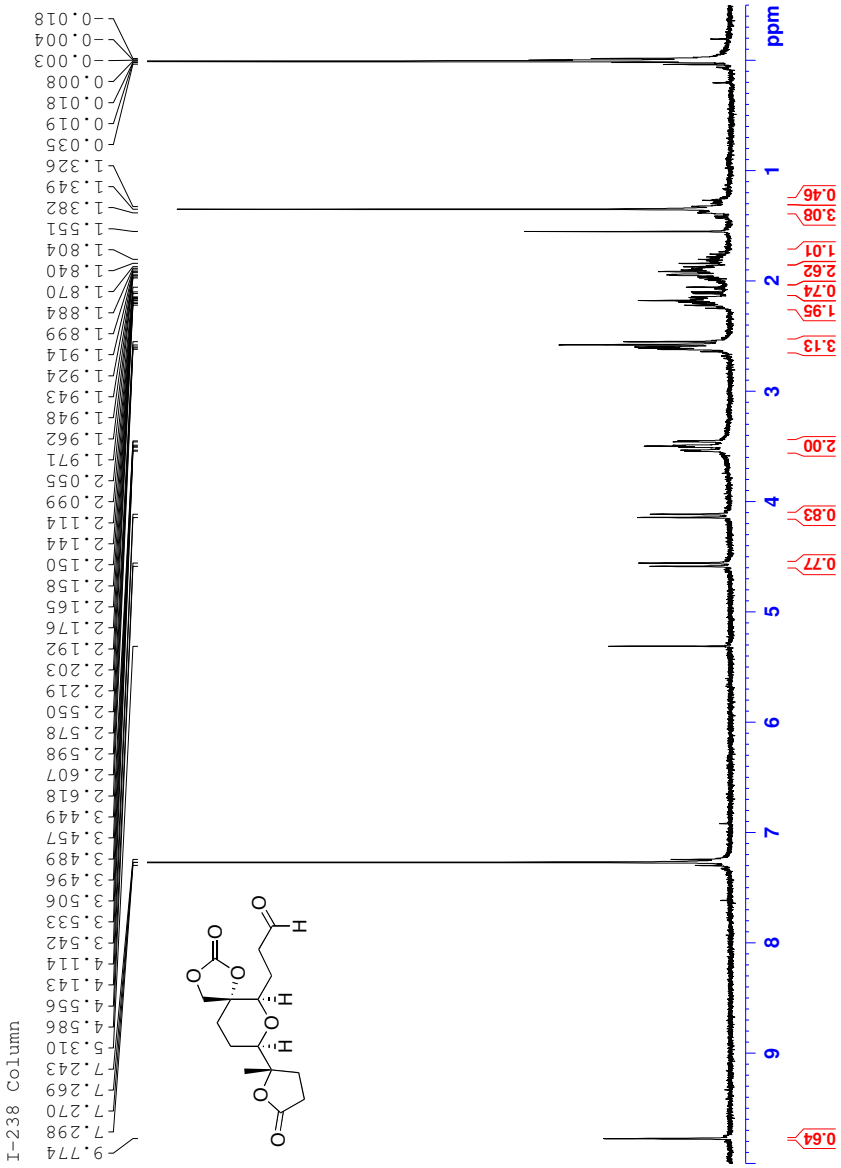

I-292 Column Carbon
153.19
142.47
142.45
142.16
142.01
135.49
133.74
129.56
128.73
128.66
128.50
128.47
128.36
128.20
127.60
126.40
126.23
83.08
83.00
82.38
77.43
77.21
77.00
76.58
66.04
63.20
62.86
62.49
60.77
60.65
60.28
57.92
57.59
56.12
55.82
33.71
33.56
30.37
29.49
27.68
27.37
27.07
26.82
24.68
23.88
19.14
OBoc
OTBDPS
Ph
OMe
Ph
ppm
200
180
160
140
120
100
80
60
40
20
0


II-96,112,113 Bottom Blue Spot
7.681
7.675
7.670
7.656
7.650
7.436
7.416
7.391
7.371
7.362
7.271
5.311
4.919
4.515
4.485
4.082
4.053
3.703
3.683
3.662
3.494
3.413
3.319
3.302
3.294
2.056
2.026
2.015
2.001
1.961
1.919
1.904
1.899
1.892
1.867
1.856
1.825
1.806
1.786
1.776
1.738
1.685
1.677
1.657
1.552
1.479
1.301
1.270
1.263
1.237
1.185
1.173
1.088
1.064
1.057
OTBDPS
MeO
H
H
O
O
O
O
ppm
1
2
3
4
5
6
7
8
9
9.75
0.93
0.59
1.69
0.93
2.22
4.08
3.74
2.12
1.08
0.47
0.37
1.23
1.69
1.08
0.40
2.00
0.14
0.37
0.96
0.85
0.92
6.59
4.29

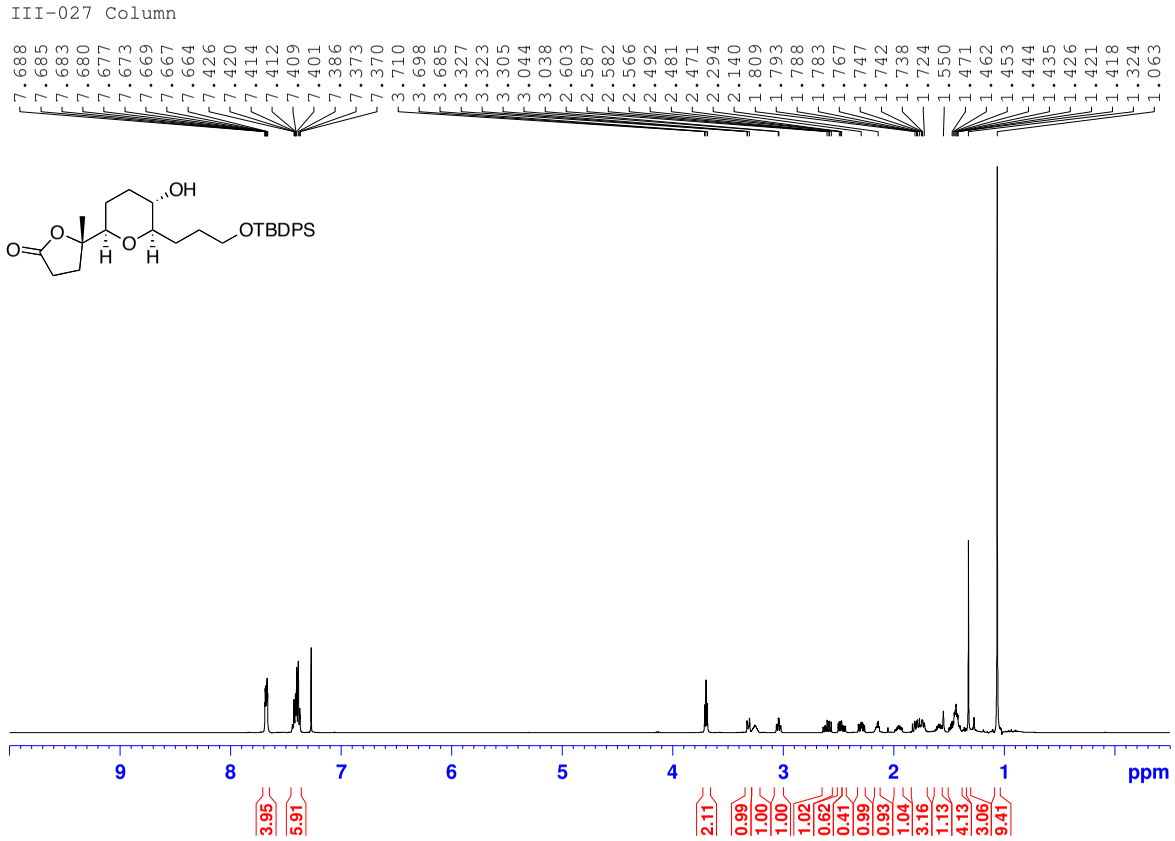

ETIC Blue Spot Carbon
154.06
135.35
133.63
133.56
133.48
129.52
129.40
127.47
105.52
105.36
85.44
85.33
84.62
84.42
83.46
82.37
82.30
80.48
80.39
80.22
79.98
77.43
77.00
76.58
76.31
73.75
70.64
69.40
63.13
62.61
54.43
54.04
34.36
34.32
34.14
33.92
32.82
32.31
31.87
28.86
28.31
27.95
27.53
26.68
25.53
24.31
24.10
24.05
23.86
23.45
21.73
21.00
20.76
18.96
OTBDPS
MeO
H
H
O
O
O
O
O
ppm
200
180
160
140
120
100
80
60
40
20
0

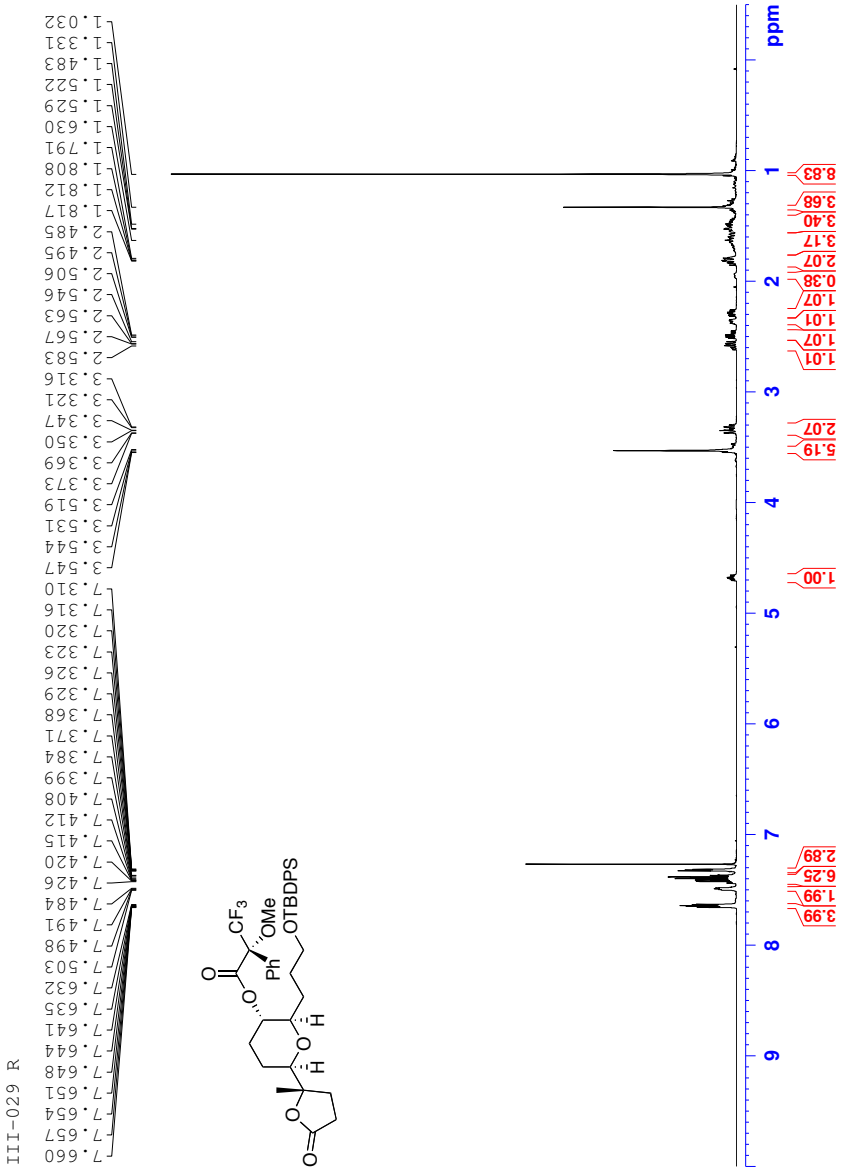

II-017_ Product
7.270
4.560
4.531
4.128
4.099
3.697
3.688
3.679
3.661
3.643
3.556
3.523
3.517
3.485
3.478
2.652
2.624
2.620
2.604
2.591
2.571
2.250
2.229
2.217
2.186
2.176
2.170
2.160
2.146
2.118
2.103
1.962
1.933
1.929
1.918
1.900
1.891
1.884
1.750
1.744
1.735
1.717
1.703
1.686
1.678
1.566
1.533
1.498
1.474
1.456
1.438
1.390
1.368
1.351
1.334
HO
O
O
O
O
H
O
H
O
ppm
1
2
3
4
5
6
7
8
9
0.84
3.73
1.26
0.90
2.47
3.48
2.21
3.03
1.88
2.00
2.20
0.89
0.85


II-017 Product_Carbon
177.06
154.01
86.49
82.03
80.28
80.16
77.43
77.00
76.58
69.35
61.80
33.99
29.45
29.04
28.46
24.18
23.53
22.83
ppm
0
20
40
60
80
100
120
140
160
180
200

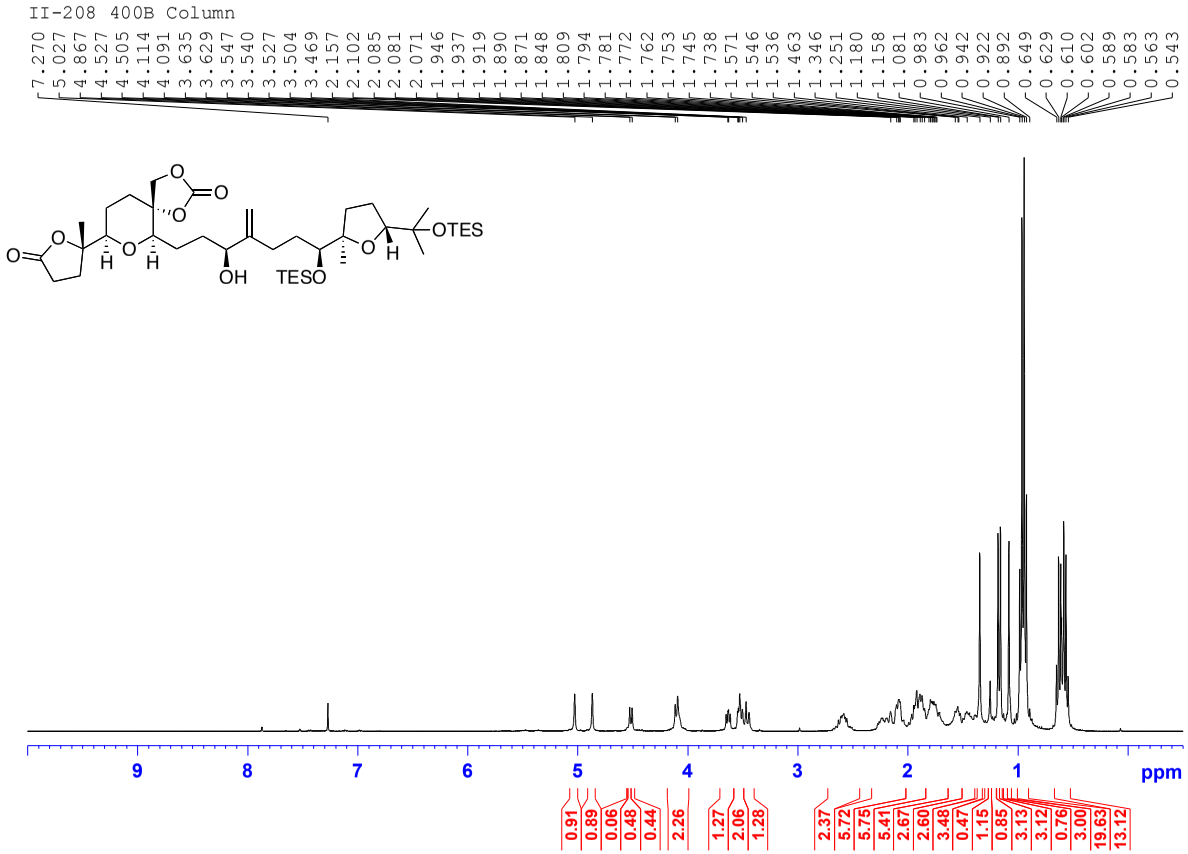

I-238 Column
9.774
7.298
7.270
7.269
7.243
5.310
4.586
4.556
4.143
4.114
3.542
3.533
3.506
3.496
3.489
3.457
3.449
2.618
2.607
2.598
2.578
2.550
2.219
2.203
2.192
2.176
2.165
2.158
2.150
2.144
2.114
2.099
2.055
1.971
1.962
1.948
1.943
1.924
1.914
1.899
1.884
1.870
1.840
1.804
1.551
1.382
1.349
1.326
0.035
0.019
0.018
0.008
-0.003
-0.004
-0.018
ppm
0.64
0.77
0.83
2.00
3.13
1.95
0.74
2.62
1.01
3.08
0.46

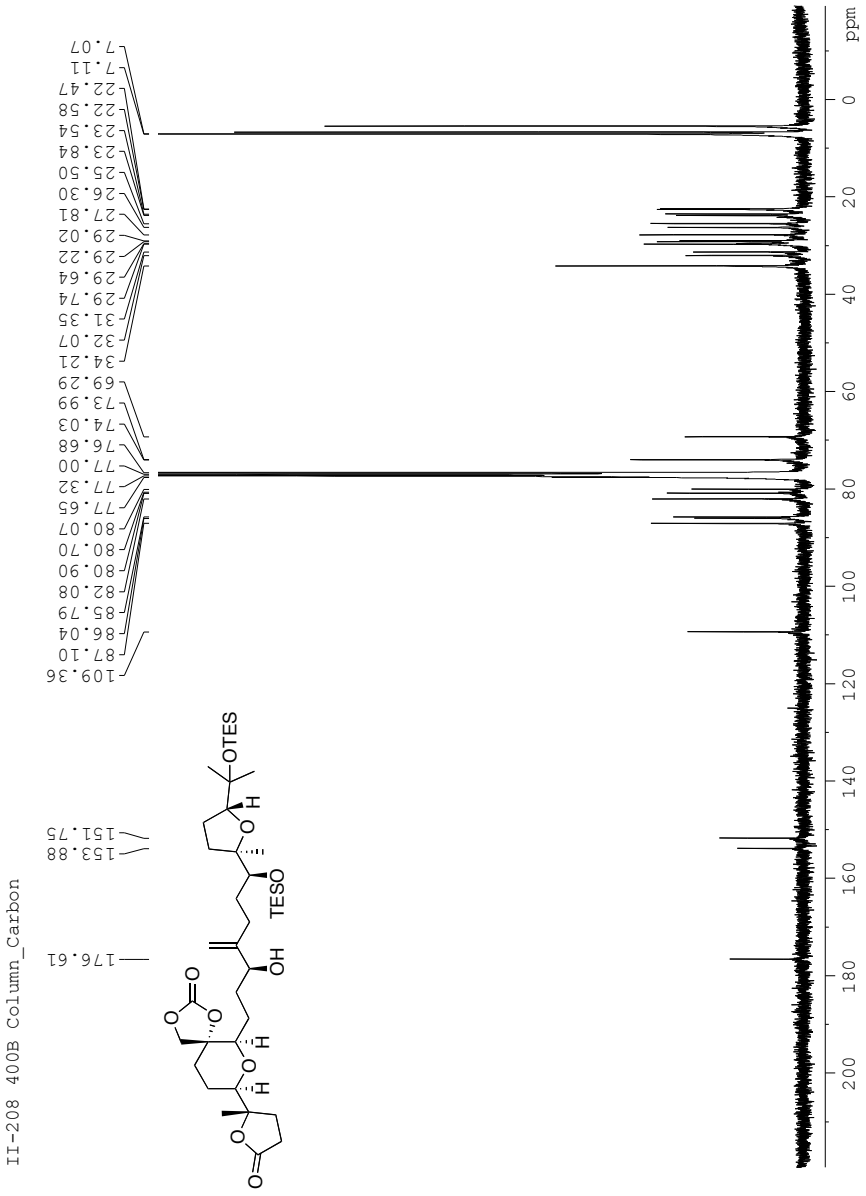
II-018 Product_Carbon
200.77
176.43
153.70
86.01
82.25
79.97
79.62
77.42
77.20
77.00
76.57
69.20
39.38
34.01
29.17
23.52
22.81
20.21
ppm
0
20
40
60
80
100
120
140
160
180
200

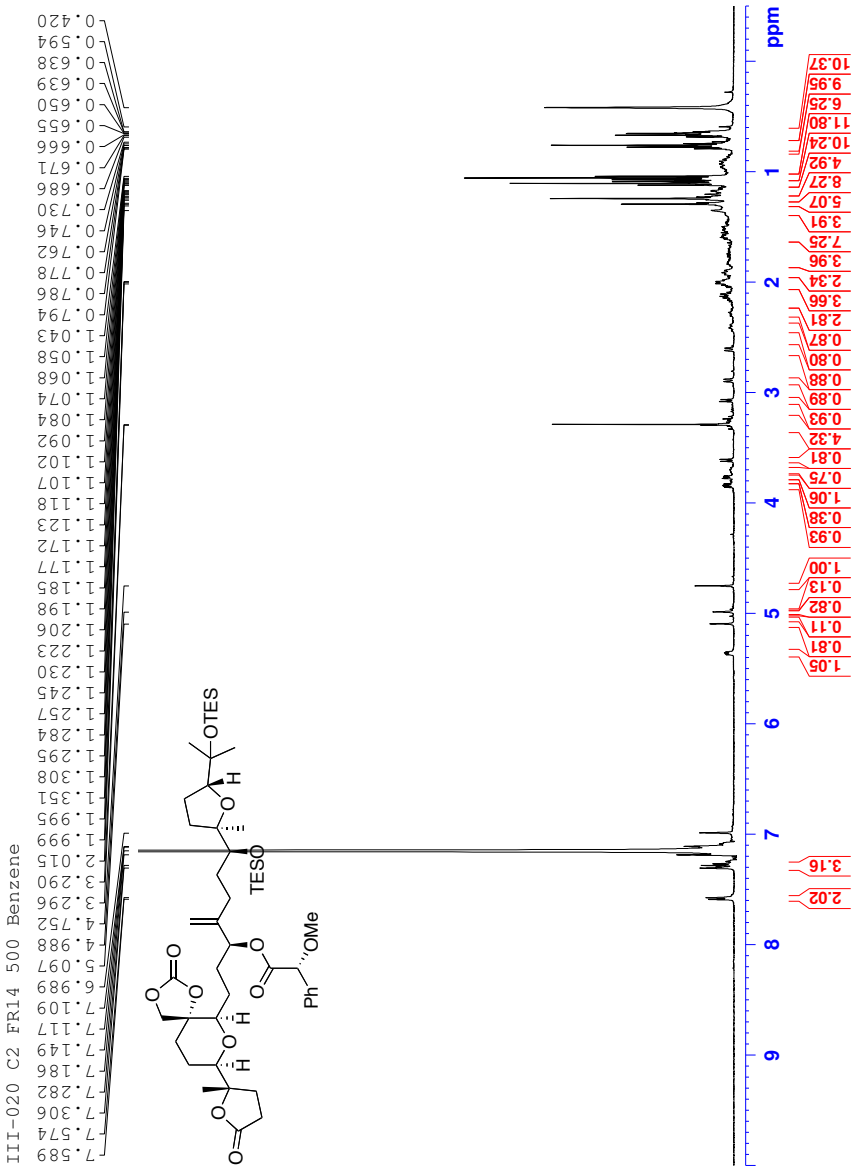

III-027 Column
7.688
7.685
7.683
7.680
7.677
7.673
7.669
7.667
7.664
7.426
7.420
7.414
7.412
7.409
7.401
7.386
7.373
7.370
3.710
3.698
3.685
3.327
3.323
3.305
3.044
3.038
2.603
2.587
2.582
2.566
2.492
2.481
2.471
2.294
2.140
1.809
1.793
1.788
1.783
1.767
1.747
1.742
1.738
1.724
1.550
1.471
1.462
1.453
1.444
1.435
1.426
1.421
1.418
1.324
1.063
OH
O
O
H
H
OTBDPS
9
8
7
6
5
4
3
2
1
ppm
3.95
5.91
2.11
0.99
1.00
1.00
1.02
0.62
0.41
0.99
0.93
1.04
3.16
1.13
4.13
3.06
9.41

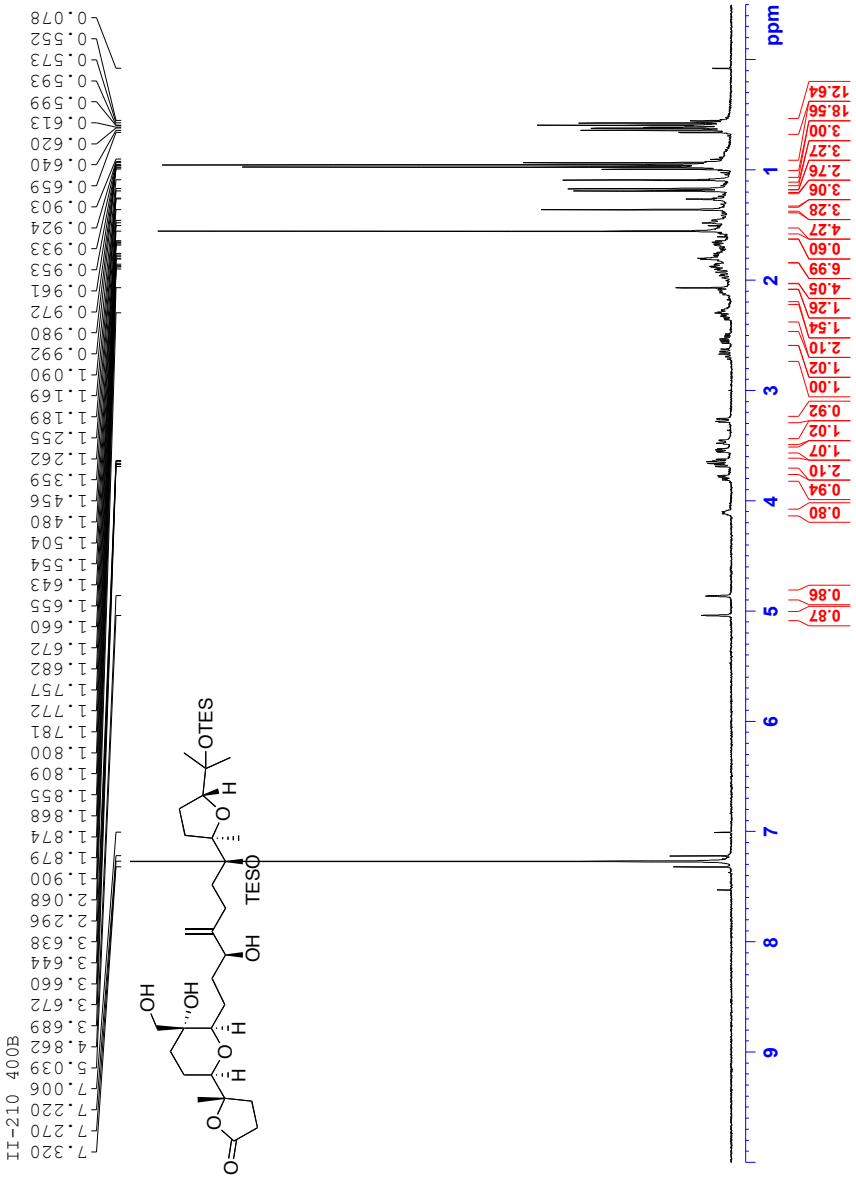

III-029 R
7.660
7.657
7.654
7.651
7.648
7.644
7.641
7.635
7.632
7.503
7.498
7.491
7.484
7.426
7.420
7.415
7.412
7.408
7.399
7.384
7.371
7.368
7.329
7.326
7.323
7.320
7.316
7.310
3.547
3.544
3.531
3.519
3.373
3.369
3.350
3.347
3.321
3.316
2.583
2.567
2.563
2.546
2.506
2.495
2.485
1.817
1.812
1.808
1.791
1.630
1.529
1.522
1.483
1.331
1.032
CF3
OMe
Ph
OTBDPS
O
O
O
O
H
H
O
ppm
1
2
3
4
5
6
7
8
9
8.83
3.68
3.40
3.17
2.07
0.38
1.07
1.01
1.07
1.01
5.19
2.07
1.00
3.99
1.99
6.25
2.89

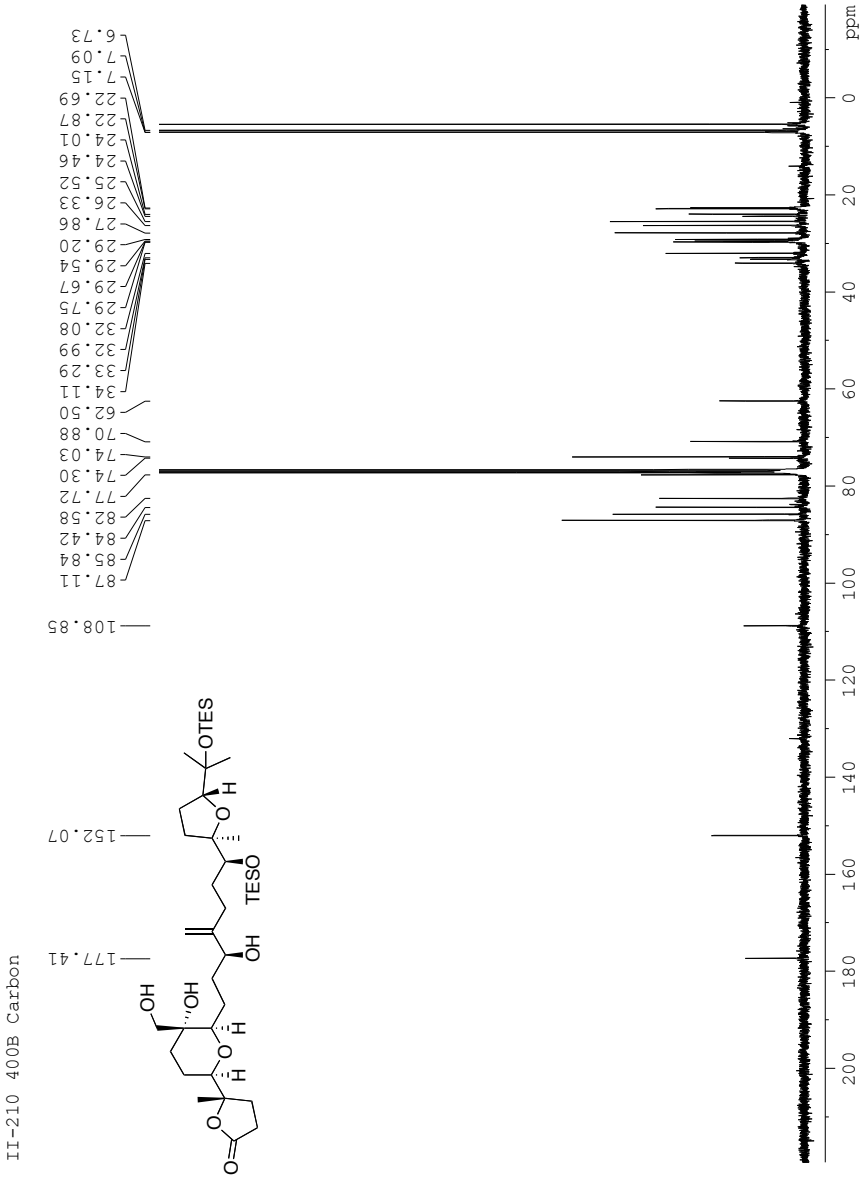
III-028 S
7.652
7.649
7.647
7.636
7.633
7.630
7.493
7.482
7.478
7.421
7.415
7.410
7.407
7.404
7.401
7.398
7.390
7.375
7.370
7.367
7.361
7.359
7.356
7.348
7.345
7.342
3.629
3.617
3.606
3.490
3.489
3.326
3.323
3.316
3.312
3.304
3.300
2.314
2.304
2.293
2.288
2.283
2.278
1.768
1.764
1.744
1.739
1.734
1.530
1.522
1.452
1.446
1.427
1.319
1.036
CF3
Ph
MeO
OTBDPS
O
O
O
O
H
H
O
ppm
9.48
3.18
3.06
2.25
4.89
0.51
2.07
1.07
1.05
2.00
3.05
2.02
1.00
9.38
2.06
4.08

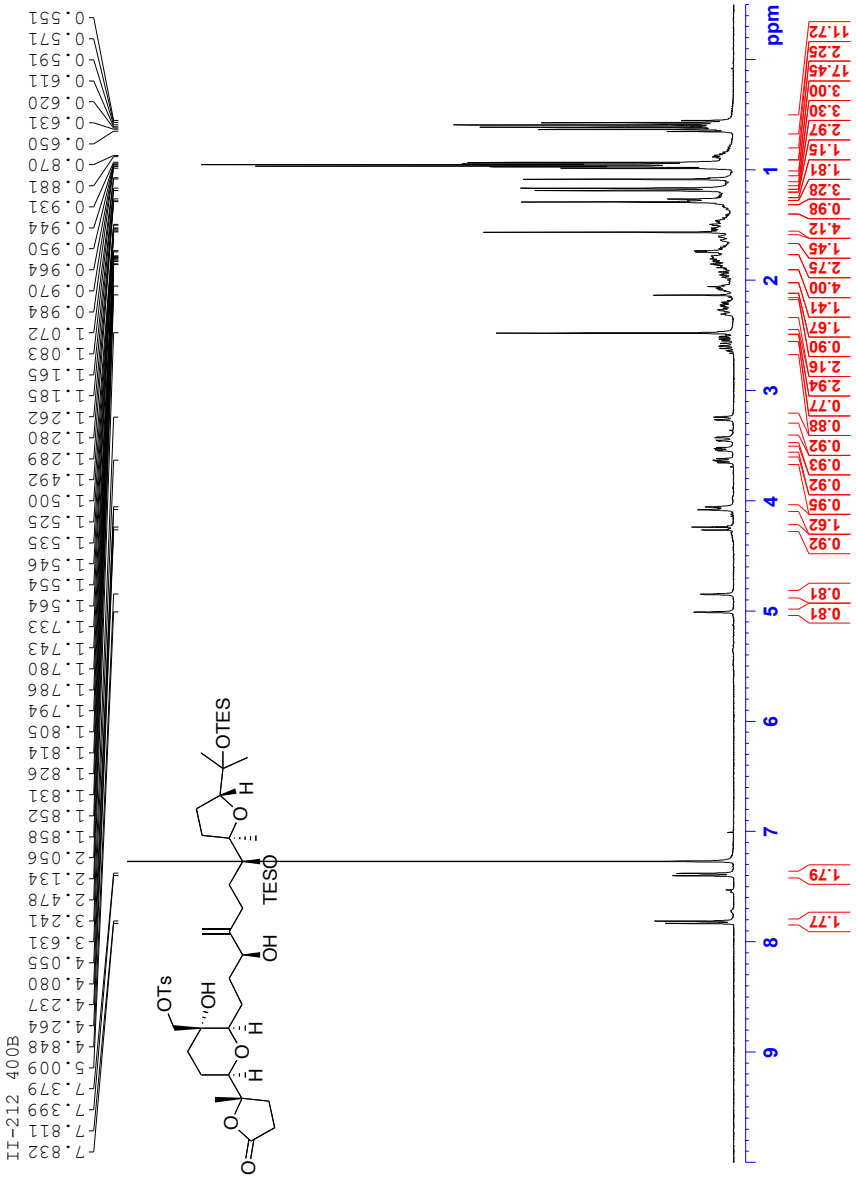

II-208 400B Column
7.270
5.027
4.867
4.527
4.505
4.114
4.091
3.635
3.629
3.547
3.540
3.527
3.504
3.469
2.157
2.102
2.085
2.081
2.071
1.946
1.937
1.919
1.890
1.871
1.848
1.809
1.794
1.781
1.772
1.762
1.753
1.745
1.738
1.571
1.546
1.536
1.463
1.346
1.251
1.180
1.158
1.081
0.983
0.962
0.942
0.922
0.892
0.649
0.629
0.610
0.602
0.589
0.583
0.563
0.543
OTES
OH
TESO
9
8
7
6
5
4
3
2
1
ppm
0.91
0.89
0.06
0.48
0.44
2.26
1.27
2.06
1.28
2.37
5.72
5.75
5.41
2.67
2.60
3.48
0.47
1.15
0.85
3.13
3.12
0.76
3.00
19.63
13.12

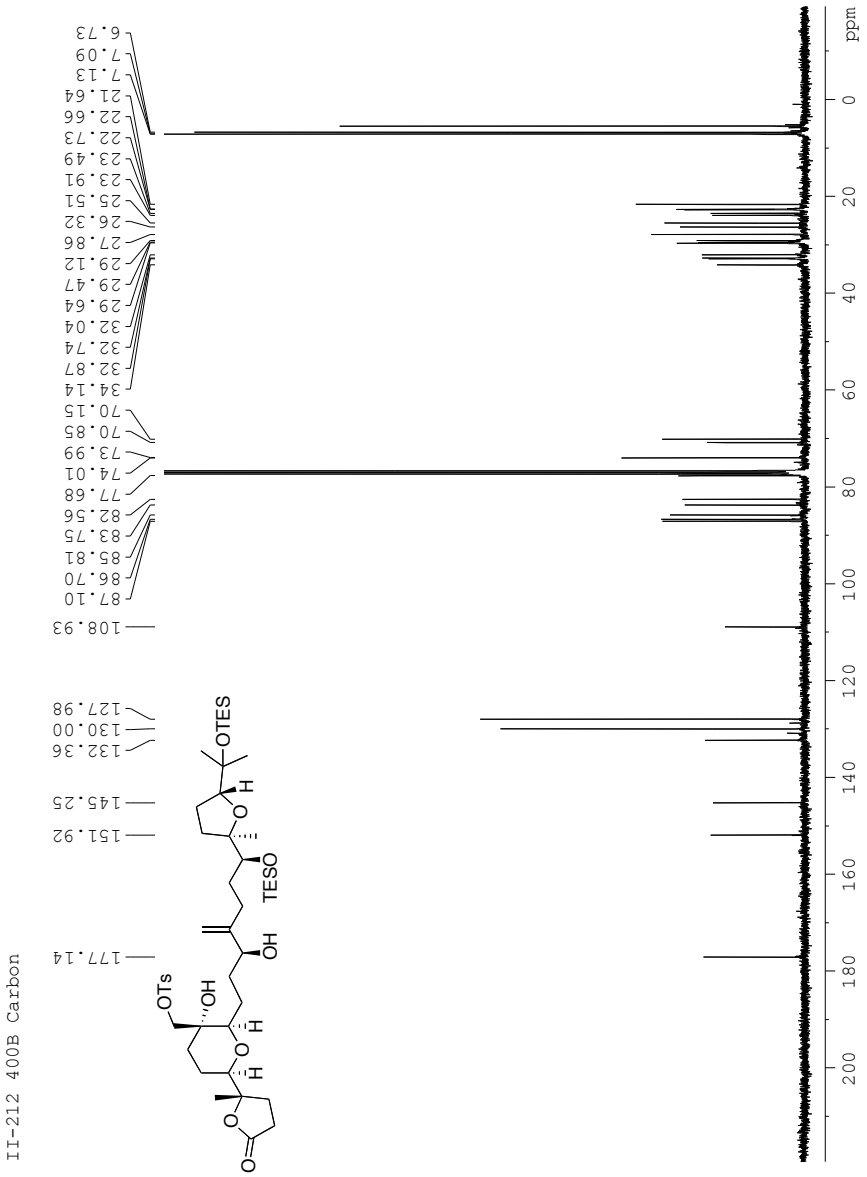

II-208 400B Column_Carbon
176.61
153.88
151.75
109.36
87.10
86.04
85.79
82.08
80.90
80.70
80.07
77.65
77.32
77.00
76.68
74.03
73.99
69.29
34.21
32.07
31.35
29.74
29.64
29.22
29.02
27.81
26.30
25.50
23.84
23.54
22.58
22.47
7.11
7.07
OTES
TESO
OH
ppm

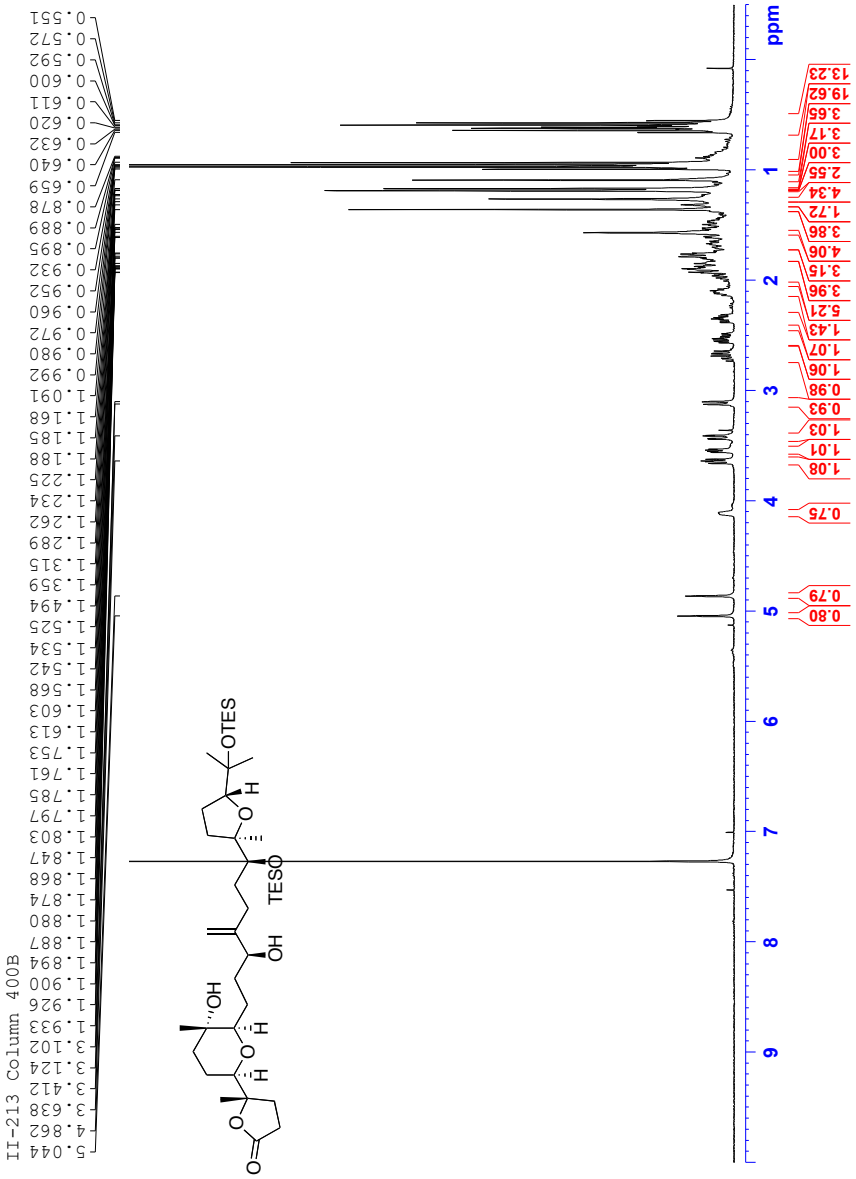

III-020 C2 FR14 500 Benzene
OTES
TESO
OMe
Ph
ppm

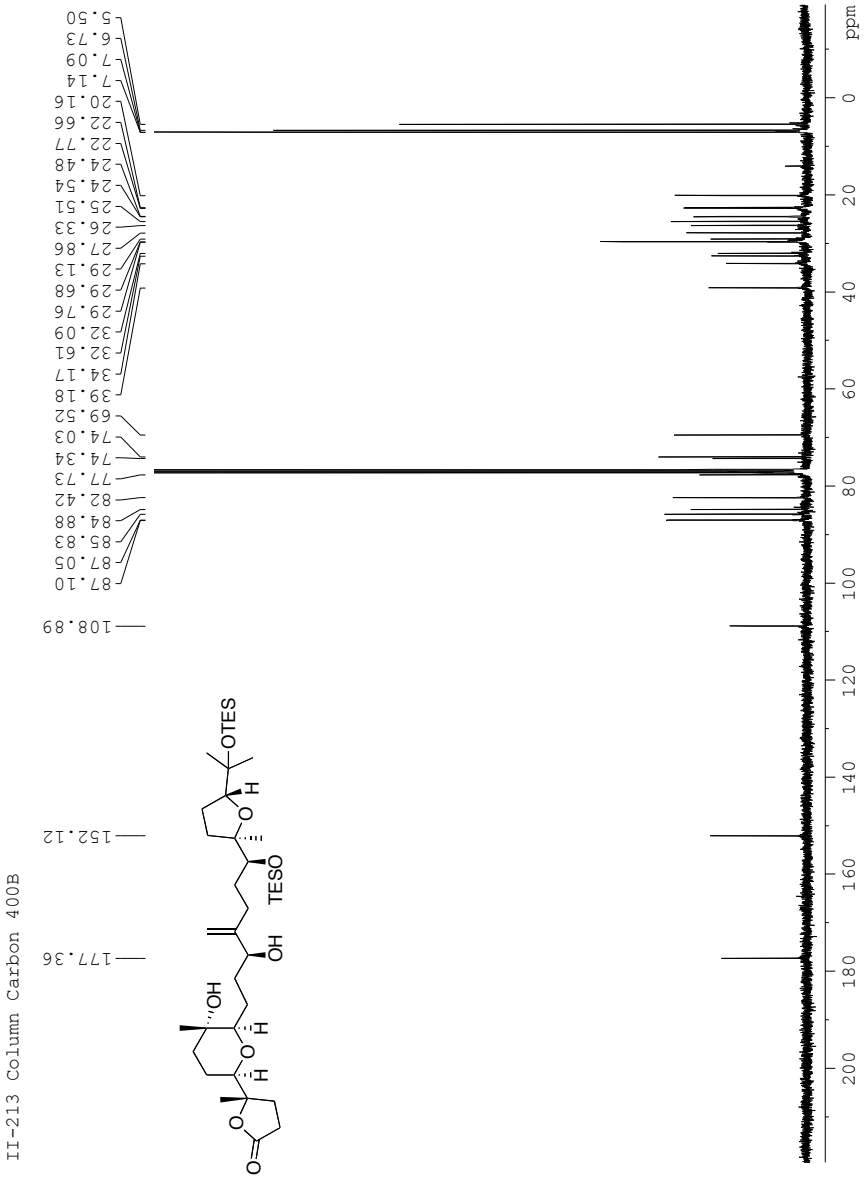

II-210 400B
ppm
OTES
TESO
OH
OH
OH
O
H
O
H
O
H
O
0.80
0.94
2.10
1.07
1.02
0.92
1.00
1.02
2.10
1.64
1.26
4.05
6.99
0.60
4.27
3.28
3.06
2.76
3.27
3.00
18.56
12.64
0.87
0.86

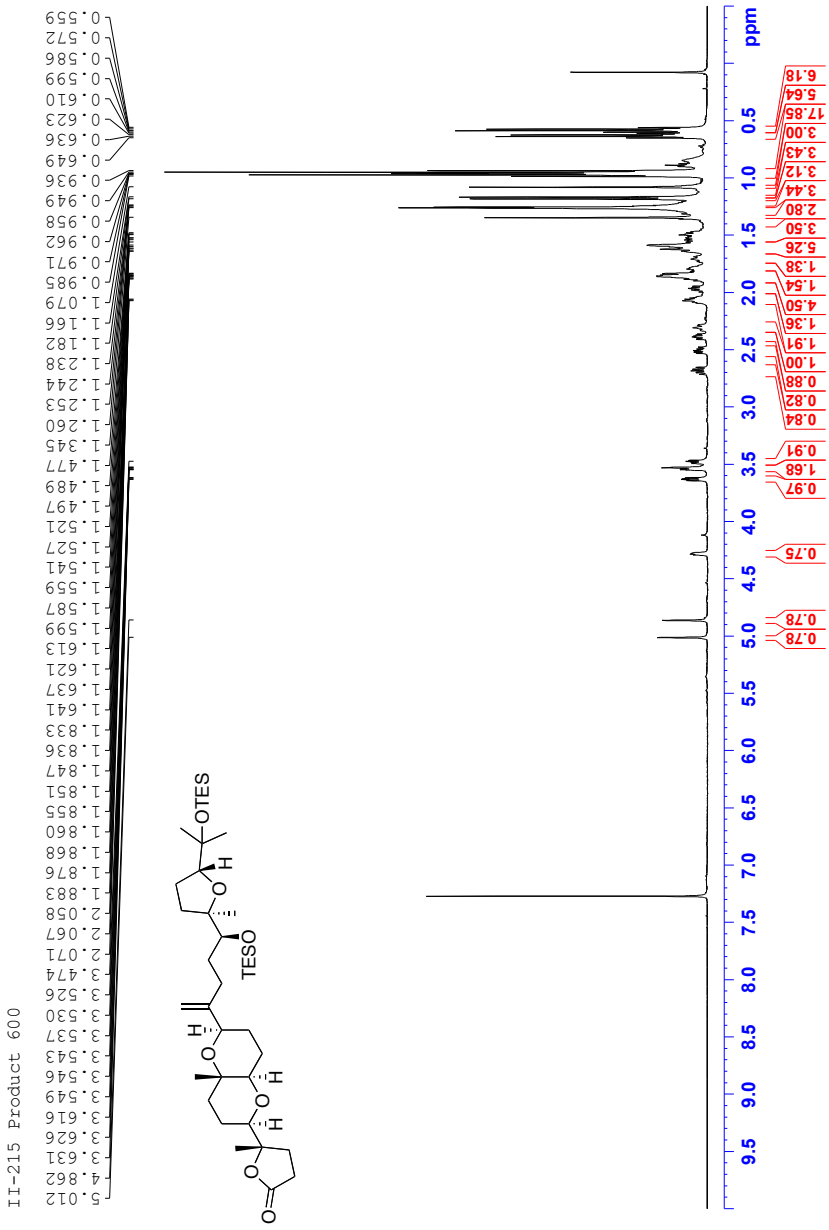

II-210 400B Carbon
177.41
152.07
108.85
87.11
85.84
84.42
82.58
77.72
74.30
74.03
70.88
62.50
34.11
33.29
32.99
32.08
29.75
29.67
29.54
29.20
27.86
26.33
25.52
24.46
24.01
22.87
22.69
7.15
7.09
6.73
OTES
TESO
OH
OH
OH
O
H
O
H
O
O
O
ppm
0
20
40
60
80
100
120
140
160
180
200


II-212 400B
ppm
OTES
TESO
OH
OH
OTs
H
O

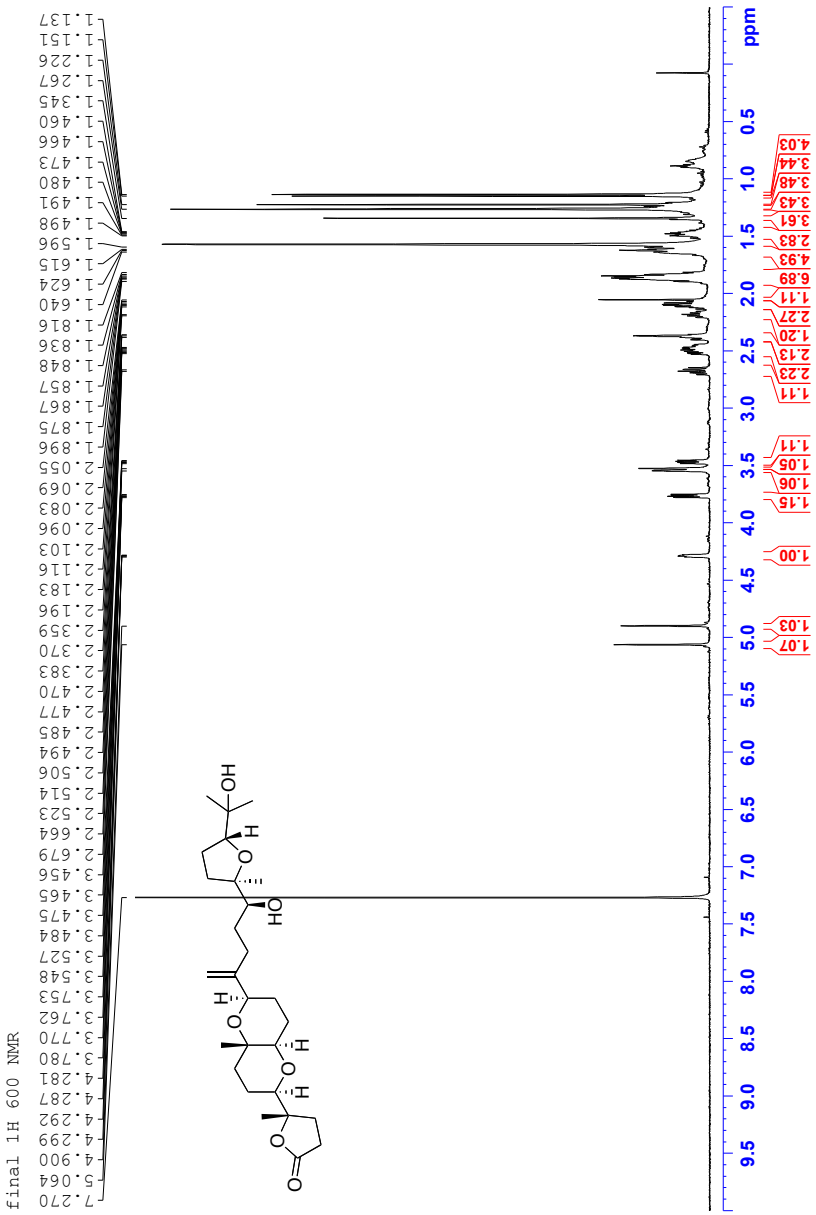

II-212 400B Carbon
177.14
151.92
145.25
132.36
130.00
127.98
108.93
87.10
86.70
85.81
83.75
82.56
77.68
74.01
73.99
70.85
70.15
34.14
32.87
32.74
32.04
29.64
29.47
29.12
27.86
26.32
25.51
23.91
23.49
22.73
22.66
21.64
7.13
7.09
6.73
OTs
OH
OH
TESO
OTES
O
H
O
H
O
H
O
O
O
ppm
0
20
40
60
80
100
120
140
160
180
200

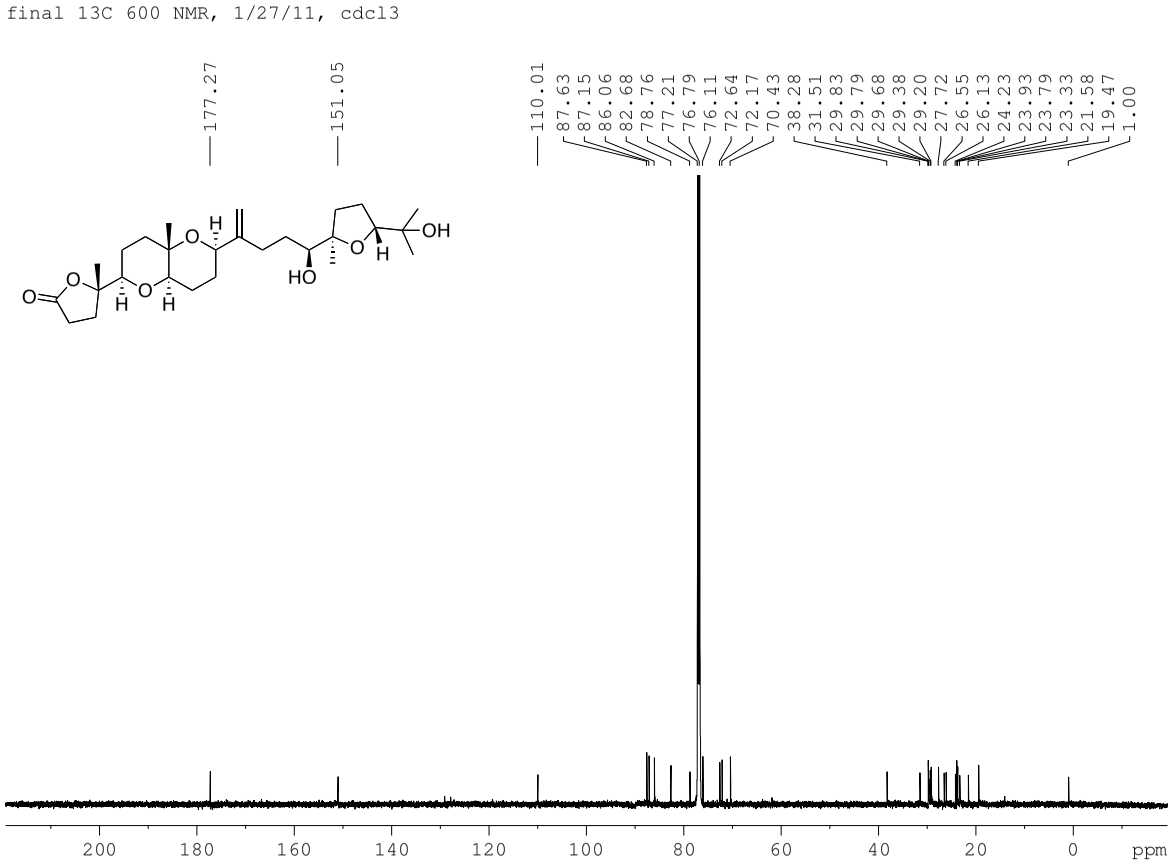

II-213 Column 400B
OTES
TESO
OH
OH
O
H
H
O
O
O
ppm
0.75
1.08
1.01
1.03
0.93
0.98
1.06
1.07
1.43
5.21
3.96
3.15
4.06
3.86
1.72
4.34
2.55
3.00
3.17
3.65
19.62
13.23
0.80
0.79


II-213 Column Carbon 400B
177.36
152.12
108.89
87.10
87.05
85.83
84.88
82.42
77.73
74.34
74.03
69.52
39.18
34.17
32.61
32.09
29.76
29.68
29.13
27.86
26.33
25.51
24.54
24.48
22.77
22.66
20.16
7.14
7.09
6.73
5.50
OTES
TESO
OH
OH
ppm
0
20
40
60
80
100
120
140
160
180
200


II-215 Product 600
5.012
4.862
3.631
3.626
3.616
3.549
3.546
3.543
3.537
3.530
3.526
3.474
2.071
2.067
2.058
1.883
1.876
1.868
1.860
1.855
1.851
1.847
1.836
1.833
1.641
1.637
1.621
1.613
1.599
1.587
1.559
1.541
1.527
1.521
1.497
1.489
1.477
1.345
1.260
1.253
1.244
1.238
1.182
1.166
1.079
0.985
0.971
0.962
0.958
0.949
0.936
0.649
0.636
0.623
0.610
0.599
0.586
0.572
0.559
OTES
TESO
H
O
ppm
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
6.18
5.64
17.85
3.00
3.43
3.12
3.44
2.80
3.50
5.26
1.38
1.54
4.60
1.36
1.91
1.00
0.88
0.82
0.84
0.91
1.68
0.97
0.75
0.78
0.78

II-215 Product 600 C13
177.29
151.90
109.34
87.18
87.09
85.82
82.67
78.70
77.90
74.04
72.73
71.99
38.30
34.37
32.27
29.81
29.69
29.55
29.22
27.88
26.40
26.21
25.45
24.25
23.33
22.59
21.64
19.60
7.15
7.11
OTES
TESO
H
O
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180

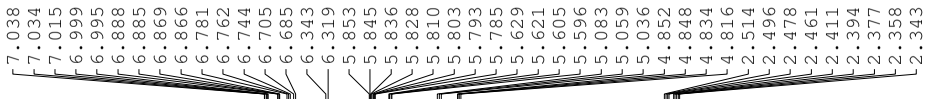

final 1H 600 NMR
7.270
5.064
4.900
4.299
4.292
4.287
4.281
3.780
3.770
3.762
3.753
3.548
3.527
3.484
3.475
3.465
3.456
2.679
2.664
2.523
2.514
2.506
2.494
2.485
2.477
2.470
2.383
2.370
2.359
2.196
2.183
2.116
2.103
2.096
2.083
2.069
2.055
1.896
1.875
1.867
1.857
1.848
1.836
1.816
1.640
1.624
1.615
1.596
1.498
1.491
1.480
1.473
1.466
1.460
1.345
1.267
1.226
1.151
1.137
OH
OH
H
O
H
O
H
O
O
O
ppm
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
1.07
1.03
1.00
1.15
1.06
1.05
1.11
1.11
2.23
2.13
1.20
2.27
1.11
6.89
4.93
2.83
3.61
3.43
3.48
3.44
4.03

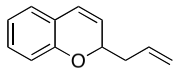

final 13C 600 NMR, 1/27/11, cdcl3
177.27
151.05
110.01
87.63
87.15
86.06
82.68
78.76
77.21
76.79
76.11
72.64
72.17
70.43
38.28
31.51
29.83
29.79
29.68
29.38
29.20
27.72
26.55
26.13
24.23
23.93
23.79
23.33
21.58
19.47
1.00
O
H
O
O
H
O
H
HO
O
H
OH
200
180
160
140
120
100
80
60
40
20
0
ppm

APPENDIX D

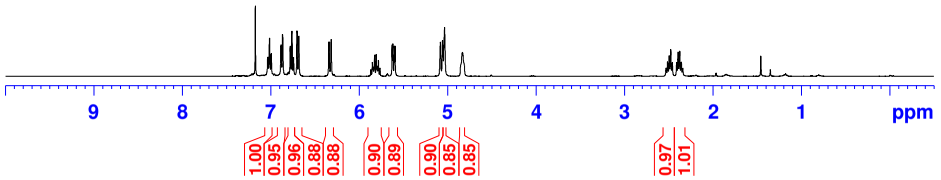
OXIDATIVE BIMOLECULAR COUPLING REACTION (^{1}H-NMR AND ^{13}C-NMR FOR COUPLING PRODUCTS)

IV-014 Column 2

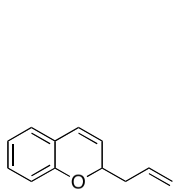


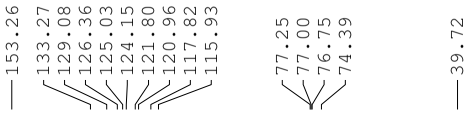


NAME	IV-014 Column 2
EXPNO	10
PROCNO	1
Date_	20120131
Time	18.07
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	128
DW	60.800 usec
DE	6.50 usec
TE	295.7 K
D1	1.00000000 sec
========	CHANNEL f1 ========
NUC1	1H
P1	14.00 usec
SI	65536
SF	400.1300432 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

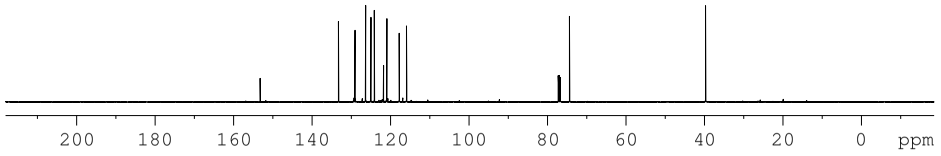


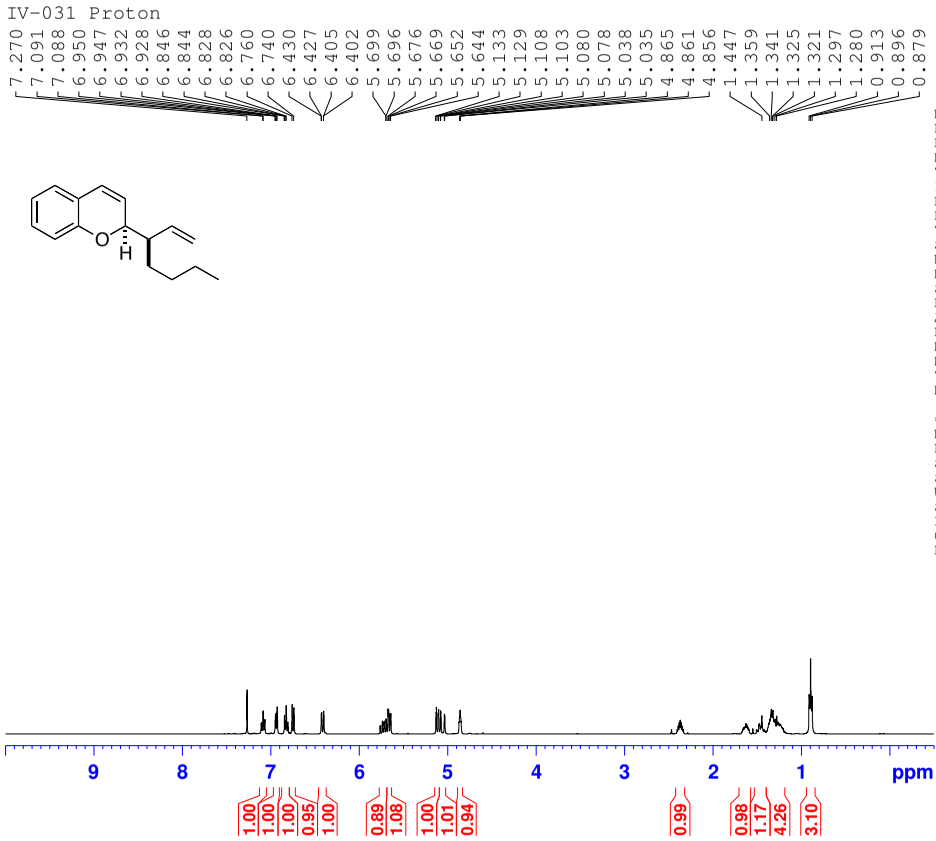
IV-014_Carbon



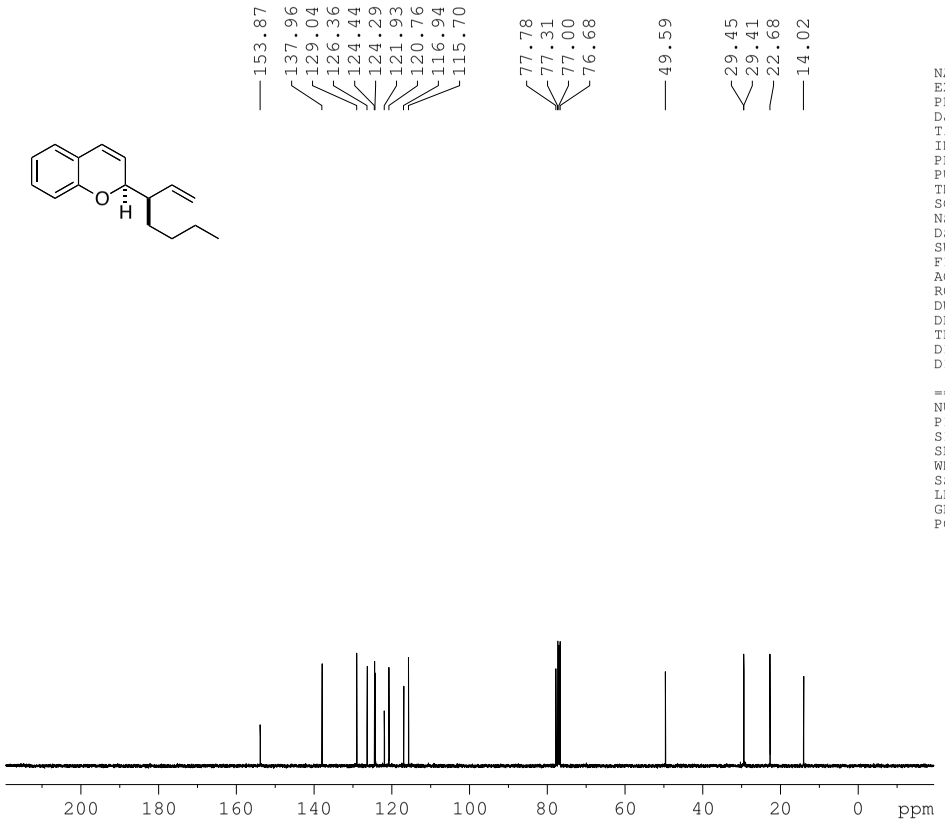


NAME	IV-014_Carbon
EXPNO	1
PROCNO	1
Date_	20120131
Time	18.28
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	64
DS	4
SWH	29761.904 Hz
FIDRES	0.454131 Hz
AQ	1.1010548 sec
RG	203
DW	16.800 usec
DE	6.50 usec
TE	295.0 K
D1	2.00000000 sec
D11	0.03000000 sec
======== CHANNEL f1 ========	
NUC1	13C
P1	8.80 usec
SI	32768
SF	125.7653568 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

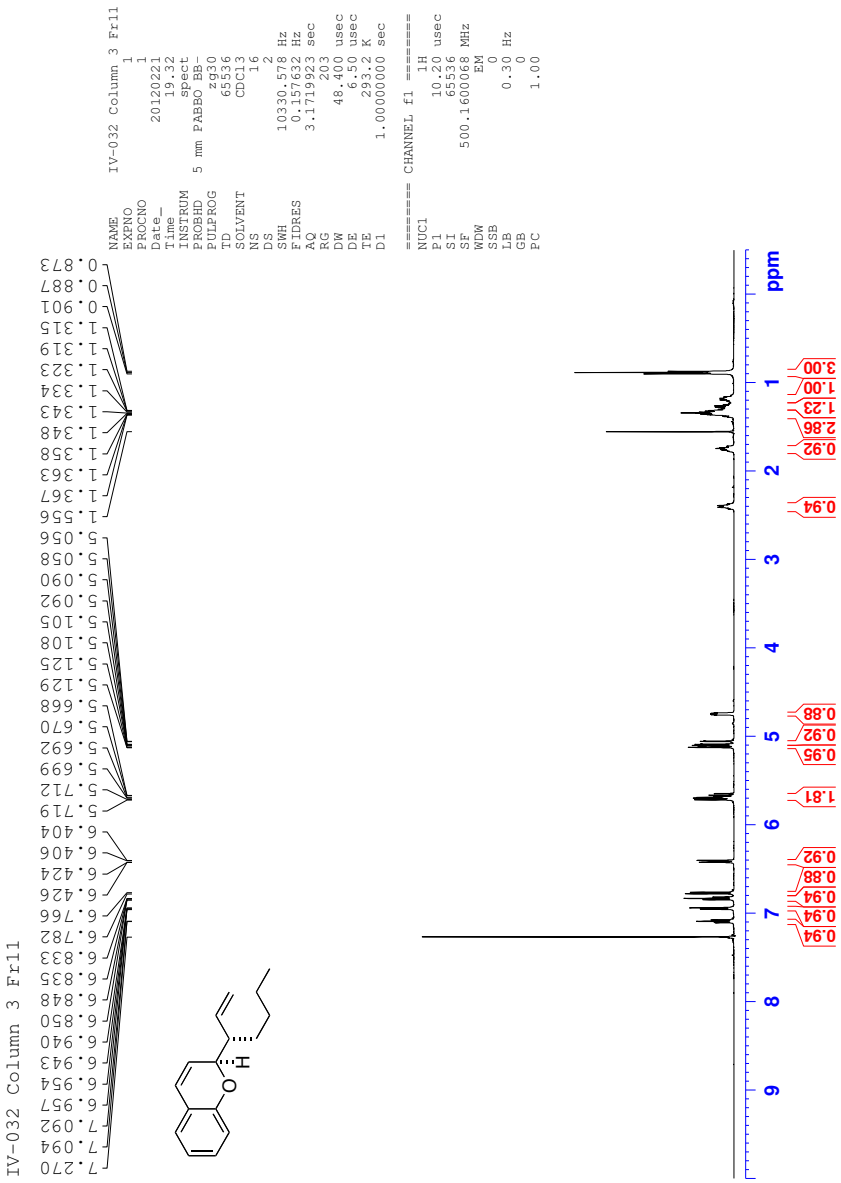


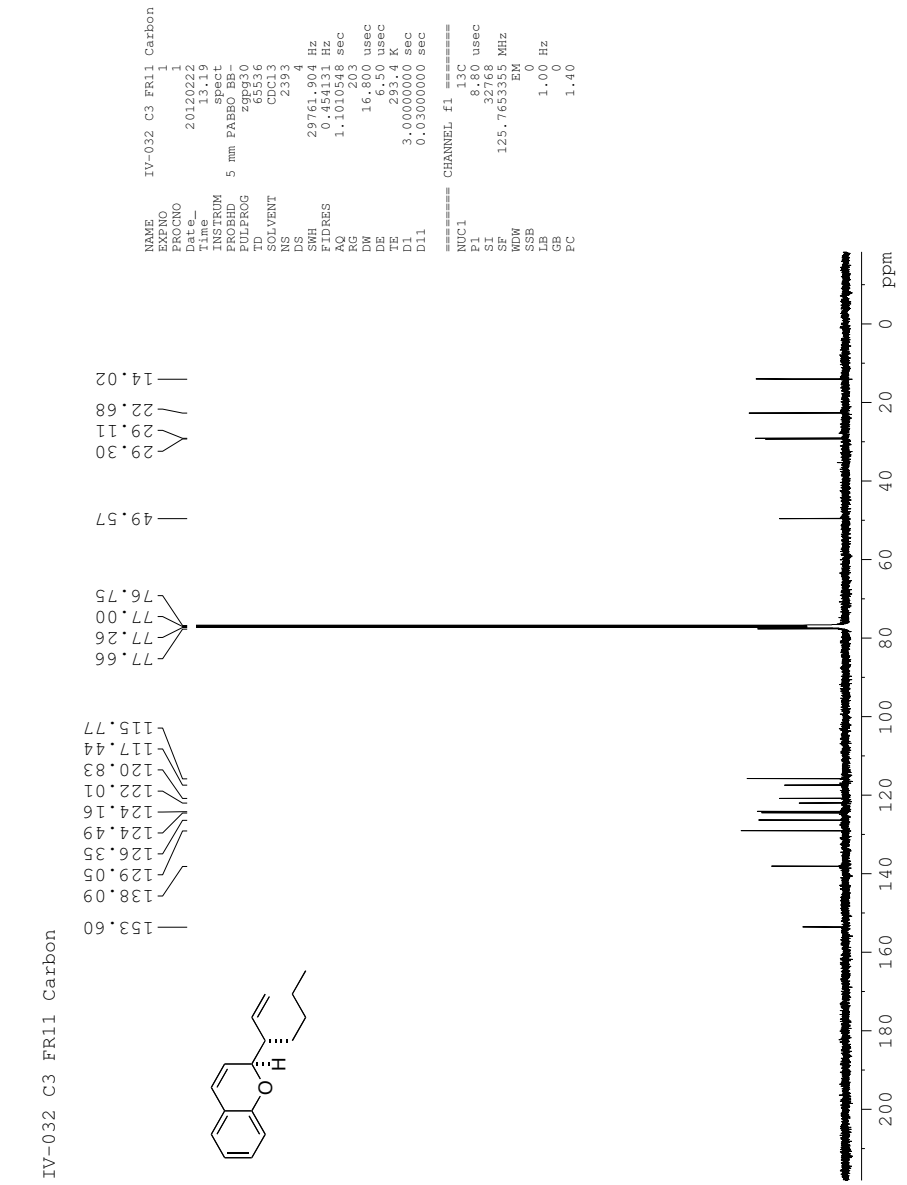

IV-031 Proton
7.270
7.091
7.088
6.950
6.947
6.932
6.928
6.846
6.844
6.828
6.826
6.760
6.740
6.430
6.427
6.405
6.402
5.699
5.696
5.676
5.669
5.652
5.644
5.133
5.129
5.108
5.103
5.080
5.078
5.038
5.035
4.865
4.861
4.856
1.447
1.359
1.341
1.325
1.321
1.297
1.280
0.913
0.896
0.879
O
H
NAME IV-031 Proton
EXPNO 10
PROCNO 1
Date_ 20120221
Time 13.11
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9846387 sec
RG 90.5
DW 60.800 usec
DE 6.50 usec
TE 295.8 K
D1 1.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
SI 65536
SF 400.1300057 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
9
8
7
6
5
4
3
2
1
ppm
1.00
1.00
1.00
0.95
1.00
0.89
1.08
1.00
1.01
0.94
0.99
0.98
1.17
4.26
3.10

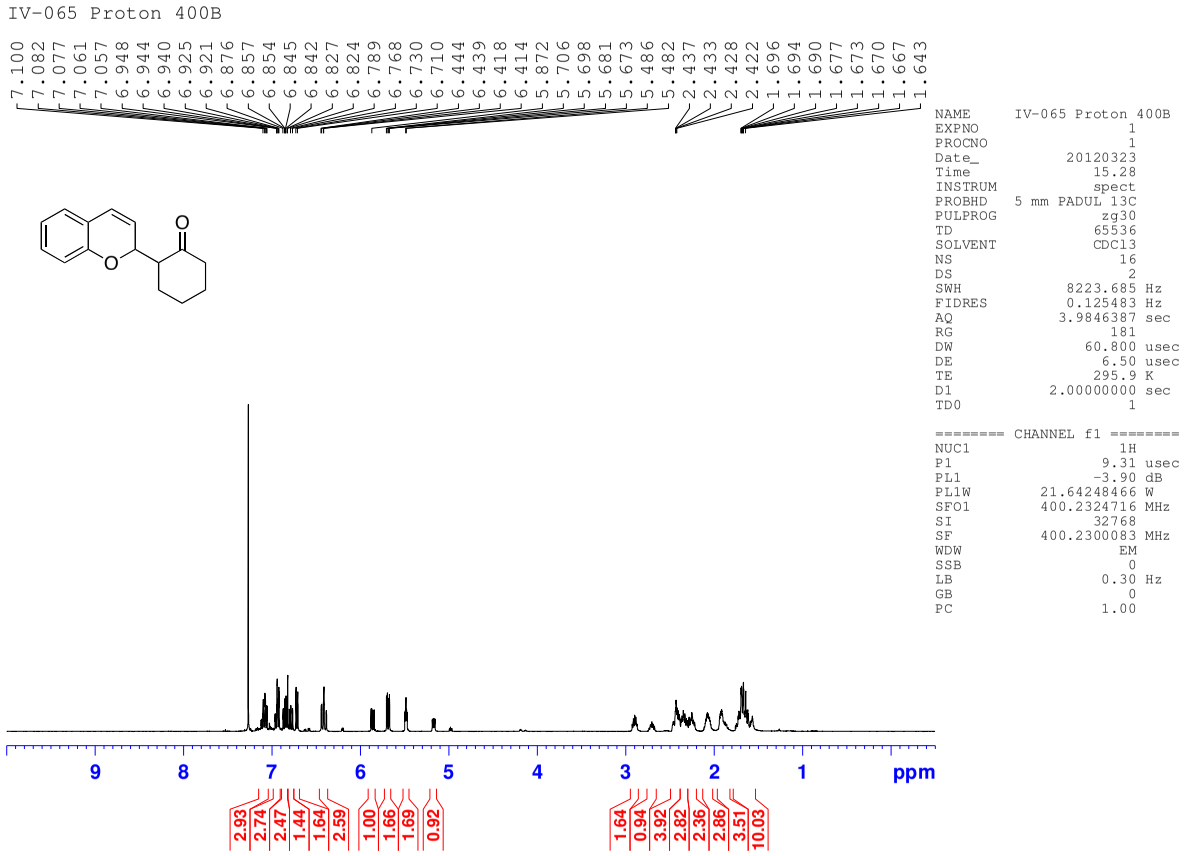
IV-031 Carbon



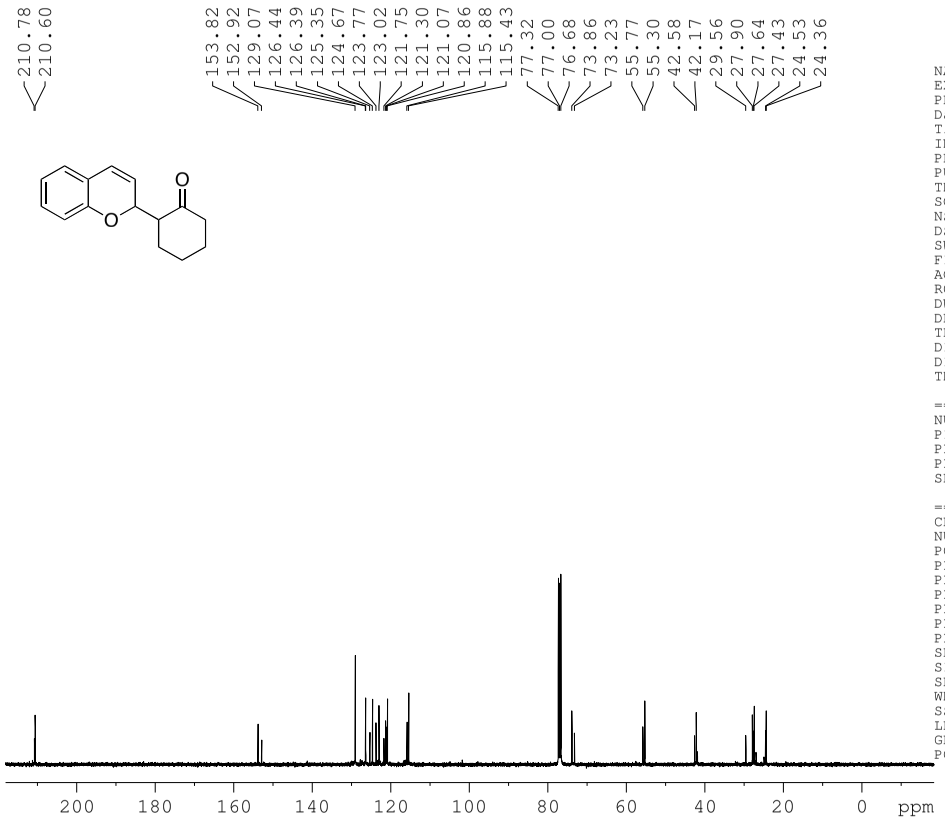
NAME	IV-031 Carbon
EXPNO	10
PROCNO	1
Date_	20120221
Time	13.24
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	160
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	203
DW	20.800 usec
DE	6.50 usec
TE	296.3 K
D1	2.00000000 sec
D11	0.03000000 sec
======== CHANNEL f1 ========	
NUC1	13C
P1	9.00 usec
SI	32768
SF	100.6127752 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40


IV-032 Column 3 Fr11
7.270
7.094
7.092
6.957
6.954
6.943
6.940
6.850
6.848
6.835
6.833
6.782
6.766
6.426
6.424
6.406
6.404
5.719
5.712
5.699
5.692
5.670
5.668
5.129
5.125
5.108
5.105
5.092
5.090
5.058
5.056
1.556
1.367
1.363
1.358
1.348
1.343
1.334
1.323
1.319
1.315
0.901
0.887
0.873
NAME IV-032 Column 3 Fr11
EXPNO 1
PROCNO 1
Date_ 20120221
Time 19.32
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 203
DW 48.400 usec
DE 6.50 usec
TE 293.2 K
D1 1.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 10.20 usec
SI 65536
SF 500.1600068 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
ppm
1 2 3 4 5 6 7 8 9
3.00
1.00
1.23
2.86
0.92
0.94
0.88
0.92
0.95
1.81
0.92
0.88
0.94
0.94
0.94

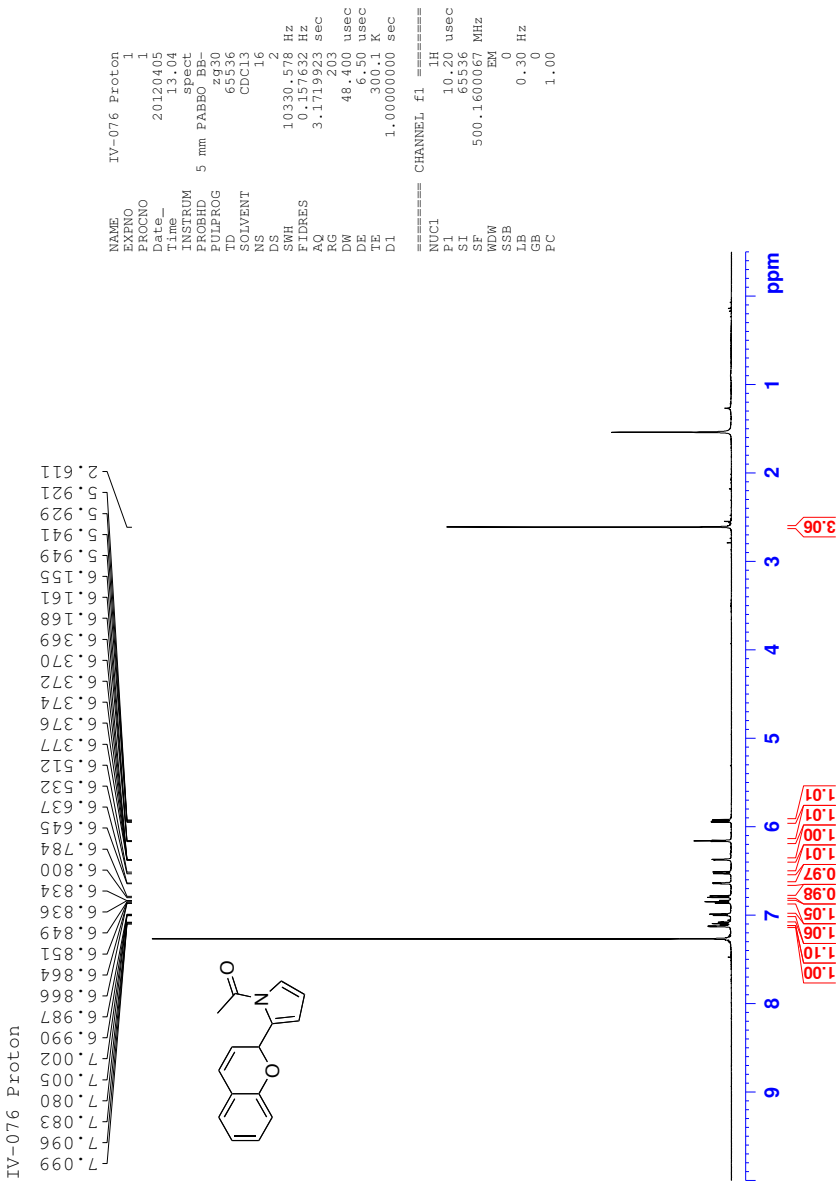

IV-032 C3 FR11 Carbon
153.60
138.09
129.05
126.35
124.49
124.16
122.01
120.83
117.44
115.77
77.66
77.26
77.00
76.75
49.57
29.30
29.11
22.68
14.02
NAME IV-032 C3 FR11 Carbon
EXPNO 1
PROCNO 1
Date_ 20120222
Time 13.19
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 2393
DS 4
SWH 29761.904 Hz
FIDRES 0.454131 Hz
AQ 1.1010548 sec
RG 203
DW 16.800 usec
DE 6.50 usec
TE 293.4 K
D1 3.00000000 sec
D11 0.03000000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 8.80 usec
SI 32768
SF 125.7653355 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
200 180 160 140 120 100 80 60 40 20 0 ppm


IV-065 Proton 400B
7.100
7.082
7.077
7.061
7.057
6.948
6.944
6.940
6.925
6.921
6.876
6.857
6.854
6.845
6.842
6.827
6.824
6.789
6.768
6.730
6.710
6.444
6.439
6.418
6.414
5.872
5.706
5.698
5.681
5.673
5.486
5.482
2.437
2.433
2.428
2.422
1.696
1.694
1.690
1.677
1.673
1.670
1.667
1.643
O
O
NAME IV-065 Proton 400B
EXPNO 1
PROCNO 1
Date_ 20120323
Time 15.28
INSTRUM spect
PROBHD 5 mm PADUL 13C
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9846387 sec
RG 181
DW 60.800 usec
DE 6.50 usec
TE 295.9 K
D1 2.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.31 usec
PL1 -3.90 dB
PL1W 21.64248466 W
SFO1 400.2324716 MHz
SI 32768
SF 400.2300083 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
9
8
7
6
5
4
3
2
1
ppm
2.93
2.74
2.47
1.44
1.64
2.59
1.00
1.66
1.69
0.92
1.64
0.94
3.92
2.82
2.36
2.86
3.51
10.03

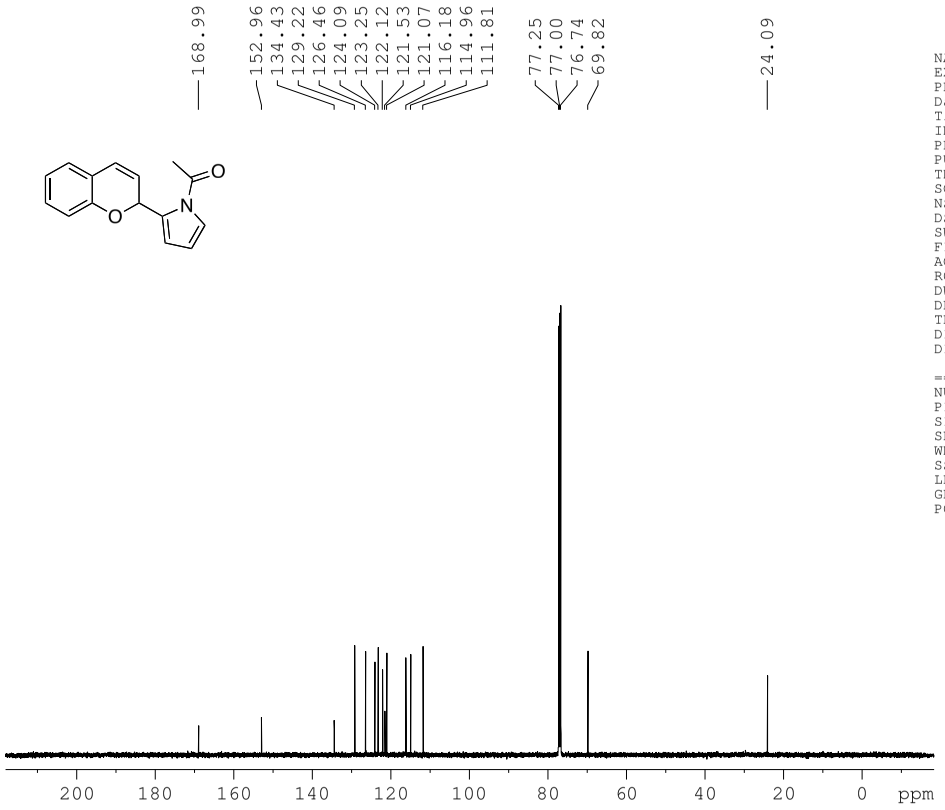
IV-065 Carbon 400B



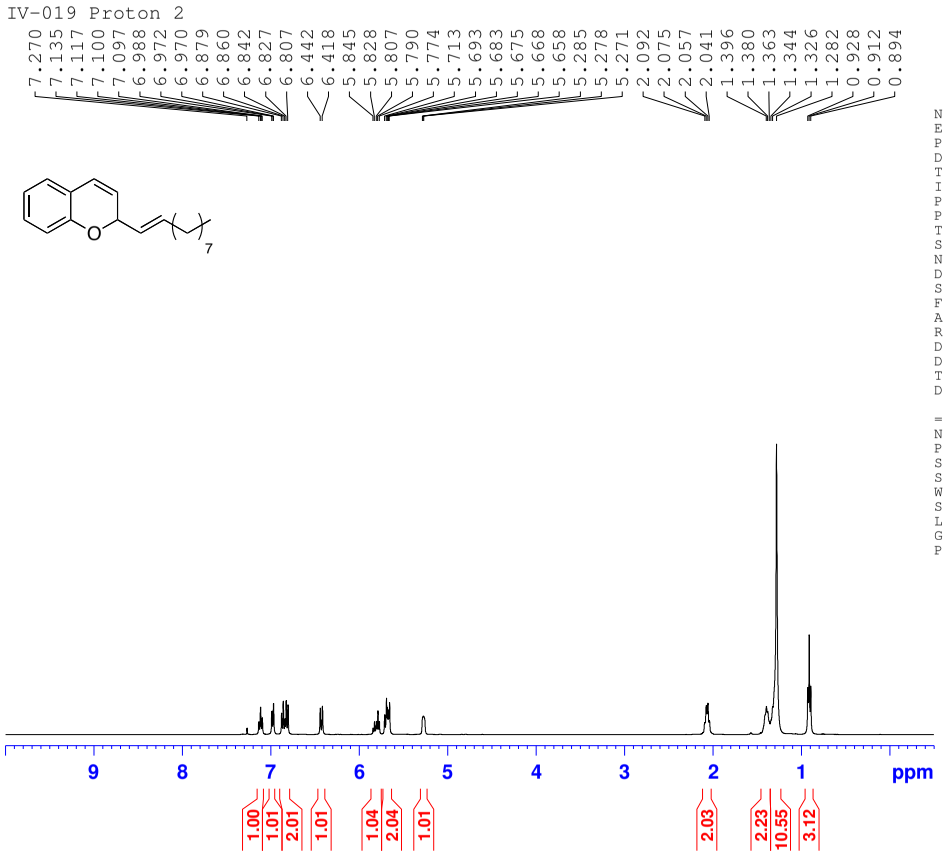
NAME	IV-065 Carbon 400B
EXPNO	1
PROCNO	1
Date_	20120323
Time	15.51
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	208
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	64
DW	20.800 usec
DE	6.50 usec
TE	296.2 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379248 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40


IV-076 Proton
7.099
7.096
7.083
7.080
7.005
7.002
6.990
6.987
6.866
6.864
6.851
6.849
6.836
6.834
6.800
6.784
6.645
6.637
6.532
6.512
6.377
6.376
6.374
6.372
6.370
6.369
6.168
6.161
6.155
5.949
5.941
5.929
5.921
2.611
NAME IV-076 Proton
EXPNO 1
PROCNO 1
Date_ 20120405
Time_ 13.04
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 203
DW 48.400 usec
DE 6.50 usec
TE 300.1 K
D1 1.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 10.20 usec
SI 65536
SF 500.1600067 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
O
N
O
3.06
1.00
1.10
1.06
1.05
0.98
0.97
1.01
1.00
1.01
1.01
ppm
9
8
7
6
5
4
3
2
1

IV-076 Carbon

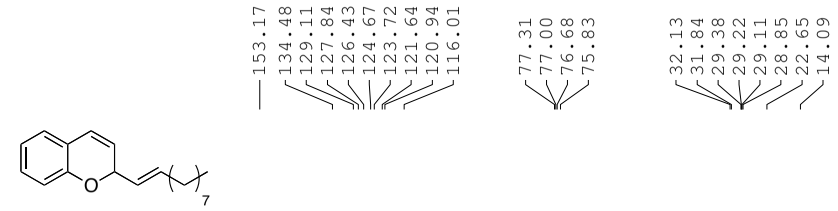


NAME	IV-076 Carbon
EXPNO	1
PROCNO	1
Date_	20120405
Time	14.04
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	982
DS	4
SWH	29761.904 Hz
FIDRES	0.454131 Hz
AQ	1.1010548 sec
RG	203
DW	16.800 usec
DE	6.50 usec
TE	300.0 K
D1	2.00000000 sec
D11	0.03000000 sec
======== CHANNEL f1 ========	
NUC1	13C
P1	8.80 usec
SI	32768
SF	125.7653339 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

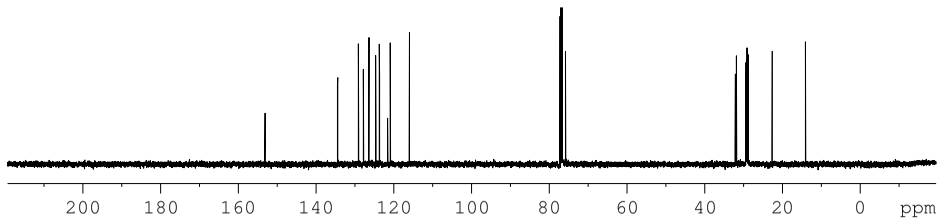


NAME	IV-019 Proton 2
EXPNO	10
PROCNO	1
Date_	20120207
Time	15.26
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	18
DW	60.800 usec
DE	6.50 usec
TE	295.7 K
D1	1.00000000 sec
========	CHANNEL f1 ========
NUC1	1H
P1	14.00 usec
SI	65536
SF	400.1300058 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

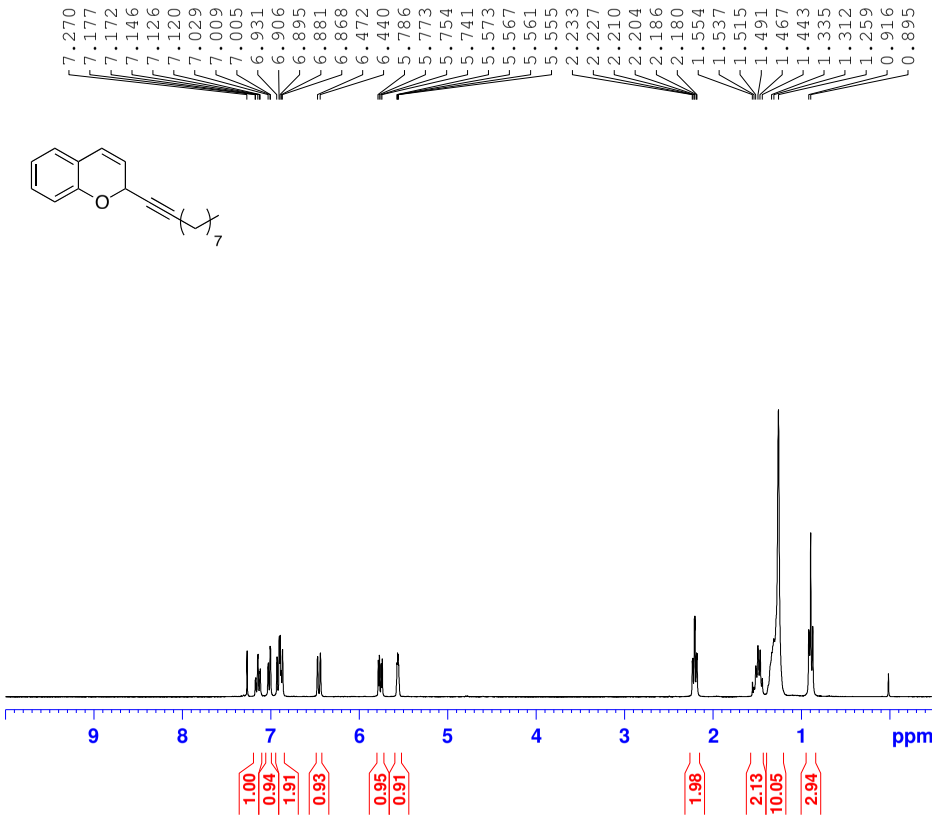
IV-019 Carbon 2



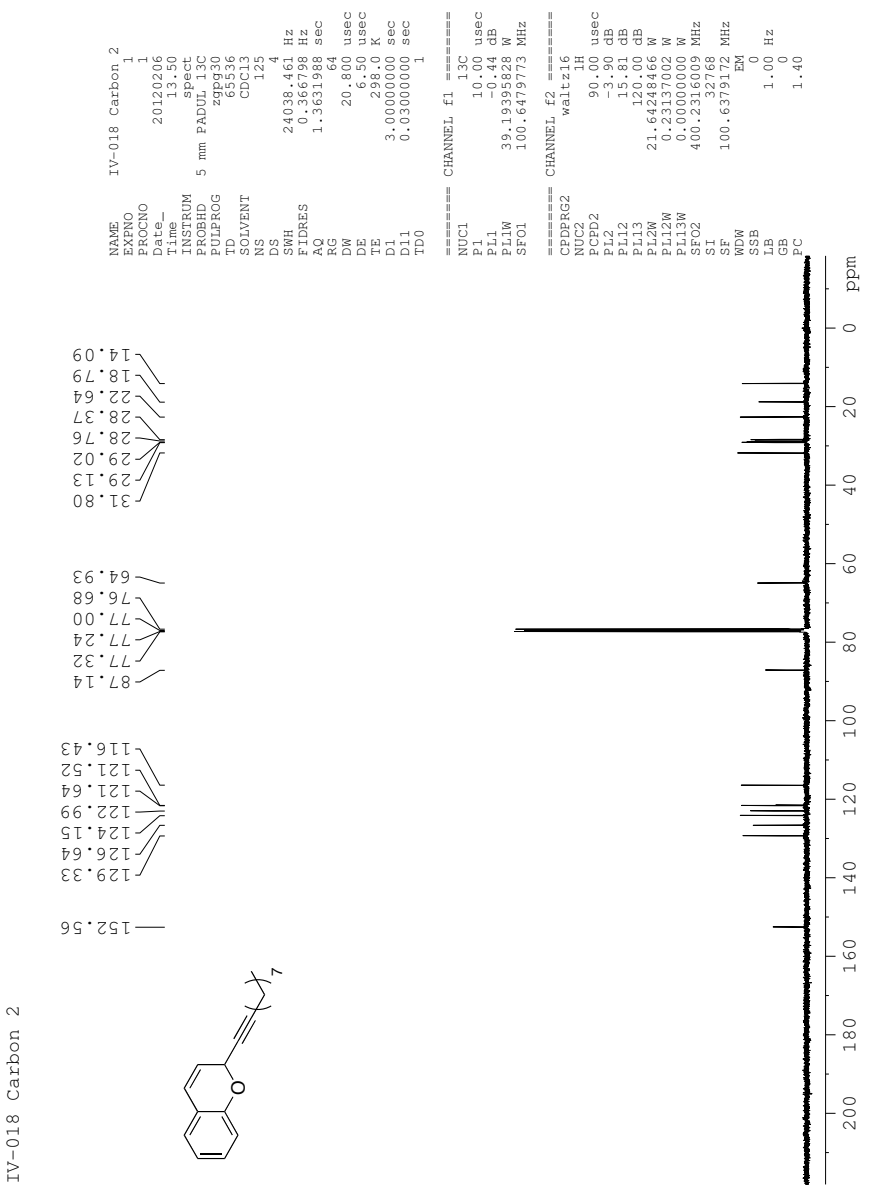
NAME	IV-019 Carbon 2
EXPNO	10
PROCNO	1
Date_	20120207
Time	15.23
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	64
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	203
DW	20.800 usec
DE	6.50 usec
TE	295.9 K
D1	2.00000000 sec
D11	0.03000000 sec
========	CHANNEL f1 ========
NUC1	13C
P1	9.00 usec
SI	32768
SF	100.6127754 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

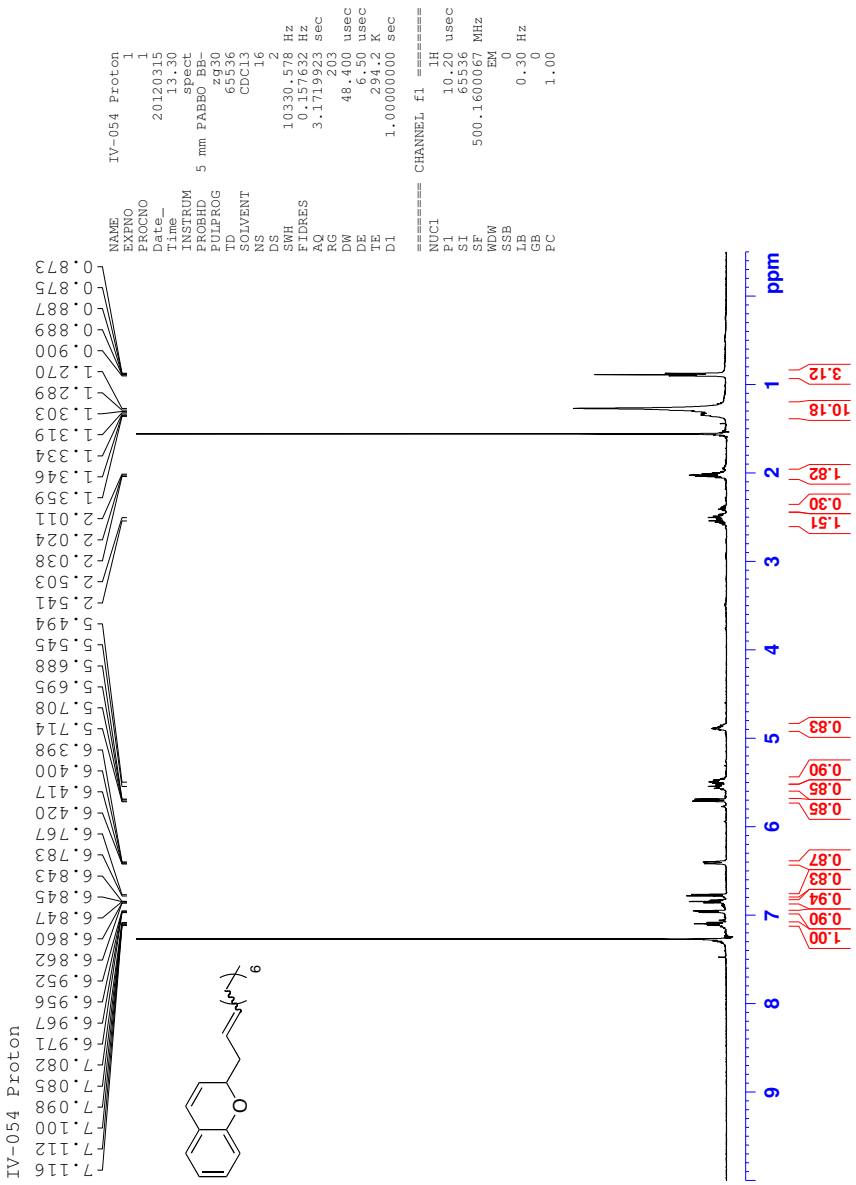


IV-018 Proton

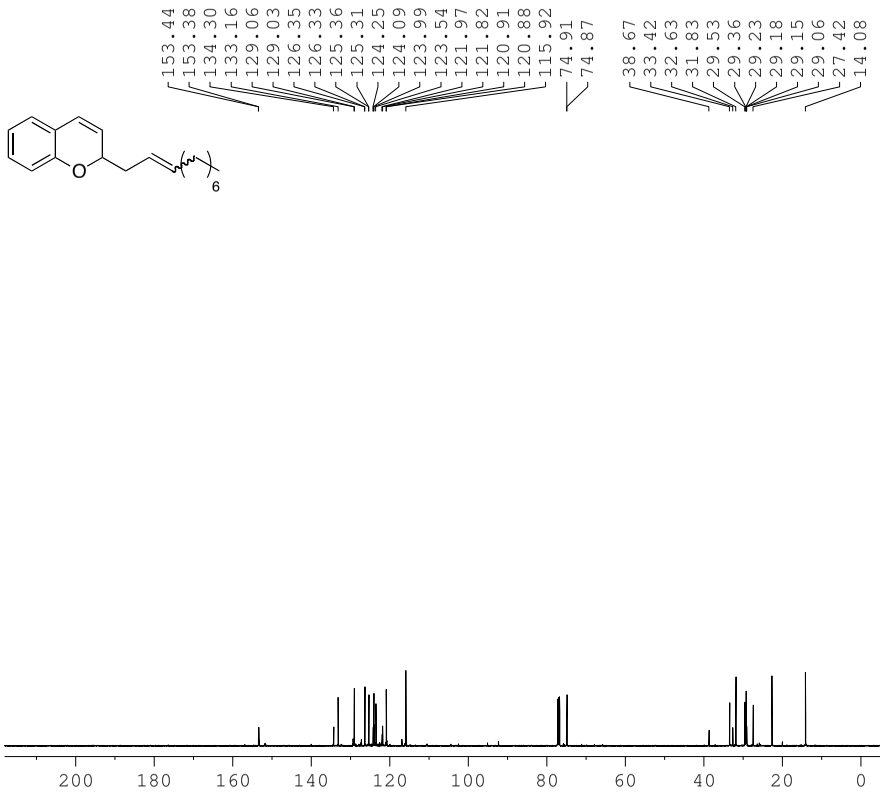


NAME	c
EXPNO	10
PROCNO	1
Date_	20120206
Time	13.35
INSTRUM	spect
PROBHD	5 mm Multinucl
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	6188.119 Hz
FIDRES	0.188846 Hz
AQ	2.6477044 sec
RG	80.6
DW	80.800 usec
DE	6.50 usec
TE	299.6 K
D1	1.00000000 sec
======== CHANNEL f1 ========	
NUC1	1H
P1	13.20 usec
SI	32768
SF	300.2300065 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

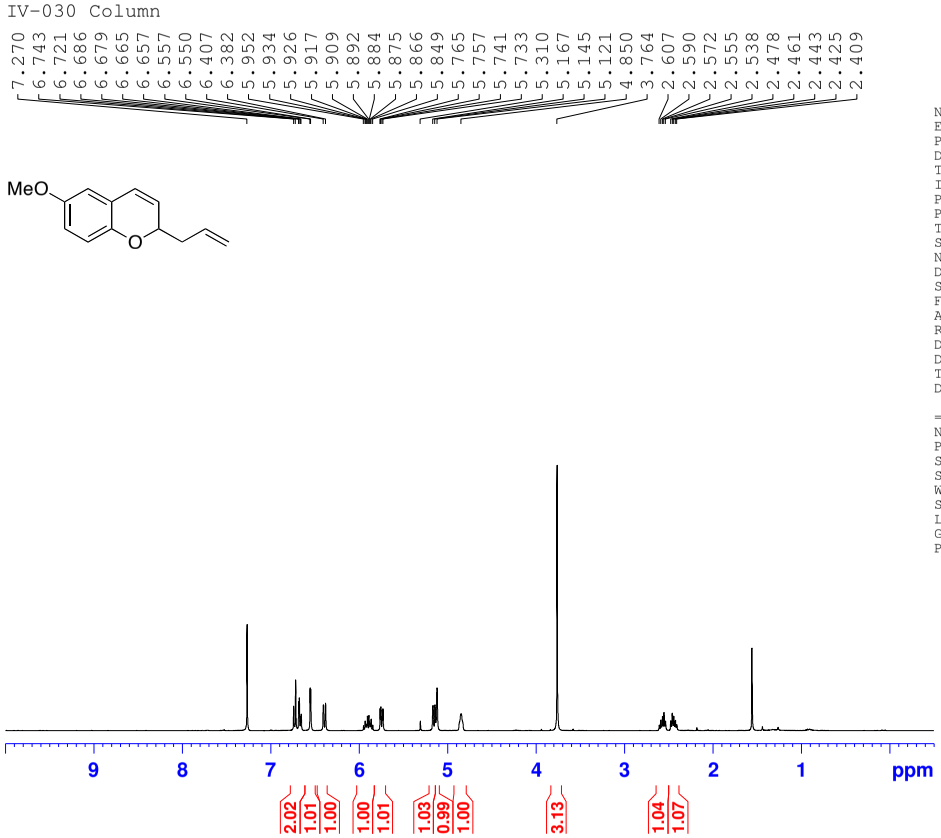

IV-018 Carbon 2
152.56
129.33
126.64
124.15
122.99
121.64
121.52
116.43
87.14
77.32
77.24
77.00
76.68
64.93
31.80
29.13
29.02
28.76
28.37
22.64
18.79
14.09
NAME IV-018 Carbon 2
EXPNO 1
PROCNO 1
Date_ 20120206
Time_ 13.50
INSTRUM spect
PROBHD 5 mm PADUL 13C
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 125
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631988 sec
RG 64
DW 20.800 usec
DE 6.50 usec
TE 298.0 K
D1 3.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 10.00 usec
PL1 -0.44 dB
PL1W 39.19395828 W
SFO1 100.64779773 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 90.00 usec
PL2 -3.90 dB
PL12 15.81 dB
PL13 120.00 dB
PL2W 21.64248466 W
PL12W 0.23137002 W
PL13W 0.00000000 W
SFO2 400.2316609 MHz
SI 32768
SF 100.6379172 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
200 180 160 140 120 100 80 60 40 20 0 ppm


IV-054 Proton
NAME IV-054 Proton
EXPNO 1
PROCNO 1
Date_ 20120315
Time_ 13.30
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 203
DW 48.400 usec
DE 6.50 usec
TE 294.2 K
D1 1.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 10.20 usec
SI 65536
SF 500.1600067 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
ppm
3.12
10.18
1.82
0.30
1.51
0.83
0.90
0.85
0.85
0.87
0.83
0.94
0.90
1.00

IV-054 Carbon

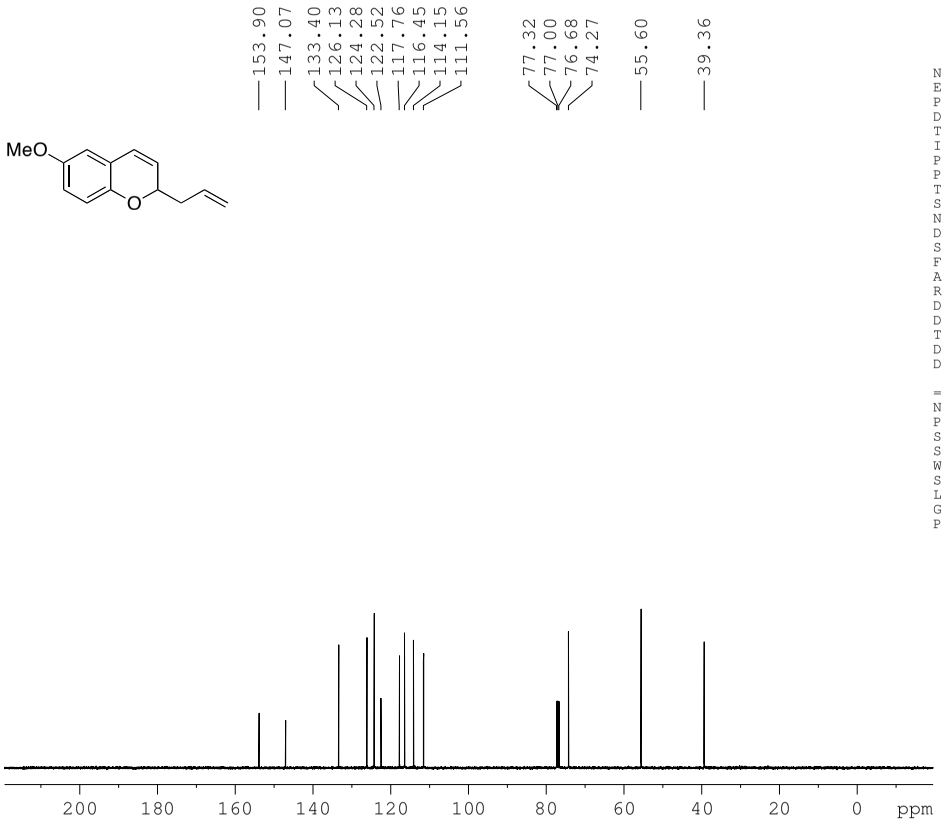


NAME	IV-054 Carbon
EXPNO	1
PROCNO	1
Date_	20120315
Time	13.50
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	256
DS	4
SWH	29761.904 Hz
FIDRES	0.454131 Hz
AQ	1.1010548 sec
RG	203
DW	16.800 usec
DE	6.50 usec
TE	294.6 K
D1	2.00000000 sec
D11	0.03000000 sec
======== CHANNEL f1 ========	
NUC1	13C
P1	8.80 usec
SI	32768
SF	125.7653455 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40



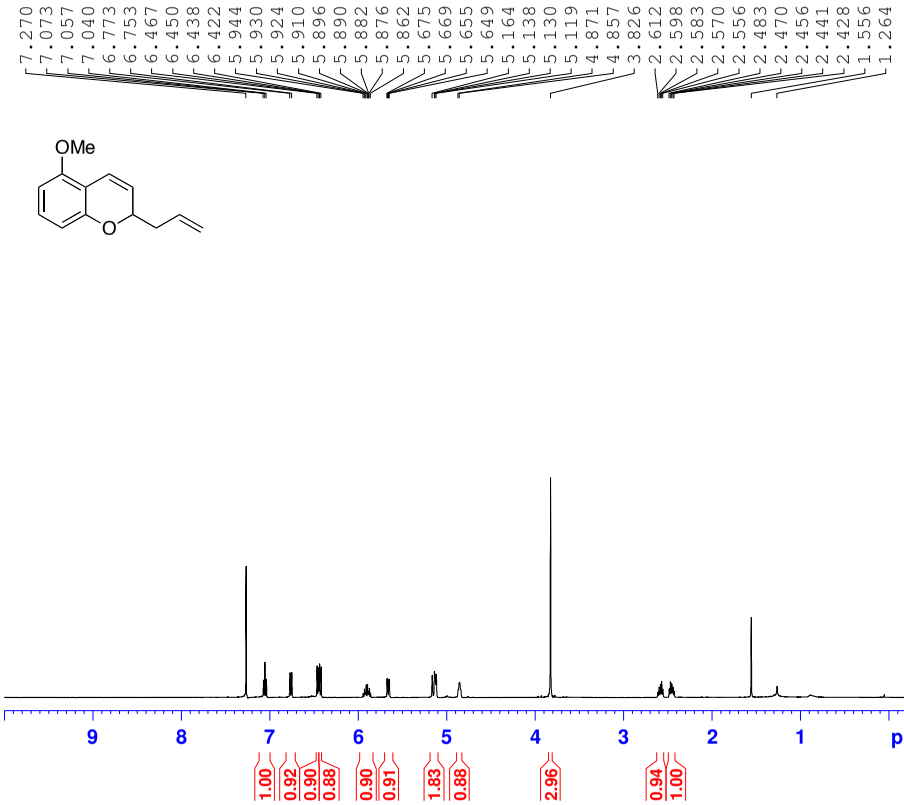
NAME	IV-030 Column
EXPNO	10
PROCNO	1
Date_	20120218
Time	17.20
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	144
DW	60.800 usec
DE	6.50 usec
TE	296.1 K
D1	1.00000000 sec
========	CHANNEL f1 ========
NUC1	1H
P1	14.00 usec
SI	65536
SF	400.1300060 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

IV-030 Carbon



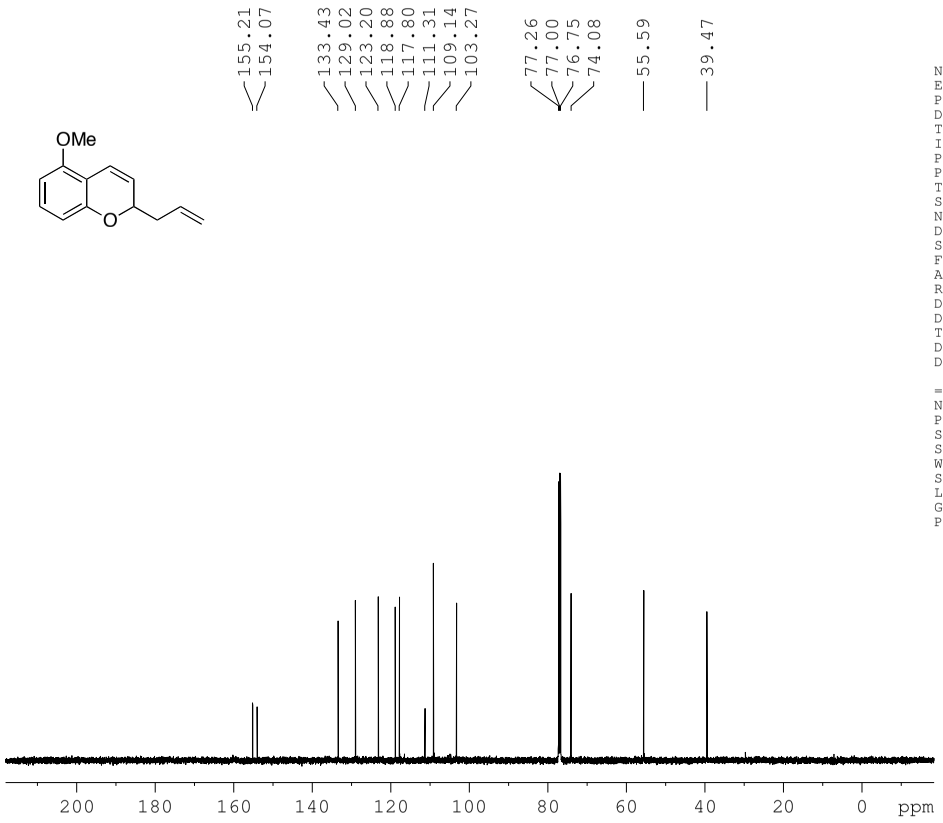
NAME	IV-030 Carbon
EXPNO	10
PROCNO	1
Date_	20120220
Time	11.23
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	128
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	203
DW	20.800 usec
DE	6.50 usec
TE	296.4 K
D1	2.00000000 sec
D11	0.03000000 sec
======== CHANNEL f1 ========	
NUC1	13C
P1	9.00 usec
SI	32768
SF	100.6127791 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

IV-052 Proton

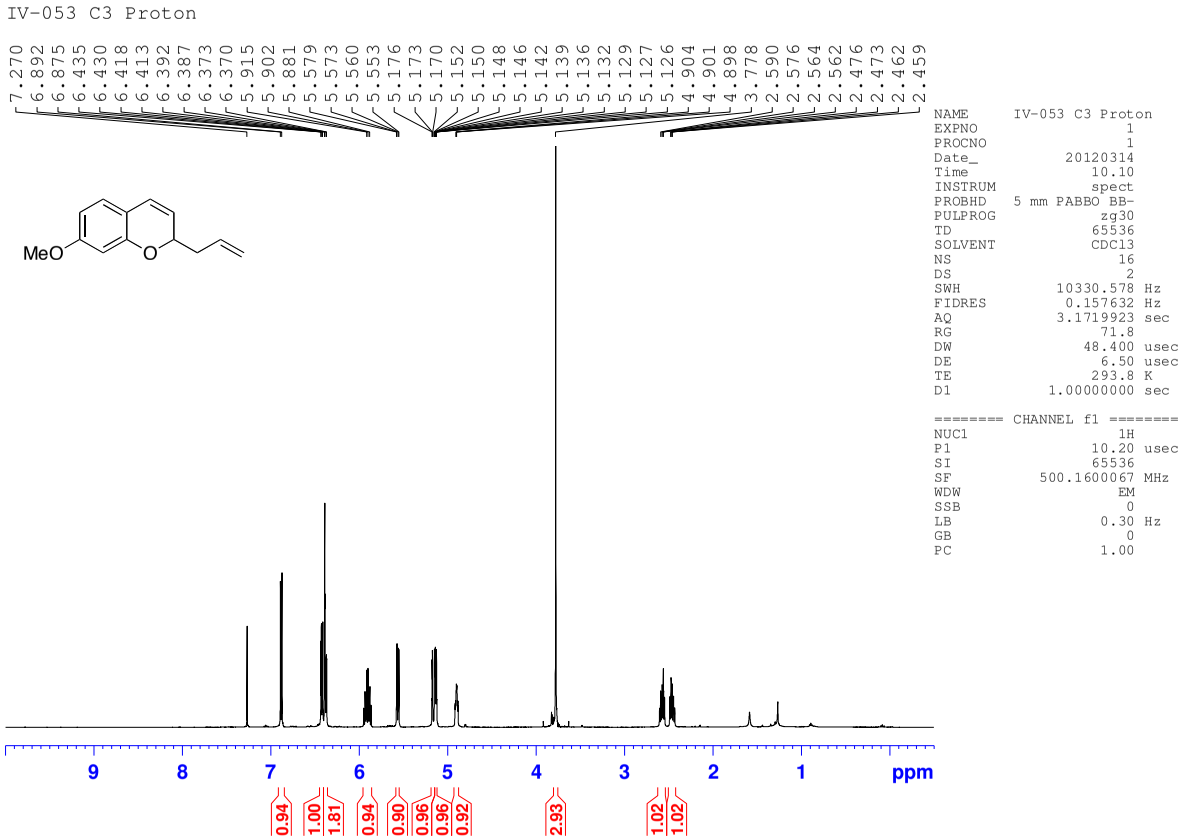


NAME	IV-052 Proton
EXPNO	1
PROCNO	1
Date_	20120312
Time	19.26
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	10330.578 Hz
FIDRES	0.157632 Hz
AQ	3.1719923 sec
RG	203
DW	48.400 usec
DE	6.50 usec
TE	294.5 K
D1	1.00000000 sec
======== CHANNEL f1 ========	
NUC1	1H
P1	10.20 usec
SI	65536
SF	500.1600068 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

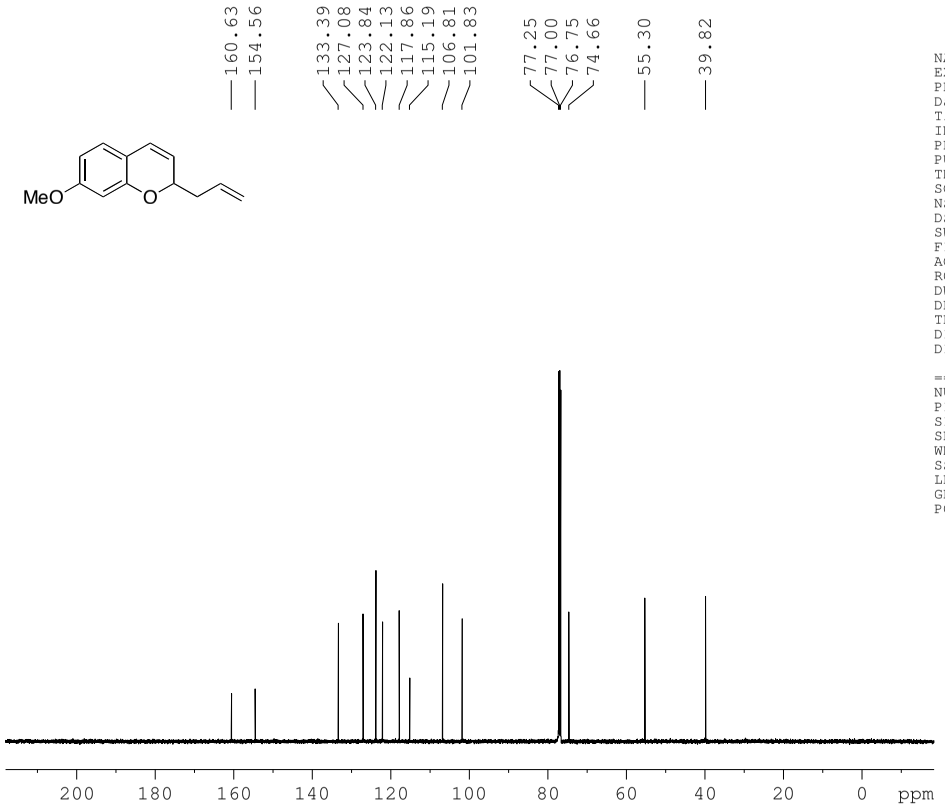
IV-052 Carbon



NAME	IV-052 Carbon
EXPNO	1
PROCNO	1
Date_	20120312
Time	19.59
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	193
DS	4
SWH	29761.904 Hz
FIDRES	0.454131 Hz
AQ	1.1010548 sec
RG	203
DW	16.800 usec
DE	6.50 usec
TE	294.8 K
D1	2.00000000 sec
D11	0.03000000 sec
======== CHANNEL f1 ========	
NUC1	13C
P1	8.80 usec
SI	32768
SF	125.7653381 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

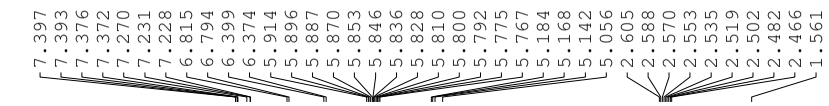

IV-053 C3 Proton
7.270
6.892
6.875
6.435
6.430
6.418
6.413
6.392
6.387
6.373
6.370
5.915
5.902
5.881
5.579
5.573
5.560
5.553
5.176
5.173
5.170
5.152
5.150
5.148
5.146
5.142
5.139
5.136
5.132
5.129
5.127
5.126
4.904
4.901
4.898
3.778
2.590
2.576
2.564
2.562
2.476
2.473
2.462
2.459
MeO
O
NAME IV-053 C3 Proton
EXPNO 1
PROCNO 1
Date_ 20120314
Time 10.10
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 71.8
DW 48.400 usec
DE 6.50 usec
TE 293.8 K
D1 1.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 10.20 usec
SI 65536
SF 500.1600067 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
9
8
7
6
5
4
3
2
1
ppm
0.94
1.00
1.81
0.94
0.90
0.96
0.96
0.92
2.93
1.02
1.02

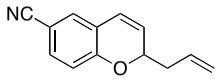
IV-053 C3 Carbon



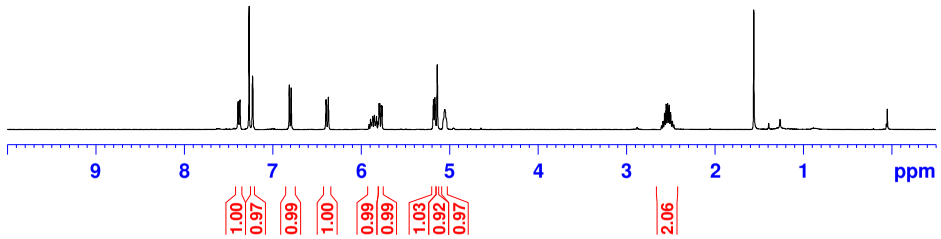
NAME	IV-053 C3 Carbon
EXPNO	1
PROCNO	1
Date_	20120314
Time	10.53
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	687
DS	4
SWH	29761.904 Hz
FIDRES	0.454131 Hz
AQ	1.1010548 sec
RG	203
DW	16.800 usec
DE	6.50 usec
TE	294.2 K
D1	2.00000000 sec
D11	0.03000000 sec
========	CHANNEL f1 ========
NUC1	13C
P1	8.80 usec
SI	32768
SF	125.7653371 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

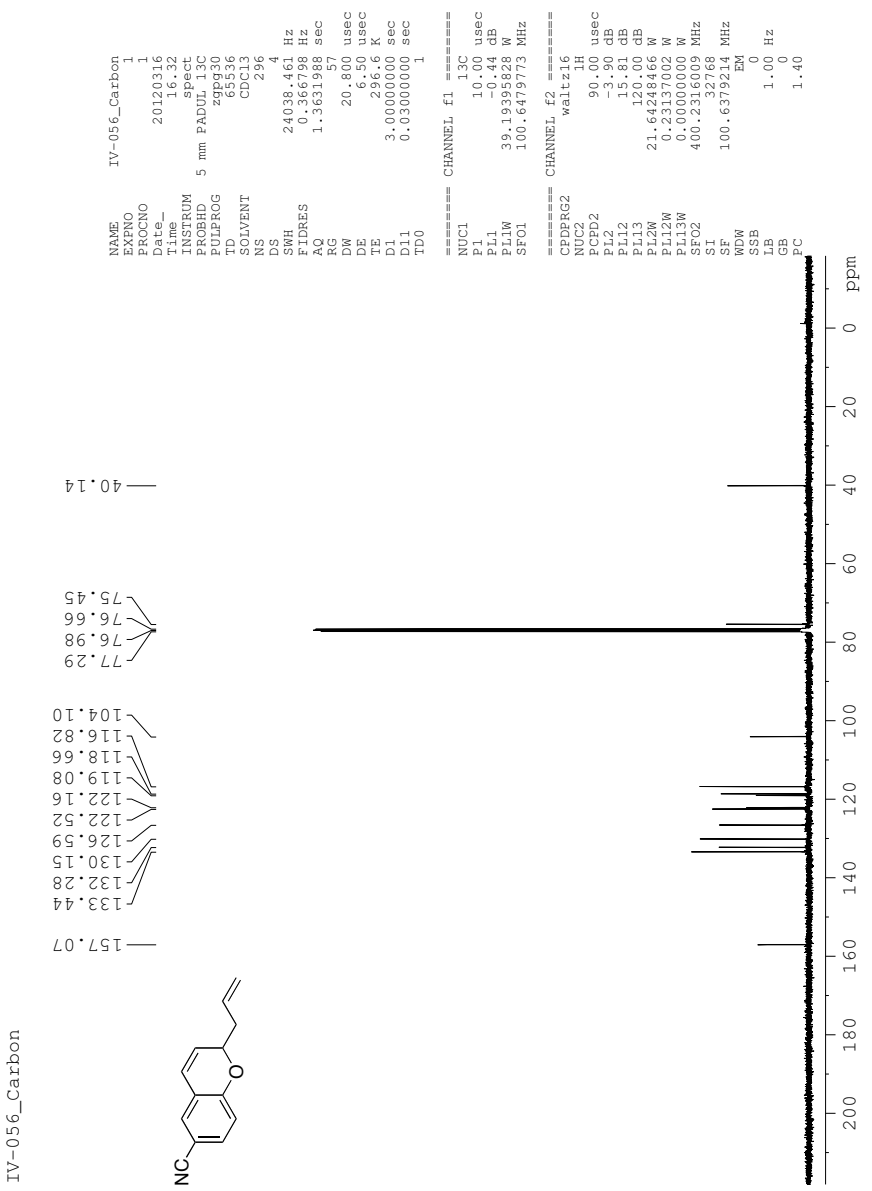
IV-056 Column



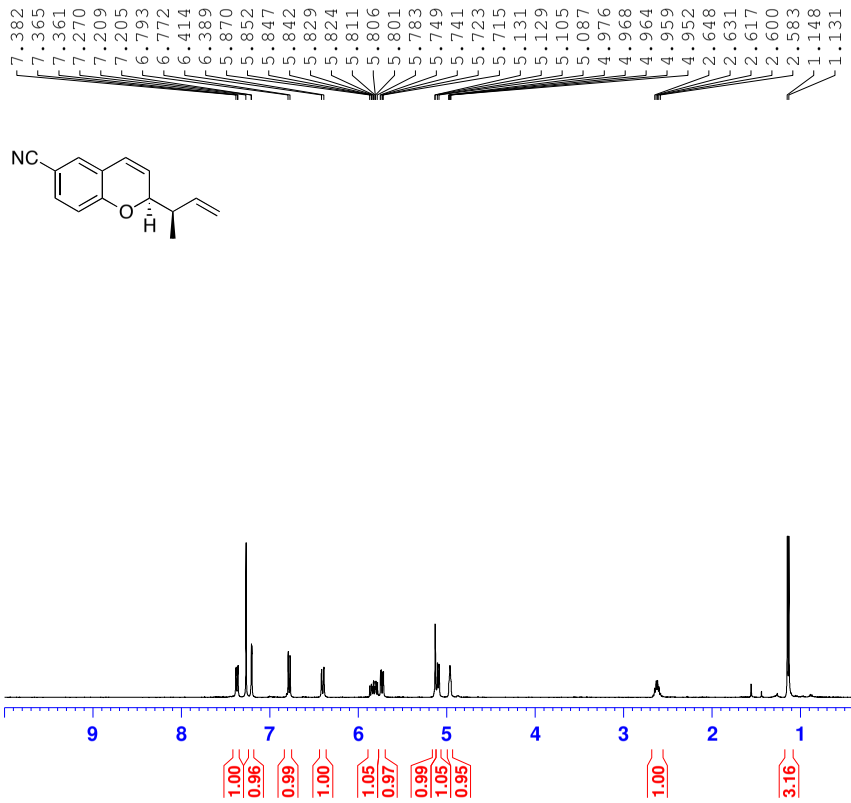


NAME	IV-056 Column
EXPNO	10
PROCNO	1
Date_	20120316
Time	11.19
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	144
DW	60.800 usec
DE	6.50 usec
TE	297.1 K
D1	1.00000000 sec
======== CHANNEL f1 ========	
NUC1	1H
P1	14.00 usec
SI	65536
SF	400.1300054 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00



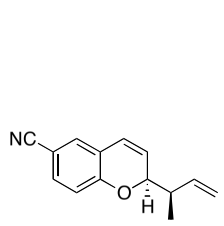

IV-056_Carbon
NC
O
157.07
133.44
132.28
130.15
126.59
122.52
122.16
119.08
118.66
116.82
104.10
77.29
76.98
76.66
75.45
40.14
200
180
160
140
120
100
80
60
40
20
0
ppm
NAME IV-056_Carbon
EXPNO 1
PROCNO 1
Date_ 20120316
Time_ 16.32
INSTRUM spect
PROBHD 5 mm PADUL 13C
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 296
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631988 sec
RG 57
DW 20.800 usec
DE 6.50 usec
TE 296.6 K
D1 3.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 10.00 usec
PL1 -0.44 dB
PL1W 39.19395828 W
SFO1 100.6479773 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 90.00 usec
PL2 -3.90 dB
PL12 15.81 dB
PL13 120.00 dB
PL2W 21.64248466 W
PL12W 0.23137002 W
PL13W 0.00000000 W
SFO2 400.2316009 MHz
SI 32768
SF 100.6379214 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

IV-009 Column



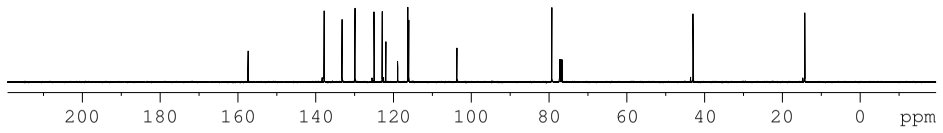
NAME	IV-009 Column
EXPNO	10
PROCNO	1
Date_	20120124
Time	14.00
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	144
DW	60.800 usec
DE	6.50 usec
TE	294.3 K
D1	1.00000000 sec
======== CHANNEL f1 ========	
NUC1	1H
P1	14.00 usec
SI	65536
SF	400.1300059 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

IV-009 Carbon

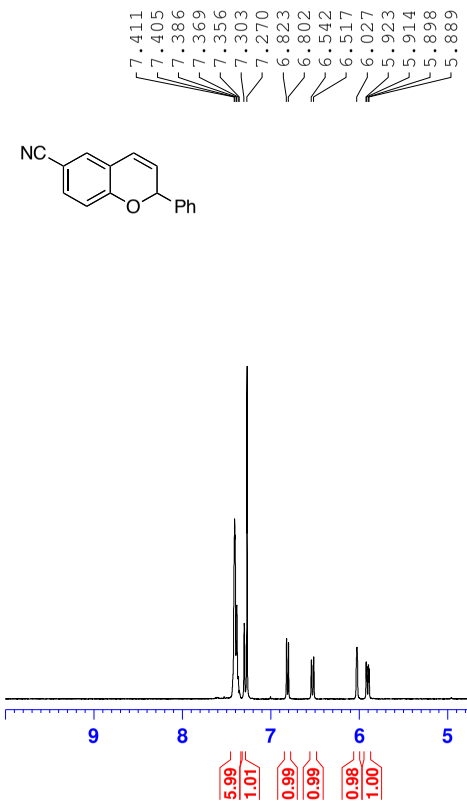


157.43
137.84
133.25
129.94
125.01
122.91
121.98
118.94
116.32
116.07
103.70
79.30
77.31
77.00
76.68
42.96
14.23

NAME	IV-009 Carbon
EXPNO	10
PROCNO	1
Date_	20120124
Time	14.35
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	128
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	203
DW	20.800 usec
DE	6.50 usec
TE	294.9 K
D1	2.00000000 sec
D11	0.03000000 sec
======== CHANNEL f1 ========	
NUC1	13C
P1	9.00 usec
SI	32768
SF	100.6127898 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

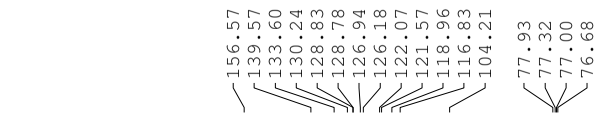


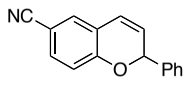
IV-057 Proton

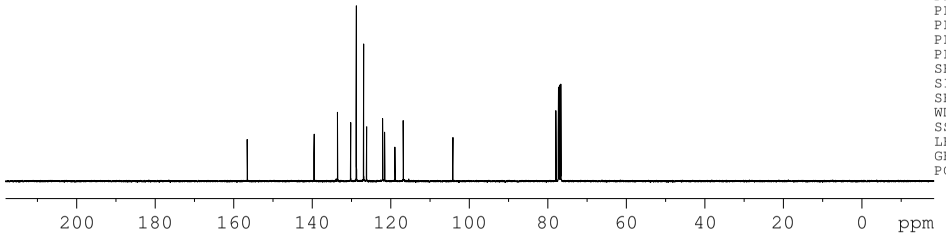


NAME	IV-057 Proton
EXPNO	10
PROCNO	1
Date_	20120316
Time	16.41
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	32
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	161
DW	60.800 usec
DE	6.50 usec
TE	297.5 K
D1	1.00000000 sec
========	CHANNEL f1 ========
NUC1	1H
P1	14.00 usec
SI	65536
SF	400.1300058 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

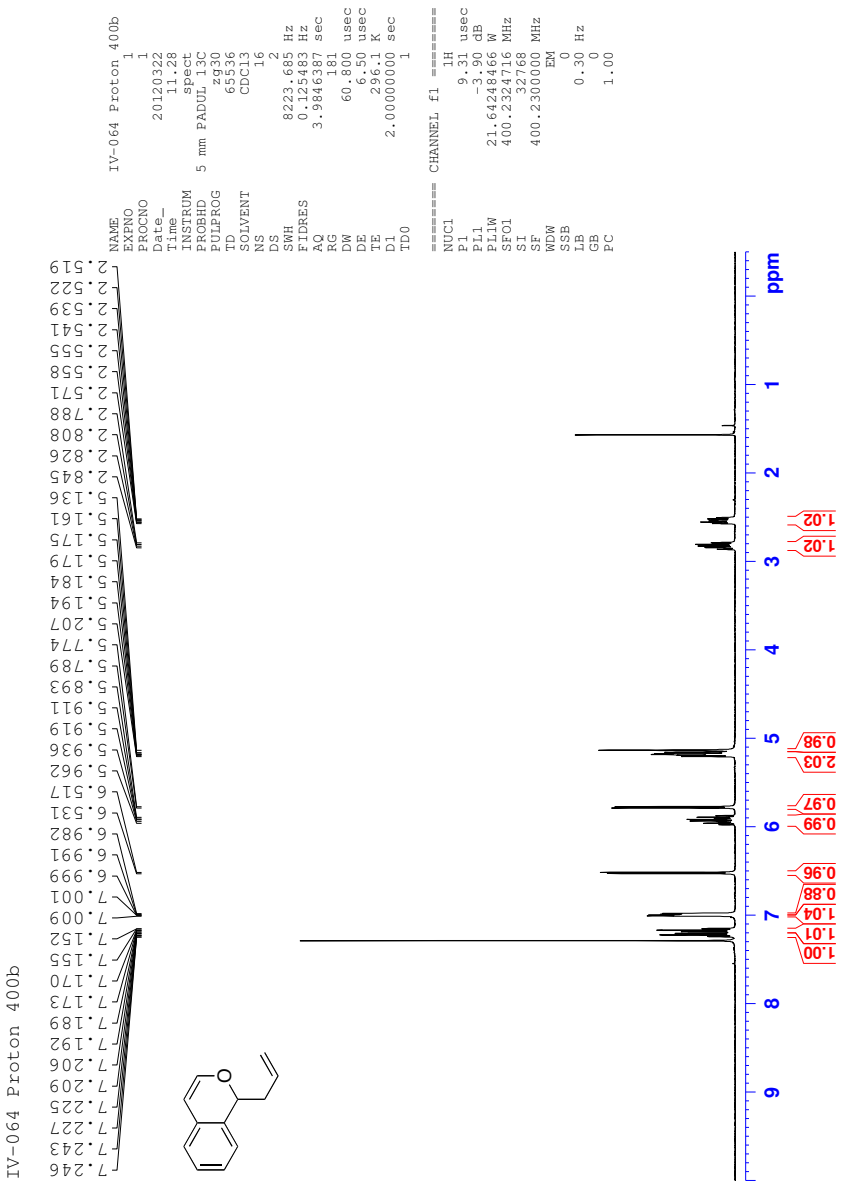
IV-057_Carbon



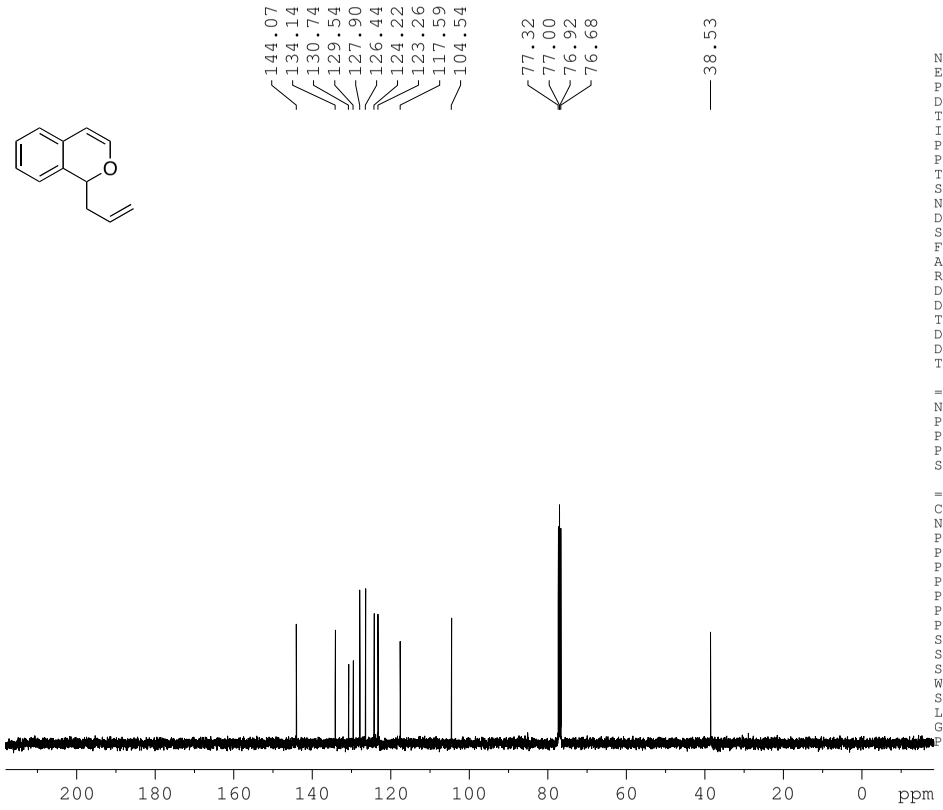




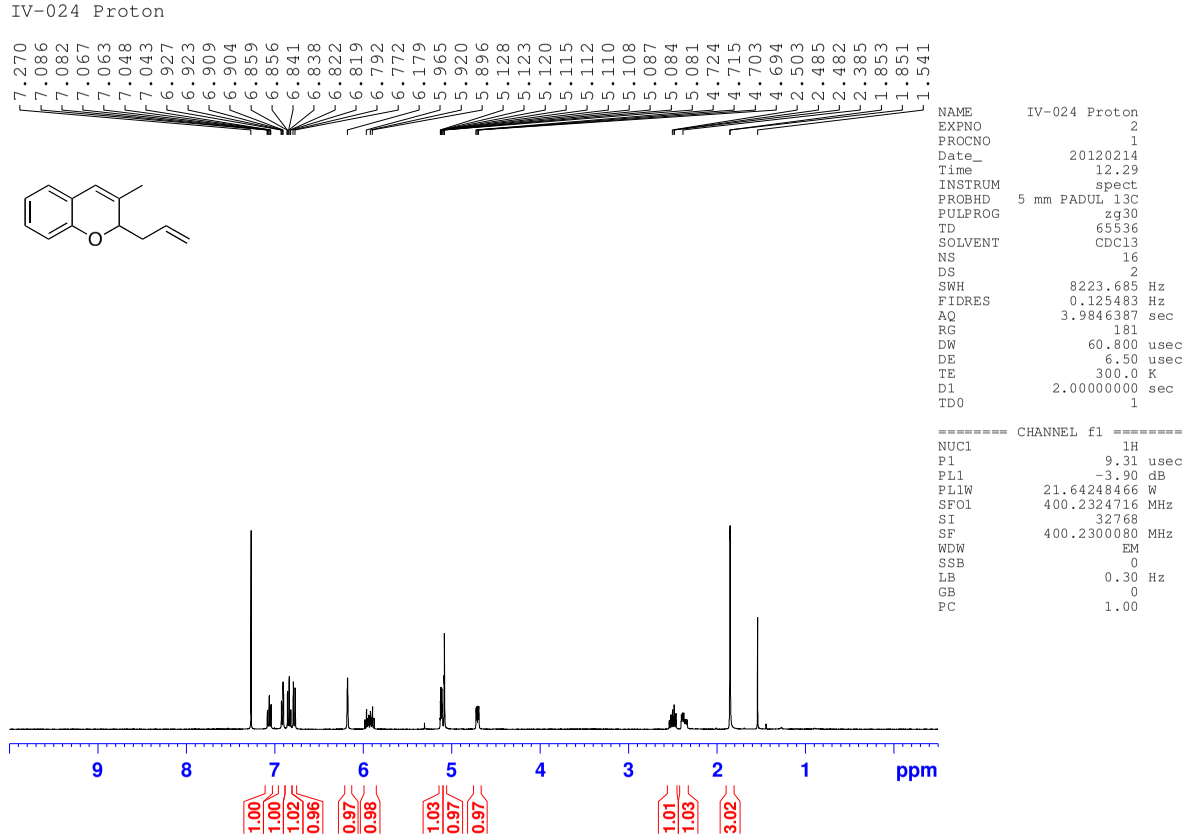
NAME	IV-057_Carbon
EXPNO	1
PROCNO	1
Date_	20120316
Time	16.53
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	217
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	71.8
DW	20.800 usec
DE	6.50 usec
TE	296.6 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379295 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40


IV-064 Proton 400b
7.246
7.243
7.227
7.225
7.209
7.206
7.192
7.189
7.173
7.170
7.155
7.152
7.009
7.001
6.999
6.991
6.982
6.531
6.517
5.962
5.936
5.919
5.911
5.893
5.789
5.774
5.207
5.194
5.184
5.179
5.175
5.161
5.136
2.845
2.826
2.808
2.788
2.571
2.558
2.555
2.541
2.539
2.522
2.519
NAME IV-064 Proton 400b
EXPNO 1
PROCNO 1
Date_ 20120322
Time_ 11.28
INSTRUM spect
PROBHD 5 mm PADUL 13C
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9846387 sec
RG 181
DW 60.800 usec
DE 6.50 usec
TE 296.1 K
D1 2.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.31 usec
PL1 -3.90 dB
PL1W 21.64248466 W
SFO1 400.2324716 MHz
SI 32768
SF 400.2300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1.02
1.02
2.03
0.98
0.97
0.99
0.96
0.88
1.04
1.01
1.00
ppm

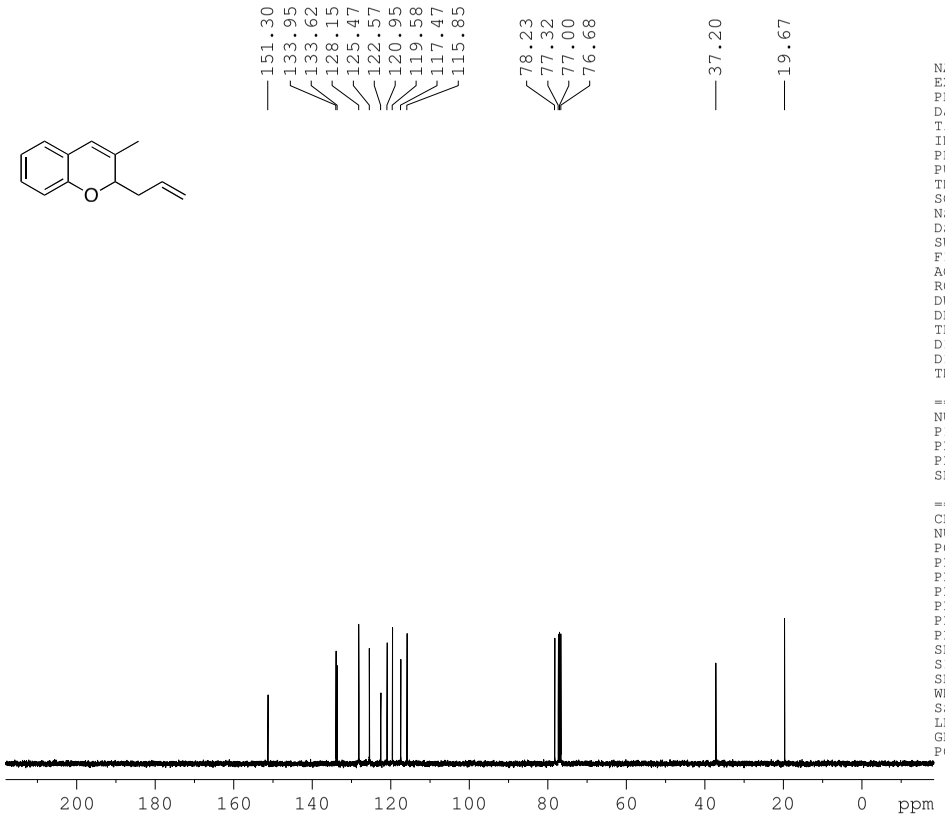
IV-064 Carbon 400b



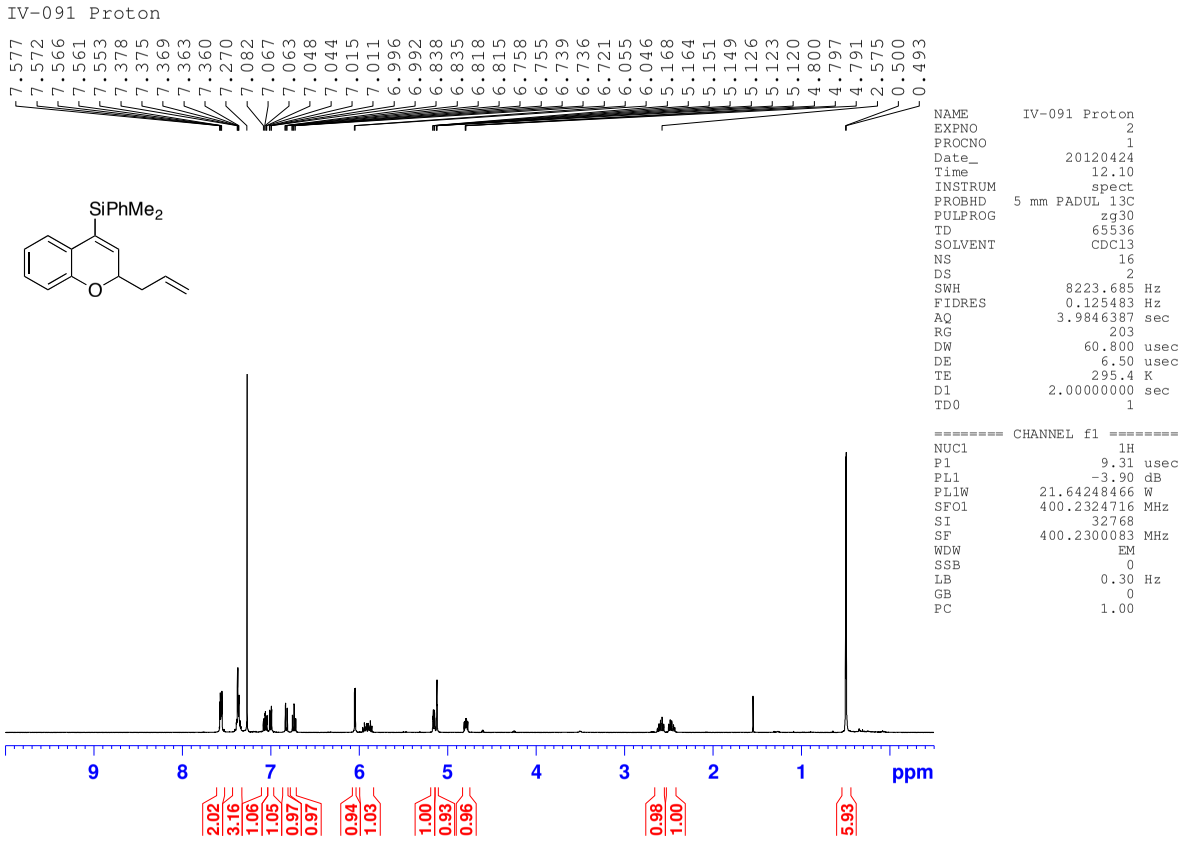
NAME	IV-064 Carbon 400b
EXPNO	1
PROCNO	1
Date_	20120322
Time	11.19
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	14
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	50.8
DW	20.800 usec
DE	6.50 usec
TE	296.4 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379222 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

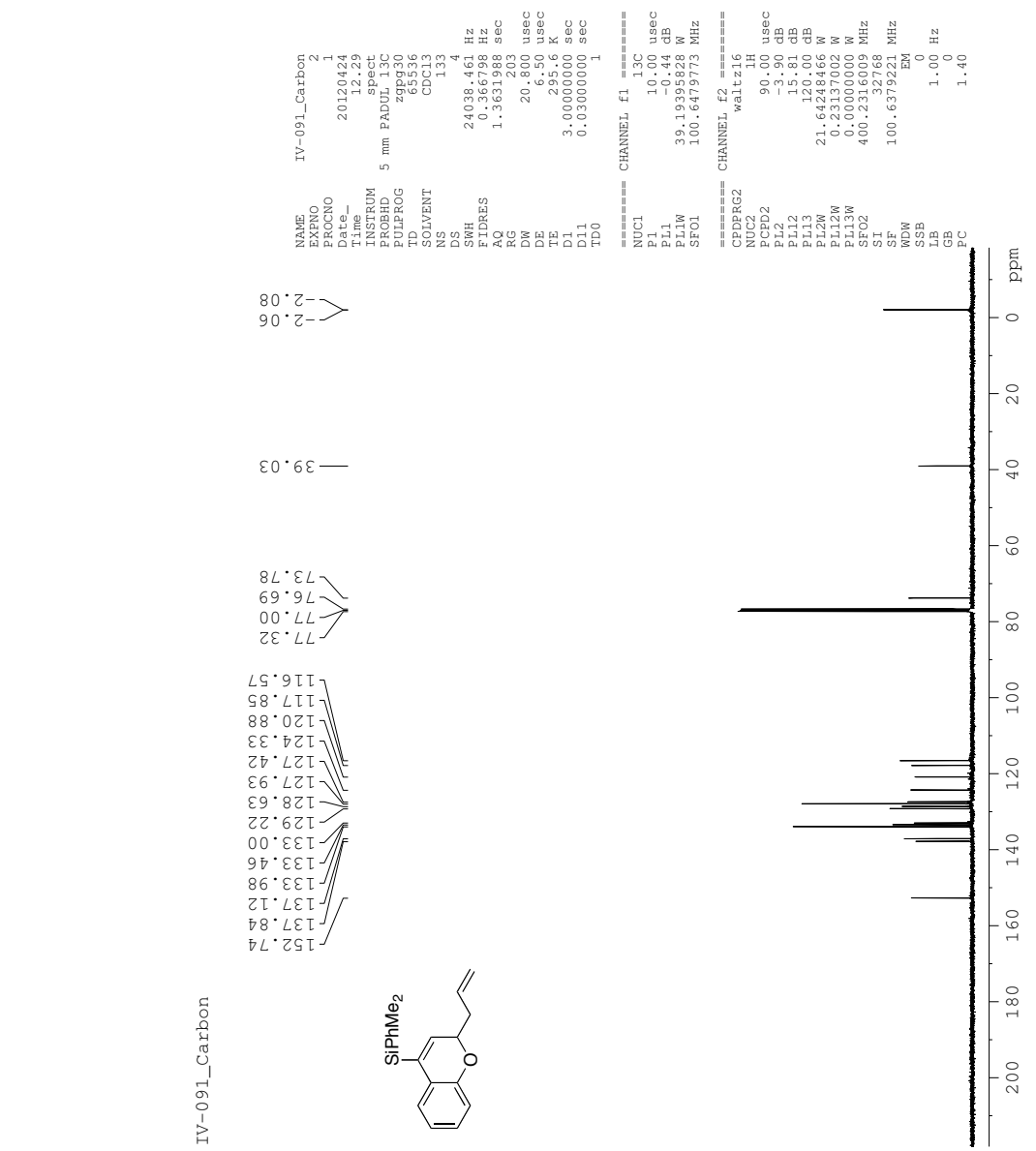

IV-024 Proton
7.270
7.086
7.082
7.067
7.063
7.048
7.043
6.927
6.923
6.909
6.904
6.859
6.856
6.841
6.838
6.822
6.819
6.792
6.772
6.179
5.965
5.920
5.896
5.128
5.123
5.120
5.115
5.112
5.110
5.108
5.087
5.084
5.081
4.724
4.715
4.703
4.694
2.503
2.485
2.482
2.385
1.853
1.851
1.541
O
NAME IV-024 Proton
EXPNO 2
PROCNO 1
Date_ 20120214
Time 12.29
INSTRUM spect
PROBHD 5 mm PADUL 13C
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9846387 sec
RG 181
DW 60.800 usec
DE 6.50 usec
TE 300.0 K
D1 2.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.31 usec
PL1 -3.90 dB
PL1W 21.64248466 W
SFO1 400.2324716 MHz
SI 32768
SF 400.2300080 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
9
8
7
6
5
4
3
2
1
ppm
1.00
1.00
1.02
0.96
0.97
0.98
1.03
0.97
0.97
1.01
1.03
3.02

IV-024 Carbon



NAME	IV-024 Carbon
EXPNO	2
PROCNO	1
Date_	20120214
Time	12.53
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	32
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	32
DW	20.800 usec
DE	6.50 usec
TE	300.0 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379237 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

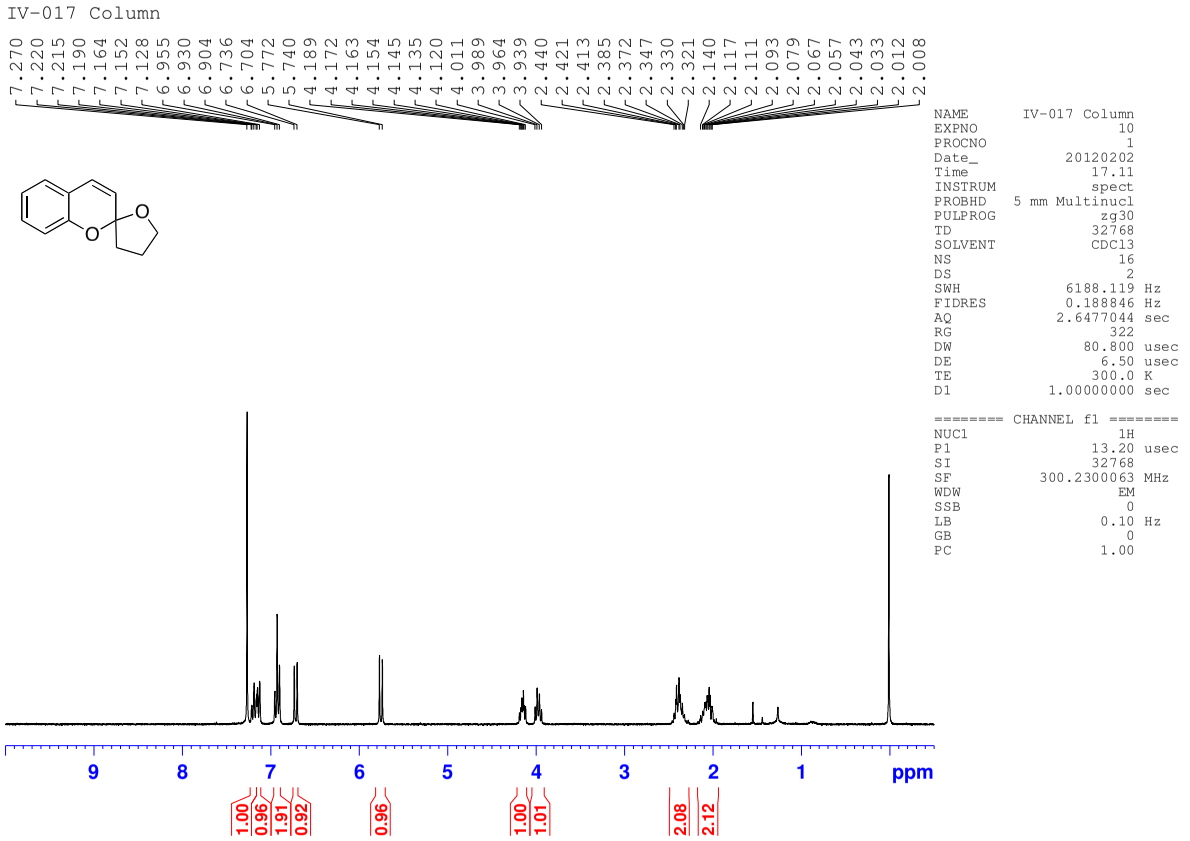

IV-091 Proton
7.577
7.572
7.566
7.561
7.553
7.378
7.375
7.369
7.363
7.360
7.270
7.082
7.067
7.063
7.048
7.044
7.015
7.011
6.996
6.992
6.838
6.835
6.818
6.815
6.758
6.755
6.739
6.736
6.721
6.055
6.046
5.168
5.164
5.151
5.149
5.126
5.123
5.120
4.800
4.797
4.791
2.575
0.500
0.493
SiPhMe2
O
NAME IV-091 Proton
EXPNO 2
PROCNO 1
Date_ 20120424
Time 12.10
INSTRUM spect
PROBHD 5 mm PADUL 13C
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9846387 sec
RG 203
DW 60.800 usec
DE 6.50 usec
TE 295.4 K
D1 2.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.31 usec
PL1 -3.90 dB
PL1W 21.64248466 W
SFO1 400.2324716 MHz
SI 32768
SF 400.2300083 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
9
8
7
6
5
4
3
2
1
ppm
2.02
3.16
1.06
1.05
0.97
0.97
0.94
1.03
1.00
0.93
0.96
0.98
1.00
5.93



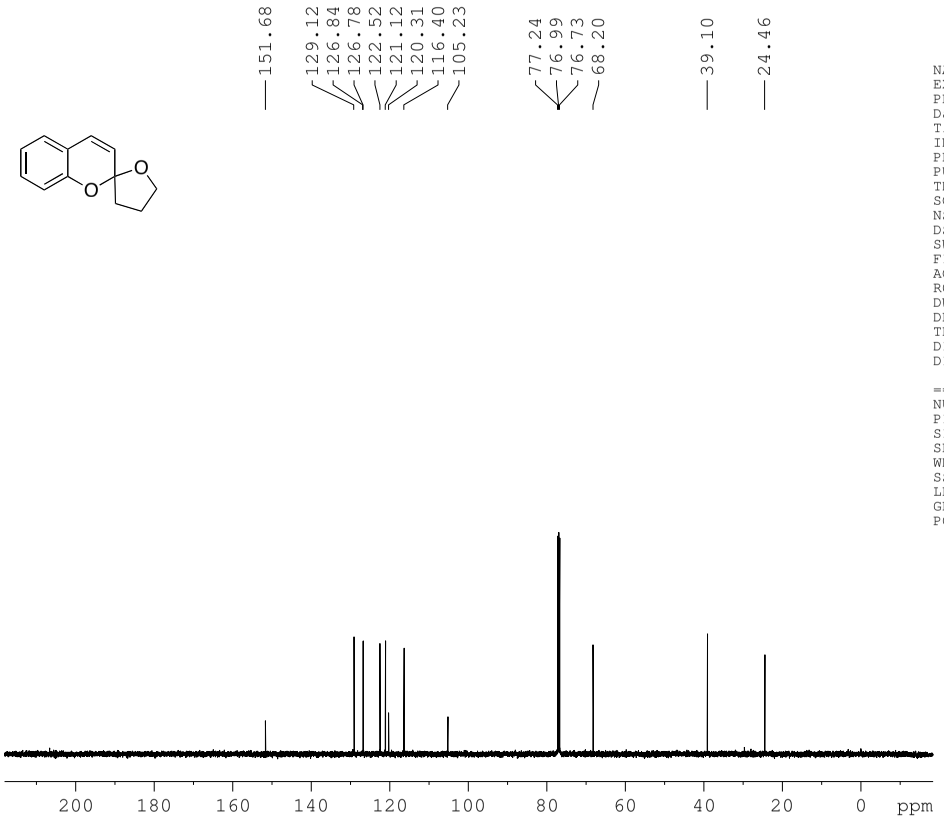
NAME IV-091_Carbon
EXPNO 2
PROCNO 1
Date_ 20120424
Time_ 12.29
INSTRUM spect
PROBHD 5 mm PADUL 13C
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 133
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631988 sec
RG 203
DW 20.800 usec
DE 6.50 usec
TE 295.6 K
D1 3.00000000 sec
D11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 10.00 usec
PL1 -0.44 dB
PL1W 39.19395828 W
SFO1 100.6479773 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 90.00 usec
PL2 -3.90 dB
PL12 15.81 dB
PL13 120.00 dB
PL2W 21.64248466 W
PL12W 0.23137002 W
PL13W 0.00000000 W
SFO2 400.2316609 MHz
SI 32768
SF 100.6379221 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40


IV-017 Column
7.270
7.220
7.215
7.190
7.164
7.152
7.128
6.955
6.930
6.904
6.736
6.704
5.772
5.740
4.189
4.172
4.163
4.154
4.145
4.135
4.120
4.011
3.989
3.964
3.939
2.440
2.421
2.413
2.385
2.372
2.347
2.330
2.321
2.140
2.117
2.111
2.093
2.079
2.067
2.057
2.043
2.033
2.012
2.008
O
O
NAME IV-017 Column
EXPNO 10
PROCNO 1
Date_ 20120202
Time 17.11
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 6188.119 Hz
FIDRES 0.188846 Hz
AQ 2.6477044 sec
RG 322
DW 80.800 usec
DE 6.50 usec
TE 300.0 K
D1 1.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 13.20 usec
SI 32768
SF 300.2300063 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00
9
8
7
6
5
4
3
2
1
ppm
1.00
0.96
1.91
0.92
0.96
1.00
1.01
2.08
2.12

IV-017 Carbon



NAME	IV-017 Carbon
EXPNO	1
PROCNO	1
Date_	20120202
Time	17.30
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	79
DS	4
SWH	29761.904 Hz
FIDRES	0.454131 Hz
AQ	1.1010548 sec
RG	203
DW	16.800 usec
DE	6.50 usec
TE	295.0 K
D1	2.00000000 sec
D11	0.03000000 sec
========	CHANNEL f1 ========
NUC1	13C
P1	8.80 usec
SI	32768
SF	125.7653403 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

BIBLIOGRAPHY

1. Schmittel, M.; Burghart, A., "Understanding Reactive Patterns of Radical Cations" *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2550-2589.
2. Popielarz, R.; Arnold, D. R., "Radical Ions in Photochemistry. Carbon-Carbon Bond Cleavage of Radical Cations in Solution: Theory and Application" *J. Am. Chem. Soc.* **1990**, *112*, 3068-3082.
3. Floreancig, P. E., "Development and Applications of Electron-Transfer-Initiated Cyclization Reactions" *Synlett* **2007**, 191-203.
4. Da Silva, G.; Hamdan, M. R.; Bozzelli, J. W., "Oxidation of the Benzyl Radical: Mechanism, Thermochemistry, and Kinetics for the Reactions of Benzyl Hydroperoxide" *J. Chem. Theory Comput.* **2009**, *5*, 3185-3194.
5. Kumar, V. S.; Floreancig, P. E., "Electron Transfer Initiated Cyclizations: Cyclic Acetal Sythesis through Carbon-Carbon σ-Bond Activation" *J. Am. Chem. Soc.* **2001**, *123*, 3842-3843.
6. Aubele, D. L.; Floreancig, P. E., "Oxidative Synthesis of Cyclic Acyl Aminals through Carbon-Carbon σ-Bond Activation" *Org. Lett.* **2002**, *4*, 3443-3446.
7. Aubele, D. L.; Rech, J. C.; Floreancig, P. E., "Catalytic Aerobic Generation of Acyliminium Ions through Electron-Transfer-Mediated Carbon-Carbon Bond Activation" *Adv. Synth. Catal.* **2004**, *346*, 359-366.

8. Wang, L.; Seiders, J. R.; Floreancig, P. E., "Structure-Reactivity Relationships in Oxidative Carbon-Carbon Bond Forming Reactions: A Mild and Efficient Approach to Stereoselective Synthesis of 2,6-Disubsitituted Tetrahydropyrones" *J. Am. Chem. Soc.* **2004**, *126*, 12596-12603.
9. Kumar, V. S.; Aubele, D. L.; Floreancig, P. E., "Aerobic Organocatalytic Photoinitiated Arene Oxidations: Application to Electron Transfer Initiated Cyclization Reactions" *Org. Lett.* **2001**, *3*, 4123-4125.
10. Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G., "Cascade Reactions in Total Synthesis" *Angew. Chem. Int. Ed.* **2006**, *45*, 7134-7186.
11. Kumar, V. S.; Wan, S.; Aubele, D. L.; Floreancig, P. E., "Oxidatively Generated Electrophiles as Initiators of Epoxide Cascade Cyclization Processes" *Tetrahedron: Asymmetry* **2005**, *16*, 3570-3578.
12. Wan, S.; Gunaydin, H.; Houk, K. N.; Floreancig, P. E., "An Experimental and Computational Approach to Defining Structure/Reactivity Relationships for Intramolecular Addition Reactions to Bicyclic Epoxonium Ions" *J. Am. Chem. Soc.* **2007**, *129*, 7915-7923.
13. Wan, S., "Study on the Structure/Reactivity of Bicyclic Epoxonium Ions towards Tethered Nucleophiles. Efforts towards the Total Synthesis of (+)-Lactodehydrothyrsiferol. Multicomponent Approach to the Synthesis of Oxidized Amides through Nitrile Hydrozirconation" (PhD dissertation) *University of Pittsburgh* **2008**, 1-32.

14. Ritleng, V.; Sirlin, C.; Pfeffer, M., "Ru-, Rh-, and Pd-Catalyzed C–C Formation Involving C–H Activation and Addition on Unsaturated Substrates: Reactions and Mechanistic Aspects" *Chem. Rev.* **2002**, *102*, 1731-1769.

15. Nicolaou, K. C.; Bulger, P. G.; Sarlah, D., "Palladium-Catalyzed Cross-Coupling Reactions in Total Synthesis" *Angew. Chem. Int. Ed.* **2005**, *44*, 4442-4489.

16. Fürstner, A., "Olefin Metathesis and Beyond" *Angew. Chem. Int. Ed.* **2000**, *39*, 3012-3043.

17. Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H., "Function-Oriented Synthesis, Step Economy, and Drug Design" *Acc. Chem. Res.* **2008**, *41*, 40-49.

18. Trost, B. M., "Atom Economy–A Challenge for Organic Synthesis: Homogeneous Catalysis Leads the Way" *Angew. Chem. Int. Ed.* **1995**, *34*, 259-281.

19. Gutekunst, W. R.; Baran, P. S., "C–H Functionalization Logic in Total Synthesis" *Chem. Soc. Rev.* **2011**, *40*, 1976-1991.

20. Walker, D.; Hiebert, J. D., "2,3-Dichloro-5,6-dicyabobenzoquinone and its Reactions" *Chem. Rev.* **1967**, *67*, 153-195.

21. Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O., "On the Selectivity of Benzyl, MPM (4-Methoxybenzyl) and DMPM (3,4-Dimethoxybenzyl) Protecting Groups for Hydroxy Functions" *Tetrahedron* **1986**, *42*, 3021-3028.

22. Hayashi, Y.; Mukaiyama, T., "New Method for Oxidative Carbon–Carbon Bond Formation by the Reaction of Allyl Ethers, 2.3-Dichloro-5.6-dicyano-*p*-benzoquinone (DDQ) and Silyl Carbon Nucleophiles" *Chem. Lett.* **1987**, 1811-1814.

23. Loupy, A.; Tchoubar, B.; Astruc, D., "Salt Effects Resulting from Exchange between Two Ion Pairs and Their Crucial Role in Reaction Pathways" *Chem. Rev.* **1992**, *92*, 1141-1165.

24. Tu. W.; Liu, L.; Floreancig, P. E., "Diastereoselective Tetrahydropyrone Synthesis through Transition-Metal-Free Oxidative Carbon–Hydrogen Bond Activation" *Angew. Chem. Int. Ed.* **2008**, *47*, 4184-4187.

25. Tu. W.; Floreancig, P. E., "Oxidative Carbocation Formation in Macrocycles: Synthesis of the Neopeltolide Macrocycle" *Angew. Chem. Int. Ed.* **2009**, *48*, 4567-4571.

26. Liu, L.; Floreancig, P. E., "Structurally and Stereochemically Diverse Tetrahydropyran Synthesis through Oxidative C–H Bond Activation" *Angew. Chem. Int. Ed.* **2010**, *49*, 3069-3072.

27. Brizgys, G. J.; Jung, H. H.; Floreancig, P. E., "Stereoselective Piperidine Synthesis Through Oxidative Carbon–Hydrogen Bond Fonctionalization of Enamides" *Chem. Sci.* **2012**, 438.

28. Cui, Y.; Floreancig, P. E., "Synthesis of Sulfur-Containing Heterocycles through Oxidative Carbon–Hydrogen Bond Functionalization" *Org. Lett.* **2012**, *14*, 1720-1723.

29. Jung, H. H.; Floreancig, P. E., "Mechanistic Analysis of Oxidative C–H Cleavages Using Inter- and Intramolecular Kinetic Isotope Effects" *Tetrahedron*, **2009**, *65*, 10830-10836.

30. Li, C., "Cross-Dehydrogenative Coupling (CDC): Exploring C–C Bond Formations Beyond Functional Group Transformations" *Acc. Chem. Res.* **2009**, *42*, 335-344.

31. Ying, B.; Trogden, B. G.; Kohlman, D. T.; Liang, S. X.; Xu, Y., "Oxidative C–C Bond-Forming Reactions of Electron-Rich Alkylbenzyl Ether with Trimethylvinyloxysilane" *Org. Lett*. **2004**, *6*, 1523-1526.

32. Park, S. J.; Price, J. R.; Todd, M. H., "Oxidative Arylation of Isochroman" *J. Org. Chem.* **2012**, *77*, 949-955.

33. Condie, A. G.; González-Gómez, J. C.; Stephenson, C. R. J., "Visible-Light Photoredox Catalysis: Aza-Henry Reactions via C–H Functionalization" *J. Am. Chem. Soc.* **2010**, *132*, 1464-1465.

34. Hayashi, Y.; Itoh, T.; Ishikawa, H., "Oxidative and Enantioselective Cross-Coupling of Aldehydes and Nitromethane Catalyzed by Diphenylprolinol Silyl Ether" *Angew. Chem. Int. Ed.* **2011**, *50*, 3920-3924.

35. Benfatti, F.; Capdevila, M. G.; Zoli, L.; Benedetto, E.; Cozzi, P. G., "Catalytic Stereoselective Benzylic C–H Functionalizations by Oxidative C–H Activation and Organocatalysis" *Chem. Commun.* **2009**, 5919-5921.

36. Xu, Y.; Kohlman, D. T.; Liang, S. X.; Erikkson, C. "Stereoselective, Oxidative C–C Bond Coupling of Baphthopyran Induced by DDQ: Sterecontrolled Total Synyhesis of Deoxfrenolicin" *Org. Lett.* **1999**, *1*, 1599-1602.

37. Blunt, J. W.; Hartshorn, M. P.; McLennan, T. J.; Munro, M. H. G.; Robinson, W. T.; Yorke, S. C., "Thyrsiferol: A Squalene-Derived Metabolite of *Laurencia thyrsifera*" *Tetrahedron Lett.* **1978**, *19*, 69-72.

38. Sakemi, S.; Higa, T.; Jefford, C. W.; Bernardinelli, G., "Venustatriol. A New, Anti-Viral, Triterpene Tetracyclic Ether from *Laurencia venusta*" *Tetrahedron Lett.* **1986**, *27*, 4287-4290.

39. Suzuki, T.; Suzuki, M.; Furosaki, A.; Natsumoto, T.; Kato, A.; Imanaka, Y.; Kurosawa, E., "Teurilene and Thyrsiferyl 23-Acetate, *Meso* and Remarkably Cytotoxic Compounds

from the Marine Red Alga *Laurencia obtusa* (Hudson) Lamouroux" *Tetrahedron Lett.* **1985**, *26*, 1329-1332.

40. Fernández, J. J.; Souto, M. L.; Norte, M., "Marine Polyether Triterpenes" *Nat. Prod. Rep.* **2000**, *17*, 235-246.
41. Souto, M. L.; Manríquez, C. P.; Norte, M.; Fernández, J. J., "Novel Marine Polyethers" *Tetrahedron* **2002**, *58*, 8119-8125.
42. Hioki, H.; Motosue, M.; Mizutani, Y.; Noda, A.; Shimoda, T.; Kubo, M.; Harada, K.; Fukuyama, Y.; Kodama, M., "Total Synthesis of Pseudodehydrothyrsiferol" *Org. Lett.* **2009**, *11*, 579-582.
43. Tanuwidjaja, J.; Ng, S.; Jamison, T. F., "Total Synthesis of *ent*-Dioxepandehydrothyrsiferol via a Bromonium-Initiated Epoxide-Opening Cascade" *J. Am. Chem. Soc.* **2009**, *131*, 12084-12805.
44. Hunter, T., "Protein Kinases and Phosphatases: The Yin and Yang of Protein Phosphorylation and Signalling" *Cell* **1995**, *80*, 225-236.
45. Souto, M. L.; Manríquez, C. P.; Norte, M.; Leira, F.; Fernández, J. J., "The Inhibitory Effect of Squalene-Derived Triterpenes on Protein Phophatase PP2A" *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1261-1264.
46. Matsuzawa, S.; Suzuki, T.; Suzuki, M.; Matsuda, A.; Kawamura, T.; Mizuno, Y.; Kikuchi, K., "Thysiferyl 23-Acetate is a Novel Specific Inhibitor of Protein Phosphatase PP2A" *FEBS Lett.* **1994**, *356*, 272-274.
47. Bialojon, C.; Takai, A., "Inhibitory Effect of a Marine-Sponge Toxin, Okadaic Acid, on Protein Phosphatases" *Biochem. J.* **1988**, *256*, 283-290.

48. Cohen, P.; Holmes, C. F. B.; Tsukitani, Y. "Okadaic Acid: A New Probe for the Study of Cellular Regulation" *TIBS* **1990**, *15*, 98-102.

49. Sheppeck, J. E.; Gauss, C. M.; Chamberlin, R. A., "Inhibition of the Ser-Thr Phosphatases PP1 and PP2A by Naturally Occurring Toxins" *Bioorg. Med. Chem.* **1997**, *5*, 1739-1750.

50. González, I. C.; Forsyth, C. J., "Total Synthesis of Thyrsiferyl 23-Acetate, a Specific Inhibitor of Protein Phosphatase 2A and an Anti-Leukemic Inducer of Apoptosis" *J. Am. Chem. Soc.* **2000**, *122*, 9099-9108.

51. Okude, Y.; Hirano, S.; Hiyama, T; Nozaki, H., "Grignard-Type Carbonyl Addition of Allyl Halides by Means of Chromous Salt. A Chemospecific Synthesis of Homoallyl Alcohols" *J. Am. Chem. Soc.* **1977**, *99*, 3179-3181.

52. Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H., "Reactions of Alkenylchromium Reagents Prepared from Alkenyl Trifluoromethanesulfonates (Triflates) with Chromium (II) Chloride under Nickel Catalysis" *J. Am. Chem. Soc.* **1986**, *108*, 6048-6050.

53. Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y., "Catalytic Effects of Nickel(II) Chloride and Palladium(II) Acetate on Chromium(II)-Mediated Coupling Reactions of Iodo Olefins and Aldehydes" *J. Am. Chem. Soc.* **1986**, *108*, 5644-5646.

54. Towne, T. B.; McDonald, F. E., "*syn*-Oxidative Polycyclizations of Hydroxypolyenes: Highly Stereoselective and Potentially Biomimetic Syntheses of *all-trans*-Polytetrahydrofurans" *J. Am. Chem. Soc.* **1997**, *119*, 6022-6028.

55. Dess, D. B.; Martin, J. C., "Readily Accessible 12-I-5 Oxidant for the Conversions of Primary and Secondary Alcohols to Aldehydes and Ketones" *J. Org. Chem.* **1983**, *48*, 4155-4156.

56. Takai, K.; Nitta, K.; Utimoto, K., "Simple and Selective Methods for RCHO → (*E*)-RCH=CHX Conversion by Means of a CHX_3–$CrCl_2$ System" *J. Am. Chem. Soc.* **1986**, *108*, 7408-7410.

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

58. Katsuki, T.; Sharpless, B., "The First Practical Method for Asymmetric Epoxidation" *J. Am. Chem. Soc.* **1980**, *102*, 5974-5976.

59. Parikh, J. R.; Doering, W. v. E., "Sulfur Trioxide in the Oxidation of Alcohols by Dimethyl Sulfoxide" *J. Am. Chem. Soc.* **1967**, *89*, 5505-5507.

60. Corey, E. J.; Fuchs, P. L., "A Synthetic Method for Formyl → Ethynyl Conversion (RCHO → RC≡CH or RC≡CR'" *Tetrahedron Lett.* **1972**, 3769-3772.

61. Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A., "Palladium-Catalyzed Inter- and Intramolecular Cross-Coupling Reactions of *B*-Alkyl-9-borabicyclo[3.3.1]nonane Derivatives with 1-Halo-1-alkenes or Haloarenes. Synthesis of Functionalized Alkenes, Arenes, and Cycloalkenes via a Hydroboration-Coupling Sequence" *J. Am. Chem. Soc.* **1989**, *111*, 314-321.

62. Miyaura, N.; Suzuki, A., "Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds" *Chem. Rev.* **1995**, *95*, 2457-2483.

63. Chemler, S. R.; Trauner, D.; Danishefsky, S. J., "The *B*-Alkyl Suzuki-Miyaura Cross-Coupling Reaction: Development, Mechanistic Study, and Applications in Natural Product Synthesis" *Angew. Chem. Int. Ed.* **2001**, *40*, 4544-4568.

64. Kodama, M.; Yoshio, S.; Tabata, T.; Deguchi, Y.; Sikiya, Y.; Fukuyama, Y., "Enatioselective Synthesis of (3*R*,6*S*,7*R*,18*R*,19*S*)-, (3*R*,6*S*,7*R*,18*R*,19*R*)-, and (3*R*,6*S*,7*R*,18*S*,19*R*)-Quassiols A. A Comment on the Stereochemistry of Natural Quassiol A" *Tetrahedron Lett.* **1997**, *38*, 4627-4630.

65. Kodama, M.; Minami, H.; Mima, Y.; Fukuyama, Y., "Convenient Synthesis of Chiral Epoxyisoprenoids by Yeast Reduction" *Tetrahedron Lett.* **1990**, *31*, 4025-4026.

66. Wang, Z.; Tu, Y.; Frohn, M.; Zhang, J.; Shi, Y., "An Efficient Catalytic Asymmetric Method" *J. Am. Chem. Soc.* **1997**, *119*, 11224-11235.

67. Kuang, C.; Senboku, H.; Tokuda, M., "Convenient and Stereoselective Synthesis of (*Z*)-1-bromo-alkenes by Microwave-Induced Reaction" *Tetrahedron Lett*. **2001**, *42*, 3893-3896.

68. Hioki, H.; Kanehara, C.; Ohnishi, Y.; Umemori, Y.; Sakai, H.; Yoshio, S.; Matsushita, M.; Kodama, M., "What is the Structure of Glabrescol? Stereoselective Synthesis of Reported Glabrescol" *Angew. Chem. Int. Ed.* **2000**, *39*, 2252-2254.

69. Mitsunobu, O.; Yamada, Y., "Preparation of Esters of Carboxylic and Phosphoric Acids via Quaternary Phophonium Salts" *Bull. Chem. Soc. Japan* **1967**, *40*, 2380-2382.

70. Sakamoto, I.; Kaku, H.; Tsunoda, T., "Preparation of (Cyanomethylene)trimethyphosphorane as a New Mitsunobu-Type Reagent" *Chem. Pharm. Bull.* **2003**, *51*, 474-476.

71. McDonald, F. E.; Bravo, F.; Wang, X.; Wei, X.; Toganoh, M.; Rodríquez, J. R.; Do, B.; Neiwert, W. A.; Hardcastle, K. I., "Endo-Oxacyclizations of Polyepoxides: Biomimetric Synthesis of Fused Polycyclic Ethers" *J. Org. Chem.* **2002**, *67*, 2515-2523.

72. Payne, G. B., "Epoxide Migrations with α,β-Epoxy Alcohols" *J. Org. Chem.* **1962**, *27*, 3819-3822.

73. Alcaraz, L.; Harnett, J. J.; Mioskowski, C.; Martel, J. P.; Gall, T. L.; Shin, D.; Falck, J. R., "Novel Conversion of Epoxides to One Carbon Homologated Allylic Alcohols by Dimethylsulfonium Methylide" *Tetrahedron Lett.* **1994**, *35*, 5449-5452.

74. Mancuso, A. J.; Swern, D., "Activated Dimethyl Sulfoxide: Useful Reagents for Synthesis" *Synthesis* **1981**, 165-185.

75. Wan, S., "Study on the Structure/Reactivity of Bicyclic Epoxonium Ions towards Tethered Nucleophiles. Efforts towards the Total Synthesis of (+)-Lactodehydrothyrsiferol. Multicomponent Approach to the Synthesis of Oxidized Amides through Nitrile Hydrozirconation" (PhD dissertation) *University of Pittsburgh* **2008**, 35-46.

76. Kolb, H. C.; VanNiewenhze, M. S.; Sharpless, K. B., "Catalytic Asymmetric Dihydroxylation" *Chem. Rev.* **1994**, *94*, 2483-2547.

77. Hicks, J. D.; Roush, W. R., "Synthesis of the C(26)-C(42) and C(43)-C(67) Fragments of Amphidinol 3 via a Common Pyran Intermediate" *Org. Lett.* **2008**, *10*, 681-684.

78. Sharma, S.; Oehlschlager, A. C., "Scope and Mechansim of Stannylalumination of 1-Alkynes" *J. Org. Chem.* **1989**, *54*, 5064-5073.

79. Corminboeuf, O.; Overman, L. E.; Pennington, L. D., "Enantioselective Total Synthesis of Briarellins E and F: The First Total Synthesis of Briarellin Diterpenes" *J. Am. Chem. Soc.* **2003**, *125*, 6650-6652.

80. Fürstner, A.; Shi, N., "Nozaki-Hiyama-Kishi Reactions Catalytic in Chromium" *J. Am. Chem. Soc.* **1996**, *118*, 12349-12357.

81. Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.; Faulkner, D. J.; Petersen, M. R., "Simple Stereoselective Version of the Claisen Rearrangement Leading to *trans*-Trisubstituted Olefinic Bonds. Synthesis of Squalene" *J. Am. Chem. Soc.* **1970**, *92*, 741-743.

82. Johnson, J. R., "Abnormal Reactions of Benzylmagnesium Chloride. II. The Mechanism of the *o*-Tolyl Rearrangement" *J. Am. Chem. Soc.* **1933**, *55*, 3029-3032.

83. Djerassi, C.; Engle, R. R.; Bowers, A., "Notes - The Direct Conversion of Steroidal Δ5-3β-Alcohols to Δ5- and Δ4-3-Ketones" *J. Org. Chem.* **1956**, *21*, 1547-1549.

84. Corey, E. J.; Kim, C. U.; Takeda, M., "A Method for Selective Conversion of Allylic and Benzylic Alcohols to Halides Under Neutral Conditions" *Tetrahedron Lett.* **1972**, *13*, 4339-4342.

85. Negishi, E.; King, A. O.; Klima, W. L., "Conversion of Methyl Ketones into Terminal Acetylenes and (*E*)-Trisubstituted Olefins of Terpenoid Origin" *J. Org. Chem.* **1980**, *45*, 2526-2528.

86. Lipshutz, B. H.; Bulow, G.; Fernandez-Lazaro, F.; Kim, S.; Lowe, R.; Mollard, P.; Stevens, K. L., "A Convergent Approach to Coenzyme Q" *J. Am. Chem. Soc.* **1999**, *121*, 11664-11673.

87. Corey, E. J.; Zhang, J., "Highly Effective Transition Structure Designed Catalyst for the Enantio- and Position-Selective Dihydroxylaytion of Polyisoprenoids" *Org. Lett.* **2001**, *3*, 3211-3214.

88. Dale, J. A.; Mosher, H. S., "Nuclear Magnetic Resonance Enantiomer Reagents. Configurational Correlations *via* Nuclear Magnetic Resonance Chemical Shifts of Diastereomeric Mandelate, *O*-Methylmandelate, and α-Methoxy-α-trifluoromethylphenylacetate (MTPA) Esters" *J. Am. Chem. Soc.* **1973**, *95*, 512-519.

89. Hoye, T. R.; Jeffrey, C. S.; Shao, F., "Mosher Ester Analysis for the Determination of Absolute Configuration of Stereogenic (Chiral) Carbinol Carbons" *Nat. Protoc.* **2007**, 2451-2458.

90. Trost, B. M.; Ball, Z. T., "Alkyne Hydrosilylation Catalyzed by a Cationic Ruthenium Complex: Efficient and General Trans Addition" *J. Am. Chem. Soc.* **2005**, *127*, 17644-17655.

91. Basel, Y.; Hassner, A., "Di-*tert*-buty Dicarbonate and 4-(Dimethylamino)pyridine Revisited. Their Reactions with Amines and Alcohols" *J. Org. Chem.* **2000**, *65*, 6368-6380.

92. Renz, M.; Meunier, B., "100 Years of Baeyer-Villiger Oxidations" *Eur. J. Org. Chem.* **1999**, 737-750.

93. Frohn, M.; Shi, Y., "Chiral Ketone-Catalyzed Asymmetric Epoxidation of Olefins" *Synthesis* **2000**, 1979-2000.

94. Wu, X.; She, X.; Shi, Y., "Highly Enantioselective Epoxidation of α,β-Unsaturated Esters by Chiral Dioxirane" *J. Am. Chem. Soc.* **2002**, *124*, 8792-8793.

95. Wang, B.; Wu, X.; Wong, O. A.; Nettles, B.; Zhao, M.; Chen, D.; Shi, Y., "A Diacetate Ketone-Catalyzed Asymmetric Epoxidation of Olefins" **2009**, *74*, 3986-3989.

96. Zhang, H. X.; Guibé, F.; Balavoine, G., "Palladium- and Molybdenum-Catalyzed Hydrostannation of Alkynes. A Novel Access to Regio- and Stereodefined Vinylstannanes" *J. Org. Chem.* **1990**, *55*, 1857-1867.

97. Wipf, P.; Lim, S., "Rapid Carboalumination of Alkynes in the Presence of Water" *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1068-1071.

98. Tamao, K.; Sumitani, K.; Kumada, M., "Selective Carbon-Carbon Bond Formation by Cross-Coupling of Grignard Reagents with Organic Halides. Catalysis by Nickle-Phosphine Complexes" *J. Am. Chem. Soc.* **1972**, *94*, 4374-4376.

99. Itoh, M.; Hagiwara, D.; Kamiya, T., "A New *tert*-Butylcarbonylating Reagent, 2-*tert*-Butyloxycarbonyloxyimino-2-phenylacetonitrile" *Tetrahedron Lett.* **1975**, *16*, 4393-4394.

100. Tago, K.; Kogen, H., "A Highly Stereoselective Synthesis of (*E*)-α-Bromoacrylates" *Tetrahedron*, **2000**, 8825-8831.

101. Littke, A. F.; Fu, G. C., "A Convenient and General Method for Pd-Catalyzed Suzuki Cross-Couplings of Aryl Chlorides and Arylboronic Acids" *Angew. Chem. Int. Ed.* **1998**, *37*, 3387-3388.

102. Littke, A. F.; Dai, C.; Fu, G. C., "Versatile Catalysts for the Suzuki Cross-Coupling of Arylboronic Acids with Aryl and Vinyl Halides and Triflates under Mild Conditions" *J. Am. Chem. Soc.* **2000**, *122*, 4020-4028.

103. Nieto, N.; Molas, P.; Benet-Buchholz, J.; Vidal-Ferran, A., "Practical Synthesis of Shi's Diester Fructose Derivative for Catalytic Asymmetric Epoxidation of Alkenes" *J. Org. Chem.* **2005**, *70*, 10143-10146.

104. Grieco, P. A.; Oguri, T.; Yokoyama, Y., "One-Step Conversion of Protected Lactols into Lactones" *Tetrahedron Lett.* **1978**, *19*, 419-420.

105. Frigerio, M.; Santagostino, M., "A Mild Oxidizing Reagent for Alcohols and 1,2-Diols: o-Iodoxybenzoic Acid (IBX) in DMSO" *Tetrahedron Lett.* **1994**, *35*, 8019-8022.

106. Karplus, M., "Vicinal Proton Couplings in Nuclear Magnetic Reasonance" *J. Am. Chem. Soc.* **1963**, 2870-2871.

107. Corey, E. J.; Shibata, S.; Bakshi, R. K., "An Efficeint and Catalytically Enantioselective Route to (*S*)-(-)-Phenyloxirane" *J. Org. Chem.* **1988**. *53*, 2861-2863.

108. Smith, A. B.; Kim, D.; Xian, M., "Anion Relay Chemistry Extended. Synthesis of a Gorgonian Sesquiterpene" *Org. Lett*. **2007**, *9*, 3307-3309.

109. Wan, Z.; Choi, H.; Kang, F.; Nakajima, K.; Demeke, D.; Kishi, Y., "Asymmetric Ni(II)/Cr(II)-Mediated Coupling Reaction: Stoichiometric Process" *Org. Lett.* **2002**, *4*, 4431-4434.

110. Namba, K.; Kishi, Y., "New Catalytic Cycle for Coupling of Aldehydes with Organochromium Reagents" *Org. Lett.* **2004**, *6*, 5031-5033.

111. Guo, H.; Dong, C.; Kim, D.; Urabe, D.; Wang, J.; Kim, J. T.; Liu, X.; Sasaki, T.; Kishi, Y., "Toolbox Approach to the Search for Effective Ligands for Catalytic Asymmetric Cr-Mediated Coupling Reactions" *J. Am. Chem. Soc.* **2009**, *131*, 15387-15393.

112. Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M., "On the Use of the *O*-Methylmandelate Ester for Establishment of Absolute Configuration of Secondary Alcohols" *J. Org. Chem.* **1986**, *51*, 2370-2374.

113. Martinelli, M. J.; Nayyar, N. K.; Moher, E. D.; Dhokte, U. P.; Pawiak, J. M.; Vaidyanathan, R., "Dibutyltin Oxide Catalyzed Selective Sulfonylation of α-Chelatable Primary Alcohols" *Org. Lett.* **1999**, *1*, 447-450.

114. Hutchins, R. O.; Kandasamy, D.; Dux III, F.; Maryanoff, C. A.; Rotstien, D.; Goldsmith, B.; Burgoyne, W.; Cistone, F.; Dalessandro, J.; Puglis, J., "Nucleophilic Borohydride: Selective Reducttive Displacement of Halides, Sulfonate Esters, Tertiary Amines, and *N*,*N*-Disulfonimimdes with Borohydride Reagents in Polar Aprotic Solvents" *J. Org. Chem.* **1978**, *43*, 2259-2267.

115. Hutchins, R. O.; Maryanoff, B. E.; Milewski, C. A., "Sodium Cyanoborohydride in Hexamethylphosphoramide. An Exceptionally Selective Reagent System for the Reduction of Alkyl Iodides, Bromides, and Tosylates" *J. Chem. Soc. D.* **1971**, 1097-1098.

116. Sperry, J.; Wilson, Z. E.; Rathwell, D. C. K.; Brimble, M. A., "Isolation, Biological Activity, and Synthesis of Benzannulated Spiroketal Natural Products" *Nat. Prod. Rep.* **2010**, *27*, 1117-1137.

117. Doodeman, R.; Rutjes, F. P. J. T.; Hiemstra, H., "Synthesis of 2-Substituted Chromenes via Ring-Closing Metathesis and Stable 1-Benzopyrylium Ions" *Tetrahedron Let.* **2000**, *41*, 5979-5983.

118. Mézailles, N.; Richard, L.; Gagosz, F., "Phosphine Gold (I) Bis-(trifluoromethanesulfonyl)inidate Complexes as New Highly Efficient and Air-Stable Catalysts for the Cycloisomerization of Enynes" *Org. Lett.* **2005**, *7*, 4133-4136.

119. Lykakis, I. N.; Efe, C.; Gryparis, C.; Stratakis, M., "$Ph_3PAuNTf_2$ as a Superior Catalyst for the Selective Synthesis of 2*H*-Chromenes: Application to the Concise Synthesis of Benzopyran Natural Products" *Eur. J. Org Chem.* **2011**, 2334-2338.

120. Nevado, C.; Echavarren, A. M., "Intramolecular Hydroarylation of Alkynes Catalyzed by Platinum or Gold: Mechanism and *endo* Selectivity" *Chem. Eur. J.* **2005**, *11*, 3155-3164.

121. Pastine, S. J.; Youn, S. W.; Sames, D., "Pt^{IV}-Catalyzed Cyclization of Arene-Alkyne Substrates via Intramolecular Electrophilic Hydroarylation" *Org. Lett.* **2003**, *5*, 1055-1058.

122. Huang, Z.; Negishi, E., "A Convenient and Genuine Equivalent to $HZrCp_2Cl$ Generated in Situ from $ZrCp_2Cl_2$–DIBAL-H" *Org. Lett.* **2006**, *8*, 3675-3678.

123. Brown, C. A.; Ahuja, V. K., "'P-2 Nickel' Catalyst with Ethylenediamine, a Novel System for Highly Stereospecific Reduction of Alkynes to *cis*-Olefins" *J. Chem. Soc., Chem. Commun.* **1973**, 553-554.

124. Frick, U.; Simchen, G., "Synthese von *O*-(Trimethylsilyl)keten-O,N-acetalen, 2,5-Bis(trimthylsiloxy)pyrrolen, -furanen, und –thiophenen" *Liebigs Ann. Chem.* **1987**, 839-845.

125. Berionni, G.; Maji, B.; Knochel, P.; Mayr, H., "Nucleophilicity Parameters for Designing Transition Metal-Free C–C Bond Forming Reactions of Organoboron Compounds" *Chem. Sci.* **2012**, *3*, 878.

126. Lee, S.; MacMillan, D. W. C., "Organocatalytic Vinyl and Friedel-Crafts Alkylations with Trifluoroborate Salts" *J. Am. Chem. Soc.* **2007**, *129*, 15438-15439.

127. Vo, C. T.; Mitchell, A.; Bode, J. W., "Expanded Substrate Scope and Improved Reactivity of Ether-Forming Cross-Coupling Reactions of Organotrifluoroborates and Acetals" *J. Am. Chem. Soc.* **2011**, *133*, 14082-14089.

128. Pereira, S.; Srebnik. M., "Hydroboration of Alkynes with Pinacolborane Catalyzed by $HZrCp_2Cl$" *Organometallics*, **1995**, *14*, 3127-3128.

129. Vieira, A. S.; Ferreira, F. P.; Fiorante, P. F.; Guadagnin, R. C.; Stefani, H. A., "Nucleophilic Additions of Potassium Organotrifluoroborates to Chiral Cyclic *N*-Acyliminium Ions: Stereoselective Synthesis of Functionalized *N*-Heterocycles" *Tetrahedron* **2008**, *64*, 3306-3314.

130. Gao, F.; Hoveyda, A. H., "α-Selective Ni-Catalyzed Hydroalumination of Aryl- and Alkyl-Substituted Terminal Alkynes: Practical Syntheses of Internal Vinyl Aluminums, Halides or Boronates" *J. Am. Chem. Soc.* **2010**, *132*, 10961-10963.

131. Cottet, F.; Cottier, L.; Descotes, G., "New Synthesis of Isochromene" *Synth. Commun.* **1987**, 497-498.

132. Fleming, I.; Henning, R.; Plaut, H., "The Phenyldimethylsilyl Group as a Masked Form of the Hydroxy Group" *J. Chem. Soc., Chem. Commun.* **1984**, 29-31.

133. Tamao, K.; Inhida, N.; Kumada, M., (Diisopropoxymethylsilyl)methyl Grignard Reagent: A New, Practically Useful Nucleophilic Hydroxymethylating Agent" *J. Org. Chem.* **1983**, *48*, 2120-2122.

134. Hatanaka, Y.; Hiyama, T., "Cross-Coupling of Organosilanes with Organic Halides Mediated by Palladium Catalyst and Tris(diethylamino)sulfonium Difluorotrimethylsilicate" *J. Org. Chem.* **1988**, *53*, 918-920.

135. Anderson, J. C.; Smith, S. C.; Swarbrick, M. E., "Diastereoselective Acylic Aza-[2,3] Wittig Sigmatropic Rearrangments" *J. Chem. Soc., Perkin Trans. 1* **1997**, 1517-1521.

136. Czaplik, W. M.; Mayer, M.; von Wangelin, A. J., "Iron-Catalyzed Reductive Aryl-Alkenyl Cross-Coupling Reactions" *Chem. Cat. Chem.* **2011**, *3*, 135-138.

137. Mayr, H.; Kempf, B.; Ofial, A. R., "π-Nucleophilicity in Carbon–Carbon Bond Forming Reactions" *Acc. Chem Res.* **2003**, *36*, 66-77.

138. Zhang, Y.; Li, C., "Highly Efficent Cross-Dehydrogenative-Coupling between Ethers and Active Methylene Compounds" *Angew. Chem. Int. Ed.* **2006**, *45*, 1949-1952.

139. Masse, C. E.; Panek, J. C., "Diastereocelective Reactions of Chiral Allyl- and Allenylsilanes with Activated C=X π-Bonds" *Chem. Rev.* **1995**, *95*, 1293-1316.

140. Davisson, V. J.; Woodside, A. B.; Neal, T. R.; Stremler, K. E.; Muehlbacher, M.; Poulter, C. D., "Phosphorylation of Isoprenoid Alcohols" *J. Org. Chem.* **1986**, *51*, 4768-4779.

141. Bortoletto, M. H.; Lavenot, L.; Larpent, C.; Roucoux, A.; Patin, H., "Catalytic Carbon-Carbon Coupling Reaction in Biphasic Liquid-Liquid Systems: Mechanistic Aspects in Vitamin E Precursor Synthesis" *Applied Catalysis A: General*, **1997**, 347-357.

142. Baeckström, P.; Li, L., "Isoprenoid Chain Elongations by Claisen Rearrangements Using Acetals as Precursors of Vinyl Ethers" *Tetrahedron* **1991**, *47*, 6521-6532.

143. Muranaka, K.; Sano, A.; Ichikawa, S.; Matsuda, A., "Synthesis of Hsp90 Inhibitor Dimers as Potential Antitumor Agents" *Bioorg. Med. Chem.* **2008**, *16*, 5862-5870.

144. Nacro, K.; Baltas, M.; Gorrichon, L., "Attempt to Rationalize the Diastereoselectivity in the Addition of Ester Enolate to Optically Active α,β-epoxyaldehydes" *Tetrahedron* **1999**, *55*, 14013-14030.

145. Groth, U.; Richter, N.; Kalogerakis, A., [2+2+2]-Cycloaddition of 4-Hydroxy-Substituted Decahydrophenanthrenes" *Eur. J. Org. Chem.* **2003**, 4634-4639.

146. Nonoshita, K.; Banno, H.; Maruoka, K.; Yamamoto, H., "Organoaluminum-Promoted Claisen Rearrangement of Allyl Vinyl Ethers" *J. Am. Chem. Soc.* **1990**, *112*, 316-322.

147. Bull, J. R.; Gordon, R.; Hunter, R., "Intramolecular Diels-Alder Reactions of 1-Phenylsulfonylalka-1,2,(ω – 3),(ω – 1)-tetranenes" *J. Chem. Soc., Perkin Trans. 1,* **2000**, 3129-3139.

148. Cheung, L. L. W.; Yudin, A. K., "Synthesis of Aminocyclobutanes through Ring Expansion of *N*-Vinyl-β-Lactams" *Org. Lett.* **2009**, *11*, 1281-1284.

149. Tietze, L. F.; Völkel, L.; Wulff, C.; Weigand, B.; Bittner, C.; McGrath, P.; Johnson, K.; Schäfer, M., "Facial Selective Allylation of Methyl Ketones for the Asymmetric Synthesis of α-Substituted Tertiary Homoallylic Ethers" *Chem. Eur. J.* **2001**, *7*, 1304-1308.

150. Mai, K.; Patil, G., "Alkylsilyl Cyanides as Silylating Agents" *J. Org. Chem.* **1986**, *51*, 3545-3548.

151. Evans, D. A.; Aye, Y.; Wu, J., "Asymmetric, Anti-Selective Scandium-Catalyzed Sakurai-Hosomi Reaction and its application to Stereoselective Syntheses of *N*-Boc- D-alloisoleucine and D-isoleucine" *Org. Lett.* **2006**, *8*, 2071-2073.

152. Takahashi, K.; Ishiyama, T., Miyaura, N., "A Borylcopper Species Generated from Bis(pinacolato)diboron and its Addition to α,β-Unsaturated Carbonyl Compounds and Terminal Alkymes" *J. Organomet. Chem.* **2001**, 47-53.

153. Molander, G. A.; Bernardi, C. R., "Suzuki-Miyaura Cross-Coupling Reactions of Potassium Alkenyltrifluoroborates" *J. Org. Chem.* **2002**, *67*, 8424-8429.

154. Molander, G. A.; Katona, B. W.; Machrouhi, F., "Development of the Suzuki-Miyaura Cross-Coupling Reaction: Use of Air-Stable Potassium Alkynyltrifluoroborates in Aryl Alkynylations" *J. Org. Chem.* **2002**, *67*, 8416-8423.

155. Gerbino, D. C.; Mandolesi, S. D.; Schmalz, H.; Podestá, J. C., "Introduction of Allyl and Phenyl Side-Chains into Aromatic Systems by Suzuki Cross-Coupling Reactions" *Eur. J. Org. Chem.* **2009**, 3964-3972.

156. Liu, G.; Zhang, J.; Wu, B.; Wang, J., "Carborane as a Tunable Tag for Ru Catalysts: Generating an Anion-Appended Recyclable and Robust Catalyst Suitable for the Noncovalent Binding Concept" *Org. Lett.* **2007**, *9*, 4263-4266.

157. Anderson, J. C.; Smith, S. C.; Swarbrick, M. E., "Diastereoselective Acyclic aza-[2,3] Wittig Sigmatropic Rearrangements" *J. Chem. Soc., Perkin Trans. 1* **1997**, 1517-1521.

158. Senboku, H.; Michinishi, J.; Hara, S., "Facile Synthesis of 2,3-Dihydrobenzofuran-3-ylacetic Acids by Novel Electro-chemical Sequential Aryl Radical Cyclization-Carboxylation of 2-Allyloxy-bromobenzenes Using Methyl 4-*tert*-Butylbenzoate as an Electron-Transfer Mediator" *Synlett* **2011**, 1567-1572.