AN ABSTRACT FOR THE DISSERTATION OF

Damien L. Kuiper for the degree of Doctor of Philosophy in Chemistry presented on February 2, 2010.

Title: Studies Toward the Total Synthesis of Azaspiracid-1.

Abstract approved:

Rich G. Carter

Azaspiracid has generated an enormous amount of scientific interest in the fourteen years since its initial discovery. The structure contains a 6,5,6 bis-spiroketal, a [3.3.1] bicyclic ketal and a 6,5-spiroaminal linkage as key moieties. With 9 rings, 20 stereocenters and three alkenes, the azaspiracid immediately attracted the interest of the synthetic community. To date, two syntheses have been reported by the Nicolaou and Evans laboratories.

An initial route to the C_{13}-C_{19} aldehyde was plagued by a problematic 1,2 silyl migration. An improved route to the C_{13}-C_{19} aldehyde was developed based on a modified protecting group strategy utilizing a PMP ketal. The improvements in the synthesis led to facile production of 250 mg of the key transoidal ABC ring bisspiroketal. This second generation route dramatically improved the efficiency of our synthesis, with the overall yield for the C_{13}-C_{19} aldehyde increasing from 2% to 15%, which allowed the synthesis of over 250 mg the bisspiroketal.

An optimized route to the FGHI spiroaminal was developed. A unique equilibration method for the construction of the anomerically-stabilized spiroaminal was discovered. After cleavage of the Cbz carbamate, an *in situ* tautomerization provided the desired doubly anomeric FGHI spiroaminal subunit. This transformed a total synthesis of FGHI spiroaminal into a process

which could easily produce gram quantities of advanced intermediates requisite for the synthesis of azaspiracid.

With an optimized synthesis of the FGHI ring system complete, a host of routes were investigated for the coupling of the C_{26}-C_{40} fragment and C_{20}-C_{25} fragment was developed. The C_{25}-C_{26} bond was formed *via* an aldol condensation between FGHI methyl ester and the C_{20}-C_{26} aldehyde. A novel TAS-F-mediated elimination was developed to provide the C_{26}-C_{44} olefin.

The Horner-Wadsworth-Emmons coupling of the C_4-C_{19} lactol and C_{20}-C_{40} ketophosphonate furnished the contiguous C_4-C_{45} framework of azaspiracid-1. Davis oxidation of C_{20} provided the requisite oxidation state. The only challenges remaining are desilylation at C_{25} and cross metathesis at C_4 to complete a formal synthesis of azaspiracid.

Studies Toward the Total Synthesis of Azaspiracid-1

by
Damien L. Kuiper

A DISSERTATION
submitted to
Oregon State University

in partial fulfillment of
the requirements for the
degree of

Doctor of Philosophy

Presented February 2, 2010
Commencement June 2010

Doctor of Philosophy dissertation of Damien L. Kuiper presented on February 2, 2010.

APPROVED:

Major Professor, representing Chemistry

Chair of Department of Chemistry

Dean of the Graduate School

I understand that my dissertation will become part of the permanent collection of Oregon State University libraries. My signature below authorizes release of my dissertation to any reader upon request.

Damien L. Kuiper, Author

ACKNOWLEDGEMENTS

I would like to thank my wife Heather, my friends, and my family for their support through my PhD studies. They have greatly enriched my life, and I am a better person because of each of them. I would like to thank Roger Kohnert for NMR advice, and Jeff Morré for mass spectroscopy assistance. I would like to thank my Committee for their time and efforts on my behalf. Lastly, I would like to thank Professor Carter for his mentorship over the last 5 years.

This work is dedicated to my late grandfather, Hank. He embodied the values that I so desperately needed to perform the work in the subsequent pages of this thesis.

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STUDIES TOWARD THE TOTAL SYNTHESIS OF AZASPIRACID 1

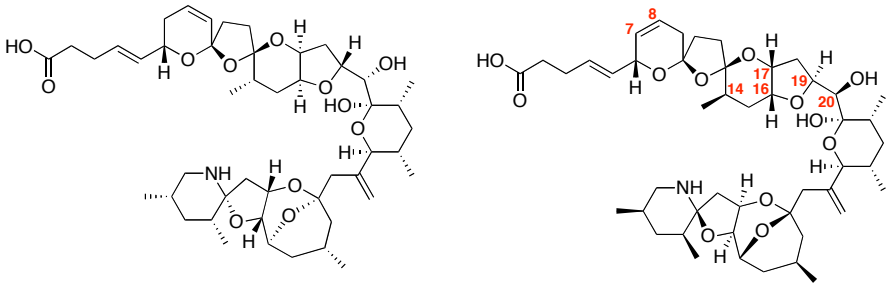
CHAPTER 1:

INTRODUCTION

1.1: ISOLATION

In the fall of 1995, at least 8 people fell ill after eating mussels (*Mytilus edulis*) in the Netherlands. Symptoms of nausea, vomiting and stomach cramps indicated diarrhetic shellfish poisoning (DSP) as a putative cause.[1] The absence of significant quantities of known DSP toxins okadoic acid and dinophysistoxins prompted investigation into the identity of the causative toxin.

In 1998, a toxin with a 0.2 mg/kg lethal dose in mice was isolated from mussel meat collected in Killary Harbor, Ireland. A putative structure for the toxin, azaspiracid-1, was proposed based on 2D-NMR analysis (Figure 1.1).[2] The structure contained a 6,5,6 bis-spiroketal, a [3.3.1] bicyclic ketal, and a 6,5-spiroaminal linkage as key moieties. With 9 rings, 20 stereocenters and three alkenes, the azaspiracid immediately attracted the interest of the synthetic community. In 2004, with mounting evidence of structural inaccuracies the Nicolaou group reported the revision of the structure of azaspiracid from **1.1.1** to **1.1.2**.[3] Independently and concurrently, the Carter laboratory arrived at the same conclusion.[4] Revisions included the migration of the A ring olefin from C_8-C_9 to C_7-C_8, the inversion of absolute configuration of the FGHI ring system and the change of absolute configurations of C_{14}, C_{16}, C_{17}, C_{19}, and C_{20}



1.1.1
Proposed Structure

1.1.2
Revised Structure

Figure 1.1: Structure of Azaspiracid-1

While azaspiracid was isolated from mussels in 1998, it was a full five years before the first report of the progenitor was divulged.[5] Therein, James reported *Protoperidinium crassipes*, a dinoflagellate, as the source of azaspiracid. Although azaspiracid was observed in homogenates

of *P. crassipes* by mass spectroscopy, repeated attempts to induce azaspiracid biosynthesis proved fruitless. Further clouding the report was the fact that *P. crassipes* is a predacious dinoflagellate known to graze upon other dinoflagellates.[6] Finally, in 2009 Tillmann reported a new, smaller dinoflagellate as the source of azaspiracid.[7] *Azadinium spinosum*, a photosynthetic dinoflagellate, was shown to produce azaspiracid in culture broths, finally ending the mystery of its origin.

1.2: Toxicology of Azaspiracid

After initial observations of nausea, vomiting, diarrhea and stomach cramps were observed in humans, a mouse model was used to test the toxicological properties of azaspiracid. Intraperitoneally injected acetone extracts of contaminated mussels induced sluggishness, respiratory difficulty, spasms, progressive paralysis and death within 20 to 90 minutes, with a minimum lethal dose of 150 µg/kg.[1] In feeding studies, treatment of mice with a single 900 µg/kg dose of azaspiracid led to no clinical illness after twenty four hours;[8] however, a host of injuries were observed upon autopsy including accumulation of fluid in the ileum, necrosis of microvilli epithelial cells and fused microvilli in the intestinal tract.

Studies on chronic exposure showed effects on the lungs, thymus, stomach, liver and spleen with doses as low as 50 µg/kg doses twice a week.[9] Inflammation, thickening of alveolar walls and pneumonia were observed in the lungs with eventual onset of lung tumors. The stomachs and intestines of these mice were also inflamed with eroded surfaces, ulcers and degradation of microvilli. The liver saw accumulation of fat droplets, with high doses. The thymus and spleen were markedly smaller.

Initially, the observed bioactivity was thought to be due to protein phosphate inhibition;[10] however, repeated attempts at proving a correlation have been unsuccessful.[11] Azaspiracid is, unlike many phycotoxins, cytotoxic which is presumably induced through necrotic lysis rather then apoptosis.[11b]

1.3: Synthetic Considerations Towards Azaspiracid

When designing the synthesis of a molecule, it is best to first look for reasons for conformational effects observed. In cyclic ketals and acetals, such as azaspiracid a key effect controlling the confirmation of the ketal is the anomeric effect (Figure 1.2). An anomerically-stabilized acetal such as compound **1.2.1** is thermodynamically favored over a non-anomerically stabilized acetal such as **1.2.2**. The origin of this stabilization is believed to be due to the additive effects of two phenomena. Firstly, the dipoles of the two carbon oxygen bonds of an anomerically stabilized ketal are pointed in roughly different directions, thus minimizing the overall dipole-dipole repulsion.[12] In contrast, a non-anomeric ketal has both dipoles pointed in roughly the same direction thus exhibiting dipole-dipole repulsion. Secondly, and maybe more importantly, is a secondary orbital interaction, between a filled orbital on oxygen and the anti-bonding orbital of the C-O bond of the other oxygen of the ketal.[13] This hyperconjugation leads to an elongation of the C-O bond, thus minimizing 1,3 diaxial interactions.

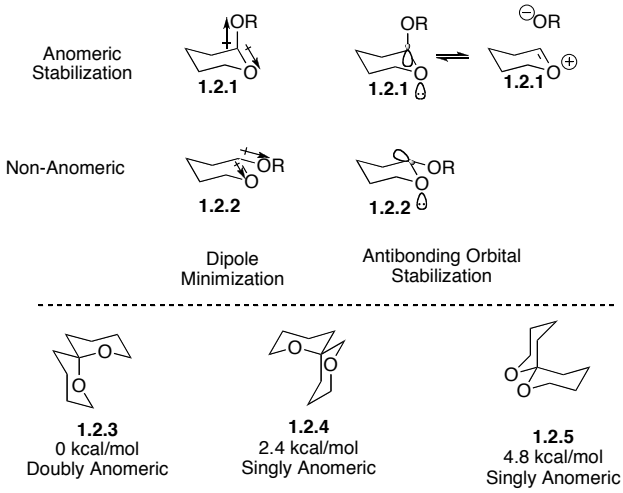


Figure 1.2: Anomeric Stabilization of Acetals

While even in these simple systems, a concrete reason for this phenomenon is often challenging to prove, a host of groups have studied these systems computationally. As early as 1981 the Deslonchamps group was investing the driving force behind the formation of

spiroketals.[14a] Simple calculations of the three possible conformers of the 1,7-dioxaspiro [5.5] undecanes (**1.2.3**, **1.2.4** and **1.2.5**) showed that the doubly anomeric stabilized was the low energy conformer, with an increase in stabilization of approximately 2.4 kCal/mol per each anomeric bond. Testing these calculations the Deslongchamps group prepared the 1,7-dioxaspiro [5.5] undecane **1.2.3** as the sole product of acid catalyzed ketal formation from the parent ketone diol. Interestingly, more then twenty years later when the Tschumpers group reinvestigated these systems using modern molecular dynamics simulations, similar energetic values were established.[14e]

Rather then a simple ketal, azaspiracid is a 6,5,6 bisspiroketal, which brings extra considerations. Firstly, a bisspiroketal can be either transoidal, the oxygens of the ketals are opposite to each other with respect to the central ring, or cisoidal, the oxygens of the ketal are on the same side. Due to dipole-dipole repulsion minimization transoidal bisspiroketals are usually slightly more stable, ~1 kCal/mol (Figure 1.3).[14] Within the group of transoidal and cisoidal compounds, there are doubly anomeric, singly anomeric and non-anomeric bisspiroketals to consider. In 1997, the McGarvey group investigated the simple 6.6.6 bispiroketal.[14b,c] The preparation of bisspiroketals **1.3.8** and **1.3.9** from ketone **1.3.7** afforded some interesting physical data. A 2:1 diastereomeric preference for the transoidal bisspiroketal **1.3.8** was observed. It was hypothesized that a dipole-dipole repulsion about the central ring in the cisoidal bisspiroketal was the reason for this phenomenon. Reequilibration of the cisoidal bisspiroketal under acid catalysis illustrates evidence for this claim. As the dielectric constant of the solvent for the equilibration increases, which would stabilize these dipole repulsions, the diasteromeric ratio of transoidal to cisoidal bisspiroketals decreased. McGarvey hypothesized that the cisoidal bisspiroketal **1.3.9** required a perturbation of the central ring to alleviate this dipole-dipole repulsion

In 2006, the Tschumpers group performed molecular dynamics simulations on these simple 6.6.6 bisspiroketals.[14e] The results suggested that a transoidal chair anomeric twistboat anomeric chair **1.3.10** was the ground state conformer for the system. Interestingly, both the transoidal **1.3.11** and cisoidal chair anomeric chair anomeric chair structures were approximately

1.7 kCal/mol higher in energy. This contradicts the earlier assertion by the McGarvey group that the fully anomeric, all chair transoidal 6.6.6 bisspiroketal **1.3.11** was the ground state product that they had observed. This illustrates a major problem with all calculations on such energetically similar bisspiroketals. Sometimes the error inherent within the calculations is greater than the difference between the two most stable conformers. McGarvey has proven experimentally that transoidal bisspiroketal **1.3.11** is the most stable conformer, while calculations suggest boat **1.3.10** is a more stable conformer, which is not observed by NMR analysis.

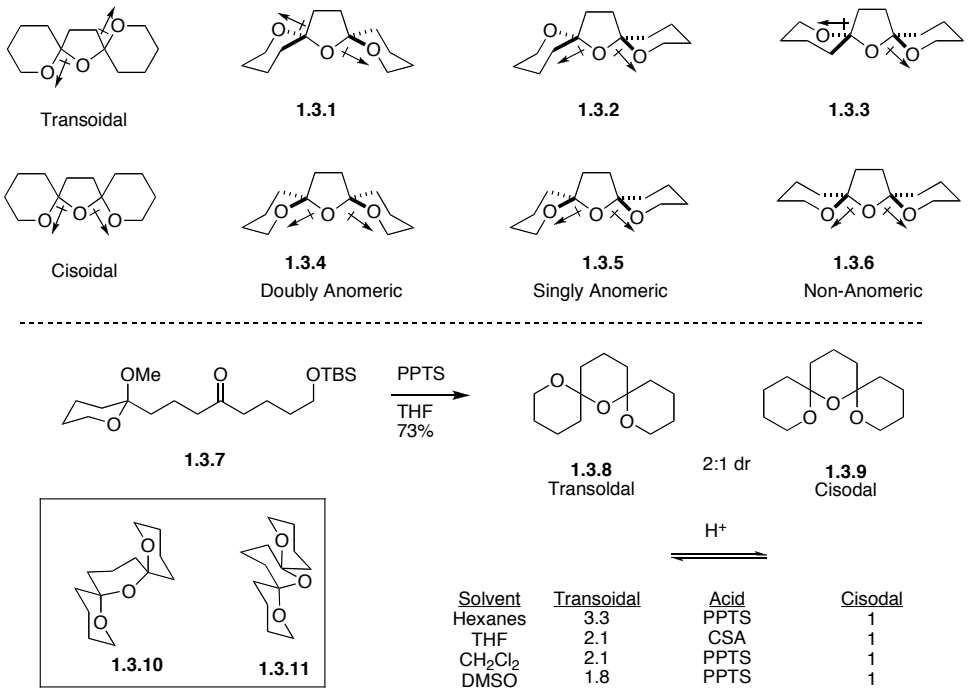


Figure 1.3: Confirmations of Bisspiroketal

Embedded within azaspiracid are four-ketal type moieties: the 6,5,6- bisspiroketal of the ABC ring system, the E ring hemiketal, the bicyclic [3.3.1] FG ring ketal and the 6,5 spiroaminal of the HI ring system (Figure 1.4). Three of these ketals are fully anomeric and should be accessible from thermodynamic ketalization method. Conversely, while the ABC bisspiroketal is transoidal and the AB ring junction is anomeric, the BC ring junction is non-anomeric in the

proposed structure of azaspiracid. As such, all syntheses must perturb the molecule to afford the desired bisspiroketal.

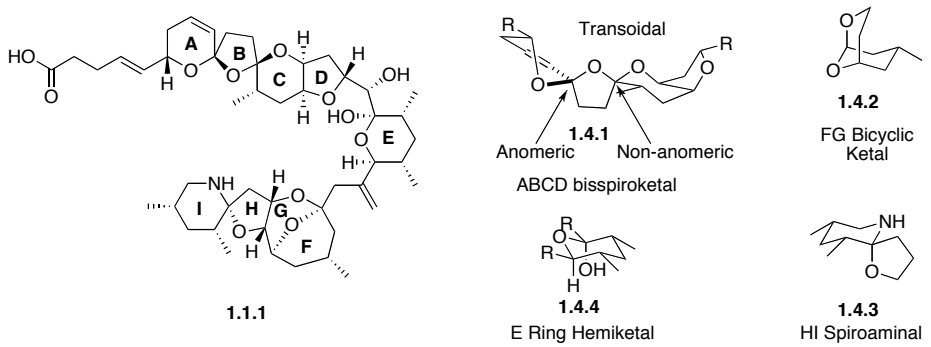


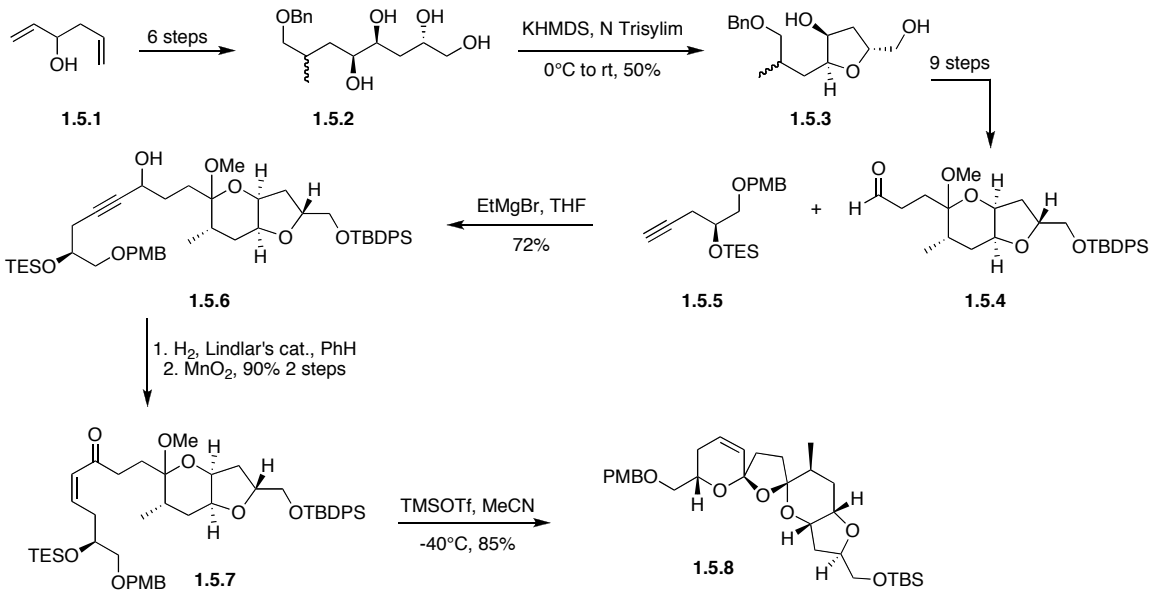
Figure 1.4: Conformational Analysis of Ketals of Azaspiracid

1.4: Synthetic Efforts toward Azaspiracid

In the 11 years since the structure of azaspiracid was disclosed, it has attracted the synthetic attention of the Carter,[4,15] Nicolaou,[3,16] Evans,[17] Forsyth[18] and Nishiyama[19] groups among others.[20] The studies have culminated in a total synthesis of the initially reported structure by Nicolaou[16c,d] and synthesis of the correctly revised structure by Nicolaou[16e,f] and Evans.[17]

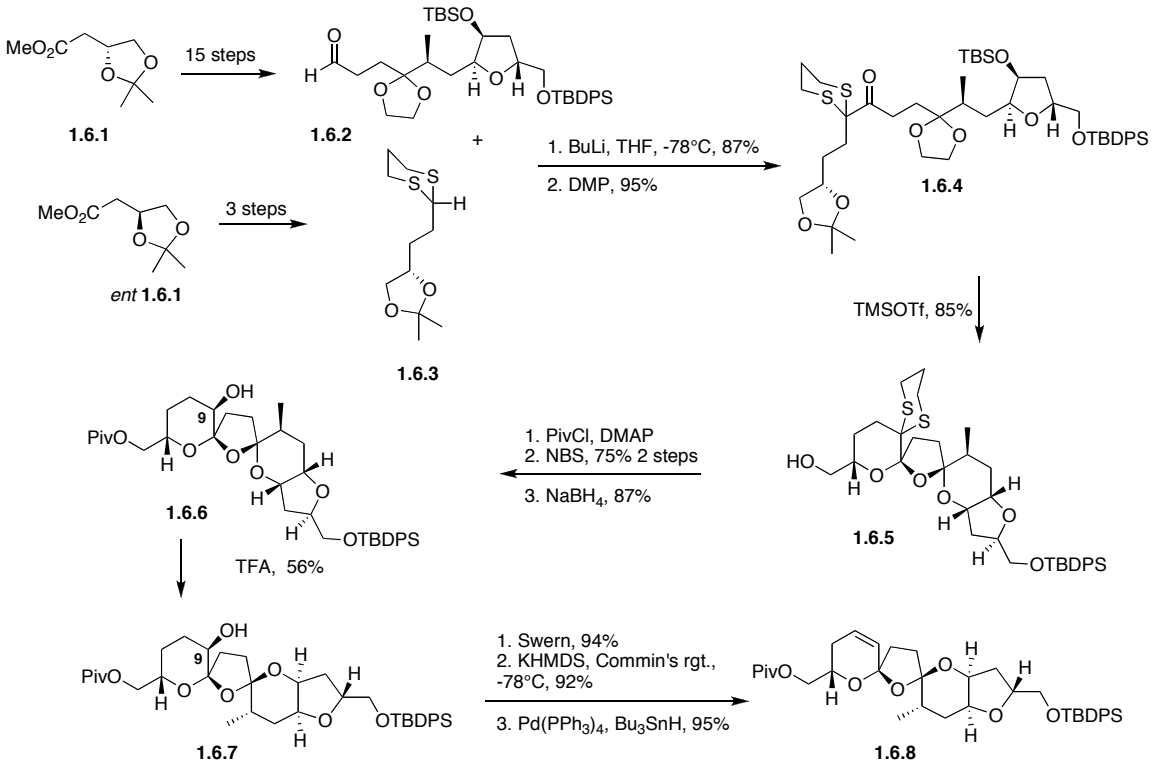
1.4.1: Studies Toward the Initially Proposed Structure of the Bisspiroketal Functionality

In 2001, the Forsyth group reported a synthesis of the ABCD ring system.[18a] Alcohol **1.5.1** was transformed into tetraol **1.5.2** in six steps (Scheme 1.5). Upon treatment with KHMDS and N-trisyl imidizole, an *in situ* epoxide formation and 5-*exo*-*tet* cyclization afforded furan **1.5.3** in 50% yield. Nine further steps transformed the furan into the CD ring system of azaspiracid **1.5.4**. The coupling of the acetylene **1.5.5** and aldehyde **1.5.4** gave all the carbons requisite for the ABCD ring system. Lindlar reduction of the acetylene and manganese dioxide oxidation of the resulting allylic alcohol furnished the enone **1.5.7**. A trimethylsilyl triflate-catalyzed ketal formation gave the bisspiroketal **1.5.8**, in 85% yield. Unfortunately, the bisspiroketal that was formed was the undesired cisoidal bisspiroketal.



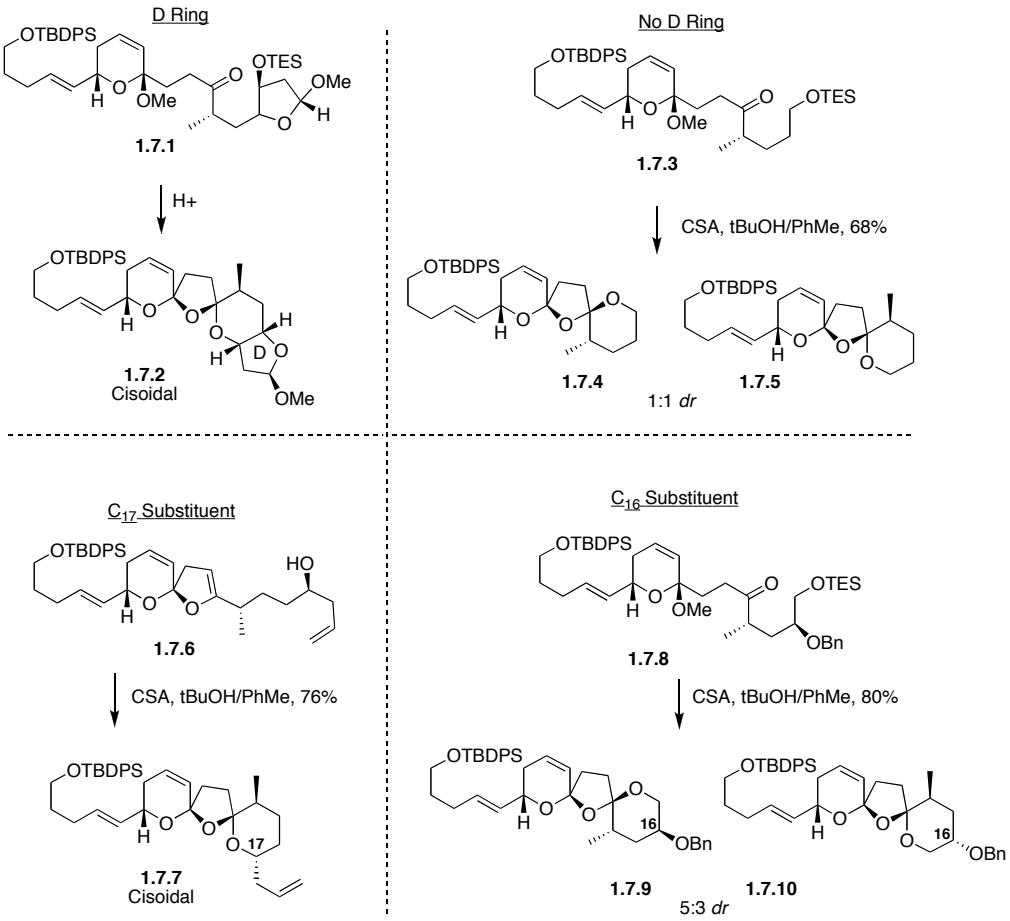
Scheme 1.5: Forsyth's Approach to the ABCD Ring System

In 2001, the Nicolaou group reported a synthesis of a similar ABCD ring system (Scheme 1.6).[16a] A dithiane coupling of aldehyde **1.6.2** and the dithiane **1.6.3** provided the carbon framework for the ring system. After subsequent Dess-Martin oxidation to the ketone **1.6.4**, the stage was set for a Lewis acid-catalyzed cyclization to give the ABCD ring system **1.6.5**. Unfortunately, the undesired fully anomeric cisoidal bisspiroketal was obtained. After protection of the primary alcohol as a pivalate ester, *n*-bromosuccinamide-mediated cleavage of the dithiane and reduction of the resultant ketone furnished β alcohol **1.6.6**. With this compound in hand, the stage was set for equilibration to the desired bisspiroketal. Nicolaou had hypothesized that a favorable hydrogen bond between the C_9 alcohol and the furan oxygen could coax the bisspiroketal into the desired configuration. Upon treatment with trifluoroacetic acid, equilibration did occur in approximately 1:1 *dr*. Purification and resubmission starting material led to an 80% yield of **1.6.7** after 3 cycles. Subsequent oxidation of the C_9 alcohol under Swern conditions, preparation of the enol triflate using Commins' reagent and reduction of the enol triflate utilizing palladium chemistry led to ABCD ring system **1.6.8**.



Scheme 1.6: Nicolaou's Synthesis of the Proposed ABCD Bisspiroketal

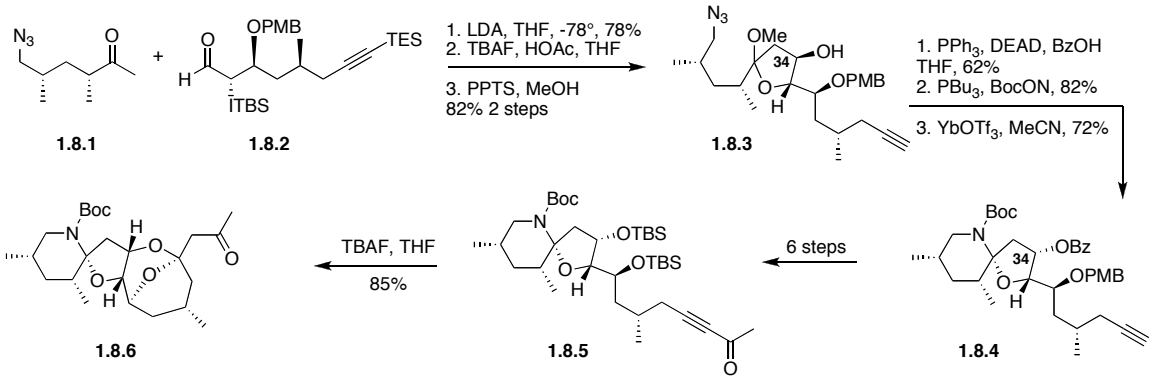
The Carter group decided to explore the effects of different substituents on the cyclization of the bisspiroketal (Scheme 1.7).[15a,b,c] After initial studies proved to induce the ABCD bisspiroketal from ketone **1.7.1** provided the undesired cisoidal product **1.7.2**, it became apparent that a need to understand which substituents controlled the stereochemistry of the ketalization. Removing the D ring led to a 1:1 diasteromeric mixture of the transoidal **1.7.4** and cisoidal **1.7.5**. Substituting at C_{17} led solely to cisoid **1.7.7**, while substituting in the C_{16} position led to a 3:5 ratio of desired transoidal **1.7.9** and undesired cisoidal **1.7.10**. More importantly in that last observation, was the fact that the undesired cisoidal **1.7.6** could be re-equilibrated into the same 3:5 thermodynamic mixture. With the combined intelligence of these experiments, it was hypothesized that the C_{17} substituent played the major role in controlling the stereochemistry of the resulting bisspiroketal.[15d]



Scheme 1.7: Carter's Observations on Substituent Effects

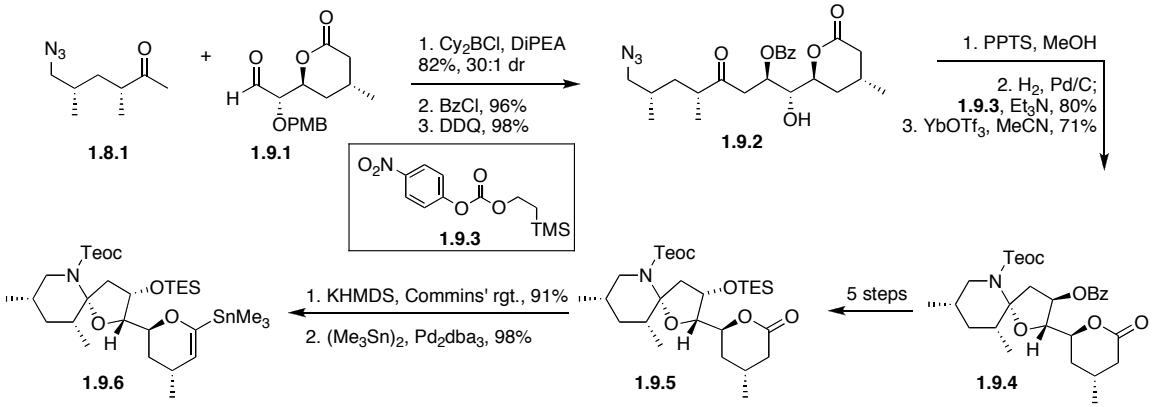
1.4.2: Studies Toward the FGHI Ring System

Forsyth's synthesis of the FGHI ring system of azaspiracid was build around a double heteroatom Michael addition to form the bicyclic ketal (Scheme 1.8).[18a] The aldol condensation of the ketone **1.8.1** and the aldehyde **1.8.2** proceeded in 78% yield. TBAF desilylation and acid-mediated ketal formation led to the substituted furan **1.8.3**. Mitsunobu inversion of the C_{34} of **1.8.3** followed by Staudinger reduction of the azide, with spontaneous Boc carbamate formation set up the ytterbium triflate-mediated spiroaminal formation of **1.8.4**. After an additional 6 steps, treatment of eynone **1.8.5** with TBAF cleaved the two TBS groups and a facile cyclization occurred to afford FGHI ring system **1.8.5**.



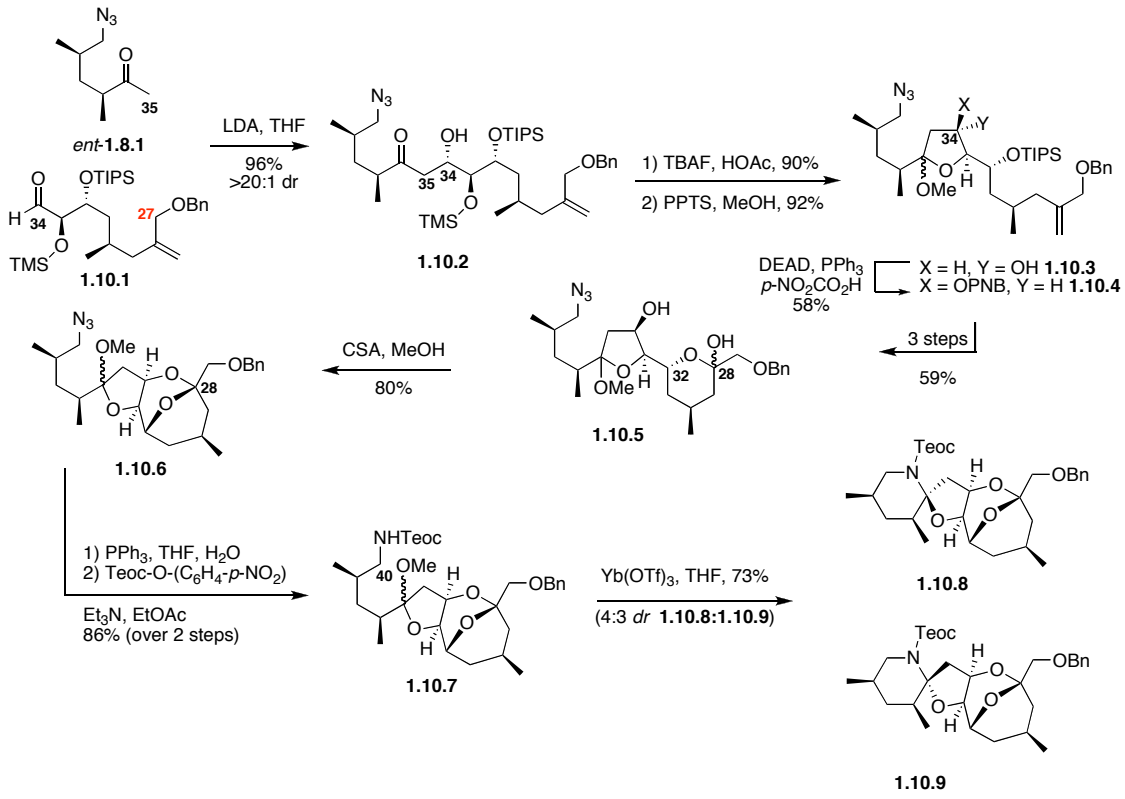
Scheme 1.8: Forsyth's Heteroatom Michael Approach to the FGHI ring system

Professor Nicolaou's synthesis of the FGHI ring system proceeded again with the aldol condensation of the ketone **1.8.1** and the aldehyde **1.9.1** (Scheme 1.9).[16b] After the aldol condensation, protection of the resulting alcohol as a benzoyl ester and removal of the paramethoxy benzyl ether afforded ketone **1.9.2**. The ketone was then ketalized under acidic conditions. Following Staudinger reduction of the azide and protection of the resulting amine, the stage was set for a ytterbium triflate-mediated formation of the spiroaminal **1.9.4**. Another five steps were necessary to manipulate protecting groups and invert the C_{34} alcohol to give lactone **1.9.5**. The lactone was then transformed into the vinyl stannane **1.9.6**, which was to be coupled to the northern half of azaspiracid prior to formation of the FG ring bicyclic ketal.



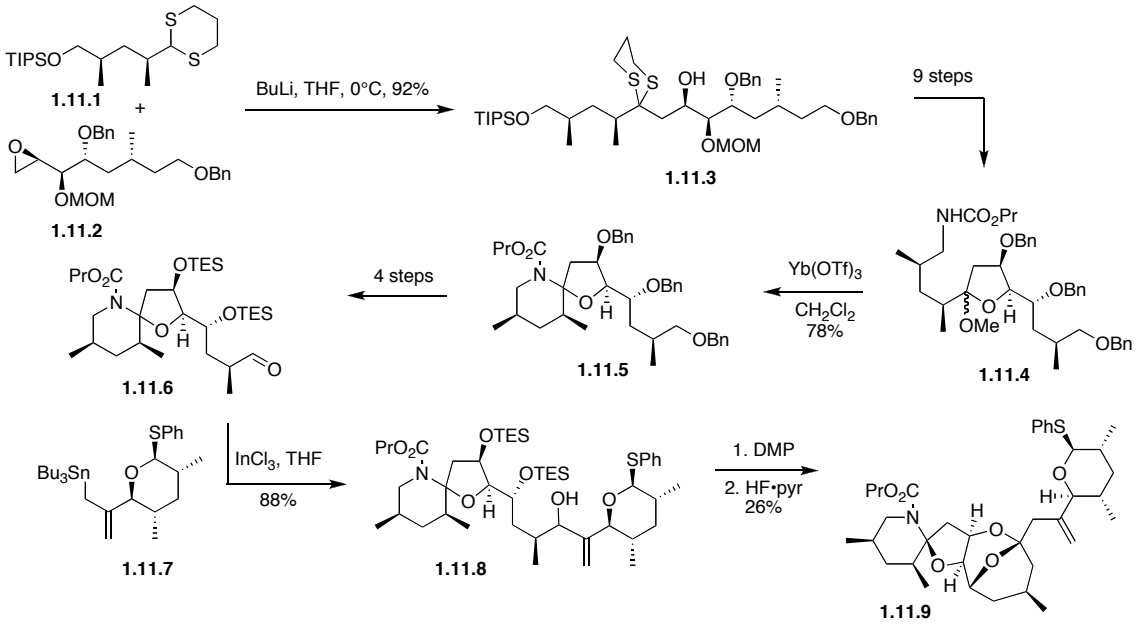
Scheme 1.9: Nicolaou's Approach to the FGHI Ring System

In 2006, the Carter group reported their synthesis of the FGHI ring system of azaspiracid (Scheme 1.10).[15g] Aldol condensation of the ketone *ent*-**1.8.1** and aldehyde **1.10.1** proceeded in 96% yield with greater then 20:1 dr. Desilylation and acid-catalyzed ketal formation led to furan **1.10.3**. Mitsunobu inversion of the C_{34} alcohol and three subsequent transformations provided hemiketal **1.10.5**. Treatment of **1.10.5** with camphorsulfonic acid afforded bicyclic ketal **1.10.6**. Statinger reduction the azide followed by Teoc protection afforded the amine **1.10.7** in 86% yield. Treatment of the amine with ytterbium triflate afforded the spiroaminals **1.10.8** and **1.10.9** in a 4:3 diasteromeric ratio. It should be noted that in all other studies only a single diastereomer for the spiroaminal formation has been report. A hypothesis for this phenomena and an approach to equilibrating this mixture are discussed in chapter three.



Scheme 1.10: Carter's approach to the FGHI Ring System

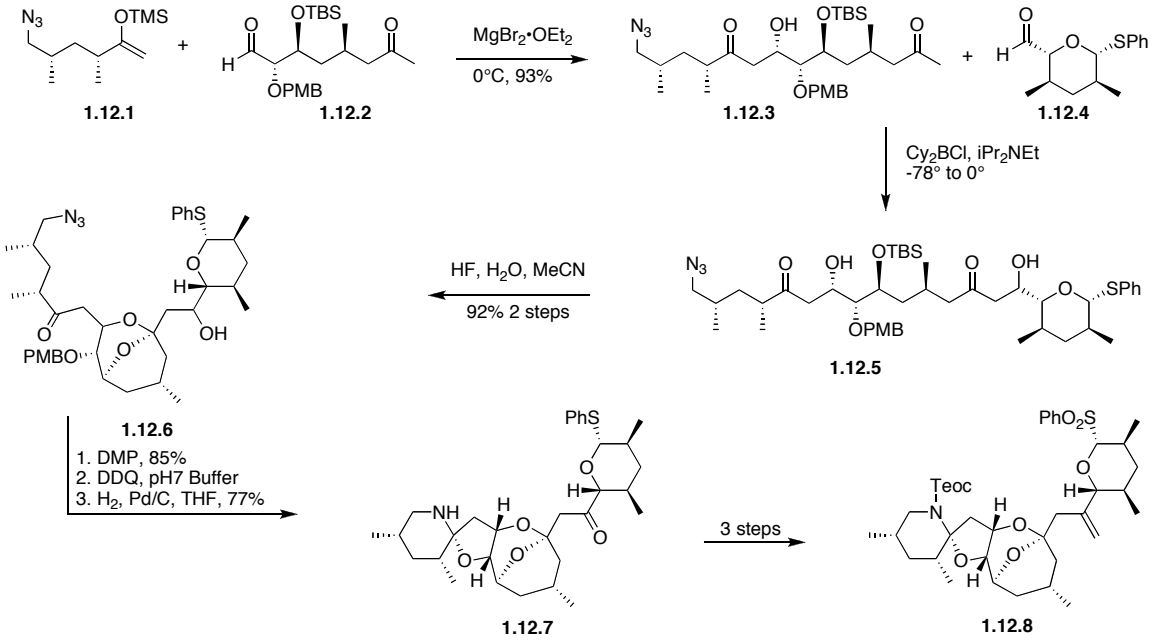
The Oikawa group utilized a different strategy for key carbon bond coupling approach (Scheme 1.11).[20a,b] Rather than an aldol-type coupling as reported by other groups, a dithiane coupling was employed (Scheme 1.11). The coupling of dithiane **1.11.1** and epoxide **1.11.2** proceeded in 92% yield affording alcohol **1.11.3** with the correct stereochemistry at C_{34} - avoiding the need for net inversion seen in other syntheses. An additional nine steps were needed to acquire furan **1.11.4**. Treatment of the amine with ytterbium triflate afforded the spiroaminal **1.11.5**. After four more steps, aldehyde **1.11.6** was primed for an indium chloride-mediated coupling with stannane **1.11.7**. The coupling of **1.11.6** and **1.11.7** afforded alcohol **1.11.8** in remarkably good 88% yield after extensive experimentation. Further oxidation of the alcohol **1.11.8** set the stage for an HF•pyr mediated desilylation with *in situ* formation of the FG bicyclic ketal **1.11.9** in a disappointing 26% yield.



Scheme 1.11: Oikawa's Synthesis of the EFGHI

In 2007, the Evans group reported a rapid assembly of the EFGHI ring systems of azaspiracid predicated on a series of aldol reactions (Scheme 1.12).[17] The magnesium bromide-mediated Mukayama aldol of enol ether **1.12.1** and the aldehyde **1.12.2** afford the methyl ketone

1.12.3 in 93% yield. A boron-mediated aldol of methyl ketone **1.12.3** and aldehyde **1.12.4** provided all the carbons requisite for the EFGHI ring structure. A desilylation with *in situ* ketal formation mediated by hydrofluoric acid transformed ketone **1.12.5** into bicyclic ketal **1.12.6**. Oxidation of the C_{27} alcohol followed by DDQ-mediated paramethoxybenyzl ether cleavage set up the formation of spiroaminal **1.12.7**. Hydrogenolysis of the azide led to the formation of the HI spiroaminal in high diastereoselectivity. In an additional three steps, sulfone **1.12.8** was prepared which was ready for coupling with a northern portion of azaspiracid.

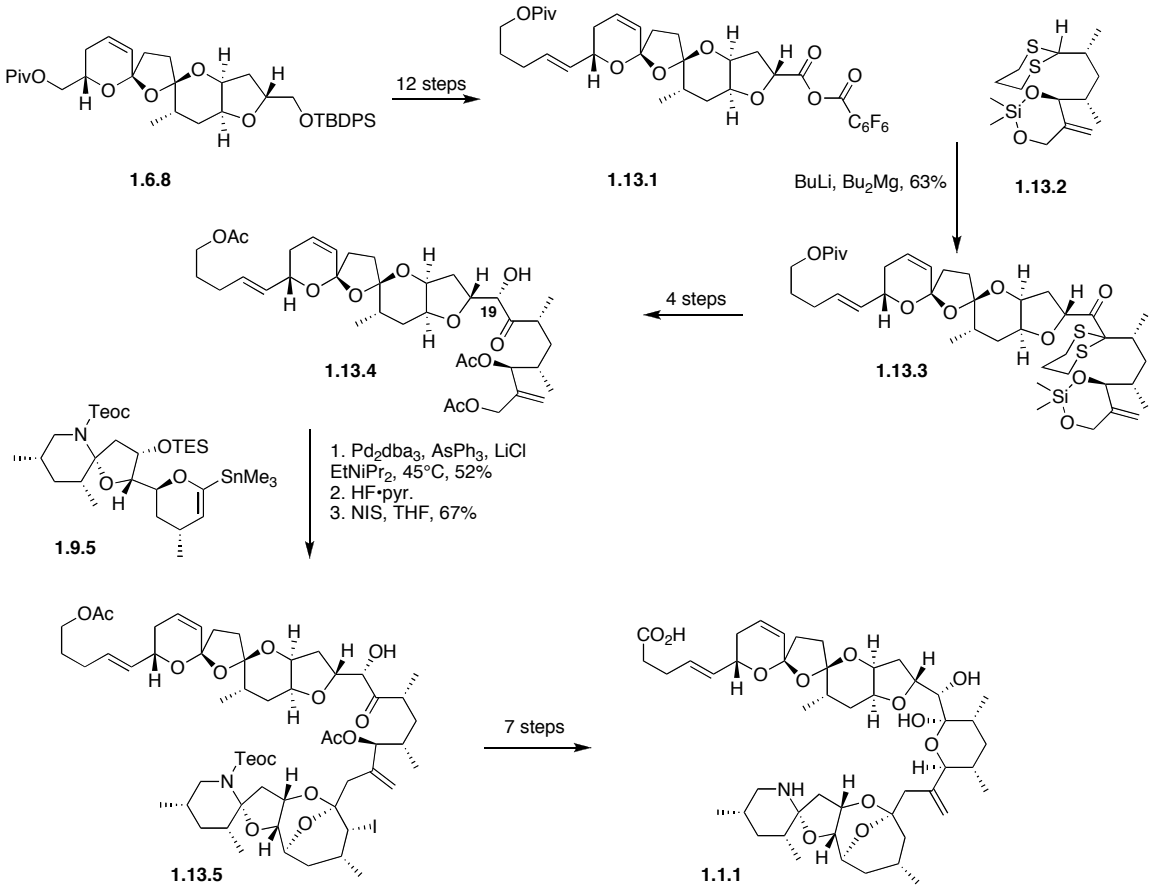


Scheme 1.12: Evans Synthesis of the EFGHI Ring System

1.4.3: Nicolaou's Synthesis of Proposed Structure 1.1.1 and Structural Revision

In 2003, the Nicolaou group disclosed a synthesis of the proposed structure of azaspiracid-1 (**1.1.1**) (Scheme 1.13).[16c,d] Bisspiroketal **1.6.8** was elaborated to mixed anhydride **1.13.1** in twelve steps. Coupling of dithiane **1.13.2** and mixed anhydride **1.13.1** provided ketone **1.13.3** in 63% yield. In an additional 4 steps, the C_{19} stereocenter was set, the C_{20} dithiane was cleaved and the protecting groups were adjusted affording allylic acetate **1.13.4**. Allylic acetate **1.13.4** was then coupled with vinyl stannane **1.9.5** in a Stille coupling. After subsequent

desilylation and iodoetherifcation, the ABCD and FGHI ring systems were fused to provide iodide **1.13.5**. An additional seven steps provided the proposed structure of azaspiracid (**1.1.1**).



1.6.8 1.13.1 1.13.2 1.13.3 1.13.4 1.9.5 1.13.5 1.1.1

Scheme 1.13: Nicolaou's Synthesis of Proposed Structure **1.1.1**

Much to the Nicolaou group's dismay, NMR analysis of **1.1.1** proved an error had been made in structural assignment. Independent analysis by the Carter[4] and Nicolaou[3] groups led to revised structure of **1.1.2** (Figure 1.14). In total, three major changes to the structure of azaspiracid were discovered. First, the A ring olefin was moved from C_8-C_9 to C_7-C_8. Secondly, the absolute configuration of the FGHI ring system was inverted. Finally, the stereochemistry of the BCD ring system was mis-assigned at C_{14}, C_{16}, C_{17}, C_{19} and C_{20}. The revision of the C and D ring stereochemistries was of most important consequence. The configuration of the bisspiroketal was greatly effected by these changes, the initially proposed structure (**1.4.1**) was

singly anomeric, while the revised structure (**1.14.1**) is doubly anomeric. The bisspiroketal, which was not thermodynamic in the initial structure, was thermodynamic after structural revisions.

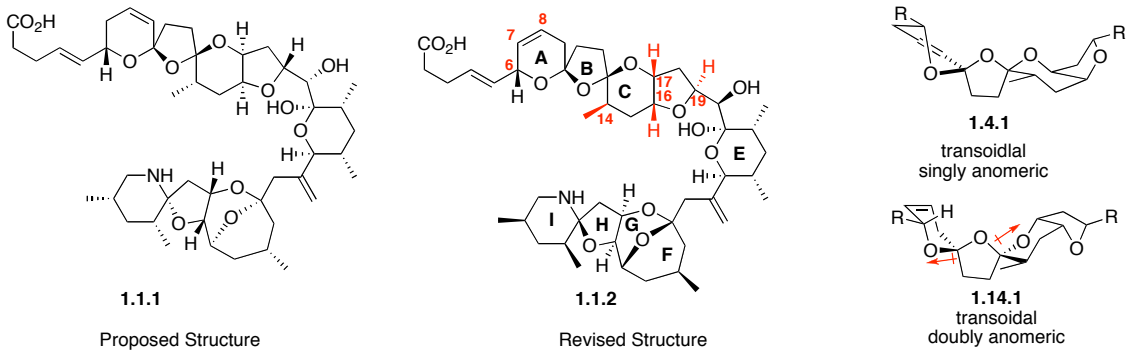
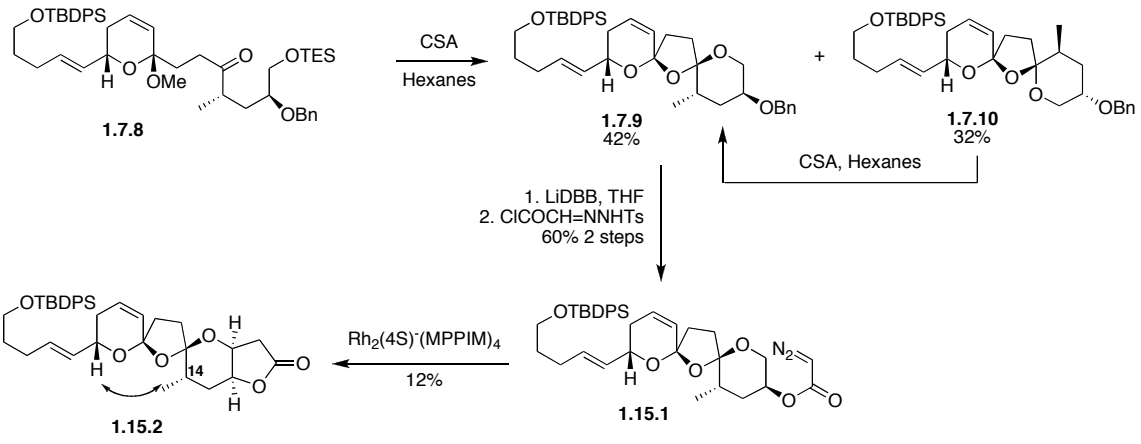


Figure 1.14: Structural Revisions

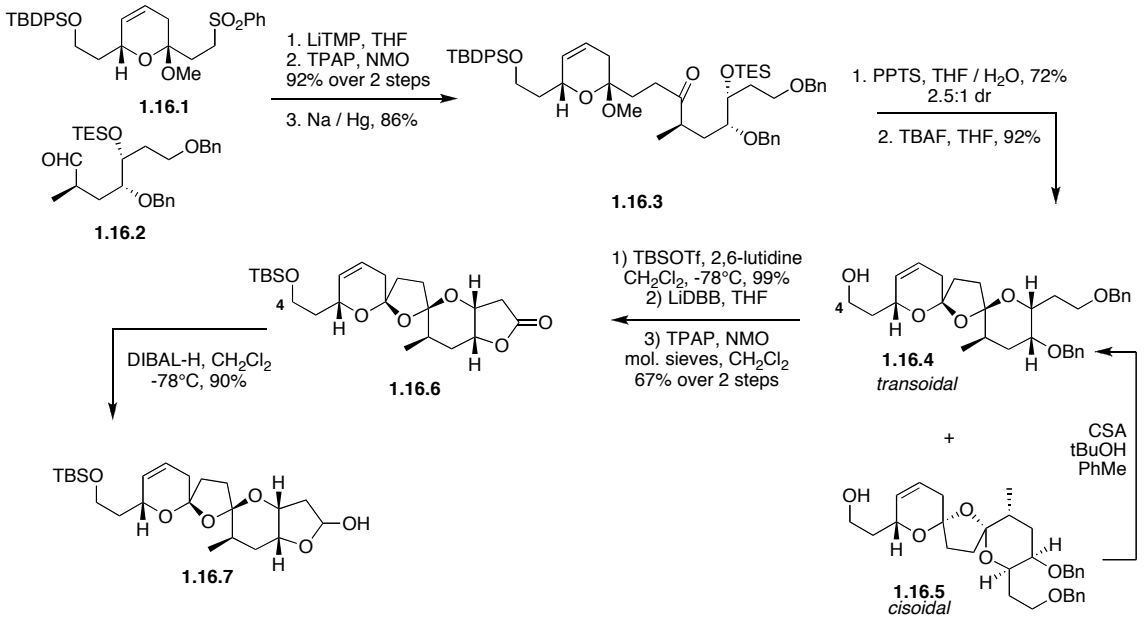
Simultaneous to Nicolaou's synthesis of the proposed structure of azaspiracid, the Carter group came upon the same structural revisions to azaspiracid (Scheme 1.15).[4] Utilizing the previously discussed bisspiroketal **1.7.9**, debenzylation and acylation gave diazoacetate **1.15.1**, which set the stage for formation of the D ring (Scheme 1.15). Treatment of diazoacetate with a chiral rhodium catalyst affected a stereoselective C-H insertion providing lactone **1.15.2**. Upon 2D-NMR investigation, a key NOE (arrowed) was not observed; interestingly inverting the C_{14} methyl provided a compound with the NOE.



Scheme 1.15: Carter's Synthesis of the ABCD ring system

1.4.4: Synthetic Efforts Toward the Revised ABCD Bisspiroketal

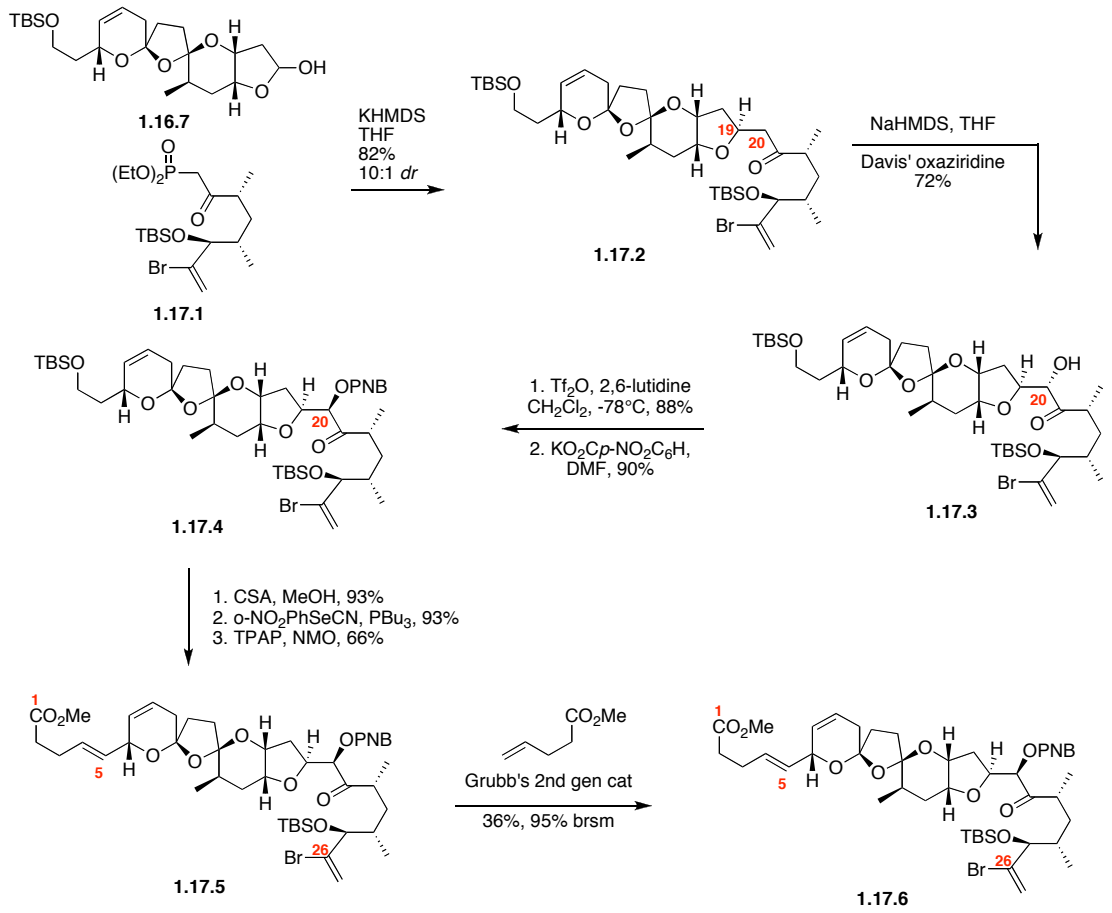
The Carter group reported a synthesis of the ABCD bisspiroketal ring system in 2006.[15f] The Julia coupling of sulfone **1.16.1** and aldehyde **1.16.2** followed by oxidation afforded a ketosulfone, which was then desulfurized into ketone **1.16.3**. Acid-catalyzed formation of the bisspiroketal and subsequent desilylation provided a separable 2.5:1 ratio of the desired transoidal **1.16.4** and the undesired cisoidal **1.16.5**. Submitting the undesired cisoidal **1.16.5** to stronger acidic condition completely equilibrated the bisspiroketal to the desired transoidal **1.16.4**. Silylation of the C_4 alcohol, cleavage of the two benzyl ethers and oxidation afforded the lactone **1.16.6**. Reduction of the lactone **1.16.6** with DIBAL-H afforded the lactol **1.16.7**, which was requisite for future elaboration.



Scheme 1.16: Carter's Approach to the ABCD Bisspiroketal

With the ABCD bisspiroketal in hand, the Carter group proceeded to elaborate the ketal, testing their end game approach (Scheme 1.17). Lactol **1.16.7** and the ketophosphonate **1.17.1** were joined in a Horner-Wadsworth-Emmons olefination with a tandem heteroatom Michael

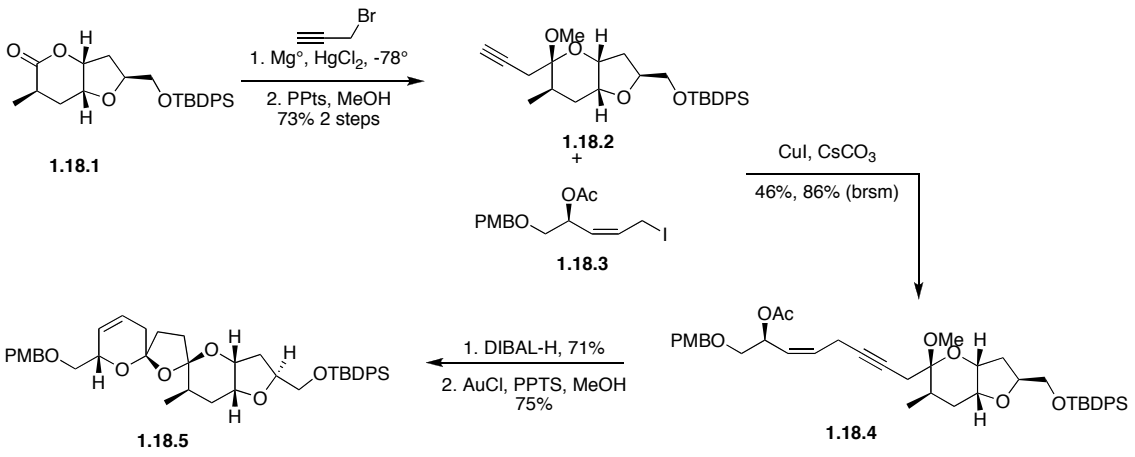
addition to provide ketone **1.17.2**. Davis oxidation of C_{20} proceeded in 72% yield with high, but undesired diastereoselectivity to provide alcohol **1.17.3**. The C_{20} stereochemistry was inverted in a two-step process. Through a triflate formation followed by inversion *via* a *SN*^{2}-type displacement by the potassium salt of para nitro benzoic acid furnishing the benzoate **1.17.4**. After an acid-catalyzed hydrolysis of the C_4 TBS ether, the C_4-C_5 olefin was installed via a two-step selenation / oxidation / elimination technique in a 61% yield over two steps. The sidechain was appended via olefin metathesis thus obtaining the C_1-C_{26} fragment **1.17.5**.



Scheme 1.17: Carter's Elaboration of lactol **1.16.6**

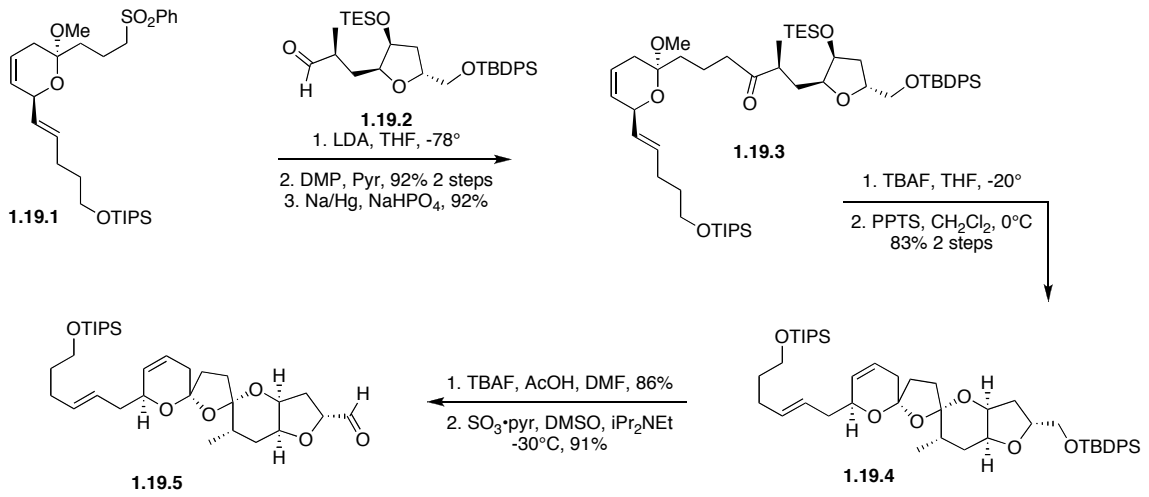
In 2006, Forsyth reported a gold-catalyzed cycloisomerization approach to the ABCD bisspiroketal moiety (Scheme 1.18).[18h] A bimetallic-mediated addition of propargyl bromide into

lactone **1.18.1** followed by methyl ketal formation afforded acetylene **1.18.2** in 73% yield. A Castro-Stephens coupling of iodide **1.18.3** and acetylene **1.18.2** netted the C_5-C_{20} fragment **1.18.4**. After DIBAL-H removal of the C_6 acetate, treatment with gold chloride and PPTS in methanol induced a cycloisomerization to yield the bisspiroketal **1.18.5**.



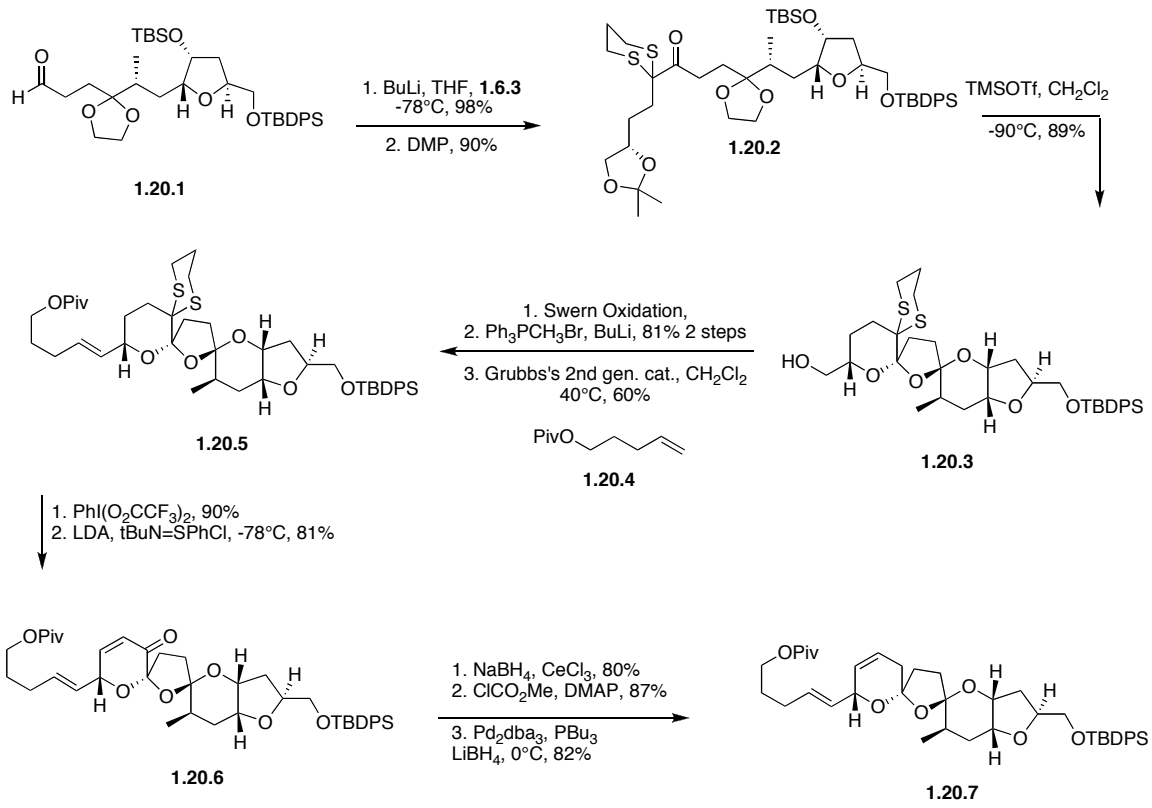
Scheme 1.18: Forsyth's Gold Mediated Cycloisomerization Approach

In 2006, Evans also reported a synthesis of the ABCD bisspiroketal moiety as part of a communication on his synthesis of the non-natural enantiomer of azaspiracid.[17] A Jullia coupling of sulfone **1.19.1** and aldehyde **1.19.3** followed by oxidation to the ketosulfone *via* Dess-Martin oxidation and desulfurization afforded ketone **1.19.3** in good yield. TBAF-mediated desilylation of TES ether **1.19.3** set the stage for a PPTS-mediated formation of the bisspiroketal **1.19.5**. After removal of the primary TBDPS ether with buffered TBAF, a Parikh-Doering oxidation was used to provide aldehyde **1.19.5**, which was required for the coupling with the southern portion of azaspiracid.



Scheme 1.19: Evans' Synthesis of ABCD Bisspiroketal

The Nicolaou group reported a synthesis of the ABCD ring system as part of his structural revision and the first total synthesis of azaspiracid in 2004. As with his previous work, a coupling of dithiane **1.6.3** and aldehyde **1.20.1** formed key ketone **1.20.2** after Dess-Martin oxidation. Treatment of ketone **1.20.2** with trimethylsilane triflate afforded desired bisspiroketal **1.20.3** in 89% yield. The side chain was then appended in three steps to gain alkene **1.20.5**. Next, the dithiane was cleaved and the resulting ketone was oxidized to the enone **1.20.6**. After Luche reduction of the enone, the resulting alcohol was activated as the methyl carbonate setting up a Tsuji-type reduction. The methyl formate was treated with palladium and lithium borohydride to deoxygenate the A ring affording bisspiroketal **1.20.7**.



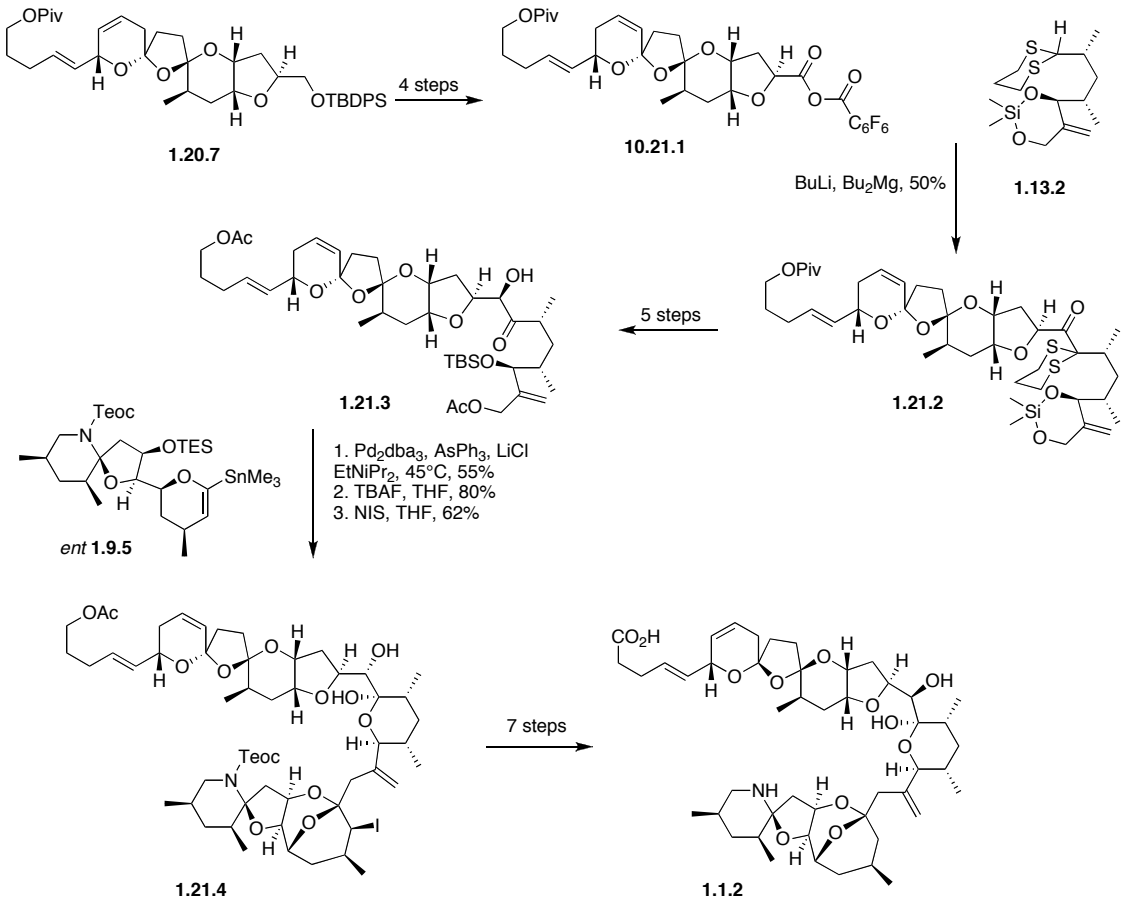
Scheme 1.20: Nicolaou's Synthesis of the ABCD Ring System

1.4.5 Endgames of Completed Synthesis of Azaspiracid 1

To date, two total syntheses of azaspiracid have been completed. First, the Nicolaou group divulged a synthesis in 2004,[3] confirming the structural revisions that had been proposed. Secondly, the Evans group reported a synthesis of the non-natural antipode of azaspiracid in 2006.[17] To date, the Carter[15f,g] and Forsyth[18g,h] groups have reported studies toward both halves of the molecule, while a host of others have worked on one of the major fragments.[20]

The endgame of Nicolaou's synthesis starts with the elaboration of ABCD ring structure **1.20.7**.[3] Four steps provide mixed anhydride **1.21.1**, which is then coupled with dithiane **1.13.2** to give major fragment **1.21.1**. An additional 5 steps installed the C_{20} stereocenter and set up for major fragment coupling. Allylic acetate **1.21.3** and vinyl stannane *ent*-**1.9.5** were coupled in a Stille coupling in 55% yield. After TBAF mediated desilylation, the stage was set for an

iodoetherification to form the bicyclic ketal **1.21.4**. An additional 7 steps furnished azaspiracid **1.1.2**, establishing the structure and absolute stereochemistry.

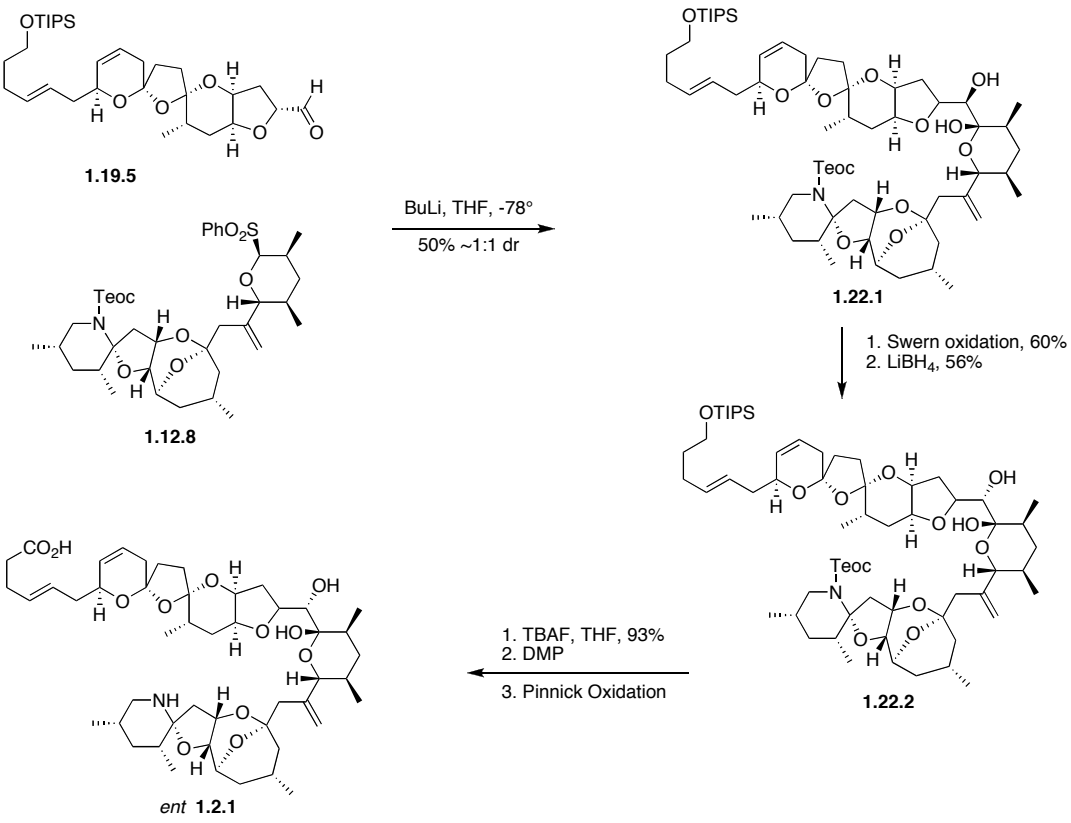


Scheme 1.21: Nicolaou's Synthesis of azaspiracid 1 (**1.1.2**)

Subsequent investigation by the Nicolaou group has afforded a second, optimized synthesis.[16h] This second synthesis furnished mixed anhydride **1.21.11** in five fewer steps and the natural product in eleven fewer steps. In addition to the improved synthesis of azaspiracid-1, two antipodes azaspiracid-2 and azaspiracid-3 were made which established their identity as well.

The endgame for the Evans group started with a Julia coupling of aldehyde **1.19.5** and sulfone **1.12.8**.[17] The coupling occurred in a 50% yield in a nearly equimolar mixture of desired C_{20} alcohol **1.22.2** and its C_{20} epimer **1.22.1**. Oxidation of the undesired epimer **1.22.1** under

Swern conditions followed by a lithium borohydride reduction provided desired alcohol **1.22.2** in 34% yield. The net yield of the transformation of aldehyde **1.19.5** and sulfone **1.12.8** into desired alcohol **1.22.2** was a 34%. Treatment of alcohol **1.22.2** with TBAF cleaved the Teoc carbamate and the TIPS ether. Oxidation of the resulting alcohol to the acid provided *ent*-azaspiracid **1.1.2**.



Scheme 1.22: Evans' Synthesis of Azaspiracid 1 (**1.1.2**)

1.5: Conclusion

Over the last thirteen years, azaspiracid has been a hotbed in science with over two hundred articles and presentations since the initial divulging of its structure. A dearth of interesting chemistry has been discovered to overcome the many challenges embedded in both the initially reported structure **1.1.1** and the revised structure **1.2.1**. To date, the Nicolaou and Evans groups have completed total synthesis of the target, while a host of other groups have contributed an enormous amount of work to the field. In addition to the work discussed in the

introduction, there are two additional groups who have contributed to the field. The Nishiyama group engaged in efforts toward the originally proposed structure in which a thiophene ring was utilized to perturb the formation of the bisspiroketal.[19] The net effect was an efficient formation of the ABCD ring system. Additionally the Mootoo group has divulged a route which involved a one pot silver (I) triflate-mediated deiodination followed by a PPTS-mediated bisspiroketalization was preformed.[20d]

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STUDIES TOWARD THE TOTAL SYNTHESIS OF AZASPIRACID 1

CHAPTER 2:

Studies on the Northern Half of Azaspiracid:

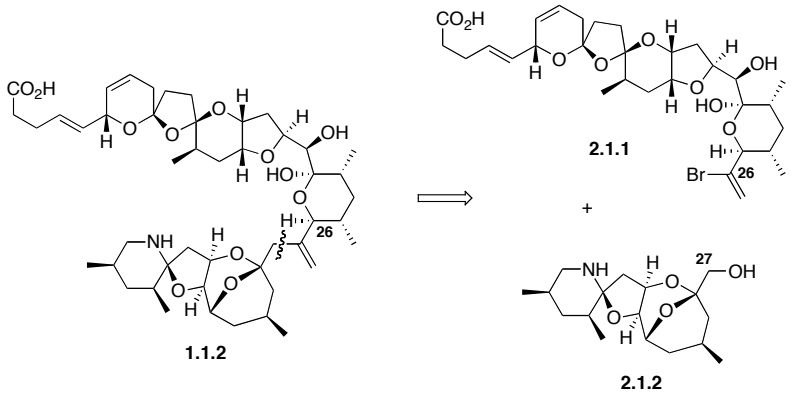
an Improved Synthesis of the C_{13}-C_{19} Aldehyde 1.16.2

and

an Expanded Look at the Formation of the Bisspiroketal Moiety

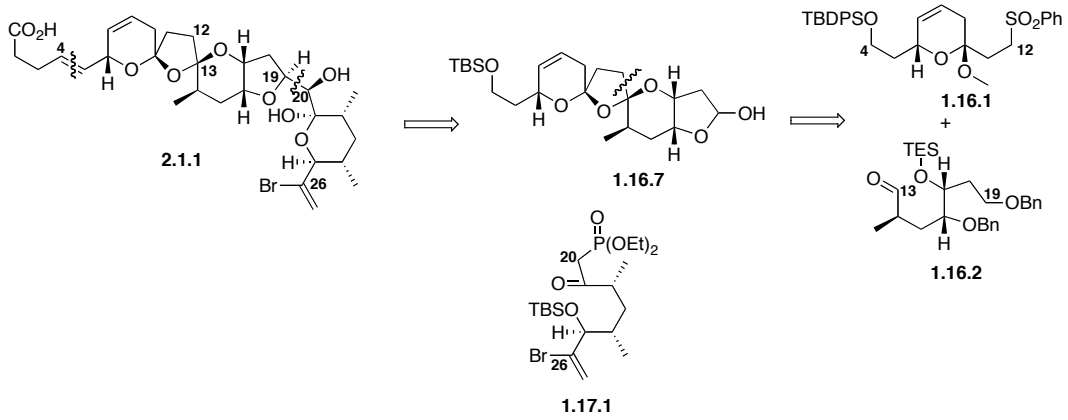
2.1: Retrosynthetic Analysis of Azaspiracid (1.1.2)

In our retrosynthetic analysis (Scheme 2.1), azaspiracid can be dissected into northern and southern portions of nearly equal size and complexity. The northern portion's ABCDE ring system **2.1.1** contains a densely functionalized array with twelve stereogenic centers and a challenging bisspiroketal functionality. The southern portion, **2.1.2**, meanwhile has eight stereocenters with a spiroaminal, a heavily oxidized tetrahydrofuran moiety, and an α-oxy bicyclic ketal, each of which are sensitive functional groups.



Scheme 2.1: Retrosynthesis of Azaspiracid

Proceeding with our retrosynthesis (Scheme 2.2), the northern portion of azaspiracid could be broken into lactol fragment **2.1.1** and the C_{20} to C_{26} linker fragment **1.17.1**. Phosphonate **1.17.1** would be used to bridge lactol **2.1.1** and alcohol **2.1.2**. Further analysis showed bisspiroketal **1.16.7** should be formed from a Julia[1] coupling of sulfone **1.16.1** and aldehyde **1.16.2**.

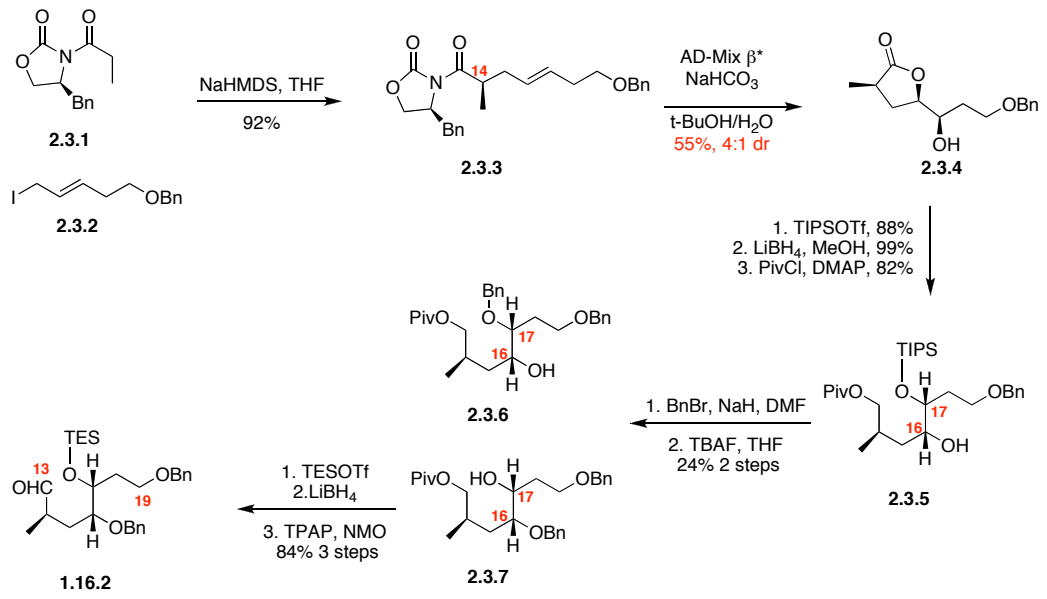


Scheme 2.2: Retrosynthetic analysis of Bisspiroketal **2.1.1**

2.2: Synthesis of Aldehyde 1.16.2

2.2.1: Initial Approach

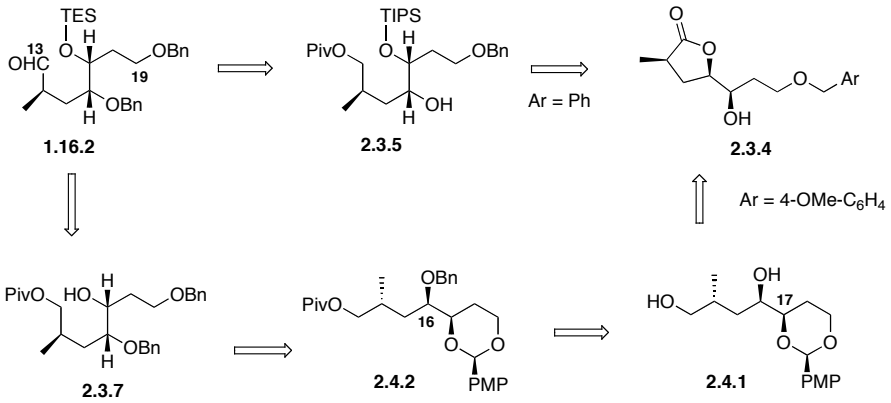
A first generation approach to the synthesis of aldehyde **1.16.2** was disclosed prior to my arrival in the Carter group[2] (Scheme 2.3). This key fragment contained much of the stereochemical complexity of the northern half of azaspiracid. The initial route relied on an Evans alkylation of allyl iodide **2.3.2**, followed by a Sharpless dihydroxylation of the alkylation substrate to quickly install all the requisite stereocenters and afforded lactone **2.3.4**. From lactone **2.3.4**, all that was necessary was selective protection of free hydroxyls. After silylation of the C_{17} alcohol, reduction of the lactone and acylation of the primary C_{13} alcohol, a benzyl ether was needed at the C_{16} hydroxyl **2.3.5**. Unfortunately, upon forming an anion at the C_{16} alcohol, a facile 1,2-silyl migration occurred regardless of the choice of silyl C_{17} protecting group. The optimized benzylation sequence nets a disappointing 24% yield of the desired C_{16} benzyl ether **2.3.7** over two steps. The remainder of the mass was the undesired C_{16} alcohol **2.3.6**. Silylation, removal of pivalate and oxidation lead to key aldehyde **1.16.2** in 84% yield over three steps.



Scheme 2.3: First Generation Approach to Aldehyde **1.16.2**

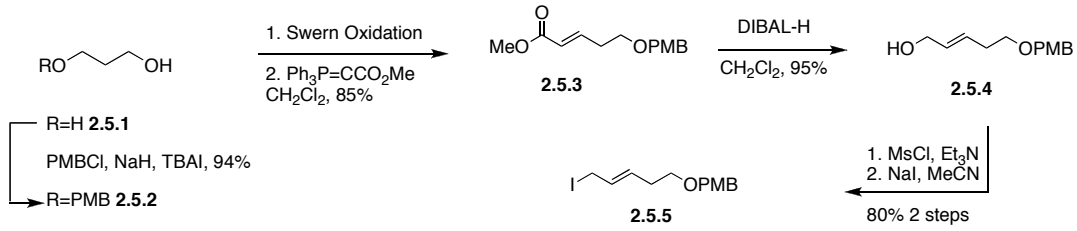
2.2.2: Improved Synthesis of Aldehyde 1.15.2

Our second-generation route to aldehyde **1.16.2** relied on a similar strategy, except that we planned to tie the C_{16} and C_{19} alcohols up in a ketal **2.4.1** (Scheme 2.4). While the alcohols were tied up as the ketal, manipulation the rest of the molecule would lead to efficient benzylation of the C_{16} and C_{19} alcohols sequentially. We will then liberate the ketal and silylate at the C_{16} position last to prevent any silyl migration.



Scheme 2.4: Revised Retrosynthetic Analysis of Aldehyde **1.16.2**

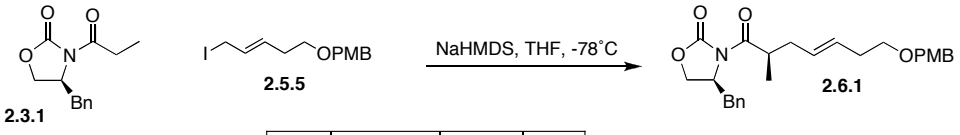
To proceed with this planned route, allylic iodide **2.5.5** was prepared (Scheme 2.4). 1,3-Propane diol was first protected to afford para-methoxybenzyl ether **2.5.2** (Scheme 2.5). Swern oxidation provided an unstable aldehyde, which was homologated *via* a Wittig olefination to afford ester **2.5.3**. After DIBAL-H reduction of the ester to allylic alcohol **2.5.4**, a two-step process afforded requisite allylic iodide **2.5.5**.



Scheme 2.5: Synthesis of Allylic Iodide **2.5.5**

It is important to note that both the mesylate and iodide are very unstable and prone to decomposition. The two-step protocol for formation must be followed in one day and the resulting iodide **2.5.5** utilized as soon as it is prepared. Efforts to store these compounds, even for a matter of hours, results in decomposition. As such the mesylation, Finklestein displacement and the subsequent Evans alkylation were always performed in one morning.

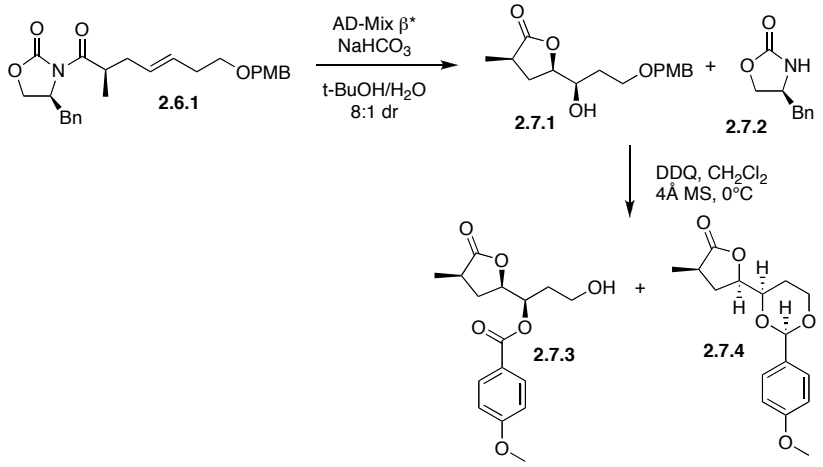
With allylic iodide **2.5.5** in hand, I proceeded to investigate the alkylation of Evans oxazolidinone **2.3.1** and iodide **2.5.5** (Scheme 2.6). Under conventional Evans conditions,[3] three equivalents of alkyl halide are reacted with an equivalent of the enolate of Evans oxazolidinone **2.3.1** to afford an alkylation product in good yield and diastereoselectivity. In order to increase the efficiency of this process, we needed to perform the reaction with as few equivalents of the iodide **2.5.5** as possible. Table 2.6 details the significant improvement made in this process. Optimized conditions are shown in Entry 5 employing 1.5 equivalents of iodide **2.5.5** with an effective molarity of 0.36 M. Unfortunately, attempts to lower the equivalents of iodide **2.5.5** further led to incomplete reaction and poor yields (Entry 6).



Entry	iodide (eq.)	Molarity	Yield
1	2.5	0.17	52%
2	2	0.27	78%
3	2	0.32	80%
4	1.8	0.35	94%
5	1.5	0.36	87%
6	1.2	0.41	65%

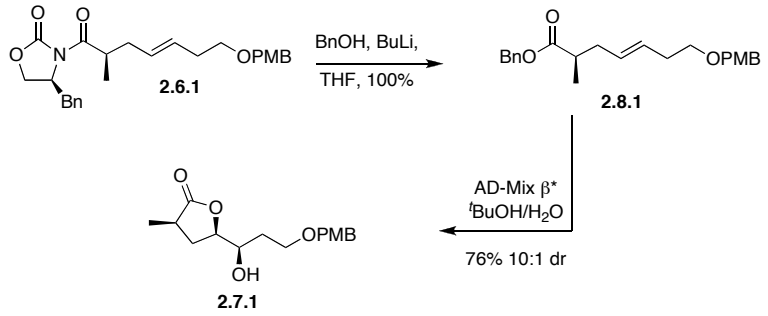
Table 2.6: Evans Alkylation of Iodide **2.5.5**

With the alkylation product in hand, our next step was to install the two hydroxyl stereocenters (Scheme 2.7). Dihydroxylation of the resulting alkylation product **2.6.1**, under modified Sharpless conditions,[4] yielded the desired lactone **2.7.1** as an inseparable 8:1 mix of diastereomers and cleaved oxazolidinone **2.7.2**. This cleaved oxazolidinone made it impossible to isolate lactone **2.7.1**. Attempts at DDQ-mediated p-methoxyphenyl ketal formation on the mixture led to an undesirable mix of the ketal **2.7.4** and an over-oxidized p-methoxybenzoate compound **2.7.3**.



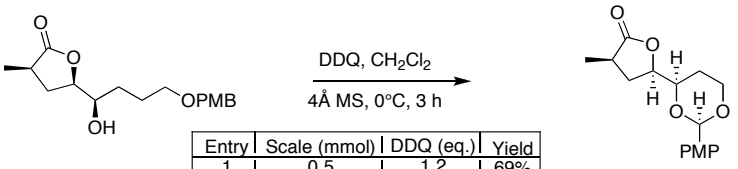
Scheme 2.7: Initial Approach to PMP Ketal

Our laboratory had previously shown that displacement of an oxazolidinone with an benzyl alkoxide can help to improve the dr in Sharpless dihydroxylation due to π stacking interaction between the chiral ligand and the benzyl ester.[5] In an effort to both improve the diastereomeric ratio of products and aid in isolation of lactone **2.7.1**, we investigated the possibility of displacing the oxazolidinone with benzyl alkoxide (Scheme 2.8). After displacement of the chiral auxiliary to form the benzyl ester **2.8.1**, the alkene was dihydroxylated. Gratifyingly, the dihydroxylation proceeded smoothly to give lactone **2.7.1** (76% yield, 10:1 dr), which was easily separable from the resultant benzyl alcohol.



Scheme 2.8: Improved Preparation of Lactone **2.7.1**

With lactone **2.7.1** in hand, the DDQ-mediated ketal formation next drew our attention (Table 2.9).[6] Initial results seemed favorable utilizing 1.2 equivalents of DDQ, with yields in the high 80% range for the formation of ketal **2.7.4** on four millimole scale (Entry 2). Upon moving to larger scale, the yields dropped dramatically (Entries 3,4). Lowering to 1.05 equivalents, led only to slightly improved yields (Entries 5-6). Switching to a portion-wise (pw) addition approach allowed the reaction to proceeded smoothly, affording acetal **2.7.4** consistently in high yield as a single diastereomer after triteration (Entry 7).



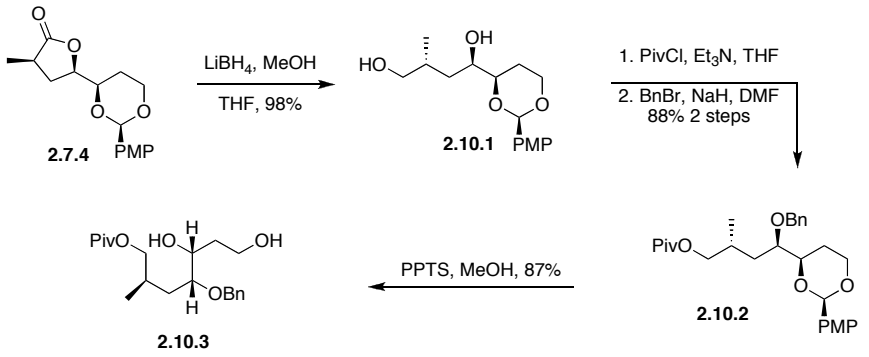
2.7.1

2.7.4

Entry	Scale (mmol)	DDQ (eq.)	Yield
1	0.5	1.2	69%
2	3.9	1.2	89%
3	16.8	1.2	38%
4	17.3	1.2	18%
5	.3	1.05	66%
6	4.3	1.05	65%
7	9.7	1.05(pw)	95%

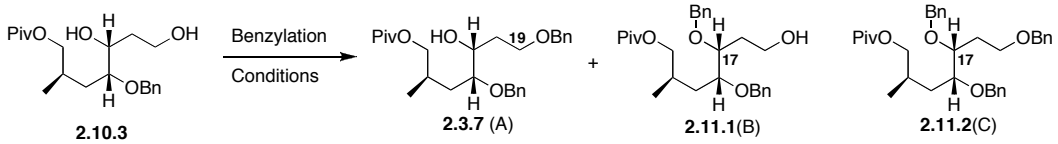
Table 2.9: DDQ Mediated Ketal Formation

With the DDQ-mediated ketal formation figured out, our next goal was the formation of diol **2.7.4** (Scheme 2.10). First, reduction of the lactone gave diol **2.10.1**. Pivalation of the primary alcohol followed by benzylation of the C_{17} alcohol led to fully protected C_{13}-C_{19} fragment **2.10.2**. Acidic hydrolysis of ketal **2.10.2** afforded the diol **2.10.3** in a good yield.



Scheme 2.10: Synthesis of Diol **2.9.3**

With diol **2.10.3** in hand, we went about investigating the benzylation of the C_{19} alcohol (Table 2.11) Initial base-mediated attempts at selective benzylation of the C_{19} hydroxyl of diol **2.10.3** provided a complex mixture of C_{17} benyzl ether **2.11.1** and C_{19} benzyl ether **2.3.7** under a host of conditions. Fortunately, switching to acid mediated conditions[7] (2,2,2-trichlorobenzyl acetimidate) led to selective protection of the primary alcohol. Initial experiments resulted in good yield (69%, 87% brsm) to give known benzyl ether **2.3.7**,[2] unfortunately attempts at forcing the reaction to completion resulted in doubly benzylated product **2.11.2**.



Entry	Bn Source	Conditions	Temp.	Yield
1	BnBr	NaH, DMF	-78°C	nr
2	BnBr	NaH, DMF	-11°C	decomposition
3	BnBr	NaH,TBAI, DMF	-78°C	37% A 20% B 10% rsm
4	BnBr	NaH, TBAI, 10:1 DMF/THF	-78°C	48% A 20% B 10% rsm
5	2x 1eq. **2.11.3**	10% TfOH, CH_2Cl_2	rt	69% A, 18% rsm
6	3x 1eq. **2.11.3**	10% TFOH, CH_2Cl_2	rt	74% A, 20% C

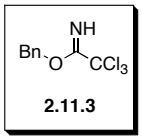


Table 2.11: Optimization of C_{19} Benzylation

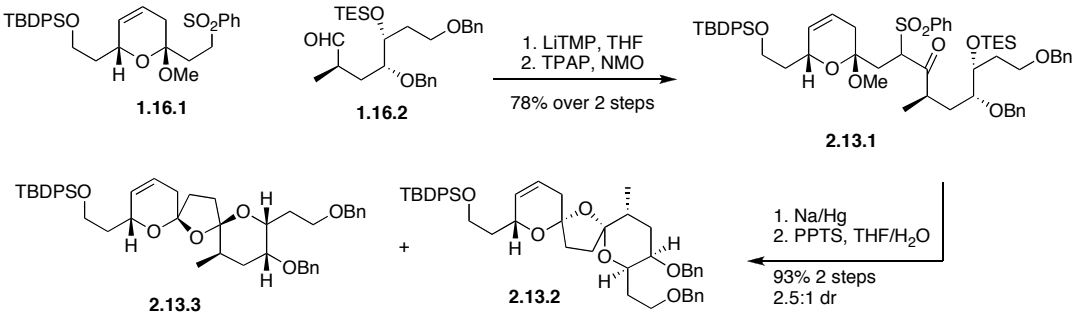
At this point, our second-generation synthesis had provided known alcohol **2.3.7**, which could be transformed to aldehyde **1.16.2** in three known steps (Scheme 2.12). Silylation of the secondary alcohol, reduction of the pivalic ester and oxidation of the resulting alcohol afforded known aldehyde **1.16.2** in 84% yield, as previously reported. This second generation route

dramatically improved the efficiency of our synthesis, with the overall yield increasing from 2% to 15%.

Scheme 2.12: Completion of the Synthesis of Aldehyde **1.16.2**

2.2.3: Elaboration of Aldehyde 1.16.2

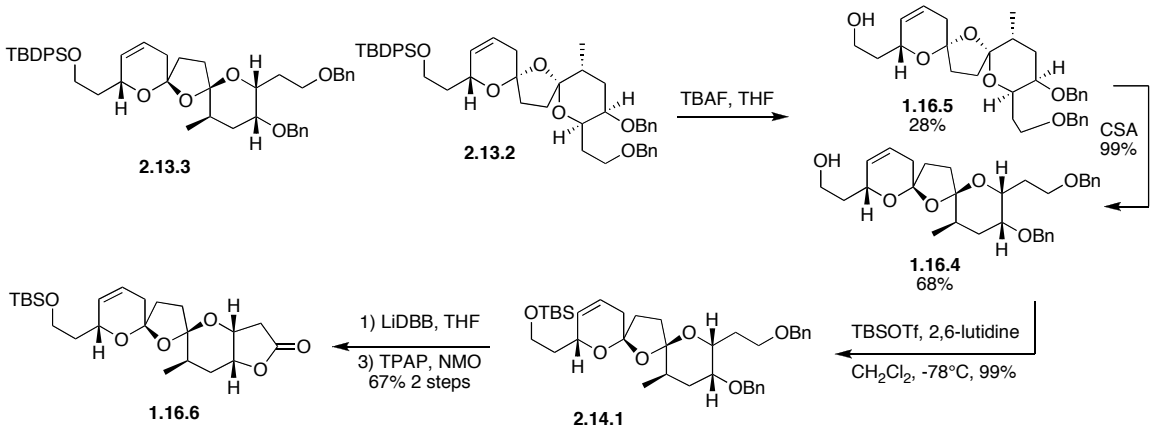
With the improved yields of aldehyde **1.16.2**, we proceeded to elaborate the aldehyde to the bisspiroketal moiety (Scheme 2.13).[8] The Julia coupling of aldehyde **1.16.2** and sulfone **1.16.1** followed by oxidation furnished keto sulfone **2.13.1** in 78% yield. Next, desulfurization using Na/Hg amalgam set the stage for the bisspiroketal formation. Treatment of the resulting ketone with PPTS afforded the bisspiroketal in a 2.5:1 mixture of transoidal ketal **2.13.3** and cisoidal ketal **2.13.2**.



Scheme 2.13: Julia coupling of aldehyde **1.16.2**

The 2.5:1 diasteromeric mixture was due to our softer kinetic PPTS mediated conditions. Treatment of the ketone resulting from ketosulfone **2.13.1** with harder thermodynamic conditions

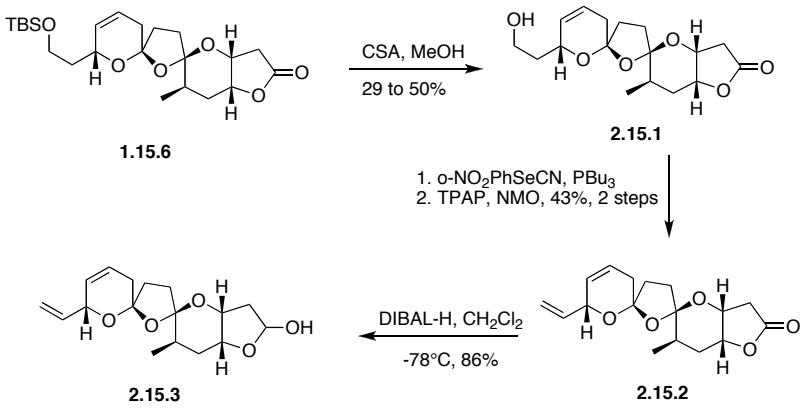
(camphorsufonic acid, toluene, t-butanol) led to solely desired transoidal bisspiroketal **2.13.3**, albeit in poor yield. While the separation of alcohol **2.13.2** and **2.13.3** was possible via silica gel chromatography, removal of the C_4 silyl group with TBAF prior to purification provided a more practical separation of alcohols **1.16.4** and **1.16.5** on scale (Scheme 2.13). Silica gel chromatography afforded 68% of transoid **1.16.4** and 28% of a mixture of the cisoidal and the transoidal compounds. The mixture was isomerized under thermodynamic conditions (camphorsulfonic acid) affording complete equilibration bisspiroketal **1.16.4**. Silylation of alcohol **1.16.4** afforded protected bisspiroketal **2.14.1**. An additional two-steps afforded lactone **1.16.6** in good yield. The improved yields for the synthesis of aldehyde **1.16.2** allowed us to synthesize over 250 mg of advanced intermediate **2.14.1**.



Scheme 2.14: Formation of Bisspiroketal **2.14.1**

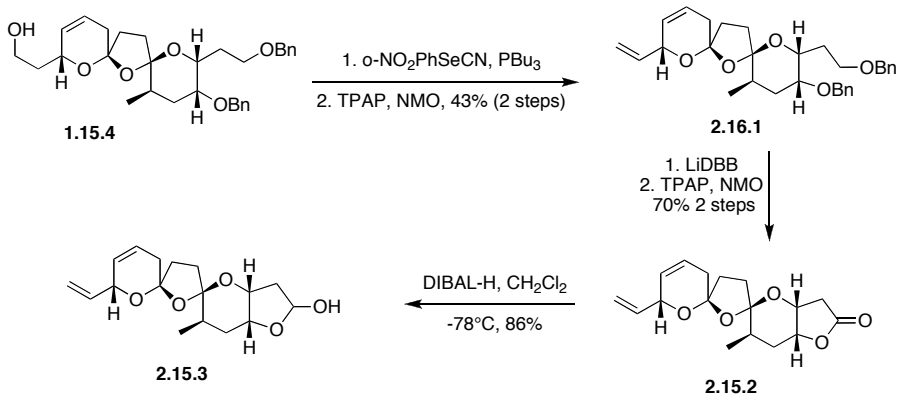
Further investigations into the installation of the C_4-C_5 olefin were then embarked upon (Scheme 2.15). Initial attempts were focused on the desilylation of lactone **1.15.6** to afford alcohol **2.15.1**. After attempts at utilizing TBAF and TASF for desilylation failed to produce free alcohol, the TBS ether was finally cleaved using camphorsulfonic acid in methanol. While the reaction netted the desired alcohol **2.15.1**, it was only available in 29 to 50% yield with the remainder of the mass appreared to be methanolysis of the lactone moiety based on crude proton

NMR. With alcohol **2.15.1** in hand a two-step selenation / oxidation / elimination afforded alkene **2.15.2**.[9] Treatment of lactone **2.15.2** with DIBAL-H proceeded to net lactol **2.15.3**.



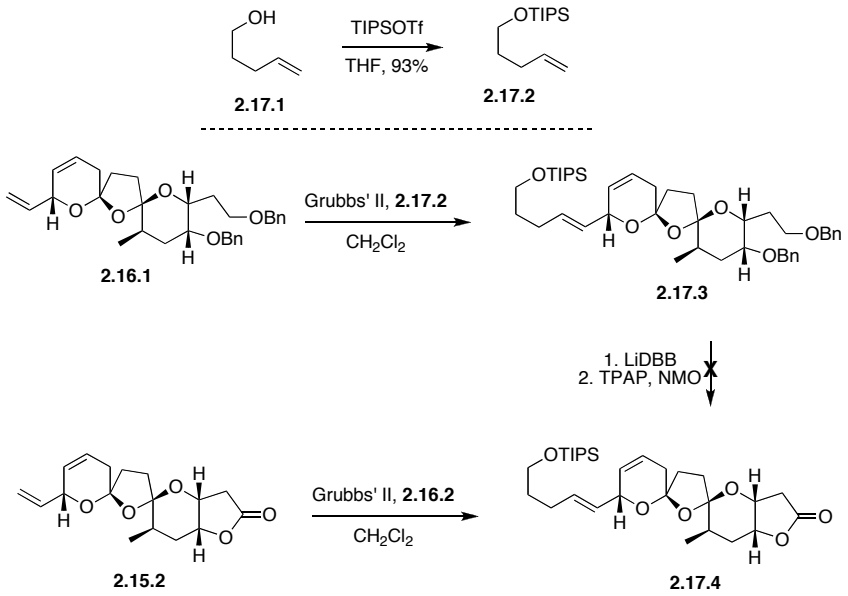
Scheme 2.15: Initial Attempts at Installation of the C_4-C_5 Olefin

Due to the poor yields in this initial route, an alternative route was desired (Scheme 2.16). Alcohol **1.15.4** was transformed into alkene **2.16.1** with the same two-step selenation protocol. Debenzylation and oxidation of alkene **2.16.1** afforded lactone **2.15.2** in 70% yield. With an effective route to lactone **2.14.2** in hand, the lactone was reduced to lactol **2.15.3** in 86% yield setting up coupling with the southern portion of azaspiracid.



Scheme 2.16: Improved Installation of the C_4-C_5 Olefin

In conjunction with the optimization of the formation lactone **2.15.2**, an initial investigation into the appending of sidechain was preformed (Scheme 2.17). The side chain was prepared from silylation of commercially available penteneol **2.17.1** to afforded TIPS ether **2.17.2**. Metathesis of alkene **2.16.1** with Grubbs' 2nd generation catalyst appeared to afford trans alkene **2.17.3** in relatively good dr (~5:1), but upon treatment with LiDBB limited material prepared decomposed. Alternatively, the metathesis of lactone **2.15.2** and alkene **2.17.2** was investigated. The crude H^1 NMR suggested a disubstituted alkene was formed, but the product co-eluted with the homo dimer of alkene **2.17.2** preventing isolation of the product.



Scheme 2.17: Attempts at Appending Sidechain

2.3: Conclusions

An improved synthesis of aldehyde **1.16.2** utilizing a PMP ketal provided a scalable route to the key fragment containing much of the stereochemistry of the ABCD ring system of azaspiracid. With a nearly tenfold improvement in yield of aldehyde **1.16.2** bisspiroketal **2.14.1** was readily available in large quantities. The establishment of a facile, scalable approach to the bisspiroketal **2.14.1** was described. An approach to installation of the C_4-C_5 alkene was

employed to afford lactone **2.15.2**. Initial studies toward the metathesis of C_1 terminus were investigated.

An improved route to the isolation of dihydroxylation product **2.7.1** from cleaved auxiliary **2.7.2** was illustrated via trans esterification to the benzyl ether with an added benefit of improved diasteromeric ratio of products. An effective equilibration of the kinetic cisoidal bisspiroketal **1.16.5** to transoidal bisspiroketal **1.16.4** was developed to effective a highly scalable synthesis of the ABC bisspiroketal.

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1 Julia, M.; Paris, J.-M. *Tetrahedon Lett.* **1973**, *14*, 4833-4836.

2 Zhou, X.-T.; Carter, R. G. *Chem. Commun*. **2004**, 2138-40.

3 Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc*. **1982**, *104*, 1737-39.

4 Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev*. **1994**, *94*, 2483-47. AD-mix β* involves 3 mol% $K_2OsO_4 \bullet 2H_2O$, 10 mol% DHQD Phal, 2.9 eq. $K_2Fe(CN)_6$ and 2.7 eq. K_2CO_3 with 1 eq. $MeSO_2NMe_2$ to enhance catalyst turnover and 5 eq. of $NaHCO_3$ to buffer the reaction.

5 Carter, R. G.; Graves, D. E.; Gronemeyer, M. A.; Tschumper, G. S. *Org. Lett*. **2002**, *4*, 2181-84.

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STUDIES TOWARD THE TOTAL SYNTHESIS OF AZASPIRACID 1

CHAPTER 3:

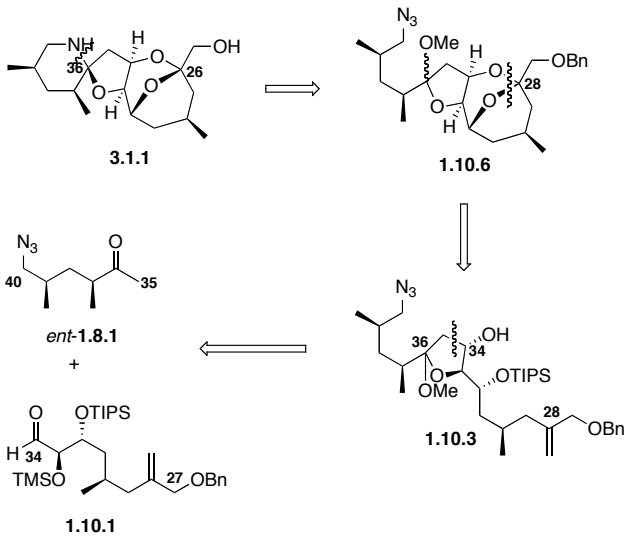
An Improved Synthesis of the

FGHI Ring System

3.1: Analysis of the FGHI Ring System

Upon completion of my work on the northern fragment of azaspiracid (Chapter 1), my focus switched to elaboration of the southern half. Our lab had published a synthesis of the FGHI ring system in 2006,[1] but much needed to be done to make this route scalable and efficient. First, an efficient, scaleable synthesis of azide **1.10.6** would be necessary to afford material for efforts toward elaboration of the southern fragment. Secondly, an improved spiroaminial formation would be sought to give the desired spiroaminal in good yield and diastereomeric purity.

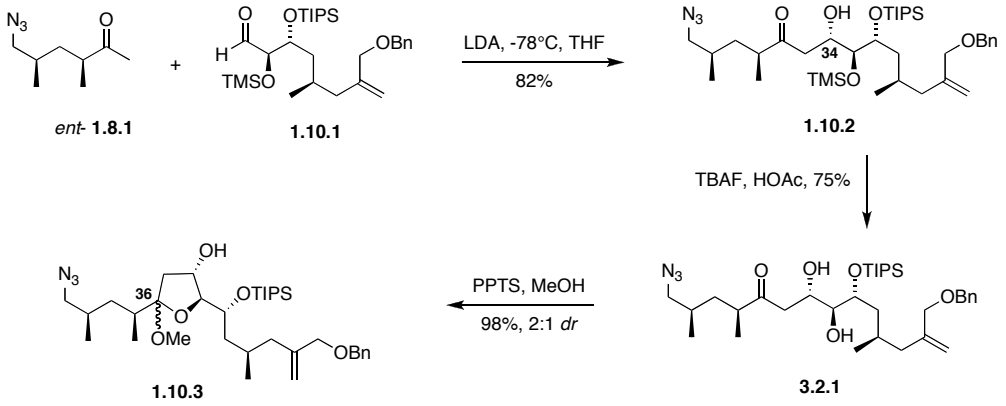
A review of this plan is shown in Scheme 3.1. Retrosynthetic analysis of spiroaminal **3.1.1** proceeded with the cleavage of the spiroaminal and bicyclic ketal bonds to afford oxygenated furan **1.10.3**. Presumably, the formation of the spiroaminal would come from reduction of the C_{40} azide, while the ketone of the bicyclic ketal was masked as an alkene. Further cleavage of the C_{34}-C_{35} bond affords ketone *ent*-**1.8.1** and aldehyde **1.10.1** as the key subunits of tetracycle **3.1.1**. These units would be merged in an aldol condensation.



Scheme 3.1: Retrosynthetic analysis of the Spiroaminal **3.1.1**

3.2: Formation of Azide 1.10.6

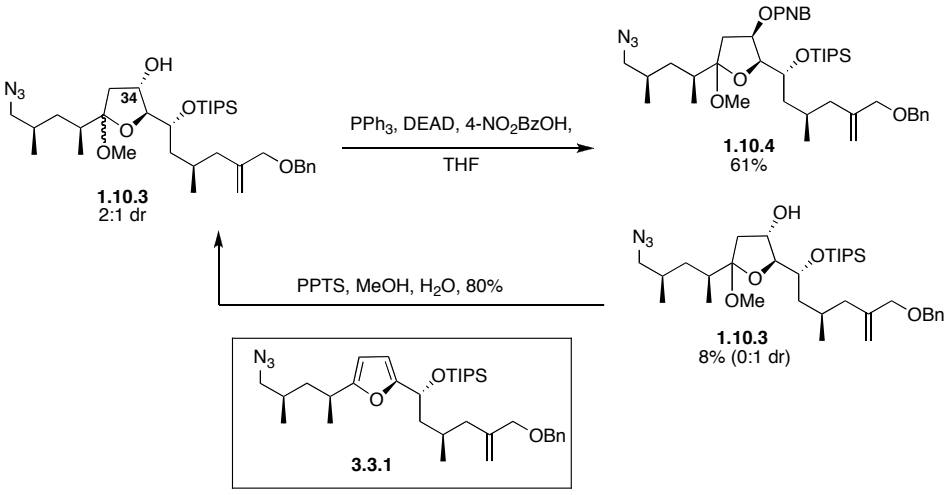
In the effort toward elaborating our southern fragment, the route first employed by Dr. Xiao-Ti Zhou needed to be scaled. Proceeding from the aldol condensation of methyl ketone *ent*-1**.8.1** and aldehyde **1.10.1**, which proceeded smoothly on scale to give aldol adduct **1.10.2** with good dr (>20:1) but the undesired C_{34} stereochemistry. Desilylation set the stage for a PPTS-mediated formation of our central furan ketal **1.10.3** which proceeds in 2:1 diasteromeric ratio at C_{36}.



Scheme 3.2: Formation of Furan **1.10.3**

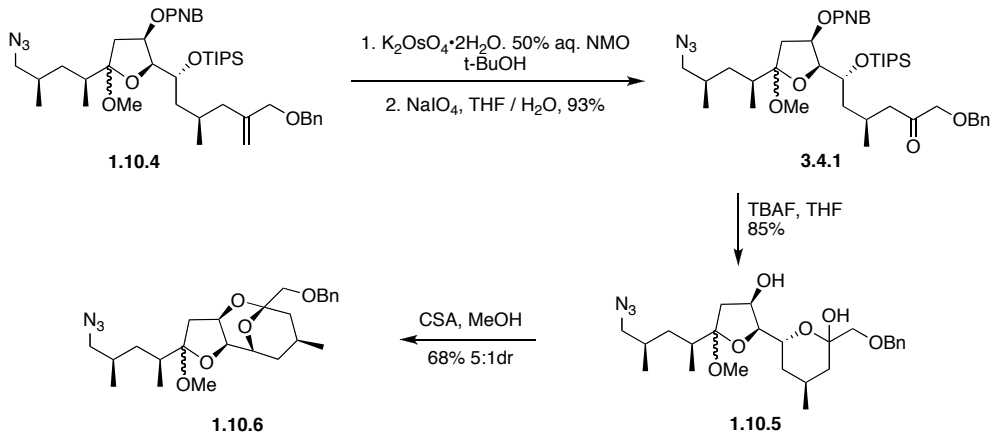
Inversion of the C_{34} alcohol was then requisite to have the correct stereochemistry of the FGHI subunit. Mitsunobu inversion alcohol **1.10.3** netted p-nitrobenzoate **1.10.4** in an modest 60% yield with recovered starting material being the remainder of the mass. Interestingly, the reaction only occurred on the major diastereomer of the furan ketal. Efforts to induce complete reaction led to poor yields and a plethora of side products. We decided to attempt to equilibrate ketal **1.10.1**. Treatment of recovered alcohol **1.10.3** with PPTS in methanol did not effect any equilibration of the furan center. Upon switching to camphorsulfonic acid, decomposition to what we presumed was furan **3.3.1**. Gratifyingly, the addition of one equivalent of water to the PPTS-mediated process afforded the 2:1 diastereomeric mixture of ketals which were then resubmitted to Mitsunobu conditions.

It is important to note that the formation of furan **3.3.1** plagued all the subsequent reactions until the stable spiroaminal **1.10.8** was formed. In order to prevent the furans formation, all silica gel columns were buffered with 1% triethyl amine and all reactions were closely monitored by TLC. Even under optimized conditions trace amounts of furan were often observed in crude reaction mixtures.



Scheme 3.3: Inversion of the C_{34} Stereocenter

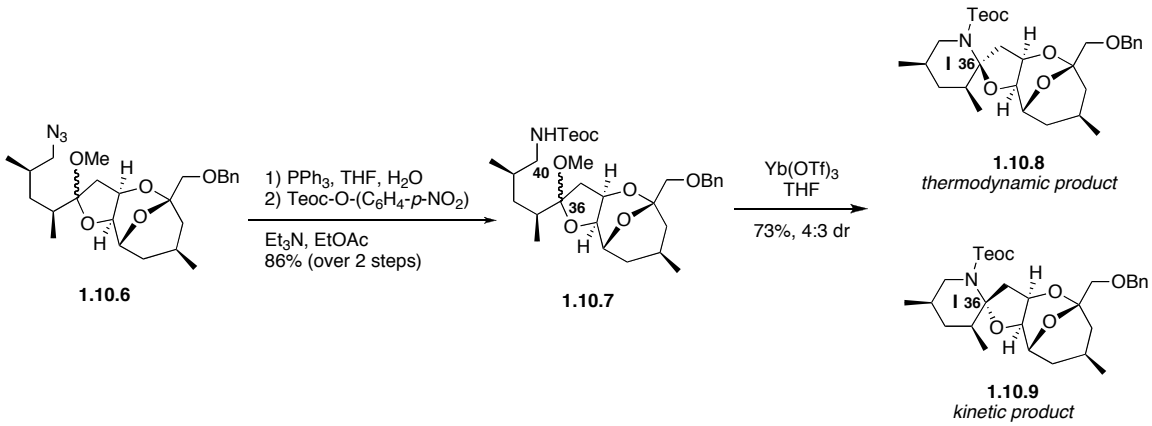
With an established inversion protocol in hand, the next step was the formation of the bicyclic ketal moiety. First, the alkene was cleaved in a two-step oxidation to afford ketone **3.4.1**. Treatment of the ketone led to TBAF cleaved the triisopropyl silyl ether and concurrently cleaved the p-nitrobenzoate ester. The C_{32} alcohol reacted with the ketone *in situ* to net hemiketal **1.10.5** as the isolated product. It is of note that this reaction proceeded faster and more smoothly with old TBAF from bottles with compromised seals. With fresh TBAF, a mixture of the desired product, products with the p-nitrobenzoate group still attached and furan **3.3.1** were observed. Treatment of hemiketal **1.10.5** with CSA afforded furan **1.10.6** as a 5:1 mixture of diastereomers at the methyl ketal.



Scheme 3.4: Formation of Bicyclic Ketal **1.10.1**

3.3: Initial Approach to the Spiraminal Synthesis

Carrying azide **1.10.6** forward, Staudinger reduction and 2-TMS ethyl carbamate protection led to amine **1.10.7** (Scheme 3.5). Lewis acid-mediated cyclization lead to a 4:3 mixture of the desired anomerically stabilized aminal **1.10.8** and undesired kinetic product **1.10.9**. These diastereomers were only separable *via* challenging silica gel chromatography.



Scheme 3.5: Initial Approach to the Synthesis of **1.10.8**

With the disappointing diastereomeric ratio for the spiroaminal formation, we then began analysis into its the origins. Analysis of the conformation of the spiroaminal, we found what we thought was the reason for the poor diastereoselectivity (Figure 3.6). Looking at the spiroaminal

we see that the unprotected desired spiroaminal **3.6.3** has a doubly anomerically stabilized spiroaminal, while the undesired spiroaminal **3.6.4** is only singly anomerically stabilized. When we switch to the protected spiroaminal we see limited anomeric stabilization of the C-O bond from the nitrogen of the carbamate due to the electron withdrawing nature of the carbamate moiety. This is presumably due to the lone pair on nitrogen being tied up in amide resonance rather then anomeric stabilization.

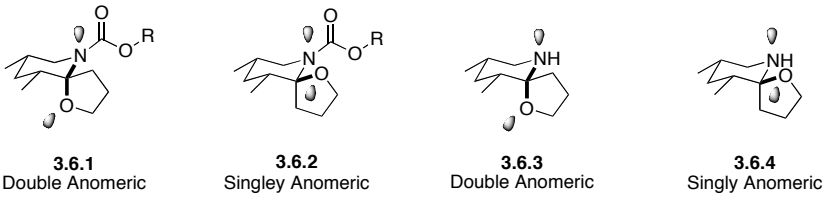
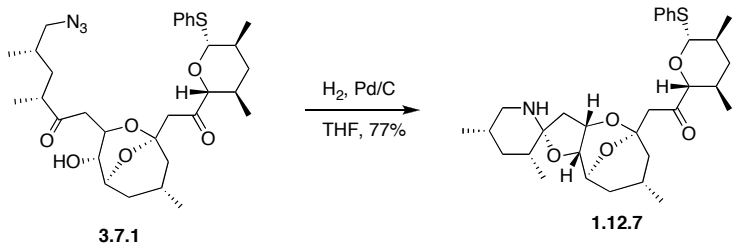


Figure 3.6: Conformational Analysis of Spiroaminal

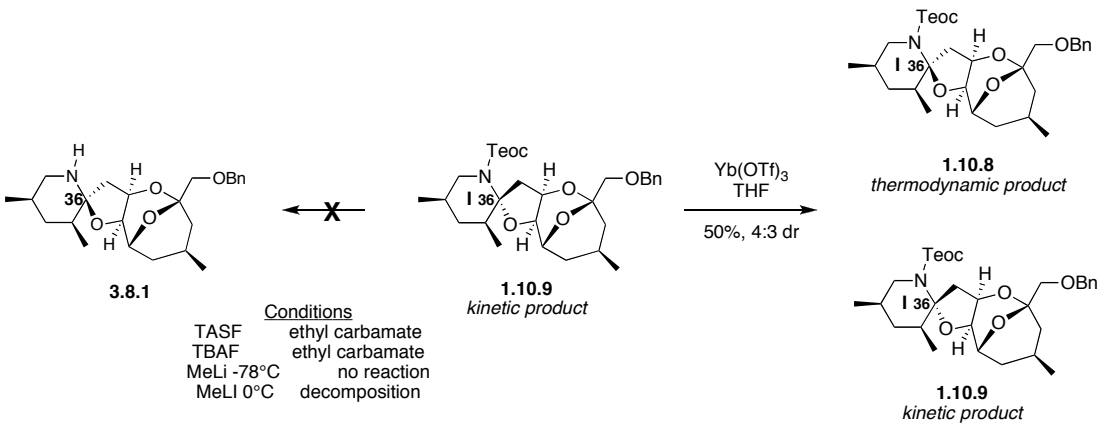
Evidence supporting our theory came in the Evans group's synthesis of the non-natural antipode of azaspiracid (Scheme 3.7).[2] When azide **3.7.1** was reduced, a spontaneous cyclization netted the desired stereochemistry about the spiroaminal linkage in greater then 20:1 selectivity. This result illustrated our theory that, while the spiroaminal naturally sits as the desired configuration, the Teoc protecting group disrupts this stereochemical preference, leading to a disappointing stereochemical mixture (See Scheme 3.5).



Scheme 3.7: Evidence Evans' Synthesis of (+) Azaspiracid

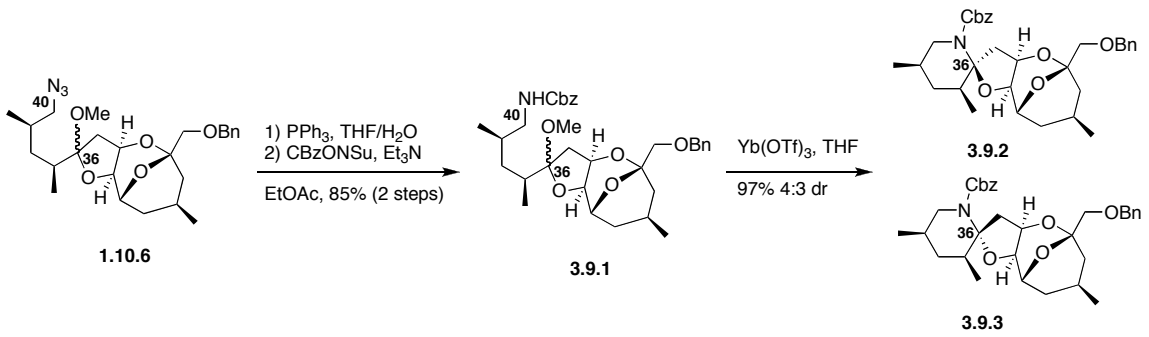
3.4: Improved Route to Spiroaminal 1.10.8

Based on our analysis for the formation of undesired spiroaminal **1.10.9,** we set out to directly address this issue (Scheme 3.8). Attempts at resubmission of the undesired aminal **1.10.9** to cyclization conditions led to a disappointing 50% yield of a 4:3 mixture of **1.10.8** to **1.8.9**. Removal of the Teoc carbamate **1.10.9** proved challenging as well. Initial investigation into utilizing standard desilylation conditions gave a complex mixture of what looked to be predominately ethyl carbamate by ^{1}H NMR. Acidic conditions led to complete decomposition and treatment with methyl lithium provided no reaction at cryogenic temperatures, and decomposition upon warming.



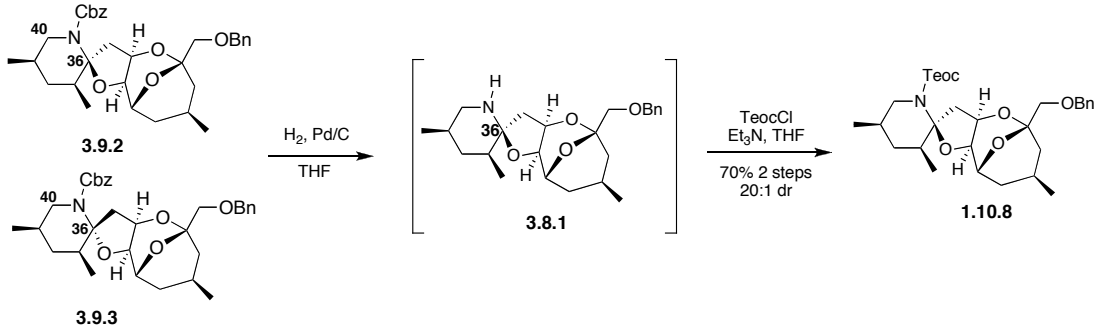
Scheme 3.8: Initial Attempts at Spiroaminal Equilibration

Upon exhaustion of possible equilibration routes for the Teoc series, the C_{40} amine protecting group was switched to a Cbz protecting group (Scheme 3.9). After Staudinger reduction of azide **1.10.6** and protection of the resulting amine as a Cbz carbamate, the stage was set for cyclization. Treatment of Cbz carbamate **3.9.1** gave aminals **3.9.2** and **3.9.3** in the same 4:3 ratio in excellent yield.



Scheme 3.9: Formation of Cbz Spiroaminals

Gratifyingly, hydrogenolysis of the mixture of spiroaminals in THF with neutral palladium on carbon led to cleavage of the Cbz carbamate in the presence of the benzyl ether **3.8.1** and led to a complete equilibration to the desired diastereomer *in situ* (Scheme 3.10). Interestingly, hydrogenolysis of the spiroaminals **3.9.2** and **3.9.3** in ethanol provided a clean cleavage of the Cbz carbamate, but no equilibration of the spiroaminal. We have postulated that this must be to a stabilization of the undesired spiroaminal through a hydrogen bond stabilized by ethanol. Aminal **2.12.4** was then protected immediately to give known tetracycle **1.10.8** in good yield.



Scheme 3.10: Improved Route to Spiroaminal **1.10.8**

3.5: Conclusion

I transformed a synthesis of spiroaminal **1.10.8** into an efficient process allowing for gram quantities to be prepared with ease. Conformational analysis of an undesirable spiroaminal

formation (Scheme 3.5) led to an interesting solution to a major quagmire (Scheme 3.10). With a scalable route in hand, studies were done toward the elaboration of spiroaminal **1.10.8** (Chapters 4-5).

An interesting muting of the anomeric effect for the formation of spiroaminals **1.10.8** and **3.9.2** were observed. After analysis, were hypothesized that the electron withdrawing nature of the carbamate protecting group muted the anomeric effect generally observed in spiroketals and spiroaminals. After initial attempts at equilibrating the undesired kinetic bisspiroketal **1.10.9** failed, a new route based upon liberating the free spiroaminal **3.8.1** to allow for equilibration were highly successful, allowing for a scalable synthesis of the FGHI ring system of azaspiracid-1.

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STUDIES TOWARD THE TOTAL SYNTHESIS OF AZASPIRACID 1

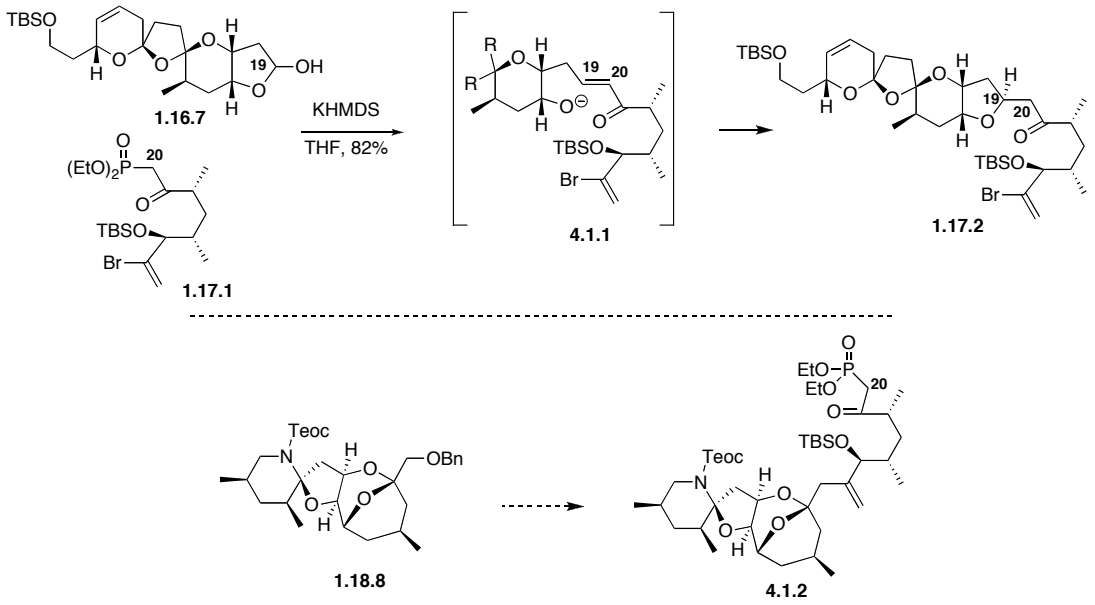
CHAPTER 4:

Initial Studies Toward the Elaboration

of the FGHI Spiroaminal Subunit

4.1: Introduction

A previous model endgame was investigated (Scheme 4.1).[1] Horner-Emmons olefination of lactol **1.16.7** and ketophosphonate **1.17.1** coupled the two fragments together to provide olefin **4.1.1**, which did an *in situ* Michael addition to form the D ring and the C_{19} stereocenter and yield ketone **1.17.1**. Based on this endgame, our initial target was the elaboration of benzyl ether **1.18.8** into ketophosphonate **4.1.2**.

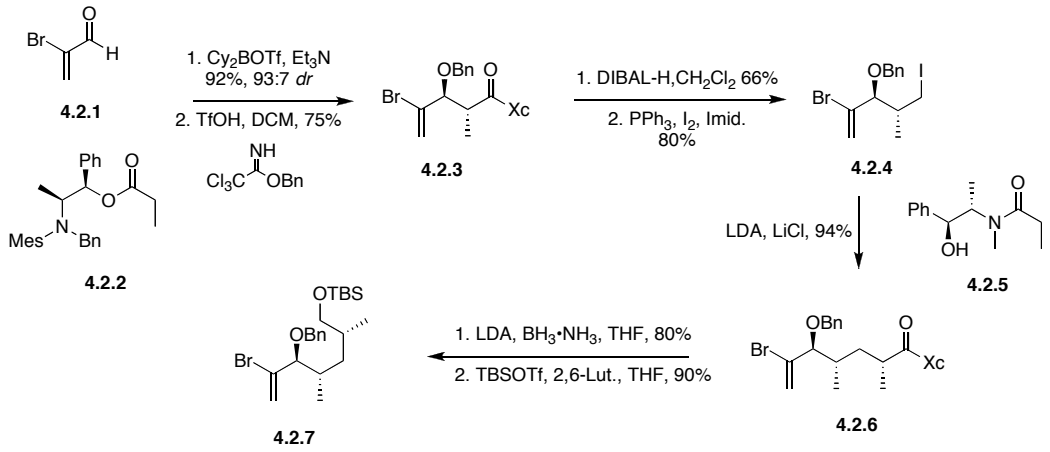


Scheme 4.1: Model Study Toward Key Tandem HWE Michael Coupling

4.2: Initial Route to Elaboration of Spiroaminal 1.18.8

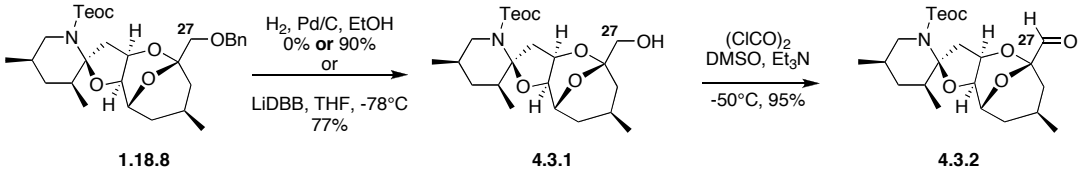
Our initial strategy for functionalization of the FGHI benzyl ether **1.18.8** was predicated on a vinyl lithium addition into a C_{27} aldehyde followed by a deoxygenation. In anticipation for this route, vinyl bromide **4.2.7** was prepared (Scheme 4.2). A Masamune aldol[2] reaction coupled 2-bromoacrolein (**4.2.1**) with chiral propionate **4.2.2**. Subsequent benzylation of the aldol adduct afforded ester **4.2.3**. The ester was then reduced with DIBAL-H and transformed into iodide **4.2.4**. Myers alkylation[3] of amide **4.2.5** and iodide **4.2.4** set the last stereocenter in high yield and

enantioselectivity, affording amide **4.2.6**. The amide was then reduced and the resultant alcohol was protected to give TBS ether **4.2.7**.



Scheme 4.2: Synthesis of Vinyl Bromide **4.2.7**

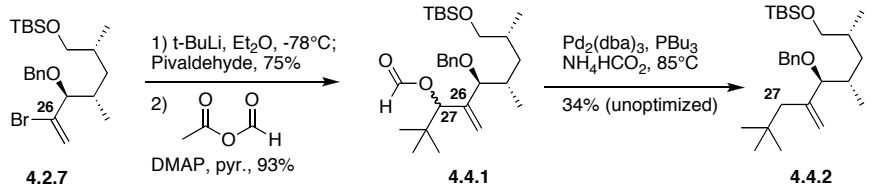
With vinyl bromide **4.2.7** in hand, the requisite aldehyde **4.3.2** was prepared (Scheme 2.14). First, the C_{27} benzyl ether was to be cleaved. Initial hydrogenolysis of benzyl ether **1.18.8** proceeded in good yield to net alcohol **4.3.1**. Unfortunately, the hydrogenolysis proved irreproducible as different batches of palladium on carbon led to complete degradation of reactivity with significant decomposition. Upon switching to LiDBB,[4] debenzylation proved reproducible with a 77% yield. Finally, Swern oxidation[5] of alcohol **4.3.1** provided aldehyde **4.3.2**.



Scheme 4.3: Elaboration of Benzyl Ether **1.18.8**

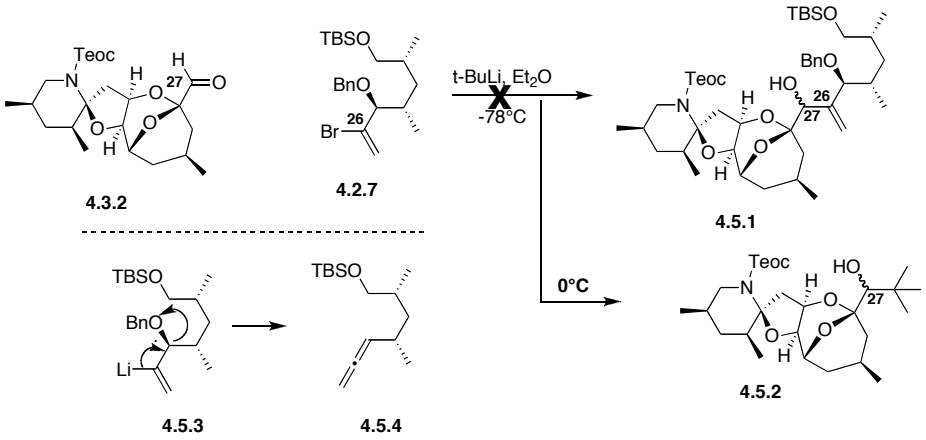
Next, the coupling of aldehyde **4.3.2** and vinyl bromide **4.2.7** was then investigated (Scheme 4.4). In a model study, vinyl bromide **4.2.7** was lithiated and trapped with pivaldehyde

to provide a 75% yield of the coupled product. After formylation with the acetic formic anhydride, Tsuji reduction[6] of formate **2.15.1** using Pd_2dba_3, PBu_3 and ammonium formate, led to alkene **2.15.2** in an unoptimized 34% yield. While the yield for this process was less than desirable, the fact that there was no observed scrambling of olefin location was a positive result.



Scheme 4.4: Model Study of Deoxygenation Strategy

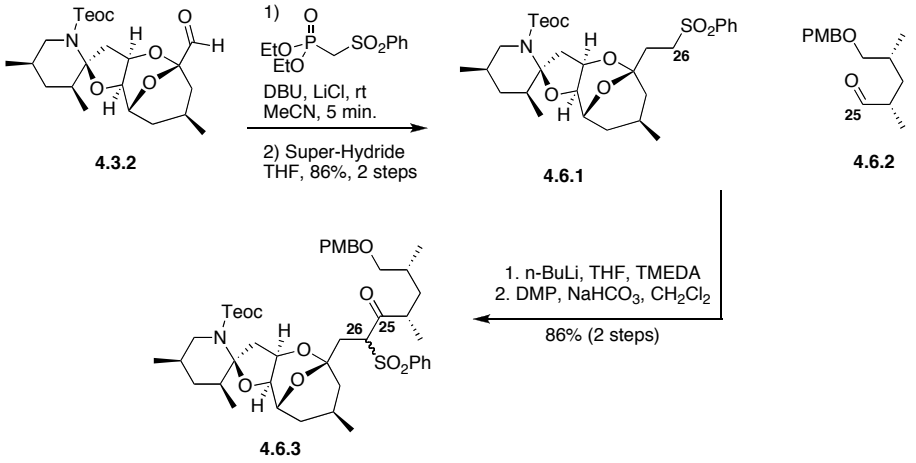
Based on the encouraging results, aldehyde **4.3.2** was treated with vinyl lithium **4.5.3** at -78°C resulted in no C-C coupling (Scheme 4.5). The reaction was quenched with methanol at -78°C to establish complete lithiation of vinyl bromide **4.2.7** had occurred. Subsequent reactions were allowed to warm to 0°C slowly. The products of these reactions appeared to be a minor amount of t-butyl lithium addition product **4.5.2** and recovered aldehyde **4.3.2**. Presumably vinyl lithium **4.5.3** decomposes to form allene **4.5.4** upon warming, rendering any vinyl addition to aldehyde **4.3.2** unlikely.



Scheme 4.5: Initial Coupling Deoxygenation Route

4.3: Julia Coupling Route

Our revised approach was predicated on a Julia coupling to append the C_{25} aldehyde **4.3.2** (Scheme 4.6). To that end, requisite sulfone **4.6.1** was made by Roush-Masamune modified HWE olefination[7] followed by a Super-Hydride reduction.[8] Initial attempts at using standard Horner-Wadsworth-Emmons condition (nBuLi, THF, -78°C) proved problematic with low yield, decomposition and recovered aldehyde.[9] Proceeding with the Julia coupling, after lithiation (nBuLi, TMEDA) of sulfone **4.6.1**, clean condensation with aldehyde **4.6.2** was observed by TLC and crude ^{1}H NMR. The resulting hydroxyl sulfone was submitted to oxidation with Dess Martin periodinane to provide key keto sulfone **4.6.3**. [10]

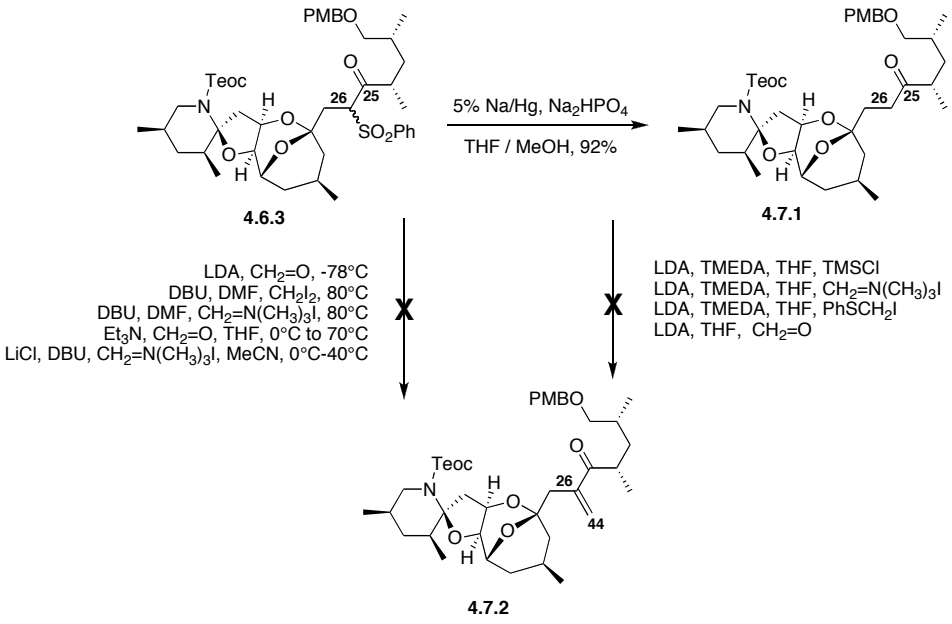


Scheme 4.6: Synthesis of Ketosulfone **4.6.3**

The installation of the C_{25}-C_{44} olefin was investigated next (Scheme 4.7). Initial attempts at alkylation of ketosulfone **4.6.3** were problematic. While over thirty different reagent combinations were attempted (a selection of failed experiments are provided in Scheme 4.7), only two reactions showed any signs of reaction. The treatment of the ketosulfone **4.6.3** with LDA and formaldehyde at -78°C showed evidence of reaction by TLC. Deuterium incorporation (LDA, TMEDA, THF, D_2O) afforded greater then 75% incorporation, which implied that, while the enolate

was formed, the reactivity of that enolate was sluggish. Presumably, steric hindrance about the reaction site and the stabilization of the enolate by the sulfone provided this lack of reactivity.

Desulfurization of ketosulfone **4.6.3** provided ketone **4.7.1** and provided a second potential enolate for olefin formation. Again, while deuterium incorporation proceeded smoothly, the reaction of the enolate with a host of electrophiles showed little actual success. Both Eschenmoser salt, and trimethylsilane chloride showed reaction by TLC analysis, but upon workup only starting material was recovered. One potential explanation for these results could be due to O-alkylation followed by hydrolysis of the resulting enol ether upon workup.

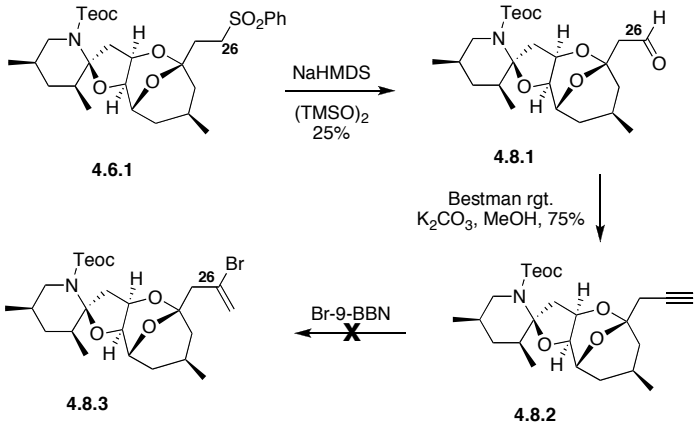


Scheme 4.7: Attempts at Formation of Enone **4.7.2**

4.4: Alternate Vinyl Anion Addition Approach

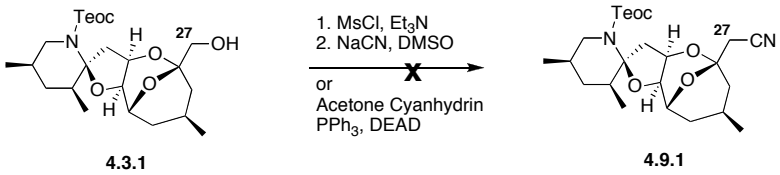
When the Julia route proved unsuccessful, we decided to change our approach. Rather then couple the southern fragment and then install the C_{26}-C_{44} olefin, we would install the alkene prior to coupling of the fragments. We began to investigate other ways to utilize the sulfone **4.6.3** (Scheme 4.8). Treatment of the anion of sulfone **4.6.3** with bis TMS peroxide afforded modest amounts of aldehyde **4.8.1** after a TBAF workup.[11] Treatment of aldehyde **4.8.1** with Ohira-

Bestmann reagent[12] afforded acetylene **4.8.2**, which was set for bromoboration. Unfortunately, attempts at bromoboration proved unsuccessful. Treatment with 9-BBN bromide consumed the acetylene, but under acidic workup, only decomposition was observed. Attempts at using a milder workup involving ethanolamine[13] proved unsuccessful at hydrolyzing the carbon boron bond to release vinyl bromide **4.8.3**.



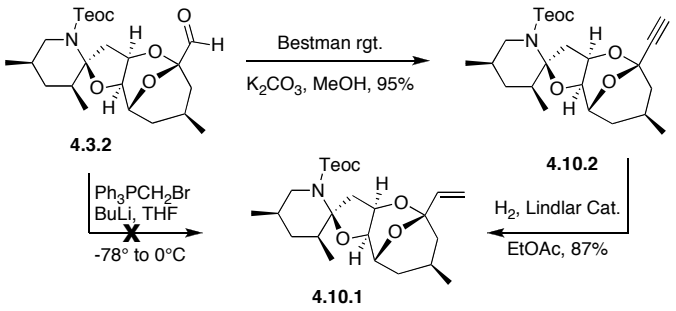
Scheme 4.8: Alternative Vinyl Lithium Route

After initial investigation of bromoboration of acetylene **4.8.2** proved fruitless, several alternative routes were briefly explored. An initial foray into alternative ways to do one carbon homologation of alcohol **4.3.1** proceeded (Scheme 4.9). Initially, we attempted to activate the alcohol as a mesylate and then displace it with cyanide. While the mesylate ester of alcohol **4.3.1** could be formed, it was unstable and only a low yield was attained (< 20%). Treatment of the resultant mesylate with sodium cyanide resulted in total decomposition. Next, Mitsunobu conditions were tried to directly incorporate the cyanide in one step. Unfortunately, no reaction occurred, even under extended reaction conditions.



Scheme 4.9: Attempted One Carbon Homologation of Alcohol **4.3.1**

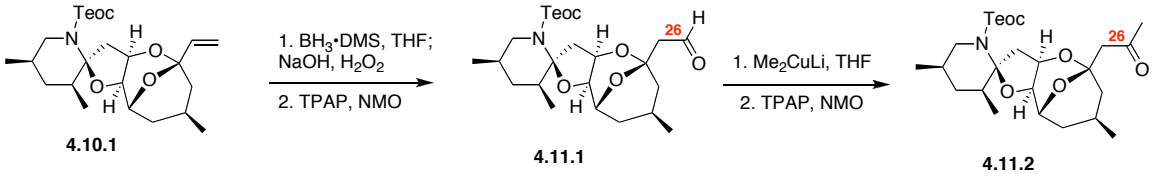
Alternatively, a one-carbon homologation could be had via Wittig chemistry (Scheme 4.10). While the direct formation of olefin **4.10.1** from aldehyde **4.3.2** was unsuccessful, an alternative was discovered. Treatment of aldehyde **4.3.2** with Ohira-Bestman, reagent afforded alkyne **4.10.2** in good yield and subsequent Lindlar reduction gave alkene **4.10.1**. Early efforts at Lindlar reduction under standard condtions (Hexanes / 1-octene, quinoline) failed to afford any reduced product. Gratifyingly, switching to the more polar ethyl acetate and the omission of the quinoline from the reaction dramatically accelerated the rate of reaction, leading to a consistent reaction that was generally done in six hours.



Scheme 4.10: Successful One Carbon Homologation

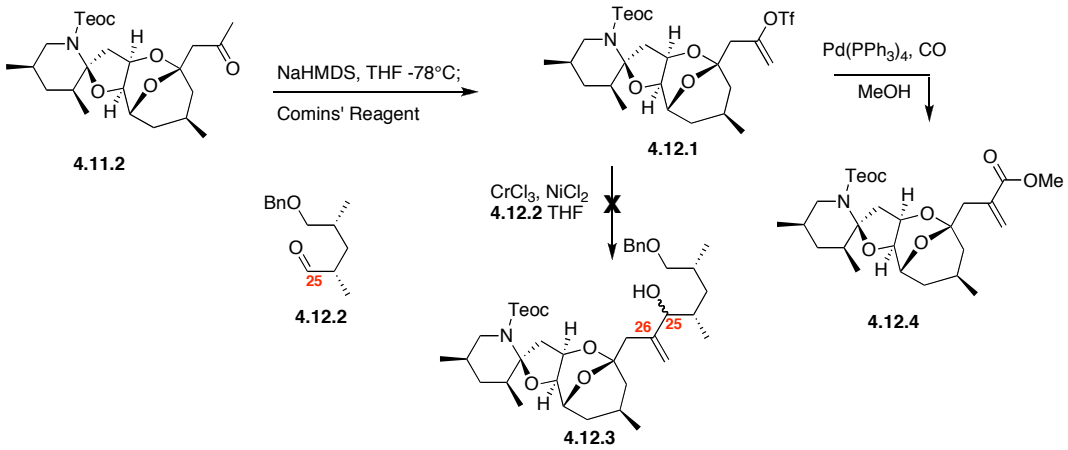
With alkene **4.10.1** in hand, we proceeded in an effort to procure methyl ketone **4.11.2** (Scheme 4.11). While attempted hydroboration / oxidation of acetylene **4.10.2** to provide a homologated aldehyde **4.10.1** proved fruitless,[14] the hydroboration of alkene **4.10.1** and oxidative workup led to an alcohol. Ley oxidation of that alcohol furnished aldehyde **4.11.1**.[15] Treatment of aldehyde **4.11.1** with dimethyl cuprate and re-oxidation led to desired methyl ketone **4.11.2**.

While this route did work, it was rife with impurities and variable yields which made characterization and accurate yields impossible to present.



Scheme 4.11: Synthesis of Ketone **4.11.2**

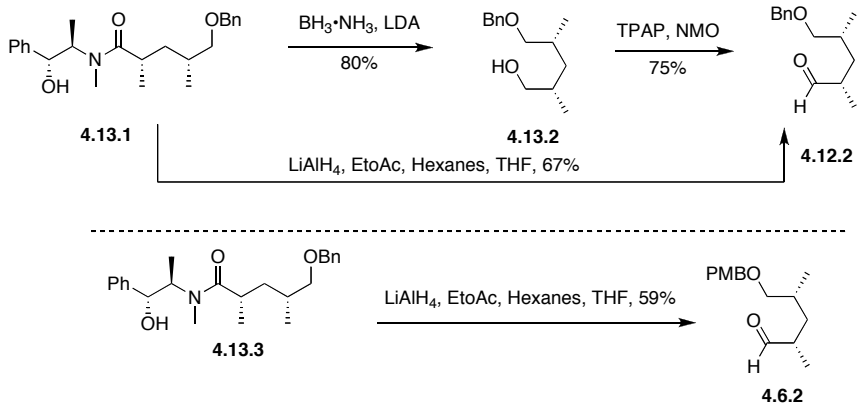
With the limited amount of methyl ketone afforded from this route preliminary trying to install the C_{44} alkene (Scheme 4.12). Treatment of methyl ketone **4.11.2** with NaHMDS and Commins' reagent afforded enol triflate **4.12.1**. Initial attempts at Nozaki-Hiyama-Kishi[16] coupling with aldehyde **4.12.2** provided a complex mixture of starting material, protodemetalated material and decomposition. Carbonylation of enol triflate **4.12.1** provided modestly successful providing minor amounts (< 20%) of ester **4.12.4**, attempts at optimization proved unsuccessful. With no tangible success, this hydroboration route was abandoned in favor of a more fruitful route.



Scheme 4.12: Enol Triflate Experiments

4.5: The Synthesis of Requisite Fragments

Aldehyde **2.18.4** was available in two steps from known Myers alkylation product **4.13.1** (Scheme 4.14). First, the amide was reduced to the alcohol **4.13.2**. The alcohol was then oxidized to aldehyde **4.12.2** by Ley oxidation. A one step process was also investigated, but the reduction led to varying yields and the acidic hydrolysis often degraded the enantiopurity of the α stereocenter of the aldehyde **4.12.2**. Aldehyde **4.6.2** was accessed through similar chemistries for couplings in the early Julia coupling routes.



Scheme 4.13: Synthesis of Aldehydes **4.12.2** and **4.6.2**

4.6: Conclusion

After our initial vinyl lithium coupling failed in elaboration of the FGHI aldehyde **4.3.2**, a host of routes were investigated. The Julia coupling route provided fast access to ketone **4.7.1**, but an adequate technology for installing the C_{26}-C_{44} alkene was not discovered. Initial forays into the NHK coupling of enol triflate **4.12.1** proved disastrous, as both the NHK coupling and the route to make the enol triflate were uninspiring.

A unique lack of reactivity for ketosulfone **4.6.3** and ketone **4.7.1** was observed. The ketosulfone appears to be a mixture of diastereomers about the C_{25}-C_{26} bond which is further complicated by the presence of the enol tautomer as both the E and Z olefin geometry. Unsurprisingly, with this complex mixture of hindered conformers reactivity was not possible. The

ketone**4.7.1** appears to be sitting in a hydrogen bonding network that elongates the C-O bond of the carbonyl more like an enol then a ketone (C_{25} is 159.0 ppm). This interesting lack of reactivity forced us to reevaluate our approach to the incorporation of the E ring substituents.

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STUDIES TOWARD THE TOTAL SYNTHESIS OF AZASPIRACID 1

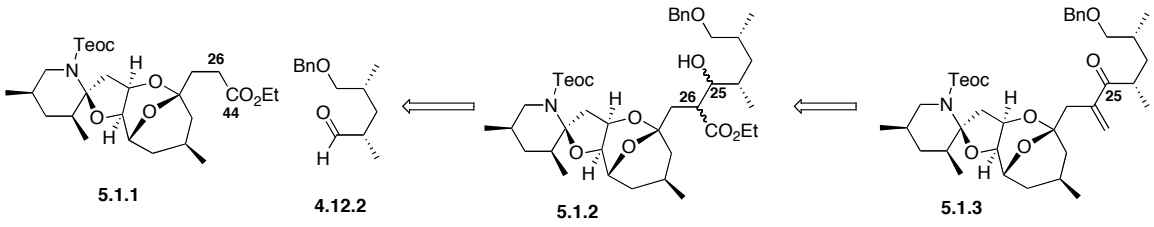
CHAPTER 5:

Aldol Route to the Elaboration

Of the FGHI Spiroaminal Subunit

5.1: Aldol Based Elaboration of Aldehyde 4.3.1

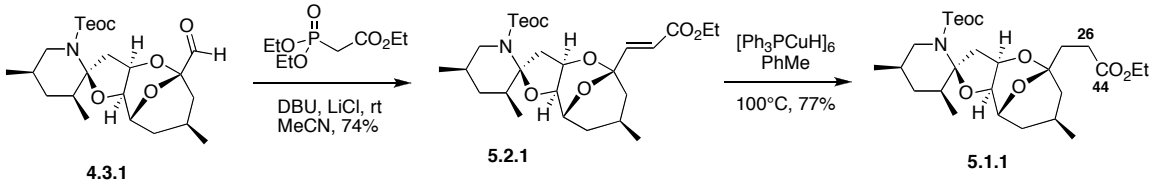
While we were investigating our options with the methyl ketone chemistry, we began to develop a new approach based on an aldol coupling (Scheme 5.1). This new route would install the carbon atoms necessary in one step, but would require a second reaction to install the C_{26}-C_{44} olefin. Our hypothetical route would utilize the aldol condensation of ester **5.1.1** and aldehyde **4.12.2** to provide all the carbon atoms requisite for our alkene. Finally, the ester moiety of aldol adduct **5.1.2** would be dehydrated to provide enone **5.1.3**.



5.1.1 4.12.2 5.1.2 5.1.3

Scheme 5.1: Aldol Route Retrosynthesis

Investigation of this new aldol route began with the synthesis of ester **5.1.1** (Scheme 5.2). Horner-Emmons olefination of aldehyde **4.3.1** under Roush-Masamune[1] conditions afforded α,β-unsaturated ester **5.2.1.** The ester was then reduced with Stryker's reagent[2] to afford ester **2.20.2**, setting the stage for implementation of our aldol coupling.

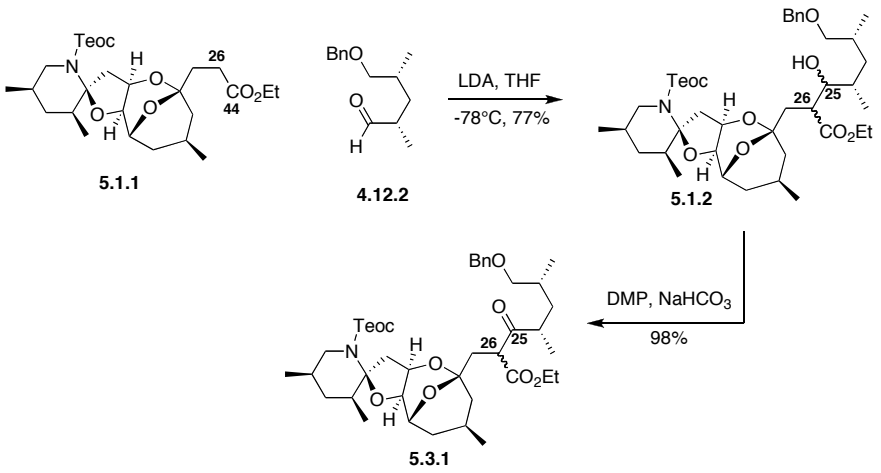


4.3.1 5.2.1 5.1.1

Scheme 5.2: Preparation of Ester **5.1.1**

Next, the aldol coupling was explored (Scheme 5.3). Initial investigation of a NaHMDS mediated aldol proved inefficient (<50% yield). Fortunately, upon treatment of ester **5.1.1** with

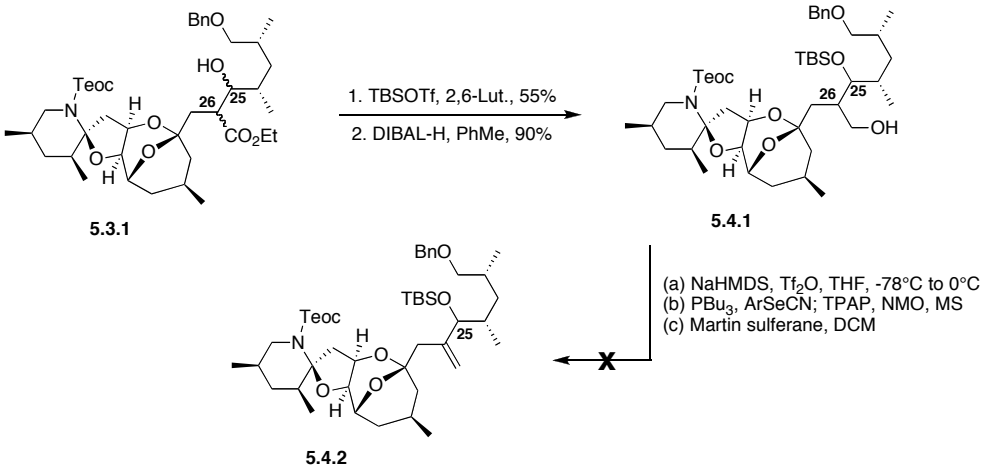
LDA and subsequent addition of aldehyde **4.12.2** to provided aldol adduct **5.1.2** as a 5:2:2:1 mixture of diastereomers. Structural confirmation was next established by oxidizing aldol adduct **5.1.2** to ketoester **5.3.1** with Dess-Martin periodinate.[3] The resulting ketoester **5.3.1** was then characterized to as a 1:1 mixture of diastereomers at C_{26}, which resided solely as the keto tautomer.



Scheme 5.3: Aldol Condensation

With aldol adduct **5.3.1** in hand, we turned our attention to the installation of the C_{26}-C_{44} alkene (Scheme 5.4). After the silylation of the C_{25} alcohol, the ester was reduced. Initial forays into reduction were problematic. Treatment of the silylated aldol adduct with DIBAL-H in methylene chloride provided no reaction after 3 hours at -78°C. Warming the reaction slowly to 0°C led to decomposition. Reduction with lithium borohydride under standard conditions (1 eq. methanol, in THF) provided no reactivity. In a previous case in our lab, the addition of saturated aqueous ammonium chloride had activated lithium borohydride reduction.[4] Unfortunately this also proved unsuccessful. Finally, upon switching to DIBAL-H in toluene for three hours, the reduction of the ester provided alcohol **5.4.1**. With the alcohol **5.4.1** in hand, we next screened dehydration reactions in hopes of attaining alkene **5.4.2**. Treatment of alcohol **5.4.1** with NaHMDS and triflic anhydride afforded no reaction. A selenation / elimination[5] strategy was also unsuccessful.

Standard 30 minute selenation reaction led to no selenation and, upon oxidation, we were afforded the resulting aldehyde in modest yield. Attempts at longer selenation reactions led to complete decomposition of starting material. Switching to Martin sulfurane[6] chemistry, which is noted for being a soft dehydration method, we faced sluggish reactivity at best. After 6 days of reaction with 10 equivalents of Martin sulfurane, greater then 85% of the mass recovery was alcohol **5.4.1**.

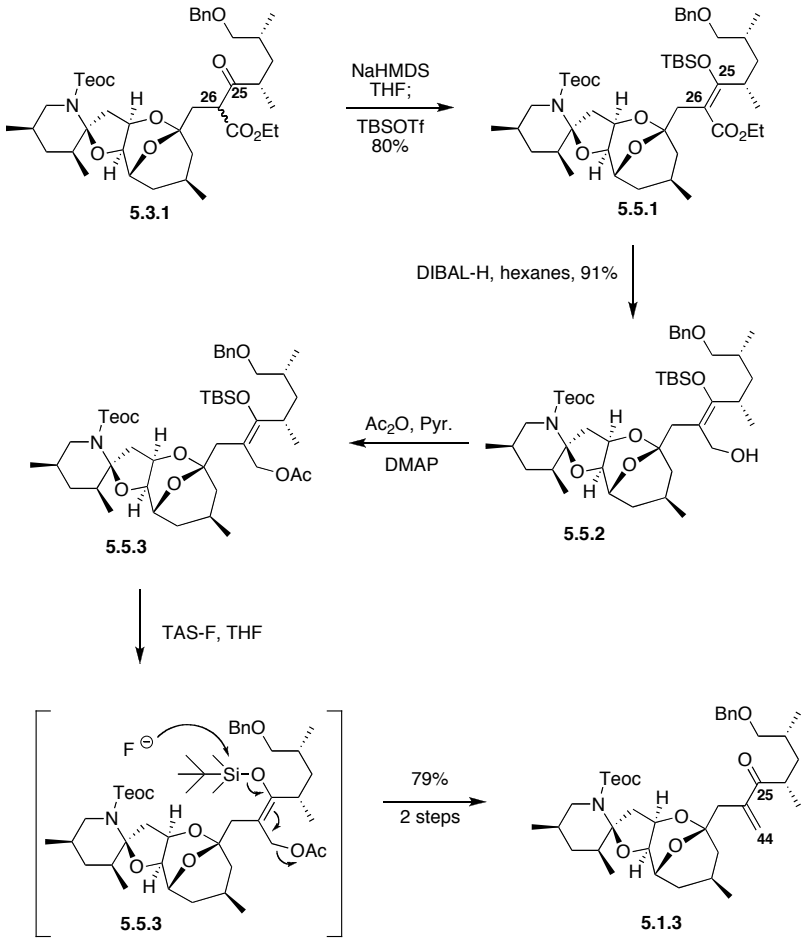


Scheme 5.4: Initial Route to Olefin Formation

5.2: Successful Synthesis of Ketophosphonate 4.1.2

With the failure of our initial route to the installation of the C_{26}-C_{44} alkene, we quickly switched to an alternative approach based on a cascade reaction to form the alkene (Scheme 5.5). First, we transformed ketoester **5.3.1** into TBS enol ether **5.5.1**. Initial attempts at effecting the transformation using 2,6-lutidine only afforded ketoester **5.3.1** in its enol form. Fortunately, use of NaHMDS as the base led to facile production of TBS enol ether **5.5.1**. Next, the ester moiety was reduced to afford alcohol **5.5.2**. A slow addition of DIBAL-H to this reaction was important. The amount of what is presumed to be 1,4-reduction product observed was related to the rate of addition. In an attempt to modulate the reactivity of the DIBAL-H, solvents were screened. Both hexanes and toluene provided similar results, with minor amounts of the 1,4

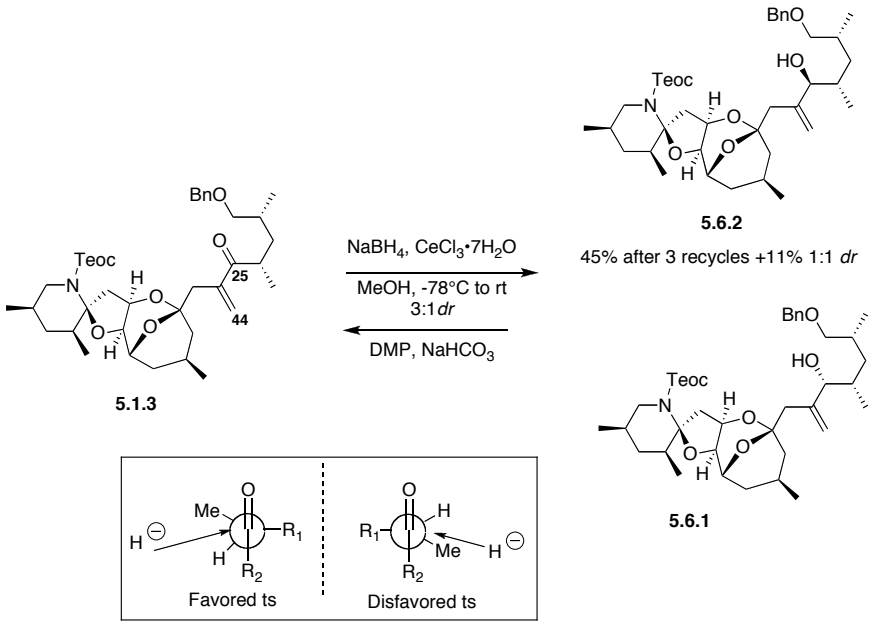
product always present, but generally between 5 and 10% of the mass recovered regardless of solvent. With alcohol **5.5.2** in hand, a two-step activation elimination process was developed. Acylation of alcohol **5.5.2** provided an unstable allylic acetate **5.5.3**, which was immediately treated with TAS-F to afford clean elimination to the desired ketone **5.1.3**. Presumably, TAS-F cleaves the TBS silyl ether then the resulting enolate collapses eliminating the acetate and installing the alkene.



Scheme 5.5: Cascade Formation of Enone **5.1.3**

With ketone **5.1.3** finally in hand we had reached a turning point in the project. After three years of work, the C_{26}-C_{44} alkene was finally installed. The next hurdle for the synthesis was the Felkin reduction of ketone **5.1.3** to provide desired allylic alcohol **5.6.2** (Scheme 5.6).

Initially, a standard Luche reduction ($NaBH_4$, $CeCl_3$) at -10°C was investigated.[7] A mixture of desired alcohol **5.6.2** and undesired anti-Felikin alcohol **5.6.1** was attained. After DIBAL-H reduction afforded a mixture of decomposition products and CBS reduction failed to reduce ketone **5.1.3**, we revisited optimization of the Luche reduction. While no reaction was observed at -78°C, slowly allowing the reaction from -78°C to 0°C afforded a 3:1 mixture of desired alcohol **5.6.2** and undesired anti-Felikin alcohol **5.6.1** in 72% yield. While separation of these two compounds was possible via silica gel chromatography, it was very challenging. To recycle our material, any fractions containing the undesired alcohol **5.6.1** were submitted to Dess-Martin oxidation and resubmitted to Luche reduction. After three recycles, a 45% yield of alcohol **5.6.2** was attained with an additional 11% of the mass as a 1:1 diastereomeric mixture of alcohols **5.6.1** and **5.6.2**.

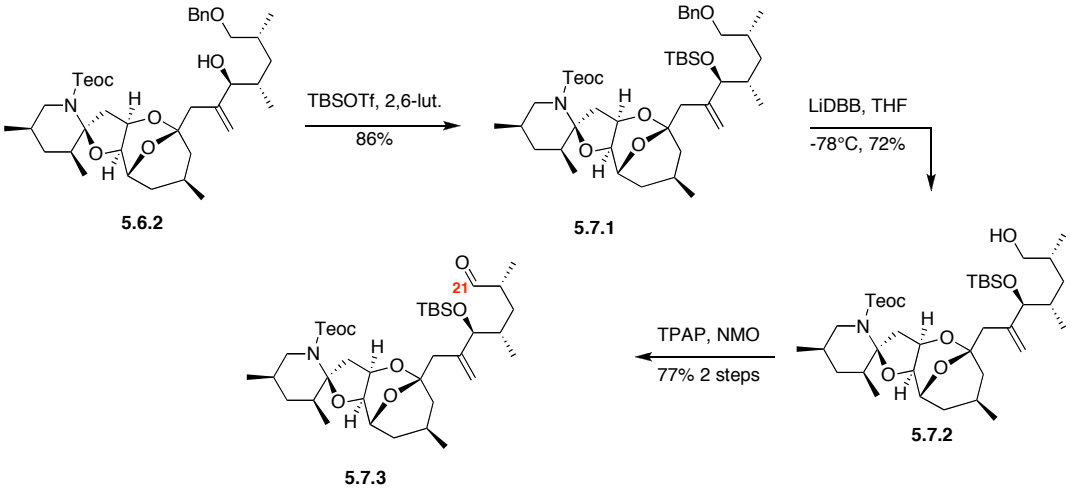


Scheme 5.6: Installation of Allylic Alcohol **5.6.2**

While the stereochemistry of the C_{25} alcohol wasn't rigorously proven, the Felkin-Ahn[8] model is a predictive tool used to predict the stereochemistry predicts the desired stereochemistry. When the largest R group of the α stereocenter is placed at 90° to the carbonyl

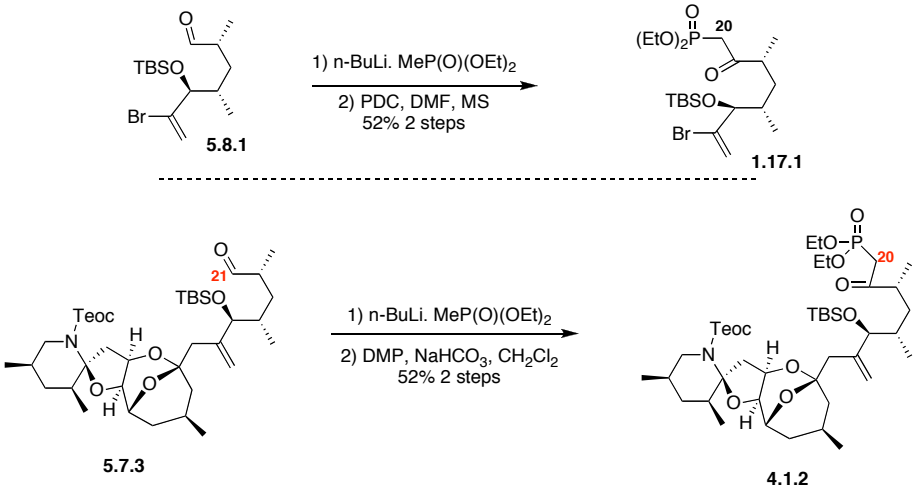
we get two transition states; the favored transition state placed the medium R group gauche to the carbonyl. While the Felkin model accurately predicts the favored transition state it does not tell the magnitude of the preference which could be 1.1:1 or >20:1 in a given system.

With the C_{25} stereocenter set, we next approached the formation of aldehyde **5.7.3** (Scheme 5.7). First, the C_{25} alcohol was protected as the TBS silyl ether **5.7.1**. Next, the primary benzyl ether was cleaved with LiDBB to provide alcohol **5.7.2**. Finally, alcohol **5.7.2** was oxidized to aldehyde **5.7.5** under Ley oxidation conditions.[9] These transformations set the stage for the formation of key ketophosphonate **4.1.2**, leaving us very close to a goal that was three years in the making.



Scheme 5.7: Elaboration of Alyllic Alcohol **5.6.2**

With aldehyde in hand, we proceeded with the formation of key ketophosphonate **4.1.2** (Scheme 5.8). While the model studies showed quick reaction for the addition of the lithiated methane phosphonate into the aldehyde **5.8.1**, the oxidation to form ketophosphonate **1.17.1** required extended treatment with PDC. Gratifyingly, after treating aldehyde **5.7.3** with the lithiated methane phosphonate, Dess-Martin oxidation[3] above gave ketophosphonate **4.1.2** in similar yield in 20 minutes.



Scheme 5.8: Synthesis of Ketophosphonate

5.3: Conclusions

An aldol base strategy provided ketone **5.1.3**. A novel cascade desilylation / elimination event was developed to install the C_{26}-C_{44} olefin that had eluded us for the better part of three years. With ketone **5.1.3** in hand, a Luche reduction provided the C_{26} stereocenter and the key ketophosphonate **4.1.2** was prepared in an additional five steps setting the stage for major fragment coupling.

An alternative to the Bayless Hillman reaction was developed for coupling of major fragments. An aldol coupling of Ester **5.1.1** and aldehyde **4.12.2** formed the key carbon carbon bond while a three step procedure installed the C_{26}-C_{44} alkene. This is of great import as the Bayless Hillman is a notoriously slow reaction that often fails to yield product on more complex substrates.

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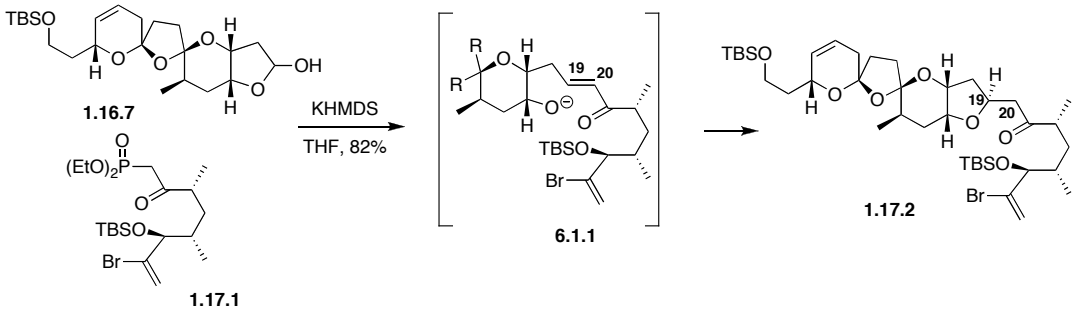
STUDIES TOWARD THE TOTAL SYNTHESIS OF AZASPIRACID 1

CHAPTER 6:

Endgame Strategy and Future Work

6.1: Model Study Toward the Total Synthesis of Azaspiracid

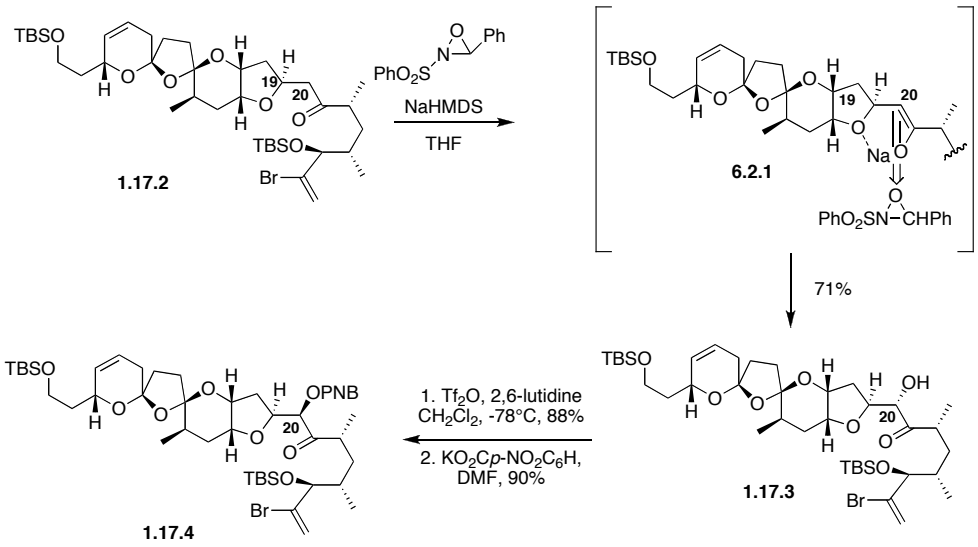
With the ABCD ring system and the ketophosphonate **4.1.2** in hand, we turned our attention to the major fragment coupling. Initial model studies toward the total synthesis were performed to ensure our endgame was viable (Scheme 6.1).[1] During the course of the reaction, one equivalent of the potassium anion of ketophosphonate **1.17.1** deprotonated the lactol **1.16.7** liberating an aldehyde which reacted with a second equivalent of ketophosphonate anion to provide alkene **6.1.1**. However, the resulting alkene **6.1.1** was unstable and a spontaneous hetero-Michael addition provided the D ring and the C_{19} stereocenter in good yield. While this reaction was high yielding, it was less than desirable for our real system. A large excess of ketophosphonate **1.17.1** (7 eq.) was utilized to enact this reactivity. While this was fine on a model system, the use of excessive amounts of precious ketophosphonate **4.1.2** would not be logistically optimal.



Scheme 6.1: Carter's Elaboration of lactol **1.16.7**

With coupled product in hand, the oxidation of C_{20} was investigated (Scheme 6.2). Oxidation of ketone **1.17.2** utilizing Davis' oxazaridine[2] provided alcohol **1.17.2** with high diastereoselctivity, but the wrong stereochemistry as indicated by Moser ester analysis. A model explaining the stereochemistry (**6.2.1**) suggests a six-membered chelation between the enolate and the oxygen of the D ring which blocks the β face leading to reaction from the α face of the enolate. A two-step process was discovered to invert the C_{20} alcohol providing benzoate **1.17.4**

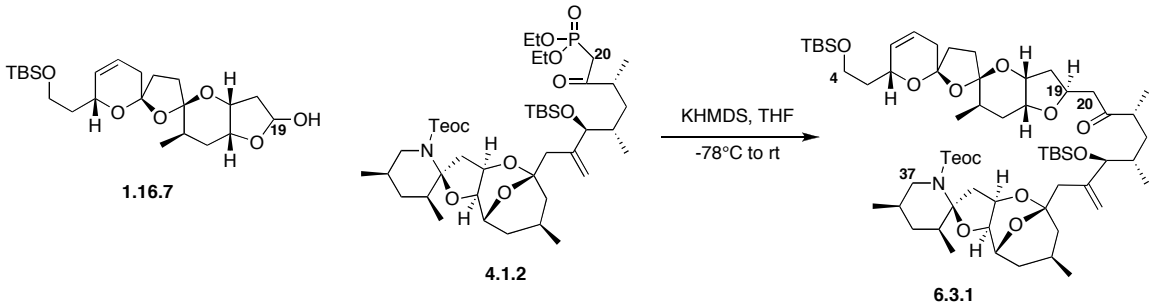
in good yield. With **1.17.4** in hand, an additional six steps would be required to install the side chain and remove the protecting groups.



Scheme 6.2: Model Study Toward Key Tandem HWE Michael Coupling

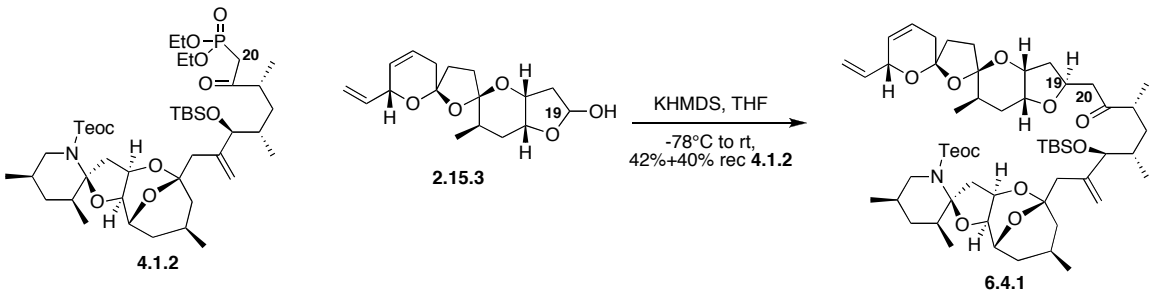
6.2: Coupling of Major Fragments

With ketophosphonate **4.1.2** in hand we proceeded to attempt the coupling with lactone **1.16.7** (Scheme 6.3). With the one milligram provided from our first campaign utilizing the aldol route, we treated 3 equivalents of ketophosphonate **4.1.2** with KHMDS and then treated lactol **1.16.1** with the resulting anion. We were able to recover ~1 mg (~70%) of crude ketone **6.3.1** whose structure was proved by ^{1}H NMR and high-resolution mass spectroscopy. A second experiment in which lactol **1.16.7** was pretreated with KHMDS to expose the aldehyde resulted in decomposition.



Scheme 6.3: Initial Horner-Wadsworth-Emmons Cascade

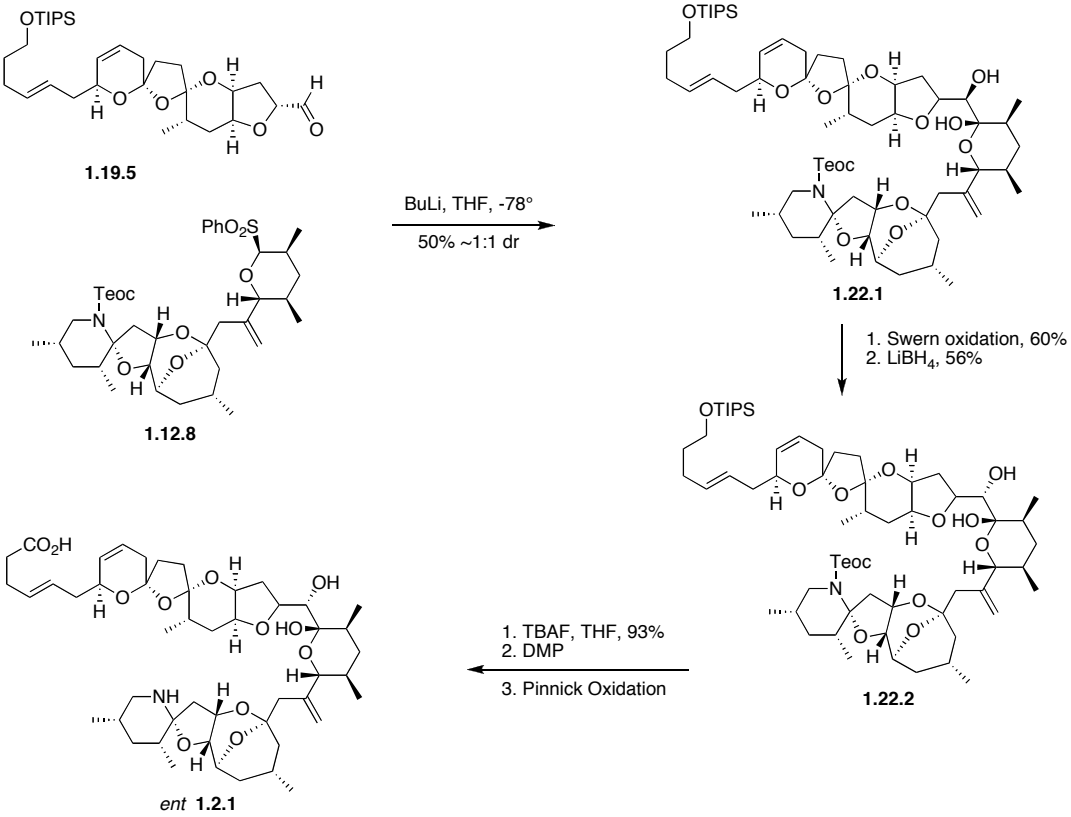
On our second attempt toward the synthesis, it was decided to switch from lactol **1.16.7** to lactol **2.15.3** (Scheme 6.4). This decision was made because it shortened the synthesis by three steps and more importantly limited the number of transformations required on the coupled product. We had postulated that the soft anion of the ketophosphonate deprotonated our lactol, while harder bases destroyed the resulting aldehyde. Testing our hypothesis, we treated lactol **2.15.3** with 1.25 equivalents of ketophosphonate anion to deprotonate the lactol and exposing the resulting aldehyde. After 10 minutes, another equivalent of KHMDS regenerated the ketophosphonate, which then reacted with the exposed aldehyde. To our delight, this approach afforded ketone **6.4.1** as a mixture of rotomers in a modest 42% yield with a majority of the remaining ketophosphonate recovered.



Scheme 6.4: Second Generation Approach to Key HWE Cascade

6.3: Evans' Endgame

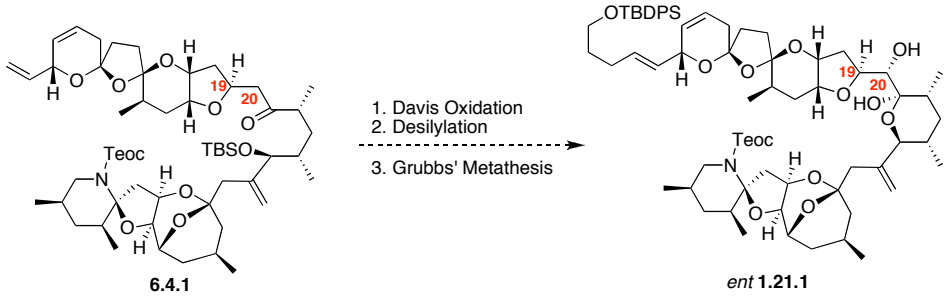
With the limited material afforded, we planned on following Evans' endgame approach (Scheme 6.4).[3] The endgame for the Evans group started with a Julia coupling of aldehyde **1.19.5** and sulfone **1.12.8**. The coupling occurred in a 50% yield in a nearly equimolar mixture of desired C_{20} alcohol **1.22.2** and its C_{20} epimer **1.22.1**. Oxidation of the undesired epimer **1.22.1** under Swern conditions followed by a lithium borohydride reduction provided desired alcohol **1.22.2** in 34% yield from aldehyde **1.19.5**. Treatment of carbamate **1.22.2** with TBAF cleaved the Teoc carbamate and the TIPS ether. Subsequent oxidation of the resulting alcohol to the acid provided *ent* -azaspiracid **1.1.2**.



Scheme 6.5: Evans' Synthesis of Azaspiracid 1 (**1.1.2**)

Based on Evans' approach, we planned a three-step process that would net us a formal synthesis of azaspiracid (Scheme 6.6). First, Davis oxidation of C_{20} would give us the C_{20}

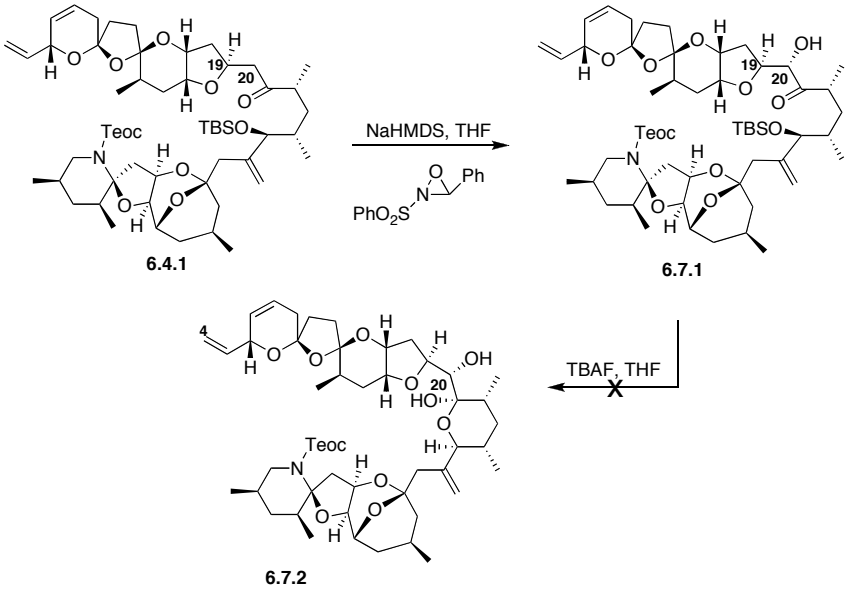
alcohol. Secondly, desilylation would cleave the C_{25} TBS silyl ether and forming the E ring *in situ*. Finally, the sidechain would be appended by olefin metathesis affording *ent*-**1.21.1**. One of the more desirable features of this approach was that, since the Evans group had made both C_{20} diastereomers, synthesis of either would constitute a formal total synthesis.



6.4.1 *ent* **1.21.1**

Scheme 6.6: Planned Endgame to the Formal Synthesis of Azaspiracid

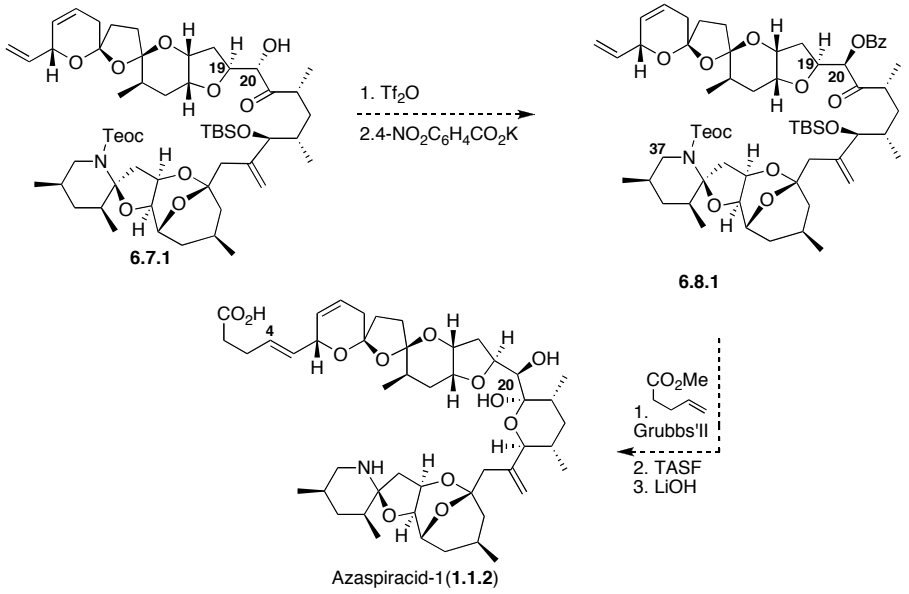
With the ketone **6.4.1** in hand, we next began to execute our endgame toward a formal synthesis (Scheme 6.7). Davis oxidation of ketone **6.4.1** provided three more polar spots by TLC. While both ^{1}H NMR and high-resolution mass spectroscopy suggested the oxidation at C_{20} and that we had made alcohol **6.7.1**, isolation of a single characterized product was unsuccessful. After much discussion, it was decided that desilylation with TBAF would be preformed in hopes of forming the E ring and attaining an isolable product. Unfortunately, upon treatment of purported ketone **6.7.1** with TBAF, complete decomposition was observed.



Scheme 6.7: Davis Oxidation

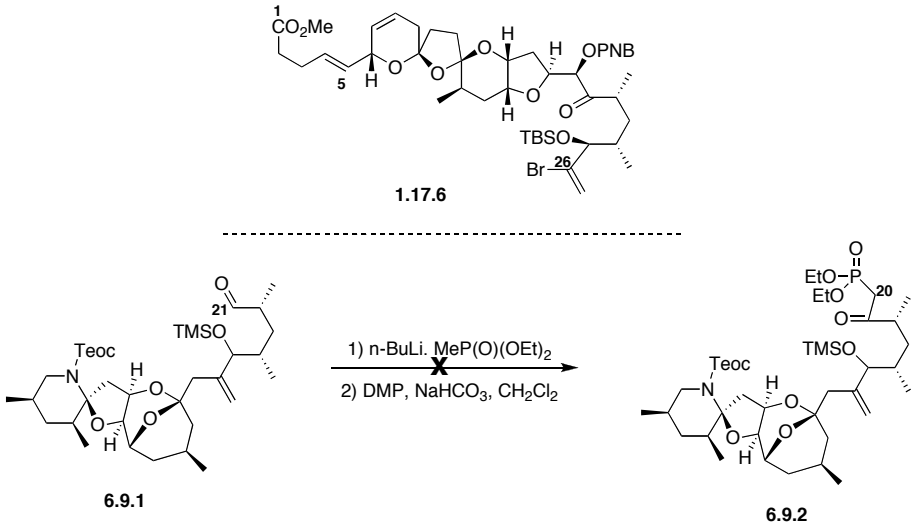
6.4: Future Work

With the preparation of alcohol **6.7.1**, the Carter laboratory is five steps from a total synthesis of azaspiracid (Scheme 6.8). Utilizing the model endgame as a guide, triflation and inversion of the C_{20} alcohol should provide benzoate **6.8.1**. Olefin metathesis should install the sidechain and two deprotection steps would then afford azaspiracid.



Scheme 6.8: Proposed Route to Azaspiracid **1.1.2**

There is potential for problems in this plan, as the desilylation step has still never been successfully done on either a model system or the actual substrate. To test the key desilylation known ester **1.17.6**, or some similar substrate should be prepared and submitted to desilylation conditions to confirm their efficacy. If the TBS silyl ether is incompatible with our techniques, another protecting group must be found. In studies toward an alternative a 1:1 dr mixture of C_{25} TMS ethers were prepared (Scheme 6.9). Unfortunately, the TMS silyl ether was not compatible with our ketophosphonate formation method. A mixture of desilylation product, were observed with little incorporation of the phosphonate observed.



Scheme 6.9: Potential Model Systems

6.5: **Conclusions**

The major fragment coupling was investigated. An effective coupling of near equimolar amounts of ketophosphonate **4.1.2** and lactol **2.15.3** was developed. Oxidation of ketone **6.4.1** was briefly investigated and appeared to work, but unfortunately TBAF desilylation proved to be an ill advised process. The project sits two steps from a formal total synthesis and five steps from a total synthesis of azaspiracid 1.

A unique utilization and regeneration of a ketophosphonate anion as a base for the tandem HWE-Michael addition was developed into a practical reaction even on the smallest of scale.

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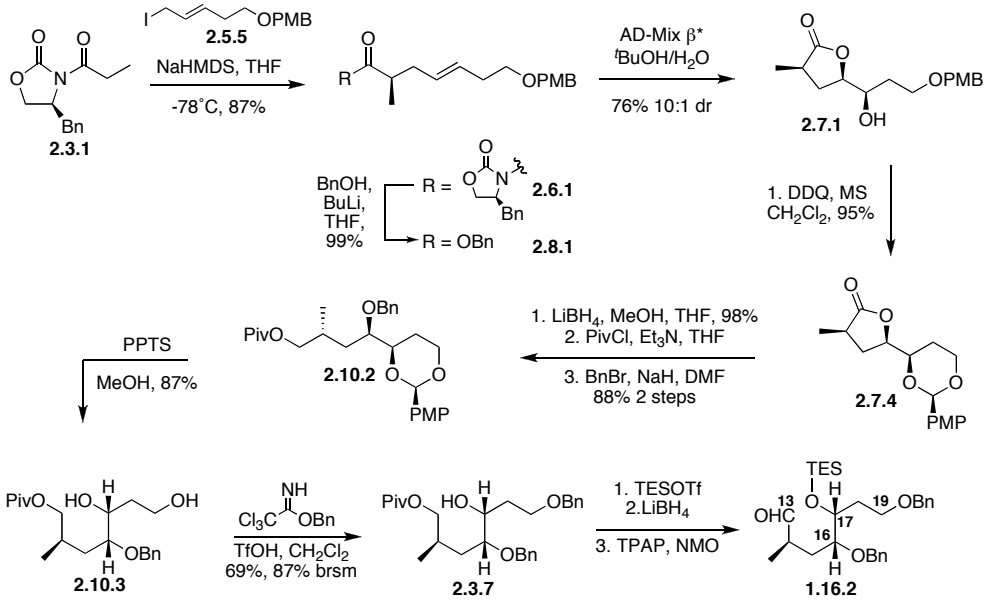
STUDIES TOWARD THE TOTAL SYNTHESIS OF AZASPIRACID 1

CHAPTER 7:

Conclusions

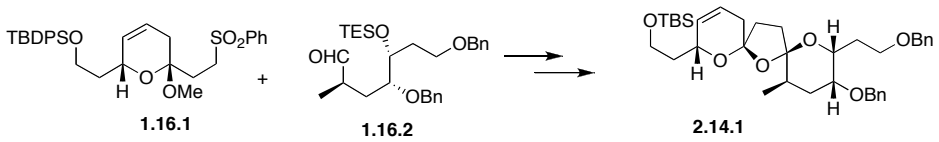
7.1: Improved Synthesis of Aldehyde 1.16.2

While a first generation approach of the C_{13}-C_{19} aldehyde **1.16.2** was reported in 2004, this initial route was plagued by a problematic 1,2-silyl migration. A modified approach involving a PMP acetal would lead to silylation at the C_{16} position last to prevent any silyl migration (Scheme 7.1). To that end, PMB ether allylic iodide **2.5.5** was made in six steps and reacted with the enolate of Evans oxazolidinone **2.3.1** to afford alkylate **2.6.1** in 94% yield. Dihydroxylation of the alkene under modified Sharpless conditions yielded the desired lactone **2.7.1** as an inseparable mix of 8:1 diastereomers and oxazolidinone. Attempts at DDQ-mediated *p*-methoxyphenyl acetal formation on the crude mixture led to an undesirable mix of the acetal **2.7.4** and over-oxidized *p*-methoxybenzoate compounds. Fortunately, after displacement to form the benzyl ester, dihydroxylation proceeded smoothly to give lactone **2.7.1** (76% yield, 10:1 dr). DDQ-mediated acetal formation proceeded smoothly to afford acetal **2.7.4** as a single diastereomer after triteration. Reduction of the lactone with $LiBH_4$, followed by pivalation of the primary alcohol and benzylation of the C_{17} alcohol led to the fully protected C_{13}-C_{19} fragment **2.10.2**. After acidic hydrolysis of acetal **2.10.2**, benzylation of the C_{19} alcohol under acid mediated conditions (2,2,2- trichlorobenzyl acetimidate) led to selective protection of the primary alcohol in good yield (69%, 87% brsm). At this point, our second-generation synthesis had provided known alcohol **2.3.7** which could be transformed to aldehyde **1.16.2** in three known steps.



Scheme 7.1: Synthesis of Aldehyde **1.16.2**

With the improved route a scaled synthesis of bisspiroketal **2.14.1** was within reach (Scheme 7.2). After Julia coupling of aldehyde **1.16.2** and sulfone **1.16.3**, the carbon framework was in place. An additional 6 step netted 250 mg of bisspiroketal **2.14.1**.

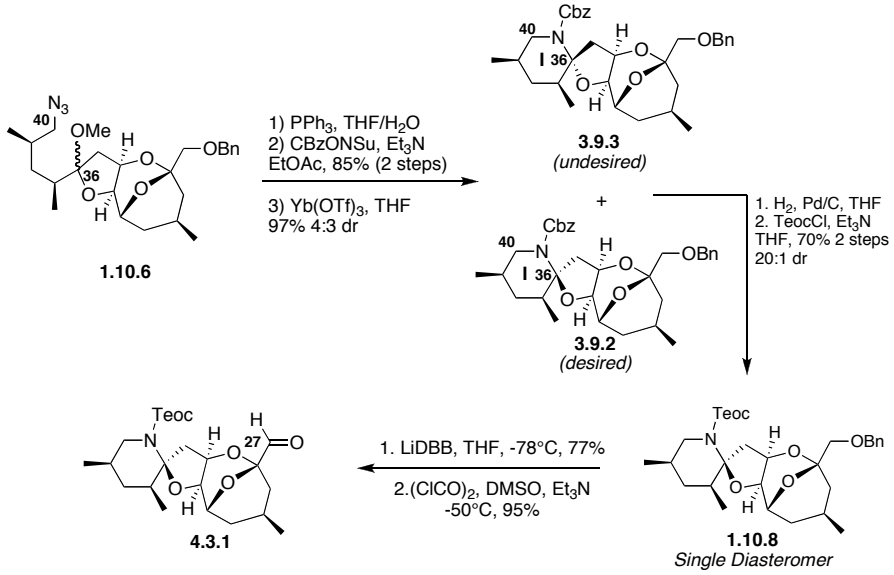


Scheme 7.2: Elaboration of Aldehyde **1.16.2**

7.2: Improved synthesis of the FGHI Spiroaminal

After an initial approach to the FGHI spiroaminal **1.10.2**, we have postulated that the formation of the undesired spiroaminal occurs due to an unfavorable sterric interaction between the Teoc protecting group and the carbon α to the aminal. Upon switching to a Cbz protecting group (Scheme 7.3), cyclization gave aminals **3.9.2** and **3.9.3** in the same 4:3 ratio. Hydrogenolysis of the mixture in THF led to cleavage of the Cbz carbamate in the presence of

the benzyl ether led to a complete equilibration to the desired thermodynamic diastereomer *in situ*. The resulting aminal was then protected immediately to give known tetracycle **1.10.4** in good yield. We then converted benzyl ether **1.10.8** to aldehyde **4.3.1** via LiDBB reduction followed by a Swern oxidation of the resulting alcohol, giving us the appropriate handle for functionalization.

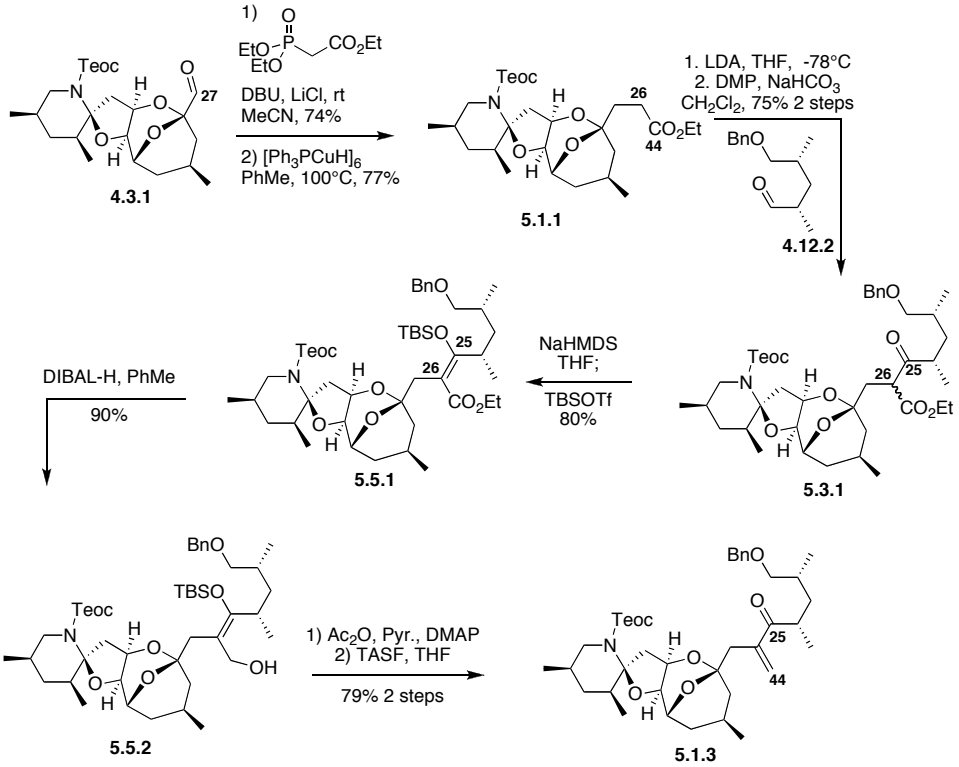


Scheme 7.3: Improved Synthesis of Spiraminal **1.10.2**

7.3: Route to Key Enone 5.1.3

After the initial routes to install the E ring proved ineffective, a host of strategies were explored before finally settling on a strategy utilizing an aldol coupling of ester **5.1.1** and aldehyde **4.12.2** to net us our C-C bond forming reaction (Scheme 7.4). Subsequent olefination, and installation of the stereodefined C_{25} alcohol could net us our E ring in quick succession. Ester **5.1.1** was prepared in two steps via an HWE olefination of aldehyde **4.3.1** followed by a reduction with Stryker's reagent. Aldol coupling proceeded smoothly to provide an inconsequential 5:2:1:1 mixture of aldol adducts, which were oxidized to provide keto ester **5.3.1** solely as the keto tautomer. While 2,6-lutidine enolized **5.3.1** to the enol isomer, it did not facilitate the transformation to the TBS enol ether. Gratifyingly, treatment of ketone **5.3.1**

NaHMDS and TBSOTf led to enol ether **5.5.1**. Reduction with DIBAL-H led to alyllic alcohol **5.5.2**. Acylation of allylic alcohol **5.5.2** followed by TASF-mediated desilylation/elimination sequence gave desired enone **5.1.3** in 79% yield over two steps. This result proved to be a watershed moment in the project, as it provided the first viable route to the elaboration of aldehyde **4.3.1**.

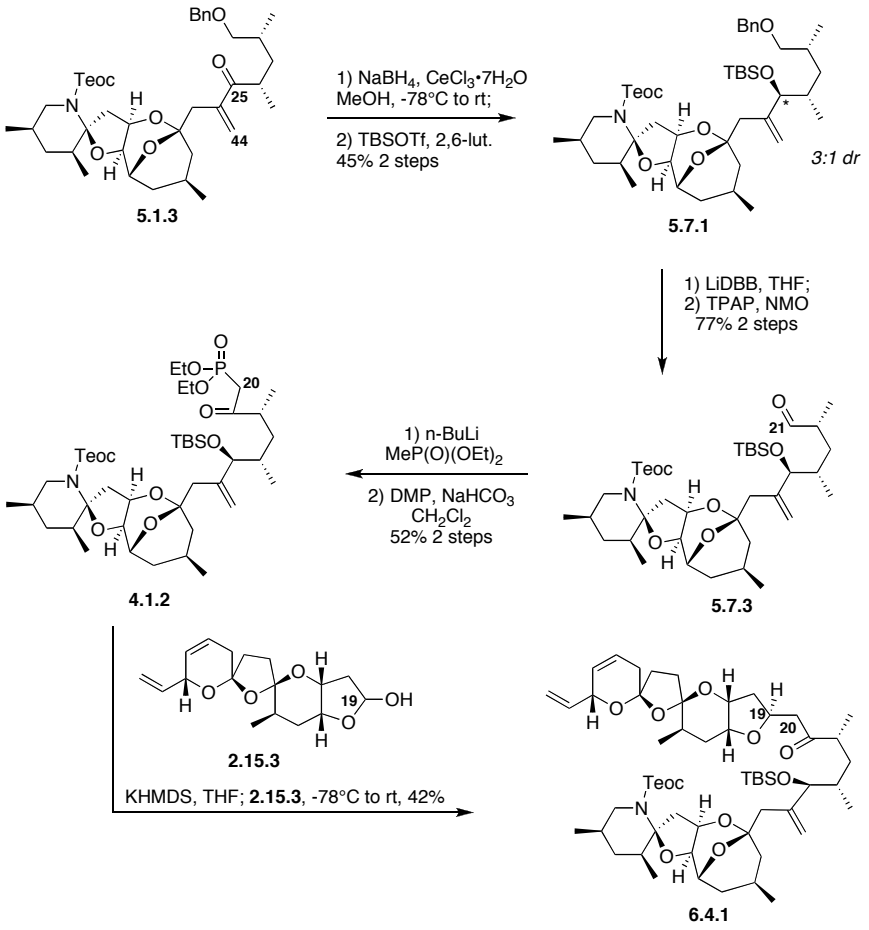


Scheme 7.4: Successful Installation of the C_{26}-C_{44} alkene

7.4: Synthesis of Ketophosphonate and Couping of Major Fragments

With our alkene installed, Felkin reduction of enone **5.1.3** and transformation of the C_{21} benzyl ether to ketophosphonate **4.1.2** were requisite for major fragment coupling (Scheme 7.5). Luche reduction and silylation of enone **5.1.3** provided C_{25} allylic alcohol silyl ether **5.7.1** in modest yield. LiDBB mediated debenzylation and TPAP oxidation of the resulting alcohol gave aldehyde **5.7.3** in good yield. Addition of the lithium anion of methyl phosphonate to aldehyde **5.7.3** followed by DMP oxidation gave key keto phosphonate **4.1.2**. Treatment of the potassium

anion phosphonate **4.1.2** with lactol **2.15.3** led first a deprotonation of lactol **2.15.2** liberating the aldehyde, which would react with the phosphonate to give an enone. An *in situ* Michael addition formed the D ring providing ketone **6.4.1** as the coupled product in greater than in greater then 80% yield based on recovered ketophosphonate.

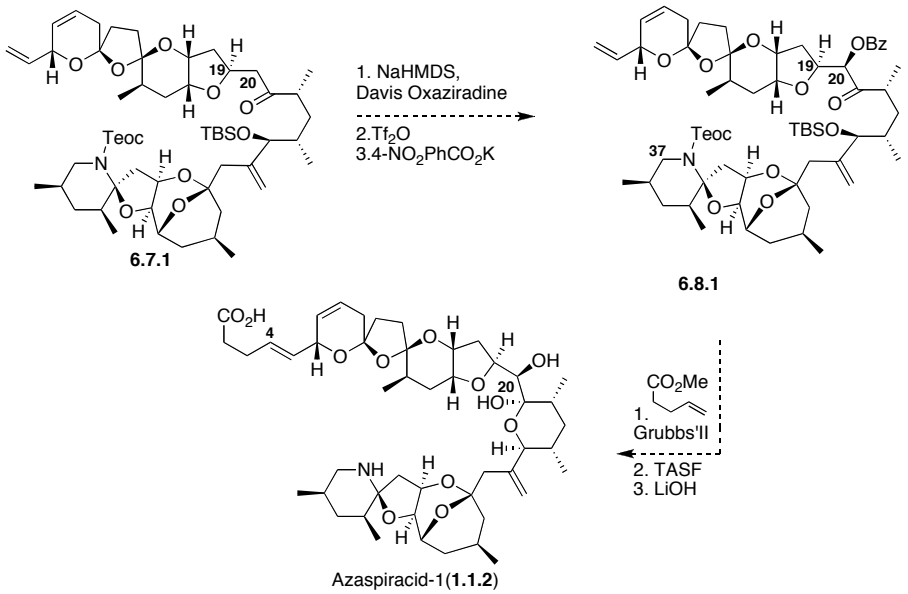


Scheme 7.5: Major Fragment Coupling

7.5: Conclusion

This step served as the coupling of the major fragments and the high water point in the project. After losing the limited material made, there are six steps involving oxidation at C_{20}, inversion of the C_{20} stereocenter, appending the sidechain and deprotection required to afford azaspiracid-1. Following an end game worked out in our lab on a model system with the

prescident set by the Nicolaou and Evans synthesis, the synthesis of azaspiracid should be possible.



Scheme 7.6: Future Route

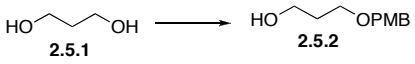
A series of new chemistries have been developed during the efforts toward the total synthesis of Azaspiracid-1. An effective equilibration of the kinetic cisoidal bisspiroketal **1.16.5** to transoidal bisspiroketal **1.16.4** was developed to promote a highly scalable synthesis of the ABC bisspiroketal. An interesting muting of the anomeric effect for the formation of spiroaminals **1.10.8** and **3.9.2** were observed. A route based upon liberating the free spiroaminal **3.8.1** to allow for equilibration were highly successful, allowing for a scalable synthesis of the FGHI ring system of azaspiracid-1. An alternative to the Bayless Hillman reaction was developed for coupling of major fragments. An aldol coupling of Ester **5.1.1** and aldehyde **4.12.2** formed the key carbon carbon bond while a three step procedure installed the C_{26}-C_{44} alkene. The major fragment coupling was investigated. An effective coupling of near equimolar amounts of ketophosphonate **4.1.2** and lactol **2.15.3** was developed. The unique utilization and regeneration of a ketophosphonate anion as a base for the tandem HWE-Michael addition proved successful.

STUDIES TOWARD THE TOTAL SYNTHESIS OF AZASPIRACID 1

CHAPTER 8:

Experimental Section

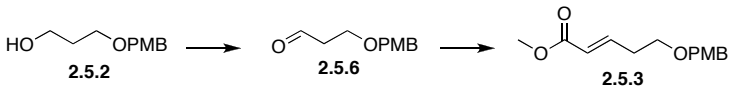
General: Infrared spectra were recorded neat unless otherwise indicated and are reported in cm^{-1}. ^1H NMR spectra were recorded in deuterated solvents and are reported in ppm relative to tetramethyl silane and referenced internally to the residually protonated solvent. ^{13}C NMR spectra were recorded in deuterated solvents and are reported in ppm relative to trimethylsilane and referenced internally to the residually protonated solvent. Optical rotations were recorded using a sodium lamp at 589 nm in $CHCl_3$. Routine monitoring of reactions was performed using EM Science DC-Alufolien silica gel, aluminum-backed TLC plates. Flash chromatography was performed with the indicated eluents on EM Science Gedurian 230-400 mesh silica gel. Air and / or moisture sensitive reactions were performed under usual inert atmosphere conditions. Reactions requiring anhydrous conditions were performed under a blanket of argon, in glassware dried in an oven at 120°C or by a bunsen flame, then cooled under argon. Solvents and commercial reagents were purified via Glass Contour® Solvent Purification Systems (SPS), in accord with Perrin and Armarego[1] or used without further purification.



2.5.1 **2.5.2**

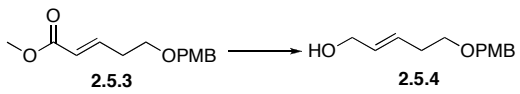
Alcohol 2.5.2: To a stirred solution of 1, 3-propanediol (**2.51**) (121 g, 115 mL, 1.595 mol, 5 eq.) in THF (600 mL) at 0^oC was added sequentially paramethoxybenzyl chloride (50 g, 43.5 mL, 319 mmol, 1eq.), tetrabutyl ammonium iodide (11.8 g, 32 mmol, 0.1 eq.), sodium hydride (12.8 g, 319 mmol, 60% dispersion in mineral oil, 1 eq.). After 20 min, reaction was warmed to rt and stirred overnight. The solution was quenched with sat. aq. ammonium chloride (100 mL) and extracted with EtOAc/Et_2O (1:1) (4 x 300 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10-40% EtOAc / hexanes, to give alcohol **2.5.2** (58.6 g, 299 mmol, 94%) as a colorless oil: IR (neat) 3400, 2936, 2864, 1513, 1090, 1034, 820 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27–7.31 (m, 2H), 6.89–6.94 (m, 2H), 4.49 (s, 2H) 3.86 (s, 3H), 3.81 (t, *J* = 5.6 Hz, 2H), 3.68 (t, *J* = 5.8 Hz, 2H), 1.90 (quin, *J* = 5.7 Hz, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 130.2, 129.3, 113.9, 72.9, 69.0, 61.7, 52.3, 32.1. (B3P61, CAS# 135362-69-5)[2]



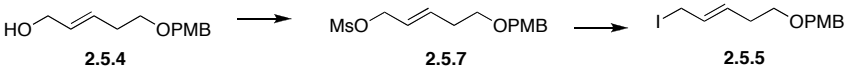
Ester 2.5.3: A solution of oxalyl chloride (2.7 g, 1.86 mL, 21.6 mmol, 1.1 eq.) in CH_2Cl_2 (10 mL) at -50°C was charged carefully with DMSO (18.46 g, 16.7 mL, 43.1 mmol, 2.2 eq.). After 10 min, a solution of alcohol **2** (3.85 g, 19.6 mmol, 1 eq.) in CH_2Cl_2 (40 mL, 2 x 5 mL rinses) was added *via* cannula . After 15 min, triethylamine (6.92 g, 9.6 mL, 68.6 mmol, 3.5 eq.) was added dropwise. After 10 min, the reaction was allowed to warm to 0°C over 30 min, then was quenched with water (50 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and used without further purification.

Crude aldehyde **2.5.6** (19.6 mmol) was diluted in CH_2Cl_2 (20 mL) and then charged with $Ph_3P{=}CHCO_2Me$ (7.2 g, 21.6 mmol). After 18 h, the reaction was concentrated *in vacuo* then diluted in 20% EtOAc / hexanes (20 mL). The suspension was filtered and rinsed with 20% EtOAc / hexanes (60 mL). Mother liquor was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 5-30% EtOAc / hexanes, to give ester **2.5.3** (4.42 g, 16.4 mmol, 85%) as a colorless oil: IR (neat) 2950, 2851, 1724, 1659, 1467, 1248, 1173, 1096, 1035, 980, 821, 757 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.39 (m, 2H), 7.01 (dt, *J* = 15.7, 6.9 Hz , 1H) 6.89–6.94 (m, 2H), 5.89 (d, *J* = 5.9 Hz, 1H), 4.49 (s, 2H), 3.85 (s, 3H), 3.76 (s, 3H), 3.59 (t, *J* = 6.4 Hz , 2H), 2.53 (dq, *J* = 6.4, 0.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 159.2, 146.6, 130.2, 129.3, 122.4, 113.8, 72.4, 68.0, 55.3, 51.5, 32.7 (B2P76, CAS# 201667-72-3)[3]



2.5.3 2.5.4

Alcohol 2.5.4: A stirred solution of ester **2.5.3** (1.6 g, 6.03 mmol, 1 eq.) in CH_2Cl_2 (36 mL) at -78°C was charged with DIBAL-H (12.6 mL, 12.6 mmol, 2.09 eq.,1 M in CH_2Cl_2). After 1 h, the reaction was allowed to warm to rt. After 1 h, the reaction was quenched with aq. sodium tartrate solution (100 mL, 10%) and stirred vigorously. After 3 h, the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 20-50% EtOAc / hexanes, to give allylic alcohol 2.5.4**4** (1.377 g, 5.7 mmol, 95%) as a colorless oil: IR (neat) 3406, 2934, 2858, 1514, 1464, 1361, 1248, 1096, 1034, 972, 820 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27–7.32 (m, 2H), 6.89-6.94 (m, 2H), 5.73-5.78 (m, 2H), 4.48 (s, 2H), 4.13 (m, 2H), 3.84 (s, 3H), 3.52 (t, *J* = 6.7 Hz, 2H), 2.37-2.43 (m, 2H), 1.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 131.0, 130.4, 129.4, 129.2, 72.6, 69.3, 63.5, 55.3, 32.7. (B3P81, CAS# 158817-21-1)[3]

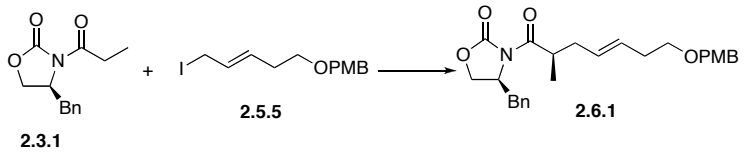


2.5.4 2.5.7 2.5.5

Iodide 2.5.5: A stirred solution of alcohol **2.5.4** (13 g, 54 mmol, 1 eq.) in CH_2Cl_2 (200 mL) at 0°C was charged sequentially with Et_3N (8.1 g, 11.3 mL, 8 mmol, 1.5 eq.) and MsCl (7.44 g, 5 mL, 65 mmol, 1.2 eq.). After 30 min, the reaction was quenched with sat. aq. ammonium chloride (100 mL). The solution was extracted with Et_2O (3 x 100 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and run through a silica gel plug, eluting with 30-50% EtOAc / hexanes, to give mesylate **2.5.7** (17.1 g, 53.5 mmol, 99%) as a colorless oil, which was very unstable: ^1H NMR (400 MHz, $CDCl_3$) δ 7.24-7.32 (m, 2H), 6.88-6.94 (m, 2H) 6.05-5.70 (m, 2H), 4.72 (d, *J* = 6.8Hz, 2H) 4.45 (s, 2H), 3.84 (s, 3H), 3.52 (t, *J* = 6.4 Hz, 2H) 2.97 (s, 3H) 2.43 (q, *J* = 6.3Hz, 2H);

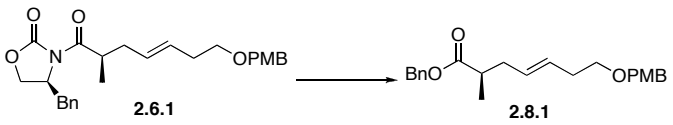
^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 136.4, 130.2, 129.4, 124.0, 113.8, 72.7, 70.8, 68.6, 55.3, 38.3, 32.7. (B3P96)

A stirred solution of mesylate **2.5.7** (17 g, 53 mmol, 1 eq.) in DMF (150mL), wrapped in foil, was charged with NaI (24 g, 160 mmol, 3 eq.). After 30 min, the reaction was quenched with sat. aq. ammonium chloride (25 mL) and extracted with ether (3 x 100 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* in the absence of light and run through a silica gel plug, eluting with 20% EtOAc / hexanes, to give crude iodide **2.5.5** (15 g, 42.9 mmol, 80%) as aN unstable pale yellow oil: IR (neat) 2933, 2855, 1513, 1248, 1173, 1053, 965, 820 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.32 (m, 2H), 6.88-6.94 (m, 2H) 5.70-5.2 (m, 2H), 4.47 (s, 2H), 3.89-3.96 (m, 2H), 3.84 (s, 3H) 3.48-3.58 (m, 2H), 2.34-2.48 (m, 2H). (B3P97)

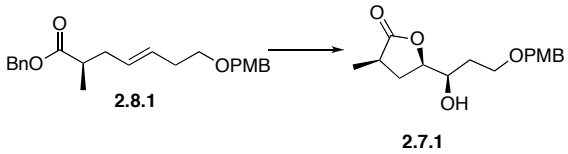


Alkylation adduct 2.6.1: To a stirred solution oxazolidinone **2.3.1** (4.3 g, 18.3 mmol, 1 eq.) in THF (10 mL) at -78^{o}C was charged with NaHMDS (22 mL, 22 mmol, 1 M in THF, 1.2 eq.). After 20 min, iodide **2.5.5** (11.5 g, 32.9 mmol, 1.8 eq.) was added *via* cannula as a solution in THF (10 mL solution, 2 x 4 mL rinse). After 3 h, the reaction was quenched with sat. aq. ammonium chloride (100 mL) and was extracted with EtOAc (3 x 100 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 5-40% EtOAc / hexanes, to give product **9** (7.9 g, 17.3 mmol, 94%) as a colorless oil: $[\alpha]_D^{23}$ +12.0° (c = 1.0, $CHCl_3$); IR (neat) 2933, 2855, 1778 1698, 1245 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.40 (m, 7H), 6.86-6.92 (m, 2H), 5.56-5.58 (m, 2H), 4.6-4.74 (m, 1H), 4.42-4.49 (m, 2H), 4.16-4.24 (m, 2H), 3.83 (s, 3H), 3.48 (t, = 6.9 Hz, 2H) 3.31 (dd, *J* = 13.2, 3.1 Hz, 1H), 2.70 (dd, *J* = 9.1, 7.5 Hz, 1H) 2.46-2.54 (m, 1H), 2.30-2.38 (m, 2H), 2.17-2.26 (m, 2H), 1.20 (d, *J* = 6.8 Hz , 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 159.1, 153.1, 135.4, 130.6, 129.5, 129.45, 129.42,

129.3, 129.0, 128.6, 127.3, 113.8, 72.5, 69.7, 66.0, 55.4, 55.3, 38.1, 37.6, 36.9, 33.0, 16.4 HRMS (CI+) Calcd. for $C_{26}H_{31}NO_5$ (M+) 437.2202, Found 437.2193. (B2P83)

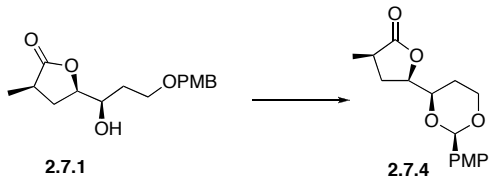


Benzyl Ester 2.8.1: A stirred solution of benzyl alcohol (3.7 g, 4 mL, 34.6 mmol, 2 eq.) in THF (30 mL) at 0°C was charged with n-butyl lithium (13.15 mL, 32.9 mmol, 2.5 M in hexanes, 1.9 eq.). After 10 min, alkylate **2.6.1** (7.9 g, 17.3 mmol, 1 eq.) in THF (10 mL, 10 mL rinse) was added *via* cannula. After 30 min, the reaction was quenched with sat. aq. ammonium chloride (50 mL). The solution was extracted with EtOAc (3 x 100 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 3-50% EtOAc / hexanes, to give benzyl ester **2.8.1** (6.1 g, 17.3 mmol, 99%) as a colorless oil: $[\alpha]_D^{23}$ +7.1° (c = 0.9, $CHCl_3$); IR (neat) 2933, 2851, 2356, 2339,1733, 1247 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 –7.27 (m, 7H), 6.89-6.94 (m, 2H), 5.44- 5.51 (m, 2H), 5.13 (s. 2H), 4.45 (s, 2H), 3.84 (s, 3H), 3.45 (t, *J* = 6.9 Hz, 2H), 2.50-2.55 (m, 1H), 2.40-2.50 (m, 2H), 2.28-2.35 (m, 2H), 2.18-2.25 (m, 1H), 1.85 (d, *J* = 6.8 Hz, 3H) ^{13}C NMR (100 MHz, $CDCl_3$) d 176.0, 159.2, 130.6, 129.3, 128.7, 128.6, 128.2, 128.1, 128.0, 113.8, 72.5, 66.1, 55.3, 39.6, 36.7, 33.0, 31.3, 28.0, 16.5; HRMS (CI+) Calcd. for $C_{23}H_{28}O_4$ (M+) 368.1987, Found 368.1975.(B2P84)



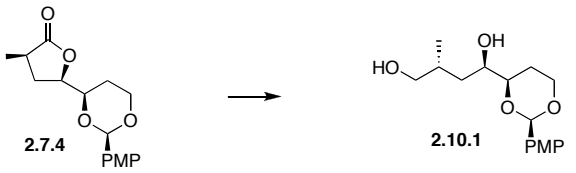
Lactone 2.7.1: To a vigorously stirred solution of ester **2.8.1** (1.8 g, 5.1 mmol, 1 eq.) in t-butanol / H_2O (1:1, 51 mL) were added sequentially $NaHCO_3$ (3.2 g, 22.5 mmol, 4.4 eq.), methane sulfonamide (0.48 g, 5.1 mmol, 1 eq.) and AD Mix β* (7.2 g).[4] After 24 h, the reaction was

quenched with sat. aq. $Na_2S_2O_3$ (20 mL) until effervescence stopped (~ 10 min). The solution was then diluted in brine (50 mL) and extracted with EtOAc (4 x 150 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 3-50% EtOAc / hexanes, to give lactone **11** (1.19 g, 3.86 mmol, 76%, dr 10:1) as a colorless oil: $[\alpha]_D^{23}$ -47.5° (c = 2.4, $CHCl_3$); IR (neat) 3462, 293, 2868, 1768, 1531, 1247 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25-7.40 (m, 2H), 688-6.94 (m, 2H), 4.49 (s, 2H), 4.25-4.35 (m, 1H), 3.83 (s, 3H), 3.76- 3.67 (m, 2H), 2.65-2.75 (m, 1H), 2.39-2.45 (m, 1H), 1.88-1.78 (m, 3H) 1.31 (d, *J* = 7.0Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 179.5, 159.2, 130.1, 129.4, 113.9, 113.8, 81.0, 72.9, 71.1, 67.1, 55.3, 43.3, 32.5, 32.3, 15.1; $CHCl_3$ HRMS (CI+) Calcd. for $C_{16}H_{22}O_5$ (M+) 294.1461, Found 294.1467. (B2P33)

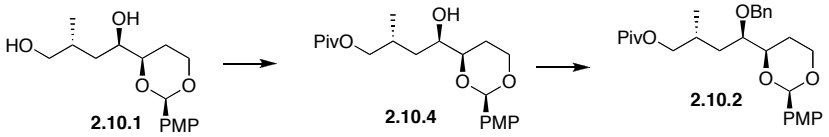


PMP Acetal 2.7.4: To a stirred suspension of lactone **2.7.1** (3 g, 9.7 mmol, 1 eq.), powdered 4Å molecular sieves (2.6 g) in CH_2Cl_2 (65 mL) at 0°C was added DDQ (2.3 g, 10.2 mmol, 1.05 eq.) in three portions over 25 min. After 2 h, the reaction was filtered through a pad of Celite® and rinsed with CH_2Cl_2 (3 x 20 mL) then quenched with deionized water (30 mL) and extracted with CH_2Cl_2 (6 x 100 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by triteration with Et_2O to give acetal **2.7.4** (2.84 g, 9.3 mmol, 95% single diastereomer) as an off white solid: Mp: 124-126°C; $[\alpha]_D^{23}$ -5.2°, (c = 1.1, $CHCl_3$); IR (neat) 2963, 2884, 1767, 1099 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.45 (m, 2H), 6.88-6.95 (m, 2H), 5.51 (s, 1H), 4.40-4.49 (m, 1H), 4.28-4.39 (m, 1H), 3.95-4.05 (m, 1H) 3.83 (s, 3H), 2.60-2.78 (m, 1H), 2.41 (dq, *J* = 8.9, 6.2 Hz, 1H), 2.05 (dq, *J* = 12.3, 5.1 Hz 1H), 1.83 (dq, *J* = 10.4, 1.1 Hz, 3H), 1.45-1.55 (m, 1H), 1.31 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.0, 160.0, 130.7, 127.5, 113.6,

101.2, 78.9, 77.4, 55.3, 35.1, 31.6, 26.0, 15.2; HRMS (CI+) Calcd. for $C_{16}H_{21}O_5$ (M+) 293.1382, Found 293.1389. (B4P13)

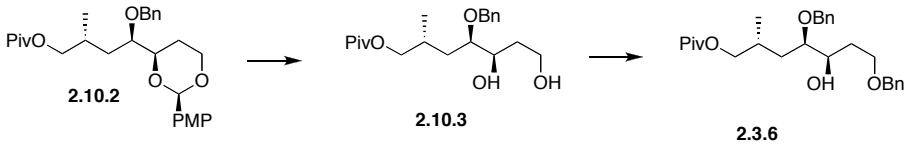


Diol 2.10.1: A stirred suspension of $LiBH_4$ (87 mg, 3.9 mmol, 3 eq.) in THF (6 mL) was charged with methanol (128 mg, 160 μL, 3.8 mmol). After 30 min, the suspension was cooled to -10°C and acetal **2.7.4** (400 mg, 1.3 mmol) in THF (6 mL, 2 x 2 mL rinse) was added *via* cannula and the reaction was warmed to rt. After 4 h, the reaction was quenched with the addition of a pH 7 buffer solution (20 mL) and extracted with Et_2O (4 x 60 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 20-50% EtOAc / hexanes, to give diol **2.10.1** (394 mg, 1.27 mmol, 98%) a white solid: Mp: 124-126°C; $[\alpha]_D^{23}$ +56.0° (c=1, $CHCl_3$); IR (neat) 3385, 2958, 2930, 2856, 1101, 1032 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32-7.42 (m, 2H), 6.88-6.96 (m, 2H), 5.49 (s, 1H), 4.31(dd, *J* = 12.6 Hz, 1H), 3.99 (dt, *J* = 12.2 Hz, 1H) 3.80 (s, 3H), 3.60-3.80 (m, 2H), 3.55 (dd, *J* = 10.9, 4.6 Hz, 1H), 3.45 (dd, *J* = 10.9, 7.0Hz, 1H), 3.05 (brS, 1.2H), 1.79-1.93 (m, 2H), 1.45-1.58 (m, 2H), 1.35-1.45 (m, 1H), 0.98 (d, *J* = 5.1 Hz, 3H), (75 MHz, $CDCl_3$) δ 160.5, 130.8, 127.4, 113.6, 101.2, 80.4, 72.7, 68.6, 66.5, 55.1, 37.0, 33.8, 27.0, 17.5; HRMS (CI+) Calcd. for $C_{16}H_{25}O_5$ (M+) 297.1702, Found 297.1703. (B4P13)



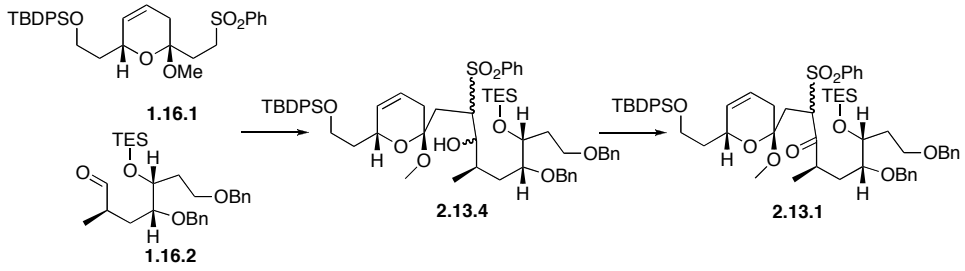
Pivalate 2.10.2: To a stirred solution of diol **2.10.1** (501 mg, 1.27 mmol, 1 eq.) in CH_2Cl_2 (8 mL) was sequentially added DMAP (15.5 mg, 0.127 mmol, 0.1 eq.) and Et_3N (160 mg, 220 μL, 1.59 mmol, 1.25 eq.). The solution was cooled to -78°C and PivCl (183 mg, 190 μL, 1.53 mmol, 1.2 eq.) was added. After 30 min, the reaction was allowed to warm to 0°C over a period of 1 h. The reaction was then quenched with with sat. aq. ammonium chloride (50 mL) and extracted with EtOAc (3 x 100 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10-40% EtOAc / hexanes, to give pivalate **2.10.4** a colorless oil (888 mg, 10:1 dr) that was used without further purification.

To a stirred solution of pivolate **2.10.4** (1.362 g, 34.6 mmol, 1 eq.) in DMF (6 mL) was added sequentially NaH (1.6 g, 41.5 mmol, 1.2 eq., 60% dispersion in mineral oil) and benzyl bromide (17.8 g, 12.4 mL, 30 eq.). After 4 h, the reaction was quenched with addition of sat. aq. ammonium chloride (200 mL) and was extracted with Et_2O (4 x 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 0-30% EtOAc / hexanes, to give pivalate **2.10.2** (1.112 g, 2.3 mmol, 66% over 2 steps) as a colorless oil: $[\alpha]_D^{23}$ +53.5° (c=0.4, $CHCl_3$); IR (neat) 2963, 2934, 2871, 1726, 1105, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.45 (m, 2H), 7.20-7.30 (m, 5H), 6.89-6.94 (m, 2H), 5.53 (s, 1H), 4.6-4.9 (m, 2H), 4.30-4.34 (dd, *J* = 11.3 and 3.8 Hz, 1H), 4.05 (ddd, *J* = 11.4, 5.8, and 2.3 Hz, 1H), 3.9-4.0 (m, 3H), 3.30 (s, 3H), 3.66-6.70 (m, 1H), 2.1-2.2 (m, 1H) 1.89 (qd *J* = 4.7 and 12.3Hz, 1H), 1.64-1.71 (ddd *J* = 24, 14, and 4 Hz, 1H) 1.50-1.55 (m, 1H) 1.37-1.43(ddd, *J* = 12.8, 9.8, and 2.8 Hz, 1H) 1.24 (s, 6H), 0.92 (d, *J* = 6.7 Hz, 3H); (100 MHz, $CDCl_3$) δ 178.5, 159.9, 138.7, 131.2, 128.3, 127.9, 127.8, 127.6, 127.3, 113.5, 101.1, 79.4, 78.3, 73.3, 69.6, 66.9, 55.3, 38.9, 22.7, 29.2, 27.2, 26.5, 16.; HRMS (FAB+) Calcd. for $C_{28}H_{39}O_6$ (M+) 471.2747, Found 471.2766. (B3P27)



Alcohol 2.3.6: To a stirred solution of acetal **2.10.2** (100 mg, 206 μmol, 1 eq.) in methanol (2 mL) was added PTSA (40 mg, 206 μmol, 1eq.). After 10 h, the reaction was quenched with addition of $NaHCO_3$ (100 mg). The slurry was stirred for 10 min, filtered, concentrated *in vacuo*, and purified by chromatography over silica gel, eluting with 0-60% EtOAc / hexanes giving diol **2.10.3** (66 mg, 180 μmol, 87%).

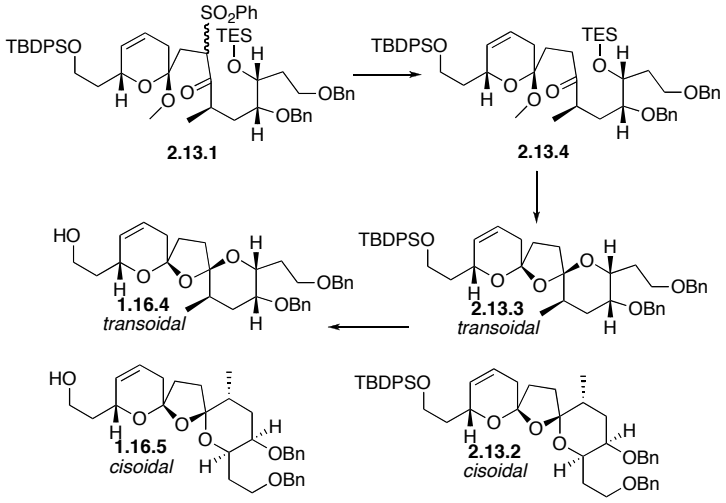
To a stirred solution of alcohol **2.10.3** (50 mg, 137 mmol, 1 eq.) in CH_2Cl_2 (1.5 mL) was added benzyl 2,2,2-trichloroacetimidate (35.6 mg, 26 μL, 1 eq.) and trifluromethanesulfonice acid (1 drop). After 2 h, and again after 3 h, an equivalent of imidate was added. After 5.5 h, the reaction was quenched with sat. aq. $NaHCO_3$ (20 mL), and extracted with CH_2Cl_2 (4 x 20 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 0-30% EtOAc / hexanes, to give known alcohol **2.3.6**[5] (43 mg, 95 μmol, 69%, 87% brsm) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.38 (m, 10H), 4.63 (s, 2H), 4.55 (s, 2H), 3.88–3.99 (m, 3H), 3.73–3.78 (m, 1H), 3.65–3.68 (m, 1H), 3.49–3.55 (m, 1H), 2.88 (d, J = 4.0 Hz, OH), 2.01–2.06 (m, 1H), 1.81–1.86 (m, 2H), 1.65–1.72 (m, 1H), 1.43–1.49 (m, 1H), 1.23 (s, 9H), 0.96 (d, J = 6.8 Hz,3 H). (B3P27)



Ketone Sulfone 2.13.1: To a stirred solution of sulfone **1.16.1** (1.0 g, 1.7 mmol) in THF (11 mL) at –78°C was added lithium 2,2,6,6-tetramethylpiperidine[6] (1.7 mL, 1.7 mmol, 1.0 M in THF) dropwise. After 25 min, a solution of the aldehyde **1.16.2** (300 mg, .637 mmol) in pre-cooled THF (1.0 mL) was added *via* cannula to the sulfone solution. After 25 min, the reaction was removed from the cooling bath, quenched with sat. aq. NH_4Cl (15 mL) and extracted with EtOAc (4 X 50 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* to give crude hydroxy sulfone **2.13.4**. The crude hydroxy sulfone **2.13.4** was used next step immediately.

To a stirred solution of crude hydroxy sulfone **2.13.4** (0.637 mmol) in CH_2Cl_2 (6.4 mL) were sequentially added powdered 4 Å mol. sieves (1 g), TPAP (223 mg, 0.635 mmol) and NMO (223 mg, 1.9 mmol). After 3 h, the reaction was diluted with 25 % EtOAc / hexanes, filtered through a small plug of silica gel, concentrated in *vacuo* and purified by chromatography over silica gel, eluting with 10-40% EtOAc / hexanes, to give ketone sulfone **2.13.1** (500 mg, 78% over two steps) as a colorless oil: IR (neat) 2955, 2880, 1844, 1696, 1570, 1309, 1090, 732, 703; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.77 (m, 25H), 5.49-5.63 (m, 2H), 4.17-4.72 (m, 7H), 3.76-3.84 (m, 1H), 3.41-3.71 (m, 4H), 3.2 2-3.30 (m, 1H), 3.15 (s, 3H of a diastereomer), 2.90 (s, 3H of a diastereomer), 2.41-2.50 (m, 1H), 1.46-2.22 (m, 12H), 1.04 (s, 9H of a diastereomer), 1.01 (s, 9H of a diastereomer), 0.92-0.96 (m, 9H), 0.56-0.62 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.2, 139.2, 136.0, 134.5, 134.2, 130.0, 129.4, 129.1, 129.0, 128.9, 128.7, 128.4, 128.2, 128.1, 127.9, 127.8, 121.2, 98.1, 79.8, 73.1, 73.0, 72.7, 69.0, 68.0, 67.4, 66.0, 60.2, 48.8, 45.2, 38.2, 31.6,

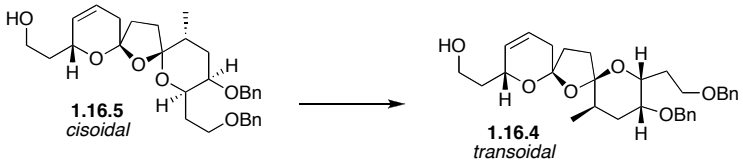
30.7, 27.2, 19.6, 15.0, 7.4, 5.4; HRMS (FAB^+) calcd. for $C_{60}H_{80}O_9SSi_2Na$ (M+Na) 1055.4959, found 1055.4915. (B5P51)



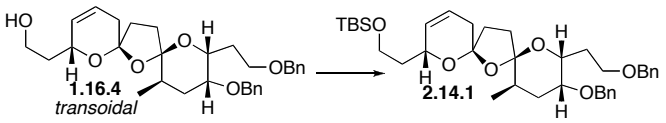
Spirocycle 2.13.3 and 3.13.2: To a stirred solution of ketosufone **2.13.1** (500 mg, .48 mmol) in THF (9.6 mL) and MeOH (32 mL) at –10°C was added Na_2HPO_4 (491 mg, 3.5 mmol). After 5 min, 5% Na / Hg amalgam (2.7 mg, 5.8 mmol, 5% in Hg) was added. After 1 h, the reaction was diluted with 20% EtOAc / hexanes, filtered through a small plug of silica gel and concentrated in *vacuo* to give crude ketone **2.13.4** which was used next step without further purification.

To a stirred solution of ketone **2.13.4** (0.48 mmol) in THF/H_2O (24 mL, 4 : 1) was added PPTS (120 mg, 0.48 mmol). After 18 h, the solution was quenched with saturated $NaHCO_3$ (20 mL) and extracted with EtOAc (3 x 50 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified chromatography over silica gel, eluting with 5-20% EtOAc / hexanes, to give two bisspiroketals **2.13.3** and **2.13.2** (330 mg, 0.45 mmol. 93%, 2.5:1 *transoidal/cisoidal*) as a colorless oil.

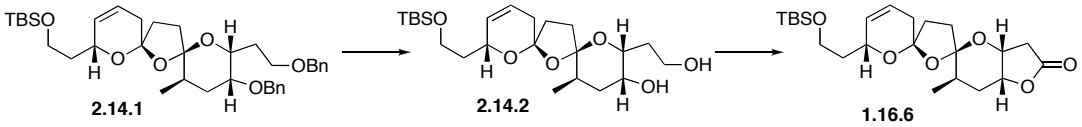
***Cis* spiroketal 1.16.5 and *trans* spiroketal 1.16.4:** To a solution of **2.13.3** and **2.13.2** (260 mg, 0.48 mmol) in THF (1.5 mL) was added TBAF (4.8 mL, 4.8 mmol, 1.0 M in THF). After 1 h, the reaction was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 x 40 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified chromatography over silica gel, eluting with 5-20% EtOAc / hexanes, to give a mixture of trans spiroketal **1.16.4** and *cis* spiroketal **1.16.5** (70 mg, 0.132 mmol, 28%) and pure *trans* spiroketal **1.16.4** (200 mg, 0.376 mmol, 68%) as a colorless oil. *Trans* spiroketal **1.16.4**: $[\alpha]_D^{23}$ + 26.3° (*c* 0.2, $CHCl_3$); IR (neat) 3461, 2955, 2930, 2846, 1360, 1212, 1086, 1056, 989, 728, 690; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.38 (m, 10H), 5.53-5.60 (m, 2H), 4.67 (d, *J* = 12.0 Hz, 1H), 4.65 (br, 1H), 4.46 (s, 2H), 4.41 (d, *J* = 12.0 Hz, 1H), 4.00 (dd, *J* = 10.0, 2.4 Hz, 1H), 3.72-3.79 (m, 2H), 3.46-3.60 (m, 2H), 3.28 (br, 1H), 2.66 (br, 1H), 2.36-2.42 (m, 1 H), 1.58-2.27 (m, 12 H), 0.97 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 138.9, 128.7, 128.6, 128.5. 128.4, 128.0, 127.9, 123.7, 110.6, 105.7, 74.1, 73.2, 71.0, 70.5, 68.5, 67.3, 61.8, 37.3, 37.0, 35.1, 32.6, 32.3, 32.1, 30.4, 16.7; HRMS (FAB^+) calcd. for $C_{31}H_{41}O_6$ (M + H) 509.2903, found 509.2897. (B5P52)



Trans Bisspiroketal 1.16.4: To a stirred solution of a mixture of trans and cis bisspiroketals **1.16.4** and **1.16.5** (200 mg, 0.376 mmol) in PhMe / tBuOH (9.4 mL, 1:1) was added camphorsulfonic acid (437 mg, 1.86 mmol). After 17 h, the reaction was quenched with $NaHCO_3$ (15 mL) and extracted with EtOAc (3 x 40 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified chromatography over silica gel, eluting with 5-20% EtOAc / hexanes, to give *trans* spiroketal **1.16.4** (200 mg, 0.376 mmol, 99%) as a colorless oil. (B6P61)

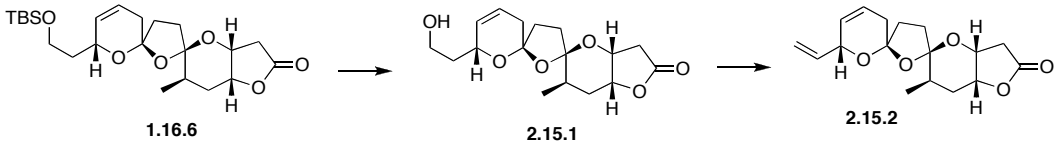


TBS ether 2.14.1: To a stirred solution of **1.16.4** (200 mg, 0.376 mmol) in CH_2Cl_2 (3.7 mL) at –78°C was sequentially added 2,6-lutidine (403 mg, 437 μL, 3.76 mmol) and TBSOTf (496 mg, 435 μL, 1.88 mmol). After 20 min, the solution was allowed to warm to 0°C, quenched by addition of saturated NH_4Cl (10 mL) and extracted with EtOAc (3 x 50 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10-40% EtOAc / hexanes, to give product **2.14.1** (232 mg, 99%) as colorless oil: $[\alpha]_D^{23}$ + 4.5° (*c* 2.5, $CHCl_3$); IR (neat) 2954, 2924, 2855, 1092, 997, 834, 778, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.41 (m, 10H), 5.68 (d, *J* = 10.0 Hz, 1H), 5.52-5.56 (m, 1H), 4.69 (d, *J* = 12.4 Hz, 1H), 4.52-4.54 (br, 1H), 4.49 (s, 1H), 4.48 (s, 1H), 4.44 (d, *J* = 12.4 Hz, 1H), 4.03 (dd, *J* = 10.0, 2.0 Hz, 1H), 3.75 (t, *J* = 6.8 Hz, 2H), 3.50-3.62 (m, 2H), 3.30 (s, 1H), 2.28-2.41 (m, 1H), 1.65-2.28 (m, 12H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.92 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 138.9, 129.4, 128.7, 128.6, 128.4, 128.0, 127.9, 127.8, 123.0, 110.3, 105.8, 74.2, 73.2, 71.0, 68.4, 67.4, 66.9, 60.1, 38.8, 37.2, 35.4, 32.8, 32.3, 32.2, 30.5, 26.3, 18.7, 16.8, -4.8; HRMS (FAB^+) calcd. for $C_{37}H_{53}O_6Si$ (M-H) 621.3611, found 621.3624. (B6P61)



Lactone 1.16.6: To a stirred solution of **2.14.1** (45 mg, 0.072 mmol) in THF (1.2 mL) at –78°C was added LiDBB (2.5 mL, 0.504 mmol, 0.4 M soln in THF). The green color solution was stirred at –78°C for 5 min, quenched by sat. aq. NH_4Cl (2 mL) and extracted with EtOAc (4 x 5 mL). The dried extract ($MgSO_4$) was filtered through a small plug of silica gel (10-50% EtOAc / hexanes), the filtrate was concentrated in *vacuo* to give diol **2.14.2**, which was used in the next step without further purification.

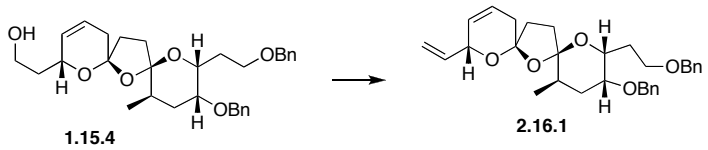
To a stirred solution of crude diol **2.14.2** (0.072 mmol) in CH_2Cl_2 (1 mL) was sequentially added 4 Å mol. sieves (60 mg), NMO (48 mg, 0.40 mmol) and TPAP (0.1 mg, 2.8 μmol). After 3 h, the solution was diluted with 50% EtOAc / hexanes, filtered through a small plug of silica gel and concentrated in *vacuo*. The crude oil was purified by chromatography over silica gel, eluting with 5-33% EtOAc / hexanes, to give lactone **1.16.6** (22 mg, 0.053 mmol, 73%) as a colorless oil: $[\alpha]_D^{23}$ + 70.8° (*c* 1.0, $CHCl_3$); IR (neat) 2954, 2933, 2855, 1784, 1251, 1092, 993, 838, 774; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70-5.71 (m, 2H), 4.47-4.52 (m, 1H), 4.35-4.39 (m, 2H), 3.71 (t, *J* = 6.6 Hz, 2H), 2.64 (dd, *J* = 17.1, 4.2 Hz, 1H), 2.43-2.52 (m, 1H), 1.64-2.32 (m, 10H), 0.94 (d, *J* = 6.3 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 129.6, 122.4, 109.8, 106.3, 78.3, 68.3, 67.0, 59.9, 38.9, 38.6, 36.9, 35.3, 32.4, 30.4, 29.5, 26.3, 16.4, -4.9; HRMS (FAB^+) calcd. for $C_{23}H_{39}O_6Si$ (M+H) 439.2516, found 439.2515.



Alkene 2.15.2: To a stirred solution of TBS ether **1.16.6** (10 mg, 23.5 µmol, 1 eq) in DCM / MeOH (1:1 800 µL, 0.03 M) was added camphosulfonic acid (5.4 mg, 23.5 µmol, 1 eq.). After 45 min, the reaction was diluted in hexanes and purified by chromatography over silica gel, eluting with 30-70% EtOAc / hexanes to give alcohol **2.15.5** as a colorless oil (4.0 mg, 12 μmol, 51%).

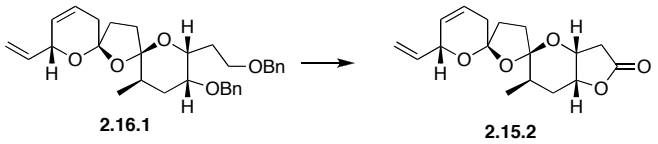
To a stirred solution of alcohol **2.15.1** (4.9 mg, 12 µmol, 1 eq.) in THF (250 µL, 0.05 M), was added sequentially 2-NO_2PhSeCN (7.0 mg, 36 µmol, 3 eq.) and PBu_3 (8.5 mg, 36 µmol, 3 eq.). After 40 min, the reaction was quenched with sodium thiosulfate (sat. aq.) (2 mL). After 5 min, reaction was extracted with EtOAc (3 x 20 mL). The dried extract ($MgSO_4$) was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10-40% EtOAc / hexanes to afford a crude selenide.

To a stirred solution of crude selenide (12 µmol) in CH_2Cl_2 (500 µL) was added sequentially TPAP (10 mg, 26 μmol, 0.3 eq.) NMO (30 mg, 256 μmol, 22 eq.) Et_3N (15.2 mg, 20 µL, 149 µmol, 12 eq.) and powdered molecular sieves (40 mg). After 1 h, the reaction was diluted in hexanes and filtered through a 1cm plug of silica eluting with 30% EtOAc / hexanes to give alkene **2.15.2** as a colorless oil (2.0 mg, 6.5 μmol, 50%). $[\alpha]_d^{23}$ +4.3 (c = 0.3 $CHCl_3$); IR (neat) 2965, 2927, 2861, 1783 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 5.80-5.95 (m, 2H), 5.65-5.75 (m, 1H), 5.28 (dt, *J* = 16.8, 1.2 Hz, 1H), 5.16 (d, *J* = 11.2 Hz, 1H), 4.75-4.88 (m, 1H), 4.42 (s, 2H), 2.67 (dd, *J* = 16.8, 3.6 Hz, 1H), 2.43-2.56 (m, 2H), 3.35 (dt, *J* = 16.4, 8.0 Hz, 1H) 1.80-2.23 (m, 6H), 1.75 (dd, *J* = 12.0, 8.4 Hz, 1H), 0.9 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 137.2, 122.5, 116.3, 109.6, 106.0, 77.8, 71.3, 68.0, 38.5, 36.5, 34.6, 31.9, 30.1, 29.7, 29.1, 15.8; HRMS (ES+) Calcd for $C_{17}H_{23}O_5$ (M+) 307.1545, Found 307.1531. (B9P42)



Alkene 2.6.1: To a stirred solution of alcohol **1.15.4** (36 mg, 70.7 µmol, 1 eq.) in THF (1.4 mL, .05 M), was added sequentially 2-NO_2PhSeCN (49 mg, 212 µmol, 3 eq.) and PBu_3 (43 mg, 53 µL, 212 µmol, 3 eq.). After 40 min, the reaction was quenched with sodium thiosulfate (sat. aq.) (4 mL). After 5 min, reaction was extracted with EtOAc (3 x 20 mL). The dried extract ($MgSO_4$) was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10-40% EtOAc / hexanes to afford a crude selenide.

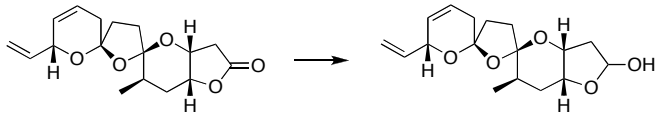
To a stirred solution of crude selenide (70.7 µmol) in CH_2Cl_2 (7 mL) was added sequentially TPAP (3.0 mg, 7.1 μmol, 0.1 eq) NMO (25 mg, 213 μmol, 3 eq.) Et_3N (35.8 mg, 50 µL, 355 µmol, 5eq.) and powdered molecular sieves (60 mg). After 1 h, the reaction was diluted in hexanes and filtered through a 1cm plug of silica eluting with 30% EtOAc / hexanes to give alkene **2.16.1** as a colorless oil (15 mg, 30.5 μmol, 43%). $[\alpha]_d^{23}$, -21.6 (c = 0.75 $CHCl_3$); IR (neat) 3025, 2921, 2856, 14.62, 1091 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.20-7.40 (m, 10H), 5.77-5.84 (m, 1H), 5.50-5.68 (m, 2H), 5.28 (dt, *J* = 16.8, 1.2 Hz, 1H), 5.16 (d, *J* = 11.2 Hz, 1H), 4.75-4.88 (m, 1H), 4.67 (d, *J* = 12.4 Hz, 1H), 4.35-4.52 (m, 3H), 3.95-4.05 (m, 1H), 3.50-3.70 (m, 2H), 3.29 (s, 1H), 2.00-2.50 (m, 8H), 1.90-1.99 (m, 1H), 1.81 (dd, *J* = 12.0, 8.4 Hz, 1H), 1.55-1.80 (m, 2H), 0.94 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 138.5, 137.7, 128.3, 128.2, 127.6, 127.5, 127.4, 123.0, 116.1, 110.0, 105.5, 73.79, 72.8, 71.2, 70.6, 68.0, 67.0, 58.3, 36.7, 34.8, 32.0, 31.8, 30.0, 16.3, 8.2; HRMS (ES+) Calcd for $C_{31}H_{38}O_5Na$ (M+Na) 513.2617, Found 513.2605. (B9P54)



2.16.1 **2.15.2**

Lactone 2.15.2: To a -78°C stirred solution of benzyl ether **2.16.1** (15 mg, 30.5 µmol, 1eq.) in THF (1.5 mL, 0.02 M) was added LiDBB (500 µL, 100 µmol, 3.27 eq., 0.2M solution in THF) After 2 min the solution had faded from dark green to a brownish red indicating consumption of the LIDBB. A second aliquot of LiDBB (500 µL) was added. After an additional 3 min, the reaction was quenched with sat. aq. ammonium chloride (1 mL) and was extracted with EtOAc (3 x 10 mL). The dried extract ($MgSO_4$) was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with eluting with 50% EtOAc / hexanes to 10% MeOH in CH_2Cl_2 to afford an unstable alcohol (10 mg) which was immediately oxidized without characterization.

To a stirred solution of crude alcohol in CH_2Cl_2 (1 mL) was added sequentially TPAP (3 mg, 7.8 μmol, 0.25 eq) NMO (20 mg, 171 μmol, 5.6 eq.) and powdered molecular sieves (60 mg). After 3 h, the reaction was diluted in hexanes and filtered through a 1 cm plug of silica eluting with 30% EtOAc / hexanes to give lactone **2.15.2** as a colorless oil (6.6 mg, 21.5 μmol, 70%). $[\alpha]_d^{23}$ +4.3 (c = 0.3 $CHCl_3$); IR (neat) 2965, 2927, 2861, 1783 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 5.80-5.95 (m, 2H), 5.65-5.75 (m, 1H), 5.28 (dt, *J* = 16.8, 1.2 Hz, 1H), 5.16 (d, *J* = 11.2 Hz, 1H), 4.75-4.88 (m, 1H), 4.42 (s, 2H), 2.67 (dd, *J* = 16.8, 3.6 Hz, 1H), 2.43-2.56 (m, 2H), 3.35 (dt, *J* = 16.4, 8.0 Hz, 1H) 1.80-2.23 (m, 6H), 1.75 (dd, *J* = 12.0, 8.4 Hz, 1H), (d, *J* = 6.8 Hz, 3H; ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 137.2, 122.5, 116.3, 109.6, 106.0, 77.8, 71.3, 68.0, 38.5, 36.5, 34.6, 31.9, 30.1, 29.7, 29.1, 15.8; HRMS (ES+) Calcd for $C_{17}H_{23}O_5$ (M+) 307.1545, Found 307.1531. (B9P63)



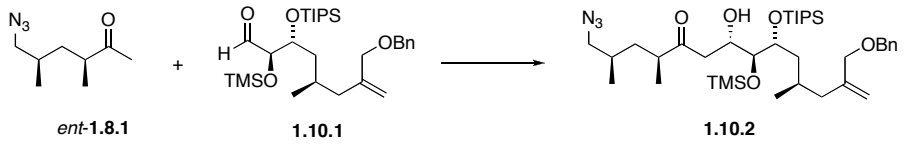
2.15.2 2.15.3

Lactol 2.15.3: To a -78°C stirred solution of lactone **2.15.2** (7.0 mg, 22.8 µmol, 1eq.) in PhMe (1.5 mL, 0.015M) was added DIBAL-H (228 µL, 22.8 µmol, 1 eq., .1M solution in PhMe). After 10 min the reaction was quenched with MeOH (1mL) and warmed to rt. The the solution was then diluted with EtOAc (10 mL) and Rochelle's salt (10 mL) and stirred vigously for 3 h. The solution was then diluted with brine (20 mL) and extracted with EtOAc (3 x 10 mL). The dried extract ($MgSO_4$) was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with eluting with 20-50% EtOAc / hexanes to afford alcohol **2.15.3** (6.0 mg, 19.5 µmol, 86%) as a colorless oil. ^{1}H NMR (400 MHz; $CDCl_3$) δ 5.77-5.84 (m, 2H), 5.69-5.71 (m, 1H), 5.28-5.36 (m, 2H), 5.17-5.21 (m, 1H), 4.86 (s, 1H), 3.91-3.92 (m, 1H), 3.00-3.20 (br s, 1H), 1.83-2.60 (m, 11H), 1.64-1.69 (dd, *J* = 12.4, 7.2 Hz, 1H), 0.98 (d, *J* = 7.6 Hz 2H), 0.96 (d *J* = 6.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.3, 127.6, 122.5, 116.3, 110.0, 106.0, 99.0, 77.6, 71.3, 70.8, 41.53, 36.4, 34.6, 32.5, 31.1, 29.7. (B9P65)

2.17.1 2.17.2

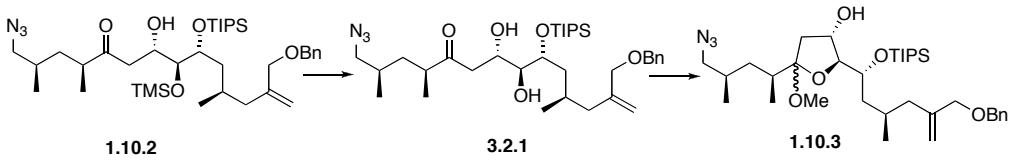
Tips Ether 2.17.2: To a -78°C stirred solution of pentenol (**2.17.1**) (1 mL, 834 mg, 9.6 mmol) in THF (19.2 mL, .5M) was added sequentially 2,6-lutidine (1.9 mL, 1.75g, 16.3 mmol, 1.7eq.) and TIPSOTf (3.1mL, 3.5 g, 11.52 mmol, 1.2 eq.). After 45 min, the reaction was quenched with sat. aq. ammonium chloride (20 mL) and was extracted with EtOAc (3 x 100 mL). The dried extract ($MgSO_4$) was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with eluting with 10-20% EtOAc / hexanes to afford TIPS ether **2.17.2** as a colorless oil (2.173 g, 8.96 mmol, 93%). IR (neat) 2948, 28.67, 14.67, 1097 cm^{-1}; ^{1}H NMR (400 MHz;

$CDCl_3$) δ 5.80-5.90 (m, 1H), 4.95-5.06 (m, 2H), 3.72 (d,d *J* = 6.4, 5.8 Hz, 2H), 2.05-2.18 (m, 2H), 1.61-1.69 (m, 2H), 1.06-1.18 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 114.4, 62.7, 32.2, 30.0, 18.0, 12.0; HRMS (CI+) Calcd. For $C_{14}H_{31}O_1Si$ (M+) 243.2144, Found 243.2133. (B9P56)



ent-**1.8.1** **1.10.1** **1.10.2**

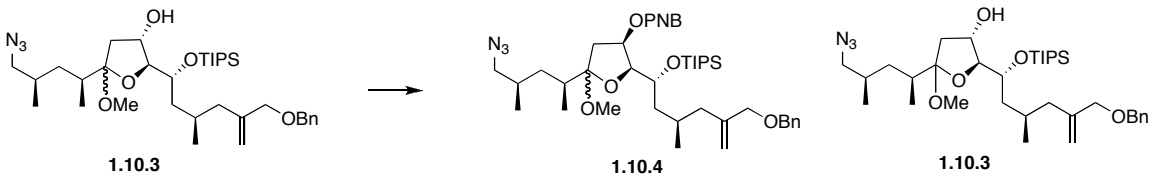
Adduct 1.10.2: To a stirred solution of methyl ketone *ent*-**1.8.1** (1.45 g, 8.53 mmol) in THF (20 mL) at –78°C was added LDA (8.53 mL, 8.53 mmol, 1.0 M in THF / hexanes)[7] dropwise. After 30 min, a solution of the aldehyde **1.10.1** (3.7 g, 7.1 mmol) in pre-cooled THF (20 mL) was added *via* cannula to the enolate solution. After 15 min, the reaction was removed from the cooling bath, quenched with sat. aq. NH_4Cl (50 mL) and extracted with EtOAc (3 X 100 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10-40% EtOAc / hexanes, to give **1.10.2** (4.3 g, 5.87 mmol, 82%) as a colorless oil: $[\alpha]_D^{23}$ -34.0 (*c* = 1.2, $CHCl_3$); IR (neat) 2946, 2864, 2103, 1703, 1453, 1251, 1101, 881, 838 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29-7.38 (m, 5H), 5.15 (s, 1H), 4.96 (s, 1H), 4.54 (d, *J* = 11.6 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.18 (m, 1H), 4.11 (m, 1H), 3.98 (d, *J* = 12.8 Hz, 1H), 3.95 (d, *J* = 12.7 Hz, 1H), 3.69 (dd, *J* = 5.2, 2.0 Hz, 1H), 3.11-3.25 (m, 3H), 3.01 (dd, *J* = 18.0, 2.0 Hz, 1H), 2.54-2.66 (m, 2H), 2.09 (dd, *J* = 14.2, 6.0 Hz, 1H), 1.95 (dd, *J* = 14.2, 6.0 Hz, 1H), 1.69-1.85 (m, 5H), 1.29-1.30 (m, 1H), 1.11-1.18 (m, 21H), 0.99 (d, *J* = 6.8 Hz, 6H), 0.96 (d, *J* = 6.4 Hz, 3H), 0.16 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.3, 144.2, 138.4, 128.3, 127.6, 127.5, 113.2, 77.9, 73.8, 73.0, 71.9, 68.1, 57.6, 44.7, 44.4, 42.4, 42.0, 37.3, 37.2, 31.5, 31.4, 27.9, 27.6,19.8, 18.2, 17.9, 17.8, 17.3, 17.2, 12.7, 0.54; HRMS (FAB^+) calcd. for $C_{37}H_{68}N_3O_5Si_2$ (M**+**H) 690.4698**,** found 690.4715. (B8P26)



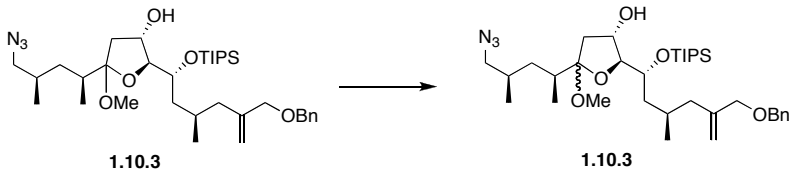
Methoxy acetal 1.10.3: To aldol adduct **1.10.2** (5.1 g, 6.99 mmol) in flask was added 12.6 mL solution of TBAF / HOAc [consisting of TBAF (10.5 mL, 10.5 mmol 1.0 M in THF) and HOAc (2.5 mL)]. After 1 h, the reaction was quenched with $NaHCO_3$ (30 mL) and extracted with EtOAc (4 x 50 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10-20% EtOAc / hexanes, to give diol **3.2.1** (3.2 g, 5.18 mmol, 75%) as colorless oil.

To a solution of diol **3.2.1** (3.2 mg, 5.28 mmol) in MeOH (70 mL) was added PPTS (87 mg, 0.30 mmol). After 1 h, the reaction was quenched with $NaHCO_3$ (20 mL) and extracted with EtOAc (3 x 40 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10-20% EtOAc / hexanes, to give product **1.10.3** as an (2 : 1) mixture (3.2 g, 5.06 mmol, 98%) as colorless oil: $[\alpha]_D^{23}$ -16.5 (*c* 0.7, $CHCl_3$); IR (neat) 3470, 2954, 2873, 2098, 1733, 1466, 1384, 1088, 683 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29-7.38 (m, 5H), 5.15 (s, 1H of a diastereomer), 5.15 (s, 1H of a diastereomer), 4.97 (s, 2H), 4.85-4.56 (m, 2H), 4.25 (t, *J* = 7.6 Hz, 1H of a diastereomer), 4.07-4.11 (m, 1H of a diastereomer), 3.94-4.03 (m, 2H), 3.87 (t, *J* = 3.2 Hz, 1H of a diastereomer), 3.53 (t, *J* = 7.6 Hz, 1H of a diastereomer), 3.33 (dd, *J* = 12.4, 4.8 Hz, 1H of a diastereomer), 3.30 (dd, *J* = 12.8, 4.8 Hz, 1H of a diastereomer), 3.22 (s, 3 H of a diastereomer), 3.18 (s, 3 H of a diastereomer), 3.14 (dd, *J* = 12.0, 6.8 Hz, 1H of a diastereomer), 3.05 (dd, *J* = 12.0, 6.8 Hz, 1H of a diastereomer), 2.84 (d, *J* = 10.4 Hz, 1H of a diastereomer), 2.34 (d, *J* = 2.0 Hz, 1H of a diastereomer), 1.39-2.19 (m, 4H), 1.10-1.13 (m, 21H), 1.04 (d, *J* = 6.8 Hz, 3H of a diastereomer), 1.02 (d, *J* = 6.8 Hz, 3H of a diastereomer), 0.98 (d, *J* = 6.4 Hz, 3H of a diastereomer), 0.92 (d, *J* = 5.6 Hz, 3H of a diastereomer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 144.2, 138.4, 128.3, 127.6, 127.5, 113.3,

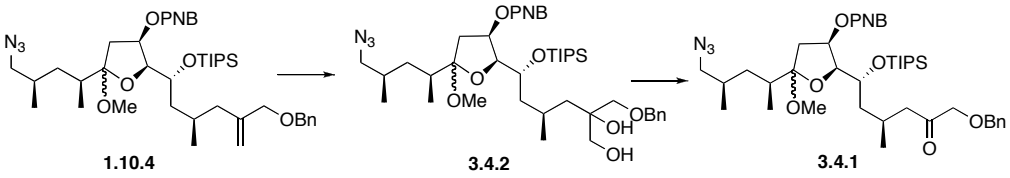
113.0, 112.8, 111.4, 90.2, 89.0, 74.1, 73.5, 73.0, 72.8, 72.0, 71.8, 71.7, 71.3, 57.2, 56.6, 47.9, 47.3, 44.8, 42.2, 39.9, 38.6, 36.7, 34.8, 31.9, 31.8, 31.0, 27.4, 26.8, 20.1, 19.9, 19.6, 19.3, 18.3, 18.2; HRMS (ES^+) calcd. for $C_{35}H_{61}N_3O_5SiNa$ (M + Na) 654.4278, found 654.4315. (B8P26)



PNB Ester 1.10.4: To a solution of **1.10.3** (5.2 g, 8.23 mmol) in THF (75 mL) was sequentially added PPh_3 (2.95 g, 11.2 mmol), *p*-nitrobenzoic acid (1.84 g, 11.02 mmol) and DEAD (1.93 g, 11.74 mL, 11.15 mmol, 40% in toluene). After 1 h, the reaction was quenched with sat. aq. $NaHCO_3$ (10 mL) and extracted with EtOAc (3 x 20 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10-20% EtOAc / hexanes, to give product **1.10.4** (3.9 g, 4.99 mmol, 61%) as colorless oil and recoved alcohol **1.10.3** (400 mg, .633 mmol, 8%): $[\alpha]_D^{23}$ -24.0 (*c* 2.5, $CHCl_3$); IR (neat) 2933, 2098, 1729, 1612, 1531, 1458, 907, 722 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.8 Hz, 2H), 8.18 (d, *J* = 8.8 Hz, 2H), 7.29-7.40 (m, 5H), 5.59 (m, 1H), 5.15 (s, 1H), 4.95 (s, 1H), 4.51 (s, 2H), 4.41-4.46 (m, 1H), 4.01 (dd, *J* = 7.6, 3.2 Hz, 1H), 3.96 (s, 2H), 3.31 (dd, *J* = 12.0, 4.4 Hz, 1H), 3.20 (s, 3H), 3.13 (dd, *J* = 12.0, 6.8 Hz, 1H), 2.30 (dd, *J* = 15.2, 6.0 Hz, 1H), 2.09-2.21 (m, 4H), 1.78-1.98 (m, 4H), 1.53-1.63 (m, 2H), 1.05 (d, *J* = 6.4 Hz, 3H), 1.00 (d, *J* = 6.4 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.93-0.97 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 150.6, 144.3, 138.4, 135.7, 130.5, 128.3, 127.5, 123.6, 113.1, 111.3, 84.3, 76.6, 72.9, 71.8, 68.1, 56.7, 48.2, 44.7, 42.2, 40.9, 36.0, 32.8, 31.0, 27.5, 20.1, 19.6, 18.2, 15.0, 13.0; HRMS (ES^+) calcd. For $C_{42}H_{64}N_4O_8SiNa$ (M + Na) 803.4391, found 803.4391. (B8P28)



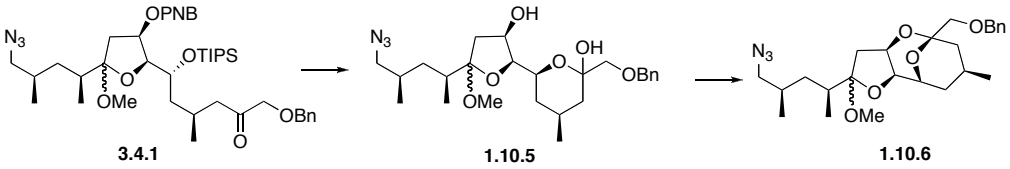
Alcohol 1.10.3: To a stirred solution of recovered methyl ketal **1.10.3** (390 mg, 617 µmol 0:1dr) in methanol (6mL) was added H_2O (11 mg, 11 µL, 617 µmol) and PPTS (5 mg, 20µmol). After 15 min, the solution was quenched with $NaHCO_3$ (5 mL) and extracted with EtOAc (4 x 50 mL) The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10-20% EtOAc / hexanes, to give alcohol **1.10.3** as a 2:1 mixture of diastereomers (350 mg, .554 mmol, 80%) as colorless oil. (B9P33)



Ketone 3.4.1: To a solution of **1.10.4** (7 g, .896 mmol) in acetone (100 mL) was added $K_2OsO_4 \cdot 2H_2O$ (106 mg, 29 μmol) and a NMO solution (25 mL, 12.5 mmol, 50% aq.). After 6 h, the reaction was quenched with $Na_2S_2O_3$ (20 mL), diluted with brine (20 mL) and extracted with EtOAc (3 x 50 mL). The dried ($MgSO_4$) solution was concentrated *in vacuo* to give crude **3.4.2** and used in the next reaction without further purification.

To a crude solution of **3.4.2** in THF / H_2O (1 : 1, 150 mL) was added $NaIO_4$ (4.8 g, 22.4 mmol. After 18 h, the reaction was quenched with NH_4Cl (100 mL) and extracted with EtOAc (3 x 50 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10-50% EtOAc / hexanes, to give product **3.4.1** (6.5 g, 830 mmol,

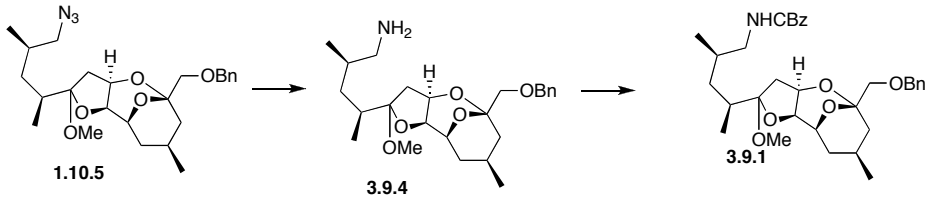
93%) as colorless oil: $[\alpha]_D^{23}$ -22.1 (*c* 2.46, $CHCl_3$); IR (neat) 2877, 2098, 1729, 1604, 1539, 1458, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.8 Hz, 2H), 8.17 (d, *J* = 8.8 Hz, 2H), 7.31-7.37 (m, 5H), 5.56-5.58 (m, 1H), 4.60 (s, 2H), 4.37-4.42 (m, 1H), 4.02 (2H), 4.01-4.04 (m, 1H), 3.32 (dd, *J* = 12.0, 4.0 Hz, 1H), 3.27 (s, 3H), 3.12 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.62-2.64 (m, 1H), 2.52 (dd, *J* = 16.8, 6.0 Hz, 1H), 2.27-2.37 (m, 2H), 2.17-2.20 (m, 1H), 2.07 (d, *J* = 15.6 Hz, 1H), 1.78-1.85 (m, 2H), 1.57-1.66 (m, 2H), 1.05 (d, *J* = 6.4 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.90-0.95 (m, 25H), ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.8, 163.9, 150.5, 137.2, 135.6, 130.5, 128.4, 128.0, 127.8, 123.6, 111.2, 83.7, 76.5, 75.4, 73.3, 67.9, 56.6, 48.3, 47.0, 44.2, 41.0, 36.0, 32.7, 30.9, 25.5, 20.4, 19.6, 18.1, 15.0, 13.0; HRMS (ES^+) calcd. for $C_{41}H_{62}N_4O_9SiNa$ (M + Na) 805.4184, found 805.4221. (B8P29)



Bicyclic Ketal 1.10.6: To a solution of ketone **3.4.1** (500 mg, 0.638 mmol) in THF (6.3 mL) was added TBAF (1.91 mL, 1.91 mmol, 1.0 M in THF). After 1 h, the reaction was quenched with NH_4Cl (10 mL) and extracted with EtOAc (3 x 20 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10-50% EtOAc / hexanes, to give product **1.10.5** (270 mg, 0.543 mmol, 85%) as colorless oil.

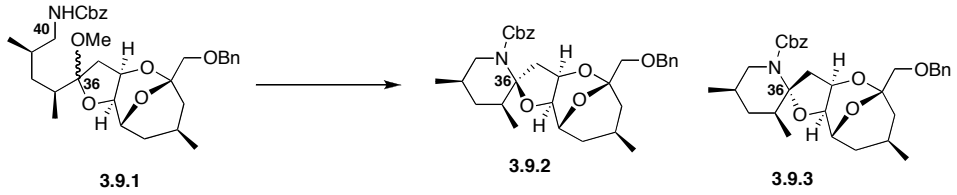
To a solution of hemiketal **1.10.5** (270.0 mg, 0.543 mmol) in MeOH (4.5 mL) was added CSA (5 mg, 22 μmol). After 15 min, the reaction was quenched with $NaHCO_3$ (5 mL) and concentrated *in vacuo*, loaded directly onto silica gel and purified by chromatography, eluting with 10-50% EtOAc / hexanes, give product **1.10.6** as an (5:1) epimeric mixture (170 mg, 0.370 mmol, 68%) as colorless oil: $[\alpha]_D^{23}$ -20.0 (*c* 0.10, $CHCl_3$); IR (neat) 2929, 2868, 2086, 1638, 1458, 1290, 1113, 1049 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.35 (m, 5H), 4.80-4.85 (m, 1H), 4.75-4.78 (m, 1H of a diastereomer), 4.65 (d, *J* = 16.4 Hz, 1H), 4.58 (d, *J* = 16.4 Hz, 1H), 4.40 (d, *J* = 5.6 Hz, 1H of a diastereomer), 4.35 (d, *J* = 5.6 Hz, 1H), 3.77 (d, *J* = 5.2 Hz, 1H), 3.69 (d, *J* = 5.2 Hz,

1H of a diastereomer), 3.30-3.38 (m, 3 H), 3.18 (s, 3H), 3.08-3.16 (m, 1H), 2.06-2.25 (m, 4H), 1.55-1.95 (m, 6H), 0.97-1.03 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 128.3, 127.7, 127.5, 111.1, 95.8, 76.1, 76.0, 73.6, 73.2, 69.9, 56.7, 47.8, 42.3, 39.0, 36.3, 34.9, 33.1, 31.0, 24.8, 23.2, 19.6, 14.9; HRMS (ES^+) calcd. for $C_{25}H_{37}N_3O_5Na$ (M + Na) 482.2631, found 482.2618. (B8P34)



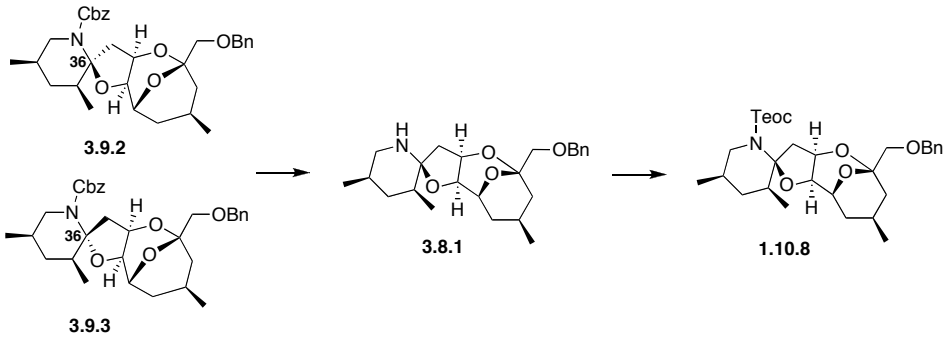
Cbz Protected Amine 3.9.1: To a stirred solution of azide **1.10.5** (152 mg, 330 mmol, 1 eq.) in THF/H_2O (5:1, 2.2 mL) was added PPh_3 (103 mg, 396 μmol, 1.2 eq). After 16 h, the reaction was diluted in EtOAc (100 mL). The dried ($MgSO_4$) solution was filtered and concentrated *in vacuo*.

Crude amine **3.9.4** was re-dissolved in EtOAc (1.7 mL) and sequentially charged with Et_3N (257 mg, 185 μL, 1.32 mmol, 4 eq.) and CbzONSu (246 mg, 990 μmol, 3 eq). After 6 h, the reaction was quenched with sat. aq. ammonium chloride (10 mL) and extracted with EtOAc (3 x 50 mL). The dried ($MgSO_4$) extract was filtered and concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10-40% EtOAc / hexanes to give Cbz-protected amine **3.9.1** (155 mg, 280 μmol, 85% over 2 steps) as a colorless oil; $[\alpha]_D^{23}$ +2.0° (c = 0.5 $CHCl_3$); IR (Neat) 33341, 2954, 2867, 1718 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) d 7.20-7-50 (m, 10H), 5.00-5.20 (m, 2H), 4.92-5.00 (m, 1H), 4.75-4.85 (m, 2H), 4.50-4.70 (m, 2H), 4.28-4.35 (m, 1H), 3.2-3.80 (m,1H), 3.10-3.40 (m, 5H), 2.80-3.00 (m, 1H), 2.00-2.38 (m, 3H), 1.89-1.99 (m, 1H), 1.40-1.75 m, 6H), 0.76-1.00 (m, 9H); ^{13}C (100 MHz, $CDCl_3$) δ 156.6, 138.1, 128.5, 128.4, 128.3, 128.0, 127.7, 127.5, 111.3, 95.7, 76.3, 76.1, 73.6, 73.3, 69.9, 66.5, 48.0, 45.3, 41.8, 39.0, 36.1, 34.8, 34.0, 31.0, 24.8, 23.3, 19.5, 15.1; HRMS (CI+) Calcd. for $C_{33}H_{46}O_7N$ (M+) 568.3274, Found 568.3256. (B7P12)



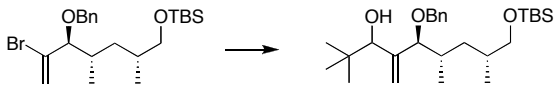
3.9.1 **3.9.2** **3.9.3**

Aminals 3.9.2 and 3.9.3: To a stirred solution of methyl ketal **3.9.1** (170 mg, 307 μmol, 1 eq.) in THF (5.1 mL) was added $Yb(OTf)_3$ (9.5 mg, 15 μmol, 0.05 eq). After 30 min, the reaction was quenched with sat. aq. $NaHCO_3$ (10 mL) and extracted with EtOAc (3 x 40 mL). The dried ($MgSO_4$) extract was filtered and concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10-30% EtOAc / hexanes to give Cbz aminal **25** as a 4:3 diastereomeric mixture of **3.9.2** and **3.9.3** (155 mg, 297 μmol, 97%) as a crude colorless oil. $[\alpha]_D^{23}$ -10.6° (c = 0.9, $CHCl_3$); IR (Neat) 2954, 2925, 2861, 2088, 1699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20-7-50 (m, 10H), 4.95-5.20 (m, 2H), 4.68-4.88 (m, 1H), 4.40-4.85 (m, 2H), 4.35-4.40 (m, 1H), 4.16-4.30 (m, 1H), 3.70-4.00 (m, 2H), 3.15-3.35 (m, 3H) 2.60-3.12 (m, 1H), 1.10-2.35 (m, 11H), 1.04-1.11 (m, 2H), 0.66-1.00(m, 9H); ^{13}C (100MHz $CDCl_3$) δ 155.6, 155.3, 138.4, 138.2, 137.3, 136.4, 128.5, 128.4, 128.2, 128.2, 128.0, 127.7, 127.6, 127.5, 127.3, 99.0, 97.1, 95.6, 95.5, 78.4, 78.3, 76.0, 75.9, 74.3, 73.5, 73.5, 71.0, 70.5, 67.0, 66.2, 48.7, 48.4, 41.6, 39.3, 39.1, 39.0, 38.4, 37.0, 36.4, 35.1, 34.7, 31.6, 28.5, 24.7, 24.5, 23.2, 23.0, 20.0, 18.6; HRMS (EI+) Calcd. for $C_{32}H_{41}O_6N$ (M+) 535.2933, Found 535.2933.



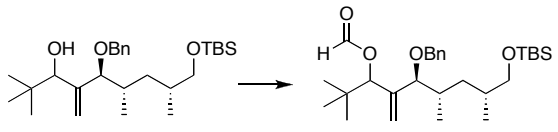
Teoc aminal 1.10.8: To a stirred solution of Cbz aminals **3.9.2** and **3.9.3** (4:3 dr) (155 mg, 297 μmol 4:3 dr, 1 eq.) in THF (5 mL) was added Pd/C (100 mg, 10% w/w) under argon. The solution was flushed with 1 balloon volume of H_2 gas and fitted with a second balloon. After 16 h, the reaction was filtered through a silica pad eluting in EtOAc and concentrated *in vacuo*.

Crude aminal **3.8.1** (1 diastereomer) was immediately dissolved in THF (2 mL) cooled to 0°C. The solution was charged sequentially with iPr_2NEt (278 mg, 200 μL, 1.4 mmol, 4.88 eq.) and Teoc-Cl (100 μL).[8] After 16 h, the reaction was quenched with sat. aq. ammonium chloride (10 mL), extracted with EtOAc (3 x 40 mL) The dried ($MgSO_4$) extract was filtered and concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10-30% EtOAc / hexanes to give known Teoc aminal **1.10.8**[9] as a single diastereomer (87 mg, 217 μmol, 70%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.38 (m, 5H), 4.78-4.81 (m,1H), 4.61 (q, J = 12.4 Hz, 2H), 4.39 (d, J = 4.8 Hz, 1H), 4.01-4.19 (m, 2H), 3.75-3.93 (m, 3H), 3.20-3.39 (m, 3H), 2.00-2.23 (m, 3H), 1.84 (dd, J = 13.6 4.4 Hz, 1H), 1.67-1.77 (m, 1H), 1.25-1.43 (m, 2H), 0.90-1.05 (m, 5H), 0.85 (d, J = 6.8 Hz, 6H), 0.05 (s, 9H); ^{13}C(100 MHz, $CDCl_3$) δ 155.8, 138.4, 128.2, 127.6, 127.4, 97.0, 95.5, 78.3, 75.9, 73.6, 71.1, 62.6, 48.5, 39.4, 39.3, 39.1, 36.4, 34.7, 31.5, 24.4, 23.0, 18.7, 17.8, 16.5, -1.4; HRMS (EI+) Calcd. for $C_{30}H_{47}O_6NSi$ (M+) 545.3173, Found 545.6162. (B7P17)



4.2.7 4.4.3

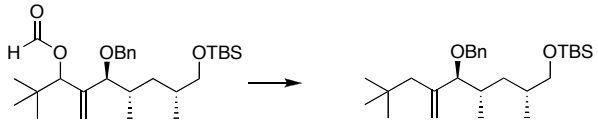
Alcohol 4.4.3: To a stirred solution of tert-butyl lithium (290 μL, 462 μmol, 1.63 M in hexanes, 2.2 eq.) in Et_2O (1 mL) at -78°C was added vinyl bromide **4.2.7** (93 mg, 210 μmol, 1 eq.) in Et_2O (600 μL, 2 x 100 μL rinse) *via cannula*. After 20, min the reaction was charged with pivaldehyde (27 mg, 35 μL, 315 μmol, 1.5 eq). After 5 min, the cooling bath was removed and the reaction was quenched with sat. aq. ammonium chloride (10 mL). The aqueous layer was extracted with Et_2O (4 x 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 0-30% EtOAc / hexanes, to give alcohol **4.4.3** as a 2:1 mixture of diastereomers (71 mg, 158 μmol, 75%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.50 (m, 5H), 5.20-5.47 (m, 2H), 4.50-4.70 (m, 1H), 4.20-4.35 (m, 1H), 3.85-3.95 (m, 1H), 3.75-3.85 (m, 1H), 3.65-3.75 (m, 1H of a diastereomer), 3.55-3.65 (m, 1H of a diastereomer) 3.40-3.55 (m, 2H), 1.60-2.20 (m, 4H), 0.80-1.26 (m, 24H), 0.9 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 147.7, 138.9, 128.8, 128.4, 128.2, 127.6, 127.5, 127.3, 116.2, 112.8, 86.4, 86.1, 80.7, 78.1, 70.8, 70.5, 68.2, 67.3, 36.0, 35.6, 34.5, 34.1, 33.4, 33.3, 22.0, 29.7, 26.8, 26.1, 26.0, 25.5, 19.0, 18.9, 18.4, 18.3, 17.7, -5.2, -5.2. (B4P77)



4.4.3 4.4.1

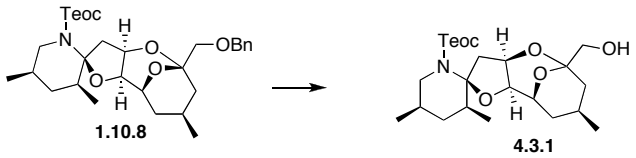
Formate 4.4.1: To a stirred solution alcohol **4.4.3** (27 mg, 60 μmol, 1 eq.) in pyridine (600 μL) at 0°C was added sequentially acetic formic anhydride (300 μL) and DMAP (10 mg, 8 μmol, .13 eq.). After 5 min, the cooling bath was removed. After 30 min, the reaction was quenched with sat. aq. ammonium chloride (50 mL) and extracted with Et_2O (4 x 40 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel,

eluting with 0-30% EtOAc / hexanes, to give formate **4.4.1** as a 2:1 mixture of diastereomers (27mg, 56 μmol, 93%) as a colorless oil. $[\alpha]_D^{23}$ -48.7° (c=0.9, $CHCl_3$); IR (neat) 2959, 2921, 2860, 1739, 1173 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.13 (s, 1H of diastereomer), 8.09 (s, 1H), 7.30-7.55 (m, 5H), 5.25-5.53 (m, 2H), 5.00-5.22 (m, 2H), 4.50-4.70 (m, 1H), 4.25-4.35 (m, 1H), 3.0-3.85 (m, 1H), 3.40- 3.70 (m, 1H), 3.00-3.38 (m, 3H of diastereomer), 1.65-2.20 (m, 3H), 0.80-1.25 (m, 24H), 0.9 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 159.8, 144.3, 143.1, 138.9, 128.8, 128.2, 127.6, 127.3, 127.3, 119.0, 115.0, 85.8, 85.5, 80.4, 78.1, 71.0, 70.3, 67.9, 35.8, 35.5, 34.6, 33.3, 33.1, 33.0, 32.6, 29.7, 26.8, 26.2, 26.0, 25.7, 18.8, 18.7, 18.3, 17.9, 1.0, -5.3; $CHCl_3$, HRMS (ES+) Calcd. for $C_{28}H_{48}O_4SiNa$ (M+Na) 499.3220, Found 499.3207. (B4P77)

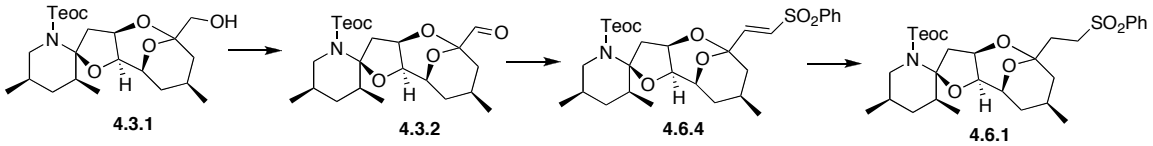


4.4.1 **4.4.2**

Alkene 4.4.2: A stirred solution formate **4.4.1** (20 mg, 42 μmol, 1 eq.) in cyclohexane (600 μL, 2 x 120 μL rinse) was added to a pressure vessel containing $Pd_2(dba)_3$ (7.7 mg, 8.4 μmol, 0.2 eq.) and ammonium formate (3 mg, 50 μmol, 1.2 eq.) *via cannula*. Next, the reaction was charged with PBu_3 (85 mg, 104 μL, 420 μmol, 10 eq.) and the vessel was sealed and heated to 85°C. After 16 h, the reaction was cooled and purified by chromatography over silica gel, eluting with 0-20% EtOAc / hexanes, to give deoxygenated product **4.4.2** (5 mg, 14 μmol, 34%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.55 (m, 5H), 5.21 (s, 1H), 5.07 (s, 1H), 4.60-4.70 (m, 2H), 4.25-4.35 (m, 2H), 3.60-3.65 (m, 1H), 3.45-3.52 (m, 1H), 3.23-3.30 (m, 1H), 1.60-2.15 (m, 4H) 0.80-1.15 (m, 31H), 0.10 (s, 6.H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 144.5, 139.2, 128.1, 127.5, 127.1, 114.1, 87.8, 70.8, 67.8, 45.5, 34.7, 33.5, 33.3, 31.6, 30.2, 29.7, 25.9, 18.7, 18.3, 18.1, -5.3. (B4P99)



Alcohol 4.3.1: To a -78°C solution of benzyl ether **1.10.8** (200 mg, 366 μmol, 1 eq.) in THF (3.7 mL) was added the green LiDBB[10] solution (0.4 M) until reaction stayed green (6 mL, 2.4 mmol). After 5 min the reaction was quenched with sat. aq. ammonium chloride (10 mL) and extracted with EtOAc (3 x 40 mL). The dried ($MgSO_4$) extract was filtered and concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10-50% EtOAc / hexanes to give alcohol **4.3.1** (145 mg, 318 μmol, 79%) as a colorless oil: $[\alpha]_D^{23}$ -7.8° (c = 0.2 $CHCl_3$); IR (neat) 3475, 2959, 2920, 1694, 1169, 1058 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.8 (t, *J* = 4.1 Hz, 1H), 4.40-4.45 (m, 1H), 4.10-4.25 (m, 2.H), 3.9 (d, *J* = 14.8 Hz, 1H), 3.70-3.80 (m, 2H), 3.20-3.42 (m, 3H), 2.22 (dd, *J* = 8.4 Hz, 1H), 2.00-2.20 (m, 4H), 1.80 (dd, *J* = 13.6, 4.8 Hz, 1H), 1.70 (dd, *J* = 9.6, 4.8 Hz, 1H) 1.52-1.75 (m, 3H), 1.20-1.40 (m, 3H), 1.01 (t, *J* = 4.4 Hz, 2H), 0.98 (d, *J* = 6.4 Hz, 3H), 0.76-0.92 (m, 6H), 0.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6, 97.3, 95.1, 78.3, 74.0, 70.5, 68.9, 63.1, 39.3, 9.1, 38.9, 36.0, 34.6, 31.3, 24.7, 23.2, 18.6, 17.7, 16.5, -1.4; HRMS (EI+) Calcd. for $C_{23}H_{41}O_6NSi$ (M+) 455.2703, Found 455.2911. (B8P74)



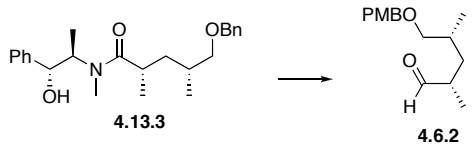
Sulfone 4.6.1: To a stirred solution of oxalyl chloride (16 mg, 24 μL, 300 μmol, 10 eq.) in CH_2Cl_2 (200 μL) at -50°C was added DMSO (47 mg, 46 μL, 600 μmol, 20 eq.) drop wise. After 10 min, a pre-cooled solution of alcohol **4.3.1** (13.5 mg, 30 μmol, 1 eq.) in CH_2Cl_2 (3 x 100 μL) was added via cannula. After 30 min, Et_3N (146 mg, 105 μL, 750 μmol, 25 eq.) was charged and the reaction was allowed to warm to 0°C over 30 min. The reaction was quenched with sat. aq.

$NaHCO_3$ (3 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The dried extracts ($MgSO_4$) were concentrated *in vacuo* and filtered through a 2 cm pad of silica gel, eluting with 25% EtOAc / hexanes to afford crude aldehyde **4.3.2** as a yellow oil which was used without further purification. An analytical was prepared for characterization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.1 (s, 1H), 4.85-4.90 (m, 1H), 4.40-4.45 (m, 1H), 4.10-4.23 (m, 2H), 3.89-4.00 (m, 1H), 3.82-3.88 (m, 1H), 3.65-3.80 (m, 2H), 3.13-3.25 (m, 1H), 2.00-2.40 (m, 5H), 1.50-1.90 (m, 7H), 1.20-1.50 (m, 5H), 0.98-1.03 (m, 5H) 0.78-0.94 (m, 6H), 0.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.4, 155.9, 97.2, 93.6, 78.1, 73.9, 71.2, 62.8, 48.5, 39.0, 37.1, 36.2, 34.6, 31.5, 29.7, 26.0, 24.2, 22.9, 18.6, 17.7, 16.4, -1.4.

To a stirred solution of LiCl (2.3 mg, 54 μmol, 1.4 eq.) in acetonitrile (250 μL) was charged sequentially phosphonate (11 mg, 36 μmol, 1.2 eq.) and DBU (5 mg, 5 μL, 33 μmol, 1.1 eq.). After 5 min, aldehyde **4.3.2** (43 μmol) in acetonitrile (100 μL, 2x 100 μL rinse) was added *via* cannula. After 5 min, the reaction filtered through a pad of silica gel, eluting with 10-40% EtOAc / hexanes to afford crude vinyl sulfone **4.6.4** as a colorless oil which was used without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80-7.90 (m, 2H), 7.50-7.70 (m, 3H), 6.75 (dd, *J* = 15.0, 0.4 Hz, 1H), 6.6 (dd, *J* = 15.0, 0.5 Hz, 1H), 4.80-4.85 (m, 1H), 4.35-4.40 (m, 1H), 3.90-4.28 (m, 2H), 3.84-4.05 (m, 1H), 3.65-3.82 (m, 4H), 3.12 (dd, *J* = 13.1, 11.5 Hz, 1H), 1.90-2.24 (m, 3H), 1.85 (dd, *J* = 13.8, 5.7 Hz, 1H), 1.42-1.75 (m, 3H), 1.20-1.45 (m, 6H), 0.95-1.13 (m, 2H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 6H), 0.05 (s, 9H); HRMS (ES+) Calcd. for $C_{30}H_{45}O_7SiNSNa$ (M+) 614.2584 Found 614.2549.

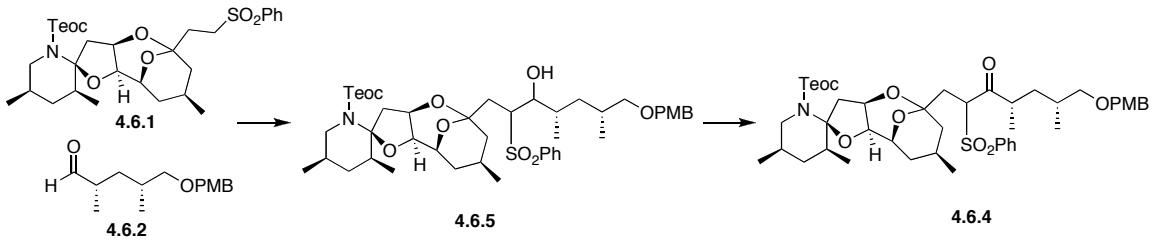
To a stirred solution of sulfone **4.6.4** (30 μmol) in THF (500 μL) at -78°C was charged $LiBHEt_3$ (150 μL, 150 μmol, 1M in THF, 5 eq.). The reaction was allowed to warm to room temperature over 1 h. After 3 h, the reaction was quenched with sat. aq. ammonium chloride (10 mL) slowly and was extracted with EtOAc (4 x 50 mL). The dried extract ($MgSO_4$) was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10-40% EtOAc / hexanes to give sulfone **4.6.1** (15.5 mg, 26 μmol, 86% 3 steps) as a colorless oil: $[\alpha]_D^{23}$ +18.0° (c = 3.3, $CHCl_3$); IR (Neat) 2955, 1692, 1146, 1062, 835 cm^{-1}; ^{1}H NMR (300 HMz, $CDCl_3$) δ 7.80-

7.90 (m, 2H), 7.50-7.70 (m, 3H), 4.75 (t, *J* = 4.0 Hz, 1H), 4.32-4.48 (m, 1H) 3.95-4.12 (m, 1H), 3.75 (d, *J* = 12.3Hz, 1H), 3.60-3.69 (m, 2H), 3.04-3.45 (m, 3H), 2.00-2.35 (m, 4H), 1.40-2.00 (m, 9H), 1.15-1.45 (m, 4H), 1.00-1.13 (m, 2H), 0.9 (d, *J* = 6.2 Hz, 3H), 0.82-0.85 (m, 6H), 0.1 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 139.5, 133.2, 129.0, 128.0, 97.1, 94.4, 78.1, 74.0, 70.4, 63.1, 50.0, 48.4, 43.2, 39.1, 38.7, 36.2, 35.1, 34.4, 31.2, 25.3, 23.3, 18.7, 17.7, 16.5, -1.4; HRMS (FAB+) Calcd. for $C_{30}H_{48}O_7SiNS$ (M+) 594.2921, Found 594.2937. (B3P61)



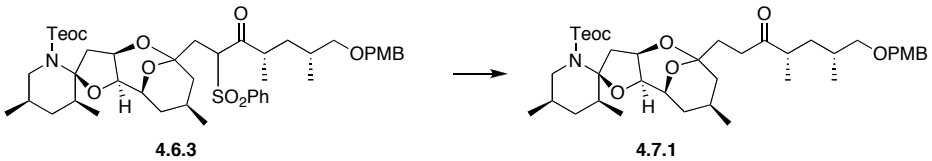
4.13.3 **4.6.2**

Aldehyde 4.6.2: To a stirred 0°C slurry of lithium aluminum hydride (45 mg, 1.17 mmol, 3.45 eq.) in hexanes (2.9 mL) was added EtOAc (154 mg,170 µL, 1.72 mmol, 5.07eq.). After 30 min, the reaction was cooled to -78°C. After 5 min, a solution of alkylate **4.13.3** (141 mg, 341 µmol, 1 eq.) in THF (800 µL, 1 x 400µL rinse). After 10 min, the reaction was allowed to warm to rt. After and additional 2 H, the reaction was quenched with a solution of trifluroaceticacid (200 µL) and 1M HCl (1.2 mL). The reaction was quenched with sat. aq. sodium chloride (40 mL) and was extracted with Et_2O (4 x 50mL). The combined extracts were washed sequentially with sat. aq. sodium chloride (10 mL) and sat. aq. $NaHCO_3$ (2 x 5 mL). The dried extract ($MgSO_4$) was concentrated *in vacuo.* The crude oil was then purified by chromatography over silica gel, eluting with 10-30% EtOAc / hexanes to give aldehyde **4.6.2** (50 mg, 200 *µ*mol, 59%) as a colorless oil. $[\alpha]_D^{23}$ +4.2° (c = 0.9, $CHCl_3$); IR (Neat) 2916, 2849, 1723, 1513, 1247, 1089 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.58 (d, *J* = 24 Hz, 1H), 7.24-7.28 (m, 2H), 6.85-6.95 (m, 2H), 4.43 (s, 2H), 3.83 (s, 3H), 3.25 (d, *J* = 5.7Hz, 2H), 2.42-2.49 (m, 2H), 1.82-1.95 (m, 2H), 1.10-1.25 (m, 1H), 1.10 (d, *J* = 6.6Hz, 3H), 0.96 (d, *J* = 6.6Hz, 3H); 13C NMR (100 MHz, $CDCl_3$) δ 205.2, 159.1, 130.6, 129.1, 113.7, 75.3, 72.7, 55.2, 44.0, 34.3, 30.9, 16.8, 13.4; HRMS (EI+) Calcd. for $C_{15}H_{22}O_3$ (M+) 250.1569, Found 250.1569. (B4P69)



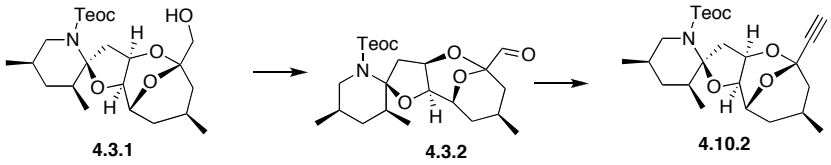
Ketosulfone 4.6.4: To a stirred -78°C solution of sulfone **6.6.1** (36 mg, 60.6 μmol, 1 eq.) in THF (200 μL) was sequentially added TMEDA (7 mg, 7 μL, 60.6 μmol, 1 eq.) and BuLi (121 μL, 303 μmol, 2.5 M in hexanes, 5 eq.). The reaction was warmed to -10° C for 15 min then cooled back to -78° C. The reaction was then charged with aldehyde **4.6.2** (123 mg, 364 μmol, 5 eq.) in THF (100 μL, 1 x 100 μL rinse) via cannula. After 30 min, reaction was quenched with sat. aq. ammonium chloride (3 mL) and was extracted with EtOAc (4 x 50mL). The dried extract ($MgSO_4$) was concentrated *in vacuo* to yield a yellow oil which was used immediately without purification.

To a stirred solution of crude hydroxyl sulfone **4.6.5** in CH_2Cl_2 (6 mL) was added powdered 4Å molecular sieves (200 mg). After 10 min, TPAP (4.6 mg, 12 μmol, 20 mol %) and NMO (15 mg, 121.2 μmol, 2 eq.) were sequentially added to the reaction. After 3 h, the reaction was filtered through a pad of silica and concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10-30% EtOAc / hexanes to give ketosulfone **4.6.4** (44 mg , 52.3 μmol, 86% over 2 steps) as a colorless oil. (B6p23)



Ketone 4.7.1: A stirred solution of ketosulfone **4.7.1** (5.5 mg, 6.5 μmol, 1 eq.) in THF (100 μL) and MeOH (300 µL) was cooled to -10°C and was charged with Na_2HPO_4 (1.1 mg, 7.8 μmol, 1.2 eq.). After 10 min, 5% Na/Hg amalgam (300 mg) was charged. After 22 h the reaction

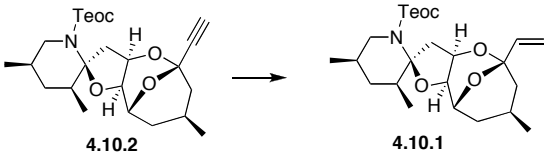
was filtered through a Celite® pad and rinsed with Et_2O (50 mL) and was concentrated *in vacuo.* The crude oil was then purified by chromatography over silica gel, eluting with 10-30% EtOAc / hexanes to give ketone **4.7.1** (4.2 mg, 5.9 μmol, 92%) as a colorless oil. $[\alpha]_D^{23}$ -8.7° (c = 4.0, $CHCl_3$); IR (Neat) 2954, 2927, 1717, 1694, 1512, 1249, 1083 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22-7.38 (m, 2H), 6.78-6.95 (m, 2H), 5.44-5.51 (m, 1H), 5.11-5.30 (m, 2H), 4.63-4.82 (m, 1H), 4.35-4.45 (m, 2H), 4.23-4.40 (m, 1H), 4.01-4.22 (m, 2H), 3.67-3.97 (m, 6H), 3.09-3.40 (m, 3H), 2.00-2.40 (m, 6.6H), 1.10-2.00 (m, 15H), 0.70-0.95 (m, 17H), 0.05 (s, 9H); δ 13C NMR (100 MHz, $CDCl_3$) δ 159.0, 155.9, 139.3, 130.9, 129.0, 123.3, 113.7, 97.0, 96.0, 78.2, 76.1, 73.5, 72.5, 71.2, 62.6, 55.2, 48.5, 45.7, 41.6, 41.1, 39.3, 39.1, 36.5, 35.1, 34.4, 31.4, 31.0, 29.7, 24.6, 23.1, 22.0, 18.7, 17.7, 16.9, 16.5, -1.4. (B6P26)



Acetylene 4.10.2: To a stirred solution of oxalyl chloride (103 mg, 155 μL, 1.96 mmol, 10 eq.) in CH_2Cl_2 (800 μL) at -50°C was added DMSO (307 mg, 300 μL, 3.92 mmol, 20 eq.) dropwise. After 10 min, a pre-cooled solution of alcohol **4.3.1** (89 mg, 196 μmol, 1 eq.) in CH_2Cl_2 (3 x 400 μL) was added via cannula. After 30 min, Et_3N (972 mg, 700 μL, 4.9 μmol, 25 eq.) was added to the solution. The reaction was allowed to warm to 0°C over 30 min then was quenched with sat. aq. $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 x 70 mL). The dried extracts ($MgSO_4$) were concentrated *in vacuo* and filtered through a 2 cm pad of silica gel, eluting with 25% EtOAc / hexanes to afford crude aldehyde **4.3.2** as a yellow oil which was used without further purification.

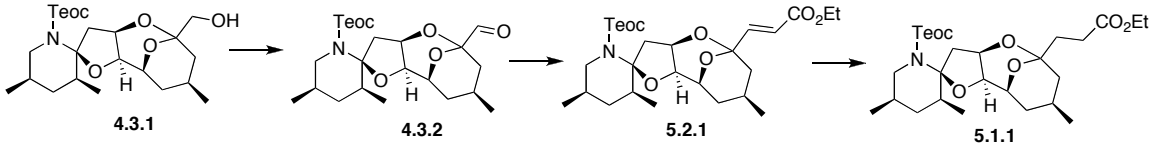
To a stirred solution of aldehyde **4.3.2** (196 μmol, 1 eq.) in methanol (4 mL) was added sequentially K_2CO_3 (163 mg, 1.18 mmol, 6 eq.) and Bestman reagent[11] (188 mg, 979 μmol, 5 eq.) After 3 h, the reaction was diluted in hexanes (10 mL) and filtered through a 4 cm plug of silica

eluting with 20% EtOAc / hexanes to give acetylene **4.10.2** (82 mg, 182 μmol, 93%) as a colorless oil: $[\alpha]_D^{23}$ -10.4° (c = 0.8, $CHCl_3$); IR (neat) 3313, 2959, 2916, 2131, 1696, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.68-4.80 (m, 1H), 4.32-4.38 (m, 1H), 4.05-4.25 (m, 2H), 3.73-3.94 (m, 3H), 3.13-3.22 (M, 2H), 2.43 (s, 1H), 1.95-2.38 (m, 6H), 1.50-1.75 (m, 10H), .070-1.05 (mm, 11H). 0.04 (s, 9H); C^{13}(75 MHz, $CDCl_3$) δ 155.9, 97.1, 90.3, 83.5, 77.6, 74.1, 73.0, 70.0, 62.7, 48.7, 45.2, 39.6, 38.7, 37.0, 34.7, 31.2, 23.8, 22.3, 18.6, 17.6, 16.4, -1.4; HRMS (EI+) Calcd. for $C_{24}H_{39}O_5NSi$ (M+) 449.2597, Found 449.2599. (B7P75)



4.10.2 **4.10.1**

Alkene 4.10.1: To a stirred solution of acetylene **4.10.2** (23 mg, 51 μmol, 1 eq.) in 10:1 EtOAc/1-octene (1 mL) was added Lindlar catalyst (28 mg) under argon. The reaction was flushed with 1 balloon of hydrogen and fitted with another. After 4 h, the reaction was diluted with hexanes (3 mL) and filtered through a plug of silica eluting with 20% EtOAc / hexanes to give alkene **4.10.1** (20 mg, 44 μmol, 87%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 5.80 (dd, *J* = 17.2, 10.8 Hz, 1H), 5.33-5.38 (m, 2H), 5.08 (d, *J* = 10.4 Hz, 1H), 4.78-4.82 (m, 1H), 4.35-4.37 (m, 1H), 4.00-4.30 (m, 3H), 3.73-3.90 (m, 3H), 3.21 (t, *J* = 13.2 Hz, 1H),1.90-2.40 (m, 1H), 1.20-1.80 (m, 12 H), 0.70-1.09 (m, 13H), 0.05 (s, 9H). (B8P44)



4.3.1 **4.3.2** **5.2.1** **5.1.1**

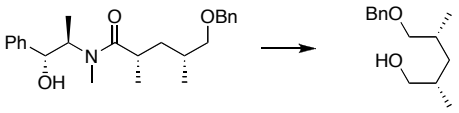
Ester 5.1.1: To a stirred solution of oxalyl chloride (58 mg, 87 μL, 1.1 mmol, 10 eq.) in CH_2Cl_2 (300 μL) at -50°C was added DMSO (172 mg, 157 μL, 2.2 mmol, 20 eq.) dropwise. After

10 min, a pre-cooled solution of alcohol **4.3.1** (50 mg, 109.9 μmol, 1 eq.) in CH_2Cl_2 (3 x 150 μL) was added via cannula. After 30 min, Et_3N (277 mg, 200 μL, 2.75 mmol, 25 eq.) was charged and reaction was allowed to warm to 0°C over 30 min. The reaction was quenched with sat. aq. $NaHCO_3$ (6 mL) and extracted with CH_2Cl_2 (3 x 40 mL). The dried extracts ($MgSO_4$) were concentrated *in vacuo* and filtered through a 2 cm pad of silica gel, eluting with 25% EtOAc / hexanes to afford crude aldehyde **4.3.2** (55 mg) as a yellow oil which was used without further purification.

To a stirred solution of LiCl (7.6 mg, 180 μmol, 1.8 eq.) in acetonitrile (1 mL) was charged sequentially ethyl (diethoxyphosphinyl)acetate (30 μL, 150 μmol, 1.5 eq.) and DBU (16.7 mg, 16 μL, 110 μmol, 1.1 eq.). After 5 min, aldehyde **4.3.2** (100 μmol, 50 mg) in acetonitrile (3 x 1.5 mL) was added *via* cannula. After 5 min, the reaction was quenched with sat. aq. ammonium chloride (3 mL) and was extracted with EtOAc (4 x 20 mL). The dried extract ($MgSO_4$) was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with eluting with 10 - 40% EtOAc / hexanes to afford ester **5.2.1** as a mixture of olefin isomers as a colorless oil (40 mg, 74 μmol, 74% over 2 steps). An analytical sample was prepared: $[\alpha]_D^{23}$ +11.0°, c = 0.1 $CHCl_3$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (d, *J* = 15.7 Hz, 1H), 6.05 (d, *J* = 15.7 Hz, 1H), 4.78-4.85 (m, 1H), 3.36-4.41 (m, 1H), 408-4.28 (m, 4H), 3.68-4.02 (m, 3H), 3.10-3.24 (m, 1H), 2.95 (d, *J* = 21.4 Hz, 1H), 2.10-2.32 (m, 2H), 1.55-2.10 (m, 6H), 1.15-1.45 (m, 3H), 0.74-1.10 (m, 11H), 0.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 155.8, 147.7, 128.3, 120.6, 97.1, 93.5, 77.9, 74.1, 71.9, 62.6, 60.2, 48.4, 43.0, 39.3, 36.5, 34.7, 31.3, 24.5, 22.8, 18.6, 17.5, 16.4, 14.2,-1.4. (B8P57)

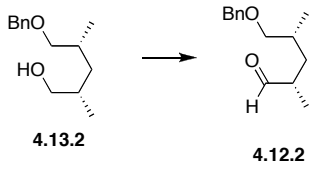
To a stirred slurry of Stryker's reagent (540 mg, 275 μmol, 2.1 eq.) in toluene (2 mL) in a sealed tube was added a solution of ester **5.3.2** (70 mg, 130 μmol, 1 eq.) in toluene (3 x 1 mL) *via cannula*. The tube was capped and placed in a 110°C oil bath. After 20 h, the reaction was cooled and filtered through a 2 cm pad of silica eluting in 30% EtOAc / hexanes. Eluant was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 0-20% EtOAc / hexanes to give ester **5.3.1** (57 mg, 100 μmol, 77%) as a colorless oil: $[\alpha]_D^{23}$ +11.0°, (c = 1.0 $CHCl_3$); IR (neat) 2948, 2916, 2867, 1739, 1690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.72-4.81 (m,

1H), 4.28-4.38 (m, 1H), 4.00-4.26 (m, 4H), 3.90 (d, *J* = 4.8 Hz, 1H), 3.72-3.84 (m 1H), 3.68-3.72 (m, 1H), 3.65 (s, 2H), 3.20 (t, *J* = 12.6 Hz, 1H), 2.30-2.52 (m, 2H), 2.10-2.24 (m, 2H), 2.01-2.10 (m, 1H), 1.90 (dd, *J* = 13.7, 5.2 Hz, 1H), 1.41-1.95 (m, 12H), 0.81-1.10 (m, 13H), 0.4 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 156.1, 97.1, 94.9, 78.1, 73.8, 70.7, 62.7, 51.3, 48.3, 43.0, 39.2, 37.0, 36.4, 34.9, 31.3, 27.6, 25.1, 23.3, 18.7, 17.7, 16.5, 14.3, -1.4; HRMS (CI+) Calcd. For $C_{27}H_{47}O_7NSiNa$ (M+Na) 548.3020, Found 548.2993 (B8P90)

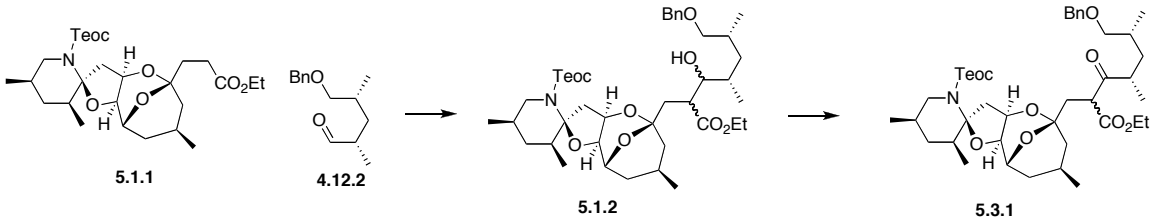


4.13.1 **4.13.2**

Alcohol 4.13.2: To a 0°C stirred solution of LDA (52.5 mL, 52.5 mmol, 1M solution in THF / hexanes) was added BH_3•NH_3 (1.8 g, 52.5 mmol, 3 eq.). After 15 min, the reaction was warmed to rt. After an additional 10 min, the reaction was cooled back to 0°C and a solution of amide **4.13.1** (6.7g, 17.5 mmol, 1eq.) in THF (20 mL) was added slowly *via cannula*. After 5 min, the reaction was then warmed to rt. After 2 h, the reaction was quenched with 3M HCl (50 mL). After 30 min, the reaction was extracted with Et_2O (3 x 100 mL). The dried extract ($MgSO_4$) was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with eluting with 10-40% EtOAc / hexanes to afford alcohol **4.13.2** (2.9 g, 13 mmol, 75%) as a mixture of rotamers in a colorless oil. $[\alpha]_D^{23}$, +6.9 (c = 0.8 $CHCl_3$); IR (neat) 3384, 2927, 2954, 1451cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.20-7.40 (m, 5H), 4.45-4.60 (m, 2H), 3.22-3.50 (m, 4H), 2.38 (s, 1H), 1.86-1.96 (m, 1H), 1.67-1.76 (m, 1H), 1.47-1.54 (m, 1H), 0.79-1.30 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 128.3, 127.6, 75.9, 73.1, 67.7, 37.7, 33.1, 31.0, 18.18, 17.6; HRMS (ES+) Calcd. for $C_{14}H_{22}O_2$ (M+) 222.1620, Found 220.1626. (B9P69)



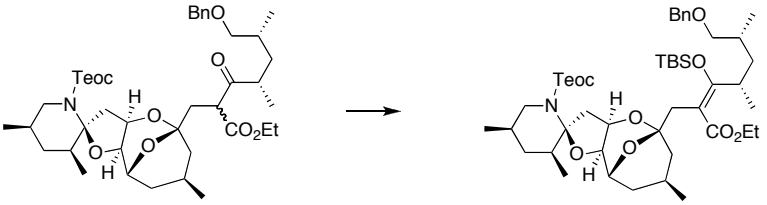
Aldehyde 4.12.2: To a stirred solution of alcohol **4.13.2** (350 mg, 1.57 mmol, 1 eq.) in CH_2Cl_2 (18 mL) was added sequentially TPAP (60 mg, 157 μmol, 0.1 eq) NMO (552 mg, 4.71 mmol, 3eq.) and powdered molecular sieves (200 mg). After 30 min, the reaction was diluted in hexanes and filtered through a 1cm plug of silica eluting with 20% EtOAc / hexanes to give aldehyde **4.12.4** as a colorless oil (250 mg, 1.14 mmol, 75%). $[\alpha]_D^{23}$, +7.2 (c = 0.8 $CHCl_3$); IR (neat) 2965, 2867, 1734, 1487, 1102 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 9.58 (s, 1H), 7.20-7.40 (m, 5H), 4.51 (s, 2H), 3.32 (d, *J* = 5.6 Hz, 2 H), 2.44-2.55 (m, 1H), 1.84-2.14 (m, 2H), 1.09-1.30 (m, 1H), 1.04 (d *J* = 6.5 Hz, 3 H), 0.98 (d *J* = 6.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.2, 138.5, 128.3, 127.5, 75.3, 73.0, 44.1, 35.0, 31.3, 17.6, 14.35; HRMS (CI+) Calcd. for $C_{14}H_{19}O_2$ (M+) 219.1385, Found 219.1399. (B9P45)



Ketoester 5.3.1: To a stirred solution of ester **5.1.1** (57 mg, 119 μmol, 1 eq.) in THF (500 μL) at -78°C was added LDA[7] (238 μL, 238 μmol, 2 eq., 1 M in THF / hexanes) reaction was brought to 0°C briefly and then cooled back to -78°C. After 20 min, a pre-cooled solution of aldehyde **4.12.2** (105 mg, 476 μmol, 4 eq.) in THF (200 μL) was added *via cannula*. After 2 h, the reaction was quenched by pouring into sat. aq. ammonium chloride (10 mL) and was extracted with Et_2O (4 x 50 mL). The dried extract ($MgSO_4$) was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with eluting with 10-40% EtOAc / hexanes to afford aldol

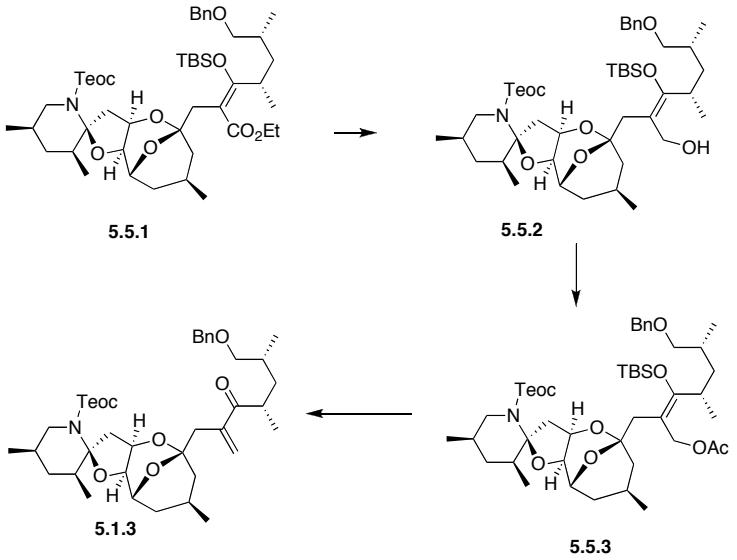
adduct **5.1.2** as a mixture of diastereomers as a colorless oil which was used immediately without further purification.

To a stirred solution of aldol adduct **5.1.2** (119 μmol, 1 eq.) in CH_2Cl_2 (6 mL) was added sequentially DMP (151 mg, 357 μmol, 3 eq.) and $NaHCO_3$ (30 mg, 357 μmol, 3 eq.). After 35 min, the reaction was diluted in hexanes (5 mL) and filtered through a plug of silica, eluting with 30% EtOAc / hexanes, to give ketoester **5.3.1** as a colorless oil (66 mg, 88.7 μmol, 75% 2 steps): $[\alpha]_D^{23}$ -12.0 (c = 0.1, $CHCl_3$); IR (neat) 2927, 2948, 2856, 1734, 1696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.70-4.78 (m, 1H), 4.50 (s, 2H), 3.93-4.40 (m, 6H), 3.72-3.85 (m, 1H), 3.52-3.70 (m, 2H), 3.30-3.40 (m, 1H), 3.16-3.30 (m, 1H), 2.80-3.10 (m, 1H), 2.22-2.40 (m, 1H), 1.78-2.20 (m, 6H), 0.65-1.10 (m, 20H), 0.04 (s, 9H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.4, 208.8, 170.3, 169.9, 156.6, 138.8, 128.2, 127.4, 127.3, 97.0, 96.9, 95.3, 78.0, 75.8, 75.7, 73.8, 65.8, 62.8, 61.1, 60.7, 52.7, 49.4, 49.1, 43.5, 42.9, 42.5, 40.5, 40.2, 39.0, 36.9, 36.7, 34.8, 34.4, 31.1, 31.0, 29.6, 24.9, 23.2, 23.1, 18.7, 18.0, 17.7, 17.7, 16.7, 16.6, 15.2, 14.1, -1.4; HRMS (ES+) Calcd. for $C_{41}H_{66}O_9NSiNa$ (MNa+) 766.5855, Found 766.4320. (B8P98)



TBS Enol Ether5.5.1: To a stirred solution of ketoester **5.3.1** (66 mg, 88.7 μmol, 1 eq.) in THF (750 μL) at -78°C was added NaHMDS (266 μL, 266 μmol, 3 eq., 1 M in THF). The reaction was warmed to -10°C briefly then cooled back to -78°C. After 10 min, the reaction was charged with TBSOTf (70 mg, 61 μL, 266 μmol, 3 eq.) After 30 min, the reaction was quenched with pH 7 buffer (5 mL) and was extracted with Et_2O (3 x 40 mL). The dried extract ($MgSO_4$) was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10 - 20% EtOAc / hexanes to afford TBS enol ether **5.5.1** (61 mg, 72 μmol, 81%) as a colorless oil: $[\alpha]_D^{23}$

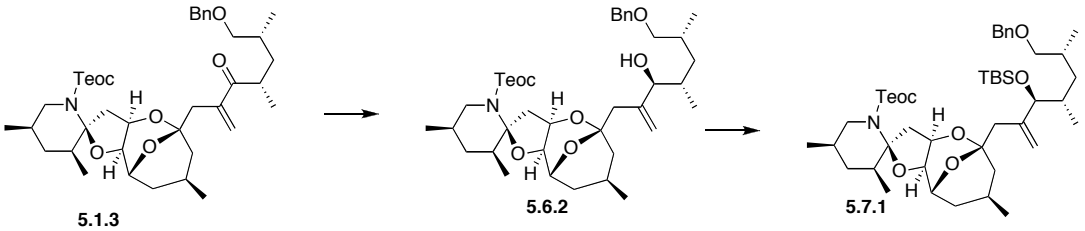
-61.7 (c = 0.6 $CHCl_3$); IR (neat) 2954, 2927, 2867, 2333, 1707, 1636 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.61-4.78 (m, 1H), 4.45-4.55 (m, 2H), 4.00-4.30 (m, 5H), 3.70-3.95 (m, 3H), 3.18-3.56 (m, 3H), 2.10-2.67 (m, 4H), 1.50-1.88 (m, 4H), 0.70-1.10 (m, 30H), -0.10-0.30 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 169.0, 159.8, 159.6, 156.1, 155.9, 138.9, 138.8, 128.2, 128.2, 127.4, 127.4, 127.2, 111.2, 109.5, 96.9, 96.8, 96.7, 78.0, 77.9, 77.2, 76.4, 76.1, 73.7, 73.3, 72.8, 72.0, 71.3, 62.6, 59.9, 59.7, 48.9, 48.5, 40.9, 40.5, 40.4, 39.9, 39.5, 39.0, 38.8, 37.7, 36.7, 36.5, 35.4, 34.7, 33.5, 31.5, 31.4, 31.3, 31.3, 29.7, 26.3, 24.3, 24.0, 22.9, 22.6, 19.2, 19.0, 18.9, 18.9, 18.6, 18.0, 17.8, 17.7, 16.9, 16.5, 14.2, 14.1, -1.4, -2.3, -2.9, -3.0, -3.4; HRMS (ES+) Calcd. for $C_{47}H_{79}O_9NSiNa$ (M+Na) 880.5191, Found 880.5238. (B8P98)



Enone 5.1.3: To a stirred -78°C solution of ester **5.5.1** (30 mg, 35 *μ*mol, 1 eq.) in hexanes (500 μL) was added DIBAL-H (1.75 mL, 175 *μ*mol, 0.1 M in hexanes, 7eq.) dropwise. After 3 h, the reaction was quenched with methanol (1 mL) and allowed to warm to rt. The reaction was stirred in sat. aq. Rochelle's salt (5 mL). After 3 h, the solution was extracted with EtOAc (3 x 20 mL). The dried extract ($MgSO_4$) was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with eluting with 10-40% EtOAc / hexanes to afford alcohol **5.5.2** as a colorless oil (26 mg, 32 *μ*mol, 91%).

To a stirred solution of alcohol **5.5.2** (15 mg, 18.4 μmol, 1 eq.) in pyridine (500 μL) was added acetic anhydride (60 μL) and DMAP (2.2 mg, 18.4 μmol, 1 eq.). After 30 min, the reaction was diluted in hexanes (1 mL) and filtered through a 1 cm plug of silica, eluting in 20% EtOAc / hexanes, to give allylic acetate **5.5.3** as a crude oil (13 mg).

To a stirred solution of crude acetate **5.5.3** (18.4 μmol) in THF (900 μL) was added TAS-F (10 mg, 36.8 μmol, 2 eq.). After 30 min, the reaction was diluted in hexanes (1 mL) and filtered through a 3 cm pad of silica to give enone **5.1.3** (10 mg, 14.6 μmol, 79% over 2 steps) as a colorless oil. $[\alpha]_D^{23}$ -9.8 (c = 0.5 $CHCl_3$); IR (neat) 2954, 2925, 2853, 1695, 1669 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.30-7.42 (m, 5H), 6.12 (s, 1H), 5.96 (s, 1H), 4.65-4.78 (m, 1H), 4.49 (s, 2H), 4.25-4.35 (m, 1H), 4.04-4.28 (m, 2H), 3.65-3.95 (m, 5H), 3.10-3.50 (m, 6H), 2.60-2.70 (m, 1H), 2.45-2.55 (m, 1H), 2.12-2.24 (m, 2H), 1.40-2.10 (m, 20H), 0.65-1.10 (m, 33H), 0.04 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.7, 155.9, 142.9, 138.7, 128.4, 128.3, 127.4, 97.0, 95.4, 78.1, 77.2, 75.7, 73.6, 72.8, 71.2, 62.6, 48.6, 41.6, 39.4, 39.0, 38.0, 37.0, 36.5, 34.5, 31.4, 30.3, 29.3, 24.6, 23.0, 22.7, 18.8, 17.8, 16.5, 14.1, -1.4; HRMS (ES+) Calcd. for $C_{39}H_{61}O_7NSiNa$ (M+Na) 706.4115, Found 706.4086. (B8P91)



TBS Ether 5.7.1: To a stirred solution of ketone **5.1.3** (45 mg, 65.9 µmol, 1 eq.) in methanol (3.3 mL) was added $CeCl_3 \cdot 7H_2O$ (74 mg, 197 μmol, 3 eq.). The reaction was cooled to -78°C and charged with $NaBH_4$ (5 mg, 197 mmol, 3 eq.). The reaction was allowed to slowly warm to rt over the course of 2 h. The reaction was then diluted with hexanes (1 mL) and filtered through a pad of silica eluting in 20% EtOAc / hexanes to afford crude alcohol **5.6.2** (49 mg, 3:1 dr) as a colorless oil which was then carefully purified by chromatography over silica gel, eluting

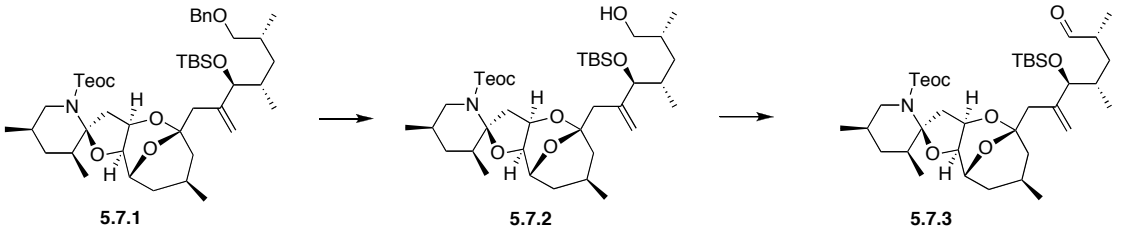
with 10 - 20% EtOAc / hexanes to afford a single diastereomer fraction of alcohol **5.6.2** (15mg) and as a ~1:1 diaseromeric mixture (20mg).

The mixture of diastereomers was then oxidized and resubmmited to reduction conditions: To a stirred solution of alcohol **5.6.2** (~20 mg, ~30 µmol) in CH_2Cl_2 (1.5 mL), was charged Dess-Martin periodinate (20 mg, 47 µmol) and $NaHCO_3$ (10 mg, 119 µmol). After 30 min, the reaction was diluted with hexanes (3 mL) and filtered through a plug of silica gel (1 cm) and eluted with 20% EtOAc / hexanes to afford analytically pure ketone **5.1.3** (~20 mg) which was resubmitted to Luche reduction.

Two recycles afforded alcohol **5.6.2** (20 mg, 29 µmol, 45%) as a single diasteromer, and (5 mg, 7.2 µmol, 11%) as a 1:1 mixture of diastereomers. $[\alpha]_D^{23}$ -2.1 (c = 1.0 $CHCl_3$); IR (neat) 3460, 2959, 2899, 1696 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.30-7.50 (m, 5H), 5.06 (s, 1H), 4.96 (s, 1H), 4.70-4.80 (m, 1H), 4.51 (q *J* = 8.0 Hz, 2H), 4.28-4.32 (m, 1H), 4.00-4.25 (m, 2H), 3.65-3.84 (m, 4H), 3.38-3.49 (m, 2H), 3.07-3.21 (m, 2H), 1.42-2.41 (m, 16H), 1.18-1.36 (m, 5H), 0.80-1.05 (m, 21H), -0.01 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 144.6, 138.9, 128.2, 127.4, 127.2, 116.9, 97.0, 96.2, 79.7, 77.8, 77.2, 75.7, 73.8, 72.8, 62.8, 48.7, 45.7, 42.3, 39.9, 38.9, 36.5, 35.1, 34.9, 31.2, 24.5, 22.9, 21.4, 19.2, 18.7, 17.7, 17.2, 16.5, -1.7; HRMS (ES+) Calcd. for $C_{39}H_{63}O_7NSiNa$ (M+Na) 708.4272, Found 708.4252.

To a stirred solution of alcohol **5.6.2** (20 mg, 29 µmol) in THF (600 *µ*L) at -78°C was added 2 6-lutidine (18.4 mg, 20 *µ*L, 175 *µ*mol, 8.75 eq.) and TBSOTf (23 mg, 20 *µ*L, 87.6 *µ*mol, 4.4 eq.) sequentially. After 1 h, the reaction was quenched with pH 7 buffer (2 mL) and was extracted with Et_2O (3 x 20 mL). The dried extract ($MgSO_4$) was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10-20% EtOAc / hexanes to afford TBS ether **5.7.1** (20 mg, 25 *µ*mol, 86%) as a colorless oil. $[\alpha]_D^{23}$ -4.5° (c = 0.2 $CHCl_3$); IR (neat) 2959, 2927, 1696 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ (7.25-7.45 (m, 5H), 5.14 (s, 1H), 4.95 (s, 1H), 4.41-4.51 (m, 1H), 4.45 (q, *J* = 12.0 Hz, 2H), 4.10-4.34 (m, 3H), 3.88-4.07 (m, 1H), 3.72-3.92 (m, 3H), 3.30-3.42 (m, 1H), 3.28 (t, *J* = 11.2 Hz, 1H), 3.06 (t, *J* = 5.6 Hz, 1H), 1.90-2.18 (m, 4H), 1.23-1.80 (m, 10H), 0.80-1.14 (m, 26H), -0.02-0.08 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9,

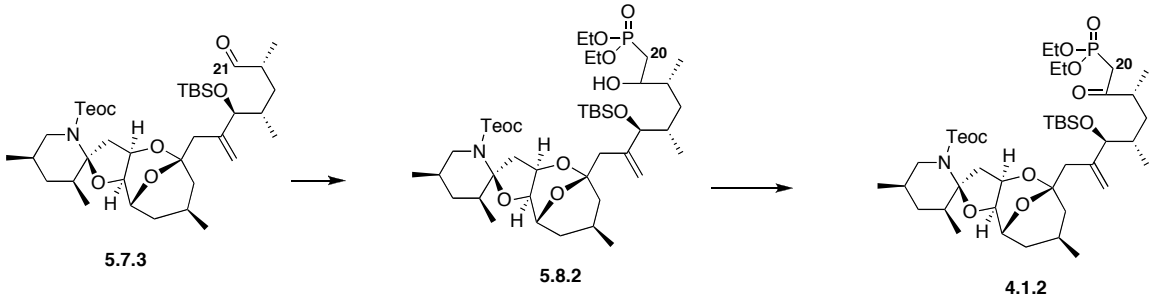
146.1, 139.0, 128.2, 127.3, 127.2, 114.1, 97.1, 96.6, 79.0, 78.1, 77.2, 75.7, 73.6, 72.8, 70.8, 62.6, 48.5, 45.1, 40.3, 39.3, 36.3, 34.5, 33.4. 33.3, 31.7, 31.4, 26.0, 24.5, 23.1, 19.3, 19.0, 18.6, 18.2, 16.4, -1.5, -3.9, -4.2; HRMS (ES+) Calcd for $C_{45}H_{77}O_7Si_2NNa$ (M+Na) 822.5136, Found 822.5084. (B8P93)



Aldehyde 5.7.3: To a stirred -78°C solution of benzyl ether **5.7.1** (20 mg, 25 μmol, 1 eq.) in THF (1 mL, 0.025 M) was added LiDBB[10] (250 μL, 50 μmol, 0.2 M in THF). After 3 min, another aliqoit of LiDBB (250 µL) was added. After another 2 min, the reaction was quenched with sat. aq. ammonium chloride (1 mL) and was extracted with Et_2O (3 x 20 mL). The dried extract ($MgSO_4$) was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with eluting with 10-20% EtOAc / hexanes to afford alcohol **5.7.2** (12.8 mg, 18.0 µmol, 72%) as a colorless oil. $[\alpha]_D^{23}$ +2.2 (c = 0.5 $CHCl_3$); IR (neat) 3324, 2954, 2927, 1690 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 5.17 (s, 1H), 4.96 (s, 1H), 4.72-4.76 (m, 1H), 4.00-4.29 (m, 4H), 3.74-3.77 (m, 2H), 3.14-3.55 (m, 3H), 1.90-2.35 (m, 6H), 1.25-1.75 (m, 16H), 0.75-1.05 (m, 26H), -0.01-0.05 (m, 15 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0, 146.5, 114.2, 97.1, 96.5, 78.5, 78.0, 73.6, 70.8, 63.0, 48.6, 45.5, 40.4, 39.0, 36.6, 34.5, 33.5, 33.0, 32.3, 31.4, 26.0, 24.5, 23.1, 18.9, 18.8, 18.6, 18.3, 18.0, 16.5, -1.5, -3.9, -4.2; HRMS (ES+) Calcd for $C_{38}H_{71}O_7Si_2NNa$ (M+Na) 732.4667, Found 732.4633.

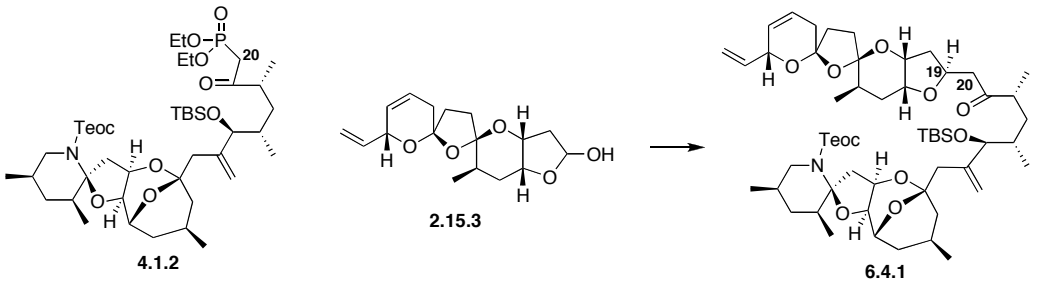
To a stirred solution of alcohol **5.7.2** (13 mg, 18.3 μmol, 1 eq.) in CH_2Cl_2 (500 μL) was added sequentially TPAP (1.7 mg, 4.5 μmol, 0.25 eq) NMO (8.1 mg, 69 μmol, 3.8 eq.) and powdered molecular sieves (60 mg). After 15 min, the reaction was diluted in hexanes and filtered through a 1 cm plug of silica eluting with 30% EtOAc / hexanes to give aldehyde **5.7.3** as

a colorless oil (12 mg, 16.9 μmol, 92%). $[\alpha]_D^{23}$ -2.0 (c = 0.6, $CHCl_3$); IR (neat) 2959, 2927, 2867, 1739, 1690 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 9.49 (s, 1H), 5.19 (s, 1H), 4.97 (s, 1H), 4.65-4.78 (m, 1H), 3.65-4.31 (m, 9H), 3.20 (t, J = 12.8 Hz, 1H), 1.45-2.44 (m, 16H), 0.82-1.19 (m, 26H), -0.07-0.03 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.5, 155.9, 146.1, 114.4, 97.1, 96.4, 78.4, 78.1, 73.6, 70.7, 62.7, 48.4, 45.3, 44.3, 40.3, 39.2, 39.1, 36.3, 34.4, 32.9, 31.4, 30.4, 26.0, 24.6, 23.1, 18.8, 18.6, 18.1, 16.4, 14.6, -1.5, -3.9, -4.2; HRMS (ES+) Calcd for $C_{38}H_{69}O_7Si_2NNa$ (M+Na) 730.4510, Found 730.4506. (B9P64)



Ketophosphonate 4.1.2: To a -78°C stirred solution of methane diethyl phosphonate (54 mg, 355 µmol, 1 eq.) in THF (3 mL) was added BuLi (142 µL, 2.5 M solution in hexanes, 355 µmol, 1 eq.). After 10 min, the phosphonate solution (200 µL, 22 µmol, 0.11 M solution in THF, 1.3 eq.) was added to a -78°C solution of aldehyde **5.7.3** (12 mg, 16.9 µmol, 1eq) in THF (500 µL, 0.03M). After 10 min, the reaction was allowed to warm to rt and was quenched with sat. aq. ammonium chloride (1 mL) and was extracted with EtOAc (3 x 10 mL). The dried extract ($MgSO_4$) was concentrated *in vacuo* and submitted to oxidation as a crude oil.

To a stirred solution of the hydroxyphosphonate **5.8.2** (16.9 µmol) in CH_2Cl_2 was added sequentially $NaHCO_3$ (5 mg, 84.5 µmol, 3 eq.) and Dess-Martin periodinate (24 mg, 84.5 µmol, 3 eq.). After 20 min, the reaction was diluted in 1 mL hexanes and purified by chromatography over silica gel, eluting with eluting with 10-30% EtOAc / hexanes to afford keto phosphonate **4.1.2** (7.5 mg, 8.7 µmol, 52% over 2 steps) as a colorless oil. (B9P64)



Ketone 6.4.1: To a -78°C solution of keto phosphonate **4.1.2** (7.5 mg, 8.7 µmol, 1.25 eq.) in THF (300 µL) was added KHMDS (20 µL, 10 µmol, 0.5M solution in PhMe, 1.15 eq.). After 10 min, keto phosphonate was added to a -78°C solution of lactol **2.15.3** (2 mg, 7 µMol, 1 eq.) in THF (100 µL) *via cannula* and was rinsed in with THF (2 x 250 µL). After 5 min, an additional aliquoit of KHMDS (10 µL, 5 µmol, 0.575 eq., 0.5 M solution in PhMe) was added to the reaction. After and additional 10 minutes the reaction was allowed to slowly warm to rt. After an additional 16 h, the reaction was with sat. aq. ammonium chloride (1 mL) and was extracted with EtOAc (3 x 10 mL). The dried extract ($MgSO_4$) was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with eluting with 10-50% EtOAc / hexanes to afford ketone **6.4.1** (3.0 mg, 3.0 µmol, 42%) as a colorless oil and ketophosphonate **4.1.2** (3.0 mg, 3.5 µmol, 40% rec.). $[\alpha]_D^{23}$ -4.0 (c = 0.2 $CHCl_3$); IR (neat) 2959, 2927, 2861, 1696 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 5.77-5.90 (m, 2H), 5.70 (d, *J* = 10.3 Hz, 1H), 5.30 (d, *J* = 17.3 Hz, 1H), 5.18 -5.23 (m, 2H), 4.99 (s, 1H), 4.88 (s, 1H), 4.78 (s, 1H), 4.55-4.63 (m, 1H), 3.65-4.43 (m, 14H), 3.18-3.39 (m, 2H), 2.87 (dd, *J* = 16.7 6.23 Hz, 1H of a rotamer), 2.83 (dd, *J* = 16.7 6.23 Hz, 1H), 2.00-2.75 (M, 8H), 1.70-2.00 (m, 3H), 0.75-1.12 (m, 29H), -0.10-0.10 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.9, 155.9, 153.8, 146.4, 138.9, 137.5, 130.1, 128.3, 127.6, 122.9, 122.6, 119.5, 116.4, 114.1, 113.2, 110.1, 105.5, 100.0, 97.1, 96.5, 78.6, 78.1, 75.9, 74.6, 73.7, 72.0, 71.1, 70.7, 62.7, 48.3, 46.4, 45.5, 45.2, 40.2, 39.3, 39.0, 36.6, 36.3, 34.8, 34.4, 32.5, 32.1, 31.9, 31.4, 29.7, 29.5, 26.1, 24.6, 23.0, 22.6, 19.5, 18.6, 18.2, 18.1, 16.8, 16.4, 16.1, 14.1, -1.4, -3.9, -5.1; HRMS (ES+) Calcd for $C_{56}H_{93}O_{11}NSi_2Na$ (M+Na) 1034.6185, Found 1034.6204. Due to a problem associated with the installation of a new 700mHz NMR there was a problematic data point in the FID for all

spectroscopy associated with this compound limiting the characterization of the compound. (B9P69)

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6. Preparation of Base: To a solution of 2,2,6,6-tetramethylpiperidine (282.8 mg, 340 µL, 2.0 mmol) in THF (0.86 mL) was added n-BuLi (0.8 mL, 2.0 mmol, 2.5 M in hexanes). The reaction was warmed to -10°C and stirred for 30 min prior to use.

7 LDA: To a stirred -78°C solution of diisopropyl amine (10.0 g, 14 mL, 100 mmol) in THF (46 mL) was added nBuLi (40 mL, 100 mmol, 2.5 M in Hexanes). After 15 min, reaction was warmed briefly to -10°C and then returned to -78°C. After 10 min, LDA had crashed out to form a white solid. The solution was then warmed to -10°C and used immediately.

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10. To a stirred solution of ditertbutlyl biphenyl (3.7 g, 13.6 mmol) in THF (34 mL, 0.4 M) at 0°C, was added lithium wire (1.3 g, ~5 eq.). The reaction was sonicated at 0°C for 10 min and then stirred at 0°C for an additional 2 h.

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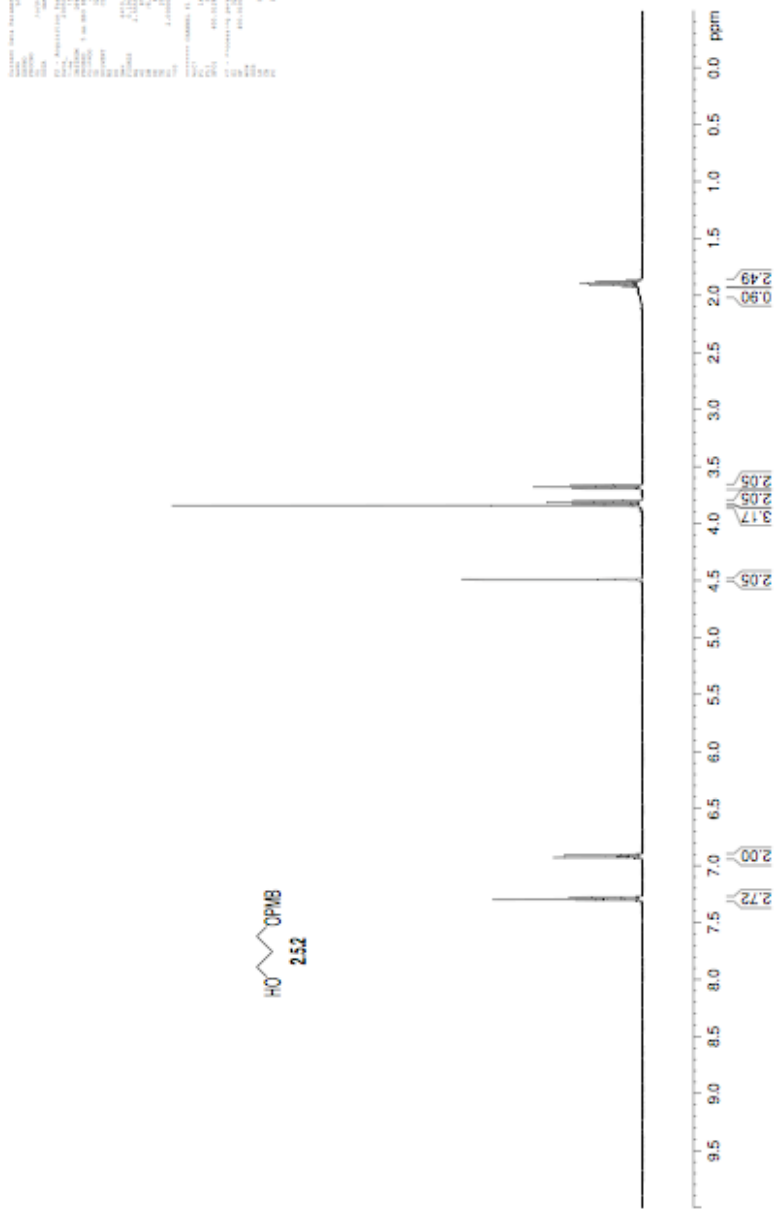
STUDIES TOWARD THE TOTAL SYNTHESIS OF AZASPIRACID 1

Appendix:

Spectrographic Data for New Compounds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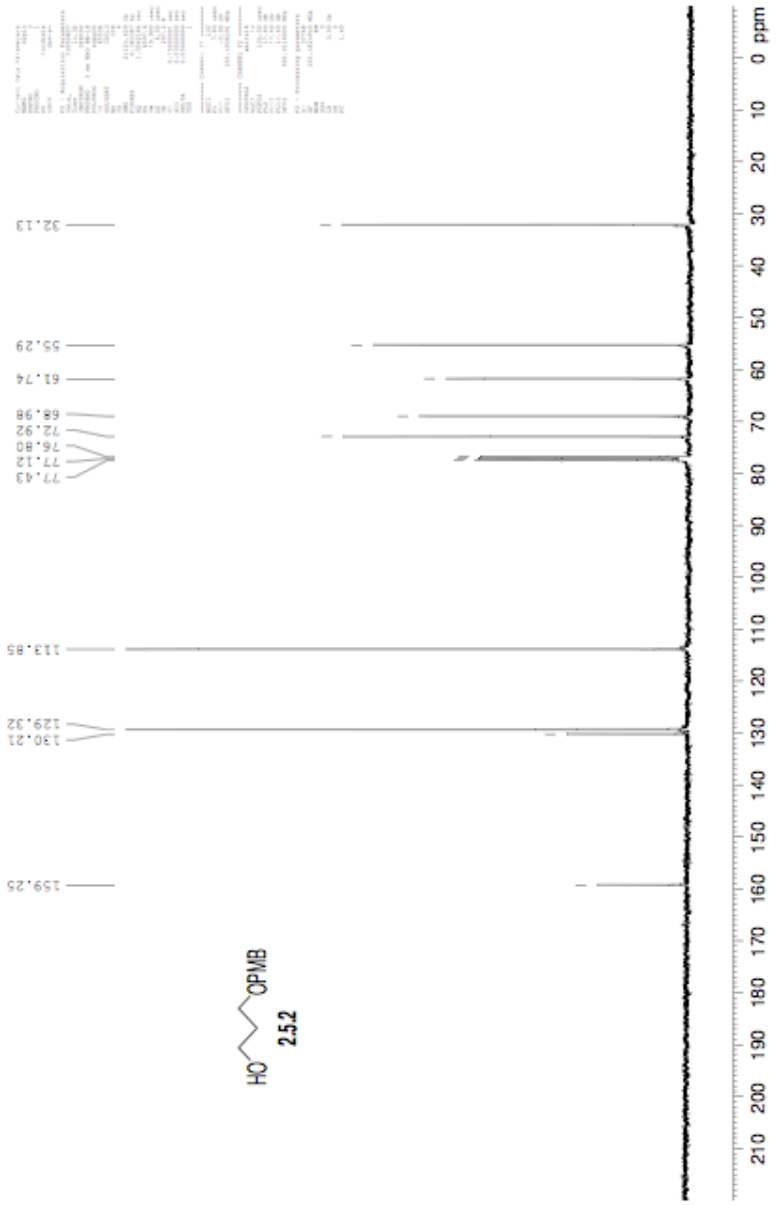
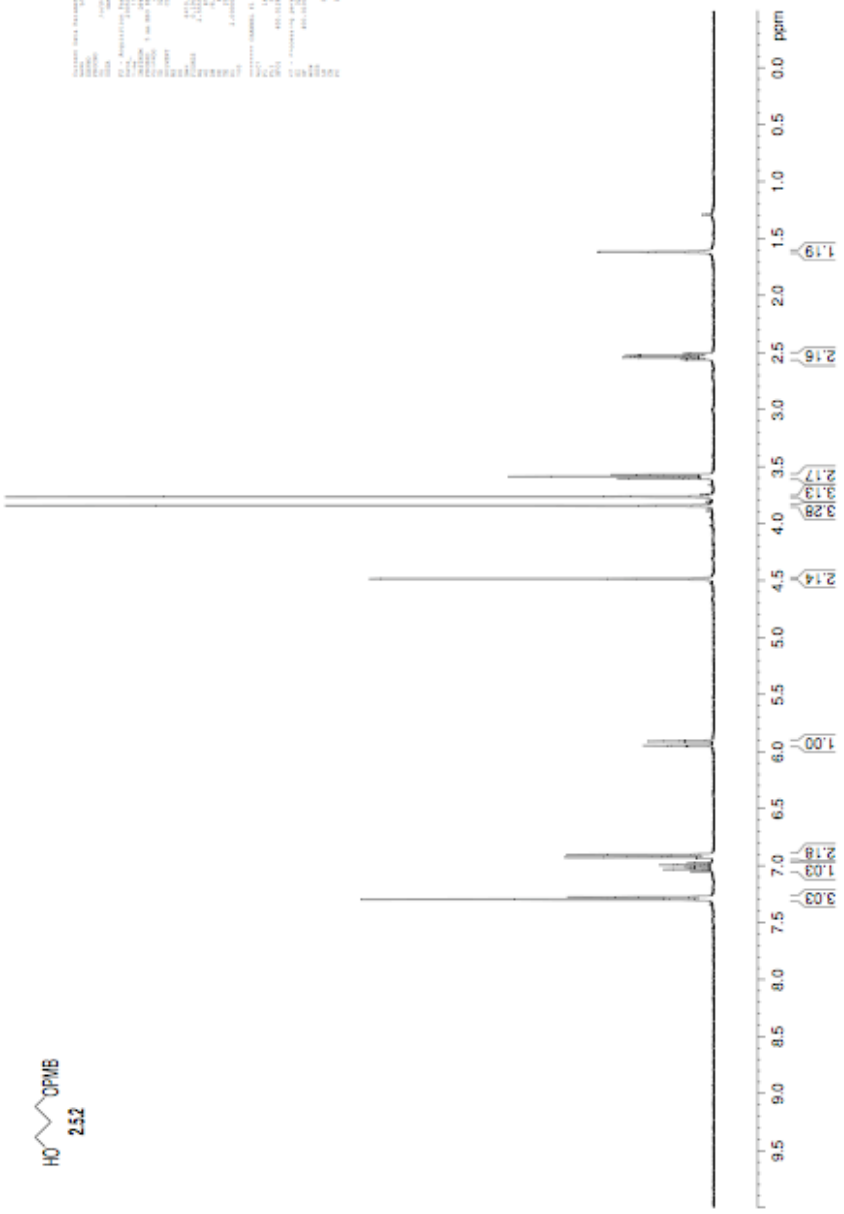
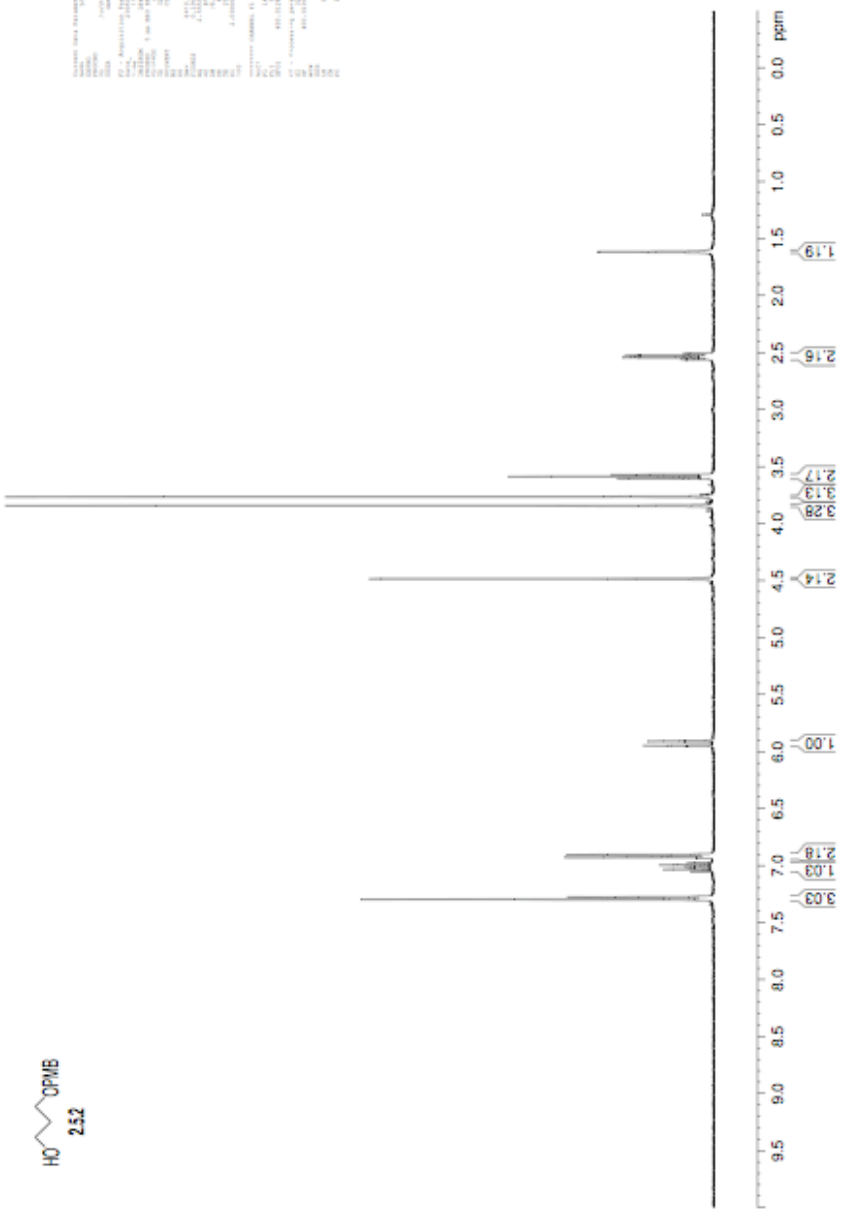
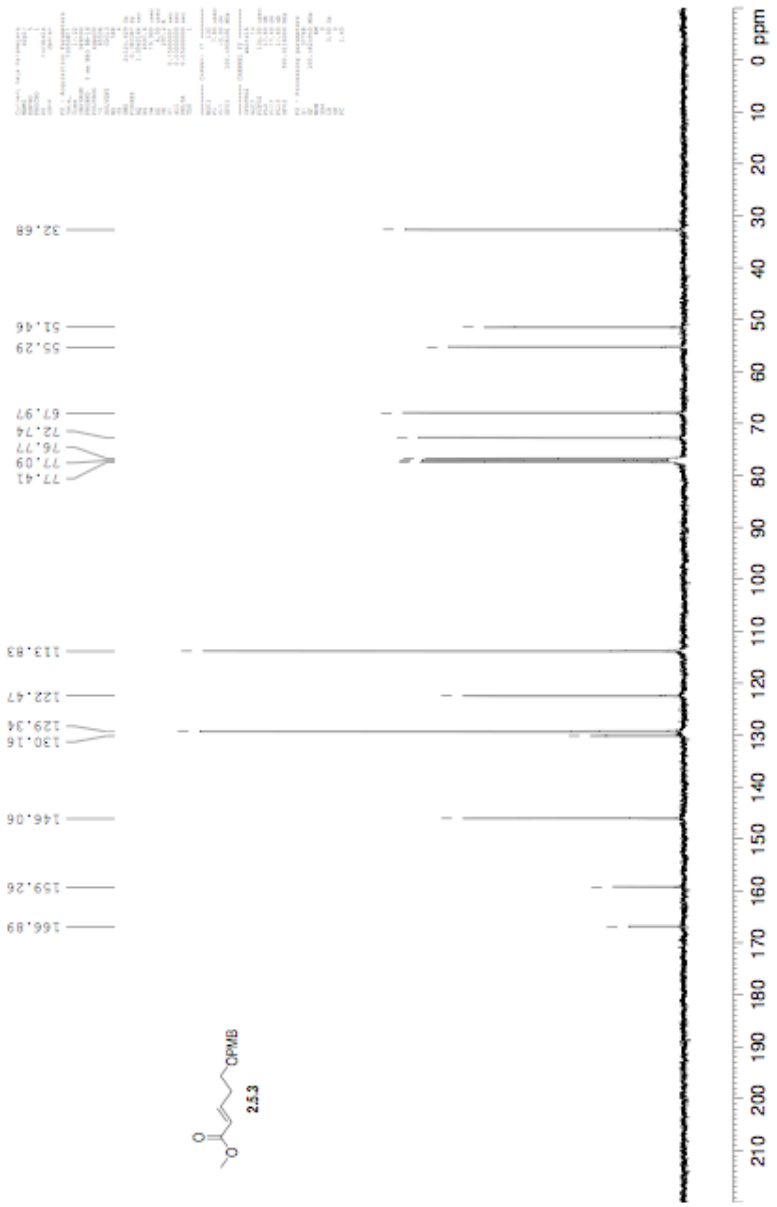
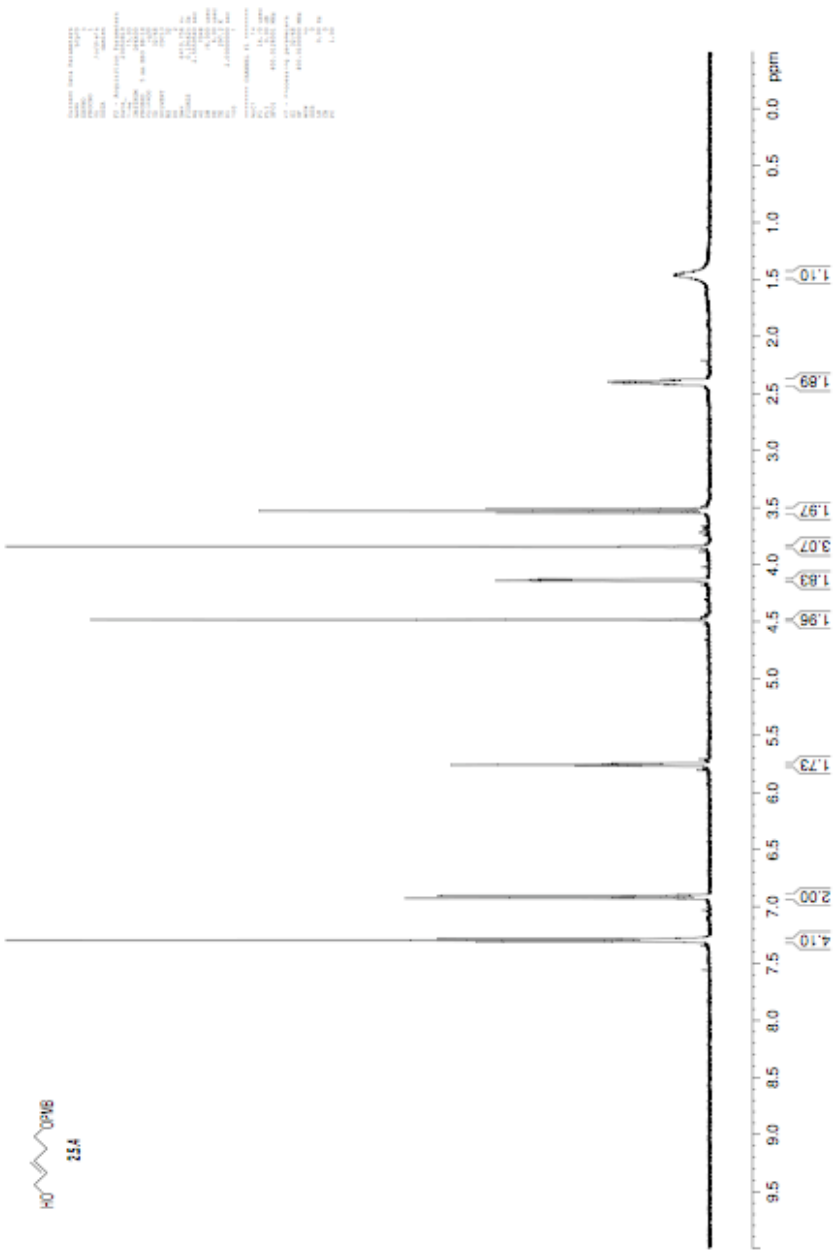
2.49
0.90
2.05
2.05
3.17
2.05
2.00
2.72
ppm


HO
OPMB
2.5.2
159.25
130.21
129.32
113.85
77.43
77.12
76.80
72.92
68.98
61.74
55.29
32.13
0 ppm


HO
OPMB
2.52
ppm
1.19
2.16
2.17
3.13
3.28
2.14
1.00
2.18
1.03
3.03


HO
OPMB
2.52
3.03
1.03
2.18
1.00
2.14
3.28
3.13
2.17
2.16
1.19
ppm


166.89
159.26
146.06
130.16
129.34
122.47
113.83
77.41
77.09
76.77
72.74
67.97
55.29
51.46
32.68
OPMB
2,5,3
0 ppm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OPMB
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ppm
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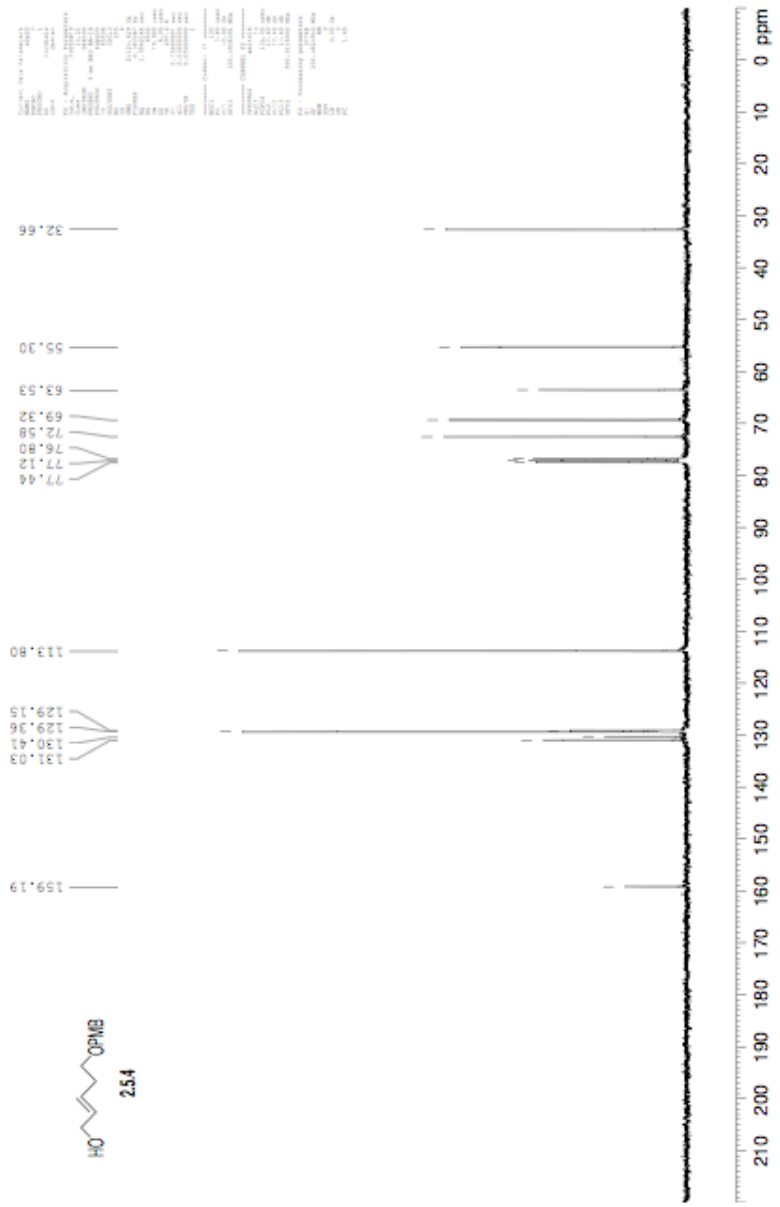
3.07
1.83
1.96
1.73
2.00
4.10


HO
OPMB
254
159.19
131.03
130.41
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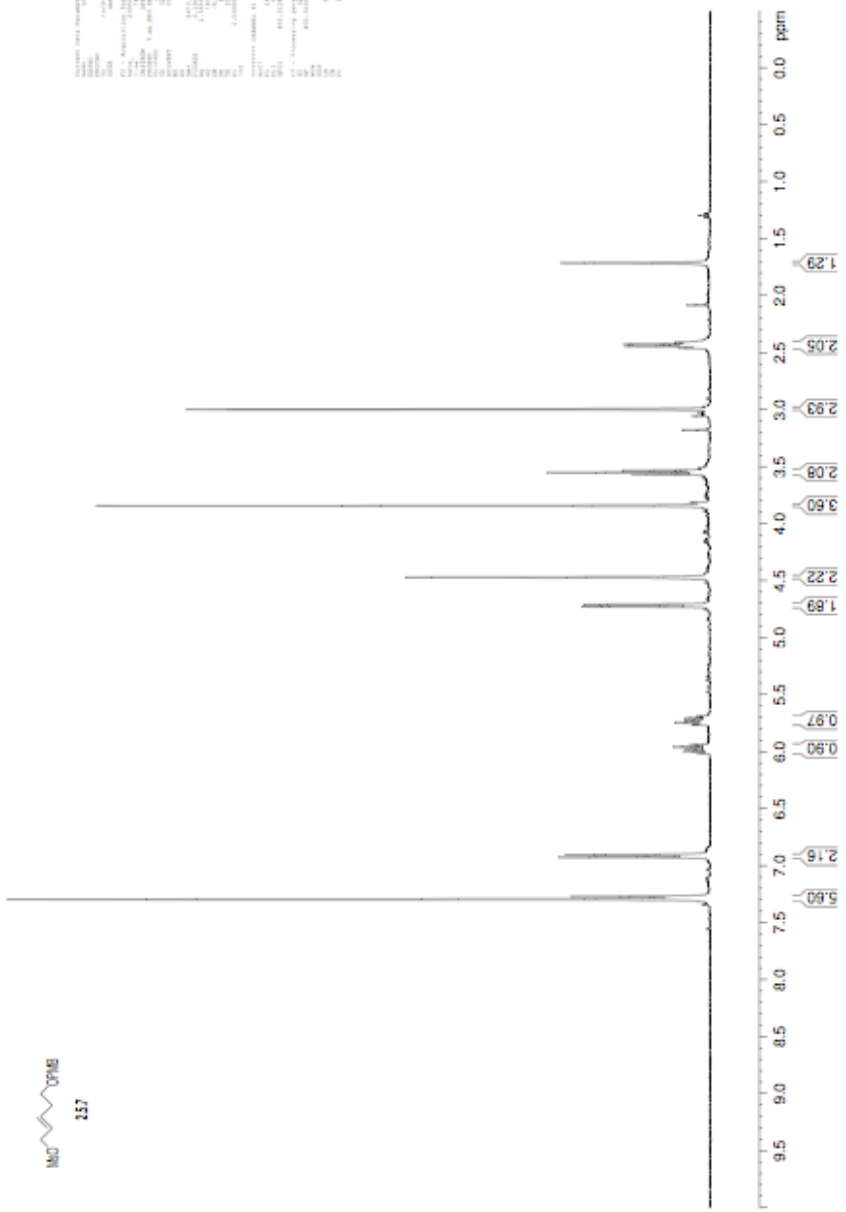
77.12
76.80
72.58
69.32
63.53
55.30
32.66
0 ppm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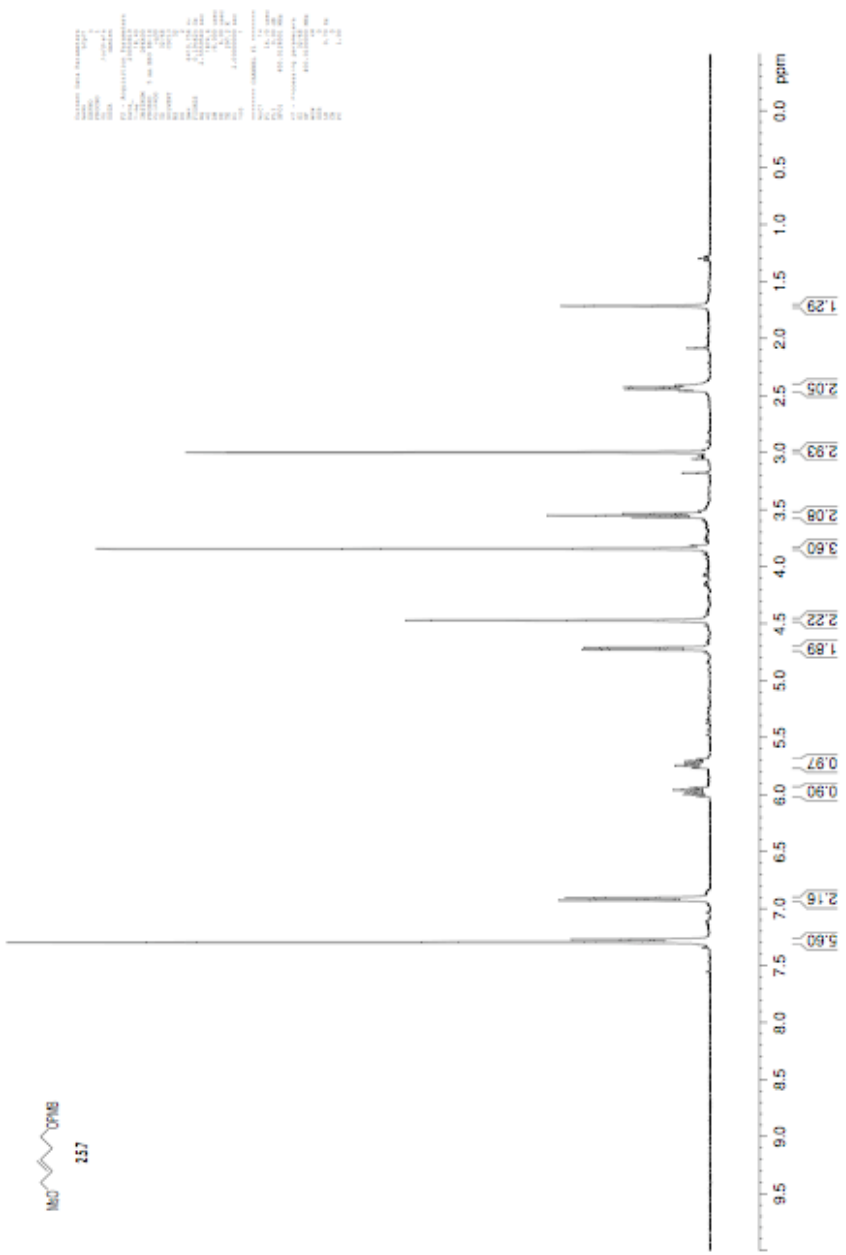
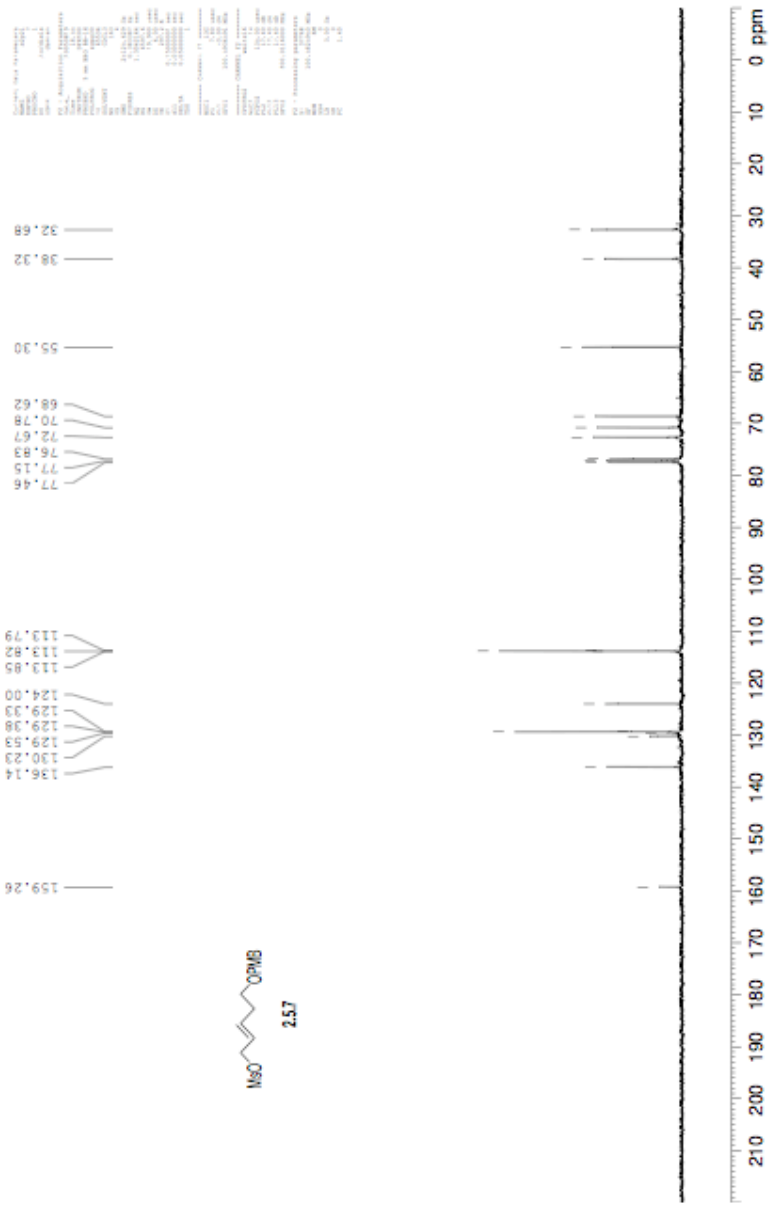
OPMB
157
5.60
2.16
0.90
0.97
1.89
2.22
3.60
2.08
2.93
2.05
1.29
ppm


MeO
OPMB
157
5.60
2.16
0.90
0.97
1.89
2.22
3.60
2.08
2.93
2.05
1.29
ppm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136.14
130.23
129.53
129.38
129.33
124.00
113.85
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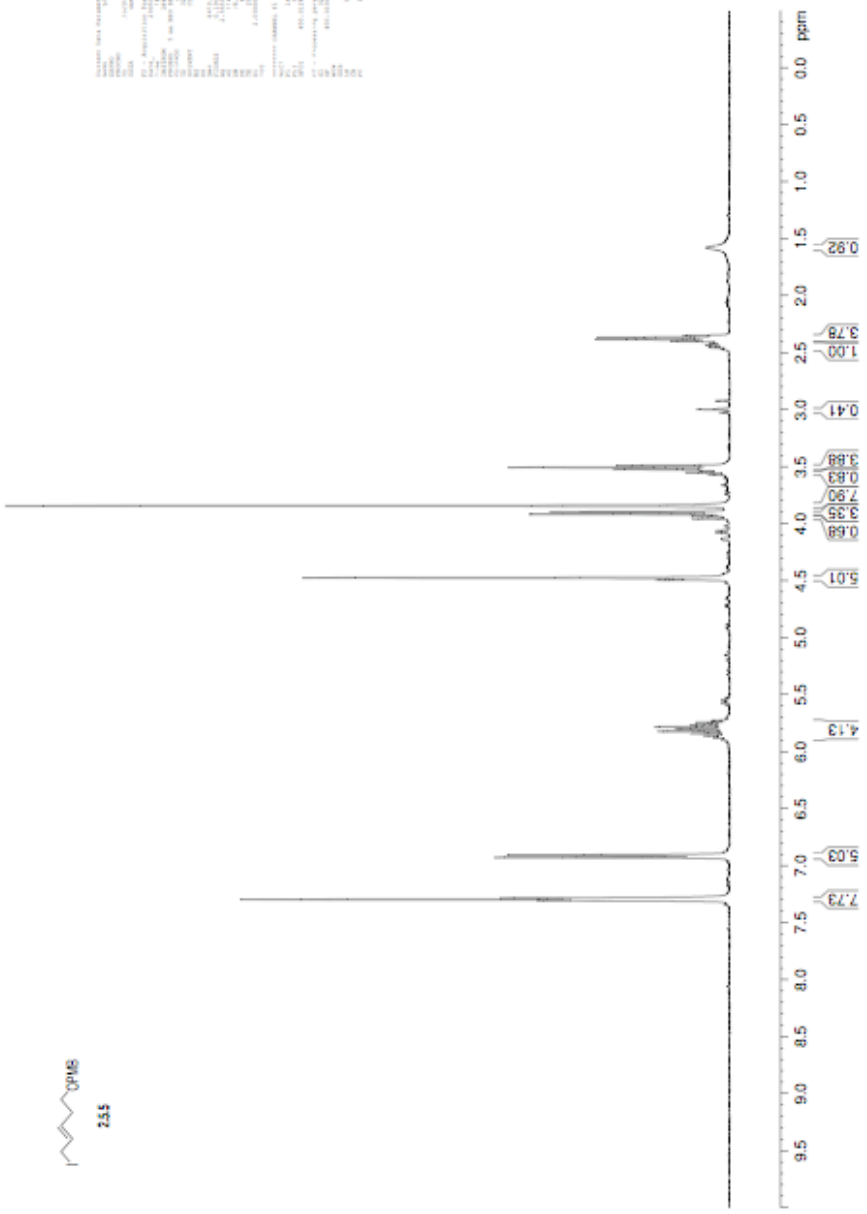
113.79
77.46
77.15
76.83
72.67
70.78
68.62
55.30
38.32
32.68
MeO
OPMB
2.57
0 ppm


DPMS
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3.35
0.68
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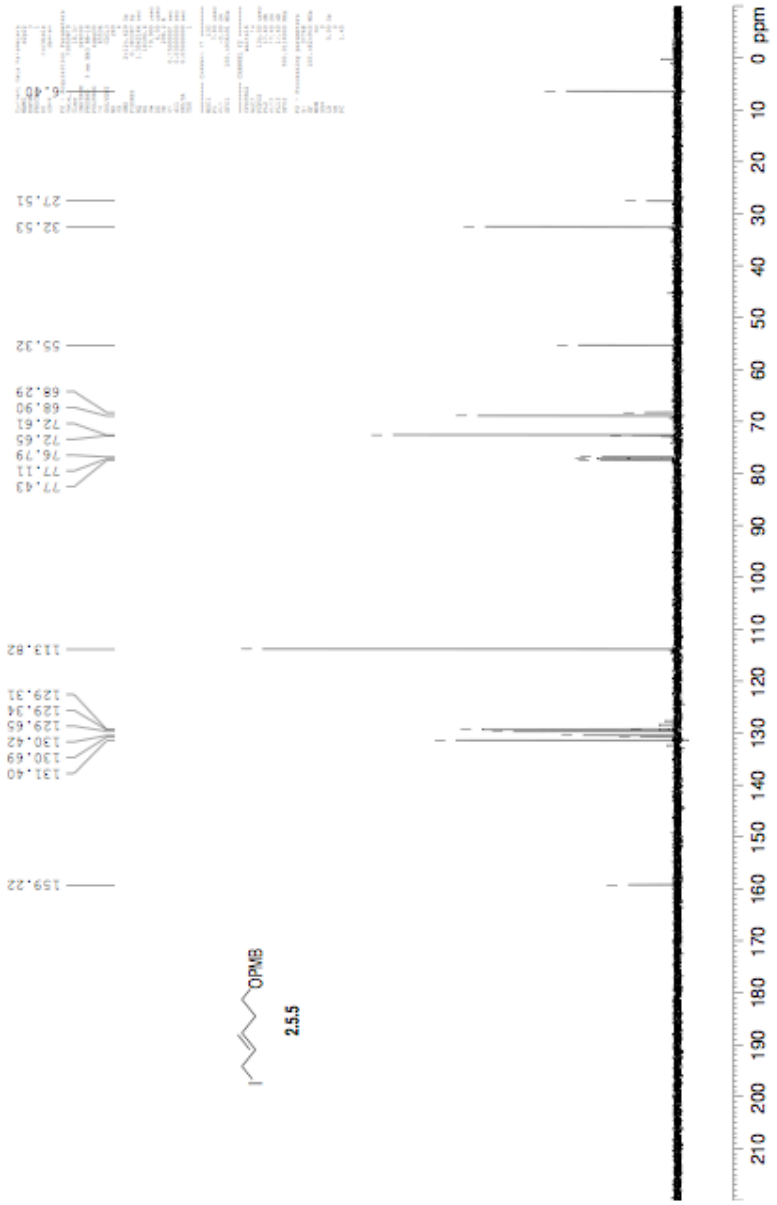
4.13
5.03
7.73
ppm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131.40
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129.34
129.31
113.82
77.43
77.11
76.79
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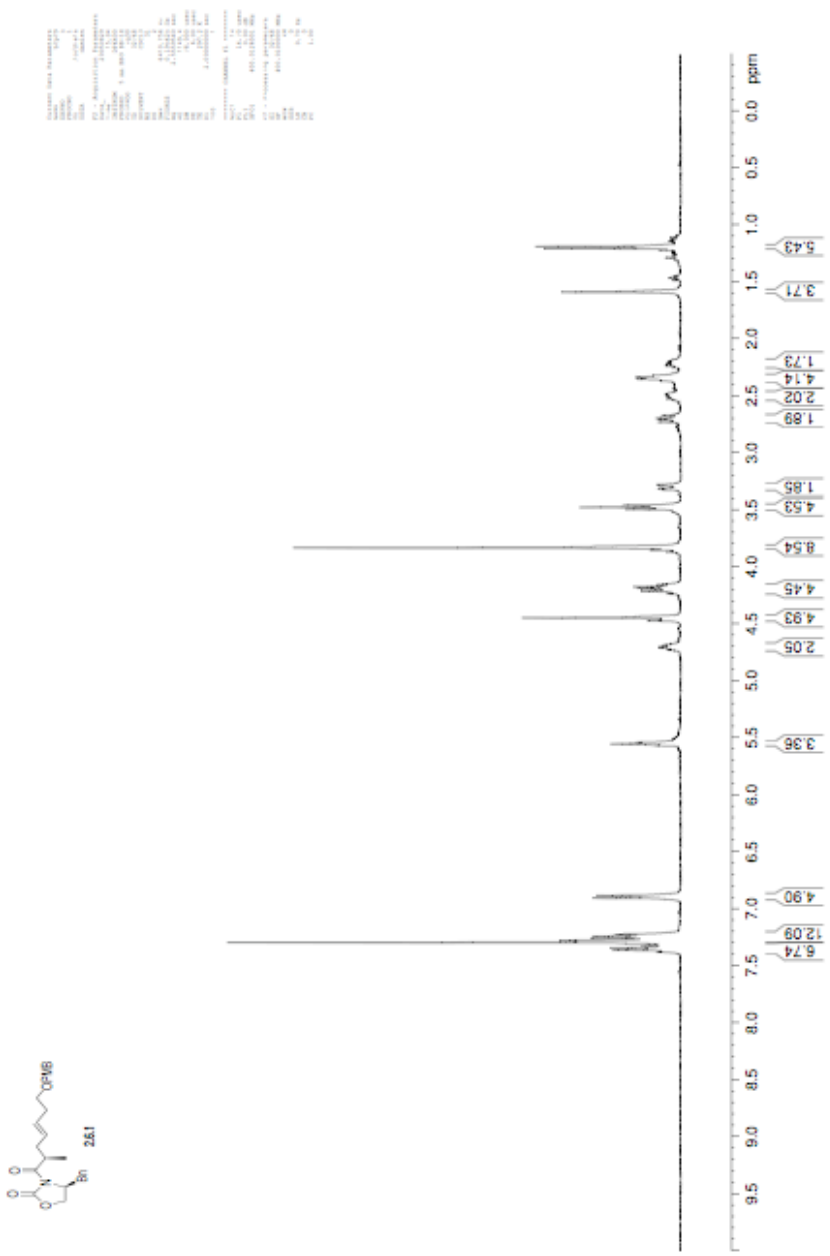
72.61
68.90
68.29
55.32
32.53
27.51
6.40
OPMB
2.5.5
0 ppm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Bn
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3.36
2.05
4.93
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1.85
1.89
2.02
4.14
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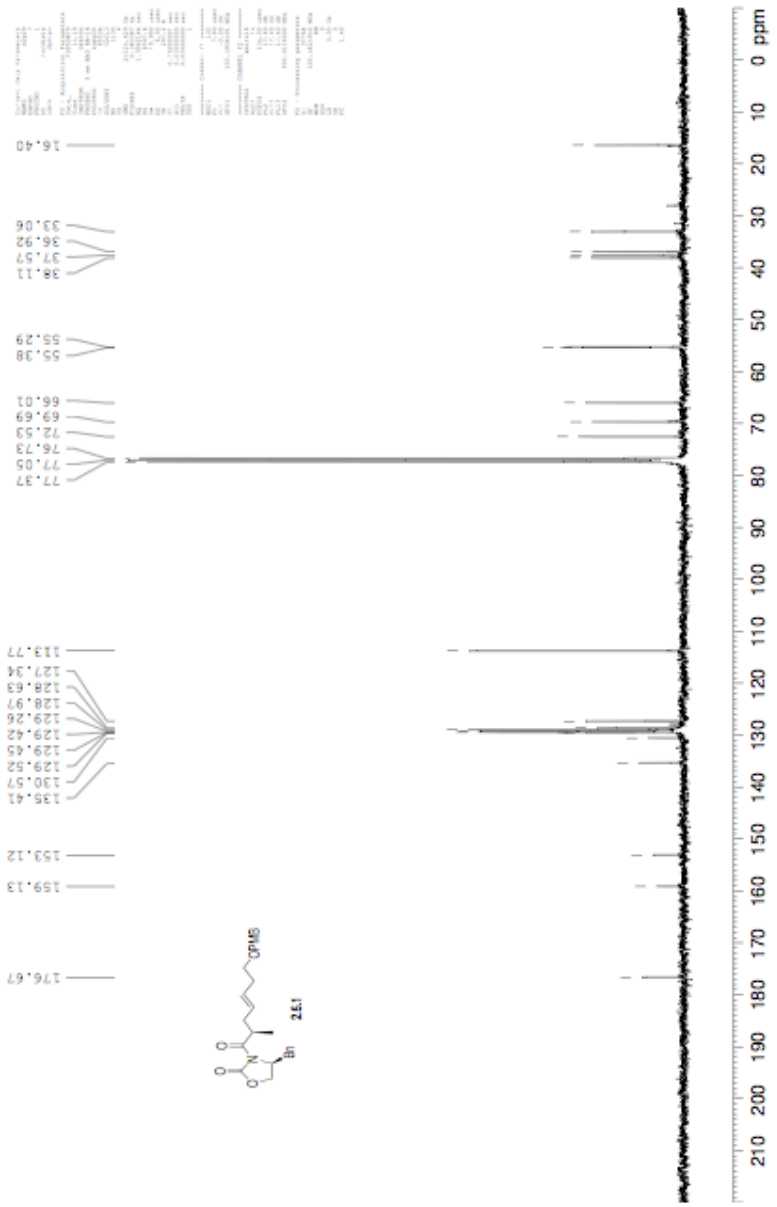
3.71
5.43
ppm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72.53
76.73
77.05
77.37
113.77
127.34
128.63
128.97
129.26
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129.52
130.57
135.41
153.12
159.13
176.67
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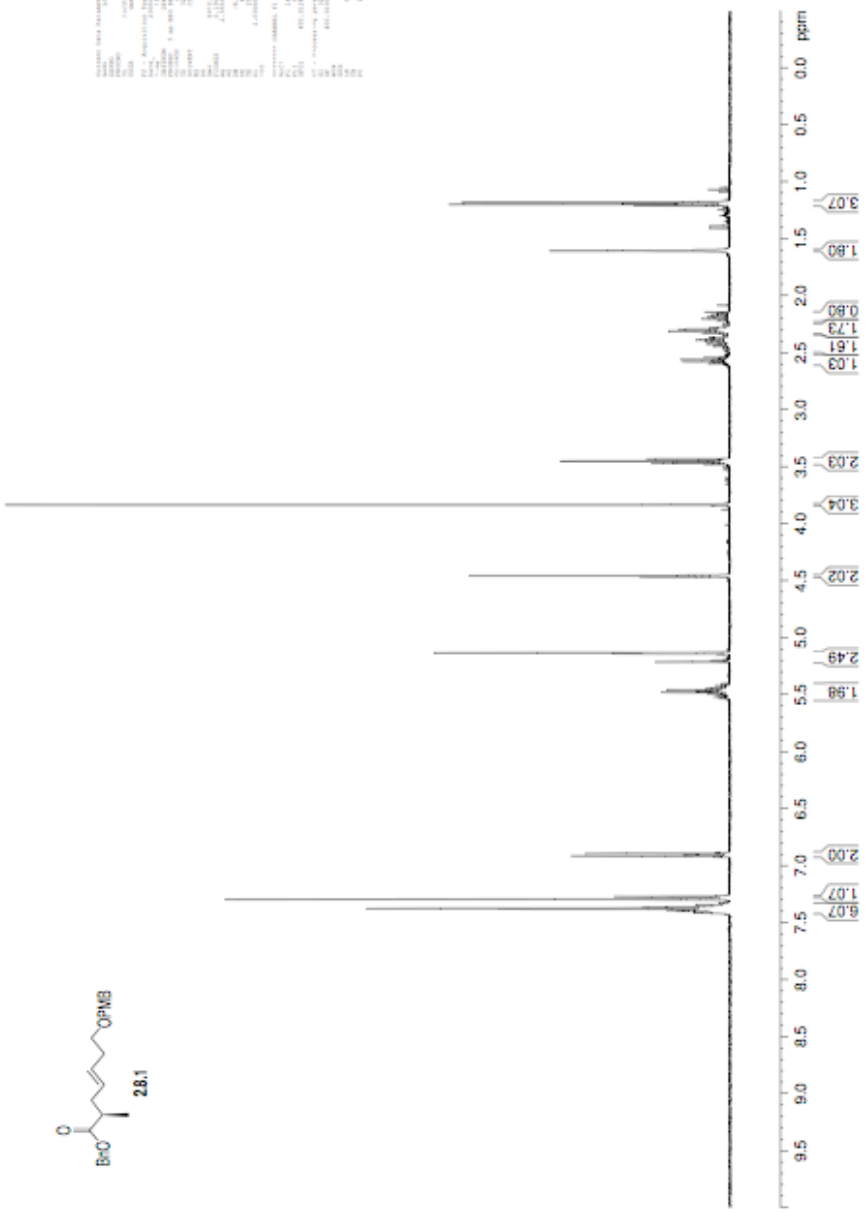
Bn
25.1
0 ppm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BnO
O
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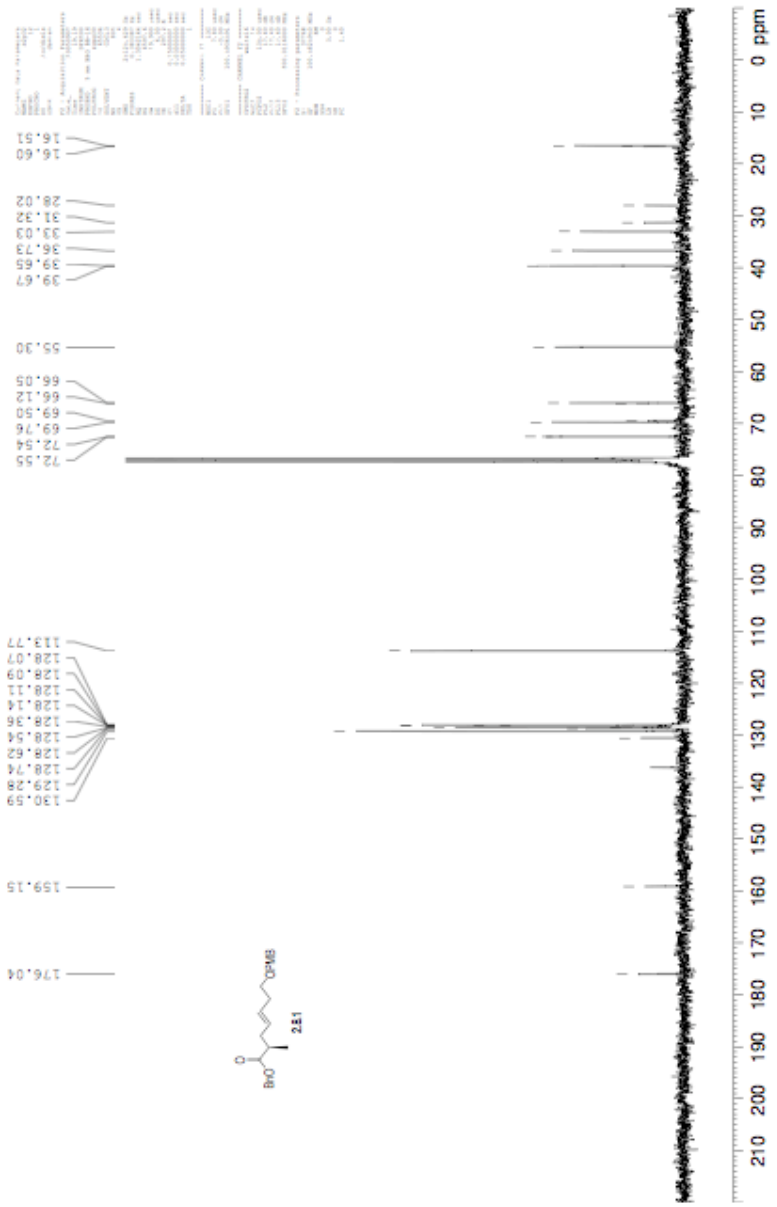
3.04
2.03
1.03
1.61
1.73
0.80
1.80
3.07
ppm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66.05
66.12
69.50
69.76
72.54
72.55
113.77
128.07
128.09
128.11
128.14
128.36
128.54
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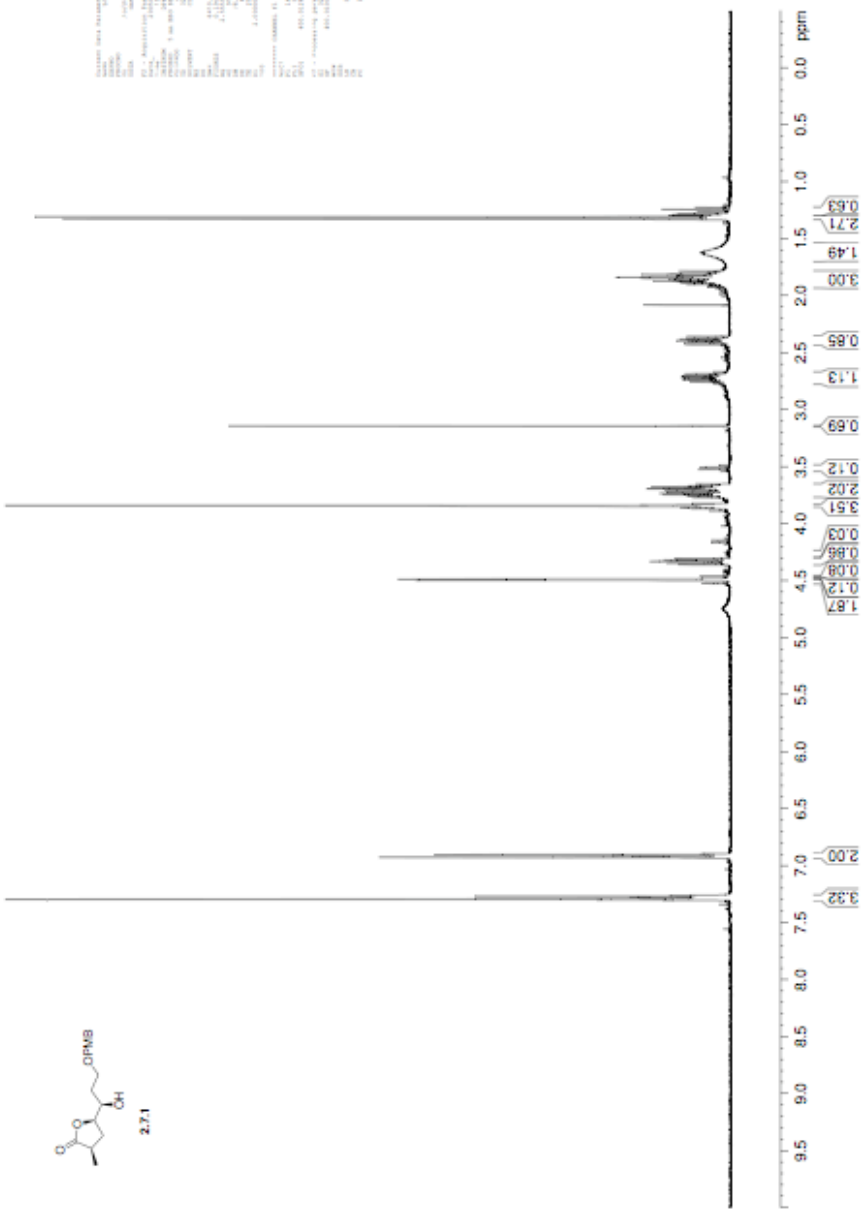
129.28
130.59
159.15
176.04
OPMB
2&1
BnO
O
0 ppm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O
O
O
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3.32
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0.08
0.86
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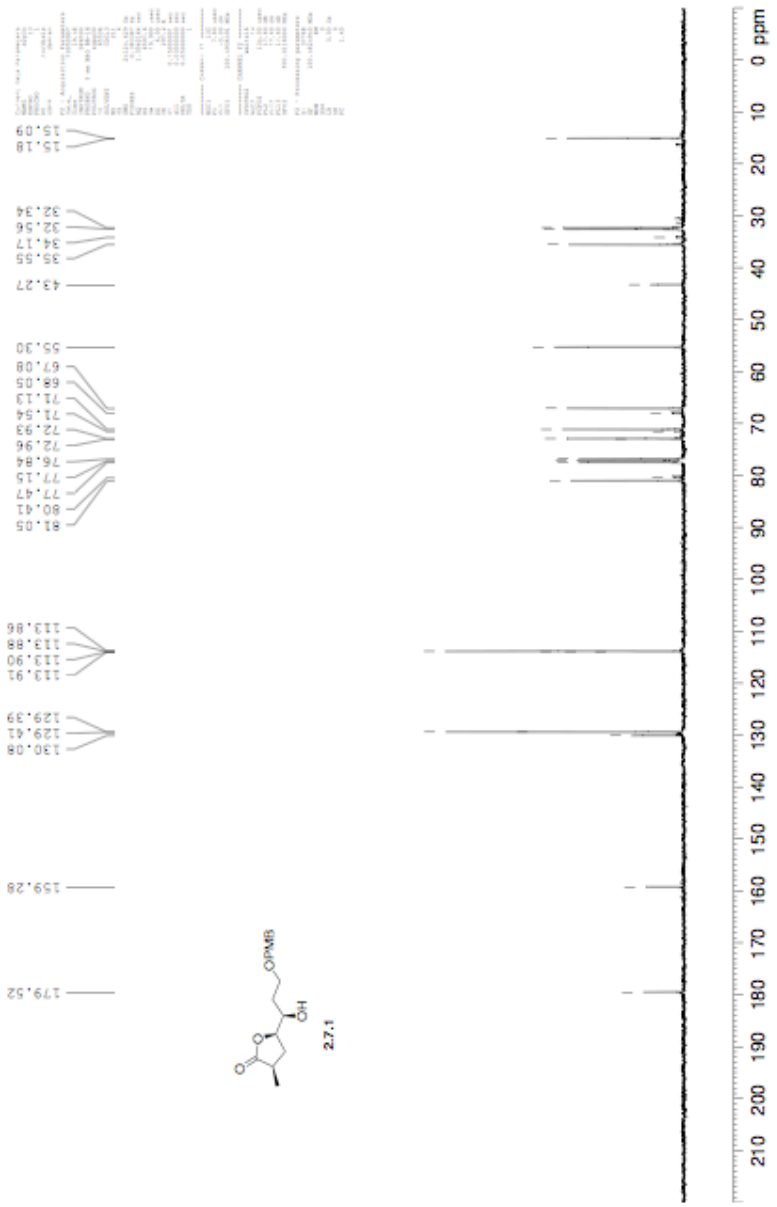
2.02
0.12
0.69
1.13
0.85
3.00
1.49
2.71
0.53
ppm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130.08
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80.41
77.47
77.15
76.84
72.96
72.93
71.54
71.13
68.05
67.08
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35.55
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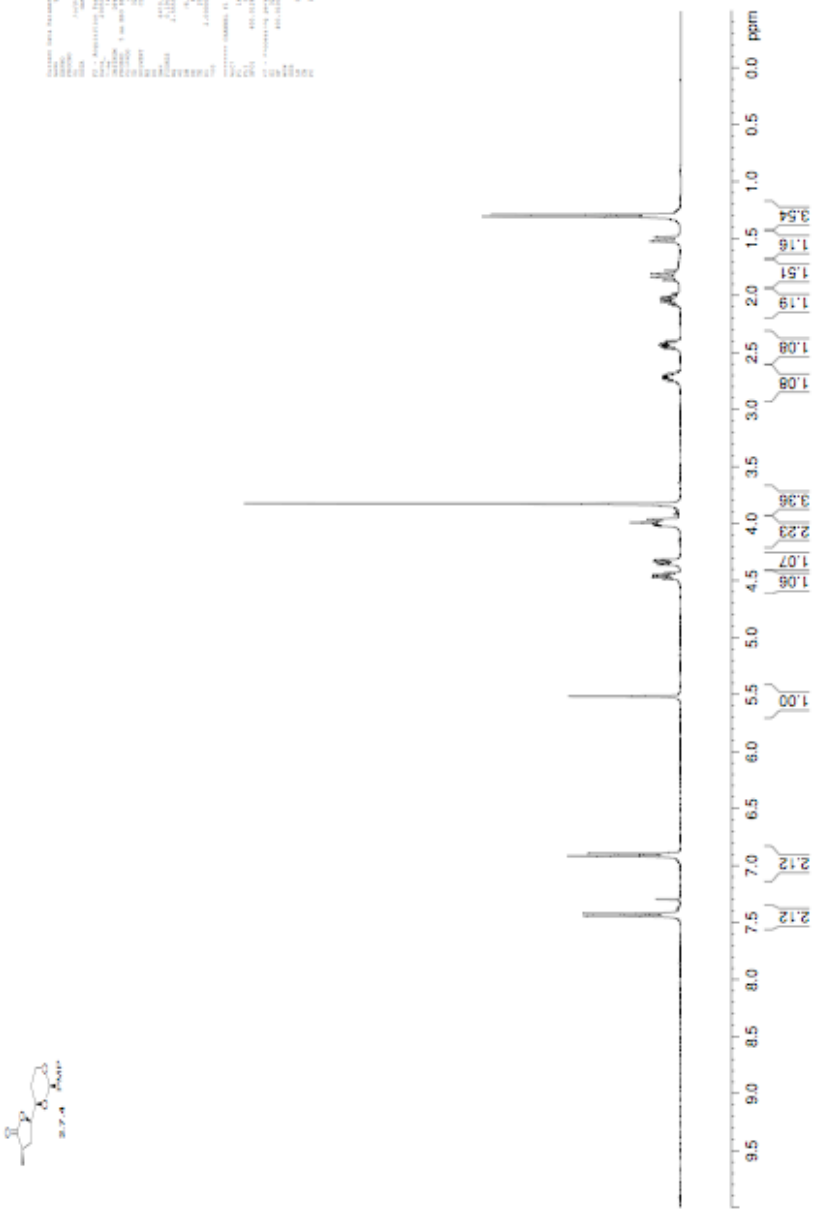
32.34
15.18
15.09
OPMB
OH
2.7.1
0 ppm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4.5
4.0
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2.5
2.0
1.5
1.0
0.5
0.0
ppm
2.12
2.12
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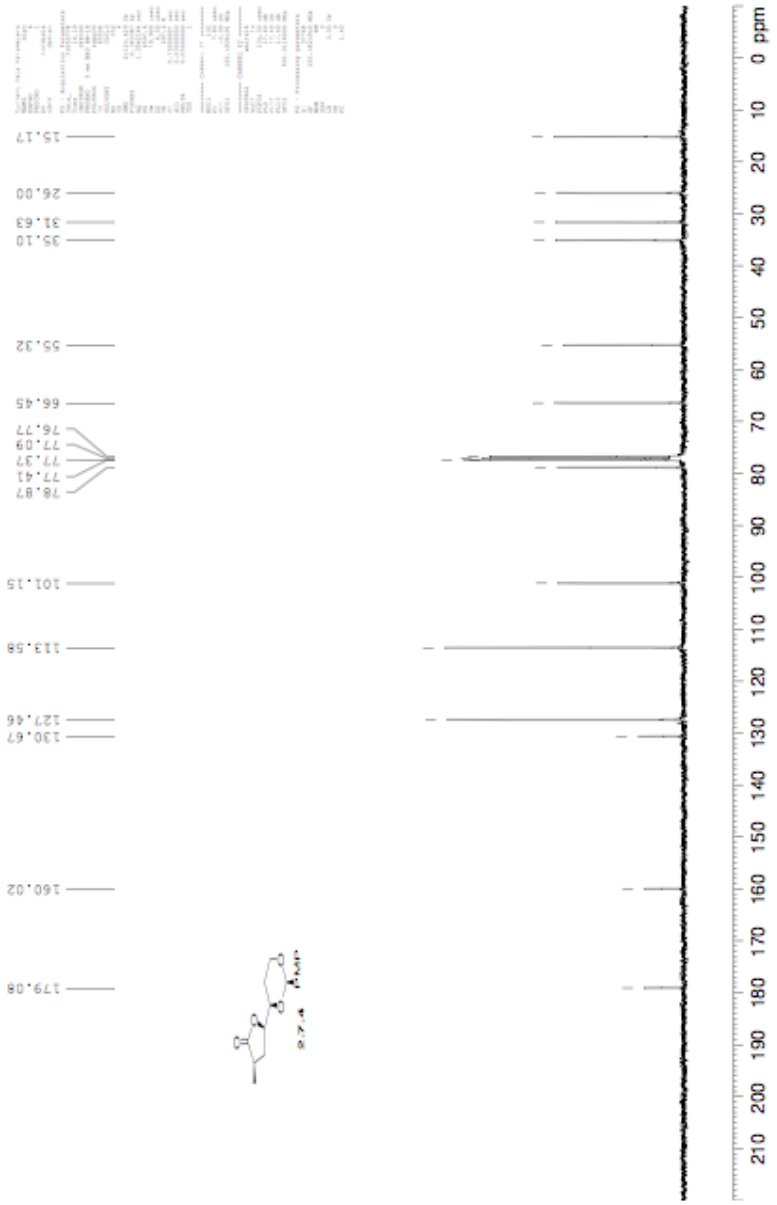
1.06
1.07
2.23
3.36
1.08
1.08
1.19
1.51
1.18
3.54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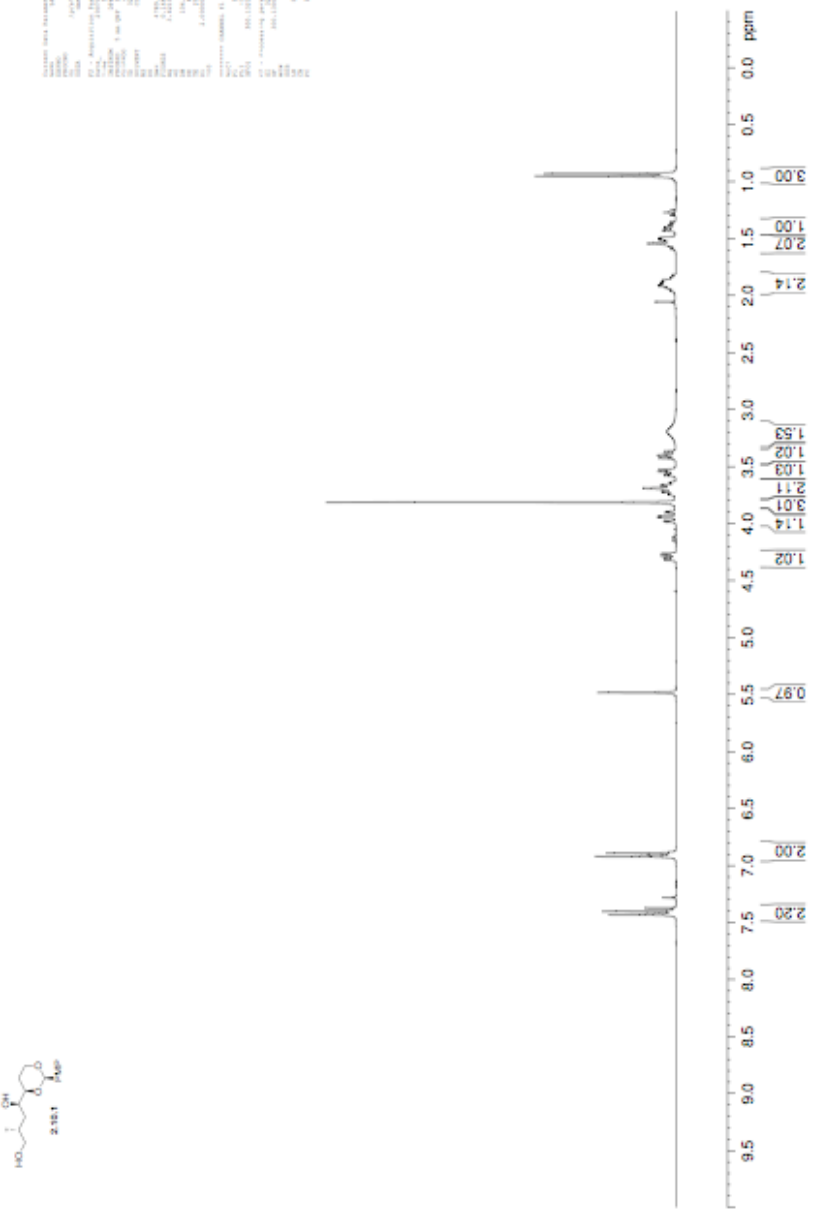
160.02
179.08
0 ppm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7.0
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4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
2.20
2.00
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3.01
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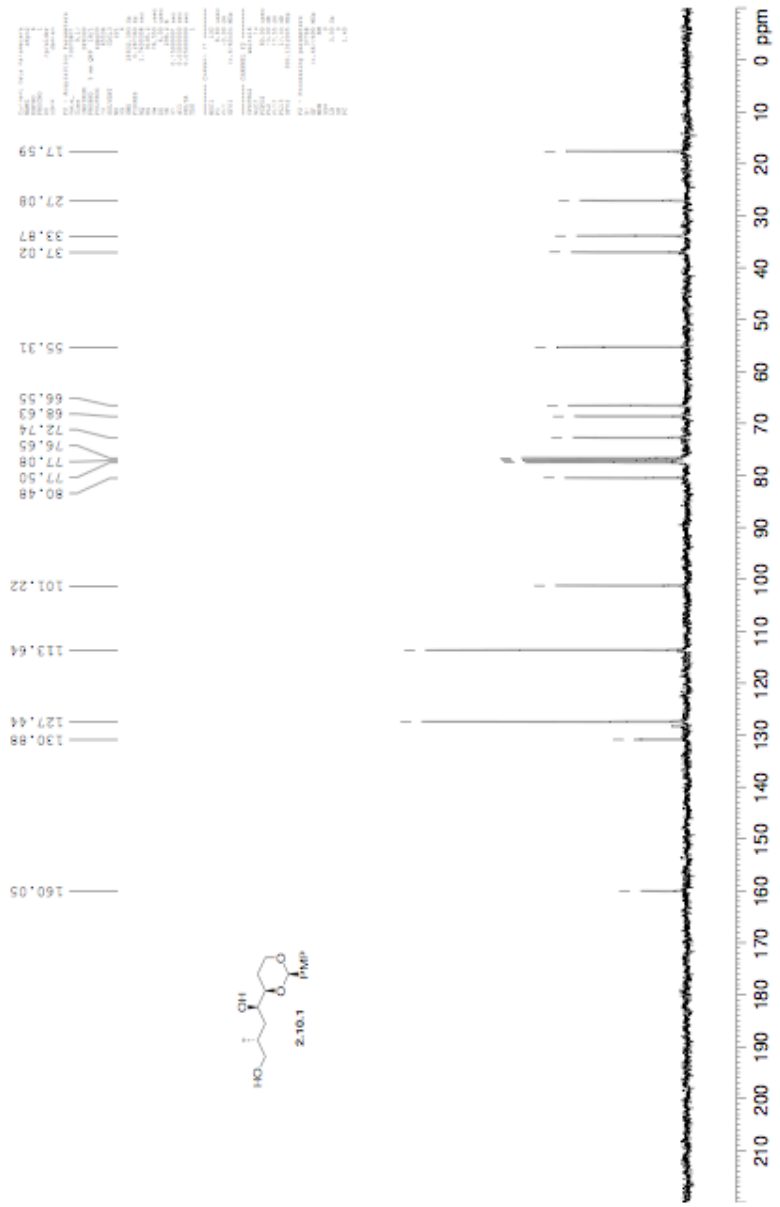
1.00
3.00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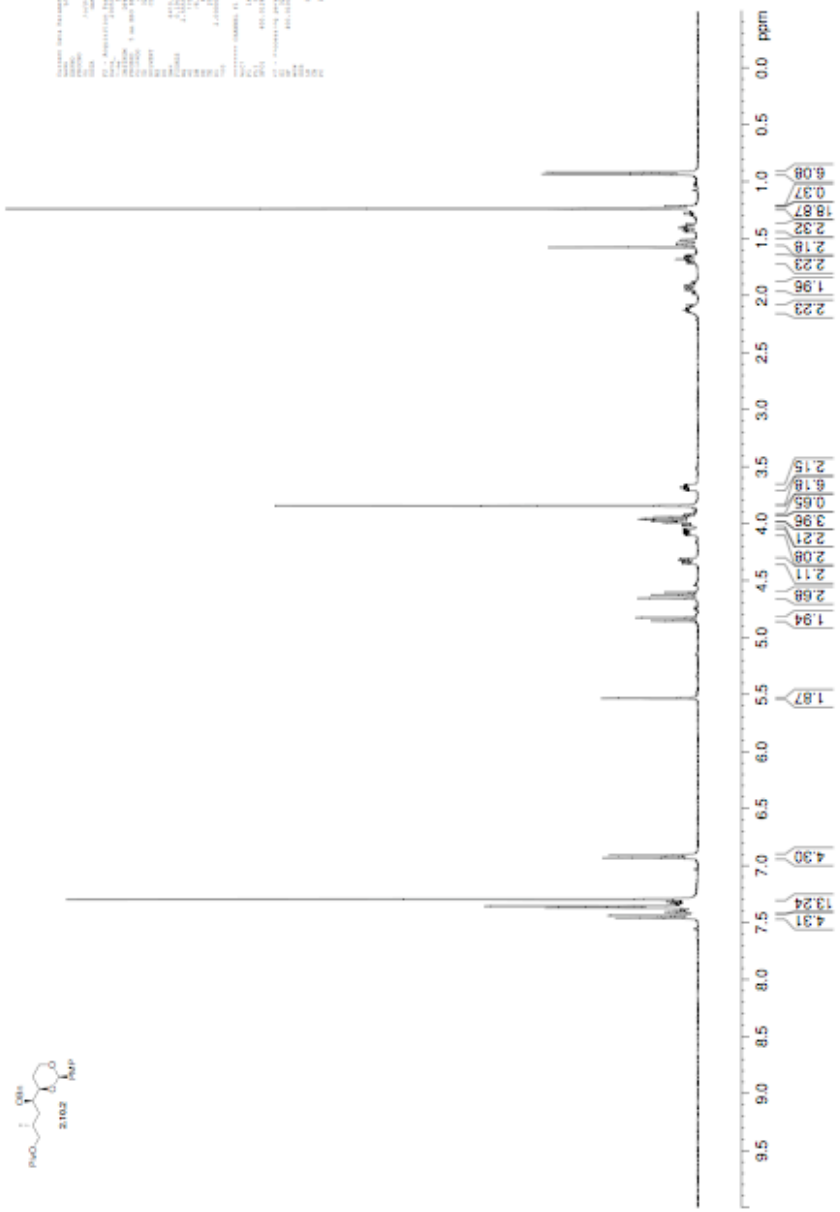
2.10.1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6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
6.08
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2.18
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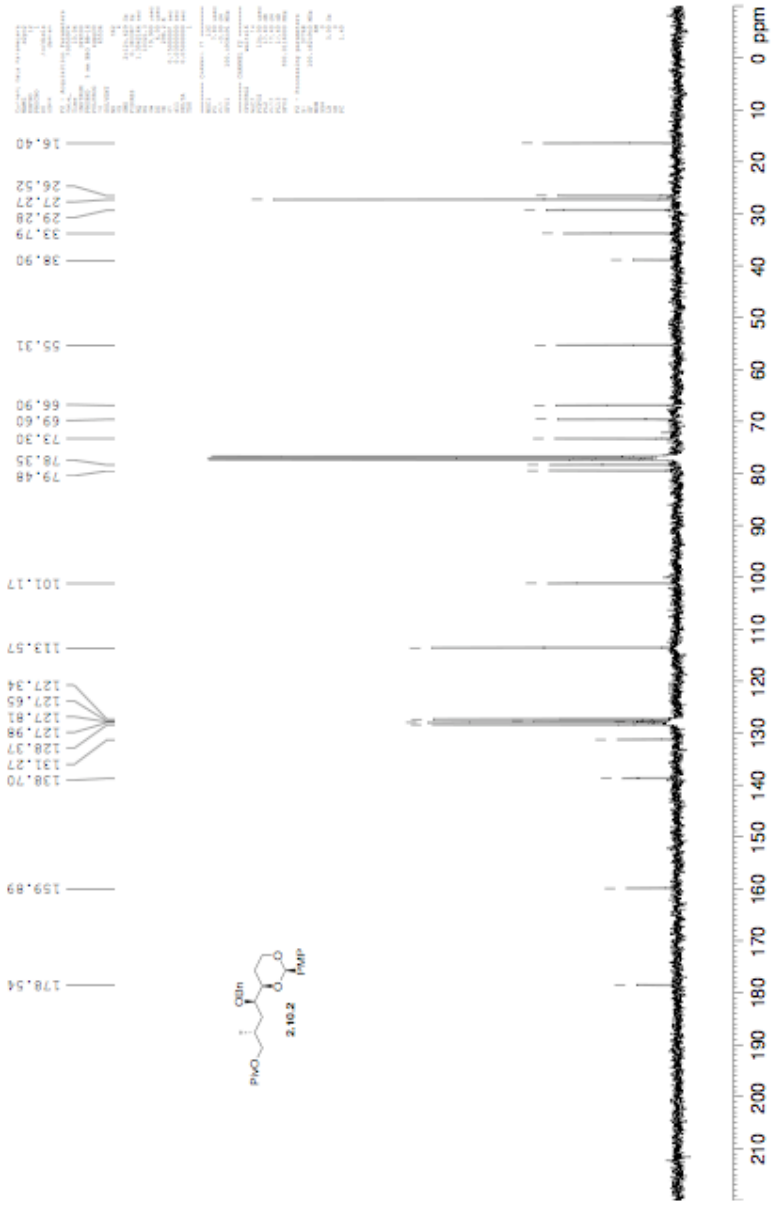
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73.30
78.35
79.48
101.17
113.57
127.34
127.65
127.81
127.98
128.37
131.27
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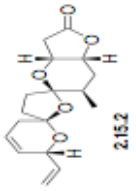
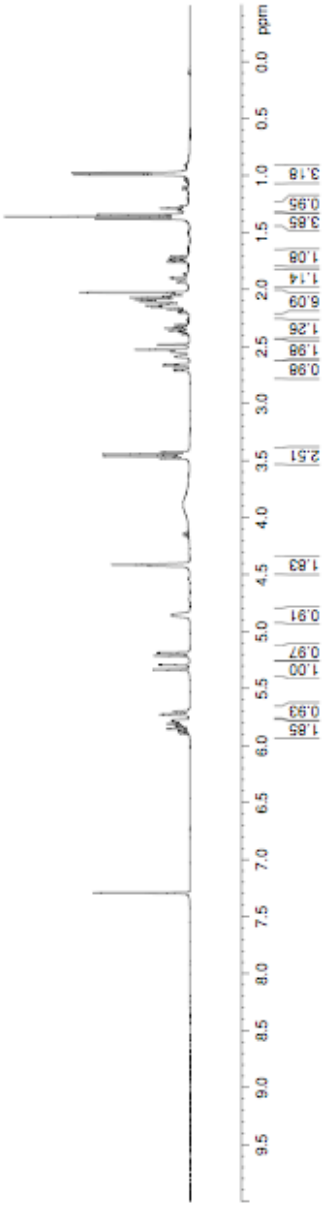
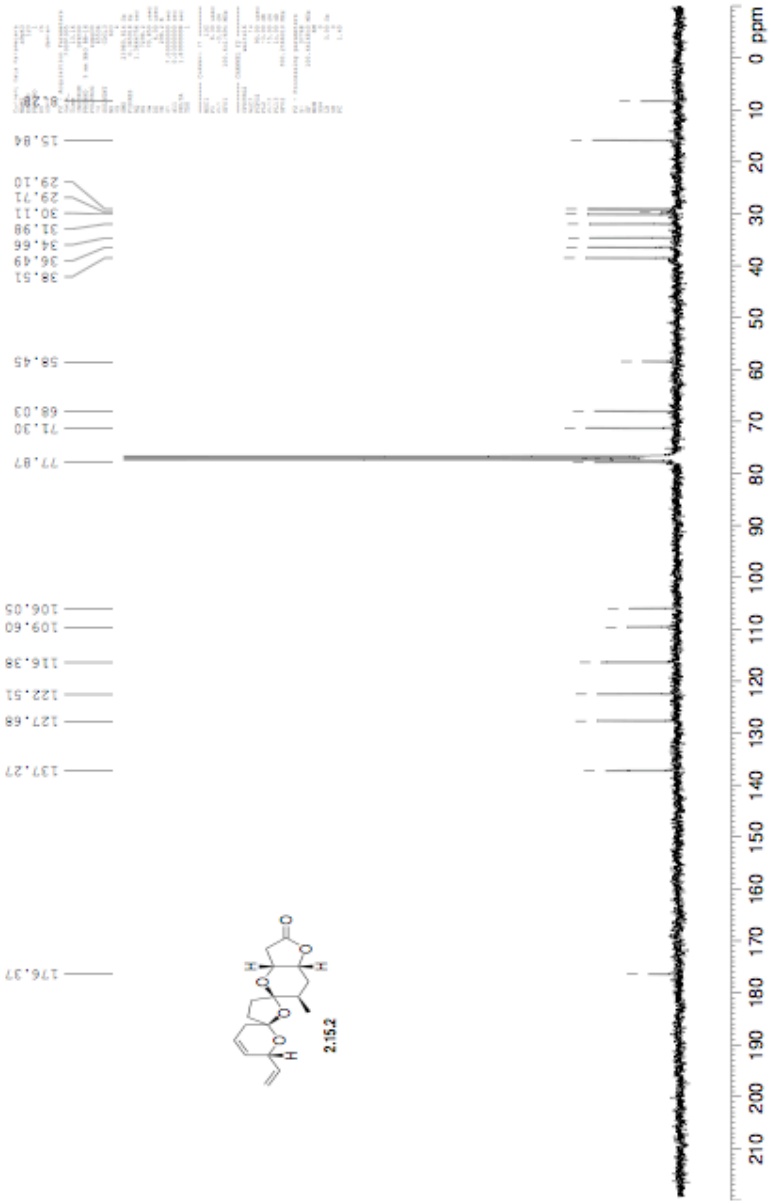
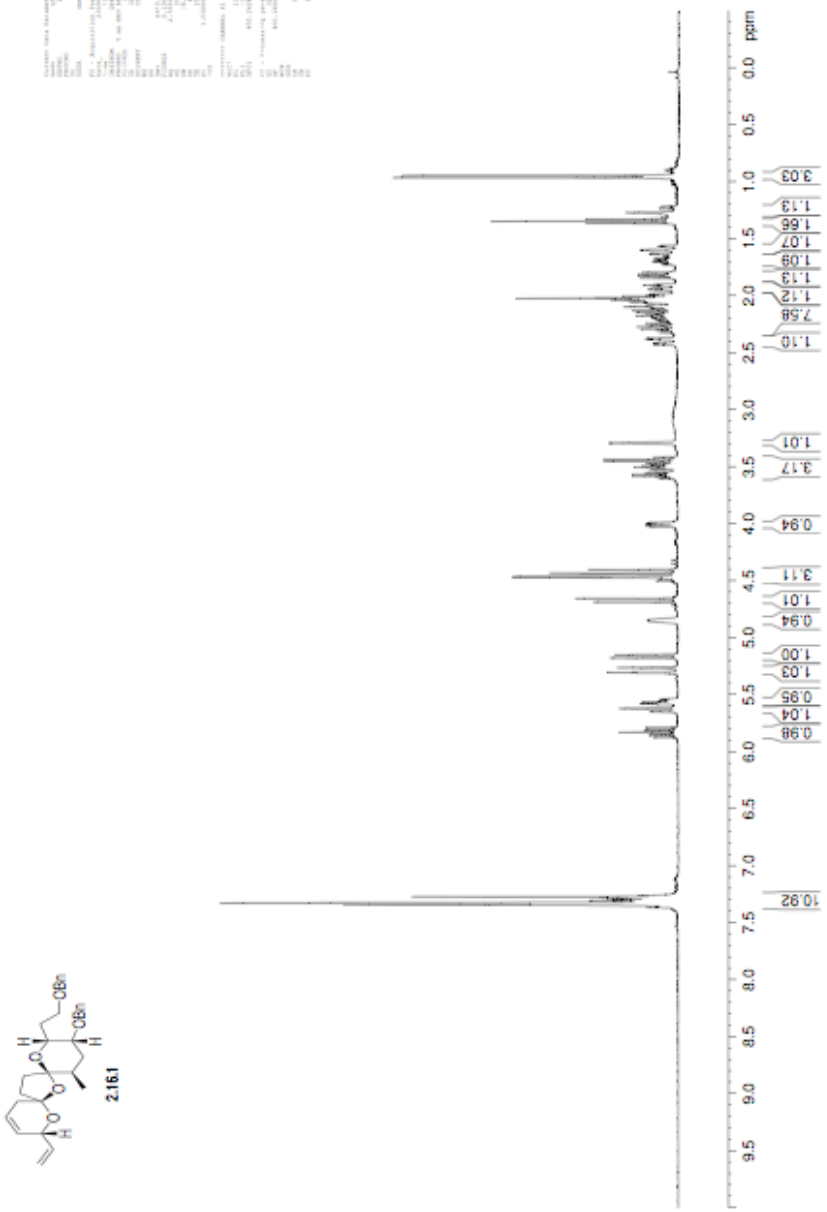
2.10.2

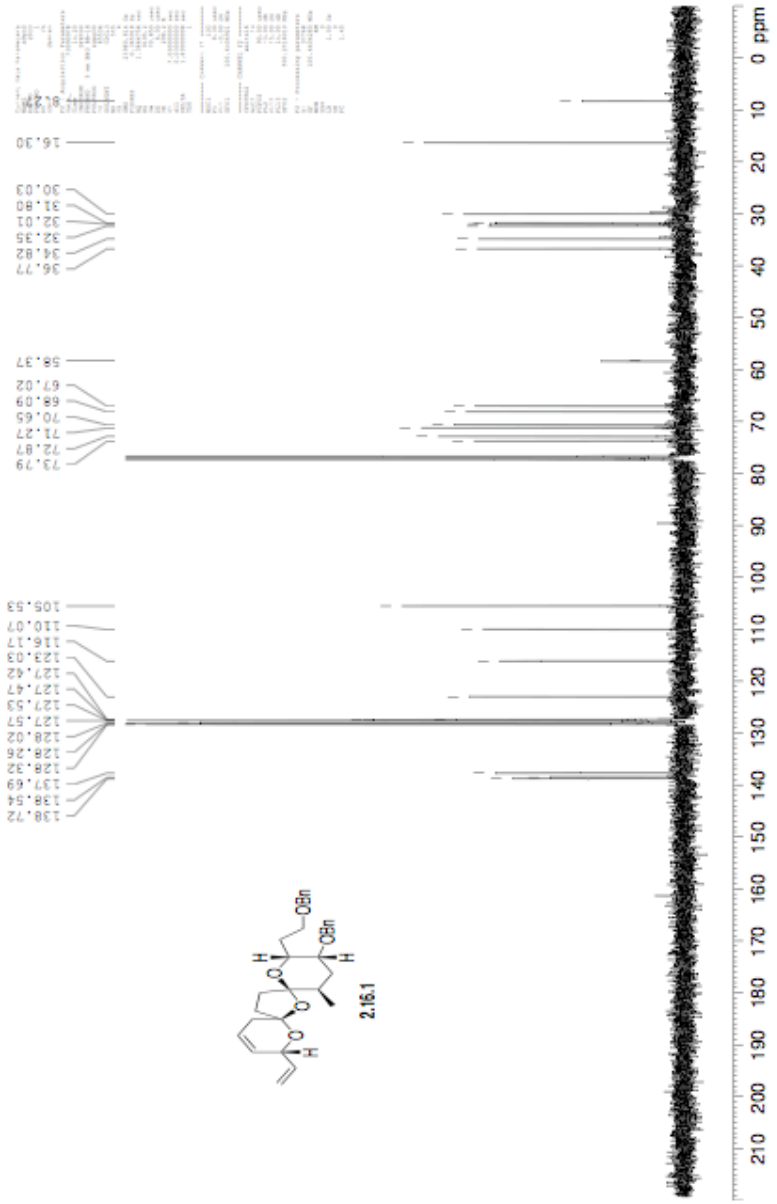


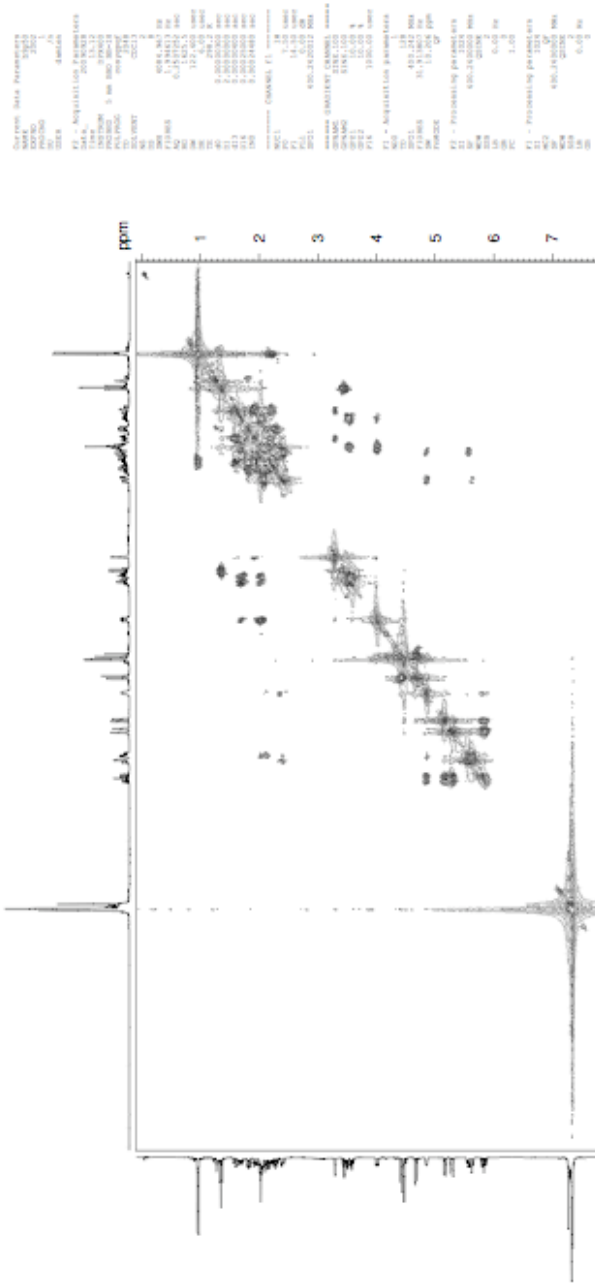
2.15.2

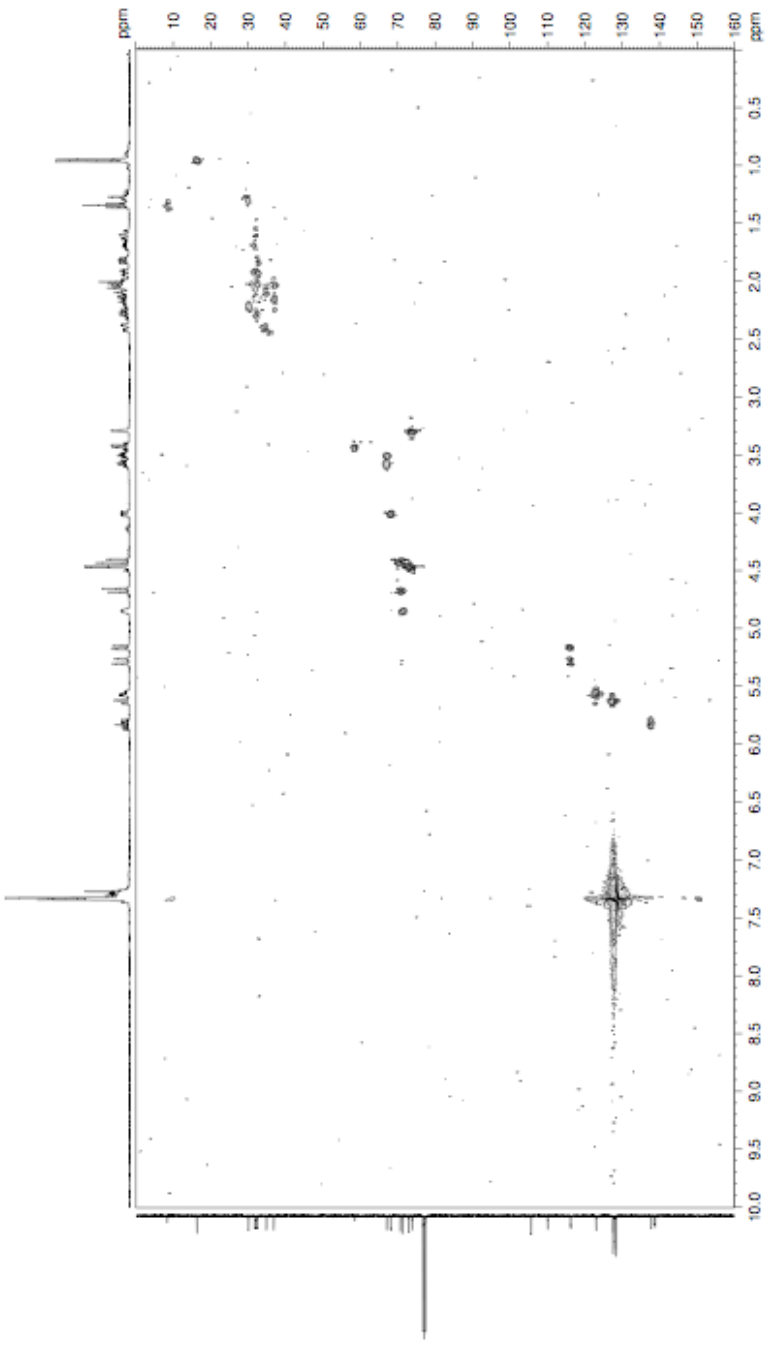

3.18
0.95
3.85
1.08
1.14
6.09
1.26
1.98
0.98
2.51
1.83
0.91
0.97
1.00
0.93
1.85
ppm

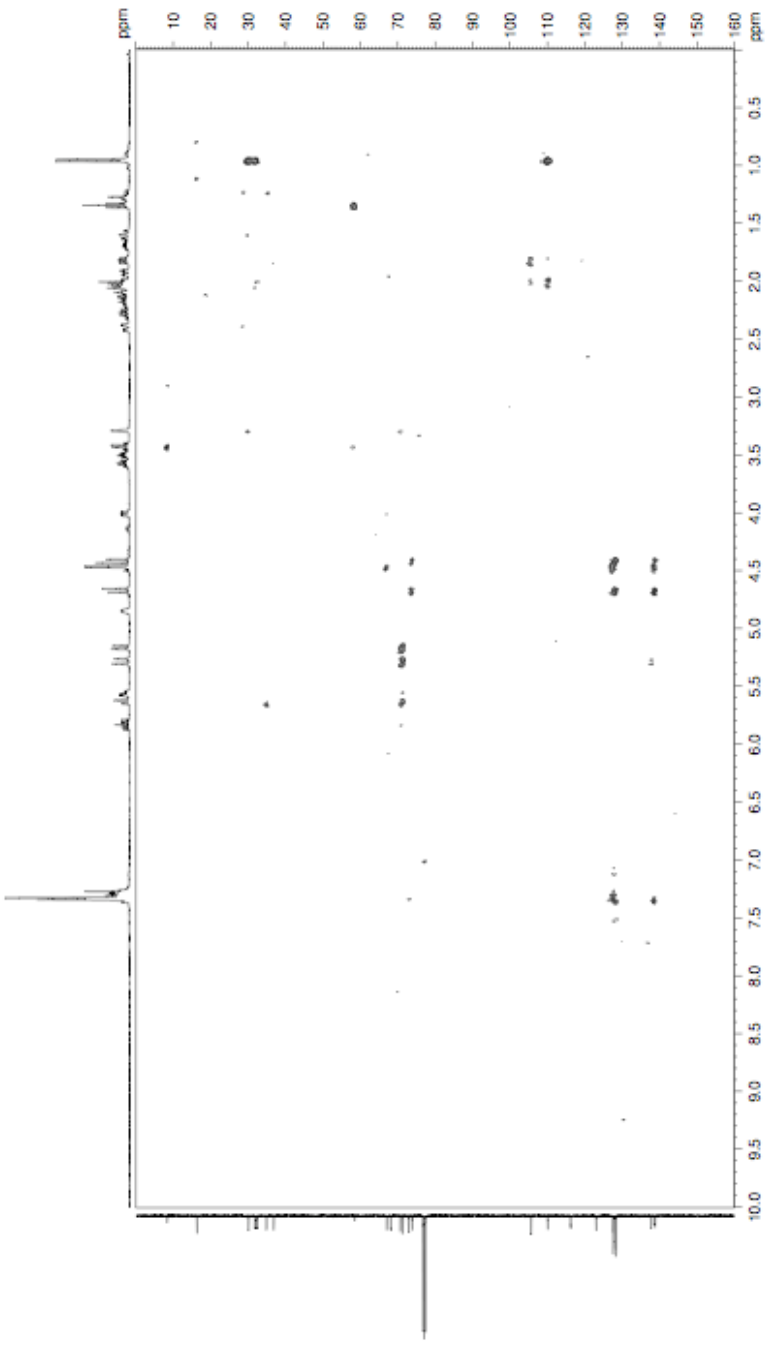

176.37
137.27
127.68
122.51
116.38
109.60
106.05
77.87
71.30
68.03
58.45
38.51
36.49
34.66
31.98
30.11
29.71
29.10
15.84
2.15.2
0 ppm

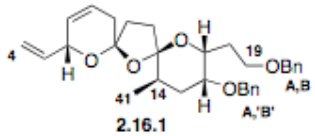

OBn
OBn
2.16.1
10.92
0.98
1.04
0.95
1.03
1.00
0.94
1.01
3.11
0.94
3.17
1.01
1.10
7.58
1.12
1.13
1.09
1.07
1.66
1.13
3.03
ppm


OBn
OBn
H
H
O
O
O
H
2.16.1
138.72
138.54
137.69
128.32
128.26
128.02
127.57
127.53
127.47
127.42
123.03
116.17
110.07
105.53
73.79
72.87
71.27
70.65
68.09
67.02
58.37
36.77
34.82
32.35
32.01
31.80
30.03
16.30
0 ppm



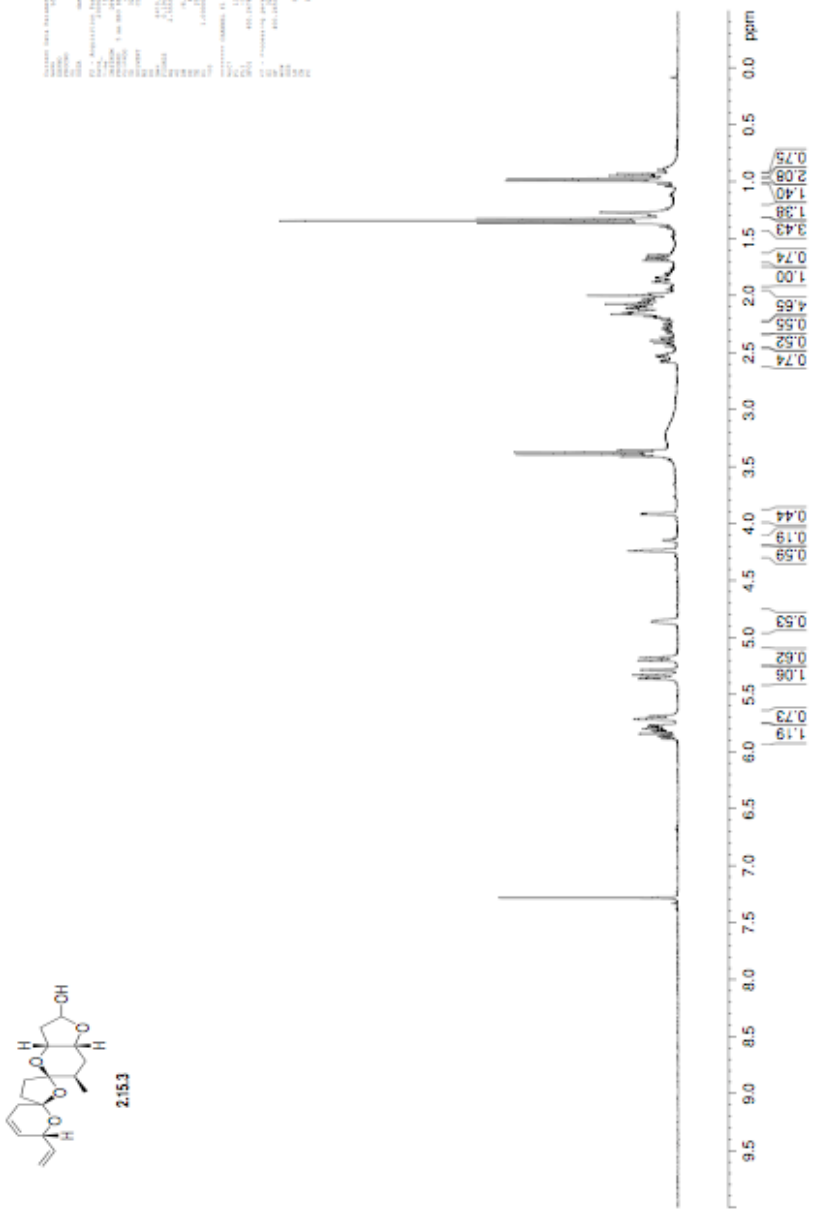

ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0

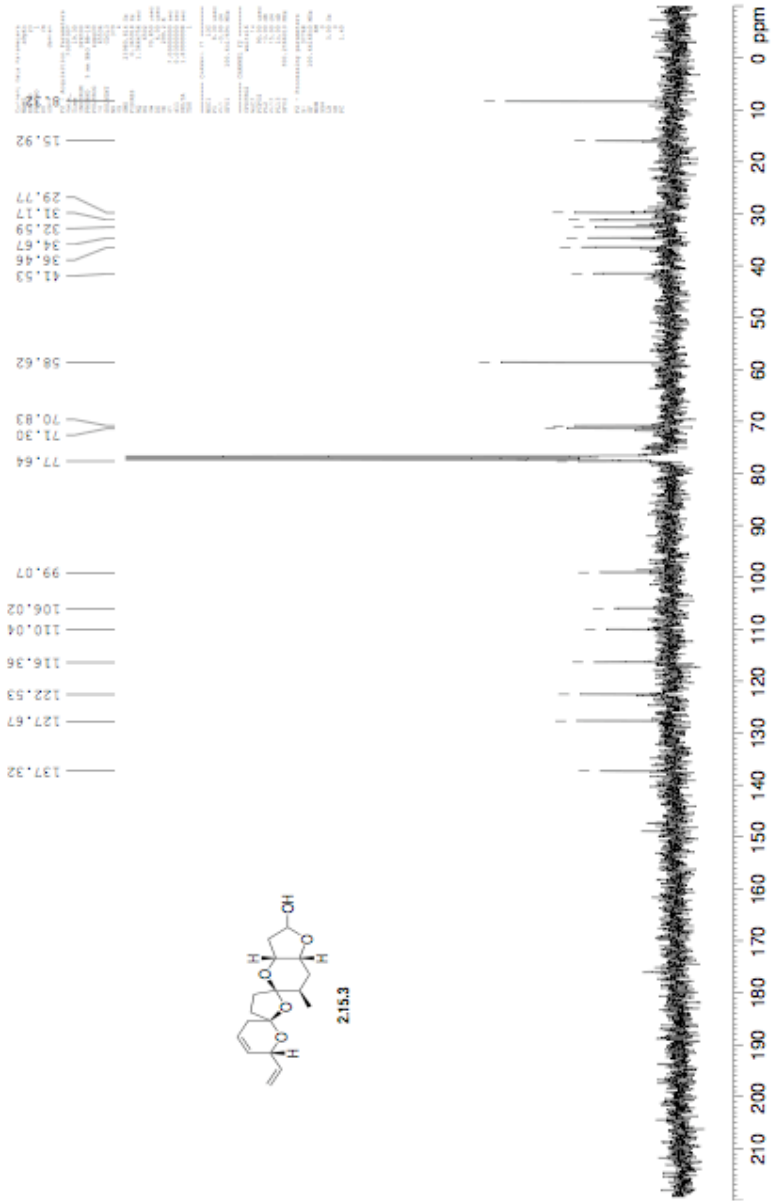

ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0

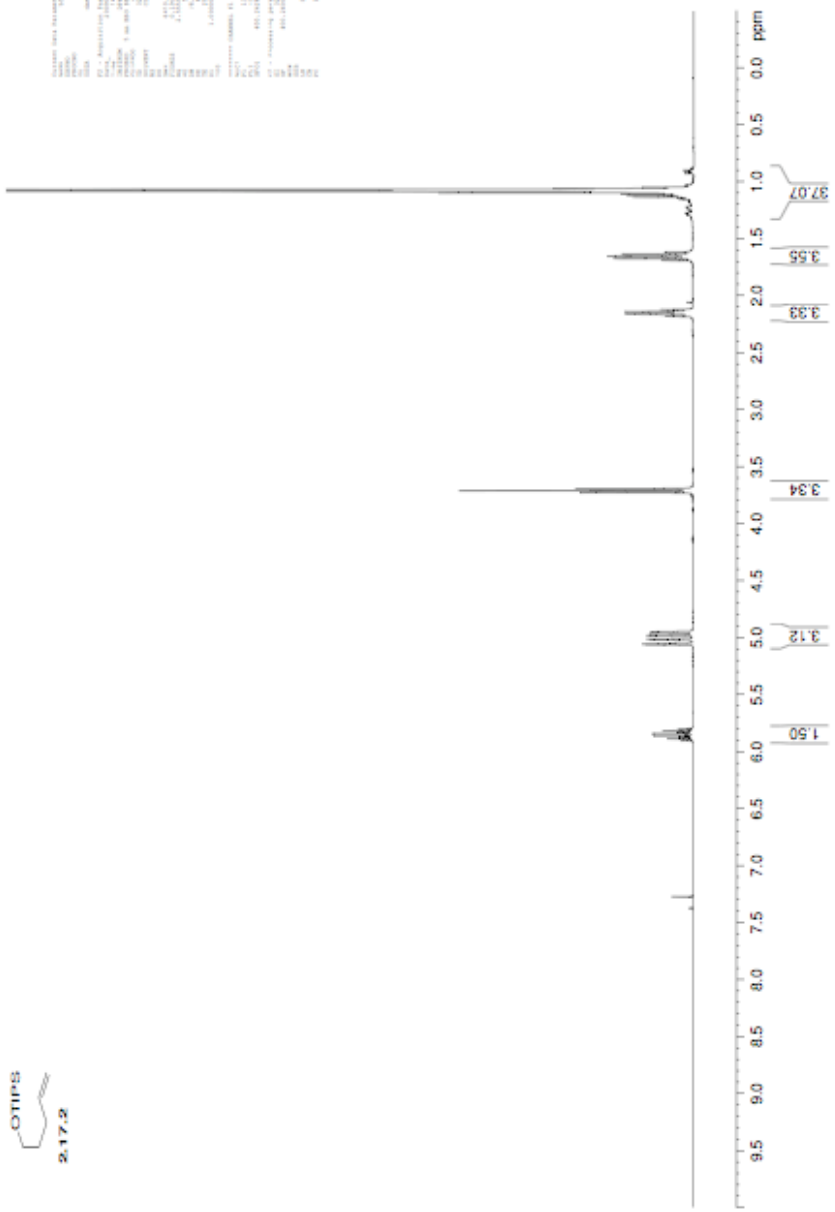


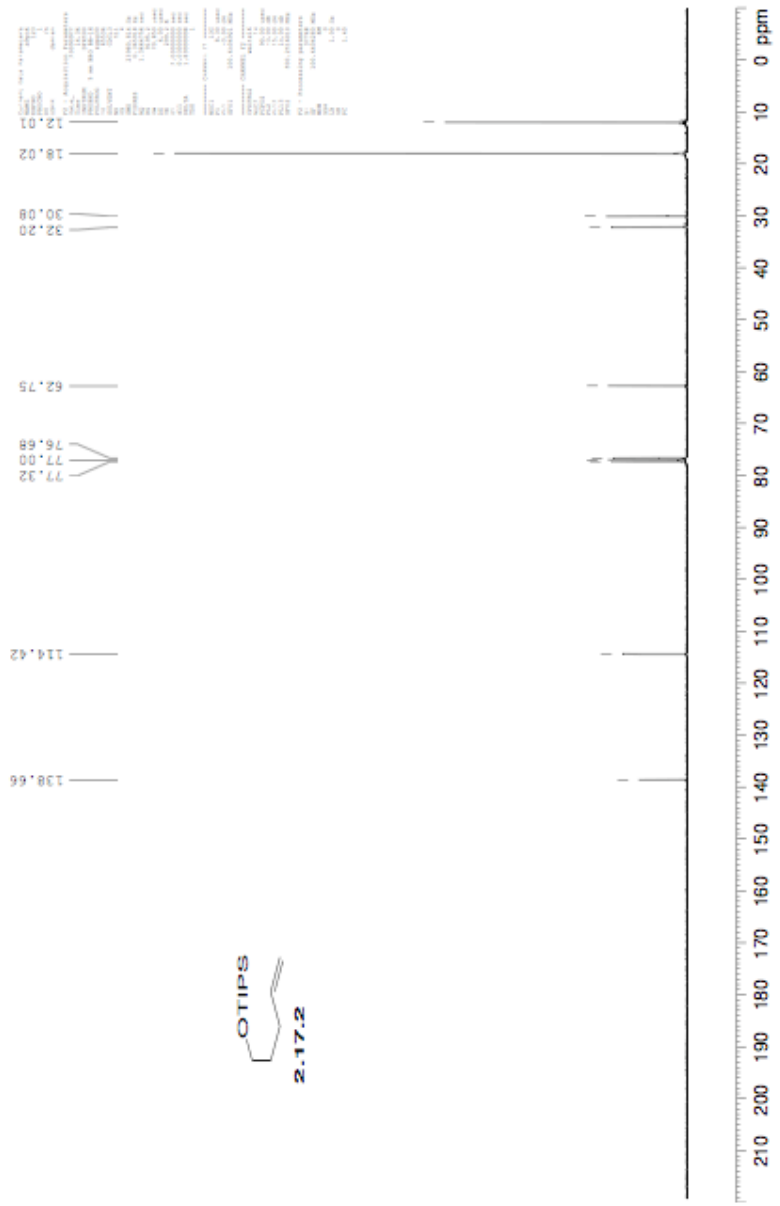
2.16.1

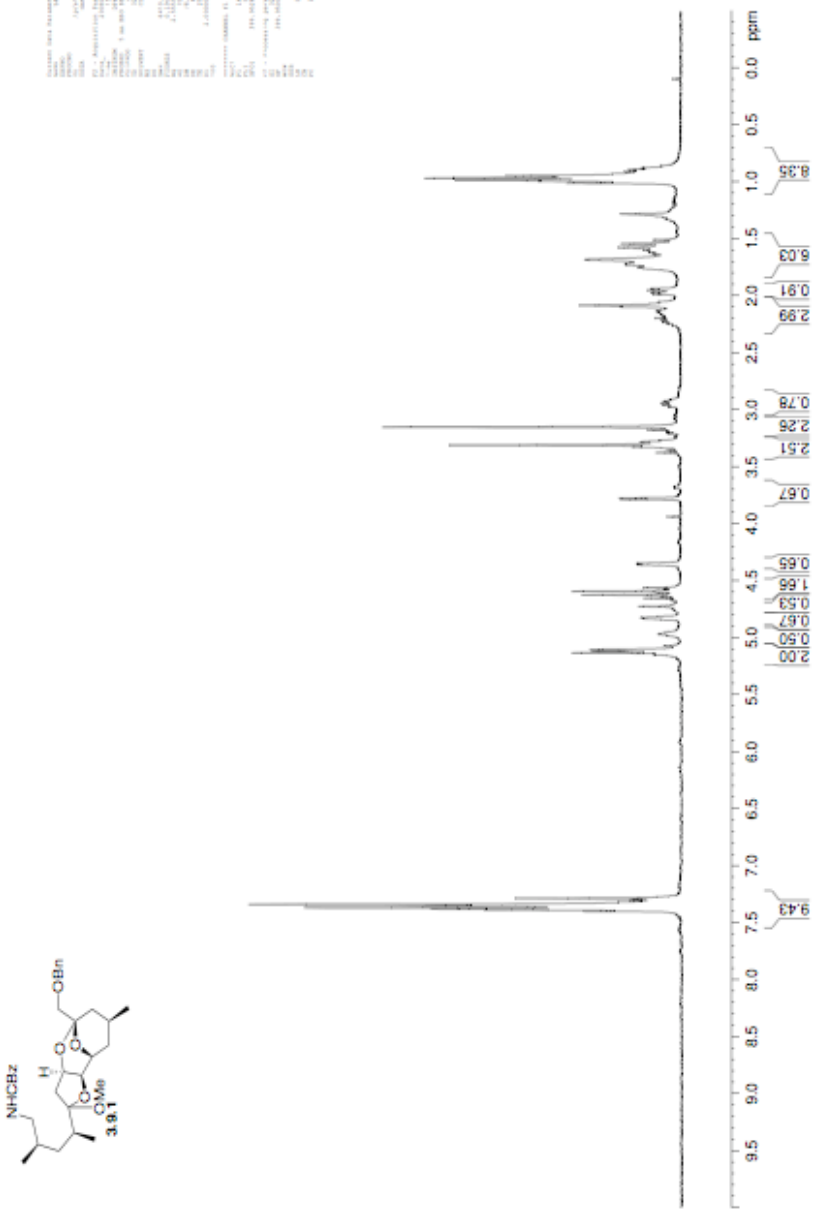
Carbon#	Carbon Signal	Proton Signal
4	123.0	5.28 (dt, *J* = 16.8, 1.2 Hz, 1H), 5.16 (d, *J* = 11.2 Hz, 1H)
5	137.7	5.77-5.84 (m, 1H)
6	71.2	4.75-4.88 (m, 1H),
7	127.6	5.50-5.68 (m, 1H)
8	127.4	5.50-5.68 (m, 1H)
9	67.0	3.50-3.70 (m, 1H)
10	105.5	-
11	34.8	2.1-2.4 (m, 2H)
12	32.0	2.0-2.3 (m, 2H)
13	110.0	-
14	31.0	2.2 (m, 1H)
15	32.3	1.65-2.25 (m, 2H)
16	68.0	3.95-4.05 (m, 1H)
17	73.7	3.29 (s, 1H)
18	30.0	1.6 (m, 2H)
19	36.7	2.05-2.15 (M, 2H)
41	16.3	0.9 (d, *J* = 6.8 Hz, 3H)
A	72.8	4.4 (m, 2H)
A'	70.6	4.4 (d,d 2H)
B, B'	138.7, 138.5, 128.3 128.2, 127.5, 127.5	7.20-7.40 (m, 10H)

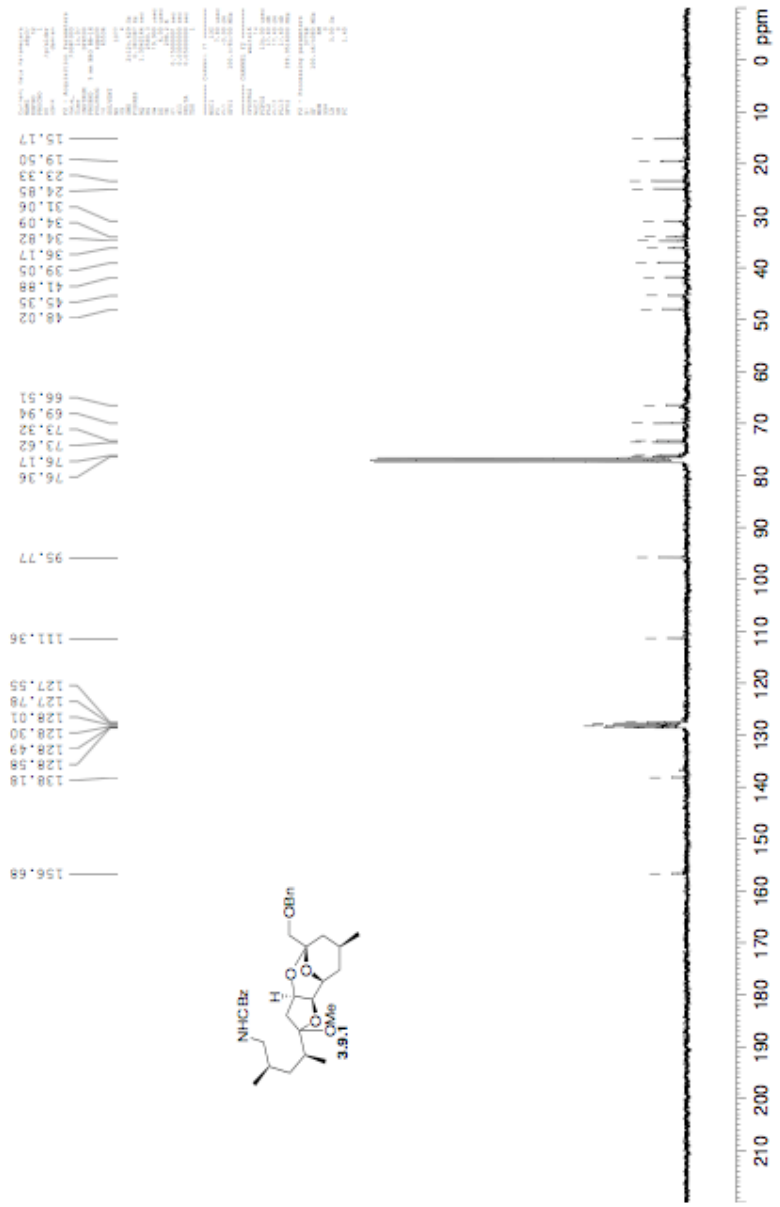

OH
O
H
O
O
O
H
O
H
2.15.3
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
0.75
2.08
1.40
1.38
3.43
0.74
1.00
4.65
0.55
0.52
0.74
0.44
0.19
0.59
0.53
0.62
1.06
0.73
1.19

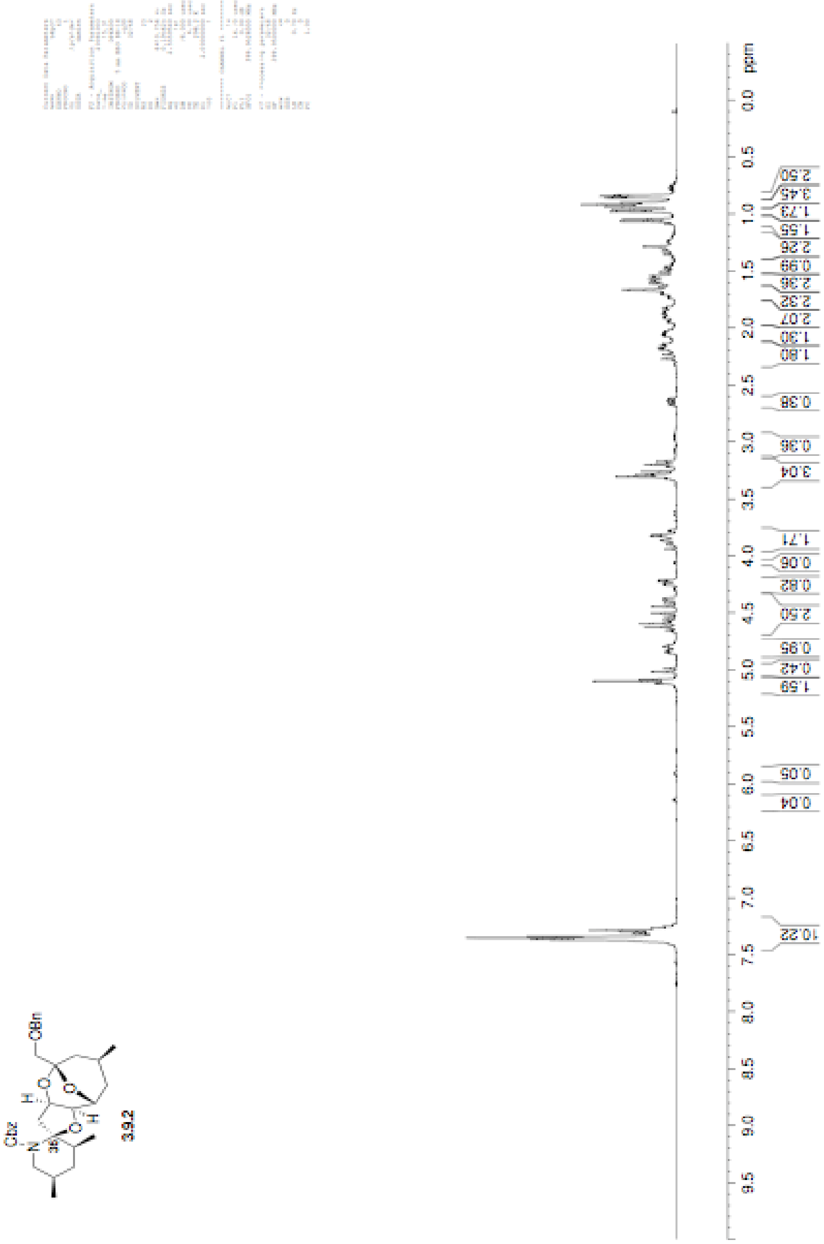

15.92
29.77
31.17
32.59
34.67
36.46
41.53
58.62
70.83
71.30
77.64
99.07
106.02
110.04
116.36
122.53
127.67
137.32
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
OH
O
H
O
O
O
H
O
2.15.3


OTIPS
2.17.2
37.07
3.55
3.33
3.34
3.12
1.50
ppm

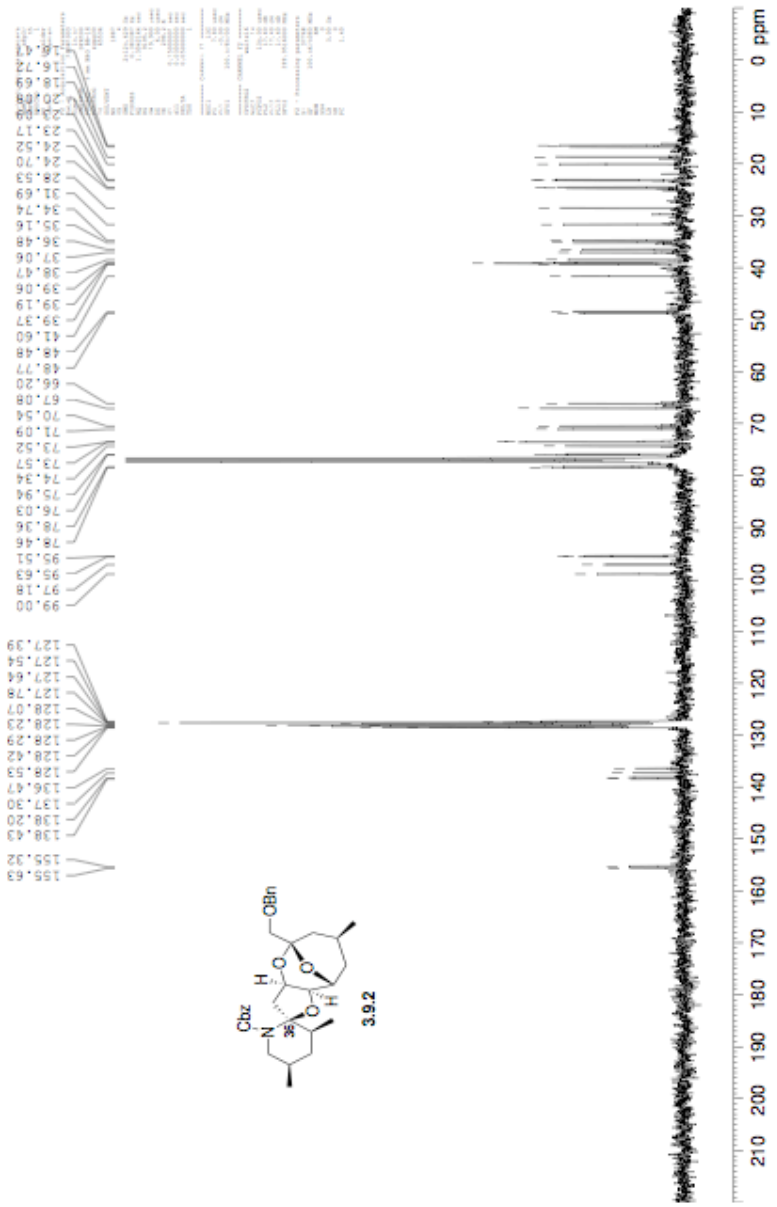

12.01
18.02
30.08
32.20
62.75
76.68
77.00
77.32
114.42
138.66
OTIPS
2.17.2
0 ppm

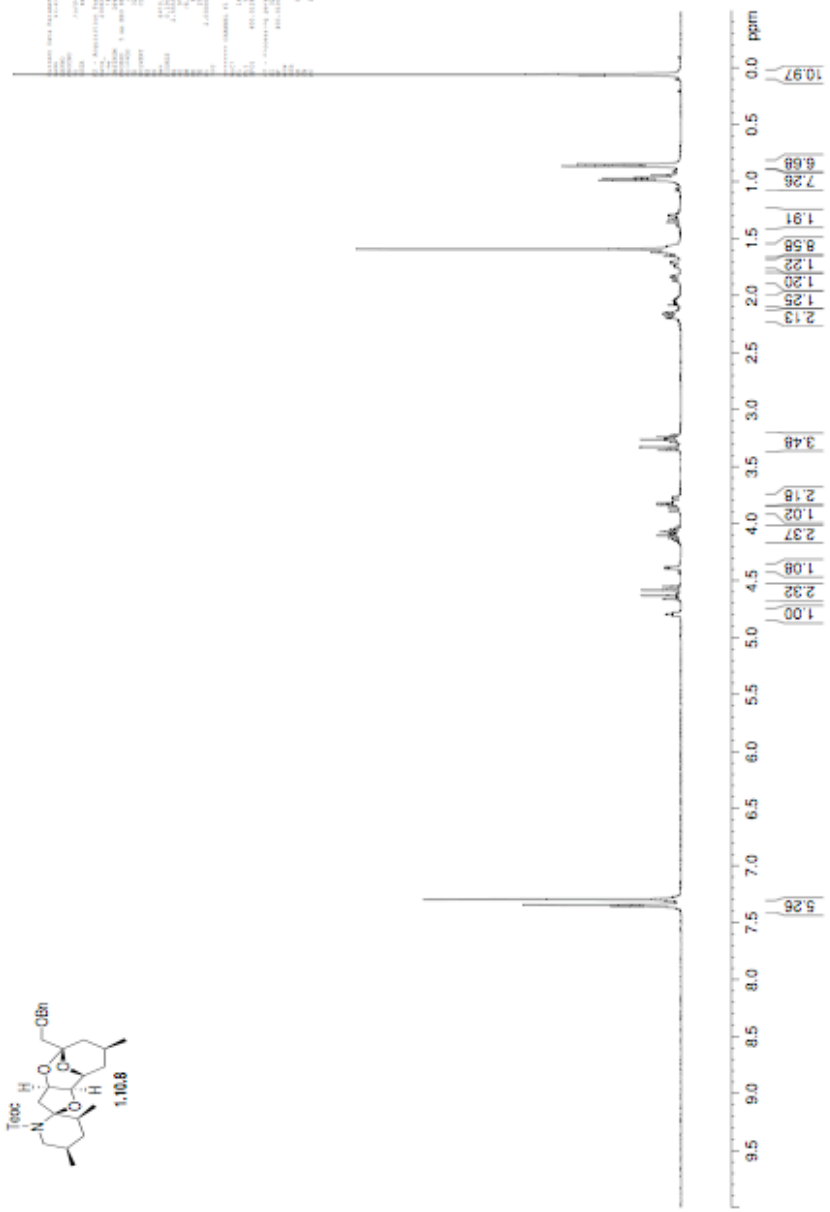

OBn
O
O
H
O
OMe
NHCBz
3.9.1
9.43
2.00
0.50
0.67
0.53
1.66
0.65
0.67
2.51
2.26
0.78
2.99
0.91
6.03
8.35
ppm

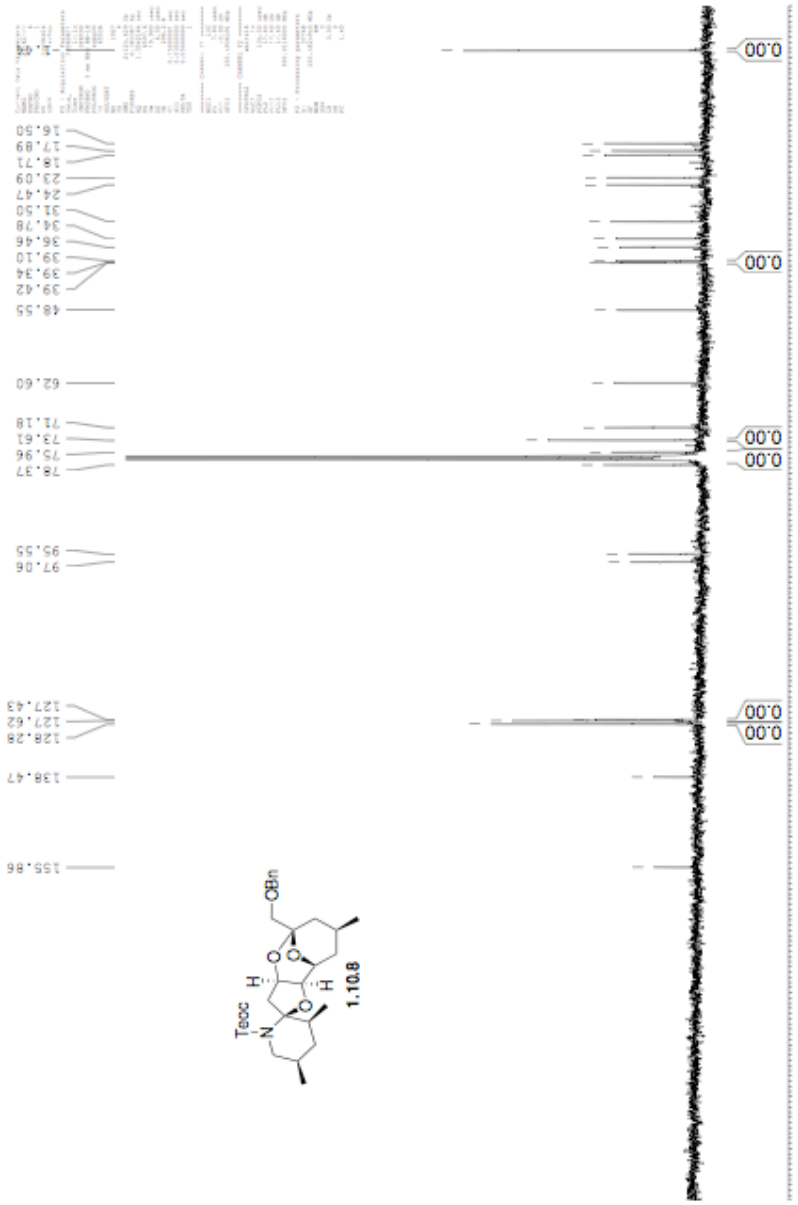

15.17
19.50
23.33
24.85
31.06
34.09
34.82
36.17
39.05
41.88
45.35
48.02
66.51
69.94
73.32
73.62
76.17
76.36
95.77
111.36
127.55
127.78
128.01
128.30
128.49
128.58
138.18
156.68
NHCBz
OMe
OBn
3.9.1
0 ppm

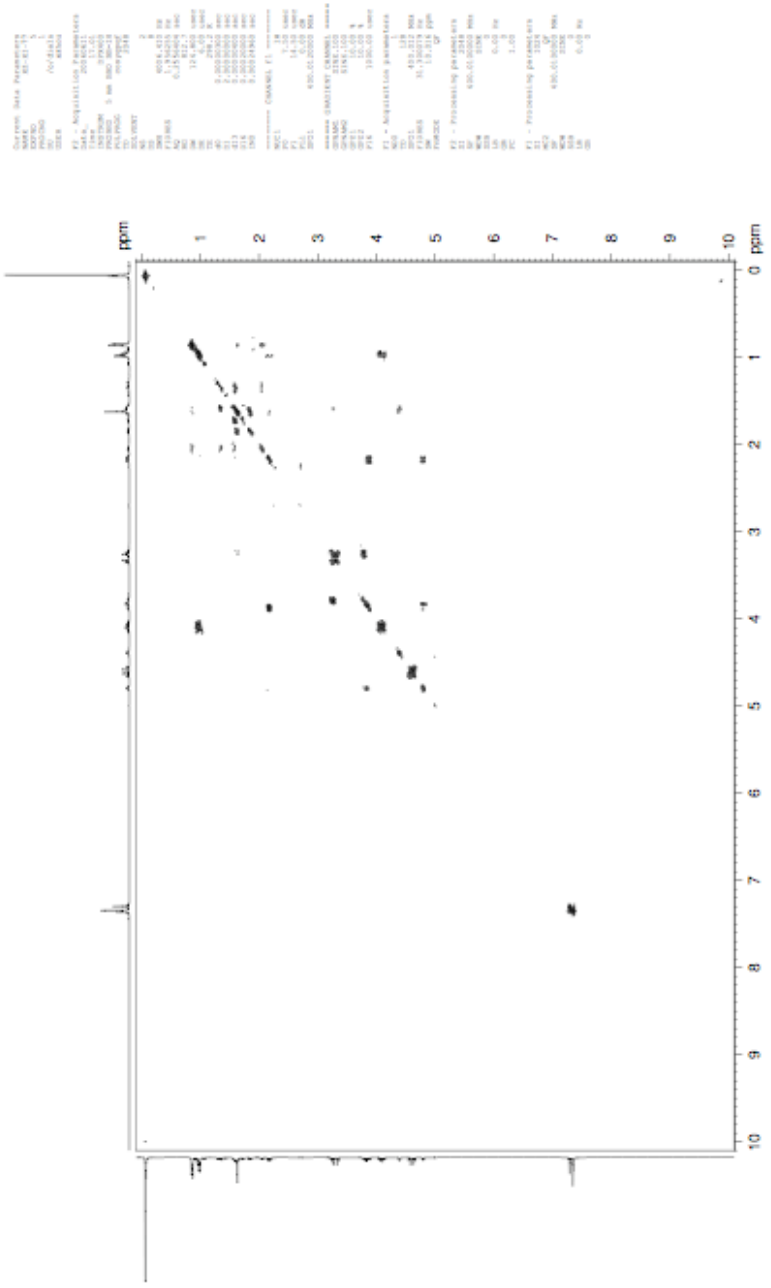


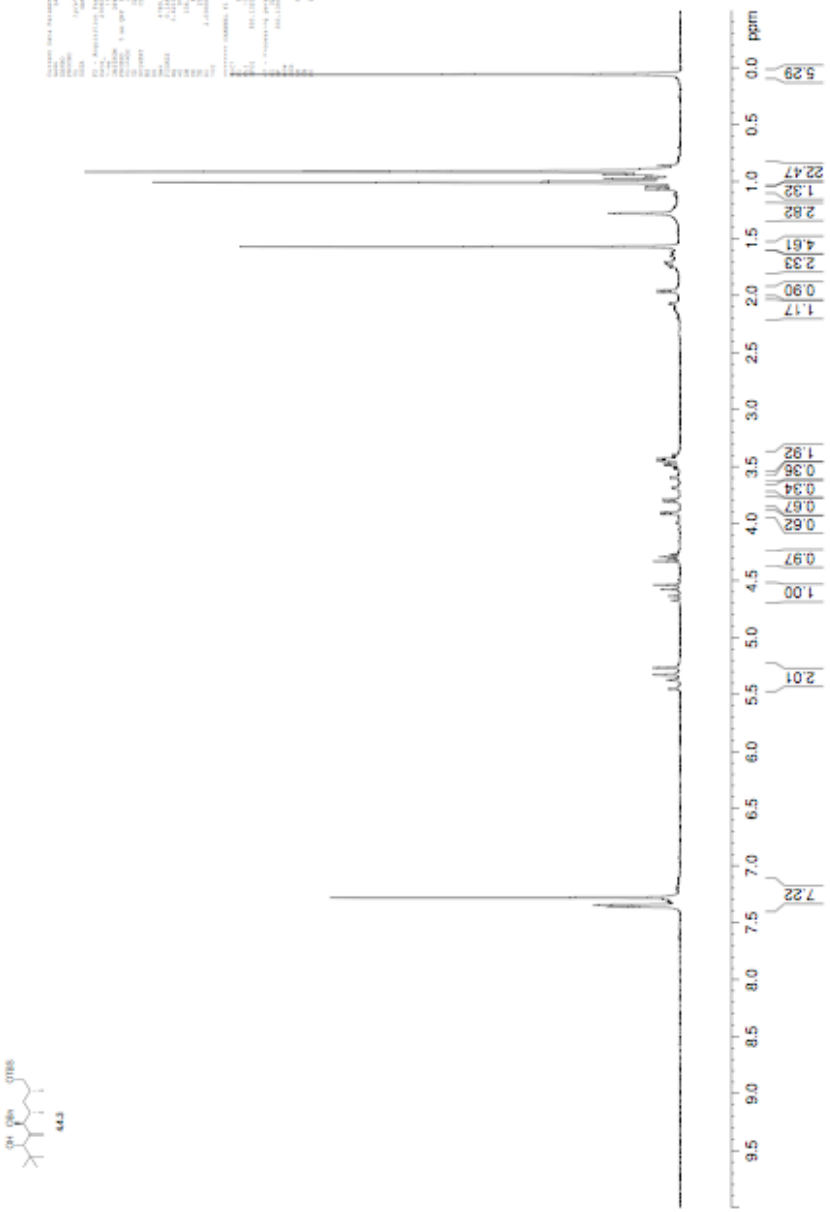
3.9.2

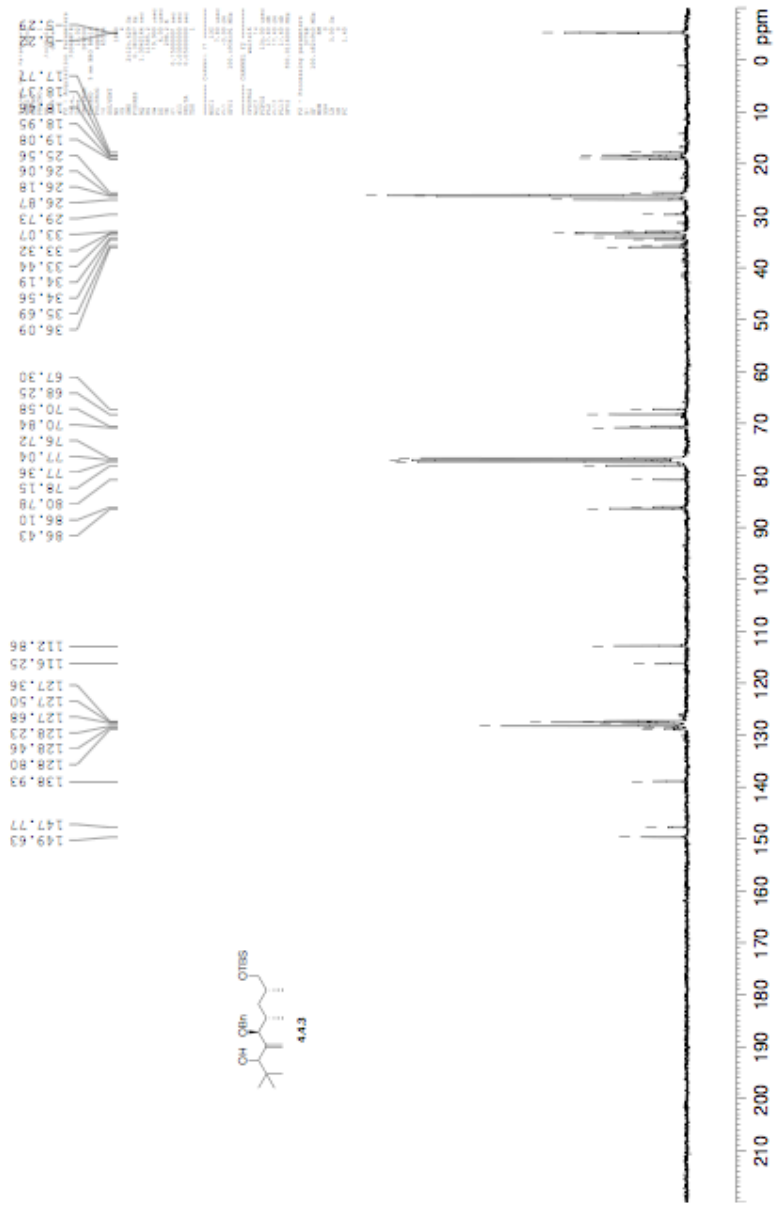

OBn
O
O
H
O
H
Cbz
N
3.9.2
0 ppm

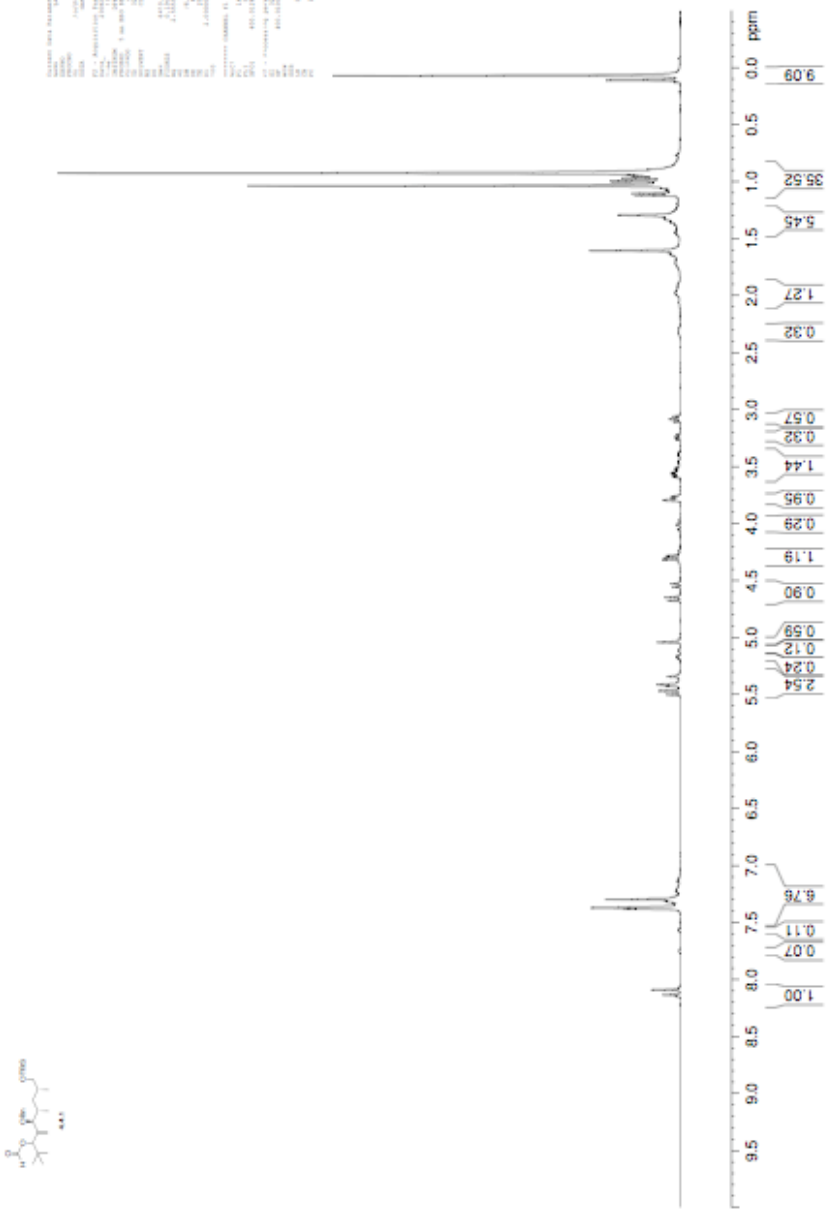

OBn
Teoc
H
H
O
O
O
N
1.16.8
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.97
6.68
7.26
1.91
8.58
1.22
1.20
1.25
2.13
3.48
2.18
1.02
2.37
1.08
2.32
1.00
5.26

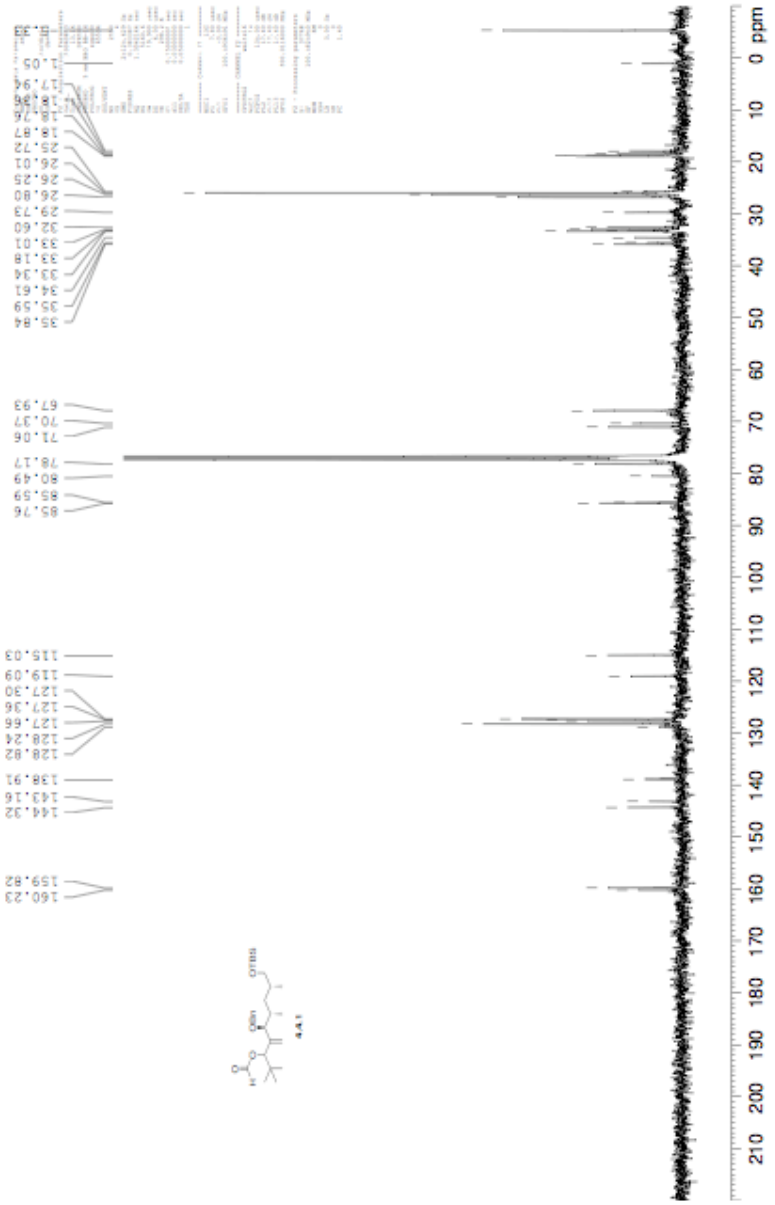

16.50
17.89
18.71
23.09
24.47
31.50
34.78
36.46
39.10
39.34
39.42
48.55
62.60
71.18
73.61
75.96
78.37
95.55
97.06
127.43
127.62
128.28
138.47
155.86
0.00
0.00
0.00
0.00
0.00
OBn
Teoc
N
H
H
O
O
O
1.10.8

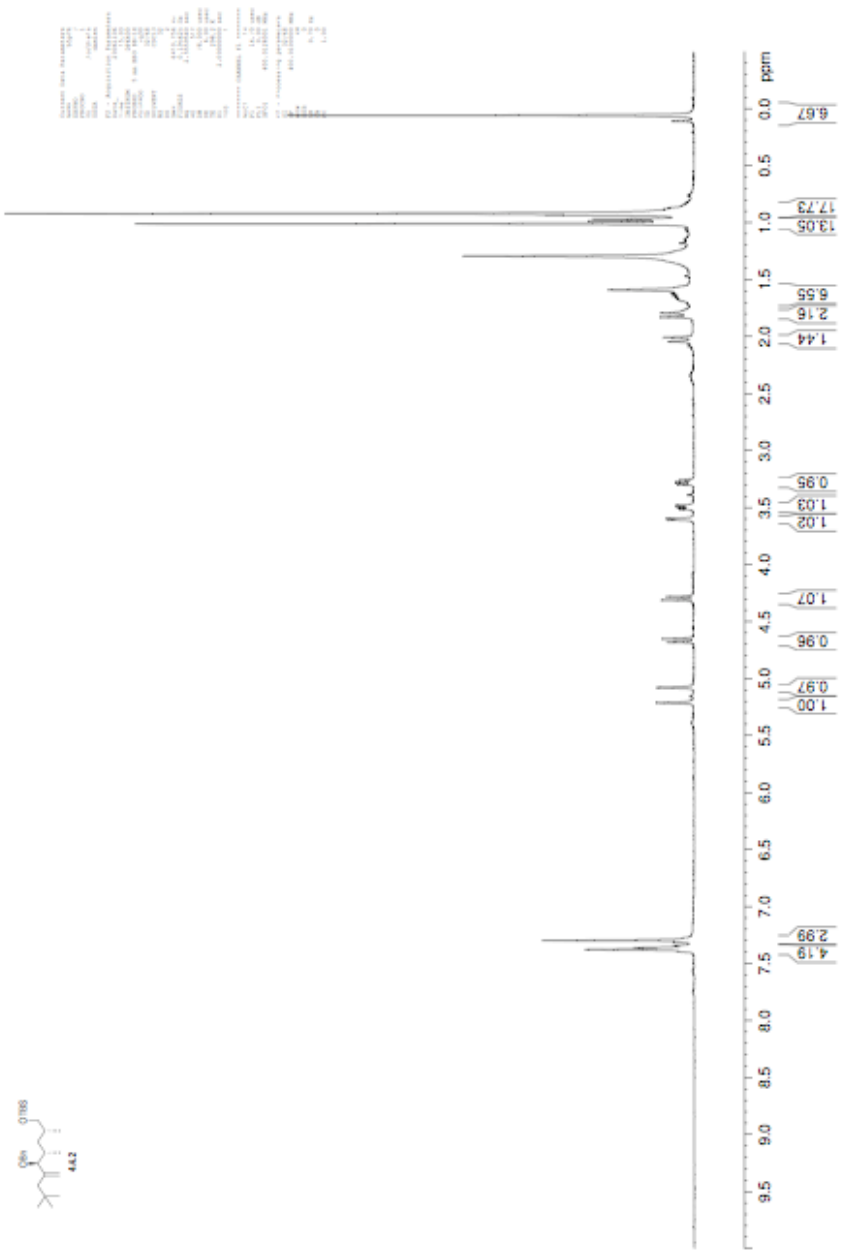


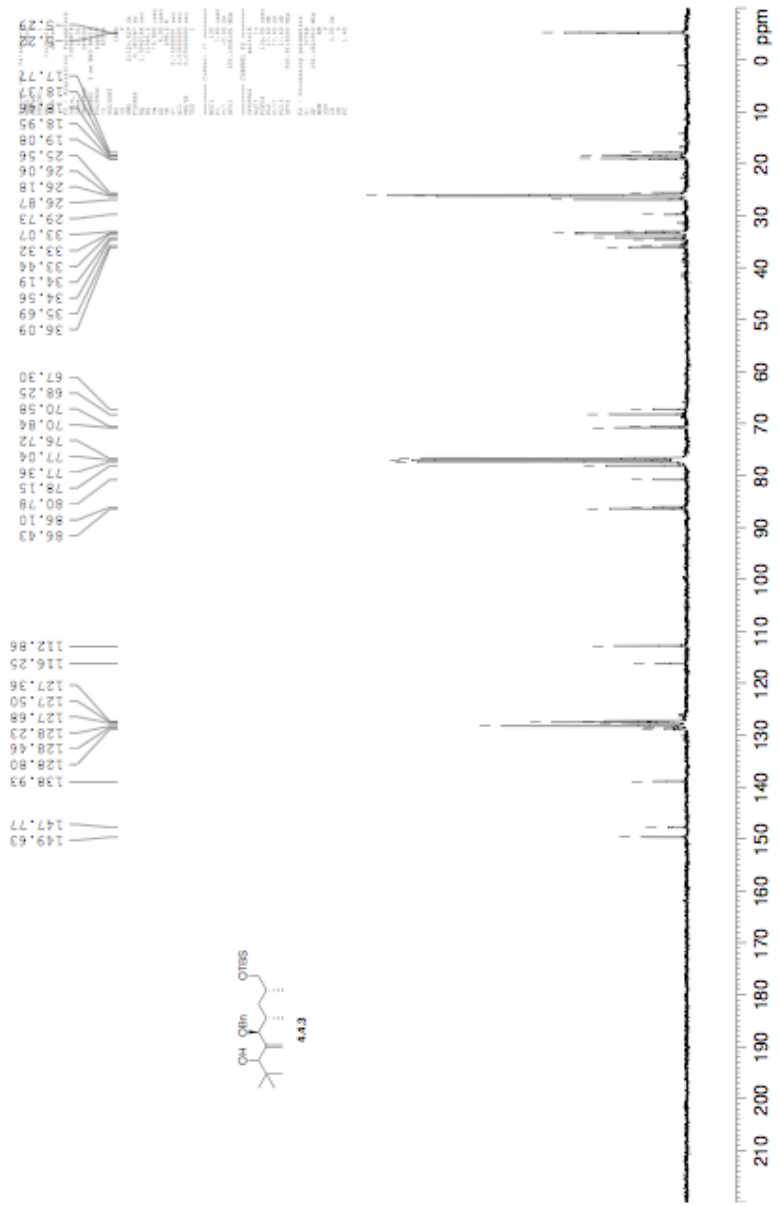

ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
5.29
22.47
1.32
2.82
4.61
2.33
0.90
1.17
1.82
0.36
0.34
0.67
0.62
0.97
1.00
2.01
7.22

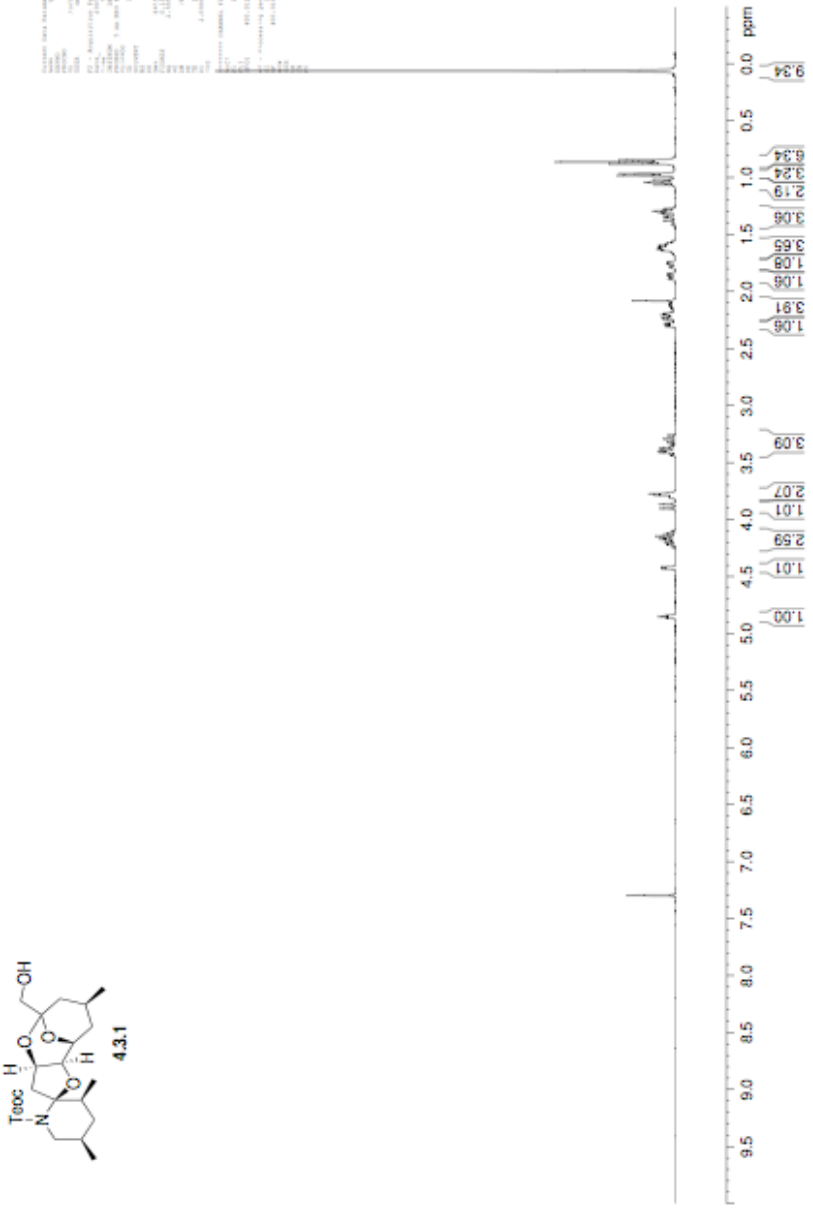

443
OH
OBn
OTBS
0 ppm

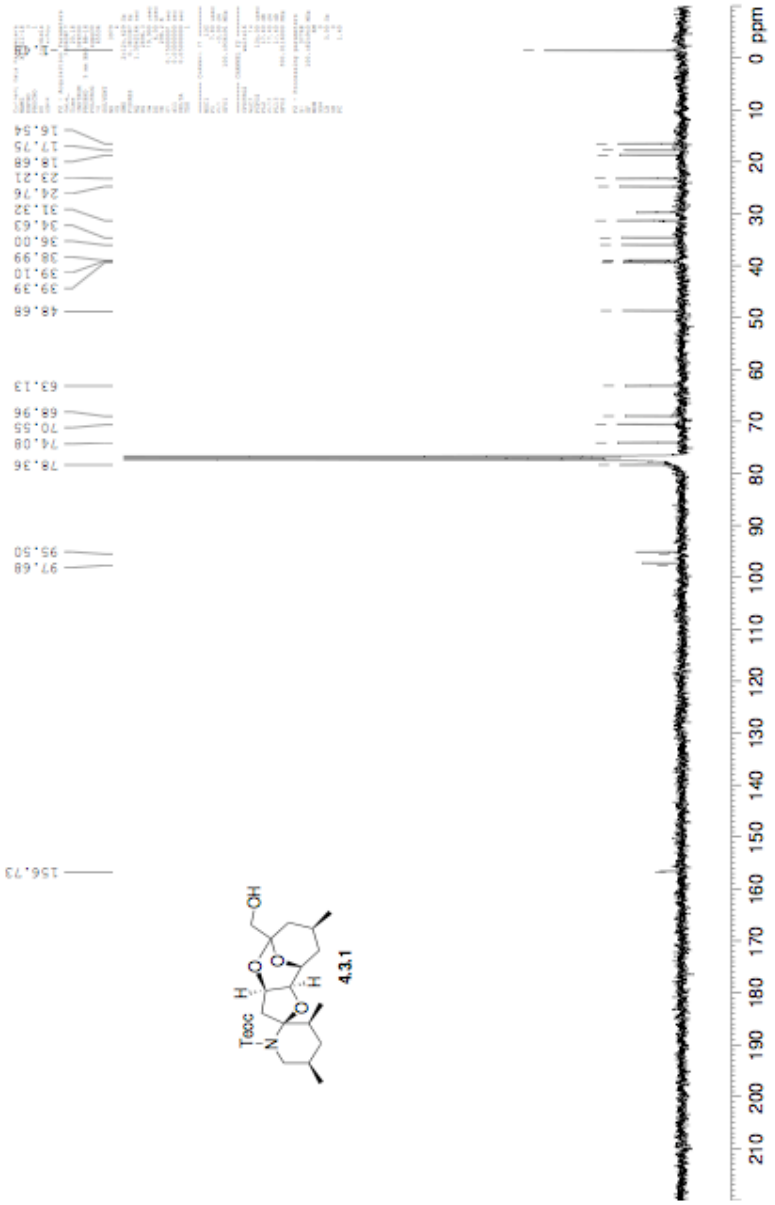

ppm
9.09
35.52
5.45
1.27
0.32
0.57
0.32
1.44
0.95
0.29
1.19
0.90
0.59
0.12
0.24
2.54
6.76
0.11
0.07
1.00

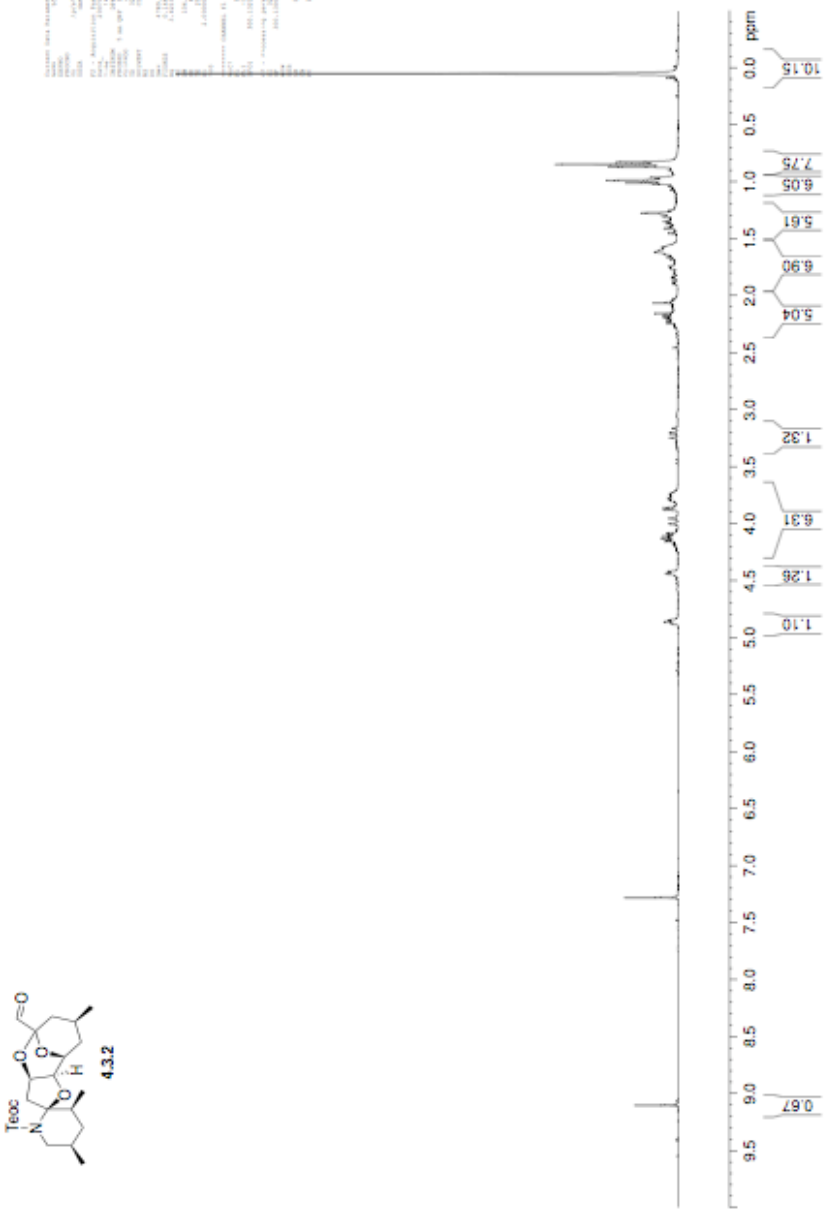


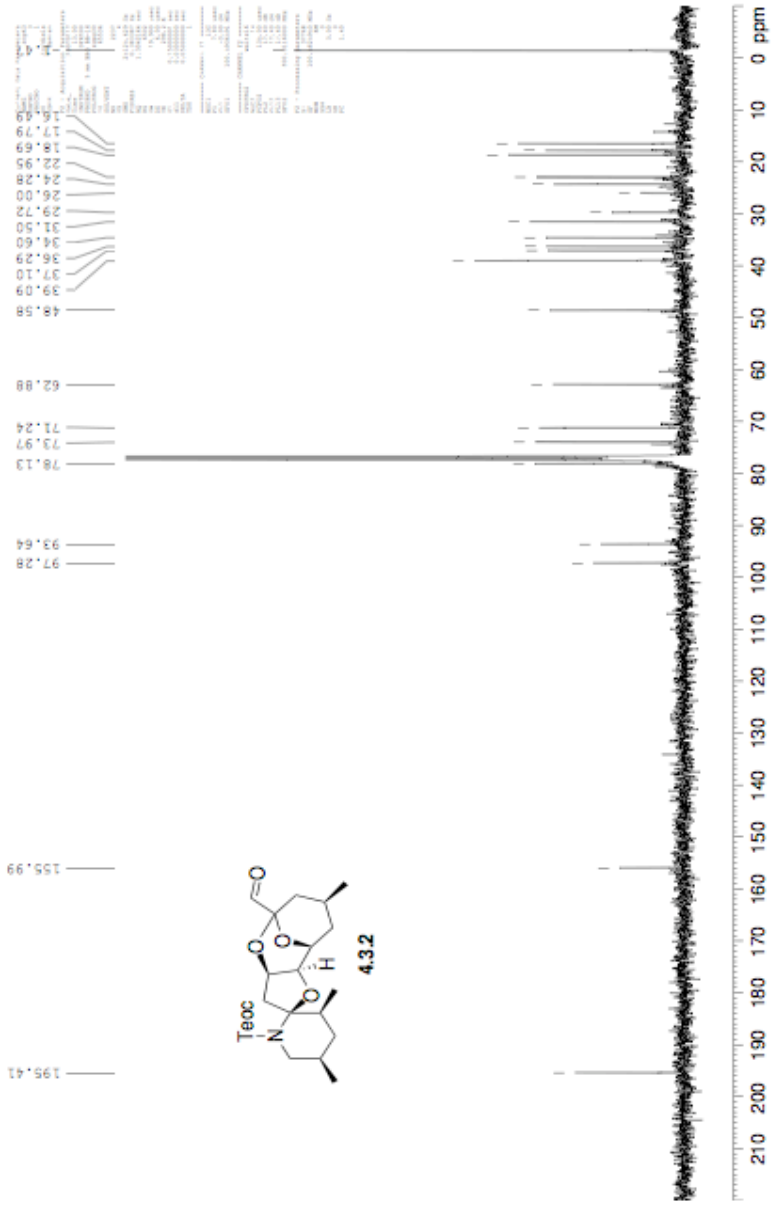

6.67
17.73
13.05
6.55
2.16
1.44
0.95
1.03
1.02
1.07
0.96
0.97
1.00
2.99
4.19
ppm

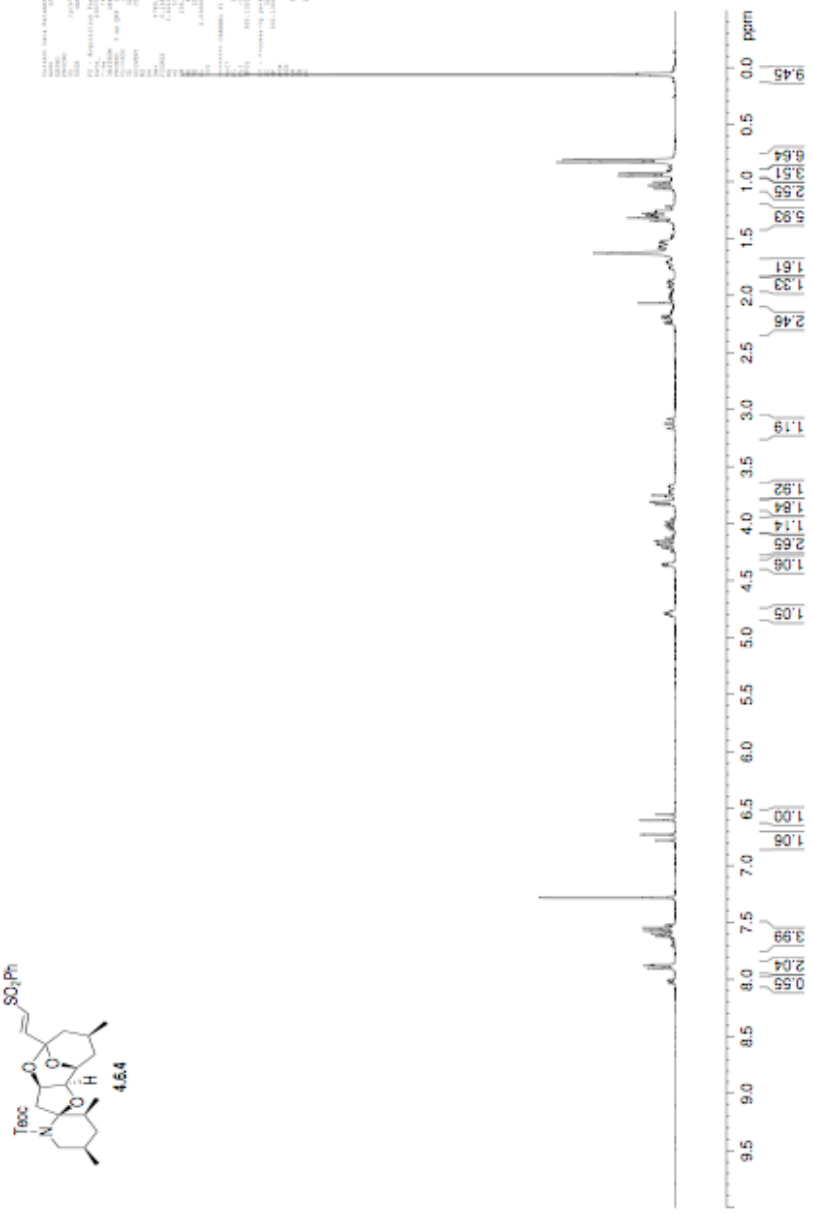

443
OH
OBn
OTBS
0 ppm

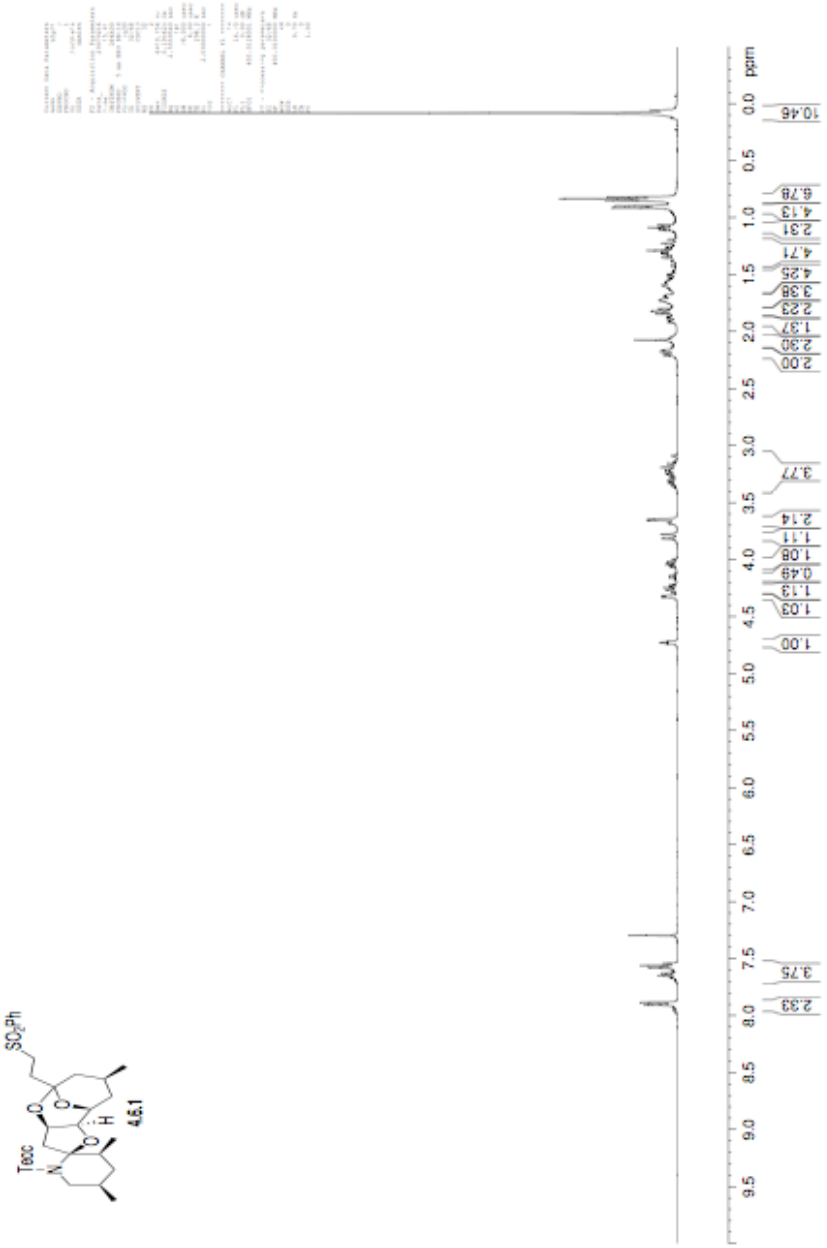

Teoc
OH
4.3.1
ppm
9.34
6.34
3.24
2.19
3.06
3.65
1.08
1.06
3.91
1.06
3.09
2.07
1.01
2.59
1.01
1.00

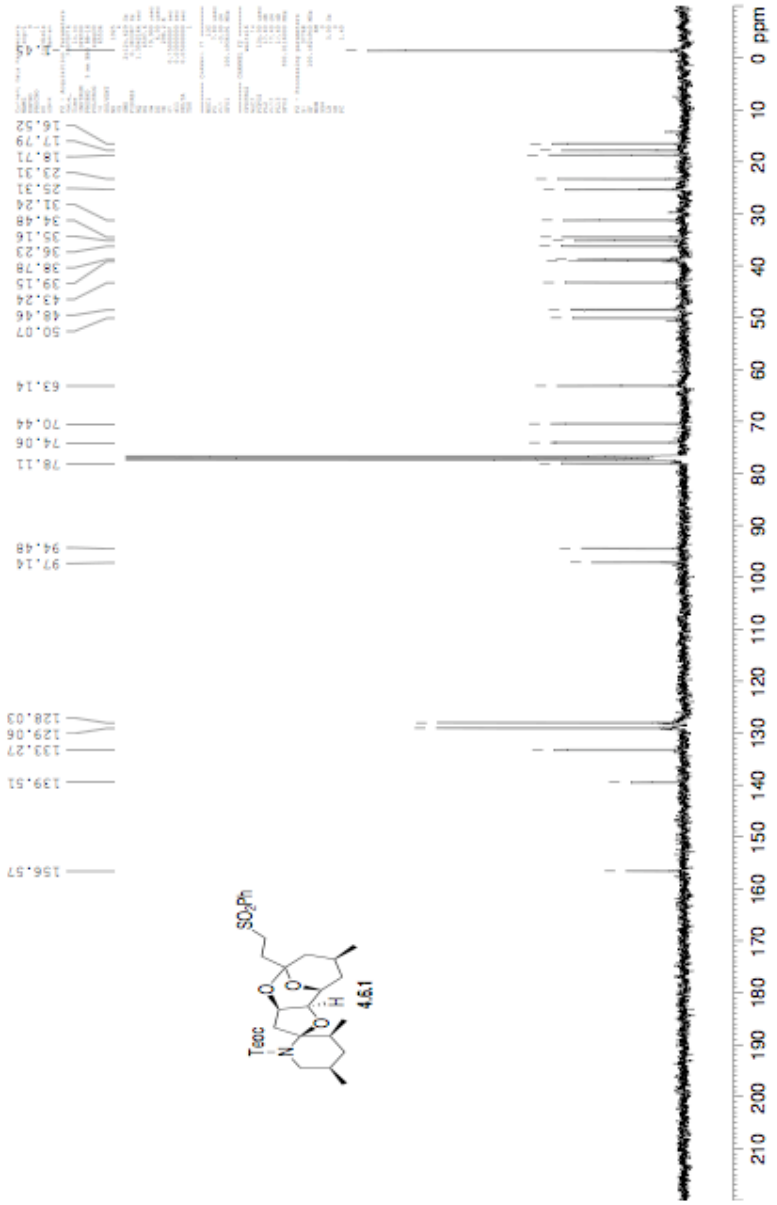

156.73
97.69
95.50
78.36
74.08
70.55
68.96
63.13
48.68
39.39
39.10
38.99
36.00
34.63
31.32
24.76
23.21
18.68
17.75
16.54
1.48
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
OH
O
O
H
H
O
Tesc
N
4.3.1

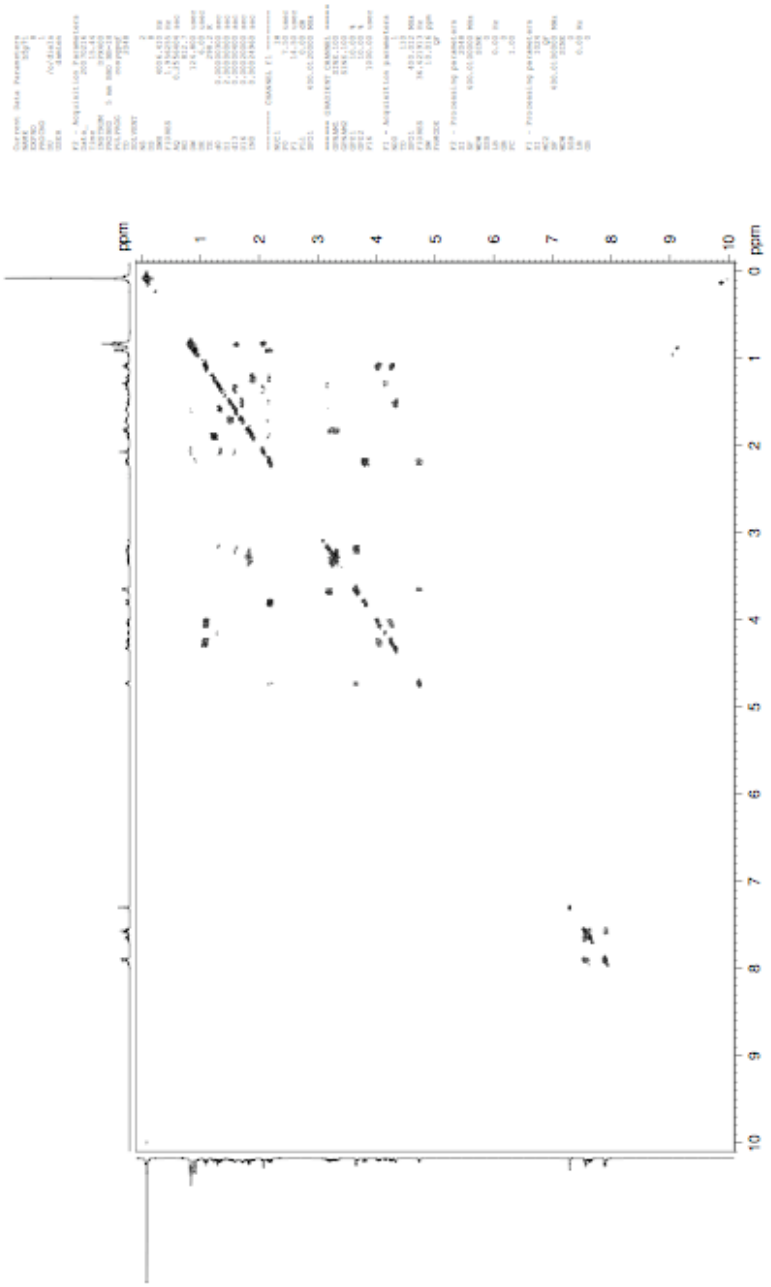

Teoc
4.3.2
ppm
10.15
7.75
6.05
5.61
6.90
5.04
1.32
6.31
1.26
1.10
0.67

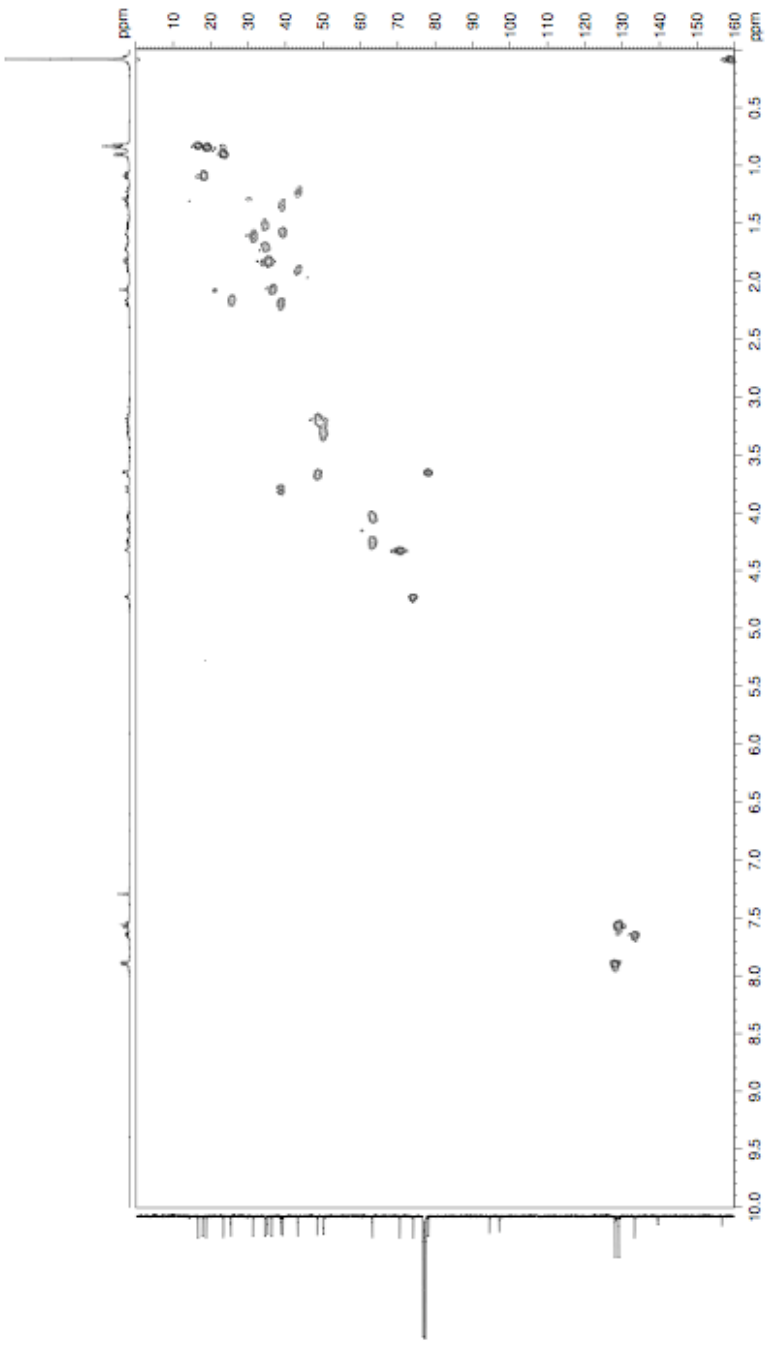

195.41
155.99
97.28
93.64
78.13
73.97
71.24
62.88
48.58
39.09
37.10
36.29
34.60
31.50
29.72
26.00
24.28
22.95
18.69
17.79
16.49
Teoc
N
O
H
4.3.2
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

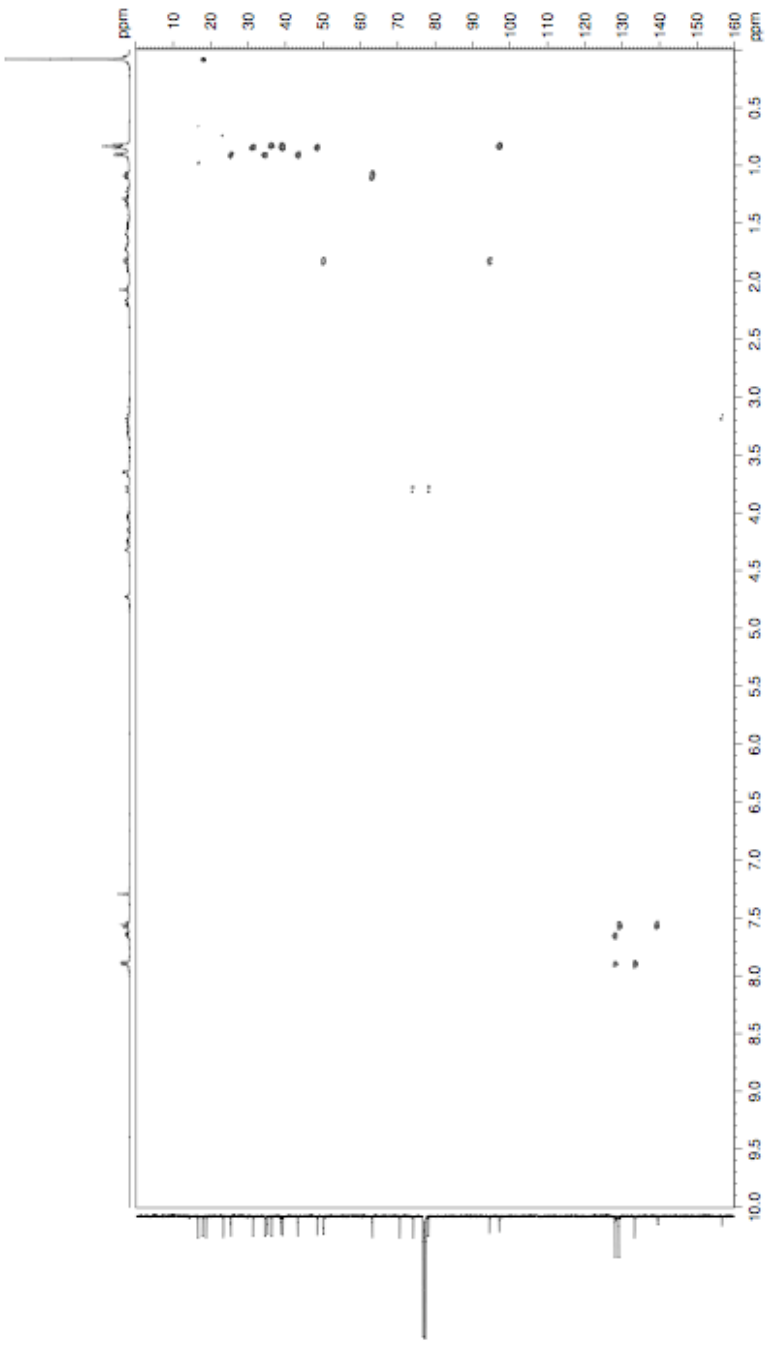

SO2Ph
Teoc
N
O
O
O
H
4.6.4
9.45
6.64
3.51
2.55
5.93
1.61
1.33
2.46
1.19
1.92
1.84
1.14
2.65
1.06
1.05
1.06
1.00
3.99
2.04
0.55
ppm

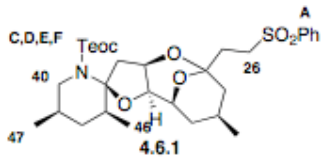

SO2Ph
Tecc
N
O
O
O
H
4&1
10.46
6.78
4.13
2.31
4.71
4.25
3.38
2.23
1.37
2.30
2.00
3.77
2.14
1.11
1.08
0.49
1.13
1.03
1.00
3.75
2.33
ppm


14.45
16.52
17.79
18.71
23.31
25.31
31.24
34.48
35.16
36.23
36.78
39.15
43.24
48.46
50.07
63.14
70.44
74.06
78.11
94.48
97.14
128.03
129.06
133.27
139.51
156.57
SO2Ph
Teoc
N
O
O
O
H
4.6.1
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210



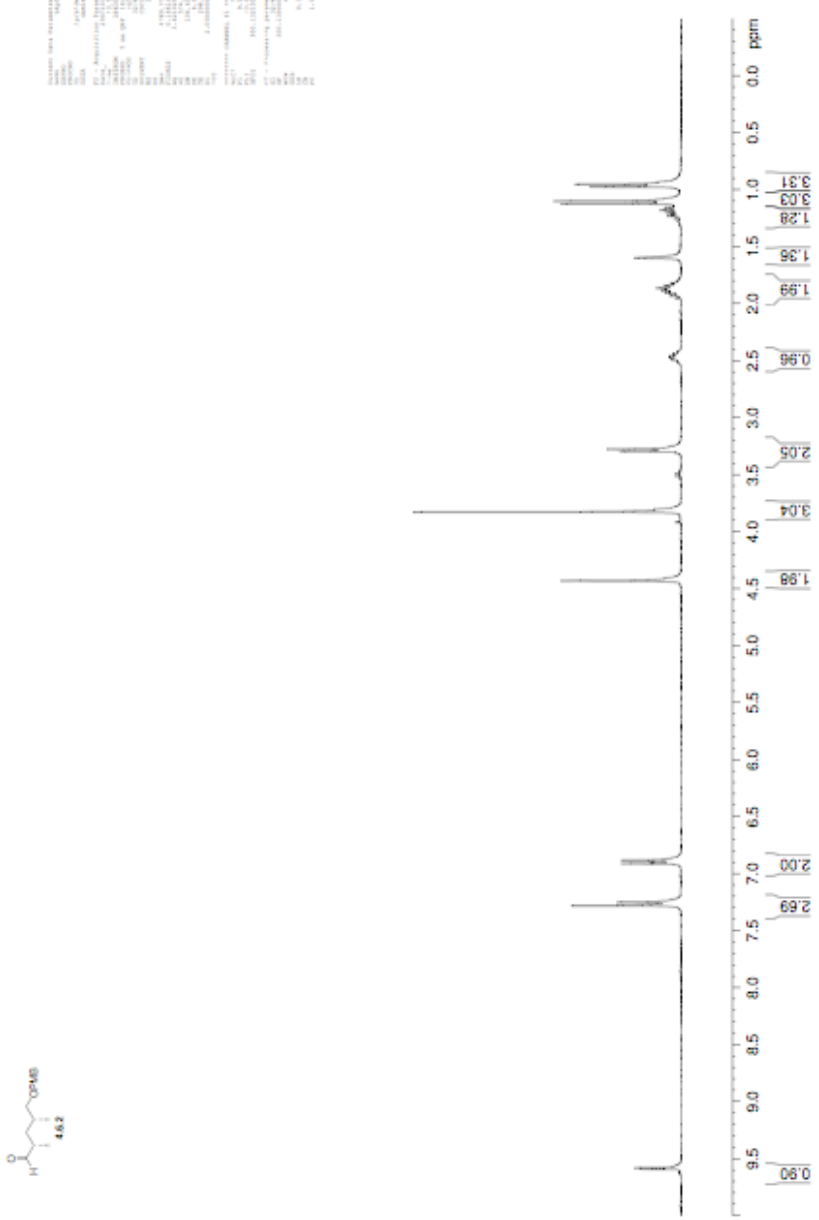

ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0

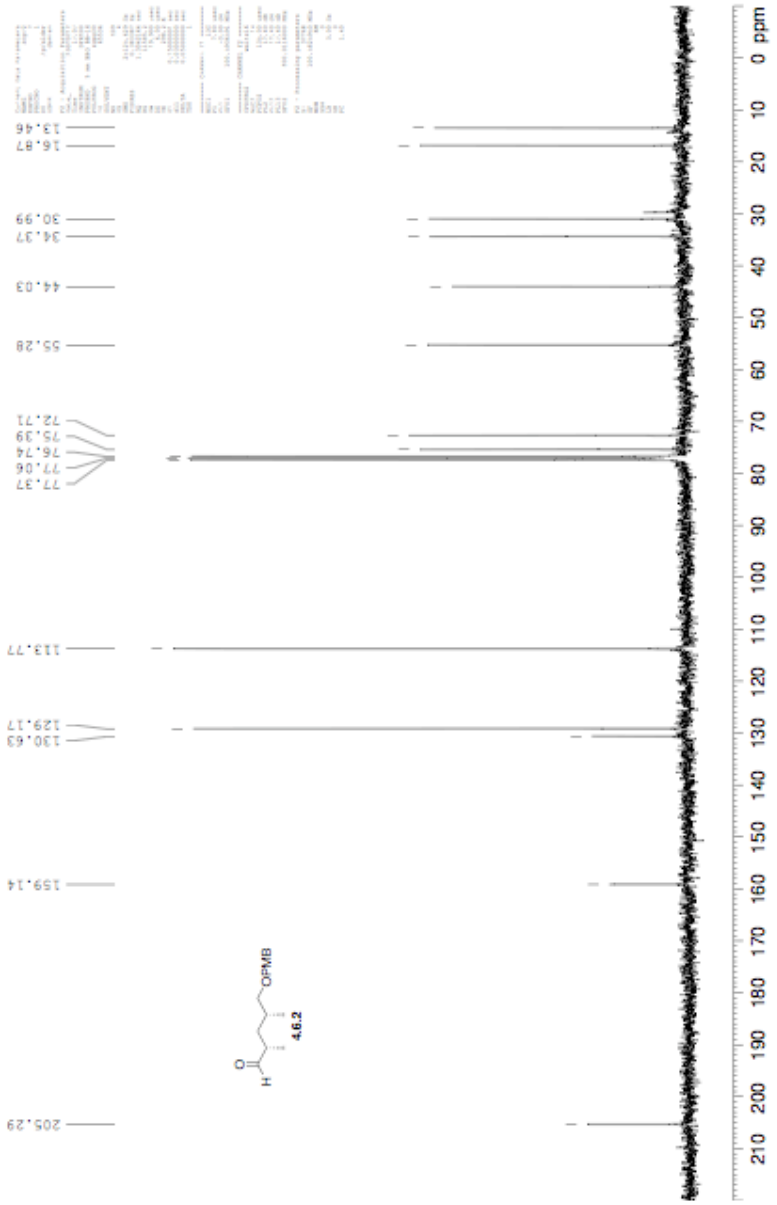

ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0

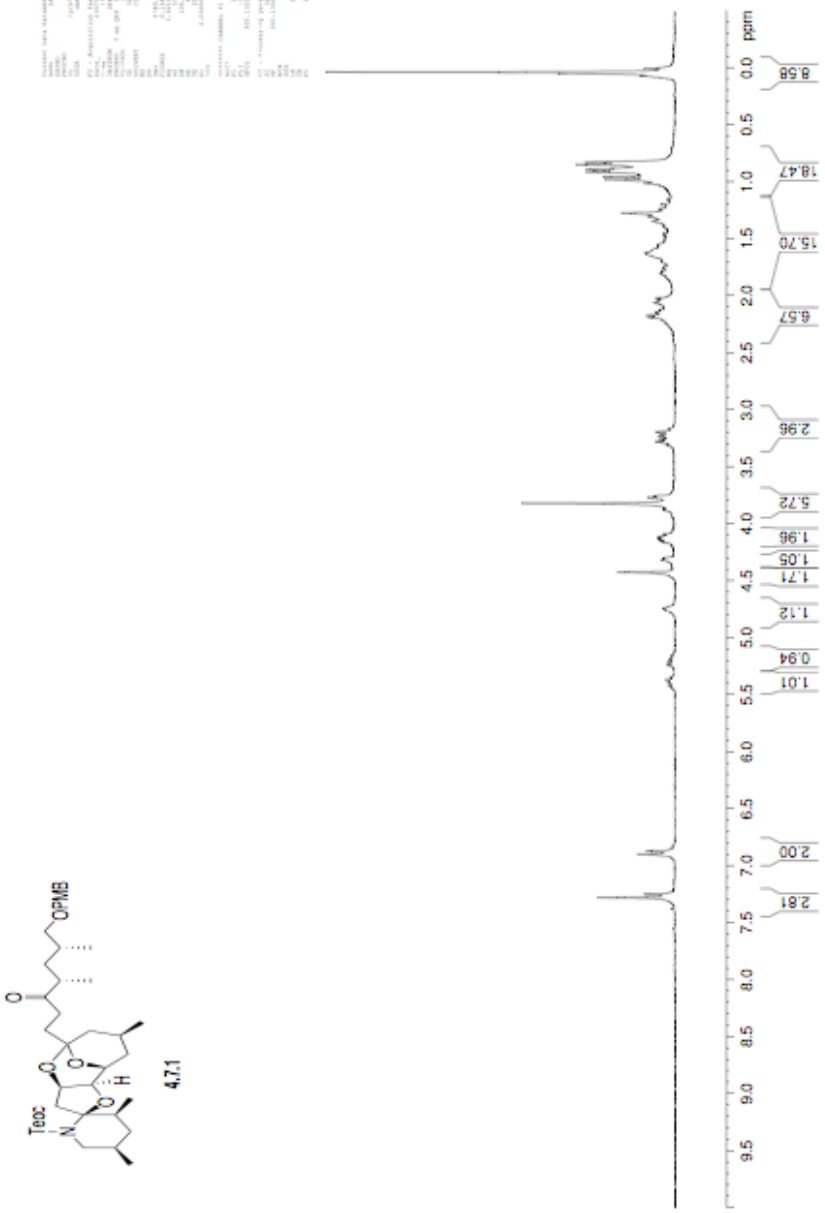


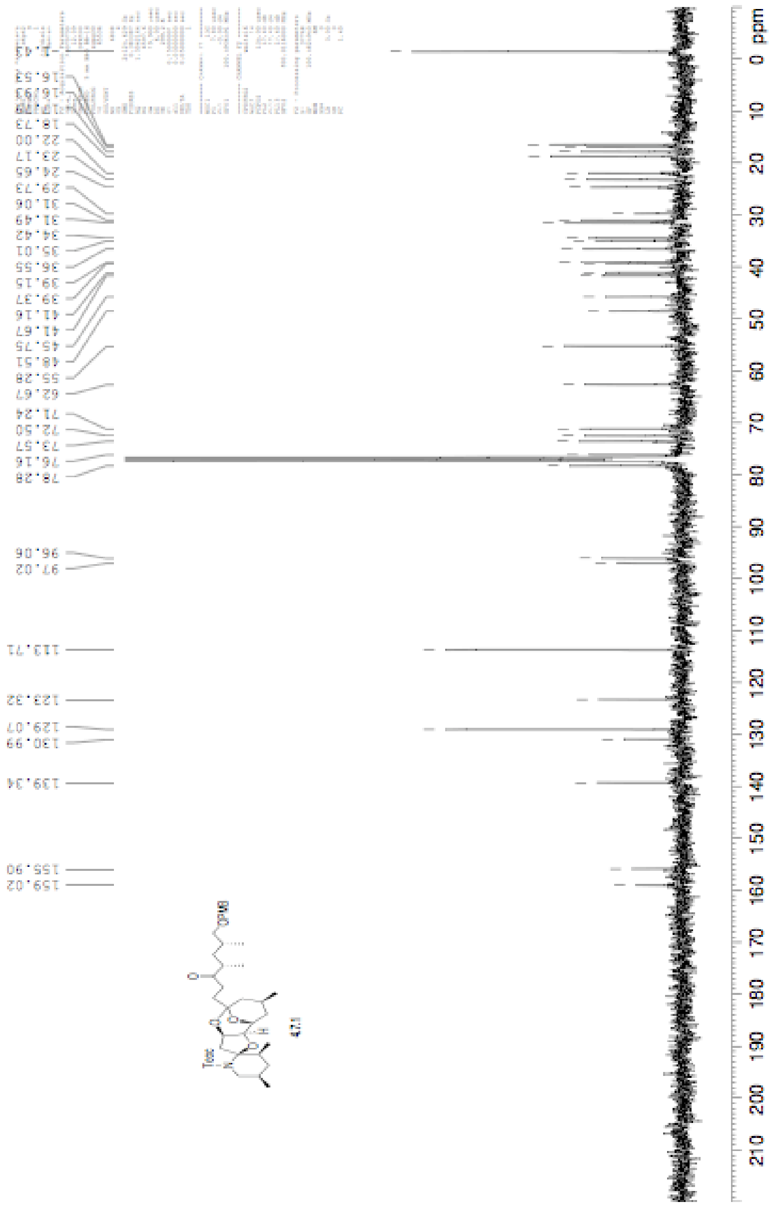
4.6.1

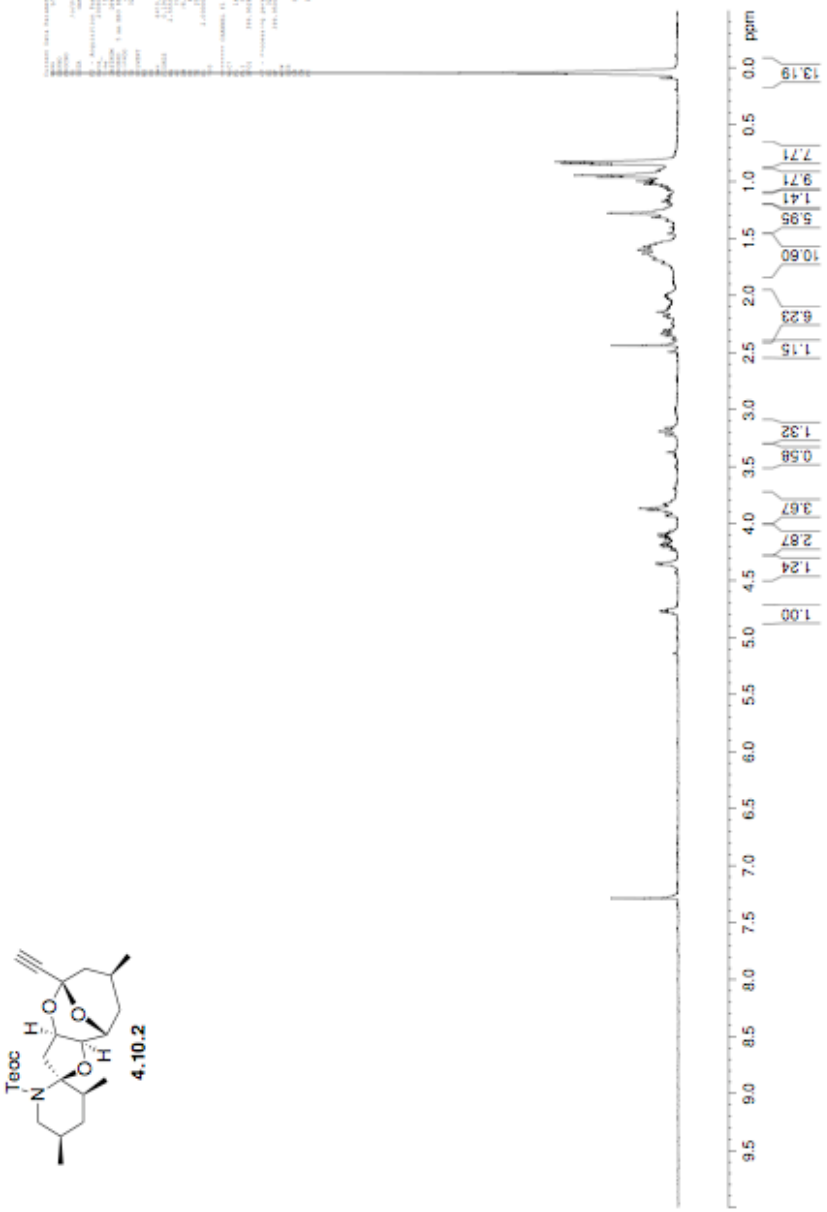
Carbon#	Carbon Signal	Proton Signal
26	50.7	3.0-3.4 (m, 2H)
27	35.1	1.8 (m, 2H)
28	94.5	-
29	31.2	1.8 (m, 2H)
30	39.2	1.6 (m, 1H)
31	35.1	1.2-1.4 (m, 2H)
32	70.4	4.3 (m, 1H)
33	48.5	3.65 (m, 1H)
34	74.0	4.7 (m, 1H)
35	38.7	2.2, 3.8 (m, 1H)
36	97.1	-
37	25.3	2.0 (m, 1H)
38	36.2	2.2 (m, 1H)
39	43.1	2.0 (m, 1H)
40	48.5	3.7, 3.2 (m, 2H)
45	16.5	0.7 (t, 3H)
46	23.3	0.9 (t, 3H)
47	18.7	(0.8 (t, 3H)
A	129.0	7.6 (m, 1H)
	133.2	7.5 (m, 2H)
	128.0	7.8 (m, 2H)
	139.5	-
C	156	-
D	63.4	4.0 (m, 2H)
E	17.9	1.1 (m, 2H)
F	-1.45	0.0 (s, 9H)

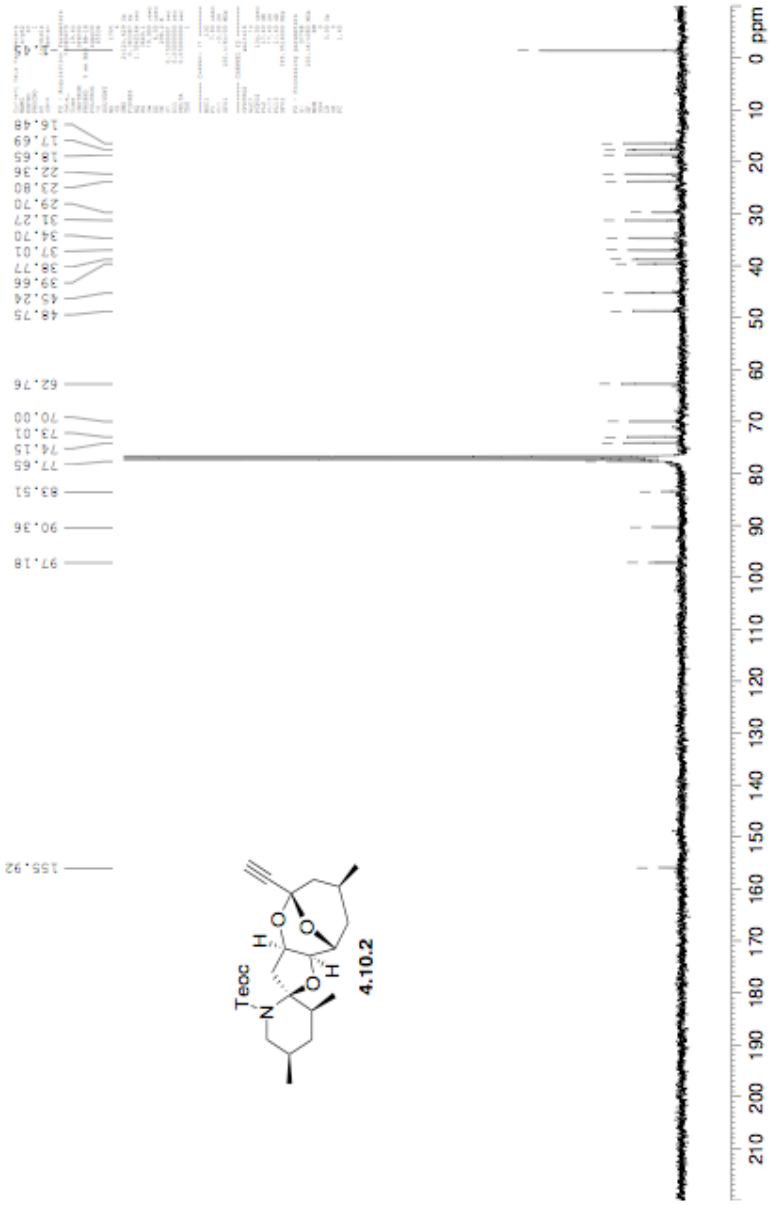

OTBS
4.62
0.90
2.69
2.00
1.98
3.04
2.05
0.96
1.99
1.36
1.28
3.03
3.31
ppm

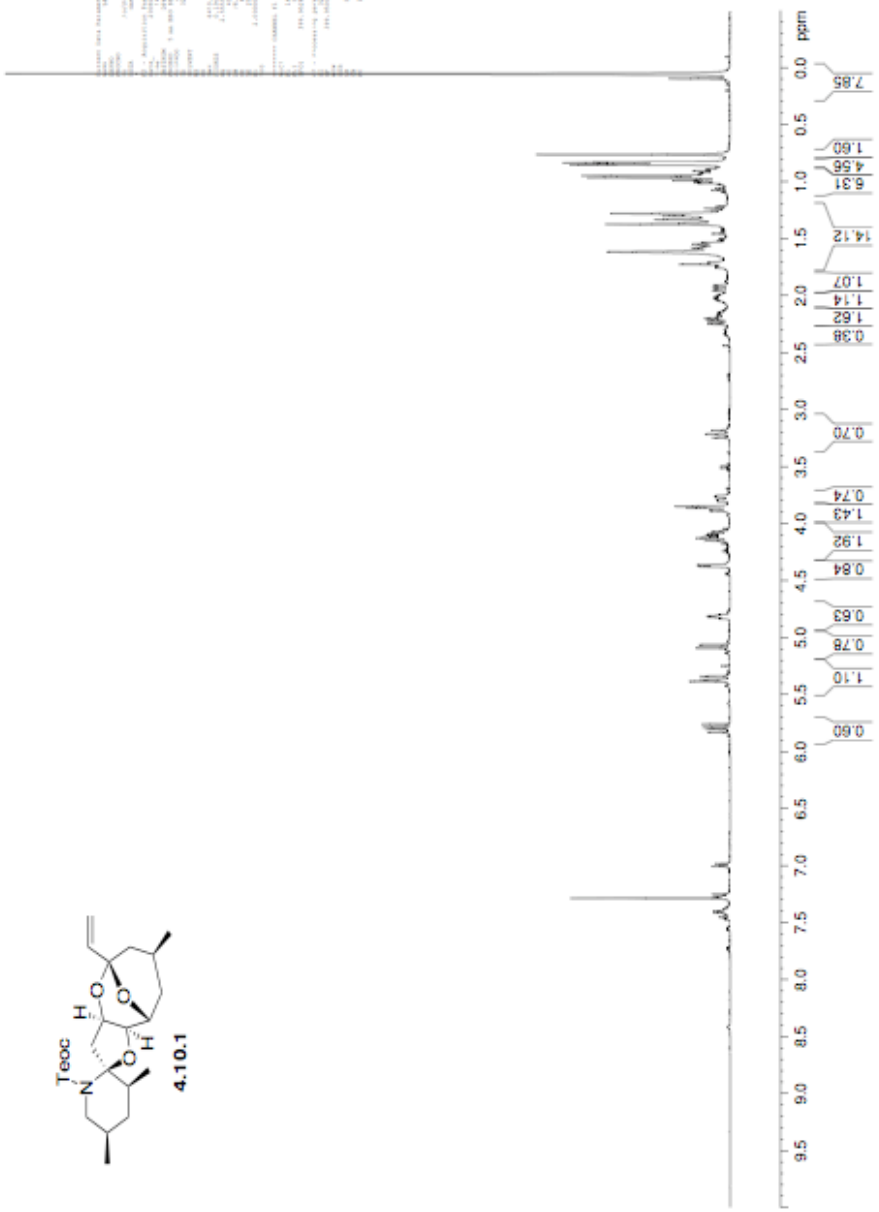

205.29
159.14
130.63
129.17
113.77
77.37
77.06
76.74
75.39
72.71
55.28
44.03
34.37
30.99
16.87
13.46
OPMB
4.6.2
O
H
0 ppm

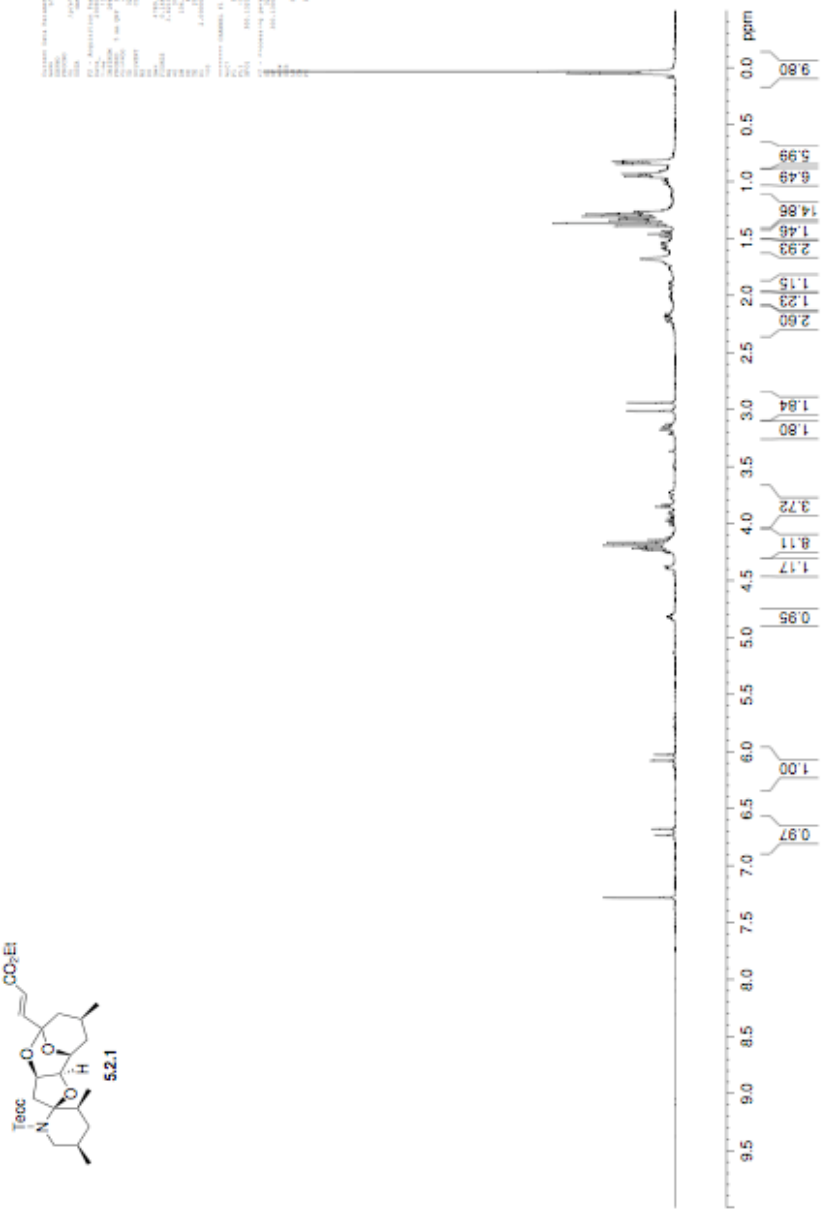

OPMB
O
Teoc
N
O
O
O
H
4,7,1
ppm
8.58
18.47
15.70
6.57
2.96
5.72
1.96
1.05
1.71
1.12
0.94
1.01
2.00
2.81

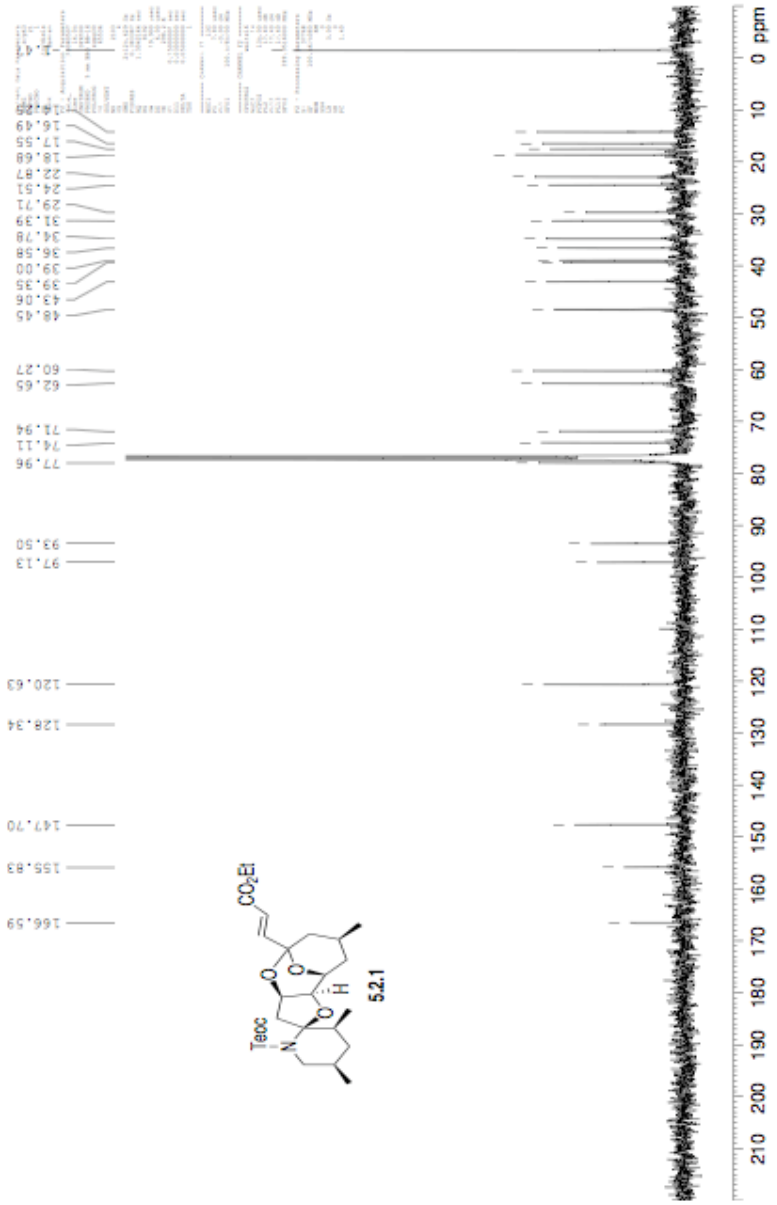

16.53
18.73
22.00
23.17
24.65
29.73
31.06
31.49
34.42
35.01
36.55
39.15
39.37
41.16
41.67
45.75
48.51
55.28
62.67
71.24
72.50
73.57
76.16
78.28
96.06
97.02
113.71
123.32
129.07
130.99
139.34
155.90
159.02
ppm

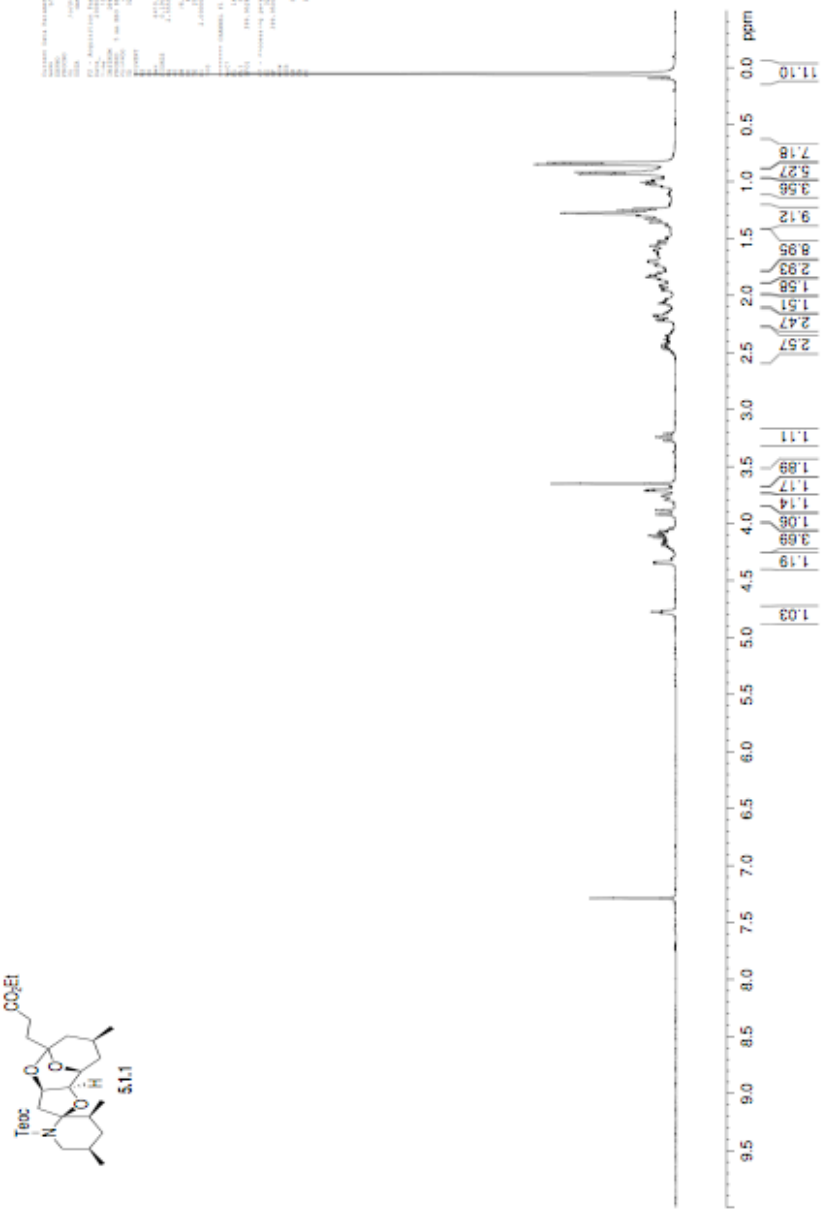

Teoc
N
O
O
O
H
H
4.10.2
ppm
13.19
7.71
9.71
1.41
5.95
10.60
6.23
1.15
1.32
0.58
3.67
2.87
1.24
1.00

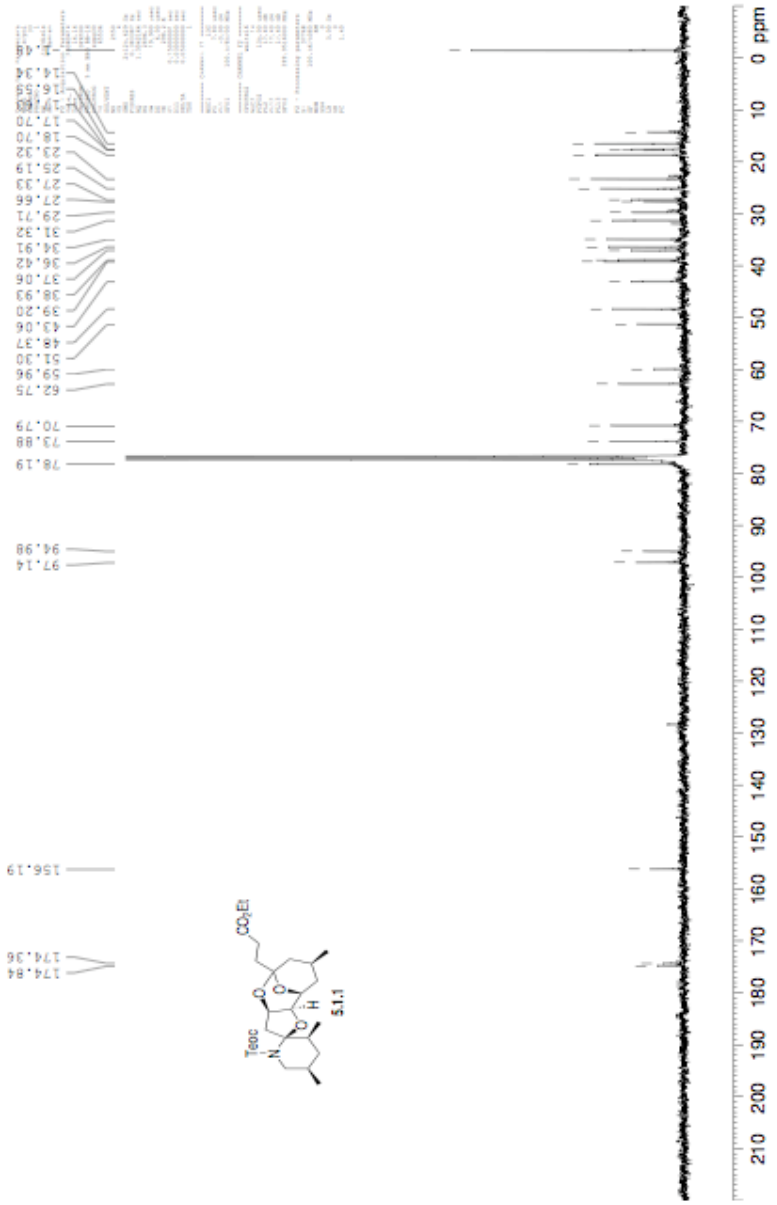

155.92
97.18
90.36
83.51
77.65
74.15
73.01
70.00
62.76
48.75
45.24
39.66
38.77
37.01
34.70
31.27
29.70
23.80
22.36
18.65
17.69
16.48
Teoc
4.10.2
0 ppm

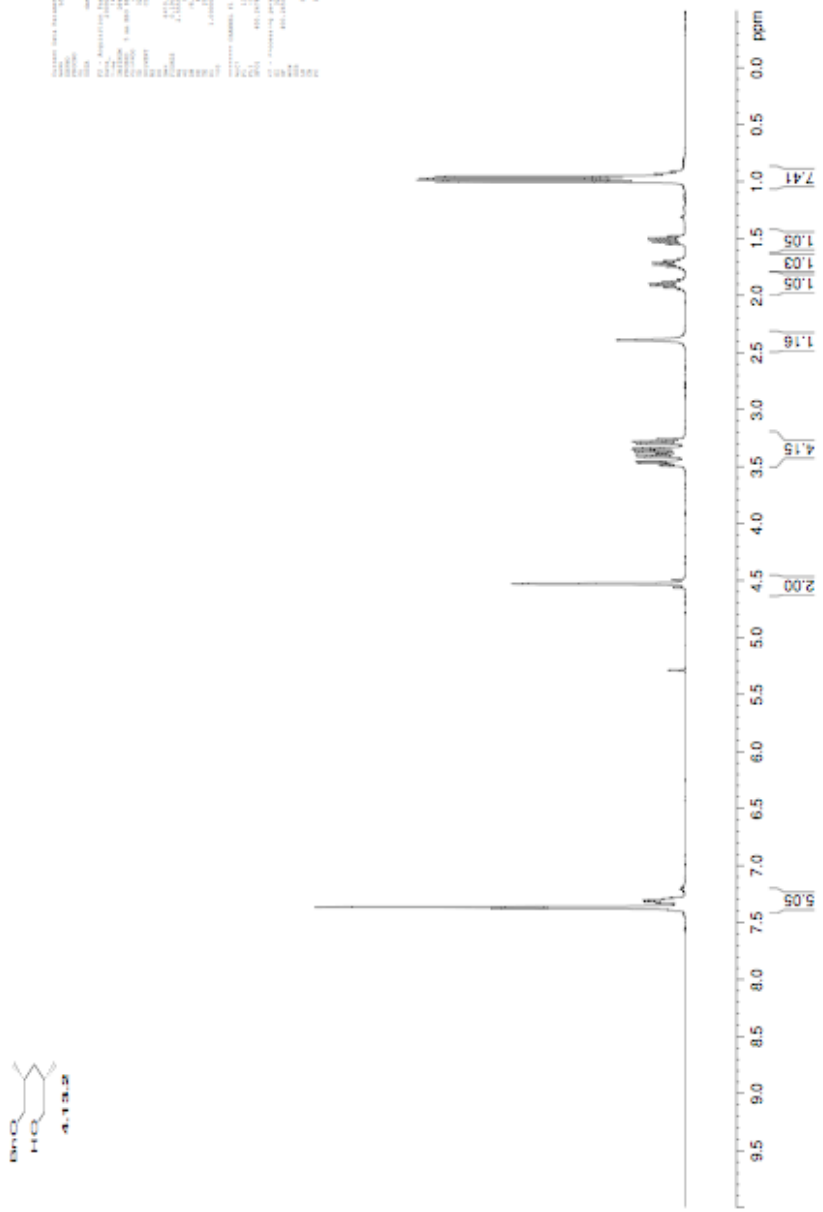

Teoc
O
O
H
H
O
N
4.10.1
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
7.85
1.60
4.56
6.31
14.12
1.07
1.14
1.62
0.38
0.70
0.74
1.43
1.92
0.84
0.63
0.78
1.10
0.60

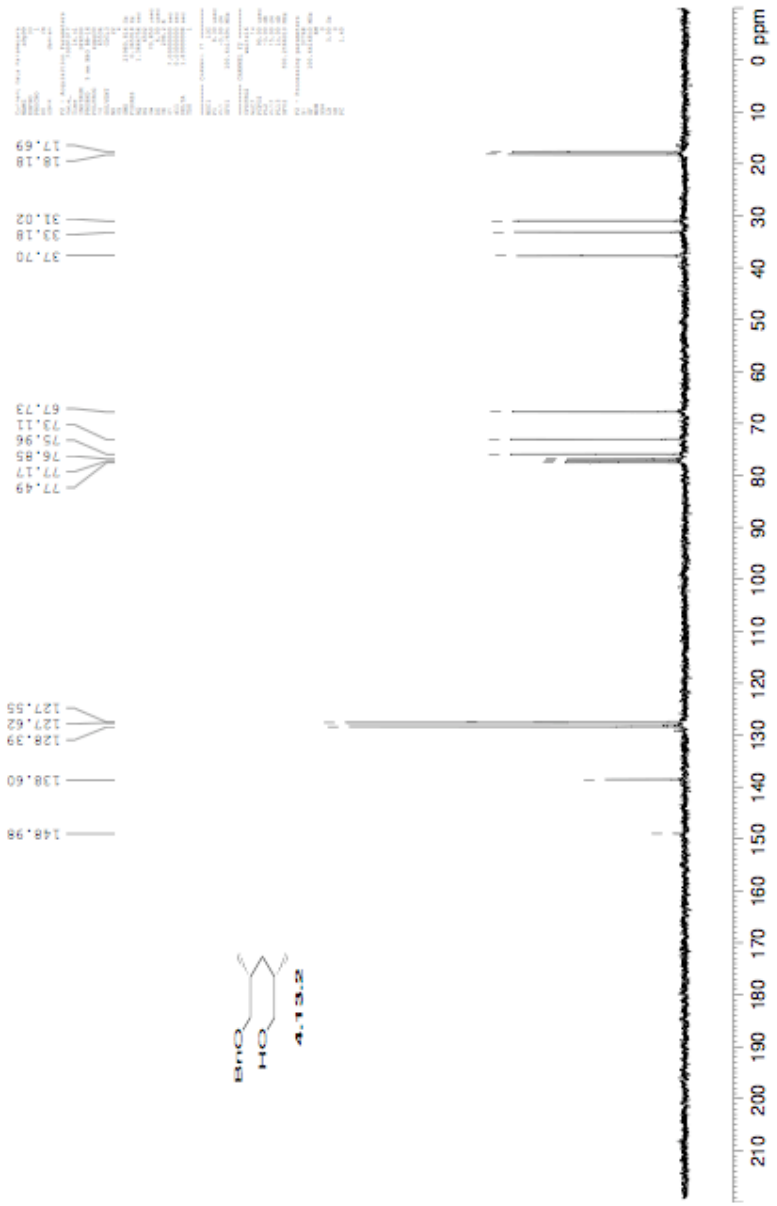

CO2Et
Teoc
N
O
O
O
O
H
5.2.1
ppm
9.80
5.99
6.49
14.86
1.46
2.93
1.15
1.23
2.60
1.84
1.80
3.72
8.11
1.17
0.95
1.00
0.97

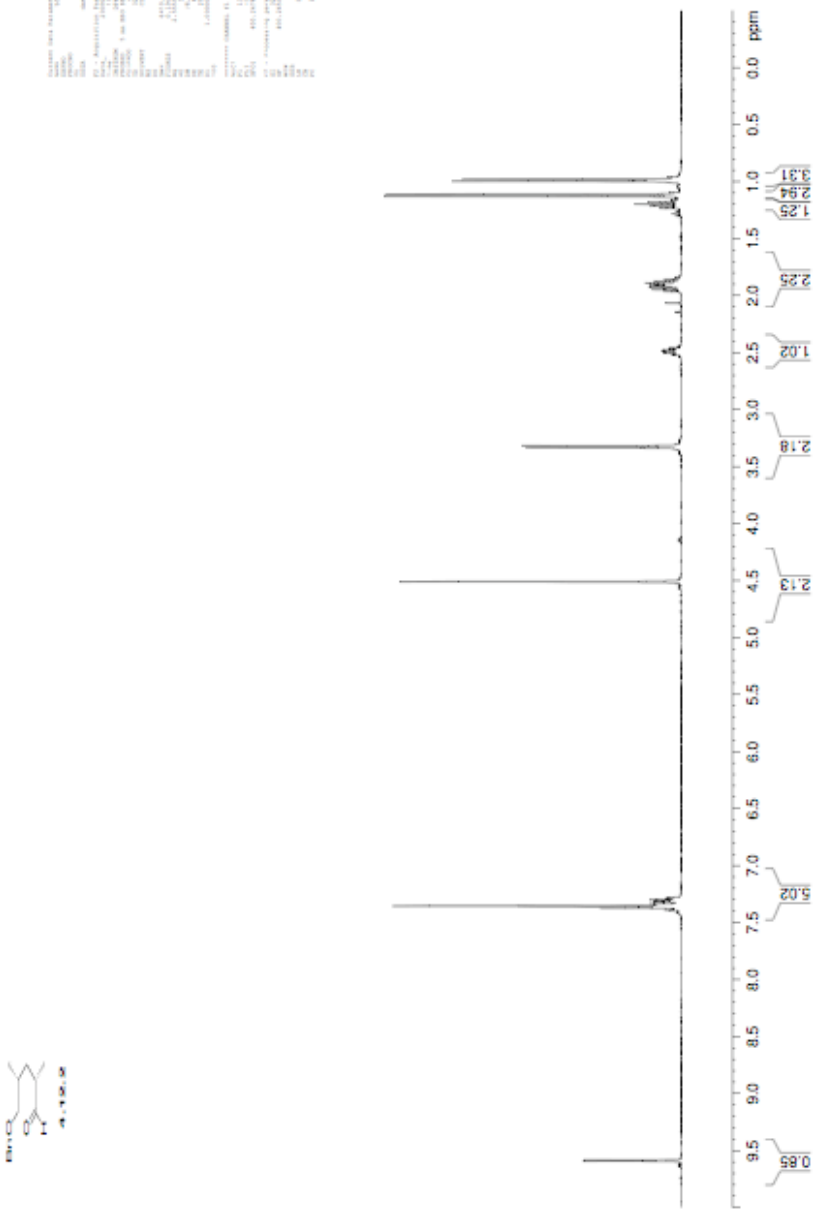

166.59
155.83
147.70
128.34
120.63
97.13
93.50
77.96
74.11
71.94
62.65
60.27
48.45
43.06
39.35
39.00
36.58
34.78
31.39
29.71
24.51
22.87
18.68
17.55
16.49
14.47
CO2Et
Teoc
N
O
O
O
H
5.2.1
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

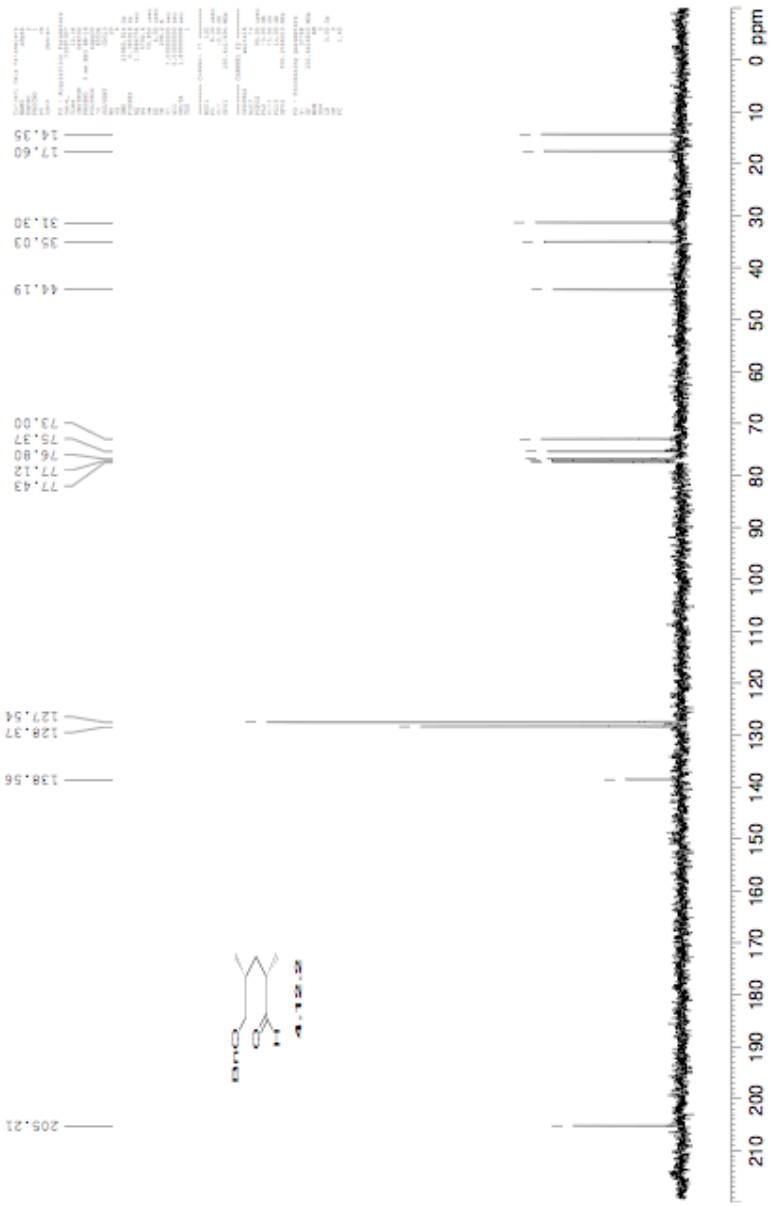

CO2Et
Teoc
N
O
O
O
H
5.1.1
ppm
11.10
7.18
5.27
3.56
9.12
8.95
2.93
1.58
1.51
2.47
2.57
1.11
1.89
1.17
1.14
1.06
3.69
1.19
1.03

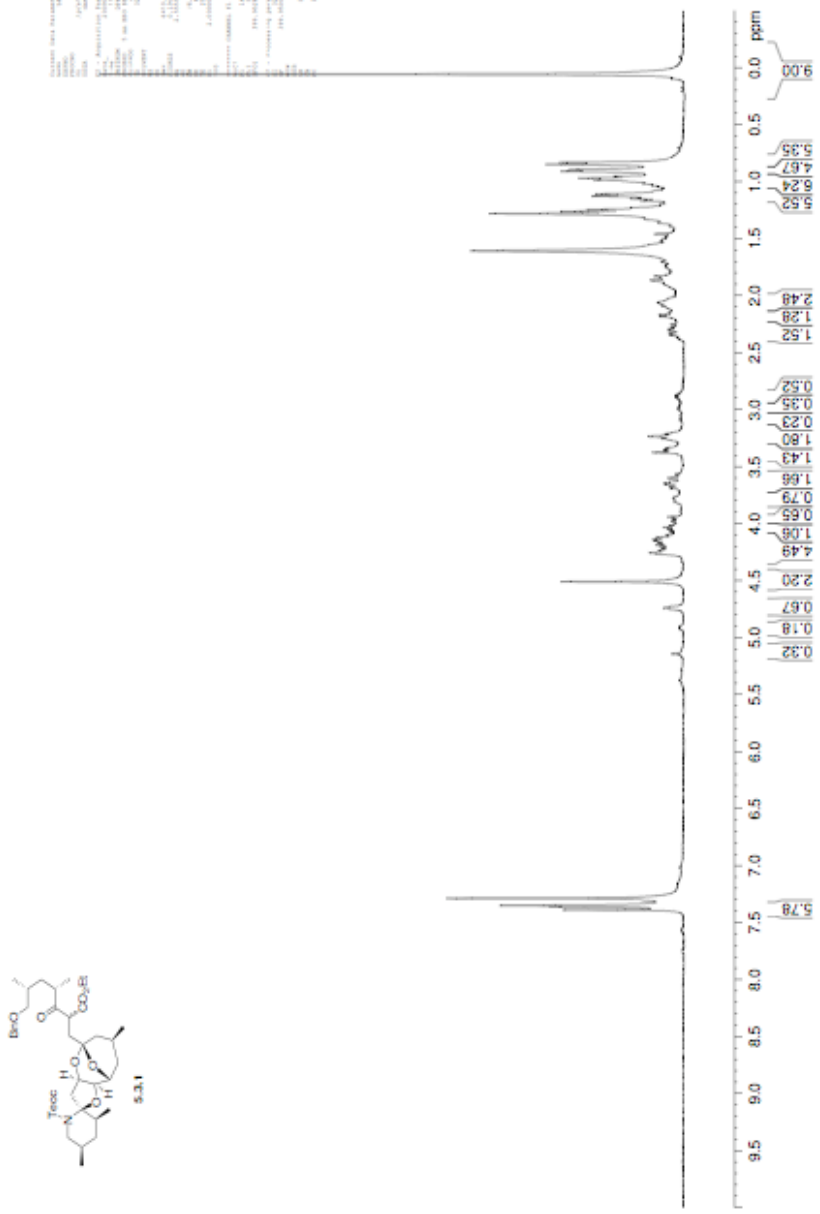

14.46
14.34
14.59
17.70
18.70
23.32
25.19
27.33
27.66
29.71
31.32
34.91
36.42
37.06
38.93
39.20
43.06
48.37
51.30
59.96
62.75
70.79
73.89
78.19
94.98
97.14
156.19
174.36
174.84
CO2Et
Teoc
H
5.1.1
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

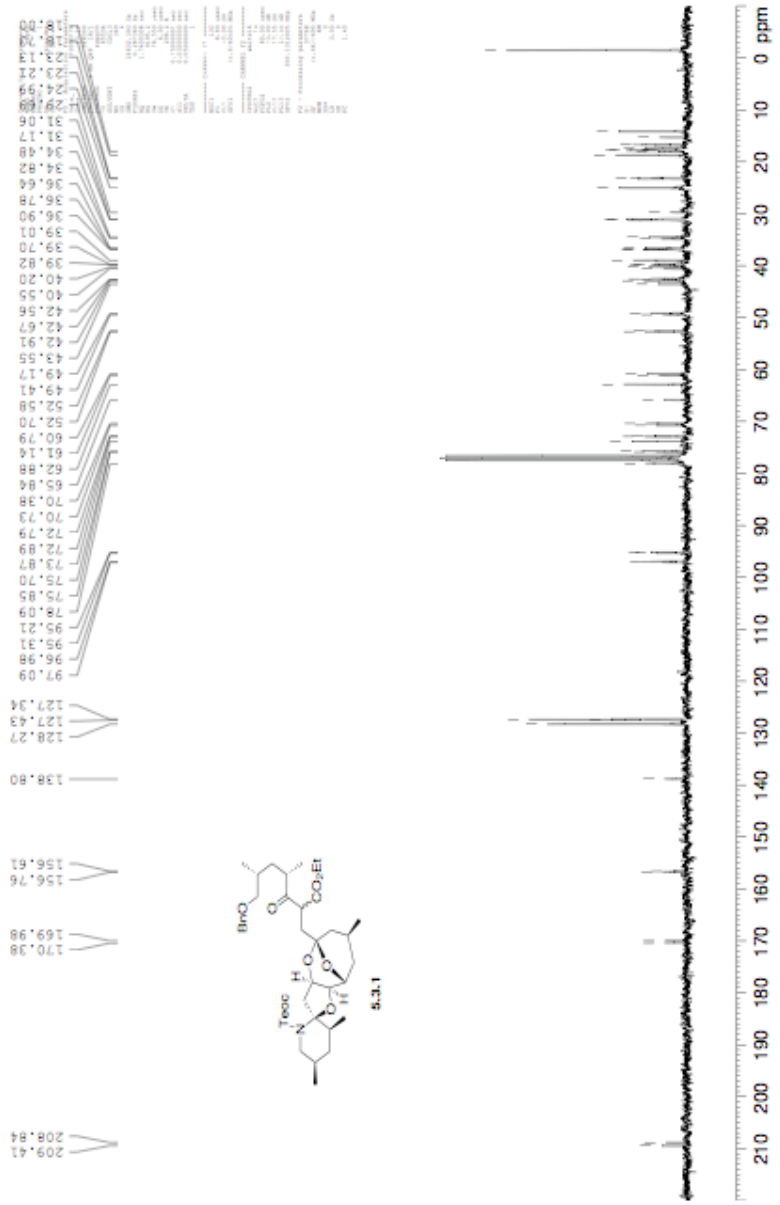

ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
7.41
1.05
1.03
1.05
1.16
4.15
2.00
5.05

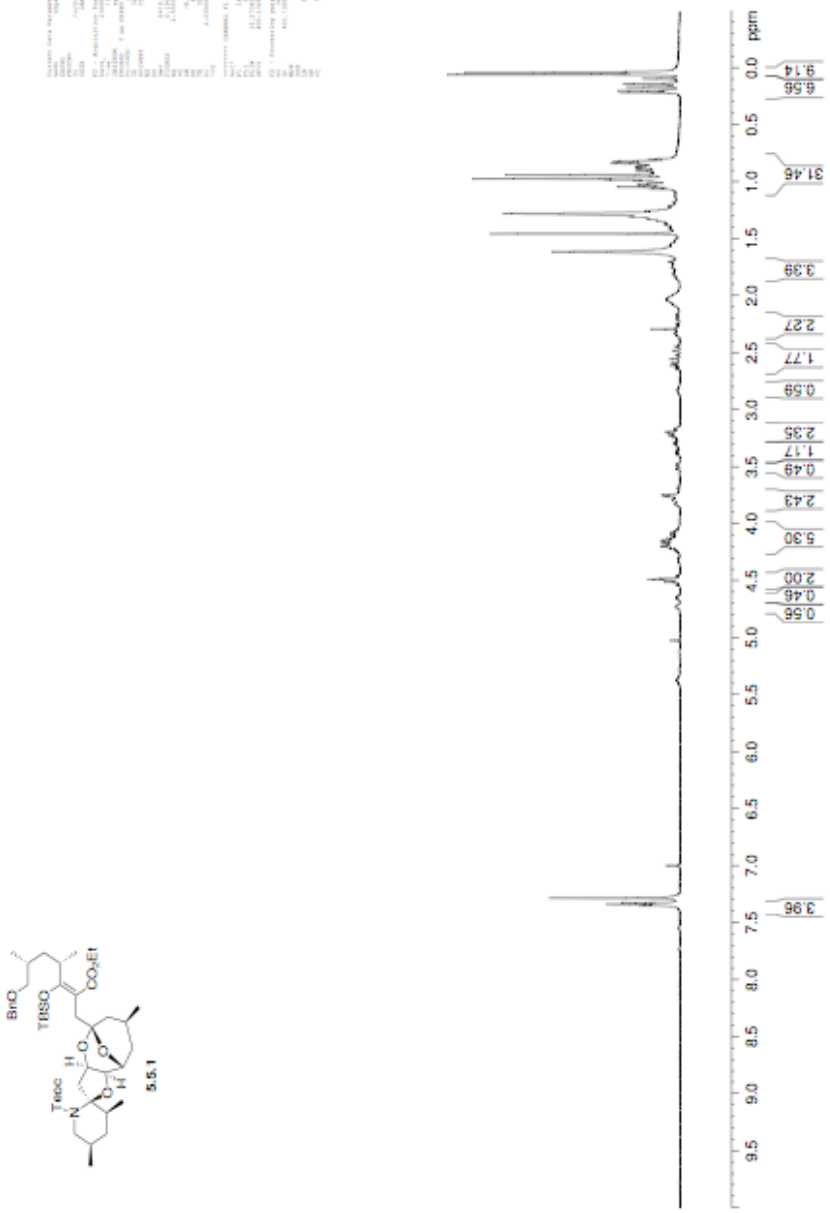

17.69
18.18
31.02
33.19
37.70
67.73
73.11
75.96
76.85
77.17
77.49
127.55
127.62
128.39
138.60
148.98
BnO
HO
4.13.2
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

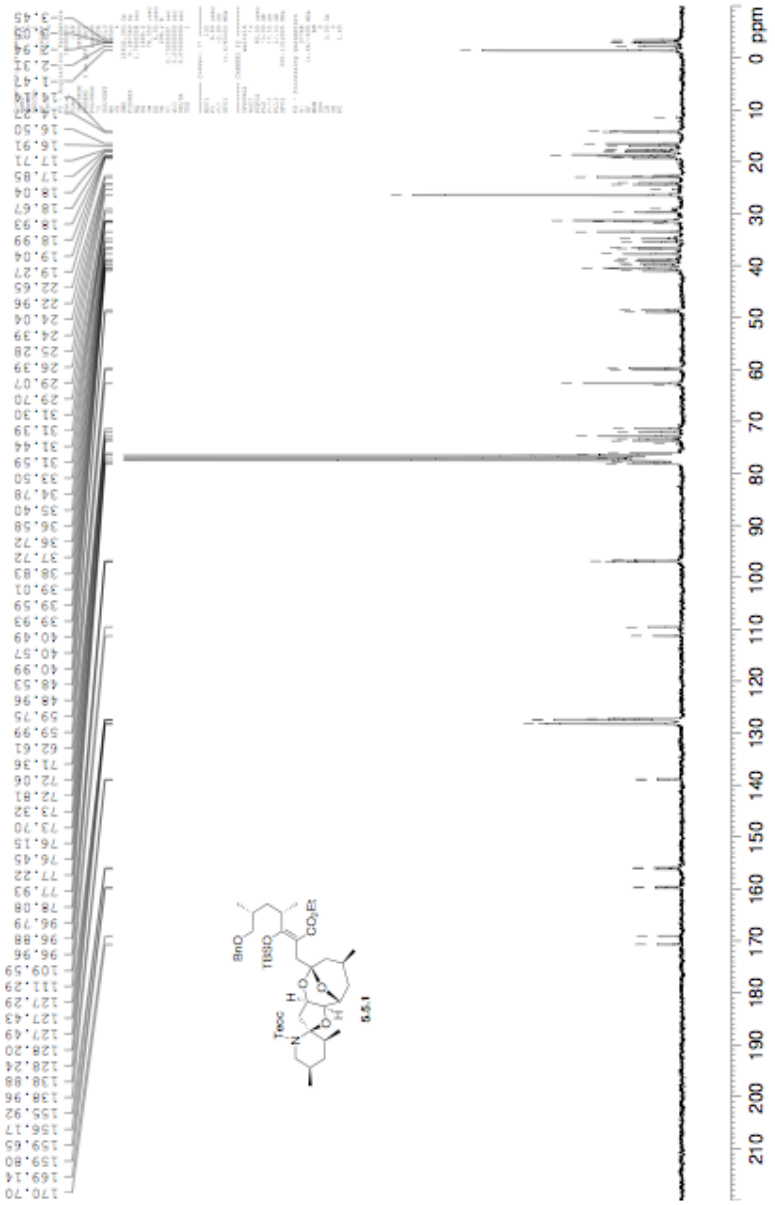

ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
3.31
2.94
1.25
2.25
1.02
2.18
2.13
5.02
0.85

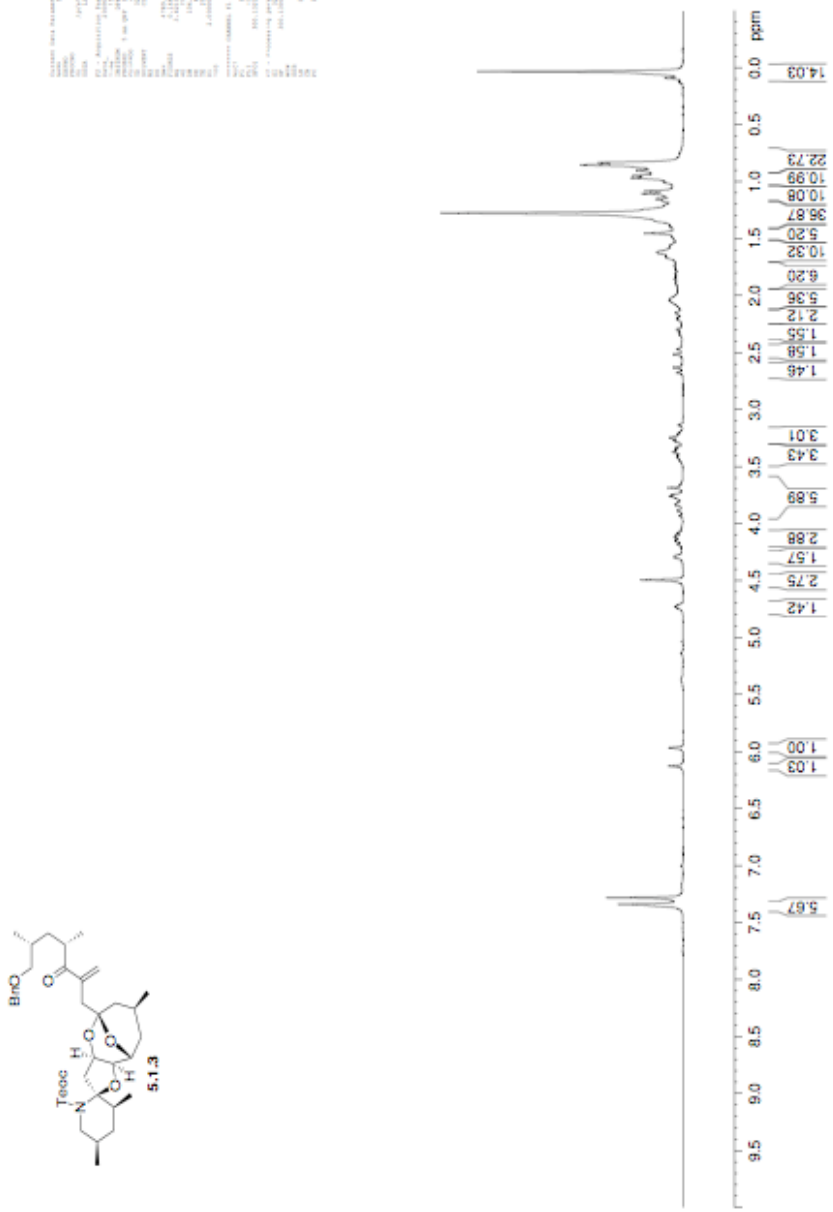

205.21
138.56
128.37
127.54
77.43
77.12
76.80
75.37
73.00
44.19
35.03
31.30
17.60
14.35
0 ppm

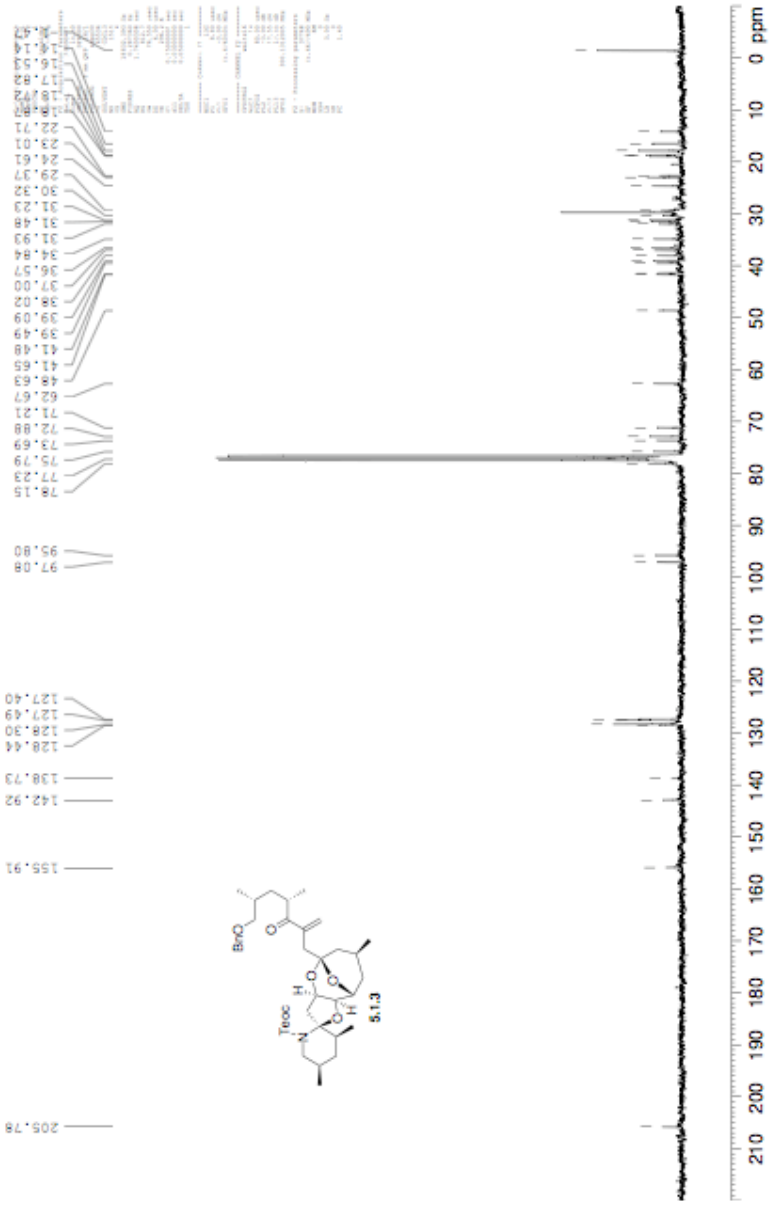

ppm
9.00
5.35
4.67
6.24
5.52
2.48
1.28
1.52
0.52
0.35
0.23
1.80
1.43
1.66
0.79
0.65
1.08
4.49
2.20
0.67
0.18
0.32
5.78
BnO
CO2Et
Teoc
5.3.1


18.00
23.13
23.22
24.99
31.06
31.17
34.48
34.82
36.64
36.78
36.90
39.01
39.70
39.82
40.20
40.55
42.56
42.67
42.91
43.55
49.17
49.41
52.58
52.70
60.79
61.14
62.88
65.84
70.38
70.73
72.79
72.89
73.87
75.70
75.85
78.09
95.21
95.31
96.98
97.09
127.34
127.43
128.27
138.80
156.76
156.61
169.98
170.38
208.84
209.41
BnO
CO2Et
Teoc
5.3.1
0 ppm


BnO
TBSO
CO2Et
Teoc
5.5.1
ppm
9.14
6.56
31.46
3.39
2.27
1.77
0.59
2.35
1.17
0.49
2.43
5.30
2.00
0.46
0.56
3.96


BnO
TBSO
CO2Et
Teoc
N
O
H
5.5.1
0 ppm


BnO
Teoc
5.13
ppm
14.03
22.73
10.99
10.08
36.87
5.20
10.32
6.20
5.36
2.12
1.55
1.58
1.46
3.01
3.43
5.89
2.88
1.57
2.75
1.42
1.00
1.03
5.67


205.78
155.91
142.92
138.73
128.44
128.30
127.69
127.40
97.08
95.80
78.15
77.23
75.79
73.69
72.88
71.21
62.67
48.63
41.65
41.48
39.49
39.09
38.02
37.00
36.57
34.84
31.93
31.48
31.23
30.32
29.37
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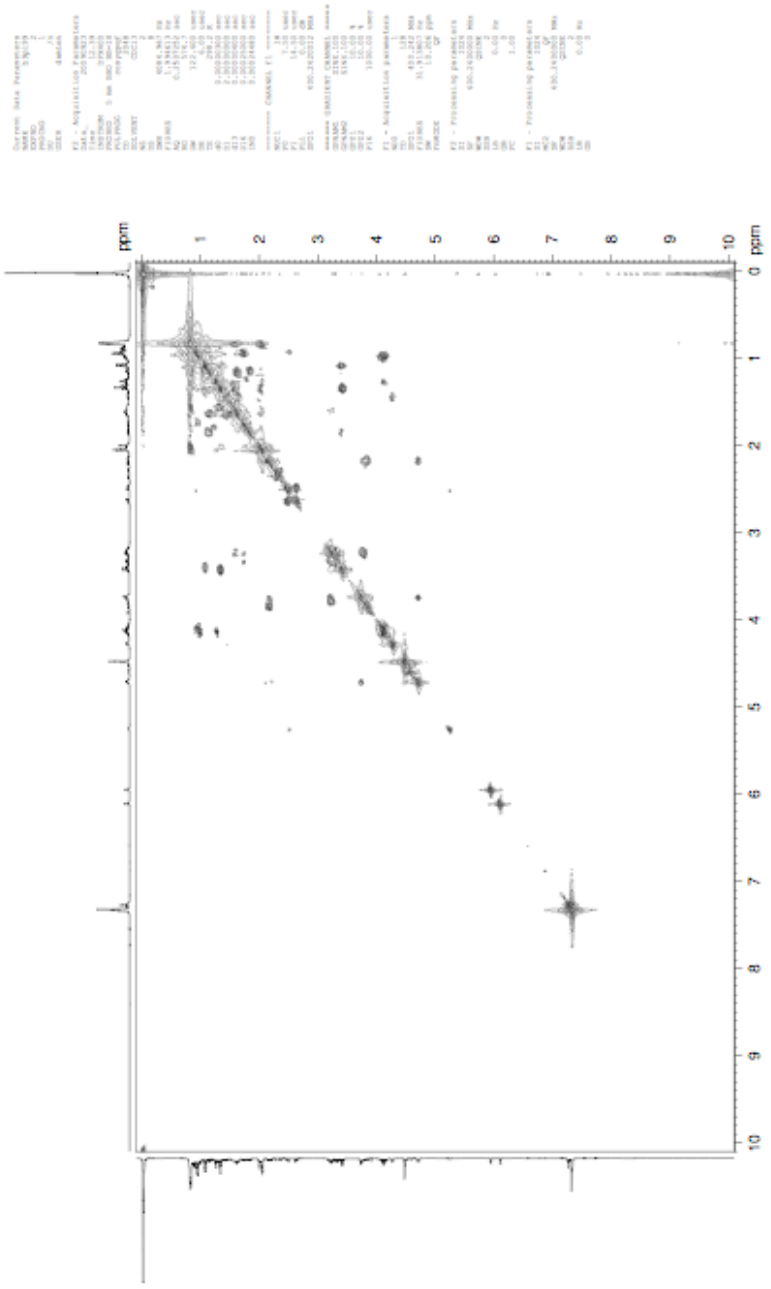
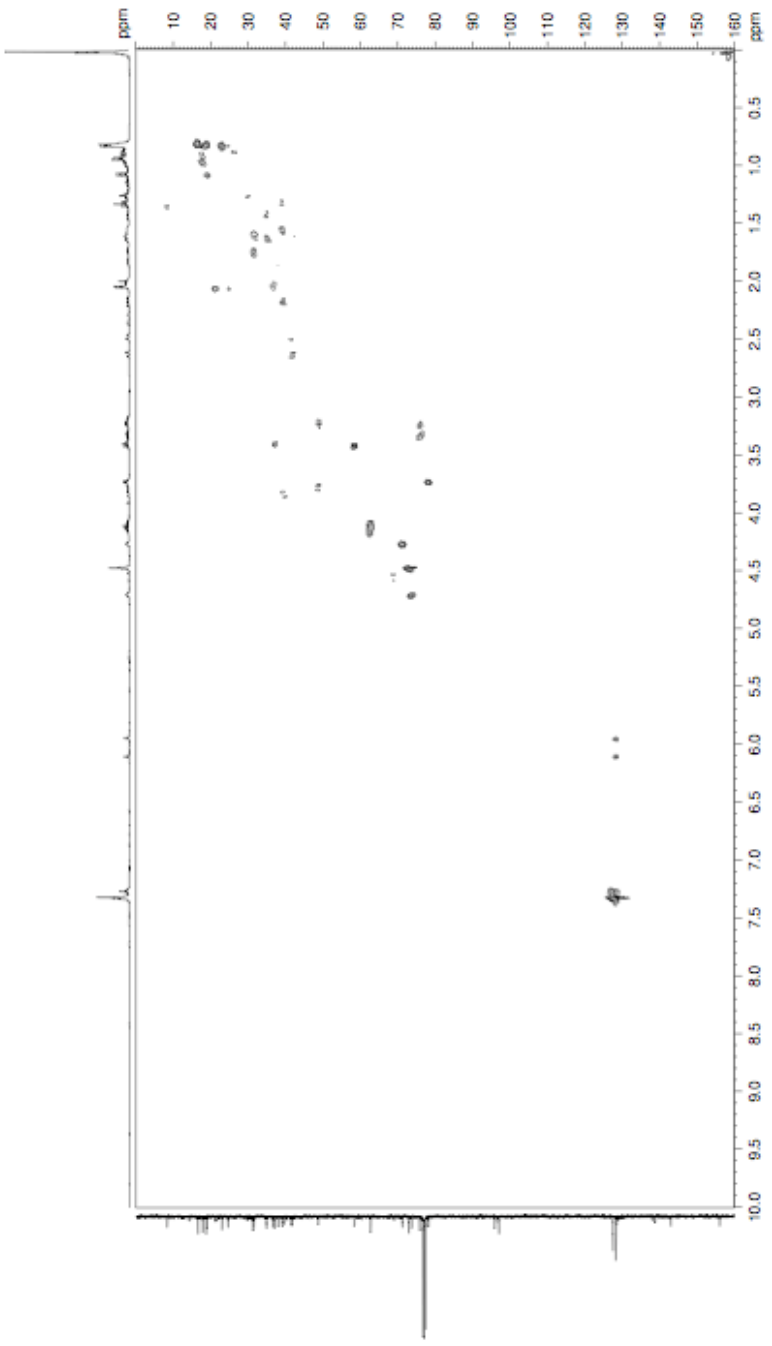
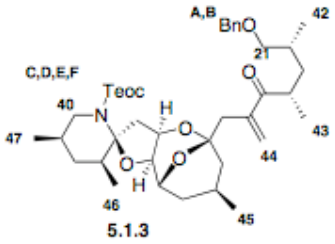
23.01
22.71
18.72
17.82
16.53
14.14
BnO
Teoc
5.1.3
0 ppm

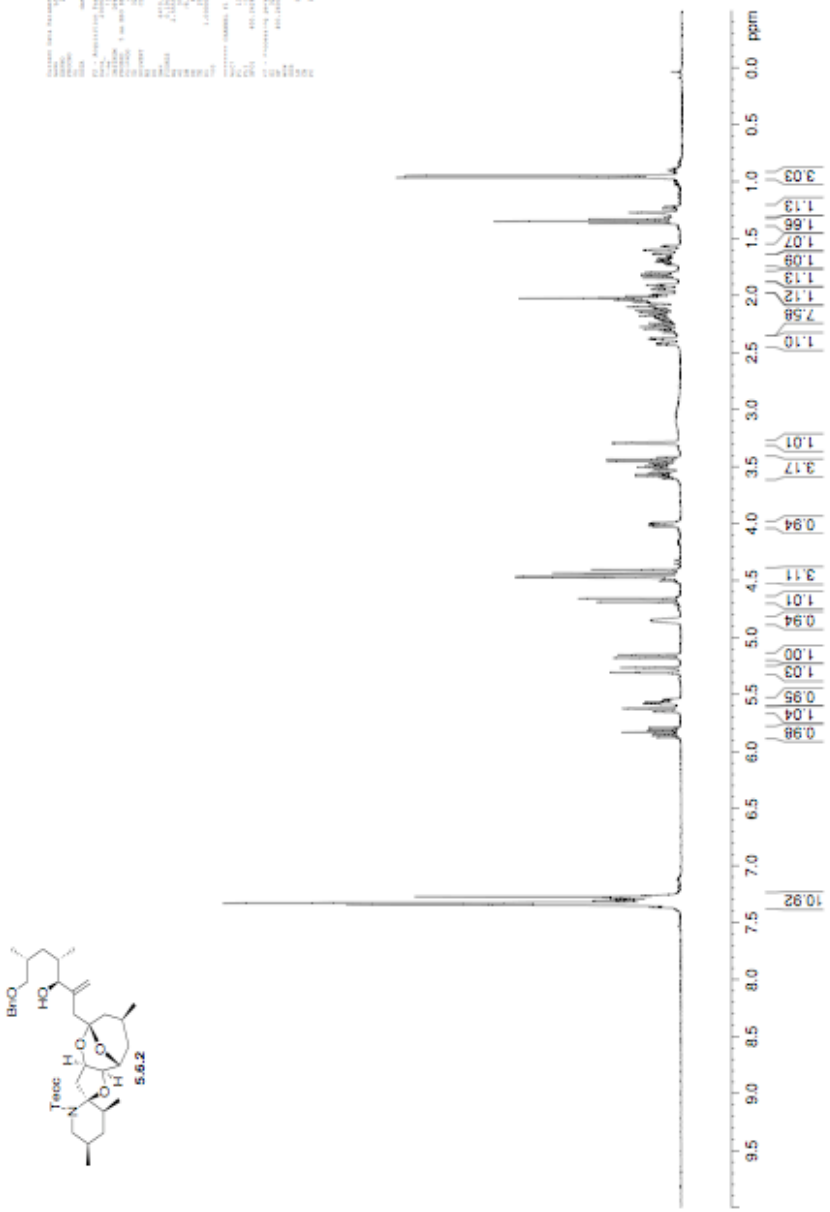

ppm
1
2
3
4
5
6
7
8
9
10
ppm
0
1
2
3
4
5
6
7
8
9
10

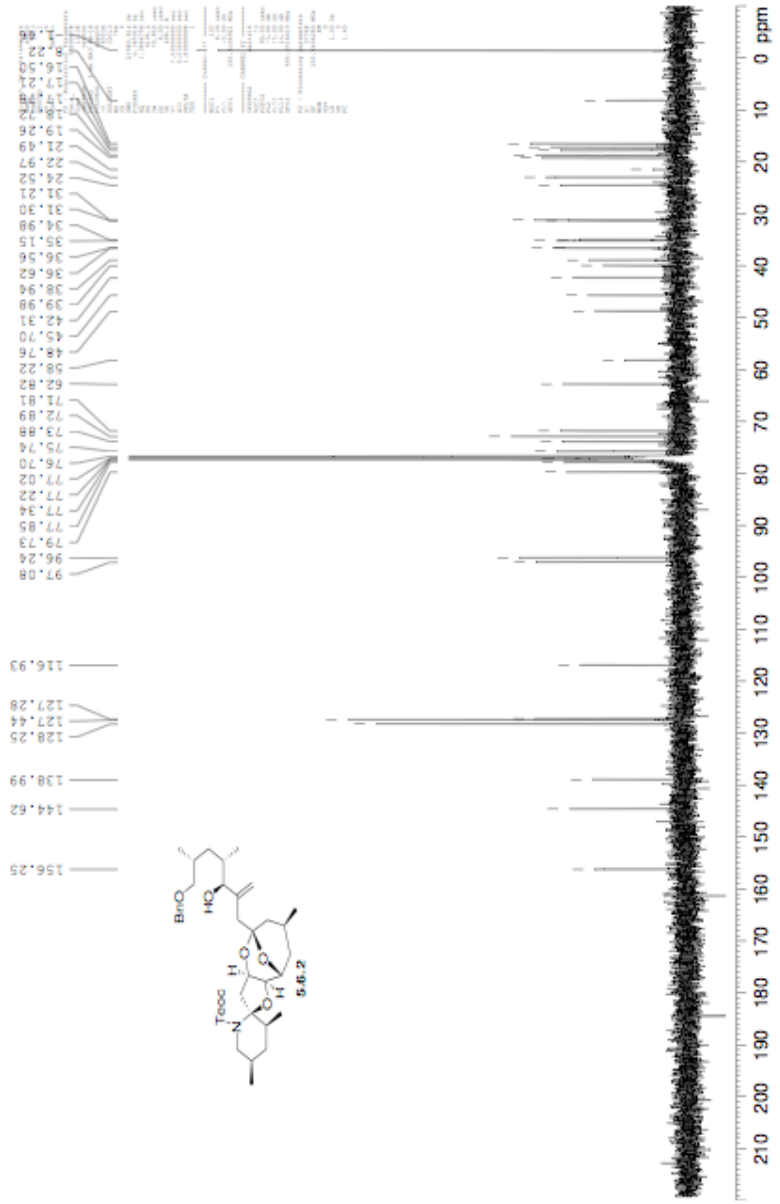

ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0

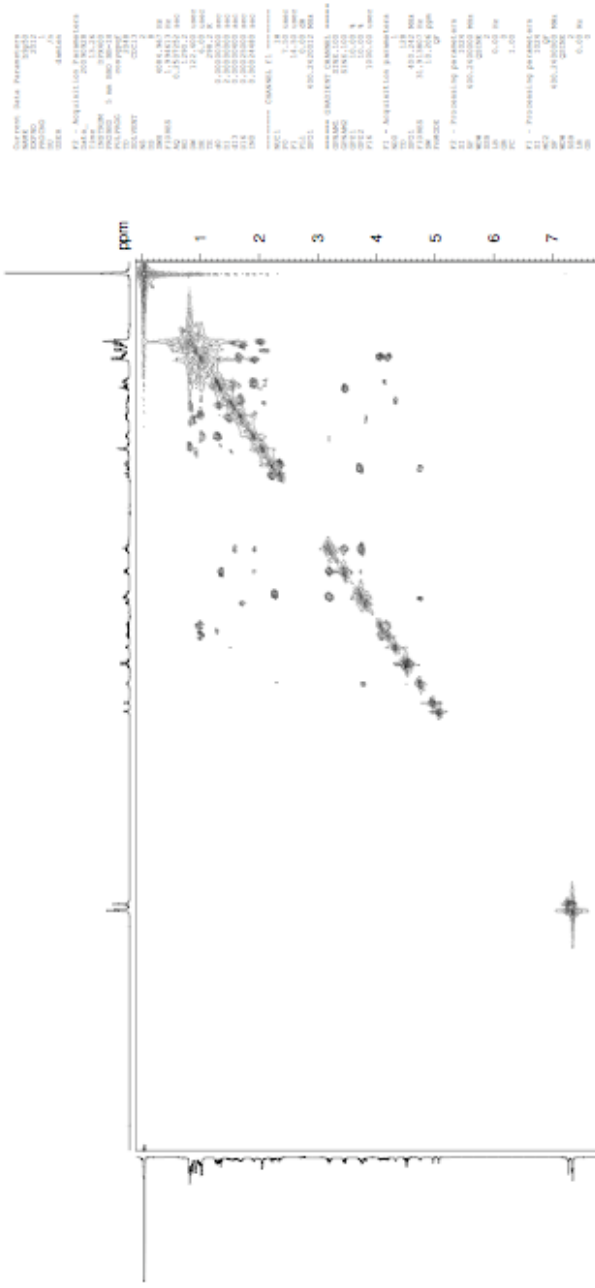


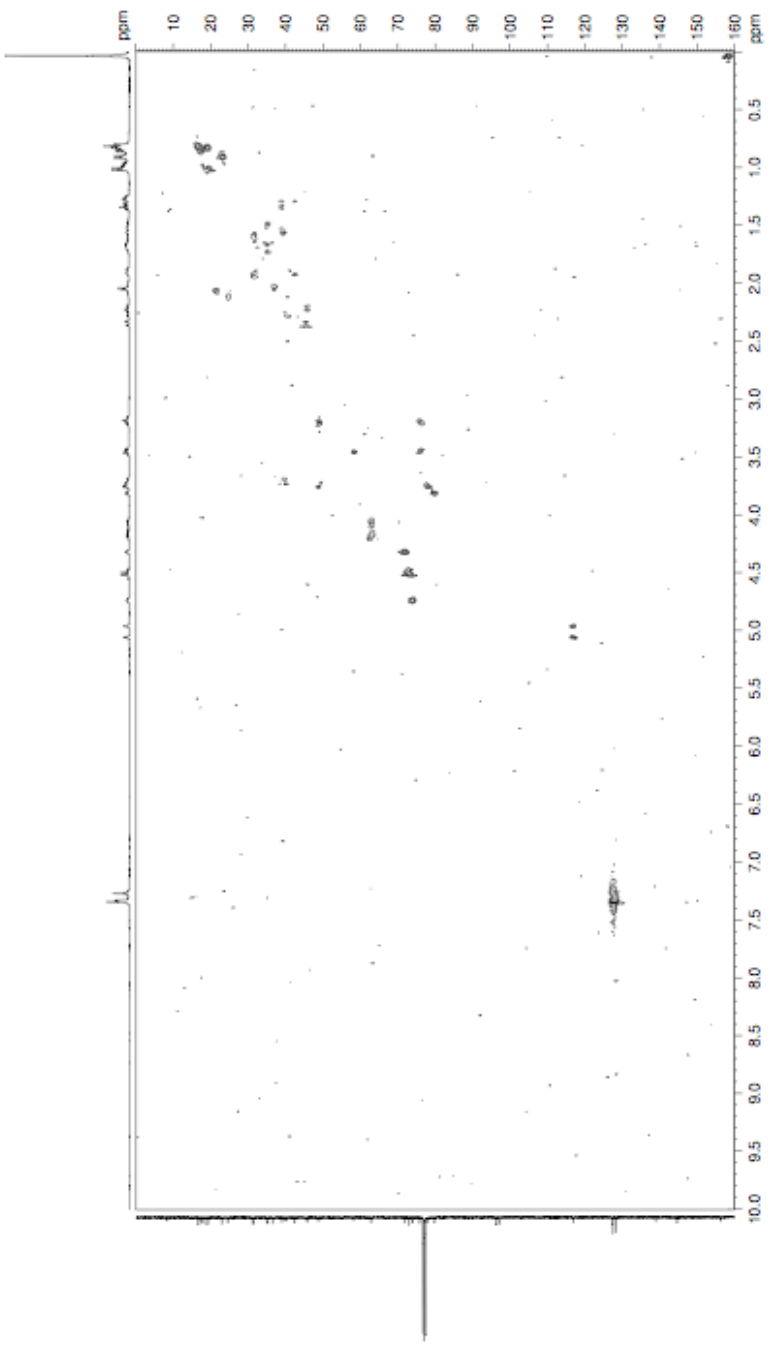
5.1.3

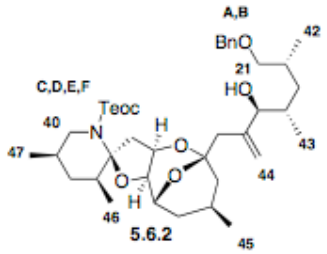
Carbon#	Carbon Signal	Proton Signal
21	41.6	2.45-2.55 (m, 1H)
22		
23	31.4	1.4 (m, 2H)
24	39.0	2.1 (m, 1H)
25	205.7	-
26	142.9	-
27	75.7	3.15 (m, 2H)
28	95.8	-
29	75.7	3.75, 1.4 (m, 2H)
30	38.0	3.75 (m, 1H)
31	31.8	1.35-1.45 (m, 2H)
32	71.2	4.25 (m, 1H)
33	78.1	3.65 (m, 1H)
34	73.6	4.8 (m, 1H)
35	39.0	3.9, 2.8 (m, 2H)
36	97.0	-
37	41.4	2.0 (m, 1H)
38	22.9	2.2 (m, 2H)
39	31.2	1.50-1.60 (m, 1H)
40	48.6	3.7, 3.15 (m, 2H)
42	16.5	0.7 (d, 3H)
43	17.2	1.1 (d, 3H)
44	128.4	6.12 (s, 1H), 5.96 (s, 1H)
45	17.7	0.8 (d, 3H)
46	17.8	0.7 (d, 3H)
47	18.7	0.7 (d, 3H)
A	72.8	4.5 (s, 2H)
B	138.7, 128.3 127.4, 127.4	7.30-7.42 (m, 5H)
C	155.9	-
D	58.3	4.0-4.2 (m, 2H)
E	8.24	.09 (m, 2H)
F	-1.4	0.04 (m, 9H)


BnO
HO
Teoc
5.6.2
10.92
0.98
1.04
0.95
1.03
1.00
0.94
1.01
3.11
0.94
3.17
1.01
1.10
7.58
1.12
1.13
1.09
1.07
1.66
1.13
3.03
ppm


BnO
HO
Troc
5.6.2
0 ppm

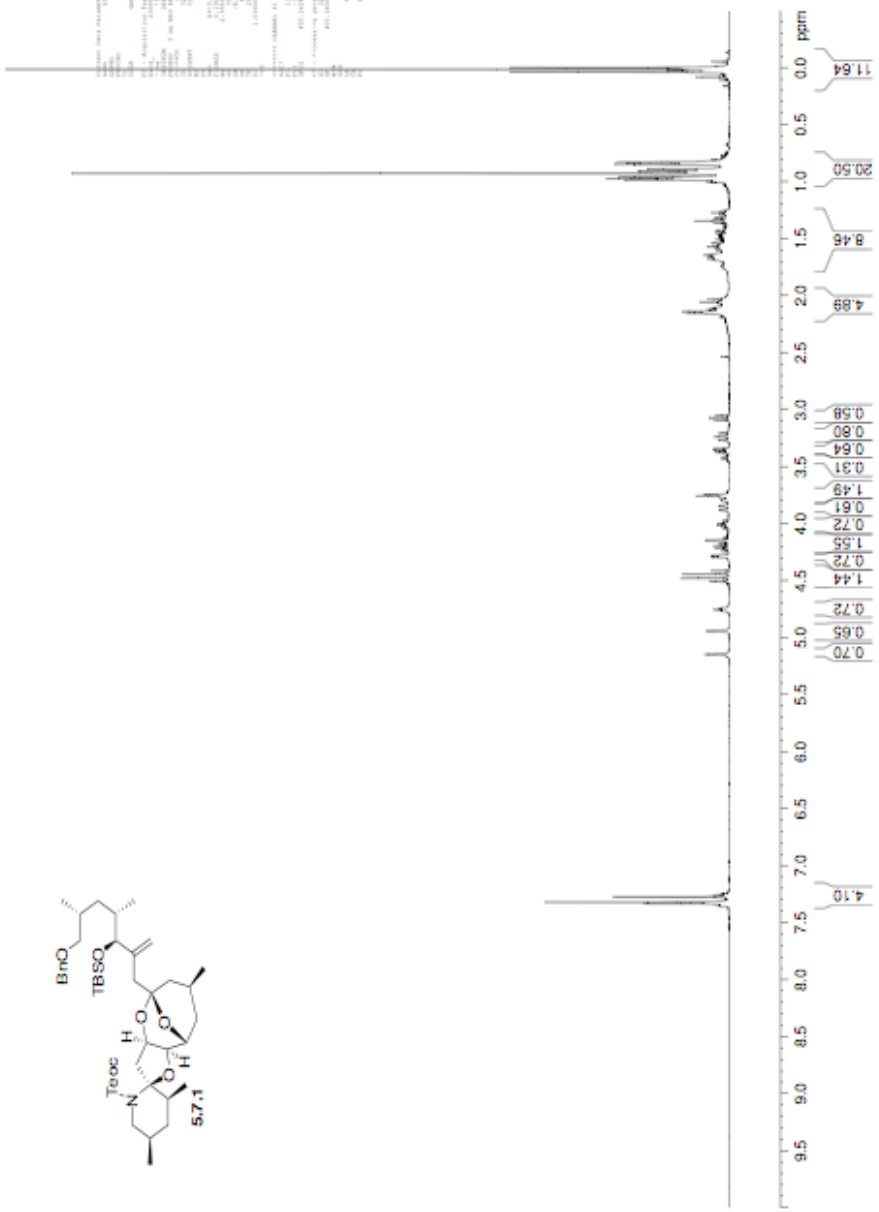

ppm
1
2
3
4
5
6
7
8
9
10
ppm
0
1
2
3
4
5
6
7
8
9
10

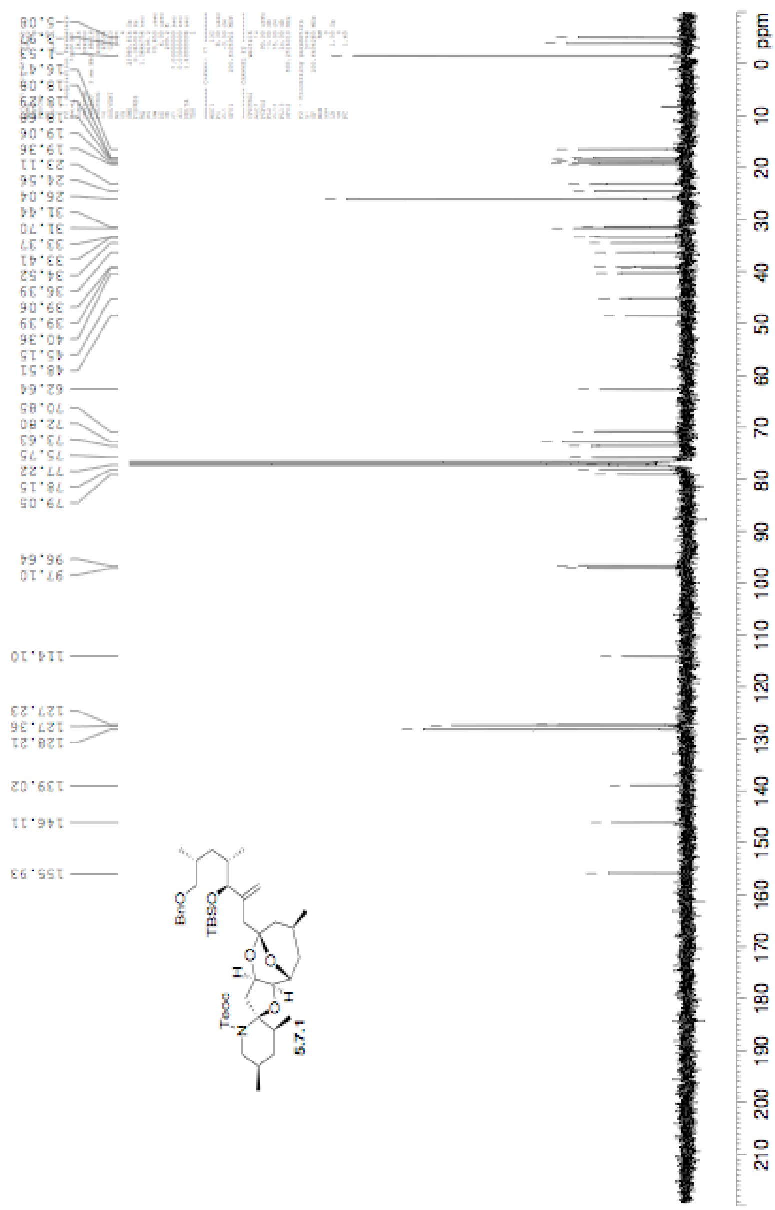

ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0

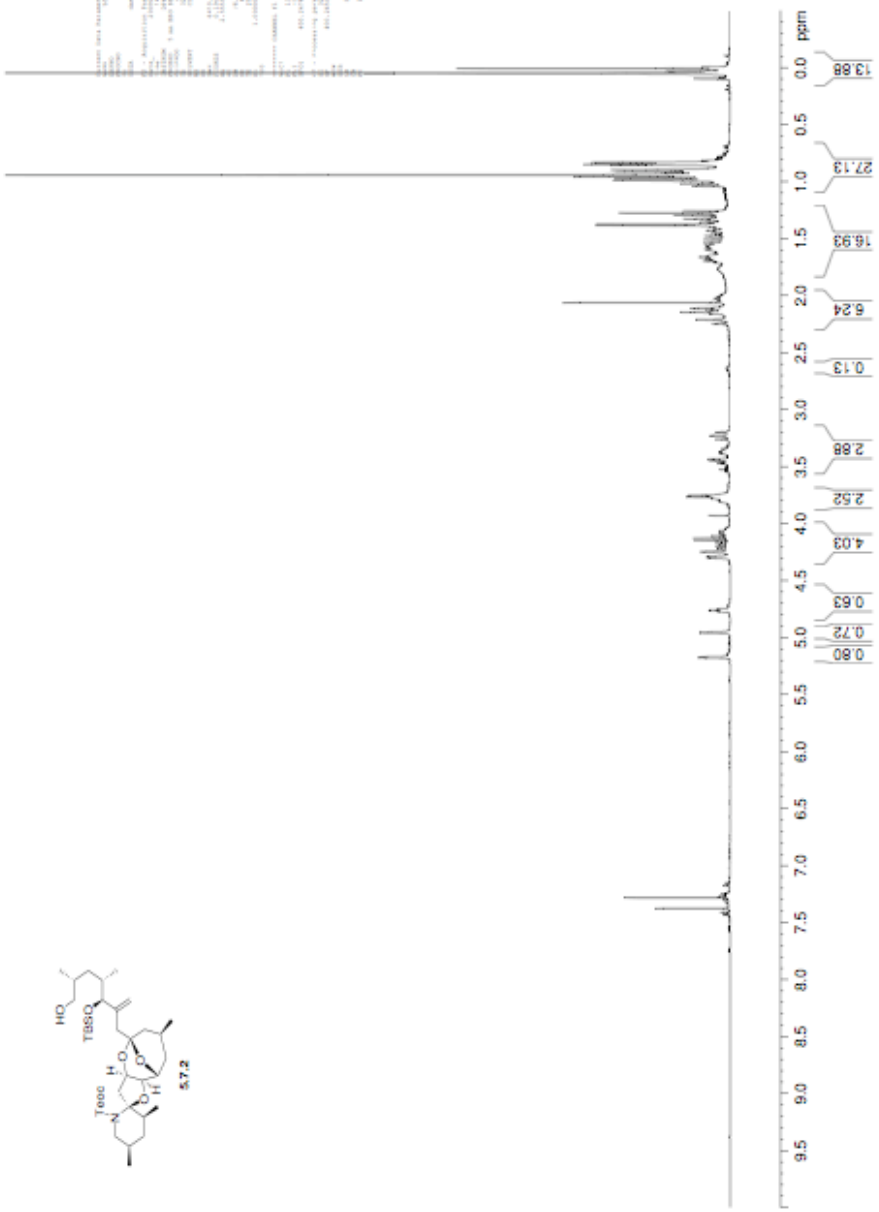


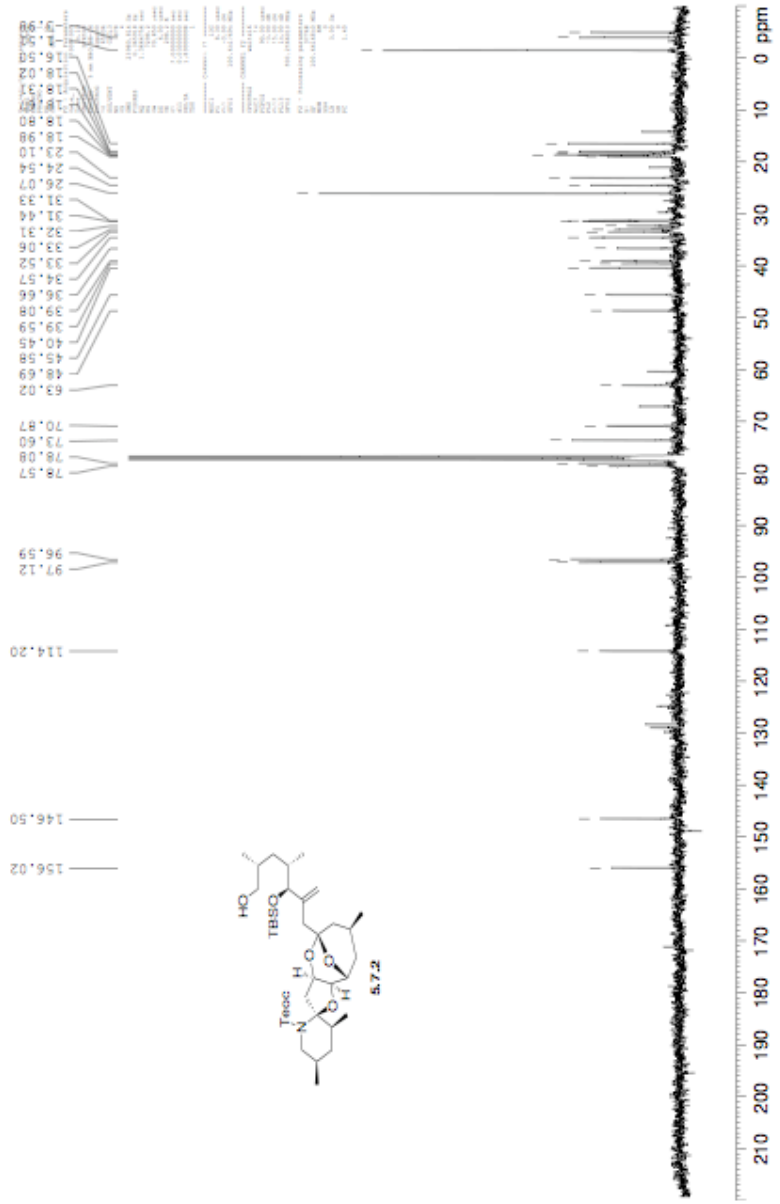
5.6.2

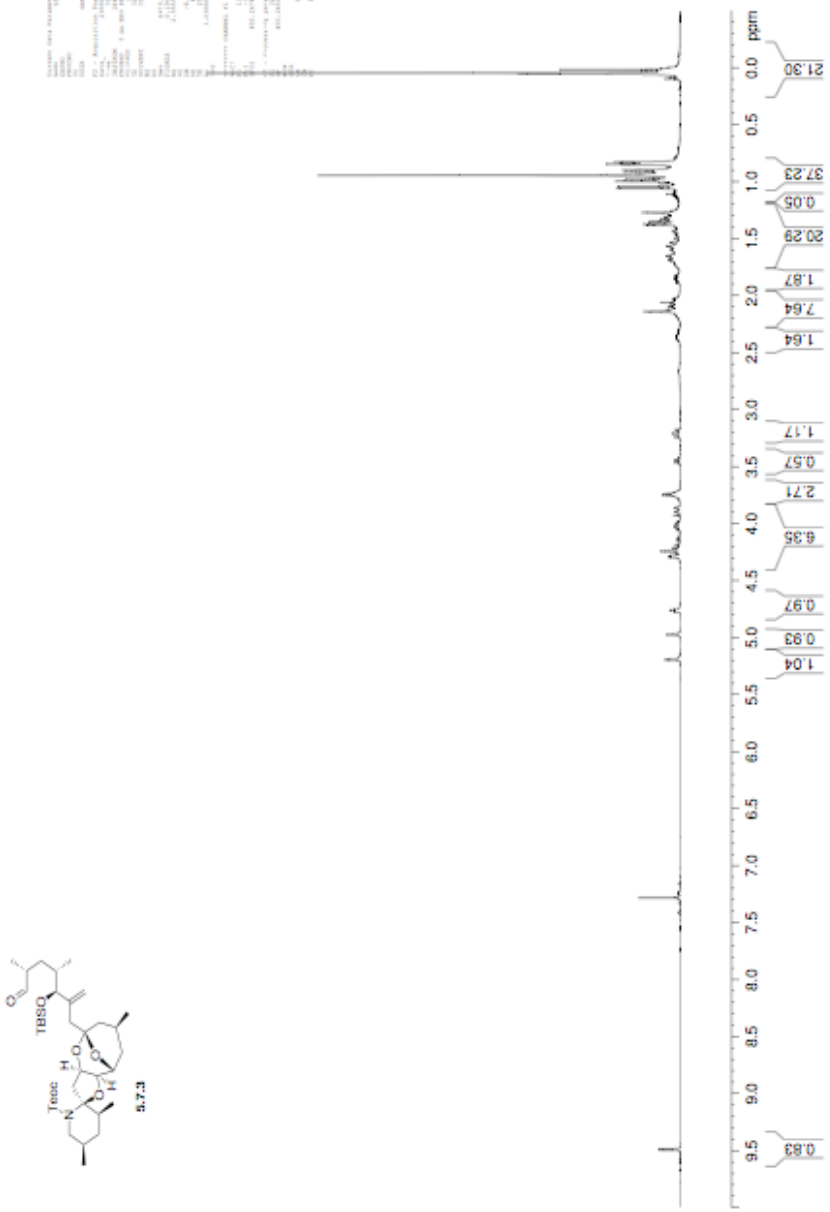
Carbon#	Carbon Signal	Proton Signal
21	39.9	2.3 (m, 2H)
22	31.2	1.6 (m, 1H)
23	17.2	1.6 (m, 2H)
24	35.1	1.7 (m, 1H)
25	77.2	3.3 (m, 1H)
26	144.6	-
27	48.7	2.3, 2.1 (m, 2H)
28	96.2	-
29	45.7	1.7 (m, 2H)
30	36.5	1.8 (m, 1H)
31	42.3	1.5 (2H)
32	72.8	4.3 (m, 1H)
33	77.8	3.7 (m, 1H)
34	73.8	4.8 (m, 1H)
35	79.7	3.8, 2.2 (m, 2H)
36	97.1	-
37	24.5	1.5 (m, 1H)
38	34.9	1.8,1.4 (m, 2H)
39	38.9	1.6 (m, 1H)
40	75.7	3.6, 3.2 (m, 2H)
42	17.7	0.7 (d, 3H)
43	18.7	0.7 (d, 3H)
44	116.9	5.0 (d, 2H)
45	16.5	0.9 (d, 3H)
46	19.2	0.8 (d, 3H)
47	22.9	0.9 (d, 3H)
A	72.8	4.5 (m, 2H)
B	138.9, 128.2 127.4, 127.2	7.4 (m, 5H)
C	156.2	-
D	62.8	4.1 (m, 2H)
E	21.4	0.8 (m, 2H)
F	-1.7	0.0 (s, 9H)

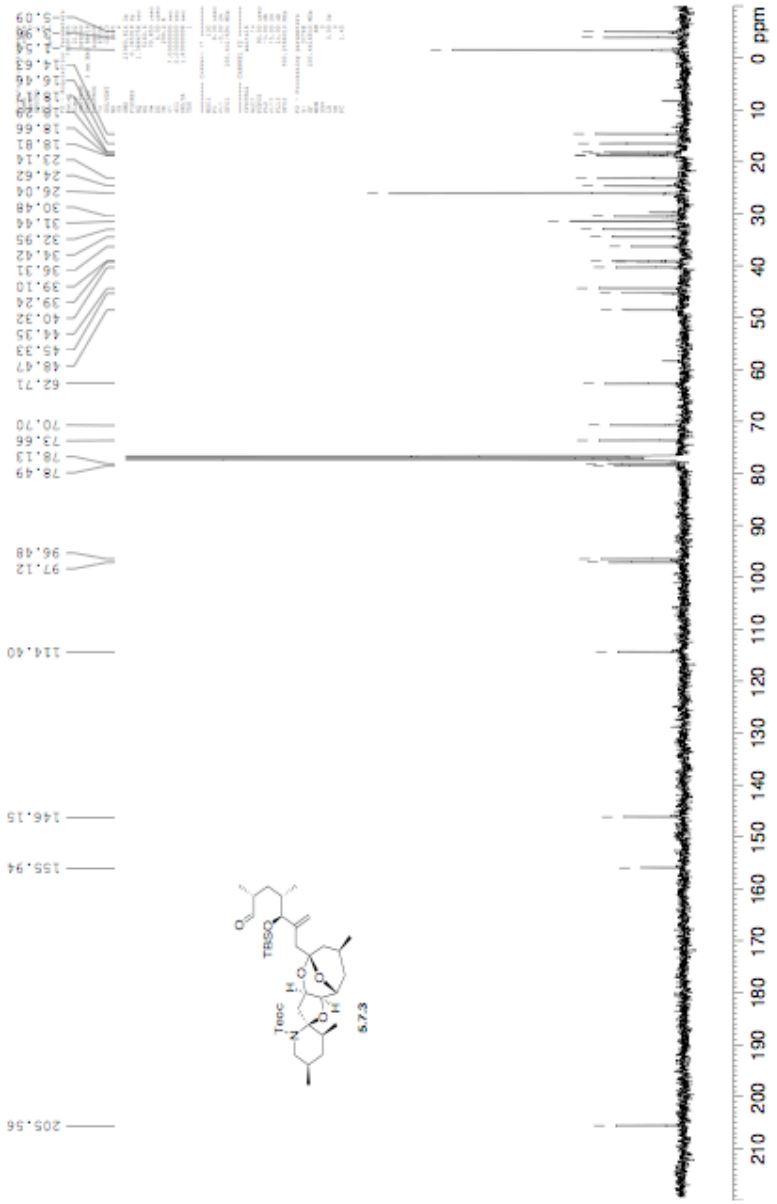

BnO
TBSO
Teoc
5.7:1
ppm
11.64
20.50
8.46
4.89
0.58
0.80
0.64
0.31
1.49
0.61
0.72
1.55
0.72
1.44
0.72
0.65
0.70
4.10

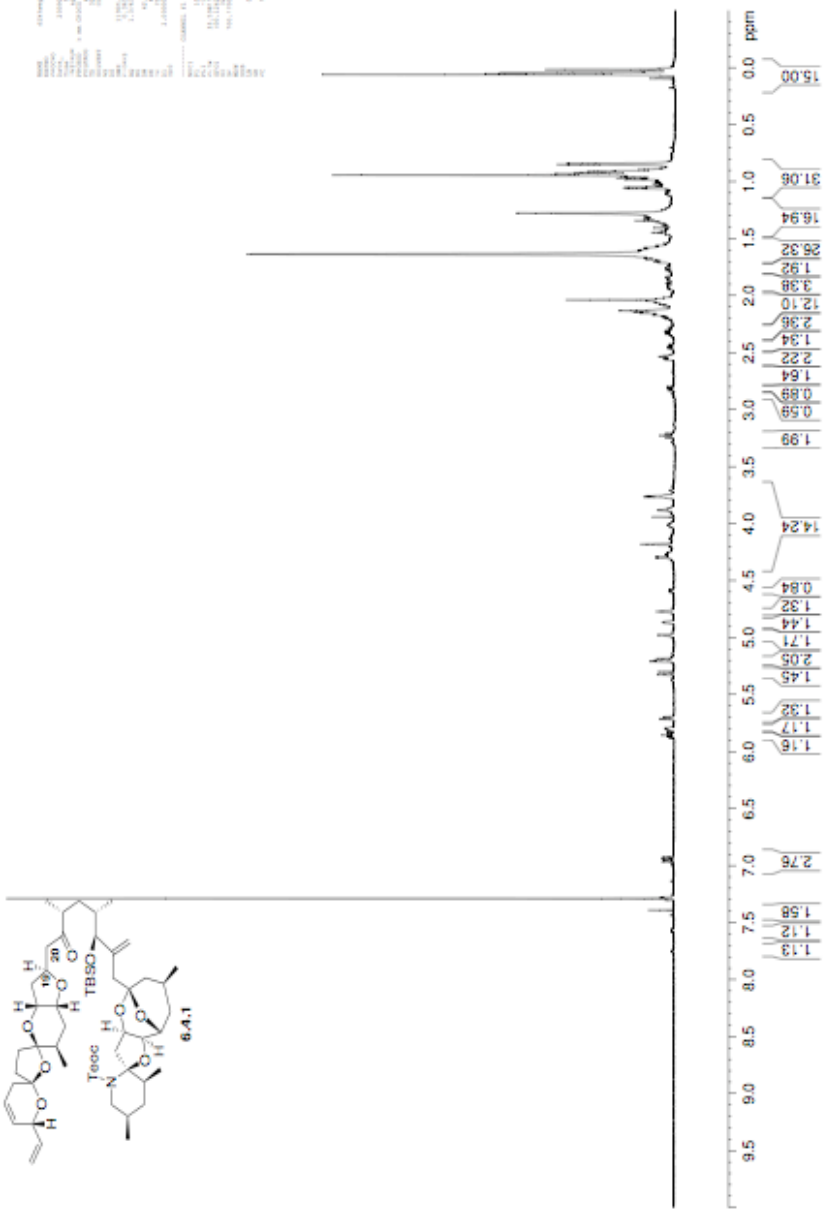

-5.08
1.53
16.47
18.08
19.06
19.36
23.11
24.56
26.04
31.44
31.70
33.37
33.41
34.52
36.39
39.06
39.39
40.36
45.15
48.51
62.64
70.85
72.80
73.63
75.75
77.22
78.15
79.05
96.64
97.10
114.10
127.23
127.36
128.21
139.02
146.11
155.93
ppm
BnO
TBSO
Teoc
N
5.7.1

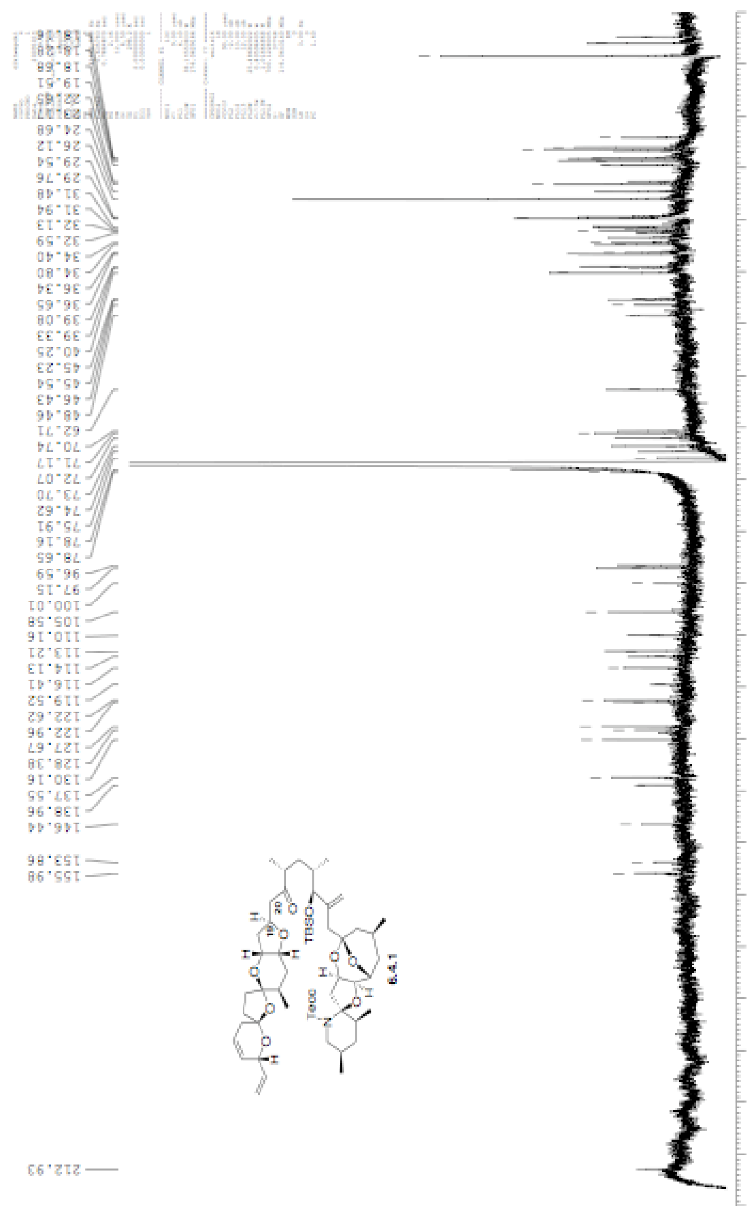

HO
TBSO
Teoc
5.7.2
ppm
13.88
27.13
16.93
6.24
0.13
2.88
2.52
4.03
0.63
0.72
0.80

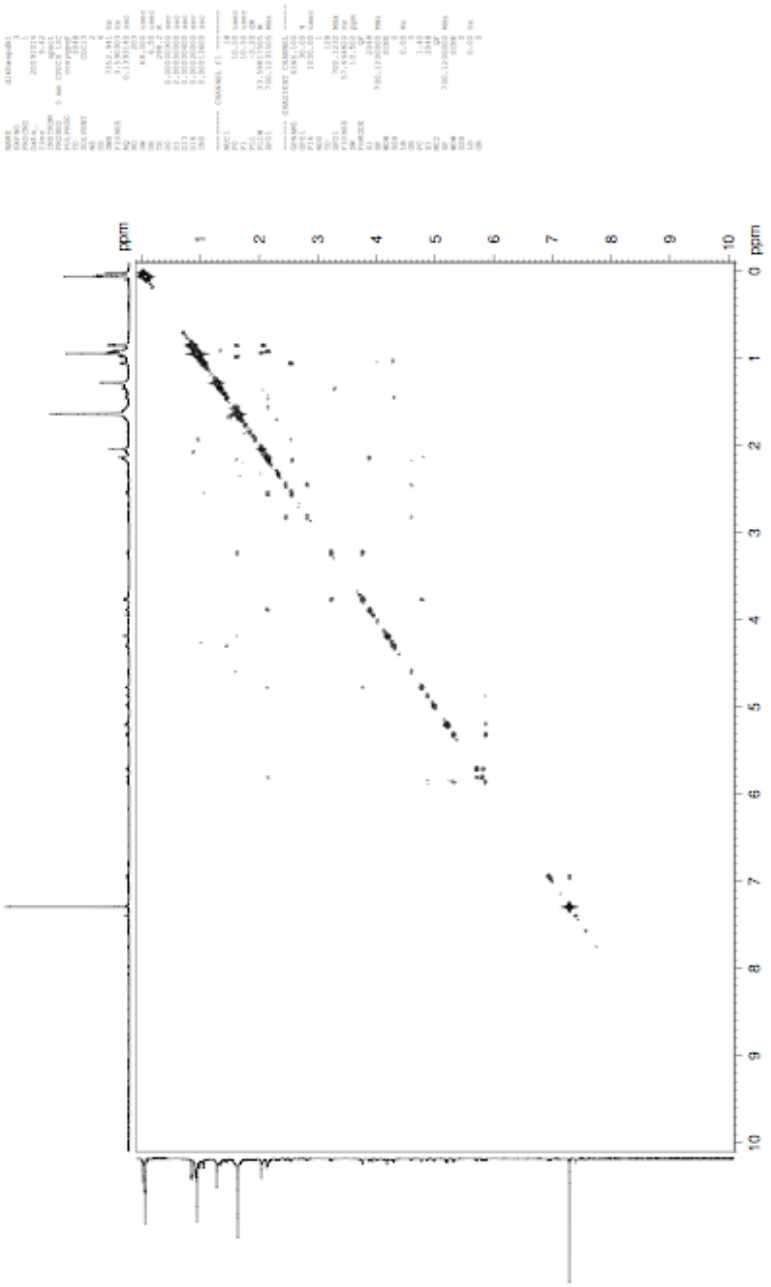

9.98
14.53
16.58
18.02
18.37
18.80
18.98
23.10
24.54
26.07
31.33
31.44
32.31
33.06
33.52
34.57
36.66
39.08
39.59
40.45
45.58
48.69
63.02
70.87
73.60
78.09
78.57
96.59
97.12
114.20
146.50
156.02
HO
TBSO
H
O
O
H
Teoc
N
5.7.2
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

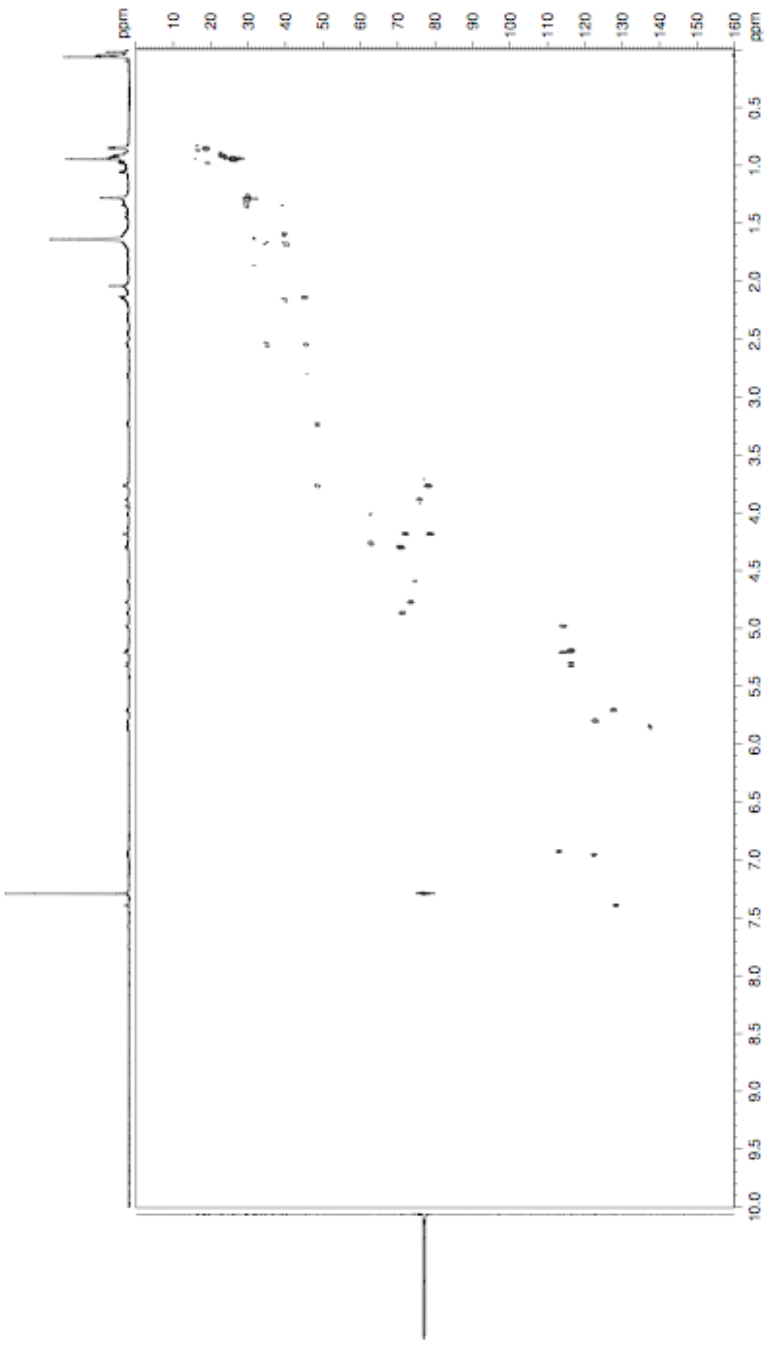

TBSO
Teoc
5.7-3
21.30
37.23
0.05
20.29
1.87
7.64
1.64
1.17
0.57
2.71
6.35
0.97
0.93
1.04
0.83
ppm

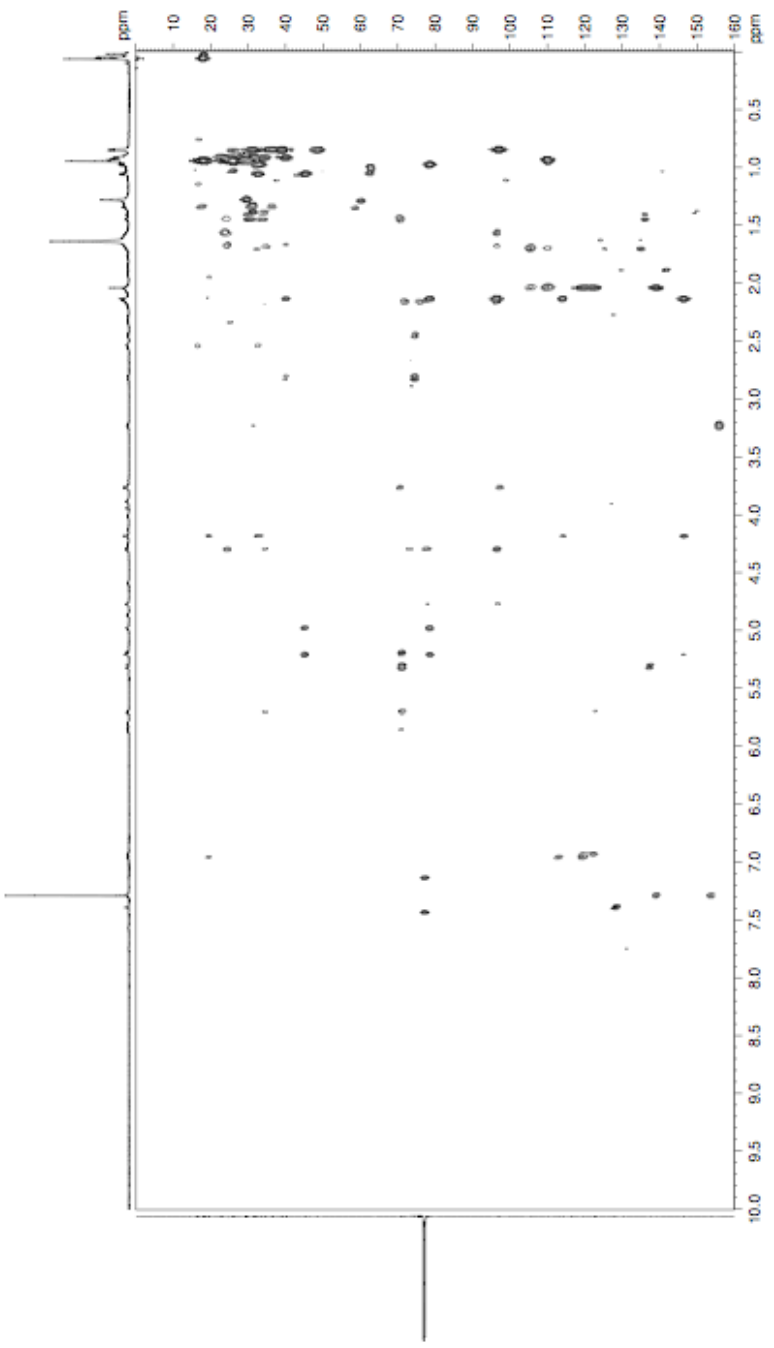

5.09
5.98
6.00
1.54
14.63
16.46
18.17
18.29
18.66
18.81
23.14
24.62
26.04
30.48
31.44
32.95
34.42
36.31
39.10
39.24
40.32
44.35
45.33
48.47
62.71
70.70
73.66
78.13
78.49
96.48
97.12
114.40
146.15
155.94
205.56
TBSO
Teoc
5.7.3
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

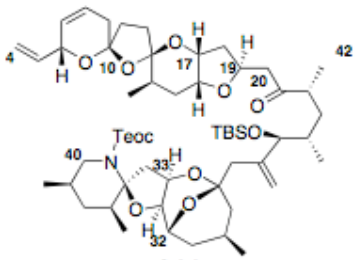

TBSO
Teoc
6.4.1
ppm
15.00
31.06
16.94
26.32
1.92
3.38
12.10
2.36
1.34
2.22
1.64
0.89
0.59
1.99
14.24
0.84
1.32
1.44
1.71
2.05
1.45
1.32
1.17
1.16
2.76
1.58
1.12
1.13


212.93
155.98
153.86
146.44
138.96
137.55
130.16
128.38
127.67
122.96
122.62
119.52
116.41
114.13
113.21
110.16
105.58
100.01
97.15
96.59
78.65
78.16
75.91
74.62
73.70
72.07
71.17
70.74
62.71
48.46
46.43
45.54
45.23
40.25
39.33
39.08
36.65
36.34
34.80
34.40
32.59
32.13
31.94
31.48
29.76
29.54
26.12
24.68
19.51
18.68
TBSO
Teoc
6.4.1
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm




ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0


ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0



6.4.1

Selected Peaks for **6.4.1**:

Carbon#	Carbon Signal	Proton Signal
4	116.4	5.2, 5.3 (d, m, 2H)
5	138.2	5.85 (m, 1H)
6	71.1	5.85 (m, 1H)
7	122.6	5.8 (m, 1H)
8	127.6	5.7 (m, 1H)
9	78.6	3.5-3.7 (m, 2H)
10	105.6	-
13	110.1	-
19	72.0	4.3 (m, 1H)
20	48.4	2.7, 3.7 (m, 2H)
21	212.9	-
22	45.5	2.9 (m, 1H)
26	155.9	-
28	96.9	-
32	74.6	4.6 (m, 1H)
33	78.1	4.3 (m, 1H)
34	73.7	4.8 (m, 1H)
35	70.7	m, (4.6, 1H)
36	96.6	-
40	62.7	3.8, 4.2 (m, 2H)
42	19.5	1.1 (d, 3H)
44	113.2	4.9, 5.2 (2 s, 2H)