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Progress Towards the Total Synthesis of Amphidinolide C

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Graduate Program in Chemistry
A thesis submitted in partial fulfillment of the requirements for the degree in Doctor of Philosophy

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Nicholas A. Morra

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THE UNIVERSITY OF WESTERN ONTARIO
THE SCHOOL OF GRADUATE AND POSTDOCTORAL STUDIES

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Abstract and Key Words

A second generation catalyst for the Mukaiyama oxidative cyclization for the formation of *trans*-THF rings is described. $Co(nmp)_2$, displays increased stability to the reaction conditions, resulting in lower catalyst loadings, lower reaction temperatures, and significantly higher purity and yields of the products. Three procedures have been developed with this new water-soluble catalyst that greatly simplifies the post-reaction purification, making this procedure the premier method of forming *trans*-THF rings.

This new catalyst has been applied towards the total synthesis of the potently bioactive macrocycle, Amphidinolide C. Herein we report the successful synthesis of several fragments of the natural product, and our attempts at coupling them to complete the synthesis. The C(1)-C(9) was achieved via two routes, both utilizing the highly effective oxidation catalyst $Co(nmp)_2$ to form the methyl substituted *trans*-THF ring. Synthetic highlights include a regioselective Shi epoxidation, and the design and introduction of a novel Lewis acid ($BF_2OBn{\cdot}OEt_2$) to facilitate a stereoselective reductive epoxide opening. The C(18)-C(34) fragment was also achieved via two routes, culminating in both the shortest (11 steps) and highest yielding (26% overall yield) approaches to this segment. Synthetic highlights of this fragment include a selective methylation of a diyne, and a highly selective alkynylation of a THF aldehyde, achieving excellent dr (>20:1) without the addition of an external chiral compound. Advanced intermediates comprising the entirety of the carbon backbone of the molecule have been synthesized, which in theory could complete the total synthesis in as few as two bond forming steps.

Key Words: Natural Product Synthesis, *trans*-THF, Amphidinolide, Mukaiyama Oxidative Cyclization, Macrocycle, Umpolung Chemistry, Synthetic Methodology, Asymmetric Alkynlation, Asymmetric Dihydroxylation, Water Soluble Catalyst

Dedicated to my failed routes.
Unpublished, but never forgotten.

Acknowledgements

First and foremost, I have to thank my friend, labmate and wife Dr. Barbora Morra for her constant love and support throughout the past 8 years. To paraphrase the fictional character Sheldon Cooper, if my life were expressed as a function on a four-dimensional Cartesian coordinate system, the day that I met her would be (0, 0, 0, 0). We've learnt and grown as chemists together from the very start, and without her I doubt that I would have made it through the process. She has been unwavering in her support, and always believed that I was capable of completing my total synthesis, even when I wasn't. My mother and father have also been a constant source of support throughout my length university tenure. Although they don't completely understand the particulars of my work, they've always shown interest in my progress and accomplishments, for which I am thankful.

I have to thank professor Pagenkopf for taking me under his wing as a second year undergrad that had no business being in a synthetic lab. He showed a confidence in me that I didn't have in myself, and my quick start and early successes were a direct result of his commitment to training me to be the best chemist I could be. Professor Pagenkopf also allowed me to pick a target molecule, and never scoffed at the obviously expensive and most likely unachievable goal of amphidinolide C. To his credit, he's given me the flexibility to achieve the total synthesis by any means necessary, no matter what the cost to him and his group, and for that I am very thankful. I would also like to thank professor Kerr for all that he has done for me in the past 5 years. The door to his unusually warm office was always open, and he is always genuinely excited to discuss chemistry ideas. The level of dedication he shows to his chemistry and his group, despite being a busy father of two girls and a bear-like dog, is impressive. I wish both professor Pagenkopf and Kerr the best of luck, and continued success at the University of Western Ontario.

I would be remiss if I didn't acknowledge the former members of the Kerr group who took my under their wing when I was a bright eyed undergraduate, full of hope and promise. When I was thrust into the position of the senior student in the Pagenkopf lab a grizzled six-month veteran of the graduate school program, I leaned heavily on them for

advice and they were more than willing to oblige. I consider Andrew Leduc a great friend and mentor (and terribly conservative poker player), whom I attribute much of my early success to. Cheryl Carson and Ian Young provided an example of how hard a chemist must work to be successful in grad school, something that I have tried to emulate in hopes of being as successful as they have. The other former members of the Kerr group, Terry Lebold, Steven Jackson, Mike Johanson, Avedis Karadeolian and Kasia Sapeta have also played a major role in my development as a chemist, and I consider myself lucky to have shared a few years of grad school with them. I know that they will all be successful members of the chemistry community, in either industry or academia, and I look forward to crossing paths with them again in the future.

The current members of the Kerr and Pagenkopf group have made the last few years an enjoyable experience and I wish them the best of luck on their current and future projects. The youthful enthusiasm that the junior grad students demonstrate is a clear sign that both groups will be prosperous for years to come, and I am sure there will be no shortage of post-work day stories to accompany the successes in lab.

My time at the University of Western Ontario was highlighted by multiple championship winning IMS sports teams, in both baseball and waterpolo, and we were close a few times in volleyball, dodgeball and European handball too. Having a venue to de-stress from a busy work schedule with sports proved an invaluable practice for maintaining sanity during the rough patches in grad school. I'd like to end my acknowledgements by thanking all of the chemists and non-chemists alike that I've played with over the last nine years, for playing their hearts out every week to satisfy my somewhat unhealthily need for competition.

Now, onwards to the next step, whatever that may be. Andrew Leduc told me that everyone who graduates with a PhD receives a pony. I'm going to name mine biscuit.

List of Abbreviations

18-C-6	18-crown-6-ether
10-CSA	10-camphor sulfonic acid
Å	Ångstrom
Ac	acetyl
ap.	apparent
atm	atmosphere
aq.	aqueous
Bn	benzyl
br	broad
BORSM	based on recovered starting material
Bu	butyl
Bz	benzoyl
calcd	calculated
cat.	catalytic amount
d	doublet
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DiBn	dibenzyl
DiPr	di-*iso*-propyl
DMAP	*N*,*N*-dimethylamino-4-pyridine
DMDO	2,2-dimethyldioxirane
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMM	dimethoxymethane
DMP	Dess-Martin periodinane
DMPU	dimethylpropyl urea
ee	enantiomeric excess
Et	ethyl
EtOAc	ethyl acetate
eq. or equiv.	equivalents
gCOSY	gradient correlation spectroscopy
gHSQC	gradient heteronuclear single quantum correlation
h	hour(s)
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
hv	light
Hz	hertz
IBX	2-iodoxybenzoic acid
IC_{50}	half maximal inhibitory concentration
LDA	lithium diisopropylamide

liq	liquid
m	*meta* substitution
M	moles per litre
Me	methyl
min	minute(s)
modp	modp ligand
MOM	methoxymethyl
Ms	methanesulfonate
MS	molecular sieves
MTBE	methyl *tert*-butyl ether
m/z	mass to charge ratio
nmp	N-methyl piperazine
NMR	nuclear magnetic resonance
o	*ortho* substitution
OTf	trifluoromethane sulfonated
p	*para* substitution
Ph	phenyl
PMB	*para*-methoxybenzyl
ppm	parts per million
PPTS	Pyridinium *p*-toluenesulfonate
Pr	propyl
q	quartet
Red-Al	sodium *bis*(2-methoxyethoxy)aluminum hydride
R_f	retention factor
rpm	revolutions per min
rt	room temperature
s	singlet
SM	starting material
S_N2	second order nucleophilic substitution
t	triplet
TBAF	tetra-n-butylammonium fluoride
TBS	*tert*-butyl dimethylsilyl
TBDPS	*tert*-butyl diphenylsilyl
TES	triethylsilyl
Tf, triflate	trifluoromethanesulfonate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
δ	chemical shifts
μ	microwave

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Chapter 1 – The Mukaiyama Oxidative Cyclization and Amphidinolide C

Section 1.1 – Importance of Total Synthesis

Synthetic organic chemistry has had a wide impact on the world around us. Everything from pharmaceuticals, high-tech materials, fertilizers, pesticides, polymers, personal care products, and even our food has been impacted by organic chemistry. At the heart of all these applications lies the ability to assemble complex molecules from commercially available chemicals.

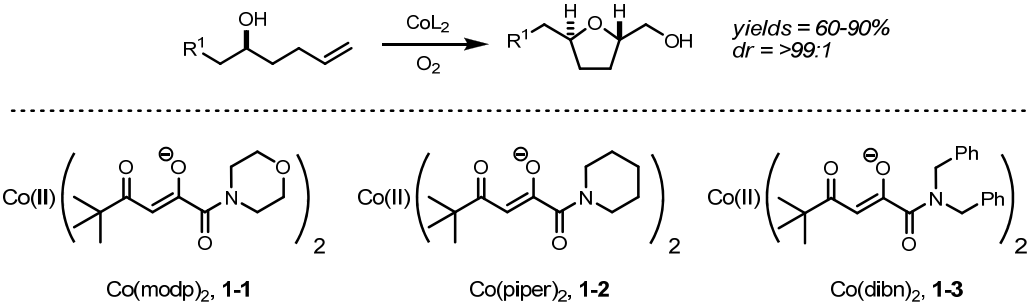
When isolation chemists find natural products with interesting biological activity, the structure of the molecule is determined using imperfect characterization methods (NMR, IR, HRMS). While the structure of the compound is assigned correctly more often than not, the only way to determine the structure of the compound with absolute certainty is through total synthesis.

Since most natural products can only be isolated in miniscule amounts, and are often very difficult to obtain, accessing them through synthetic means can be tremendously useful. A completed total synthesis not only provides a blueprint towards making this molecule on laboratory scale, but also a venue for the synthesis of derivatives of the natural product. This flexibility is the basis for drug design, allowing for selective functionalization of molecules to manipulate its properties, such as bioactivity, half-life, and minimization of side effects.

Perhaps the most important opportunity that total synthesis provides is the venue to discover new chemistry and new methodologies. During the course of a total synthesis you will inevitably encounter difficulty with a synthetic transformation for which there is no solution reported in the literature. Through the rigorous process of a total synthesis, chemists will discover novel and innovative transformations that will help them to achieve their goal. These solutions are added to the pool of chemical knowledge that has been developed over several hundred years, which furthers our understanding of chemistry and propels the field of synthetic chemistry forward.

Section 1.2 – The History of the Mukaiyama Oxidative Cyclization

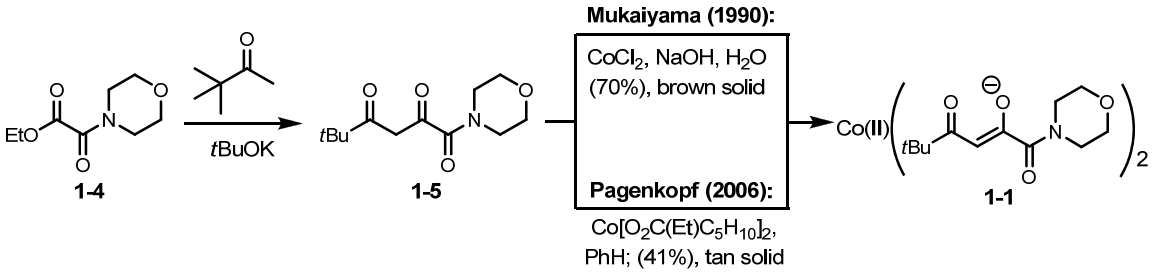
The ubiquitous nature of tetrahydrofuran (THF) rings in a wide variety of biologically active natural products has inspired the development of methods for their synthesis and derivatization.[1] In particular, the ability to form 2,5-*trans*-THF rings in an efficient and diastereoselective manner is essential for the synthesis of many natural products containing this structural motif. Numerous methods have been utilized to access *trans*-THF rings, however, most of them suffer from poor yields or low diastereoselectivity.[2] Recently, the Mukaiyama oxidative cyclization has emerged as a powerful synthetic tool that uses molecular oxygen as the stoichiometric oxidant to convert pentenols to *trans*-THF rings with >99:1 *trans*:*cis* diastereoselectivity and good to excellent yields (Scheme 1.1). The paramagnetic nature of the catalysts has led to very little mechanistic studies of the reaction, but some pioneering mechanistic investigations have been reported by Hartung.[3]



Scheme 1.1. Representative Muykaiyama aerobic oxidative cyclization

The oxidative cyclization was first discovered by Mukaiyama in 1990,[4] when he utilized several different cobalt (III) complexes (oxidized *in situ* from the parent Co(II) complex using a peroxide) to achieve the cyclization in low to moderate yields. His original conditions to complex the acac-type ligands to form the Co(II) precatalysts (**1-1**, **1-2**, and **1-3**) used aqueous alkaline conditions ($CoCl_2$, NaOH, H_2O), resulting in brown amorphous solids of dubious purity, which undoubtedly decreased the yield of the cyclization reactions (Scheme 1.2). In an attempt to improve the procedure for use in total synthesis, our group endeavoured to modify the complexation conditions to create catalysts of higher purity. We replaced the cobalt source ($CoCl_2$) with Co(2-ethyl-

hexanoate)$_2$, allowing us to conduct the complexation reaction in organic solvents. The result, for the traditional catalyst Co(modp)$_2$ (**1-1**), was a lower yielding reaction that produced higher purity catalyst, which we isolated as a tan solid. The same complexation conditions were used for other first generation catalysts, Co(piper)$_2$ (**1-2**), and Co(dibn)$_2$ (**1-3**), also resulting in tan solids.



Scheme 1.2. Our improved synthesis of the first generation catalyst

Over time, crystals were grown of both Co(II) and Co(III) complexes, providing invaluable information regarding the structure of the catalysts.[5] We found that the Co(II) complex is comprised of three cobalt atoms, each separated by 4.870 Å (Figure 1.1). The two outer cobalt atoms are each surrounded by three dioxoamide ligands, and their negative charge is balanced by a central Co(II)$(H_2O)_6$.

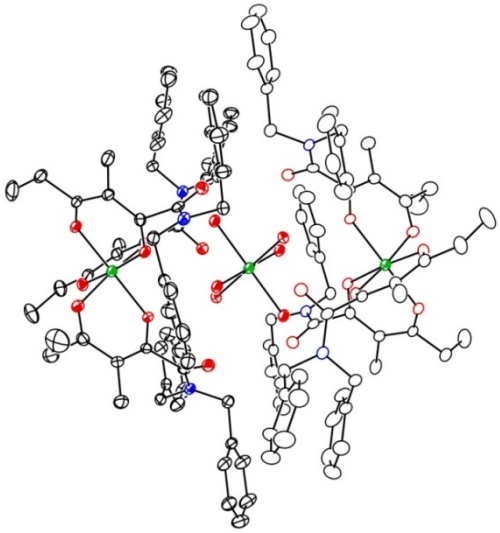


Figure 1.1. Crystal structures of a Co(II) complex: $[(C_{21}H_{22}NO_3)_3Co]_2$–$Co(H_2O)_6$

Upon oxidation to the Co(III) complex, ligand redistribution resulted in a binuclear cluster where the two central cobalt atoms are bridged by two hydroxyl groups (Figure 1.2). Both cobalt atoms are surrounded by two chelating ligands, maintaining the empirical formula CoL_2.

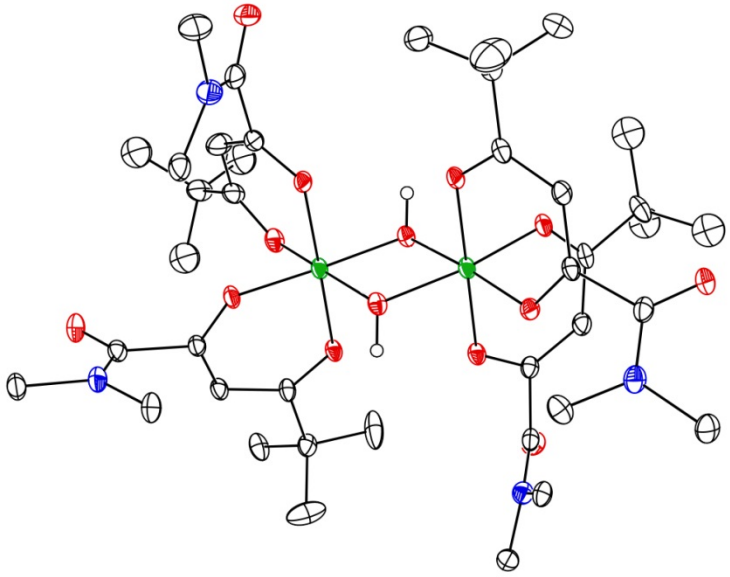


Figure 1.2. Crystal structures of a Co(III) complex: $[(C_{34}H_{32}NO_3)_3Co]_2(\mu\text{–}OH)_2$

The superior quality of the catalysts generated via our new procedure resulted in an increase in both yield and purity of the reactions, with the average yield of the cyclization reaction being 70-80%.

Section 1.2.2 – The Mukaiyama Oxidation in Total Synthesis

Using our higher quality first generation catalyst, the Pagenkopf group set out to synthesize multiple *trans*-THF containing natural products. In 2006, Hongda Zhao reported the total synthesis of bullatacin (**1-6**),[6] and a year later the synthesis of aplysiallene (**1-7**) was completed by Jian Wang (Figure 1.3).[7]

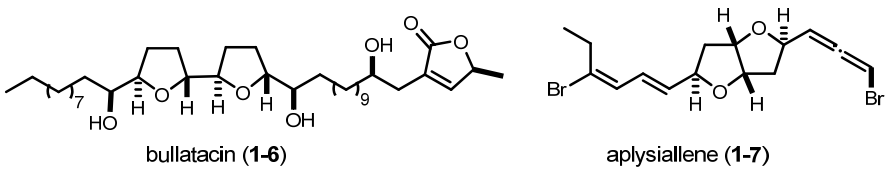
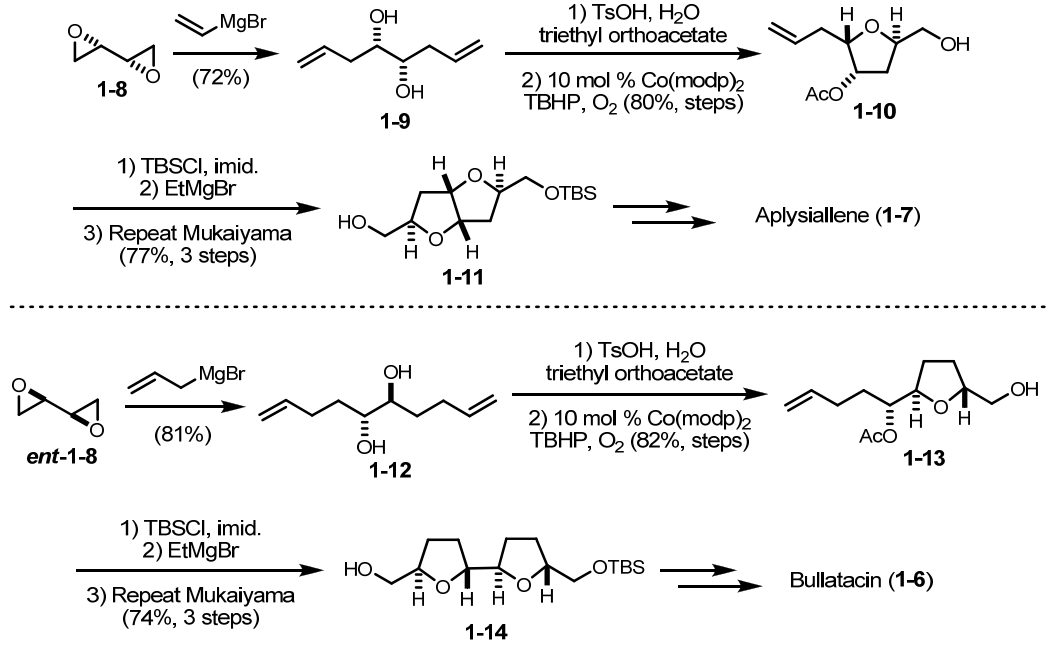


Figure 1.3. Two *trans*-THF containing natural products made in the Pagenkopf lab

Access to the *trans*-THF cores of these molecules started from the di-epoxide **1-8** and its enantiomer ***ent*-1-8**, which was opened using either allyl or vinyl grignard to give di-pentenols **1-9** or **1-12** (Scheme 1.3). Both diols were then desymmetrized via mono-acylation and subjected to the oxidative cyclization using $Co(modp)_2$ (**1-1**). Following protection of the resulting primary alcohol and removal of the acyl groups, a second Muykaiyama reaction was performed to give either the fused *bis*-THF **1-11** of aplysiallene, or the bridged *bis*-THF **1-14** found in bullatacin. Further manipulation of the fragments eventually led to the total synthesis of the natural products.



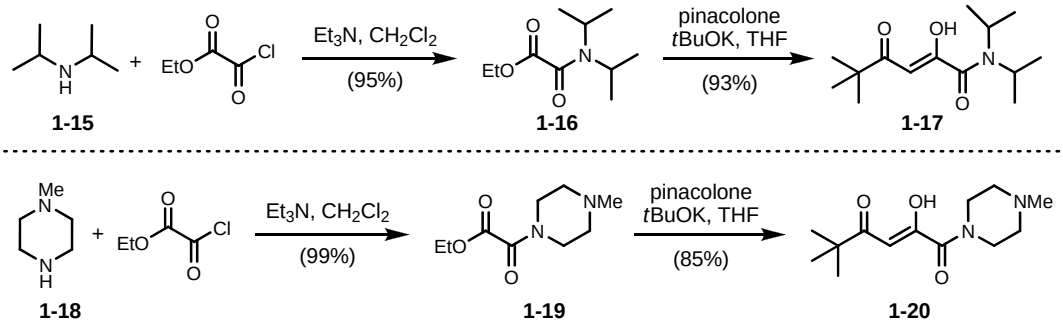
Scheme 1.3. Synthesis of the cores of Bullatacin (**1-6**) and Aplysiallene (**1-7**)

Although the catalysts performed admirably in the total syntheses, with perfect diastereoselectivity and excellent yields, the oxidative cyclization still suffered from a significant setback when dealing with post-reaction purification. It was found that during the course of the oxidation, the catalyst decomposed into a multitude of catalytically

active complexes of varying R_f values. These residues significantly complicate purification by column chromatography, often resulting in impure *trans*-THF products, which are uncharacterizable by NMR due to the paramagnetic nature of the cobalt contaminants.

Section 1.2.3 – A Water Soluble Variant of the Mukaiyama Catalyst

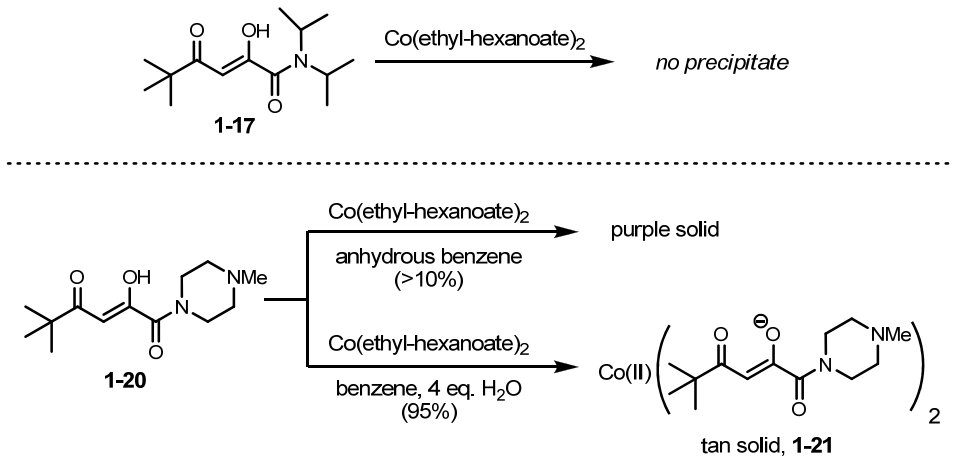
To circumvent the difficulties associated with purification by column chromatography, we set out to synthesize a second generation catalyst that retains high efficiency but also exhibits increased polarity. This and related strategies have seen great success with EDC, water-soluble ligands, sulfonated phosphines, fluorous phases, and ionic liquids.[8] Using the first generation catalysts as a blueprint, we deigned two possible ligands, both containing a polar tri-substituted amine. The two ligands were assigned the abbreviations dipr (after the di-*iso*propyl subunit) and nmp (after the *N*-methyl piperazine subunit). The synthesis of the new ligands began with the reaction of ethyloxalyl chloride with the corresponding secondary amine **1-15** or **1-18** (Scheme 1.4). Subsequent Claisen condensation with pinacolone followed by non-aqueous acidic quench[9] (HOAc, CH_2Cl_2) furnished the dipr (**1-17**) and nmp (**1-20**) ligands in excellent overall yields.



Scheme 1.4. Synthesis of the second generation ligands dipr (**1-17**) and nmp (**1-20**)

Several attempts were made at complexion of the dipr ligand (**1-17**) with Co(2-ethyl-hexanoate)$_2$, however successful precipitation the catalyst was never achieved (Scheme 1.5). Initial complexation reactions using the nmp ligand **1-20** provided trace amounts of a purple solid (<10% yield) that performed poorly in oxidative cyclization reactions.

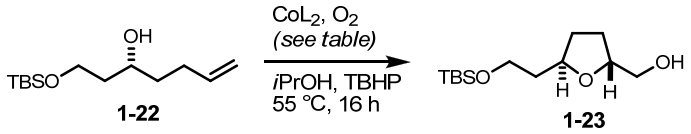
Eventually, given the unusual color of the catalyst (purple, not tan), and the x-ray data of first generation catalysts that clearly showed the incorporation of water in the structures, we rationalized that the complexation yield would benefit from being run in aqueous benzene. Indeed, the addition of four equivalents of water in the complexation reaction gave a nearly quantitative yield of $Co(nmp)_2$ (**1-21**) as a tan solid, which was isolated by centrifugation of the mixture.



Scheme 1.5. Complexation of the ligands to form the Co(II) pre-catalysts

Gratifyingly, $Co(nmp)_2$ (**1-21**) displayed remarkable improvement in the yield of the oxidative cyclization process (Table 1.1, entries 1-6). The reason, as we later discovered, was that the catalyst displayed outstanding stability under the reaction conditions leading to increased catalyst longevity. Also, the longevity of the catalyst circumvented undesired side reactions which typically resulted in over oxidation or protocyclization products, resulting in cleaner crude reaction mixtures. Using a simple TBS protected pentenol **1-22** we showed that, for the first time, complete conversion of starting material could be achieved with catalyst loadings as low as 5% (Table 1.1, entry 7). Reactions using catalyst loadings lower than 5% (Table 1.1, entry 8) did not progress to completion, but still gave excellent yields based on recovered starting material.

Table 1.1. Comparison of $Co(nmp)_2$ (**1-21**) performance to the first generation catalysts



Entry	Catalyst	Catalyst loading (mol %)	Yield (%)
1	$Co(modp)_2$	5	47[a]
2	$Co(modp)_2$	10	65
3	$Co(modp)_2$	15	68
4	$Co(dibn)_2$	10	68
5	$Co(piper)_2$	10	70
6	$Co(nmp)_2$	10	97
7	$Co(nmp)_2$	5	93
8	$Co(nmp)_2$	3	57 (93)[b]

[a] All starting material was consumed. [b] Based on recovered starting material

With regards to product purification, we initially accomplished complete removal of the cobalt residues from the *trans*-THF products via aqueous workup by washing the organic layer with a pH 4 phosphate buffer solution. Understanding that a pH 4 workup procedure may be incompatible with some acid-sensitive substrates, an alternative procedure of quaternization of the tertiary amine using methyl iodide was developed. While both procedures performed well, removing all traces of the catalyst and retaining high isolated yields of purified product, we recognized that they both had substantial drawbacks. The acidic workup would be obviously incompatible with a variety of functionalities and protecting groups, while the overnight methylation of the catalyst was time consuming, and also had the potential of substrate compatibility issues. So, a third workup procedure was invented, after the highly polar nature of the oxidized catalyst was realized (R_f 100% EtOAc: 0.00). Upon completion of the reaction, all traces of *iso*-propanol were removed by rotary evaporation, followed by high vacuum (0.01 mmHg, 10 min) with rigorous stirring. The crude green oil was then diluted with ethyl acetate and filtered through a thin pad of silica on celite to provide the *trans*-THF product with no traces of cobalt residues.

Our work on the Mukaiyama oxidative cyclization reaction resulted in a dramatic improvement in yields and purities of the *trans*-THF products. We have also reported a second-generation catalyst, $Co(nmp)_2$, and demonstrated the improvement with regard to

post-reaction purification, replacing a difficult and costly column chromatography with an aqueous workup, or simple filtration. The catalyst can be easily synthesized on gram scale in nearly quantitative yield with centrifugation as the only means of purification. Given the improvements that we have pioneered, we believe that this procedure is now the premier method for forming *trans*-THF rings, and set out to showcase its utility in the total synthesis of a complex natural product.

Section 1.3 – Amphidinolide C: A Potently Bioactive Macrocyclic Lactone

The Amphidinolides are a series of 34 macrolactides and 8 linear polyketides isolated from laboratory-cultured marine dinoflagellates *Amphidinium sp.* possessing unique structural features and varying degrees of biological activity.[10] The five most cytotoxic members of the family are amphidinolides B, C, G, H, and N (Figure 1.4, brackets contain IC_{50} (μg/mL) values towards murine lymphoma and human epimeroid cancer cells respectively)[11], four of which have been synthesized in a laboratory. In 2006, Nicolaou completed the synthesis of amphidinolide N,[12] Fürstner finished amphidinolide G and H in 2007,[13] and most recently, in 2008, Carter achieved in the total synthesis of amphidinolide B.[14]

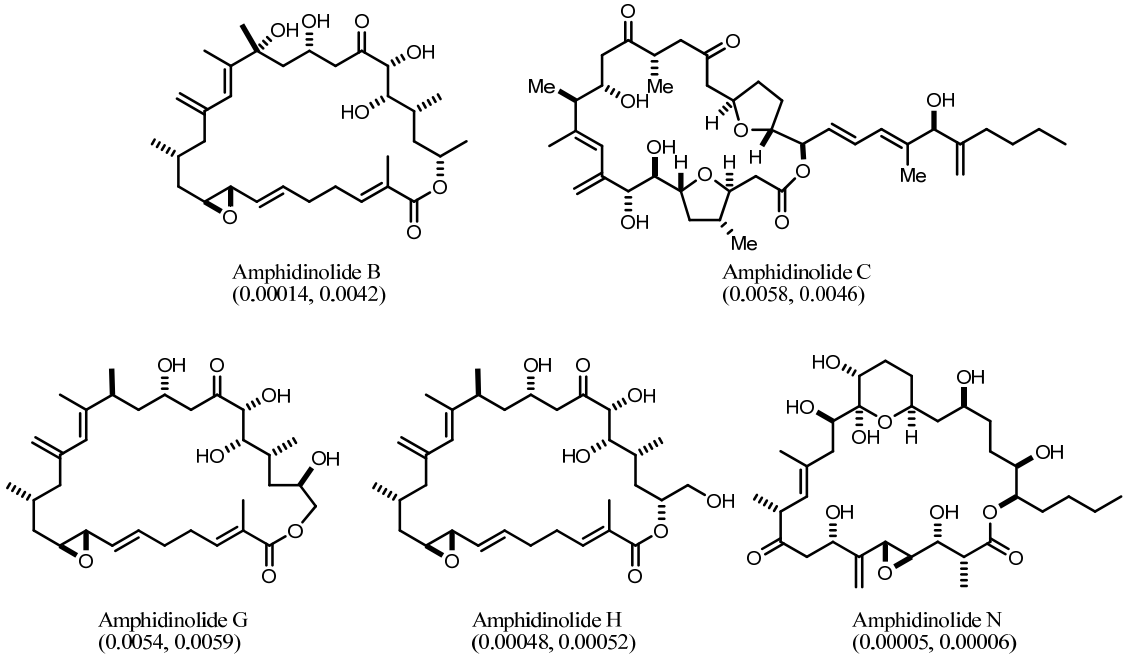


Figure 1.4. The five most cytotoxic members of the amphidinolide family

The absolute stereochemistry of amphidinolide C (**1-24**) was established by Kobayashi in 2001.[15] Somewhat surprisingly, it has yet to be completed by total synthesis, which is a reflection of the complexity of the natural product.[16] The 25-membered macrocycle includes 12 chiral centers, five of which are contained in two *trans*-THF rings, and several vicinally located one-carbon branches (Figure 1.5).

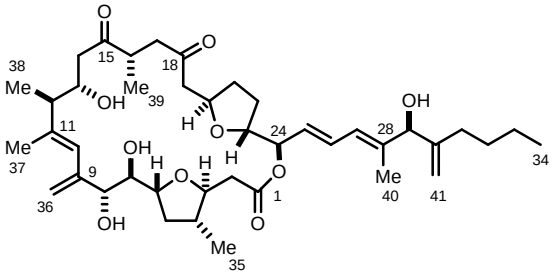


Figure 1.5. Amphidinolide C, and the numbering of the natural product

Other key aspects of the structure include the 1,4-diketone species from C(15)-C(18) and the unusually substituted diene system from C(9)-C(11). These unique structural features, combined with the potent cytotoxicity, have attracted the synthetic attention of many research groups, including our own. We believe that our recent work on the Mukaiyama oxidative cyclization and the improved catalyst $Co(nmp)_2$ could provide expedient access to the *trans*-THF rings, and lead to a concise total synthesis of amphidinolide C.

Section 1.4 – Previous Synthesis of the Amphidinolide C Fragments

Section 1.4.1 – Roush's Synthesis of the C(1)-C(9) and C(11)-C(29) Fragment

One of the earliest reports on progress towards the synthesis of amphidinolide C was from the Roush group. In 2004 he reported the synthesis of the C(11)-C(29) fragment of amphidinolide F[14h] (which is nearly identical to the C(11)-C(29) fragment of amphidinolide C), followed thereafter by his report of the synthesis of the C(1)-C(9) fragment in 2008.[14f] In his work, Roush relies on the diastereoselective [3+2]-annulation reaction of allylsilanes and aldehydes, pioneered by Panek,[17] to prepare the key *trans*-

THF rings. His initial retrosynthetic disconnections resulted in the C(1)-C(9) fragment (**1-26**) being attached via a Stille cross-coupling reaction,[18] and macrolactonization (Figure 1.6). Roush's retrosynthesis also entails forming the C(14)-C(15) bond via a 2 step boron mediated aldol/Evans-Tishchenko reduction procedure.

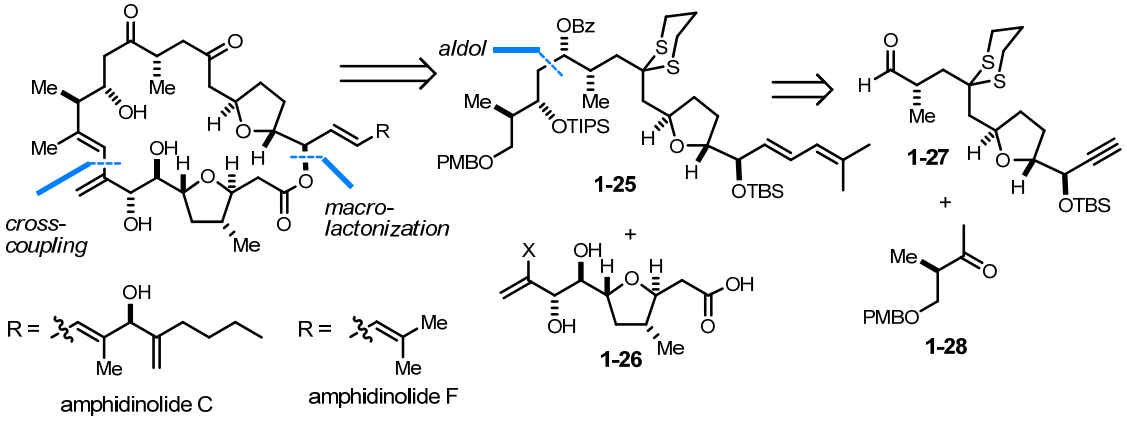
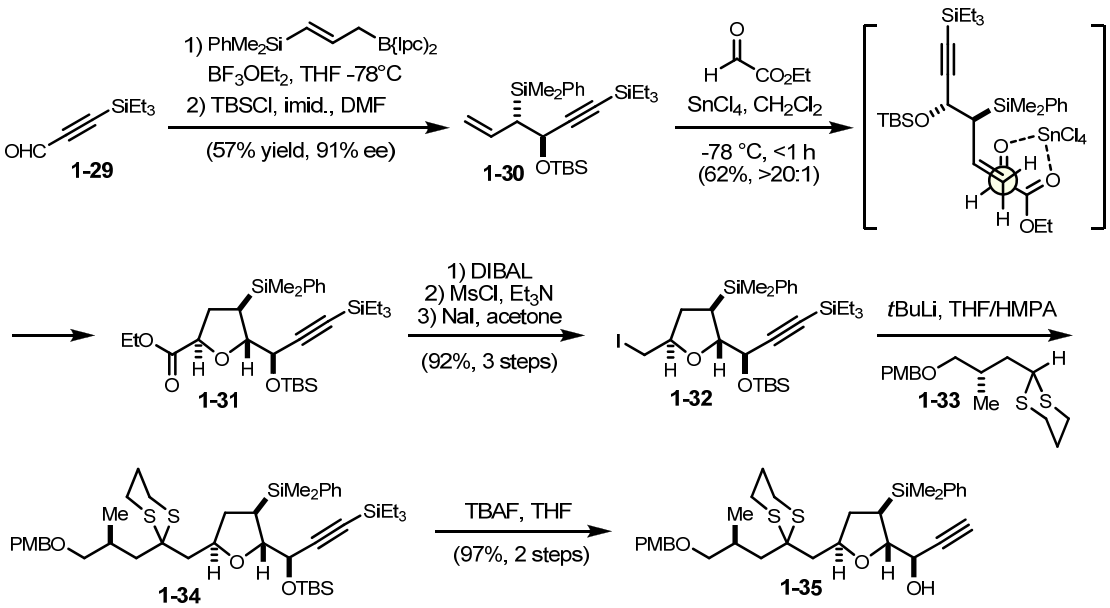


Figure 1.6. Roush's key retrosynthetic disconnections of amphidinolide C and F

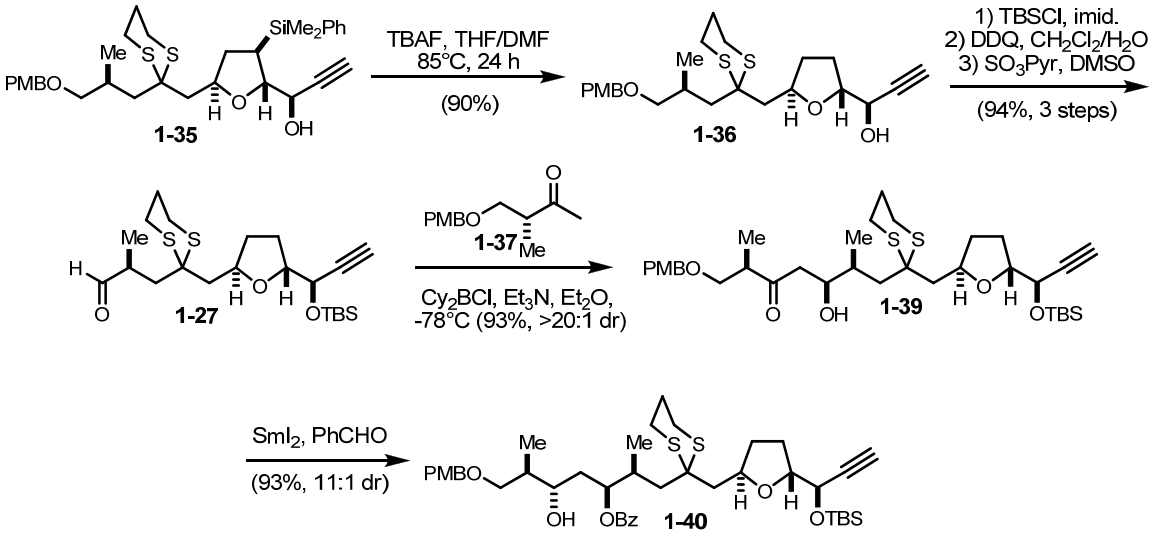
Roush's synthetic efforts towards the C(11)-C(29) fragment began with known aldehyde **1-29**, which was silylallylborated with a (+)-pinene-derived allyl borane, followed by TBS protection to afford allylsilane **1-30** in 57% yield and 91% *ee* (Scheme 1.6).



Scheme 1.6. Synthesis of the silyl substituted trans-THF ring via [3+2] annulation

This silane then underwent the aforementioned tin-mediated annulation reaction with ethyl glyoxylate to give the silyl substituted THF **1-31** in 62% yield and excellent dr. The THF ring was then converted into the iodide **1-32** via a 3-step procedure in 92% yield, and that iodide was displaced by dithiane **1-33** (which was derived from Roche ester)[19] and treated with TBAF to give the silylated C(15)-C(26) fragment **1-35**.

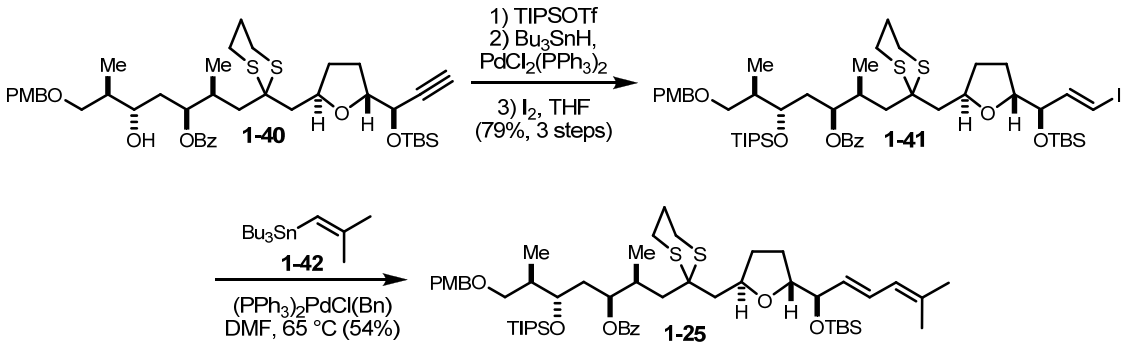
The protiodesilylation of **1-35** proved to be a troublesome reaction, but optimized conditions were eventually found (TBAF, THF/DMF, 85 °C, 24h) that allowed for a 90% yield of the desilylated product **1-36** (Scheme 1.7). After TBS protection of the secondary alcohol, conversion of the primary PMB ether to the corresponding aldehyde **1-27** was achieved, setting the stage for their aldol/Evans-Tishchenko reaction sequence. Using dicyclohexylchloroborane, aldol reaction between aldehyde **1-27** and ketone **1-37** was accomplished with perfect diastereoselectivity, followed by the Evans-Tishchenko reaction which proceeded with 11:1 dr to give **1-40**.



Scheme 1.7. Roush's aldol/Evans-Tishchenko strategy

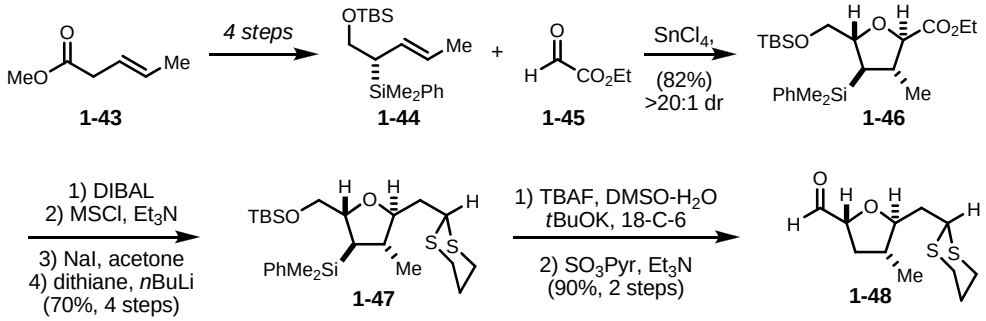
To complete the synthesis of the fragment, the secondary alcohol **1-40** was protected as the TIPS ether prior to regioselective hydro-stannylation of the alkyne and subsequent displacement of the stannane with iodide in 79% yield over 3 steps (Scheme 1.8). Iodide **1-41** was then coupled with stannane **1-42**, thereby completing the synthesis of the C(11)-C(29) fragment of amphidinolide F (**1-25**). Presumably, by altering their choice of

stannane, they could use the same intermediate (**1-41**) in the total synthesis of amphidinolide C.



Scheme 1.8. Completion of the C(11)-C(29) fragment of amphidinolide F

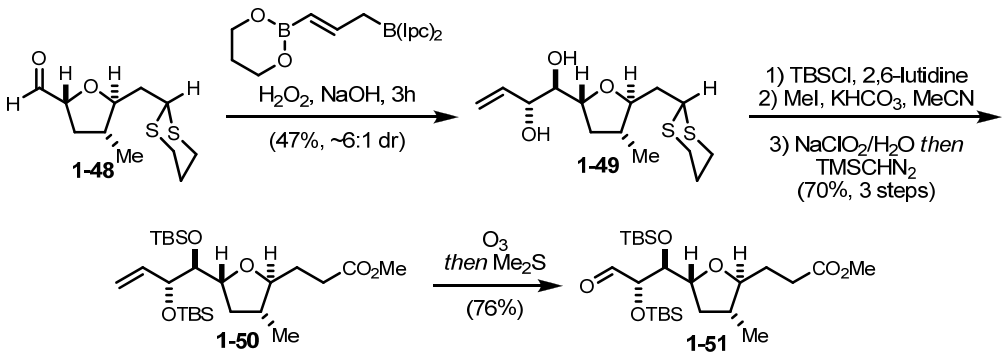
In a separate communication on the synthesis of the C(1)-C(9) fragment,[14f] Roush applied the same [3+2] annulation reaction to form the methyl substituted THF ring of amphidinolide C (Scheme 1.9), utilizing allyl silane **1-44** (made in four steps from **1-43**). The THF-ester **1-46** was converted to an iodide via a 3-step procedure, which was displaced by 1,3-dithiane to give **1-47** in 70% over 4 steps. The ring was protiodesilylated with concurrent deprotection of the TBS ether, using TBAF and *t*BuOK in a DMSO/water/18-crown-6 solvent mixture, which was followed by oxidation of the alcohol to aldehyde **1-48**.



Scheme 1.9. Roush's synthesis of THF-aldehyde **1-48**

To complete the synthesis, aldehyde **1-48** was treated with a custom made allylboration reagent, resulting in a 47% yield of a 6:1 diastereomeric ratio of diol **1-49** (Scheme 1.10). Diol protection, dithiane deprotection and aldehyde oxidation/esterification resulted in

ester **1-50** in 70% yield over three steps. Ozonolysis of the alkene **1-50** revealed aldehyde **1-51** which, presumably, could be elaborated into the C(9)-C(11) diene portion of amphidinolides C and F.



Scheme 1.10. Roush's completion of the C(1)-C(9) fragment

Section 1.4.2 – Carter's Synthesis of the C(7)-C(20) Fragment

Carter's work towards amphidinolide C was unique because unlike the other reports, they did not address the formation of the *trans*-THF rings.[14d] His retrosynthesis of the C(7)-C(20) fragment had two key disconnections, a sulfone (**1-53**) alkylation to form the C(14)-C(15) bond, and an organolithium addition/olefination sequence utilizing **1-54** and **1-55** to access the C(9)-C(11) diene (Figure 1.7).

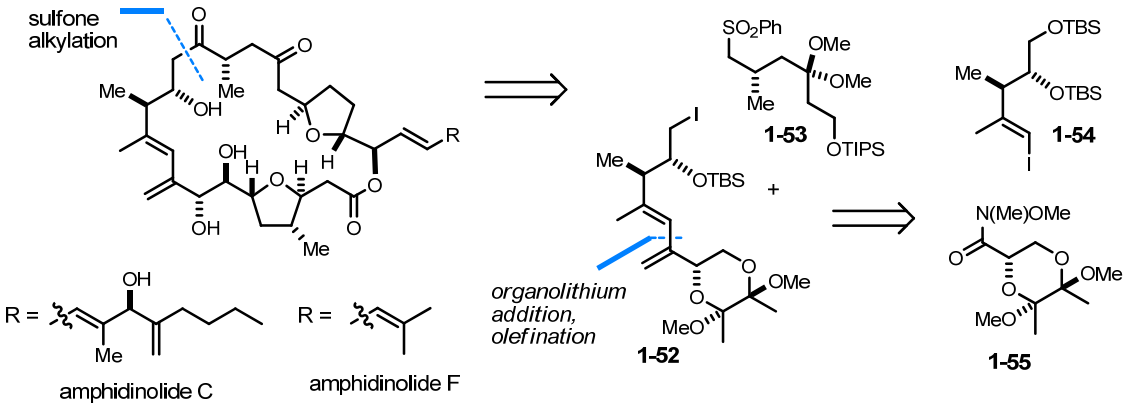
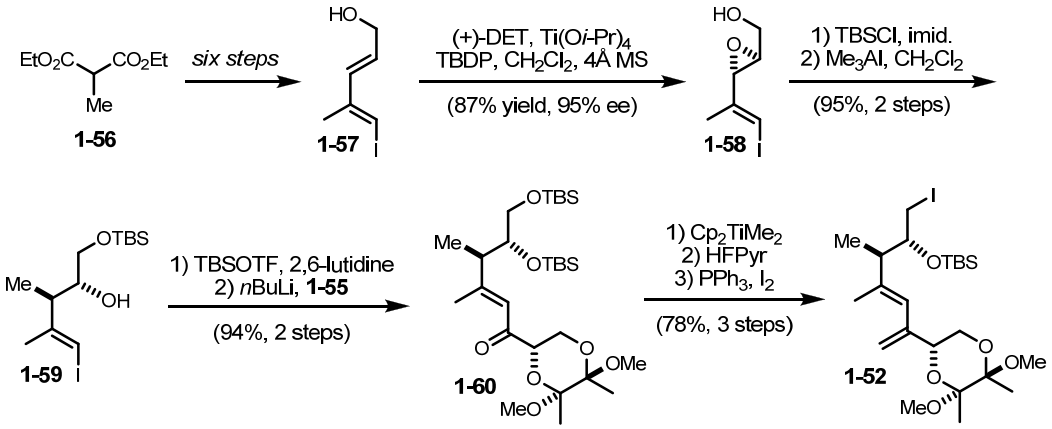


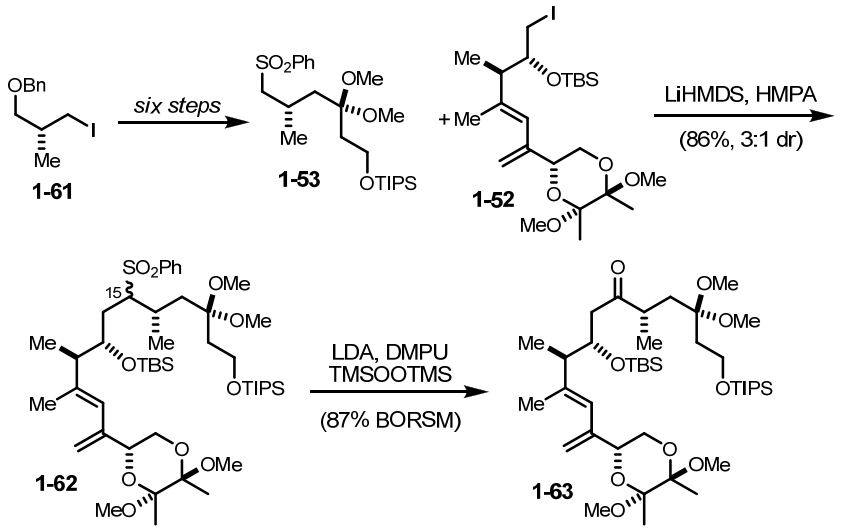
Figure 1.7. Carter's retrosynthesis of the C(7)-C(20) fragment

In the forward direction, malonate **1-56** was elaborated into iodoalkene **1-57** via a six step sequence, followed by Sharpless epoxidation to form epoxide **1-58** in 87% yield and 95% *ee* (Scheme 1.11). To install the methyl group in a stereoselective manner, the alcohol was protected as the TBS ether before being treated with trimethylaluminum to give alcohol **1-59** in 95% yield as a single diastereomer. To complete the C(9)-C(11) diene, the secondary alcohol **1-59** was protected prior to lithium-halogen exchange of the iodoalkene and addition of the resulting anion into Weinreb amide **1-55**, to give enone **1-60**. Subsequent olefination via the Petasis reagent completed formation of the diene subunit, and the primary TBS ether was converted to the corresponding iodide **1-52** for fragment coupling.



Scheme 1.11. Synthesis of the C(7)-C(14) fragment via metallation/olefination

To complete the synthesis of the fragment, the C(15)-C(20) subunit **1-53** was prepared from iodide **1-61** via a six-step procedure (Scheme 1.12). The sulfone **1-53** was then lithiated and treated with iodide **1-52**, resulting in an 86% yield of an inconsequential 3:1 ratio of diastereomers at C(15). The sulfone (**1-62**) was then converted to the desired ketone oxidation state by treatment with TMS peroxide and LDA in THF/DMPU, completing the synthesis of the C(7)-C(20) fragment (**1-63**) of amphidinolides C and F.



Scheme 1.12. Carter's completion of the C(7)-C(20) fragment

Section 1.4.3 – Figadére Synthesis of the C(1)-C(9) Fragment

Most recently, Figadére reported his synthesis of the C(1)-C(9) fragment, again taking advantage of the popular cross-coupling disconnection between the C(9)-C(10) bond and a macrolactonization to form the ring (Figure 1.8).[14c] To form the C(1)-C(9) fragment he used a vinylogous Mukaiyama aldol between chiral aldehyde **1-66** and siloxyfuran **1-67** followed by a C-glycosylation with *N*-acetyl-oxazolidinethione **1-68**.

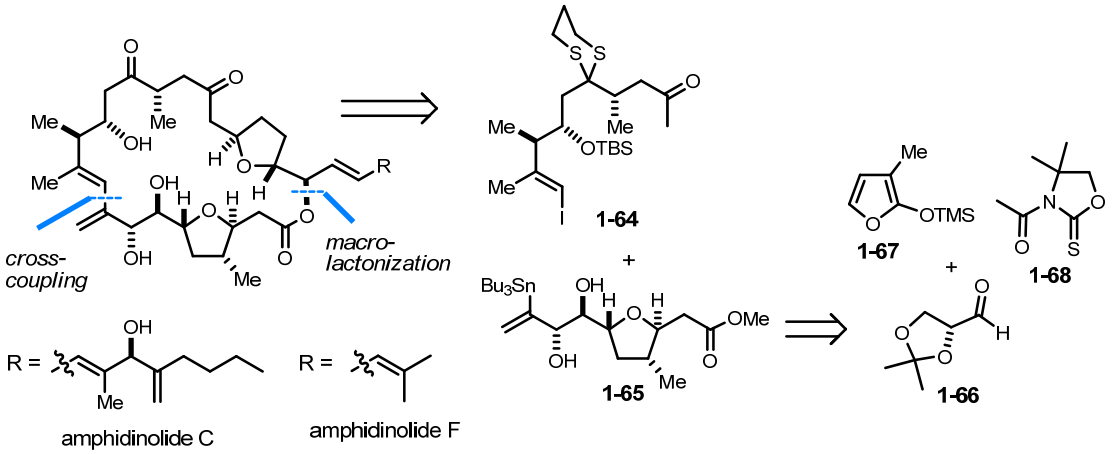
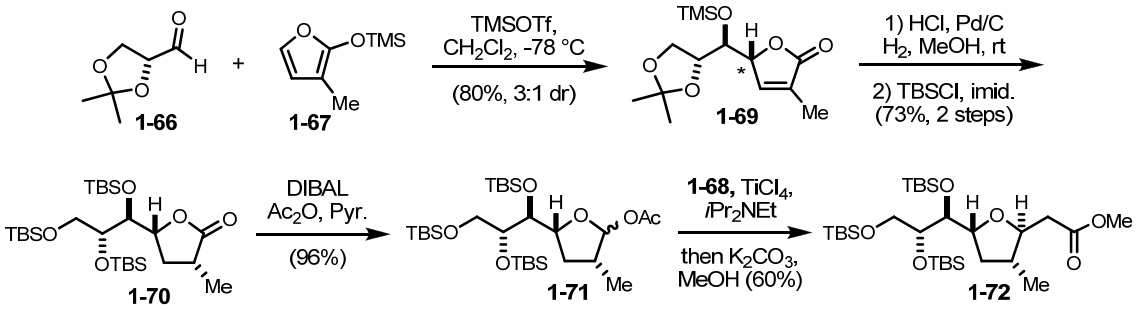


Figure 1.8. Figadére's retrosynthesis of the C(1)-C(9) fragment

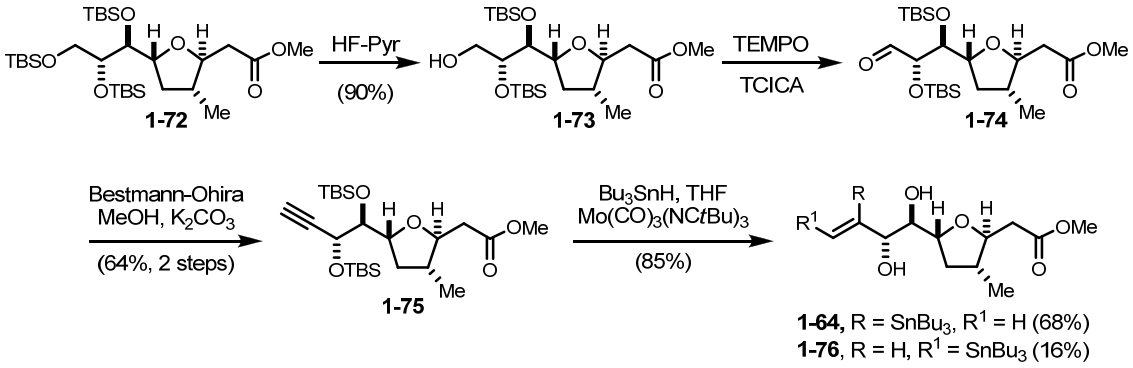
Figadére's synthesis began with a TMSOTf catalyzed vinylogous aldol reaction between siloxyfuran **1-67** and aldehyde **1-66**, resulting in a 3:1 ratio of diastereomers of **1-69** in 80% yield (Scheme 1.13). Catalytic hydrogenation of the major diastereomer of **1-69** in

acidic methanol afforded a triol which was converted to the tri-TBS ether **1-70** in 73% yield over 2 steps. Lactone **1-70** was then converted into **1-71** by one-pot reduction and acylation in 96% yield, and was then C-glycosylated with the titanium enolate of oxazolidinethione **1-72**.



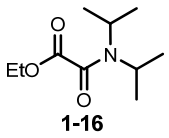
Scheme 1.13. Figadére's synthesis of the C(1)-C(9) fragment

With all the stereogenic centers installed, attention was directed towards functionalization of the left side of the fragment for cross-coupling (Scheme 1.14). The primary TBS ether **1-72** was selectively cleaved using HF·pyridine, and oxidized with TEMPO using trichloroisocyanuric acid as a co-oxidant. The resulting aldehyde **1-74** was converted into alkyne **1-75** using the Bestmann-Ohira reagent in 64% yield, and a regioselective hydrostannylation afforded the stannane **1-64** as a 4:1 mixture of separable regioisomers.



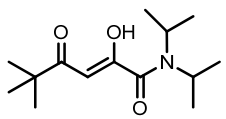
Scheme 1.14. Figadére's functionalization of the C(1)-C(9) fragment

Section 1.5 – Experimental



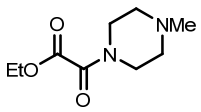
1-16

To a solution of di-*iso*-propylamine (**1-15**) (1.40 mL, 10 mmol, 1 eq) and triethyl amine (1.39 mL, 10 mmol, 1 eq) in CH_2Cl_2 (25 mL) at 0 °C was added ethyl oxalyl chloride (1.12 mL, 10 mmol, 1 eq). The ice bath was removed and the reaction was allowed to warm to rt and stirred for 16 h. The resulting heterogeneous mixture was quenched with a solution of half saturated $NaHCO_3$ (100 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL), then the organic phases were combined and washed with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford **1-16** as an orange oil (2.01 g, 9.5 mmol, 95%) which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.28 (q, *J* = 7.0 Hz, 2H), 3.67 (quin, *J* = 6.6 Hz, 1H), 3.48 (quin, *J* = 6.6 Hz, 1H), 1.42 (d, *J* = 7.0 Hz, 6H), 1.33 (t, *J* = 7.0 Hz, 3H), 1.22 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 163.4, 161.6, 61.6, 50.6, 45.9, 20.6, 20.0, 14.0.



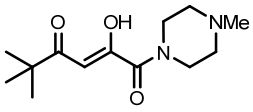
1-17

A 0 °C solution of *t*-BuOK (1.79 g, 16 mmol, 2 eq) in THF (30 mL) was added to a 0 °C solution of pinacolone (1.0 mL, 8 mmol, 1 eq) and **1-16** (4.00 g, 20 mmol, 1 eq) in THF (20 mL) via cannula. Upon completion of the addition, the solution was warmed to rt and stirred for 16 hours before treated with 20 mL of 1N HOAc in CH_2Cl_2. After stirring for 30 minutes the slurry was filtered through a pad of celite and the filtrate was concentrated under reduced pressure to afford **1-17** as an orange solid (2.04 g, 93%), which was used without further purification R_f 0.10 (66% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (s, 0.75H), 4.10 (quin, *J* = 6.6 Hz, 0.25H), 3.96 (s, 0.5H), 3.93 (quin, *J* = 6.6 Hz, 0.75H), 3.53-3.43 (m, 1H), 1.44 (d, *J* = 7.0 Hz, 4.75 H), 1.40 (d, *J* = 7.0 Hz, 1.25H), 1.23 (d, *J* = 7.0 Hz, 1.25H), 1.20 (d, *J* = 7.0 Hz, 4.75H), 1.18 (s, 7.25 H), 1.15 (s, 1.75H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 187.5, 165.4, 94.1, 50.2, 49.8, 47.9, 46.0, 45.9, 38.8, 27.3, 27.2, 25.9, 20.8, 20.4, 20.2, 19.9.



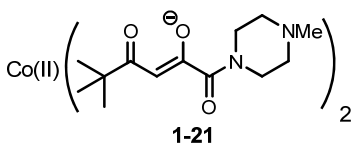
1-19

To a solution of *N*-methylpiperazine (**1-18**) (22.2 mL, 200 mmol, 1 eq) and triethyl amine (27.8 mL, 200 mmol, 1 eq) in CH_2Cl_2 (200 mL) at 0 °C was added ethyl oxalyl chloride (22.4 mL, 200 mmol, 1 eq). The ice bath was removed and the reaction was allowed to warm to rt and stirred for 16 h. The resulting heterogeneous mixture was quenched with a solution of half saturated $NaHCO_3$ (200 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL), then the organic phases were combined and washed with brine (200 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford **1-19** as an orange oil (39.6 g, 99%) which was used without further purification. R_f 0.10 (66% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.30 (q, J = 7.2 Hz, 2H), 3.64-3.61 (m, 2H), 3.43-3.41 (m, 2H), 2.42-2.40 (m, 4H), 2.29 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 160.3, 62.3, 55.1, 54.3, 46.2, 41.4, 14.2; HRMS m/z calcd for $C_9H_{16}N_2O_3$ [M+H$^+$]: 200.1161, found: 200.1163.



1-20

A 0 °C solution of *t*-BuOK (4.48 g, 40 mmol, 2 eq) in THF (100 mL) was added to a 0 °C solution of pinacolone (2.50 mL, 20 mmol, 1 eq) and **1-19** (4.00 g, 20 mmol, 1 eq) in THF (20 mL) via cannula. Upon completion of the addition, the solution was warmed to rt and stirred for 16 hours before treated with 40 mL of 1N HOAc in CH_2Cl_2. After stirring for 30 minutes the slurry was filtered through a pad of celite and the filtrate was concentrated under reduced pressure to afford **1-20** as an orange syrup (4.32 g, 85%), which was used without further purification. R_f 0.15 (5% MeOH/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97 (s, 1H), 3.66-3.58 (m, 4H), 2.46-2.43 (m, 4H), 2.31 (s, 3H), 1.19 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.9, 185.3, 163.8, 95.3, 55.1, 54.3, 45.8, 41.6, 27.2; HRMS m/z calcd for $C_{13}H_{22}N_2O_3$ [M+H$^+$]: 254.1630, found: 254.1644.



1-21

To a solution of nmp ligand **1-20** (2.54 g, 10 mmol, 2 eq) in benzene (50 mL) was added Co(II) ethylhexanoate (65 wt% solution, 1.88 M in mineral spirits, 5 mmol, 1 eq). The reaction was stirred for 30 min before water (720 mg, 40 mmol, 4 eq) was added and the reaction stirred for 16 h at room temperature. Hexanes (200 mL) was added and the tan solids were separated by centrifugation. The solvent was decanted and the catalyst was washed by the addition of hexanes. This slurry was centrifuged again, and the solids were washed an additional three times. The product was then transferred to a flask and the remaining solvent was removed under reduced pressure to afford the $Co(nmp)_2$ catalyst **1-21** (2.69 g, 95%) as a tan solid. LRMS: *m/z* $[M + Na]^+$ calc. for $C_{78}Co_3H_{126}N_{12}NaO_{18}$: 1718.72; found: 1718.8; combustion analysis: calc. for $Co(nmp)_2 \cdot (H_2O)_{3.5}$, C 49.68, H 7.86, N 8.91; found: C 49.58%, H 7.53%, N 8.84%. Based on crystal structures we have previously obtained of related compounds,[20] we believe that the structure of the catalyst is similar, comprising of three cobalt atoms and six ligands per unit cell. Two outer cobalt atoms, each surrounded by three ligands, flank an inner cobalt atom. Inclusion of water in the crystal structure is likely, as elemental analysis of samples after prolonged drying over P_2O_5 in a drying pistol results in data that requires 3.5 water molecules per cobalt atom.

Section 1.6 - References

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Chapter 2 – First Generation Approach to Amphidinolide C

Section 2.1 – Initial Retrosynthetic Approach

Given the size and complexity of amphidinolide C (**1-24**), we decided that the most prudent course of action was to pursue a highly convergent route that would break the molecule into several pieces. In so doing, we would limit the number of linear steps that material would be carried through, and also ensure that potential problems encountered in the later stages of the synthesis could be easily addressed by modification of a fragment.

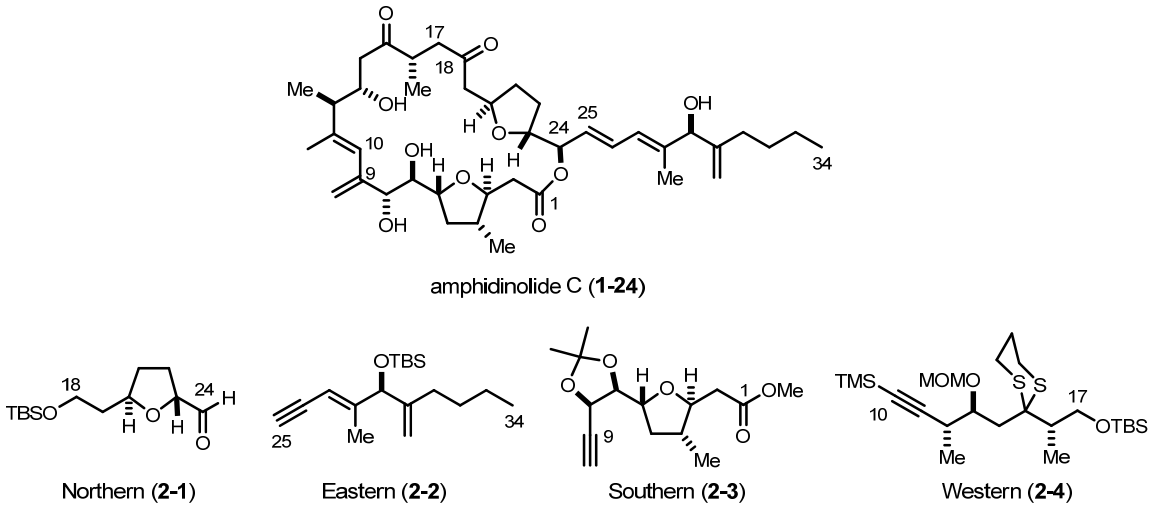


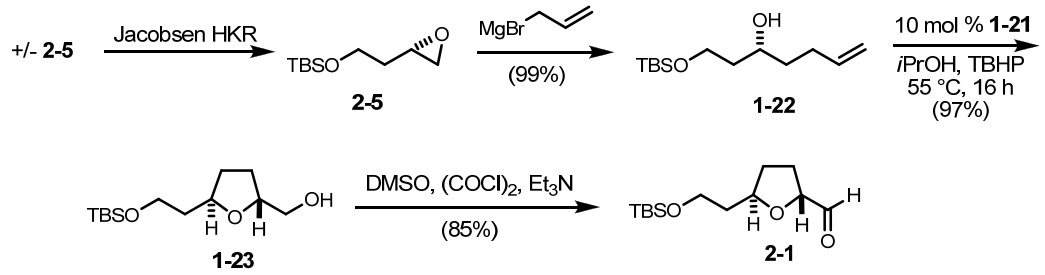
Figure 2.1. Initially planned fragments of amphidinolide C

Our initial retrosynthetic disconnections included a macrolactonization, which is a mild and reliable method of closing macrocyclic natural products,[1] and a dithiane alkylation to form the C(17)-C(18) bond (Figure 2.1). The North-Eastern half of amphidinolide C was envisioned to be formed via an asymmetric alkynylation of aldehyde **2-1** with alkyne **2-2** to form the C(24)-C(25) bond. The South-Western fragment would utilize a Stille cross-coupling to form the C(9)-C(10) bond, which has been thoroughly studied by F*ü*rstner during his total synthesis of amphidinolides G and H.[2] The resulting four pieces from these disconnections were THF-aldehyde **2-1**, ene-yne **2-2**, substituted *trans*-THF **2-3**, and alkyne **2-4**, henceforth referred to as the Northern, Eastern, Southern and Western fragments of amphidinolide C.

Section 2.2 – Synthesis of the Northern-Eastern Fragment

Section 2.2.1 – Formation of the *trans*-THF Ring via Oxidative Cyclization

The synthesis began with the opening of known epoxide **2-5** (which can be accessed on large scale via Jacobsen's hydrolytic kinetic resolution procedure)[3] with allyl Grignard to provide the cyclization precursor (**1-22**) in near quantitative yield (Scheme 2.1). Using our second generation water soluble catalyst $Co(nmp)_2$ (**1-21**) and previously optimized conditions (see section **1.1.3**) the *trans*-THF ring **1-23** was formed in 97% yield, utilizing filtration as the purification method to remove the cobalt residues.



Scheme 2.1. Synthesis of the Northern fragment via Mukaiyama oxidative cyclization

Synthesis of the Northern fragment was completed by oxidation of the primary alcohol (**1-23**) to THF aldehyde **2-1** using Swern conditions (oxalyl chloride/DMSO) in 85% yield, thereby setting the stage for coupling to the Eastern fragment.

Section 2.2.2 – First Generation Synthesis of the Eastern Fragment

The Eastern fragment was initially envisioned to be formed via a concise route involving the selective methylation of diyne **2-6** (Figure 2.2), which would be formed by asymmetric alkynlation of 2-methylenehexenal[4] (**2-7**) with triethylsilyldiyne (**2-8**).

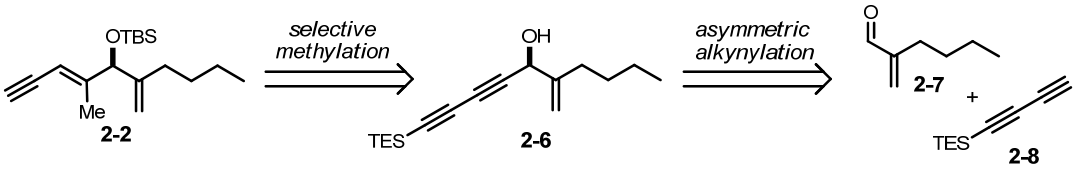
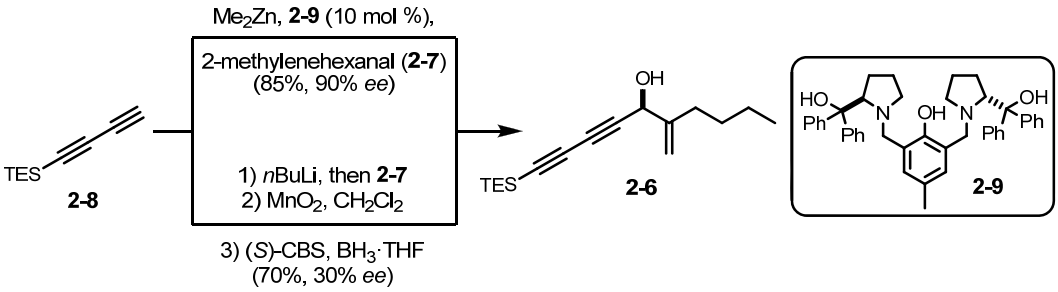


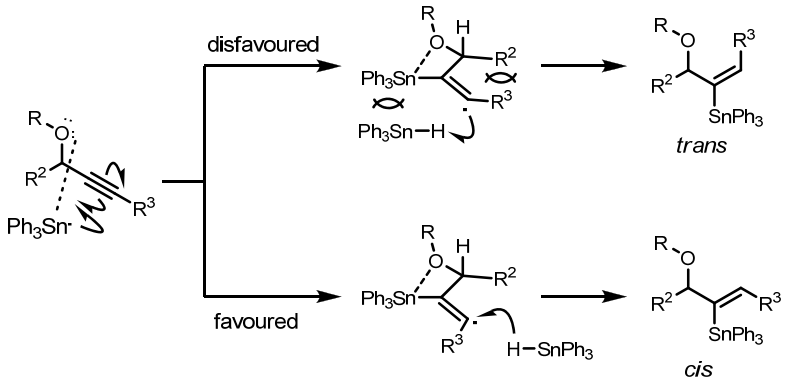
Figure 2.2. Initial retrosynthetic analysis of the Eastern fragment **2-2**

Initial results utilizing the Carreira alkynlation reaction[5] were derailed by inconsistent conversions and yields, so the *ee* of the product **2-6** was never determined. Fortuitously, the Trost procedure[6] provided a much more reliable and reproducible method of forming **2-6** in a respectable 85% yield and 90% *ee* as determined by Mosher ester analysis (Scheme 2.2).[7] At the time, this was the first reported example of a diyne being used in the Trost procedure, but other reports have been published since.[8] Attempts to access **2-6** utilizing an alternative 3-step procedure of non-selective addition, oxidation using MnO_2, and reduction using a chiral reducing reagent gave disappointing results, where 30% was the highest *ee* obtained (using CBS reagent). As we later realized, this phenomenon is well documented throughout the literature.[9] This is fairly surprising, as these diyne ketones look to be model substrates for asymmetric reducing reagents that rely on size differential of the ketone substitutions.



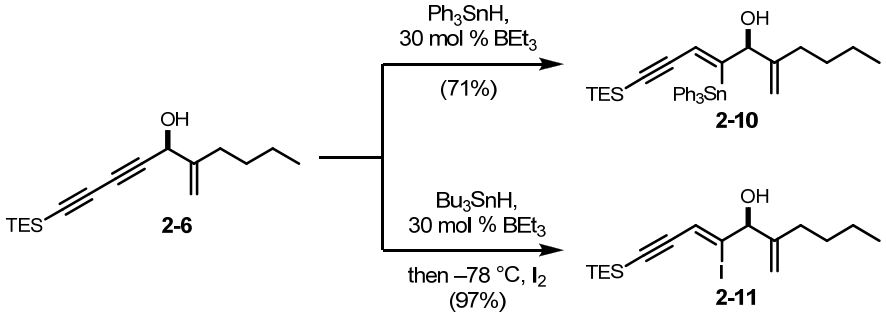
Scheme 2.2. Stereoselective synthesis of diyne **2-6**

All that remained to complete the Eastern fragment was selective methylation at one of the four positions along diyne **2-6**. To accomplish this transformation we utilized a procedure described by Hale in 2005,[10] where he reported the hydroxyl-directed radical stannylation of propargyl alcohols which proceeded through a sterically unhindered transition state to form a *cis*-stannane (Scheme 2.3). In his pioneering work, Hale reports that use of the smaller and less expensive tributyltinhydride in the place of the bulky triphenyltinhydride resulted in decreased regioselectivity, leading to a mixture of *cis*- and *trans*- products.



Scheme 2.3. Hale's mechanism for hydroxyl-directed radical stannylation

Our substrate performed admirably in the stannylation reaction, resulting in a 71% yield of the triphenyl stannane **2-10** as a single regioisomer (Scheme 2.4). Contrary to Hale's initial report, we found that reactions using tributyltin hydride maintained perfect regioselectivity, while proceeding in an improved yield. Not only did reaction with the tributyltinhydride result in a higher yield, it also facilitated a mild and quantitative conversion of the stannane to the iodide by treatment with I_2 at low temperatures. The result was a one-pot conversion of diyne **2-6** to iodide **2-11** using readily available Bu_3SnH and sub-stoichiometric amounts of a trialkyl borane in an impressive 97% yield.

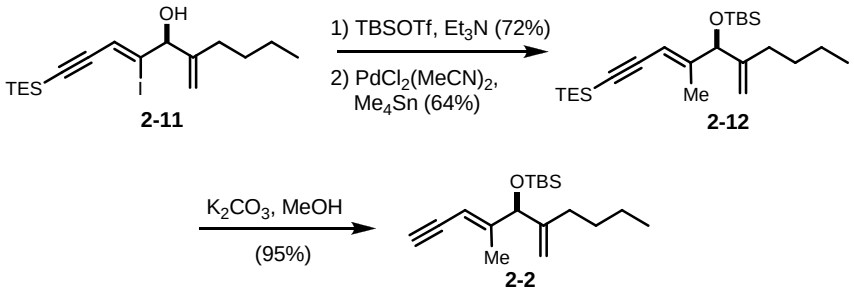


Scheme 2.4. Hydroxyl-directed radical stannylation of diyne **2-6**

To the best of our knowledge, this is the first reported example of a selective stannylation/iodination sequence on a 5-hydroxy-1,3-diyne, and this procedure provides an attractive alternative to accessing these types of highly unsaturated systems.[11]

A surprisingly difficult TBS protection of alcohol **2-11** was accomplished using TBSOTf when milder conditions failed, was followed by a Stille cross coupling using tetramethyltin to afford **2-12** in a modest 46% yield over 2 steps (Scheme 2.5). The

terminal alkyne was revealed under basic conditions ($MeOH/K_2CO_3$) thus completing the synthesis of the Eastern fragment (**2-2**) in a concise 6 steps and 34% overall yield from commercially available hexanal.

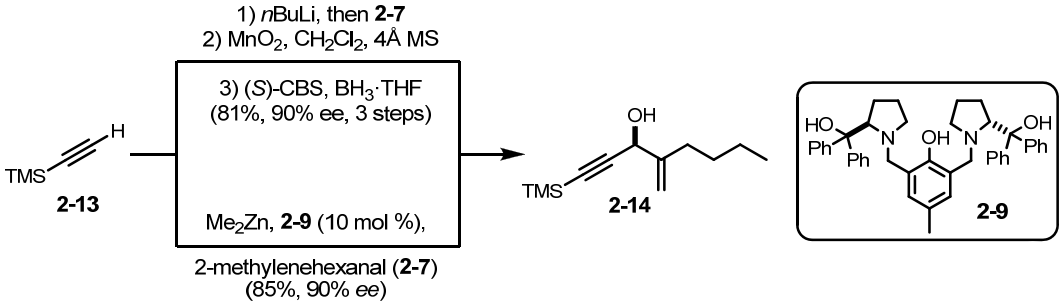


Scheme 2.5. Completion of the Eastern fragment **2-2**

While we were pleased with the relatively short and high yielding synthesis of **2-2**, difficulties were encountered upon scale-up of the synthesis to access gram quantities of the material. Although the Trost asymmetric alkynylation reaction performed exceptionally well on small scale to provide **2-6**, difficulties with scalability and the prohibitively high cost of dimethyl zinc urged us to pursue a route that was not reliant on asymmetric alkynlation chemistry.

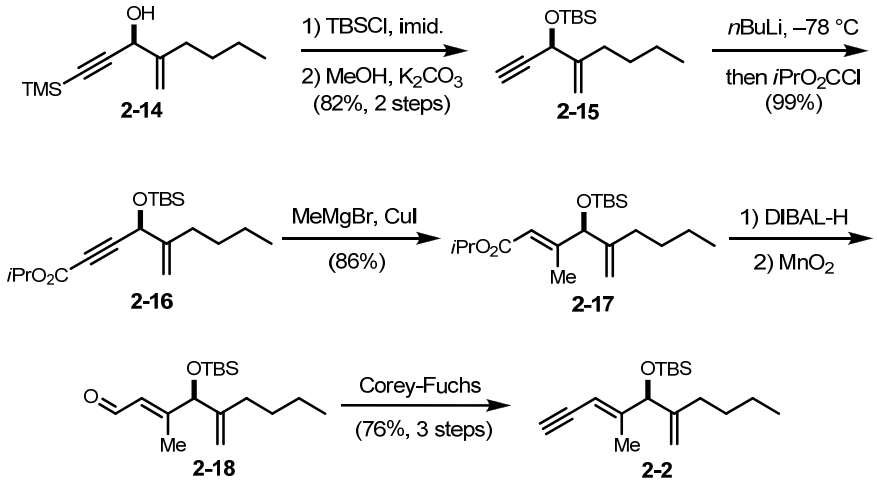
Section 2.2.3 – Second Generation Synthesis of the Eastern Fragment

Although attempts to access diyne **2-6** via asymmetric reduction of the parent ketone were thwarted by inexplicably low *ee*'s, the reduction of propargyl alcohols using the same reducing reagents has been reported to proceed with *ee*'s in the 90's. Thus, our second generation route also started with 2-methylenehexenal **2-7** which was elaborated through a three-step procedure consisting of a racemic acetylide addition, oxidation of the resulting alcohol to the ketone, and subsequent CBS reduction (Scheme 2.6). Alcohol **2-14** was obtained in a 90% *ee*, even while using a high catalyst loading of the CBS reagent (10 mol %). This level of selectivity is relatively low when compared to many other CBS reductions,[12] but is consistent with other reported asymmetric reductions of propargyl ketones.[13] Alcohol **2-14** could also be accessed via the Trost-asymmetric alkynylation procedure, resulting in a comparable 90% *ee* and 85% yield.



Scheme 2.6. Synthesis of propargyl alcohol **2-14**

The secondary alcohol was then protected as a TBS ether (TBSCl/imidazole) and the alkyne was deprotected using basic conditions ($MeOH/K_2CO_3$) to give propargyl ether **2-15** (Scheme 2.7). From this point, a second alkyne could have been added to converge the material with the first generation stannylation route, but the relatively low yield of the subsequent steps compelled us to install the methyl group using an alternative method. Ultimately, we discovered that the conversion of the propargyl ether to a Michael acceptor followed by treatment with methyl Grignard provided **2-17** via a copper catalyzed Michael addition in an excellent 85% yield over 2 steps. Having installed the desired methyl group regioselectivly, the desired terminal alkyne was formed via 3-step conversion of the isopropyl ester to the aldehyde (DIBAL-H, then MnO_2), followed by Corey-Fuchs conditions (CBr_4/PPh_3, then *n*BuLi) to afford alkyne **2-2** in 76% yield.



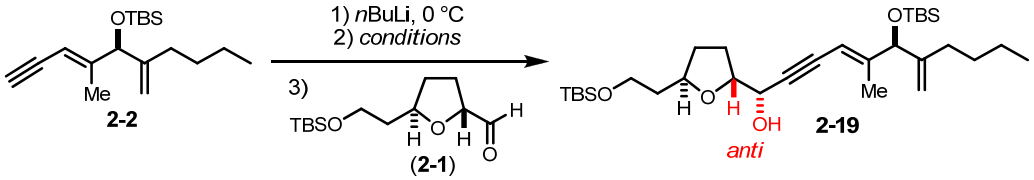
Scheme 2.7. Second generation synthesis of the Eastern fragment **2-2**

Overall, the second generation route towards the Eastern fragment was considerably longer (11 steps) but higher yielding (46% overall yield), but most importantly, provided access to multi-gram quantities of **2-2**.

Section 2.2.4 – Coupling of the North and Eastern Fragments

With a cost effective and scalable route to both the Northern and Eastern fragments and grams of material in hand, efforts were made to couple the two fragments stereoselectively. Originally, it was envisioned that an asymmetric method could be used to enhance the diastereoselectivity of the addition, given our previous success with this strategy.[14] Unfortunately, after initial attempts proved unsuccessful using both the Trost and Carreira alkynylation methods, we turned to traditional substrate controlled diastereoselective additions (Table 2.1). In this regard, a variety of solvents, additives and counter ions were explored. In each case, the desired *syn* diastereomer was never observed as the major product, which was indicative of non-chelation Felkin-Ahn addition. Also, attempts to oxidize the secondary alcohol to the ketone and perform an asymmetric reduction resulted in poor dr's.[15]

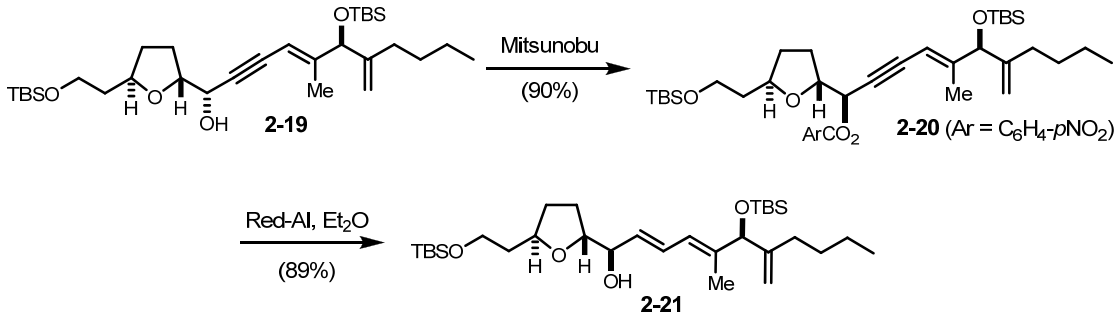
Table 2.1. Coupling of ene-yne **2-2** and THF-aldehyde **2-1**



entry	conditions	yield (%)[a]	*anti*:*syn*
1	toluene, -78 °C	95	1.5:1
2	DME, -78 °C	83	2.5:1
3	THF, -78 °C	87	3:1
4	Et_2O, -78 °C	98	4:1
5	Et_2O, 3 eq LiCl,-78 °C	86	5:1
6	toluene, Et_2AlCl, -78 °C	68	1.5:1
7	Et_2O, $Ti(OiPr)_3Cl$, -78 °C	72	2:1
8	MTBE, -78 °C	92[b]	8:1
9	MTBE, -90 °C	93[b]	20:1

a) 0.1 mmol scale b) 2.0 mmol scale

Initial reactions in toluene, dimethoxyethane and THF (Table 2.1, entries 1-3) provided at best a 3:1 selectivity for the *anti* diastereomer **2-19**. Performing the reaction in diethyl ether provided a modest increase in dr (Table 2.1, entry 4), while adding 3 or more equivalents of dry LiCl increased selectivity to 5:1 (Table 2.1, entry 5). Transmetallation of the acetylide to the aluminum or titanium derivative has been shown to increase dr in alkynylation reactions of this type;[16] however a drop in selectivity and yield was observed (Table 2.1, entries 6-7). After a seemingly endless number of other conditions were screened, we were relieved to find treatment of the lithium acetylide of **2-2** with THF-aldehyde **2-1** in dry methyl-*tert*-butyl ether (MTBE) resulted in a promising 8:1 dr. Ultimately, it was discovered that cooling the reaction to -90 °C prior to aldehyde addition resulted in an increase in selectivity to 20:1 for **2-19** (Table 2.1, entries 8-9), which proved reproducible over multiple runs on gram scale. It was later discovered that the purity of the starting materials was essential for obtaining a high dr, and as such the aldehyde **2-1** was purified by column chromatography immediately before use in the coupling reaction.



Scheme 2.8. Completion of the North-Eastern fragment **2-21**

To complete the synthesis of the North-Eastern fragment (**2-21**), the alcohol at C(24) was inverted using standard Mitsunobu conditions (DIAD, 4-nitrobenzoic acid, PPh_3) to give the desired *syn* configuration in 90% yield (Scheme 2.8). Finally, treatment of **2-20** with Red-Al concurrently removed the artifact benzoyl group and reduced the alkyne via a *trans*-selective hydro-alumination to provide **2-21** in 89% yield.

Section 2.3 – Synthesis of the Western Fragment

Section 2.3.1 - Formation of Western Fragment

The originally envisioned disconnection of the Western fragment **2-4** was an alkylation of epoxide **2-22** with dithiane **2-23** which can be accessed in expedient fashion from commercially available Roche ester **2-24** (Figure 2.3).

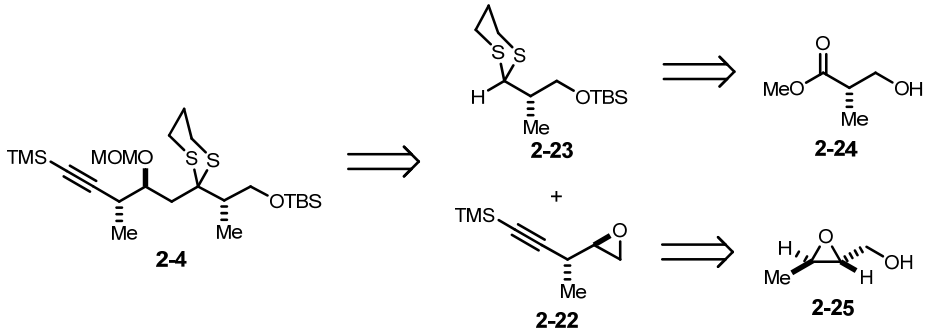
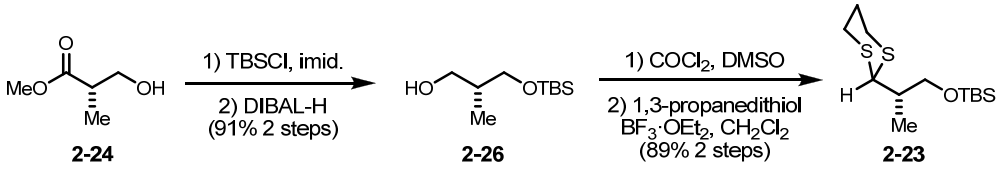


Figure 2.3. Further retrosynthesis of the Western fragment **2-4**

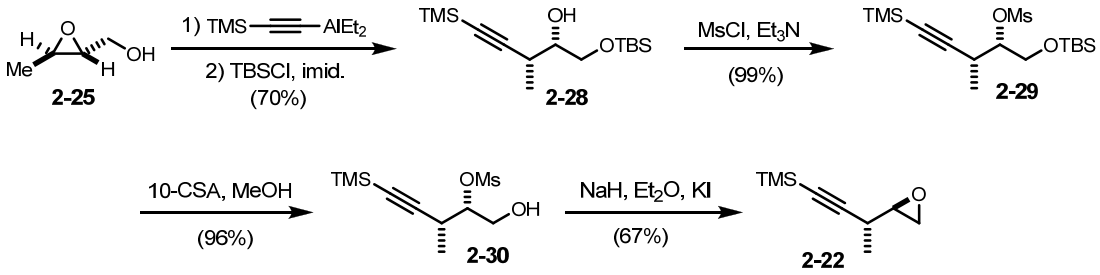
First, alcohol **2-24** was protected as a TBS ether using standard conditions (TBSCl, imidazole), followed by reduction to alcohol **2-26** in 91% yield over 2 steps (Scheme 2.9). The alcohol was then converted into the corresponding aldehyde, followed by dithianation using 1,3-propanedithiol in the presence of catalytic $BF_3{\cdot}OEt_2$ to form dithiane **2-23** in 89% yield over 2 steps.



Scheme 2.9. Preparation of the dithiane **2-23**

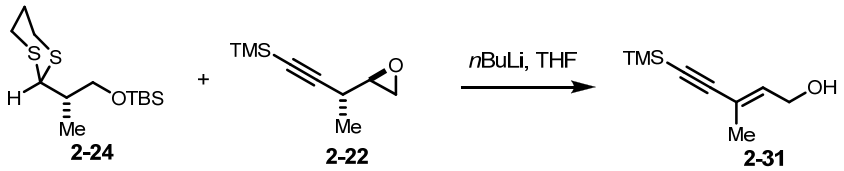
The coupling partner was accessed in five steps from known Sharpless epoxide **2-25**[17] (Scheme 2.10). Epoxide **2-25** was opened using TMS acetylene to give the diol as a 3:1 mixture of regioisomers, the primary alcohol of which was selectively protected

(TBSCl/imidazole) and separated via column chromatography to give **2-28** as a single diastereomer in 70% yield. The secondary alcohol was then converted to mesylate **2-29** (MsCl/Et_3N) followed by acidic removal of the TBS group (10-CSA) to give the epoxide precursor **2-30** in 95% yield over 2 steps. Formation of the epoxide proved to be a fickle procedure, complicated by the volatility of the product epoxide (**2-22**, boiling point ~80-100 °C). Eventually, it was found that the addition of excess KI facilitated the formation of the epoxide in 67% yield, presumably by reversible ion exchange to give the potassium alkoxide, which would be more likely to displace the mesylate.



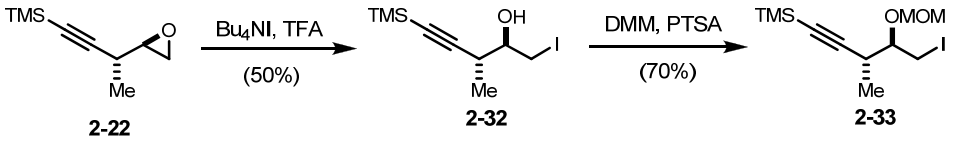
Scheme 2.10. Preparation of the epoxide **2-22**

Unfortunately, our initial attempts at alkylating the epoxide **2-22** with dithiane **2-24** were immediately met with failure. The result of the alkylation was instantaneous and quantitative deprotonation of the epoxide to give unsaturated alcohol **2-31** (Scheme 2.11).



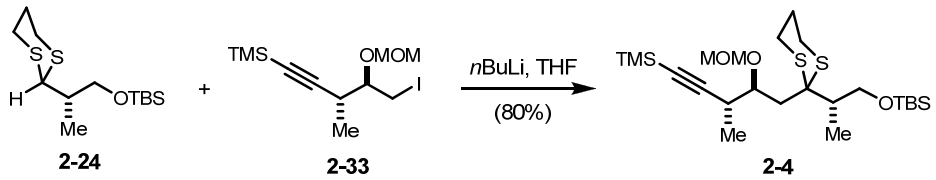
Scheme 2.11. Failed alkylation attempts of epoxide **2-22**

In an attempt to circumvent the acidity of the epoxide, we converted **2-22** into iodohydrin **2-32** (Bu_4NI, TFA) in a modest 50% yield, followed by protection of the resulting alcohol as the MOM ether (DMM, PTSA) in 70% yield (Scheme 2.12).



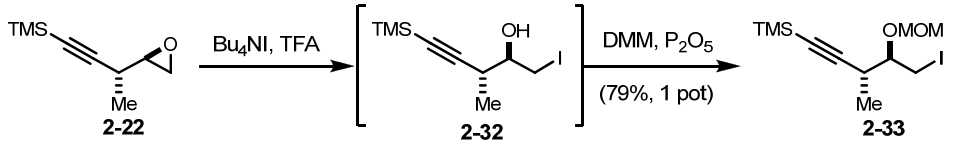
Scheme 2.12. Conversion of epoxide **2-22** to protected iodohydrin **2-33**

To our relief, protected iodohydrin **2-33** underwent clean alkylation by dithiane **2-24** to furnish the carbon backbone of the Western fragment (**2-4**) in 80% yield (Scheme 2.13).



Scheme 2.13. Completion of the Western fragment **2-4**

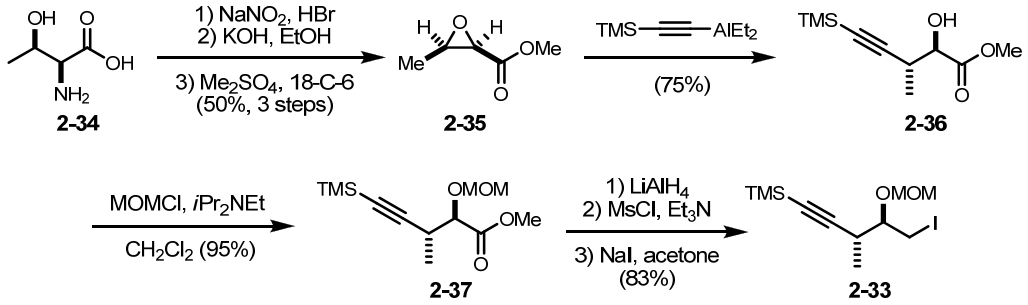
Our excitement over the successful formation of **2-4** was tempered by the terrible yield of the conversion of epoxide **2-22** to protected iodohydrin **2-33** (2 steps, 35% yield), and the difficulties associated with the formation and handling of epoxide **2-22**. The epoxide opening was eventually streamlined to a one pot procedure (Bu_4NI/TFA then DMM/P_2O_5), which avoided isolation of the unstable unprotected iodohydrin, and improved the yield of the procedure to 79% (Scheme 2.14). However, the procedure to form the highly volatile epoxide **2-22** proved to be too inconsistent upon scale-up to be a viable route towards the required amount of material.



Scheme 2.14. Improvement of the epoxide opening procedure to a one-pot reaction

A second synthesis was designed to access protected iodohydrin **2-33**, starting from a commercially available and inexpensive amino acid, threonine (Scheme 2.15). Using a literature procedure,[18] **2-34** was converted to epoxide **2-35** (3 steps, 50% overall yield), which was opened with TMS acetylene to give **2-36** as a single diastereomer in 75% yield. Protection of the secondary alcohol (MOMCl, *i*Pr_2NEt) to give **2-37**, followed by

reduction of the ester to the alcohol ($LiAlH_4$) and 2-step conversion to the corresponding iodide (MsCl *then* NaI) provided the iodohydrin **2-33** via a more reliable and scalable procedure.

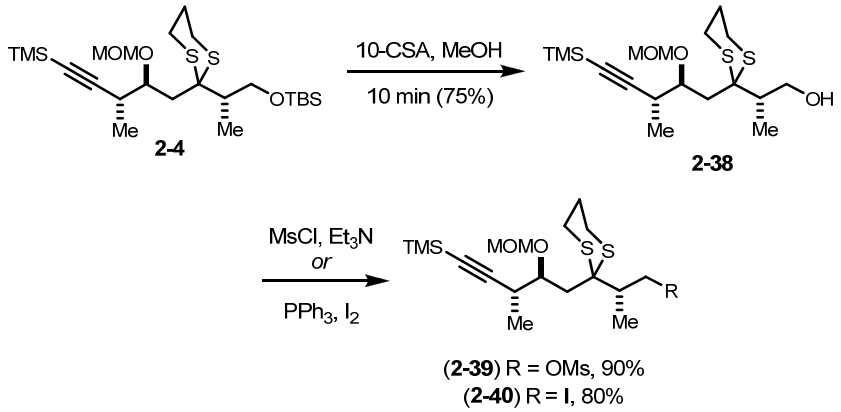


Scheme 2.15. Alternative synthesis of protected iodohydrin **2-33**

Section 2.3.2 – Functionalization of the Western Fragment for Assembly

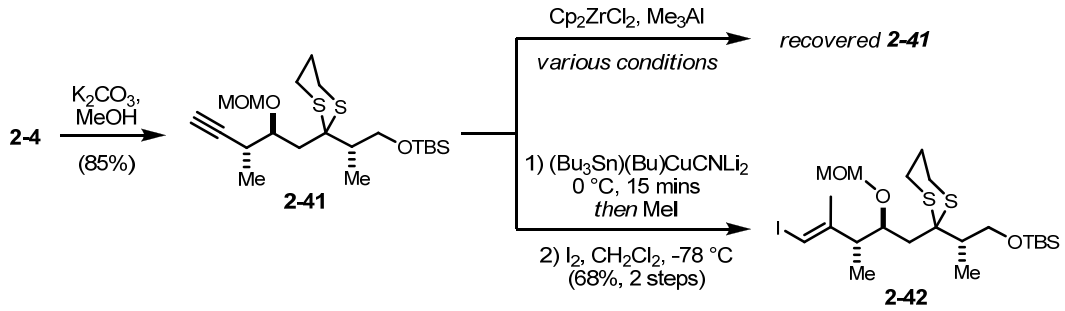
Although the majority of the Western fragment material was stored as the stable and fully protected **2-4**, we decided to test functionalization of both ends for eventual coupling to both the North-Eastern and Southern fragment. The order of fragment assembly had not yet been determined, so we felt that being able to functionalize both sides of the fragment, in either order, would provide valuable flexibility for fragment assembly.

Selective removal of the primary TBS despite the presence of the sensitive MOM group was achieved using a carefully monitored acidic reaction (10-CSA, MeOH, 10 min) to give alcohol **2-38** (Scheme 2.16). This alcohol could then be converted to an appropriate leaving group, either a mesylate (**2-39**) in 91% yield, or an iodide (**2-40**) in a 90% yield. The hope was that this leaving group could be displaced by the North-Eastern fragment to form the C(17)-C(18) bond of amphidinolide C.



Scheme 2.16. Functionalization of the right side of the Western fragment (**2-4**)

We anticipated difficulties with carbo-metalation of the alkyne on the left side of **2-4**, as the literature evidence for reaction of such hindered alkynes was sparse.[19] Indeed, any attempts at Negishi's zirconium catalyzed carboalumination[20] (Cp_2ZrCl_2, Me_3Al) of **2-41** resulted in recovered starting material, including using stoichiometric zirconocene dichloride, forcing conditions (refluxing DCE), and water accelerated carbo-metalation (Scheme 2.17). [21] Presumably, the steric bulk of the substrate prevented the di-metallic species formed *in situ* from reacting with the alkyne.



Scheme 2.17. Functionalization of the left side of the Western fragment (**2-4**)

Our attention was turned to alternative methods, and we found success using higher order cuprates in the copper catalyzed stannylation of alkynes. Initial reactions utilizing cuprate $(Bu_3Sn)(Bu)CuCNLi_2$ were performed at −78 °C, resulting in acceptable yields (ca. 70% BORSM) and 10:1 selectivity for the desired regioisomer. To improve the selectivity, the metalation reaction was be run at 0 °C, which afforded a single regioisomer as the product, while maintaining a respectable yield of 68% (78% BORSM).[22] The reaction

never went to completion, due to the well documented side reaction involving the deprotonation of the acetylene by the relatively basic metalation reagent.[23] To accomplish the eventual cross coupling reaction, the stannane could be quantitatively converted to the corresponding iodide **2-42** by titration with I_2 in CH_2Cl_2 at -78 °C. Having accomplished these transformations, we believed that we had given ourselves considerable flexibility with regard to the order that the fragments could be assembled.

Section 2.4 – Synthesis of the Southern Fragment

Section 2.4.1 – Synthesis of the *trans*-THF ring via Epoxide Opening

We viewed the formation of the methyl substituted *trans*-THF (**2-43**) ring as the key reaction in the completion of the Southern fragment, and envisioned the use of our improved $Co(nmp)_2$ in the oxidative cyclization as the key step (Figure 2.4). The cyclization precursor in this case would be methyl substituted pentenol **2-44**, which at first glance appeared to be a straightforward piece to make, but upon further research we realized that the isolated chiral centers would not be easily achievable.

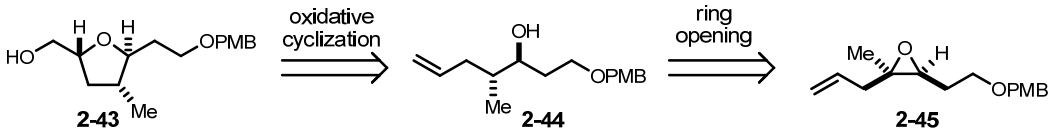
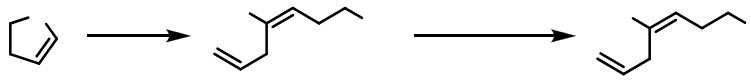


Figure 2.4. Further retrosynthesis of the methyl substituted *trans*-THF **2-43**

Our first attempt at the cyclization precursor (**2-44**) involved a regio- and stereoselective epoxidation of the trisubstituted olefin in diene **2-48** followed by a regio- and stereoselective reductive epoxide opening. Diene **2-47** was achieved via a 1,2-metallate rearrangement reaction of dihydrofuran (**2-46**) in a one pot procedure,[24] followed by protection of the alcohol as PMB ether **2-48** (PMBBr, NaH) which was accomplished in 90% yield (Scheme 2.18).



Scheme 2.18. Synthesis of skipped diene 2-48 via 1,2-metallate rearrangement

The stage was then set for a selective epoxidation of the tri-substituted olefin contained in diene 2-48. To achieve this transformation we envisioned the use of the Shi epoxidation catalyst, which is a fructose derived catalyst that epoxidizes unactivated olefins, with a slight preference for the more substituted/electron rich olefin.[25] Model studies and literature reports suggested that the unnatural enantiomer of the Shi's catalyst (nt-49) would be required, which is considerably more expensive than the natural isomer 49 ($526/g vs. $29/g)[26] and notoriously difficult to make from commercially available starting materials (Figure 2.5).[27]

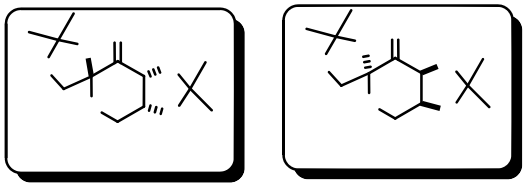


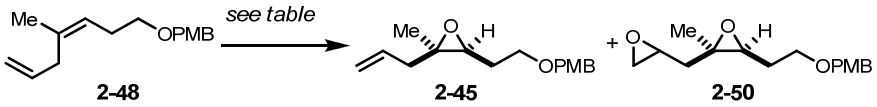
Figure 2.5. The natural (49) and unnatural (nt-49) enantiomer of the Shi catalyst

Undaunted, we performed optimization studies using the inexpensive natural enantiomer 49. Initial reactions using the standard conditions resulted in a disappointing 45% yield and dismal 2:1 ratio of desired mono-epoxide 2-45 to diepoxide 2-50 (Table 2.2, entry 1). By increasing the addition time of the oxidant and base to 4 hours, we were able to increase the selectivity to a more respectable 7:1 ratio, while an even longer addition time maintained the excellent ratio but suffered from a decrease in conversion (Table 2.2, entries 2-3). Attempts to lower the catalyst loading to 25 mol % also resulted in a lower conversion (Table 2.2, entry 4), which was unsurprising considering that the catalyst 49 is known to slowly decompose during the course of the reaction.

Given the incomplete conversions at longer reaction times, we reasoned that the catalyst was decomposing within the first few hours, essentially causing the conversion to cease. However, longer reaction times were shown to increase selectivity, which presented us with a difficult compromise. Eventually, we decided that we would maintain the longer

reaction times to achieve the desired selectivity, but would add the catalyst portion-wise over the course of the reaction to ensure that active catalyst was present throughout. Gratifyingly, the reaction proceeded to complete conversion, while maintaining a respectable 7:1 selectivity for the mono-epoxide **2-45** (Table 2.2, entry 5). Through further optimization, we discovered that the yield and selectivity could be maintained with catalyst loadings as low as 25 mol % (Table 2.2, entry 6). Yield and selectivity were maintained while using the correct enantiomer of the catalyst (***ent*-49**), and the *ee* of the product was determined to be an acceptable 85%.

Table 2.2. Optimization of the Shi epoxidation of diene **2-48**



2-48 **2-45** **2-50**

Entry	Oxone (eq)	49 (eq)	Addition Time (h)	2-45 (%)	2-50 (%)	Recovered 2-48 (%)
1	1.14	0.35	2	45	22	32
2	1.14	0.35	4	54	9	34
3	1.14	0.35	8	16	3	66
4	1.14	0.25	4	35	6	49
5	1.14	0.35[a]	4	75	10	0
6	1.14	0.25[a]	4	74	11	0

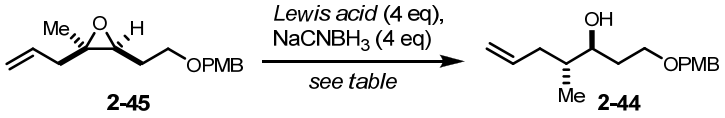
[a] catalyst was added in four equal portions at the beginning of every hour.

To affect the conversion of mono-epoxide **2-45** to alcohol **2-44** required a regio-selective hydride delivery at the more hindered carbon. To achieve this transformation we envisioned using the Hutchin's protocol, which has been reported to proceed via S_N2 reaction with inversion of stereochemistry.[28] Unfortunately, upon treatment of epoxide **2-45** to Hutchin's conditions ($BF_3{\cdot}OEt_2$, $NaCNBH_3$), a variety of products were isolated that indicated premature epoxide opening to give a formal carbocation, resulting in either S_N1 hydride delivery to give an unfavorable mixture of diastereomers, or pinacol-like hydride shift (Table 2.3, entries 1-5). The tertiary carbocation that results from premature epoxide opening can theoretically be stabilized by the olefin in a similar manner to the stabilization of a methyl cyclopropane primary cation.

A variety of Lewis acids (Table 2.3, entries 6-7) were screened to achieve the desired transformation, without success. Ultimately, we decided that the best course of action was to modify $BF_3{\cdot}OEt_2$ by attenuating its Lewis acidity through an anionic redistribution

reaction to replace one of the fluorines with a less electronegative group. We had previously seen success with this strategy when we generated the highly Lewis acidic $BF_2OTf{\cdot}OEt_2$ and $BF_2OMs{\cdot}OEt_2$, which were used in the direct reduction of esters to ethers.[29]

Table 2.3. Optimization of the epoxide opening procedure, use of $BF_2OBn{\cdot}OEt_2$ (**2-51**)



2-45 **2-44**

Entry	Lewis Acid (4 eq)	Addition Time (h)	Yield (%)	d.r (*anti*:*syn*)
1	$BF_3{\cdot}OEt_2$	-	23	2:1
2	$BF_3{\cdot}OEt_2$	0.5	51	2:1
3	$BF_3{\cdot}OEt_2$	3	66	2:1
4	$BF_3{\cdot}OEt_2$	4	90	2:1
5	$BF_3{\cdot}OEt_2$	4	0[a]	-
6	InBr	-	0[b]	-
7	BEt_3	4	0[b]	-
8	$BF_2OBn{\cdot}OEt_2$ (**2-51**)	4	91	>20:1

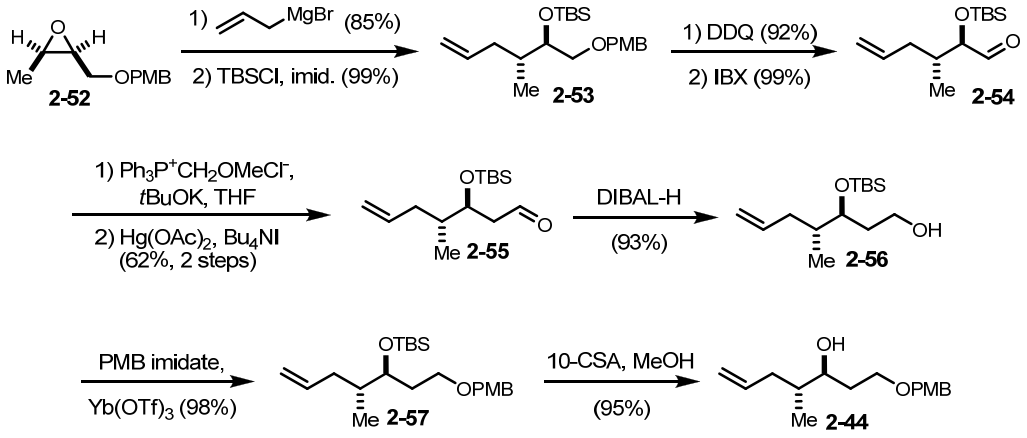
[a] only product observed was ketone formed by pinacol-like hydride shift
[b] starting material recovered

Thus, treatment of $BF_3{\cdot}OEt_2$ with TMSOBn generated the modified Lewis acid $BF_2OBn{\cdot}OEt_2$ (**2-51**) that displayed a characteristic ^{19}F NMR peak at -151.3 ppm, which is consistent with lower Lewis acidity than the parent compound.[30] Gratifyingly, this new Lewis acid (**2-51**) displayed sufficient Lewis acidity to facilitate the desired S_N2 reaction, without promoting the undesired side reactions originally encountered with the use of $BF_3{\cdot}OEt_2$ (Table 2.3, entry 8).

While pleased with the synthesis of cyclization precursor **2-44**, which was achieved in only 4 steps and 52% yield from inexpensive dihydrofuran, this route required considerable amounts (25 mol %) of the expensive unnatural enantiomer of the Shi catalyst (***ent*-49**). Having determined this in the initial retrosynthesis, an alternative route was concurrently explored that would provide gram quantities of **2-44**, while avoiding the use of expensive materials.

Section 2.4.2 – Alternative Synthesis via Homologation Route

The second generation route began with opening of known epoxide **2-52** using allyl Grignard followed by conversion of the resulting alcohol into silyl ether **2-53** (Scheme 2.19). The primary alcohol was then deprotected using DDQ and oxidized to the corresponding aldehyde (**2-54**), which was homologated via a 2-step procedure; conversion of the aldehyde to the enol ether by Wittig reaction followed by hydrolysis to give aldehyde **2-55** in 62% yield.[31] The homologated aldehyde (**2-55**) was reduced using DIBAL-H to give the primary alcohol (**2-56**), which was protected as the PMB ether. Finally, treatment of **2-57** with catalytic 10-CSA in methanol completed the second route towards pentenol **2-44**. Although this process is longer (9 vs. 4 steps) and lower yielding (41% vs 52%), it is inexpensive, easily scalable and successfully provided multi-gram quantities of **2-44**.

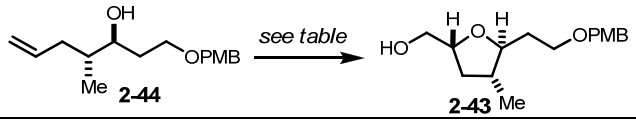


Scheme 2.19. Second generation route towards cyclization precursor **2-44**

With a cost effective and scalable route to pentenol **2-44**, attention was given to the oxidative cyclization to form *trans*-THF ring **2-43** (Table 2.4). The first generation catalyst $Co(modp)_2$ (**1-1**) has been previously shown to be incompatible with the easily oxidized PMB group,[32] and attempts to cyclize **2-44** were unsuccessful as expected (Table 2.4, entry 1). Using the standard oxidation conditions, the second generation $Co(nmp)_2$ (**2-21**) also afforded little success (Table 2.4, entry 2). In an attempt to reduce

the amount of over-oxidation byproducts formed during the course of the reaction, lower reaction temperatures were examined and an optimal yield of 81% was obtained at 35 °C. It is noteworthy that even at room temperature a comparable yield of 85% BORSM was obtained (Table 2.4, entries 3-5). Exasperatingly, upon scale-up of the lower temperature cyclizations, yields were found to be uncharacteristically erratic and we speculated that the peroxide used during catalyst activation could be contributing to the over-oxidation byproducts.

Table 2.4. Optimization of oxidative cyclization of **2-44**



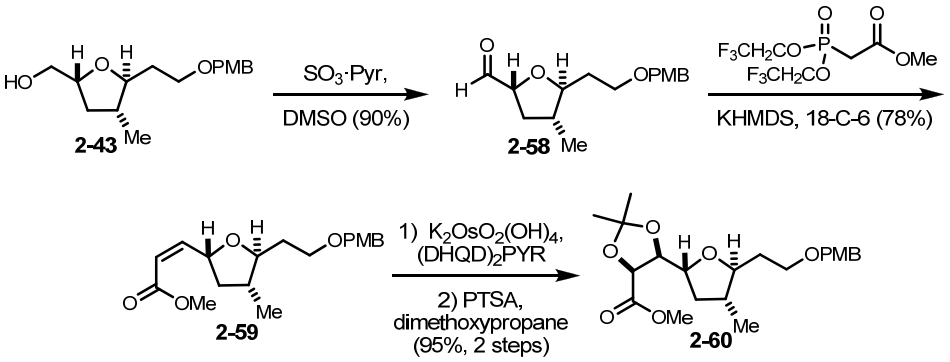
Entry	Catalyst	Loading (mol %)	Temp (°C)	Time (h)	Yield (%)
1	$Co(modp)_2$	15	55	16	0
2	$Co(nmp)_2$	15	55	16	10
3	$Co(nmp)_2$	15	45	16	55
4	$Co(nmp)_2$	15	35	16	81
5	$Co(nmp)_2$	15	22	16	67 (85[a])
6	$Co(nmp)_2$[b]	15	35	16	80
7	$Co(nmp)_2$[b]	15	55	1	91
8	$Co(nmp)_2$[b]	10	55	1	94[c]
9	$Co(nmp)_2$[b]	5	55	16	77 (92[a])

[a] yields based on recovered starting material [b] catalyst was pre-activated
[c] reaction performed on a 15 mmol scale

Thus, an alternative protocol was performed to activate the catalyst in a separate flask, to ensure no peroxides were present upon addition of the pentenol. Initial reactions using this pre-activated **1-21** provided significant advantages in terms of yield reproducibility (Table 2.4, entry 6), although prolonged reaction times were still leading to over-oxidation. Eventually, careful monitoring of the reactions by aliquot resulted in a surprising finding: the reaction was complete after 1 h (Table 2.4, entry 7). Further optimization showed that a lower catalyst loading of 10 mol % resulted in the highest yield (94%) and the cleanest reactions, with further lowering of catalyst loading leading to incomplete conversions (Table 2.4, entries 8-9). These optimized conditions proved reproducible over multiple runs on multi-gram scale.

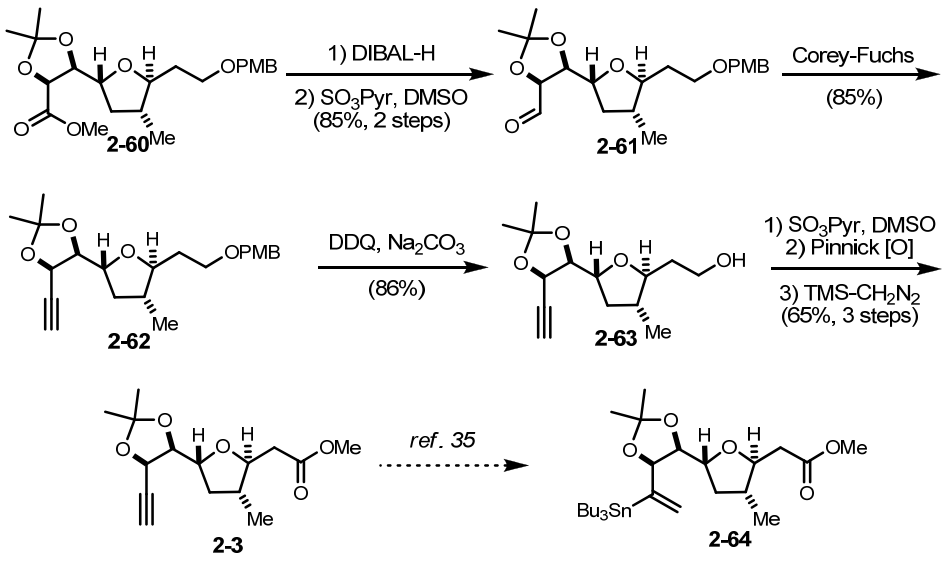
Section 2.4.3 – Completion of the Southern Fragment

To complete the synthesis, alcohol **2-43** was subjected to Parikh-Doering oxidation conditions (SO_3·Pyr, DMSO) to furnish aldehyde **2-58**, which was treated with a Still-Gennari phosphonate to give the *cis* α,β-unsaturated ester **2-59** with 14:1 *cis*:*trans* selectivity (Scheme 2.20).[33] The ester was dihydroxylated via Sharpless asymmetric dihydroxylation (using $(DHQD)_2PYR$ as a ligand)[34] to give the diol as a 5:1 ratio of diastereomers, which were protected as acetonide. This completed the synthesis of **2-60** which contained all of the carbons and stereocenters of the Southern fragment.



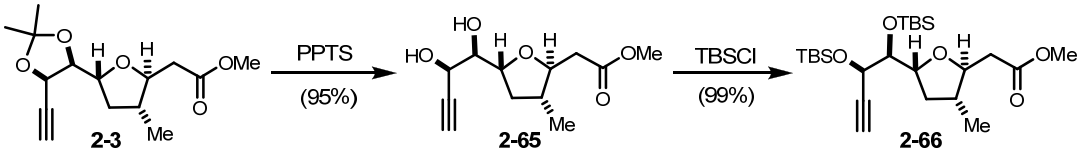
Scheme 2.20. Assembly of the C(7)-C(8) diol via asymmetric dihydroxylation

As before, the bulk of material was stored as the fully protected and stable **2-60**, but to prepare for fragment assembly, a small amount of material was functionalized to allow for flexibility in the order of fragment assembly. Ester **2-60** was converted to the terminal alkyne (**2-62**) in a 4-step procedure. First, reduction of the ester (DIBAL) followed by oxidation to aldehyde **2-61** in 85% yield over 2 steps, and then a Corey-Fuchs reaction (CBr_4/PPh_3 then *n*BuLi) furnished the alkyne in 85% yield (Scheme 2.21). The PMB ether **2-62** was deprotected using standard conditions to reveal alcohol **2-63** in 86% yield, which was oxidized to the acid and quantitatively methylated to give methyl ester **2-3**. The bis-siylated derivative (**2-66**) has been previously shown to undergo regioselective hydro-stannylation, thereby setting the stage for coupling to the Western fragment.[35]



Scheme 2.21. Completion of the Western fragment **2-3**

To ensure that we had made the correct diastereomer at C(7)-C(8) diol, which was previously determined solely by literature analogy, we converted a small amount of acetonide **2-3** to the known *bis*-silylated species (**2-66**).[35] To that end, **2-3** was subjected to acidic conditions to remove the acetonide, followed by treatment of diol **2-65** with 2 equivalents of TBSCl to form **2-66** in 94% yield over 2 steps (Scheme 2.22). The spectral data of **2-66** matched the reported spectra exactly, confirming that we had made the correct diastereomer.[35]



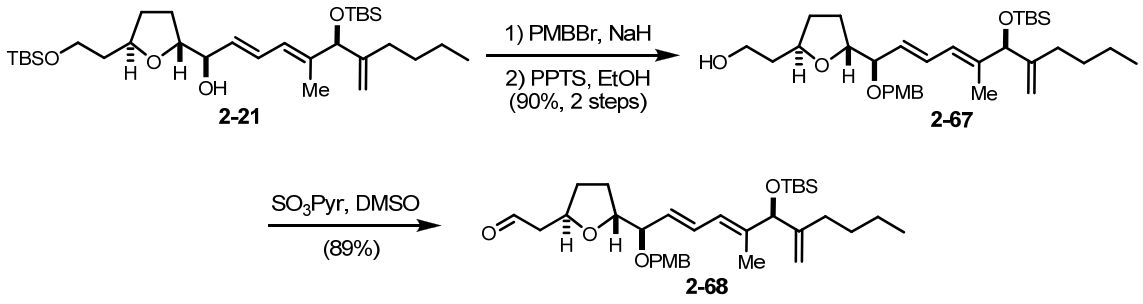
Scheme 2.22. Conversion of **2-3** to known compound to confirm stereochemistry

With successful routes to the North-Eastern, Western and Southern fragments, and grams of the fragments and their precursors in hand, the completion of amphidinolide C appeared to be within reach, and our attention turned to final fragment coupling.

Section 2.5 – Attempted Fragment Assembly

Section 2.5.1 – Assembly Attempts via Dithiane Alkylation

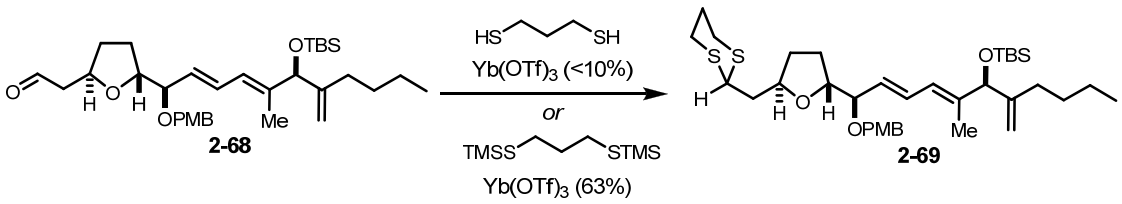
Our initial retrosynthesis concluded that the easiest way to join the North-Eastern and Western fragment would be a dithiane displacement of a suitable leaving group. Dithianes have historically been one of the most effective ways of achieving umpolung reactivity of carbonyls.[36] An added bonus would be the streamlining of the synthesis, having both carbonyls in the natural product protected as dithianes. Accordingly, the secondary alcohol on the North-Eastern fragment **2-21** was protected as the PMB ether before the primary TBS ether was selectively deprotected (PPTS/EtOH) in 90% yield over 2 steps (Scheme 2.23). Primary alcohol **2-67** was cleanly oxidized to aldehyde **2-68** using Parikh-Doering conditions (SO_3·Pyr/DMSO) in 89% yield.



Scheme 2.23. Preparation of the North-Eastern fragment **2-21** for coupling

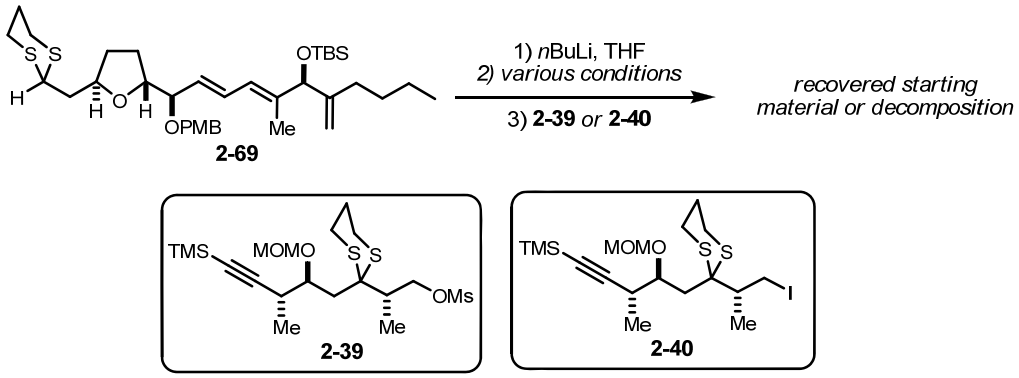
The remaining reaction, conversion of the aldehyde to dithiane **2-69,** proved to be a troublesome transformation. Fluorine based reagents (BF_3·OEt_2) caused complications resulting from TBS removal, whereas mild Lewis acids ($MgBr_2$, $ZnCl_2$) resulted in recovered starting material, and harsh Lewis acids ($TiCl_4$, $SnCl_4$) led to product decomposition. Eventually, it was found that 1,3-propanedithiol and $Yb(OTf)_3$ could affect the transformation, albeit in only trace yields of the desired dithiane **2-69** (Scheme 2.24). By replacing the 1,3-propanedithiol with the disilylated equivalent in the same reaction, it was found that the yield was improved significantly to 63%. A major side product of the reaction (ca. 10-20%) was a product with similar NMR characteristics, and upon careful review of the literature,[37] we have tentatively assigned it as the *cis*-THF

equivalent of **2-69**, caused by retro-Michael ring opening and recycliczation in the *cis* configuration. Regardless of the modest yield of the dithianation, we proceeded to attempt coupling of the North-Eastern dithiane **2-69** and the Western fragment.



Scheme 2.24. Completion of the fully functionalized North-Eastern fragment **2-69**

Disappointingly, all attempts to alkylate the Western fragment as either iodide **2-40** or mesylate **2-39** were met with failure (Scheme 2.25). In all cases, the two components of the reaction were recovered upon protic quench of the reaction mixture. Deuterated quench (using D_2O) confirmed that the dithiane anion was being formed, so we rationalized that the problem lay in the steric bulk surrounding the electrophile, which was too highly congested to allow S_N2 reaction of a bulky nucleophile such as a dithiane.



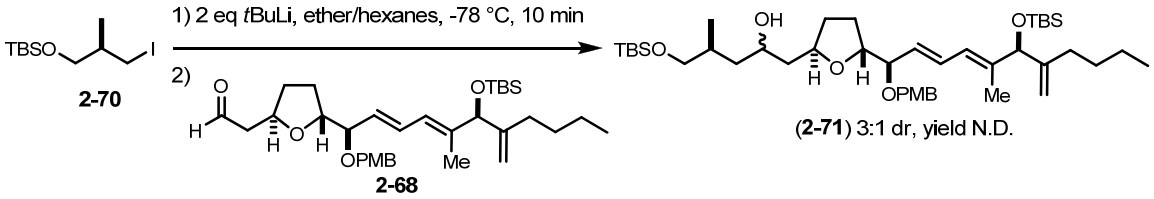
Scheme 2.25. Attempts at joining the North-Eastern (**2-69**) and Western fragment

Additives such as HMPA, DMPU and LiCl have been shown to facilitate troublesome alkylation reactions by breaking up aggregates, but in this case had no effect (LiCl), or resulted in decomposition of the nucleophile (HMPA, DMPU). Harsher alkylation temperatures were explored (increased reaction temperature) that also led primarily to decomposition of the dithiane **2-69**. In an attempt to probe the extent of the steric hindrance around the alkyl iodide Western fragment **2-40**, we attempted to add smaller

nucleophiles. Exasperatingly, even a miniscule MeLi did not add into the congested Western fragment, leading us to abandon its use as an S_N2 electrophile.

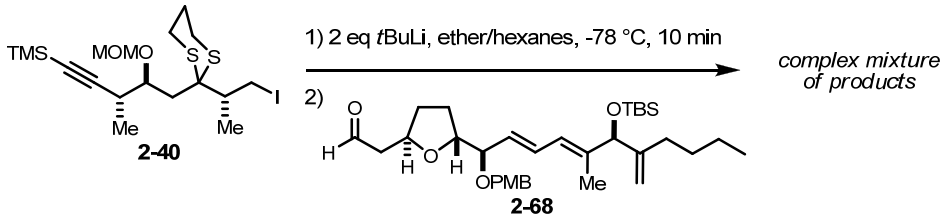
Section 2.5.2 –Attempts at Joining the Fragments via Bailey Reaction

With the Western fragment too hindered to act as an electrophile, it was decided that we would attempt to lithiate the alkyl iodide, to form a stable primary anion which could add into the modified North-Eastern fragment. Utilizing Bailey's reaction conditions (2 eq *t*BuLi, -78 °C)[38], a model alkyl iodide **2-70** was added into the aldehyde derivative of the North-Eastern fragment **2-68**, in an inconsequential 3:1 dr, and an undetermined, but encouraging yield (Scheme 2.26).



Scheme 2.26. A model study of the proposed Bailey reaction

Unfortunately, when the actual Western fragment (**2-40**) was used, the reaction yielded a complex mixture of products, the overwhelming number of which persuaded us to abandon this route (Scheme 2.27).



Scheme 2.27. Failure to join the two fragments using the Bailey reaction

This was not a completely unexpected outcome, as this lithiation chemistry generates a relatively unstable and highly reactive primary anion, so is typically performed on simple substrates, and with great excess and subsequent loss of the alkyl iodide.

Section 2.5.3 – Nitro-Aldol Attempts to Join the Fragments

In a final attempt to utilize the North-Eastern and Western material that we had prepared, we turned to the Henry (or nitro-aldol) reaction. Our hope was that by changing the nature of the electrophile (from alkyl iodide to aldehyde), the Bürgi–Dunitz angle of attack would be altered, which could circumvent the steric hindrance around that position. The result of a successful nitro-aldol, upon elimination, would be a nitro alkene which could be converted into an oxime, an uncommon ketone protecting group (Figure 2.6). This strategy was previously utilized and recommended by Dr. Beauchemin when similar difficulties with a dithiane alkylation were experienced.[39]

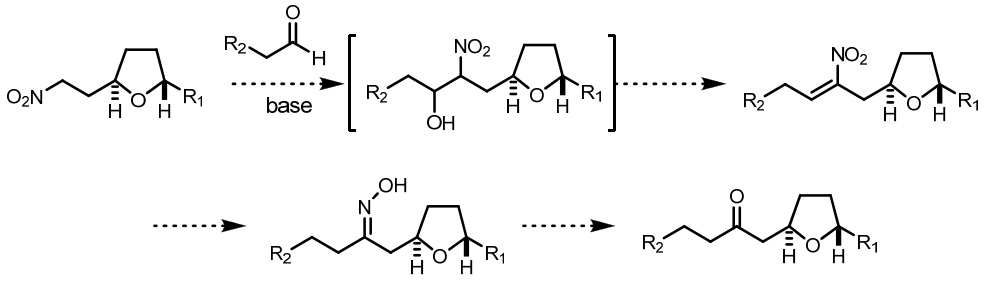
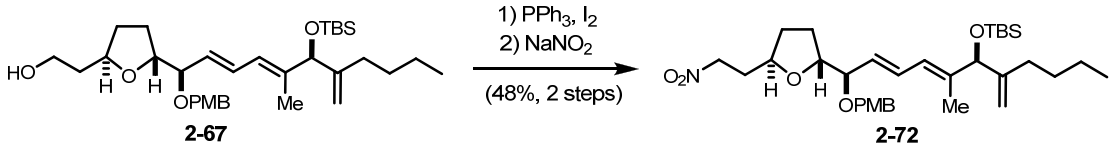


Figure 2.6. A general depiction of joining the fragments via the Henry reaction

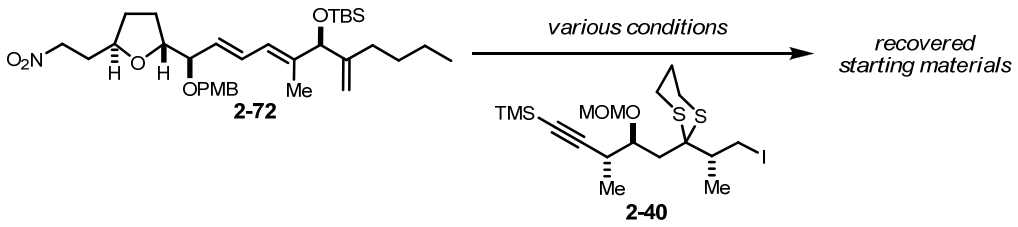
Thus, a nitro-derivative of the Northern fragment **2-72** was prepared. Starting with alcohol **2-67**, treatment with PPh_3 and I_2, yielded the alkyl iodide, which was converted to the nitro compound **2-72** in a modest 48% yield over 2 steps (Scheme 2.28).



2-67 **2-72**

Scheme 2.28. Preparation of the nitro derivative of the North-Eastern fragment **2-72**

Again, we were ultimately met with disappointment, as a variety of conditions were screened to effect the desired aldol reaction without success (Scheme 2.29). Indeed, the electrophile again proved to be the problem, when simple nitro ethane proved an ineffective nucleophile for reactions with **2-40** under all reaction conditions.

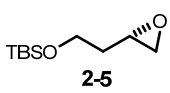


Scheme 2.29. Failed attempts to join the fragments using the Henry reaction

Section 2.5.4 – Summary of Western-Northern-Eastern Fragment

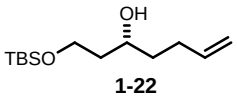
By the end of our attempts, it was becoming increasingly clear that the initial synthetic disconnection would not lead to the completion of Amphidinolide C. We had planned an S_N2 nucleophilic attack into a center that was far too hindered, and approaching neo-pentyl in terms of steric bulk. Changing the nature of the nucleophile to another acyl-anion equivalent seemed futile, as the problem lay in the steric bulk of the electrophile. Attempts to decrease the steric bulk of the Western fragment were also considered but ultimately dismissed, as we felt that adding further manipulations to an already lengthy synthesis would be indicative of poor planning, and reduce the overall elegance of the synthesis. The overall steps required to construct the current Western and North-Eastern fragment was approaching 30 steps, which would bring the total number well over 50 once the Southern fragment was included in the synthesis. We strongly felt that given the knowledge we have obtained thus far in the project, a revision of strategy could lead to a significantly shorter and more elegant route, although it would require starting over "from scratch".

Section 2.6 – Experimental



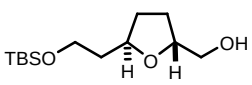
2-5

To a 50 mL round bottom flask charged with (*S*,*S*)-Co(salen) complex (450 mg, 0.74 mmol, 0.0075 eq) in wet toluene (10 mL) was added acetic acid (1.36 mL). The reaction was allowed to stir at rt for 30 min before the volatiles were removed under reduced pressure (1 mmHg). Racemic epoxide[40] **(±)-2-5** (20 g, 98.94 mmol, 1 eq) was added neat, followed by distilled water (0.98 g, 54.41 mmol, 0.55 eq), and the reaction was allowed to stir at rt for 18h. A distillation apparatus was attached to the flask and the resolved epoxide was distilled under reduced pressure (1 mmHg, 40 °C) to give the enantiopure epoxide (9.32 g, 46.10 mmol, 46% yield). The spectral data of this compound match previously reported literature.[41] $[\alpha]^{20}_{D} = -6.47°$ (*c* 1.0, $CHCl_3$).



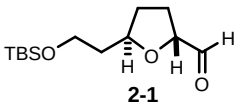
1-22

A 250 mL round bottom flask equipped with a reflux condenser was charged with freshly made allyl magnesium bromide (1.0 M solution in diethyl ether, 60 mL, 60 mmol, 1.3 eq) and cooled to 0 °C using a water-ice bath. Neat epoxide **2-5** (9.32 g, 46.1 mmol, 1 eq) was added through the reflux condenser via syringe at a rate sufficient to maintain a steady reflux of the strongly exothermic reaction. Once the addition was complete the inside of the condenser was rinsed with 10 mL of dry diethyl ether, the ice bath was removed and the reaction was stirred at room temperature for 10 min. The reaction was poured into a solution of half saturated NH_4Cl (200 mL), the aqueous layer was extracted with ethyl acetate (3 x 40 mL) and the combined organics were washed with brine, dried with $MgSO_4$ and filtered through a pad of celite. Solvent was removed under reduced pressure, to afford **1-22** as a colorless oil (11.2 g, 45.9 mmol, 99% yield) which was used without further purification. R_f 0.60 (33% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88-5.78 (ddd, *J* = 17.05, 10.31, 6.64 Hz, 1H), 5.08-4.92 (m, 2H), 3.92-3.78 (m, 3H), 3.45 (bs, 1H), 2.25-2.05 (m, 2H), 1.72-1.48 (m, 4H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 114.5, 71.6, 62.8, 38.2, 36.6, 29.8, 25.8, 18.1, -5.5.; HRMS *m/z* 243.9947 (calcd for $C_{13}H_{28}O_2Si$, 244.1859).



1-23

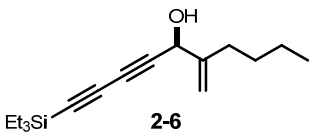
The cyclization precursor **1-22** (2.44 g, 10 mmol, 1.0 eq) was added as a solution in 100 mL *i*PrOH to a flask charged with $Co(nmp)_2$ (**1-21**) (565 mg, 1.0 mmol, 0.1 eq) under 1 atm of O_2 (via balloon). At room temperature, *tert*-butyl hydrogen peroxide (5.33 M in isooctane, 0.19 mL, 1.0 mmol, 0.1 eq) was added in one portion, and the resulting solution was heated to 55 °C for 16 h. The flask was then cooled to room temperature, purged with argon and methyl iodide (0.62 mL, 1.0 mmol, 1.0 eq) was added to the reaction mixture at room temperature and stirred for 24 h. The solution was concentrated under reduced pressure (0.1 mm Hg) to remove all traces of *i*PrOH, and the residue was dissolved in water (100 mL) and CH_2Cl_2 (200 mL). The heterogeneous mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered through a thin pad of silica on top of a thin pad of celite and concentrated under reduced pressure to yield **1-23** as a yellow oil (2.52 g, 9.7 mmol, 97%) which was used without further purification. The spectral data of the compound matches that previously reported.[42] $[\alpha]^{20}_D = -14.4°$ (*c* 1.0, $CHCl_3$); literature: -14° at *c* 1.0; R_f 0.33 (33% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.07-3.98 (m, 2H), 3.65 (t, *J* = 6.3 Hz), 3.57-3.54 (dd, *J* = 11.3, 3.04 Hz), 3.45-3.41 (dd, *J* = 11.6, 6.21 Hz), 2.55 (bs, 1H), 2.04-1.88 (m, 2H), 1.79-1.71 (dt, *J* = 13.3, 5.8 Hz, 1H), 1.66-1.47 (m, 2H), 0.84 (s, 9H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 78.8, 76.4, 64.9, 60.3, 38.6, 32.1, 27.5, 25.8, 18.2, -5.4; HRMS *m/z* 260.1809 (calcd for $C_{13}H_{28}O_3Si$, 260.1808).



2-1

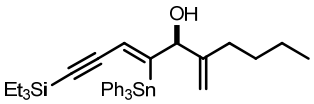
A 250 mL round bottom flask containing oxalyl chloride (1.0 mL, 12 mmol, 1.2 eq) in 90 mL of CH_2Cl_2 was cooled to -78 °C and DMSO (1.7 mL, 24 mmol, 2.4 eq) in 30 mL CH_2Cl_2 was added slowly portion wise over 20 min. After stirring for 45 min, alcohol **1-23** (2.60 g, 10 mmol, 1 eq) was added in 10 mL CH_2Cl_2 over 5 min slowly drop wise. After stirring for 1.5 h at -78 °C, triethylamine (7 mL, 50 mmol, 5 eq) was added portion wise over 5 min. After stirring for 15 min the dry ice/acetone bath was replaced with a water ice/ice bath and the reaction was allowed to warm to 0 °C, and stirred for 15 min. The reaction was poured into 10% HCl (200 mL), extracted with CH_2Cl_2 (3 x 50 mL), and the combined organic layers were washed with saturated sodium bicarbonate (100 mL), brine (100 mL) and dried over $MgSO_4$. Excess

solvent was removed under reduced pressure, giving the crude oil which was immediately purified by column chromatography (20% EtOAc/Hex) to give **2-1** as a yellow oil (2.19 g, 8.5 mmol, 85% yield) which was used in the next step immediately. Epimerization of the THF ring was not observed, but slow decomposition took place over time. R_f 0.20 (20% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (d, *J* = 1.76 Hz, 1H), 4.29 (dt, *J* = 6.44, 2.3 Hz, 1H), 4.14 (tt, *J* = 7.76, 5.4 Hz, 1H), 3.73 (dd, *J* = 7.03, 5.9 Hz, 2H), 2.21-2.16 (m, 1H), 2.07-2.02 (m, 1H), 1.98-1.92 (m, 1H), 1.85-1.80 (m, 1H), 1.75-1.70 (m, 1H), 1.59 (dq, *J* = 12.1, 8.5 Hz, 1H), 0.88 (s, 9H), 0.04 (d, *J* = 2.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0, 82.2, 78.2, 60.2, 38.4, 31.3, 27.2, 25.9, 18.2, -5.4.



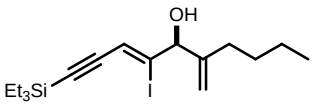
2-6

To a 100 mL round bottom flask containing dimethylzinc (8.33 mL, 1.2 M in toluene, 10 mmol, 3 eq) in toluene (20 mL) was added diyne **2-6**[43] (1.52 g, 9.32 mmol, 2.8 eq). The mixture was allowed to stand at rt for 90 min without stirring, after which the solution was transferred to a 100 mL round bottom flask with (*R*,*R*) ligand **2-9** (201 mg, 0.333 mmol, 0.1 eq). After bubbling had ceased (ca. 10 min), aldehyde **2-7** (373 mg, 3.3 mmol, 1 eq) was added neat. The reaction was stirred at 0 °C for 48 h, after which it was poured into a solution of half saturated NH_4Cl, the aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organics were washed with brine, dried with $MgSO_4$ and filtered through a thin pad of celite. Solvent was removed under reduced pressure, and the crude mixture was purified by column chromatography (10% EtOAc/Hex) to afford **2-6** as a yellow oil (786 mg, 2.84 mmol, 85% yield) which was used without further purification. Absolute stereochemistry of the secondary alcohol was assigned by analogy, using reported examples in the literature.[44] The *ee* of the alcohol was determined to be 90% by Mosher's ester analysis using (*S*)-(+)-α-Methoxy-α-trifluoromethylphenylacetyl chloride: ^{19}F NMR (376 MHz, $CDCl_3$) δ -72.0 (*S* enantiomer), -72.2 (*R* enantiomer); R_f 0.37 (10% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.26 (s, 1H), 4.97 (s, 1H), 4.87 (d, *J* = 6.5 Hz, 1H), 2.18 (td, *J* = 8.4, 7.2 Hz, 2H), 1.92 (d, *J* = 6.4 Hz, 1H), 1.52-1.44 (m, 2H), 1.35 (dq, *J* = 14.9, 7.2 Hz, 2H), 0.99 (t, *J* = 7.8 Hz, 9H), 0.92 (t, *J* = 7.2 Hz, 3H), 0.62 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 147.7, 112.1, 88.4, 86.6, 76.2, 71.2, 66.2, 21.8, 30.2, 22.7, 14.2, 7.6, 4.4; HRMS *m/z* 276.1909 (calcd for $C_{17}H_{28}OSi$, 276.1904).



2-10

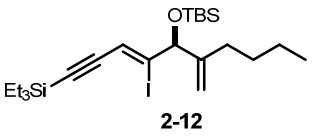
To a 10 mL round bottom flask containing diyne **2-6** (90 mg, 0.336 mmol. 1 eq) in toluene (3.5 mL) was added triphenyltinhydride (177 mg, 0.505 mmol, 1.5 eq) followed by triethylborane in toluene (1.0 M, 0.04 mL, 0.034 mmol, 0.1 eq), and air (1 mL). The reaction was stirred and monitored by aliquot until completion (~24 h). Solvent was removed under reduced pressure, and the crude mixture was purified by column chromatography (10% EtOAc/Hex) to afford **2-10** as a yellow oil (145 mg, 0.238 mmol, 71% yield). R_f 0.35 (10% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.59 (m, 5H), 7.36-7.30 (m, 10H), 6.67 (d, J = 1.4 Hz, 1H), 4.76 (s, 1H), 4.73 (bs, 1H), 4.71 (s, 1H), 1.84 (q, J = 7.2 Hz, 2H), 1.73 (bs, 1H), 1.32-1.20 (m, 4H), 1.01 (t, J = 7.9 Hz, 1H), 0.92 (q, J = 7.7 Hz, 1H), 0.66 (t, J = 7.8 Hz, 9H), 0.19 (q, J = 7.9 Hz, 6H).



2-11

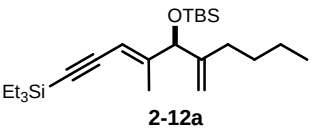
To a 10 mL round bottom flask containing diyne **2-6** (317 mg, 1.15 mmol. 1 eq) in toluene (5 mL) was added tributyltinhydride (502 mg, 1.72 mmol, 1.5 eq) followed by triethylborane in toluene (1.0 M, 0.35 mL, 0.345 mmol, 0.3 eq), and air (1 mL). The reaction was stirred and monitored by aliquot until completion (~24 h). Volatiles were removed under reduced pressure (0.1 mm Hg, 5 min), and the crude stannane was dissolved in THF (20 mL), cooled to -78 °C, and iodine (350 mg, 1.38 mmol, 1.2 eq) was added in one portion. The reaction was stirred at -78 °C for 15 min, the dry ice/acetone bath was removed and was replaced with a water ice bath and the reaction was stirred at 0 °C for 5 min. A saturated solution of sodium sulfite was added until the iodine color dissipated, and the solution was diluted with EtOAc (50 mL) and water (20 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organics were washed with brine, dried with $MgSO_4$ and filtered through a pad of celite. Solvent was removed under reduced pressure, and the crude mixture was purified by column chromatography (10% EtOAc/Hex) to afford **2-11** as a yellow oil (452 mg, 1.12 mmol, 97% yield) which was used without further purification. R_f 0.26 (10% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49 (d, J = 0.98 Hz, 1H), 5.21 (s, 1H), 5.08 (s, 1H), 4.41 (s, 1H), 2.03-1.98 (m, 3H), 1.43-1.39 (m, 2H), 1.35-1.29 (m, 2H), 1.03 (t, J = 7.8 Hz, 9),

0.90 (t, J = 7.0 Hz, 3H), 0.65 (q, J = 7.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 147.7, 123.6, 119.4, 112.6, 105.1, 99.6, 80.7, 31.6, 29.9, 22.5, 14.0, 7.5, 4.3; HRMS *m/z* 404.1030 (calcd for $C_{17}H_{29}IOSi$, 404.1032).



2-12

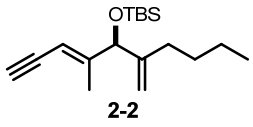
To iodide **2-11** (447 mg, 1.10 mmol, 1 eq) and triethylamine (0.5 mL, 4.4 mmol, 4 eq) in CH_2Cl_2 (20 mL) was added TBSOTf (0.5 mL, 1.65 mmol, 1.5 eq), and the reaction was stirred at rt for 16 h. The reaction was poured into a solution of half saturated NH_4Cl, the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organics were washed with brine, dried with $MgSO_4$ and filtered through a thin pad of celite. Solvent was removed under reduced pressure to afford **2-12** as a yellow oil (413 mg, 0.8 mmol, 72% yield) which was used without further purification. R_f 0.78 (10% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (d, J = 1.37 Hz, 1H), 5.15 (s, 1H), 4.99 (d, J = 1.37 Hz, 1H), 4.52 (s, 1H), 1.98-1.91 (m, 1H), 1.85-1.77 (m, 1H), 1.43-1.37 (m, 2H), 1.30-1.26 (m, 2H), 1.03 (t, J = 7.9 Hz, 9), 0.89 (s, 9H), 0.89 (t, J = 7.8 Hz, 3H), 0.65 (q, J = 7.9 Hz, 6H), 0.04 (d, J = 14.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 147.6, 124.0, 117.8, 113.4, 105.7, 98.6, 82.7, 29.8, 29.4, 25.8, 22.6, 18.2, 14.0, 7.5, 4.3; HRMS *m/z* 519.1966 (calcd for $C_{23}H_{43}IOSi_2$, 518.1897).



2-12a

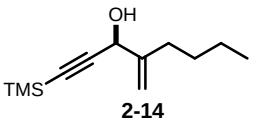
To a solution of iodide **2-12** (165 mg, 0.318 mmol, 1 eq), in DMF (4 mL) and triethylamine (0.3 mL, 3.18 mmol, 10 eq) was added Me_4Sn (169 mg, 0.342 mmol, 3 eq), CuI (5.8 mg, 0.0318 mmol, 0.1 eq), Ph_3As (9.7 mg, 0.0318 mmol, 0.1 eq), and $PdCl_2(MeCN)_2$ (8.3 mg, 0.0318 mmol, 0.1 eq). The solution was thoroughly degassed with argon before being heated to 130 °C overnight (16 h). The reaction was then allowed to cool before being poured into water (20 mL) and diluted with EtOAc (20 mL). The aqueous layer was extracted with EtOAc (5 x 20 mL) and the combined organics were washed with brine, dried with $MgSO_4$ and filtered through a pad of celite. Solvent was removed under reduced pressure, and the crude mixture was purified by column chromatography (100% Hex) to afford **2-12a** as a yellow oil (77.7 mg, 0.203 mmol, 64% yield) which was used without further purification. R_f 0.47 (10% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ

5.66 (s, 1H), 5.06 (s, 1H), 4.86 (s, 1H), 4.43 (s, 1H), 1.92 (m, 1H), 1.78 (m, 1H), 1.74 (s, 3H), 1.41-1.35 (m, 2H), 1.30 (ap, J = 7.0 Hz, 2H), 1.00 (t, J = 8.9 Hz, 9), 0.89 (s, 9H), 0.89 (t, J = 7.8 Hz, 3H), 0.62 (q, J = 8.0 Hz, 6H), 0.02 (d, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 152.9, 149.2, 110.8, 105.7, 104.4, 95.3, 80.1, 29.9, 29.8, 25.8, 22.6, 18.3, 15.4, 14.0, 7.5, 4.5, -5.0, -5.1; HRMS *m/z* 406.3082 (calcd for $C_{24}H_{46}IOSi_2$, 406.3087).



2-2

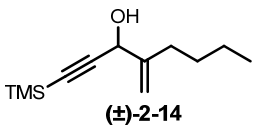
To a solution of silane **2-12a** (57.7 mg, 0.141 mmol, 1 eq) in wet MeOH:THF (1 mL:1 mL) was added K_2CO_3 (20 mg, 1.42 mmol, 10 eq), and the solution was stirred for 24 h at room temperature. Upon completion, the volatiles were removed under reduced pressure, and the residue was dissolved in water (20 mL) and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (2 x 20 mL) and the combined organics were washed with brine, dried with $MgSO_4$ and filtered through celite. Solvent was removed under reduced pressure to afford **2-2** as a yellow oil (39.4 mg, 0.133 mmol, 95% yield) which was used without further purification. $[\alpha]^{20}_D$ = +7.09° (*c* 1.0, $CHCl_3$); R_f 0.40 (100% Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63 (dt, J = 2.34, 1.17 Hz, 1H), 5.06 (s, 1H), 4.88 (d, J = 1.56 Hz, 1H), 4.43 (s, 1H), 3.07 (d, J = 2.34 Hz, 1H), 1.95-1.87 (m, 1H), 1.80-1.73 (m, 1H), 1.74 (s, 3H), 1.41-1.24 (m, 4H), 0.88 (t, J = 8.7 Hz, 3H), 0.88 (s, 9H), 0.02 (d, J = 2.54 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 149.0, 111.0, 104.3, 81.5, 80.7, 80.0, 29.9, 29.7, 25.7, 22.6, 18.3, 15.2, 14.0, -5.0, -5.1; HRMS *m/z* 292.2222 (calcd for $C_{18}H_{32}OSi$, 292.2222).



2-14

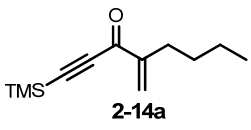
Via Trost A-A: To a 10 mL round bottom flask containing dimethylzinc (0.83 mL, 1.2 M in toluene, 1 mmol, 3 eq) in toluene (2 mL) was added TMS acetylene (91.3 mg, 0.333 mmol, 2.8 eq). The mixture was allowed to stand at rt for 90 min without stirring, after which the solution was transferred to a 10 mL round bottom flask with (*R*,*R*) ligand **2-9** (20.1 mg, 0.033 mmol, 0.1 eq). After bubbling had ceased (ca. 10 min), aldehyde **2-7** (37.3 mg, 0.33 mmol, 1 eq) was added neat. The reaction was stirred at 0 °C for 48 h, after which it was poured into a solution of half saturated NH_4Cl (20 mL), the aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organics were washed with brine, dried with $MgSO_4$ and filtered through a thin pad of celite. Solvent was removed under

reduced pressure, and the crude mixture was purified by column chromatography (10% EtOAc/Hex) to afford **2-14** as a yellow oil (48 mg, 0.231 mmol, 70% yield) which was used without further purification. Absolute stereochemistry of the secondary alcohol was assigned by analogy, using reported examples in the literature.[45] R_f 0.37 (10% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.26 (s, 1H), 4.94 (s, 1H), 4.80 (s, 1H), 2.18 (t, J = 8.0 Hz, 2H), 2.10 (bs, 1H), 1.51-1.45 (m, 2H), 1.35 (dq, J = 14.9, 7.2 Hz, 2H), 0.92 (t, J = 7.2 Hz, 3H), 0.17 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 11.2, 104.7, 90.6, 65.9, 31.4, 30.0, 22.4, 13.9, -0.3; HRMS *m/z* 210.1444 (calcd for $C_{12}H_{22}OSi$, 210.1440). The *ee* of the alcohol was determined to be 90% by Mosher's ester analysis using (*S*)-(+)-α-Methoxy-α-trifluoromethylphenylacetyl chloride: ^{19}F NMR (376 MHz, $CDCl_3$) δ -71.7 (*R* enantiomer), -71.9 (*S* enantiomer).



(±)-2-14

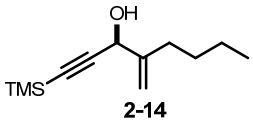
To a 250 mL flask containing TMS acetylene (3.41 mL, 24.7 mmol, 1.05 eq), in THF (50 mL) cooled to 0 °C was added *n*BuLi (2.55 M, 9.21 mL, 23.5 mmol, 1 eq) portion wise over 10 min, and the reaction was stirred at 0 °C for 10 min. To the flask was added aldehyde **2-7** (2.64 g, 23.5 mmol, 1 eq) drop wise. The reaction was stirred for 15 min, and was then poured into half saturated solution of NH_4Cl (100 mL), the aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure to afford a yellow oil (5.14 g, 24.4 mmol, 99% yield) which was used without further purification. R_f 0.37 (10% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.26 (s, 1H), 4.94 (s, 1H), 4.80 (s, 1H), 2.18 (t, J = 8.0 Hz, 2H), 2.10 (bs, 1H), 1.54-1.45 (m, 2H), 1.35 (dq, J = 14.9, 7.2 Hz, 2H), 0.92 (t, J = 7.2 Hz, 3H), 0.17 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 11.2, 104.7, 90.6, 65.9, 31.4, 30.0, 22.4, 13.9, -0.3; HRMS *m/z* 210.1444 (calcd for $C_{12}H_{22}OSi$, 210.1440).



2-14a

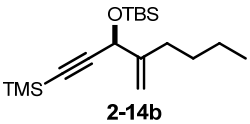
To a 500 mL flask containing propargyl alcohol **(±)-2-14** (4.93 g, 23.4 mmol, 1 eq) in CH_2Cl_2 was added 20 g of powdered 4Å molecular sieves, and activated manganese dioxide (16.3 g, 234.2 mmol, 10 eq). The reaction was heated to reflux and stirred overnight (ca. 16 h) after which the reaction was cooled, filtered through a pad of celite and concentrated under

reduced pressure, to afford the propargyl ketone **2-14a** as yellow oil (3.99 g, 19.2 mmol, 82% yield). The ketone was of sufficient purity to use in the next step without purification, and was found to decompose on silica gel. R_f 0.72 (10% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 (s, 1H), 5.98 (s, 1H), 2.28 (t, J = 7.2 Hz, 2H), 1.41-1.31 (m, 4H), 0.89 (t, J = 7.0 Hz, 3H), 0.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.6, 149.2, 130.5, 100.3, 98.2, 30.2, 29.0, 22.3, 13.8, -0.7; HRMS *m/z* 208.1283 (calcd for $C_{12}H_{20}OSi$, 208.1283).



2-14

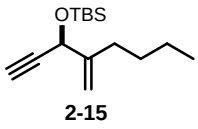
To a solution of ketone **2-14a** (3.12 g, 15 mmol, 1 eq) in THF (40 mL) at -30 °C was added (*S*)-CBS catalyst (0.33 M, 6.77 mL, 2.25 mmol, 0.15 eq), followed by drop wise addition of BH_3·THF (1.0 M, 18 mL, 18 mmol, 1.2 eq) over 40 min. The reaction was stirred at -30 °C for 2 h until completion, indicated by TLC. To the reaction mixture was added MeOH (20 mL) at -30 °C, followed by pouring the solution into a half saturated solution of NH_4Cl (100 mL), the aqueous layer was extracted with EtOAc (3x50 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure to afford **2-14** as a yellow oil (3.15 g, 15 mmol, 100% yield) which was used without further purification. The absolute stereochemistry of the secondary alcohol was assigned by analogy, using reported examples in the literature.[46] The *ee* of the alcohol was determined to be 90% by Mosher's ester analysis using (*S*)-(+)-α-Methoxy-α-trifluoromethylphenylacetyl chloride: ^{19}F NMR (376 MHz, $CDCl_3$) δ -71.7 (*R* enantiomer), -71.9 (*S* enantiomer).



2-14b

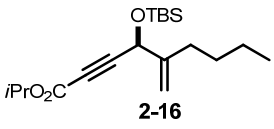
A 100 mL round bottom flask was charged with *tert*-butylsilylchloride (1.94 g, 12.9 mmol, 1 eq), diluted with CH_2Cl_2 (50 mL) and cooled to 0 °C. Imidazole (1.75 g, 25.8 mmol, 2 eq) was added in one portion, followed by a catalytic amount of DMAP, and alcohol **2-14** (2.71 g, 12.9 mmol, 1 eq). The ice bath was removed and the reaction was stirred at rt overnight (approx. 16 h). The reaction was poured into a half-saturated solution of NH_4Cl (100 mL), the aqueous layer was extracted with CH_2Cl_2 (3x30 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under

reduced pressure, to afford **2-14b** as a colorless oil (3.65 g, 11.2 mmol, 87% yield) which was used without further purification. R_f 0.90 (10% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.22 (s, 1H), 4.86 (s, 1H), 4.79 (s, 1H), 2.14 (t, *J* = 7.6 Hz, 2H), 1.47 (asex, *J* = 7.2 Hz, 2H), 1.33 (asex, *J* = 7.2 Hz, 2H), 0.91 (t, *J* = 7.2 Hz, 3H), 0.91 (s, 9H), 0.15 (s, 6H); HRMS *m/z* 324.2305 (calcd for $C_{18}H_{36}OSi_2$, 324.2305).



2-15

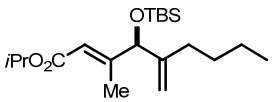
A 100 mL round bottom flask was cooled to 0 °C and charged with TBS alcohol (**2-14b**) (3.65 g, 11.2 mmol, 1 eq) and diluted with wet MeOH (50 mL). K_2CO_3 (5 g, excess) was added in one portion and the reaction was stirred at 0 °C until judged complete by TLC (approx. 3h). The reaction was poured through a thin pad of celite and washed with 100 mL of CH_2Cl_2. The reaction was poured into a half-saturated solution of NH_4Cl (100 mL), the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, to afford **2-15** as a colorless oil (2.68 g, 10.62 mmol, 95% yield) which was used without further purification. R_f 0.85 (10% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.21 (s, 1H), 4.88 (s, 1H), 4.80 (s, 1H), 2.44 (d, *J* = 2.3 Hz, 2H), 2.16 (q, *J* = 6.0 Hz, 2H), 1.47 (m, 2H), 1.34 (dq, *J* = 14.8, 7.2 Hz, 2H), 0.91 (t, *J* = 7.2 Hz, 3H), 0.91 (s, 9H), 0.12 (d, *J* = 10.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 110.2, 84.1, 72.8, 65.9, 31.1, 29.9, 25.8, 22.5, 18.3, 14.0, -4.7, -5.1.



2-16

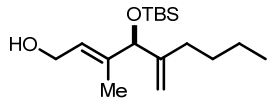
A 250 mL round bottom flask was charged with alkyne **2-15** (2.68 g, 10.6 mmol, 1 eq), diluted with THF (60 mL) and cooled to -78 °C. Then, *n*BuLi (2.50 M, 5.5 mL, 13.8 mmol, 1.5 eq) was added over 10 min drop wise. The reaction was stirred for 15 min, at which point *iso*propylchloroformate was added (1.0 M, 11.9 mL, 11.9 mmol, 1.3 eq) drop wise over 10 min. The reaction was stirred at -78 °C for 1 h and warmed to 0 °C using a water ice bath. The reaction was poured slowly into a half-saturated solution of NH_4Cl (100 mL), the aqueous layer was extracted with EtOAc (3 x 30 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, to afford **2-16** as a colorless oil (3.90 g, 10.5 mmol, 99% yield) which was used

without further purification. R_f 0.61 (10% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.20 (s, 1H), 5.07 (dt, *J* = 12.5, 6.2 Hz, 1H), 4.90 (d, *J* = 10.8 Hz, 2H), 2.14 (q, *J* = 7.4 Hz, 2H), 1.47 (m, 2H), 1.34 (m, 2H), 1.27 (d, *J* = 6.2 Hz, 6H), 0.90 (t, *J* = 7.8 Hz, 3H), 0.90 (s, 9H), 0.13 (d, *J* = 16.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 147.0, 138.0, 111.4, 110.2, 86.6, 84.0, 72.8, 69.9, 66.0, 65.9, 31.0, 29.9, 25.7, 25.7, 22.5, 22.5, 21.6, 18.3, 18.2, 14.0, -4.8, -5.1; HRMS *m/z* 337.2197 (calcd for $C_{19}H_{34}O_3Si$, 338.2277).



2-17

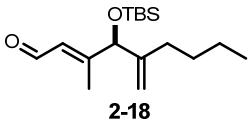
A 500 mL round bottom flask was charged with CuI (11.6 g, 61.4 mmol, 3 eq), diluted with THF (200 mL) and cooled to -40 °C. Methyl magnesium bromide (3.0 M in ether, 40.9 mL, 122.8 mmol, 6 eq) was added slowly drop wise, and the reaction was stirred for 15 min before cooling to -78 °C. Alkyne **2-16** (6.93 g, 20.47 mmol, 1 eq) in THF (50 mL) was added drop wise over 15 min. The reaction was stirred at -78 °C for 2 h, at which point the dry ice bath was allowed to evaporate, and the reaction was allowed to slowly warm to rt overnight (ca 16 h). The reaction was poured into a half-saturated solution of NH_4Cl (500 mL), the aqueous layer was extracted with EtOAc (3 x 100 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, and the crude product was purified by column chromatography (5% EtOAc/Hex) to afford methylated product **2-17** as a yellow oil (6.25 g, 17.6 mmol, 86% yield). $[\alpha]^{20}_D$ = +5.30° (*c* 1.0, $CHCl_3$); R_f 0.63 (10% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 (t, *J* = 1.4 Hz, 1H), 5.11 (s, 1H), 5.03 (dt, *J* = 12.6, 6.2 Hz, 1H), 4.91 (d, *J* = 1.4 Hz, 1H), 4.42 (s, 1H), 1.97 (s, 3H), 1.97-1.88 (m, 1H), 1.84-1.72 (m, 1H), 1.40-1.28 (m, 4H), 1.26 (dd, *J* = 6.25, 1.76 Hz, 6H), 0.89 (s, 9H), 0.87 (t, *J* = 7.8 Hz, 3H), 0.02 (d, *J* = 1.76 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 158.0, 148.5, 116.2, 111.5, 80.9, 66.9, 29.9, 29.8, 25.8, 22.5, 22.0, 18.3, 14.4, 14.0, -5.0, -5.1; HRMS *m/z* 355.2683 (calcd for $C_{20}H_{38}O_3Si$, 354.2590).



2-17a

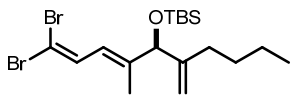
A 250 mL round bottom flask was charged with ester **2-17** (2.49 g, 7.02 mmol, 1 eq), diluted with CH_2Cl_2 (100 mL) and cooled to -78 °C. A solution of DIBAL-H (1.0 M, 24.6 mL, 24.6 mmol, 3.5 eq) was added portion wise over 10 min. The reaction was stirred for 1 h at -78 °C before it

was warmed to 0 °C using a water ice bath, and stirred for 1 h. The reaction was slowly poured into a half-saturated solution of NH_4Cl (200 mL), and a saturated solution of Rochelle's salt was added (200 mL), and the slurry was stirred vigorously overnight (ca. 16 h). The aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, and the crude product was purified by column chromatography (20% EtOAc/Hex) to afford alcohol **2-17a** as a yellow oil (2.05 g, 6.87 mmol, 98% yield). R_f 0.24 (10% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66 (tt, J = 6.64, 1.25 Hz, 1H), 5.10 (s, 1H), 4.84 (s, 1H), 4.37 (s, 1H), 4.19 (d, J = 6.64 Hz, 2H), 1.92-1.73 (m, 2H), 1.49 (s, 3H), 1.42-1.23 (m, 7H), 0.87 (s, 9H), 0.01 (d, J = 3.13 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 139.4, 124.8, 109.9, 80.4, 59.4, 30.7, 30.0, 25.8, 22.6, 18.3, 14.0, 11.5, -5.0; HRMS *m/z* 299.2412 (calcd for $C_{17}H_{34}O_2Si$, 298.2328).



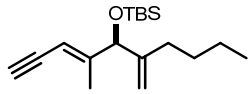
2-18

To a 100 mL flask containing alcohol **2-17a** (2.05 g, 6.87 mmol, 1 eq) in CH_2Cl_2 was added 100 g of powdered 4Å molecular sieves, and activated manganese dioxide (6.09 g, 70.0 mmol, 10 eq). The reaction was heated to reflux and stirred overnight (ca. 16 h) after which the reaction was cooled, filtered through a pad of celite and concentrated under reduced pressure, to afford the α,β-unsaturated aldehyde **2-18** as yellow oil which was used immediately in the next step without further purification. The spectral data of the compound matches the racemic compound previously reported.[47] R_f 0.39 (10% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.03, (d, J = 8.01 Hz, 1H), 6.18 (d, J = 8.21, 1.37 Hz, 1H), 5.13 (s, 1H), 4.96 (s, 1H), 4.49 (s, 1H), 2.01 (s, 1H), 1.91 (dt, J = 15.87, 7.79 Hz, 1H), 1.75 (dt, J = 15.87, 7.79 Hz, 1H), 1.40-1.24 (m, 4H), 0.89 (t, J =7.8 Hz, 3H), 0.89 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.7, 148.1, 126.3, 112.2, 80.6, 29.9, 29.8, 25.7, 22.5, 18.2, 14.0, 13.1, -5.0, -5.2; HRMS *m/z* 297.2238 (calcd for $C_{17}H_{32}O_2Si$, 296.2172).



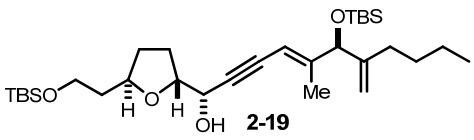
2-18b

A 250 mL flask was charged with triphenylphosphine (4.60 g, 17.55 mmol, 2.5 eq) and CH_2Cl_2 (100 mL) and was cooled to 0 °C. The septum was temporarily removed to add carbon tetrabromide (3.02 g, 9.13 mmol, 1.3 eq) in one portion. The ice bath was removed and the reaction was stirred at room temperature for 30 min, after which it was re-cooled to 0 °C. The above crude aldehyde **2-18** (~2.03 g, ~6.87 mmol, ~1 eq) was added in one portion and the reaction was stirred for 30 min, at which point it was judged complete by TLC. Hexanes (100 mL) was added, and the reaction was allowed to warm to rt, at which point it was filtered through celite, and concentrated to dryness. To the crude oil was added more hexanes (100 mL), filtered, and concentrated. This procedure was repeated for a total of 3 filtrations at which point the crude oil was purified by column chromatography (100% Hexanes) to afford **2-18b** as a yellow oil (2.48 g, 5.49 mmol, 78% yield). R_f 0.85 (10% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, J = 10.55 Hz, 1H), 6.21 (dt, J = 10.6, 1.34 Hz, 1H), 5.08 (s, 1H), 4.88 (s, 1H), 4.40 (s, 1H), 1.94-1.86 (m, 1H), 1.81-1.73 (m, 1H), 1.58 (d, J = 1.37 Hz, 3H), 1.42-1.25 (m, 4H), 0.89 (t, J = 8.7 Hz, 3H), 0.89 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 143.8, 133.3, 121.9, 110.8, 90.9, 80.6, 30.1, 30.0, 25.8, 22.6, 18.3, 14.0, 13.5, -5.0; HRMS *m/z* 450.0580 (calcd for $C_{18}H_{32}Br_2OSi$, 450.0589).



2-2

A 250 mL flask was charged with dibromde **2-18b** (2.48 g, 5.49 mmol, 1 eq), diluted with THF (100 mL) and cooled to -78 °C. *n*BuLi (2.50 M, 5.48 mL, 13.70 mmol, 2.5 eq) was added slowly drop wise over 15 min. The reaction was stirred at -78 °C for 1 h at which point it was judged complete by TLC. The reaction was slowly poured into a half-saturated solution of NH_4Cl (50 mL), the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, and the crude product was purified by column chromatography (2% EtOAc/Hex) to afford alkyne **2-2** as a yellow oil (1.57 g, 5.38 mmol, 98% yield). Characterization data was identical to alkyne **2-2** made previously.

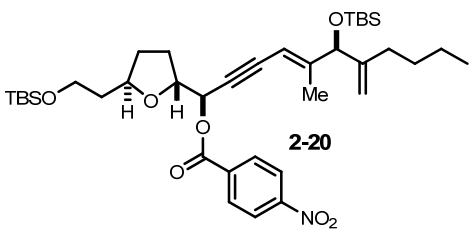


2-19

To a solution of alkyne **2-2** (890 mg, 3.04 mmol, 1.3 eq) in MTBE (21 mL) at 0 °C was added *n*BuLi (2.66 M, 1.14 mL, 3.04 mmol, 1.3 eq), and the reaction was stirred at 0 °C for 1 h before being cooled to -90 °C using a liquid nitrogen/hexanes bath. After stirring for 15 min at -90 °C, freshly purified aldehyde **2-1** (664 mg, 2.34 mmol, 1 eq) dissolved in a minimal amount of MTBE was added over 15 min drop wise. The slow addition, low temperature of the reaction and the purity of both **2-2** and **2-1** were essential conditions to ensure a high dr. After stirring at -90 °C for 4 h, the reaction was treated at -90 °C with 20 mL of saturated NH_4Cl, before being allowed to warm to rt and diluted with water (50 mL) and EtOAc (50 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, and the crude product was purified by column chromatography (20% EtOAc/Hex) to afford recovered alkyne (180 mg) and alkynlation adduct as a single diastereomer **2-19** as a yellow oil (1.19 g, 2.17 mmol, 93% yield). The addition of acetylides to THF aldehydes are well documented to result in an *anti* relationship with the corresponding alcohol.[48] $[\alpha]^{20}_D$ = +8.97° (*c* 1.0, $CHCl_3$); R_f 0.22 (10% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.63 (s, 1H), 5.05 (s, 1H), 4.86 (s, 1H), 4.60 (bs, 1H), 4.42 (s, 1H), 4.19 (ap, *J* = 6.26 Hz, 1H), 4.14 (dt, *J* = 7.32, 3.51 Hz, 1H), 3.70 (adt, *J* = 6.21, 2.66 Hz, 2H), 2.41 (bd, *J* = 5.27 Hz, 1H), 2.10 (dt, *J* = 11.56, 6.15 Hz, 1H), 2.05-2.01 (m, 2H), 1.89 (dt, J = 15.81, 7.90 Hz, 1H), 1.81-1.73 (m, 2H), 1.70 (s, 3H), 1.70-1.63 (m, 1H), 1.57 (dq, J = 11.93, 8.51 Hz, 1H), 1.39-1.34 (m, 2H), 1.28 (dt, *J* = 16.64, 7.32 Hz, 2H), 0.87 (t, *J* = 7.8 Hz, 3H), 0.87 (s, 18H), 0.03 (s, 6H), 0.00 (d, *J* = 1.17 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 149.1, 110.8, 104.8, 90.6, 83.6, 80.8, 80.0, 78.0, 65.2, 60.4, 38.9, 32.3, 29.9, 29.8, 26.7, 25.9, 25.8, 22.6, 18.3, 18.2, 15.2, 14.0, -5.0, -5.1, -5.3; HRMS *m/z* 550.3853 (calcd for $C_{31}H_{58}O_4Si_2$, 550.3874).

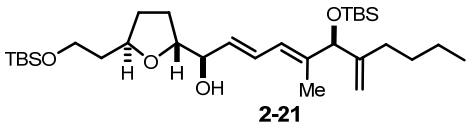
Attempts at Forming 2-19 via Asymmetric Reduction: After initial failures of asymmetric alkynlation of **2-1** and **2-2**, and exhaustive efforts at achieving substrate controlled diastereoselective additions (prior to success using MTBE), it was envisioned that a facial selective reduction of the ketone could be a viable option. Literature

precedent of this reaction was abundant,[49] with some examples coming from our own lab. However, in previous studies we had found that the dr of the reduction was unusually dependent on remote protecting groups.[50] Alkylation adduct **2-19** was oxidized to the corresponding propargylic ketone using activated manganese dioxide. Several attempts at asymmetric reduction were made using L-selectride and (*R*)-CBS reagent at low temperatures and a disappointing mixture of inseparable diastereomers was achieved in all cases. The most successful reagent was L-selectride, which at -78 °C gave a near quantitative yield of a 2:1 ratio of separable diastereomers. Although this route could conceivably give us access to enantiopure material after careful column chromatography, our initial alkylation attempts gave a comparable dr in one step. Gratifyingly, further optimization of the alkylation led to conditions that resulted in a single diastereomer (MTBE, -90 °C).



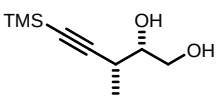
A 250 mL round bottom flask was charged with 4-nitro benzoic acid (1.91 g, 11.48 mmol, 4 eq), triphenylphosphine (3.01g, 11.48 mmol, 4 eq), alcohol **2-19** (1. 58 g, 2.87 mmol, 1 eq), diluted with THF (80 mL) and cooled to 0 °C. DIAD (2.25 mL, 11.48 mmol, 4 eq) was added drop wise over 10 min, and the ice bath was removed. The reaction monitored by TLC and upon completion (ca. 2h) was slowly poured into a half-saturated solution of sodium bicarbonate (100 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, and the crude product was purified by filtration through a thin plug of silica gel (10% EtOAc/Hex) to afford **2-20** as a yellow oil (1.81 g, 2.58 mmol, 90% yield). R_f 0.70 (20% EtOAc/Hex); ^{1}H NMR (600MHz, $CDCl_3$) δ 8.28-8.23 (m, 4H), 5.73 (d, *J* = 7.6 Hz, 1H), 5.64 (s, 1H), 5.04 (s, 1H), 4.87 (s, 1H), 4.42 (s, 1H), 4.35 (q, *J* = 7.2 Hz, 1H), 4.12-4.08 (m, 1H), 3.66-3.63 (m, 2H), 2.25-2.20 (m, 1H), 2.14-2.09 (m, 1H), 2.02-1.95 (m, 1H), 1.89 (dt, *J* = 15.8, 7.9 Hz, 1H), 1.79-1.73 (m, 2H), 1.73-1.65 (m, 1H), 1.72 (s, 3H), 1.60 (dq, *J* = 12.1, 8.9 Hz, 2H), 1.40-1.32 (m, 3H), 1.30-1.24 (m, 4H), 0.87 (t, *J* = 7.8 Hz, 3H), 0.87 (s, 9H), 0.84 (s, 9H), 0.00 (d, *J* = 2.3 Hz, 6H), -0.02 (s, 6H); ^{13}C NMR (150MHz,

$CDCl_3$) δ 163.8, 153.7, 150.6, 148.9, 135.5, 131.0, 123.4, 111.1, 104.1, 87.1, 84.7, 80.0, 79.2, 68.7, 60.3, 38.5, 31.9, 29.9, 29.7, 28.7, 25.9, 25.8, 22.6, 18.2, 15.5, 14.0, -5.0, -5.2, -5.4.



2-21

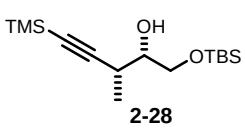
A 250 mL round bottom flask was charged with **2-20** (1.88 g, 2.68 mmol, 1 eq), diluted with ether (80 mL) and cooled to 0 °C. Red-Al (65% w/w in toluene, 3.33 g, 10.72 mmol, 4 eq) was added drop wise over 10 min. The ice bath was removed and the reaction was stirred for 30 min at rt before being slowly poured into a half-saturated solution of NH_4Cl (100 mL), and a saturated solution of Rochelle's salt was added (100 mL), and the slurry was stirred vigorously for 30 min. The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, and the crude product was purified by column chromatography (10% EtOAc/Hex) to afford alcohol **2-21** as a yellow oil (1.36 g, 2.38 mmol, 89% yield). $[\alpha]^{20}_D$ = –5.25° (*c* 1.0, $CHCl_3$); R_f 0.48 (20% EtOAc/Hex); ^{1}H NMR (600MHz, $CDCl_3$) δ 6.53 (dd, *J* = 14.93, 10.83 Hz, 1H), 6.05 (d, *J* = 11.2 Hz, 1H), 5.57 (dd, *J* = 15.22, 7.03 Hz, 1H), 5.09 (s, 1H), 4.84 (s, 1H), 4.38 (s, 1H), 4.09-4.05 (m, 1H), 3.95 (t, *J* = 7.32 Hz, 1H), 3.86 (q, *J* = 7.03 Hz, 1 H), 3.71 (t, *J* = 6.44 Hz, 2H), 2.61 (bs, 1H), 2. 08-2.03 (m, 1H), 1.88-1.94 (m, 1H), 1.90-1.85 (m, 1H), 1.80-1.75 (m, 2H), 1.72-1.65 (m, 2H), 1.61-1.53 (m, 1H), 1.59 (s, 3H), 1.41-1.33 (m, 2H), 1.32-1.25 (m, 2H), 0.890 (s, 9H), 0.88 (s, 9H), 0.87 (t, *J* = 7.8 Hz, 3H), 0.04 (d, *J* = 2.93 Hz, 6H), 0.00 (d, *J* = 9.95 Hz, 6H); ^{13}C NMR (151MHz, $CDCl_3$) δ 149.6, 139.6, 130.4, 128.8, 124.8, 109.7, 81.7, 80.7, 76.4, 75.5, 60.4, 38.7, 32.3, 30.7, 30.0, 28.1, 25.9, 25.8, 22.6, 18.3, 14.0, 12.1, -5.0, -5.1, -5.3; HRMS *m/z* 552.4019 (calcd for $C_{31}H_{60}O_4Si_2$, 552.4030).



2-25a

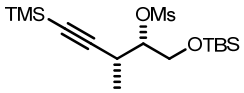
To a solution of TMS acetylene (13.7 mL, 99.8 mmol, 2.2 eq) in toluene (180 mL) cooled to 0 °C was added *n*BuLi (2.57M, 35.3 mL, 90.8 mmol, 2.0 eq) drop wise over 10 min. The reaction was allowed to stir for 15 min at which point Et_2AlCl (1.80M, 50.44 mL, 90.8 mmol, 2.0 eq) was added drop wise over 10 min. The reaction was allowed to stir for 1 hour while

maintaining a temperature of 0 °C, after which epoxide **2-25**[51] (4.0 g, 45.4 mmol, 1 eq) was added in one portion. The ice-water bath was removed, allowing the reaction to warm to room temperature, and was allowed to stir overnight (ca. 16h). The reaction was quenched by pouring into half saturated solution of NH_4Cl (400 mL) and diluted with EtOAc (100 mL), the aqueous layer was extracted with EtOAc (3 x 100 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, to afford a yellow oil, which was purified by column chromatography (70% EtOAc). The reaction yields the expected product **2-25a** (6.08 g, 32.68 mmol, 72% yield), as well as the regioisomer (2.03 g, 10.90 mmol, 24% yield) as an inseparable mixture.



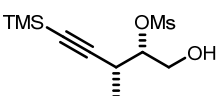
2-28

To a solution of the above regioisomers (8.11g, 43.58 mmol, 1 eq) in CH_2Cl_2 (150 mL) was added imidazole (6.22 g, 91.58 mmol, 2.2 eq), followed by TBSCl (6.56 g, 43.58 mmol, 1 eq), and a catalytic amount of DMAP. The reaction was allowed to stir for 3h, and upon completion by TLC analysis, the reaction was poured into half saturated solution of NH_4Cl (300 mL) and diluted with CH_2Cl_2 (50 mL), the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, to afford a yellow oil, which was purified by column chromatography (10% EtOAc). The reaction yields diol **2-28** (9.62 g, 32.02 mmol, 73% yield), and the regioisomer (3.21g, 10.62 mmol, 24% yield), which were separable by column chromatography. The overall yield of diol **2-28** from epoxide **2-25** was 70.5% over 2 steps. R_f 0.37 (10% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (dd, J = 10.0, 3.5 Hz, 1H), 3.72 (dd, J = 5.9, 5.9 Hz, 1H), 3.47-3.42 (m, 1H), 2.56-2.49 (m, 1H), 2.47 (d, J = 5.5 Hz, 1H), 1.25 (d, J = 7.0 Hz, 3H), 0.90 (s, 9H), 0.13 (s, 9H), 0.08 (d, J = 2.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 108.2, 64.4, 74.7, 65.0, 30.2, 25.9, 18.3, 17.2, 0.1, -5.4; HRMS m/z calcd for $C_{15}H_{32}O_2Si_2$ [$M+H^+$]: 301.1941, found: 301.2025.



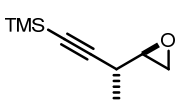
2-29

To a solution of diol **2-28** (4.0 g, 13.32 mmol, 1 eq) in CH_2Cl_2 (50 mL) was added triethylamine (2.0 mL, 19.98 mmol, 1.5 eq) and methanesulfonyl chloride (1.05 mL, 13.58 mmol, 1.02 eq). The reaction was allowed to stir at rt overnight (ca. 16 h). The reaction was poured into half saturated solution of NH_4Cl (200 mL) and diluted with CH_2Cl_2 (50 mL), the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, to afford **2-29** as a yellow oil, which was used in the next step without purification. R_f 0.344 (10% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.54 (td, J = 7.2, 3.5 Hz, 1H), 4.01 (dd, J = 11.5, 3.5 Hz, 1H), 3.86 (dd, J = 11.5, 6.7 Hz, 1H), 3.09 (s, 3H), 2.82 (p, J = 7.2 Hz, 1H), 1.27 (d, J = 7.0 Hz, 3H), 0.90 (s, 9H), 0.13 (s, 9H), 0.08 (d, J = 1.9 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 106.1, 87.4, 85.7, 63.4, 38.8, 28.4, 25.8, 18.3, 16.8, -0.1, -5.5; HRMS m/z calcd for $C_{16}H_{34}O_4SSi_2$ [M+H$^+$]: 379.1716, found: 379.1785.



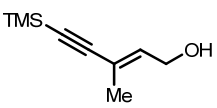
2-30

To a solution of the crude mesylate from above **2-29** in wet methanol (150 mL) was added 10-CSA (0.2 g, catalytic). The reaction was allowed to stir at rt until completion by TLC analysis (ca. 4h). The reaction was poured into half saturated solution of sodium bicarbonate (200 mL) and diluted with CH_2Cl_2 (100 mL), the aqueous layer was extracted with CH_2Cl_2 (5 x 100 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure to afford a yellow oil, which was purified by column chromatography (50% EtOAc) to afford **2-30** a yellow oil (3.38 g, 12.78 mmol, 96% yield over 2 steps). R_f 0.47 (50% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.58 (td, J = 7.1, 2.9 Hz, 1H), 3.99 (dd, J = 11.5, 3.5 Hz, 1H), 3.85 (dd, J = 11.5, 6.7 Hz, 1H), 3.11 (s, 3H), 2.84 (p, J = 7.1 Hz, 1H), 2.64 (bs, 1H), 1.28 (d, J = 7.0 Hz, 3H), 0.13 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 105.3, 88.1, 85.2, 63.1, 38.7, 28.9, 17.2, -0.1; HRMS m/z calcd for $C_{10}H_{20}O_4SSi$ [M+H$^+$]: 265.0852, found: 265.0927.



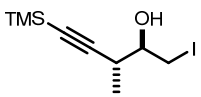
2-22

To a solution of NaH (100% stored in a glovebox, 1.54 g, 64.4 mmol, 5 eq) in diethyl ether (130 mL) was added mesylate **2-30** (3.40 g, 12.88 mmol, 1 eq) in one portion. The reaction was stirred for 15 min at rt before KI (2.17 g, 12.9 mmol, 1 eq) was added in one portion under a cone of nitrogen. The reaction was allowed to stir at rt for 24h, at which point it was carefully poured onto a half saturated solution of NH_4Cl (100 mL) and water ice (100 g). The solution diluted with (200 mL) and the aqueous layer was extracted with diethyl ether (3 x 50 mL) and the combined organics were washed with brine, dried with $MgSO_4$ and filtered through a thin pad of celite. Solvent was cautiously removed under reduced pressure (100 mmHg, water bath at 25°C) to afford **2-22** as a yellow oil, which was used crude in the next reaction immediately (1.45 g, 8.63 mmol, 67% yield). Extreme care must be taken to not lose the highly volatile product. R_f 0.354 (10% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.99 (ddd, J = 5.0, 3.9, 2.5 Hz, 1H), 2.75 (dd, J = 5.0, 3.8 Hz, 1H), 2.69 (dd, J = 5.0, 2.3 Hz, 1H), 2.63 (qd, J = 7.1, 5.0 Hz, 1H), 1.22 (d, J = 7.1 Hz, 3H), 0.14 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 106.1, 86.4, 54.4, 45.6, 29.1, 16.8, 0.1.



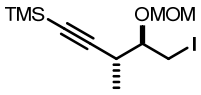
2-31

To a solution of dithiane **2-24** (336 mg, 1.15 mmol, 2 eq) in THF (10 mL) at 0 °C was added *n*BuLi (2.55 M, 0.45 mL, 1.15 mmol, 2 eq) drop wise. The solution was allowed to stir at 0 °C for 10 min before a catalytic amount of HMPA (3 drops) was added, followed by epoxide **2-22** (97 mg, 0.58 mmol, 1eq) in a minimal amount of THF. The reaction was allowed to stir at 0 °C for 1 h before being poured into a half saturated solution of NH_4Cl and diluted with EtOAc (10 mL), the aqueous layer was extracted with EtOAc (3 x 30 mL) and the combined organics were washed with brine, dried with $MgSO_4$ and filtered through a thin pad of celite. Solvent was removed under reduced pressure and the crude oil was purified by column chromatography to give alcohol **2-31** (95 mg, 0.57 mmol, 99%) as a yellow oil. R_f 0.40 (10% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.04 (tq, J = 8.6, 1.5 Hz, 1H), 4.20 (d, J = 6.6 Hz, 2H), 1.81 (d, J = 1.4 Hz, 3H), 0.17 (s, 9H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.4, 120.8, 107.3, 92.2, 59.2, 17.4, 0.0.



2-32

To a solution of epoxide **2-22** (71.6 mg, 0.453 mmol, 1 eq) in wet $CHCl_3$ (1.5 mL) was added tetrabutylammonium iodide (500 mg, 1.36 mmol, 3 eq) and trifluoroacetic acid (0.05 mL, 0.679 mmol, 1.5 eq). The reaction was allowed to stir at room temperature for 1 h, at which time the solution changes color from yellow to orange. The reaction was quenched by pouring into half saturated sodium bicarbonate (10 mL) and diluted with EtOAc (10 mL) the aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure to afford **2-32** as a yellow oil which was used crude in the next reaction. Note: The yellow oil contains the product iodohydrin **2-32** and tetrabutylammonium species. To obtain a pure sample of **2-32**, the EtOAc in the workup can be replaced by hexanes. Doing so results in a slight drop in yield, but an organic layer free of contaminants. R_f 0.35 (10% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.51-3.47 (m, 1H), 3.37 (d, J = 9.9, 5.3 Hz, 1H), 3.27 (dd, J = 10.1, 6.4 Hz, 1H), 2.90 (qd, J = 7.1, 4.4 Hz, 1H), 2.25 (d, J = 7.0 Hz, 1H), 1.21 (d, J = 7.0 Hz, 3H), 0.15 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 105.5, 88.7, 73.3, 33.2, 17.4, 10.4, 0.0; HRMS m/z calcd for $C_9H_{17}IOSi$: 296.0093, found: 296.0088.

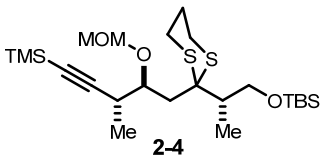


2-33

From iodohydrin 2-32: The crude iodohydrin **2-32** above was dissolved in $CHCl_3$ (1 mL) and dimethoxymethane (3 mL), and in one portion P_2O_5 (257 mg, 0.91 mmol, 2 eq) was added. The reaction was allowed to stir at room temperature and monitored by TLC upon completion (ca. 2 h). The reaction was then poured into half saturated solution of NH_4Cl (20 mL) and ice (10 mL) and diluted with hexanes (10 mL), the aqueous layer was extracted with hexanes (5 x 10 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure to afford a crude yellow oil which can be purified by column chromatography (10% EtOAc) to give pure **2-33** (81 mg, 0.240 mmol, 53% yield over 2 steps).

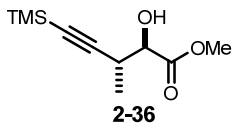
As a one pot procedure from epoxide 2-22: To a solution of epoxide **2-22** (71.6 mg, 0.453 mmol, 1 eq) in wet $CHCl_3$ (1.5 mL) was added tetrabutylammonium iodide (500 mg, 1.36 mmol, 3 eq) and trifluoroacetic acid (0.05 mL, 0.679 mmol, 1.5 eq). The reaction was allowed to stir at room temperature for 1 h, at which time the solution

changes color from yellow to orange. Dimethoxymethane (3 mL) was added, follow by the addition of P_2O_5 (257 mg, 0.91 mmol, 2 eq) in one portion. The reaction was allowed to stir at room temperature and monitored by TLC upon completion (ca. 2 hours). The reaction was then poured into half saturated solution of NH_4Cl (20 mL) and ice (10 mL) and diluted with hexanes (10 mL), the aqueous layer was extracted with hexanes (5 x 10 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure to afford a yellow oil which can be purified by column chromatography (10% EtOAc) to give pure **2-33** (121 mg, 0.358 mmol, 79% yield over 2 steps). R_f 0.45 (10% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.74 (s, 2H), 3.56-3.47 (m, 2H), 3.43 (s, 3H), 3.29 (dd, J = 10.0, 5.4 Hz, 1H), 2.97 (p, J = 7.1 Hz, 1H), 1.16 (d, J = 7.0 Hz, 3H), 0.14 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 107.1, 96.7, 86.6, 79.6, 56.1, 31.7, 15.8, 7.2, 0.1; HRMS m/z calcd for $C_{11}H_{21}IO_2Si$: 340.0356, found: 340.0360.



2-4

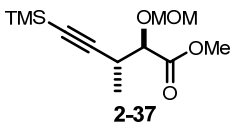
To a solution of dithiane **2-24** (336 mg, 1.15 mmol, 2 eq) in THF (10 mL) at 0 °C was added *n*BuLi (2.55 M, 0.45 mL, 1.15 mmol, 2 eq) drop wise. The solution was allowed to stir at 0 °C for 10 min before a catalytic amount of HMPA (3 drops) was added, followed by iodide **2-33** (196 mg, 0.58 mmol, 1eq) in a minimal amount of THF. The reaction was allowed to stir at 0 °C for 24 h before being poured into a half saturated solution of NH_4Cl and diluted with EtOAc (10 mL), the aqueous layer was extracted with EtOAc (3 x 30 mL) and the combined organics were washed with brine, dried with $MgSO_4$ and filtered through a thin pad of celite. Solvent was removed under reduced pressure to afford a yellow oil which was used without purification in the next step. The product **2-4** co-elutes with excess dithiane **2-24**.



2-36

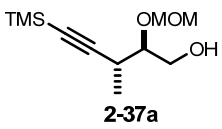
To a flask charged with TMS acetylene (6.37 g, 65 mmol, 2.0 eq) in toluene (200 mL) cooled to 0 °C was added *n*BuLi (2.2 M, 30 mL, 65 mmol, 2.0 eq) drop wise. The reaction was allowed to stir 10 min before diethyl aluminum chloride (1.8 M in toluene, 36.1 mL, 65 mmol, 2.0 eq) was added over 10 min. The reaction was stirred for 30 min before being cooled to -40 °C.

Epoxide **2-35** (2.86 g, 32.5 mmol, 1.0 eq) was added drop wise over 10 min. The cooling bath was replaced with an ice water bath and the reaction was allowed to stir at 0 °C for 30 min before being poured into a half saturated solution of ammonium chloride (200 mL) and diluted with EtOAc (100 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organics were washed with brine, dried with $MgSO_4$ and filtered through a thin pad of celite. Solvent was removed under reduced pressure to afford a yellow oil which was purified by column chromatography to afford alcohol **2-36** as a yellow oil (4.53 g, 24.4 mmol, 75%). R_f 0.58 (30% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.06 (d, J = 3.1 Hz, 1H), 3.79 (s, 3H), 2.99 (qd, J = 7.1, 3.3 Hz, 1H), 1.28 (d, J = 7.0 Hz, 3H), 0.12 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 104.9, 87.9, 73.4, 52.6, 32.2, 17.2, 0.0.



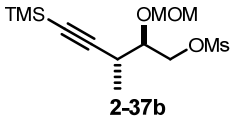
2-37

To a flask charged with alcohol **2-36** (3.45 g, 16.1 mmol, 1.0 eq), Hunig's base (10.2 g, 80.5 mmol, 5.0 eq) diluted with CH_2Cl_2 (100 mL) and equipped with a reflux condenser was added MOMCl (3.24 g, 40.2 mmol, 2.5 eq) drop wise over 10 min. The reaction was heated to reflux overnight (ca. 16h). The reaction was cooled before being poured into a half saturated solution of sodium bicarbonate (200 mL) and diluted with CH_2Cl_2 (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organics were washed with brine, dried with $MgSO_4$ and filtered through a thin pad of celite. Solvent was removed under reduced pressure to afford a yellow oil which dissolved in EtOAc (200 mL) and diluted with water (100 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organics were washed with brine, dried with $MgSO_4$ and filtered through a thin pad of celite. Solvent was removed under reduced pressure to afford **2-37** as a yellow oil (3.95 g, 15.3 mmol, 95%) which was used without further purification. R_f 0.60 (30% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.70 (s, 2H), 4.06 (d, J = 7.0 Hz, 1H), 3.74 (s, 3H), 3.39 (s, 3H), 2.99 (quin, J = 7.0, 1H), 1.19 (d, J = 7.0 Hz, 3H), 0.12 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 106.5, 96.3, 86.4, 78.3, 56.1, 51.9, 30.6, 16.7, 0.0.



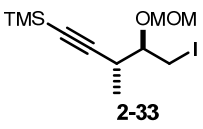
2-37a

To a flask charged with $LiAlH_4$ (872 mg, 22.9 mmol, 1.5 eq) and diluted with diethyl ether (100 mL) cooled to 0 °C was added ester **2-37** (3.95 g, 15.3 mmol, 1.0 eq) drop wise over 10 min. The reaction was monitored by TLC until complete (~1h) before being poured into a half saturated solution of ammonium chloride (200 mL) and diluted with EtOAc (100 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organics were washed with brine, dried with $MgSO_4$ and filtered through a thin pad of celite. Solvent was removed under reduced pressure to afford alcohol **2-37a** as a yellow oil (3.17 g, 13.8 mmol, 90%) which was used without further purification. R_f 0.34 (30% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.74 (q, J = 7.8 Hz, 2H), 3.76 (ABd, 7.0, 2.7 Hz, 1H), 3.65 (ABd, J = 7.0, 2.7 Hz, 1H), 3.58-3.54 (m, 1H), 3.43 (s, 3H), 2.78 (qd, J = 7.0, 5.5 Hz, 1H), 1.17 (d, J = 7.0 Hz, 3H), 0.13 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 97.3, 86.2, 83.3, 63.3, 55.8, 41.9, 29.6, 16.3, 0.1.



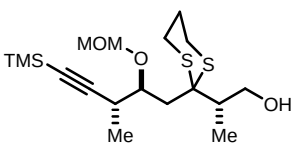
2-37b

To a flask charged with alcohol **2-37a** (3.0 g, 13.0 mmol, 1.0 eq), triethylamine (2.60 g, 26.0 mmol, 2.0 eq), diluted with CH_2Cl_2 (50 mL) and cooled to 0 °C was added methanesulfonyl chloride (1.63 g, 14.3 mmol, 1.1 eq) drop wise. The reaction was allowed to stir at rt for 30 min before being poured into a half saturated solution of ammonium chloride (100 mL) and diluted with CH_2Cl_2 (500 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organics were washed with brine, dried with $MgSO_4$ and filtered through a thin pad of celite. Solvent was removed under reduced pressure to afford mesylate **2-37b** as a yellow oil (4.0 g, 13.0 mmol, 100%) which was used without further purification. R_f 0.42 (30% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.71 (s, 2H), 4.44 (dd, J = 10.5, 3.9 Hz, 1H), 4.28 (dd, J = 10.7, 6.4 Hz, 1H), 3.82 (ddd, J = 6.2, 5.1, 3.9 Hz, 1H), 3.40 (s, 3H), 3.03 (s, 3H), 2.87 (qd, J = 7.1, 5.1 Hz, 1H), 1.20 (d, J = 7.0 Hz, 1H), 0.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 106.5, 96.7, 87.2, 69.6, 55.9, 27.4, 29.2, 15.7, 0.0.



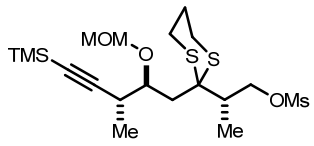
2-33

To a flask charged with mesylate **2-37b** (4.0 g, 13.0 mmol, 1 eq) in wet acetone (50 mL) equipped with a reflux condenser was added NaI (5.85 g, 39.0 mmol, 3.0 eq). The reaction was heated to vigorous reflux and allowed to stir overnight (ca. 16h) before being cooled to 0 °C and filtered through a thin pad of silica over celite. Solvent was removed under reduced pressure to afford a yellow oil which was purified by column chromatography (10% EtOAc/Hex) to afford **2-33** (4.07 g, 12.0 mmol, 92%) as a yellow oil. R_f 0.45 (10% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.74 (s, 2H), 3.56-3.47 (m, 2H), 3.43 (s, 3H), 3.29 (dd, J = 10.0, 5.4 Hz, 1H), 2.97 (p, J = 7.1 Hz, 1H), 1.16 (d, J = 7.0 Hz, 3H), 0.14 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 107.1, 96.7, 86.6, 79.6, 56.1, 31.7, 15.8, 7.2, 0.1; HRMS m/z calcd for $C_{11}H_{21}IO_2Si$: 340.0356, found: 340.0360.



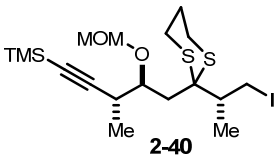
2-38

To a solution of TBS ether **2-4** (600 mg, 1.19 mmol, 1 eq) in wet methanol (20 mL) was added a catalytic amount of 10-champhorsulfonic acid. The reaction was allowed to stir at rt for 15 min before being poured into a half saturated solution of sodium bicarbonate (50 mL) and diluted with EtOAc (50 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL) and the combined organics were washed with brine, dried with $MgSO_4$ and filtered through a thin pad of celite. Solvent was removed under reduced pressure to afford a yellow oil which was purified by column chromatography (20% EtOAc/Hex) to give the product alcohol **2-38** (316 mg, 0.81 mmol, 68% yield). R_f 0.45 (40% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.77 (d, J = 7.0 Hz, 1H), 4.59 (d, J = 7.0 Hz, 1H), 4.12-4.10 (m, 1H), 3.96 (dd, J = 11.7, 5.3 Hz, 1H), 3.77 (dd, J = 11.4, 5.0 Hz, 1H), 3.33 (s, 3H), 3.07-3.02 (m, 1H), 3.01-2.97 (m, 1H), 2.95-2.89 (m, 1H), 2.67-2.63 (m, 1H), 2.49 (d, J =15.2 Hz, 1H), 2.46 (bs, 1H), 2.33 (q, J = 6.4 Hz, 1H), 2.10 (dd, J = 15.5, 9.1 Hz, 1H), 1.99-1.94 (m, 1H), 1.92-1.88 (m, 1H), 1.18 (d, J = 7.0 Hz, 3H), 1.13 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.2, 97.5, 86.5, 65.6, 56.6, 56.1, 42.2, 35.5, 31.7, 26.0, 25.7, 25.1, 13.8, 12.7, 0.1.



2-39

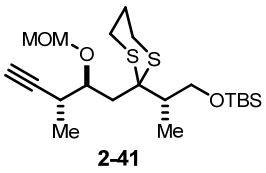
To a solution of alcohol **2-38** (35.7 mg, 0.0913 mmol, 1 eq) in CH_2Cl_2 (1 mL) at rt was added triethylamine (36 mg, 0.365 mmol, 4 eq) followed by methanesulfonyl chloride (20.8 mg, 0.183 mmol, 2 eq). The reaction was stirred at rt until complete as indicated by TLC (ca. 15 min) before being poured into a half saturated solution of NH_4Cl (20 mL) and diluted with EtOAc (20 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL) and the combined organics were washed with brine, dried with $MgSO_4$ and filtered through a thin pad of celite. Solvent was removed under reduced pressure to afford mesylate **2-39** as a yellow oil which was used without further purification (38.7 mg, 0.0825 mmol, 91% yield). R_f 0.20 (20% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.92 (dd, *J* = 10.0, 2.9 Hz, 1H), 4.75 (d, *J* = 6.4 Hz, 1H), 4.60 (d, *J* = 7.0 Hz, 1H), 4.21 (t, *J* = 6.7 Hz, 1H), 4.14 (dd, *J* = 8.8, 2.9 Hz, 1H), 3.35 (s, 3H), 3.06-3.01 (m, 2H), 3.01 (s, 3H), 2.95-2.90 (m, 1H), 2.78-2.75 (m, 1H), 2.63-2.59 (m, 1H), 2.51-2.48 (m, 2H), 2.14 (dd, *J* = 15.8, 9.4 Hz, 1H), 2.04-1.95 (m, 1H), 1.99-1.85 (m, 1H), 1.23 (d, *J* = 7.0 Hz, 3H), 1.20 (d, *J* = 7.0 Hz, 3H), 0.12 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.2, 97.4, 86.5, 79.2, 73.8, 56.2, 55.8, 40.4, 47.2, 35.2, 31.4, 25.8, 25.7, 25.0, 13.7, 12.3, 0.1.



2-40

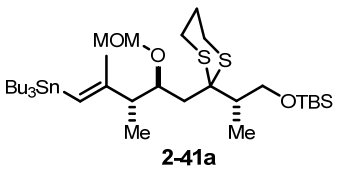
To a solution of alcohol **2-39** (30 mg, 0.0768 mmol, 1.0 eq) in toluene (2 mL) cooled to 0 °C was added triphenylphosphine (26.2 mg, 0.1 mmol, 1.3 eq), followed by imidazole (8 mg, 0.115 mmol, 1.5 eq), and iodine (30 mg, 0.119 mmol, 1.55 eq). The reaction was monitored by TLC until completion (ca. 1 h) before being poured into a half saturated solution of sodium thiosulfate (20 mL) and diluted with EtOAc (20 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL) and the combined organics were washed with brine, dried with $MgSO_4$ and filtered through a thin pad of celite. Solvent was removed under reduced pressure to afford iodide **2-40** as a yellow oil which was used without further purification (34.6 mg, 0.069 mmol, 90% yield). R_f 0.48 (10% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.75 (d, *J* = 7.0 Hz, 1H), 4.60 (d, *J* = 7.0 Hz, 1H), 4.16 (d, *J* = 9.4 Hz, 1H), 4.13-4.11 (dd, *J* = 8.5, 3.2 Hz, 1H), 3.37 (s, 3H), 3.10 (t, *J* = 10.0 Hz, 1H), 3.06-3.02 (m, 1H), 3.02-2.97 (m, 1H), 2.91-2.87 (m, 1H), 2.81-2.75 (m,

1H), 2.67-2.60 (m, 1H), 2.13 (dd, *J* = 15.5, 9.1 Hz, 1H), 1.98-1.93 (m, 1H), 1.89-1.84 (m, 1H), 1.33 (d, *J* = 7.0 Hz, 3H), 1.18 (d, *J* = 7.0 Hz, 3H), 0.13 (s, 9H).



2-41

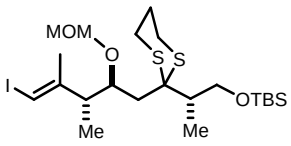
The crude TMS alkyne **2-4** (ca. 1.15 mmol) was dissolved in wet methanol (20 mL), and a K_2CO_3 was added (317 mg, 2.30 mmol, 2 eq). The reaction was stirred at 0 °C for 10 h before being filtered through a pad of celite into a solution of half saturated NH_4Cl (100 mL). The celite pad was washed with EtOAc (50 mL) and the filtrate was transferred to a separatory funnel, and the aqueous layer was extracted with EtOAc (3 x 30 mL) and the combined organics were washed with brine, dried with $MgSO_4$ and filtered through a thin pad of celite. Solvent was removed under reduced pressure to afford a yellow oil which was purified by column chromatography (5-10% EtOAc/Hex) to give the product **2-41** (162 mg, 0.38 mmol, 65% yield). R_f 0.43 (10% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.81 (d, *J* = 6.4 Hz, 1H), 4.62 (d, *J* = 6.4 Hz, 1H), 4.17 (dd, *J* = 9.6, 3.2 Hz, 1H), 4.05 (dt, *J* = 9.6, 3.2 Hz, 1H), 3.60 (t, *J* = 8.8 Hz, 1H), 3.37 (s, 3H), 3.05 (dt, *J* = 6.9, 3.3 Hz, 1H), 2.91 (ddd, *J* = 14.2, 8.9, 3.2 Hz, 1H), 2.85-2.81 (m, 1H), 2.80-2.75 (m, 1H), 2.71-2.65 (ddd, *J* = 14.3, 7.2, 2.9 Hz, 1H), 2.40 (dd, *J* = 15.5, 2.6 Hz, 1H), 2.25-2.20 (m, 1H), 2.12 (dd, *J* = 8.9, 7.3, 1H), 2.11 (d, *J* = 2.4 Hz, 1), 1.95-1.90 (m, 2H), 1.23 (d, *J* = 7.0 Hz, 3H), (1.17 (d, *J* = 7.0 Hz, 3H), 0.89 s, 9H), 0.05 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ97.3, 86.4, 78.7, 70.3, 65.2, 56.1, 45.6, 42.1, 36.8, 31.2, 29.7, 26.0, 25.1, 18.3, 14.8, 12.5, 8.5, -5.2; HRMS m/z calcd: 432.2188, found: 432.2190.



2-41a

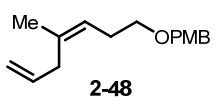
To a solution of hexabutylditin (650 mg, 1.16 mmol, 4 eq) in THF (10 mL) cooled to -20 °C was added *n*BuLi (1.90 M, 0.61 mL, 1.16 mmol, 4 eq) drop wise. The reaction was allowed to stir at -20 °C for 10 min followed by the drop wise addition of freshly prepared MeMgI (1.0 M in ether, 1.16 mL, 1.16 mmol, 4 eq). The reaction was stirred another 10 min before CuCN (104 mg, 1.16 mmol, 4 eq) was added in one portion. The reaction was stirred another 5 min at -20 °C before alkyne **2-41** (126 mg, 0.292 mmol, 1 eq) was added in one portion. After 20 min of stirring at -20 °C, MeI (0.18 mL, 2.92 mmol, 20 eq) was added and the cooling bath was removed to allow

the reaction to warm to rt, where it was allowed to stir for an additional 10 min before being poured into a half saturated solution of NH_4Cl (50 mL) and diluted with EtOAc (50 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL) and the combined organics were washed with brine, dried with $MgSO_4$ and filtered through a thin pad of celite. Solvent was removed under reduced pressure to afford a yellow oil which was purified by column chromatography (5% EtOAc/Hex) to give the product stannane **2-41a** (146 mg, 0.198 mmol, 68% yield) as a single regioisomer and recovered starting material **2-41** (12.5 mg, 0.029 mmol, 10% yield). R_f 0.37 (5% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63 (s, 1H), 4.82 (d, J = 7.0 Hz, 1H), 4.68 (d, J = 7.0 Hz, 1H), 4.18 (d, J = 9.9, 3.5 Hz, 1H), 4.12-4.09 (m, 1H), 3.47 (t, J = 9.7 Hz, 1H), 3.40 (s, 3H), 2.76-2.59 (m, 5H), 2.25-2.21 (m, 1H), 1.97-1.95 (m, 1H), 1.89 (s, 3H), 1.89-1.84 (m, 2H), 1.50-1.45 (m, 5H), 1.32-1.25 (m, 8H), 1.16 (d, J = 7.0 Hz, 3H), 1.08 (d, J = 6.4 Hz, 3H), 0.90-0.86 (m, 26H), 0.04 (s, 6H).



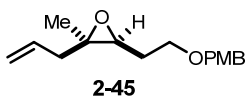
2-42

To a solution of stannane **2-41a** (11 mg, 0.015 mmol, 1 eq) in CH_2Cl_2 (1 mL) cooled to 0 °C was added a solution of I_2 (1.0 M in CH_2Cl_2) drop wise until the color persisted (ca. 0.1 mL). The reaction was allowed to stir at 0 °C for 10 min before being poured into a half saturated solution of sodium thiosulfate (20 mL) and diluted with CH_2Cl_2 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organics were washed with brine, dried with $MgSO_4$ and filtered through a thin pad of celite. Solvent was removed under reduced pressure to afford iodide **2-42** as a yellow oil (8.8 mg, 0.015 mmol, 99% yield) which was used without further purification. The product co-eluted with excess tin compounds, so it was treated with excess TBAF and characterized as the alcohol. R_f 0.40 (45% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.06 (s, 1H), 4.80 (d, J = 7.0 Hz, 1H), 4.66 (d, J = 7.0 Hz, 1H), 4.06 (d, J = 6.1, 3.2 Hz, 1H), 3.92 (dd, J = 11.4, 5.6 Hz, 1H), 3.73 (dd, J = 11.7, 5.3 Hz, 1H), 2.85-2.77 (m, 3H), 2.70-2.62 (m, 2H), 2.28 (q, J = 7.0 Hz, 1H), 2.07-2.03 (m, 1H), 1.94 (s, 3H), 1.89-1.85 (m, 1H), 1.14 (d, J = 7.0 Hz, 3H), 1.11 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.4, 97.3, 77.8, 77.6, 65.5, 56.5, 56.3, 47.1, 41.7, 35.5, 26.1, 25.6, 25.0, 12.8, 11.9.



2-48

To a suspension of NaH (780 mg, 32.5 mmol, 1.3 eq) in THF (150 mL) at 0 °C was added freshly prepared PMBBr (6.53 g, 32.5 mmol, 1.3 eq), followed by alcohol **2-47**[52] (2.15 g, 25 mmol, 1.0 eq). The ice-bath was removed and after ca. 16 h the reaction was poured into a half saturated solution NH_4Cl (100 mL) in water ice (200 mL) and stirred for 5 min, after which the aqueous layer was extracted with EtOAc (150 mL x 3). The combined organics were washed with brine, dried over $MgSO_4$, and filtered through a thin pad of packed celite. Solvent was removed under reduced pressure and the crude oil was purified by flash chromatography (10% EtOAc/Hex) to yield the PMB ether (**2-48**) as a colorless oil (5.54 g, 22.5 mmol, 90%). R_f 0.42 (10% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 5.72 (ddt, J = 16.7, 10.1, 6.4 Hz, 1H), 5.22 (t, J = 6.7 Hz, 1H), 5.03-4.96 (m, 1H), 4.44 (s, 2H), 3.78 (s, 3H), 3.42 (t, J = 7.0 Hz, 2H), 2.76 (d, J = 6.4 Hz, 2H), 2.31 (q, J = 7.0 Hz, 2H), 1.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 135.9, 135.1, 130.6, 129.2, 121.8, 115.2, 113.7, 72.5, 69.8, 55.3, 36.5, 28.5, 23.4.



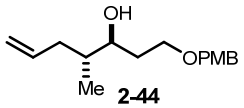
2-45

To a flask charged with diene **2-48** (2.46 g, 10 mmol, 1.0 eq) was added dimethoxymethane (100 mL), acetonitrile (50 mL), buffer[53] (100 mL), ***ent*-2-49** (157 mg), and $Bu_4N{\cdot}H_2SO_4$ (50 mg, catalytic) and the flask was cooled to 0 °C. A syringe pump was fitted with two 60 mL syringes, one charged with K_2CO_3 (6.90 g) in distilled water (60 mL), the second charged with oxone® (6.90 g) in distilled water (60 mL). The syringes were added to the rigorously stirred solution over 4 h, and (***ent*-2-49**) was added portion-wise at the 1 h, 2 h and 3 h time mark (157 mg per addition, 630 mg total, 2.50 mmol, 0.25 eq). The reaction was stirred for 15 min after additions of the base and oxone® were complete, at which point hexanes (200 mL) was added. The solution was transferred to a separatory funnel and the aqueous layer was extracted with hexanes (100 mL x 4). The combined organics were washed with brine, dried over $MgSO_4$, and filtered through a thin pad of celite. Solvent was removed under reduced pressure and the crude oil was purified by column chromatography (20% EtOAc/Hex) to yield the mono-epoxide **2-45** (1.93 g, 7.40 mmol, 74%) and the di-epoxide **2-50** (305 mg, 1.10 mmol, 11%) as yellow oils. R_f 0.17 (10% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz,

2H), 5.77 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.10-5.05 (m, 2H), 4.43 (ABd, *J* = 11.7 Hz, 2H), 3.59-3.56 (m, 2H), 2.86 (dd, *J* = 7.4, 4.7 Hz, 1H), 2.30 (dd, *J* = 7.0, 7.0 Hz, 1H), 2.18 (dd, *J* = 7.0, 7.0 Hz, 1H), 1.98-1.89 (m, 1H), 1.77-1.68 (m, 1H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 133.5, 130.4, 129.3, 117.8, 113.8, 72.8, 67.3, 61.9, 60.1, 55.3, 37.9, 29.4, 22.1. HRMS *m/z* 262.1576 (calcd for $C_{16}H_{22}O_3$, 262.1569).

$BF_2OBn{\cdot}OEt_2$
2-51

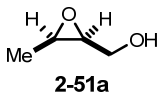
To a vigorously stirred solution of TMSOBn (1.90 g, 10.5 mmol, 1.05 eq) in diethyl ether (100 mL) was added $BF_3{\cdot}OEt_2$ (1.26 mL, 10 mmol, 1.0 eq). The septum was pierced with a 20.5 gauge needle to allow release of argon from a balloon over the solution fitted with a 20.5 gauge needle. The argon balloon was replaced as necessary to ensure the flask was always under an inert, positive pressure atmosphere.[54] The solution was allowed to evaporate to dryness (ca. 1 h), and the argon flow was continued for an additional 10 min. To the residual yellow oil was added an additional portion of diethyl ether (10 mL) to give a 1.0 M solution of $BF_2OBn{\cdot}OEt_2$ (**2-51**).[55] It may be necessary to repeat the evaporation process, see footnote 6. The solution displays remarkable stability (no decrease in concentration over 2 weeks, sealed, stored in a refrigerator (-20 °C) or at rt). Solvents other than diethyl ether caused decomposition of the Lewis acid. Characterization of **2-51** and reactions employing **2-51** must be run in diethyl ether. ^{19}F NMR (375 MHz, Et_2O) δ -151.5 ppm. Trifluorotoluene (-63.9 ppm) was used as an internal standard.



2-44

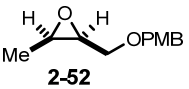
To a flask charged with $NaCNBH_3$ (255 mg, 4.0 mmol, 4.0 eq) in diethyl ether (15 mL) was added epoxide **2-45** (262 mg, 1.0 mmol, 1.0 eq). A solution of $BF_2OBn{\cdot}OEt_2$ (1.0 M, 4.0 mL, 4.0 mmol, 4.0 eq) was added to the vigorously stirred solution via syringe pump over 4 h. After the addition was complete, the reaction was stirred for 15 min before being poured into a half saturated solution of sodium bicarbonate (100 mL). The solution was transferred to a separatory funnel and the aqueous layer was extracted with EtOAc (50 mL x 3). The combined organics were washed with brine, dried over $MgSO_4$, and filtered through a thin pad of packed celite. Solvent was removed under reduced pressure and the crude oil was purified by flash chromatography (30% EtOAc/Hex) to yield alcohol **2-44** (240 mg,

0.91 mmol, 91%) as a yellow oil. R_f 0.50 (40% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.79 (ddt, *J* = 17.3, 10.0, 7.1 Hz, 1H), 5.04-4.97 (m, 2H), 4.45 (m, 2H), 4.45 (s, 2H), 3.79 (s, 3H), 3.71 (dt, *J* = 9.5, 4.9 Hz, 1H), 3.61 (q, *J* = 6.4 Hz, 2H), 3.00 (d, *J* = 2.3 Hz, 1H), 2.30-2.26 (m, 1H), 1.90 (dt, *J* = 13.9, 8.3 Hz, 1H), 1.73-1.70 (m, 2H), 1.64-1.59 (m, 1H), 0.86 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.3, 137.6, 130.0, 129.3, 115.8, 113.8, 75.2, 73.0, 69.4, 55.3, 38.6, 36.9, 32.8, 15.1. HRMS *m/z* 264.1725 (calcd for $C_{16}H_{24}O_3$, 264.1725). $[\alpha]^{20}_D$ = +1.73° (*c* 1.0, $CHCl_3$). The ee was determined to be 85% by (*R*)-Mosher's analysis.



2-51a

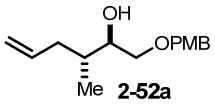
To a 500 mL round bottom flask containing 200 g of activated 4Å molecular sieves was added CH_2Cl_2 (250 mL), and the flask was placed in a -20 °C cooling bath. (+)-Diethyl tartrate (1.73 g, 8.4 mmol, 0.06 eq) was added, followed by Ti(O*i*Pr)$_4$ (2.05 mL, 7 mmol, 0.05 eq), and *cis*-butenol (10 g, 140 mmol, 1 eq). After 1 h, *t*BuOOH (5.33 M, 52.5 mL, 280 mmol, 2 eq) was added portion wise over 30 min. After 24 h the septum was removed and dimethylsulfide (20.7 mL, 280 mmol, 2 eq) was added. The reaction was stirred open to atmosphere for another 24 h before being filtered through a thin pad of packed celite, and washed with CH_2Cl_2 (500 mL). Solvent was removed under reduced pressure and the crude oil purified by flash chromatography (100% hexanes, 1 L, followed by 70% EtOAc/Hex) to give pure epoxide (**2-51a**) (9.47 g, 107.8 mmol, 77% yield) as a yellow oil. Spectral data matches literature values, $[\alpha]^{20}_D$ = -4.28° (*c* 1.0, $CHCl_3$); literature $[\alpha]^{20}_D$ = -4.26° (*c* 1.0, $CHCl_3$).[56]



2-52

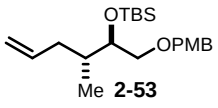
To a solution of NaH (2.3 g, 95.7 mmol, 1.1 eq) in DMF (200 mL) cooled to 0 °C was added 4-methoxybenzyl bromide (20.3 g, 100.8 mmol, 1.16 eq), followed by drop wise addition of epoxide **2-51a** (7.7 g, 87 mmol, 1 eq). The reaction was warmed to rt and after 30 min, at which time it was judged to be complete by TLC analysis. The reaction mixture was carefully poured into a solution of saturated NH_4Cl (200 mL) in water ice (500 mL) and stirred for 10 min, after which the aqueous layer was extracted with EtOAc (300 mL x 3). The combined organics were washed with brine, dried over $MgSO_4$, and filtered through a thin pad of packed celite. Solvent was removed under reduced pressure and the crude oil was purified by flash

chromatography (20% EtOAc/Hex) to yield **2-52** (15.6 g, 74.8 mmol, 86%) as a yellow oil. R_f 0.40 (30% EtOAc/Hex); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.27 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 4.51 (ABd, J = 11.7 Hz, 2H), 3.79 (s, 3H), 3.63 (dd, J = 10.5, 4.7 Hz, 1H), 3.53 (dd, J = 11.3, 6.4 Hz, 1H), 3.14 (dt, J = 6.2, 4.2 Hz, 1H), 3.08 (pent, J = 5.1 Hz, 1H), 1.25 (d, J = 5.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.2, 129.9, 129.4, 113.9, 72.9, 67.7, 55.2, 55.0, 51.7, 13.3. HRMS *m/z* 208.1099 (calcd for $C_{12}H_{16}O_3$, 208.1099).



2-52a

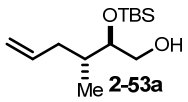
To a freshly prepared solution of allyl Grignard (1.0 M in ether, 90 mL, 90 mmol, 1.5 eq) was added to a flask charged with CuI (1.12 g, 5.88 mmol, 0.1 eq) cooled to -78 °C. The cuperate was stirred for 30 min at -78 °C before epoxide **2-52** (12.26 g, 58.9 mmol, 1 eq) was added neat. The cooling bath was packed with dry ice and the reaction was allowed to warm to rt overnight (ca. 16 h). The reaction mixture was carefully poured into a half saturated solution NH_4Cl (200 mL) in water ice (400 mL) and stirred for 30 min, after which the aqueous layer was extracted with EtOAc (300 mL x 3). The combined organics were washed with brine, dried over $MgSO_4$, and filtered through a thin pad of packed celite. Solvent was removed under reduced pressure and the crude oil was purified by flash chromatography (20% EtOAc/Hex) to yield the major diastereomer **2-52a** (12.06 g, 48.2 mmol, 85%) as a yellow oil and the minor diastereomer (1.34 g, 5.36 mmol, 9%) as a yellow oil. R_f 0.28 (20% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 5.77 (dddd, J = 16.9, 10.2, 7.8, 6.4 Hz, 1H), 5.03-4.99 (m, 2H), 4.48 (d, J = 1.6 Hz, 2H) 3.79 (s, 3H), 3.56-3.53 (m, 1H), 3.39-3.35 (m, 1H), 2.42 (bs, 1H), 2.37-2.31 (m, 1H), 1.98-1.89 (m, 1H), 1.73-1.63 (m, 1H), 0.85 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 137.0, 130.0, 129.2, 116.0, 113.7, 73.6, 72.9, 72.1, 55.1, 36.9, 35.7, 15.1. HRMS *m/z* 250.1572 (calcd for $C_{15}H_{22}O_3$, 250.1569).



2-53

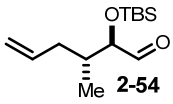
To a solution of alcohol (**2-52a**) (10.7 g, 42.6 mmol, 1 eq) in DMF (300 mL) was added imidazole (5.8 g, 85.2 mmol, 2 eq), followed by TBSCl (6.6 g, 42.6 mmol, 1 eq) and DMAP (50 mg, catalytic). The reaction was stirred overnight (ca. 16 h) before being poured into a half saturated solution

of NH_4Cl, and the aqeous layer was extracted with CH_2Cl_2 (5 x 200 mL) and the combined organics were washed with brine and dried over $MgSO_4$. Solvent was removed under reduced pressure to give the TBS alcohol, which was purified by flash chromatography (5% EtOAc/Hex) to give the pure alcohol (**2-53**) as a yellow oil (15.3 g, 42.2 mmol, 99% yield). R_f 0.53 (10% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 5.80-5.75 (m, 1H), 5.01-4.97 (m, 2H), 4.44 (q, *J* = 9.4 Hz, 2H), 3.80 (s, 3H), 3.71 (q, *J* = 4.8 Hz, 1H), 3.46 (dd, *J* = 9.7, 5.0 Hz, 1H), 3.37 (dd, *J* = 9.7, 6.2 Hz, 1H), 2.25-2.21 (m, 1H), 1.87-1.82 (m, 1H), 1.79-1.72 (m, 1H), 0.89 (s, 3H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.0, 138.0, 130.5, 129.2, 115.5, 113.6, 75.1, 72.9, 72.5, 55.2, 36.5, 36.0, 25.9, 18.2, 15.9, -4.2, -4.9. HRMS *m/z* 363.2341 (calcd for $C_{21}H_{36}O_3Si$, 364.2434). $[\alpha]^{20}_D$ = +4.11° (*c* 1.0, $CHCl_3$).



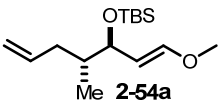
2-53a

PMB alcohol (**2-53**) (6.89 g, 18.9 mmol, 1 eq) was dissolved in CH_2Cl_2 (140 mL), water (35 mL) and saturated sodium bicarbonate (10 mL). DDQ (8.58 g, 37.8 mmol, 2 eq) was added in one portion and the reaction was rigorouly stirred for 1.5 h at which point the reaction was judged to be complete by TLC analysis. The reaction mixture was poured into a rapidly stirring solution of half saturated sodium bicarbonate (100 mL) and half saturated sodium thiosulfate (200 mL), and the aqeous layer was extracted with CH_2Cl_2 (5 x 200 mL) and the combined organics were washed with brine and dried over $MgSO_4$. Solvent was removed under reduced pressure to give the cude alcohol, which was purified by flash chromatography (10% EtOAc/Hex) to give the pure alcohol **2-53a** as a yellow oil (4.24 g, 17.4 mmol, 92% yield). R_f 0.51 (20% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.74 (ddd, *J* = 17.0, 10.1, 7.0 Hz, 1H), 5.03-4.98 (m, 2H), 3.59-3.55 (m, 3H), 2.25-2.21 (m, 1H) 1.84-1.77 (m, 3H), 0.90 (s, 9H), 0.87 (s, *J* = 7.0 Hz, 3H), 0.06 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.3, 115.9, 76.2, 63.5, 37.2, 36.3, 25.8, 18.1, 14.9, -4.4, -4.5. HRMS *m/z* 245.1942 (calcd for $C_{13}H_{28}O_2Si$, 244.1859). $[\alpha]^{20}_D$ = -4.36°, (*c* 1.0, $CHCl_3$).



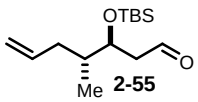
2-54

Alchol (**2-53a**) (4.02 g, 16.4 mmol, 1 eq) was disolved in wet EtOAc (120 mL), and IBX (9.2 g, 32.9 mmol. 2 eq) was added. The suspension was stirred at 80 °C for 5 h, at which point the reaction was judged complete by TLC analysis. The flask was removed from the heat and allowed to cool to rt before the solution was filtered through a thin pad of silica over a pad of packed celite, and the filter cake was washed with 400 mL EtOAc. Solvent was removed under reduced pressure to give the pure aldehyde **2-54** (3.97 g, 16.3 mmol, 99% yield), which was used in the next step without further purification. R_f 0.72 (20% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (d, J = 2.0 Hz, 1H), 5.69 (ddd, J = 17.0, 10.0, 7.2 Hz, 1H), 5.05-4.99 (m, 2H), 3.79 (dd, J = 4.3, 2.0 Hz, 1H), 2.26-2.20 (m, 1H) 2.05-1.89 (m, 2H), 0.95 (s, 9H), 0.92 (d, J = 6.6 Hz, 3H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.0, 136.9, 116.8, 81.2, 37.3, 35.8, 25.7, 18.2, 16.1, -4.5, -4.6.



2-54a

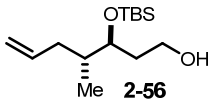
To a solution of *t*BuOK (3.90 g, 34.8 mmol, 2.0 eq) in THF (200 mL) was added Ph_3PCH_2OMeCl (13.1 g, 38.3 mmol, 2.2 eq) in one portion, and the red solution was stirred at rt for 1 h. To the red solution was added crude aldehyde (**2-54**) (3.97 g, 16.4 mmol, 1 eq) in a minimal ammount of THF (ca. 20 mL). After 16 h the crude reaction was poured into a rapidly stirring solution of half saturated NH_4Cl (300 mL), and the aqeous layer was extracted with CH_2Cl_2 (3 x 200 mL) and the combined organics were washed with brine, dried over $MgSO_4$ and filtered through a thin pad of packed celite/silica. Solvent was removed under reduced pressure to give the crude enol ether (**2-54a**) which was contaminated with some Wittig byproducts, and the crude mixture was used in the next reaction without further purification.



2-55

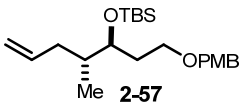
The crude mixture of enol ether and Wittig byproducts was dissolved in wet THF (300 mL) and water (30 mL), and $Hg(OAc)_2$ (7.84 g, 24.6 mmol, 1.5 eq) was added in one portion. The solution was stirred at rt for 1.5 h at which point disapearance of the enol ether was confirmed by TLC analysis. Tetrabutylammonium iodide (18.1 g, 49.2 mmol, 3 eq) was added in one portion, and the reaction was stirred for 1 h at rt before being poured into a rapidly stirring solution of half

saturated KI (100 mL) and half saturated sodium thiosulfate (200 mL), and the aqeous layer was extracted with CH_2Cl_2 (4 x 200 mL) and the combined organics were washed with brine dried over $MgSO_4$ and filtered through a thin pad of packed celite. Solvent was removed under reduced pressure to give the cude aldehyde, which was purified by flash chromatography (20% EtOAc/Hex) to give the pure aldehyde **2-55** (2.60 g, 10.2 mmol, 62% yield over 2 steps). R_f 0.50 (10% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (s, 1H), 5.78-5.71 (m, 1H), 5.02-5.00 (m, 2H), 4.14 (dt, *J* = 8.2, 4.1 Hz, 1H), 2.54-2.49 (m, 1H), 2.42-2.26 (m, 1H), 2.11-2.07 (m, 1H), 1.85 (dt, *J* = 14.3, 7.5 Hz, 1H), 1.74 (dt, *J* = 12.9, 6.4 Hz, 1H), 0.88 (d, *J* = 7.0 Hz, 3H), 0.86 (s, 9H), 0.04 (d, *J* = 17.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 136.8, 116.2, 71.0, 46.5, 39.1, 37.4, 25.7, 18.0, 14.0, -4.5, -4.6.



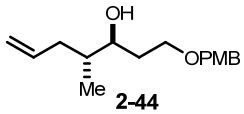
2-56

To a round bottom flask cooled to 0 °C and charged with DIBAL-H (1.0 M, 82 mL, 82 mmol, 2.0 eq) in CH_2Cl_2 (200 mL) was added aldehyde (**2-55**) (10.5 g, 41 mmol, 1 eq) portion-wise over 10 min. The reaction was stirred at rt until completion by TLC analysis (ca. 0.5h). The reaction was poured into half saturated solution of NH_4Cl (200 mL) and a solution of Rochelle's salt (25 g in 100 mL water), and CH_2Cl_2 was added. The solution was stirred vigorously until it became homogenous (ca. 16 h), after which the aqueous layer was extracted with CH_2Cl_2 (3x 100 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure to afford the crude product which was purified by flash chromatography (10% EtOAc/Hex) to give alcohol (**2-56**) as a yellow oil (9.85 g, 38.1 mmol, 93% yield). R_f 0.46 (20% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.74 (ddt, *J* = 17.3, 10.0, 7.1 Hz, 1H), 5.01-4.97 (m, 2H), 3.79-c.71 (m, 3H), 2.21 (bt, *J* = 4.9 Hz, 1H), 2.13-2.06 (m, 1H), 1.85-1.75 (m, 1H), 1.74-1.68 (m, 1H), 1.68-1.61 (m, 2H), 0.88 (s, 9H), 0.85 (d, *J* = 6.6 Hz, 3H), 0.06 (d, *J* = 3.9 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.3, 115.8, 74.4, 60.7, 38.4, 37.8, 33.3, 25.8, 18.0, 13.8, -4.4, -4.6. HRMS *m/z* 259.2085 (calcd for $C_{14}H_{30}O_2Si$, 258.2015).



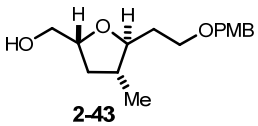
2-57

To a solution of freshly prepared imidate (9.0 g, 31.9 mmol, 1.5 eq) in toluene (150 mL) was added alcohol (**2-56**) (5.50 g, 21.3 mmol, 1 eq) followed by $Yb(OTf)_3$ (20 mg, catalytic). The reaction was stirred at rt until completion by TLC analysis (ca. 0.5 h). Solvent was removed under reduced pressure to afford the crude product, which was purified by flash chromatography (2% EtOAc/Hex) to yield (**2-57**) as a yellow oil (7.89 g, 20.8 mmol, 98% yield). R_f 0.71 (20% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 5.75 (ddt, J = 17.0, 10.0, 7.2 Hz, 1H), 5.01-4.95 (m, 2H), 4.40 (ABd, J = 11/7 Hz, 2H), 3.80 (s, 3H), 3.72 (dt, J = 8.1, 4.0 Hz, 1H), 3.50 (sex, J = 7.4 Hz, 2H), 2.13-2.07 (m, 1H), 1.85-1.78 (m, 1H), 1.71-1.63 (m, 2H), 0.86 (s, 9H), 0.83 (d, J = 6.6 Hz, 3H), 0.00 (d, J = 3.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 137.7, 130.7, 129.2, 115.5, 113.7, 72.5, 72.4, 67.3, 55.2, 38.7, 37.3, 32.1, 25.9, 18.1, 14.1, -4.4, -4.6. HRMS *m/z* 377.2524 (calcd for $C_{22}H_{38}O_3Si$, 378.2590).



2-44

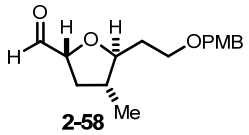
To a solution of PMB ether (**2-57**) (3.06 g, 8.08 mmol, 1 eq) in MeOH (150 mL) was added 10-CSA (100 mg, catalytic). The reaction was stirred at rt until completion by TLC analysis (ca. 1 h). The reaction was poured into half saturated solution of sodium bicarbonate (200 mL) and diluted with EtOAc (200 mL), the aqueous layer was extracted with EtOAc (4 x100 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure to afford **2-44** as a yellow oil, which was used without further purification (2.03 g, 7.70 mmol, 95% yield). Spectral data was identical to **2-44** produced from **2-45** (vide supra). $[\alpha]^{20}_D$ = -2.14° (*c* 1.0, $CHCl_3$).



2-43

Procedure to pre-activate Co(nmp)$_2$: To a flask charged with $Co(nmp)_2$ (**1-21**) (452 mg, 0.8 mmol, 0.1 eq) and *i*PrOH (100 mL) was added *t*BuOOH (5.33 M, 0.2 mL, 1.08 mmol, 0.14 eq). The reaction was heated to 55 °C under an oxygen atmosphere for 1 h, and solvent was removed under reduced pressure. The activated $Co(nmp)_2$ was dried under high vacuum (0.1 mmHg) for 5 min to ensure that any remaining peroxide was been removed. **Cyclization:** The pre-activated $Co(nmp)_2$ (**1-21**) (prepared above, 0.8 mmol, 0.1 eq) was

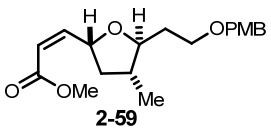
diluted with 100 mL *i*PrOH and alcohol **2-44** was added (2.06 g, 7.8 mmol, 1 eq). The reaction was heated to 55 °C under an oxygen atmosphere for exactly 1 h, and allowed to cool to rt. Solvent was removed under reduced pressure, followed by high vacuum (0.1 mmHg) to remove all traces of *i*PrOH. The crude mixture was diluted with EtOAc (40 mL) and filtered through a thin pad of silica (<1 cm) over packed celite to remove the catalyst. The pad was washed with EtOAc (400 mL) and the filtrate was concentrated under reduced pressure to give THF-alcohol **2-43** (2.05 g, 7.34 mmol, 94%) as a yellow oil, which was used without further purification. The product rapidly decomposes, and the decomposition product characteristically results in broad peaks at 3.65 and 3.45 ppm. The presence of the decomposition product leads to the loss of fine splitting and peaks were reported as multiplets. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 4.43 (d, J = 2.0 Hz, 2H), 4.06 (ddt, J = 9.4, 6.2, 3.1 Hz, 1H), 3.79 (s, 3H), 3.62 – 3.48 (m, 4H), 2.09-2.03 (m, 1H), 1.94-1.85 (m, 2H), 1.73-1.65 (m, 1H), 1.37-1.29 (m, 1H), 1.01 (d, J = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.1, 130.6, 129.2, 113.7, 82.4, 78.3, 72.6, 67.4, 65.2, 55.3, 40.1, 36.6, 34.3, 16.4. HRMS *m/z* 280.1667 (calcd for $C_{16}H_{24}O_4$, 280.1675).



2-58

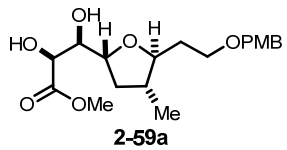
A flask charged with freshly prepared alcohol **2-43** (2.24 g, 8 mmol, 1 eq), and DMSO (3.12 g, 40 mmol, 5 eq) in CH_2Cl_2 (120 mL) was cooled to 0 °C and Hünig's base (9.6 mL, 56 mmol, 7 eq) was added. The reaction was stirred for 5 min before sulfur trioxide pyridine complex (3.82 g, 24 mmol, 3 eq) was added in one portion. The reaction was stirred at 0 °C for 2 h before being poured into half saturated solution of sodium bicarbonate (150 mL) and diluted with CH_2Cl_2 (100 mL), the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure to afford the crude product which was purified by flash chromatography (40% EtOAc/Hex) to yield aldehyde **2-58** (2.0 g, 7.4 mmol, 90% yield) as a yellow oil. R_f 0.62 (70% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.63 (s, 1H), 7.25 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 4.44 (s, 2H), 4.26-4.23 (m, 1H), 3.79 (s, 3H), 3.63-3.56 (m, 3H), 2.33 (dt, J = 12.9, 7.6 Hz, 1H), 1.95-1.89 (m, 2H), 1.73 (dt, J = 14.3, 5.9 Hz, 1H), 1.58-1.53 (m, 1H), 1.00 (d, J = 7.0 Hz, 3H); ^{13}C NMR (150 MHz,

$CDCl_3$) δ 203.0, 159.1, 130.5, 129.2, 113.7, 84.2, 81.6, 72.7, 67.1, 55.2, 39.3, 36.0, 34.0, 16.2. HRMS *m/z* 278.1510 (calcd for $C_{16}H_{22}O_4$, 278.1518).



2-59

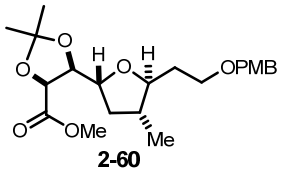
To a solution of the Still-Gennari phosphonate (5.10 g, 16.0 mmol, 1.5 eq) in THF (60 mL) and 18-crown-6 ether (11.3 g, 42.8 mmol, 4.0 eq) cooled to -78 °C was added KHMDS (0.91 M, 17.6 mL, 16.0 mmol, 1.5 eq) drop wise over 5 min. The reaction was stirred at -78 °C for 20 min before a solution of aldehyde **2-58** (2.98 g, 10.7 mmol, 1.0 eq) in THF (20 mL) was added drop wise over 10 min. The reaction was stirred at rt for 3 h at -78 °C, warmed to rt and stirred for an additional 10 min before being poured into a half saturated solution NH_4Cl (150 mL). The aqueous layer was extracted with EtOAc (50 mL x 3), and the combined organics were washed with brine, dried over $MgSO_4$, and filtered through a thin pad of packed celite. Solvent was removed under reduced pressure and the crude oil was purified by flash chromatography (20% EtOAc/Hex) to yield **2-59** (2.79 g, 8.35 mmol, 78%) as a yellow oil. R_f 0.68 (50% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.29 (dd, *J* = 11.5, 7.2 Hz, 1H), 5.73 (dd, *J* = 11.5, 1.5 Hz, 1H), 5.38 (ddd, *J* = 13.8, 9.8, 1.5 Hz, 1H), 4.43 (s, 2H), 3.79 (s, 3H), 3.68 (s, 3H), 3.63-3.52 (m, 3H), 2.49 (dt, *J* = 12.7, 6.5 Hz, 1H), 1.98-1.85 (m, 2H), 1.76 (m, 2H), 1.31-1.23 (m, 1H), 1.00 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 159.1, 152.4, 130.7, 129.2, 118.2, 113.7, 82.9, 74.8, 72.6, 67.4, 55.2, 51.2, 41.2, 40.0, 34.3, 16.4. HRMS *m/z* 334.1773 (calcd for $C_{19}H_{26}O_5$, 334.1780).



2-59a

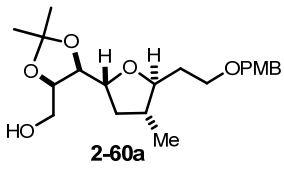
To a solution of alkene **2-59** (1.32 g, 4.0 mmol, 1 eq) in *t*BuOH (15 mL) and distilled water (15 mL) cooled to 0 °C was added AD-mix (5.6 g), K_2OsO_4 (140 mg, 0.12 mmol, 0.06 eq), and $(DHQD)_2PYR$ (104 mg, 0.06 mmol, 0.03 eq). The reaction was stirred at 0 °C and monitored by TLC analysis until complete (ca. 3 days). Upon completion, the contents were poured into a solution consisting of half saturated NH_4Cl (50 mL), half saturated sodium thiosulfate (50 mL), and water (50 mL). The reaction was stirred rigorously for 10 min, diluted with CH_2Cl_2 (100 mL), and the aqueous layer was extracted with CH_2Cl_2 (50 mL x 4), and the combined organics were washed with brine, dried over $MgSO_4$, and

filtered through a thin pad of packed celite. Solvent was removed under reduced pressure and the crude oil (**2-59a**) was used in the next reaction without further purification. R_f 0.73 (75% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$, major diastereomer) δ 7.22 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 4.40 (s, 2H), 4.25 (dd, J = 8.2, 4.1 Hz, 1H), 4.01 (ddd, J = 9.7, 6.2, 2.9 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.75-3.68 (m, 1H), 3.56-3.48 (m, 3H), 3.41 (d, J = 9.4 Hz, 1H), 2.70 (d, J = 7.6 Hz, 1H), 2.04 (dt, J = 12.4, 6.4 Hz, 1H), 1.89-1.82 (m, 2H), 1.65-1.57 (m, 2H), 1.00 (d, J = 6.4, 3H).



2-60

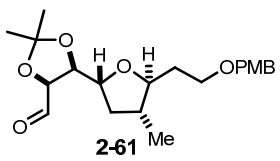
The crude diol **2-59a** was dissolved in 2,2-dimethoxy propane (50 mL), and *p*-toluene sulfonic acid (50 mg, catalytic) was added in one portion. The reaction was stirred at rt overnight (ca. 16 h) before being poured into a half saturated solution $NaHCO_3$ (100 mL). The aqueous layer was extracted with EtOAc (50 mL x 3), and the combined organics were washed with brine, dried over $MgSO_4$, and filtered through a thin pad of packed celite. Solvent was removed under reduced pressure and the crude oil was purified by flash chromatography (50% EtOAc/Hex) to yield **2-60** as an inseparable mixture of diastereomers (1.55 g, 3.80 mmol, 95%) as a yellow oil. R_f 0.73 (75% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$, major diastereomer) δ 7.25 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 4.55 (d, J = 7.0 Hz, 1H), 4.42 (ABd, J = 11.1 Hz, 2H), 4.26 (dd, J = 7.0, 4.7 Hz, 1H), 4.05 (ddd, J = 8.8, 6.7, 5.0 Hz, 1H), 3.79 (s, 3H), 3.68 (s, 3H), 3.60-3.48 (m, 3H), 2.17 (dt, J = 12.1, 7.1 Hz, 1H), 1.86-1.83 (m, 2H), 1.68-1.61 (m, 1H), 1.59 (s, 3H), 1.56 (d, J = 13.5 Hz, 1H), 1.52-1.46 (m, 1H), 1.41 (s, 1H), 1.38 (s, 3H) 1.01 (d, J = 6.4 Hz, 3H); HRMS *m/z* 408.2152 (calcd for $C_{22}H_{32}O_7$, 408.2148).



2-60a

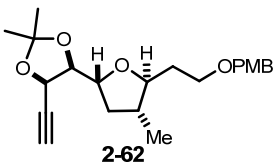
To a solution of DIBAL-H (1.0 M, 7.60 mL, 7.60 mmol, 2.0 eq) in CH_2Cl_2 (20 mL) cooled to 0 °C was added the mixture of diastereomeric esters **2-60** (1.55 g, 3.80 mmol, 1 eq) in CH_2Cl_2 (10 mL) portion-wise over 10 min. The reaction was stirred at rt until complete by TLC analysis (ca. 3 h). The reaction was poured into half saturated solution of NH_4Cl (100 mL) and a solution of Rochelle's salt (10 g in 50 mL water), and CH_2Cl_2 (100 mL) was added. The solution was stirred vigorously until it became

homogenous (ca. 16 h), after which the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure to afford the crude product which was purified by flash chromatography (50% EtOAc/Hex) to give alcohol **2-60a** as a yellow oil (1.14 g, 3.01 mmol, 79% yield) and the diastereomer (285 mg, 0.75 mmol, 19%). R_f 0.22 (50% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 8.2 Hz, 2H), 6.85 (d, J = 8.2Hz, 2H), 4.42 (ABd, J = 11.1 Hz, 2H), 4.17-4.12 (m, 2H), 4.07-4.05 (dd, J = 6.4, 3.5 Hz, 1H), 3.79 (s, 3H), 3.72-3.64 (m, 3H), 3.61-3.57 (m, 1H), 3.57-3.51 (m, 1H), 3.21 (dd, J = 8.8, 4.7 Hz, 1H), 2.15 (dt, J = 12.3, 6.7 Hz, 1H), 1.92-1.87 (m, 2H), 1.71-1.63 (m, 2H), 1.49 (s, 3H), 1.36 (s, 3H), 1.02 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 130.6, 129.3, 113.7, 108.4, 83.5, 78.9, 77.5, 75.0, 72.7, 67.4, 61.5, 55.2, 39.6, 27.9, 34.0, 27.4, 25.6, 15.8. HRMS *m/z* 380.2198 (calcd for $C_{21}H_{32}O_6$, 380.2199).



2-61

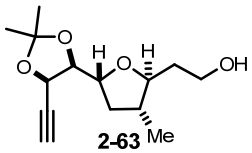
Alcohol **2-60a** was oxidized to the corresponding aldehyde using a procedure analogous to that used for **2-58**, on a 0.344 mmol scale resulting in aldehyde **2-61** (130 mg, 0.344 mmol, 100%) which was used without further purification. R_f 0.19 (20% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (d, J = 2.3 Hz, 1H), 7.24 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 4.41 (s, 2H), 4.32 (dd, J = 4.1, 2.3 Hz, 2H), 4.05 (ddd, J = 9.0, 6.7, 2.9 Hz, 1H), 3.78 (s, 3H), 3.59 (td, J = 9.2, 2.6 Hz, 1H), 3.55 (ddd, J = 9.2, 7.2, 4.7 Hz, 1H), 3.52-3.48 (m, 1H), 2.10 (dt, J = 12.0, 7.5 Hz, 1H), 1.87-1.80 (m, 2H), 1.63-1.58 (m, 2H), 1.55 (s, 3H), 1.38 (s, 3H), 0.99 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.6, 159.1, 130.7, 129.2, 113.7, 111.0, 83.3, 81.7, 81.2, 74.4, 72.7, 67.5, 55.2, 40.3, 36.5, 33.9, 26.9, 25.2, 15.8.



2-62

A 25 mL flask was charged with triphenylphosphine (186 mg, 0.714 mmol, 2.5 eq) and CH_2Cl_2 (10 mL) and was cooled to 0 °C. The septum was temporarily removed to add carbon tetrabromide (123 mg, 0.371 mmol, 1.3 eq) in one portion. The ice bath was removed and the reaction was stirred at room temperature for 30 min, after which it was re-cooled to 0 °C. The above crude aldehyde **2-61** (108 mg, 0.277 mmol, 1 eq) was added

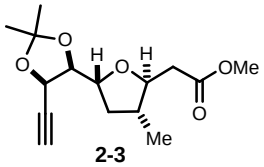
in one portion and the reaction was stirred for 30 min, at which point it was judged complete by TLC. Hexanes (50 mL) was added, and the reaction was allowed to warm to rt, at which point it was filtered through celite, and concentrated to dryness. To the crude oil was added more hexanes (100 mL), filtered, and concentrated. This procedure was repeated for a total of 3 filtrations at which point the crude oil was purified by column chromatography (20% EtOAc/Hex) to afford the dibromide as a yellow oil (133 mg, 0.249 mmol, 90% yield). A 25 mL flask was charged with dibromde (133 mg, 0.249 mmol, 1 eq), diluted with THF (10 mL) and cooled to -78 °C. *n*BuLi (2.50 M, 0.25 mL, 0.62 mmol, 2.5 eq) was added slowly drop wise over 15 min. The reaction was stirred at -78 °C for 1 h at which point it was judged complete by TLC. The reaction was slowly poured into a half-saturated solution of NH_4Cl (20 mL), the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, and the crude product was purified by column chromatography (2% EtOAc/Hex) to afford alkyne **2-62** as a yellow oil (88 mg, 0.236 mmol, 95% yield). R_f 0.57 (50% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.66 (dd, *J* = 5.5, 2.3 Hz, 1H), 4.42 (s, 2H), 4.23 (td, *J* = 8.8, 6.2 Hz, 1H), 3.97 (dd, *J* = 8.4, 5.7 Hz, 1H), 3.79 (s, 3H), 3.67-3.55 (m, 3H), 2.47 (d, *J* = 1.9 Hz, 1H), 2.33 (dt, *J* = 12.4, 6.5 Hz, 1H), 2.02-1.93 (m, 1H), 1.89 (ddd, *J* = 14.3, 7.2, 3.1 Hz, 1H), 1.84-1.77 (m, 1H), 1.57 (s, 3H), 1.38 (s, 3H), 1.24-1.13 (m, 2H), 1.02 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 130.7, 129.2, 113.7, 111.5, 83.1, 81.4, 80.1, 77.8, 75.4, 72.6, 67.3, 66.7, 55.2, 39.3, 37.7, 33.8, 29.7, 27.8, 26.3, 16.5.



2-63

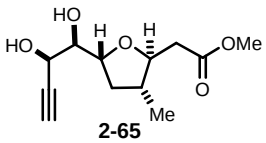
PMB alcohol (**2-62**) (53 mg, 0.141 mmol, 1 eq) was dissolved in CH_2Cl_2 (4 mL), water (0.5 mL) and saturated sodium bicarbonate (0.5 mL). DDQ (64 g, 0.282 mmol, 2 eq) was added in one portion and the reaction was rigorouly stirred for 1.5 h at which point the reaction was judged to be complete by TLC analysis. The reaction mixture was poured into a rapidly stirring solution of half saturated sodium bicarbonate (30 mL) and half saturated sodium thiosulfate (30 mL), and the aqeous layer was extracted with CH_2Cl_2 (5 x 30 mL) and the combined organics were washed with brine and dried over $MgSO_4$. Solvent was removed

under reduced pressure to give the cude alcohol, which was purified by flash chromatography (50% EtOAc/Hex) to give the pure alcohol **2-63** as a yellow oil (31.1 mg, 0.122 mmol, 86% yield). R_f 0.22 (50% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69 (dd, *J* = 5.8, 2.3 Hz, 1H), 4.26 (dt, *J* = 9.1, 6.9 Hz, 1H), 3.98 (dd, *J* = 7.6, 5.9 Hz, 1H), 3.82-3.75 (m, 2H), 3.63 (td, *J* = 8.6, 3.2 Hz, 1H), 2.79 (bs, 1H), 2.50 (d, *J* = 2.3 Hz, 1H), 2.31 (dt, *J* = 5.9, 5.9 Hz, 1H), 2.00-1.95 (m, 1H), 1.90-1.85 (m, 1H), 1.72-1.66 (m, 1H), 1.53 (s, 3H), 1.35 (s, 3H), 1.27-1.22 (m, 1H), 1.01 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 111.1, 85.2, 80.8, 79.8, 77.7, 75.6, 66.7, 60.9, 39.4, 37.2, 35.3, 29.6, 27.5, 26.0, 16.0



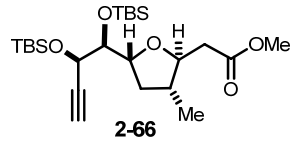
2-3

Alcohol **2-63** was oxidized to the corresponding aldehyde using a procedure analogous to that used for **2-58**, on a 0.108 mmol scale resulting in the aldehyde (22.4 mg, 0.089 mmol, 83%) which was used without further purification. To the crude aldehyde (22.4 mg, 0.089 mmol, 1.0 eq) and 2-methyl-2-butene (24 mg, 0.35 mmol, 4 eq) in *t*BuOH (1 mL) and pH 7 buffer (0.67M, 0.3 mL) was added $NaClO_2$ (24 mg, 0.218 mmol, 2.5 eq) in water (0.37 mL). The reaction was monitored by TLC until completion (ca. 30 min) at which point it was poured into a half saturated solution of sodium sulfate (10 mL) and acidified with HCl (2M solution, 1 mL). The aqueous layer was extracted with CH_2Cl_2 (5 x 20 mL) and the combined organics were washed with brine and dried over $MgSO_4$. Solvent was removed under reduced pressure, and the crude oil was dissolved in MeOH (10 mL) and CH_2Cl_2 (10 mL) and a stir bar was added. To the solution was added TMS-diazomethane (1.0 M solution) drop wise until the yellow color persists (ca. 0.1 mL). The reaction was stirred an additional 5 min before excess acetic acid (1 mL) was added in one portion and the color dissipates. Volatiles were removed under reduced pressure and the oil was purified by flash chromatography (20% EtOAc/Hex) to give pure methyl ester **2-3** (16.1 mg, 0.058, 65%). R_f 0.32 (50% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.66 (dd, *J* = 5.6, 2.0 Hz, 1H), 4.26 (dd, *J* = 15.2, 8.8 Hz, 1H), 3.99 (dd, *J* = 8.2, 5.9 Hz, 1H), 3.93 (dt, *J* = 8.5, 6.0 Hz, 1H), 3.66 (s, 3H), 2.66 (dd, *J* = 15.5, 6.1 Hz, 1H), 2.51 (dd, *J* = 15.5, 6.1 Hz, 1H), 2.48 (d, *J* = 2.3 Hz, 1H), 2.36 (dt, *J* = 12.4, 6.4 Hz, 1H), 2.10-2.04 (m, 1H), 1.55 (s, 3H), 1.36 (s, 3H), 1.25-1.19 (m, 1H), 1.02 (d, *J* = 7.0 Hz, 3H).



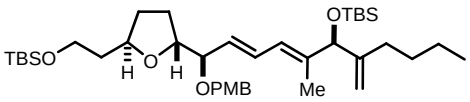
2-65

To 5 mL round bottom flask charged with acetonide **2-3** (24.5 mg, 0.087 mmol, 1 eq) was added wet methanol (2 mL) and a catalytic amount of PPTS was added in one portion. The reaction was monitered by TLC until complete (ca 6 h), at which point it was diluted with water (30 mL) and EtOAc (30 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, and the crude product was purified by column chromatography (50% EtOAc/Hex) to afford alcohol **2-65** as a yellow oil (17.7 mg, 0.073 mmol, 84.3% yield). R_f 0.73 (60% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.51-4.43 (m, 2H), 3.87 (td, *J* = 8.9, 3.7 Hz, 1H), 3.68 (s, 3H), 3.56-3.54 (m, 1H), 3.49 (bd, *J* = 9.8 Hz, 1H), 2.82 (bd, *J* = 8.2 Hz, 1H), 2.59-2.52 (m, 2H), 2.48-2.42 (m, 1H), 2.12 (dt, *J* = 14.0, 6.1 Hz, 1H), 2.01-1.89 (m, 1H), 1.80-1.72 (m, 1H), 1.05 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 115.3, 111.5, 81.8, 81.7, 81.2, 81.1, 79.9, 78.0, 75.6, 75.5, 66.7, 66.6, 51.6, 51.5, 39.5, 38.9, 38.8, 38.8, 37.4, 27.6, 26.2, 26.2, 16.6.



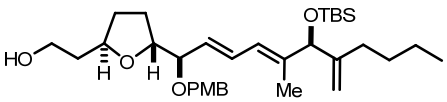
2-66

To a solution of alcohol **2-65** (17.7 mg, 0.073 mmol, 1 eq) in DMF (2 mL) was added imidazole (25 mg, 0.365 mmol, 5.0 eq), followed by TBSCl (28.4 mg, 0.182 mmol, 2.5 eq) and DMAP (5 mg, catalytic). The reaction was heated to 60 °C allowed to stir overnight (ca. 16h) before being cooled to rt and poured into a half saturated solution of NH_4Cl (20 mL), and the aqeous layer was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organics were washed with brine and dried over $MgSO_4$. Solvent was removed under reduced pressure to give the TBS alcohol **2-66**, which was purified by column chromatography (5% EtOAc/Hex) to give the pure alcohol as a yellow oil (33.4 mg, 0.071 mmol, 97% yield). Spectral data was identical to the reported literature.[57]



2-66a

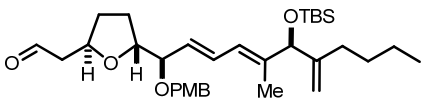
A 250 mL round bottom flask was charged with **2-21** (3.60 g, 6.50 mmol, 1 eq) and diluted with toluene (100 mL). The PMB-imine (2.75 g, 9.78 mmol, 1.5 eq) was added in one portion followed by a catalytic amount of $Yb(OTf)_3$. The reaction was stirred for 30 min, at rt at which point it was judge complete by TLC, before being slowly poured into a half-saturated solution of sodium bicarbonate (100 mL), and diluted with EtOAc (100 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, and the crude product was purified by column chromatography (10% EtOAc/Hex) to afford alcohol **2-67** as a yellow oil (3.83 g, 5.98 mmol, 92% yield). R_f 0.53 (20% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 6.42 (dd, J = 15.5, 10.8 Hz, 1H), 6.09 (d, J = 10.0 Hz, 1H), 5.57 (dd, J = 15.2, 8.2 Hz, 1H), 5.10 (s, 1H), 4.86 (s, 1H), 4.58 (d, J = 11.7 Hz, 1H), 4.41 (s, 1H), 4.40 (d, J = 11.7 Hz, 1H), 4.06-4.00 (m, 2H), 3.79 (s, 1H), 3.77 (at, J = 7.0 Hz, 1H), 3.74-3.67 (m, 2H), 2.00-1.96 (m, 1H), 1.93-1.85 (m, 2H), 1.84-1.78 (m, 2H), 1.72-1.62 (m, 2H), 1.59 (s, 3H), 1.52-1.47 (m, 1H), 1.43-1.36 (m, 2H), 1.32-1.26 (m, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.88 (at, J = 8.8 Hz, 3H), 0.04 (s, 6H), 0.01 (d, J = 9.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 149.6, 139.2, 131.0, 129.9, 129.7, 129.2, 124.8, 113.6, 109.8, 81.9, 80.7, 77.2, 76.8, 70.0, 60.6, 55.2, 38.9, 32.1, 30.7, 30.1, 28.1, 26.0, 25.8, 22.6, 18.3, 14.0, 12.2, -5.0, -5.3.



2-67

To 250 mL round bottom flask charged with TBS alcohol **2-66a** (2.18 g, 3.40 mmol, 1 eq) was added wet ethanol (100 mL) and PPTS (1.02 g, 4.08 mmol, 1.2 eq) was added in one portion. The reaction was monitered by TLC until complete (ca. 2-4 h), at which point it was diluted with water (100 mL) and EtOAc (100 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, and the crude product was purified by column chromatography (40% EtOAc/Hex) to afford alcohol **2-67** as a yellow oil (1.85 g, 3.33 mmol, 98% yield). R_f 0.36 (50% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz,

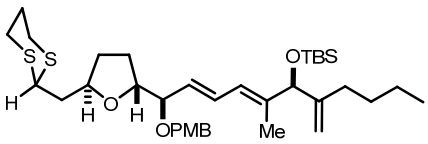
2H), 6.42 (dd, *J* = 15.2, 11.1 Hz, 1H), 6.09 (d, *J* = 10.5 Hz, 1H), 5.55 (dd, *J* = 15.2, 7.6 Hz, 1H), 5.10 (s, 1H), 4.85 (s, 1H), 4.57 (d, *J* = 11.7 Hz, 1H), 4.40 (s, 1H), 4.36 (d, *J* = 11.7 Hz, 3H), 4.10-4.06 (m, 2H), 3.78 (s, 3H), 3.78-3.74 (m, 3H), 2.02-1.98 (m, 1H), 1.91-1.87 (m, 2H), 1.85-1.77 (m, 1H), 1.75-1.65 (m, 4H), 1.57-1.51 (m, 1H), 1.41-1.36 (m, 2H), 1.31-1.26 (m, 2H), 0.89 (s, 9H), 0.88 (s, 9H), 0.01 (d, *J* = 9.4 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.0, 149.5, 139.5, 130.7, 130.1, 129.2, 124.7, 113.6, 109.8, 81.5, 81.0, 80.6, 79.6, 69.9, 61.9, 55.2, 37.3, 32.2, 30.7, 30.1, 27.7, 25.8, 22.5, 18.3, 14.0, 12.1, -5.0.



2-68

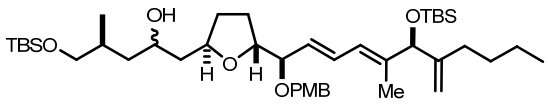
A 250 mL round bottom flask was charged with alcohol **2-67** (1.92 g, 3.44 mmol, 1 eq), diluted with CH_2Cl_2 (70 mL) and cooled to 0 °C. DMSO (1.4 g, 17.9 mmol, 5 eq) was added, followed by Hunig's base (3.2 g, 25.0 mmol, 7 eq). The reaction mixture was allowed to stir for 10 min before SO_3•Pyr (1.20 g, 10.7 mmol, 3 eq) was added portion wise over 5 min. The reaction was monitored by TLC until completion (ca. 2h) before being slowly poured into a half-saturated solution of sodium bicarbonate (100 mL), and diluted with CH_2Cl_2 (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, and the crude residue was dissolved in EtOAc (100 mL) and water (100 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, to afford a **2-68** as a yellow oil (1.36 g, 2.38 mmol, 89% yield) which was used without further purification. The second extraction using EtOAc removes oxidation byproducts from the reaction without using column chromatography, which was shown to epimerize the aldehyde. R_f 0.73 (50% EtOAc/Hex) ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 7.25 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.42 (dd, *J* = 15.2, 11.1 Hz, 1H), 6.09 (d, *J* = 11.1 Hz, 1H), 5.55 (dd, *J* = 15.2, 8.2 Hz, 1H), 5.10 (s, 1H), 4.85 (s, 1H), 4.59 (d, *J* = 11.7 Hz, 1H), 4.40 (s, 1H), 4.37 (d, *J* = 11.7 Hz, 1H), 4.39-4.33 (m, 1H), 4.10 (q, *J* = 7.0 Hz, 1H), 3.79 (s, 3H), 3.76 (dd, *J* = 7.6, 6.4 Hz, 1H), 2.72-2.68 (m, 1H), 2.57-2.53 (m, 1H), 2.13- 2.08 (m, 1H), 1.93-1.86 (m, 2H), 1.83-1.72 (m, 2H), 1.59 (s, 3H), 1.53-1.49 (m, 1H), 1.50-1.35 (m, 2H),

1.32-1.27 (m, 2H), 0.89 (s, 9H), 0.87 (t, *J* = 8.7 Hz, 3H), 0.01 (d, *J* = 7.0 Hz, 6H).



2-69

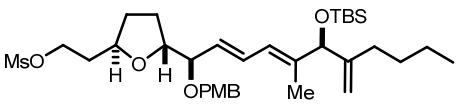
A 25 mL round bottom flask was charged with aldehyde **2-68** (20 mg, 0.036 mmol, 1 eq) and diluted with diethyl ether (1 mL). Silylated propanedithiol (13.5 mg, 0.053 mmol, 1.5 eq) was added followed by anhydrous $ZnCl_2$ (5 mg, 0.036 mmol, 1 eq). The reaction was monitored by TLC until completion (ca. 2h) before being slowly poured into a half-saturated solution of sodium bicarbonate (10 mL), and diluted with EtOAc (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, and the crude product was purified by column chromatography (10% EtOAc/Hex) to afford dithiane **2-69** as a yellow film (16 mg, 0.025 mmol, 70% yield). The yield and purity of the final product was found to be inconsistent for larger scale reactions. R_f 0.47 (20% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.40 (dd, *J* = 15.5, 10.8 Hz, 1H), 6.09 (d, *J* = 10.8 Hz, 1H), 5.54 (dd, *J* = 15.5, 8.2 Hz, 1H), 5.09 (s, 1H), 4.85 (s, 1H), 4.60 (d, *J* = 11.7 Hz, 1H), 4.43 (d, *J* = 11.7 Hz, 1H), 4.40 (s, 1H), 4.23-4.20 (m, 1H), 4.07 (q, *J* = 6.6 Hz, 1H), 2.92-2.85 (m, 2H), 2.85-2.79 (m, 2H), 2.15-2.09 (m, 1H), 2.02-1.97 (m, 2H), 1.93-1.87 (m, 3H), 1.82-1.79 (m, 2H), 1.71-1.68 (m, 1H), 1.59 (s, 3H), 1.50-1.47 (m, 1H), 1.41-1.36 (m, 2H), 1.32-1.25 (m, 2H), 0.89 (s, 12H), 0.00 (d, *J* = 6.4 Hz, 6H).



2-71

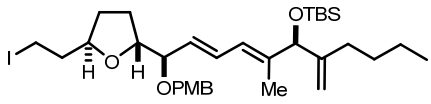
A 10 mL round bottom flask was charged with iodide **2-70** (14.9 mg, 0.047 mmol, 1 eq), diluted with diethyl ether (2.5 mL) and cooled to -78 °C. Then, *t*BuLi (1.50 M, 0.14 mL, 0.095 mmol, 2 eq) was added drop wise and the reaction was stirred at -78 °C for 10 min before aldehyde **2-68** (26 mg, 0.047 mmol, 1 eq) was added in minimal ether. The reaction was stirred for 30 min before being quenched with a half saturated solution of NH_4Cl (30 mL), and diluted with EtOAc (30 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL) and the combined organics were washed with brine, and dried with

$MgSO_4$. Solvent was removed under reduced pressure, and the crude product was purified by column chromatography (30% EtOAc/Hex) to afford **2-71** as a yellow film (undetermined yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.43 (dd, *J* = 15.2, 10.5 Hz, 1H), 6.09 (d, *J* = 11.1 Hz, 1H), 5.54 (dd, *J* = 15.5, 8.0 Hz, 1H), 5.10 (s, 1H), 4.86 (s, 1H), 4.57 (d, *J* = 11.7 Hz, 1H), 4.41 (s, 1H), 4.36 (d, *J* = 11.7 Hz, 1H), 4.12-4.07 (m, 3H), 3.80-3.75 (m, 3H), 3.79 (s, 3H), 3.60 (dd, *J* = 9.9, 4.7 Hz, 1H), 3.42 (dd, *J* = 9.9, 7.6 Hz, 1H), 2.60-2.52 (m, 2H), 2.24 (dd, *J* = 15.8, 6.4 Hz, 1H), 2.03-1.98 (m, 1H), 1.94-1.88 (m, 2H), 1.84-1.79 (m, 1H), 1.76-1.70 (m, 2H), 1.56-1.50 (m, 4H), 1.41-1.36 (m, 4H), 1.35-1.24 (m, 4H), 0.96 (d, *J* = 6.4 Hz, 3H), 0.88 (s, 18H), 0.06 (d, *J* = 2.9 Hz, 6H), 0.01 (d, *J* = 9.4 Hz, 6H).



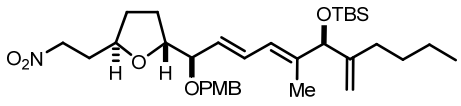
2-71a

A 100 mL round bottom flask flask was charged with alcohol **2-67** (550 mg, 1.0 mmol, 1 eq) and diluted with CH_2Cl_2 (30 mL). Triethylamine (400 mg, 4.0 mmol, 4 eq) was added followed by methanesulfonyl chloride (229 mg, 2.0 mmol, 2 eq). The reaction was monitored by TLC until complete (ca. 30 min) at which point it was poured into a half-saturated solution of NH_4Cl (100 mL), and diluted with CH_2Cl_2 (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure to afford mesylate **2-71a** (600 mg, 0.98 mmol, 98% yield) as a yellow oil which was used without further purification. R_f 0.47 (50% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.41 (dd, *J* = 15.2, 10.9 Hz, 1H), 6.10 (d, *J* = 10.9 Hz, 1H), 5.54 (dd, *J* = 15.2, 8.2 Hz, 1H), 5.10 (s, 1H), 4.85 (s, 1H), 4.57 (d, *J* = 11.7 Hz, 1H), 4.41 (s, 1H), 4.36-4.33 (m, 3H), 4.07-4.02 (m, 2H), 3.78 (s, 3H), 3.73 (dd, *J* = 7.8, 5.9 Hz, 1H), 2.97 (s, 3H), 2.05-2.00 (m, 2H), 1.95-.187 (m, 4H), 1.86-1.80 (m, 1H), 1.77-1.70 (m, 1H), 1.59 (s, 3H), 1.52-1.47 (m,1H), 1.43-1.35 (m, 2H), 1.35-1.24 (m 2H), 0.89 (s, 9H), 0.87 (t, *J* = 8.7 Hz, 3H), 0.01 (d, *J* = 5.9 Hz, 6H); ^{13}C NMR (100 MHz , $CDCl_3$) δ = 159.0, 149.5, 139.7, 130.7, 130.3, 129.2, 124.5, 113.7, 109.9, 81.8, 81.0, 80.6, 77.3, 76.7, 75.4, 69.9, 68.0, 55.2, 37.1, 35.0, 31.9, 31.5, 30.7, 30.1, 28.1, 25.8, 22.5, 18.3, 14.0, 12.2, 1.0, -5.0.



2-71b

A 50 mL round bottom flask was charged with mesylate **2-71a** (311 mg, 0.5 mmol, 1 eq) and diluted with acetone (20 mL). Sodium iodide (450 mg, 1.5 mmol, 3 eq) was added and the reaction was heated to a vigorous reflux. The reaction was monitored by TLC until complete (ca. 2 h) at which point it was cooled and filtered through a thin pad of celite into a half saturated solution of sodium bicarbonate (50 mL). The pad was washed with EtOAc (100 mL) and the filtrate was transferred to a separatory funnel. The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure and the curde oil was purified by column chromatography (20% EtOAc/Hex) to afford iodide **2-71b** (291 mg, 0.445 mmol, 89% yield) as a yellow oil. R_f 0.58 (20% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 6.42 (dd, J = 11.1, 15.2 Hz, 1H), 6.10 (d, J = 11.1 Hz, 1H), 5.55 (dd, J = 8.2, 15.2 Hz, 1H), 5.10 (s, 1H), 4.86 (s, 1H), 4.60 (d, J = 12.3 Hz, 1H), 4.41 (s, 1H), 4.40 (d, J = 12.3 Hz, 1H), 4.05 (q, J = 7.0 Hz, 1H), 4.00-3.94 (m, 1H), 3.79 (s, 3 H), 3.73 - 3.79 (m, 1H), 3.30-3.22 (m, 2H), 2.05 (dt, J = 7.0, 14.1 Hz, 2H), 2.02-1.95 (m, 2H), 1.95-1.86 (m, 2H), 1.85- 1.80 (m, 1H), 1.76-1.68 (m, 1H), 1.60 (s, 3H), 1.51-1.44 (m, 1H), 1.43-1.35 (m, 3H), 1.33-1.26 (m, 3H), 0.89 (s, 9H), 0.88 (t, J = 8.7 Hz, 1H), 0.01 (d, J = 5.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.6, 153.7, 150.5, 148.9, 135.6, 131.0, 123.4, 111.1, 104.1, 87.1, 84.7, 80.0, 79.1, 77.3, 76.7, 76.5, 68.6, 52.6, 44.6, 41.5, 33.6, 32.6, 29.9, 29.6, 28.7, 26.3, 26.2, 25.9, 25.7, 25.0, 22.5, 19.2, 18.3, 18.2, 15.5, 14.0, -5.0, -5.2, -5.3.



2-72

To a solution of iodide **2-71b** (55.6 mg, 0.083 mmol, 1 eq) in dry DMSO (1.5 mL) was added urea (35 mg, 0.581 mmol, 7 eq) followed by $NaNO_2$ (11.5 mg, 0.166 mmol, 2 eq). The reaction was allowed to stir until complete as indicated by TLC (ca. 1h) at which point it was poured into a brine solution (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics were

dried with $MgSO_4$. Solvent was removed under reduced pressure to afford a yellow oil which was purified by column chromatography (15% EtOAc/Hex) to afford **2-72** (26.2 mg, 0.045 mmol, 54% yield) as a yellow oil. R_f 0.31 (20% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.41 (dd, *J* = 15.0, 11.1 Hz, 1H), 6.10 (d, *J* = 11.1 Hz, 1H), 5.55 (dd, *J* = 15.2, 8.2, Hz, 1H), 5.10 (s, 1H), 4.86 (s, 1H), 4.58 (d, *J* = 11.7 Hz, 1H), 4.51 (t, *J* = 7.0 Hz, 2H), 4.41 (s, 1H), 4.36 (d, *J* = 11.7 Hz, 1H), 4.05 (q, *J* = 6.77 Hz, 1H), 4.00-3.94 (m, 1H), 3.80 (s, 3 H), 3.73 (dd, *J* = 7.8, 6.2 Hz, 1H), 2.28-2.20 (m, 1H), 2.15-2.00 (m, 2H), 1.95-1.87 (m, 2H), 1.85-1.70 (m, 2H), 1.60 (s, 3H), 1.54-1.47 (m, 1H), 1.45-1.35 (m, 2H), 1.33-1.25 (m, 2H), 0.89 (s, 9H), 0.88 (t, *J* = 8.7 Hz, 1H), 0.01 (d, *J* = 5.9 Hz, 6H).

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[53] Buffer is a solution of 0.05 M Na_2BO_4 and 1 x 10^{-4} M EDTA in distilled H_2O

[54] The evaporation of the solvent also removes the volatile TMSF from solution, at a rate that was found to be optimal for production of $BF_2OBn{\cdot}OEt_2$ without forming any $BFOBn_2{\cdot}OEt_2$. Alternative procedures including heat application, reduced pressure and Shlenk line nitrogen flow were attempted but did not produce clean product.

[55] If the solution contains significant amounts of $BF_3{\cdot}OEt_2$, the evaporation procedure can be repeated until the ^{19}F NMR shows only product. If trace amounts of $BF_3{\cdot}OEt_2$ persist, drops of TMSOBn can be added and the evaporation procedure repeated. The concentration of the solution can be more accurately determined by adding a known amount of fluorine containing internal standard (trufluorotoluene) and comparing peak integration using no D ^{19}F NMR. See: Hoye, T. R.; Eklov, B. M.; Voloshin, M. *J. Am. Chem. Soc.* **2004**, *126*, 2567-2570.

[56] Harris, R. N.; Sundararaman, P.; Djerassi, C.; *J. Am. Chem. Soc.* **1983**, *105*, 2408-2413.

[57] Ferrié, L.; Figadére, B. *Org. Lett.* **2010**, *12*, 4976-4979.

Chapter 3 – Second Generation Approach to Amphidinolide C

Section 3.1 – Alternative Approach to the Western-Northern-Eastern Fragment

In our second generation retrosynthesis, the initial disconnection was modified from a dithiane alkylation to form the C(17)-C(18) bond, to a dithiane alkylation to form the C(18)-C(19) bond (Figure 3.1).

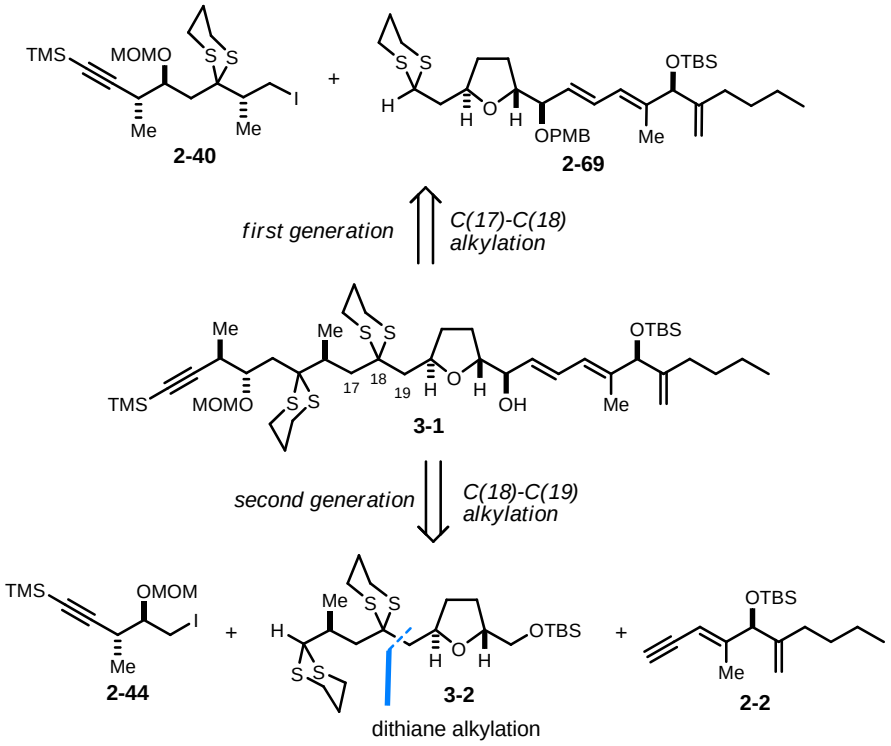
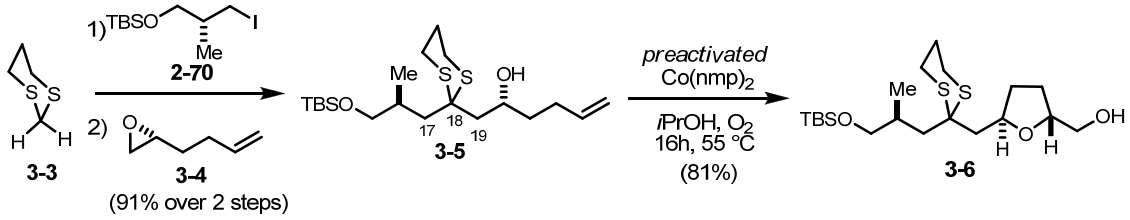


Figure 3.1. Revision of the initial retrosynthetic disconnections

The perceived improvements were three-fold; first and foremost, the alkylation step would no longer be retarded by hindrance, as the electrophile in this case would be sterically accessible. Other advantages would be the early formation of the troublesome 1,4-diketone subunit from C(15)-C(18), and the increased flexibility in the order of assembly on the new Northern fragment (**3-2**) using familiar pieces. The protected iodohydrin (**2-44**) and the unchanged Eastern fragment (**2-2**) would both be utilized, both of which we had in ample quantities.

Section 3.1.1 – Synthesis of the 3-Carbon Homologated Northern Fragment

With the aim of forming the troublesome C(17)-C(18) bond early in the synthesis to make the 1,4-diketone, we homologated alkyl iodide **2-70** (derived in 3 steps from Roche ester)[1] with 1,3-dithiane (**3-3**) (Scheme 3.1). The dithiane was then lithiated and treated with enantiopure epoxide **3-4** which was commercially available, and resolved using Jacobsen's hydrolytic kinetic resolution procedure,[2] to give cyclization precursor **3-5** in 91% yield over 2 steps. Using pre-activated $Co(nmp)_2$ to avoid the potential oxidation of the dithiane by excess peroxide, the pentenol **3-5** was successfully cyclized in 81% yield.

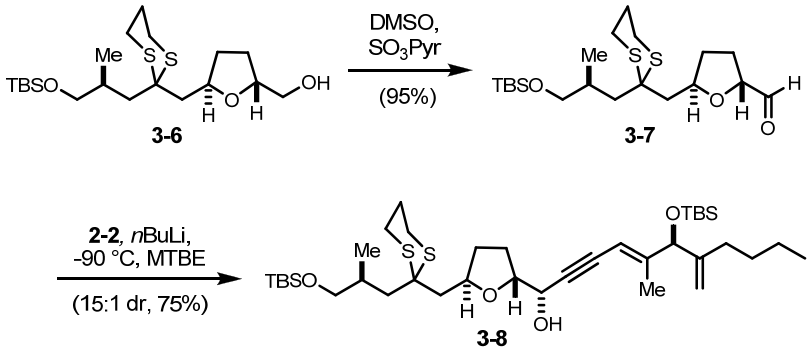


Scheme 3.1. Synthesis of the homologated Northern fragment **3-6**

THF alcohol **3-6** was a key intermediate in our retrosynthesis, and could either be functionalized first at the left side to include the remainder of the Western fragment, or the right side to introduce the Eastern fragment.

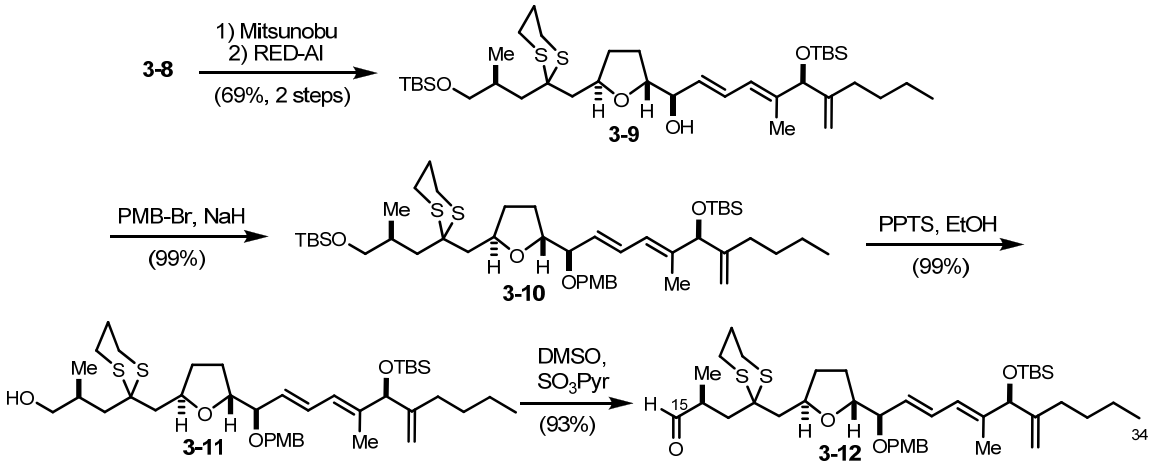
Section 3.1.2 – Synthesis of the New North-Eastern Fragment

Our initial plan was to connect the Eastern fragment **2-2** first, which began with a Parikh-Doering oxidation (SO_3·Pyr/DMSO) of **3-6** to the corresponding aldehyde in 95% yield (Scheme 3.2). Using our previously optimized conditions (MTBE/*n*BuLi at −90 °C), we were thrilled to find that the excellent dr was retained in the alkynlation reaction joining the THF-aldehyde **3-7** and the Eastern fragment **2-2**, yielding the homologated North-Eastern fragment (**3-8**) in 75% yield and 15:1 dr.



Scheme 3.2. Coupling of the homologated Northern (**3-7**) and Eastern fragment **2-2**

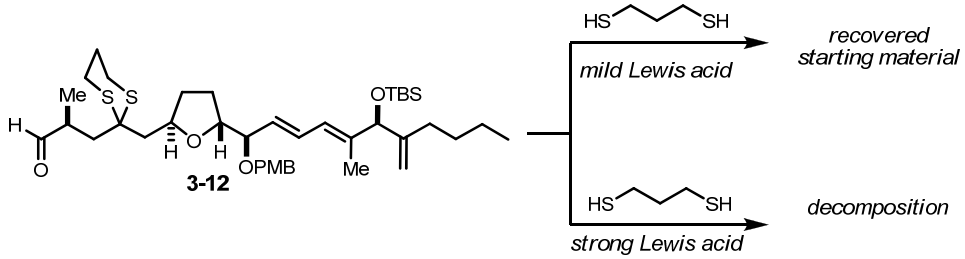
As previously, the *anti* configuration was the major diastereomer, so a Mitsunobu reaction was performed to invert the stereocenter (DIAD/*p*-nitrobenzoic acid) resulting in the desired *syn* conformation (Scheme 3.3). Treatment with RED-Al concurrently deprotected the alcohol and reduced the ene-yne to furnish the carbon backbone, and the alcohol (**3-9**) was protected as a PMB ether (PMBBr/NaH) to give **3-10** in 99% yield. The primary TBS group was selectively removed under acidic conditions (PPTS/EtOH) followed by oxidation to the corresponding aldehyde **3-12** in 95% yield over 2 steps. All that remained was conversion of the aldehyde to a dithiane, and use of that dithiane to alkylate protected iodohydrin **2-44** to complete the C(15)-C(34) fragment.



Scheme 3.3. Completion of aldehyde **3-12**

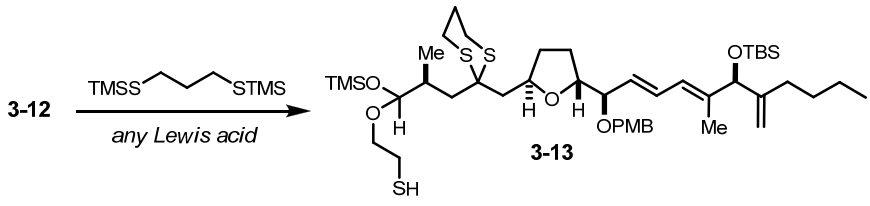
Unfortunately, we were unable to form the dithiane under all attempted conditions. Attempts with unprotected 1,3-propanedithiol and mild Lewis acids ($MgBr_2$, $ZnCl_2$) gave

no reaction, whereas strong Lewis acids ($BF_3{\cdot}OEt_2$, $TiCl_4$, $Yb(OTf)_3$, $Sc(OTf)_3$) led to substrate decomposition (Scheme 3.4). The exact nature of the decomposition was not determined, but shifting and/or disappearance of signals in the ^1H NMR indicative of the Eastern fragment protons suggested that the skipped triene may be involved in the decomposition process.



Scheme 3.4. Failed attempts at forming a dithiane using 1,3-propanedithiol

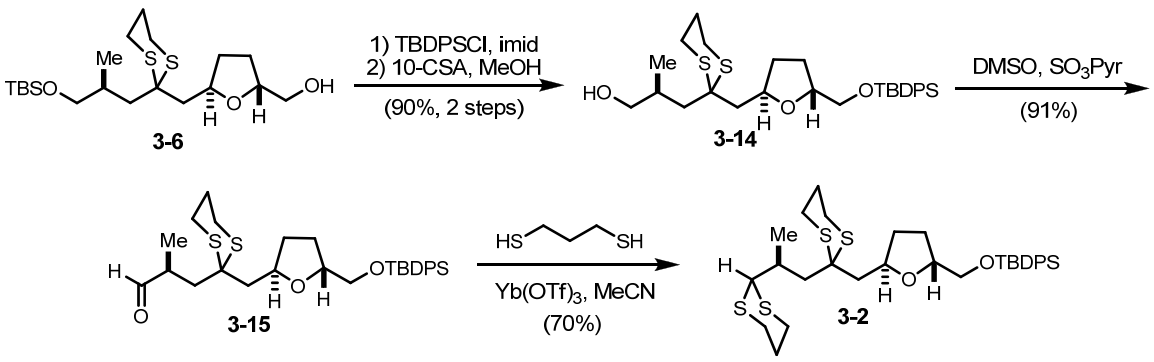
Previously, success had been achieved in the use of a milder silylated 1,3-propanedithiol with either $Yb(OTf)_3$ or $Sc(OTf)_3$ as Lewis acids. However, in the case of aldehyde **3-12** the most common result of dithianation attempts using the silylated propanedithiol resulted in the isolation of a partially protected carbonyl compound **3-13**, presumably a stable intermediate formed during the protection process (Scheme 3.5). One can easily envision the completion of the protection, by attack of the thiol and loss of the silylated oxygen, forming the dithiane, but in the case of this particular substrate, the protection does not proceed to completion. Irritatingly, it appeared that again steric bulk was to blame, as the only difference between this compound (**3-12**) and aldehyde **2-68** was the presence of the methyl group at C(16).



Scheme 3.5. Isolation of a silyl-thioacetal intermediate (**3-13**)

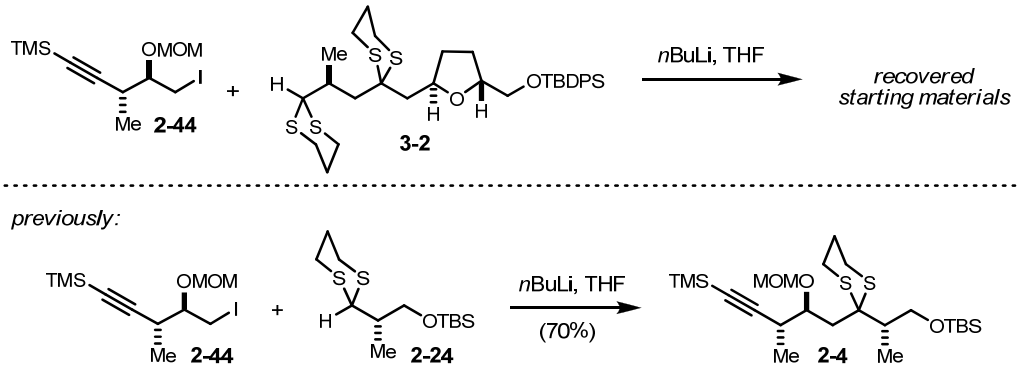
All attempts to convert thioacetal **3-13** to the dithiane were unsuccessful, and it was becoming clear that to form a dithiane at C(15), a more aggressive Lewis acid and

unprotected propanedithiol must be used, with which the skipped triene on the Eastern fragment appears incompatible. To that end, we endeavored to first functionalize the left side of the new Northern fragment **3-6** before adding the Eastern fragment. Starting from THF-alcohol **3-6** we capped the right hand side of the molecule as a *tert*butyldiphenylsilyl ether (TBDPSCl, DMF) allowing for selective removal of the primary TBS group (10-CSA/MeOH) in 90% yield over 2 steps (Scheme 3.6). The alcohol **3-14** was then oxidized to the corresponding aldehyde **3-15** using Parikh-Doering conditions (SO_3·Pyr/DMSO) in 91% yield. This time, using harsh conditions that resulted in decomposition of the skipped triene on aldehyde **3-12** (propanedithiol, $Yb(OTf)_3$, MeCN), the dithiane **3-2** was finally formed in 70% yield.



Scheme 3.6. Conversion of the homologated Northern fragment to dithiane **3-**.

To complete the North-Western fragment, dithiane **3-2** would need to be coupled to protected iodohydrin **2-44**, which we expected to proceed smoothly, given previous success with a similar dithiane. Astonishingly, we were unable to perform the alkylation under a variety of conditions, which was confounding considering the similarity between the Roche ester derived dithiane **2-24** that did work, and the 1,4-di-dithiane **3-2** that didn't work (Scheme 3.7).

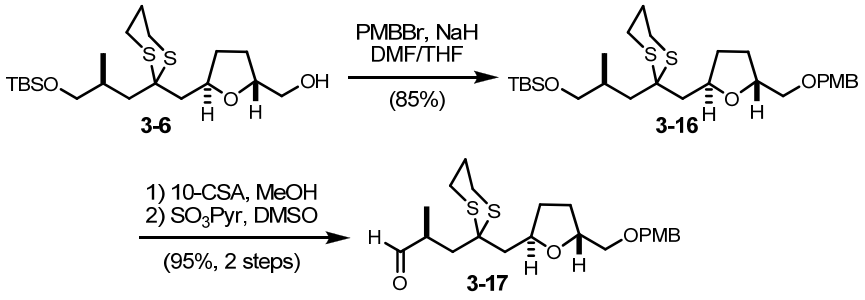


Scheme 3.7. A comparison of the failed and successful alkylations of **2-44**

Exasperated at the constant failures to perform key dithiane alkylations in multiple steps, and with dithiane related nightmares haunting my dreams, we turned our attention to the literature for inspiration.

Section 3.1.3 – Formation of the North-Western Fragment via Aldol Strategy

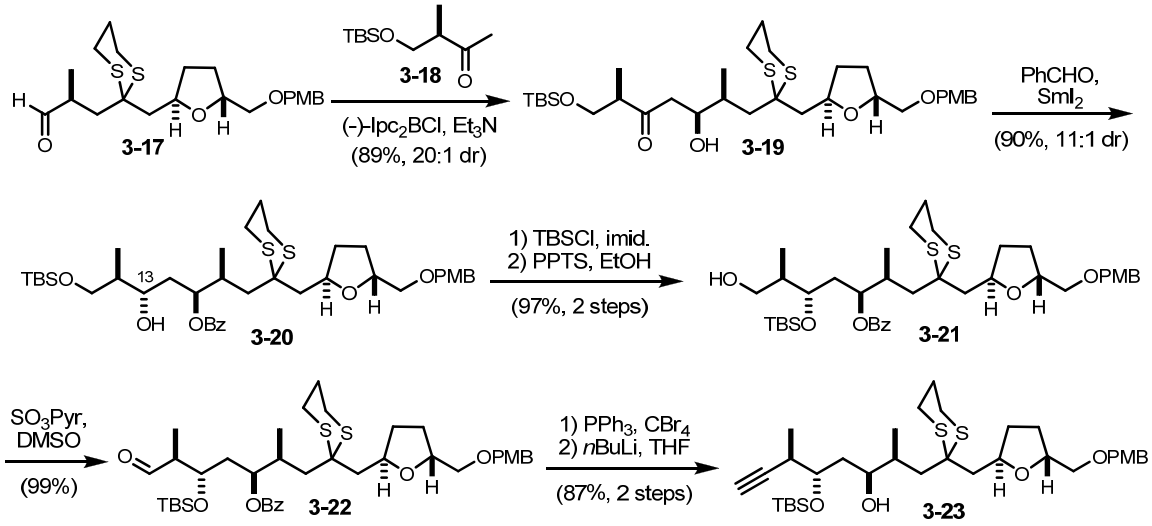
As reported earlier, Roush reported the successful completion of the C(11)-C(29) fragment of Amphidinolide C via an aldol/Evans-Tishchenko reaction, setting the desired stereochemistry at C(13) by means of an intramolecular reduction.[3] We felt as though this strategy could be easily applied to our substrate, given the similarities of the compounds. To facilitate late stage deprotection, THF-alcohol **3-6** was protected as the PMB ether (**3-16**) (PMBBr/NaH) in 85% yield (Scheme 3.8). The TBS was cleaved (10-CSA/MeOH) and the resulting primary alcohol was oxidized to the aldehyde (**3-17**) (SO_3·Pyr/DMSO) in 95% yield over 2 steps, setting the stage for the boron-mediated aldol reaction.



Scheme 3.8. Prepareation of aldehyde **3-17** for the aldol reaction

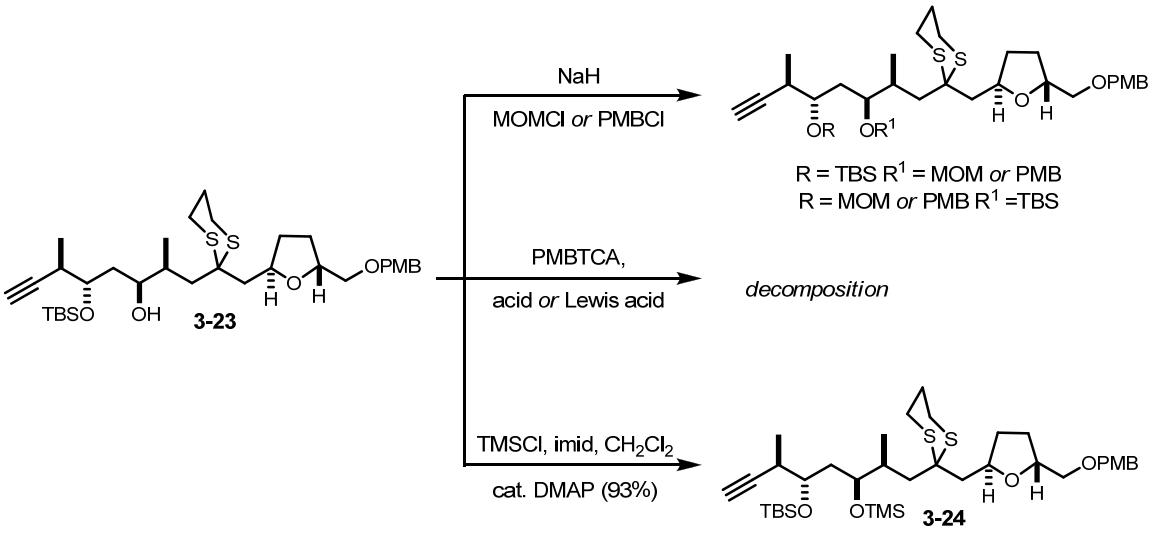
Initial reactions using dicyclohexylchloroborane resulted in poor dr (ca. 4:1), which was

improved upon by using (−)-diisopinocamphenylchloroborane,[4] resulting in a 20:1 dr and 89% yield of the aldol product **3-19** (Scheme 3.9). Evans-Tishchenko reduction proceeded smoothly (PhCHO, SmI_2) ensuing in 90% yield of **3-20** as a 11:1 ratio of inseparable diastereomers at C(13). The secondary alcohol was protected as a TBS ether in 99% yield, and the primary alcohol was selectively deprotected under acidic conditions (PPTS/EtOH) in 98% yield. The primary alcohol **3-21** was oxidized to the aldehyde (**3-22**) before being converted to the dibromoalkene (PPh_3/CBr_4). Treatment with excess *n*BuLi simultaneously formed the alkyne while removing the benzoyl group to afford alcohol **3-23** in 99% yield without any TBS migration.



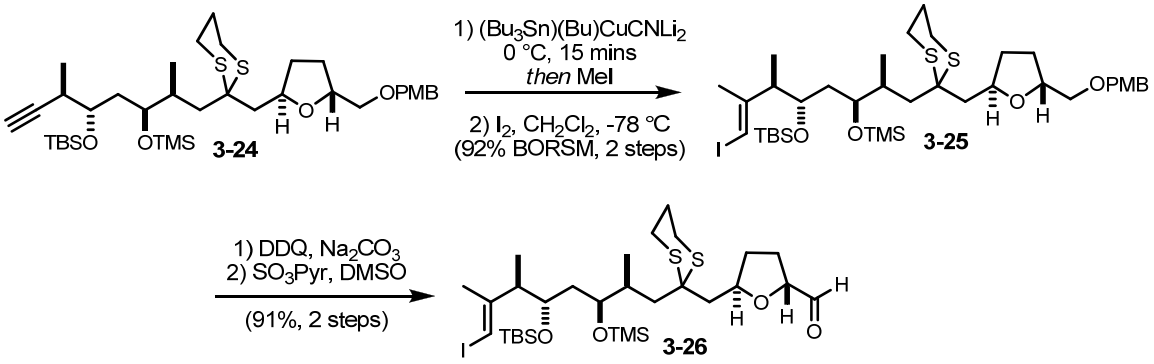
Scheme 3.9. Formation of the North-Western fragment via aldol/Evans-Tishchenko

Our original plan was to oxidize the alcohol (**3-23**) at C(15) to the desired carbonyl oxidation state and protect it until the end-game deprotection. Several methods of oxidation were attempted with no success,[5] so we decided to protect it with an orthogonal protecting group, with the goal of a late stage oxidation in mind. Conditions that required deprotonation of the alcohol (NaH and either PMBBr or MOMCl) resulted in TBS migration, and Lewis acid catalyzed reactions (PMBTCA, $Yb(OTf)_3$) resulted in product decomposition (Scheme 3.10). Ultimately, we settled on using a highly labile TMS group (**3-24)**, which is not typically used as a protecting group due to its instability, but in this case we were hoping that the steric bulk around the TMS group would work in our favor to increase its longevity.



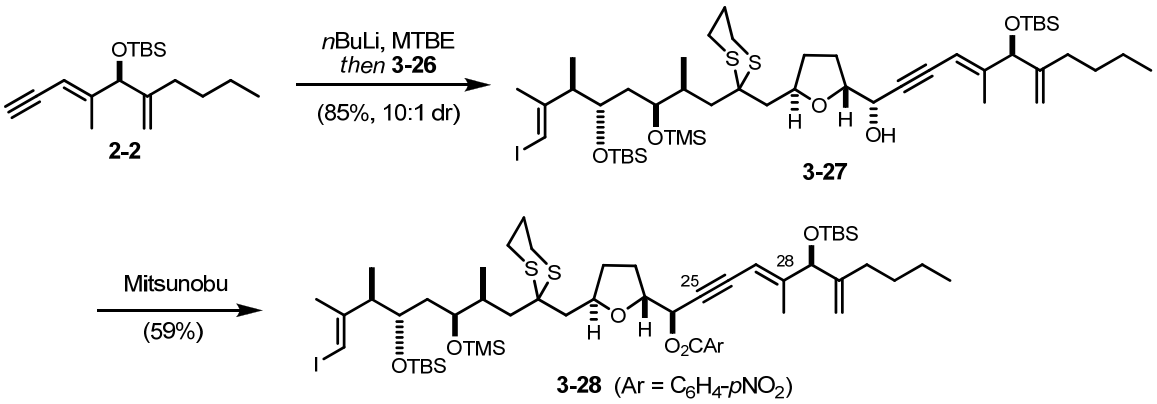
Scheme 3.10. Attempts at protecting the alcohol at C(15) of alkyne **3-23**

Now that the alcohol was protected, we turned our attention to functionalization of the alkyne, using the carbo-stannylation method formerly utilized. The alkyne **3-24** was converted into stannane using our previously optimized conditions resulting in a 94% yield (BORSM) of a single regioisomer (Scheme 3.11). The stannane was carefully converted to the iodide **3-25** at -78°C, as increased temperatures resulted in deprotection of the TMS group. Then, to prepare for the addition of the Eastern fragment (**2-2**), the PMB group was removed using buffered conditions (DDQ/Na_2CO_3) and the primary alcohol was oxidized to the aldehyde **3-26** (SO_3·Pyr/DMSO) in 91% yield over 2 steps.



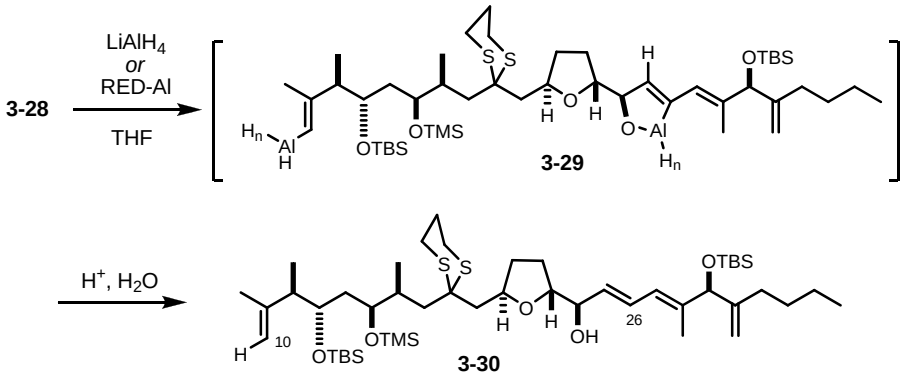
Scheme 3.11. Preparation of aldehyde **3-26** for fragment coupling

We were pleased to see that the excellent selectivity was again maintained in the coupling reaction, resulting in an *anti*- product **3-27** in a 85% yield and 10:1 dr utilizing the previously optimized conditions (Scheme 3.12). Mitsunobu inversion of the secondary alcohol furnished the desired *syn*- configuration in 59% yield, and one of the few remaining steps was concurrent benzoyl deprotection and hydroalumination of the alkyne to complete the C(25)-C(28) diene, with either $LiAlH_4$ or RED-Al.



Scheme 3.12. Coupling of **2-2** and **3-26**

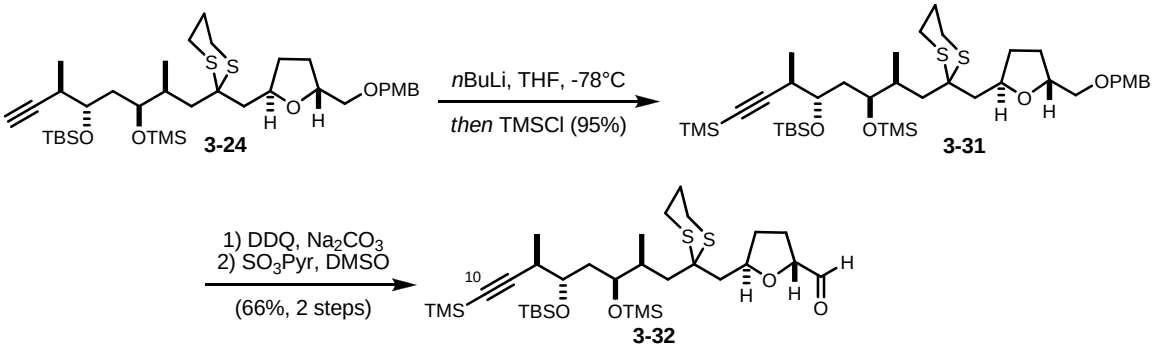
Unfortunately, all attempts to hydroaluminate **3-28** resulted in the isolation of protonated product **3-30** (Scheme 3.13). It was reasoned that **3-30** was formed upon protic quench of the unisolated intermediate **3-29**, a product that would be formed upon removal of the benzoyl group, hydroalumination of the alkyne, and metal-halogen exchange of the vinyl iodide.



Scheme 3.13. Protonated product **3-30** formed via protonation of intermediate **3-29**

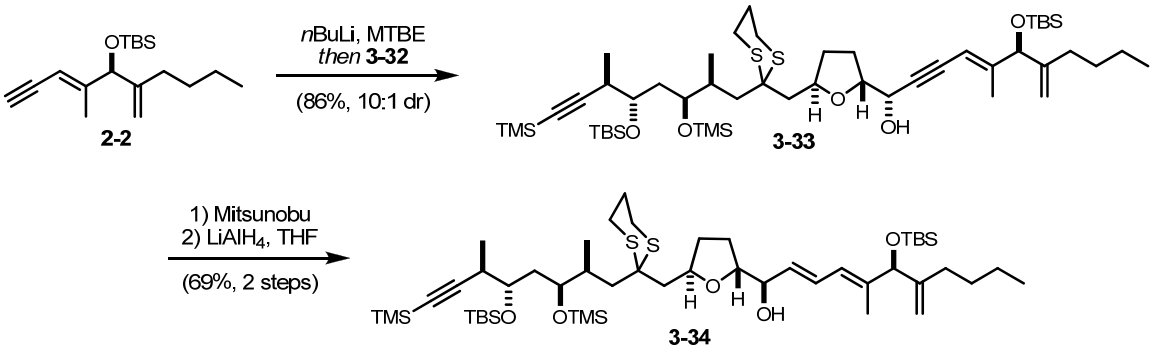
We considered several options to circumvent this problem. Our first thought was to limit the amount of aluminum hydride in the reaction hoping for selectivity through a rate difference of the two alumination reactions; however initial attempts concluded that there was no exploitable rate difference. We briefly considered quenching the reaction with iodine, which would regenerate the iodoalkene at C(10).[6] However, we realized that the iodine quench would result in a second iodoalkene at C(26), which we would have to remove, so that idea was abandoned as well. Lastly, we considered utilizing the alkene-aluminum compound **3-29** directly in cross coupling without isolation,[7] and hope that there would be some selectivity for cross coupling at C(10) over C(26). Given the reported sensitivity of the uniquely substituted diene system that would be formed, this thought was also quickly abandoned.

Alternative aluminum hydrides were considered, but literature reports of hydro-aluminations using reagents other than the standard DIBAL-H, $LiAlH_4$, and RED-Al were scarce, and offered no suggestion that the iodoalkene would survive the reaction.[8] Finally, we considered alternative hydroxyl-directed hydrometallations (hydrostannylation, hydrosiliconation, hydroboration, hydrotelluration, etc), but literature evidence of the potential advantages of using other metal hydrides was sparse.[9] In the end, we decided that leaving the C(10) end of the molecule as either a TMS alkyne or a unprotected alkyne would be the easiest way to circumvent the metal-halogen exchange.[10] To that end, the previously formed alkyne **3-24** was deprotonated and protected as the TMS alkyne **3-31** in 95% yield (Scheme 3.14). Subsequent deprotection of the PMB ether and oxidation to the aldehyde **3-32** furnished the new coupling partner in 66% yield.



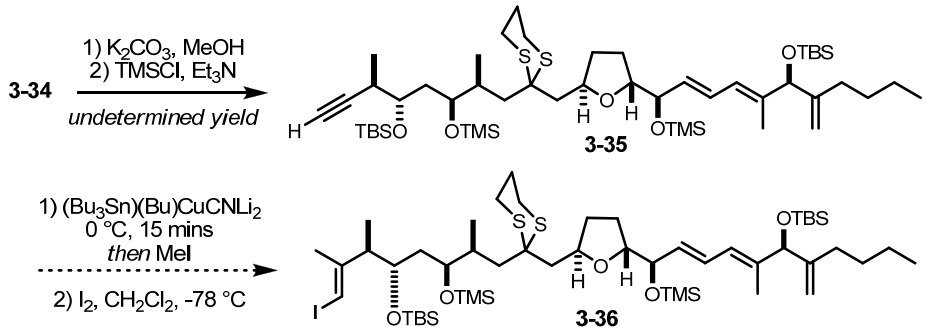
Scheme 3.14. Formation of the new coupling partner **3-32**

Again, the addition of the Eastern fragment proceeded with excellent yield and selectivity (86% and 10:1 dr) to give **3-33**, and Mitsunobu inversion cleanly provided the *syn* configuration (Scheme 3.15). As expected, the unactivated TMS protected alkyne did not undergo hydroalumination, and the diene **3-34** was formed in 99% yield.



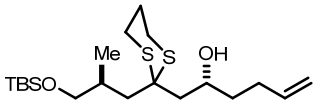
Scheme 3.15. Successful hydroalumination to form the diene **3-34**

Basic deprotection of the alkyne (K_2CO_3, MeOH) followed by selective TMS re-protection of the alcohols (TMSCl, Et_3N) furnished alkyne **3-35** in an undetermined yield over 2 steps (Scheme 3.16). Unfortunately, the amount and purity of **3-35** was insufficient to perform the carbostannylation reaction with confidence. Making the assumption that the reaction would proceed as planned, more material is currently being brought up with the intention of completing the total synthesis.



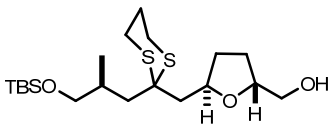
Scheme 3.16. Proposed completion of the North-Eastern-Western fragment **3-36**

Section 3.2 – Experimental



3-5

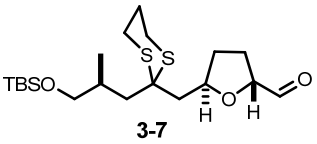
To a 250 mL round bottom flask charged with dithiane (2.78 g, 9.08 mmol, 1.3 eq) diluted with THF (50 mL) and HMPA (5 mL) and cooled to -25 °C was added *n*BuLi (1.48 M, 6.14 mL, 9.08 mmol, 1.3 eq) drop wise over 10 min. The reaction was allowed to stir for 30 min before being cooled to -50 °C, after which epoxide **3-4** (696 mg, 7.0 mmol, 1.0 eq) was added in one portion and the reaction was allowed to warm to 0 °C and stirred for 2 h. The reaction mixture was poured into a half saturated solution of NH_4Cl (200 mL) and diluted with EtOAc (100 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, and the crude product was purified by column chromatography (15% EtOAc/Hex) to afford alcohol **3-5** as a yellow oil (2.58 g, 6.4 mmol, 91% yield; R_f 0.46 (20% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (ddt, *J* = 17.0, 10.2, 6.9 Hz, 1H), 5.05-4.95 (m, 2H), 4.03-3.98 (m, 1H), 3.57 (bs, 1H), 3.40 (d, *J* = 6.4 Hz, 2H), 3.03-2.90 (m, 2H), 2.81-2.74 (m, 2H), 2.36 (dd, *J* = 15.2, 9.4 Hz, 1H, 2.26-2.10 (m, 2H), 2.05 (dd, *J* = 14.6, 3.5 Hz, 1H), 2.04-1.97 (m, 1H), 1.97-1.85 (m, 3H), 1.70 (dd, *J* = 14.9, 6.7 Hz, 1H), 1.62-1.56 (m, 1H), 1.56-1.42 (m, 1H), 1.03 (dd, *J* = 6.4 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 114.6, 68.7, 67.8, 52.6, 45.6, 43.2, 36.9, 32.4, 27.8, 26.7, 26.3, 26.0, 24.7, 19.4, -5.3. HRMS *m/z* 404.2240 (calcd for $C_{20}H_{40}O_2S_2Si$, 404.2239).



3-6

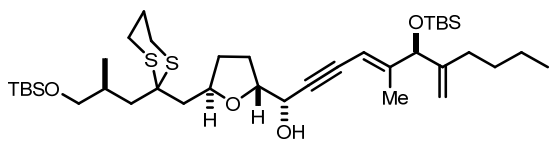
Prep to pre-activate Co(nmp)$_2$: To a flask charged with Co(nmp)$_2$ (**1-21**) (354 mg, 0.63 mmol, 0.1 eq) and *i*PrOH (60 mL) was added *t*BuOOH (5.33 M, 0.12 mL, 0.63 mmol, 0.1 eq). The reaction was heated to 55 °C under oxygen for 1h, and solvent was removed under reduced pressure. The activated Co(nmp)$_2$ was dried under highvac (0.1 mmHg) for 5 min to ensure that all traces of peroxide have been removed. **Cyclization:**The pre-activated Co(nmp)$_2$ (prepared above, 0.63 mmol, 0.1 eq) was diluted with 60 mL *i*PrOH and alcohol (**3-5**) was added (2.54 g, 6.30 mmol, 1 eq). The reaction was heated to 55 °C under an oxygen atmosphere for 16 h, and allowed to

cool to rt. Solvent was removed under reduced pressure, followed by highvac (0.1 mmHg) to remove all traces of *i*PrOH. The crude mixture was diluted with EtOAc (30 mL) and filtered through a thin pad of silica (<1 cm) over celite to remove the catalyst. The pad was washed with EtOAc (300 mL) and the filtrate was concentrated under reduced pressure to give THF-alcohol (**3-6**) (2.14 g, 5.10 mmol, 81%) as a yellow oil, which was used without further purification. R_f 0.39 (50% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.25-4.19 (m, 1H), 4.11-4.06 (m, 1H), 3.59-3.55 (m, 1H), 3.47-3.38 (m, 3H), 2.88-2.71 (m, 4H), 2.25-2.05 (m, 5H), 1.97-1.87 (m, 4H), 1.70-1.52 (m, 3H), 1.00 (d, J = 6.4 Hz), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 78.7, 75.8, 68.6, 64.9, 52.9, 45.1, 42.0, 33.9, 32.6, 27.4, 26.3, 25.9, 25.0, 19.3, 18.3, -5.4.



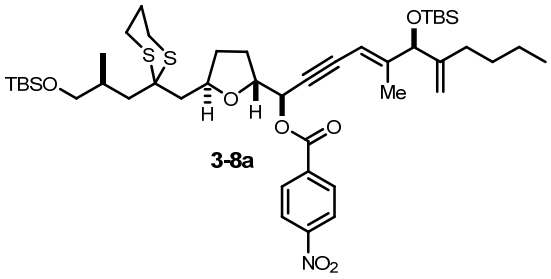
3-7

A 250 mL round bottom flask was charged with alcohol **3-6** (1.00 g, 2.38 mmol, 1 eq), diluted with CH_2Cl_2 (70 mL) and cooled to 0 °C. DMSO (556 mg, 7.14 mmol, 3 eq) was added, followed by Hunig's base (1.51 mL, 11.9 mmol, 5 eq). The reaction mixture was allowed to stir for 10 min before SO_3•Pyr (760 mg, 4.76 mmol, 2 eq) was added portion wise over 5 min. The reaction was monitored by TLC until completion (ca. 2h) before being slowly poured into a half-saturated solution of sodium bicarbonate (100 mL), and diluted with CH_2Cl_2 (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, and the crude residue was dissolved in EtOAc (100 mL) and water (100 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, to afford **3-7** as a yellow oil (944 mg, 2.26 mmol, 95% yield) which was used without further purification. The second extraction using EtOAc removes oxidation byproducts from the reaction without using column chromatography. R_f 0.61 (50% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.66 (d, *J* = 2.3 Hz, 1H), 4.35-4.29 (m, 1H), 4.28 (dt, *J* = 11.7, 6.4, 5.8 Hz, 1H), 3.48-3.42 (m, 2H), 2.88-2.74 (m, 5H), 2.39-2.27 (m, 1H), 2.21-2.14 (m, 4H), 1.70 (dd, *J* = 14.6, 5.8, 1H), 1.63-1.59 (m, 1H), 1.01 (d, *J* = 6.4 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 203.5, 82.3, 77.9, 68.6, 52.7, 45.0, 42.0, 33.1, 32.7, 27.3, 26.4, 26.0, 25.0, 19.4, -5.3.



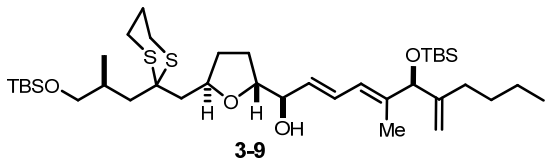
3-8

To a solution of alkyne **2-2** (1.16 g, 4.0 mmol, 2 eq) in MTBE (20 mL) at 0 °C was added *n*BuLi (2.07 M, 2.0 mL, 4.0 mmol, 2 eq), and the reaction was stirred at 0 °C for 30 min before being cooled to -90 °C using a liquid nitrogen/hexanes bath. After stirring for 15 min at -90 °C, freshly purified aldehyde **3-7** (850 mg, 2.03 mmol, 1 eq) dissolved in a minimal amount of MTBE was added over 15 min drop wise. The slow addition, low temperature of the reaction and the purity of both **2-2** and **3-7** were essential conditions to ensure a high dr. After stirring at -90 °C for 3 h, the reaction was treated at -90 °C with 20 mL of saturated NH_4Cl, before allowing to warm to rt and being diluted with water (50 mL) and EtOAc (50 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, and the crude product was purified by column chromatography (20% EtOAc/Hex) to afford recovered alkyne (600 mg) and alkynlation adduct **3-8** as a 10:1 ratio of diastereomers as a yellow oil (1.07 g, 1.50 mmol, 75% yield). R_f 0.48 (20% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63 (s, 1H), 5.05 (s, 1H), 4.86 (s, 1H), 4.61 (bs, 1H), 4.41 (s, 1H), 4.41-4.39 (m, 1H), 4.16 (dt, *J* = 7.6, 3.5 Hz, 1H), 3.48 (d, *J* = 5.6, 3.5 Hz, 1H), 3.41 (d, *J* = 5.6, 3.5 Hz, 1H), 2.86-2.73 (m, 4H), 2.50 (d, *J* = 5.3 Hz, 1H), 2.28-2.17 (m, 3H), 2.16-2.07 (m, 2H), 2.06-2.02 (m, 1H), 1.97-1.87 (m, 3H), 1.78-1.75 (m, 1H), 1.71 (s, 3H), 1.71-1.67 (m, 1H), 1.63-1.58 (m, 1H), 1.40-1.34 (m, 2H), 1.28 (q, *J* = 7.3 Hz, 2H), 1.00 (d, *J* = 6.4 Hz, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.87 (at, *J* = 8.2 Hz, 3H), 0.03 (s, 6H), 0.00 (d, *J* = 2.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 149.1, 110.7, 104.8, 90.5, 83.6, 80.8, 80.0, 77.5, 68.7, 65.0, 52.8, 45.1, 42.0, 41.7, 33.9, 32.6, 29.9, 29.8, 28.2, 26.5, 26.3, 26.0, 25.8, 25.0, 22.6, 19.4, 18.3, 18.2, 15.3, 14.0, -5.1, -5.3.



3-8a

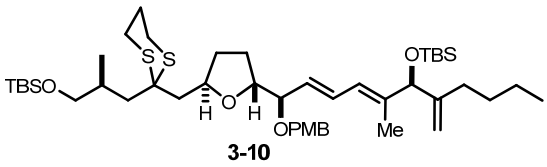
A 250 mL round bottom flask was charged with 4-nitro benzoic acid (400 mg, 2.36 mmol, 4 eq), triphenylphosphine (616 mg, 2.36 mmol, 4 eq), alcohol **3-8** (420 mg, 0.588 mmol, 1 eq), diluted with THF (30 mL) and cooled to 0 °C. DIAD (280 mg, 2.36 mmol, 4 eq) was added drop wise over 10 min, and the ice bath was removed. The reaction was stirred overnight (ca. 16 h) before being slowly poured into a half-saturated solution of sodium bicarbonate (50 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, and the crude product was purified by filtration through a thin plug of silica gel (20% EtOAc/Hex) to afford **3-8a** as a yellow oil (394 mg, 0.46 mmol, 78% yield). R_f 0.56 (20% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 4H), 5.73 (d, J = 7.4 Hz, 1H), 5.64 (s, 1H), 5.04 (s, 1H), 4.86 (s, 1H), 4.41 (s, 1H), 4.36 (q, J = 7.0 Hz, 1H), 4.28 (dq, J = 9.5, 5.0 Hz, 1H), 3.42 (dd, J = 9.6, 5.7 Hz, 1H), 3.30 (dd, J = 9.4, 6.6 Hz, 1H), 2.80-2.67 (m, 4H), 2.28-2.17 (m, 3H), 2.14-2.02 (m, 2H), 1.95-1.86 (m, 4H), 1.77-1.73 (m, 1H), 1.70 (s, 3H), 1.65-1.58 (m, 2H), 1.40-1.32 (m, 2H), 1.32-1.23 (m, 2H), 0.88 (at, J = 8.2 Hz, 3H), 0.86 (s, 12H), 0.85 (s, 9H), -0.01 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 153.7, 150.5, 148.9, 135.6, 131.0, 123.4, 111.1, 104.1, 87.1, 84.7, 80.0, 79.1, 76.5, 68.6, 52.6, 44.6, 41.5, 33.6, 32.6, 29.9, 29.6, 28.7, 26.3, 26.2, 25.9, 25.8, 25.0, 22.6, 19.2, 18.3, 18.2, 15.5, 14.0, -5.0, -5.2, -5.3. HRMS *m/z* 859.4359 (calcd for $C_{45}H_{73}NO_7S_2Si_2$, 859.4367).



3-9

A 250 mL round bottom flask was charged with **3-8a** (342 mg, 0.397 mmol, 1 eq), diluted with ether (30 mL) and cooled to 0 °C. Red-Al (65% w/w in toluene, 620 mg, 2.0 mmol, 5 eq) was added drop wise over 10 min. The ice bath was removed and the reaction was stirred for 30 min at rt before being slowly poured into a half-saturated solution of NH_4Cl (50 mL), and a saturated solution of Rochelle's salt was added (50

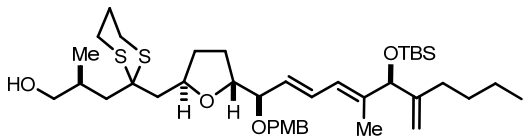
mL), and the slurry was stirred vigorously for 30 min. The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, and the crude product was purified by column chromatography (10% EtOAc/Hex) to afford alcohol **3-9** as a yellow oil (251 mg, 0.353 mmol, 89% yield). R_f 0.50 (20% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.52, (dd, *J* = 15.2, 11.1, 1H), 6.05 (d, *J* = 11.1 Hz, 1H), 5.55 (dd, *J* = 15.2, 6.4 Hz, 1H), 5.09 (s, 1H), 4.83 (s, 1H), 4.38 (s, 1H), 4.23-4.19 (m, 1H), 3.96 (t, *J* = 7.3 Hz, 1H), 3.86 (q, *J* = 7.0 Hz, 1H), 3.45 (ABd, *J* = 11.4, 6.1 Hz, 1H), 3.42 (ABd, *J* = 11.4, 6.1 Hz, 1H), 2.87-2.75 (m, 4H), 2.74 (bs, 1H), 2.27 (dd, *J* = 15.2, 6.4 Hz, 1H), 2.17-2.12 (m, 2H), 2.08 (dd, *J* = 14.9, 3.8 Hz, 1H), 1.98-1.90 (m, 4H), 1.90-1.85 (m, 1H), 1.80-1.75 (m, 1H), 1.70 (dd, *J* = 14.6, 5.9, 1H), 1.65-1.60 (m, 1H), 1.58 (s, 3H), 1.39-1.33 (m, 2H), 1.30-1.24 (m, 2H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.04 (s, 6H), 0.00 (d, *J* = 9.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 139.5, 130.2, 128.8, 124.8, 109.7, 81.7, 80.6, 75.7, 75.2, 68.7, 52.9, 44.8, 42.2, 33.9, 32.7, 30.7, 30.0, 27.9, 26.4, 26.0, 25.8, 25.0, 22.5, 19.4, 18.4, 18.3, 14.0, 12.0, -5.0, -5.1. HRMS *m/z* 712.4432 (calcd for $C_{38}H_{72}O_4S_2Si_2$, 712.4411).



3-10

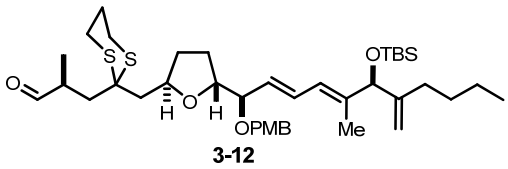
A 50 mL round bottom flask was charged sodium hydride (27 mg, 1.12 mmol, 4.0 eq) and diluted with THF (3 mL) and DMF (3 mL). To that solution was added PMB-Br (58.8 mg, 0.28 mmol, 1.0 eq) followed by alcohol **3-9** (200 mg, 0.28 mmol, 1 eq). The reaction was allowed to stir overnight (ca. 16 h) before being slowly poured into a half-saturated solution of NH_4Cl (50 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, and the crude product was purified by column chromatography (10% EtOAc/Hex) to afford alcohol **3-10** as a yellow oil (230 mg, 0.277 mmol, 99% yield). R_f 0.26 (10% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.42 (dd, *J* = 15.2, 11.1 Hz, 1H), 6.08 (d, *J* = 11.1 Hz, 1H), 5.55 (dd, *J* = 15.2, 7.6 Hz), 5.11 (s, 1H), 4.86 (s, 1H), 4.61 (d, *J* = 11.7 Hz, 1H), 4.43 (d, *J* = 11.7 Hz, 1H), 4.40 (s, 1H), 4.21-4.17 (m, 1H), 4.06 (aq, *J* = 7.6

Hz, 1H), 3.81-3.78 (m, 1H), 3.78 (s, 3H), 3.50 (dd, *J* = 6.7, 5.6 Hz, 1H), 3.41 (dd, *J* = 9.4, 6.4 Hz, 1H), 2.83-2.79 (m, 4H), 2.32 (dd, *J* = 14.9, 5.6 Hz), 2.15-2.08 (m, 2H), 2.02-1.94 (m, 1H), 1.93-1.87 (m, 3H), 1.84-1.78 (m, 1H), 1.71-1.65 (m, 2H), 1.59 (s, 3H), 1.56-1.52 (m, 1H), 1.42-1.36 (m, 2H), 1.33-1.28 (m, 2H), 1.03 (d, *J* = 6.4 Hz, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.88 (at, *J* = 8.2 Hz, 3H), 0.04 (s, 6H), 0.03 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 149.6, 139.1, 131.0, 129.8, 129.6, 129.2, 124.8, 113.6, 109.7, 81.9, 80.6, 80.6, 76.2, 70.0, 68.7, 55.2, 52.8, 45.0, 41.9, 33.9, 32.6, 30.8, 30.1, 28.2, 26.3, 26.3, 25.0, 25.8, 25.1, 22.5, 19.4, 18.3, 18.3, 14.0, 12.1, -5.0, -5.3. HRMS *m/z* 832.4966 (calcd for $C_{46}H_{80}O_5S_2Si_2$, 832.4986).



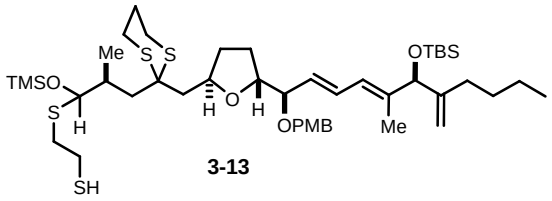
3-11

To 25 mL round bottom flask charged with TBS alcohol **3-10** (35 mg, 0.042 mmol, 1 eq) was added wet ethanol (20 mL) and a catalytic amount of PPTS was added in one portion. The reaction was monitored by TLC until complete (ca. 2-4 h), at which point it was diluted with water (30 mL) and EtOAc (30 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, and the crude product was purified by column chromatography (40% EtOAc/Hex) to afford alcohol **3-11** as a yellow oil (30.2 mg, 0.042 mmol, 100% yield). R_f 0.33 (40% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.8Hz, 2H), 6.41 (d, *J* =15.2, 11.1 Hz, 1H), 6.08 (d, *J* = 11.1 Hz, 1H), 5.53 (dd, *J* = 15.2, 7.6 Hz, 1H), 5.10 (s, 1H), 4.85 (s, 1H), 4.58 (d,*J* = 11.7 Hz, 1H), 4.41 (d, *J* = 11.7 Hz, 1H), 4.40 (s, 1H), 4.42-4.18 (m, 1H), 4.06 (q, *J* = 6.6 Hz, 1H), 3.79-3.77 (, 1H), 3.78 (s, 3H), 3.51-3.48 (m, 2H), 2.89-2.84 (m, 1H), 2.81-2.75 (m, 3H), 2.25 (dd, *J* = 6.4, 5.9 Hz, 1H), 2.18 (td, *J* = 14.6, 4.7 Hz, 2H), 2.11-2.03 (m, 2H), 1.96-1.85 (m, 4H), 1.83-1.76 (m, 2H) 1.67-1.62 (m, 1H), 1.58 (s, 3H), 1.56-1.51 (m, 1H), 1.41-1.35 (m, 2H), 1.30-1.26 (m, 2H), 1.03 (d, *J* = 7.0 Hz, 3H), 0.89 (t, *J* = 8.7 Hz, 3H), 0.89 (s, 9H), 0.01 (d, *J* = 5.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 149.6, 139.3, 130.9, 130.0, 129.4, 129.2, 124.8, 113.6, 109.8, 82.0, 80.7, 80.6, 76.2, 70.0, 68.6, 55.2, 52.8, 45.1, 42.9, 33.9, 32.6, 30.7, 30.1, 28.2, 26.4, 26.2, 25.8, 25.0, 22.5, 19.5, 18.3, 14.0, 12.1, -5.0.



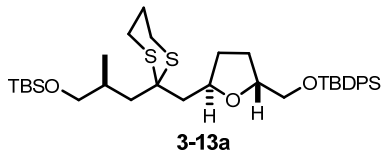
3-12

A 50 mL round bottom flask was charged with alcohol **3-11** (76.7 mg, 0.106 mmol, 1 eq), diluted with CH_2Cl_2 (2 mL) and cooled to 0 °C. DMSO (24 mg, 0.3 mmol, 3 eq) was added, followed by Hunig's base (63.5 mg, 0.5 mmol, 5 eq). The reaction mixture was allowed to stir for 10 min before SO_3•Pyr (32 mg, 0.2 mmol, 2 eq) was added. The reaction was monitored by TLC until completion (ca. 2h) before being slowly poured into a half-saturated solution of sodium bicarbonate (10 mL), and diluted with CH_2Cl_2 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, and the crude residue was dissolved in EtOAc (50 mL) and water (50 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, to afford **3-12** as a yellow oil (71.1 mg, 0.098 mmol, 93% yield) which was used without further purification. The second extraction using EtOAc removes oxidation byproducts from the reaction without using column chromatography, which was shown to epimerize the aldehyde. R_f 0.41 (20% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.76 (s, 1H), 7.25 (d, J = 8.2, 1H), 6.84 (d, J = 8.2 Hz, 2H), 6.42 (dd, J = 15.2, 11.1 Hz, 1H), 6.08 (d, J = 10.5 Hz, 1H), 5.54 (dd, J = 15.2, 8.2 Hz, 1H), 5.10 (s, 1H), 4.85 (s, 1H) 4.56 (d, J = 11.7 Hz, 1H), 4.40 (s, 1H), 4.36 (d, J = 11.7 Hz, 1H), 4.27-4.24 (m, 1H), 4.04 (q, J = 6.6 Hz, 1H), 3.78 (s, 3H), 3.78-3.76 (m, 1H), 2.95-2.87 (m, 2H), 2.80-2.70 (m, 4H), 2.69-2.56 (m, 1H), 2.13-1.97 (m, 5H), 1.92-1.78 (m, 4H), 1.67-1.62 (m, 1H), 1.59 (s, 3H), 1.52-1.46 (m, 1H), 1.42-1.35 (m, 2H), 1.32-1.25 (m, 2H), 1.06 (d, J = 7.0 Hz, 3H), 0.89 (s, 9H), 0.87 (t, J = 8.8 Hz, 3H), 0.01 (d, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ204.2, 159.0, 149.5, 139.4, 130.8, 130.0, 129.5, 129.2, 124.6, 113.6, 109.8, 82.2, 81.1, 80.6, 75.0, 70.0, 55.2, 51.8, 45.2, 43.3, 41.7, 40.3, 36.7, 33.7, 30.7, 30.1, 27.9, 26.3, 26.0, 25.8, 24.9, 22.5, 18.3, 16.0, 14.0, 12.1, -5.0.



3-13

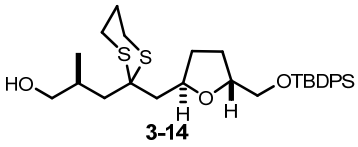
To a solution of aldehyde **3-12** (15.2 mg, 0.021 mmol, 1 eq) in diethyl ether (1 mL) was added silylated propanedithiol (3 drops, excess) and ZnI_2 (10 mg, excess). The reaction mixture was stirred overnight (ca. 16 h) before being poured into a half-saturated solution of sodium bicarbonate (10 mL), and diluted with EtOAc (10 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, and the crude yellow oil which was purified by column chromatography to afford **3-13** (10 mg, 0.010 mmol, 50% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.2 Hz, 2H), 6.41 (dd, *J* = 15.2, 11.1 Hz, 1H), 6.08 (d, *J* = 10.5 Hz, 1H), 5.54 (dd, *J* = 15.2, 7.6 Hz, 1H), 5.10 (s, 1H), 4.85 (s, 1H), 4.82 (d, *J* = 4.1 Hz, 1H), 4.59 (d, *J* = 11.7 Hz, 1H), 4.43 (d, *J* = 11.7 Hz, 1H), 4.40 (s, 1H), 4.20-4.17 (m, 1H), 4.05 (q, *J* = 6.4 Hz, 1H), 3.78 (s, 4H), 2.83-2.79 (m, 4H), 2.73-2.65 (m, 2H), 2.64-2.60 (m, 2H), 2.36-2.28 (m, 2H), 2.22-2.17 (m, 1H), 2.15-2.10 (m, 1H), 2.08-2.05 (m, 1H), 1.85-1.78 (m, 1H), 1.71 (dd, *J* = 14.9, 6.7 Hz, 1H), 1.70-1.64 (m, 1H), 1.58 (s, 3H), 1.56-1.49 (m, 1H), 1.41-1.33 (m, 4H), 1.30-1.27 (m, 2H), 1.14 (d, *J* = 7.0 Hz, 3H), 0.89 (s, 9H), 0.87 (t, *J* = 8.7 Hz, 3H), 0.18 (s, 9H), 0.02 (d, *J* = 6.4 Hz, 6H).



3-13a

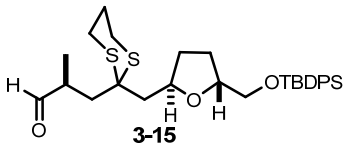
A flask was charged with alcohol **3-6** (4.2 g, 10 mmol, 1.0 eq), diluted with DMF (100 mL) and imidazole (2.04 g, 30 mmol, 3.0 eq) was added in one portion. The reaction was allowed to stir for 2 min before TBDPSCl (4.12 g, 15 mmol, 1.5 eq) was added followed by a catalytic amount of DMAP. The flask was equipped with a reflux condenser, heated to 50 °C and stirred overnight (ca. 16 h). The flask was cooled to rt before the contents were poured into a half-saturated solution of NH_4Cl (100 mL), and diluted with EtOAc (100 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure to afford **3-13a** as a yellow oil (6.2 g, 9.5 mmol, 95% yield) which was used without further purification. R_f 0.61 (50% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71-7.66 (m, 4H), 7.42-7.34 (m, 6H), 4.27 (dd, *J* = 8.6, 4.7 Hz,

1H), 4.14-4.08 (m, 1H), 3.62 (dq, *J* = 5.1, 4.7 Hz, 2H), 3.50 (dd, *J* = 9.6, 5.7 Hz, 1H), 3.38 (dd, *J* = 7.0, 6.6 Hz, 1H), 2.82-2.78 (m, 4H), 2.29-2.24 (m, 1H), 2.20-2.08 (m, 3H), 2.01-1.87 (m, 4H), 1.83-1.76 (m, 1H), 1.71 (dd, *J* = 14.9, 5.5, 1H), 1.62-1.52 (m, 1H), 1.04 (s, 9H), 1.00 (d, *J* = 7.0, 3H), 0.08 (s, 9H), 0.02 (s, 6H).



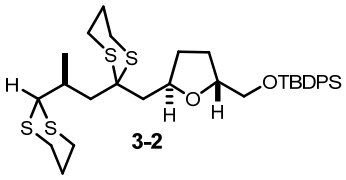
3-14

To a flask charged with TBS ether **3-13a** (659 mg, 1.0 mmol, 1 eq) was added wet MeOH (10 mL) and THF (3 mL). The mixture was stirred for 10 min to allow complete dissolution of the alcohol into the solution, before 10-CSA was added (10 mg, catalytic). After exactly 10 min, the contents were poured into a half-saturated solution of sodium bicarbonate (50 mL), and diluted with EtOAc (50 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure to afford **3-14** as a yellow oil (424 mg, 0.78 mmol, 78% yield) which was used without further purification. R_f 0.69 (20% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.67 (m, 4H), 7.43-7.35 (m, 6H), 4.3404.27 (m, 1H), 4.16-4.10 (m, 1H), 3.64 (d, *J* = 4.7 Hz, 2H), 3.50 (d, *J* = 5.9 Hz, 1H), 2.87-2.78 (m, 4H), 2.28-2.14 (m, 4H), 2.09-1.86 (m, 5H), 1.85-1.77 (m, 2H), 1.63-1.53 (m, 1H), 1.05 (s, 9H), 1.03 (d, *J* = 6.6 Hz, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 135.6, 133.6, 129.5, 127.6, 78.9, 76.2, 68.6, 66.5, 52.7, 45.3, 42.7, 41.7, 33.9, 32.6, 28.0, 26.8, 26.3, 26.2, 25.0, 19.4, 19.2.



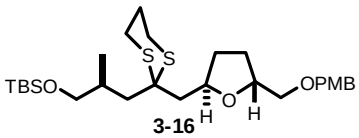
3-15

Alcohol **3-14** was oxidized using an analogous procedure to that of **3-12** on a 1 mmol scale, resulting in a 98% yield of **3-15** which was used without purification. R_f 0.46 (20% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (d, *J* = 2.4 Hz, 1H), 7.70-7.66 (m, 4H), 7.43-7.35 (m, 6H), 4.33 (ddt, *J* = 12.4, 5.6, 3.7 Hz, 1H), 4.11 (tt, *J* = 7.1, 4.6 Hz, 1H), 3.65-3.58 (m, 2H), 2.98-2.87 (m, 2H), 2.82-2.69 (m, 3H), 2.61-2.56 (m, 1H), 2.14-2.05 (m, 3H), 2.03-1.94 (m, 2H), 1.88-1.81 (m, 1H), 1.80-1.74 (m, 1H), 1.59-1.49 (m, 1H), 1.04 (d, *J* = 7.0 Hz, 3H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.2, 135.6, 133.6, 129.5, 127.6, 79.4, 75.0, 66.6, 51.8, 45.4, 43.4, 41.8, 40.2, 33.8, 27.8, 26.8, 26.3, 26.0, 24.8, 19.2, 16.0.



3-2

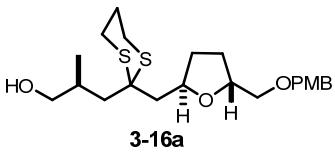
To a flask charged with aldehyde **3-2** (143 mg, 0.264 mmol, 1 eq) and diluted with wet MeCN (3 mL) was added 1,3-propanedithiol (0.04 mL, 0.395 mmol, 1.5 eq) in one portion, followed by $Yb(OTf)_3$ (10 mg, catalytic). The reaction was stirred at rt for 48 h before the contents were poured into a half-saturated solution of sodium bicarbonate (30 mL), and diluted with EtOAc (30 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure and the crude oil was purified by column chromatography (10% EtOAc/Hex) to afford **3-2** as a yellow oil (106 mg, 0.167 mmol, 63.4% yield) and recovered aldehyde **3-15** (15.2 mg, 0.0028 mmol, 10.6% yield). R_f 0.43 (20% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.66 (m, 4H), 7.42-7.34 (m, 6H), 4.48 (d, J = 3.1 Hz, 1H), 4.32-4.26 (m, 1H), 4.11 (tt, J = 7.1, 4.8 Hz, 1H), 3.66-3.58 (m, 2H), 2.96-2.76 (m, 8H), 2.53 (dd, J = 15.2, 5.5 Hz, 1H), 2.35-2.28 (m, 1H), 2.26 (dd, J = 15.0, 6.4 Hz, 1H) 2.20-2.05 (m, 3H), 2.00-1.90 (m, 3H), 1.87-1.75 (m, 3H), 1.62-1.54 (m, 1H), 1.16 (d, J = 7.0 Hz, 3H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 133.7, 129.5, 127.6, 78.9, 75.9, 66.6, 56.7, 52.7, 45.3, 42.7, 35.6, 33.9, 31.4, 30.,8 28.1, 26.8, 26.5, 26.3, 25.0, 19.2, 19.0.



3-16

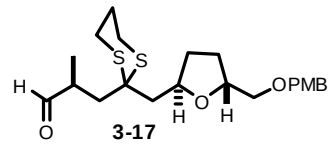
To a suspension of NaH (45 mg, 3.72 mmol, 2.0 eq) in THF (40 mL) and DMF (10 mL) at 0 °C was added freshly prepared PMBBr (373 mg, 1.86 mmol, 1.0 eq), followed by alcohol **3-6** (781 mg, 1.86 mmol, 1.0 eq). The ice-bath was removed and after ca. 16 h the reaction was poured into a half saturated solution NH_4Cl (50 mL) in water ice (50 mL) and stirred for 5 min, after which the aqueous layer was extracted with EtOAc (50 mL x 3). The combined organics were washed with brine, dried over $MgSO_4$, and filtered through a thin pad of packed celite. Solvent was removed under reduced pressure and the crude oil was purified by flash chromatography (10% EtOAc/Hex) to yield the PMB ether (**3-16**) as a colorless oil (853 mg, 1.58 mmol, 85%). R_f 0.51 (20% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 4.50 (q, J = 7.8 Hz, 2H), 4.23 (dq, J = 8.1, 5.3 Hz, 1H), 4.15 (quin, J = 6.1 Hz, 1H), 3.79 (s, 4H),

3.50-3.44 (m, 2H), 3.43-3.36 (m, 2H), 2.82-2.77 (m, 4H), 2.29 (dd, *J* = 15.0, 5.6 Hz, 1H), 2.19-2.06 (m, 3H), 2.03-1.88 (m, 4H), 1.70-1.51 (m, 3H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 130.6, 129.2, 113.7, 77.4, 76.1, 72.8, 72.7, 68.7, 55.2, 52.9, 45.3, 42.0, 33.8, 32.6, 29.0, 26.3, 26.0, 25.0, 19.4, 18.3, -5.3.



3-16a

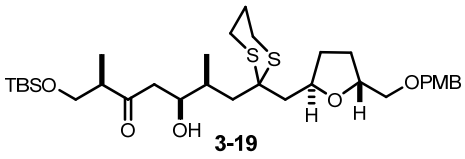
To a solution of PMB ether (**3-16**) (548 mg, 1.0 mmol, 1 eq) in MeOH (20 mL) was added 10-CSA (10 mg, catalytic). The reaction was stirred at rt until completion by TLC analysis (ca. 1 h). The reaction was poured into half saturated solution of sodium bicarbonate (50 mL) and diluted with EtOAc (50 mL), the aqueous layer was extracted with EtOAc (4 x 30 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure to afford **3-16a** as a yellow oil, which was used without further purification (408 mg, 0.96 mmol, 96% yield). R_f 0.25 (40% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.2 Hz, 2H), 6.84 (d, *J* = 8.2 Hz, 2H), 4.49 (q, *J* = 12.3 Hz, 2H), 4.26-4.21 (m, 1H), 4.17-4.13 (m, 1H), 3.77 (s, 3H), 3.48 (d, *J* = 4.7 Hz, 2H), 3.34-3.41 (m, 1H), 3.40-3.36 (m, 1H), 2.85-2.75 (m, 4H), 2.25-2.22 (m, 1H), 2.18-2.14 (m, 3H), 2.03-1.90 (m, 6H), 1.75 (dd, *J* = 15.2, 5.3 Hz, 1H), 1.65-1.54 (m, 2H), 1.03 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 130.5, 129.2, 113.6, 77.4, 76.0, 72.9, 72.6, 68.5, 55.2, 52.6, 45.2, 42.8, 33.7, 32.6, 28.7, 26.3, 26.2, 24.9, 19.4.



3-17

A 250 mL round bottom flask was charged with alcohol **3-16a** (409 mg, 0.96 mmol, 1 eq), diluted with CH_2Cl_2 (15 mL) and cooled to 0 °C. DMSO (374 mg, 4.80 mmol, 5 eq) was added, followed by Hunig's base (868 mg, 6.73 mmol, 7 eq). The reaction mixture was allowed to stir for 10 min before SO_3•Pyr (449 mg, 2.88 mmol, 3 eq) was added portion wise over 5 min. The reaction was monitored by TLC until completion (ca. 1h) before being slowly poured into a half-saturated solution of sodium bicarbonate (50 mL), and diluted with CH_2Cl_2 (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed

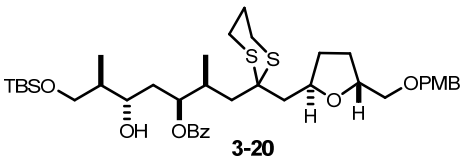
under reduced pressure, and the crude residue was dissolved in EtOAc (100 mL) and water (100 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, to afford **3-17** as a yellow oil (406 mg, 0.96 mmol, 99% yield) which was used without further purification. R_f 0.59 (40% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.76 (d, *J* = 2.3 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 4.47 (q, *J* = 8.2 Hz, 2H), 4.29-4.25 (m, 1H), 4.14 (dt, *J* = 12.3, 6.1 Hz, 1H), 3.78 (s, 3H), 3.34 (ABd, *J* = 5.9, 4.1 Hz, 1H), 3.39 (ABd, *J* = 5.9, 4.1 Hz, 1H), 2.95-2.87 (m, 2H), 2.80-2.68 (m, 3H), 2.57 (ddd, *J* = 14.0, 6.4, 2.9 Hz, 1H), 2.13-2.06 (m, 3H), 2.04-1.95 (m, 4H), 1.89-1.82 (m, 1H), 1.64-1.58 (m, 1H), 1.56-1.49 (m, 1H), 1.07 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.1, 159.1, 130.4, 129.2, 113.7, 77.8, 74.8, 72.9, 72.7, 55.2, 51.7, 45.3, 43.3, 40.3, 33.6, 28.5, 26.3, 26.0, 24.8, 16.0.



3-19

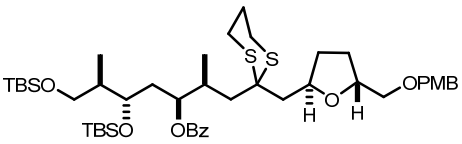
To a solution of ketone **3-18** (540 mg, 2.5 mmol, 2.5 eq) in diethyl ether (15 mL) cooled to -78 °C was added (+)-(*i*Pc)$_2$BCl (1.6 M, 1.5 mL, 2.4 mmol, 2.4 eq) drop wise, followed by triethylamine (0.55 mL, 4.0 mmol, 4.0 eq) drop wise. The reaction was stirred for 1 h at -78 °C before aldehyde **3-17** (424 mg, 1.0 mmol, 1.0 eq) was added drop wise over 10 min. The reaction was stirred an additional 30 min before methanol (10 mL) was added and the cooling back was removed and the reaction warmed to rt, at which point pH 7 buffer (20 mL) was added and the mixture was stirred for an additional 30 min. The mixture was diluted with EtOAc (20 mL) and the aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure to afford the crude oil which was purified by column chromatography (20-40% EtOAc/Hex) to afford **3-19** as a yellow oil (570 mg, 0.89 mmol, 89% yield). R_f 0.32 (30% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.2 Hz, 2H), 6.84 (d, *J* = 8.2 Hz, 2H), 4.49 (dd, *J* = 15.8, 10.1 Hz, 2H), 4.23 (dd, *J* = 8.5, 5.6 Hz, 1H), 4.14 (t, *J* = 5.9 Hz, 1H), 3.77 (s, 3H), 3.69 (dd, *J* = 9.7, 7.9 Hz, 1H), 3.61 (dd, *J* = 6.0, 5.3 Hz, 1H), 3.43 (abd, *J* = 9.9, 5.3 Hz, 1H), 3.37 (abd, *J* = 9.9, 5.3 Hz, 1H), 3.03 (d, *J* = 2.3 Hz, 1H), 2.82-2.74 (m, 5H), 2.63-2.56 (m, 2H), 2.37 (dd, *J* = 14.9,

3.8 Hz, 1H), 2.27 (dd, *J* = 14.9, 5.6 Hz, 1H), 2.18-2.13 (m, 1H), 2.08 (dd, *J* = 14.9, 5.0 Hz, 1H), 2.00-1.95 (m, 1H), 1.95-1.87 (m, 3H), 1.70 (dd, *J* = 15.2, 5.3 Hz, 1H), 1.65-1.50 (m, 3H), 0.99 (dd, *J* = 7.0, 5.3 Hz, 6H), 0.84 (s, 9H), 0.01 (d, *J* = 7.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.9, 158.8, 130.3, 129.0, 113.4, 77.2, 75.8, 72.7, 72.4, 70.6, 65.4, 55.0, 52.8, 48.7, 46.2, 45.1, 41.9, 34.2, 33.6, 34.2, 33.6, 28.6, 26.0, 25.6, 24.8, 18.0, 16.2, 12.5, -5.8



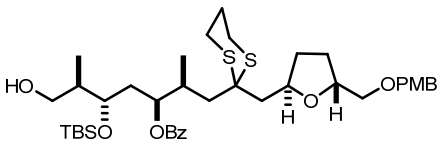
3-20

To a solution of alcohol **3-19** (568 mg, 0.89 mmol, 1.0 eq) and benzaldehyde (470 mg, 4.43 mmol, 5.0 eq) in THF (10 mL) cooled to -20 °C was added a freshly prepared solution of samarium iodide[11] (0.1 M, 2.66 mL, 0.27 mmol, 0.3 eq) drop wise over 20 min. The reaction was stirred for 30 min at -20 °C before being pourted into a half saturated solution of sodium bicarbonate (50 mL) and diluted with EtOAc (30 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure to afford the crude oil which was purified by column chromatography (20% EtOAc/Hex) to afford **3-20** as a yellow oil (585 mg, 0.80 mmol, 90.2% yield). R_f 0.44 (30% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.0 Hz, 2H), 7.54 (t, *J* = 7.0 Hz, 1H), 7.42 (t, *J* = 7.0 Hz, 2H), 7.23 (d, *J* = 8.2 Hz, 2H), 6.84 (d, *J* = 8.2 Hz, 2H), 5.44 (d, *J* = 10.5 Hz, 1H), 4.49 (dd, *J* = 15.8, 10.1 Hz, 2H), 4.20 (dd, *J* = 8.2, 5.3 Hz, 1H), 4.10 (quin, *J* = 6.3 Hz, 1H), 3.78 (s, 3H), 3.70 (dd, *J* = 9.9, 4.7 Hz, 1H), 3.58-3.56 (m, 2H), 3.50-3.46 (m, 1H), 3.38 (ABd, *J* = 9.9, 5.3 Hz, 1H), 3.31 (ABd, *J* = 9.9, 5.3 Hz, 1H), 2.82-2.71 (m, 4H), 2.28-2.19 (m, 2H), 2.11-2.06 (m, 2H), 1.95-1.90 (m, 1H), 1.90-1.85 (m, 3H), 1.79 (dd, *J* = 14.6, 5.3 Hz, 1H), 1.73-1.64 (m, 2H), 1.60-1.47 (m, 2H), 1.20 (d, *J* = 6.4 Hz, 3H), 0.88 (d, *J* = 7.0 Hz, 3H), 0.80 (s, 9H), -0.01 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 159.0, 132.9, 130.6, 130.3, 129.8, 129.2, 128.3, 113.7, 77.4, 76.4, 75.9, 72.9, 72.6, 70.4, 66.3, 55.2, 52.8, 45.2, 42.6, 40.4, 36.9, 34.1, 33.7, 29.7, 28.9, 26.4, 25.8, 24.9, 19.1, 17.0, 13.5, -5.6.



3-20a

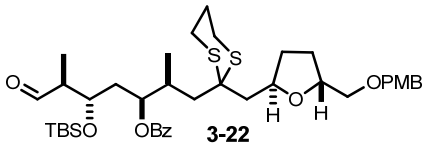
To a solution of alcohol (**3-20**) (10.7 g, 42.6 mmol, 1 eq) in DMF (300 mL) was added imidazole (5.8 g, 85.2 mmol, 2 eq), followed by TBSCl (6.6 g, 42.6 mmol, 1 eq) and DMAP (50 mg, catalytic). The reaction was stirred overnight (ca. 16 h) before being poured into a half saturated solution of NH_4Cl, and the aqeous layer was extracted with CH_2Cl_2 (5 x 200 mL) and the combined organics were washed with brine and dried over $MgSO_4$. Solvent was removed under reduced pressure to give the TBS alcohol, which was purified by flash chromatography (5% EtOAc/Hex) to give the pure alcohol (**3-20a**) as a yellow oil (15.3 g, 42.2 mmol, 99% yield). R_f 0.47 (20% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.0 Hz, 2H), 7.51 (t, *J* = 7.0 Hz, 1H), 7.39 (t, *J* = 7.0 Hz, 2H), 7.24 (d, *J* = 8.2 Hz, 2H), 6.85 (d, *J* = 8.2 Hz, 2H), 5.24 (d, *J* = 10.2 Hz, 1H), 4.49 (dd, *J* = 15.8, 10.1 Hz, 2H), 4.18 (dd, *J* = 8.0, 5.3 Hz, 1H), 4.07 (quin, *J* = 6.3 Hz, 1H), 3.90 (dd, *J* = 6.6, 3.2 Hz, 1H), 3.78 (s, 3H), 3.49-3.42 (m, 2H), 3.38 (ABd, *J* = 9.9, 5.3 Hz, 1H), 3.30 (ABd, *J* = 9.9, 5.3 Hz, 1H), 2.82-2.58 (m, 5H), 2.35 (d, *J* = 14.8 Hz, 1H), 2.30-2.20 (m, 2H), 2.06-1.72 (m, 8H), 1.62-1.41 (m, 4H), 1.15 (d, *J* = 6.6 Hz, 3H), 0.88 (s, 9H), 0.80 (s, 9H), 0.02 (d, *J* = 5.1 Hz, 6H), -0.01 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 159.0, 132.6, 130.9, 130.6, 129.6, 129.2, 128.2, 113.7, 75.8, 72.9, 72.7, 69.6, 65.2, 55.2, 55.7, 45.4, 42.0, 41.8, 41.5, 33.9, 33.8, 33.0, 29.7, 29.0, 26.3, 26.0, 25.8, 25.7, 24.9, 18.1, 18.1, 17.8, 10.7, -2.9, -4.3, -4.6, -5.4, -5.5.



3-21

To a solution of TBS ether (**3-20a**) (134 mg, 0.162 mmol, 1 eq) in wet EtOH (5 mL) was added PPTS (10 mg, catalytic). The reaction was stirred overnight (ca. 16 h) at rt before being poured into a half saturated solution of sodium bicarbonate (50 mL) and diluted with EtOAc (50 mL), the aqueous layer was extracted with EtOAc (4 x 20 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure to afford **3-21** as a yellow oil, which was used without further purification (118 mg, 0.159 mmol, 98% yield). R_f 0.26 (30% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.01 (d, *J* =

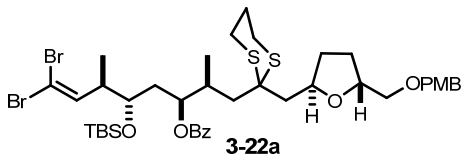
7.6 Hz, 2H), 7.53 (t, *J* = 7.3 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.23 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.19 (bs, 1H), 4.44 (q, *J* = 11.7 Hz, 2H), 4.19-4.15 (m, 1H), 4.09 (q, *J* = 7.0 Hz, 1H), 3.86-3.85 (m, 2H), 3.78 (s, 3H), 3.54-3.52 (m, 1H), 3.37 (ABd, *J* = 9.9, 5.3 Hz, 1H), 3.31 (ABd, *J* = 9.9, 5.3 Hz, 1H), 2.79-2.68 (m, 4H), 2.36 (bs, 1H), 2.29 (d, *J* = 14.6 Hz, 1H), 2.25 (bs, 1H), 2.18-2.17 (m, 1H), 2.07-1.98 (m, 3H), 1.94-1.83 (m, 4H), 1.82-1.73 (m, 2H), 1.57-1.50 (m, 1H), 1.50-1.44 (m, 1H), 1.18 (d, *J* = 7.0 Hz, 3H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.88 (s, 9H), 0.07 (d, *J* = 10.5 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 159.1, 132.8, 130.6, 129.5, 129.2, 128.3, 113.7, 77.4, 76.6, 75.8, 73.6, 72.9, 72.6, 64.6, 55.2, 52.8, 45.5, 42.0, 39.1, 35.8, 33.7, 33.1, 29.7, 28.8, 26.3, 25.9, 24.9, 17.9, 17.0, 13.9, -4.4, -4.6.



3-22

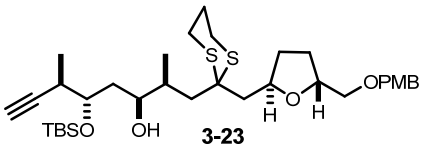
A 25 mL round bottom flask was charged with alcohol **3-21** (484 g, 0.661 mmol, 1 eq), diluted with CH_2Cl_2 (10 mL) and cooled to 0 °C. DMSO (257 mg, 3.30 mmol, 5 eq) was added, followed by Hunig's base (600 mg, 4.63 mmol, 7 eq). The reaction mixture was allowed to stir for 10 min before SO_3•Pyr (309 mg, 1.98 mmol, 3 eq) was added. The reaction was monitored by TLC until completion (ca. 1h) before being slowly poured into a half-saturated solution of sodium bicarbonate (100 mL), and diluted with CH_2Cl_2 (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, and the crude residue was dissolved in EtOAc (100 mL) and water (100 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, to afford **3-22** as a yellow oil which was used without further purification. R_f 0.38 (30% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.76 (s, 1H), 8.05 (d, *J* = 7.0 Hz, 1H), 7.55 (t, *J* = 6.8 Hz, 1H), 7.44 (t, *J* = 6.8 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.29-5.25 (m, 1H), 4.47 (q, *J* = 7.0 Hz, 2H), 4.22-4.16 (m, 1H), 4.14-4.08 (m, 2H), 3.80 (s, 3H), 3.40 (ABd, *J* = 9.9, 5.3 Hz, 1H), 3.33 (ABd, *J* = 9.9, 5.3 Hz, 1H), 2.83-2.64 (m, 4H), 2.35-2.27 (m, 2H), 2.20 (dd, *J* = 15.0, 5.6 Hz, 1H), 2.09-2.01 (m, 2H), 1.95-1.82 (m, 4H), 1.76-1.71 (m, 1H), 1.58-1.44 (m, 2H), 1.17 (d, *J* = 7.0 Hz, 3H), 1.13 (d, *J* = 7.0 Hz, 3H), 0.88 (s, 9H), 0.06 (d, *J* = 18.7 Hz, 6H). ^{13}C NMR

(100 MHz, $CDCl_3$) δ 205.8, 166.1, 159.0, 132.8, 130.5, 129.6, 129.2, 128.3, 113.6, 77.4, 76.2, 75.8, 82.9, 72.6, 69.8, 63.0, 55.2, 52.7, 52.0, 45.4, 41.8, 41.7, 36.1, 33.7, 33.4, 28.9, 26.3, 26.2, 25.8, 24.8, 19.4, 18.0, 17.4, 9.3, -4.5.



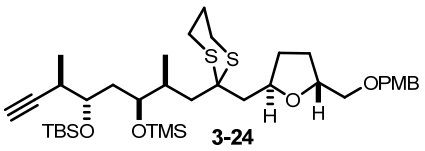
3-22a

A 25 mL flask was charged with triphenylphosphine (866 mg, 3.30 mmol, 5.0 eq) and CH_2Cl_2 (10 mL) and was cooled to 0 °C. The septum was temporarily removed to add carbon tetrabromide (540 mg, 1.65 mmol, 2.5 eq) in one portion. The ice bath was removed and the reaction was stirred at room temperature for 30 min, after which it was re-cooled to 0 °C. The above crude aldehyde **3-22** from above (~477 mg, ~0.661 mmol, ~1 eq) was added in one portion in minimal CH_2Cl_2. The reaction was monitored by TLC until completion (ca. 10 min) before being slowly poured into a half-saturated solution of sodium bicarbonate (50 mL), and diluted with CH_2Cl_2 (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, and the crude oil was purified by column chromatography (20% EtOAc/Hex) to afford **3-22a** as a yellow oil (520 mg, 0.58 mmol, 88% yield over 2 steps). R_f 0.54 (30% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.0 Hz, 2H), 7.54 (t, *J* = 7.0 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.24 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.37 (d, *J* = 9.4 Hz, 1H), 5.19 (dt, *J* = 9.1, 3.4 Hz, 1H), 4.46 (q, *J* = 11.7 Hz, 2H), 4.19-4.15 (m, 1H), 4.09 (dt, *J* = 12.6, 6.0 Hz, 1H), 3.79 (s, 3H), 3.73-3.70 (m, 1H), 3.40 (dd, *J* = 9.9, 5.9 Hz, 1H), 3.32 (dd, *J* = 9.9, 5.9 Hz, 1H), 2.84-2.59 (m, 5H), 2.33 (dd, *J* = 14.6, 2.3 Hz, 1H), 2.25 (dd, *J* = 9.8, 6.6, 2.9 Hz, 1H), 2.21 (dd, *J* = 14.9, 5.6 Hz, 1H), 2.07-2.03 (m, 1H), 2.00 (dd, *J* = 14.9, 5.0 Hz, 1H), 1.94-1.84 (m, 3H), 1.78-1.66 (m, 3H), 1.55-1.43 (m, 2H), 1.16 (d, *J* = 7.0 Hz, 3H), 1.00 (d, *J* = 6.4 Hz, 3H), 0.89 (s, 9H), 0.05 (d, *J* = 12.9 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 159.0, 140.1, 132.7, 130.6, 129.6, 129.2, 128.3, 113.6, 89.0, 77.3, 76.6, 75.8, 72.9, 72.6, 71.2, 55.2, 52.7, 45.4, 44.1, 41.7, 36.0, 33.7, 33.5, 28.9, 26.4, 26.3, 25.9, 24.9, 18.0, 17.4, 14.3, -4.4.



3-23

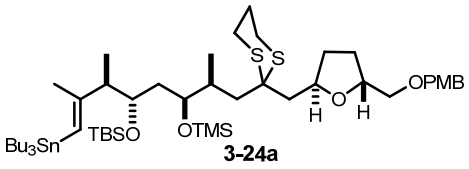
A 50 mL flask was charged with dibromde **3-22a** (520 mg, 0.58 mmol, 1 eq), diluted with THF (10 mL) and cooled to -78 °C. *n*BuLi (2.10 M, 1.40 mL, 2.88 mmol, 5.0 eq) was added slowly drop wise over 15 min. The reaction was stirred at -78 °C for 30 min at which point it was judged complete by TLC. The reaction was slowly poured into a half-saturated solution of NH_4Cl (50 mL), the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, and the crude product was purified by column chromatography (20% EtOAc/Hex) to afford alkyne **3-23** as a yellow oil (360 mg, 0.57 mmol, 99% yield). R_f 0.14 (20% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 4.50 (q, *J* = 7.0 Hz, 2H), 4.27-4.21 (m, 1H), 4.17-4.12 (quin, *J* = 6.1 Hz, 1H), 3.98 (ddd, *J* = 7.7, 5.0, 2.9 Hz, 1H), 3.88-3.86 (m, 1H), 3.78 (s, 3H), 3.44 (ABd, *J* = 6.6, 5.9 Hz, 1H), 3.37 (ABd, *J* = 6.6, 5.9 Hz, 1H), 2.85-2.78 (m, 4H), 2.69 (ddd, *J* = 7.1, 4.8, 2.5 Hz, 1H), 2.35 (dd, *J* = 15.0, 4.1 Hz, 1H), 2.27 (dd, *J* = 15.0, 5.7 Hz, 1H), 2.21 (d, *J* = 4.3 Hz, 1H), 2.19-2.08 (m, 2H), 2.05 (d, *J* = 2.3 Hz, 1H), 2.01-1.89 (m, 4H), 1.73-1.48 (m, 5H), 1.14 (d, *J* = 7.0 Hz, 3H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.88 (s, 9H), 0.09 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 130.6, 129.2, 113.7, 86.7, 77.4, 76.0, 72.9, 72.6, 72.0, 71.6, 70.0, 55.2, 52.9, 45.4, 42.2, 35.9, 35.5, 33.8, 32.1, 28.9, 26.3, 26.2, 25.8, 24.9, 18.0, 16.6, 15.1, -4.5, -4.6.



3-24

To a solution of alcohol **3-23** (360 mg, 0.57 mmol, 1 eq) in CH_2Cl_2 (10 mL) and Et_3N (291 mg, 2.99 mmol, 5.0 eq) was added TMSCl (0.18 mL, 1.44 mmol, 2.5 eq) drop wise followed by 4-DMAP (2 mg, catalytic). The reaction was monitored by TLC until completion (ca. 30 min) before being slowly poured into a half-saturated solution of sodium bicarbonate (50 mL), and diluted with CH_2Cl_2 (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, and the crude oil was purified by column chromatography (20% EtOAc/Hex) to afford **3-24** as a yellow oil (375 mg, 0.53 mmol, 93%). R_f 0.57 (30% EtOAc/Hex); ^{1}H NMR (600 MHz,

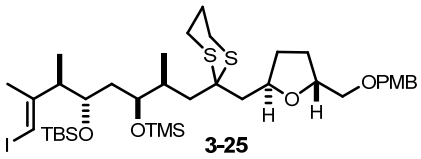
$CDCl_3$) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 4.50 (q, *J* = 6.2 Hz, 2H), 4.25-4.19 (m, 1H), 4.15 (quin, *J* = 6.5 Hz, 1H), 3.78 (s, 3H), 3.72 (td, *J* = 6.5, 2.3 Hz, 1H), 3.67 (td, *J* = 6.1, 2.7 Hz, 1H), 3.45 (ABd, *J* = 6.6, 5.9 Hz, 1H), 3.37 (ABd, *J* = 6.6, 5.9 Hz, 1H), 2.88-2.69 (m, 5H), 2.31 (dd, *J* = 14.8, 5.1 Hz, 1H), 2.22-2.14 (m, 2H), 2.09 (dd, *J* = 15.0, 5.7 Hz, 1H), 2.03 (d, *J* = 2.7 Hz, 1H), 2.04-1.98 (m, 1H), 1.96-1.80 (m, 4H), 1.69-1.54 (m, 4H), 1.15 (d, *J* = 7.0 Hz, 3H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.88 (s, 9H), 0.13 (s, 9H), 0.07 (d, *J* = 11.3 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 130.6, 129.2, 113.7, 85.8, 76.3, 74.8, 72.9, 72.7, 72.1, 69.8, 55.2, 53.4, 45.8, 42.9, 39.2, 34.6, 33.9, 32.0, 29.1, 26.3, 26.3, 25.8, 25.0, 18.1, 16.4, 16.0, 0.9, -4.0, -4.3.



3-24a

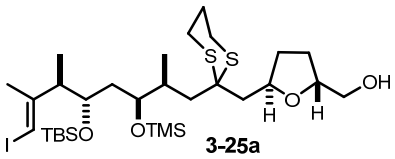
To a solution of hexabutylditin (700 mg, 1.25 mmol, 4 eq) in THF (10 mL) cooled to -20 °C was added *n*BuLi (2.10 M, 0.60 mL, 1.26 mmol, 4 eq) drop wise. The reaction was allowed to stir at -20 °C for 10 min followed by the drop wise addition of freshly prepared MeMgI (1.0 M in ether, 1.25 mL, 1.25 mmol, 4 eq). The reaction was stirred another 10 min before CuCN (28 mg, 0.31 mmol, 4 eq) was added in one portion. The reaction was stirred another 5 min at -20 °C before alkyne **3-24** (221 mg, 0.31 mmol, 1 eq) was added in one portion. After 20 min of stirring at -20 °C, MeI (0.39 mL, 6.20 mmol, 20 eq) was added and the cooling bath was removed to allow the reaction to warm to rt, where it was allowed to stir for an additional 10 min before being poured into a half saturated solution of NH_4Cl (50 mL) and diluted with EtOAc (50 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL) and the combined organics were washed with brine, dried with $MgSO_4$ and filtered through a thin pad of celite. Solvent was removed under reduced pressure to afford a yellow oil which was purified by column chromatography (10% EtOAc/Hex) to give the product stannane (**3-24a**) (118 mg, 0.12 mmol, 37% yield, 94% BORSM) as a single regioisomer and recovered starting material (**3-24**) (133 mg, 0.19 mmol, 60% yield). R_f 0.47 (20% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 5.55 (s, 1H), 4.49 (q, *J* = 13.5 Hz, 2H), 4.24-4.20 (m, 1H), 4.14 (dt, *J* = 12.4, 6.4 Hz, 1H), 3.78 (s, 3H), 3.71 (bs, 1H), 3.45 (ABd, *J* = 9.9, 5.3 Hz, 1H), 3.37 (ABd, *J* = 9.9, 5.3 Hz, 1H), 2.82-2.77 (m, 4H), 2.47 (dd, *J* = 7.0, 2.9 Hz, 1H),

2.31 (dd, *J* = 14.9, 5.0 Hz, 1H), 2.22-2.15 (m, 2H), 2.06-1.98 (m, 2H), 1.92-1.84 (m, 3H), 1.78 (s, 3H), 1.67-1.55 (m, 3H), 1.50-1.41 (m, 8H), 1.29 (q, *J* = 7.6 Hz, 6H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.96 (d, *J* = 7.0 Hz, 3H), 0.88 (s, 9H), 0.87 (t, *J* = 7.6 Hz, 9H), 0.09 (s, 9H), 0.08 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 156.2, 130.6, 129.2, 123.4, 113.7, 76.2, 75.0, 72.9, 72.7, 55.2, 53.3, 49.4, 45.8, 42.7, 38.1, 34.8, 33.9, 29.2, 27.3, 26.3, 26.3, 25.9, 25.1, 24.4, 18.1, 16.6, 14.6, 13.7, 10.1, 1.0, -4.1, -4.1.



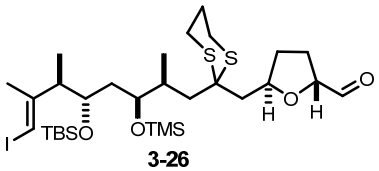
3-25

To a solution of stannane **3-24a** (118 mg, 0.117 mmol, 1 eq) in THF (5 mL) cooled to -78 °C was added a solution of I_2 (1.0 M in CH_2Cl_2) drop wise until the color persisted (ca. 0.15 mL). The reaction was allowed to stir at 0 °C for 10 min before being poured into a half saturated solution of sodium thiosulfate (20 mL) and diluted with EtOAc (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics were washed with brine, dried with $MgSO_4$ and filtered through a thin pad of celite. Solvent was removed under reduced pressure and the crude oil was purified by flash chromatography (10% EtOAc/Hex) to afford iodide **3-25** as a yellow oil (97.3 mg, 0.114 mmol, 98% yield) which was used without further purification. R_f 0.45 (20% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.04 (s, 1H), 4.49 (q, *J* = 11.7 Hz, 2H), 4.25-4.18 (m, 1H), 4.14 (t, *J* = 6.1 Hz, 1H), 3.78 (s, 3H), 3.69 (d, *J* = 7.6 Hz, 1H), 3.45 (ABd, *J* = 9.9, 5.3 Hz, 1H), 3.36 (ABd, *J* = 9.9, 5.3 Hz, 1H), 2.86-2.67 (m, 5H), 2.29 (dd, *J* = 14.9, 5.0 Hz, 1H), 2.21-2.18 (m, 2H), 2.09 (dd, *J* = 14.9, 5.6 Hz, 1H), 2.01-1.99 (m, 1H), 1.92-1.83 (m, 3H), 1.85 (s, 3H), 1.66-1.44 (m, 5H), 1.31-1.24 (m, 2H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.95 (d, *J* = 7.0 Hz, 3H), 0.87 (s, 9H), 0.10 (s, 9H), 0.07 (d, *J* = 5.3 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 149. 9, 130.6, 129.2, 113.7, 77.5, 76.3, 74.5, 72.9, 72.9, 72.7, 55.2, 53.5, 47.5, 45.8, 42.8, 39.0, 34.0, 33.9, 29.7, 29.2, 26.3, 26.3, 25.9, 25.0, 23.1, 19.4, 18.0, 16.5, 15.6, 13.7, 8.2, 0.9, -4.1, -4.4.



3-25a

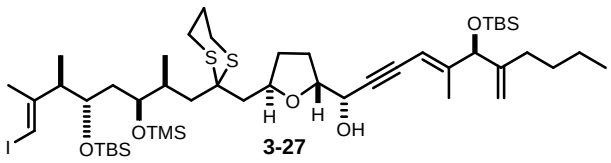
PMB alcohol (**3-25**) (97.3 mg, 0.114 mmol, 1 eq) was dissolved in CH_2Cl_2 (4 mL), water (1 mL) and saturated sodium bicarbonate (0.5 mL). DDQ (65 mg, 0.286 mmol, 2.5 eq) was added in one portion and the reaction was rigorouly stirred for 2 h at which point the reaction was judged to be complete by TLC analysis. The reaction mixture was poured into a rapidly stirring solution of half saturated sodium bicarbonate (50 mL) and half saturated sodium thiosulfate (20 mL), and the aqeous layer was extracted with CH_2Cl_2 (5 x 20 mL) and the combined organics were washed with brine and dried over $MgSO_4$. Solvent was removed under reduced pressure to give the cude alcohol, which was purified by flash chromatography (30% EtOAc/Hex) to give the pure alcohol **3-25a** as a yellow oil (77 mg, 0.105 mmol, 92% yield). R_f 0.17 (20% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.06 (s, 1H), 3.25-3.24 (m, 1H), 4.15-4.10 (m, 1H), 3.7 (bs, 2H), 3.61 (d, J = 9.9 Hz, 1H), 3.48 (dd, J = 10.8, 6.1 Hz, 1H), 2.88-2.80 (m, 4H), 2.68 (d, J = 4.1 Hz, 1H), 2.27-2.24 (m, 2H), 2.18-2.13 (m, 2H), 2.0- 1.85 (m, 5H), 1.87 (s, 3H), 1.70-1.50 (m, 5H), 1.07 (d, J = 6.4 Hz, 3H), 0.98 (d, J = 7.0 Hz, 3H), 0.90 (s, 9H), 0.13 (s, 9H), 0.08 (d, J = 5.9 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 78.7, 77.6, 76.1, 74.6, 72.8, 64.9, 53.6, 47.6, 45.7, 42.7, 38.7, 34.2, 34.0, 27.6, 26.4, 26.3, 25.9, 25.0, 23.2, 18.0, 16.7, 15.4, 0.9, -4.1, -4.4.



3-26

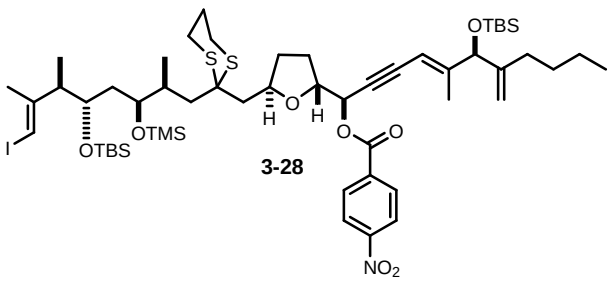
A 10 mL round bottom flask was charged with alcohol **3-25a** (57.8 mg, 0.079 mmol, 1 eq), diluted with CH_2Cl_2 (3 mL) and cooled to 0 °C. DMSO (31 mg, 0.396 mmol, 5 eq) was added, followed by Hunig's base (71 mg, 0.554 mmol, 7 eq). The reaction mixture was allowed to stir for 10 min before SO_3•Pyr (37 mg, 0.237 mmol, 3 eq) was added. The reaction was monitored by TLC until completion (ca. 2 h) before being slowly poured into a half-saturated solution of sodium bicarbonate (50 mL), and diluted with CH_2Cl_2 (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, and the crude residue was dissolved in EtOAc (100 mL) and water (100 mL). The aqueous layer was extracted with EtOAc (3 x

30 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, to afford **3-26** as a yellow oil (57 mg, 0.079 mmol, 99% yield) which was used without further purification. R_f 0.46 (30% EtOAc/Hex).



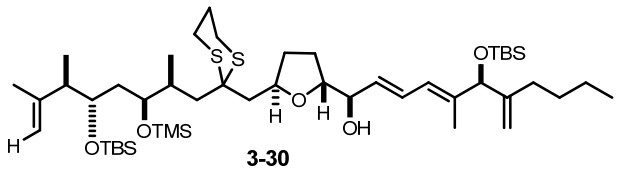
3-27

To a solution of alkyne **2-2** (110 mg, 0.38 mmol, 5 eq) in MTBE (3 mL) at 0 °C was added *n*BuLi (2.05 M, 0.19 mL, 0.38 mmol, 5 eq), and the reaction was stirred at 0 °C for 1 h before being cooled to -90 °C using a liquid nitrogen/hexanes bath. After stirring for 15 min at -90 °C, aldehyde **3-26** (110 mg, 0.076 mmol, 1 eq) dissolved in a minimal amount of MTBE was added over 15 min drop wise. After stirring at -90 °C for 2 h, the reaction was treated at -90 °C with 20 mL of saturated NH_4Cl, before being allowed to warm to rt and diluted with water (50 mL) and EtOAc (50 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, and the crude product was purified by column chromatography (10% EtOAc/Hex) to afford recovered alkyne (88 mg) and alkynlation adduct **3-27** as a 10:1 ratio of diastereomers as a yellow oil (66 mg, 0.065 mmol, 85% yield). R_f 0.47 (20% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.04 (s, 1H), 5.63 (s, 1H), 5.05 (s, 1H), 4.86 (s, 1H), 4.63 (s, 1H), 4.41 (s, 1H), 4.41-4.36 (m, 1H), 4.18-4.15 (m, 1H), 3.70-3.68 (m, 2H), 2.83-2.76 (m, 4H), 2.66 (dd, J = 7.0, 3.1 Hz, 1H), 2.39 (bs, 1H), 2.25-2.18 (m, 3H), 2.11-2.00 (m, 3H), 1.97-1.85 (m, 4H), 1.85 (s, 3H), 1.80-.170 (m, 2H), 1.70 (s, 3H), 1.66-1.47 (m, 6H), 1.40-1.24 (m, 8H), 1.05 (d, J = 6.6 Hz, 3H), 0.95 (s, 3H), 0.87 (s, 21 H), 0.11 (s, 9H), 0.06 (d, J = 3.6 Hz, 6H), 0.00 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 149.9, 149.1, 110.8, 104.8, 90.4, 83.7, 80.8, 80.0, 77.9, 77.6, 74.5, 72.9, 64.9, 53.6, 47.6, 45.8, 42.9, 41.8, 38.8, 34.2, 34.0,29.9, 29.8, 29.7, 26.5, 26.4, 26.3, 25.9, 25.8, 25.0, 23.2, 22.6, 19.4, 18.2, 18.0, 16.6, 15.5, 15.3, 14.0, 0.9, -4.0, -4.4, -5.0, -5.1.



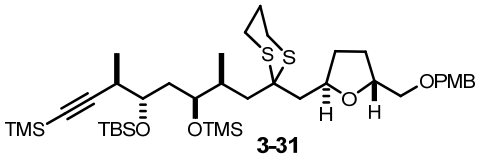
3-28

A 10 mL round bottom flask was charged with 4-nitro benzoic acid (19.3 mg, 0.116 mmol, 3 eq), PPh_3 (30.4 mg, 0.116 mmol, 3 eq), alcohol **3-27** (39.1 mg, 0.039 mmol, 1 eq), diluted with THF (3 mL) and cooled to 0 °C. DIAD (23.4 mg, 0.116 mmol, 3 eq) was added drop wise over 10 min, and the ice bath was removed. The reaction monitored by TLC and upon completion (ca. 2h) was slowly poured into a half-saturated solution of sodium bicarbonate (50 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, and the crude product was purified by flash chromatography (10% EtOAc/Hex) to afford **3-28** as a yellow oil (26.8 mg, 0.023 mmol, 59% yield). R_f 0.41 (10% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.26 (d, *J* = 5.3 Hz, 4H), 6.03 (s, 1H), 5.75 (d, *J* = 7.6 Hz, 1H), 5.65 (s, 1H), 5.05 (s, 1H), 4.87 (s, 1H), 4.42 (s, 1H), 4.37 (q, *J* = 7.2 Hz, 1H), 4.25 (dd, *J* = 8.8, 5.3 Hz, 1H), 3.69-3.65 (m, 2H), 2.77-2.71 (m, 4H), 2.65 (dd, *J* = 7.0, 2.9 Hz, 1H), 2.31-2.33 (m, 3H), 2.17-2.14 (m, 1H), 2.06 (dd, *J* = 14.6, 5.9 Hz, 1H), 2.01-1.97 (m, 1H), 1.93-1.85 (m, 3H), 1.85 (s, 3H), 1.80-1.71 (m, 2H), 1.71 (s, 3H), 1.70-1.62 (m, 2H), 1.55-1.51 (dd, *J* = 14.9, 5.6 Hz, 1H), 1.50-1.43 (m, 2H), 1.40-1.33 (m, 2H), 1.30-1.26 (aq, 7.6 Hz, 4H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.87 (m, 24H), 0.09 (s, 9H), 0.05 (s, 6H), 0.00 (d, *J* = 2.3 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 153.7, 150.5, 149.9, 149.0, 135.6, 131.0, 123.4, 111.0, 104.1, 87.0, 84.8, 80.0, 78.9, 77.5, 74.4, 72.9, 68.5, 53.0, 47.6, 45.2, 42.6, 41.8, 38.8, 34.0, 33.8, 29.9, 29.7, 29.7, 29.0, 26.4, 25.9, 25.8, 25.0, 23.1, 22.6, 18.2, 18.0, 16.4, 15.6, 14.0, 0.9, -4.1, -4.4, -5.0, -5.1.



3-30

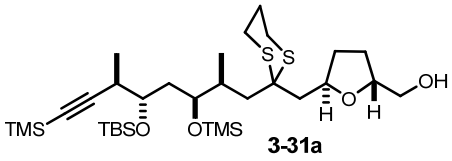
A 10 mL round bottom flask was charged with **3-28** (26.8 mg, 0.023 mmol, 1 eq), diluted with diethyl ether (3 mL) and cooled to 0 °C. $LiAlH_4$ (4 mg, 0.200 mmol, 4 eq) was added. The reaction was stirred for 30 min at 0 °C before being slowly poured into a half-saturated solution of NH_4Cl (20 mL), and a saturated solution of Rochelle's salt was added (10 mL), and the slurry was stirred vigorously for 30 min. The aqueous layer was extracted with EtOAc (3 x 30 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, and the crude product was purified by column chromatography (10% EtOAc/Hex) to afford alcohol **3-30** as a yellow oil (19.4 mg, 0.216 mmol, 94% yield). The NMR showed a mixture of the ene-yne and diene, integration of a peak indicative of the two protons on the 1,1-disubstituted alkene suggested 100% conversion of the iodoalkene. R_f 0.22 (10% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ Key peaks: 6.55 (dd, J = 15.2, 11.1 Hz, 1H), 6.07 (dd, J = 10.5 Hz, 1H), 5.57 (dd, J = 15.2, 7.0 Hz, 1H), 5.11 (s, 1H), 4.86 (s, 1H), 4.83 (s, 1H), 4.79 (s, 1H), 4.40 (s, 1H).



3-31

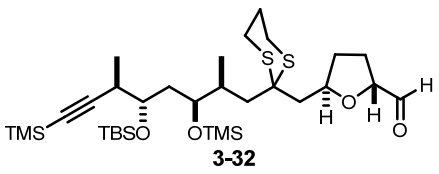
To a solution of alkyne **3-24** (133 mg, 0.187 mmol, 1 eq) in THF (5 mL) cooled to -78 °C was added *n*BuLi (2.0 M, 0.122 mL, 0.244 mmol, 1.3 eq) drop wise. After stirring for 30 min at -78 °C, TMSCl (50 mg, 0.47 mmol, 2.5 eq) was added in one portion and the reaction was stirred until completion as indicated by TLC (ca. 30 min). The solution was poured into a half saturated solution of NH_4Cl (40 mL), and diluted with EtOAc (40 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, and the crude product was purified by column chromatography (10% EtOAc/Hex) to afford alkyne **3-31** as a yellow oil (137 mg, 0.176 mmol, 94% yield). R_f 0.17 (10% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 (d, J = 7.6 Hz, 2H), 6.86 (d, J = 7.6 Hz, 2H), 4.50 (q, J = 14.0 Hz, 2H), 4.23-4.21 (m, 1H), 4.16-4.14 (m, 1H), 3.79 (s, 3H), 3.70-3.65 (m, 2H),

3.46 (dd, *J* = 9.4, 4.7 Hz, 1H), 3.36 (dd, *J* = 9.4, 4.7 Hz, 1H), 2.85-2.75 (m, 4H), 2.68 (d, *J* = 6.4 Hz, 1H), 2.31 (dd, *J* = 14.6, 4.7 Hz, 1H), 2.23 (d, *J* = 14.6 Hz, 1H), 2.19 (bs, 1H), 2.07 (dd, *J* = 14.9, 5.6 Hz, 1H), 2.04-1.99 (m, 1H), 1.95-1.81 (m, 5H), 1.68-1.54 (m, 5H), 1.12 (d, *J* = 6.4 Hz, 3H), 0.99 (d, *J* = 6.4 Hz, 3H), 0.88 (s, 9H), 0.14 (s, 9H), 0.13 (s, 9H), 0.07 (d, *J* = 19.9 Hz, 6H).^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 130.6, 129.2, 113.7, 108.9, 85.8, 77.3, 76.3, 74.8, 72.9, 72.7, 72.3, 55.2, 53.4, 45.8, 42.7, 39.0, 34.7, 33.9, 33.2, 29.2, 26.3, 26.3, 26.0, 25.8, 25.0, 18.1, 16.5, 15.9, 1.0, 0.9, 0.2, -4.0, -4.2.



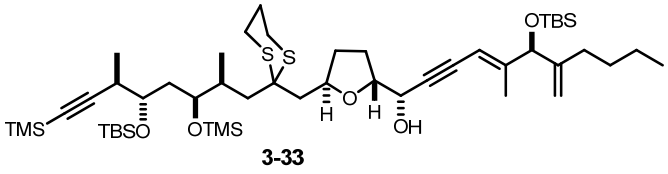
3-31a

PMB alcohol (**3-31**) (107 g, 0.137 mmol, 1 eq) was dissolved in CH_2Cl_2 (4 mL), water (0.5 mL) and saturated sodium bicarbonate (0.5 mL). DDQ (193 mg, 0.455 mmol, 2.5 eq) was added in one portion and the reaction was rigorouly stirred for 1.5 h at which point the reaction was judged to be complete by TLC analysis. The reaction mixture was poured into a rapidly stirring solution of half saturated sodium bicarbonate (10 mL) and half saturated sodium thiosulfate (20 mL), and the aqeous layer was extracted with CH_2Cl_2 (5 x 20 mL) and the combined organics were washed with brine and dried over $MgSO_4$. Solvent was removed under reduced pressure to give the cude alcohol, which was purified by flash chromatography (10% EtOAc/Hex) to give the pure alcohol **3-31a** as a yellow oil (60 mg, 0.091 mmol, 66% yield). R_f 0.17 (20% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.21 (dd, *J* = 7.8, 5.1 Hz, 1H), 4.09 (dd, *J* = 6.6, 3.5 Hz, 1H), 3.70-3.65 (m, 2H), 3.60-3.57 (m, 1H), 3.48-3.44 (m, 1H), 2.79 (dt, *J* = 13.5, 5.7 Hz, 4H), 2.66 (qd, *J* = 7.1, 2.9 Hz, 1H), 2.27-2.20 (m, 2H), 2.17-2.12 (1H), 2.08 (dd, *J* = 15.0, 4.5 Hz, 1H), 2.04-1.99 (m, 1H), 1.97-1.85 (m, 4H), 1.85-1.77 (m, 1H), 1.67-1.50 (m, 4H), 1.12 (d, *J* = 7.0 Hz, 3H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.87 (s, 9H), 0.13 (s, 9H), 0.12 (s, 9H), 0.06 (d, *J* = 13.3 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 108.9, 85.8, 78.7, 76.0, 74.8, 72.3, 64.9, 55.5, 45.6, 42.6, 38.8, 34.9, 34.0, 33.3, 27.5, 26.4, 26.3, 26.0, 25.8, 25.0, 18.1, 16.6, 15.8, 0.9, 0.9, 0.2, -4.0, -4.2.



3-32

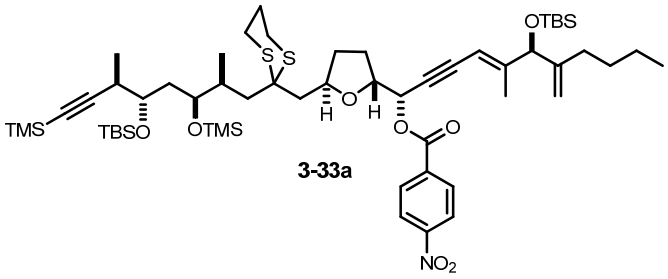
A 10 mL round bottom flask was charged with alcohol **3-31a** (60 mg, 0.091 mmol, 1 eq), diluted with CH_2Cl_2 (3 mL) and cooled to 0 °C. DMSO (35 mg, 0.45 mmol, 5 eq) was added, followed by Hunig's base (81 mg, 0.634 mmol, 7 eq). The reaction mixture was allowed to stir for 10 min before SO_3•Pyr (42 mg, 0.272 mmol, 3 eq) was added portion wise over 5 min. The reaction was monitored by TLC until completion (ca. 2h) before being slowly poured into a half-saturated solution of sodium bicarbonate (10 mL), and diluted with CH_2Cl_2 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, and the crude residue was dissolved in EtOAc (50 mL) and water (100 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, to afford a **3-32** as a yellow oil (59.7 mg, 0.091 mmol, 100% yield) which was used without further purification. R_f 0.37 (20% EtOAc/Hex).



3-33

To a solution of alkyne **2-2** (132.4 mg, 0.453 mmol, 5.0 eq) in MTBE (3 mL) at 0 °C was added *n*BuLi (2.75 M, 0.165 mL, 0.453 mmol, 5.0 eq), and the reaction was stirred at 0 °C for 1 h before being cooled to -90 °C using a liquid nitrogen/hexanes bath. After stirring for 15 min at -90 °C, aldehyde **3-32** (59.7 mg, 0.091 mmol, 1 eq) dissolved in a minimal amount of MTBE was added over 15 min drop wise. After stirring at -90 °C for 2 h, the reaction was treated at -90 °C with 20 mL of saturated NH_4Cl, before being allowed to warm to rt and diluted with water (50 mL) and EtOAc (50 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, and the crude product was purified by column chromatography (20% EtOAc/Hex) to afford recovered alkyne (ca. 100 mg) and alkynlation adduct as a single diastereomer **3-33** as a yellow oil (74 mg, 0.078 mmol, 86% yield). R_f 0.19 (10% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.63 (s, 1H), 5.05 (s, 1H), 4.86 (s, 1H), 4.64

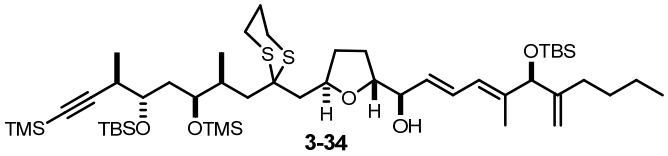
(bs, 1H), 4.42 (s, 1H), 4.42-4.36 (m, 1H), 4.17-4.14 (m, 1H), 3.68-3.67 (m, 2H), 2.78 (dt, J = 17.6, 5.6 Hz, 4H), 2.67 (dd, J = 7.0, 2.9 Hz, 1H), 2.43 (bs, 1H), 2.25-2.20 (m, 3H), 2.08-2.00 (m, 3H), 1.94-1.87 (m, 4H), 1.83 (dd, J = 13.5, 6.4 Hz, 1H), 1.78-1.72 (m, 2H), 1.71 (s, 3H), 1.64-1.56 (m, 2H), 1.56-1.52 (m, 1H), 1.40-1.34 (m, 2H), 1.30-1.26 (m, 3H), 1.12 (d, J = 7.0 Hz, 3H), 0.98 (d, J = 7.0 Hz, 3H), 0.89 (t, J = 7.0 Hz, 3H), 0.89 (s, 18H), 0.14 (s, 9H), 0.12 (s, 9H), 0.06 (d, J = 19.9 Hz, 6H), 0.00 (d, J = 2.3, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 149.1, 110.8, 108.9, 104.8, 90.4, 85.8, 83.6, 80.7, 80.0, 77.9, 74.8, 72.3, 64.9, 53.5, 45.8, 42.8, 39.0, 34.9, 34.0, 33.2, 29.9, 29.8, 29.7, 26.5, 26.4, 26.3, 26.0, 25.8, 25.8, 25.0, 22.6, 18.2, 18.1, 16.6, 15.9, 15.3, 14.0, 1.0, 0.9, 0.2, -4.0, -4.2, -5.0, -5.1.



3-33a

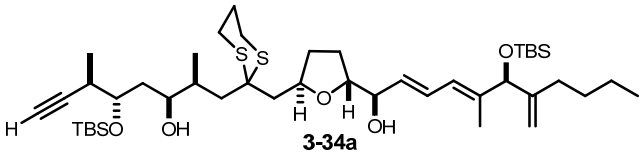
A 10 mL round bottom flask was charged with 4-nitro benzoic acid (24 mg, 0.141 mmol, 3 eq), triphenylphosphine (37 mg, 0.141 mmol, 3 eq), alcohol **3-33** (44.8 mg, 0.0471 mmol, 1 eq), diluted with THF (30 mL) and cooled to 0 °C. DIAD (29 mg, 0.141 mmol, 3 eq) was added drop wise over 10 min, and the ice bath was removed. The reaction monitored by TLC and upon completion (ca. 1h) was poured into a half-saturated solution of sodium bicarbonate (10 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, and the crude product was purified by filtration through a thin plug of silica gel (10% EtOAc/Hex) to afford **3-33a** as a yellow oil (36.2 mg, 0.033 mmol, 70% yield). R_f 0.39 (10% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.26 (d, J = 4.1 Hz, 4H), 5.74 (d, J = 7.0 Hz, 1H), 5.85 (s, 1H), 5.05 (s, 1H), 4.87 (s, 1H), 4.42 (s, 1H), 4.36 (q, J = 7.0 Hz, 1H), 4.27 (dd, J = 8.8, 5.3 Hz, 1H), 3.70-3.60 (m, 1H), 2.78-2.73 (m, 4H), 2.66 (dd, J = 6.7, 2.6 Hz, 1H), 2.31-2.22 (m, 3H), 2.18 (d, J = 14.6 Hz, 1H), 2.03 (dd, J = 14.6, 5.9 Hz, 1H), 1.99-1.96 (m, 1H), 1.92-1.85 (m, 3H), 1.83-1.79 (m, 2H), 1.75 (dd, J = 16.7, 8.5 Hz, 1H), 1.73 (s, 3H), 1.66-1.61 (m, 1H), 1.57 (dd, J = 14.9, 6.1 Hz, 1H), 1.53-1.49 (m, 1H), 1.38-1.34 (m, 2H), 1.28 (dd, J = 14.3, 7.3 Hz, 2H), 1.11 (d, J = 7.0 Hz,

3H), 0.90 (d, J = 7.0 Hz, 3H), 0.87 (t, J = 7.0 Hz, 3H), 0.87 (s, 18H), 0.12 (s, 9H), 0.11 (s, 9H), 0.05 (d, J = 15.2 Hz, 6H), 0.01 (d, J = 2.9 Hz, 6H).



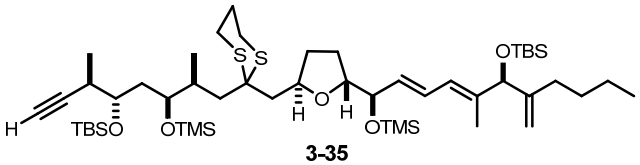
3-34

A 5 mL round bottom flask was charged with **3-33a** (36.2 mg, 0.33 mmol, 1 eq), diluted with diethyl ether (3 mL) and cooled to 0 °C. $LiAlH_4$ (9 mg, 0.235 mmol, 5.0 eq) was added. The reaction was stirred for 1h at 0 °C before being poured into a half-saturated solution of NH_4Cl (10 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, and the crude product was purified by column chromatography (10% EtOAc/Hex) to afford alcohol **3-34** as a yellow oil (31 mg, 0.032 mmol, 99% yield). There were several peaks indicating the presence of benzoyl-deprotected ene-yne, indicative of complete benzoyl deprotection of the starting material (**3-33a**), but incomplete hydroalumination of the ene-yne. R_f 0.17 (10% EtOAc/Hex)



3-34a

The mixture from above (**3-34**) (ca. 0.032 mmol) was dissolved in wet methanol (10 mL), and a K_2CO_3 was added (10 mg, catalytic). The reaction was stirred at rt for 1 day before being filtered through a pad of celite into a solution of half saturated NH_4Cl (100 mL). The celite pad was washed with EtOAc (50 mL) and the filtrate was transferred to a separatory funnel, and the aqueous layer was extracted with EtOAc (3 x 30 mL) and the combined organics were washed with brine, dried with $MgSO_4$ and filtered through a thin pad of celite. Solvent was removed under reduced pressure to afford (**3-34a**) a yellow oil (20 mg) which was used in the next step without purification.



3-35

The crude mixture from above was dissolved in CH_2Cl_2 (5 mL) and Et_3N (1 mL) and

TMSCl was added (10 drops, excess) followed by DMAP (1mg, catalytic). The reaction was stirred for 30 min before being poured into a half-saturated solution of sodium bicarbonate (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organics were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, and the crude product was purified by column chromatography (10% EtOAc/Hex) to afford TMS ether **3-35** as a yellow film. Key and integrations led us to believe that the reaction was successful to form **3-35**, but the amount of material (~10 mg, ca. 0.01 mmol) and the dubious purity was determined insufficient to run subsequent reactions. R_f 0.50 (10% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55 (dd, *J* = 14.7, 11.1 Hz, 1H), 6.07 (d, *J* = 10.6 Hz, 1H), 5.57 (dd, *J* = 15.2, 7.0 Hz, 1H), 5.11 (s, 1H), 4.86 (s, 1H), 4.40 (s, 1H), 4.25-4.21 (m, 1H), 4.02-3.97 (m, 2H), 3.91-3.87 (m, 2H), 2.85-2.80 (m, 5H), 2.74-2.71 (m, 1H), 2.38 (dd, *J* = 15.0, 3.8 Hz, 1H), 2.27 (dd, *J* = 15.0, 6.7 Hz, 1H), 2.18-2.13 (m, 3H), 2.09 (s, 1H), 2.00-1.87 (m, 5H), 1.82-1.78 (m, 1H), 1.76-1.71 (m, 2H), 1.68-1.63 (m, 2H), 1.60 (s, 3H), 1.57-1.53 (m, 1H), 1.42-1.36 (m, 2H), 1.32-1.28 (m, 2H), 1.16 (d, *J* = 7.0 Hz, 3H), 1.02 (d, *J* = 7.0 Hz, 3H), 0.91 (s, 9H), 0.90 (s, 9H), 0.89 (t, *J* = 7.0 Hz, 3H), 0.12 (d, *J* = 11.7 Hz, 6H), 0.02 (d, *J* = 9.9 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5, 139.4, 130.2, 129.7, 124.7, 109.7, 86.6, 81.8, 80.6, 75.7, 75.2, 72.0, 71.7, 70.0, 53.1, 44.7, 42.3, 35.8, 35.5, 33.9, 32.0, 30.7, 30.0, 27.8, 26.4, 26.3, 25.8, 25.8, 24.9, 22.5, 18.2, 18.0, 16.6, 15.0, 14.0, 12.0, -4.5, 4.6, -5.0, -5.1.

Section 3.4 - References

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Chapter 4 – Summary and Outlook

Section 4.1 – Summary of Progress

Our initial retrosynthesis of amphidinolide C led to the Northern (**2-1**), Eastern (**2-2**), Southern (**2-3**), and Western (**2-4**) fragments, which were achieved in laboratory with some notable transformation achieved in the process.

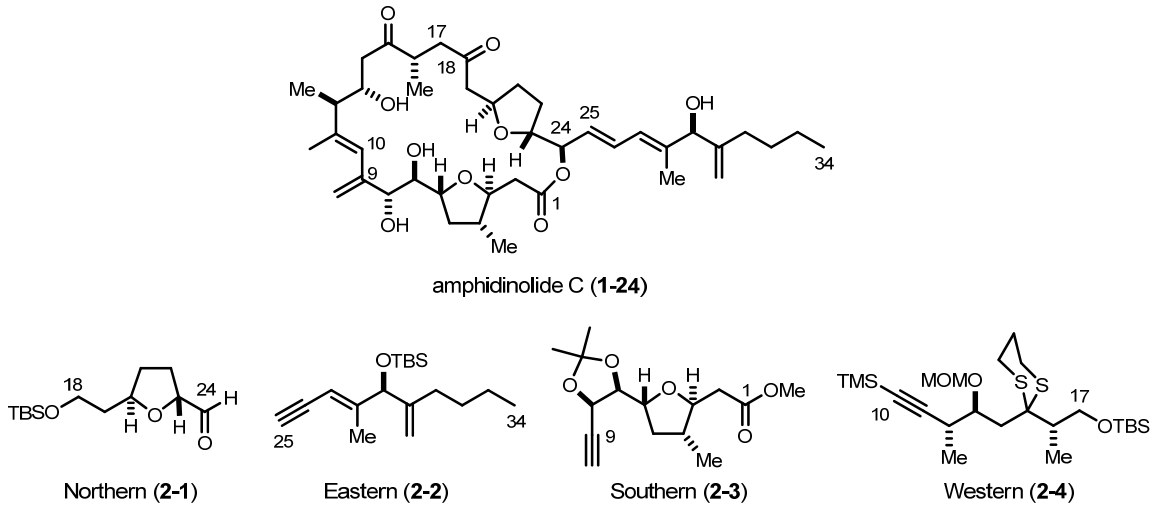


Figure 4.1. Initially synthesized fragments of amphidinolide C

Difficulties associated with the large scale post-reaction purification of Mukaiyama oxidative cyclization reactions towards the Northern fragment (**2-1**) led to the design and synthesis of a second generation, water-soluble catalyst, $Co(nmp)_2$ (**1-21**) (Figure 4.2). This catalyst displayed increase longevity in the cyclization reaction, which allowed for lower catalyst loadings, lower reaction temperature and times, and greatly improved yields in all cases. We believe that $Co(nmp)_2$ now stands alone as the premier method of forming *trans*-THF rings, giving the desired products in perfect *cis*/*trans* ratio, excellent yields, and high purity from easily accessed pentenols.

The Eastern fragment (**2-2**) was synthesized using two routes, one of which demonstrated the use of diyne functionalization resulting in ene-yne systems found in a variety of natural products (Figure 4.3).

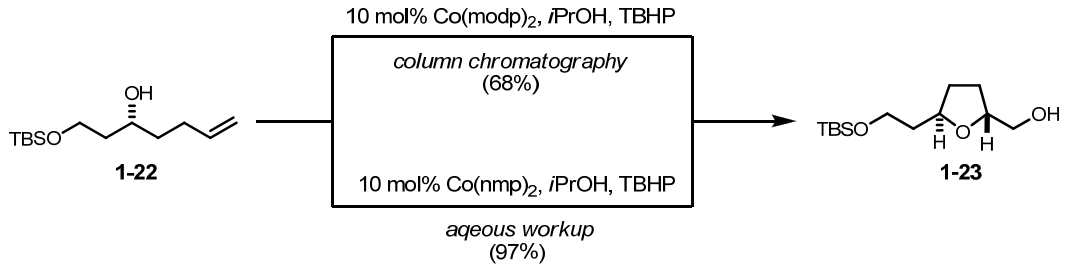


Figure 4.2. Summary of the Northern fragment (**2-1**) synthesis.

We have demonstrated that the regioselective hydrostannylation reaction pioneered by Hale can be modified for diyne systems to use the commercially available and inexpensive tributyltinhydride in place of the more expensive triphenyltinhydride. We also showed that the tin moiety can be displaced with an iodine in a one-pot procedure to give the vinyl iodide.

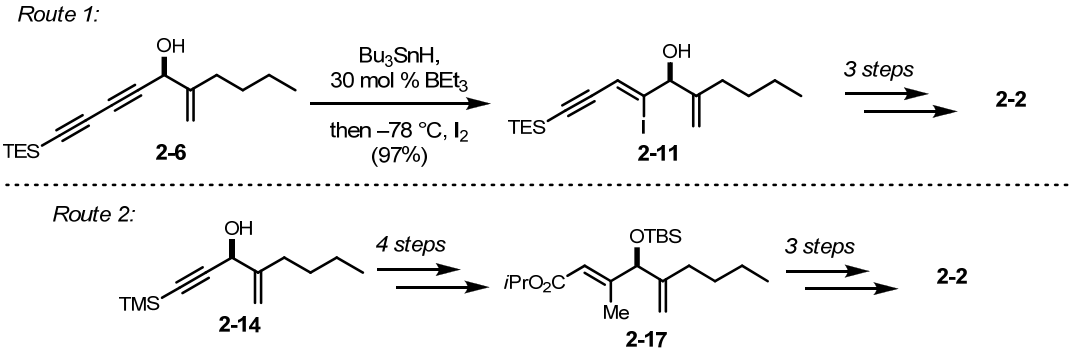


Figure 4.3. Summary of the Eastern fragment (**2-2**) syntheses.

The southern fragment (**2-3**) was also achieved via two routes, one of which exploited a remarkably selective Shi epoxidation, followed by a modified reductive epoxide opening reaction. The achieve perfect selectivity in the epoxide opening reaction, a novel Lewis acid, $BF_2OBn{\cdot}OEt_2$ (**2-51**), was designed and synthesized, which showed attenuated Lewic acidity compared to that of the parent compound $BF_3{\cdot}OEt_2$. This modification introduces an intriguing possibility of synthesizing a library of electronically fine-tuned boron based Lewis acids to suit specific needs. As with the Northern fragment (**2-1**), $Co(nmp)_2$ (**1-21**) was used in the Mukaiyama oxidative cyclization and again showed tremendously improved yields when compared to the first generation catalysts.

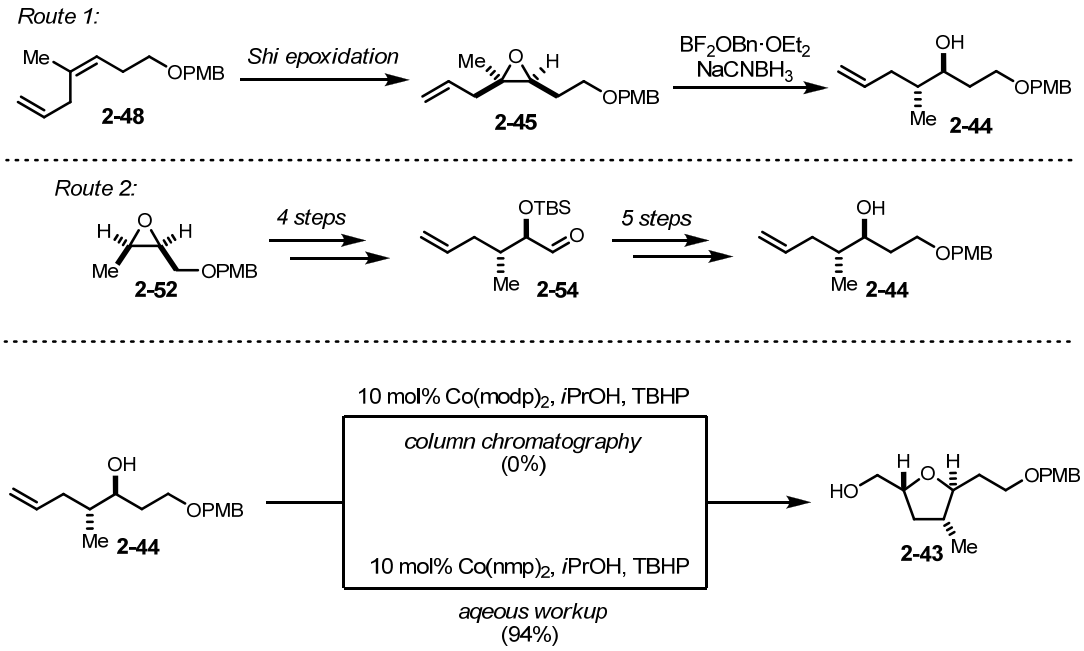


Figure 4.4. Summary of the Southern fragment (**2-3**) synthesis.

The western fragment (**2-4**) was synthesized from easily accessible precursors, and led to a novel one-pot conversion of terminal epoxides to protected iodohydrins (Figure 4.5). The utility of a copper-stannylation reaction was shown to provide a working alternative to typically used carbo-metallation reactions for the functionalization of alkynes.

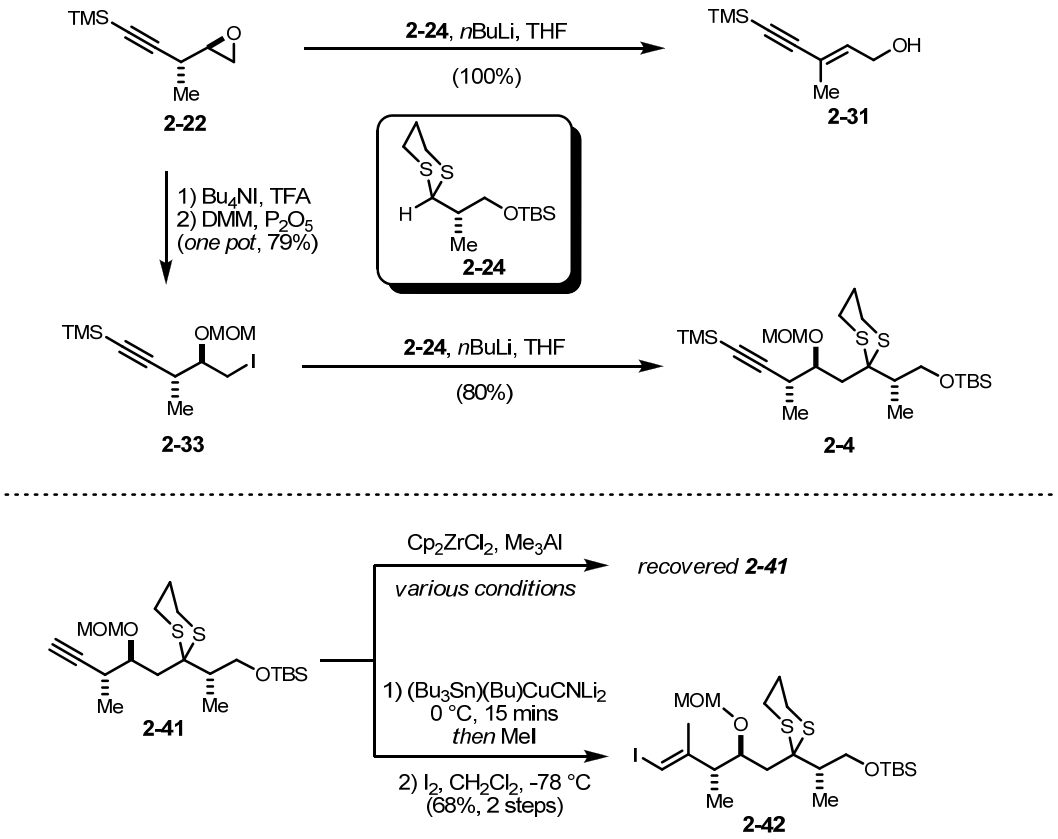


Figure 4.5. Summary of the Western fragment (**2-4**) synthesis.

After extensive studies towards fragment couplings, a novel procedure for the highly selective alkynylation of THF aldehydes has been developed (Figure 4.6). By careful choice of reaction conditions (MTBE, -90 °C), the Eastern fragment (**2-2**) has been shown to add into a handful of differentially functionalized *trans*-THF aldehydes, with a high level of selectivity and excellent yields. The diastereoselectivity achieved from these reactions is a tremendous accomplishment considering the operationally simple procedure and lack of externally added chiral element to influence the facial selectivity.

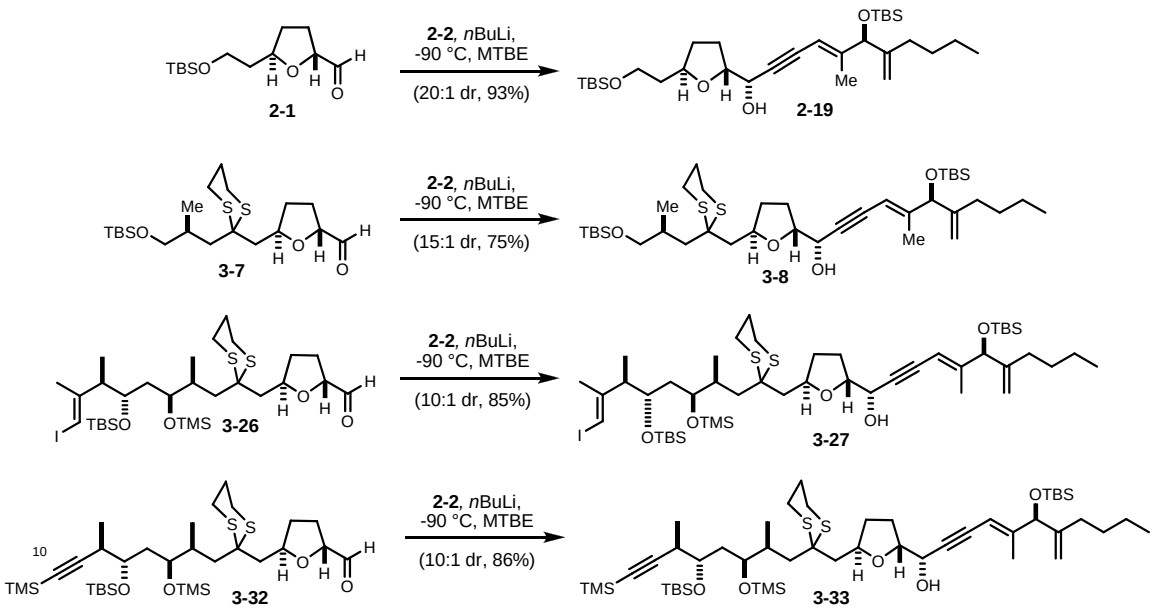


Figure 4.6. Summary of the North-Eastern fragment couplings.

Although the total synthesis of amphidinolide C has not yet been achieved, several important contributions have been made to the literature that are a direct result of work on this project.

Section 4.2 – Future Completion of Amphidinolide C

Due to time constraints and dwindling amounts of material, progress was halted at this point. In the near future, large amounts of the fully functionalized North-Eastern-Western fragment **3-36** will be made, and combined with the Southern fragment **2-3**, to complete the total synthesis of amphidinolide C. The remaining steps are envisioned to include a Stille cross coupling of iodide **3-36** with stannane **2-3**, followed by saponification of the methyl ester and concurrent TMS deprotection to form the open, protected, carboxylic acid form of Amphidinolide C (**4-1**) (Figure 4.7). We are then hoping that the steric hindrance around the alcohol at C(15) will work in our favor to allow selective macrolactonization at the desired alcohol on C(24), resulting in macrocycle **4-2**.

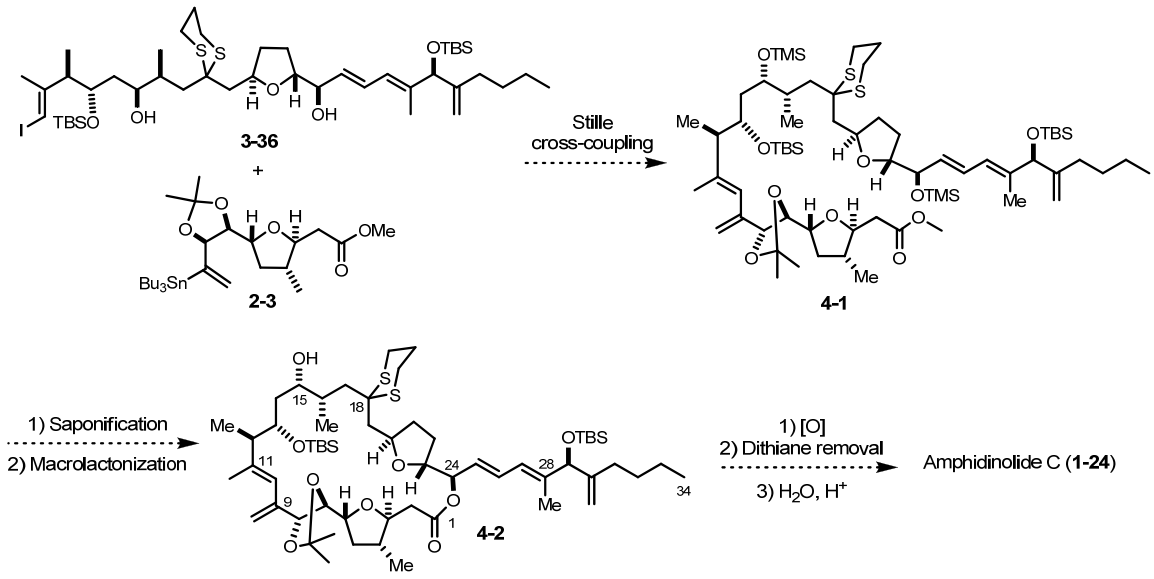
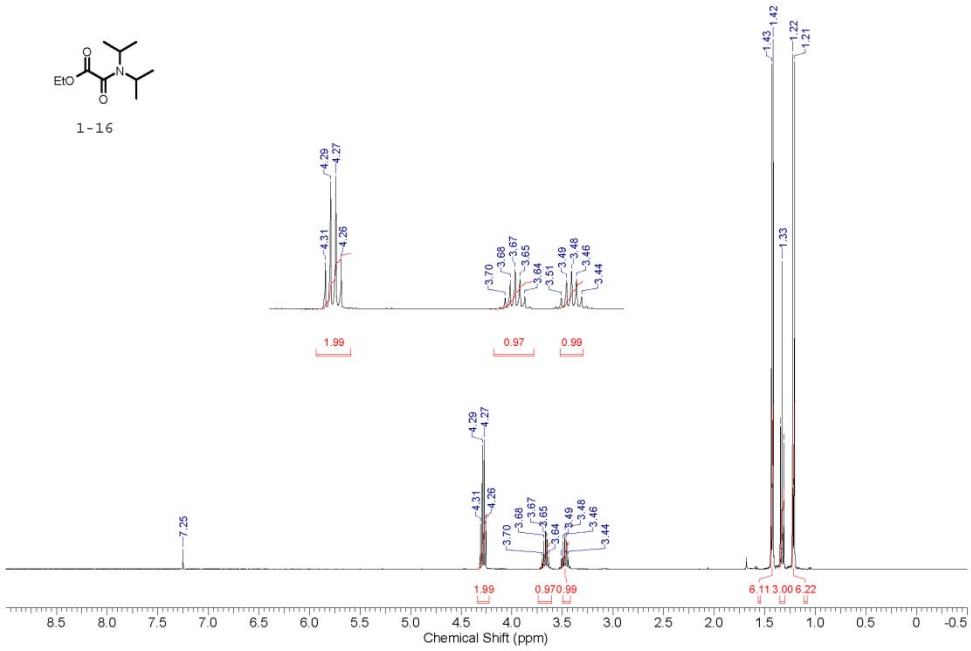


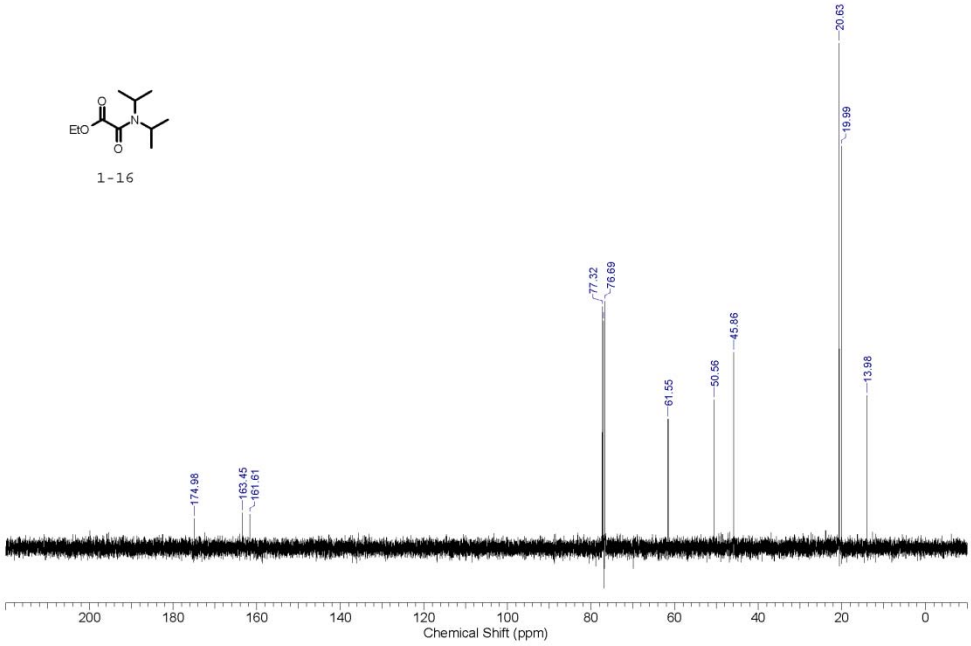
Figure 4.7. The six remaining steps envisioned to complete amphidinolide C

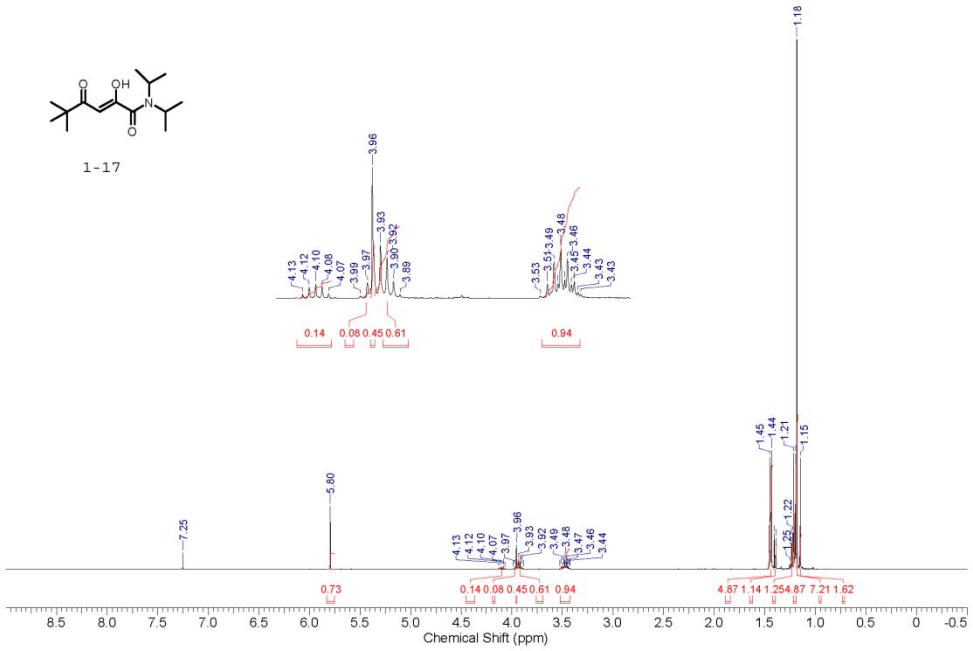
To complete the synthesis from macrocycle **4-2**, we would oxidize the secondary alcohol at C(15) to the desired ketone oxidation state, followed by dithiane removal and global acidic deprotection to furnish amphidinolide C (**1-24**). Time permitting; the chemistry can be reproduced using similar pieces to complete the total synthesis of amphidinolide F.

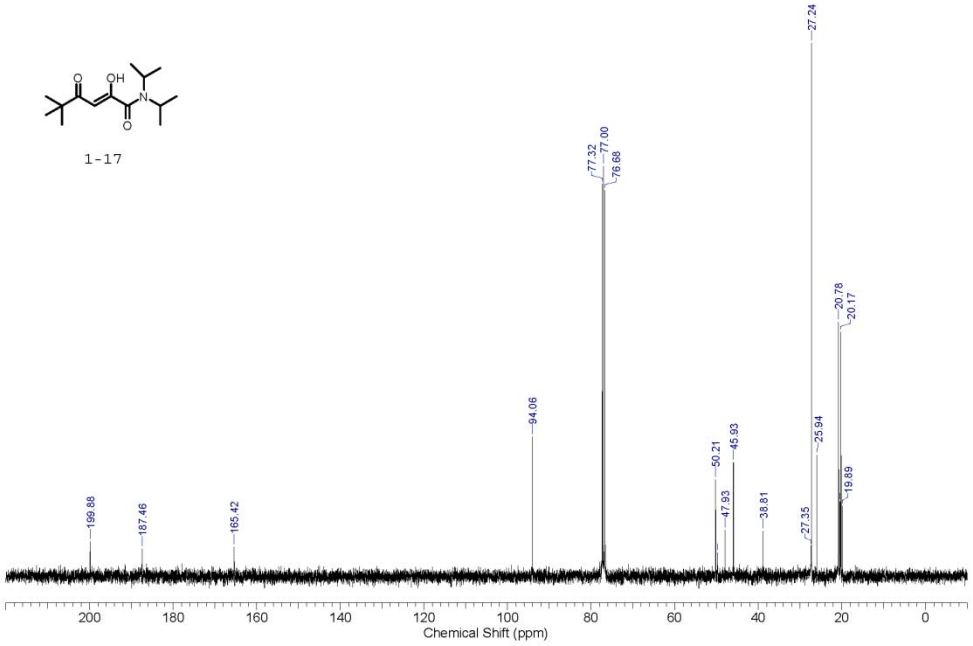
Appendix

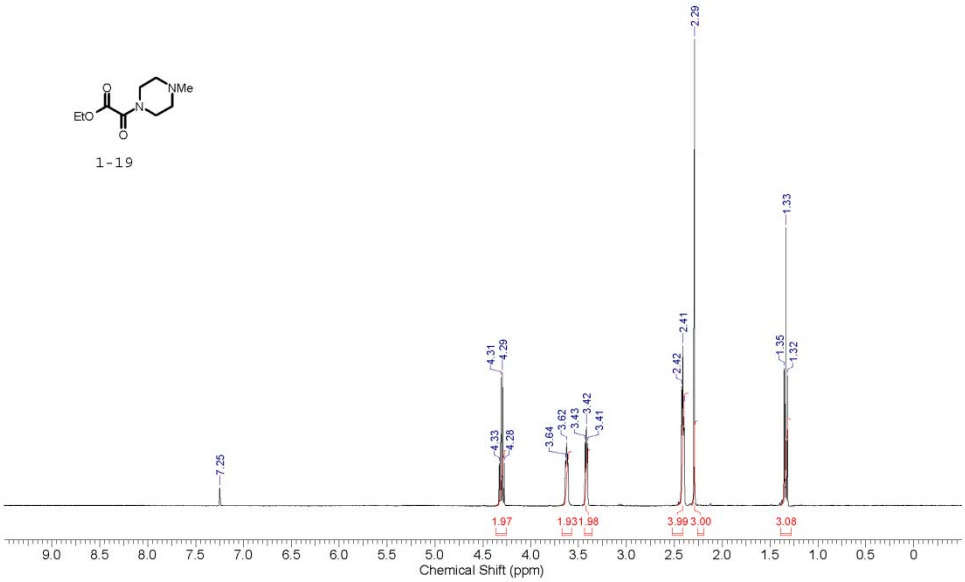
Appendix 1 – Spectra for Chapter 1 Compounds


1-16
4.29
4.27
4.31
4.26
3.70
3.68
3.67
3.65
3.64
3.51
3.49
3.48
3.46
3.44
1.43
1.42
1.22
1.21
1.33
7.25
1.99
0.97
0.99
6.11
3.00
6.22
Chemical Shift (ppm)


1-16
20.63
19.99
77.32
76.69
45.86
50.56
61.55
13.98
174.98
163.45
161.61
Chemical Shift (ppm)


1-17
Chemical Shift (ppm)


1-17
Chemical Shift (ppm)


EtO
NMe
1-19
2.29
1.33
4.31
4.29
2.41
2.42
1.35
1.32
4.33
4.28
3.64
3.62
3.43
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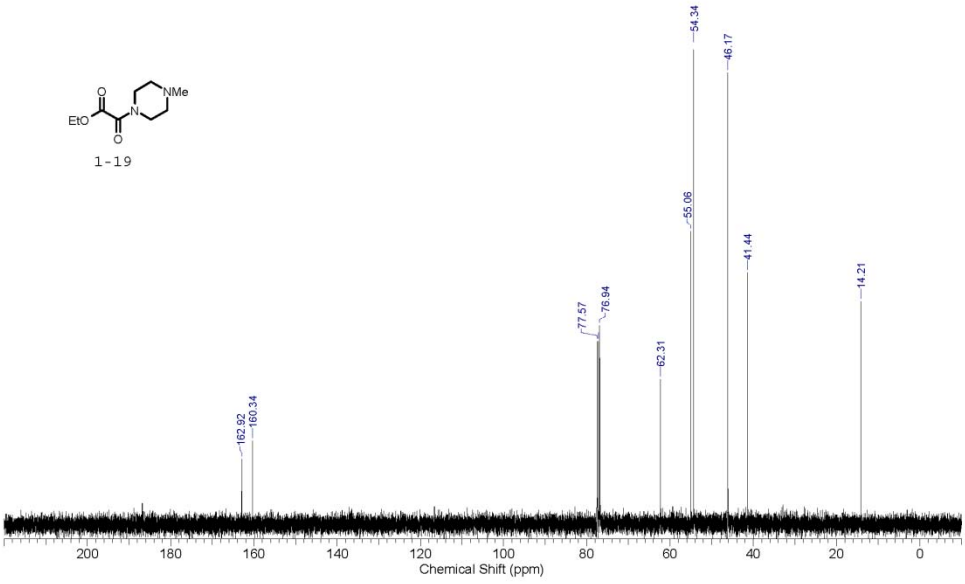
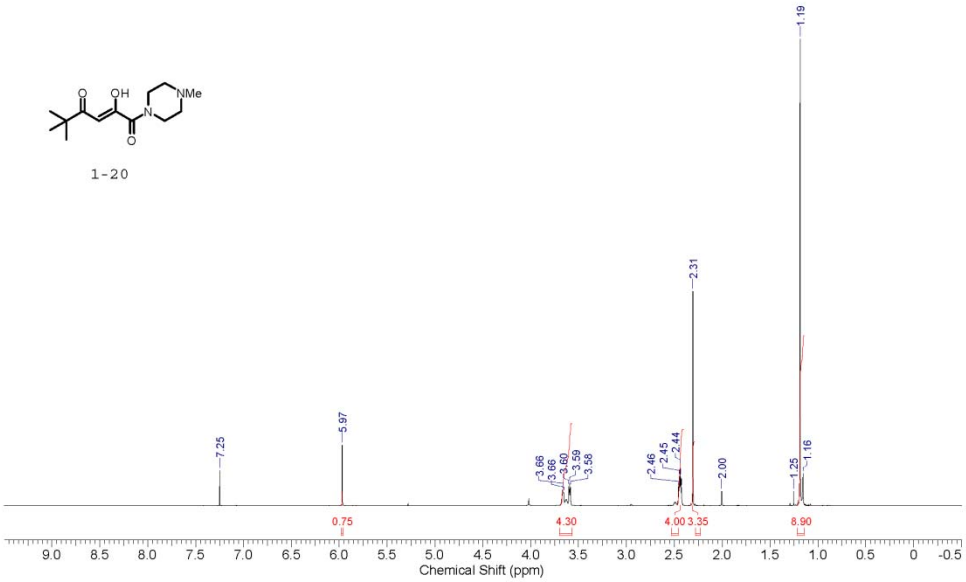
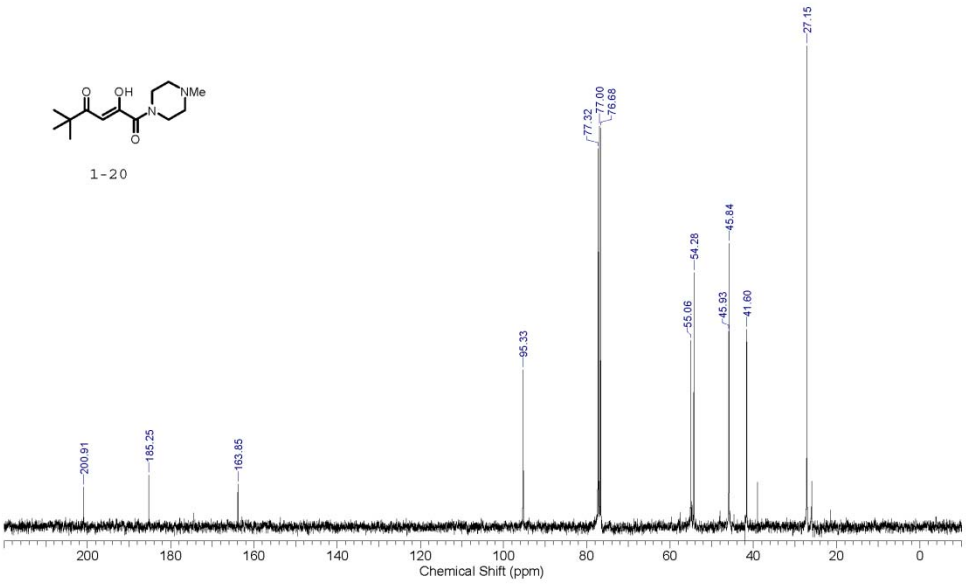
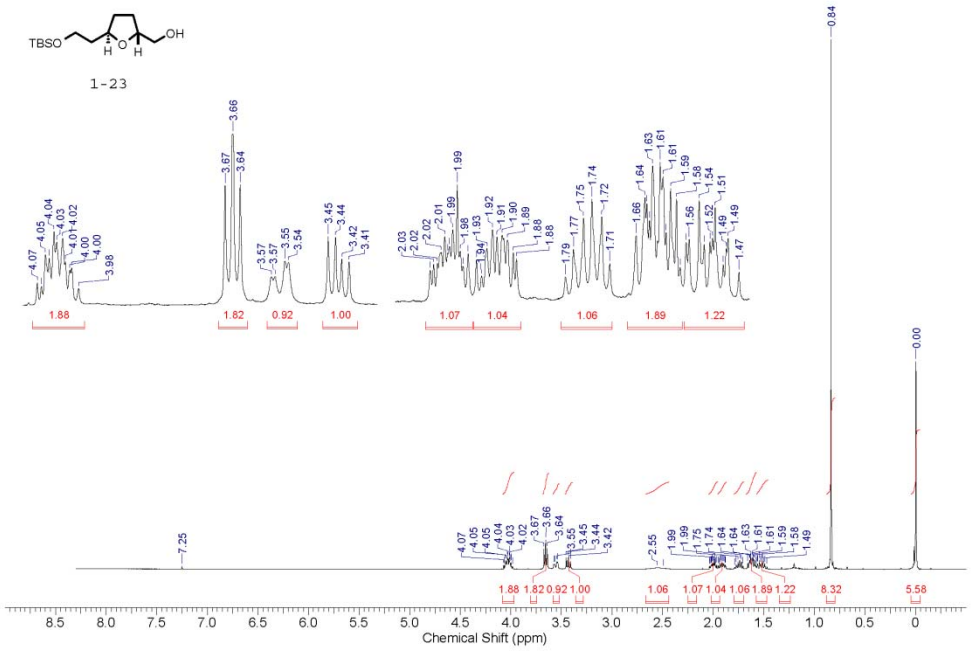
3.41
7.25
1.97
1.93
1.98
3.99
3.00
3.08
Chemical Shift (ppm)

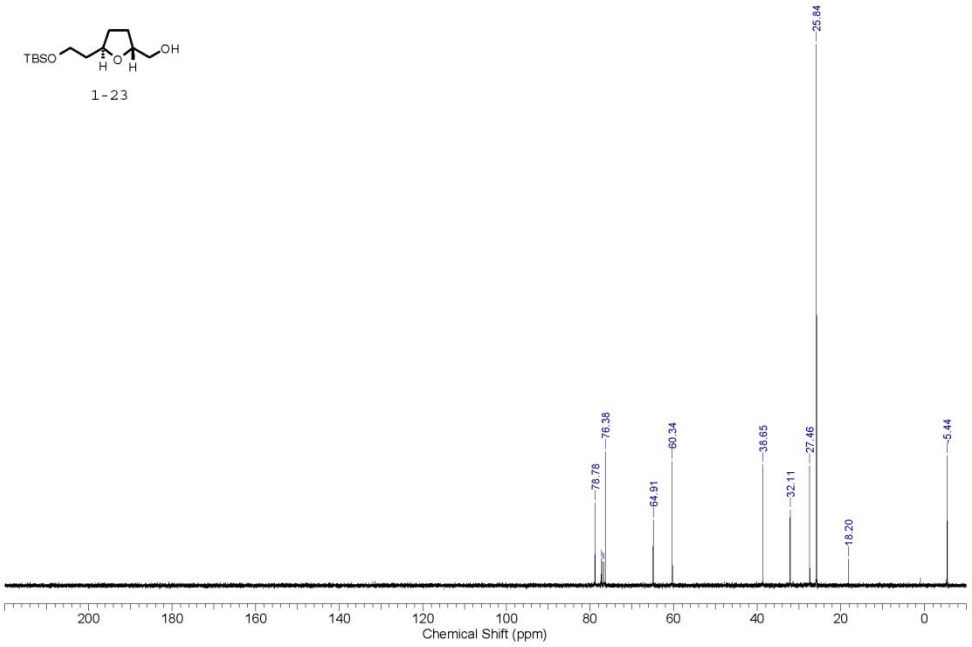

EtO
NMe
1-19
54.34
46.17
55.06
41.44
14.21
77.57
76.94
62.31
162.92
160.34
Chemical Shift (ppm)

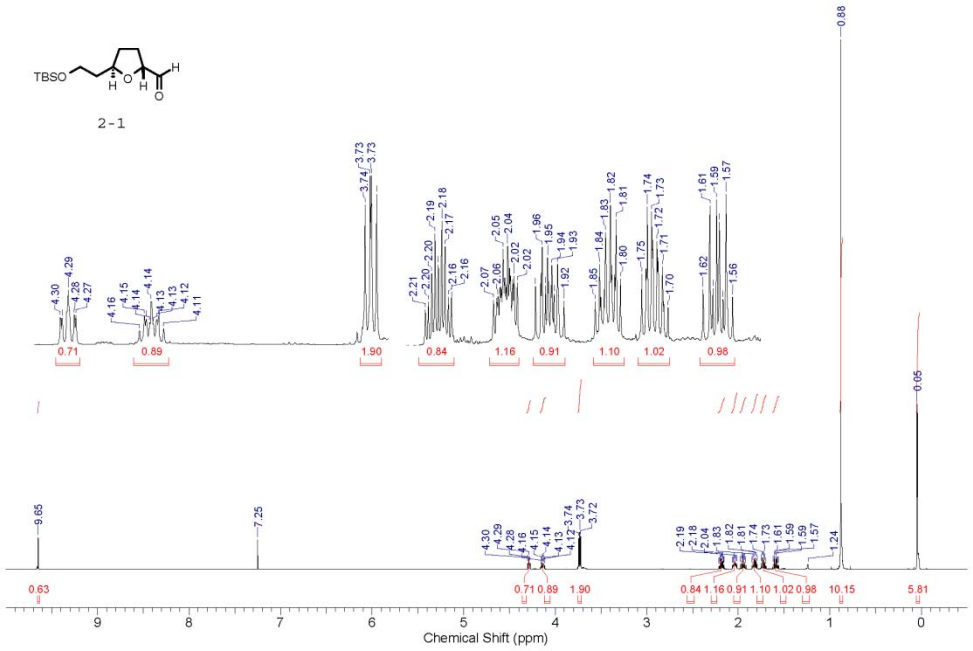

1-20
7.25
5.97
3.68
3.66
3.60
3.59
3.58
2.46
2.45
2.44
2.31
2.00
1.25
1.19
1.16
0.75
4.30
4.00
3.35
8.90
Chemical Shift (ppm)

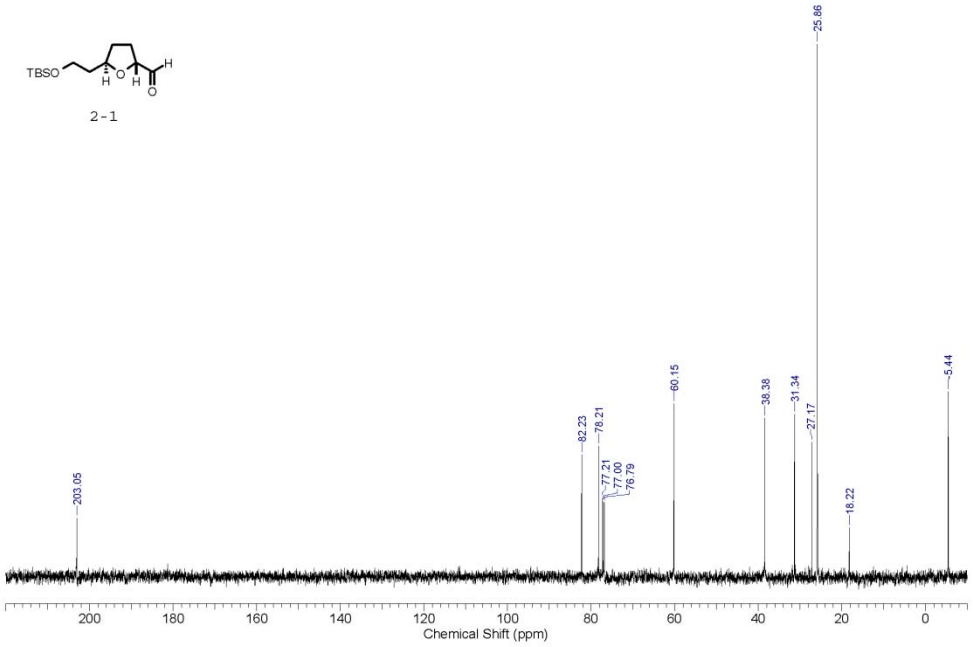

1-20
200.91
185.25
163.85
95.33
77.32
77.00
76.68
55.06
54.28
45.93
45.84
41.60
27.15
Chemical Shift (ppm)

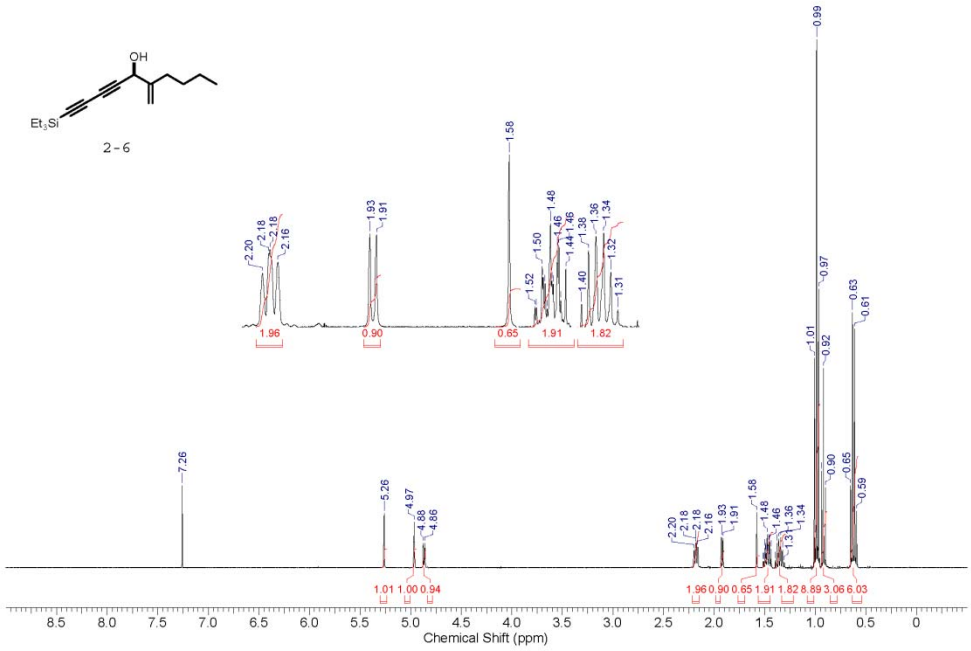
Appendix 2 – Spectra for Chapter 2 Compounds

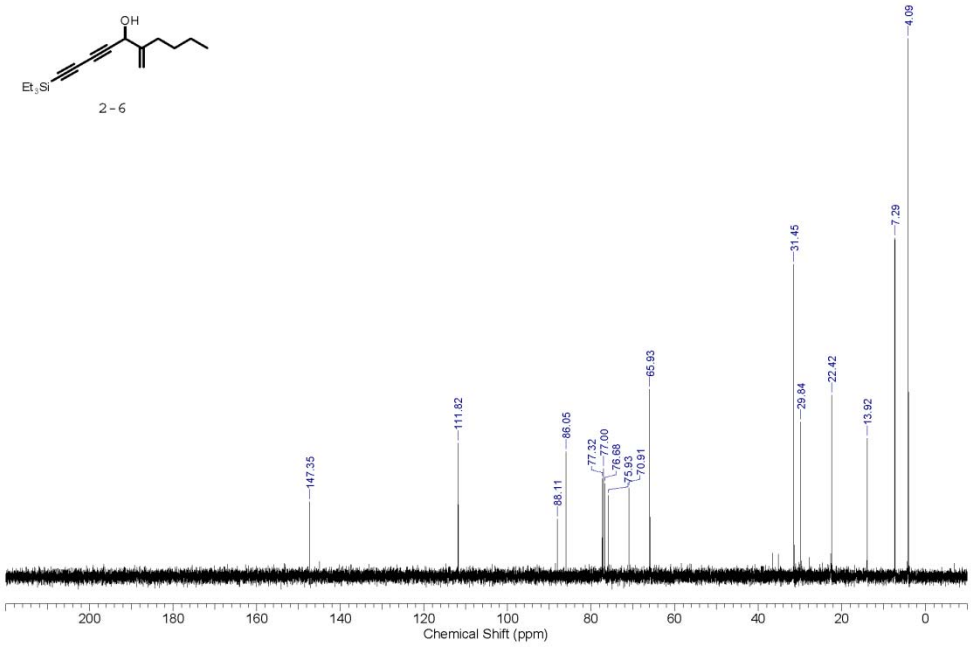

TBSO
OH
H
O
H
1-23
Chemical Shift (ppm)

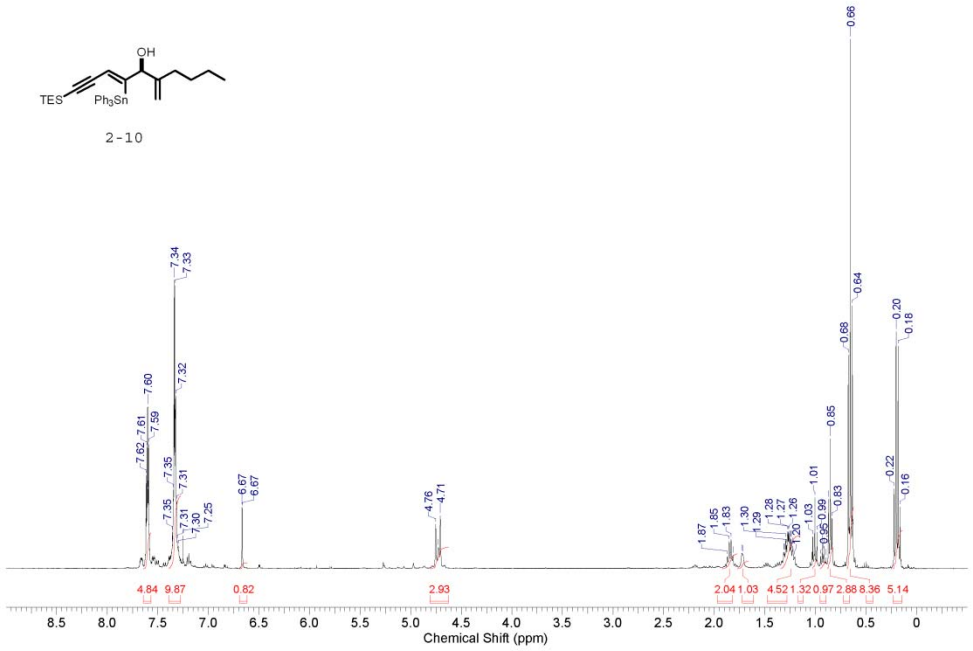

TBSO
OH
H
O
H
1-23
Chemical Shift (ppm)


TBSO
H
O
H
O
H
2-1
9.65
7.25
0.88
0.05
Chemical Shift (ppm)


TBSO
H
O
H
O
H
2-1
203.05
82.23
78.21
77.21
77.00
76.79
60.15
38.38
31.34
27.17
25.86
18.22
5.44
Chemical Shift (ppm)


OH
Et3Si
2-6
Chemical Shift (ppm)


OH
Et3Si
2-6
Chemical Shift (ppm)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TES
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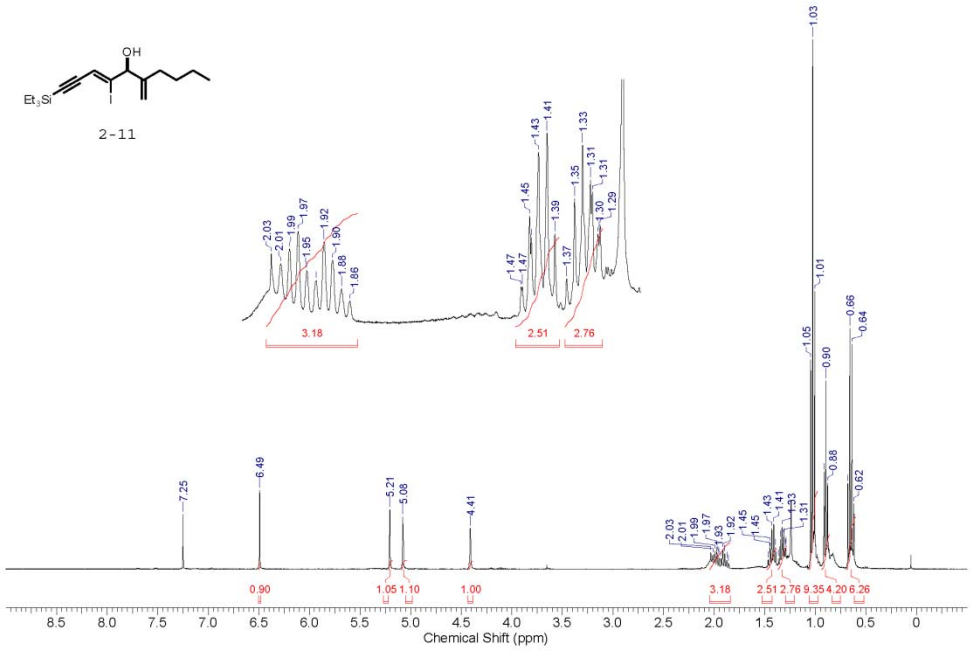
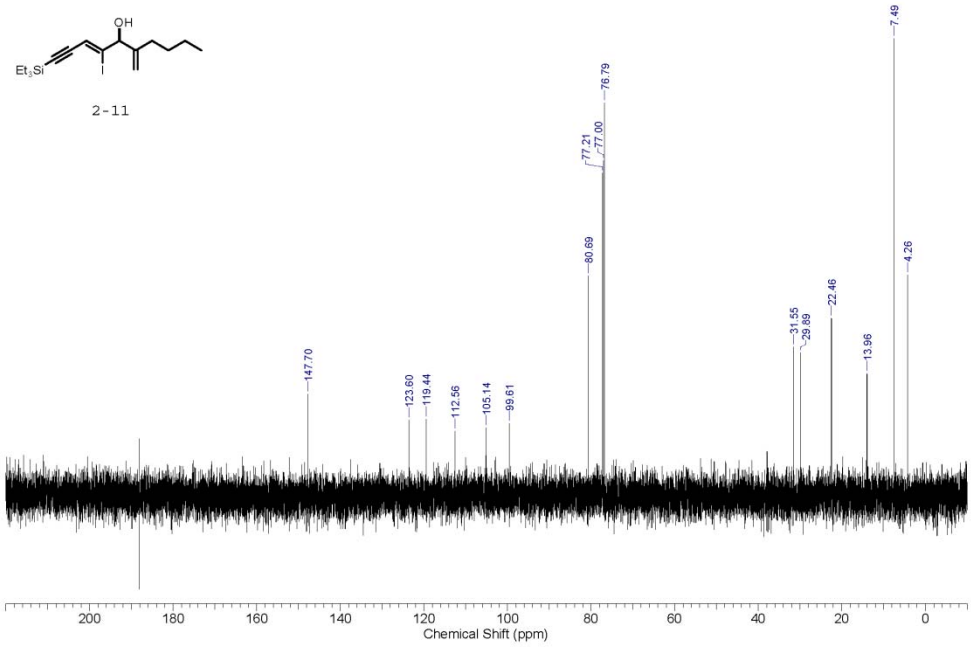
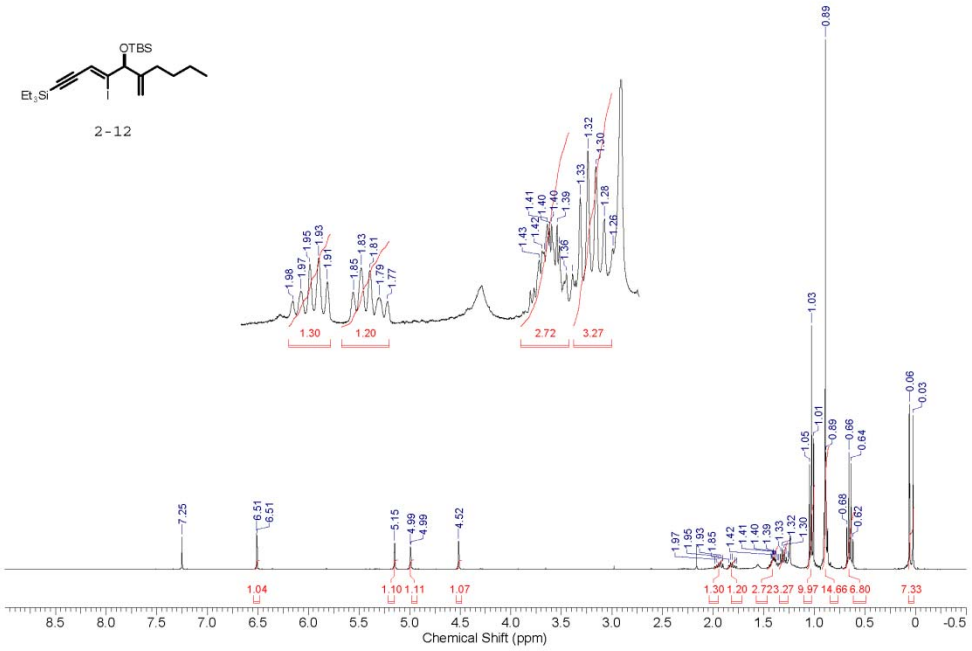
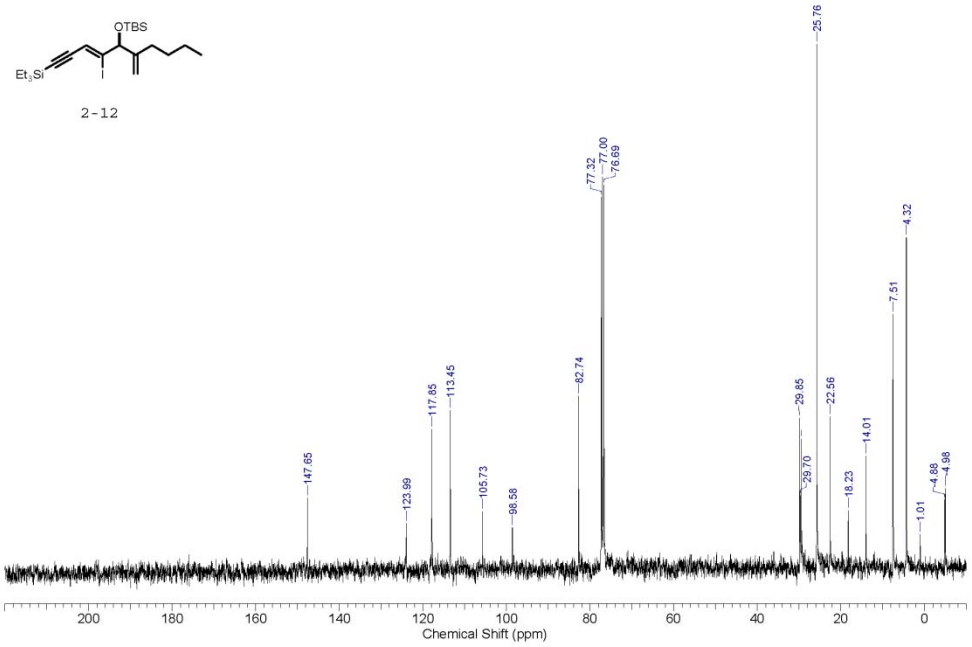
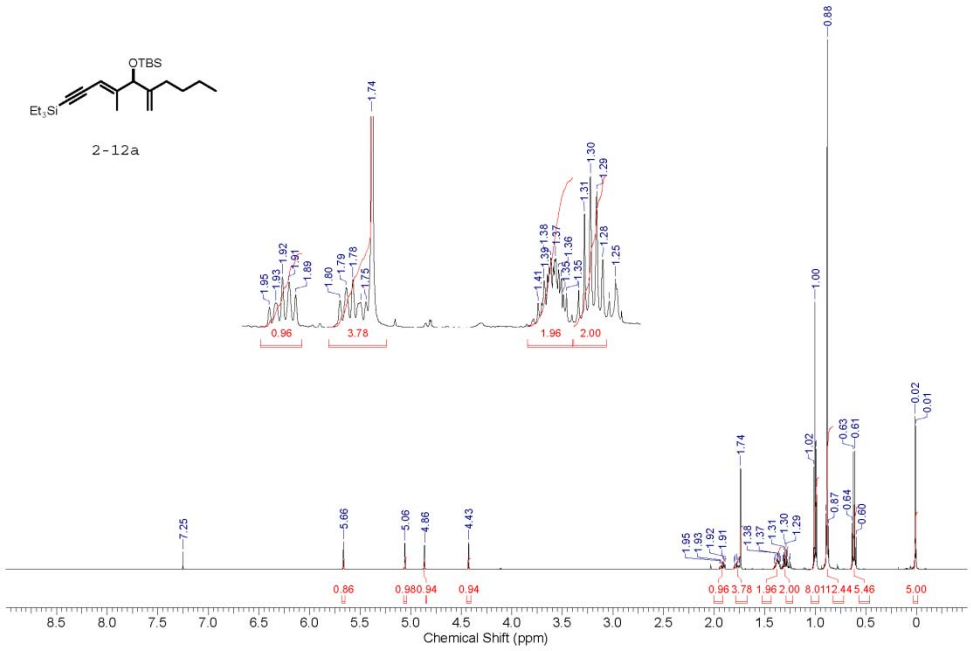
Chemical Shift (ppm)

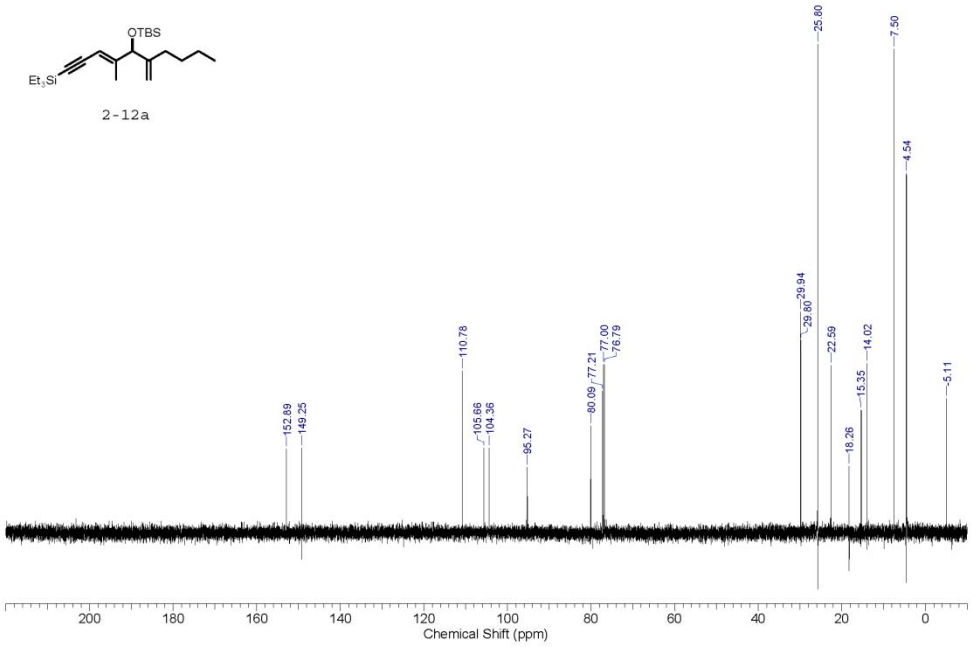

OH
Et3Si
I
2-11
Chemical Shift (ppm)

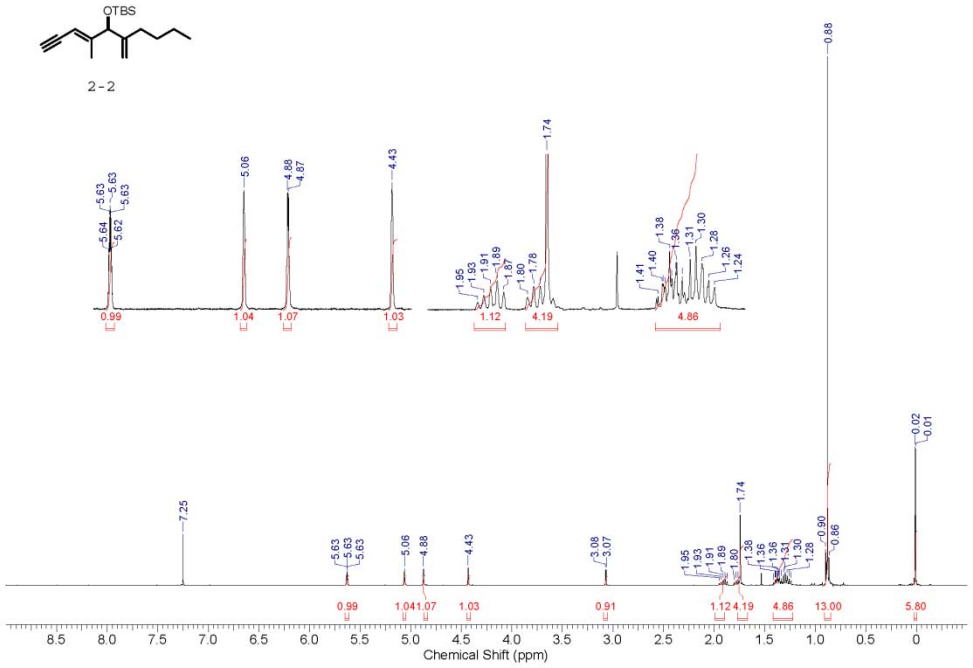

OH
Et3Si
I
2-11
Chemical Shift (ppm)

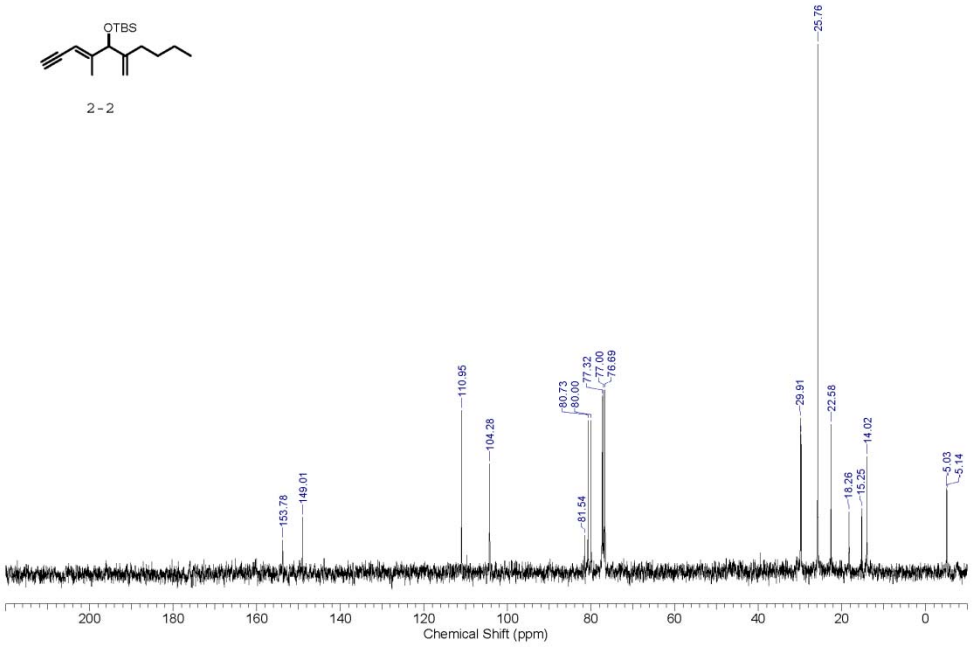

OTBS
Et3Si
I
2-12
Chemical Shift (ppm)

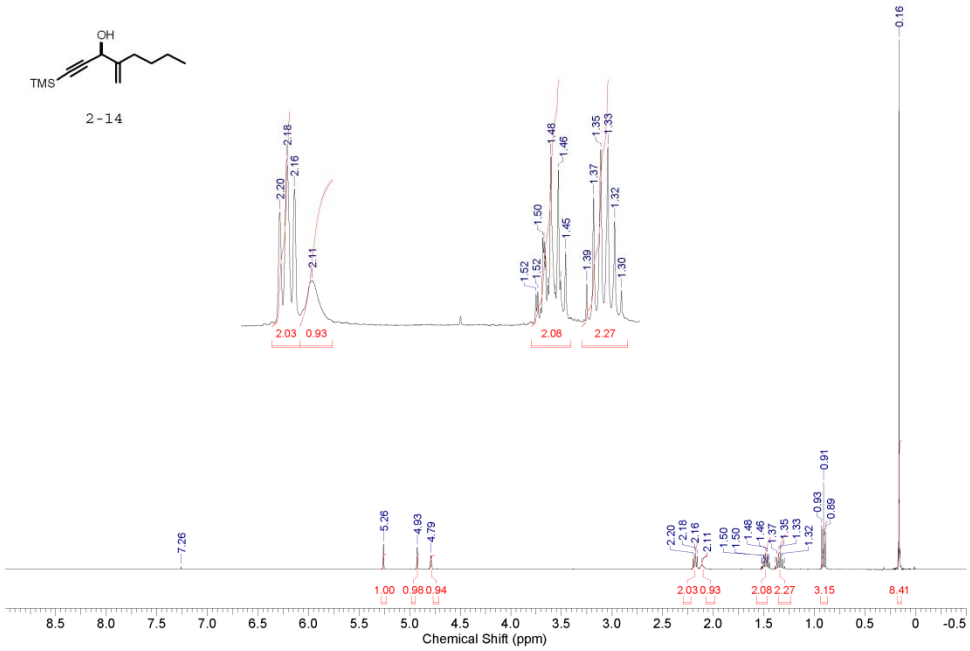

OTBS
Et3Si
I
2-12
Chemical Shift (ppm)

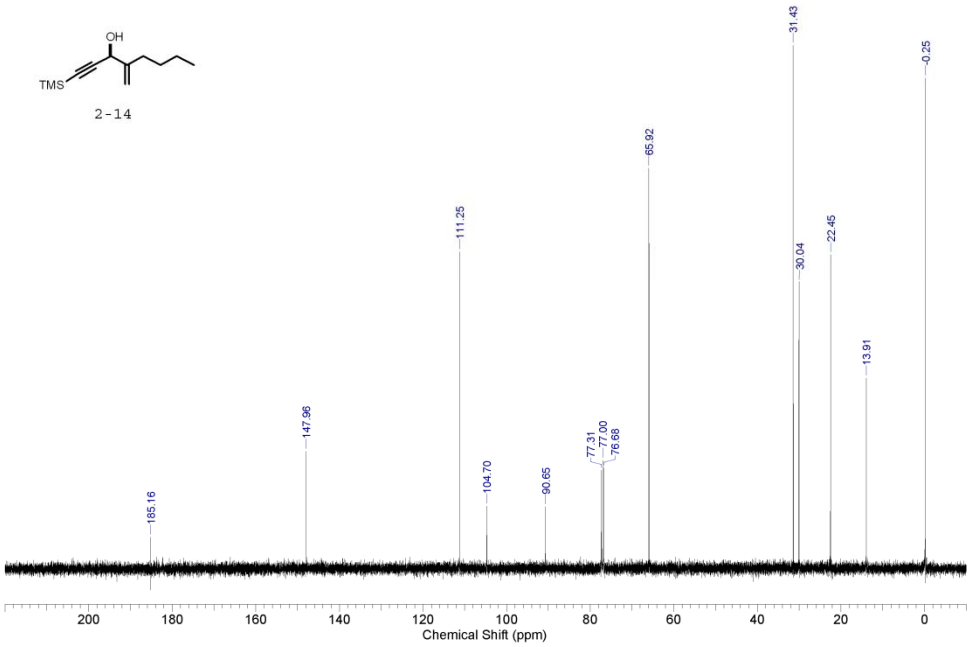

OTBS
Et3Si
2-12a
Chemical Shift (ppm)

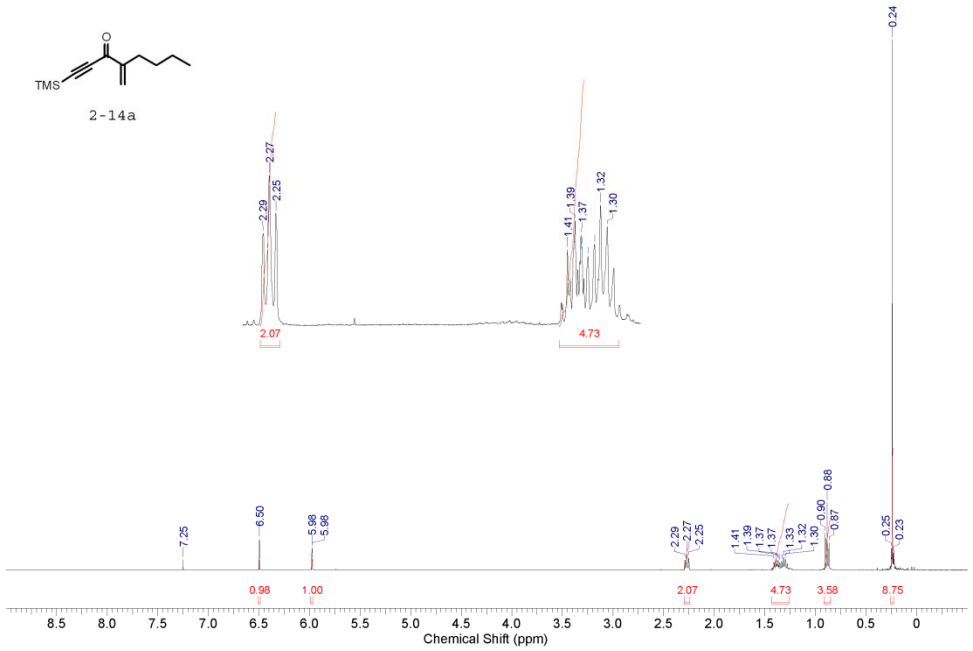

OTBS
Et3Si
2-12a
Chemical Shift (ppm)

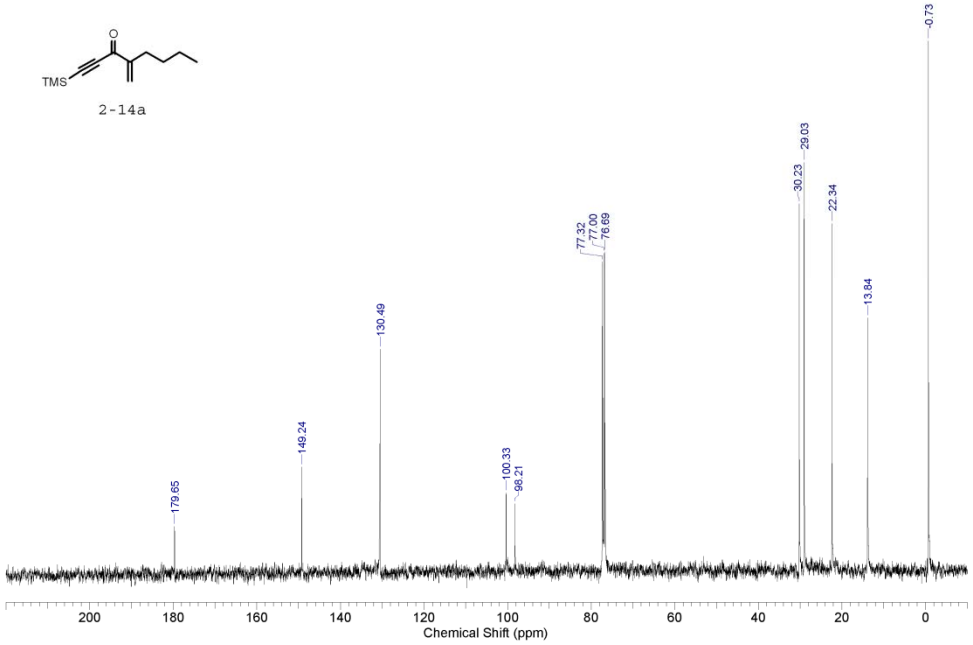

OTBS
2-2
Chemical Shift (ppm)

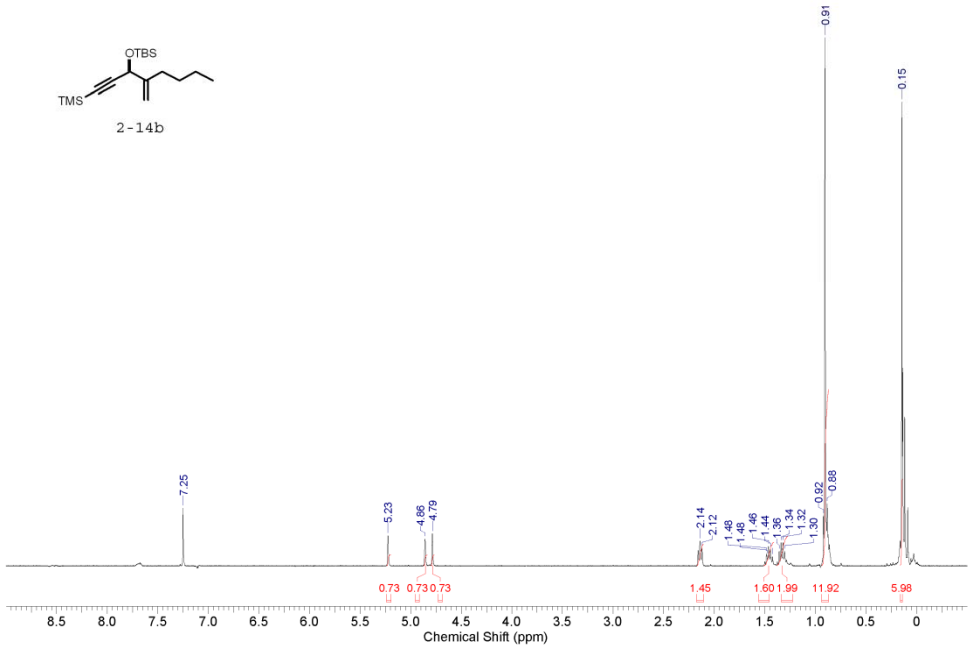

OTBS
2-2
Chemical Shift (ppm)

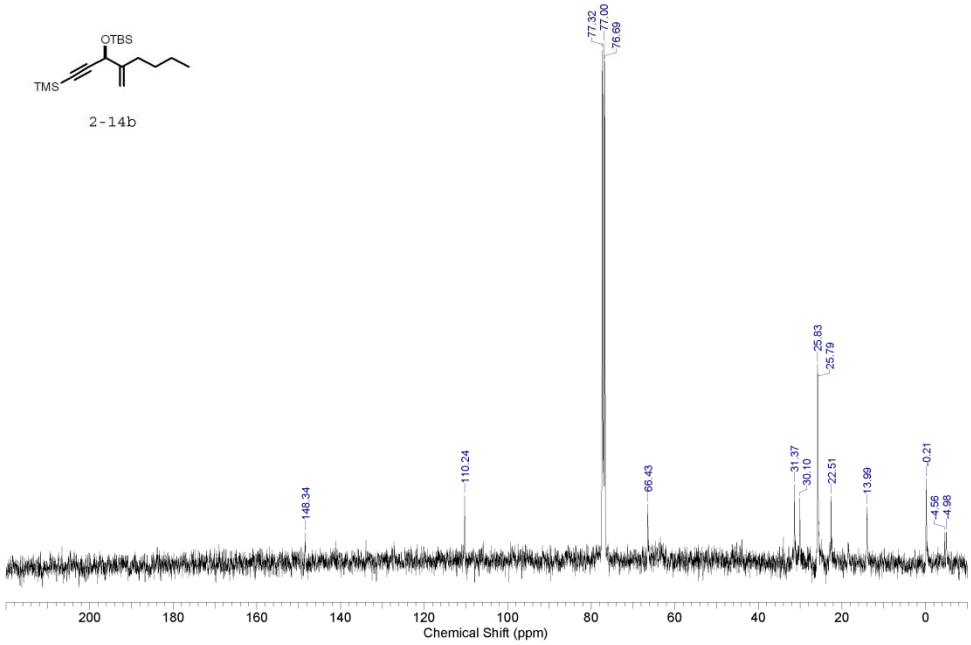

OH
TMS
2-14
Chemical Shift (ppm)

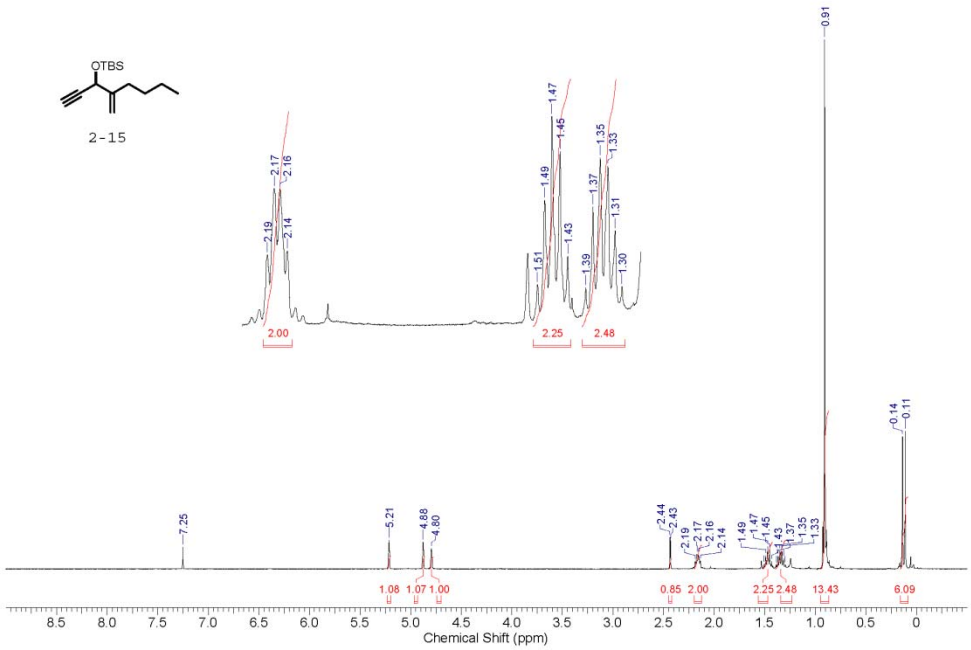

OH
TMS
2-14
Chemical Shift (ppm)

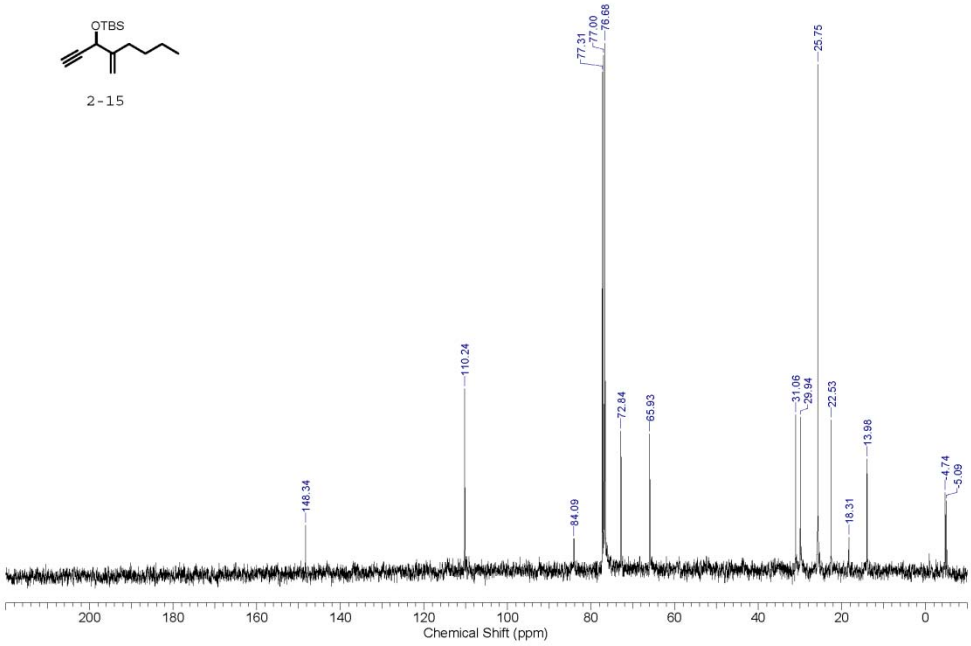

TMS
O
2-14a
2.27
2.29
2.25
1.41
1.39
1.37
1.32
1.30
2.07
4.73
0.24
7.25
6.50
5.98
5.98
2.29
2.27
2.25
1.41
1.39
1.37
1.37
1.33
1.32
1.30
0.90
0.88
0.87
0.25
0.23
0.98
1.00
2.07
4.73
3.58
8.75
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

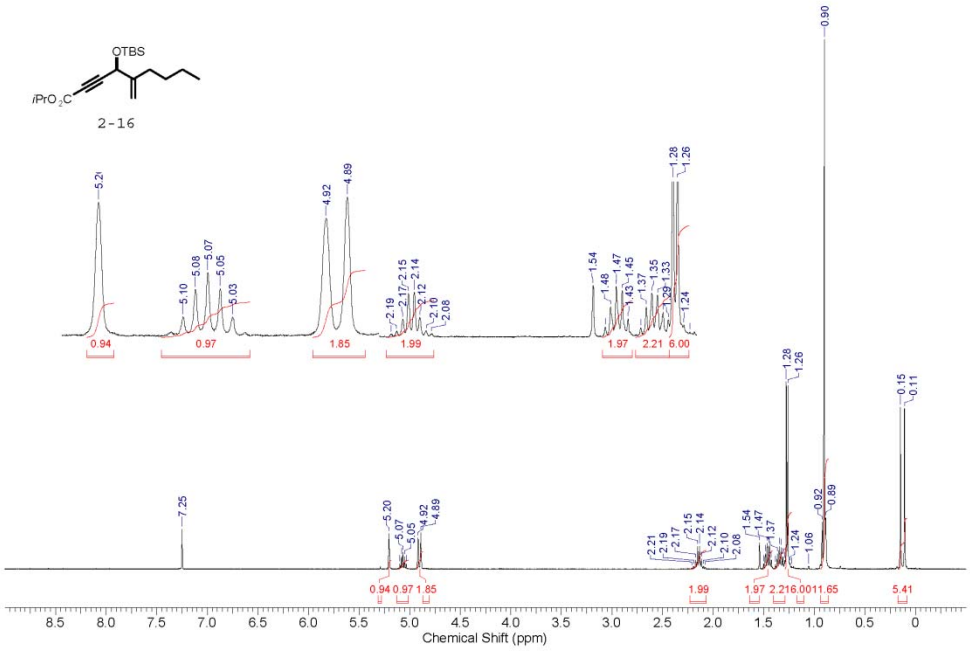

TMS
O
2-14a
-0.73
29.03
30.23
22.34
13.84
77.32
77.00
76.69
130.49
149.24
100.33
98.21
179.65
200 180 160 140 120 100 80 60 40 20 0
Chemical Shift (ppm)

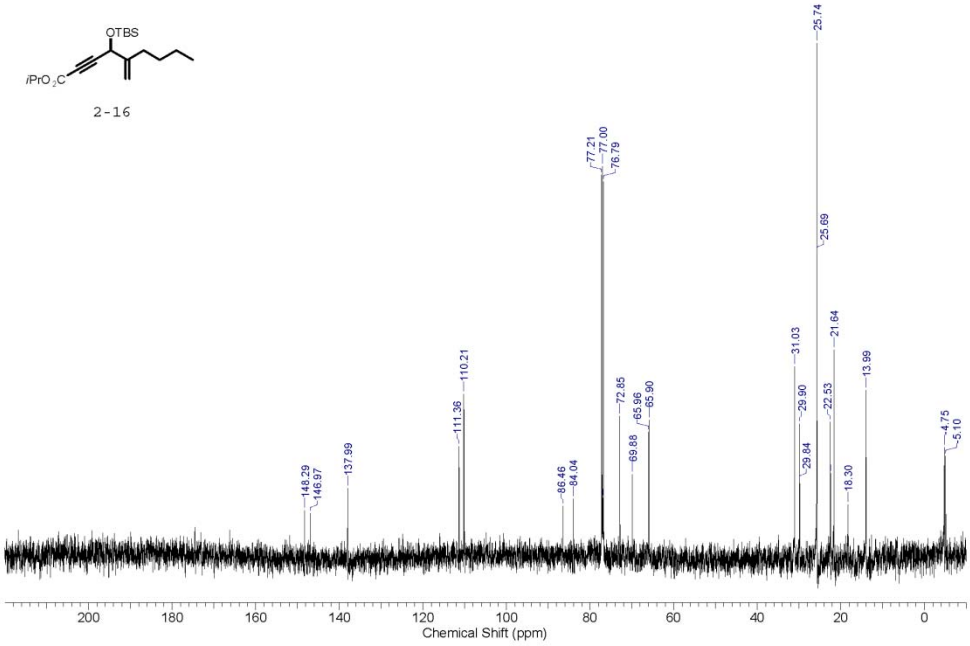

OTBS
TMS
2-14b
0.91
0.15
7.25
5.23
4.86
4.79
2.14
2.12
1.48
1.46
1.44
1.36
1.34
1.32
1.30
0.92
0.88
0.73 0.73 0.73
1.45
1.60 1.99
11.92
5.98
Chemical Shift (ppm)

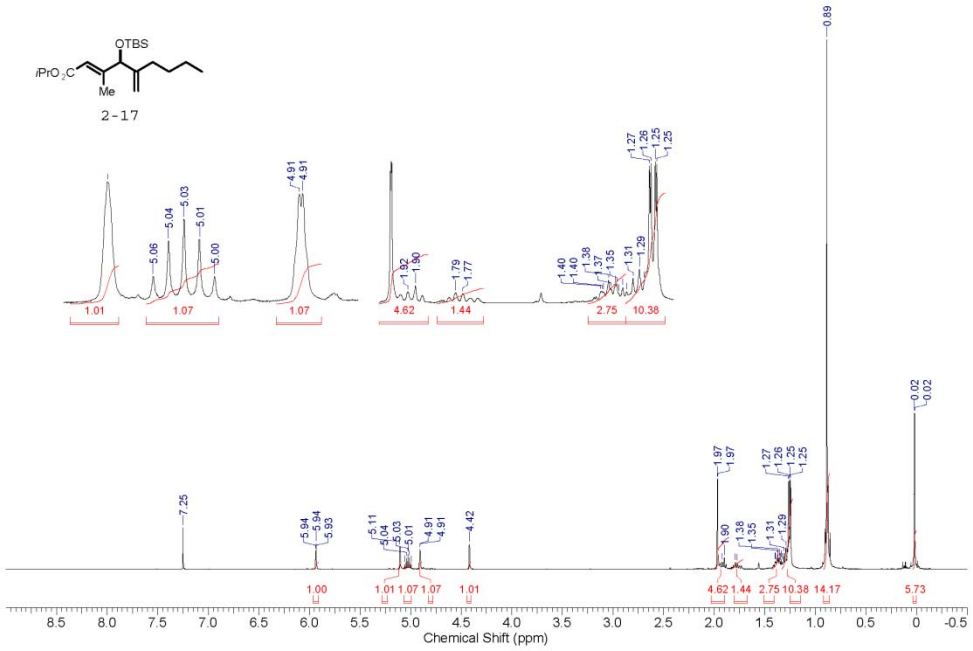

OTBS
TMS
2-14b
77.32
77.00
76.69
148.34
110.24
66.43
31.37
30.10
25.83
25.79
22.51
13.99
0.21
-4.56
-4.98
Chemical Shift (ppm)

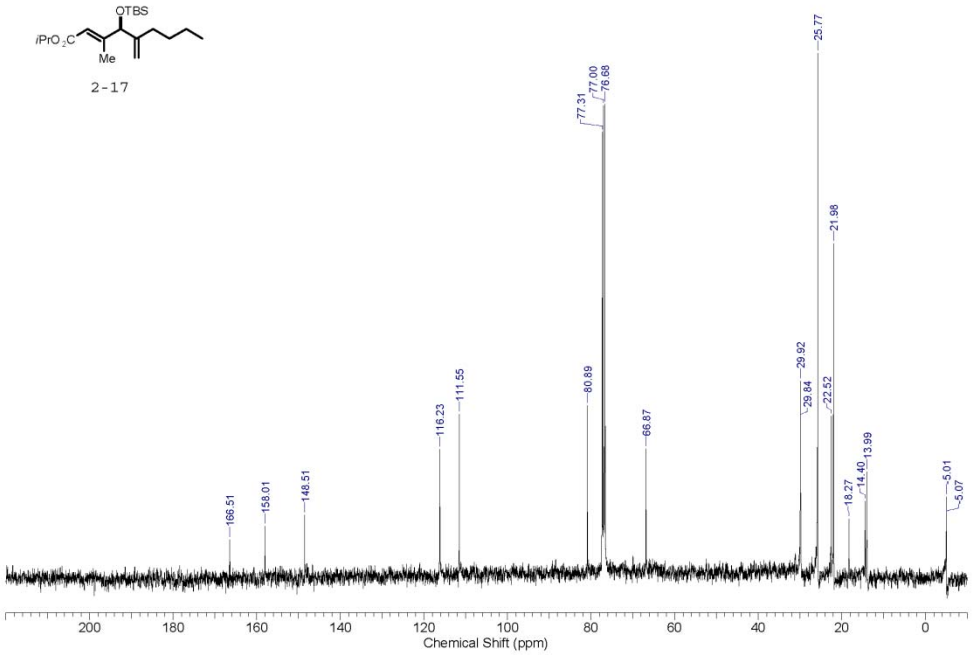

OTBS
2-15
Chemical Shift (ppm)

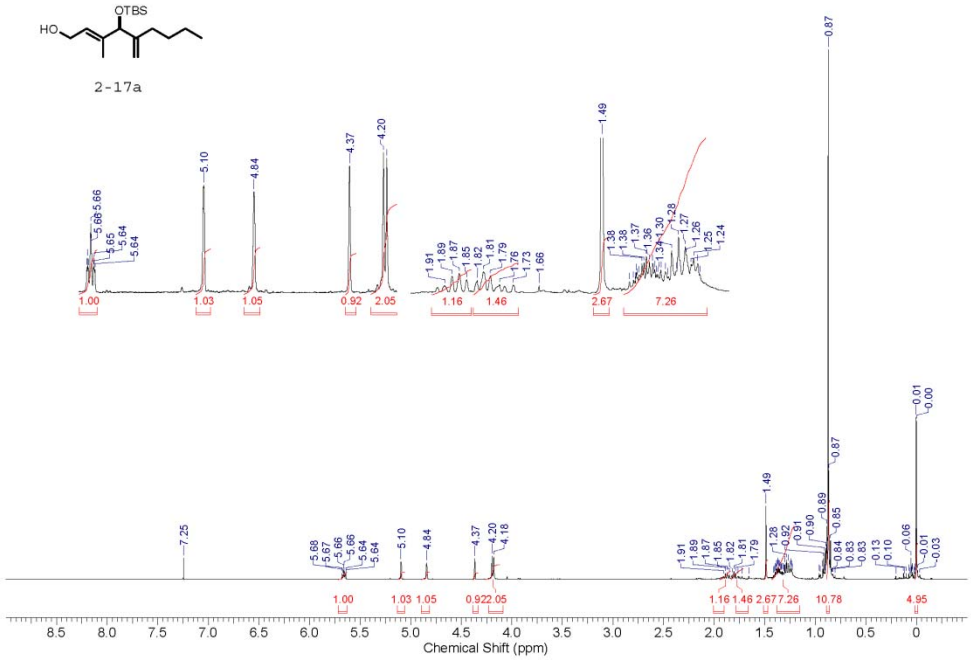

OTBS
2-15
Chemical Shift (ppm)

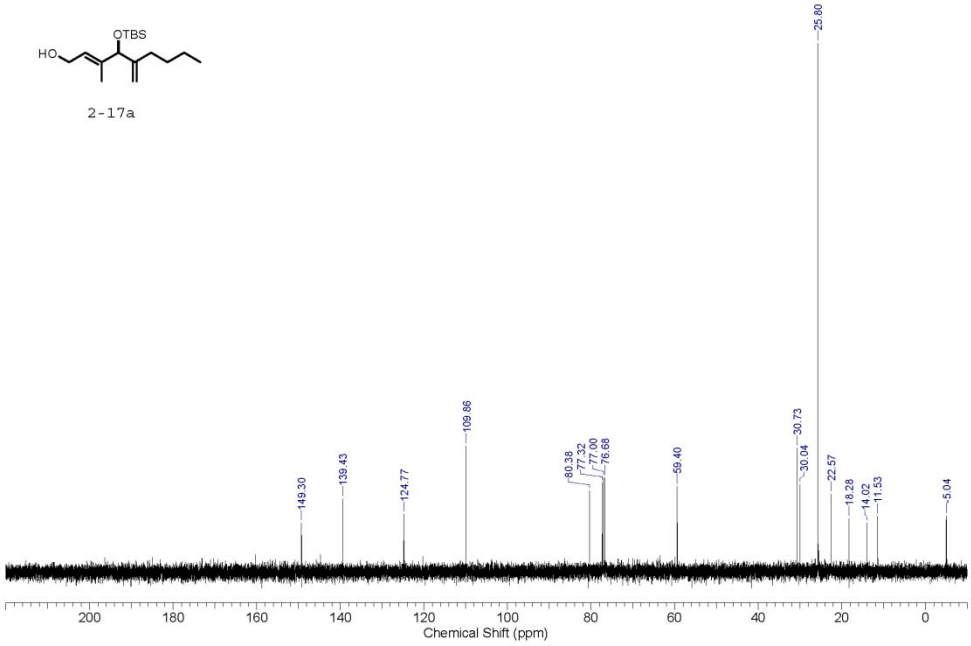

OTBS
iPrO2C
2-16
Chemical Shift (ppm)

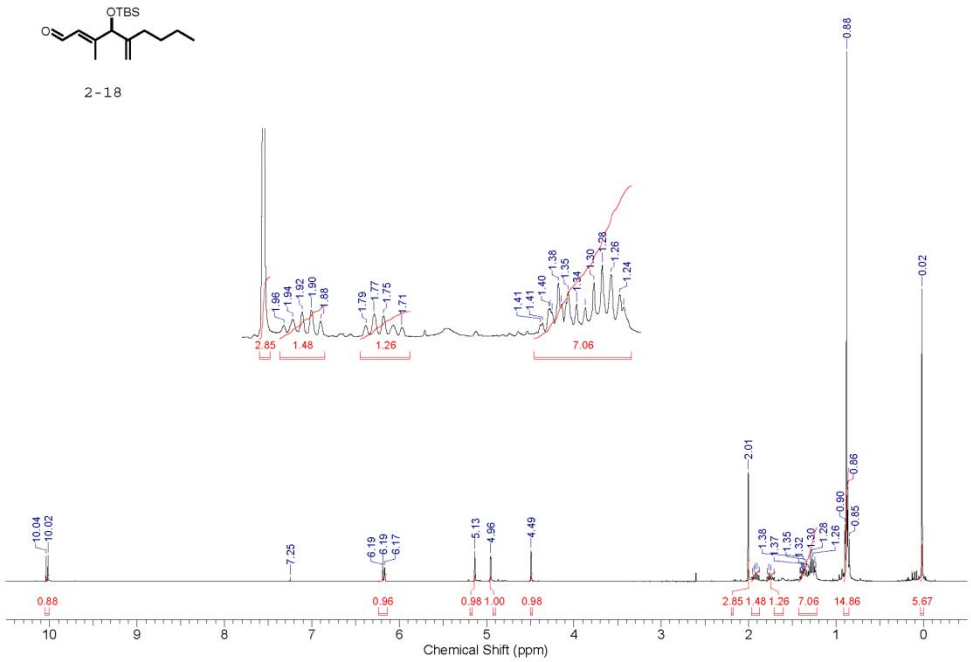

OTBS
iPrO2C
2-16
Chemical Shift (ppm)

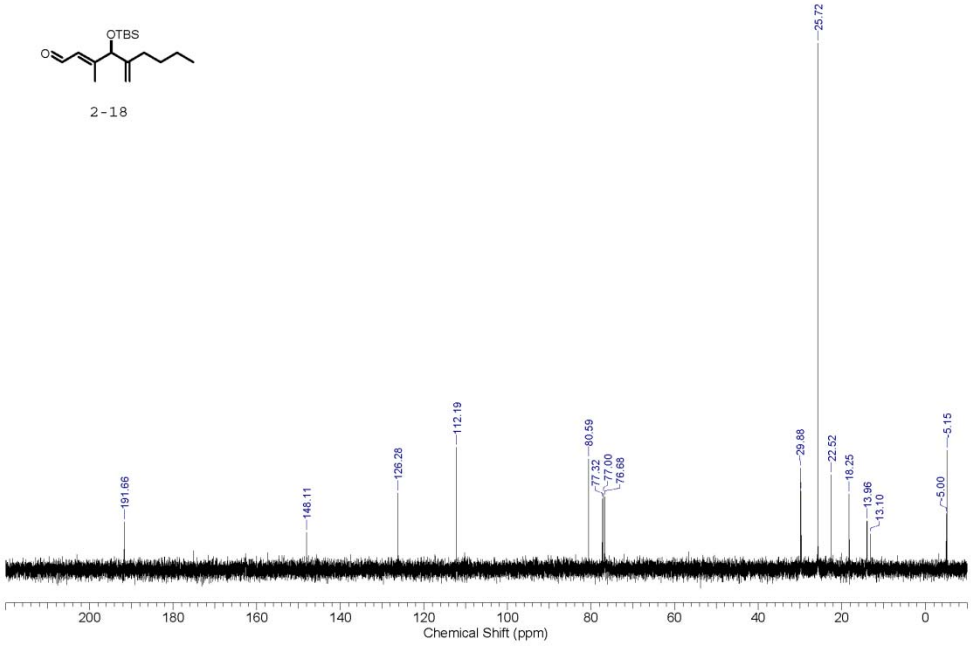

OTBS
iPrO2C
Me
2-17
Chemical Shift (ppm)

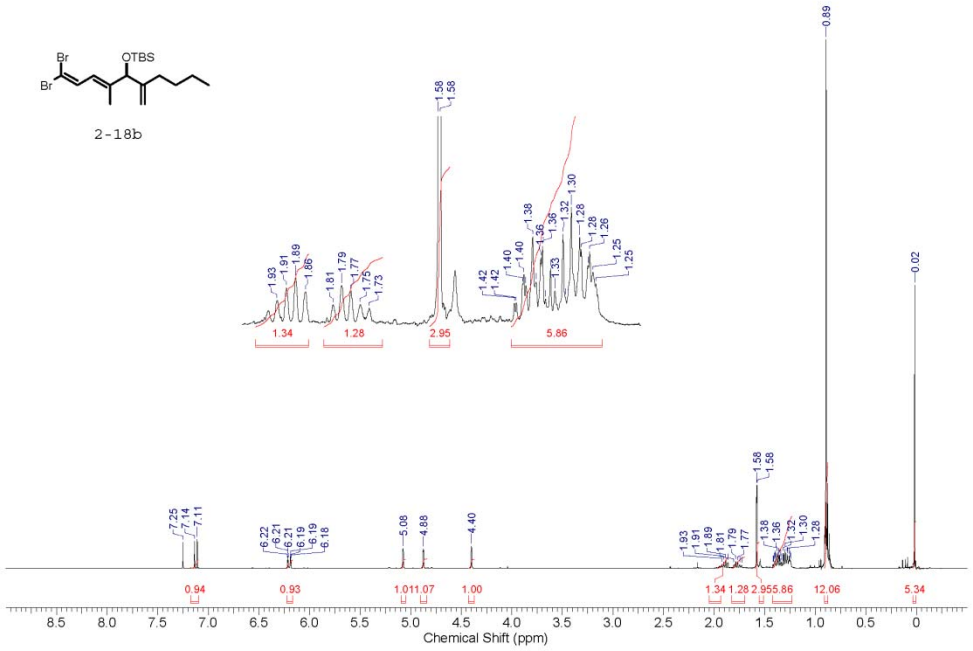

OTBS
iPrO2C
Me
2-17
Chemical Shift (ppm)

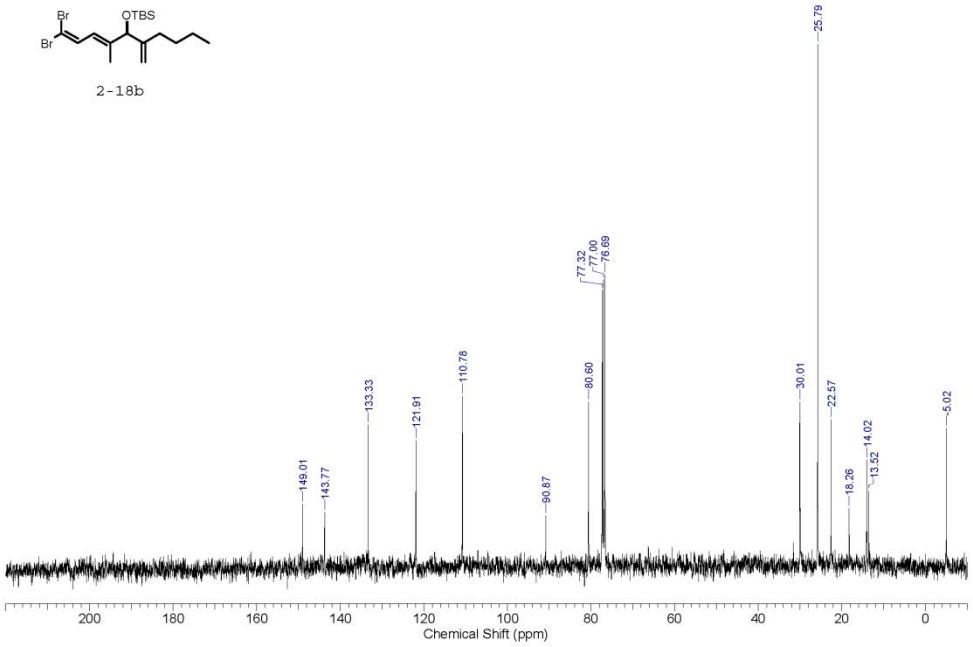

OTBS
HO
2-17a
Chemical Shift (ppm)

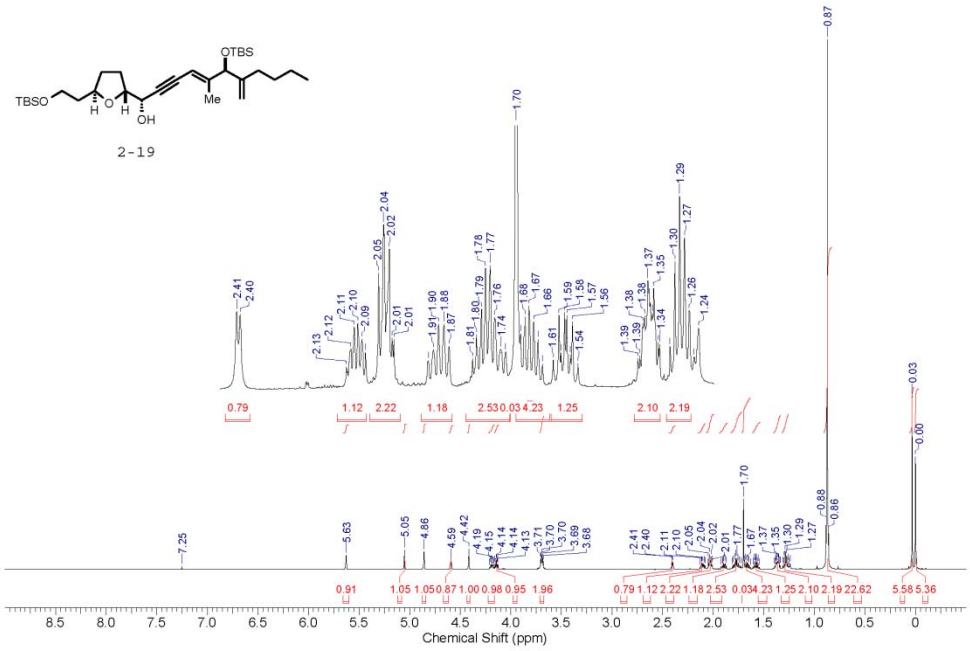

OTBS
HO
2-17a
Chemical Shift (ppm)

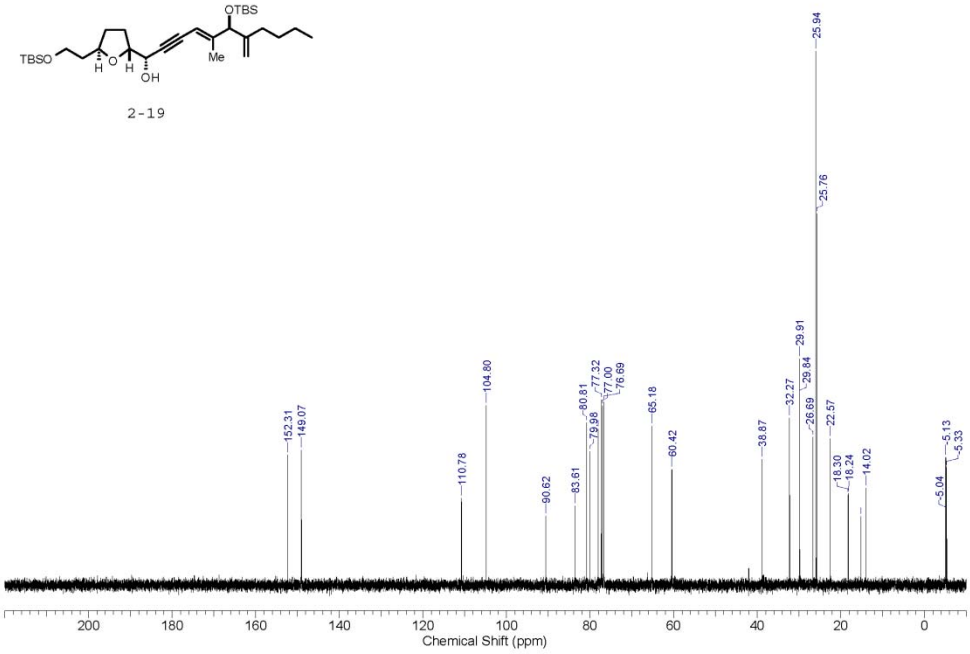

OTBS
O
2-18
10.04
10.02
7.25
6.19
6.19
6.17
5.13
4.96
4.49
2.01
1.38
1.37
1.35
1.32
1.30
1.28
1.26
0.90
0.86
0.85
0.88
0.02
0.88
0.96
0.98
1.00
0.98
2.85
1.48
1.26
7.06
14.86
5.67
Chemical Shift (ppm)

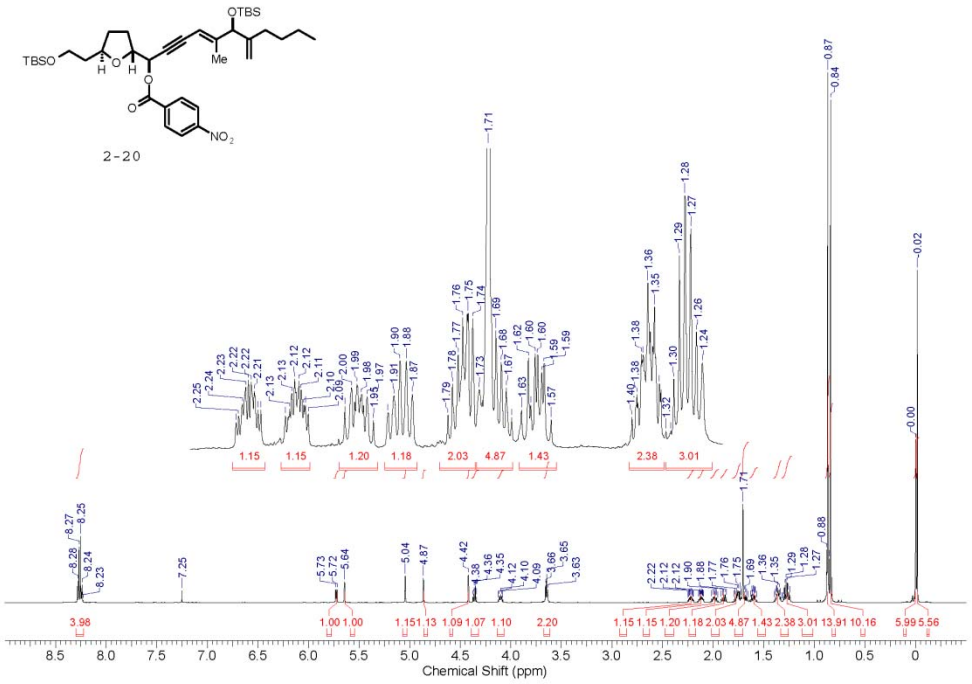

OTBS
O
2-18
191.66
148.11
126.28
112.19
80.59
77.32
77.00
76.68
29.88
25.72
22.52
18.25
13.96
13.10
5.00
5.15
Chemical Shift (ppm)

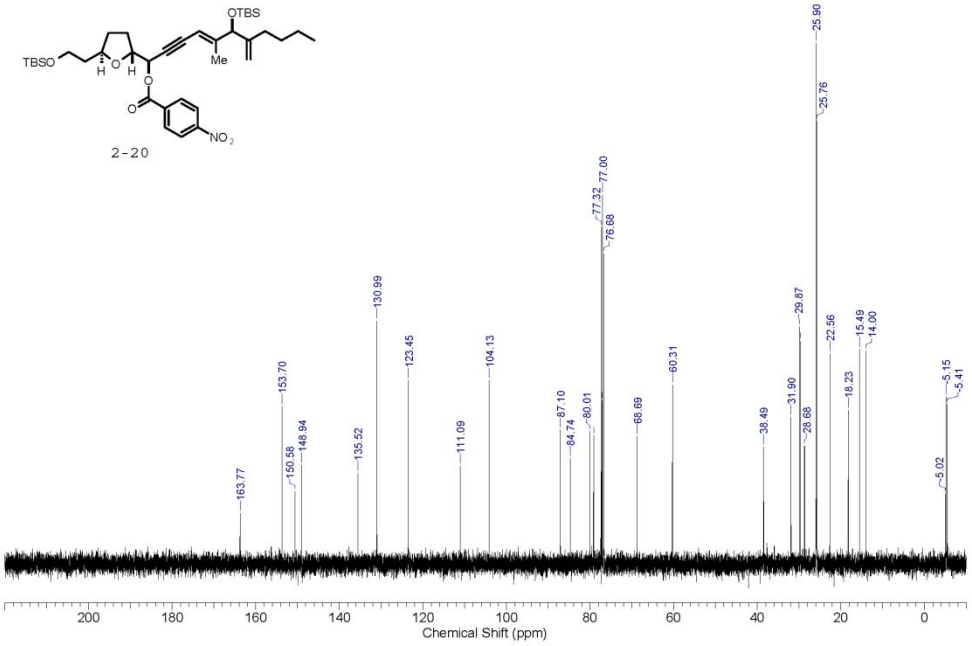

Br
Br
OTBS
2-18b
Chemical Shift (ppm)

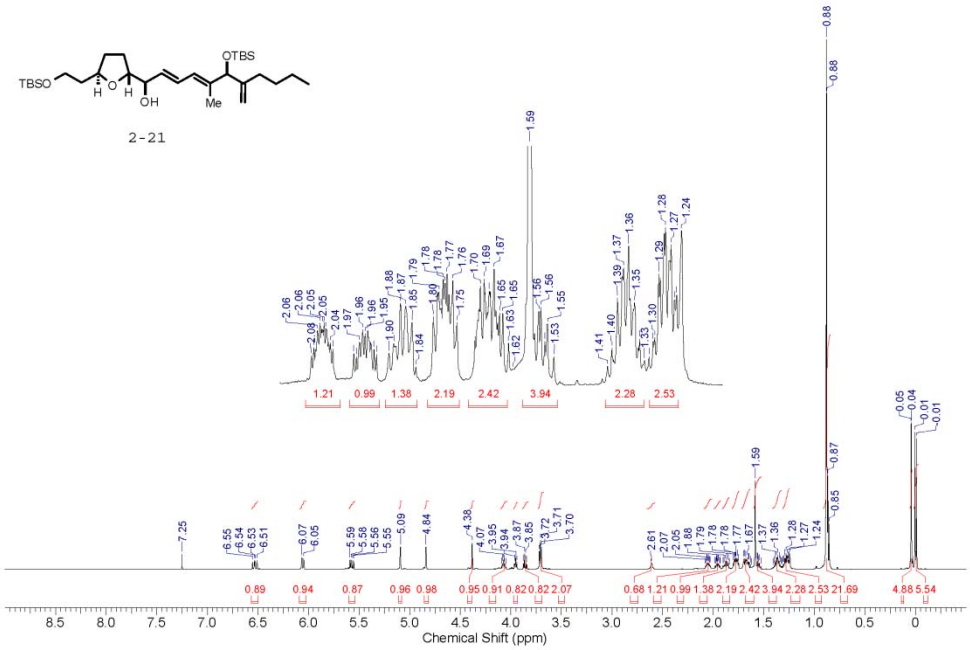

Br
Br
OTBS
2-18b
Chemical Shift (ppm)

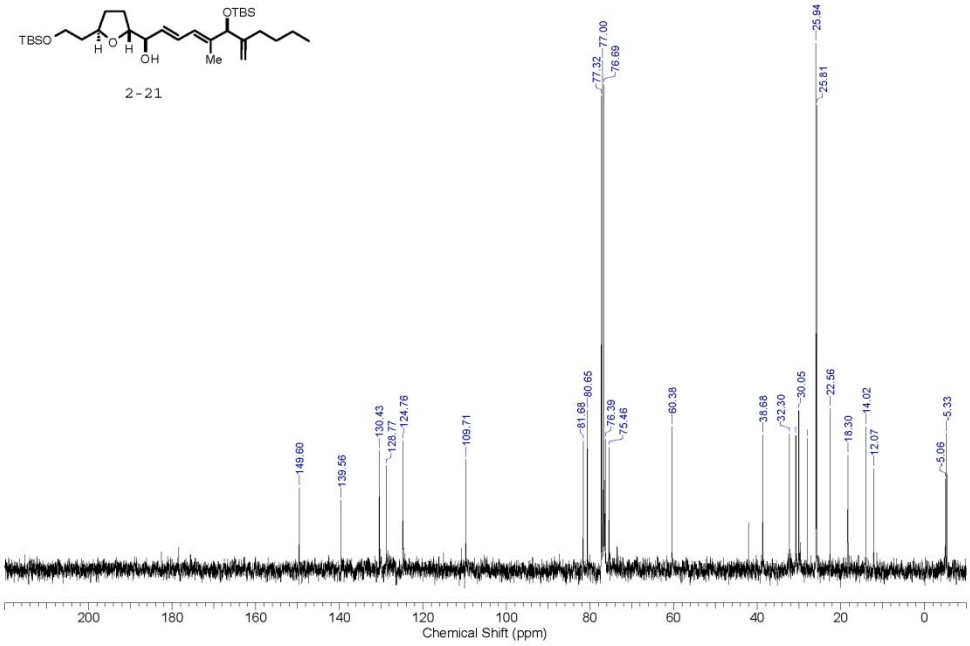

TBSO
OTBS
Me
H
O
H
OH
2-19
Chemical Shift (ppm)

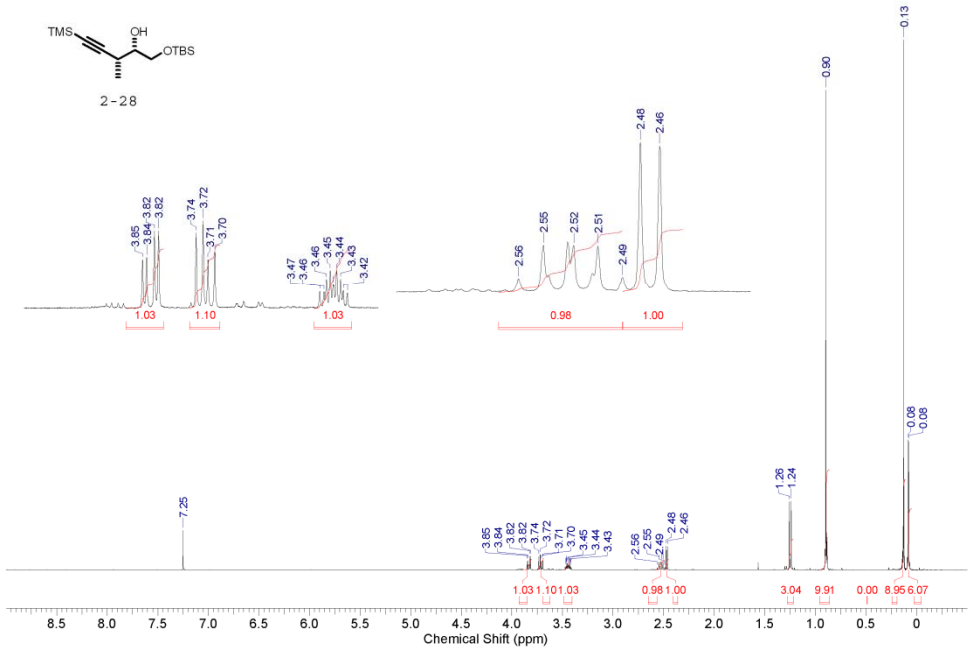

TBSO
OTBS
Me
H
O
H
OH
2-19
Chemical Shift (ppm)

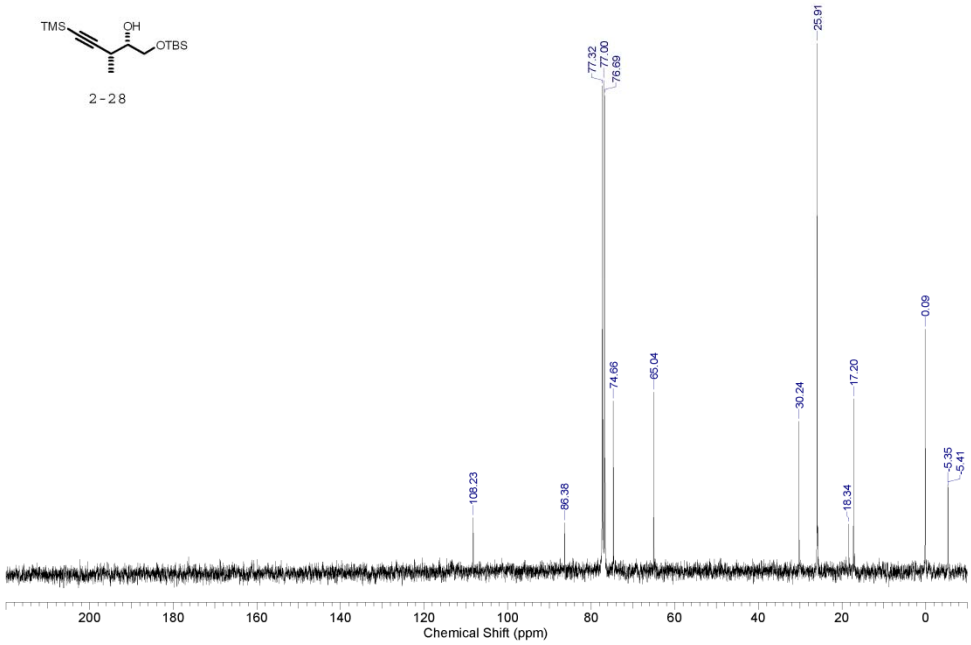

OTBS
TBSO
Me
NO2
2-20
Chemical Shift (ppm)

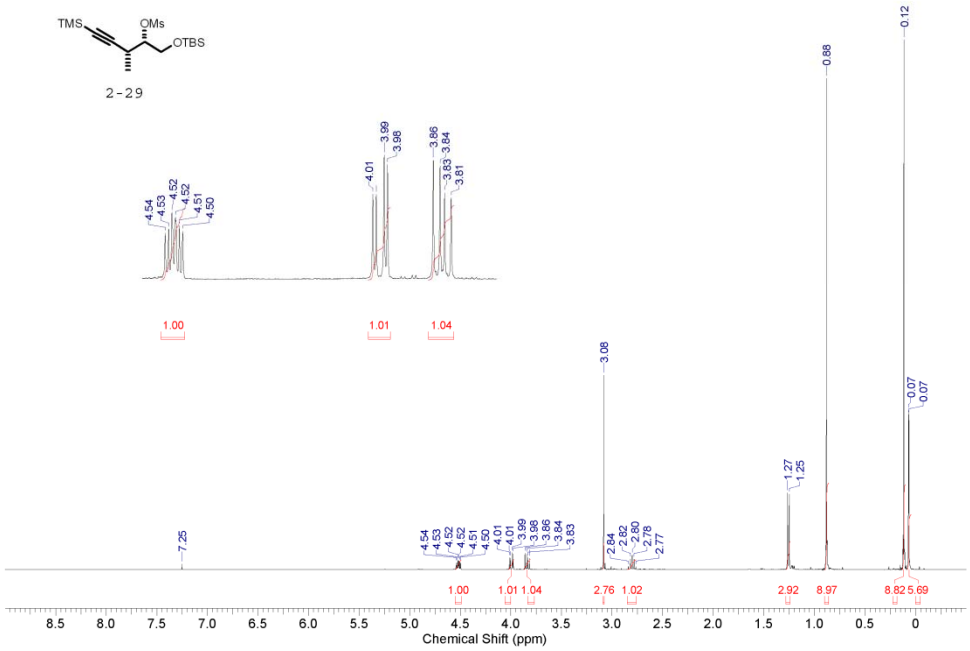

OTBS
TBSO
Me
NO2
2-20
Chemical Shift (ppm)

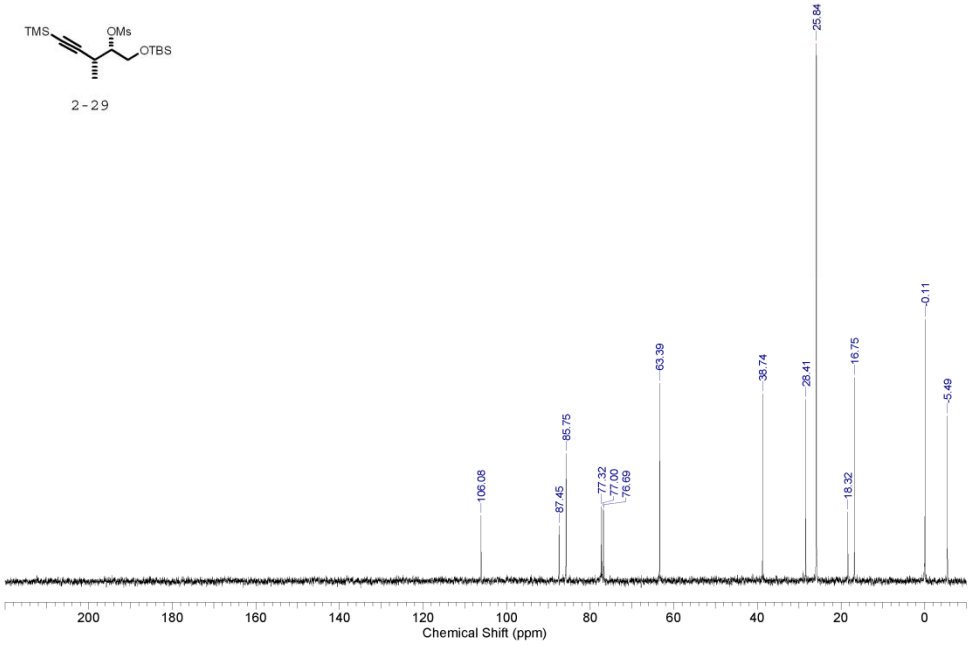

TBSO
OTBS
OH
Me
H
O
2-21
Chemical Shift (ppm)

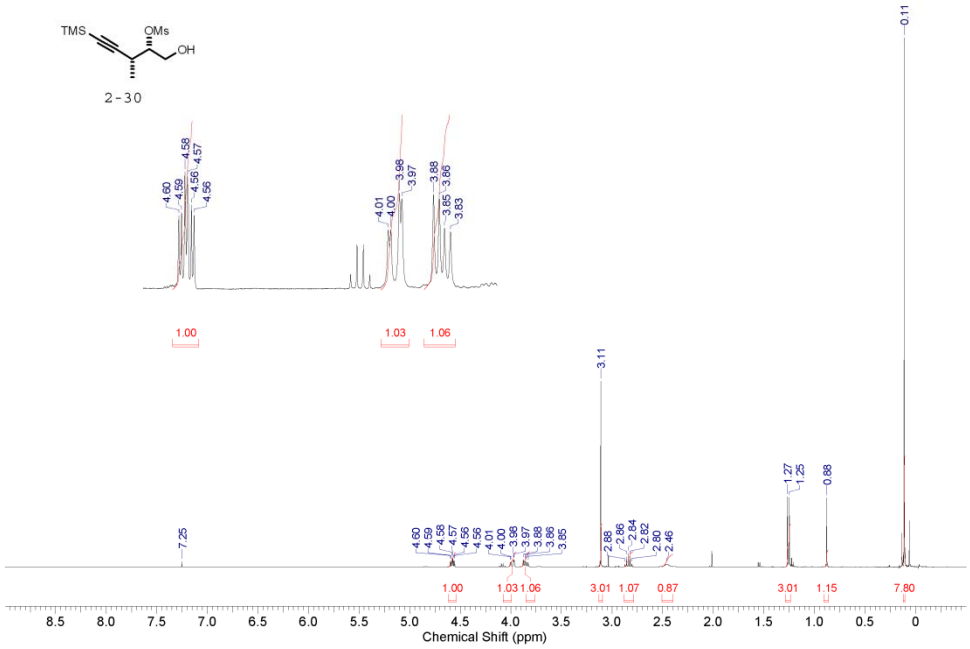

TBSO
OTBS
OH
Me
H
O
2-21
Chemical Shift (ppm)

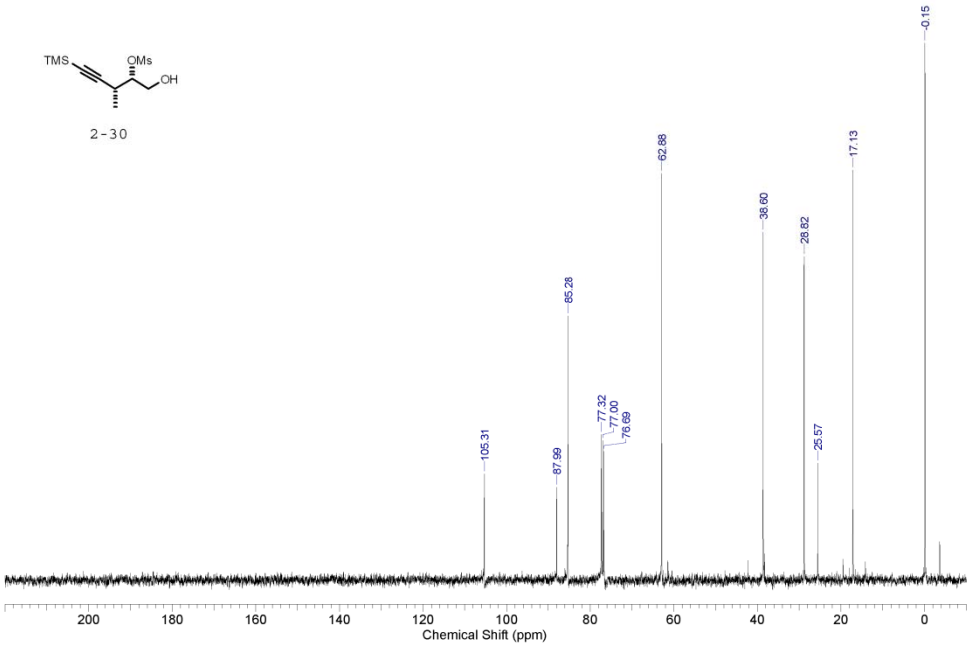

TMS
OH
OTBS
2-28
Chemical Shift (ppm)

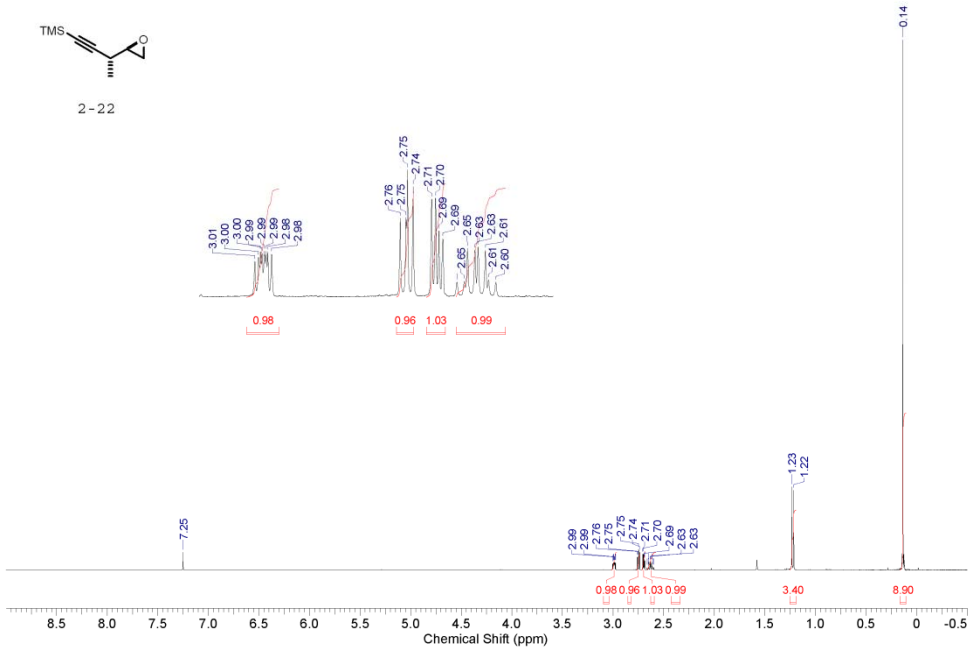

TMS
OH
OTBS
2-28
Chemical Shift (ppm)

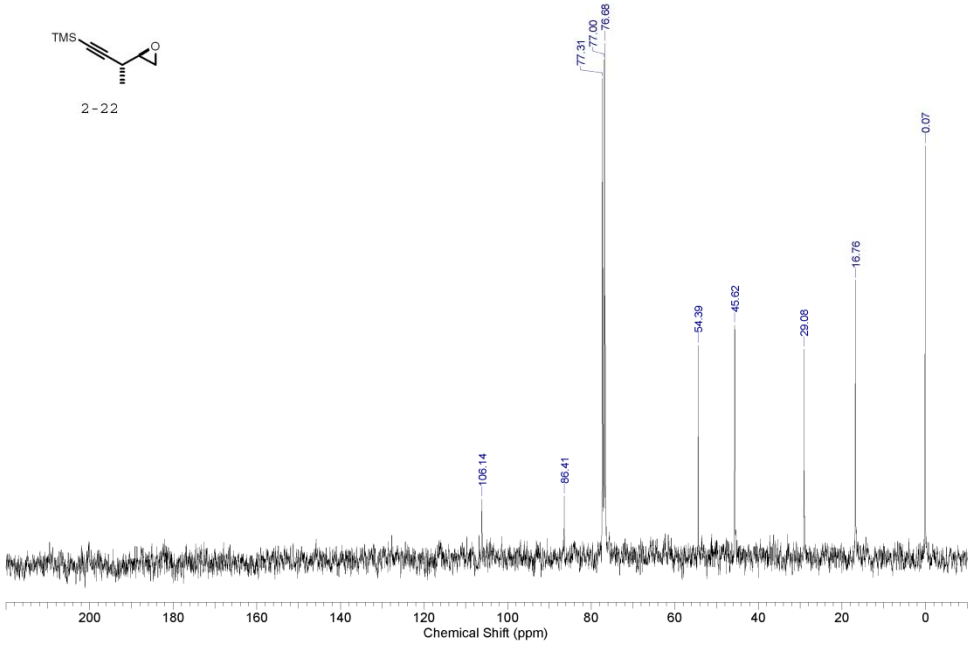

TMS
OMs
OTBS
2-29
Chemical Shift (ppm)

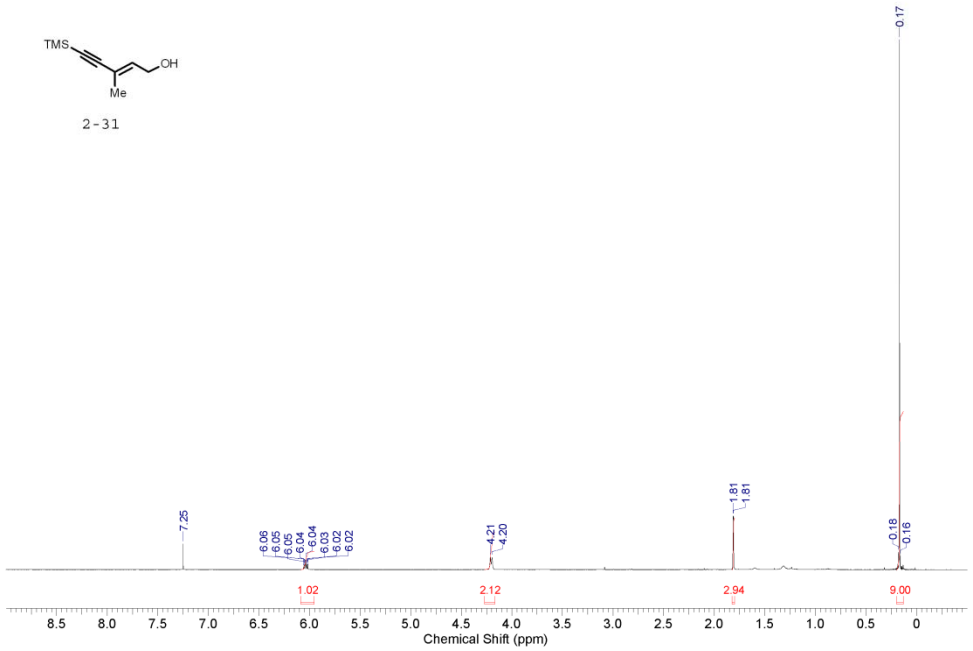

TMS
OMs
OTBS
2-29
Chemical Shift (ppm)

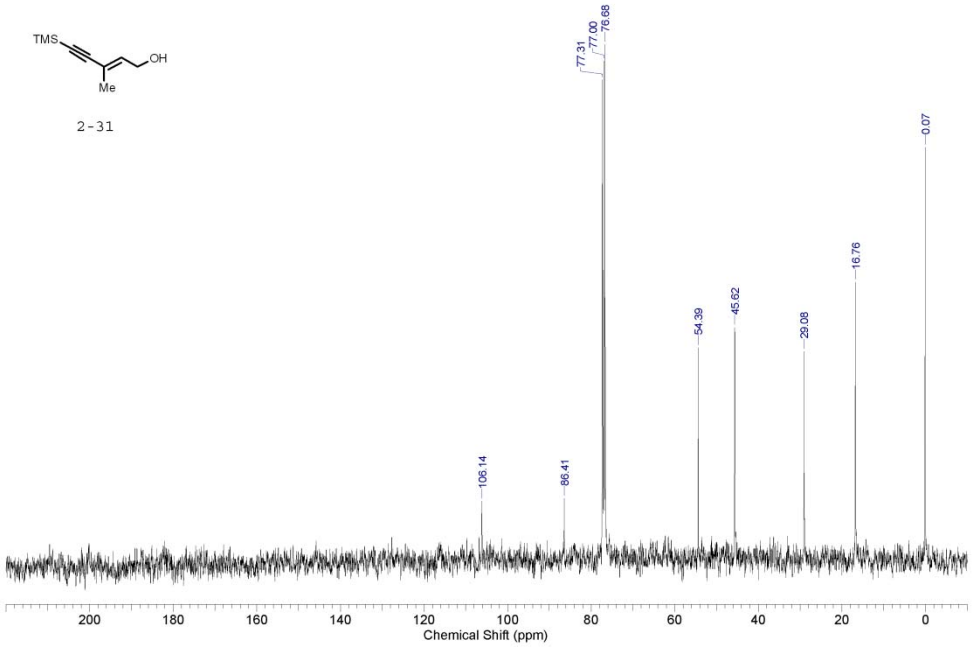

TMS
OMs
OH
2-30
4.60
4.59
4.58
4.57
4.56
4.55
4.01
4.00
3.98
3.97
3.88
3.86
3.85
3.83
1.00
1.03
1.06
3.11
1.27
1.25
0.88
0.11
7.25
2.88
2.86
2.84
2.82
2.80
2.46
1.00
1.03
1.06
3.01
1.07
0.87
3.01
1.15
7.80
Chemical Shift (ppm)

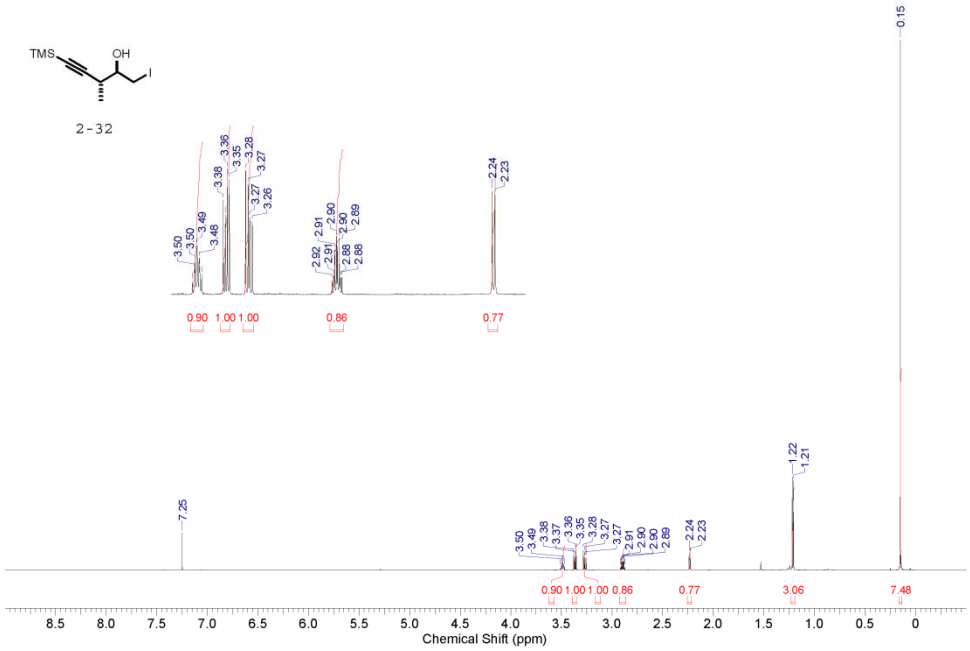

TMS
OMs
OH
2-30
0.15
62.88
38.60
28.82
17.13
65.28
77.32
77.00
76.68
105.31
87.99
25.57
Chemical Shift (ppm)

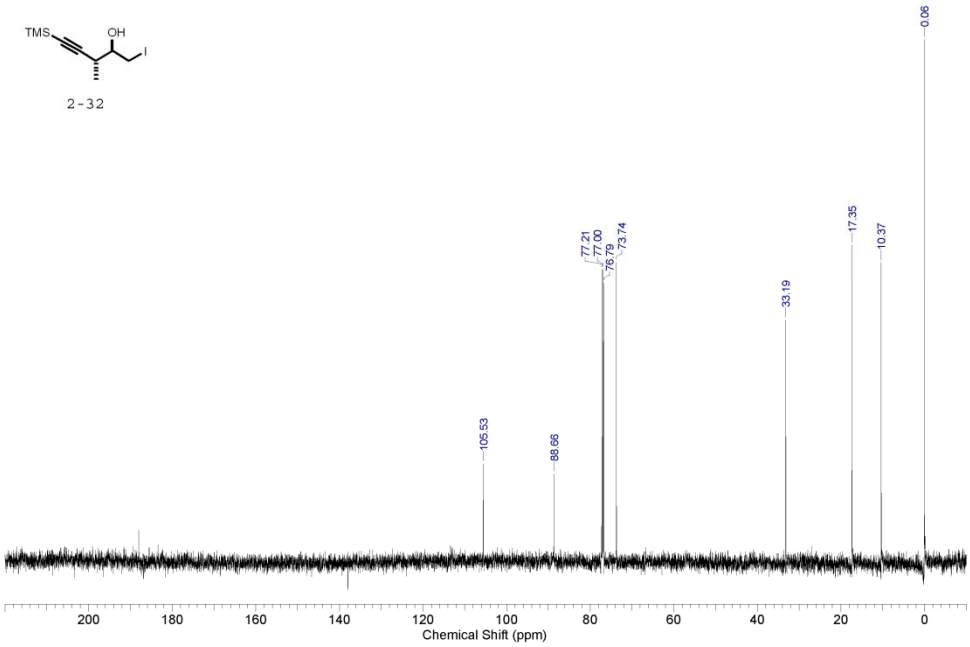

TMS
2-22
Chemical Shift (ppm)

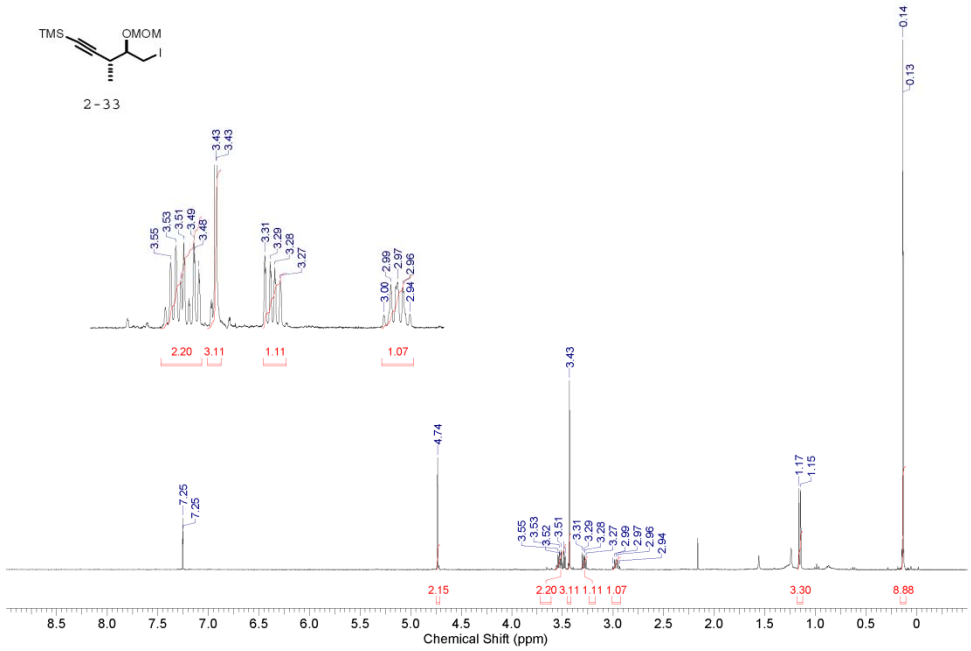

TMS
2-22
Chemical Shift (ppm)

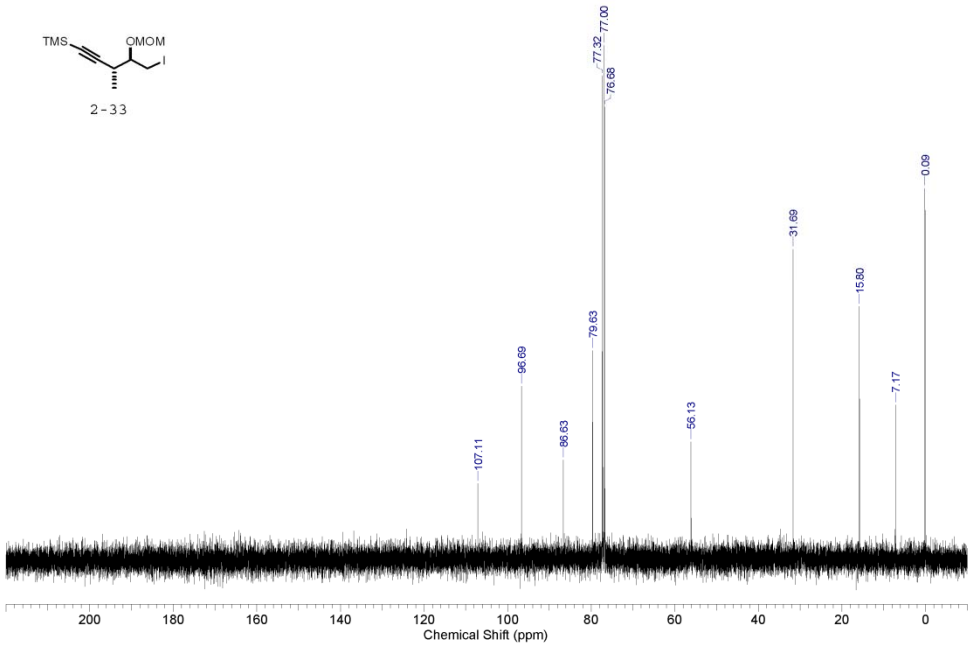

TMS
OH
Me
2-31
0.17
7.25
6.06
6.05
6.05
6.04
6.04
6.03
6.02
6.02
4.21
4.20
1.81
1.81
0.18
0.16
1.02
2.12
2.94
9.00
Chemical Shift (ppm)

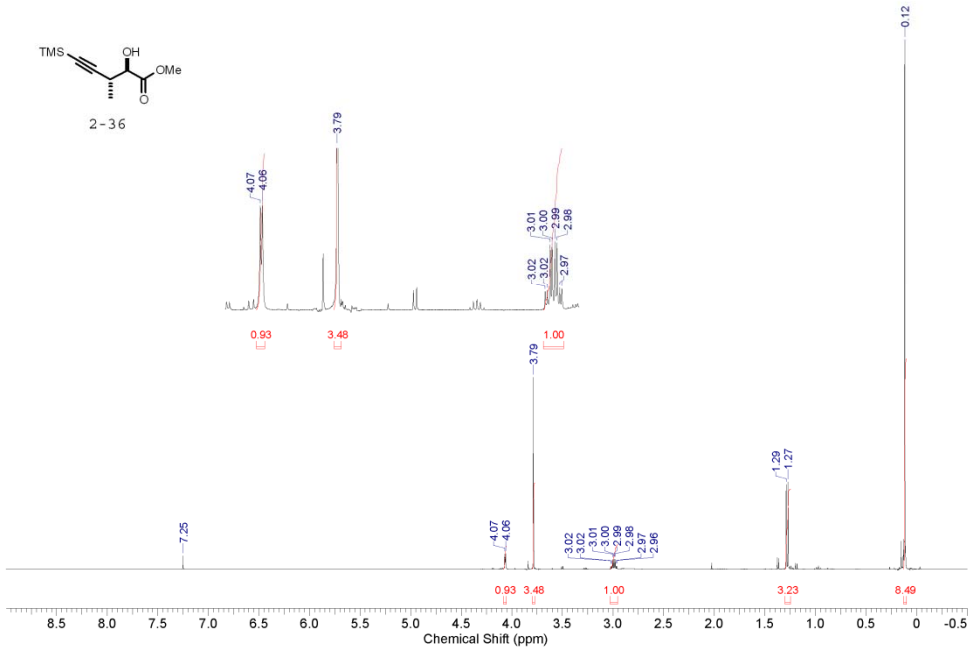

TMS
OH
Me
2-31
77.31
77.00
76.68
106.14
86.41
54.39
45.62
29.08
16.76
0.07
Chemical Shift (ppm)

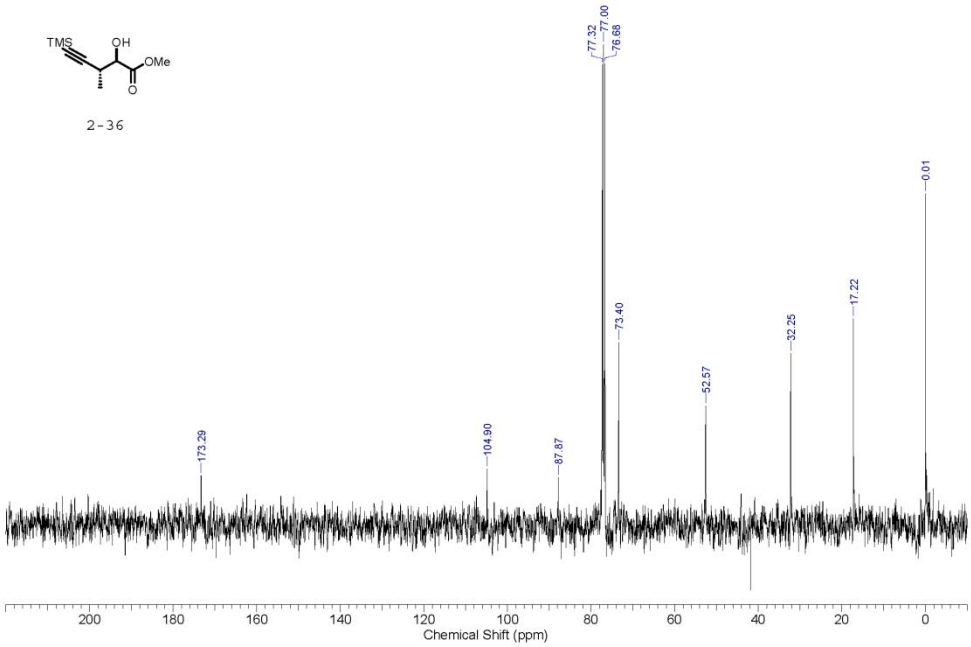

TMS
OH
I
2-32
0.15
7.25
1.22
1.21
2.24
2.23
3.50
3.49
3.48
3.38
3.37
3.36
3.35
3.28
3.27
3.26
2.92
2.91
2.90
2.89
2.88
0.90 1.00 1.00 0.86 0.77 3.06 7.48
Chemical Shift (ppm)

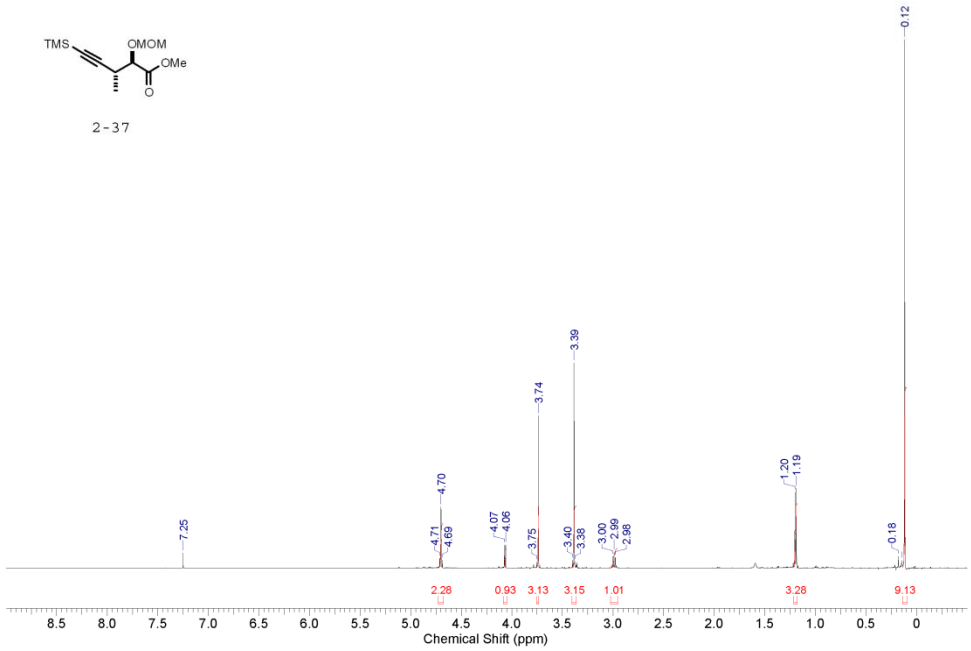

TMS
OH
I
2-32
0.06
77.21
77.00
76.79
73.74
105.53
88.66
33.19
17.35
10.37
Chemical Shift (ppm)

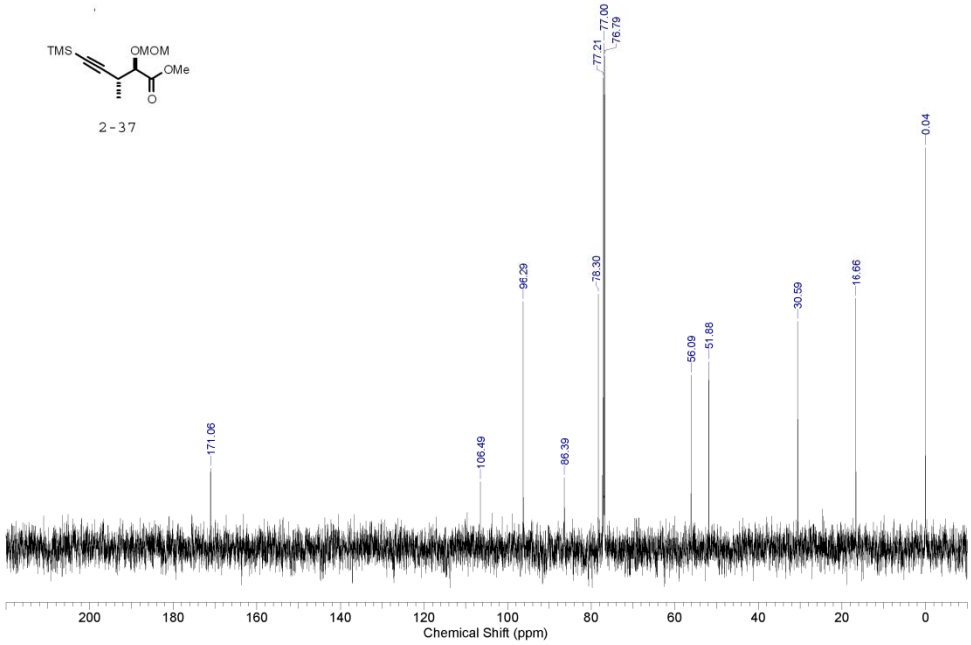

TMS
OMOM
I
2-33
Chemical Shift (ppm)

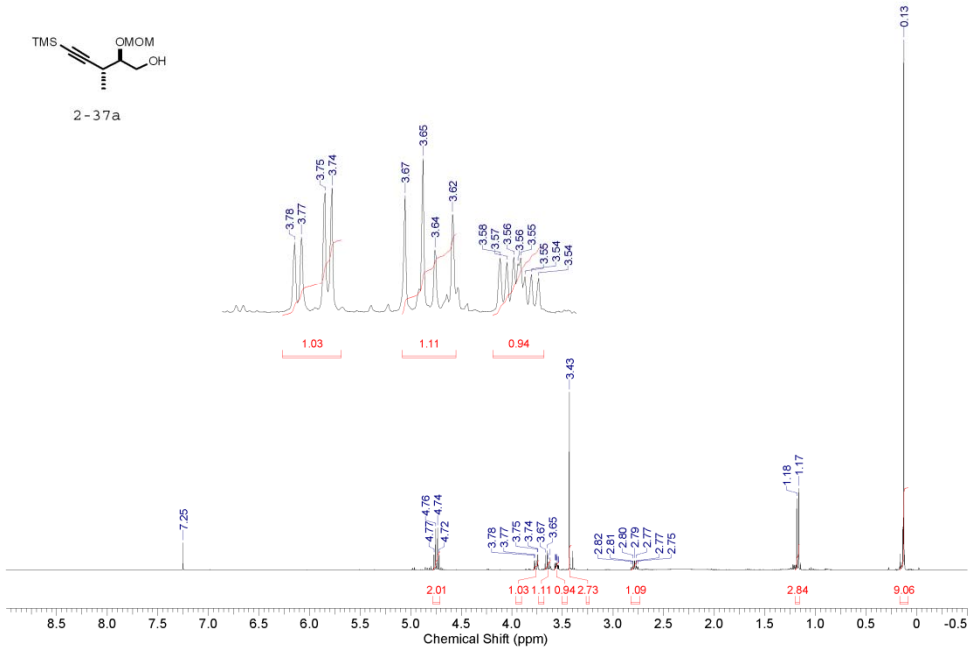

TMS
OMOM
I
2-33
Chemical Shift (ppm)

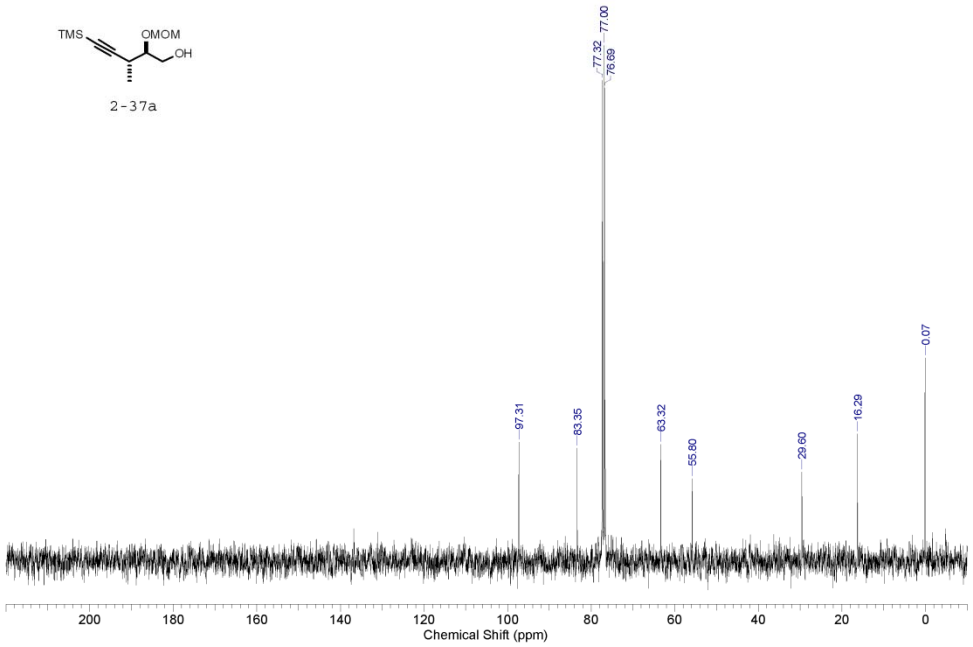

TMS
OH
OMe
O
2-36
Chemical Shift (ppm)

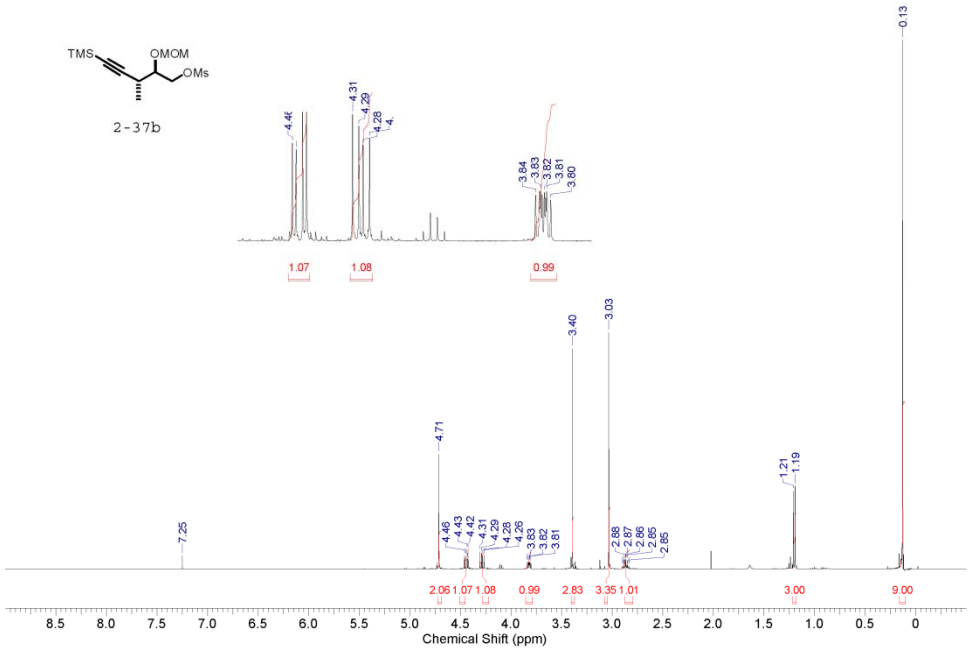

TMS
OH
OMe
O
2-36
Chemical Shift (ppm)

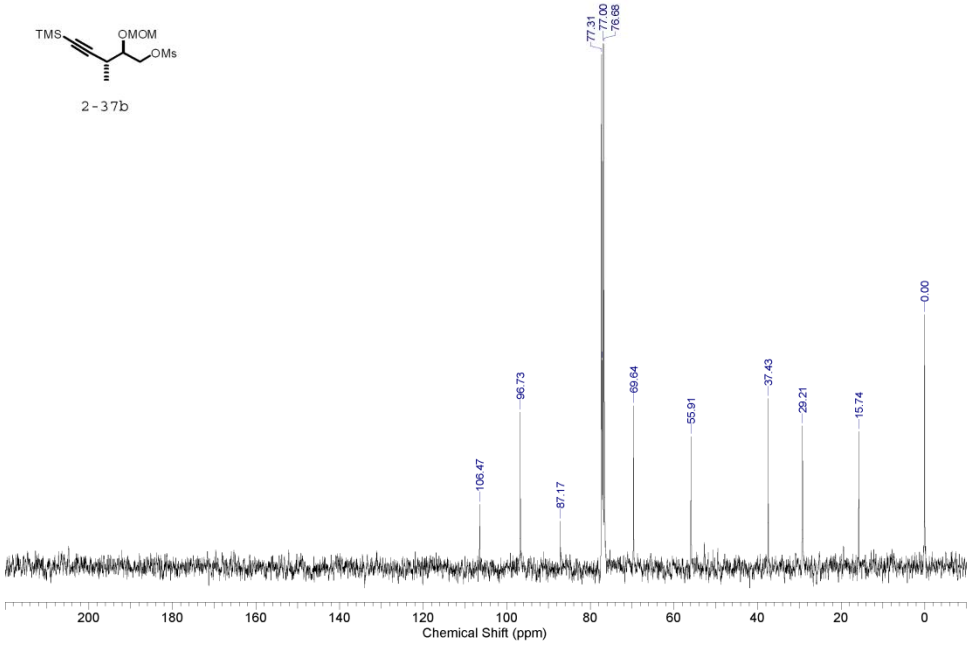

TMS
OMOM
OMe
O
2-37
7.25
4.71
4.70
4.69
4.07
4.06
3.75
3.74
3.40
3.39
3.38
3.00
2.99
2.98
1.20
1.19
0.18
0.12
2.28
0.93
3.13
3.15
1.01
3.28
9.13
Chemical Shift (ppm)

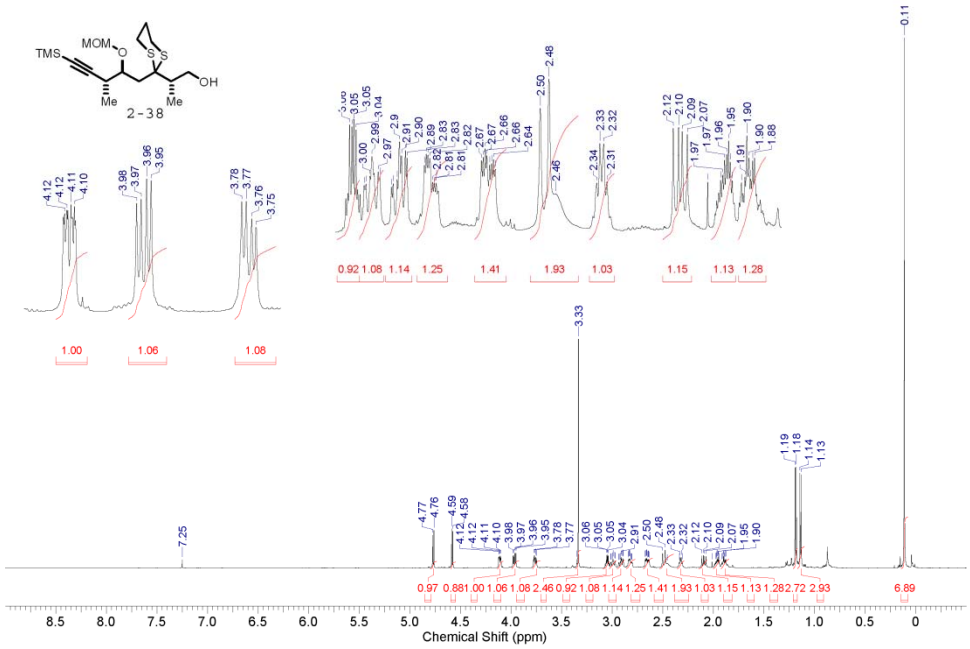

TMS
OMOM
OMe
O
2-37
171.06
106.49
96.29
86.39
78.30
77.21
77.00
76.79
56.09
51.88
30.59
16.66
0.04
Chemical Shift (ppm)

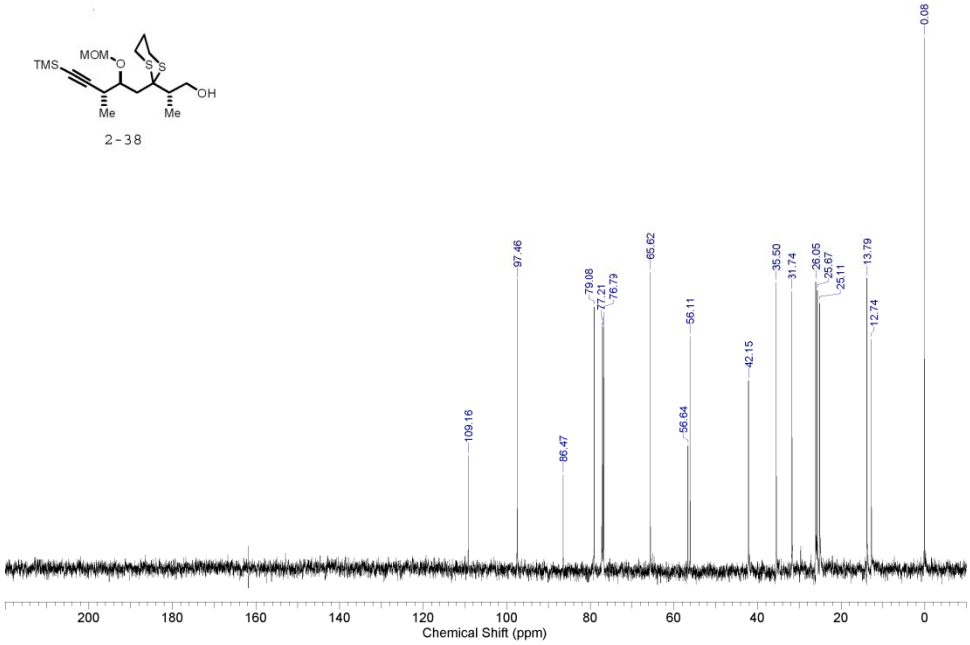

TMS
OMOM
OH
2-37a
Chemical Shift (ppm)

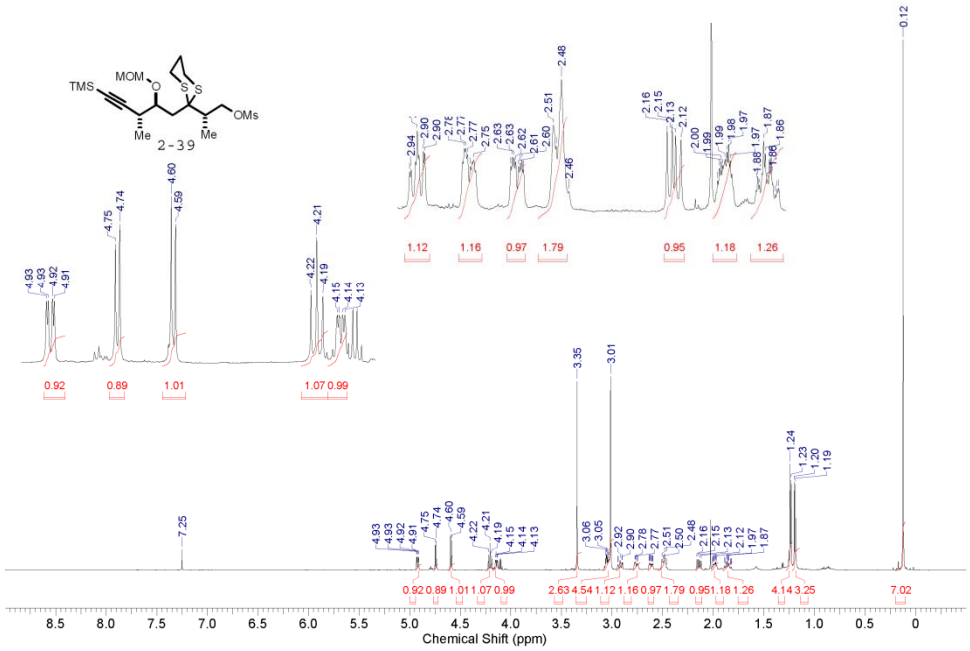

TMS
OMOM
OH
2-37a
Chemical Shift (ppm)

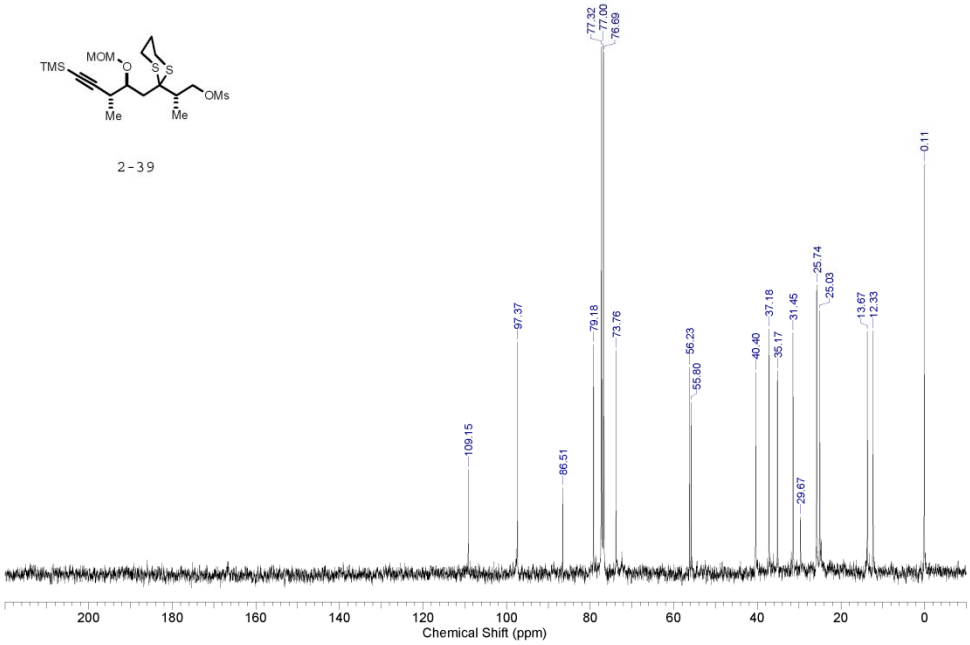

TMS
OMOM
OMs
2-37b
Chemical Shift (ppm)

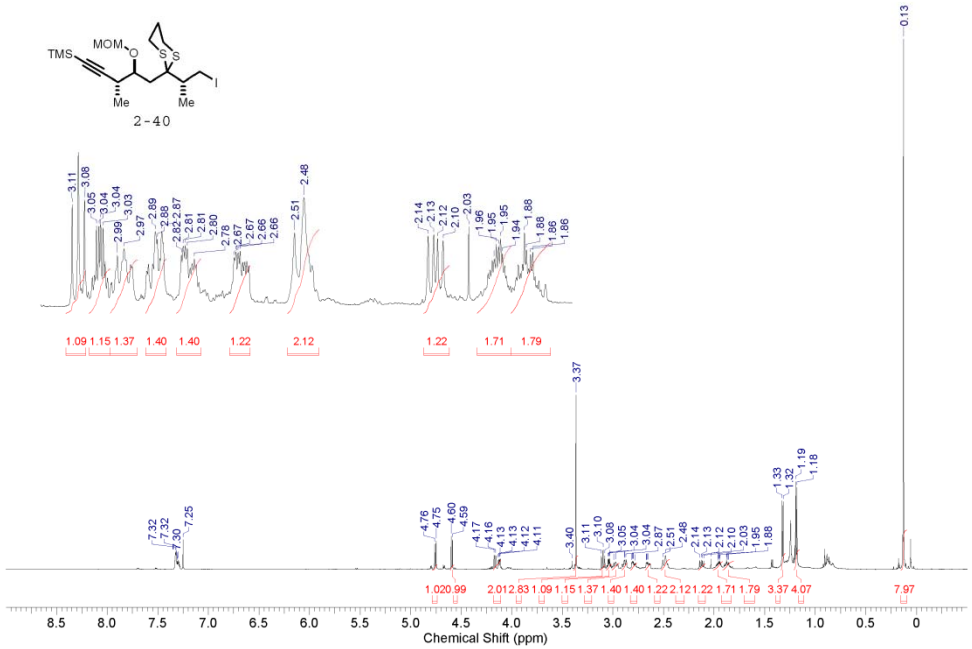

TMS
OMOM
OMs
2-37b
Chemical Shift (ppm)

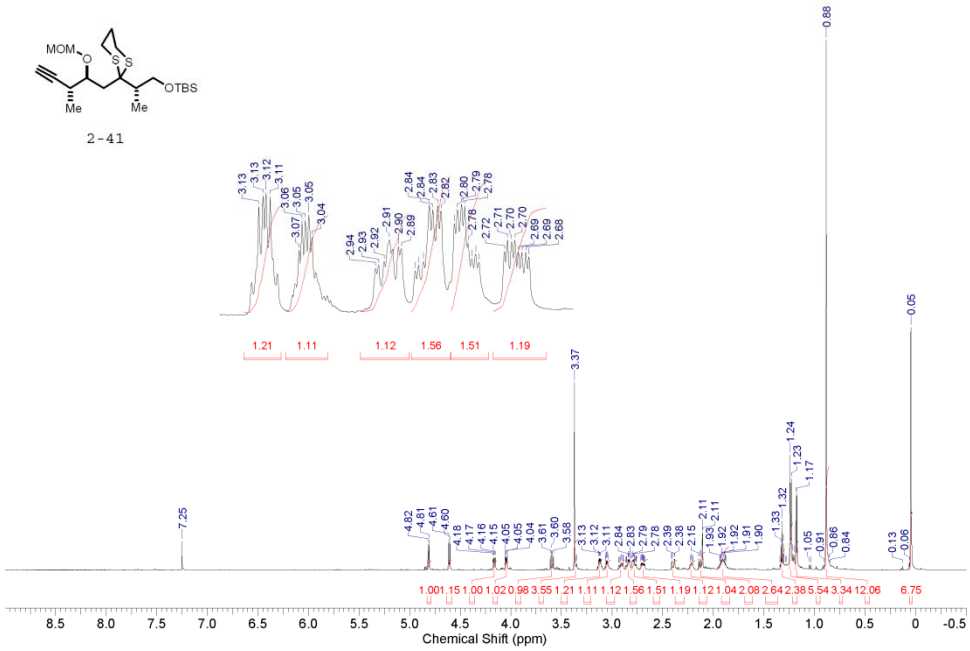

TMS
MOM
O
S
S
OH
Me
Me
2-38
Chemical Shift (ppm)

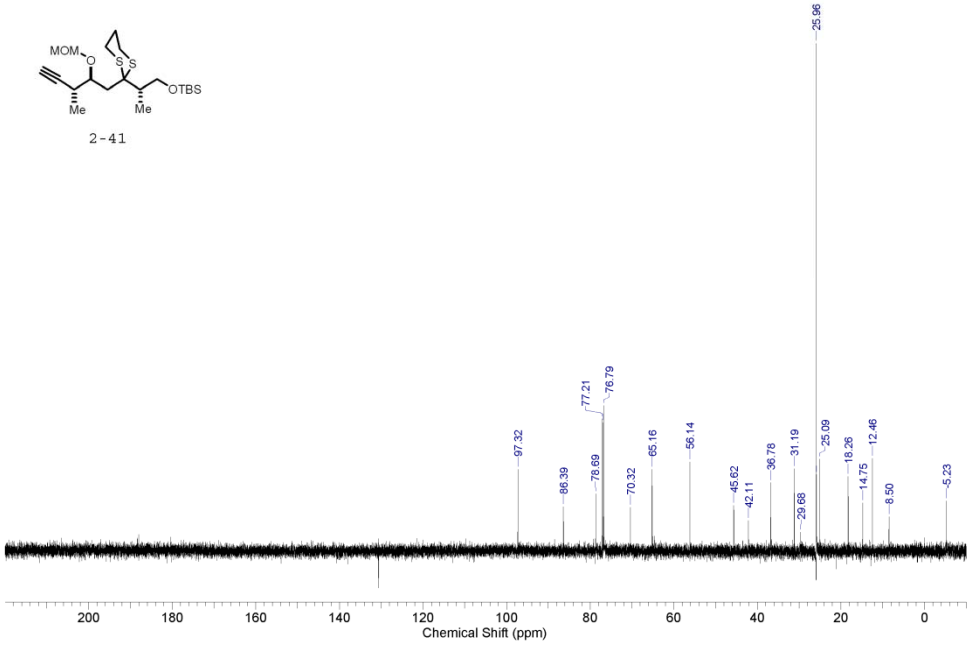

TMS
MOM
O
S
S
OH
Me
Me
2-38
Chemical Shift (ppm)

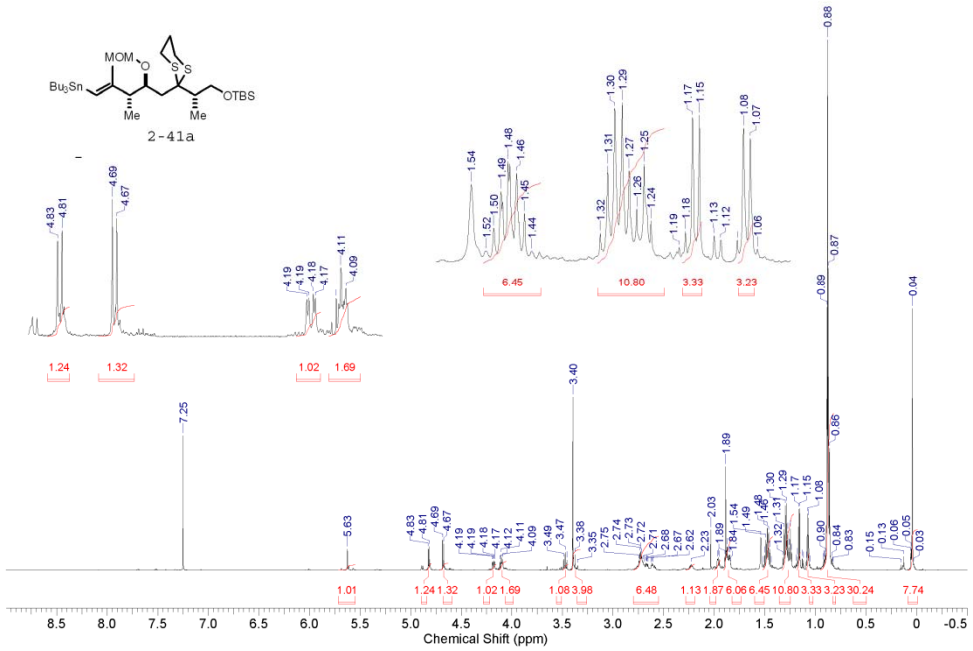

TMS
MOM
O
S
S
OMs
Me
Me
2-39
Chemical Shift (ppm)

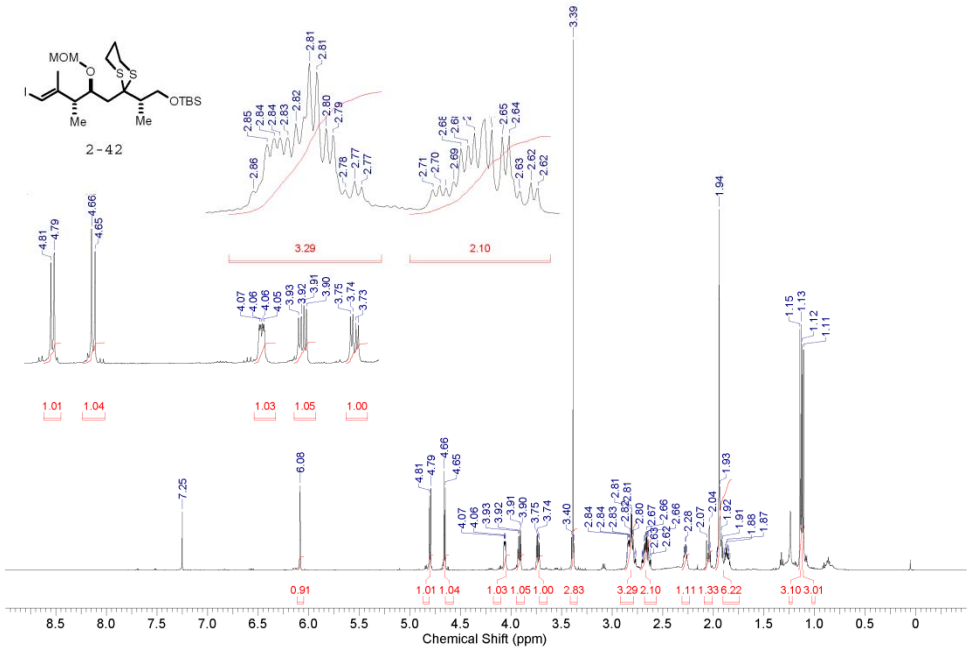

TMS
MOM
O
S
S
OMs
Me
Me
2-39
Chemical Shift (ppm)

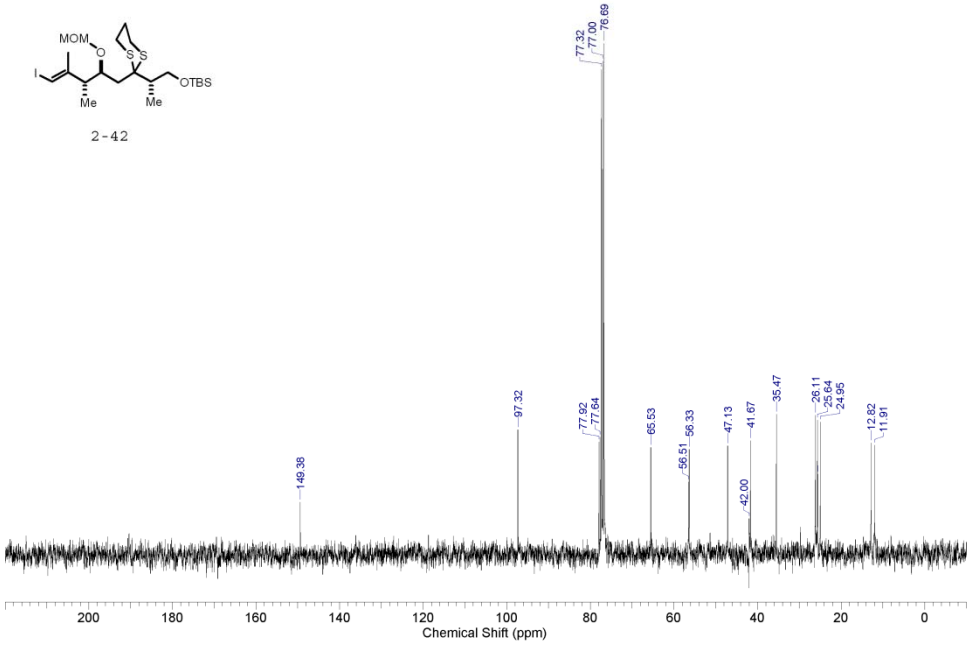

TMS
MOM
O
S
S
I
Me
Me
2-40
Chemical Shift (ppm)

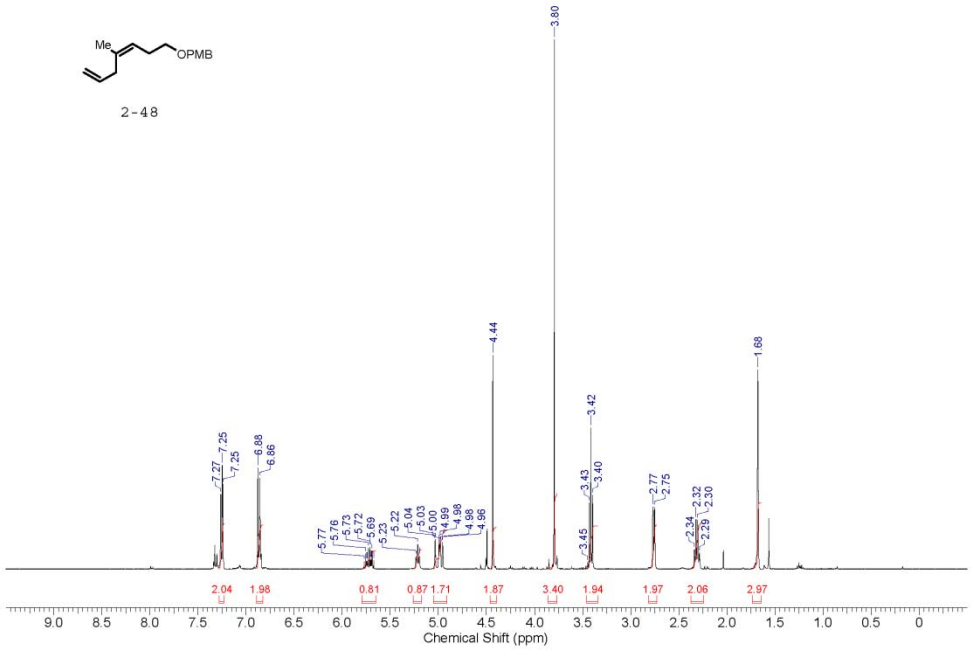

MOM
O
S
S
OTBS
Me
Me
2-41
Chemical Shift (ppm)

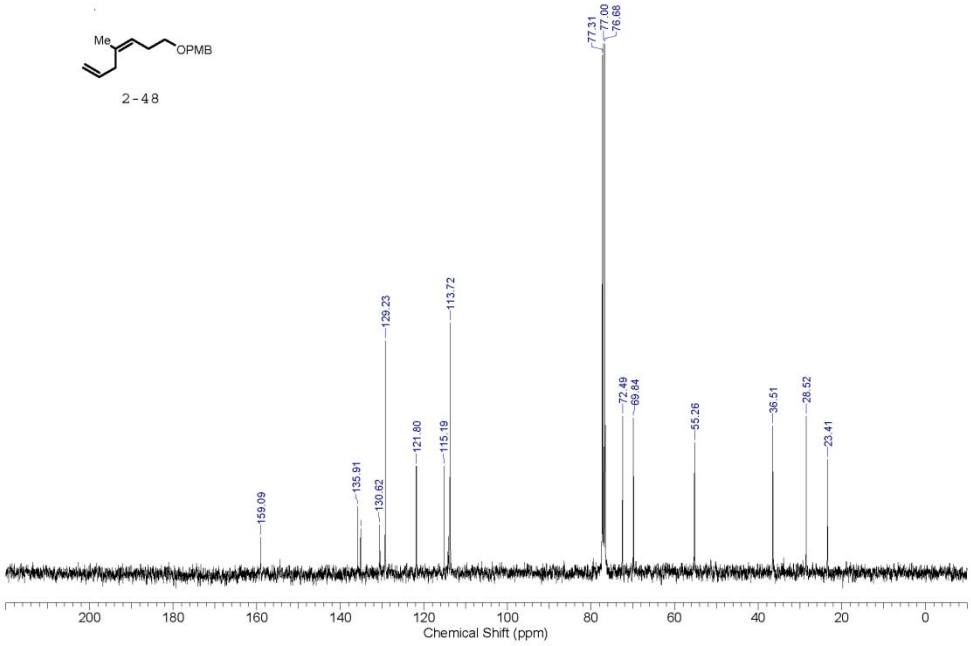

MOM
O
S
S
OTBS
Me
Me
2-41
Chemical Shift (ppm)

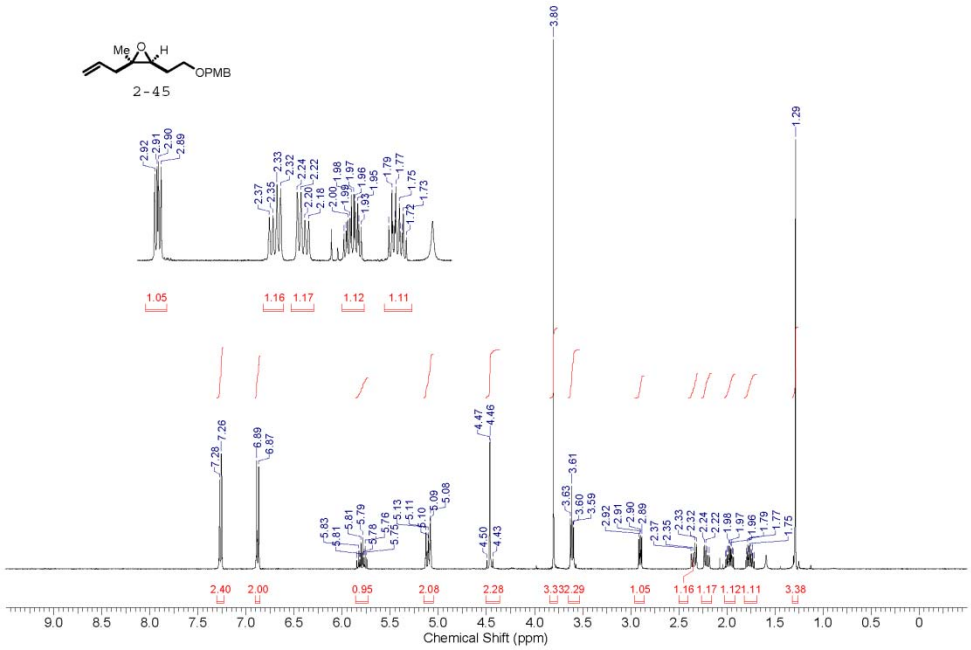

MOM
O
S
S
Bu3Sn
OTBS
Me
Me
2-41a
Chemical Shift (ppm)

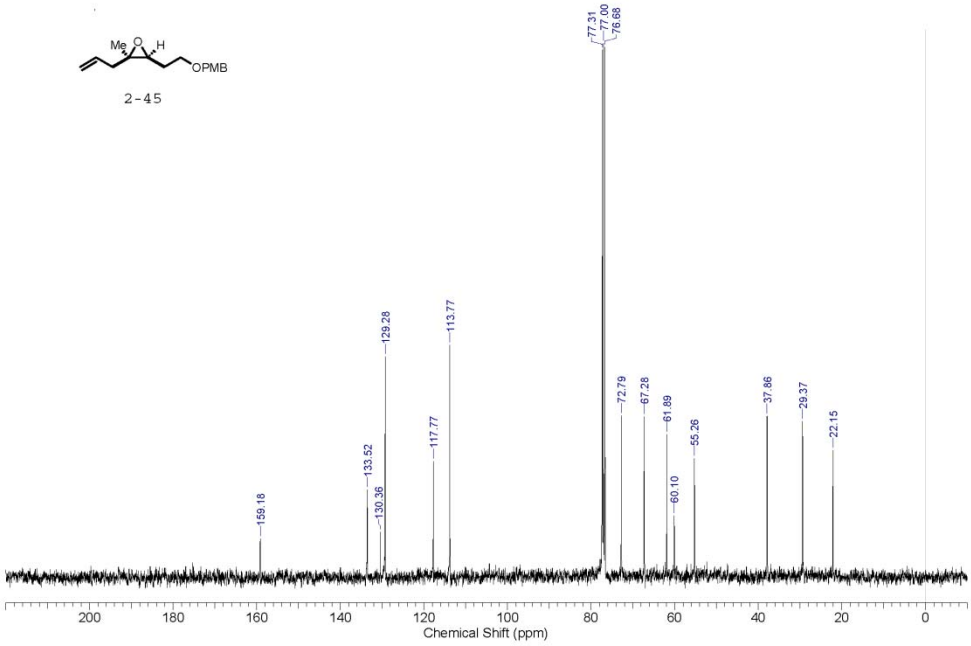

MOM
O
S
S
I
OTBS
Me
Me
2-42
Chemical Shift (ppm)

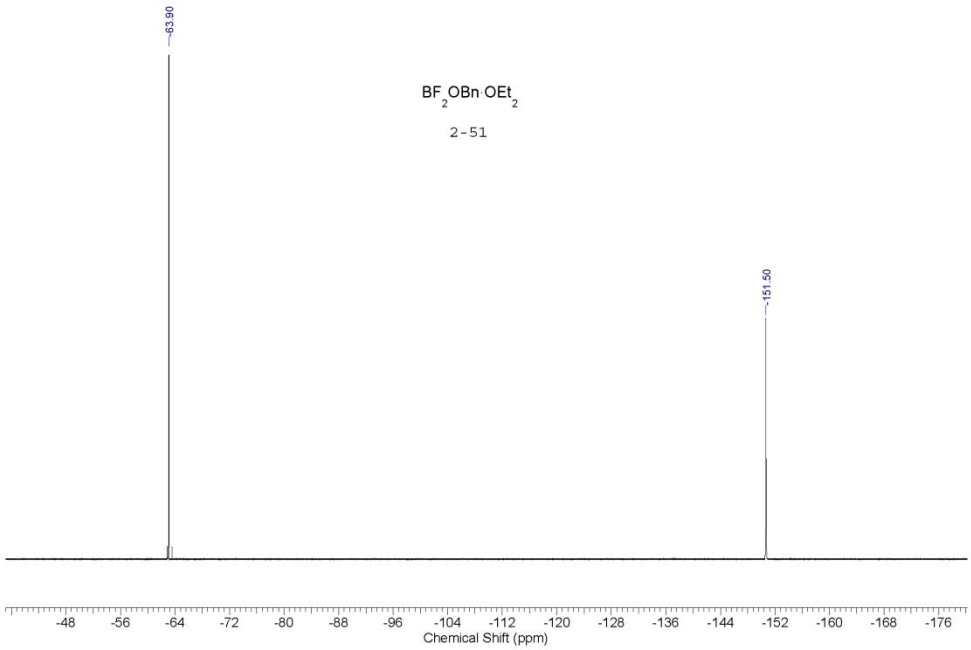

MOM
O
S
S
I
OTBS
Me
Me
2-42
Chemical Shift (ppm)

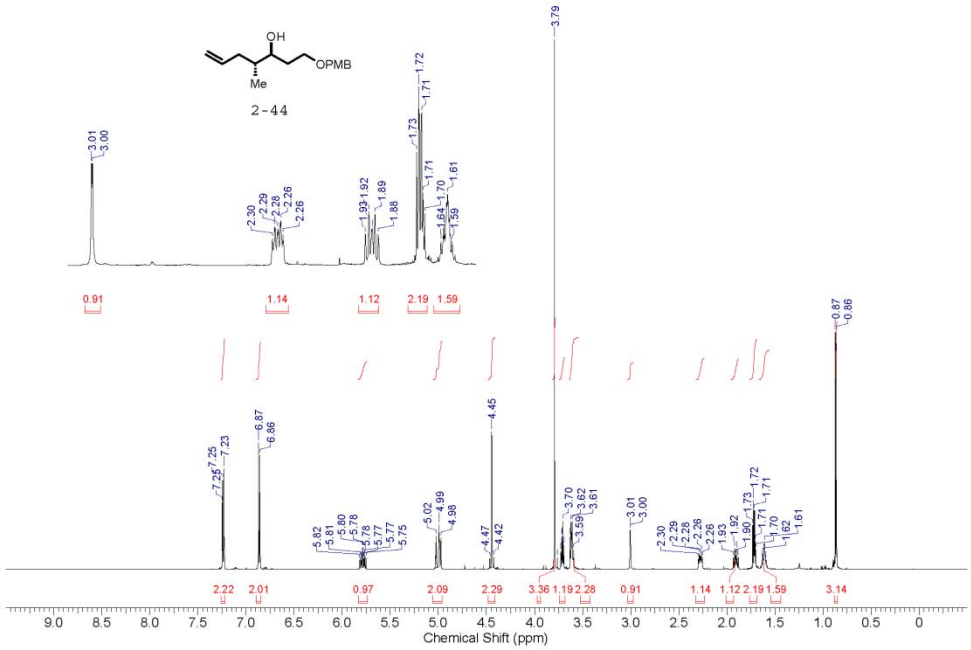

Me
OPMB
2-48
3.80
4.44
1.68
3.42
7.27
7.25
6.88
6.86
3.43
3.40
2.77
2.75
2.32
2.30
2.34
2.29
5.77
5.76
5.73
5.72
5.69
5.23
5.22
5.04
5.03
5.00
4.99
4.98
4.98
4.96
3.45
2.04
1.98
0.81
0.87
1.71
1.87
3.40
1.94
1.97
2.06
2.97
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

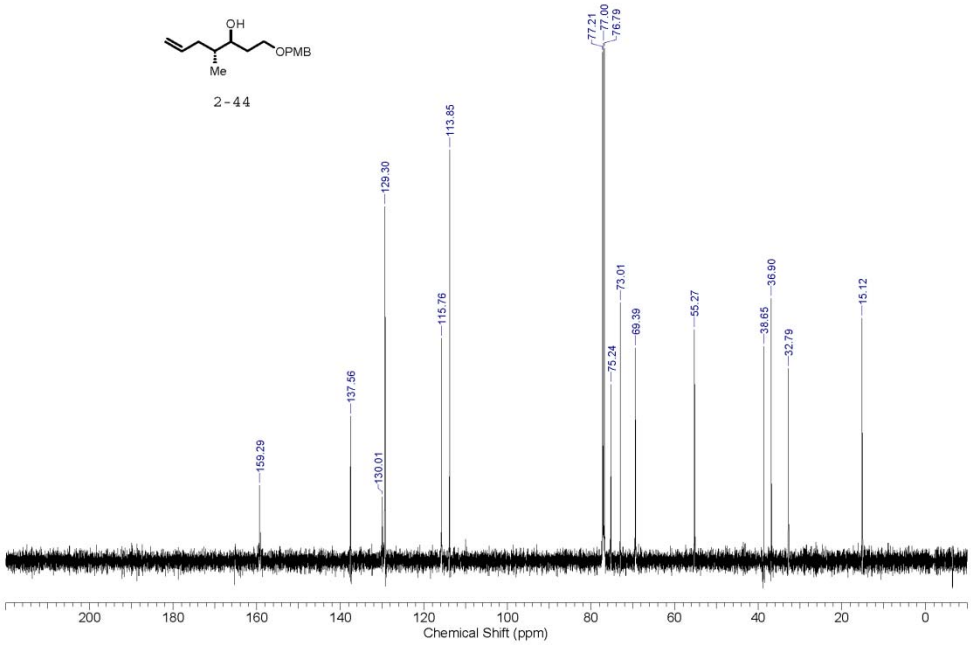

Me
OPMB
2-48
77.31
77.00
76.68
129.23
113.72
72.49
69.84
55.26
36.51
28.52
23.41
121.80
115.19
135.91
130.62
159.09
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

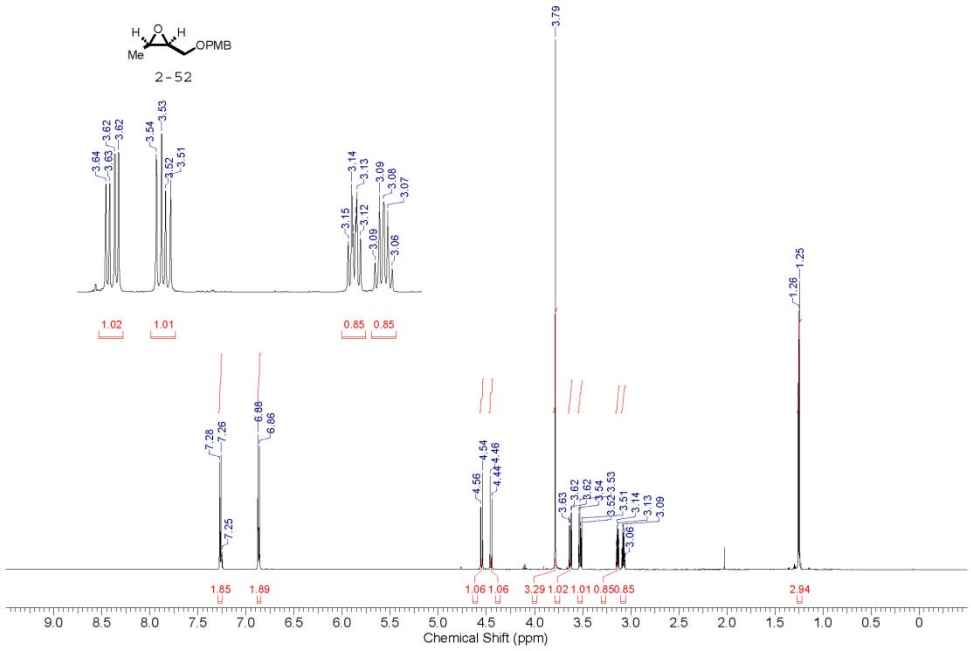

Me
O
H
OPMB
2-45
Chemical Shift (ppm)

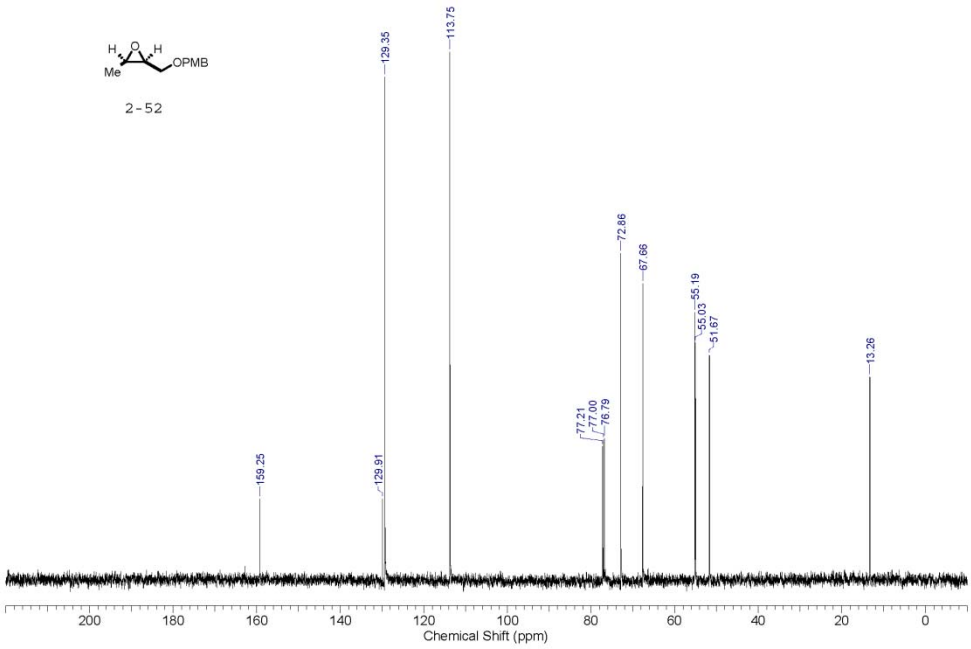

Me
O
H
OPMB
2-45
Chemical Shift (ppm)

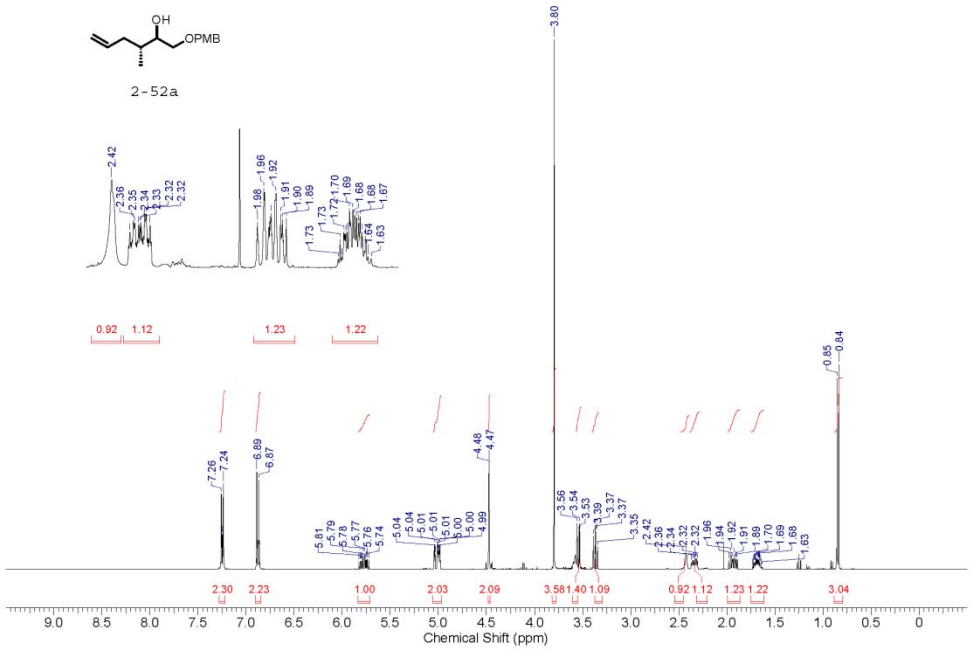

-63.90
BF2OBn·OEt2
2-51
-151.50
-48
-56
-64
-72
-80
-88
-96
-104
-112
-120
-128
-136
-144
-152
-160
-168
-176
Chemical Shift (ppm)

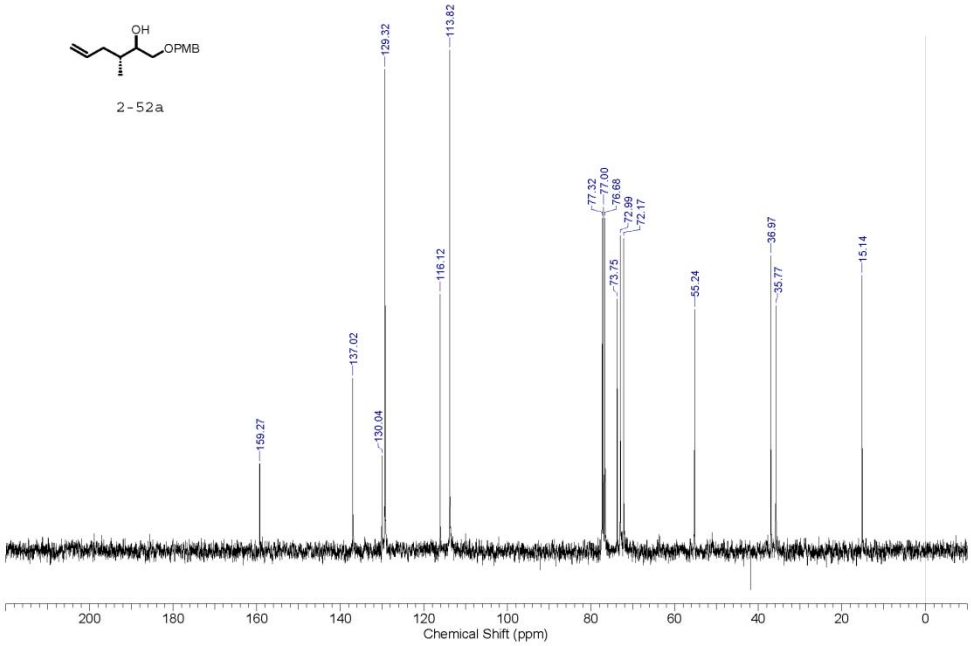

OH
OPMB
Me
2-44
Chemical Shift (ppm)

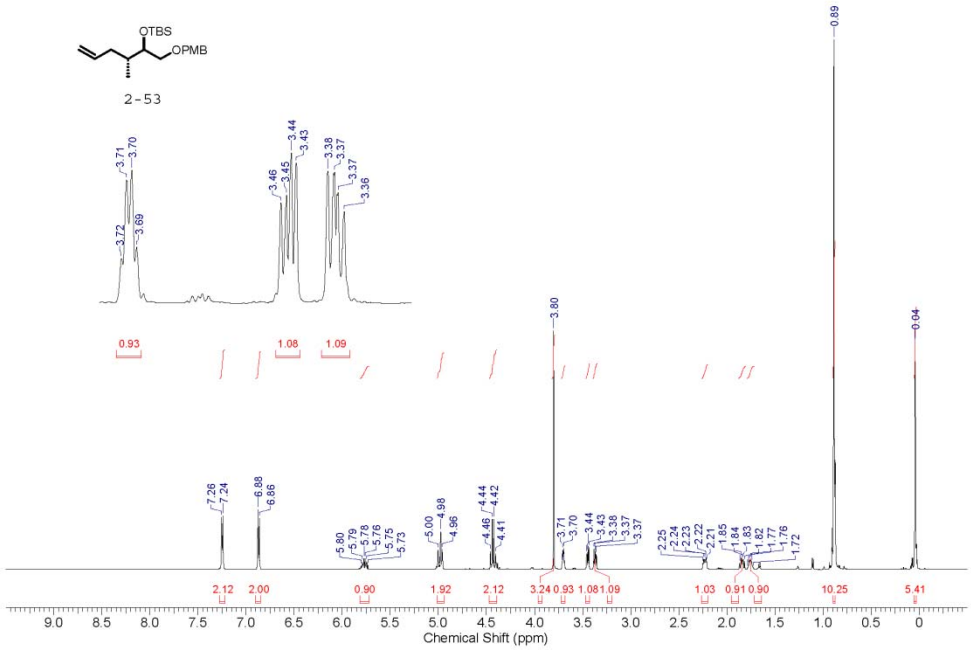

OH
OPMB
Me
2-44
Chemical Shift (ppm)

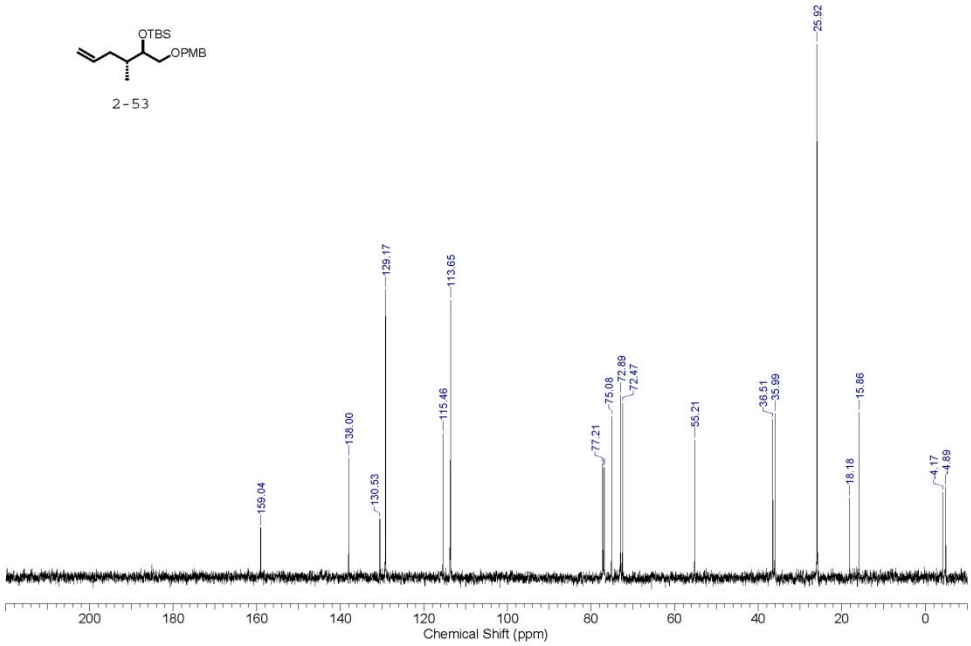

OPMB
Me
2-52
Chemical Shift (ppm)

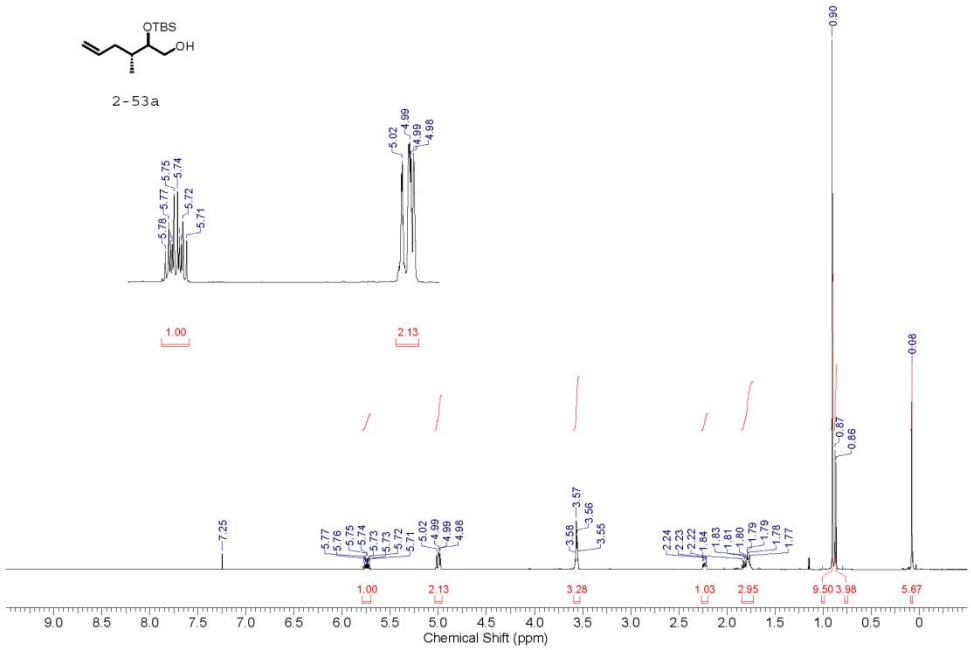

OPMB
Me
2-52
Chemical Shift (ppm)

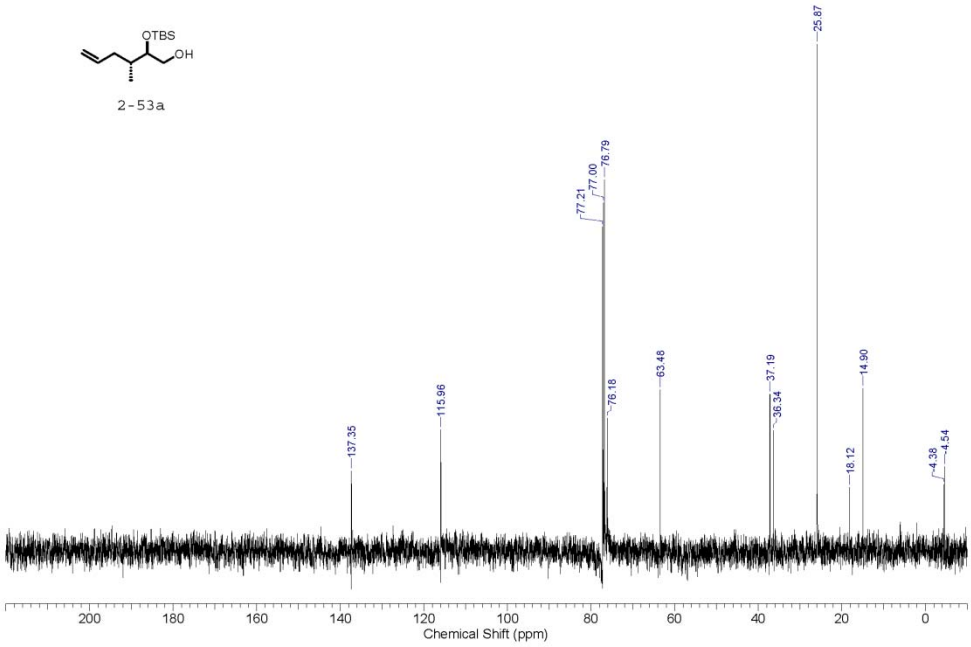

OH
OPMB
2-52a
Chemical Shift (ppm)

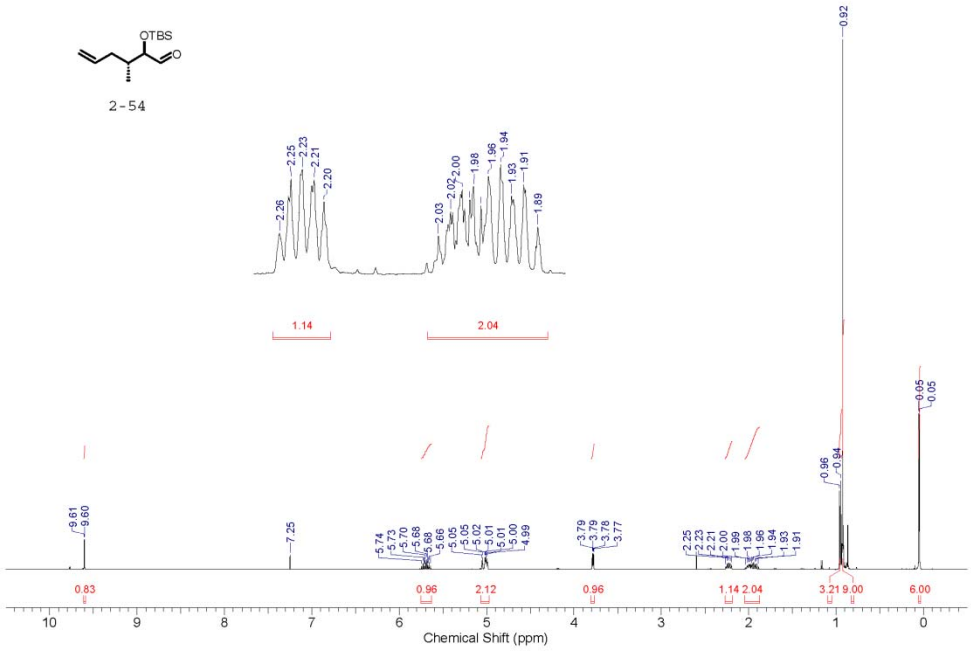

OH
OPMB
2-52a
Chemical Shift (ppm)

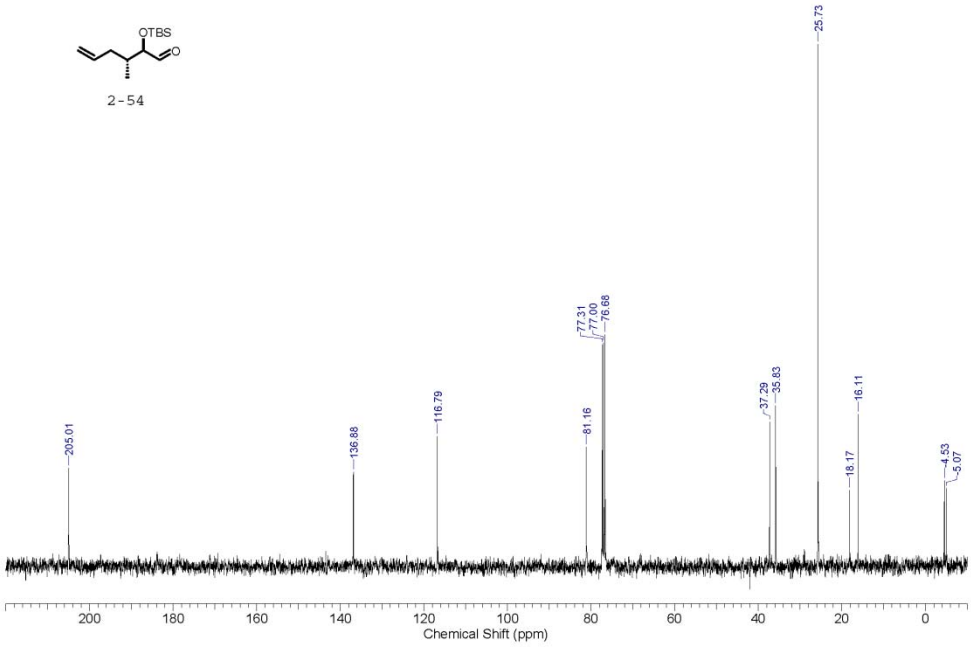

OTBS
OPMB
2-53
Chemical Shift (ppm)

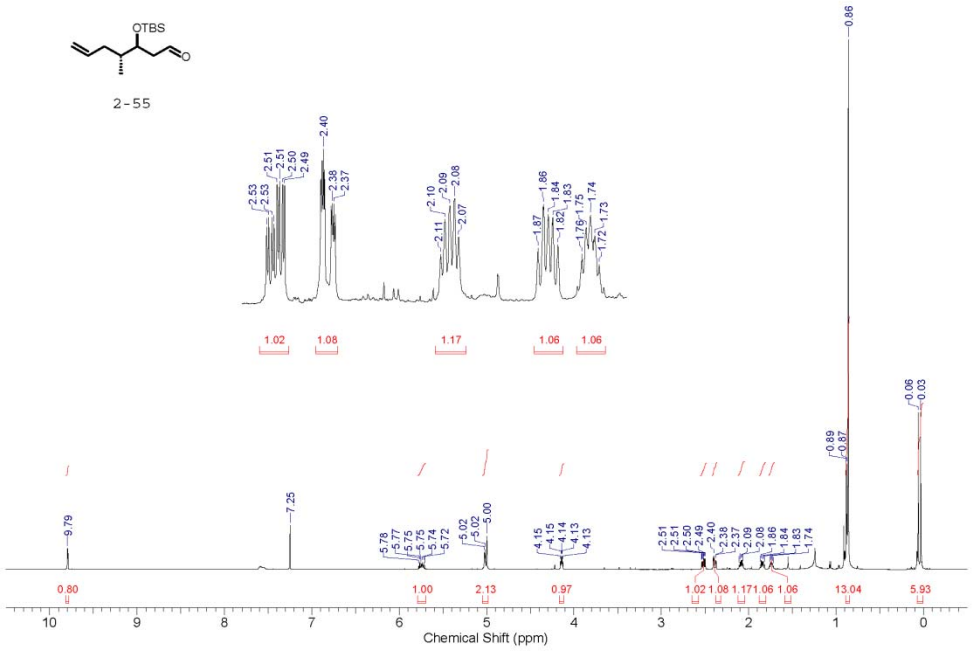

OTBS
OPMB
2-53
Chemical Shift (ppm)

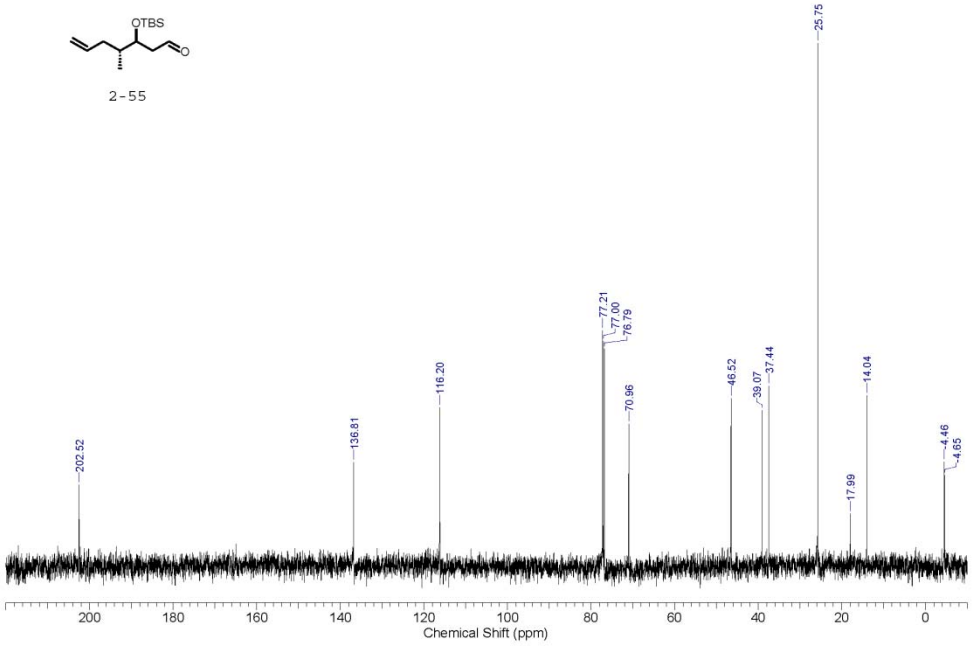

OTBS
OH
2-53a
Chemical Shift (ppm)

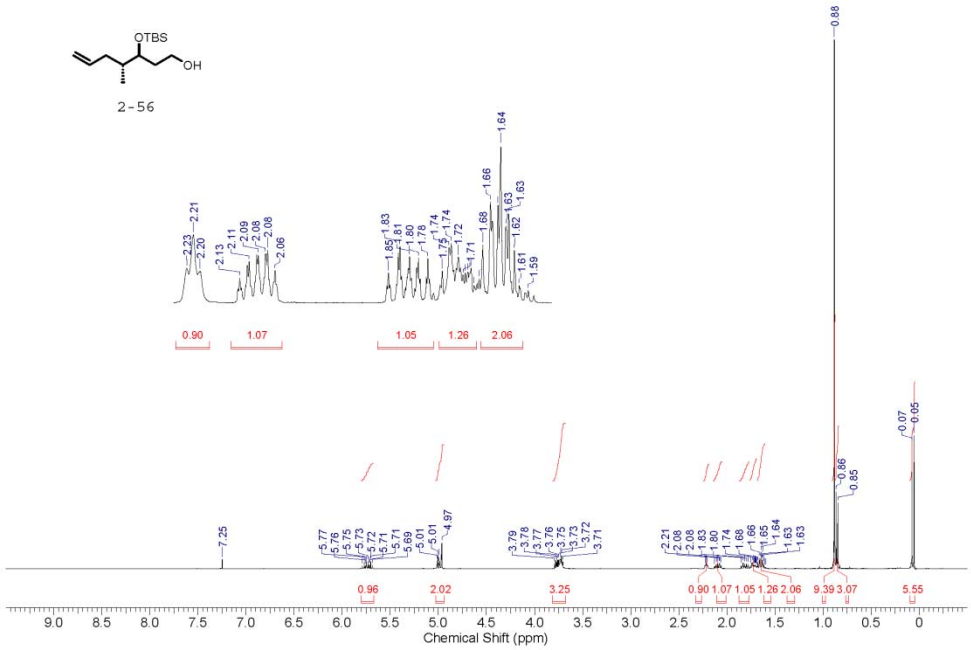

OTBS
OH
2-53a
Chemical Shift (ppm)

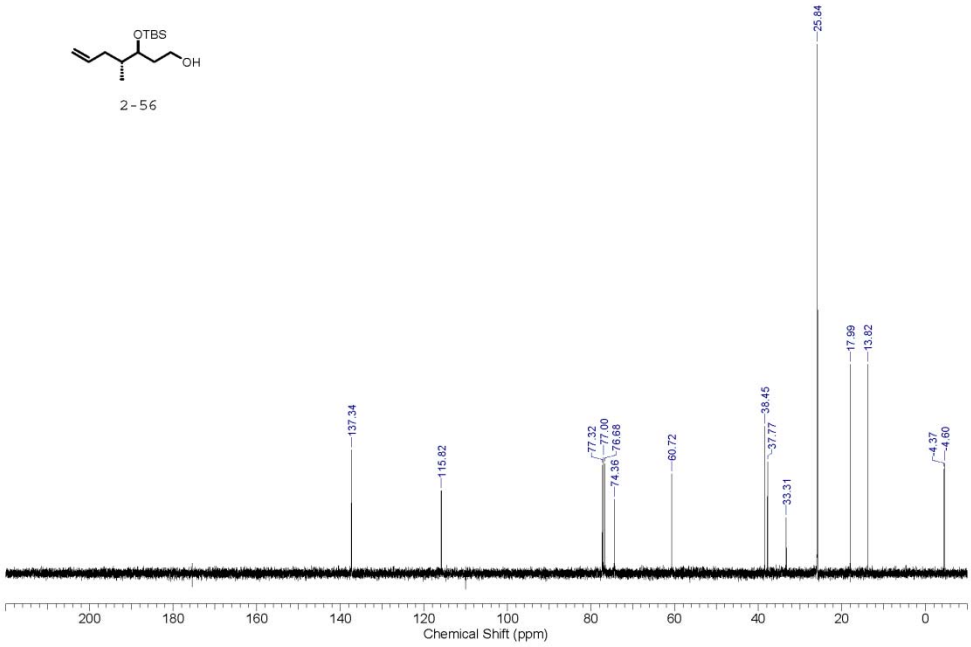

OTBS
O
2-54
Chemical Shift (ppm)

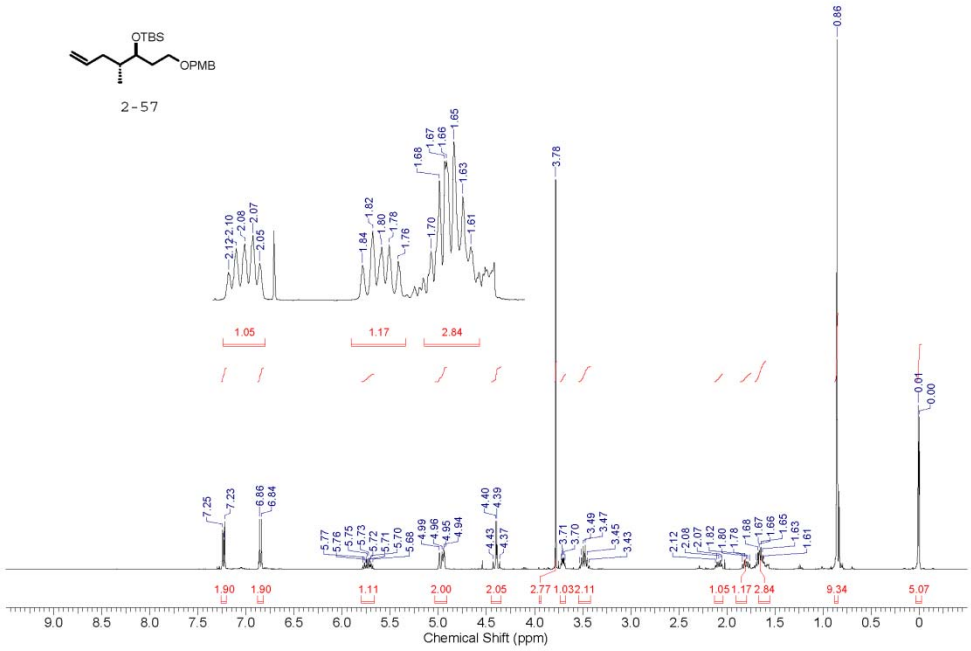

OTBS
O
2-54
Chemical Shift (ppm)

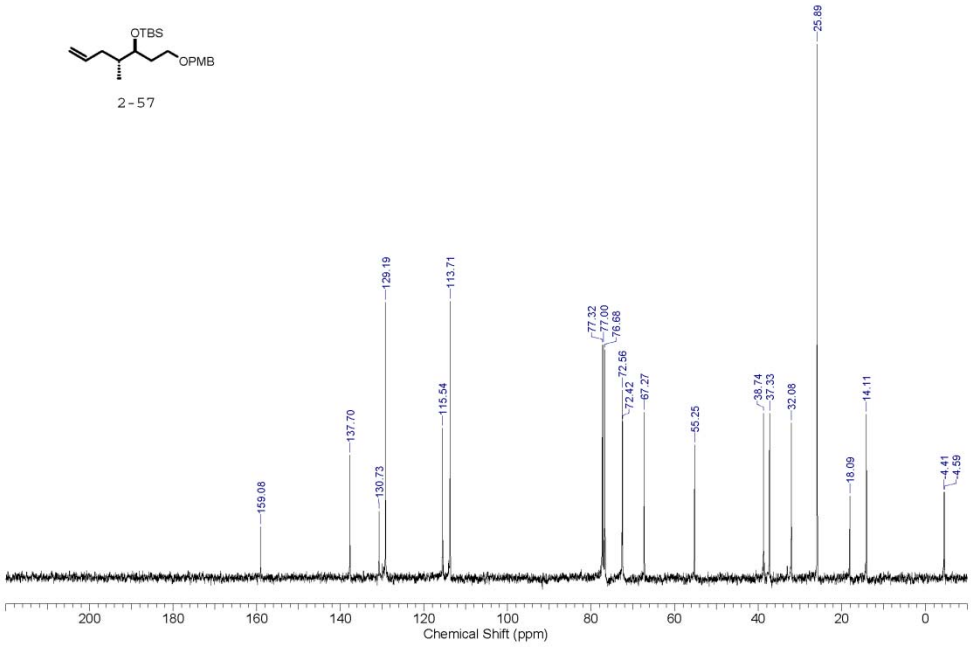

OTBS
O
2-55
Chemical Shift (ppm)

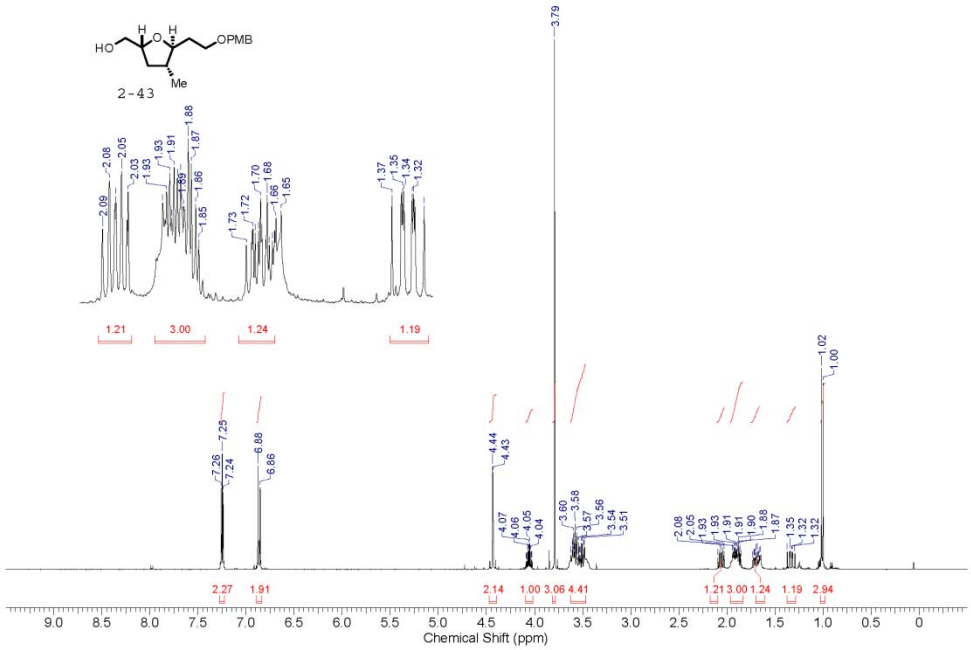

OTBS
O
2-55
Chemical Shift (ppm)

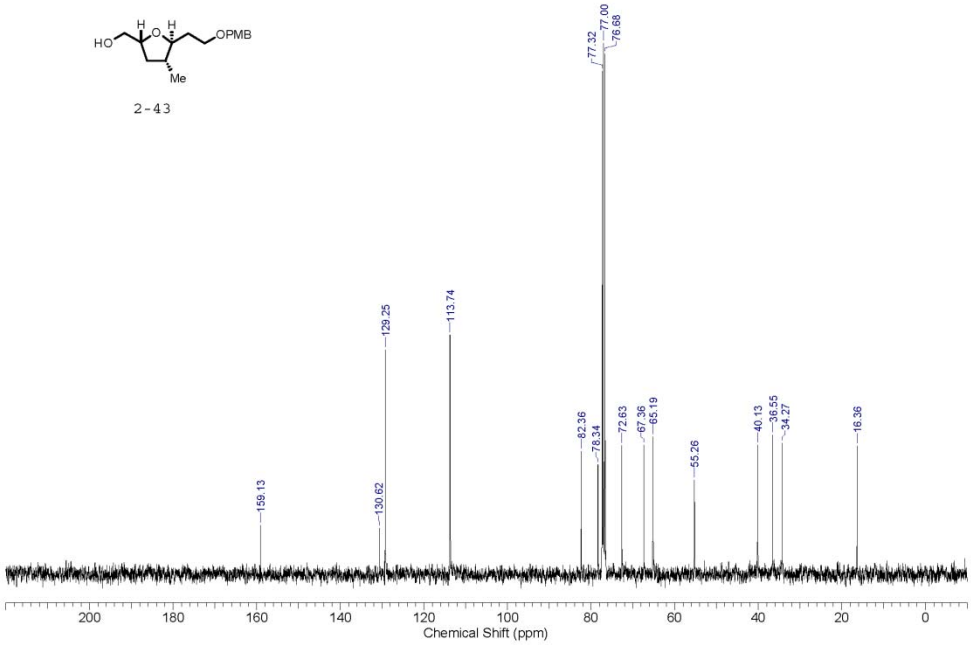

OTBS
OH
2-56
Chemical Shift (ppm)

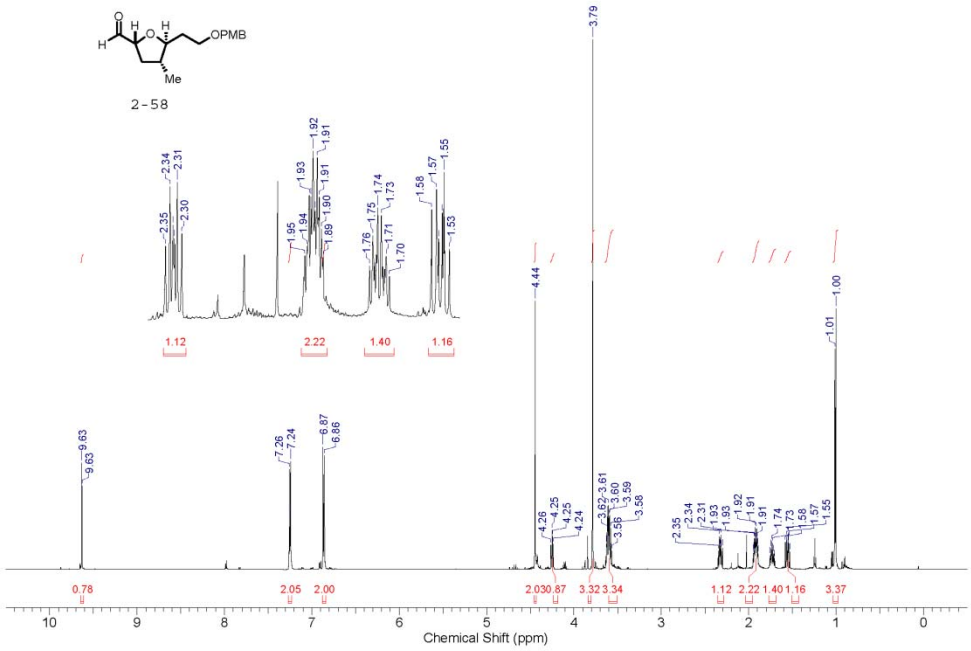

OTBS
OH
2-56
Chemical Shift (ppm)

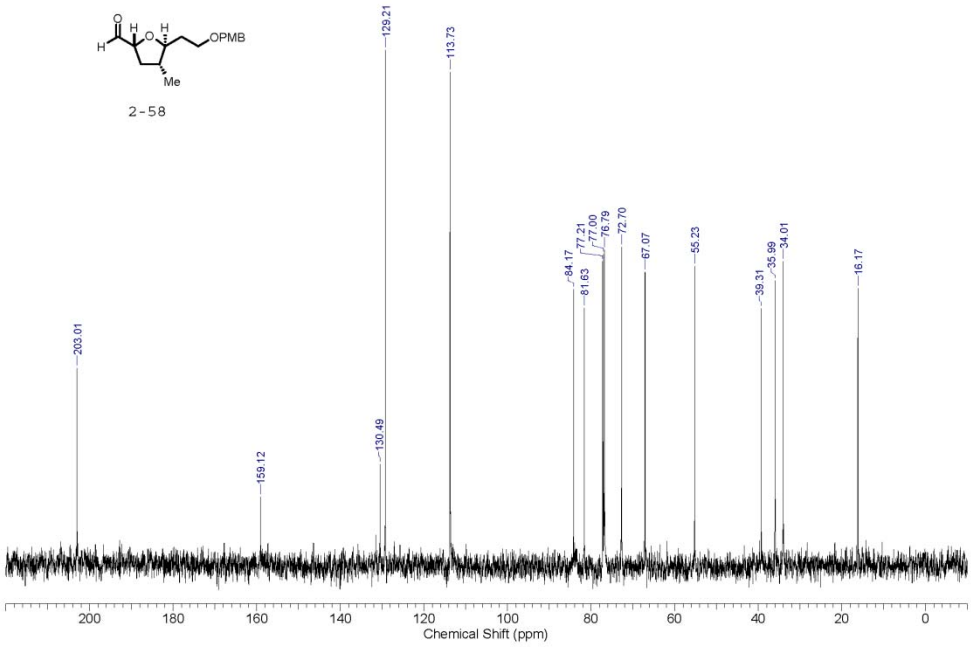

OTBS
OPMB
2-57
Chemical Shift (ppm)

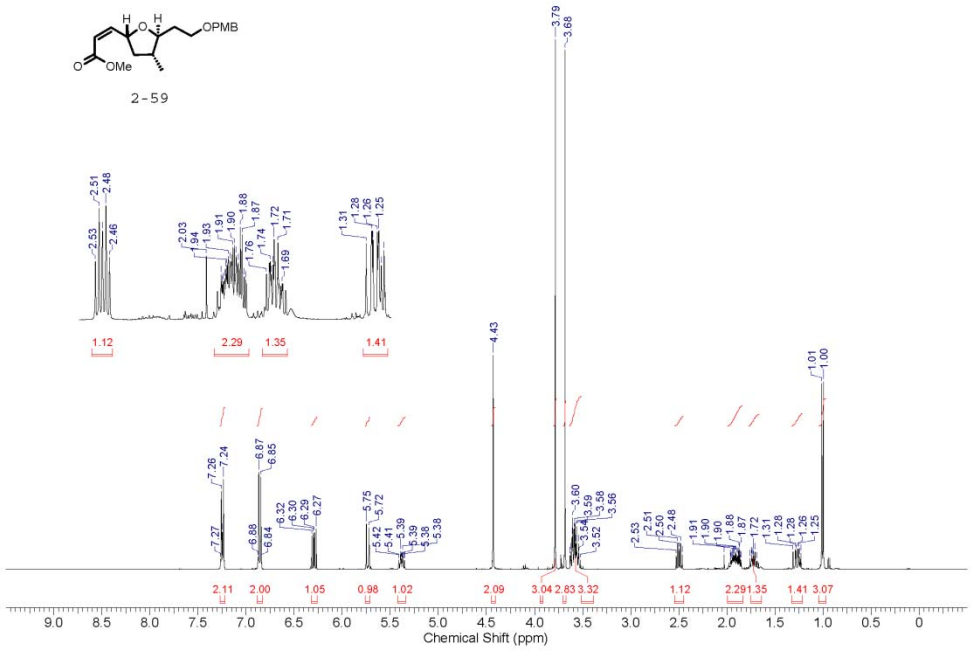

OTBS
OPMB
2-57
Chemical Shift (ppm)

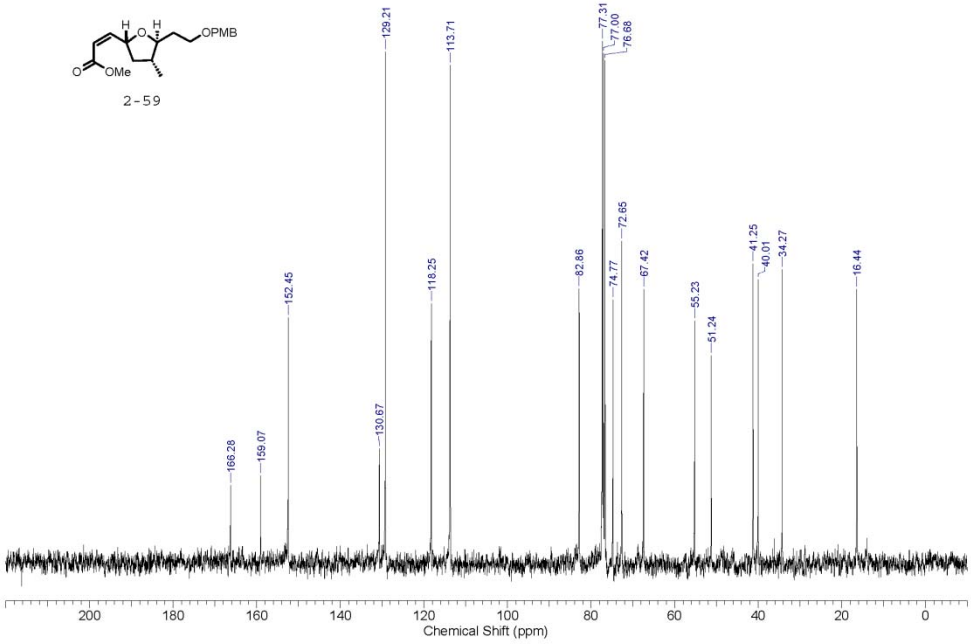

HO
OPMB
Me
2-43
Chemical Shift (ppm)

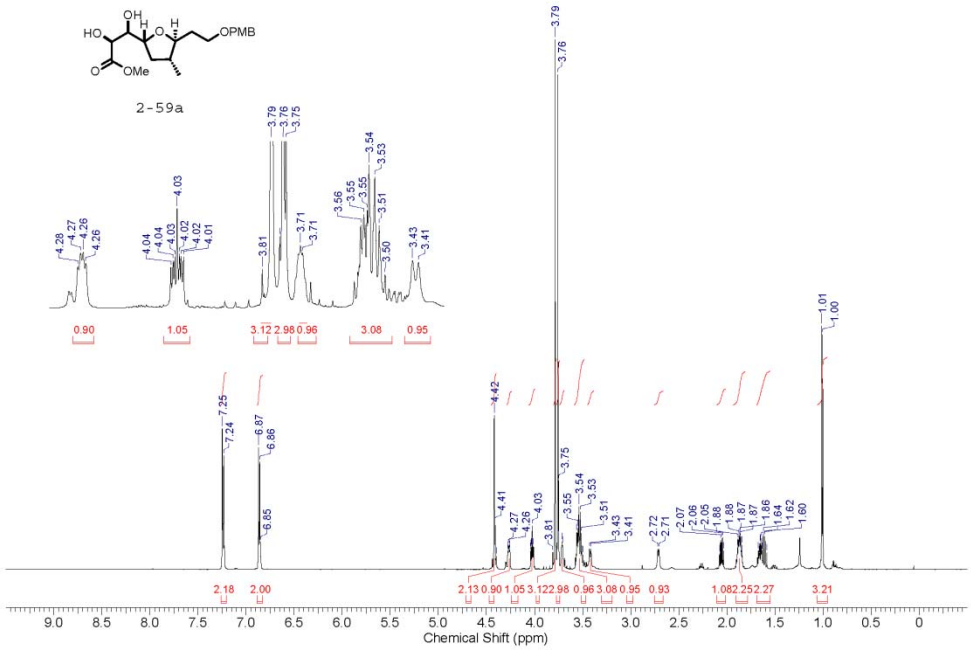

HO
OPMB
Me
2-43
Chemical Shift (ppm)

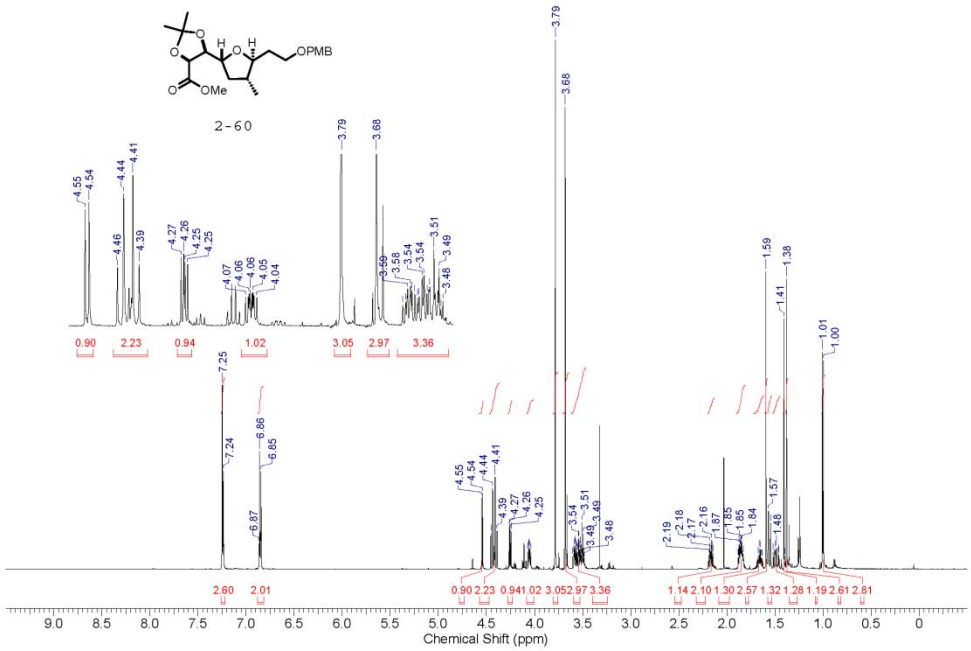

OPMB
Me
2-58
Chemical Shift (ppm)

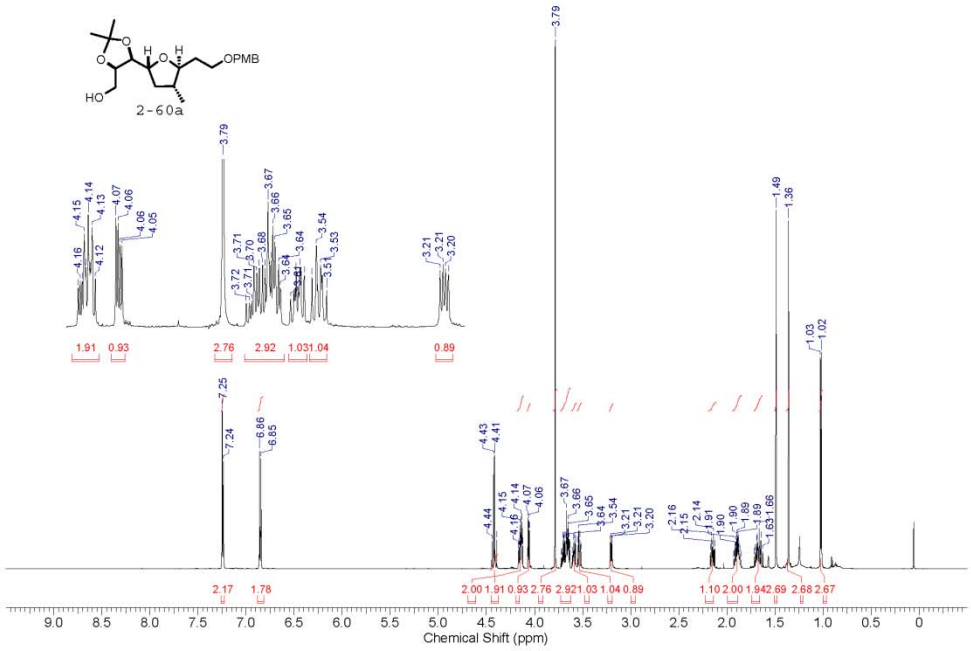

OPMB
Me
2-58
Chemical Shift (ppm)

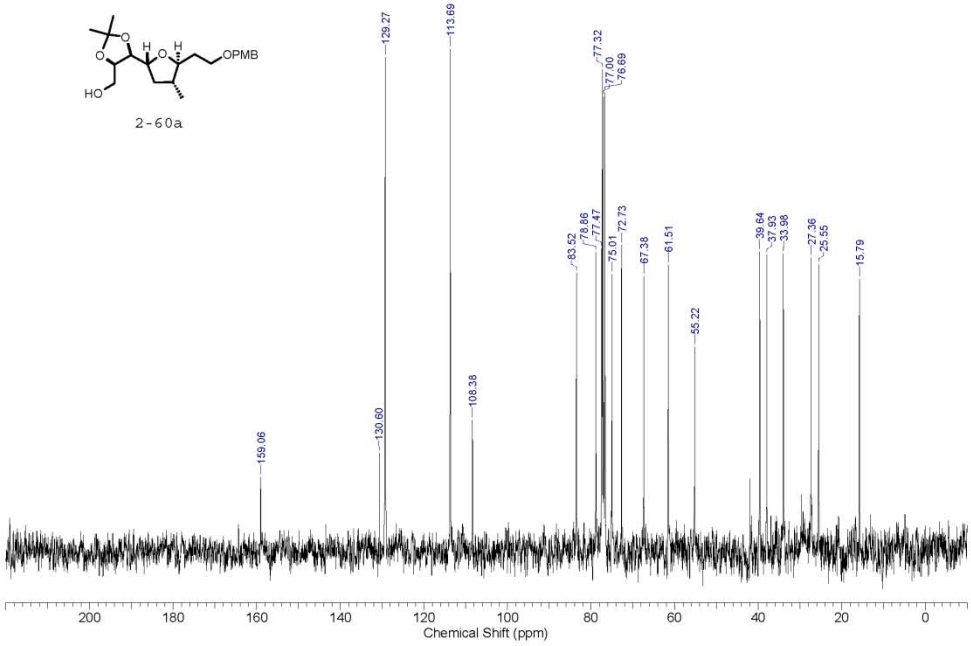

OPMB
OMe
2-59
Chemical Shift (ppm)

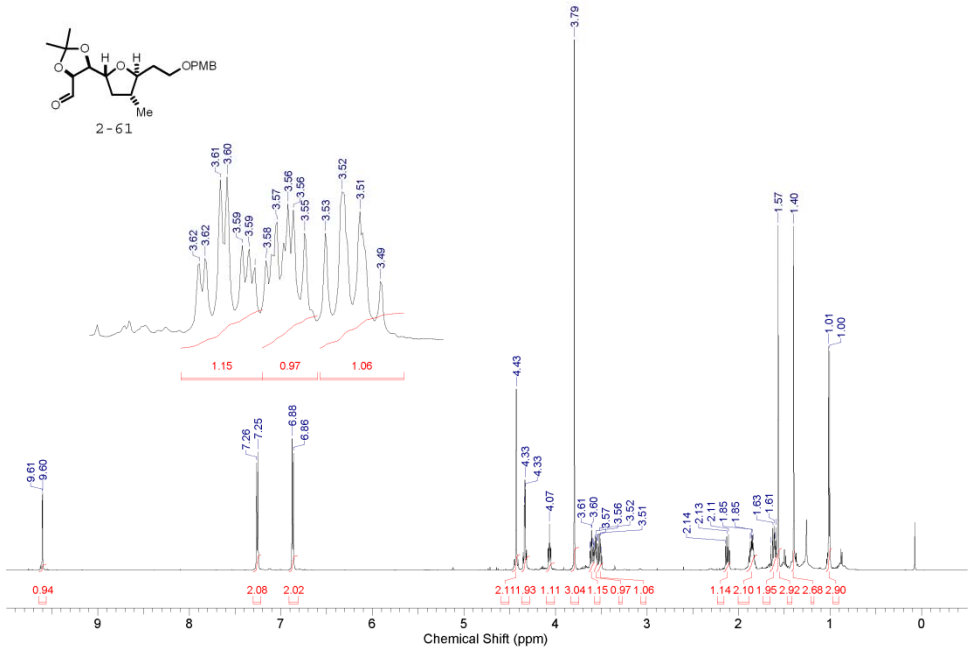

OPMB
OMe
2-59
Chemical Shift (ppm)

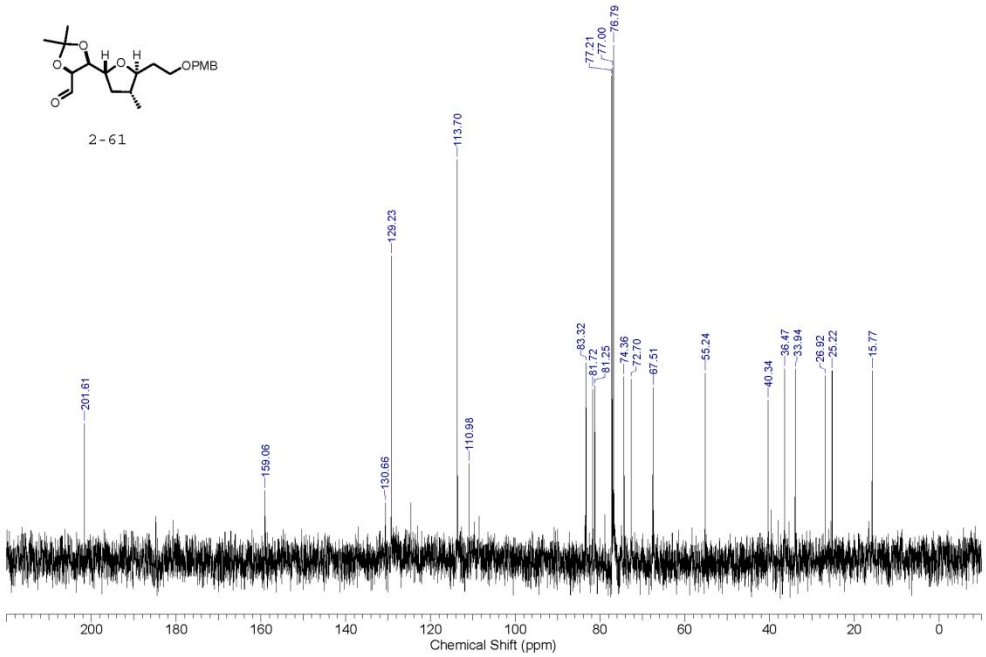

OH
H
HO
O
H
OPMB
O
OMe
2-59a
Chemical Shift (ppm)

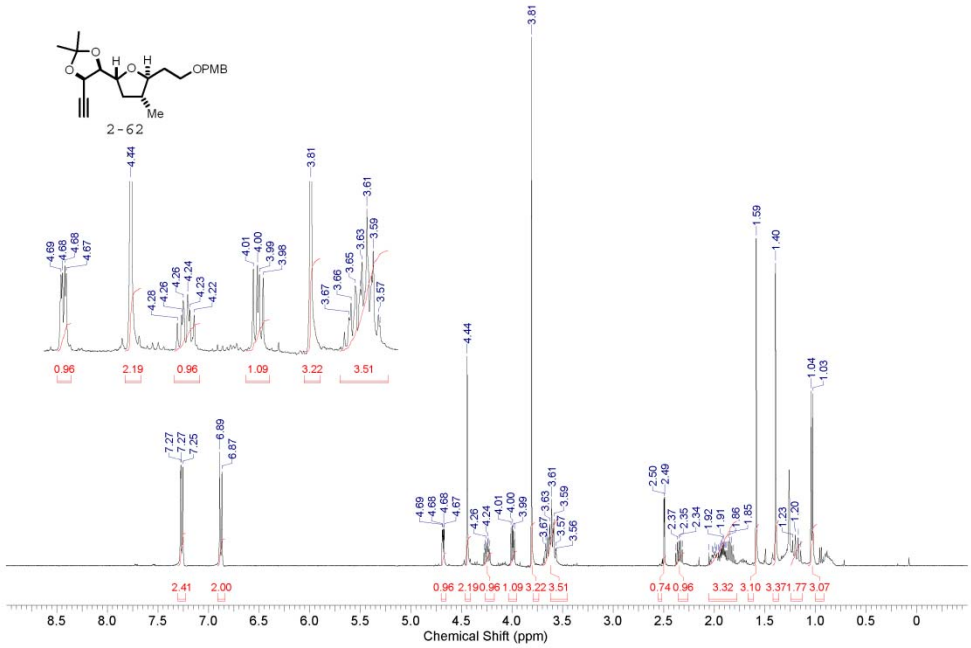

H
H
O
O
O
OPMB
OMe
2-60
Chemical Shift (ppm)

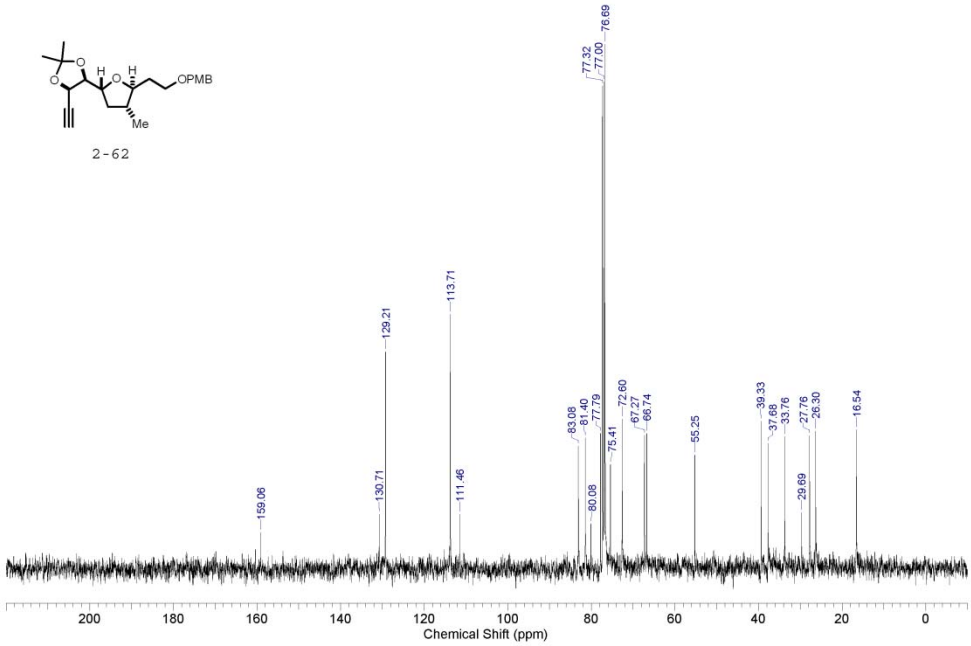

OPMB
HO
2-60a
Chemical Shift (ppm)

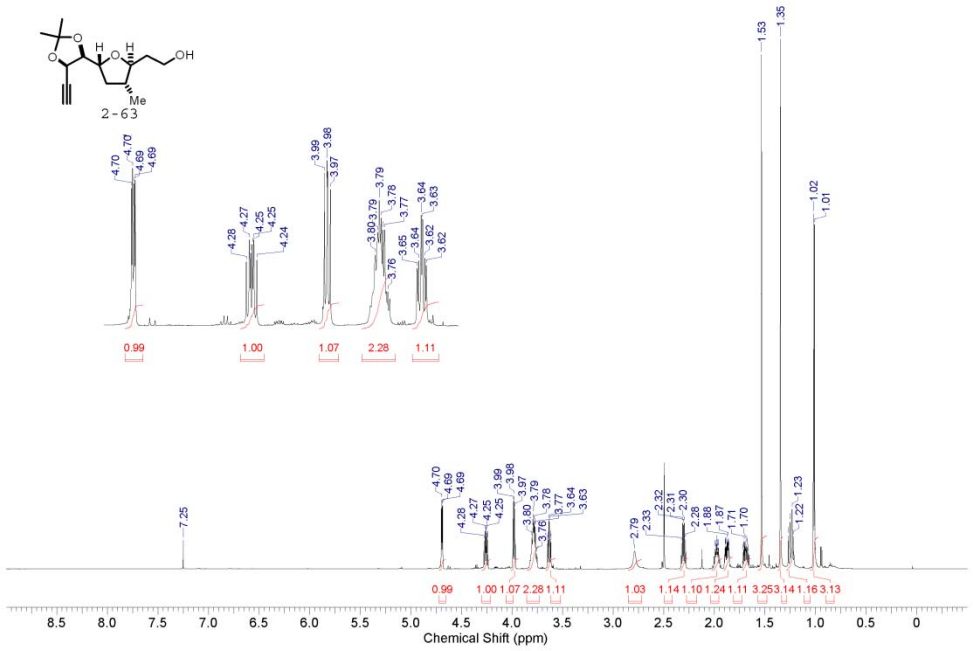

OPMB
HO
2-60a
Chemical Shift (ppm)

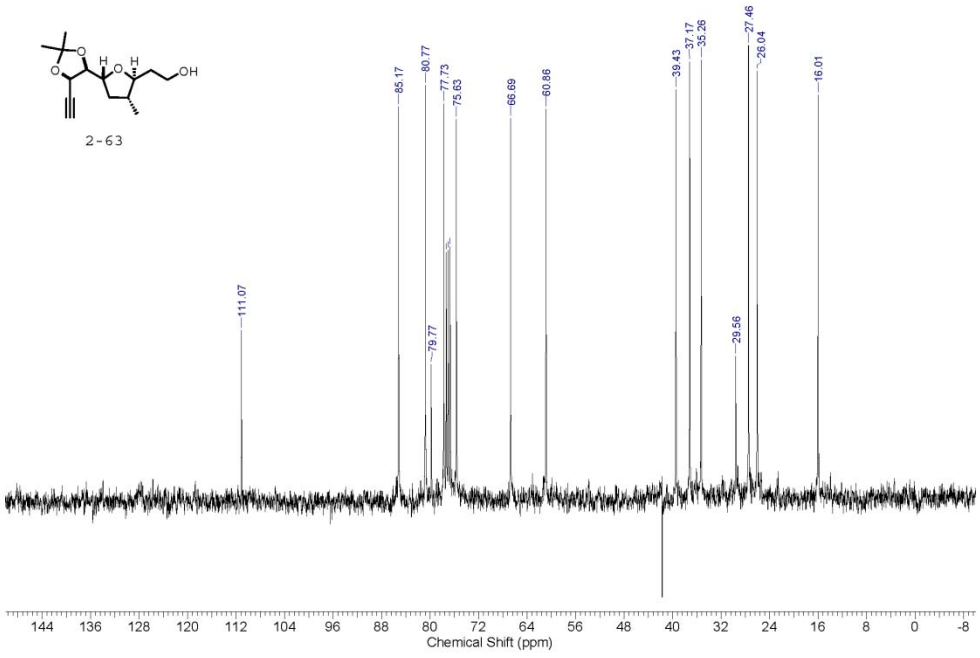

OPMB
Me
2-61
Chemical Shift (ppm)

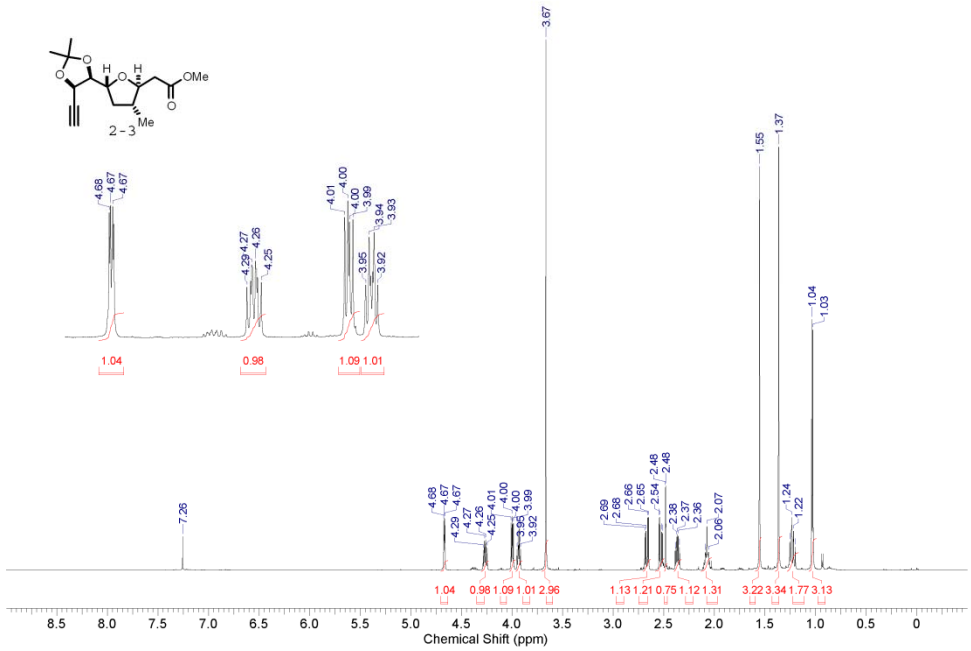

OPMB
2-61
Chemical Shift (ppm)

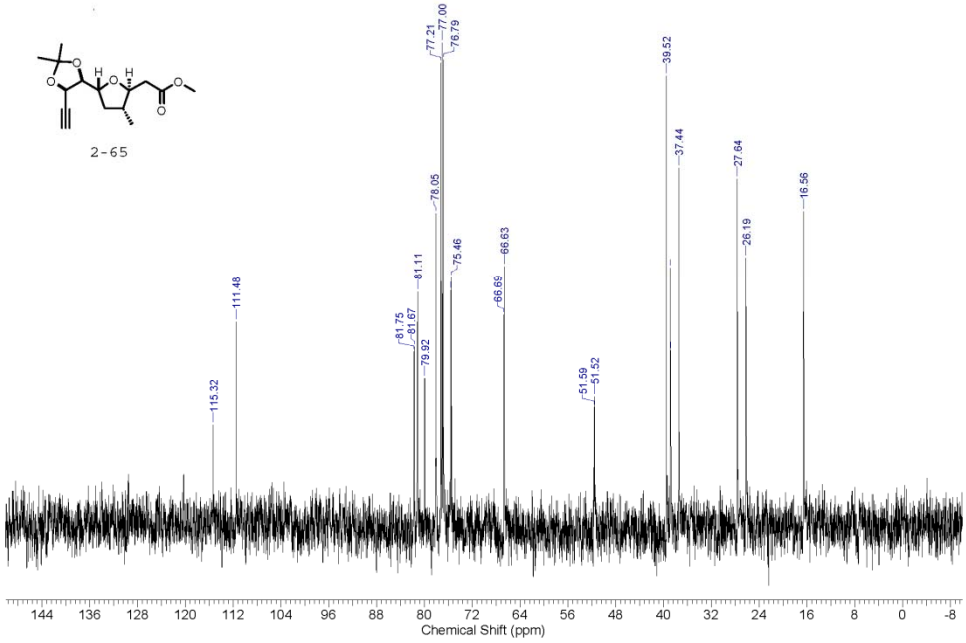

OPMB
Me
2-62
Chemical Shift (ppm)

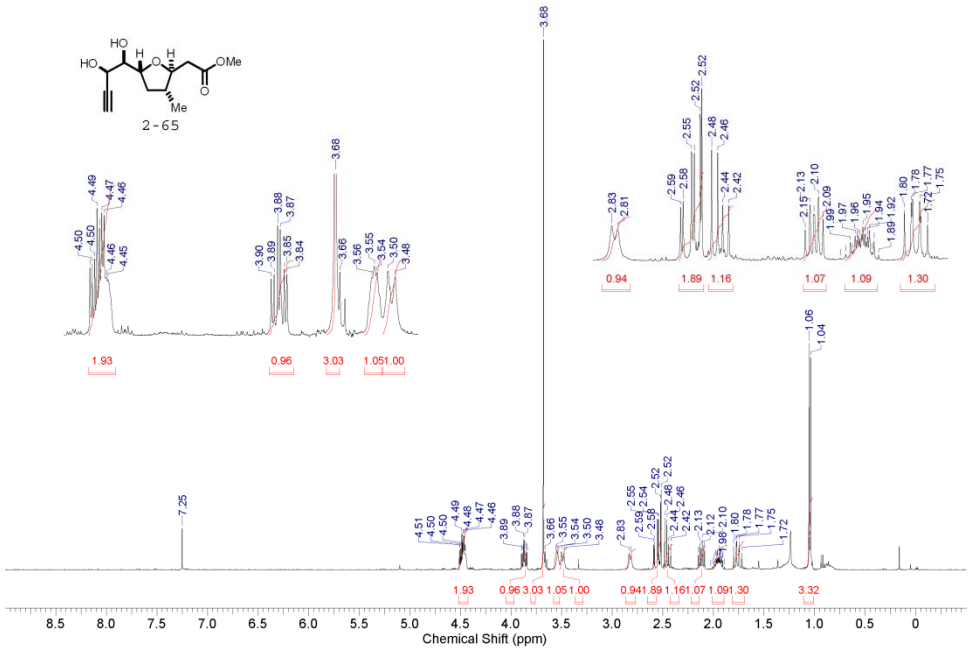

OPMB
Me
2-62
Chemical Shift (ppm)

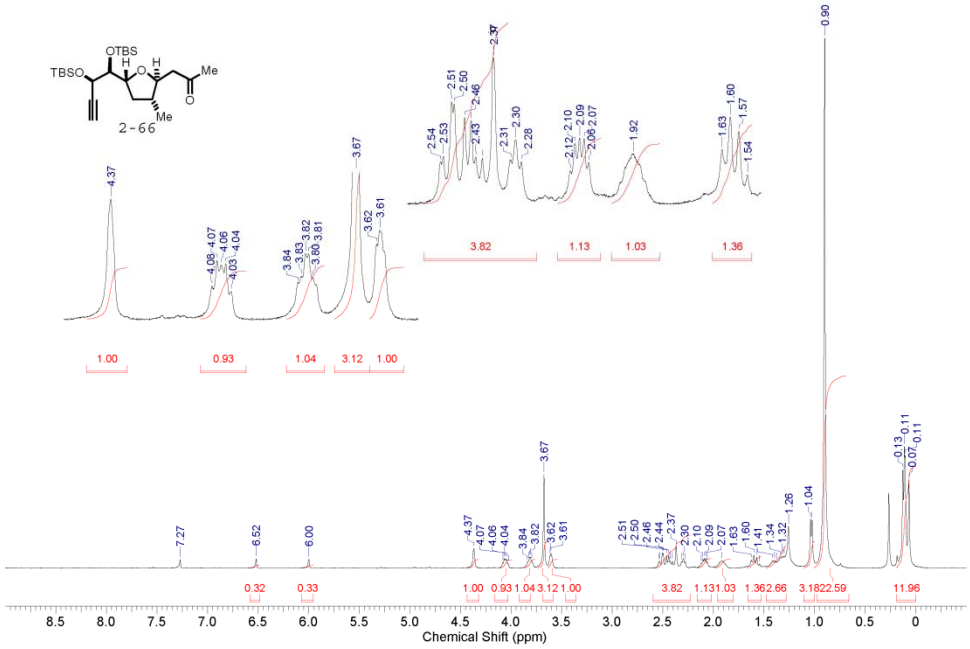

2-63
Chemical Shift (ppm)

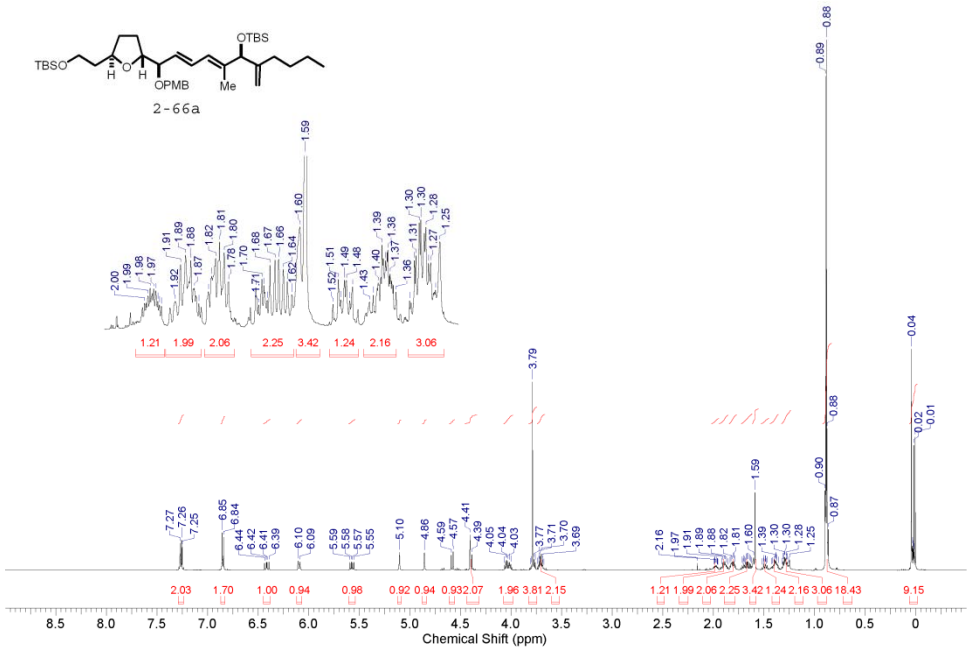

2-63
Chemical Shift (ppm)

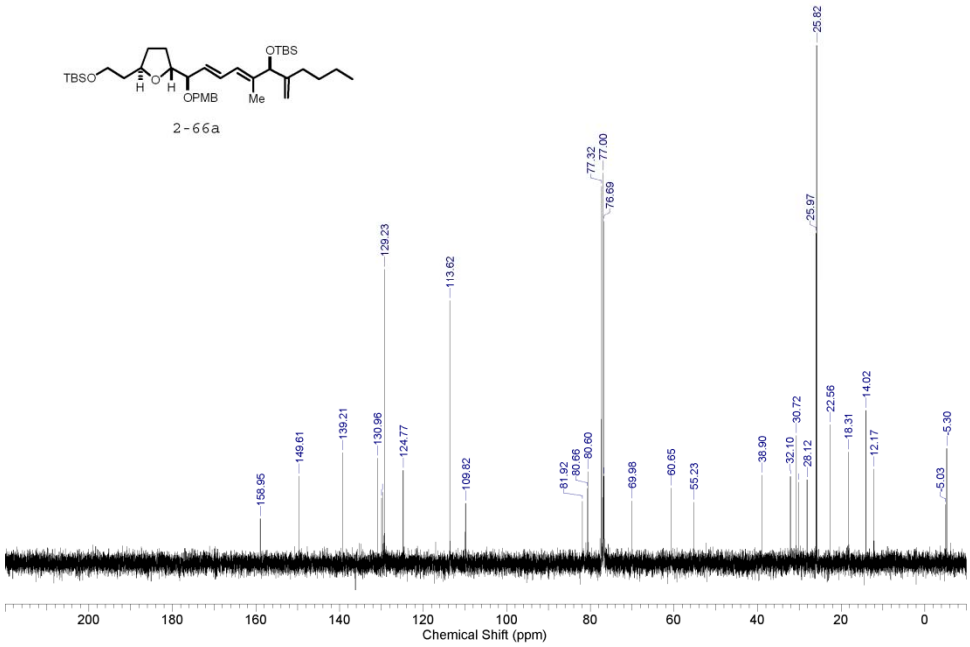

2-3
Chemical Shift (ppm)

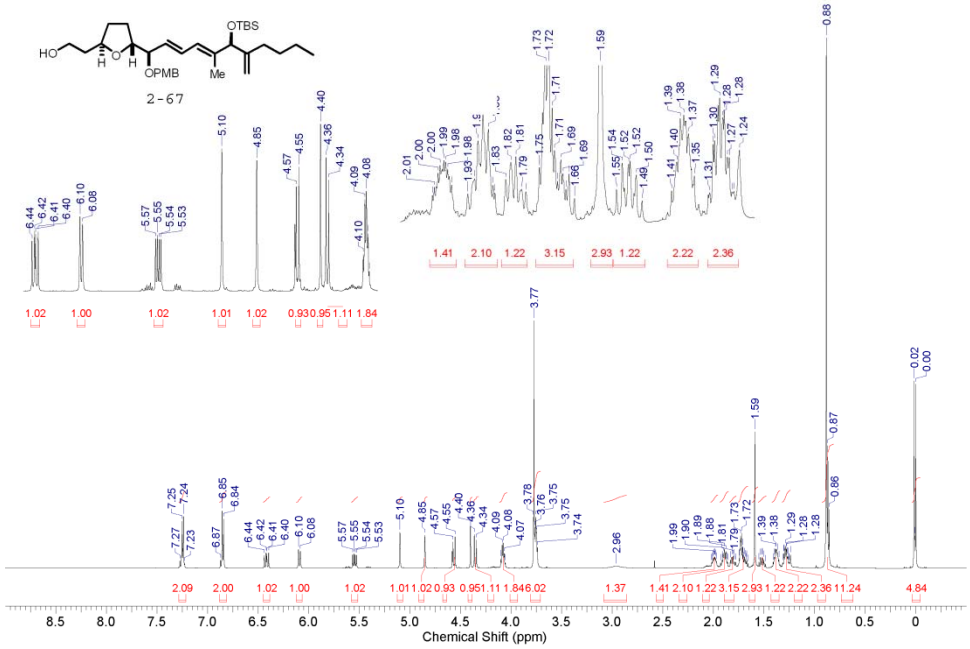

2-65
Chemical Shift (ppm)

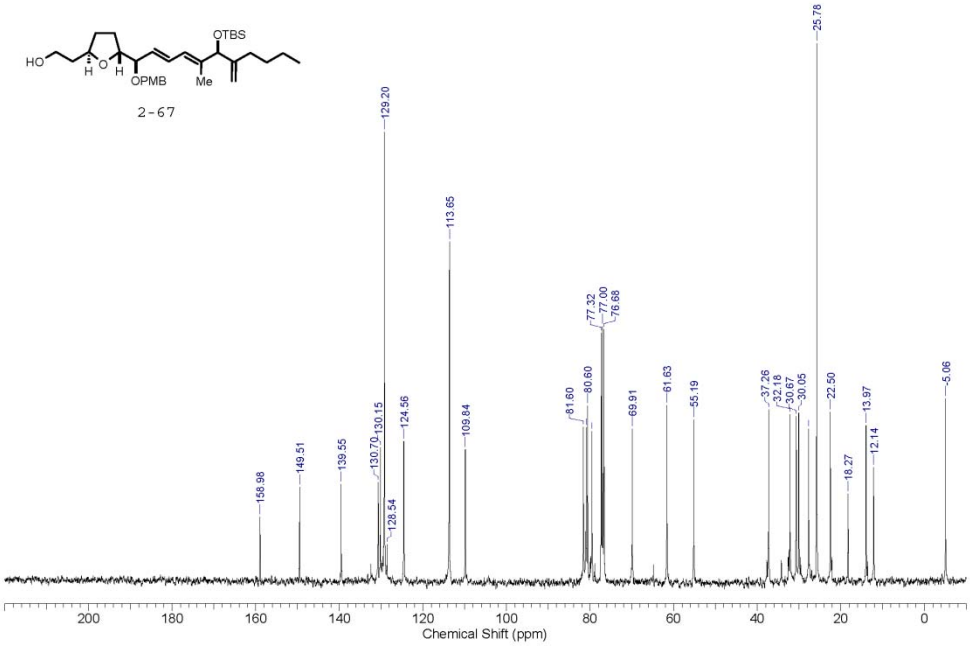

HO
HO
H
O
H
OMe
O
Me
2-65
Chemical Shift (ppm)

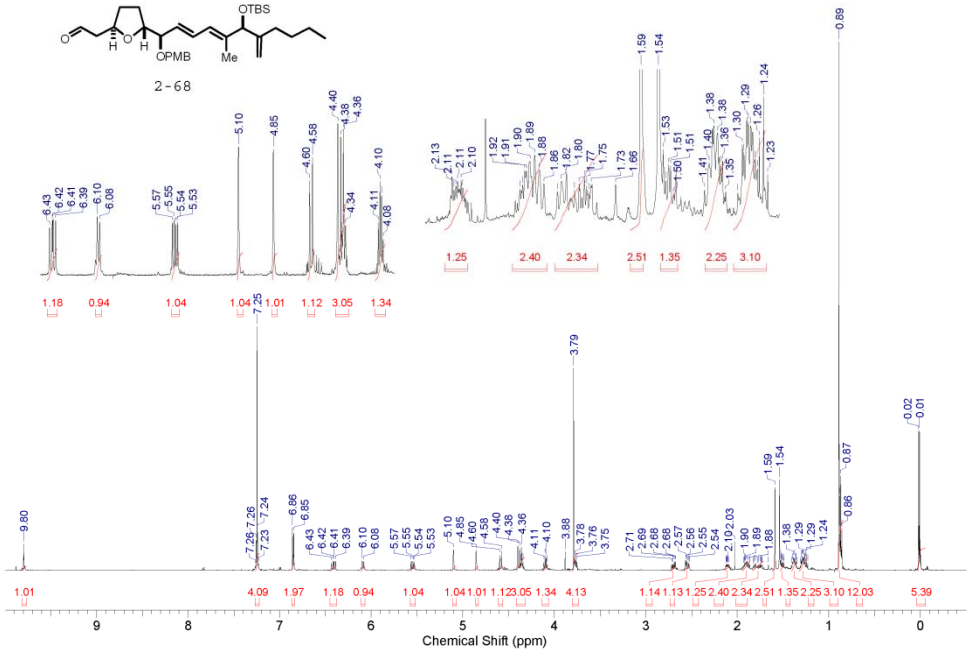

OTBS
TBSO
H
O
H
Me
O
Me
2-66
Chemical Shift (ppm)

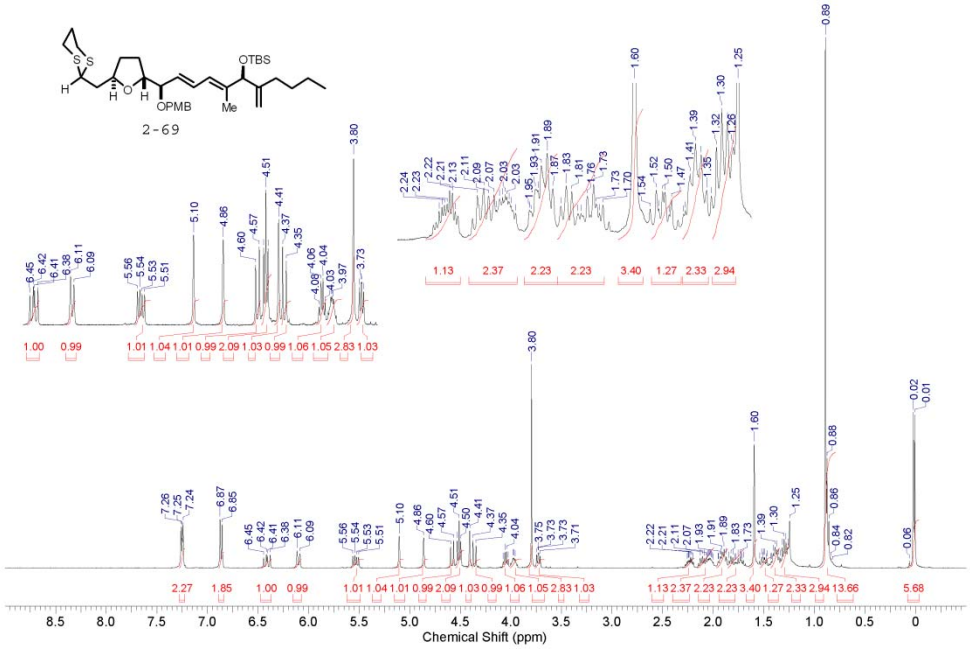

TBSO
OTBS
OPMB
Me
2-66a
Chemical Shift (ppm)

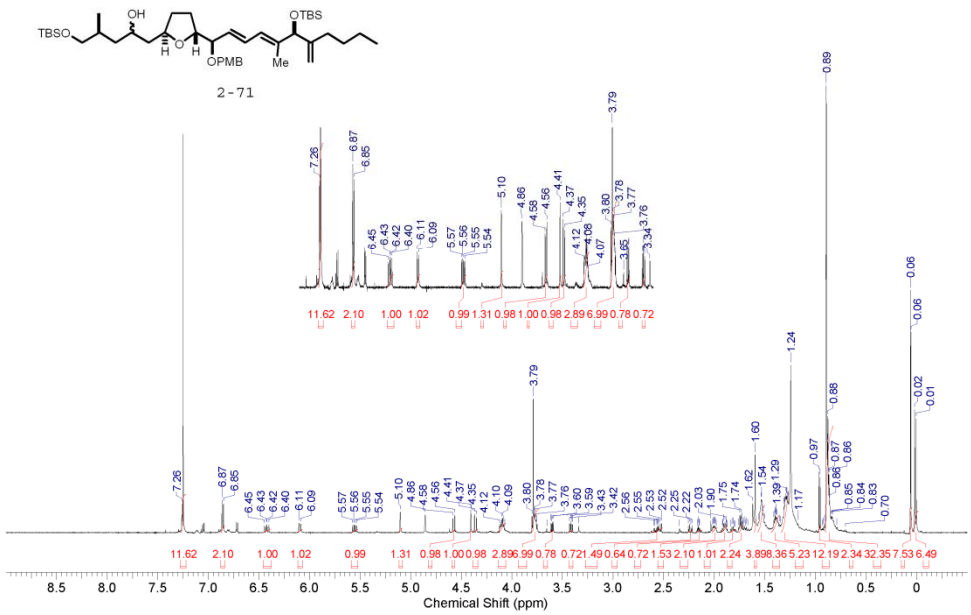

TBSO
OTBS
OPMB
Me
2-66a
Chemical Shift (ppm)

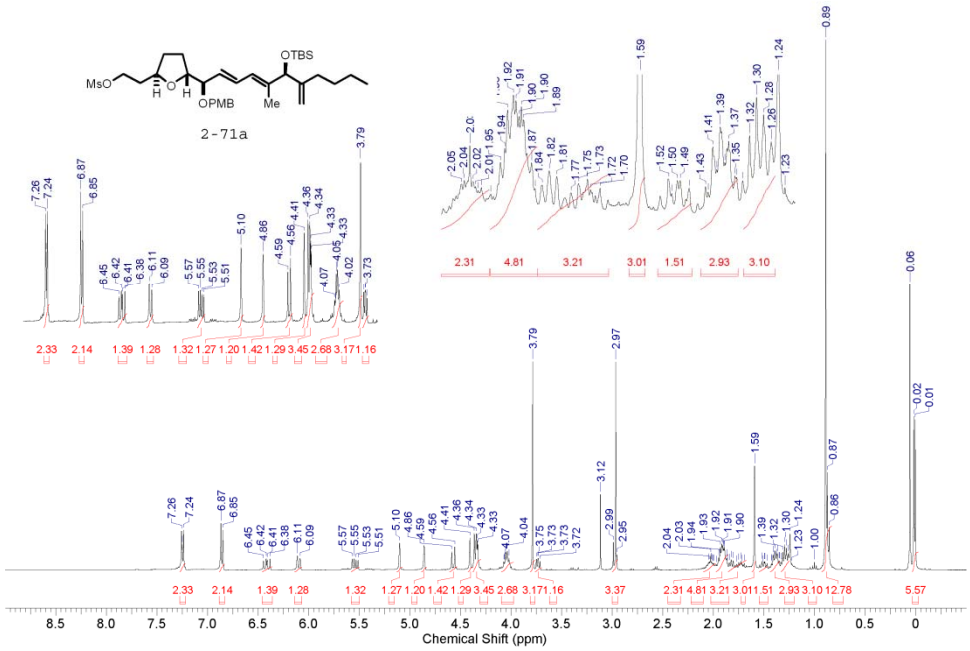

HO
OTBS
OPMB
Me
2-67
Chemical Shift (ppm)

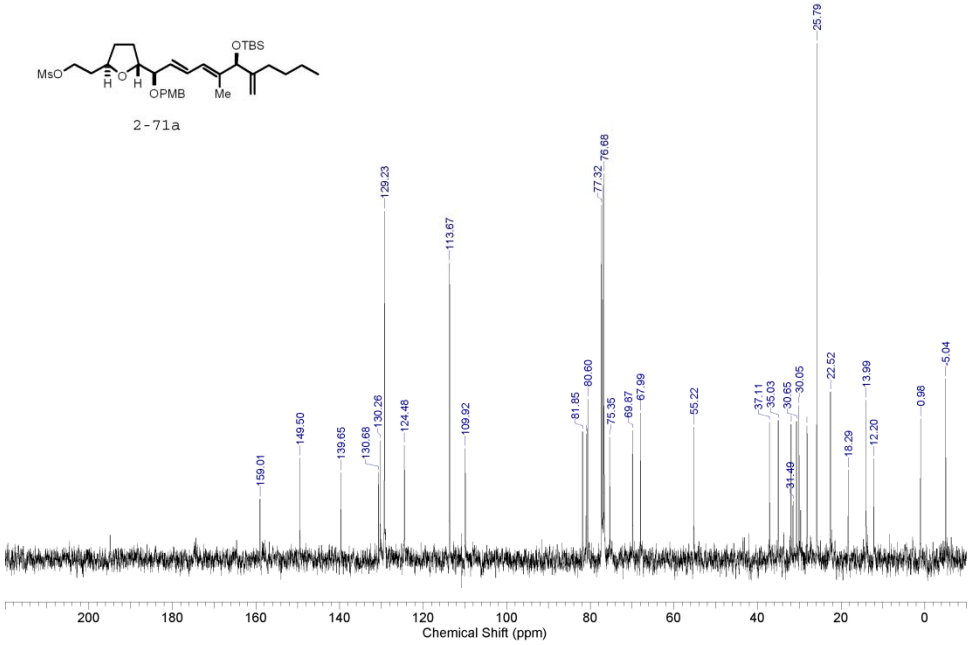

HO
OTBS
OPMB
Me
2-67
Chemical Shift (ppm)

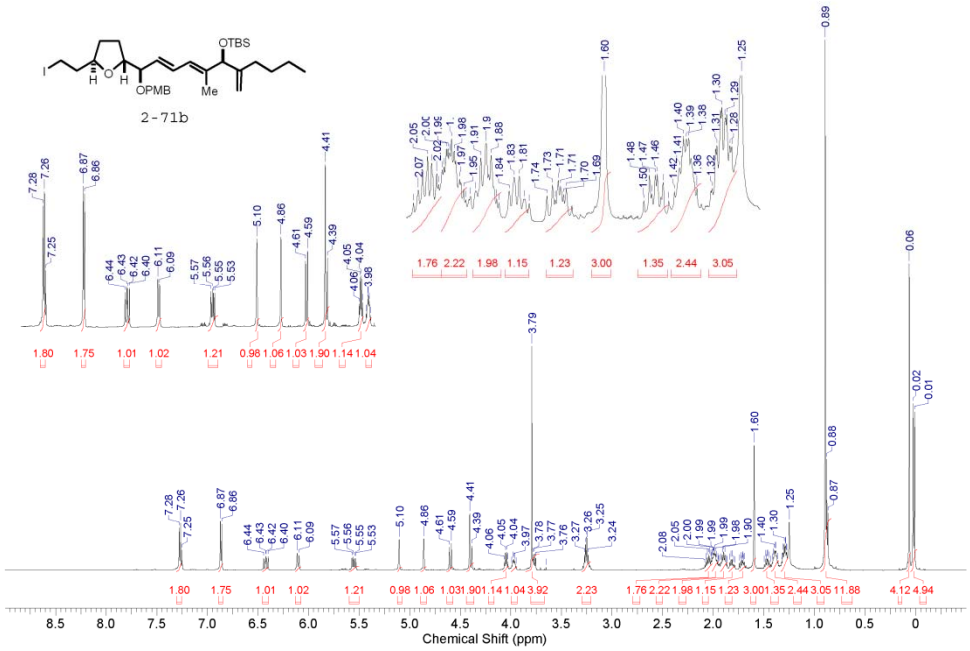

OTBS
OPMB
Me
2-68
Chemical Shift (ppm)

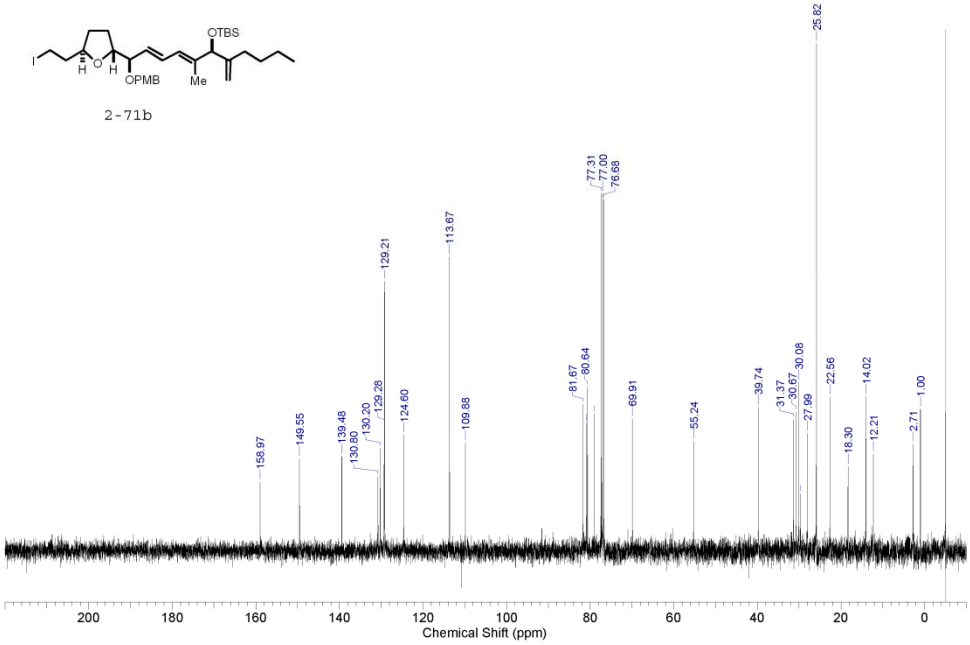

OTBS
OPMB
Me
2-69
Chemical Shift (ppm)

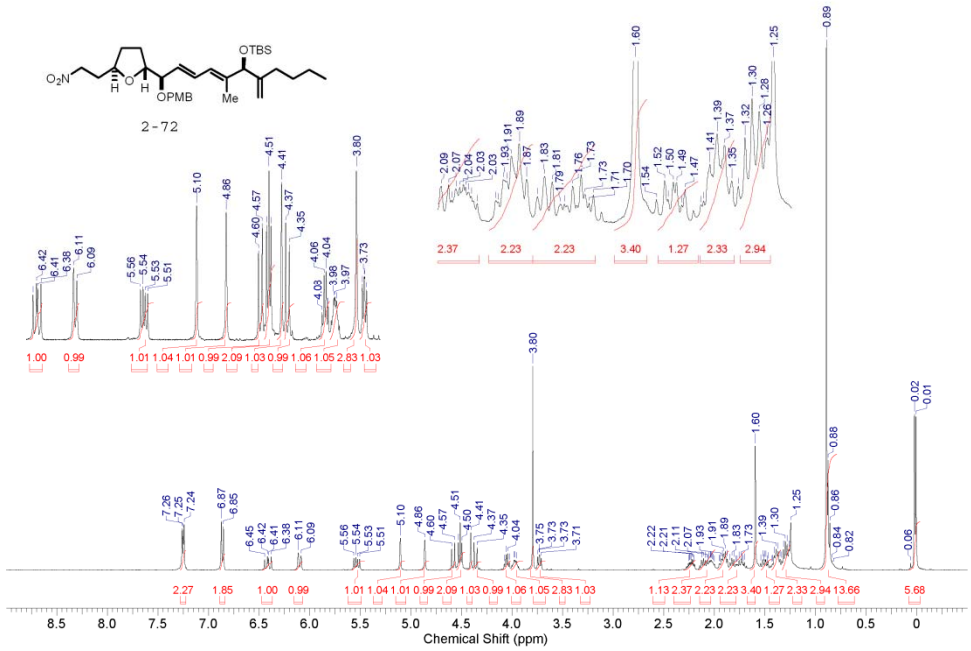

TBSO
OH
OTBS
OPMB
Me
2-71
Chemical Shift (ppm)


MsO
OTBS
OPMB
Me
2-71a
Chemical Shift (ppm)

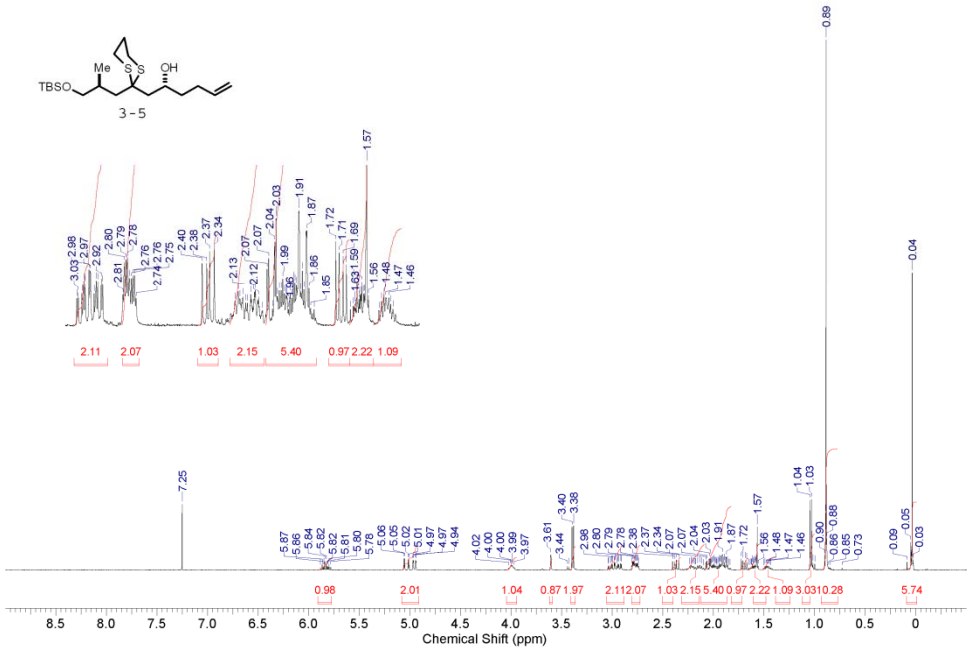

MsO
OTBS
OPMB
Me
2-71a
Chemical Shift (ppm)

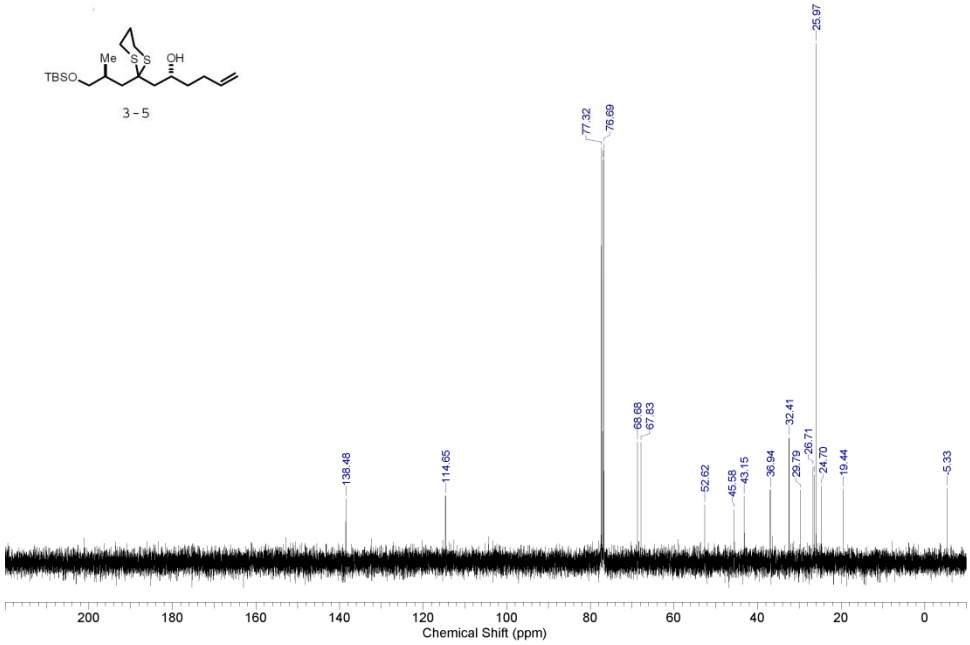

OTBS
OPMB
Me
2-71b
Chemical Shift (ppm)

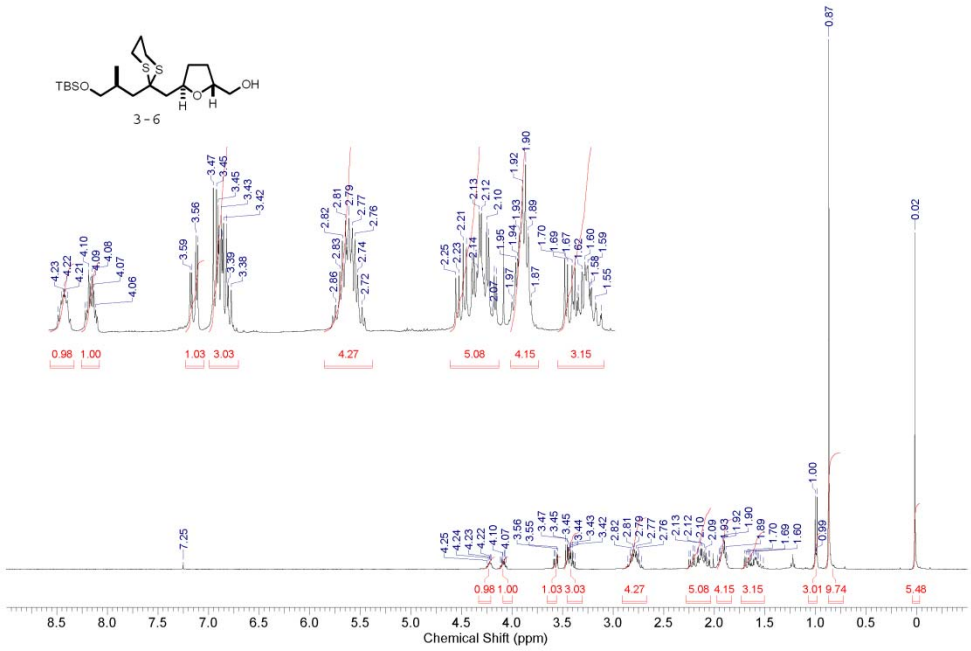

OTBS
OPMB
Me
2-71b
Chemical Shift (ppm)

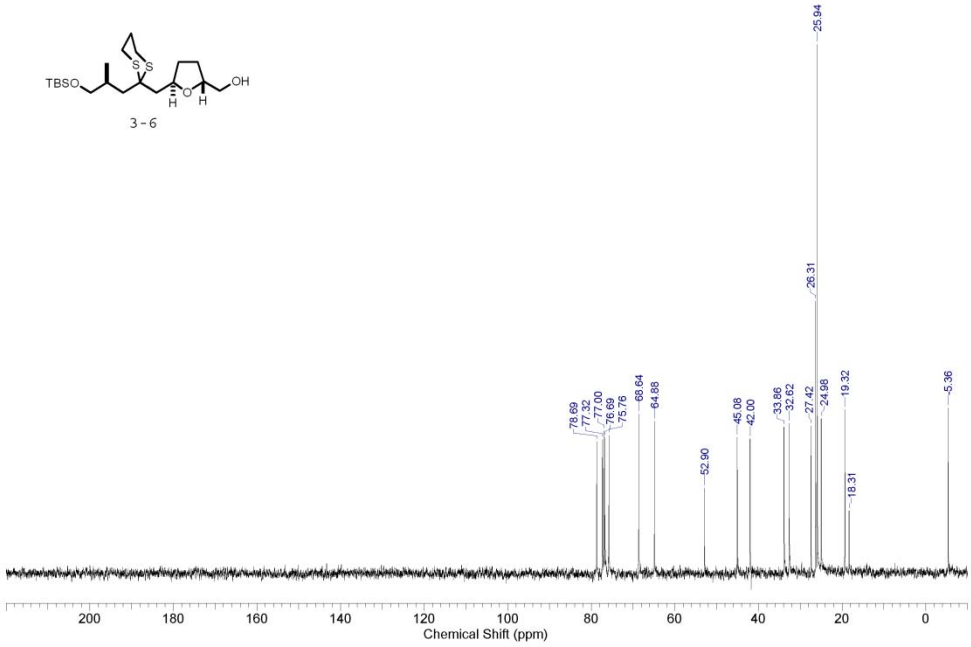

OTBS
O2N
H
O
H
OPMB
Me
2-72
Chemical Shift (ppm)

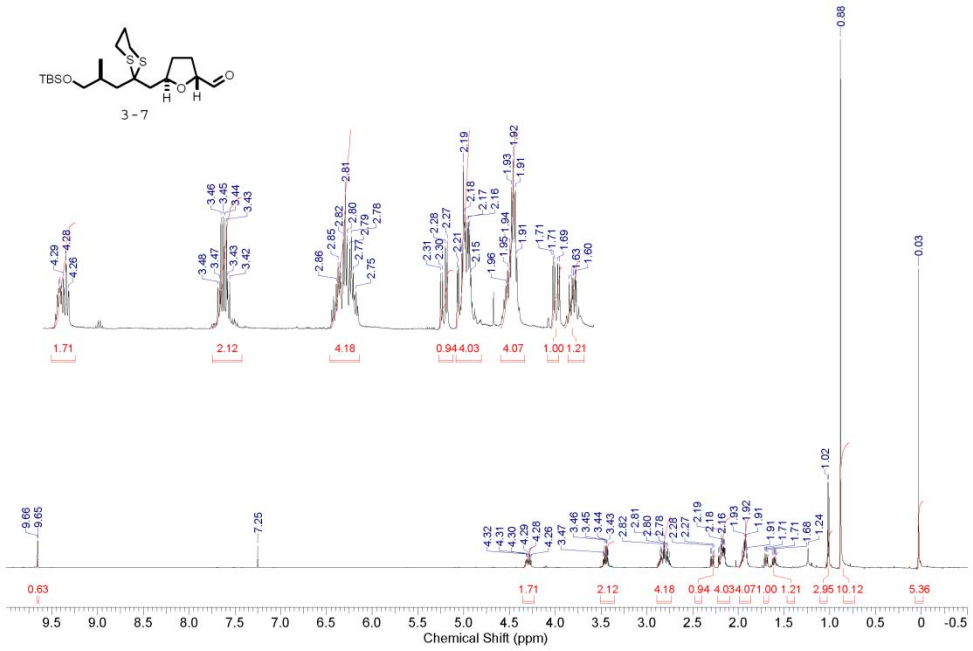
Appendix 3 – Spectra for Chapter 3 Compounds

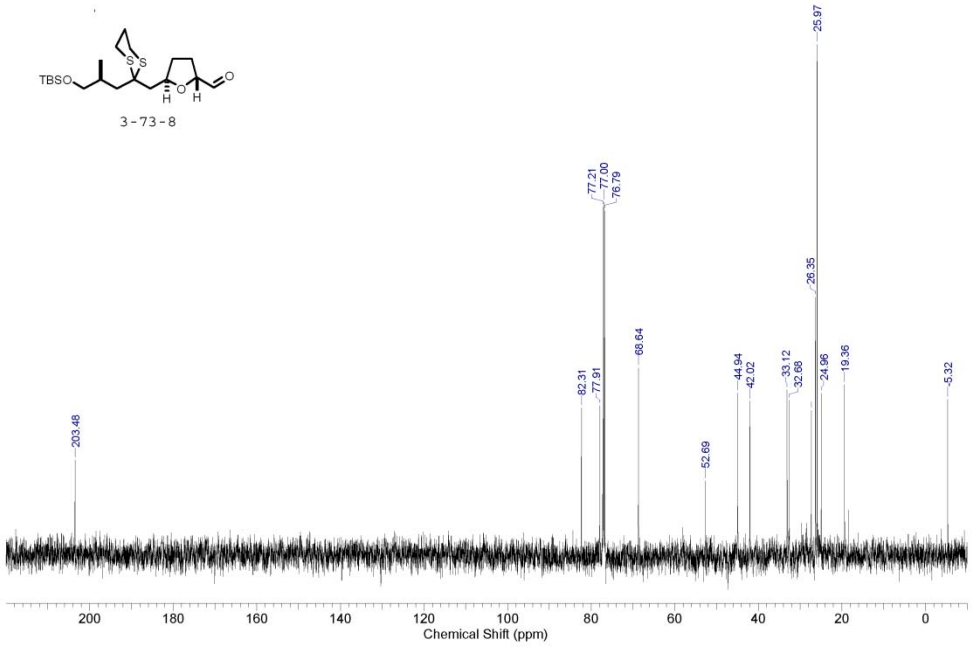

Me
S
S
OH
TBSO
3-5
Chemical Shift (ppm)

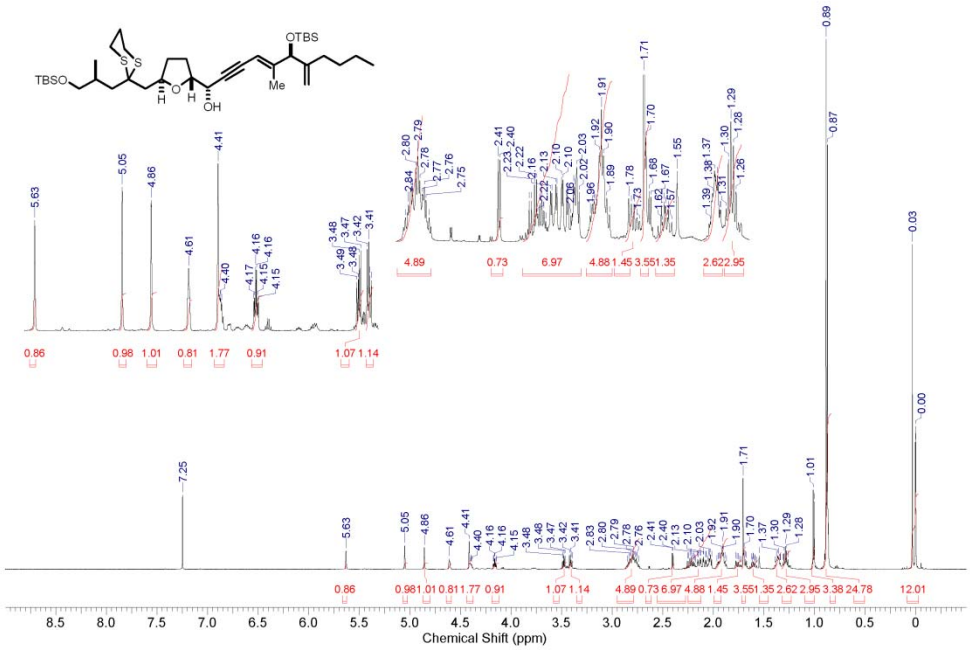

Me
S
S
OH
TBSO
3-5
Chemical Shift (ppm)

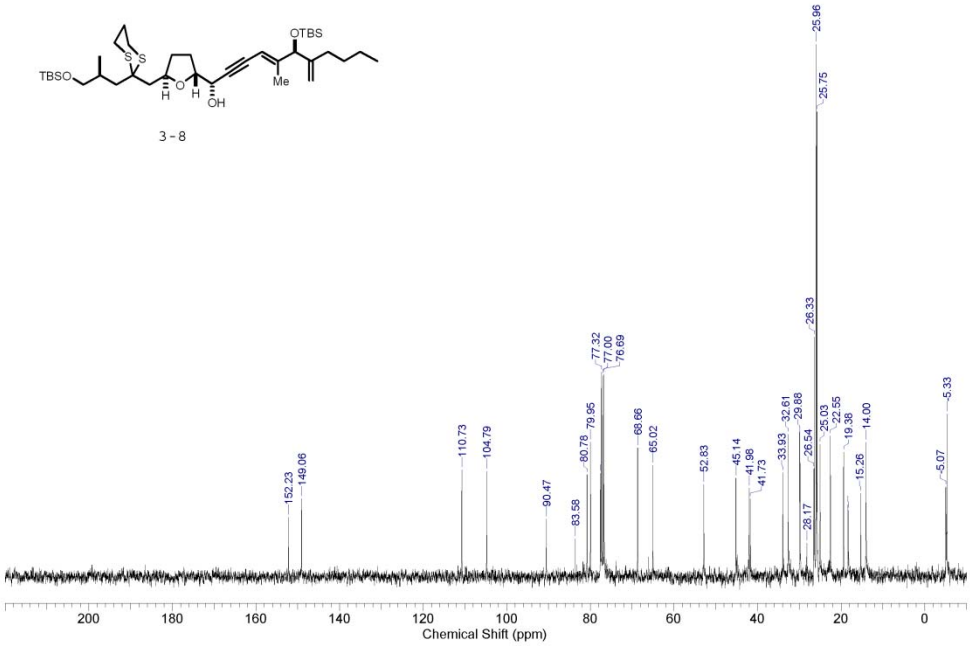

TBSO
OH
3-6
Chemical Shift (ppm)

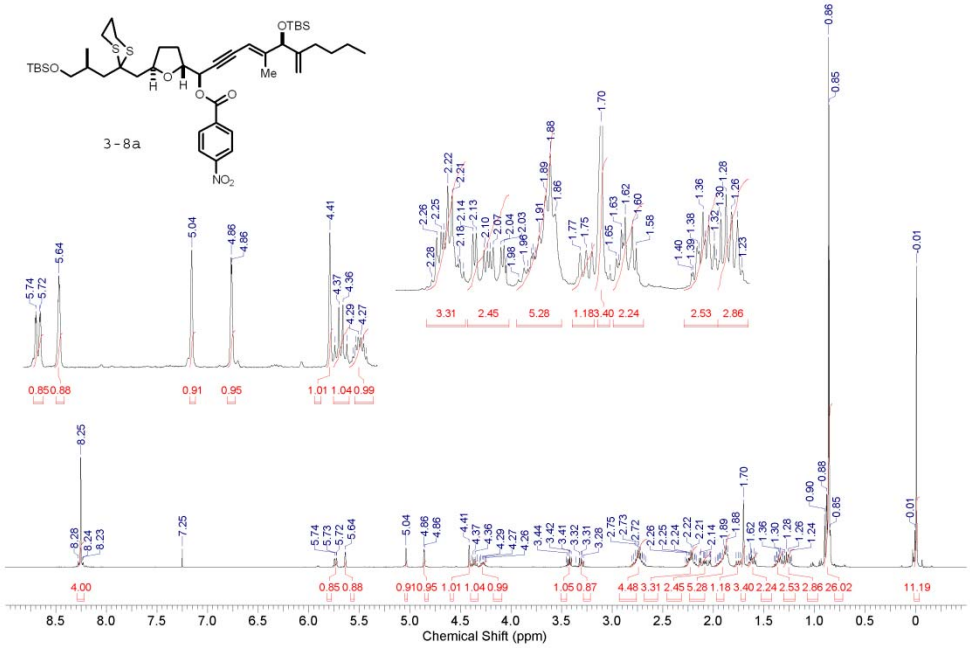

TBSO
OH
3-6
Chemical Shift (ppm)

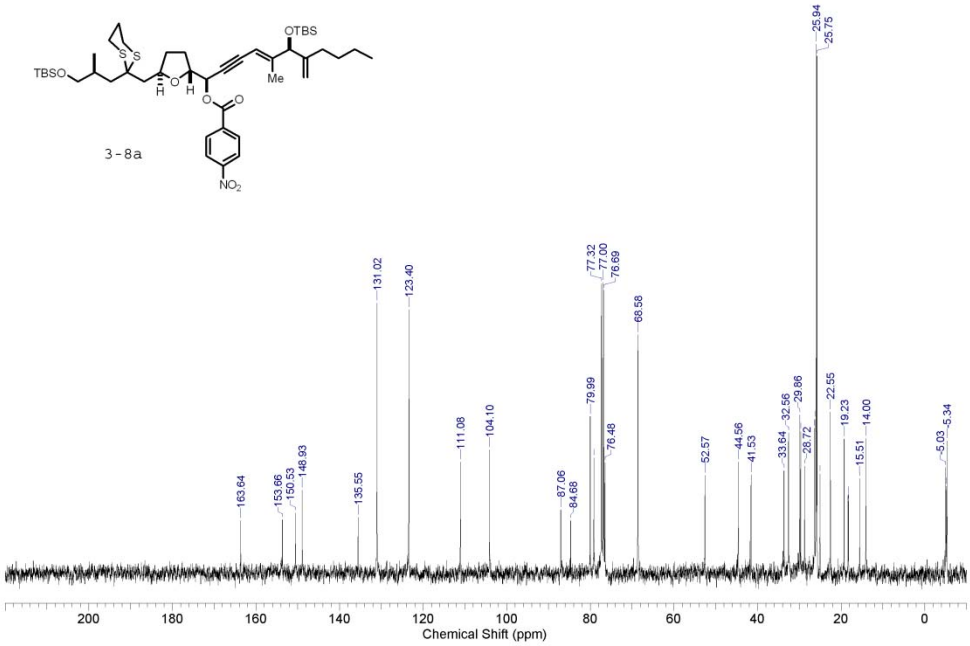

TBSO
3-7
Chemical Shift (ppm)

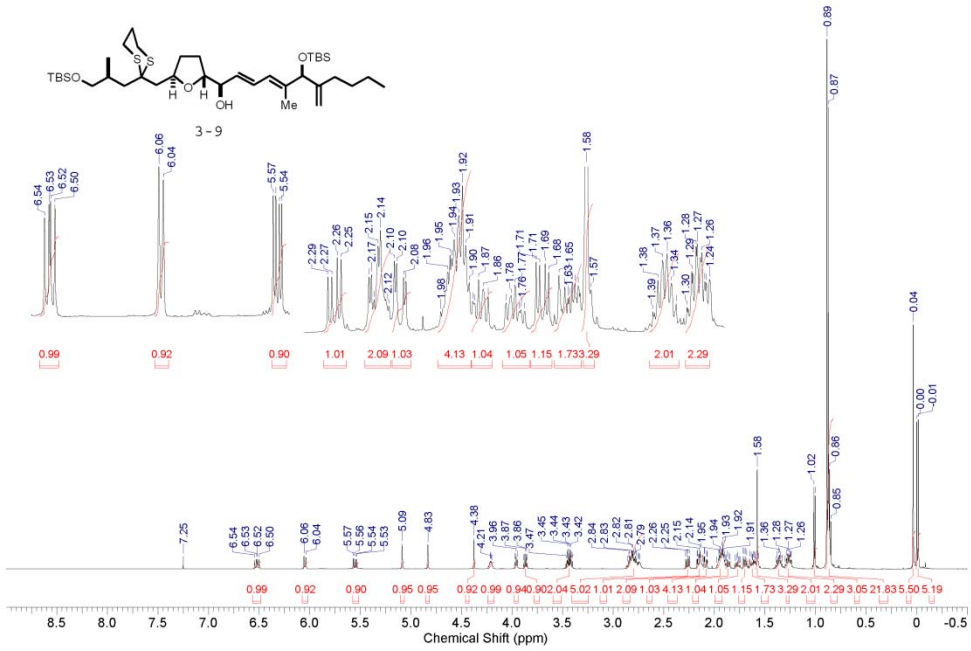

TBSO
3-73-8
Chemical Shift (ppm)

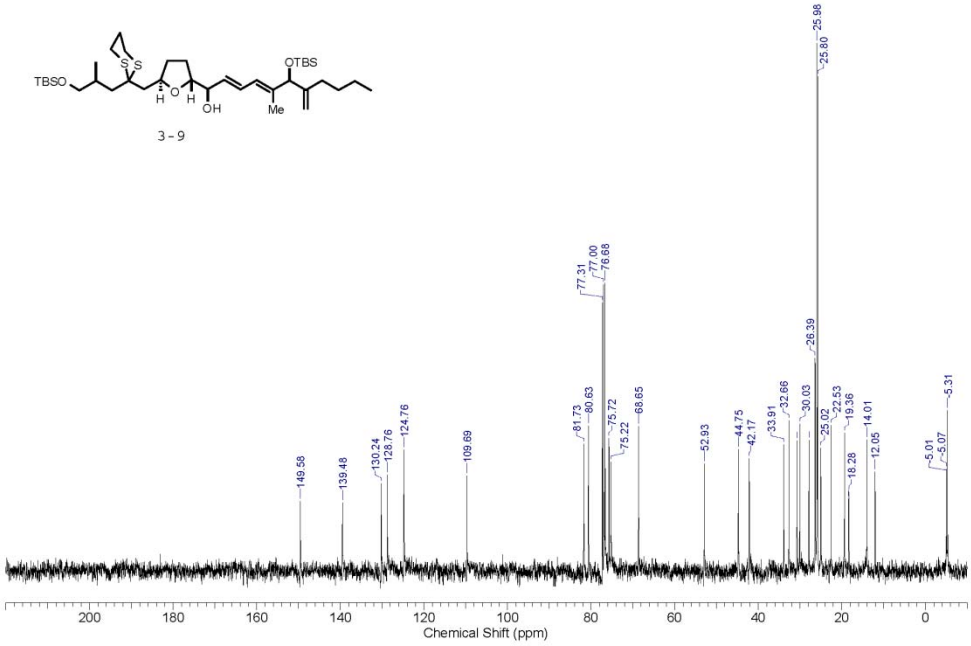

OTBS
TBSO
Me
OH
Chemical Shift (ppm)

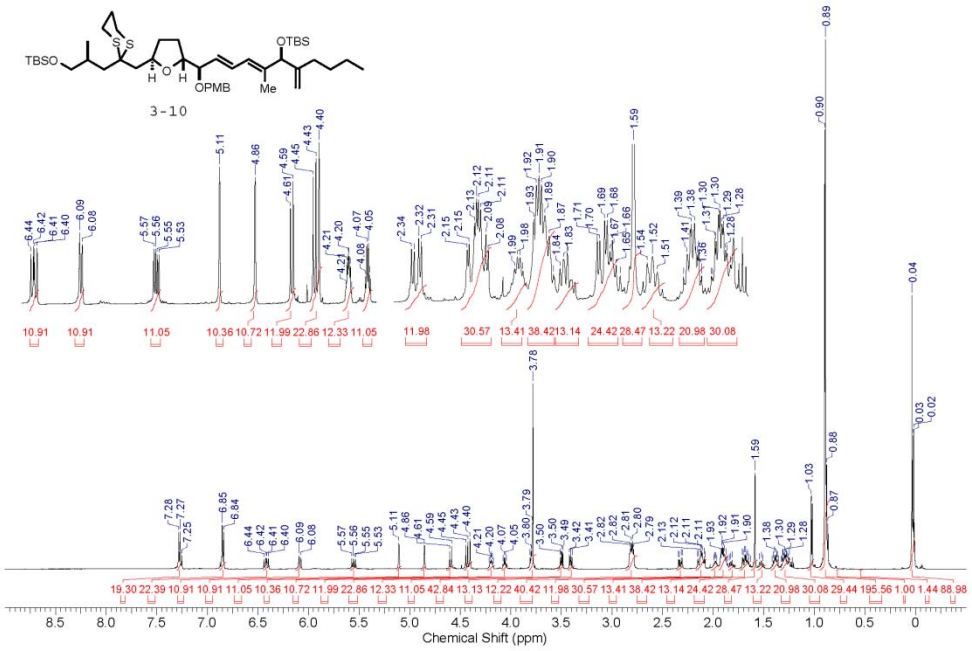

OTBS
TBSO
Me
OH
3 - 8
Chemical Shift (ppm)

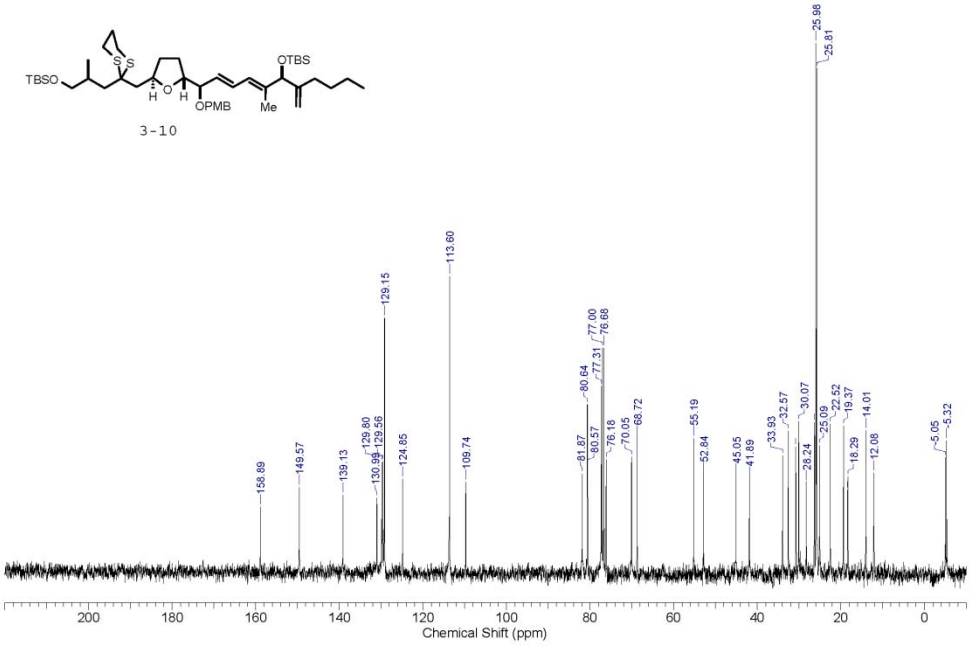

OTBS
TBSO
Me
3-8a
NO2
Chemical Shift (ppm)

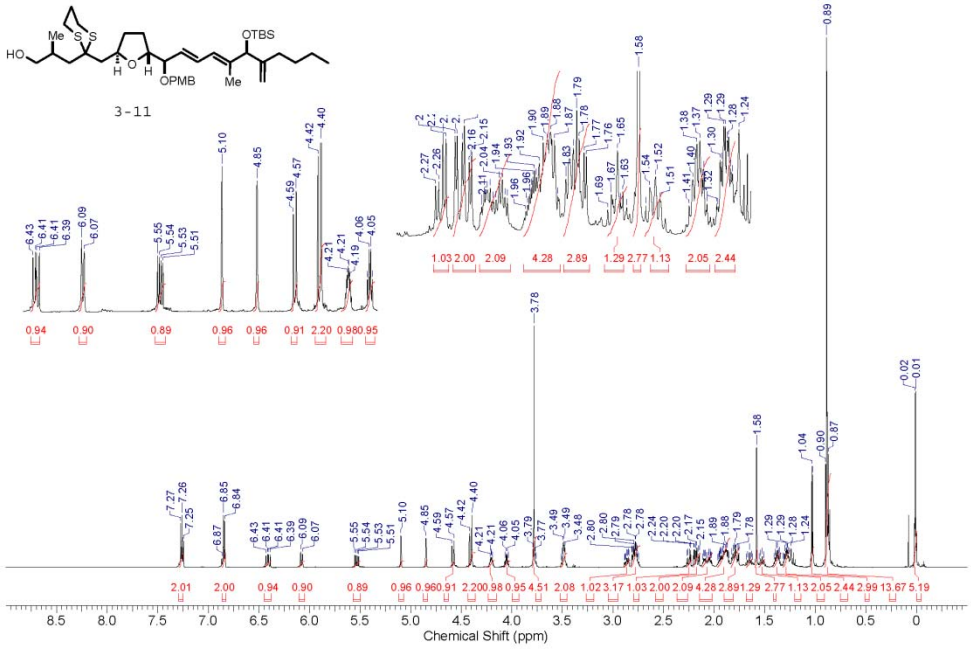

OTBS
TBSO
Me
3-8a
NO2
Chemical Shift (ppm)

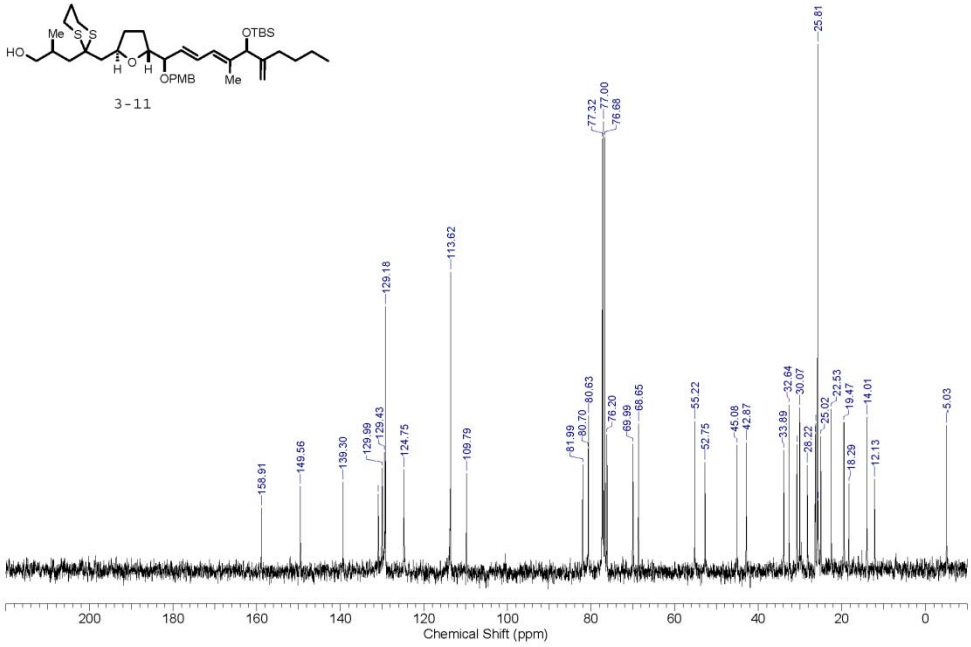

TBSO
OTBS
OH
Me
3 - 9
Chemical Shift (ppm)

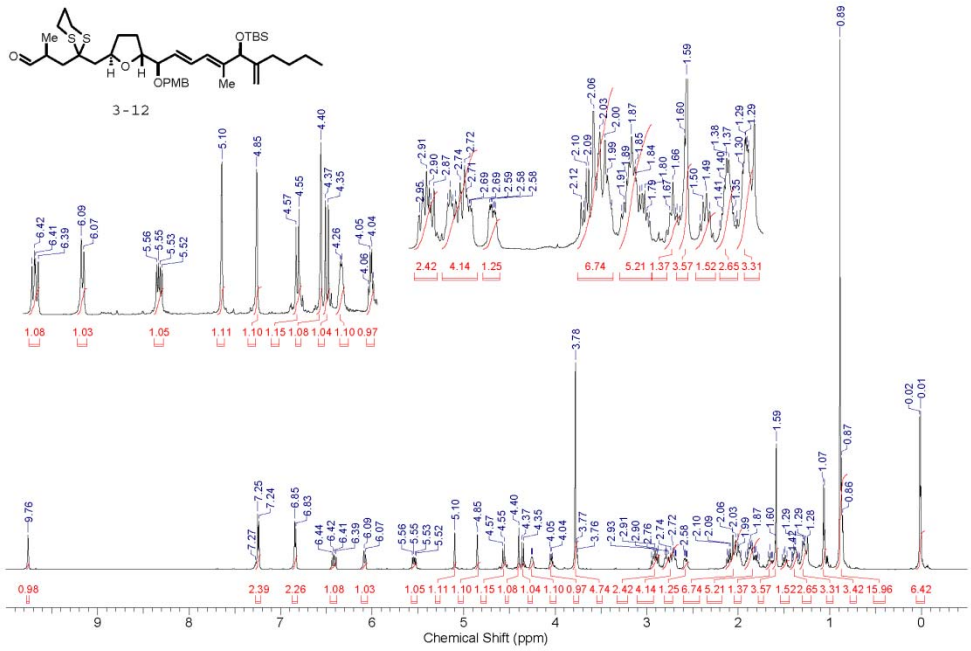

TBSO
OTBS
OH
Me
3 - 9
Chemical Shift (ppm)

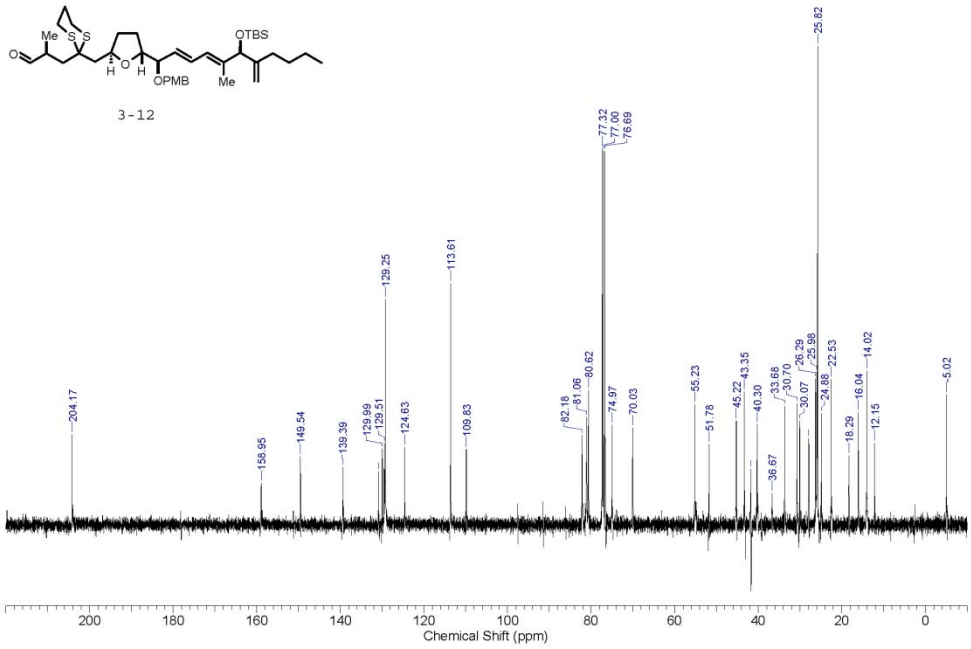

TBSO
OTBS
OPMB
Me
3-10
Chemical Shift (ppm)

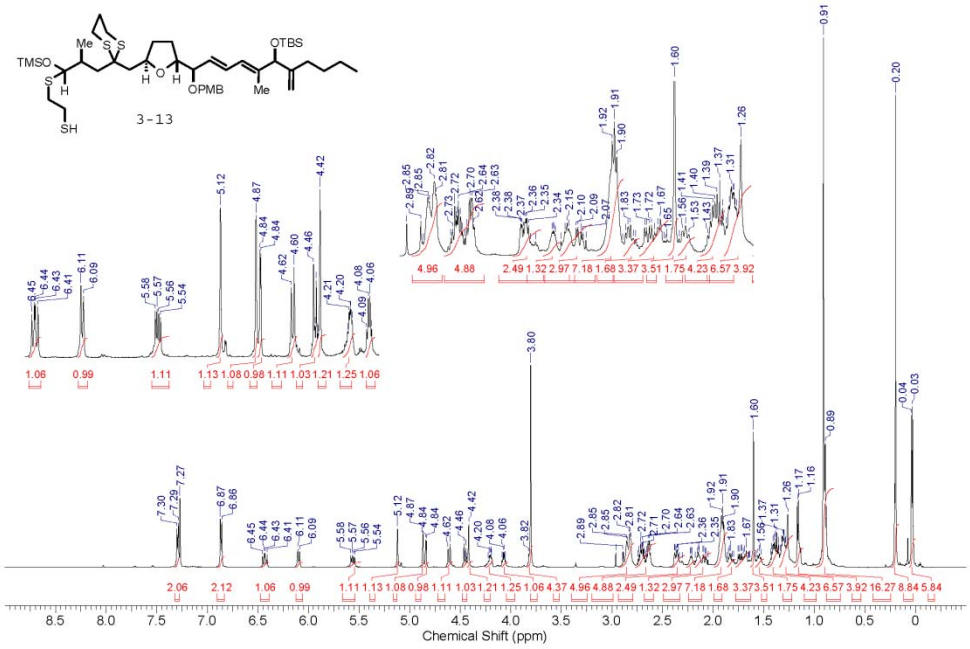

TBSO
OTBS
OPMB
Me
3-10
Chemical Shift (ppm)

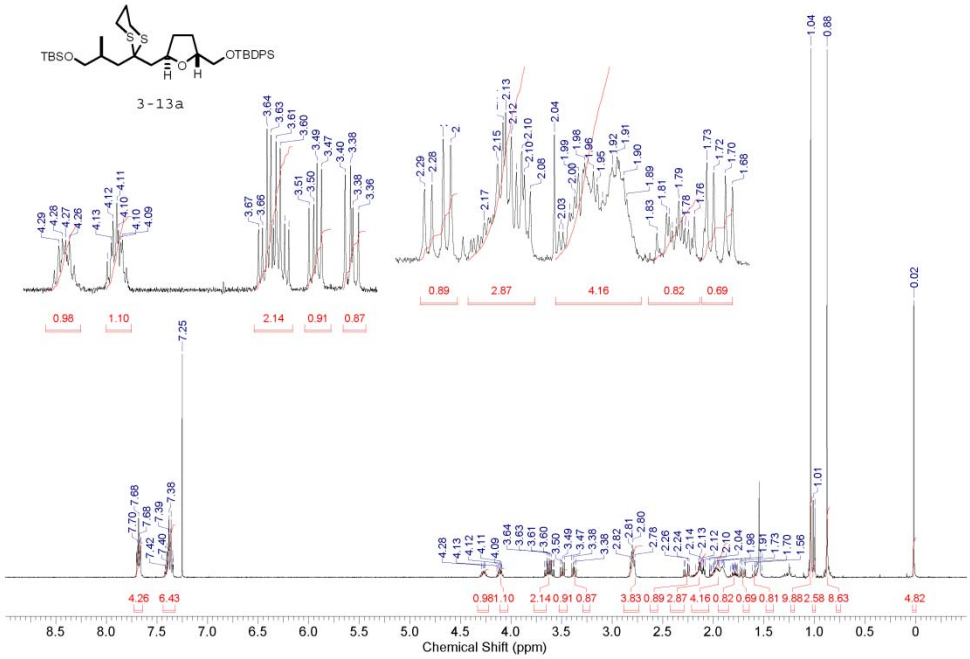

3-11
Chemical Shift (ppm)

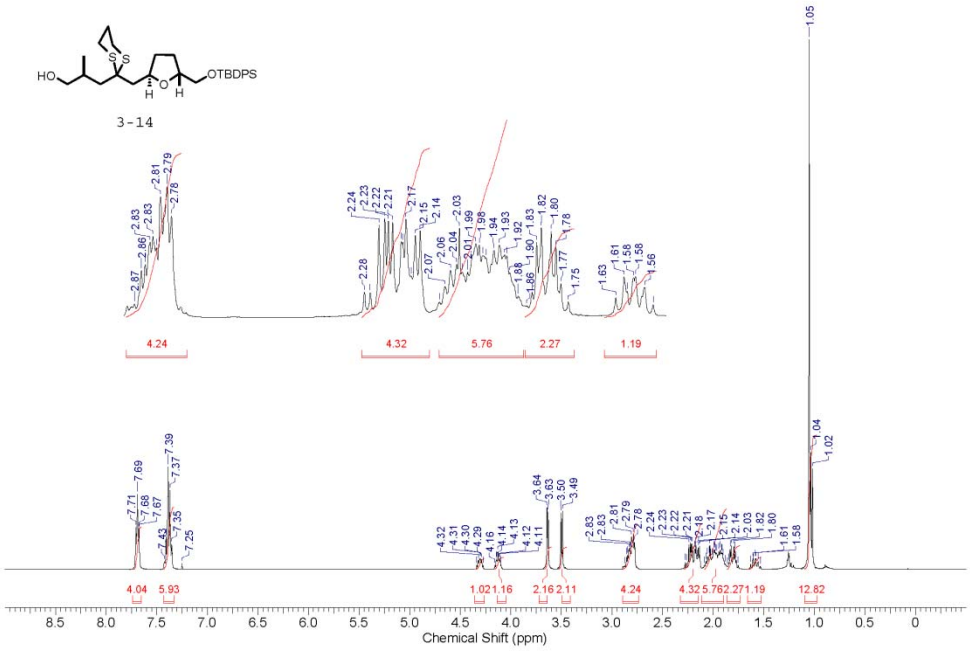

3-11
Chemical Shift (ppm)

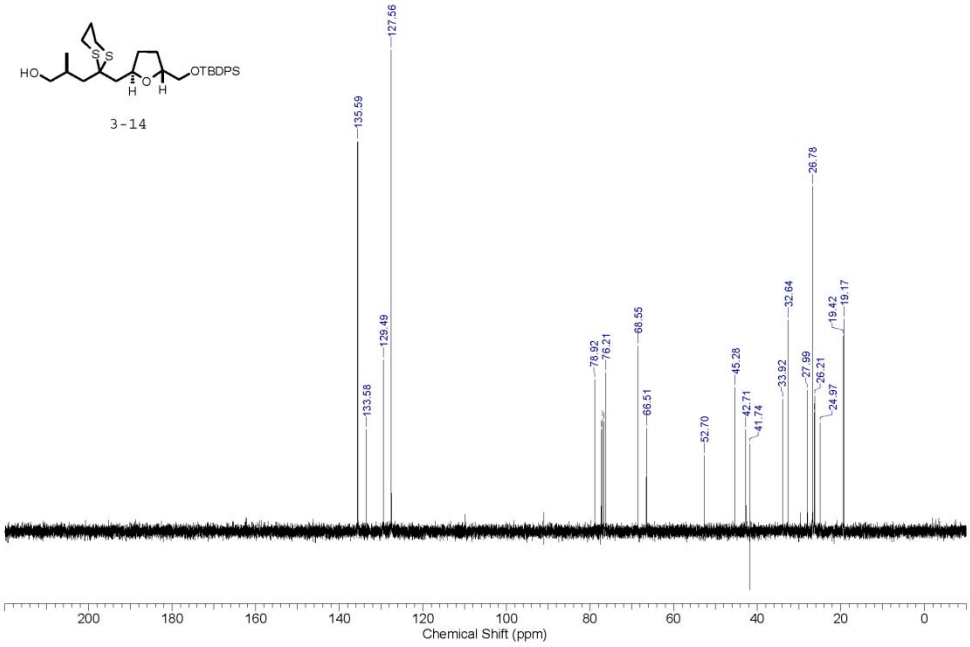

Me
S
S
O
H
O
H
OPMB
Me
OTBS
3-12
Chemical Shift (ppm)

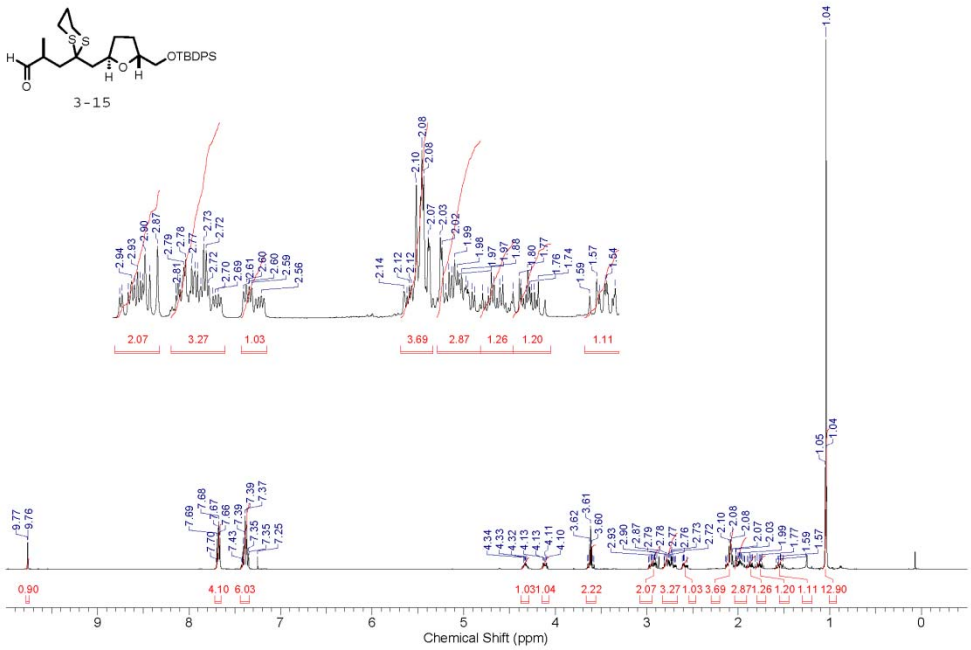

Me
S
S
O
H
O
H
OPMB
Me
OTBS
3-12
Chemical Shift (ppm)

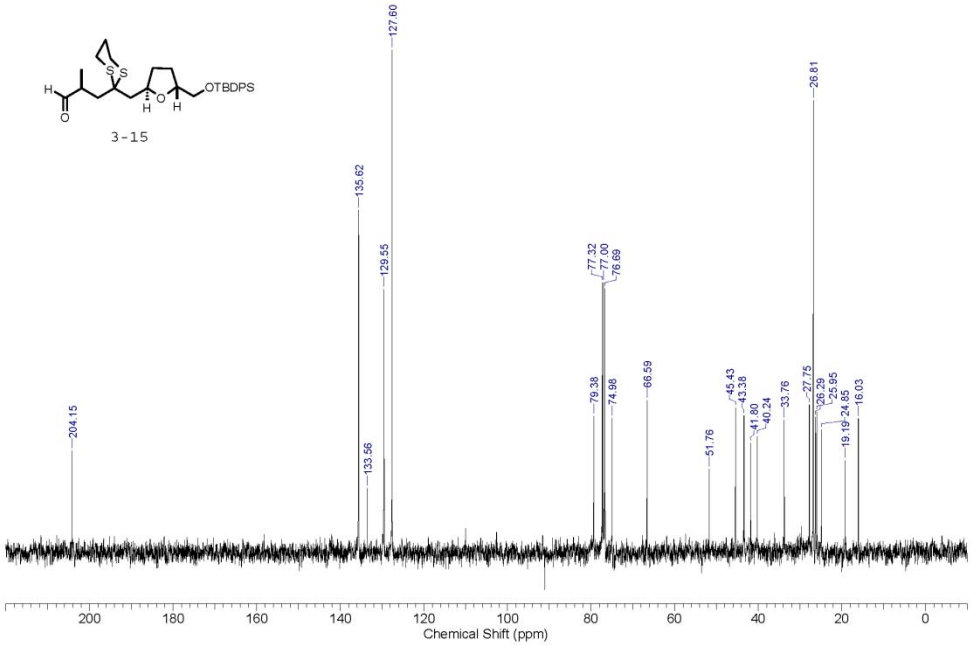

TMSO
Me
OTBS
OPMB
Me
SH
3-13
Chemical Shift (ppm)

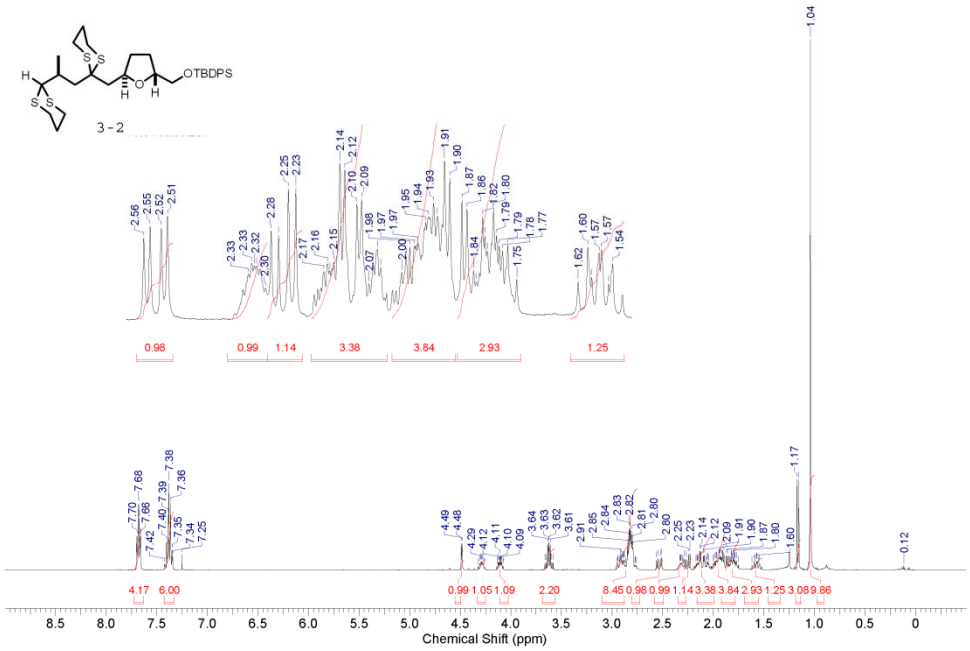

TBSO
OTBDPS
3-13a
Chemical Shift (ppm)

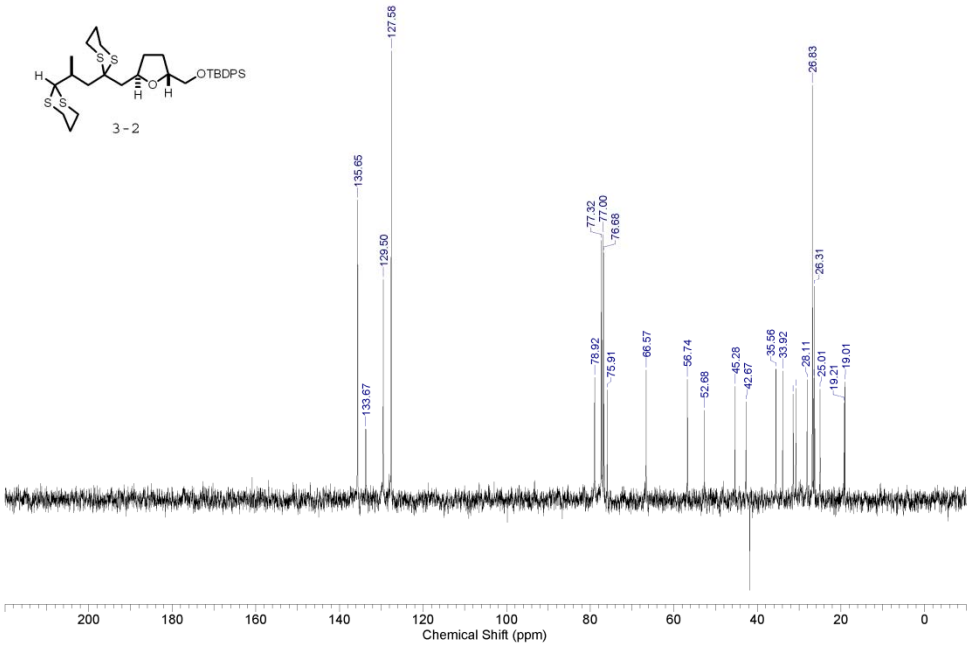

HO
OTBDPS
3-14
Chemical Shift (ppm)

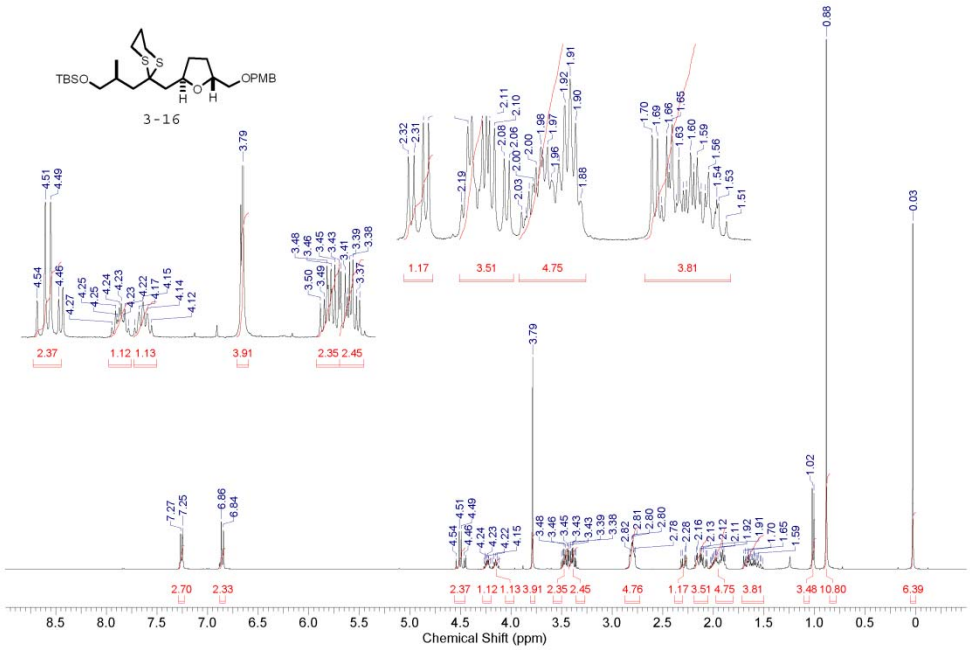

HO
OTBDPS
3-14
Chemical Shift (ppm)

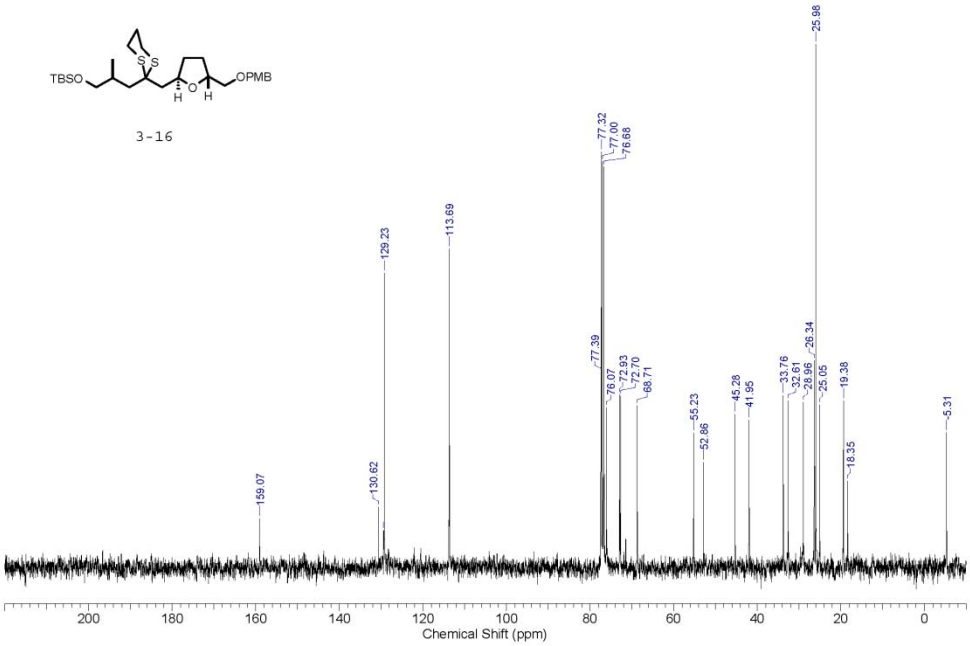

OTBDPS
3-15
Chemical Shift (ppm)

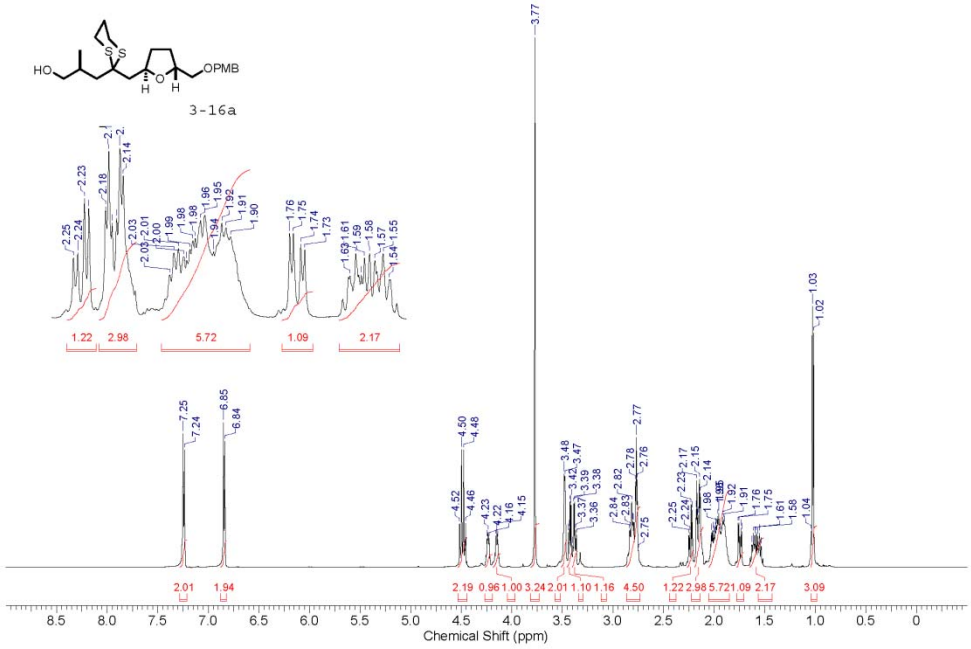

OTBDPS
3-15
Chemical Shift (ppm)

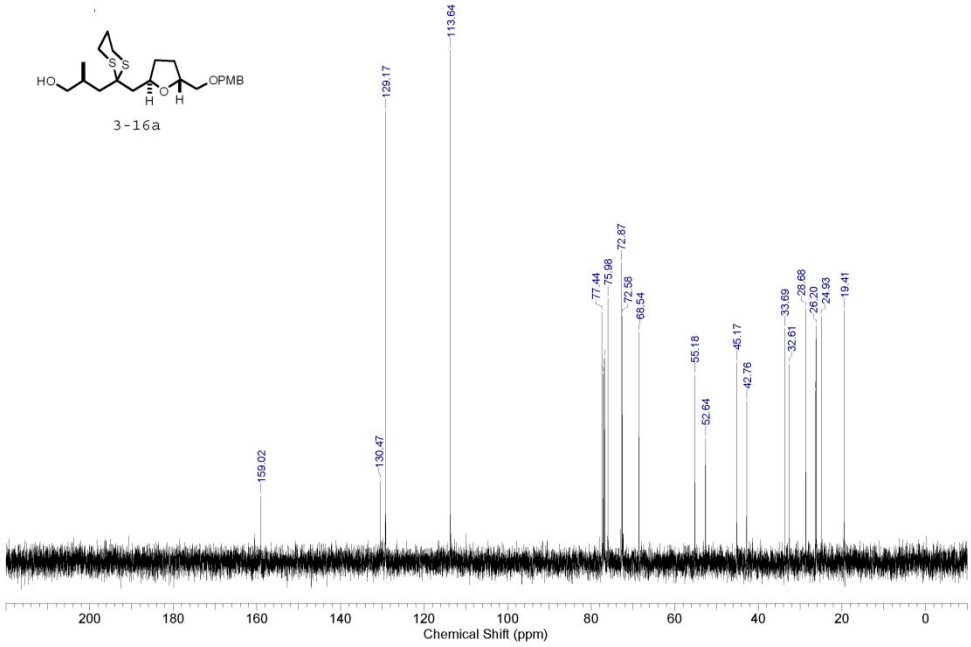

OTBDPS
3-2
Chemical Shift (ppm)

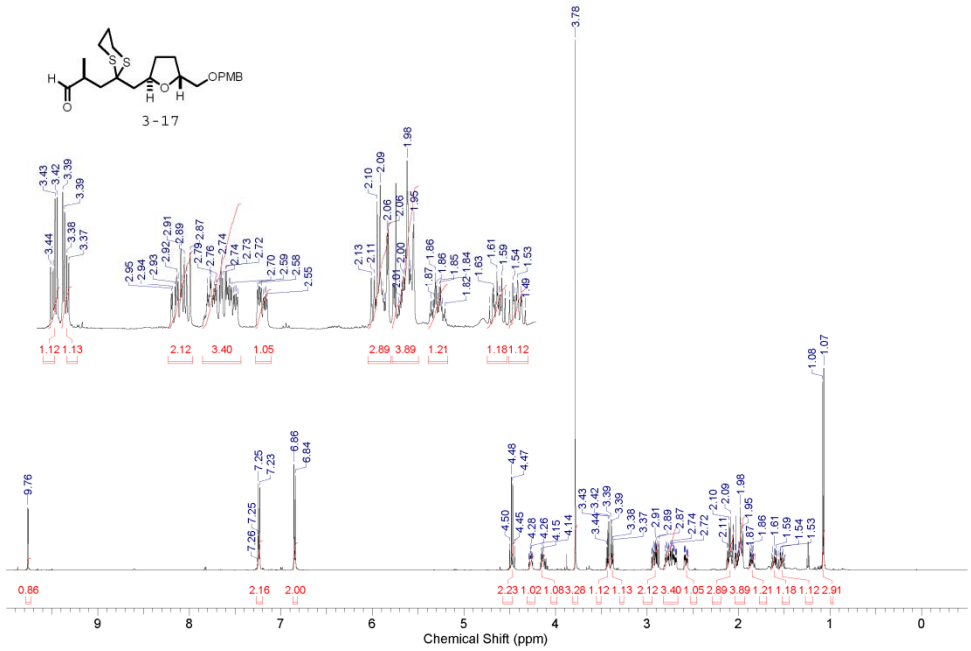

OTBDPS
3-2
Chemical Shift (ppm)

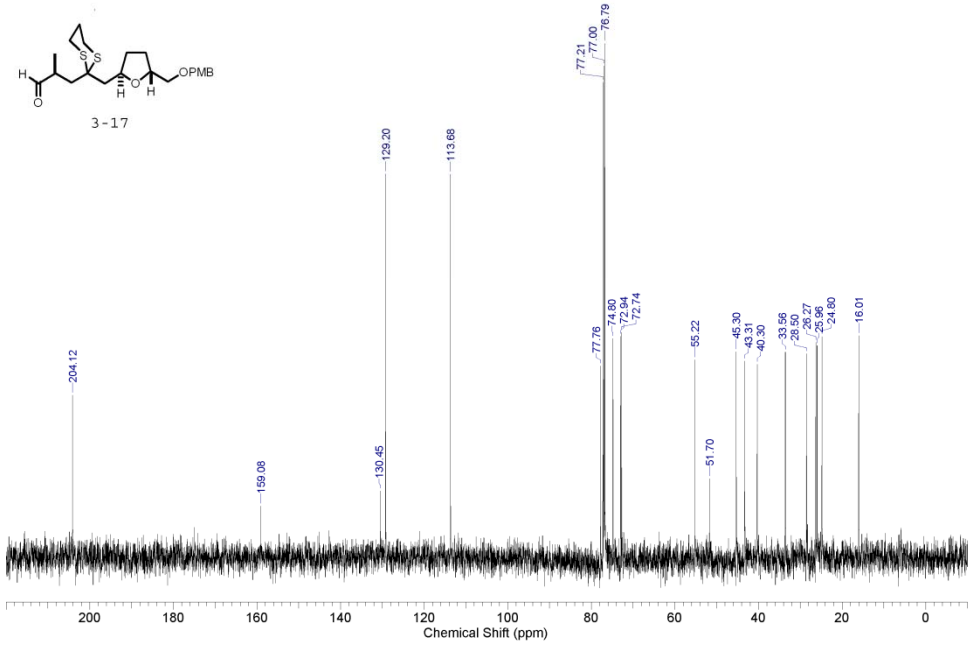

TBSO
OPMB
3-16
Chemical Shift (ppm)

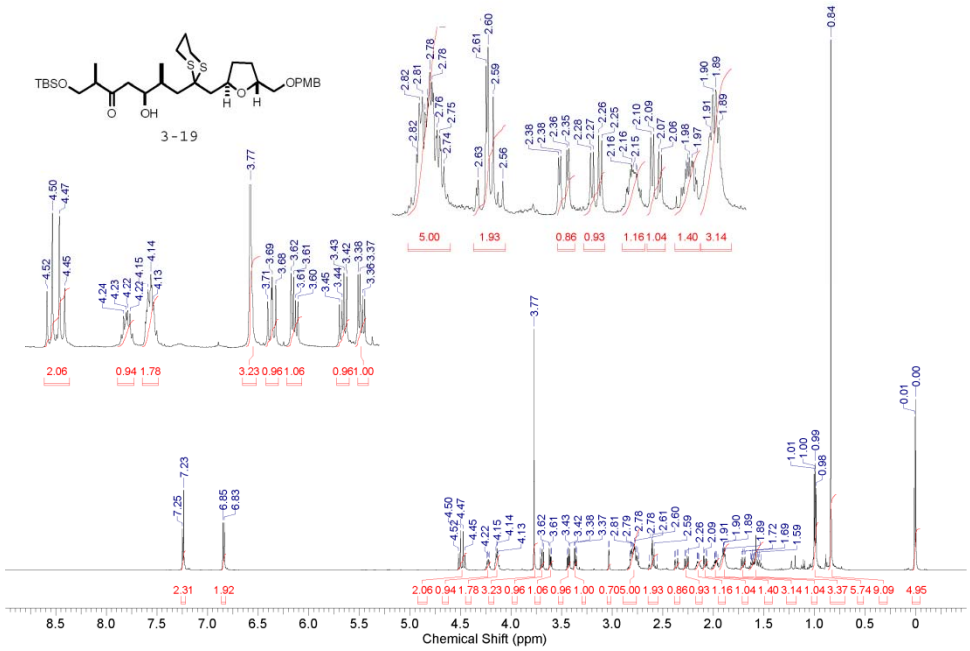

TBSO
OPMB
3-16
Chemical Shift (ppm)

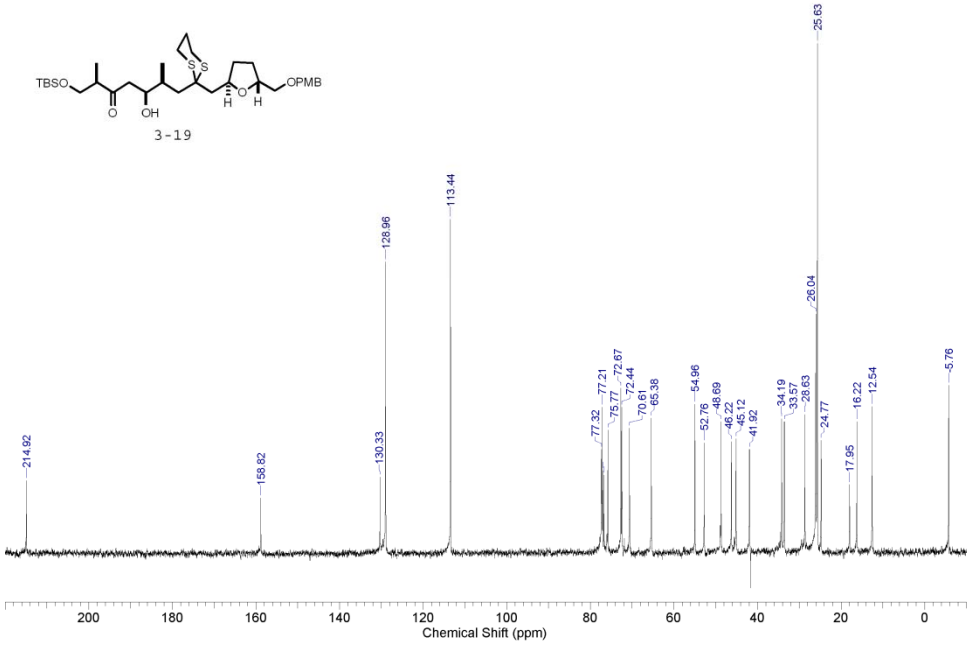

HO
OPMB
3-16a
Chemical Shift (ppm)

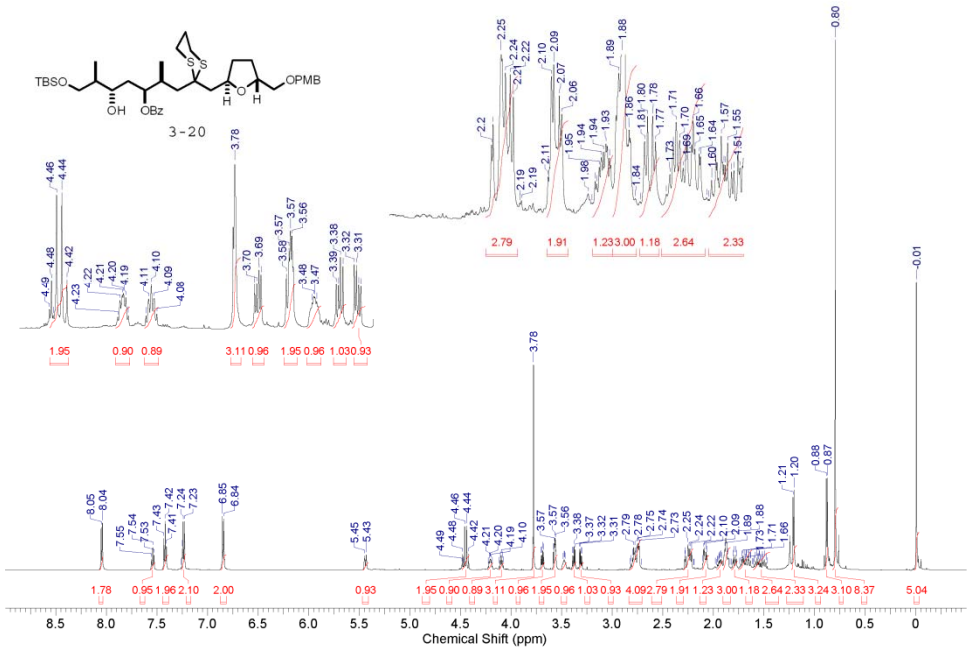

HO
OPMB
3-16a
Chemical Shift (ppm)

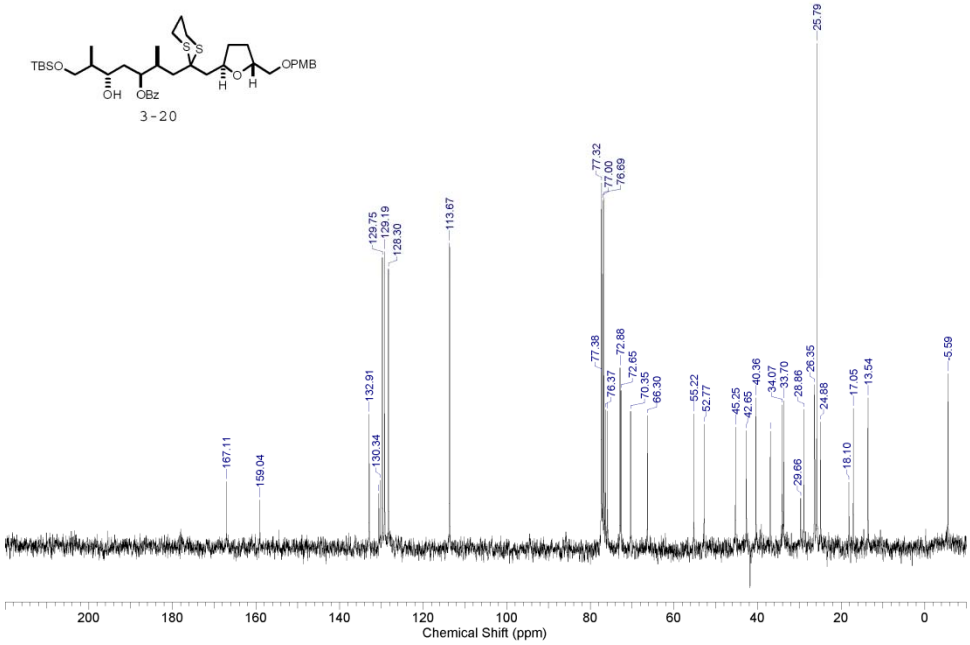

OPMB
3-17
Chemical Shift (ppm)

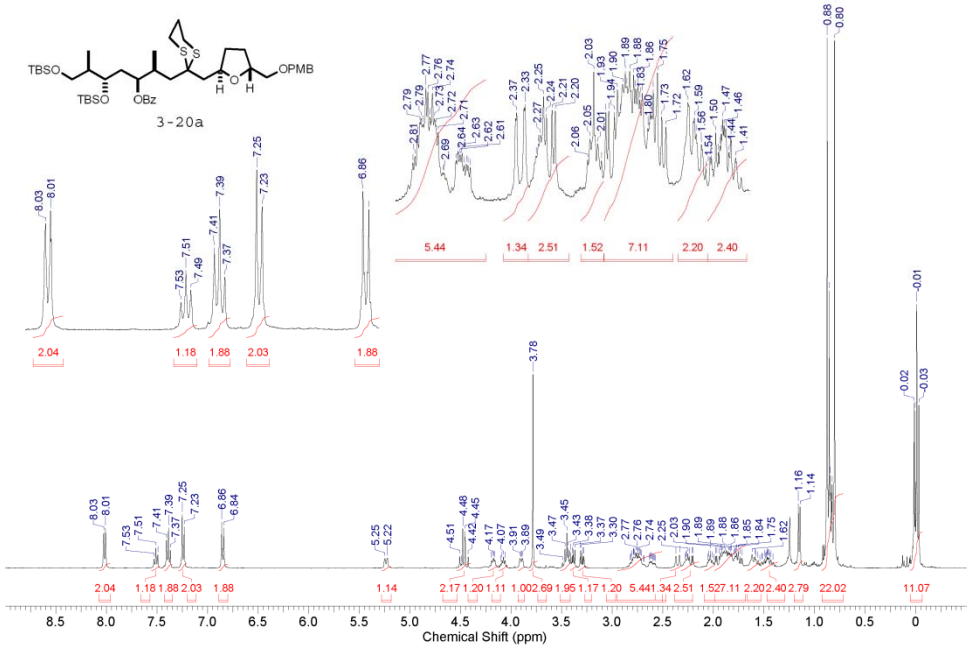

OPMB
3-17
Chemical Shift (ppm)

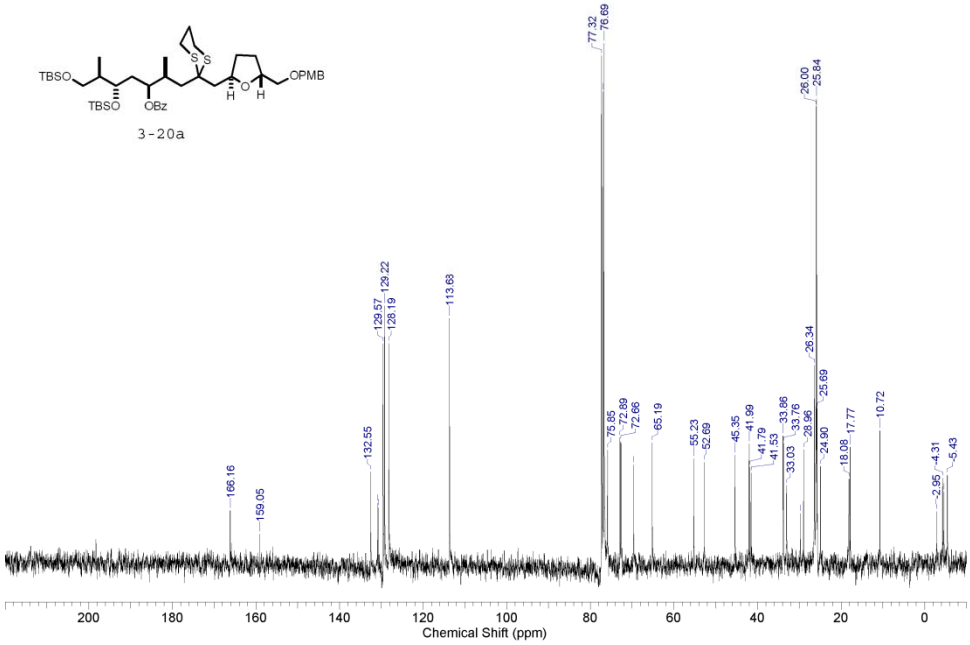

TBSO
OPMB
OH
3-19
Chemical Shift (ppm)

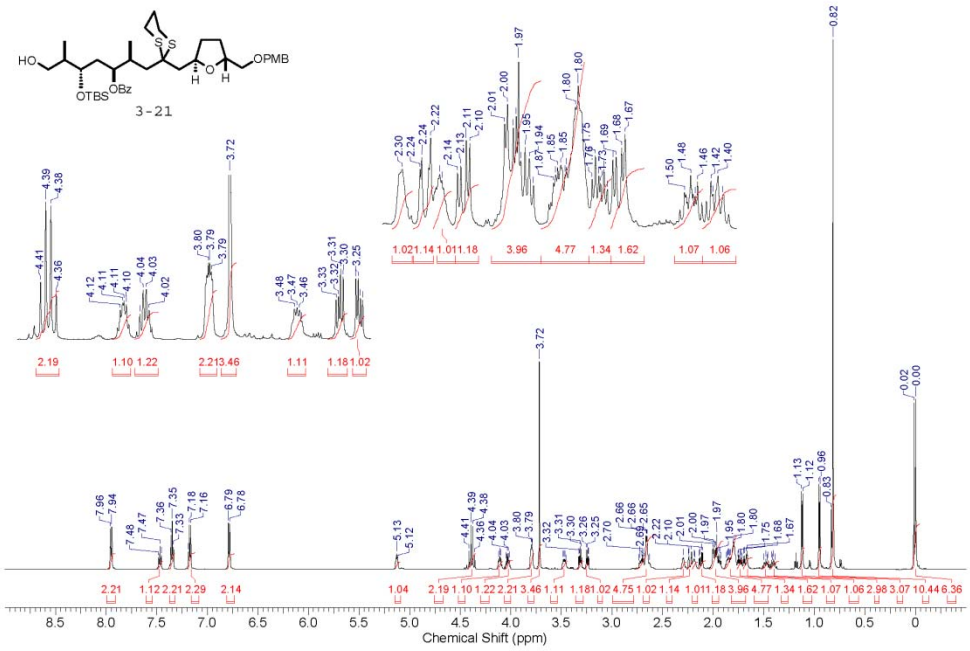

TBSO
OPMB
OH
3-19
Chemical Shift (ppm)

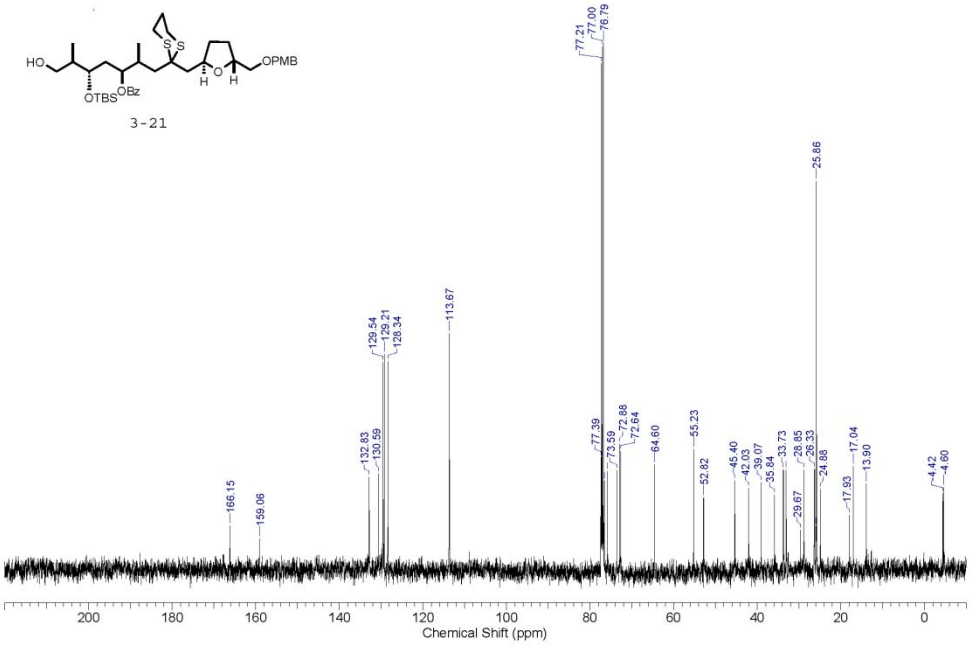

TBSO
OH
OBz
S
S
O
H
H
OPMB
3-20
Chemical Shift (ppm)

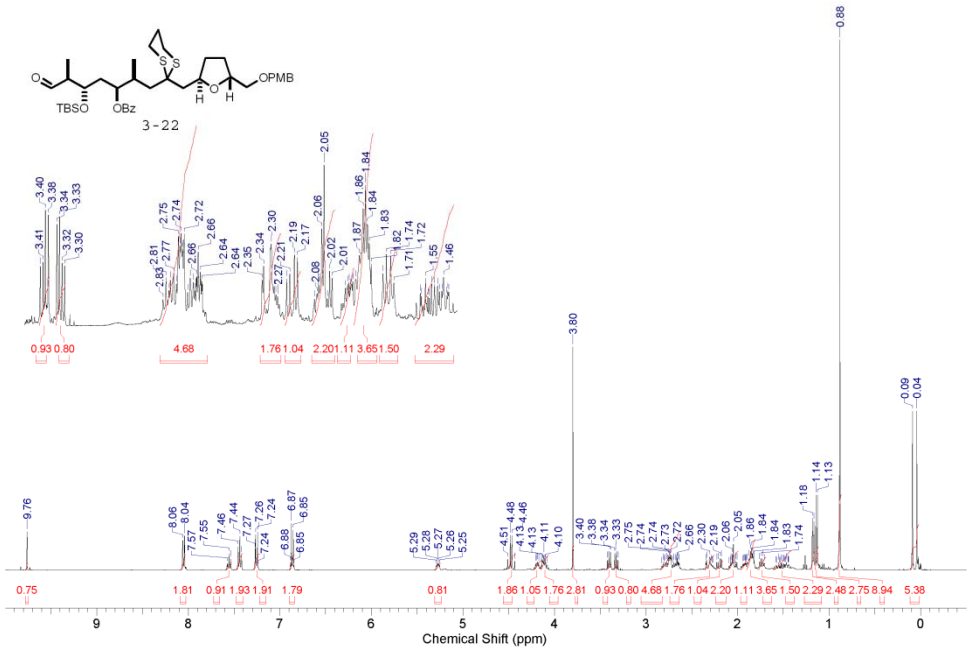

TBSO
OH
OBz
S
S
O
H
H
OPMB
3-20
Chemical Shift (ppm)

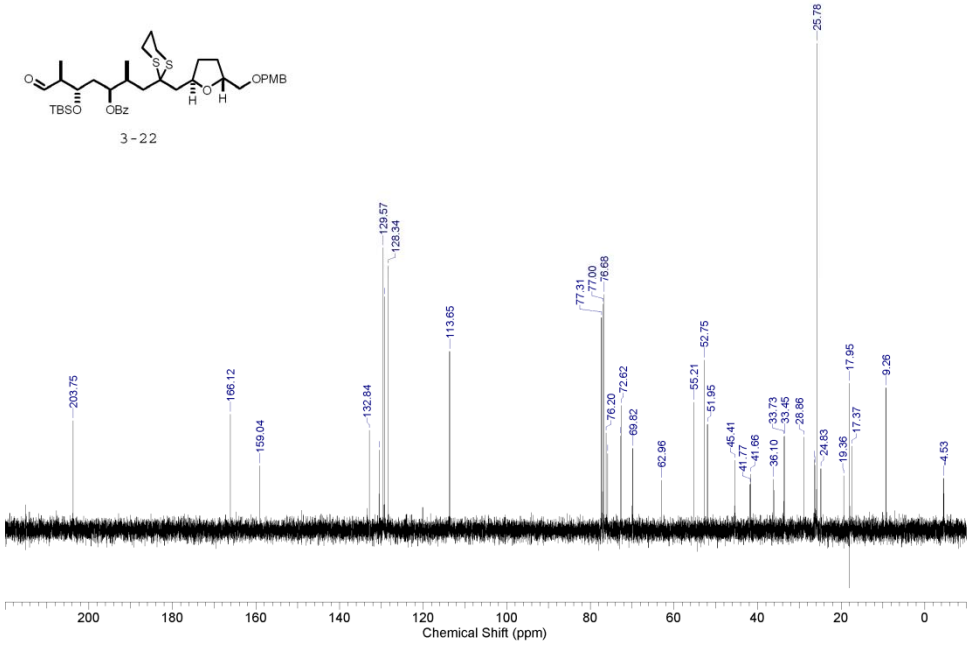

TBSO
TBSO
OBz
OPMB
3-20a
Chemical Shift (ppm)

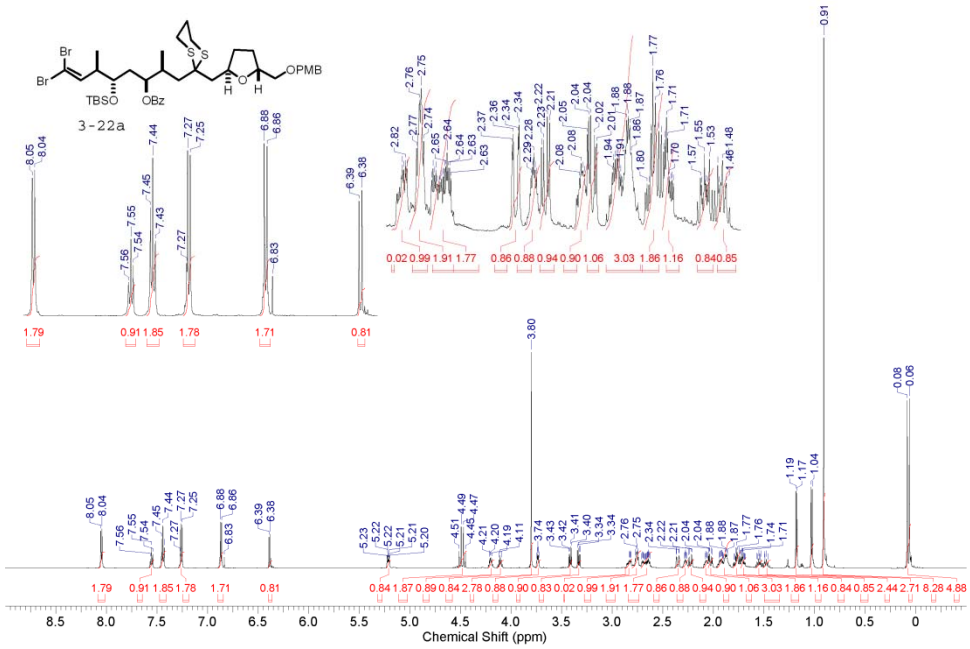

TBSO
TBSO
OBz
OPMB
3-20a
Chemical Shift (ppm)

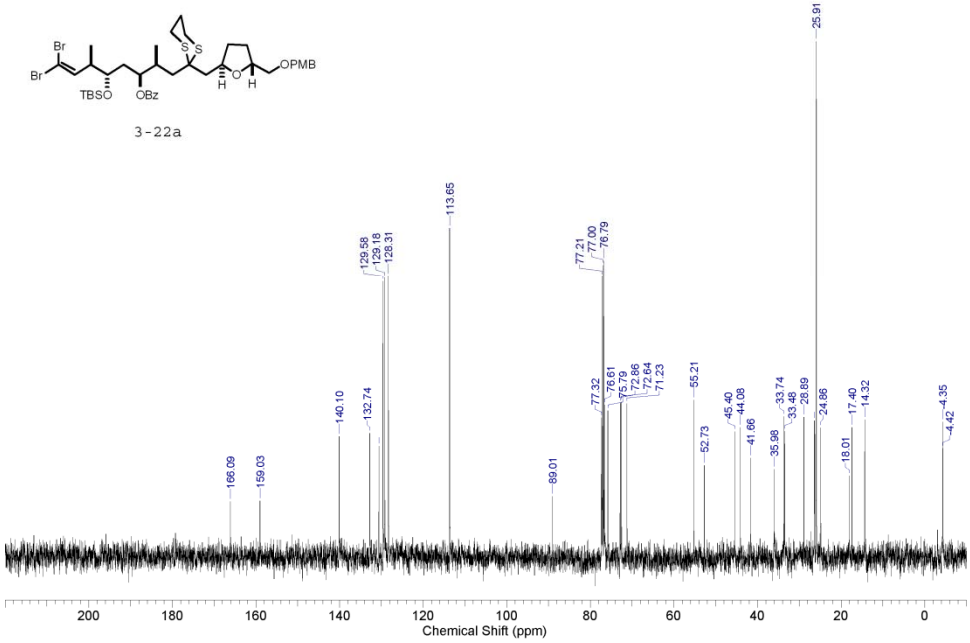

HO
OTBS
OBz
OPMB
3-21
Chemical Shift (ppm)

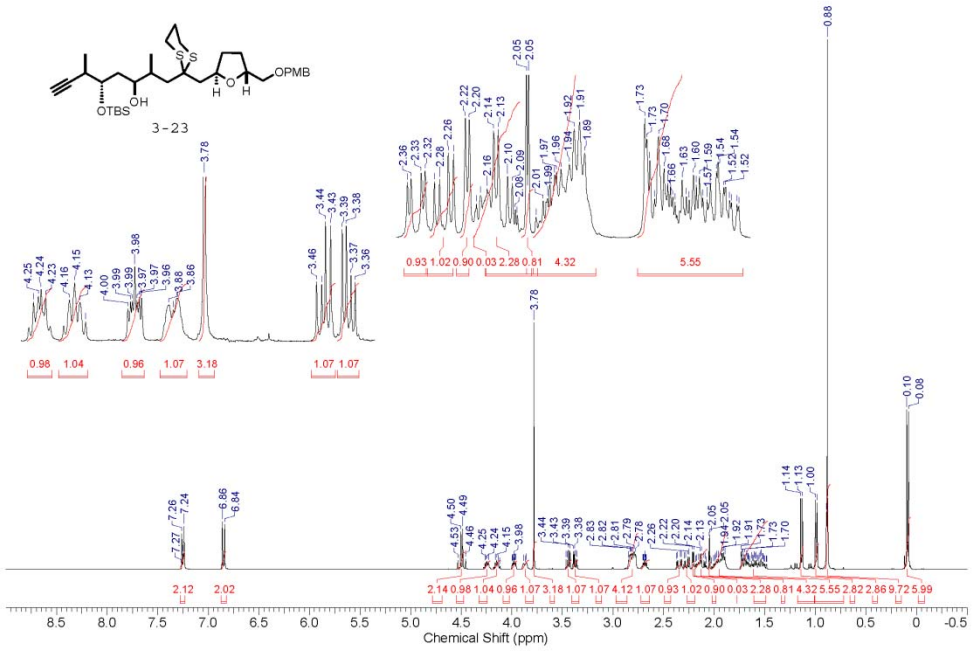

HO
OTBS
OBz
OPMB
3-21
Chemical Shift (ppm)

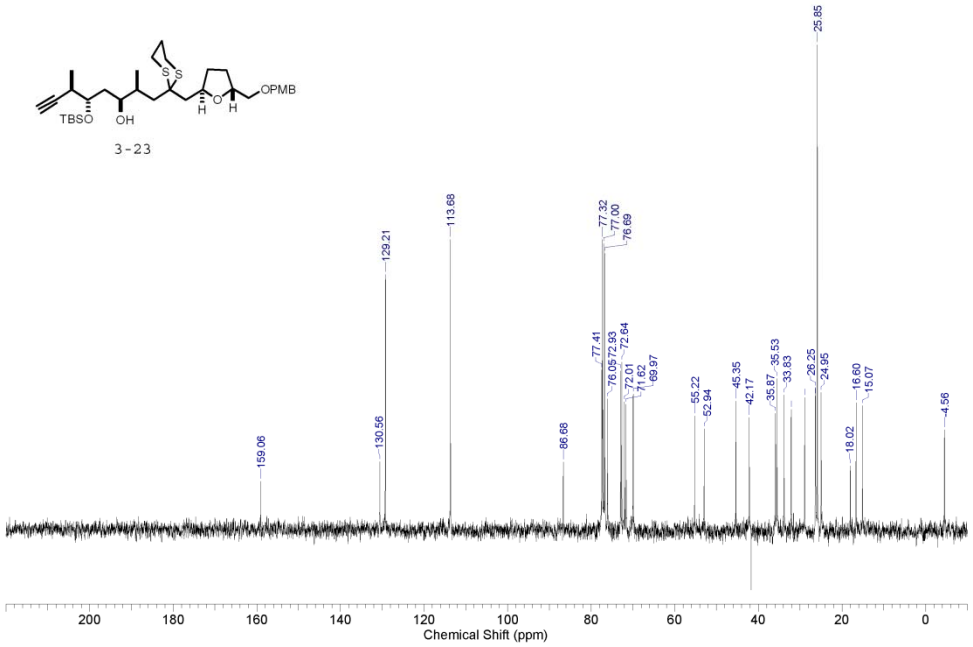

TBSO
OBz
OPMB
3-22
Chemical Shift (ppm)

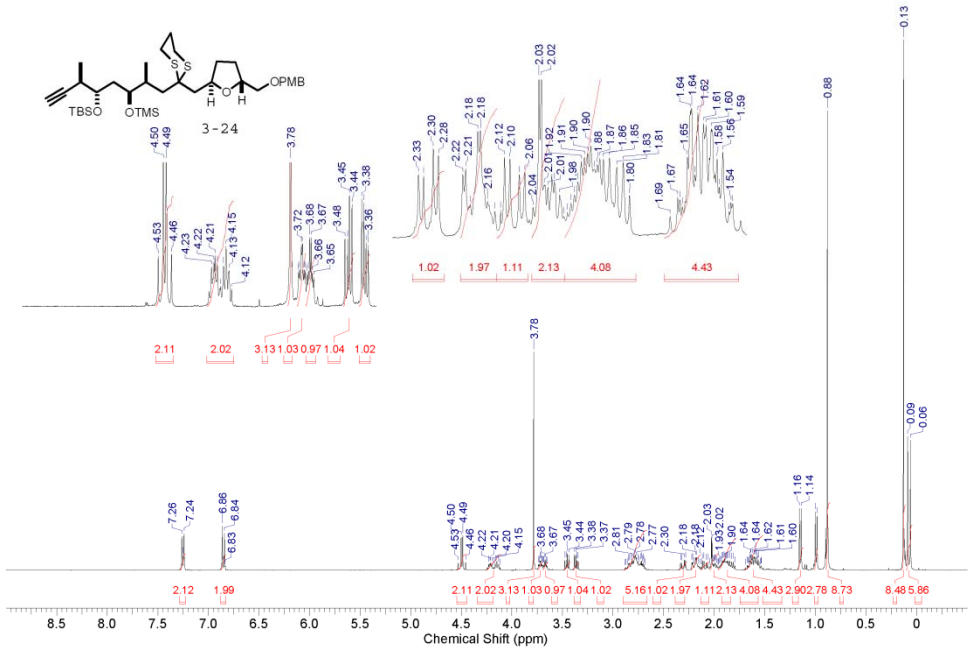

TBSO
OBz
OPMB
3-22
Chemical Shift (ppm)

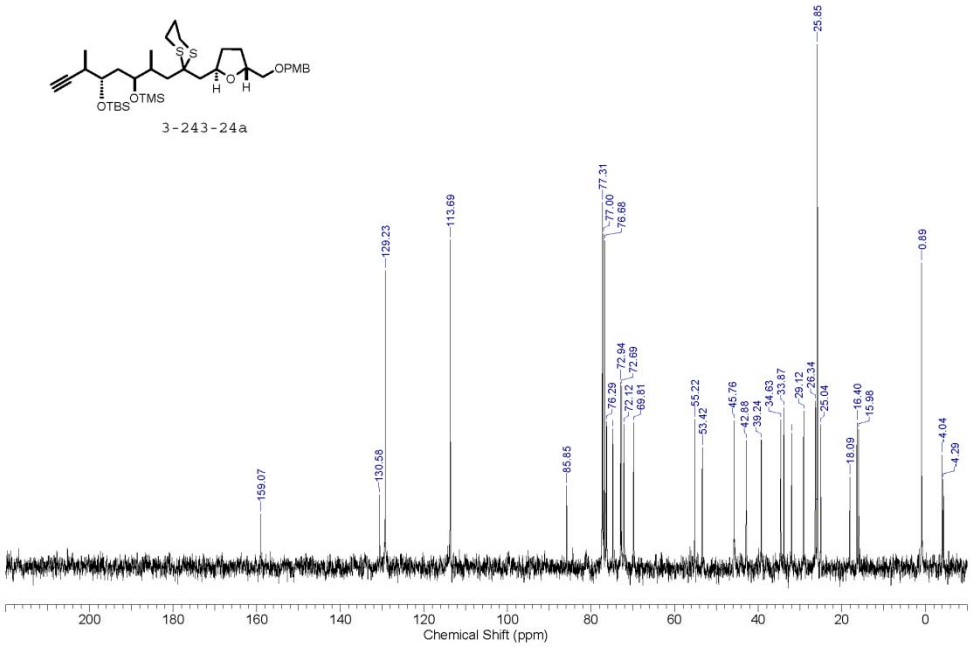

Br
Br
TBSO
OBz
OPMB
3-22a
Chemical Shift (ppm)

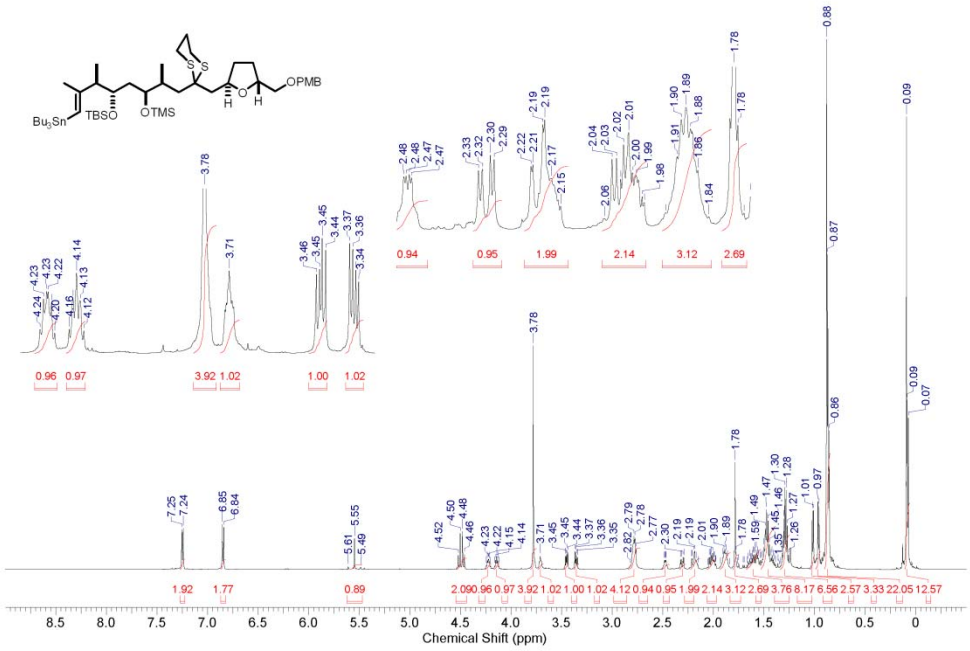

Br
Br
TBSO
OBz
OPMB
3-22a
Chemical Shift (ppm)

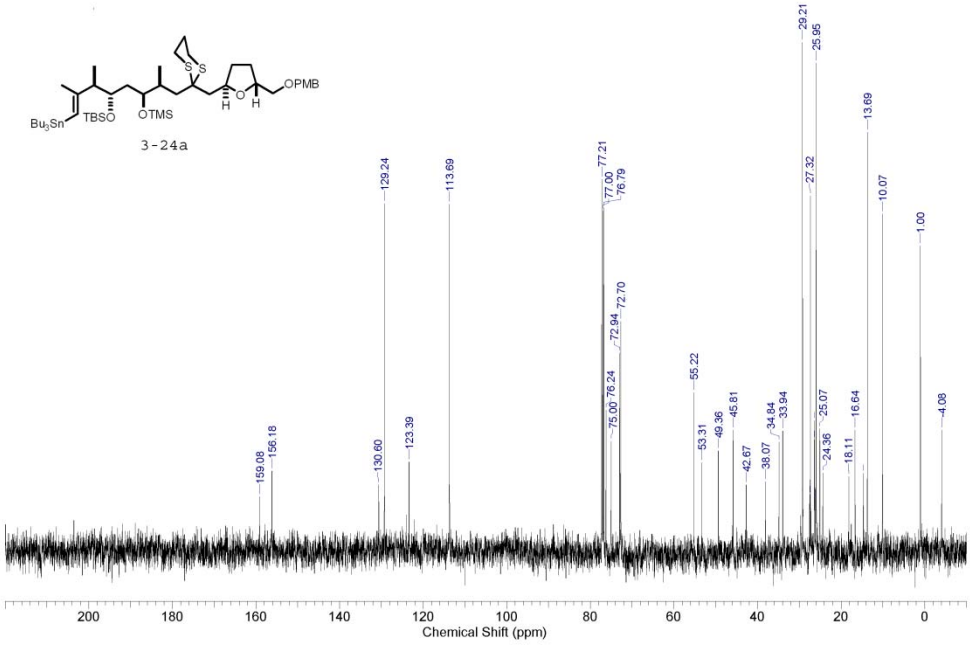

OPMB
OTBS
OH
3-23
Chemical Shift (ppm)

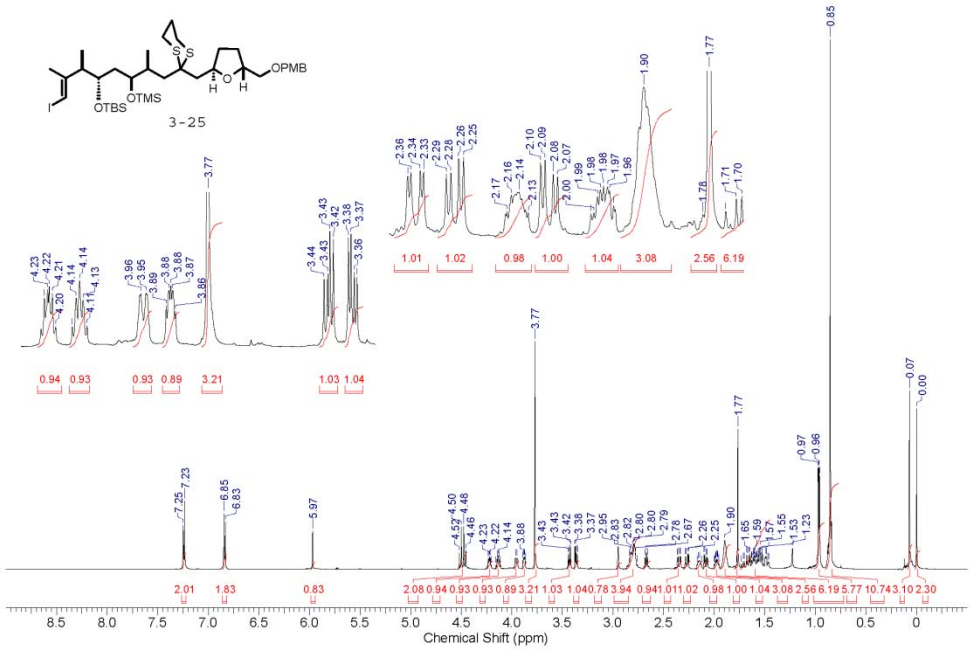

OPMB
TBSO
OH
3-23
Chemical Shift (ppm)

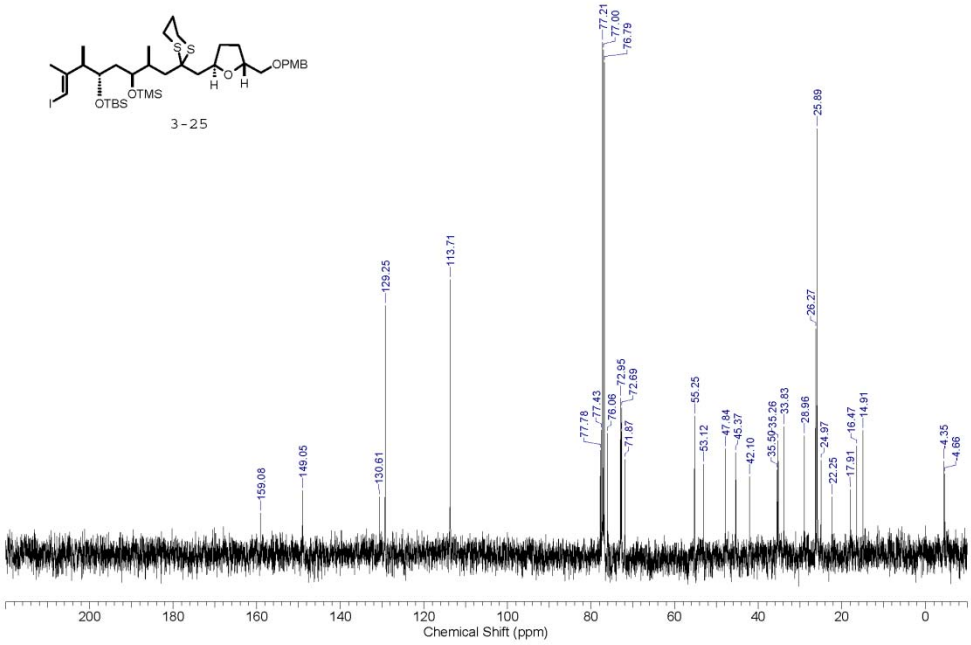

TBSO
OTMS
OPMB
3-24
Chemical Shift (ppm)

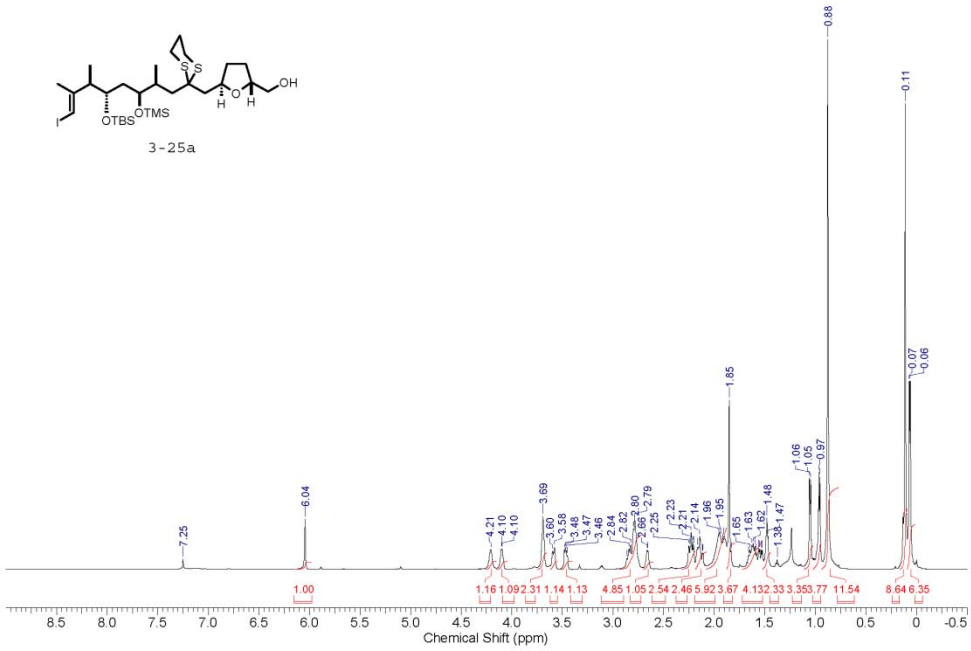

OTBS
OTMS
OPMB
3-243-24a
Chemical Shift (ppm)

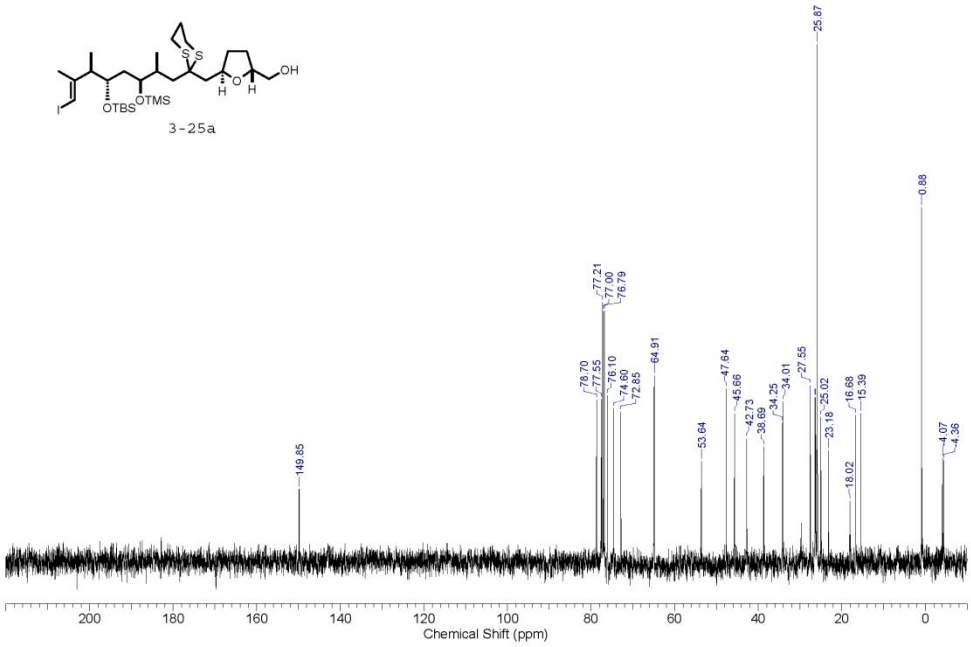

Bu3Sn
TBSO
OTMS
OPMB
Chemical Shift (ppm)

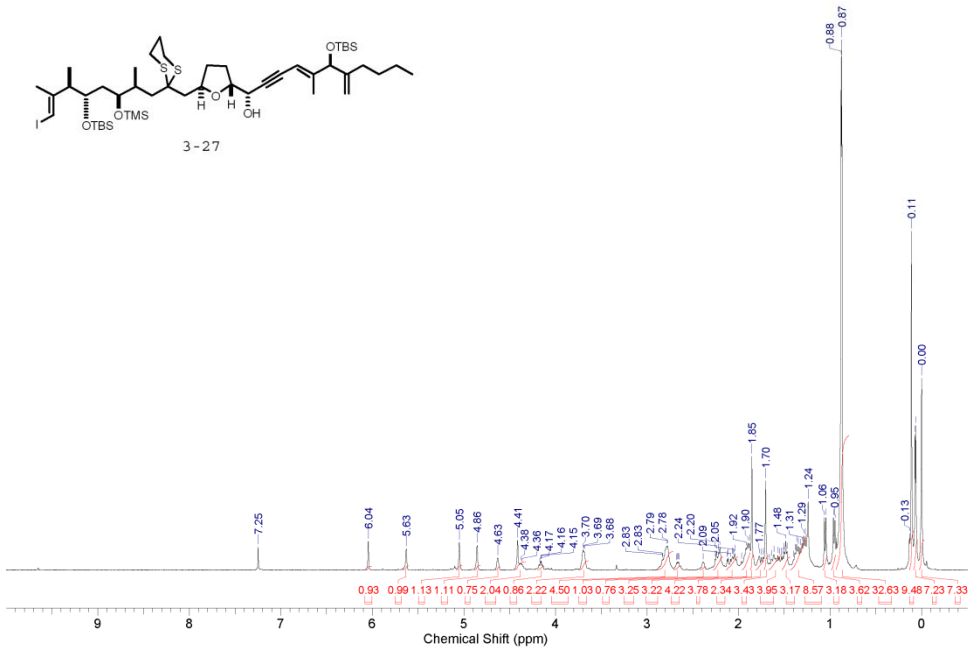

Bu3Sn
TBSO
OTMS
OPMB
3-24a
Chemical Shift (ppm)

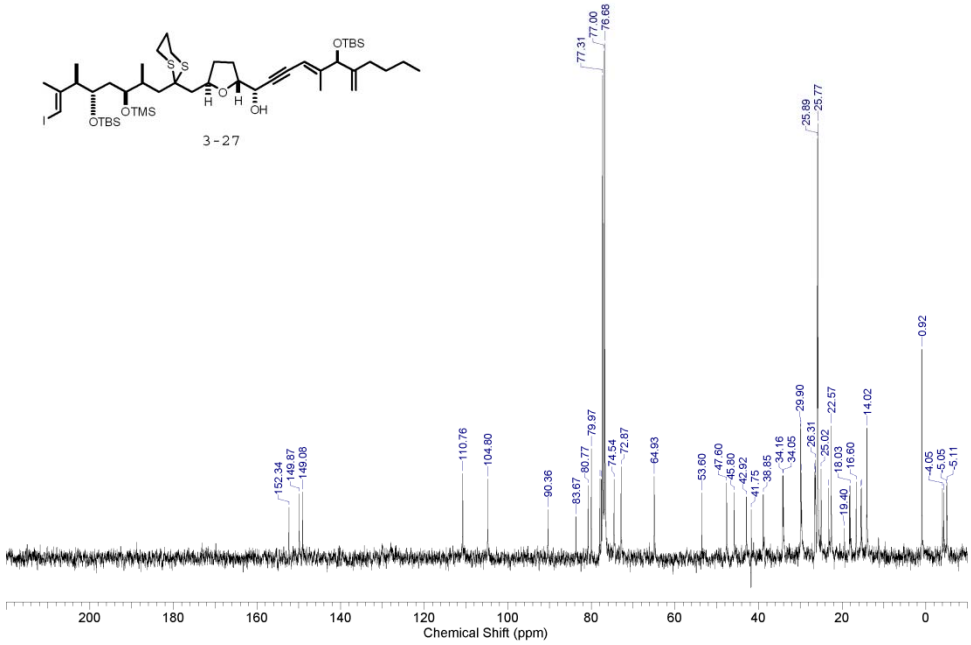

OPMB
OTMS
OTBS
3-25
Chemical Shift (ppm)

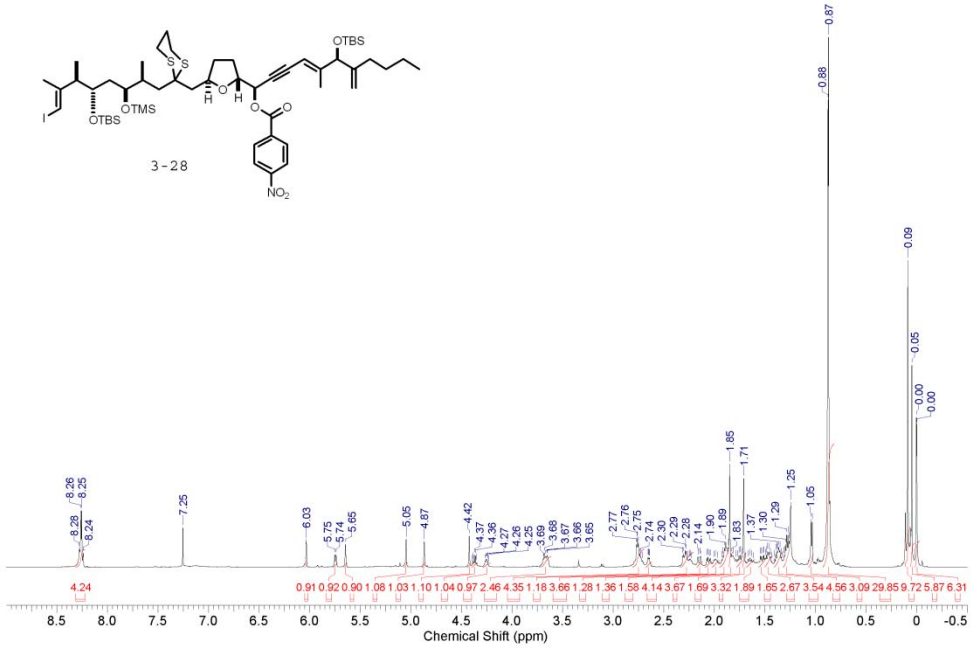

OPMB
OTMS
OTBS
3-25
Chemical Shift (ppm)

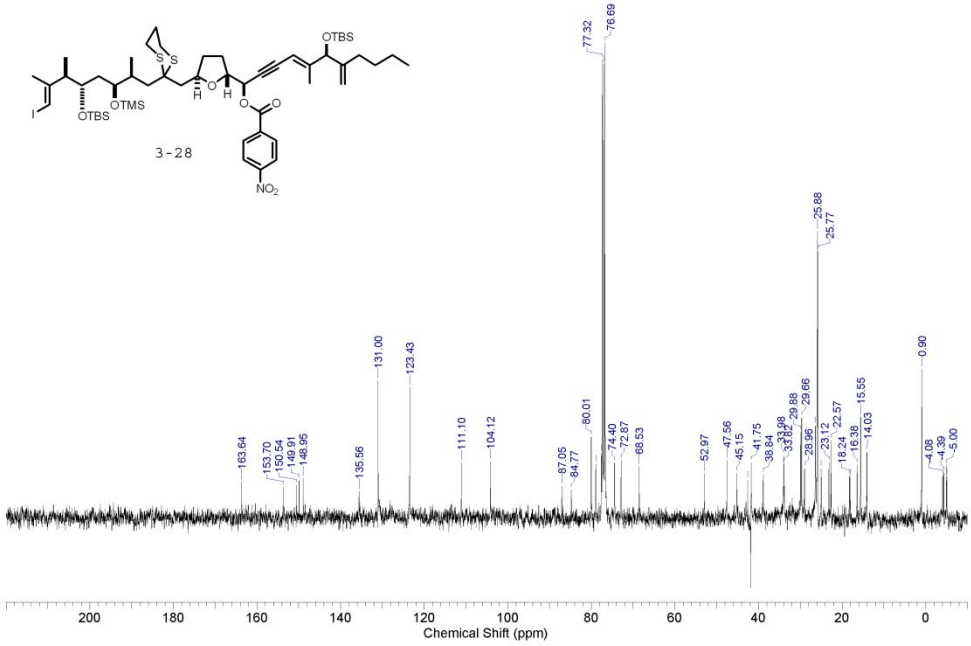

3-25a
Chemical Shift (ppm)

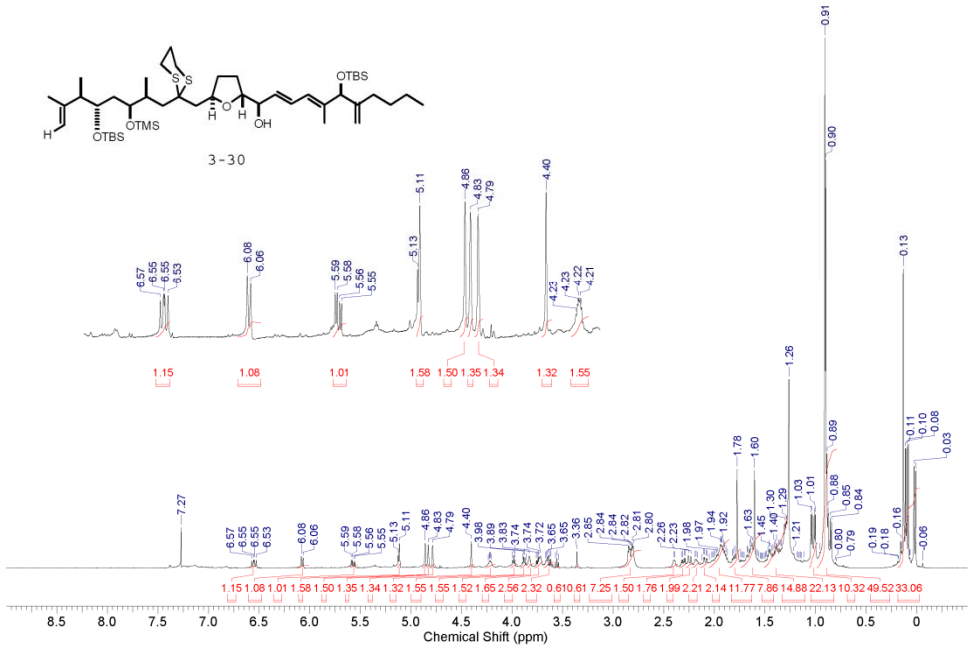

3-25a
Chemical Shift (ppm)

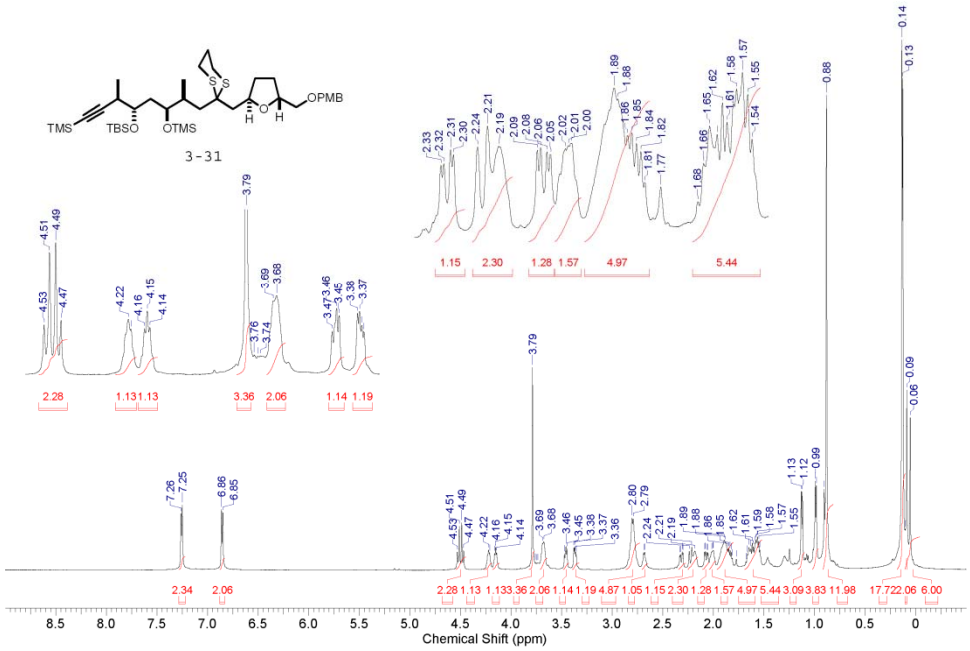

OTBS
OTMS
OTBS
OH
3-27
Chemical Shift (ppm)

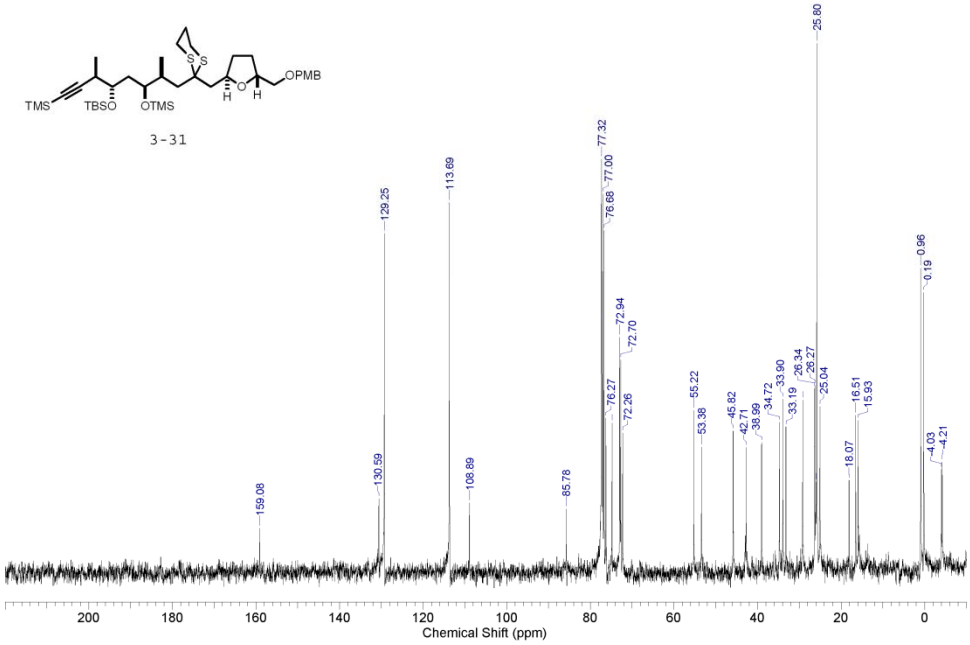

OTBS
OTMS
OTBS
OH
3-27
Chemical Shift (ppm)

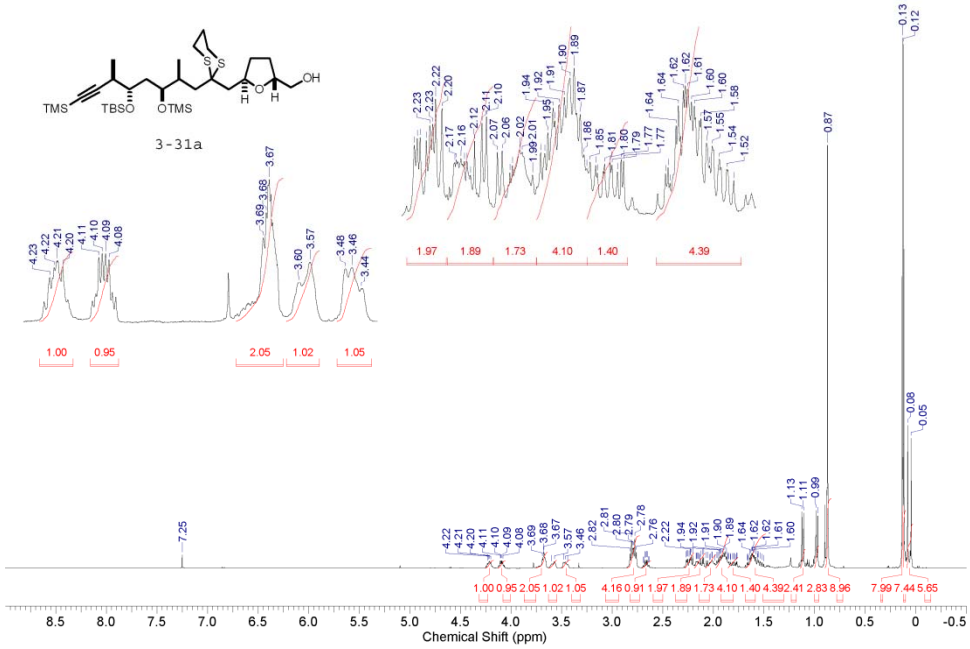

OTBS
OTMS
OTBS
I
3-28
NO2
Chemical Shift (ppm)

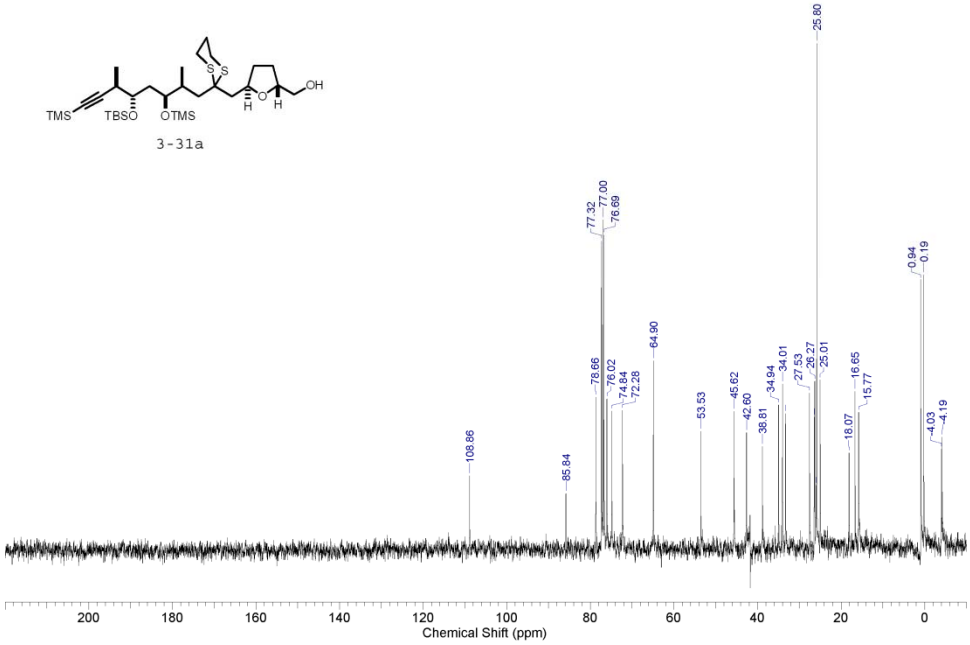

OTBS
OTMS
OTBS
I
3-28
NO2
Chemical Shift (ppm)

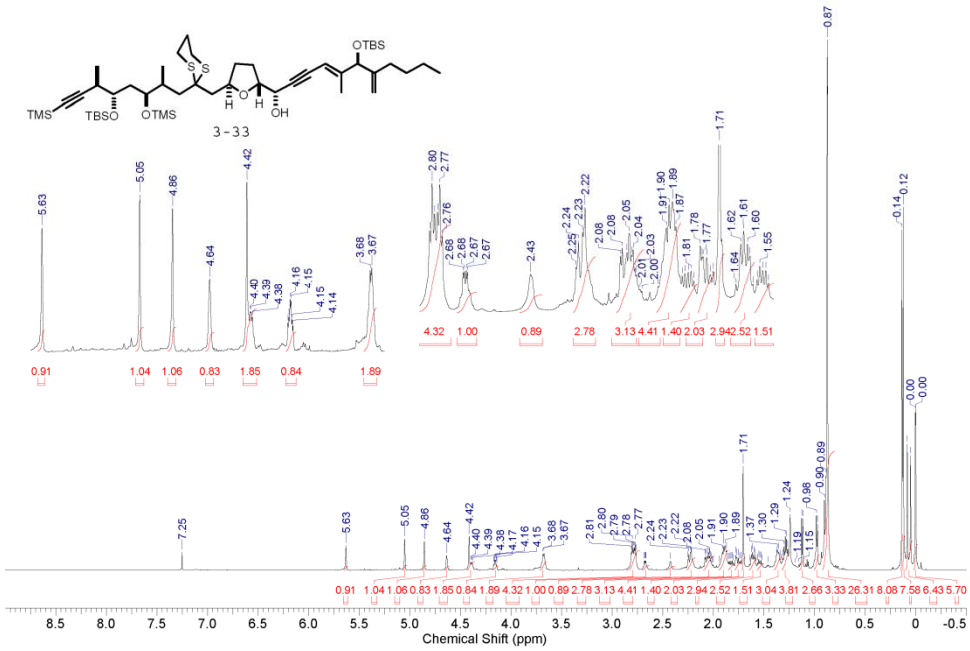

OTBS
OTMS
OTBS
OH
3-30
Chemical Shift (ppm)

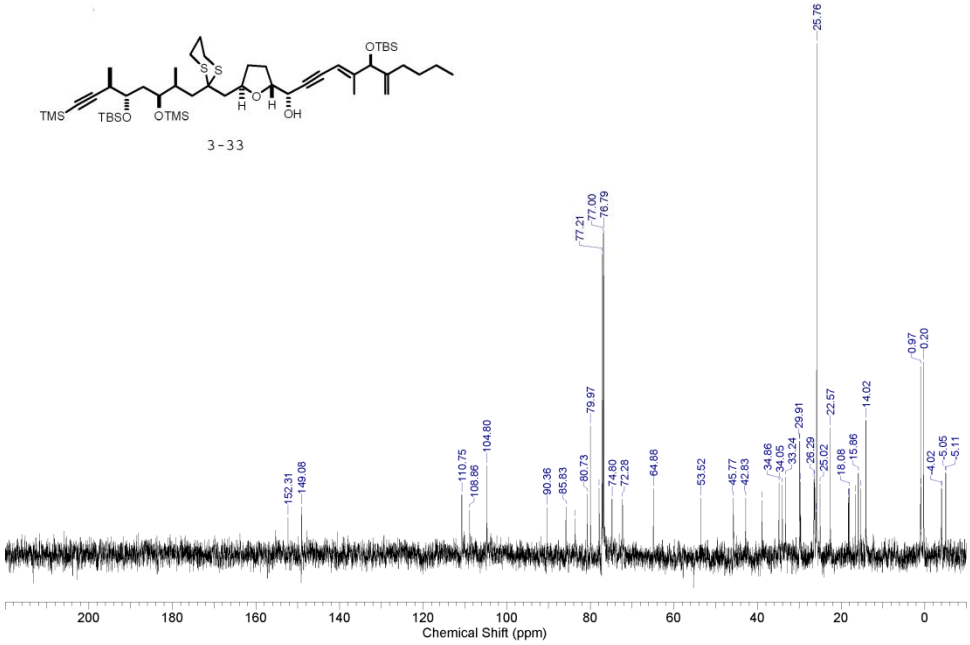

TMS
TBSO
OTMS
OPMB
3-31
Chemical Shift (ppm)

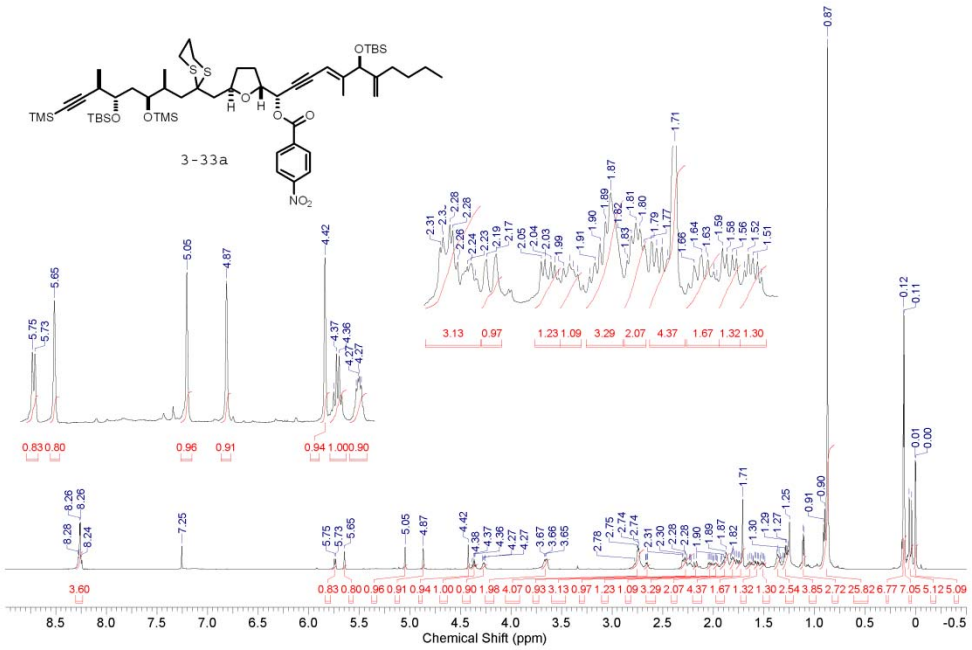

TMS
TBSO
OTMS
OPMB
3-31
Chemical Shift (ppm)

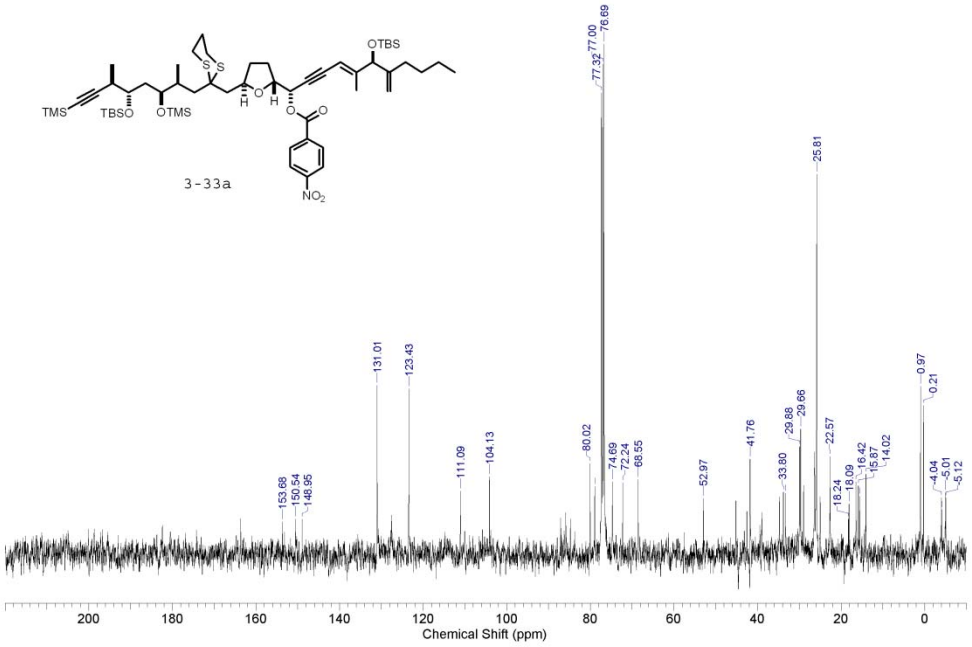

TMS
TBSO
OTMS
OH
3-31a
Chemical Shift (ppm)

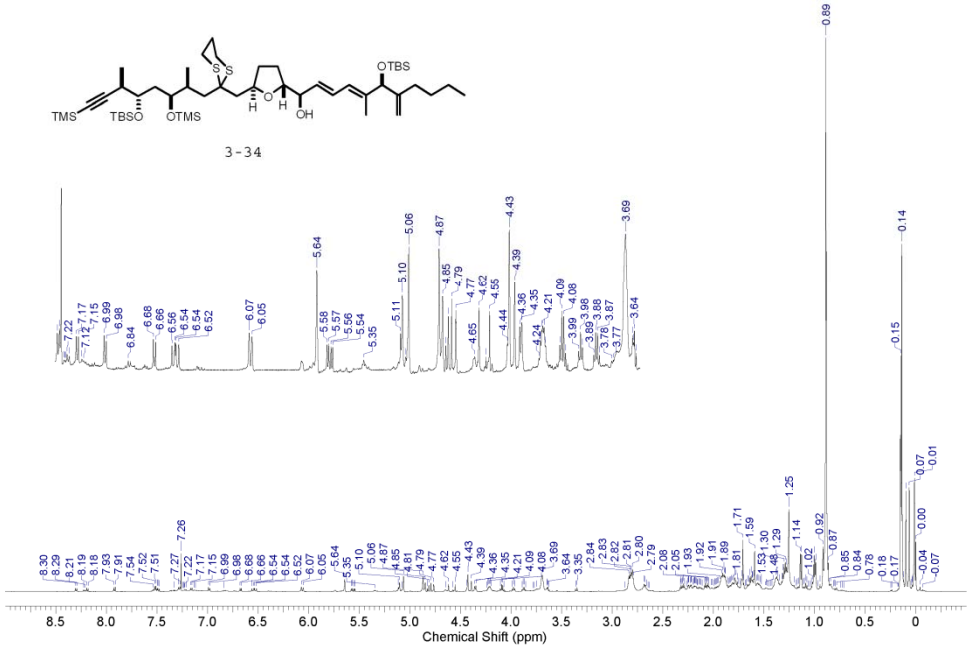

TMS
TBSO
OTMS
OH
3-31a
Chemical Shift (ppm)

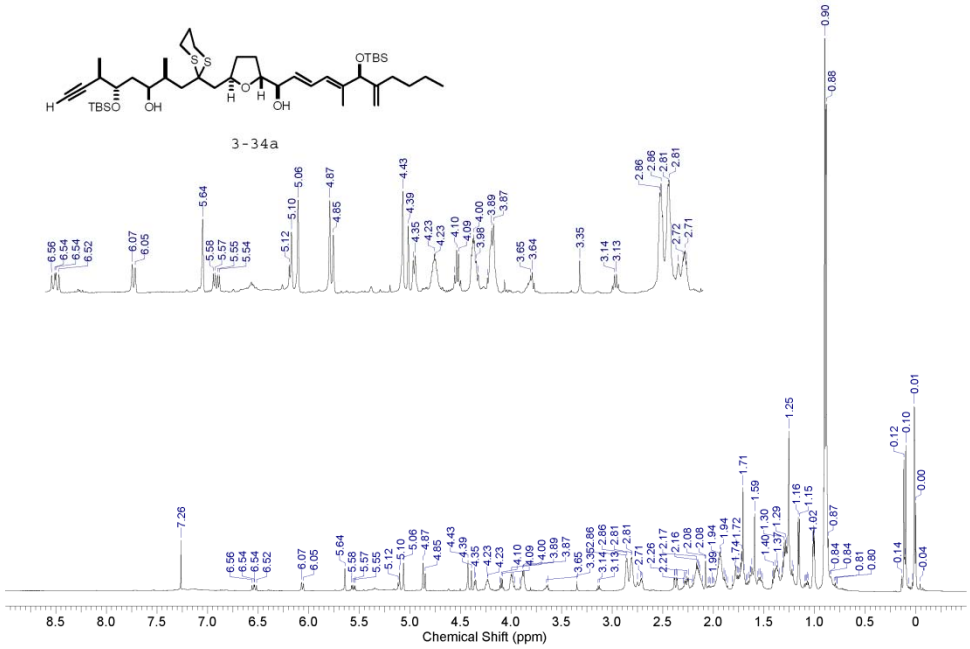

TMS
TBSO
OTMS
OTBS
OH
3-33
Chemical Shift (ppm)

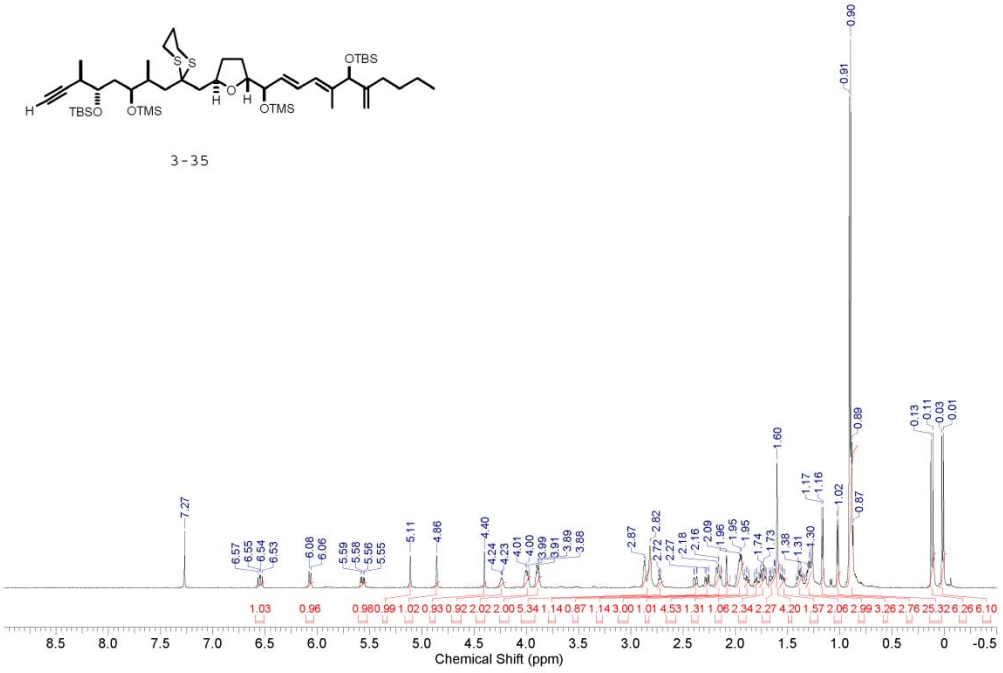

TMS
TBSO
OTMS
OTBS
OH
3-33
Chemical Shift (ppm)


TMS
TBSO
OTMS
OTBS
3-33a
NO2
Chemical Shift (ppm)


TMS
TBSO
OTMS
OTBS
3-33a
NO2
Chemical Shift (ppm)


TMS
TBSO
OTMS
OTBS
OH
3-34
Chemical Shift (ppm)


H
TBSO
OH
OTBS
OH
3-34a
Chemical Shift (ppm)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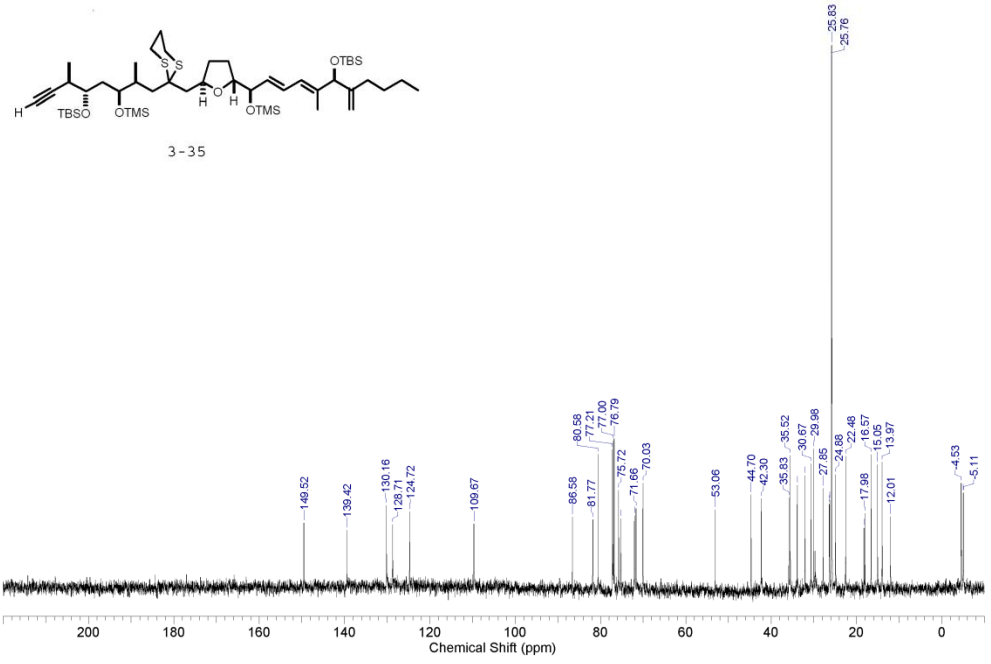
TBSO
OTMS
OTMS
3-35
Chemical Shift (ppm)


OTBS
TBSO
OTMS
OTMS
3-35
Chemical Shift (ppm)

Curriculum Vitae

Nicholas A. Morra

ACADEMIC INFORMATION

Doctor of Philosophy Candidate **September 2007 - Present**
Synthetic Organic Chemistry
University of Western Ontario, London, Ontario
Research Advisor: Dr. Brian L. Pagenkopf

Doctoral Thesis (in progress):
The Total Synthesis of Amphidinolide C

Bachelor of Science
April 2007
Honors Specialization of Chemistry
University of Western Ontario, London, Ontario
- *Dean's Honor List September 2005 – April 2007*

Undergraduate Research Thesis:
Direct Reduction of Esters to Ethers

RESEARCH AND TEACHING EXPERIENCE

Graduate Student Researcher September 2007 – Present
University of Western Ontario, London, Ontario
Research Advisor: Dr. Brian L. Pagenkopf

- Designed and synthesized several cobalt catalysts for the formation of *trans*-THF rings
- Employed an oxidative cyclization of substituted pentenols to form *trans*-THF rings towards the total synthesis of amphidinolide C
- Actively presented research results at national and international conferences
- Composed manuscripts for publication upon project completion
- Trained, supervised and mentored several junior graduate and undergraduate student researchers
- Actively participated in weekly group meetings with the Pagenkopf and Kerr research group members to present and discuss pertinent literature, research updates, and interactive learning sessions

Undergraduate Student Supervisor September 2008 – April 2011
University of Western Ontario, London, Ontario

- Supervised and mentored several undergraduate students, including summer and research thesis students
- Trained students to execute a variety of common laboratory techniques effectively and safely, while supporting their research progress by assisting in data analysis, problem solving and technical report writing
- Prepared a working plan and timeline for each project

Graduate Teaching Assistant September 2007 – April 2009
University of Western Ontario, London, Ontario

- Coordinated laboratory sessions for a second year chemistry course (UWO 2223b: Organic Chemistry of Biological Molecules), and a third year organic chemistry course (UWO 3373f: Reactions and Strategies for Synthesis)
- Conducted a pre-laboratory discussion detailing safety precautions, proper techniques and expectations for each session and assisted students as they conducted experiments and wrote technical reports
- Evaluated reports and examinations

Summer Research Assistant May 2007 – August 2007
University of Western Ontario, London, Ontario
Supervisor: Dr. Brian L. Pagenkopf

- Synthesized a small library of cobalt catalysts for use in Mukaiyama cyclization
- Explored scope and compared reactivity of catalysts
- Elucidated information from X-ray crystals of catalysts and prepared ORTEP diagrams for publication

Undergraduate Research Thesis Student September 2006 – April 2007
University of Western Ontario, London, Ontario
Supervisor: Dr. Brian L. Pagenkopf

- Independently explored the direct reduction of esters to ethers using novel boron based Lewis acids
- Presented work at regional undergraduate conference
- Wrote and published manuscript upon project completion

Research Assistant September 2005 – August 2006
University of Western Ontario, London, Ontario
Supervisor: Dr. Brian L. Pagenkopf

- Acted as project leader to coordinate graduate and undergraduate students to complete a project within a given time frame
- Assisted in the development of an efficient methodology for the formation of indolizines and benzoindolizines via annulation of donor-acceptor cyclopropanes with electron-deficient pyridines and quinolones

Summer Research Assistant May 2005 – August 2005
University of Western Ontario, London, Ontario
Supervisor: Dr. Brian L. Pagenkopf

- Optimized and fine-tuned the synthesis of 2,5-dihalosiloles for the purpose of publication in Organic Syntheses
- Wrote and published manuscript upon project completion

PUBLICATIONS

(7) Synthesis of $Co(nmp)_2$ for use in the Formation of *trans*-THF Rings. Nicholas A. Morra and Brian L. Pagenkopf, *Org. Synth*., submitted, DOI #P-1601.

(6) Gram Scale Synthesis of the C(18)-C(34) Fragment of Amphidinolide C. Nicholas A. Morra and Brian L. Pagenkopf, *Org. Lett*. **2011**, *13*, 572-575.

(5) Improved Yields and Simplified Purification with a Second Generation Cobalt Catalyst for the Oxidative Formation of *trans*-THF Rings. Cory Palmer, Nicholas A. Morra, Andrew C. Stevens, Barbora Bajtos, Benjamin P. Machin and Brian L. Pagenkopf, *Org. Lett.* **2009**, *24*, 5614-5617.

(4) Synthesis and First X-ray Structures of Cobalt(II) and Cobalt(III) Complexes Bearing 2,4-dioxo-alkanoic Acid Dialkylamide Ligands. Jian Wang, Nicholas A. Morra, Hongda Zhao, Jeffrey S. T. Gorman, Vincent Lynch, Robert McDonald, John F. Reichwein and Brian L. Pagenkopf, *Can. J. Chem*. **2009**, *87*, 328-334.

(3) Reduction of Esters to Ethers Utilizing the Powerful Lewis Acid $BF_2OTf{\bullet}OEt_2$. Nichloas A. Morra, Brian L. Pagenkopf, *Synthesis* **2008**, *4*, 511-514.

(2) Direct Synthesis of 2,5-Dihalosiloles. Nicholas A. Morra and Brian L. Pagenkopf, *Org. Synth*. **2008**, *85*, 53-63.

(1) Synthesis of Indolizines and Benzoindolizines by Annulation of Donor-Acceptor Cyclopropanes with Electron Deficient Pyridines and Quinolines. Nicholas A. Morra, Christian L. Morales, Barbora Bajtos, Xin Wang, Hyosook Jang, Jian Wang, Ming Yu and Brian L. Pagenkopf, *Adv. Synth. Catal*. **2006**, *348*, 2385-2390.

PRESENTATIONS

Oral Presentations

(5) Nicholas Morra, *The Total Synthesis (?) of Amphidinolide C*. The 94th Canadian Chemistry Conference and Exhibition. Montreal, QC, **2011**.

(4) Nicholas Morra, *Amphidinolide C: Adventures in Total Synthesis.* The 21st Quebec and Ontario Mini-symposium on Biological and Organic Chemistry. St. Catherines, ON, **2010**.

(3) Nicholas Morra, *Amphidinolide C: Two ways*. The 93rd Canadian Chemistry Conference and Exhibition. Toronto, ON, **2010**.

(2) Nicholas Morra, *Progress Towards Amphidinolide C*. The 92nd Canadian Chemistry Conference and Exhibition. Hamilton, ON, **2009**.

(1) Nicholas Morra, *Reduction of Esters to Ethers.* The 35th Southern Ontario Undergraduate Student Chemistry Conference. Oshawa, ON, **2007**.

Poster Presentations

(7) Nicholas Morra, *Progress Towards the Total Synthesis of Amphidinolide C*. Latest Trends in Organic Synthesis 14. St. Catherines, ON, **2010**.

(6) Nicholas Morra, *Progress Towards the Total Synthesis of Amphidinolide C*. The 19th Quebec and Ontario Mini-symposium on Biological and Organic Chemistry, Toronto, ON, **2009**.

(5) Nicholas Morra, *A New Generation of Cobalt Catalysts and Their use in Total Synthesis*. Latest Trends in Organic Synthesis 13. St. Catherines, ON, **2008**.

(4) Nicholas Morra, *Reduction of Esters to Ethers Utilizing the Powerful Lewis Acid $BF_2OTF{\bullet}OEt_2$*. Latest Trends in Organic Synthesis 13. St. Catherines, ON, **2008**.

(3) Nicholas Morra, *A New Generation of Cobalt Catalysts and Their use in Total Synthesis*. ACS Summer School on Sustainability and Green Chemistry. Golden, CO, **2008**.

(2) Nicholas Morra, *Reduction of Esters to Ethers Utilizing the Powerful Lewis Acid $BF_2OTF{\bullet}OEt_2$*. The 18th Quebec and Ontario Mini-symposium on Biological and Organic Chemistry. Montreal, QC, **2007**.

(1) Nicholas Morra and Barbora Bajtos, Synthesis of Indolizines and Benzoindolizines by Annulation of Donor-Acceptor Cyclopropanes with Electron Deficient Pyridines and Quinolines. The 17th Quebec and Ontario Mini-symposium on Biological and Organic Chemistry, London, ON, **2006**.

AWARDS

Award	Value	Location	Tenure
Oral Presentation Award *94th Canadian Chemistry Conference (organic division)*	$100	Montreal, QC	June 2011
Oral Presentation Award *93rd Canadian Chemistry Conference (organic division)*	$100	Toronto, ON	June 2010
Graduate Thesis Research Award	$750	UWO	March 2010
Alexander Graham Bell Canadian Graduate Scholarship (CGS-D3)	$36,000/yr	UWO	May 2009 – April 2012
Ontario Graduate Scholarship *Declined for NSERC CGS-D3*	$15,000	UWO	N/A
Ontario Graduate Scholarship	$15,000	UWO	May 2008 – April 2009
Poster Presentation Award	N/A	St. Catherines, ON	August 2008
Western Admission Scholarship	$2,000	UWO	September 2003

SKILLS AND QUALIFICATIONS

- Proven success in the design and execution of synthetic strategies including optimizing synthetic methods, reaction scope development, and implementation of scale up procedures for multi-step syntheses
- Extensive retrosynthetic analysis experience for the design of complex organic molecules
- Tenacious approach to problem solving by thinking critically and creatively
- Expertise in a wide variety of laboratory techniques including air/moisture sensitive procedures and modern methods such as microwave assisted synthesis
- Exceptional ability in the purification, analysis and identification of organic compounds using modern elucidation and analytical techniques such as NMR, FT-IR, UV-VIS, HPLC, GC, and HRMS
- Excellent data management and organizational skills
- Ability to work independently and within a team to achieve a common goal
- Highly focused, driven, and goal-oriented
- Ability to communicate complex ideas through oral presentations and by manuscript and technical report preparation
- Outstanding ability to mentor students and support learning
- Extensive experience using computer software, including SciFinder, ChemBioDraw, ACD Labs, Excel, Powerpoint, Microsoft Office and Adobe