Synthesis and Conformational Analysis of Model Systems of the Spirocyclic Moiety of Neaumycin B

by

Nicholas Andrew Cinti

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This thesis was presented

by

Nicholas Andrew Cinti

It was defended on

December 13, 2022

and approved by

Dr. Yiming Wang, Assistant Professor, Department of Chemistry

Dr. Kazunori Koide, Professor, Department of Chemistry

Thesis Advisor/Dissertation Director: Dr. Paul Floreancig, Professor, Department of Chemistry

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Nicholas Andrew Cinti, MS

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Neaumycin B is a potent anti-cancer agent that exhibits high selectivity toward human glioblastoma cells. The stability of this natural product, however, has made its isolation in larger quantities from natural sources difficult. A synthetic route to afford neaumycin B could aid in its isolation in appreciable amounts in order to conduct biological studies. Additionally, analogs of the macrolide could potentially be synthesized to offer improved stability while maintaining similar cytotoxicity levels. This total synthesis would need to include a method for the formation of the singly anomeric spiroketal moiety and a detailed analysis of its configuration.

This document describes the approaches taken to successfully afford and characterize models of the spirocyclic core found within neaumycin B. Models of increasing complexity were synthesized in the attempts to find the most favorable approach to afford spirocycle formation within this system. Aldol chemistry was carried out under Felkin control to afford the spirocycle precursor and set one of the stereocenters substituted on the bicyclic ring system. The results indicate that the singly anomeric spiroketal provides the most thermodynamically stable isomer, although it was shown that epimerization at the spirocenter is possible under equilibrative conditions. Conditions were formulated to deliver the desired spiroketal in a 3:1 ratio with its epimeric counterpart, going through orthogonal protecting group manipulations and cyclization in a one pot process.

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List of Schemes

List of Abbreviations

9-BBN	9-Borabicyclo[3.3.1] nonane
Å	Angstrom
Ac	Acetate
AcOH	Acetic Acid
$AgSbF_6$	Silver hexafluoroantimonate (V)
Ar	Argon
$BF_3{\cdot}OEt_2$	Boron trifluoride diethyl etherate
Bn	Benzyl
BnBr	Benzyl bromide
CaH_2	Calcium Hydride
CCl_4	Carbon tetrachloride
C_6D_6	Benzene-d6
$CDCl_3$	Chloroform-D
CD_3CN	Acetonitrile-d3
CH_2Cl_2	Dichloromethane
$[Cl_2Pt(CH_2CH_2)]_2$	Zeise's dimer
Cl_3SiH	Trichlorosilane
$(COCl)_2$	Oxalyl chloride
COSY	Correlation Spectroscopy
Cp_2TiMe_2	Petasis reagent
$CrCl_3{\cdot}THF$	Chromium (III) chloride tetrahydrofuran complex
CSA	Camphor-10-sulfonic acid
CuBr	Copper (I) bromide
CuCl	Copper (I) chloride
D_2O	Deuterium oxide
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone

DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*,-dimethylformamide
DMSO	Dimethylsulfoxide
d.r.	Diastereomeric ratio
ee	Enantiomeric excess
ESI	Electrospray Ionization
Et_2BOMe	Diethylmethoxyborane
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
$Eu(fod)_3$	Sievers' reagent
g	Grams
h	Hours
H_2	Hydrogen gas
H_2O	Water
HCl	Hydrochloric acid
HF	Hydrofluoric acid
$HgCl_2$	Mercury (II) chloride
HMBC	Heteronuclear multiple bond correlation
HRMS	High resolution mass spectrometry
Hz	Hertz
iPr	Isopropyl
$(iPr)_2NEt$	*N*,*N*-diisopropylethylamine
$(iPr)_2NH$	Diisopropylamine
K_2CO_3	Potassium carbonate
$K_3PO_4 \cdot H_2O$	Potassium phosphate tribasic monohydrate
kcal/mol	Kilocalories per mole
KHMDS	Potassium Hexamethyldisilazide

KO^tBu	Potassium *tert*-butoxide
L	Liter
L.A.	Lewis acid
LCMS	Liquid chromatography-mass spectrometry
LiCl	Lithium chloride
$LiClO_4$	Lithium perchlorate
LiHMDS	Lithium hexamethyldisilazide
LiI	Lithium iodide
M	Molar
Me	Methyl
Me_2AlCl	Dimethylaluminum chloride
Me_2BnSi	Benzyldimethyl silyl
Me_2CuLi	Dimethyllithium cuprate
MeCN	Acetonitrile
MeOH	Methanol
MeI	Methyl iodide
MeMgBr	Methyl magnesium bromide
mg	Milligrams
$MgSO_4$	Magnesium sulfate
MHz	Megahertz
min	Minutes
mm	Millimeters
mmol	Millimolar
mL	Milliliter
M.S.	Molecular sieves
N_2	Nitrogen gas
$Na_2S_2O_3$	Sodium thiosulfate
$NaBH_4$	Sodium borohydride

NaH	Sodium hydride
$NaHCO_3$	Sodium bicarbonate
$NaIO_4$	Sodium periodate
NaOH	Sodium hydroxide
nBu	n-Butyl
n-BuLi	n-Butyllithium
n-Bu_4NBr	Tetrabutylammonium bromide
NCI	National cancer institute
NEt_3	Triethylamine
NH_4Cl	Ammonium chloride
nm	Nanometers
NMO	4-methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
NOE	Nuclear overhauser effect
Nu	Nucleophile
OsO_4	Osmium tetroxide
Pd/C	Palladium on carbon
$PdCl_2$	Palladium (II) chloride
PG	Protecting group
$[Pd(dppf)Cl_2]\cdot CH_2Cl_2$	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) dichloromethane complex
pM	Picomolar
PMB	Paramethoxybenzyl
PMP	Paramethoxyphenyl
ppm	Parts per million
PPTS	Pyridinium *p*-toluenesulfonate
p-$TsOH\cdot H_2O$	*p*-Toluenesulfonic acid monohydrate
Quant.	Quantitative yield

(*R*)-BINOL	(*R*)-(+)-1,1'-Bi(2-naphthol)
R_f	Retention factor
ROESY	Rotating frame overhauser spectroscopy
rt	Room temperature
SiO_2	Silicon dioxide
$SnCl_4$	Tin tetrachloride
$SO_3 \cdot py$	Sulfur trioxide pyridine complex
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDPS	*Tert*-butyldiphenylsilyl
TBME	*Tert*-butyl methyl ether
TBS	*Tert*-butyldimethylsilyl
TBSCl	*Tert*-butyldimethylsilyl chloride
TBSOTf	*Tert*-butyldimethylsilyl triflate
^{t}BuOOH	*Tert*-butyl hydroperoxide
TES	Triethylsilyl
TESCl	Triethylsilyl chloride
TESOTf	Triethylsilyl triflate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran
$Ti(OiPr)_4$	Titanium (IV) isopropoxide
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMG	1,1,3,3-tetramethylguanidine
TMS	Trimethylsilyl
TMSCl	Trimethylsilyl chloride
TMSQ	Trimethylsilyl quinidine

UV	Ultraviolet
µL	Microliters
µm	Micrometers

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1.0 Efforts Toward the Synthesis and Structural Elucidation of the Spirocyclic Moiety of Neaumycin B

1.1 Significance and Structural Nuances of Neaumycin B

Neaumycin B (**1**, Figure 1) is a macrolide containing a 28-membered macrolactone along with 19 stereocenters and is a member of the cytovaricin-ossamycin-oligomycin class of macrolides.[1–3] This natural product was isolated from the *Micromonospora* strain CNY-101 by Fenical and co-workers[4] and was screened for its cytotoxicity against the NCI's 60 cell line panel. In addition to this screen, in-house assays were carried out due to difficulty in the handling of this natural product. These assays unveiled the significant potency and selectivity neaumycin B has for U87 human glioblastoma cells, with an LD_{50} value of 64 pM. Glioblastoma is the most common and deadly glioma sub-type found in adults, showing a 5 year relative survival rate of about 5%.[5] Due to the prevalence and poor survival rate of this affliction, along with the recently discovered potency and selectivity neaumycin B has toward these cells, it is clear that this macrolide may act as an impactful lead candidate in glioblastoma therapy.

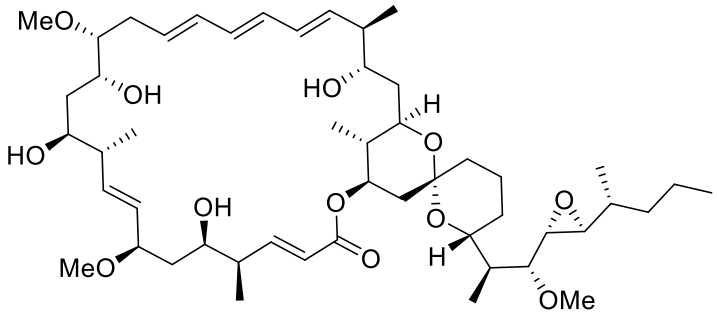

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Figure 1. Structure of Neaumycin B

The accepted structure of neaumycin B was first proposed in 2015 by Donadio and co-workers.[6] Although this provided valuable information in terms of connectivity, this report was lacking valuable stereochemical information and many spectroscopic details. Fenical's work employed a strategy combining bioinformatic assessments with rigorous spectroscopic analysis. They obtained the full genomic sequence of the *Micromonospora* strain of interest and identified a biosynthetic gene cluster that was consistent with the 41-carbon backbone of neaumycin B, allowing predictions for many of the chiral centers which were then confirmed through spectroscopic means. COSY and HMBC NMR experiments were used to accurately determine the structure of the backbone of neaumycin B, while ROESY NMR data aided in the determination of the configuration of the spiroketal moiety.[4]

The spectroscopic analysis was carried out with tremendous attention to detail, making the authors of this work fairly confident that the proposed structure seen in Figure 1 is, in fact, the correct structure of neaumycin B. However, some uncertainty still surrounds the identity of a select few stereocenters. Furthermore, the process used by Fenical to isolate neaumycin B from its *Micromonospora* source proved to be low yielding, granting only 20 mg of product from 36 L of media. Additionally, the compound exhibited limited stability which may have interfered with biological studies as well as its isolation in any appreciable quantity. Thus, a synthetic approach to afford neaumycin B would be valuable as it could lead to the acquisition of larger quantities of the material to accurately test its biological properties and confirm or deny the results of Fenical's work. Furthermore, the synthesis of more stable and similarly potent analogs would aid in this process as well.

The total synthesis of neaumycin B is no trivial task. The presence of 19 stereocenters, a triene subunit, and a singly anomeric spiroketal are all contributing factors to the complexity of

this synthetic pathway. To this end, a modular approach has been proposed to obtain this natural product. Four major disconnections have been envisioned in order to bring this convergent approach to fruition (Figure 2). For example, a Hiyama coupling could be employed to bring together the triene subunit, a Nozaki-Hiyama-Kishi coupling could afford the connection adjacent to the allyl methyl ether, and a macrolactonization of choice can close the 28-membered macrolactone. The last portion of the molecule to focus on would then be the spirocyle, which is where my research efforts have been devoted. My work has focused primarily on determining the optimal method to deliver this spirocycle, both in terms of bond connectivity and the formation of the desired configuration.

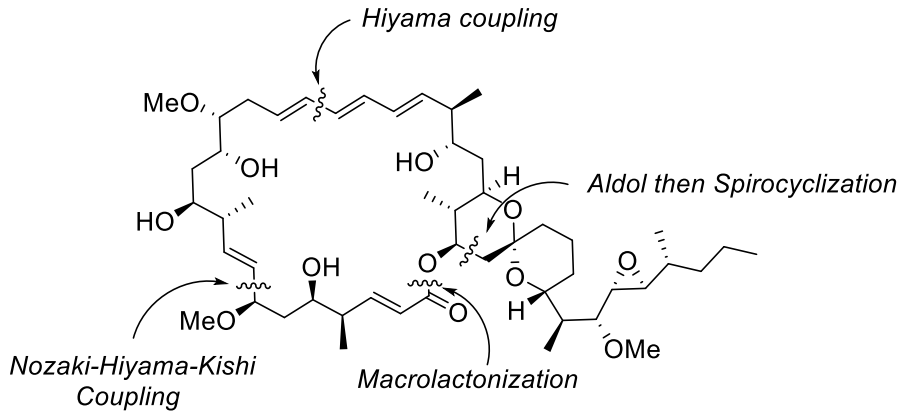
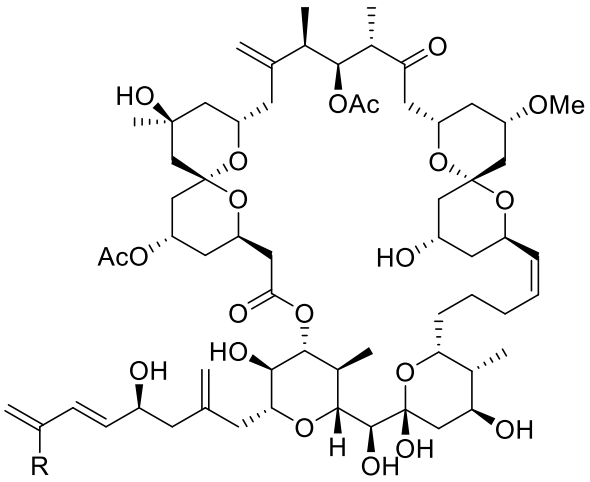


Figure 2. Disconnections in the Modular Synthetic Design of Neaumycin B

1.2 Spiroketals and Their Prevalence in Natural Products

Spiroketals are a key motif present in several biologically active natural products coming from sources such as marine macrolides and ionophores.[7] One such family of spiroketal-containing natural products are the various spongistatin derivatives of the genus *Spongia*. Shown below are two members of this family, spongistatin 1 and spongistatin 2, differing in structure only

by a single substitution (Figure 3). These natural products contain unique structures that lead to challenging total synthetic endeavors. However, routes affording spongistatin 1 and spongistatin 2 have been reported by Kishi[8] and Evans[9], respectively. Although the syntheses of such natural products can be a difficult task, it could very well lead to an exciting new antineoplastic agent. Pettit and co-workers isolated and determined the structure of spongistatin 1 in 1992 from samples found in the Eastern Indian Ocean. Upon its isolation, spongistatin 1 was then tested against the NCI panel of 60 human cancer cell lines. Spongistatin 1 proved to be effectively cytotoxic toward a number of cell lines on this panel, showing particular sensitivity for cell lines derived from human melanoma and lung, colon, and brain cancers.[10]



R= Cl, Spongistatin 1
R= H, Spongistatin 2

Figure 3. Structures of Spongistatins 1 and 2

Another family of therapeutic, spiroketal-containing natural products are the reveromycins. Reveromycins A, B, C, and D were isolated from a soil actinomycete belonging to the *Streptomyces* genus by Isono and co-workers in 1992.[11] In addition to their isolation, the reveromycins were characterized by spectroscopic means[12] and had their biological activities tested.[13] The work of Isono showed that the reveromycins were active as inhibitors of mitogenic

activity induced by epidermal growth factor. This serves as yet another example of the value of natural products containing spirocyclic moieties as drug candidates. Similar to the spongistatins, efforts have been made toward the total synthesis of members of the reveromycin family. Theodorakis first proposed a total synthetic route to afford reveromycin B (Figure 4) in 1998.[14] Additionally, this route was expanded upon by the work of Nakata[15] and Rizzacasa[16] employing unique methods to afford the desired spirocycle.

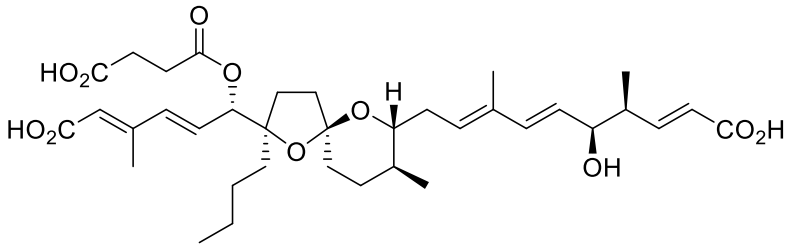


Figure 4. Structure of Reveromycin B

Work from the Andersen group at the University of British Columbia involves the detection of new natural products that display antimitotic properties, making them promising anticancer agents. They do so by screening extracts from marine invertebrates in a cell-based assay that detects mitotic arrest. During their research, they found that the extracts of a Caribbean marine sea sponge *Spirastrella coccinea* displayed potent activity and became a target of interest.[17] The compound within the extract that displayed this activity was found to be spirastrellolide A, a marine macrolide containing two spirocycles (Figure 5). Shortly after its discovery, six structurally related congeners were discovered, although spirastrellolide A remains the most naturally abundant. Much work has been devoted to the elucidation of the absolute stereochemistry of this marine natural product by Andersen. Additionally, much research has revolved around spirastrellolide A regarding its total synthesis. It was determined that in order to properly isolate spirastrellolide A from its related congeners, the methyl ester needed to be synthesized rather than the carboxylic acid.[18] The methyl ester was also found to exhibit

antiproliferative properties against a number of the NCI's cancer cell lines. In 2008, Paterson and co-workers published their total synthetic route to afford spirastrellolide A methyl ester.[19,20]

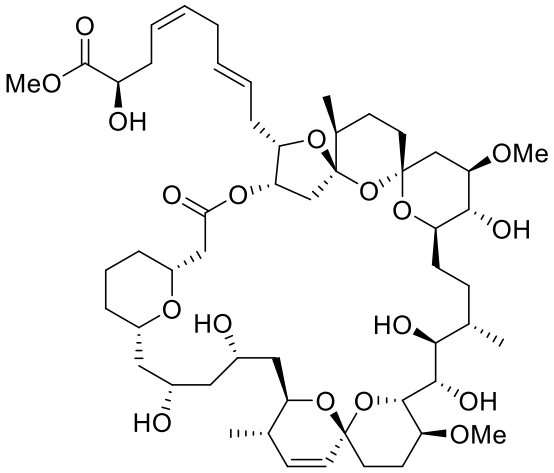


Figure 5. Structure of Spirastrellolide A

The examples provided in this section showcase the presence of spirocyclic moieties in natural products with potent therapeutic properties. Additionally, the scarce abundance of these natural products along with their structural complexity displays their value as synthetic targets. Thus, the emergence of neaumycin B provides us with an exciting new potential lead drug candidate that could have a profound impact in the field of anticancer agents.

1.3 Stabilization Effects in Spiroketals

A number of factors need to be considered when assessing the stability of spiroketals. Potentially the most significant contributing factor would be the presence or absence of the anomeric effect between oxygen atoms within the spiroketal core. The anomeric effect is a phenomenon that occurs widely in tetrahydropyran rings, where heteroatomic substituents adjacent to the heteroatom within the ring preferentially wish to adopt an axial orientation rather

than the less hindered equatorial orientation.[21] Although some stabilization is granted to the ring system as a result of the anomeric effect, the presence of axial substituents over equatorial substituents still needs to be considered. These effects, in certain cases, can even override the propensity for spiroketals to exist in their preferred doubly anomeric configuration. Electronic effects, which go hand in hand with the anomeric effect, need to be considered as well, along with any influence that may be contributed by the chosen solvent which may stabilize or destabilize certain configurations of the spiroketal.

As was previously stated, the anomeric effect plays a key role in the configuration of spiroketals. Deslongchamps and co-workers conducted research in this area to show that the entirely unsubstituted [6,6] spirocyclic system displays a strong preference to exist in its doubly anomeric configuration.[22] In his work, Deslongchamps took the accepted energetic benefit of one anomeric effect, 1.4 kcal/mol, and factored in the effect of having a methylene group axially oriented relative to an oxygen atom. Ultimately, it was concluded that each anomeric effect would contribute an energetic benefit of 2.4 kcal/mol in the unsubstituted [6,6] spirocyclic system. Thus, the non-anomeric spiroketal comes with a 4.8 kcal/mol penalty while its singly anomeric counterpart is attributed with a 2.4 kcal/mol energetic penalty compared to the preferred doubly anomeric configuration.

These factors are important to include, as they shed some light on the stabilizing impact of this effect albeit in the absence of any other influence. However, focusing on substituted spiroketals is extremely important since those substitutions will play a role in the thermodynamic tug-of-war taking place. When axial substituents are minimized and anomeric effects are maximized, the configuration of spiroketals can be confidently predicted, but these predictions can be more challenging to make when the effects are not reinforcing. Take, for example, a simple

asymmetrically substituted system (Figure 6). In such a system there are four possible configurations, each corresponding to the independent inversion of each chair. In the figure shown below, the doubly anomeric spiroketal on the left is accepted to be the most stable of the four. Epimerization of either ring within this hypothetical system would lead to the singly anomeric configurations shown, and subsequent inversion of the remaining ring would afford the non-anomeric system shown on the right-hand side.

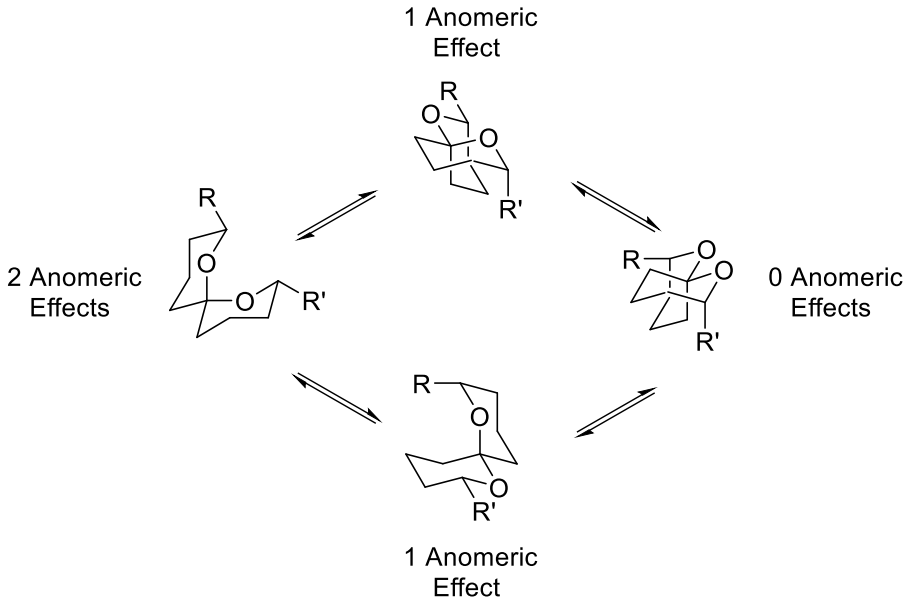


Figure 6. Four Possible Configurations of Asymmetrically Substituted Spiroketals

Taking note of this phenomenon and remembering the preferred geometry of these systems is important but understanding why it occurs is crucial. A popular explanation for the anomeric effect was first proposed by Altona over 60 years ago and is still widely accepted as a strong contributing factor.[23] Altona proposed that this contrasteric bias toward the axial substitution of a heteroatomic substituent adjacent to the heteroatom within the ring arises from stabilization due to orbital overlap (Figure 7). When oriented axially, the anti-bonding orbital of the C-O bond of the heteroatomic substituent is aligned with one of the lone pairs of the adjacent oxygen atom within

the ring, allowing for delocalization of electrons and creating a hyperconjugative interaction. When oriented equatorially, it can be seen that this anti-bonding orbital experiences no overlap.

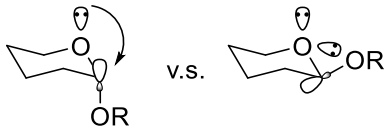


Figure 7. Anti-Bonding Orbital-Lone Pair Overlap and the Anomeric Effect

In addition to the hyperconjugative interaction seen above, the bias toward axial substitution has been attributed to other factors as well. A simpler model that also justifies the axial orientation of the heteroatomic substituent involves the resulting dipole from either configuration (Figure 8). When substituted axially, the dipole resulting from the lone pair of the oxygen atom within the ring is opposite the dipole formed from the electronegative substituent. However, when the substituent is equatorial, the dipoles are now pulling in similar directions.[24] In this case, the ring with the equatorially substituted heteroatom has a larger net dipole moment than the one with the axial substituent. The spirocycle maintaining the smaller dipole moment is expected to be the more stable of the two.

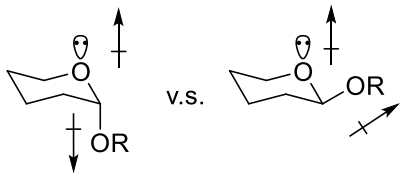


Figure 8. Dipole Cancellation and its Effect on Stability

To build on the notion that dipole minimization influences the structural integrity of spiroketals, it is also important to note other stereoelectronic factors at play. Newman projections of each of the hypothetical tetrahydropyrans shown in Figure 8 can provide valuable insight into the repulsions that play a role in the stability of the axial substituent (Figure 9). When the heteroatomic substituent is substituted axially, not only are the dipoles minimized, but the electronegative atom is not positioned between the electron pairs of the oxygen atom within the

ring. When contrasted with the equatorial substituent, it can be seen that the substituent is now wedged between each of the lone pairs. This suggests that electrostatic repulsions also play an important role upon inspection of the resulting Newman projections. This effect was first postulated by Lemieux, an earlier pioneer in the studies of anomeric systems.[25]

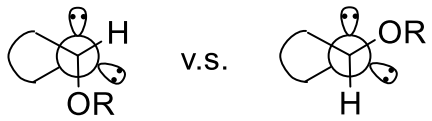


Figure 9. Effects of Electrostatic Repulsions

Lemieux conducted much of the early research that has contributed to our knowledge of spiroketals that we have today. It is well understood that stereoelectronic factors play an important role in determining the configuration that the spiroketal wishes to adopt, but Lemieux showed that the environment surrounding the molecule has a profound impact as well.[26] Regardless of the previously mentioned effects that lead to stabilization within the spiroketal moiety, Lemieux's studies indicate that the solvent can shift the equilibrium toward the configuration maintaining an equatorial substituent at the 2-position. In order to investigate this parameter, he screened different solvents and their effects on the configurational equilibrium of 2-methoxytetrahydropyran.[27] From his research, he noticed that more polar solvents slightly favored the more polar spiroketals, containing the equatorial substitution at the 2-position . For instance, in CD_3CN, the configuration containing the equatorial methoxy group was found to be present as 32% of the mixture. This was compared to the equilibrium observed in the less polar solvent, CCl_4, where it only accounted for 17% of the mixture, suggesting that more polar solvents blunt the effects of anomeric stability. Furthermore, in D_2O, the two spirocycles were found to exist at nearly equal concentrations. These results are supported by a more recent study carried out by Tvaroska and co-workers.[28] Their studies were conducted on a similar system, 2-hydroxytetrahydropyran, except their results were

based on *ab initio* methods used to assess the conformational properties of the anomeric effect of the hydroxy group. They state that the solvation energy calculated using their software is a sum of hydrophobic effects as well as the electrostatic contributions and nonpolar contributions arising from van der Waals interactions with the solvent. Upon modeling all of the potential configurations, it was shown that the non-polar component played a very small role in the changes in solvation energy, but the electrostatic contributions varied greatly. In short, these studies bolstered Lemieux's results from his early work, providing calculations to show that polar solvents do play a key role in the resulting outcome of an anomeric center. Both Lemieux and Tvaroska suggest that this phenomenon could be a result of the different environments' influences on the interactions of the unshared pairs of electrons around the anomeric site.[26,28]

One last factor to account for in the determination of the configurational outcome of a spiroketal is the simple thermodynamic penalties or benefits of the substitutions across the ring system. Regardless of all of the benefits that arise from anomeric stabilization that were previously discussed, some natural products may prefer to reside in a singly anomeric or non-anomeric form when one or more of the rings has too many axial substituents. This trend can be seen in a number of natural products. A fitting example of this phenomenon can be seen in neaumycin B. As was determined by Fenical, neaumycin B exists in its singly anomeric form[4], however a competing doubly anomeric configuration could exist (Figure 10). Upon inspection of the epimeric structures of neaumycin B, it can be seen that the doubly anomeric form contains an axial substitution while the singly anomeric form has all of its substituents in the equatorial position. Taking these effects into account prior to carrying out a total synthesis is of utmost importance since there may be some competition in the formation of either of these configurations.

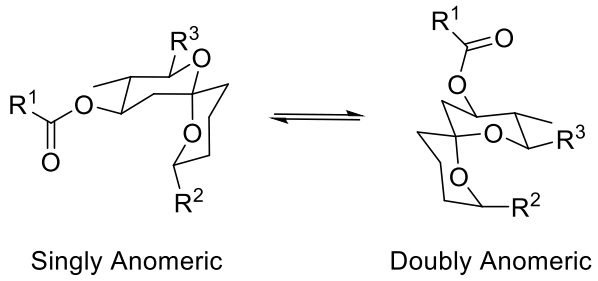


Figure 10. Possible Configurations of Neaumycin B

In addition to the preference for equatorial substituents, it is a possibility that neaumycin B experiences an intramolecular hydrogen bonding effect that further stabilizes its singly anomeric form. Extending R^3 seen in Figure 10 reveals that there is a free alcohol in proximity to the oxygen within the ring of the spiroketal core when in its desired, singly anomeric form (Figure 11). In the doubly anomeric form, this interaction would likely not be present due to the steric limitations of the macrocycle. Stereoelectronic factors such as this also need to be considered when determining the most stable configuration of an intended spiroketal and bring attention to the demand for methods to form spiroketals under non-equilibrative conditions.

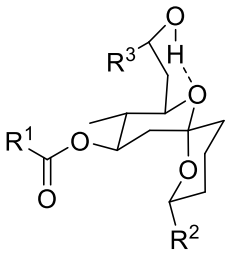
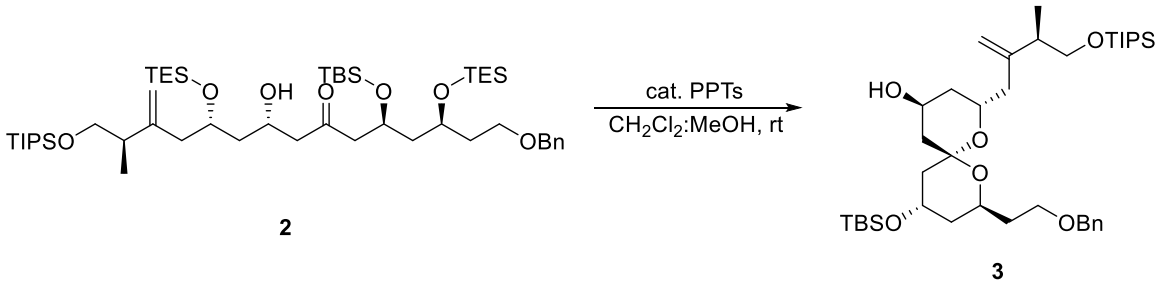


Figure 11. Intramolecular Hydrogen Bonding Event Observed in Neaumycin B

1.4 Synthetic Strategies Toward the Formation of Spiroketals

Spiroketals are coveted synthetic targets due to their presence across a variety of natural products and structural complexity. Much work has been devoted to uncovering synthetic means

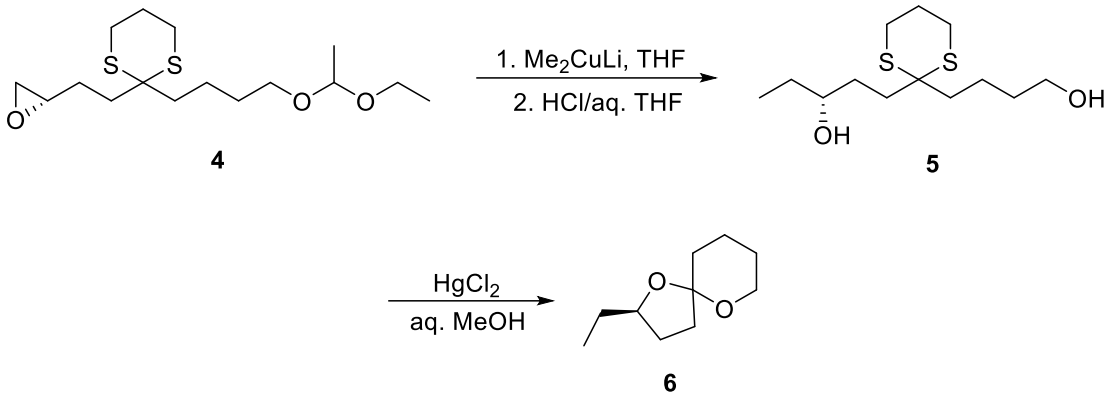
to access these molecules reliably and effectively. Likely the most popular method to afford spiroketals is through the acid-mediated spirocyclization of dihydroxy ketones. This method dates back to the early days of spiroketal chemistry and is still commonly used to this day, although other methods exist. An example of this process carried out by Paterson can be seen below (Scheme 1).[29] In this method, precursor **2** was first formed through a boron-mediated aldol condensation. With this aldol adduct in hand, treatment with PPTS in a CH_2Cl_2:MeOH mixture would allow for bis-desilylation followed by concomitant spirocyclization to afford spirocycle **3**. This transformation benefits from the acid-mediated nature of the cyclization since the desired spirocycle is the thermodynamically favorable product, having both oxygens in the rings axial with respect to each other.



Scheme 1. Acid-Catalyzed Spiroketalization of Dihydroxyketone

Although this method is seen widely in the realm of spiroketal formation, the ketone at the position of the resulting spirocyclic carbon can be masked as alternative functional groups. A good alternative is the use of a 1,3-Dithiane moiety in place of a carbonyl. 1,3-Dithianes can act as carbonyl protecting groups that can be subsequently deprotected to allow for spirocyclization. 1,3-Dithianes and related compounds are ideal candidates for connecting two hydroxyalkyl nucleophiles together at a pro-carbonyl group which will go on to be the spirocyclic carbon of the spiroketal.[21] An example of this process was shown by Seebach and co-workers (Scheme 2).[30] In this work, optically active epoxide **4** was first generated then the desired methylation could be

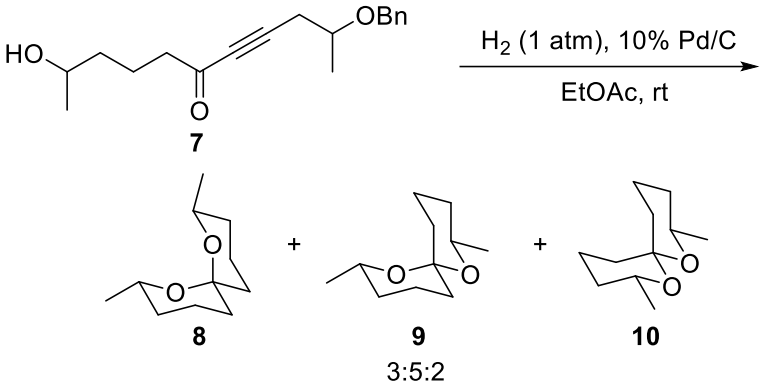
successfully carried out without any interference from the carbonyl that the 1,3-Dithiane is masking, to afford **5**. Finally, exposure to mercury (II) chloride in the presence of aqueous methanol allowed for the removal of the 1,3-Dithiane and spirocyclization all in one step.



Scheme 2. 1,3-Dithiane as a Carbonyl Surrogate for Spiroketalization

In certain instances, the use of an acid-catalyzed method is not necessary. Under acidic conditions, it is likely that the spiroketalization process will lead to the most thermodynamically stable product, containing maximized anomeric effects and minimized axial substituents. Even though nature commonly provides the most thermodynamically stable product, there are examples where a less favorable configuration is present in the natural product of interest. Pihko[31] and co-workers encountered an example of this in their efforts toward the spirocyclic unit observed in pectenotoxin. The pectenotoxins make up a family of marine natural products isolated from *Patinopecten yessoensis* and were first isolated by Yamamoto and co-workers in 1985.[32] Of the pectenotoxins, 10 congeners have been discovered and displayed a degree of cytotoxicity toward a number of lung, colon, and breast cancer cell lines. The most cytotoxic congener within the family, however, contains a [6,5]-spirocyclic subunit that exhibits no anomeric stabilization.[31] This highlights the need for methodology that allows access to thermodynamically unfavorable spirocycles. Koutek and co-workers have described a unique method to access spiroketals under mild, nonacidic conditions which should resist isomerization at the spirocenter and allow access

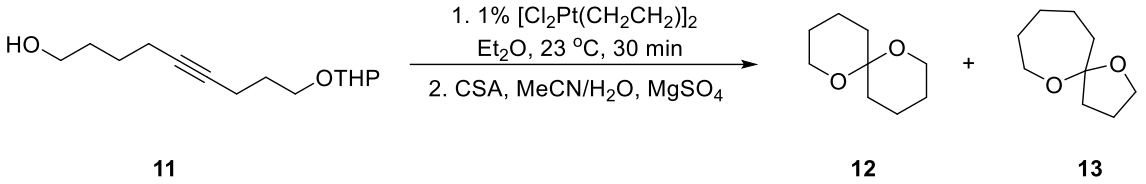
to multiple different isomers of the desired product.[33] This was done through the exposure of functionalized hydroxy α-alkynones to palladium-catalyzed hydrogenation conditions. This allowed for a one-pot cascade involving hydrogenation of the triple bond, benzyl deprotection of the benzyl ether, and subsequent spirocyclization under nonacidic conditions. Using this method, isomers with and without anomeric stabilization can be obtained. The three products observed (Scheme 3) were formed in a 3:5:2 ratio, respectively.



Scheme 3. Nonacidic Conditions to Afford Nonanomeric Spiroketals

The previously displayed method makes use of α-alkynones, but there are a number of transition metal-mediated processes that are able to afford spiroketalization using only an alkyne as the electrophile which acts as a latent ketone. One of the most commonly employed methods for the formation of spiroketals using a transition metal-mediated process is through the dihydroalkoxylation of alkynediols.[34] This work was originally pioneered by Utimoto,[35] using palladium(II) salts in the hydroalkoxylation of internal alkynediols but there have been many developments in this work throughout the years. For example, De Brabander and co-workers developed a platinum-catalyzed, regioselective method for the formation of spirocycles from these alkynediol motifs.[36] Through the use of Zeise's dimer ($[Cl_2Pt(CH_2CH_2)]_2$) and subsequent acid treatment, alkynediol derivative **11** could be effectively converted into the corresponding

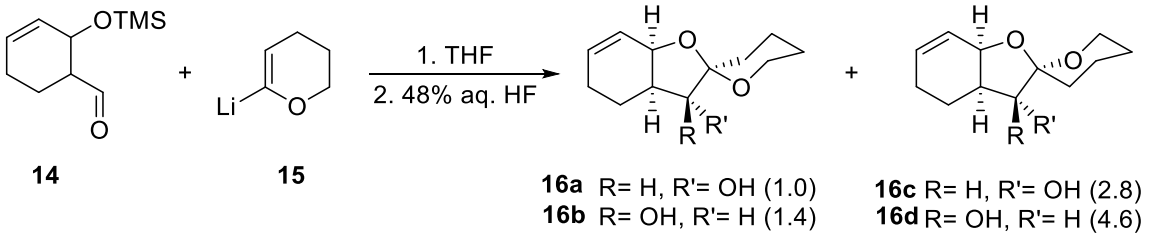
spirocycles **12** and **13**. They were able to optimize these parameters, forming the [6,6]-spirocyclic product in a 30:1 ratio.



11 **12** **13**

Scheme 4. Transition Metal Mediated Spirocycle Formation

Although alcohols and their protected counterparts are common nucleophiles in the formation of spiroketals, other alternatives have been successfully employed. Kurth and co-workers displayed a method for spiroketal formation during their studies toward the syntheses of phyllanthoside and breynolide.[37] They originally attempted to form their desired ring system through an aldol condensation followed by an acidic procedure, adhering to the preferred synthetic pathway for spiroketals. Unfortunately, their initial attempts led to complex mixtures from which neither starting material nor product could be isolated. Rather than approaching their desired spirocycle through conventional means, Diels-Alder adduct **14** was reacted with α-lithiodihydropyran **15**, which serves as the nucleophile in this example. The intermediate formed from this reaction was then treated with hydrofluoric acid, allowing the TMS ether to effectively add into the dihydropyran ring and ultimately leading to their desired spiroketal, albeit as a mixture.

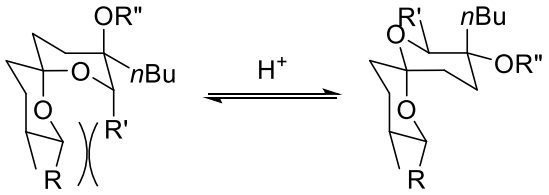


14 **15**

16a R= H, R'= OH (1.0)
16b R= OH, R'= H (1.4)
16c R= H, R'= OH (2.8)
16d R= OH, R'= H (4.6)

Scheme 5. Stepwise Formation of Spiroketal from Organolithium Species

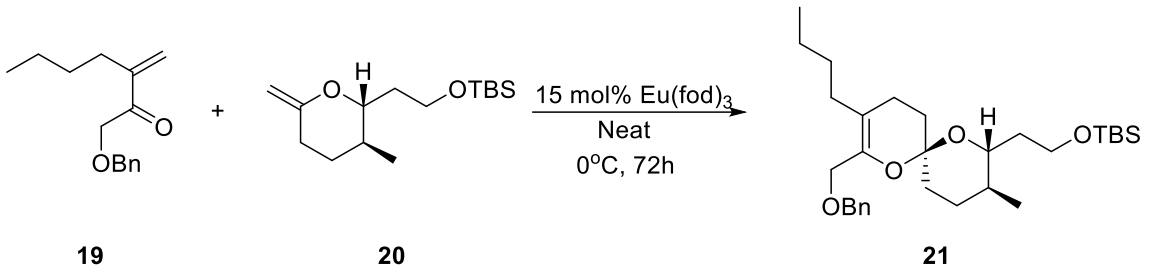
2-Methylenetetrahydropyrans are known to act as synthetically useful intermediates commonly used in the synthesis of spiroketals.[32,33,37] The exocyclic alkene can serve as a valuable handle for a number of different functionalizations such as radical processes, halogenations, or even by acting as a nucleophile. Furthermore, Rizzacasa and co-workers employed a 2-methylenetetrahydropyran in their synthesis of reveromycin A as a partner in a hetero Diels-Alder reaction with an α,β-unsaturated carbonyl compound.[38] The spirocyclic moiety within reveromycin A exists in a doubly anomeric configuration **17**, however a key steric interaction makes the singly anomeric isomer **18** exist at the cost of just a small energetic difference (Scheme 5). The steric interaction occurring between R and R' in the model shown in Scheme 5 complicates the formation of this spirocyclic moiety using acid-catalyzed means.



17 **18**

Scheme 6. Acid-Catalyzed Isomerization of Reveromycin A

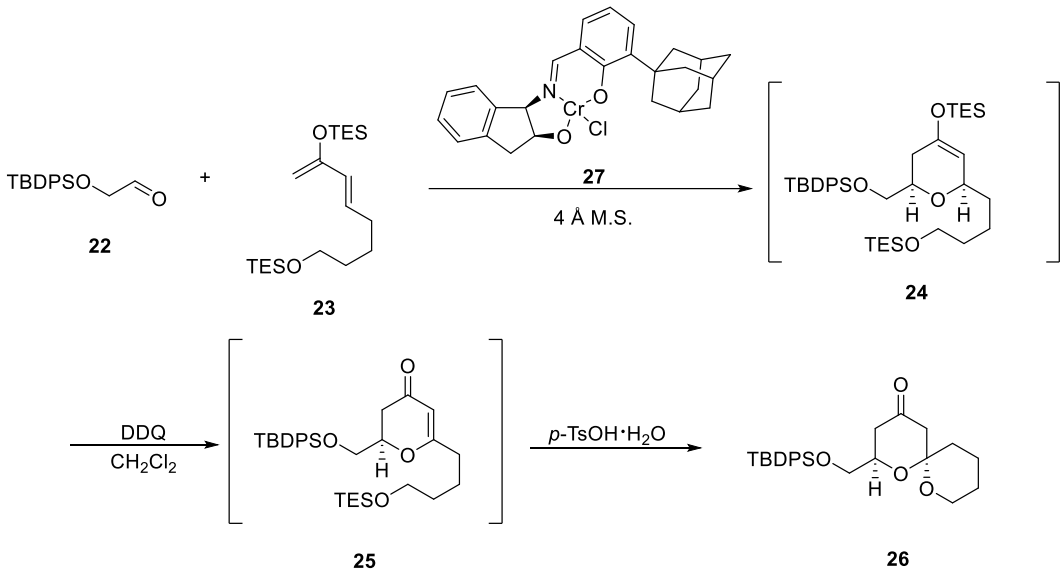
To circumvent this issue, Rizzacasa envisioned going through a kinetic pathway to afford the spiroketal in reveromycin A to avoid any acid-catalyzed isomerization to the undesired isomer. Through the union of α,β-unsaturated carbonyl compound **19** with chiral 2-methylenetetrahydropyran **20** in an inverse electron demand hetero-Diels-Alder reaction, the spirocycle **21** could be formed selectively. This process was catalyzed by a europium(III) catalyst and is able to control the stereochemistry at the spirocenter through the preferred axial approach to the carbonyl in the hetero-Diels-Alder transition state.



19 **20** **21**

Scheme 7. Lewis Acid Mediated Hetero-Diels-Alder to Afford Spiroketals

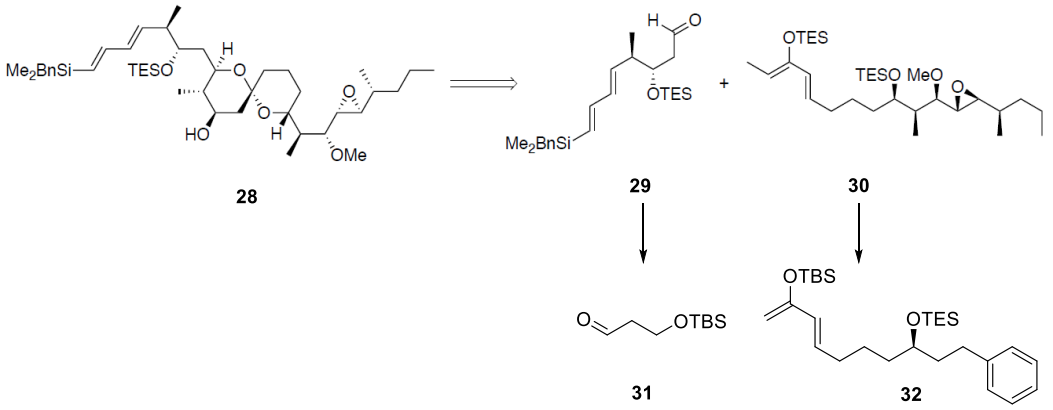
Hetero-Diels-Alder chemistry provides an excellent way to afford spiroketals through the use of a convergent methodology. A strategy implementing this chemistry was carried out by the Floreancig group and demonstrated in their total synthesis of bistramide A (Scheme 8).[39] This method employs a hetero-Diels-Alder reaction between aldehyde **22** and silyloxydiene **23** in the presence of Jacobsen's catalyst, **27**, and molecular sieves. The catalyst used here aids in setting the stereochemistry at the 1- and 5-positions of dihydropyran intermediate **24**. Once **24** is afforded, the reaction mixture is diluted with dichloromethane and is exposed to 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) which promotes hydrogen bond cleavage and subsequent silyl group loss from the corresponding oxocarbenium ion, resulting in the formation of dihydropyrone **25**. This process is concluded with protodesilylation induced by *para*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O) which results in the successful production of spiroketal **26**. This protocol offers a mild and step-economical convergent strategy for the synthesis of stereochemically defined spiroketals.



Scheme 8. Hetero Diels-Alder Approach to Spiroketals

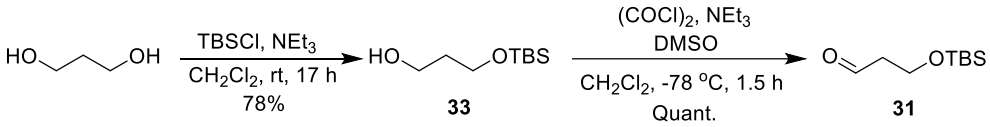
1.5 Initial Synthetic Efforts

The main purpose of my research was to find an optimal approach to the spirocyclic moiety found in neaumycin B. Ideally the method used would be high yielding and provide the correct stereochemical outcome, affording the singly anomeric spiroketal with all equatorial substituents. To do this, I prepared several model systems of the spiroketal in order to test out a variety of different conditions. My early research endeavors involved the implementation of the hetero Diels-Alder chemistry mentioned previously.[39] It was originally envisioned that one of the major fragments of neaumycin B, **28**, would be brought together using this strategy through the union of aldehyde **29** and silyloxydiene **30.** To test out this strategy, model aldehyde **31** and silyloxydiene **32** were envisioned to provide a simple model system that would give access to important information regarding the connectivity and stereochemical outcome of the reaction.



Scheme 9. Initial Synthetic Analysis for Model Spiroketal

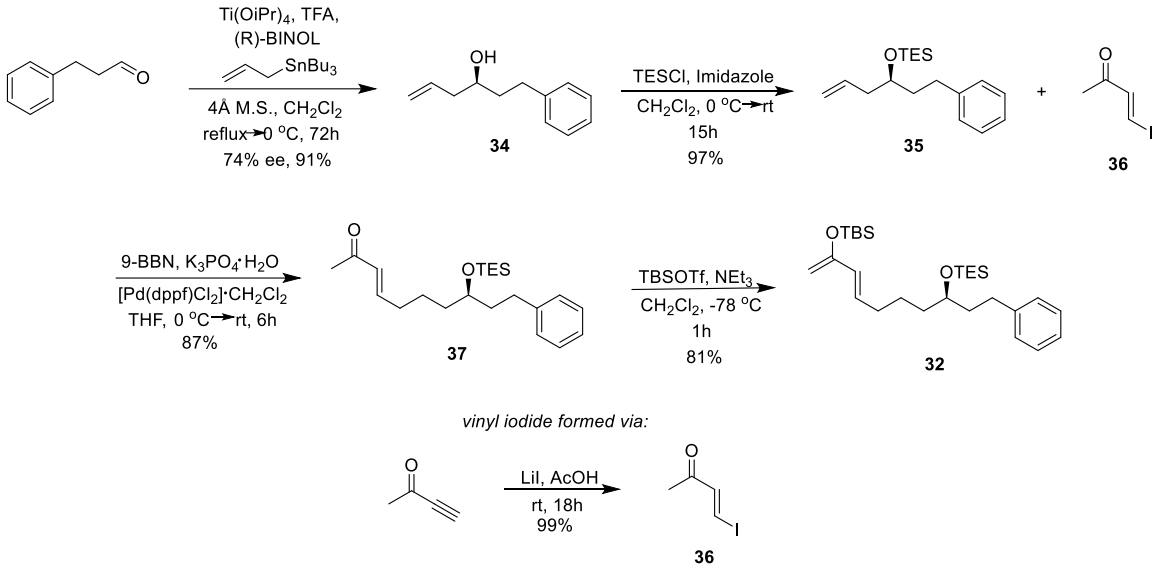
Forming aldehyde **31** was a fairly simple process. Beginning with 1,3-propanediol, mono-silylation was carried out to afford the protected alcohol **33**. With this material, a Swern oxidation[40] could then be employed to oxidize the alcohol to the resulting aldehyde **31**, leading to one of the fragments necessary for the hetero Diels-Alder reaction.



Scheme 10. Synthesis of Aldehyde 31

With one fragment in hand, diene **32** now had to be synthesized to carry out the hetero Diels-Alder reaction (Scheme 11). Beginning with hydrocinnamaldehyde, a Keck asymmetric allylation[41] was carried out to for homoallylic alcohol **34** in good yield and 74% ee which was deemed sufficient to carry out the intended experiments. The analogous Brown allylation[42] procedure was attempted as well, although diminished yields were observed along with a more challenging separation. Subsequent protection with chlorotriethylsilane gave silyl ether **35** which was poised to undergo efficient coupling with vinyl iodide **36**. This vinyl iodide could be conveniently prepared prior to the intended coupling through treatment of 3-butyn-2-one with lithium iodide in acetic acid.[43] This process led to the desired coupling partner which was deemed

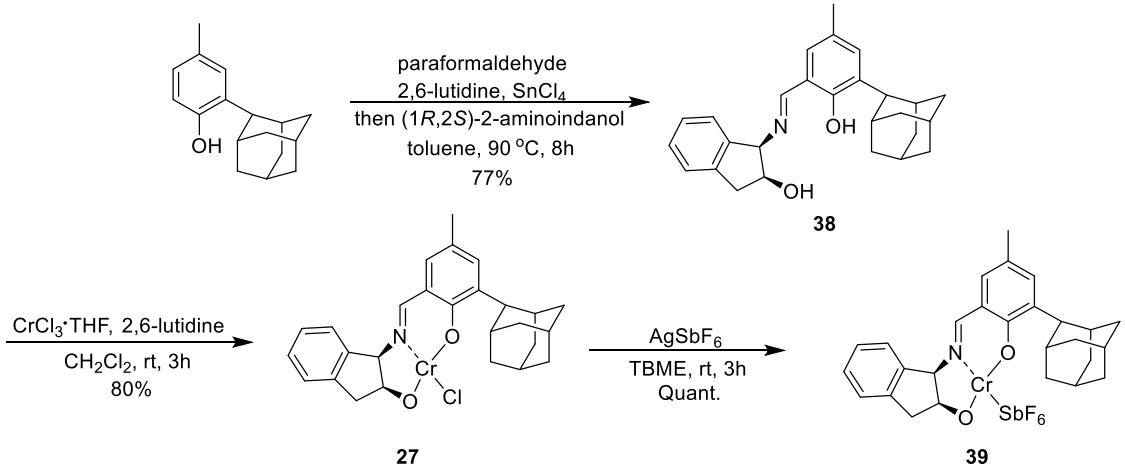
pure enough to use crude by ^{1}H NMR. With both coupling partners in hand, a B-alkyl Suzuki homologation[44] could be conducted. This process proved to be very efficient, delivering the desired α,β-unsaturated ketone in 87% yield. From **37**, the corresponding silyl enol ether **32** could be conveniently prepared using *tert*-butyldimethylsilyl triflate and triethylamine. It should be noted that due to the sensitivity of the hetero Diels-Alder reaction, **32** was purified before use. It was found that this silyl enol ether could be isolated on basic alumina without any observed decomposition.



Scheme 11. Synthesis of Silyloxydiene 32

The hetero Diels-Alder needs to be carried out in the presence of a chiral catalyst in order to deliver the desired dihydropyran. Jacobsen and co-workers have conducted outstanding research involving this cyclization and have developed a catalyst and method to allow for the formation of asymmetric hetero Diels-Alder adducts.[45] This work requires the use of a chromium(III) complex and was shown to deliver the desired hetero Diels-Alder adducts in >90% ee. The catalyst, however, is not commercially available and needs to be prepared prior to the intended reaction (Scheme 12). The first step in the synthesis of Jacobsen's catalyst involves an

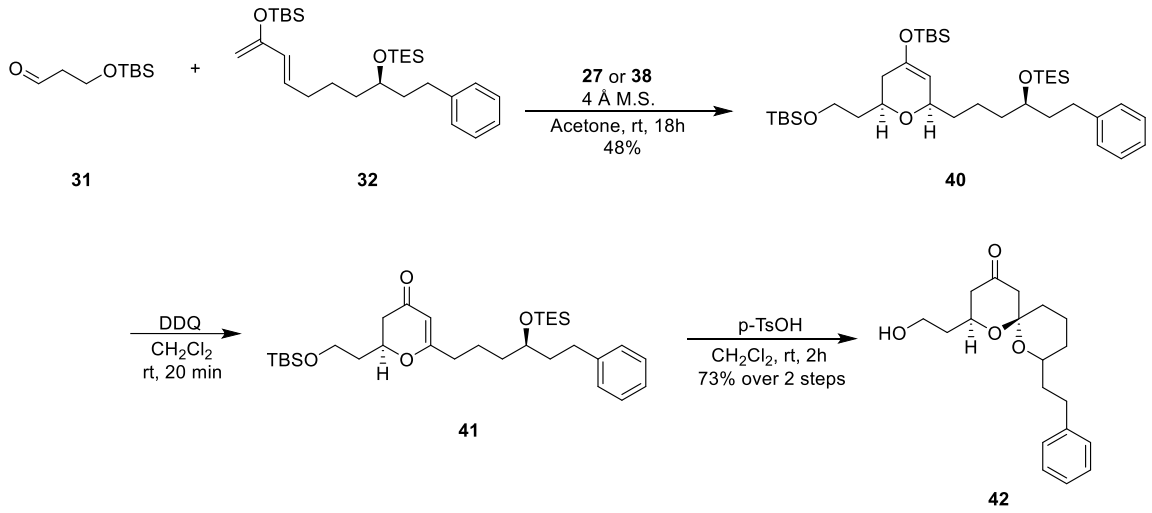
imine condensation between 2-adamantyl-4-methylphenol and (1*R*, 2*S*)-1-amino-2-indanol. This amine serves as the source of chirality in the system and promotes the asymmetric nature of Jacobsen's protocol. This leads to the formation of imine **38**, which has three heteroatoms appropriately placed to coordinate to chromium and form the desired catalyst **27**. Furthermore, Jacobsen's studies show that certain systems call for an alternate counterion. To address this, it was found that a hexafluoroantimonate counterion could serve as an adequate variant. Treatment of **27** with silver hexafluoroantimonate(V) in *tert*-butyl methyl ether was found to successfully form alternate catalyst **39**.[46]



Scheme 12. Formation of Jacobsen's Catalyst

With all the necessary components in hand, the protocol to synthesize the desired model spirocycle could be carried out. Since the process involves three steps, it was decided to first carry out each step individually rather than attempt a one-pot process in order to properly evaluate the reaction sequence. First, aldehyde **31** and silyl enol ether **32** needed to be joined together through a hetero Diels-Alder using either catalyst **27** or **39**. Prior research within the group employed the chloride catalyst **27** so this was attempted first along with µL quantities of acetone. It was found that minute quantities of acetone can help facilitate the reaction since it is carried out neat and proper stirring may not be achieved. Ultimately, it was observed that the use of catalyst **27** led to

extremely long reaction times and no observed product formation, with or without acetone. It is possible that the components of the reaction were decomposing faster than the reaction was taking place. Next, catalyst **39** was tested. Complete consumption of starting material could be seen overnight, which was an improvement compared to **27**. Hetero Diels-Alder adduct **40** was successfully formed using this catalyst at 48% yield. Dihydropyrone **40** needed to be purified in order to move forward with this sequence. Once **40** was isolated, DDQ could be added to allow for oxidation to the corresponding dihydropyrone **41**. Once the reaction was deemed complete by TLC, *p*-toluenesulfonic acid monohydrate was delivered to the reaction mixture to deprotect the silyl ether and promote cyclization to model spiroketal **42**.

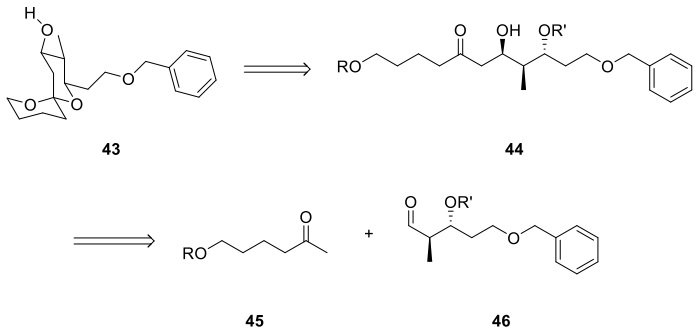


Scheme 13. Hetero Diels-Alder Approach to Model Spiroketal 42

Although this method allows for a unique approach to the spirocyclic unit of neaumycin B, it is accompanied by some obstacles of its own. First, the 48% yield seen in the hetero Diels-Alder was a poorly reproducible result. The same reaction conditions were carried out several times with 48% being the highest observed yield on one of the attempts. The remaining attempts furnished **40** in much lower yields, if at all. Second, carrying out this sequence as a one pot process proved unsuccessful. When attempted as a one pot reaction, the main product observed was the

tetrahydropyran ring as a result of an intramolecular conjugate addition of α,β-unsaturated ketone **37**. Furthermore, to be properly applied to the synthesis of neaumycin B, an ethyl ketone would need to be used as a precursor to the silyloxy diene rather than a methyl ketone to place a methyl group on the spiroketal in the appropriate position. This methyl group could prove to be a significant synthetic hurdle since the formation of the silyl enol ether could produce *cis*- and *trans*-isomers and lead to a difficult separation, or lead to two spirocycles that are epimeric at the carbon substituted with the methyl group. Lastly, the resulting carbonyl on the ring would have to be properly functionalized after being reduced to the corresponding alcohol stereoselectively. This, again, could result in a difficult separation or even functional group incompatibility with the necessary reduction method. Ultimately, it was determined that other routes should be explored in order to obtain the spirocyclic moiety of neaumycin B.

Upon consideration of alternate routes to afford the desired spiroketal, it was conceived that this could be accomplished through the use of an aldol reaction and subsequent acid treatment to induce spiroketalization. The general retrosynthetic scheme is shown below (Scheme 14) to illustrate this idea. It can be seen that this protocol can conveniently provide the spiroketal with the methyl in the correct position simply by setting the stereochemistry correctly in the synthesis of aldehyde **46**.



Scheme 14. Retrosynthetic Analysis for Spiroketal Formation Using Aldol Chemistry

This method provides other reinforcing factors that make it seem to be a favorable protocol. The desired stereochemistry of the resulting alcohol in **44** from the aldol reaction exhibits a *syn* relationship with the adjacent methyl group, which is a result of Felkin selectivity[47] and can be achieved using Mukaiyama aldol conditions.[48] Similarly, the protected ether at the β-position is *anti* to the resulting alcohol. It has been shown that 1,3-stereoinduction in Mukaiyama aldol processes plays a key role and preferentially provides the 1,3-*anti* diastereomer.[49] Evans proposed a model for this merged selectivity for the Felkin and 1,3-*anti* product.[50] The α-stereocenter will situate itself in such a way where the largest group will be orthogonal to the aldehyde and the proton will be in proximity to the proton of the aldehyde, providing the least hindered pathway for the nucleophile to attack. The β-stereocenter will then orient itself to minimize steric and electrostatic interactions to deliver the desired Felkin and 1,3-*anti* aldol adduct (Figure 12).

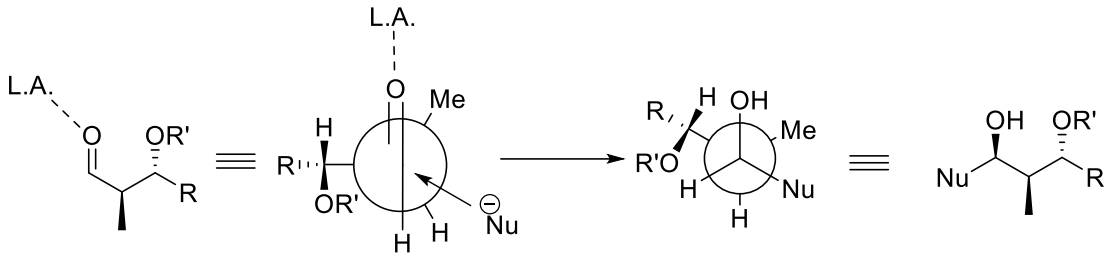
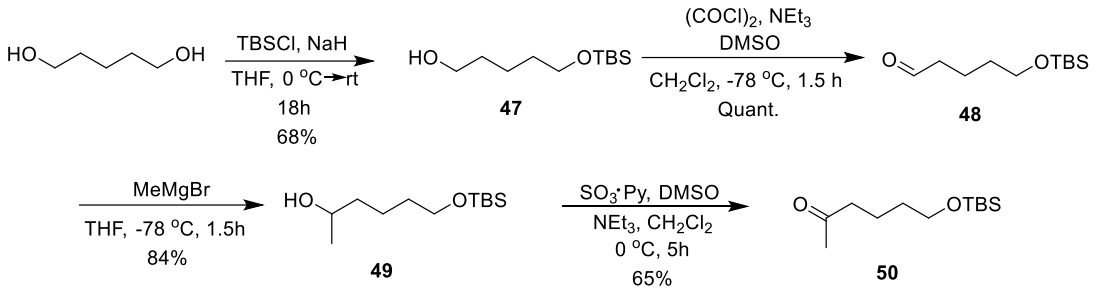


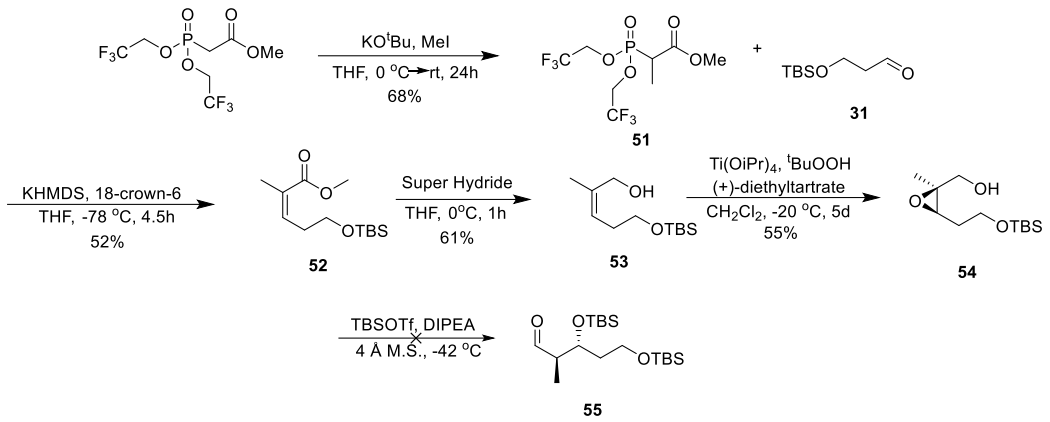
Figure 12. Model for Reinforcing 1,2- and 1,3-Stereoinduction

With a synthetic plan in hand, each of the components of the aldol needed to be prepared. Initially, a simple methyl ketone was employed in order to quickly test this method. The synthesis of methyl ketone **50** began with the mono-protection of 1,5-pentanediol to afford silyl ether **47**. A Swern oxidation[40] was then carried out to deliver aldehyde **48** in quantitative yields. Grignard addition of methyl magnesium bromide into aldehyde **48** provided alcohol **49** which could then be oxidized using a Parikh-Doering oxidation[51] to give the desired methyl ketone **50**.



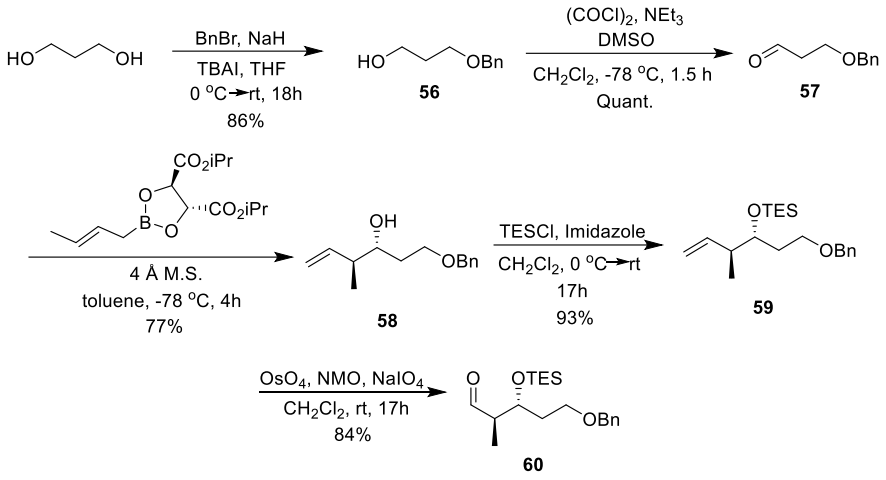
Scheme 15. Synthesis of Methyl Ketone 50

A few routes were employed in the attempts to obtain aldehyde **55** for the intended aldol reaction. The first route began with methyl *P,P*-bis-(2,2,2-trifluoroethyl)phosphonoacetate which needed to be methylated to give phosphonoacetate **51**. This material could then be coupled with aldehyde **31** using the Z-selective Still-Gennari modification of the Horner-Wadsworth-Emmons reaction.[52] This led to the formation of *cis*-unsaturated ester **52**. Subsequent reduction of this methyl ester using Super Hydride® delivered allylic alcohol **53** which was then exposed to Sharpless asymmetric epoxidation conditions.[53] Using (+)-diethyltartrate furnished stereodefined epoxide **54** in 55% yield. Epoxide **54** is then poised to undergo an iterative non-aldol aldol process developed by Jung and co-workers[54] to deliver aldehyde **55**. Upon investigation of this reaction, no product was observed. The methylene β to the methyl group could be playing a key role in this lack of reactivity. Jung has reported that substrates used in this reaction need a key steric interaction between a substituent on the α-carbon and the methyl group on the other side of the epoxide in order to undergo this process and resist cyclization to the corresponding THF ring.[55] In light of this lack of reactivity and the otherwise moderate yields observed throughout this reaction scheme, a new pathway needed to be employed.



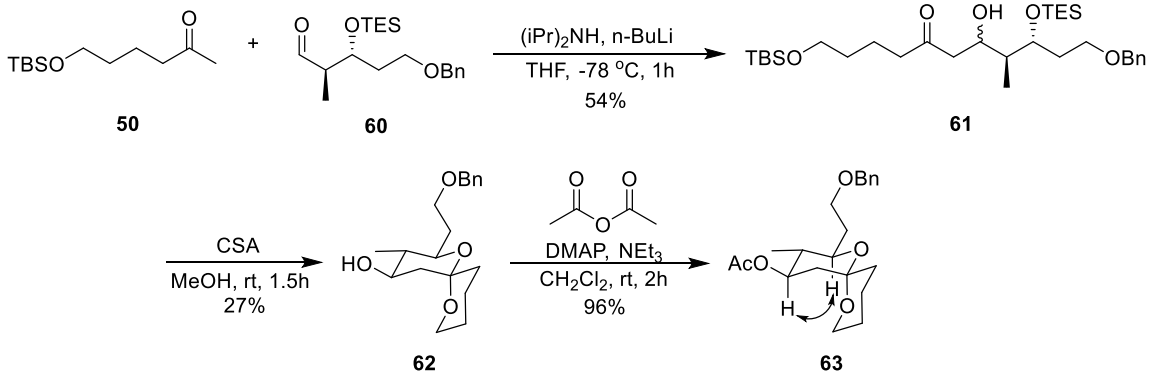
Scheme 16. Initial Synthetic Efforts Toward Aldehyde 55

An improved synthesis of the aldehyde for the intended aldol reaction is shown below (Scheme 17). This route began with the mono-protection of 1,3-propanediol, although as the benzyl ether rather than a silyl ether. It was thought that using a benzyl protecting group could help downstream since it would remain protected after the acid catalyzed cyclization. A Swern oxidation[40] followed by a Roush crotylation[56] cleanly provided *anti*-alcohol **58** in 77% yield and 78% ee. Silylation of the free alcohol gave the protected adduct **59** which was then followed by a Lemieux-Johnson oxidation[57] to convert the terminal alkene into the corresponding aldehyde. This route ultimately provided a higher yielding route to aldehyde **60** and the aldol reaction could now be conducted.



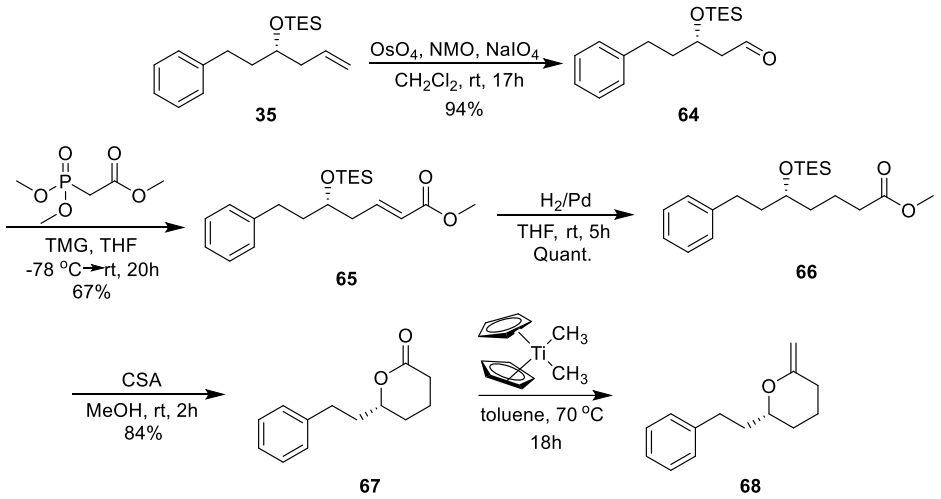
Scheme 17. Synthesis of Aldehyde 60

Due to initial difficulties with the Mukaiyama conditions, the aldol reaction was first carried out with the lithium enolate of the methyl ketone. Simply obtaining the desired spiroketal along with some stereochemical information was of the utmost importance at the time. Thus, an aldol reaction was carried out with methyl ketone **50** and aldehyde **60** to afford aldol adduct **61**. Once cyclization was carried out to deliver spiroketal **62**, the free alcohol was acylated to trigger a downfield shift of the adjacent proton by ^{1}H NMR. In doing so, an NOE signal was observed between the two indicated protons of compound **63** (Scheme 18), supporting that the desired configuration was achieved in this process and showing that this protocol could lead to the desired spiroketal.



Scheme 18. Synthesis of Model Spiroketal 63

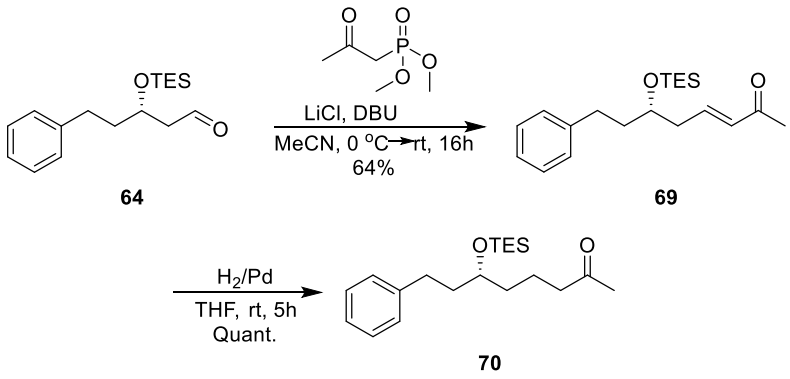
After successfully synthesizing the spiroketal through an aldol reaction between a methyl ketone and an aldehyde, it was then conceived that a different nucleophile could be employed. Through the use of a tetrahydropyran ring with an exocyclic alkene at the 2-position, it is possible to obtain nucleophilic addition into an aldehyde under Lewis acidic conditions. This method would come with the added benefit that one of the rings of the spiroketal would already be formed prior to the reaction. Once nucleophilic addition is achieved, the resulting oxocarbenium ion within the tetrahydropyran ring can act as an electrophile which could be trapped intramolecularly by the silyl ether of the aldehyde and lead to the spiroketal. The synthesis of this 2-methylenetetrahydropyran began with allylic silyl ether **35** which was synthesized in a similar fashion as described earlier. A Lemieux-Johnson oxidation[57] afforded aldehyde **64** which could then be used in a subsequent Horner-Wadsworth-Emmons reaction[58] with trimethylphosphonoacetate to form conjugated methyl ester **65**. Saturation of the alkene was then carried out in quantitative yields using a traditional hydrogenation method, followed by cyclization to the corresponding lactone **67** under acidic conditions. Then, the carbonyl was to be converted to the exocyclic alkene using the Petasis reagent.[59]



Scheme 19. Synthesis of 2-methylenetetrahydropyran 68

This reaction, although successful, led to complications when attempting to achieve nucleophilic addition into aldehyde **60** and when determining an accurate yield of **68**. Stoichiometric excess of titanium needed to be employed to afford the 2-methylenetetrahydropyran and it was extremely difficult to remove. Multiple filtrations on different stationary phases were carried out but the entirety of the titanium could not be removed. Additionally, the acid sensitivity of **68** meant silica gel could not be used. When placed under Lewis acidic conditions with aldehyde **60**, no desired product was observed. The residual titanium likely played a role in this lack of reactivity, acting as a Lewis acid itself. In light of these results, it was determined that elaborating on the aldol carried out in Scheme 18 would be the best course of action.

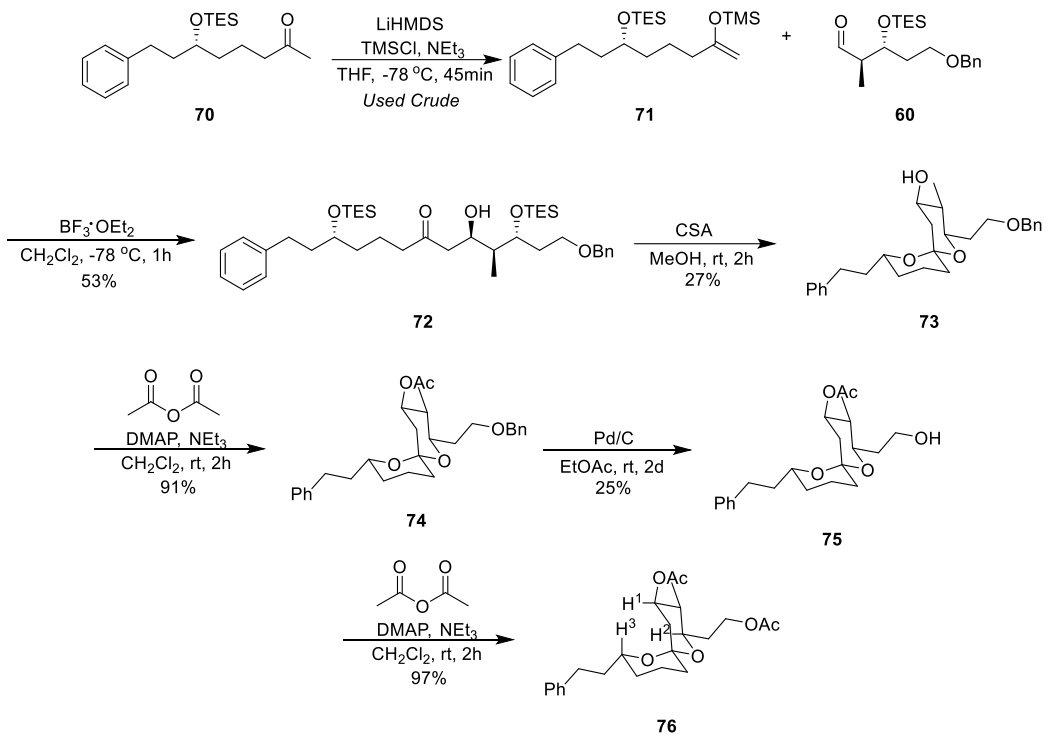
Luckily, aldehyde **64** was only a few steps away from granting a nucleophile that could be used in the desired aldol reaction. Additionally, it would provide a substitution on the ring of the spiroketal that was entirely unsubstituted in **62**. Homologation of aldehyde **64** with dimethyl acetonylphosphonate gave α,β-unsaturated ketone **69** which was then hydrogenated to form the corresponding saturated methyl ketone **70**.



Scheme 20. Synthesis of Methyl Ketone 70

With both components in hand, it came time to carry out the desired aldol reaction. Methyl ketone **70** was converted to the trimethyl silyl enol ether **71** using lithium bis(trimethylsilyl)amide

and trimethyl silyl chloride which was then used crude in the following step. Mukaiyama aldol conditions were carried out using boron trifluoride diethyl etherate as the Lewis acid and successfully formed aldol adduct **72** in 53% yield and about 2.4:1 selectivity for the Felkin:anti-Felkin diastereomers, respectively. Subsequent spiroketalization with CSA afforded the corresponding spirocycle, although only at 27% yield. A complex reaction mixture was observed during the cyclization process, with many products being formed possessing similar R_f values. Successful isolation of each of the products followed by LCMS experiments revealed that they each had the same mass, leading me to believe at the time that I was observing the result of acid catalyzed isomerization of the spiroketal. Since the desired product should be the most thermodynamically stable, the major product from this cyclization was carried on to the next step, where the secondary alcohol was acylated to deliver **74**. To isolate as many NMR signals as possible, the benzyl ether needed to be deprotected and converted to the primary acetate as well. Cleavage of this benzyl ether proved to be difficult and full consumption of starting material was not observed after two days. The reaction was stopped and the product that was formed was separated from the starting material and carried on to the subsequent acylation to provide spiroketal **76**, which was accompanied by a clean spectrum that aided in the conformational analysis of this compound.

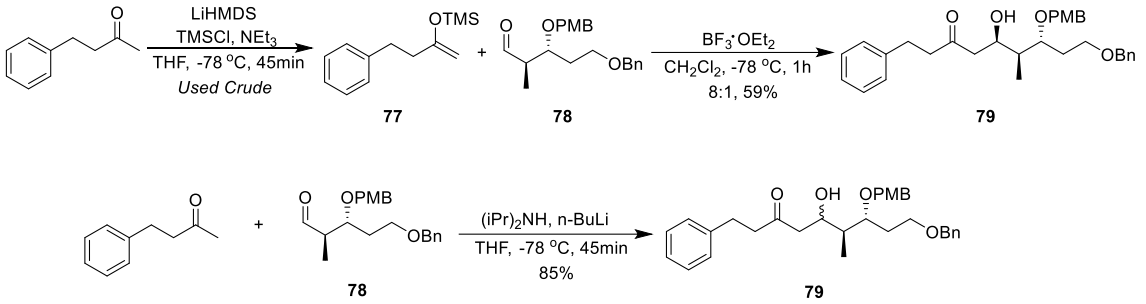


Scheme 21. Synthesis of Spiroketal 76

Spirocycle **76** contains the same substitution pattern that is observed in neaumycin B, with one ring containing substitutions in the 2-, 3-, and 4-positions while the other ring only has one substitution at the 2-position. In Scheme 21, the protons that offer the most information are labeled. H^1 and H^2 show an intersecting NOE signal indicating that they are likely both axial. This is similar to the result obtained from the last model system, indicating that the highly substituted ring is likely in the desired configuration. No NOE signal was observed between H^2 and H^3, but this is the case for the corresponding protons within neaumycin B. The main point of concern with this molecule was the lack of an NOE signal between H^1 and H^3. The equivalent of these two protons on neaumycin B show an NOE signal with each other[4] and should, in theory, be near each other in this molecule as well. It was theorized at the time that adding complexity to the molecule may contort it into a configuration closer to the one observed in neaumycin B and produce an NOE signal between these two hydrogen atoms. With this hypothesis in hand, the next

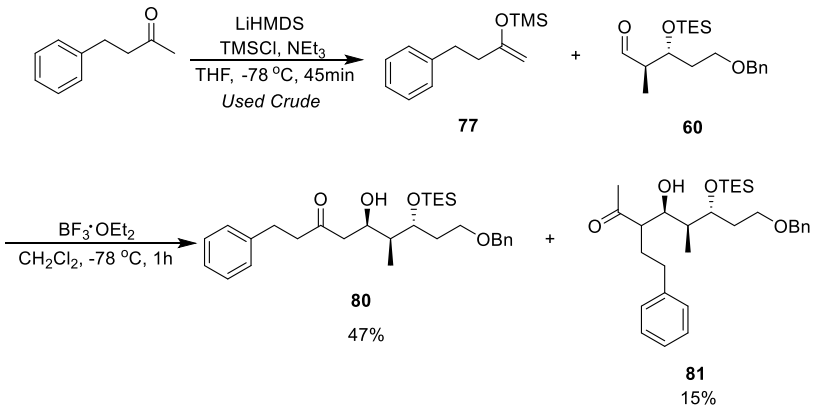
step was to build upon this model spiroketal. Additionally, the aldol needed to be investigated to produce the optimal selectivity for the Felkin product.

Upon going through the synthetic route for methyl ketone **70** to make more material, a Mosher ester analysis[60] revealed poor selectivity in the Keck allylation[41] of hydrocinnamaldehyde. This lack of selectivity was likely an issue in the prior cyclizations, with the diastereomers from this reaction forming byproducts rather than acid-catalyzed isomerization. The method to afford the methyl ketone would be optimized at a later time, however, while the aldol was being investigated a simpler nucleophile was going to be used. Benzylacetone was the nucleophile of choice since it is commercially available, possesses no stereocenters to contribute additional complexity to the system, and is substituted with an aromatic ring to act as a UV tag. A few different protecting groups at the β-position were to be tested as Evans has shown this can have a profound effect on the selectivity of Mukaiyama aldol reactions.[49] Initially, β-PMB ether **78** was employed since Evans' research determined this protecting group resulted in favorable selectivity. However, when attempting to carry out these experiments, it was observed that the Mukaiayama conditions were providing four aldol adducts, indicating an unknown side reaction taking place. To determine which peaks were a result of the desired reaction, the aldol was carried out in tandem with the Mukaiyama conditions and racemic conditions (Scheme 22). After overlapping the resulting spectra from each set of reaction conditions, it was found that the Felkin and anti-Felkin aldol adducts were formed in approximately an 8:1 ratio, respectively. Carrying out the aldol reaction with this protecting group in the β-position resulted in a great improvement compared to the triethylsilyl ether used previously.



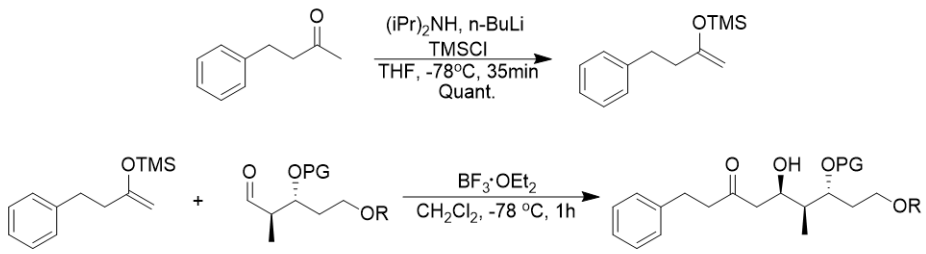
Scheme 22. Stereoselective and Racemic Syntheses of 79

Even though this protecting group displayed a noticeable improvement in selectivity from the tritheylsilyl ether, this substrate needed to be tested again with this simpler nucleophile. When carrying out the Mukaiayama aldol with aldehyde **60** and benzylacetone, a key separation could be achieved that was not possible when using aldehyde **78**. It appeared that each of the products isolated contained two diastereomers, accounting for the four adducts observed in earlier experiments. The major product was a mixture of the Felkin and anti-Felkin aldol adducts, present at about a 2.5:1 ratio, respectively. The impurity was analyzed by COSY NMR to determine the connectivity within the molecule. After COSY analysis, it was determined that the byproduct was a diastereomeric mixture of the alternate adduct **81**, revealing a regioisomeric issue with the silyl enol ether synthesis.



Scheme 23. Studies Toward the Optimization of the Aldol Process

Luckily, this issue regarding regioisomers can be resolved through some simple optimization. After screening a variety of conditions, it was determined that a method developed by Ireland and co-workers[61] provided the correct regioisomer of silyl enol ether **77** with excellent selectivity, forming the terminal alkene in greater than 20:1 selectivity. It should be noted that the trimethylsilyl chloride needs to be distilled in order to observe conversion to the silyl enol ether. With the previous conditions, quenching any HCl present with triethylamine was sufficient to gain reactivity, but that was not successful using the conditions formulated by Ireland.



Entry	PG	Yield	d.r.
1	TES	57%	2.6:1
2	PMB	59%	7.7:1
3	PMP Acetal	51%	2.2:1

Scheme 24. Protecting Group Screen for Felkin Selectivity

The exact conditions for the silyl enol ether synthesis can be seen above in Scheme 24, along with the protecting group screen for the ether in the β-position. The triethylsilyl ether was tested again to see if these improved conditions for the silyl enol ether would result in a higher yield or selectivity. Essentially the same selectivity was seen for this substrate, favoring the Felkin aldol adduct at a 2.6:1 ratio. Next, the PMB ether was tested again. Similarly, a reproducible selectivity of 7.7:1 was observed. Lastly, an acetal was tested. The corresponding PMP acetal was synthesized through cyclization of a variation of crotylation adduct **58**, where the primary alcohol is capped as a PMB ether rather than the benzyl ether. Exposure of this crotylation adduct to DDQ and 4 Å molecular sieves promotes the cyclization to the acetal which can then be oxidized

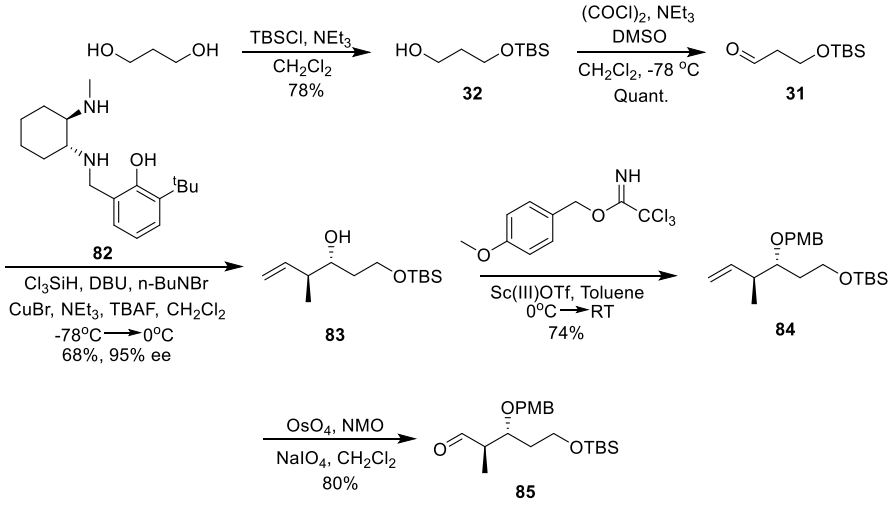
to the intended aldehyde. This protecting group, however, resulted in the least favorable selectivity forming the Felkin diastereomer in a 2.2:1 ratio. These results showcase two important results. The protecting group present at the β-position of the aldehyde does not have a profound effect on the yield of this process and, in alignment with Evans' results, a β-PMB ether provides a diastereomeric ratio that greatly favors the Felkin aldol adduct.

1.6 Progress Towards Optimized Conditions for Spiroketal Formation

Now that the conditions of the aldol were investigated and optimized, it came time to prepare a model spiroketal utilizing this method with material of higher stereochemical integrity. Similar to the lack of consistency with the enantioselectivity of the Keck allylation,[41] the Roush crotylation[56] was found to produce the crotylation adduct with inconsistent enantioselectivities as well. When taking into account the lack of enantioselectivity for both of these processes, as well as the poor regioselectivity of the initial silyl enol ether synthesis and the low diastereoselectivity of the Mukaiyama aldol with a β-triethylsilyl ether, it is reasonable that the spirocyclization seen in Scheme 21 resulted in a complex mixture. Forming these components of the aldol with higher enantiopurity would be crucial as well as building out the fragments in order to closely mimic the structure seen in neaumycin B.

Starting with the electrophile from the aldol reaction, no more effort was focused on building out the molecule to make it larger, but a crotylation process with higher enantioselectivity was pursued instead. A process developed by the Leighton group was employed, as it boasted crotylations and allylations with good yields and excellent enantioselectivities. The synthesis of this fragment, again, began with the mono-protection of 1,3-propanediol to deliver silyl ether **33**.

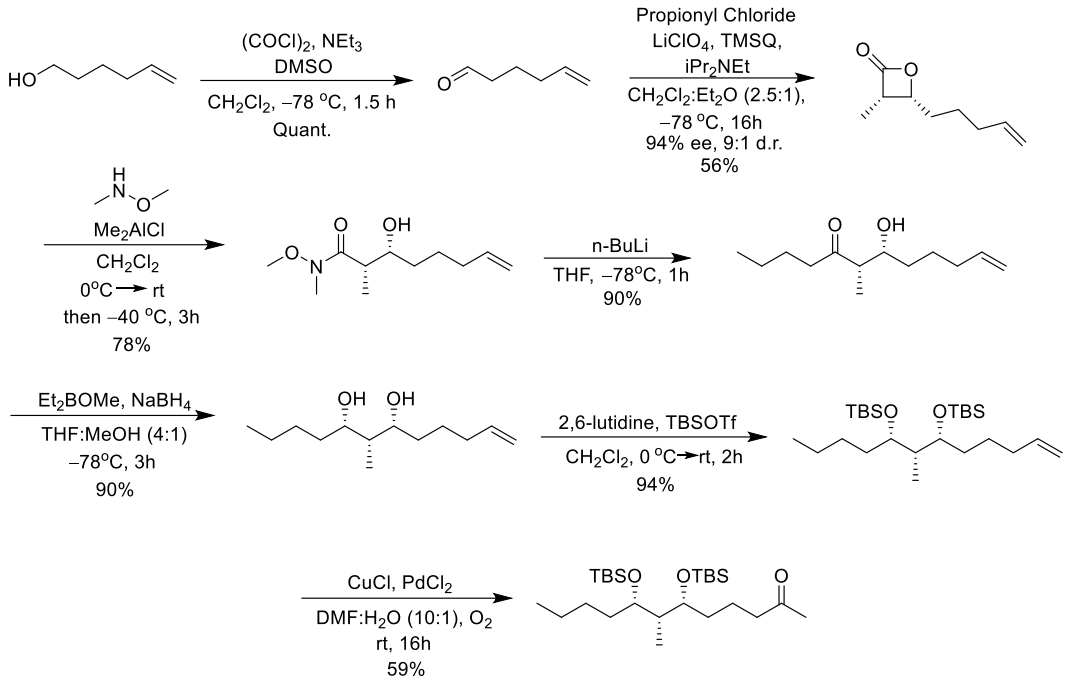
The silyl ether was employed this time to allow for easier deprotection downstream, in comparison to the benzyl ether that was used earlier, which will ultimately aid in conformational analyses of the resulting spiroketal. A Swern oxidation[40] on this compound cleanly afforded aldehyde **31** which was poised to undergo the intended crotylation. This crotylation chemistry developed by Leighton and co-workers makes use of ligand **82** to promote the enantioselectivity of this process. It should be noted that this process requires quenching with TBAF, which led to minor deprotection of the primary silyl ether. This diol, however, could be isolated and selectively re-protected at the primary position. This method proved successful, delivering crotylation adduct **83** in 68% yield and 95% ee, as was determined by Mosher ester analysis. The enantiopure material could then be protected as the PMB ether **84** with the corresponding trichloroacetimidate and scandium (III) triflate in toluene. Lastly, a Lemieux-Johnson oxidation[57] was employed to convert the terminal alkene to the desired aldehyde **85**.



Scheme 25. Synthesis of Enantioenriched Aldehyde 85

With the aldehyde component of the aldol successfully prepared in high enantiomeric excess, it came time to synthesize the methyl ketone implementing a route developed by Anna Healy. This synthetic plan would be able to deliver a ketone of greater stereochemical integrity

and higher complexity. The synthesis of this methyl ketone began with 5-hexen-1-ol, which was oxidized to the corresponding aldehyde **86** in quantitative yields using a Swern oxidation.[40] This aldehyde could then be converted into the enantioenriched β-lactone **87** implementing chemistry developed by Nelson and co-workers.[62] Through the use of an asymmetric cinchona alkaloid, trimethylsilyl quinidine, aldehydes can be conveniently converted to their corresponding *syn*-β-lactones by going through a [2+2] cycloaddition with a ketene intermediate. This process is carried out with high enantiocontrol, setting the stereocenters with excellent selectivity. Subsequent ring opening to the Weinreb amide **88** was carried out using N,O-dimethylhydroxylamine and dimethyl aluminum chloride in 78% yield. Mono-addition of *n*-butyl lithium into the Weinreb amide then gave β-hydroxy ketone **89**. This compound could subsequently be selectively converted to *syn*-diol **90** through the use of a Narasaka reduction.[63] Again, no evidence of a minor diastereomer could be detected. Protection of both free alcohols was then carried out followed by a Wacker oxidation[64] on the terminal alkene to convert it into the desired methyl ketone **92**. This methyl ketone offers an additional 2 stereocenters, which are well defined, in comparison to **70**. Ideally, this additional complexity will aid in the conformational analysis of the resulting spirocycle.



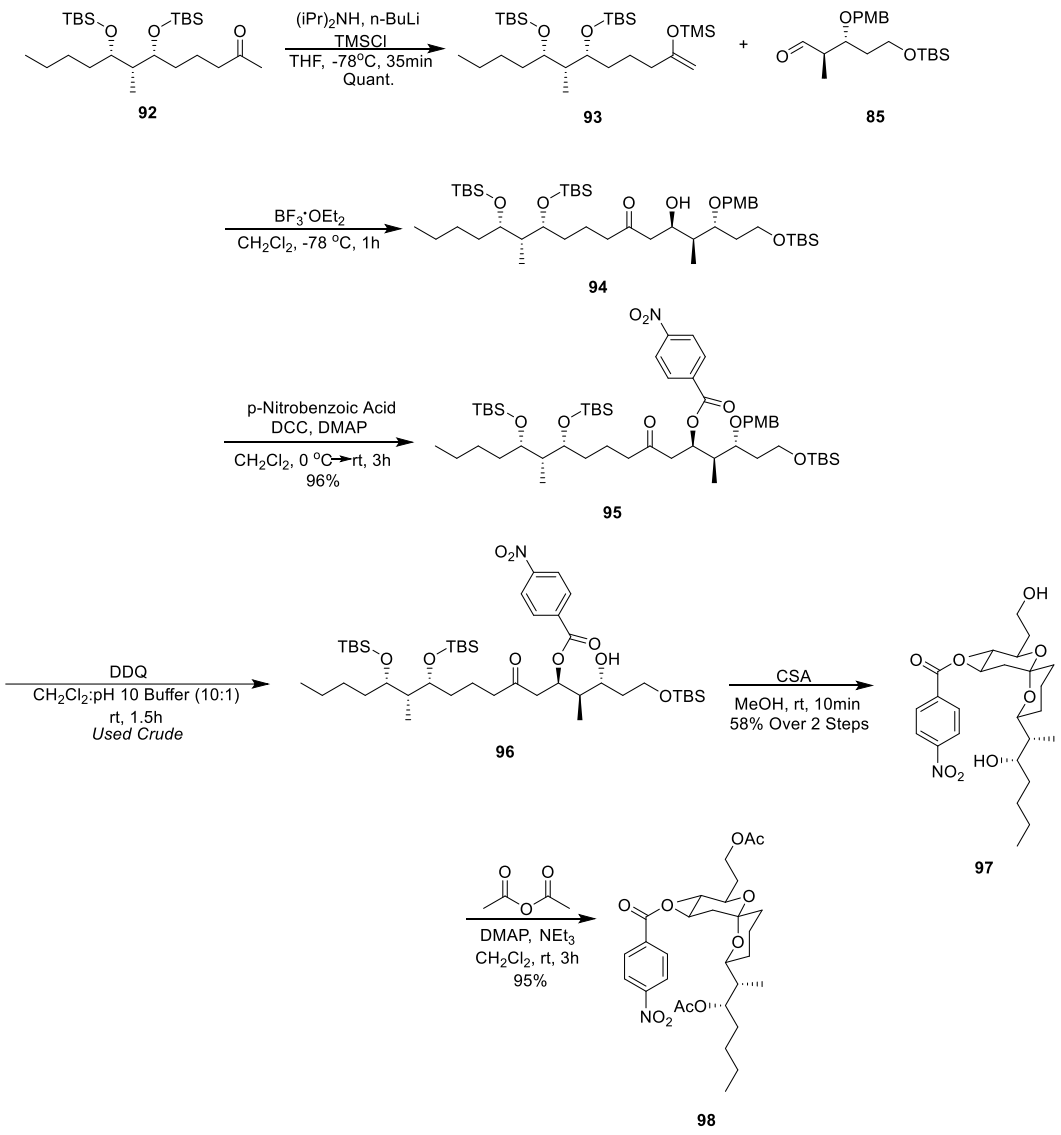
Scheme 26. Synthesis of Enantioenriched Methyl Ketone 92

With fully optimized conditions for the Mukaiyama aldol along with stereochemically enriched fragments, the process to afford the model spiroketal could be carried out. Starting with methyl ketone **92**, the optimized conditions to form the corresponding trimethyl silyl enol ether were carried out, affording **93** which could then be used in the aldol reaction. This fragment and aldehyde **85** were brought together to form the Felkin aldol adduct **94** in 51% yield and a similar selectivity to the one seen previously, approximately 8:1. The resulting free alcohol was capped with nitrobenzoic acid to form acetate **95**. Protecting the alcohol is necessary to resist acetal formation in the subsequent PMB deprotection using DDQ as an oxidant in an aqueous environment. This deprotection leads to the production of alcohol **96** which is used crude in the following step where CSA is employed to achieve silyl deprotection followed by spiroketalization, successfully synthesizing spiroketal **97**. It was observed that the spiroketal presented itself as a mixture of two isomers which were extremely difficult to separate using flash chromatography. Preparative TLC utilizing 20% hexanes in tert-butyl methyl ether allowed for adequate isolation

of each of the two isomers. Since it was hypothesized at the time that our desired spiroketal would be the most thermodynamically preferable configuration, the major compound from the mixture was acylated to form both the primary and secondary acetates observed on spiroketal **98**.

COSY and NOESY experiments were then carried out to confirm the connectivity and three-dimensional configuration of **98**. One strongly indicative sign that the correct configuration was formed was the signal corresponding to the equatorial proton on the methylene adjacent to the benzoate. This proton appears as a strong doublet of doublets and appears fairly downfield, around 2.8 ppm. Furthermore, the expected NOE signals, which were observed in **76**, were seen in this substrate as well. Additionally, the NOE signal that was missing from **76** was now present. This would correspond to proton adjacent to the benzoate being in proximity to the axial proton on the singly substituted ring. This result further supports that the correct configuration was formed and that the additional complexity of this system more closely resembles that of neaumycin B. Furthermore, in the competing doubly anomeric spiroketal this signal would not be expected.

The majority of the protons in **98** were identified and the resulting NOE signals were compared with the analogous signals from neaumycin B, provided by Fenical.[4] Every signal that could be relayed from neaumycin B to this system was accounted for except for one, which would account for a weak NOE signal between the proton of the secondary acetate and the axial proton adjacent the ethyl acetyl group in the highly substituted ring. When drawn in the three-dimensional configuration it is reasonable to believe that these two protons are not in extremely close proximity to each other. Additionally, it was shown that added complexity unveiled signals that were not present in simpler systems and may be necessary to uncover this NOE signal.



Scheme 27. Synthesis of Model Spiroketal 98

Now that the conditions for the aldol were optimized, and the material used in this reaction has proven to be of sufficient stereochemical purity to deliver a valuable model system, the process to form the spiroketal needed to be investigated. First, the identity of the minor byproduct from the cyclization needed to be determined. In a similar fashion to the major product, the minor compound was isolated using preparatory TLC and acylated to cap its primary and secondary alcohols. Initially, it was believed that the minor compound would be doubly anomeric spiroketal **99**, a result of acid-catalyzed isomerization to a competing configuration. However, spectroscopic

evidence supports an alternate spiroketal **100**. This compound, epimeric at the spirocenter, would arise from ring closure through addition at the opposite face of the oxocarbenium ion formed in the spiroketalization process.

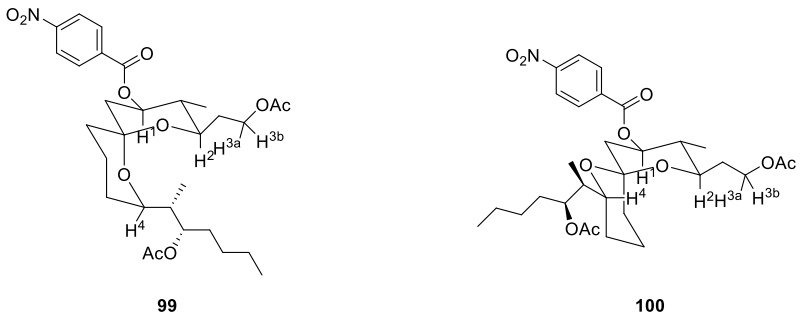


Figure 13. Potential Byproducts of the Spiroketalization Process

Many different factors need to be taken into account to properly differentiate the two spiroketals shown in Figure 13. Since the highly substituted ring is in the same configuration, interactions involving the singly substituted ring will offer the most valuable information. First, one of the key distinctions between **99** and **100** is the orientation of the substitution on the southern ring. As a result, H^4 resides equatorially in **99** while it is in the axial position in **100**. One of the coupling constants extracted from this proton was 11.8 Hz, indicating an axial-axial interaction, supporting the structure seen in **100**.

Additionally, the chemical shifts of certain protons indicate **100** was formed as opposed to **99**. It has been shown that protons maintaining a 1,3-diaxial relationship with an anomeric oxygen atom experience a deshielding effect, resulting in a downfield shift.[65] The minor compound of the cyclization experiences an upfield shift of the benzoate proton, when compared to **98**, indicating that this effect may not be present. Upon inspection of **99** and **100** (Figure 14), it is clear that this effect would be present in the doubly anomeric isomer, however, it is not present in the epimeric compound. This 1,3-interaction can be extended to protons H^2 and H^4 as well. H^2 experiences a 1,3-diaxial interaction with an anomeric oxygen in **98** and **99** but not in **100**. This is marked by a

large upfield shift of 1.17 ppm in the minor compound. Similarly, H^4 does not experience this interaction in **98**, but it is present in **100**. Following this trend, a notable downfield shift of 0.49 ppm is observed in the minor compound.

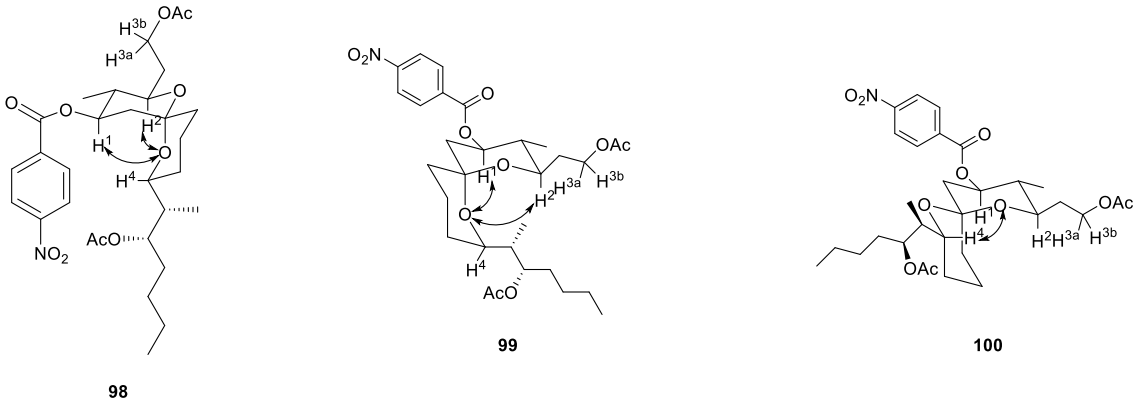
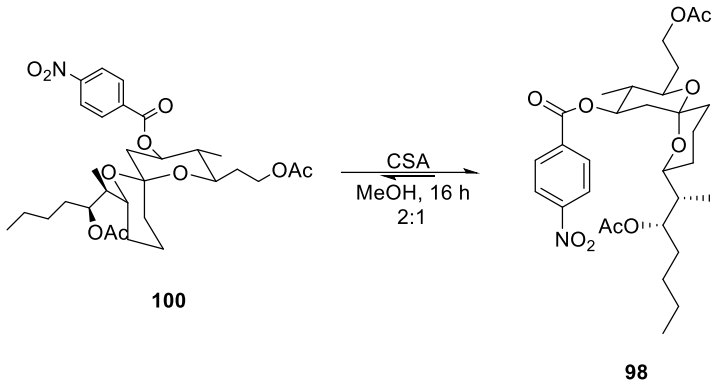


Figure 14. Protons having 1,3-Diaxial Relationship with Anomeric Oxygen Atoms

All of the aforementioned spectroscopic details strongly support **100** as the observed byproduct in the spiroketalization process. However, the strongest piece of evidence is a clear NOE signal seen between H^3 and H^4. Many of the differing NOE signals would lie within the alkyl region, making them difficult to see. This interaction strongly indicates **100** was formed since it should not be observed in **99**. H^4 is in the equatorial position and pointed away from the highly substituted ring in **99**, out of proximity of H^3. The presence of this signal along with the coupling constant of H^4 and the chemical shift trends serve as strong supporting evidence for the conclusion that the minor cyclization product is the epimer **100**.

Another factor that had to be tested regarding this cyclization stems from this epimerization process. It needed to be determined if this 2:1 selectivity arose solely during the spiroketalization process or if it was a result of equilibration. To test this, **100** was exposed to the acidic conditions used for cyclization and was allowed to equilibrate overnight to detect the presence of the major epimer. Crude ^1H NMR analysis showed that the major epimer was produced in an excess of

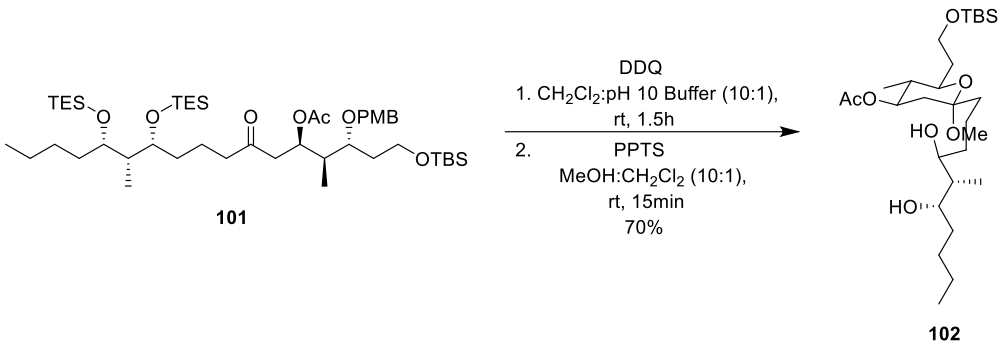
approximately 2:1. These results indicate that the undesired product can be further epimerized in order to obtain the desired epimer.



100 98

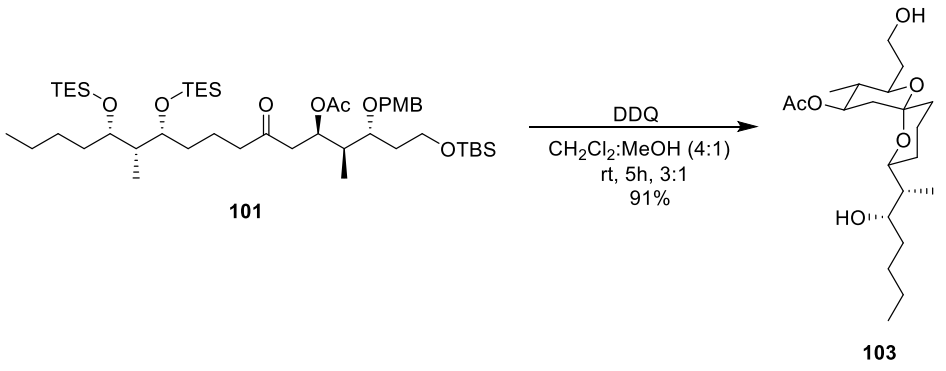
Scheme 28. Regeneration of 98 with Acid-Catalyzed Equilibration

Next, the equilibrative conditions were to be tested with a slightly milder acid commonly used in spirocyclization reactions, pyridinium *p*-toluenesulfonate (PPTS). This acid is not strong enough to deprotect the secondary TBS ethers present in **93** so some protecting group manipulation needed to be carried out to afford the corresponding TES ethers. Furthermore, the free alcohol arising from the aldol reaction was capped as an acetate on this substrate rather than the benzoate. This aldol adduct **101** was first oxidized in a similar fashion to remove the PMB ether then exposed to PPTS in a mixture of methanol and dichloromethane. It appeared that a single product was obtained using this method, but after careful examination it was determined that these conditions were leading to the methanol addition product **102**. With this material in hand, it was then exposed to the same conditions in the absence of methanol to see if PPTS could carry out the intended cyclization. Additionally, if the cyclization proved successful, I wanted to see if a more favorable mixture of epimers was observed. Cyclization was observed, however only a mild improvement in selectivity was observed with the desired epimer being formed in a 2.3:1 ratio.



Scheme 29. Formation of Methanol Addition Product 102

Finally, it was hypothesized that carrying out the PMB deprotection protocol in the presence of methanol may afford the deprotection of this slightly more labile TES ether. The resulting DDQ-derived hydroquinone in the presence of methanol may be acidic enough and if so, it could potentially trigger the cyclization as well and lead to a one-pot process. When aldol adduct **101** was exposed to these conditions this hypothesis was strongly supported as the adduct was carried all the way through to cyclization. The acidity of the hydroquinone in methanol proved to be sufficient for this transformation, even going as far as to deprotect the primary TBS ether. Furthermore, the ratio of epimers was found to be similar to the results seen before with a 3:1 mixture observed.



Scheme 30. Current Optimal Conditions for the Synthesis of the Spirocyclic Moeity in Neaumycin B

1.7 Conclusions

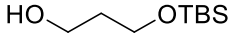
Various conditions were carried out in the effort towards the synthesis of multiple model systems of the spiroketal unit found in neaumycin B. Additionally, in depth two-dimensional NMR analysis has been carried out to determine that the methods implemented in this strategy form the configuration observed within the natural product. Ultimately, a strategy involving a Mukaiyama aldol process, which was optimized to form the Felkin adduct in an 8:1 ratio, will be carried out to bring together the fragments of the spirocycle. The following step can then be carried out in a one pot process to deprotect the PMB and silyl ethers while affording subsequent cyclization to the resulting spiroketal in a favorable ratio. Furthermore, the byproduct of this process has been identified and can successfully be re-exposed to equilibrative conditions to return the desired spirocycle.

Appendix A

Supporting Information: Efforts Towards the Synthesis and Structural Elucidation of the Spirocyclic Moiety of Neaumycin B

(^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were taken on a Bruker Avance 300 spectrometer at 300 MHz and 75 MHz respectively, a Bruker Avance 400 spectrometer at 400 MHz and 100 MHz, a Bruker Avance 500 spectrometer at 500 MHz and 125 MHz, or a Bruker Avance 600 spectrometer at 600 MHz and 150 MHz as specified. The chemical shifts are reported in parts per million (ppm) on the delta (δ) scale. The solvent peak was used as a reference value, for ^{1}H NMR: $CDCl_3$ = 7.26 ppm or C_6D_6 = 7.16 ppm, for ^{13}C NMR: $CDCl_3$ = 77.16 ppm or C_6D_6 = 128.06 ppm. Data are reported as follows: m = multiplet, s = singlet; d = doublet; t = triplet; dd = doublet of doublets; dt = doublet of triplets; ddq = doublet of doublet of quartets; ddd = doublet of doublet of doublets etc. Methylene chloride was distilled under N_2 from CaH_2. Diethyl Ether and tetrahydrofuran were distilled over sodium/benzophenone under N_2. Analytical TLC was performed on E. Merck pre-coated (25 mm) silica gel 60 F254 plates. Visualization was done under UV (254 nm) or by staining by staining (95mL ethanol, 3mL conc. H_2SO_4, 2 mL acetic acid, 5 mL anisaldehyde). Flash chromatography was done using SiliCycle SiliaFlash P60 40-63μm 60 Å silica gel. Reagent grade ethyl acetate, diethyl ether, dichloromethane, methanol, and hexanes (commercial mixture) were purchased from Fisher Scientific and were used as-is for chromatography. All reactions were performed in flame-dried glassware under a positive pressure of either Ar or N_2 with magnetic stirring unless noted otherwise. All reagents were purified according to “Purification of Laboratory Chemicals Sixth edition”.

Experimental Protocols



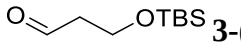
3-((*tert*-butyldimethylsilyl)oxy)propan-1-ol (33)

1,3-propanediol (1.05 mL, 6.57 mmol) was added to a flame dried round bottom flask in CH_2Cl_2 (9.8 mL, 0.67 M). Triethylamine (0.55 mL, 3.94 mmol) was then added and the solution was cooled to 0° C. *Tert*-butyldimethylsilyl chloride (495.3 mg, 3.29 mmol) was then delivered in one portion. The reaction mixture was warmed to room temperature and was allowed to stir for 17 hours. Upon completion, the reaction was quenched with saturated NH_4Cl. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3x). The organic layer was washed with brine, dried with $MgSO_4$, and filtered then solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography (5% EtOAc in hexanes to 15% EtOAc in hexanes), and **33** was isolated as a clear oil (488 mg, 78%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.83 (t, *J*=5.6 Hz, 2H), 3.80 (t, *J*= 5.5 Hz, 2H), 2.61 (bs, 1H), 1.78 (p, *J*= 5.6 Hz, 2H), 0.87 (s, 9H), 0,74 (s, 6H).

^{13}C NMR (300 MHz, $CDCl_3$) δ 62.9, 62.4, 34.2, 25.9, 18.2, -5.5.

HRMS (ESI) *m/z* calcd. for $C_9H_{23}O_2Si$ $[M+H]^+$ 190.1462, found 190.1463



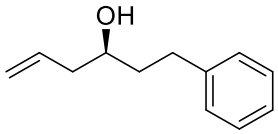
3-((*tert*-butyldimethylsilyl)oxy)propanal (30)

A solution of DMSO (2.69 mL, 37.82 mmol) in CH_2Cl_2 (40 mL, 0.2 M) was cooled to -78° C in a flame dried round bottom flask. Oxalyl chloride (1.49 mL, 17.34 mmol) was then delivered dropwise and the solution was allowed to stir at -78° C for 20 minutes. **33** (1.5 g, 7.88 mmol) was then added to the solution and the reaction mixture was then allowed to stir at -78° C for 1.5 hours. Triethylamine (8.01 ml, 57.52 mmol) was then delivered to the reaction mixture dropwise at -78° C, and the mixture was allowed to slowly warm to room temperature. The reaction was then quenched with water, the organic layer was separated, and then the aqueous layer was extracted

with CH_2Cl_2 (3x). The organic layer was then washed with saturated $NaHCO_3$, 1 M HCl, then brine and dried with $MgSO_4$ and filtered. The solvent was then removed under reduced pressure. **31** was obtained as a yellow oil (1.48 g, quant.) and used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.80 (t, J= 2.1 Hz, 1H), 3.99 (t, *J*= 6.0 Hz, 2H), 2.60 (td, *J*= 6.0, 2.1, 2H), 0.88 (s, 9H), 0.64 (s, 6H).

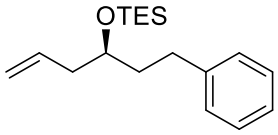
^{13}C NMR (300 MHz, $CDCl_3$) δ 202.1, 57.4, 46.6, 25.8, 18.2, -5.4.



(S)-1-phenylhex-5-en-3-ol (34)

4 Å molecular sieves (3 g, 1 mass eq.) were delivered to a flame dried two-neck round bottom flask fitted with a reflux condenser and were suspended in CH_2Cl_2 (45 mL, 0.5 M). (R)-BINOL (1.28 g, 4.47 mmol), trifluoroacetic acid (5 µL, 0.07 mmol), and $Ti(OiPr)_4$ (0.66 mL, 2.24 mmol) were added to the solution which was then heated to reflux for 1 hour. The solution was allowed to cool to room temperature before adding hydrocinnamaldehyde (2.95 mL, 22.36 mmol) in CH_2Cl_2 (45 mL). The reaction mixture was stirred for 5 minutes, then allowed to cool to -78° C before adding allyltributyl stannane (10.4 mL, 33.54 mmol). The reaction mixture was stirred for 15 minutes at -78° C. The reaction flask was then transferred to a fridge for 72 hours. The reaction was then quenched with saturated $NaHCO_3$ and allowed to stir at room temperature for 2 hours. The resulting biphasic mixture was filtered through Celite® and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3x). The organic layers were combined, dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography (100% hexanes to 15% EtOAc in hexanes), and **34** was isolated as a pale yellow oil (3.59 g, 91%).

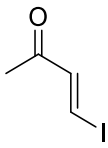
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.30 (m, 2H), 7.28-7.20 (m, 3H), 5.86 (m, 1H), 5.17 (m, 2H), 3.71 (m, 1H), 2.85 (ddd, *J*= 13.9, 8.6, 6.6 Hz, 1H), 2.73 (ddd, *J*= 13.8, 8.7, 7.4 Hz, 1H), 2.35 (m, 1H), 2.23 (m, 1H), 1.93 (bs, 1H), 1.86-1.80 (m, 2H).



(S)-triethyl((1-phenylhex-5-en-3-yl)oxy)silane (35)

To a flame dried round bottom flask was added **34** (3.80 g, 21.56 mmol) in CH_2Cl_2 (56 mL, 0.4 M). To this solution, imidazole (4.70 g, 68.99 mmol) was added in one portion and the resulting mixture was cooled to 0° C. TESCl (5.8 mL, 34.56 mmol) was then added to the reaction mixture, which was then allowed to stir at 0° C for 2 hours and subsequently allowed to warm to room temperature and stir for 15 hours. The reaction was quenched with the addition of methanol. Water was then added, and the organic and aqueous layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography (1% EtOAc in hexanes to 5% EtOAc in hexanes), and **35** was isolated as a pale yellow oil (6.07 g, 97%).

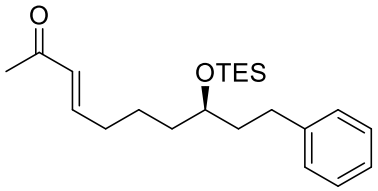
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.26 (m, 2H), 7.20-7.16 (m, 3H), 5.83 (ddt, *J*= 17.2, 10.1, 7.1 Hz, 1H), 5.05 (m, 2H), 3.77 (p, *J*= 5.8 Hz, 1H), 2.73 (ddd, *J*= 13.6, 11.0, 5.7 Hz, 1H), 2.60 (ddd, *J*= 13.6, 11.2, 5.7 Hz 1H), 2.28 (m, 2H), 1.83-1.69 (m, 2H), 0.98 (t, *J*= 7.8 Hz, 9H), 0.62 (q, *J*= 7.9 Hz, 6H).



(E)-4-iodobut-3-en-2-one (36)

To a flame dried round bottom flask was added acetic acid (1.47 mL, 1M) and lithium iodide (235.9 mg, 1.76 mmol). To this solution was added 3-butyn-2-one (0.12 mL, 1.47 mmol) and the resulting mixture was allowed to stir at room temperature for 18 hours. Water was then added to the reaction mixture, which was subsequently extracted with Et_2O (3x). The organic layers were combined, dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure. **36** was obtained as a yellow solid (1.19 g, 99%) and used without further purification.

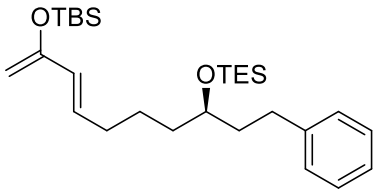
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J*= 15.1 Hz, 1H), 7.07 (d, *J*= 15.1 Hz, 1H), 2.17 (s, 3H).



(R,E)-10-phenyl-8-((triethylsilyl)oxy)dec-3-en-2-one (37)

To a solution of 9-BBN dimer (983.0 mg, 4.03 mmol) in THF (5.9 mL) was added **35** (1.30 g, 4.475 mmol) in THF (5.9 mL, 0.38 mmol) dropwise at 0° C. The mixture was warmed to room temperature and allow to stir for 4 hours. Water (1 mL) was then added followed by an aqueous solution of $K_3PO_4 \cdot H_2O$ (2.6 mL, 2.6 M). **36** (921.0 mg, 4.70 mmol) was then delivered to the solution followed by $[Pd(dppf)Cl_2)] \cdot CH_2Cl_2$ (36.6 mg, 0.05 mmol), and the reaction flask was wrapped in aluminum foil and allowed to stir for 2 hours. The reaction mixture was then poured in water, the organic layer was separated, and the aqueous layer was extracted with Et_2O (3x). The organic layers were combined, dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography (3% EtOAc in hexanes to 10% EtOAc in hexanes), and **37** was isolated as a clear oil (1.40 g, 87%).

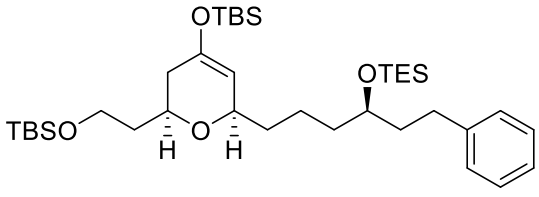
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.30 (m, 2H), 7.28-7.20 (m, 3H), 6.87 (dt, *J*= 15.9, 6.8 Hz, 1H), 6.15 (dt, *J*= 15.9, 1.4 Hz, 1H), 3.81 (m, 1H), 2.82-2.61 (m, 2H), 2.48 (m, 2H), 2.31 (s, 3H), 1.94, (m, 2H), 1.84 (m, 2H), 1.64 (m, 2H), 1.05 (t, *J*= 7.9 Hz, 9H), 0.68 (q, *J*= 7.9 Hz, 6H).



(R,E)-13,13-diethyl-2,2,3,3-tetramethyl-5-methylene-11-phenethyl-4,12-dioxa-3,13-disilapentadec-6-ene (32)

A solution of **37** (150 mg, 0.42 mmol) in CH_2Cl_2 (1.4 mL, 0.3 M) was prepared in a flame dried round bottom flask and was cooled to -78° C. Triethylamine (0.09 mL, 0.62 mmol) was then added to the solution followed by dropwise addition of *tert*-butyldimethylsilyl triflate (0.12 mL, 0.50 mmol). The reaction mixture was stirred at -78° C for 1 hour then quenched with saturated $NaHCO_3$. The biphasic mixture was allowed to warm to room temperature and diluted with EtOAc. The organic phase was separated, and the aqueous phase was extracted with EtOAc (3x). The organic layers were combined, dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude mixture was then purified on basic alumina (1% EtOAc in hexanes), and **31** was isolated as a pale yellow oil (160 mg, 81%).

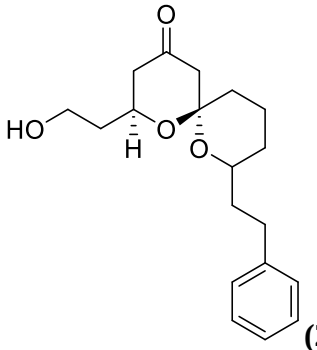
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.28 (m, 2H), 7.28-7.24 (m, 2H), 7.17 (m, 1H), 6.36 (dt, *J*= 14.8, 7.2 Hz 1H), 6.08 (dt, *J*= 15.3, 1.2 Hz, 1H), 4.44 (s, 1H), 4.39 (s, 1H), 3.78 (p, *J*= 5.4 Hz, 1H), 2.81 (ddd, *J*= 14.0, 9.8, 7.2 Hz, 1H), 2.73 (ddd, *J*= 13.7, 9.3, 7.2 Hz, 1H), 2.17 (m, 2H), 1.87 (m, 2H), 1.66-1.52 (m, 4H), 1.14 (m, 18 H), 0.73 (q, *J*= 7.9 Hz, 6H), 0.29 (s, 6H).



***tert*-butyl(2-((2*S*,6*R*)-4-((*tert*-butyldimethylsilyl) oxy)-6-((R)-6-phenyl-4-((triethylsilyl)oxy)hexyl)-3,6-dihydro-2*H*-pyran-2-yl)ethoxy) dimethylsilane (40)**

31 (40 mg, 0.21 mmol) and **32** (50 mg, 0.11 mmol) were transferred to a flame dried 2-dram vial using minimal THF, which was then placed under vacuum for 2 hours to remove any residual solvent. **39** (7.2 mg, 0.01 mmol) was then delivered to the vial along with 4 Å molecular sieves (1 mg) and a stir bar and the vial was placed back under vacuum for 30 minutes and wrapped in aluminum foil. The vial was then backfilled with argon (3x), wrapped in parafilm, and allowed to stir at room temperature for 18 hours. The neat mixture was filtered through Celite® with CH_2Cl_2 and the solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography (1% EtOAc in hexanes to 5% EtOAc in hexanes), and **40** was isolated as a clear oil (33 mg, 48%).

^{1}H NMR (500 MHz, C_6D_6) δ 7.22-7.17 (m, 4H), 7.08 (m, 1H), 4.90 (dt, *J*= 5.3, 1.6 Hz, 1H), 3.88-3.82 (m, 2H), 3.77-3.70 (m, 3H), 2.74 (m, 1H), 2.65 (m, 1H), 2.16 (m, 1H), 1.94 (dt, *J*= 16.4 Hz, 2.8 Hz, 1H), 1.90 (q, *J*= 5.8 Hz, 1H), 1.85-1.78 (m, 3H), 1.76-1.69 (m, 2H), 1.65-1.56 (m, 4H), 1.05 (td, *J*= 8.0, 2.2 Hz, 9H), 1.00 (s, 18 H), 0.65 (qd, *J*= 7.9, 2.4 Hz, 6H), 0.19 (s, 6H), 0.17 (s, 6H).



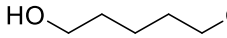
(2*S*,6*R*)-2-(2-hydroxyethyl)-8-phenethyl-1,7-dioxaspiro[5.5]undecane-4-one (42)

In a flame dried 2-dram vial **40** (20 mg, 0.03 mmol) was diluted in CH_2Cl_2 (0.30 mL, 0.1 M). DDQ (8.2 mg, 0.036 mmol) was then added in on portion and the reaction mixture was stirred for 20 minutes. *p*-TsOH·H_2O (11.4 mg, 0.06 mmol) was then delivered to the reaction flask and the

mixture was allowed to stir for 2 hours. The crude mixture was quenched with triethylamine then filtered through a silica plug using 25% EtOAc in hexanes and the solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography (15% EtOAc in hexanes to 30% EtOAc in hexanes), and **42** was isolated as a clear oil (7 mg, 73%).

^{1}H NMR (500 MHz, C_6D_6) δ 7.14-7.11 (m, 2H), 7.07-7.02 (m, 3H), 3.84 (ddt, *J*= 11.6, 9.4, 3.0 Hz, 1H), 3.54-3.44 (m, 2H), 3.39 (ddd, *J*= 10.7, 7.1, 4.5 Hz, 1H), 2.73 (ddd, *J*= 13.8, 9.9, 5.5 Hz, 1H), 2.56 (ddd, *J*= 13.9, 9.6, 6.6 Hz, 1H), 2.41 (dd, *J*= 14.3, 1.9 Hz, 1H), 2.13 (ddd, *J*= 14.2, 2.5, 2.1 Hz, 1H), 1.81 (dd, *J*= 14.1, 11.7 Hz, 1H), 1.74-1.65 (m, 3H), 1.61-1.48 (m, 4H), 1.47-1.42 (m, 3H), 1.05 (td, *J*= 13.5, 4.6 Hz, 1H).

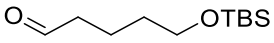
^{13}C NMR (500 MHz, C_6D_6) δ 203.1, 142.3, 128.8, 128.7, 126.1, 99.5, 69.5, 68.0, 60.2, 51.9, 47.0, 38.5, 37.8, 34.6, 32.0, 19.3, 1.4.



5-((*tert*-butyldimethylsilyl)oxy)pentan-1-ol (47)

To a flame dried round bottom flask was added NaH (845.0 mg, 21.12 mmol) which was then suspended in THF (96 mL, 0.2 M). The resulting solution was cooled to 0° C then 1,5-pentanediol (2.02 mL, 19.20 mmol) was delivered dropwise. This solution was allowed to stir at room temperature for 45 minutes, then cooled back to 0° C and TBSCl (2.89 g, 19.20 mmol) was added in 3 portions. The resulting solution was allowed to stir for 18 hours. The reaction was then quenched with 10% aqueous solution of K_2CO_3. The aqueous layer was then extracted with Et_2O (3x). The organic layers were combined, dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography (5% EtOAc in hexanes to 15% EtOAc in hexanes), and **47** was isolated as a clear oil (2.85 g, 68%).

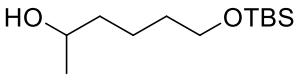
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.65 (t, *J*= 6.5 Hz, 2H), 3.62 (t, *J*= 6.4 2H), 1.63-1.50 (m, 4H), 1.46-1.37 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H).



5-((*tert*-butyldimethylsilyl)oxy)pentanal (48)

A solution of DMSO (2.34 mL, 32.97 mmol) in CH_2Cl_2 (34 mL, 0.2 M) was cooled to -78° C in a flame dried round bottom flask. Oxalyl chloride (1.30 mL, 15.11 mmol) was then delivered dropwise and the solution was allowed to stir at -78° C for 20 minutes. **47** (1.5 g, 6.87 mmol) was then added to the solution and the reaction mixture was then allowed to stir at -78° C for 1.5 hours. Triethylamine (6.99 ml, 50.14 mmol) was then delivered to the reaction mixture dropwise at -78° C, and the mixture was allowed to slowly warm to room temperature. The reaction was then quenched with water, the organic layer was separated, and then the aqueous layer was extracted with CH_2Cl_2 (3x). The organic layer was then washed with saturated $NaHCO_3$, 1 M HCl, then brine and dried with $MgSO_4$ and filtered. The solvent was then removed under reduced pressure. **48** was obtained as a yellow oil (1.48 g, quant.) and used without further purification.

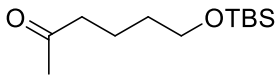
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (t, *J*= 1.8 Hz, 1H), 3.62 (t, *J*= 6.1 Hz, 2H), 2.46 (td, *J*= 7.3, 1.8 Hz, 2H), 1.70 (p, *J*= 7.4 Hz, 2H), 1.54 (p, *J*= 7.0 Hz, 2H), 0.89 (s, 9H), 0.43 (s, 6H).



6-((*tert*-butyldimethylsilyl)oxy)hexan-2-ol (49)

A solution of **48** (1.48 g, 6.87 mmol) in THF (27 mL, 0.25 M) was added to a flame dried round bottom flask then cooled to -78° C. MeMgBr (3 M in Et_2O, 4.58 mL) was then delivered to the solution dropwise and the reaction mixture was allowed to stir at -78° C for 1.5 hours. The mixture was then warmed up to 0° C and quenched with saturated NH_4Cl. The aqueous layer was then extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography after quenching the silica gel with a 1% NEt_3 in hexanes solution (1% EtOAc in hexanes to 5% EtOAc in hexanes), and **49** was isolated as a pale yellow oil (1.34 g, 84%).

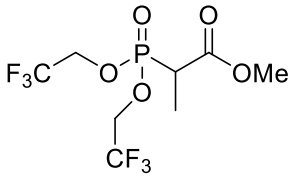
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.80 (m, 1H), 3.62 (t, *J*= 3.6 Hz, 2H), 1.57-1.49 (m, 2H), 1.48-1.43 (m, 2H), 1.42-1.38 (m, 2H), 1.19 (d, *J*= 6.4, 3H), 0.89 (s, 9H), 0.05 (s, 6H).



6-((*tert*-butyldimethylsilyl)oxy)hexan-2-one (50)

A solution of **49** (990 mg, 4.26 mmol) in CH_2Cl_2 (43 mL, 0.1 M) was added to a flame dried round bottom flask and cooled to 0° C. NEt_3 (4.16 mL, 29.81 mmol) was then delivered to the solution, which was allowed to stir at 0° C for 10 minutes. DMSO (3.03 mL, 42.59 mmol) was then added to the solution which was allowed to stir at 0° C for 10 minutes. SO_3·pyridine complex (2.71 g, 17.04 mmol) was then delivered in one portion and the resulting reaction mixture was allowed to stir at 0° C for 5 hours. The reaction was then quenched with saturated $NaHCO_3$ and the resulting biphasic mixture was allowed to warm to room temperature. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3x). The organic layers were combined, dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography after quenching the silica gel with a 1% NEt_3 in hexanes solution (1% EtOAc in hexanes to 5% EtOAc in hexanes), and **50** was isolated as a clear oil (638 mg, 65%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.61 (t, *J*= 6.2 Hz, 2H), 2.45 (t, *J*= 7.2 Hz 2H), 2.13 (s, 3H), 1.69-1.56 (m, 2H), 1.56-1.45 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H).

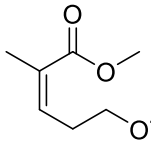


methyl 2-(bis(2,2,2-trifluoroethoxy)phosphoryl)propanoate (51)

A solution of bis-(2,2,2-trifluoroethyl)phosphonoacetate (3 g, 9.43 mmol) in THF (30 mL, 0.3 M) was added to a flame dried round bottom flask and cooled to 0° C. To this solution was added a solution of KO^tBu (1.38 g) in THF (12.30 mL, 1 M) dropwise. The resulting mixture was allowed

to stir at 0° C for 30 minutes. Methyl iodide (2.94 mL, 47.16 mmol) was then delivered to the reaction mixture dropwise, which was then allowed to warm to room temperature and stirred for 24 hours. The reaction was then quenched with saturated NH_4Cl and the aqueous phase was extracted with EtOAC (3x). The organic layers were combined, dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography (10% EtOAc in hexanes to 20% EtOAc in hexanes), and **51** was isolated as a pale yellow oil (2.13 g, 68%).

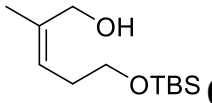
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.41 (m, 4H), 3.75 (s, 3 H), 3.18 (dq, *J*= 22.7, 7.5 Hz, 1H), 1.49 (dd, *J*= 19.3, 7.4 Hz, 3H).



methyl (*Z*)-5-((*tert*-butyldimethylsilyl)oxy)-2-methylpent-2-enoate (52)

To a flame dried round bottom flask was added 18-crown-6 (172.3 mg, 0.65 mmol) and **51** (65 mg, 0.196 mmol) in THF (2.70 mL, 0.07 M). The resulting solution was cooled to -78° C and KHMDS (0.5 M in toluene, 0.38 mL) was added dropwise. The mixture was allowed to stir at -78° C for 30 minutes. **31** (30 mg, 0.157 mmol) in THF (1.80 mL, 0.09 M) was then added to the reaction mixture which was then allowed to stir at -78° C for 4.5 hours. The reaction was then quenched with saturated NH_4Cl and the aqueous layer was extracted with Et_2O (3x). The organic layers were combined, dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography (1% EtOAc in hexanes to 5% EtOAc in hexanes), and **52** was isolated as a pale yellow oil (25 mg, 62%).

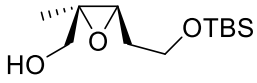
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02 (tq, *J*= 10.8, 1.1 Hz, 1H), 3.73 (s, 3H), 3.67 (t, *J*= 6.5 Hz, 2H), 2.68 (q, *J*= 6.5 Hz, 2H), 1.91 (s, 3H), 0.88 (s, 9H), 0.05 (s, 6H).



(*Z*)-5-((*tert*-butyldimethylsilyl)oxy)-2-methylpent-2-en-1-ol (53)

A solution of **52** (130 mg, 0.50 mmol) in THF (1.50 mL, 0.35 M) was added to a flame dried round bottom flask and cooled to 0° C. Super Hydride® (1 M in THF, 1.50 mL) was then added to this solution dropwise. The resulting mixture was allowed to stir at 0° C for 1 hour. The reaction was quenched with MeOH at 0° C and the solvent was removed under reduced pressure. Saturated NH_4Cl was then added to the flask and was then extracted with EtOAc (3x). The organic layers were combined, dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography (1% EtOAc in hexanes to 8% EtOAc in hexanes), and **53** was isolated as a clear oil (70 mg, 61%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.29 (m, 1H), 4.04 (s, 2H), 3.61 (t, *J*= 6.4 Hz, 2H), 2.29 (q, *J*= 6.4 Hz, 2H), 1.80 (s, 3H), 0.88 (s, 9H), 0.05 (s, 6H).

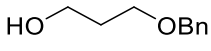


((2*S*,3*r*)-3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-methyloxiran-2-yl)methanol (54)

To a flame dried round bottom flask was added 4 Å molecular sieves (217 mg, 0.5 g/mmol **54**) and $Ti(OiPr)_4$ (0.14 mL, 0.48 mmol) in CH_2Cl_2 (1.1 mL, 0.4 M). This solution was cooled to -20° C then (+)-diethyl L-tartrate (0.08 mL, 0.48 mmol) and a solution of **53** (100 mg, 0.43 mmol) in CH_2Cl_2 (0.5 mL) were added and the resulting reaction mixture was allowed to stir at -20° C for 15 minutes. ^{t}BuOOH (5.5 M in decane, 0.17 mL) was then delivered to the reaction mixture which was then placed in a fridge for 5 days. The reaction was quenched at -20° C with a 10% aqueous solution of tartaric acid and was then warmed to 0° C and stirred for 30 minutes. The resulting biphasic mixture was filtered through Celite®, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3x). The organic layers were combined, washed with saturated

$Na_2S_2O_3$ and the solvent was removed under reduced pressure. The crude oil was then diluted with Et_2O and a 1 M NaOH solution was added dropwise at 0° C, and the resulting biphasic mixture was allowed to stir at 0° C for 30 minutes. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3x). The organic layers were combined, dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography (10% EtOAc in hexanes to 25% EtOAc in hexanes), and **54** was isolated as a clear oil (58 mg, 55%).

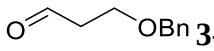
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (dt, *J*= 10.0, 4.1 Hz, 1H), 3.74 (td, *J*= 10.6, 2.4 Hz, 1H), 3.65 (d, *J*= 10.9 Hz, 1H), 3.51 (d, *J*= 11.7 Hz, 1H), 3.17 (bs, 1H), 2.80 (dd, *J*= 9.4, 3.9 Hz, 1H), 2.00 (m, 1H), 1.71 (m, 1H), 1.42 (s, 3H), 0.91 (s, 9H), 0.09 (s, 6H).



3-(benzyloxy)propan-1-ol (56)

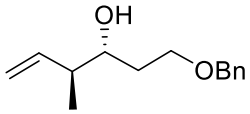
A solution of 1,3-propanediol (4.75 mL, 65.71 mmol) in THF (130 mL, 0.5 M) was added to a flame dried round bottom flask and was cooled to 0° C. To this solution was added NaH (1.73 g, 72.28 mmol) and TBAI (2.43 g, 6.57 mmol). Benzyl bromide (7.80 mL, 65.71 mmol) was then added to the reaction mixture which was then allowed to warm to room temperature and was stirred for 18 hours. The reaction was then quenched with saturated NH_4Cl and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3x). The organic layers were combined and washed with brine, dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography (15% EtOAc in hexanes to 25% EtOAc in hexanes), and **56** was isolated as a yellow oil (9.39 g, 86%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.28 (m, 5H), 4.53 (s, 2H), 3.79 (t, *J*= 5.6 Hz, 2H), 3.67 (t, *J*= 5.6 Hz, 2H), 1.88 (p, *J*= 5.6 Hz, 2H).



3-(benzyloxy)propanal (57)

A solution of DMSO (1.37 mL, 19.25 mmol) in CH_2Cl_2 (30 mL, 0.2 M) was cooled to -78° C in a flame dried round bottom flask. Oxalyl chloride (0.83 mL, 9.63 mmol) was then delivered dropwise and the solution was allowed to stir at -78° C for 20 minutes. **56** (1 g, 6.02 mmol) was then added to the solution and the reaction mixture was then allowed to stir at -78° C for 1.5 hours. Triethylamine (4.36 ml, 31.28 mmol) was then delivered to the reaction mixture dropwise at -78° C, and the mixture was allowed to slowly warm to room temperature. The reaction was then quenched with water, the organic layer was separated, and then the aqueous layer was extracted with CH_2Cl_2 (3x). The organic layers were then combined, washed with saturated $NaHCO_3$, 1 M HCl, then brine and dried with $MgSO_4$ and filtered. The solvent was then removed under reduced pressure. **57** was obtained as a yellow oil (987 mg, quant.) and used without further purification. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.80 (t, *J*= 1.8 Hz, 1H), 7.39-7.28 (m, 5H), 4.54 (s, 2H), 3.82 (t, *J*= 6.1 Hz, 2H), 2.70 (td, *J*= 6.1, 1.8 Hz, 2H).

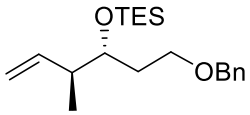


(3*R*,4*S*)-1-(benzyloxy)-4-methylhex-5-en-3-ol (58)

To a flame dried round bottom flask were added 4 Å molecular sieves (1.80 g, 2 g/1 g **57**), toluene (22 mL, 0.25 M) and a solution of *R,R*-diisopropyl tartrate (*E*)-crotylboronate (1.96 g, 6.58 mmol) in toluene (13 mL, 0.5 M). The mixture was allowed to stir at room temperature for 30 minutes then was cooled to -78° C. A solution of **57** (900 mg, 5.48 mmol) in toluene (2 mL, 2.75 M) was then added dropwise and the resulting reaction mixture was allowed to stir at -78° C for 4 hours. The reaction was then quenched at -78° C with a 2 M NaOH solution and the reaction mixture was allowed to warm to room temperature. The organic phase was separated, and the aqueous phase was extracted with Et_2O (3x). The organic layers were combined and washed with saturated $NaHCO_3$ then brine, dried with $MgSO_4$, filtered, and the solvent was removed under reduced

pressure. The crude mixture was then purified by flash column chromatography (5% EtOAc in hexanes to 12% EtOAc in hexanes), and **58** was isolated as a pale yellow oil (928 mg, 77%).

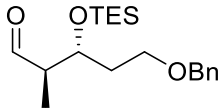
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.27 (m, 5H), 5.81 (m, 1H), 5.08 (m, 2H), 4.52 (s, 2H), 3.72 (dt, *J*= 9.2, 5.4 Hz, 1H), 3.69-3.63 (m, 2H), 2.24 (m, 1H), 1.74 (m, 2H), 1.04 (d, *J*= 6.9 Hz, 3H).



(((3*R*,4*S*)-1-(benzyloxy)-4-methylhex-5-en-3-yl)oxy)triethylsilane (59)

A solution of **58** (950 mg, 4.31 mmol) and imidazole (939.4 mg, 13.80 mmol) in CH_2Cl_2 (13 mL, 0.35 M) was added to a flame dried round bottom flask and was cooled down to 0° C. TESCl (1.16 mL, 6.90 mmol) was then added to the reaction mixture, which was then allowed to stir at 0° C for 2 hours and subsequently allowed to warm to room temperature and stir for 15 hours. The reaction was quenched with the addition of methanol. Water was then added, and the organic and aqueous layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography (3% EtOAc in hexanes to 10% EtOAc in hexanes), and **59** was isolated as a clear oil (1.34 g, 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.27 (m, 5H), 5.78 (m, 1H), 5.00 (m, 2H), 4.50 (d, *J*= 11.9 Hz, 1H), 4.45 (d, *J*= 11.9 Hz, 1H), 3.81 (dt, *J*= 7.9, 4.0 Hz, 1H), 3.52 (t, *J*= 6.6 Hz, 2H), 2.29 (m, 1H), 1.69 (m, 2H), 1.01 (d, *J*= 6.9 Hz, 3H), 0.95 (t, *J*= 7.7 Hz, 9H), 0.59 (q, *J*= 7.7 Hz, 6H),

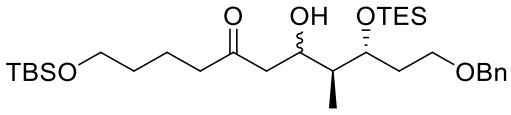


(2*R*,3*R*)-5-(benzyloxy)-2-methy-3-((triethylsilyl)oxy)pentanal (60)

To a flame dried round bottom flask was added **59** (500 mg, 1.49 mmol) and a 4:1 mixture of THF:H_2O (6 mL:1.5 mL, 0.2 M). 4-methylmorpholine oxide monohydrate (302.9 mg, 2.24 mmol) was then added to this solution followed by a 4% aqueous solution of OsO_4 (0.4 mL, 0.06 mmol).

The resulting reaction mixture was allowed to stir at room temperature for 15 hours. $NaIO_4$ (383.5 mg, 1.79 mmol) was then added to the reaction mixture which was allowed to stir for 2 hours. The aqueous layer was then extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography (1% EtOAc in hexanes to 5% EtOAc in hexanes), and **60** was isolated as a clear oil (412 mg, 82%).

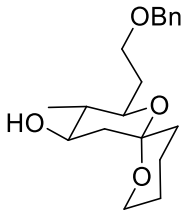
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.73 (d, *J*= 2.1 Hz, 1H), 7.38-7.27 (m, 5H), 4.51 (d, *J*= 11.9 Hz, 1H), 4.46 (d, *J*= 11.9 Hz, 1H), 4.18 (m, 1H), 3.56 (t, *J*= 6.6 Hz, 2H), 2.52 (m, 1H), 1.82 (m, 2H), 1.11 (d, *J*= 7.0 Hz, 3H), 0.95 (t, *J*= 7.9 Hz, 9H), 0.60 (q, *J*= 7.9 Hz, 6H).



(12*S*,13*R*)-13-(2-(benzyloxy)ethyl)-15,15-diethyl-11,hydroxy-2,2,3,3,12-pentamethyl-4,14-dioxa-3,15-disilaheptadecan-9-one (61)

To a flame dried round bottom flask was added $(iPr)_2NH$ (0.11 mL, 0.78 mmol) in THF (2.5 mL, 0.3 M), and the resulting solution was cooled to 0° C. n-BuLi (2.5 M in hexanes, 0.31 mL) was then delivered dropwise to the solution which was allowed to stir at 0° C for 30 minutes. The mixture was then cooled to -78° C and **50** (171.2 mg, 0.74 mmol) in THF (1 mL, 0.75 M) was added over 30 minutes, then the mixture was allowed to stir at -78° C for 1 hour. **60** (250 mg, 0.74 mmol) in THF (1 mL, 0.75 M) was then added over the course of 30 minutes and the reaction mixture was allowed to stir at -78° C for 1 hour. The reaction was then quenched with saturated NH_4Cl at -78° and allowed to warm to room temperature. The aqueous layer was then extracted with Et_2O (3x). The organic layers were combined, dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude mixture was then purified by flash column

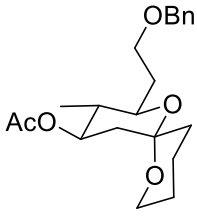
chromatography (5% Et_2O in hexanes to 20% Et_2O in hexanes), and **61** was isolated as a pale yellow oil (227 mg, 54%).



(2*R*,3*S*,4*R*,6*S*)-2-(2-(benzyloxy)ethyl)-3-methyl-1,7-dioxaspiro[5.5]undecane-4-ol (62)

To a flame dried 2-dram vial was added racemic **61** (100 mg, 0.177 mmol) in MeOH (1.8 mL, 1 M). CSA (8.2 mg, 0.04 mmol) was then added to the prepared solution and this mixture was allowed to stir at room temperature for 1.5 hours. The crude mixture then had the solvent removed under reduced pressure and was then purified by flash column chromatography (5% EtOAc in hexanes to 20% EtOAc in hexanes). The diastereomers resulting from the previous reaction were successfully separated and **62** was isolated as a clear oil (15 mg, 27%).

^{1}H NMR (500 MHz, C_6D_6) δ 7.30 (d, *J*= 7.4 Hz, 2H), 7.16 (m, 2H), 7.07 (t, *J*= 7.3 Hz, 1H), 4.38 (d, *J*= 12.0 Hz, 1H), 4.33 (d, *J*= 12.0 Hz, 1H), 3.77 (m, 1H), 3.68 (m, 1H), 3.61 (m, 1H), 3.57 (m, 2H), 3.46 (dd, *J*= 11.0, 4.4 Hz, 1H), 2.04 (m, 2H), 1.85 (m, 1H), 1.59 (m, 2H), 1.48-1.24 (m, 6H), 0.89 (d, *J*= 6.5 Hz, 3H).



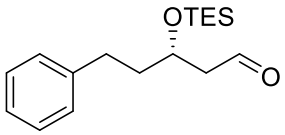
(2*R*,3*R*,4*R*,6*S*)-2-(2-(benzyloxy)ethyl)-3-methyl-1,7-dioxaspiro[5.5]undecane-4-yl acetate (63)

To a flame dried 2-dram vial was added **62** (15 mg, 0.05 mmol) in CH_2Cl_2 (0.5 mL, 0.1 M). To this solution was added NEt_3 (0.08 mL, 0.59 mmol) and DMAP (0.3 mg, $2x10^{-3}$ mmol). Acetic

anhydride (0.03 mL, 0.28 mmol) was then delivered to the mixture which was then allowed to stir at room temperature for 2 hours. The reaction was quenched with saturated $NaHCO_3$, and the organic and aqueous layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3x). The organic layers were combined, dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography (5% Et_2O in hexanes to 25% Et_2O in hexanes), and **63** was isolated as a clear oil (16 mg, 96%).

^{1}H NMR (500 MHz, C_6D_6) δ 7.31 (d, *J*= 7.6 Hz, 2H), 7.17 (t, *J*= 7.6 Hz, 2H), 7.08 (t, *J*= 7.6 Hz, 1H), 5.29 (ddd, *J*= 15.8, 10.7, 4.9 Hz, 1H), 4.37 (d, *J*= 11.9 Hz, 1H), 4.33 (d, *J*= 11.9 Hz, 1H), 3.74 (m, 1H), 3.67 (m, 1H), 3.58 (m, 2H), 3.47 (m, 1H), 2.28 (dt, *J*= 12.1, 4.3 Hz, 1H), 2.01 (m, 1H), 1.80 (m, 1H), 1.68 (s, 3H), 1.60-1.51 (m, 2H), 1.49-1.37 (m, 2H), 1.37-1.26 (m, 4H), 1.18 (m, 1H), 0.77 (d, *J*= 6.5 Hz, 3H).

^{13}C NMR 169.6, 139.3, 128.6, 128.3, 127.7, 96.5 73.2, 72.8, 69.8, 67.0, 60.4, 41.9, 41.3, 35.6, 33.7, 25.5, 20.8, 19.2, 12.9.

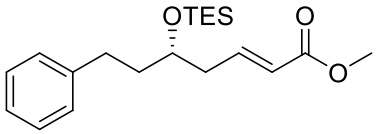


(*S*)-5-phenyl-3-((triethylsilyl)oxy)pentanal (64)

To a flame dried round bottom flask was added **35** (250 mg, 0.861 mmol) and a 4:1 mixture of THF:H_2O (3.45 mL:0.85 mL, 0.2 M). 4-methylmorpholine oxide monohydrate (174.6 mg, 1.29 mmol) was then added to this solution followed by a 4% aqueous solution of OsO_4 (0.22 mL, 0.03 mmol). The resulting reaction mixture was allowed to stir at room temperature for 15 hours. $NaIO_4$ (220.9 mg, 1.03 mmol) was then added to the reaction mixture which was allowed to stir for 2 hours. The aqueous layer was then extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography (1%

EtOAc in hexanes to 5% EtOAc in hexanes), and **64** was isolated as a pale yellow oil (236 mg, 94%).

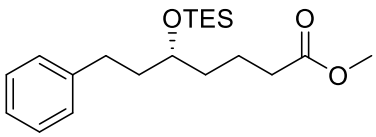
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.83 (t, *J*= 2.3 Hz, 1H), 7.29 (t, *J*= 7.6 Hz, 2H), 7.22-7.16 (m, 3H), 4.27 (p, *J*= 5.8 Hz, 1H), 2.67 (dd, *J*= 16.3, 8.1 Hz, 2H), 2.59 (td, *J*= 5.7, 2.4 Hz, 2H), 1.87 (m, 2H), 0.96 (t, *J*= 7.9 Hz, 9H), 0.62 (q, *J*= 7.9 Hz, 6H).



methyl (*S*,*E*)-7-phenyl-5-((triethylsilyl)oxy)hept-2-enoate (65)

A solution of **64** (820 mg, 2.80 mmol) and trimethyl phosphonoacetate (0.50 mL, 3.08 mmol) in THF (40 mL, 0.07 M) was added to a flame dried round bottom flask and cooled to -78° C. To this solution was added tetramethyl guanidine (0.39 mL, 3.08 mmol) and the reaction mixture was stirred at -78° C for 30 minutes then allowed to warm to room temperature and stirred for 20 hours. The reaction mixture was then diluted with water and extracted with Et_2O (3x). The organic layers were combined, washed with water then brine, dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography (3% EtOAc in hexanes to 10% EtOAc in hexanes), and **65** was isolated as a pale yellow oil (236 mg, 94%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.24 (m, 2H), 7.22-7.14 (m, 3H), 6.83 (dt, *J*= 15.9, 7.4 Hz, 1H), 6.10 (dt, *J*= 16.2, 1.4 Hz, 1H), 3.88 (p, *J*= 5.8 Hz, 1H), 2.66 (m, 2H), 2.44 (m, 2H), 2.25 (s, 3H), 1.76 (td, *J*= 8.2, 5.9 Hz, 2H), 0.98 (t, *J*= 7.8 Hz, 9H), 0.61 (q, *J*= 7.8 Hz, 6H).

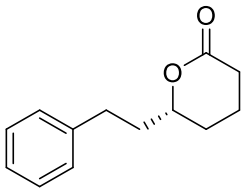


methyl (*R*)-7-phenyl-5-((triethylsilyl)oxy)heptanoate (66)

To a flame dried round bottom flask was added Pd/C (65 mg, 10% wt.) followed by **65** (650 mg, 1.87 mmol) in THF (43 mL, 0.04 M). The reaction flask was then backfilled with H_2 gas and fitted

with a H_2 balloon. The heterogeneous mixture was allowed to stir at room temperature for 5 hours before being filtered through Celite®. The solvent was removed under reduced pressure and **66** was obtained as a pale yellow oil (650 mg, 99%) and carried on without further purification.

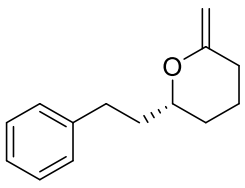
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23-7.17 (m, 2H), 7.13-7.06 (m, 3H), 3.65 (p, *J*= 5.7 Hz, 1H), 2.57 (m, 2H), 2.35 (t, *J*= 7.2 Hz, 2H), 2.06 (s, 3H), 1.69 (m, 2H), 1.54 (m, 2H), 1.42 (m, 2H), 0.90 (t, *J*= 7.9 Hz, 9H), 0.53 (q, *J*= 7.9 Hz, 6H).



(*R*)-6-phenethyltetrahydro-2*H*-pyran-2-one (67)

To a flame dried round bottom flask was added **66** (150 mg, 0.43 mmol) and MeOH (4.28 mL, 0.1M). CSA (20 mg, 0.09 mmol) was added to the solution and the resulting mixture was allowed to stir at room temperature for 2 hours. The crude mixture then had the solvent removed under reduced pressure and was then purified by flash column chromatography (5% EtOAc in hexanes to 30% EtOAc in hexanes), and **67** was obtained as a clear oil (73 mg, 84%).

^{1}H NMR (500 MHz, C_6D_6) δ 7.31-7.27 (m, 2H), 7.22-7.18 (m, 3H), 4.27 (m, 1H), 2.86 (ddd, *J*= 13.8, 9.6, 5.4 Hz, 1H), 2.75 (ddd, *J*= 13.8, 9.2, 7.1 Hz, 1H), 2.58 (m, 1H), 2.46 (m, 1H), 2.03 (m, 1H), 1.94-1.87 (m, 3H), 1.63-1.55 (m, 2H).

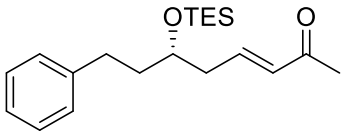


(*R*)-2-methylene-6-phenethyltetrahydro-2*H*-pyran (68)

To a flame dried round bottom flask was added **67** (95 mg, 0.47 mmol) and toluene (1 mL, 0.47 M). To this solution was added a solution of Cp_2TiMe_2 (0.38 M in toluene, 3.6 mL). The reaction flask was fitted with a reflux condenser and wrapped in aluminum foil. The mixture was then

heated to 65-70° C and stirred for 18 hours. The reaction was cooled to room temperature, treated with cold pentanes, and filtered through Celite®. The crude mixture then had the solvent removed under reduced pressure and was then purified by flash column chromatography using basic alumina (100% hexanes to 5% Et_2O in hexanes), and **68** was obtained with inseparable impurities from the titanium catalyst.

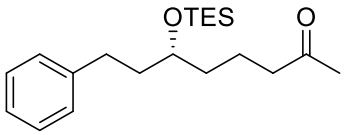
^{1}H NMR (500 MHz, C_6D_6) δ 7.09-6.97 (m, 5H), 4.56 (s, 1H), 4.06 (s, 1H), 3.36 (m, 1H), 2.72 (ddd, *J*= 13.6, 9.6, 5.3 Hz, 1H), 2.61 (ddd, *J*= 13.6, 9.1, 7.4 Hz, 1H), 2.00-1.73 (m, 3H), 1.49 (m, 1H), 1.37 (m, 1H), 1.24-1.12 (m, 3H).



(*S*,*E*)-8-phenyl-6-((triethylsilyl)oxy)oct-3-en-2-one (69)

A solution of dimethyl acetylmethylphosphonate (1.08 mL, 7.80 mmol) in MeCN (15 mL) was added to a flame dried round bottom flask and cooled to 0° C. To this solution was added LiCl (330.4 mg, 7.80 mmol) and DBU (1.17 mL, 7.80 mmol), and the mixture was allowed to stir at 0° C for 30 mins. A solution of **64** (1.90 g, 6.50 mmol) in MeCN (15 mL, 0.22 M) was then added dropwise and the reaction mixture was allowed to warm to room temperature and stir for 16 hours. The reaction was then diluted with water and extracted with Et_2O (3x). The organic layers were combined, dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography (1% EtOAc in hexanes to 10% EtOAc in hexanes), and **69** was isolated as a clear oil (1.36 g, 63%).

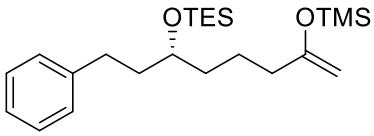
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.26 (m, 2H), 7.22-7.14 (m, 3H), 6.82 (dt, *J*= 15.9, 7.4 Hz, 1H), 6.10 (dt, *J*= 16.0, 1.1 Hz, 1H), 3.88 (p, *J*= 5.8 Hz, 1H), 2.76-2.55 (m, 2H), 2.47-2.39 (m, 2H), 2.25 (s, 3H), 1.78 (td, *J*= 8.2, 5.9 Hz, 2H), 0.97 (t, *J*= 7.9 Hz, 9H), 0.61 (q, *J*= 7.9 Hz, 6H).



(*R*)-8-phenyl-6-((triethylsilyl)oxy)octan-2-one (70)

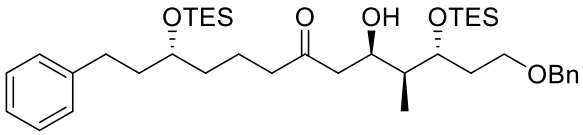
To a flame dried round bottom flask was added Pd/C (17.5 mg, 10% wt.) followed by **69** (175 mg, 0.52 mmol) in THF (12 mL, 0.04 M). The reaction flask was then backfilled with H_2 gas and fitted with a H_2 balloon. The heterogeneous mixture was allowed to stir at room temperature for 5 hours before being filtered through Celite®. The solvent was removed under reduced pressure and **70** was obtained as a pale yellow oil (175 mg, quant.) and carried on without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.26 (m, 2H), 7.21-7.15 (m, 3H), 3.72 (p, *J*= 5.7 Hz, 1H), 2.72-2.56 (m, 2H), 2.43 (t, *J*= 7.2 Hz, 2H), 2.13 (s, 3H), 1.80-1.73 (m, 2H), 1.69-1.57 (m, 2H), 1.52-1.44 (m, 2H).



(*R*)-10,10-diethyl-2,2-dimethyl-4-methylene-8-phenethyl-3,9-dioxa-2,10,disildodecane (71)

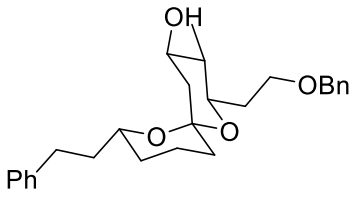
A solution of **70** (75 mg, 0.22 mmol) in THF (1.15 mL, 0.2 M) was added to a flame dried round bottom flask and cooled to -78° C. LiHMDS (1 M in THF, 0.57 mL) was added to the prepared solution which was then allowed to stir at -78° C. To this solution was added a 1:1 mixture of TMSCl (0.21 mL, 1.67 mmol) and NEt_3 (0.23 mL, 1.67 mmol) and the mixture was stirred for 45 minutes at -78° C. The reaction was quenched with pH 7 buffer solution, allowed to warm to room temperature, and diluted with EtOAc. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure. **71** was obtained as a yellow oil (90 mg, quant.) and carried on without further purification.



(5*R*,6*S*,7*R*,13*R*)-5-(2-(benzyloxy)ethyl)-3,3,15,15,-tetraethyl-7-hydroxy-6-methyl-13-phenethyl-4,14-dioxa-3,15-disilaheptadecan-9-one (72).

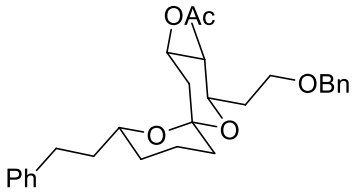
A solution of **60** (67.6 mg, 0.20 mmol) in CH_2Cl_2 (2.0 mL, 0.1 M) was added to a flame dried round bottom flask and cooled to -78° C. $BF_3 \cdot OEt_2$ (25 µL, 0.20 mmol) was then delivered to this solution dropwise and the mixture was stirred for 5 minutes. A solution of **71** (90 mg, 0.22 mmol) in CH_2Cl_2 (0.25 mL) was then added dropwise to the mixture which was then allowed to stir at -78° C for 1 hour. The reaction was then quenched with saturated NH_4Cl and allowed to warm to room temperature. The organic and aqueous layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3x). The organic layers were combined, dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography (5% Et_2O in hexanes to 30% Et_2O in hexanes), and **72** was isolated as a clear oil (71 mg, 53%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.26 (m, 6H), 7.20-7.14 (m, 4H), 4.51 (d, *J*= 11.9 Hz, 1H), 4.45 (d, *J*= 11.9 Hz, 1H) 3.96 (td, *J*= 6.4, 3.1 Hz, 1H), 3.71 (p, *J*= 5.6 Hz, 1H), 3.58-3.45 (m, 3H), 2.72-2.54 (m, 4H), 2.43 (dd, *J*= 16.2, 4.4 Hz, 1H), 1.95 (m, 2H), 1.80-1.70 (m, 3H), 1.65-1.57 (m, 2H), 1.51-1.43 (m, 3H), 1.00-0.92 (m, 21H), 0.65-0.56 (m, 12H).



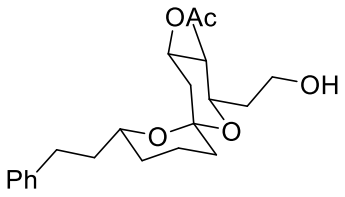
(2*R*,3*S*,4*R*,6*S*,8*R*)-2-(2-(benzyloxy)ethyl)-3-methyl-8-phenethyl-1,7-dioxaspiro[5.5]undecane-4-ol (73)

To a flame dried round bottom flask was added **72** (70 mg, 0.10 mmol) and MeOH (1 mL, 0.1 M). CSA (5 mg, 0.02 mmol) was then added to this mixture which was then allowed to stir for 2 hours. The crude reaction mixture had the solvent removed under reduced pressure and was purified by flash column chromatography (5% EtOAc in hexanes to 20% EtOAc in hexanes), and **73** was obtained as a clear oil (11.5 mg, 27%) which was a complex mixture by ^{1}H NMR. This mixture was carried on to the following step without any further purification.



(2*R*,3*R*,4*R*,6*S*,8*R*)-2-(2-(benzyloxy)ethyl)-3-methyl-8-phenethyl-1,7-dioxaspiro[5.5]undecane-4-yl acetate (74)

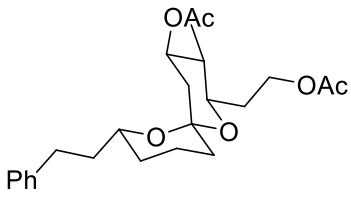
To a flame dried 2-dram vial was added **73** (10 mg, 0.02 mmol) in CH_2Cl_2 (0.2 mL, 0.1 M). To this solution was added NEt_3 (41 µL, 0.30 mmol) and DMAP (0.2 mg, $1.2x10^{-3}$ mmol). Acetic anhydride (14 µL, 0.14 mmol) was then delivered to the mixture which was then allowed to stir at room temperature for 2 hours. The reaction was quenched with saturated $NaHCO_3$, and the organic and aqueous layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3x). The organic layers were combined, dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography (5% Et_2O in hexanes to 15% Et_2O in hexanes), and **74** was isolated as a clear oil (10.2 mg, 91%) which was a complex mixture by ^{1}H NMR. This mixture was carried on to the following step without any further purification.



(2*R*,3*R*,4*R*,6*S*,8*R*)-2-(2-hydroxyethyl)-3-methyl-8-phenethyl-1,7-dioxaspiro[5.5]undecane-4-yl acetate (75)

To a flame dried 2-dram vial was added **74** (7.5 mg, 0.02 mmol) and EtOAc (0.2 mL, 0.1 M). To this solution, Pd/C (1 mg, 13% wt.) was added and then the flask was backfilled with H_2 gas then fitted with a H_2 balloon. The reaction mixture was stirred at room temperature for 2 days before being filtered through Celite®. The solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography (5% Et_2O in hexanes to 20% Et_2O in hexanes and **75** was obtained as a clear oil (1.5 mg, 25%).

^{1}H NMR (500 MHz, C_6D_6) δ 7.13-7.02 (m, 5H), 5.28 (td, *J*= 10.8, 4.8 Hz, 1H), 3.65 (m, 1H), 3.57-3.48 (m, 2H), 3.44 (m, 1H), 2.82 (ddd, *J*= 14.3, 9.2, 5.2 Hz, 1H), 2.65 (ddd, *J*= 14.1, 9.2, 6.7 Hz, 1H), 2.23 (dd, *J*= 12.1, 5.0 Hz, 1H), 1.70 (s, 3H), 1.65-1.42 (m, 5H), 1.35-1.19 (m, 7H), 0.76 (d, *J*= 6.5 Hz, 3H).



2-((2*R*,3*R*,4*R*,6*S*,8*R*)-4-acetoxy-3-methyl-8-phenethyl-1,7-dioxaspiro[5.5]undecane-2-yl)ethyl acetate (76)

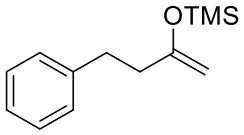
To a flame dried 2-dram vial was added **75** (1.5 mg, $4x10^{-3}$ mmol) in CH_2Cl_2 (0.5 mL, $8x10^{-3}$ M). To this solution was added NEt_3 (7 µL, 0.05 mmol) and DMAP (0.02 mg, $2x10^{-4}$ mmol). Acetic anhydride (2.5 µL, 0.02 mmol) was then delivered to the mixture which was then allowed to stir at room temperature for 2 hours. The reaction was quenched with saturated $NaHCO_3$, and the organic and aqueous layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3x).

The organic layers were combined, dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography (5% Et_2O in hexanes to 25% Et_2O in hexanes), and **76** was isolated as a clear oil (1.6 mg, 97%).

^{1}H NMR (500 MHz, C_6D_6) δ 7.12-7.05 (m, 5H), 5.31 (td, *J*= 10.8, 4.9 Hz, 1H), 4.31 (ddd, *J*= 10.8, 7.4, 4.5 Hz, 1H), 4.17 (ddd, *J*= 10.7, 8.0, 7.0 Hz, 1H), 3.51 (dddd, *J*= 11.2, 9.0, 3.7, 2.2 Hz, 1H), 3.45 (td, *J*= 10.0, 2.4 Hz, 1H), 2.88 (ddd, *J*= 13.9, 10.2, 5.0 Hz, 1H), 2.64 (ddd, *J*= 13.8, 10.1, 6.5 Hz, 1H), 2.26 (dd, *J*= 12.2, 4.9 Hz, 1H), 1.91-1.75 (m, 4H), 1.73 (s, 3H), 1.70(s, 3H), 1.63 (m, 2H), 1.57-1.47 (m, 3H), 1.23 (td, *J*= 13.2, 4.4 Hz, 2H), 1.06 (m, 1H), 0.79 (d, *J*= 6.5 Hz, 3H).

^{13}C NMR 170.2, 169.6, 128.8, 128.7, 126.1, 97.2, 72.6, 69.9, 69.2, 61.5, 41.9, 41.1, 38.1, 35.2, 32.5, 32.4, 31.2, 20.7, 20.6, 19.3, 13.0, 1.4.

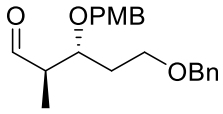
HRMS (ESI) *m/z* calcd. for $C_{24}H_{35}O_6$ $[M+H]^+$ 419.2429, found 419.2430.



trimethyl((4-phenylbut-1-en-2-yl)oxy)silane (77)

A solution of $(iPr)_2NH$ (57 µL, 0.41 mmol) in THF (0.7 mL, 0.5 M) was added to a flame dried round bottom flask and cooled to 0° C. n-BuLi (2.5 M in hexanes, 0.15 mL) was then added to the solution drop wise which was then allowed to stir for 15 minutes before being cooled to -78° C. Benzylacetone (51 µL, 0.34 mmol) was then added to the solution dropwise, using minimal THF to quantitate the transfer. The mixture was allowed to stir for 10 minutes at -78° C then TMSCl (47 µL, 0.37 mmol) was delivered dropwise. The reaction mixture was stirred for 10 minutes before being quenched with pH 7 buffer at -78° C. The aqueous layer was then extracted with Et_2O (3x). The organic layers were combined, dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude mixture was then placed under vacuum for 1 hour, and **77** was obtained as a clear oil (73 mg, 99%) and was used crude in the following step.

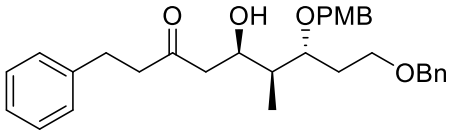
^{1}H NMR (300 MHz, C_6D_6) δ 7.27-7.18 (m, 3H), 7.15-7.09 (m, 2H), 4.20 (s, 1H), 4.14 (s, 1H), 2.86 (t, *J*= 7.9 Hz, 2H), 2.41 (t, *J*= 7.9 Hz, 2H), 0.24 (s, 9H).



(2*R*,3*R*)-5-(benzyloxy)-3-((4-methoxybenzyl)oxy)-2-methylpentanal (78)

To a flame dried round bottom flask was added **1-((((3*R*,4*S*)-1-(benzyloxy)-4-methylhex-5-en-3-yl)oxy)methyl-4-methoxybenzene** (1 g, 2.94 mmol) and a 4:1 mixture of THF:H_2O (12 mL:3 mL, 0.2 M). 4-methylmorpholine oxide monohydrate (595.5 mg, 4.41 mmol) was then added to this solution followed by a 4% aqueous solution of OsO_4 (0.75 mL, 0.12 mmol). The resulting reaction mixture was allowed to stir at room temperature for 15 hours. $NaIO_4$ (753.7 mg, 3.52 mmol) was then added to the reaction mixture which was allowed to stir for 2 hours. The aqueous layer was then extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography (1% EtOAc in hexanes to 5% EtOAc in hexanes), and **78** was isolated as a clear oil (814.6 mg, 81%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.71 (d, *J*= 2.0 Hz, 1H), 7.37-7.27 (m, 5H), 7.19 (d, *J*= 8.6 Hz, 2H), 6.85 (d, *J*= 8.7 Hz, 2H), 4.52-4.42 (m, 4H), 3.93 (q, *J*= 5.9 Hz, 1H), 3.80 (s, 3H), 3.65-3.53 (m, 2H), 2.69 (m, 1H), 1.85 (q, *J*= 6.5 Hz, 2H), 1.10 (d, *J*= 7.1 Hz, 3H).

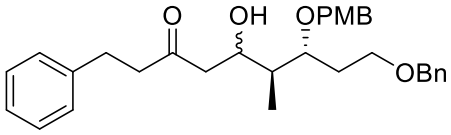


(5*R*,6*S*,7*R*)-9-(benzyloxy)-5-hydroxy-7-((4-methoxybenzyl)oxy)-6-methyl-1-phenylnonan-3-one (79)

A solution of **78** (50 mg, 0.15 mmol) in CH_2Cl_2 (1.6 mL, 0.1 M) was added to a flame dried round bottom flask and cooled to -78° C. $BF_3{\cdot}OEt_2$ (18 µL, 0.15 mmol) was then added to this solution dropwise, which was then allowed to stir for 5 minutes. A solution of **77** (35.5 mg, 0.16 mmol) in

CH_2Cl_2 (0.3 mL) was delivered dropwise to the reaction mixture over the course of 45 minutes. The reaction was allowed to stir for 1 hour at -78° C, then was quenched with saturated NH_4Cl and allowed to warm to room temperature. The resulting biphasic mixture was poured into water, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3x). The organic layers were combined, dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography (10% Et_2O in hexanes to 35% Et_2O in hexanes), and **79** was isolated as a clear oil (42 mg, 59%).

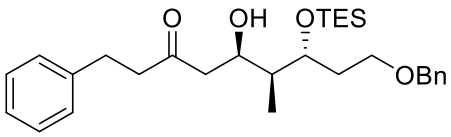
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.17 (m, 4H), 7.16-7.07 (m, 7H), 6.81-6.75 (m, 3H), 4.45-4.39 (m, 4H), 3.70 (s, 3H), 3.60-3.39 (m, 4H), 2.81 (t, *J*= 7.5 Hz, 2H), 2.71-2.63 (m, 2H), 2.53 (dd, *J*= 16.4, 9.0 Hz, 1H), 2.27 (dd, *J*= 16.3, 3.7 Hz, 1H), 1.86 (m, 2H), 1.57 (m, 1H), 0.88 (d, *J*= 7.0 Hz, 3H).



(6*S*,7*R*)-9-(benzyloxy)-5-hydroxy-7-((4-methoxybenzyl)oxy)-6-methyl-1-phenylnonan-3-one ((±)79)

A solution of $(iPr)_2NH$ (21 µL, 0.15 mmol) in THF (1 mL, 0.15 M) was added to a flame dried round bottom flask and cooled to 0° C. n-BuLi (2.5 M in hexanes, 0.06 mL) was then added to the solution which was allowed to stir for 30 minutes at 0° C before being cooled to -78° C. Benzylacetone (21 µL, 0.14 mmol) in THF (0.25 mL) was then added to the mixture dropwise which was allowed to stir for 45 minutes. **78** (50 mg, 0.15 mmol) in THF (0.25 mL) was then delivered to the solution dropwise over the course of 25 minutes which was then allowed to stir for 1 hour at -78° C before being quenched with saturated NH_4Cl and warmed to room temperature. The aqueous layer was extracted with Et_2O (3x). The organic layers were combined, dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude mixture was then

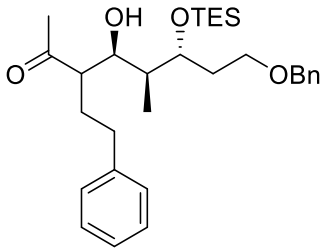
purified by flash column chromatography (10% Et_2O in hexanes to 35% Et_2O in hexanes), and (±) **79** was isolated as a clear oil (58 mg, 85%).



(5*R*,6*S*,7*R*)-9-(benzyloxy)-5-hydroxy-6-methyl-1-phenyl-7-((triethylsilyl)-oxy)nonan-3-one (80)

A solution of **60** (50 mg, 0.15 mmol) in CH_2Cl_2 (1.5 mL, 0.1 M) was added to a flame dried round bottom flask and cooled to -78° C. $BF_3{\cdot}OEt_2$ (18 µL, 0.15 mmol) was then added to this solution dropwise, which was then allowed to stir for 5 minutes. A solution of **77** (35.5 mg, 0.16 mmol) in CH_2Cl_2 (0.3 mL) was delivered dropwise to the reaction mixture over the course of 45 minutes. The reaction was allowed to stir for 1 hour at -78° C, then was quenched with saturated NH_4Cl and allowed to warm to room temperature. The resulting biphasic mixture was poured into water, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3x). The organic layers were combined, dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography (10% Et_2O in hexanes to 25% Et_2O in hexanes), and **80** was isolated as a clear oil (34 mg, 47%).

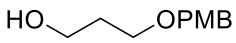
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.32 (m, 4H), 7.30-7.28 (m, 2H), 7.22-7.16 (m, 4H), 4.54-4.43 (m, 3H), 3.98 (td, *J*= 6.4, 3.0 Hz, 1H), 3.51 (m, 2H), 2.90 (t, *J*= 6.9 Hz, 2H), 2.77 (m, 2H), 2.66 (dd, *J*= 8.6, 16.3 Hz, 1H), 2.32 (dd, *J*= 16.4, 4.4 Hz, 1H), 1.96 (m, 2H), 1.52 (m, 1H), 1.00-0.94 (m, 12H), 0.63 (q, *J*= 7.7 Hz, 6H).



(4*S*,5*S*,6*R*)-8-(benzyloxy)-4-hydroxy-5-methyl-3-phenethyl-6-((triethylsilyl)oxy)octan-2-one (81)

81 was obtained as a clear oil (11 mg, 15%) as a byproduct of the previous reaction.

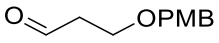
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.30 (m, 3H), 7.30-7.24 (m, 4H), 7.20-7.14 (t, *J*= 8.7 Hz, 3H), 4.51 (dd, *J*= 12.0 Hz, 1H), 4.42 (dd, *J*= 12.0 Hz, 1H), 4.19 (dd, *J*= 9.5, 1.3 Hz, 1H), 3.99 (td, *J*= 10.4, 1.6 Hz, 1H), 3.49 (m, 1H), 3.37 (dt, *J*= 9.6, 6.6 Hz, 1H), 3.31 (dd, *J*= 13.3, 3.8 Hz, 1H), 3.06 (td, *J*= 15.2, 4.2 Hz, 1H), 2.73 (dd, *J*= 13.2, 11.3 Hz, 1H), 1.95 (q, *J*= 6.5 Hz, 2H), 1.66 (s, 3H), 1.40 (m, 1H), 1.07 (d, *J*= 7.1 Hz, 3H), 0.98 (t, *J*= 8.0 Hz, 9H), 0.64 (q, *J*= 8.0 Hz, 6H).



3-((4-methoxybenzyl)oxy)propan-1-ol (S1)

To a flame dried round bottom flask was added NaH (1.40 g, 34.95 mmol) and THF (48 mL, 0.66 M). This solution was cooled to 0° C. 1,3-propanediol (2.3 mL, 31.77 mmol) was then delivered to the solution dropwise which was then stirred for 30 minutes. TBAI (1.17 g, 0.32 mmol) and 1-(bromomethyl)-4-methoxybenzene (5.75 g, 28.59 mmol) were then delivered to the mixture which was then warmed to room temperature and allowed to stir for 18 hours. The reaction was quenched with water and the aqueous layer was extracted with EtOAc (3x). The organic layers were combined, washed with brine, dried with Mg_2SO_4, filtered and the solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography (15% EtOAc in hexanes to 30% EtOAc in hexanes), and **S1** was isolated as a clear oil (4.3 g, 69%).

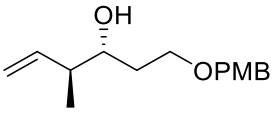
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J*= 8.5 Hz, 2H), 6.90 (d, *J*= 8.6 Hz, 2H), 4.48 (s, 2H), 3.82 (s, 3H), 3.80 (t, *J*= 5.7 Hz, 2H), 3.66 (t, *J*= 5.8 Hz, 2H), 1.88 (p, *J*= 5.7 Hz, 2H).



3-((4-methoxybenzyl)oxy)propanal (S2)

A solution of DMSO (2.61 mL, 36.69 mmol) in CH_2Cl_2 (38 mL, 0.2 M) was cooled to -78° C in a flame dried round bottom flask. Oxalyl chloride (1.44 mL, 16.81 mmol) was then delivered dropwise and the solution was allowed to stir at -78° C for 20 minutes. **S1** (1.5 g, 7.64 mmol) was then added to the solution and the reaction mixture was then allowed to stir at -78° C for 1.5 hours. Triethylamine (7.78 ml, 55.79 mmol) was then delivered to the reaction mixture dropwise at -78° C, and the mixture was allowed to slowly warm to room temperature. The reaction was then quenched with water, the organic layer was separated, and then the aqueous layer was extracted with CH_2Cl_2 (3x). The organic layers were then combined, washed with saturated $NaHCO_3$, 1 M HCl, then brine and dried with $MgSO_4$ and filtered. The solvent was then removed under reduced pressure. **S1** was obtained as a yellow oil (1.48 g, quant.) and used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.81 (t, *J*= 1.8 Hz, 1H), 7.27 (d, *J*= 8.6 Hz, 2H), 6.91 (d, *J*= 8.6 Hz, 2H), 4.49 (s, 2H), 3.83 (s, 3H), 3.81 (t, *J*= 6.0 Hz, 2H), 2.70 (td, *J*= 6.1, 1.8 Hz, 2H).

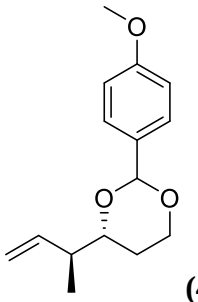


(3*R*,4*S*)-1-((4-methoxybenzyl)oxy)-4-methylhex-5-en-3-ol (S3)

To a flame dried round bottom flask were added 4 Å molecular sieves (3 g, 2 g/1 g **S2**), toluene (30 mL, 0.25 M) and a solution of *R,R*-diisopropyl tartrate (*E*)-crotylboronate (2.74 g, 9.17 mmol) in toluene (17 mL, 0.5 M). The mixture was allowed to stir at room temperature for 30 minutes then was cooled to -78° C. A solution of **S2** (1.48 g, 7.64 mmol) in toluene (3 mL, 2.5 M) was then added dropwise and the resulting reaction mixture was allowed to stir at -78° C for 4 hours. The reaction was then quenched at -78° C with a 2 M NaOH solution and the reaction mixture was allowed to warm to room temperature. The organic phase was separated, and the aqueous phase was extracted with Et_2O (3x). The organic layers were combined and washed with saturated

$NaHCO_3$ then brine, dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography (5% EtOAc in hexanes to 12% EtOAc in hexanes), and **S3** was isolated as a pale yellow oil (1.66 g, 87%).

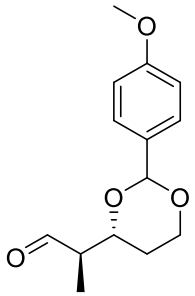
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, *J*= 8.6 Hz, 2H), 6.89 (d, *J*= 8.6 Hz, 2H), 5.83 (m, 1H), 5.09 (m, 2H), 4.47 (s, 2H), 3.82 (s, 3H), 3.75-3.61 (m, 3H), 2.25 (m, 1H), 1.75 (t, *J*= 6.3 Hz, 2H), 1.06 (d, *J*= 6.9 Hz, 3H).



(4*R*)-4-((*S*)-but-3-en-2-yl)-2-(4-methoxyphenyl)-1,3-dioxane (S4)

To a flame dried round bottom flask was added **S3** (250 mg, 1.00 mmol), CH_2Cl_2 (4 mL, 0.2 M), and 4 Å molecular sieves (250 mg, 1 g/1 g **S3**). This solution was cooled to 0° C then DDQ (238.1 mg, 1.05 mmol) was added in 3 portions over 5 minute intervals. The reaction mixture was allowed to stir at 0° C for 2 hours, then filtered through Celite®, washed with saturated $NaHCO_3$, then brine. The organic layer was dried with Mg_2SO_4, filtered, and the solvent was removed under reduced pressure. The crude mixture was purified by flash column chromatography (5% EtOAc in hexanes to 10% EtOAc in hexanes), and **S4** was obtained as a pale yellow oil (137 mg, 55%).

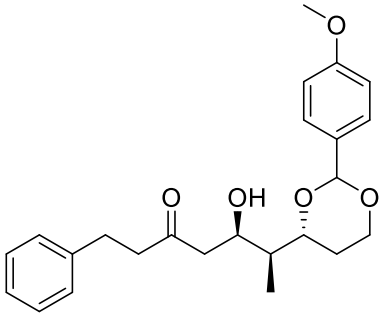
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, *J*= 8.8 Hz, 2H), 6.88 (d, *J*= 8.8 Hz, 2H), 5.92 (m, 1H), 5.46 (s, 1H), 5.07 (m, 2H), 4.26 (ddd, *J*= 11.4, 5.1, 1.2 Hz, 1H), 3.93 (td, *J*= 11.9, 2.5 Hz, 1H), 3.80 (s, 3H), 3.72 (ddd, *J*= 5.6, 2.3 Hz, 1H), 2.41 (m, 1H), 1.86 (ddt, *J*= 12.5, 12.3, 5.2 Hz, 1H), 1.43 (m, 1H), 1.09 (d, *J*= 6.9 Hz, 3H).



(2*R*)-2-((4*R*)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)propanal (S5)

To a flame dried round bottom flask was added **S4** (200 mg, 0.81 mmol) and a 4:1 mixture of THF:H_2O (3.2 mL:0.8 mL, 0.2 M). 4-methylmorpholine oxide (141.5 mg, 1.21 mmol) was then added to this solution followed by a 4% aqueous solution of OsO_4 (0.2 mL, 0.03 mmol). The resulting reaction mixture was allowed to stir at room temperature for 15 hours. $NaIO_4$ (206.6 mg, 0.97 mmol) was then added to the reaction mixture which was allowed to stir for 2 hours. The aqueous layer was then extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography (5% EtOAc in hexanes to 15% EtOAc in hexanes), and **S5** was isolated as a clear oil (167 mg, 83%).

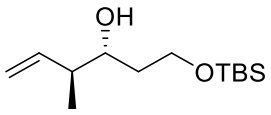
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.84 (d, *J*= 2.1 Hz, 1H), 7.38 (d, *J*= 8.8 Hz, 2H), 6.88 (d, *J*= 8.8 Hz, 2H), 5.49 (s, 1H), 4.30 (ddd, *J*= 11.5, 5.1, 1.3 Hz, 1H), 4.11 (ddd, *J*= 11.4, 7.2, 2.4 Hz, 1H), 3.98 (td, *J*= 11.9, 2.5 Hz, 1H), 3.80 (s, 3H), 2.63 (m, 1H), 1.92 (m, 1H), 1.57 (m, 1H), 1.14 (d, *J*= 7.2 Hz, 3H).



(5*R*,6*S*)-5-hydroxy-6-((4*R*)-2-(4-methoxyphenyl-1,3-dioxan-4-yl)-1-phenylheotan-3-one (S6)

A solution of **S5** (50 mg, 0.20 mmol) in CH_2Cl_2 (2 mL, 0.1 M) was added to a flame dried round bottom flask and cooled to -78° C. $BF_3{\cdot}OEt_2$ (25 µL, 0.20 mmol) was then added to this solution dropwise, which was then allowed to stir for 5 minutes. A solution of **77** (48.5 mg, 0.2 mmol) in CH_2Cl_2 (0.3 mL) was delivered dropwise to the reaction mixture over the course of 45 minutes. The reaction was allowed to stir for 1 hour at -78° C, then was quenched with saturated NH_4Cl and allowed to warm to room temperature. The resulting biphasic mixture was poured into water, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3x). The organic layers were combined, dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography (15% Et_2O in hexanes to 45% Et_2O in hexanes), and **S6** was isolated as a clear oil (41 mg, 51%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J*= 8.5 Hz, 2H), 7.30-7.25 (m, 2H), 7.20-7.13 (m, 3H), 6.88 (d, *J*= 8.6 Hz, 2H), 5.47 (s, 1H), 4.49 (m, 1H), 4.29 (m, 1H), 3.95 (td, *J*= 18.0, 1.9 Hz, 1H), 3.88 (ddd, *J*= 11.4, 7.4, 2.2 Hz, 1H), 3.80 (s, 3H), 2.93-2.87 (m, 2H), 2.81-2.75 (m, 2H), 2.69 (dd, *J*= 16.6, 9.7 Hz, 1H), 2.42 (dd, *J*= 16.6, 3.0 Hz, 1H), 1.88 (m, 1H), 1.66 (m, 1H), 1.57 (m, 1H), 0.93 (d, *J*= 7.1 Hz, 3H).



(3*R*,4*S*)-1-((*tert*-butyldimethylsilyl)oxy)-4-methylhex-5-en-3-ol (83)

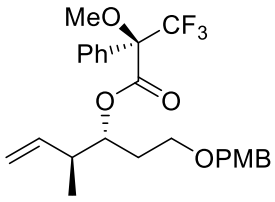
To a flame dried round bottom flask was added CuBr (58.8 mg, 0.41 mmol), NEt_3 (1.61 mL, 11.58 mmol), and n-Bu_4Br (132.2 mg, 0.41 mmol) in CH_2Cl_2 (25 mL). This solution was cooled to 0° C. In a separate flask *trans*-crotyl chloride (0.81 mL, 8.27 mmol), Cl_3SiH (1.00 mL, 9.93 mmol), and CH_2Cl_2 (18 mL) were combined then added to the cooled solution dropwise. The resulting mixture was allowed to stir at 0° C for 2 hours. **82** (2.40 g, 8.27 mmol) and DBU (3.72 mL, 24.82 mmol) in CH_2Cl_2 (18 mL) were then added to the mixture which was then allowed to reach room

temperature and stir for 1 hour. The reaction was then cooled to -78° C and **31** (1.48 g, 7.88 mmol) added slowly. The reaction mixture was then stirred for 16 hours at 0° C. The solvent was removed under reduced pressure and the crude mixture was suspended in Et_2O (15 mL) and allowed to stir for 20 minutes. The mixture was filtered then treated with n-Bu_4NF (1 M in THF, 9.40 mL) at -40° C and allowed to stir at this temperature for 1 hour before being treated with 1 M HCl (38 mL) and transferred to a separatory funnel. The organic layer was separated. The aqueous layer was extracted with Et_2O (3x). The organic layers were combined, washed with water then saturated $NaHCO_3$, dried with Mg_2SO_4, filtered through SiO_2, and the solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography (5% EtOAc in hexanes to 10% EtOAc in hexanes), and **83** was isolated as a pale yellow oil (1.31 g, 68%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (m, 1H), 5.07 (m, 2H), 3.89 (m, 1H), 3.81 (m, 1H), 3.69 (m, 1H), 2.24 (m, 1H), 1.63 (m, 2H), 1.04 (d, *J*= 6.9 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H).

^{13}C NMR 140.88, 115.26, 75.20, 62.93, 44.10, 35.69, 26.03, 18.31, 15.91, -5.36.

HRMS (ESI) *m/z* calcd. for $C_{13}H_{29}O_2Si$ $[M+H]^+$ 245.1932, found 245.1936.

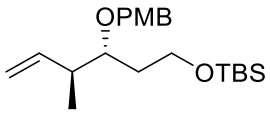


(3*R*,4*S*)-1-((4-methoxybenzyl)oxy)-4-methylhex-5-en-3-yl-(*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (S7)

To a flame dried 2-dram vial was added a solution of **S3** (10 mg, 0.04 mmol), made according to Leighton's protocol, and (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (29 mg, 0.12 mmol) in CH_2Cl_2 (0.65 mL, 0.064 M). To this solution was added DCC (25.6 mg, 0.12 mmol) then DMAP (15.1 mg, 0.12 mmol) and the resulting reaction mixture was allowed to stir at room

temperature for 16 hours. The crude reaction mixture was then filtered to remove any solids then purified by flash column chromatography (2% EtOAc in hexanes to 5% EtOAc in hexanes), and **S7** was isolated as a clear oil (17.2 mg, 92%, 95% ee).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (m, 2H), 7.38 (m, 3H), 7.23 (d, *J*= 8.6 Hz, 2H), 6.87 (d, *J*= 8.6 Hz, 2H), 5.72 (m, 1H), 5.28 (m, 1H), 5.06 (m, 2H), 4.35 (d, *J*= 11.4 Hz, 1H), 4.29 (d, *J*= 11.5 Hz, 1H), 3.80 (s, 3H), 3.53 (m , 3H), 3.30 (m, 2H), 2.53 (m, 1H), 1.83 (q, *J*= 6.5 Hz, 2H), 1.02 (d, *J*= 6.9 Hz, 3H).



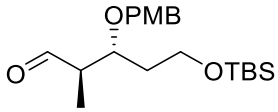
***tert*-butyl(((3*R*,4*S*)-3-((4-methoxybenzyl)oxy)-4-methylhex-5-en-1-yl)oxy)dimethylsilane (84)**

83 (700 mg, 2.86 mmol) and 4-methoxybenzyl-2,2,2-trichloroacetimidate (1.64 g, 5.81 mmol) were added to a flame dried round bottom flask in toluene (30 mL, 0.1 M). The resulting solution was cooled to 0° C then Sc(III)OTf (70 mg, 0.15 mmol) was delivered and the resulting reaction mixture was warmed to room temperature and stirred for 16 hours. The reaction was quenched with saturated NH_4Cl then diluted with EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc (3x). The organic layers were combined, washed with brine, dried with Mg_2SO_4, filtered, and the solvent was removed under reduced pressure. The crude mixture was purified by flash column chromatography (1% Et_2O in hexanes to 3% Et_2O in hexanes), and **84** was isolated as a pale yellow oil and carried forward with inseparable PMB impurities which can be separated after the following step.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J*= 8.6 Hz, 2H), 6.87 (d, *J*= 8.6 Hz, 2H), 5.81 (m, 1H), 5.04 (m, 2H), 4.52 (d, *J*= 11.0 Hz, 1H), 4.43 (d, *J*= 11.1 Hz, 1H), 3.80 (s, 3H), 3.68 (t, *J*= 6.4 Hz, 2H),

3.50 (m, 1H), 2.51 (m, 1H), 1.65 (q, *J*= 6.3 Hz, 2H), 1.03 (d, *J*= 6.9 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H).

HRMS (ESI) *m/z* calcd. for $C_{21}H_{37}O_3Si$ $[M+H]^+$ 365.2507, found 365.2515.



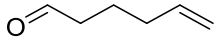
(2*R*,3*R*)-5-((*tert*-butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)oxy)-2-methylpentanal (85)

To a flame dried round bottom flask was added **84** (930 mg, 2.55 mmol) and a 4:1 mixture of THF:H_2O (10.2 mL:2.6 mL, 0.2 M). 4-methylmorpholine oxide (448.2 mg, 3.83 mmol) was then added to this solution followed by a 4% aqueous solution of OsO_4 (0.65 mL, 0.10 mmol). The resulting reaction mixture was allowed to stir at room temperature for 15 hours. $NaIO_4$ (654.7 mg, 3.061 mmol) was then added to the reaction mixture which was allowed to stir for 2 hours. The aqueous layer was then extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography (3% Et_2O in hexanes to 10% Et_2O in hexanes), and **85** was isolated as a clear oil (467 mg, 45% over 2 steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.71 (d, *J*= 2.0 Hz, 1H), 7.24 (d, *J*= 8.6 Hz, 2H), 6.87 (d, *J*= 8.6 Hz, 2H), 4.51 (d, *J*= 11.1 Hz, 1H), 4.45 (d, *J*= 11.1 Hz, 1H), 3.92 (ddd, *J*= 7.5, 5.7, 4.4 Hz, 1H), 3.80 (s, 3H), 3.73 (m, 2H), 2.70 (m, 1H), 1.79 (m, 1H), 1.71 (m, 1H), 1.10 (d, *J*= 7.0 Hz, 3H), 0.89 (s, 9H), 0.05 (d, *J*= 2.7 Hz, 6H).

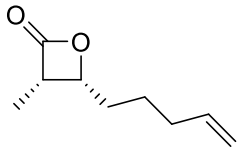
^{13}C NMR 204.51, 159.42, 129.54, 113.98, 71.88, 66.00, 59.25, 55.43, 49.99, 34.84, 26.06, 18.38, 15.42, 10.03, -5.21.

HRMS (ESI) *m/z* calcd. for $C_{20}H_{35}O_4Si$ $[M+H]^+$ 367.2300, found 367.2307.



hex-5-enal (86)

A solution of DMSO (11.45 mL, 161.24 mmol) in CH_2Cl_2 (100 mL, 0.5 M) was cooled to -78° C in a flame dried round bottom flask. Oxalyl chloride (7.02 mL, 81.87 mmol) was then delivered dropwise and the solution was allowed to stir at -78° C for 20 minutes. 5-hexen-1-ol (5 g, 49.92 mmol) was then added to the solution and the reaction mixture was then allowed to stir at -78° C for 1.5 hours. Triethylamine (40.40 ml, 290.04 mmol) was then delivered to the reaction mixture dropwise at -78° C, and the mixture was allowed to slowly warm to room temperature. The reaction was then quenched with water, the organic layer was separated, and then the aqueous layer was extracted with CH_2Cl_2 (3x). The organic layers were then combined, washed with saturated $NaHCO_3$, 1 M HCl, then brine and dried with $MgSO_4$ and filtered. **86** was used directly in the following reaction using the solvent from these extractions due to volatility of the aldehyde. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.73 (t, *J*= 1.6 Hz, 1H), 5.75 (ddt, *J*= 17.1, 10.2, 6.7 Hz, 1H), 5.00 (m, 2H), 2.41 (td, *J*= 7.3, 1.6 Hz, 2H), 2.06 (m, 2H), 1.70 (p, *J*= 7.3 Hz, 2H).



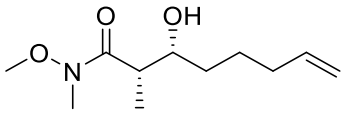
(3*S*,4*R*)-3-methyl-4-(pent-4-en-1-yl)oxetan-2-one (87)

To a flame dried round bottom flask were added $LiClO_4$ (5.31 g, 49.92 mmol) and trimethylsilyl quinidine (0.5 M in Et_2O, 9.98 mL) in Et_2O (83 mL, 0.6 M). This mixture was then cooled to -78° C and **86** (4.90 g, 49.92 mmol) in CH_2Cl_2 (150 mL, 0.2 M) was delivered dropwise followed by iPr_2NEt (21.74 mL, 124.80 mmol). A solution of propionyl chloride (8.72 mL, 99.84 mmol) in CH_2Cl_2 (90 mL, 1.1 M) was then added to the solution via syringe pump over the course of 3 hours then the reaction mixture was stirred at -78° C for 16 hours. The reaction was diluted with Et_2O, filtered, and the solvent was removed under reduced pressure. The crude mixture was purified by flash column chromatography (10% Et_2O in hexanes to 25% Et_2O in hexanes), and **87** was isolated as a pale yellow oil (4.22 g, 56%).

^{1}H NMR (300 MHz, $CDCl_3$) 5.79 (m, 1H), 5.02 (m, 2H), 4.55 (ddd, *J*= 9.0, 6.4, 4.5 Hz, 1H), 3.74 (dq, *J*= 7.7, 6.5 Hz, 1H), 2.14 (m, 2H), 1.80-1.46 (m, 4H), 1.27 (d, *J*= 7.8 Hz, 3H).

^{13}C NMR 172.64, 137.78, 115.34, 95.50, 47.29, 33.22, 29.36, 24.61, 8.10.

HRMS (ESI) *m/z* calcd. for $C_9H_{14}O_2$ $[M+H]^+$ 155.1067, found 155.1068.



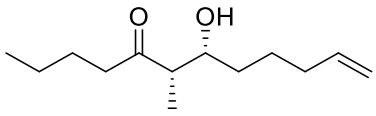
(2*S*,3*R*)-3-hydroxy-*N*-methoxy-*N*,2-dimethyloct-7-enamide (88)

A solution of N,O-dimethylhydroxylamine·HCl (1.27 g, 12.97 mmol) in CH_2Cl_2 (24 mL, 0.5 M) was added to a flame dried round bottom flask and cooled to 0° C. To this solution was added Me_2AlCl (0.9 M in heptanes, 14.4 mL) dropwise over 30 minutes then the resulting mixture was allowed to warm to room temperature and stir for 1 hour. The reaction was the cooled to -40° C and a solution of **87** (1 g, 6.49 mmol) in CH_2Cl_2 (8 mL, 0.8 M) was added dropwise then the resulting reaction mixture was allowed to stir for 3 hours. The reaction was then quenched with saturated potassium sodium tartrate and the resulting biphasic mixture was allowed to warm to room temperature and stir until two distinct layers could be seen. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3x). The organic layers were combined, dried with Mg_2SO_4, filtered, and the solvent was removed under reduced pressure. The crude mixture was purified by flash column chromatography (10% EtOAc in hexanes to 40% EtOAc in hexanes), and **88** was isolated as a clear oil (1.08 g, 78%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (ddt, *J*= 17.0, 10.3, 6.7 Hz, 1H), 4.99 (m, 2H), 3.86 (ddd, *J*= 7.9, 4.5, 2.5 Hz, 1H), 3.70 (s, 3H), 3.20 (s, 3H), 2.87 (m, 1H), 2.09 (m, 2H), 1.66-1.52 (m, 3H), 1.50-1.29 (m, 3H), 1.17 (d, *J*= 7.1 Hz, 3H).

^{13}C NMR 207.2, 138.7, 114.6, 71.4, 61.3, 33.7, 33.5, 25.4, 13.2, 10.2, 7.7.

HRMS (ESI) *m/z* calcd. for $C_{11}H_{22}NO_3$ $[M+H]^+$ 216.1595, found 216.1594.



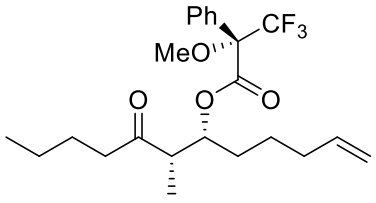
(6*S*,7*R*)-7-hydroxy-6-methyldodec-11-en-5-one (89)

A solution of **88** (1.18 g, 5.48 mmol) in THF (16 mL, 0.35 M) was added to a flame dried round bottom flask and cooled to -78° C. To this solution was added n-BuLi (2.5 M in hexanes, 6.6 mL) dropwise and the resulting reaction mixture was allowed to stir for 1 hour. The reaction was quenched with saturated NH_4Cl then allowed to warm to room temperature. The aqueous layer was extracted with Et_2O (3x). The organic layers were combined, dried with Mg_2SO_4, filtered, and the solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography (5% EtOAc in hexanes to 15% EtOAc in hexanes), and **89** was obtained as a clear oil (1.05 g, 90%).

^{1}H NMR (300 MHz, $CDCl_3$) 5.79 (ddt, *J*= 17.2, 10.1, 6.6 Hz, 1H), 4.98 (m, 2H), 3.89 (m, 1H), 2.56 (dq, *J*= 7.2, 3.0 Hz, 1H), 2.48 (m, 2H), 2.07 (m, 2H), 1.64-1.45 (m, 4H), 1.39-1.22 (m, 4H), 1.12 (d, *J*= 7.3 Hz, 3H), 0.90 (t, *J*= 7.4 Hz, 3H).

^{13}C NMR 216.65, 138.70, 114.84, 70.98, 50.02, 41.84, 33.74, 33.56, 25.77, 25.45, 22.47, 14.00, 9.98.

HRMS (ESI) *m/z* calcd. for $C_{13}H_{25}O_2$ $[M+H]^+$ 213.1850, found 213.1852.

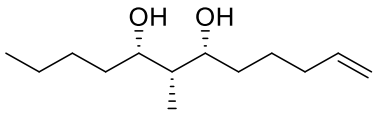


(6*R*,7*S*)-7-methyl-8-oxododec-1-en-6-yl-(*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (S8)

To a flame dried 2-dram vial was added a solution of **89** (10 mg, 0.05 mmol), made according to Leighton's protocol, and (*S*)-(-)-α-methoxy-α-trifluoromethylphenylacetic acid (34 mg, 0.15 mmol) in CH_2Cl_2 (0.73 mL, 0.064 M). To this solution was added DCC (30 mg, 0.15 mmol) then

DMAP (18 mg, 0.15 mmol) and the resulting reaction mixture was allowed to stir at room temperature for 16 hours. The crude reaction mixture was then filtered to remove any solids then purified by flash column chromatography (2% EtOAc in hexanes to 5% EtOAc in hexanes), and **S8** was isolated as a clear oil (18.1 mg, 90%, 94% ee).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (m, 2H), 7.38 (m, 3H), 5.72 (ddt, *J*= 17.0, 10.3, 6.7 Hz, 1H), 5.40 (dt, *J*= 7.8, 5.0 Hz, 1H), 4.97 (m, 2H), 3.53 (s, 3H), 2.72 (dq, *J*= 7.0, 5.5 Hz, 1H), 2.33 (m, 3H), 2.04 (m, 2H), 1.56 (m, 6H), 1.46 (m, 2H), 1.02 (d, *J*= 7.09 Hz, 3H), 0.87 (t, *J*= 7.3 Hz, 3H).



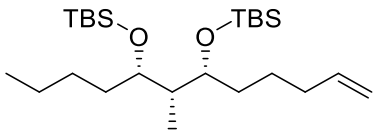
(5*S*,6*R*,7*R*)-6-methyldodec-11-ene-5,7-diol (90)

To a flame dried round bottom flask was added **89** (1.05 g, 4.95 mmol) in a 4:1 mixture of THF:MeOH (40 mL:10 mL, 0.1 M). This solution was cooled to -78° C then Et_2BOMe (0.81 mL, 6.18 mmol) was added dropwise, and the resulting mixture was allowed to stir for 1 hour. $NaBH_4$ (280.6 mg, 7.42 mmol) was then added to the mixture in one portion and the reaction was allowed to continue stirring for 3 hours. The reaction was quenched with a 30% aqueous solution of H_2O_2 and allowed to slowly warm to room temperature. The resulting mixture was diluted with water and the aqueous layer was extracted with EtOAc (3x). The organic layers were combined, washed with saturated $NaHCO_3$, Na_2SO_3, and brine, then dried with Mg_2SO_4 and filtered. The solvent was removed under reduced pressure. The crude oil was purified by flash column chromatography (5% EtOAc in hexanes to 20% EtOAc in hexanes), and **90** was isolated as a clear oil (955 mg, 90%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (ddt, *J*= 17.0, 10.2, 6.8 Hz, 1H), 5.00 (m, 2H), 3.85 (m, 2H), 2.09 (q, *J*= 6.8 Hz, 2H), 1.60-1.23 (m, 13H), 0.91 (t, *J*= 6.8 Hz, 3H), 0.89 (d, *J*= 7.2 Hz, 3H).

^{13}C NMR 138.75, 114.80, 77.50, 77.31, 40.38, 35.20, 34.90, 33.82, 28.37, 25.51, 22.84, 14.17, 4.25.

HRMS (ESI) *m/z* calcd. for $C_{13}H_{22}$ $[M\text{-}2\ OH]^+$ 179.1795, found 179.1793.



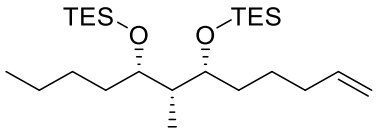
(5*S*,6*R*,7*R*)-5-butyl-2,2,3,3,6,9,9,10,10-nonamethyl-7-(pent-4-en-1-yl)-4,8-dioxa-3,9-disilaundecane (91)

A solution of **90** (60 mg, 0.28 mmol) in CH_2Cl_2 (2.8 mL, 0.1 M) was added to a flame dried round bottom flask and cooled to 0° C. To this solution was added 2,6-lutidine (0.26 mL, 2.24 mmol) followed by dropwise addition of TBSOTf (0.25 mL, 1.12 mmol). The reaction mixture was warmed to room temperature and allowed to stir for 2 hours. The reaction was then quenched with saturated $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3x). The organic layers were combined, washed with saturated NH_4Cl then brine, dried with Mg_2SO_4, filtered, and the solvent was removed under reduced pressure. The crude mixture was purified by flash column chromatography (100% hexanes to 2% EtOAc in hexanes), and **91** was isolated as a clear oil (116 mg, 94%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (ddt, *J*= 16.9, 10.3, 6.7 Hz, 1H), 4.97 (m, 2H), 3.67 (dq, *J*= 5.3, 2.0 Hz, 2H), 2.02 (q, *J*= 7.1 Hz, 2H), 1.59 (m, 1H), 1.52-1.42 (m, 4H), 1.41-1.22 (m, 6H), 0.87 (m, 21 H), 0.83 (d, *J*= 6.8 Hz, 3H), 0.02 (d, *J*= 2.9 Hz, 12H).

^{13}C NMR 139.05, 114.60, 72.95, 72.92, 40.64, 34.67, 34.30, 34.21, 27.07, 26.13, 24.10, 23.22, 18.32, 14.27, 9.77, -3.69, -3.71, -4.30.

HRMS (ESI) *m/z* calcd. for $C_{25}H_{55}O_2Si_2$ $[M+H]^+$ 443.3736, found 443.3742.



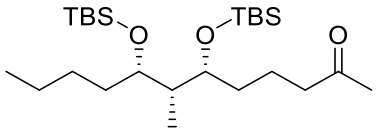
(5*S*,6*R*,7*R*)-5-butyl-3,3,9,9-tetraethyl-6-methyl-7-(pent-4-en-1-yl)-4,8-dioxa-3,9-disilaundecane (S9)

A solution of **90** (430 mg, 2.00 mmol) in CH_2Cl_2 (15 mL, 0.13 M) was added to a flame dried round bottom flask and cooled to 0° C. To this solution was added 2,6-lutidine (1.87 mL, 16.05 mmol) followed by dropwise addition of TESOTf (1.81 mL, 8.02 mmol). The reaction mixture was warmed to room temperature and allowed to stir for 2 hours. The reaction was then quenched with saturated $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3x). The organic layers were combined, washed with saturated NH_4Cl then brine, dried with Mg_2SO_4, filtered, and the solvent was removed under reduced pressure. The crude mixture was purified by flash column chromatography (100% hexanes to 2% EtOAc in hexanes), and **S9** was isolated as a clear oil (850 mg, 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (ddt, *J*= 17.0, 10.3, 6.7 Hz, 1H), 4.98 (m, 2H), 3.71 (m, 2H), 2.04 (q, *J*= 7.3 Hz, 2H), 1.58 (m, 1H), 1.54-1.45 (m, 4H), 1.43-1.34 (m, 2H), 1.31-1.19 (m, 4H), 0.95 (t, *J*= 8.1 Hz, 18H), 0.86 (d, *J*= 6.8 Hz, 3H), 0.59 (t, *J*= 8.1 Hz, 12H), 0.52 (t, *J*= 8.0 Hz, 3H).

^{13}C NMR 139.04, 114.58, 73.29, 73.24, 41.20, 34.86, 34.53, 34.22, 27.37, 24.42, 23.22, 14.27, 9.71, 7.18, 6.94, 6.58, 5.58, 5.57

HRMS (ESI) *m/z* calcd. for $C_{25}H_{55}O_2Si_2$ $[M+H]^+$ 443.3736, found 443.3737.



(6*R*,7*R*,8*S*)-6,8-bis((*tert*-butyldimethylsilyl)oxy)-7-methyldodecan-2-one (92)

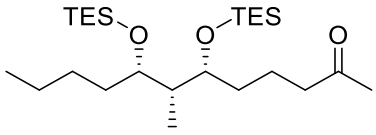
A solution of $PdCl_2$ (56 mg, 0.316 mmol) in a 10:1 mixture of DMF:H_2O (15.8 mL:1.58 mL, 0.09 M) was added to a flame dried round bottom flask. CuCl (156.5 mg, 0.32 mmol) was then added

to the solution, and the reaction flask was backfilled with O_2 gas. The mixture was allowed to stir for 1 hour then **91** (700 mg, 1.58 mmol) was delivered and the resulting reaction mixture was allowed to stir for 16 hours. The reactiom was then quenched with saturated NH_4Cl and filtered through Celite®. The aqueous layer was extracted with EtOAc (3x). The organic layers were combined, washed with water, dried with Mg_2SO_4, filtered, and the solvent was removed under reduced pressure. The crude mixture was purified by flash column chromatography (100% hexanes to 5% EtOAc in hexanes), and **92** was isolated as a clear oil (486 mg, 67%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.69 (m, 2H), 2.41 (td, *J*= 7.0, 2.9 Hz, 2H), 2.13 (s, 3H), 1.66-1.56 (m, 2H), 1.53-1.42 (m, 5H), 1.34-1.21 (m, 4H), 0.92-0.86 (m, 21H), 0.84 (d, *J*= 3.1 Hz, 3H), 0.03 (m, 12H).

^{13}C NMR 208.94, 72.91, 72.76, 44.21, 40.62, 34.78, 34.27, 29.93, 27.21, 26.11, 23.22, 19.19, 18.31, 18.29, 14.26, 9.75, -3.64, -3.78, -4.31.

HRMS (ESI) *m/z* calcd. for $C_{25}H_{55}O_3Si_2$ $[M+H]^+$ 443.3685, found 459.3686.



(6*R*,7*R*,8*S*)-6,8-bis((triethylsilyl)oxy)dodecan-2-one (S10)

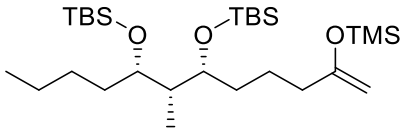
A solution of $PdCl_2$ (70.9 mg, 0.40 mmol) in a 10:1 mixture of DMF:H_2O (20 mL:2 mL, 0.09 M) was added to a flame dried round bottom flask. CuCl (197 mg, 1.99 mmol) was then added to the solution, and the reaction flask was backfilled with O_2 gas. The mixture was allowed to stir for 1 hour then **S9** (880 mg, 1.99 mmol) was delivered and the resulting reaction mixture was allowed to stir for 16 hours. The reactiom was then quenched with saturated NH_4Cl and filtered through Celite®. The aqueous layer was extracted with EtOAc (3x). The organic layers were combined, washed with water, dried with Mg_2SO_4, filtered, and the solvent was removed under reduced

pressure. The crude mixture was purified by flash column chromatography (100% hexanes to 5% EtOAc in hexanes), and **S10** was isolated as a clear oil (468 mg, 51%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (m, 2H), 2.41 (td, *J*= 7.1, 2.2 Hz, 2H), 2.13 (s, 3H), 1.61-1.55 (m, 3H), 1.52-1.44 (m, 4H), 1.33-1.19 (m, 4H), 0.95 (t, *J*= 8.0 Hz, 18H), 0.90 (t, *J*= 6.9 Hz, 3H), 0.86 (d, *J*= 6.9 Hz, 3H), 0.58 (m, *J*= 8.0, 3.2 Hz, 12H)

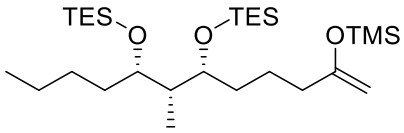
^{13}C NMR 208.95, 73.24, 73.07, 44.22, 41.18, 34.92, 34.49, 29.91, 27.46, 23.21, 19.60, 14.26, 9.72, 7.17, 5.58, 5.51.

HRMS (ESI) *m/z* calcd. for $C_{25}H_{55}O_3Si_2$ $[M+H]^+$ 459.3685, found 459.3687.



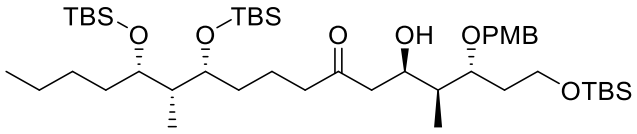
(8*R*,9*R*,10*S*)-10-butyl-8-((*tert*-butyldimethylsilyl)oxy)2,2,9,12,12,13,13-heptamethyl-4-methylene-3,11-dioxa-2-12-disilatetradecane (93)

A solution of $(iPr)_2NH$ (0.10 mL, 0.74 mmol) in THF (1.2 mL, 0.5 M) was added to a flame dried round bottom flask and cooled to 0° C. n-BuLi (2.5 M in hexanes, 0.27 mL) was then added to the solution drop wise which was then allowed to stir for 15 minutes before being cooled to -78° C. **92** (280 mg, 0.61 mmol) was then added to the solution dropwise, using minimal THF to quantitate the transfer. The mixture was allowed to stir for 10 minutes at -78° C then TMSCl (0.09 mL, 0.68 mmol) was delivered dropwise. The reaction mixture was stirred for 10 minutes before being quenched with pH 7 buffer at -78° C. The aqueous layer was then extracted with Et_2O (3x). The organic layers were combined, dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude mixture was then placed under vacuum for 1 hour, and **93** was obtained as a clear oil (321 mg, 99%) and was used crude in the following step.



(8*R*,9*R*,10*S*)-10-butyl-12,12-diethyl-2,2,9-trimethyl-4-methylene-8-((triethylsilyl)oxy)-3,11-dioxa-2,12-disilatetradecane (S11)

A solution of $(iPr)_2NH$ (34 µL mL, 0.24 mmol) in THF (0.4 mL, 0.5 M) was added to a flame dried round bottom flask and cooled to 0° C. n-BuLi (2.5 M in hexanes, 90 µL) was then added to the solution drop wise which was then allowed to stir for 15 minutes before being cooled to -78° C. **S10** (91.8 mg, 0.20 mmol) was then added to the solution dropwise, using minimal THF to quantitate the transfer. The mixture was allowed to stir for 10 minutes at -78° C then TMSCl (28 µL, 0.22 mmol) was delivered dropwise. The reaction mixture was stirred for 10 minutes before being quenched with pH 7 buffer at -78° C. The aqueous layer was then extracted with Et_2O (3x). The organic layers were combined, dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude mixture was then placed under vacuum for 1 hour, and **S11** was obtained as a clear oil (105 mg, 99%) and used crude in the following step.



(5*S*,6*R*,7*R*,13*R*,14*S*,15*R*)-5-butyl-7-((*tert*-butyldimethylsilyl)oxy)-13-hydroxy-15-((4-methoxybenzyl)oxy)2,2,3,3,6,14,19,19,20,20-decamethyl-4,18-dioxa-3,19-disilahenicosan-11-one (94)

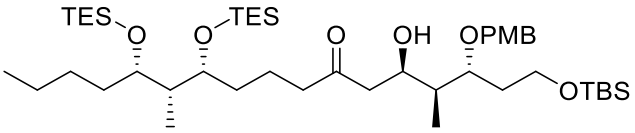
A solution of **85** (36.7 mg, 0.10 mmol) in CH_2Cl_2 (1.0 mL, 0.1 M) was added to a flame dried round bottom flask and cooled to -78° C. $BF_3{\cdot}OEt_2$ (12 µL, 0.10 mmol) was then added to this solution dropwise, which was then allowed to stir for 5 minutes. A solution of **93** (58.4 mg, 0.11 mmol) in CH_2Cl_2 (0.3 mL) was delivered dropwise to the reaction mixture over the course of 45 minutes. The reaction was allowed to stir for 1 hour at -78° C, then was quenched with saturated NH_4Cl and allowed to warm to room temperature. The resulting biphasic mixture was poured into

water, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3x). The organic layers were combined, dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography (10% Et_2O in hexanes to 25% Et_2O in hexanes), and **94** was isolated as a clear oil (44 mg, 51%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J*= 8.6 Hz, 2H), 6.86 (d, *J*= 8.6 Hz, 2H), 4.53 (d, *J*= 10.8 Hz, 1H), 4.43 (d, *J*= 10.8 Hz, 1H), 4.39 (dt, *J*= 9.1, 3.2 Hz, 1H), 3.79 (s, 3H), 3.75-3.62 (m, 5H), 2.62 (dd, *J*= 16.4, 8.9 Hz, 1H), 2.46-2.32 (m, 3H), 1.84 (m, 2H), 1.66 (m, 1H), 1.63-1.57 (m, 2H), 1.56-1.41 (m, 7H), 1.33-1.24 (m, 5H), 0.97 (d, *J*= 7.0 Hz, 3H), 0.88 (m, 27H), 0.84 (d, *J*= 6.8 Hz, 3H), 0.03 (m, 18H).

^{13}C NMR 210.79, 159.42, 130.62, 129.68, 114.00, 79.86, 72.89, 72.80, 72.52, 67.53, 59.74, 55.41, 47.34, 44.16, 40.60, 40.37, 34.97, 34.74, 34.33, 29.84, 27.13, 26.11, 23.23, 18.90, 18.40, 18.30, 18.29, 14.26, 11.08, 9.74, -3.66, -3.74, -4.29, -5.19.

HRMS (ESI) *m/z* calcd. for $C_{45}H_{89}O_7Si_3$ $[M+H]^+$ 825.5911, found 825.6108.



(7*R*,8*S*,9*R*,15*R*,16*R*,17*S*)-17-butyl-19,19-diethyl-9-hydroxy-7-((4-methoxybenzyl)oxy)2,2,3,3,8,16-hexamethyl-15-((triethylsilyl)oxy)-4,18-dioxa-3,19-disilahenicosan-11-one (S12)

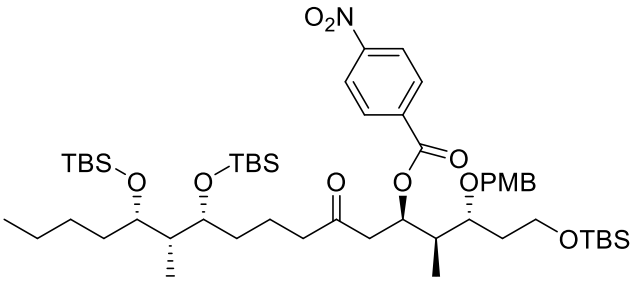
A solution of **85** (50 mg, 0.14 mmol) in CH_2Cl_2 (1.4 mL, 0.1 M) was added to a flame dried round bottom flask and cooled to -78° C. $BF_3{\cdot}Oet_2$ (17 µL, 0.14 mmol) was then added to this solution dropwise, which was then allowed to stir for 5 minutes. A solution of **S11** (79.4 mg, 0.15 mmol) in CH_2Cl_2 (0.5 mL) was delivered dropwise to the reaction mixture over the course of 45 minutes. The reaction was allowed to stir for 1 hour at -78° C, then was quenched with saturated NH_4Cl and allowed to warm to room temperature. The resulting biphasic mixture was poured into water,

the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3x). The organic layers were combined, dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography (5% Et_2O in hexanes to 20% Et_2O in hexanes), and **S12** was isolated as a clear oil (85 mg, 69%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J*= 8.6 Hz, 2H), 6.86 (d, *J*= 8.6 Hz, 2H), 4.53 (d, *J*= 10.9 Hz, 1H), 4.43 (d, *J*= 10.9 Hz, 1H), 4.39 (dt, *J*= 8.7, 3.1 Hz, 1H), 3.79 (s, 3H), 3.76-3.67 (m, 4H), 3.65 (m, 1H), 3.35 (bs, 1H), 2.62 (dd, *J*= 16.4, 8.9 Hz, 1H), 2.42 (m, 2H), 2.34 (dd, *J*= 21.3, 3.5 Hz, 1H), 1.83 (m, 2H), 1.67 (m, 1H), 1.52-1.44 (m, 4H), 1.33-1.19 (m, 7H), 0.98-0.92 (m, 21H), 0.91-0.87 (m, 12H), 0.85 (d, *J*= 6.8 Hz, 3H), 0.57 (q, *J*= 8.0 Hz, 12H), 0.05 (d, *J*= 2.6 Hz, 6H).

^{13}C NMR 210.77, 159.43, 130.63, 129.66, 114.00, 79.85, 73.23, 73.11, 72.52, 67.53, 59.75, 55.40, 47.33, 44.17, 41.21, 40.38, 34.98, 34.91, 34.55, 30.47, 29.84, 27.41, 26.08, 23.22, 19.31, 18.39, 14.25, 11.04, 9.71, 7.17, 5.58, 5.52.

HRMS (ESI) *m/z* calcd. for $C_{45}H_{89}O_7Si_3$ $[M+H]^+$ 825.5911, found 825.5934.



(7*R*,8*R*,9*R*,15*R*,16*R*,17*S*)-17-butyl-15-((*tert*-butyldimethylsilyl)oxy)-7-((4-methoxybenzyl)oxy)2,2,3,3,8,16,19,19,20,20-decamethyl-11-oxo-4,18-dioxa-3,19-disilahenicosan-9-yl 4-nitrobenzoate (95)

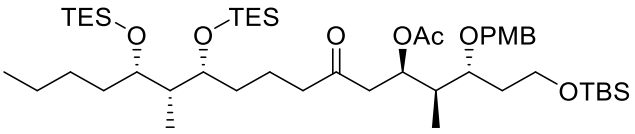
A solution of **94** (39 mg, 0.05 mmol) and *p*-nitrobenzoic acid (15.7 mg, 0.09 mmol) in CH_2Cl_2 (1.5 mL, 0.03 M) was added to a flame dried 2-dram vial and cooled to 0° C. To this solution DCC (19.4 mg, 0.09 mmol) and DMAP (3.4 mg, 0.03 mmol) were added. The reaction mixture was warmed to room temperature and allowed to stir for 3 hours. The reaction was then filtered through

Celite® and washed with saturate NH_4Cl and brine. The organic layer was separated, dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography (5% Et_2O in hexanes to 15% Et_2O in hexanes), and **95** was isolated as a clear oil (44 mg, 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J*= 8.9 Hz, 2H), 8.06 (d, *J*= 8.9 Hz, 2H), 7.19 (d, *J*= 8.6 Hz, 2H), 6.75 (d, *J*= 8.6 Hz, 2H), 5.81 (ddd, *J*= 6.9, 5.9, 3.6 Hz, 1H), 4.42 (d, *J*= 10.7 Hz, 1H), 4.33 (d, *J*= 10.7 Hz, 1H), 3.74 (s, 3H), 3.72 (td, *J*= 6.3, 1.7 Hz, 1H), 3.69-3.63 (m, 3H), 3.55 (td, *J*= 6.5, 4.3 Hz, 1H), 2.88 (dd, *J*= 16.3, 7.2 Hz, 1H), 2.73 (dd, *J*= 16.1, 5.7 Hz, 1H), 2.42 (m, 2H), 2.11 (td, *J*= 6.7, 3.5 Hz, 1H), 1.86-1.73 (m, 3H), 1.53-1.40 (m, 7H), 1.31-1.18 (m, 6H), 1.07 (d, *J*= 7.0 Hz, 3H), 0.86 (s, 27H), 0.81 (d, *J*= 7.0 Hz, 3H), 0.06 (m, 18H).

^{13}C NMR 207.15, 164.05, 159.26, 150.52, 135.96, 130.77, 129.76, 123.53, 113.78, 72.87, 72.76, 71.94, 71.68, 59.42, 55.29, 45.37, 43.69, 40.63, 39.78, 34.71, 34.33, 34.18, 27.10, 26.10, 23.21, 18.96, 18.36, 18.29, 18.27, 14.25, 10.80, 9.73, 1.17, -3.66, -3.74, -4.29, -4.32, -5.20, -5.21.

HRMS (ESI) *m/z* calcd. for $C_{52}H_{93}NO_{11}Si_3$ [M+H_2O] 991.6056, found 991.6296.



(7*R*,8*R*,9*R*,15*R*,16*R*,17*S*)-17-butyl-19,19-diethyl-7-((4-methoxybenzyl)oxy)2,2,3,3,8,16-hexamethyl-11-oxo-15-((triethylsilyl)oxy)-4,18-dioxa-3,19-disilahenicosan-9-yl acetate (101)

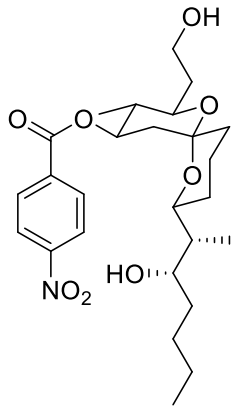
To a flame round bottom flask was added **S12** (85 mg, 0.10 mmol) in CH_2Cl_2 (1 mL, 0.1 M). To this solution was added NEt_3 (0.09 mL, 0.62 mmol) and DMAP (1.2 mg, 0.01 mmol). Acetic anhydride (0.04 µL, 0.41 mmol) was then delivered to the mixture which was then allowed to stir at room temperature for 2 hours. The reaction was quenched with saturated $NaHCO_3$, and the organic and aqueous layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3x).

The organic layers were combined, dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography (5% Et_2O in hexanes to 15% Et_2O in hexanes), and **101** was isolated as a clear oil (75 mg, 86%).

^{1}H NMR (500 MHz, C_6D_6) δ 7.27 (d, *J*= 8.6 Hz, 2H), 6.86 (d, *J*= 8.6 Hz, 2H), 5.47 (ddd, *J*= 7.3, 5.2, 4.7 Hz, 1H), 4.40 (s, 2H), 3.79 (s, 3H), 3.73-3.67 (m, 4H), 3.49 (m, 1H), 2.70 (dd, *J*= 15.7, 7.5 Hz, 1H), 2.61 (dd, *J*= 15.7, 5.4 Hz, 1H), 2.44-2.35 (m, 2H), 2.01 (m, 1H), 1.98 (s, 3H), 1.76-1.66 (m, 2H), 1.61-1.54 (m, 2H), 1.51-1.44 (m, 6H), 1.32-1.26 (m, 3H), 0.97-0.92 (m, 21H), 0.89-0.87 (m, 12H), 0.85 (d, *J*= 6.8 Hz, 3H), 0.57 (q, *J*= 7.8 Hz, 12H), 0.04 (d, *J*= 1 Hz, 6H).

^{13}C NMR 207.61, 170.45, 159.29, 130.94, 129.73, 113.90, 76.61, 73.20, 73.13, 71.45, 70.75, 59.52, 55.39, 45.46, 43.62, 41.18, 39.42, 34.88, 34.57, 34.09, 27.35, 26.08, 23.23, 21.16, 19.31, 18.38, 14.26, 10.20, 9.70, 7.18, 5.56, 5.51, -5.19, -5.22.

HRMS (ESI) *m/z* calcd. for $C_{47}H_{90}NaO8Si3$ $[M+Na]^+$ 889.5863, found 889.5846.



(2*R*,3*R*,4*R*,6*S*,8*R*)-2-(2-hydroxyethyl)-8-((2*R*,3*S*)-3-hydroxyheptan-2-yl)-3-methyl-1,7-dioxaspiro[5.5]undecane-4-yl 4-nitrobenzoate (97)

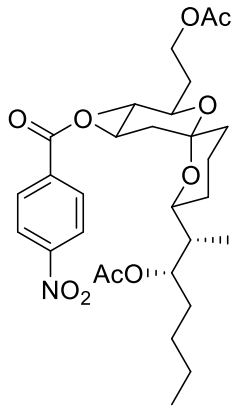
A solution of **95** (20 mg, 0.02 mmol) in a 10:1 mixture of CH_2Cl_2:pH 7 buffer (0.9 mL:0.09 mL, 0.02 M) was added to a flame dried 2-dram vial and cooled to 0° C. DDQ (7.3 mg, 0.03 mmol) was then added to the solution which was allowed to warm to room temperature and stirred for 1.5 hours. The reaction was quenched with $NaHCO_3$ and the organic layer was separated. The

aqueous layer was extracted with EtOAc (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$, filtered, and solvent was removed under reduced pressure to obtain **94** which was used directly in the following reaction. The crude mixture was dissolved in MeOH (1 mL, 0.02 M) and CSA (1 mg, $4x10^{-3}$ mmol) was added. The reaction was allowed to stir for 10 minutes. The solvent was then removed under reduced pressure and the crude mixture was purified by flash column chromatography (30% Et_2O in hexanes to 60% Et_2O in hexanes), and **95** was obtained as a 2:1 mixture of epimers (6 mg, 58%). The mixture was able to be purified by preparatory TLC (80% MTBE in hexanes) to deliver **97** as a clear oil (3 mg, 29%).

^{1}H NMR (500 MHz, C_6D_6) 7.78 (d, *J*= 8.9 Hz, 2H), 7.71 (d, *J*= 8.9 Hz, 2H), 5.18 (td, *J*= 16.7, 4.4 Hz, 1H), 4.01 (m, 2H), 3.81-3.73 (m, 3H), 2.81 (dd, *J*= 12.7, 4.4 Hz, 1H), 2.26 (m, 1H), 1.76-1.51 (m, 8H), 1.47-1.41 (m, 4H), 1.40-1.32 (m, 5H), 1.25-1.17 (m, 3H), 1.12 (d, *J*= 7.1 Hz, 3H), 0.78 (d, *J*= 6.5 Hz, 3H)

^{13}C NMR 164.34, 150.81, 135.48, 130.47, 123.60, 99.19, 78.12, 74.64, 74.58, 60.62, 60.60, 42.55, 40.84, 35.76, 35.53, 35.40, 34.65, 29.01, 28.21, 23.20, 20.08, 14.42, 13.08, 7.30.

HRMS (ESI) *m/z* calcd. for $C_{26}H_{40}NO_8$ $[M+H]^+$ 494.2749, found 494.2752.



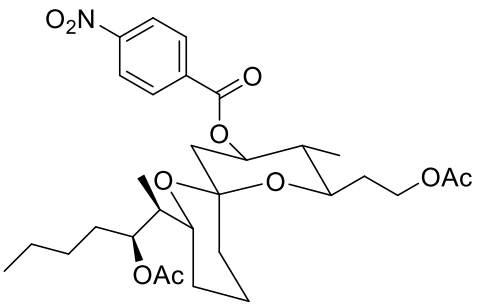
(2*R*,3*R*,4*R*,6*S*,8*R*)-2-(acetoxyethyl)-8-((2*S*,3*S*)-3-acetoxyheptan-2-yl)-3-methyl-1,7-dioxaspiro[5.5]undecane-4-yl 4-nitrobenzoate (98)

A solution **97** (1.5 mg, $3x10^{-3}$ mmol) in CH_2Cl_2 (0.3 mL, 0.01 M) was added to a flame dried 2-dram vial. NEt_3 (7 µL, 0.05 mmol) and DMAP (0.05 mg, $4x10^{-4}$ mmol) were then added to the resulting solution before delivering acetic anhydride (3 µL, 0.03 mmol) dropwise. The reaction mixture was allowed to stir for 3 hours. The solvent was removed under reduced pressure and the crude reaction mixture was purified by flash column chromatography (5% Et_2O in hexanes to 20% Et_2O in hexanes) and **98** was obtained as a clear oil (1.7 mg, 95%).

^{1}H NMR (500 MHz, C_6D_6) δ 7.75 (d, *J*= 9.0 Hz, 2H), 7.71 (d, *J*= 9.0 Hz, 2H), 5.33 (ddd, *J*= 8.5, 4.6, 4.0 Hz, 1H), 5.10 (td, *J*= 16.2, 4.5 Hz, 1H), 4.43 (m, 2H), 4.12 (ddd, *J*= 10.2, 9.2, 2.5 Hz, 1H), 3.63 (ddd, *J*= 11.2, 7.0, 1.9 Hz, 1H), 2.83 (dd, *J*= 12.7, 4.4 Hz, 1H), 2.04 (m, 1H), 2.00 (s, 3H), 1.77 (s, 3H), 1.76-1.71 (m, 3H), 1.69-1.62 (m, 3H), 1.56 (dd, *J*= 13.6, 5.3 Hz, 1H), 1.52-1.44 (m, 3H), 1.34-1.28 (m, 7H), 1.26 (d, *J*= 6.9 Hz, 3H), 1.19-1.15 (m, 2H), 0.83 (d, *J*= 6.5 Hz, 3H).

^{13}C NMR 170.34, 170.16, 164.32, 150.74, 135.50, 130.40, 123.57, 98.72, 75.17, 74.27, 73.89, 71.40, 61.30, 43.13, 40.72, 35.52, 34.43, 32.70, 32.41, 28.86, 28.60, 22.98, 20.88, 20.63, 20.27, 14.34, 13.07, 10.29

HRMS (ESI) *m/z* calcd. for $C_{30}H_{44}O_{10}$ $[M+H]^+$ 578.2960, found 578.2955.



(2*R*,3*R*,4*R*,6*R*,8*R*)-2-(acetoxyethyl)-8-((2*S*,3*S*)-3-acetoxyheptan-2-yl)-3-methyl-1,7-dioxaspiro[5.5]undecane-4-yl 4-nitrobenzoate (100)

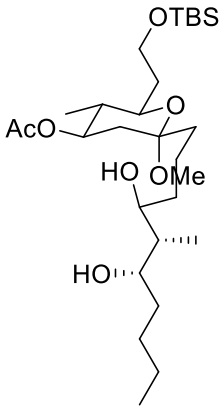
A solution of *epi*-**97** (1.5 mg, $3x10^{-3}$ mmol) in CH_2Cl_2 (0.3 mL, 0.01 M) was added to a flame dried 2-dram vial. NEt_3 (7 µL, 0.05 mmol) and DMAP (0.05 mg, $4x10^{-4}$ mmol) were then added to the resulting solution before delivering acetic anhydride (3 µL, 0.03 mmol) dropwise. The

reaction mixture was allowed to stir for 3 hours. The solvent was removed under reduced pressure and the crude reaction mixture was purified by flash column chromatography (5% Et_2O in hexanes to 20% Et_2O in hexanes) and **100** was obtained as a clear oil (1.5 mg, 87%).

^{1}H NMR (500 MHz, C_6D_6) δ 7.76 (d, *J*= 9.0 Hz, 2H), 7.72 (d, *J*= 9.0 Hz, 2H), 5.35 (ddd, *J*= 7.0, 5.6, 5.4 Hz, 1H), 4.92 (td, *J*= 11.0, 4.9 Hz, 1H), 4.33 (dd, *J*= 7.6, 5.8 Hz, 2H), 4.12 (ddd, *J*= 11.8, 4.7, 1.9 Hz, 1H), 2.95 (td, *J*= 9.9, 2.4 Hz, 1H), 2.16 (dd, *J*= 12.2, 4.9 Hz, 1H), 1.86 (s, 3H), 1.74 (s, 3H), 1.72-1.64 (m, 4H), 1.64-1.56 (m, 2H), 1.54-1.43 (m, 4H), 1.33-1.26 (m, 7H), 1.24-1.19 (m, 2H), 1.10 (d, *J*= 7.1 Hz, 3H), 1.03 (dd, *J*= 13.5, 4.2 Hz, 1H), 0.65 (d, *J*= 6.6 Hz, 3H).

^{13}C NMR 170.09, 164.20, 150.82, 135.39, 130.59, 123.55, 97.60, 74.94, 74.73, 72.13, 71.56, 61.28, 42.56, 41.69, 41.33, 33.00, 32.12, 30.21, 29.47, 28.51, 28.02, 23.02, 20.89, 20.55, 18.85, 14.20, 12.83, 10.21

HRMS (ESI) *m/z* calcd. for $C_{30}H_{44}NO10$ $[M+H]^+$ 578.2960, found 578.2958.

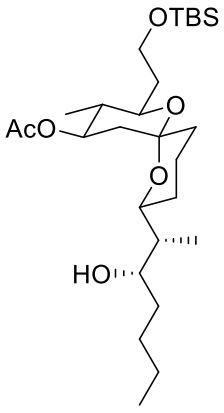


(2*S*,4*R*,5*R*,6*R*)-6-(-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-((5*R*,6*S*)-4,6-dihydroxy-5-methyldecyl)-2-methoxy-5-methyltetrathydro-2*H*-pyran-4-yl acetate (102)

A solution of **101** (10 mg, 0.01 mmol) in a 9:1 mixture of CH_2Cl_2:pH 7 buffer (0.9 mL:0.1 mL, 0.01 M) was added to a flame dried 2-dram vial and cooled to 0° C. DDQ (3.9 mg, 0.02 mmol) was then added to the solution which was allowed to warm to room temperature and stirred for 1.5 hours. The reaction was quenched with saturated $NaHCO_3$, the organic layer was separated, and

the aqueous layer was extracted with CH_2Cl_2 (3x). The organic layers were combined, dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude mixture was then dissolved in a 9:1 mixture of CH_2Cl_2:MeOH (0.9 mL:0.1 mL, 0.01 M) and PPTS (2.9 mg, 0.01 mmol) was delivered to the solution which was then stirred for 15 minutes before being quenched with saturated $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (5x). The organic layers were combined, dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude mixture was then purified by flash column chromatography (20% Et_2O in hexanes to 45% Et_2O in hexanes) and **102** was obtained as a clear oil (4.3 mg, 70%) which was carried on immediately to the next step.

^{1}H NMR δ (500 MHz, C_6D_6) δ 5.31 (m, 1H), 3.93 (dt, *J*= 9.1, 5.8 Hz, 1H), 3.82 (ddd, *J*= 9.8, 6.8, 4.3 Hz, 1H), 3.64 (m, 3H), 3.14 (s, 3H), 2.49 (dd, *J*= 12.1, 4.9 Hz, 1H), 1.92 (m, 1H), 1.77 (td, *J*= 13.1, 3.7 Hz, 1H), 1.71 (s, 3H), 1.65-1.51 (m, 4H), 1.49-1.44 (m, 2H), 1.39-1.37 (m, 2H), 1.34-1.16 (m, 12H), 0.99 (s, 9H), 0.89 (d, *J*= 6.9 Hz, 3H), 0.84 (d, *J*= 6.4 Hz, 3H), 0.08 (d, *J*= 1.4 Hz, 6H).

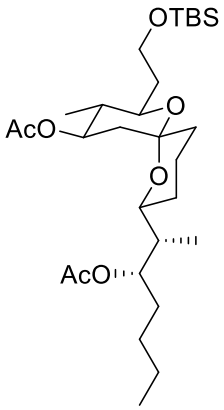


(2*R*,3*R*,4*R*,6*S*,8*R*)-2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-8-((2*R*,3*S*)-3-hydroxyheptan-2-yl)-3-methyl-1,7-dioxaspiro[5.5]undecane-4-yl acetate (S13)

A solution of **102** (4 mg, $8x10^{-3}$ mmol) in CH_2Cl_2 (0.8 mL, 0.01 M) was added to a flame dried 2-dram vial. To this solution was added PPTS (2 mg, $8x10^{-3}$ mmol). The reaction was stirred for

1.5 hours then the solvent was removed under reduced pressure and the crude mixture was purified by flash column chromatography (5% Et_2O in hexanes to 15% Et_2O in hexanes), and **S13** was successfully separated from *epi*-**S13** as a clear oil (2.8 mg, 70%).

^{1}H NMR δ (500 MHz, C_6D_6) 5.03 (td, 1H), 4.07 (m, 1H), 4.00 (td, 1H), 3.91 (dt, 1H), 3.86-3.79 (m, 2H), 2.87 (dd, 1H), 2.44 (bs, 1H), 1.98 (m, 1H), 1.63-1.50 (m, 5H), 1.46-1.39 (m, 4H), 1.37-1.25 (m, 7H), 1.14-1.09 (m, 6H), 1.02 (s, 9H), 0.91 (d, 3H), 0.13 (d, 6H).



(2*S*,3*S*)-2-((2*R*,6*S*,8*R*,9*R*,10*R*)-10-acetoxy-8-(2-((*tert*-butyldimethylsilyl) oxy)ethyl)-9-methyl-1,7-dioxaspiro[5.5]undecane-2-yl)heptan-3-yl acetate (S14)

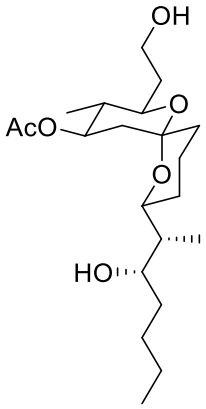
A solution of **S13** (2 mg, $4x10^{-3}$ mmol) in CH_2Cl_2 (0.4 mL, 0.01 M) was added to a flame dried 2-dram vial. NEt_3 (3.5 µL, 0.02 mmol) and DMAP (0.05 mg, $4x10^{-4}$ mmol) were then added to the resulting solution before delivering acetic anhydride (2 µL, 0.02 mmol) dropwise. The reaction mixture was allowed to stir for 3 hours. The solvent was removed under reduced pressure and the crude reaction mixture was purified by flash column chromatography (5% Et_2O in hexanes to 15% Et_2O in hexanes) and **S14** was obtained as a clear oil (2 mg, 93%).

^{1}H NMR (500 MHz, C_6D_6) 5.30 (ddd, *J*= 8.4, 5.2, 2.8 Hz, 1H), 4.94 (td, *J*= 10.9, 4.2 Hz, 1H), 4.18 (td, *J*= 9.9, 2.2 Hz, 1H), 3.95 (ddd, *J*= 9.7, 8.5, 5.6 Hz, 1H), 3.86 (ddd, *J*= 9.7, 6.6, 4.3 Hz, 1H), 3.60 (m, 1H), 2.85 (dd, *J*= 12.6, 4.3 Hz, 1H), 2.06-1.97 (m, 4H), 1.94 (m, 1H), 1.81-1.71 (m, 2H),

1.67 (s, 3H), 1.65-1.57 (m, 3H), 1.57-1.46 (m, 4H), 1.34 (d, *J*= 6.8 Hz, 3H), 1.32-1.24 (m, 6H), 1.12 (t, *J*= 7.0 Hz, 3H), 1.03 (s, 9H), 0.91 (d, *J*= 6.5 Hz, 3H), 0.13 (d, *J*= 8.6 Hz, 6H).

^{13}C NMR 170.47, 170.03, 98.72, 74.37, 73.49, 73.34, 71.42, 59.95, 43.40, 41.02, 36.93, 35.86, 34.44, 32.57, 29.28, 28.57, 26.28, 22.88, 20.87, 20.76, 20.61, 18.58, 14.27, 13.34, 10.37, -5.08.

HRMS (ESI) *m/z* calcd. for $C_{29}H_{55}O_7$ $[M+H]^+$ 543.3712, found 543.3697.



(2*R*,3*R*,4*R*,6*S*,8*R*)-2-(2-hydroxyethyl)-8-((2*R*,3*S*)-3-hydroxyheptan-2-yl)-3-methyl-1,7-dioxaspiro[5.5]undecane-4-yl acetate (103)

A solution of **101** (10 mg, 0.01 mmol) in a 4:1 mixture of CH_2Cl_2:MeOH (0.8 mL:0.2 mL, 0.01 M) was added to a flame dried 2-dam vial and cooled to 0° C. To this solution was added DDQ (4 mg, 0.02 mmol). The reaction mixture was allowed to warm to room temperature and stir for 5 hours. The reaction was then quenched with saturated $NaHCO_3$, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3x). The organic layers were combined, dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude mixture was purified by flash column chromatography (20% Et_2O in hexanes to 70% Et_2O in hexanes), and **103** was obtained as a yellow oil (4.2 mg, 91%) containing a 3:1 mixture of spirocycles, epimeric at the spirocenter.

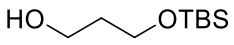
^{1}H NMR (500 MHz, C_6D_6) 4.96 (td, *J*= 16.5, 4.3 Hz, 1H), 3.99 (ddd, *J*= 8.2, 4.8, 2.0 Hz, 1H), 3.95 (td, *J*= 9.7, 2.7 Hz, 1H), 3.77-3.69 (m, 3H), 2.77 (dd, *J*= 12.8, 4.3 Hz, 1H), 1.70 (s, 3H), 1.67-1.63 (m, 2H), 1.58-1.50 (m, 5H), 1.43-1.33 (m, 13H), 1.08 (d, *J*= 7.1 Hz, 3H), 0.77 (d, *J*= 6.5 Hz, 3H).

^{13}C NMR 169.7, 98.9, 77.7, 74.7, 74.3, 72.2, 60.5, 42.0, 40.4, 35.4, 35.0, 34.9, 34.2, 28.6, 27.8, 22.8, 20.3, 19.8, 14.1, 12.7, 6.7.

HRMS (ESI) *m/z* calcd. for $C_{21}H_{39}O_6$ $[M+H]^+$ 387.2741, found 387.2746.

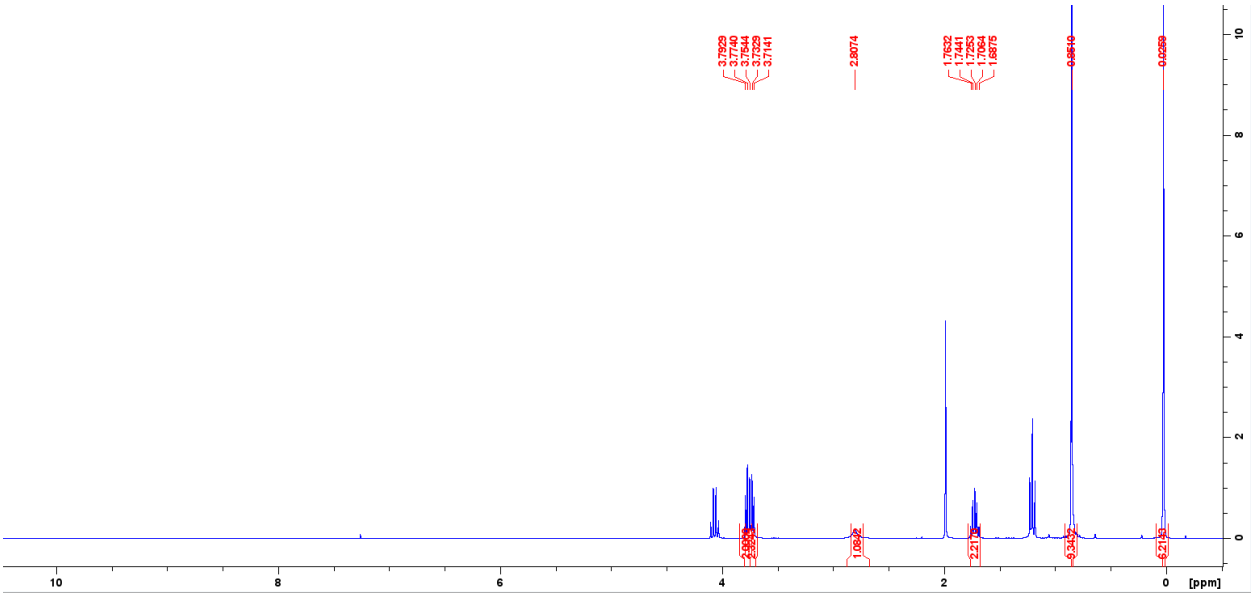
Appendix B

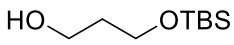
NMR Spectra



33

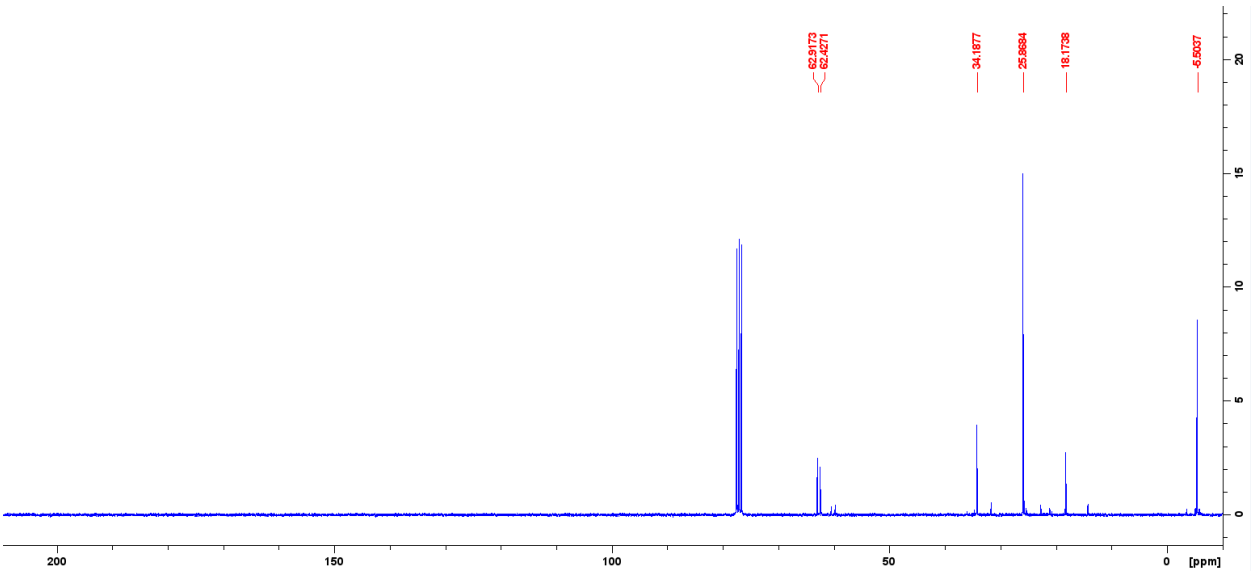
^{1}H NMR (500 MHz, $CDCl_3$)

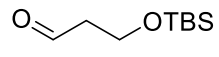




33

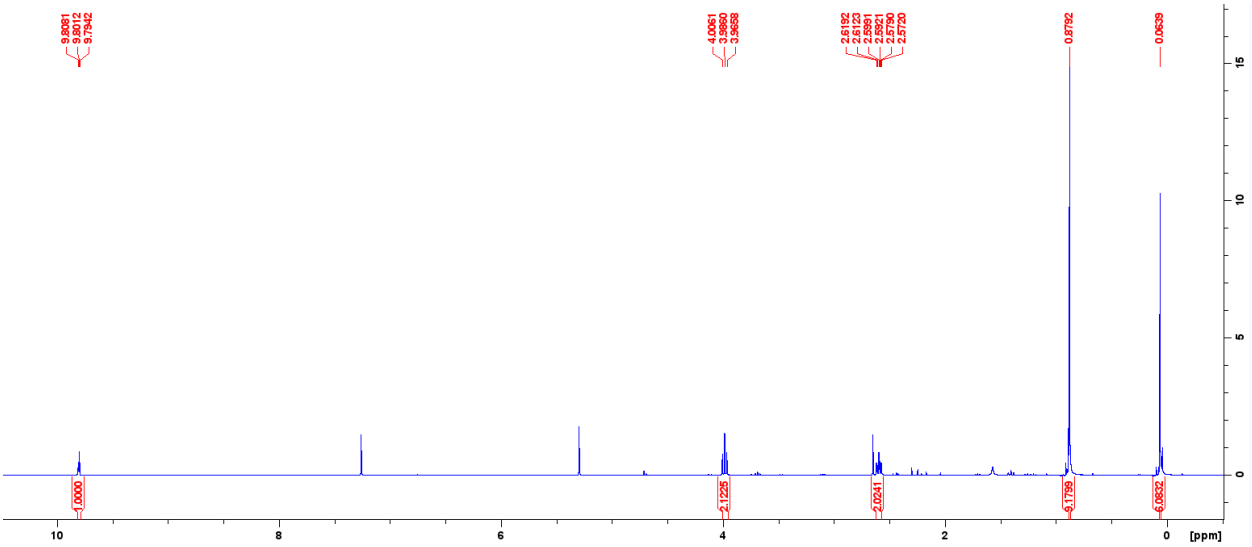
^{13}C NMR (500 MHz, $CDCl_3$)

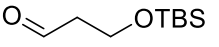




31

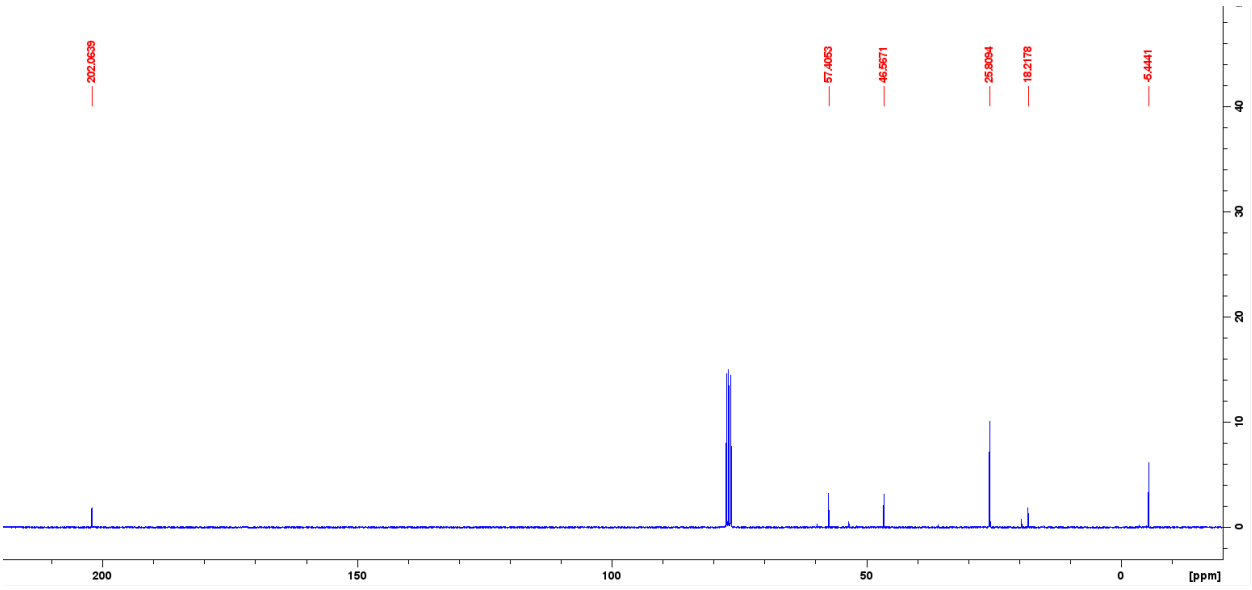
^{1}H NMR (300 MHz, $CDCl_3$)

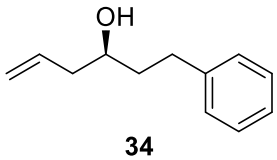




31

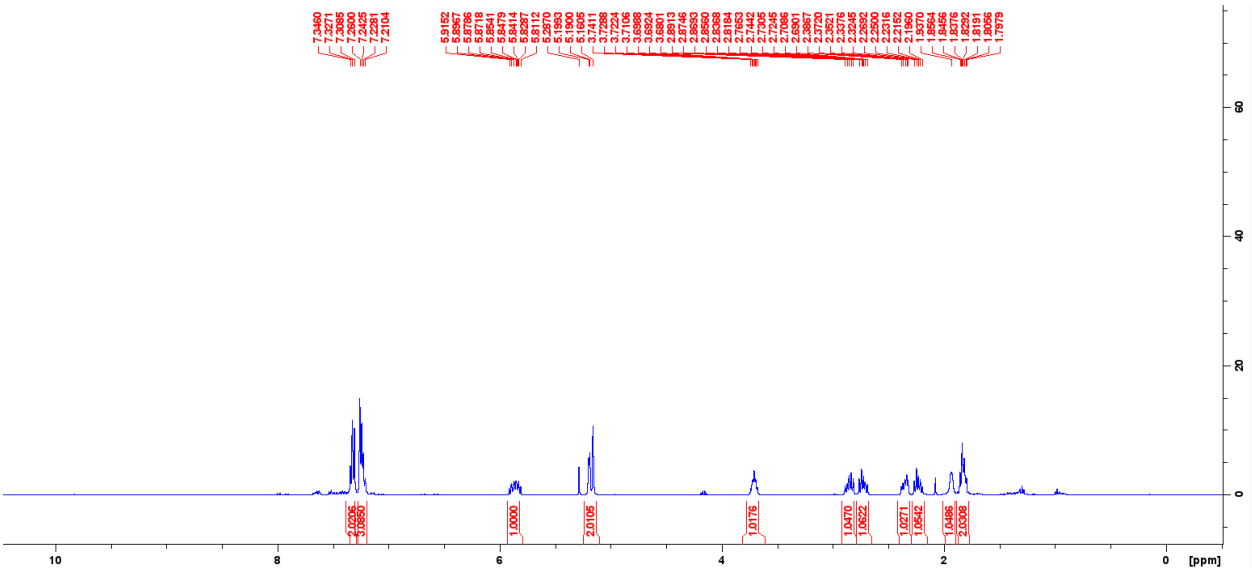
^{13}C NMR (300 MHz, $CDCl_3$)

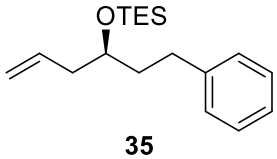




34

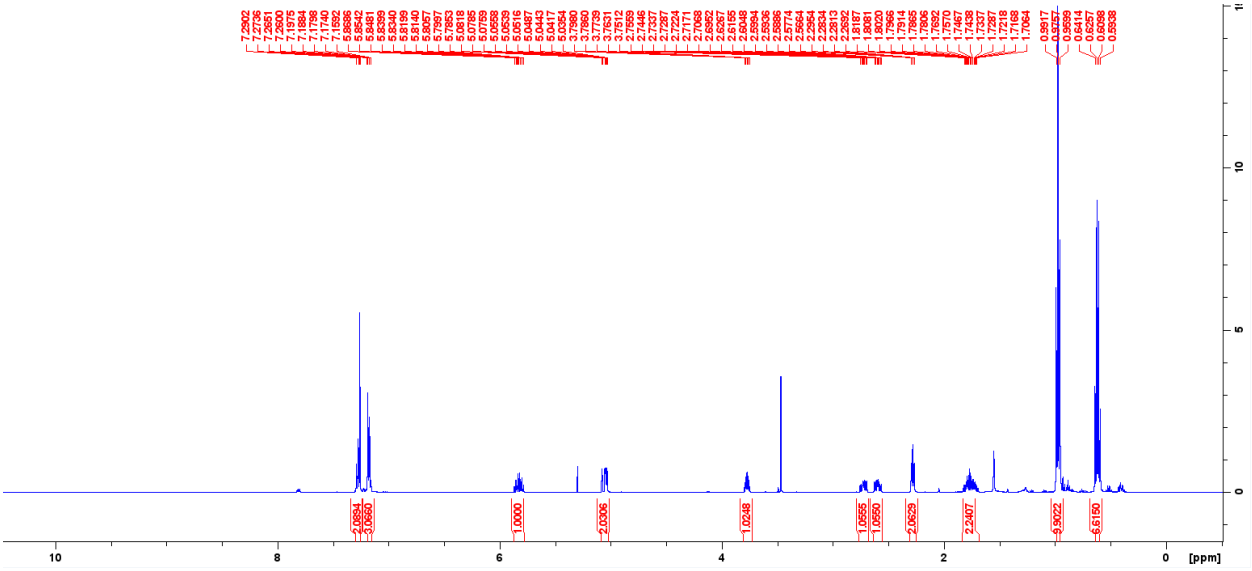
^{1}H NMR (400 MHz, $CDCl_3$)

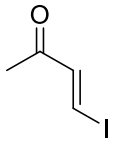




35

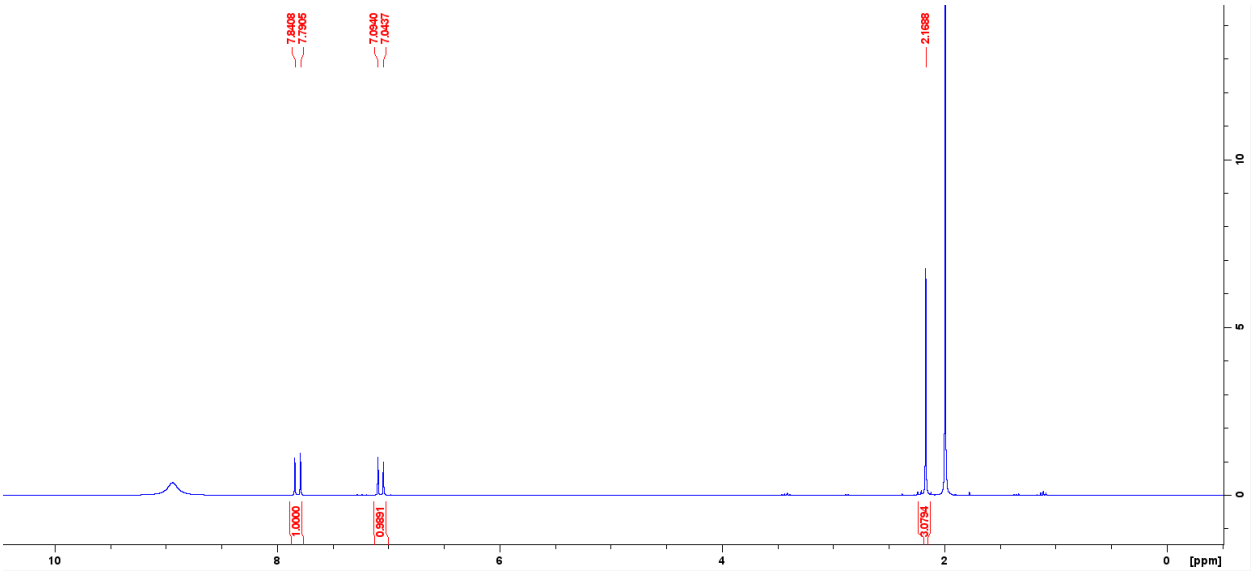
^{1}H NMR (500 MHz, $CDCl_3$)

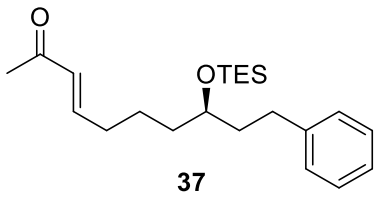




36

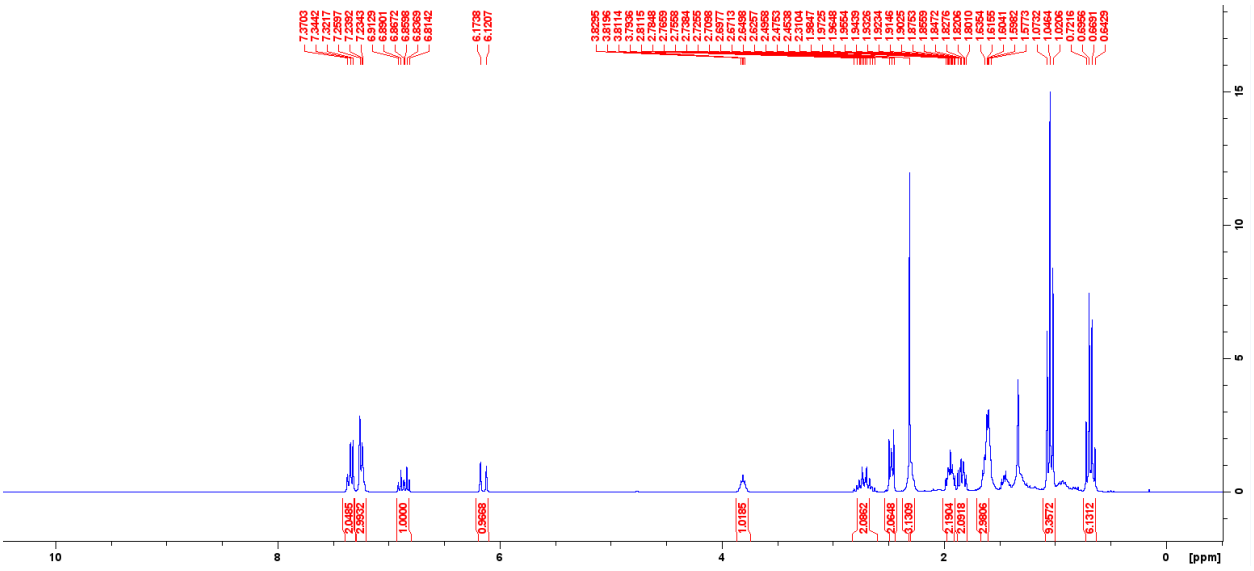
^{1}H NMR (500 MHz, $CDCl_3$)

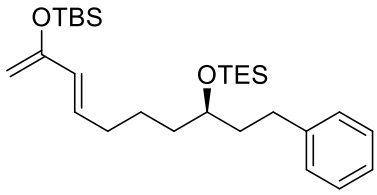




37

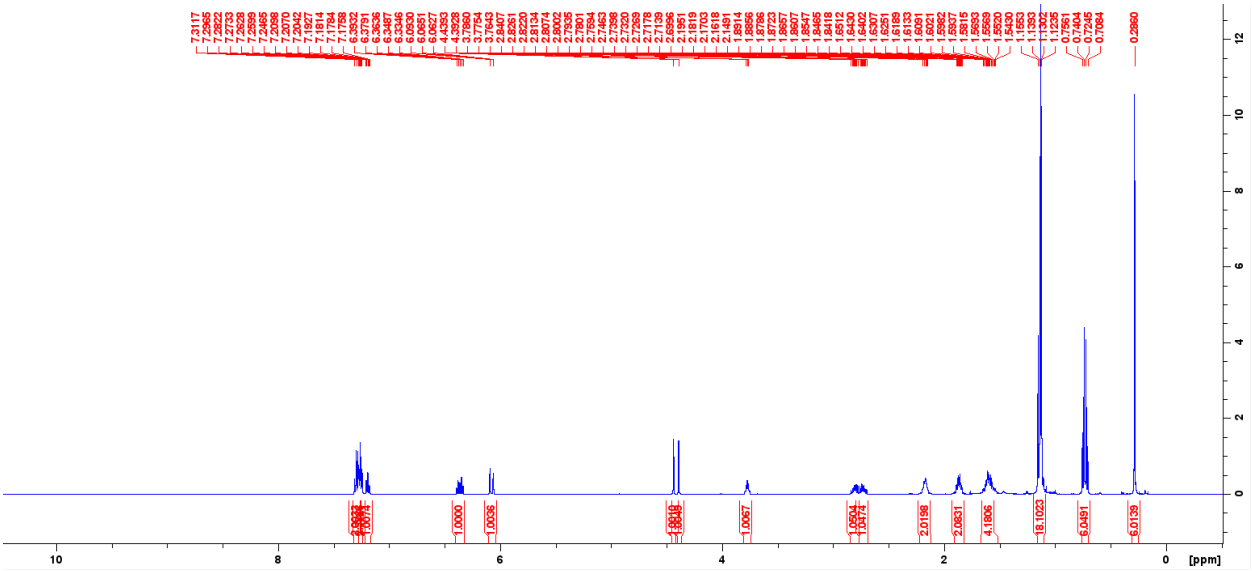
^{1}H NMR (300 MHz, $CDCl_3$)

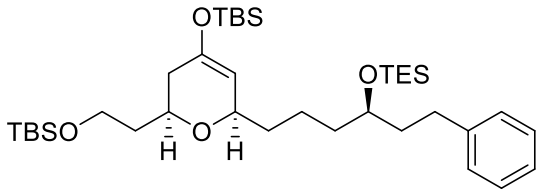




32

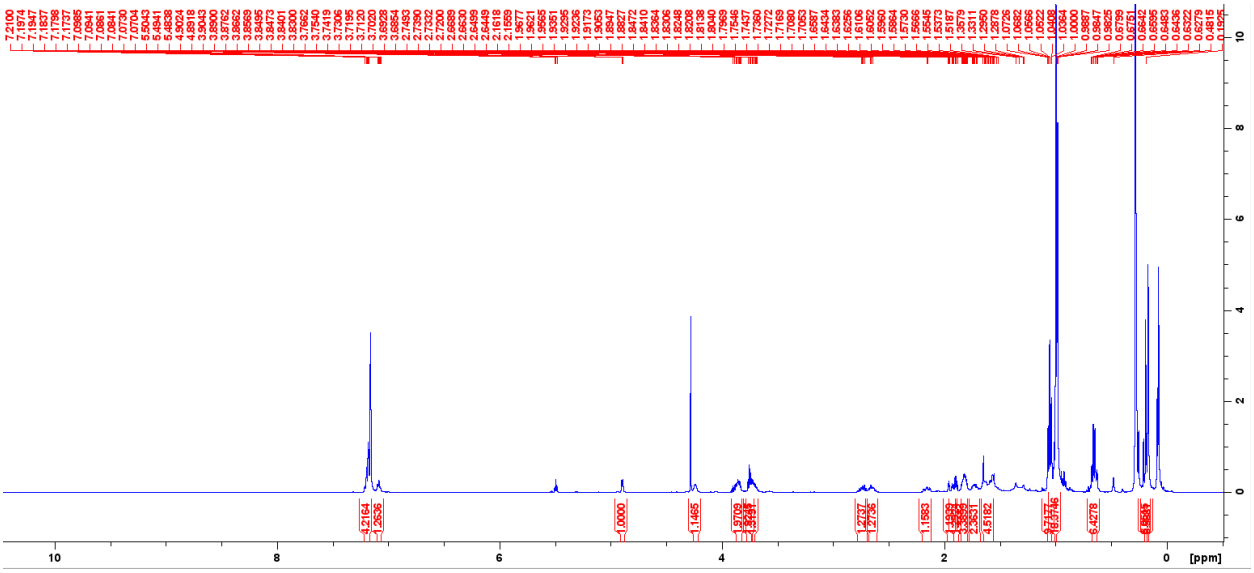
^{1}H NMR (500 MHz, $CDCl_3$)

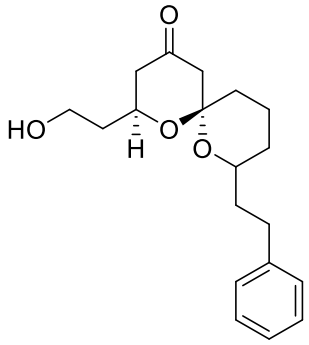




40

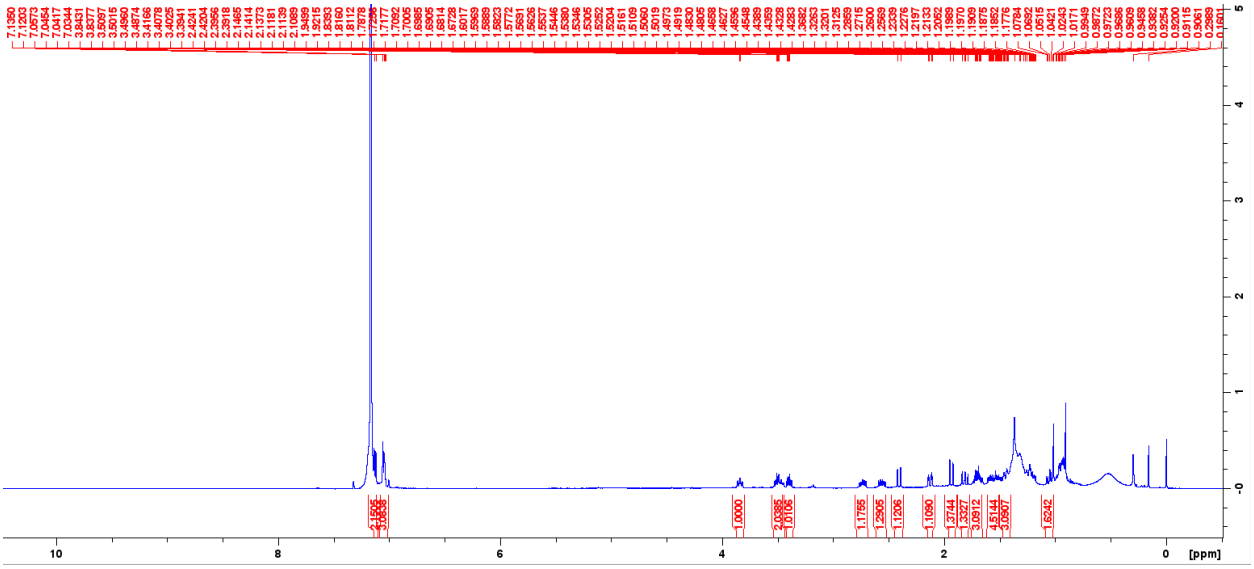
^{1}H NMR (500 MHz, C_6D_6)

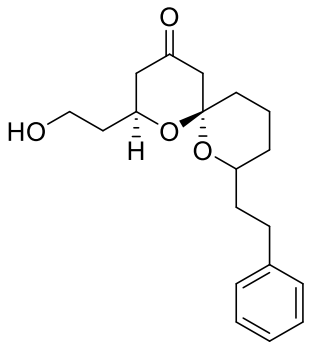




42

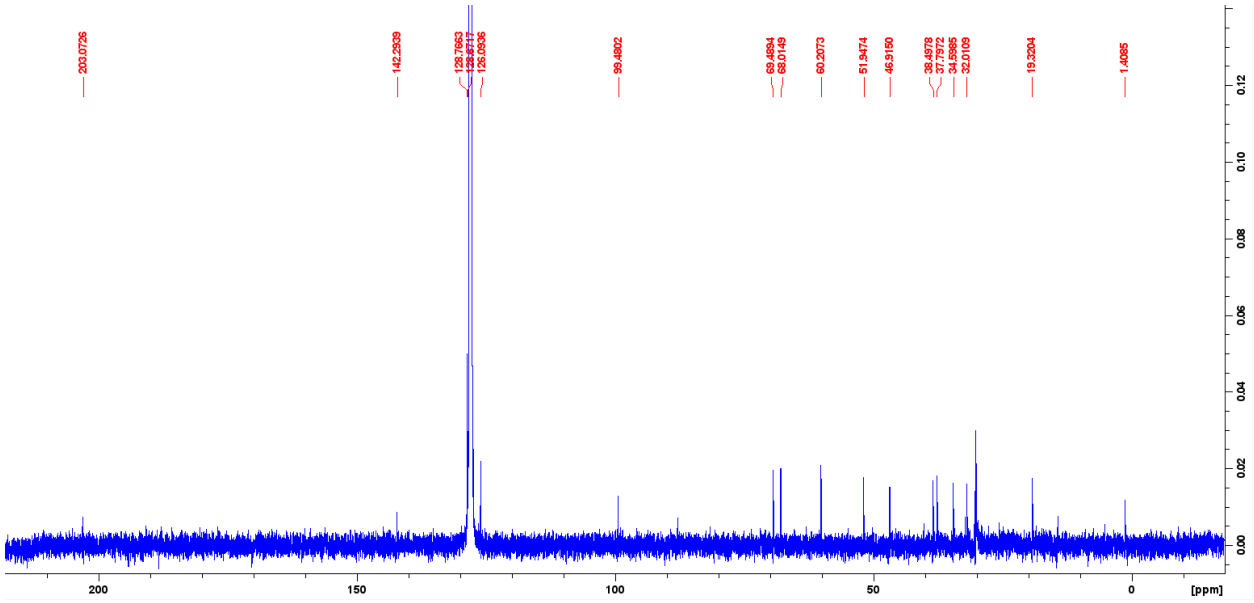
^{1}H NMR (500 MHz, C_6D_6)

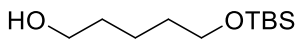




42

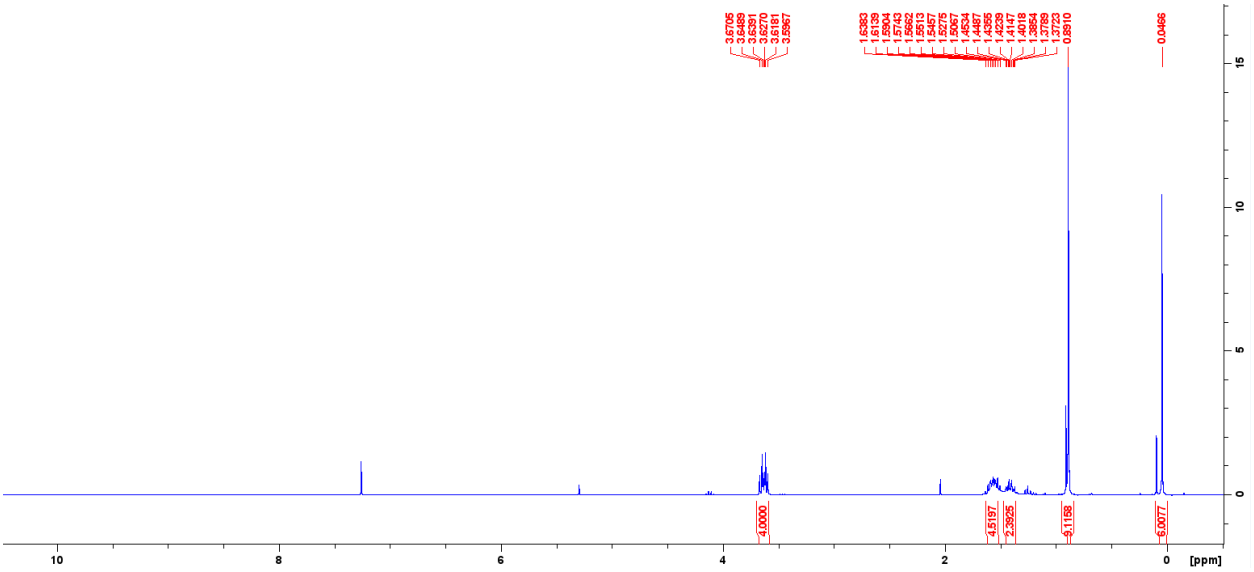
^{13}C NMR (300 MHz, $CDCl_3$)

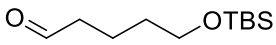




47

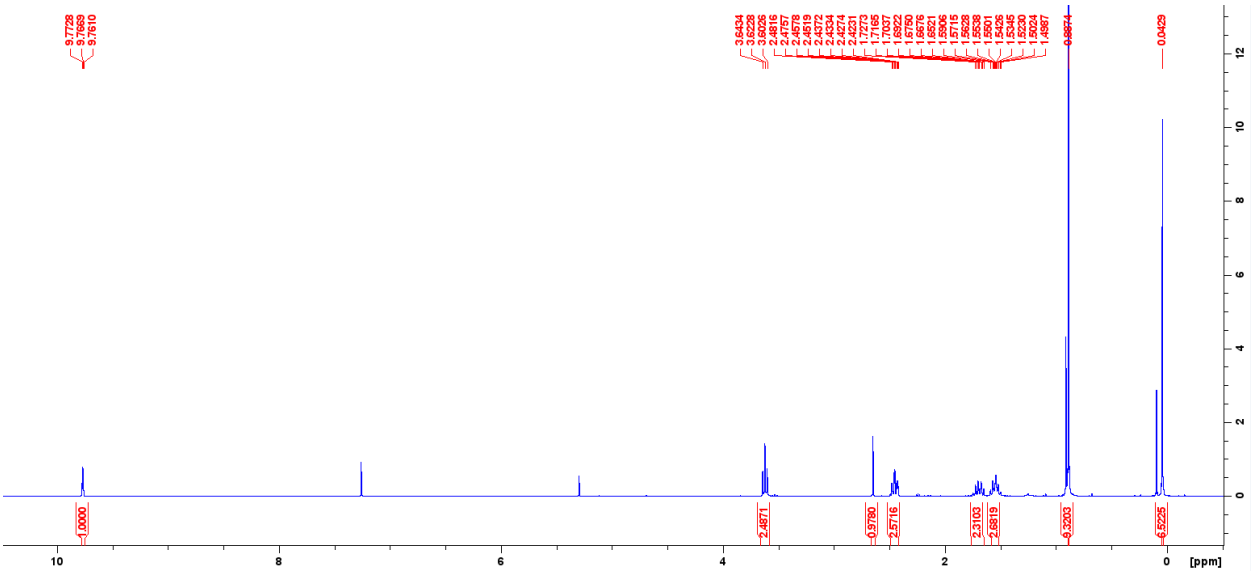
^{1}H NMR (300 MHz, $CDCl_3$)

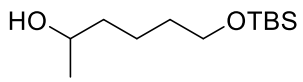




48

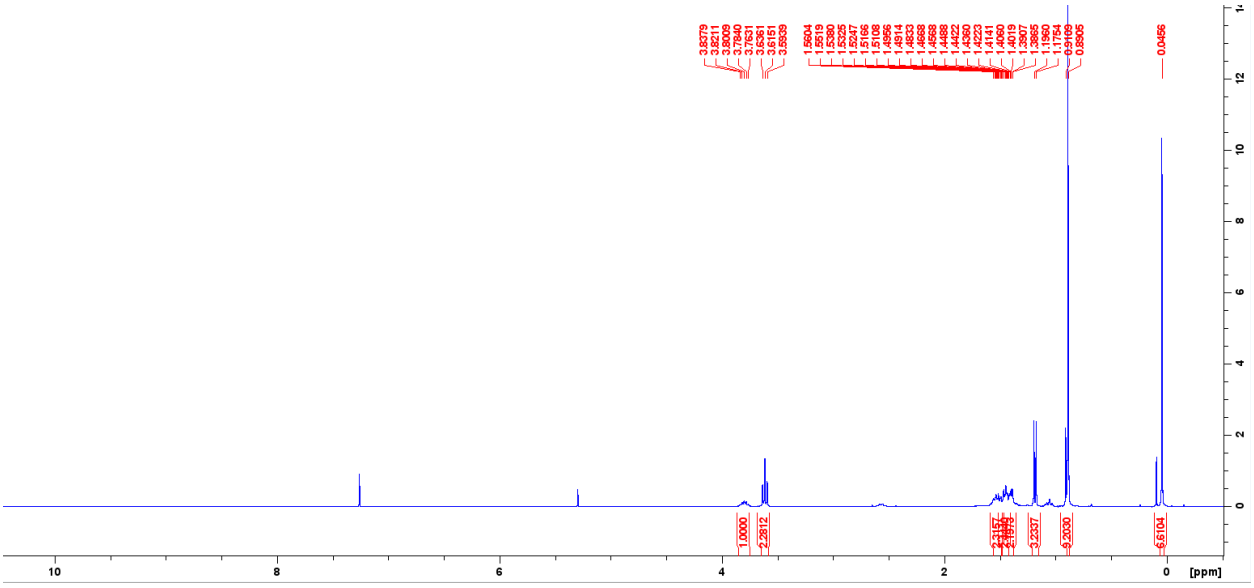
^{1}H NMR (300 MHz, $CDCl_3$)

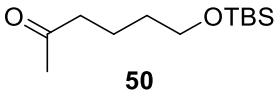




49

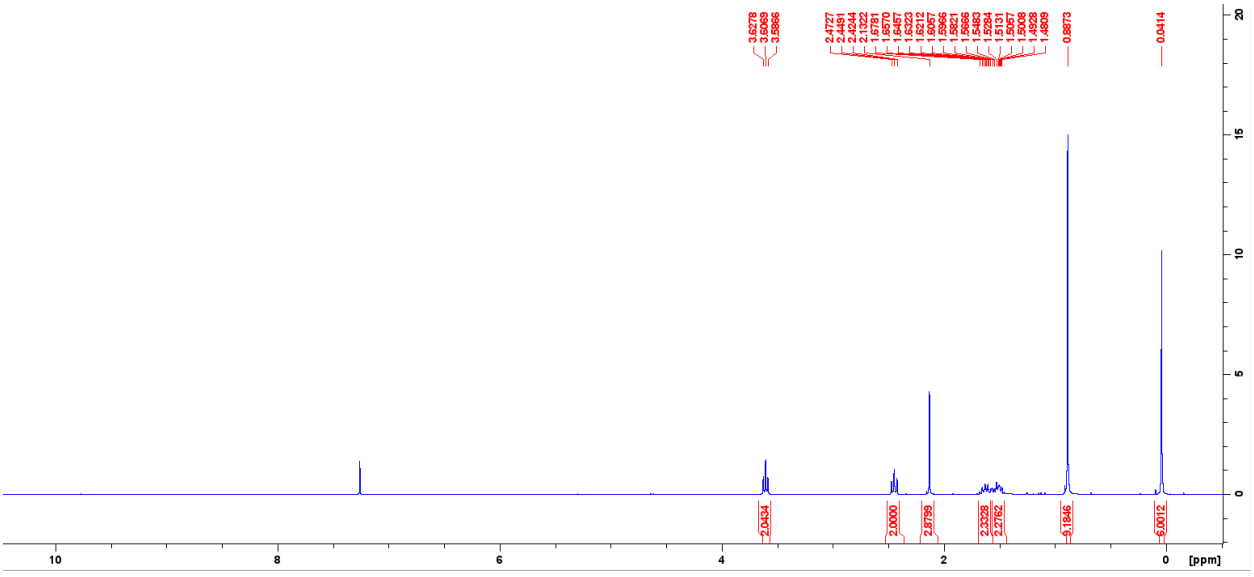
^{1}H NMR (300 MHz, $CDCl_3$)

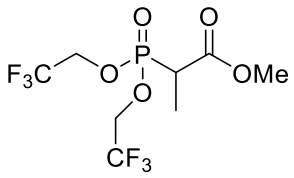




50

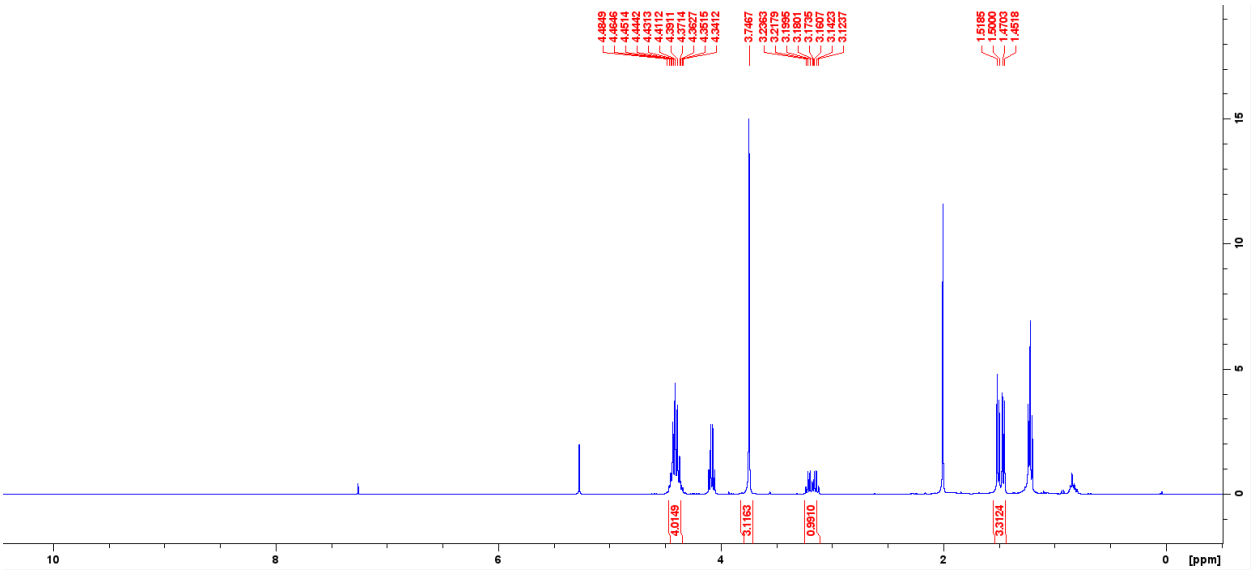
^{1}H NMR (300 MHz, $CDCl_3$)

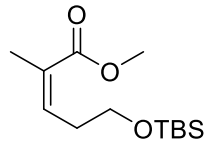




51

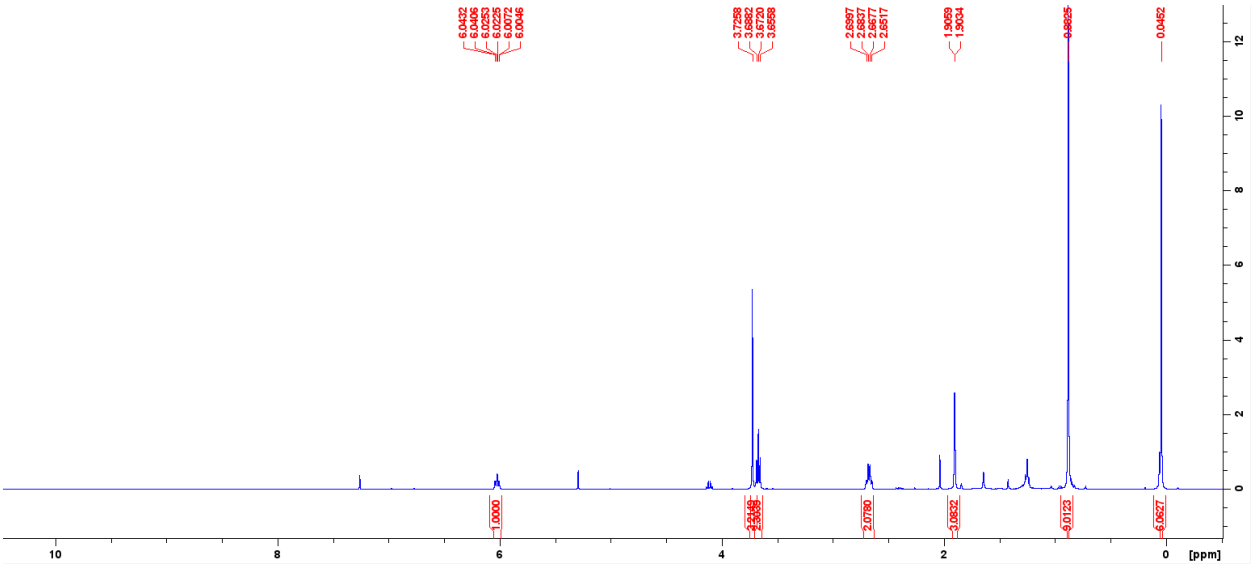
^{1}H NMR (400 MHz, $CDCl_3$)

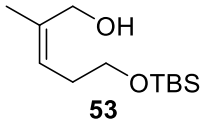




52

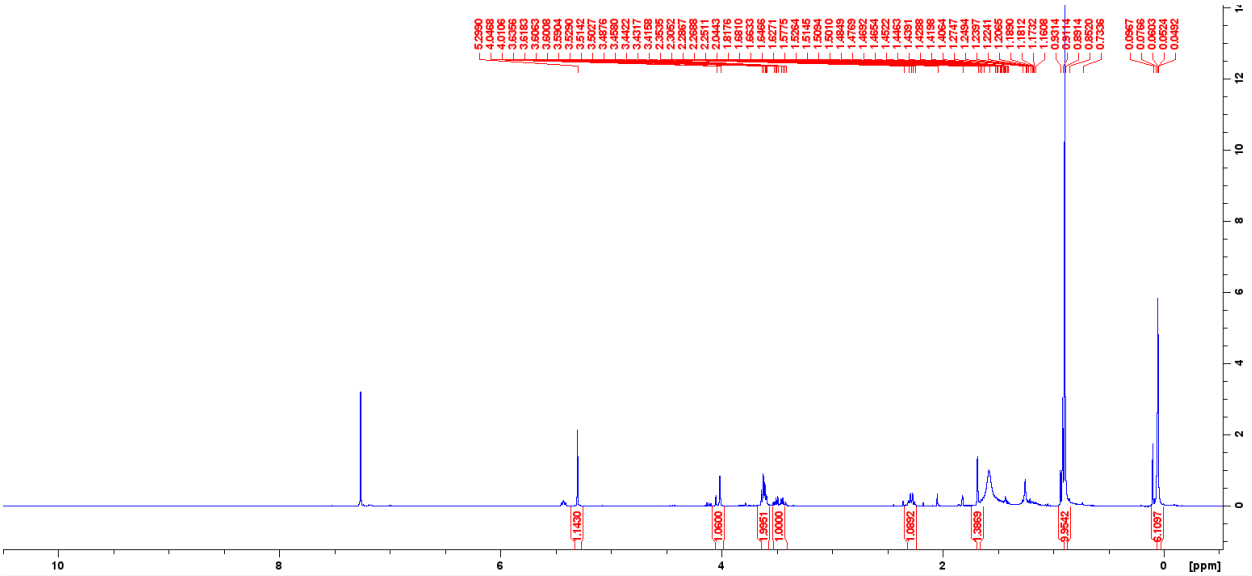
^{1}H NMR (400 MHz, $CDCl_3$)

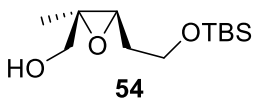




53

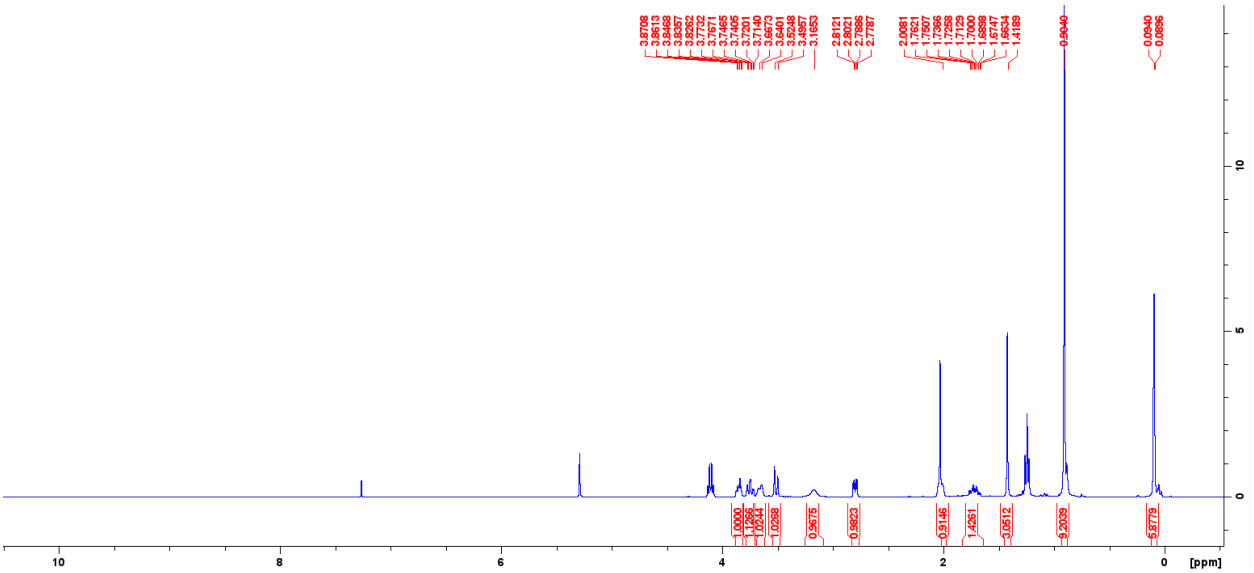
^{1}H NMR (500 MHz, $CDCl_3$)

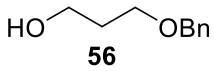




54

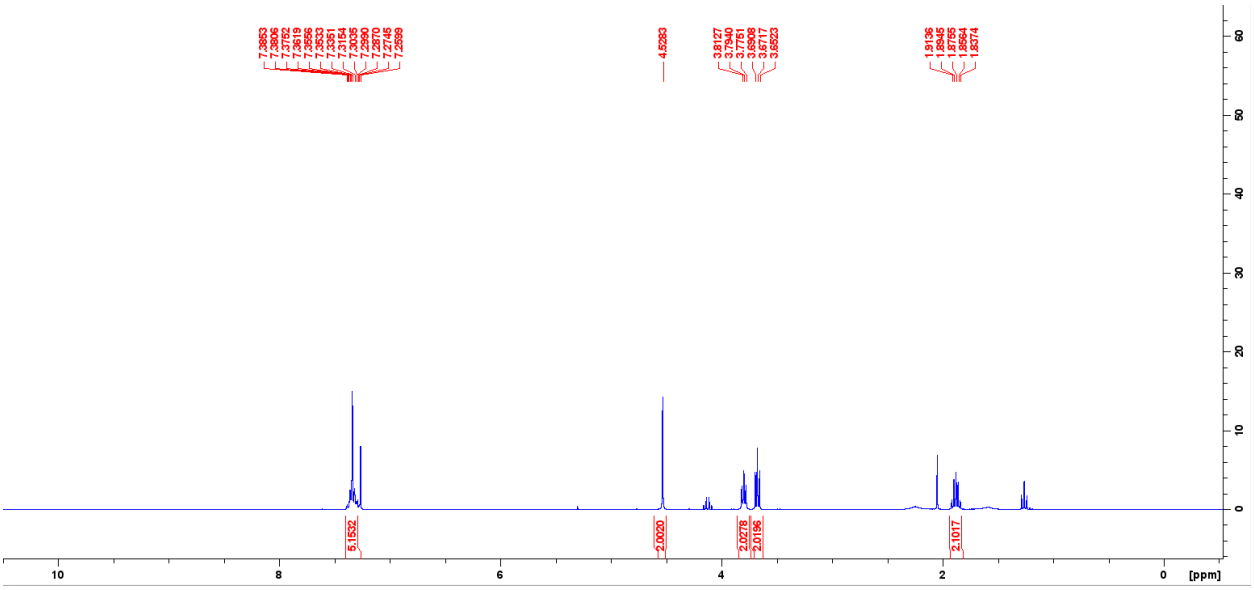
^{1}H NMR (400 MHz, $CDCl_3$)

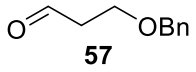




56

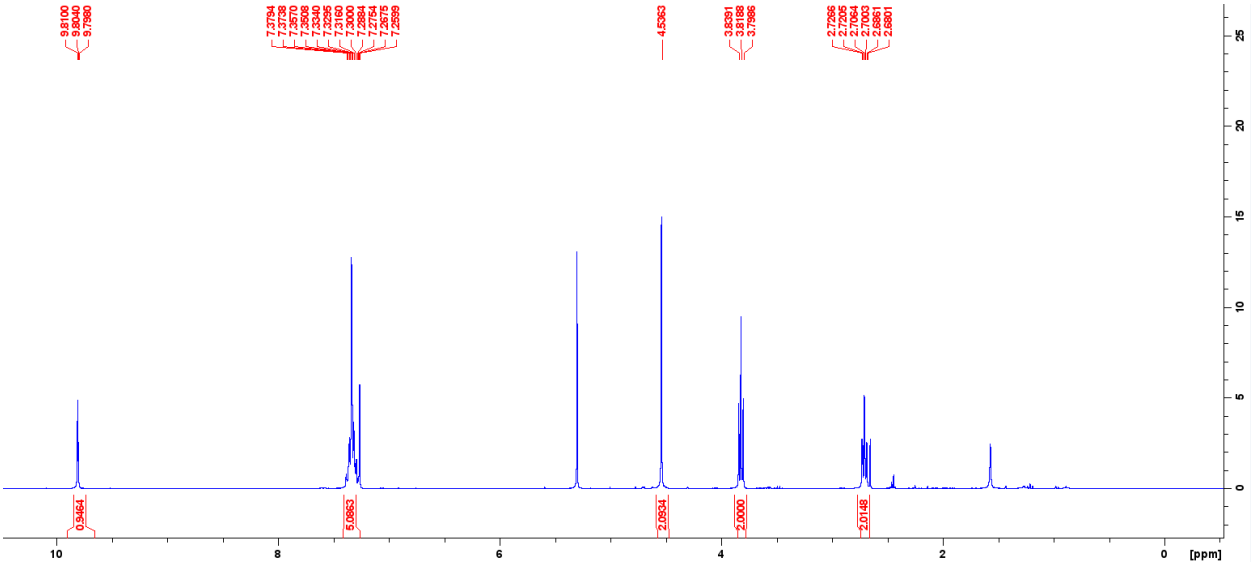
^{1}H NMR (300 MHz, $CDCl_3$)

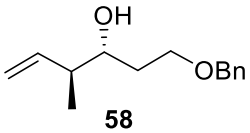




57

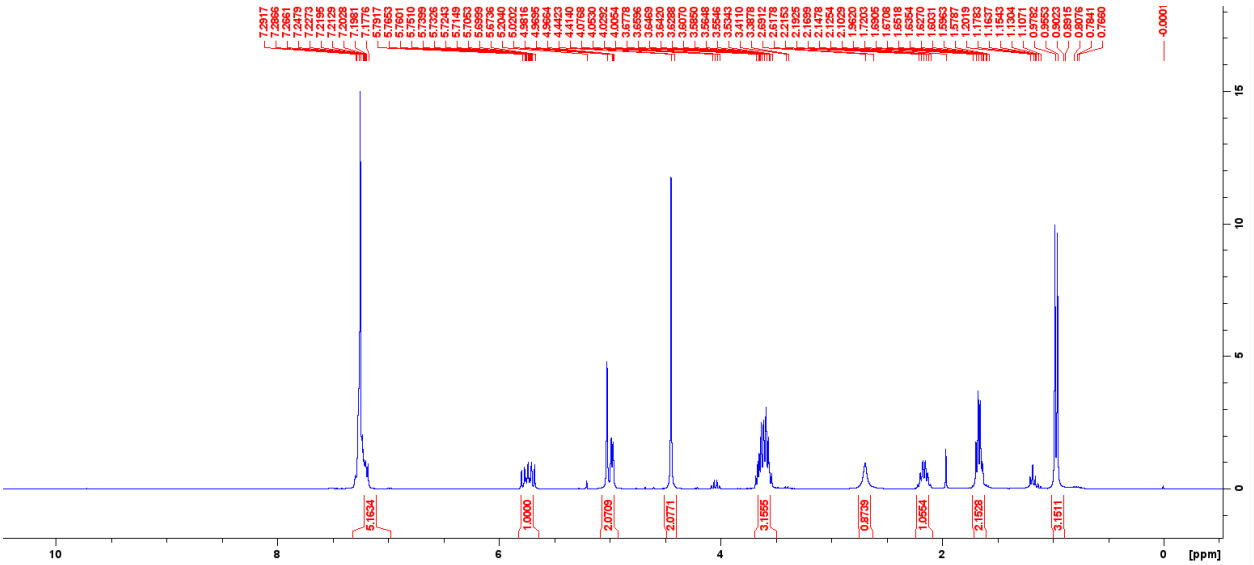
^{1}H NMR (300 MHz, $CDCl_3$)

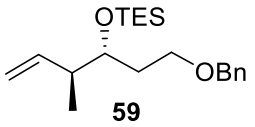




58

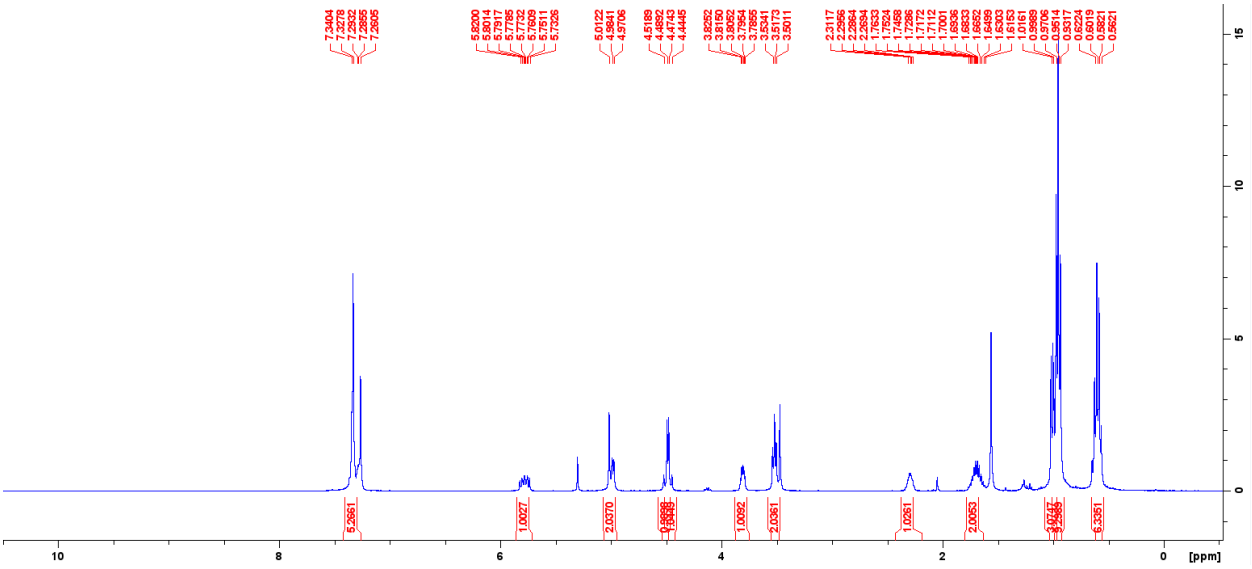
^{1}H NMR (300 MHz, $CDCl_3$)

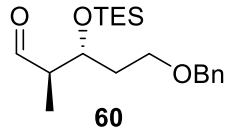




59

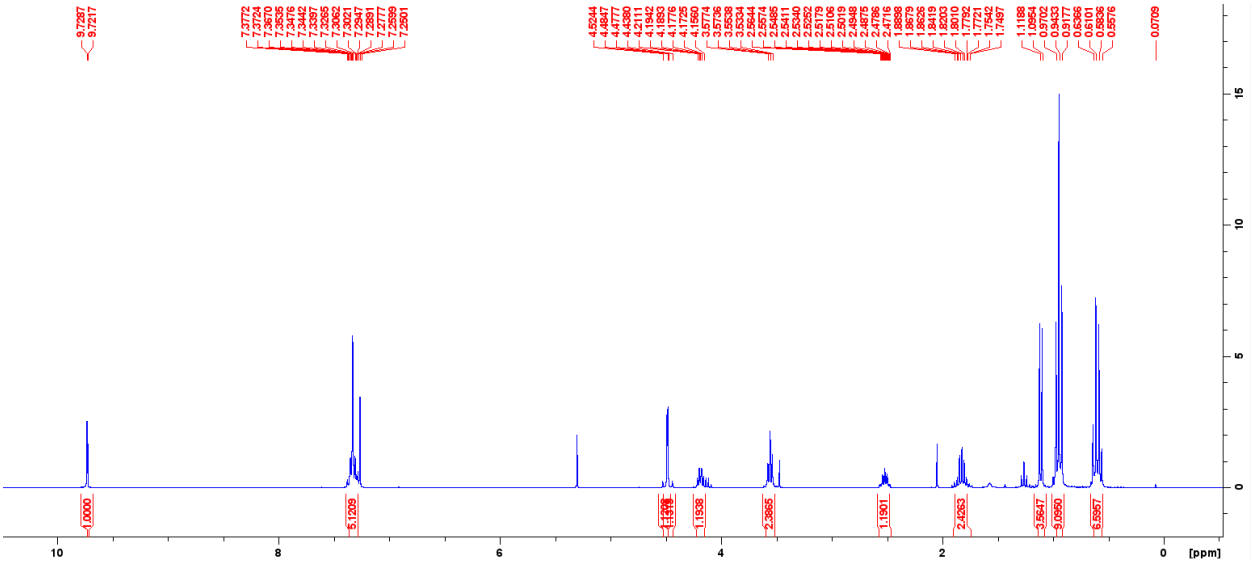
^{1}H NMR (400 MHz, $CDCl_3$)

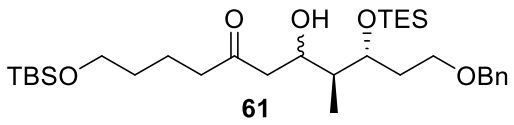




60

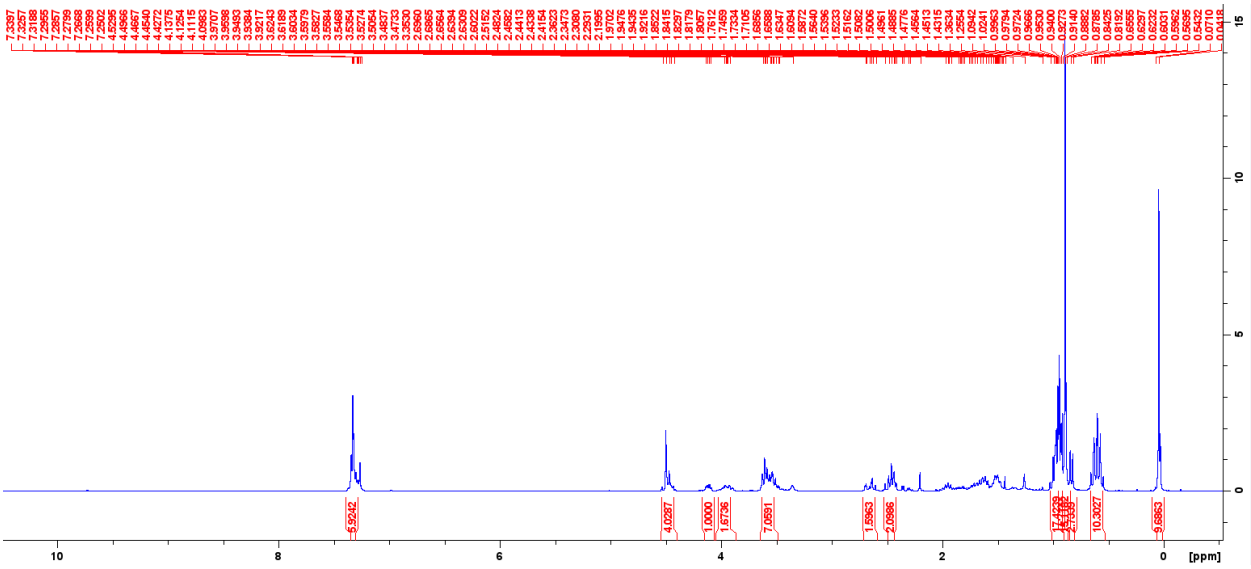
^{1}H NMR (300 MHz, $CDCl_3$)

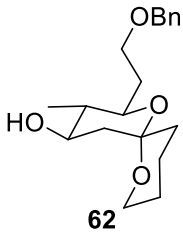




61

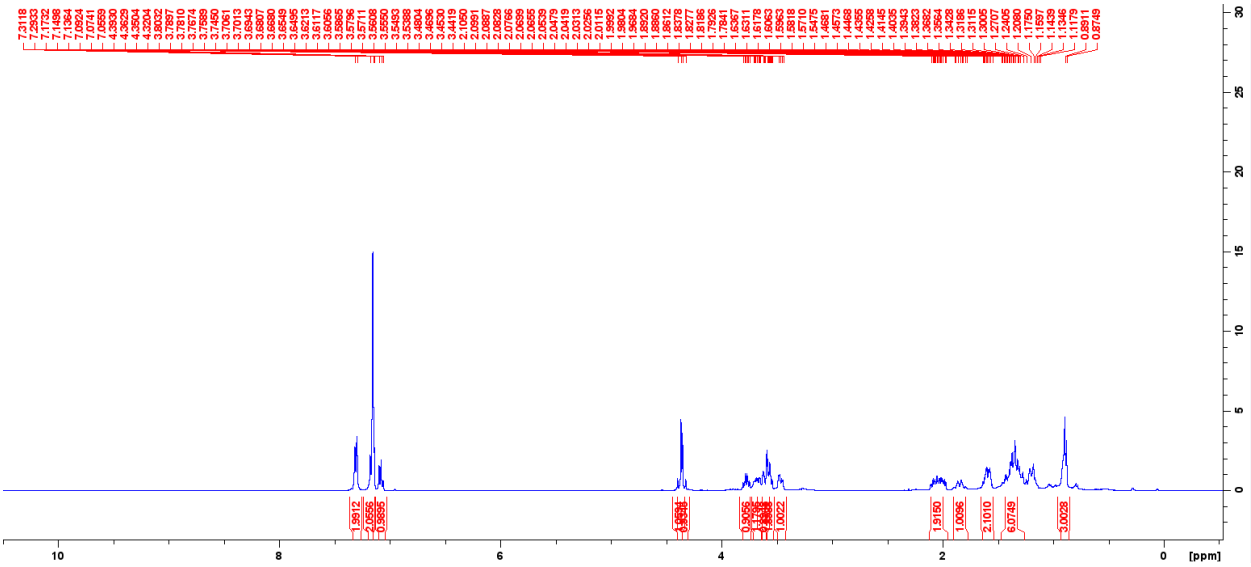
^{1}H NMR (400 MHz, $CDCl_3$)

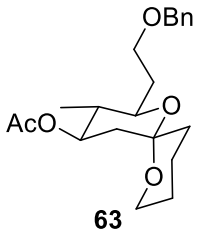




62

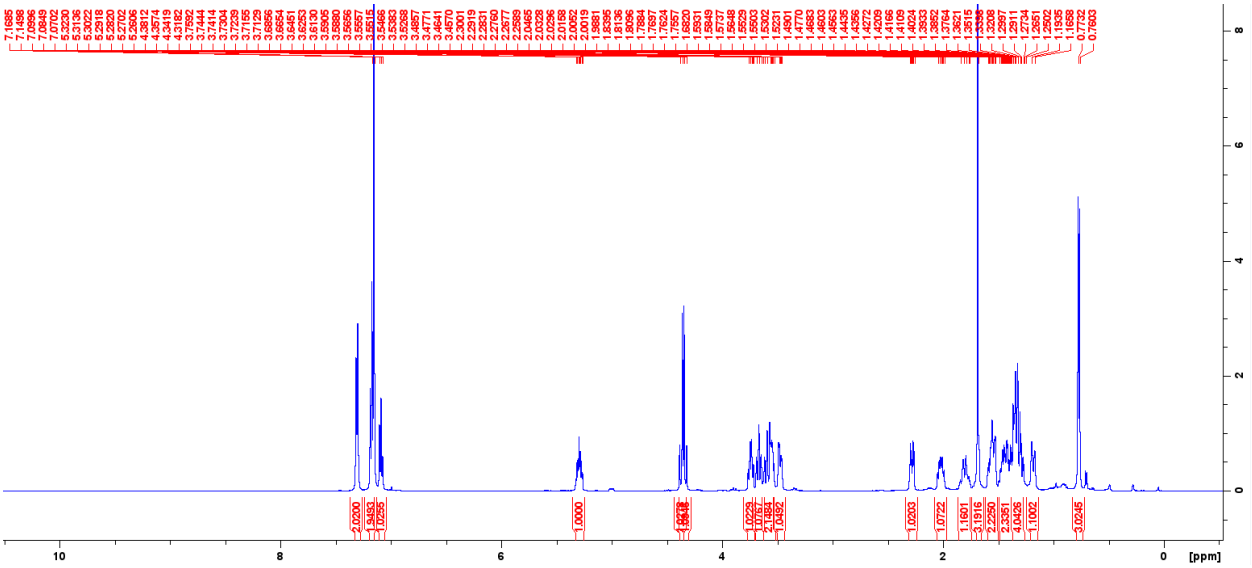
^{1}H NMR (500 MHz, C_6D_6)

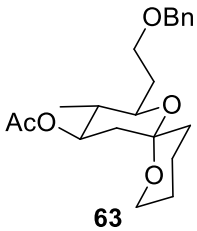




63

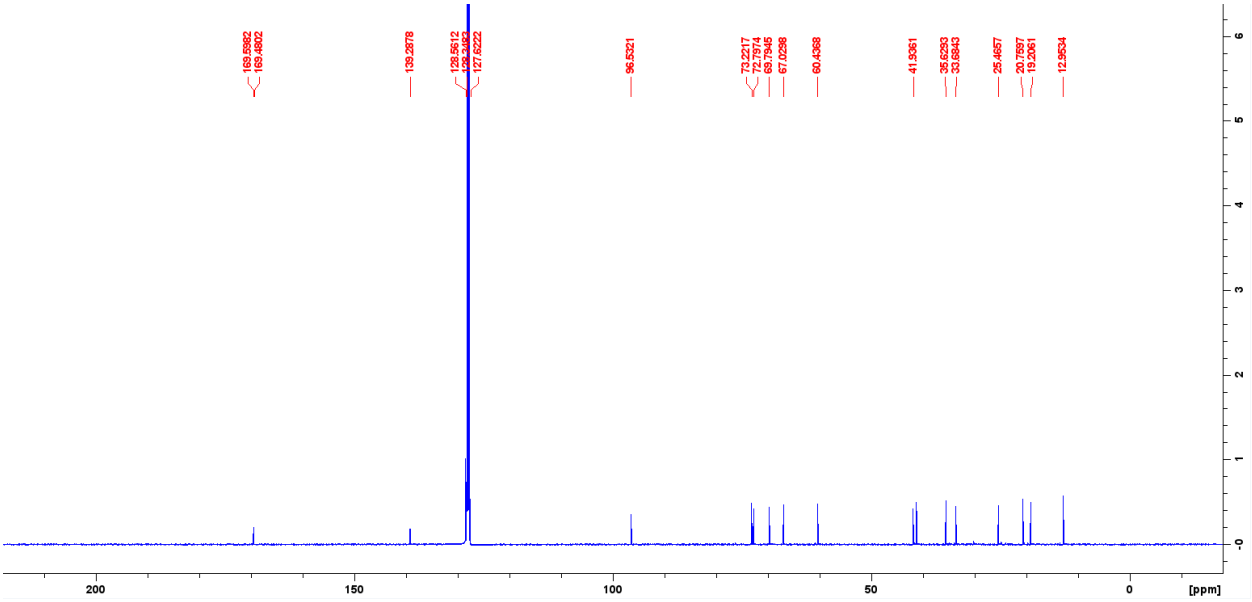
^{1}H NMR (500 MHz, C_6D_6)



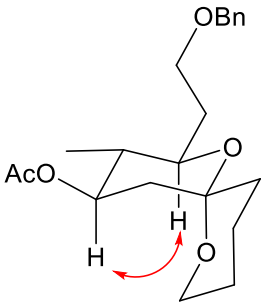


63

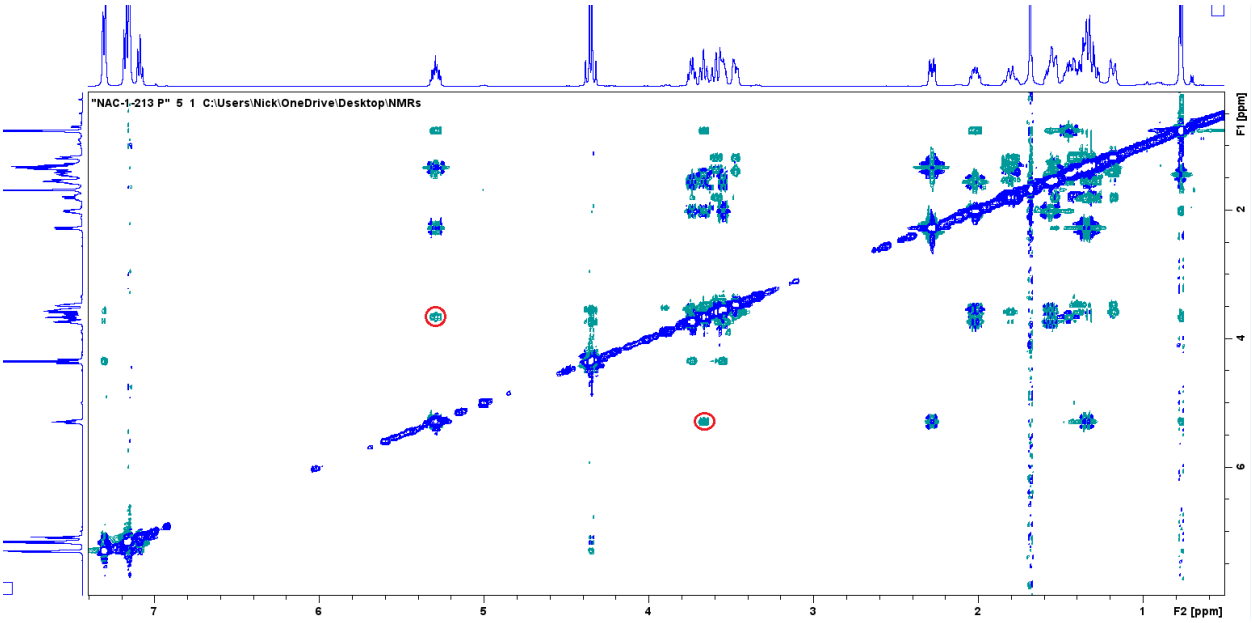
^{13}C NMR (500 MHz, C_6D_6)

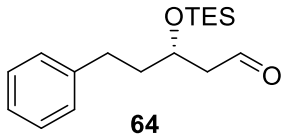


NOESY Spectrum



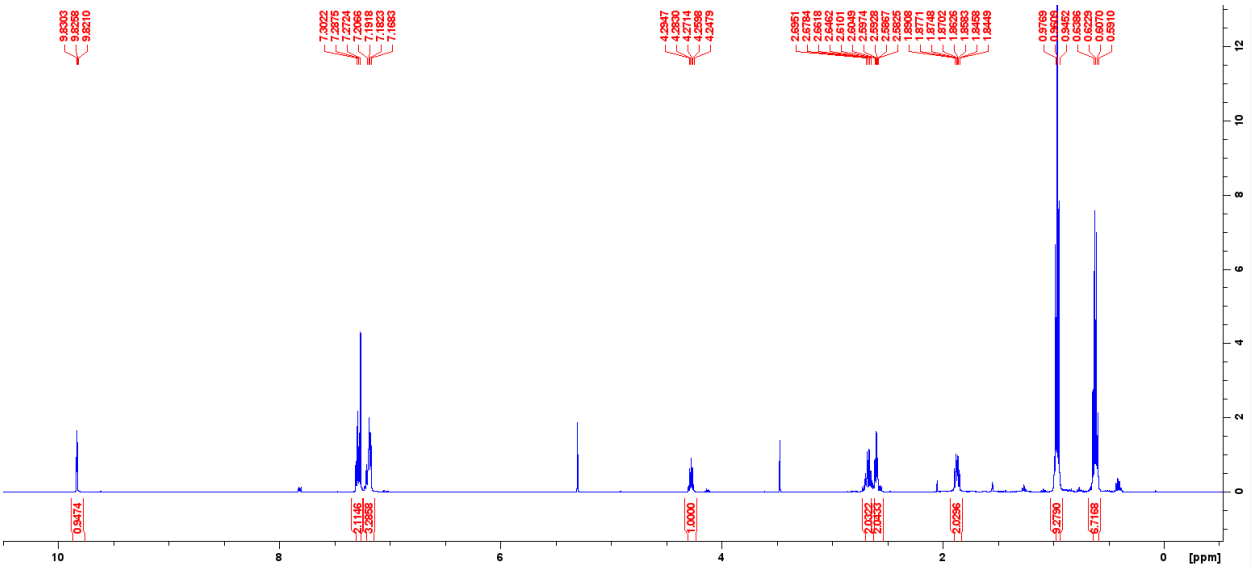
63

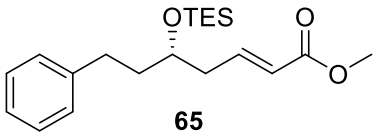




64

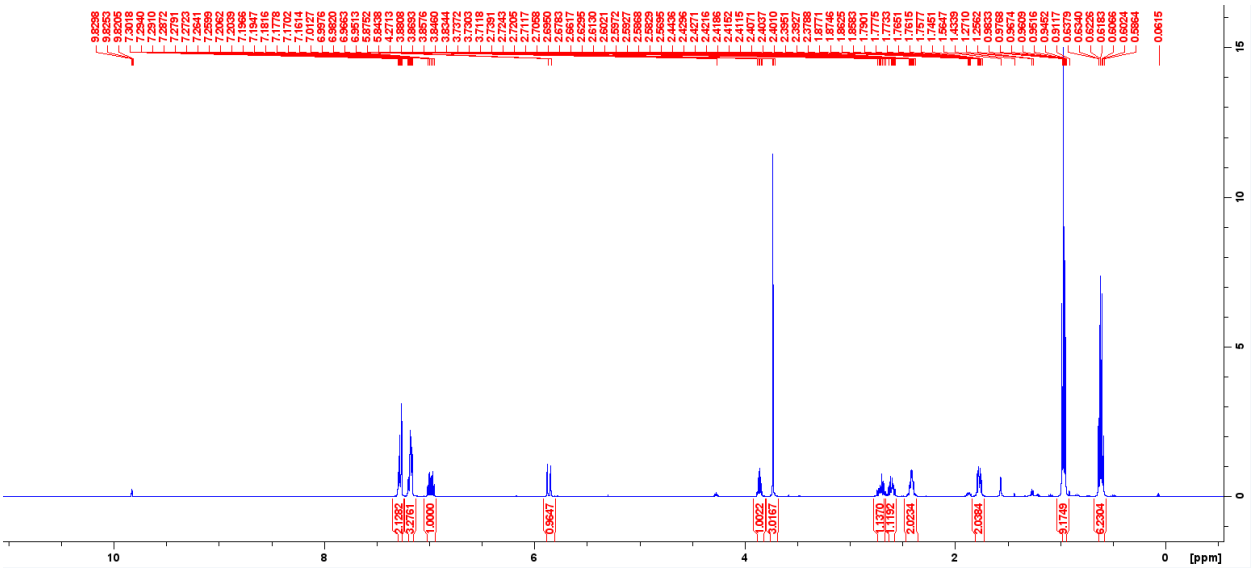
^{1}H NMR (500 MHz, $CDCl_3$)

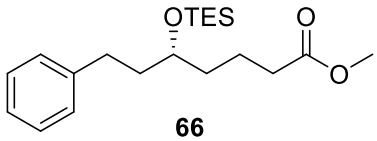




65

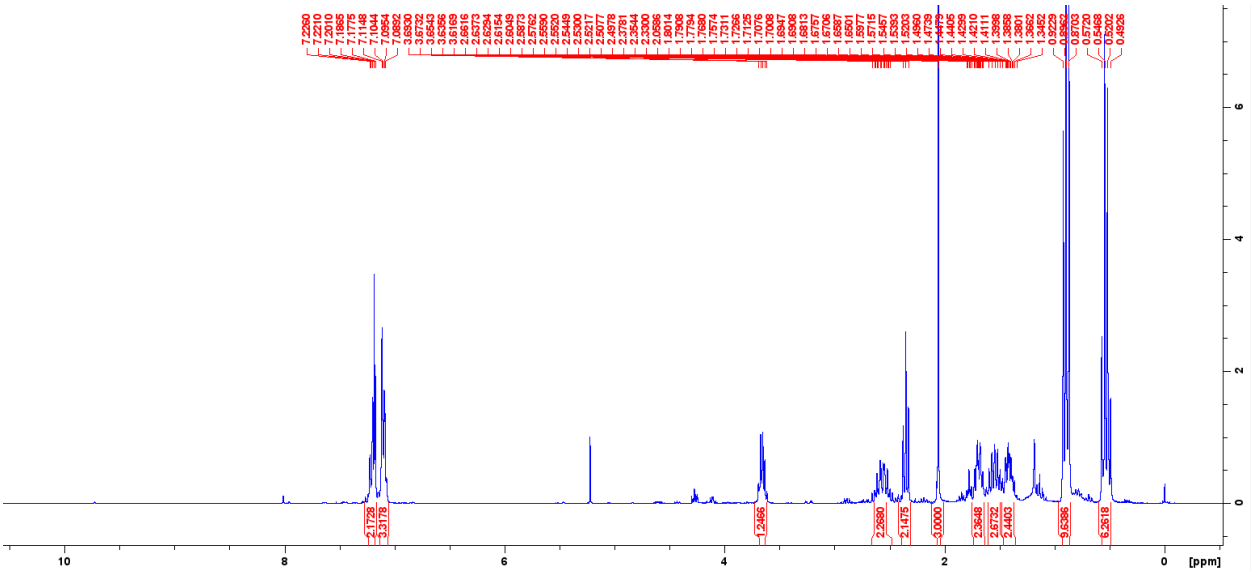
^{1}H NMR (300 MHz, $CDCl_3$)

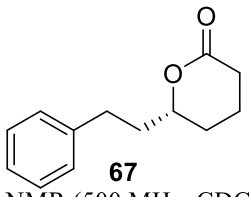




66

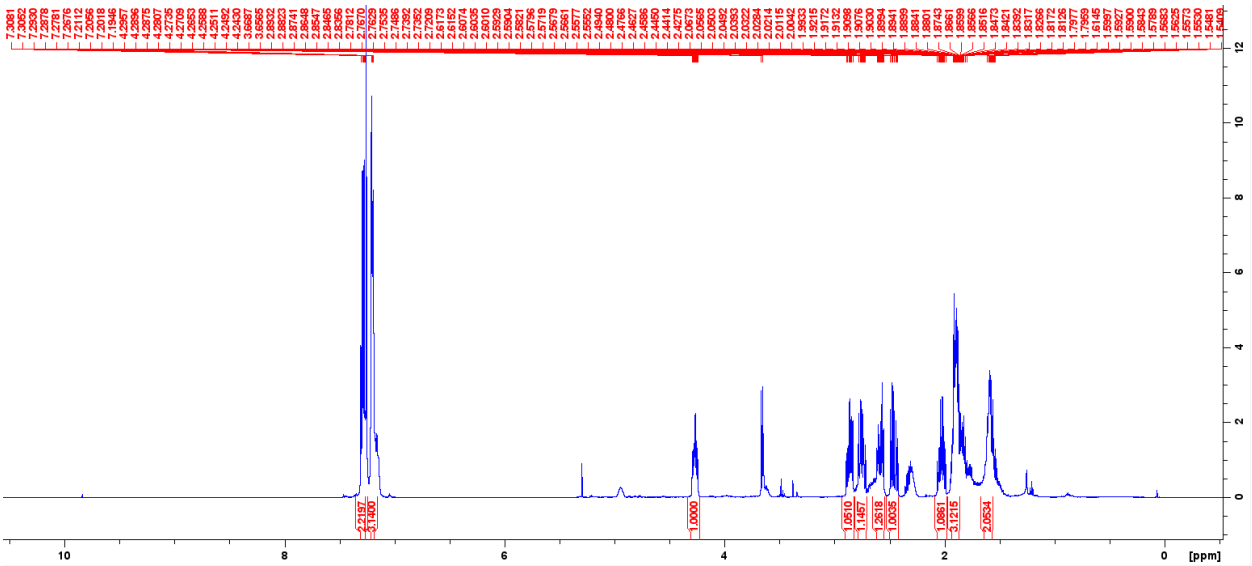
^{1}H NMR (300 MHz, $CDCl_3$)

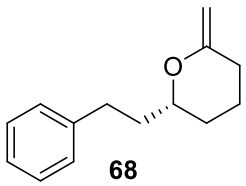




67

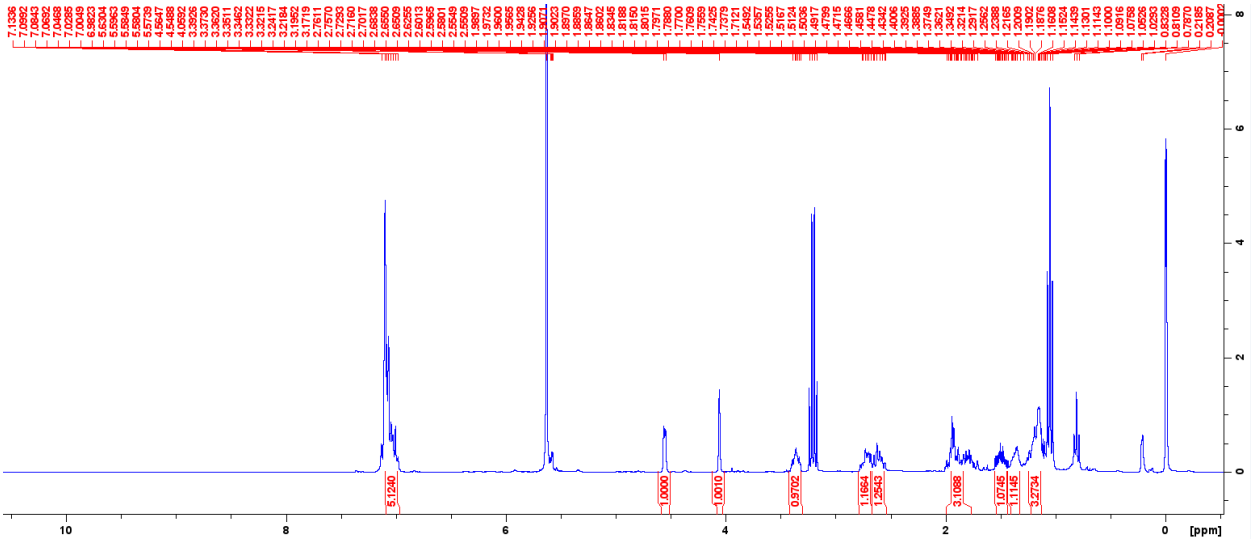
^{1}H NMR (500 MHz, $CDCl_3$)

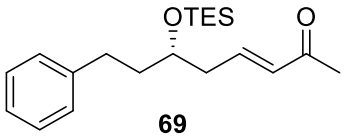




68

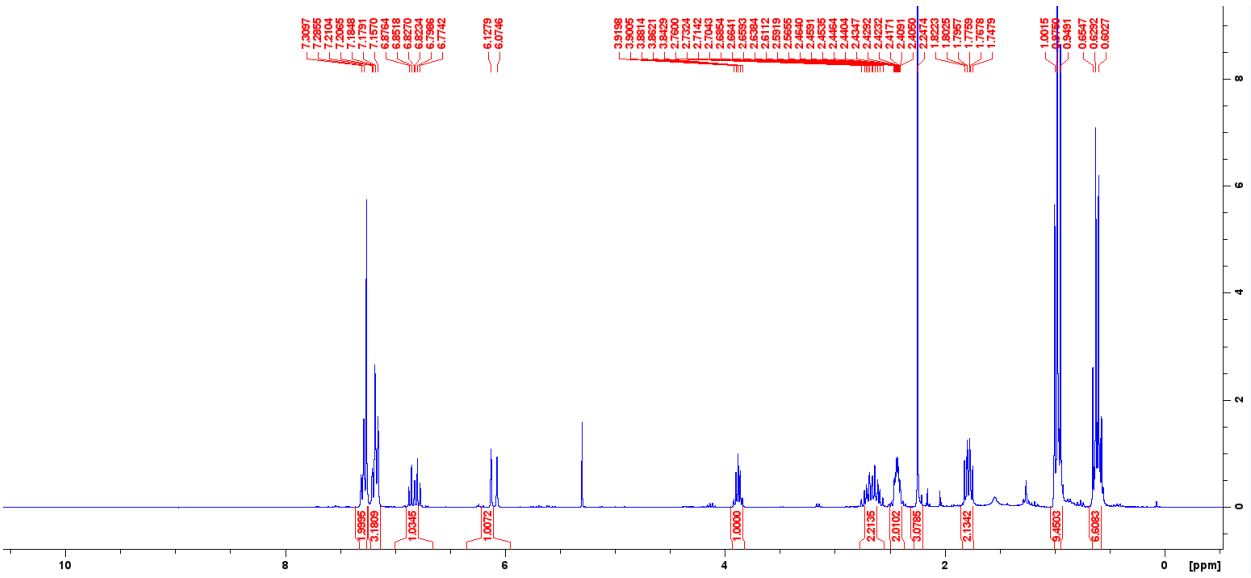
^{1}H NMR (500 MHz, $CDCl_3$)

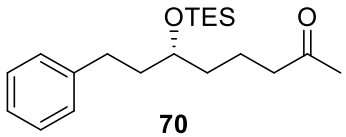




69

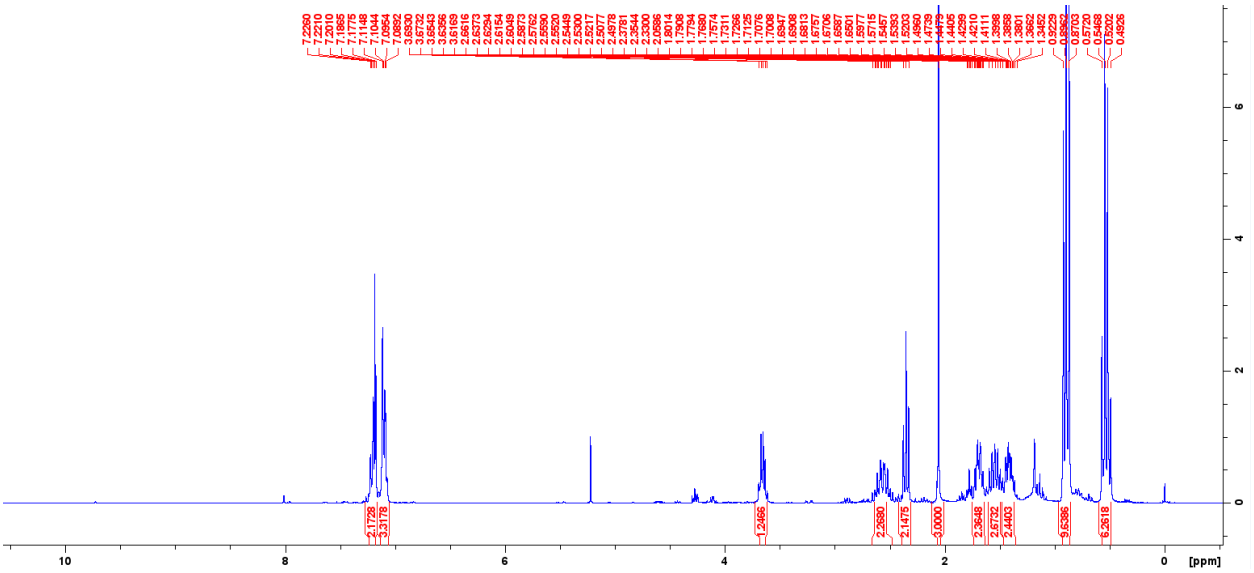
^{1}H NMR (300 MHz, $CDCl_3$)

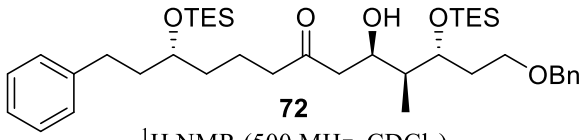




70

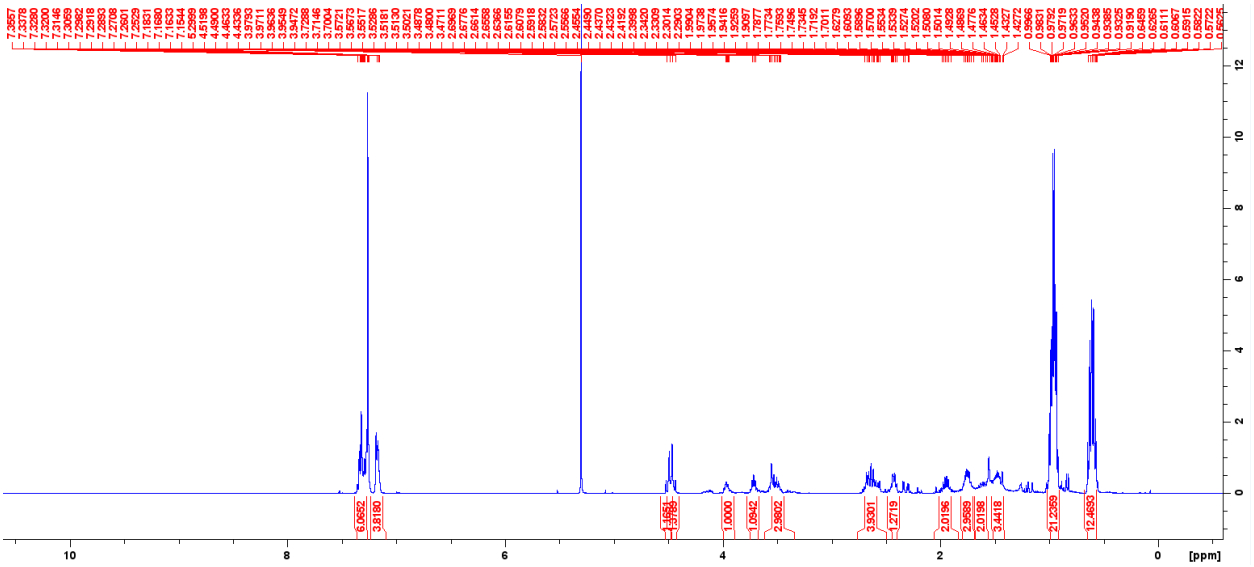
^{1}H NMR (300 MHz, $CDCl_3$)

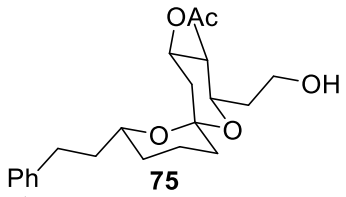




72

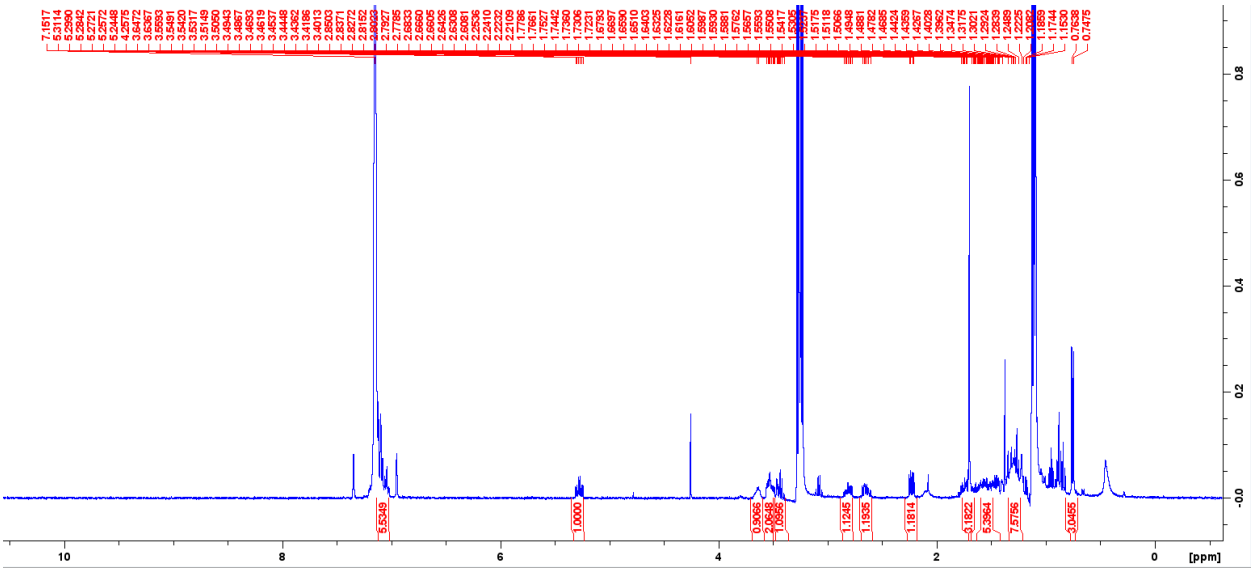
^{1}H NMR (500 MHz, $CDCl_3$)

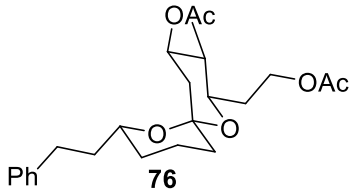




75

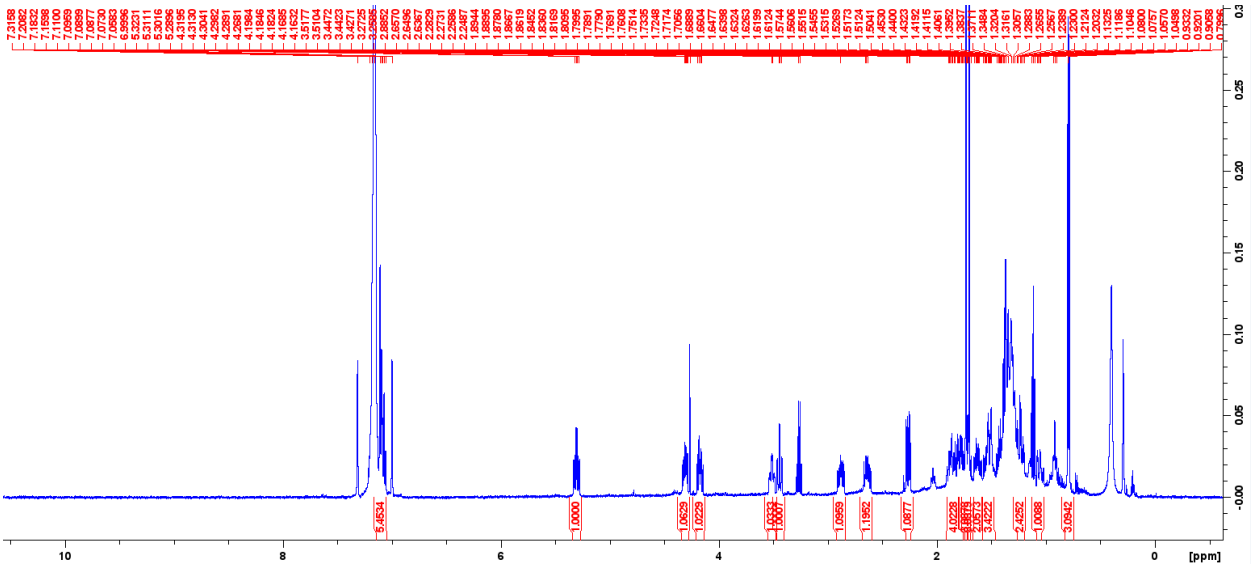
^{1}H NMR (500 MHz, C_6D_6)

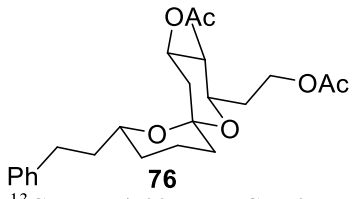




76

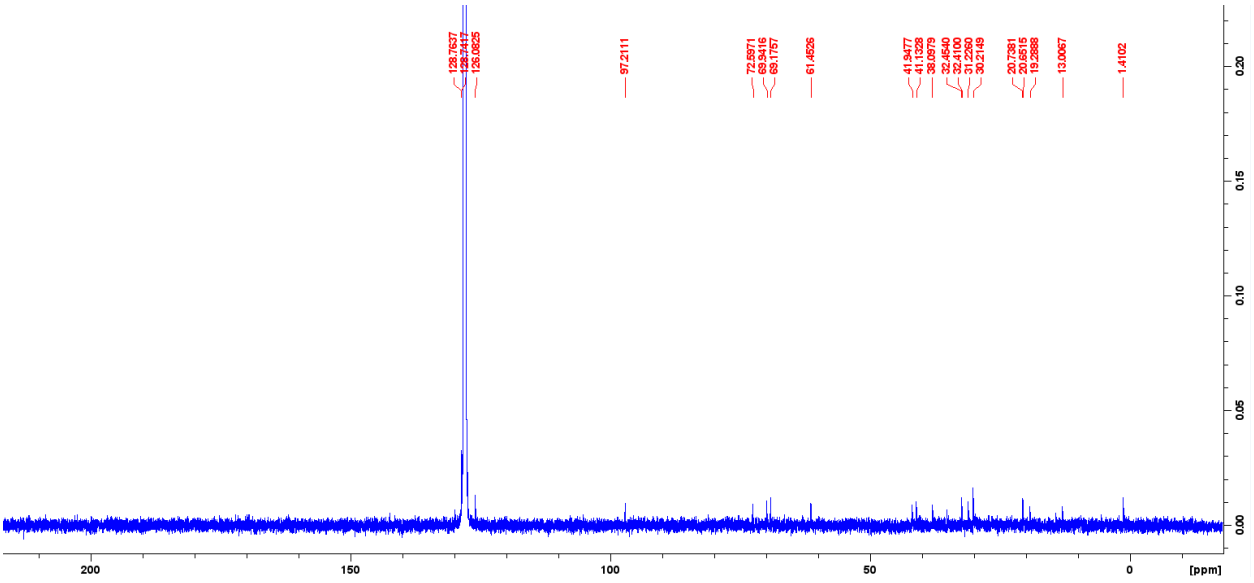
^{1}H NMR (500 MHz, C_6D_6)



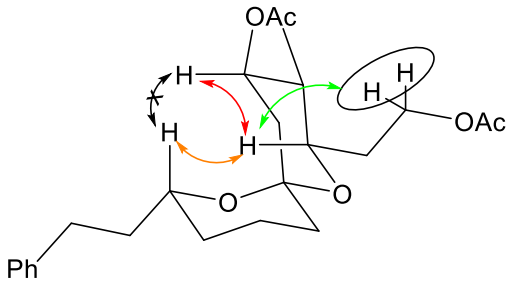


76

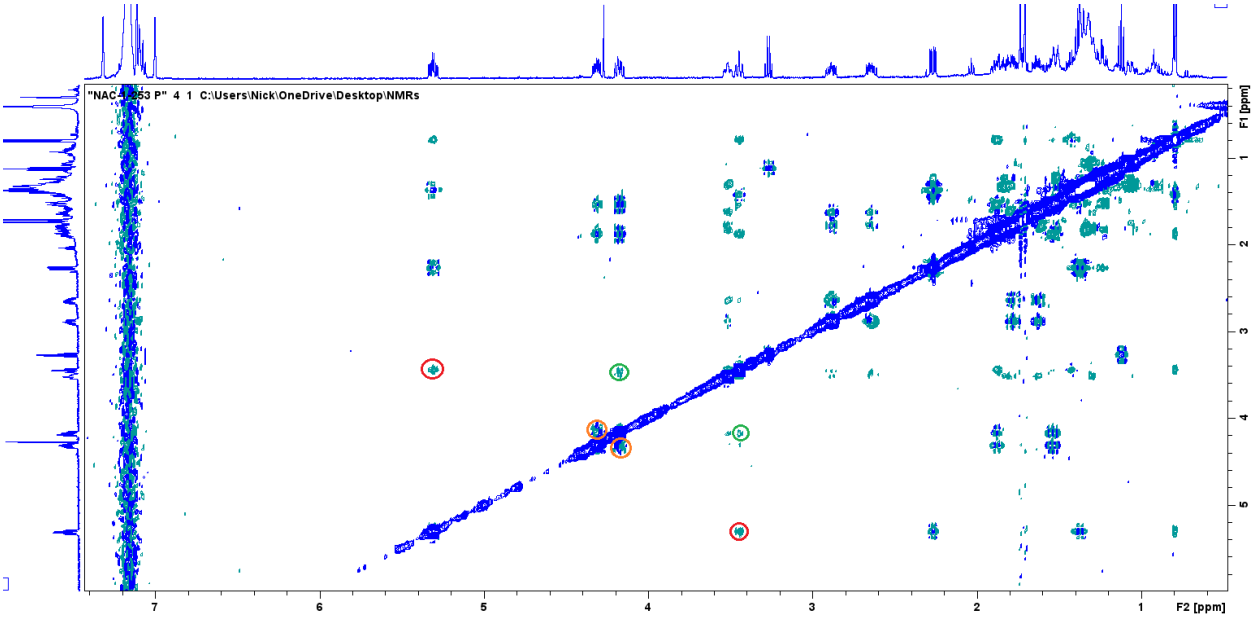
^{13}C NMR (500 MHz, C_6D_6)

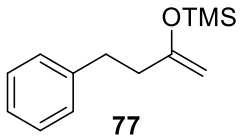


NOESY Spectrum



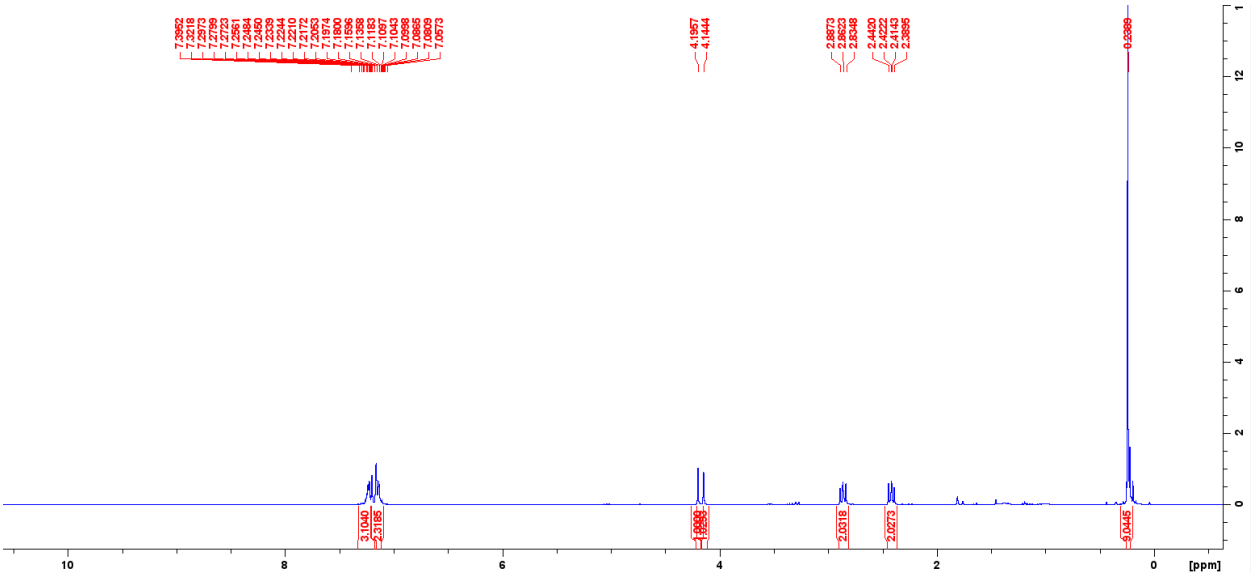
76

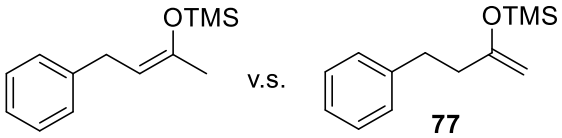




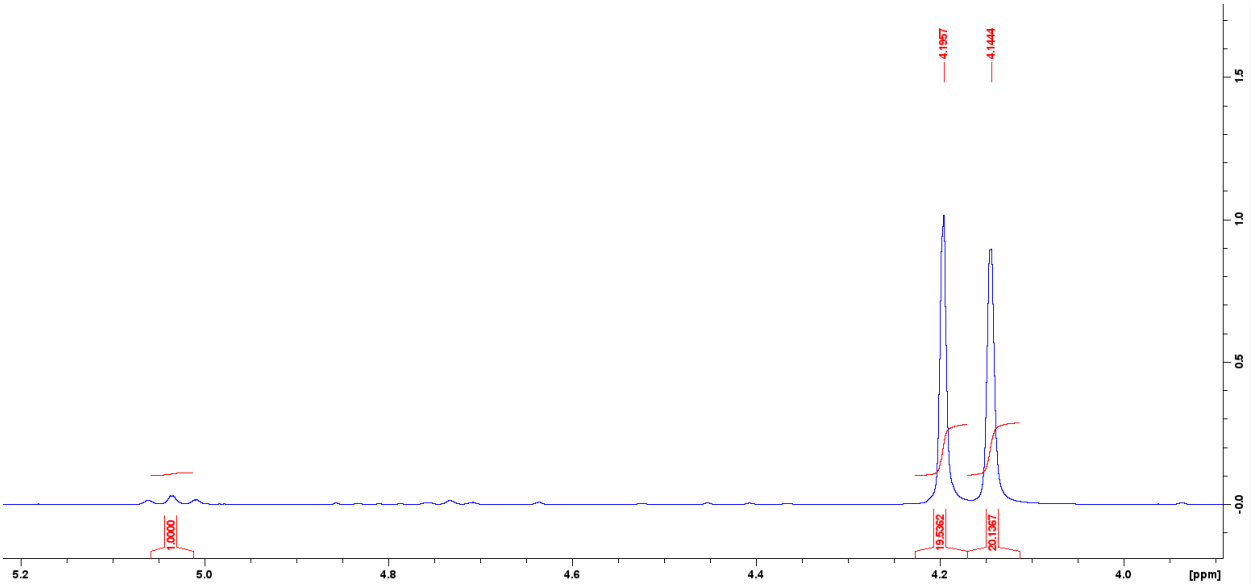
77

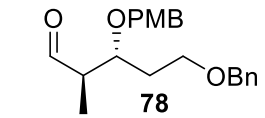
^{1}H NMR (300 MHz, C_6D_6)





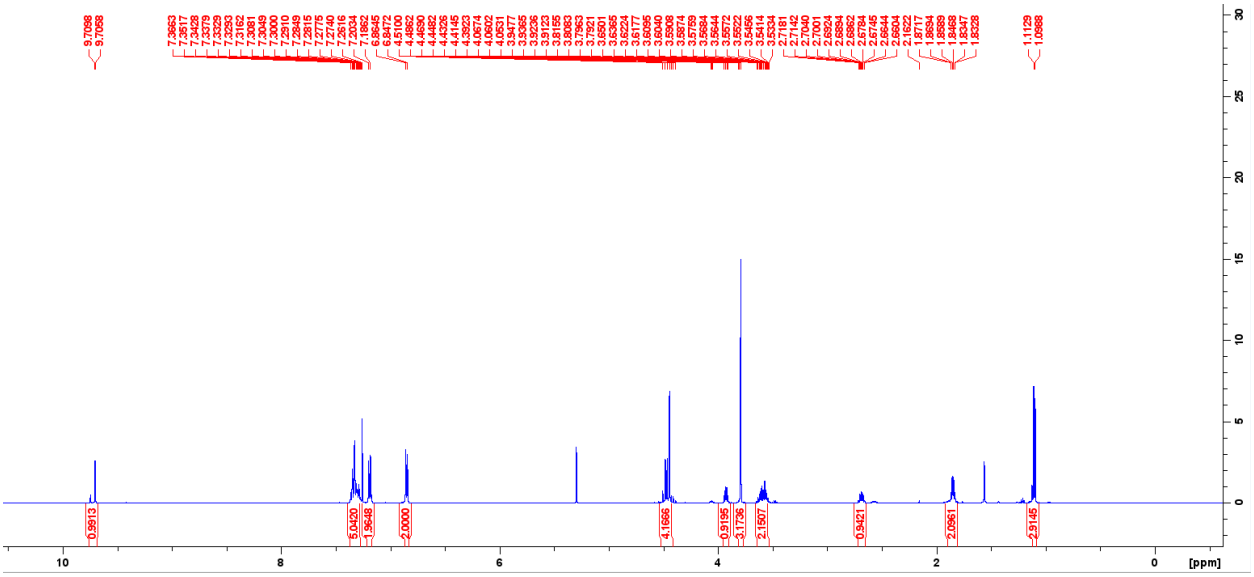
77

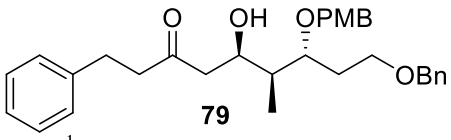




78

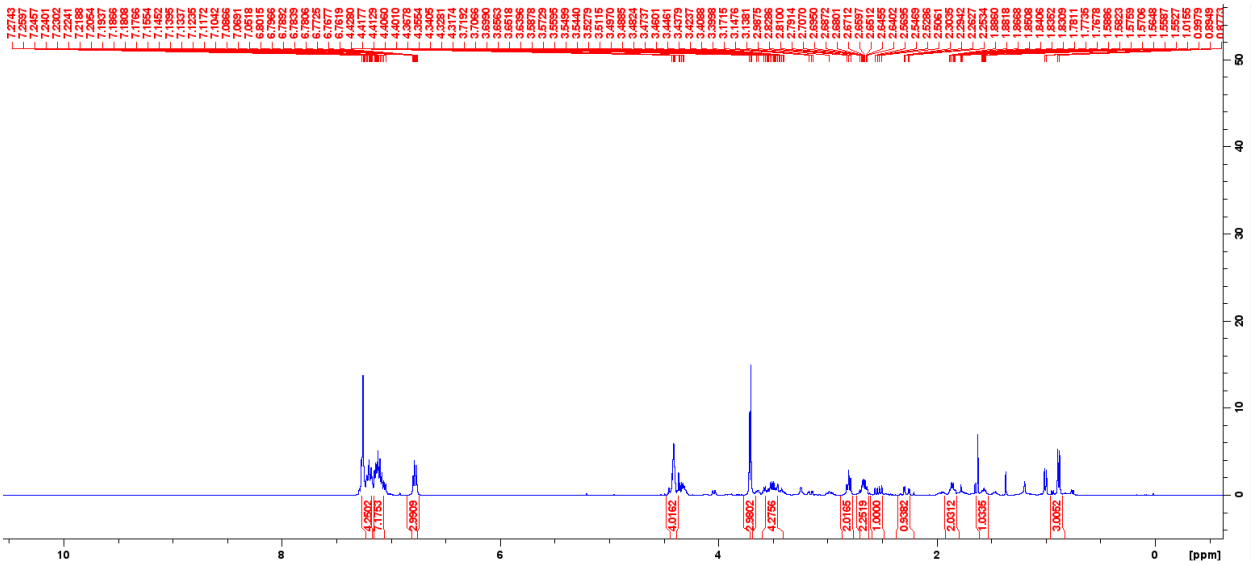
^{1}H NMR (500 MHz, $CDCl_3$)

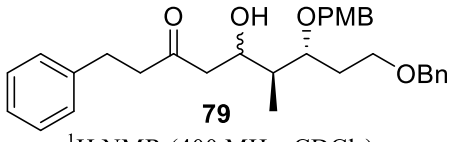




79

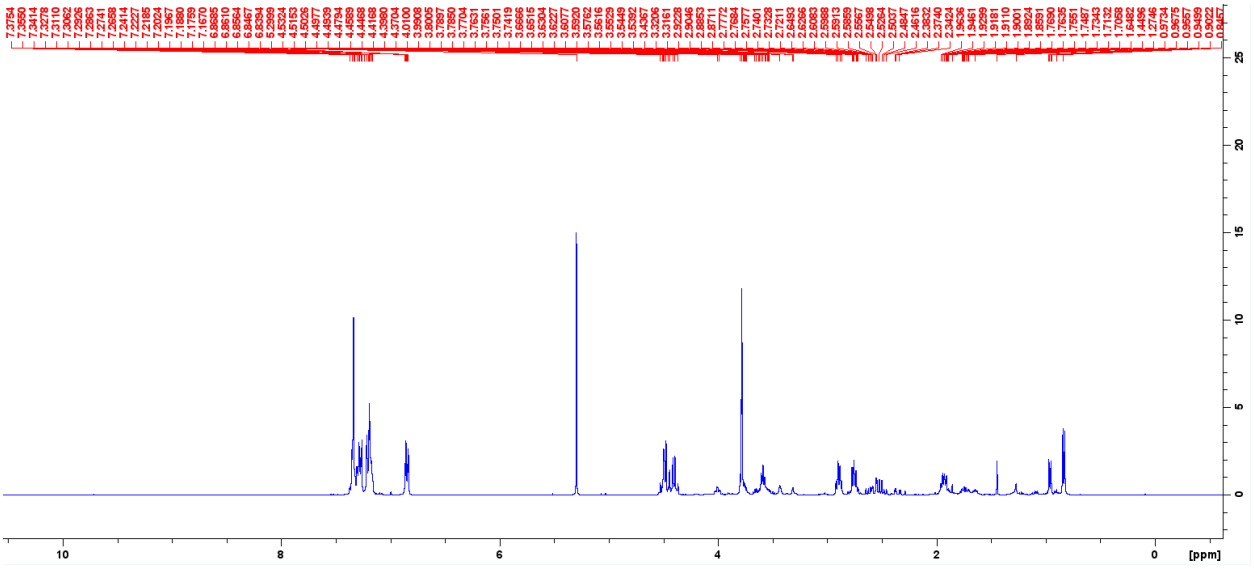
^{1}H NMR (400 MHz, $CDCl_3$)

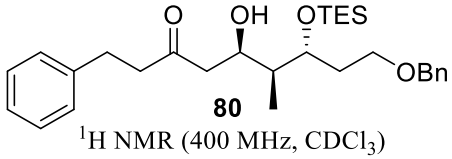




79

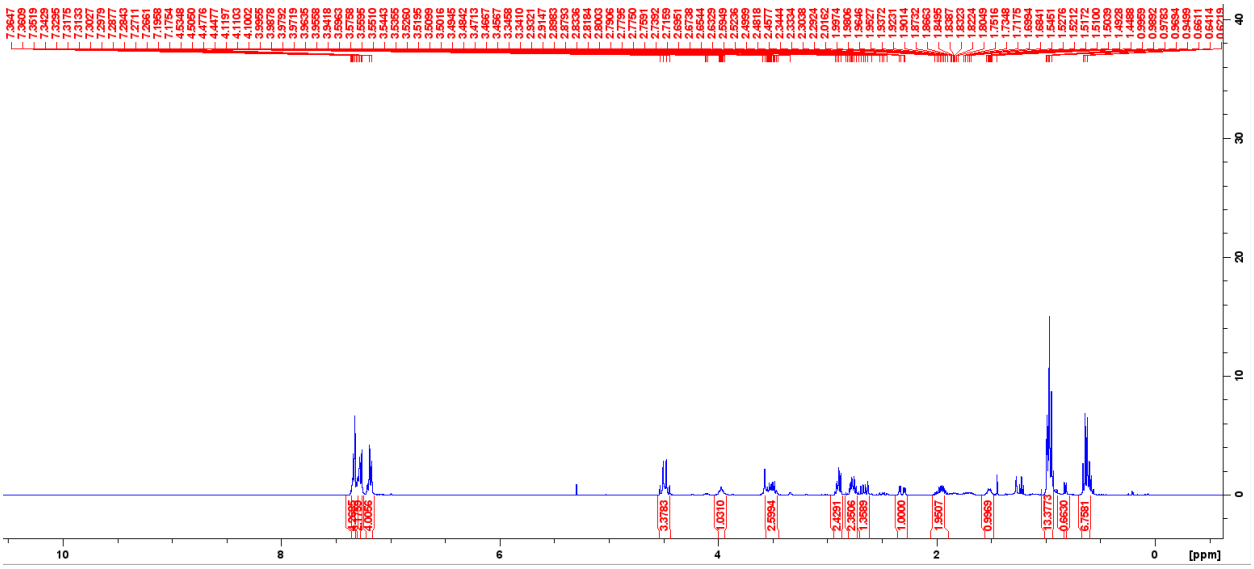
^{1}H NMR (400 MHz, $CDCl_3$)

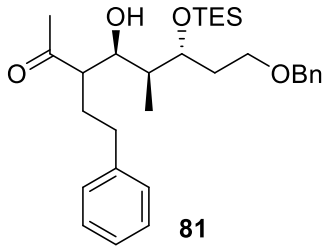




80

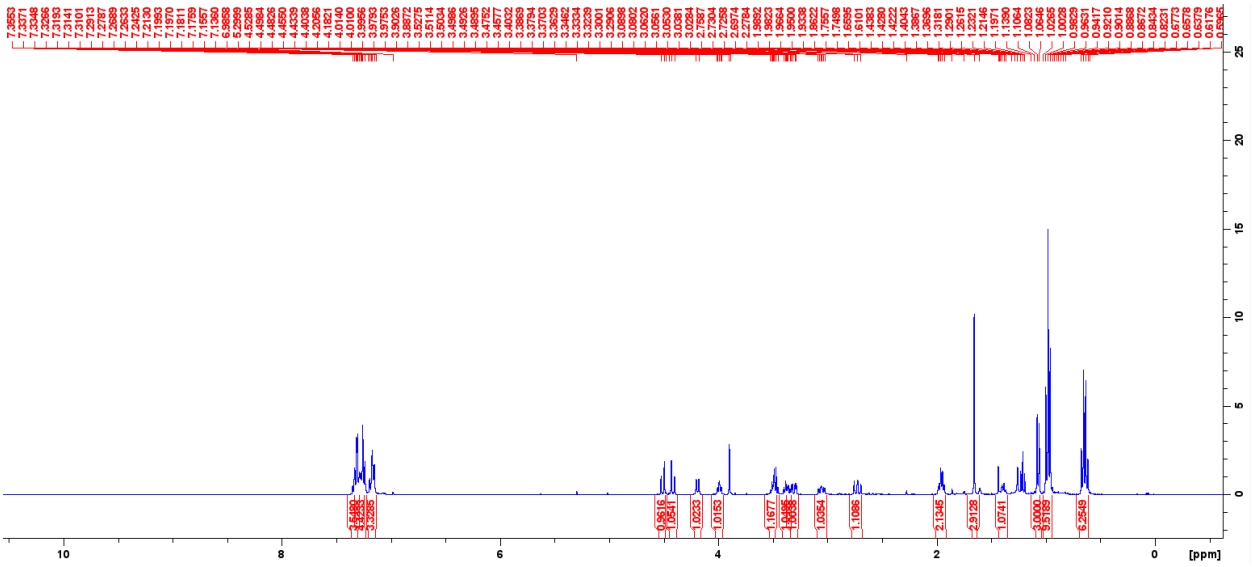
^{1}H NMR (400 MHz, $CDCl_3$)



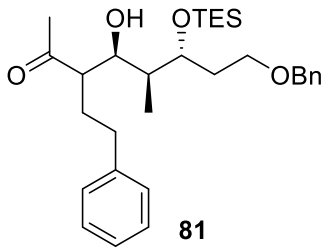


81

^{1}H NMR (400 MHz, $CDCl_3$)

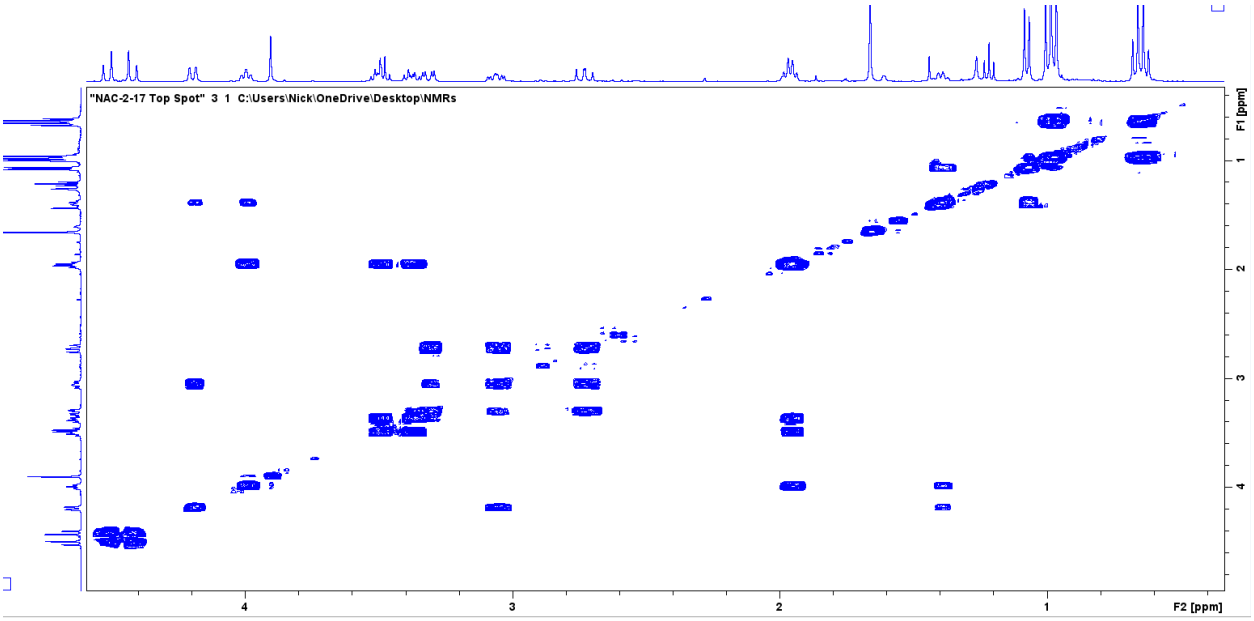


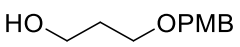
COSY Spectrum



81

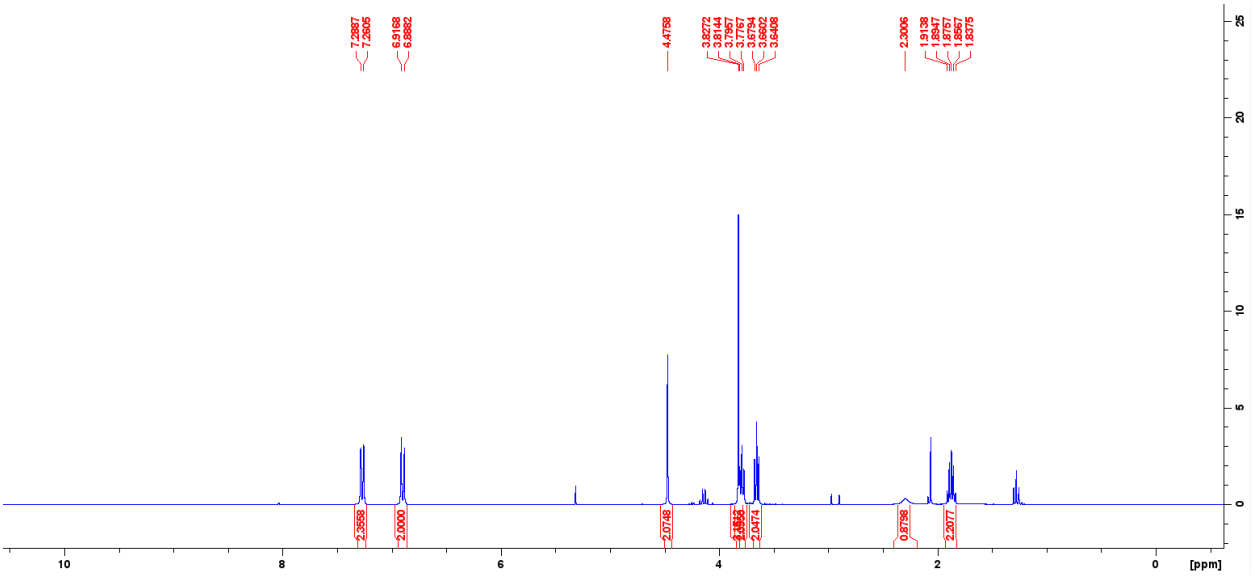
^{1}H NMR (400 MHz, $CDCl_3$)

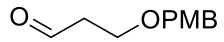




S1

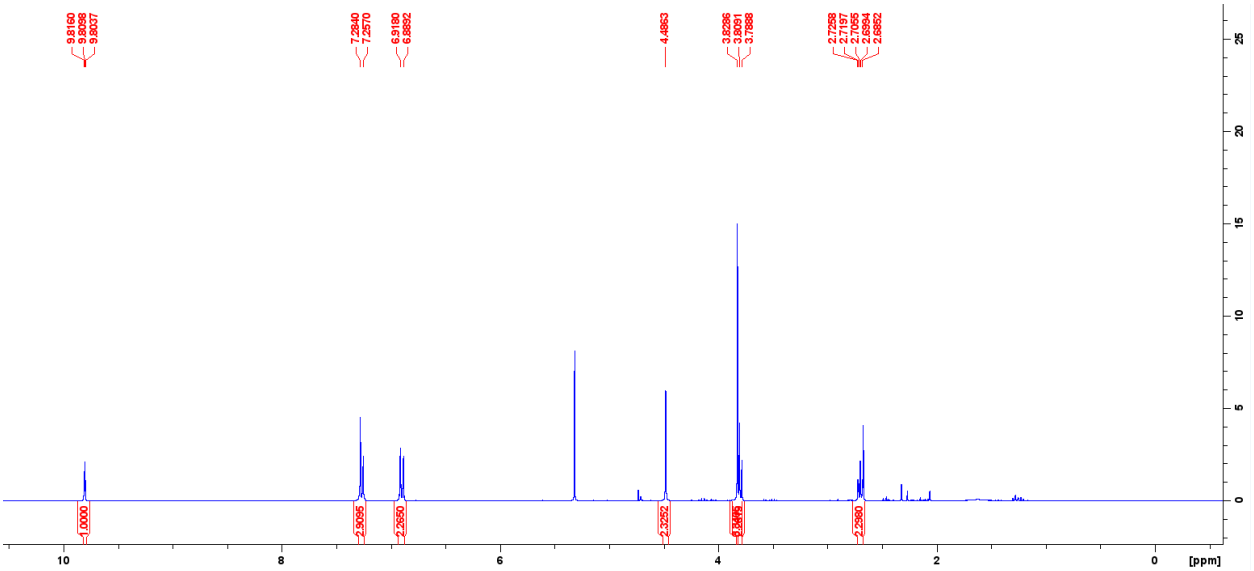
^{1}H NMR (400 MHz, $CDCl_3$)

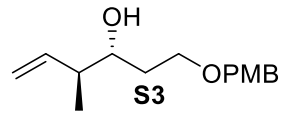




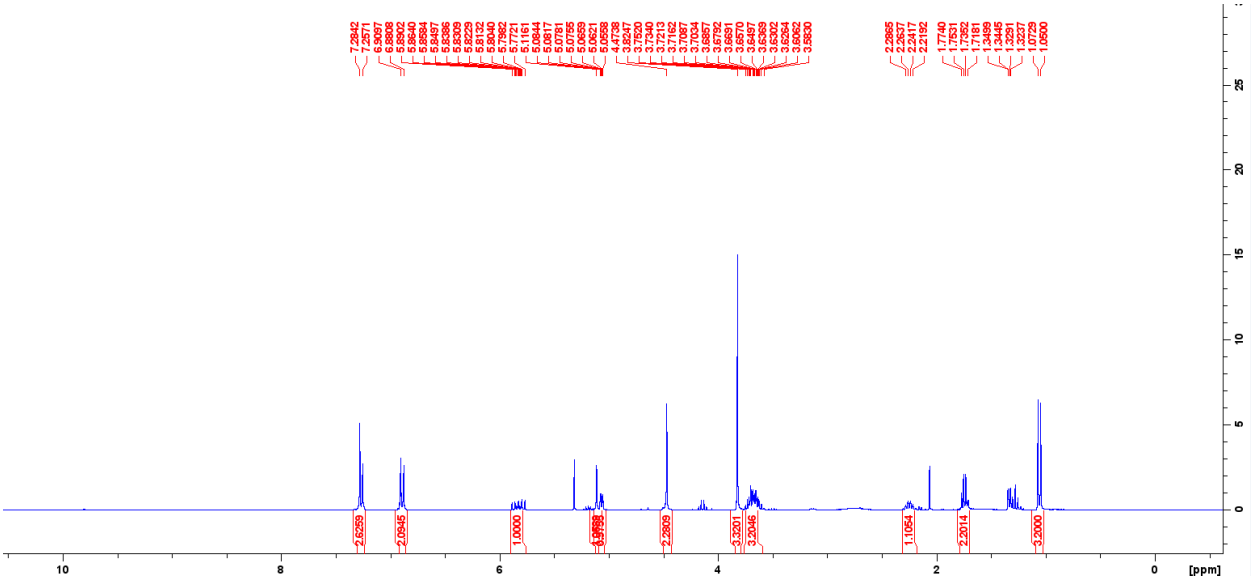
S2

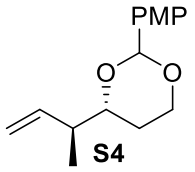
^{1}H NMR (300 MHz, $CDCl_3$)



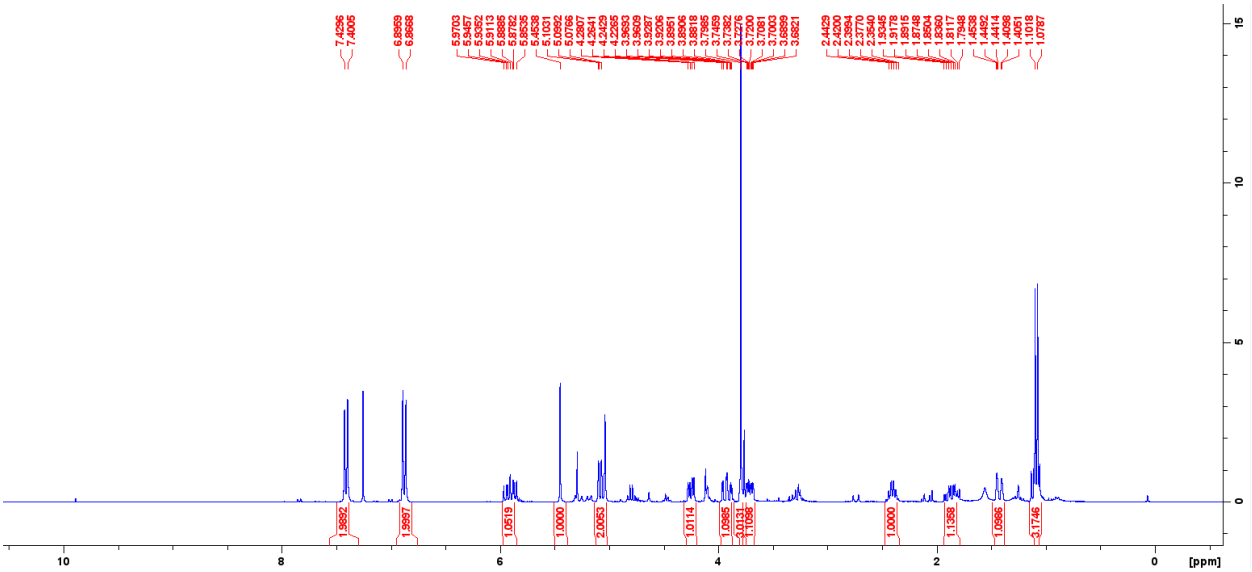


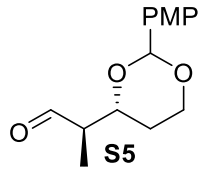
^{1}H NMR (300 MHz, $CDCl_3$)



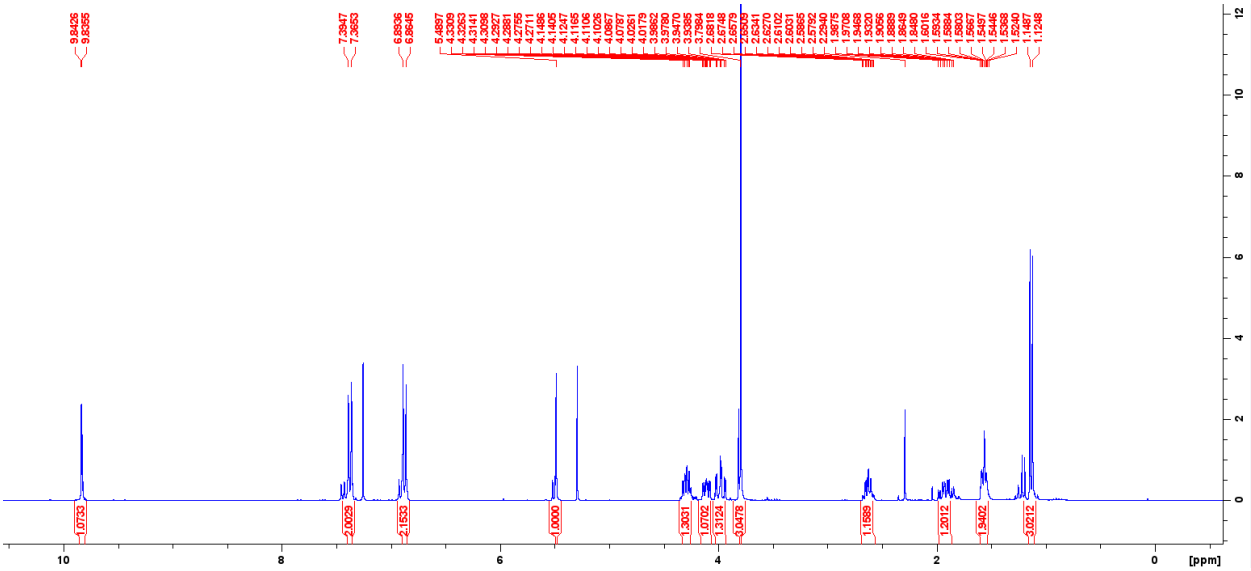


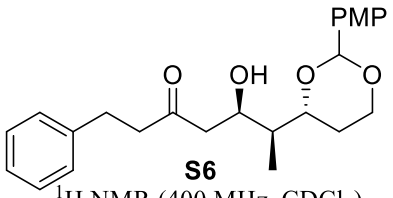
^{1}H NMR (300 MHz, $CDCl_3$)



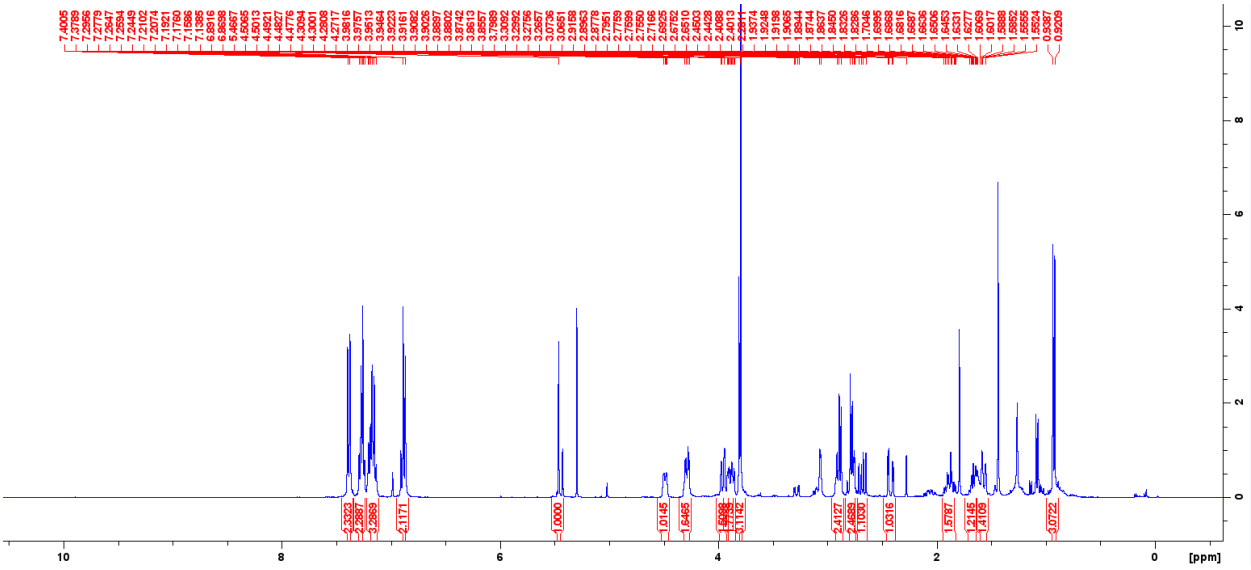


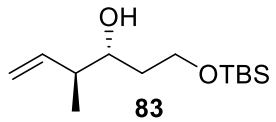
^{1}H NMR (300 MHz, $CDCl_3$)





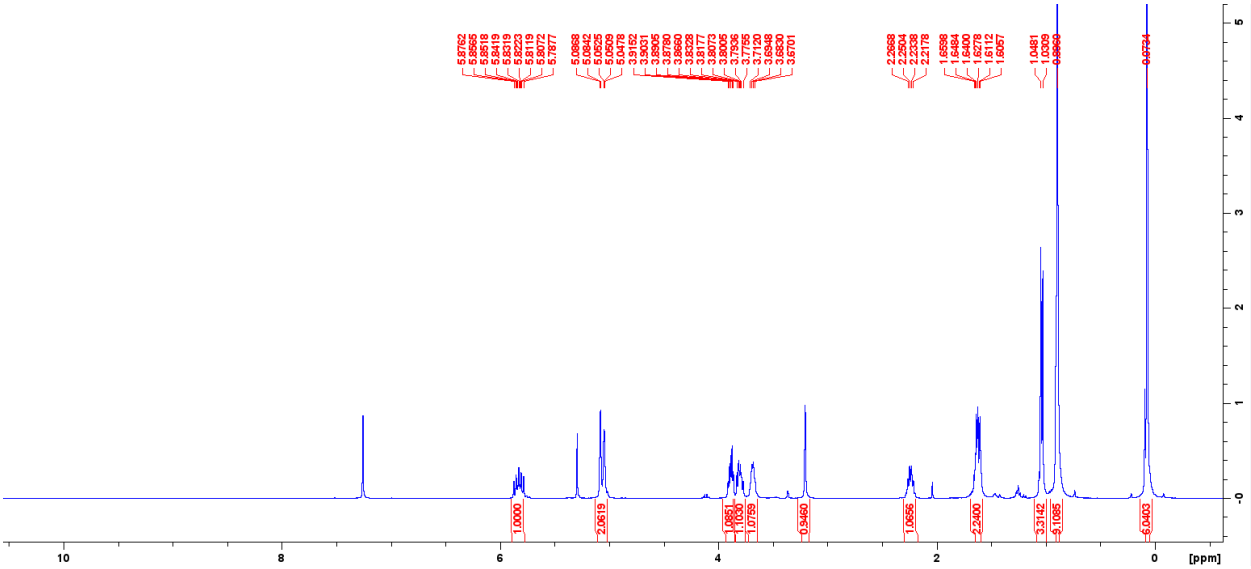
^{1}H NMR (400 MHz, $CDCl_3$)

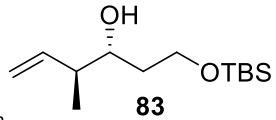




83

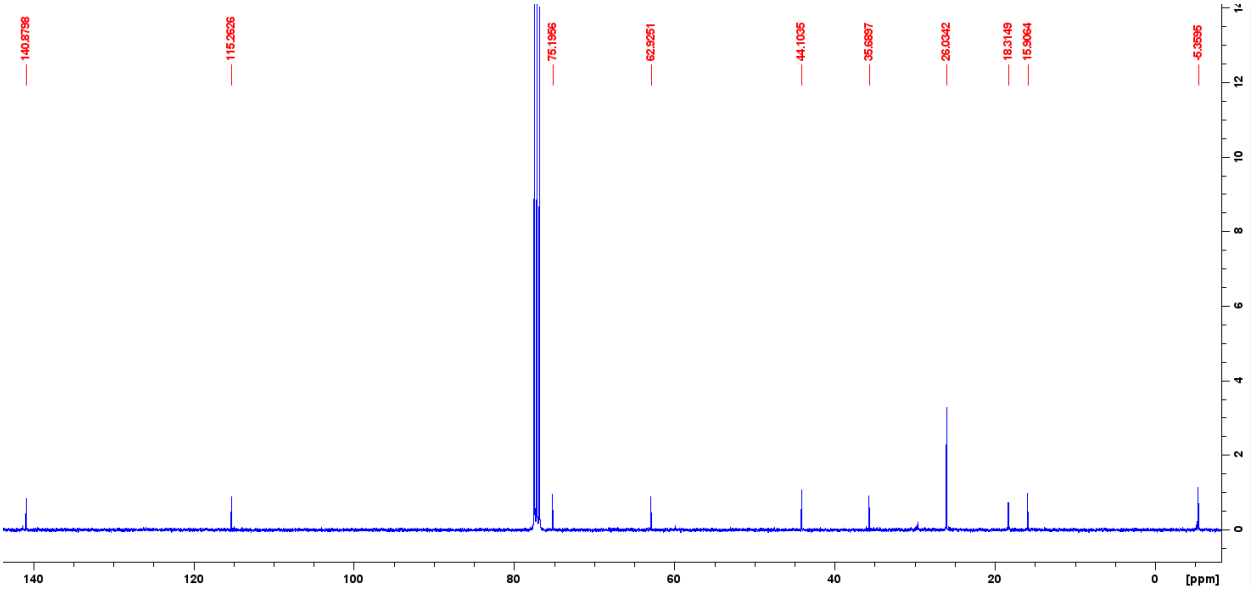
^{1}H NMR (400 MHz, $CDCl_3$)

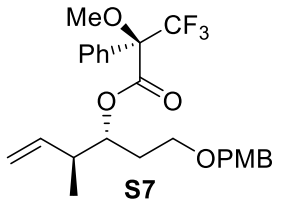




83

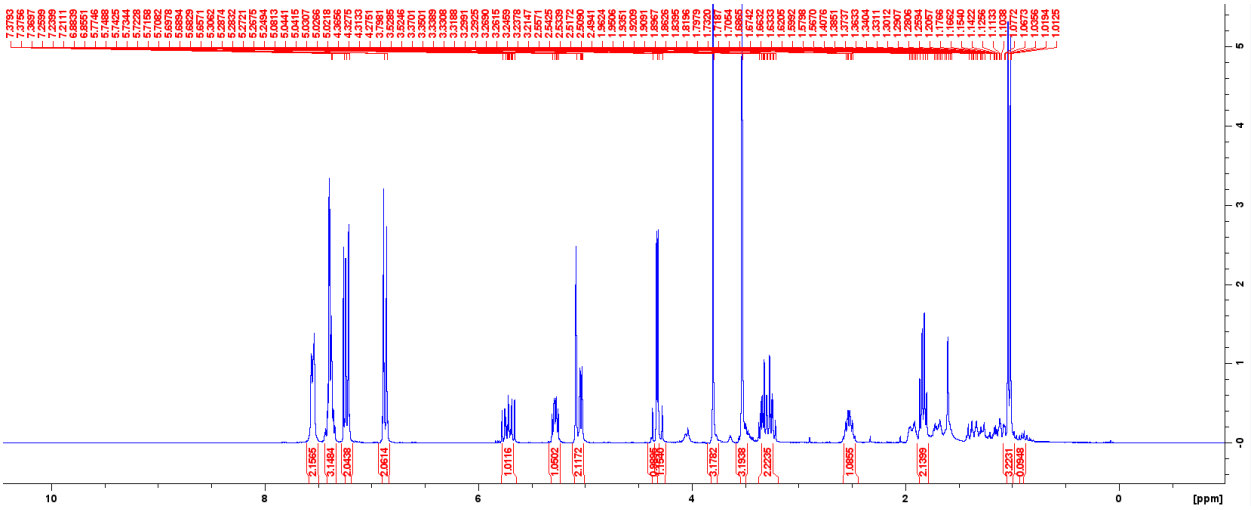
^{13}C NMR (400 MHz, $CDCl_3$)

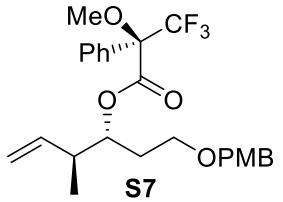




S7

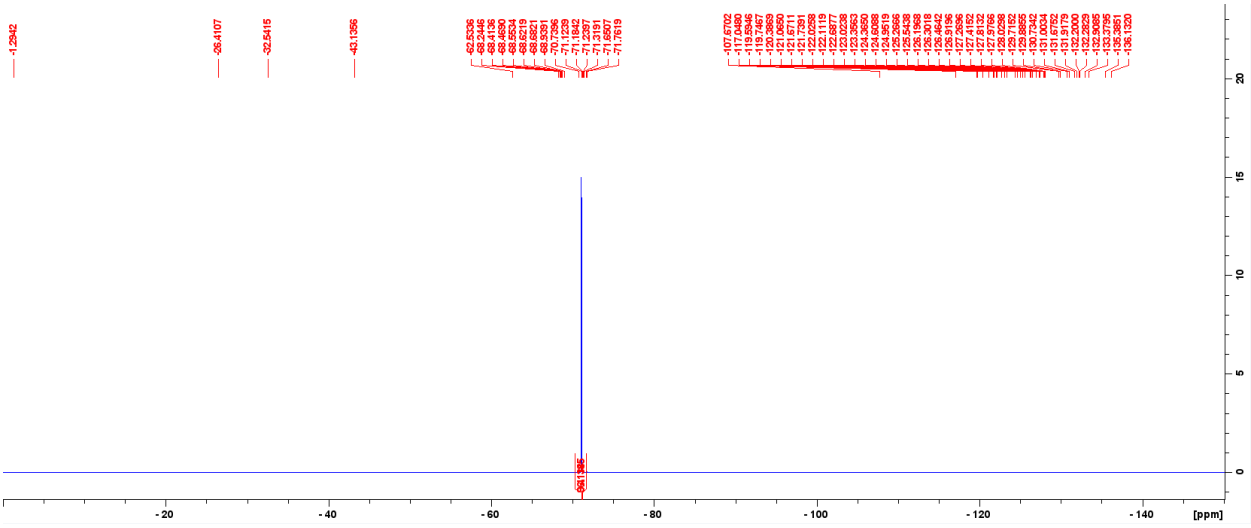
^{1}H NMR (300 MHz, $CDCl_3$)

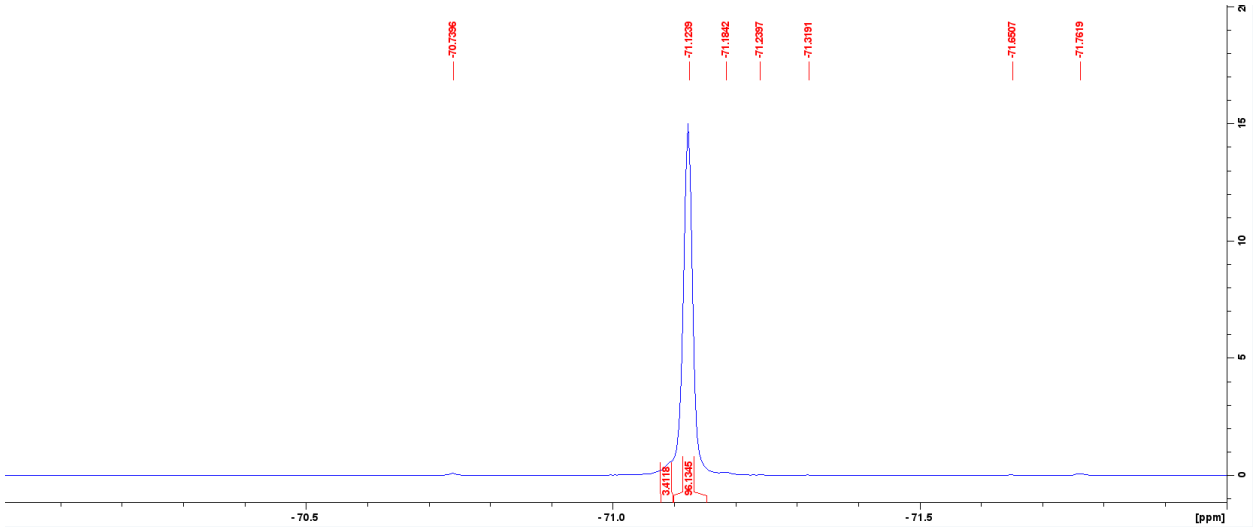




S7

^{19}F NMR (300 MHz, $CDCl_3$)

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-71.1239
-71.1842
-71.2397
-71.3191
-71.6507
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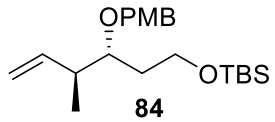
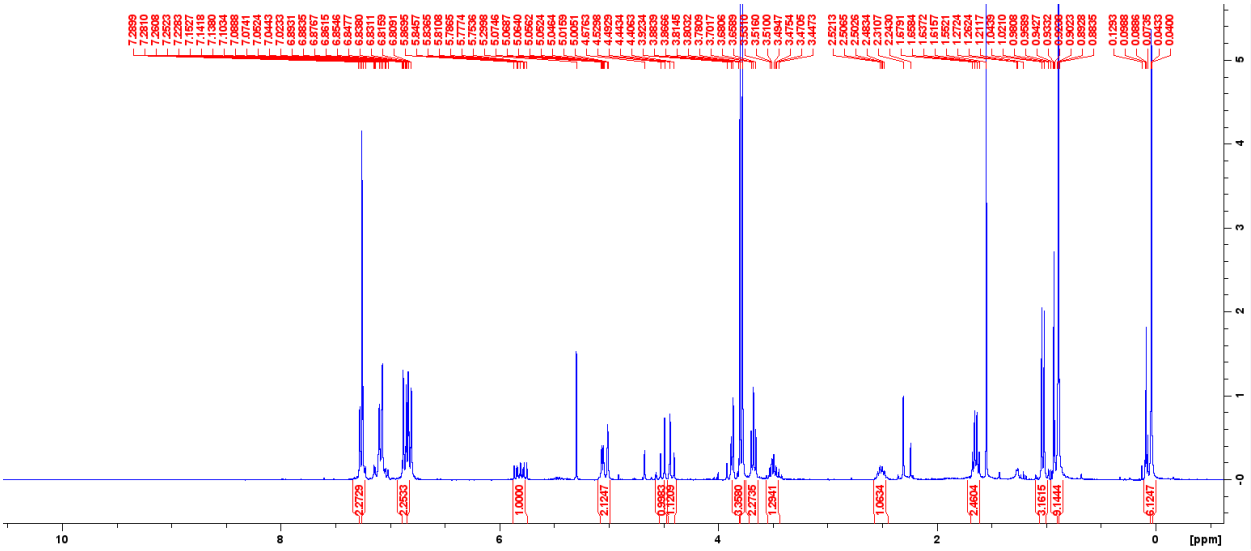
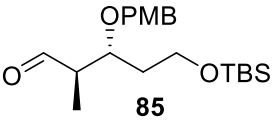
3.4118
96.1345
-70.5
-71.0
-71.5
[ppm]
0
5
10
15
20



84

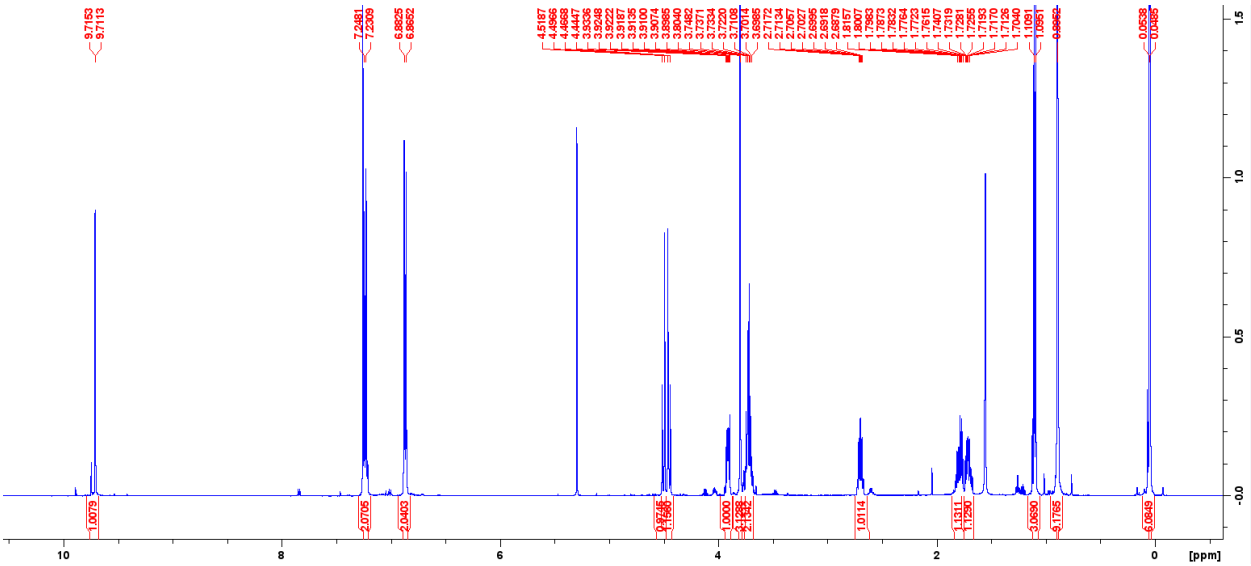
^{1}H NMR (400 MHz, $CDCl_3$)

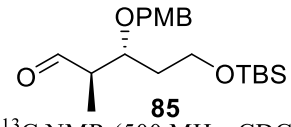




85

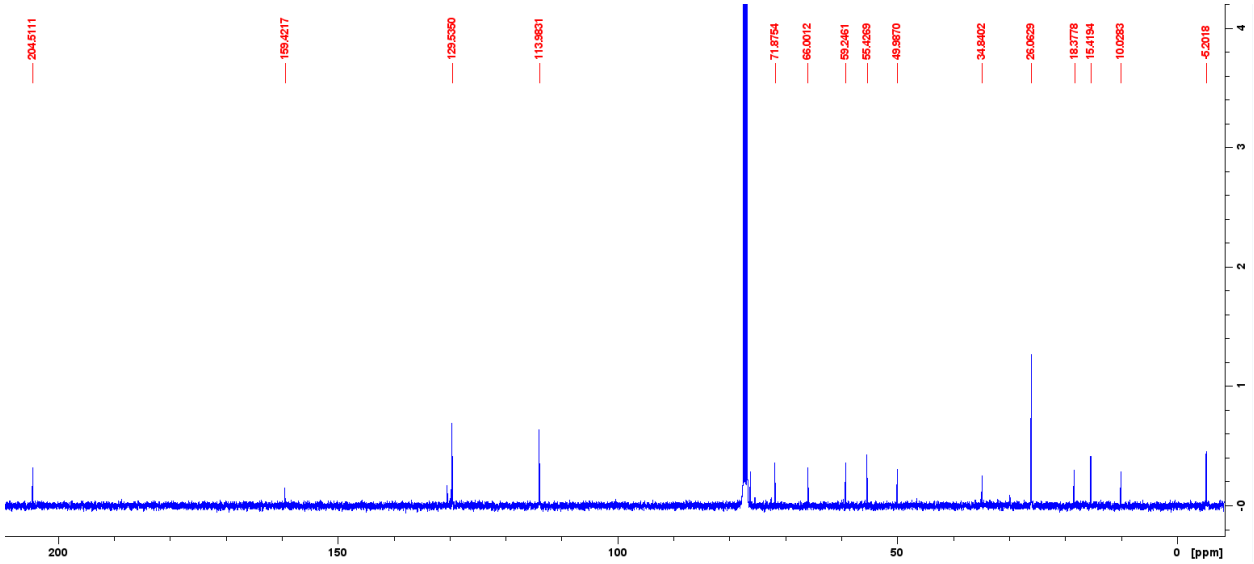
^{1}H NMR (500 MHz, $CDCl_3$)

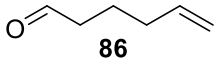




85

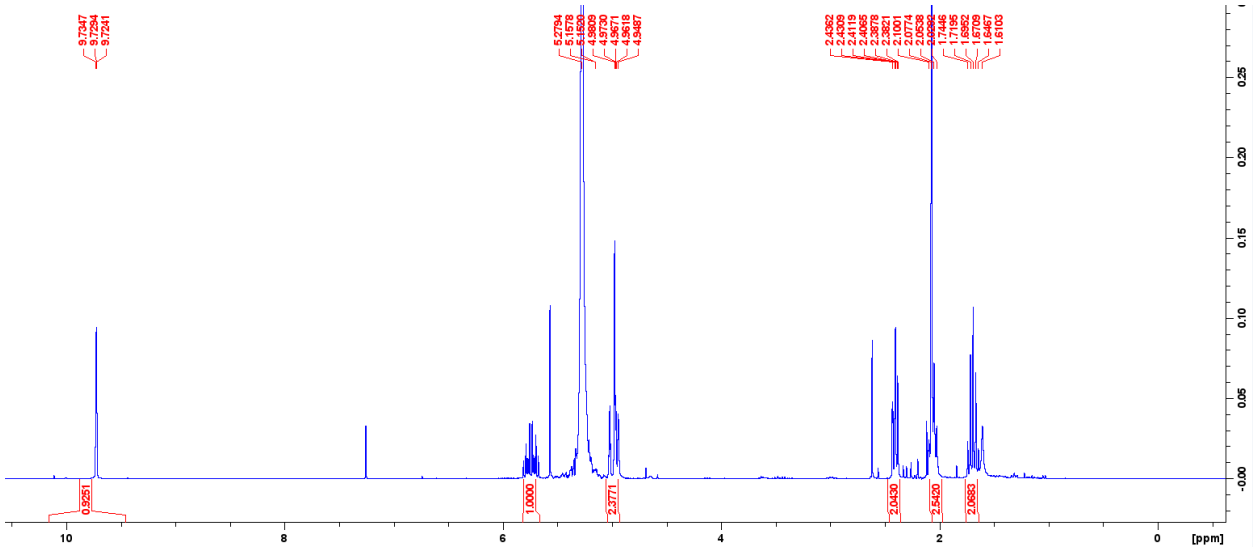
^{13}C NMR (500 MHz, $CDCl_3$)

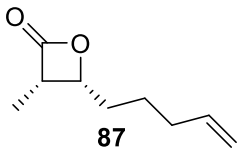




86

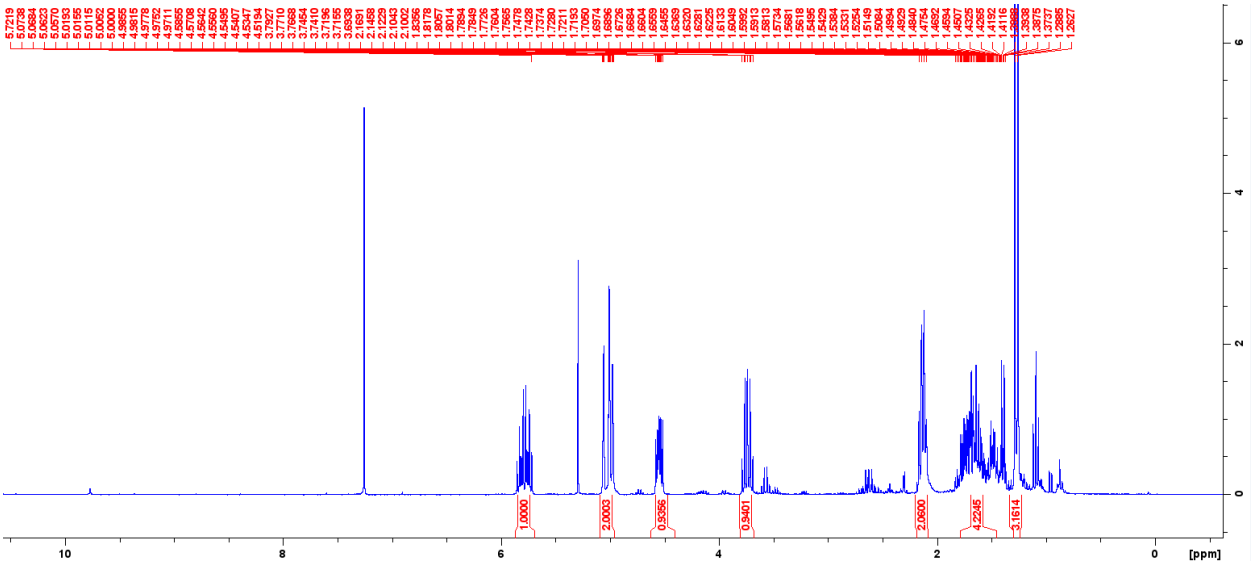
^{1}H NMR (300 MHz, $CDCl_3$)

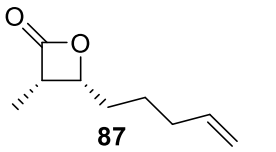




87

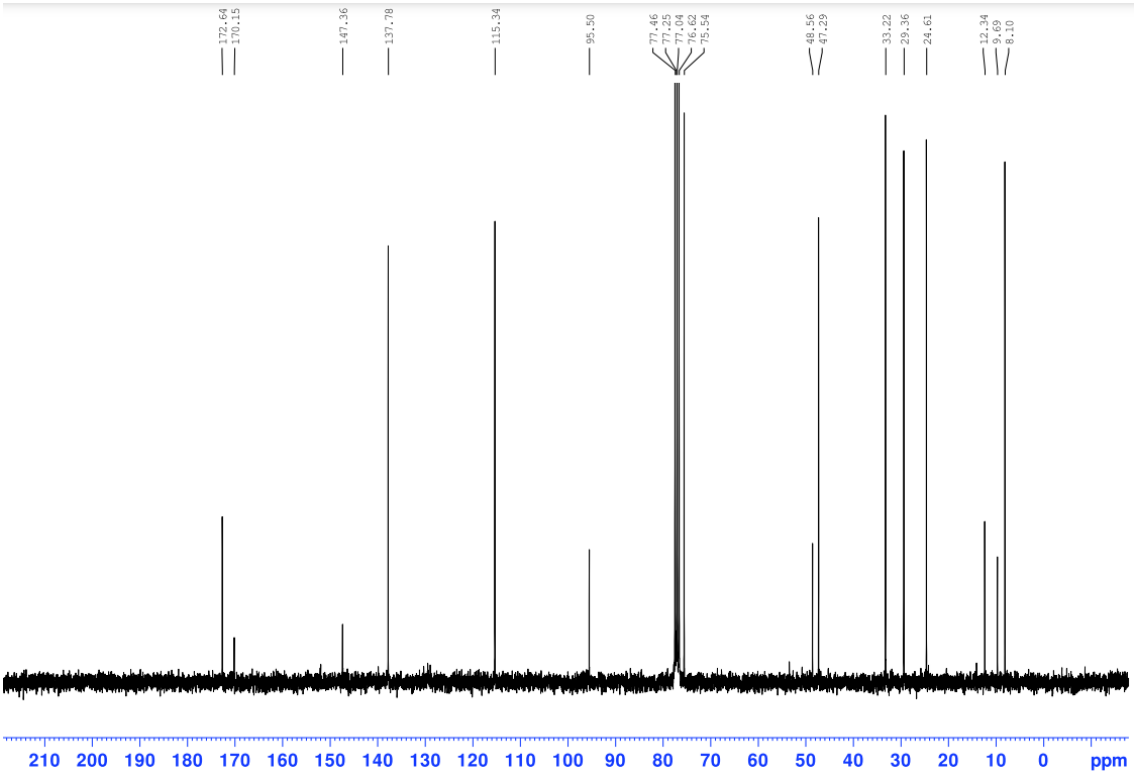
^{1}H NMR (300 MHz, $CDCl_3$)

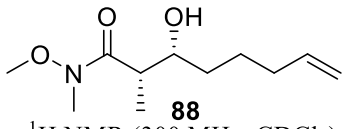




87

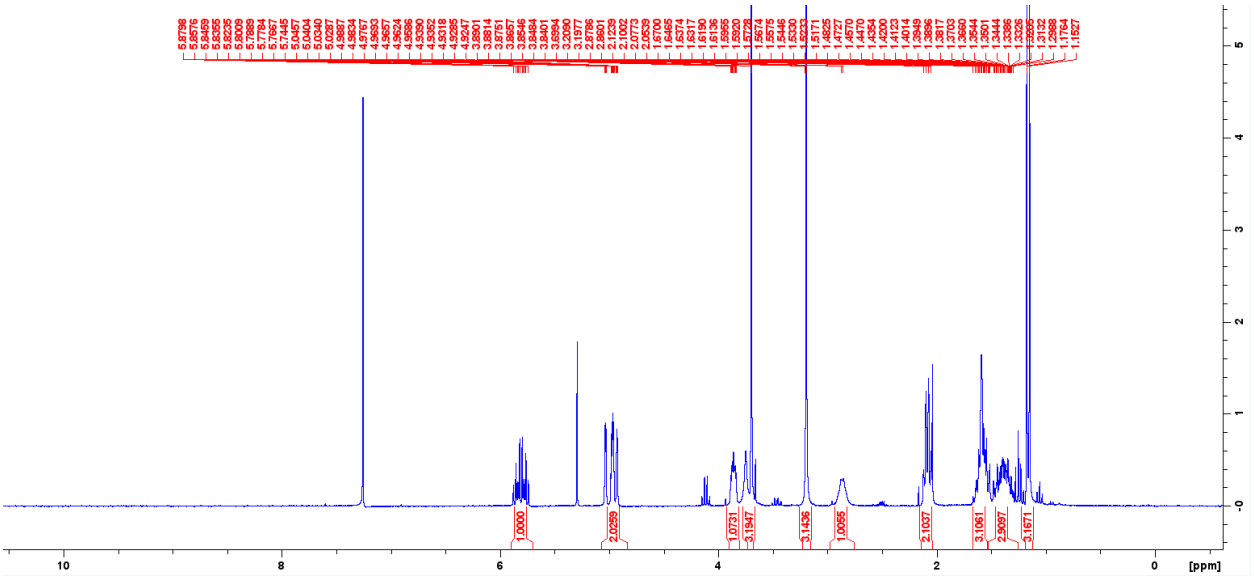
^{13}C NMR (300 MHz, $CDCl_3$)

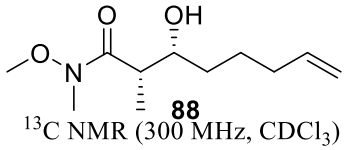




88

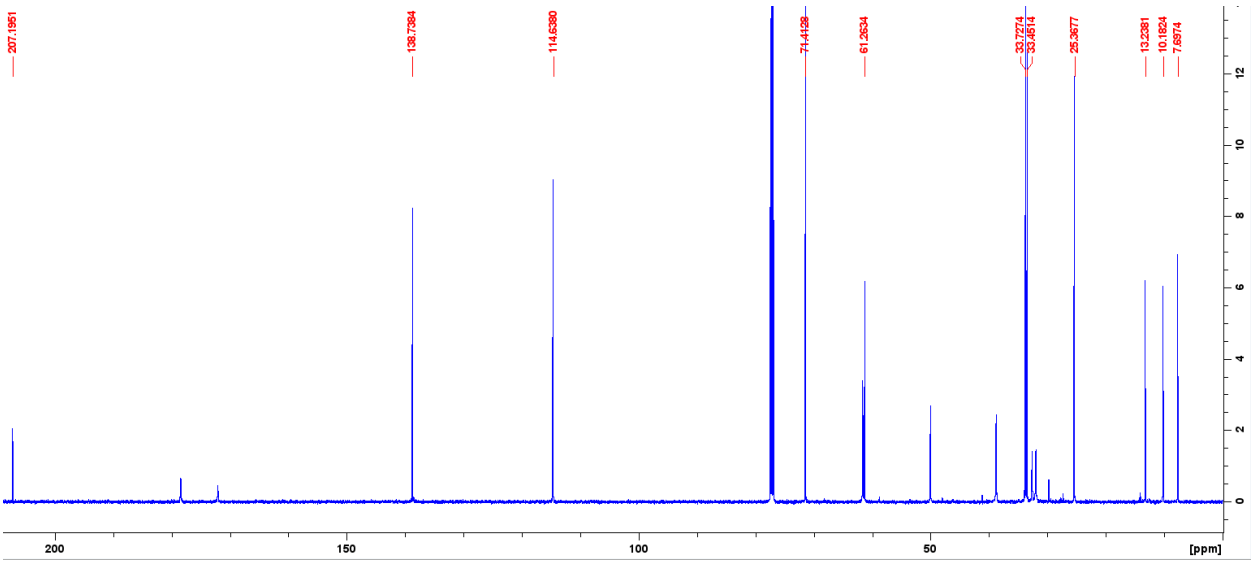
^{1}H NMR (300 MHz, $CDCl_3$)

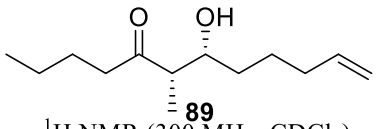




88

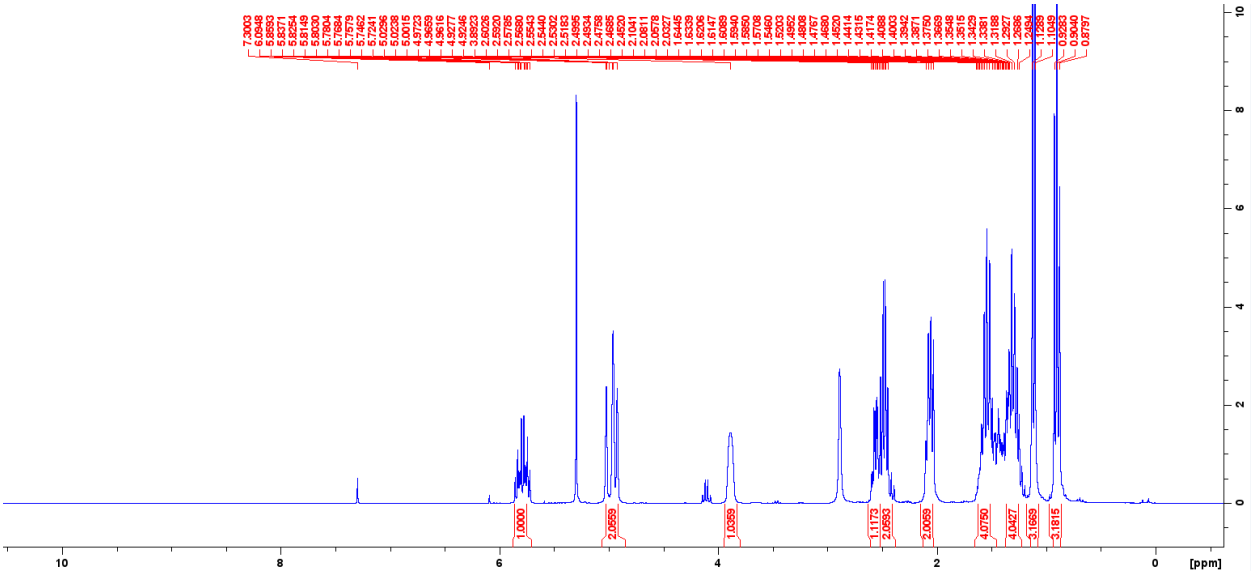
^{13}C NMR (300 MHz, $CDCl_3$)

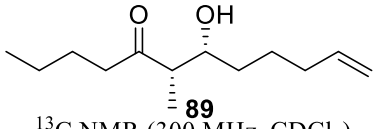




89

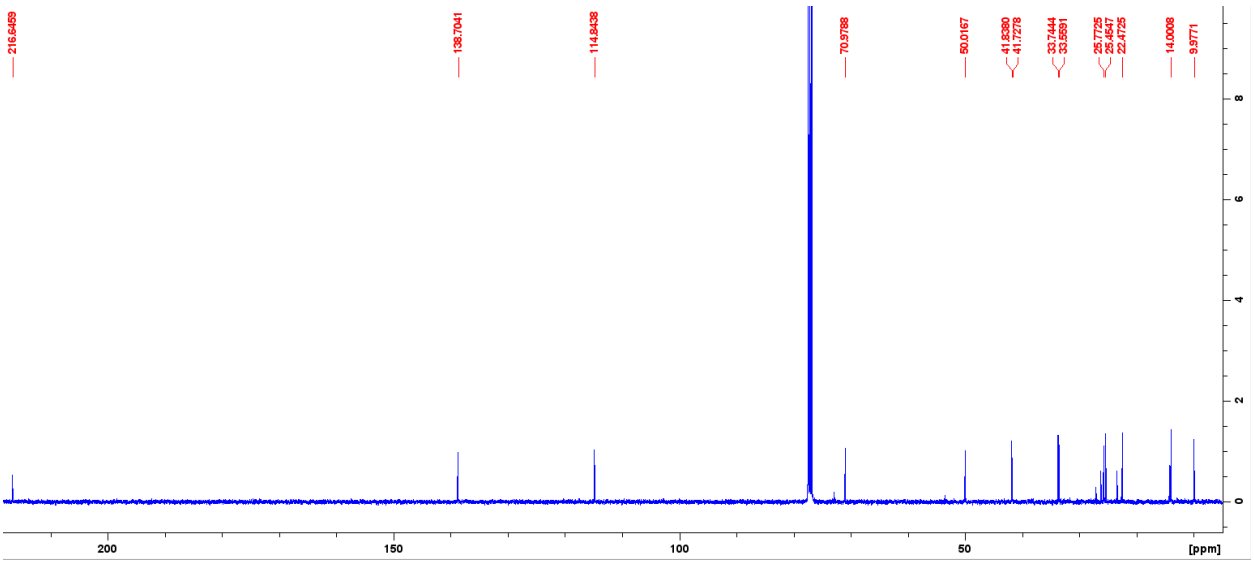
^{1}H NMR (300 MHz, $CDCl_3$)

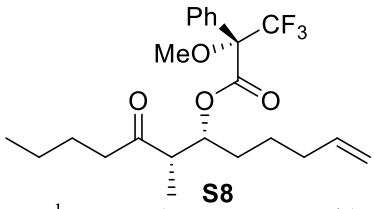




89

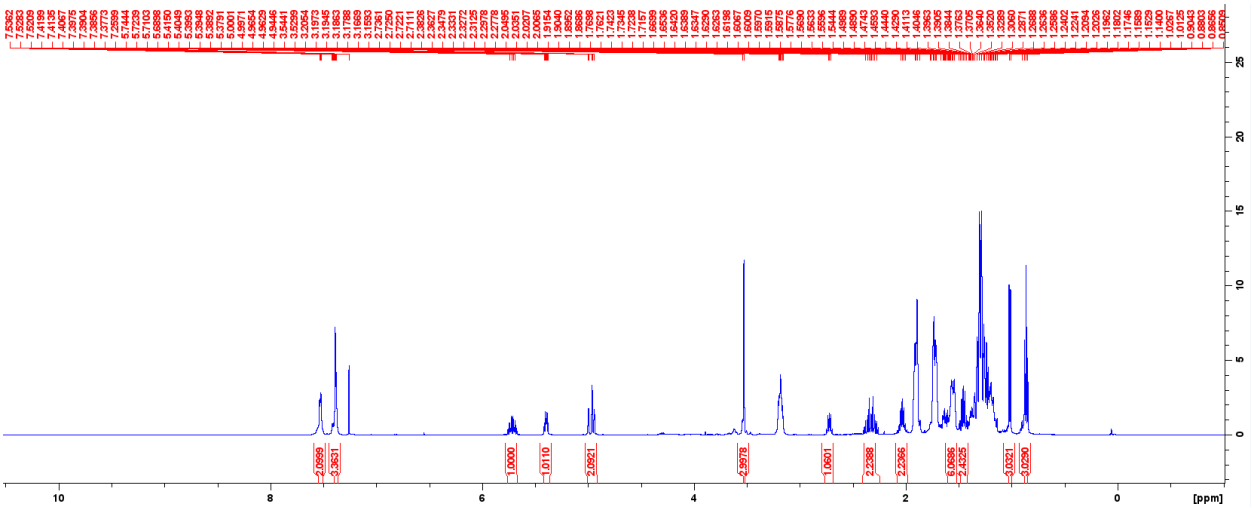
^{13}C NMR (300 MHz, $CDCl_3$)

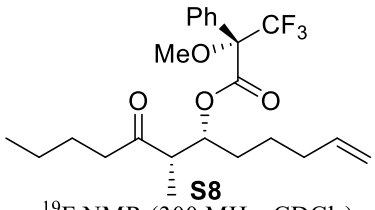




S8

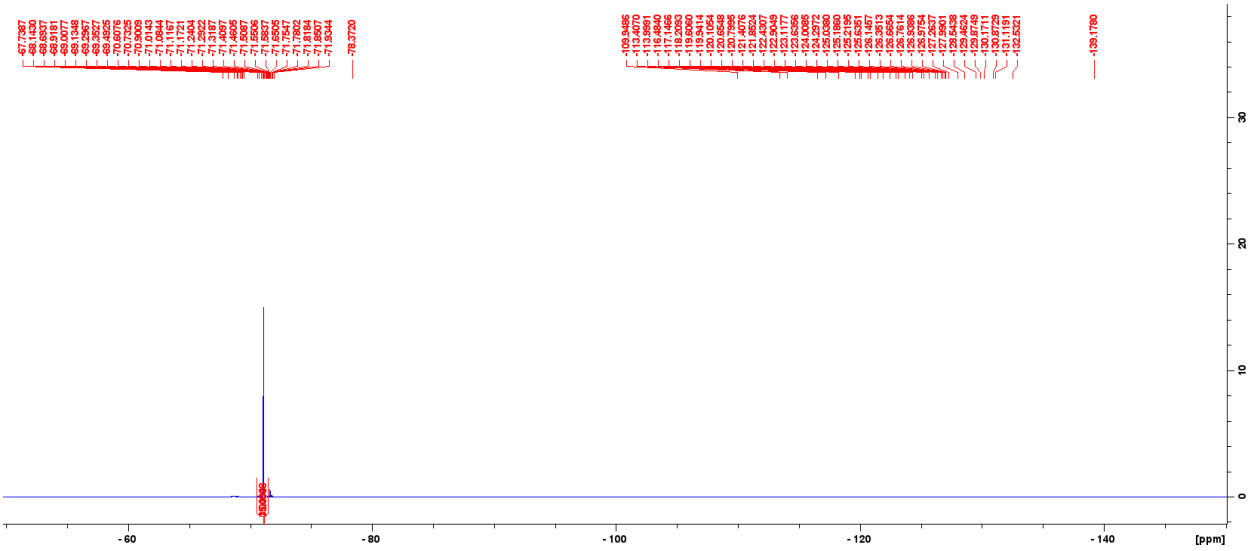
^{1}H NMR (300 MHz, $CDCl_3$)

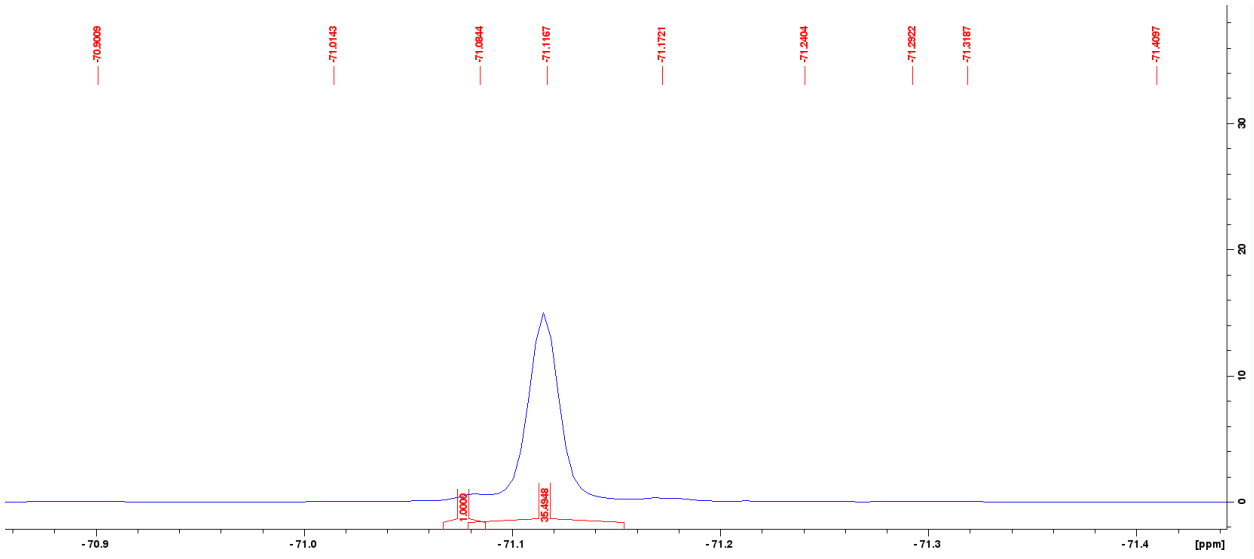




S8

^{19}F NMR (300 MHz, $CDCl_3$)

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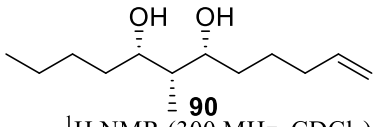
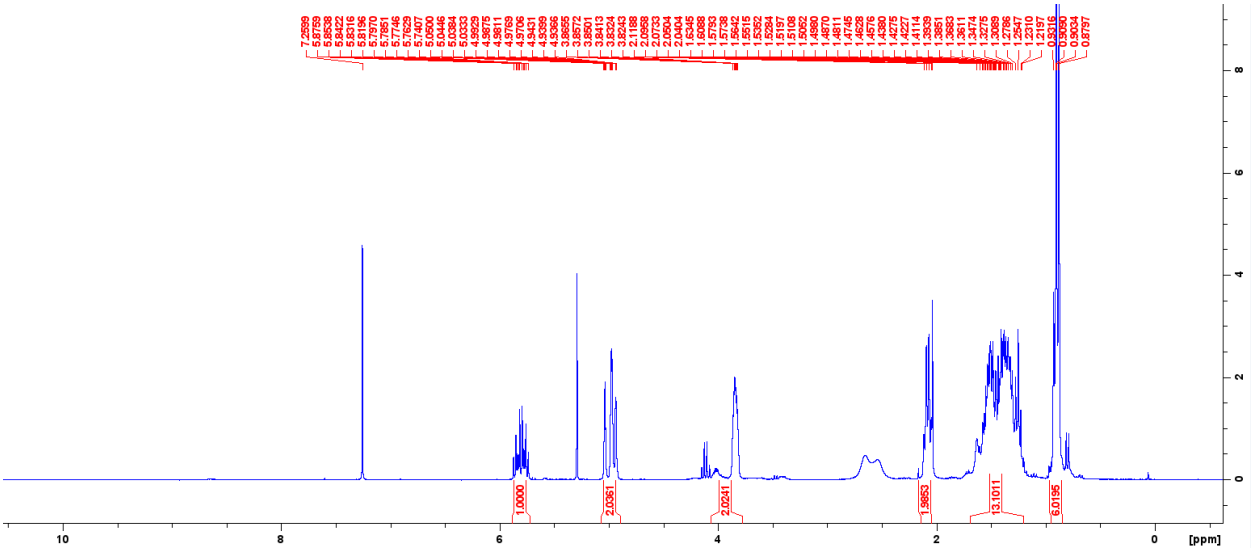
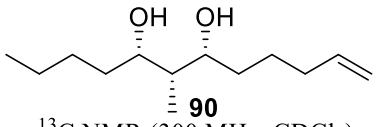
-71.0844
-71.1167
-71.1721
-71.2404
-71.2922
-71.3187
-71.4097
30
20
10
0
1.0000
35.4948
-70.9
-71.0
-71.1
-71.2
-71.3
-71.4
[ppm]



90

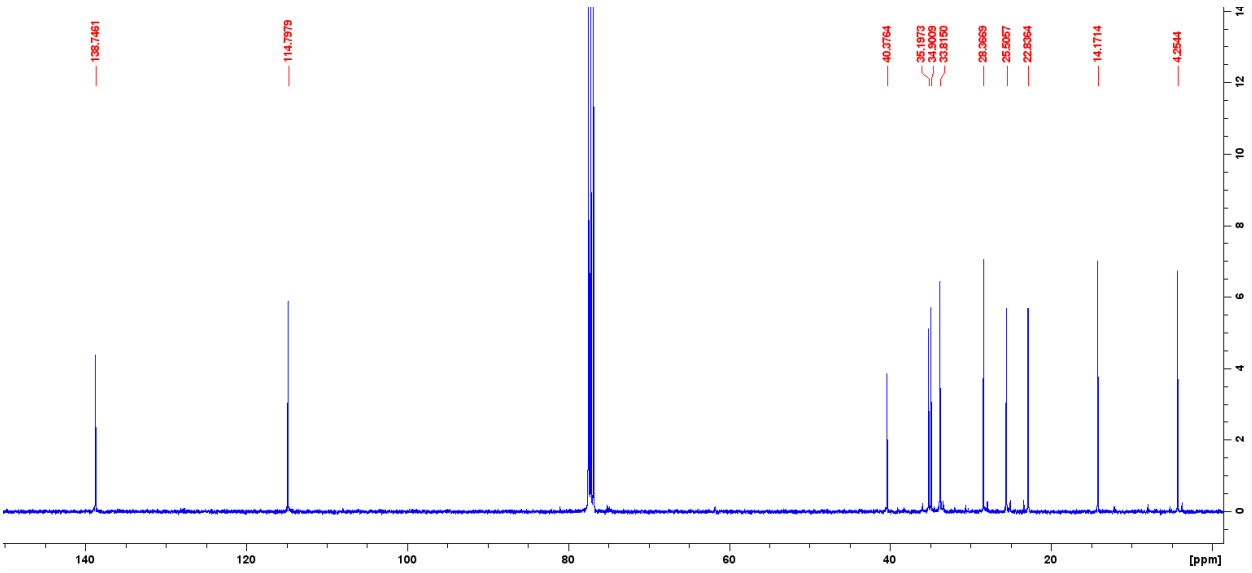
^{1}H NMR (300 MHz, $CDCl_3$)

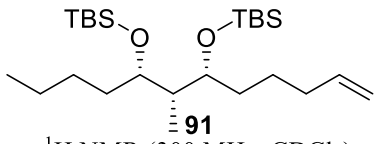




90

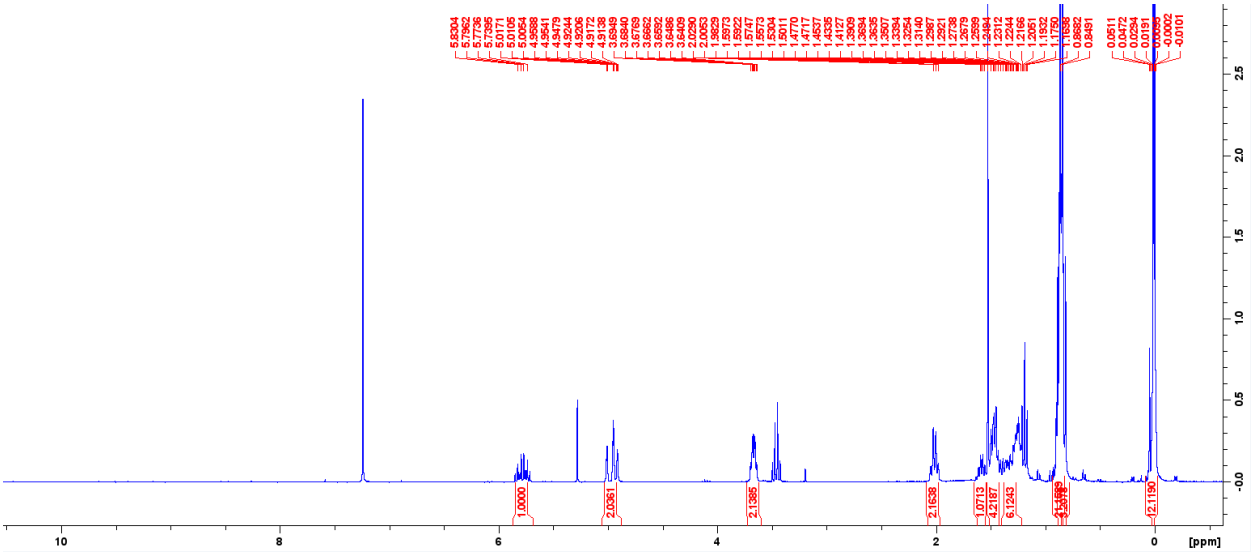
^{13}C NMR (300 MHz, $CDCl_3$)

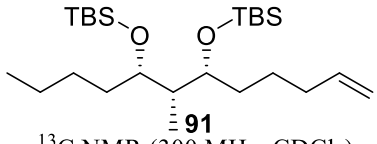




91

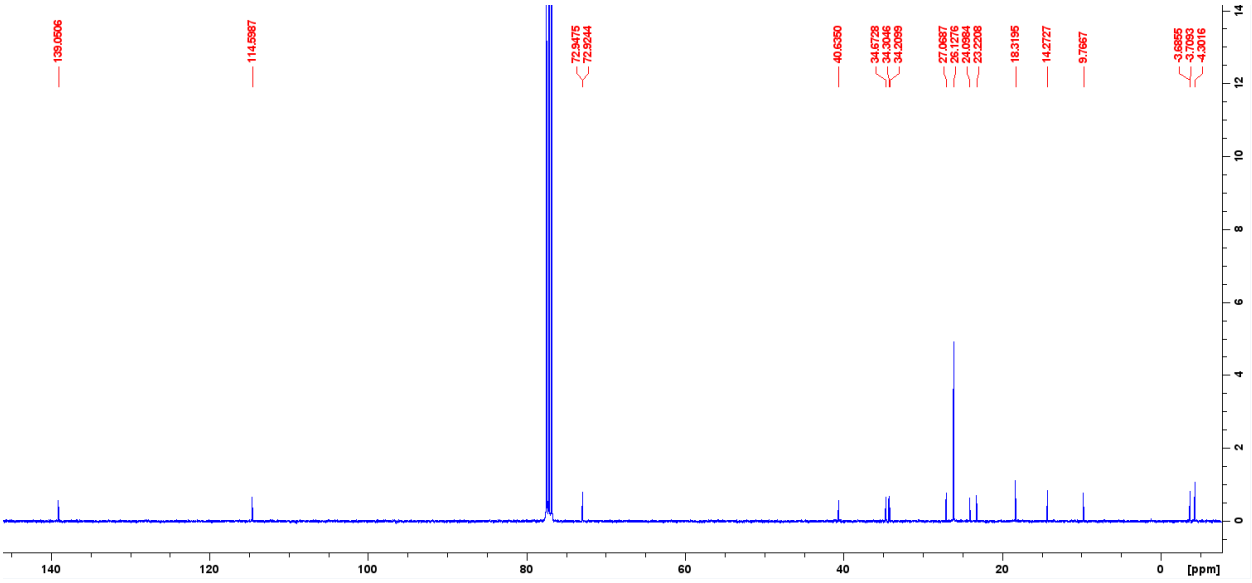
^{1}H NMR (300 MHz, $CDCl_3$)

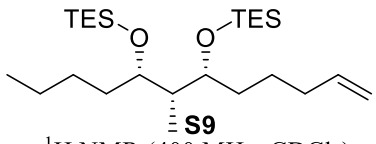




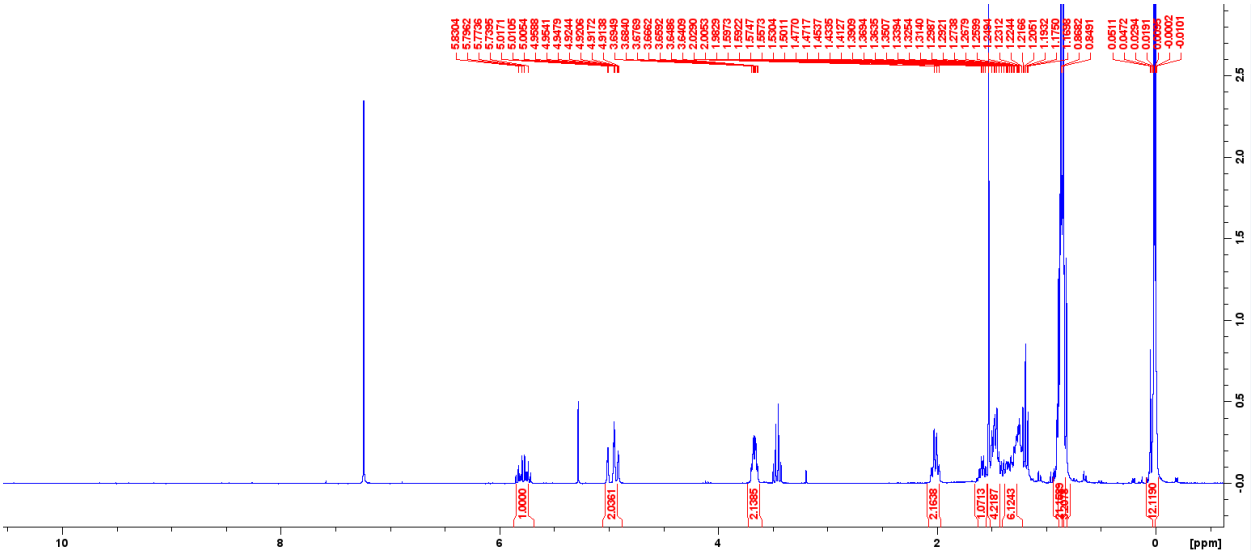
91

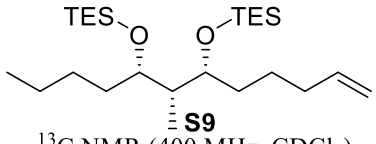
^{13}C NMR (300 MHz, $CDCl_3$)



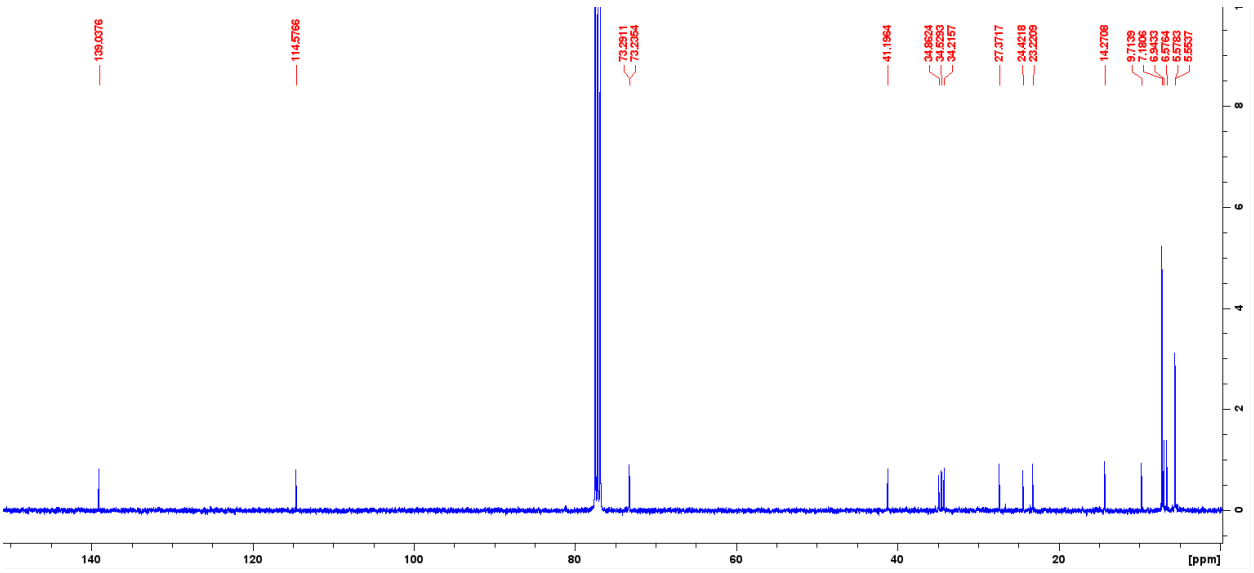


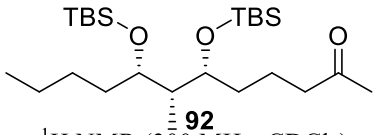
^{1}H NMR (400 MHz, $CDCl_3$)





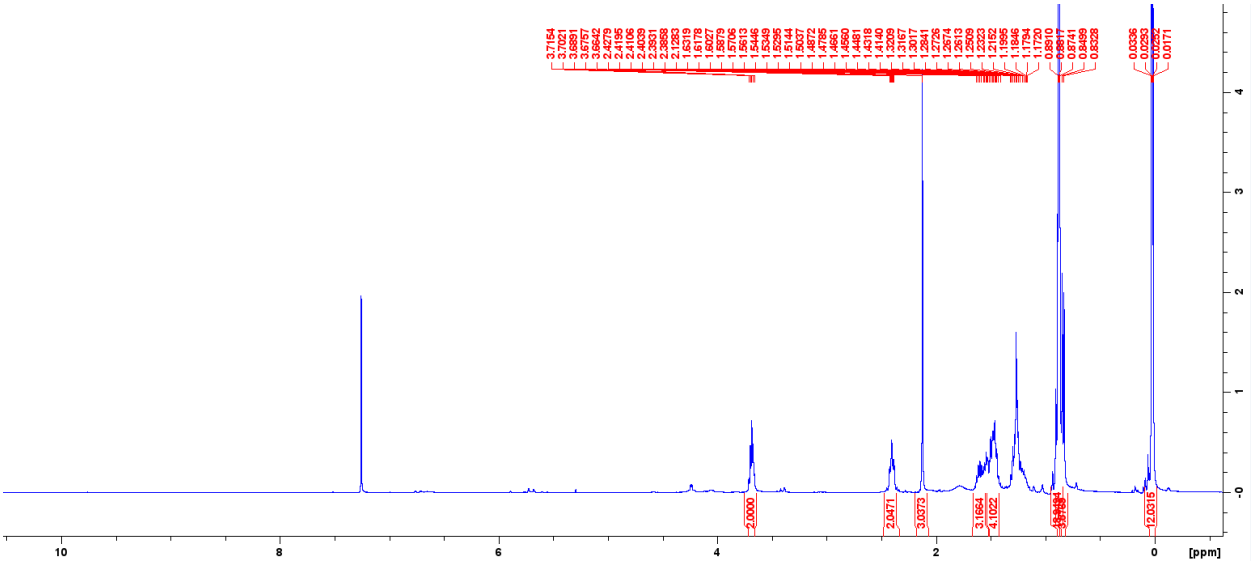
^{13}C NMR (400 MHz, $CDCl_3$)

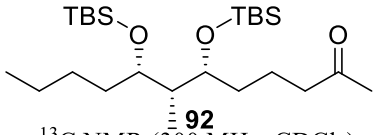




92

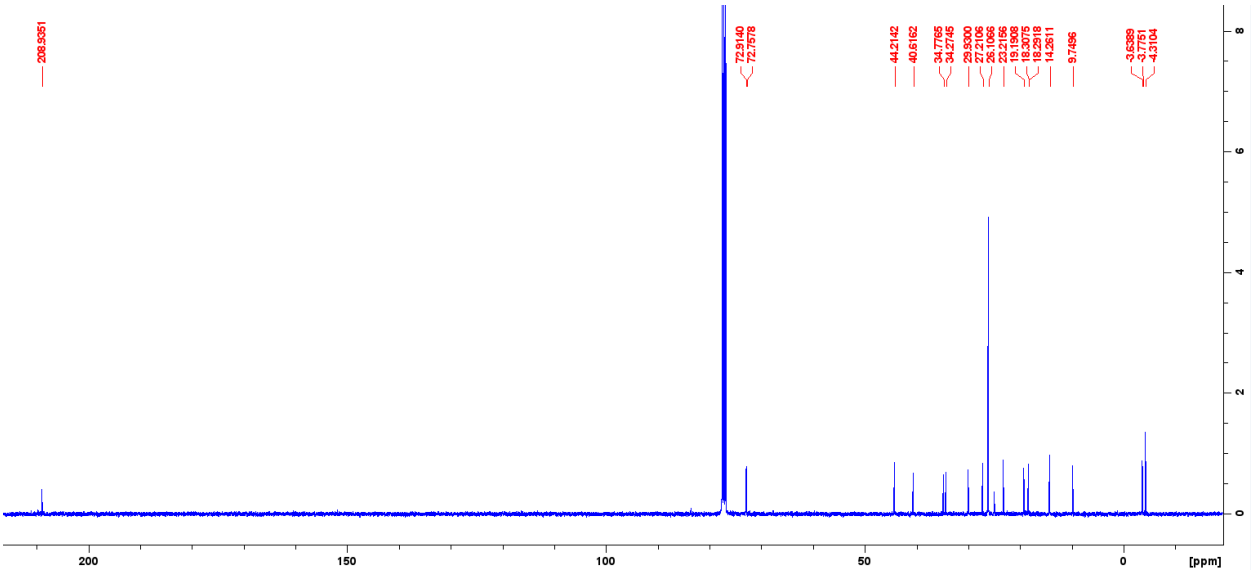
^{1}H NMR (300 MHz, $CDCl_3$)

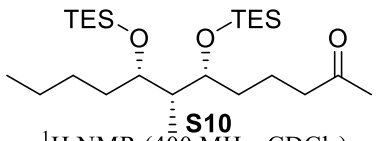




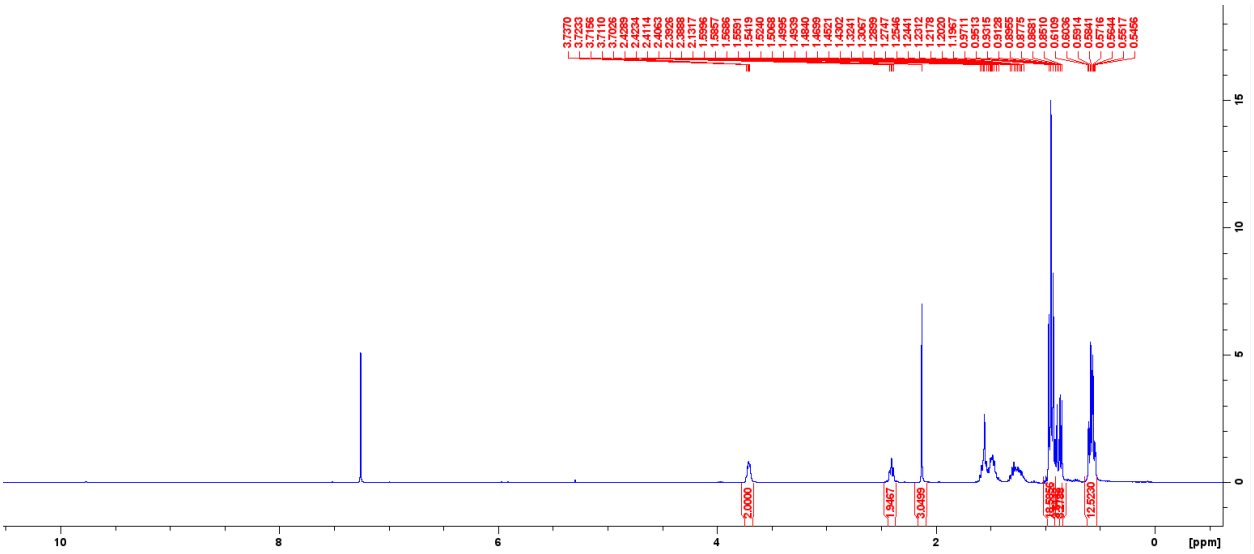
92

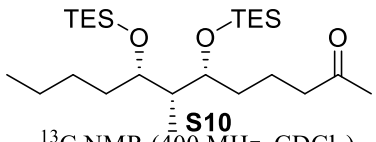
^{13}C NMR (300 MHz, $CDCl_3$)



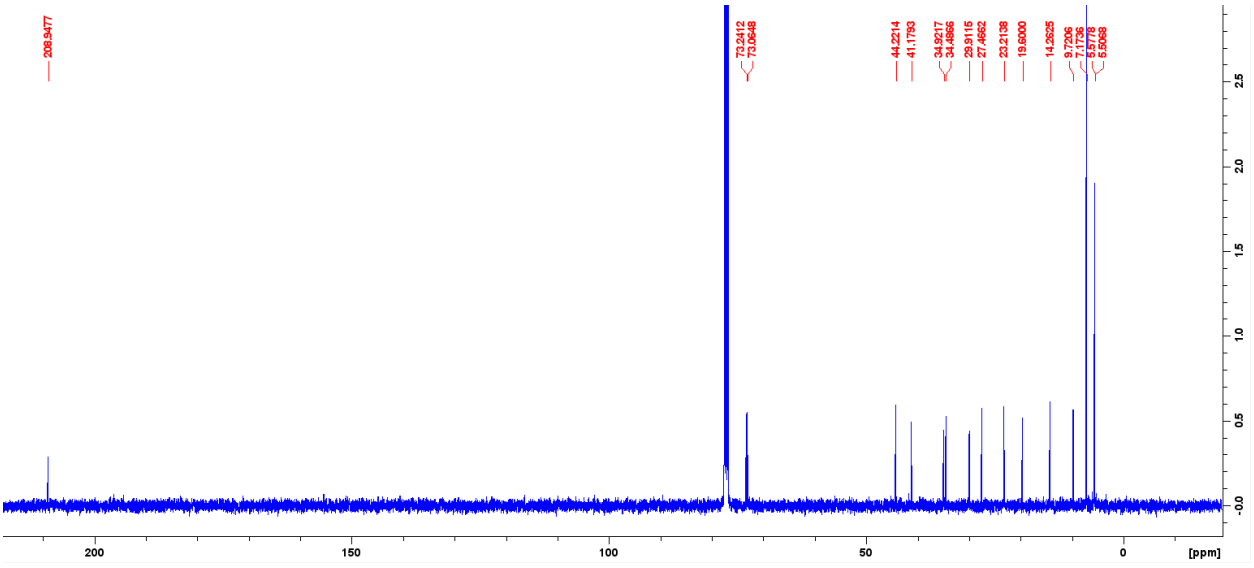


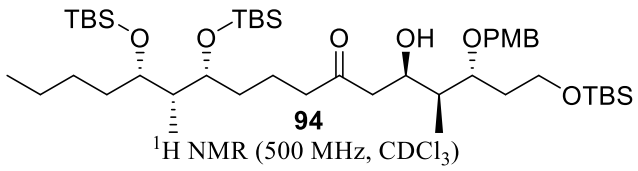
^{1}H NMR (400 MHz, $CDCl_3$)





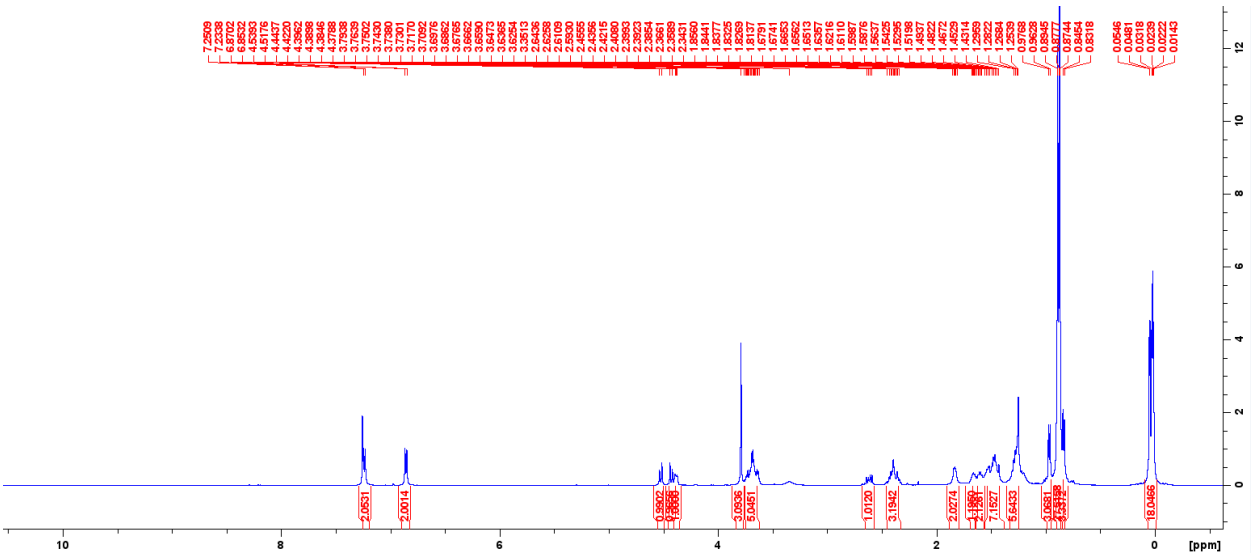
^{13}C NMR (400 MHz, $CDCl_3$)

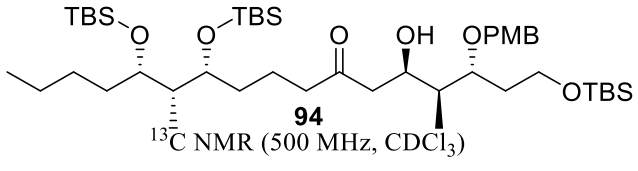




94

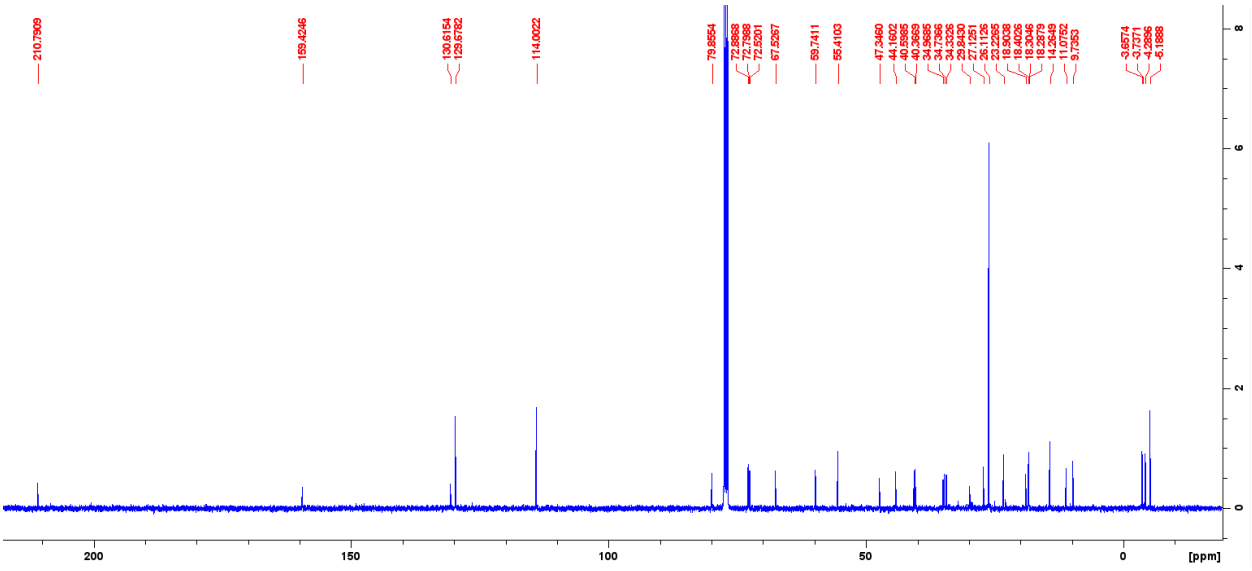
^{1}H NMR (500 MHz, $CDCl_3$)

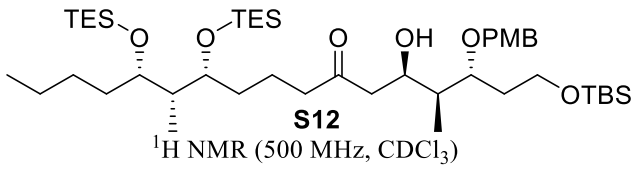




94

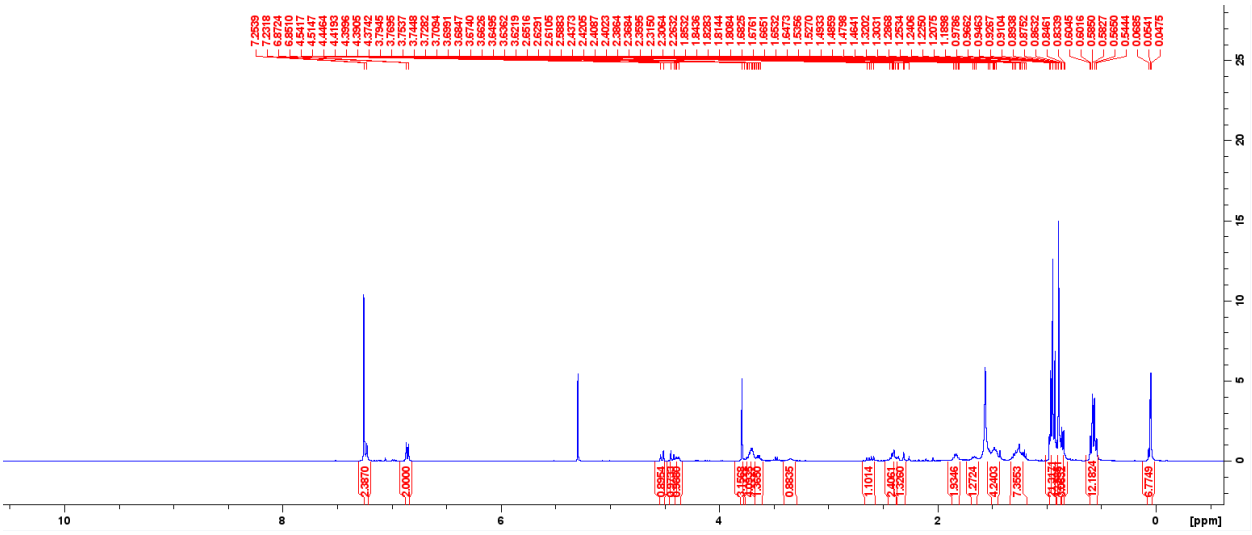
^{13}C NMR (500 MHz, $CDCl_3$)

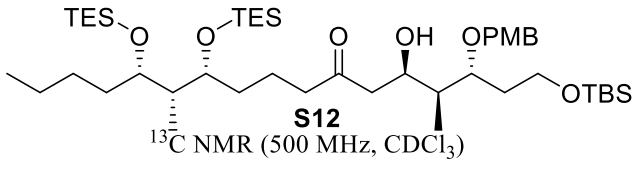




S12

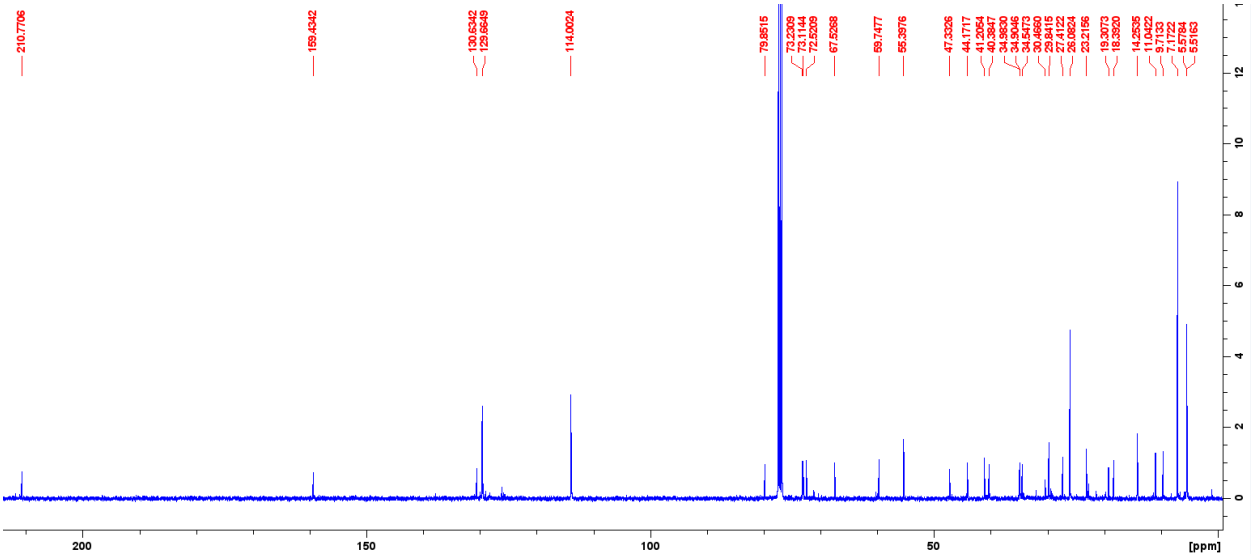
^{1}H NMR (500 MHz, $CDCl_3$)

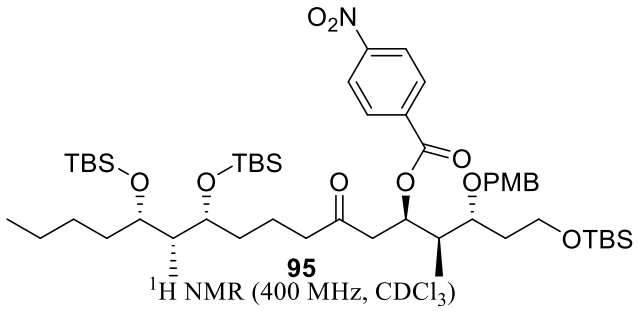




S12

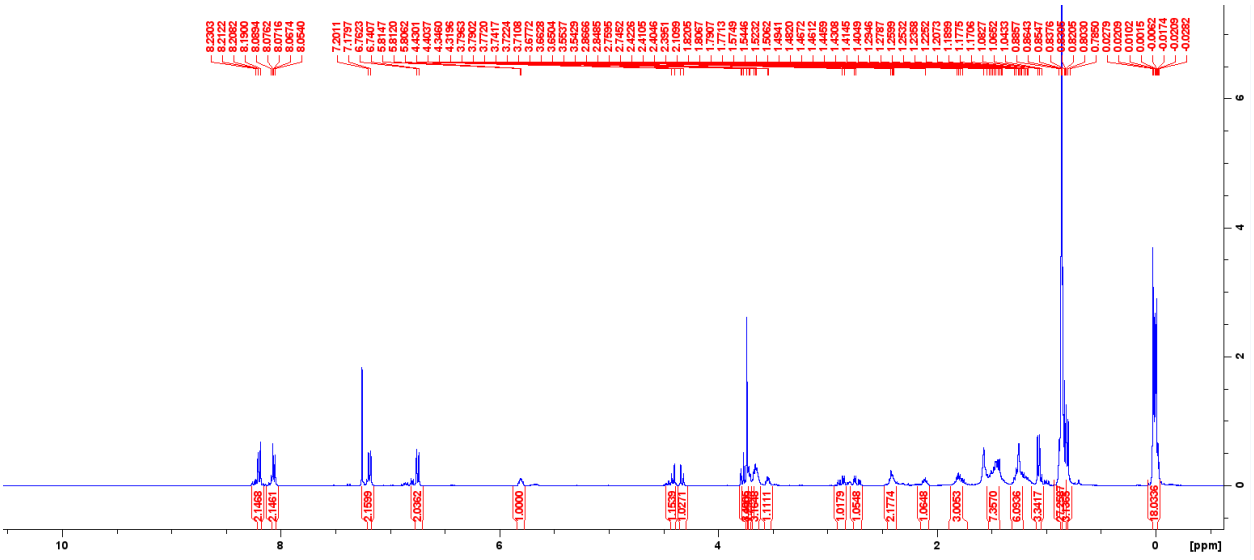
^{13}C NMR (500 MHz, $CDCl_3$)

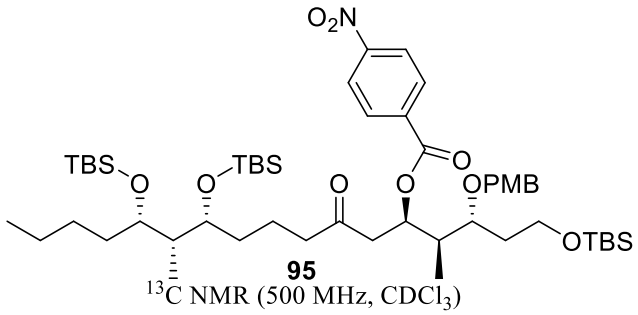




95

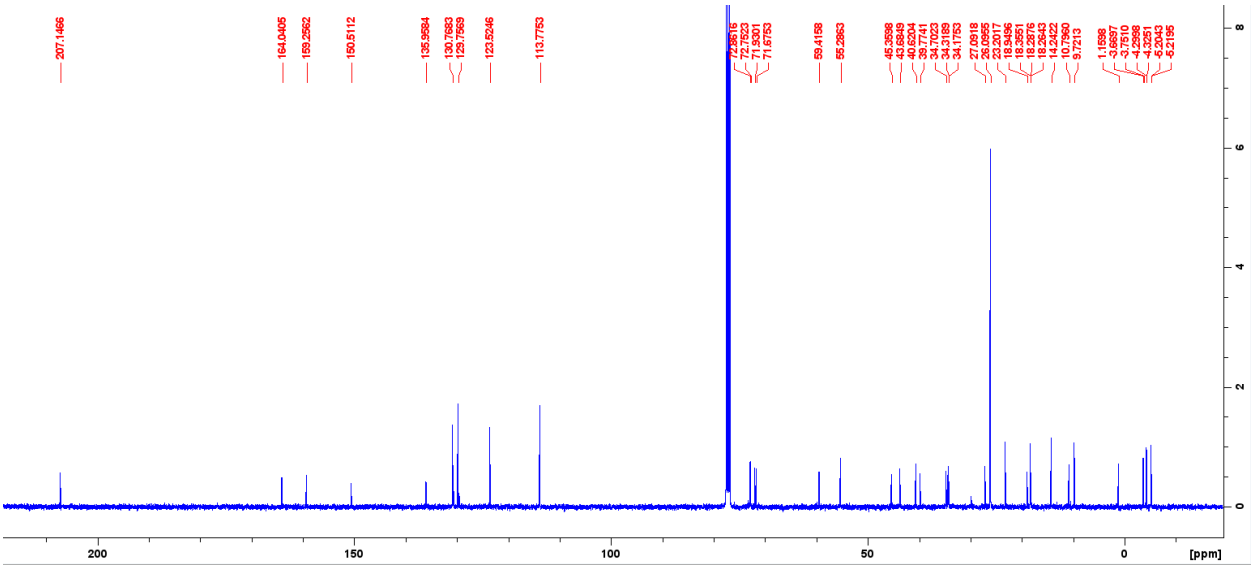
^{1}H NMR (400 MHz, $CDCl_3$)

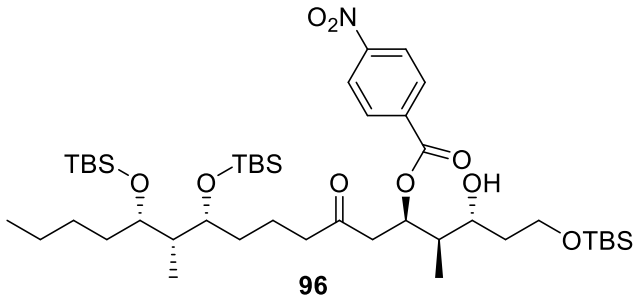




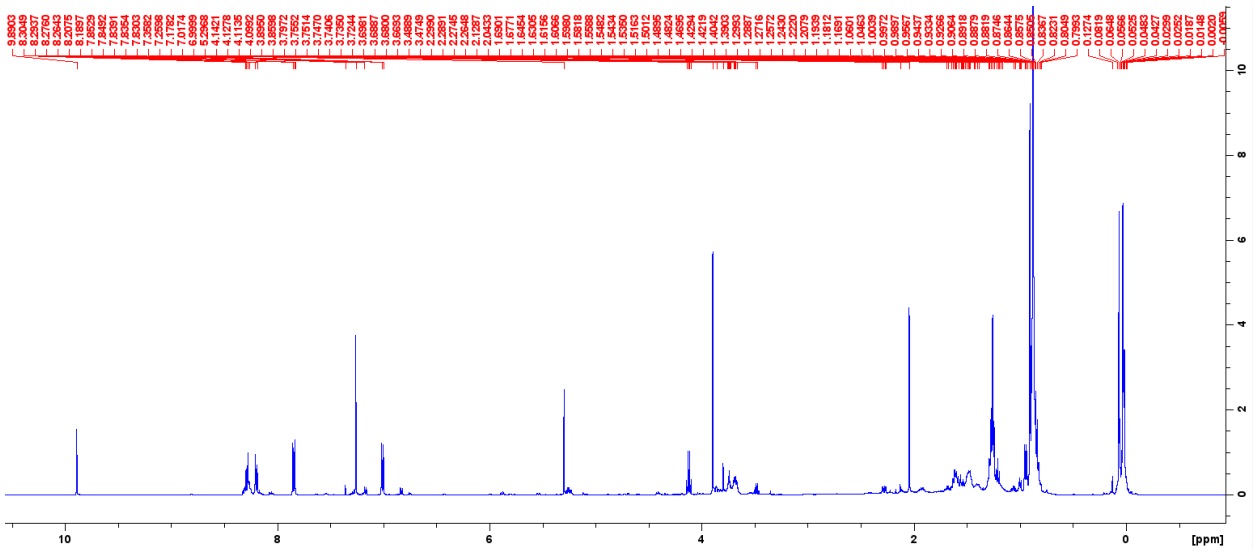
95

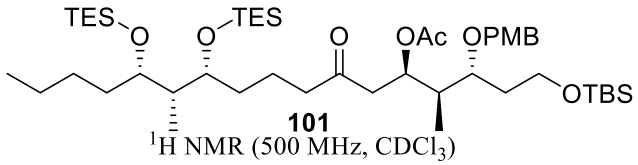
^{13}C NMR (500 MHz, $CDCl_3$)





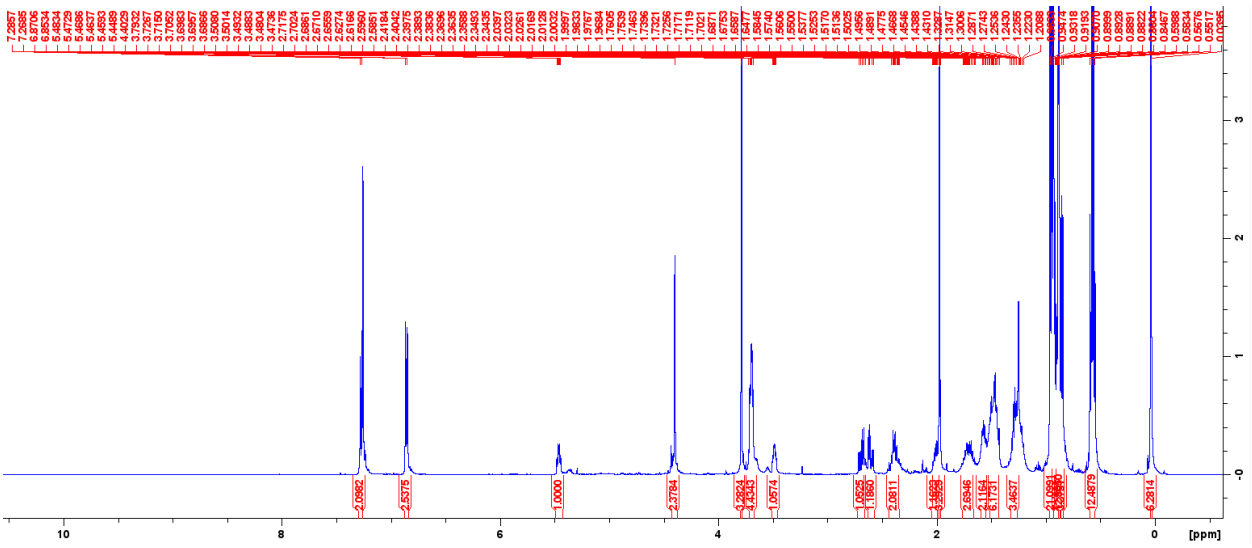
96

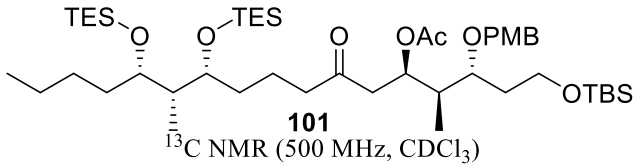




101

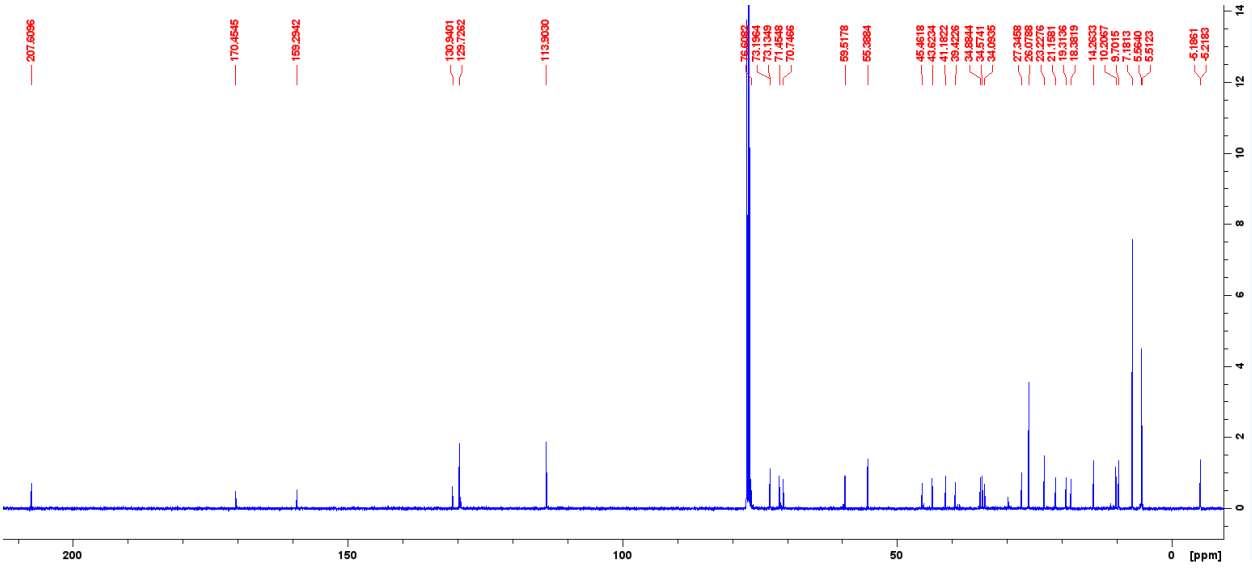
^{1}H NMR (500 MHz, $CDCl_3$)

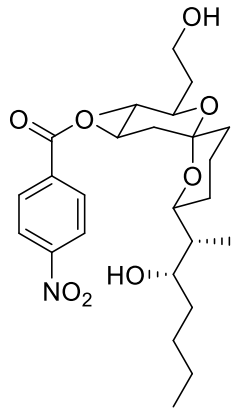




101

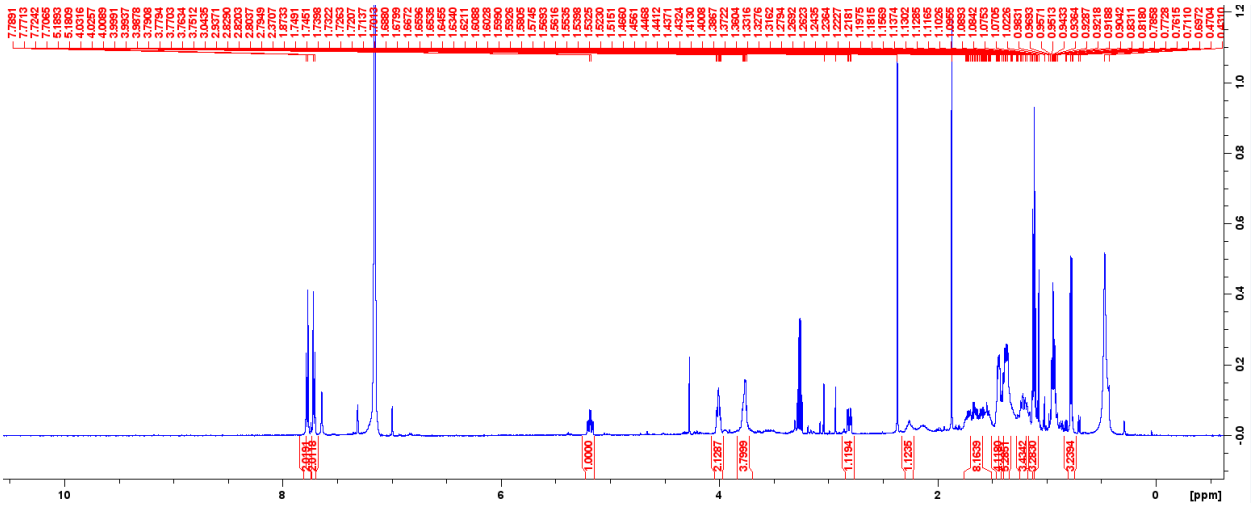
^{13}C NMR (500 MHz, $CDCl_3$)

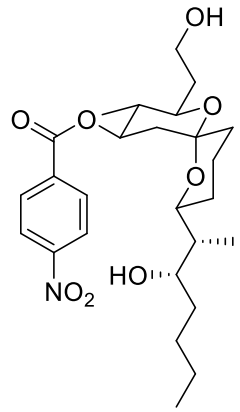




97

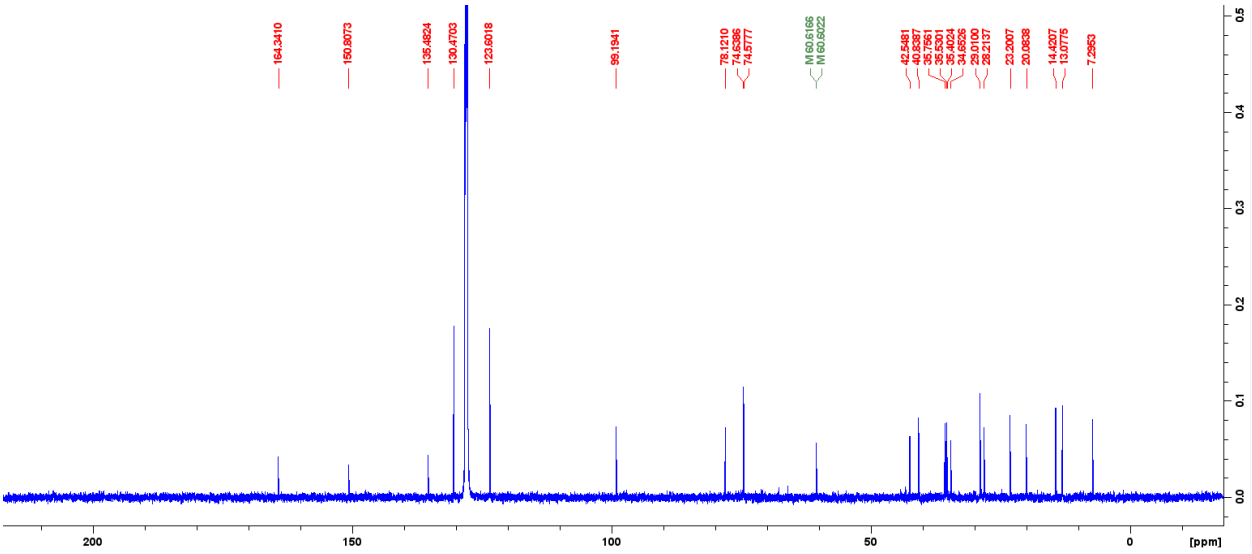
^{1}H NMR (500 MHz, C_6D_6)

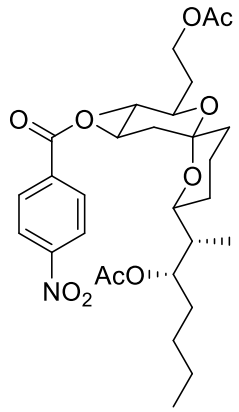




97

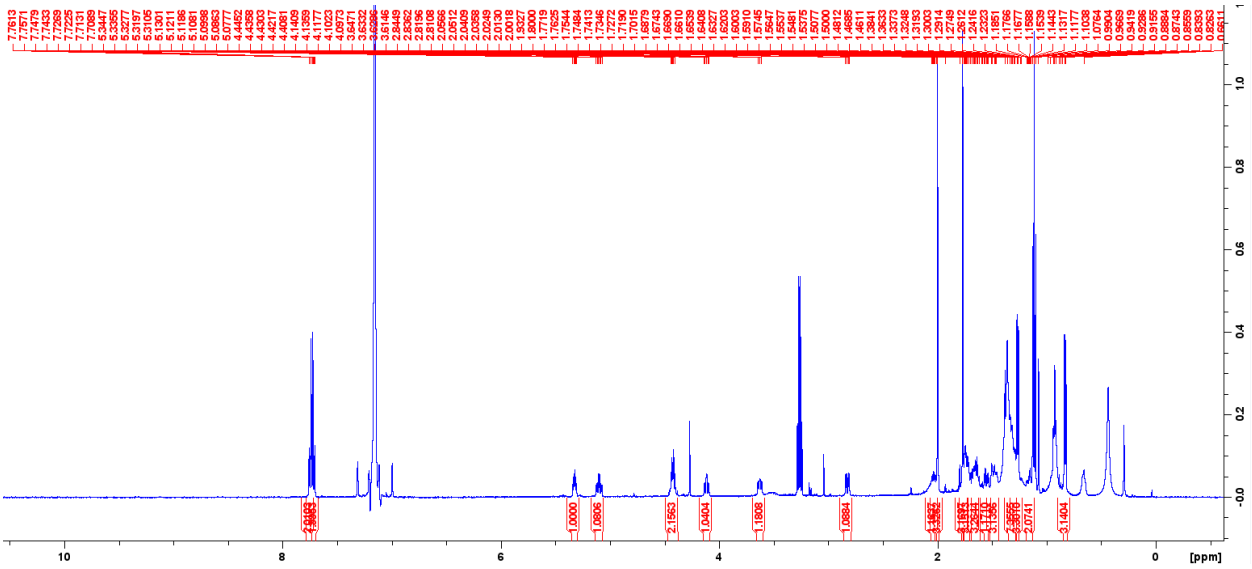
^{13}C NMR (500 MHz, C_6D_6)

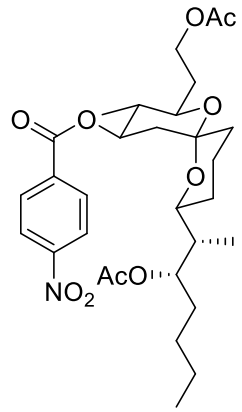




98

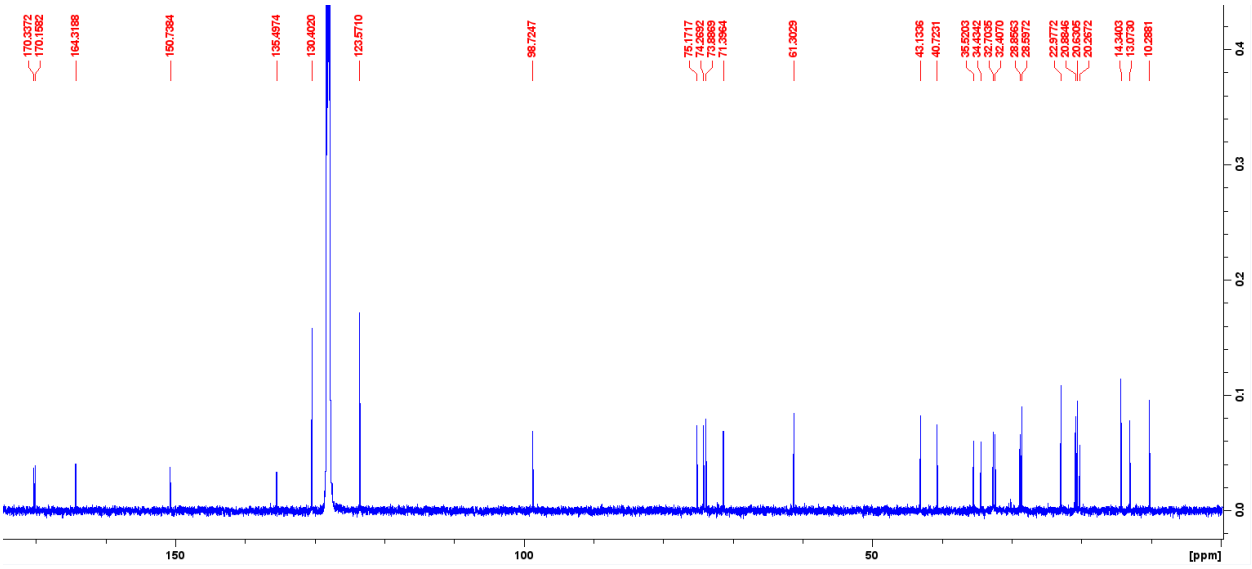
^{1}H NMR (500 MHz, C_6D_6)



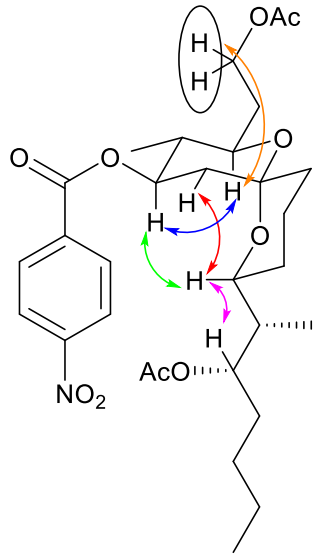


98

^{13}C NMR (500 MHz, C_6D_6)



NOESY Spectrum



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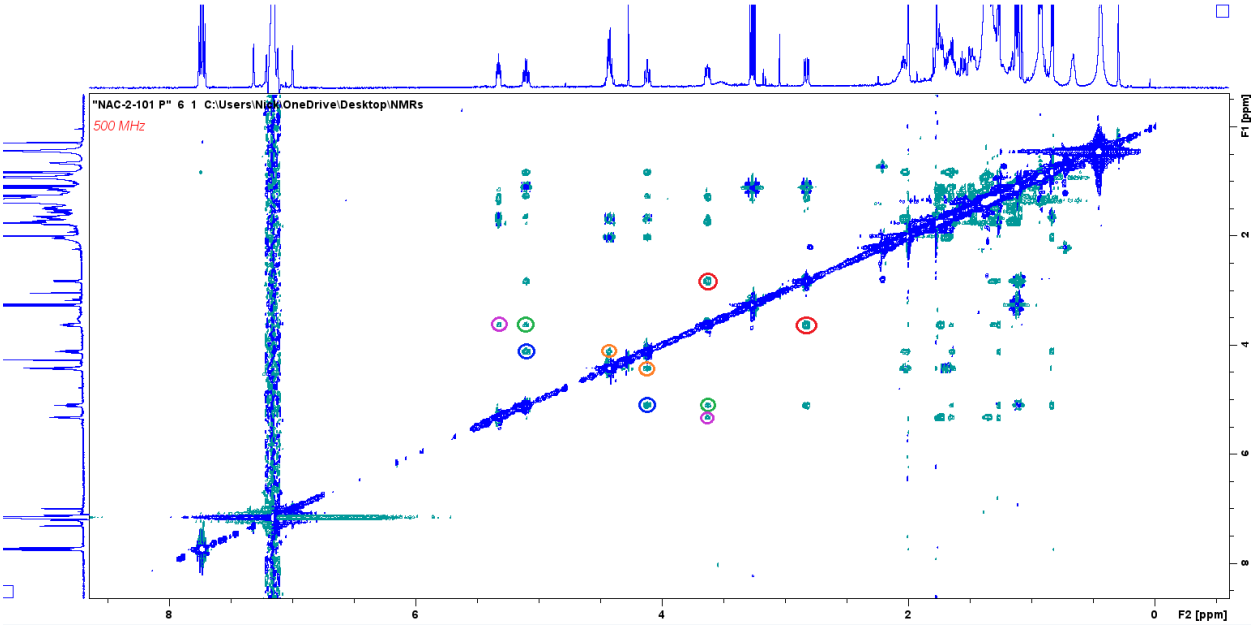

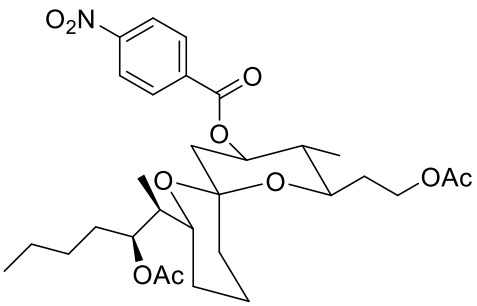

100

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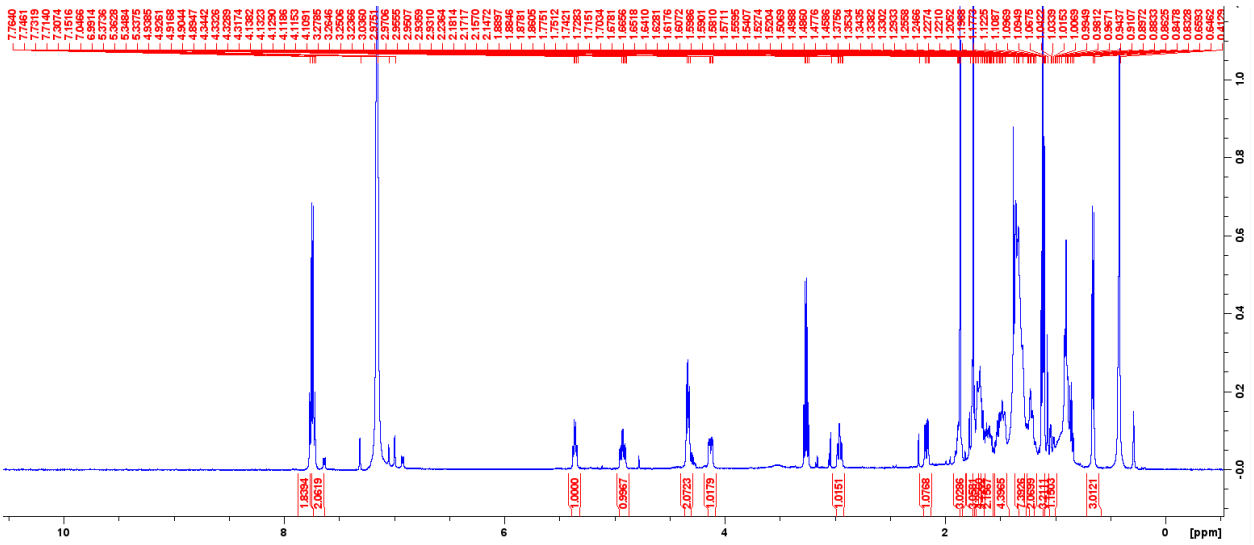

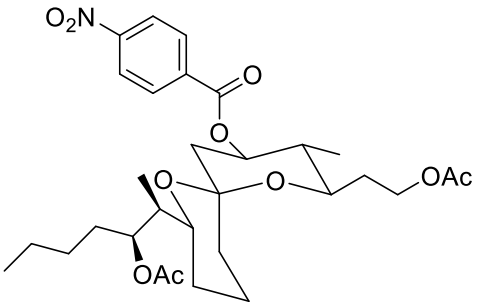

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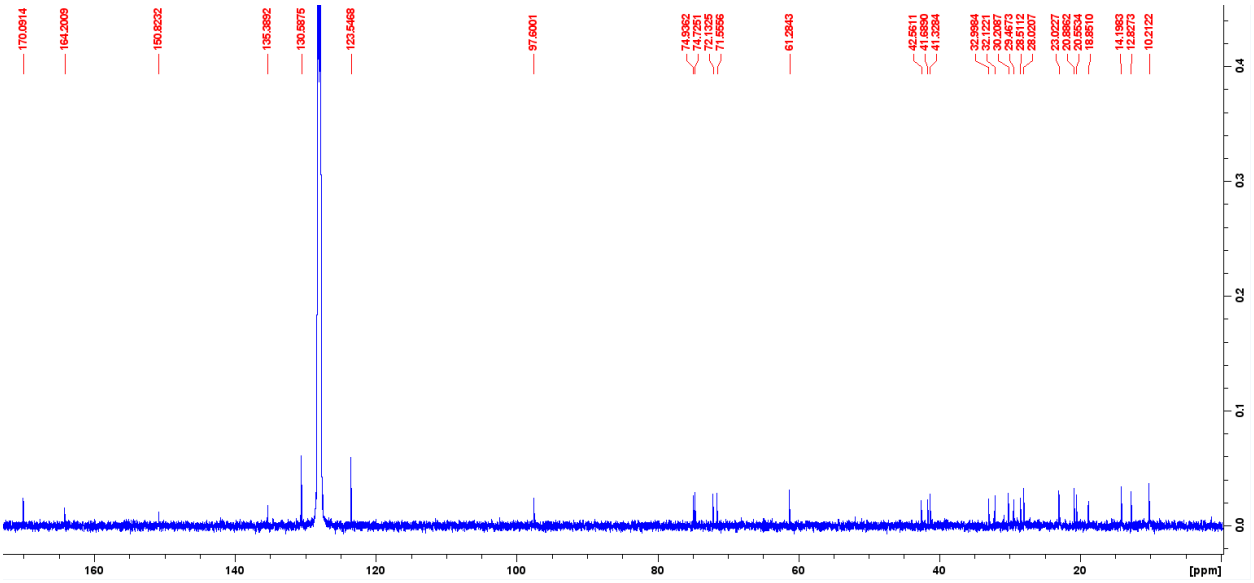
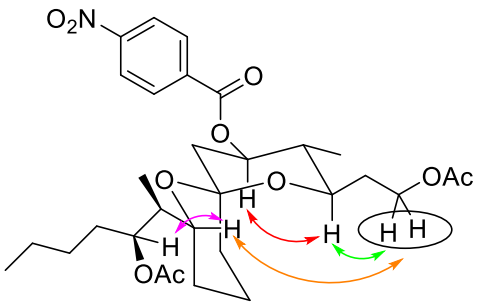


NOESY Spectrum



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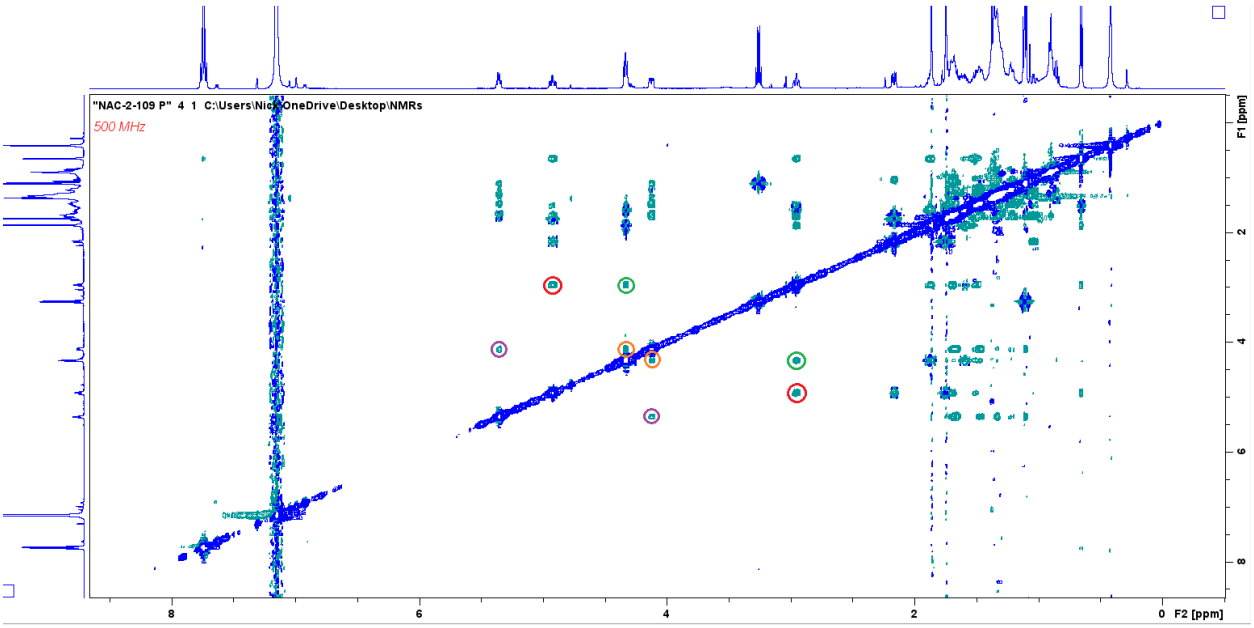
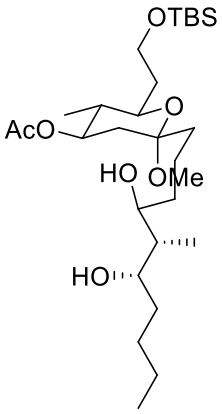
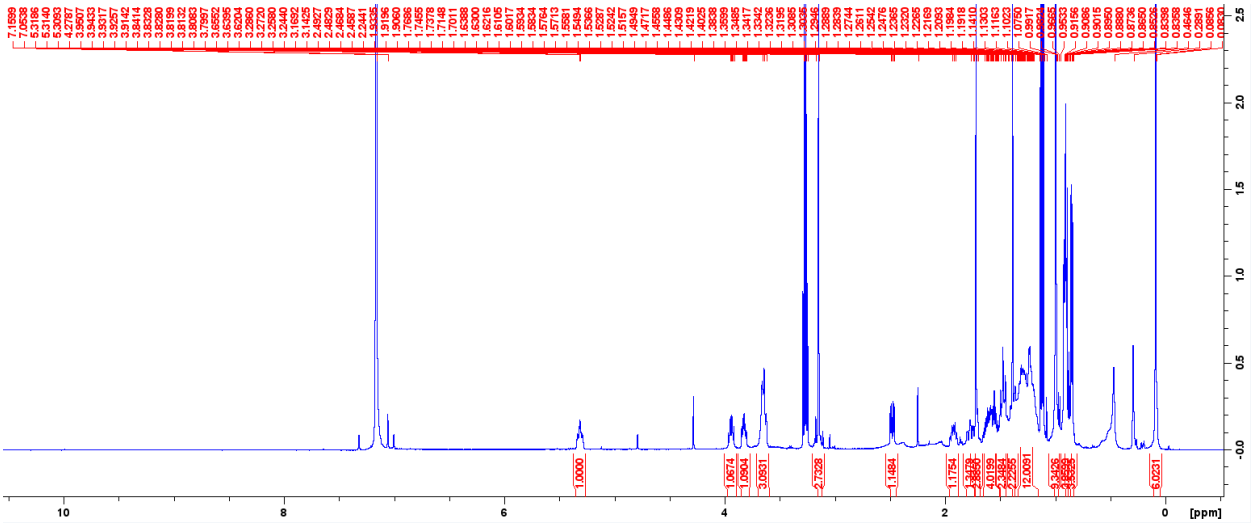
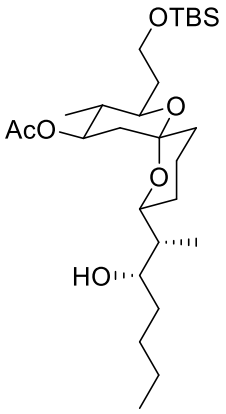




102

^{1}H NMR (500 MHz, C_6D_6)





S13

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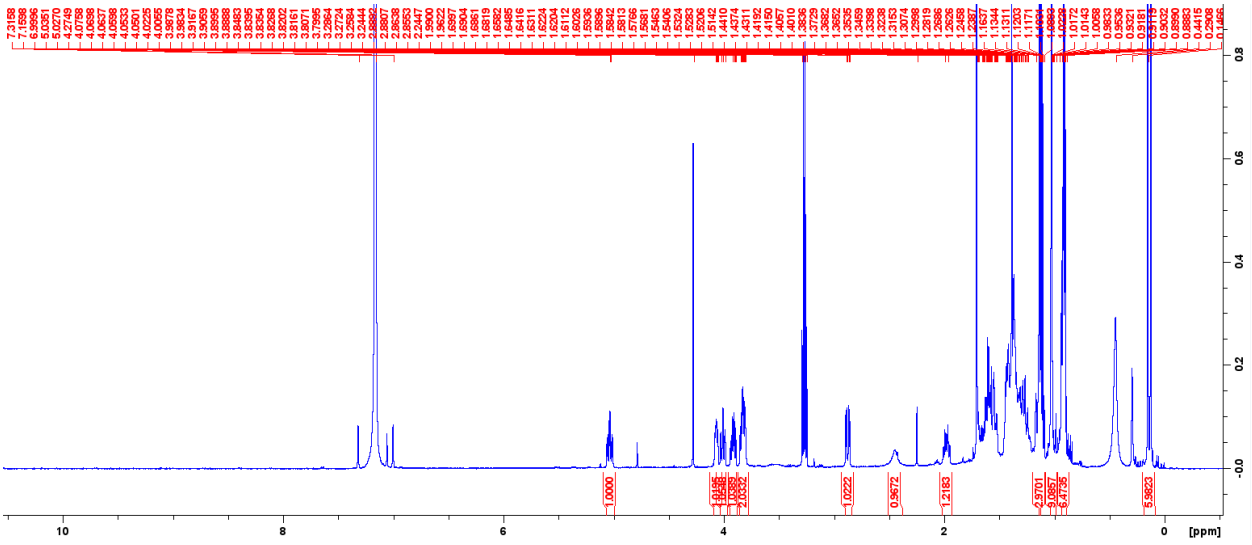
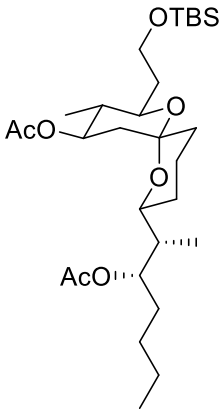
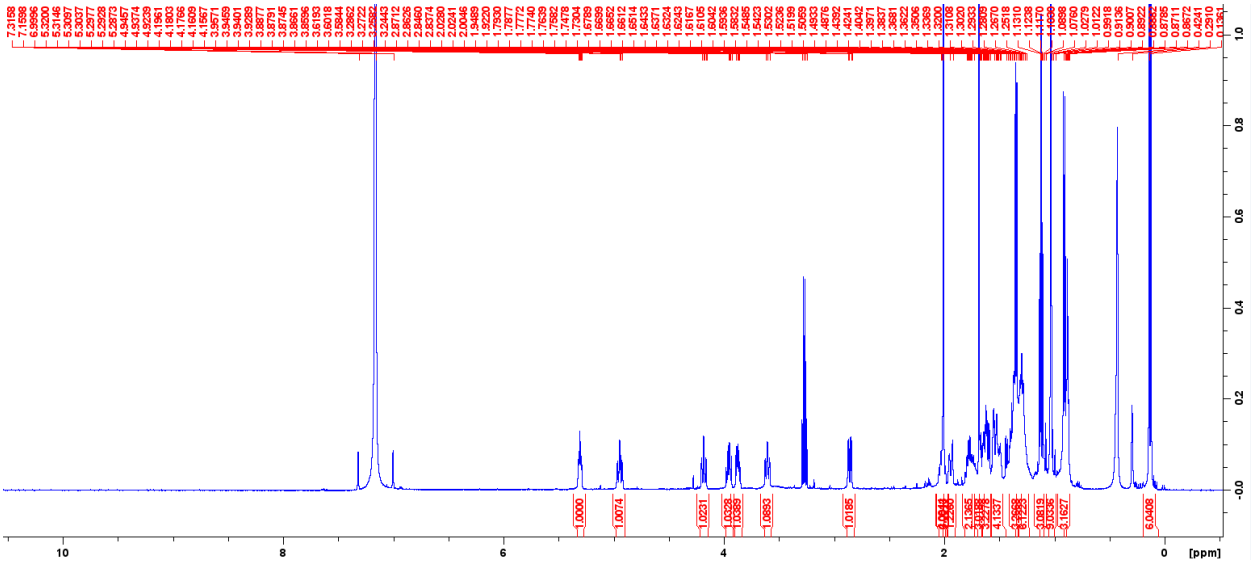
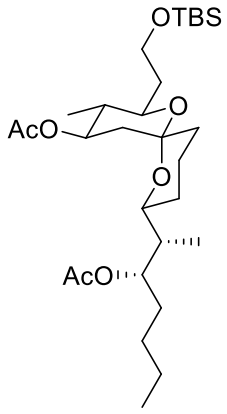




S14

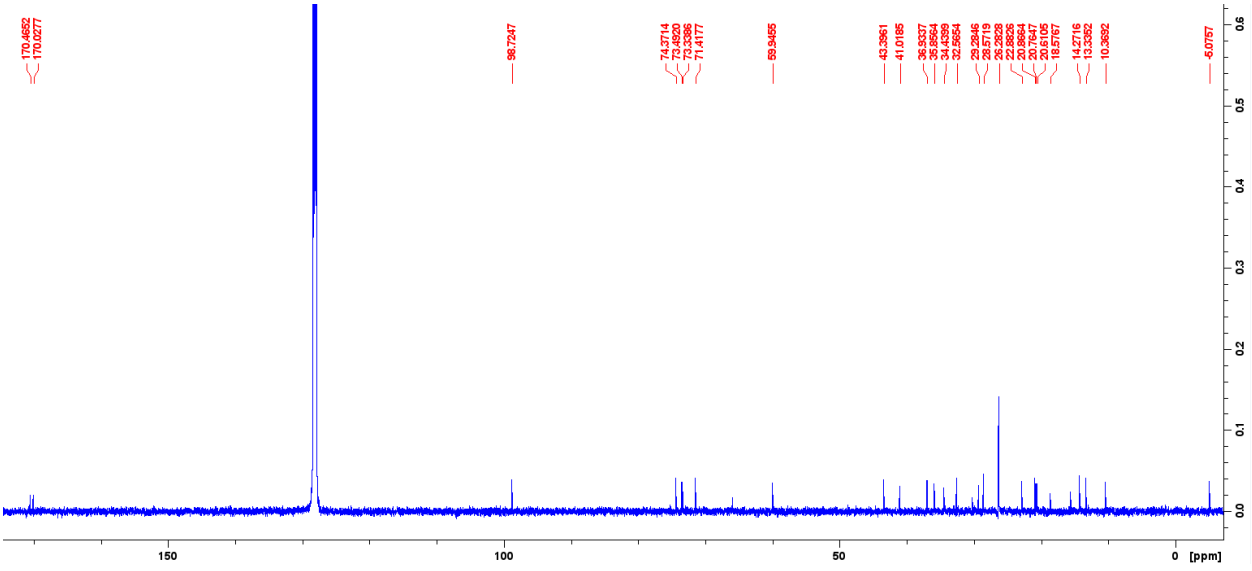
^{1}H NMR (500 MHz, C_6D_6)

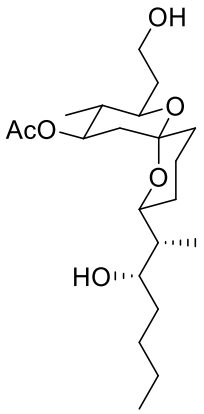




S14

^{13}C NMR (500 MHz, C_6D_6)





103

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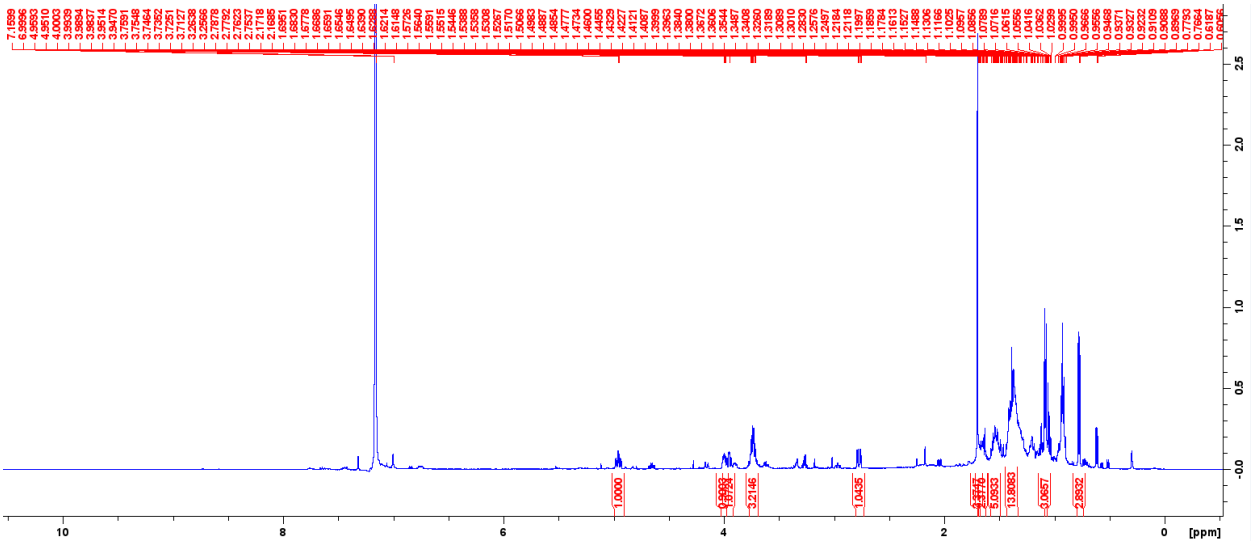

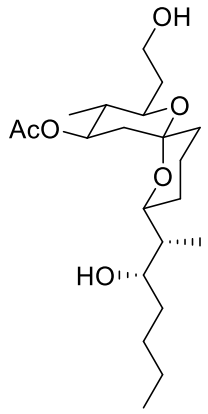

103

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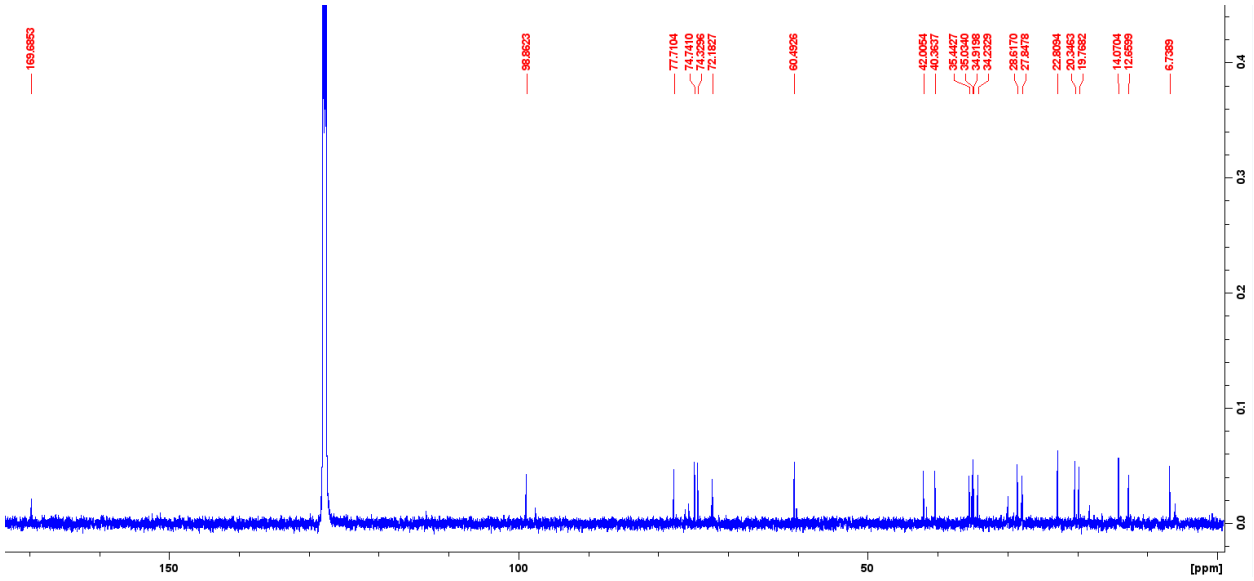

Bibliography

(1) Kihara, T.; Kusakabe, H.; Nakamura, G.; Sakurai, T.; Isono, K. Cytovaricin, a Novel Antibiotic. *J. Antibiot.* **1981**, *34* (8), 1073–1074.

(2) Kirst, H. A.; Mynderse, J. S.; Martin, J. W.; Baker, P. J.; Paschal, J. W.; Rios Steiner, J. L.; Lobkovsky, E.; Clardy, J. Structure of the Spiroketal-Macrolide Ossamycin. *J. Antibiot.* **1996**, *49* (2), 162–167.

(3) Carter, G. T. Structure Determination of Oligomycins A and Cla. *J. Org. Chem.* **1986**, *51* (22), 4264–4271.

(4) Kim, M. C.; Machado, H.; Jang, K. H.; Trzoss, L.; Jensen, P. R.; Fenical, W. Integration of Genomic Data with NMR Analysis Enables Assignment of the Full Stereostructure of Neaumycin B, a Potent Inhibitor of Glioblastoma from a Marine-Derived Micromonospora. *J. Am. Chem. Soc.* **2018**, *140* (34), 10775–10784.

(5) Ostrom, Q. T.; Bauchet, L.; Davis, F. G.; Deltour, I.; Fisher, J. L.; Langer, C. E.; Pekmezci, M.; Schwartzbaum, J. A.; Turner, M. C.; Walsh, K. M.; et al. The Epidemiology of Glioma in Adults: A "State of the Science" Review. *Neuro Oncol.* **2014**, *16* (7), 896–913.

(6) Simone, M.; Maffioli, S. I.; Tocchetti, A.; Tretter, S.; Cattaneo, M.; Biunno, I.; Gaspari, E.; Donadio, S. Additional Congeners of the Macrolide Neaumycin: Structure Revision and Biological Activity. *J. Antibiot.* **2015**, *68* (6), 406–408.

(7) Favre, S.; Vogel, P.; Gerber-Lemaire, S. Recent Synthetic Approaches toward Non-Anomeric Spiroketals in Natural Products. *Molecules* **2008**, *13* (10), 2570–2600.

(8) Guo, J.; Duffy, K. J.; Stevens, K. L.; Dalko, P. I.; Roth, R. M.; Hayward, M. M.; Kishi, Y. Total Synthesis of Altohyrtin A (Spongistatin 1): Part 1. *Angew. Chem. Int. Ed* **1998**, *37* (1–2), 187–190.

(9) Evans, D. A.; Coleman, P. J.; Dias, L. C. Enantioselective Synthesis of Altohyrtin C(Spongistatin 2): Synthesis of the AB- and CD-Spiroketal Subunits. *Angew. Chem. Int. Ed. Engl.* **1997**, *36* (24), 2738–2741.

(10) Pettit, G. R.; Chicacz, Z. A.; Gao, F.; Herald, C. L.; Boyd, M. R.; Schmidt, J. M.; Hooper, J. N. A. Antineoplastic Agents. 257. Isolation and Structure of Spongistatin 1. *J. Org. Chem.* **1993**, *58* (6), 1302–1304.

(11) Takahashi, H.; Osada, H.; Koshino, H.; Kudo, T.; Amano, S.; Shimizu, S.; Yoshihama, M.; Isono, K. Reveromycins, New Inhibitors of Eukaryotic Cell Growth. I. Producing Organism, Fermentation, Isolation and Physico-Chemical Properties. *J. Antibiot.* **1992**, *45* (9), 1409–1413.

(12) Koshino, H.; Takahashi, H.; Osada, H.; Isono, K. Reveromycins, New Inhibitors of Eukaryotic Cell Growth. III. Structures of Reveromycins A, B, C and D. *J. Antibiot.* **1992**, *45* (9), 1420–1427.

(13) Takahashi, H.; Osada, H.; Koshino, H.; Sasaki, M.; Onose, R.; Nakakoshi, M.; Yoshihama, M.; Isono, K. Reveromycins, New Inhibitors of Eukaryotic Cell Growth. II. Biological Activities. *J. Antibiot.* **1992**, *45* (9), 1414–1419.

(14) Drouet, K. E.; Theodorakis, E. A. Enantioselective Total Synthesis of Reveromycin B. *J. Am. Chem. Soc.* **1999**, *121* (2), 456–457.

(15) Masuda, T.; Osako, K.; Shimizu, T.; Nakata, T. Total Synthesis of Reveromycin B. *Org. Lett.* **1999**, *1* (6), 941–944.
(16) Cuzzupe, A. N.; Hutton, C. A.; Lilly, M. J.; Mann, R. K.; Rizzacasa, M. A.; Zammit, S. C. Total Synthesis of (-)-Reveromycin B. *Org. Lett.* **2000**, *2* (2), 191–194.
(17) Williams, D. E.; Roberge, M.; Van Soest, R.; Andersen, R. J. Spirastrellolide A, an Antimitotic Macrolide Isolated from the Caribbean Marine Sponge Spirastrella Coccinea. *J. Am. Chem. Soc.* **2003**, *125* (18), 5296–5297.
(18) Paterson, I.; Anderson, E. A.; Dalby, S. M.; Lim, J. H.; Maltas, P.; Loiseleur, O.; Genovino, J.; Moessner, C. The Stereocontrolled Total Synthesis of Spirastrellolide A Methyl Ester. Expedient Construction of the Key Fragments. *Org. Biomol. Chem.* **2012**, *10* (30), 5861–5872.
(19) Paterson, I.; Anderson, E. A.; Dalby, S. M.; Lim, J. H.; Genovino, J.; Maltas, P.; Moessner, C. Total Synthesis of Spirastrellolide A Methyl Ester--Part 1: Synthesis of an Advanced C17-C40 Bis-Spiroacetal Subunit. *Angew. Chem. Int. Ed* **2008**, *47* (16), 3016–3020.
(20) Paterson, I.; Anderson, E. A.; Dalby, S. M.; Lim, J. H.; Genovino, J.; Maltas, P.; Moessner, C. Total Synthesis of Spirastrellolide A Methyl Ester--Part 2: Subunit Union and Completion of the Synthesis. *Angew. Chem. Int. Ed* **2008**, *47* (16), 3021–3025.
(21) Perron, F.; Albizati, K. F. Chemistry of Spiroketals. *Chem. Rev.* **1989**, *89* (7), 1617–1661.
(22) Deslongchamps, P. 1,7-Dioxaspiro[5.5]Undecanes. An Excellent System for the Study of Stereoelectroniceffects (Anomeric and Exo-Anomeric Effects) in Acetals. *Can J Chem* **1981**, *59* (12), 1105–1121.
(23) Altona, C.; Romers, C.; Havinga, E. Molecular Structure and Conformation of Some Dihalogenodioxanes. *Tetrahedron Lett.* **1959**, *1* (10), 16–20.
(24) Wiberg, K. B.; Bailey, W. F.; Lambert, K. M.; Stempel, Z. D. The Anomeric Effect: It's Complicated. *J. Org. Chem.* **2018**, *83* (9), 5242–5255.
(25) Lemieux, R. U. Effects of Unshared Pairs of Electrons and Their Solvation on Conformational Equilibria. *Pure Appl. Chem.* **1971**, *25* (3), 527–548.
(26) Praly, J. P.; Lemieux, R. U. Influence of Solvent on the Magnitude of the Anomeric Effect. *Can. J. Chem.* **1987**, *65* (1), 213–223.
(27) Lemieux, R. U.; Pavia, A. A.; Martin, J. C.; Watanabe, K. A. Solvation Effects on Conformational Equilibria. Studies Related to the Conformational Properties of 2-Methoxytetrahydropyran and Related Methyl Glycopyranosides. *Can. J. Chem.* **1969**, *47* (23), 4427–4439.
(28) Tvaroska, I.; Carver, J. P. The Anomeric and Exo-Anomeric Effects of a Hydroxyl Group and the Stereochemistry of the Hemiacetal Linkage11Ab Initio Molecular Orbital Calculation of Carbohydrate Model Compounds. Part 7. For Part 6, See Ref[1]. *Carbohydr. Res.* **1998**, *309* (1), 1–9.
(29) Paterson, I.; Coster, M. J.; Chen, D. Y.-K.; Oballa, R. M.; Wallace, D. J.; Norcross, R. D. The Stereocontrolled Total Synthesis of Altohyrtin A/Spongistatin 1: The AB-Spiroacetal Segment. *Org. Biomol. Chem.* **2005**, *3* (13), 2399–2409.
(30) Hungerbühler, E.; Naef, R.; Wasmuth, D.; Seebach, D.; Loosli, H.-R.; Wehrli, A. Synthese Optisch Aktiver 2-Methyl- Und 2-Äthyl-1, 6-Dioxaspiro [4.4]-Nonan- Und -[4.5]Decan-Pheromone Aus Einem Gemeinsamen Chiralen Vorläufer. *Helv. Chim. Acta* **1980**, *63* (7), 1960–1970.
(31) Pihko, P. M.; Aho, J. E. Access to Both Anomers of Pectenotoxin Spiroketals by Kinetic Spiroketalization. *Org. Lett.* **2004**, *6* (21), 3849–3852.

(32) Yasumoto, T.; Murata, M.; Oshima, Y.; Sano, M.; Matsumoto, G. K.; Clardy, J. Diarrhetic Shellfish Toxins. *Tetrahedron* **1985**, *41* (6), 1019–1025.
(33) Doubský, J.; Šaman, D.; Zedník, J.; Vašíčková, S.; Koutek, B. A Convenient Access to Thermodynamically Nonstabilised Spiroketal Isomers: The First Synthesis of (Z)-7-Methyl-1,6-Dioxaspiro[4.5]Decane. *Tetrahedron Lett.* **2005**, *46* (46), 7923–7926.
(34) Palmes, J.; Aponick, A. Strategies for Spiroketal Synthesis Based on Transition-Metal Catalysis. *Synthesis (Mass)* **2012**, *44* (24), 3699–3721.
(35) Utimoto, K. Palladium Catalyzed Synthesis of Heterocycles. *Pure Appl. Chem.* **1983**, *55* (11), 1845–1852.
(36) Liu, B.; De Brabander, J. K. Metal-Catalyzed Regioselective Oxy-Functionalization of Internal Alkynes: An Entry into Ketones, Acetals, and Spiroketals. *Org. Lett.* **2006**, *8* (21), 4907–4910.
(37) Kurth, M. J.; Brown, E. G.; Hendra, E.; Hope, H. Stereoselective Synthesis of Octahydro-3-Oxospiro[Benzofuran-2(3H),2'-[2H]Pyran]Systems. *J. Org. Chem.* **1985**, *50* (7), 1115–1117.
(38) El Sous, M.; Ganame, D.; Tregloan, P. A.; Rizzacasa, M. A. Total Synthesis of (-)-Reveromycin a. *Org. Lett.* **2004**, *6* (17), 3001–3004.
(39) Han, X.; Floreancig, P. E. Spiroacetal Formation through Telescoped Cycloaddition and Carbon-Hydrogen Bond Functionalization: Total Synthesis of Bistramide A. *Angew. Chem. Int. Ed* **2014**, *53* (41), 11075–11078.
(40) Omura, K.; Swern, D. Oxidation of Alcohols by "Activated" Dimethyl Sulfoxide. a Preparative, Steric and Mechanistic Study. *Tetrahedron* **1978**, *34* (11), 1651–1660.
(41) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. Catalytic Asymmetric Allylation of Aldehydes. *J. Am. Chem. Soc.* **1993**, *115* (18), 8467–8468.
(42) Brown, H. C.; Desai, M. C.; Jadhav, P. K. Hydroboration. 61. Diisopinocampheylborane of High Optical Purity. Improved Preparation and Asymmetric Hydroboration of Representative Cis-Disubstituted Alkenes. *J. Org. Chem.* **1982**, *47* (26), 5065–5069.
(43) Rivero, M. R.; Buchwald, S. L. Copper-Catalyzed Vinylation of Hydrazides. A Regioselective Entry to Highly Substituted Pyrroles. *Org. Lett.* **2007**, *9* (6), 973–976.
(44) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Sato, M.; Suzuki, A. Palladium-Catalyzed Inter- and Intramolecular Cross-Coupling Reactions of B-Alkyl-9-Borabicyclo[3.3.1]Nonane Derivatives with 1-Halo-1-Alkenes or Haloarenes. Syntheses of Functionalized Alkenes, Arenes, and Cycloalkenes via a Hydroboration-Coupling Sequence. *J. Am. Chem. Soc.* **1989**, *111* (1), 314–321.
(45) Jacobsen, E. N.; Dossetter, A. G.; Jamison, T. F. Highly Enantio- and DiastereoselectiveHetero-Diels ± Alder Reactions Catalyzed ByNew Chiral Tridentate Chromium(Iii)Catalysts. *Angew. Chem. Int. Ed* **1999**, *38* (16), 2398–2400.
(46) Jacobsen, E. AN EFFICIENT, HIGHLY DIASTEREO- ANDENANTIOSELECTIVE HETERO-DIELS-ALDER CATALYST.PREPARATION OF (2S,6R)-6-(Tert-BUTYLDIMETHYLSILYLOXYMETHYL)-2-METHOXY-2,5-DIHYDROPYRAN. *Organic Synth* **2009**, *82*, 34–42.
(47) Chérest, M.; Felkin, H.; Prudent, N. Torsional Strain Involving Partial Bonds. The Stereochemistry of the Lithium Aluminium Hydride Reduction of Some Simple Open-Chain Ketones. *Tetrahedron Lett.* **1968**, *9* (18), 2199–2204.

(48) Mukaiyama, T.; Banno, K.; Narasaka, K. New Cross-Aldol Reactions. Reactions of Silyl Enol Ethers with Carbonyl Compounds Activated by Titanium Tetrachloride. *J. Am. Chem. Soc.* **1974**, *96* (24), 7503–7509.
(49) Evans, D. A.; Duffy, J. L.; Dart, M. J. 1,3-Asymmetric Induction in the Aldol Addition Reactions of Methyl Ketone Enolates and Enolsilanes to β-Substituted Aldehydes. A Model for Chirality Transfer. *Tetrahedron Lett.* **1994**, *35* (46), 8537–8540.
(50) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. A Stereochemical Model for Merged 1,2- and 1,3-Asymmetric Induction in Diastereoselective Mukaiyama Aldol Addition Reactions and Related Processes. *J. Am. Chem. Soc.* **1996**, *118* (18), 4322–4343.
(51) Parikh, J. R.; Doering, W. v. E. Sulfur Trioxide in the Oxidation of Alcohols by Dimethyl Sulfoxide. *J. Am. Chem. Soc.* **1967**, *89* (21), 5505–5507.
(52) Still, W. C.; Gennari, C. Direct Synthesis of Z-Unsaturated Esters. A Useful Modification of the Horner-Emmons Olefination. *Tetrahedron Lett.* **1983**, *24* (41), 4405–4408.
(53) Gao, Y.; Klunder, J. M.; Hanson, R. M.; Masamune, H.; Ko, S. Y.; Sharpless, K. B. Catalytic Asymmetric Epoxidation and Kinetic Resolution: Modified Procedures Including in Situ Derivatization. *J. Am. Chem. Soc.* **1987**, *109* (19), 5765–5780.
(54) Jung, M. E.; D'Amico, D. C. Enantiospecific Synthesis of All Four Diastereomers of 2-Methyl-3-[(Trialkylsilyl)Oxy]Alkanals: Facile Preparation of Aldols by Non-Aldol Chemistry. *J. Am. Chem. Soc.* **1993**, *115* (25), 12208–12209.
(55) Jung, M. E.; Hoffmann, B.; Rausch, B.; Contreras, J.-M. Use of Hindered Silyl Ethers as Protecting Groups for the Non-Aldol Aldol Process. *Org. Lett.* **2003**, *5* (17), 3159–3161.
(56) Roush, W. R.; Walts, A. E.; Hoong, L. K. Diastereo- and Enantioselective Aldehyde Addition Reactions of 2-Allyl-1,3,2-Dioxaborolane-4,5-Dicarboxylic Esters, a Useful Class of Tartrate Ester Modified Allylboronates. *J. Am. Chem. Soc.* **1985**, *107* (26), 8186–8190.
(57) Pappo, R.; Allen, Jr., D.; Lemieux, R.; Johnson, W. Notes - Osmium Tetroxide-Catalyzed Periodate Oxidation of Olefinic Bonds. *J. Org. Chem.* **1956**, *21* (4), 478–479.
(58) Wadsworth, W. S.; Emmons, W. D. The Utility of Phosphonate Carbanions in Olefin Synthesis. *J. Am. Chem. Soc.* **1961**, *83* (7), 1733–1738.
(59) Petasis, N. A.; Bzowej, E. I. Titanium-Mediated Carbonyl Olefinations. 1. Methylenations of Carbonyl Compounds with Dimethyltitanocene. *J. Am. Chem. Soc.* **1990**, *112* (17), 6392–6394.
(60) Hoye, T. R.; Jeffrey, C. S.; Shao, F. Mosher Ester Analysis for the Determination of Absolute Configuration of Stereogenic (Chiral) Carbinol Carbons. *Nat. Protoc.* **2007**, *2* (10), 2451–2458.
(61) Ireland, R. E.; Mueller, R. H.; Willard, A. K. The Ester Enolate Claisen Rearrangement. Stereochemical Control through Stereoselective Enolate Formation. *J. Am. Chem. Soc.* **1976**, *98* (10), 2868–2877.
(62) Zhu, C.; Shen, X.; Nelson, S. G. Cinchona Alkaloid-Lewis Acid Catalyst Systems for Enantioselective Ketene-Aldehyde Cycloadditions. *J. Am. Chem. Soc.* **2004**, *126* (17), 5352–5353.
(63) Narasaka, K.; Pai, F.-C. Stereoselective Reduction of β Hydroxyketones to 1,3-Diols Highly Selective 1,3-Asymmetric Induction via Boron Chelates. *Tetrahedron* **1984**, *40* (12), 2233–2238.
(64) A General Synthetic Method for the Preparation of Methyl Ketones from Terminal Olefins: 2-Decanone. *Org. Synth.* **1984**, *62*, 9.

(65) Ireland, R. E.; Daub, J. P. Macrolide Total Synthesis. The Synthesis of Spiro Ketal Intermediates and Their Cleavage into Open-Chain Derivatives. *J. Org. Chem.* **1983**, *48* (8), 1303–1312. Sciwheel inserting bibliography...