SYNTHETIC EFFORTS TOWARD HYPOESTOXIDE, PLATENSIMYCIN, AND GUTTIFERONE G

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Hypoestoxide is a novel diterpenoid isolated from a tropical shrub, *hypoestes rosea*. It has been shown to exhibit promising anti - cancer, malarial, and inflammatory activity. In particular, the *in vivo* anti-angiogenic activity that inhibits vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) make it especially interesting. Along with this biological profile, the challenging macrocyclic structure of hypoestoxide makes it a target of great interest to the synthetic community. The synthesis of this molecule's complex macrocyclic core was accomplished by using relay ring closing metathesis, and post-cyclization modifications were controlled by the shape of the molecule.

Platensimycin is a recently isolated natural product produced by *Streptomyces platensis*. It was discovered in a novel antibiotic assay by screening a large number of South African soil samples. Platensimycin has been shown to have a unique mechanism of action by inhibiting Fab F, an enzyme responsible for bacterial fatty acid synthesis. In addition to the exciting biological activity, platensimycin has an intriguing molecular structure consisting of a hydrophobic and structurally compact core, and a hydrophilic aromatic head group. The synthesis of this molecule relied on a novel vinyl oxirane ring expansion to access the oxa-bicyclic moiety and an alkylative dearomatization to complete the carbocyclic core.

Guttiferone G belongs to the family of [3.3.1] bicyclic polyprenylated phloroglucinol derived natural products, which have been isolated from various plant species found primarily in the tropical or subtropical regions. Their biological profiles have been shown to rival any known natural product class in terms of diversity and activity. It is this vast biological activity and structural similarity that make the development of a general approach to this family of particular interest. The common bicyclic core of these compounds was accessed by using an intramolecular bis-radical cyclization into a dienone that was itself made by oxidative dearomatization.

BIOGRAPHICAL SKETCH

Nicholas Adam McGrath was born in Fairmont, Minnesota, on September 11, 1980, the son of James and Ruth McGrath. From an early age he excelled in school and particularly enjoyed courses in mathematics and science. He attended 1st through 7th grades at three schools while growing up: Budd Elementary (1st - 2nd), Lincoln Elementary (3rd - 4th), and Fairmont Junior High (5th - 7th). Even though classes were easy for him, at that time he was more interested in gym class and chasing girls around the playground than thinking about the underlying scientific principles that surrounded him.

After finishing his elementary education he attended 8th through 12th grades at Fairmont High School. Here he continued with his scholastic success even with much of his time being devoted to football or track practice, and the rest working part-time at the local grocery store. It was during this time that his interest in science was really triggered. The excitement and enthusiasm that both his biology teacher Mr. Kerburg and his chemistry teacher Mr. Segar displayed in class inspired him to learn more about the world around him.

After graduation, Nick attended the University of Minnesota-Duluth on a full scholarship to study chemistry. During his undergraduate studies at UMD, he was fortunate for the opportunity to conduct research in the lab of Professor Ron Caple studying the stabilizing effect of sulfur on proximal carbocation intermediates. After graduation, Nick elected to stay at UMD and joined the research group of Professor Robert Carlson, this time working with sulfur-stabilized carbanions and their utility in organic synthesis. This two year hiatus was well planned because his fiancée (now wife), Jillian, had two years remaining in her psychology studies at UMD.

With Nick's studies in Duluth drawing to a close, he and Jillian were married on June 11, 2005. They moved across the country so that Nick could begin his doctoral studies at Cornell University. There Nick joined the relatively new research group of assistant professor Jón Njarðarson to work on natural product total synthesis. Spending five years at Cornell certainly opened his eyes to the world around him and gave him a taste of life outside the Midwest. Nick has really enjoyed his time in Ithaca and especially appreciates all of people he has met and the countless relationships he had the opportunity to build. He now looks forward to his new position in the lab of Professor Ronald Raines at the University of Wisconsin, Madison and all of the opportunities that will come his way in the future.

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Thanks to my family for their praise and love throughout the years. Thanks to my wife, Jillian, for putting up with my long hours and for being there when I needed support. Thanks to the entire Njarðarson group past and present for everything they have taught me over the past 5 years. Thanks to my advisor, Jón Njarðarson, and my committee members, Bruce Ganem and Geoff Coates, for their support and praise during my graduate studies at Cornell. Finally, thanks to all of the wonderful people that I have met and have developed long lasting friendships with while in graduate school.

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LIST OF ABBREVIATIONS

AIBN	Azobisisobutyronitrile
BFGF	Basic fibroblast growth factor
BHT	Butylated hydroxytoluene
CAN	Ceric ammonium nitrate
COD	1,5-Cyclooctadiene
DBU	1,8-Diazabicycloundec-7-ene
DCM	Dichloromethane
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutylaluminum hydride
DMAP	4-Dimethylaminopyridine
DMDO	Dimethyldioxirane
DMF	*N,N*-Dimethylformamide
DMP	Dess–Martin periodinane
DMSO	Dimethyl sulfoxide
HATU	2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HFIP	Hexafluoro-2-propanol
HMPA	Hexamethylphosphoramide
IBDA	Phenyliodine(III) diacetate, $PhI(OAc)_2$
KHMDS	Potassium bis(trimethylsilyl)amide
LDA	Lithium diisopropyl amide
LHMDS	Lithium bis(trimethylsilyl)amide
LTA	Lead tetraacetate, $Pb(OAc)_4$
mCPBA	*meta*-Chloroperoxybenzoic acid

MOM	Methoxymethyl
Ms	Mesyl
NBS	*N*-Bromosuccinimide
NMO	*N*-Methylmorpholine *N*-oxide
OTf	Trifluoromethanesulfonate
PCC	Pyridinium chlorochromate
PIFA	Phenyliodine bis(trifluoroacetate)
PTSA	*p*-Toluenesulfonic acid
RRCM	Relay ring closing metathesis
RT	Room temperature
TBAF	Tetra-n-butylammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMEDA	*N,N,N',N'*-Tetramethylethylenediamine
TMS	Trimethylsilyl
TPAP	Tetrapropylammonium perruthenate
Tr	Triphenylmethyl
Ts	*p*-Toluenesulfonyl (Tosyl)
VEGF	Vascular endothelial growth factor

PREFACE

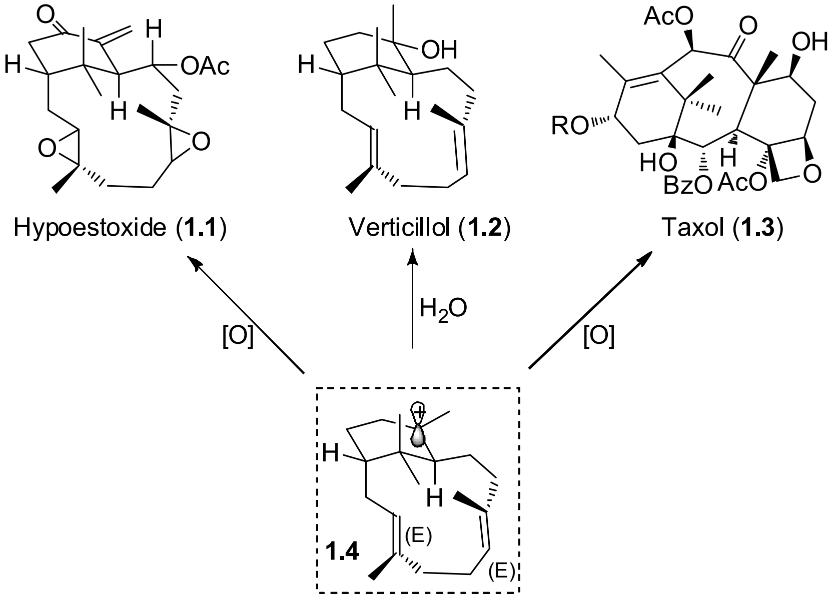
Natural product total synthesis is an exciting area of research for many reasons. Organic synthesis makes it possible to assemble molecules of varying complexity in creative and efficient ways. These molecules might possess interesting biological activity, or have a really unique and challenging structure. Regardless, the ability to make complex molecules efficiently from readily available starting materials will always be an important accomplishment. In addition, synthesis gives us the opportunity to make minor modifications to the route and generate a vast array of structural analogs that can be screened for their activity. During the process of completing a total synthesis, obstacles may arise that require innovative thinking and often the design of new methods to overcome them. It is often these methods that are of most use to the chemical community. Finally, the training one receives while working on the total synthesis of a natural product can often be considered as valuable as the eventual outcome of the project. Organic synthesis is a discipline that is central to all areas of chemistry and the skills attained can be applied to countless areas of research.

Chapter 1

Hypoestoxide and Verticillol

1.1 Background and Significance

Hypoestoxide (**1.1**, Scheme 1.1) was isolated from the tropical shrub *hypoestes rosea*, found in the Nigerian rain forests.[1] The extracts from these shrubs have been used for generations in folk medicine to treat various skin rashes and infections. Hypoestoxide has been shown in recent studies to exhibit promising anti- cancer,[2] malarial,[3] and inflammatory activity.[4] Our interest stems primarily from encouraging anti-angiogenic activities, in which hypoestoxide was shown to inhibit the growth of a number of human and murine tumor cell lines *in vivo*. In terms of angiogenesis, hypoestoxide inhibited vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (BFGF). Hypoestoxide is a bicyclo[9.3.1]pentadecane diterpenoid containing a rigid "inside-outside" ring system decorated with an exocyclic enone, two epoxides and an acetate moiety. This rare ring system has also been described for the *verticillanes*,[5] of which verticillol (**1.2**)[6] is the most well known. It is tempting to propose that hypoestoxide, as a more oxygenated variant of verticillol, is formed from the same common cationic precursor (**1.4**) as both verticillol[7] and taxol (**1.3**),[8] which in turn originates from consecutive cyclizations of geranyl-geranyl pyrophosphate. In the case of verticillol, the cation (**1.4**) is trapped with water, while for taxol and hypoestoxide it undergoes endocyclic and exocyclic elimination followed by oxygenation and cyclization. As part of our efforts to evaluate the molecular mechanisms[9] of promising natural product anticancer agents, we have focused our investigations on hypoestoxide and the verticillanes.

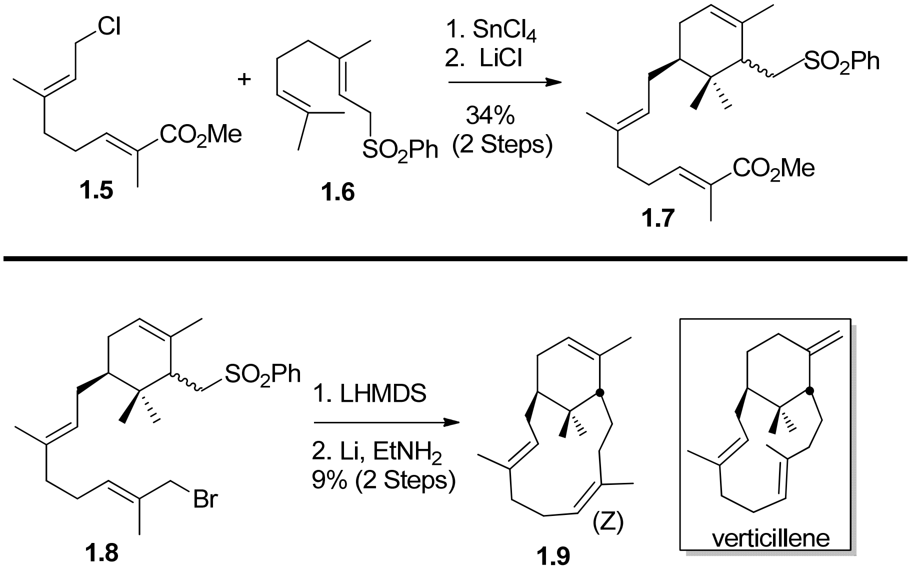


Scheme 1.1. Proposed Biosynthetic Origin of Hypoestoxide and Verticillol

1.2 Other Relevant Synthetic Work

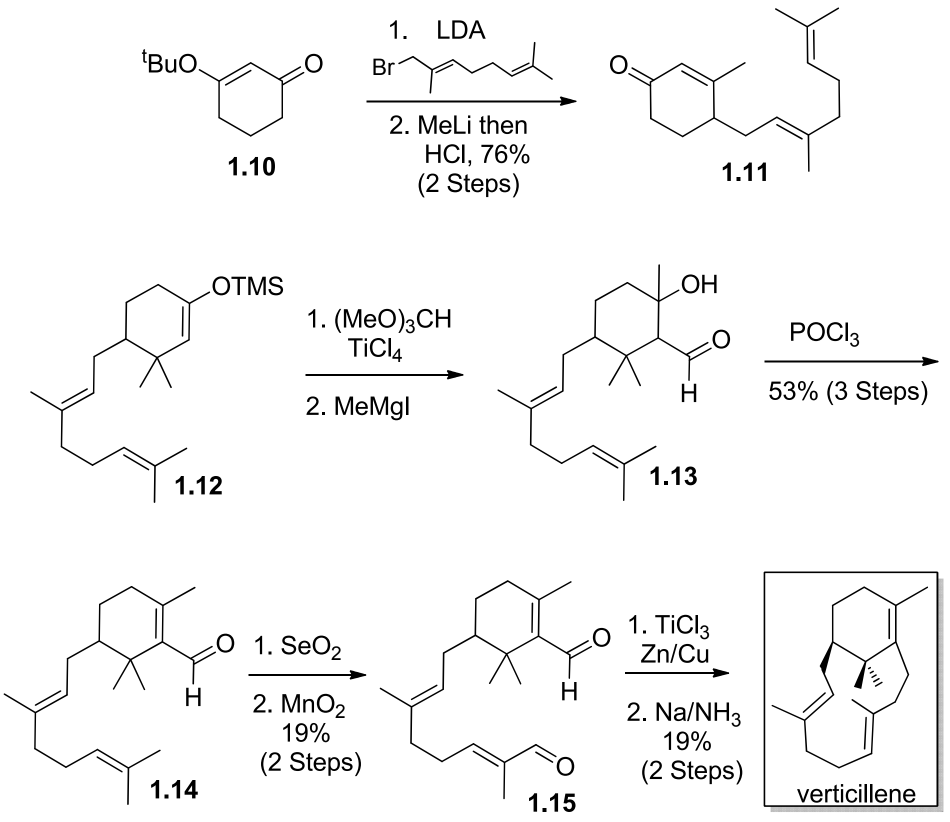
Although no other synthetic efforts toward hypoestoxide have been published to date, work has been done toward verticillol and verticillene (dehydrated verticillol) and these efforts will be summarized below. Despite their complex structure and promising biological activity a surprisingly small number of accounts have been published in this area to date.

The first synthetic work came in 1981 from the lab of Tadahiro Kato (Scheme 1.2).[10] The first key step in the synthesis involves a bio-inspired carbocation cascade triggered by the addition of $SnCl_4$ to form the six-membered ring and bring together all of the carbons of the verticillene core (**1.7**). Their plan to assemble the macrocycle was to deprotonate α to the sulfone in order to displace the allylic bromide to access the core. Unfortunately under the conditions of the reaction, the allylic bromide isomerized from E to Z prior to being displaced, affording only the Z-olefin in the newly formed macrocycle **1.9** in rather low yield.



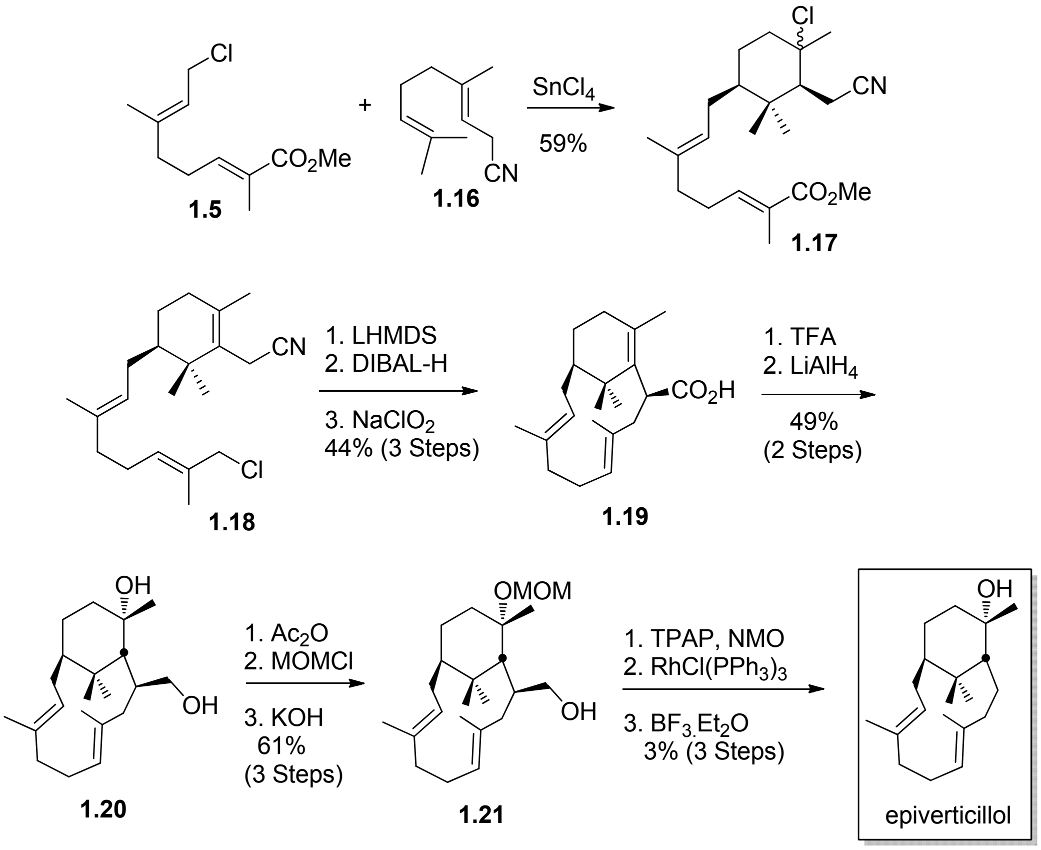
Scheme 1.2. Kato's First Synthetic Efforts Toward Verticillene

The second paper detailing work toward verticillene was published in 1990 by the Pattenden group (Scheme 1.3).[11] This synthesis uses Stork-Danheiser chemistry to attach the diene chain needed for the macrocycle (**1.11**). The final carbon of the macrocycle is then installed by formylating the silyl enol ether followed by Grignard addition and dehydration to afford enal **1.13**. A selective allylic oxidation with selenium and subsequent manganese dioxide oxidation gave the bis-aldehyde **1.15** needed to faciliate macrocylization. The aldehydes were reductively coupled with titanium trichloride and zinc copper couple to give the macrocycle. Verticillene was formed by 1,4-reduction of the resulting tetraene with sodium and liquid ammonia.



Scheme 1.3. Pattenden's Synthesis of Verticillene

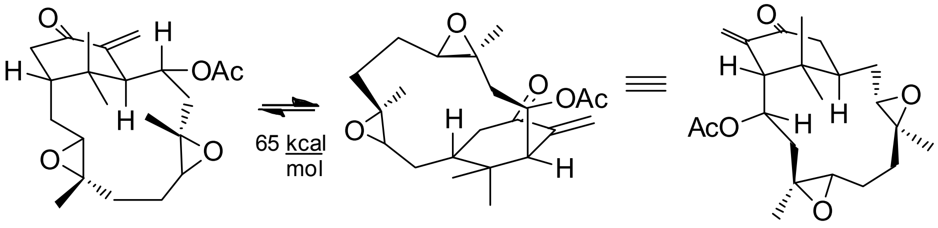
The third paper in this area was again the work of Kato and used much of the same chemistry as before (Scheme 1.4).[12] An analogous cationic cyclization was carried out as before using allylic chloride **1.18** with the hope of eliminating the troublesome allylic scrambling that occurred in their first paper during the cyclization step. With the chloride in place, the macrocyclization proceeded smoothly without any mention of olefin scrambling. With this success behind them, they installed the required tertiary alcohol by lactonization and reduction to diol **1.21**, albeit with the wrong tertiary alcohol stereochemistry. Their synthesis of epiverticillol was completed by oxidizing the primary alcohol and deformylating using Wilkinson's catalyst.



Scheme 1.4. Kato's Synthesis of Epiverticillol

1.3 Our Synthetic Efforts[13]

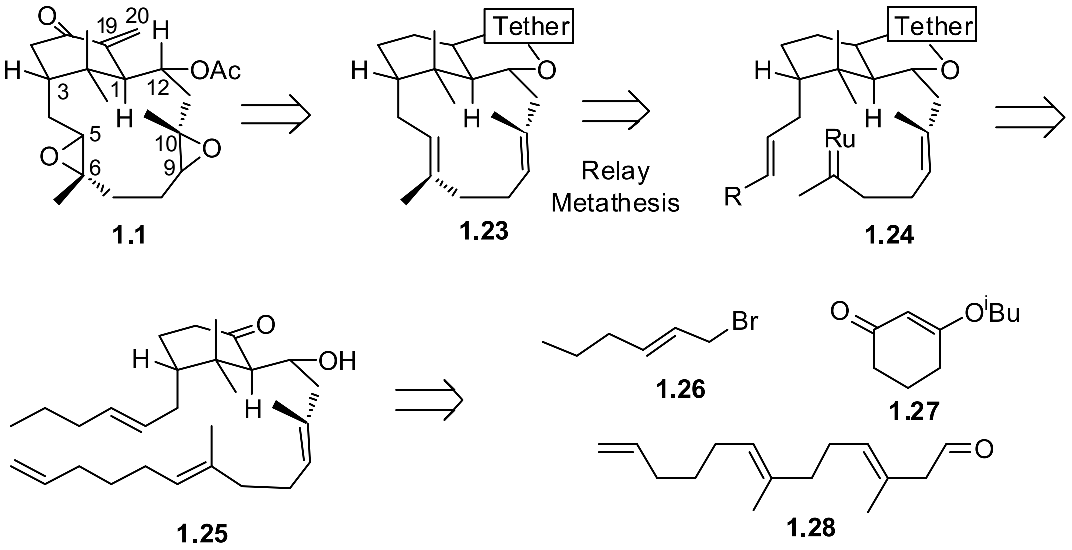
Several factors were considered before beginning our synthetic efforts. First, with a *trans*-[9.3.1] bicyclic framework two different atropisomers are possible for hypoestoxide (Scheme 1.5). We were encouraged by calculations indicating that hypoestoxide was 4.1 kcal/mol (B3LYP/6-311+G(d,p)) more stable than the atropisomer (**1.22**). Therefore, we imagined that a macrocyclization would preferentially form the natural atropisomer. In addition, the barrier to interconvert hypoestoxide and its atropisomer was estimated to be 65 kcal/mol, suggesting that atropisomer interconversion would not be possible.



Hypoestoxide (**1.1**) Atrop-Hypoestoxide (**1.22**)

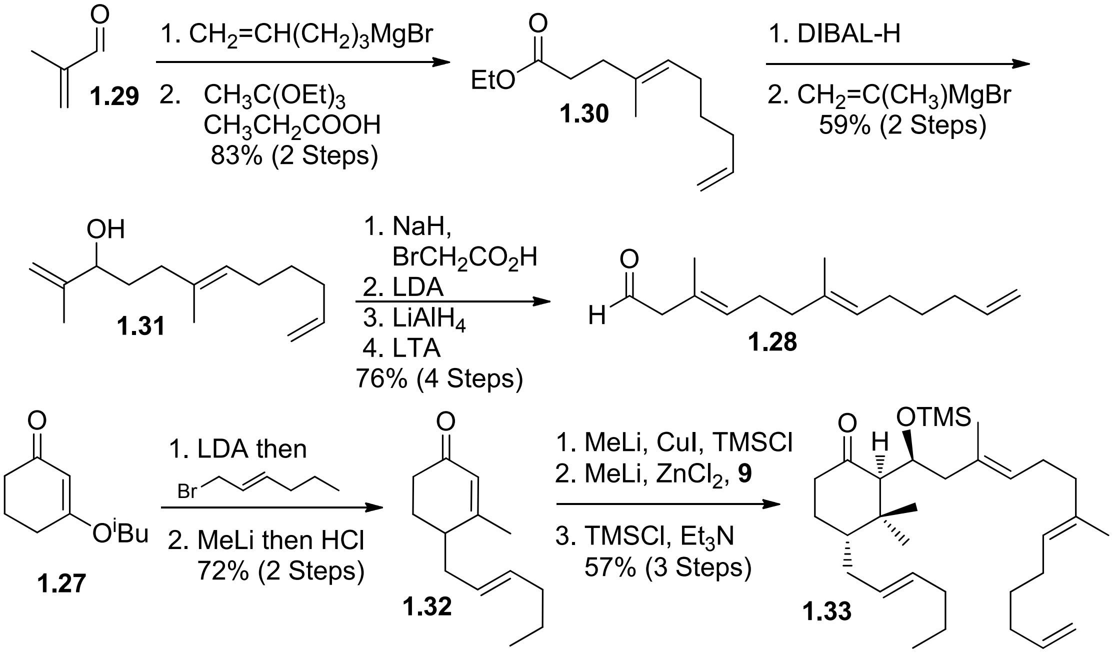
Scheme 1.5. Possible Atropisomers of Hypoestoxide

Taking these observations into consideration, diene **1.23** seemed like an ideal target, and we decided to construct it using a conformationally controlled ring closing metathesis (Scheme 1.6). This diene provided four different ring closing metathesis options. The C5-C6 and C9-C10 olefins would originate from a standard *mono*-substituted carbenoid or alternatively from a *di*-substituted carbenoid, such as **1.24**, which would be accessed using relay ring closing metathesis (RRCM).[14] Our analysis suggested that in closing the macrocycle it would be advantageous to bring together a more substituted carbene with a less hindered terminus to minimize competing dimerization pathways. We further postulated that ruthenium carbene **1.24** (C5-C6 disconnection) would be the better candidate for macrocyclization, since the equivalent C10-*di*-substituted carbene would be more sterically hindered and suffer from unfavorable interactions with the C12 hydroxy group. Concurrently, we proposed to rigidify the macrocyclization substrate in order to bring the two olefin termini closer together[15] and ensure formation of the correct atropisomer. Ketone **1.25** would serve as the branch-point that would allow us at a late stage to evaluate several fused ring sizes. Cyclization precursor **1.25** would be assembled from three simple building blocks (**1.26-1.28**). Our endgame towards hypoestoxide would rely on substrate controlled *bis*-epoxidation.



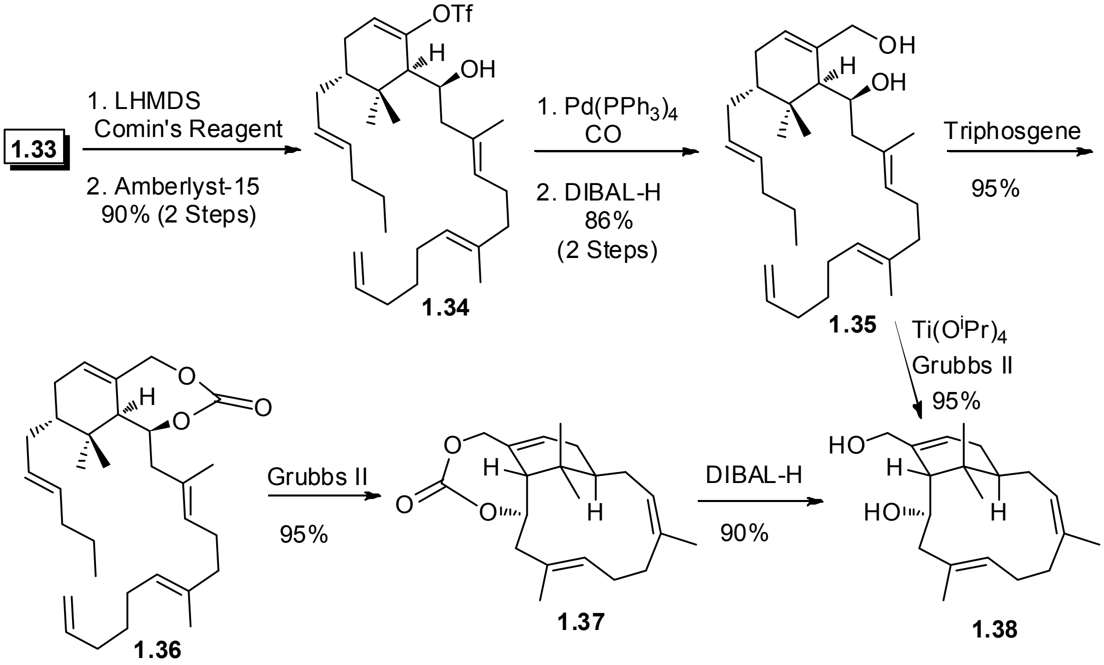
Scheme 1.6. Retrosynthesis of Hypoestoxide

Our synthetic efforts commenced with a Grignard addition to methacrolein **1.29**, followed by a Johnson-Claisen rearrangement[16] to generate ethyl ester **1.30** (Scheme 1.7). This ester was reduced to the aldehyde with DIBAL-H, and another Grignard addition afforded allylic alcohol **1.31**. We next utilized a [2,3]-rearrangement[17] to stereoselectively install the second trisubstituted olefin. The hydroxyacid was exhaustively reduced and the resulting diol was cleaved with lead tetraacetate to give aldehyde **1.28**. The other key component, enone **1.32**, was readily assembled by employing the Stork-Danheiser methodology.[18] This enone was then subjected to a conjugate addition and *in situ* trapping to form the trimethylsilyl enol ether[19] needed to couple with aldehyde **1.28**. It was determined that the addition of $ZnCl_2$[20] was required to promote the desired aldol reaction to form tetraene **1.33** with the desired *trans* arrangement[21] on the six-membered ring. This route efficiently assembled the versatile synthetic intermediate **1.33** in only 10 steps from methacrolein.



Scheme 1.7. Synthesis of Metathesis Precursor

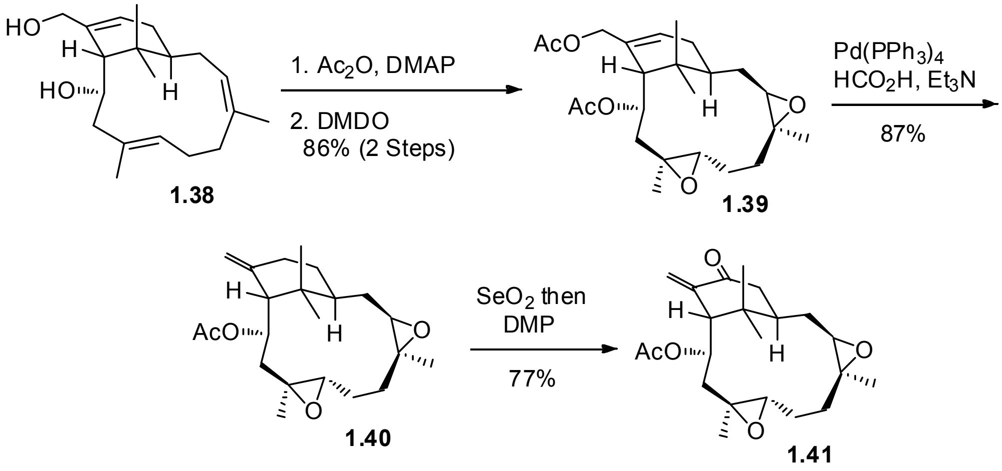
Encouraged by the rapid assembly of metathesis precursor **1.33**, we decided to evaluate 5- and 7-membered ring tethers. Accordingly, we converted ketone **1.33** to an enol triflate and deprotected the silyl ether to give **1.34** (Scheme 1.8). The 5-membered ring tether was accessed *via* carbonylation[22] of **1.34** to give the lactone, however, this lactone and its reduced variants (1,4 and 1,2-reductions) failed to undergo ring closing metathesis. The 7-membered ring series was accessed by reducing the lactone to diol **1.35** and tethering the two hydroxyl groups with triphosgene to give carbonate **1.36**. This carbonate turned out to be an ideal macrocyclization substrate. Optimized conditions using Grubbs second generation catalyst[23] in refluxing toluene afforded bicyclic substrate **1.37** in excellent yield. Deprotection of **1.37** gave diol **1.38**. Successful metathesis cyclizations took place using Grubbs 2nd generation catalyst. With a successful cyclization substrate in hand, we wondered if two steps could be eliminated from the synthetic sequence by tethering the diol *in situ* using titanium additives.[24] Gratifyingly, adding excess titanium isopropoxide prior to the metathesis catalyst formed triene **1.38** in equally high yield directly from diol **1.35**.



Scheme 1.8. Tether-Assisted Ring Closing Metathesis

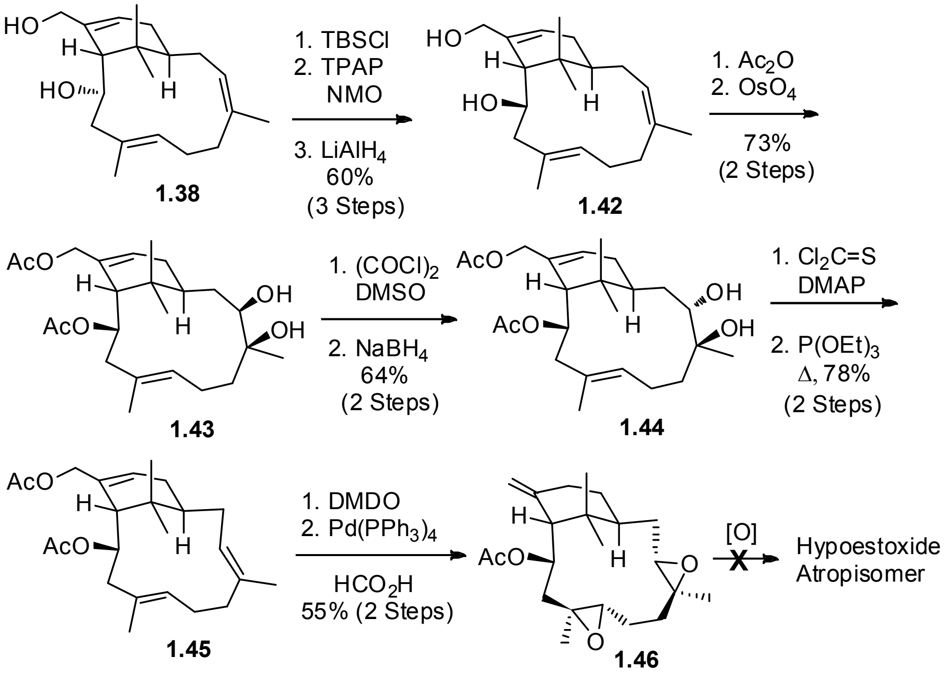
Extensive NMR analysis of **1.38** revealed a couple of additional problems with the structure. The ring closing metathesis not only gave the undesired *Z*-olefin, but had done so with the C12-bearing tether in an axial position instead of the more stable equatorial position thus forming the wrong atropisomer of the natural product. Although this unexpected result revealed a flaw in our planned facial bias, it did confirm our tethered-cyclization strategy. This metathesis product (**1.38**) was then *bis*-acetylated, and the two trisubstituted macrocyclic olefins were subjected to substrate controlled *bis*-epoxidation, which afforded **1.39** as the only product. Tsuji's reductive allylic transposition[25] was used to form the desired *exo*-methylene moiety in

1.40. Allylic oxidation was achieved with selenium dioxide and the resulting alcohol was oxidized with Dess-Martin periodinane to enone **1.41**. This nineteen step synthesis of an isomer of hypoestoxide highlights the efficiency of our synthetic assembly.



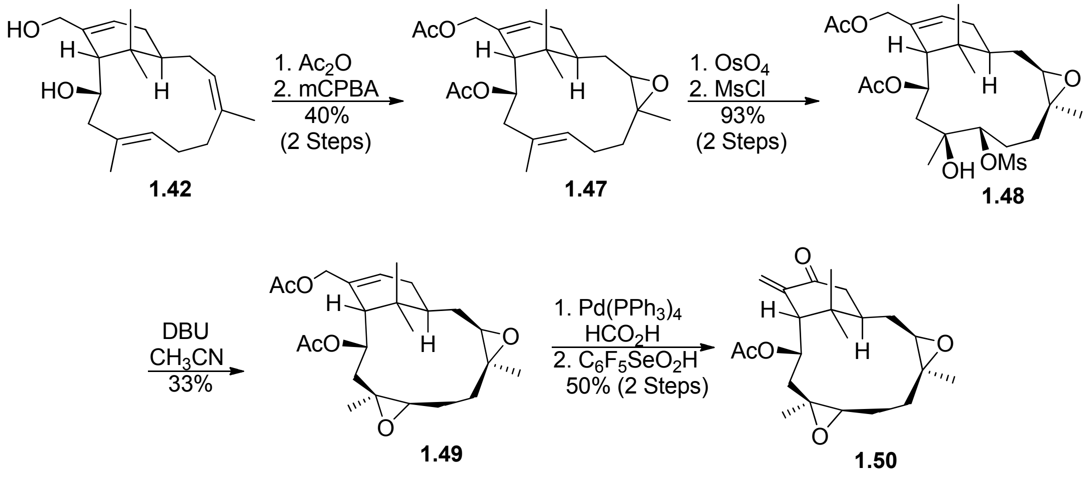
Scheme 1.9. Synthesis of Hypoestoxide Isomer

To complete a total synthesis of *atrop*-hypoestoxide we needed to invert both the C12 stereocenter and the C5-C6 olefin geometry. Toward that end, the primary alcohol group in metathesis product **1.38** (Scheme 1.10) was selectively protected and the C12 alcohol was converted to a ketone using the Ley oxidation. Substrate controlled reduction of the ketone gave the inverted diol **1.42** as a single product.[26] We then turned our attention to the more challenging task of inverting the C5-C6 trisubstituted olefin. We accomplished this by acylating the diol and dihydroxylating the more reactive C5-C6 olefin to give **1.43**. The inversion was solved by forming diol **1.44** using a substrate controlled oxidation/reduction sequence. The hydroxyl groups of **1.44** could then be tied together to form a cyclic thiocarbonate, which when subjected to the Corey-Winter deoxygenation conditions[27] afforded the desired *E,E*-triene **1.45**. Following *bis*-epoxidation of the macrocyclic diene moiety, palladium mediated allylic transposition was again successfully employed to form the desired *exo*-methylene group. Unfortunately, **1.46** could not be oxidized to *atrop*-hypoestoxide.



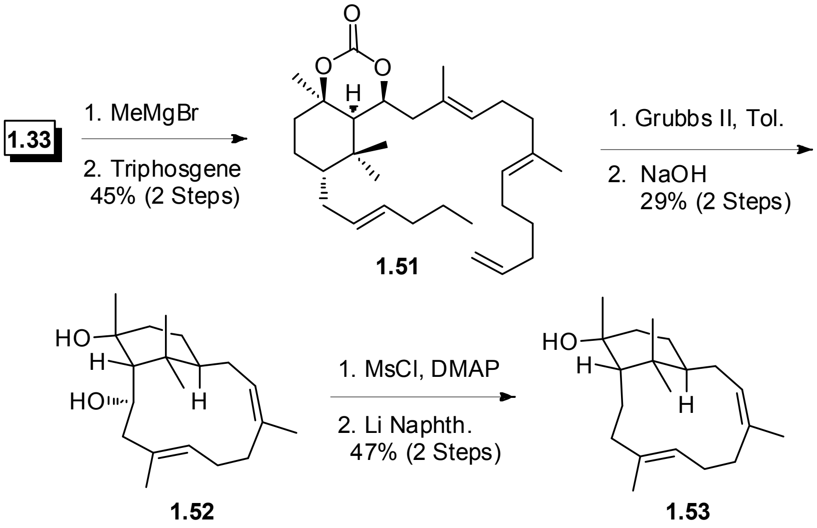
Scheme 1.10. Synthesis of Desoxy *atrop*-Hypoestoxide

In an effort to further test the final allylic oxidation protocol, diol **1.42** was again bis-acetylated and then subjected to mCPBA which selectively epoxidized the more reactive Z-double bond to give **1.47**. The remaining macrocyclic double bond was then dihydroxylated and the secondary alcohol was selectively converted to the hydroxy mesylate **1.48**. Treatment with DBU afforded the *cis*-epoxide **1.49**. Palladium catalyzed transposition of the allylic acetate in **1.49** gave the desired exocyclic olefin to test the allylic oxidation. This double *cis*-epoxide isomer of *atrop*-hypoestoxide smoothly afforded another isomer of hypoestoxide (**1.50**) when treated with pentafluorophenylselenic acid.



Scheme 1.11. Synthesis of Another Isomer of *atrop*-Hypoestoxide

We decided to explore an additional tethering strategy to achieve an even more expedient synthetic assembly of both hypoestoxide and verticillol. We were interested in learning how a six-membered ring tether would affect the selectivity of the ring closing metathesis (Scheme 1.12). Grignard addition to ketone **1.33** afforded a single diol diastereomer, which could be readily tethered as a cyclic carbonate (**1.51**). When treated with Grubbs second generation catalyst **1.51** formed a single macrocyclic isomer which, upon deprotection, afforded diol **1.52**. NMR analysis of **1.52** indicated that the undesired *Z*-olefin and incorrect atropisomer were again formed as the only bicyclic product in the ring closing metathesis reaction. This diol could, however, be converted to an isomer of verticillol (**1.53**) by selective mesylation of the secondary alcohol and reductive removal of the resulting sulfonate ester. This synthetic route to an isomer of verticillol constituted only sixteen synthetic steps from methacrolein.



Scheme 1.12. Synthesis of a Verticillol Isomer

In summary, we have reported the first synthetic efforts towards the natural product hypoestoxide. An efficient flexible synthetic route that also provides access to the verticillane family of natural products has been devised. This synthetic roadmap has been utilized to accomplish a synthesis of 18-*desoxy*-*atrop*-hypoestoxide as well as isomers of both hypoestoxide and verticillol.

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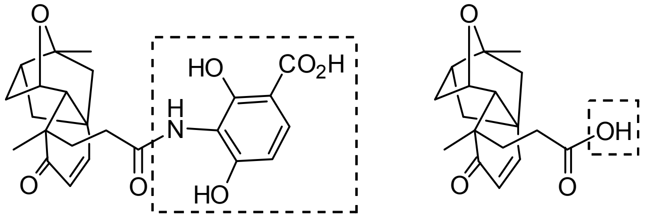
Chapter 2

Platensimycin

2.1 Background and Significance

Recently, researchers at Merck disclosed a new natural product, platensimycin (**2.1**, Figure 2.1),[1] which was obtained by screening a large collection of South African soil samples using a novel antibiotic assay. Characterization revealed a unique compact core connected to an aminohydroxy salicylic acid group *via* a propionate tether. Platensimycin has a novel mechanism of action, inhibiting the β-ketoacyl-(acyl carrier protein) synthase (FabF) in the bacterial fatty acid synthetic pathway.[2] It was shown that the salicylic acid group present in platensimycin competes with the malonyl-acyl-carrier-protein for the malonyl binding site of FabF. Platensimycin is quite effective towards various gram-positive bacteria including multiresistant strains of *staphylococci* and *enterococci*. Due to its unique mechanism of action, no cross resistance to existing drugs have been reported to date. Several new members of this class have since been reported,[3] differing only in functionalization of the carboxylate terminus. This attractive natural product target has also encouraged researchers to engineer strains to improve its production.[4] Recently, several derivatives obtained by modifying platensimycin have been reported.[5] Nicolaou has pursued a different approach, replacing the oxatetracyclic core with carbocyclic and adamantyl mimics, which were equipotent with the natural product.[6] These results bode well for analog approaches utilizing diverted total synthetic strategies.[7]



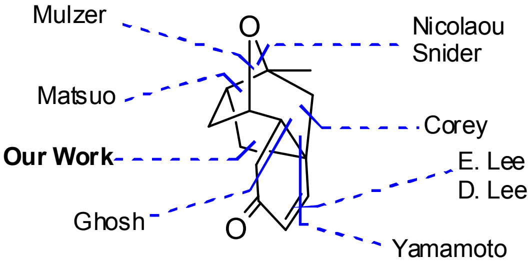
Platensimycin (**2.1**)

Platensic Acid (**2.2**)

Figure 2.1. Structures of Platensimycin and Platensic Acid

2.2 Other Relevant Synthetic Work

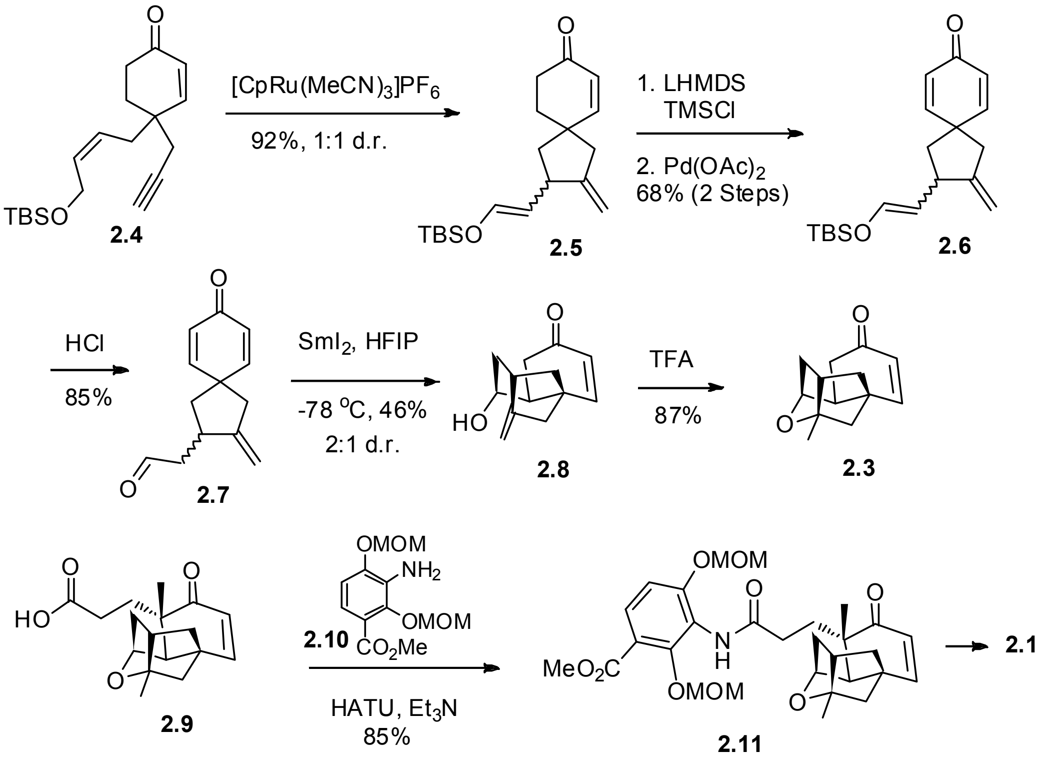
Despite a flurry of synthetic activity,[8] only two groups have completed total syntheses of platensimycin (**2.1**) to date. All other reported efforts have focused on constructing the platensimycin core (**2.3**). To highlight the diversity of these synthetic approaches we have chosen to emphasize the final bond formed by each group to complete the polycyclic core of platensimycin (Figure 2.2). Altogether there have been fourteen unique approaches to this exciting molecule and each of these efforts is summarized below.



Platensimycin Core (**2.3**)

Figure 2.2. Synthetic Approaches to Complete the Platensimycin Core

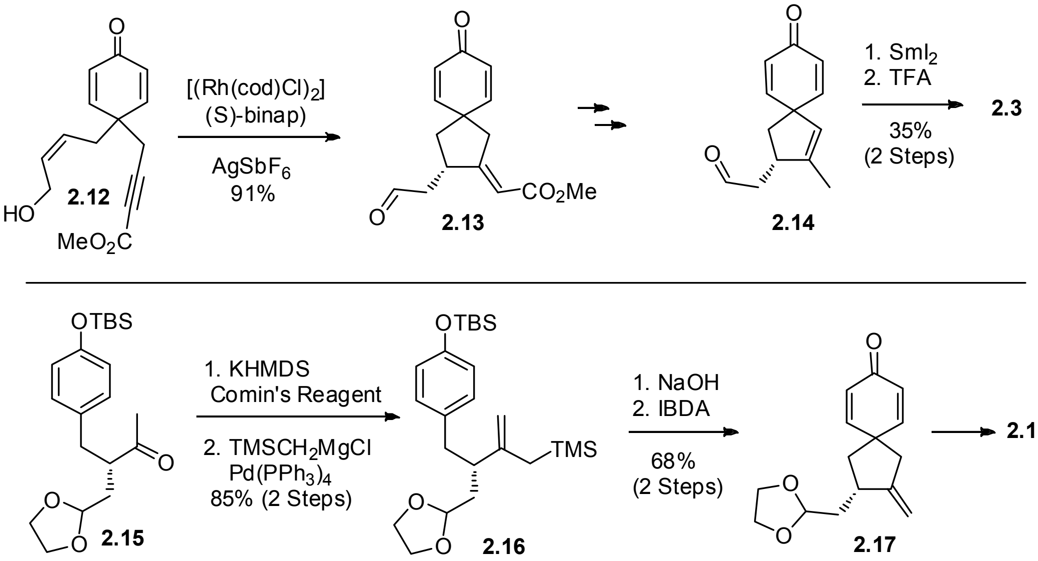
The first total synthesis of platensimycin was published in 2006 by K. C. Nicolaou (Scheme 2.1).[9] The first key step in the synthesis was a ruthenium-catalyzed cycloisomerization to generate the spirocyclic compound **2.5**. The next ring was constructed using a samarium iodide mediated radical cyclization and the final ring was achieved through an acid-catalyzed etherification with trifluoroacetic acid. Having attained the tetracyclic core of platensimycin (**2.3)**, the next task was to attach the aromatic sidechain. This was accomplished by using a HATU mediated amide coupling reaction between the carboxylic acid **2.9** and protected aniline **2.10**. Then, the first total synthesis of platensimycin was completed by straightforward protecting group removal.



Scheme 2.1. Nicolaou's Total Synthesis of Platensimycin

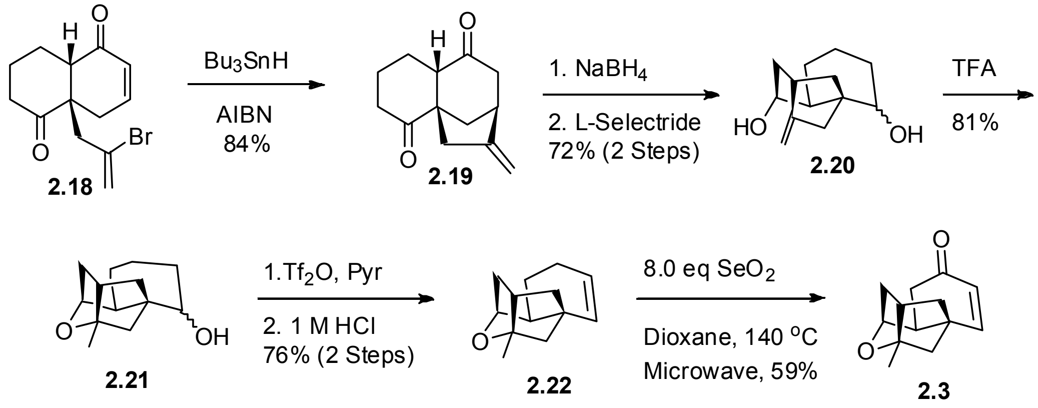
The Nicolaou group subsequently reported two unique enantioselective approaches (Scheme 2.2) to the platensimycin core.[10] The first asymmetric approach mirrors that of their first paper and uses a cycloisomerization to install the spiro-ring system. Asymmetric induction was achieved by employing a rhodium-catalyzed cycloisomerization in the presence of (*S*)-BINAP to give **2.13** in greater than 95% *ee*. This route was completed as before, utilizing first a samarium iodide mediated cyclization followed by a trifluoroacetic acid catalyzed etherification to give the first enantioselective synthesis of the platensimycin core **2.3**.

Another route described in the same paper uses a chiral auxiliary approach to assemble the platensimycin core in an asymmetric fashion. The asymmetry was achieved using Myers' asymmetric alkylation method[11] with (*S*,*S*)-pseudoephedrine to bring together the aryl group and the amide auxiliary in 85% *de*. After cleaving the auxiliary and carrying out minor structural modifications, the key spiro system was constructed using a iodine-catalyzed cyclodearomatization reaction with an allyl silane as the required nucleophile to generate **2.17**. This enantioenriched product was then carried forward using the previously described method (Scheme 2.1) to complete the first asymmetric total synthesis of (-)-platensimycin.



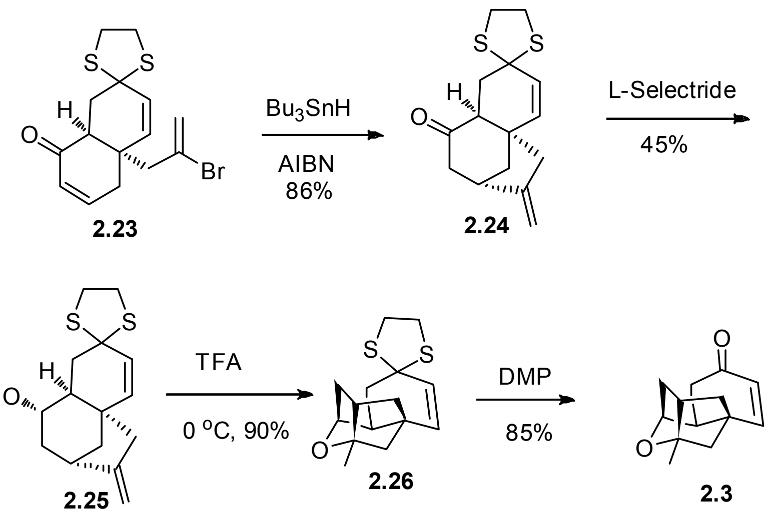
Scheme 2.2. Nicolaou's Asymmetric Syntheses of Platensimycin

Recently, the Snider group described a very concise route to the platensimycin core (Scheme 2.3).[12] The synthesis begins with an intramolecular 5-*exo*-trig radical cyclization between a vinyl radical and an α,β-unsaturated ketone to give **2.19**. After ketone reduction, the final ring was formed by an acid-catalyzed etherification reaction forming **2.21**. The formal synthesis was completed by carrying out a dehydration and subsequent allylic oxidation with selenium dioxide.



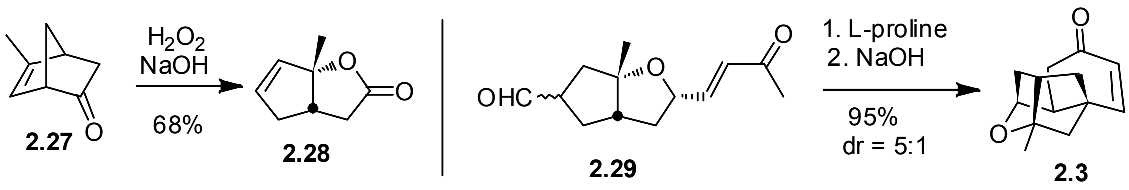
Scheme 2.3. Snider's Synthesis of Platensimycin

Nicolaou and coworkers followed up by publishing an alternate formal synthesis of racemic platensimycin (Scheme 2.4).[13] The 6,6-fused ring system of **2.23** was accessed by using an intramolecular Stetter reaction and the subsequent ring was achieved through a 5-*exo*-trig radical cyclization into the remaining α,β-unsaturated ketone to give **2.24**. After ketone reduction, the final ring of the core was again accessed by using acid-catalyzed etherification. The ketone reduction unfortunately gave a 1:1 mixture of diastereomers that were separated and the undesired alcohol was re-oxidized and reduced to give more of the desired alcohol that was competent for the cyclization. The thioketal of **2.26** was then oxidatively removed with Dess-Martin periodinane to complete the formal synthesis of platensimycin.



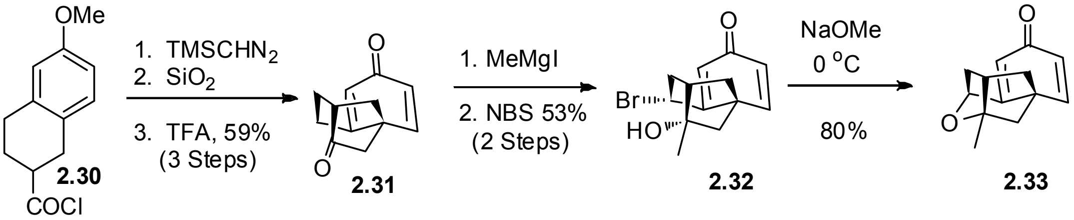
Scheme 2.4. Nicolaou's Stetter/Radical Based Synthesis of Platensimycin

The research group of Hisashi Yamamoto was the next to produce a synthesis of platensimycin (Scheme 2.5).[14] Lactone **2.28** was prepared using a Baeyer-Villiger oxidation of ketone **2.27**. Under the reaction conditions the initially formed lactone isomerized to form the more stable fused lactone **2.28**. Functionalizing both five membered rings led to the α,β-unsaturated ketone **2.29**, which was used to test the key annulation. The reaction was accomplished in one pot using L-proline as a catalyst to mediate the initial intramolecular Michael addition, followed by sodium hydroxide treatment to facilitate the subsequent aldol condensation.



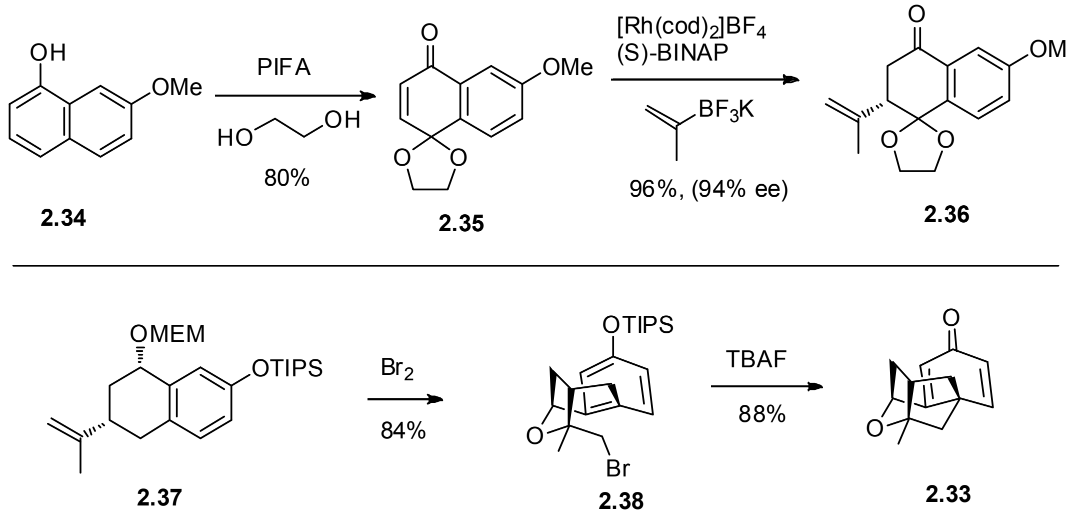
Scheme 2.5. Yamamoto's Synthesis of Platensimycin

Mulzer et al. also reported an approach to platensimycin (Scheme 2.6).[15] The synthesis of the diketone **2.31**, previously reported by Mander,[16] involves the cyclodearomatization of a diazo-ketone generated by addition of TMS-diazomethane to acid chloride **2.30**. The regio- and stereoselective addition of methylmagnesium iodide to **2.31** followed by stereoselective allylic bromination provided **2.32**, which subsequently cyclized under basic conditions to complete the core of platensimycin. The core was then exhaustively hydrogenated and re-oxidized to complete the formal synthesis.



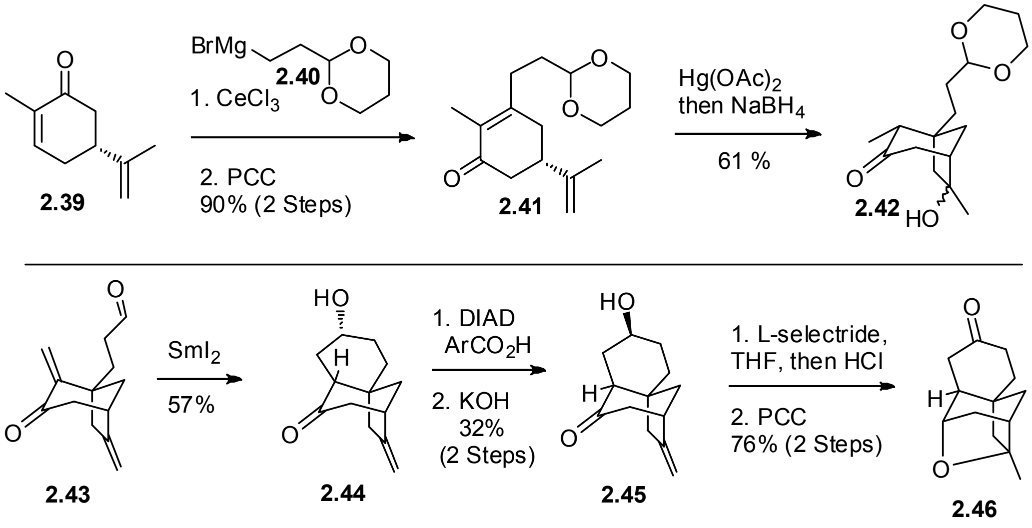
Scheme 2.6. Mulzer's Synthesis of Platensimycin

The next approach came from the lab of Corey and coworkers (Scheme 2.7).[17] The first step of the synthesis was an oxidative acetalization of **2.34** with ethylene glycol to give the α,β-unsaturated ketone **2.35**, which was then subjected to an enantioselective conjugate addition to introduce the asymmetry in the synthesis. The synthesis later relied on an intramolecular bromoetherification reaction of MEM-ether **2.37** to install the tetrahydrofuran moiety and the bromine atom necessary to complete the core. The next step was to remove the silyl protecting group thereby allowing for the desired alkylative dearomatization to give the platensimycin core.



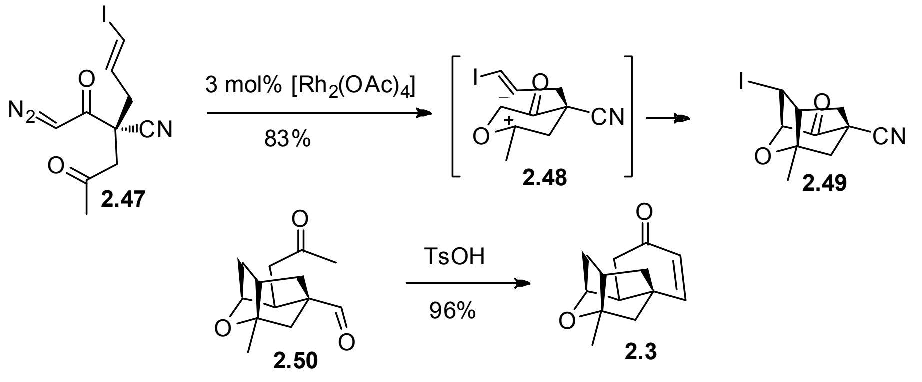
Scheme 2.7. Corey's Synthesis of Platensimycin

Another route based on chiral pool reactants again came from the Nicolaou group (Scheme 2.8).[18] The synthesis started from (*R*)-(-) carvone **2.39**, which was treated with Grignard reagent **2.40** followed by oxidation of the resulting tertiary alcohol to give the desired enone **2.41**. This was followed by regioselective oxymercuration of the disubstituted olefin. When the resulting organo-mercury species was reduced with sodium borohydride, the resulting primary radical underwent 1,4-addition to the enone generating the [3.2.1] bicyclic system **2.42**. Other key steps in the synthesis included a samarium iodide mediated 6-*endo* radical cyclization and an acid-catalyzed etherification to complete the core of platensimycin.



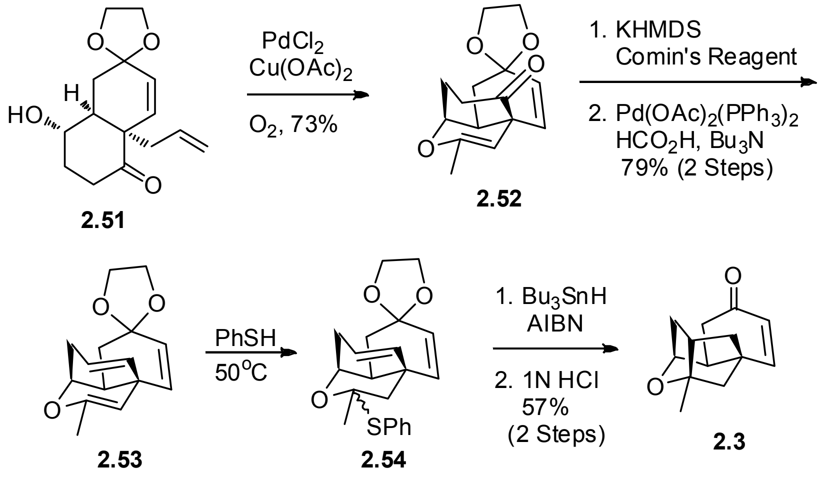
Scheme 2.8. Nicolaou's Chiral Pool Based Synthesis of Platensimycin

The next paper published was from the research group of Eun Lee (Scheme 2.9).[19] The key step in the synthesis involved a carbonyl ylide cycloaddition of **2.48** to generate all but one of the rings in the platensimycin core. The final step to complete the core was a high yielding aldol condensation under acidic conditions.



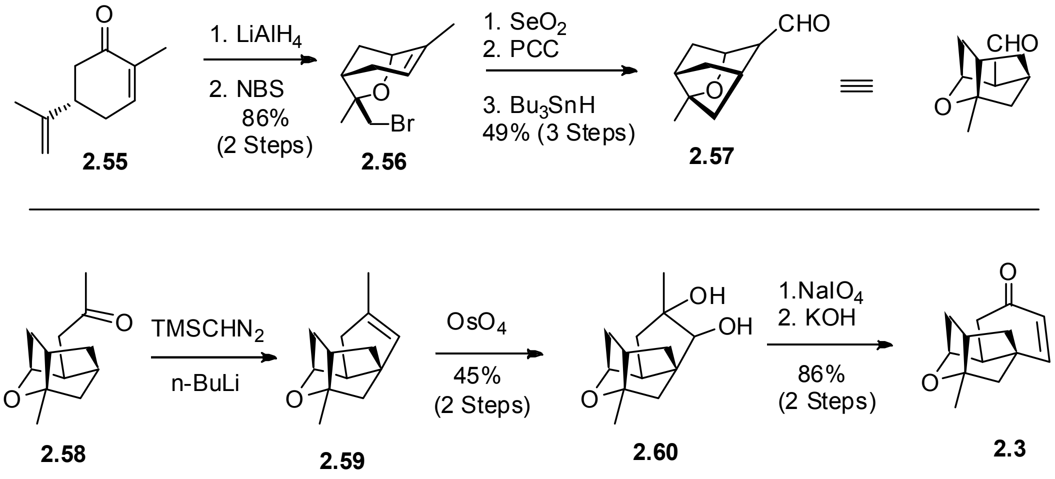
Scheme 2.9. Eun Lee's Synthesis of Platensimycin

A synthetic approach by Matsuo and coworkers is summarized in Scheme 2.10.[20] The first key step in the sequence was a palladium catalyzed cyclization of 2.51 to form dihydropyran **2.52**. The ketone group in **2.52** was then converted to the vinyl triflate and reduced to **2.53**. Selective addition of thiophenol to the enol ether in **2.53** generated the monothioketal **2.54**, which was poised to form the final C-C bond of the core. A transannular radical cyclization was realized using standard conditions to afford **2.3** after deacetylization.



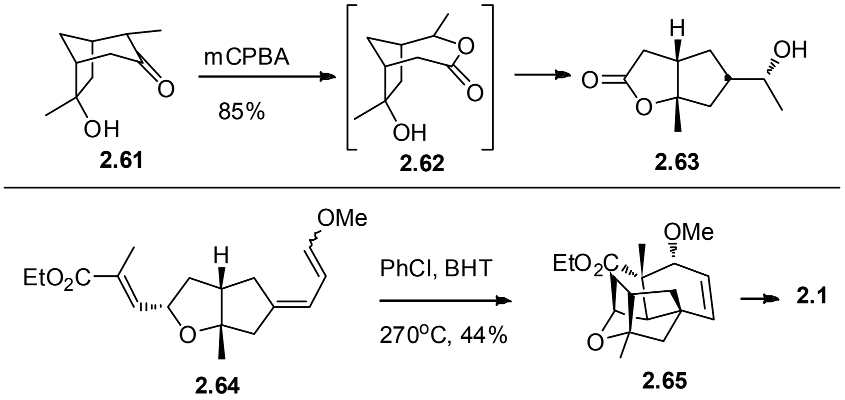
Scheme 2.10. Matsuo's Synthesis of Platensimycin

An approach by Daesung Lee (Scheme 2.11)[21] was also based on (*S*)-carvone **2.55**, which was reduced and cyclized to give **2.56**. Allylic oxidation followed by a 5-*exo* radical cyclization provided **2.57**. After extending the aldehyde chain to ketone **2.58**, they converted the ketone to the alkylidene carbene which underwent the desired C-H insertion to form **2.59**. Subsequent dihydroxylation to **2.60** and diol cleavage afforded the ketoaldehyde previously reported by Eun Lee, which underwent a base catalyzed aldol condensation to give the core of platensimycin.



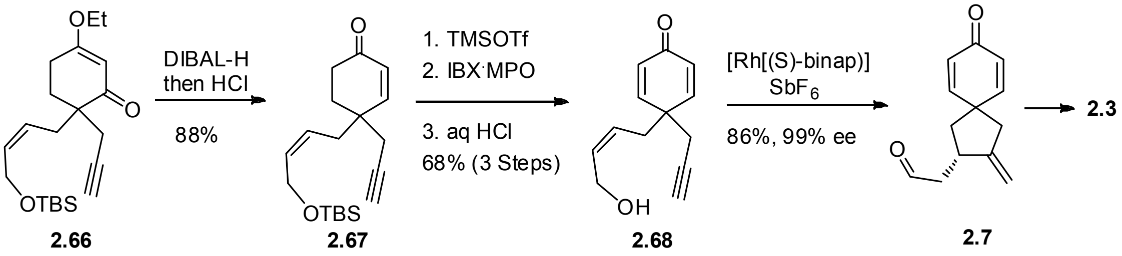
Scheme 2.11. Daesung Lee's Synthesis of Platensimycin

The next synthesis of platensimycin was achieved by the research group of Arun Ghosh, starting from carvone (Scheme 2.12) [22]. A key step was a Baeyer-Villiger oxidation of **2.61** to give the seven membered ring lactone **2.62**, which subsequently isomerized to the 5,5-fused lactone **2.63**. Each ring of the fused bicyclic system was then elaborated to produce triene **2.64** necessary for the crucial intramolecular Diels-Alder reaction. Standard conditions failed to provide the Diels-Alder adduct, but by increasing the temperature and pressure (270°C, sealed tube) a reasonable yield of cycloaddition product **2.65** could be attained. Ghosh et al. went on to elaborate their system to complete a total synthesis of (-)-platensimycin.



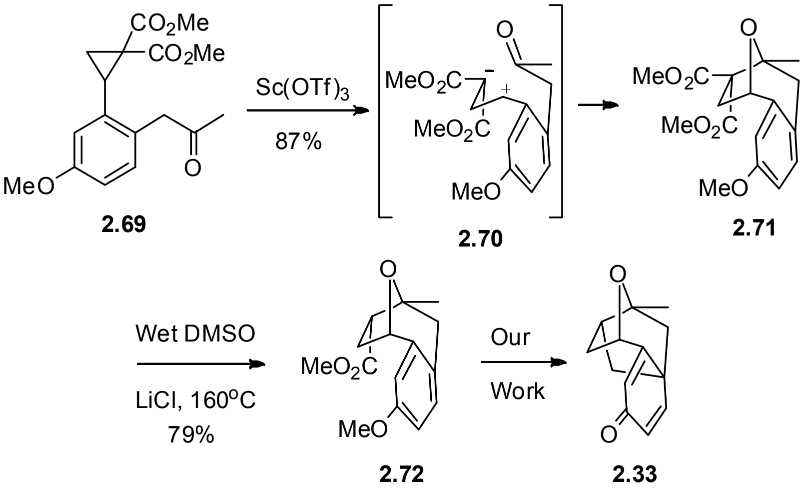
Scheme 2.12. Ghosh's Synthesis of Platensimycin

Another report from the Nicolaou lab highlighted further development of the cycloisomerization reaction described in two of their previous routes (Scheme 2.1, Scheme 2.2) to platensimycin.[23] This involved the use of a terminal alkyne in the cycloisomerization reaction to form **2.7** (Scheme 2.13). Enyne precursor **2.68**, was assembled using Stork-Danheiser chemistry and the core was completed in a similar fashion to their previous routes.



Scheme 2.13. Nicolaou's Fifth Synthesis of Platensimycin

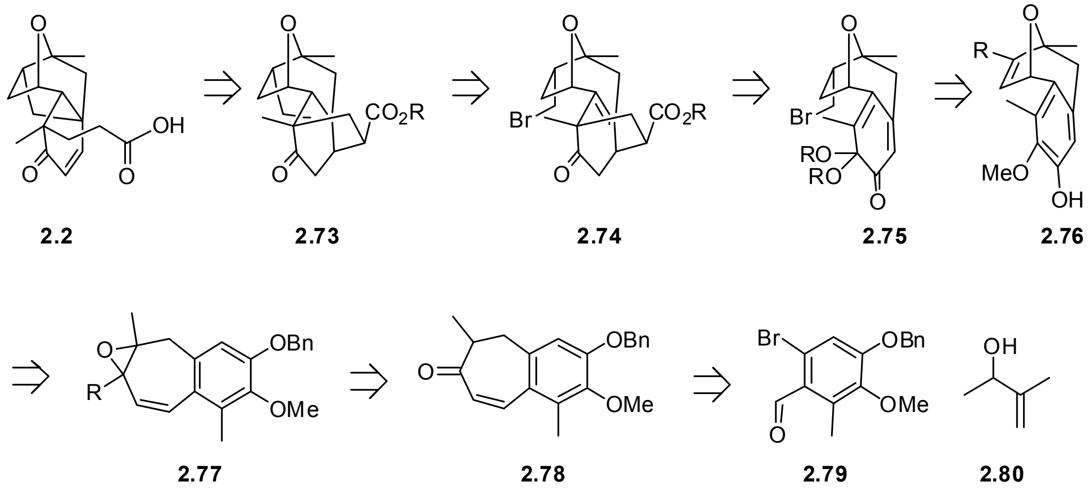
A platensimycin approach by Wang and coworkers (Scheme 2.14)[24] utilized an intramolecular [3+2] cycloaddition of a cyclopropane 1,1-diester with a ketone to assemble the oxatropane *via* ylide **2.70**. Decarboxylation of **2.71** converged with intermediate **2.72** from our synthesis to complete their formal synthesis of platensimycin.



Scheme 2.14. Wang's Synthesis of Platensimycin

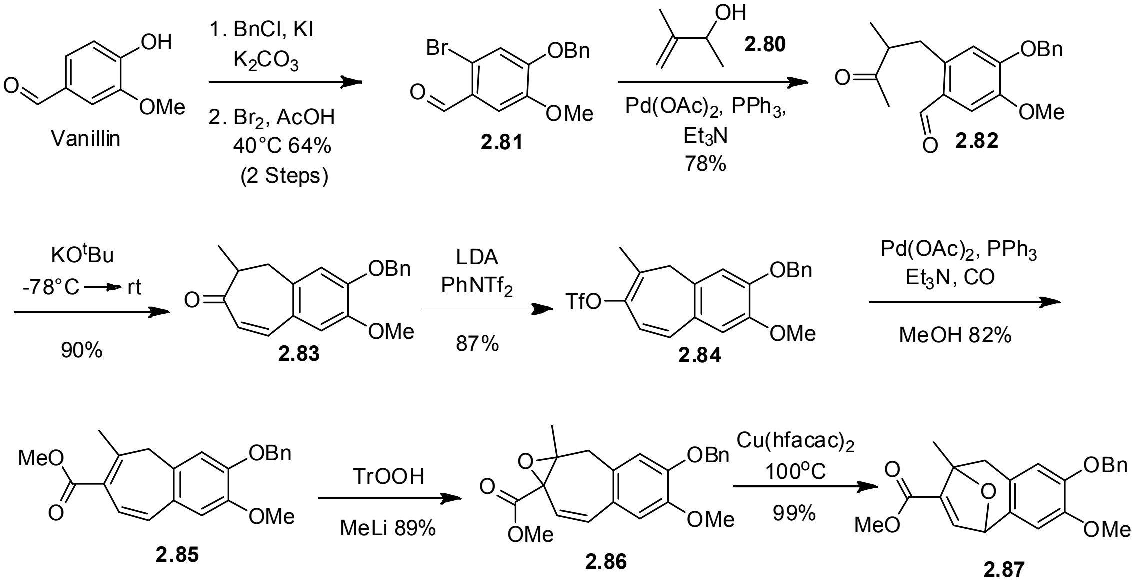
2.3 Our Synthetic Efforts[25]

We envisioned a concise retrosynthetic plan for the total synthesis of platensimycin (Scheme 2.15). Platensic acid (**2.2**) would serve as our immediate target as it represented a natural branch point for accessing all the other members of this natural product family. We proposed that **2.2** could be made from **2.73** *via* a *retro*-Michael ring opening reaction followed by hydrolysis of the resulting ester. Radical cyclization of bromide **2.74** would be expected to afford the platensimycin carbocyclic core (**2.73**). Oxidative dearomatization of **2.76** and *in situ* trapping of the *ortho*-quinone *mono*-ketal (**2.75**) with methyl acrylate was expected to provide **2.74** as the only cycloadduct. In this one remarkable transformation, the aromatic core would be unraveled and primed for the following cyclization step. At the same time, the quaternary center bearing the sidechain with the desired oxidation state would be installed *via* a substrate and regiocontrolled Diels-Alder cycloaddition. Oxatropane **2.76** would originate from vinyl oxirane **2.77** using our newly described copper catalyzed ring expansion.[26] Epoxidation of the diene obtained from enone **2.78** could also serve as the asymmetric entry point for this synthesis, which in turn would be assembled in two steps from **2.79**[27] and **2.80** using a Heck coupling followed by an intramolecular aldol condensation. Although this design allows direct access to the platensimycin core including the propionic acid and methyl group, we decided to initially take a more conservative approach.



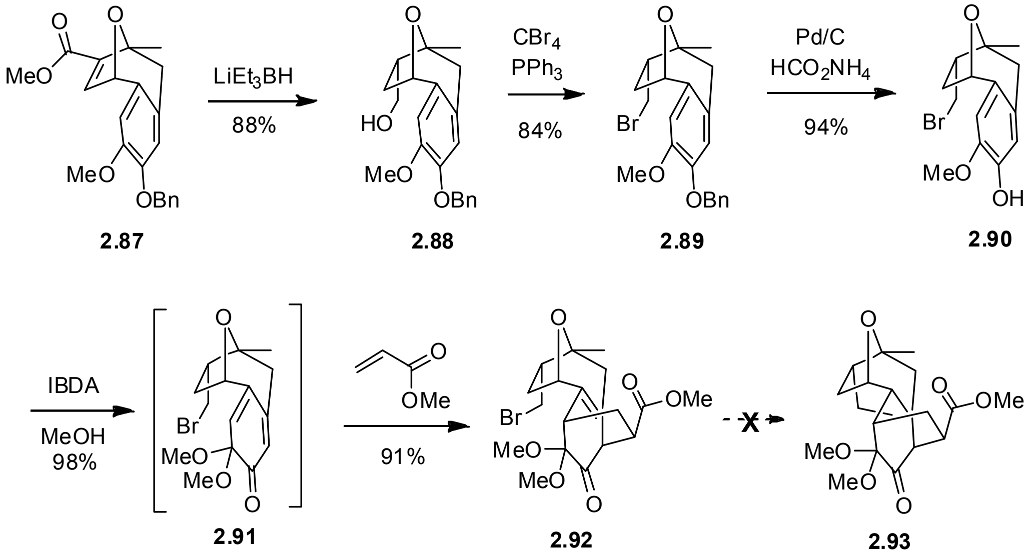
Scheme 2.15. Retrosynthetic Analysis of Platensimycin

Our synthetic efforts commenced with vanillin, which was regioselectively brominated and protected to **2.81** following known procedures (Scheme 2.16).[28] Although **2.81** lacked the requisite methyl group in **2.79**, its availability made it a nice model system. This substrate was subjected to Heck coupling conditions in the presence of allylic alcohol **2.80**, which furnished keto-aldehyde **2.82**.[29] The methyl branching was key to the rapid assembly of the fused ring system (**2.83**), ensuring that under the thermodynamic conditions employed, only the seven membered ring enone could form. Deprotonation[30] of **2.83** and trapping of the resulting enolate with N-phenyltriflamide afforded triflate **2.84**. Palladium mediated carbonylation afforded dienoate **2.85** in excellent yield.[31] Regioselective epoxidation was accomplished using the highly reactive trityl hydroperoxide,[32] and our new copper catalyzed ring expansion protocol formed oxatropane **2.87**.



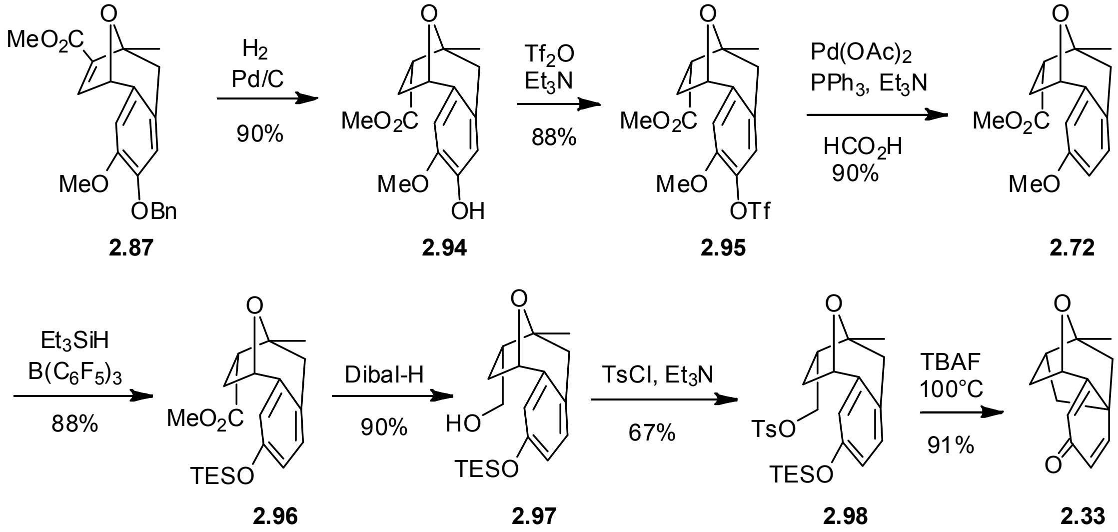
Scheme 2.16. Synthesis of the Functionalized Aryl Fused Oxatropane

Ester **2.87** (Scheme 2.17) underwent stereoselective reduction using lithium triethyl borohydride to form alcohol **2.88**, which formed bromide **2.89** using carbon tetrabromide and triphenylphosphine. After hydrogenolysis of the benzyl ether oxidation of **2.90** using iodobenzene diacetate (IBDA) afforded dimethyl ketal **2.91** which underwent a facile Diels-Alder dimerization. This process was slow enough however to test the proposed cyclization. Unfortunately, all efforts using either radical or anionic conditions did not form the desired core, instead giving only the product of bromide reduction and no C-C bond formation. Regardless, diene **2.91** could be trapped *in-situ* after oxidative dearomatization with methyl acrylate to give the desired cycloadduct **2.92**. Our calculations had indicated that the structure of the new six membered ring would bring the radical accepting olefin in closer proximity with the primary radical compared to **2.91** and therefore make the cyclization more likely. Unfortunately all attempts to form **2.93** were unsuccessful, again giving only the product of bromine atom abstraction and subsequent radical quenching.



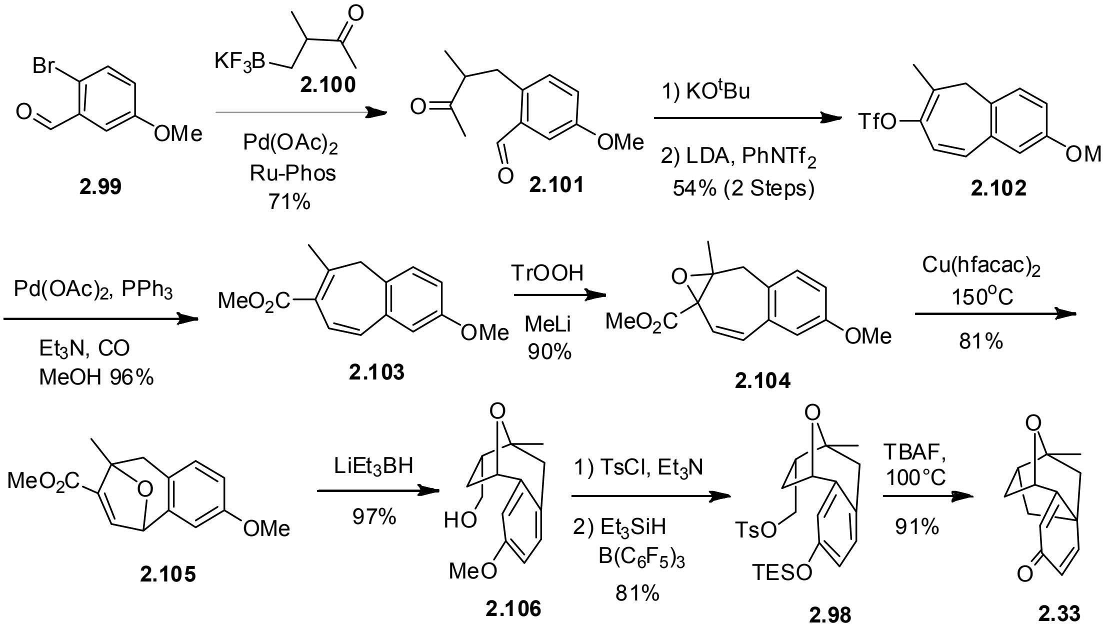
Scheme 2.17. Oxidative Dearomatization/Cyclization Attempts

We decided to evaluate a slightly different substrate to determine whether our proposed C-C cyclization strategy to form the platensimycin core was feasible. To this end oxatropane **2.87** was converted to **2.94** by alkene reduction and hydrogenolysis of the benzyl protecting group. Deoxygenation was then accomplished by forming aryl triflate **2.95** followed by reductive cleavage using palladium and formic acid to give **2.72**. A mild phenolic silylation of the remaining aryl methyl ether with triethylsilane and tris(pentafluorophenyl)borane furnished TES-protected phenol **2.96**.[33] The ester was reduced with DIBAL-H to give primary alcohol **2.97**, which was converted to the tosylate **2.98**. When this cyclization precursor was heated with tetrabutylammonium fluoride (TBAF) it rapidly underwent cyclization in excellent yield to form the platensimycin core (**2.33**). The ^{1}H and ^{13}C NMR spectra of **2.33** were identical to those previously reported, thus completing our formal synthesis of platensimycin.



Scheme 2.18. Intramolecular Alkylative Dearomatization

This success inspired us to improve the synthetic approach using brominated anisaldehyde **2.99** (Scheme 2.19). This route would circumvent with the late stage deoxygenation necessary in Scheme 2.18. Commercially available bromide **2.99** was converted to **2.101** using Molander's new trifluoroborate cross-coupling strategy.[34] Ketoaldehyde **2.101** cleanly underwent the analogous condensation, triflate formation, and carbonylation using the previously optimized conditions to give **2.103**. Nucleophilic epoxidation with trityl hydroperoxide afforded vinyl oxirane **2.104**, which subsequently underwent ring expansion to oxatropane **2.105** when subjected to our Cu(hfacac)$_2$ conditions. Substrate controlled reduction afforded primary alcohol **2.106** which was converted to the tosylate and again hydrosilated to give TES-protected phenol **2.98**. The platensimycin core (**2.33**) was again accessed by alkylative dearomatization, this time completing the formal synthesis in only ten steps from commercially available precursor **2.99**.



Scheme 2.19. Efficient Synthesis of the Platensimycin Core

In summary, we have developed a very efficient route to the compact platensimycin core. Our architectural assembly relied on the use of a new copper catalyzed oxirane ring expansion in combination with an alkylative dearomatization to complete the core. Other notable features of this synthetic approach include an underutilized phenol ether deprotection, nucleophilic enoate epoxidation and a mild introduction of a substituted alkyl ketone using a trifluoroborate cross coupling.

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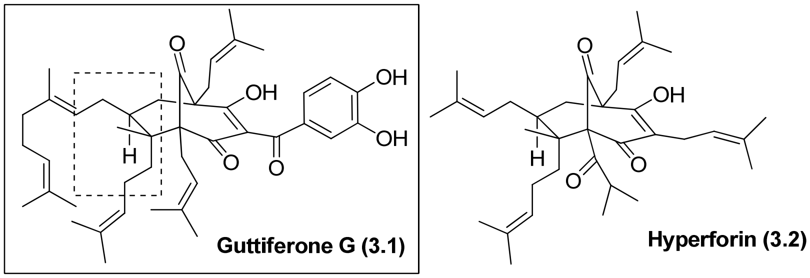
Chapter 3

Guttiferone G

3.1 Background and Significance

In recent years a number of bridged bicyclic polyprenylated acylphloroglucinol natural products have been reported.[1] The most famous being hyperforin, which is one of the main chemical constituents of the commonly used natural remedy St. John's wort. Recently, hyperforin has also shown promise as an anticancer agent.[2] We have established a research program focused on synthesizing and evaluating unique bridged bicyclic natural product anti-cancer agents. The bridged phloroglucinol family drew our attention early on, but the catalyst for launching a synthetic program towards their synthesis was a report detailing the sirtuin inhibitory activity of hyperforin and guttiferone G (Figure 3.1).[3] The sirtuins are considered high value targets for developing new anticancer agents and gaining more insight into improving longevity.[4] Not surprisingly, there has been great interest in finding small molecule inhibitors, which selectively block the function of any of the seven known enzymes of the sirtuin family (SIRT1-7).[5]



Guttiferone G (3.1)

Hyperforin (3.2)

Figure 3.1. Guttiferone G and Hyperforin

Hyperforin and guttiferone G share many structural similiarities in addition to the common [3.3.1] bridged bicyclic trione core and neither natural product has been synthesized to date.[6] In our minds the most attractive difference is the *bis*-prenyl bridgehead substitution of guttiferone G, which means that the fully substituted trione part of the molecule is symmetrical. This local symmetry opens the door for exciting synthetic designs and more importantly for late introduction of chirality. We chose to limit our efforts to compounds containing stereocenters at both C5 and C6, thus excluding a number of symmetrically substituted compounds containing the C5 *gem*-dimethyl substitution pattern. Eight guttiferones sharing a symmetrical [3.3.1] bridged bicyclic core have been reported in the last twenty years since the first was discovered (guttiferone A).[7] The only structural difference between members of this family are the substitution of the two adjacent stereocenters (C5 and C6), the benzoyl group oxidation state and the absolute configuration of the desymmetrized core (Figure 3.2).

A closer look at the published data for these eight compounds revealed that although there are four possible arrangements for each C5/C6 substitution pattern, it seems nature has prefered to place the two large groups (geranyl and prenyl) *trans* to each other. Guttiferone A is the only member of this natural product class whose absolute configuration has been unambiguously established.[8] The data suggests that guttiferone A and I belong to the same enantiomeric series[9] and that the other six (guttiferones I, J, K, L, G and garcicowin B) belong to the opposite.[10] The latter six structures are remarkably similar, differing only in the benzoyl group and whether there is a prenyl or geranyl group at the C6-position.

Although this natural product collection has never been tested as one, each member has been shown to exhibit anti-cancer activity ranging from general cytotoxicity[11] to potential protease inhibitors,[12] antiapoptotic[13] or antiproliferative agents. In addition, several studies have been reported on their various biological functions beyond cancer.[14] As stated above, we were most excited about the sirtuin inhibitory activity of guttiferone G and to learn how the other seven members of this family compare. Such a study would provide important SAR clues on the relative importance of the C5, C6 or benzoyl substitutions on sirtuin inhibition.

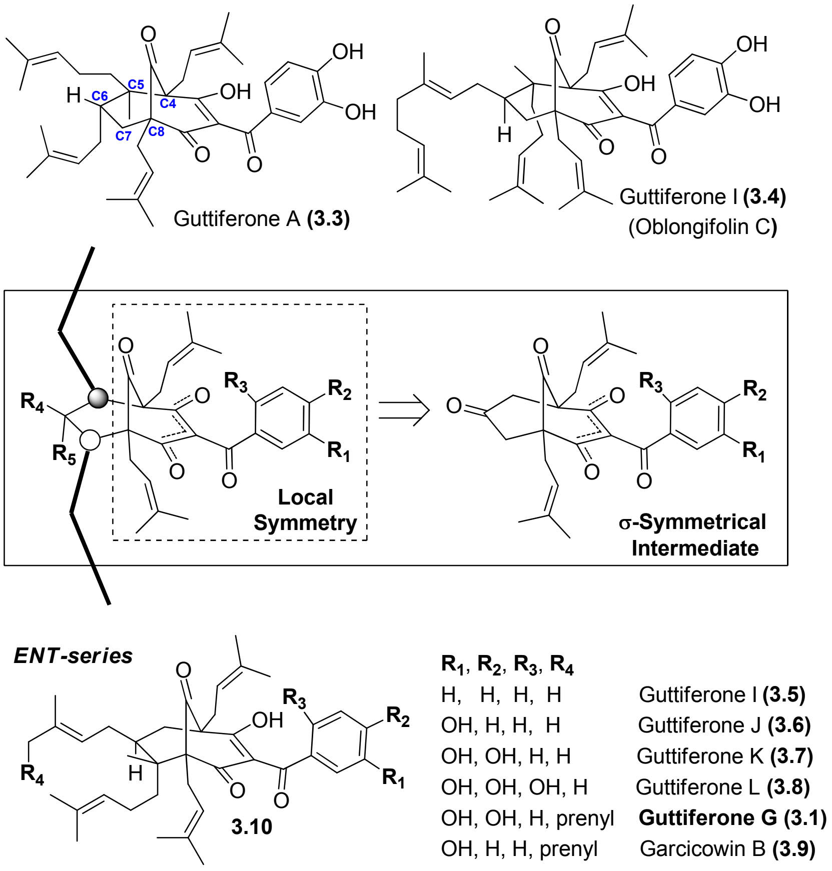
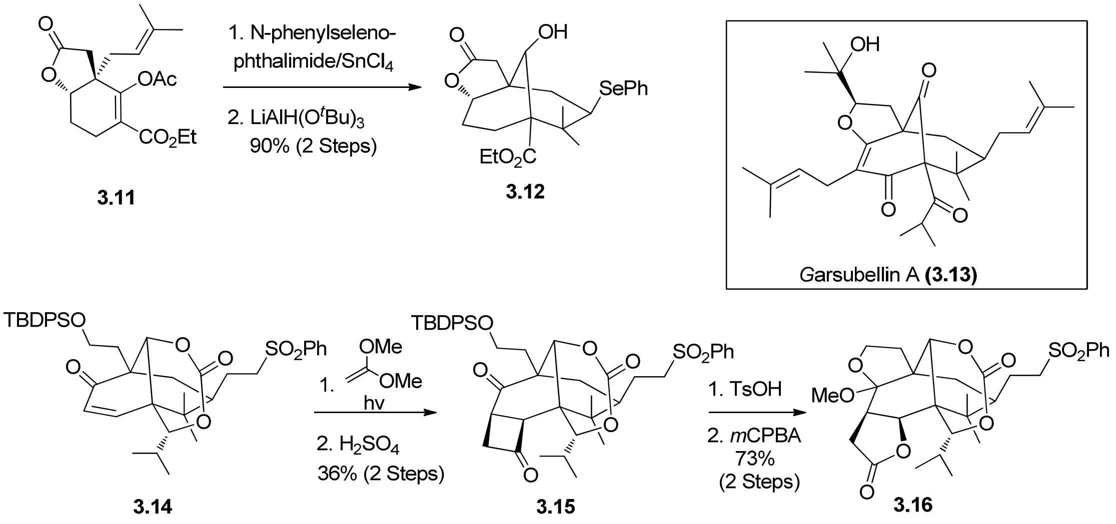


Figure 3.2. Guttiferones Containing Locally Symmetrical Bicyclic Cores

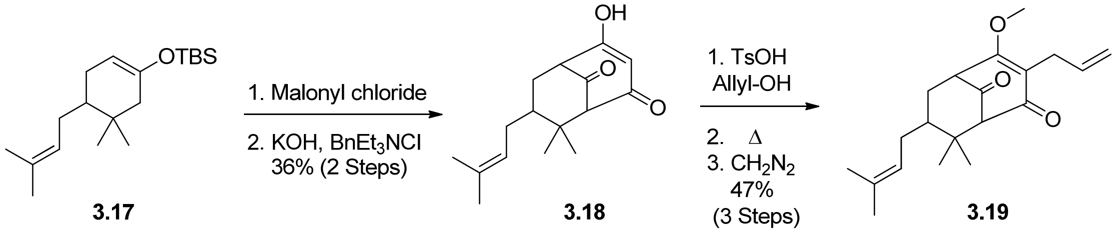
3.2 Other Relevant Synthetic Work

A considerable amount of synthetic effort has gone into this class of natural products due to their biological activity. The first work was by the Nicolaou group which first published their efforts toward Garsubellin A in 1999 (Scheme 3.1).[15] The first key step was a selenium-mediated cyclization to generate the bicyclic core (**3.12**). They concluded their efforts by carrying out a [2+2] cycloaddition followed by Baeyer-Villager oxidation to assemble much of the garsubellin A core (**3.16**).



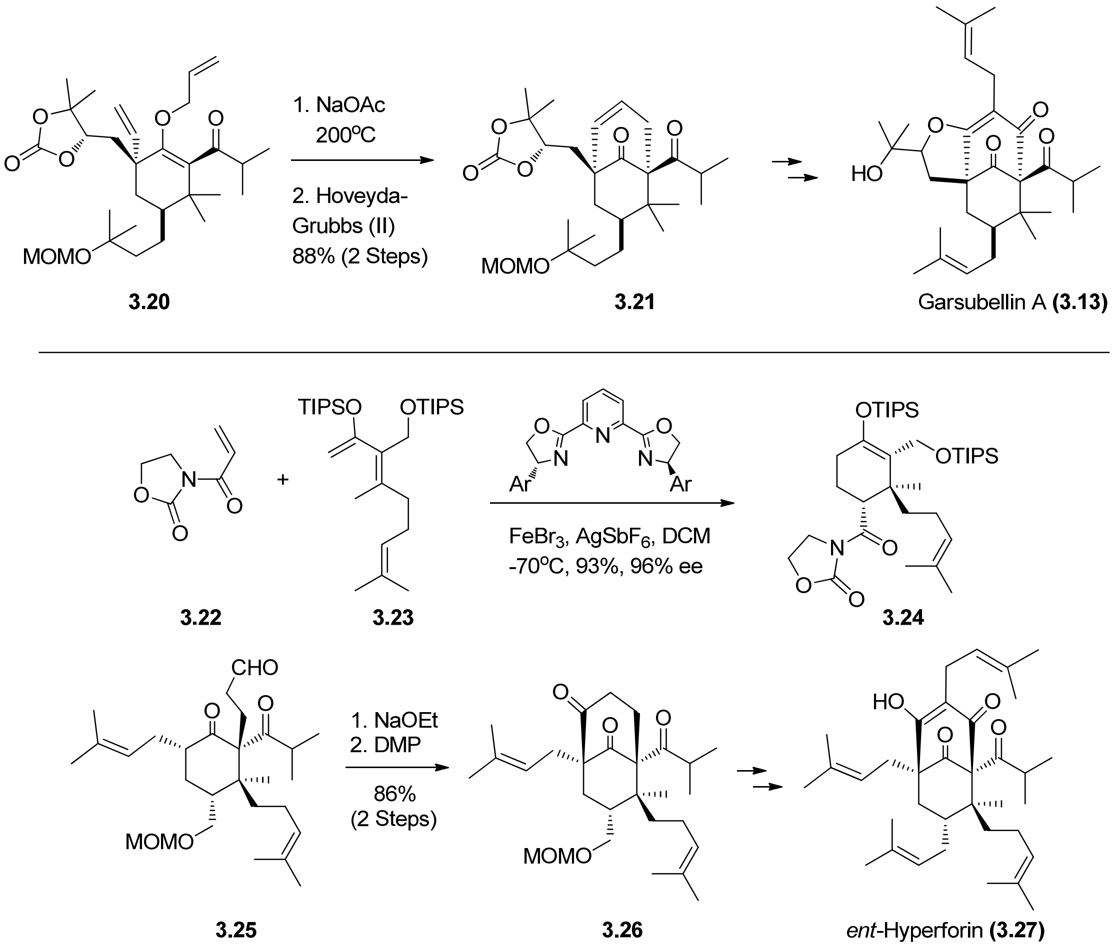
Scheme 3.1. Nicolaou's Synthetic Efforts Toward Garsubellin A

The research group of Brian Stoltz published a paper in 2002 detailing their work in this area (Scheme 3.2).[16] After the straight-forward synthesis of the silyl enol ether **3.17**, treatment with malonyl chloride and base gave the desired bicyclic core. The additional allyl group was installed by allylating **3.18** followed by a Claisen rearrangement in which the resulting enol was capped with diazomethane.



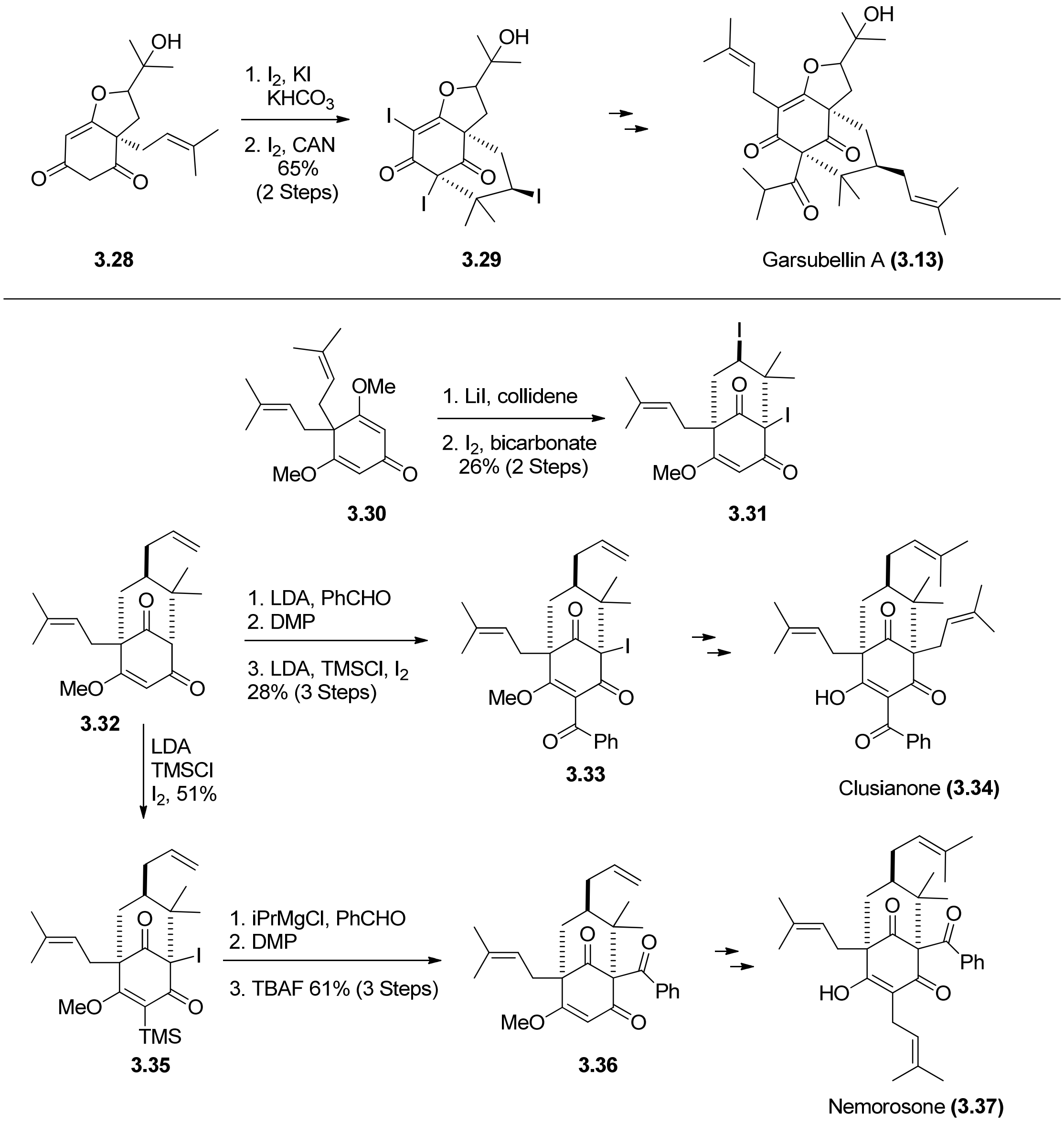
Scheme 3.2. Stoltz's Synthetic Approach to [3.3.1] Bicyclic Core

The first total synthesis of a member of this family came from the group of Masakatsu Shibasaki[17] in 2005 when they finished garsubellin A[18] which was followed up by an asymmetric total synthesis of *ent*-hyperforin (Scheme 3.3).[19] The key step in assembling garsubellin A (**3.21**) was a ring closing metathesis, set up by an allylation/Claisen rearrangement similar to that used by Stoltz. In their asymmetric approach to *ent*-hyperforin, the initial three stereocenters were set in an asymmetric Diels-Alder reaction promoted by a cationic iron complex to give **3.24**. The bicyclic core was made by an aldol addition/oxidation sequence to give the triketone **3.26** which was carried forward to the enantiomer of hyperforin.



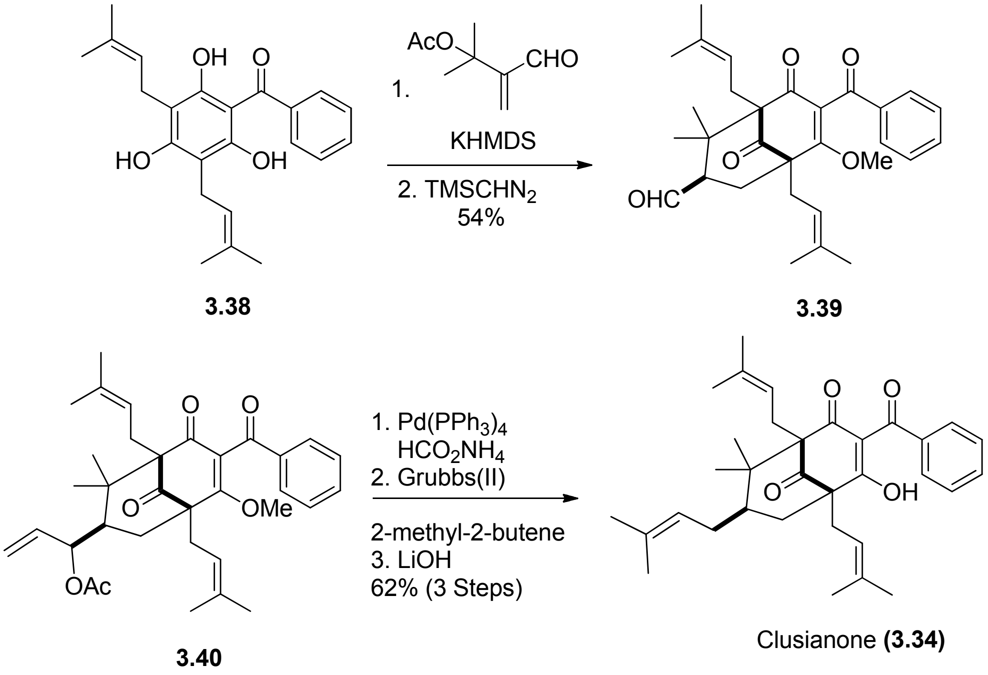
Scheme 3.3. Shibasaki's Synthesis of Garsubellin A and *ent*-Hyperforin

Danishefsky first published a total synthesis of garsubellin A in 2006[20] and a year later completed nemorosone and clusianone (Scheme 3.4).[21] The synthesis of garsubellin A relied on an iodocarbocyclization to produce the bicyclic core (**3.29**). Iodocarbocyclization was also used in their syntheses of nemorosone and clusianone and a common intermediate (**3.32**) was diverted to each of the natural products.



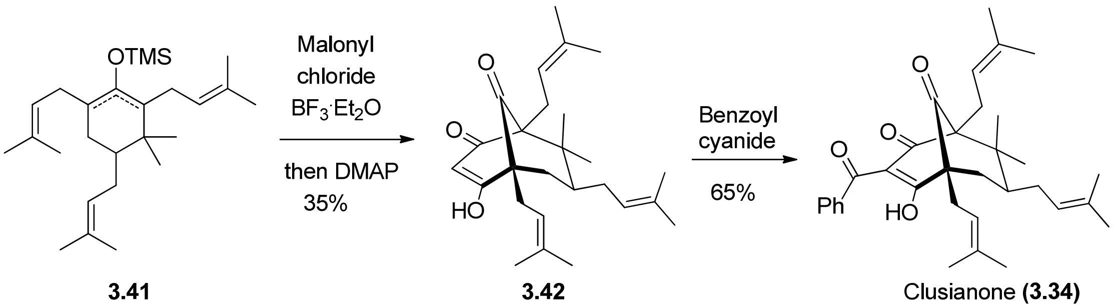
Scheme 3.4. Danishefsky's Total Synthesis of Three Members of This Family

A synthesis of clusianone was published by the Porco group in 2007 (Scheme 3.5).[22] The bicyclic core was constructed using a double alkylative dearomatization of a 1,3,5-trihydroxybenzene (phloroglucinol) derivative **3.38** with a versatile “double-Michael acceptor”. In this reaction the initial Michael addition causes elimination of the acetate group to generate another Michael acceptor which subsequently reacts in an intramolecular fashion to assemble the bicyclic core. The synthesis was completed by converting the allyl group to a prenyl *via* metathesis and deprotection.



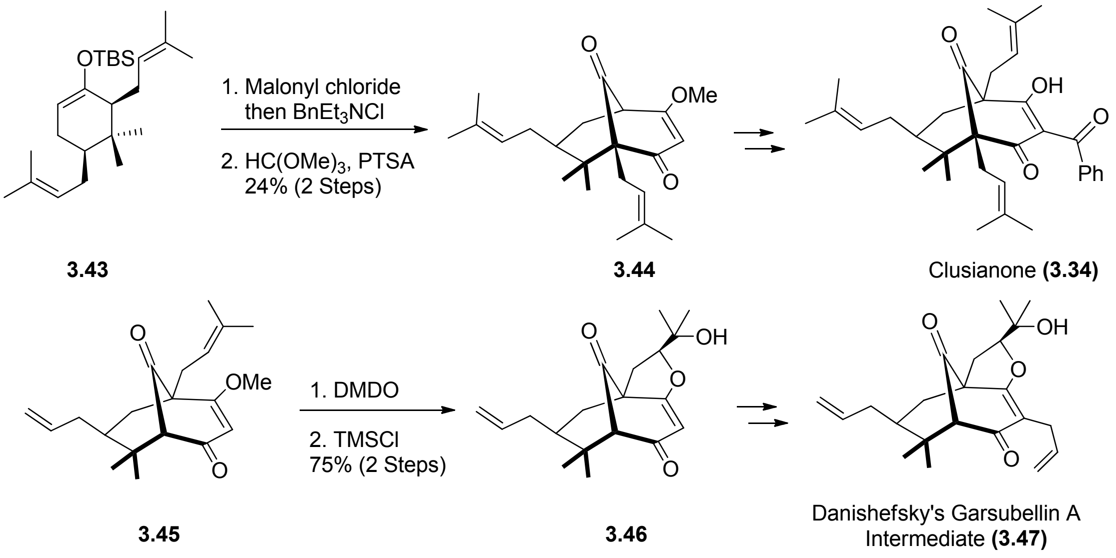
Scheme 3.5. Porco’s Synthesis of Clusianone

Clusianone was recently synthesized by the Marazano group (Scheme 3.6).[23] Their synthesis built off of the early success by Stoltz. They were able to use an adequately functionalized 6-membered ring (**3.41**) with malonyl chloride to give the bicyclic core **3.42**. An acylation of **3.42** completed their synthesis of clusianone.



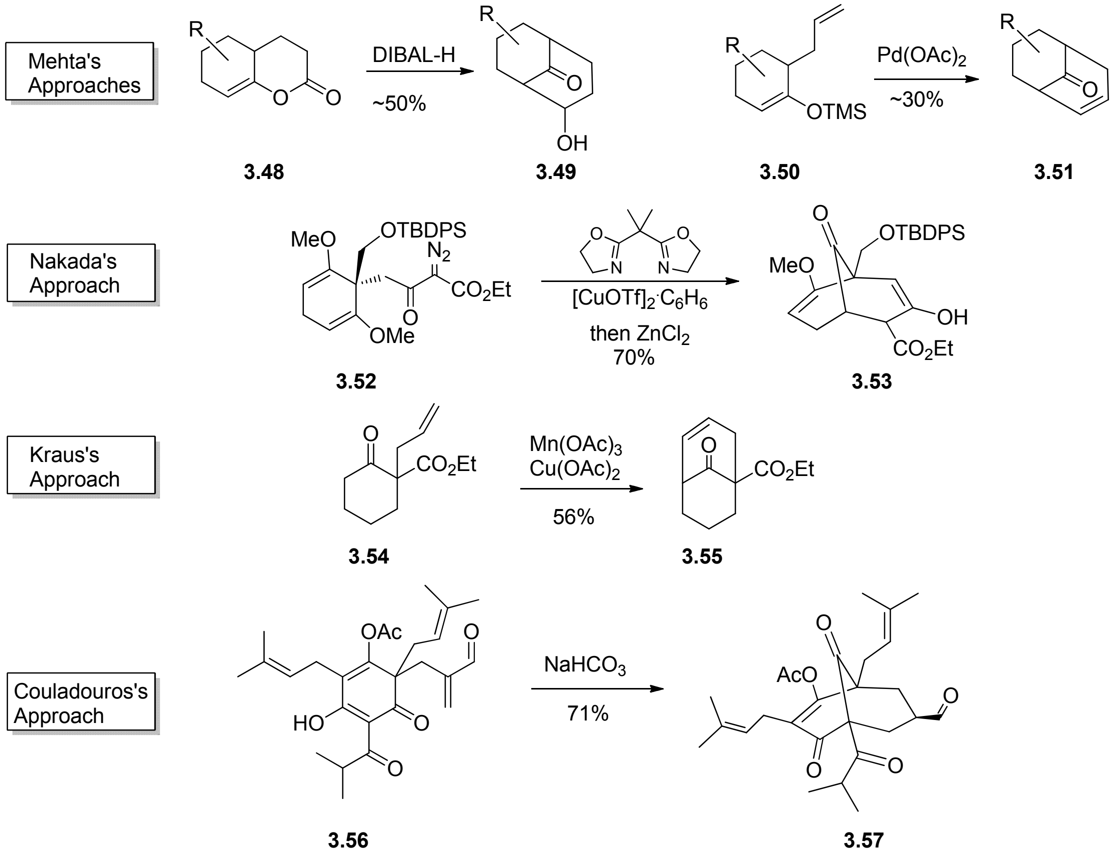
Scheme 3.6. Marazano’s Synthesis of Clusianone

Simpkins[24] published syntheses of clusianone and garsubellin A (Scheme 3.7).[25] Malonyl chloride was used to assemble the bicyclic core of clusianone and a DMDO epoxidation followed by an intramolecular etherification generated the THF subunit (**3.46**) of garsubellin A. They completed their formal synthesis by using a protection/allylation/deprotection sequence.



Scheme 3.7. Simpkins’s Synthesis of Clusianone and Garsubellin A

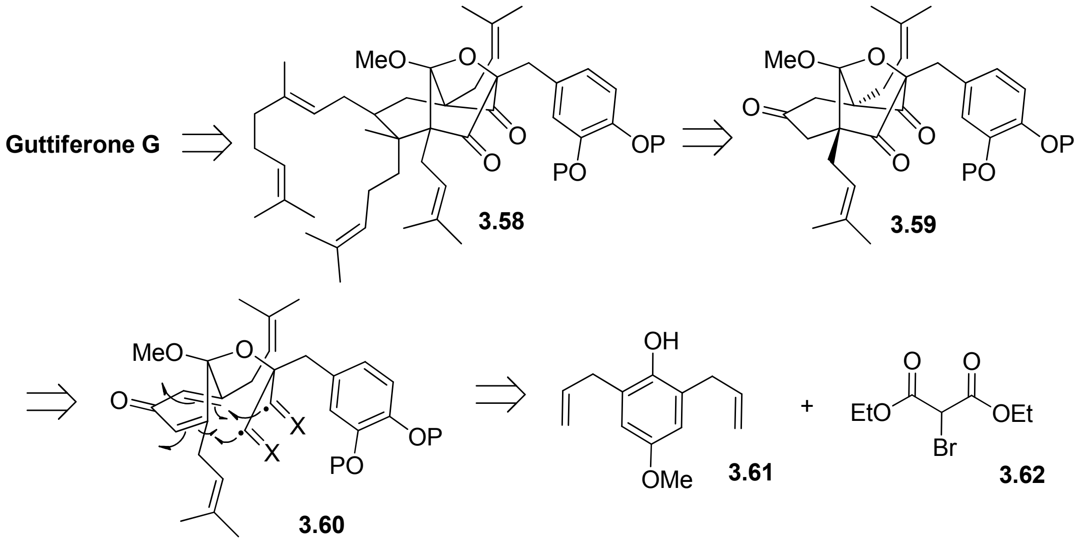
In addition to the approaches highlighted above, a number of groups have made noteworthy contributions to this area of research (Scheme 3.8). The first are from the Mehta group and involve either a lactone opening/aldol addition sequence[26] (**3.48**) or a palladium catalyzed ring closure (**3.50**).[27] Nakada's work involves the synthesis and in-situ opening of a methoxy cyclopropane to generate the core (**3.53**).[28] Kraus uses a copper and manganese catalyzed cyclization to assemble the bicyclic core (**3.55**).[29] The final example is a Michael-based approach from **3.56** to assemble the core by the research group of Couladouros.[30]



Scheme 3.8. Other Synthetic Contributions

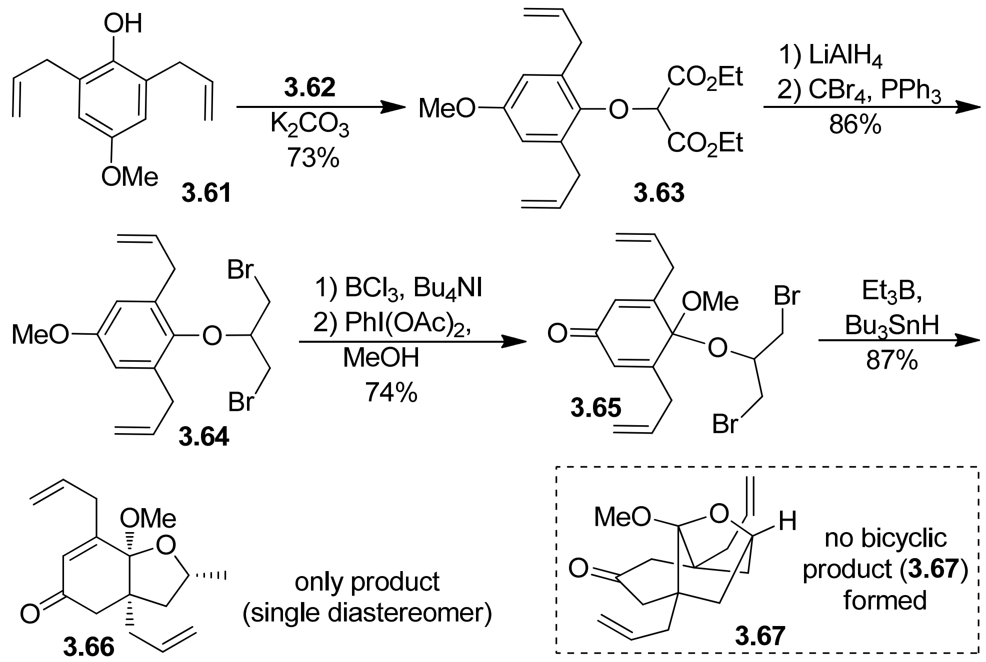
3.3 Our Synthetic Efforts

Our retrosynthetic analysis (Scheme 3.9) relies on the late stage desymmetrization of **3.59**, which could be diverted to all eight targeted natural products. This intermediate could be accessed *via* tandem *5-exo* radical cyclizations (**3.60**) enabled by oxidative dearomatization of a *para*-hydroquinone, which is assembled from phenol **3.61**[31] and malonate derivative **3.62**.



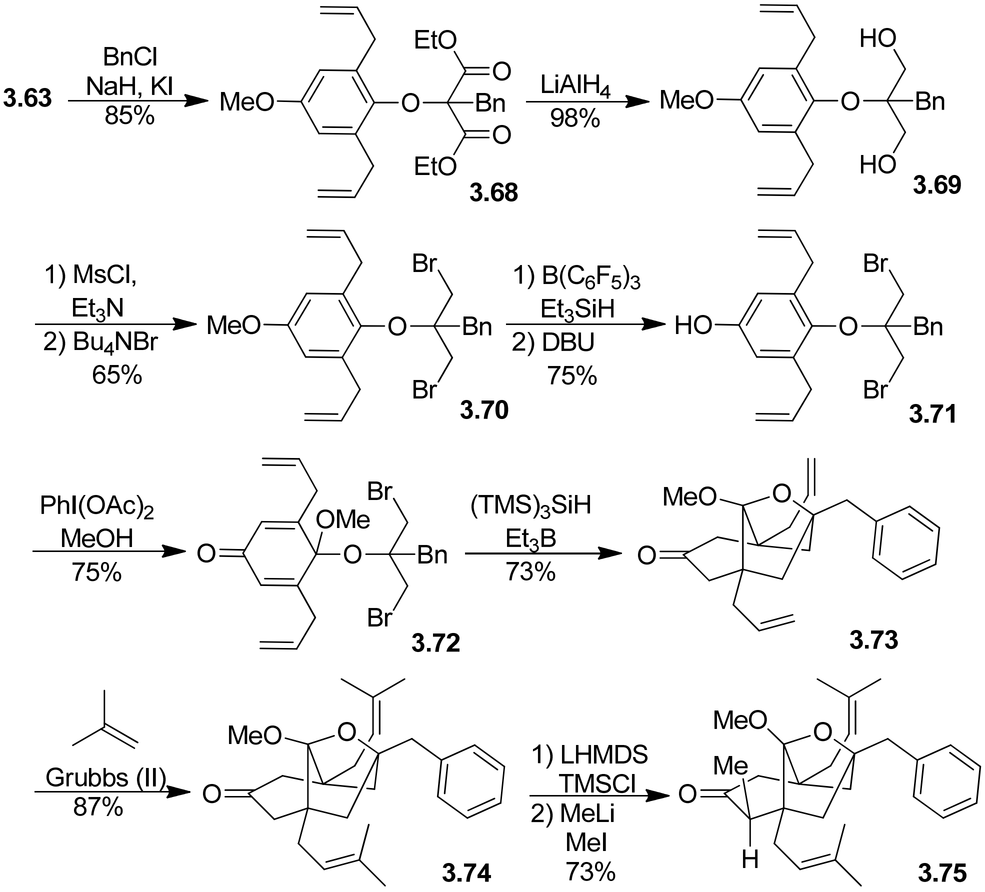
Scheme 3.9. Guttiferone G Retrosynthesis

Our synthetic efforts commenced with known diallyl ether **3.61**, which was readily accessible from 4-methoxy phenol. The free phenol was alkylated with diethyl 2-bromomalonate (**3.62**) to afford **3.63**. The esters were converted into bromomethyl groups (**3.64**) in two steps. Selective deprotection of the methyl capped phenol using BCl_3 and hypervalent iodine mediated oxidative deromatization yielded the desired dienone acetal radical cyclization precursor **3.65**. Despite discouraging literature precedents,[32] which suggested preferential formation of **3.66** over **3.67** we decided to test the tandem 5-*exo*/5-*exo* radical cyclization thesis. Cyclization proceeded smoothly and selectively affording only acetal **3.66** and no evidence of bridged bicyclic acetal **3.67**.



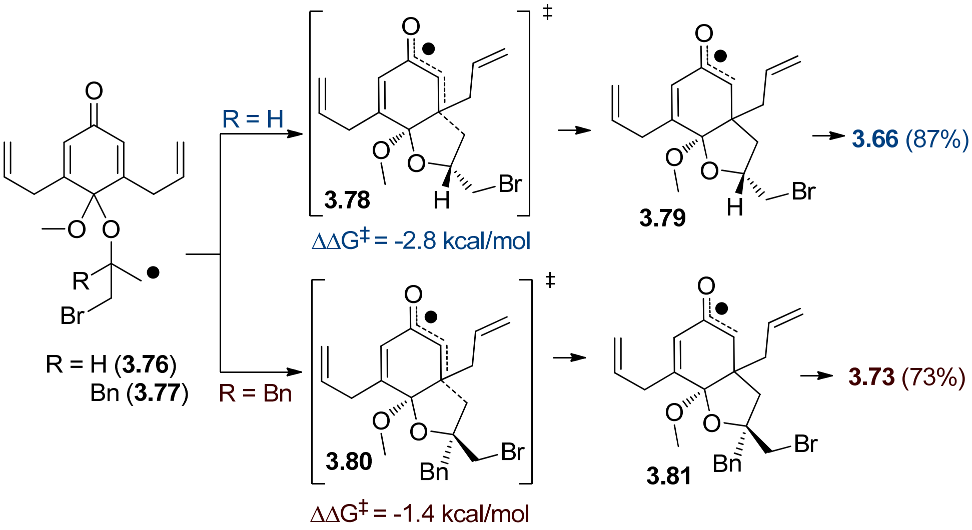
Scheme 3.10. Attempted Bis-Radical Cyclization

We postulated that placing a large group between the two radical sites would force the two radicals to same face, which is critical for accessing the bicyclic motif. This logic flows well with our synthetic design because an oxygenated phenacyl group resides in this exact position on the guttiferones. Diester **3.63** was alkylated (**3.68**) and reduced to diol **3.69** (Scheme 3.11). Bromination of the neopentyl alcohols was accomplished in two steps to give **3.70**. Selective deprotection of the methyl ether was accomplished using $B(C_6F_5)_3$ in the presence of triethylsilane.[33] Dearomatization proceeded as expected to produce acetal **3.72**, which we were gratified to learn cyclized to form the desired symmetrical bridged bicyclic product **3.73** as the only product. Cross metathesis of **3.73** with 2-methyl propene in the presence of Grubbs second generation catalyst gave **3.74**.[34] To test the facial selectivity in the alkylation of the bicyclic ketone **3.74**, the enolate generated with LHMDS was trapped as the silyl ether. When this enol ether was treated with MeLi and MeI, the only product observed was determined to be that of methyl trapping on the *exo* face of the bicylic structure (**3.75**). This exclusive bias for alkylation on the *exo*-face lends promise to being able to access any member of this natural product class by changing the order of the alkylation sequence.



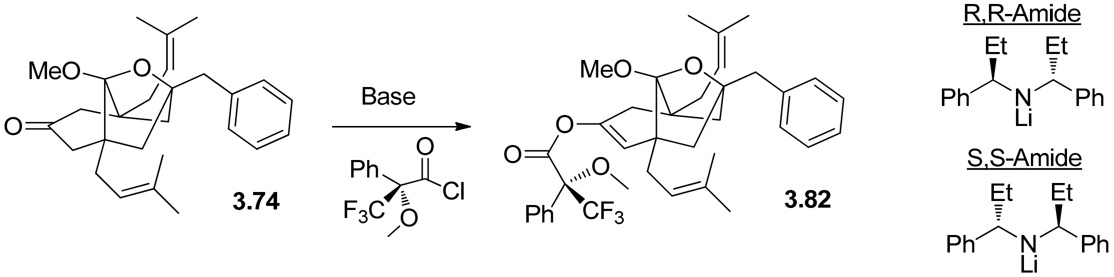
Scheme 3.11. Synthesis of the Bridged Bicyclic Core of the Guttiferones

In order to explain the profound reversal of selectivity in the cyclization of **3.65** and **3.72**, we performed density functional theory calculations (UB3LYP 6-31G(d)). The two possible transition states for the first radical cyclization were found and the more stable in each case (**3.78, 3.80**) is depicted in Scheme 3.12. We see that in the case of R=H, the transition state having the methylene bromide on the *exo* face of the fused bicylic system is preferred by 2.8 kcal/mol. Alternatively with R=Bn, steric interactions with the benzyl group force it to the less hindered *exo* face and the methylene bromide to the endo which is competent for further cyclization. These calculations are in complete agreement with experimental findings and explain the high selectivity attained in each case.



Scheme 3.12. Rationalization of Stereochemical Outcome

In order to assess our ability to carry out a late-stage desymmetrization to access either enantiomeric series of this natural product family, we employed chiral amide bases (Table 3.1).[35] The asymmetry in the deprotonation was determined by trapping the enolate as a Mosher ester. Both enantiomers of the enolate were trapped to give the corresponding diastereomeric Mosher esters. An increased selectivity was observed with LiCl being added prior to deprotonation.



Base	Additive	Temp (^{o}C)	Yield	dr
LHMDS	--	-78	85%	1.1:1
RR-Amide	--	-78	87%	3:1
RR-Amide	**LiCl**	**-78**	**83%**	**10:1**
SS-Amide	LiCl	-78	75%	1:6
RR-Amide	LiCl	-100	72%	3:1

Table 3.1. Asymmetric Desymmetrization of **3.74**

In conclusion, we have developed an efficient approach to this exciting class of natural products that takes advantage of the inherent local symmetry present in the bicyclic structure. The complex core was accessed by employing a unique double radical cyclization of a *p*-quinone ketal derived from a simple aromatic precursor. The shape of the molecule controls the facial selectivity during the ketone alkylation and the use of a chiral amide base provides access to either enantiomeric series.

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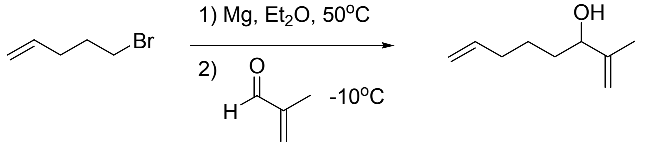
APPENDIX 1

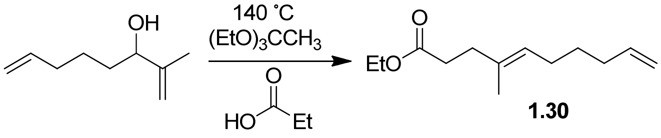
A1.1 Experimental Procedures for Chapter 1

General Information: Commercial reagents were purchased and used without further purification. All glassware was flame dried and reactions were performed under a nitrogen atmosphere, unless otherwise stated. Toluene, dichloromethane, diethyl ether, and THF were dried over a column of alumina. Flash chromatography was done with MP Silitech 32-63D 60Å silica, and thin layer chromatography (TLC) was performed with EMD 250 μm silica gel 60-F_{254} plates. ^1H and ^{13}C NMR data was acquired on a Varian Inova 400, 500, or 600 (400, 500 or 600 MHz) spectrometer and referenced to residual protic solvent or TMS. IR spectroscopy was done on a Nicolet Avatar 370 OTGS spectrometer. High-resolution mass spectrometry was performed at the University of Illinois at Urbana-Champaign facility.



A mixture of magnesium turnings (1.600 g, 0.067 mol) and a crystal of I_2 in diethyl ether (60.0 mL) was refluxed at 45°C. Through a condenser 5-bromo-1-pentene (5.000 g, 0.034 mol) was added over 30 minutes. The reaction was refluxed an additional hour. In a separate flask, a solution of methacrolein (3.9 mL, 47.5 mmol) in diethyl ether (5.0 mL) was cooled to -10°C. The Grignard solution was cannulated into the solution of methacrolein over 30 min. The reaction was stirred an additional 30 min at -10°C and then warmed to room temperature over 2.5 hr. The reaction was subsequently quenched over ice with sat. NH_4Cl followed by 2M HCl. The aqueous layer was extracted with ethyl acetate (3 x 30.0 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to give a residue, which was purified by column chromatography (15% EtOAc: hexanes) to give the allylic alcohol (4.200 g, 90%) as a light yellow oil.

FTIR (thin film/NaCl) 3368, 3075, 2976, 2935, 2861, 1641, 1442, 1066, 1029, 995 cm^{-1}; ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 5.78 (m, 1H), 4.98 (m, 1H), 4.92 (m, 1H), 4.90 (m, 1H), 4.80 (m, 1H), 4.02 (t, J=6.1 Hz, 1H), 2.05 (m, 2H), 1.95 (bs, 1H), 1.69 (s, 3H), 1.59-1.21 (m, 4H); ^{13}**C NMR** (75 MHz, $CDCl_3$) δ 147.5, 138.6, 114.5, 110.9, 75.7, 34.2, 33.5, 24.8, 17.3.



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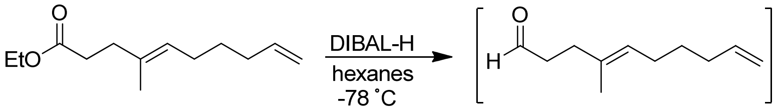
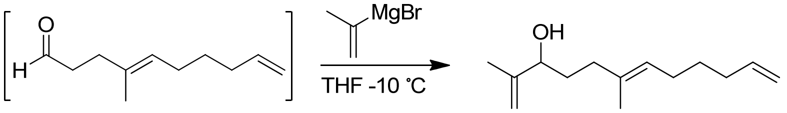
A solution of the allylic alcohol (6.100 g, 0.044 mol), triethyl orthoacetate (39.7 mL, 217.7 mmol), and propionic acid (0.08 mL, 1.10 mmol) was refluxed at 140°C for 1.5 hr and then 145°C for 0.5 hr. The low boiling components were collected in a sidearm flask cooled to -78°C. The solution was then cooled to room temperature. The reaction was quenched over ice with 2M HCl. The aqueous layer was extracted with ethyl acetate (3 x 50.0 mL). The combined organic layers were dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (5% EtOAc: hexanes) to give ethyl ester (8.400 g, 92%) as a clear oil.

FTIR (thin film/NaCl) 2980, 2928, 2850, 1737, 1440, 1156 cm^{-1}; ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 5.80 (m, 1H), 5.15 (m, 1H), 4.99 (m, 1H), 4.94 (m, 1H), 4.12 (q, J=7.1 Hz, 2H), 2.46-2.23 (m, 4H), 2.12-1.90 (m, 4H), 1.60 (s, 3H), 1.41 (m, 2H), 1.25 (t, J=7.1 Hz, 3H); ^{13}**C NMR** (75 MHz, $CDCl_3$) δ 173.7, 139.2, 133.8, 125.4, 114.6, 60.5, 34.9, 33.6, 33.5, 29.1, 27.5, 16.2, 14.5; **HRMS** (EI) *m/z* 210.1618 [calc'd for $C_{13}H_{22}O_2$ (M+) 210.1620].



Ethyl ester (4.400 g, 0.021 mol) in 95% n-hexane (175.0 mL) was cooled to -78°C. Diisobutyl aluminum hydride (22.0 mL, 1.0 M in hexanes) was added down the side of the cooled reaction flask over 1 hr. After the addition, the solution was stirred an additional 30 min. The reaction was quenched at -78°C with 20% sodium potassium tartrate (125.0 mL) and immediately warmed to room temperature. Brine was added to help with the separation of the organic and aqueous layers. The aqueous layer was extracted with ethyl acetate (5 x 50.0 mL). The combined organic layers were dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded the aldehyde which was taken on crude.

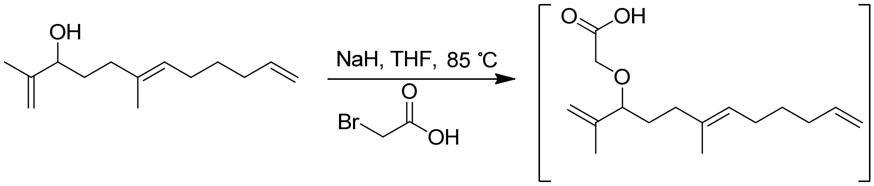
FTIR (thin film/NaCl) 3075, 2924, 2856, 1726, 1677, 1640, 1440, 1382, 1237, 992, 909 cm^{-1}; ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 9.76 (t, J=1.9 Hz, 1H), 5.80 (m, 1H), 5.16 (m, 1H), 4.99 (m, 1H), 4.95 (m, 1H), 2.52 (m, 2H), 2.33 (m, 2H), 2.11-1.94 (m, 4H), 1.61 (s, 3H), 1.42 (m, 2H).



1.31

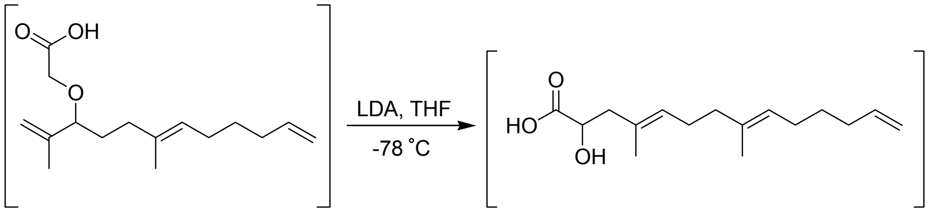
The aldehyde (3.500 g, 0.021 mol) in 35 mL THF was cooled to -10°C. Isopropenyl magnesium bromide (63.0 mL, 0.5 M in THF) was added over 1 hr via addition funnel. The reaction stirred at -10°C for an additional 15 min and then warmed to room temperature over 45 min. The reaction was quenched with sat. NH_4Cl and then acidified to pH 2.0 using 2 M HCl. The aqueous layer was extracted with ethyl acetate (3 x 30.0 mL). The combined organic layers were dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (15% EtOAc: hexanes) to give the alcohol (2.500 g, 62%) as a yellow oil.

FTIR (thin film/NaCl) 3364, 3075, 2974, 2920, 2855, 1640, 1441, 1374, 992, 907 cm^{-1}; ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 5.81 (m, 1H), 5.17 (m, 1H), 5.00 (m, 1H), 4.95 (m, 1H), 4.94 (m, 1H), 4.84 (m, 1H), 4.05 (dd, J=6.3, 10.1 Hz, 1H), 2.13-1.92 (m, 6H), 1.73 (s, 3H), 1.70-1.51 (m, 2H), 1.61 (s, 3H), 1.43 (m, 2H); ^{13}**C NMR** (75 MHz, $CDCl_3$) δ 147.4, 138.8, 134.8, 124.6, 114.3, 110.9, 75.5, 35.6, 33.3, 33.1, 28.9, 27.2, 17.4, 15.9; **HRMS** (EI) *m/z* 208.1826 [calc'd for $C_{14}H_{24}O$ (M+) 208.1827].



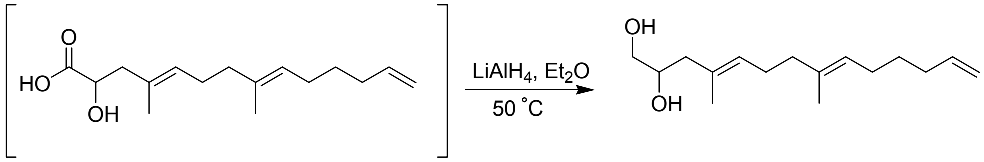
Sodium hydride (1.400 g, 0.035 mol, 60% in mineral oil) was washed with *n*-hexane (4 x 10.0 mL) and dried *in vacuo*. The resultant residue was suspended in THF (8.0 mL). Alcohol (1.600 g, 7.800 mmol) dissolved in THF (16.0 mL) was added to the NaH suspension and stirred for 1 hr. A solution of bromoacetic acid (1.100 g, 8.200 mmol) in THF (5.0 mL) was added via reflux condenser over 20 min. The reaction refluxed at 85°C for 6 hr and subsequently cooled to room temperature. The reaction was quenched dropwise with 2 M HCl and then acidified to pH 1. The aqueous layer was extracted with ethyl acetate (4 x 30.0 mL). The combined organic layers were dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded the acid which was taken on crude to the next step.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (m, 1H), 5.14 (m, 1H), 5.04-4.92 (m, 4H), 4.06 (d, J=16.6 Hz, 1H), 3.90 (d, J=16.6 Hz, 1H), 3.75 (m, 1H), 2.08-1.93 (m, 8H), 1.66 (dd, J=0.9, 1.5 Hz, 3H), 1.60 (s, 3H), 1.42 (m, 2H).



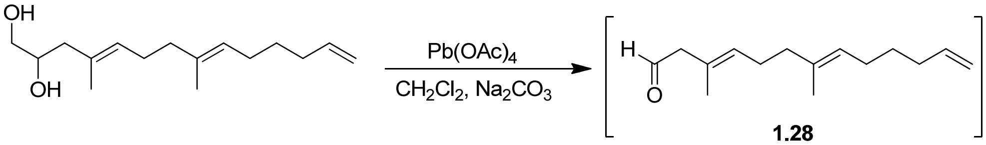
Diisopropyl amine (3.9 mL, 28.1 mmol) in THF (20.0 mL) was cooled to -78°C. To this solution, *n*BuLi (17.8 mL, 1.6 M in hexane) was added slowly. The solution was warmed to 0°C over 1hr. Upon cooling back down to -78°C, the crude acid in THF (9.0 mL) was slowly added. The reaction was warmed to -45°C for 3.5 hr. The reaction was quenched dropwise with 2 M HCl and then acidified to pH 1. The aqueous layer was extracted with ethyl acetate (4 x 30.0 mL). The combined organic layers were dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded the new acid which was taken on crude to the next step.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (m, 1H), 5.27 (m, 1H), 5.12 (m, 1H), 5.00 (m, 1H), 4.94 (m, 1H), 4.28 (dd, J=3.9, 9.1 Hz, 1H), 2.62 (dd, J=3.9, 13.7 Hz, 1H), 2.32 (dd, J=9.1, 13.7 Hz, 1H), 2.23-1.91 (m, 8H), 1.67 (s, 3H), 1.59 (s, 3H), 1.51-1.35 (m, 2H).



A suspension of lithium aluminum hydride (0.750 g, 0.020 mol) in diethyl ether (25.0 mL) was stirred at room temperature. The crude acid in diethyl ether (25.0 mL) was added via reflux condenser. The reaction was refluxed at 50°C for 1.5 hr and was subsequently cooled to room temperature. The reaction was quenched slowly over ice using 3M HCl (40.0 mL) and then stirred vigorously for 30 min at room temperature. The mixture was filtered through Celite and washed with ethyl acetate (3 x 20.0 mL). The filtrate was washed with brine. The aqueous layer was extracted with ethyl acetate (5 x 50.0 mL). The combined organic layers were dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue which was purified by column chromatography (gradient, 50% EtOAc: hexanes to 100% EtOAc) to give the diol (1.700 g, 80% over 3 steps).

FTIR (thin film/NaCl) 3368, 2920, 2840, 2800, 1640, 1441, 1380, 1100, 1040, 909 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.80 (m, 1H), 5.20 (m, 1H), 5.11 (m, 1H), 4.98 (m, 1H), 4.93 (m, 1H), 3.78 (m, 1H), 3.64 (m, 1H), 3.44 (dd, J=6.7, 11.2 Hz, 1H), 2.38 (bs, 1H), 2.25 (bs, 1H), 2.19-1.92 (m, 10H), 1.64 (s, 3H), 1.58 (s, 3H), 1.41 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 138.9, 134.8, 131.1, 128.5, 124.8, 114.3, 69.1, 66.5, 43.6, 39.5, 33.3, 29.0, 27.3, 26.4, 16.1, 15.8; **HRMS** (EI) *m/z* 252.2088 [calc'd for $C_{16}H_{28}O_2$ (M+) 252.2089].



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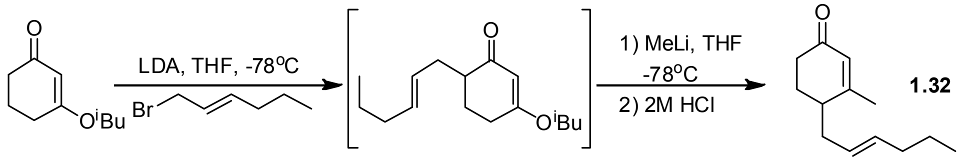
A solution of lead tetraacetate (0.920 g, 2.100 mmol) and sodium carbonate (0.220 g, 2.100 mmol) in methylene chloride (15.0 mL) was cooled to 0°C. The diol (0.500 g, 2.000 mmol) in methylene chloride (5.0 mL) was added to the solution at 0°C. After an additional 10 min the reaction was warmed to room temperature over 1 hr. The reaction was quenched with ethylene glycol (2.0 mL). The mixture was filtered through Celite and rinsed with methylene chloride (3 x 15.0 mL). The combined organic layers were washed with saturated sodium bicarbonate solution and then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded aldehyde, which was taken on crude to the next step.

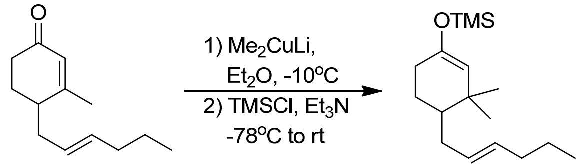
FTIR (thin film/NaCl) 3075, 2924, 2856, 1726, 1677, 1640, 1440, 1382, 1237, 992, 909 cm^{-1}; **^{1}H NMR** (600 MHz, C_6D_6) δ 9.28 (t, J=2.4 Hz, 1H), 5.78 (m, 1H), 5.16 (m, 1H), 5.07 (m, 1H), 5.04 (m, 1H), 4.99 (m, 1H), 2.57 (s, 2H), 2.08-1.93 (m, 8H), 1.52 (s, 3H), 1.44-1.38 (m, 2H), 1.41 (s, 3H); **^{13}C NMR** (125 MHz, C_6D_6) δ 198.8, 139.4, 135.1, 130.6, 127.3, 125.5, 115.1, 54.6, 40.0, 34.0, 29.8, 28.0, 27.3, 17.1, 16.4; **HRMS** (ES+) *m/z* 220.1823 [calc'd for $C_{15}H_{24}O$ (M+H$^+$) 220.1827].



1.32

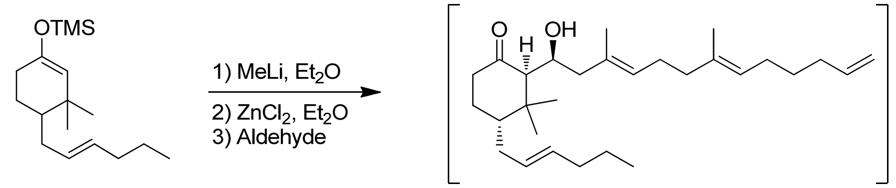
A tetrahydrofuran (16.0 mL) solution of enol ether (8.120 g, 0.048 mol) was added dropwise to a solution (64.0 mL THF) of freshly prepared LDA (0.051 mol) at -78°C. This mixture was stirred at -78°C for 1 hour before addition of allyl bromide (9.490 g, 0.058 mol) in 16.0 mL of THF. [*For preparation of allyl bromide see:* a) Kim, S.; Park, J. H. *J. Org. Chem.* **1988**, *53*, 3111-3113; b) Gomez, L.; Gellibert, F.; Wagner, A.; Mioskowski, C. *Tetrahedron Lett.* **2000**, *41*, 6049-6052**].** Stirring was continued at -78°C for an hour before warming to 0°C. This mixture was diluted with water (100.0 mL) and ethyl acetate (60.0 mL). The aqueous layer was extracted with ethyl acetate, dried over $MgSO_4$ and concentrated. This product was dissolved in 87.0 mL of dry THF and cooled to -78°C before MeLi (80.5 mL, 1.6M, 0.129 mol) was added. This temperature was maintained for 30 minutes before warming to 0°C. After an hour 2M HCl (65.0 mL) was added and stirring was continued for 12 hours before diluting with water (100.0 mL). The aqueous layer was extracted with ethyl acetate (3 x 80.0 mL) and dried over $MgSO_4$, concentrated, and purified by silica gel chromatography (20% EtOAc/Hexanes) to give enone (6.700 g, 72%, 2 Steps).

FTIR (thin film/NaCl) 2958, 2874, 1737, 1690, 1436, 1376, 1217, 968, 858 cm^{-1}; ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 5.79 (s, 1H), 5.46 (m, 1H), 5.33 (m, 1H), 2.39 (m, 1H), 2.32 (m, 1H), 2.29-2.19 (m, 2H), 2.10 (m, 1H), 2.02-1.92 (m, 3H), 1.93 (s, 3H), 1.87 (m, 1H), 1.34 (m, 2H), 0.85 (t, J=7.4 Hz, 3H); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ 199.4, 165.4, 133.2, 127.3, 126.8, 39.5, 34.5, 34.3, 33.7, 26.2, 23.0, 22.4, 13.5; **HRMS** (EI+) *m/z* 192.1512 [calc'd for $C_{13}H_{20}O$ (M+) 192.1515].

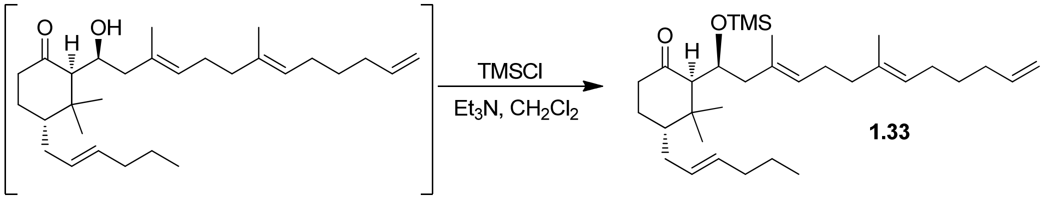


An ethereal (14.0 mL) solution of CuI (0.700 g, 3.670 mmol) was cooled to -5°C before dropwise addition of MeLi (4.6 mL, 1.6M, 7.35 mmol). After 30 minutes at -5°C enone (0.565 g, 2.940 mmol) in ether (4.3 mL) was added dropwise and stirred 90 minutes. The reaction was cooled to -78°C before dropwise addition of distilled TMSCl (1.9 mL, 14.7 mmol), followed by dropwise addition of distilled Et_3N (2.1 mL, 14.7 mmol). This mixture was warmed to room temperature over 1 hour and poured slowly over ice, diluted with water (20.0 mL) and methylene chloride (20.0 mL). The aqueous layer was extracted with methylene chloride (2 x 20.0 mL) and the combined organic extracts were dried over Na_2SO_4, concentrated, and purified with silica gel chromatography (92:4:4 hexane: EtOAc: Et_3N) to give silyl enol ether (0.725 g, 88%).

FTIR (thin film/NaCl) 2957, 2929, 2865, 1722, 1668, 1463, 1367, 1252, 1206, 1154, 966, 933, 823, 805 cm^{-1}; ^{1}**H NMR** (600 MHz, C_6D_6) δ 5.44-5.34 (m, 2H), 4.75 (m, 1H), 2.26 (m, 1H), 2.06 (m, 2H), 1.98 (dd, J=6.9, 13.4 Hz, 2H), 1.77 (m, 1H), 1.63 (m, 1H), 1.43-1.29 (m, 3H), 1.25 (m, 1H), 1.03 (s, 1H), 0.88 (t, J=7.4 Hz, 3H), 0.86 (s, 3H), 0.18 (s, 9H); ^{13}**C NMR** (125 MHz, C_6D_6) δ 149.4, 131.7, 130.4, 116.4, 44.2, 35.2, 34.7, 33.6, 30.3, 24.4, 24.2, 23.2, 13.9; **HRMS** (EI+) *m/z* 280.2211 [calc'd for $C_{17}H_{32}OSi$ (M+) 280.2223].



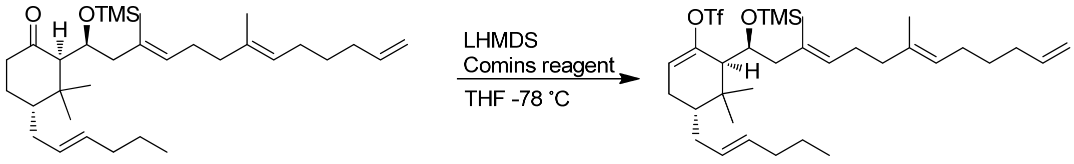
TMS enol ether (0.422 g, 1.500 mmol) in diethyl ether (2.9 mL) was cooled to 0°C. Methyl lithium (1.0 mL, 1.6 M in diethyl ether) was added dropwise. The solution was warmed to room temperature over 1.25 hr. The reaction was cooled to -10°C and zinc chloride (1.7 mL, 1.0 M in diethyl ether) was added dropwise over 15 min. The reaction stirred at -10°C for 20 min and then the bath was removed and allowed to sit at room temperature for 1 min before cooling to -45°C. Aldehyde (0.166 g, 0.750 mmol) in diethyl ether (1.3 mL) was added dropwise over 15 min. The reaction was allowed to warm to -35°C over 1.5 hr. The reaction was then poured onto saturated NH_4Cl (15.0 mL). The organic layer was diluted with ethyl acetate (10.0 mL) and then washed with sat. NH_4Cl (2 x 10.0 mL) and brine (2 x 10.0 mL). The aqueous layers were extracted with ethyl acetate (3 x 10.0 mL). The combined organic layers were dried over Na_2SO_4. Concentrating the solvent *in vacuo* afforded the aldol adduct, which was taken on crude to the next step.



1.33

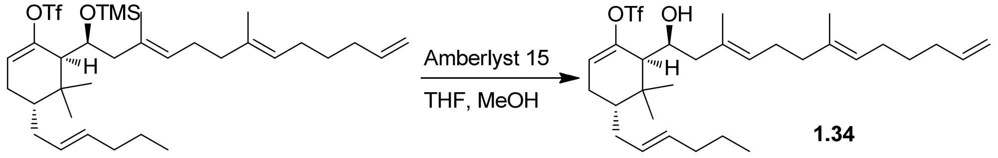
Crude aldol product in methylene chloride (7.2 mL) and triethylamine (5.8 mL) was cooled to 0°C in a sealed tube. Chlorotrimethylsilane (0.36 mL, 2.80 mmol) was added slowly. The tube was sealed and warmed to room temperature over 18 hr. The reaction was quenched by diluting with methylene chloride (10.0 mL) and brine (20.0 mL). The aqueous layer was extracted with methylene chloride (3 x 10.0 mL) and dried over Na_2SO_4. Solvent was removed and residue filtered through Celite (2:5:93 Et_3N: EtOAc: hexanes, 50.0 mL). Concentration of the solvent and silica purification (2:5:93 Et_3N: EtOAc: hexanes) gave TMS aldol product (0.490 g, 65%).

FTIR (thin film/NaCl) 2957, 2929, 2871, 1716, 1457, 1249, 968, 841 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.81 (m, 1H), 5.39 (m, 2H), 5.12 (m, 2H), 4.99 (m, 1H), 4.93 (m, 1H), 4.34 (m, 1H), 2.44-2.14 (m, 5H), 2.13-1.86 (m, 13H), 1.59 (s, 6H), 1.49-1.26 (m, 6H), 1.09 (s, 3H), 0.96 (s, 3H), 0.88 (t, J=7.3 Hz, 3H), 0.12 (s,9H); **^{13}C NMR (**75MHz,$CDCl_3$) d 213.8, 139.0, 135.0, 132.0, 131.9, 129.4, 128.3, 124.4, 114.3, 69.8, 61.7, 48.1, 44.1, 41.0, 40.0, 39.5, 34.7, 33.3, 32.0, 29.0, 27.3, 26.6, 26.2, 25.7, 24.8, 22.7, 16.4, 16.0, 13.6, 0.8; **HRMS** (ES+) *m/z* 501.4119 [calc'd for $C_{32}H_{57}O_2Si$ (M+H$^+$) 501.4128].



TMS aldol adduct (0.580 g, 1.200 mmol) in THF (30.0 mL) was cooled to -78°C. Lithium hexamethyldisilazide (3.5 mL, 1.0 M in THF) was added dropwise over 35 min. A solution of Comin's reagent (0.910 g, 2.300 mmol) in THF (5.0 mL) was added over 30 min. The reaction was stirred at -78°C for an additional 4.5 hr. The reaction was quenched with brine (5.0 mL) and warmed to room temperature. The mixture was washed with brine (30.0 mL) and NaOH (1 M, 30.0 mL). The aqueous layer was extracted with ethyl acetate (3 x 30.0 mL). The organics were dried over Na_2SO_4, concentrated and purified with silica (10% EtOAc: hexanes) to give vinyl triflate (0.702 g, 95%).

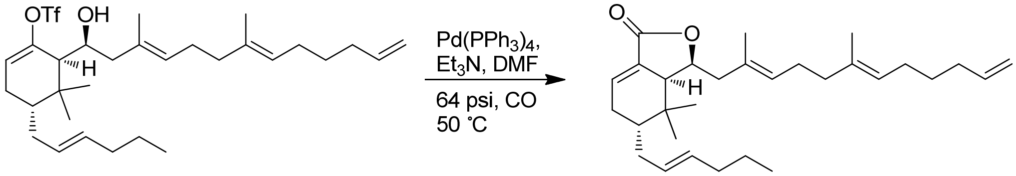
FTIR (thin film/NaCl) 2960, 2927, 1690, 1641, 1419, 1247, 1200, 1146, 1087, 1024, 903, 841 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.92-5.71 (m, 2H), 5.49-5.09 (m, 4H), 5.00 (m, 1H), 4.94 (m, 1H), 4.13 (m, 1H), 2.40-2.15 (m, 5H), 2.14-1.89 (m, 12H), 1.63 (s, 3H), 1.60 (s, 2H), 1.51-1.30 (m, 5H), 1.16 (s, 3H), 0.91 (s, 3H), 0.89 (t, J=7.2 Hz, 3H), 0.06 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 150.2, 139.0, 135.1, 132.0, 131.9, 128.9, 128.2, 124.4, 118.6, 114.3, 70.6, 54.4, 47.4, 39.5, 37.6, 34.7, 33.4, 32.4, 29.1, 27.5, 27.4, 27.3, 26.7, 26.0, 23.6, 22.7, 16.6, 15.9, 13.7, 0.2; **HRMS** (ES+) *m/z* 655.3437 [calc'd for $C_{33}H_{55}O_4NaF_3SSi$ (M+Na) 655.3440].



1.34

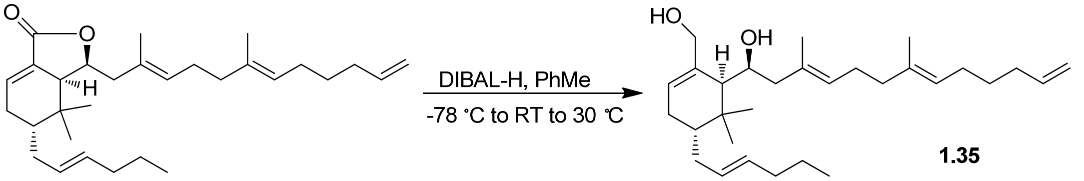
The TMS-protected vinyl triflate (0.050 g, 0.079 mmol) in THF (2.0 mL) and methanol (2.0 mL) was stirred at room temperature. Approximately 10 pieces of Amberlyst 15 resin were added to the solution. After 3 hr, the reaction was filtered through Celite using diethyl ether (15.0 mL). Triethylamine (2.0 mL) was added to the filtrate. Concentration of the solvent *in vacuo* afforded a residue which was purified with silica (8% Et_2O: hexanes) to give the alcohol (0.042 g, 95%).

FTIR (thin film/NaCl) 3500, 2959, 2922, 2857, 1417, 1245, 1210, 1144, 1022, 915, 861 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.89-5.74 (m, 2H), 5.49-5.20 (m, 3H), 5.12 (m, 1H), 5.00 (m, 1H), 4.94 (m, 1H), 3.85 (m, 1H), 2.41-1.90 (m, 17H), 1.64 (s, 3H), 1.59 (s, 3H), 1.48-1.31 (m, 5H), 1.25 (bs, 1H), 1.12 (s, 3H), 0.94 (s, 3H), 0.89 (t, J=7.4 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 149.3, 139.2, 134.9, 132.5, 131.8, 129.8, 128.7, 125.2, 119.7, 114.5, 67.5, 55.8, 46.5, 39.7, 38.0, 37.5, 34.9, 33.6, 32.7, 29.2, 28.1, 27.6, 26.6, 26.0, 22.9, 22.8, 16.1, 16.0, 13.9; **HRMS** (ES+) *m/z* 561.3249 [calc'd for $C_{30}H_{48}O_4F_3S$ ($M+H^+$) 561.3225].



Palladium tetrakis (0.207 g, 0.180 mmol) was added to an 18 x 150 mm test tube with stir bar inserted into a Fisher-Porter bottle which was evacuated (100 torr) and backfilled with argon three times. A degassed solution of vinyl triflate (0.400 g, 0.720 mmol) and triethylamine (0.30 mL, 2.2 mmol) in DMF (7.0 mL) was added. The bottle was pressured to 62 psi CO then heated to 50°C for 15 hr. Upon cooling, the CO was released and air bubbled through for 10 min. Solvent was removed and the residue dissolved in methylene chloride (10.0 mL) and washed with H_2O (20.0 mL) and HCl (1 M, 3.0 mL). The aqueous layer was extracted with 50:50 Et_2O: hexanes (7 x 10.0 mL) and dried over Na_2SO_4. The extracts were concentrated and purified by column chromatography (7% EtOAc: hexanes) to give lactone (0.289 g, 92%).

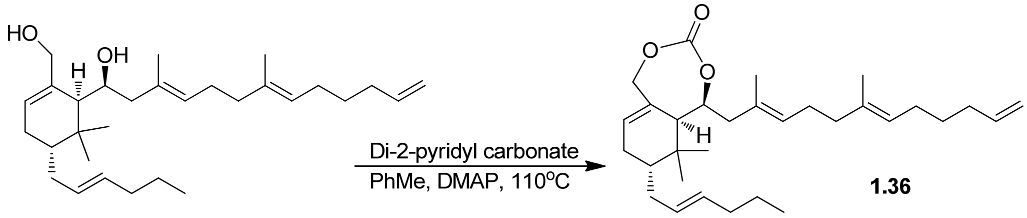
FTIR (thin film/NaCl) 2958, 2925, 2872, 1740, 1686, 1428, 1320, 1215, 1141, 1000, 971 cm^{-1}; ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 6.82 (dd, J=3.4, 3.5 Hz, 1H), 5.81 (m, 1H), 5.47-5.05 (m, 4H), 4.99 (m, 1H), 4.93 (m, 1H), 4.85 (m, 1H), 2.94 (m, 1H), 2.46-2.16 (m, 4H), 2.16-1.87 (m, 12H), 1.67 (s, 3H), 1.58 (s, 3H), 1.52-1.23 (m, 5H), 1.15 (s, 3H), 0.98 (s, 3H), 0.88 (t, J=7.4 Hz, 3H); ^{13}**C NMR** (75 MHz, $CDCl_3$) δ 170.1, 139.3, 135.2, 135.0, 133.1, 130.8, 128.7, 127.9, 124.7, 114.5, 81.9, 46.9, 45.6, 44.2, 40.0, 35.0, 34.9, 33.6, 32.6, 29.3, 27.6, 27.0, 26.9, 25.8, 24.9, 22.8, 16.6, 16.2, 13.9; **HRMS** (ES+) *m/z* 439.3571 [calc'd for $C_{30}H_{47}O_2$ (M+H$^+$) 439.3576].



1.35

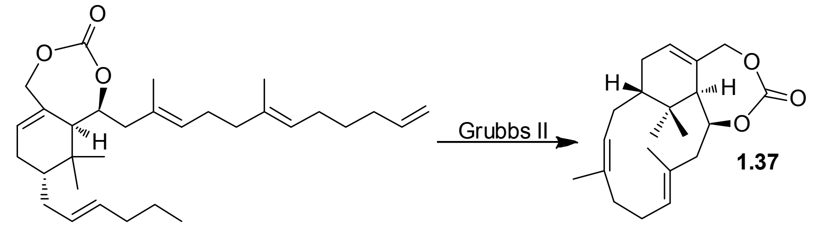
A solution of lactone (0.246 g, 0.560 mmol) in toluene (16.0 mL) was cooled to -78°C and treated with diisobutylaluminum hydride (4.5 mL, 1.0 M toluene) dropwise over 20 min. After 5 min, the reaction was warmed to 0°C for 30 min and then 30°C for another 30 min. The reaction was quenched with HCl (3 M, 8.0 mL) and stirred for 25 min at room temperature. The mixture was saturated with NaCl and the aqueous layer was extracted with ethyl acetate (5 x 10.0 mL) and dried over Na_2SO_4. Removal of solvent gave a residue which was purified with silica (25% EtOAc: hexanes) to give the diol (0.231 g, 93%).

FTIR (thin film/NaCl) 3285, 2940, 2871, 1667, 1640, 1438, 1384, 1052, 998, 969, 909 cm^{-1}; ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 5.87-5.66 (m, 2H), 5.48-5.22 (m, 2H), 5.17 (m, 1H), 5.09 (m, 1H), 4.98 (m, 1H), 4.92 (m, 1H), 4.15-3.89 (m, 3H), 3.73 (bs, 1H), 2.55 (bs, 1H), 2.33-1.82 (m, 17H), 1.63 (s, 3H), 1.56 (s, 3H), 1.50-1.22 (m, 5H), 1.07 (s, 3H), 0.86 (t, J=7.3 Hz, 3H), 0.79 (s, 3H); ^{13}**C NMR** (75 MHz, $CDCl_3$) δ 138.9, 135.8, 134.7, 132.0, 131.4, 129.1, 128.9, 125.9, 124.9, 114.2, 68.6, 67.9, 53.7, 45.6, 39.4, 38.4, 34.6, 33.6, 33.3, 29.5, 28.9, 27.3, 26.5, 26.3, 23.2, 22.6, 16.0, 15.8, 13.6; **HRMS** (ES+) *m/z* 443.3880 [calc'd for $C_{30}H_{51}O_2$ (M+H$^+$) 443.3889].



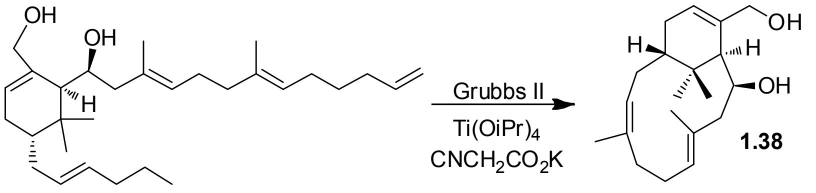
Pyridyl carbonate (0.029 g, 0.136 mmol) was added to the diol (0.050 g, 0.113 mmol) in dry toluene (2.5 mL). This reaction mixture was heated at 110°C for 19 hours, cooled to room temperature, and concentrated *in vacuo*. Purification using silica gel chromatography (20% EtOAc/hexanes) afforded carbonate (0.038 g, 73%).

FTIR (thin film/NaCl) 2959, 2925, 2873, 1740, 1454, 1389, 1368, 1264, 1168, 1143, 1062, 969, 909 cm^{-1}; ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 6.04 (m, 1H), 5.81 (m, 1H), 5.50-5.06 (m, 4H), 4.99 (m, 1H), 4.93 (m, 1H), 4.75 (m, 1H), 4.41 (s, 2H), 2.50 (m, 1H), 2.38-2.13 (m, 4H), 2.13-1.86 (m, 10H), 1.70 (s, 3H), 1.68-1.60 (m, 2H), 1.57 (s, 3H), 1.51-1.26 (m, 5H), 1.06 (s, 3H), 0.93-0.83 (m, 6H); ^{13}**C NMR** (75 MHz, $CDCl_3$) δ 153.9, 139.1, 135.0, 132.1, 131.8, 129.2, 129.1, 128.7, 124.3, 114.2, 109.7, 80.1, 75.4, 53.3, 53.3, 53.2, 42.0, 39.1, 34.7, 34.1, 33.3, 32.7, 29.0, 28.3, 27.3, 26.6, 24.4, 22.6, 16.0, 15.5, 13.7; **HRMS** (ES+) *m/z* 491.2500 [calc'd for $C_{31}H_{48}O_3Na$ (M+Na) 491.3501].



The carbonate (0.008 g, 0.018 mmol) was dissolved in dry toluene (37.0 mL) and refluxed under nitrogen, before addition of Grubbs second generation catalyst (0.005 g, 0.005 mmol). After 8 minutes the reaction was immediately cooled to 0°C in an ice bath and then warmed to room temperature. The reaction mixture was filtered through a plug of silica. The plug was thoroughly rinsed with 35% EtOAc/hexanes. The solvent was evaporated and the residue was purified on silica using 20% EtOAc/hexanes affording diene (0.006 g, 95%).

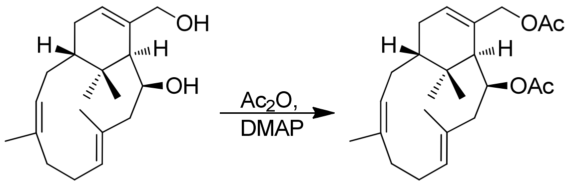
^{1}**H NMR** (400 MHz, $CDCl_3$) δ 6.09 (m, 1H), 5.47 (m, 1H), 5.20 (m, 1H), 4.72 (m, 1H), 4.38 (s, 2H), 2.61 (m, 1H), 2.44-1.80 (m, 8H), 1.74-1.69 (m, 6H), 1.67 (m, 1H), 1.25 (m, 2H), 0.96 (s, 3H), 0.80 (s, 3H); ^{13}**C NMR** δ 154.7, 135.2, 133.2, 132.4, 131.1, 128.6, 125.0, 80.7, 75.7, 57.0, 42.8, 40.6, 33.6, 32.1, 29.6, 28.0, 25.1, 24.2, 22.8, 22.4, 15.0; **HRMS** (EI+) *m/z* 330.2195 [calc'd for $C_{21}H_{30}O_3$ (M+) 330.2195]. **Carbon shifts extracted from HSQC and HMBC spectra.**



1.38

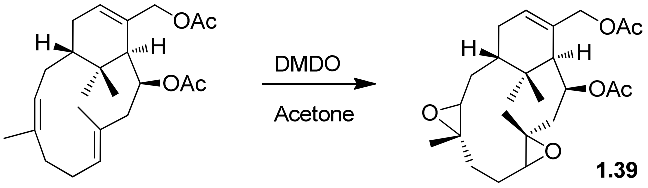
Titanium isopropoxide (0.07 mL, 0.23 mmol) in toluene (0.8 mL) was added to allylic alcohol (0.010 g, 0.023 mmol) in toluene (46.0 mL) in a three neck round bottom flask with thermometer, reflux condenser, and nitrogen sparging tube. The solution was heated to an internal temp of 80°C for 1 hr. The sparging tube was immersed in the mixture, and the internal temp was increased to 111°C. A fresh solution of second generation Grubbs (0.006 g, 0.007 mmol) in toluene (0.4 mL) was added. The reaction was stirred for 8 min then immersed in an ice bath. NaOH (3 M, 5 mL) and an isocyanide (0.003 g, 0.027 mmol) in 0.5 mL of methanol was added to render the catalyst inactive by stirring 15 min at room temp. [*For preparation and use of the isocyanide see:* Diver, S.T. *Org. Lett.* **2007**, 9, 1203-1206]. The mixture was acidified with HCl (2 M, 8.0 mL), extracted with toluene (3 x 50.0 mL), and dried over Na_2SO_4. Concentration of the solvent *in vacuo* and silica gel chromatography afforded triene diol (0.007 g, 95%).

FTIR (thin film/NaCl) 3269, 2940, 2915, 1662, 1451, 1384, 1364, 1265, 1034, 1006, 952, 888, 807 cm^{-1}; ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 5.88 (m, 1H), 5.41 (m, 1H), 5.10 (m, 1H), 4.18-4.07 (m, 2H), 3.92 (d, J=11.7 Hz, 1H), 2.52 (dd, J=8.7, 14.1 Hz, 1H), 2.37-1.77 (m, 9H), 1.72 (s, 3H), 1.70 (s, 3H), 1.51-0.99 (m, 2H), 0.95 (s, 3H), 0.74 (s, 3H); ^{13}**C NMR** δ 135.4, 134.9, 131.7, 129.9, 129.7, 124.2, 69.6, 69.3, 59.8, 47.7, 40.4, 35.0, 34.0, 32.3, 26.8, 24.2, 23.4, 22.8, 21.8, 15.1; **HRMS** (ES+) *m/z* 327.2306 [calc'd for $C_{20}H_{32}O_2Na$ (M+Na) 327.2300]. **Carbon shifts extracted from HSQC and HMBC spectra.**



To a solution of diol (0.012 g, 0.039 mmol) in methylene chloride (0.4 mL) was added triethylamine (0.11 mL, 0.78 mmol), dimethylaminopyridine (0.010 g, 0.080 mmol) in methylene chloride (0.4 mL), and acetic anhydride (0.04 mL, 0.39 mmol) in methylene chloride (0.4 mL). The reaction was stirred for 1 hr at room temperature. Upon completion, the reaction was quenched with brine (3.0 mL). The aqueous layer was extracted with ethyl acetate (3 x 2.0 mL) and dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue which was purified by column chromatography (25% EtOAc: hexanes) to give bis-acetate (0.014 g, 92%).

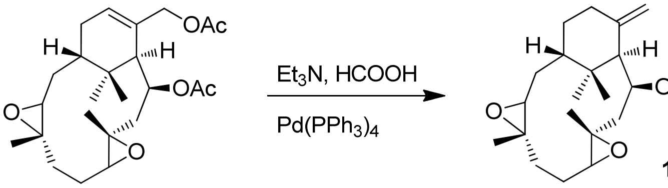
^{1}**H NMR** (600 MHz, $CDCl_3$) δ 5.94 (m, 1H), 5.45-5.35 (m, 2H), 5.14 (m, 1H), 4.63 (d, J=12.5 Hz, 1H), 4.52 (d, J=12.5 Hz, 1H), 2.48 (dd, J=14.2, 9.4 Hz, 1H), 2.36-2.06 (m, 6H), 2.05 (s, 3H), 2.01 (s, 3H), 1.71 (s, 3H), 1.68-1.53 (m, 3H), 1.58 (s, 3H), 1.48-1.38 (m, 2H), 1.04 (s, 3H), 0.77 (s, 3H); ^{13}**C NMR** δ 170.8, 170.0, 132.6, 135.5, 131.3, 130.8, 130.7, 129.7, 72.9, 68.6, 54.0, 43.8, 42.2, 41.4, 36.7, 32.5, 30.1, 26.3, 24.3, 23.0, 21.6, 21.6, 21.0, 15.1; **HRMS** (EI+) *m/z* 411.2511 [calc'd for $C_{24}H_{36}O_6Na$ (M+Na) 411.2492]. **Carbon chemical shifts extracted from HSQC and HMBC data.**



1.39

Triene (0.010 g, 0.026 mmol) was dissolved in acetone (0.3 mL) and treated with a freshly prepared dimethyl dioxirane solution (0.5 mL, 0.1M in acetone, 0.052 mmol). The reaction is stirred 10 minutes while being monitored by TLC. The solvent was evaporated to yield pure bis epoxide (0.010 g, 93%).

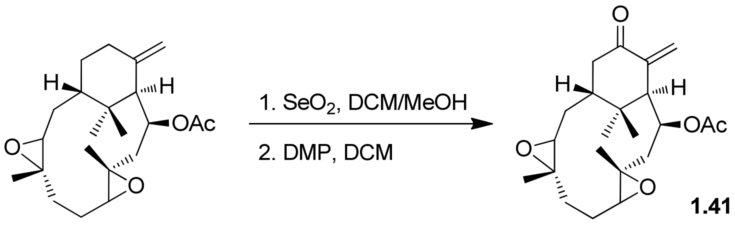
^{1}H NMR (600 MHz, $CDCl_3$) δ 5.91 (m, 1H), 5.42 (d, J=7.6 Hz, 1H), 4.56 (d, J=12.6 Hz, 1H), 4.49 (d, J=12.6 Hz, 1H), 2.91 (dd, J=4.8, 9.6 Hz, 1H), 2.71 (d, 11.3 Hz, 1H), 2.23-2.11 (m, 2H), 2.06 (s, 3H), 2.04 (s, 3H), 2.10-1.82 (m, 5H), 1.77-1.63 (m, 5H), 1.46 (s, 3H), 1.39 (s, 3H), 1.15 (s, 3H), 0.83 (s, 3H); **^{13}C NMR** δ 170.5, 169.9, 132.3, 127.6, 71.1, 67.8, 65.9, 63.7, 59.7, 59.0, 53.4, 42.5, 35.4, 34.7, 29.3, 28.5, 27.3, 26.7, 25.5, 22.1, 21.4, 21.3, 21.0, 16.4; **HRMS** (EI+) *m/z* 420.2519 [calc'd for $C_{24}H_{36}O_6$ (M+) 420.2512]. **Carbon chemical shifts extracted from HSQC and HMBC data.**



1.40

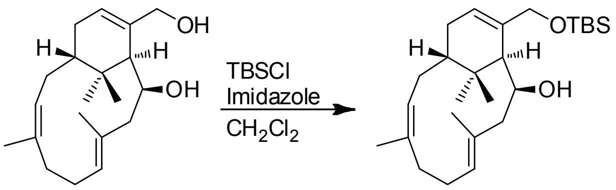
Bis-epoxide (0.008 g, 0.190 mmol) was dissolved in dry THF (1.9 mL) and treated consecutively with triethylamine and formic acid (26 μL Et_3N and 7.2 μL HCOOH, 0.190 mmol each dissolved in 0.2 mL THF) and $Pd(PPh_3)_4$ (0.011 g, 0.008 mmol). This reaction mixture was heated at 75°C for 15 hours before being evaporated to dryness. Purification using silica gel chromatography (33% EtOAc/hexanes) afforded the desired exo-olefin containing product (0.006 g, 87%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.38 (dd, J = 2.3, 9.3 Hz, 1H), 5.03 (m, 1H), 4.71 (m, 1H), 3.07-2.95 (m, 2H), 2.27-1.98 (m, 8H), 2.14 (s, 3H), 1.95-1.85 (m, 2H), 1.54 (s, 3H), 1.49-1.34 (m, 4H), 1.44 (s, 3H), 1.14 (s, 3H), 0.84 (s, 3H); **^{13}C NMR** δ 170.4, 143.4, 116.1, 71.1, 65.9, 64.4, 60.0, 59.6, 59.2, 43.1, 38.0, 35.7, 33.2, 28.5, 27.2, 27.0, 26.4, 25.3, 22.2, 22.2, 21.8, 16.7; **HRMS** (ES+) *m/z* 385.2355 [calc'd for $C_{22}H_{34}O_4Na$ (M+Na) 385.2355]. **Carbon chemical shifts extracted from HSQC and HMBC data.**



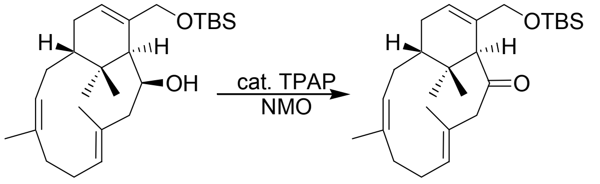
Exocyclic olefin product (0.001 g, 0.003 mmol) was dissolved in dry 50:50 DCM:MeOH (0.8 mL) and selenium dioxide was added in one portion. The reaction was then heated at 65°C for 15 hours. The reaction was concentrated to remove the methanol and brought up in dry methylene chloride (0.8 mL). Freshly prepared Dess-Martin Periodinane was then added and the reaction was stirred for 1 hour. The reaction was concentrated and purified using silica gel chromatography (33% EtOAc/hexanes) affording enone (0.0008 g, 77%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.23 (m, 1H), 5.40 (d, J = 7.8 Hz, 1H), 5.31 (m, 1H), 2.87 (m, 1H), 2.70 (m, 1H), 2.59 (m, 1H), 2.53 (s, 1H), 2.31-1.99 (m, 4H), 2.07 (s, 3H), 1.86 (m, 1H), 1.47 (s, 3H), 1.39 (s, 3H), 1.37-1.20 (m, 5H), 1.22 (s, 3H), 0.94 (s, 3H); **^{13}C NMR** δ 199.1, 169.8, 141.5, 127.7, 70.6, 65.7, 62.7, 59.6, 59.2, 58.7, 42.3, 41.1, 36.2, 35.1, 26.3, 22.0, 21.5, 31.6, 27.2, 22.8, 21.4, 16.4; **HRMS** (ES+) *m/z* 399.2138 [calc'd for $C_{22}H_{32}O_5Na$ (M+Na) 399.2147]. **Carbon chemical shifts extracted from HSQC and HMBC data.**

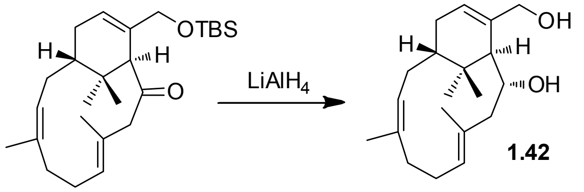


Crude macrocycle (0.11 mmol) in methylene chloride (5.0 mL) was stirred at room temperature. Imidazole (0.068 g, 1.000 mmol) and *tert*-butylchlorodimethylsilane (0.050 g, 0.330 mmol) were added to the solution. After 30 min, the mixture was filtered through a plug of silica and eluted with 20% EtOAc: hexanes (30.0 mL). Concentration of the solvent *in vacuo* afforded a residue which was purified by column chromatography (9% EtOAc: hexanes) to give the protected alcohol (0.028 g, 62%).

FTIR (thin film/NaCl) 3428, 2945, 2932, 2859, 1461, 1384, 1363, 1254, 1125, 1085, 1031, 1006, 860 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.82 (m, 1H), 5.41 (m, 1H), 5.09 (m, 1H), 4.12 (d, J=11.2 Hz, 1H), 4.04-3.97 (m, 2H), 2.46 (dd, J=8.7, 14.0 Hz, 1H), 2.38-1.87 (m, 9H), 1.74 (s, 3H), 1.70 (s, 3H), 1.67-1.50 (m, 2H), 0.95 (s, 3H), 0.89 (s, 9H), 0.72 (s, 3H), 0.09 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 135.0, 134.9, 134.8, 132.7, 130.0, 129.1, 70.7, 68.9, 60.4, 48.1, 40.3, 34.0, 32.3, 25.9, 25.8, 25.6, 24.2, 22.9, 21.7, 18.3, 15.1, -3.6, -5.1, -5.4; **HRMS** (ES+) *m/z* 419.3343 [calc'd for $C_{26}H_{47}O_2Si$ ($M+H^+$) 419.3345].



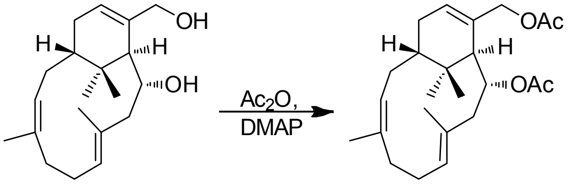
To a mixture of *N*-methylmorpholine oxide (0.021 g, 0.180 mmol) and oven dried powdered 4Å sieves (0.060 g) was added TBS ether (0.050 g, 0.120 mmol) in methylene chloride (2.0 mL) and acetonitrile (0.4 mL). Tetrapropylammonium perruthenate (0.002 g, 0.006 mmol) in methylene chloride (0.2 mL) was added and the reaction was stirred for 45 min at room temperature. Concentration of the solvent *in vacuo* afforded a residue which was filtered through a plug of silica with ethyl acetate (20.0 mL). Concentration of the solvent *in vacuo* afforded the ketone which was taken on crude to the next step.



1.42

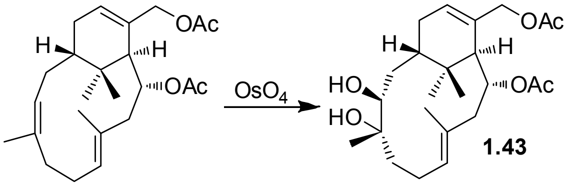
A solution of crude ketone (0.120 mmol) in THF (5.0 mL) was cooled to 0°C. Lithium aluminum hydride (0.115 g, 3.000 mmol) was slowly added to the solution and stirred 10 min before warming to room temp (1 hr). The reaction was quenched with ethyl acetate and then acidified to pH 1 with HCl (3 M, 3.0 mL). Solid NaCl (0.500 g) and brine (3.0 mL) were added followed by ethyl acetate extraction (5 x 5.0 mL). The organics were dried over Na_2SO_4, concentrated, and purified by column chromatography (60% EtOAc: hexanes) to give diol (0.035 g, 96% over 2 steps).

FTIR (thin film/NaCl) 3341, 2958, 2935, 2868, 1659, 1453, 1384, 1364, 1265, 1099, 1043, 1002, 883 cm^{-1}; ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 5.75 (m, 1H), 5.44 (m, 1H), 5.22 (m, 1H), 4.37 (m, 1H), 4.11 (d, J=11.9, 1H), 3.98 (d, J=11.9 Hz, 1H), 2.54 (dd, J=8.4, 14.8 Hz, 1H), 2.46-1.91 (m, 9H), 1.81 (bs, 2H), 1.75-1.69 (m, 6H), 1.68-1.59 (m, 2H), 1.16 (s, 3H), 0.76 (s, 3H); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ 134.8, 133.8, 130.1, 127.3, 126.9, 125.5, 75.1, 67.1, 57.9, 42.7, 40.7, 35.6, 32.0, 29.7, 29.3, 27.0, 26.8, 24.6, 22.9, 17.6; **HRMS** (ES+) *m/z* 327.2328 [calc'd for $C_{20}H_{32}O_2Na$ (M+Na) 327.2300]. **Carbon shifts extracted from HSQC and HMBC spectra.**



To a solution of diol (0.023 g, 0.076 mmol) in methylene chloride (0.8 mL) was added triethylamine (0.21 mL, 1.50 mmol), dimethylaminopyridine (0.018 g, 0.150 mmol) in methylene chloride (0.8 mL), and acetic anhydride (0.07 mL, 0.76 mmol) in methylene chloride (0.8 mL). The reaction was stirred for 1.5 hr at room temperature. Upon completion, the reaction was quenched with brine (3.0 mL). The aqueous layer was extracted with ethyl acetate (3 x 2.0 mL) and dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue which was purified by column chromatography (25% EtOAc: hexanes) to give the product (0.030 g, 98%).

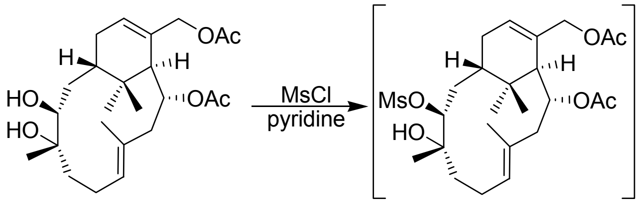
FTIR (thin film/NaCl) 2961, 2921, 2871, 1730, 1455, 1430, 1364, 1210, 1092, 1025 cm^{-1}; ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 5.88 (m, 1H), 5.50-5.40 (m, 2H), 5.19 (m, 1H), 4.63 (d, J=12.5 Hz, 1H), 4.44 (d, J=12.5 Hz, 1H), 2.59-2.11 (m, 7H), 2.08 (s, 3H), 2.05 (s, 3H), 2.03-1.84 (m, 3H), 1.74 (s, 3H), 1.72 (s, 3H), 1.66-1.15 (m, 2H), 1.05 (s, 3H), 0.71 (s, 3H); **HRMS** (ES+) *m/z* 411.2521 [calc'd for $C_{24}H_{36}O_4Na$ (M+Na) 411.2511].



1.43

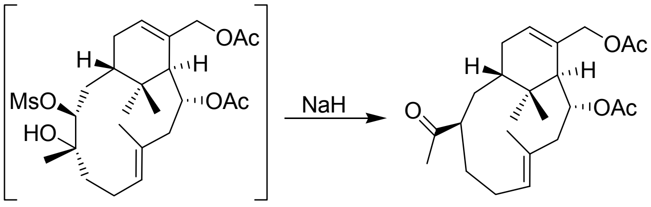
A solution of starting material (0.023 g, 0.059 mmol) in THF (3.0 mL) was cooled to 0°C. Osmium tetroxide in *t*-butanol (0.662 g, 2.5 wt %) was diluted in THF (3.0 mL) and slowly added to the solution at 0°C. After 15 min, the reaction was warmed to room temp over 3 h. The reaction was quenched by stirring 48 h with saturated $NaHSO_3$ (6.0 mL). The reaction was filtered through a plug of Celite with ethyl acetate (5 x 3.0 mL) and dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue which was purified by column chromatography (50% EtOAc: hexanes) to give diol (0.019 g, 74%).

FTIR (thin film/NaCl) 3452, 2925, 2874, 1735, 1671, 1451, 1376, 1220, 1079, 1029 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 5.95 (m, 1H), 5.46 (m, 1H), 5.39 (m, 1H), 4.65 (d, J=12.4 Hz, 1H), 4.47 (d, 12.4 Hz, 1H), 3.36 (m, 1H), 2.68 (m, 1H), 2.53 (dd, J=8.4, 15.0 Hz, 1H), 2.45-2.14 (m, 8H), 2.09 (s, 3H), 2.06 (s, 3H), 1.88-1.75 (m, 2H), 1.73 (s, 3H), 1.35 (s, 3H), 1.05 (s, 3H), 0.71 (s, 3H); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ 170.9, 169.9, 135.5, 132.3, 132.3, 130.8, 95.0, 78.0, 74.2, 67.3, 55.0, 40.6, 38.9, 35.3, 34.5, 32.4, 28.8, 26.0, 25.0, 22.7, 22.1, 21.6, 21.0, 17.1; **HRMS** (ES+) *m/z* 445.2583 [calc'd for $C_{24}H_{38}O_6Na$ (M+Na) 445.2566].



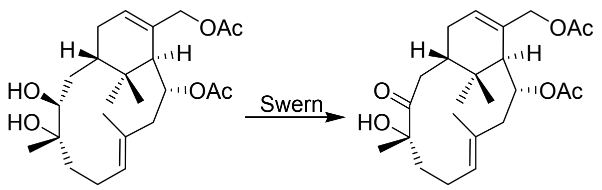
Diol (0.005 g, 0.012 mmol) was dissolved in methylene chloride (1.2 mL) and cooled to 0°C. Pyridine (0.019 g, 0.237 mmol) and methanesulfonyl chloride (0.020 g, 0.177 mmol) were added consecutively and the reaction was stirred for 15 minutes before being warmed to room temp for 2 hours. Solvent was evaporated and residue was carried on to the next step.

FTIR (thin film/NaCl) 3472, 2952, 2853, 1738, 1727, 1601, 1332, 1230, 1172, 1124, 1071, 1030, 919 cm^{-1}; ^{1}**H NMR** (400 MHz, C_6D_6) δ 5.55 (m, 1H), 5.45 (m, 1H), 4.51 (m, 1H), 4.33 (m, 1H), 4.25-4.21 (m, 1H), 2.84-2.63 (m, 2H), 2.50-2.39 (m, 2H), 2.31 (m, 1H), 2.20 (s, 3H), 2.14-2.01 (m, 3H), 1.90-1.78 (m, 2H), 1.75 (s, 3H), 1.72-1.62 (m, 2H), 1.60 (s, 3H), 1.25 (s, 3H), 1.15 (s, 3H), 1.07 (s, 3H), 0.66 (s, 3H); **HRMS** (ES+) *m/z* 523.2337 [calc'd for $C_{25}H_{40}O_8S$ (M+Na) 523.2342].



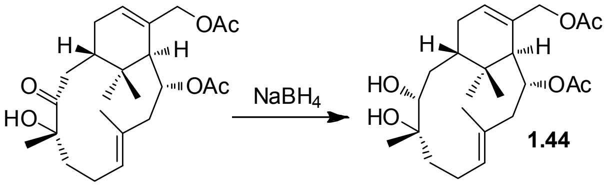
Mesylate (0.003 g, 0.006 mmol) in dry THF (1.0 mL) was treated with excess NaH (0.002 g) and stirred at room temperature for 8 hours before quenching with sat NH_4Cl (1.0 mL) and extraction with ethyl acetate (3 x 3.0 mL). The organics were washed with brine, dried over $MgSO_4$ and concentrated. Purification using silica gel (20% EtOAc: hexanes) afforded ketone.

FTIR (thin film/NaCl) 2940, 2920, 2868, 1738, 1715, 1454, 1366, 1245, 1096, 1021, 954 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 5.96 (m, 1H), 5.41 (m, 1H), 5.31 (m, 1H), 4.64 (m, 1H), 4.54 (m, 1H), 2.73-2.15 (m, 8H), 2.14 (s, 3H), 2.07 (s, 3H), 2.02 (s, 3H), 1.74 (s, 3H), 1.72-1.52 (m, 5H), 1.00 (s, 3H), 0.78 (s, 3H); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ 211.5, 170.8, 169.8, 134.3, 131.7, 130.2, 128.4, 72.6, 68.1, 55.3, 51.2, 44.0, 34.5, 33.3, 33.0, 32.6, 30.0, 29.1, 28.0, 27.5. 26.5, 21.7, 21.0, 15.4; **HRMS** (ES+) *m/z* 427.2476 [calc'd for $C_{24}H_{36}O_5$ (M+Na) 427.2460].



A dry methylene chloride (1.0 mL) solution of oxalyl chloride (0.03 mL, 0.34 mmol) was cooled to -78°C before slow addition of dimethyl sulfoxide (0.05 mL, 0.70 mmol) in methylene chloride (0.5 mL). Ten min later a solution of diol (0.015 g, 0.037 mmol) in methylene chloride (1.5 mL) was added dropwise and stirred 15 minutes. Triethylamine (0.2 mL, 1.4 mmol) was added and the mixture was warmed to 0°C over 30 minutes. The reaction was quenched with sat NH_4Cl and extracted with methylene chloride (3 x 5.0 mL). The extracts were dried over $MgSO_4$ and evaporated. Purification using silica gel (10%-25% EtOAc/hexanes) afforded ketone (0.012 g, 80%).

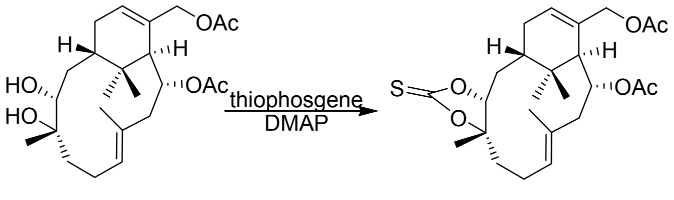
FTIR (thin film/NaCl) 3483, 2930, 2877, 1738, 1432, 1375, 1241, 1028, 930 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.87 (m, 1H), 5.45 (m, 1H), 5.03 (m, 1H), 4.63 (d, J=12.6 Hz, 1H), 4.48 (d, J=12.6 Hz, 1H), 3.22 (m, 1H), 2.76 (m, 1H), 2.58-2.15 (m, 7H), 2.08 (s, 3H), 2.06 (s, 3H), 1.95-1.78 (m, 2H), 1.71 (s, 3H), 1.27 (s, 3H), 1.17 (s, 3H), 0.74 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 217.5, 170.8, 169.8, 135.4, 132.3, 130.6, 130.1, 79.2, 73.7, 67.1, 54.0, 38.1, 35.4, 35.0, 34.6, 31.7, 29.7, 28.3, 26.5, 22.9, 22.4, 21.6, 21.0, 17.1; **HRMS** (ES+) *m/z* 443.2413 [calc'd for $C_{24}H_{36}O_6Na$ (M+Na) 443.2410].



1.44

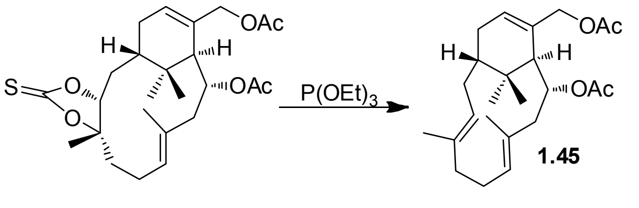
To a methanol (3.0 mL) solution of ketone (0.012 g, 0.029 mmol) was added $NaBH_4$ (0.011 g, 0.290 mmol). This reaction mixture was stirred at room temperature for 30 minutes before being quenched with 1M HCl (3.0 mL) and stirred for additional 30 minutes. At this point brine (4.0 mL) was added and the reaction mixture was extracted with ethyl acetate (3 x 5.0 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification using silica gel chromatography (50% EtOAc/hexanes) afforded 0.010 g of the product (80%).

FTIR (thin film/NaCl) 3482, 2921, 2851, 1737, 1454, 1376, 1245, 1078, 1027, 956 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.83 (m, 1H), 5.50 (m, 1H), 5.17 (m, 1H), 4.67 (d, J=12.8 Hz, 1H), 4.46 (d, J=12.8 Hz, 1H), 3.62 (m, 1H), 3.04-2.91 (bs, 2H), 2.77-2.13 (m, 8H), 2.08 (s, 3H), 2.07 (s, 3H), 2.01-1.84 (m, 2H), 1.75 (s, 3H), 1.64-1.37 (m, 2H), 1.25 (s, 3H), 1.17 (s, 3H), 0.73 (s, 3H); **HRMS** (ES+) *m/z* 445.2577 [calc'd for $C_{24}H_{38}O_6Na$ (M+Na) 445.2566].



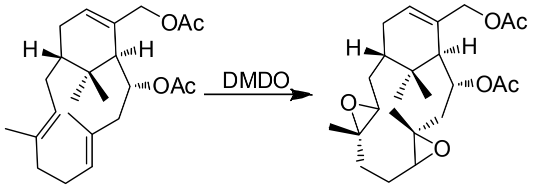
Diol (0.007 g, 0.017 mmol) was dissolved in methylene chloride (1.5 mL), and then treated with DMAP (0.081 g, 0.663 mmol) and thiophosgene (0.020 g, 0.174 mmol) dissolved in 0.5 mL methylene chloride. This reaction mixture was heated at 45°C for 20 hours at which point SiO_2 was added (color of solution changes from red to yellow) and stirring was continued for additional 10 minutes before passing the crude reaction mixture through a silica plug using 50% EtOAc/hexanes as the eluent. Further purification using silica gel chromatography (33% EtOAc/hexanes) afforded thiocarbonate (0.007 g, 91%).

FTIR (thin film/NaCl) 2953, 2884, 1800, 1734, 1436, 1368, 1300, 1240, 1096, 1025, 951, 917, 852 cm^{-1}; ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 5.77 (m, 1H), 5.45 (m, 1H), 5.21 (m, 1H), 4.78 (m, 1H), 4.63 (m, 1H), 4.46 (m, 1H), 2.60 (m, 1H), 2.43-2.18 (m, 7H), 2.08 (s, 3H), 2.06 (s, 3H), 2.04-1.98 (m, 2H), 1.89-1.75 (m, 2H), 1.72 (s, 3H), 1.45 (s, 3H), 1.22 (s, 3H), 0.77 (s, 3H); **HRMS** (ES+) *m/z* 487.2125 [calc'd for $C_{25}H_{36}O_6NaS$ (M+Na) 487.2130].



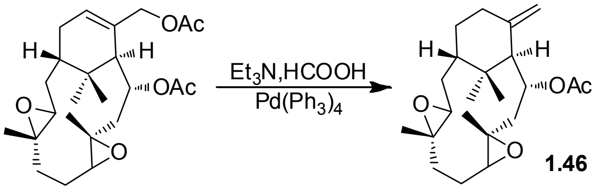
Thiocarbonate (0.007 g, 0.015 mmol), dissolved in neat triethyl phosphate (1.5 mL, 7.7 mmol) was heated at 160°C for 15 hours. The reaction mixture was cooled to room temperature and all excess triethyl phosphate was removed *in vacuo*. Purification using silica gel chromatography (12% EtOAc/hexanes) afforded 0.005 g of product (86%).

FTIR (thin film/NaCl) 2921, 2854, 1735, 1661, 1434, 1371, 1240, 1021, 957, 803, 737 cm^{-1}; ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 5.65 (m, 1H), 5.38 (m, 1H), 5.23 (m, 1H), 5.10 (m, 1H), 4.53 (m, 1H), 4.40 (m, 1H), 2.75 (m, 1H), 2.46-2.08 (m, 7H), 2.05 (s, 3H), 2.04 (s, 3H), 1.92-1.73 (m, 4H), 1.72 (s, 3H), 1.54 (s, 3H), 1.30 (s, 3H), 0.79 (s, 3H); ^{13}**C NMR** δ 171.0, 170.0, 137.4, 134.3, 132.1, 129.6, 128.7, 127.8, 78.6, 68.6, 54.8, 44.6, 42.8, 39.2, 36.6, 33.3, 29.5, 28.7, 26.3, 23.9, 21.9, 21.3, 16.5, 15.0; **HRMS** (EI) *m/z* 411.2524 [calc'd for $C_{24}H_{36}O_4$ (M+Na) 411.2511]. **Carbon shifts extracted from HSQC and HMBC spectra.**



Triene starting material (0.002 g, 0.005 mmol) was dissolved in acetone (1.0 mL) and treated with a freshly prepared DMDO solution (0.05 mL, 0.1M in acetone, 0.005 mmol). The C5-C6 olefin is rapidly consumed (5 minutes), while the C9-C12 olefin takes another 4 hours to be oxidized. The solvent was evaporated the crude reaction mixture was carried on to the next step.

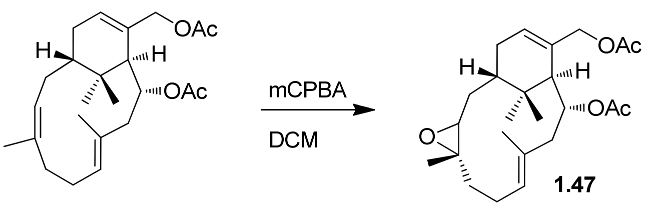
^{1}H NMR (600 MHz, $CDCl_3$) δ 5.96 (m, 1H), 5.58 (m, 1H), 4.67 (d, J=12.4 Hz, 1H), 4.58 (d, J=12.4 Hz, 1H), 2.95 (dd, J=4.9, 8.2 Hz, 1H), 2.84 (dd, 3.0, 7.4 Hz, 1H), 2.49-2.27 (m, 3H), 2.13 (m, 1H), 2.06 (s, 3H), 2.05 (s, 3H), 2.04-2.00 (m, 2H), 1.95-1.85 (m, 2H), 1.78 (m, 1H), 1.69 (m, 1H), 1.46 (m, 2H), 1.35 (s, 3H), 1.31 (s, 3H), 1.09 (s, 3H), 0.76 (s, 3H); **HRMS** (ES+) *m/z* 443.2402 [calc'd for $C_{24}H_{36}O_6$ (M+Na) 443.2410].



1.46

Bis-epoxide starting material was dissolved in dry THF (0.6 mL) and treated consecutively with Et_3N/HCOOH (0.005 g Et_3N and 0.002 g HCOOH, 0.050 mmol dissolved in 0.2 mL THF) and $Pd(PPh_3)_4$ (0.006 g, 0.005 mmol dissolved 0.1 mL THF). This reaction mixture was heated at 75°C for 15 hours before being evaporated to dryness. Purification using silica gel chromatography (33% EtOAc/hexanes) afforded exo-olefin product (0.001 g, 55%).

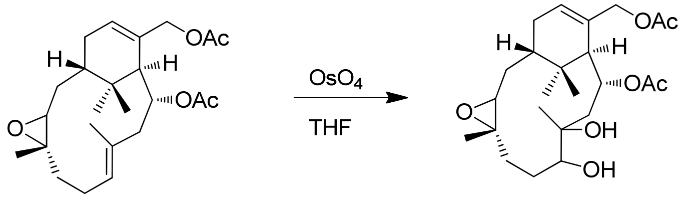
FTIR (thin film/NaCl) 2993, 2920, 2854, 1734, 1600, 1462, 1451, 1248, 1235, 1078, 1018, 957, 889 cm^{-1}; **^{1}H NMR** (400 MHz, C_6D_6) δ 5.52 (m, 1H), 4.70 (m, 1H), 4.58 (m, 1H), 3.09-3.01 (m, 2H), 2.62-2.50 (m, 1H), 2.28-2.02 (m, 8H), 1.97 (s, 3H), 1.93 (m, 1H), 1.79-1.65 (m, 2H), 1.51 (s, 3H), 1.31 (s, 3H), 1.26 (s, 3H), 0.98-0.85 (m, 2H), 0.83 (s, 3H); **^{13}C NMR** δ 168.6, 127.9, 111.7, 70.4, 65.1, 64.7, 61.2, 60.4, 58.8, 43.2, 40.0, 37.6, 36.8, 32.9, 31.3, 30.4, 30.2, 30.1, 24.5, 20.7, 18.7, 15.9; **HRMS** (ES+) *m/z* 363.2538 [calc'd for $C_{22}H_{35}O_4$ (M+H) 363.2535]. **Carbon chemical shifts extracted from HSQC and HMBC data.**



Diene starting material (0.014 g, 0.036 mmol) was dissolved in dry DCM and cooled to 0°C. A freshly prepared solution of mCPBA (0.013 g, 0.072 mmol) in 2.0 mL of DCM was added drop-wise over 10 minutes and the reaction was stirred an additional 20 minutes. The reaction was then quenched by adding 3.0 mL of saturated sodium thiosulfate, extracted with DCM, and dried over sodium sulfate. Purification using silica gel chromatography (20% EtOAc/hexanes) afforded monoepoxide (0.006 g, 40%).

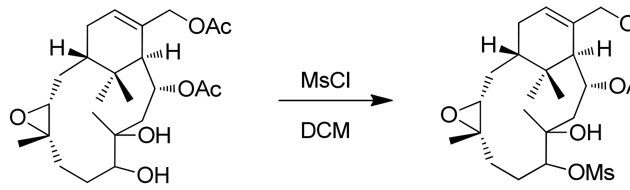
1.47

^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.92 (m, 1H), 5.47 (m, 1H), 5.36 (m, 1H), 4.66 (d, J=12.4 Hz, 1H), 4.48 (d, J=12.4 Hz, 1H), 2.90 (m, 1H), 2.81 (m, 1H), 2.60-2.14 (m, 9H), 2.09 (s, 3H), 2.07 (s, 3H), 2.04-1.88 (m, 2H), 1.74 (s, 3H), 1.37 (s, 3H), 0.98 (s, 3H), 0.73 (s, 3H).



Bis-acetate epoxide (0.024 g, 0.059 mmol) was dissolved in THF (3.0 mL) and cooled to 0°C. Freshly distilled pyridine (0.065 g) was added followed by OsO_4 in THF (0.693 g, 1.15 eq, 0.9 mL) and the reaction was stirred for 10 min and then the bath was removed. After 18 hours at room temperature, $NaHSO_3$ (2.0 mL) and $MeSO_2NH_2$ were added and stirred 24 hours to ensure complete quenching of the osmium. The reaction was then concentrated and purified with silica gel chromatography (50% EtOAc/hexanes) to give epoxy-diol (0.024 g, 93%).

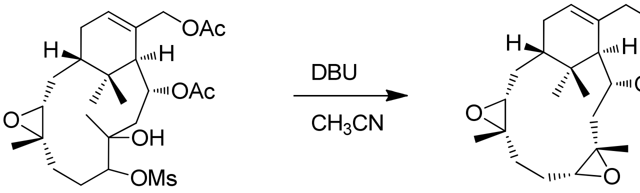
^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.90 (m, 1H), 5.48 (m, 1H), 4.69 (d, J = 12.7 Hz, 1H), 4.58 (d, J = 12.7 Hz, 1H), 3.74 (m, 1H), 2.95 (dd, J = 15.8, 9.3, 1H), 2.86 (m, 1H), 2.35-2.11 (m, 4H), 2.10 (s, 3H), 2.04 (s, 3H), 1.99-1.76 (m, 5H), 1.65-1.48 (m, 2H), 1.33 (s, 3H), 1.28 (s, 3H), 1.14 (s, 3H).



1.48

Diol starting material (0.024 g, 0.055 mmol) was dissolved in dry DCM (1.2 mL) and cooled to 0°C. Freshly distilled pyridine (0.086 g, 20 eq.) was added followed by MsCl (0.093 g, 15 eq.) in DCM (0.3 mL). The reaction was maintained 10 minutes before the bath was removed and stirred 2 additional hours. The volatiles were then removed and the residue was purified using silica gel chromatography (50% EtOAc/hexanes) to give mono mesylate (0.028 g, 99%).

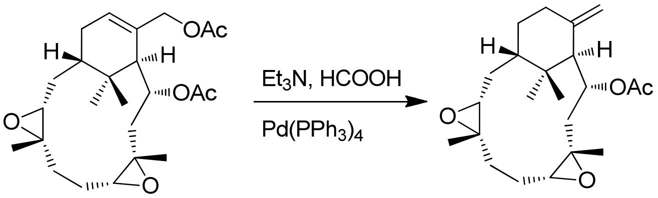
^{1}H-NMR (500 MHz, CDCl$_3$) δ 5.88 (m, 1H), 5.47 (d, J = 9.42 Hz, 1H), 4.76 (d, J = 13.2 Hz, 1H), 4.62 (m, 1H), 4.53 (d, J = 13.2 Hz, 1H), 3.07 (s, 3H), 2.85 (m, 1H), 2.32-2.02 (m, 5H), 2.11 (s, 3H), 2.06 (s, 3H), 1.95-1.80 (m, 3H), 1.65-1.51 (m, 3H), 1.41 (s, 3H), 1.26 (s, 3H), 1.13 (s, 3H), 0.76 (s, 3H).



1.49

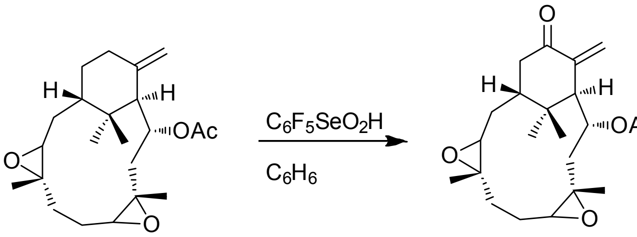
Mono mesylate (0.028 g, 0.054 mmol) was dissolved in dry CH$_3$CN (1.2 mL) at room temperature. Excess DBU (0.058 g, 7 eq.) was then added and the reaction was stirred 12 hours until starting material was consumed. The solvent was removed and the residue was purified using silica gel chromatography (50% EtOAc/hexanes) to give desired bis epoxide (0.007 g, 33%).

^{1}H-NMR (300 MHz, CDCl$_3$) δ 5.96 (m, 1H), 5.58 (m, 1H), 4.68 (d, J = 11.9 Hz, 1H), 4.58 (d, J = 11.9 Hz, 1H), 2.95 (m, 1H), 2.85 (m, 1H), 2.56-2.25 (m, 5H), 2.06 (s, 3H), 2.05 (s, 3H), 1.97-1.61 (m, 4H), 1.53-1.39 (m, 2H), 1.35 (s, 3H), 1.31 (s, 3H), 1.10 (s, 3H), 0.76 (s, 3H); **^{13}C NMR** δ 170.8, 170.0, 131.0, 130.7, 70.7, 67.2, 64.4, 62.6, 59.8, 58.5, 51.5, 34.1, 33.3, 32.6, 29.8, 28.4, 27.3, 25.0, 22.9, 22.3, 22.3, 22.2, 21.5, 20.9. **Carbon chemical shifts extracted from HSQC and HMBC data.**



Bis-epoxide (0.004 g, 0.008 mmol) was added to a flame dried flask along with freshly prepared $Pd(PPh_3)_4$ and degassed THF (1.2 mL). To this solution was added a solution of formic acid (3.2 µL, 0.08 mmol), triethylamine (0.01 mL, 0.08 mmol) and THF (0.6 mL). This mixture was heated at 75°C for 18 hours. The solvent was then removed and the residue was purified using silica gel chromatography (30% EtOAc/hexane) to give pure exo olefin (0.003 g, 98%).

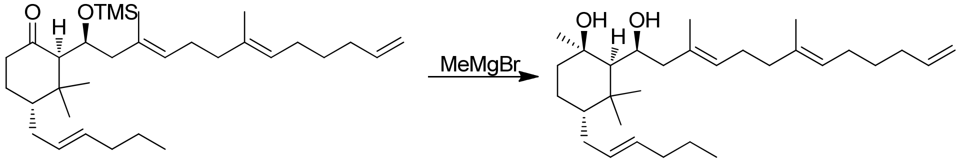
^{1}H-NMR (400 MHz, C_6D_6) δ 5.63 (m, 1H), 4.73 (m, 1H), 4.65 (m, 1H), 2.85-2.69 (m, 2H), 2.59 (dd, J = 3.4, 16.2 Hz, 1H), 2.35 (dd, J = 4.5, 9.9 Hz, 1H), 2.13 (dd, J = 6.0, 15.1 Hz, 1H), 2.00-1.89 (m, 2H), 1.87-1.76 (m, 1H), 1.74 (s, 3H), 1.71-1.16 (m, 8H), 1.13 (s, 3H), 1.04 (s, 3H), 0.88 (s, 3H), 0.67 (s, 3H).



1.50

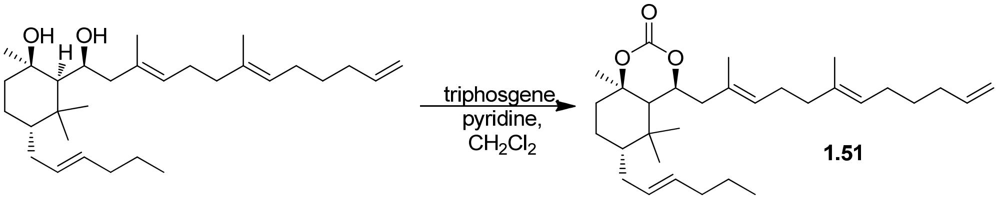
Exo-olefin (0.003 g, 0.008 mmol) was dissolved in dry benzene (3.5 mL) and then freshly distilled pyridine (0.07 mL, 0.83 mmol) was added at room temperature. To this was added pentafluorobenzene selenic acid and the reaction was heated at 80°C for 2 hrs. The solvent was then removed and the residue was purified using silica gel chromatography (50% EtOAc/hexanes) to yield an isomer of hypoestoxide (0.001 g).

^{1}H-NMR (600 MHz, $CDCl_3$) δ 6.32 (m, 1H), 5.53 (m, 1H), 5.35 (m, 1H), 2.92 (m, 1H), 2.82 (m, 1H), 2.76 (d, J = 4.8 Hz, 1H), 2.70-2.62 (m, 2H), 2.50 (dd, J = 1.7, 15.2 Hz, 1H), 2.23 (m, 1H), 2.15-2.00 (m, 2H), 2.06 (s, 3H), 1.95-1.81 (m, 3H), 1.78-1.59 (m, 2H), 1.33 (s, 3H), 1.21 (s, 3H), 1.17 (s, 3H), 0.86 (s, 3H);); **^{13}C NMR** δ 198.7, 169.9, 144.4, 127.1, 75.7, 63.8, 61.9, 60.4, 58.5, 55.5, 42.1, 35.5, 34.3, 33.3, 29.2, 27.5, 26.1, 24.1, 23.9, 23.4, 22.9, 21.7. **HRMS** (ES+) *m/z* 399.2159 [calc'd for $C_{22}H_{32}O_5Na$ (M+Na) 399.2147]. **Carbon chemical shifts extracted from HSQC and HMBC data.**



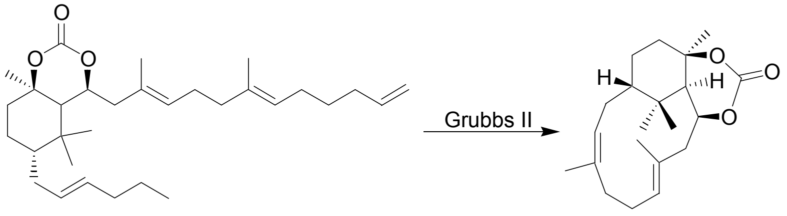
Ketone starting material (0.058 g, 0.120 mmol) was dissolved in dry THF (2.5 mL), cooled to 0°C when an ethereal solution of MeMgBr (0.43 mL, 3.0M, 1.28 mmol) was added dropwise. After 15 minutes the reaction was allowed to warm to room temperature over an hour. This mixture was quenched with sat. NH_4Cl, acidified to pH 1 (HCl), and stirred 10 minutes. Addition of NaCl and extraction with EtOAc (8 x 8.0 mL) followed by drying over $MgSO_4$ and concentration gave yellow oil that was purified over silica gel (15% EtOAc/hexanes) to give product (0.060 g, 60%).

FTIR (thin film/NaCl) 3392, 2957, 2940, 2871, 1453, 1386, 1180, 1102, 1043, 993, 968, 910 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.81 (m, 1H), 5.35 (m, 2H), 5.23 (m, 1H), 5.12 (m, 1H), 4.99 (m, 1H), 4.94 (m, 1H), 4.37 (m, 1H), 2.51 (dd, J=10.8, 13.4 Hz, 1H), 2.32-1.77 (m, 16H), 1.64 (s, 3H), 1.59 (s, 3H), 1.51-1.37 (m, 7H), 1.35 (s, 3H), 1.33 (s, 3H), 1.05 (s,3H),0.88(t, J=7.3 Hz,3H); **^{13}C NMR** (75MHz,$CDCl_3$) δ 138.9, 134.8, 133.0, 131.0, 130.2, 128.4, 124.9, 114.3, 74.2, 70.1, 51.8, 48.4, 48.3, 39.5, 37.3, 36.2, 34.7, 33.4, 32.4, 30.9, 30.4, 29.0, 27.4, 27.3, 26.4, 22.7, 20.1, 15.8, 15.7, 13.7; **HRMS** (ES+) *m/z* 467.3867 [calc'd for $C_{30}H_{52}O_2Na$ (M+Na$^+$) 467.3865].



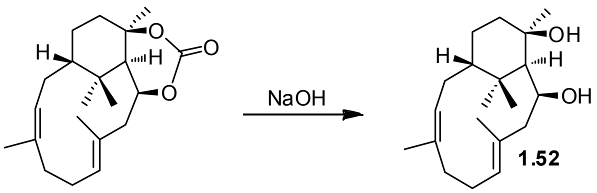
Pyridine (0.17 mL, 2.03 mmol) was added to the diol (0.060 g, 0.140 mmol) dissolved in methylene chloride (5.0 mL). This mixture was cooled to -78°C and a methylene chloride (3.0 mL) solution of triphosgene (0.040 g, 0.140 mmol) was added slowly. The reaction was warmed to room temperature (1 hour) and stirred for 18 hours. The reaction mixture was quenched with sat. NH_4Cl (2.0 mL), and acidified using 1M HCl (1.0 mL). The organic layer was separated and the aqueous layer was extracted using ethyl acetate (6 x 5.0 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification with silica gel (16% EtOAc/hexanes) afforded the carbonate product (0.048 g, 75%).

FTIR (thin film/NaCl) 2955, 2926, 2872, 1735, 1451, 1368, 1294, 1215, 1166, 1085, 969, 909, 770 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.82 (m, 1H), 5.51-5.18 (m, 3H), 5.12 (m, 1H), 4.99 (m, 1H), 4.94 (m, 1H), 2.59 (m, 1H), 2.42-2.17 (m, 3H), 2.19-1.73 (m, 12H), 1.69 (s, 3H), 1.59 (s, 1H), 1.54 (s, 3H), 1.52-1.23 (m, 9H), 1.18 (s, 3H), 1.09 (s, 3H), 0.88 (m, 3H); **^{13}C NMR** δ 150.3, 139.0, 135.2, 132.2, 131.0, 129.0, 128.3, 124.9, 114.5, 79.5, 79.1, 43.6, 39.5, 39.2, 35.9, 34.7, 33.6, 32.9, 31.0, 30.3, 29.9, 29.3, 27.5, 26.9, 25.6, 24.0, 23.7, 22.9, 16.7, 16.1, 13.9; **HRMS** (ES+) *m/z* 471.3853 [calc'd for $C_{31}H_{51}O_3$ (M+H$^+$) 471.3838].



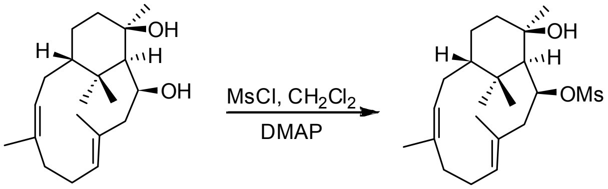
The metathesis precursor (0.046 g, 0.098 mmol) was dissolved in dry toluene (204.0 mL). This mixture was brought to reflux, with a stream of nitrogen constantly bubbling through the solution, before addition of Grubbs second generation catalyst (0.025 g, 0.030 mmol). After 8 minutes the crude reaction mixture was immersed in an ice-water bath and the before mentioned isocyanide (0.006 g, 0.054 mmol) in 0.5 mL of methanol was added to render the catalyst inactive by stirring 15 min at room temp. The cold toluene solution was then filtered through a plug of silica washing with 30% EtOAc/hexanes. The solvent was evaporated and the crude mixture was purified on silica using 10% EtOAc/hexanes affording the macrocycle (0.013 g, 40%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.55 (m, 1H), 5.38 (m, 1H), 4.60 (m, 1H), 3.03 (dd, J=14.1, 11.7 Hz, 1H), 2.52 (d, 14.1 Hz, 1H), 2.38-1.89 (m, 13H), 1.74 (s, 3H), 1.61 (s, 3H), 1.26 (s, 3H), 0.99 (s, 3H), 0.98 (s, 3H); **^{13}C NMR** δ 154.5, 135.9, 132.8, 128.8, 125.2, 86.1, 77.34, 56.4, 44.1, 43.8, 38.2, 35.6, 33.5, 32.0, 30.5, 29.7, 27.6, 25.3, 24.2, 24.1, 15.2; **HRMS** (EI+) *m/z* 332.2347 [calc'd for $C_{21}H_{32}O_3$ (M+) 332.2352]. **Carbon chemical shifts extracted from HSQC and HMBC data.**



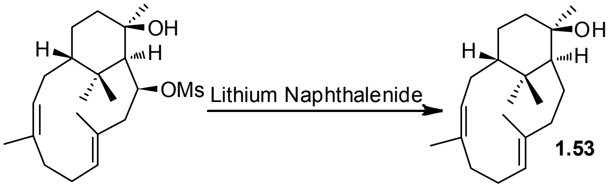
To a dioxane (1.5 mL) solution of the carbonate (0.024 g, 0.074 mmol) was added 1M NaOH (1.5 mL). This mixture was stirred vigorously at room temperature for 6 hours, at which point it was diluted with brine (2.0 mL), saturated with solid NaCl and extracted with ethyl acetate (5 x 3.0 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification using silica gel chromatography (30% EtOAc/hexanes) gave diol product (0.018 g, 71%).

FTIR (thin film/NaCl) 3316, 2947, 2927, 2870, 1653, 1558, 1540, 1457, 1341, 1109, 1000, 913, 801 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.50 (m, 1H), 5.31 (m, 1H), 4.12 (d, J=9.7 Hz, 1H), 3.13 (dd, J=14.2, 9.7 Hz, 1H), 2.41-1.79 (m, 15H), 1.74 (s, 3H), 1.72 (s, 3H), 1.48 (s, 3H), 0.96 (s, 3H), 0.94 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 135.2, 132.3, 129.9, 125.8, 75.8, 71.7, 63.0, 47.9, 44.8, 41.0, 36.4, 35.9, 32.2, 29.7, 24.8, 24.5, 24.4, 24.1, 22.9, 15.3; **HRMS** (ES+) *m/z* 329.245 [calc'd for $C_{20}H_{34}O_2$ (M+Na) 329.2457].



To a dichloromethane (1.5 mL) solution of the diol (0.005 g, 0.016 mmol) was added dimethyl amino pyridine (0.002 g, 0.016 mmol) and pyridine (0.013 g, 0.163 mmol). A stock solution of mesyl chloride (0.019 g, 0.163 mmol) was next added at room temperature and was stirred 20 hours. The reaction mixture was concentrated *in vacuo* and purified using silica gel chromatography (30% EtOAc/hexanes) afforded mesylate (0.003 g, 51%).

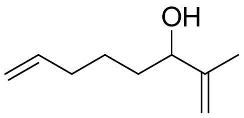
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.51 (m, 1H), 5.42-5.36 (m, 2H), 3.45 (dd, J=10.1, 14.9 Hz, 1H), 2.49-1.83 (m, 15H), 1.80 (s, 3H), 1.73 (s, 3H), 1.47 (s, 3H), 1.07 (s, 3H), 0.98 (s, 3H).

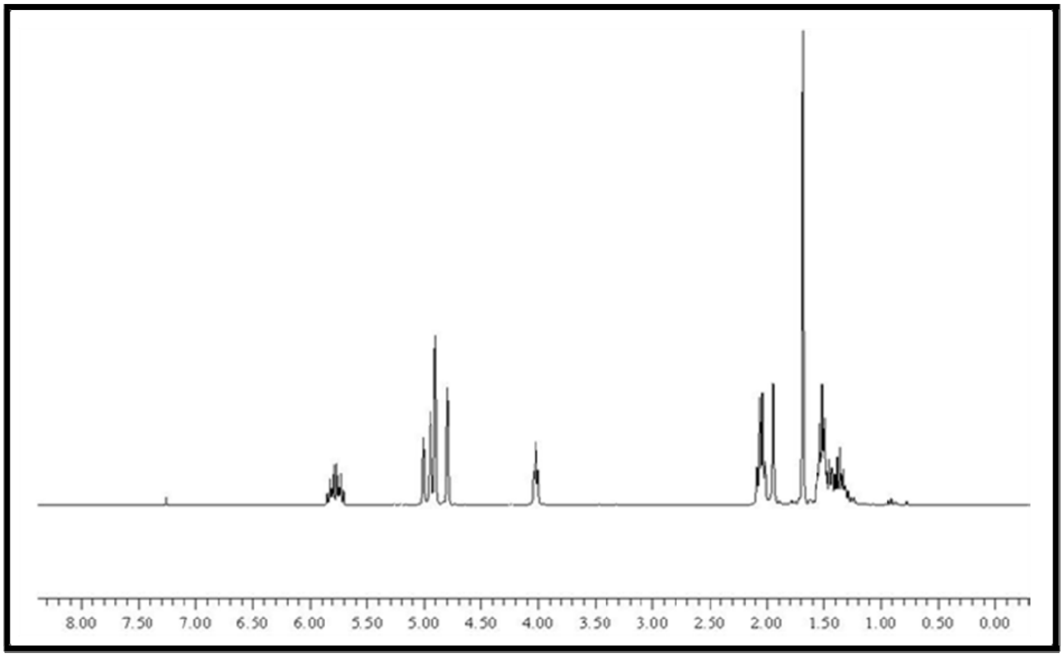


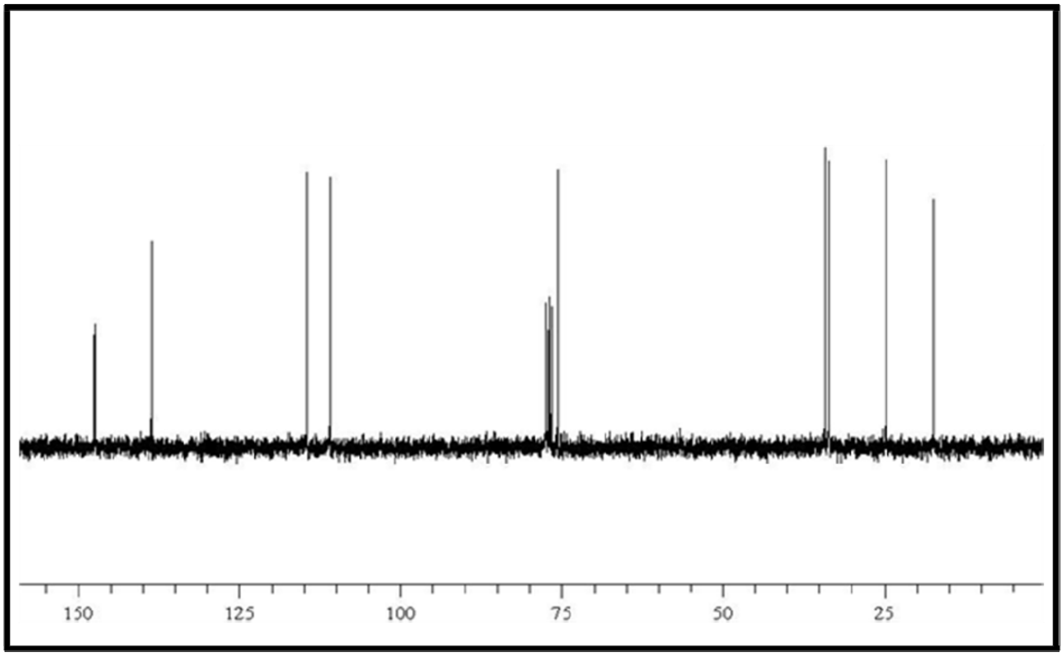
A solution of naphthalene (1.300 g, 0.010 mol) and THF (10 mL) was stirred at 23°C for 10 minutes. Freshly cleaned lithium wire was next added to the reaction and allowed to stir 2 hours at which point it had assumed a dark green color. An aliquot of this was transferred to a fresh vial and cooled to -78°C under nitrogen. Next starting mesylate (0.002 g, 0.005 mmol) was dissolved in dry THF (0.5 mL) and added slowly to the reaction mixture over 3 minutes. The reaction was allowed to stir 10 minutes and then it was quenched with saturated ammonium chloride. The reaction was brought to room temp and extracted with ethyl acetate (4 x 2.0 mL) and dried over $MgSO_4$. The extracts were concentrated and purified with silica gel chromatography to give pure deoxygenated product (1.4 mg, 93%).

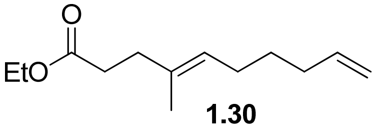
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.54 (m, 1H), 5.26 (m, 1H), 2.50-1.77 (m, 17H), 1.75 (s, 3H), 1.67 (s, 3H), 1.42 (s, 3H), 1.28 (s, 3H), 0.92 (s, 3H)**;** **^{13}C NMR** δ 135.0, 134.9, 128.6, 125.7, 73.4, 57.8, 44.6, 40.6, 37.4, 36.5, 34.6, 32.2, 29.7, 29.6, 27.2, 24.9, 24.6, 24.0, 22.9, 15.2; **HRMS** (EI+) *m/z* 290.2613 [calc'd for $C_{20}H_{34}O$ (M+) 290.2610]. **Carbon chemical shifts extracted from HSQC and HMBC data.**

A1.2 NMR Data for Chapter 1





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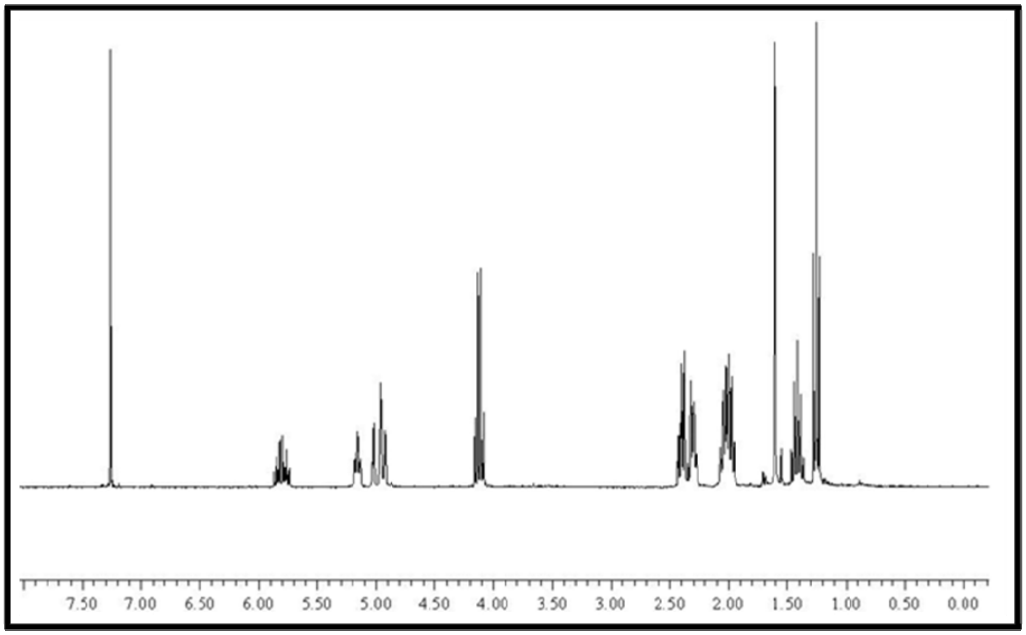
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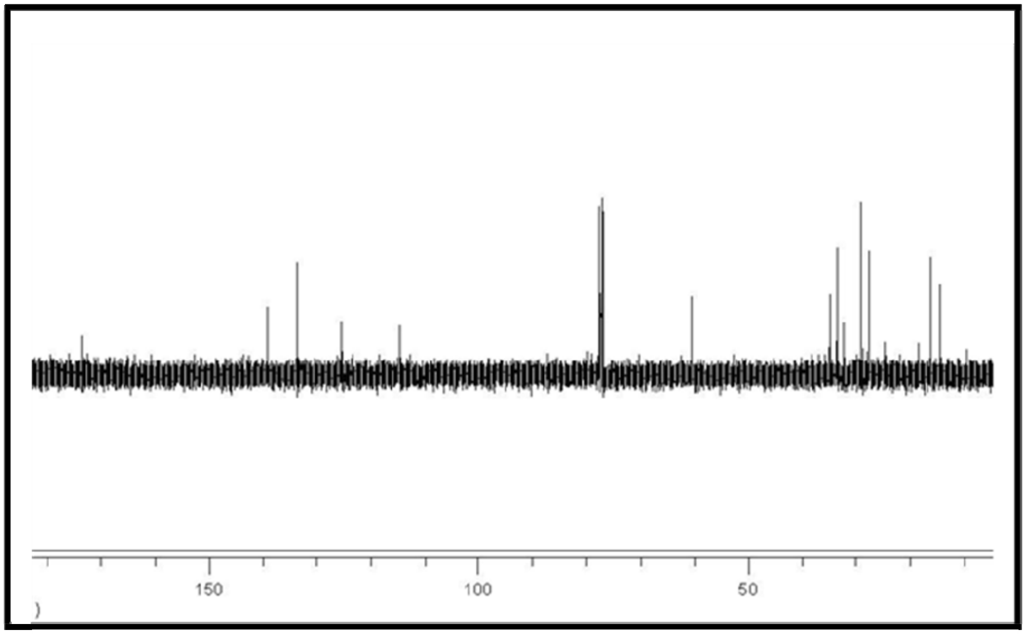
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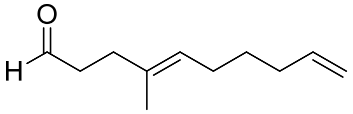
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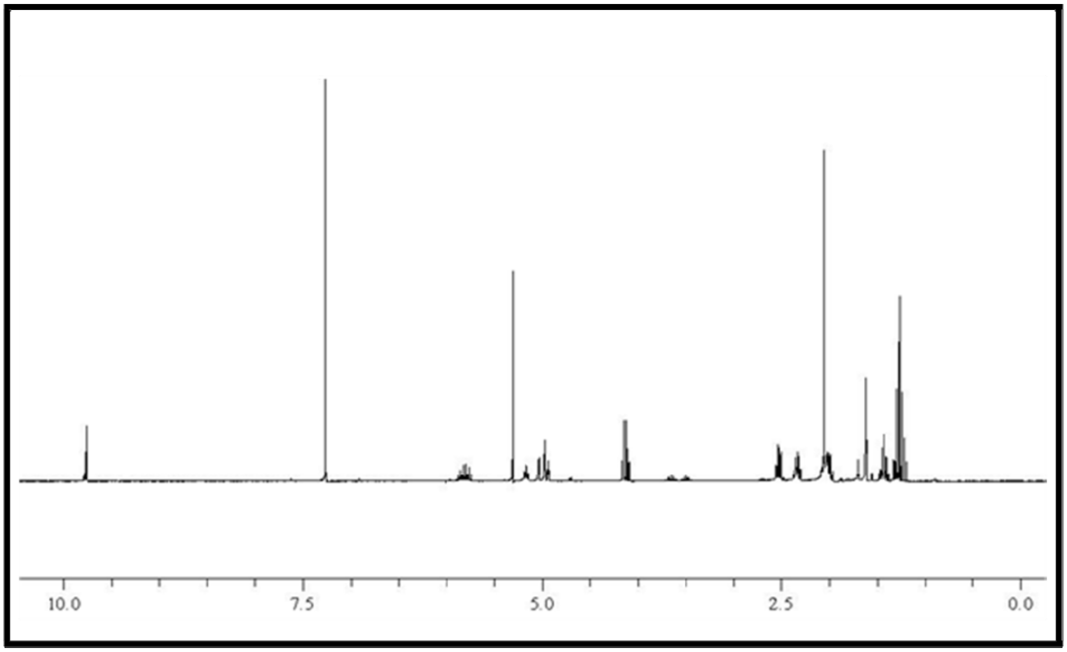
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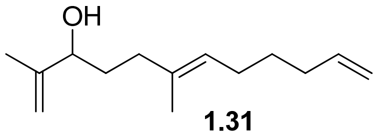

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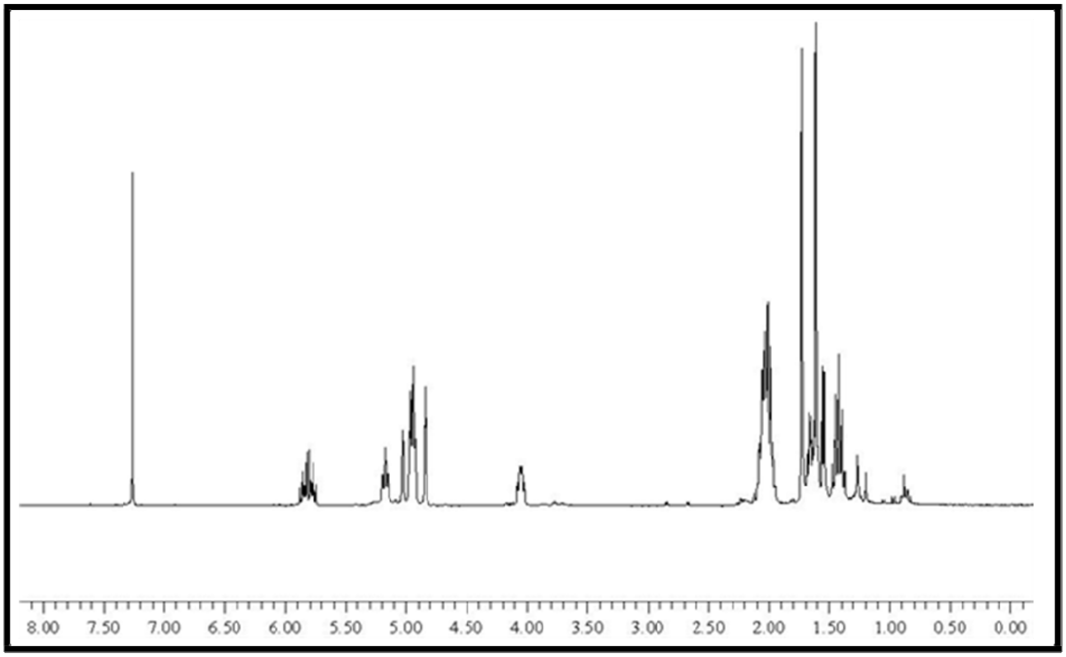
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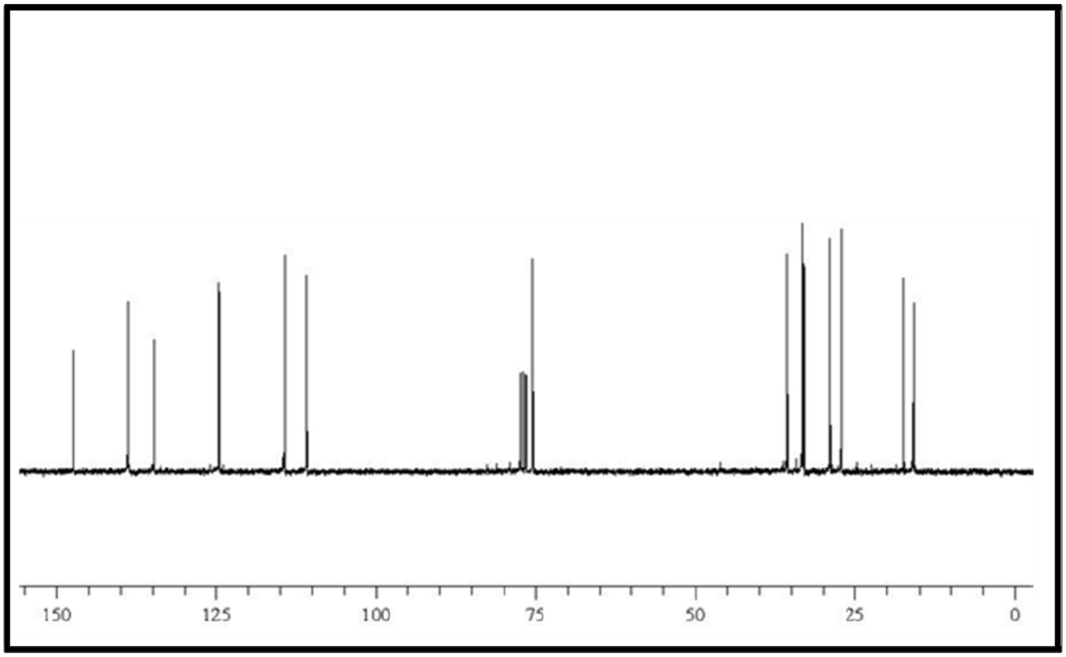
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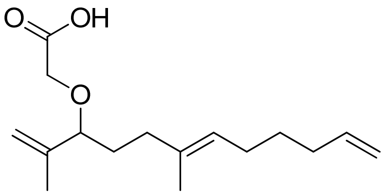
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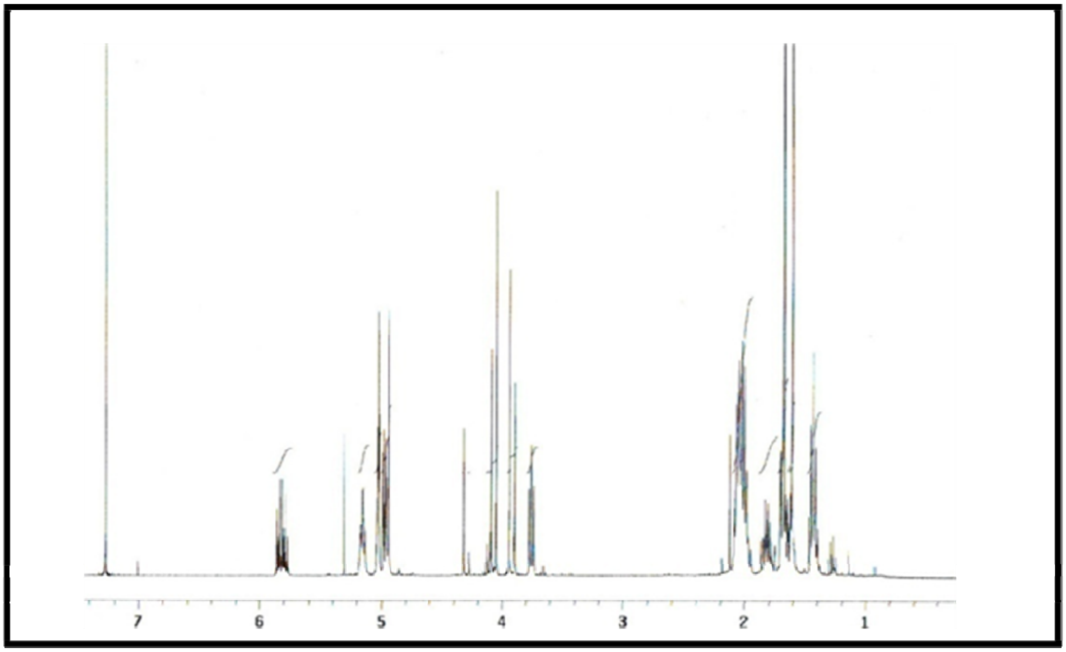
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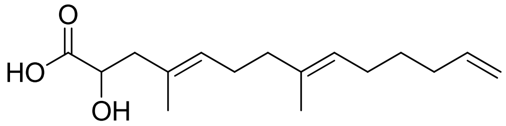
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HO
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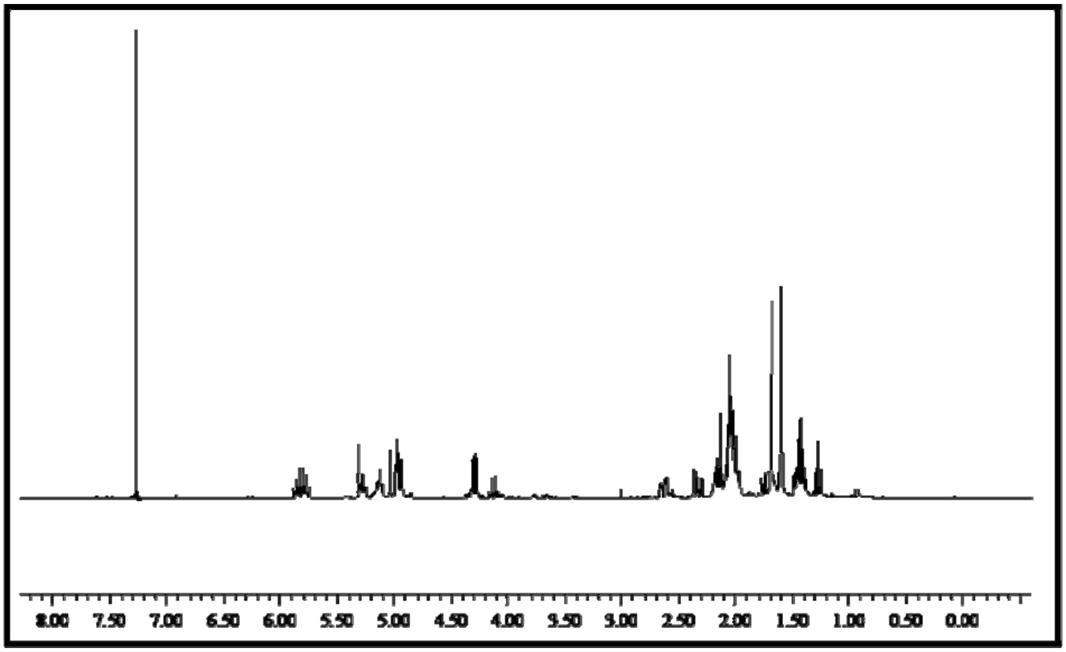
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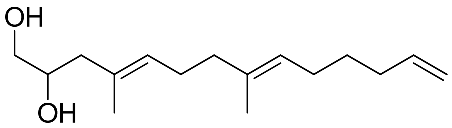
OH
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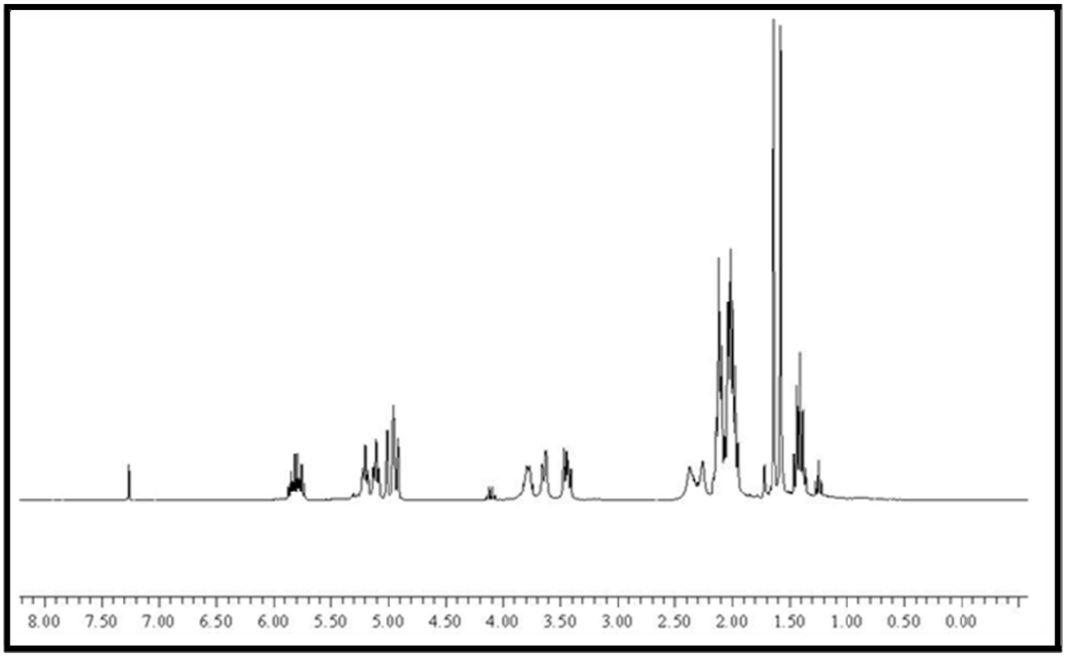
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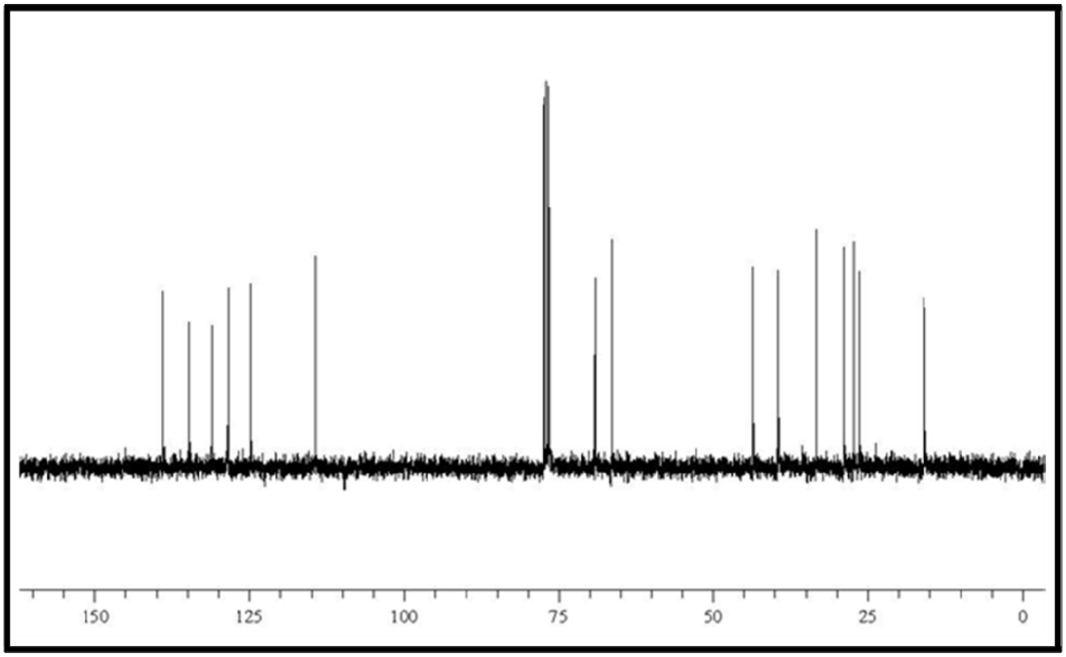
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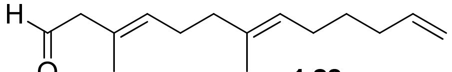

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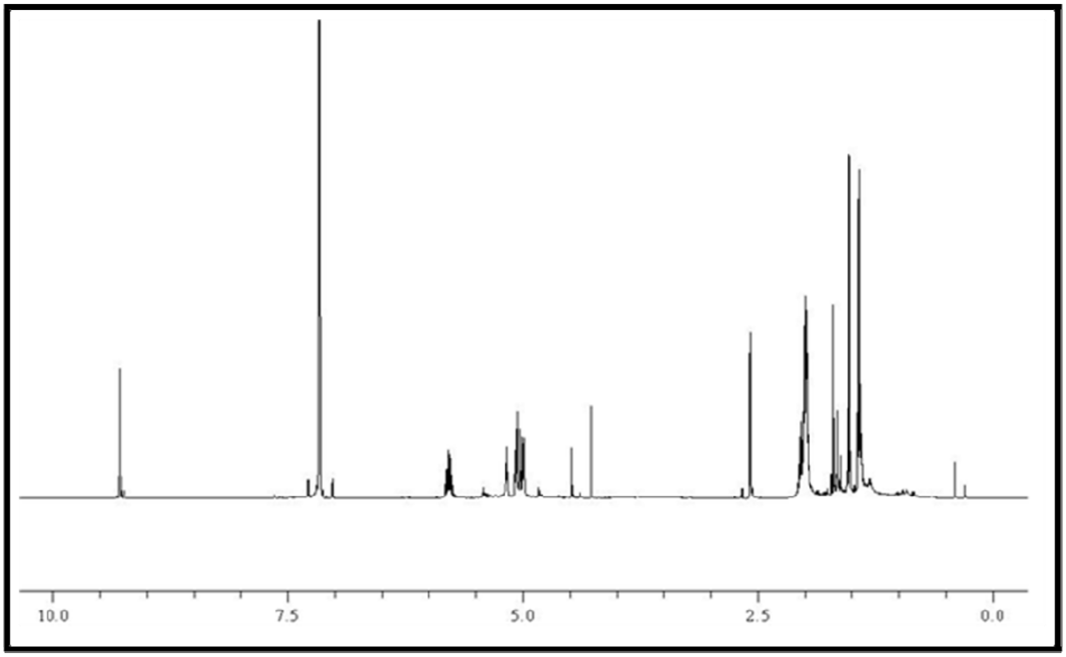

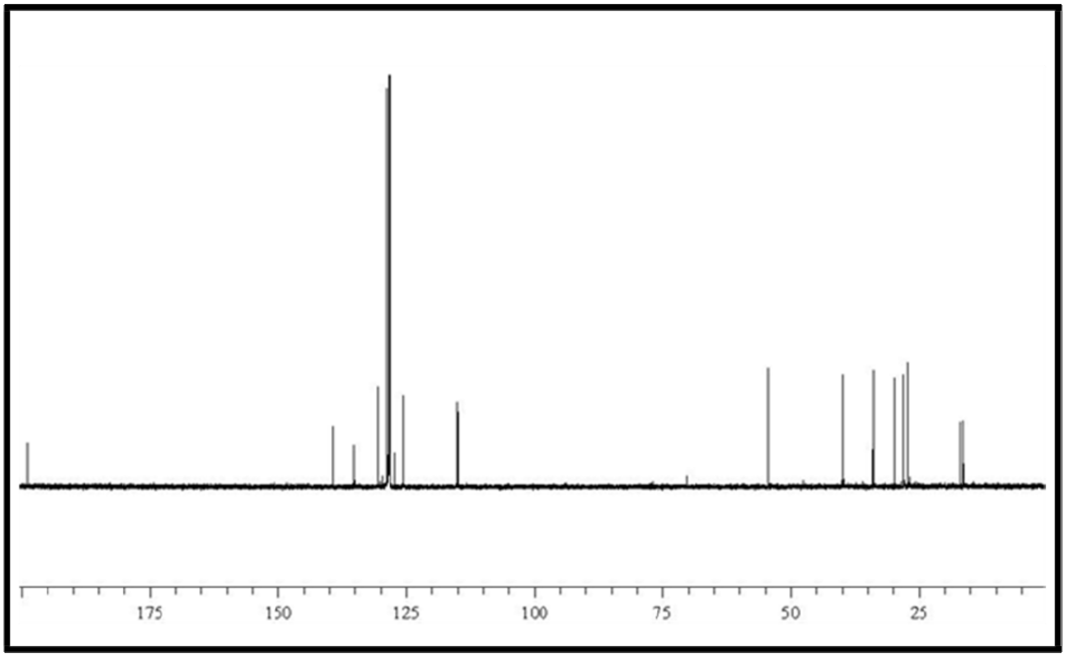

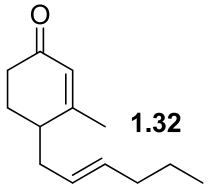

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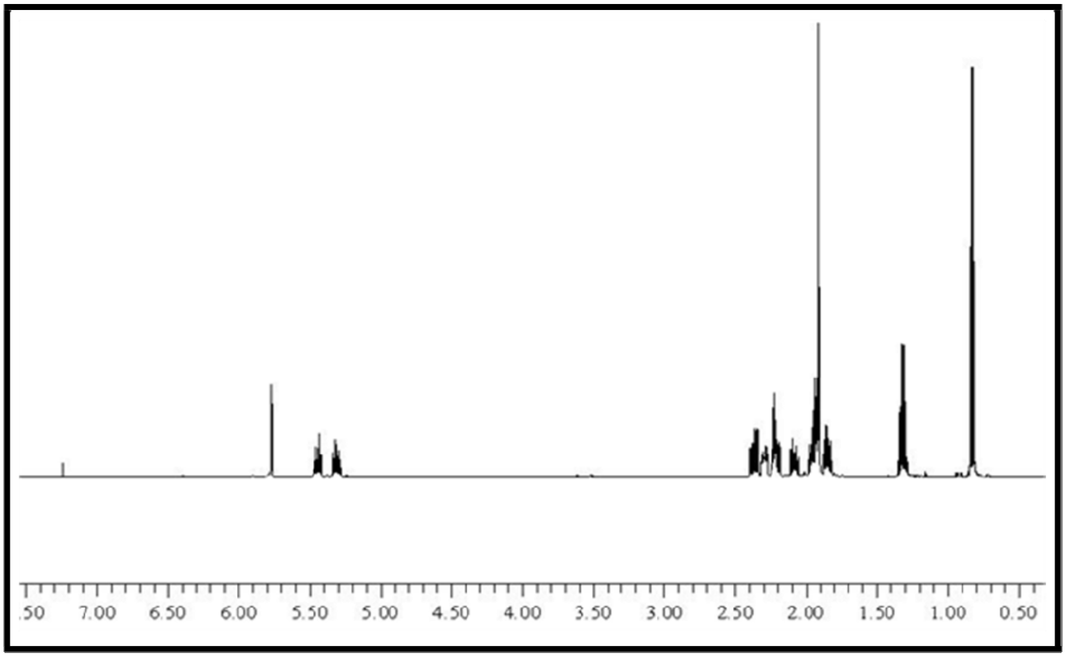

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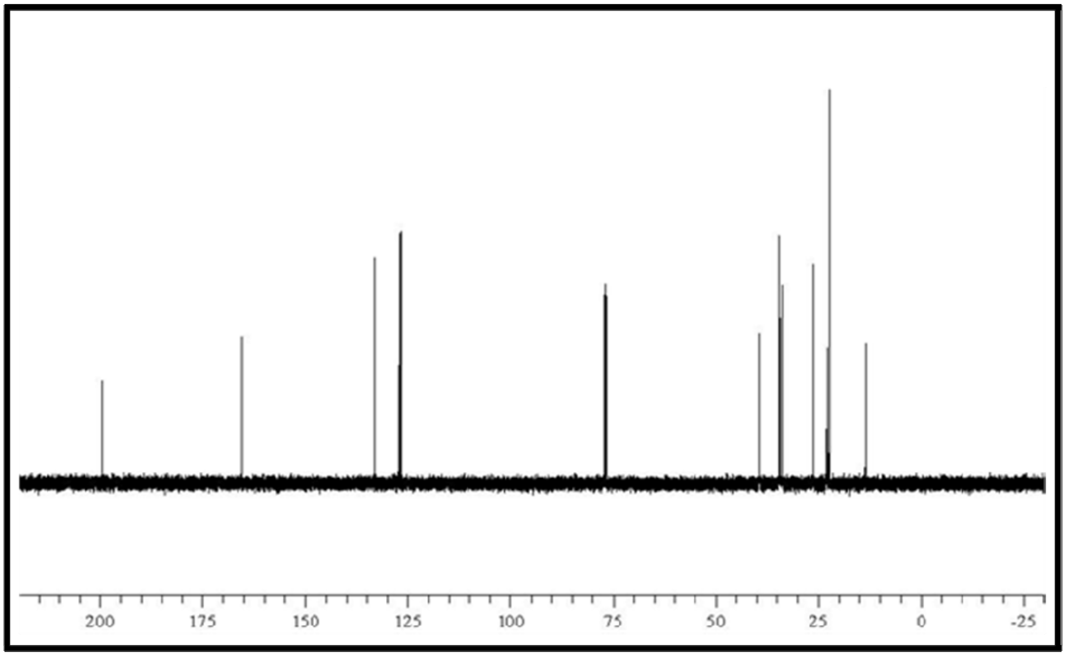
3.00
2.50
2.00
1.50
1.00
0.50



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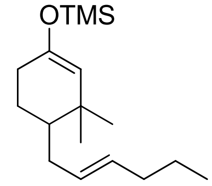
75
50
25
0
-25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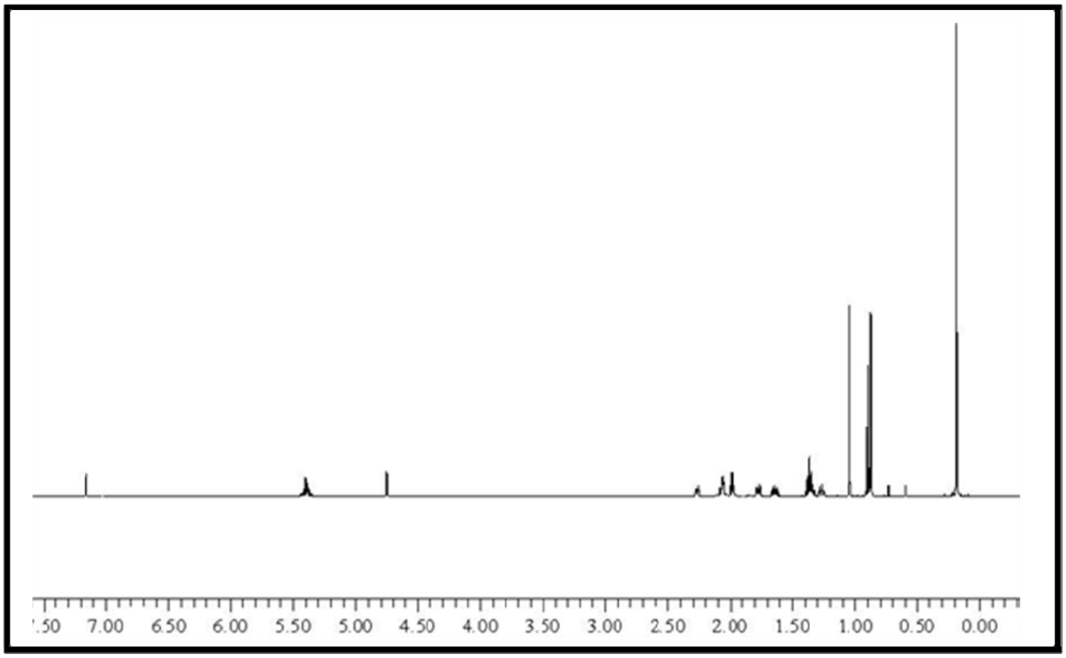
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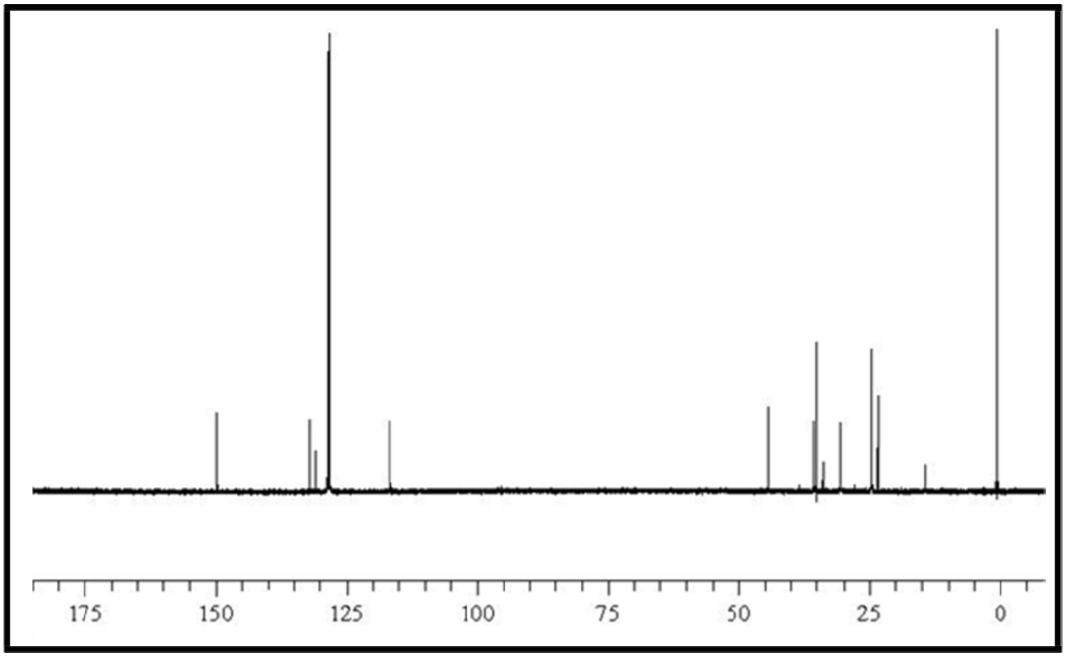
0.00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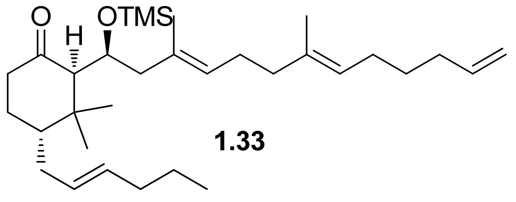
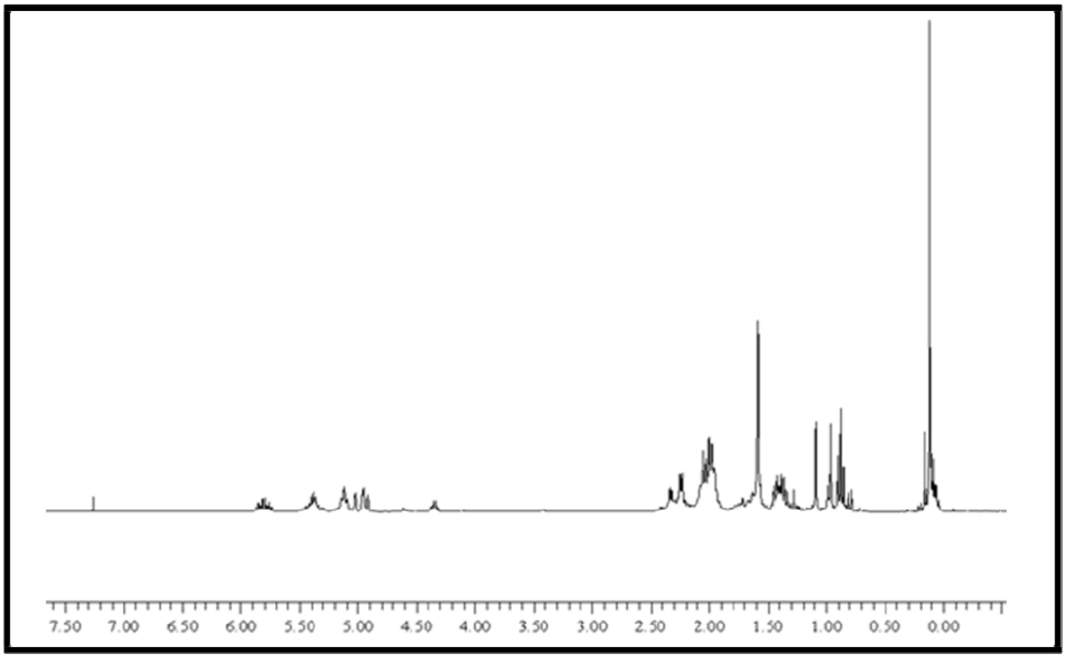

O
H
OTMS

1.33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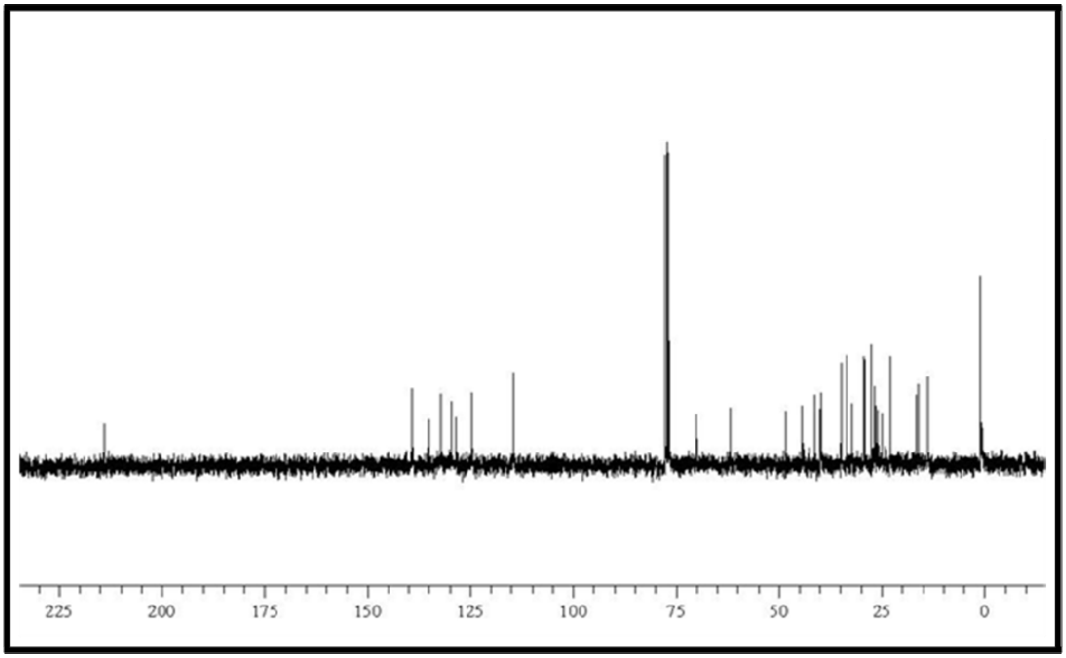
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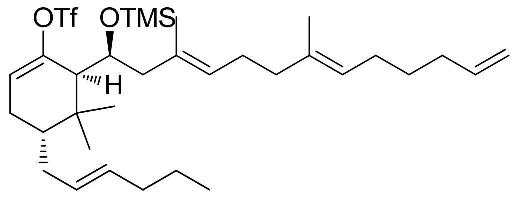
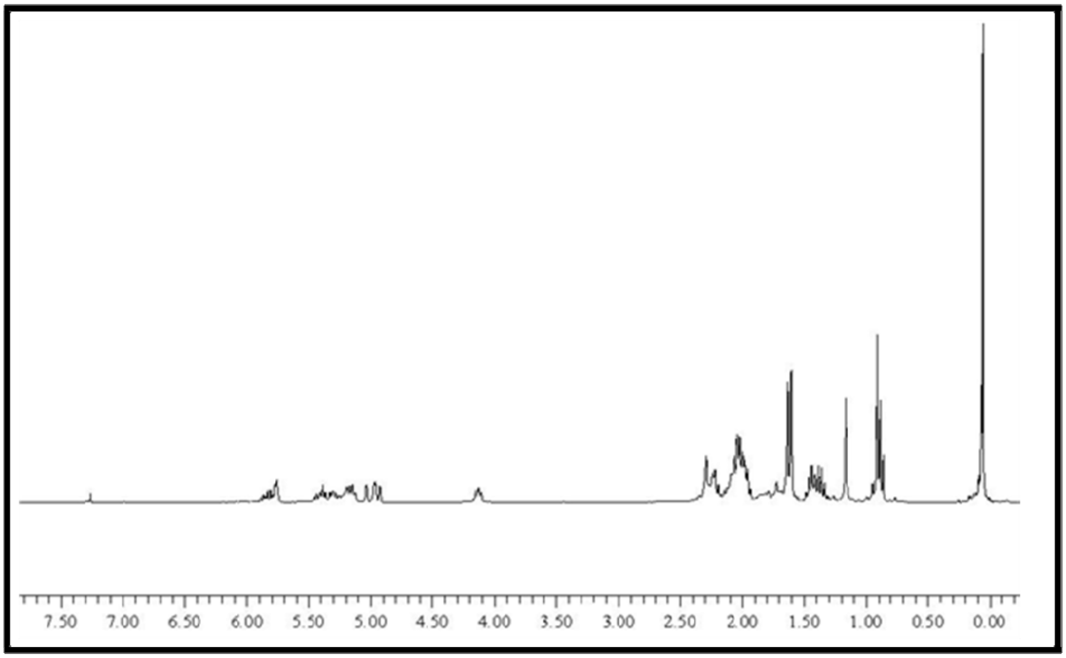

OTf
OTMS
H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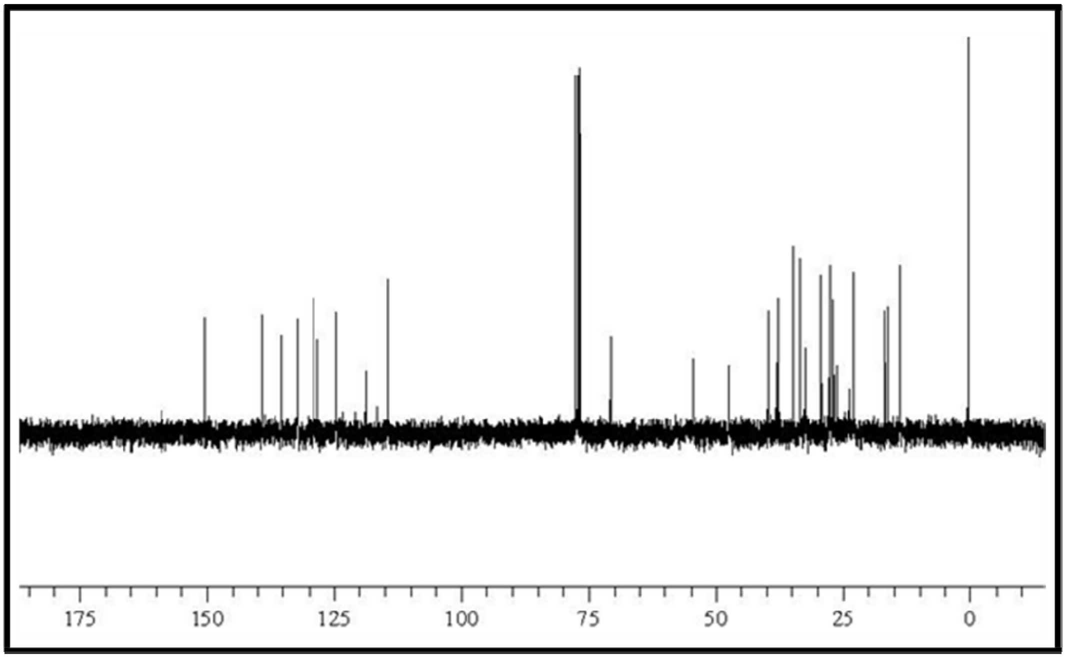
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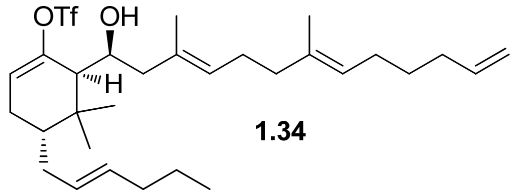
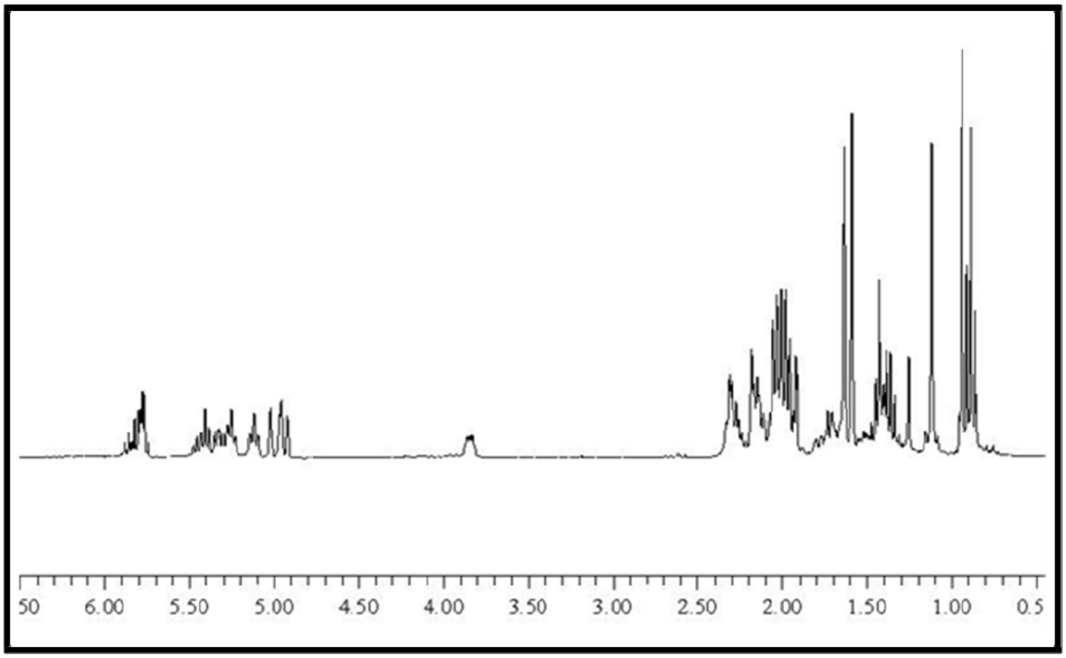

OTf
OH
H

1.34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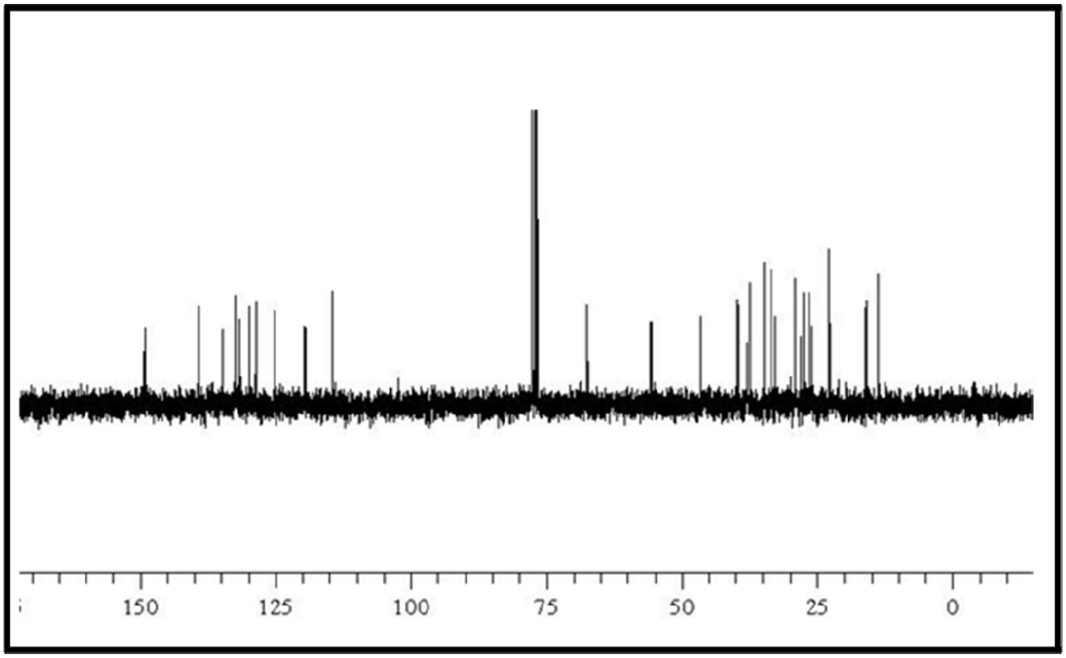
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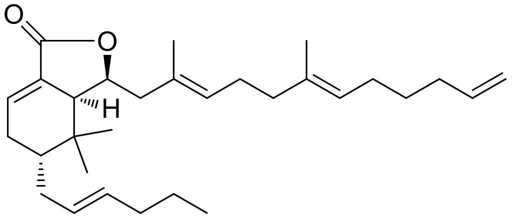
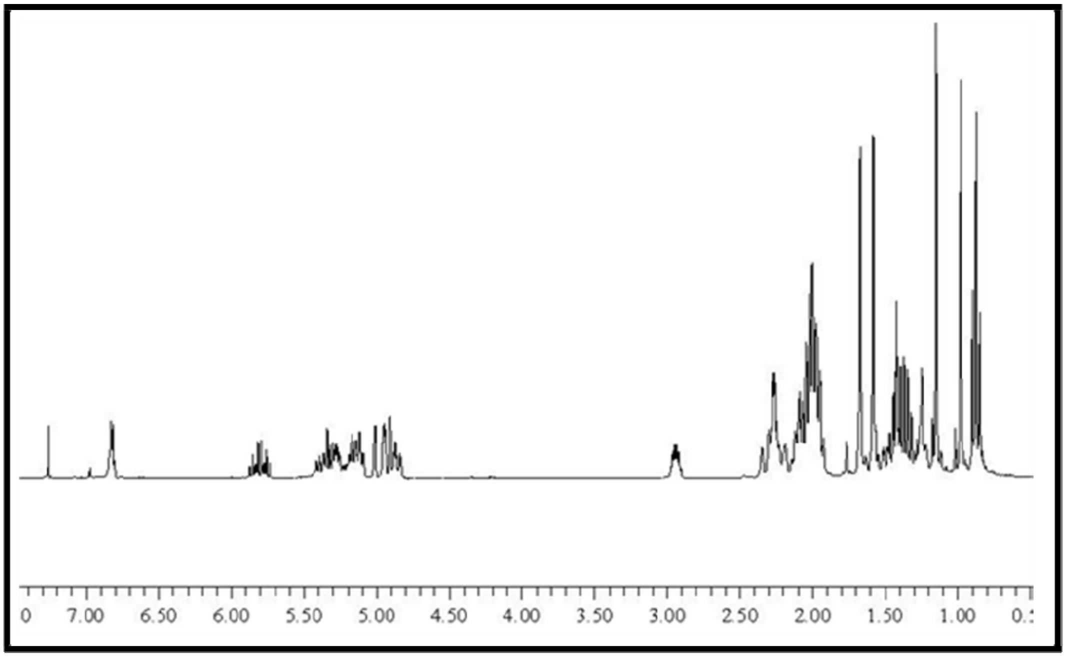


O
O
H



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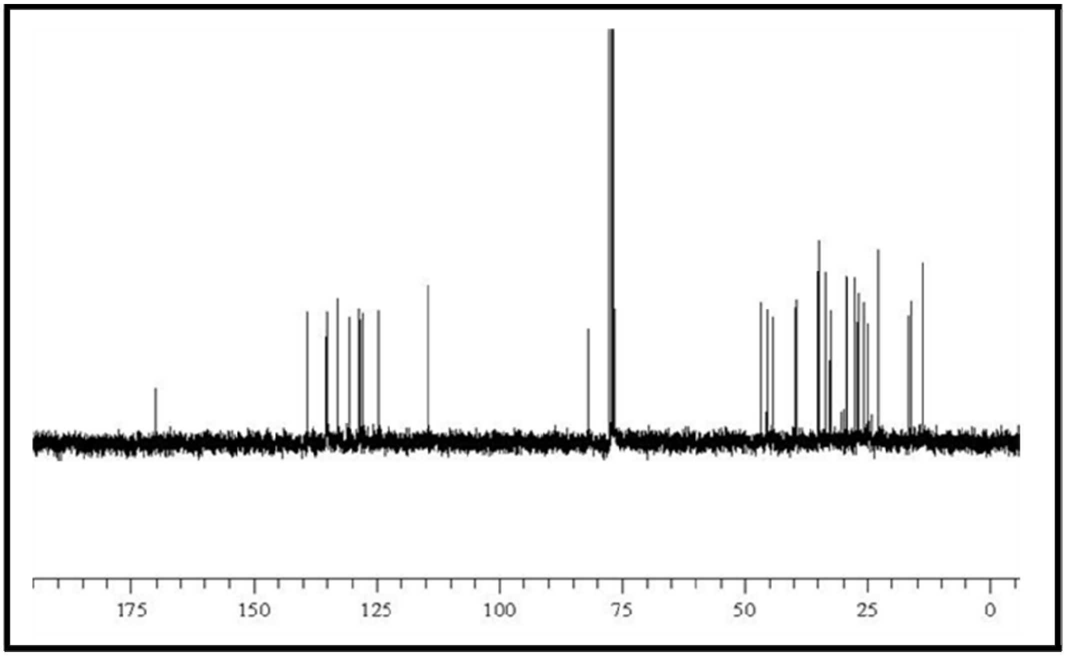

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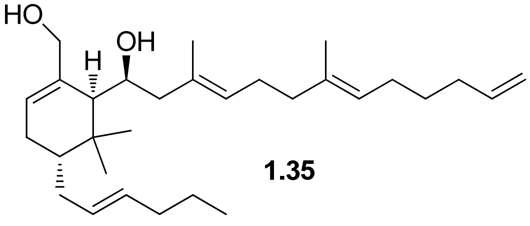
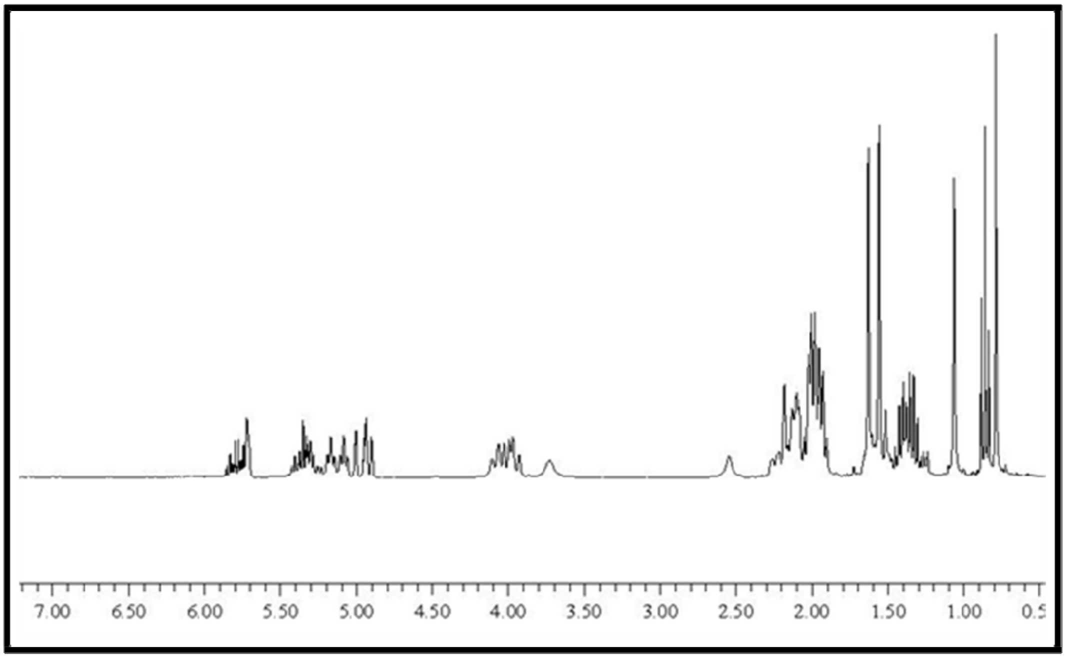

HO
OH
H

1.35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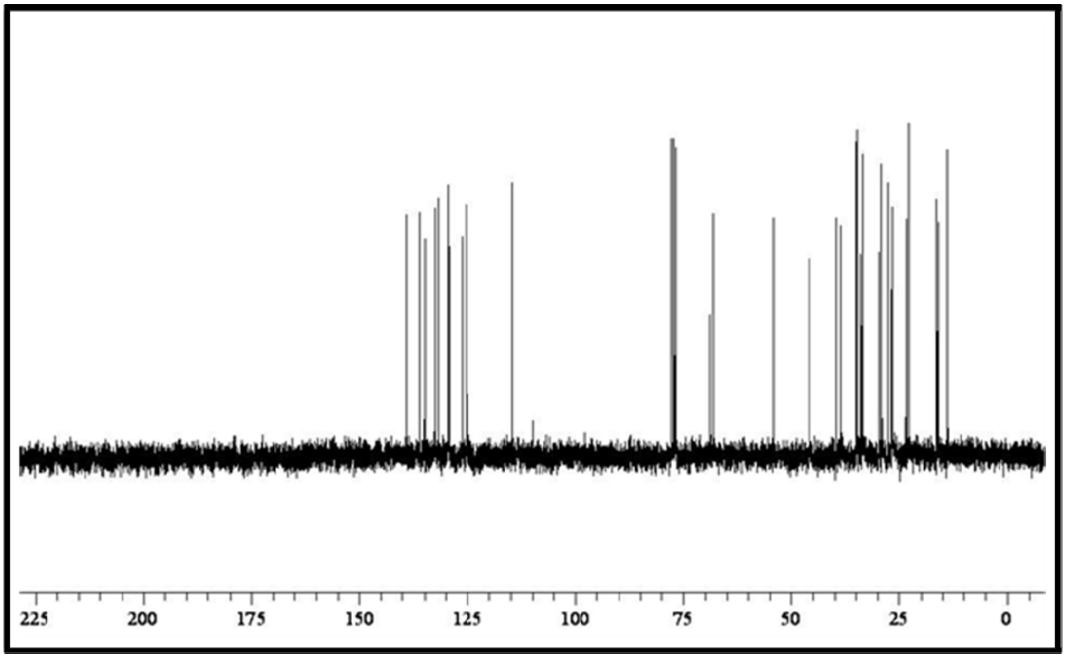
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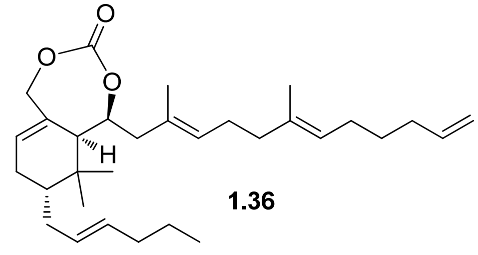

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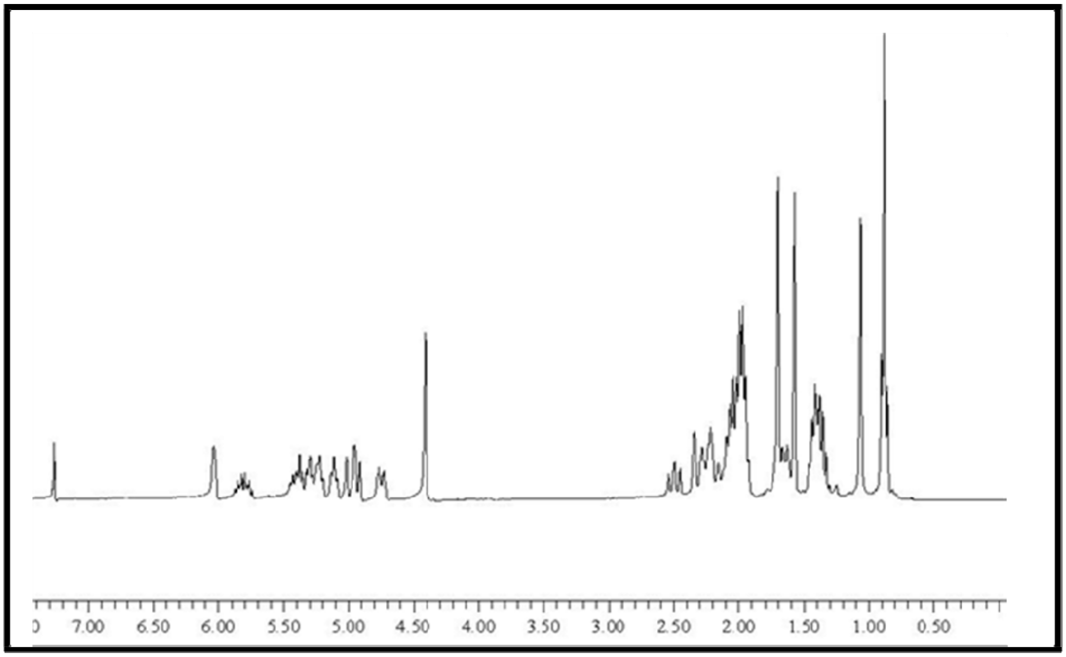

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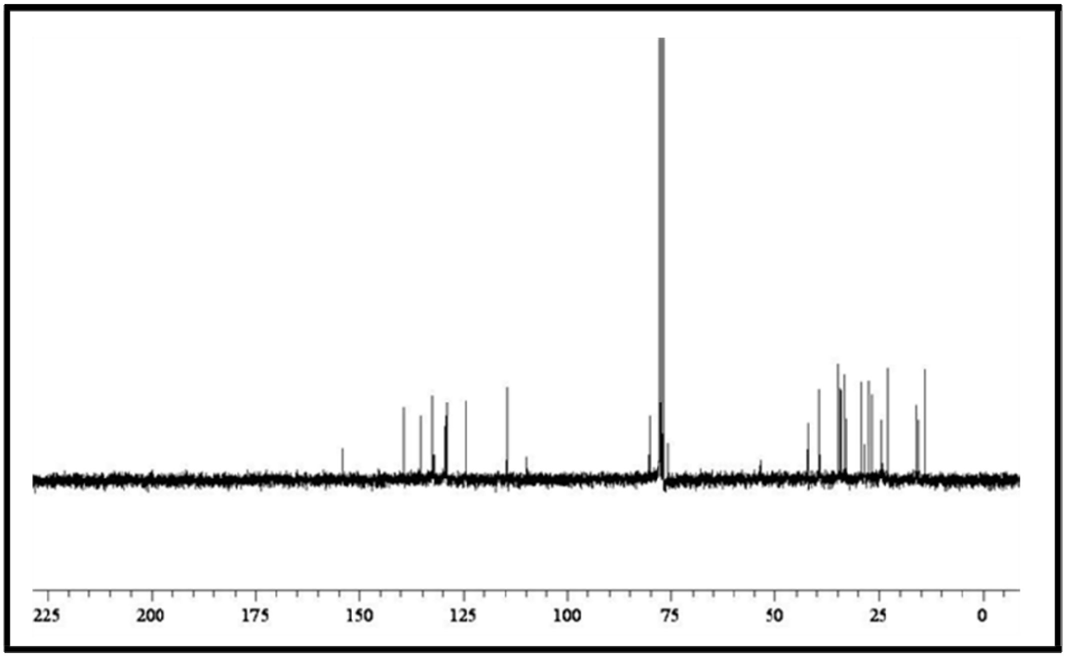

225
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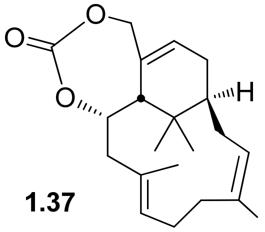
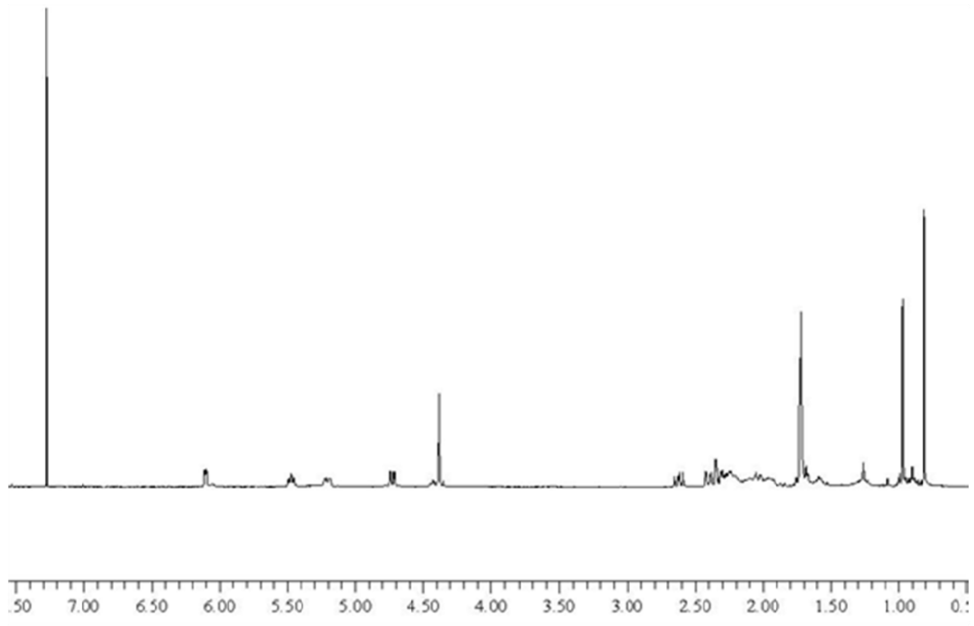


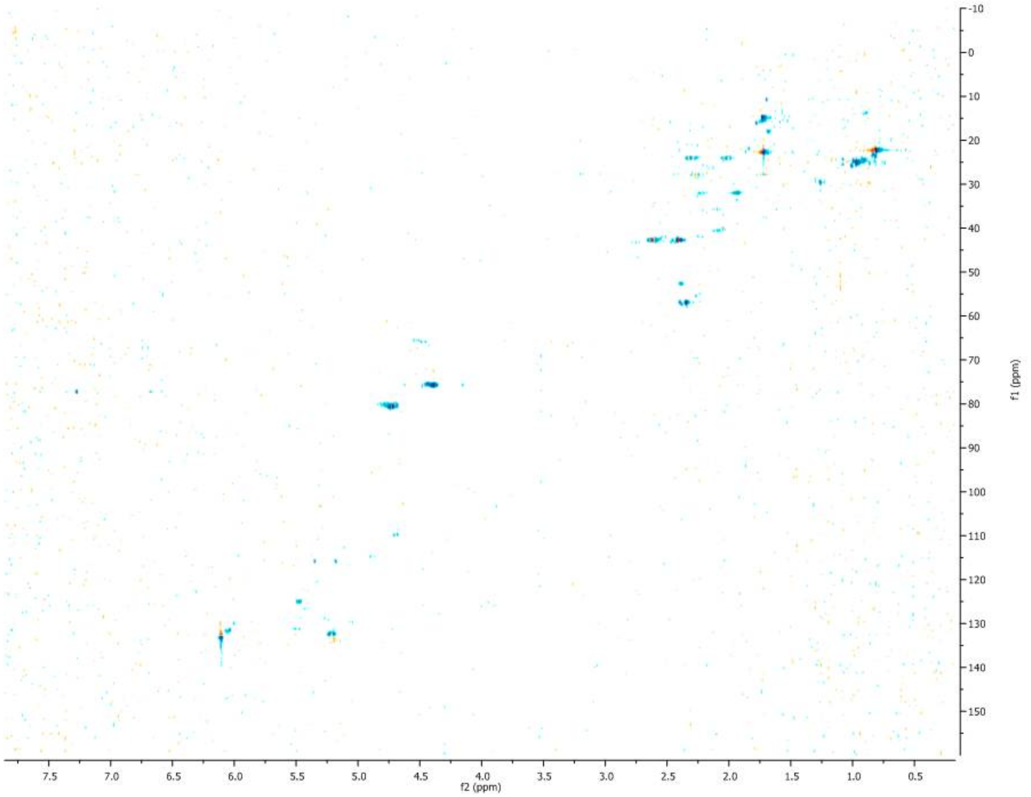
1.37



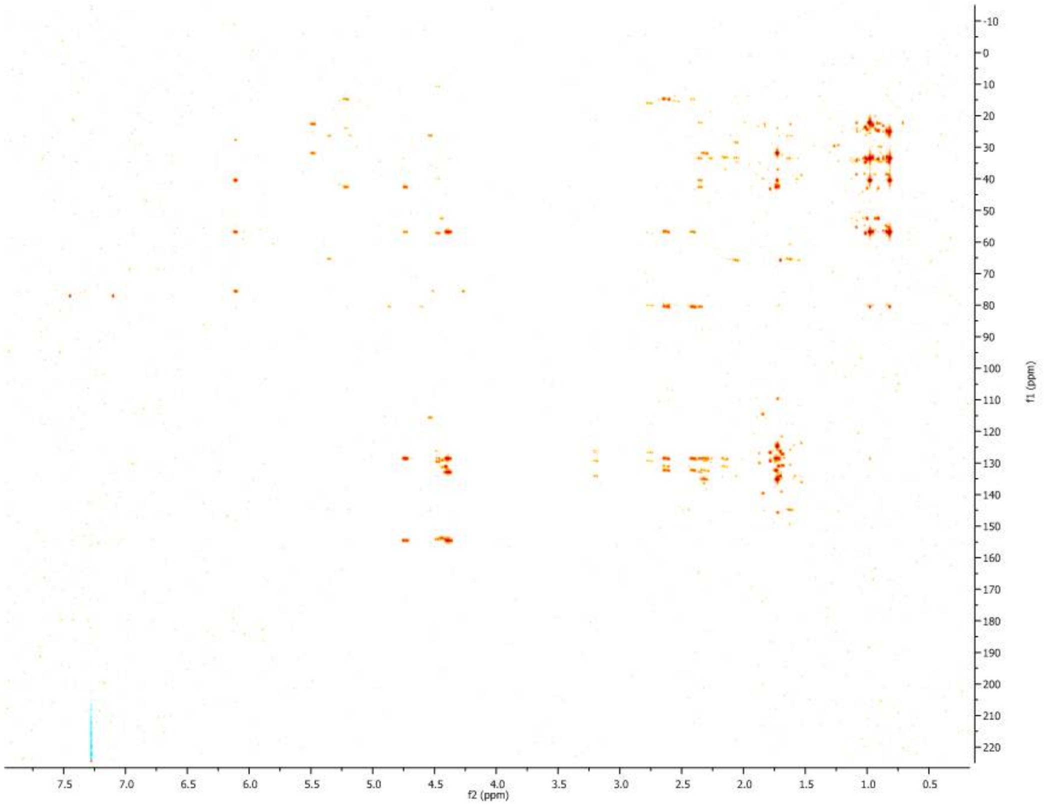
Carbon Chemical Shifts Extracted
From HSQC and HMBC Spectra

Spectral Confirmation of Incorrect C12, Olefin Geometery (Z) and Atropisomer

HSQC (1.37)



HMBC (1.37)



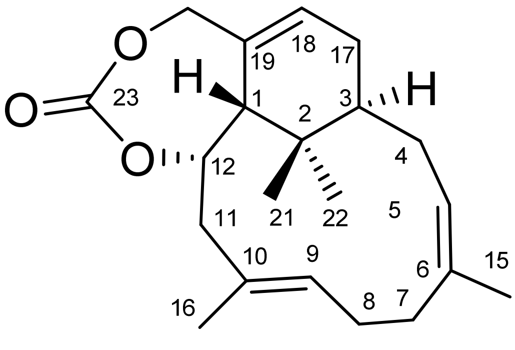
f1 (ppm)
f2 (ppm)
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

Carbon and Proton Assignments From HSQC and HMBC Data (1.37):

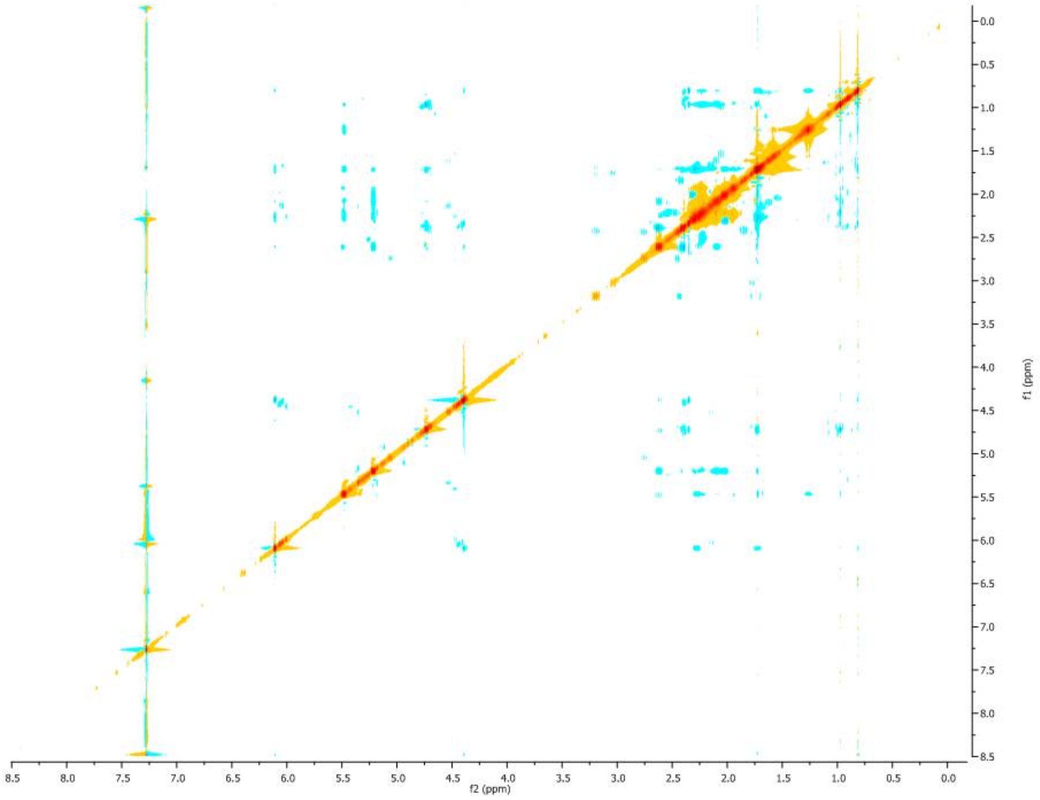
All carbons chemical shifts and the chemical shifts of the protons that are attached to them have been mapped out using both HSQC and HMBC techniques. These values can then be used to map out stereochemical relationships given NOE correlations.

C	δ ppm	HMQC (δ ppm)	HMBC (δ ppm)
1	57.0	2.32	6.07,4.70,2.59,0.95,0.79
2	33.6		2.32,2.24,0.95,0.79
3	40.6	2.07	6.07,2.32,1.70,0.95,0.79
4	24.2	2.28,1.99	1.70
5	125.0	5.45	1.70
6	135.2		2.28,1.70
7	32.1	2.21,1.92	5.45,2.28,1.70
8	28.0	2.24,1.69	6.07
9	132.4	5.18	2.59,2.38,1.71
10	131.1		2.59,1.69
11	42.8	2.59,2.38	5.18,4.70,2.32,1.69
12	80.7	4.70	2.59,2.32,0.95,0.79
15	22.8	1.70	5.45
16	15.0	1.71	5.18,2.59
17	29.6	1.24	
18	133.2	6.07	4.34,2.32
19	128.6		4.70,4.34,2.59,2.38,2.32
20	75.7	4.39,4.34	6.07
21	22.4	0.79	0.95
22	25.1	0.95	0.79
23	154.7		4.70,4.34

Table A1.1 2D-NMR Data for **1.37**

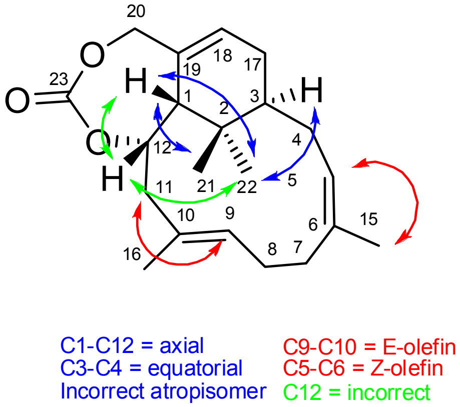


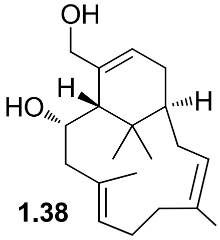
NOESY (1.37)



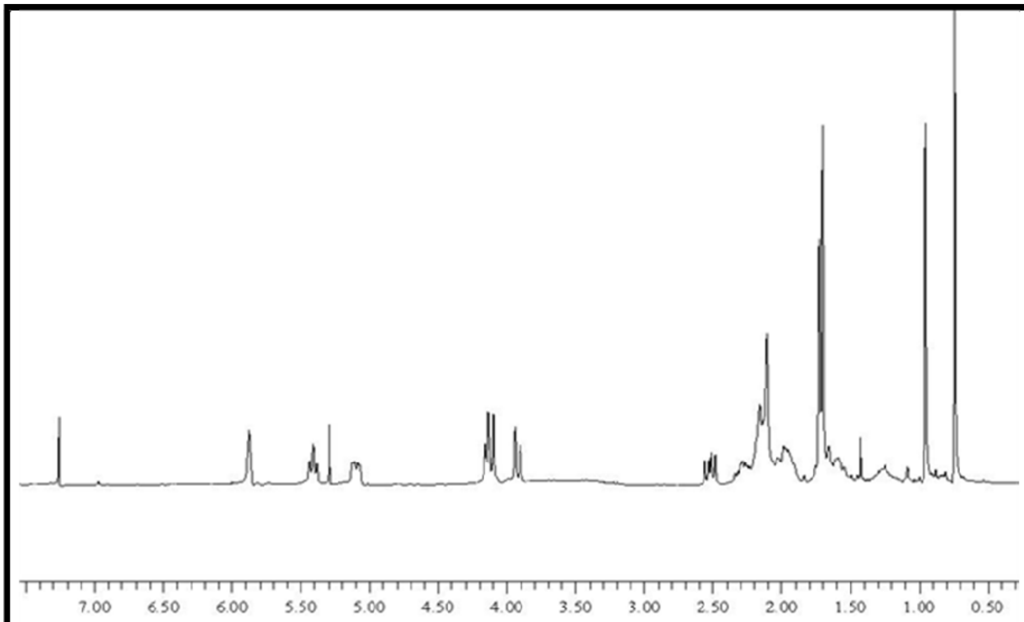
Important NOE Correlations For Proving Stereochemical Assignments:

Pictured are the relevant NOE correlations to prove the stereochemical assignments for the metathesis product.





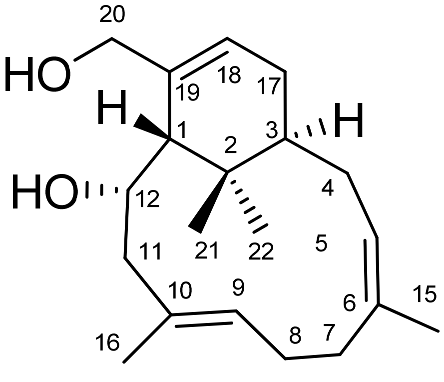
1.38

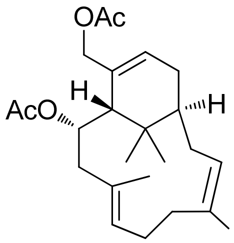


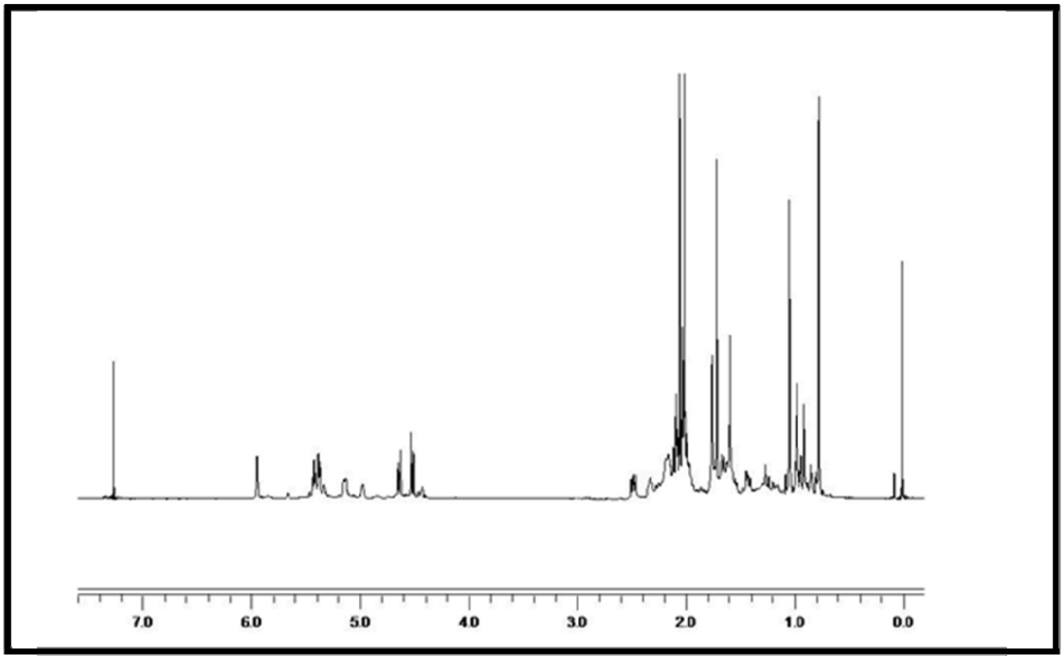
Carbon Chemical Shifts Extracted
From HSQC and HMBC Spectra

δ ppm	HMBC (δ ppm)
135.4	4.13,3.95,2.13
134.9	4.16,2.52,1.71
131.7	2.15,1.73
129.9	4.13,3.95,2.13
129.7	2.13,1.73
124.2	1.73
69.6	0.76
69.3	2.35
59.8	0.96,0.76
47.7	2.12,1.73
40.4	2.13,1.71,0.96,0.76
35.0	1.09,0.76
34.0	2.12,0.96,0.76
32.3	1.71,0.96
26.8	0.76
24.2	1.71
23.4	1.60,0.96
22.8	0.76
21.8	2.13,0.96
15.1	5.10

Table A1.2 2D-NMR Data for **1.38**



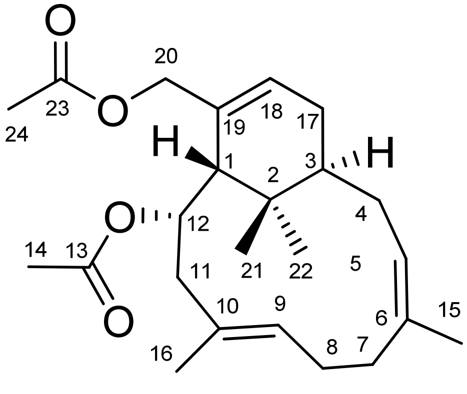


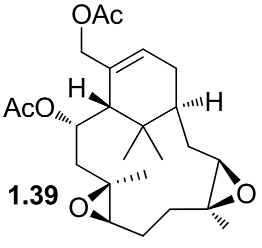


Carbon Chemical Shifts Extracted
From HSQC and HMBC Spectra

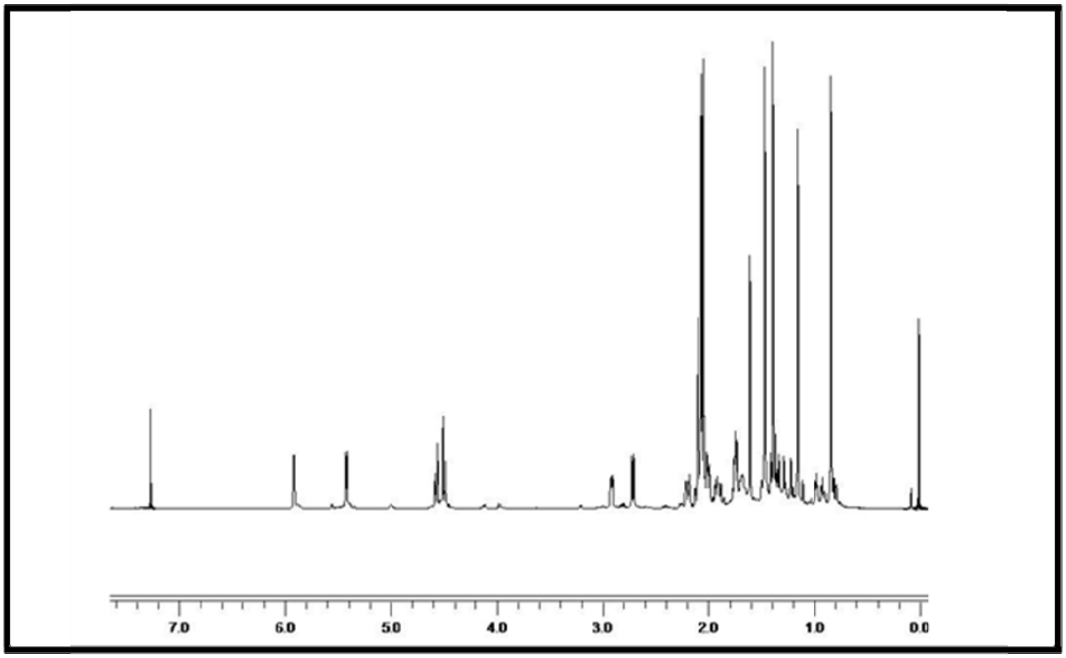
C	δ ppm	HSQC (δ ppm)	HMBC (δ ppm)
1	54.0	2.08	4.51
2	36.7		0.77
3	42.2	1.41	
4	30.1	1.04	
5	130.7	5.13	
6	135.5		1.71
7	41.7	2.06,1.77	
8	24.3	2.36,2.28	1.71
9	130.8	5.35	
10	132.6		5.37
11	43.8	2.48,2.09	
12	72.9	5.37	2.48
13	170.0		5.37,2.01
14	21.6	2.01	
15	23.0	1.71	
16	15.1	1.75	2.48
17	32.5	2.30,1.73	
18	129.7	5.94	
19	131.3		1.73
20	68.6	4.62,4.51	
21	21.6	0.77	
22	26.3	0.97	5.37
23	170.8		4.62,4.51,2.05
24	21.0	2.05	

Table A1.3 2D-NMR Data for **1.38-(Bis-Acetate)**





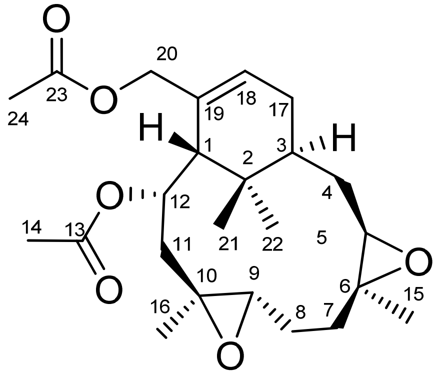
1.39

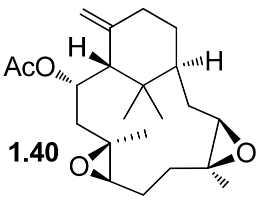


Carbon Chemical Shifts Extracted
From HSQC and HMBC Spectra

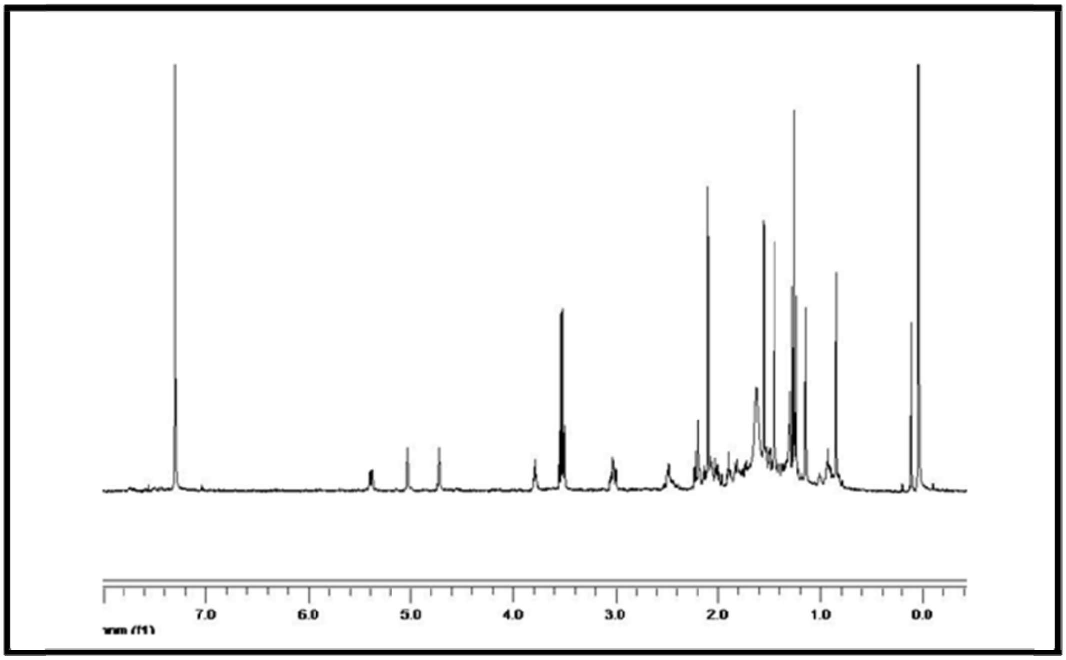
C	δ ppm	HSQC (δ ppm)	HMBC (δ ppm)
	29.3	2.18,1.89	
	28.5	1.72,1.35	2.90
	27.3	1.98,1.38	
	26.7	1.14	
	25.5	2.09,1.46	2.70
	22.1	1.38	
	21.3	0.83	
	16.4	1.46	1.72
1	53.4	2.09	4.49,1.14
2	34.7		1.14,0.73
3	35.4	1.66	
5	65.9	2.70	1.72,1.46
6	59.0		1.37
9	63.7	2.90	1.73
10	59.7		5.41,1.45
11	42.5	2.07,1.73	
12	71.1	5.41	
13	169.9		2.03,5.41
14	21.4	2.03	
18	127.6	5.91	
19	132.3		5.41
20	67.8	4.55,4.49	
23	170.5		2.05,4.49
24	21.0	2.05	1.14

Table A1.4 2D-NMR Data for **1.39**





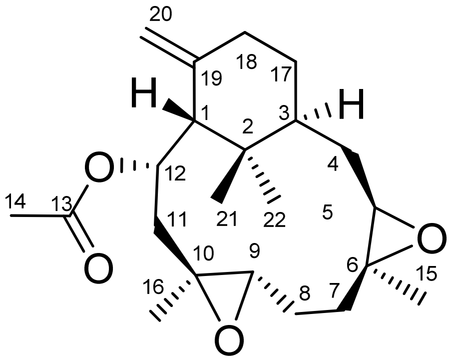
1.40

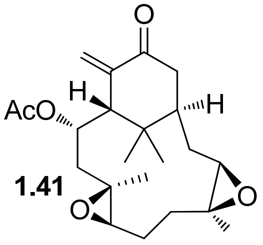


Carbon Chemical Shifts Extracted
From HSQC and HMBC Spectra

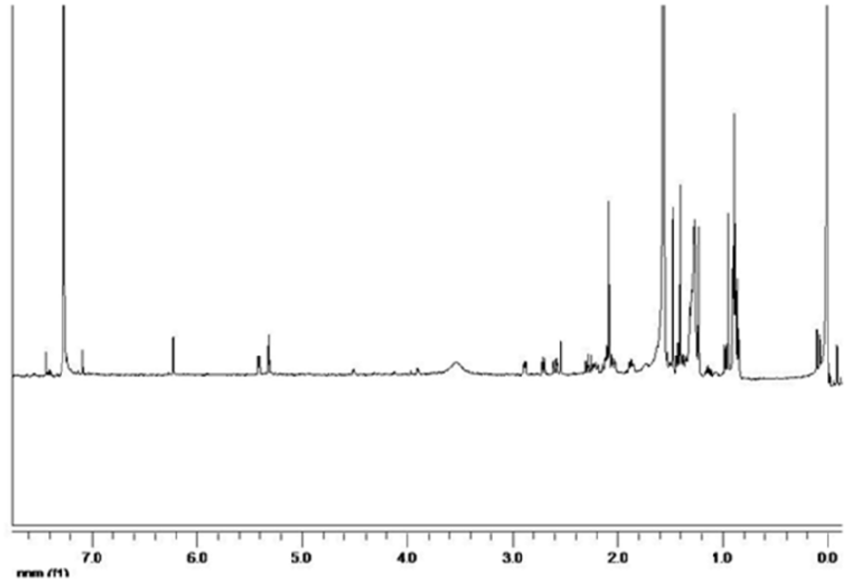
C	δ ppm	HSQC (δ ppm)	HMBC (δ ppm)
1	60.0	2.15	1.95,1.50
2	35.7		1.10, 0.80
3	38.0	1.77	2.96,1.10,0.80
4	25.3	2.10,1.49	
5	64.4	2.98	1.68,1.40
6	59.2		1.40
7	27.0	1.96,1.43	1.40
8	28.5	1.67,1.34	
9	65.9	2.96	2.15,1.50
10	59.6		1.10, 0.80
11	43.1	2.15,1.95	1.50
12	71.1	5.35	2.15,1.95
13	170.4		2.05
14	21.8	2.05	
15	22.2	1.40	
16	16.7	1.50	1.95
17	26.4	1.74,1.39	
18	33.2	2.42,2.36	4.99,4.68
19	143.4		2.15,5.35
20	116.1	4.99,4.68	
21	22.2	0.8	1.10
22	27.2	1.10	0.80

Table A1.5 2D-NMR Data for **1.40**





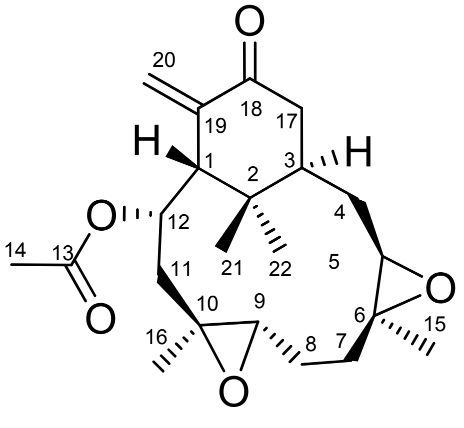
1.41

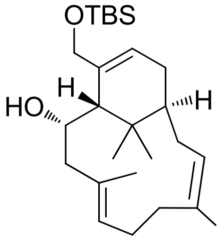


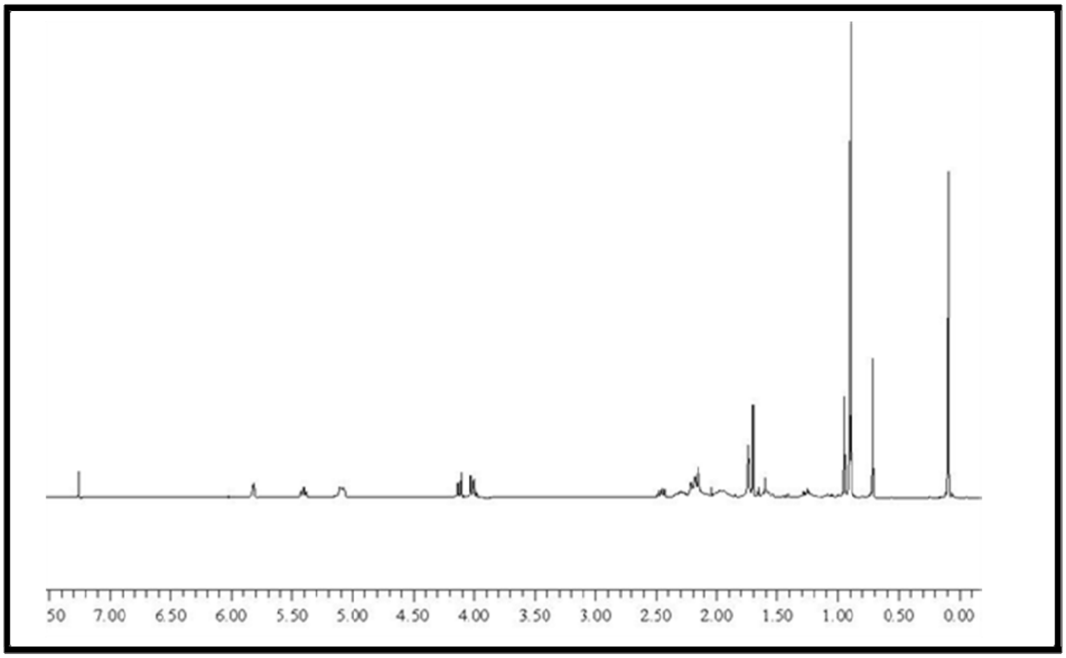
Carbon Chemical Shifts Extracted
From HSQC and HMBC Spectra

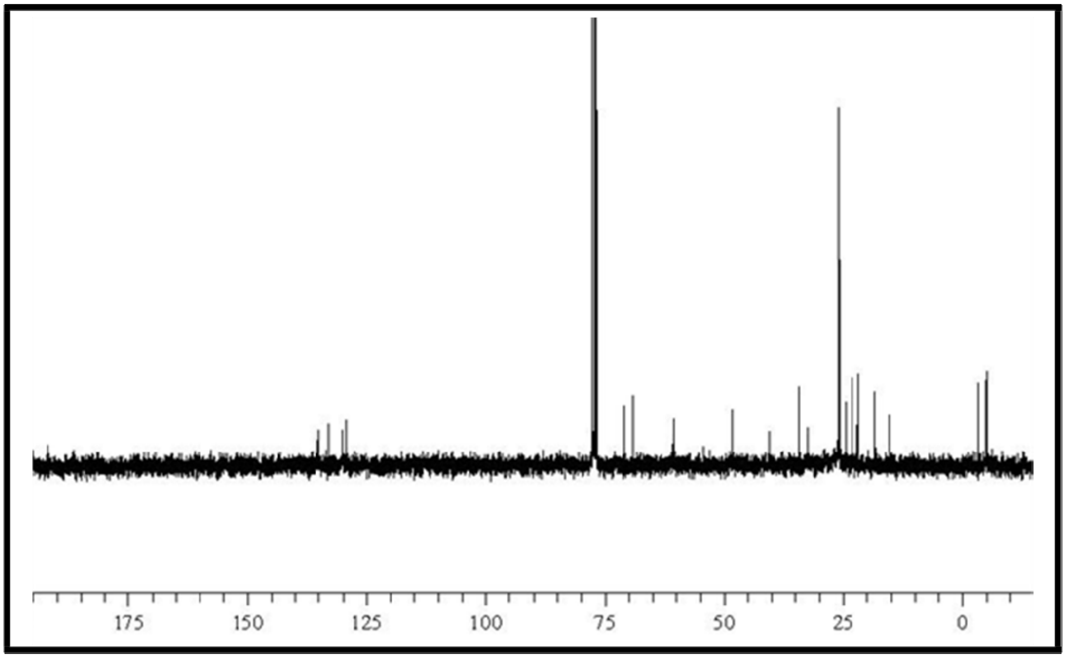
C	δ ppm	HSQC (δ ppm)	HMBC (δ ppm)
1	58.7	2.53	1.86,1.22,0.94
2	36.2		1.22,0.94
3	35.1	1.86	1.22,0.94
4	31.6	1.26	1.29
5	62.7	2.87	1.39
6	59.2		1.39
7	27.2	2.01,1.37	1.39
8	22.8	1.29	
9	65.7	2.71	2.06,1.47
10	59.6		2.06,1.47
11	42.3	2.06,1.26	
12	70.6	5.40	
13	169.8		2.08
14	21.4	2.07	
15	22.0	1.39	
16	16.4	1.47	
17	41.1	2.60,2.24	
18	199.1		6.22,5.31,2.53
19	141.5		5.40,2.53
20	127.7	6.22,5.31	
21	21.5	0.94	1.22
22	26.3	1.22	0.94

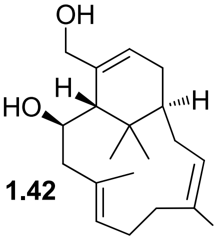
Table A1.6 2D-NMR Data for **1.41**



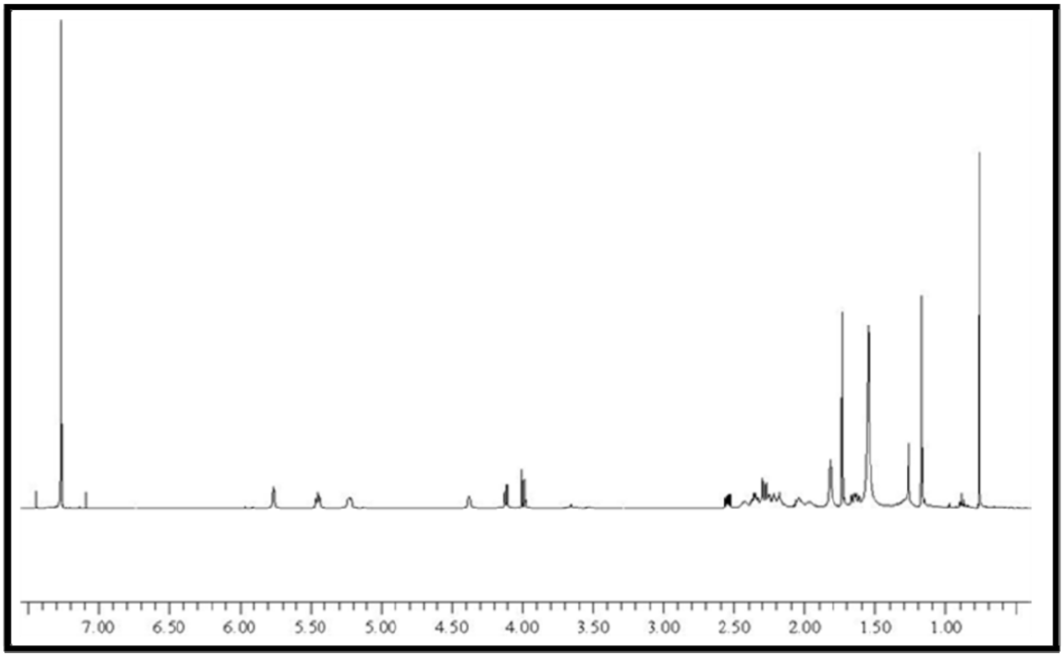

OTBS
H
HO
H


50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00


175
150
125
100
75
50
25
0



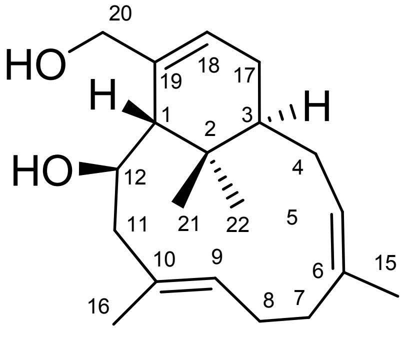
1.42

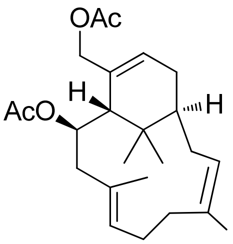


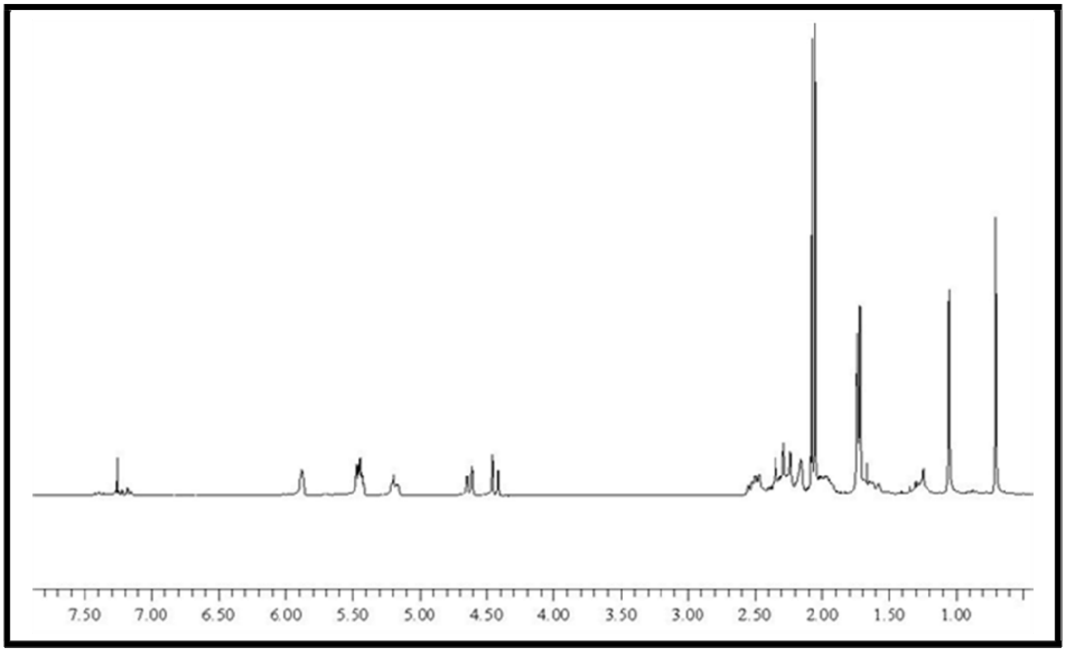
Carbon Chemical Shifts Extracted
From HSQC and HMBC Spectra

C	δ ppm	HSQC (δ ppm)	HMBC (δ ppm)
	134.8		1.72
	133.8		2.25, 2.51
	130.1		
	127.3	5.76	2.01, 1.72
	125.5		1.72
	57.9		1.16, 0.74
	42.7		
	40.7		1.16, 0.74
	35.6		1.16, 0.74
	32.0		1.72
	29.7	1.26	
	29.3		
	27.0		
	26.8	1.16	0.76
	24.6	0.76	
	22.9	1.72	
	17.6	1.81	2.25
12	75.1	4.37	2.51
18	126.9		3.98
20	67.1	4.10,3.98	

Table A1.7 2D-NMR Data for **1.42**




OAc
AcO
H
H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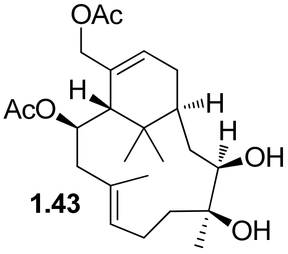
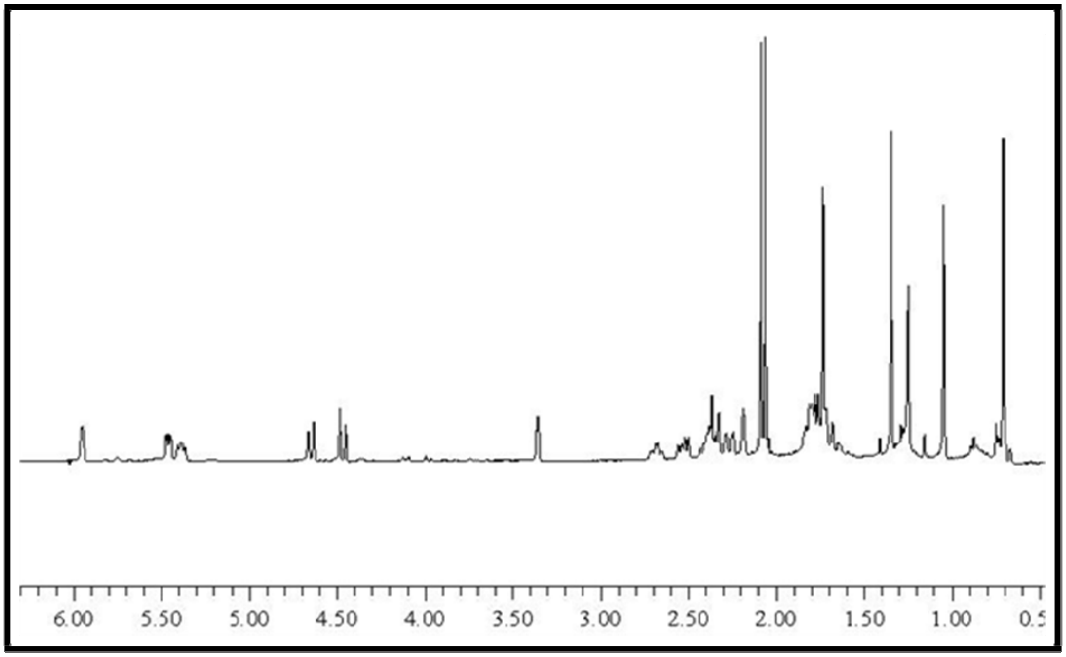
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00


OAc
AcO
H
H
H
OH
OH

1.43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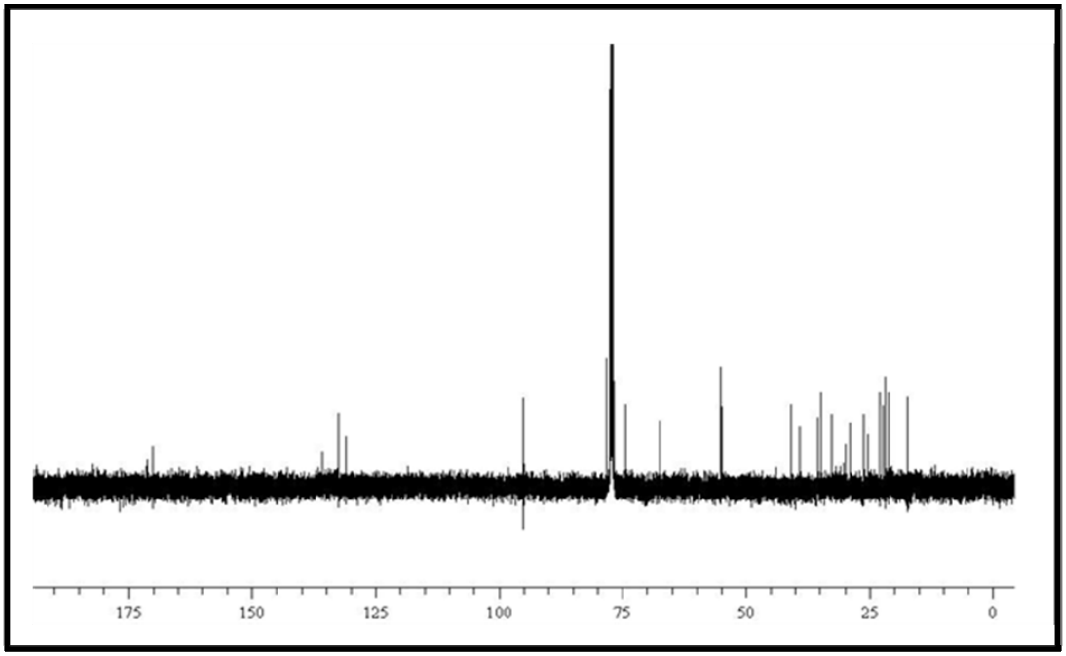
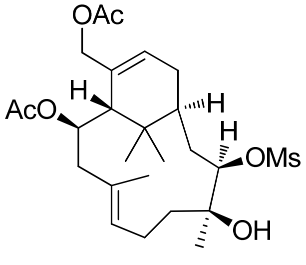
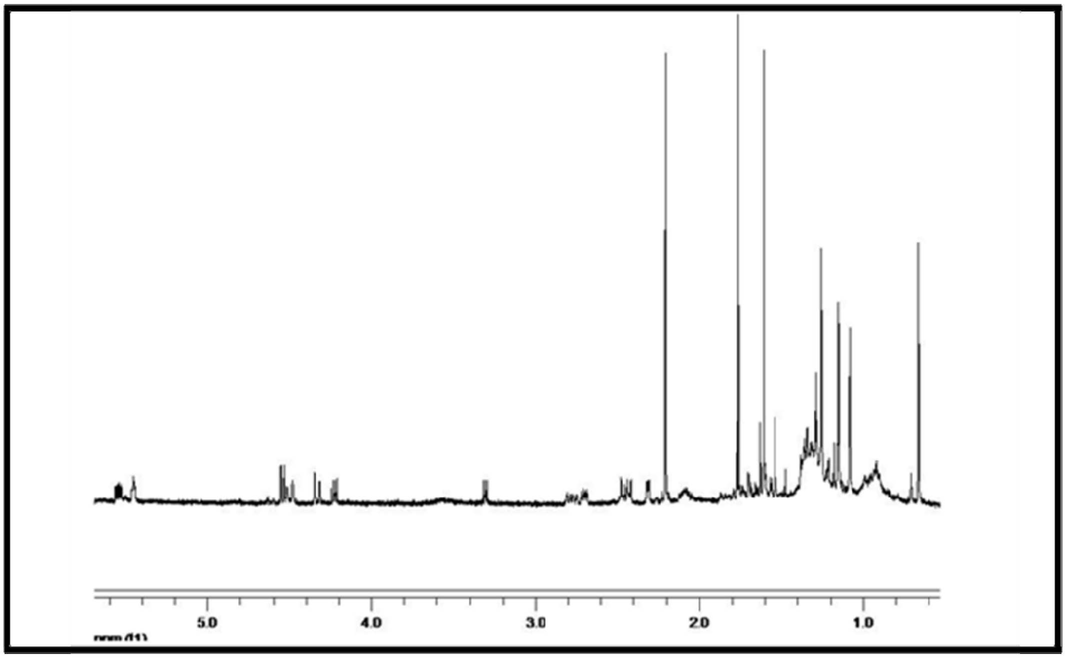
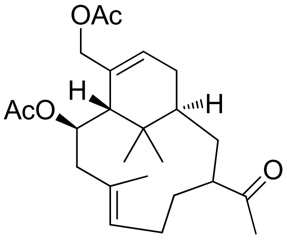
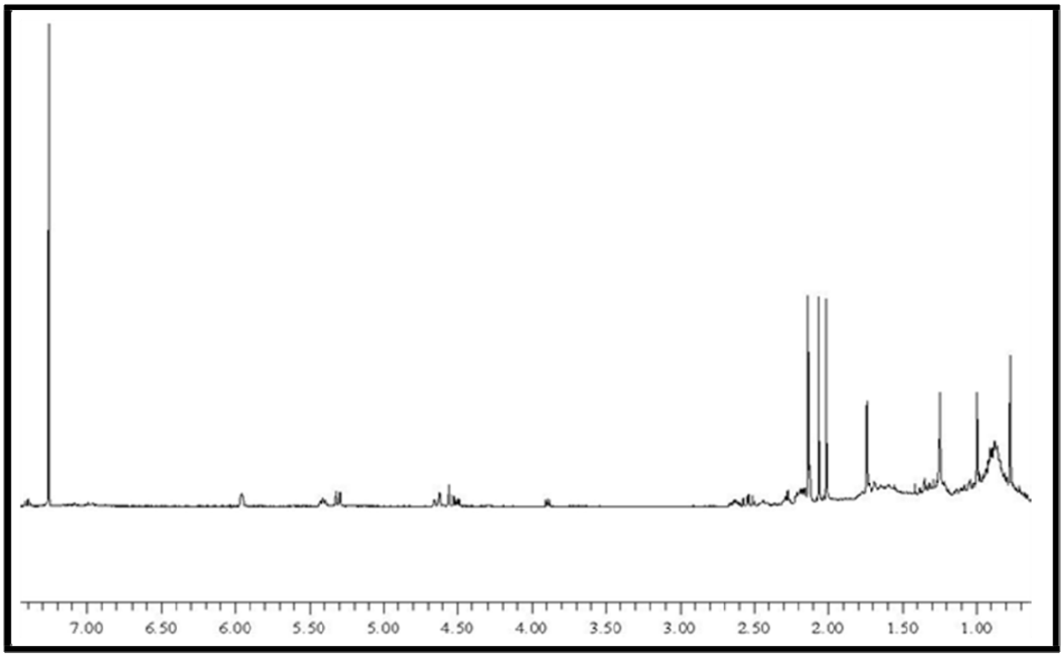
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.5


175
150
125
100
75
50
25
0

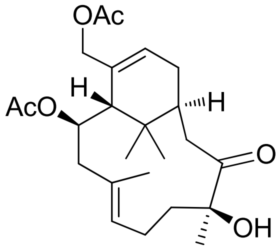

OAc
AcO
H
H
H
OMs
OH

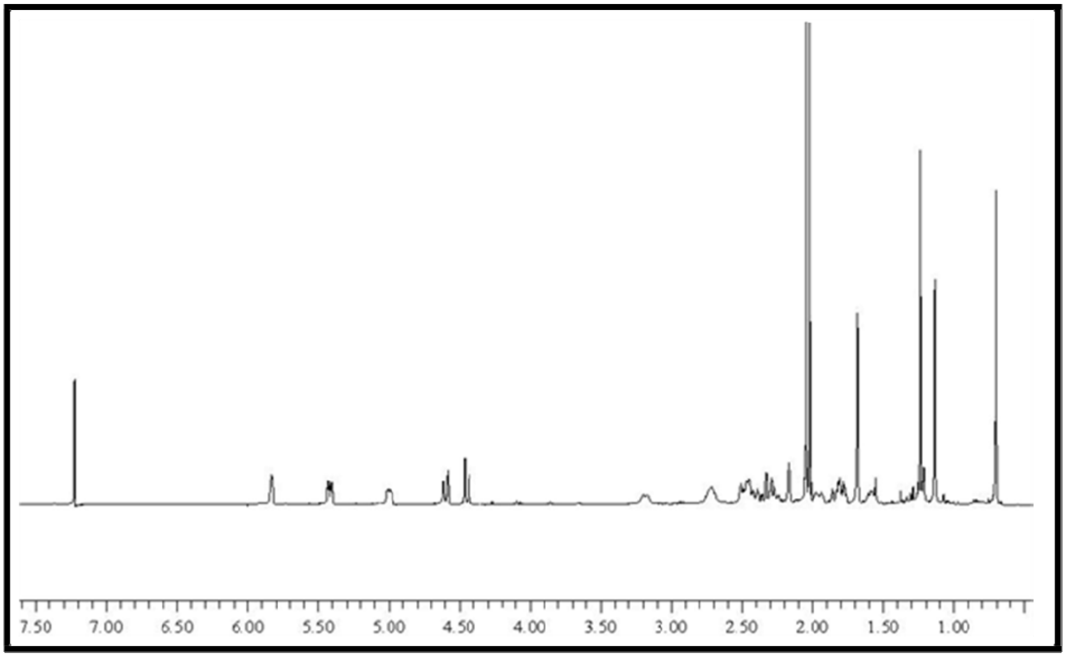

5.0
4.0
3.0
2.0
1.0
ppm (f1)





Carbon Chemical Shifts Extracted
From HSQC and HMBC Spectra


OAc
H
AcO
H
O
OH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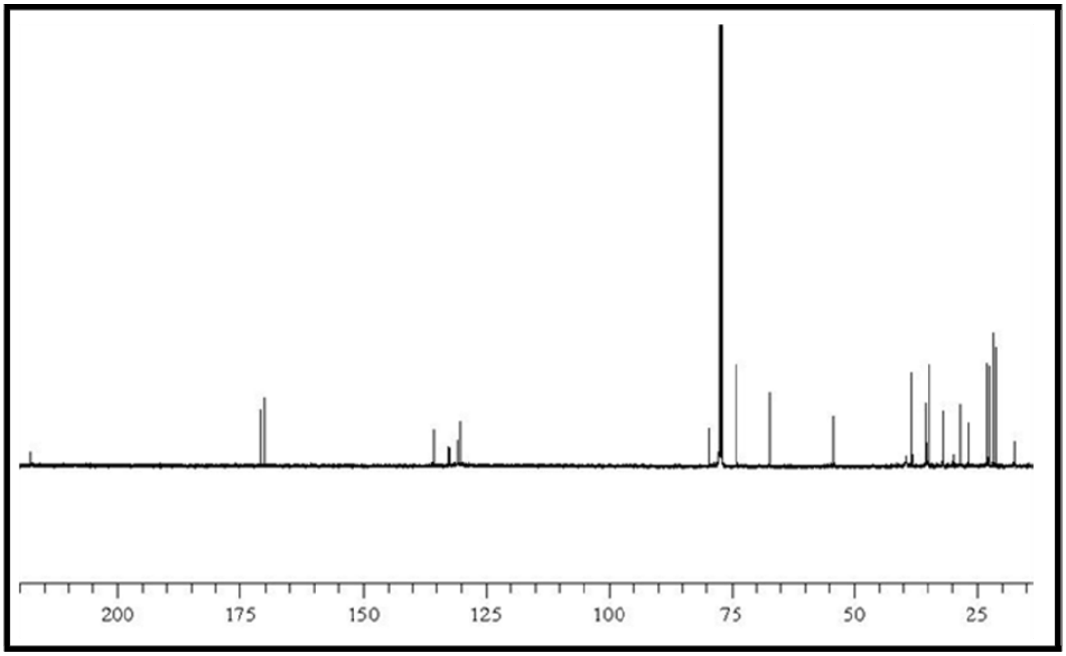
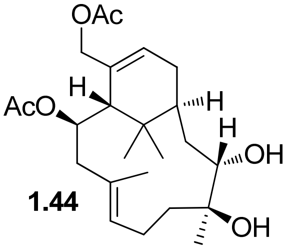
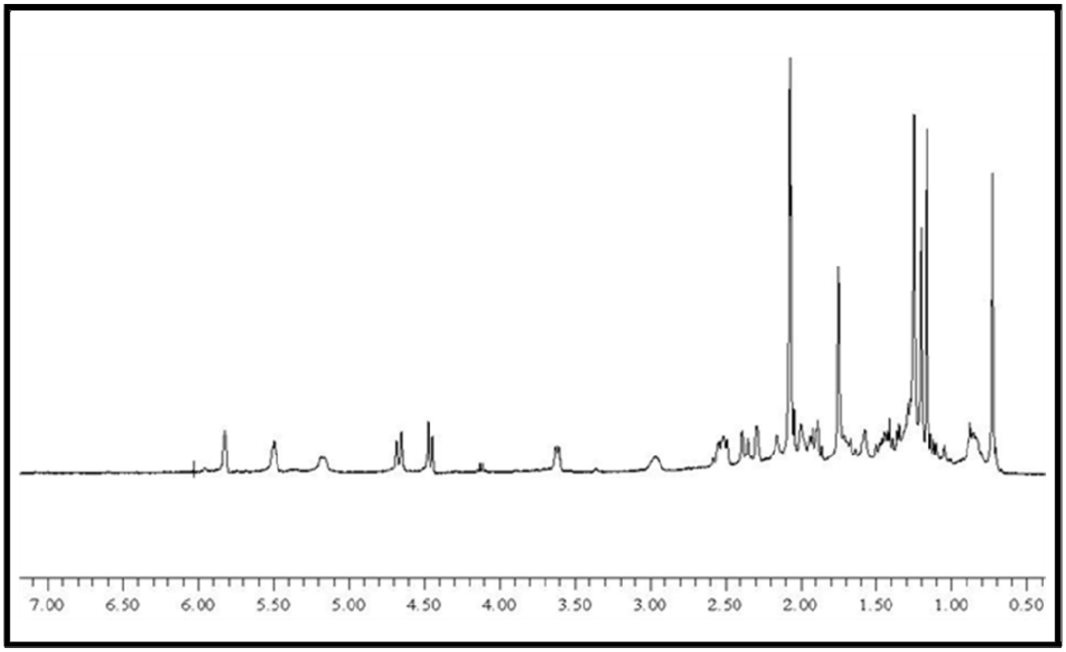
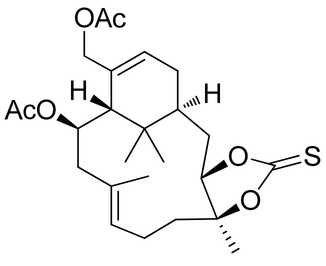
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00

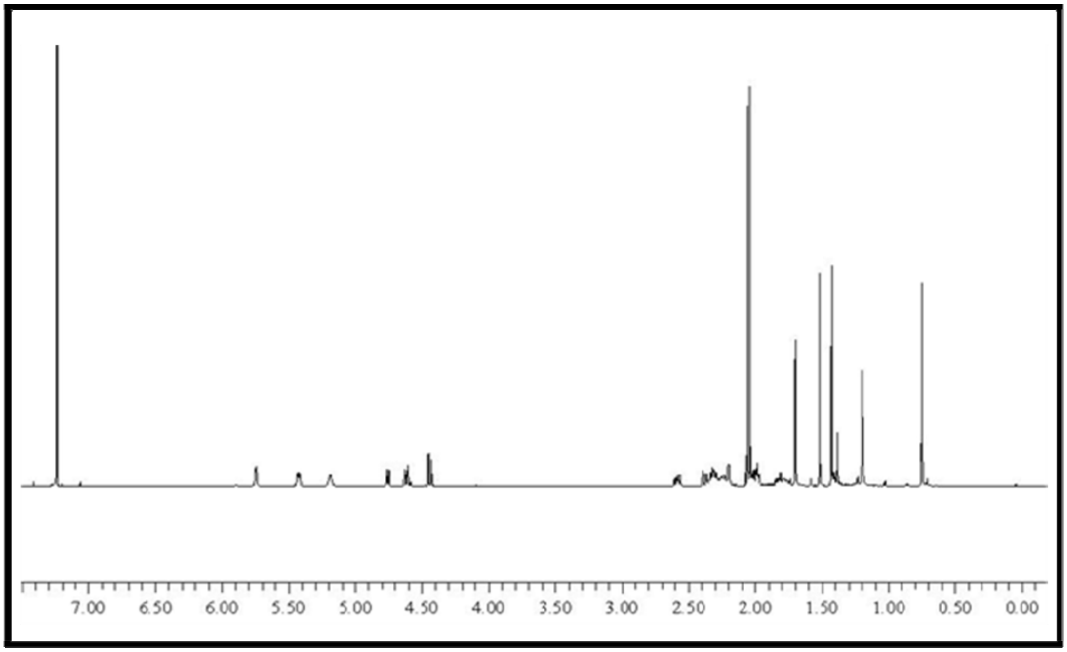

200
175
150
125
100
75
50
25



1.44




OAc
H
H
AcO
O
S
O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6.50
6.00
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5.00
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3.00
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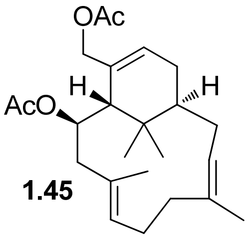
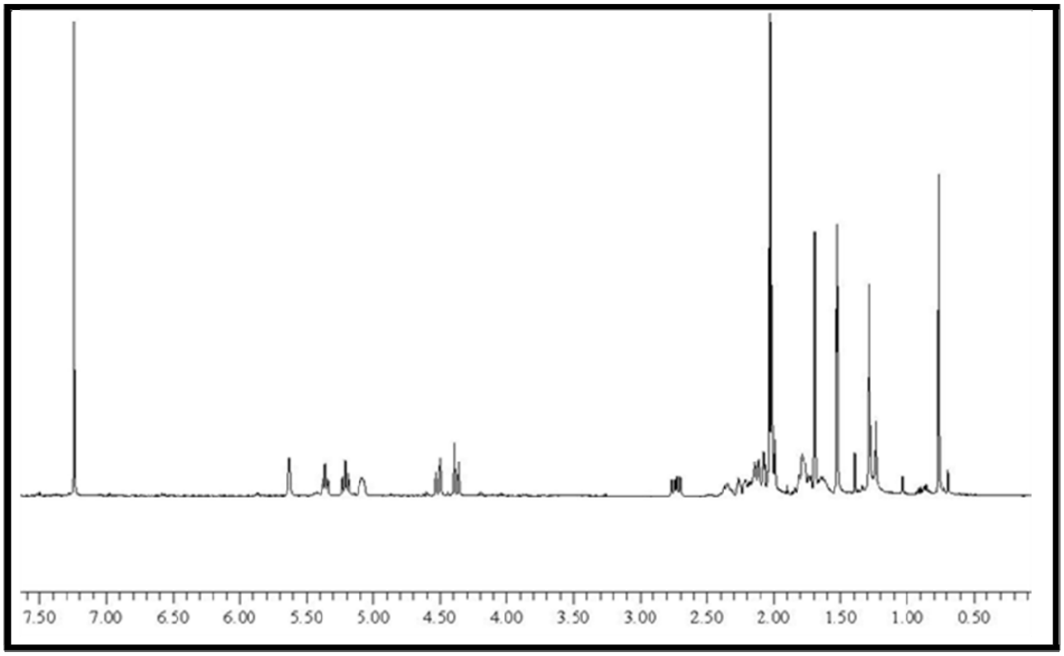
2.00
1.50
1.00
0.50
0.00



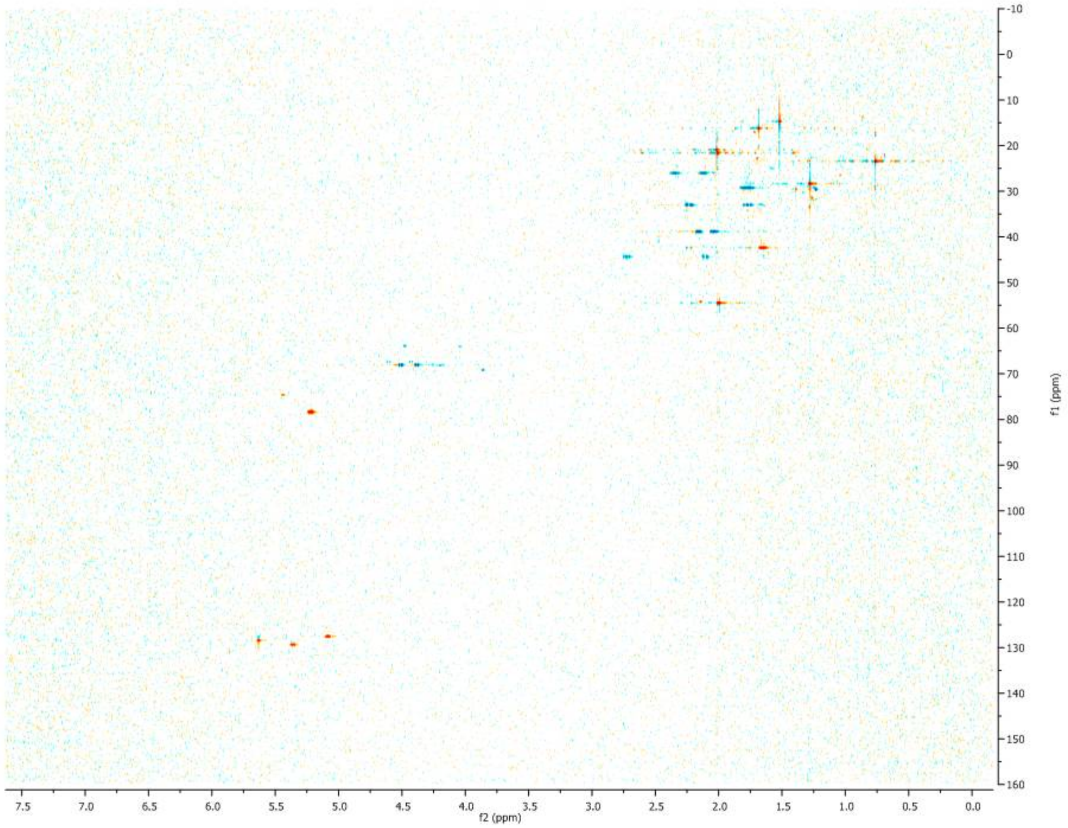
1.45



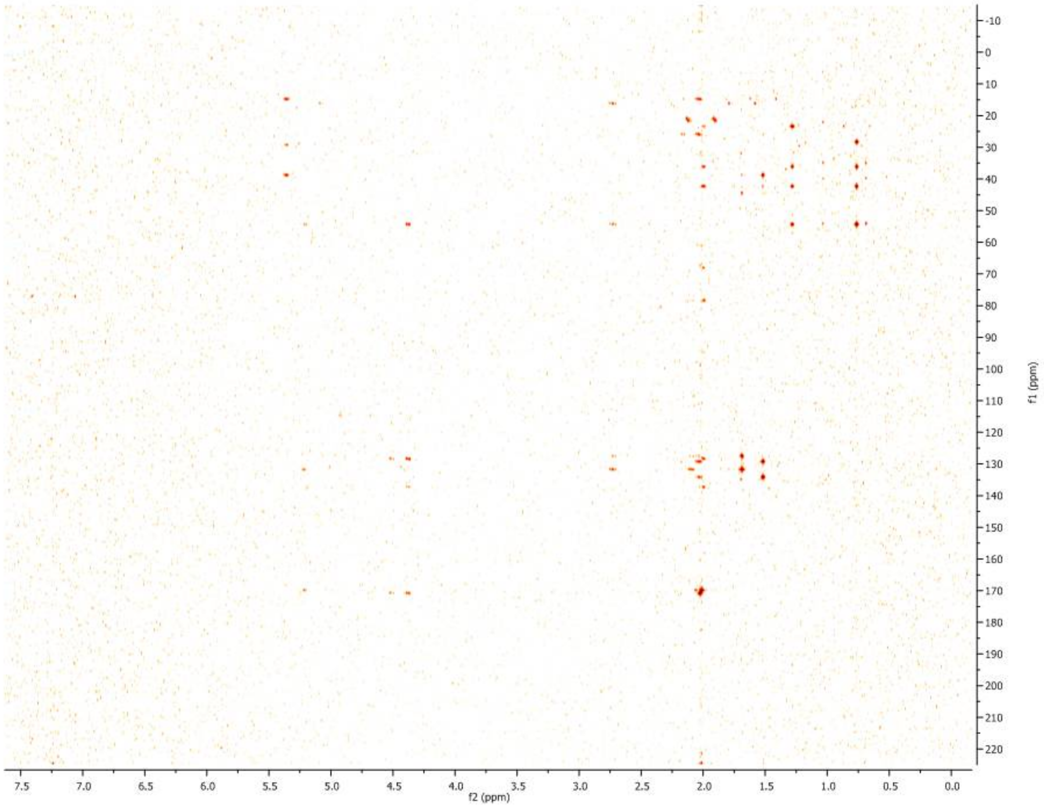
Carbon Chemical Shifts Extracted
From HSQC and HMBC Spectra

Spectral Confirmation for Correction of: C12 and Olefin Geometry (EE)

HSQC-AD (1.45)



HMBC-AD (1.45)

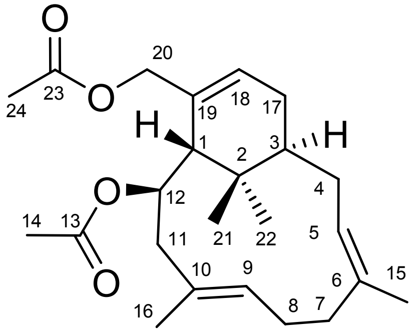

f2 (ppm)
f1 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220

Carbon and Proton Assignments From HSQC and HMBC Data:

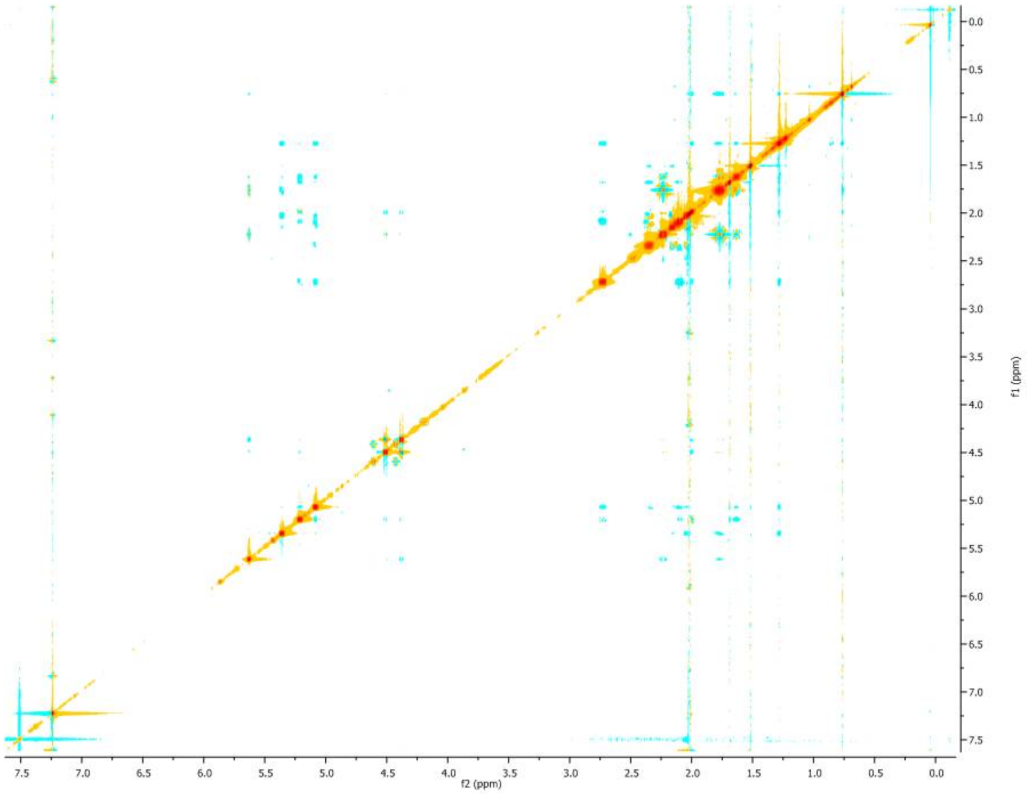
All carbons chemical shifts and the chemical shifts of the protons that are attached to them have been mapped out using both HSQC and HMBC techniques. These values can then be used to map out stereochemical relationships given NOE correlations.

C	δ ppm	HSQC (δ ppm)	HMBC (δ ppm)
1	54.8	2.00	0.77
2	36.6		0.77
3	42.8	1.65	1.52,0.77
4	29.5	1.80,1.76	5.36,1.52
5	129.6	5.36	
6	134.3		2.16,2.04,1.52
7	39.2	2.16,2.04	5.36,2.12,1.52
8	26.3	2.35,2.12	1.69,1.52
9	127.8	5.08	1.69
10	132.1		5.22,2.73,2.11,1.69
11	44.6	2.73,2.11	1.69
12	78.6	5.22	
13	170.0		5.22,2.04,2.01
14	21.9	2.01	
15	15.0	1.52	5.36
16	16.5	1.69	
17	33.3	2.24,1.77	
18	128.7	5.63	4.51,4.38,2.24,2.00
19	137.4		5.22,4.51,4.38,2.00
20	68.6	4.51,4.38	
21	23.9	0.77	
22	28.7	1.28	0.77
23	171.0		4.51.4.38,2.02
24	21.3	2.02	

Table A1.8 2D-NMR Data for **1.45**

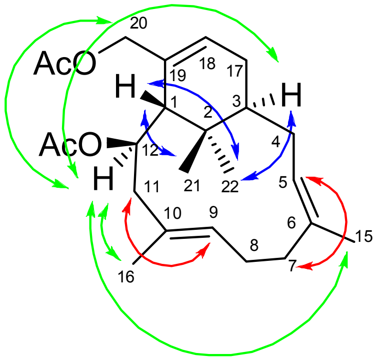


NOESY (1.45)



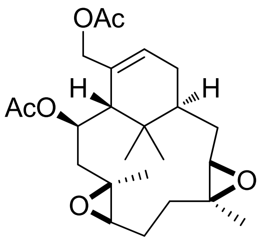
Important NOE Correlations For Proving Stereochemical Assignments:

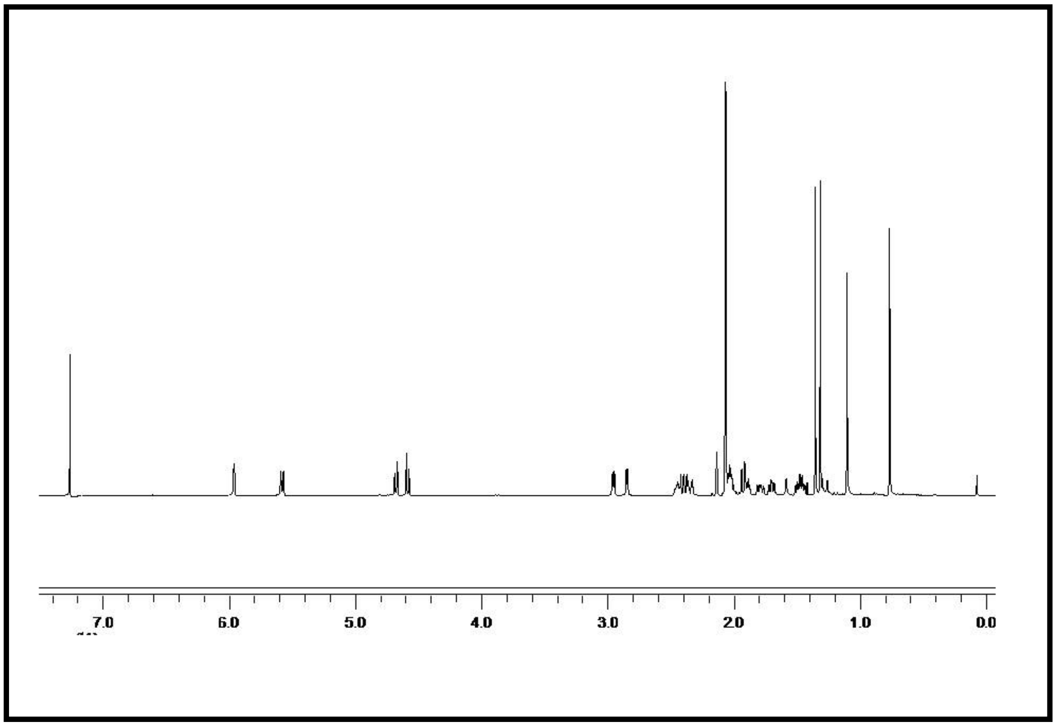
Pictured are the relevant NOE correlations to prove the stereochemical assignments. This shows correct C12 and olefin geometries (EE).

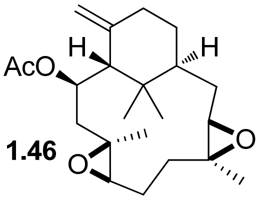


C1-C12 = axial
C3-C4 = equatorial
Incorrect atropisomer

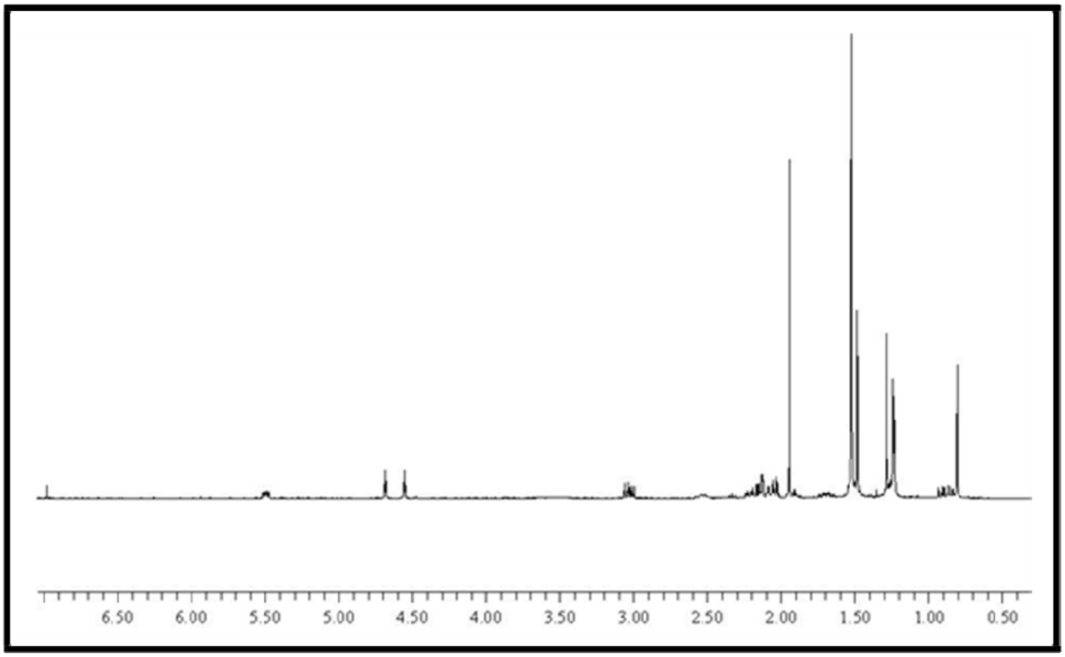
C9-C10 = E-olefin
C5-C6 = E-olefin
C12 = correct


OAc
H
H
AcO
O
O


7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0



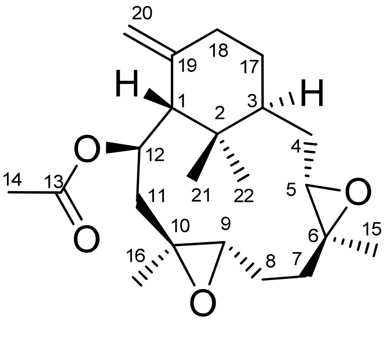
1.46

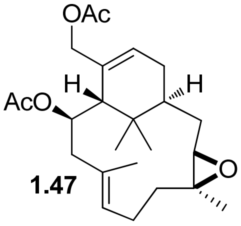


Carbon Chemical Shifts Extracted
From HSQC and HMBC Spectra

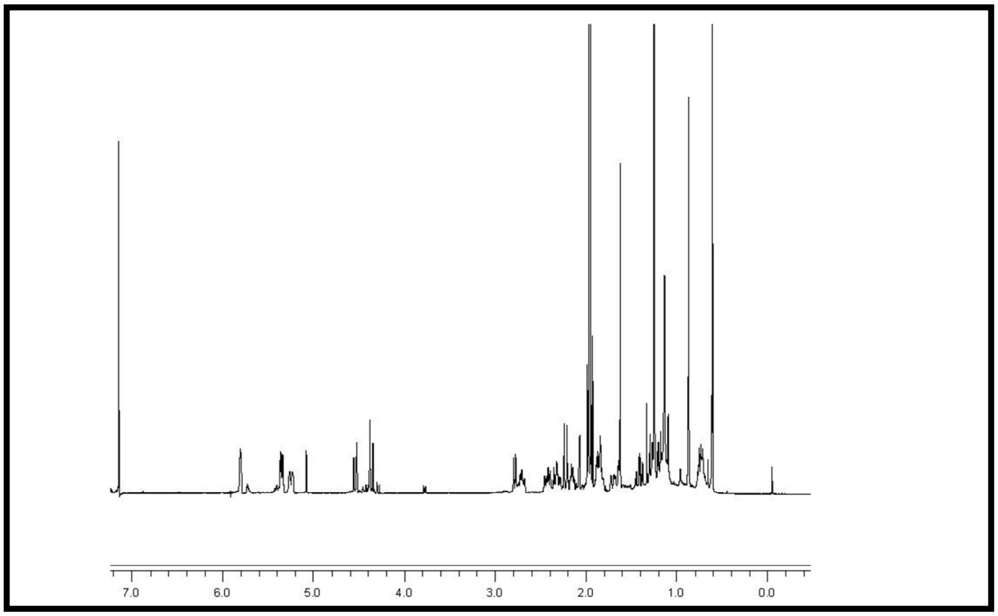
C	δ ppm	HSQC (δ ppm)	HMBC (δ ppm)
	40.0		0.89,0.61
	36.8		0.89.0.61
	31.3	1.23,1.20	
	30.2	1.98,1.36	
	30.1	1.56,1.31	
1	61.2	1.86	0.89,0.61
5	64.7	2.76	1.02
6	58.8		1.02
9	65.1	2.81	2.25,1.56
10	60.4		1.56
11	43.2	2.25,2.15	1.54
12	70.4	5.60	2.25
13	168.6		1.68
14	20.7	1.68	
15	15.9	1.02	
16	18.7	1.53	
17	32.9	1.78,0.82	
18	37.6	1.93,1.04	
19	127.9		4.64
20	111.7	4.64,4.53	
21	24.5	0.61	0.89
22	30.4	0.89	0.61

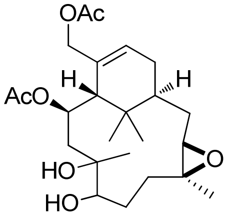
Table A1.9 2D-NMR Data for **1.46**

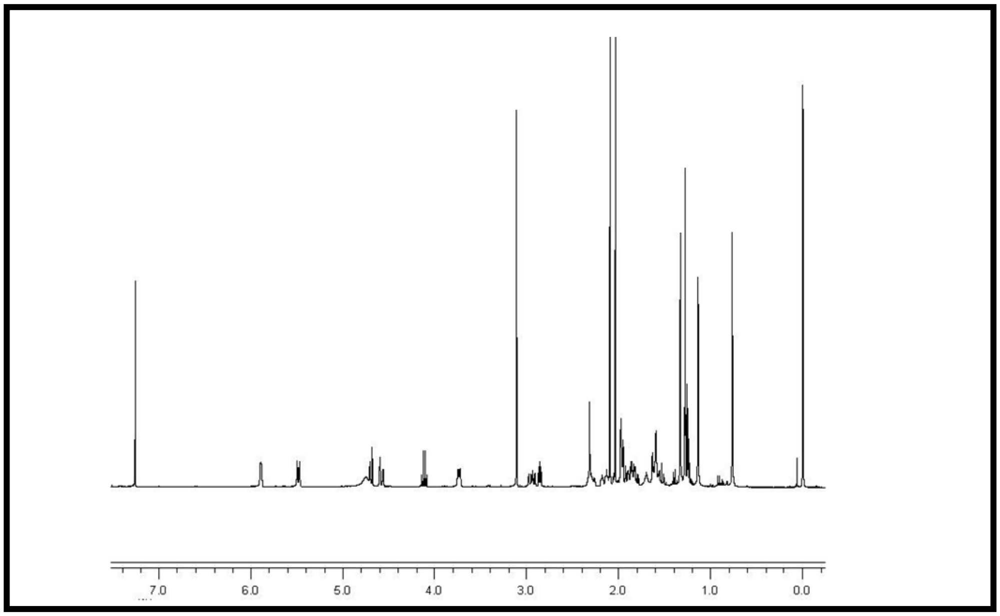


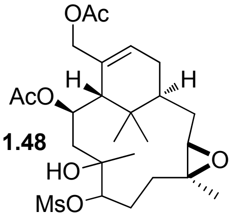


1.47

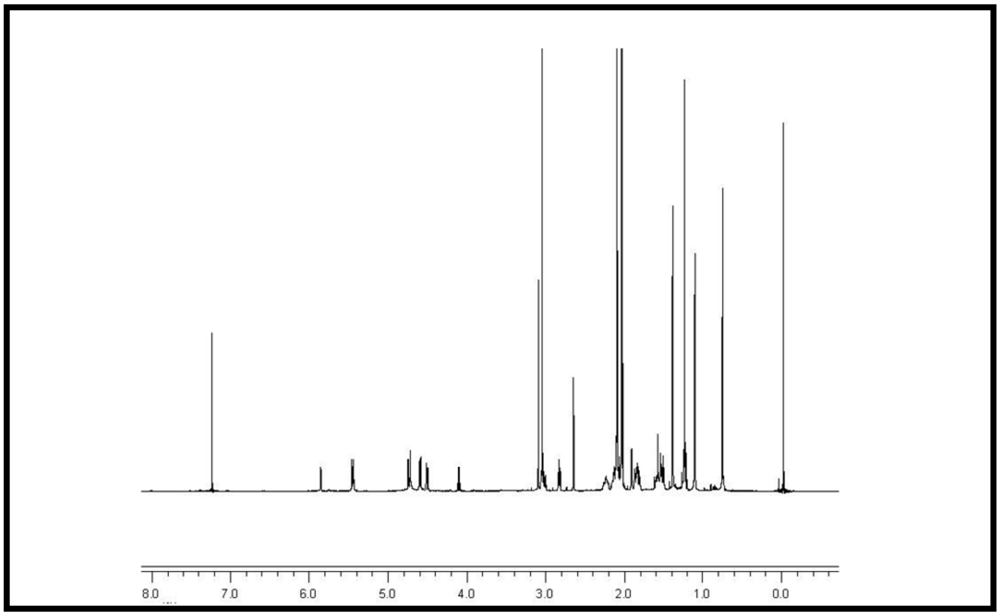


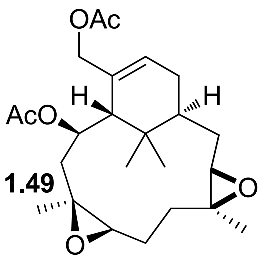

OAc
H
AcO
H
HO
O
HO

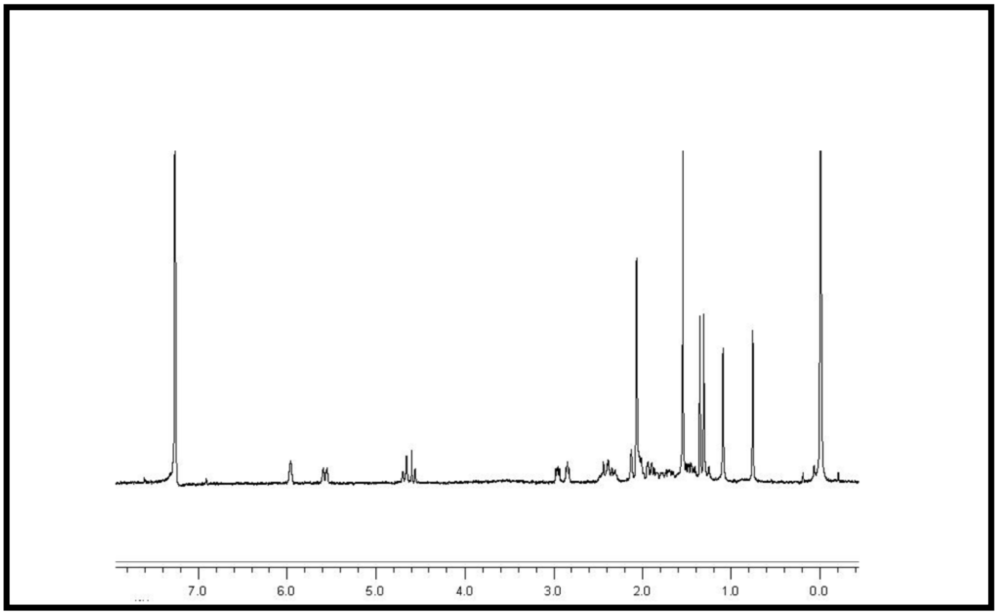

7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0



1.48

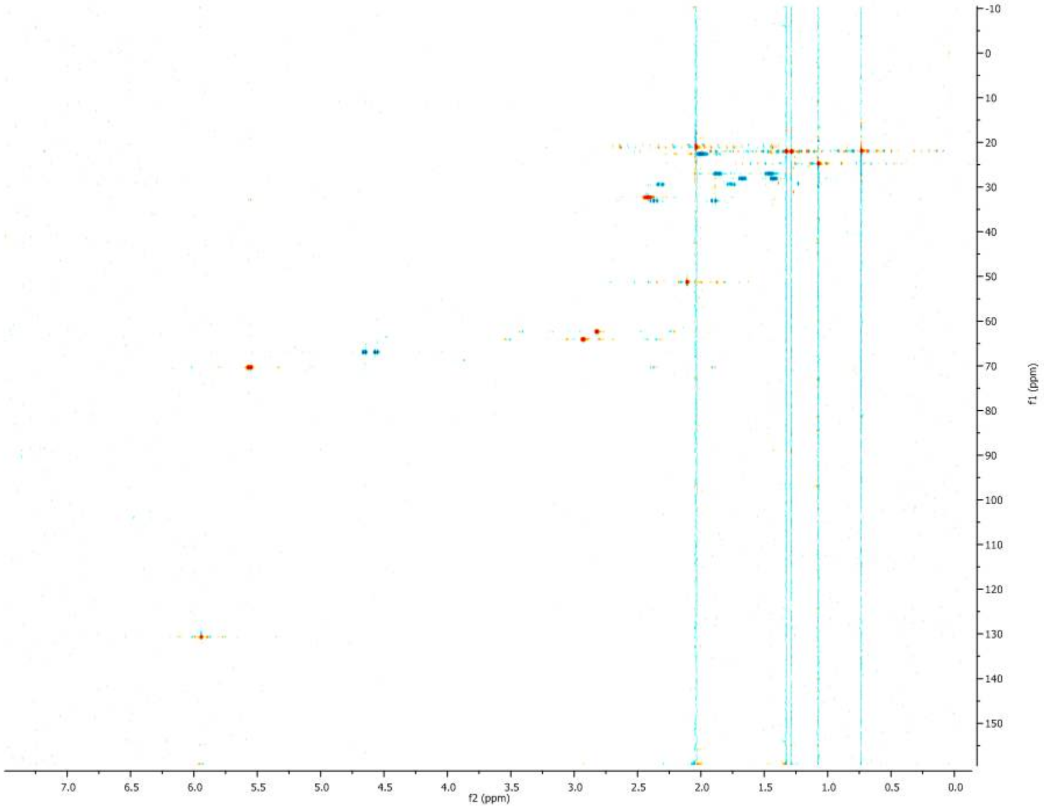




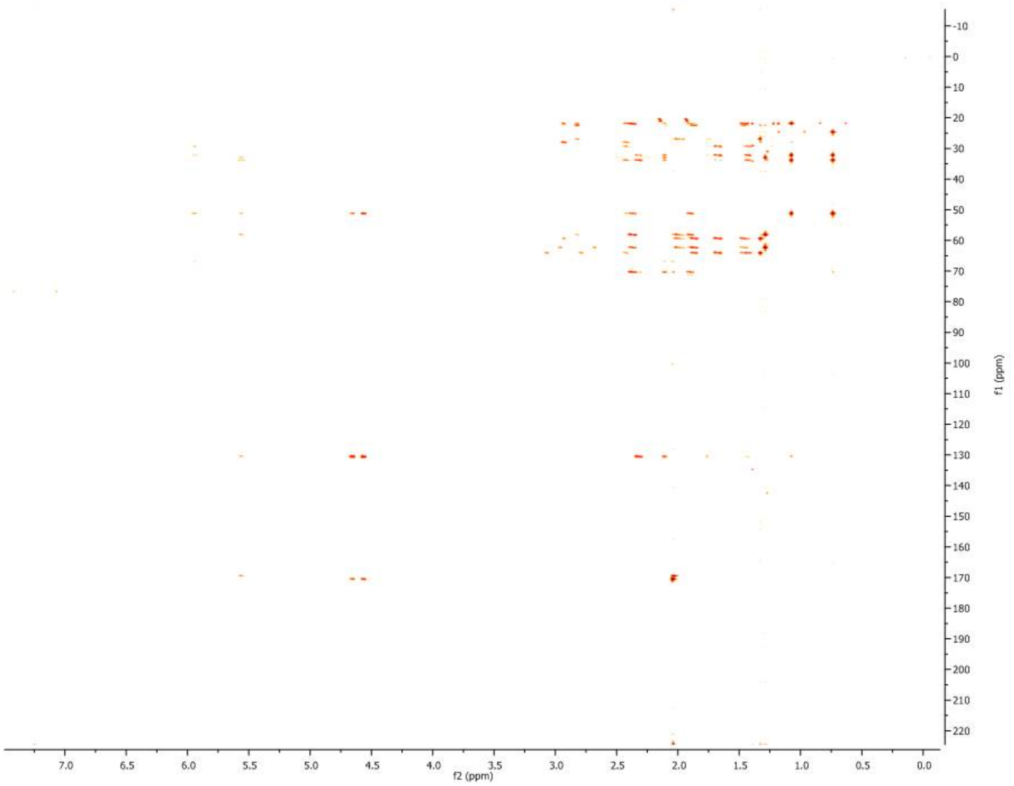


Carbon Chemical Shifts Extracted
From HSQC and HMBC Spectra

HSQC-AD (1.49)


7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f2 (ppm)
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
f1 (ppm)

HMBC-AD (1.49)

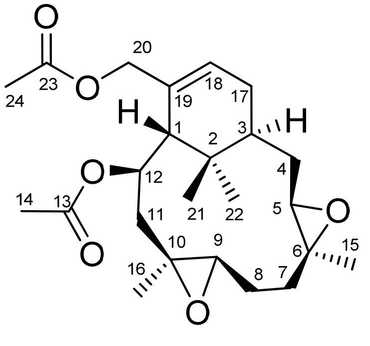

f2 (ppm)
f1 (ppm)
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220

Carbon and Proton Assignments From HSQC and HMBC Data:

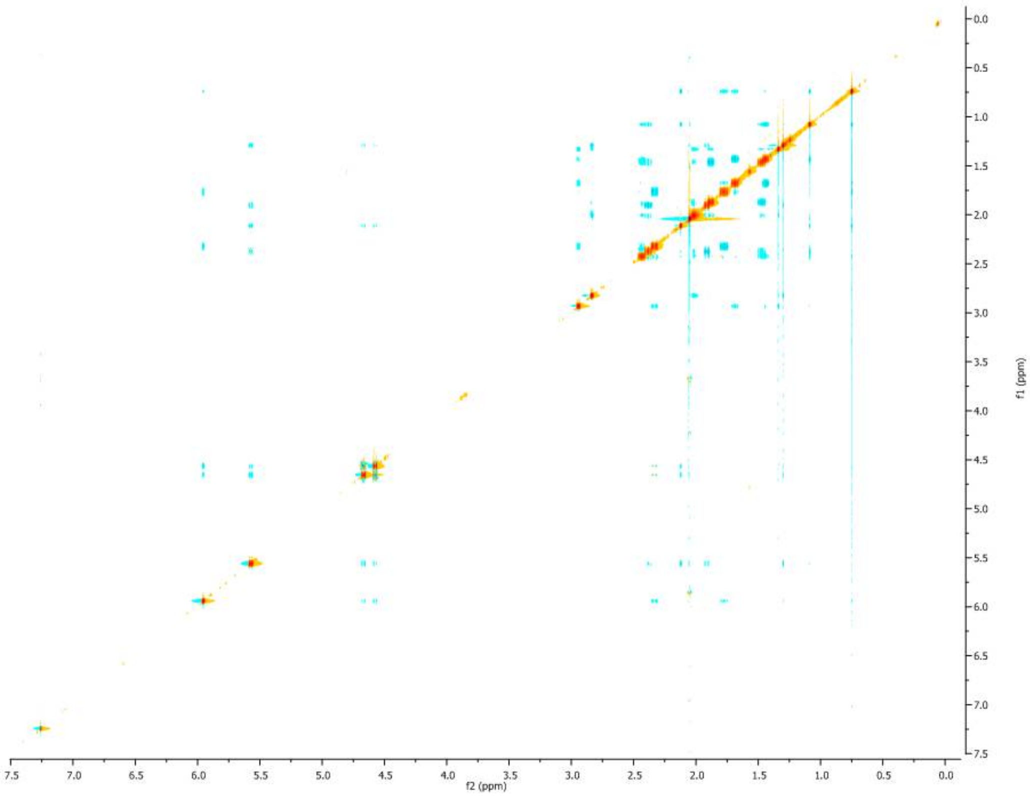
All carbons chemical shifts and the chemical shifts of the protons that are attached to them have been mapped out using both HSQC and HMBC techniques. These values can then be used to map out stereochemical relationships given NOE correlations.

C	δ ppm	HSQC (δ ppm)	HMBC (δ ppm)
1	51.5	2.11	5.94,5.56,4.65,4.56
2	34.1		5.56
3	32.6	2.42	5.94,2.93
4	28.4	1.64,1.43	2.93,1.33
5	64.4	2.93	1.33
6	59.8		2.93,1.33
7	27.3	1.87,1.46	2.82,1.33
8	22.9	2.00	2.82
9	62.6	2.82	1.29
10	58.5		5.56,1.29
11	33.3	2.37,1.90	1.29
12	70.7	5.56	
13	170.0		5.56,2.04
14	21.5	2.04	
15	22.3	1.33	2.93
16	22.3	1.29	2.82
17	29.8	2.32,1.76	5.94
18	131.0	5.94	5.56,4.56,1.43,1.08
19	130.7		5.56
20	67.2	4.65,4.56	5.94
21	22.2	0.74	
22	25.0	1.08	
23	170.8		2.05,4.65,4.56
24	20.9	2.04	

Table A1.10 2D-NMR Data for **1.49**

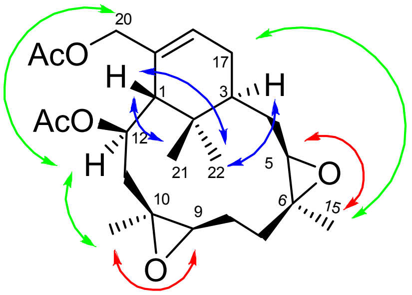


NOESY (1.49)



Important NOE Correlations For Proving Stereochemical Assignments:

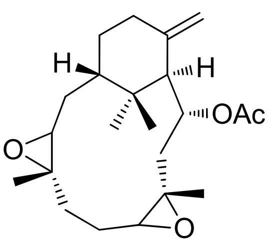
Pictured are the relevant NOE correlations to prove the stereochemical assignments. This shows correct C12 and the unnatural epoxide geometries (ZZ).

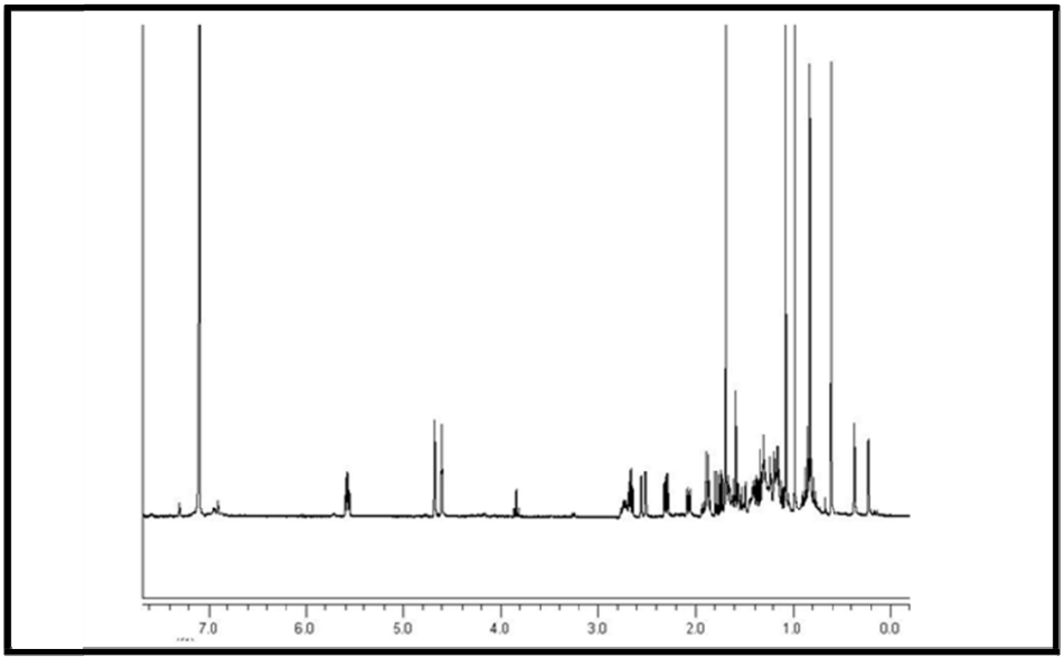


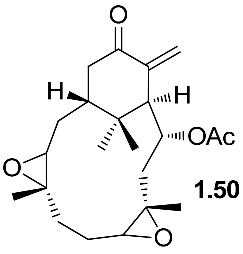
C9-C10 = Z-epoxide
C5-C6 = Z-epoxide

C1-C12 = axial
C3-C4 = equatorial
Incorrect atropisomer

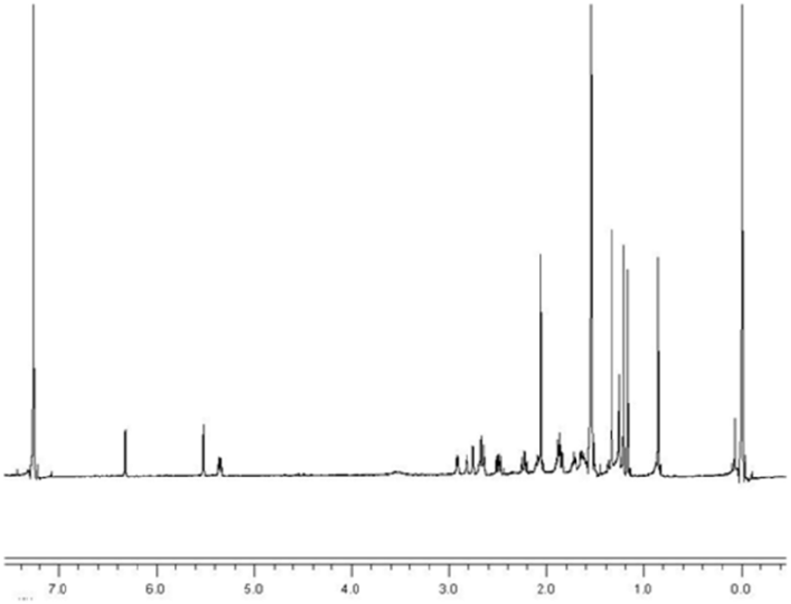
C12 = correct
C5,C6,C9,C10 relative stereochemistry correct


H
H
OAc
O
O


7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0



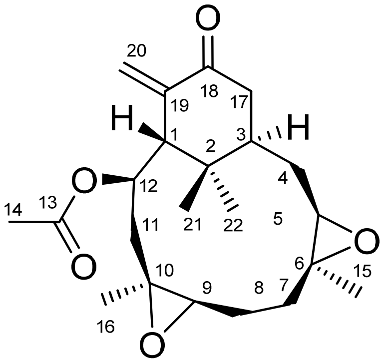
1.50

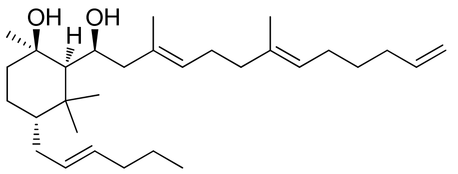


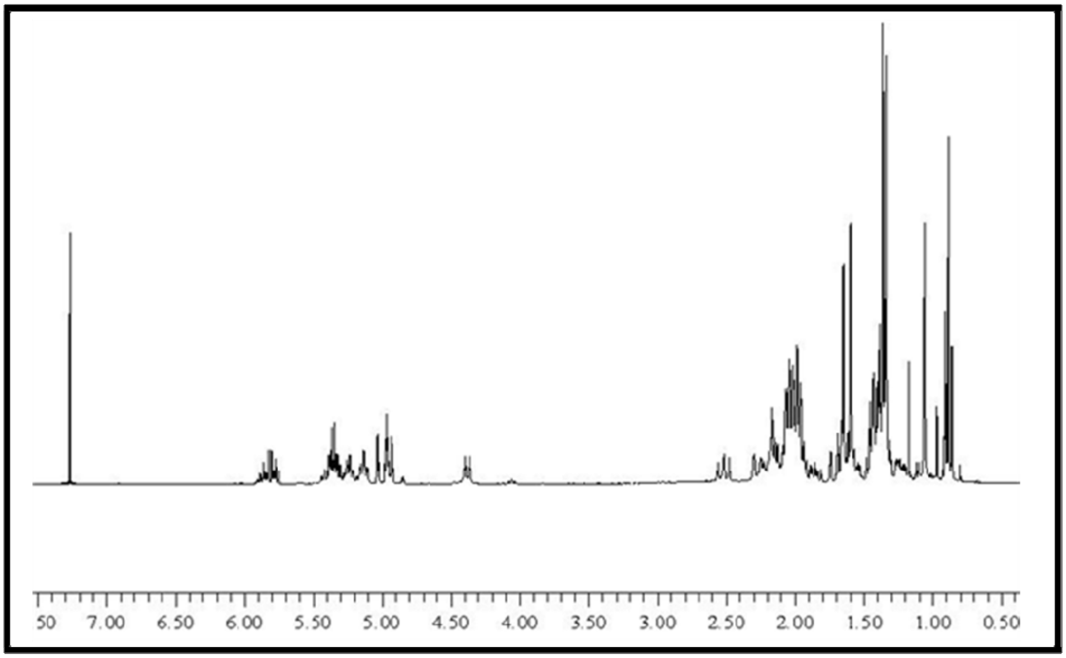
Carbon Chemical Shifts Extracted From HSQC and HMBC Spectra

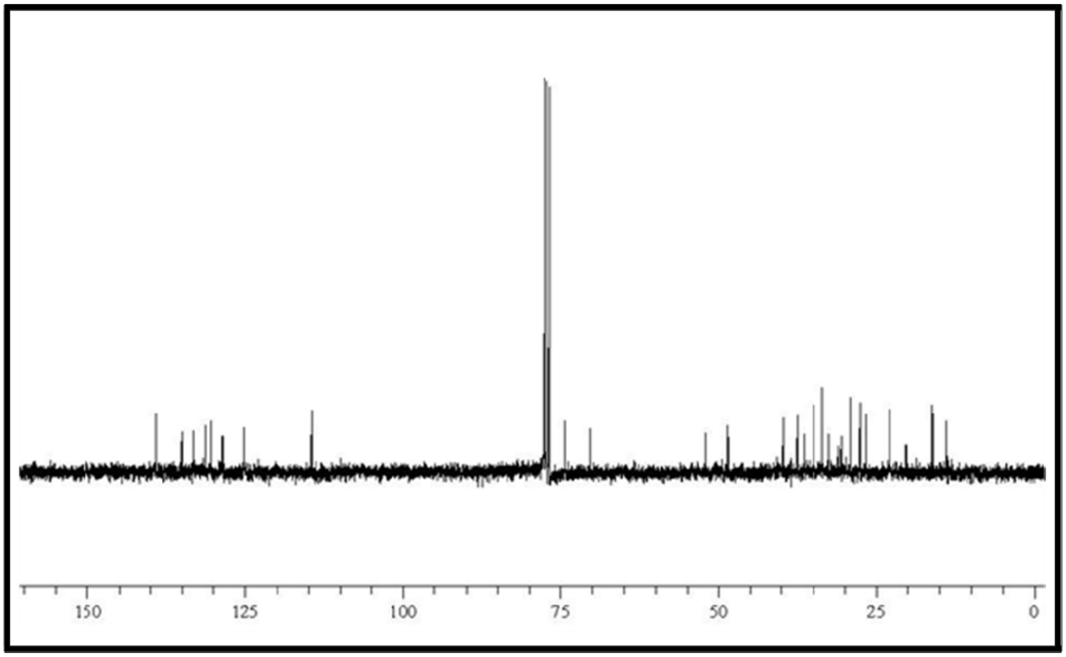
C	δ ppm	HSQC (δ ppm)	HMBC (δ ppm)
1	55.5	2.76	6.33,5.53,1.85,1.16,0.85
2	35.5		2.76,2.65,1.16,0.85
3	33.3	2.67	2.76,2.24,1.16,0.85
4	29.2	1.72,1.63	2.92,2.24
5	63.8	2.92	1.32
6	60.4		1.32
7	27.5	1.87,1.51	1.88,1.32
8	23.9	2.09,1.88	1.51
9	61.9	2.82	1.21
10	58.5		2.49,1.85,1.21
11	34.3	2.49,1.85	2.76,1.21
12	75.7	5.35	2.76,2.49,1.85
13	169.9		2.05
14	21.7	2.05	
15	23.4	1.32	1.51
16	22.9	1.21	2.49
17	42.1	2.65,2.24	1.63
18	198.7		6.33,5.53,2.65,2.24
19	144.4		6.33,2.76
20	127.1	6.33,5.53	2.76,2.09
21	24.1	0.85	2.76,1.16
22	26.1	1.16	0.85

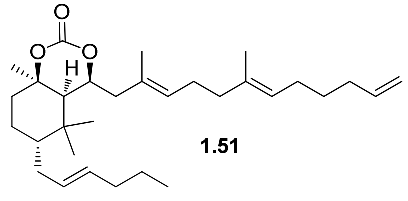
Table A1.11 2D-NMR Data for **1.50**



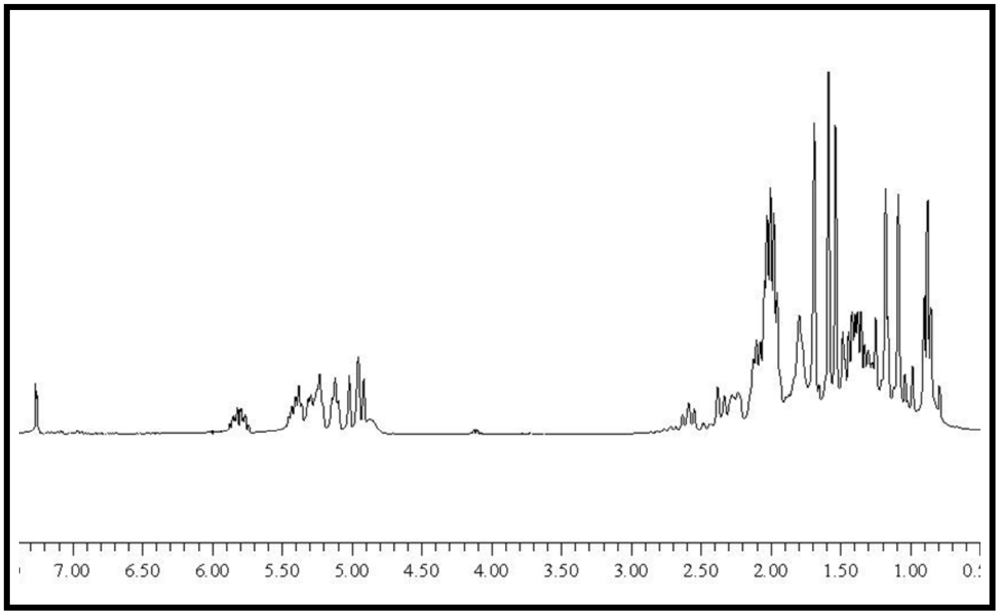

OH
H
OH


50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50

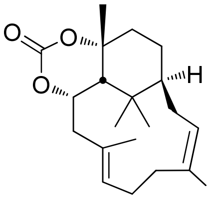

150
125
100
75
50
25
0

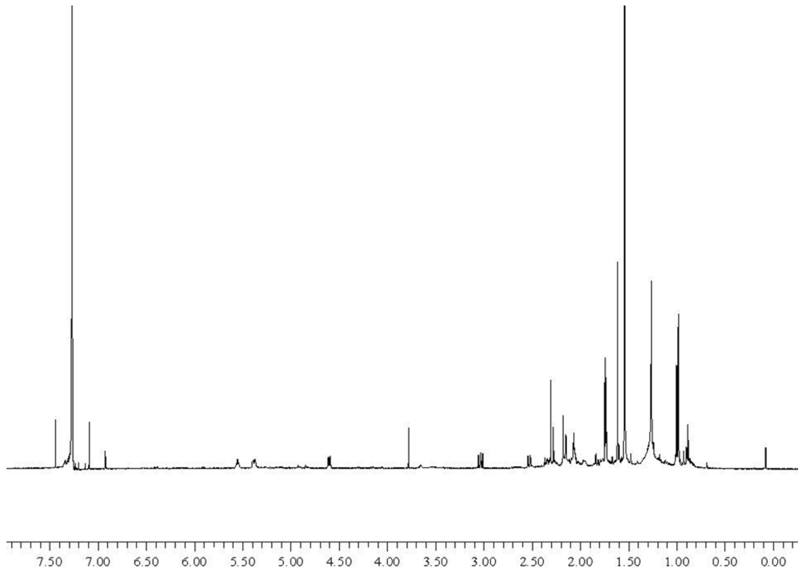


1.51



Carbon Chemical Shifts Extracted
From HSQC and HMBC Spectra

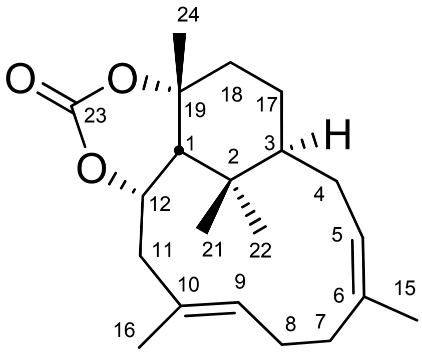


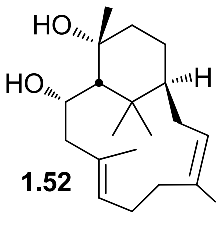


Carbon Chemical Shifts Extracted
From HSQC and HMBC Spectra

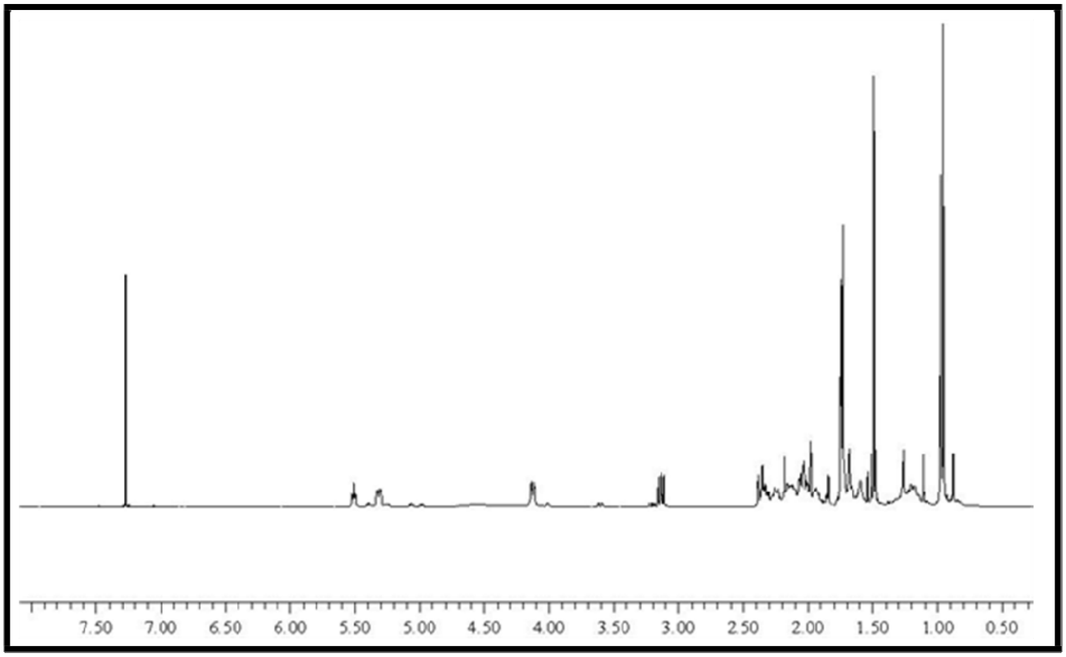
C	δ ppm	HSQC (δ ppm)	HMBC (δ ppm)
	135.9		1.72,1.43
	132.8	5.38	
	128.8		2.19,1.73
	125.2	5.54	
	43.8	3.03,2.52	
	38.2	2.05	
	33.5	1.61	
	32.0	2.26,1.95	
	30.5	1.43	
	29.7	1.26	
	27.6	1.00	
	25.3	2.16	
	24.2	0.98	
	24.1	2.34,2.08	
	15.2	1.72	
1	56.4	2.16	
2	35.6		0.98
3	44.1	2.14	
12	77.3	4.60	
19	86.1		1.61
23	154.5		4.60

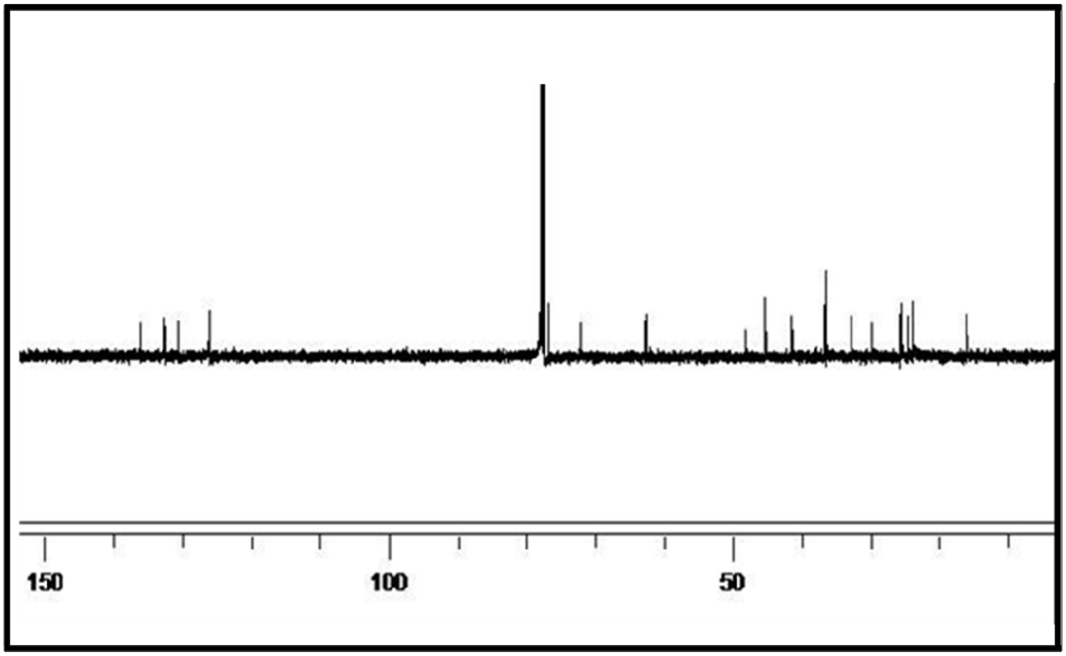
Table A1.12 2D-NMR Data for **1.52-(Carbonate)**





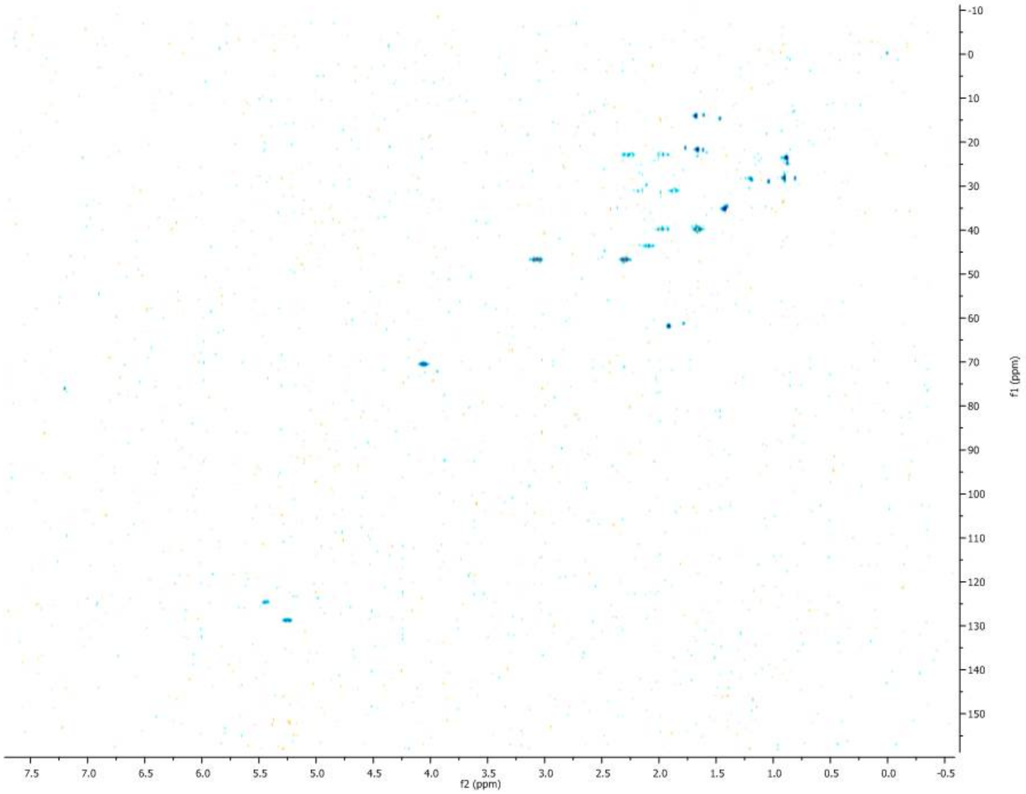
1.52


7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50

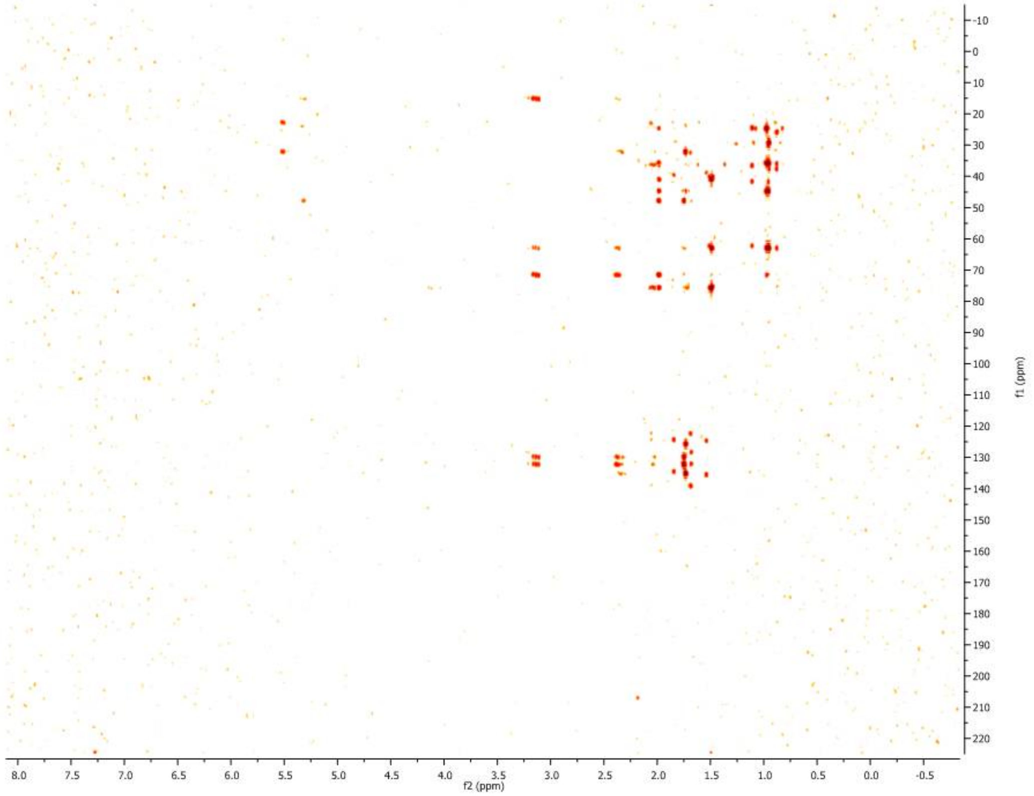

150
100
50

Spectral Confirmation of Verticillol Diol Stereochemistry

HSQC-AD (1.52)



HMBC-AD (1.52)



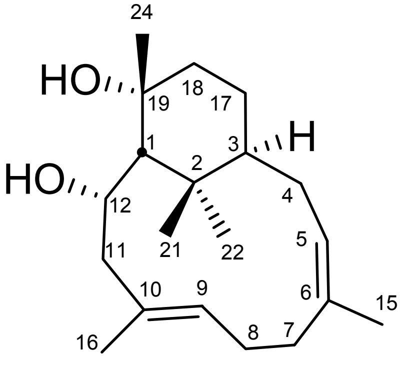
f1 (ppm)
f2 (ppm)
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

Carbon and Proton Assignments From HSQC and HMBC Data:

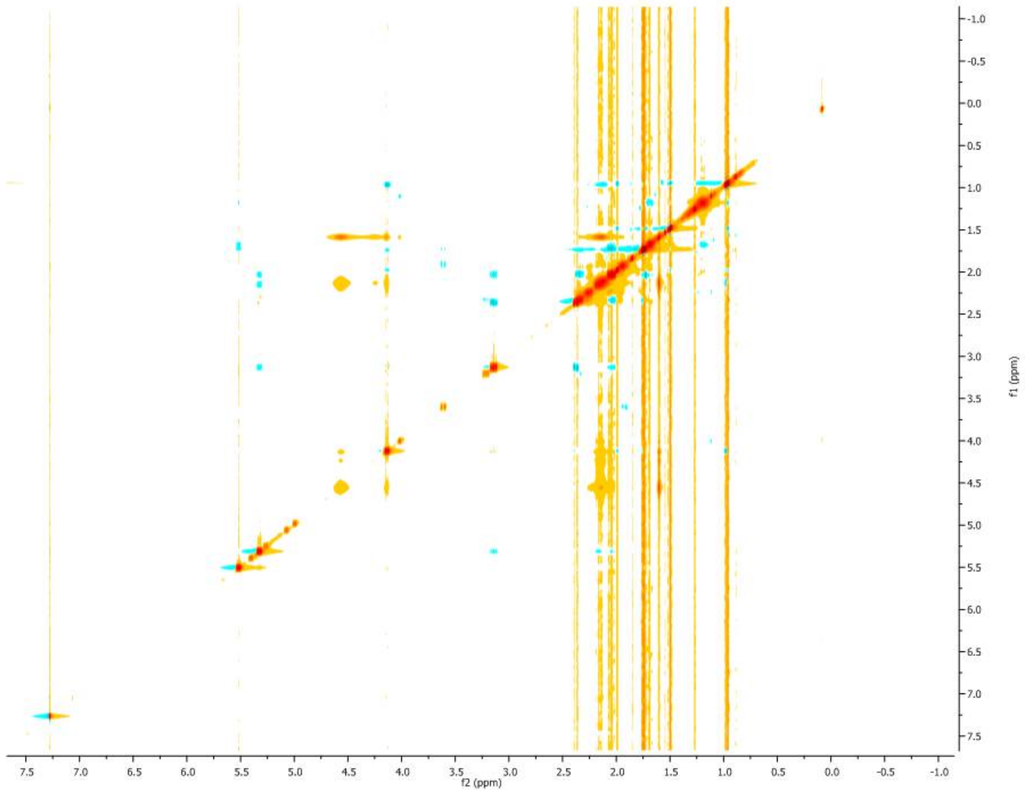
All carbons chemical shifts and the chemical shifts of the protons that are attached to them have been mapped out using both HSQC and HMBC techniques. These values can then be used to map out stereochemical relationships given NOE correlations.

C	δ ppm	HSQC (δ ppm)	HMBC (δ ppm)
1	62.0	1.91	3.06,2.29,1.42,0.88
2	43.7		1.91,0.88
3	34.8	2.09	1.91,0.88
4	24.3	1.11,2.04	5.44,1.91
5	124.7	5.44	1.66
6	134.2		2.26,1.66
7	31.3	2.18,1.86	5.44
8	23.0	2.26,1.97	1.68
9	128.8	5.24	3.06,2.29
10	131.2		3.06,2.29
11	47.0	2.29,3.06	5.24,1.91
12	70.7	4.06	3.06,2.29,1.91,0.88
15	21.9	1.66	5.44
16	14.3	1.68	5.24
17	35.6	1.61,1.12	1.96
18	40.3	1.66,1.96	1.91,1.42
19	74.9		1.91,1.66,1.42
21	23.8	0.88	0.90
22	28.5	0.90	0.88
24	35.4	1.42	1.96,1.91

Table A1.13 2D-NMR Data for **1.52**

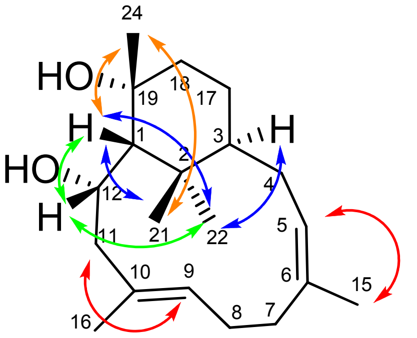


NOESY (1.52)



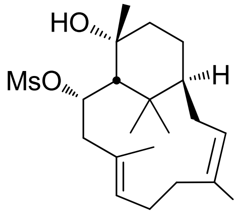
Important NOE Correlations For Proving Stereochemical Assignments:

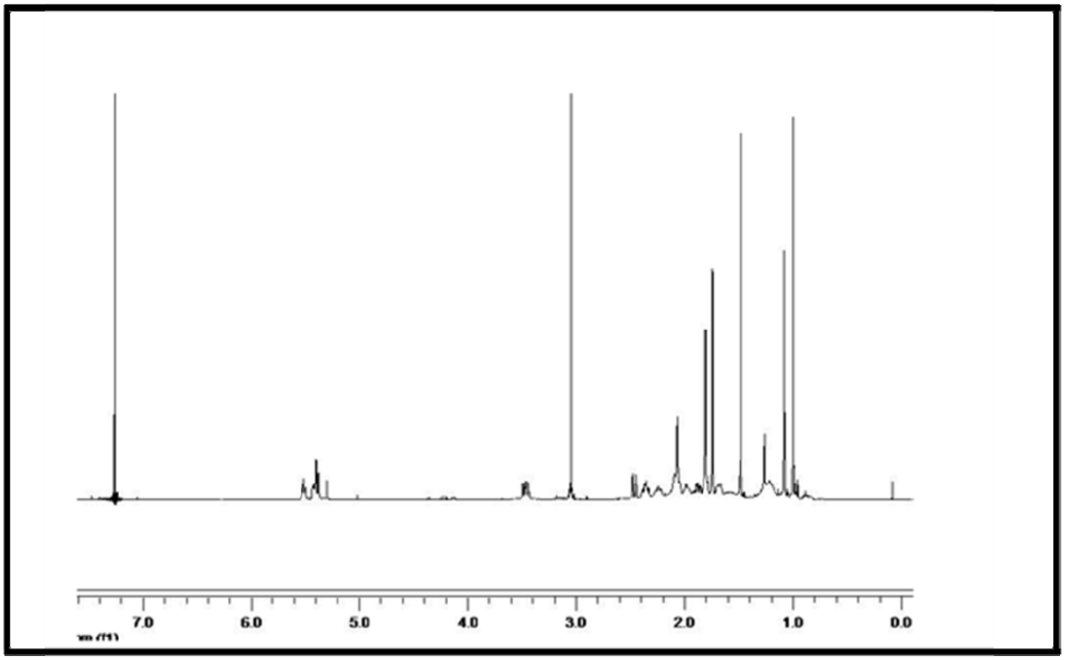
Pictured are the relevant NOE correlations to prove the stereochemical assignments. This shows incorrect C19 and C12 stereochemistry and incorrect olefin geometry (EZ).

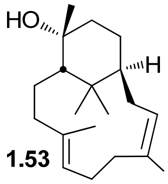


C1-C12 = axial
C3-C4 = equatorial
Incorrect atropisomer

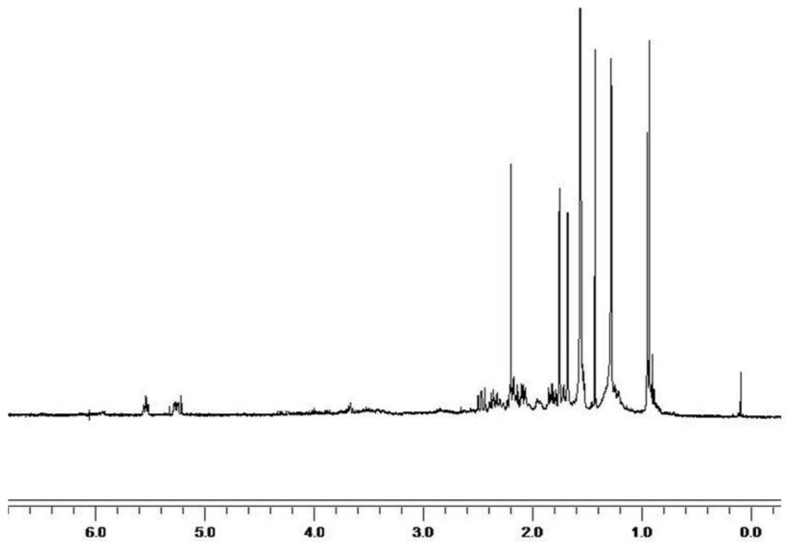
C9-C10 = E-olefin
C5-C6 = Z-olefin
C12 = incorrect
C19 = incorrect


HO
MsO
H


7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
pm (f1)



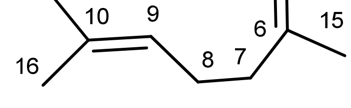
1.53



Carbon Chemical Shifts Extracted From HSQC and HMBC Spectra

C	δ ppm	HSQC (δ ppm)	HMBC (δ ppm)
	135.0		1.65
	134.9		1.73
	128.6	5.24	1.65
	125.7	5.52	1.73
	40.6	1.80,1.72	1.40
	37.4	2.43,2.17	1.65
	32.2	2.87,1.91	1.73
	29.7	0.92	
	29.6	1.32,1.26	0.91
	27.2	2.01	
	24.9	0.91	0.92
	24.6	2.33,2.05	
	24.0	2.08,1.79	
	22.9	1.73	
	15.2	1.65	
1	57.8	1.51	1.40,0.91
2	36.5		0.91,0.92
3	44.6	2.14	0.92
19	73.4		1.40
24	34.6	1.40	

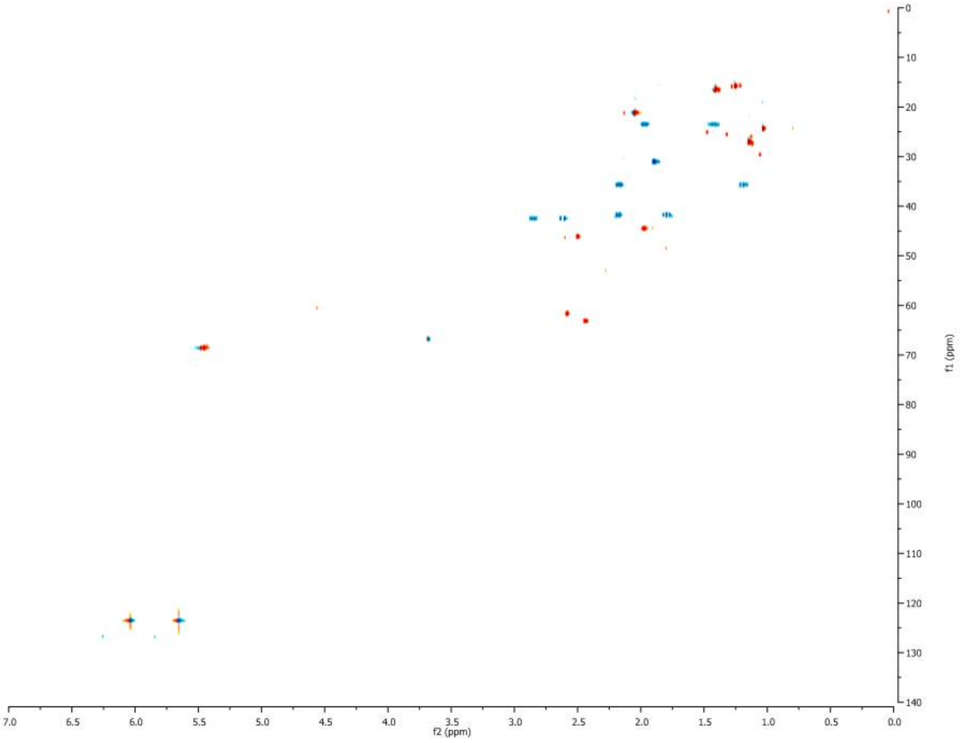
Table A1.14 2D-NMR Data for **1.53**



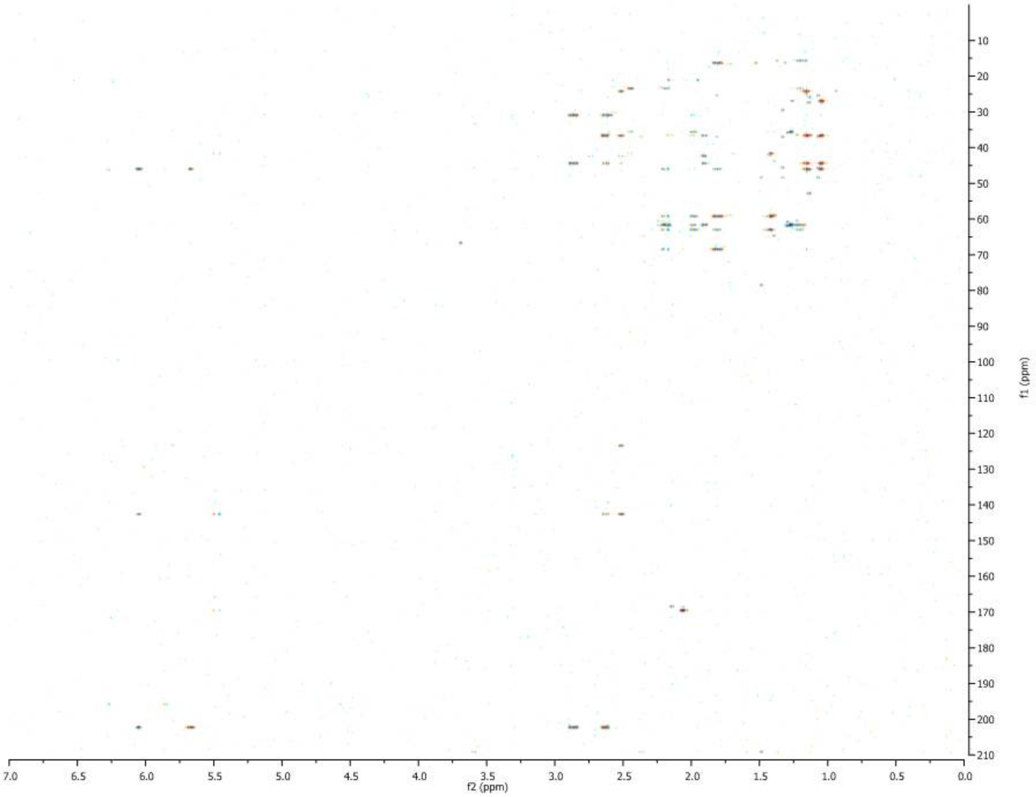
Spectral Data for Authentic Hypoestoxide

2-D NMR analysis of Hypoestoxide is consistent with previously published crystal structure from isolation paper.

Hypoestoxide HSQC-AD (1.1)



Hypoestoxide HMBC-AD (1.1)

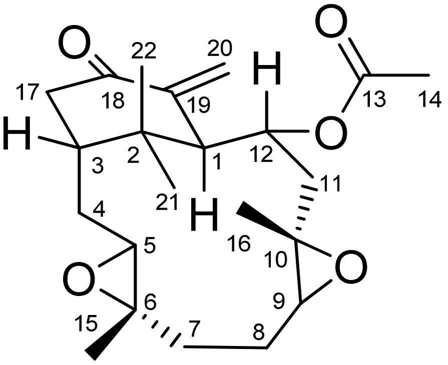


Carbon and Proton Assignments From HSQC and HMBC Data:

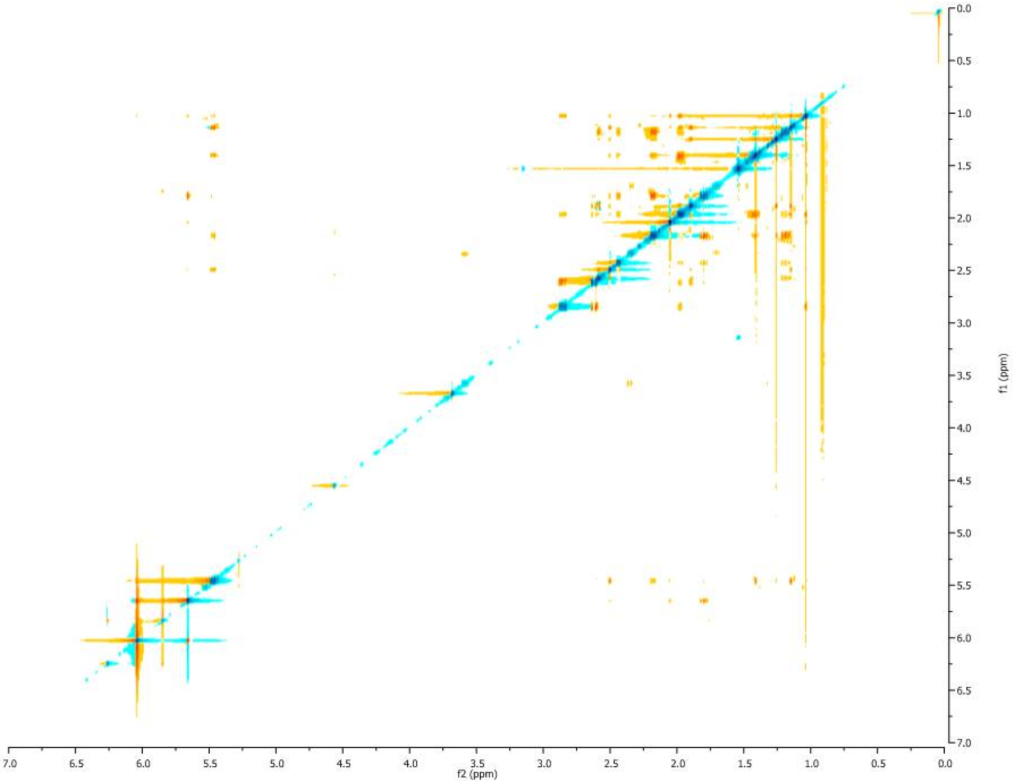
All carbons chemical shifts and the chemical shifts of the protons that are attached to them have been mapped out using both HSQC and HMBC techniques. These values can then be used to map out stereochemical relationships given NOE correlations.

C	δ ppm	HSQC (δ ppm)	HMBC (δ ppm)
1	46.7	2.51	6.05,5.66,1.15,1.04
2	37.3		2.62,2.51,1.90,1.15,1.04
3	45.0	1.98	2.86,2.62,1.90,1.15,1.04
4	31.6	1.90,1.90	2.86,2.62
5	62.2	2.59	1.27
6	62.3		
7	36.2	2.18,1.20	1.98,1.27
8	24.1	1.98,1.43	2.45,2.19
9	63.7	2.44	1.98,1.43
10	59.9		1.80,1.43
11	42.3	2.19,1.80	1.42
12	69.1	5.47	2.19,1.80
13	170.2		2.05
14	21.7	2.05	
15	16.3	1.27	
16	16.9	1.42	1.80
17	43.0	2.86,2.62	1.90
18	203.0		6.04,5.66,2.86,2.62
19	143.3		6.05,2.52
20	124.1	6.04,5.66	2.51
21	24.9	1.04	2.52,1.15
22	27.6	1.15	1.04

Table A1.15 2D-NMR Data for Authentic Hypoestoxide **1.1**



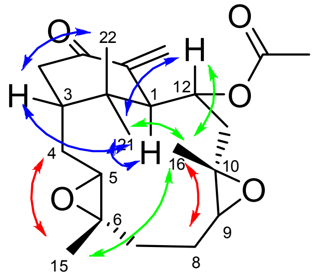
Hypoestoxide NOESY (1.1)



Important NOE Correlations For Proving Stereochemical Assignments:

Pictured are the relevant NOE correlations to prove the stereochemical assignments for Hypoestoxide.

Hypoestoxide



C1-C12 = equatorial
C3-C4 = axial
Atropisomer defined

C9-C10 = E-epoxide
C5-C6 = E-epoxide

C12 stereochemistry defined
C5,C6,C9,C10 relative stereochemistry defined

Hypoestoxide Isomer Comparison

Authentic Hypoestoxide (1.1)

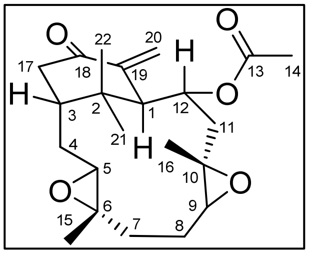
C	δ ppm	^{1}H δ ppm
18	203.0	
13	170.2	
19	143.3	
20	124.1	6.04,5.66
12	69.1	5.47
9	63.7	2.44
6	62.3	
5	62.2	2.59
10	59.9	
1	46.7	2.51
3	45.0	1.98
17	43.0	2.86,2.62
11	42.3	2.19,1.80
2	37.3	
7	36.2	2.18,1.20
4	31.6	1.90,1.90
22	27.6	1.15
21	24.9	1.04
8	24.1	1.98,1.43
14	21.7	2.05
16	16.9	1.42
15	16.3	1.27

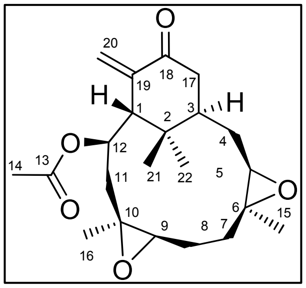
Z,Z-Atrop-Hypoesotoxide (1.50)

C	δ ppm	^{1}H δ ppm
18	198.7	
13	169.9	
19	144.4	
20	127.1	6.33,5.53
12	75.7	5.35
5	63.8	2.92
9	61.9	2.82
6	60.4	
10	58.5	
1	55.5	2.76
17	42.1	2.65,2.24
2	35.5	
11	34.3	2.49,1.85
3	33.3	2.67
4	29.2	1.72,1.63
7	27.5	1.87,1.51
22	26.1	1.16
21	24.1	0.85
8	23.9	2.09,1.88
15	23.4	1.32
16	22.9	1.21
14	21.7	2.05

E,Z-epi-Atrop-Hypoestoxide (1.41)

C	δ ppm	^{1}H δ ppm
18	199.1	
13	169.8	
19	141.5	
20	127.7	6.22,5.31
12	70.6	5.4
9	65.7	2.71
5	62.7	2.87
10	59.6	
6	59.2	
1	58.7	2.53
11	42.3	2.06,1.26
17	41.1	2.60,2.24
2	36.2	
3	35.1	1.86
4	31.6	1.26
7	27.2	2.01,1.37
22	26.3	1.22
8	22.8	1.29
15	22	1.39
21	21.5	0.94
14	21.4	2.07
16	16.4	1.47





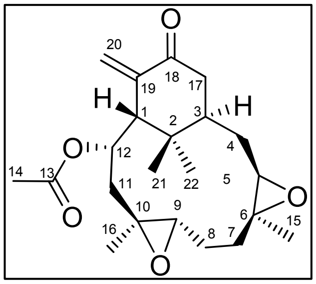


Table A1.16 Hypoestoxide Isomer Analysis

Proton Spectra Overlay For Isomers of Hypoestoxide

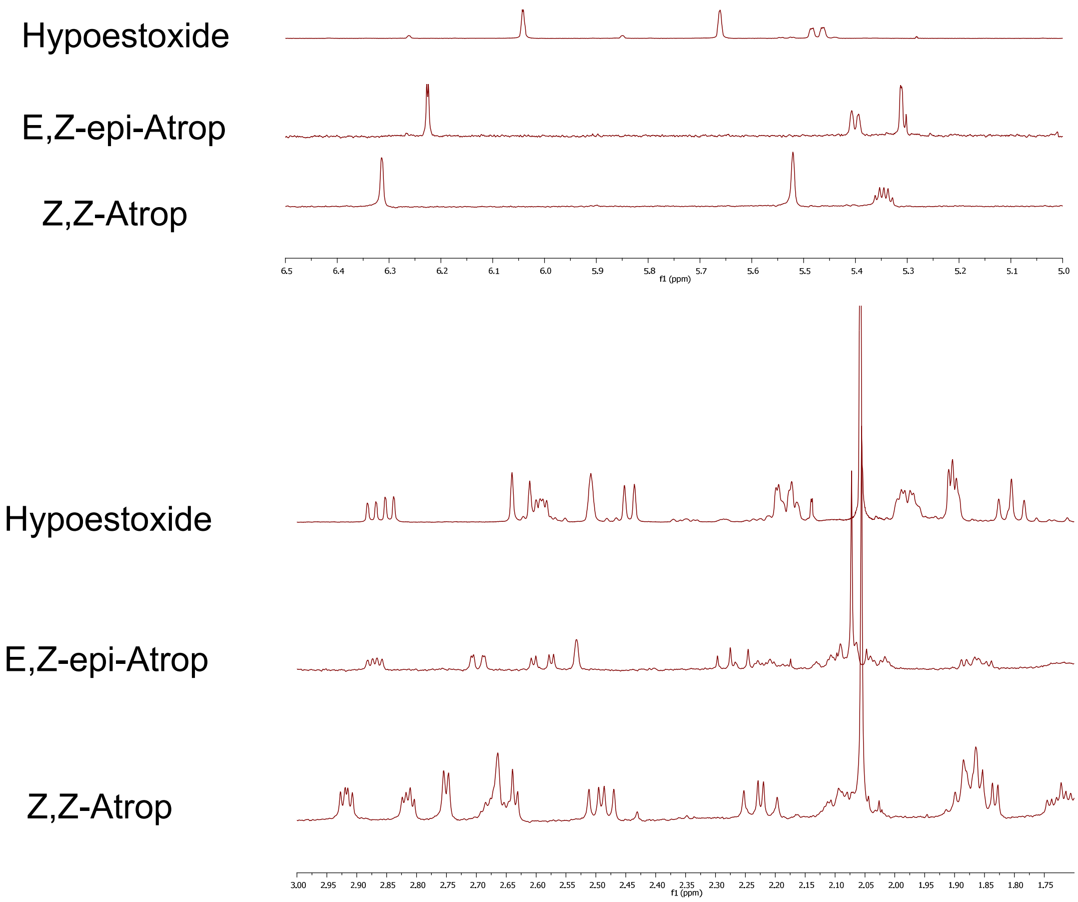


Figure A1.1 NMR Overlay of Hypoestoxide Isomers

A1.3 DFT Calculations for Chapter 1

Coordinates and calculated energies

DFT calculations were performed with the program Gaussian03[1] by using the WebMO interface (WebMO, version 6.0.003; www.webmo.net) for importing and constructing models.

[1]Gaussian 03 (Revision C.02); M. J. Frisch,G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, and J. A. Pople, Gaussian, Inc., Wallingford CT, 2004.

Structure	Method	Basis Set	Uncorrected Energy (hartrees)	Corrected Energy (hartree)	Corrected Energy (kcal/mol)	Relative E(kcal/ mol)	Freq. (cm^{-1})
Hypoestoxide	B3LYP	6-311+G(d,p)	-1233.994224	-1233.54252	-774059.7832	0	
Atrop-hypo	B3LYP	6-311+G(d,p)	-1233.986218	-1233.535978	-774055.678	4.11	
TS-1	B3LYP	6-311+G(d,p)	-1233.892363	-1233.438121	-773994.2718	65.51	-112.6

Table A1.17 Calculated Energies for Atropisomers of Hypoestoxide

```
Hypoestoxide  B3LYP/6-311+G(d,p)
C1     0.00000000  0.00000000  0.00000000
C2     0.02583700 -0.68570800  1.36209000
C3    -1.00160500 -1.76657500  1.57880400
C4    -1.30489700 -2.65823700  0.38634200
C5    -1.26270600 -1.97804200 -0.99899100
C6    -0.00330600 -1.05954400 -1.16546100
C7     1.26101300 -1.94691600 -1.13775000
H8     1.18400600 -2.73110800 -1.89734800
H9     1.42012400 -2.42556300 -0.17028200
H10    2.15400600 -1.36089300 -1.35681300
C11   -0.05894100 -0.37172100 -2.54407400
H12    0.89460800  0.09349400 -2.80189500
H13   -0.27504800 -1.11046100 -3.32190500
H14   -0.83198500  0.39865000 -2.59612400
C15   -2.64686800 -1.38090900 -1.37423000
C16   -3.33080200 -0.42096900 -0.41339500
C17   -3.87752000  0.92770900 -0.72834300
O18   -4.73466300 -0.23090700 -0.66319100
C19   -4.17911300  1.90004400  0.40836000
C20   -3.29032400  3.14722900  0.55151800
C21   -1.88084400  2.87467400  1.03336600
C22   -0.61787600  3.17402000  0.31095100
C23    0.64565600  2.41397600  0.69775700
C24    0.96267800  1.18984300 -0.17995000
O25    2.33445200  0.76947000  0.08633300
C26    3.31667500  1.31368300 -0.67164500
C27    4.67311100  0.83887700 -0.21781800
H28    5.41511800  1.08325400 -0.97539200
H29    4.66438300 -0.23376800 -0.01921700
H30    4.93494400  1.34589600  0.71522600
O31    3.11687100  2.08361500 -1.57990600
H32    0.93494800  1.50530100 -1.22007900
H33    1.48637700  3.11002700  0.60998600
H34    0.56768900  2.13083700  1.74725800
C35   -0.59694700  3.83655900 -1.04973200
H36   -1.48132900  4.45313600 -1.20517000
H37   -0.53449000  3.10441800 -1.85939100
H38    0.28114000  4.48397900 -1.12627700
O39   -1.08968800  4.02529500  1.37542800
H40   -1.82286600  2.09005100  1.79063200
H41   -3.75307200  3.79547600  1.30423600
H42   -3.28242100  3.72682500 -0.37393800
H43   -4.18833700  1.34027500  1.34910300
H44   -5.20978900  2.23867600  0.25077400
C45   -3.75933500  1.53938900 -2.10694000
H46   -3.71740000  0.77238200 -2.87968900
H47   -4.63521800  2.16404900 -2.30810500
H48   -2.87229200  2.17183400 -2.19188100
H49   -3.13079200 -0.60706800  0.64174500
H50   -3.32976800 -2.23558200 -1.44890700
H51   -2.61091600 -0.95442800 -2.37709900
H52   -1.11982500 -2.78038200 -1.73218000
H53   -0.54156100 -3.44498400  0.42651900
H54   -2.26182000 -3.15385200  0.56548700
O55   -1.50150600 -1.97526800  2.66685900
C56    0.87829800 -0.47285300  2.36985800
H57    0.75587400 -1.02977100  3.29190800
H58    1.70373400  0.22079500  2.30622700
H59   -0.98533900  0.47891900 -0.07214600
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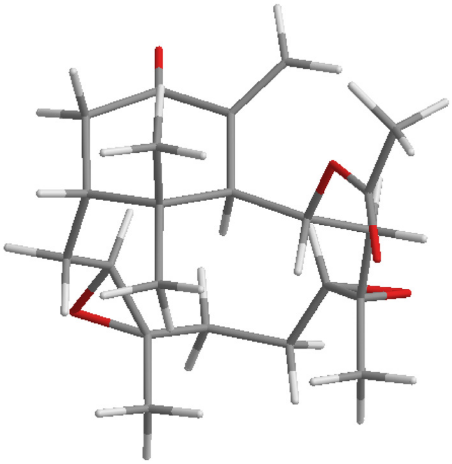
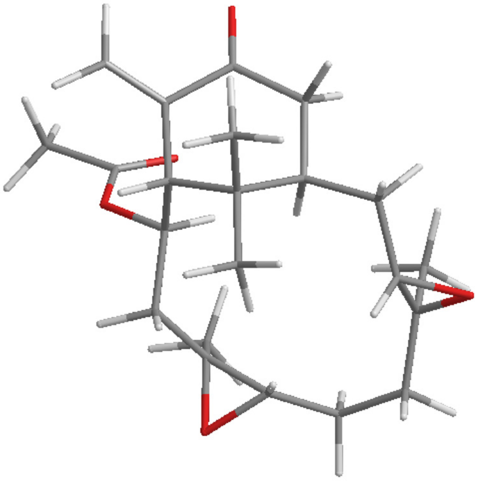


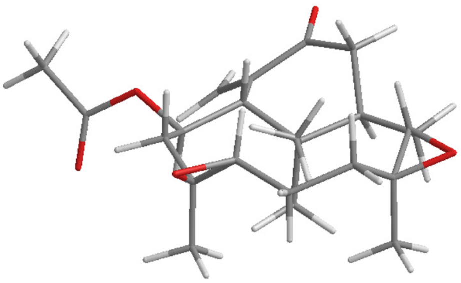
Atrop-Hypoestoxide B3LYP/6-311+G(d,p)

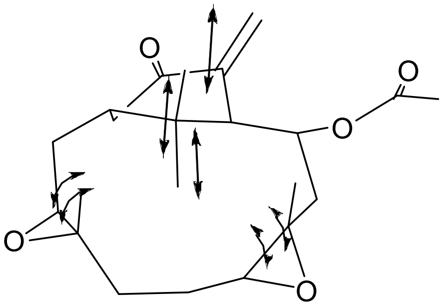
C1	0.00000000	0.00000000	0.00000000
C2	1.10411800	-0.59353600	-0.86334300
C3	0.71417600	-1.31819300	-2.12907100
C4	-0.72958100	-1.79619500	-2.27902400
C5	-1.77518100	-1.22374300	-1.30100600
C6	-1.15622100	-1.06967300	0.12576500
C7	-2.19790500	-0.68579400	1.19202800
H8	-2.83900800	0.13783900	0.89667000
H9	-2.84345900	-1.53994300	1.41068300
H10	-1.70380900	-0.41134100	2.12882700
C11	-0.54655400	-2.40072000	0.63535700
H12	-0.11986300	-2.25493400	1.63238500
H13	0.24540000	-2.80308300	0.00560200
H14	-1.32464000	-3.16374600	0.72251800
C15	-3.11001400	-2.00335200	-1.42061600
C16	-4.34387800	-1.15163100	-1.17154600
C17	-4.86631600	-0.12760100	-2.10919200
O18	-5.51364100	-1.41438200	-1.96512100
C19	-5.70851900	1.02026000	-1.56192400
C20	-5.00312300	2.38115800	-1.38466400
C21	-3.86913600	2.34789700	-0.37460300
C22	-2.50113000	2.90185700	-0.55377600
C23	-1.33396800	2.30973700	0.23953700
C24	-0.40079700	1.39520100	-0.59213500
O25	0.83263900	2.15351000	-0.78408100
C26	1.27297900	2.36680000	-2.04919100
C27	2.58912500	3.09760600	-2.04159600
H28	2.81380800	3.45107700	-3.04587300
H29	3.37426100	2.40825500	-1.71953200
H30	2.56662500	3.92973000	-1.33624600
O31	0.67955400	2.01142500	-3.03841600
H32	-0.81361300	1.24636700	-1.58602300
H33	-0.72640700	3.14027500	0.61094200
H34	-1.72160000	1.80353800	1.12005300
C35	-2.12681500	3.68275100	-1.79650100
H36	-1.64863000	3.05916000	-2.55486600
H37	-1.42153400	4.47449300	-1.52533900
H38	-3.00257400	4.16092800	-2.23391000
O39	-3.47888500	3.57515700	0.26553200
H40	-3.97424900	1.54261900	0.34971100
H41	-5.74581800	3.09917500	-1.02116700
H42	-4.66094800	2.76259000	-2.34951800
H43	-6.13664700	0.70247200	-0.60592700
H44	-6.55496700	1.15799300	-2.24448600
C45	-4.24338700	0.10920100	-3.46899000
H46	-3.74076800	-0.78233100	-3.84158900
H47	-5.02380400	0.37644700	-4.18826400
H48	-3.51992400	0.92841600	-3.44324000
H49	-4.59169700	-0.99602100	-0.12358000
H50	-3.12799000	-2.87099600	-0.75215300
H51	-3.18853900	-2.40825400	-2.43231200
H52	-2.01453200	-0.21667900	-1.64692300
H53	-1.02074900	-1.60692100	-3.31584400
H54	-0.68268800	-2.88799100	-2.18298000
O55	1.53038700	-1.58564400	-2.98730900
C56	2.39720100	-0.55727100	-0.53186400
H57	3.13905400	-1.01214900	-1.17847600
H58	2.73593200	-0.08409100	0.38317900
H59	0.40750000	0.17824700	1.00140000



TS-1 B3LYP/6-311+G(d,p)

C1	0.00000000	0.00000000	0.00000000
C2	0.86000300	1.21988600	0.21682300
C3	0.20772900	2.46099500	-0.37573600
C4	-1.29889700	2.36345400	-0.68497400
C5	-2.01031000	1.67561000	0.49703400
C6	-1.38161800	0.25278100	0.71439400
C7	-1.29442400	0.00481100	2.22861200
H8	-0.99311900	-1.00931000	2.48818600
H9	-0.57313600	0.68791300	2.68631400
H10	-2.26443400	0.18553700	2.69937900
C11	-2.22269300	-0.72573700	-0.04480100
H12	-1.59423300	-1.45590900	-0.46996800
H13	-2.66685000	-0.26152100	-0.91234700
H14	-2.95836100	-1.20995100	0.56613400
C15	-3.60961300	1.69854800	0.50223100
C16	-4.42509900	0.66601000	-0.30533200
C17	-4.99990200	-0.60291500	0.20484900
O18	-5.85244700	0.51542100	-0.17844000
C19	-5.01765000	-1.87480600	-0.69358400
C20	-4.17383700	-3.16766600	-0.31425000
C21	-2.69592700	-3.26033600	-0.75674900
C22	-1.48427100	-3.41643200	0.09530900
C23	-0.12102800	-2.77685600	-0.34712600
C24	0.56493300	-1.45538900	0.27684600
O25	1.86948100	-1.45929000	-0.37157400
C26	2.90795500	-2.04810900	0.26908300
C27	4.15364200	-1.99500000	-0.57576600
H28	4.33782500	-0.97408200	-0.91551900
H29	4.01757100	-2.61682500	-1.46432600
H30	4.99989800	-2.36252500	0.00082100
O31	2.82486600	-2.54308000	1.36720400
H32	0.72966200	-1.61096400	1.34189000
H33	0.63113200	-3.55055400	-0.16325100
H34	-0.15249400	-2.63466400	-1.43206300
C35	-1.59212800	-3.74516200	1.56817700
H36	-1.59320400	-2.85236600	2.19454300
H37	-0.73760500	-4.35907000	1.86763300
H38	-2.49834300	-4.31560900	1.77197000
O39	-1.96964600	-4.50319800	-0.73652600
H40	-2.53089100	-2.74214400	-1.70257600
H41	-4.68096200	-3.99874200	-0.81624700
H42	-4.26713800	-3.37413000	0.75436300
H43	-4.78223800	-1.58169200	-1.72184400
H44	-6.06120500	-2.20714500	-0.71200500
C45	-5.13764000	-0.88264300	1.69138700
H46	-5.19345300	0.04404000	2.26100500
H47	-6.07181700	-1.42777900	1.86003200
H48	-4.32469900	-1.49127800	2.09332400
H49	-4.16468100	0.65735900	-1.36351200
H50	-3.90937500	2.69559000	0.15987500
H51	-3.92539700	1.64292500	1.54637100
H52	-1.75978100	2.29067100	1.36942700
H53	-1.66129400	3.37843300	-0.85668700
H54	-1.43532300	1.80766600	-1.62159700
O55	0.82414000	3.48874300	-0.56169600
C56	1.98947400	1.35351000	0.91486600
H57	2.44392600	2.33256600	1.01792100
H58	2.48030900	0.51740900	1.39743800
H59	-0.22016000	-0.00019700	-1.07508200

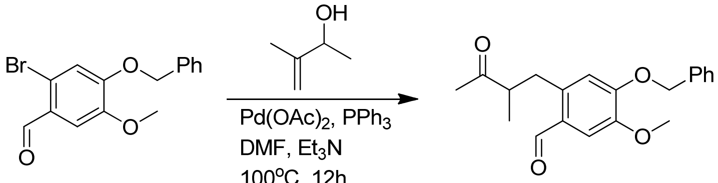




APPENDIX 2

A2.1 Experimental Procedures for Chapter 2

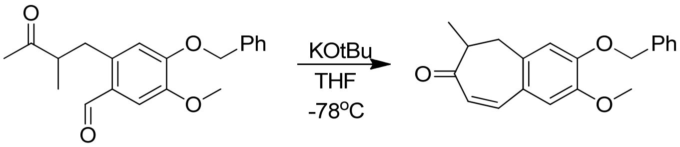
General Information: Commercial reagents were purchased and used without further purification. All glassware was flame dried and reactions were performed under a nitrogen atmosphere, unless otherwise stated. Toluene, dichloromethane, diethyl ether, and THF were dried over a column of alumina. Flash chromatography was done with MP Silitech 32-63D 60Å silica, and thin layer chromatography (TLC) was performed with EMD 250 μm silica gel 60-F_{254} plates. ^{1}H and ^{13}C NMR data was acquired on a Varian Inova 400, 500, or 600 (400, 500 or 600 MHz) spectrometer and referenced to residual protic solvent or TMS. IR spectroscopy was done on a Nicolet Avatar 370 OTGS spectrometer. High-resolution mass spectrometry was performed at the University of Illinois at Urbana-Champaign facility.



2.82

The known bromoaldehyde (10.000 g, 0.031 mol), was added to a flame-dried round bottom flask and dissolved in dry DMF (311.4 mL). Triethyl amine (5.4 mL, 38.9 mmol) was added followed by palladium acetate (0.350 g, 0.002 mol) and triphenylphosphine (0.820 g, 0.003 mol). Then the allylic alcohol (13.400 g, 0.156 mol) was added and the reaction was heated at 100°C for 12 hours. Upon completion, the reaction mixture was quenched with one molar hydrochloric acid (100.0 mL) and extracted with ether. The combined ether extracts were subsequently washed with distilled water and dried with sodium sulfate. The ethereal solution was concentrated and purified with silica gel (70% hexanes, 30% ethyl acetate) to yield keto-aldehyde (7.900 g, 78%).

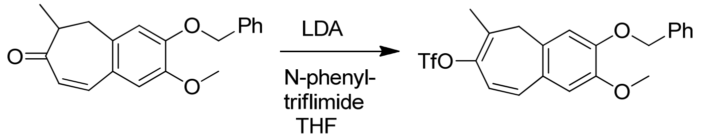
FTIR (thin film/NaCl) 2958, 2930, 1708, 1677, 1597, 1511, 1354, 1270, 1108 cm^{-1}; **^{1}H NMR (400 MHz, C_6D_6)** δ = 10.02 (s, 1H), 7.27-7.21 (m, 3H), 7.14-7.01 (m, 3H), 6.63 (s, 1H), 4.82-4.70 (m, 2H), 3.32 (s, 3H), 3.28 (dd, *J*=7.1, 13.2, 1H), 2.76 (dd, *J*=7.1, 13.2, 1H), 2.61-2.58 (m, 1H), 1.68 (s, 3H), 0.86 (d, *J*=7.1, 3H); **^{13}C NMR (126 MHz, C_6D_6)** δ = 210.2, 190.2, 153.3, 149.3, 137.7, 137.1, 129.1, 128.7, 128.1, 127.9, 117.0, 115.0, 71.0, 55.8, 49.3, 35.4, 29.1, 16.8; **HRMS** (EI) *m/z* 349.1408 [calc'd for $C_{20}H_{22}O_4Na$ (M+Na) 349.1416].



2.83

Potassium tert-butoxide (2.020 g, 0.017 mol) was added to a flame-dried round bottom flask and dry THF (300.0 mL) was added under a nitrogen atmosphere at -78°C. The starting material (5.070 g, 0.016 mol) was dissolved in dry THF (11.0 mL) and added drop-wise to the butoxide slurry. Upon complete addition, the reaction was allowed to stir for an additional 30 minutes at -78°C at which time the bath was removed and the reaction allowed to warm to room temperature. The reaction was neutralized with saturated sodium bicarbonate and extracted with ether. The combined extracts were dried over sodium sulfate, concentrated, and purified by column chromatography (70% hexanes, 30% ethyl acetate) to yield enone (4.310 g, 90%).

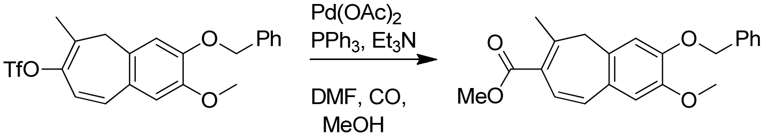
FTIR (thin film/NaCl) 2964, 2933, 1651, 1567, 1519, 1455, 1354, 1268, 1164, 1098 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.41-7.30 (m, 5H), 6.95 (d, *J*=12.6, 1H), 6.84 (s, 1H), 6.76 (s, 1H), 6.04 (d, *J*=12.6, 1H), 5.18 (s, 2H), 3.88 (s, 3H), 2.89-2.72 (m, 2H), 2.66 (m, 1H), 1.07 (d, *J*=7.1, 3H); **^{13}C NMR (75 MHz, $CDCl_3$)** δ = 203.5, 149.4, 148.2, 142.0, 136.6, 134.2, 128.8, 128.2, 127.5, 127.4, 127.4, 115.9, 115.3, 71.1, 56.4, 44.7, 37.0, 15.7; **HRMS** (EI) *m/z* 309.1483 [calc'd for $C_{20}H_{21}O_3$ (M+H) 309.1491].



2.84

Freshly distilled diisopropyl amine (2.50 mL, 0.02 mol) was added to a flame-dried flask and diluted with dry THF (60.0 mL) and cooled to -78°C under nitrogen. Butyl lithium (2.5M, 6.5 mL, 0.02 mol) was then added and allowed to react for 30 minutes. Starting material (2.500 g, 0.008 mol) was then dissolved in THF (10.0 mL) and added drop-wise to the LDA solution over 1 minute and allowed to stir for an additional 15 minutes. A stock solution of N-phenyl triflimide (3.190 g, 8.900 mmol) was then added and the bath removed as the reaction warmed to room temperature. After 1 hour the reaction was diluted with ether (500.0 mL) and washed with NaOH solution (0.1M, 200.0 mL). The ethereal solution was then dried over sodium sulfate, concentrated, and purified with column chromatography (70% hexanes, 30% ethyl acetate) to yield vinyl triflate (3.100 g, 87%).

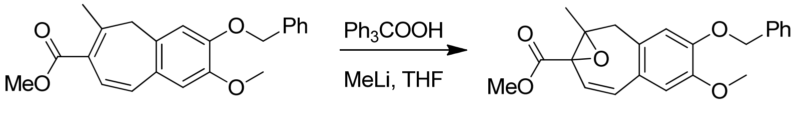
FTIR (thin film/NaCl) 3033, 2963, 2840, 1736, 1657, 1603, 1561, 1512, 1413, 1211, 1141, 1029 cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$)** δ = 7.48-7.30 (m, 5H), 7.04 (d, *J*=11.8, 1H), 6.84 (s, 1H), 6.68 (s, 1H), 6.26 (d, *J*=11.8, 1H), 5.18 (s, 2H), 3.88 (s, 3H), 2.97 (s, 2H), 2.03 (s, 3H); **^{13}C NMR (75 MHz, CDCl$_3$)** δ = 150.2, 148.4, 140.5, 136.9, 134.7, 128.8, 128.5, 128.3, 128.2, 127.6, 127.4, 121.1, 116.5, 113.1, 111.5, 71.3, 56.3, 38.1, 18.8; **HRMS** (EI) *m/z* 440.0901 [calc'd for $C_{21}H_{19}F_3O_5S$ (M+) 440.0905].



2.85

Palladium acetate (0.087 g, 0.390 mmol) and triphenylphosphine (0.203 g, 0.780 mmol) were added to a flame-dried flask at room temperature under nitrogen. Dry DMF (30.0 mL) was added followed by triethylamine (0.54 mL, 3.86 mmol) and methanol (6.2 mL, 0.154 mol). Starting triflate (1.700 g, 3.860 mmol) was dissolved in dry DMF (9.0 mL) and added to the reaction and a balloon of carbon monoxide was attached *via* needle through a septum. The reaction was heated at 80°C for 3 hours until the starting material was consumed. The reaction was then diluted with ethyl acetate (300.0 mL) and washed with distilled water (3 x 50.0 mL). The organics were then dried over sodium sulfate and purified with silica gel chromatography (70% hexanes, 30% ethyl acetate) to yield enoate (1.110 g, 82%).

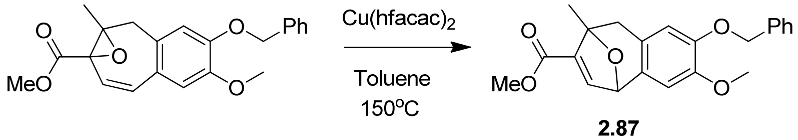
FTIR (thin film/NaCl) 3029, 2936, 1713, 1602, 1509, 1453, 1222 cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$)** δ = 7.47-7.30 (m, 5H), 7.02 (d, *J*=11.6, 1H), 6.83 (s, 1H), 6.80 (d, *J*=11.6, 1H), 6.70 (s, 1H), 5.17 (s, 2H), 3.87 (s, 3H), 3.74 (s, 3H), 2.94 (s, 2H), 2.31 (s, 3H); **^{13}C NMR (126 MHz, CDCl$_3$)** δ = 168.2, 149.6, 148.3, 146.9, 137.1, 131.6, 128.9, 128.7, 128.1, 127.8, 127.6, 127.2, 124.0, 112.7, 110.8, 71.3, 56.3, 51.7, 43.2, 22.8; **HRMS** (EI) *m/z* 351.1584 [calc'd for $C_{22}H_{23}O_4$ (M+H) 351.1596].



2.86

Triphenylmethyl hydroperoxide (0.166 g, 0.600 mmol) was added to a flame-dried flask and dissolved in dry THF (7.0 mL) under nitrogen and then cooled to -78°C. Methyl lithium (1.6M, 0.33 mL, 0.52 mmol) was added and the reaction was stirred for 10 minutes. Starting diene (0.140 g, 0.400 mmol) was then dissolved in dry THF (1.0 mL), added to the reaction, and allowed to stir at -78°C for 1 hour. The reaction was then warmed to room temperature and quenched with saturated ammonium chloride (50.0 mL) and extracted with ethyl acetate (3 x 100.0 mL). The organics were then dried over sodium sulfate, concentrated, and purified by silica gel chromatography (80% hexanes, 20% ethyl acetate) to yield epoxide (0.129 g, 89%).

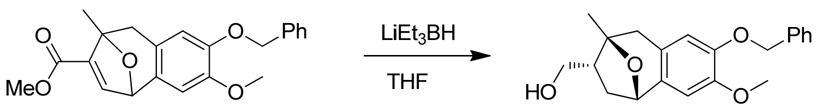
FTIR (thin film/NaCl) 2953, 2935, 1747, 1604, 1518, 1267, 1099, 1064, 1454 cm^{-1}; **^{1}H NMR (300 MHz, CDCl$_3$)** δ = 7.51-7.28 (m, 5H), 6.81 (s, 1H), 6.74 (s, 1H), 6.68 (d, *J*=11.4, 1H), 6.16 (d, *J*=11.4, 1H), 5.17 (s, 2H), 3.89 (s, 3H), 3.72 (s, 3H), 2.97 (d, *J*=13.6, 1H), 2.78 (d, *J*=13.6, 1H), 1.36 (s, 3H); **^{13}C NMR (126 MHz, CDCl$_3$)** δ = 169.6, 148.8, 147.9, 137.1, 134.1, 128.9, 128.8, 128.5, 128.2, 127.6, 124.2, 115.7, 113.6, 71.6, 71.4, 62.9, 56.4, 52.9, 43.4, 18.7; **HRMS** (EI) *m/z* 367.1541 [calc'd for $C_{22}H_{23}O_5$ (M+H) 367.1545].



2.87

Starting epoxide (0.120 g, 0.330 mmol) was dissolved in dry toluene (0.33 mL) and dry Cu(hfacac)$_2$ (0.008 g, 0.017 mmol, dried on vacuum pump for 2 hours prior to use) was added at room temperature. The vial was sealed well and the reaction heated at 100°C for 12 hours. After allowing the reaction to cool to room temperature, it was filtered through neutral alumina (activity grade 1), concentrated and purified with silica gel chromatography (80% hexanes, 20% ethyl acetate) to give the ring expansion product (0.118 g, 99%).

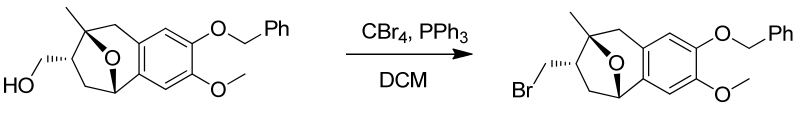
FTIR (thin film/NaCl) 2952, 2935, 1714, 1611, 1506, 1452, 1307, 1261, 1100, 1070, cm^{-1}; **^{1}H NMR (600 MHz, CDCl$_3$)** δ = 7.44-7.28 (m, 5H), 7.21 (s, 1H), 6.63 (s, 1H), 6.61 (s, 1H), 5.27 (d, *J*=2.0, 1H), 5.08 (s, 2H), 3.85 (s, 3H), 3.71 (s, 3H), 2.85 (d, *J*=17.1, 1H), 2.70 (d, *J*=17.1, 1H), 1.70 (s, 3H); **^{13}C NMR (126 MHz, CDCl$_3$)** δ = 164.2, 148.3, 147.8, 147.6, 137.3, 135.2, 128.8, 128.8, 128.1, 127.5, 126.3, 116.4, 108.4, 84.2, 79.7, 71.4, 56.5, 51.7, 34.7, 23.6; **HRMS** (EI) *m/z* 367.1531 [calc'd for $C_{22}H_{23}O_5$ (M+H) 367.1545].



2.88

Methyl enoate (0.080 g, 0.219 mmol) was dissolved in dry THF (4.4 mL) and the solution cooled to -78°C under nitrogen. Lithium triethylborohydride (1M, 0.88 mL, 0.88 mmol) was added drop-wise and the reaction stirred for 90 minutes. The bath was then removed and when the reaction had come to room temperature it was quenched with saturated ammonium chloride and extracted with DCM. The organics were dried over sodium sulfate, concentrated, and chromatographed (50% hexanes, 50% ethyl acetate) to give the alcohol (0.065 g, 88%).

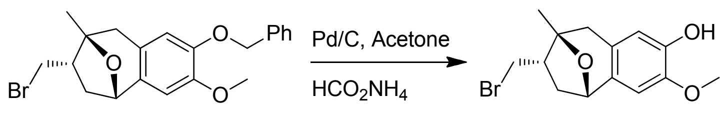
FTIR (thin film/NaCl) 2922, 2939, 1509, 1454, 1333, 1257, 1223, 1117, 1073, 1015 cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$)** δ = 7.46-7.28 (m, 5H), 6.59 (s, 1H), 6.51 (s, 1H), 5.09 (s, 2H), 4.93 (d, *J*=6.9, 1H), 3.84 (s, 3H), 3.62-3.56 (m, 1H), 3.49-3.42 (m, 1H), 2.89 (d, *J*=17.0, 1H), 2.75 (d, *J*=17.0, 1H), 2.58-2.44 (m, 1H), 2.38-2.20 (m, 1H), 1.52 (s, 3H), 1.51-1.46 (m, 1H); **^{13}C NMR (126 MHz, CDCl$_3$)** δ = 148.1, 147.4, 137.4, 134.4, 128.7, 128.0, 127.5, 124.4, 114.6, 107.9, 81.8, 77.3, 71.5, 64.9, 56.3, 49.8, 40.1, 36.5, 28.4; **HRMS** (EI) *m/z* 341.1758 [calc'd for $C_{21}H_{25}O_4$(M+H) 341.1753].



2.89

Primary alcohol (0.010 g, 0.030 mmol) was dissolved in dry DCM (0.6 mL) at room temperature. Triphenyl phosphine (0.012 g, 0.045 mmol) was then added followed by carbon tetrabromide (0.015 g, 0.045 mmol) and the reaction was stirred for 4 hours until the starting material was consumed. The crude reaction mixture was concentrated and directly purified by silica gel chromatography (30% ethyl acetate, 70% hexanes) to give bromide (0.010 g, 84%).

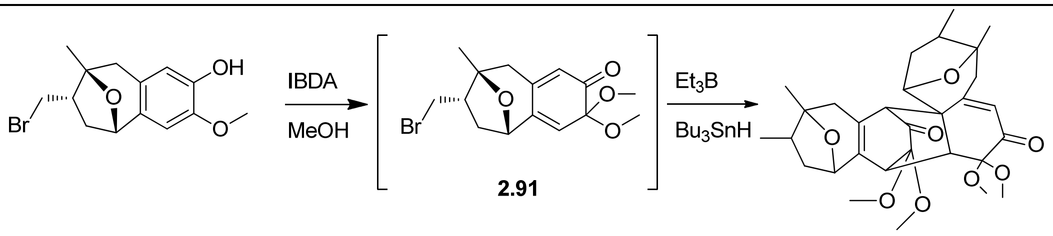
FTIR (thin film/NaCl) 2953, 2917, 1653, 1507, 1457, 1338, 1257, 1225, 1012 cm^{-1}; **^{1}H NMR (600 MHz, CDCl$_3$)** δ = 7.45-7.29 (m, 5H), 6.60 (s, 1H), 6.51 (s, 1H), 5.14-5.06 (m, 2H), 4.91 (d, *J*=6.7, 1H), 3.85 (s, 3H), 3.31-3.22 (m, 2H), 2.88 (d, *J*=17.1, 1H), 2.77 (d, *J*=17.1, 1H), 2.68-2.60 (m, 1H), 2.56-2.48 (m, 1H), 1.62 (dd, *J*=3.8, 12.3, 1H), 1.55 (s, 3H); **^{13}C NMR (126 MHz, CDCl$_3$)** δ = 148.4, 147.6, 137.3, 134.0, 128.8, 128.1, 127.6, 123.8, 114.6, 108.0, 82.2, 76.6, 71.5, 56.4, 50.2, 43.3, 36.1, 35.1, 28.1; **HRMS** (EI) *m/z* 403.0908 [calc'd for $C_{21}H_{24}O_3Br$ (M+H) 403.0909].



2.90

Benzyl-protected phenol (0.011 g, 0.027 mmol) was dissolved in dry acetone (2.7 mL) at room temperature. 10% Pd/C (0.020 g) was added followed by ammonium formate (0.009 g, 0.135 mmol). The reaction was sealed in a vial and heated at 60°C for 4 hours. The reaction was filtered through Celite and concentrated to yield pure phenol (0.008 g, 94%).

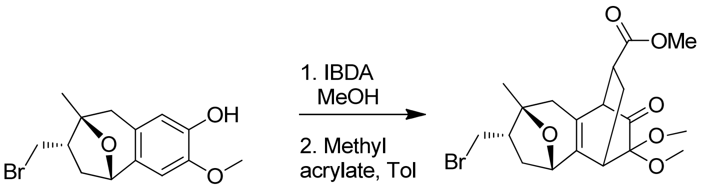
FTIR (thin film/NaCl) 2967, 2880, 1591, 1451, 1247, 1099, 1070, 1024 cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$)** δ = 6.64 (s, 1H), 6.47 (s, 1H), 4.90 (d, *J*=6.6, 1H), 3.86 (s, 3H), 3.32-3.26 (m, 2H), 2.91 (d, *J*=17.2, 1H), 2.80 (d, *J*=17.2, 1H), 2.69-2.59 (m, 1H), 2.58-2.49 (m, 1H), 1.64-1.58 (m, 1H), 1.55 (s, 3H); **^{13}C NMR (126 MHz, CDCl$_3$)** δ = 145.1, 144.9, 132.8, 124.6, 114.4, 106.7, 82.2, 76.7, 56.2, 50.2, 43.4, 36.0, 35.1, 28.1; **HRMS** (EI) *m/z* 312.0356 [calc'd for $C_{14}H_{17}O_3Br$ (M+) 312.0361].



Starting phenol (0.005 g, 0.016 mmol) was dissolved in anhydrous methanol (2.0 mL) and stirred at room temperature. Iodobenzene diacetate (0.006 g, 0.018 mmol) was added to the reaction and after a few seconds, the reaction turned a bright yellow. The reaction was stirred for 10 minutes before being concentrated and directly purified using silica gel chromatography (30% ethyl acetate, 70% hexanes) to give dearomatized product (0.005 g, 91%). This *ortho*-quinone *mono*-ketal was dissolved in dry toluene (2.0 mL) and tributyltin hydride (0.01 mL, 0.03 mmol) was added at -78°C, followed by active triethylborane (1M, 0.01 mL, 0.01 mmol). The reaction was warmed to room temperature and was diluted with ethyl acetate and washed with brine, dried over sodium sulfate, and the organics were concentrated. The product was purified using silica gel chromatography to give the quenched, dimerized product (0.003 g, 55%).

Monomer: **^{1}H NMR (400 MHz, CDCl$_3$)** δ = 5.97 (s, 1H), 5.87 (s, 1H), 4.74 (d, *J*=7.8, 1H), 3.38 (s, 3H), 3.37-3.33 (m, 2H), 3.30 (s, 3H), 2.80-2.68 (m, 3H), 2.51-2.40 (m, 1H), 1.52-1.48 (m, 1H), 1.47 (s, 3H).

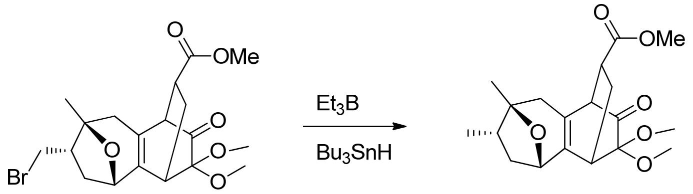
Dimer: **^{1}H NMR (600 MHz, C$_6$D$_6$)** δ = 5.78-5.75 (m, 1H), 4.50 (d, *J*=6.5, 1H), 4.31 (d, *J*=7.5, 1H), 3.78 (s, 1H), 3.14 (s, 3H), 3.13 (s, 3H), 3.13 (s, 3H), 2.98-2.95 (m, 1H), 2.88 (s, 3H), 2.61-2.57 (m, 1H), 2.39-2.35 (m, 1H), 2.28-2.22 (m, 1H), 2.15-2.06 (m, 2H), 1.92-1.88 (m, 1H), 1.88-1.82 (m, 1H), 1.80-1.65 (m, 2H), 1.24 (s, 3H), 1.17 (s, 3H), 0.94-0.82 (m, 2H), 0.83 (d, *J*=7.3, 3H), 0.70 (d, *J*=7.1, 3H); **HRMS** (EI) *m/z* 513.24973 [calc'd for $C_{29}H_{37}O_8$ (M (–CH$_3$) +) 513.24883].



2.92

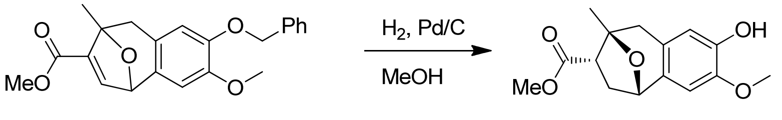
Phenol (0.004 g, 0.013 mmol) was dissolved in dry methanol (0.2 mL) at room temperature. Solid iodobenzene diacetate (0.005 g, 0.014 mmol) was added and the reaction turned a bright yellow over the course of five minutes. The reaction was concentrated and filtered through a plug of silica to give the crude oxidation product. This product was next dissolved in dry toluene (0.2 mL) and methyl acrylate (0.01 mL, 0.13 mmol) was added. The reaction was stirred at 50°C for five hours at which time the solvent was evacuated and the crude oil subjected to silica gel chromatography to give the product (0.005 g, 91%).

^{1}H NMR (400 MHz, CDCl$_3$) δ = 4.36 (d, *J*=6.5, 1H), 3.69 (s, 3H), 3.36 (s, 3H), 3.30 (s, 3H), 3.18-3.12 (m, 1H), 3.06-3.00 (m, 1H), 2.94-2.85 (m, 1H), 2.53-2.28 (m, 6H), 2.18 (d, *J*=18.0, 1H), 2.00 (d, *J*=11.9, 1H), 1.80-1.71 (m, 1H), 1.47 (s, 3H); **HRMS** (EI) *m/z* 429.0896 [calc'd for $C_{19}H_{26}O_6Br$ (M+H) 429.0913].



A solution of Diels-Alder product (0.010 g, 0.023 mmol) and dry toluene (2.3 mL) was purged with nitrogen and cooled to -78°C. To this was added tributyltin hydride (10% in toluene, 0.07 mL, 0.03 mmol) followed by triethyl borane (1M, 0.02 mL) that had been activated by addition of dry air. The reaction was allowed to stir for 10 minutes and the bath was removed. After 30 minutes, the reaction was concentrated and purified using silica gel chromatography to give quenched product (0.007 g, 86%).

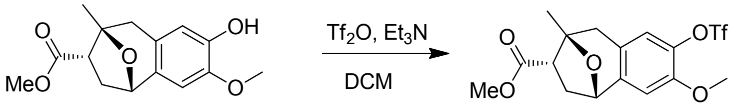
FTIR (thin film/NaCl) 2966, 2950, 1734, 1456, 1437, 1202, 1135, 1096, 1055, 750 cm^{-1}; **^{1}H NMR (600 MHz, CDCl$_3$)** δ = 4.35-4.28 (m, 1H), 3.68 (s, 3H), 3.34 (s, 3H), 3.30 (s, 3H), 3.04-2.99 (m, 1H), 2.94-2.88 (m, 1H), 2.42-2.31 (m, 1H), 2.29-2.23 (m, 1H), 2.17 (s, 1H), 2.10-2.02 (m, 1H), 1.80-1.75 (m, 1H), 1.75-1.69 (m, 1H), 1.64-1.56 (m, 2H), 1.34 (s, 3H), 0.94-0.88 (m, 3H); **HRMS** (EI) *m/z* 351.1813 [calc'd for $C_{19}H_{27}O_6$ (M+H) 351.1808].



2.94

Starting material (0.035 g, 0.096 mmol) was dissolved in dry methanol (1.9 mL) at room temperature under nitrogen. Palladium on carbon (10%, 0.030 g) was added to the reaction and the nitrogen was replaced by a balloon of hydrogen gas. The reaction was heated at 50°C for 12 hours and then filtered through a plug of Celite. The reaction was concentrated and loaded directly onto a silica gel column for purification yielding deprotected product (0.024 g, 90%).

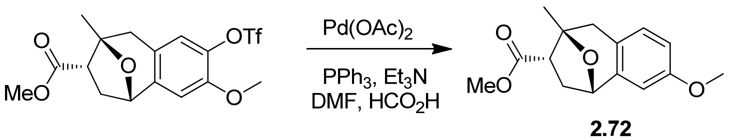
FTIR (thin film/NaCl) 2973, 2939, 1736, 1509, 1343, 1284, 1199, 1108 cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$)** δ = 6.55 (s, 1H), 6.49 (s, 1H), 5.48 (bs, 1H), 4.98 (d, *J*=6.8, 1H), 3.85 (s, 3H), 3.64 (s, 3H), 3.02-2.86 (m, 1H), 2.90 (d, *J*=17.0, 1H), 2.56 (d, *J*=17.0, 1H), 2.52-2.43 (m, 1H), 2.42-2.34 (m, 1H), 1.64 (s, 3H); **^{13}C NMR (126 MHz, CDCl$_3$)** δ = 172.9, 144.9, 144.8, 132.0, 124.4, 114.3, 106.5, 82.4, 77.7, 56.1, 53.6, 52.1, 38.9, 37.6, 28.0; **HRMS** (EI) *m/z* 278.1154 [calc'd for $C_{15}H_{18}O_5$ (M+) 278.1154].



2.95

Starting phenol (0.034 g, 0.122 mmol) was dissolved in dry DCM (2.5 mL) at 0°C under nitrogen. To this was added freshly distilled triethylamine (0.04 mL, 0.24 mmol) and then triflic anhydride (0.02 mL, 0.14 mmol). The reaction was stirred for 10 minutes until the reaction was complete. The solvent was partially removed and the residue purified by silica gel chromatography to yield the triflate (0.044 g, 88%).

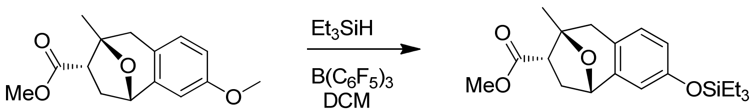
FTIR (thin film/NaCl) 2982, 2957, 1737, 1614, 1508, 1421, 1206, 1141, 1082 cm^{-1}; **^{1}H NMR (600 MHz, CDCl$_3$)** δ = 6.85 (s, 1H), 6.67 (s, 1H), 5.04 (d, *J*=7.1, 1H), 3.88 (s, 3H), 3.63 (s, 3H), 3.03-3.00 (m, 1H), 2.93 (d, *J*=17.2, 1H), 2.62 (d, *J*=17.2, 1H), 2.55-2.48 (m, 1H), 2.40 (dd, *J*=4.1, 12.5, 1H), 1.65 (s, 3H); **^{13}C NMR (126 MHz, CDCl$_3$)** δ = 172.6, 157.8, 149.6, 141.3, 137.7, 124.7, 122.2, 108.8, 82.4, 56.4, 54.8, 53.7, 52.2, 38.7, 37.2, 27.8.; **HRMS** (EI) *m/z* 410.06474 [calc'd for $C_{16}H_{17}F_3O_7S$ (M+) 410.06471].



2.72

Starting triflate (0.026 g, 0.063 mmol) was dissolved in anhydrous DMF (1.3 mL) at room temperature. To this was added freshly distilled triethylamine (0.09 mL, 6.30 mmol), palladium acetate (0.001 g, 0.006 mmol), and triphenylphosphine (0.003 g, 0.012 mmol). Upon addition of formic acid (0.02 mL, 0.63 mmol), a white smoke was observed and the reaction was sealed and heated at 100°C for 15 hours. After cooling to room temperature the reaction was quenched with saturated sodium bicarbonate (10.0 mL) and extracted with ethyl acetate (3 x 50.0 mL). The extracts were dried over sodium sulfate, concentrated and purified with silica gel chromatography to give the product (0.015 g, 90%).

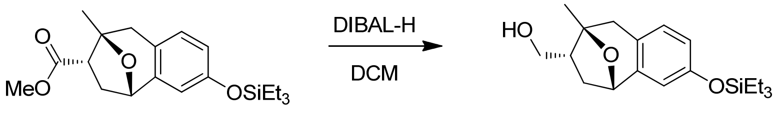
FTIR (thin film/NaCl) 2950, 2902, 1736, 1613, 1503, 1433, 1251, 1198, 1164, 1035 cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$)** δ = 6.90 (d, *J*=8.5, 1H), 6.70 (dd, *J*=2.6, 8.5, 1H), 6.55 (d, *J*=2.6, 1H), 5.01 (d, *J*=6.9, 1H), 3.77 (s, 3H), 3.63 (s, 3H), 3.02-2.97 (m, 1H), 2.93 (d, *J*=17.0, 1H), 2.62 (d, *J*=17.0, 1H), 2.55-2.46 (m, 1H), 2.42-2.37 (m, 1H), 1.65 (s, 3H); **^{13}C NMR (75 MHz, CDCl$_3$)** δ = 172.9, 157.9, 141.3, 129.3, 123.7, 113.0, 109.1, 82.6, 78.0, 55.4, 53.7, 52.1, 38.7, 37.4, 28.0; **HRMS** (EI) *m/z* 262.12055 [calc'd for $C_{15}H_{18}O_4$ (M+) 262.12051].



2.96

Starting material (0.009 g, 0.031 mmol) was dissolved in DCM (0.62 mL) at room temperature. The tris(pentafluorophenyl)borane (0.002 g, 0.003 mmol) was then added followed by a 10% stock solution of triethylsilane (0.06 mL, 0.034 mmol) and the reaction was allowed to stir at room temperature for 1 hour. After starting material was consumed, the reaction was quenched with 3 drops of triethyl amine and filtered through a Celite plug before being purified by silica gel chromatography (80% hexanes, 20% ethyl acetate) to give the TES-ether (0.011 g, 88%).

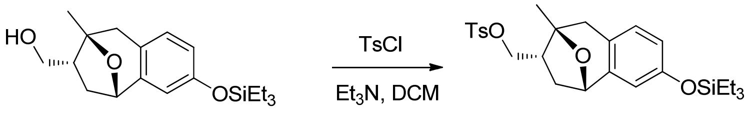
FTIR (thin film/NaCl) 3014, 2993, 1770, 1374, 1241, 1057, 914 cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$)** δ = 6.83 (d, *J*=8.2, 1H), 6.64 (dd, *J*=8.2, 2.3, 1H), 6.50 (d, *J*=2.3, 1H), 4.97 (d, *J*=7.0, 1H), 3.61 (s, 3H), 3.05-2.95 (m, 1H), 2.92 (d, *J*=17.1, 1H), 2.62 (d, *J*=17.1, 1H), 2.55-2.43 (m, 1H), 2.41-2.32 (m, 1H), 1.65 (s, 3H), 0.98 (t, *J*=7.9, 9H), 0.72 (q, *J*=7.9, 6H); **^{13}C NMR (126 MHz, CDCl$_3$)** δ = 172.8, 153.7, 141.3, 129.2, 124.3, 118.9, 115.2, 82.6, 77.8, 53.7, 52.0, 38.7, 37.4, 28.0, 6.9, 5.2; **HRMS** (EI) *m/z* 362.1911 [calc'd for $C_{20}H_{30}O_4Si$ (M+) 362.1913].



2.97

Starting ester (0.006 g, 0.018 mmol) was dissolved dry DCM (0.9 mL) under nitrogen at -78°C. To this was added 20% by weight DIBAL-H in THF (0.04 mL, 0.05 mmol) drop-wise and the reaction was then maintained at -78°C for 30 minutes. The bath was removed and when the reaction reached room temperature, saturated sodium potassium tartrate (0.2 mL) was added followed by ethyl acetate (0.2 mL) to quench remaining DIBAL-H. The reaction was extracted with ethyl acetate, dried over sodium sulfate, concentrated, and purified with silica gel chromatography to give the primary alcohol (0.005 g, 90%).

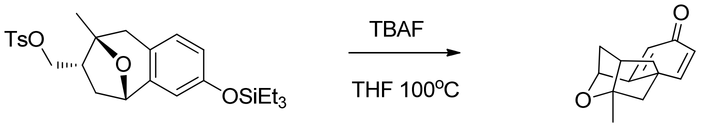
FTIR (thin film/NaCl) 2958, 2922, 2875, 1499, 1279, 1264, 1015, 974, 905 cm^{-1}; **^{1}H NMR (300 MHz, CDCl$_3$)** δ = 6.90 (d, *J*=8.3, 1H), 6.64 (dd, *J*=8.3, 2.7, 1H), 6.47 (d, *J*=2.7, 1H), 4.91 (d, *J*=7.2, 1H), 3.65-3.42 (m, 2H), 2.90 (d, *J*=17.0, 1H), 2.85 (d, *J*=17.0, 1H), 2.60-2.44 (m, 1H), 2.37-2.18 (m, 1H), 1.54 (s, 3H), 1.50-1.43 (m, 1H), 0.98 (t, *J*=7.8, 9H), 0.72 (q, *J*=7.8, 6H); **^{13}C NMR (600 MHz HSQCAD/gHMBCAD, CDCl$_3$)** δ = 152.4, 141.3, 128.5, 123.4, 113.0, 109.4, 80.7, 75.9, 63.7, 48.4, 38.8, 34.9, 27.2, 5.6, 3.9; **HRMS** (EI) *m/z* 334.1964 [calc'd for $C_{19}H_{30}O_3Si$ (M+) 334.1964].



2.98

Starting alcohol (0.002 g, 0.007 mmol) was dissolved in dry DCM (0.3 mL) at 0°C under nitrogen. Freshly distilled triethylamine (0.01 mL, 0.07 mmol) was added followed by *p*-toluenesulfonyl chloride (0.006 g, 0.032 mmol). The bath was removed and the reaction stirred for 16 hours. The reaction was quenched with water (1.0 mL) and extracted with DCM (3 x 5.0 mL). The organics were dried with sodium sulfate, concentrated and purified with silica gel chromatography to give the tosylate (0.002 g, 67%).

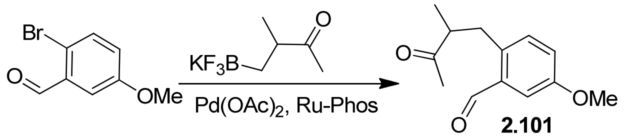
FTIR (thin film/NaCl) 2954, 2915, 1674, 1622, 1497, 1457, 1372, 1243, 1177, 1156, 1124, 1062, 1011 cm^{-1}; **^{1}H NMR (600 MHz, CDCl$_3$)** δ = 7.72 (d, *J*=8.0, 1H), 7.33 (d, *J*=8.0, 1H), 6.69 (d, *J*=8.2, 1H), 6.59 (dd, *J*=2.5, 8.2, 1H), 6.38 (d, *J*=2.5, 1H), 4.85 (d, *J*=6.9, 1H), 4.01-3.94 (m, 1H), 3.79-3.73 (m, 1H), 2.86 (d, *J*=17.1, 1H), 2.54 (d, *J*=17.1, 1H), 2.51-2.45 (m, 1H), 2.47 (s, 3H), 2.40-2.35 (m, 1H), 1.47 (s, 3H), 1.31 (dd, *J*=3.9, 12.3, 1H), 0.97 (t, *J*=7.8, 9H), 0.71 (q, *J*=7.8, 6H); **^{13}C NMR (600 MHz HSQCAD/gHMBCAD, CDCl$_3$)** 153.7, 144.9, 141.6, 130.8, 129.9, 129.1, 128.0, 124.0, 118.8, 115.1, 81.8, 76.8, 71.4, 46.0, 39.7, 35.9, 27.9, 21.5, 6.7, 4.8; **HRMS** (EI) *m/z* 489.2151 [calc'd for $C_{26}H_{37}O_5SiS$ (M+H) 489.2131].



2.33

Starting tosylate (0.016 g, 0.033 mmol) was dissolved in dry THF (2.0 mL) at room temperature. A 10% stock solution of TBAF (0.4 mL, 0.04 mmol) was added and the reaction allowed to stir for 1 hour at 100°C. The reaction was then concentrated and purified with silica gel to yield known dienone (0.006 g, 91%).

FTIR (thin film/NaCl) 2963, 2942, 1659, 1626, 1149 cm^{-1}; **^{1}H NMR (600 MHz, CDCl$_3$)** δ = 6.66 (d, *J*=10.0, 1H), 6.32 (dd, *J*=1.6, 10.0, 1H), 6.12 (d, *J*=1.6, 1H), 4.71 (d, *J*=4.3, 1H), 2.59 (t, *J*=6.2, 1H), 2.27-2.21 (m, 1H), 2.20-2.15 (m, 1H), 2.01-1.92 (m, 2H), 1.78 (d, *J*=11.4, 1H), 1.56-1.50 (m, 1H), 1.51 (s, 3H); **^{13}C NMR (600 MHz HSQCAD/gHMBC, CDCl$_3$)** 187.1, 160.4, 150.9, 130.1, 121.9, 87.1, 80.0, 54.9, 49.9, 48.7, 44.4, 42.6, 22.2; **HRMS** (EI) *m/z* 202.0993 [calc'd for $C_{13}H_{14}O_2$ (M+) 202.0994].



2.101

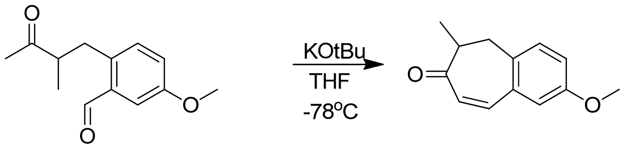
Starting bromide (1.000 g, 4.650 mmol) was mixed with keto-boronate (1.790 g, 9.300 mmol), K_2CO_3 (1.930 g, 0.014 mol), palladium acetate (0.026 g, 0.120 mmol), and RuPhos (2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl) (0.108 g, 0.230 mmol) under an atmosphere of nitrogen. Freshly degassed dry toluene (18.6 mL) and freshly degassed distilled water (4.7 mL) were sequentially added and the reaction was heated at 85°C for 16 hours. The reaction was then quenched with pH 7.5 phosphate buffer and extracted with ethyl acetate. The organics were dried over sodium sulfate, concentrated and purified with silica gel to give the keto-aldehyde (0.725 g, 71%).

FTIR (thin film/NaCl) 2970, 2935, 1706, 1608, 1572, 1499, 1263, 1164, 1037 cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$)** δ = 10.20 (s, 1H), 7.34 (d, *J*=2.9, 1H), 7.17 (d, *J*=8.4, 1H), 7.05 (dd, *J*=2.9, 8.4, 1H), 3.86 (s, 3H), 3.42-3.30 (m, 1H), 2.90-2.77 (m, 2H), 2.11 (s, 3H), 1.11-1.08 (m, 3H); **^{13}C NMR (75 MHz, CDCl$_3$)** δ = 212.3, 192.5, 158.7, 134.8, 134.7, 133.6, 120.3, 116.9, 55.7, 48.9, 34.8, 29.3, 16.5; **HRMS** (EI) *m/z* 220.1099 [calc'd for $C_{13}H_{16}O_3$ (M+) 220.1100].

Synthesis of keto-boronate:

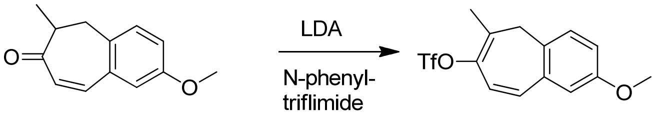
Copper chloride (0.035 g, 0.360 mmol), sodium tert-butoxide (0.103 g, 1.070 mmol), and DPEPhos (0.192 g, 0.360 mmol) were mixed under nitrogen. THF (15.0 mL) was added at room temperature and the mixture was stirred for 30 minutes. Bispinacolato diboron (3.170 g, 0.013 mol) in THF (9.0 mL) was added and the reaction was stirred for 15 minutes. 3-methyl-3-butene-2-one (1.000 g, 0.012 mol) was then added followed by anhydrous methanol (0.9 mL) and the reaction was stirred for 2 hours. This mixture was then filtered through Celite, concentrated to an oil, and subsequently dissolved in acetonitrile (60.0 mL) and cooled to 0°C. Saturated KHF_2 (3.710 g, 0.047 mol, 10 mL H_2O) was added drop-wise and the reaction was stirred 2 hours. The solvent was then removed. The solids were triturated with hot acetone and the acetone washings combined and concentrated to 10% of the original volume. The product was precipitated by adding diethyl ether and recrystallized with acetone (1.950 g, 85%, mp=110-112°C).

^{1}H NMR (400 MHz, (CD$_3$)$_2$CO) δ = 2.49-2.40 (m, 1H), 2.03-1.98 (m, 2H), 1.95 (s, 3H), 0.94 (d, *J*=6.8, 3H); **^{13}C NMR (75 MHz, (CD$_3$)$_2$CO)** δ = 205.6, 44.9, 29.2, 26.1, 18.3.



Potassium tert-butoxide (3.240 g, 0.027 mol) was added to a flame-dried round bottom flask and dry THF (360.0 mL) was added under a nitrogen atmosphere at -78°C. The starting material (4.010 g, 0.018 mol) was dissolved in dry THF (10.0 mL) and added drop-wise to the butoxide slurry. Upon complete addition, the reaction was allowed to stir for an additional 30 minutes at -78°C at which time the bath was removed and the reaction allowed warming to room temperature. The reaction was neutralized with saturated sodium bicarbonate and extracted with ether. The combined extracts were dried over sodium sulfate, concentrated, and purified by column chromatography (70% hexanes, 30% ethyl acetate) to yield enone (3.420 g, 93%).

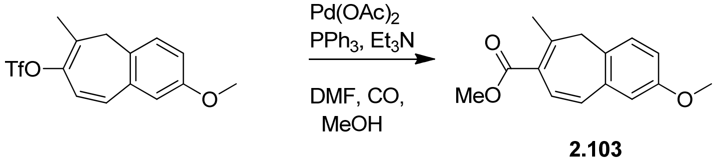
FTIR (thin film/NaCl) 2970, 2935, 1657, 1600, 1569, 1504, 1275, 1175, 1327 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.20 (d, *J*=7.2, 1H), 7.02 (d, *J*=12.8, 1H), 6.90-6.84 (m, 2H), 6.15 (d, *J*=12.8, 1H), 3.83 (s, 3H), 2.96-2.84 (m, 2H), 2.75-2.62 (m, 1H), 1.12 (d, *J*= 7.1, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 203.7, 158.7, 142.0, 135.3, 132.7, 131.1, 129.4, 117.5, 115.5, 55.7, 45.3, 36.5, 15.9; **HRMS** (EI) *m/z* 202.0993 [calc'd for $C_{13}H_{14}O_2$ (M+) 202.0994].



2.102

Freshly distilled diisopropyl amine (5.2 mL, 0.037 mol) was added to a flame-dried flask and diluted with dry THF (160.0 mL) and cooled to -78°C under nitrogen. Butyl lithium (1.6M, 21.0 mL, 0.034 mol) was then added and allowed to react for 30 minutes. Starting enone (3.400 g, 0.017 mol) was then dissolved in THF (8.0 mL) and added drop-wise to the LDA solution over 1 minute and allowed to stir for an additional 15 minutes. A stock solution of N-phenyl triflimide (6.610 g, 0.019 mol) was then added and the bath removed as the reaction warmed to room temperature. After 1 hour the reaction was diluted with ether (250.0 mL) and washed with NaOH solution (0.1M, 100.0 mL). The ethereal solution was then dried over sodium sulfate, concentrated, and purified with column chromatography (70% hexanes, 30% ethyl acetate) to yield the vinyl triflate (3.240 g, 58%).

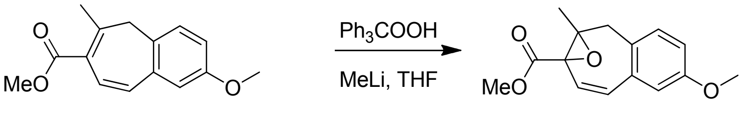
FTIR (thin film/NaCl) 2945, 2838, 1498, 1414, 1206, 1139, 1032 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.10-7.02 (m, 2H), 6.93 (dd, *J*=2.6, 8.3, 1H), 6.83 (d, *J*=2.6, 1H), 6.32 (d, *J*=11.9, 1H), 3.79 (s, 3H), 3.05 (s, 2H), 2.07 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$)** δ = 158.5, 140.3, 135.8, 135.0, 129.5, 128.9, 128.5, 122.9, 120.8, 116.3, 112.8, 55.6, 37.8, 18.9; **HRMS** (EI) *m/z* 335.0558 [calc'd for $C_{14}H_{14}O_4F_3S$ (M+H) 335.0565].



2.103

Palladium acetate (0.046 g, 0.210 mmol) and triphenylphosphine (0.108 g, 0.420 mmol) were added to a flame-dried flask at room temperature under nitrogen. Dry DMF (21.0 mL) was added followed by triethylamine (0.8 mL, 6.200 mmol) and methanol (3.4 mL, 0.083 mol). Starting triflate (0.690 g, 2.070 mmol) was dissolved in dry DMF (3.0 mL) and added to the reaction and a balloon of carbon monoxide was attached *via* needle through a septum. The reaction was heated at 80°C for 3 hours until the starting material was consumed. The reaction was then diluted with ethyl acetate (250.0 mL) and washed with distilled water (3 x 50.0 mL). The organics were then dried over sodium sulfate and purified with silica gel chromatography (70% hexanes, 30% ethyl acetate) to yield the enoate (0.485 g, 96%).

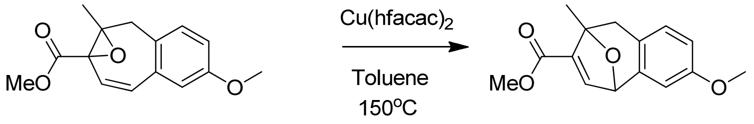
FTIR (thin film/NaCl) 2952, 1716, 1604, 1495, 1434, 1257, 1221 cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$)** δ = 7.09 (d, *J*=8.4, 1H), 7.03 (d, *J*=11.8, 1H), 6.90 (dd, *J*=2.7, 8.4, 1H), 6.86 (d, *J*=11.8, 1H), 6.82 (d, *J*=2.7, 1H), 3.78 (s, 3H), 3.72 (s, 3H), 3.03 (s, 2H), 2.36 (s, 3H); **^{13}C NMR (75 MHz, CDCl$_3$)** δ = 168.1, 158.2, 148.9, 136.4, 131.9, 128.8, 128.3, 128.2, 124.0, 115.6, 111.7, 55.6, 51.7, 42.9, 22.9; **HRMS** (EI) *m/z* 244.1097 [calc'd for $C_{15}H_{16}O_3$ (M+) 244.1100].



2.104

Triphenylmethyl hydroperoxide (0.153 g, 0.554 mmol) was added to a flame-dried flask and dissolved in dry THF (7.0 mL) under nitrogen and then cooled to -78°C. Methyl lithium (1.6M, 0.3 mL, 0.480 mmol) was added and the reaction was stirred for 10 minutes. Starting diene (0.090 g, 0.368 mmol) was then dissolved in dry THF (0.4 mL), added to the reaction, and allowed to stir at -78°C for 1 hour. The reaction was then warmed to room temperature and quenched with saturated ammonium chloride (5.0 mL) and extracted with ethyl acetate (3 x 50.0 mL). The organics were then dried over sodium sulfate, concentrated, and purified by silica gel chromatography (80% hexanes, 20% ethyl acetate) to yield the epoxide (0.086 g, 90%).

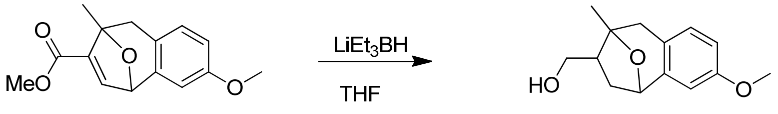
FTIR (thin film/NaCl) 2957, 1749, 1605, 1572, 1503, 1435, 1266, 1045 cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$)** δ = 7.01-6.96 (m, 2H), 6.77 (dd, *J*=2.7, 8.3, 1H), 4.23 (d, *J*=4.3, 1H), 4.18 (d, *J*=4.3, 1H), 3.96 (d, *J*=13.6, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.26 (d, *J*=13.6, 1H), 2.24 (s, 3H); **^{13}C NMR (75 MHz, CDCl$_3$)** δ = 169.5, 158.9, 136.9, 134.2, 130.6, 127.9, 125.7, 115.1, 113.6, 71.6, 62.7, 55.5, 52.9, 42.8, 18.6; **HRMS** (EI) *m/z* 260.1050 [calc'd for $C_{15}H_{16}O_4$ (M+) 260.1049].



2.105

Starting epoxide (0.062 g, 0.238 mmol) was dissolved in dry toluene (0.5 mL) and dry Cu(hfacac)$_2$ (0.035 g, 0.071 mmol, dried on vacuum pump for 2 hours prior to use) was added at room temperature. The vial was sealed well and the reaction heated at 150°C for 30 minutes. After allowing the reaction to cool to room temperature, it was filtered through neutral alumina (activity grade 1), concentrated and purified with silica gel chromatography (80% hexanes, 20% ethyl acetate) to give the ring expanded product (0.050 g, 81%).

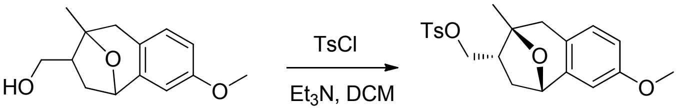
FTIR (thin film/NaCl) 2947, 2933, 1714, 1598, 1494, 1437, 1253 cm^{-1}; **^{1}H NMR (300 MHz, CDCl$_3$)** δ = 6.98 (d, *J*=8.5, 1H), 6.76 (dd, *J*=8.5, 2.6, 1H), 6.63 (d, *J*=2.6, 1H), 5.30 (d, *J*=1.8, 1H), 3.77 (s, 3H), 3.71 (s, 3H), 2.92 (d, *J*=17.0, 1H), 2.78 (d, *J*=17.0, 1H), 1.72 (s, 3H); **^{13}C NMR (151 MHz, CDCl$_3$)** δ = 164.1, 157.6, 147.4, 137.0, 135.7, 131.3, 126.1, 113.4, 110.0, 84.5, 80.2, 55.6, 51.7, 34.6, 23.6; **HRMS** (EI) *m/z* 261.1129 [calc'd for $C_{15}H_{17}O_4$ (M+H) 261.1127].



2.106

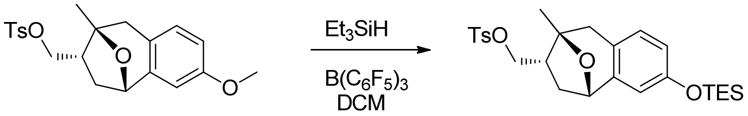
Methyl enoate (0.135 g, 0.520 mmol) was dissolved in dry THF (26.0 mL) and the solution cooled to -78°C under nitrogen. Lithium triethylborohydride (1M, 2.08 mL, 2.08 mmol) was added drop-wise and the reaction stirred for 90 minutes. The bath was then removed and when the reaction had come to room temperature it was quenched with saturated ammonium chloride and extracted with DCM. The organics were dried over sodium sulfate, concentrated, and chromatographed (50% hexanes, 50% ethyl acetate) to give the primary alcohol (0.118 g, 97%).

FTIR (thin film/NaCl) 2953, 2922, 1610, 1502, 1451, 1382, 1258, 1155, 1034 cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$)** δ = 6.97 (d, *J*=8.1, 1H), 6.70 (dd, *J*=2.5, 8.1, 1H), 6.51 (d, *J*=2.5, 1H), 4.95 (d, *J*=7.2, 1H), 3.77 (s, 3H), 3.64-3.55 (m, 1H), 3.54-3.44 (m, 1H), 2.94 (d, *J*=17.0, 1H), 2.83 (d, *J*=17.0, 1H), 2.60-2.50 (m, 1H), 2.33-2.24 (m, 1H), 1.54 (s, 3H), 1.50 (dd, *J*=4.2, 12.2, 1H); **^{13}C NMR (600 MHz HSQCAD/gHMBC, CDCl$_3$)** δ =157.7, 142.3, 129.3, 124.3, 112.7, 109.0, 81.8, 77.1, 64.8, 55.4, 49.5, 40.0, 36.2, 28.3; **HRMS** (EI) *m/z* 234.1259 [calc'd for $C_{14}H_{18}O_3$ (M+) 234.1256]..



Starting alcohol (0.049 g, 0.210 mmol) was dissolved in dry DCM (4.2 mL) at 0°C under nitrogen. Freshly distilled triethylamine (0.3 mL, 2.1 mmol) was added followed by *p*-toluenesulfonyl chloride (0.060 g, 0.315 mmol). The bath was removed and the reaction stirred for 10 hours. The reaction was quenched with water (2.0 mL) and extracted with DCM (3 x 5.0 mL). The organics were dried with sodium sulfate, concentrated and purified with silica gel chromatography to give the tosylate (0.078 g, 96%).

FTIR (thin film/NaCl) 2970, 2929, 1612, 1503, 1452, 1360, 1253, 1176, 1096, 1017, 950 cm^{-1} ; ^{1}**H NMR (400 MHz, CDCl$_3$)** δ = 7.73 (d, *J*=8.2, 2H), 7.33 (d, *J*=8.2, 2H), 6.77 (d, *J*=8.3, 1H), 6.66 (dd, *J*=2.6, 8.3, 1H), 6.43 (d, *J*=2.6, 1H), 4.90 (d, *J*=6.8, 1H), 4.00-3.94 (m, 1H), 3.82-3.76 (m, 1H), 3.76 (s, 3H), 2.87 (d, *J*=17.0, 1H), 2.56 (d, *J*=17.0, 1H), 2.53-2.35 (m, 2H), 2.47 (s, 3H), 1.48 (s, 3H), 1.34 (dd, *J*=3.7, 12.1, 1H); ^{13}**C NMR (600 MHz HSQCAD/gHMBC, CDCl$_3$)** δ =157.8, 144.9, 141.7, 132.7, 129.7, 129.0, 127.6, 123.1, 112.6, 108.7, 81.5, 76.5, 71.2, 55.0, 45.7, 39.4, 35.6, 27.6, 21.3; **HRMS** (EI) *m/z* 389.1417 [calc'd for $C_{21}H_{25}O_5S$ (M+H) 389.1423].

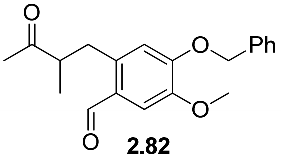


2.98

Starting tosylate (0.034 g, 0.088 mmol) was dissolved in DCM (1.8 mL) at room temperature. The tris(pentafluorophenyl)borane (0.005 g, 0.009 mmol) was then added followed by a 10% stock solution of triethylsilane (0.15 mL, 0.097 mmol) and the reaction was allowed to stir at room temperature for 1 hour. After the starting material was consumed, the reaction was purified by silica gel chromatography (80% hexanes, 20% ethyl acetate) to give pure TES-ether (0.036 g, 84%).

FTIR (thin film/NaCl) 2954, 2915, 1674, 1622, 1497, 1457, 1372, 1243, 1177, 1156, 1124, 1062, 1011 cm^{-1}; ^{1}**H NMR (600 MHz, CDCl$_3$)** δ = 7.72 (d, *J*=8.0, 1H), 7.33 (d, *J*=8.0, 1H), 6.69 (d, *J*=8.2, 1H), 6.59 (dd, *J*=2.5, 8.2, 1H), 6.38 (d, *J*=2.5, 1H), 4.85 (d, *J*=6.9, 1H), 4.01-3.94 (m, 1H), 3.79-3.73 (m, 1H), 2.86 (d, *J*=17.1, 1H), 2.54 (d, *J*=17.1, 1H), 2.51-2.45 (m, 1H), 2.47 (s, 3H), 2.40-2.35 (m, 1H), 1.47 (s, 3H), 1.31 (dd, *J*=3.9, 12.3, 1H), 0.97 (t, *J*=7.8, 9H), 0.71 (q, *J*=7.8, 6H); ^{13}**C NMR (600 MHz HSQCAD/gHMBCAD, CDCl$_3$)** 153.7, 144.9, 141.6, 130.8, 129.9, 129.1, 128.0, 124.0, 118.8, 115.1, 81.8, 76.8, 71.4, 46.0, 39.7, 35.9, 27.9, 21.5, 6.7, 4.8; **HRMS** (EI) *m/z* 489.2151 [calc'd for $C_{26}H_{37}O_5SiS$ (M+H) 489.2131].

A2.2 NMR Data for Chapter 2



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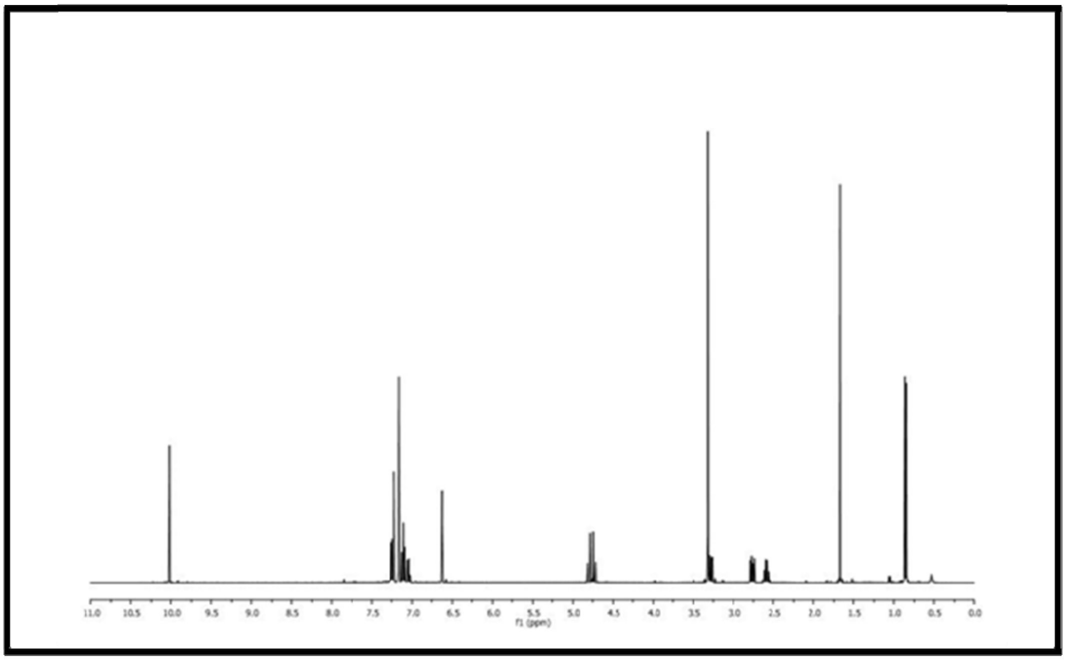

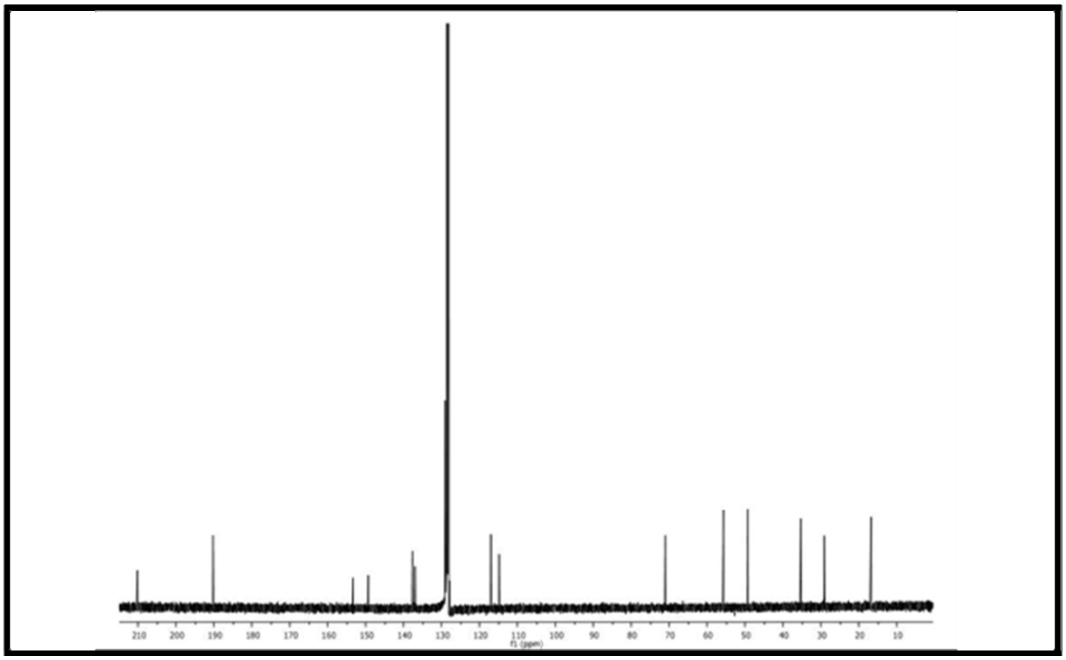

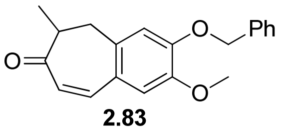
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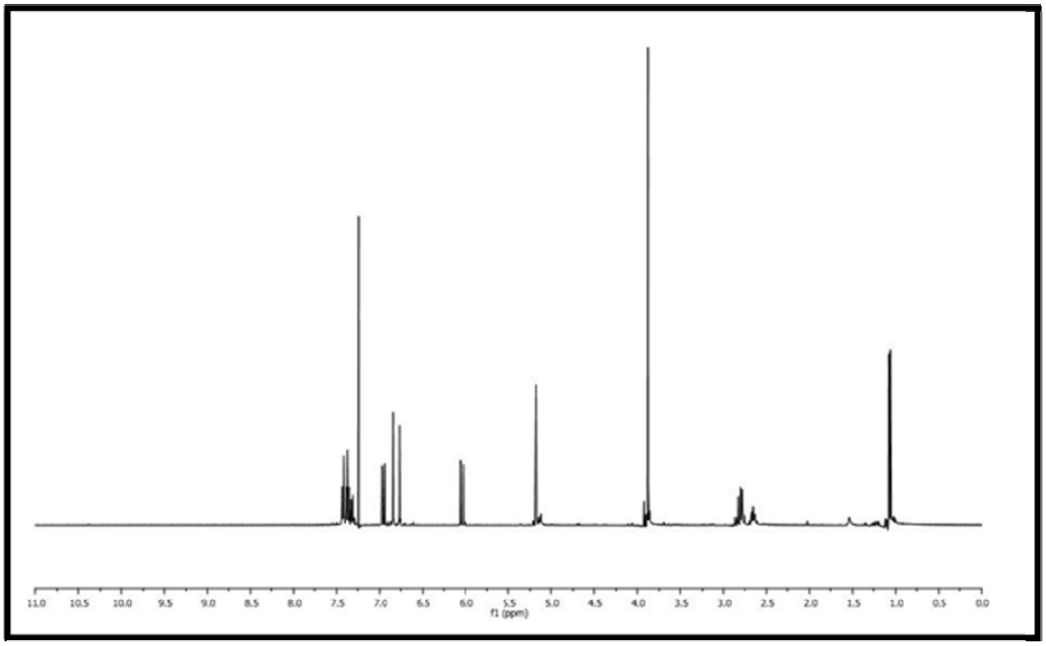
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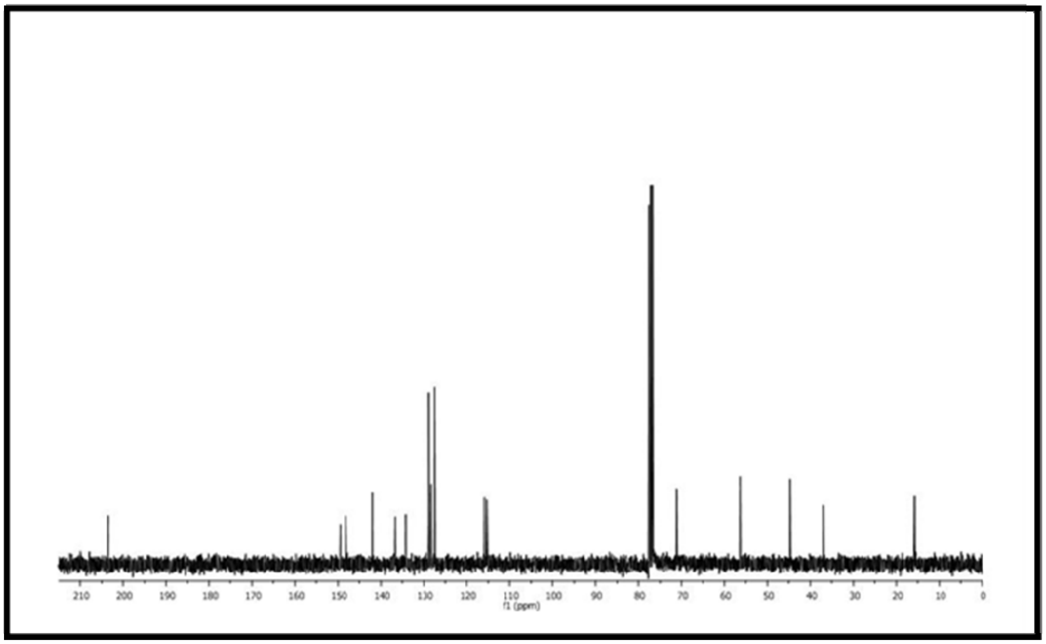
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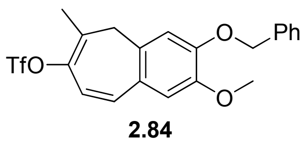

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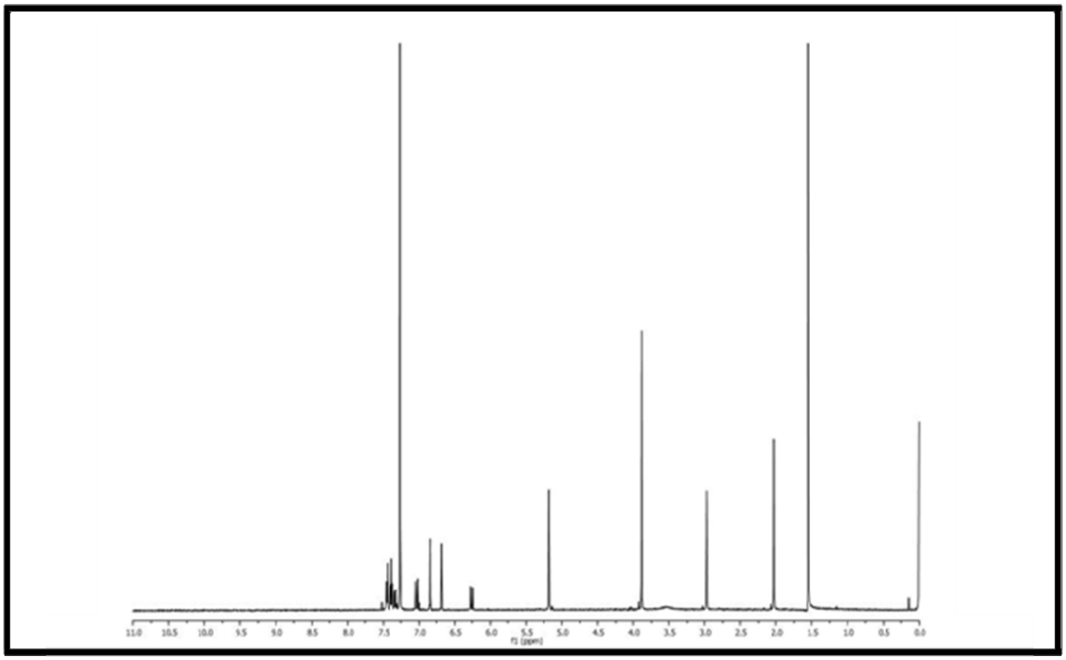

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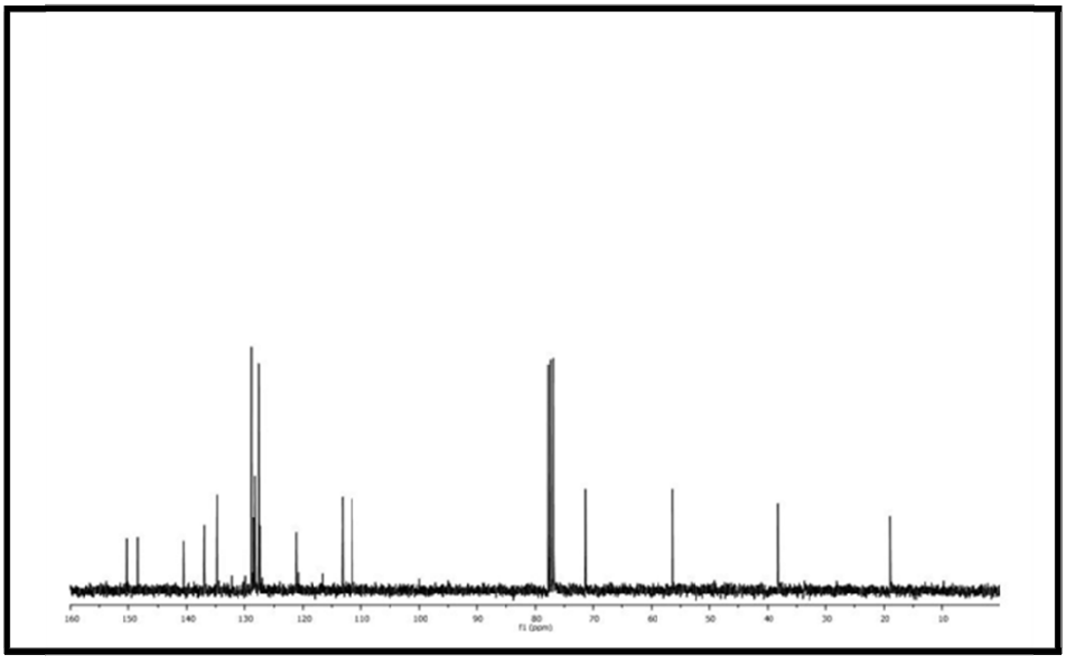

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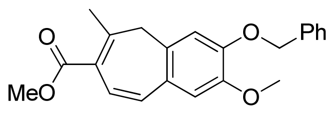
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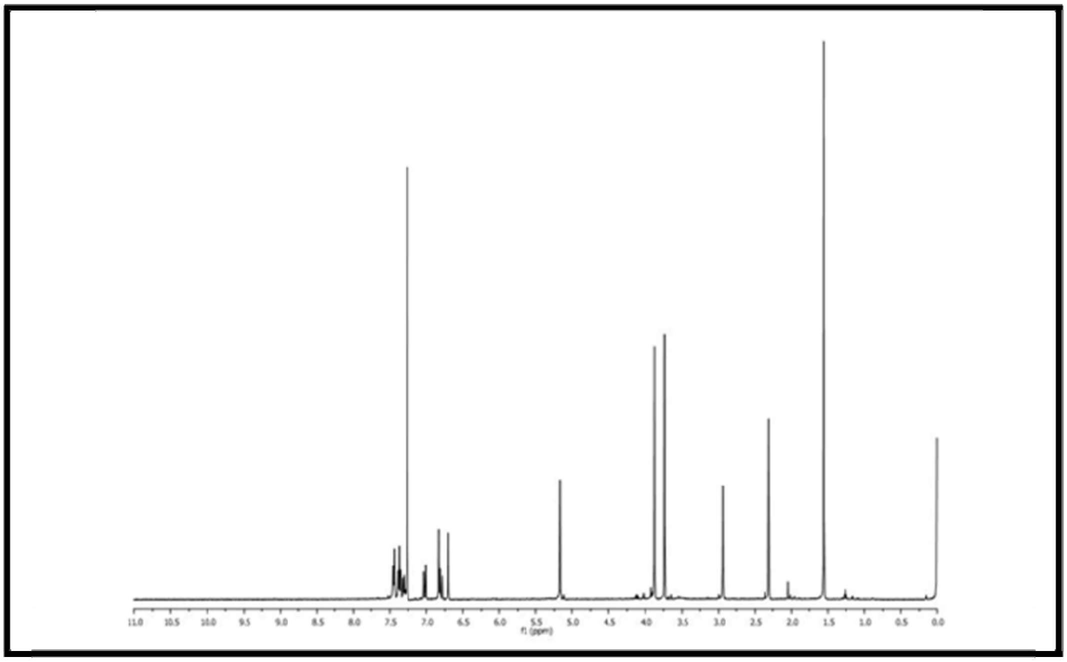
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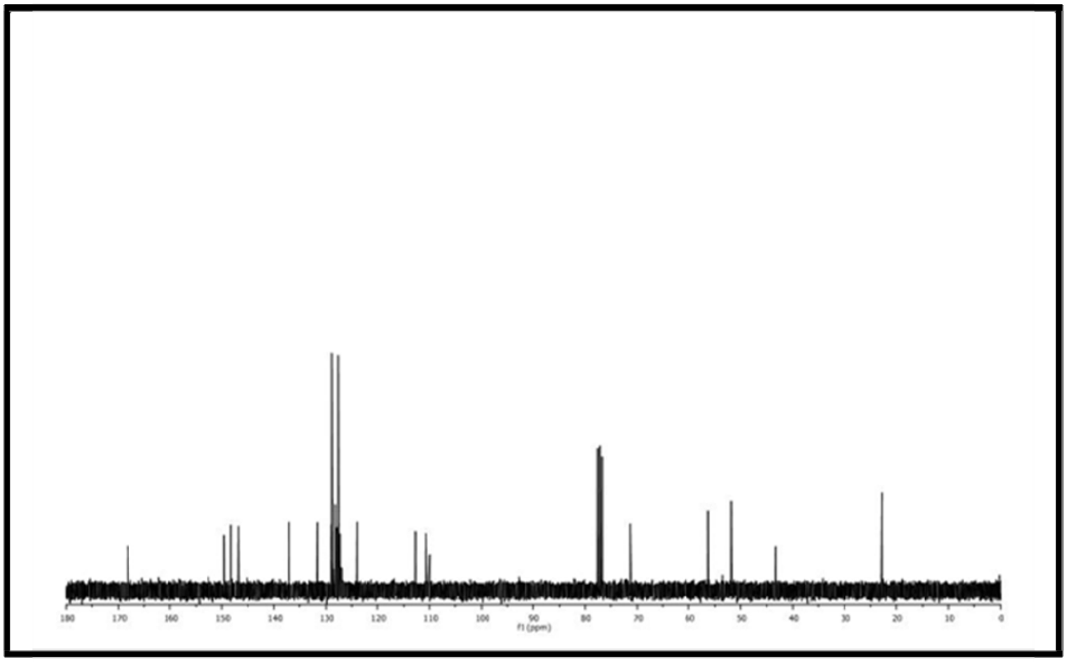
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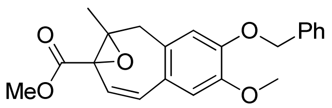
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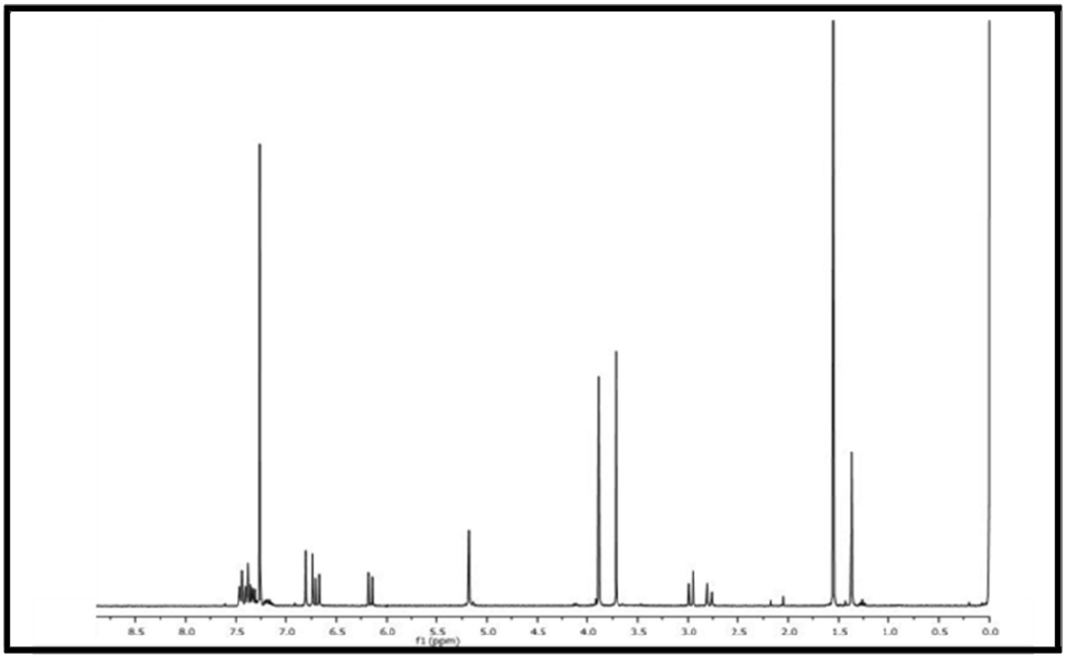
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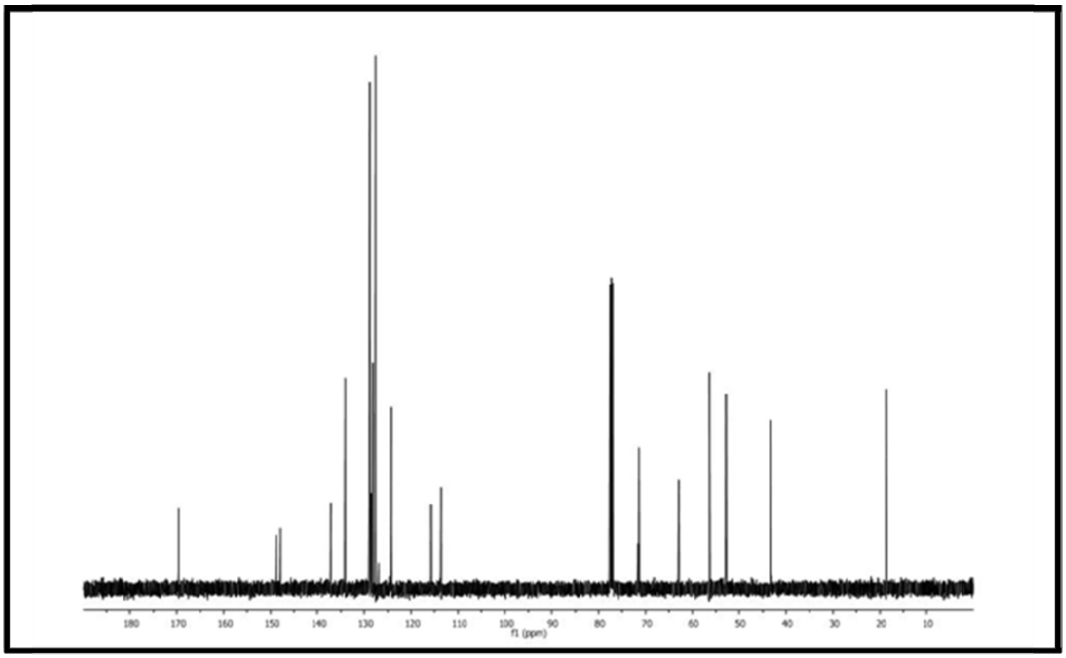
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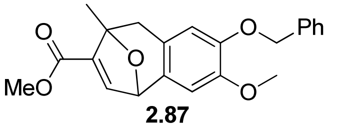
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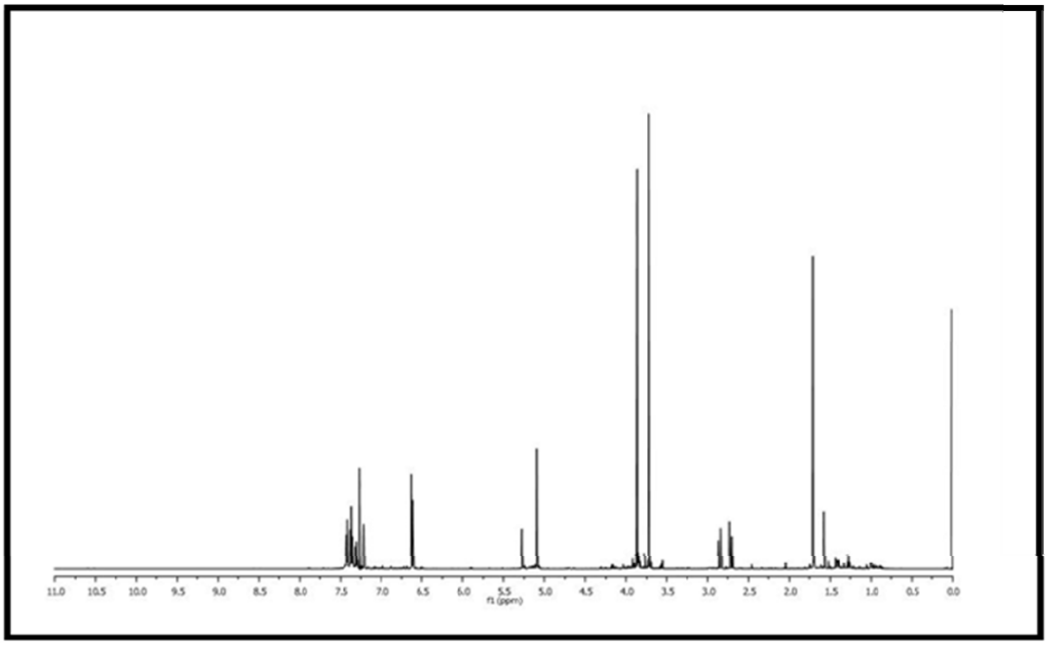
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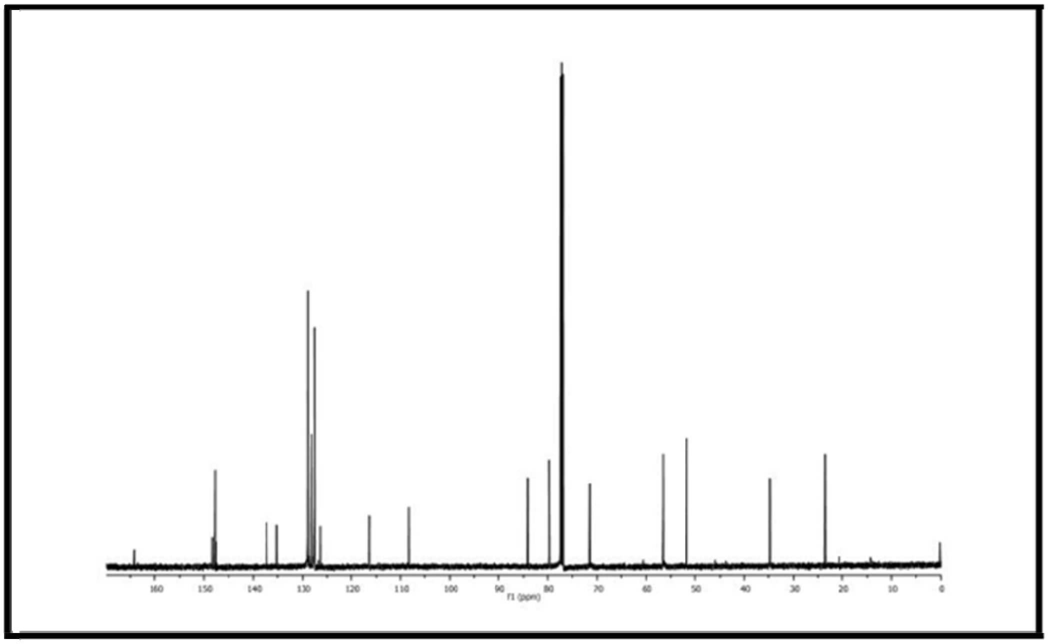
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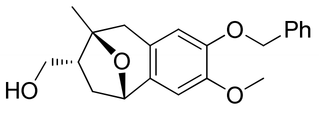
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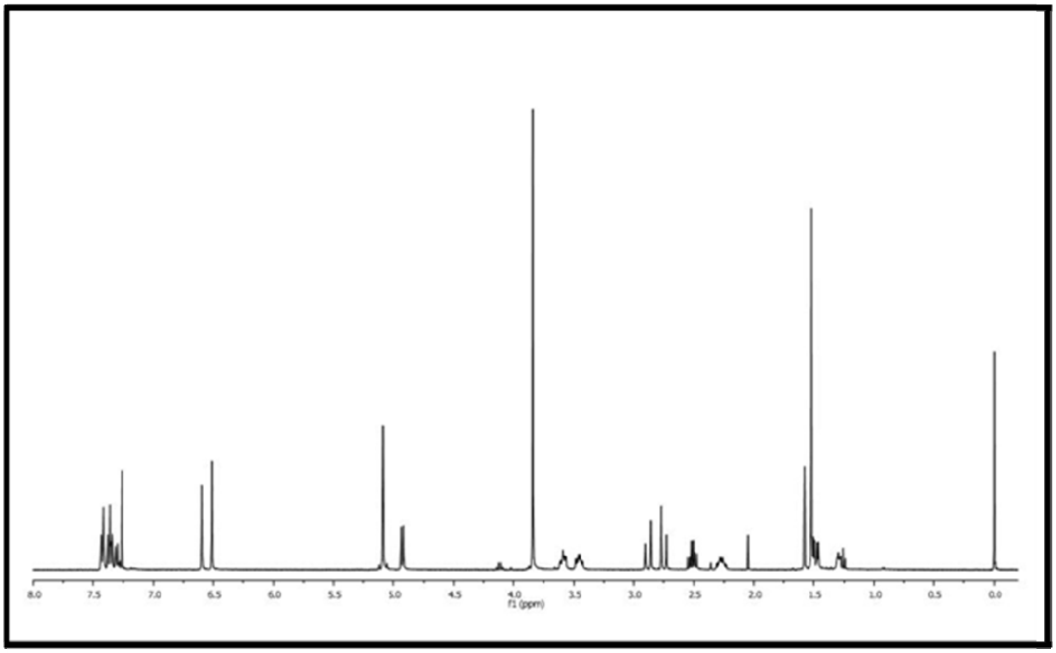
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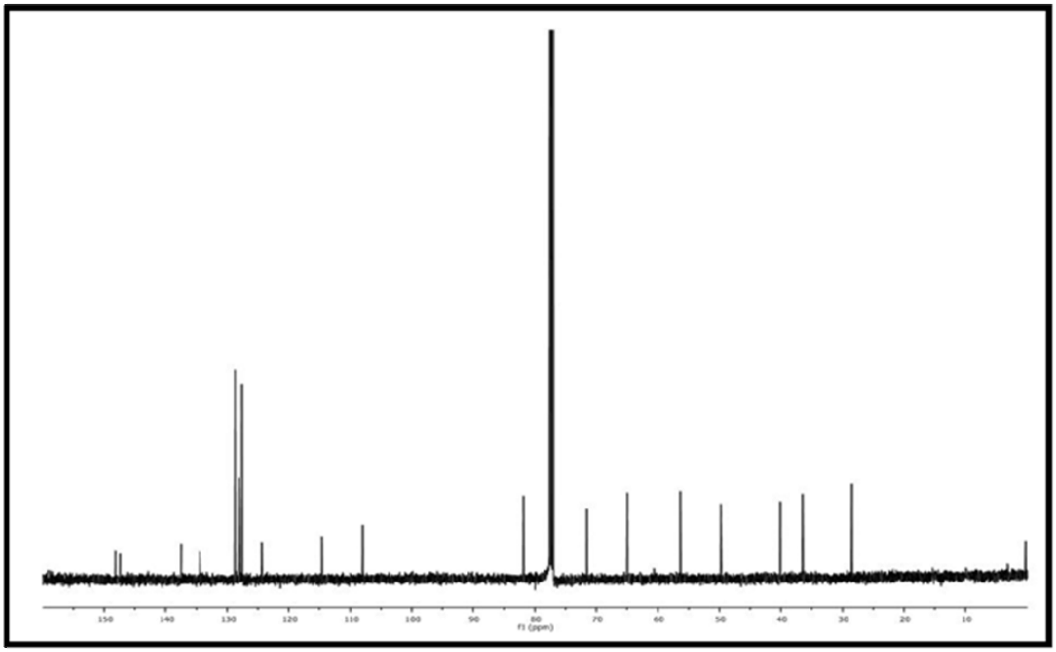
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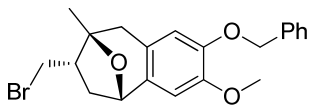
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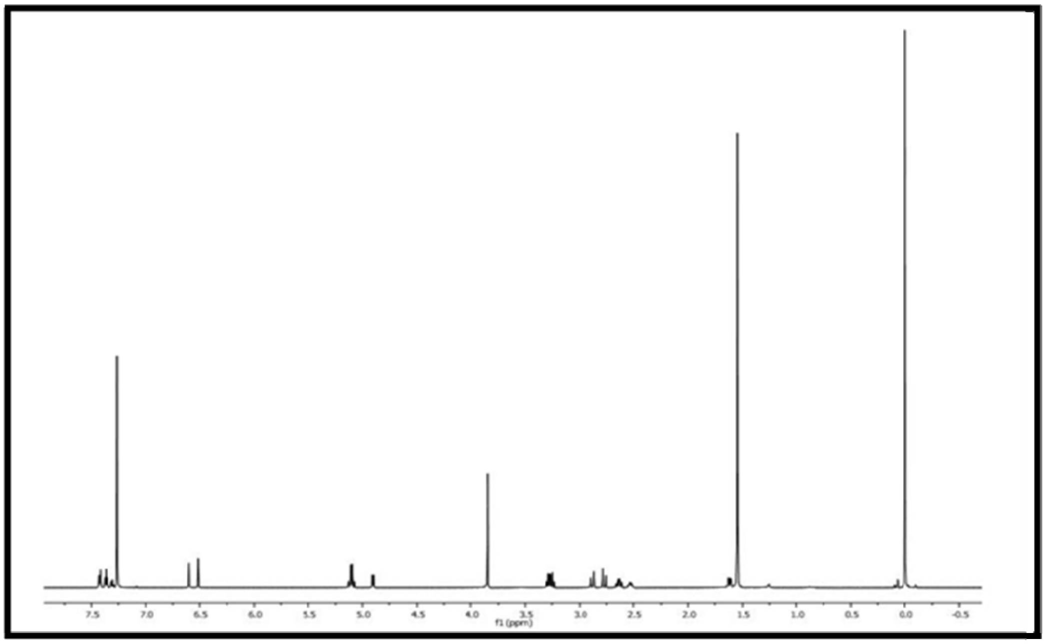
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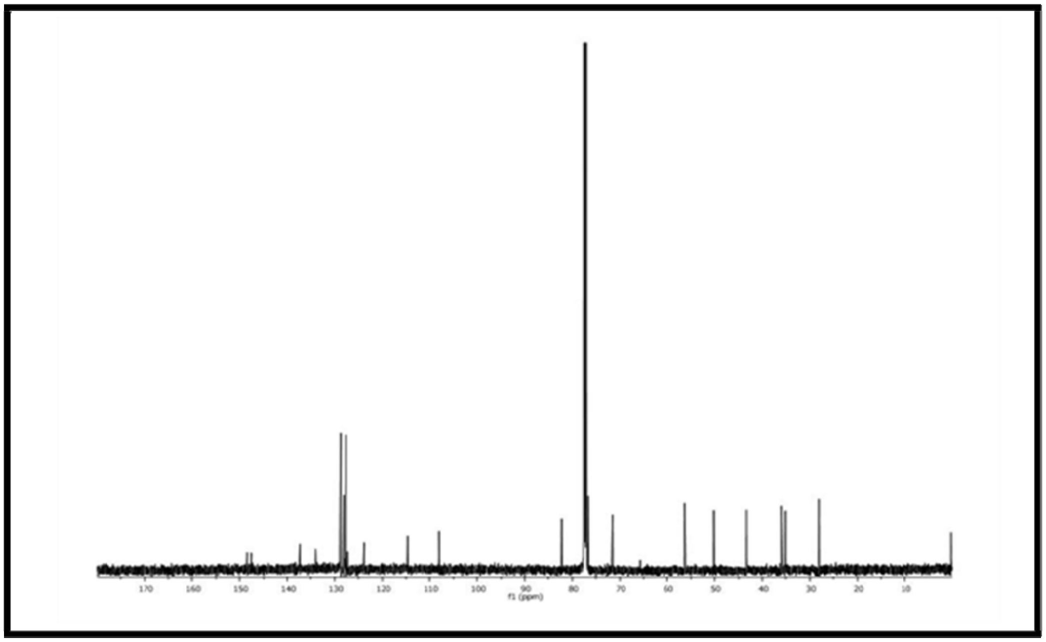
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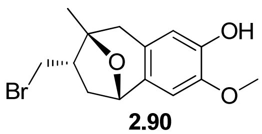
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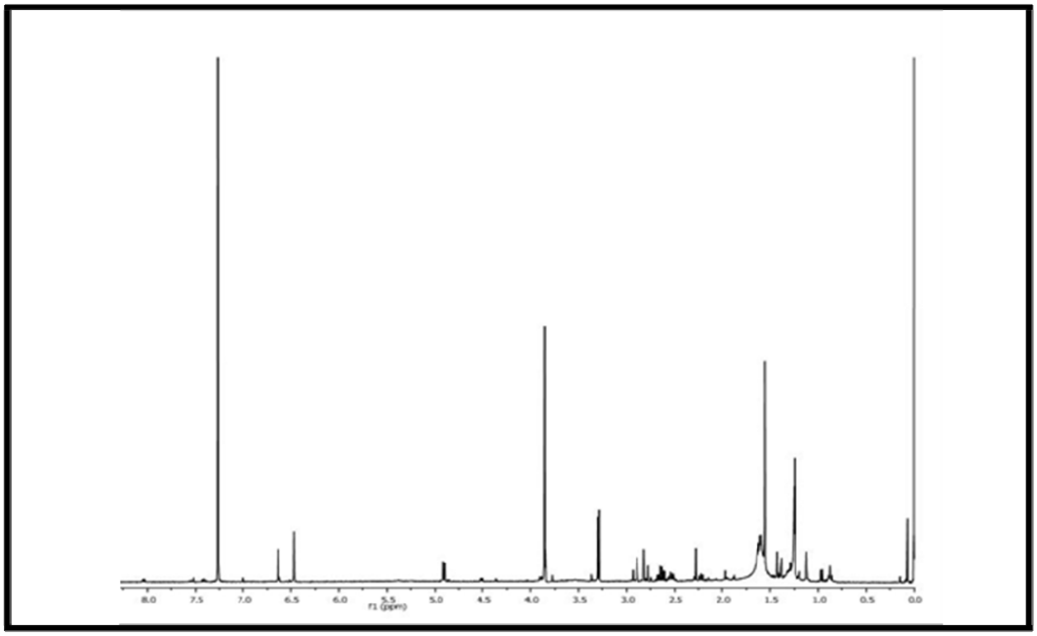
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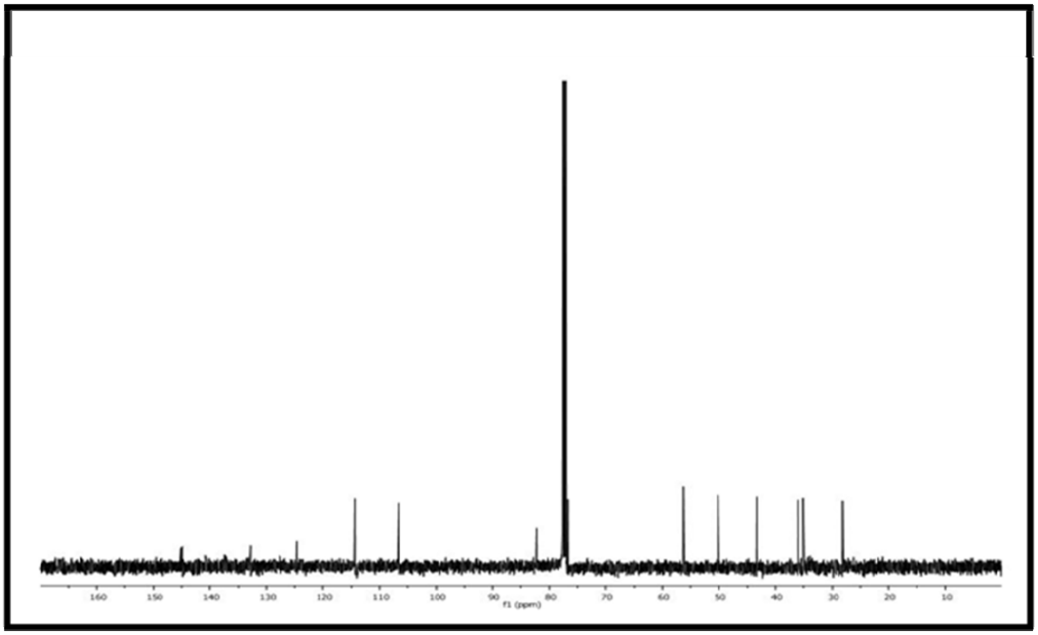
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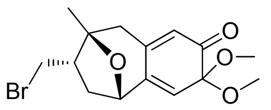

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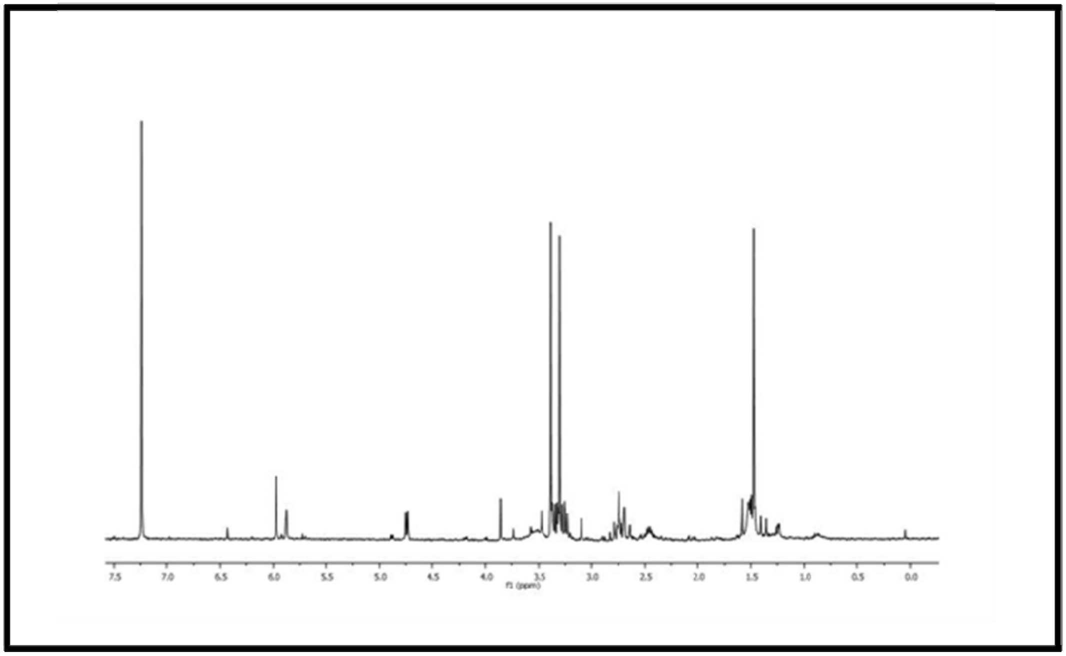

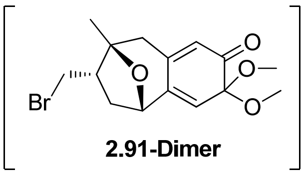

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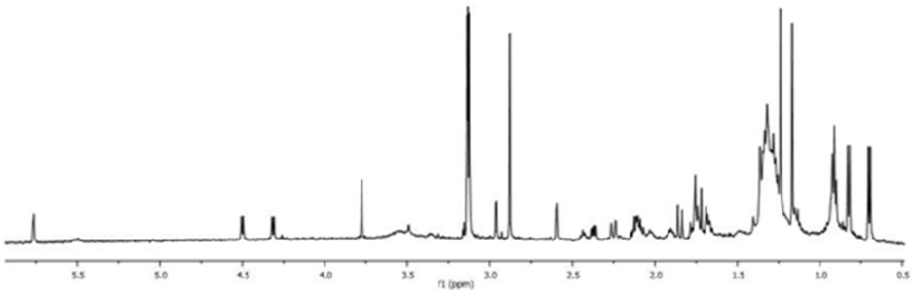

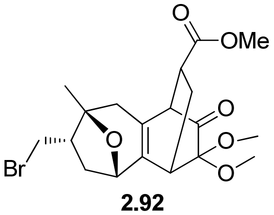

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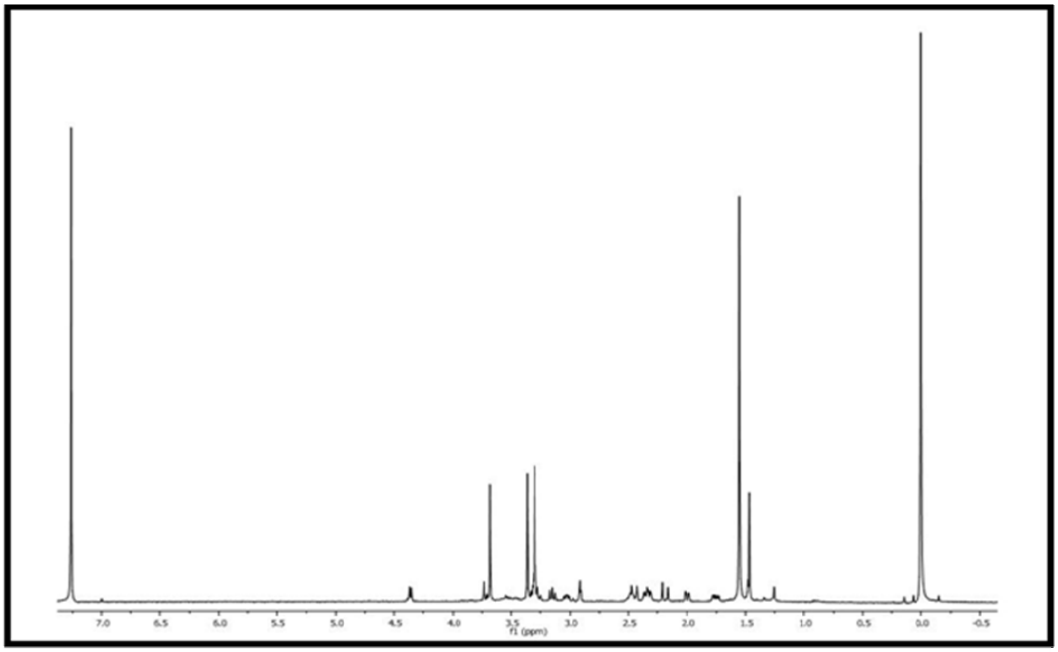

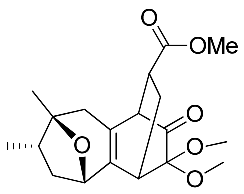
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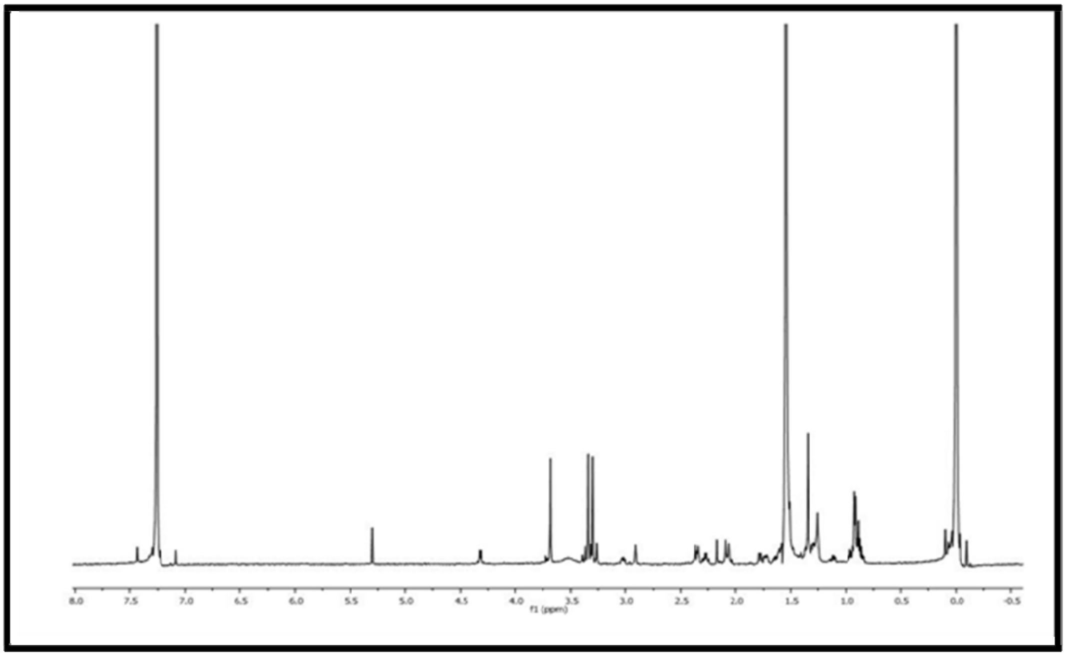
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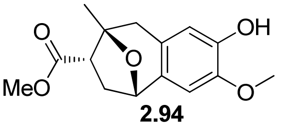
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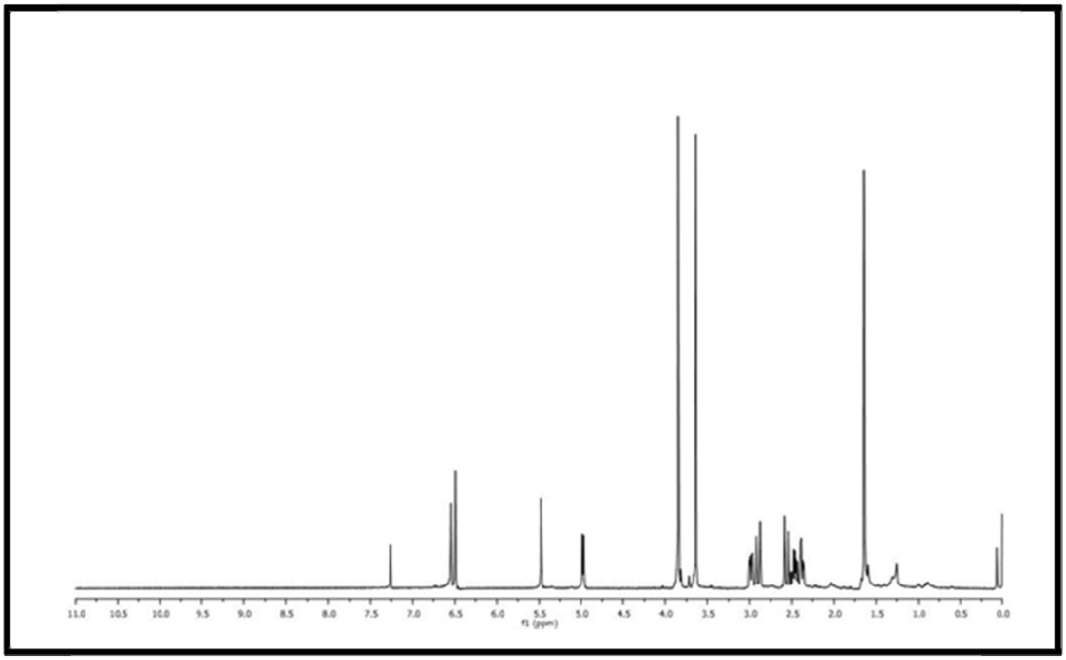
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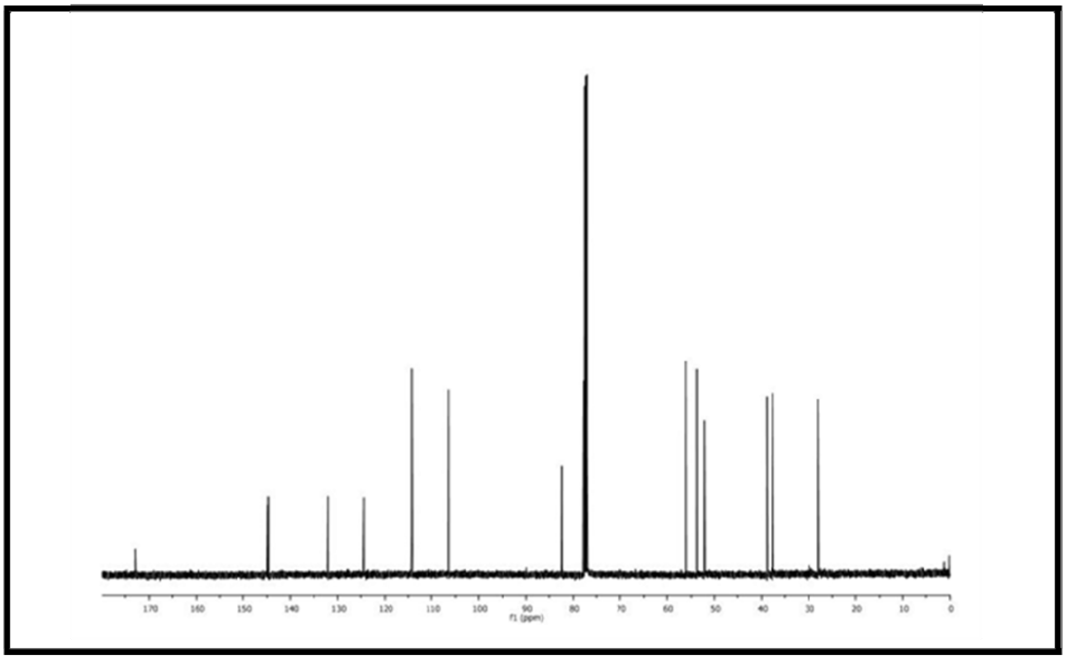
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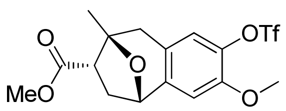
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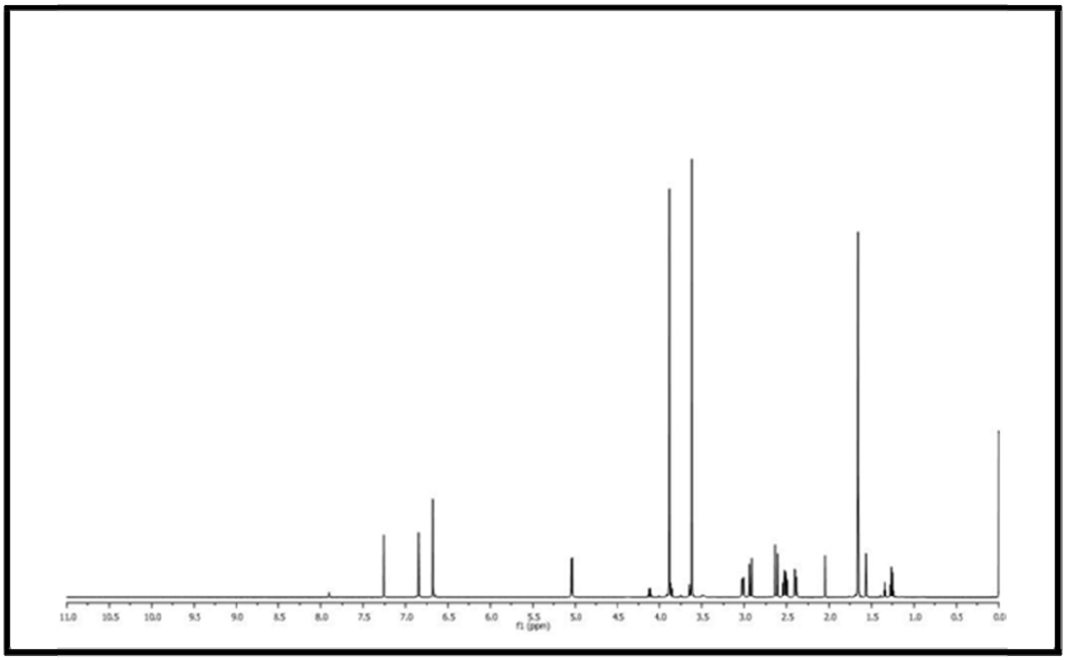
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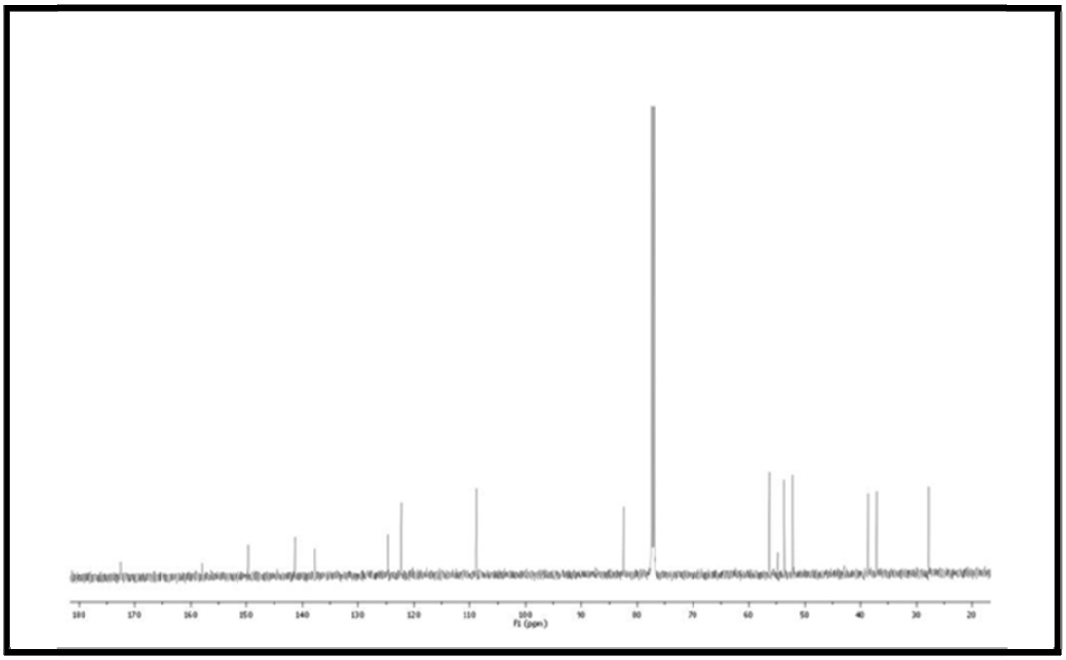
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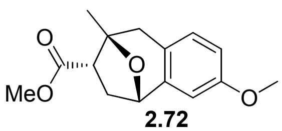
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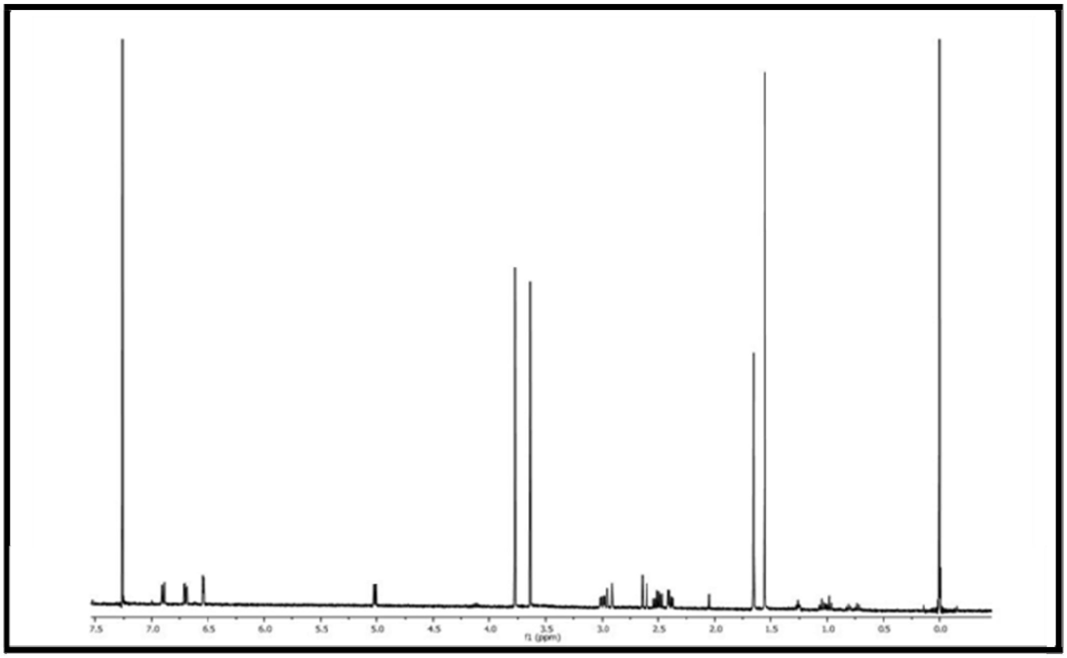
MeO
O
O

2.72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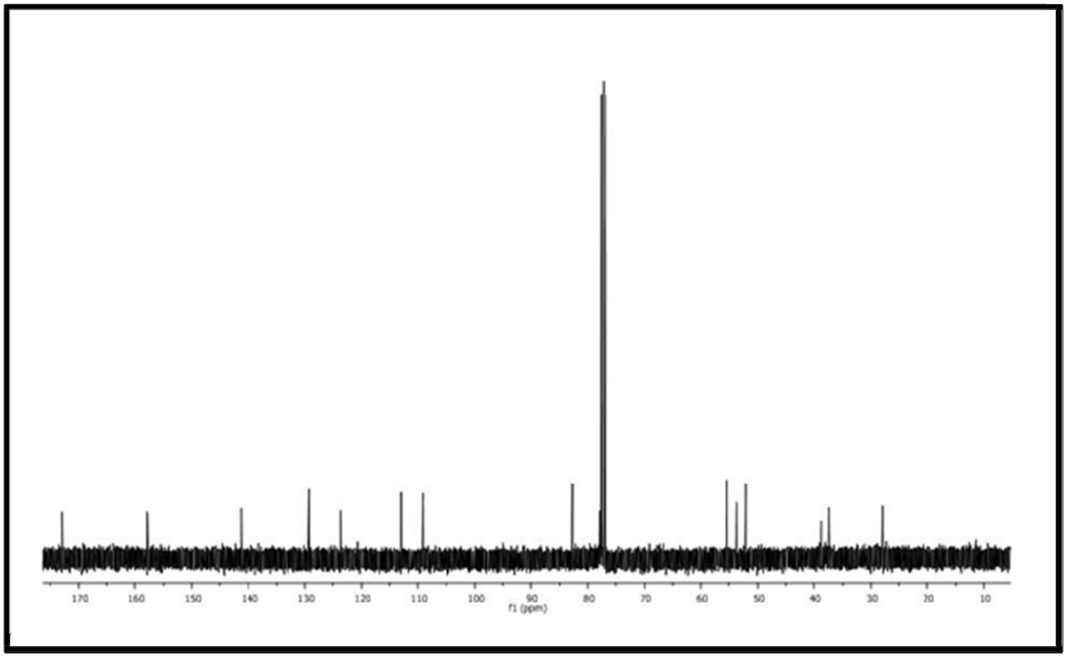
0.0
f1 (ppm)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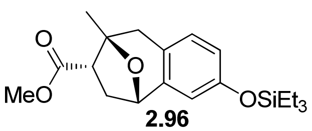
f1 (ppm)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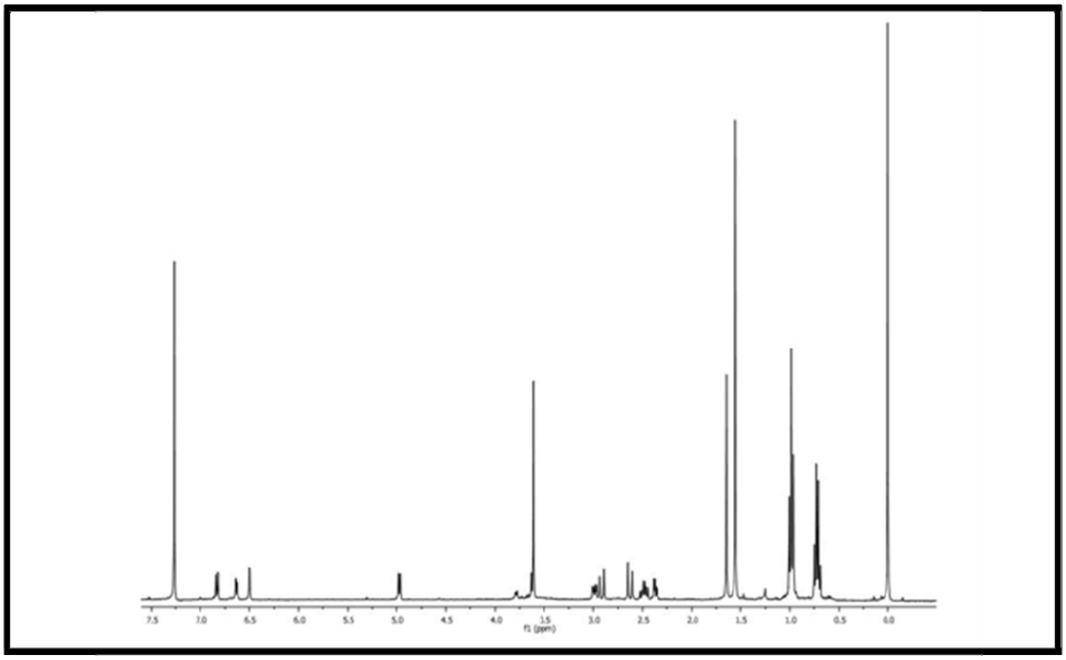
O
OSiEt3

2.96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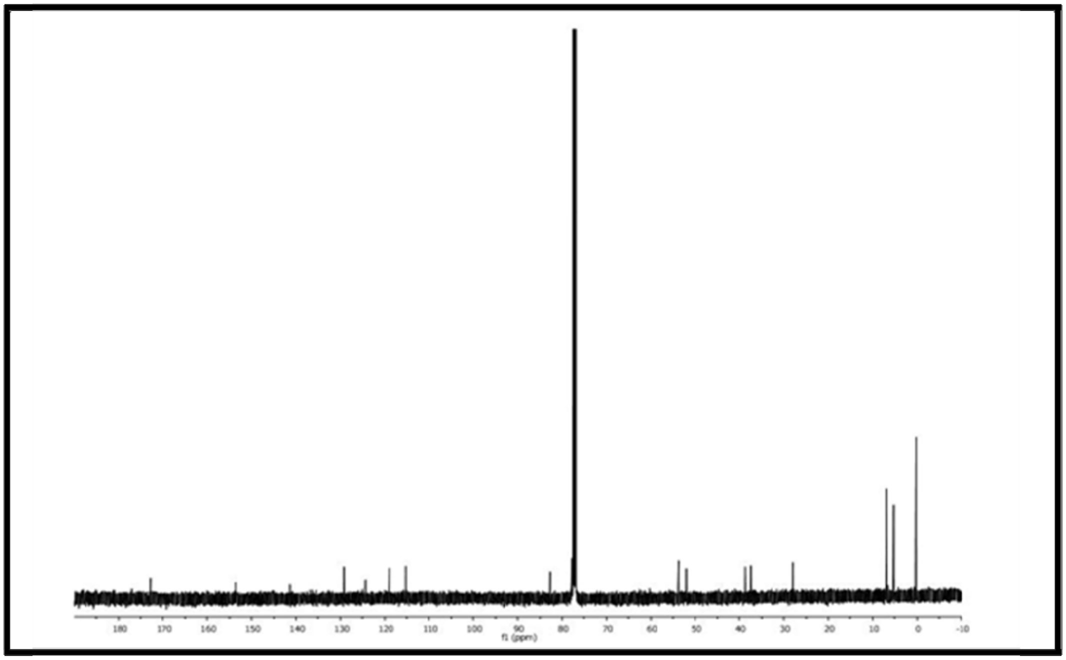
0.0
f1 (ppm)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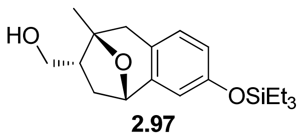
f1 (ppm)



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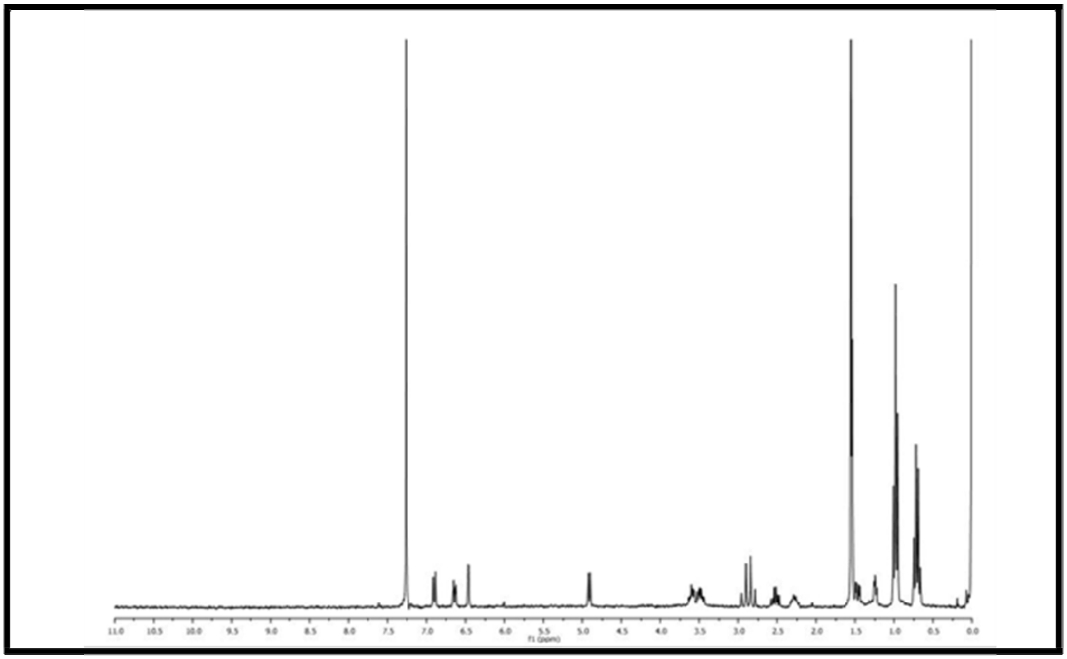
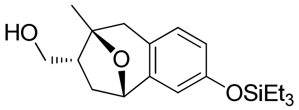


Carbon Chemical Shifts Were Determined
From HSQCAD and gHMBCAD Experiments



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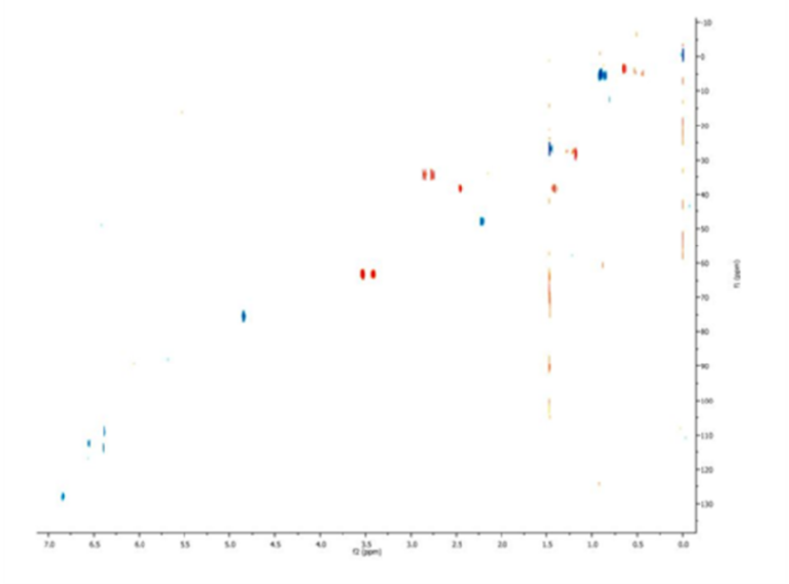

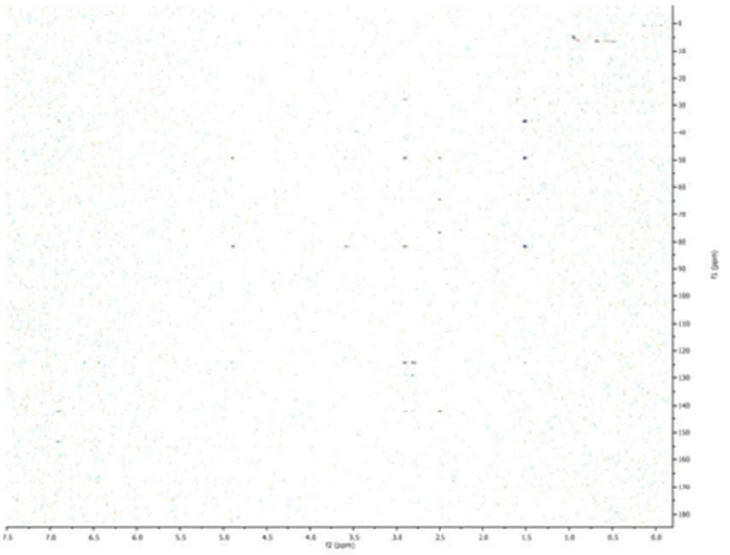

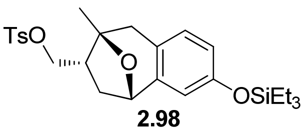

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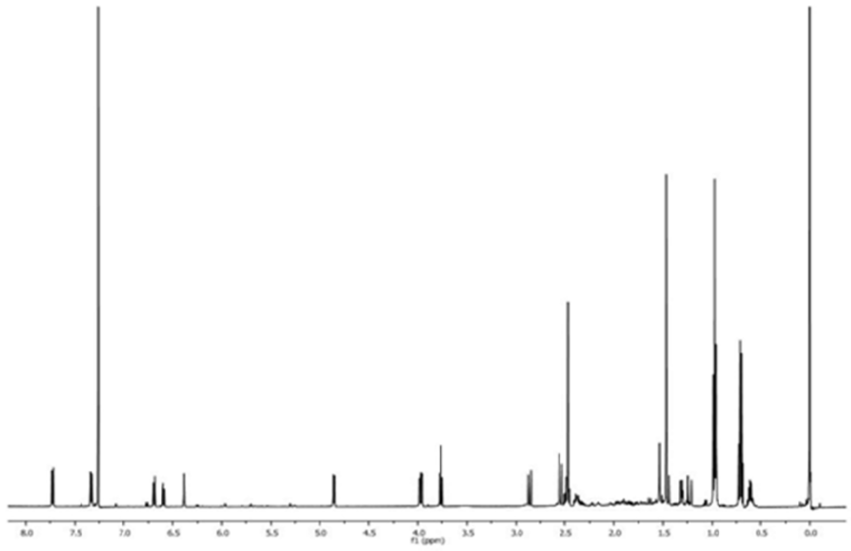
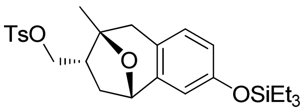


Carbon Chemical Shifts Were Determined
From HSQCAD and gHMBCAD Experiments



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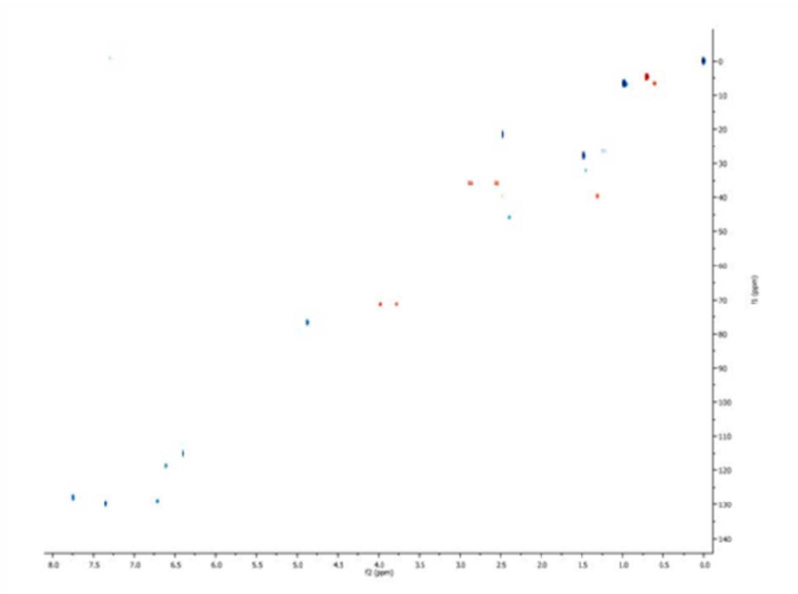

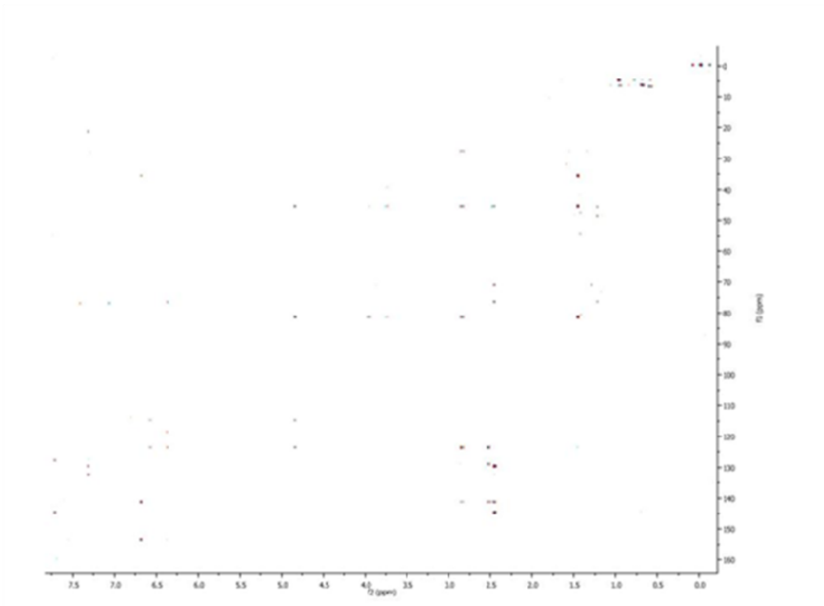

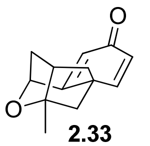

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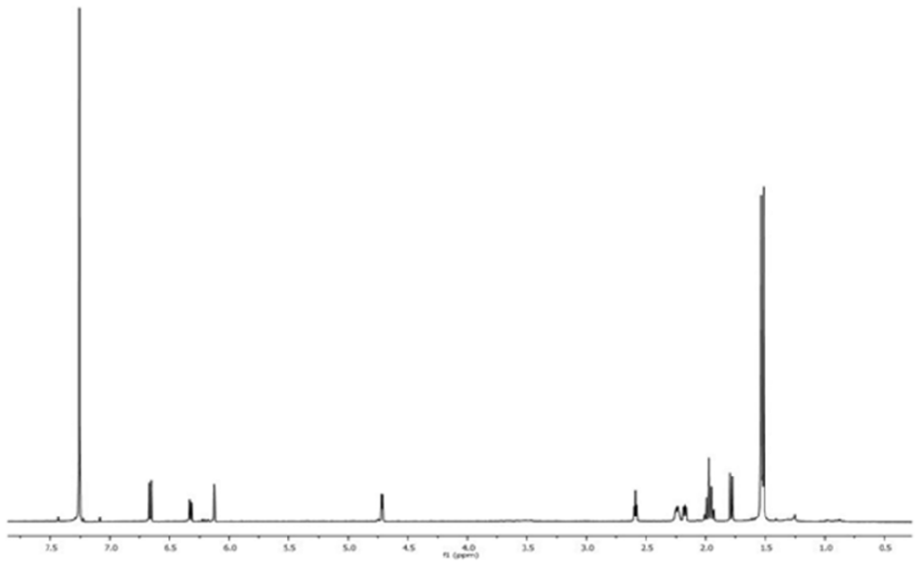
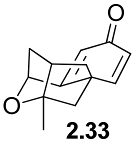


Carbon Chemical Shifts Were Determined
From HSQCAD and gHMBCAD Experiments



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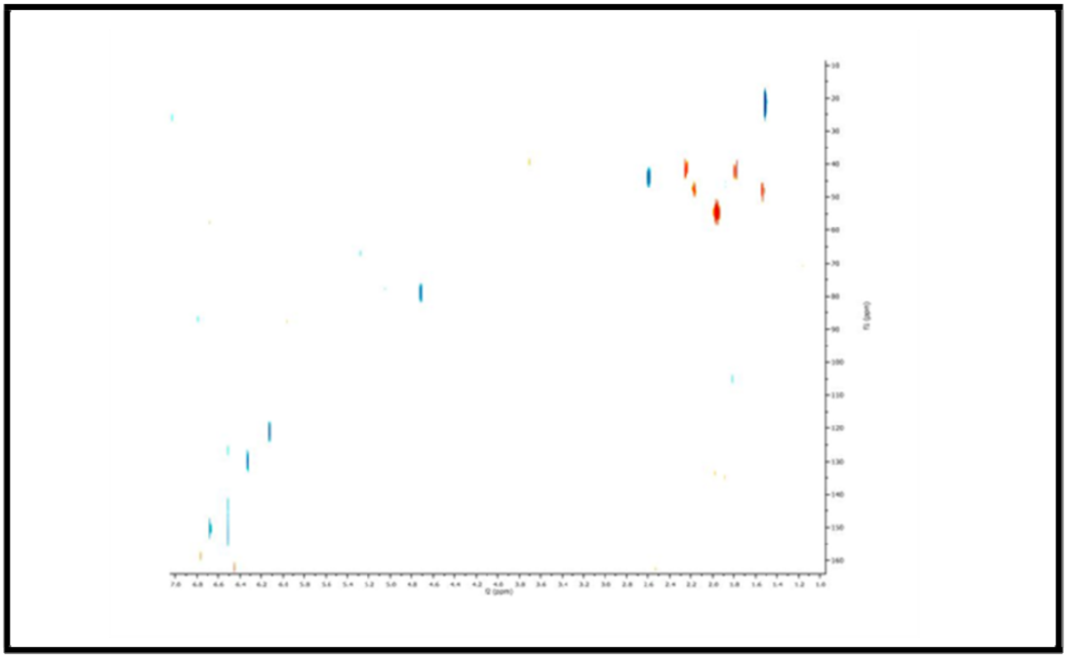

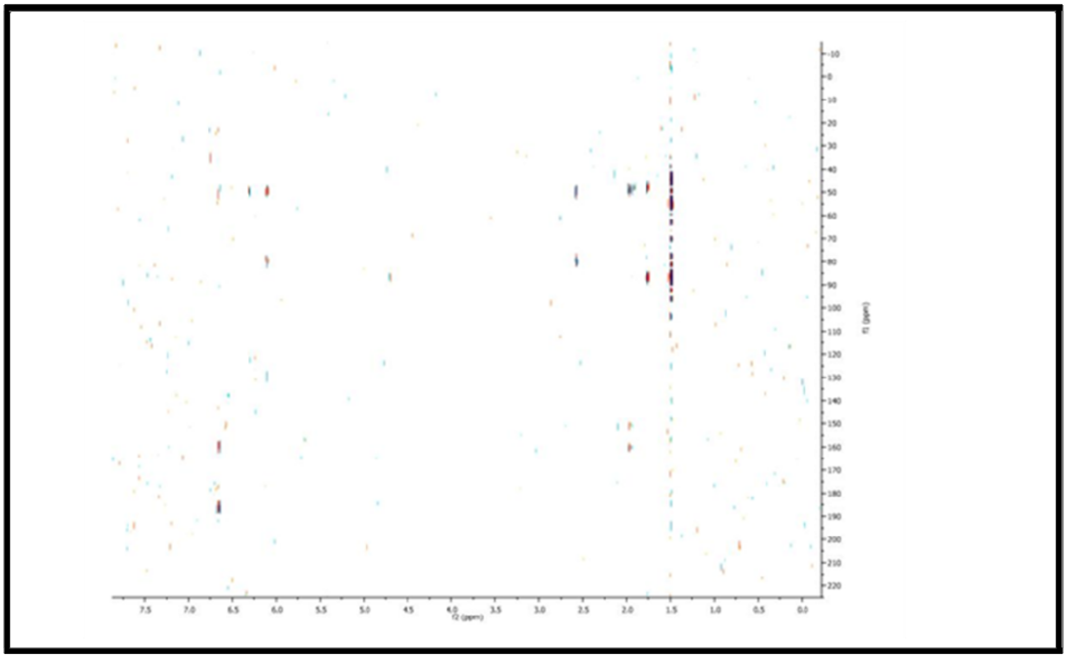

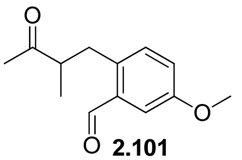

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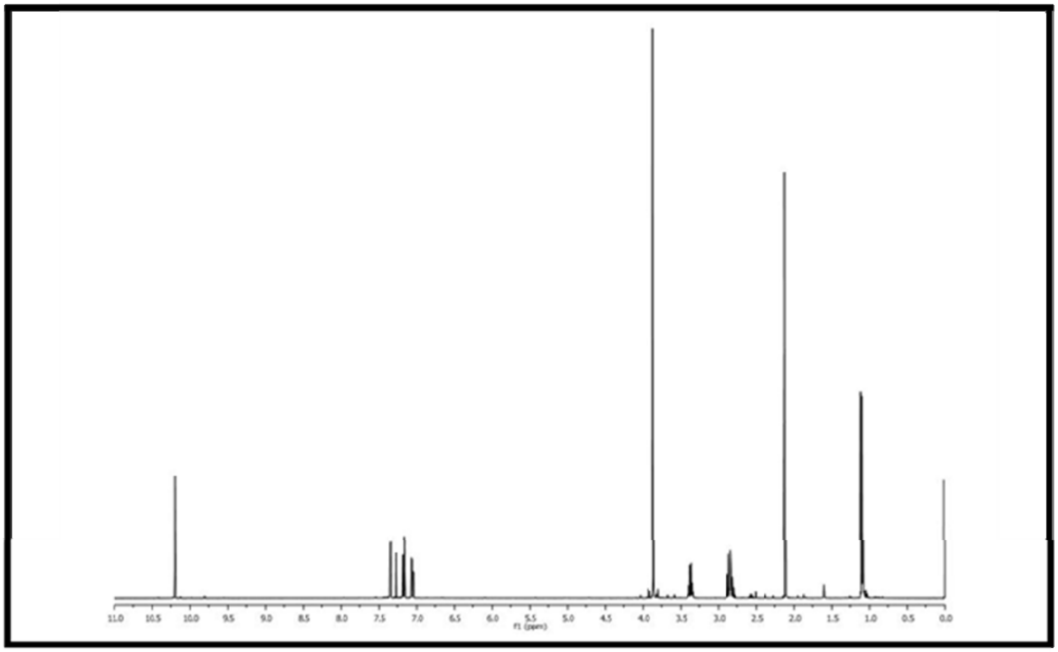
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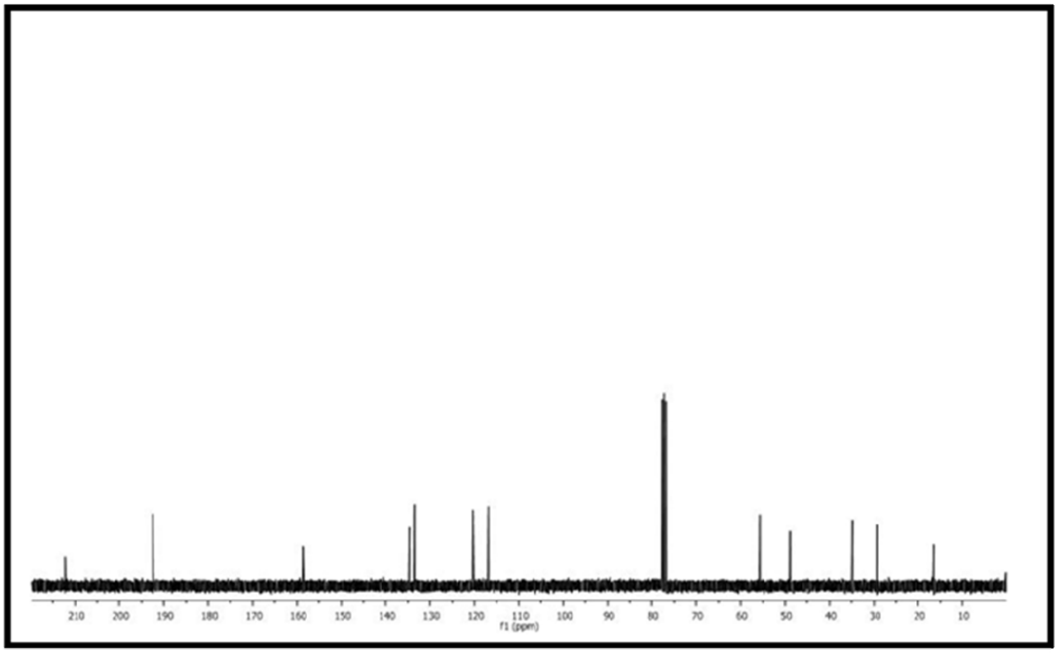
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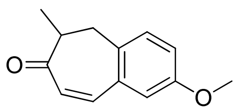
f1 (ppm)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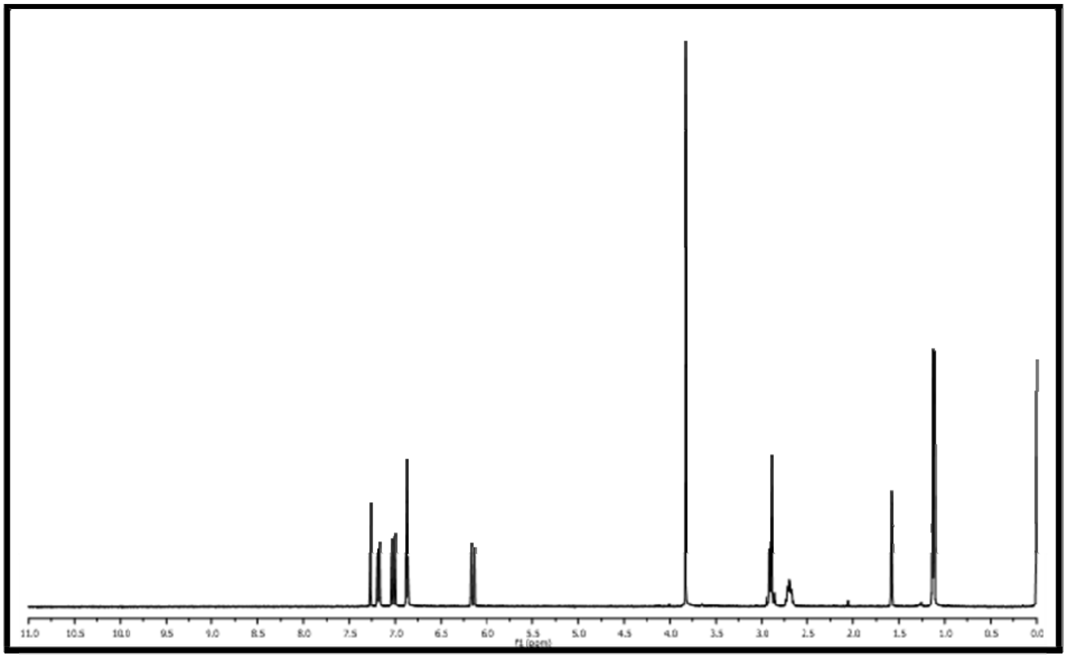
O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10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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4.5
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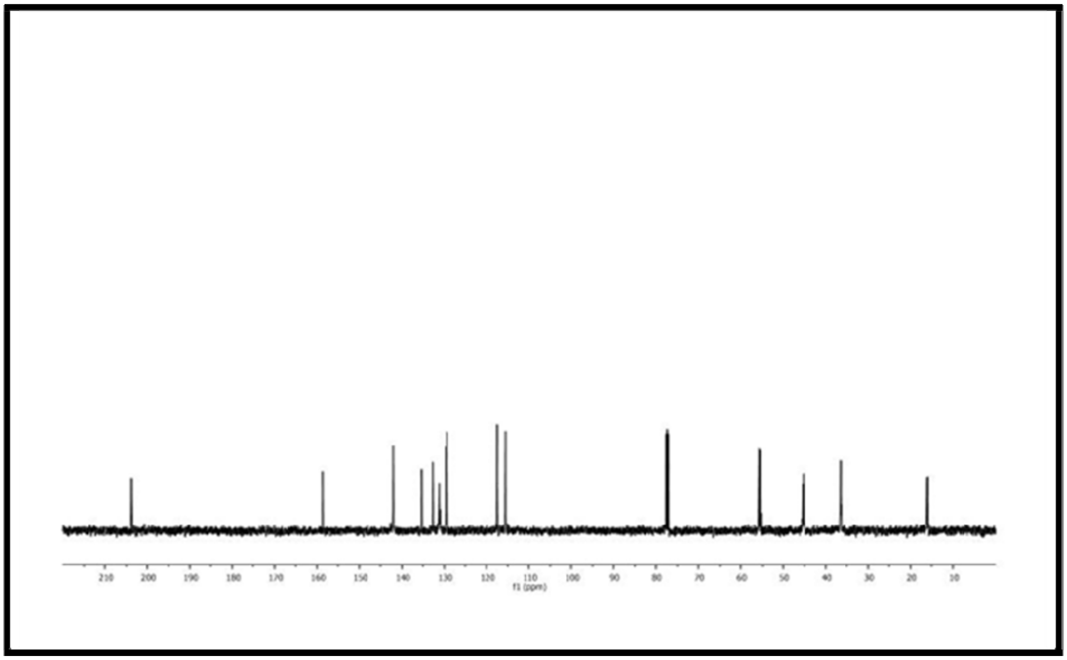
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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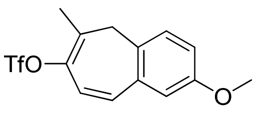
10
f1 (ppm)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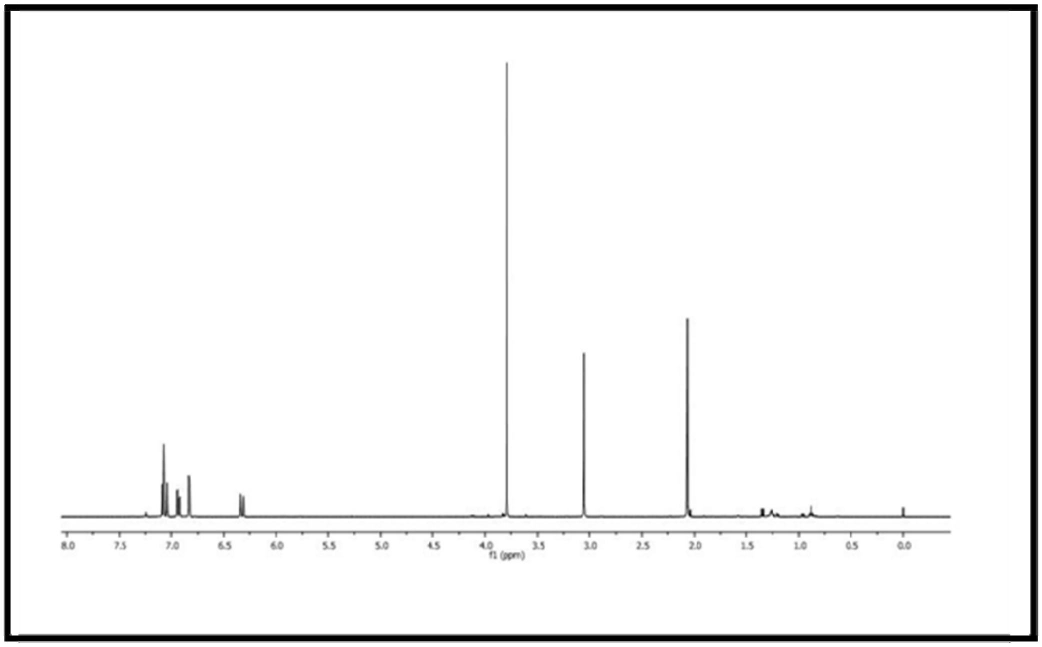
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6.0
5.5
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4.5
4.0
3.5
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2.0
1.5
1.0
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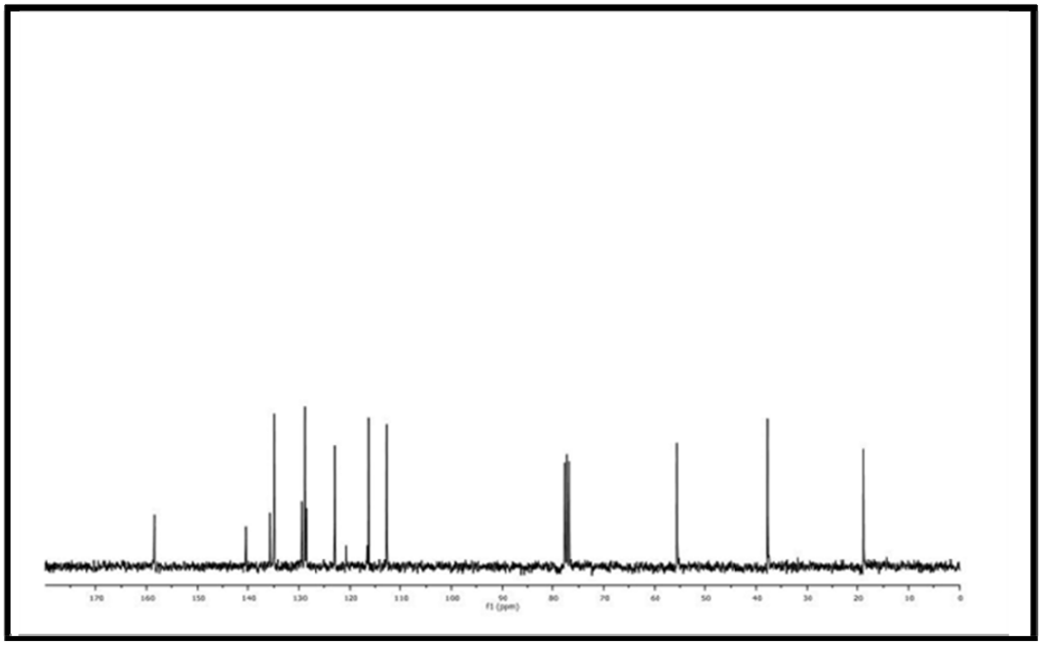
0.0
f1 (ppm)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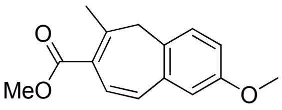
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O

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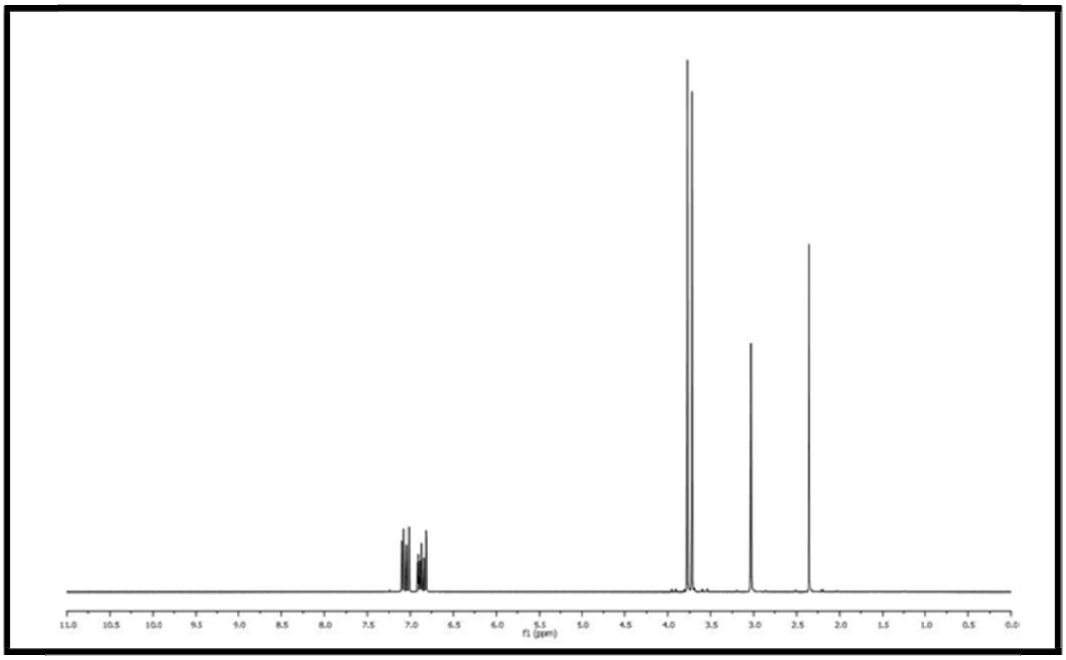
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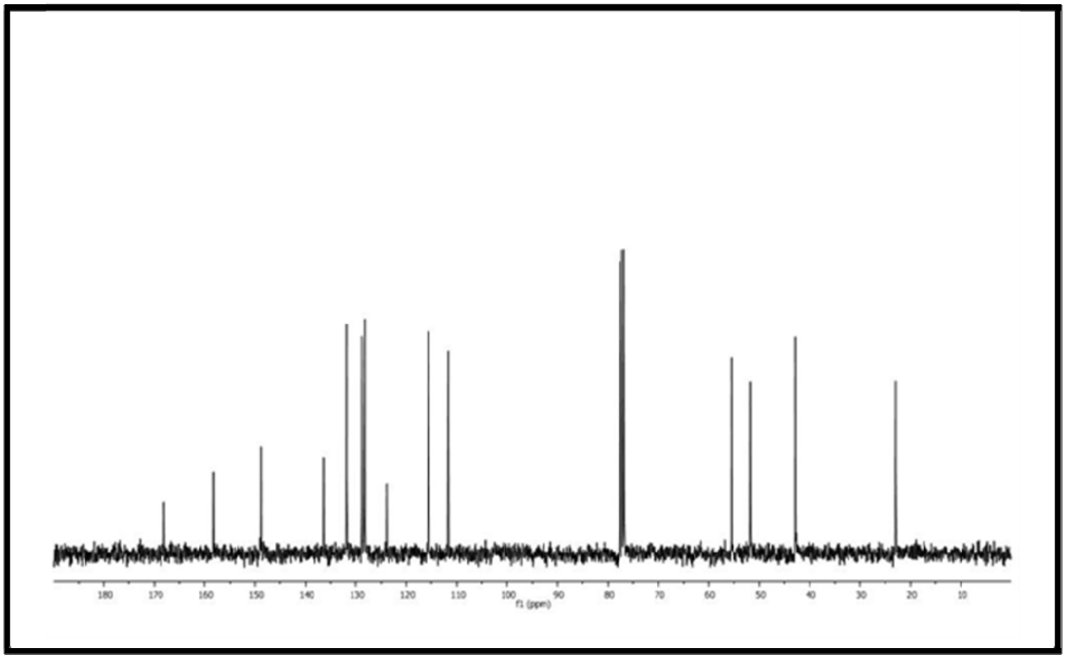
f1 (ppm)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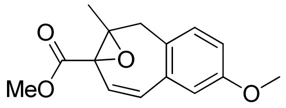
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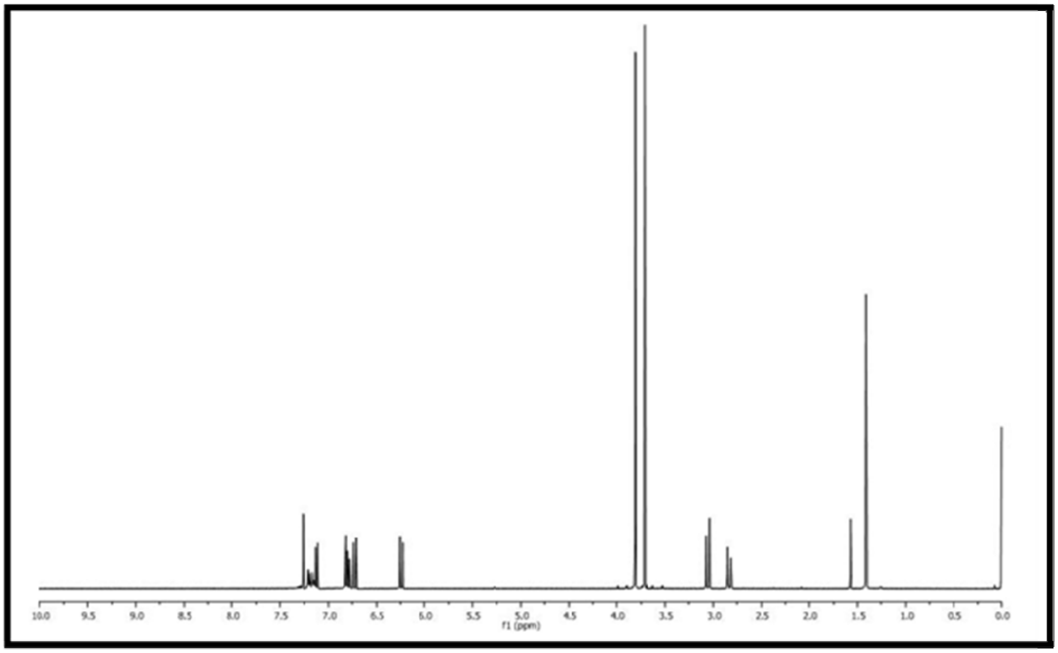
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2.0
1.5
1.0
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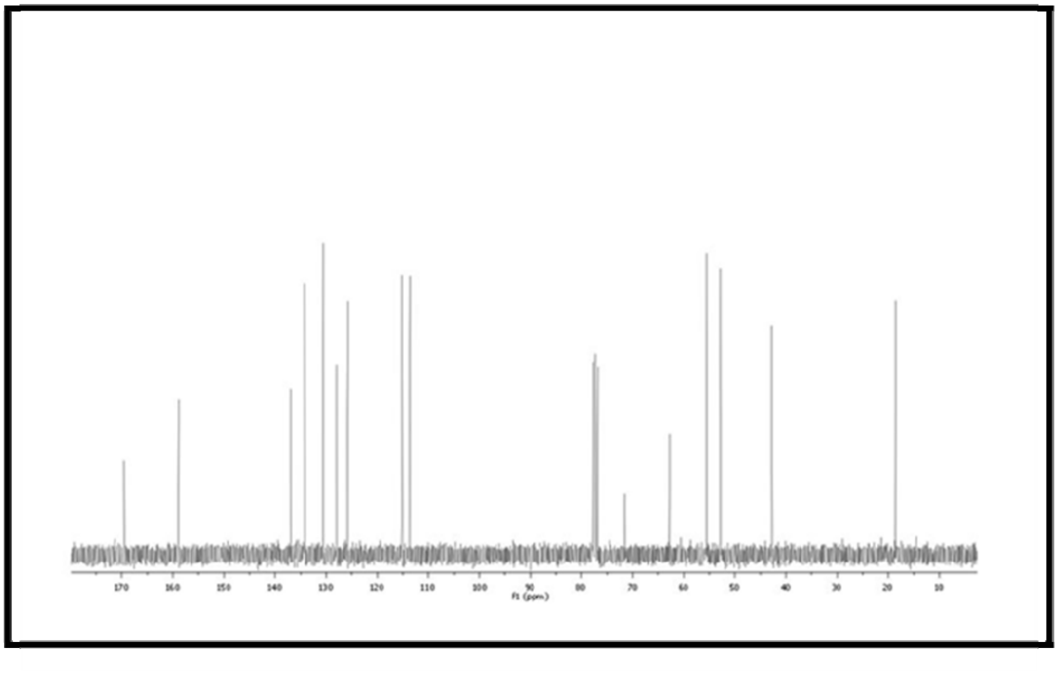
0.0
f1 (ppm)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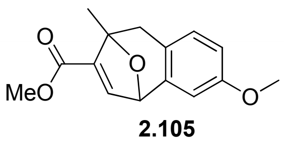
f1 (ppm)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O
MeO
O

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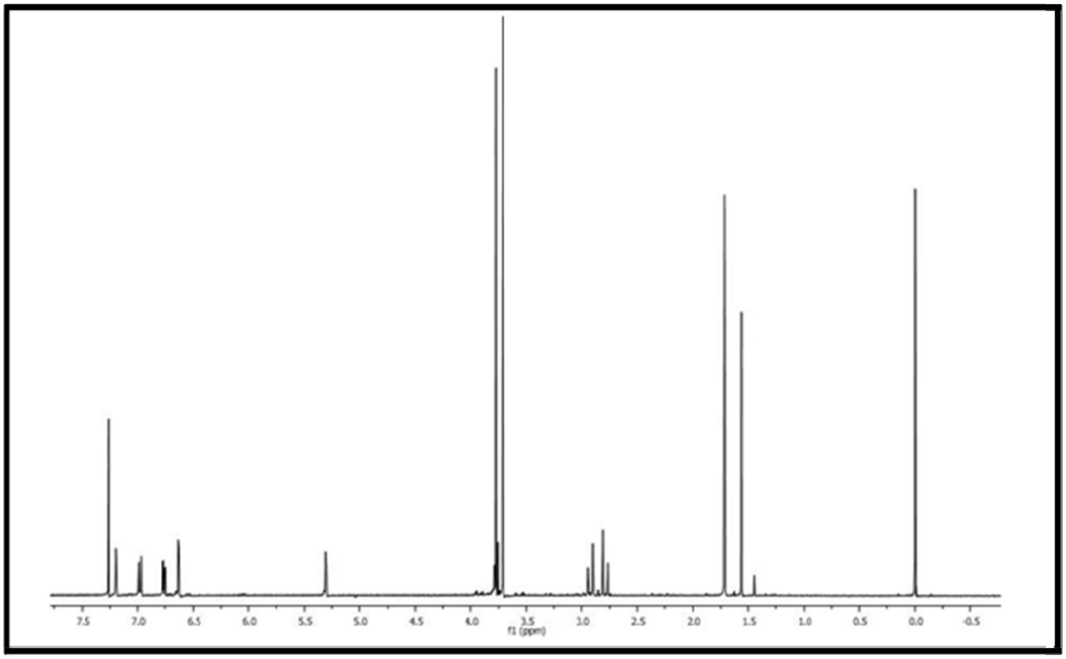
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1.5
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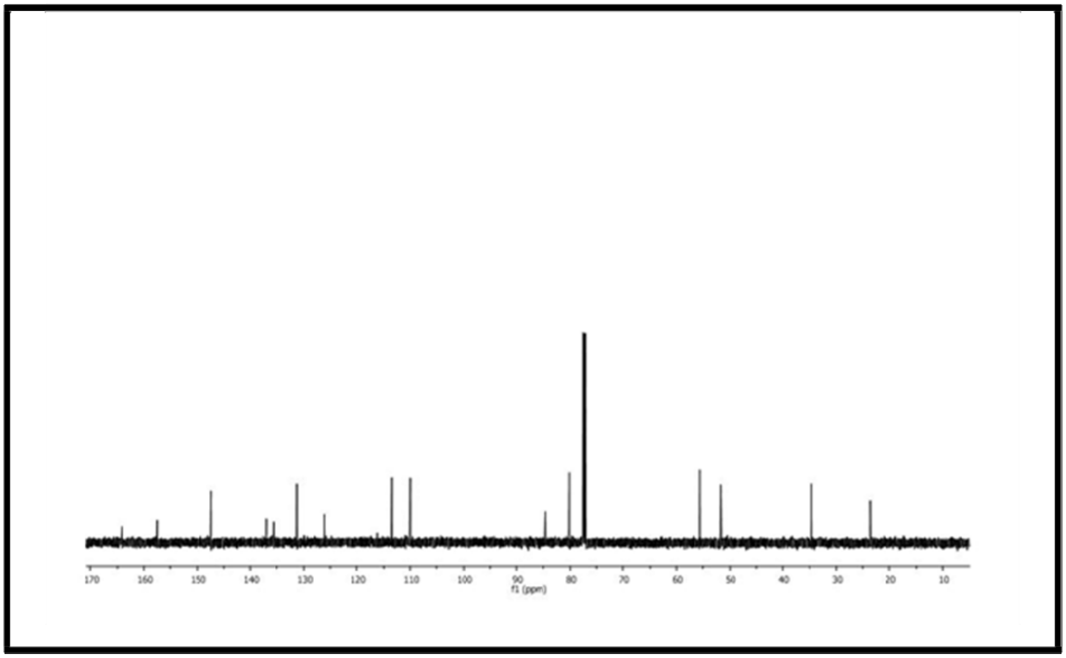
f1 (ppm)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50
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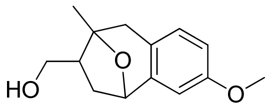
20
10
f1 (ppm)



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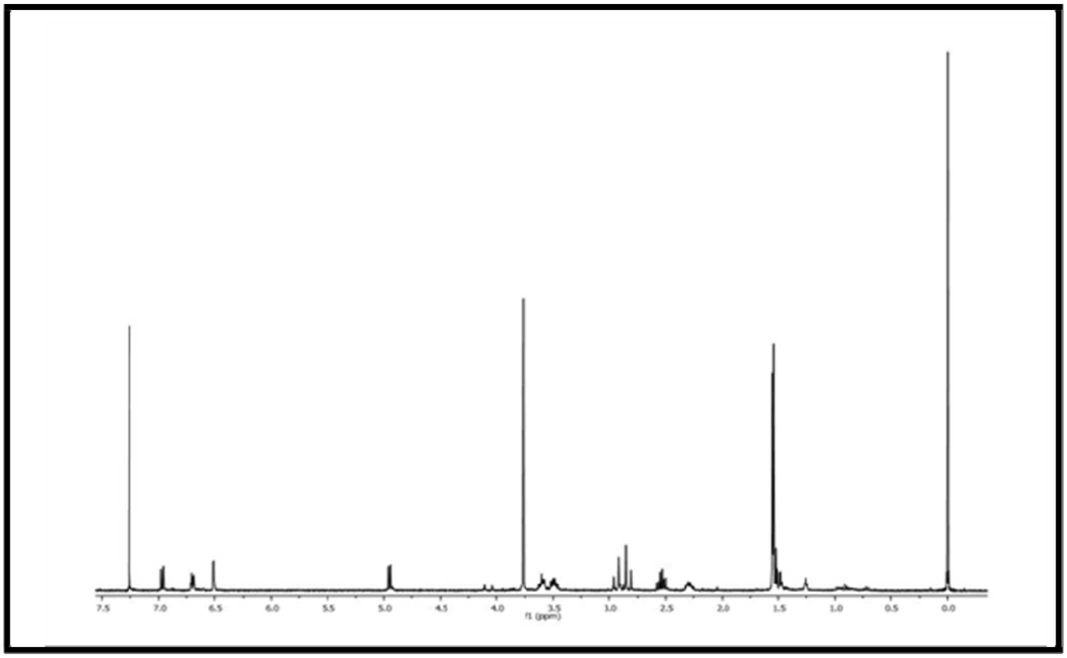
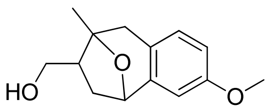
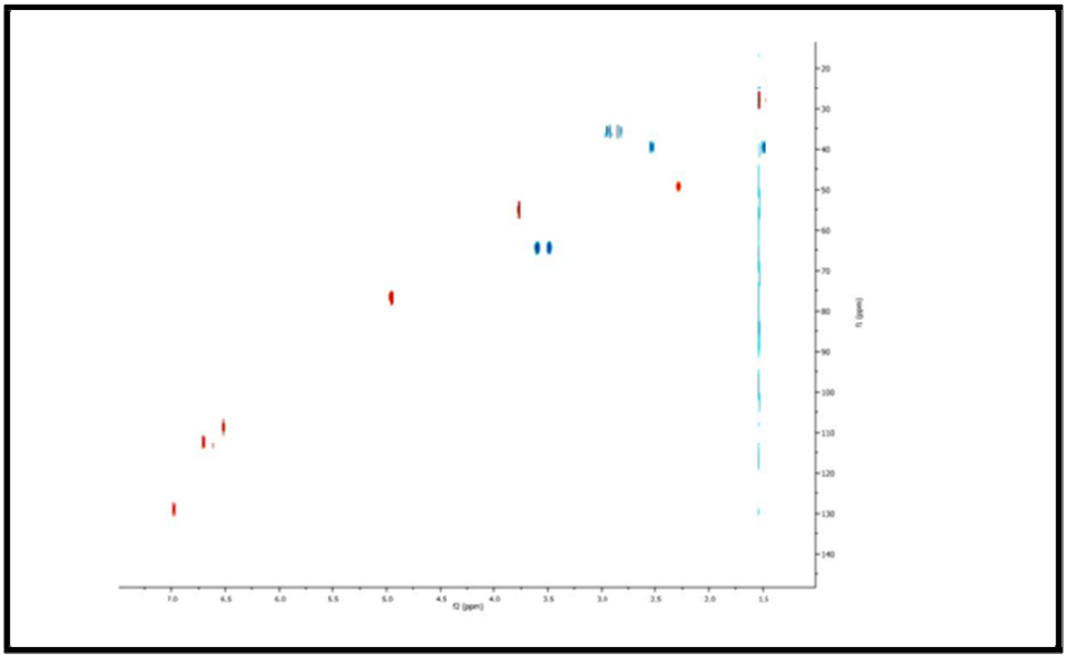


Carbon Chemical Shifts Were Determined
From HSQCAD and gHMBCAD Experiments


HO
O
O

2.106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f1 (ppm)
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6.0
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5.0
4.5
4.0
3.5
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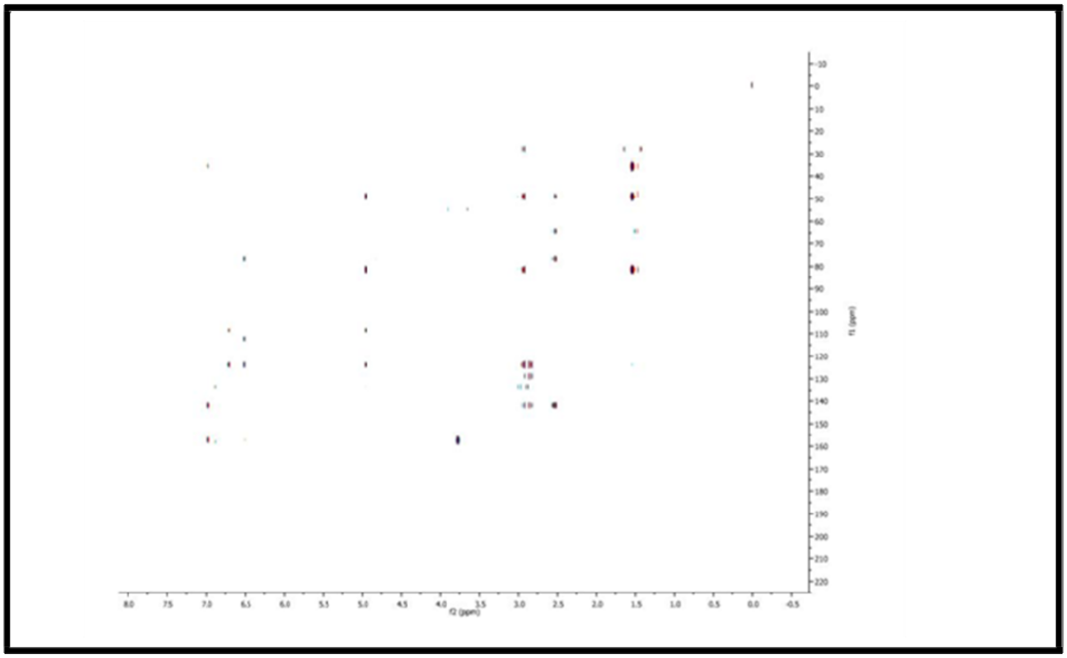
100
110
120
130
140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f1 (ppm)
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5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
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-0.5
-10
0
10
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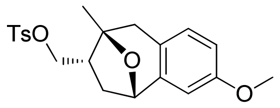
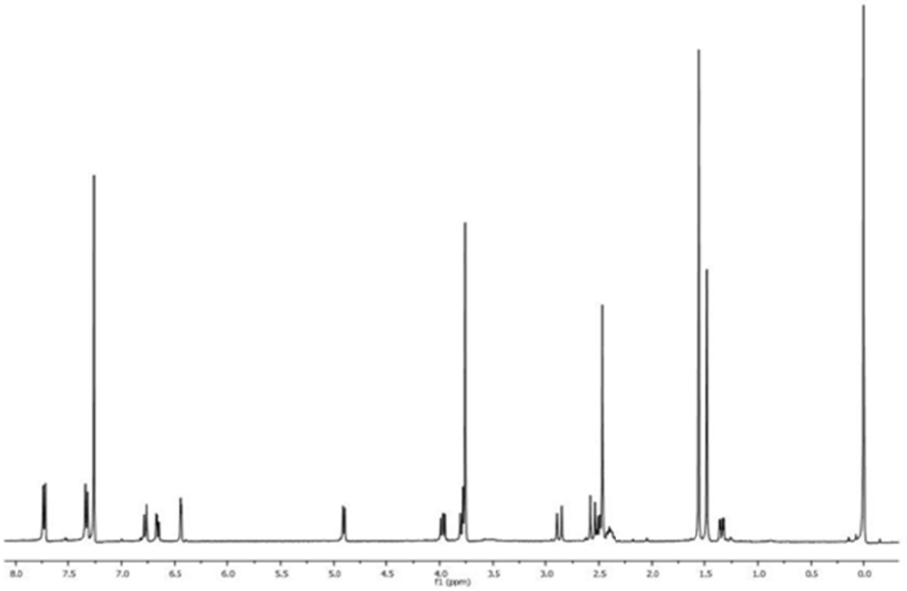
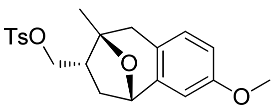
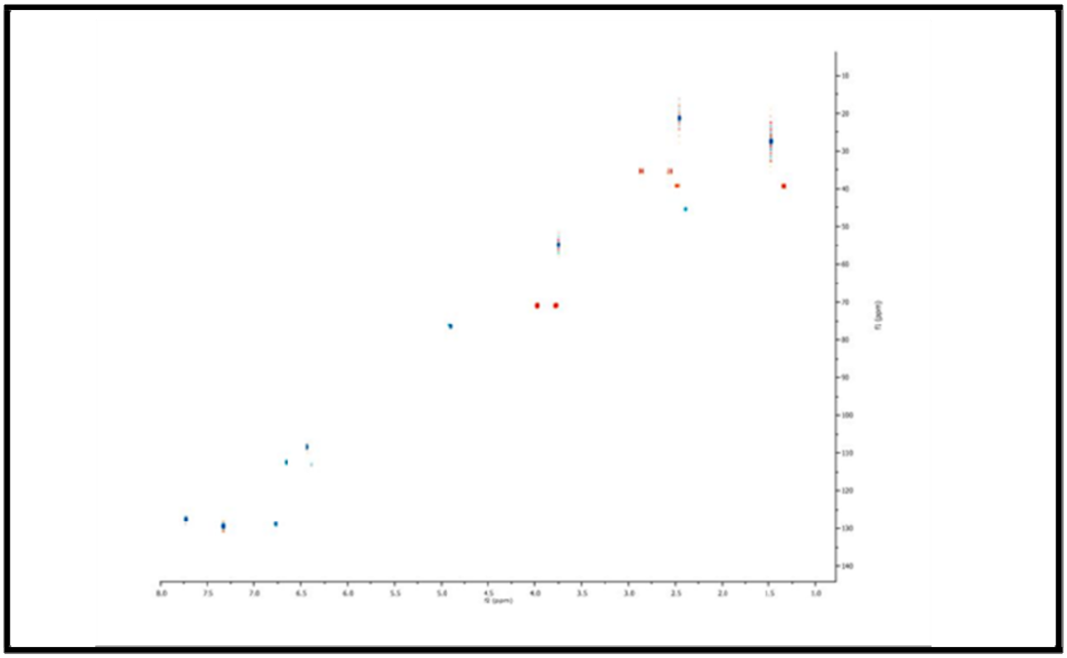




Carbon Chemical Shifts Were Determined
From HSQCAD and gHMBCAD Experiments


TsO
O
O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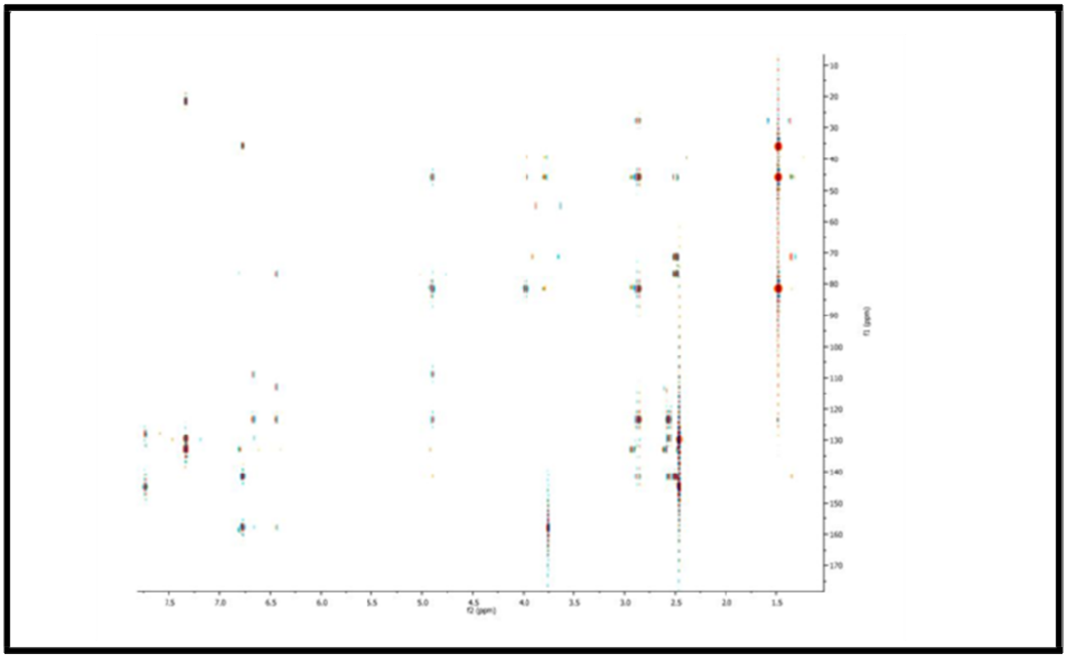
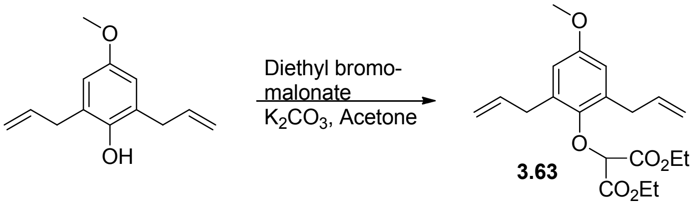
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)
10
20
30
40
50
60
70
80
90
100
110
120
130
140
f1 (ppm)


7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f2 (ppm)
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
f1 (ppm)

APPENDIX 3

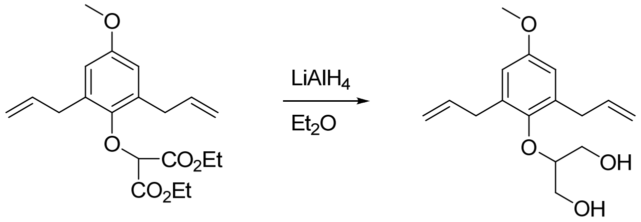
A3.1 Experimental Procedures for Chapter 3

General Information: Commercial reagents were purchased and used without further purification. All glassware was flame dried and reactions were performed under a nitrogen atmosphere, unless otherwise stated. Toluene, dichloromethane, diethyl ether, and THF were dried over a column of alumina. Flash chromatography was done with MP Silitech 32-63D 60Å silica, and thin layer chromatography (TLC) was performed with EMD 250 μm silica gel 60-F_{254} plates. ^{1}H and ^{13}C NMR data was acquired on a Varian Inova 400, 500, or 600 (400, 500 or 600 MHz) spectrometer and referenced to residual protic solvent or TMS. IR spectroscopy was done on a Nicolet Avatar 370 OTGS spectrometer. High-resolution mass spectrometry was performed at the University of Illinois at Urbana-Champaign facility.



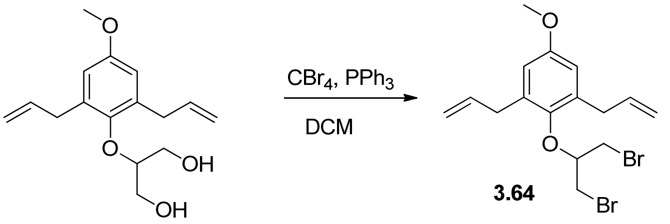
Starting phenol (3.480 g, 0.017 mol) was dissolved in dry acetone (34.8 ml) and anhydrous potassium carbonate (4.800 g, 0.035 mol) was added. Diethyl bromomalonate (14.6 ml, 0.087 mol) was then added and a reflux condenser was attached to the flask. The reaction was refluxed for 14 hours until starting material was consumed. The potassium carbonate was filtered off and the reaction was diluted with diethyl ether and subsequently washed with brine and dried over sodium sulfate. The solvent was removed and the residue was purified with silica gel chromatography to give the malonyl ether (4.300 g, 70%).

FT-IR (thin film/NaCl) 2917, 1743, 1595, 1466, 1195, 1078, 915 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ = 6.54 (s, 2H), 5.89 (ddt, *J*=6.4, 10.2, 16.6, 2H), 5.07 – 4.98 (m, 4H), 4.75 (s, 1H), 4.32 – 4.15 (m, 4H), 3.70 (s, 3H), 3.38 (d, *J*=6.4, 4H), 1.27 – 1.23 (t, *J*=7.1, 6H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ = 166.3, 156.3, 148.3, 136.9, 133.9, 116.5, 113.8, 81.9, 62.3, 55.5, 34.3, 14.1; **HRMS** (EI) m/z 362.1741 [calc'd for $C_{20}H_{26}O_6$ (M+) 362.1729].



Lithium aluminum hydride (1.570 g, 0.041 mol) was placed in a flask and ether (37.0 mL) was added slowly at room temperature. To this slurry was added drop-wise a solution of starting material (3.740 g, 0.010 mol) and ether (4.0 mL) over ten minutes and the reaction was allowed to stir an additional 2 hours. The reaction was quenched by slow addition of ethyl acetate followed by water and 1 M HCl. The reaction was then diluted with ether and washed with brine. The ether was concentrated and the oil was purified with silica gel chromatography to give diol (2.680 g, 93%).

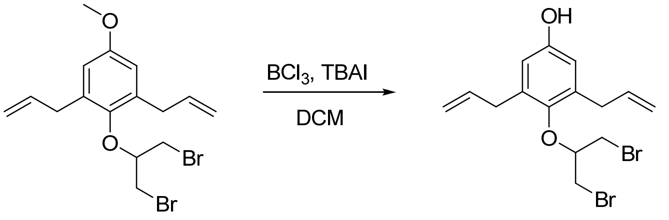
FT-IR (thin film/NaCl) 3406, 2938, 1602, 1466, 1323, 1197, 1050, 915 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ = 6.58 (s, 2H), 5.97 – 5.83 (m, 2H), 5.11 – 5.01 (m, 4H), 3.96 – 3.90 (m, 1H), 3.87 (dd, *J*=4.7, 11.6, 2H), 3.79 (dd, *J*=4.1, 11.4, 2H), 3.72 (s, 3H), 3.41 – 3.38 (m, 4H), 2.64 (bs, 2H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ = 155.8, 146.8, 137.0, 134.1, 116.5, 113.9, 82.1, 62.3, 55.6, 34.5; **HRMS** (EI) m/z 278.1521 [calc'd for $C_{16}H_{22}O_4$ (M+) 278.1518].



3.64

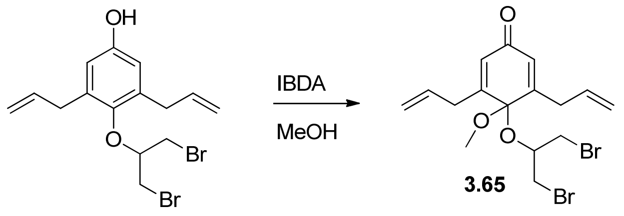
Starting diol (0.318 g, 1.140 mmol) and triphenylphosphine (1.050 g, 0.004 mol) were dissolved in dry dichloromethane (11.4 ml) at 0°C and carbon tetrabromide (1.330 g, 0.004 mol) was then added. The ice bath was removed and the reaction was allowed to stir 12 hours to ensure completion. The reaction mixture was then concentrated and purified directly with silica gel chromatography to give pure dibromide (0.427 g, 92%).

FT-IR (thin film/NaCl) 2937, 1638, 1602, 1465, 1327, 1186, 1052, 915 cm^{-1}; **^{1}H NMR** (400 MHz, CDCl$_3$) δ = 6.59 (s, 2H), 5.92 (m, 2H), 5.20 – 4.97 (m, 4H), 4.21 (m, 1H), 3.74 (s, 3H), 3.73 (dd, *J*=3.7, 10.4, 2H), 3.64 (dd, *J*=3.7, 10.4, 2H), 3.40 (m, 4H); **^{13}C NMR** (126 MHz, CDCl$_3$) δ = 156.2, 145.8, 136.7, 134.2, 116.8, 114.1, 79.5, 55.6, 34.7, 32.4; **HRMS** (EI) m/z 401.98379 [calc'd for $C_{16}H_{20}O_2Br_2$ (M+) 401.98303].



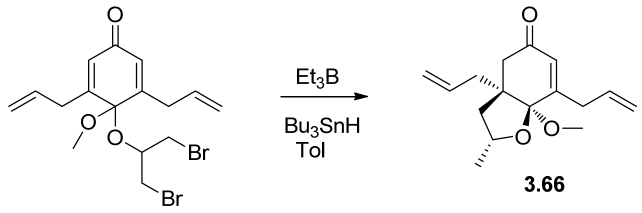
Dibromide (0.019 g, 0.048 mmol) was dissolved in dichloromethane (0.24 ml) and tetrabutylammonium iodide (0.020 g, 0.053 mmol) was added. The reaction was cooled to -78°C and boron trichloride solution (0.06 ml, 1M, 0.06 mmol) was added slowly. The reaction was then placed in a -10°C bath and stirred two hours. When complete, the reaction was quenched with saturated sodium bicarbonate and extracted with dichloromethane. The organics were dried over sodium sulfate, concentrated and purified with silica gel chromatography to give phenol (0.015 g, 80%).

FT-IR (thin film/NaCl) 3387, 2917, 1598, 1454, 1322, 916 cm^{-1}; **^{1}H NMR** (400 MHz, CDCl$_3$) δ = 6.53 (s, 2H), 5.90 (m, 2H), 5.10 (m, 4H), 4.20 (m, 1H), 3.72 (dd, *J*=6.2, 10.4, 2H), 3.63 (dd, *J*=6.2, 10.4, 2H), 3.37 (m, 4H); **^{13}C NMR** (101 MHz, CDCl$_3$) δ = 152.2, 145.8, 136.6, 134.5, 116.9, 115.5, 79.5, 34.5, 32.3; **HRMS** (EI) m/z 387.9670 [calc'd for $C_{15}H_{18}O_2Br_2$ (M+) 387.9674].



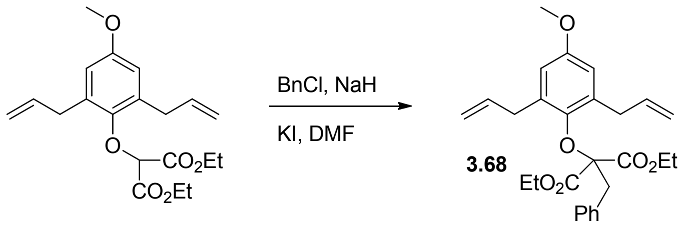
Dibromide phenol (1.000 g, 2.560 mmol) was dissolved in dry methanol (23.3 ml) and cooled to 0°C. Iodobenzene diacetate (0.908 g, 2.820 mmol) was added and the reaction turned bright yellow immediately. The reaction was concentrated and purified with a plug of silica gel to give pure dearomatized product (1.010 g, 94%).

FT-IR (thin film/NaCl) 2977, 2944, 1675, 1640, 1427, 1294, 1102, 1061, 1037, 923 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.33 (s, 2H), 5.84 (m, 2H), 5.35 – 5.19 (m, 4H), 3.83 (tt, *J*=3.3, 6.5, 1H), 3.62-3.50 (m, 4H), 3.30 – 3.17 (m, 2H), 3.09 (s, 3H), 3.10 – 2.99 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 184.5, 157.2, 132.3, 130.5, 120.1, 98.4, 72.0, 51.6, 33.4, 33.0; **HRMS** (EI) m/z 417.9782 [calc'd for $C_{16}H_{20}O_3Br_2$ (M+) 417.9780].



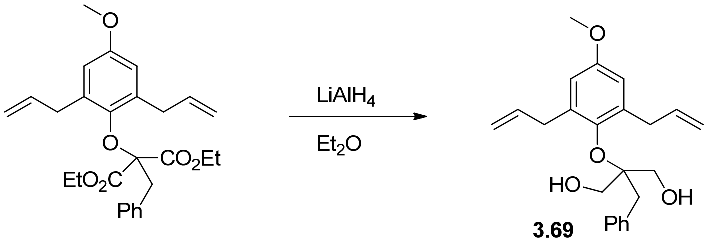
Starting material (0.046 g, 0.110 mmol) was dissolved in freshly distilled toluene (11.0 ml) and was cooled to -78° C. Tributyltin hydride (0.09 ml, 0.330 mmol) was added to the reaction followed by triethylborane (0.01 ml, 0.01 mmol). The reaction was allowed to stir 30 minutes and the bath was removed. After 30 additional minutes at room temperature, the reaction was concentrated and purified with silica gel chromatography to give mono cyclized product (0.025 g, 87%).

FT-IR (thin film/NaCl) 2970, 2935, 1678, 1262, 1122, 1026, 669 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.85 (s, 1H), 5.85 – 5.65 (m, 2H), 5.21 – 5.05 (m, 4H), 4.33 (m, 1H), 3.48 (s, 3H), 3.11 – 3.05 (m, 2H), 2.56 – 2.36 (m, 3H), 2.19 (dd, *J*=7.8, 13.9, 1H), 2.10 (m, 1H), 1.92 – 1.71 (m, 2H), 1.36 (d, *J*=6.2, 4H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 198.1, 159.5, 133.9, 133.9, 127.2, 119.3, 118.8, 105.3, 75.2, 52.6, 52.3, 44.3, 43.2, 39.3, 35.3, 21.4; **HRMS** (EI) m/z 262.1566 [calc'd for $C_{16}H_{22}O_3$ (M+) 262.1569].



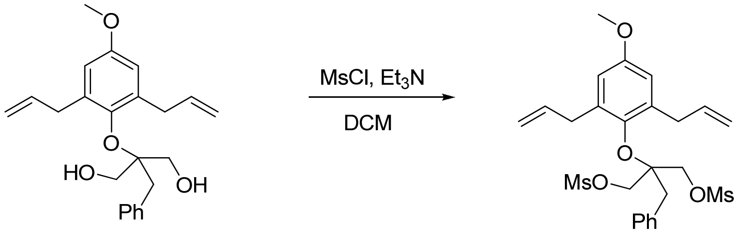
Potassium iodide (1.260 g, 7.620 mmol) and sodium hydride (0.112 g, 2.790 mmol) were mixed and dry DMF (25.4 ml) was added and cooled to -10°C. The starting material (0.920 g, 2.540 mmol) was dissolved in dry DMF (2.0 ml) and added slowly to the slurry. After complete addition, benzyl chloride (0.44 ml, 3.81 mmol) was added and the bath was removed. After 4 hours the reaction was diluted with ether and washed with distilled water. The ethereal solution was dried over sodium sulfate, concentrated and purified with silica gel chromatography to give benzylated product (0.980 g, 85%).

FT-IR (thin film/NaCl) 3073, 2981, 2838, 1741, 1602, 1463, 1247, 1195, 1055, 914, 700 cm^{-1}; ^{1}**H NMR** (300 MHz, $CDCl_3$) δ = 7.21 – 7.05 (m, 5H), 6.52 (s, 2H), 5.97 – 5.79 (m, 2H), 5.14 – 5.00 (m, 4H), 4.05 – 3.94 (m, 4H), 3.73 (s, 3H), 3.49 (s, 2H), 3.42 (d, *J*=6.8, 4H), 1.06 (t, *J*=7.2, 6H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ = 168.2, 156.5, 145.6, 136.8, 134.8, 130.5, 128.3, 128.1, 127.2, 116.7, 112.9, 88.6, 62.0, 55.5, 41.1, 35.4, 13.8. **HRMS** (EI) m/z 452.2198 [calc'd for $C_{27}H_{32}O_6$ (M+) 452.2199].



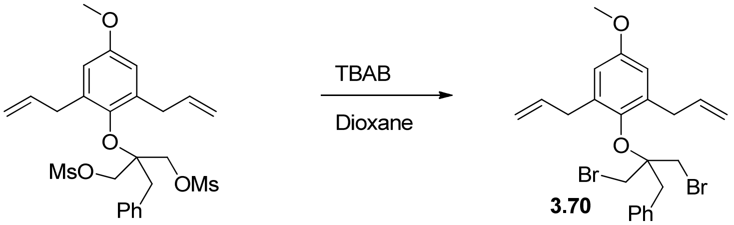
Lithium aluminum hydride (0.147 g, 3.870 mmol) was added to a flask and dry ether (8.7 ml) was added carefully. Starting material (0.875 g, 1.940 mmol) was dissolved in ether (1.0 ml) and added drop-wise to the LAH solution over twenty minutes. The reaction was allowed to stir 1 hour and then quenched with ethyl acetate followed by water and 1 M HCl. The product was extracted with ether, dried over sodium sulfate and concentrated to an oil. The oil was purified with silica gel chromatography to give pure diol (0.700 g, 98%).

FT-IR (thin film/NaCl) 3460, 2938, 1638, 1602, 1461, 1320, 1197, 1052, 915 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ = 7.30 – 7.15 (m, 5H), 6.63 (s, 2H), 5.91 (m, 2H), 5.16 – 5.06 (m, 4H), 3.76 – 3.75 (m, 7H), 3.48 (d, *J*=6.4, 4H), 3.05 (s, 2H). ^{13}**C NMR** (101 MHz, $CDCl_3$) δ = 155.9, 145.3, 136.9, 136.5, 135.9, 130.7, 128.5, 128.3, 116.9, 113.9, 86.4, 65.0, 55.5, 39.1, 35.7; **HRMS** (EI) m/z 368.1987 [calc'd for $C_{23}H_{28}O_4$ (M+) 368.1988].



Starting diol (0.075 g, 0.200 mmol) was dissolved in dry dichloromethane at 0°C. Freshly distilled triethylamine (0.11 ml, 0.80 mmol) was added followed by drop-wise addition of methane sulfonyl chloride (0.04 ml, 0.44 mmol). The reaction was stirred ten minutes and then neutralized with saturated sodium bicarbonate and extracted with dichloromethane. The combined extracts were dried over sodium sulfate, concentrated and subjected to silica gel chromatography to yield bis-mesylate (0.081 g, 76%).

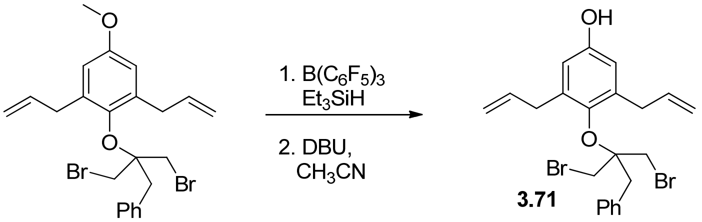
FT-IR (thin film/NaCl) 3028, 2938, 1639, 1602, 1464, 1367, 1343, 1175, 1053 cm^{-1}; ^{1}**H NMR** (400 MHz, CDCl$_3$) δ = 7.42 – 7.13 (m, 5H), 6.63 (s, 2H), 5.89 (m, 2H), 5.18 – 5.09 (m, 4H), 4.34 (m, 4H), 3.76 (s, 3H), 3.40 (d, *J*=6.3, 4H), 3.02 (s, 2H), 2.88 (s, 6H); ^{13}**C NMR (75 MHz, CDCl$_3$)** δ = 156.4, 144.5, 136.6, 135.8, 134.1, 130.9, 128.8, 127.7, 117.4, 114.0, 81.8, 68.1, 55.7, 39.5, 37.5, 35.3; **HRMS** (ESI) m/z 547.1437 [calc'd for $C_{25}H_{32}O_8S_2Na$ (M+Na) 547.1436].



3.70

Starting material (0.080 g, 0.150 mmol) and tetrabutyl ammonium bromide (0.500 g, 1.500 mmol) were dissolved in dioxane (1.6 ml) and sealed tightly in a small vial. The reaction was heated at 130°C for 18 hours until TLC showed complete conversion. The solids were filtered and the solvent removed. The resulting residue was purified with silica gel chromatography to give dibromide (0.065 g, 86%).

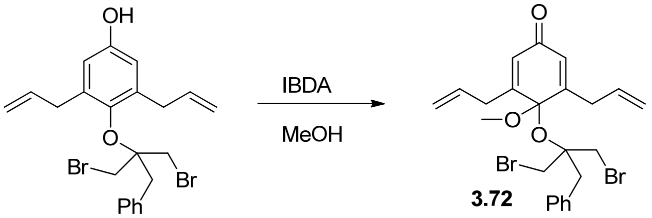
FT-IR (thin film/NaCl) 3076, 2977, 2936, 1602, 1462, 1321, 1195, 1054, 997, 916 cm^{-1}; ^{1}**H NMR** (400 MHz, CDCl$_3$) δ = 7.32 – 7.03 (m, 5H), 6.58 (s, 2H), 5.83 (m, 2H), 5.16 – 5.00 (m, 4H), 3.80 (s, 4H), 3.76 (s, 3H), 3.34 (d, *J*=6.5, 4H), 3.27 (s, 2H); ^{13}**C NMR** (101 MHz, CDCl$_3$) δ = 156.2, 145.1, 136.8, 135.9, 135.2, 131.1, 128.4, 127.3, 117.1, 113.6, 82.5, 55.6, 41.3, 37.4, 35.6; **HRMS** (ESI) m/z 515.0209 [calc'd for $C_{23}H_{26}Br_2O_2$ (M+Na) 515.0197].



3.71

Starting material (0.025 g, 0.051 mmol) and tris(pentafluorobenzene) borane (0.003 g, 0.005 mmol) were mixed at room temperature and 0.5 ml of a 10% solution of triethylsilane (0.09 ml, 0.56 mmol) in dichloromethane (4.9 ml) was added. The reaction was allowed to stir 36 hours for complete consumption of starting material. The TES group was then removed by addition of DBU (0.01 ml) and 0.5 ml of acetonitrile and stirring 5 minutes. The reaction was treated with saturated ammonium chloride and extracted with dichloromethane. The organics were then dried over sodium sulfate, concentrated down and purified with silica gel to give free phenol (0.018 g, 75%).

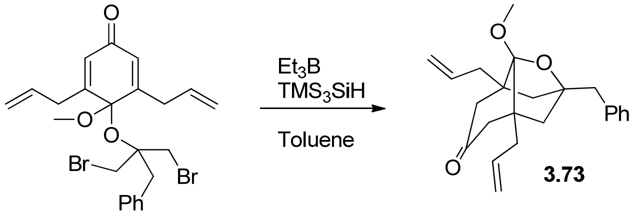
FT-IR (thin film/NaCl) 3061, 2956, 2930, 1600, 1496, 1452, 1184, 996, 703 cm^{-1}; **^{1}H NMR** (400 MHz, CDCl$_3$) δ = 7.26-7.14 (m, 5H), 6.52 (s, 2H), 5.81 (m, 2H), 5.14-5.05 (m, 4H), 4.56 (bs, 1H), 3.79 (s, 3H), 3.31 (d, *J*=6.4, 4H), 3.27 (s, 2H); **^{13}C NMR** (101 MHz, CDCl$_3$) δ = 152.2, 145.2, 136.6, 136.3, 135.2, 131.1, 128.4, 127.4, 117.2, 115.1, 82.6, 41.4, 37.4, 35.4; **HRMS** (EI) m/z 478.0139 [calc'd for $C_{22}H_{24}O_2Br_2$ (M+) 478.0143].



3.72

Starting phenol (0.008 g, 0.016 mmol) and anhydrous methanol (0.2 ml) were mixed at room temperature and iodobenzene diacetate (0.005 g, 0.016 mmol) was added. The reaction was stirred five minutes and then the solvent was removed and the residue purified with silica gel chromatography to yield pure dearomatized bis-bromide (0006 g, 75%).

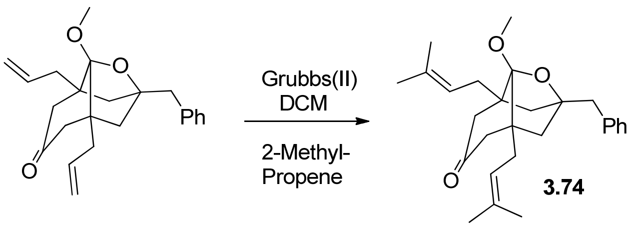
FT-IR (thin film/NaCl) 2965, 1657, 1640, 1495, 1426, 1294, 1015, 922, 703 cm^{-1}; **^{1}H NMR** (400 MHz, CDCl$_3$) δ = 7.38 – 7.14 (m, 5H), 6.22 (s, 2H), 5.69 (m, 2H), 5.25 – 4.99 (m, 4H), 3.54 (q, *J*=11.4, 4H), 3.26 – 3.10 (m, 4H), 2.92 (s, 3H), 2.84 (m, 2H); **^{13}C NMR** (101 MHz, CDCl$_3$) δ = 184.7, 159.5, 135.2, 132.8, 131.1, 129.9, 128.8, 127.8, 120.0, 97.6, 81.5, 50.7, 41.8, 37.8, 33.8; **HRMS** (DART) m/z 509.03447 [calc'd for $C_{23}H_{27}O_3Br_2$ (M+H) 509.03273].



3.73

Starting material (0.040 g, 0.078 mmol) was dissolved in dry toluene (1.6 ml) at room temperature and tris(trimethylsilyl)silane (0.07 ml, 0.24 mmol) was added followed by triethyl borane (0.07 ml, 0.07 mmol). The reaction was purged with air and subsequently stirred for 4 hour. The reaction was loaded directly onto a silica gel column and purified to provide the bicyclic product (0.020 g, 73%).

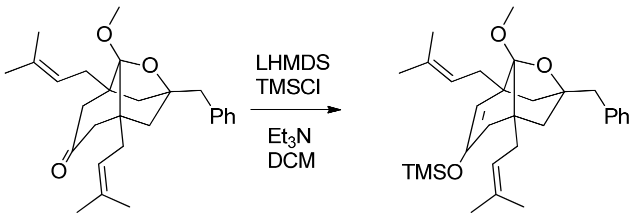
FT-IR (thin film/NaCl) 2952, 2892, 1672, 1455, 1244, 1083, 914 cm^{-1}; **^{1}H NMR** (600 MHz, CDCl$_3$) δ = 7.31-7.18 (m, 5H), 5.62 (dd, *J*=10.0, 16.0, 2H), 5.03 (d, *J*=10.0, 2H), 4.92 (d, *J*=16.0, 2H), 3.67 (s, 3H), 2.96 (s, 2H), 2.40 (d, *J*=13.3, 1H), 2.33 (dd, *J*=7.4, 13.7, 1H), 2.26 (d, *J*=13.3, 1H), 2.15 (dd, *J*=8.5, 13.7, 1H), 1.74 (d, *J*=11.5, 1H), 1.18 (d, *J*=11.5, 1H); **^{13}C NMR** (HSQC-AD/gHMBC-AD Derived 150 MHz, CDCl$_3$) δ = 211.0, 136.9, 133.6, 130.0, 128.2, 126.6, 118.8, 108.1, 79.4, 55.5, 51.1, 47.4, 44.5, 42.6, 42.3; **HRMS** (ESI) m/z 375.1935 [calc'd for C$_{23}$H$_{28}$O$_3$ (M+Na) 375.1936].



3.74

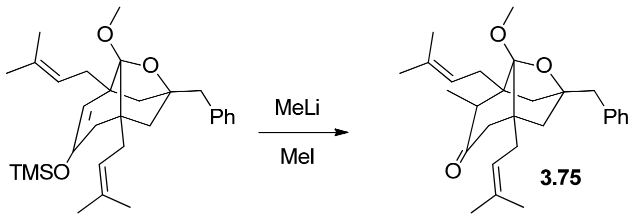
Starting material (0.010 g, 0.028 mmol) was dissolved in dry dichloromethane (2.0 ml) and to this was added Grubbs second generation catalyst (0.002 g, 0.003 mmol). Meanwhile, 2-methyl-propene (2.0 ml) was condensed into a pressure vessel at -78°C and to this was added the starting material/Grubbs mixture. The pressure vessel was sealed and heated at 40°C for 8 hours. The reaction was then removed from the bath and pressure was carefully allowed to escape. The remaining solution was filtered through a plug of silica gel with 30% ethyl acetate 70% hexanes to afford pure prenylated product (0.010 g, 87%).

FT-IR (thin film/NaCl) 2957, 2926, 2855, 1715, 1455, 1251, 1066, 841 cm^{-1}; **^{1}H NMR** (600 MHz, CDCl$_3$) δ = 7.25-7.18 (m, 5H), 4.98 (t, *J* = 7.6, 2H), 3.69 (s, 3H), 2.94 (s, 2H), 2.37 (d, *J* = 13.3, 2H), 2.29 (d, *J* = 13.3, 2H), 2.27 (dd, *J* = 7.5, 13.9, 2H), 2.13 (dd, *J* = 7.6, 13.9, 2H), 1.70-1.66 (m, 8H), 1.49 (s, 6H), 1.17 (d, *J* = 11.4, 2H); **^{13}C NMR** (HSQC-AD/gHMBC-AD Derived 150 MHz, CDCl$_3$) δ = 211.7, 136.7, 134.6, 129.9, 128.1, 126.5, 118.9, 108.3, 79.3, 55.2, 52.1, 46.8, 44.5, 42.3, 35.7, 26.0, 17.8; **HRMS** (EI) m/z 408.2662 [calc'd for C$_{27}$H$_{36}$O$_3$ (M+) 408.2665].



Starting ketone (0.005 g, 0.012 mmol) was dissolved in dry THF (0.25 mL) and cooled to 0°C under nitrogen. A solution of LHMDS (1M, 0.06 mmol, 0.06 mL) was added over the course of 2 minutes. The reaction was allowed to stir 10 additional minutes before a 3:1 mixture of TMSCl:Et$_3$N (0.06 mmol, 0.01 mL) was added and the reaction was allowed to warm to room temperature. After 30 minutes, the reaction was diluted with ether and washed with water. The combined organics were concentrated and purified with silica gel chromatography to give the TMS enol ether (0.005 g, 85%)

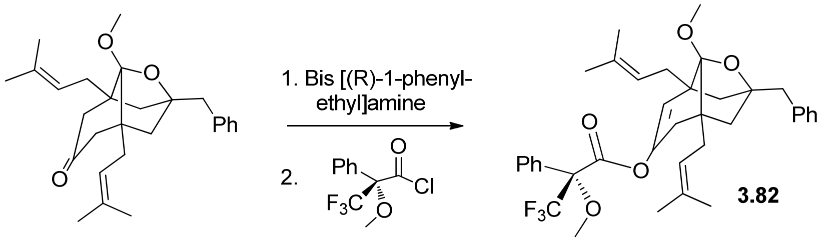
FT-IR (thin film/NaCl) 2956, 2924, 2853, 1454, 1250, 1164, 1064, 1031, 841 cm^{-1}; **^{1}H NMR** (600 MHz, CDCl$_3$) δ = 7.25-7.16 (m, 5H), 5.15 (t, *J* = 7.4, 1H), 5.04 (t, *J* = 7.4, 1H), 4.92 (s, 1H), 3.58 (s, 3H), 2.95 – 2.92 (m, 2H), 2.31 – 2.02 (m, 6H), 1.78 (dd, *J* = 12.2, 2.9, 1H) 1.73 – 1.71 (m, 1H), 1.72 (s, 3H), 1.71 (s, 3H), 1.56 (s, 3H), 1.51 (s, 3H), 1.39 (d, *J* = 11.1, 1H), 1.32 (d, *J* = 12.2, 1H), 0.14 (s, 9H); **^{13}C NMR** (HSQC-AD/gHMBC-AD Derived 150 MHz, CDCl$_3$) δ = 146.6, 137.4, 133.9, 133.5, 130.1, 128.5, 128.1, 126.4, 125.7, 120.6, 119.9, 111.2, 108.6, 78.9, 54.2, 51.8, 47.7, 47.1, 45.1, 42.6, 37.7, 35.2, 34.6, 26.2, 26.1, 18.1, 18.0, 0.49; **HRMS** (EI) m/z 480.3050 [calc'd for $C_{30}H_{44}O_3Si$ (M+) 480.3060].



3.75

The TMS enol ether (0.002 g, 0.004 mmol) was dissolved in dry DME (0.1 mL) and cooled to 0°C under nitrogen. To this was added MeLi (0.04 mmol, 0.04 mL) and the reaction was allowed to stir for 5 minutes. Methyl iodide (0.04 mmol, 0.01 mL) was then added and the bath was removed. After 45 minutes at room temperature, the reaction was diluted with ether and washed with water. The combined organics were dried over sodium sulfate, concentrated and purified with silica gel chromatography to give the methylated product (0.003 g, 86%).

FT-IR (thin film/NaCl) 2917, 2849, 1735, 1559, 1365, 1275, 1222, 750 cm^{-1}; **^{1}H NMR** (600 MHz, CDCl$_3$) δ 7.26-7.18 (m, 5H), 5.00 (t, *J* = 7.3, 1H), 4.89 (t, *J* = 7.3, 1H), 3.67 (s, 3H), 2.91 (s, 2H), 2.60 (d, *J* = 13.7, 1H), 2.47 (dd, *J* = 7.3, 14.0, 1H), 2.38 (q, *J* = 7.0, 1H), 2.28 (dd, *J* = 7.5, 13.7, 1H), 2.16 (d, *J* = 13.7, 1H), 2.16 – 2.04 (m, 2H), 1.73 – 1.63 (m, 2H), 1.68 (s, 3H), 1.67 (s, 3H), 1.50 (s, 3H), 1.48 (s, 3H), 1.23 – 1.10 (m, 2H), 1.13 (d, *J* = 7.0, 3H); **^{13}C NMR** (HSQC-AD/gHMBC-AD Derived 150 MHz, CDCl$_3$) δ = 130.0, 129.9, 128.4, 128.2, 126.5, 119.1, 118.1, 55.4, 50.1, 45.6, 45.1, 42.8, 42.5, 35.8, 30.7, 26.0, 26.0, 17.9, 17.9, 13.8; **HRMS** (EI) m/z 422.2832 [calc'd for $C_{28}H_{38}O_3$ (M+) 422.2821].

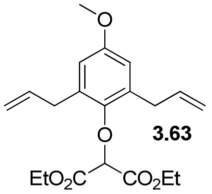


3.82

Bis [(R)-1-phenylethyl]amine (0.03 mmol, 0.01 mL) was added to a reaction vial along with dry THF (0.2 mL). After cooling to -78^{o}C, ^{n}BuLi (0.03 mmol, 0.02 mL) was added and the reaction was allowed to stir 15 minutes. LiCl (0.5 eq, 0.2 mg) was added immediately following the ^{n}BuLi. At which time the starting ketone (0.004 g, 0.010 mmol) was added drop-wise and allowed to stir 15 minutes. To this was added (S)-Mosher acid chloride (0.012 mmol, 0.002 mL) and the reaction was maintained at -78^{o}C for 30 minutes. The bath was then removed and at room temperature the reaction was loaded directly on a silica gel plug and eluted with 30% ethyl acetate: 70% hexanes to give the respective Mosher ester (0.005 g, 83%, 10:1). The product ratios were simply determined by ^{19}F NMR peak integration. The two respective diastereomers have ^{19}F NMR shifts of -74.942 and -74.970 relative to an internal standard of hexafluorobenzene.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.55-7.00 (m, 10H), 5.49 (s, 1H), 5.15 – 5.06 (m, 1H), 5.03 – 4.94 (m, 1H), 3.61 (s, 3H), 3.57 (s, 3H), 3.01 – 2.89 (m, 2H), 2.39 – 2.08 (m, 6H), 1.85 – 1.65 (m, 2H), 1.71 (s, 3H), 1.70 (s, 3H), 1.51 (s, 6H), 1.48 – 1.40 (m, 2H).

A3.2 NMR Data for Chapter 3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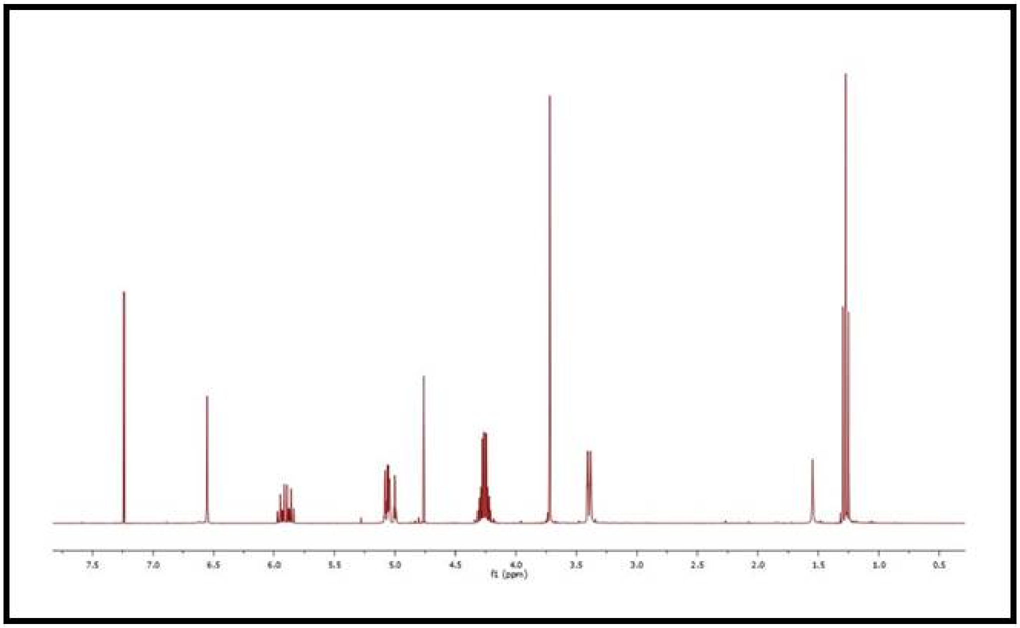

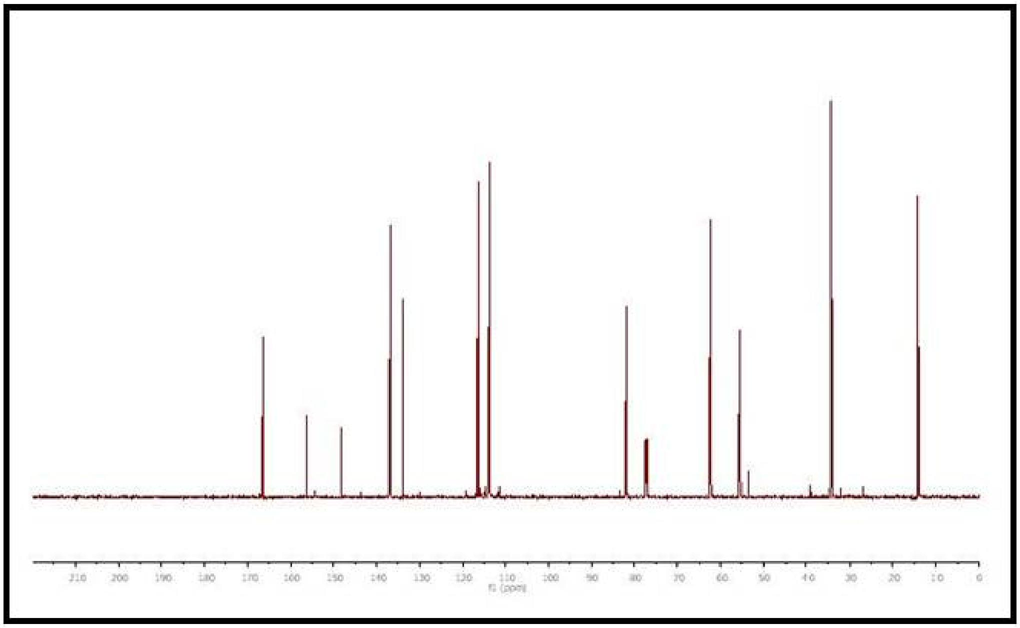

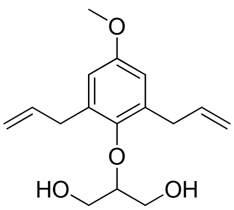
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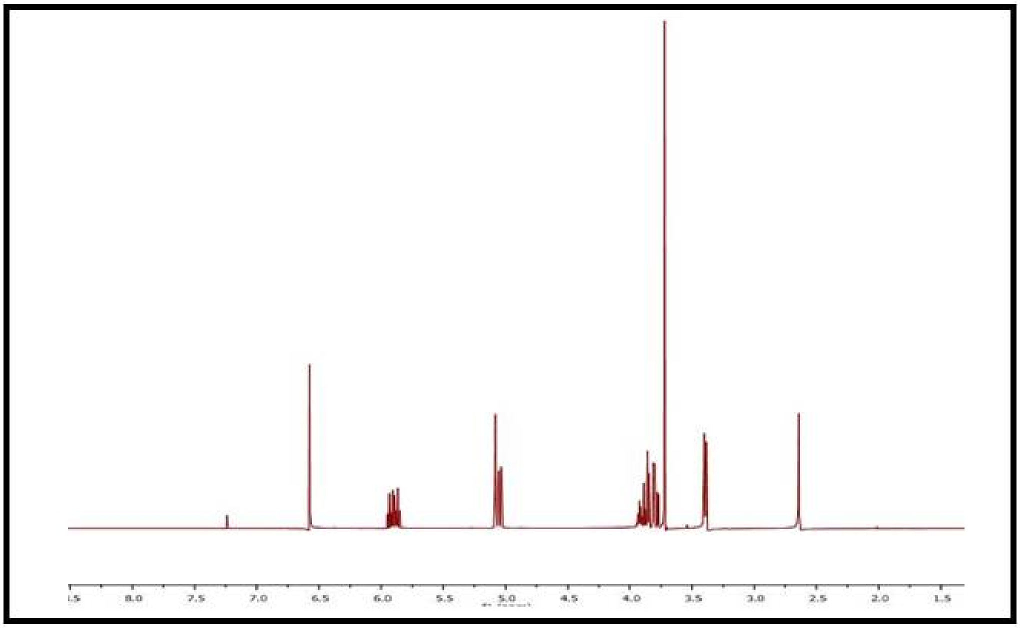
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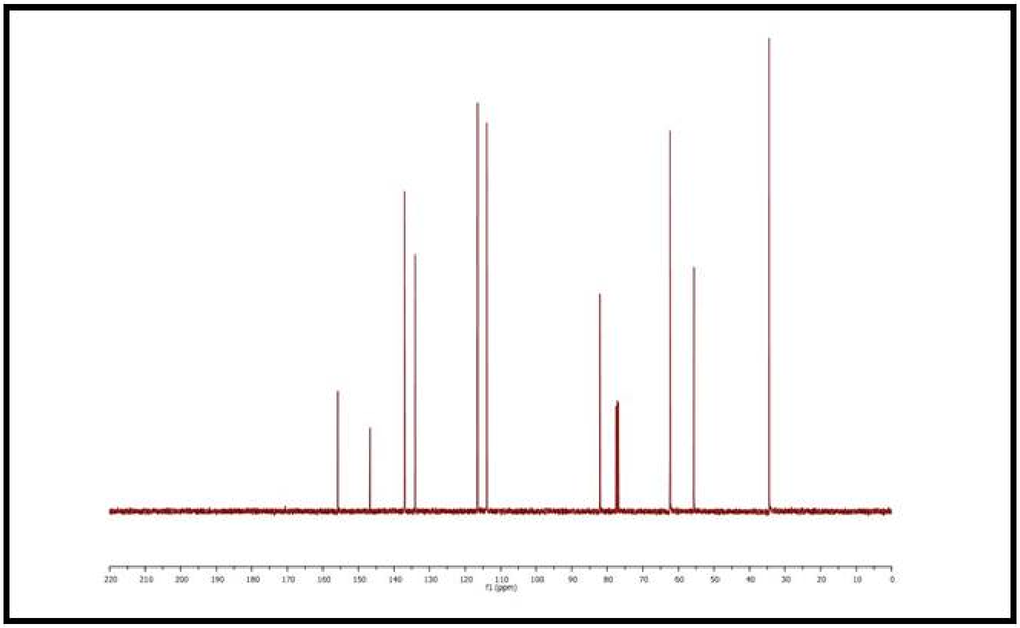
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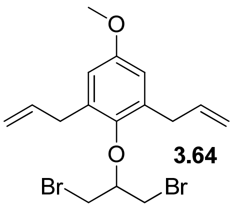

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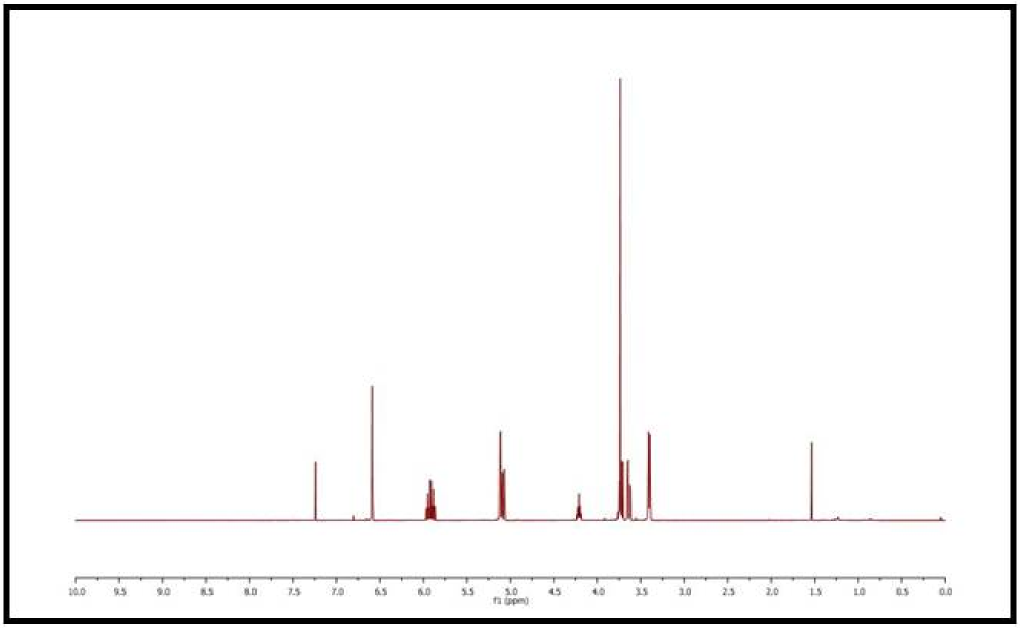

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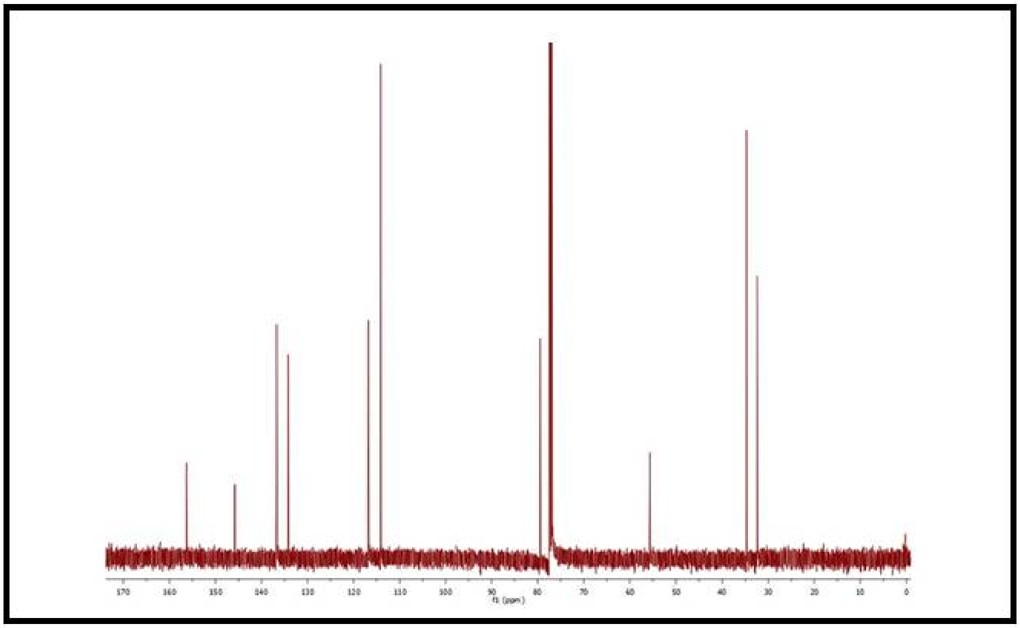

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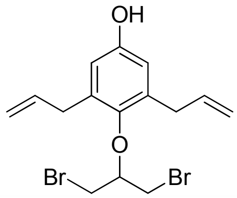
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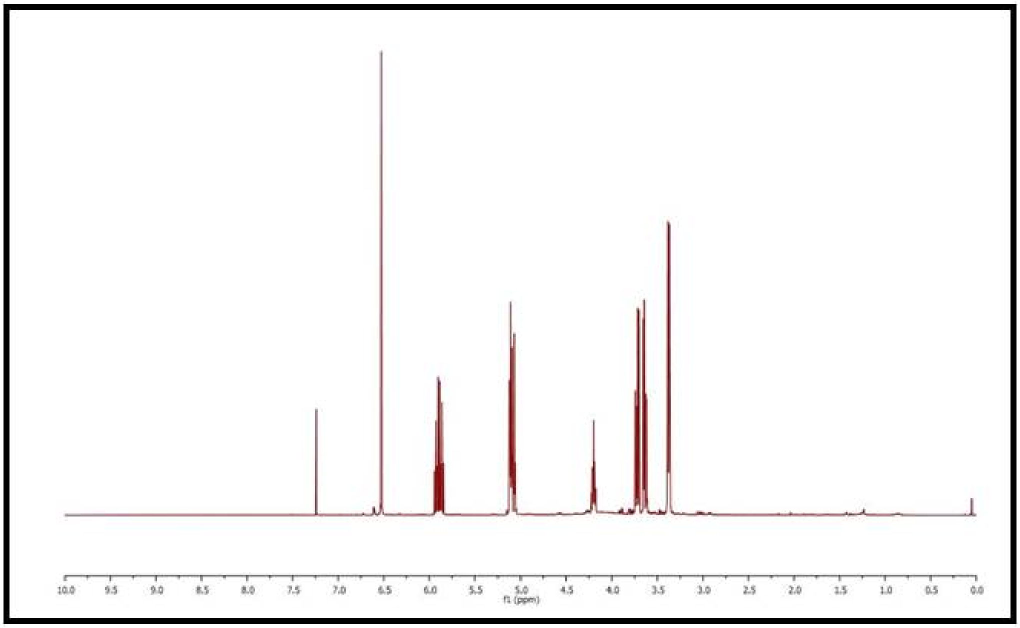
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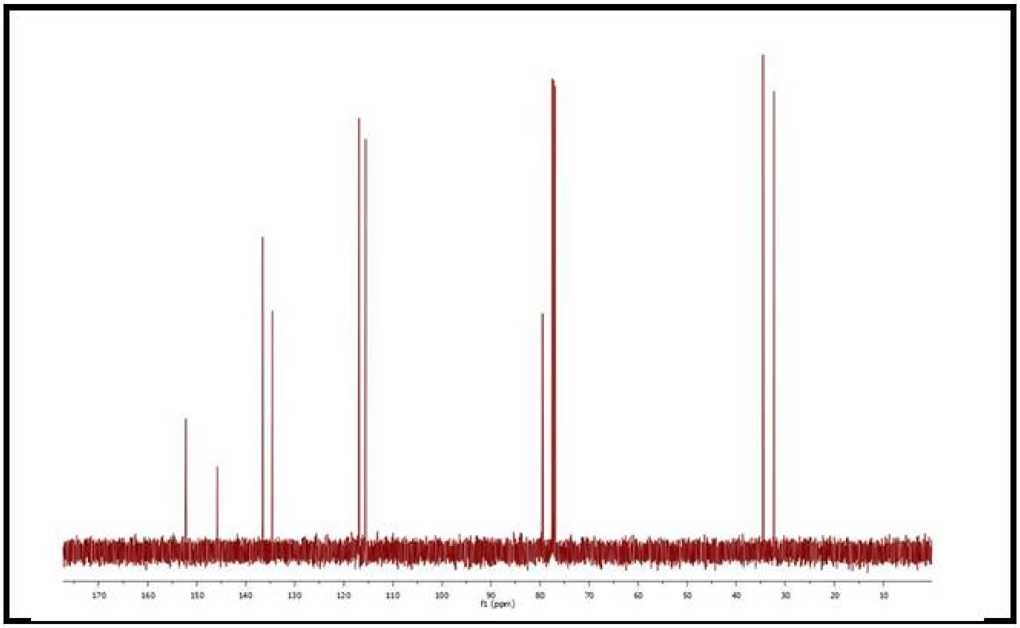
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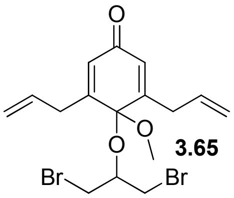

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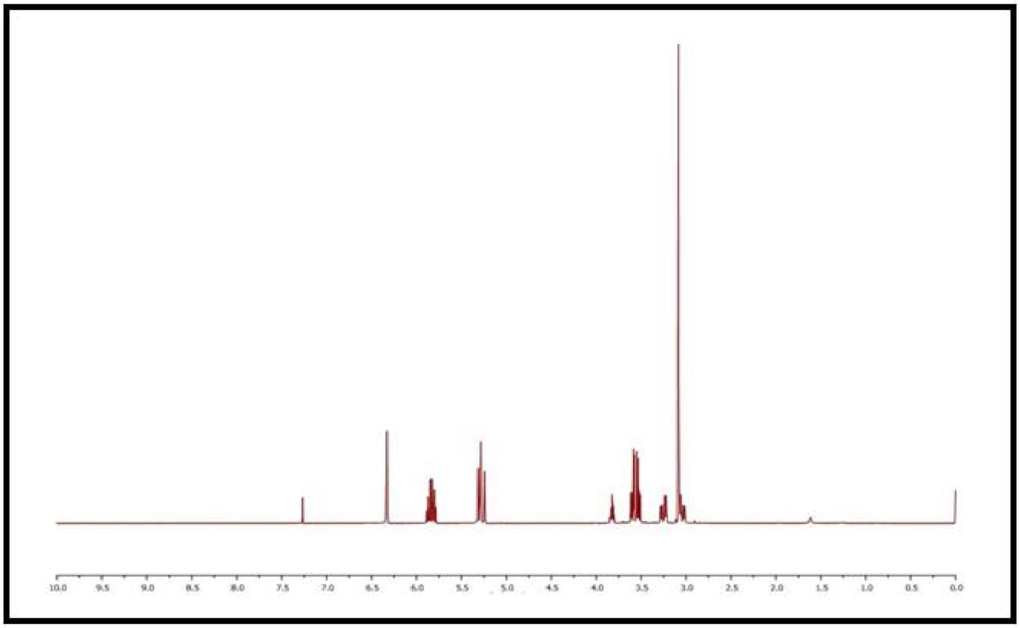

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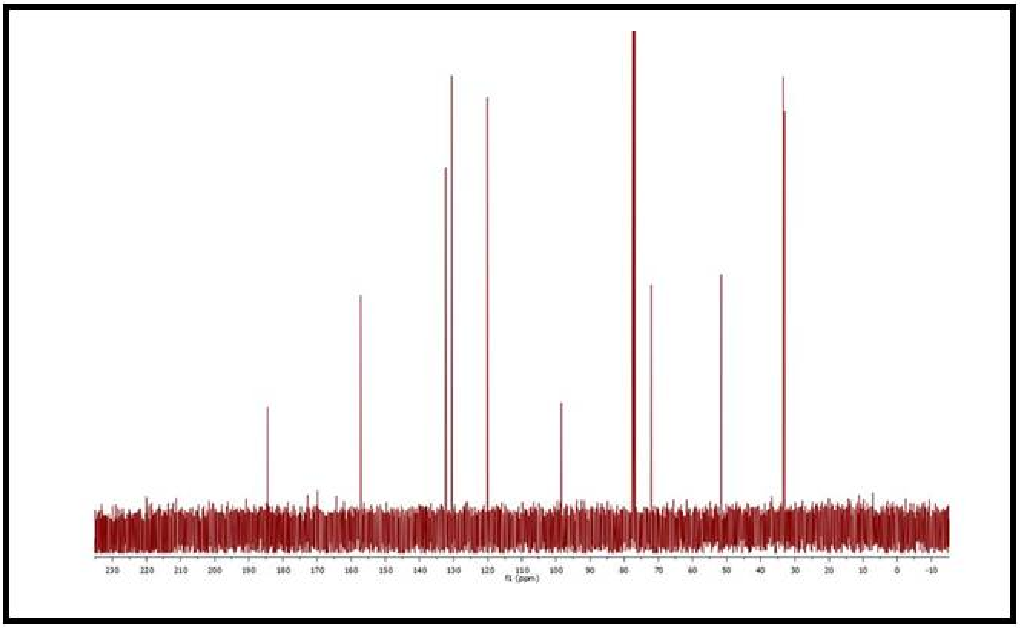

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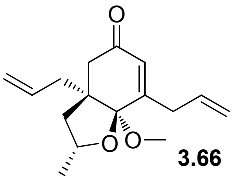

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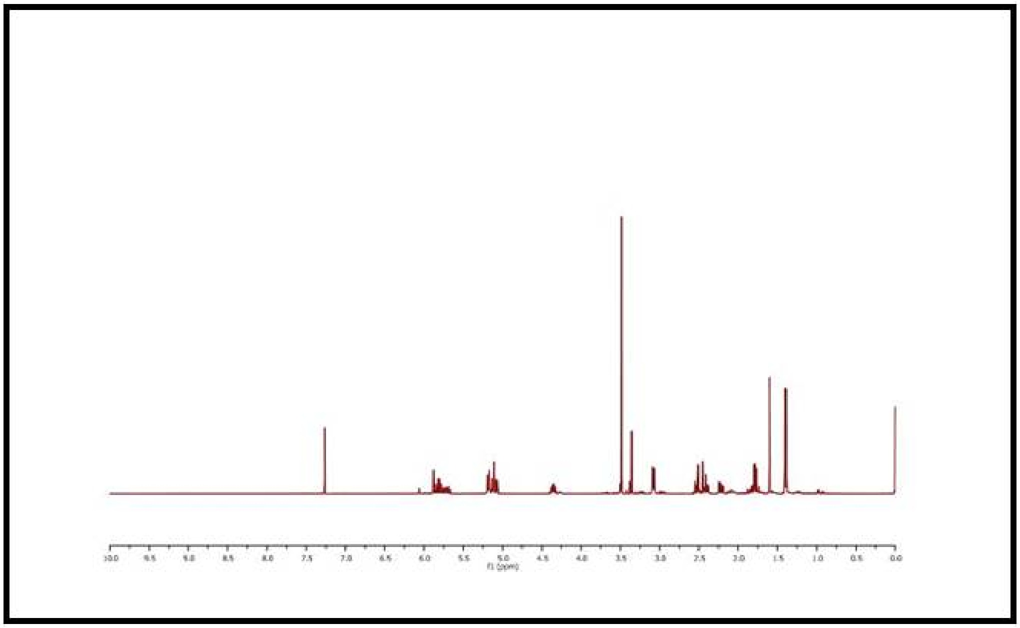
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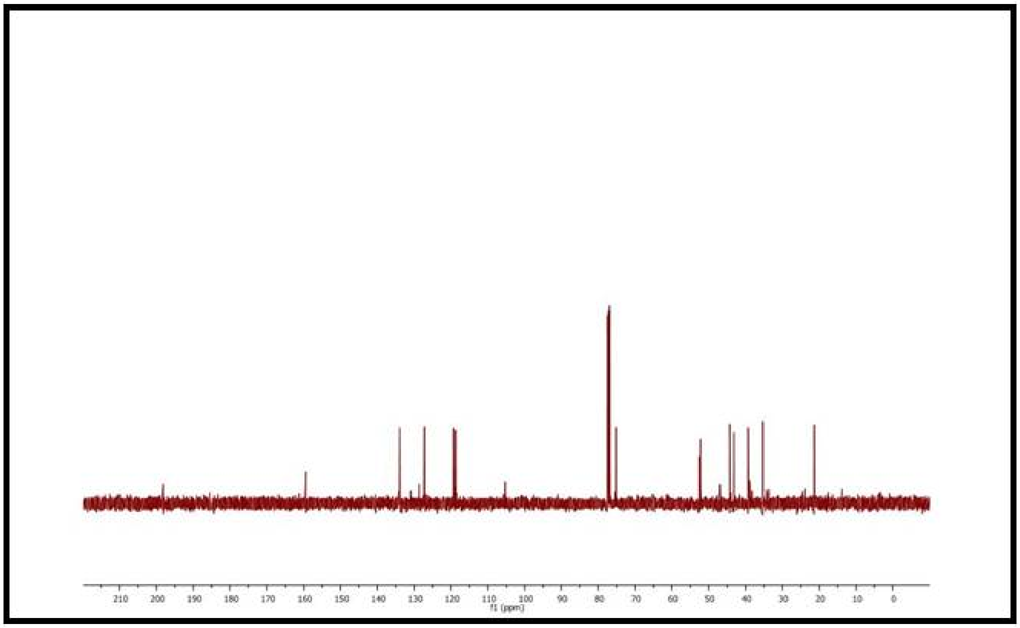
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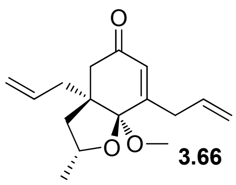

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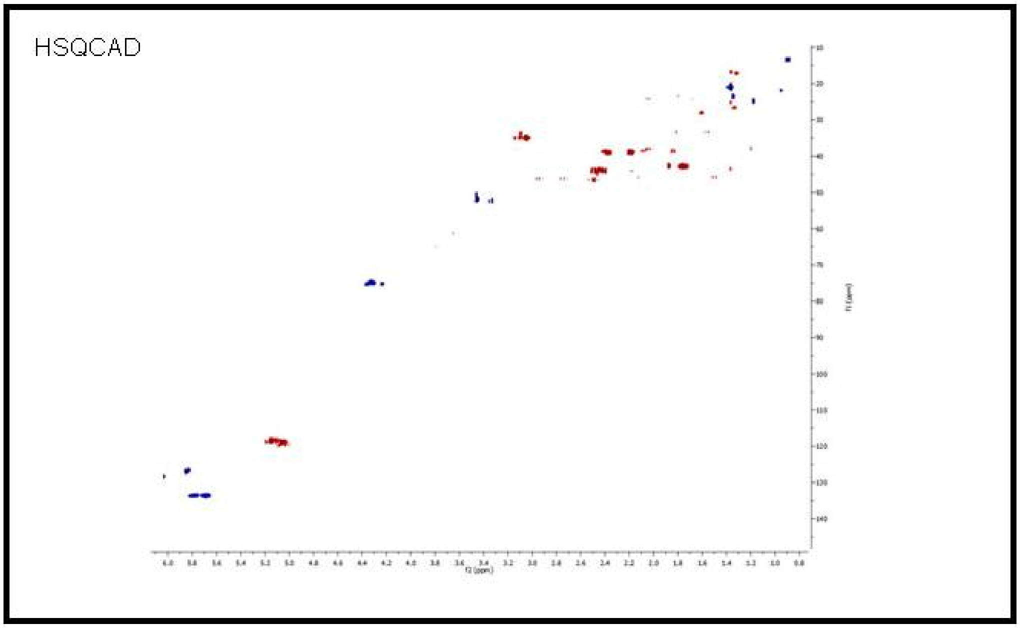

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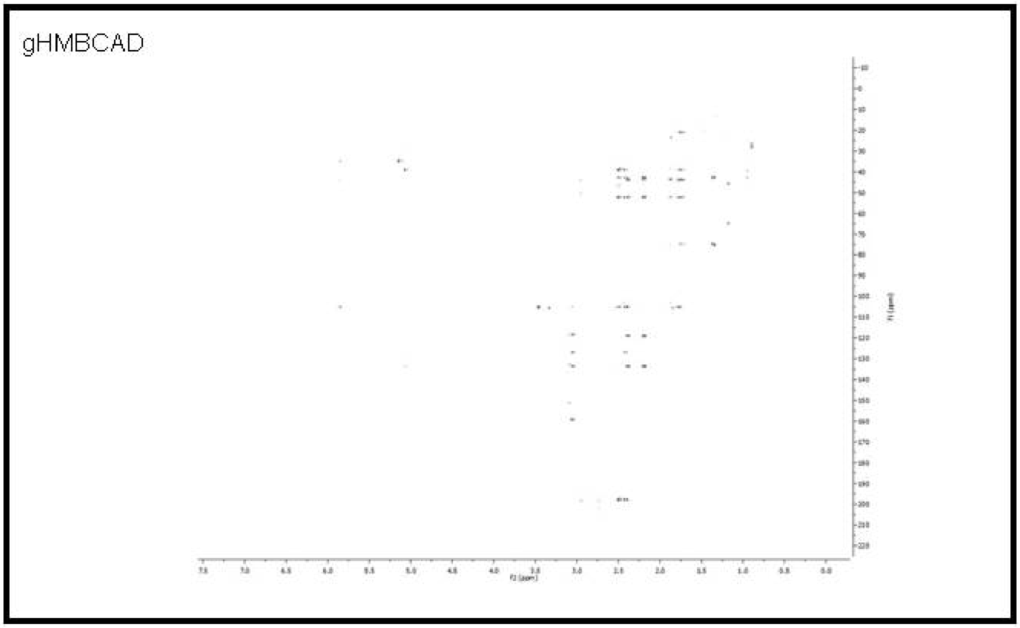

gHMBCAD

C	^{13}C (δ ppm)	HSQC-AD ^{1}H (δ ppm)	gHMBC-AD (^{1}H-Correlations)
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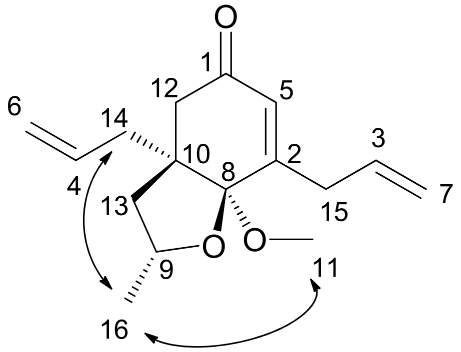
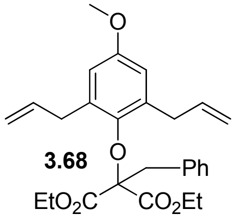
2	159.5	---	3.05
3	133.9	5.80	3.05
4	133.9	5.69	5.06, 2.38, 2.19
5	127.1	5.85	3.05, 2.42
6	119.3	5.04, 5.06	2.38, 2.19
7	118.8	5.12, 5.16	3.05
8	105.3	---	5.85, 3.46, 3.05, 2.49, 2.38. 1.75
9	75.2	4.33	1.87, 1.75, 1.36
10	52.6	---	2.49, 2.42, 2.38, 2.19, 1.87, 1.75
11	52.3	3.46	----
12	44.3	2.49, 2.42	5.85, 2.38, 2.19, 1.87, 1.75
13	43.2	1.87, 1.75	2.49, 2.42, 2.19, 1.36
14	39.3	2.38, 2.19	5.69, 5.06, 2.49, 2.42, 1.75
15	35.3	3.05	5.85, 5.16
16	21.4	1.36	1.75

Table A3.1 2D-NMR Data for **3.66**

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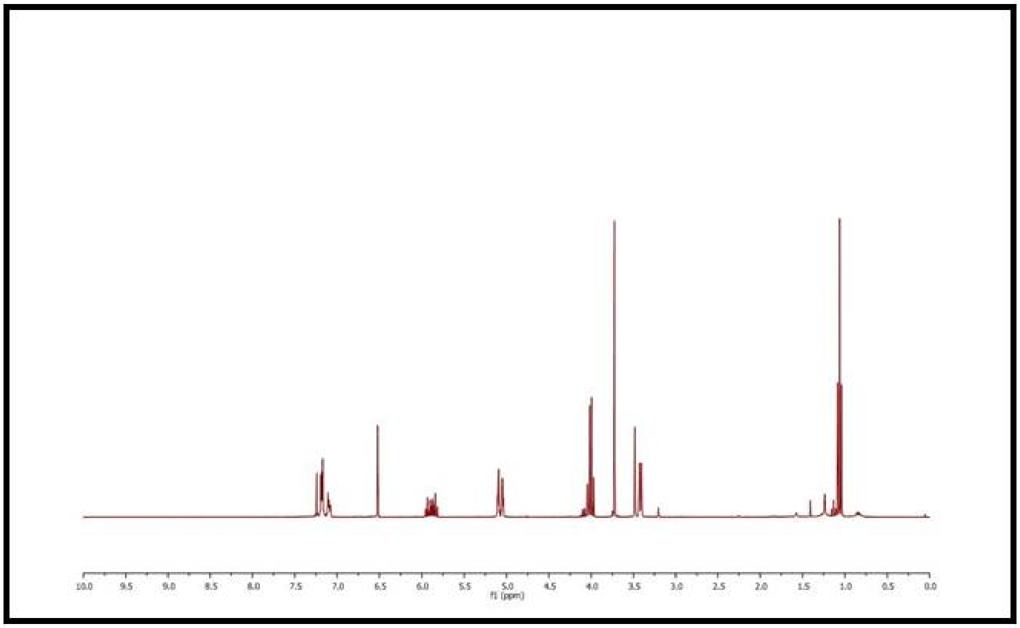
3.68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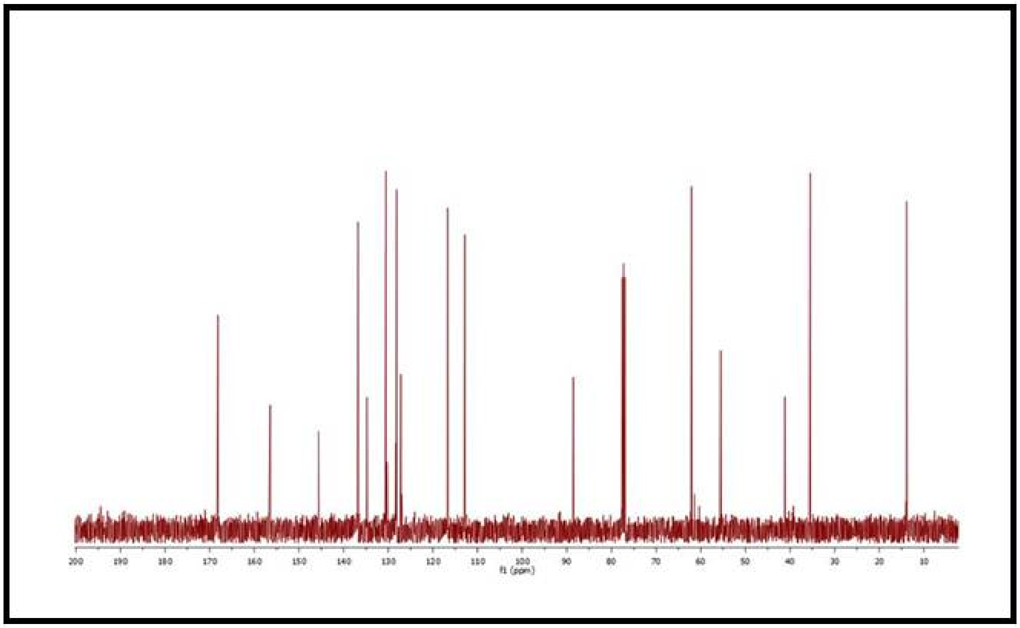
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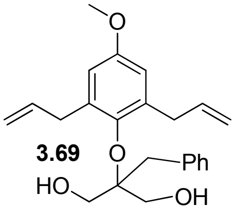
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Ph
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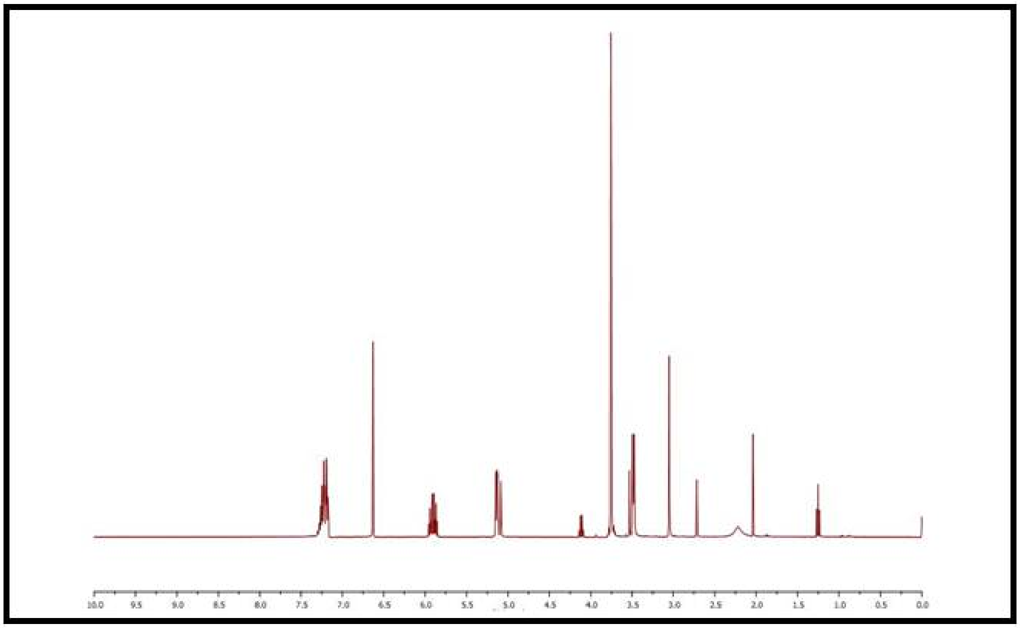
3.69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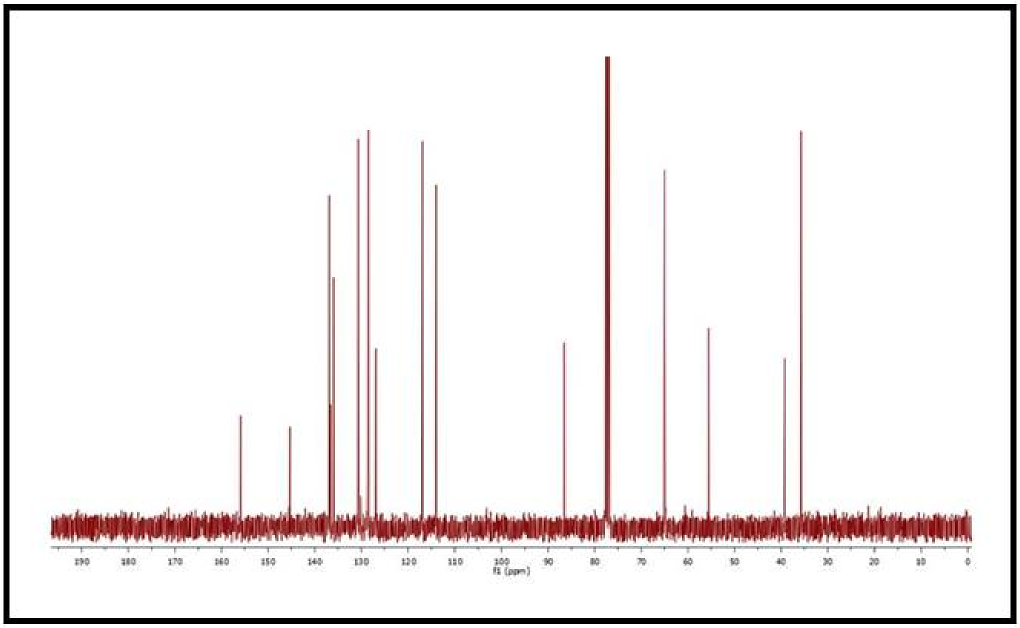
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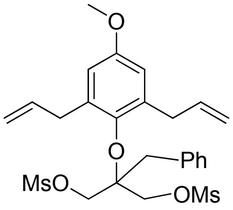
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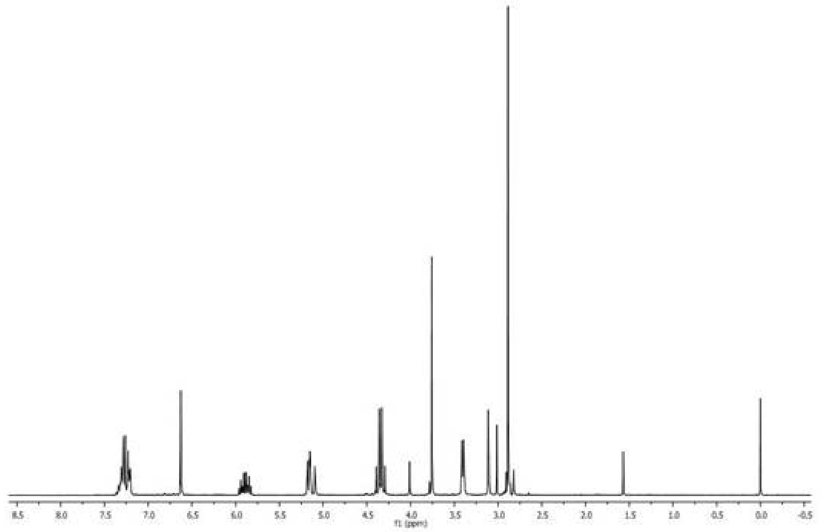
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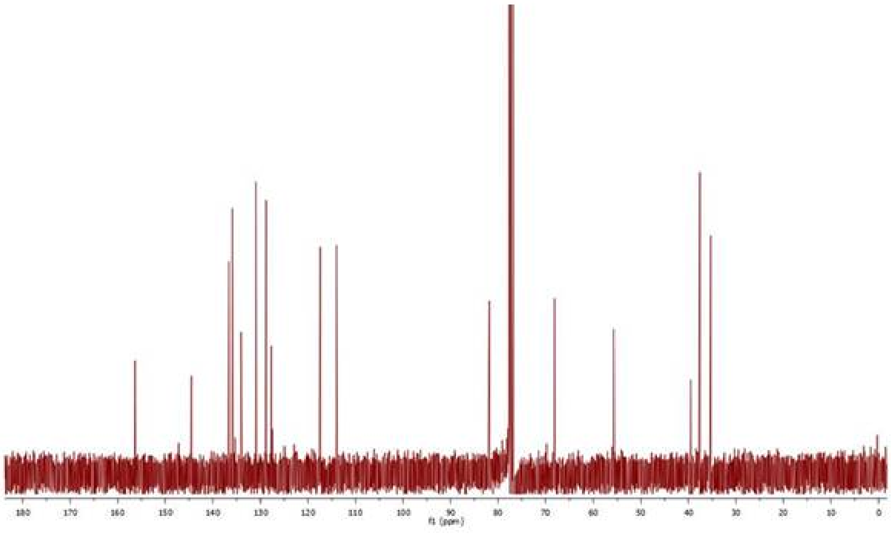
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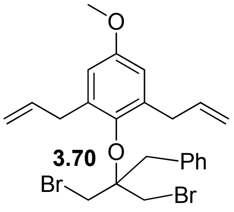

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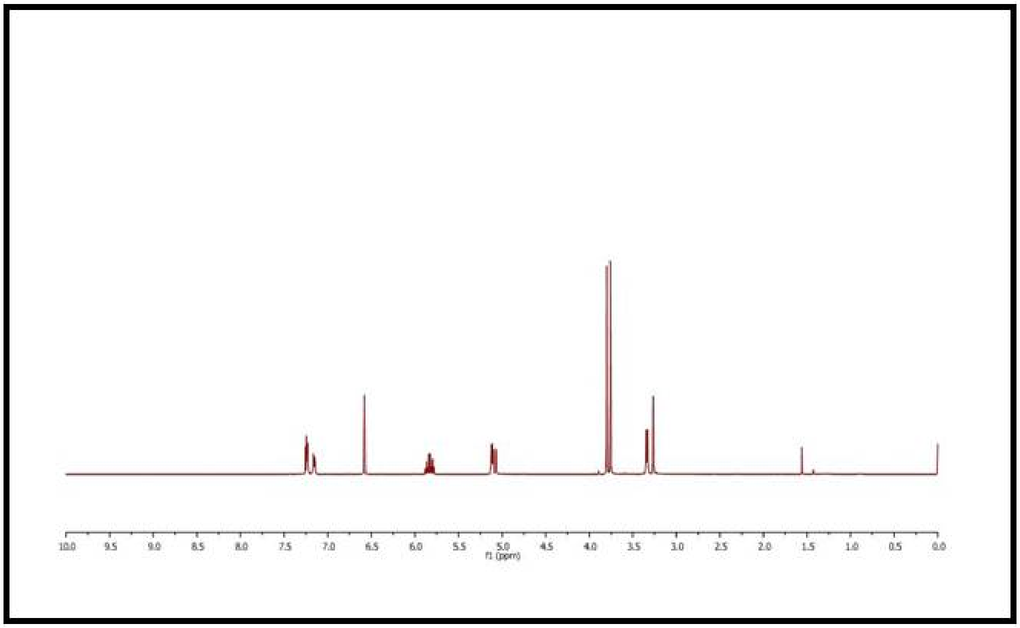
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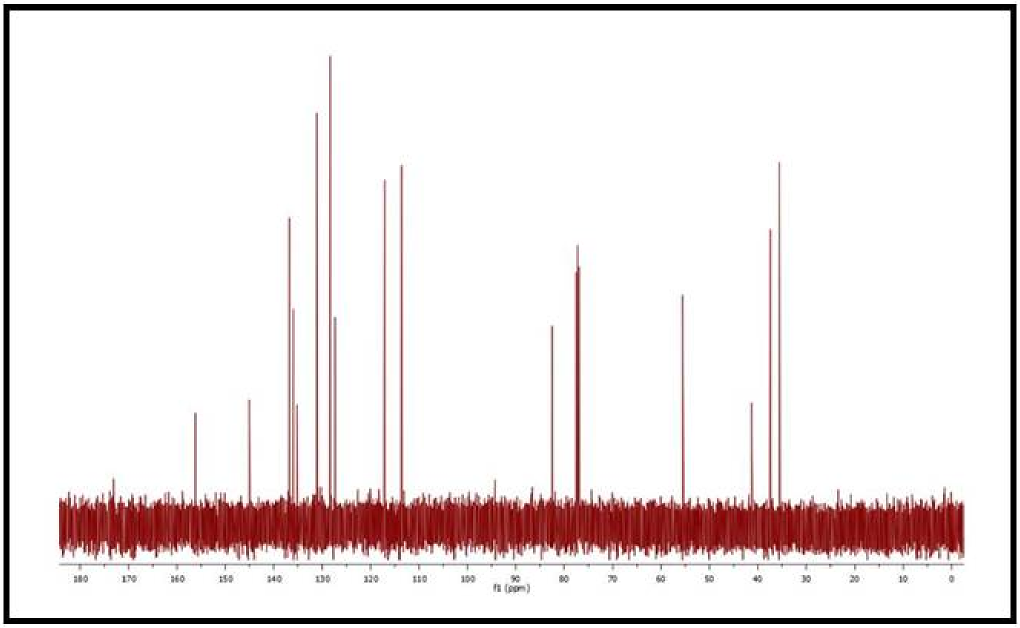
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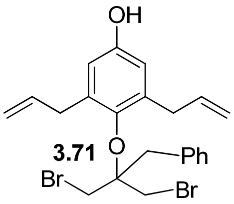
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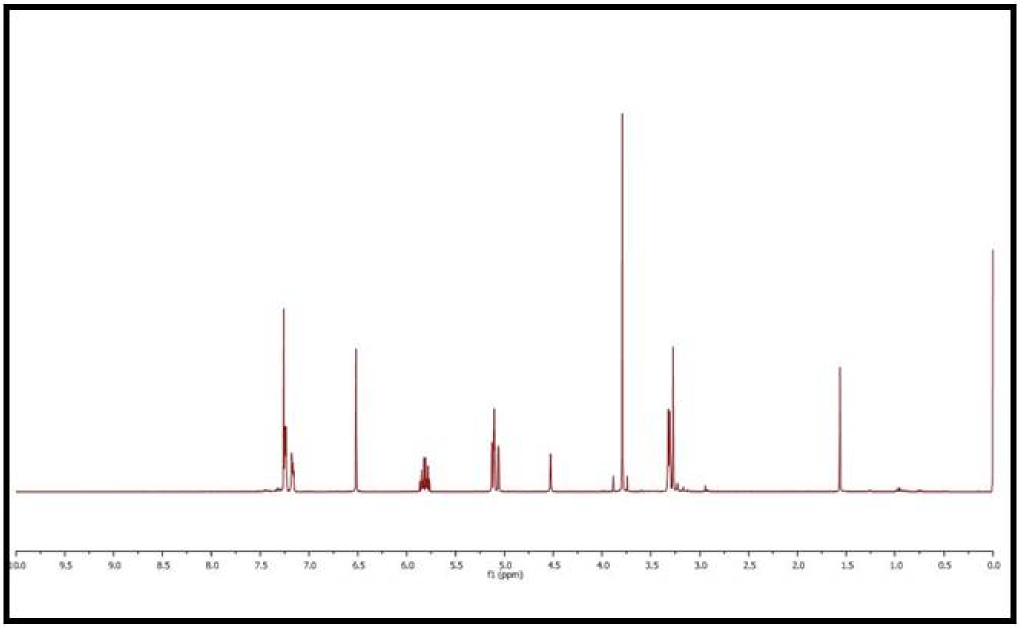
3.71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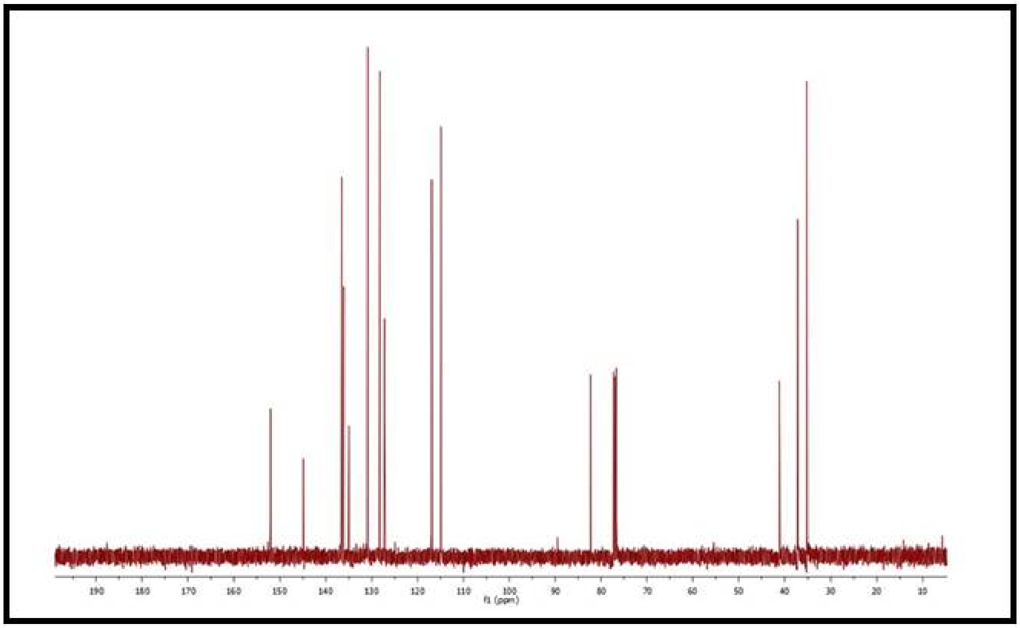
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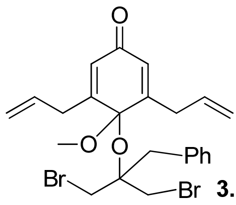
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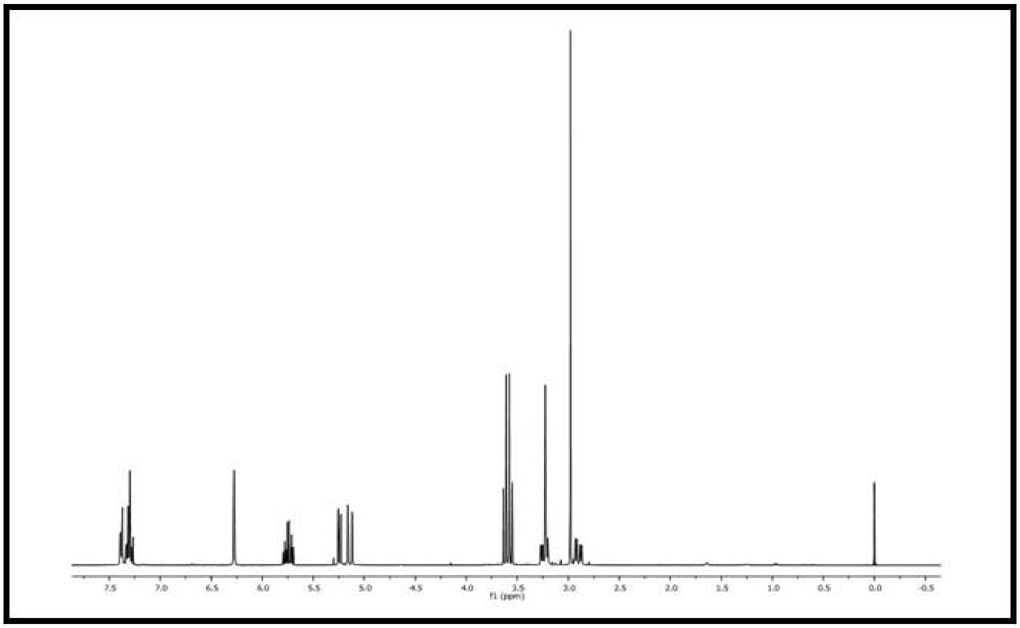
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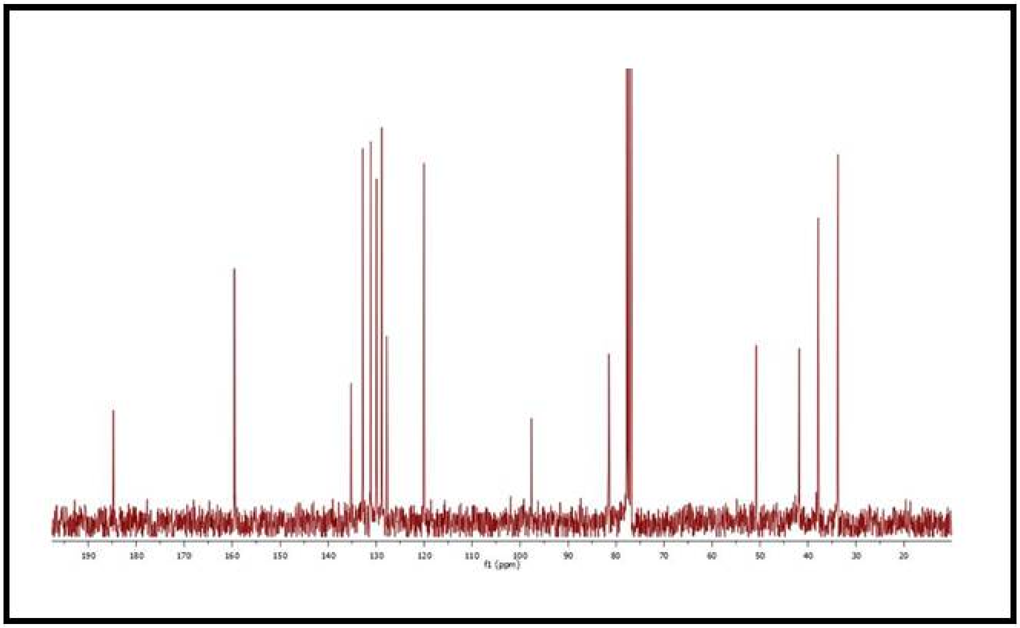
f1 (ppm)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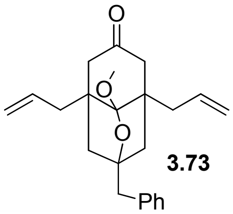
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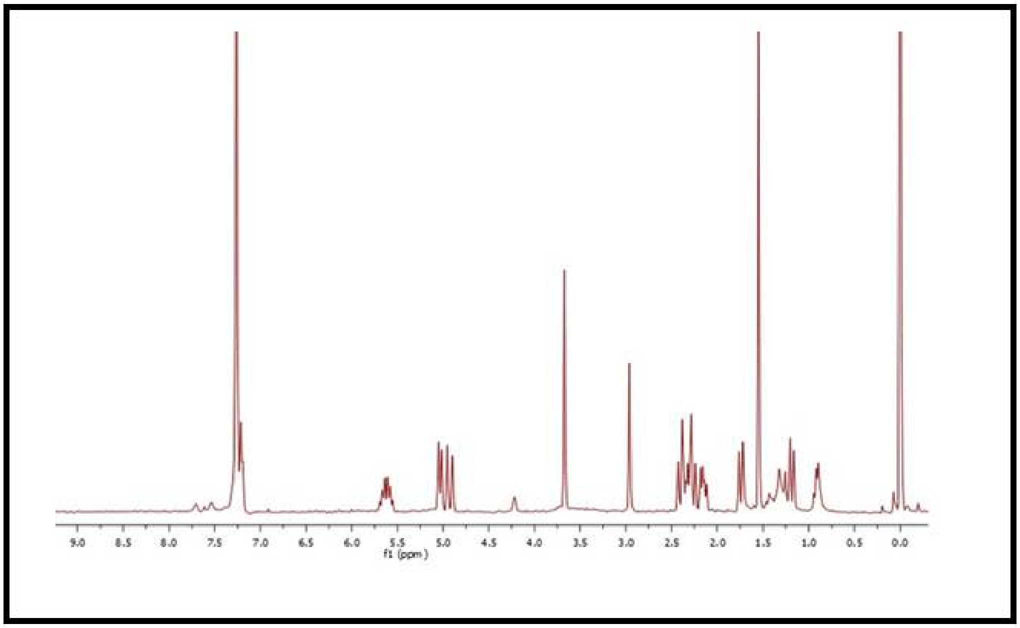
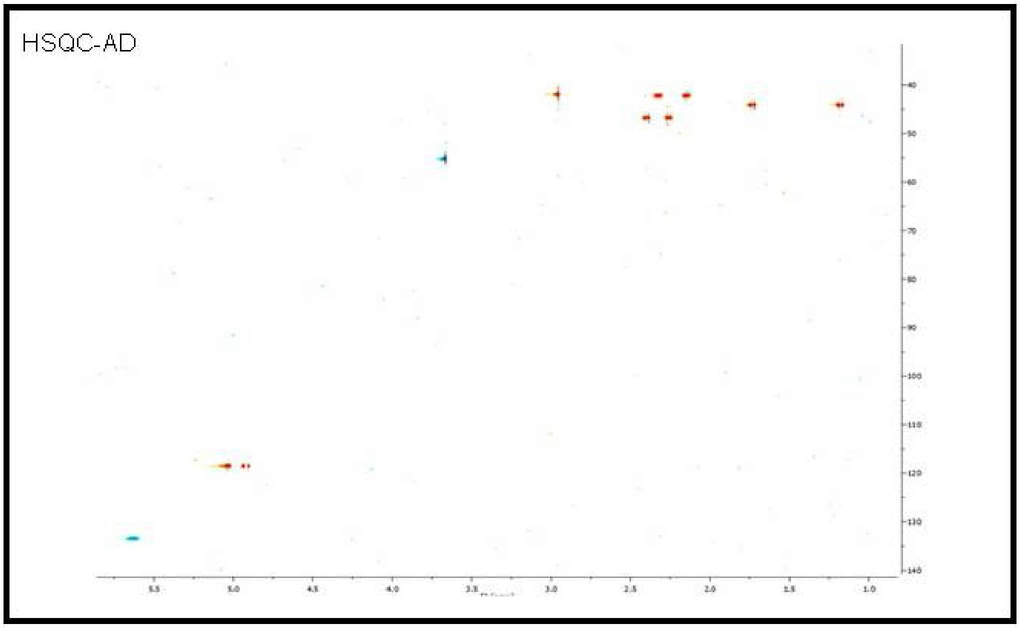
Ph

3.73


9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


HSQC-AD
40
50
60
70
80
90
100
110
120
130
140
5.5
5.0
4.5
4.0
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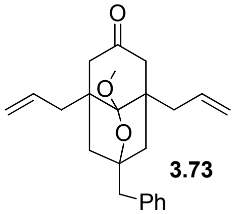
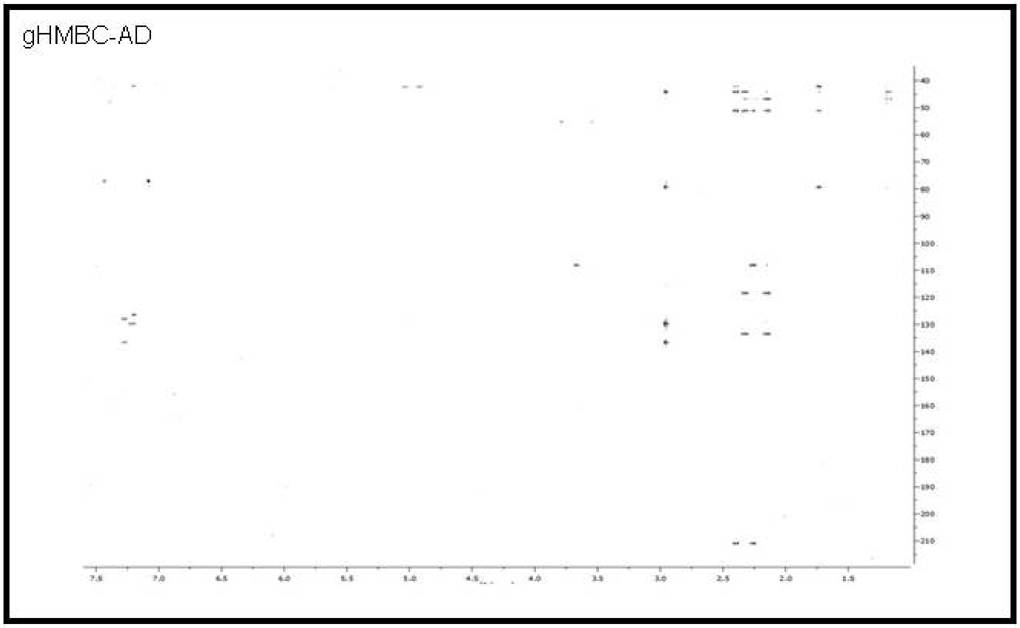
2.5
2.0
1.5
1.0

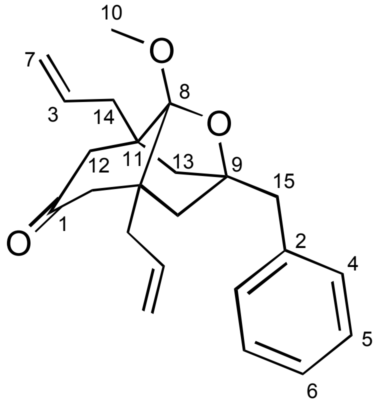

O
O
O
Ph

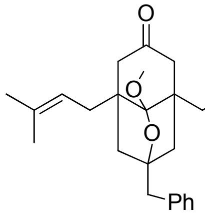
3.73


gHMBC-AD
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

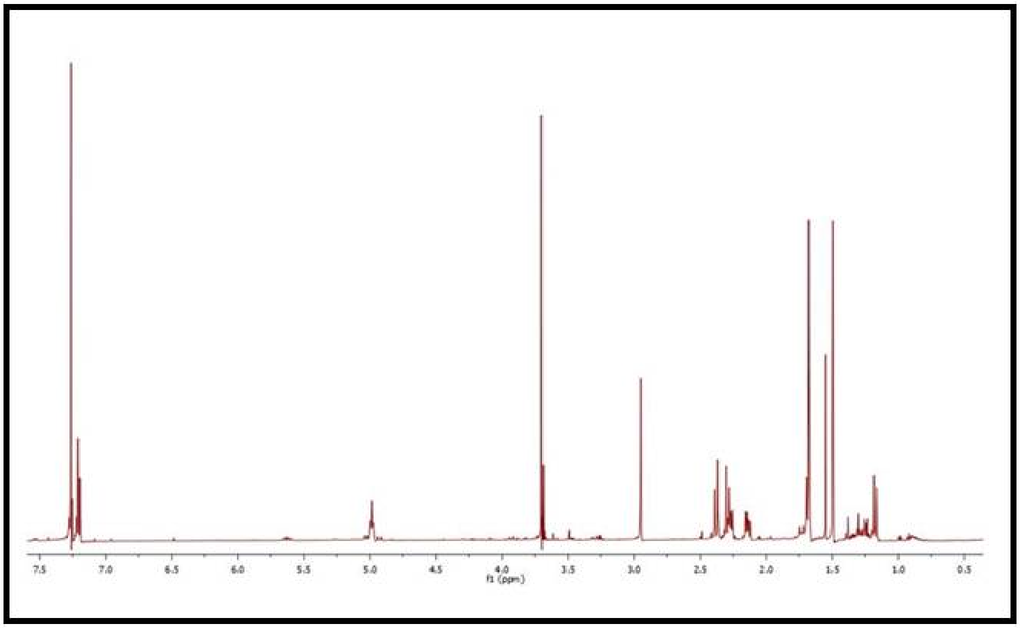
C	^{13}C (δ ppm)	HSQC-AD (δ ppm)	gHMBC-AD (^{1}H-Correlations)
1	211.0	-----	2.40, 2.26
2	136.9	-----	7.28, 2.96
3	133.6	5.62	2.33, 2.15
4	130.0	7.21	7.24, 7.21, 2.96
5	128.2	7.28	7.28, 7.21
6	126.6	7.24	7.21
7	118.8	5.03, 4.92	2.33, 2.15
8	108.1	-----	3.67, 2.26, 2.15, 1.19
9	79.4	-----	2.96, 1.74, 1.19
10	55.5	3.67	-----
11	51.1	-----	2.40, 2.33, 2.26, 2.15, 1.74, 1.19
12	47.4	2.40, 2.26	2.33, 2.15, 1.19
13	44.5	1.74, 1.19	2.96, 2.40, 2.33, 2.26, 2.15, 1.74, 1.19
14	42.6	2.33, 2.15	5.62, 5.03, 4.92, 2.40, 1.19
15	42.3	2.96	7.21, 1.74

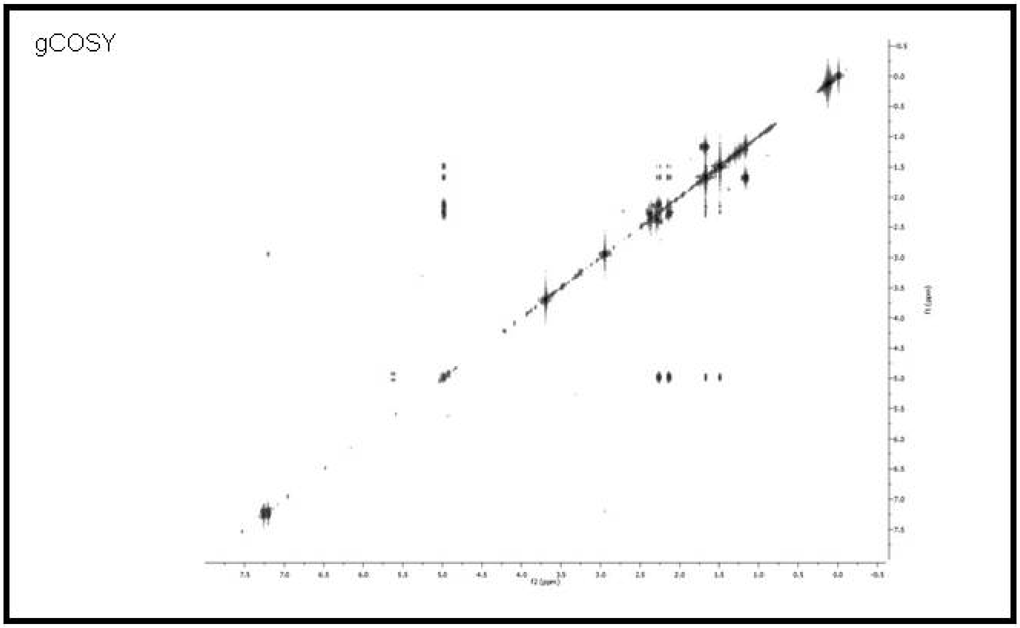
Table A3.2 2D-NMR Data for **3.73**

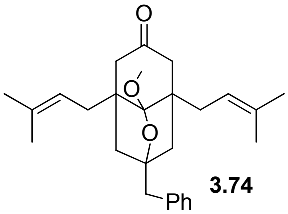



O
O
O
Ph

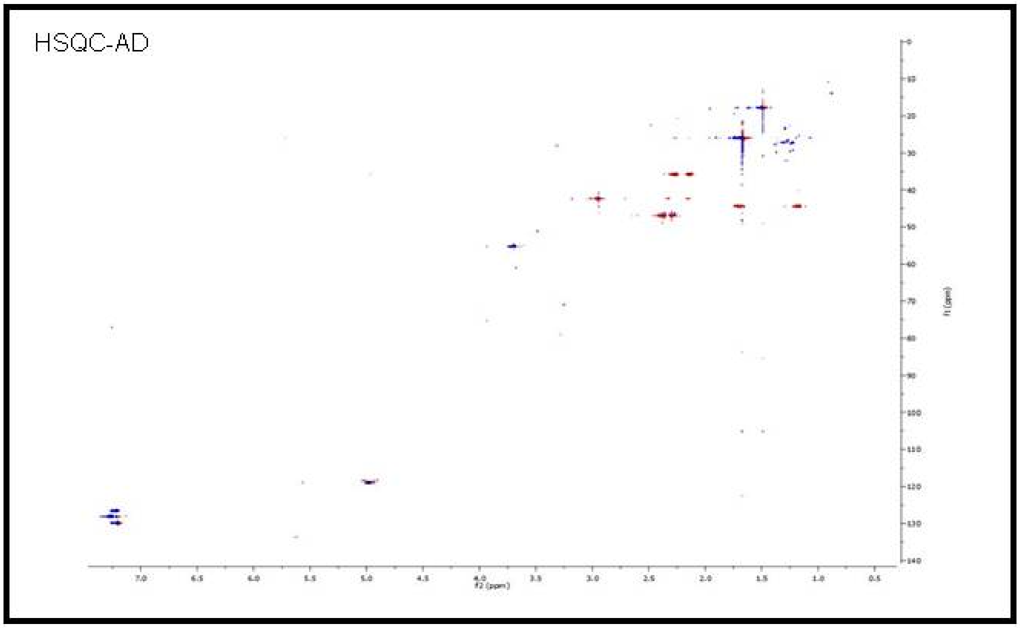
3.74

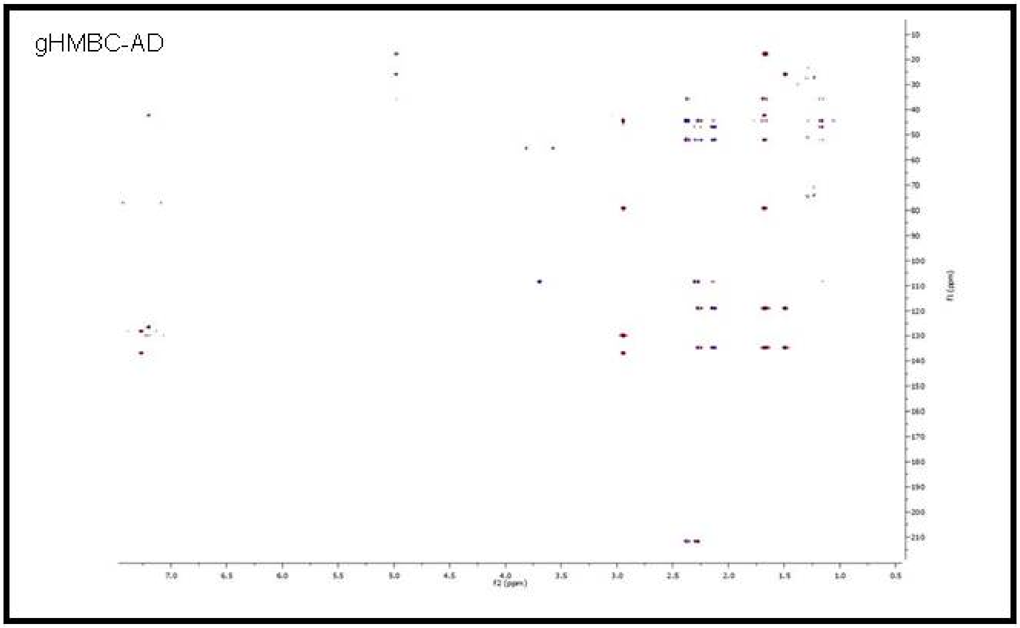

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


gCOSY
f2 (ppm)
f1 (ppm)


O
O
O
Ph

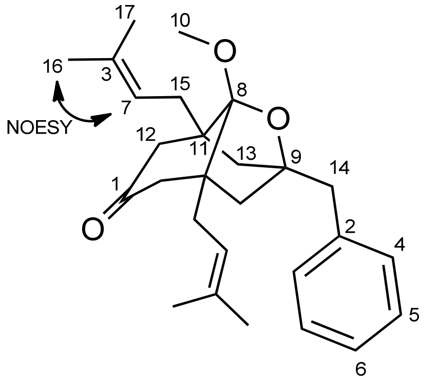
3.74

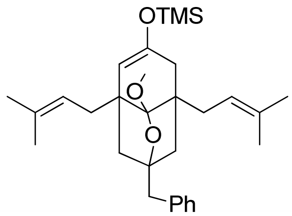

HSQC-AD
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140

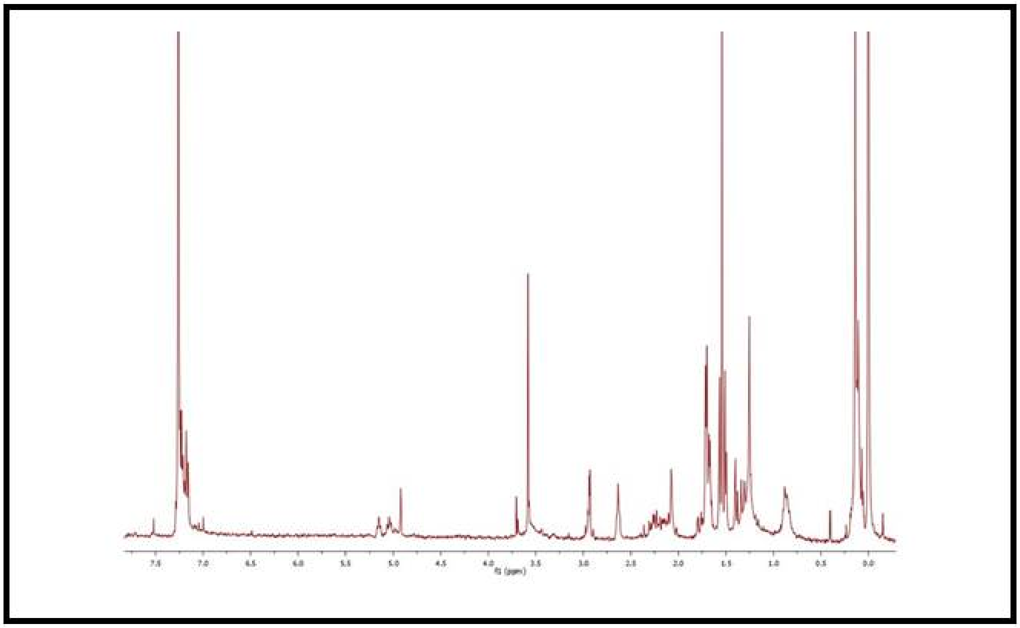

gHMBC-AD
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)
f1 (ppm)
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

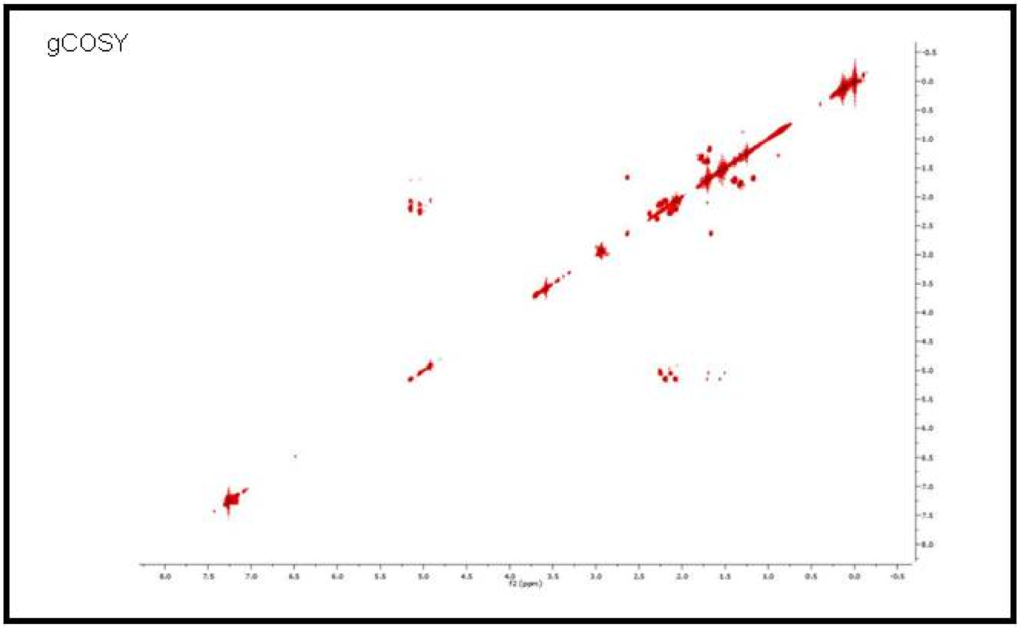
C	^{13}C (δ ppm)	HSQC-AD ^{1}H (δ ppm)	gHMBC-AD (^{1}H-Correlations)
1	211.7	-----	2.37, 2.29
2	136.7	-----	7.22, 2.94
3	134.6	-----	2.27, 2.13, 1.67, 1.49
4	129.9	7.22	2.94
5	128.1	7.23	7.22
6	126.5	7.22	7.22
7	118.9	4.98	2.27, 2.13, 1.67, 1.49
8	108.3	-----	2.29, 2.13, 1.67, 1.17
9	79.3	-----	2.94, 1.67
10	55.2	3.69	-----
11	52.1	-----	2.37, 2.27, 2.13, 1.67, 1.17
12	46.8	2.37, 2.29	2.13, 1.17
13	44.5	1.67, 1.17	2.94, 2.37, 2.27, 1.17
14	42.3	2.94	1.67
15	35.7	2.27, 2.13	2.37, 1.67
16	26.0	1.67	4.98, 1.49
17	17.8	1.49	4.98, 1.67

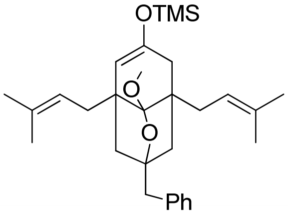
Table A3.3 2D-NMR Data for **3.74**

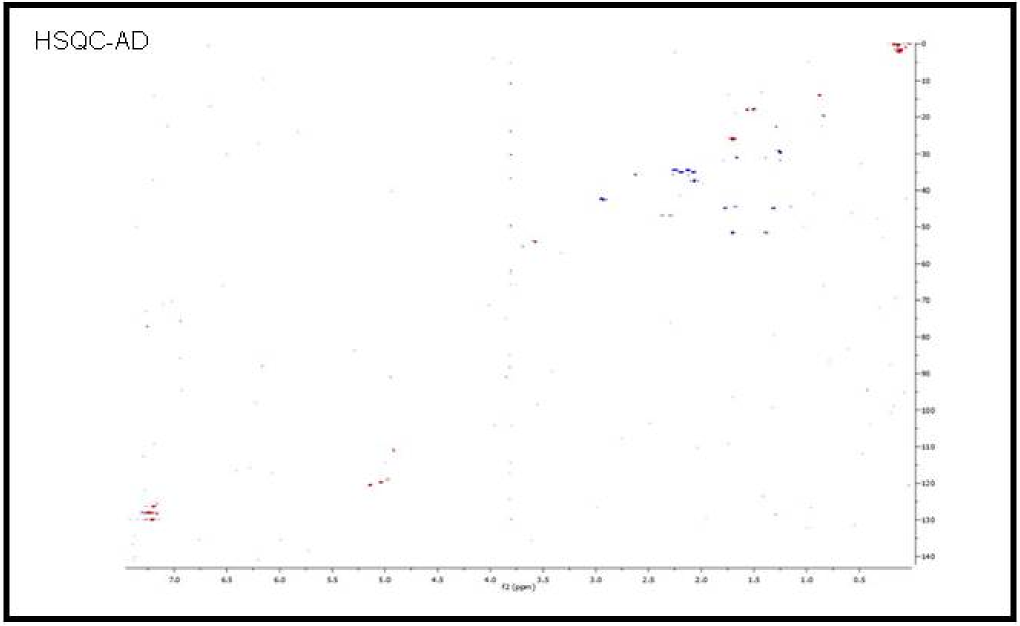


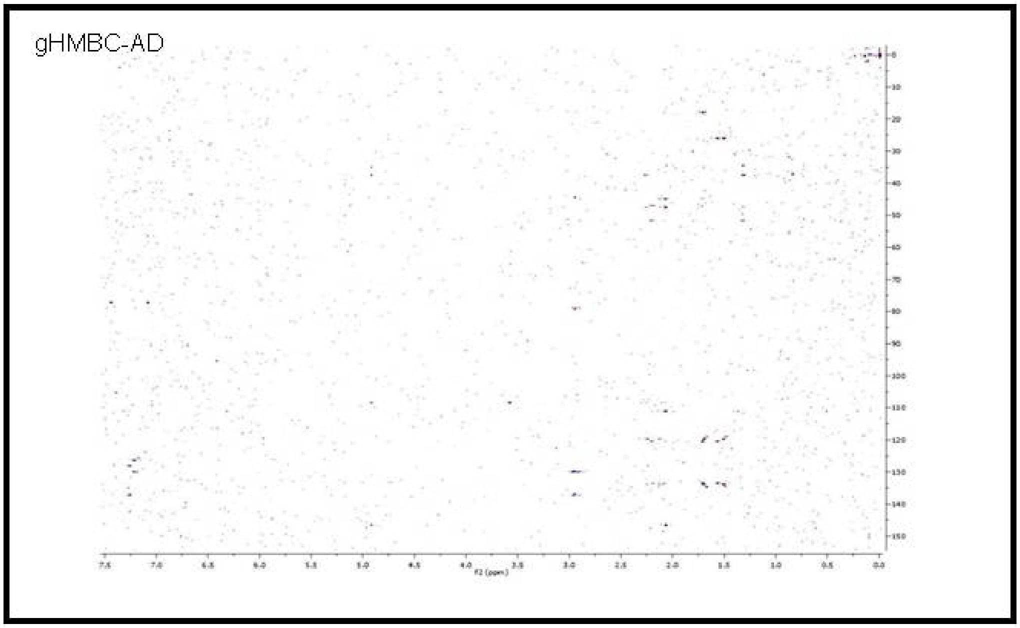

OTMS
O
O
Ph


7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


gCOSY
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f2 (ppm)

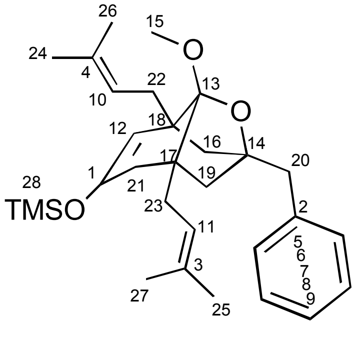

OTMS
O
O
Ph

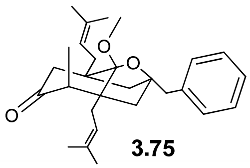

HSQC-AD
f2 (ppm)


gHMBC-AD
f2 (ppm)

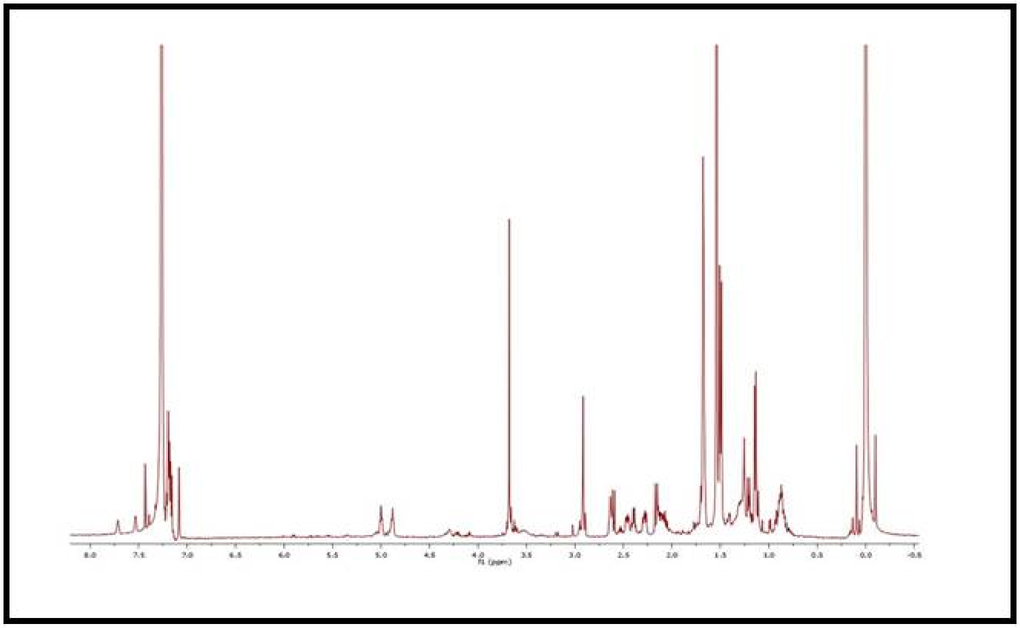
C	^{13}C (δ ppm)	HSQC-AD ^{1}H (δ ppm)	gHMBC-AD (^{1}H-Correlations)
1	146.6	-----	4.92, 2.07
2	137.4	-----	7.25, 2.94, 2.93
3	133.9	-----	2.25, 2.13, 1.71, 1.51
4	133.5	-----	2.20, 2.07, 1.72, 1.56
5	130.1	7.21	7.20, 2.94, 2.93
6	128.5	7.17	7.25
7	128.1	7.25	-----
8	126.4	7.20	7.21
9	125.7	7.16	-----
10	120.6	5.15	2.20, 2.07, 1.72, 1.56
11	119.9	5.04	2.25, 2.13, 1.71, 1.51
12	111.2	4.92	2.07, 1.39
13	108.6	-----	4.92, 3.58, 2.07, 1.39
14	78.9	-----	2.94, 2.93
15	54.2	3.58	-----
16	51.8	1.71, 1.39	2.20
17	47.7	-----	2.25, 2.07
18	47.1	-----	2.20, 2.07
19	45.1	1.78, 1.32	2.94, 2.07
20	42.6	2.94, 2.93	7.21
21	37.7	2.07	4.92
22	35.2	2.20, 2.07	4.92
23	34.6	2.25, 2.13	2.07, 1.78, 1.32
24	26.2	1.72	1.56
25	26.1	1.71	1.51
26	18.1	1.56	1.72
27	18.0	1.51	1.71
28	0.49	0.14	-----

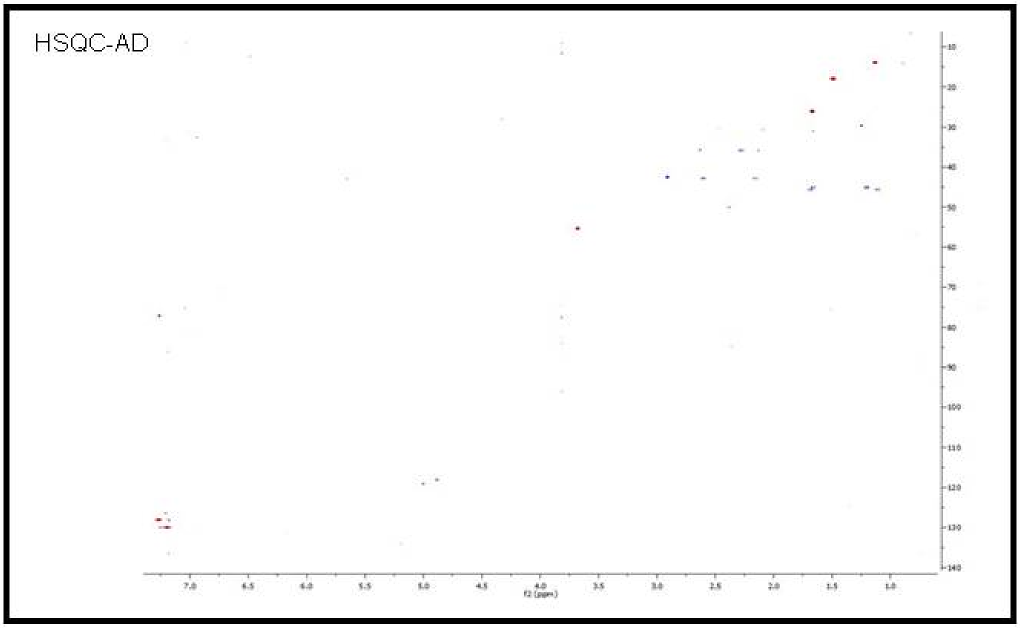
Table A3.4 2D-NMR Data for **3.74 (Enol Ether)**

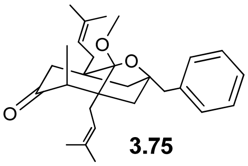



O
O
O

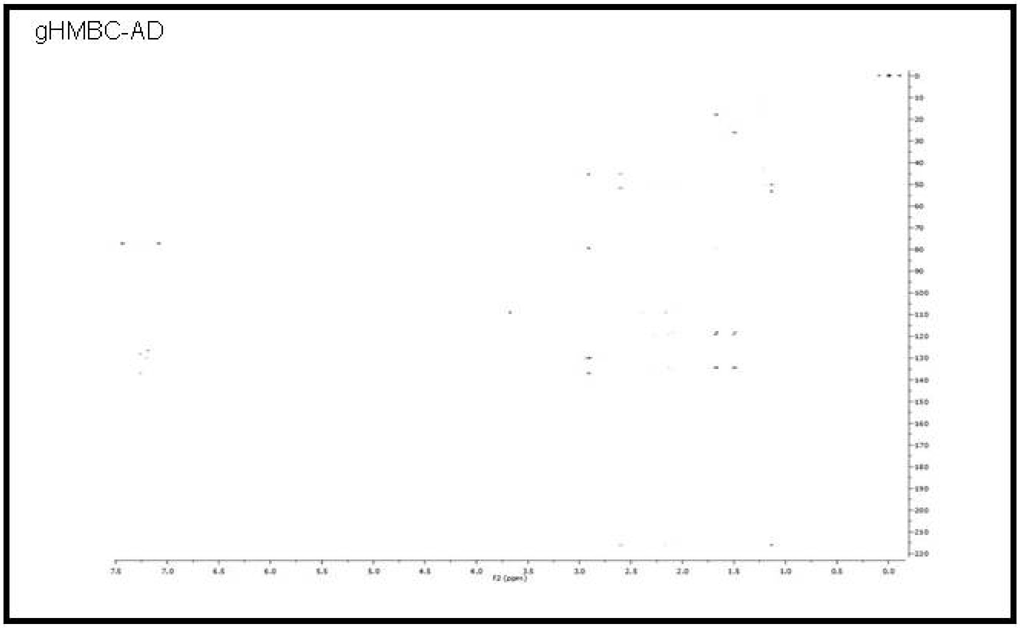
3.75


8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

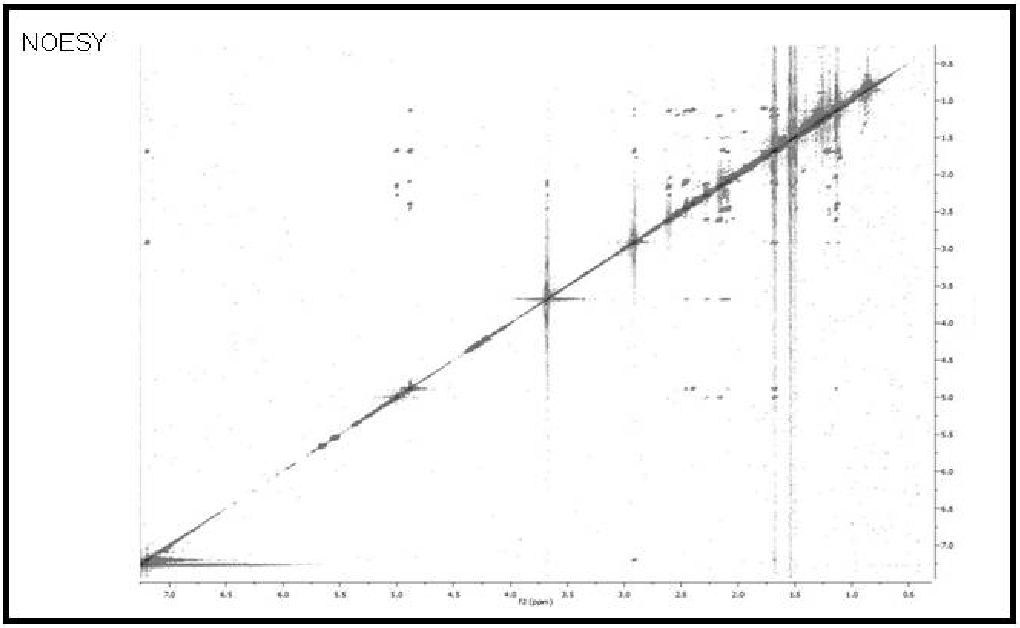

HSQC-AD
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)
10
20
30
40
50
60
70
80
90
100
110
120
130
140



3.75



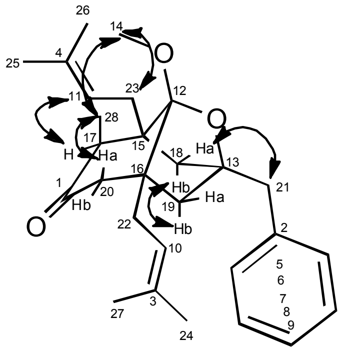
gHMBC-AD

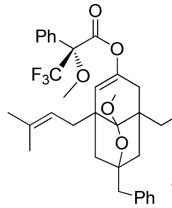


NOESY

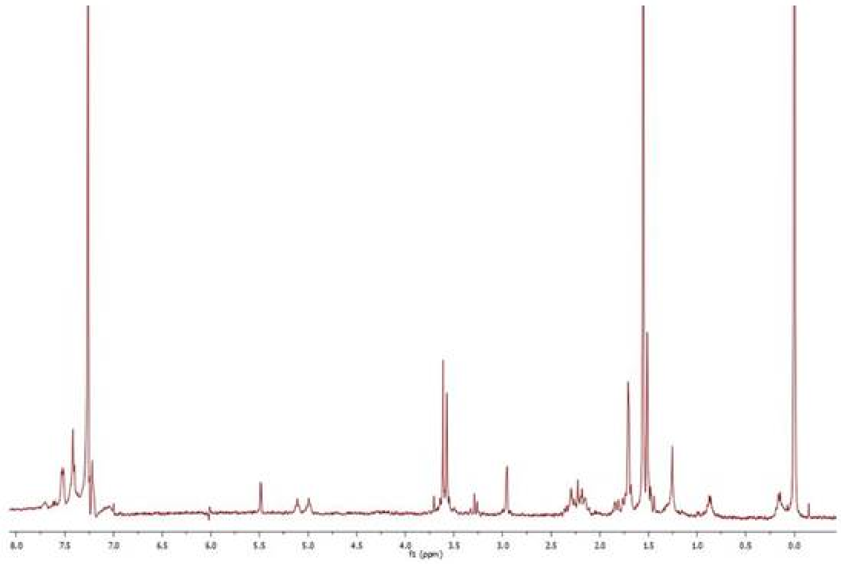
C	^{13}C (δ ppm)	HSQC-AD ^{1}H (δ ppm)	gHMBC-AD (^{1}H-Correlations)
1	216.2	-----	2.60, 2.38, 2.16, 1.13
2	136.9	-----	7.26, 2.91
3	134.5	-----	1.68, 1.67, 1.50, 1.48
4	134.5	-----	1.68, 1.67, 1.50, 1.48
5	130.0	7.25	2.91
6	129.9	7.20	7.21, 2.91
7	128.4	7.18	7.25
8	128.2	7.26	7.25
9	126.5	7.21	7.20, 7.18
10	119.1	5.00	2.28, 2.13, 1.68, 1.50
11	118.1	4.89	2.47, 2.09, 1.67, 1.48
12	108.9	-----	3.67, 2.38, 2.16
13	79.4	-----	2.91, 1.66
14	55.4	3.67	-----
15	53.1	-----	1.13
16	51.7	-----	2.60, 2.28, 2.13
17	50.1	2.38	1.13, 1.11
18	45.6	(a)1.69, (b)1.11	2.91
19	45.1	(a)1.66, (b)1.20	2.91, 2.60, 2.28
20	42.8	(a)2.60, (b)2.16	2.13, 1.20
21	42.5	2.91	1.66
22	35.8	2.28, 2.13	2.60
23	30.7	2.47, 2.09	1.11
24	26.0	1.68	1.50, 1.48
25	26.0	1.67	1.50, 1.48
26	17.9	1.48	1.68, 1.67
27	17.9	1.50	1.68, 1.67
28	13.8	1.13	2.38

Table A3.5 2D-NMR Data for **3.75**

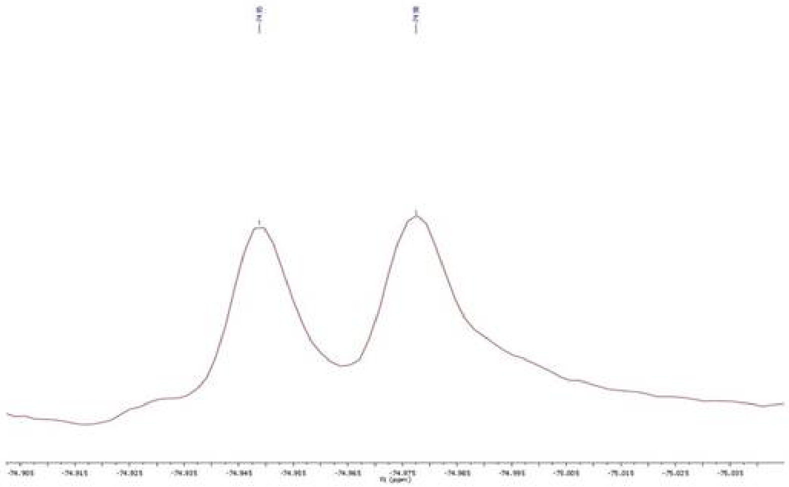


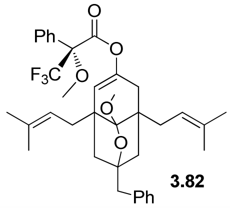


3.82



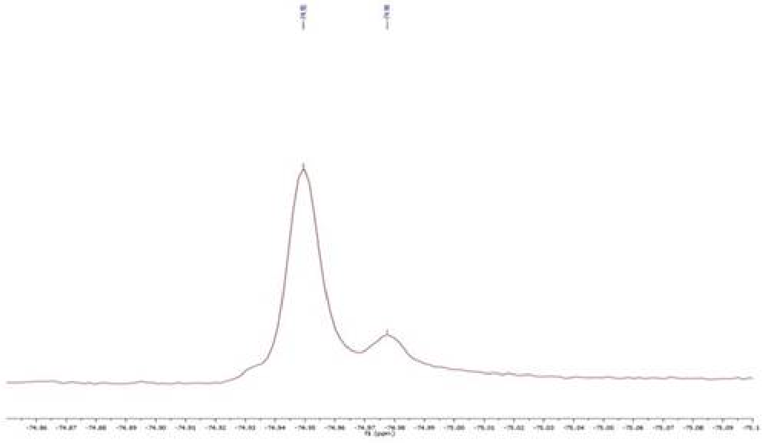
LHMDS Product Ratio



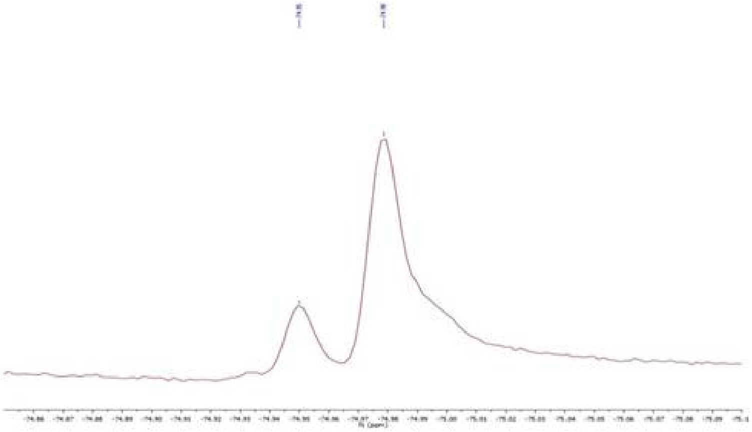


3.82

Bis [(R)-1-phenylethyl]amine Best Product Ratio



Bis [(S)-1-phenylethyl]amine Best Product Ratio



A3.3 DFT Calculations for Chapter 3

Coordinates and calculated energies

DFT calculations were performed with the program Gaussian03[1] by using the WebMO interface (WebMO, version 9.1.002p; www.webmo.net) for importing and constructing models. Transition states were verified by following the reaction coordinate forward and reverse (IRC).

[1] Gaussian 03, Revision E.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, and J. A. Pople, Gaussian, Inc., Wallingford CT, 2004.

Structure	Method	Basis Set	Coorected Energy (hartree)	Corrected Energy (kcal/mol)	Relative Energy (kcal/mol)	Frequency (cm^{-1})
3.76	UB3LYP	6-31G(d)	-3418.68	-2153769	0	
3.78	UB3LYP	6-31G(d)	-3418.67	-2153765	3.6	-376.28
3.79	UB3LYP	6-31G(d)	-3418.72	-2153791	-22.1	
3.78b	UB3LYP	6-31G(d)	-3418.67	-2153762	6.3	-315.96
3.79b	UB3LYP	6-31G(d)	-3418.71	-2153790	-21.6	
3.77	UB3LYP	6-31G(d)	-3688.94	-2324032	0	
3.80	UB3LYP	6-31G(d)	-3688.94	-2324029	2.7	-267.35
3.81	UB3LYP	6-31G(d)	-3688.98	-2324057	-25.0	
3.80b	UB3LYP	6-31G(d)	-3688.93	-2324028	4.1	-313.73
3.81b	UB3LYP	6-31G(d)	-3688.97	-2324054	-21.7	

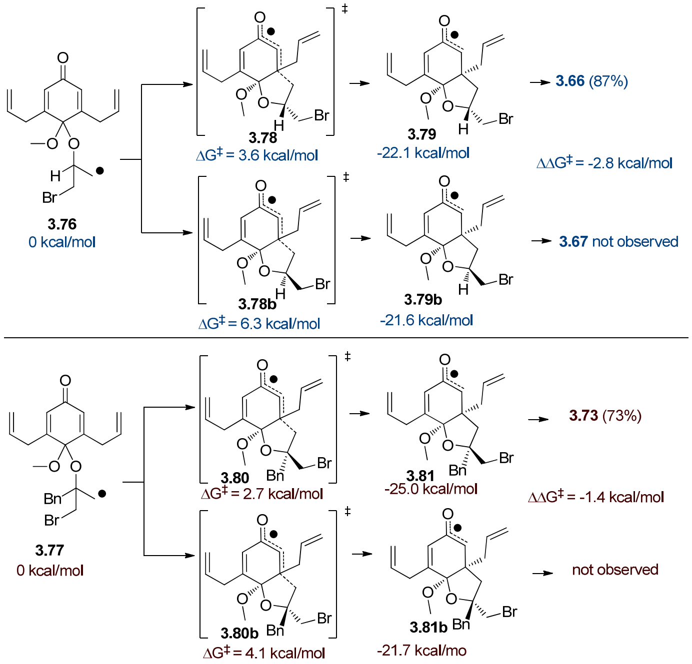
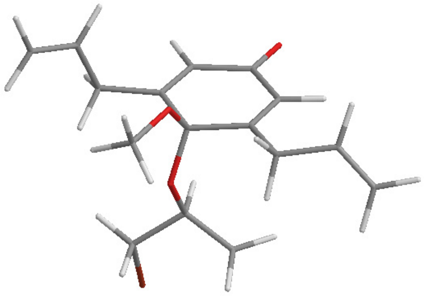


Table A3.6 Calculated Energies For Cyclization

3.76



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C	-0.63759200	-1.34408100	0.37255100
C	-0.79721100	-1.70603500	1.65568700
C	-0.45514800	-0.81875000	2.78492700
C	0.05763400	0.52623000	2.44586900
C	0.25225900	0.93849600	1.18253300
C	0.73175400	2.34538000	0.88207400
C	-0.37496900	3.31587700	0.52283300
C	-0.27863500	4.26258100	-0.41034900
H	-1.08796000	4.96350200	-0.59503200
H	0.61437100	4.38028500	-1.02138200
H	-1.28384400	3.23361700	1.11788300
H	1.47938000	2.33392600	0.08072000
H	1.23858300	2.71711300	1.78369000
H	0.25579300	1.17803700	3.29411800
O	-0.60596500	-1.16980900	3.95121900
H	-1.21204600	-2.67271100	1.92643200
C	-1.04458800	-2.20850900	-0.80288200
C	-1.80801100	-3.45505300	-0.45055100
C	-1.40877500	-4.69601900	-0.73030000
H	-2.01179500	-5.56245600	-0.47285900
H	-0.46470200	-4.89395600	-1.23439100
H	-2.76208300	-3.30361000	0.05533200
H	-1.65650100	-1.57639700	-1.46178300
H	-0.14752000	-2.46439300	-1.38217200
O	-0.89248000	0.64131600	-0.89524100
C	-0.42794300	1.10543300	-2.16326700
H	-1.30499900	1.56580600	-2.62348200
H	0.35956100	1.85911700	-2.07145700
H	-0.07040200	0.28483600	-2.79278500
O	1.23090800	-0.22898000	-0.70451800
C	2.32651500	-0.89326200	0.00303700
C	2.41211900	-2.33318900	-0.36716600
H	2.85102300	-2.62450900	-1.31654000
H	1.95964900	-3.09812700	0.25241400
C	3.55839500	-0.09317600	-0.41686600
Br	5.17238300	-0.79138200	0.47830500
H	3.47626400	0.95292900	-0.12705500
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3.78

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C	1.72037600	-1.78107600	-2.38331000
C	2.73690300	-2.25917100	-3.10135500
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H	1.00372100	-2.46150700	-1.92908100
H	0.54920800	0.00748500	-2.61994300
H	2.29158900	0.26419000	-2.59079200
H	3.50216200	-0.24376500	-0.30712800
O	3.50996800	-0.08407300	2.28078400
H	1.14006200	0.02383400	3.32105400
C	-1.37680600	0.03355800	2.16712000
C	-1.40075100	-0.19589100	3.65332600
C	-1.85718500	0.68197700	4.54690300
H	-1.87247800	0.45995300	5.61054500
H	-2.23811800	1.65644000	4.24748200
H	-1.02520700	-1.16099800	3.99512400
H	-1.97973700	-0.74096800	1.67098400
H	-1.86295700	0.98758500	1.92202000
O	-0.64950200	-1.18968100	-0.42762500
C	-1.83753800	-1.09722700	-1.21904400
H	-2.16468800	-2.13196000	-1.34566200
H	-2.62158800	-0.52121100	-0.71952900
H	-1.64867000	-0.65595200	-2.20376900
O	-0.77087400	1.10771600	-0.45891700
C	-0.10591700	2.35451200	-0.22577400
C	-1.02681900	3.44661300	-0.75375700
Br	-2.73507700	3.50042700	0.25257500
H	-0.58059000	4.43284100	-0.63398800
H	-1.29694600	3.27143500	-1.79514800
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H	1.22607200	2.34417400	-2.00699100
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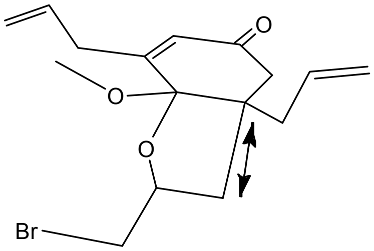

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C	-1.16580300	-1.76958600	1.40551600
C	-0.66731300	-1.42254700	0.03721900
C	-1.82952200	-1.62361000	-0.99217300
C	-3.01621500	-0.71644700	-0.81080300
C	-4.23670600	-1.12644100	-0.46394200
H	-5.06466800	-0.43078100	-0.35772500
H	-4.45782800	-2.17485400	-0.27236700
H	-2.83520900	0.34104800	-0.99527900
H	-1.40333400	-1.47177700	-1.98964500
H	-2.15159500	-2.67041000	-0.92318200
C	0.54941600	-2.30813900	-0.33230900
C	1.70118000	-1.60489300	0.39040100
O	1.36545800	-0.20722000	0.34597800
C	3.05513400	-1.83701700	-0.24953500
Br	4.51064000	-0.96710800	0.76341700
H	3.30128600	-2.89943000	-0.26793600
H	3.10100000	-1.42089600	-1.25580200
H	1.74300700	-1.91550200	1.44284400
H	0.70476200	-2.28969100	-1.41790100
H	0.42741900	-3.34926900	-0.01913500
H	-1.38324400	-2.81037100	1.63599200
O	-2.02599100	-1.12970200	3.48740600
H	-1.61473900	1.33803400	2.80320000
C	-0.28477700	2.49405800	0.75962200
C	1.13543900	2.91096000	1.08444500
C	1.85888200	3.76885500	0.36429600
H	2.85876500	4.06507900	0.66917200
H	1.47779000	4.21481500	-0.55265200
H	1.55348100	2.48776200	1.99691500
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H	0.64452600	1.49548100	-2.89174800
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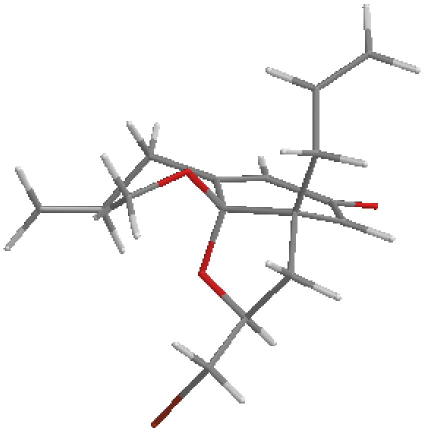

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C	1.39314800	-0.11740700	-2.15386100
C	2.73330200	-0.38904800	-2.77971400
C	3.34935900	0.42288800	-3.63916100
H	4.30813400	0.16665000	-4.08177900
H	2.91464600	1.37479500	-3.93814400
H	3.20525300	-1.33285200	-2.50444700
H	0.68773400	-0.90977100	-2.43982200
H	0.97061100	0.81606400	-2.54790100
H	3.49134700	0.07890400	-0.37138200
O	3.53424600	0.21447100	2.22420100
H	1.22216600	-0.06993100	3.30432300
C	-1.28133700	-0.49045600	2.22957900
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C	-2.15812900	0.25360100	4.46375000
H	-2.14137100	0.23041600	5.54980900
H	-2.92998400	0.86899300	4.00458300
H	-0.54901100	-1.06305600	4.24278700
H	-1.40641600	-1.53185900	1.89941000
H	-2.15840700	0.04477600	1.85337400
O	-0.68583000	-1.17263800	-0.44686900
C	-2.00626600	-1.04609700	-0.97535800
H	-2.21193900	-2.00133200	-1.46446700
H	-2.75445100	-0.89005700	-0.18625800
H	-2.08205100	-0.23243700	-1.70047100
O	-0.57799600	1.17442200	-0.56239100
C	-1.31351000	2.05882800	0.29329000
C	-1.53418600	3.33141000	-0.51953700
Br	-2.62479600	2.97769500	-2.13983700
H	-2.08654800	4.07531800	0.05277000
H	-0.58952700	3.74070100	-0.87623300
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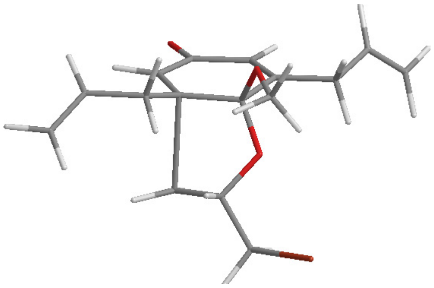

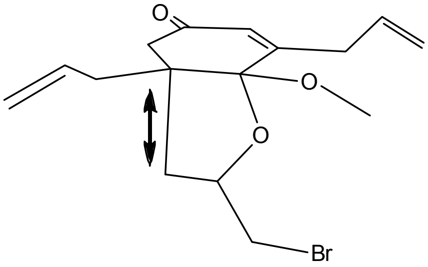

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C	-1.94498400	-1.53925500	-0.90065800
C	-3.07961400	-0.90282800	-0.14544700
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H	-4.91107300	-1.06002700	0.90595600
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H	-3.03783700	0.18122900	-0.05296900
H	-1.84642400	-1.05939400	-1.88033200
H	-2.16419100	-2.60118900	-1.06956500
C	0.55200300	-2.01960800	-1.15979400
C	1.84319100	-1.29035300	-0.73533700
O	1.41261800	-0.12329300	-0.01280100
C	2.73717900	-2.13781500	0.15704600
Br	4.37687300	-1.16929700	0.67874100
H	2.23821500	-2.40694800	1.08837400
H	3.07650600	-3.03363800	-0.36455700
H	2.42236900	-0.96105900	-1.60594200
H	0.30578400	-1.77075700	-2.19674700
H	0.63659600	-3.10893100	-1.09036300
H	-0.64120300	-3.29901900	1.04647400
O	-0.86427000	-2.26001500	3.39982700
H	-0.91821900	0.33534100	3.35768100
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C	1.11030400	2.70300900	1.59314800
C	1.54203200	3.83330000	1.03256600
H	2.55291700	4.19755500	1.19359700
H	0.90039600	4.44306600	0.39882300
H	1.78424200	2.12051200	2.22008200
H	-0.85636300	2.43509500	2.37397400
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H	-0.15876700	2.22379100	-2.45754800
H	1.04467300	2.23500800	-1.13508800
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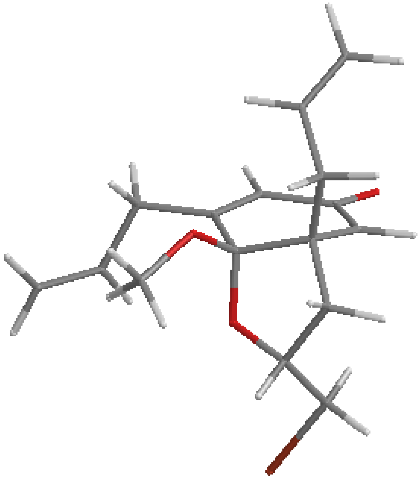

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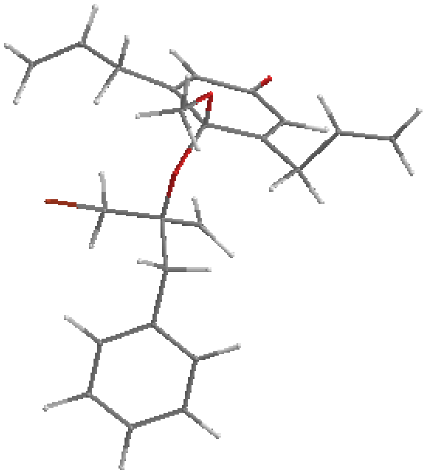

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C	-0.20178000	2.55106300	0.29458600
C	-0.29140800	3.71150300	1.25009000
C	0.72112700	4.54252300	1.50438100
H	0.61460500	5.37917200	2.18982900
H	1.69219300	4.41514200	1.02959100
H	-1.25272500	3.87532200	1.73720900
H	0.75637600	2.58560200	-0.23219800
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H	-1.18468100	1.78360600	2.78010100
O	-1.72622900	-0.54388400	3.75309300
H	-1.29232500	-2.49975600	2.09962300
C	-0.14389800	-2.55532200	-0.38871500
C	-1.41470800	-3.02852000	-1.05596200
C	-1.89476700	-4.26896700	-0.96874900
H	-2.81414900	-4.56036600	-1.46936400
H	-1.38737100	-5.04322300	-0.39616700
H	-1.94876100	-2.27243900	-1.62827300
H	0.29442100	-3.38377500	0.18059100
H	0.58856600	-2.26202800	-1.14961000
O	-0.73655200	0.14180700	-1.21827700
C	-0.05367700	0.48040800	-2.42968800
H	-0.85365700	0.68286200	-3.14635700
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H	0.56107600	-0.34782900	-2.79815800
O	1.37750000	0.04667100	-0.36947900
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C	2.19536500	-0.89894500	1.78824000
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H	2.48094300	-1.93901100	1.88641100
C	3.01312500	1.24867500	0.99973400
Br	3.46122400	2.46325100	-0.50719200
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H	3.93335300	1.15504900	1.57430200
C	3.53899600	-0.88174100	-0.34735600
C	4.87928900	-1.19595800	0.28735100
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C	6.36021200	-2.76893000	1.41502900
C	7.37250600	-1.80930500	1.45335300
C	7.14399700	-0.54714900	0.90250400
C	5.91119600	-0.24447900	0.32313700
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H	7.92960500	0.20385600	0.91584300
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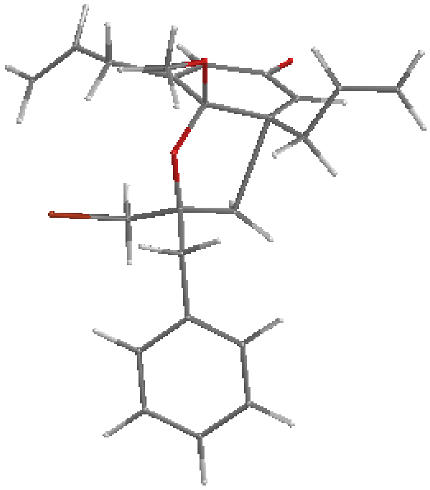

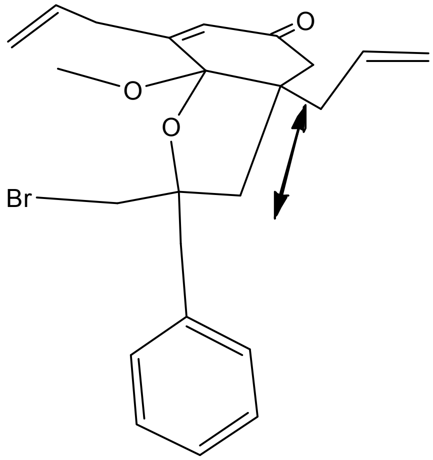

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H	3.67287200	-2.23626800	-3.93863000
H	1.86481600	-2.52774600	-3.64958400
H	3.56656400	-0.17080700	-2.64314800
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H	1.22901400	0.77799700	-2.47229000
H	3.44535600	-0.60066600	-0.31033700
O	3.50006100	-0.37001100	2.25860200
H	1.18169500	0.15371300	3.30958700
C	-1.30177700	0.42704800	2.20958300
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O	-0.40694700	1.32035700	-0.36460800
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H	-1.48942300	2.58354900	-1.48483600
H	-1.14666800	1.04409700	-2.31906800
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O	-0.97529700	-0.89406500	-0.52230100
C	-1.05995700	-2.25146400	0.00278200
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Br	-1.00007600	-3.14539200	-2.81357800
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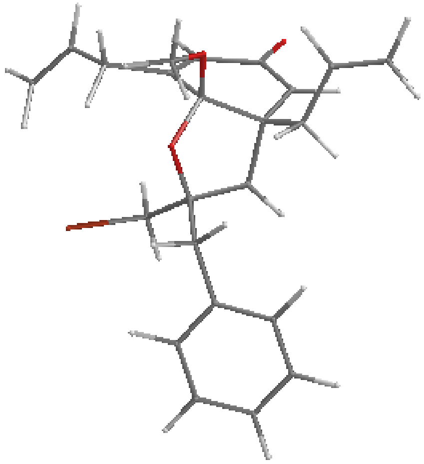

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C	0.69887900	-1.09135400	0.81884100
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3.80b

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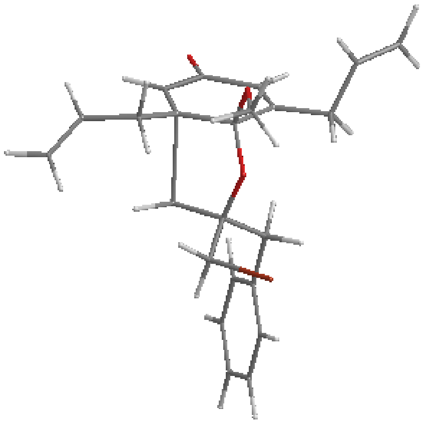

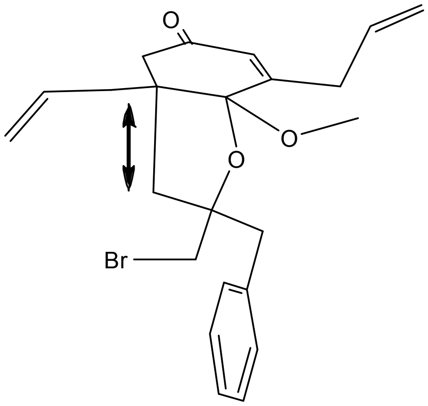

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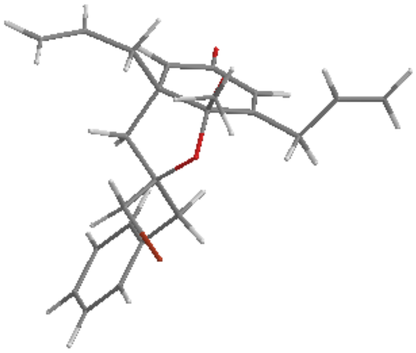


APPENDIX 4

A4.1 A Graphical Journey of Organic Architectures That Have Improved Our Lives

Just like there is a great need for advancing the frontiers of the field of chemistry, chemists are often faced with the equally important task of finding new and more effective ways to both communicate the results of their research activities and justify why investing in chemistry is important for society. Although classically inspired by the architectures of natural products in many of our chemical development endeavors we have become equally inspired and intrigued by the diverse pharmaceutical structural space.[1] We decided to graphically capture this wealth of information on single page (posters),[2] which in turn would allow anyone to easily visually mine it for a wealth of interesting information, statistics, structural patterns, etc. The fruits of our labor can now be found at the following web address, where high resolution PDF files of each of the posters can now be downloaded and printed in any size: http://www.chem.cornell.edu/jn96/outreach.html. In addition to the electronic form, a graphical representation of one of the drug posters can be found in A4.2.

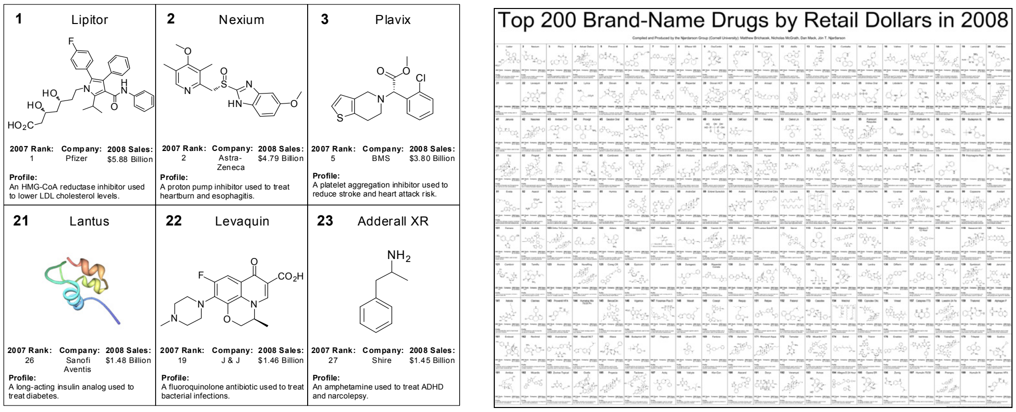


Figure A4.1. Graphical Representation of the 2008 Top Selling Drugs

We and others (in academia and industry) have learned over the last few years that hanging large printed versions of the posters in public spaces results in a magnetic effect, wherein people tend to be attracted by the visual language of organic chemistry.[3] The posters can also serve as useful tools for educating the public, teaching both undergraduate and graduate students, and serving as a spring board of ideas for researchers interested in the development of new synthetic methods and strategies. The following questions are examples of the wealth of information that can be gathered about the organic architectures used for pharmaceuticals simply by looking at the structures shown on these posters, and without reading a book![4]

Sample Questions:

1. How many of the top 20 brand name drugs contain:
a) an aromatic ring? **b)** a heterocycle? **c)** a fused ring system?

2. Which of the top 20 brand name drugs:
a) promote cardiovascular health? **b)** affect neurotransmitters?
c) suppress immune system activity? **d)** decrease stomach acid production?

3. In addition to carbon, hydrogen, oxygen, and nitrogen what are the three most commonly used elements found in brand name drugs?

4. Identify at least one brand name drug that contains:
a) an adamantane **b)** an alkyne **c)** an azide
d) a nitrile **e)** a cyclopropane **f)** no rings

5. Locate a brand name drug that is clearly derived from:
a) a steroid **b)** an alkaloid **c)** a nucleoside

6. Randomly choose 3 generic drugs and assign the hybridization of each carbon atom. Is there a trend in the relative number of sp, sp^2, and sp^3 hybridized carbons found in generic drugs?

7. Five and six membered rings are most frequently used for pharmaceutical structures. In general, are small rings (3-4) or large rings (7+) more common in the generic drugs?

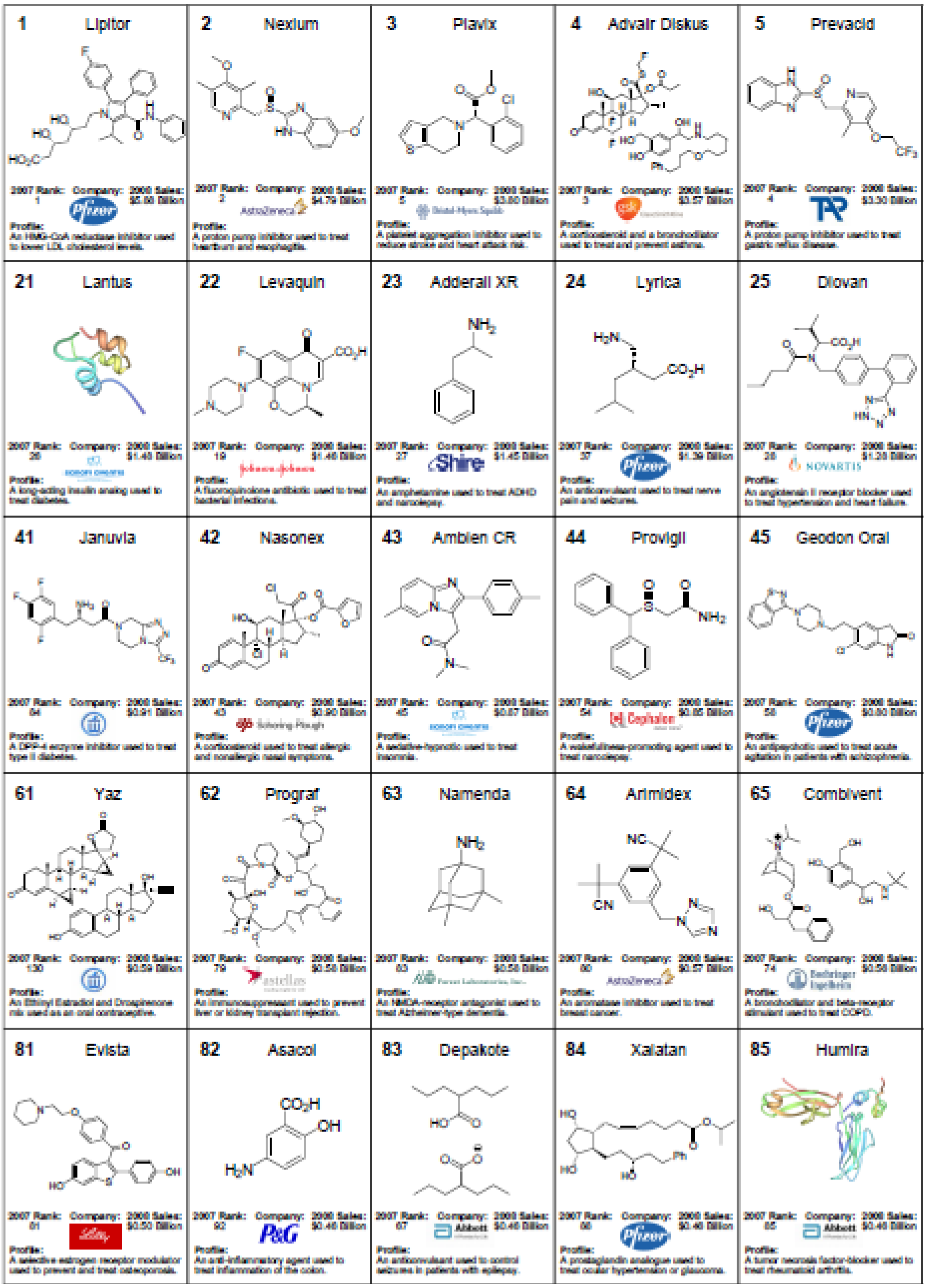
8. Randomly choose 3 generic drugs and identify all the asymmetric carbon atoms.

9. Are there more macromolecules (biologics or polymers) present in the brand name or generic drug poster?

10. Comparing the brand name and generic drug posters, which has a greater number of drugs with more than one active ingredient (combination therapies)?

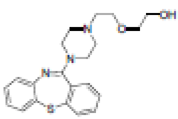
Visually exploring the drug posters either on your own or by answering the above questions leads to a greater understanding of the organic architectures that affect our everyday life. Displaying this information in the form of an interactive website that enables simple mining of the data would serve as a nice supplement to this manuscript and will be explored in the future.

A4.2 Top Selling Brand Name Drugs in 2008



		2007 Rank:	Company:	2008 Sales:	Profile:
1	Lipitor	1	Pfizer	$5.88 Billion	An HMG-CoA reductase inhibitor used to lower LDL cholesterol levels.
2	Nexium	2	AstraZeneca	$4.79 Billion	A proton pump inhibitor used to treat heartburn and esophagitis.
3	Plavix	5	Bristol-Myers Squibb	$3.80 Billion	A platelet aggregation inhibitor used to reduce stroke and heart attack risk.
4	Advair Diskus	3	gsk	$3.57 Billion	A corticosteroid and a bronchodilator used to treat and prevent asthma.
5	Prevacid	4	TAP	$3.30 Billion	A proton pump inhibitor used to treat gastric reflux disease.
21	Lantus	26	sanofi aventis	$1.45 Billion	A long-acting insulin analog used to treat diabetes.
22	Levaquin	19	Johnson & Johnson	$1.46 Billion	A fluoroquinolone antibiotic used to treat bacterial infections.
23	Adderall XR	27	Shire	$1.45 Billion	An amphetamine used to treat ADHD and narcolepsy.
24	Lyrica	37	Pfizer	$1.39 Billion	An anticonvulsant used to treat nerve pain and seizures.
25	Diovan	28	NOVARTIS	$1.28 Billion	An angiotensin II receptor blocker used to treat hypertension and heart failure.
41	Januvia	64		$0.91 Billion	A DPP-4 enzyme inhibitor used to treat type II diabetes.
42	Nasonex	43	Schering-Plough	$0.90 Billion	A corticosteroid used to treat allergic and nonallergic nasal symptoms.
43	Ambien CR	45	sanofi aventis	$0.87 Billion	A sedative-hypnotic used to treat insomnia.
44	Provigil	54	Cephalon	$0.85 Billion	A wakefulness-promoting agent used to treat narcolepsy.
45	Geodon Oral	58	Pfizer	$0.80 Billion	An antipsychotic used to treat acute agitation in patients with schizophrenia.
61	Yaz	130		$0.59 Billion	An Ethinyl Estradiol and Drospirenone mix used as an oral contraceptive.
62	Prograf	79	astellas	$0.58 Billion	An immunosuppressant used to prevent liver or kidney transplant rejection.
63	Namenda	63	Forest Laboratories, Inc.	$0.58 Billion	An NMDA-receptor antagonist used to treat Alzheimer-type dementia.
64	Arimidex	60	AstraZeneca	$0.57 Billion	An aromatase inhibitor used to treat breast cancer.
65	Combivent	74	Boehringer Ingelheim	$0.56 Billion	A bronchodilator and beta-receptor stimulant used to treat COPD.
81	Evista	61	Lilly	$0.50 Billion	A selective estrogen receptor modulator used to prevent and treat osteoporosis.
82	Asacol	92	P&G	$0.46 Billion	An anti-inflammatory agent used to treat inflammation of the colon.
83	Depakote	67	Abbott	$0.46 Billion	An anticonvulsant used to control seizures in patients with epilepsy.
84	Xalatan	68	Pfizer	$0.46 Billion	A prostaglandin analogue used to treat ocular hypertension or glaucoma.
85	Humira	85	Abbott	$0.46 Billion	A tumor necrosis factor-blocker used to treat rheumatoid arthritis.

6 Seroquel



2007 Rank: 7 | Company: AstraZeneca | 2008 Sales: $2.91 Billion

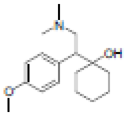
Profile:
An antipsychotic used to treat schizophrenia and bipolar mania.

7 Singulair

2007 Rank: 6 | Company: MERCK | 2008 Sales: $2.90 Billion

Profile:
A leukotriene receptor antagonist used to treat asthma and allergies.

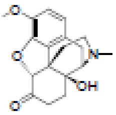
8 Effexor XR



2007 Rank: 8 | Company: Wyeth | 2008 Sales: $2.88 Billion

Profile:
A serotonin and norepinephrine reuptake inhibitor used to treat depression.

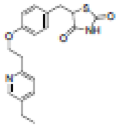
9 OxyContin



2007 Rank: 33 | Company: PURDUE | 2008 Sales: $2.50 Billion

Profile:
An opioid analgesic used to treat moderate to severe pain.

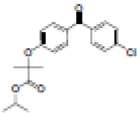
10 Actos



2007 Rank: 10 | Company: Lilly | 2008 Sales: $2.45 Billion

Profile:
A thiazolidinedione used to treat type 2 diabetes.

26 Tricor



2007 Rank: 30 | Company: Abbott | 2008 Sales: $1.25 Billion

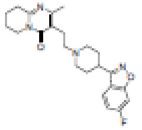
Profile:
A lipid-lowering agent used to treat high cholesterol and triglyceride levels.

27 Flomax

2007 Rank: 36 | Company: Abbott | 2008 Sales: $1.24 Billion

Profile:
An alpha blocker used to treat enlarged prostates.

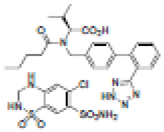
28 Risperdal



2007 Rank: 14 | Company: Johnson & Johnson | 2008 Sales: $1.22 Billion

Profile:
An antipsychotic used to treat schizophrenia and bipolar mania.

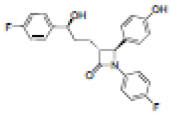
29 Diovan HCT



2007 Rank: 32 | Company: NOVARTIS | 2008 Sales: $1.21 Billion

Profile:
An angiotensin II receptor blocker and a diuretic used to treat hypertension.

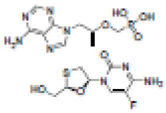
30 Zetia



2007 Rank: 21 | Company: Schering-Plough | 2008 Sales: $1.18 Billion

Profile:
An antihyperlipidemic agent used to lower cholesterol levels.

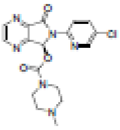
46 Truvada



2007 Rank: 62 | Company: GILEAD | 2008 Sales: $0.78 Billion

Profile:
Two reverse transcriptase inhibitors used to treat HIV.

47 Lunesta



2007 Rank: 55 | Company: SEPRACOR | 2008 Sales: $0.77 Billion

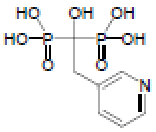
Profile:
A hypnotic agent used to treat insomnia.

48 Enbrel

2007 Rank: 46 | Company: AMGEN | 2008 Sales: $0.78 Billion

Profile:
A tumor necrosis factor inhibitor used to treat arthritis and psoriasis.

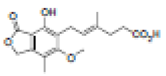
49 Actonel



2007 Rank: 50 | Company: P&G | 2008 Sales: $0.71 Billion

Profile:
A bisphosphonate used to treat and prevent osteoporosis.

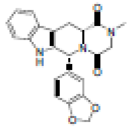
50 CellCept



2007 Rank: 63 | Company: Roche | 2008 Sales: $0.71 Billion

Profile:
An immunosuppressant used to prevent organ transplant rejection.

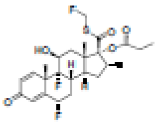
66 Cialis



2007 Rank: 66 | Company: Lilly | 2008 Sales: $0.58 Billion

Profile:
A phosphodiesterase inhibitor used to treat erectile dysfunction.

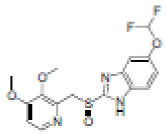
67 Flovent HFA



2007 Rank: 77 | Company: gsk | 2008 Sales: $0.55 Billion

Profile:
A corticosteroid used to prevent and to reduce the frequency of asthma attacks.

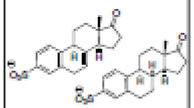
68 Protonix



2007 Rank: 11 | Company: Wyeth | 2008 Sales: $0.55 Billion

Profile:
A proton pump inhibitor used to treat esophagus inflammation and erosion.

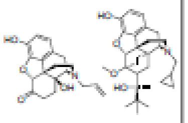
69 Premarin Tabs



2007 Rank: 68 | Company: Wyeth | 2008 Sales: $0.55 Billion

Profile:
Estrogen mixture used to treat breast cancer and menopausal symptoms.

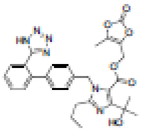
70 Suboxone



2007 Rank: 120 | Company: Reckitt Benckiser | 2008 Sales: $0.53 Billion

Profile:
An opioid agonist/antagonist and an anti-agonist used to treat opioid dependence.

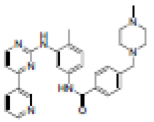
86 Benicar



2007 Rank: 102 | Company: Daiichi Sankyo / Forest Laboratories, Inc. | 2008 Sales: $0.48 Billion

Profile:
An angiotensin II receptor blocker used to treat hypertension.

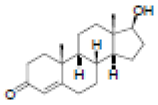
87 Gleevec



2007 Rank: 99 | Company: NOVARTIS | 2008 Sales: $0.45 Billion

Profile:
A protein-tyrosine kinase inhibitor used to treat chronic myeloid leukemia.

88 AndroGel



2007 Rank: 103 | Company: SOLVAY | 2008 Sales: $0.44 Billion

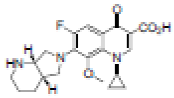
Profile:
A testosterone gel used to treat men with testosterone deficiencies.

89 Enbrel Sureclick

2007 Rank: 115 | Company: AMGEN | 2008 Sales: $0.43 Billion

Profile:
A tumor necrosis factor inhibitor used to treat arthritis and psoriasis.

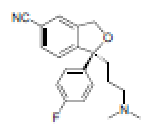
90 Avelox



2007 Rank: 90 | Company: Schering-Plough | 2008 Sales: $0.43 Billion

Profile:
A fluoroquinolone antibiotic used to treat bacterial infections.

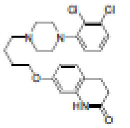
11 Lexapro



2007 Rank: 9 | Company: Forest Laboratories, Inc. | 2008 Sales: $2.41 Billion

Profile: A selective serotonin reuptake inhibitor used to treat depression and anxiety.

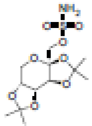
12 Abilify



2007 Rank: 15 | Company: | 2008 Sales: $2.37 Billion

Profile: An antipsychotic used to treat schizophrenia and bipolar mania.

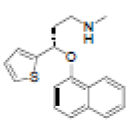
13 Topamax



2007 Rank: 13 | Company: Johnson & Johnson | 2008 Sales: $2.18 Billion

Profile: A carbonic anhydrase inhibitor used to treat seizures and prevent migraines.

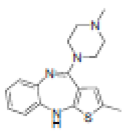
14 Cymbalta



2007 Rank: 18 | Company: Lilly | 2008 Sales: $2.17 Billion

Profile: A serotonin and norepinephrine reuptake inhibitor used to treat depression.

15 Zyprexa



2007 Rank: 10 | Company: Lilly | 2008 Sales: $1.75 Billion

Profile: A thienobenzodiazepine used to treat schizophrenia and bipolar mania.

31 Aricept

2007 Rank: 39 | Company: Eisai | 2008 Sales: $1.15 Billion

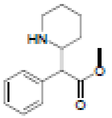
Profile: A cholinesterase inhibitor used to treat Alzheimer's disease.

32 Spiriva

2007 Rank: 47 | Company: Pfizer, Boehringer Ingelheim | 2008 Sales: $1.14 Billion

Profile: An anticholinergic agent used to treat chronic obstructive pulmonary disease.

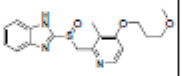
33 Concerta



2007 Rank: 34 | Company: Johnson & Johnson | 2008 Sales: $1.10 Billion

Profile: A central nervous system stimulant used to treat ADHD.

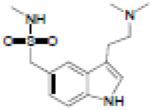
34 Aciphex



2007 Rank: 31 | Company: Eisai | 2008 Sales: $1.05 Billion

Profile: A proton pump inhibitor used to treat duodenal ulcers and acid reflux.

35 Imitrex Oral



2007 Rank: 40 | Company: GSK GlaxoSmithKline | 2008 Sales: $0.97 Billion

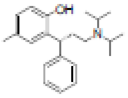
Profile: A serotonin receptor agonist used to treat migraines.

51 Humalog

2007 Rank: 65 | Company: Lilly | 2008 Sales: $0.70 Billion

Profile: A rapid acting insulin analog used to treat diabetes.

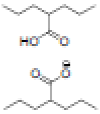
52 Detrol LA



2007 Rank: 60 | Company: Pfizer | 2008 Sales: $0.70 Billion

Profile: An antimuscarinic agent used to treat overactive bladders.

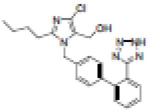
53 Depakote ER



2007 Rank: 66 | Company: Abbott | 2008 Sales: $0.69 Billion

Profile: An anticonvulsant used to control seizures in patients with epilepsy.

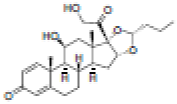
54 Cozaar



2007 Rank: 59 | Company: MERCK | 2008 Sales: $0.69 Billion

Profile: An angiotensin II receptor blocker used to treat hypertension.

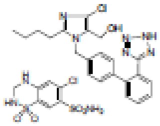
55 Pulmicort Respules



2007 Rank: 64 | Company: AstraZeneca | 2008 Sales: $0.65 Billion

Profile: An inhaled corticosteroid used to treat and prevent asthma.

71 Hyzaar



2007 Rank: 62 | Company: MERCK | 2008 Sales: $0.53 Billion

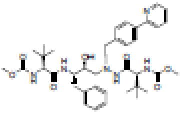
Profile: An angiotensin II receptor blocker and a diuretic used to treat hypertension.

72 ProAir HFA

2007 Rank: 91 | Company: TEVA | 2008 Sales: $0.53 Billion

Profile: Inhaler used to treat obstructive airway disease and prevent bronchiospasms .

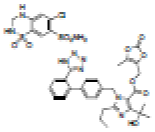
73 Reyataz



2007 Rank: 67 | Company: Bristol-Myers Squibb | 2008 Sales: $0.52 Billion

Profile: A protease inhibitor used to treat HIV.

74 Benicar HCT



2007 Rank: 80 | Company: Forest Laboratories, Inc. | 2008 Sales: $0.52 Billion

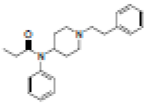
Profile: An angiotensin II receptor blocker and a diuretic used to treat hypertension.

75 Synthroid

2007 Rank: 69 | Company: Abbott | 2008 Sales: $0.51 Billion

Profile: A thyroid hormone used to treat hypothyroidism and to suppress goiters.

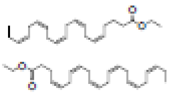
91 Fantanyl Oral Citra



2007 Rank: 94 | Company: | 2008 Sales: $0.42 Billion

Profile: An opioid analgesic used to manage breakthrough cancer pain.

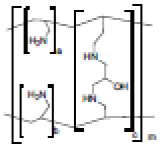
92 Lovaza



2007 Rank: 131 | Company: | 2008 Sales: $0.42 Billion

Profile: Ethyl esters from omega-3 fatty acids used to lower high triglyceride levels.

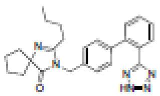
93 RenaGel



2007 Rank: 113 | Company: genzyme | 2008 Sales: $0.41 Billion

Profile: A phosphate binder used for patients with chronic kidney disease on dialysis.

94 Avapro



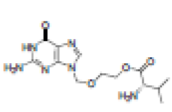
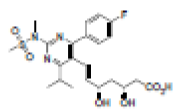
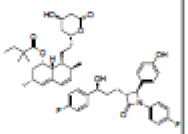
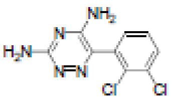
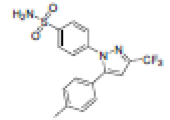
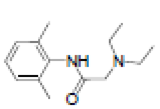
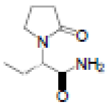
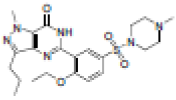
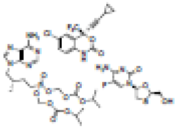
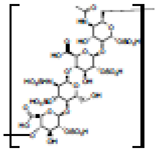
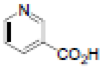
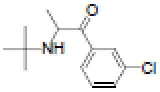
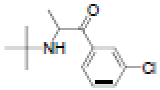
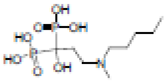
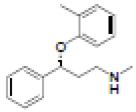
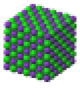
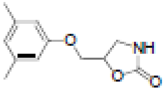
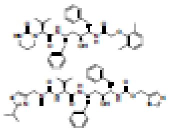
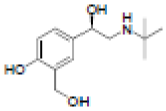
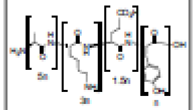
2007 Rank: 90 | Company: Bristol-Myers Squibb | 2008 Sales: $0.41 Billion

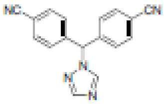
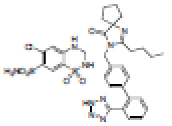
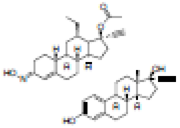
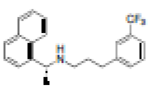
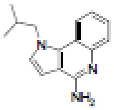
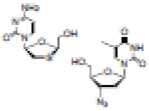
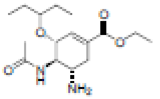
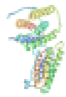
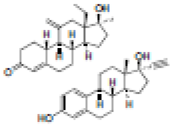
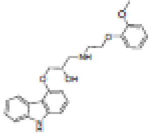
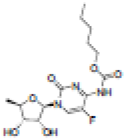
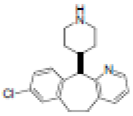
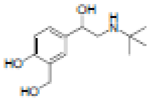
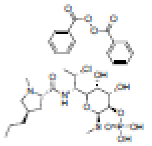
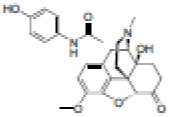
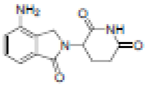
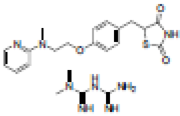
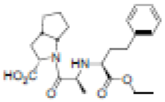
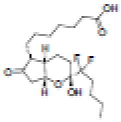
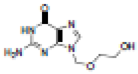
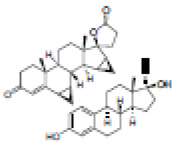
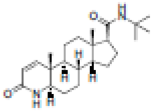
Profile: An angiotensin II receptor blocker used to treat hypertension.

95 Humira Pen

2007 Rank: 102 | Company: Abbott | 2008 Sales: $0.38 Billion

Profile: A tumor necrosis factor-blocker used to treat rheumatoid arthritis.

16 Valtrex  2007 Rank: 22 Company: gsk GlaxoSmithKline 2008 Sales: $1.68 Billion Profile: An antiviral agent for treating shingles, cold sores, and genital herpes.	**17** Crestor  2007 Rank: 23 Company: AstraZeneca 2008 Sales: $1.68 Billion Profile: An HMG-CoA reductase inhibitor used to lower LDL cholesterol levels.	**18** Vytorin  2007 Rank: 12 Company: MERCK 2008 Sales: $1.55 Billion Profile: A statin and a cholesterol absorption blocker used to treat high cholesterol.	**19** Lamictal  2007 Rank: 17 Company: gsk GlaxoSmithKline 2008 Sales: $1.54 Billion Profile: An anticonvulsant used to treat seizures and bipolar disorder.	**20** Celebrex  2007 Rank: 20 Company: Pfizer 2008 Sales: $1.53 Billion Profile: A COX-2 inhibitor NSAID used to treat arthritis pain.
36 Lidoderm  2007 Rank: 49 Company: ENDO PHARMACEUTICALS 2008 Sales: $0.97 Billion Profile: A local anesthetic used to relieve pain associated with shingles.	**37** Keppra  2007 Rank: 57 Company: ucb 2008 Sales: $0.94 Billion Profile: An anticonvulsant used to treat seizures in patients with epilepsy.	**38** Viagra  2007 Rank: 48 Company: Pfizer 2008 Sales: $0.92Billion Profile: A phosphodiesterase inhibitor used to treat erectile dysfunction.	**39** Atripla  2007 Rank: 61 Company: 2008 Sales: $0.92 Billion Profile: Efavirenz, Emtricitabine, and Tenofovir DF combination used to treat HIV.	**40** Lovenox  2007 Rank: 53 Company: sanofi aventis 2008 Sales: $0.91 Billion Profile: An antithrombotic used to prevent blood clots.
56 Niaspan  2007 Rank: 70 Company: KOS 2008 Sales: $0.64 Billion Profile: A vitamin used to lower LDL and raise HDL cholesterol levels.	**57** Wellbutrin XL  2007 Rank: 38 Company: gsk GlaxoSmithKline 2008 Sales: $0.61 Billion Profile: A norepinephrine and dopamine reuptake inhibitor that treats depression.	**58** Chantix  2007 Rank: 51 Company: Pfizer 2008 Sales: $0.61 Billion Profile: An oral tablet taken to aid in smoking cessation.	**59** Budeprion XL  2007 Rank: 72 Company: gsk GlaxoSmithKline 2008 Sales: $0.60 Billion Profile: A norepinephrine and dopamine reuptake inhibitor used to treat depression.	**60** Byetta  2007 Rank: 71 Company: Lilly 2008 Sales: $0.59 Billion Profile: An incretin mimetic used to treat type 2 diabetes.
76 Avandia  2007 Rank: 29 Company: gsk GlaxoSmithKline 2008 Sales: $0.51 Billion Profile: A thiazolidinedione used to treat type 2 diabetes.	**77** Boniva  2007 Rank: 96 Company: Roche 2008 Sales: $0.51 Billion Profile: A bisphosphonate used to treat and prevent osteoporosis.	**78** Strattera  2007 Rank: 73 Company: Lilly 2008 Sales: $0.51 Billion Profile: A selective norepinephrine reuptake inhibitor used to treat ADHD.	**79** Polymagma Plain  2007 Rank: N/A Company: Wyeth 2008 Sales: $0.51 Billion Profile: A fluid absorbent used to control diarrhea.	**80** Skelaxin  2007 Rank: 78 Company: King Pharmaceuticals 2008 Sales: $0.50 Billion Profile: A muscle relaxant used to treat musculoskeletal discomfort.
96 Vyvanse  2007 Rank: N/A Company: Shire 2008 Sales: $0.37 Billion Profile: A central nervous system stimulant for treatment of ADHD.	**97** Kaletra  2007 Rank: 100 Company: Abbott 2008 Sales: $0.37 Billion Profile: Two protease inhibitors used to treat HIV.	**98** Xopenex  2007 Rank: 104 Company: SEPRACOR 2008 Sales: $0.37 Billion Profile: A bronchodilator used to treat and prevent asthma attacks.	**99** Copaxone  2007 Rank: 112 Company: sanofi aventis 2008 Sales: $0.37 Billion Profile: A polypeptide mixture used to treat relapsing-remitting multiple sclerosis.	**100** Avodart  2007 Rank: 121 Company: gsk GlaxoSmithKline 2008 Sales: $0.36 Billion Profile: A 5-alpha-reductase inhibitor used to treat enlarged prostates.

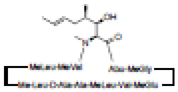
101 Femara  2007 Rank: 114 Company: NOVARTIS 2008 Sales: $0.36 Billion **Profile:** An aromatase inhibitor used to treat breast cancer.	**102** Avalide  2007 Rank: 107 Company: Bristol-Myers Squibb 2008 Sales: $0.36 Billion **Profile:** An angiotensin II receptor blocker and a diuretic used to treat hypertension.	**103** Ortho TriCyclen Lo  2007 Rank: 101 Company: Johnson & Johnson 2008 Sales: $0.35 Billion **Profile:** An estrogen and progestin combination used as birth control.	**104** Sensipar  2007 Rank: 127 Company: AMGEN 2008 Sales: $0.35 Billion **Profile:** A calcimimetic agent used to treat hyperparathyroidism in dialysis patients.	**105** Aldara  2007 Rank: 118 Company: 3M 2008 Sales: $0.35 Billion **Profile:** An immune response modifier used to treat skin cancer and genital warts.
121 Combivir  2007 Rank: 109 Company: gsk GlaxoSmithKline 2008 Sales: $0.28 Billion **Profile:** Two reverse transcriptase inhibitors used to treat HIV.	**122** Tamiflu  2007 Rank: N/A Company: Roche 2008 Sales: $0.28 Billion **Profile:** A viral neuraminidase inhibitor used to treat influenza types A and B.	**123** Avonex  2007 Rank: 126 Company: biogen idec 2008 Sales: $0.27 Billion **Profile:** An interferon used to treat relapsing forms of multiple sclerosis.	**124** NuvaRing  2007 Rank: 137 Company: Organon 2008 Sales: $0.27 Billion **Profile:** An estrogen and progestin combination used as birth control.	**125** Coreg CR  2007 Rank: 199 Company: 2008 Sales: $0.27 Billion **Profile:** A β-adrenergic blocking agent used to treat mild to severe heart failure.
141 Xeloda  2007 Rank: 150 Company: Roche 2008 Sales: $0.24 Billion **Profile:** An antimetabolite used to treat breast and colon cancers.	**142** Clarinex  2007 Rank: 117 Company: Schering-Plough 2008 Sales: $0.23 Billion **Profile:** An antihistamine used to treat the symptoms of allergies.	**143** Proventil HFA  2007 Rank: N/A Company: Schering-Plough 2008 Sales: $0.23 Billion **Profile:** A bronchodilator used to treat asthma and obstructive pulmonary disease	**144** Humalog Mix 75/25 Pn  2007 Rank: 153 Company: Lilly 2008 Sales: $0.23 Billion **Profile:** A mixture of insulin analogs used to treat diabetes.	**145** BenzaClin  2007 Rank: 147 Company: 2008 Sales: $0.23 Billion **Profile:** An antibiotic and a drying agent used to treat acne.
161 Endocet  2007 Rank: 159 Company: PURDUE 2008 Sales: $0.19 Billion **Profile:** A narcotic and an analgesic/antipyretic used to treat moderate pain.	**162** Revlimid  2007 Rank: N/A Company: Celgene 2008 Sales: $0.19 Billion **Profile:** An immunomodulatory compound to treat multiple myeloma.	**163** Avandamet  2007 Rank: 124 Company: gsk GlaxoSmithKline 2008 Sales: $0.19 Billion **Profile:** An insulin resistance reducer and a biguanide used to treat type 2 diabetes.	**164** Maxalt MLT  2007 Rank: 177 Company: MERCK 2008 Sales: $0.19 Billion **Profile:** A serotonin receptor agonist used to treat migraines.	**165** Altace  2007 Rank: 56 Company: King Pharmaceuticals 2008 Sales: $0.19 Billion **Profile:** An ACE inhibitor used to treat hypertension and heart disease.
181 Amitiza  2007 Rank: N/A Company: Takeda 2008 Sales: $0.17 Billion **Profile:** A chloride channel activator that is used to for chronic constipation.	**182** Micardis  2007 Rank: N/A Company: Boehringer Ingelheim 2008 Sales: $0.17 Billion **Profile:** An orally active angiotensin II antagonist used to treat hypertension.	**183** Zovirax Topical  2007 Rank: 186 Company: 2008 Sales: $0.16 Billion **Profile:** An antiviral used to treat the symptoms of herpes simplex virus infections.	**184** Ocella  2007 Rank: N/A Company: TEVA 2008 Sales: $0.16 Billion **Profile:** An ethinyl estradiol and drospirenone mix used as an oral contraceptive.	**185** Propecia  2007 Rank: N/A Company: MERCK 2008 Sales: $0.16 Billion **Profile:** An azasteroid used for the treatment of male pattern hair loss.

106 NovoLog Mix 70/30

2007 Rank:	Company:	2008 Sales:
116	novo nordisk	$0.35 Billion

Profile:
A mixture of insulin analogs used to treat diabetes.

107 Restasis



2007 Rank:	Company:	2008 Sales:
125	ALLERGAN	$0.34 Billion

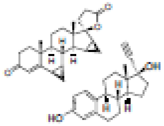
Profile:
An immunomodulator used to treat chronic dry eyes.

108 Mirapex

2007 Rank:	Company:	2008 Sales:
132	Boehringer Ingelheim	$0.34 Billion

Profile:
A dopamine agonist used to treat Parkinson's disease.

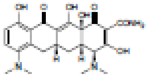
109 Yasmin 28



2007 Rank:	Company:	2008 Sales:
78		$0.33 Billion

Profile:
An estrogen and progestin combination used as birth control.

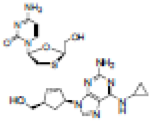
110 Solodyn



2007 Rank:	Company:	2008 Sales:
143		$0.32 Billion

Profile:
A semi synthetic tracycline derivative used to treat severe acne vulagris.

126 Epzicom



2007 Rank:	Company:	2008 Sales:
136	gsk GlaxoSmithKline	$0.27 Billion

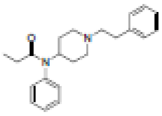
Profile:
Two reverse transcriptase inhibitors used to treat HIV.

127 Levemir

2007 Rank:	Company:	2008 Sales:
N/A	novo nordisk	$0.26 Billion

Profile:
A long-acting insulin analog used to treat diabetes.

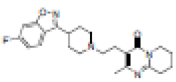
128 Duragesic



2007 Rank:	Company:	2008 Sales:
111	Johnson & Johnson	$0.25 Billion

Profile:
An opioid analgesic used to manage chronic pain.

129 Risperdal Consta



2007 Rank:	Company:	2008 Sales:
100	Johnson & Johnson	$0.25 Billion

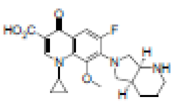
Profile:
An antipsychotic used to treat schizophrenia and bipolar mania.

130 Zyvox

2007 Rank:	Company:	2008 Sales:
135	Pfizer	$0.25 Billion

Profile:
An oxizolidinone antibiotic used to treat serious bacterial infections.

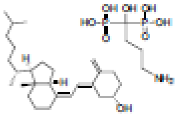
146 Vigamox



2007 Rank:	Company:	2008 Sales:
151	Alcon	$0.22 Billion

Profile:
A fluoroquinolone antibiotic used to treat eye infections.

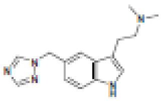
147 Foxamax Plus D



2007 Rank:	Company:	2008 Sales:
139	MERCK	$0.22 Billion

Profile:
A bisphosphonate and vitamin D used to treat and prevent osteoporosis.

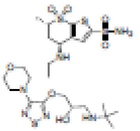
148 Maxalt



2007 Rank:	Company:	2008 Sales:
169	MERCK	$0.22 Billion

Profile:
A serotonin receptor agonist used to treat migraines.

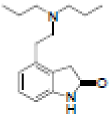
149 Cosopt



2007 Rank:	Company:	2008 Sales:
134	MERCK	$0.22 Billion

Profile:
A carbonic anhydrase inhibitor and a beta blocker used to treat glaucoma.

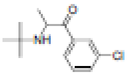
150 Requip



2007 Rank:	Company:	2008 Sales:
95	gsk GlaxoSmithKline	$0.21 Billion

Profile:
A dopamine agonist used to treat Parkinson's disease and RLS.

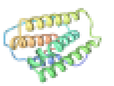
166 Budeprion SR



2007 Rank:	Company:	2008 Sales:
155	gsk GlaxoSmithKline	$0.19 Billion

Profile:
A norepinephrine and dopamine reuptake inhibitor used to treat depression.

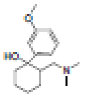
167 Pegasys



2007 Rank:	Company:	2008 Sales:
183	Roche	$0.19 Billion

Profile:
An interferon used to treat chronic hepatitis C infection.

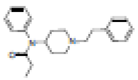
168 Ultram ER



2007 Rank:	Company:	2008 Sales:
184		$0.19 Billion

Profile:
An analgesic used to treat severe to moderate chronic pain.

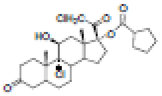
169 Fentora



2007 Rank:	Company:	2008 Sales:
194		$0.19 Billion

Profile:
An opeoid analgesic intended for opeoid tolerant cancer patients.

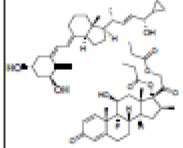
170 Asmanex



2007 Rank:	Company:	2008 Sales:
178		$0.19 Billion

Profile:
A corticosteroid inhaler used to treat asthma.

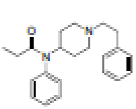
186 Taclonex



2007 Rank:	Company:	2008 Sales:
N/A	Warner Chilcott	$0.16 Billion

Profile:
Combination of a corticosteroid and a vitamin D analogue used for psoriasis.

187 Actiq



2007 Rank:	Company:	2008 Sales:
138	Cephalon	$0.16 Billion

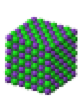
Profile:
An opioid analgesic used to manage continual breakthrough cancer pain.

188 Valcyte

2007 Rank:	Company:	2008 Sales:
N/A	Roche	$0.16 Billion

Profile:
An inhibitor viral DNA synthesis used to treat cytomegalovirus retinitis.

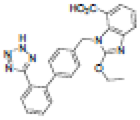
189 Klor-Con



2007 Rank:	Company:	2008 Sales:
182	UPSHER-SMITH	$0.16 Billion

Profile:
Potassium chloride used as potassium supplementation.

190 Atacand



2007 Rank:	Company:	2008 Sales:
179	AstraZeneca	$0.16 Billion

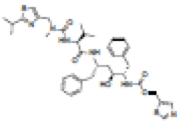
Profile:
An angiotensin II receptor blocker used to treat hypertension and heart failure.

111 Lantus SoloSTAR

2007 Rank: N/A
Company: sanofi aventis
2008 Sales: $0.32 Billion

Profile:
A long-acting insulin analog used to treat diabetes.

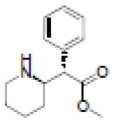
112 Norvir



2007 Rank: 123
Company: Abbott
2008 Sales: $0.31 Billion

Profile:
A protease inhibitor used to treat HIV.

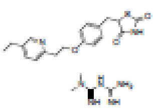
113 Focalin XR



2007 Rank: 133
Company: NOVARTIS
2008 Sales: $0.31 Billion

Profile:
A central nervous system stimulant used to treat ADHD.

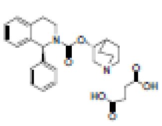
114 Actoplus Met



2007 Rank: 140
Company:
2008 Sales: $0.30 Billion

Profile:
Combination of two antihyperglycemics used to treat type II diabetes.

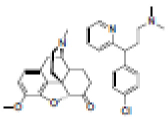
115 Vesicare



2007 Rank: 152
Company:
2008 Sales: $0.30 Billion

Profile:
A muscarinic receptor antagonist used to treat overactive bladder.

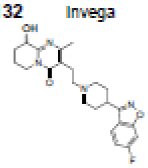
131 Tussionex



2007 Rank: 167
Company: ucb
2008 Sales: $0.25 Billion

Profile:
A cough-suppressant and antihistamine used to treat colds and allergies.

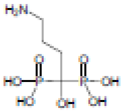
132 Invega



2007 Rank: N/A
Company: Johnson & Johnson
2008 Sales: $0.25 Billion

Profile:
An antipsychotic used to treat schizophrenia

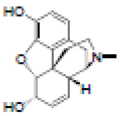
133 Fosamax



2007 Rank: 24
Company: MERCK
2008 Sales: $0.24 Billion

Profile:
A bisphosphonate used to treat Paget's disease and osteoporosis.

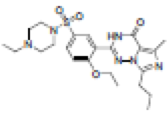
134 Kadian



2007 Rank: 163
Company: ALPHARMA
2008 Sales: $0.24 Billion

Profile:
An opiate analgesic used to treat moderate to severe pain.

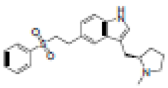
135 Levitra



2007 Rank: 158
Company:
2008 Sales: $0.24 Billion

Profile:
A phosphodiesterase inhibitor used to treat erectile dysfunction.

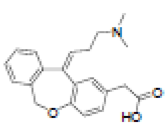
151 Relpax



2007 Rank: 148
Company: Pfizer
2008 Sales: $0.21 Billion

Profile:
A serotonin receptor agonist used to treat migraines.

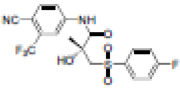
152 Patanol



2007 Rank: 129
Company: Alcon
2008 Sales: $0.21 Billion

Profile:
An antihistamine used to relieve watery, red, or itchy eyes caused by allergies.

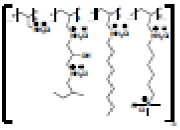
153 Casodex



2007 Rank: 150
Company: AstraZeneca
2008 Sales: $0.21 Billion

Profile:
A nonsteroidal antiandrogen used to treat prostate cancer.

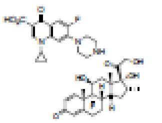
154 Welchol



2007 Rank: 176
Company:
2008 Sales: $0.21 Billion

Profile:
A non-absorbed polymeric LDL-C and glucose-lowering agent.

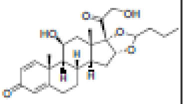
155 Ciprodex Otic



2007 Rank: 172
Company: Alcon
2008 Sales: $0.21 Billion

Profile:
An antibiotic and a corticosteroid used to treat ear infections.

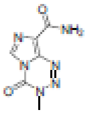
171 Rhinocort Aqua



2007 Rank: 142
Company: AstraZeneca
2008 Sales: $0.18 Billion

Profile:
A corticosteroid used to treat nasal allergy symptoms.

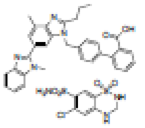
172 Temodar



2007 Rank: 173
Company: Schering-Plough
2008 Sales: $0.18 Billion

Profile:
An antineoplastic agent used to treat recurrent malignant brain tumors.

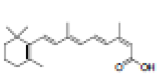
173 Micardis HCT



2007 Rank: 191
Company:
2008 Sales: $0.18 Billion

Profile:
An orally active angiotensin II antagonist used to treat hypertension.

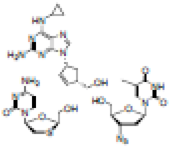
174 Sotret



2007 Rank: N/A
Company: RANBAXY
2008 Sales: $0.18 Billion

Profile:
A retinoid that inhibits sebaceous gland function used to treat nodular acne

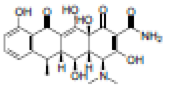
175 Trizivir



2007 Rank: 154
Company: gsk GlaxoSmithKline
2008 Sales: $0.18 Billion

Profile:
Three reverse transcriptase inhibitors used to treat HIV.

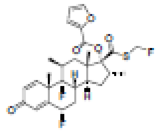
191 Doryx



2007 Rank: N/A
Company: Warner Chilcott
2008 Sales: $0.18 Billion

Profile:
A tetracycline broad-spectrum antibiotic used to treat a variety of infections.

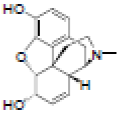
192 Veramyst



2007 Rank: N/A
Company: gsk GlaxoSmithKline
2008 Sales: $0.18 Billion

Profile:
An anti-inflammatory corticosteroid used to treat nasal symptoms and allergies.

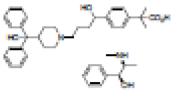
193 Avinza



2007 Rank: 197
Company: King Pharmaceuticals
2008 Sales: $0.18 Billion

Profile:
An opioid analgesic used to treat moderate to severe pain.

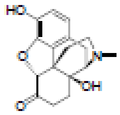
194 Allegra-D 24 Hour



2007 Rank: N/A
Company: sanofi aventis
2008 Sales: $0.18 Billion

Profile:
An antihistamine and a decongestant used to treat seasonal allergies.

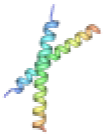
195 Opana ER



2007 Rank: N/A
Company:
2008 Sales: $0.18 Billion

Profile:
An opiate analgesic used to treat moderate to severe pain.

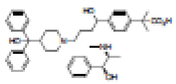
116 **Forteo**



2007 Rank: 119 Company: Lilly 2008 Sales: $0.29 Billion

Profile:
A synthetic parathyroid hormone used to treat osteoporosis.

117 **Allegra-D 12 Hour**



2007 Rank: 110 Company: sanofi aventis 2008 Sales: $0.29 Billion

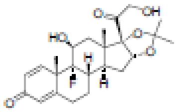
Profile:
An antihistamine and a decongestant used to treat seasonal allergies.

118 **Procrit**

2007 Rank: 105 Company: Johnson & Johnson 2008 Sales: $0.29 Billion

Profile:
A glycoprotein used to treat anemia in patients with kidney failure or cancer.

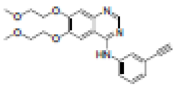
119 **Nasacort AQ**



2007 Rank: 108 Company: sanofi aventis 2008 Sales: $0.29 Billion

Profile:
An adrenocortical steroid used to treat nasal allergy symptoms.

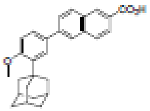
120 **Tarceva**



2007 Rank: 128 Company: Genentech 2008 Sales: $0.28 Billion

Profile:
A tyrosine kinase inhibitor used to treat lung cancer.

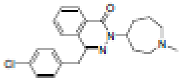
136 **Differin**



2007 Rank: 164 Company: GALDERMA 2008 Sales: $0.24 Billion

Profile:
A retinoid used to treat acne.

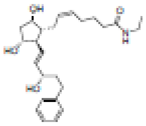
137 **Astelin**



2007 Rank: 146 Company: MedPointe 2008 Sales: $0.24 Billion

Profile:
An antihistamine used to treat nasal allergy symptoms.

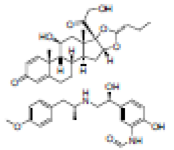
138 **Lumigan**



2007 Rank: 141 Company: ALLERGAN 2008 Sales: $0.24 Billion

Profile:
A prostaglandin analog used to treat glaucoma and ocular hypertension.

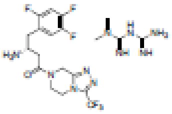
139 **Symbicort**



2007 Rank: N/A Company: AstraZeneca 2008 Sales: $0.24 Billion

Profile:
Combination of bronchodilator and anti-inflammatory used for asthma.

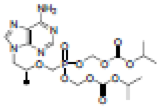
140 **Janumet**



2007 Rank: N/A Company: MERCK 2008 Sales: $0.24 Billion

Profile:
A combination of two complementary antihyperglycemic agents for diabetes.

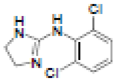
156 **Viread**



2007 Rank: 149 Company: GILEAD 2008 Sales: $0.21 Billion

Profile:
A reverse transcriptase inhibitor used to treat HIV.

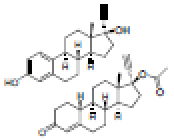
157 **Catapres-TTS**



2007 Rank: 165 Company: Boehringer Ingelheim 2008 Sales: $0.20 Billion

Profile:
An alpha agonist used to treat hypertension.

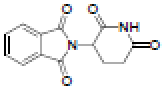
158 **Loestrin 24 Fe**



2007 Rank: N/A Company: Warner Chilcott 2008 Sales: $0.20 Billion

Profile:
An estrogen and progestin combination used as an oral contraceptive.

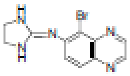
159 **Thalomid**



2007 Rank: 144 Company: Celgene 2008 Sales: $0.20 Billion

Profile:
An immunomodulator used to treat skin inflammation and multiple myeloma.

160 **Alphagan P**



2007 Rank: 160 Company: ALLERGAN 2008 Sales: $0.20 Billion

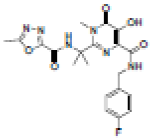
Profile:
An adrenergic agonist used to treat glaucoma and ocular hypertension.

176 **Enablex**

2007 Rank: 185 Company: 2008 Sales: $0.18 Billion

Profile:
A muscarinic receptor antagonist used to treat overactive bladder.

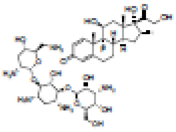
177 **Isentress**



2007 Rank: N/A Company: MERCK 2008 Sales: $0.18 Billion

Profile:
An antiviral that inhibits HIV-1 integrase used to treat HIV.

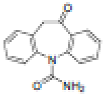
178 **TobraDex**



2007 Rank: 174 Company: Alcon 2008 Sales: $0.18 Billion

Profile:
An antibiotic and a glucocorticoid used to treat eye infections.

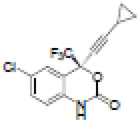
179 **Trileptal**



2007 Rank: 75 Company: NOVARTIS 2008 Sales: $0.17 Billion

Profile:
An anticonvulsant used to treat seizures in patients with epilepsy.

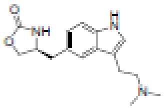
180 **Sustiva**



2007 Rank: 157 Company: Bristol-Myers Squibb 2008 Sales: $0.17 Billion

Profile:
A non-nucleoside reverse transcriptase inhibitor used to treat HIV.

196 **Zomig**



2007 Rank: N/A Company: AstraZeneca 2008 Sales: $0.15 Billion

Profile:
A serotonin receptor agonist used to treat migraines.

197 **Humulin 70/30**

2007 Rank: N/A Company: Lilly 2008 Sales: $0.15 Billion

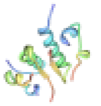
Profile:
An insulin analog used to treat diabetes.

198 **Prempro**

2007 Rank: 198 Company: Wyeth 2008 Sales: $0.15 Billion

Profile:
A combination of hormones used to treat menopausal symptoms.

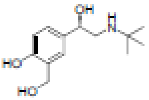
199 **Humulin N**



2007 Rank: 190 Company: Lilly 2008 Sales: $0.15 Billion

Profile:
An insulin analog used to treat diabetes.

200 **Xopenex HFA**



2007 Rank: N/A Company: SEPRACOR 2008 Sales: $0.15 Billion

Profile:
A bronchodilator used to treat and prevent asthma attacks.

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(2) McGrath, N. A.; Brichacek, M.; Njardarson, J. T. *J. Chem. Ed*. **2010**, *Accepted*

(3) Njardarson, J. T., The development of new synthetic methods. *Abstracts of Papers, 238th ACS National Meeting, Washington, DC, United States, August 16-20, 2009* **2009**, ORGN-220.

(4) Kleemann, A.; Engel, J.; *Pharmaceutical Substances: Synthesis, Patents, and Application*, 4th ed.; Thieme: Germany, 2001; p 2488.