APPLICATIONS OF Rh(I)-CATALYSIS TO NATURAL PRODUCT SYNTHESIS: ROUTES TO OVALICIN AND GUANACASTEPENE A

by

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B.A., Hamilton College, 2001

Submitted to the Graduate Faculty of

University of Pittsburgh in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2007

UNIVERSITY OF PITTSBURGH

FACULTY OF ARTS AND SCIENCES

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February 28th, 2007

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Dedicated to my grandmother, Magdalene McCabe, for always believing in me

I Love You, Gram, may you rest in peace

APPLICATIONS OF Rh(I)-CATALYSIS TO NATURAL PRODUCT SYNTHESIS: ROUTES TO OVALICIN AND GUANACASTEPENE A

Jamie Marie M^{c}Cabe, PhD

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Transition metal-catalyzed carbon-carbon bond formation is an efficient method to rapidly increase molecular complexity via skeletal reorganization and/or cycloaddition processes. The mild conditions, functional group compatibility, and high regio- and stereoselectivities of these transition metal-catalyzed reactions are just a few reasons for their prominence in natural product synthesis.

The first section describes a route to ovalicin via an allenic Alder-ene reaction using Rh(I)-catalysis. The scope of the novel allenic Alder-ene reaction using Rh(I) and Ir(I) catalysts has been extended to differentially substituted 1,1,3-trisubstituted allenes. The allenyl substitution pattern can give three possible cross-conjugated triene products. The selectivity of this transformation can be controlled by varying reaction temperature, solvent, catalyst and functional groups. Progress towards the synthesis of ovalicin using this triene forming protocol is described.

The second section describes a route to guanacastepene A via a Rh(I)-catalyzed allenic cyclocarbonylation reaction. Efficient synthetic reactions, readily available and inexpensive starting materials and practical and convenient conditions all contribute to the success of a synthesis of the carbocyclic core of guanacastepene A and are the primary focus of the first half

on this chapter. Upon the highly efficient formation of the carbocyclic core to guanacastepene A, our attention turned to the installation of an angular methyl group at C13. The routes evaluated to effect this transformation were a 1,4-conjugate addition, a reductive ring opening of a cyclopropyl ketone, and a radical cyclization of a bromo-silane moiety.

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PREFACE

I would like to thank my research advisor, Professor Kay M. Brummond, for her support and patience during my PhD studies. I greatly appreciated the freedom that she gave me in my research project along with her guidance when it was needed. In addition, I would like to thank all of the Brummond group members past and present for their friendship, helpfulness and many laughs.

I would also like to acknowledge Professors Curran, Floreancig, and Lazo for serving on my dissertation committee and Professor Wipf for helping me with my proposal. I would like to thank Drs. Fu-Tyan and Fu-Mei Lin, Schafmeister, and Damodaran for assistance with the high-field NMR spectroscopy, Dr. Kasi Somayajula for mass spectral analysis and Dr. Steven Geib for x-ray diffraction analysis.

I thank the University of Pittsburgh for financial support including the graduate excellent awards. Additional funding was provided by the National Institutes of Health, National Science Foundation and Johnson & Johnson. Lastly, Pfizer is acknowledged for providing a graduate fellowship award.

On a personal note I would like to thank Nilu Jayasuriya for her incredible support and friendship over the last 6 years. Nilu, I will especially miss your company during lunch, our conversation concerning the most recent reality TV show and stressing together. Good luck finishing up (don't stress) and I will see you soon!

A special thanks to my husband, Tom Dunn, for his patience and understanding while completing my PhD. The endless love and support you gave me this last year is indescribable and I can't wait to start our new life together.

Last but not least I would like to thank my parents, Terry and Cindy McCabe, my brother, Justin McCabe, and my sister/friend, Kate Whelley McCabe for their love and encouragement. I know my stress resonated in your lives and I couldn't have gotten through this without all your support. I am forever grateful. Although I will be far away you are close to my heart and always in my thoughts.

ABBREVIATIONS

acac	Acetylacetone
AIBN	2,2'-Azobis(2-methylpropionitrile)
APA	3-Aminopropylamine
BIAB	Bis(acetoxy)iodobenzene
BINAP	2,2’-Bis(diphenylphosphanyl)-1,1’-binaphthyl
BTAF	Benzyltrimethyl ammonium fluoride
CAMEO	Computer assisted mechanistic evaluation of organic reactions
COD	1,5-Cyclooctadiene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-en
DCE	Dichloroethane
DCM	Dichloromethane
DEAD	Diethylazodicarboxylate
DIAD	Diisopropylazodicarboxylate
DIBAL-H	Diisobutylaluminum hydride
DMAP	4-Dimethylaminopyridine
DMDO	Dimethoxyoxirane
DMF	Dimethylformamide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone

DMS	Dimethylsulfide
DMSO	Dimethylsulfoxide
dppb	Bis(diphenylphosphino)butane
DPS	Dimethylphenylsilane
GC	Gas Chromatography
HMPA	Hexamethylphosphoric triamide
HPLC	High Pressure Liquid Chromatography
IR	Infrared
KHMDS	Potassium hexamethyldisilazide
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamine
m-CPBA	*m*-Chloroperoxybenzoic acid
MetAP	Methionine amino peptidase
MRSA	Methicillin-resistant *Staphylococcus aureu*
NaHMDS	Sodium hexamethyldisilazide
NIS	N-Iodosucinimide
NMR	Nuclear Magnetic Resonance
nOe	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Enhancement Spectroscopy
PAA	*para*-anisaldehyde
PDC	Pyridinium dichlorochromate
PMB	*para*-Methoxy benzyl
PPTS	Pyridinium p-toluenesulfonate

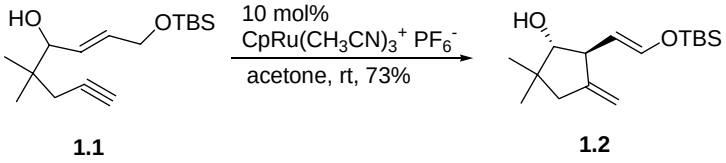
R_f	Retention Factor
ROESY	Rotating Frame Overhauser Enhancement Spectroscopy
SM	Starting Material
TBAF	Tetrabutylammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBDPSCl	*tert*-Butyldiphenylsilyl chloride
TBS	*tert*-Butyldimethylsilyl
TBSCl	*tert*-Butyldimethylsilyl chloride
TBSOTf	*tert*-Butyldiphenylsilyl trifluoromethanesulfonate
TEA	Triethylamine
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy, free radical
TESOTf	Triethylsilyl trifluoromethanesulfonate
THF	Tetrahydrofuran
THP	Tetrahydropyran
TIPS	Triisopropylsilyl
TLC	Thin Layer Chromatography
TMA	Trimethylaluminum
TMEDA	N,N,N',N'-Tetramethylethylenediamine
TMS	Trimethylsilyl
TMSCl	Trimethylsilyl chloride
TMSCN	Trimethylsilyl cyanide
TMSI	Trimethylsilyl iodide
TMSOTf	Trimethylsilyl trifluoromethanesulfonate

VREF	Vancomycin-resistance *Enterococcus faecalis*

1.0 CONSTITUTIONAL GROUP SELECTIVITY IN THE RHODIUM(I)-CATALYZED ALLENIC ALDER-ENE REACTION WITH PROGRESS TOWARDS OVALICIN

1.1 INTRODUCTION: TRANSITION METAL CATALYZED CYCLOISOMERIZATION REACTIONS

Transition metal catalyzed carbon-carbon bond formation is an efficient method to rapidly increase molecular complexity via skeletal reorganization and/or cycloaddition processes. [1] The mild conditions, functional group compatibility, and high regio- and stereoselectivities of these transition metal catalyzed reactions are just a few reasons for their prominence in natural product synthesis. Transition metal catalyzed cycloisomerizations such as the formal Alder-ene reaction utilizes functionalized enynes or allenynes to access a unique array of cyclic structures.[2]

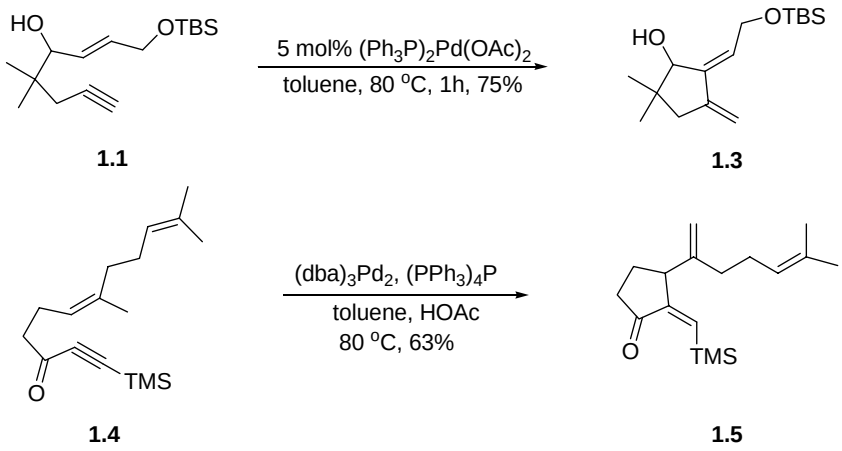


1.1 **1.2**

Scheme 1. Trost's Ru-catalyzed cycloisomerization reaction

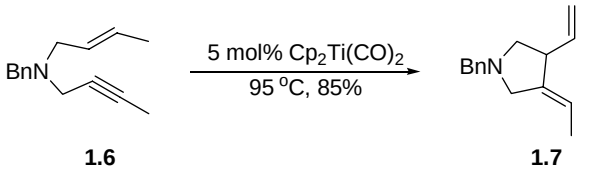
For example, Trost[3] has worked extensively on the intramolecular Alder-ene reaction of 1,6-enynes using palladium or ruthenium to obtain 1,3-dienes or 1,4-dienes. Subjection of enyne **1.1** to ruthenium gives exclusively the 1,4-diene **1.2** in high yields and under mild reaction

conditions (Scheme 1). On the other hand treatment with palladium gives regioisomeric ratios dependent on the substrate (Scheme 2). For example, enyne **1.1** when subjected to catalytic amounts of palladium gives the 1,3-diene **1.3** exclusively, while subjection of **1.4** to catalytic palladium gives the 1,4-diene **1.5** exclusively.[4]



Scheme 2. Trost's palladium catalyzed cycloisomerization reaction

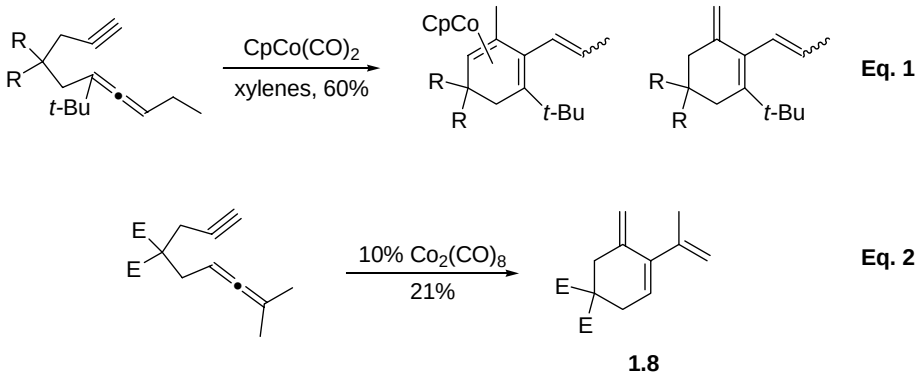
Also, Buchwald[5] formed a 1,4-diene **1.7** from enyne **1.6** regioselectivity using titanium; however, high temperatures and long reaction times (24-48 h) were necessary (Scheme 3).



Scheme 3: Buchwald's titanium catalyzed cycloisomerization reactions

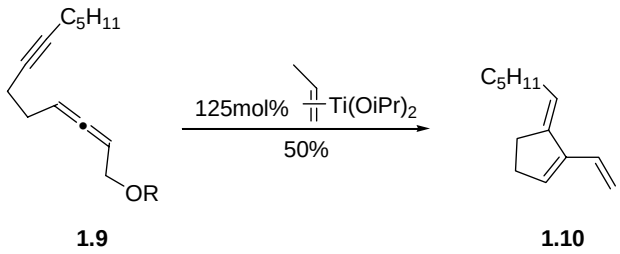
Changing the olefin to an allene gives an entirely different cycloisomerization product. The intramolecular Alder-ene reactions of allene-ynes are not as widely studied as their enyne counterparts and only a few examples are known. Malacria[6] and Livinghouse[7] both used cobalt to effect an intramolecular allenic Alder-ene reaction (Scheme 4, Eq 1 and 2, respectively).

Malacria used his cycloisomerization product in a synthesis of steroidal analogs,[8] while the triene **1.8** was obtained as a by-product in a 21% yield by Livinghouse.



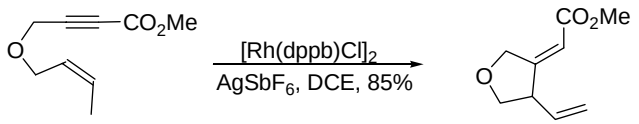
Scheme 4. Alder-ene reactions using cobalt catalysis

Sato[9] demonstrated an allenic Alder-ene reaction of enyne **1.9** that afforded triene **1.10** in a 50% yield using stoichiometric amounts of (η^2-propene)Ti(O-*i*-Pr)$_2$ (Scheme 5). Unfortunately, he notes that the 5-membered ring product **1.10** is unstable.



Scheme 5. Sato's titanium Alder-ene reaction

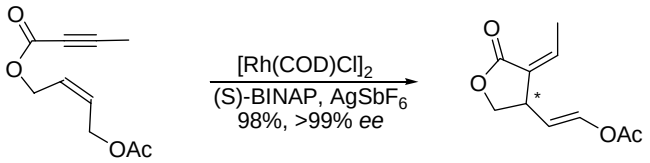
Recently, rhodium(I) has stepped into the limelight and proven itself as a useful and powerful transition metal catalyst for the Alder-ene reaction.[10] In 2000, Zhang demonstrated the first Rh(I)-catalyzed Alder-ene reaction with 1,6-enynes, yielding 1,4-dienes (Scheme 6).[11] Subjection of enyne **1.11** to [Rh(dppb)Cl]$_2$ and $AgSbF_6$ at room temperature gave a 85% yield of tetrahydrofuran **1.12**.



1.11 **1.12**

Scheme 6. Zhang's Rh(I)-catalyzed Alder-ene reaction

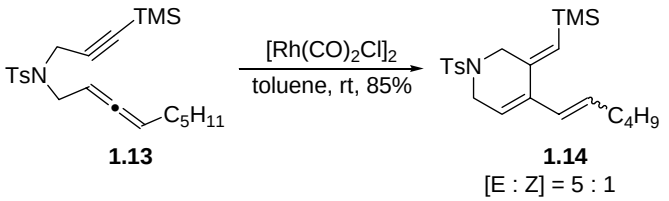
Rhodium was beneficial over ruthenium, cobalt, or titanium because the reactions could be performed at room temperature and the ligands on the catalyst could be easily tuned to accommodate steric or electronic factors in the enyne substrates. Furthermore, the use of a chiral ligand, (S)-BINAP, used in conjunction with $[Rh(COD)Cl]_2$ and $AgSbF_6$ at room temperature gave enantiomerically enriched products from achiral starting materials (Scheme 7).[12]



Scheme 7. Zhang's Alder-ene reaction to obtain enantiomerically enriched material

Due to our group's continued interest in developing new and useful transition metal catalyzed reactions using allenes,[13] subjection of $[Rh(CO)_2Cl]_2$ to allenyne **1.13** gave the cross conjugated triene **1.14** in good yield (Scheme 8).[14] This formal allenic Alder-ene reaction is unique from others because the reaction conditions are used to direct which double bond of the allene reacts. For example, Malacria's[8] and Sato's[9] report a reaction with the distal π-bond using cobalt and titanium, respectively; however, π-bond selectivity was obtained using substrate control. In Malacria's case a *t*-butyl group on the proximal double bond of the allene was essential for reaction to occur at the distal double bond of the allene (Scheme 4, Eq 1). Likewise, Sato's substrate required a short two carbon tether on the allenyne in order for the reaction to

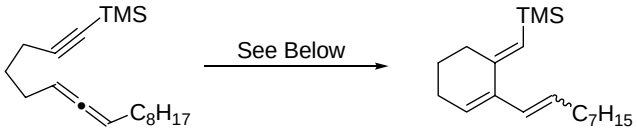
occur at the distal double bond of the allene (Scheme 5). Rhodium(I) catalysts, unlike other transition metals, were found to give selective cyclization with the distal double bond of the allene regardless of the substitution pattern on the allene or tether length.[15]



1.13 **1.14**
[E : Z] = 5 : 1

Scheme 8. Brummond and coworkers' Alder-ene reaction to form cross-conjugated trienes

The easy access to a relatively unexplored substructure,[16] a cross conjugated triene, prompted us explore the scope and limitations of this transformation. We discovered that the formal Alder-ene reaction with allenynes gives high yields of trienes with moderate E/Z selectivity for a variety of substrates and that rhodium biscarbonyl chloride dimer is a general catalyst. Also the E/Z selectivity could be enhanced by changing the neutral Rh(I) catalyst to a cationic Rh(I) or Ir(I) catalyst; altering the selectivity from 5 : 1 to 13 : 1 or >20 : 1, respectively (Scheme 9).[14]



$[Rh(CO)_2Cl]_2$ [E : Z] = 5 : 1
$[Rh(COD)Cl]_2$, $AgSbF_6$ [E : Z] = 13 : 1
$[Ir(COD)Cl]_2$, $AgBF_4$ [E : Z] = >20 : 1

Scheme 9. Increasing the E : Z selectivity of the olefinic side chain using cationic Rh or Ir catalysis

The high yields and mild conditions of the Rh(I)-catalyzed allenic Alder-ene reaction motivated us to examine its value in natural product synthesis. The application of this

carbocyclization process to the ovalicin/fumagillol class of sesquiterpenoids was the most exciting, due in part to the potentially rapid access to the entire carbocyclic skeleton in one step and the interesting biological activity associated with these compounds (Figure 1).

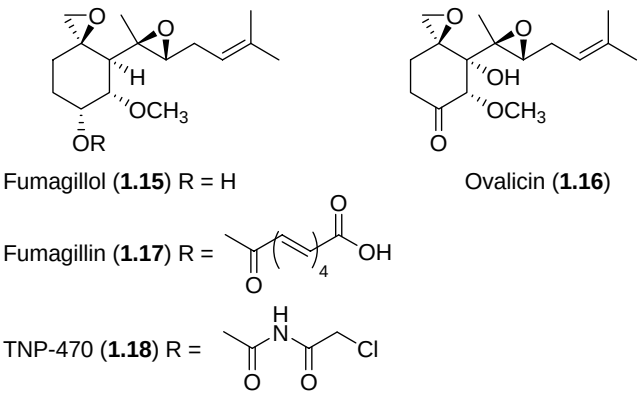


Figure 1. Structures of fumagillol, ovalicin, fumagillin, and TNP-470

1.2 BIOLOGICAL ACTIVITY OF OVALICIN AND ANALOGS

Fungi are known to contain a vast source of biologically active compounds including anti cancer agents.[17] Ovalicin (**1.16**) is one example of a biological active compound that was isolated from cultures of the fungus *Pseudorotium ovalis*.[18] This sesquiterpene has been found to display antibiotic, antitumor, and immunosuppressive activity; however, the majority of the biological investigations associated with ovalicin have focused on its anti-angiogenic activity. Structurally similar fumagillin (**1.17**) and TNP-470 (**1.18**) have also been shown to inhibit angiogenesis *in vivo*;[19] however, ovalicin has an advantage as an anti-cancer agent since it is more stable during storage than fumagillin and administration of TNP-470 caused patients to experience neurotoxicity at doses where antitumor activity was seen.[20]

Angiogenesis is essential for tumor growth, and by suppressing this process it prevents the tumor from growing beyond a few cubic millimeters or metastasizing.[21] Fumagillol (**1.15**), ovalicin, and the analog TNP-470 (**1.18**)[22] have been found to have an inhibitory effect on the growth and metastasis of various cancers including breast, colon, gastric, renal, ovarian, and prostate.[23]

It is known that endothelial cells play a necessary role in angiogenesis, and both ovalicin and TNP-470 were found to inhibit endothelial cell proliferation. However, the mechanism of action for this inhibition is still unclear. Clardy[24] illustrated that fumagillin, ovalicin, and TNP-470 covalently bind to a cobalt-containing enzyme called methionine amino peptidase (MetAP-2), and have a low affinity for binding to the closely related MetAP-1 (Figure 2).[25] The covalent bond is formed by nucleophilic attack of the His^{231} residue of MetAP-2 onto the exocyclic epoxide of fumagillin, ovalicin, or TNP-470.

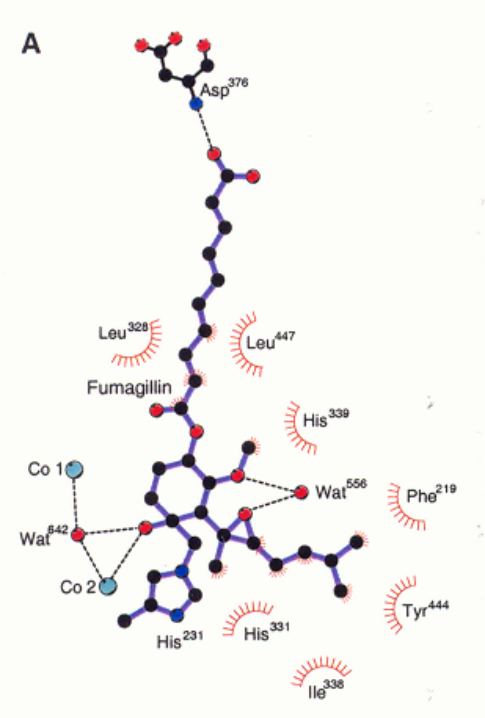


Figure 2. LIGPLOT of fumagillin in the binding pocket of MetAP-2 published by Clardy

It is significant that this binding is selective since inhibition of both MetAP-1 and MetAP-2 is lethal.[26] Methionine amino peptidase-2 removes methionine residues from the N-termini of proteins in a critical co-translational processing event and there is a correlation between inhibition of endothelial cell proliferation and the inhibition of MetAP-2.[27] While it was reported that MetAP-2 function is independent of endothelial cell production,[28] higher levels of MetAP-2 are expressed in malignant mesothelioma cells;[29] and therefore this could be why normal endothelial cells are not affected by MetAP-2 inhibition. Despite the enigmatic mechanisms of action for these natural products, fumagillin and ovalicin are still under investigation in the biological and clinical sector and remain synthetically popular targets.[30]

1.3 PREVIOUS SYNTHESES OF OVALICIN

Corey was the first to synthesize (±)-ovalicin in 1985. After the novel formation of the epoxy ketone **1.19**, the lithiated diene **1.20** was stereoselectively added to give the desired carbocyclic skeleton **1.27** (Figure 3).[31] Nearly a decade later, Corey published an asymmetric synthesis of ovalicin by preparing the enantiomerically enriched epoxy ketone **1.19** via an asymmetric dihydroxylation reaction.[32] Bath[33] and Barco[34] gained access to (-)-ovalicin by manipulating naturally occurring optically pure building blocks L-quebrachitol (**1.21**) and (-)-quinic acid (**1.22**), respectively. The most recent syntheses of (-)-ovalicin were reported by: Takahashi who starts with a simple sugar, D-mannose (**1.23**), and also features a ring closing metathesis; and by Hayashi, whose approach is similar to Corey's and utilizes an asymmetric α-aminoxylation with L-proline and a unique double epoxidation protocol.[35]

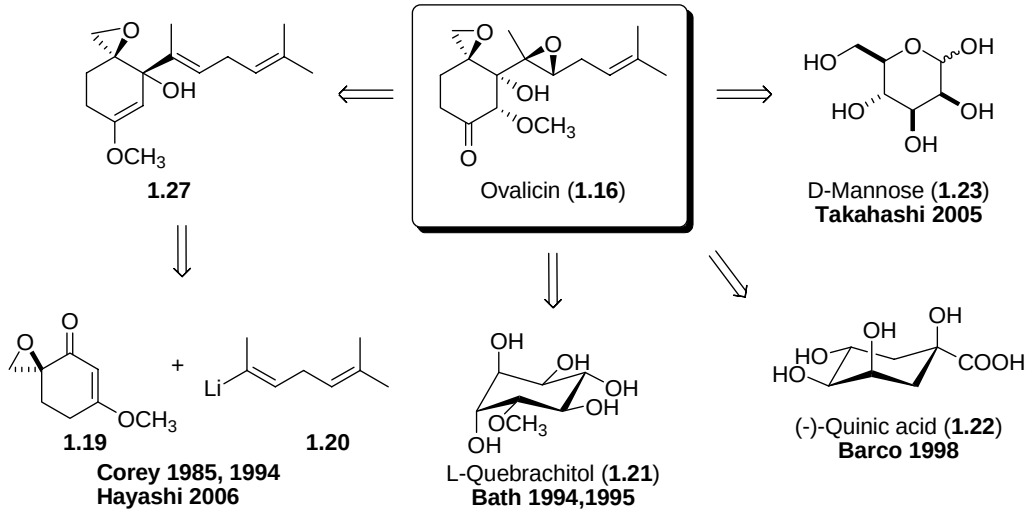


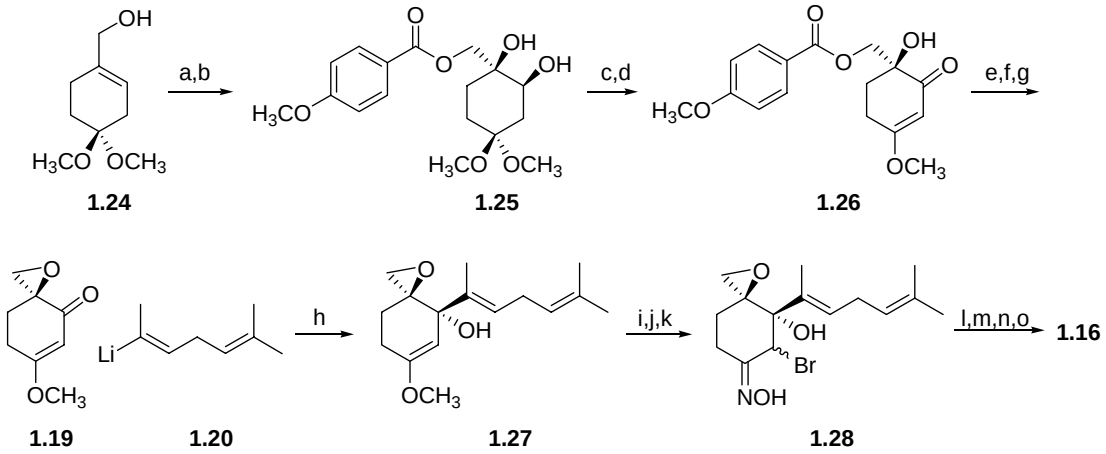
Figure 3. Starting materials used for the synthesis of ovalicin

There are two main strategies groups have taken to synthesize ovalicin. The first approach, demonstrated by Corey and Hayashi, uses achiral starting materials and focuses on

obtaining optically enriched material by asymmetric catalysts; and performs selective oxidation reactions. The second approach, demonstrated by Bath, Barco, and Takahashi, uses highly oxygenated, natural, enantiomerically pure starting materials; and focuses on reducing undesired oxygenations. While all the syntheses of (-)-ovalicin (**1.16**) are interesting and educationally valuable, only close examination of Corey's and Hayashi's routes will be described in detail since this is the type of approach used in our route to ovalicin.

1.3.1 Corey's Synthesis of Ovalicin Demonstrating a Unique Diastereoselective Alkylation using a Vinyllithium Species

Corey's asymmetric synthesis of (-)-ovalicin is accomplished in 17 steps starting from *p*-methoxybenzyl alcohol (Scheme 10). Corey and coworkers synthesized the allylic alcohol **1.24** in two steps, which was acylated and then subjected to an asymmetric dihydroxylation protocol to obtain diol **1.25**. They found the *p*-methoxybenzoyl group was imperative for the excellent enantiomeric selectivity. Swern oxidation of the secondary alcohol and subsequent treatment with acid gave the vinylogous ester **1.26**. A three step process transformed **1.26** into the desired epoxy-ketone **1.19**. Subsequent addition of (*Z*)-(6-methylhepta-2,5-dien-2-yl)lithium (**1.20**) to **1.19** gave alcohol **1.27** with excellent diastereoselectivity (17 : 1) favoring the desired diastereomer. Completion of the synthesis entails formation of the vinyl bromide and acid hydrolysis to give the ketone, which is then transformed into oxime **1.28**. Subjection of oxime **1.28** to methanol and TEA replaces the bromide with a methoxy group. The oxime is then transformed back to the ketone and an alcohol directed epoxidation with vanadium gave (-)-ovalicin (**1.16**). In summary, Corey's synthesis highlights the effectiveness of the Sharpless dihydroxylation protocol and a unique diastereoselective alkylation of a vinyllithium species.



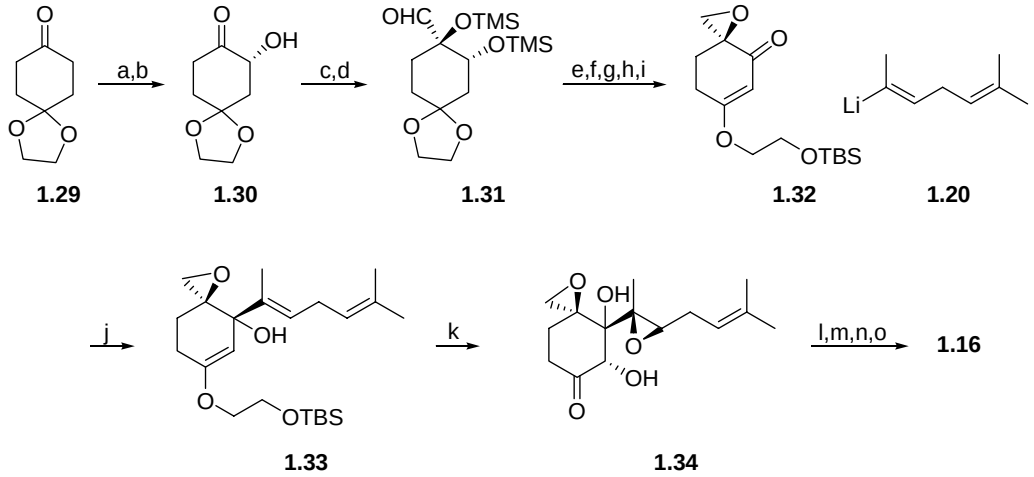
Reaction Conditions: (a) *p*-methoxylbenyzoyl chloride, TEA, DMAP, 98% (b)K_2OsO_4, $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, $CH_3SO_2NH_2$, 93% yield and >99% ee (c) Swern, 87% (d) PTSA, 93% (e) K_2CO_3, 93% (f) CH_3SO_2Cl, TEA (g) NaOH, 82% two steps (h) t-BuLi, 83% (i) N-bromosuccinimide (j) p-TSA, 55% two steps (k) $HONH_2HCl$, AcOH, KOAc, quant. (l) CH_3OH, TEA (m) $TiCl_4$ (n) K_2CO_3, 63% (o) vanadyl$(acac)_2$, tBuOOH, 89%

Scheme 10. Corey's synthesis of (-)-ovalicin (1.16)

1.3.2 Hayashi's Synthesis of Ovalicin Demonstrating an Asymmetric α-Aminoxylation

Hayashi's total, asymmetric synthesis starts with commercially available 1,4-cyclohexanedione monoethylene ketal **1.29** and forms (–)-ovalicin in 15 steps (Scheme 11). An asymmetric α-aminoxylation by addition of $_L$-proline and nitrosobenzene followed by hydrogenation gives the α-hydroxyl ketone **1.30** in high yields and excellent enantiomeric purity. Cyanation of ketone **1.30** followed by DIBAL-H reduction gave aldehyde **1.31**. Subsequent reduction of the aldehyde and epoxide formation via a similar protocol as Corey's route, gave the corresponding secondary alcohol. The secondary alcohol was then oxidized with Dess-Martin periodinane and treated sequentially with acid and TBSCl giving enone **1.32**. As in Corey's route, (*Z*)-(6-methylhepta-2,5-dien-2-yl)lithium (**1.20**) was added to epoxide **1.32** to give alcohol **1.33**; however, diverging from Corey's route Hayashi uses $VO(OiPr)_3$, which accomplishes a diastereoselective double

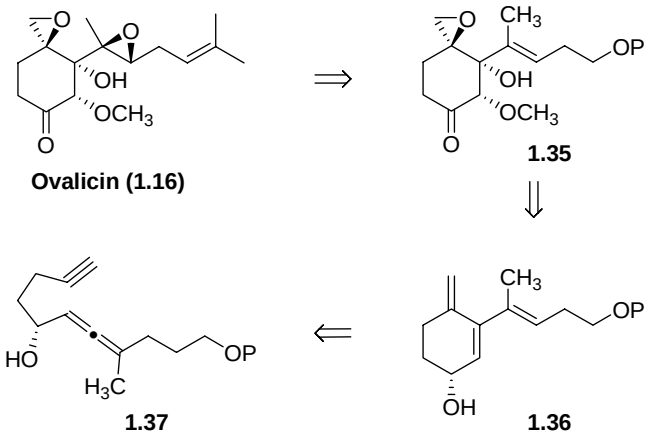
epoxidation to yield **1.34** in one step. Completion of the synthesis of (–)-ovalicin only requires methylation of the secondary alcohol; unfortunately, due to sterics a four step protocol had to be used to accomplish this goal. In summary, Hayashi demonstrated the usefulness of the L-proline mediated asymmetric α-aminoxylation and double epoxidation protocols for the synthesis of (-)-ovalicin (**1.16**).



Reaction Conditions: (a) $_L$-proline, PhN=O, 93%, >99% ee (b) Pd/H, H_2, 90% (c) TMSCN, TEA, 68% (d) DIBAL-H, 72% (e) DIBAL-H (f) MsCl, TEA, DMAP (g) K_2CO_3, 81%, 3-steps (h) DMP, then TLC (i) TBSCl, imidazole, 60% 2-steps (j) t-BuLi, 91% (k) $VO(OiPr)_3$, TBHP, 64% (l) PivCl, TEA, DMAP, 84% (m) NH_2OHHCl, TEA, 90% (n) K_2CO_3 (o) MeOTf, 2,6-tBu_2Py, 72% 2-steps

Scheme 11. Hayashi's synthesis of (-)-ovalicin (1.16)

1.3.3 Retrosynthetic Analysis: Brummond / McCabe Approach Utilizing an Allenic Alder-ene Reaction

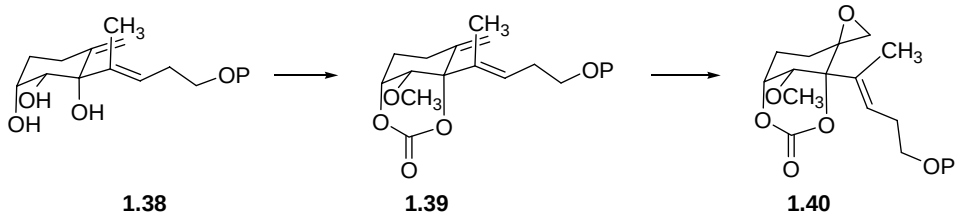


Scheme 12. Brummond/McCabe's retrosynthetic analysis to ovalicin

Our retrosynthetic analysis of (–)-ovalicin (**1.16**) utilizes the Rh(I)-catalyzed allenic Alder-ene reaction and is outlined in scheme 12. Ovalicin could be obtained from **1.35** using a stereoselective hydroxyl directed epoxidation of the remaining double bond, and conversion of the primary hydroxyl group into the terminally trisubstituted double bond via an oxidation and homologation sequence similar to the strategy used by Taber in his synthesis of fumagillin.[36]

Ketone **1.35** in turn could be formed from triene **1.36** which possesses double bonds that are well-matched for the synthesis; since selective oxygenation at each double bond leads to ovalicin (compare **1.36** and **1.16**). We plan to use the secondary hydroxyl group on triene **1.36** to direct the regio- and stereoselectivity in a dihydroxylation reaction (Scheme 13). Preferential methylation of the equatorial secondary alcohol on **1.38** followed by protection of the remaining diol as the carbonate should give intermediate **1.39**. It is expected that ozonolysis of the less substituted olefin of **1.39** will occur preferentially. The newly formed ketone in turn can be

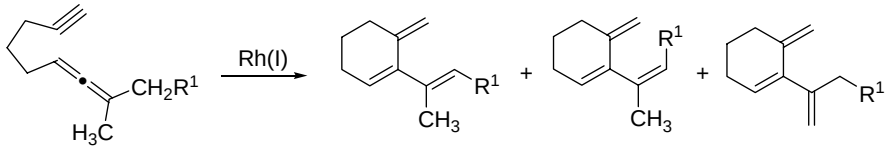
converted into the desired epoxide **1.40**. Ketone **1.35** is then obtained by subsequent cleavage of the carbonate followed by oxidation of the resulting secondary alcohol.



1.38 **1.39** **1.40**

Scheme 13. A route to intermediate 1.40

It was predicted that the desired triene **1.36** would arise from allenyne **1.37** via a formal allenic Alder-ene reaction. The successful conversion of allene **1.37** to the desired triene **1.36** will require regio- and stereoselective β-hydride elimination. For example, when 1,1,3-trisubstituted allene **1.40** is used, β-hydride elimination can occur to give *E*-**1.42**, *Z*-**1.42**, and the constitutional isomer **1.43** (Scheme 14). Selective transformations of this type have not been previously addressed in our group[1,10,37] and to the best of our knowledge, little is known about the selectivity of these elimination reactions.

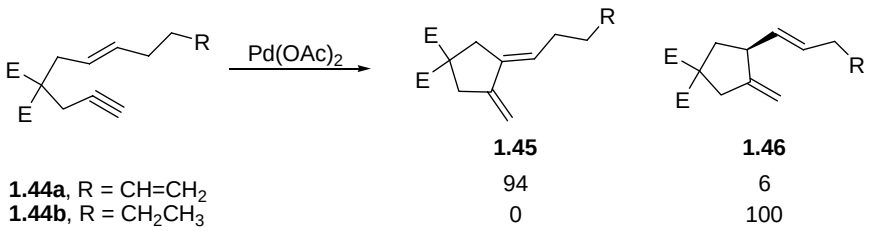


1.41, $R^1 \neq H$ *E*-**1.42** *Z*-**1.42** **1.43**

Scheme 14. Constitutional group selectivity in the allenic Alder-ene reaction

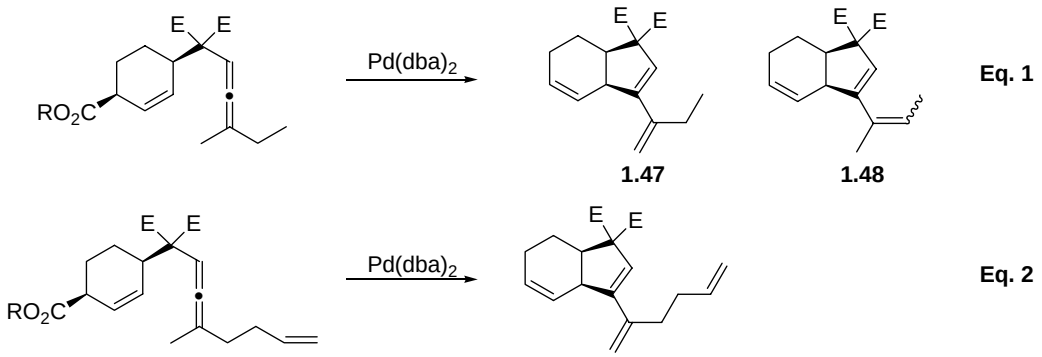
Trost observed competing β-hydride eliminations in a Pd-catalyzed cycloisomerization of 1,6-enyne **1.44**; however, this case was different than ours because the elimination reaction gave either 1,3-diene **1.45** or 1,4-diene **1.46** (Scheme 15). Trost was able to alter the product distribution by changing the functional groups on the substrates.[38] For example, when R =

$CH{=}CH_2$, 1,3-diene **1.45** was obtained and when R = CH_2CH_3, the 1,4-diene **1.46** was obtained, exclusively. This selectivity was attributed to remote binding of the mono-substituted olefin to the palladium metallocycle. This binding determines which hydrogen can effectively undergo β-hydrogen elimination; therefore giving diene **1.45** selectively.



Scheme 15. Trost's constitutional group selectivity influenced by coordination of an olefin

Furthermore, Bäckvall's Pd-catalyzed carbocyclization of ene-allenes[39] gave constitutional isomers resulting from β-hydride elimination of differentially substituted allenes. Subjection of the ene-allenes to $Pd(dba)_2$ gave the 1,4-dienes **1.47** and **1.48** in a 1 : 1 ratio (Eq. 1, Scheme 16). Again due to the remote binding that can occur in the metallocycle, altering the functional groups on the starting material gave complete constitutional group selectivity (Eq.2, Scheme 16).



Scheme 16. Bäckvall's Pd-catalyzed cycloisomerization of ene-allenes

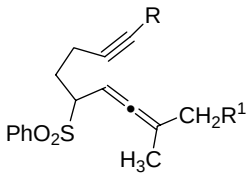
Because so little is known about the selectivity of the β-hydride elimination of

differentially substituted allenes, we initiated our synthesis of ovalicin by first examining the selectivity of the key Alder-ene reaction on a readily available precursor. Moreover, since we have previously demonstrated that E/Z isomeric ratios can be significantly increased by altering the catalyst,[14] we planned on first taking advantage of reagent control and then if necessary substrate control.

1.4 A STUDY OF THE CONSTITUTIONAL GROUP SELECTIVITY IN THE ALLENIC ALDER-ENE REACTION

1.4.1 Explorations of the Constitutional Group Selectivity of Sulfonyl Allenynes 1.49

1.4.1.1 Preparation of Sulfonyl Allenynes

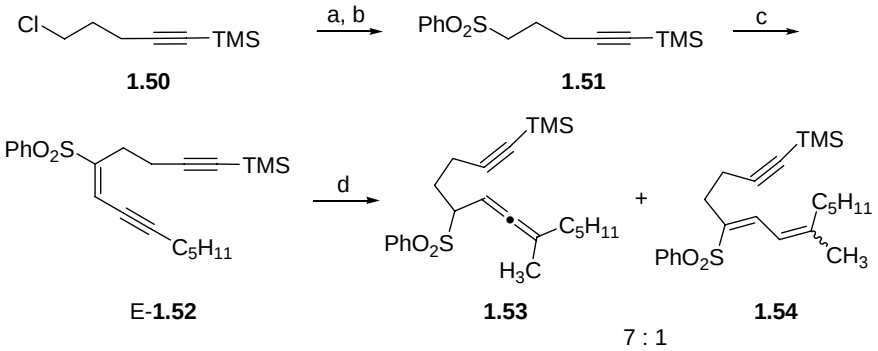


1.49

Figure 4. Model sulfonyl allenyne 1.49

With an eye towards the synthesis of ovalicin, model sulfonyl allenyne **1.49** was prepared to explore the constitutional group selectivity of the β-hydride elimination in the Alder-ene reaction (Figure 4). It was advantageous to use allenyne **1.49** as a model substrate because it could be easily prepared in a short number of steps. Reaction of commercially available 5-chloro-1-(trimethylsilyl)-1-pentyne (**1.50**) with NaI/acetone gave 5-iodo-1-(trimethylsilyl)-1-pentyne in a 99% yield (Scheme 18). Treatment of the resulting iodide with benzenesulphinic acid sodium

salt formed sulfone **1.51** in 2 h in 76% yield. Interestingly, direct nucleophilic addition of benzenesulphinic acid sodium salt to 5-chloro-1-(trimethylsilyl)-1-pentyne (**1.50**) gave a 26% yield of sulfone **1.51** and a large amount of the $_O$-alkylated by-product. Addition of α-sulfonyl anion to 2-octynal followed by quenching with acetic anhydride gave the crude acetate as a 1 : 1 mixture of diastereomers, as determined by ^{1}H NMR spectroscopy. This diastereomeric mixture was reacted with DBU to give enyne *E*-**1.52** selectively in 60% yield (3 steps). Then a conjugate 1,6-addition of lithium dimethylcuprate to enyne **1.52** gave a mixture of allene **1.53** and diene **1.54** in 67% yield.[40] Unfortunately, compounds **1.53** and **1.54** were only separable via HPLC; therefore, they were taken on as a mixture to the next step.



[a] Reagents and Conditions: (a) NaI, acetone, reflux, 99%; (b) benzenesulphinic acid sodium salt, DMF, 50 °C, 76%; (c) 2-octynal, *n*-BuLi, THF, -78 °C, quench Ac_2O; DBU, THF, 0 °C, 60%(3-steps); (d) CuI, MeLi, TMSOTf, ether, -30 °C, 67% [**1.53** :**1.54** = 7 : 1].

Scheme 17. Preparation of allenyne 1.53

1.4.1.2 Alder-ene Studies on Sulfonyl Allenynes; Analysis of Group Selectivity

Treatment of sulfonyl allene **1.53** and diene **1.54** with 5 mol% of $[Rh(CO)_2Cl]_2$ gave trienes *E*-**1.55**, *Z*-**1.55**, **1.56**, and unreacted **1.54** in a 90% yield as a 3 : 5 : 1 ratio, respectively. This is a rare example of the *Z*-isomer **1.55** predominating in any transition metal-catalyzed Alder-ene reaction (Entry 1, Table 1).[2,41] This anomalous result can be understood by considering the metallocycle intermediates **I** and **II** (Figure 5). In order for β-hydride elimination to occur, the

Rh-C-C-H_a arrangement must be almost *syn* periplanar. Two competing conformations are depicted in **I** and **II**, leading to the *E*-**1.55** and *Z*-**1.55** isomers, respectively. Conformation **I** reveals an eclipsing interaction between the methyl and butyl group as well as possible steric interference between the butyl group and the ligands on the rhodium. Conformation **II** alleviates these steric and eclipsing interactions but possesses $A^{1,3}$ strain. Thus, it is postulated that the *Z*-isomer is formed preferentially via the selective reaction of conformation **II**. Interestingly, removal of the TMS moiety from the terminus of the alkyne caused a reversal in the E/Z selectivity (Table 1, compare entries 2 and 12).

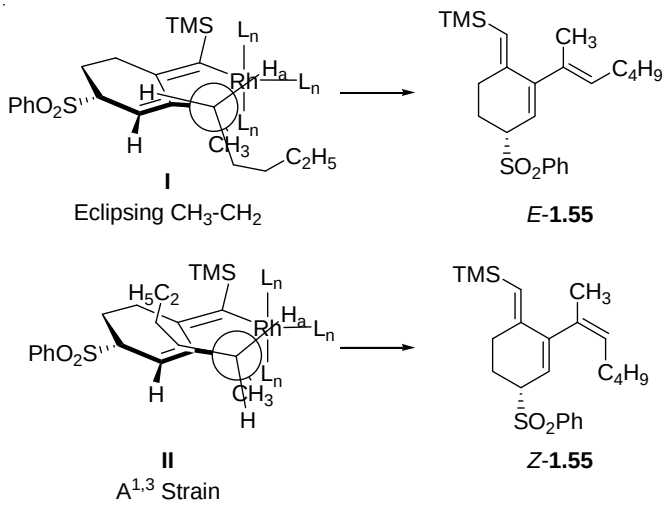
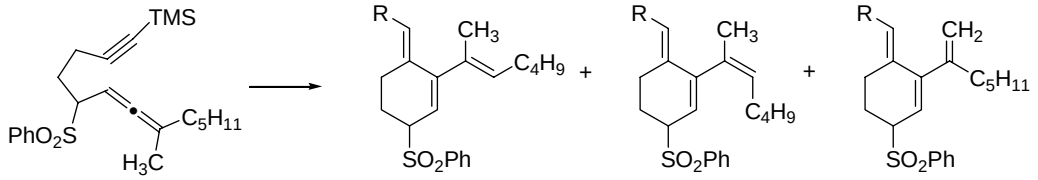


Figure 5. Explanation of E/Z selectivity in the Alder-ene reaction using allenyne 1.53

Triene *E*-**1.55** is the desired isomer for the synthesis of ovalicin; therefore, a systematic study to obtain *E*-**1.55** selectively by changing the catalyst, solvent, and temperature was initiated and the results are summarized in Table 1. Reaction of allenyne **1.53** with $[Rh(CO)_2Cl]_2$ gave *Z*-**1.55** as the major product at 50 ˚C and room temperature (entries 1 and 2 , Table 1). Because cationic Rh(I) or Ir(I) catalysts have been shown to give the *E*-isomer preferentially,[14] allene **1.53** was subjected to $[Rh(COD)Cl]_2/AgBF_4$. This afforded *E*-**1.55** in preference to *Z*-**1.55**,

but significant quantities of the constitutional isomer **1.56** were also formed (*E*-**1.55** : **1.56** ; 1 : 1) (Entry 3, Table 1). Exposure of **1.53** to the cationic iridium conditions ($[Ir(COD)Cl]_2/AgBF_4$) gave a 9 : 1 : 5 ratio of trienes *E*-**1.55** : *Z*-**1.55** : **1.56**, respectively (Entry 4, Table 1). The use of cationic Rh(I) and Ir(I) catalysts reversed the *E/Z* selectivity (1 : 2 to 9 : 1), as expected, yet decreased the constitutional group selectivity (8 : 1 to 2 : 1) (Entries 1-4, Table 1).

Table 1. [a]Results of the Alder-ene reaction with sulfonyl allenynes 1.53 and 1.53a



E-**1.55** *Z*-**1.55** **1.56**
E-**1.55a** *Z*-**1.55a** **1.56a**

Entry	Substrate	Catalyst[b]	Solvent	t(^{o}C)	*E*-**1.55** : *Z*-**1.55** : **1.56**	*E/Z*-**1.55** : **1.56**	*E*-**1.55** : *Z*-**1.55**	Yield(%)[e]
1	**1.53**	A	Toluene	50	33 : 56 : 11	89 : 11	38 : 62	73[d]
2	**1.53**	A	Toluene	rt	29 : 57 : 14	86 : 14	33 : 67	93
3	**1.53**	B	DCE	rt	50 : 0 : 50	50 : 50	100 : 0	97
4[c]	**1.53**	C	DCE	rt	60 : 7 : 33	67 : 33	90 : 10	44[d]
5	**1.53**	C	DCE	0	66 : 17 : 17	83 : 17	80 : 20	80
6	**1.53**	C	DCE	-10	63 : 12 : 25	75 : 25	83 : 17	
7	**1.53**	C	DCE	-30	76 : 12 : 12	82 : 12	86 : 14	80
8[c]	**1.53**	D	Acetone/DCE	rt	57 : 14 : 29	71 : 29	80 : 20	85
9	**1.53**	D	Acetone/DCE	-30	66 : 17 : 17	83 : 17	80 : 20	80
10	**1.53**	D	Toluene	-40	NR			
11	**1.53**	D	Toluene	-60	NR			
12	**1.53a**	A	Toluene	rt	50 : 25 : 25	75 : 25	67 : 33	87

[a] For reaction conditions see experimental section. Product ratios were determined by integration of olefin peaks in the ^{1}H NMR. [b] A: 3-5 mol% $[Rh(CO)_2Cl]_2$; B: 5 mol% $[Rh(COD)Cl]_2$, 10 mol% $AgBF_4$; C: 10 mol% $[Ir(COD)Cl]_2$, 20 mol% $AgBF_4$; D: 5 mol% $[Ir(COD)Cl]_2$, 10 mol% $In(OTf)_3$. [c] Desilylated trienes E/Z-**1.55a** and **1.56a** were obtained. [d]Non-polar impurity was seen during reaction.[e]Yield of the mixture of trienes *E/Z*-**1.55** and **1.56**

Next, a series of reactions were performed on allene **1.53** using $[Ir(COD)Cl]_2/AgBF_4$ as the catalyst (Entries 4-7, Table 1) and varying only the temperature. These experiments revealed an increase in *E*-**1.55** selectivity at lower reaction temperature. At -30 ˚C a 6 : 1 *E/Z* isomeric ratio was obtained and a 7 : 1 constitutional isomer ratio (Entry 7, Table 1). The lower

temperature also gave a 3 : 1 ratio (*E*-**1.55** to *Z*-**1.55**+**1.56**) and confirms that the regio- and stereoselectivity can be governed by the reaction conditions.

The Alder-ene reactions summarized in Table 1 illustrate that one constitutional isomer (*E/Z*-**1.55**) is preferred over the other (**1.56**). In the absence of additional metal coordinating groups, other than the alkyne and allene, the selectivity between the constitutional isomers is rationalized by the ability of either group (methylene or methyl) to stabilize the partial positive charge developing in the β-hydride elimination step of the reaction (Figure 6). Consequently, the β-hydride elimination of the hydrogen from the methylene group in **III** gives a more stabilized intermediate; ultimately favoring elimination from intermediate **III** to give *E/Z*-**1.55**, predominately.

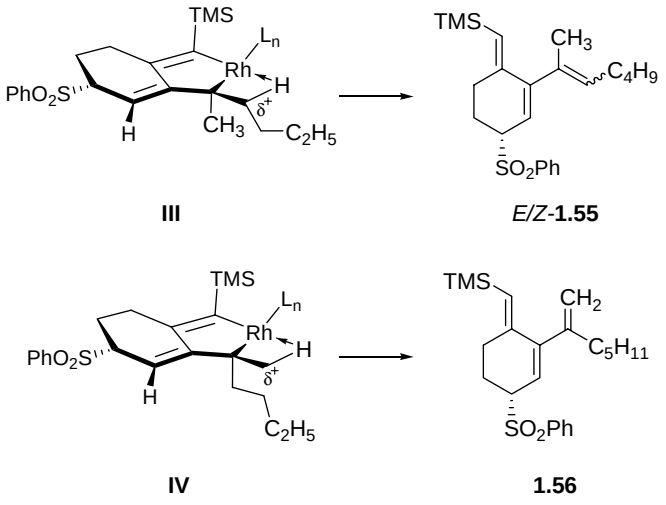
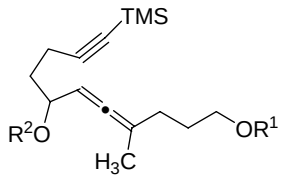


Figure 6. Explanation of constitutional group selectivity in the Alder-ene reaction of 1.53

1.4.2 Explorations of the Constitutional Group Selectivity of Silyloxy Allenynes 1.57

These studies suggested that we could obtain some of the desired selectivity by altering the reaction conditions; however, we predicted that even better selectivity could be obtained by

making changes to the substrate. Therefore, we turned our focus to the preparation of allenyne **1.57**, which is particularly advantageous because of the changes that can easily be made to the substrate R^1 and R^2 and it is an intermediate in our route to ovalicin (see scheme 12, page 14 and Figure 7).

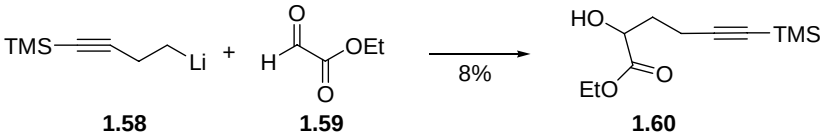


1.57

Figure 7. New target to study the regioselectivity of the Alder-ene reaction; allenyne 1.57

1.4.2.1 Preparation of Silyloxy Allenynes 1.57

4-(Trimethylsilyl)but-3-ynyl lithium (**1.58**), formed by treatment of (4-iodobut-1-ynyl)trimethylsilane with *t*-BuLi, was added to ethyl glyoxylate to give a 2-8% yield of ester **1.60** (Scheme 19). Furthermore the addition of *n*-BuLi to glyoxylate **1.59** also gave only a small amount of the expected addition product; therefore, this was not a suitable method to form ester **1.60**.

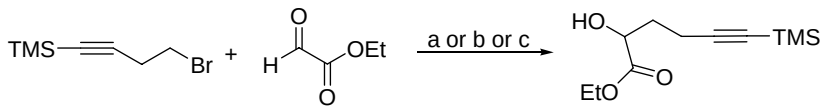


1.58 **1.59** **1.60**

Scheme 18. Synthesis of ester 1.60

Alternatively, Grignard reagents have been shown to add to glyoxylate esters.[42] After synthesis of (4-bromobut-1-ynyl)trimethylsilane (**1.61**),[43] we formed (4-(trimethylsilyl)but-3-ynyl)magnesium bromide using the highly activated Rieke magnesium, which was formed *in situ* by heating $MgCl_2$ and potassium metal for 3 h. Addition of (4-(trimethylsilyl)but-3-

ynyl)magnesium bromide to ethyl glyoxylate (**1.59**) gave the hydroxyl ester **1.60** in a 15% yield (Scheme 12). Purchasing Rieke magnesium to form the desired Grignard reagent only slightly increased the yield to 20-30%.



1.61 **1.59** **1.60**

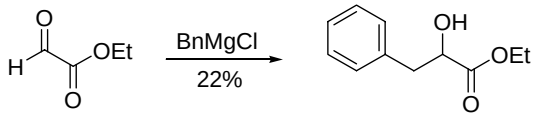
[a]Reaction conditions: (a) Mg turnings, NR (b) $MgCl_2$, $K_{(m)}$, 15% (c) Rieke Mg, 20-30%

Scheme 19. Formation of ester 1.60 via Grignard reaction

It was apparent that the ethyl glyoxylate was very unstable under the reaction conditions and only 20-30% yields were obtained even with using extreme precautions. For example, it was imperative that the ethyl glyoxylate (**1.59**) was freshly distilled from P_2O_5 immediately before use. Immediately after distillation, the glyoxylate was diluted with diethyl ether (0.2 M) to prevent polymerization. If the glyoxylate was diluted with THF, a by-product could be seen by TLC. It was presumed that either the THF was causing polymerization of the glyoxylate or a reaction was occurring between the glyoxylate and the THF. This discovery revealed one problem with this reaction. The Rieke magnesium was typically formed in THF and upon Grignard formation this solution was added to the glyoxylate. The formation of (4-(trimethylsilyl)but-3-ynyl)magnesium bromide using Rieke magnesium was attempted in DME but $MgCl_2$ would not dissolve. Therefore, (4-(Trimethylsilyl)but-3-ynyl)magnesium bromide in THF was added to a solution of ethyl glyoxylate in diethyl ether at -78 ˚C in order to prevent by-product formation.

To ensure that the problem with this reaction was the not Grignard formation, commercially available benzyl magnesium chloride was added to freshly distilled glyoxylate

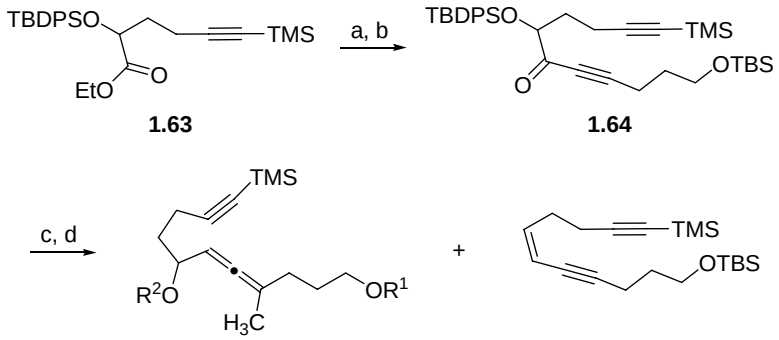
1.59 in diethyl ether to give a 22% yield of **1.62** (Scheme 20).



1.59 **1.62**

Scheme 20. Addition of benzyl magnesium chloride to ethyl glyoxylate 1.59

Despite the low yield of ester **1.60**, we continued with the synthesis of allene **1.57** by protecting the hydroxyl group with a TBDPS-group to give silyl ether **1.63** in a 65% yield (2-steps). Ester **1.63** was transformed into the Weinreb amide in an 80% yield with MeNHOMe·HCl and *i*-PrMgCl (Scheme 21). Addition of the lithium anion of silyl protected 4-pentyn-1-ol[44] to the Weinreb amide gave alkynone **1.64**.[45] Exposure of ketone **1.64** to the Luche reduction conditions gave the desired propargylic alcohol in a 58% yield (over two steps) as a single diastereomer by ^{1}H NMR. This reduction should give the hydroxyl group and silyl enol ether group in a syn relationship based upon the Felkin-Anh model and literature precedence.[46]



1.63 **1.64**

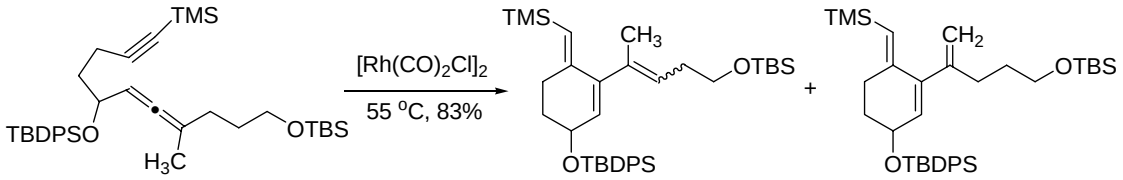
1.57a R^1 = TBS, R^2 = TBDPS **1.65**

Reagents and Conditions: (a) MeNHOMe HCl, *i*-PrMgCl, THF, 0 ^oC, 80%; (b) *n*-BuLi, *tert*-butyldimethyl(pent-4-ynyloxy)silane, -78 ^oC-0 ^oC; (c) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, -20 ^oC-0 ^oC, 58% (2-steps); (d) MsCl, TEA,CH_2Cl_2 0 ^oC; CuI, MeLi, THF, -30 ^oC, 80% [**1.57a : 1.65** = 23 : 1].

Scheme 21 Preparation of allenyne 1.57a

The propargylic alcohol was converted to a mesylate with TEA and MsCl (Scheme 21).

After workup the crude mesylate was subjected to lithium dimethylcuprate (Me_2CuLi) at -78 ˚C forming allenyne **1.57a** and enyne **1.65** in 80% yield in a 23 : 1 ratio. Interestingly, using Me_4CuLi gave a 2 : 1 ratio of **1.57a** : **1.65** and formation of **1.65** was believed to result from a two electron transfer process.[47] Treatment of allenyne **1.57a** to $[Rh(CO)_2Cl]_2$ at 55 ˚C gave an 83% yield of trienes *E*-**1.66a**, *Z*-**1.66a**, and **1.67a** in a 13 : 5 : 2 ratio, respectively (Scheme 22 and Entry 1, Table 5).



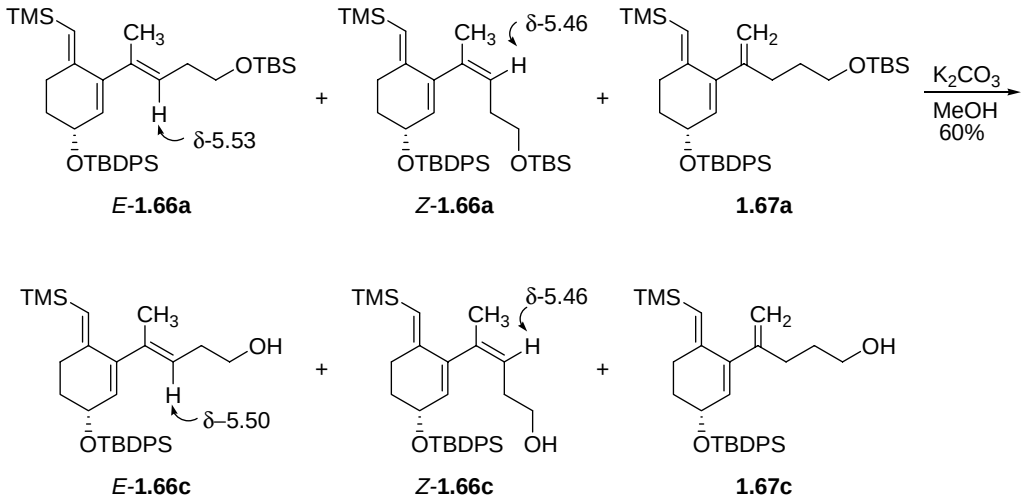
1.57a *E/Z*-**1.66a** **1.67a**

E-**1.66a** : *Z*-**1.66a** : **1.67a** = 65 : 25 : 10

Scheme 22. Synthesis of trienes E/Z-1.66a and 1.67a

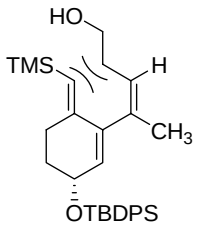
This result was interesting considering the *E/Z* ratios were reversed for the sulfone system (*E/Z*-**1.66**) (Table 1 entry 1 & 2, page 21). It is possible that this reversal is due to the differing electronic natures of the sulfone group of **1.53** and the disilylether groups of **1.57a**.

1.4.2.2 Structural Determination of Silyloxy Allenynes *E/Z*-1.66



Scheme 23. Desilylation of trienes E/Z-1.66a and 1.67a

Characterization of the geometrical isomers in the mixture of trienes *E/Z*-**1.66a** and **1.67** was determined using ROESY experiments; following separation of the isomers. Treatment of *E/Z*-**1.66a** and **1.67a** with K_2CO_3 and wet MeOH gave a 60% yield of trienes *E/Z*-**1.66c** and **1.67c** (Scheme 23). When comparing the ^{1}H NMR spectrum of the starting material (E/Z-**1.66a** and **1.67a**) to the products (*E/Z*-**1.66c**and **1.67c**) the olefinic protons are almost identical in chemical shift as depicted in scheme 23. This makes it possible to identify the major and minor geometrical isomers after they are separated. The minor geometrical isomer *Z*-**1.66c** could be separated on a standard silica gel column, while HPLC was needed for the separation of the major geometrical isomer *E*-**1.66c** and regio-isomer **1.67c**. The ^{1}H NMR spectrum of the *Z*-geometrical isomer showed broad the peaks, which suggests that there are rotational constraints present in the compound. This was not seen with the other isomers (Figure 8).

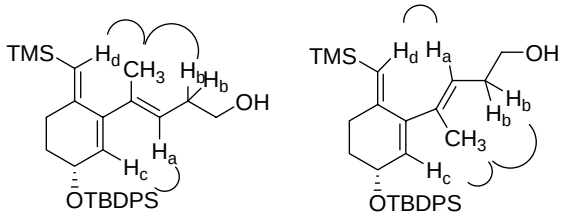


Z-**1.66c**

Figure 8. Possible steric interaction restricting the rotation of *Z*-1.66c

This would be indicative of the Z-isomer **1.66c** since this isomer's rotation can be restricted by interaction with the exocyclic double bond and the side chain. Heating the NMR sample of this isomer to 330 K in d^8 toluene caused broad peaks, observed in the ^1H NMR, spectrum to appear as sharp peaks.

Initially, nOe experiments were done on the major and minor geometrical isomers, but reliable data could not be obtained. Instead ROESY experiments were done on each isomer confirming the initial assignment (from the restricted rotation of the Z-isomer **1.66c**) of the major isomer **1.66c** as the *E*-isomer and the minor isomer **1.66c** as the *Z*-isomer. Analyzing the major isomer *E*-**1.66c** there is a correlation between Ha and Hc and Hd (Figure 9).



***E*-1.66c**

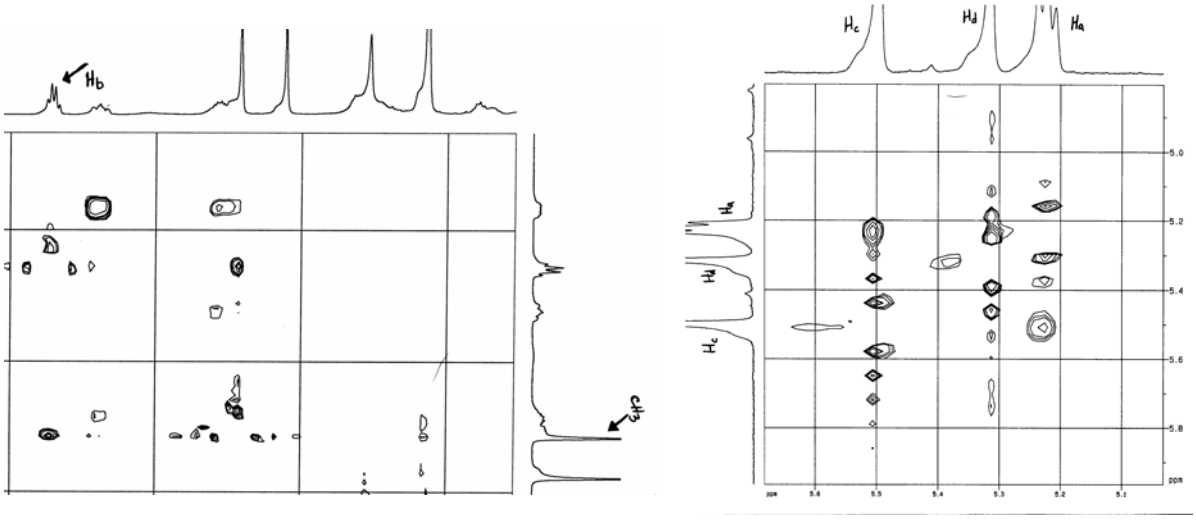


Figure 9. ROESY spectrum of *E*-1.66c

There is also a strong correlation between the methylene Hb and the vinyl methyl group, which signifies that they are on the same side of the double bond. The vinyl methyl also correlates with Hc and Hd, while there is no correlation between Ha and the vinyl methyl. All of these correlations justify the structural assignment of the E isomer as major isomer.

Analysis of the minor isomer *Z*-**1.66c** shows correlation between Hg and the vinyl methyl group. The vinyl methyl also correlates with Hf and He, whereas there is no correlation between Hg and Hf or He. These positive and negative correlations all indicate that the minor isomer possesses the Z stereochemistry (Figure 10).

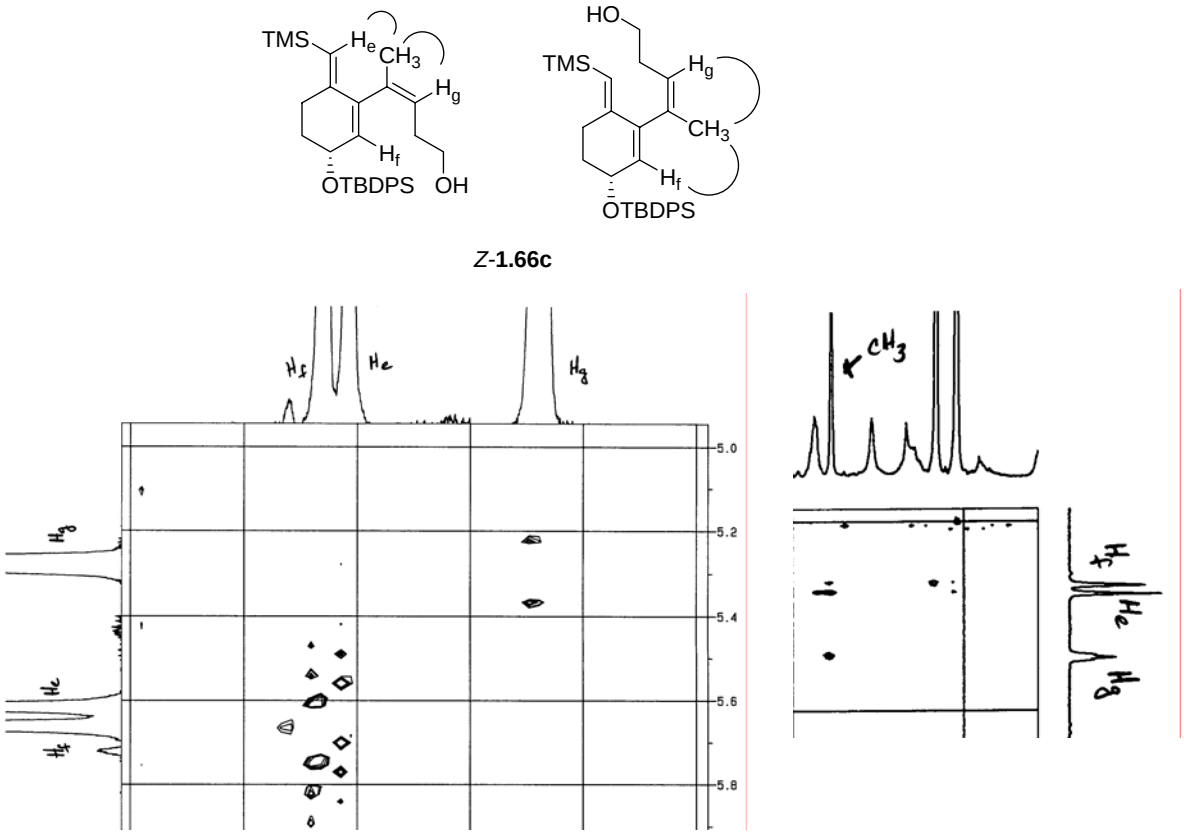
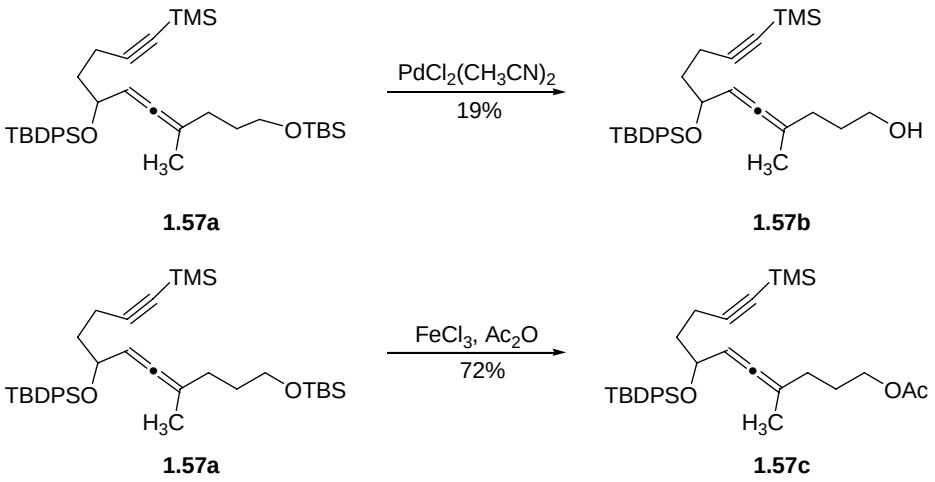


Figure 10. ROESY spectrum of Z-1.66c

1.4.2.3 Synthesis of α-Silyloxy Allenynes 1.57b-f

Since the Alder-ene reaction on the silyloxy allene **1.57a** was giving different results than seen in the sulfone system **1.53**, a variety of substrates were made in order to sufficiently explore this reaction process. The R^1 and R^2 groups on the allenyne **1.57a** were altered and synthesis of the substrates is described as follows. Allenyne **1.57b** and **1.57c** were prepared by subjecting **1.57a** to $PdCl_2(CH_3CN)_2$, which gave **1.57b** in a 19% yield,[48] and $FeCl_3$ and acetic anhydride, which gave **1.57c** in a 72% yield (Scheme 24).[49]

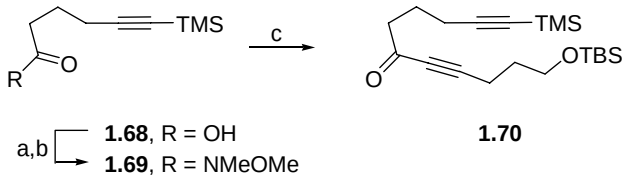


Scheme 24. Synthesis of 1.57b and 1.57c

1.4.2.4 An Alternative Route to Allenyne 1.57d

Because it was not possible to change the robust TBDPS-group of **1.57a** in the presence of the TBS-group; this alteration was done at the beginning of the synthesis. Due to the low yields of the α-hydroxy ester **1.60** an alternative route was developed.

The alternative synthesis of **1.71** starts with trimethylsilyl hexynoic acid **1.68**, which was prepared using a known procedure (Scheme 25).[50] Esterification of carboxylic acid **1.68** with MeI and $KHCO_3$ to give a 76% yield of the desired ester, which was treated with MeNHOMe·HCl and *i*-PrMgCl to give amide **1.69** in a 91% yield. Then, (5-(*tert*-butyldimethylsilyloxy)pent-1-ynyl)lithium was added to amide **1.69** prosecuting ketone **1.70** in a 63% yield.

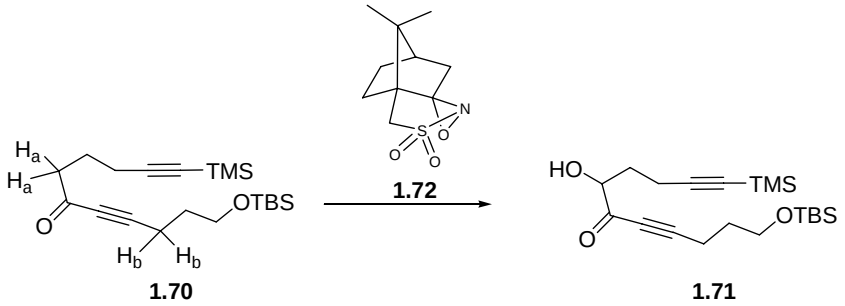


Reagents and Conditions: (a) $KHCO_3$, MeI, DMF, 76%; (b) MeNHOMe·HCl, *i*-PrMgCl, THF, 0 °C, 91%; (c) *n*-BuLi, *tert*-butyldimethyl(pent-4-ynyloxy)silane, -78 °C-0 °C, 63%

Scheme 25. Synthesis of ketone 1.70

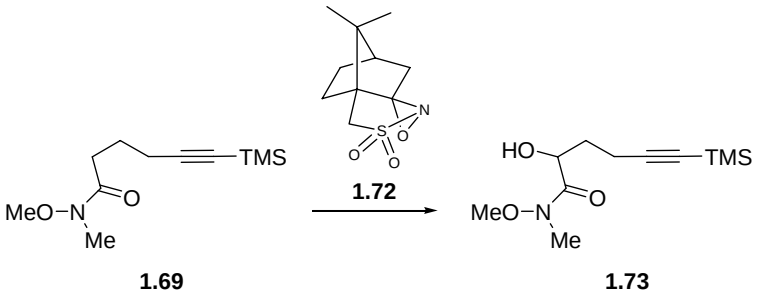
To allow for the possibility of an asymmetric synthesis of ovalicin (**1.16**) the Davis reagent was chosen as the oxidant for the α-hydroxylation of ketone **1.70**. Initially, commercially available asymmetric Davis reagent **1.72** was used to test the oxidation reaction. The results are shown in Table 2.

Table 2. Oxidation of ketone 1.70



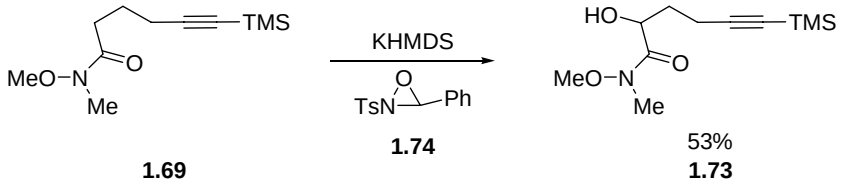
Entry	Davis reagent	Base	yield (**1.71**)
1	(S)-**1.72**	KHMDS	16-30%
2	(S)-**1.72**	NaHMDS	20%
3	(S)-**1.72**	LDA	--
4	(R)-**1.72**	KHMDS	--

Addition of ketone **1.70** to a solution of KHMDS followed by addition of the either (*R*) or (*S*)-Davis reagent **1.72** gave little to no product formation (Entries 1 and 4, Table 2). Changing the base to NaHMDS or LDA did not improve the yield of **1.71** (Entries 2 and 3, Table 2). It is possible that the low product formation results from an unselective enolate formation. A pKa calculation using CAMEO[51] software predicts the pKa's for H_a and H_b were the same; therefore, it is speculated that there is competing enolate formation between the α-protons (H_a) and γ-protons (H_b) on ketone **1.70**. To solve this problem, oxidation of the Weinreb amide **1.69** was preformed instead. Treatment of amide **1.69** with NaHMDS and (*S*)-Davis reagent **1.72** gave significant formation of **1.73** as seen by ^{1}H NMR (Scheme 26).



Scheme 26. Oxidation of amide 1.69

Typically, the by-product of this reaction, (camphorsulfonyl)imine, and excess Davis reagent **1.72** are separated from the product by dilution with pentane and then filtration. Unfortunately, α-hydroxyl amide **1.73** was insoluble in pentanes and separation could not be obtained using this method. Column chromatography of **1.73** still gave impurities evidenced by ^{1}H NMR spectrum and a 114% yield for this reaction. However, it was found that the racemic Davis reagent **1.74**, while typically removed by dilution with pentanes, could be removed by dilution with a (3 : 1) ratio of hexanes : chloroform, a solvent system that amide **1.73** was soluble in. Subjection of **1.69** to KHMDS and 3-phenyl-2-(phenylsulfonyl)-1,2-oxaziridine (**1.74**) gave a 53% yield of **1.73** (Scheme 27).

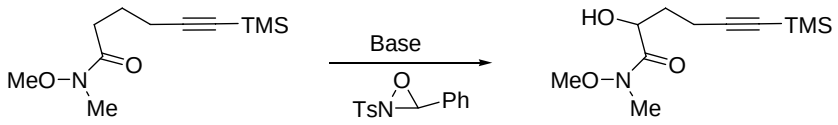


Scheme 27. Synthesis of amide 1.73 using Davis' reagent 1.74

As predicted, the *N*-benzylidenebenzenesulfonamide and oxaziridine **1.74** were separated from **1.73** by diluting with a hexanes : chloroform (3 : 1) solution followed by gravity filtration. This reaction was subsequently optimized and the results are summarized in Table 3.

As revealed by entries 1-6 in Table 3, sodium hexamethyldisilazide was found to be the best base for the Davis reaction, giving **1.73** in a 65% yield when the reaction was performed on small scale (compare entries 2 & 4). Also, 1.5 equiv of base and oxaziridine **1.74** gave the best results (compare entries 4 & 5, Table 3), and when the scale was increased, the yield of the reaction rose to a 91% yield of **1.73** (Entry 6, Table 3).

Table 3. Oxidation of amide 1.69



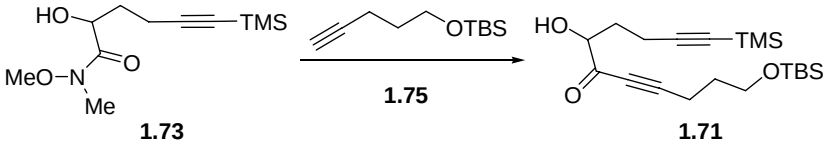
1.69 **1.74** **1.73**

Entry	Base	Equiv(base)	Equiv(**1.74**)	Yield (**1.73**)
1	LDA	1.2	1.5	--
2	KHMDS	1.2	1.2	53
3	KHMDS	1.2	1.5	70
4	NaHMDS	1.2	1.2	65
5	NaHMDS	1.5	1.5	74
6	NaHMDS	1.5	1.5	91[b]

[a] Reaction scale approximately 100 mg of **1.69**. [b] This reaction was done on 3.4 g of **1.69**.

In order to eliminate a protection/deprotection step in the synthesis, (5-(*tert*-butyldimethylsilyloxy)pent-1-ynyl)lithium was added to the carbonyl group of **1.73** without protection of the hydroxyl group, giving a 35% yield of ketone **1.71**. Attempts to optimize this reaction by changing the base did not give an increase in the yield of **1.71** (Table 4).

Table 4. Acetylide addition to amide 1.73

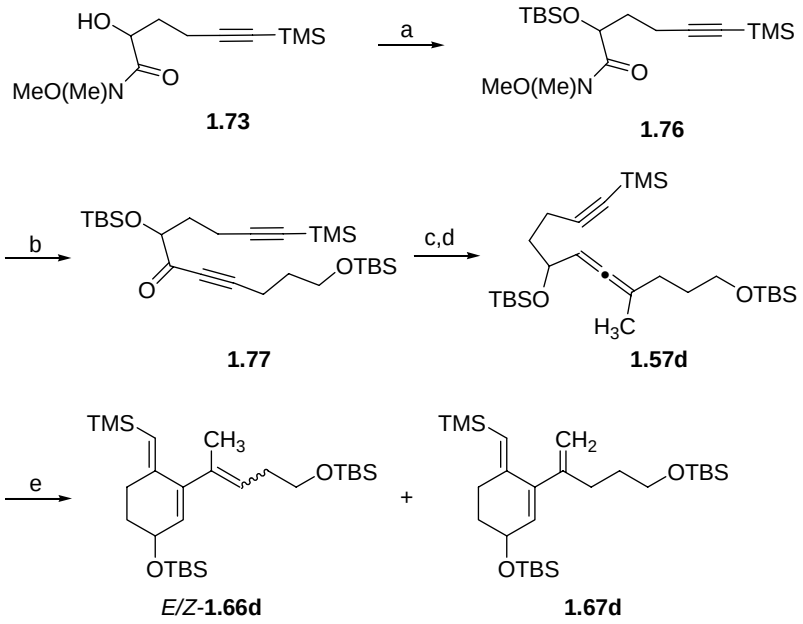


1.73 **1.71**

Entry	Base 1(equiv)	Base 2(equiv)	Equiv (**1.75**)	Yield (**1.71**)
1	NaHMDS (1.2)	*n*-BuLi (1.2)	1.2	35%
2	NaHMDS (1.5)	*n*- BuLi (2.0)	2.0	33%
3	LDA (1.5)	LDA (1.5)	1.5	25%

[a] Base 1 was added to amide **1.73** and Base 2 was added to alkyne

The α-hydroxy group of amide **1.73** was protected with as a *tert*-butyldimethylsilyl ether using TEA and TBSOTf to give silyloxy amide **1.76** (Scheme 28). Amide **1.76** was then subjected to the lithium anion of alkyne **1.75** to give a 77% yield of ketone **1.77**.



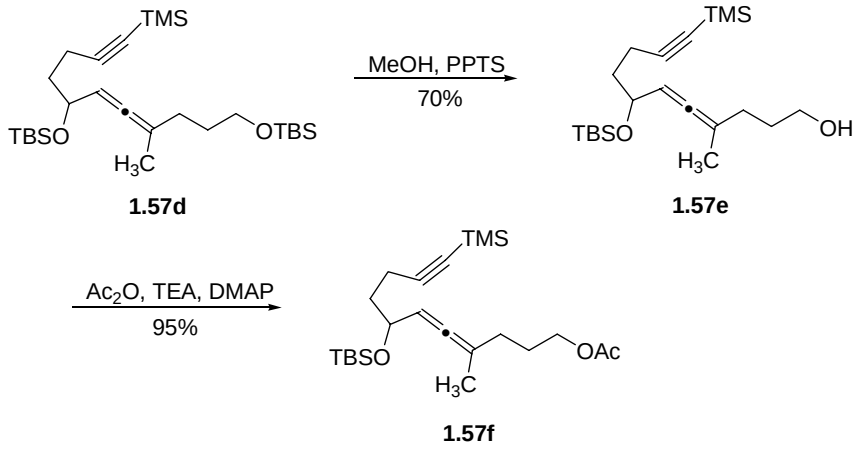
1.73 **1.76** **1.77** **1.57d** ***E/Z*-1.66d** **1.67d**

Reagents and Conditions: (a)TEA, TBSOTf, CH_2Cl_2, 94%; (b) *n*-BuLi,**1.75**, -78 °C - 0 °C, 77%; (c) $CeCl_3$ $7H_2O$, $NaBH_4$, -20 °C - 0 °C, 88%; (d) MsCl, TEA,CH_2Cl_2, 0 °C; CuI, MeLi, THF, -30 °C, 86% [**1.57d : 1.65** = 7 : 1]; (e) 5 mol% $[Rh(CO)_2Cl]_2$, tol., 80 °C, 95% [*E*-**1.668d** : *Z*-**1.66d** : **1.67d** = 6 : 3 : 1].

Scheme 28. Alternative preparation of trienes *E/Z*-1.66d and 1.67d

Ketone **1.77** was reduced using Luche conditions[52] to yield a propargylic alcohol in a 7 :

1 diastereomeric ratio. The diastereomers were not separated but taken on to the next step. The propargylic alcohol was converted to its mesylate using TEA and MsCl, then after workup the crude mesylate was subjected to lithium dimethylcuprate. Allenyne **1.57d** and enyne **1.65** (page 26) were obtained in an 86% yield in a 7 : 1 ratio as determined by ^{1}H NMR spectrum and **1.57d** was a single diastereomer by ^{1}H NMR spectrum. Selective deprotection of the primary alcohol of allenyne **1.57d** using PPTS in MeOH gave a 70% yield of allenyne **1.57f**; and subsequent acetylation with Ac_2O and TEA gave allenyne **1.57e** in 95% yield (Scheme 29).



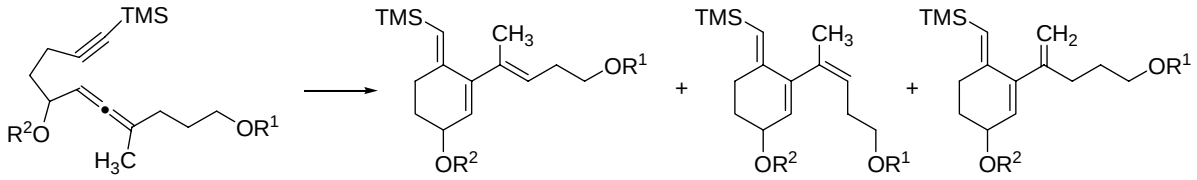
Scheme 29. Synthesis of 1.57e and 1.57f

1.4.2.5 Alder-ene Studies of Silyloxy Allenynes 1.57a-f

With allenynes **1.57a-f** in hand, a systematic study focusing on obtaining the *E*-isomer of **166a-f** was initiated and the results are summarized in Table 5. Treatment of allenyne **1.57d** with 5 mol% $[Rh(CO)_2Cl]_2$ at 80 ˚C gave an 85% yield of trienes *E*-**1.66d** : *Z*-**1.66d** : **1.67d** in a 6 : 3 : 1 ratio, which is the same yield and ratio obtained for trienes *E/Z*-**1.66a** and **1.67a** (compare entries 1 and 9, Table 5). Allenyne **1.57a** was subjected to the optimized cationic iridium reaction conditions worked out for sulfone **1.53**, $[Ir(COD)Cl]_2/AgBF_4$, which led to complete decomposition of the starting material. Switching the additive from $AgBF_4$ to $In(OTf)_3$ in DCE

gave good selectivity but only a trace amount of product formation and mostly starting material were seen by H^1 NMR (Entry 4). Also, this result was irreproducible. As seen with the sulfone system, the E/Z ratio was enhanced (7 : 3 to 10 : 0) and constitutional group selectivity was decreased (18 : 2 to 13 : 7) (compare entries 1 to 4). The insolubility of indium triflate in DCE was a likely reason for the reaction inhibition; however, changing from DCE to acetone, a solvent that indium triflate was soluble in, resulted in complete decomposition of all material.

Table 5. [a]Results of the Rh(I)-catalyzed Alder-ene reaction on allenynes 1.57a-f



1.57a-f *E*-**1.66a-f** *Z*-**1.66a-f** **1.67a-f**

Entry	Substrate	R^1	R^2	Catalyst[b]	Solvent	T(^{o}C)	*E*/*Z*-**1.66** : **1.67**	**1.66** : **1.67**	*E*/*Z*-**1.66**	Yield(%)[g]
1	**1.57a**	TBS	TBDPS	A	Toluene	55	65 : 25 : 10	90 : 10	70 : 30	83
2	**1.57a**			A[c]	Toluene-d^8	rt	55 : 30 : 15	85 : 15	60 : 40	
3	**1.57a**			A	DCE	rt	45 : 40 : 15	85 : 15	50 : 50	55
4[d]	**1.57b**			B	DCE	rt	65 : 0 : 35	65 : 35	100 : 0	NA
5	**1.57b**	Ac	TBDPS	A	Toluene	55	50 : 30 : 20	80 : 20	60 : 40	87
6	**1.57b**			A	Toluene	rt	55 : 30 :15	85 : 15	60 : 40	85
7	**1.57b**			C	DCE	rt	60 : 15 : 25	75 : 25	80 : 20	67[e]
8	**1.57c**	H	TBDPS	A	DCE	rt	25 : 35 : 40	60 : 40	40 : 60	50
9	**1.57d**	TBS	TBS	A	Toluene	80	60 : 30 : 10	90 : 10	70 : 30	85
10	**1.57d**			A	Toluene	55	60 : 25 : 15	85 : 15	70 : 30	95
11[f]	**1.57d**			A	DCE	55	40 : 50 : 10	90 : 10	40 : 60	
12[d]	**1.57d**			B	DCE	55				NA
13[f]	**1.57e**	Ac	TBS	A	Toluene	rt	55 : 30 : 15	85 : 15	60 : 40	
14	**1.57e**			A	DCE	rt	40 : 45 : 15	85 : 15	50 : 50	60
15	**1.57f**	H	TBS	A	DCE	rt	35 : 40 : 25	75 : 25	50 : 50	66
16	**1.57f**			A	DCE	0	15 : 50 : 35	65 : 35	20 : 80	60

[a] For reaction conditions see experimental section. Product ratios were determined by integration of olefin peaks in the ^{1}H NMR. [b] A: 5-10 mol% $[Rh(CO)_2Cl]_2$; B: 10 mol% $[Ir(COD)Cl]_2$, 20 mol% $In(OTf)_3$; C: 10 mol% $[Ir(COD)Cl]_2$, 20 mol% $AgBF_4$. [c] 1eq of catalyst used in NMR experiment no yield calculated. [d] Starting materials were recovered and experiments were irreproducable.[e] Yield includes a mixture of inseparable by-products. [f] Large amount of product obtained; exact yield not calculated.[g]Yield of the mixture of trienes *E*/*Z*-**1.66** and **1.67**.

Since the cationic iridium conditions were not applicable to this system, only variations in rhodium catalyzed reaction conditions could be made. Changing the reaction solvent from

toluene to DCE showed a rate enhancement, (12 h at 55 ˚C to 30 min at rt) and a reversal in E/Z selectivity (7 : 3 to 4 : 6) (See entry 10 vs. 11 and 13 vs. 14, Table 5). More polar solvents are known to increase the reaction rates in Pd-catalyzed Alder-ene reactions[53] and Rh-catalyzed cycloadditions[54] due to their ability to stabilize charge separation. Also, changing the solvent from toluene (polar index 2.4) to DCE (polar index 3.5) gave isomeric ratios closer to that seen for the sulfone system (3 : 5 : 1 vs. 4 : 5 : 1) of the E : Z : constitutional isomer (compare entry 1, Table 1 to entry 11, Table 5). Altering the temperature had no effect on the E/Z selectivity or constitutional selectivity when toluene was used as the solvent (compare entries 1 vs. 2, 5 vs. 6, and 9 vs. 10, Table 5); however, decreasing the reaction temperature when using DCE as the solvent further increased the amount kinetic product shifting the E/Z ratio from 1 : 1 to 1 : 4 (Entry 15 vs. 16, Table 5).

Further attempts were made to increase formation of the desired isomer *E*-**1.66** by modifying R^1 of **1.57**. Changing R^1 from a silyl ether to an ester functionality revealed a slight decrease in constitutional group selectivity (9 : 1 to 4 : 1) of **1.66** : **1.67** and E/Z selectivity (7 : 3 to 6 : 4) for *E*-**1.66** : *Z*-**1.66** (compare entries 1 and 5, Table 5). The free hydroxyl group had a similar, yet more enhanced effect decreasing the constitutional group selectivity from 9 : 1 to 3 : 2 or 1 ratio, and it did not effect on the E/Z selectivity (compare entries 3 vs. 8 and 11 vs. 15, Table 5). This increase in the amount of isomer **1.67** is believed to result from coordination of the free hydroxyl **V** and ester group **VI** to the rhodium metallocycle (Figure 11). *Syn*-periplanar alignment of the Rh-C-C-H_a during the β-hydride elimination step is conformationally restricted by this coordination; leading to an increase in the formation of triene **1.67**.

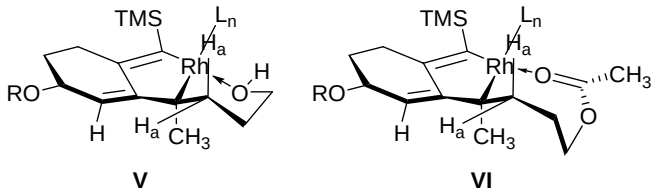
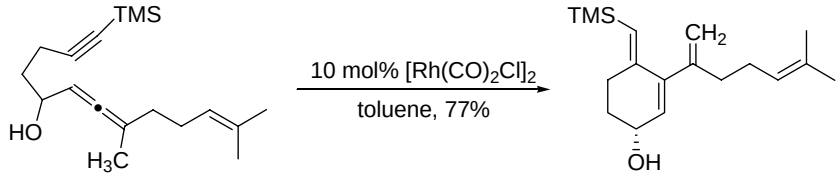


Figure 11. Conformation representation of the constitutional group selectivity using the silyloxy allenynes 1.57b and 1.57e

This hypothesis is supported by the experimental evidence that the strongest coordinating group (hydroxyl group) yielded the largest amount of the constitutional isomer **1.67**, and by literature precedence (compare entries 14 to 15, Table 5).[4] Furthermore, Jolie DeForrest[55] has shown that addition of 10 mol% $[Rh(CO)_2Cl]_2$ to allenyne **1.78** to give exclusively the constitutional isomer **1.79** in an 85% yield (Scheme 30).



1.78 **1.79**

Scheme 30. Complete constitutional group selectivity using remote binding of an alkene

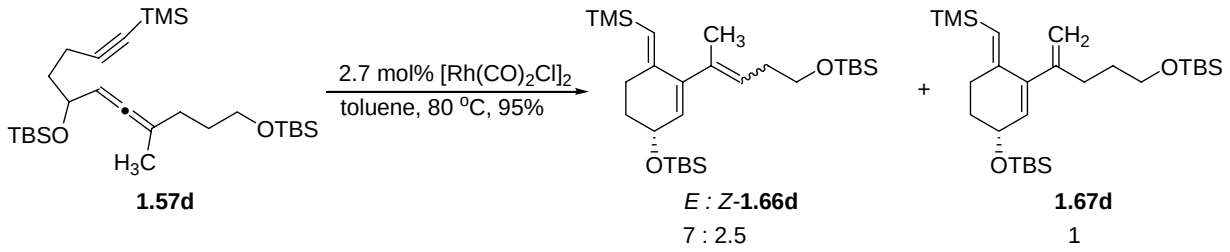
Allenynes **1.57b** and **1.57b** were subjected to the iridium conditions ($[Ir(COD)Cl]_2/AgBF_4$) with the thought that they would tolerate these conditions better than the bis-silylated allenyne **1.57a**. Addition of $[Ir(COD)Cl]_2/AgBF_4$ to allenyne **1.57b** gave a 67% yield of trienes *E/Z*-**1.66b** and **1.67b**; however, the yield includes a mixture of inseparable by-products and the reaction was irreproducible (Entry 7, Table 5). Subjection of allenyne **1.57b** to $[Ir(COD)Cl]_2/AgBF_4$ led to complete decomposition of the starting material.

In summary, the best ratio obtained was a 6 : 3 : 1 ratio of **1.66d** : **1.66d** : **1.67d** in a 85%

by subjecting allenyne **1.57d** to $[Rh(CO)_2Cl]_2$ at 80 ˚C. Unfortunately, we were not able to use any cationic iridium or rhodium conditions to increase the selectivity; exposure of the allenynes **1.57a-f** to these conditions caused decomposition of all materials or irreproducible results. Also, it was found that the ratio of products was unaffected by temperature if toluene was used as the solvent. Whereas, the use of DCE as the solvent gave a reversal in E/Z selectivity, increased reaction rates, and the ratio of products was influenced by the reaction temperature.

1.5 PROGRESS TOWARDS THE SYNTHESIS OF OVALICIN

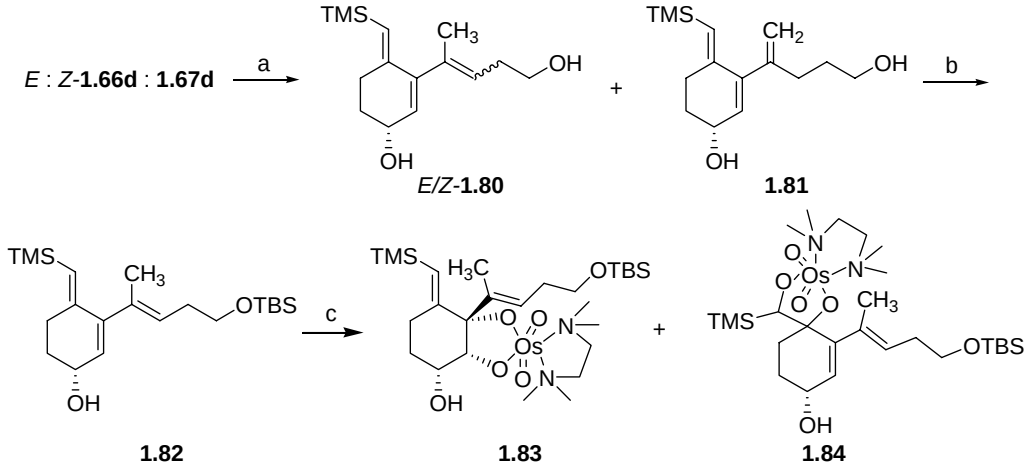
After finding the best isomeric ratios were obtained using the bis(silylated) allenyne systems (**1.57a** and **1.57d**) we decided to separate the desired isomer *E*-**1.66** and turned our attention to the functionalization of these trienes and the synthesis of ovalicin. Interestingly, scaling up the amount of allenyne **1.57d** (3.4 mmol) subjected to the Alder-ene reaction conditions and decreasing the amount of $[Rh(CO)_2Cl]_2$ (2.7 mol%) used gave a ratio of 67 : 24 : 9 of *E*-**1.66d** : *Z*-**1.66d** : **1.67d** in a 95% yield; an improvement compared to the 80% yield and 60 : 30 : 10 ratio obtained on small scale (compare Scheme 31 to entry 9, Table 5). The ratios were determined by ^{1}H NMR spectrum.



1.57d | *E* : *Z*-**1.66d** 7 : 2.5 | **1.67d** 1

Scheme 31. Allenic Alder-ene reaction on 3.4 mmol of allenyne 1.57d

Separation of these trienes required removal of both silyl ether protecting groups (Scheme 32).[36] Buffering this deprotection reaction was essential, since decomposition of the trienes occurred in the absence of NH_4Cl. After 12 h at 50 ˚C, complete bis-desilylation was observed, to give trienes E/Z-**1.80** and **1.81** in a 79% yield. The trienes were separated using silica gel chromatography; eluting with isopropanol / pentanes to give a 5 : 1.2 : 1 ratio of *E*-**1.80** : *Z*-**1.80** : **1.81** as calculated by isolation of material. The primary hydroxyl group on *E*-**1.80** was selectively protected using TEA and TBSCl to give a 75% yield of triene **1.82**.



Reagents and Conditions: (a) TBAF, NH_4Cl, THF, 50 ^oC, 79%, (5 : 1: 1.2; *E*-**1.80** : *Z*-**1.80** : **1.81**); (b) TBSCl, TEA, CH_2Cl_2, 75%; (c) TMEDA, OsO_4, CH_2Cl_2, -78 ^oC, 90%, (6 :1; **1.83** : **1.84**).

Scheme 32. Synthesis of triene *E*-1.82 and subsequent oxidation

Next, a stereo- and chemoselective dihydroxylation of the endocyclic double bond of **1.82** was done via a hydroxyl directed dihydroxylation protocol developed by Donohoe.[56] The ability to obtain an hydroxyl directed osmylation comes from the use of TMEDA as a bidentate ligand. It is reported that the TMEDA coordinates to the osmium and increases the electron density at the metal center. This in turn allows the oxygen on the osmium to hydrogen bond to the hydroxyl group. This hydrogen bond then directs the chemo- and facial selectivity of the

reaction (Figure 12).

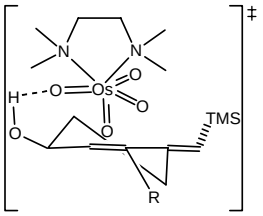


Figure 12. Basis for stereo- and chemoselectivity obtained for 1.83

When triene **1.82** was subjected to TMEDA and 1 equivalent of OsO_4 in CH_2Cl_2 at -78 ˚C, osmylation is believed to occur forming the stable osmate esters **1.83** and a by-product **1.84** in a 6 : 1 ratio, respectively. Due to the isolation of a very small amount of the by-product we were not able to completely characterize this compound, but based upon the disappearance of the exocyclic olefin peak in the H^1 NMR spectrum we suggest that it is the regioisomer **1.84**. Osmates **1.83** and **1.84** were not characterized at this stage but were taken on as a mixture to the next step and then separated. The chemoselectivity for this reaction is not absolute since a small amount of the regio-isomer **1.84** is produced during this reaction as determined by ^{1}H NMR spectrum. However, none of the third possible regio isomer, where osmylation would occur at the appending double bond, is detected, possibly due to sterics and electronics. Unfortunately, it was evident there was a small discrepancy in the ^{1}H NMR of **1.83**. It is predicted that the resonance for Ha in **1.83** should be a doublet (d) and Hb should be a doublet of a doublet of a doublet (ddd); while it was found that Hb was in fact a ddd, the resonance assigned to be Ha appears to be a singlet (s) (Figure 13).

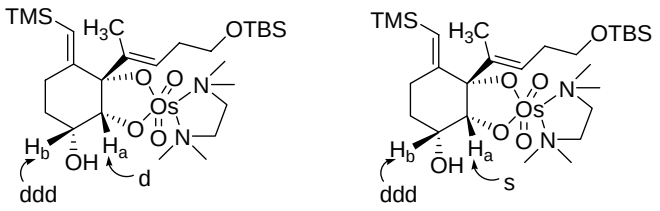
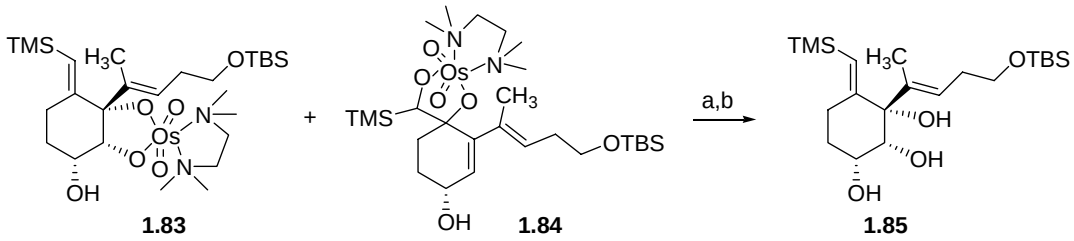


Figure 13. Analysis of the splitting patterns in the ^{1}H NMR spectra for 1.83 in $CDCl_3$

It was not clear if this abnormal spitting pattern was a result of the osmate ester moiety; therefore, we decided to cleave the osmate ester in order to get a cleaner proton spectrum that could be compared to a known spectra of compounds used in previous syntheses of ovalicin and fumagillol. Since the resulting osmate ester is a stable 18e$^-$ system, cleavage can be quite a challenge. Typically, an osmate ester moiety is cleaved using 6 M HCl in MeOH; however, this method also cleaves the silyl protecting groups. Alternatively, the osmate can be treated with saturated sodium sulfite solution or ethylene diamine.[57] Surprisingly, refluxing **1.83** in saturated sodium sulfite THF solution did not give any of the desired products.



[a] Reagents and Conditions: (a) Sodium Sulfite sat'd solution, (b) ethylene diamine, 8 h, 16%

Scheme 33. Formation of triol 1.85 from osmate 1.83

Treatment of osmate ester **1.83** with ethylene diamine for 8 h gave a 16% yield of triol **1.85** (Scheme 33). Unfortunately, cleaving the osmate ester moiety cannot be monitored by TLC. First, the starting material disappears forming a polar intermediate. Eventually, product

formation is seen on TLC, but it is unclear when the reaction is complete. To ensure the reaction is complete when using these methods, Donohoe uses standard reaction times for each cleavage reaction. For example, when he use ethylene diamine they allow the reaction to run for 48 h.

The low yield was also attributed to the instability of triol **1.85** as evidenced by decomposition of the triol **1.85** while trying to obtain a ^{13}C NMR spectrum. Plus, decomposition of **1.85** was seen even when the material was stored in a frozen benzene matrix. Most likely the long reaction time of the ethylene diamine cleavage reaction enhances the amount of decomposition of triol **1.85** prior to isolation. We were, however, able to obtain a clean proton spectrum of triol **1.85**, which again shows a singlet resonance for Ha (Figure 14). As a result of the instability of triol **1.85** more characterization data could not be obtained; therefore we decided to try and synthesize a more stable substrate.

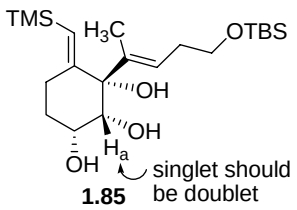
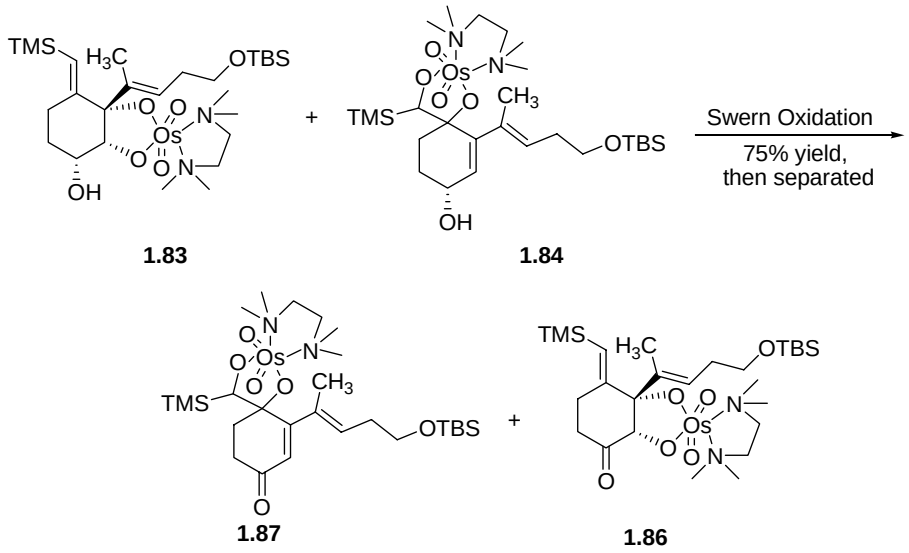


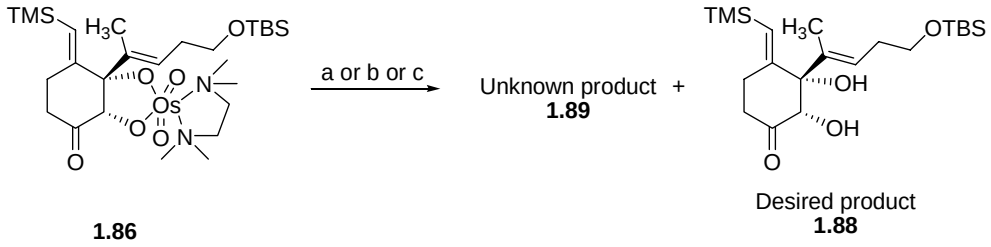
Figure 14. Discrepancy in the ^{1}H NMR of triol 1.85

In an attempt to obtain a more stable product, osmate alcohol **1.83** was oxidized prior to cleavage of the osmate ester. Subjection of **1.83** and **1.84** to Swern oxidation conditions gave a 75% yield of the desired ketones **1.86** and **1.87**, and the isomers were able to be separated using silica gel chromatography (Scheme 34). At this point full data was obtained for ketone **1.86** and the proton and carbon NMRs showed resonances that were expected for the desired product **1.86**.



Scheme 34. Swern oxidation of osmate 1.83

With ketone **1.86** in hand, the synthetic strategy was to cleave the osmate ester moiety from **1.86** forming diol **1.88**, followed by methylation of the secondary alcohol and protection of the ketone. When osmate **1.86** was refluxed in saturated sodium sulfite for several hours, no cleavage was observed (Scheme 35).



Reagents and Conditions: (a) Sodium Sulfite saturated solution, no reaction (b) ethylene diamine, 15-40% (c) H_2S, 60% of **1.89**

Scheme 35. Attempts to cleave the osmate ester moiety from ketone 1.86

However, subjection of osmate **1.86** to ethylene diamine did give some cleaved product with approximate yields ranging between 15-40%. It was unclear why the reaction was so inconsistent, but the low yields were thought to be attributed again to the long reaction times.

Ketone **1.88** was found to be more stable than the triol **1.85**, but still decomposition occurred over time. More extensive searches in the literature revealed that hydrogen sulfide can cleave osmate ester moieties in a variety of complex molecules,[58] and typically cleavage was achieved by bubbling H_2S through the reaction flask for a short period of time (10-30 min). This would hopefully prevent decomposition and produce the desired ketone **1.88** in a more suitable time frame. When osmate **1.86** was subjected to H_2S in methanol for 30 minutes at 0 ˚C, a complete cleavage of the osmate ester moiety was observed.

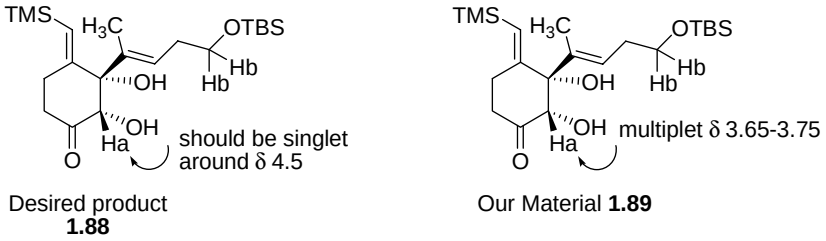


Figure 15. Discussion of ^{1}H NMR coupling for intermediate 1.89

While the many resonances in the ^{1}H NMR correlated with the expected resonances for diol **1.88**, the spitting of Ha, which is expected to be a singlet was a complex multiplet overlapping with the methylene Hb's at δ 3.65-3.75 (Figure 15). Comparing the ^{1}H NMR, ^{13}C NMR, and IR spectrums with a similar intermediate in Taber's fumagillol synthesis suggested that it is not our desired product **1.88** (Figure 16).[36]

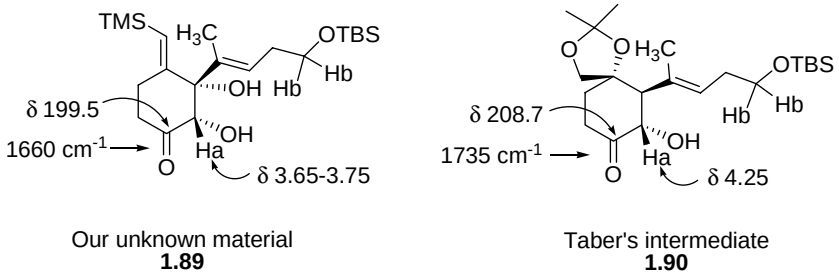


Figure 16. Comparing intermediate 1.89 to Taber's intermediate 1.90

As depicted in figure 16 the Ha resonance on Taber's intermediate **1.90** has a chemical shift of 4.25 ppm, which is further downfield than the Ha resonance on our material **1.89**. Also, the carbonyl stretch and carbon shift are significantly different from one another 1735 cm^{-1} and 208.7 ppm for Taber's intermediate **1.90** and 1660 cm^{-1} and 199.5 ppm for **1.89**. The IR and ^{13}C NMR values obtained for intermediate **1.89** suggest that the carbonyl is conjugated; however, the remainder of the ^{13}C NMR spectrum does support the presence of an enone moiety in that there are only four olefinic carbons. These findings suggest that the osmylation reaction did not give us our desired product **1.83**. Future work entails complete determination of the dihydroxylation **1.83** product followed by further steps to complete the synthesis of ovalicin (**1.16**).

1.5.1 Summary and Conclusions

In summary, Rh(I)-catalyzed allenic Alder-ene reaction of **1.53** and **1.57a-f** leads to the formation of trienes E/Z-**1.55**, E/Z-**1.66a-f**, **1.56**, and **1.67** in good yields and moderate regioselectivities (Tables 1 & 2). The regioselectivities of the Alder-ene reaction are found to be dependant on a number of factors: temperature, solvent, catalyst (cationic vs. neutral), and the ability of the substrate to coordinate to the catalyst. Furthermore, the products from the allenic Alder-ene reaction are useful substrates for further functionalization; and in turn will be a synthetically useful intermediate for the synthesis of ovalicin (**1.16**).

1.6 EXPERIMENTAL

1.6.1 General

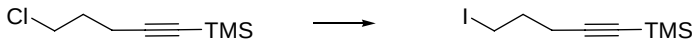
All reactions were performed using syringe-septum cap techniques under a nitrogen atmosphere and glassware was flame dried prior to use. All commercially available compounds were purchased from Aldrich Chemical Co., GFS Chemicals, Strem Chemicals, and Acros Organics and used as received, unless otherwise specified. Tetrahydrofuran (THF), diethyl ether (Et_2O), and dichloromethane (DCM) were purified with alumina using the Sol-Tek ST-002 solvent purification system. Toluene, N,N,N',N'-Tetramethylethylenediamine (TMEDA), and triethylamine (Et_3N) were freshly distilled from CaH_2 prior to use. Trimethylsilyl trifluoromethanesulfonate (TMSOTf) was distilled from phosphorus pentoxide (P_2O_5) and stored in a septum sealed flask in the freezer. Copper iodide (CuI) was purified by following the procedure in *Purification of Laboratory Chemicals* by D.D. Perrin and W. L. F. Armarego.

Purification of the products by flash chromatography was performed using silica gel (32-63 μm particle size, 60 Å pore size) purchased from SAI. TLC analyses were performed on EM Science Silica Gel 60 F254 plates (250 μm thickness). HPLC purification was performed on a Varian-Prostar 210 instrument using a Varian Microsorb Dynamax 100-5 Si column (5 μm packing, 250 mm x 10 mm) or Varian Pursuit C8 column (5μ packing, 250 mm x 10mm).

Melting points were determined using a Laboratory Devices Mel-Temp II apparatus. All ^{1}H and ^{13}C spectra were obtained on either Bruker Avance 300 MHz or Bruker Avance DRX 500 MHz instruments, and chemical shifts (δ) reported relative to residual peak $CHCl_3$ or toluene. All NMR spectra were obtained at room temperature unless otherwise specified and are tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet,

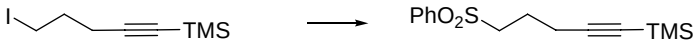
m = multiplet), coupling constant(s), number of protons. IR spectra were obtained using a Nicolet Avatar E.S.P. 360 FT-IR. EI mass spectrometry was performed on a Micromass Autospec high resolution mass spectrometer. ES low resolution mass spectrometry was performed on a HPMSD 1100 LCMS and high resolution was performed on ESI Biosystem time of flight mass spectrometer.

1.6.2 Experimental Procedures



1.50 **1.91**

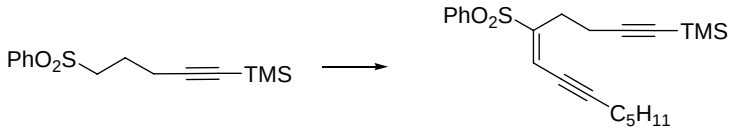
5-Iodo-1-(trimethylsilyl)-1-pentyne (1.91). To a solution of 5-chloro-1-(trimethylsilyl)-1-pentyne (**1.50**, 4.47 mL, 22.9 mmol) in 8 mL of acetone was added NaI (5.15 g, 34.4 mmol). The mixture was brought to reflux and the progress of the reaction was monitored by ^{1}H NMR spectroscopy. After 24 h the mixture was quenched by addition of water and the aqueous layer was extracted with Et_2O (3x). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with hexanes to afford the iodide **1.91** (6.06 g, 99% yield) as a colorless liquid. The spectroscopic data for this compound matched that in the literature.



1.91 **1.51**

1-Phenylsulfonyl-5-(trimethylsilyl)-4-pentyne (1.51). To a solution of iodide **1.91** (11.3 g, 42.3 mmol) in 50 mL of DMF was added anhydrous benzenesulphinic acid, sodium salt (8.34 g, 50.7 mmol). The mixture was warmed to 50 ˚C and after 1.5 h complete consumption of the starting

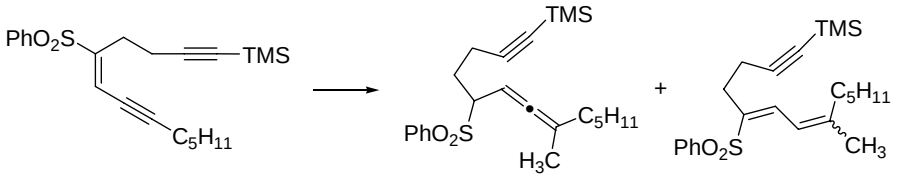
material was seen by TLC. The mixture was poured into an Et_2O / water mixture. The aqueous layer was separated and extracted with Et_2O (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 10% EtOAc / hexanes to afford sulfone **1.51** (9.08 g, 76% yield) as a white solid. R_f = 0.2 (20% EtOAc / hexanes); mp = 33 ˚C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.12 (s, 9H), 1.78-1.87 (m, 2H), 2.26 (t, *J* = 6.8 Hz, 2H), 3.15-3.20 (m, 2H), 7.48-7.64 (m, 3H), 7.82-7.86 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ -0.18 (3), 18.4, 21.7, 54.8, 86.3, 104.2, 127.7 (2), 129.1 (2), 133.5, 138.9; IR (neat) 2958, 2175, 1447, 1307 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 280 ($[M-CH_3]^+$, 0.4), 265 (50), 135 (100), 77 (51), 73 (63): HRMS calcd for $C_{13}H_{17}O_2SiS$: 265.0719 $[M-CH_3]^+$; found: 265.0721 $[M-CH_3]^+$.



1.51 ***E*-1.52**

(5-Benzenesulfonyltridec-5-ene-1,7-diynyl)trimethylsilane (*E*-1.52). To a solution of sulfone **1.51** (1.00 g, 3.57 mmol) in 15 mL of THF at -78 ˚C was added *n*-butyllithium (2.7 mL of a 1.6 M hexanes solution, 4.3 mmol) dropwise over 10 min. After 1 h at -78 ˚C, a solution of 2-octynal (0.53 g, 4.3 mmol) in 3 mL of THF was added via cannula and the mixture was kept at -78 ˚C for 1 h and then allowed to warm to 10 ˚C at which time complete consumption of starting material was observed by TLC. The mixture was then cooled to -78 ˚C and acetic anhydride (1.47 g, 14.4 mmol) was added. The mixture was quenched at ambient temperature with a sat. aqueous NH_4Cl solution, and the aqueous layer was separated and washed with Et_2O (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by silica gel chromatography eluting with 10% EtOAc / hexanes. The mixture of diastereomers were collected (1.40 g, 3.14 mmol) and azeotroped *in*

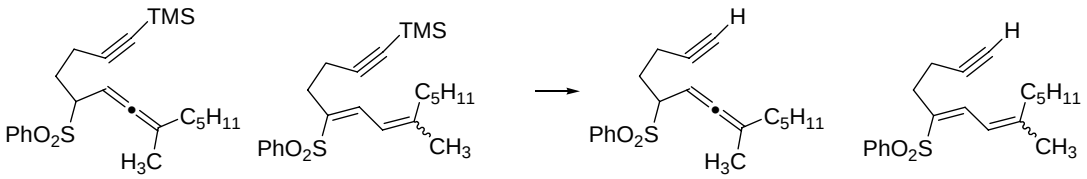
vacuo with benzene (3x), diluted with 8 mL of THF, and cooled to 0 ˚C. DBU (0.52 g, 3.5 mmol) was added to the solution and after 30 min a 10% HCl / ether solution was added to the reaction. The aqueous layer was separated and extracted with Et_2O (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 10% EtOAc / hexanes to afford enyne *E*-**1.52** (738 mg, 60% yield over two steps) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.13 (s, 9H), 0.92 (t, *J* = 7.0 Hz, 3H), 1.28-1.45 (m, 4H), 1.59 (quin, *J* = 7.1 Hz, 2H), 2.35-2.47 (m, 4H), 2.59-2.65 (m, 2H), 6.84 (t, *J* = 2.2 Hz, 1H), 7.52-7.67 (m, 3H), 7.87-7.90 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.0 (3), 13.8, 19.0, 19.8, 22.0, 27.8, 28.0, 30.9, 75.0, 85.2, 105.0, 106.7, 122.3, 128.0 (2), 129.2 (2), 133.5, 139.1, 148.5; IR (neat) 2958, 2932, 2860, 2213, 2177, 1446 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 386 ([M]$^+$, 2), 371 (3), 135 (45), 73 (100): HRMS calcd for $C_{22}H_{30}O_2SiS$: 386.1736; found: 386.1739.



E-**1.52** **1.53** **1.54**

(5-Benzenesulfonyl-8-methyltrideca-6,7-dien-1-ynyl)-trimethylsilane (1.53). To a suspension of CuI (1.51 g, 7.94 mmol) in 40 mL of ether at -30 ˚C was added MeLi (12.4 mL of a 1.3 M diethyl ether solution, 15.8 mmol) dropwise. The mixture was allowed to warm to 0 ˚C over a 30 min period and it changed from cloudy yellow to a clear solution. The flask was cooled to -50 ˚C and a solution of enyne *E*-**1.52** (1.53 g, 3.97 mmol) and TMSOTf (0.77 mL, 4.0 mmol) in 20 mL of ether was added dropwise with a cannula. The mixture was kept at -50 ˚C to -30 ˚C for 3 h and then was warmed to -15 ˚C and kept at that temperature for 7 h before a sat. aqueous NH_4Cl solution and ether were added. The biphasic solution was stirred vigorously until the aqueous

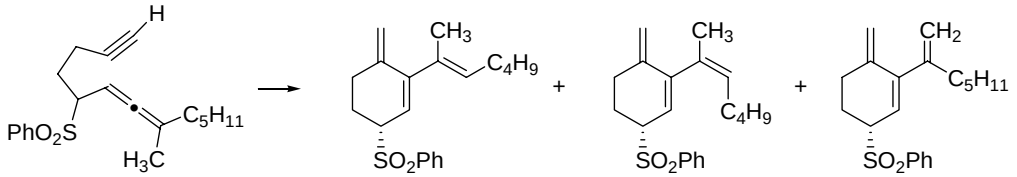
layer turned deep blue. The solution was then filtered through a sintered glass funnel of medium porosity packed with celite to remove the copper salts and aqueous layer. The celite was rinsed with ether to assure complete filtration of products. The organic layer was concentrated under reduced pressure and the residue was purified by silica gel chromatography eluting with 3% EtOAc / hexanes to afford a mixture of allene **1.53** and diene **1.54** (1.08 g, 67% yield) a 7 : 1 ratio as determined by ^{1}H NMR. The mixture was taken on to the next step. However, pure allene **1.53** was obtained by HPLC for spectroscopic purposes (Varian Microsorb Dynamax 100-5 Si column, 23 ˚C, EtOAc / hexanes = 5%, flow rate = 3 mL/min). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.14 (s, 9H), 0.88 (t, *J* = 6.3 Hz, 3H), 1.19-1.35 (m, 4H), 1.30 (d, *J* = 2.3 Hz, 3H), 1.75-1.90 (m, 4H), 2.18-2.52 (m, 4H), 3.68 (ddd, *J* = 2.8 Hz, *J* = 8.5 Hz, and *J* = 11.1 Hz, 1H), 4.88-4.97 (m, 1H), 7.53-7.70 (m, 3H), 7.87-7.92 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.5 (3), 14.4, 17.8, 18.2, 22.8, 26.5, 27.3, 31.9, 33.9, 66.1, 84.0, 86.7, 103.2, 105.3, 129.2 (2), 129.7 (2), 133.8, 138.4, 206.0; IR (neat) 2957, 2858, 2175, 1950, 1447, 1307 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 402 ([M]$^+$, 0.6), 387 (0.6), 277 (12), 125 (12), 73 (100): HRMS calcd for $C_{23}H_{34}O_2Si_1S_1$: 402.2049; found: 402.2047.



1.53 **1.54** **1.53a** **1.54a**

(5-Benzenesulfonyl-8-methyltrideca-6,7-dien-1-ynyl) (1.53a). To a solution of a x : x mixture of allenyne **1.53** and diene **1.54** (0.11 g, 0.26 mmol) in 1.3 mL of THF at 0 ˚C was added a mixture of TBAF (0.26 mL of a 1 M THF solution, 0.26 mmol) and 0.02 mL of pH 7.38 phosphate buffer solution dropwise via syringe. The reaction flask was allowed to warm to ambient temperature and after 1 h the reaction was quenched with a sat. aqueous NH_4Cl solution,

and the aqueous layer was separated and washed with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 5% EtOAc / hexanes to afford allenyne **1.53a** and diene **1.54a** (81 mg, 94% yield) as a colorless oil in a 3 : 1 mixture, but pure material could be obtained using HPLC. ^{1}H NMR (300 MHz, $CDCl_3$): allene **1.53a** δ 0.87 (t, *J* = 7.2 Hz, 3H), 1.12-1.29 (m, 7H), 1.76-1.90 (m, 4H), 1.07 (t, *J* = 2.4 Hz, 1H), 2.18-2.48 (m, 4H), 3.69 (ddd, *J* = 2.9, 8.6, and 11.0 Hz, 1H), 4.90-4.96 (m, 1H), 7.53-7.67 (m, 3H), 7.88-7.91 (m, 2H); ^{1}H NMR (300 MHz, $CDCl_3$) diene **1.54a**: δ 0.93 (t, *J* = 6.7 Hz, 3H), 1.27-1.51 (m, 6H), 1.94 (m, 4H), 2.28-2.37 (m, 4H), 2.52-2.57 (m, 2H), 6.07 (d, *J* = 11.8 Hz, 1H), 7.52-7.66 (m, 4H), 7.86-7.90 (m, 2H).



1.53a *E*-**1.55a** *Z*-**1.55a** **1.56a**

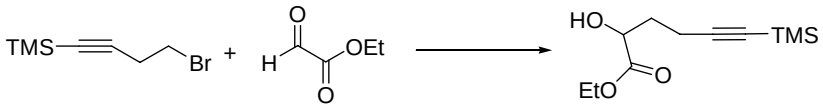
General procedure for Allenic Alder-ene reaction (Table 1). [4-Benzenesulfonyl-2-(1-methylhept-1E-enyl)-cyclohex-2-enylidenemethyl] trimethylsilane (E-1.55a), [4-methylene-3-(1-methylhept-1Z-enyl)-cyclohex-2-enesulfonylbenzene]trimethylsilane (Z-1.55a), and [4-methylene-3-(1-methyleneheptyl)-cyclohex-2-enesulfonylbenzene] trimethylsilane (1.56a):

Method A. (Entries 1, 2, & 12, Table 1) To a 13 x 100 mm test tube was added a mixture of allene **1.53a** and diene **1.54a** and the tests tube was sealed with a #17 SUBA·SEAL® rubber septum. Next, benzene (≈0.1 mL) was added and subsequently removed under vacuum (3x), by insertion an 18 gauge needle connected to a vac-line (7 mm Hg) into the septum. Once the benzene was evaporated the test tube was charged with N_2. The residue was then dilute with

toluene (0.2 M) and the test tube was evacuated under vacuum and charged with N_2 three times. Then, 5 mol% $[Rh(CO)_2Cl]_2$ was added at ambient temperature and the system was evacuated and charged with N_2 once more. The reaction was monitored by GC and quenched by direct addition to a silica gel plug eluting with 5% EtOAc / hexanes to afford trienes *E*-**1.55**, *Z*-**1.55**, and **1.56** and recovered **1.54a** or *E*-**1.55a**, *Z*-**1.55a**, and **1.56a**. The crude mixture was analyzed by ^{1}H NMR and the ratios were determined by integration of distinct olefinic peaks from each isomer.

Method B: (Entries 3-11, Table 1) To a 13 x 100 mm test tube was added a mixture of allene **1.53** and diene **1.54** and the tests tube was sealed with a #17 SUBA·SEAL® rubber septum. Next, benzene (≈0.1 mL) was added and subsequently removed under vacuum (3x), by insertion an 18 gauge needle connected to a vac-line (7 mm Hg) into the septum. Once the benzene was evaporated the test tube was charged with N_2. The residue was then dilute with dichloroethane (0.2 M) and the test tube was evacuated under vacuum and charged with N_2 three times. Then, 10 mol% $[Ir(COD)Cl]_2$ or 10 mol% $[Rh(COD)Cl]_2$ was added followed by 20 mol% $AgBF_4$ (0.05 M dichloroethane solution) or 20 mol% $In(OTf)_3$ (0.05 M acetone solution) and the system was evacuated and charged with N_2 once more. The mixture was monitored by GC and quenched by direct addition to a silica gel plug eluting with 5% EtOAc / hexanes to afford a mixture of trienes *E*-**1.55**, *Z*-**1.55**, and **1.56** and recovered **1.54** or *E*-**1.55a**, *Z*-**1.55a**, and **1.56a** depending on conditions (see table 1). The crude mixture was analyzed by ^{1}H NMR and the ratios were determined by integration of distinct olefinic peaks from each isomer; however, pure trienes *E*-**1.55a**, *Z*-**1.55a**, and **1.56a** were obtained by HPLC for spectroscopic purposes (Varian Microsorb Dynamax 100-5 Si column, 23 ˚C, EtOAc / hexanes = 5%, flow rate = 3 mL/min [*E*-**1.55a** and **1.56a**], Varian Pursuit C8, 5µ, 23 ºC, H_2O / MeCN = 25%, flow rate = 5 mL/min [*Z*-**1.55a**]). ^{1}H

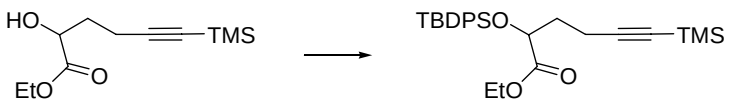
NMR (300 MHz, $CDCl_3$) *E*-**1.55a** : δ 0.93 (t, *J* = 7.0 Hz, 3H), 1.30-1.44 (m, 4H), 1.70 (s, 3H), 1.85-1.98 (m, 1H), 2.00-2.31 (m, 4H), 2.32-2.45 (m, 1H), 3.86-3.98 (m, 1H), 4.89 (s, 1H), 4.92 (s, 1H), 5.27 (t, *J* = 7.2 Hz, 1H), 5.67 (d, *J* = 2.7 Hz, 1H), 7.50-7.70 (m, 3H), 7.85-7.92 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 14.2, 16.9, 22.6, 23.8, 27.9, 29.5, 31.8, 63.2, 114.3, 116.2, 129.1 (2), 129.5 (2), 130.6, 134.0, 134.5, 137.3, 140.0, 150.2; ^1H NMR (300 MHz, $CDCl_3$) *Z*-**1.55a** : δ 0.80-0.90 (m, 3H), 1.18-1.28 (m, 6H), 1.74 (s, 3H), 1.90-2.05 (m, 1H), 2.05-2.20 (m, 1H), 2.21-2.35 (m, 1H), 2.40-2.53 (m, 1H), 3.90-3.98 (m, 1H), 4.88 (s, 1H), 4.94 (s, 1H), 5.30-5.38 (m, 1H), 5.56-5.60 (m, 1H), 7.52-7.69 (m, 3H), 7.86-7.91 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 14.0, 22.3, 23.3, 24.3, 28.9, 29.7, 32.0, 63.0, 113.4, 117.1, 128.9, 129.0 (2), 129.2 (2), 133.7, 133.9, 137.5, 138.8, 146.5; IR (neat) 2956, 2927, 1447, 1306 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) Constitutional isomer **1.56a** : δ 0.89 (t, *J* = 6.6 Hz, 3H), 1.00-1.42 (m, 6H), 1.88-2.30 (m, 5H), 2.38-2.49 (m, 1H), 3.88-3.96 (m, 1H), 4.80 (d, *J* = 2.2 Hz, 1H), 4.90-4.99 (m, 3H), 5.67 (d, *J* = 2.8 Hz, 1H), 7.52-7.69 (m, 3H), 7.86-7.92 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 14.2, 22.6, 23.6, 27.9, 29.3, 31.5, 36.1, 63.0, 114.3, 114.5, 117.0, 129.1 (2), 129.4 (2), 133.9, 137.2, 139.8, 147.6, 148.9.



1.61 **1.59** **1.60**

2-Hydroxy-6-trimethylsilylhex-5-ynoic acid, ethyl ester (1.60). To a flame dried 2-neck flask containing a suspension of Rieke Mg® (8.00 mL of a 0.025 g/L solution in THF, 8.23 mmol) at 0 ˚C was added a solution of bromide **1.61** (1.40 g, 6.82 mmol) in 7 mL of THF using a cannula. The mixture was allowed to warm to ambient temperature and after 30 min this solution was added to a solution of freshly distilled ethyl glyoxylate (**1.59**) (approximately 0.69 g, 6.82 mmol) in 30 mL of Et_2O at -78 ˚C. The mixture was quenched by the addition of acetic acid after 1.5 h

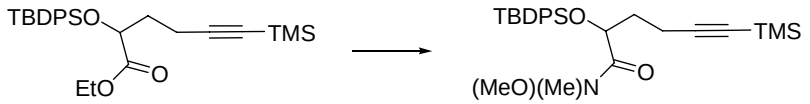
at -78 ˚C and allowed to warm to ambient temperature. Water was then added and the aqueous layer was extracted with Et_2O (3x). The combined organic layers were washed with a sat. aqueous $NaHCO_3$ solution, brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 5% EtOAc / hexanes to afford ester **1.60** (364 mg, 25% yield). R_f = 0.4 (20% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.14 (s, 9H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.83 (ddt, *J* = 5.9 Hz, *J* = 7.9 Hz, *J* = 13.9 Hz, 1H), 2.04 (ddt, *J* = 3.9 Hz, *J* = 7.9 Hz, *J* = 13.7 Hz, 1H), 2.37 (ddd, *J* = 5.9 Hz, *J* = 7.9 Hz, *J* = 16.8 Hz, 1H), 2.46 (m, 1H), 4.30-4.22 (m, 3H); ^{13}C NMR(75 MHz, $CDCl_3$): δ 0.01 (3), 14.1, 15.7, 33.3, 61.8, 69.2, 85.3, 105.8, 174.8; IR (neat) 3492, 2961, 2175, 1732 cm^{-1}. MS (GC/MS) *m/e* (relative intensity) 213 ($[M-CH_3]^+$, 30), 84 (100), 73 (75).



1.60 **1.63**

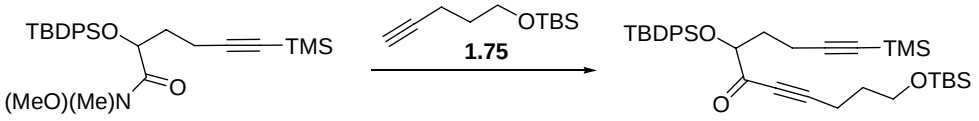
2-(*tert*-Butyldiphenylsilyloxy)-6-trimethylsilylhex-5-ynoic acid ethyl ester (1.63). To a solution of the α-hydroxy-ester **1.60** (0.20 g, 0.88 mmol) in 0.5 mL of DMF was added imidazole (0.17 g, 2.5 mmol) and then TBDPSCl (0.34 g, 1.2 mmol). The mixture was left at ambient temperature for 1 h at which time complete consumption of starting material was observed by TLC. The mixture was quenched by addition to a silica gel column eluting with 5% EtOAc / hexanes to afford ester **1.63** and TBDPSCl (463 mg, 113% yield) as a colorless oil. Pure ester **1.63** was obtained for spectroscopic purposes. R_f = 0.6 (20% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.15 (s, 9H), 1.05 (t, *J* = 7.1 Hz, 3H), 1.12 (s, 9H), 2.06-1.90 (m, 2H), 2.52-2.22 (m, 2H), 3.97-3.77 (m, 2H), 4.34 (t, *J* = 5.4 Hz, 1H), 7.72-7.61 (m, 4H), 7.48-7.33 (m, 6H); ^{13}C NMR(75 MHz, $CDCl_3$): δ 0.1 (3), 13.9, 15.6, 19.5, 26.9 (3), 34.2, 60.5, 71.5, 84.9,

106.2, 127.4 (2), 127.6 (2), 129.8 (2), 133.2 (2), 135.8 (2), 135.9 (2), 172.6; IR (neat) 2959, 2858, 2176, 1754 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 409 ($[M\text{-}C(CH_3)_3]^+$, 100), 271 (76), 227 (84): HRMS calcd for $C_{23}H_{29}O_3Si_2$: 409.1655 $[M\text{-}C(CH_3)_3]^+$; found: 409.1668 $[M\text{-}C(CH_3)_3]^+$.



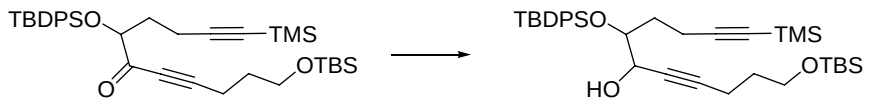
1.63 **1.92**

2-(*tert*-Butyldiphenylsilyloxy)-6-trimethylsilylhex-5-ynoic acid methoxy methyl amide (1.92). To a solution of ester **1.63** (1.20 g, 2.57 mmol) in 5 mL of THF was added MeNHOMe·HCl (0.38 g, 3.9 mmol) and the flask was cooled to 0 ˚C. Then *i*-PrMgCl (2.60 mL of a 2.0 M THF solution, 5.15 mmol) was added dropwise and after addition was finished complete consumption of the starting material was seen by TLC. The mixture was quenched with a sat. aqueous NH_4Cl solution, and the aqueous layer was separated and washed with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 10% - 15% EtOAc / hexanes to afford the desired amide **1.92** (1.01 g, 80% yield) as a colorless oil. R_f = 0.4 (20% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.12 (s, 9H), 1.10 (s, 9H), 1.91-1.98 (m, 2H), 2.36 (dt, *J* = 6.6 Hz, *J* = 17.1 Hz, 1H), 2.49 (dt, *J* = 7.8 Hz, *J* = 17.1 Hz, 1H), 2.90 (s, 3H), 3.11 (s, 3H), 4.66 (t, *J* = 5.8 Hz, 1H), 7.33-7.45 (m, 6H), 7.68-7.75 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.1 (3), 15.9, 19.5, 27.0 (3), 32.2, 33.7, 60.7, 68.9, 84.8, 106.7, 127.3 (2), 127.5 (2), 129.5, 129.6, 133.5 (2), 133.6 (2), 136.0, 136.2, 173.1; IR (neat) 2959, 2933, 2857, 2174, 1681 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 466 ($[M\text{-}CH_3]^+$, 7), 424 (100): HRMS calcd for $C_{26}H_{36}N_1O_3Si_2$: 466.2234 $[M\text{-}CH_3]^+$; found: 466.2244 $[M\text{-}CH_3]^+$.



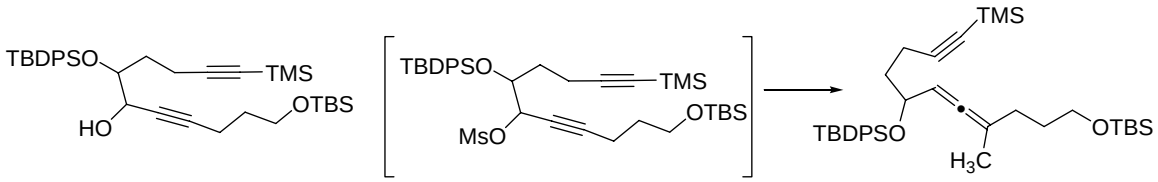
1.92 **1.64**

11-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxy)-1-trimethylsilylundeca-1,7-diyn-6-one (1.64). To a solution of alkyne **1.75** (0.82 g, 4.2 mmol) in 14 mL of THF at -78 ˚C was added *n*-butyllithium (1.74 mL of a 2.5 M hexane solution, 4.36 mmol) dropwise. The flask was kept at -78 ˚C for 10 min and then placed in a -20 ˚C bath for 20 min. It was then cooled to -78 ˚C and added to a solution of amide **1.92** (1.0 g, 2.1 mmol) in 5 mL of THF at -78 ˚C via cannulation. The mixture was then allowed to slowly warm over 2 h to 0 ˚C at which time complete consumption of the starting material was seen by TLC. The reaction was quenched with a sat. aqueous NH_4Cl solution, and the aqueous layer was separated and extracted with Et_2O (3x). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 5% EtOAc / hexanes to afford ketone **1.64** and alkyne **1.75**. The mixture was not separated at this point but pure ketone **1.64** was obtained for spectroscopic purposes. R_f = 0.7 (20% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.13 (s, 9H), 0.90 (s, 9H), 1.12 (s, 9H), 1.66-1.75 (m, 2H), 1.85-2.06 (m, 2H), 2.21-2.41 (m, 4H), 3.65 (t, *J* = 6.5 Hz, 2H), 4.30 (t, *J* = 5.6 Hz, 1H), 7.33-7.47 (m, 6H), 7.64-7.68 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ -5.4 (2C), 0.1 (3C), 15.3, 15.7, 18.3, 19.5, 25.9 (3), 27.0 (3), 30.7, 33.7, 61.3, 78.2, 79.4, 85.2, 97.7, 106.1, 127.6 (2), 127.7 (2), 129.8, 129.9, 133.1 (2), 133.3 (2), 135.8, 136.0, 188.3; IR (neat) 2956, 2857, 2211, 2176, 1675 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 603 ([M-CH_3]$^+$, 1.6), 516 (60), 197 (60), 135 (100): HRMS calcd for $C_{35}H_{51}O_3Si_3$: 603.3146 [M-CH_3]$^+$; found: 603.3120 [M-CH_3]$^+$.



1.64 **1.93**

11-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxy)-1-trimethylsilyl-1-undeca-1,7-diyn-6-ol (1.93). Ketone **1.64** and alkyne **1.75** (≈2.1 mmol) were diluted with $CeCl_3 \cdot 7H_2O$ (6.8 mL of a 0.4 M methanol solution, 2.7 mmol), cooled to -20 ˚C, and $NaBH_4$ (0.10 g, 2.7 mmol) was added in one portion. The mixture was allowed to warm to 0 ˚C and after 30 min complete consumption of starting material was observed by TLC. The reaction was quenched with slow addition of H_2O, and the aqueous layer was separated and washed with Et_2O (3x). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 3% - 10% EtOAc / hexanes to afford the desired alcohol **1.93** (772 mg, 58% yield) over 2 steps. R_f = 0.6 (20% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.06 (s, 6H), 0.12 (s, 9H), 0.90 (s, 9H), 1.10 (s, 9H), 1.65-1.91 (m, 3H), 2.12-2.32 (m, 5H), 3.66 (t, *J* = 6.1 Hz, 2H), 3.88 (q, *J* = 5.3 Hz, 1H), 4.30 (m, 1H), 7.37-7.49 (m, 6H), 7.72 (t, *J* = 6.8 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ -5.3 (2), 0.1 (3), 15.2, 15.8, 18.3, 19.5, 25.9 (3), 27.1 (3), 31.6, 31.9, 61.6, 65.3, 75.5, 79.0, 84.7, 86.2, 106.5, 127.6 (2), 127.7 (2), 129.8 (2), 133.4 (2), 133.6 (2), 135.87 (2); IR (neat) 3451, 2956, 2858, 2175 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 620 ($[M]^+$, 0.3), 563 (10), 199 (97), 135 (100): HRMS calcd for $C_{32}H_{47}O_3Si_3$: 563.2833 $[M\text{-}C(CH_3)_3]^+$; found: 563.2830 $[M\text{-}C(CH_3)_3]^+$.

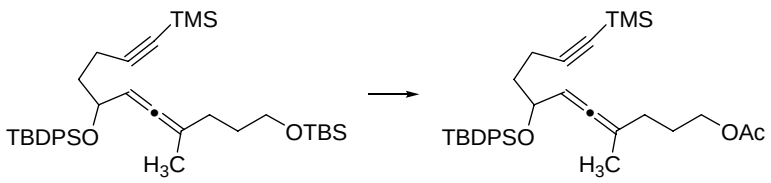


1.93 **1.94** **1.57a**

11-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxy)-8-methyl-1-

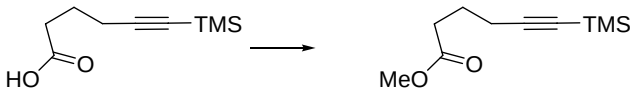
trimethylsilylundeca-6,7-dien-1-yne (1.57a). To a solution of the alcohol **1.93** (0.33 g, 0.51 mmol) in 1.7 mL of CH_2Cl_2 was added TEA (96 μL, 0.69 mmol) and the solution was cooled to 0 ˚C. Then MsCl (48 μL, 0.62 mmol) was added and after 30 min at 0 ˚C the reaction was diluted with pentanes. The solution was then filtered through a sintered glass funnel of medium porosity packed with celite and the resulting solution was washed with a sat. aqueous $NaHCO_3$ solution and brine. The organic layer were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mesylate **1.94** was used immediately without further purification.

To a suspension of CuI (0.12 g, 0.62 mmol) in 2 mL of THF at -30 ˚C was added MeLi (0.64 mL of a 1.6 M diethyl ether solution, 1.0 mmol) dropwise. The reaction was allowed to warm to 0 ˚C over a 30 min period while it changed from a cloudy yellow to clear solution. It was cooled to -78 ˚C and a solution of the mesylate **1.94** in 1.7 mL of THF was added dropwise with a cannula. The reaction kept at that temperature for 1 h before a sat. aqueous NH_4Cl solution and Et_2O were added. The biphasic solution was stirred vigorously until the aqueous layer turned a deep blue. The solution was then filtered through a sintered glass funnel of medium porosity packed with celite to remove the copper salts and aqueous layer. The organic layer was concentrated under reduced pressure and the residue was purified by silica gel chromatography eluting with 3% EtOAc / hexanes to afford allene **1.57a** and enyne **1.65** (256 mg, 80% yield) as a colorless oil 23 : 1 ratio as determined by ^{1}H NMR) R_f = 0.8 (20% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.12 (s, 9H), 0.98 (s, 9H), 1.06 (s, 9H), 1.42-1.52 (m, 2H), 1.60 (d, *J* = 2.8 Hz, 3H), 1.65-1.90 (m, 4H), 2.25-2.34 (m, 2H), 3.51 (t, *J* = 6.4 Hz, 2H), 4.27-4.38 (m, 1H), 4.95-5.02 (m, 1H), 7.33-7.45 (m, 6H), 7.67-7.71 (m, 4H). IR (neat) 2956, 2858, 2175, 1966 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 618 ($[M]^+$, 5), 561 (100), 199 (94): HRMS calcd for $C_{37}H_{58}O_2Si_3$: 618.3745; found: 618.3751.



1.57a **1.57b**

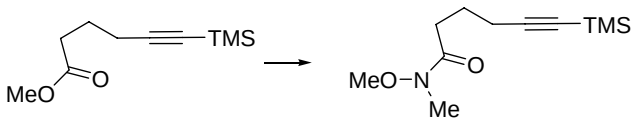
7-(tert-Butyldiphenylsilyloxy)-4-methyl-11-(trimethylsilyl)undeca-4,5-dien-10-ynyl acetate (1.57b). To a solution of allene **1.57a** and enyne **1.65** (36 mg, 0.06 mmol) in 40 μL of acetic anhydride at 0 ˚C was added $FeCl_3$ (1.0 mg, 0.01 mmol) and the solution instantly turned maroon color. After 10 min complete consumption of the starting material was seen by TLC, and the mixture was quenched by addition of hexanes / water. The aqueous layer was separated and washed with Et_2O (3x) and the combined organic layers concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 5% EtOAc / hexanes to afford allenic acetate **1.57b** and enyne **1.65b** (23 mg, 72% yield) of a colorless oil in a 3.7 : ratio as determined by ^{1}H NMR. *denoted product **1.57b** where peaks are resolved. R_f = 0.4 (10% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.12* (s, 9H), 0.16 (s, 3H), 1.06* (s, 9H), 1.11 (s, 3H), 1.59-1.49 (m, 3H), 1.60* (d, *J* = 2.8 Hz, 3H), 1.96-1.64 (m, 8H), 2.04* (s, 3H), 2.07 (s, 1H), 2.55-2.25 (m, 5H), 3.96* (t, *J* = 6.5 Hz, 2H), 4.19 (t, *J* = 6.3 Hz, 0.6H), 5.05-4.97* (m, 1H), 5.65-5.47 (m, 0.3H), 5.91 (dt, *J* = 7.1 Hz, *J* = 10.7 Hz, 0.3H), 7.48-7.33 (m, 8H), 7.73-7.66 (m, 5H).



1.68 **1.95**

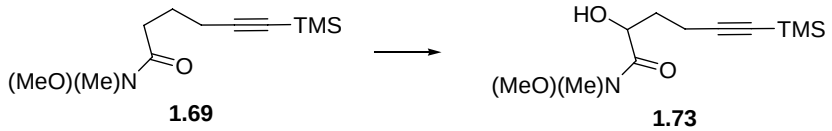
6-Trimethylsilylhex-5-ynoic acid methyl ester 1.95. To a solution of acid **1.68** (0.60 g, 3.3 mmol) in 2 mL of DMF was added $KHCO_3$ (0.82 g, 8.2 mmol) and MeI (1.16 g, 8.15 mmol). The mixture changed from to clear to yellow to orange/brown color and was left at ambient temperature. After 24 h complete consumption of starting material was seen by TLC, and the

mixture was poured into EtOAc / water solution. The aqueous layer was separated and extracted with EtOAc (3x). The combined organic layers were washed with H_2O, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 5% EtOAc / hexanes to afford the ester **1.95** (499 mg, 76% yield) as a yellow oil. R_f = 0.4 (20% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.15 (s, 9H), 1.85 (quin, *J* = 7.2 Hz, 2H), 2.30 (t, *J* = 6.9 Hz, 2H), 2.45 (t, *J* = 7.4 Hz, 2H), 3.69 (s, 3H).



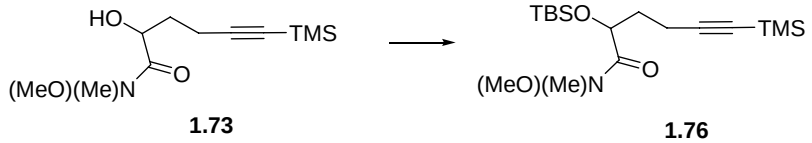
1.95 **1.69**

6-Trimethylsilylhex-5-ynoic acid methoxy methyl amide (1.69). To a solution of ester **1.95** (0.50 g, 2.5 mmol) in 5 mL of THF was added MeNHOMe·HCl (0.37 g, 3.8 mmol) and the flask was cooled to -25 ˚C. Then *i*-PrMgCl (3.8 mL of a 2.0 M THF solution, 7.6 mmol) was added dropwise and after addition was finished complete consumption of the starting material was seen by TLC. The mixture was quenched with a sat. aqueous NH_4Cl solution, and the aqueous layer was separated and washed with Et_2O (3x). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 20% EtOAc / hexanes to afford amide **1.69** (520 mg, 91% yield) as a colorless oil. R_f = 0.2 (20% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.12 (s, 9H), 1.77-1.86 (m, 2H), 2.29 (t, *J* = 6.8 Hz, 2H), 2.54 (t, *J* = 7.4 Hz, 2H), 3.16 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.0 (3), 19.3, 23.2, 30.4, 32.1, 61.1, 85.1, 106.5, 173.8; IR (neat) 3483, 2959, 2901, 2174, 1667 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 227 ($[M]^+$, 10), 212 (18), 167 (65), 73 (100): HRMS calcd for $C_{11}H_{21}N_1O_2Si_1$: 227.1342; found: 227.1341.



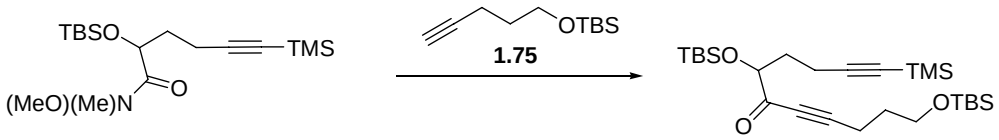
1.69 **1.73**

2-Hydroxy-6-trimethylsilylhex-5-ynoic acid methoxy methyl amide (1.73). To a flame dried round bottom flask was added 20 mL of THF and the flask was cooled to -78 ˚C. NaHMDS (8.58 mL of a 1 M THF solution, 8.58 mmol) was first added and then a solution of amide **1.69** (1.30 g, 5.72 mmol) in 40 mL of THF was added. The solution was left at -78 ˚C for 30 min and then a solution of $PhSO_2NOCHPh$ (2.24 g, 8.58 mmol) in 30 mL of THF was added via cannulation. After 30 min complete consumption of starting material was seen by TLC. The mixture was quenched with a sat. aqueous NH_4Cl solution, and allowed to warm to ambient temperature. The stir bar was removed and the organic layer was removed under reduced pressure. The mixture was diluted with Et_2O and the aqueous layer was separated and washed with Et_2O (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting solids were diluted with 3 : 1 hexane : chloroform solution and filtered via gravity filtration. After removal of solvent, the residue was purified by silica gel chromatography eluting with 20% EtOAc / hexanes to afford α-hydroxy amide **1.73** (1.20 g, 86% yield). R_f = 0.2 (30% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.13 (s, 9H), 1.57-1.70 (m, 1H), 1.89-2.06 (m, 1H), 2.37-2.54 (m, 2H), 3.25 (s, 3H), 3.24 (bd, *J* = 4.9 Hz, 1H), 3.72 (s, 3H), 4.49 (t, *J* = 6.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.1 (3), 16.0, 32.4, 33.7, 61.4, 67.3, 84.8, 106.2, 174.5; IR (neat) 3445, 2960, 2174, 1660 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 228 ($[M\text{-}CH_3]^+$, 40), 155 (30), 73 (100), 61 (91): HRMS calcd for $C_{10}H_{18}N_1O_3Si_1$: 228.1056 $[M\text{-}CH_3]^+$; found: 228.1052 $[M\text{-}CH_3]^+$.



1.73 **1.76**

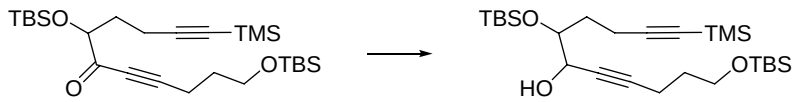
2-(*tert*-Butyldimethylsilyloxy)-6-trimethylsilylhex-5-ynoic acid methoxymethylamide (1.76). To a solution of amide **1.73** (1.20 g, 4.93 mmol) in 15 mL of CH_2Cl_2 at 0 ˚C was added TEA (1.37 mL, 9.86 mmol) and then TBSOTf (1.70 mL, 7.40 mmol). After 20 min at 0 ˚C a complete loss of starting material was seen by TLC. The solution was quenched with a sat. aqueous NH_4Cl solution and Et_2O, and the aqueous layer was separated and washed with Et_2O (3x). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 10% EtOAc / hexanes to afford **1.76** (1.65 g, 94% yield) as a colorless oil. R_f = 0.5 (20% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.09 (s, 3H), 0.10 (s, 3H), 0.14 (s, 9H), 0.91 (s, 9H), 1.72-1.91 (m, 2H), 2.28-2.51 (m, 2H), 3.19 (s, 3H), 3.72 (s, 3H), 4.72-4.83 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ -5.3, -4.7, 0.1 (3), 16.0, 18.3, 25.8 (3), 32.7, 33.1, 61.4, 68.0, 85.2, 106.3, 174.5; IR (neat) 3445, 2960, 2174, 1660 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 342 ([M-CH_3]$^+$, 0.1), 300 (80), 73 (100): HRMS calcd for $C_{13}H_{26}NO_3Si_2$: 300.1451 [M-$C(CH_3)_3$]$^+$; found: 300.1445 [M- $C(CH_3)_3$]$^+$.



1.76 **1.77**

5,11-bis-(*tert*-Butyldimethylsilyloxy)-1-trimethylsilylundeca-1,7-diyn-6-one (1.77). To a solution of alkyne **1.75** (1.30 g, 6.51 mmol) in 18 mL of THF at -78 ˚C was added *n*-butyllithium (4.07 mL of a 1.6 M hexane solution, 6.51 mmol) dropwise. The flask was left at -78 ˚C for 10 min and then placed in a -20 ˚C bath for 20 min and was then cooled to -78 ˚C and added to a solution of amide **1.76** (1.55 g, 4.34 mmol) in 9 mL of THF at -78 ˚C via cannula. The mixture was then allowed to slowly warm over 2 h to -10 ˚C and the temperature was kept at -10 ˚C for

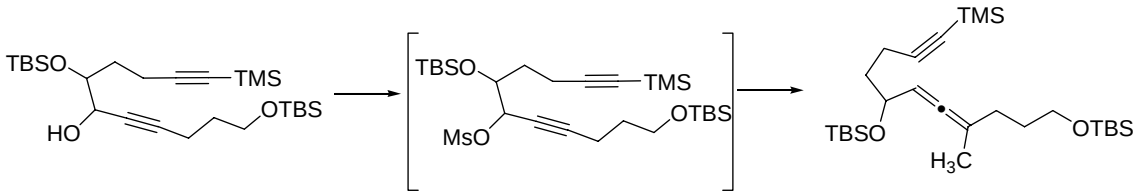
30 min at which time complete consumption of the starting material was seen by TLC. The solution was quenched with a sat. aqueous NH_4Cl solution, the stir bar was removed, and the organic layer was removed under reduced pressure. The mixture was diluted with Et_2O and the aqueous layer was separated and washed with Et_2O (3x). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 1% - 5% EtOAc / hexanes to afford ketone **1.77** (1.66 g, 77% yield). R_f = 0.8 (20% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.03 (s, 6H), 0.06 (s, 3H), 0.08 (s, 3H), 0.12 (s, 9H), 0.87 (s, 9H), 0.91 (s, 9H), 1.70-1.86 (m, 3H), 1.87-2.01 (m, 1H), 2.34 (t, *J* = 6.6 Hz, 2H), 2.47 (t, *J* = 7.1 Hz, 2H), 3.67 (t, *J* = 5.8 Hz, 2H), 4.24 (dd, *J* = 3.8 Hz, *J* = 8.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ -5.4 (2), -5.2, -4.6, 0.1 (3), 15.7, 15.8, 18.2 (2), 25.8 (3), 25.9 (3), 30.8, 33.3, 61.2, 77.5, 79.3, 85.7, 97.5, 105.9, 189.3; IR (neat) 2956, 2930, 2858, 2211, 2176, 1676 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 479 ($[M-CH_3]^+$, 2), 269 (58), 73 (100): HRMS calcd for $C_{25}H_{47}O_3Si_3$: 479.2833 $[M-CH_3]^+$; found: 479.2844 $[M-CH_3]^+$.



1.77 **1.96**

5,11-bis-(*tert*-Butyldimethylsilyloxy)-1-trimethylsilylundeca-1,7-diyn-6-ol (1.96). Ketone **1.77** (0.44, 0.89 mmol) was diluted with a solution of $CeCl_3 \cdot 7H_2O$ (2.89 mL of a 0.4 M solution in methanol, 1.16 mmol), cooled to -20 ˚C, and $NaBH_4$ (0.04 g, 1.2 mmol) was added in one portion. The mixture was allowed to warm to 0 ˚C and after 30 min complete consumption of starting material was observed by TLC. The solution was quenched with slow addition of H_2O, and the aqueous layer was separated and washed with Et_2O (3x). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was

purified by silica gel chromatography eluting with 5% EtOAc / hexanes to the afford alcohol **1.96** (388 mg, 88% yield) as a 7 : 1 diastereomeric ratio as determined by ^{1}H NMR). *denotes minor diastereomer where peaks were resolved. R_f = 0.6 (20% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.03 (s, 6H), 0.12 (s, 15H), 0.87 (s, 9H), 0.90 (s, 9H), 1.63-1.91 (m, 4H), 2.23-2.32 (m, 4H), 2.38 (d, *J* = 6.7 Hz, 1H), 3.65 (t, *J* = 6.0 Hz, 2H), 3.81-3.91 (m, 1H), 4.15-4.22 (m, 1H), 4.32-4.36* (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer) : δ -5.4 (2), -4.50, -4.47, 0.0 (3), 15.2, 15.9, 18.1, 18.2, 25.9 (6), 31.6, 32.2, 61.6, 65.3, 74.2, 79.5, 85.1, 85.7, 106.6; IR (neat) 3456, 2956, 2857, 2175 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 496 ([M]$^+$, 0.2), 307 (4), 73 (100): HRMS calcd for $C_{22}H_{43}O_3Si_3$: 439.2520 [M-C$(CH_3)_3$]$^+$; found: 439.2526 [M-C$(CH_3)_3$]$^+$.



1.96 **1.97** **1.57d**

5,11-bis-(*tert*-Butyldimethylsilyloxy)-8-methyl-1-trimethylsilylundeca-6,7-dien-1-yne (1.57d). To a solution of alcohol **1.96** (0.39 g, 0.78 mmol) in 2.6 mL of CH_2Cl_2 was added TEA (0.14 mL, 1.00 mmol) and the solution was cooled to 0 ˚C. Then MsCl (73 μL, 0.94 mmol) was added and after 30 min at 0 ˚C the mixture was diluted with pentanes. The mixture was then filtered through a sintered glass funnel of medium porosity packed with celite and the resulting solution was washed with a sat. aqueous $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mesylate **1.97** was used immediately without further purification.

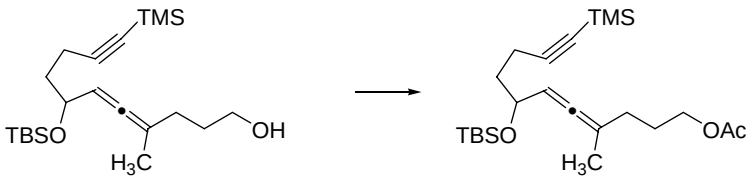
A separate round bottom flask was charged with CuI (0.18 g, 0.94 mmol) and 3.1 mL of THF was added. This suspension was cooled to -30 ˚C and MeLi (977 μL of a 1.6 M diethyl ether

solution, 1.56 mmol) was added dropwise. The mixture was allowed to warm to 0 ˚C over a 30 min period while it changed from a cloudy yellow to clear solution. It was then cooled to -78 ˚C and a solution of mesylate **1.97** in 2.6 mL of THF was added dropwise with a cannula. The mixture was kept at that temperature for 45 min before a sat. aqueous NH_4Cl solution and Et_2O were added. The biphasic solution was stirred vigorously until the aqueous layer turned a deep blue. The solution was then filtered through a sintered glass funnel of medium porosity packed with celite to remove the copper salts and aqueous layer. The organic layer was concentrated under reduced pressure and the residue was purified by silica gel chromatography eluting with 1% EtOAc / hexanes to afford allene **1.57d** and enyne **1.65** (330 mg, 86% yield) in a 7 : 1 ratio as determined by ^{1}H NMR. Pure allene **1.57d** was obtained by HPLC for spectroscopic purposes (Varian Microsorb Dynamax 100-5 Si column, 23 ˚C, EtOAc / hexanes = 1%, flow rate = 3 mL/min). R_f = 0.8 (10% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.07 (s, 3H), 0.08 (s, 3H), 0.15 (s, 9H), 0.89 (s, 9H), 0.90 (s, 9H), 1.60-1.82 (m, 4H), 1.69 (d, *J* = 2.8 Hz, 3H), 1.90-2.10 (m, 2H), 2.29 (t, *J* = 7.3 Hz, 2H), 3.63 (t, *J* = 6.4 Hz, 2H), 4.22 (dd, J = 6.7 Hz, *J* = 12.4 Hz, 1H), 4.95-5.03 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ -5.3 (2), -4.9, -4.3, 0.1 (3), 16.1, 18.2, 18.3, 19.3, 25.9 (3), 26.0 (3), 30.2, 31.0, 37.4, 62.8, 70.5, 84.5, 94.7, 100.9, 107.3, 199.7; IR (neat) 2956, 2857, 2176, 1965 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 494 ([M]$^+$, 1.2), 479 (1.5), 269 (45), 73 (100): HRMS calcd for $C_{27}H_{54}O_2Si_3$: 494.432; found: 494.3442.

1.57d **1.57e**

7-(*tert*-Butyldimethylsilyloxy)-4-methyl-11-trimethylsilyl-1-undeca-4,5-dien-10-ynyl-1-ol (1.57e). To a solution of a mixture of allene **1.57d** and enyne **1.65** (15 mg, 0.03 mmol) in 0.3 mL

of EtOH at ambient temperature was added PPTS (2.0 mg, 0.01 mmol). After 18 h at ambient temperature complete consumption of the starting material was observed by TLC. The solution was quenched with brine, diluted with Et_2O, and the aqueous layer was separated and washed with Et_2O (3x). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 10% EtOAc / hexanes to afford pure alcohol **1.57e** (5.3 mg, ≈ 70% yield). R_f = 0.3 (20% EtOAc / hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.05 (s, 3H), 0.06 (s, 3H), 0.12 (s, 9H), 0.87 (s, 9H), 1.62-1.78 (m, 4H), 1.67 (d, *J* = 3.0 Hz, 3H), 1.95-2.08 (m, 2H), 2.20-2.31 (m, 2H), 3.64 (t, *J* = 6.4 Hz, 2H), 4.22 (dd, *J* = 6.2 Hz, *J* = 12.5 Hz, 1H), 4.95-5.02 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.0, -4.4, 0.1 (3), 16.0, 18.1, 19.1, 25.8 (3), 30.2, 30.4, 37.3, 62.3, 70.2, 84.6, 94.8, 100.7, 107.2, 199.7; IR (neat) 3347, 2955, 2929, 2175, 1250 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 380 ([M]$^+$, 30), 323 (20), 269 (60), 75 (100): HRMS calcd for $C_{21}H_{40}O_2Si_2$: 380.2567; found: 380.2558.



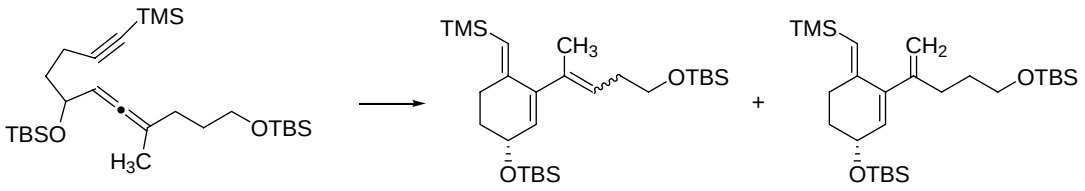
1.57e **1.57f**

7-(*tert*-Butyldimethylsilyloxy)-4-methyl-11-trimethylsilyl-1-undeca-4,5-dien-10-ynyl acetate (1.57f). To a solution of allene **1.57e** (0.05 g, 0.13 mmol) in 1.3 mL of CH_2Cl_2 at ambient temperature was added DMAP (6.0 mg, 0.05 mmol) and TEA (44 μL, 0.32 mmol). The mixture was then cooled to 0 ºC and Ac_2O (15 μL, 0.16 mmol) was added and the mixture was allowed to slowly warm to ambient temperature. After complete consumption of starting material was observed by TLC the solution was quenched with a sat. aqueous NH_4Cl solution, diluted with Et_2O, and the aqueous layer was separated and washed with Et_2O (3x). The combined organic

layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 5% EtOAc / hexanes to afford allene **1.57f** (52.0 mg, 95% yield). R_f = 0.7 (20% EtOAc / hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.07 (s, 3H), 0.14 (s, 9H), 0.89 (s, 9H), 1.60-1.81 (m, 4H), 1.69 (d, *J* = 2.8 Hz, 3H), 1.95-2.05 (m, 2H), 2.03 (s, 3H), 2.25-2.31 (m, 2H), 4.08 (t, *J* = 6.6 Hz, 2H), 4.22 (dd, *J* = 6.3, *J* = 12.5 Hz, 1H), 4.98-5.05 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ -4.9, -4.4, 0.1 (3), 16.1, 18.1, 18.2, 20.9, 25.8 (3), 26.7, 30.1, 37.4, 64.0, 70.2, 84.6, 95.2, 100.2, 107.2, 171.1, 199.7; IR (neat) 2956, 2929, 2174, 1744 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 422 ($[M]^+$, 38), 365 (45), 269 (60), 73 (100): HRMS calcd for $C_{23}H_{42}O_3Si_2$: 422.2673; found: 422.2664.

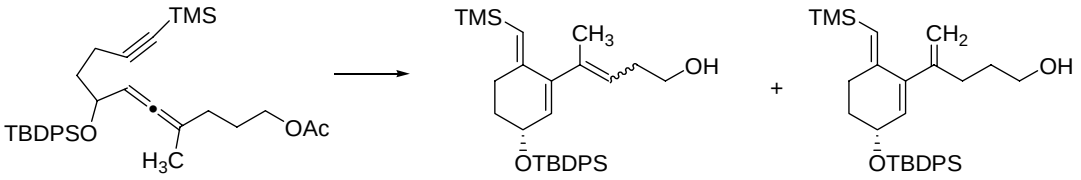
Procedures for data in Table 5. (Entries 1-3,5-11,13-16) Followed general procedure for allenic Alder-ene reaction using method A. The crude mixture of products was analyzed by ^{1}H NMR and the ratios were determined by integration of distinct olefinic peaks from each isomer.

(Entries 4 and 12) Followed general procedure for allenic Alder-ene reaction using method B. The crude mixture of products was analyzed by ^{1}H NMR and the ratios were determined by integration of distinct olefinic peaks from each isomer.



3-(*tert*-Butyldimethylsilyloxy)-1-[4-(*tert*-butyldimethylsilyloxy)-1-methylbut-1E-enyl]-6-trimethylsilylmethylenecyclohexene (*E*-1.58d), 3-(*tert*-butyldimethylsilyloxy)-1-[4-(*tert*-butyldimethylsilyloxy)-1-methyl-but-1Z-enyl]-6-trimethylsilylmethylenecyclohexene (*Z*-1.58d), 3-(*tert*-butyldimethylsilyloxy)-1-[4-(*tert*-butyldimethylsilyloxy)-1-methylen-butyl]-6-trimethylsilylmethylenecyclohexene (1.59d). To a 16 x 150 mm test tube was added allene

1.49d (1.66 g, 3.36 mmol) and the tests tube was sealed with a #17 SUBA·SEAL® rubber septum. Next, benzene (≈0.5 mL) was added and subsequently removed under vacuum (3x), by insertion an 18 gauge needle connected to a vac-line (7 mm Hg) into the septum. Once the benzene was evaporated the test tube was charged with N_2. The residue was then dilute with 17 mL of toluene and the test tube was evacuated under vacuum and charged with N_2 three times. Then, $[Rh(CO)_2Cl]_2$ (35 mg, 0.09 mmol) was added at ambient temperature and the system was evacuated and charged with N_2 once more. The mixture was heated to 80 ˚C and followed by GC analysis. The mixture was quenched after 1 h by direct addition to a silica gel column eluting with 5% EtOAc / hexanes to afford trienes *E*-**1.58d**, *Z*-**1.58d**, and **1.58d** (1.57 g, 95% yield) in a (7 : 2.5 : 1) ratio, respectively, as determined by ^{1}H NMR.

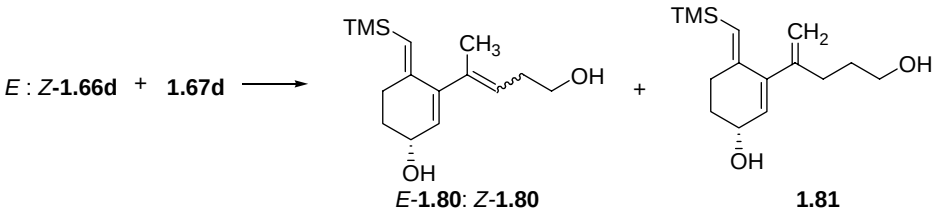


1.57b *E* : *Z*-**1.66c** **1.67c**

4-[3-(*tert*-Butyldiphenylsilyloxy)-6-trimethylsilylmethylenecyclohex-1-enyl]-pent-3E-en-1-ol (*E*-1.66c), 4-[3-(*tert*-butyldiphenylsilyloxy)-6-trimethylsilylmethylenecyclohex-1-enyl]-pent-3*Z*-en-1-ol (*Z*-1.66c), **4-[3-(*tert*-butyldiphenylsilyloxy)-6-trimethylsilylmethylenecyclohex-1-enyl]-pent-4-en-1-ol (1.67c)**. To a 13 x 100 mm test tube was added allene **1.57b** (0.01 g, 0.02 mmol) and the tests tube was sealed with a #17 SUBA·SEAL® rubber septum. Next, benzene (≈0.1 mL) was added and subsequently removed under vacuum (3x), by insertion an 18 gauge needle connected to a vac-line (7 mm Hg) into the septum. Once the benzene was evaporated the test tube was charged with N_2. The residue was then dilute with 0.3 mL of dichloroethane and the test tube was evacuated under vacuum and charged with N_2 three times. $[Ir(COD)Cl]_2$ (2.0 mg, 2.0 μmol) was added followed by $AgBF_4$ (85

μL of a .05 M dichloroethane solution, 4.0 μmol) and the system was evacuated and charged with N_2 once more. The solution was quenched after 1.75 h by direct addition to a silica gel plug eluting with 5% EtOAc / hexanes to afford 9 mg of a mixture of products. This mixture of products was diluted with 1.6 mL of undistilled MeOH and 1 drop of water. Then the solution was cooled to 0 ˚C and K_2CO_3 (0.02 g, 0.11 mmol) was added. The reaction flask was then allowed to warm to ambient temperature and after 2 h complete consumption of starting material was seen by TLC. The mixture was filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 10% EtOAc / hexanes to afford trienes *E*-**1.66c**, *Z*-**1.66c**, and **1.67c** (5 mg, 60% yield). Pure trienes could be obtained when a larger scale reaction was performed. The minor isomer was separated with silica gel chromatography and the other two isomers were separated on HPLC for spectroscopic purposes (Varian Microsorb Dynamax 100-5 Si column, 23 ˚C, EtOAc / hexanes = 5%, flow rate = 4 $mL \cdot min^{-1}$). R_f = 0.3 (10% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) major isomer *E*-**1.66c** : δ 0.10 (s, 9H), 1.07 (s, 9H), 1.20-1.33 (m, 1H), 1.71 (s, 3H), 1.74-1.83 (m, 2H), 2.15-2.24 (m, 1H), 2.35 (q, *J* = 6.8 Hz, 2H), 2.54-2.62 (m, 1H), 3.67 (dd, *J* = 6.3 Hz, *J* = 11.9 Hz, 2H), 4.32-4.37 (m, 1H), 5.23 (dt, *J* = 1.3 Hz, *J* = 7.3 Hz, 1H), 5.31 (s, 1H), 5.50 (d, *J* = 3.2 Hz, 1H), 7.35-7.47 (m, 6H), 7.68-7.73 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.1 (3), 17.3, 19.3, 27.0 (3), 28.4, 29.7, 31.8, 33.1, 62.4, 68.0, 124.3, 126.1, 127.5 (2), 127.6 (2), 129.5, 129.6, 134.5, 134.6, 135.8 (2), 135.9 (2), 139.1, 146.5, 149.9; IR (neat) 3374, 2957, 2929, 2856, 1472, 1428 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 504 ($[M]^+$, 4), 199 (94), 73 (100): HRMS calcd for $C_{31}H_{44}O_2Si_2$: 504.2880; found: 504.2903; Minor isomer at 343K with unknown TBDPS impurity from prior reaction. * designates product *Z*-**1.66c** where peaks were resolved. ^{1}H NMR (300 MHz, tol d^8): δ 0.12* (s, 9H), 1.04* (s, 18H), 1.16* (s, 9H), 1.77* (s, 3H), 1.82-1.90 (m, 4H),

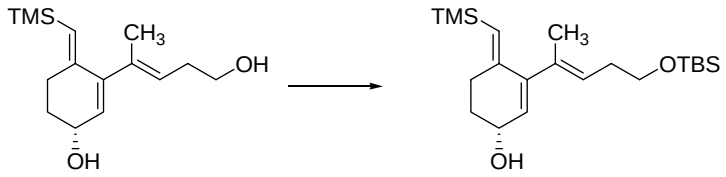
2.00-2.12 (m, 2H), 2.16-2.30 (m, 2H), 2.65-2.75* (m, 1H), 3.32-3.40* (m, 2H), 4.50* (dt, J = 3.3 Hz, J = 9.5 Hz, 1H), 5.23-5.32* (m, 1H), 5.61* (s, 1H), 5.65* (d, J = 3.4 Hz, 1H), 7.16-7.21 (m, 20H), 7.60-7.68* (m, 6H), 7.72-7.79* (m, 4H); IR (neat) 3383, 2957, 2857, 1427 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 504 ($[M]^+$, 55), 199 (85), 73 (100): HRMS calcd for $C_{31}H_{44}O_2Si_2$: 504.2880; found: 504.2899; Constitutional isomer **1.67c**: ^1H NMR (300 MHz, $CDCl_3$): δ 0.10 (s, 9H), 1.07 (s, 9H), 1.56-1.64 (m, 3H), 1.75-1.85 (m, 2H), 2.16-2.26 (m, 3H), 2.55-2.64 (m, 1H), 3.60 (dd, J = 11.6 Hz, J = 6.3 Hz, 2H), 4.34 (m, 1H), 4.82 (d, J = 2.3 Hz, 1H), 4.96 (m, 1H), 5.41 (s, 1H), 5.51 (d, J = 3.3 Hz, 1H), 7.34-7.47 (m, 6H), 7.68-7.71 (m, 4H); IR (neat) 3373, 2926, 2855, 1463, 1428 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 504 ($[M]^+$, 18), 199 (100), 73 (89): HRMS calcd for $C_{31}H_{44}O_2Si_2$: 504.2880; found: 504.2882.



3-(4-Hydroxy-1-methylbut-1E-enyl)-4-trimethylsilylmethylenecyclohex-2-enol (*E*-1.80), 3-(4-hydroxy-1-methylbut-1Z-enyl)-4-trimethylsilylmethylenecyclohex-2-enol (*Z*-1.80), 3-(4-hydroxy-1-methylenebutyl)-4-trimethylsilylmethylenecyclohex-2-enol (1.81). To a solution of trienes *E*-**1.66d**, *Z*-**1.66d**, and **1.67d** as a 7 : 2.5 : 1 ratio (1.57 g, 3.17 mmol) in 80 mL of THF was added NH_4Cl(s) (1.0 g, 19 mmol) and then TBAF (13 mL of a 1 M THF solution, 13 mmol). The mixture was heated to 50 ˚C and after 12 h was quenched by addition of water. The stir bar was removed and the organic layer was evaporated under reduced pressure. The mixture was diluted with Et_2O and the aqueous layer was separated and washed with Et_2O (3x). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 30% EtOAc /

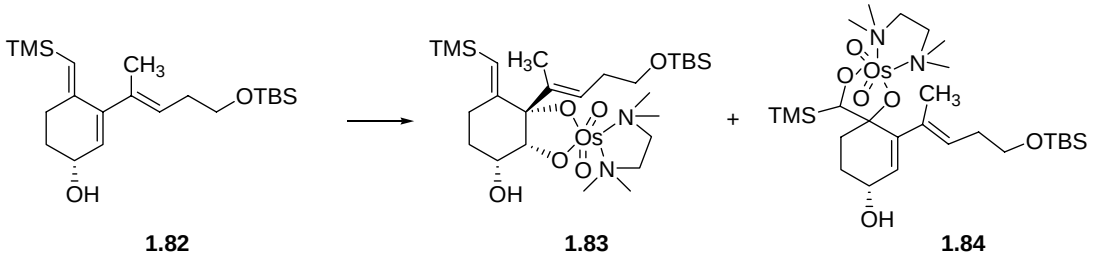
hexanes to afford trienes *E*-**1.80,** *Z*-**1.80**, and **1.81** (78 mg, 79% yield) as a 5 : 1.2 : 1 ratio, respectively, as determined by isolation of material. R_f = 0.1 (30% EtOAc / hexanes); R_f = 0.42, 0.6, 0.45 (*E*-**1.80,** *Z*-**1.80, 1.81**) (10% isopropanol / pentanes); ^{1}H NMR (300 MHz, $CDCl_3$): *E*-**1.80** δ 0.11 (s, 9H), 1.58-1.70 (m, 1H), 1.72 (d, *J* = 0.5 Hz, 3H), 2.00 (ddd, *J* = 4.2 Hz, *J* = 8.1 Hz, *J* = 16.5 Hz, 1H), 2.10 (bs, 1H), 2.25-2.40 (m, 3H), 2.55 (ddd, *J* = 3.7 Hz, *J* = 7.8 Hz, J = 14.6, 1H), 3.66 (t, *J* = 6.6 Hz, 2H), 4.27-4.35 (m, 1H), 5.31 (dt, *J* = 1.3 Hz, *J* = 7.2 Hz, 1H), 5.37 (s, 1H), 5.63 (d, *J* = 3.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.0 (3), 17.2, 28.1, 31.6, 32.8, 62.1, 66.2, 124.7, 127.0, 128.4, 138.5, 147.5, 149.3; IR (neat) 3319, 2952, 1578, 1437 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 266 ($[M]^+$, 1), 192 (34), 145 (100): HRMS calcd for $C_{15}H_{26}O_2Si$: 266.1702; found: 266.1693; ^{1}H NMR (300 MHz, $CDCl_3$): *Z*-**1.80** δ 0.12 (s, 9H), 1.60-1.75 (m, 1H), 1.81 (s, 3H), 2.00-2.19 (m, 3H), 2.29-2.41 (m, 1H), 2.62 (ddd, *J* = 3.7 Hz, *J* = 6.8 Hz, *J* = 14.6 Hz, 1H), 3.51-3.63 (m, 2H), 4.31-4.38 (m, 1H), 5.36 (dt, *J* = 1.0 Hz, *J* = 6.4 Hz, 1H), 5.44 (s, 1H), 5.60 (d, *J* = 3.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.0 (3), 24.9, 27.9, 29.7, 32.7, 62.5, 66.3, 123.6, 126.0, 129.7, 138.5, 143.3, 148.5; IR (neat) 3318, 2953, 1577, 1434 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 266 ($[M]^+$, 1.4), 248 (8.4), 73 (100): HRMS calcd for $C_{15}H_{26}O_2Si$: 266.1702; found: 266.1698; ^{1}H NMR (300 MHz, $CDCl_3$): Constitutional isomer **1.81** δ 0.13 (s, 9H), 1.59-1.76 (m, 3H), 2.03 (ddd, *J* = 4.3 Hz, *J* = 8.1 Hz, *J* = 16.8 Hz, 1H), 2.23 (t, *J* = 7.6 Hz, 2H), 2.36 (dddd, *J* = 1.3 Hz, *J* = 3.7 Hz, *J* = 9.8 Hz, *J* = 14.7 Hz, 1H), 2.57 (ddd, *J* = 3.8 Hz, *J* = 7.9 Hz, *J* = 14.6 Hz, 1H), 3.63 (t, *J* = 6.6 Hz, 2H), 4.32-4.37 (m, 1H), 4.89 (d, *J* = 2.2 Hz, 1H), 5.02 (dt, *J* = 1.3 Hz, *J* = 2.2 Hz, 1H), 5.49 (s, 1H), 5.67 (d, *J* = 3.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.0 (3), 27.9, 31.2, 32.3, 32.8, 62.4, 66.2, 114.3, 127.5, 129.2, 144.9, 148.8, 149.1; IR (neat) 3332, 2949, 1577, 1435 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 248 ($[M-H_2O]^+$, 8), 73 (100): HRMS calcd for $C_{15}H_{24}OSi$: 248.1596 $[M-H_2O]^+$; found: 248.1588 [M-

$H_2O]^+$.



1.81 **1.82**

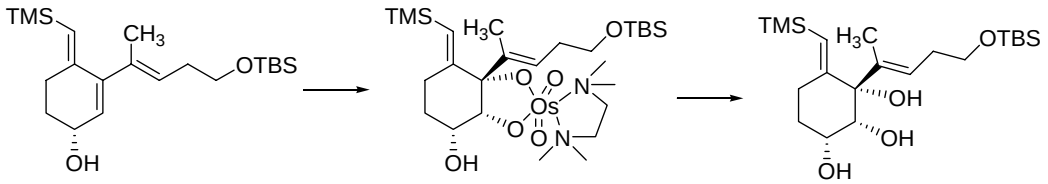
3-[4-(tert-Butyldimethylsilyloxy)-1-methylbut-1-enyl]-4-trimethylsilyl methylenecyclohex-2-enol (1.82). To a solution of triene *E*-**1.81** (0.07 g, 0.26 mmol) in 1.3 mL of CH_2Cl_2 was added TEA (150 μL, 1.10 mmol) and TBSCl (0.08 g, 0.29 mmol) at 0 ˚C. The solution then was warmed to ambient temperature and left overnight. The mixture was quenched with addition of water, and the aqueous layer was separated and washed with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 5% EtOAc / hexanes to afford **182** (74 mg, 75% yield). R_f = 0.6 (30% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.07 (s, 6H), 0.12 (s, 9H), 0.90 (s, 9H), 1.62-1.70 (m, 1H), 1.73 (s, 3H), 1.93-2.05 (m, 1H), 2.28-2.38 (m, 3H), 2.55 (ddd, *J* = 3.6 Hz, *J* = 7.9 Hz, *J* = 14.5 Hz, 1H), 3.65 (t, *J* = 7.0 Hz, 2H), 4.24-4.28 (m, 1H), 5.31 (t, *J* = 7.2 Hz, 1H) 5.41 (s, 1H), 5.62 (d, *J* = 3.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ -5.2 (2), 0.1 (3), 17.2, 18.3, 26.0 (3), 28.0, 32.0, 32.9, 62.8, 66.3, 125.4, 127.1, 128.0, 137.2, 147.9, 149.3; IR (neat) 3334, 2954, 2858, 1578 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 380 ($[M]^+$, 3), 145 (40), 73 (100): HRMS calcd for $C_{21}H_{40}O_2Si_2$: 380.2567; found: 380.2567.



1.82 **1.83** **1.84**

1-[4-(*tert*-Butyl-dimethyl-silyloxy)-1-methyl-but-1-enyl]-6-trimethylsilylmethylene-

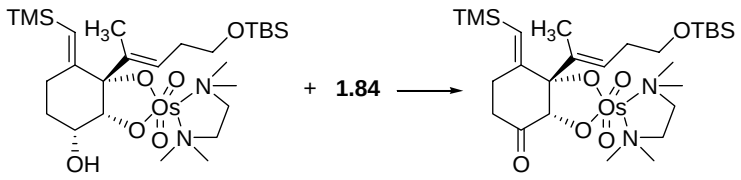
cyclohexane-1-ol-2,3-[N′,N′,N″,N″-tetramethylethylene-diamine] osmate diester (1.83). To a solution of alcohol **1.82** (0.97 g, 0.26 mmol) in 26 mL of CH_2Cl_2 was added freshly distilled TMEDA (42 μL, 0.28 mmol). The mixture was then cooled to -78 ˚C and OsO_4 (0.69 mL of a 0.39 M CH_2Cl_2 solution, 0.27 mmol) was added dropwise. The mixture turned yellow / red to dark brown. After 1 h at -78 ˚C the mixture was allowed to warm to ambient temperature at which time it turned black. The stir bar was removed and the solution was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 10% - 40% Acetone / EtOAc to afford osmate alcohol **1.83** and **1.84** (161 mg, 90% yield) of a brown solid as a 6 : 1 ratio as determined by ^{1}H NMR. R_f = 0.1 (20% Acetone / EtOAc). Mixture of **1.83** and **1.84** was taken on to next step and separated at that point; however, a pure ^{1}H NMR was obtained for **1.83** after storing in the freezer for 2 years (**1.84** must have decomposed). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.06 (s, 15H), 0.90 (s, 9H), 1.43 (dt, *J* = 2.5 Hz, *J* = 13.4 Hz, 2H), 1.80 (s, 3H), 2.23 (A of an ABq, *J* = 7.4 Hz, 1H), 2.28 (B of an ABq, *J* = 7.4 Hz, 1H), 2.35 (ddd, 2H), 2.77 (s, 3H), 2.79 (s, 3H), 2.82 (s, 3H), 2.85 (s, 3H), 2.86-2.90 (m, 1H), 2.96-3.10 (m, 4H), 3.59 (t, *J* = 7.4 Hz, 2H), 4.22 (s, 1H), 4.25 (ddd, 1H), 5.36 (t, *J* = 7.4 Hz, 1H), 5.67 (s, 1H).



1.82 **1.83** **1.85**

(1S*,2R*,3R*,E)-1-((E)-5-(tert-Butyldimethylsilyloxy)pent-2-en-2-yl)-6-((trimethylsilyl)methylene)cyclohexane-1,2,3-triol (1.85). To a solution of alcohol **1.82** (0.15 g, 0.39 mmol) in 40 mL of CH_2Cl_2 was added freshly distilled TMEDA (65 μL, 0.43 mmol). The mixture was then cooled to -78 ˚C and OsO_4 (1.1 mL of a 0.4 M CH_2Cl_2 solution, 0.43 mmol) was added dropwise. The mixture turned yellow / red to dark brown. After 10 h at -78 ˚C the

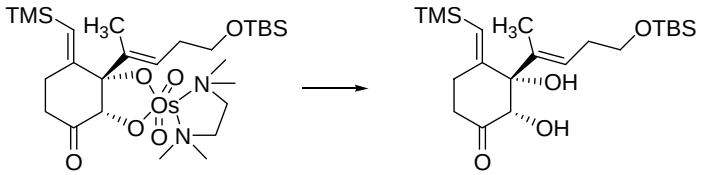
mixture was allowed to warm to ambient temperature at which time it turn black. The reaction flask was left at that temperature overnight. Then ethylenediamine (0.13 mL, 2.0 mmol) was added and the mixture was left for 8 h after which time complete consumption of the starting material **1.83** (R_f = 0.3 (20% Acetone / EtOAc)) was observed by TLC. The solution was diluted with H_2O and EtOAc, and the aqueous layer was separated and washed with EtOAc (3x). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 50% EtOAc / hexanes to afford allene **1.85** (27.0 mg, 16% yield). R_f = 0.7 (20% Acetone / EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.07 (s, 6H), 0.08 (s, 9H), 0.90 (s, 9H), 1.47 (dt, *J* = 2.5 Hz, *J* = 13.6 Hz, 1H), 1.62-1.78 (m, 2H), 1.88 (s, 3H), 1.92 (dd, *J* = 2.5 Hz, *J* = 5.0 Hz, 1H), 1.94-2.10 (m, 2H), 2.18-2.39 (m, 3H), 3.58 (s, 1H), 3.64 (dddd, *J* = 4.5 Hz, *J* = 6.6 Hz, *J* = 9.9 Hz, *J* = 14.4 Hz, 2H), 4.13 (ddd, *J* = 2.0 Hz, *J* = 5.3 Hz, *J* = 7.5 Hz, 1H), 5.48 (td, *J* = 1.0 Hz, *J* = 7.2 Hz, 1H), 5.63 (s, 1H).



1.83 **1.86**

3-[4-(tert-Butyl-dimethyl-silyloxy)-1-methyl-but-1-enyl]-2,3-[(N′,N′,N″,N″-tetramethylethylene-diamine) osmate diester]-4-trimethylsilylmethylene-cyclohexanone (1.86). To a solution of oxalyl chloride (24 μL, 0.27 mmol) in 1.0 mL of CH_2Cl_2 at -78 ˚C was added DMSO (37 μL, 0.52 mmol). The mixture was left at -78 ˚C for 15 min and then a solution of osmate alcohol **1.83** and **1.84** as a 6 : 1 ratio (0.17 g, 0.23 mmol) in 0.5 mL of CH_2Cl_2 was added with a cannula. The mixture was left for 30 min at -78 ˚C and then TEA (157 μL, 1.13 mmol) was added and mixture was kept at -78 ˚C. After 1 h complete consumption of starting

material was seen by TLC and the mixture was diluted with Et_2O and 0.5 M HCl was added. The aqueous layer was separated and washed with EtOAc (3x). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 10% acetone / EtOAc to afford of alcohol **1.86** (131 mg, 76% yield) as a brown solid. R_f = 0.2 (20% acetone / EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.07 (s, 9H), 0.89 (s, 9H), 1.87 (s, 3H), 1.94 (dt, *J* = 3.8 Hz, *J* = 13.4 Hz, 1H), 2.34-2.22 (m, 3H), 2.72-2.55 (m, 2H), 2.78 (s, 3H), 2.83 (s, 3H), 2.86 (s, 6H), 3.18-3.05 (m, 4H), 3.62 (t, *J* = 7.2 Hz, 2H), 4.33 (s, 1H), 5.78 (t, *J* = 7.2 Hz, 1H), 5.84 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ -5.3 (2), -1.8 (3), 16.0, 18.3, 26.0 (3), 30.8, 32.1, 34.1, 51.1, 51.4, 51.5, 51.8, 62.5, 64.0, 64.2, 90.0, 90.1, 126.6, 127.8, 138.1, 166.2, 202.1; IR (neat) 2953, 2856, 1664 cm^{-1}; MS (API-ES) *m/e* (relative intensity) 751 $[M+H]^+$, 100: HRMS calcd for $C_{27}H_{55}N_2O_6Si_2Os$: 751.3214 $[M+H]^+$; found: 751.3204 $[M+H]^+$.



1.86 **1.89**
unknown product

3-[4-(tert-Butyl-dimethyl-silyloxy)-1-methyl-but-1-enyl]-2,3-dihydroxy-4-trimethylsilylmethylene-cyclohexanone (1.89). H_2S was bubbled through a solution of osmate ketone **1.86** (0.06 g, 0.08 mmol) in 7 mL of MeOH at 0 ˚C. After 1 h the needle was removed and the flask was charged with N_2 for 30 min while the mixture warmed to ambient temperature. Then the mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography eluting with 20% EtOAc / hexanes to afford ketone **1.89** (18 mg, 57% yield) as a yellow oil. R_f = 0.4 (40% EtOAc / hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.08 (s, 6H), 0.13 (s, 9H), 0.91 (s, 9H), 1.96 (s, 3H), 2.04 (ddd, *J* = 4.5 Hz, *J* = 9.6 Hz, *J* = 13.6, 1H), 2.25 (m,

1H), 2.27-2.40 (m, 3H), 2.71 (ddd, J = 4.9 Hz, J = 9.6 Hz, J = 16.9 Hz, 1H), 3.34 (s, 1H), 3.75-3.65 (m, 4H), 5.70 (t, J = 7.1 Hz, 1H), 5.80 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.3 (2), -1.6 (3), 17.8, 18.5, 26.0 (3), 31.9, 33.8, 33.9, 62.4, 71.4, 74.9, 126.4, 128.7, 137.6, 166.9, 199.5; IR (neat) 3450, 2955, 2857, 1660 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 337 ($[M-C_4H_9, -OH_2]^+$, 17), 84 (94), 73 (100): HRMS calcd for $C_{21}H_{38}O_3Si_2$: 394.2360 $[M-OH_2]^+$; found: 394.2358 $[M-OH_2]^+$.

2.0 A RHODIUM(I)-CATALYZED ALLENIC CYCLOCARBONYLATION REACTION: PROGRESS TOWARDS THE SYNTHESIS OF GUANACASTEPENE A.

2.1 BIOLOGICAL ACTIVITY OF THE GUANACASTEPENES

Nosocomial infections, infections which are acquired in a hospital, infect approximately five percent of patients admitted to an acute-care hospital. A number of factors contribute to this problem: increasing age of patients, lengthened surgical procedure times, and complexity of procedures available i.e. transplant surgeries. One common nosocomial infection is from Gram-positive cocci: *Streptococcus pneumoniae, Streptococcus pyogenes*, and *Staphylococcus aureus*.[59] The symptoms of *Staphylococcus aureus* can be mild, causing pimples or boils, to serious affecting one's bloodstream, bones, and joints. Depending on the initial health of the person affected, it can cause death. Transmission of the bacteria is quite easy because it is commonly found on a person's hands and nostrils that is harmless unless it enters the body through a break in the skin.[60]

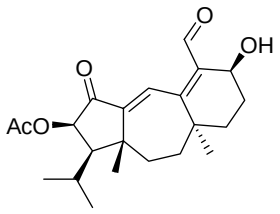
In the 1940s with the discovery of penicillin G, it was thought that the dangers of common bacterial infections were over; however, while in 1946 approximately ninety percent of *S. aureus* were susceptible to penicillin G by the 1970s approximately seventy-five percent of *S. aureus* were resistant. Currently, greater than ninty-five percent of *S. aureua* are resistant to

penicillin. To combat this resistance, methicillin, a semi-synthetic penicillin, was developed, but in 1961 the United Kingdom reported the discovery of methicillin-resistant *Staphylococcus aureus* (MRSA), which reached the United States in the 1980s. MRSA is resistant to all β-lactams, penicillins, cephalosporins, carbapenems, and penems, and is commonly named 'superbug.' To demonstrate the power and problem of MRSA in the mid-1980s a purely synthetic antibiotic, fluoroquinolone, was developed. Within one year the resistance of MRSA to fluoroquinolone went from five percent to greater than eighty percent in one hospital. In 1992 the only agent that effectively treated MRSA infections was vancomycin, which now has caused an outbreak of vancomycin-resistance *Enterococcus faecalis* (VREF).[61] Even worse, MRSA bacteria are no longer isolated to hospitals settings, in the last decade it has emerged as a problem in the community.[62]

Ways to combat MRSA range from very simple to extremely complex. One step being taken requires hospital staff, visitors, and infected patients to frequently and scrupulously wash their hands. Also, it is necessary for antibiotics to be used appropriately, and this responsibility rests on patients who insist on medication for viral infections as well as the doctors that prescribe them. Lastly, and the most difficult way to fight MRSA, is the development of new antibiotics. Due to the incredible ability for bacteria to become resistant to antibiotics by chromosomal changes or exchanges of genetic material, it is essential for new antibiotics to be structurally different from current antibiotics and ideally have a different mechanism of action.[63]

As seen in Chapter 2, an abundant source of new biologically active natural products are found in fungi. While five to seven thousand fungal species are currently readily available for

study, there are an estimated 1.5 million fungal species still undiscovered. In search of new fungi species containing biologically active natural products, Clardy[64] isolated a fungus (CR115) from a branch of a *Daphnopsis americana* tree found in the Guanacaste conservation area in Costa Rica. This extract was found to exhibit superb activity against MRSA and VREF.[65] Upon isolation and x-ray crystal structural determination, the active compound was found to be the diterpene now known as guanacastepene A (**2.1**) (Figure 17).



Guanacastepene A (**2.1**)

Figure 17. Structure of guanacastepene A

After the isolation of guanacastepene A, it was discovered that CR115 yields a family of diverse guanacastepene analogs, namely B-O (Figure 18).[66] Unfortunately, guanacastepenes B-O were only isolated in small amounts due to inconsistency from one fermentation to the next; however, characterization and some biological testing on these substrates were obtained. Guanacastepene I was the only analog to show MRSA activity, revealing that the aldehyde 'type' moiety might be necessary for antibacterial activity. Due to the limited amount of guanacastepenes B-O, testing on bacteria other than MRSA and VREF was not performed.

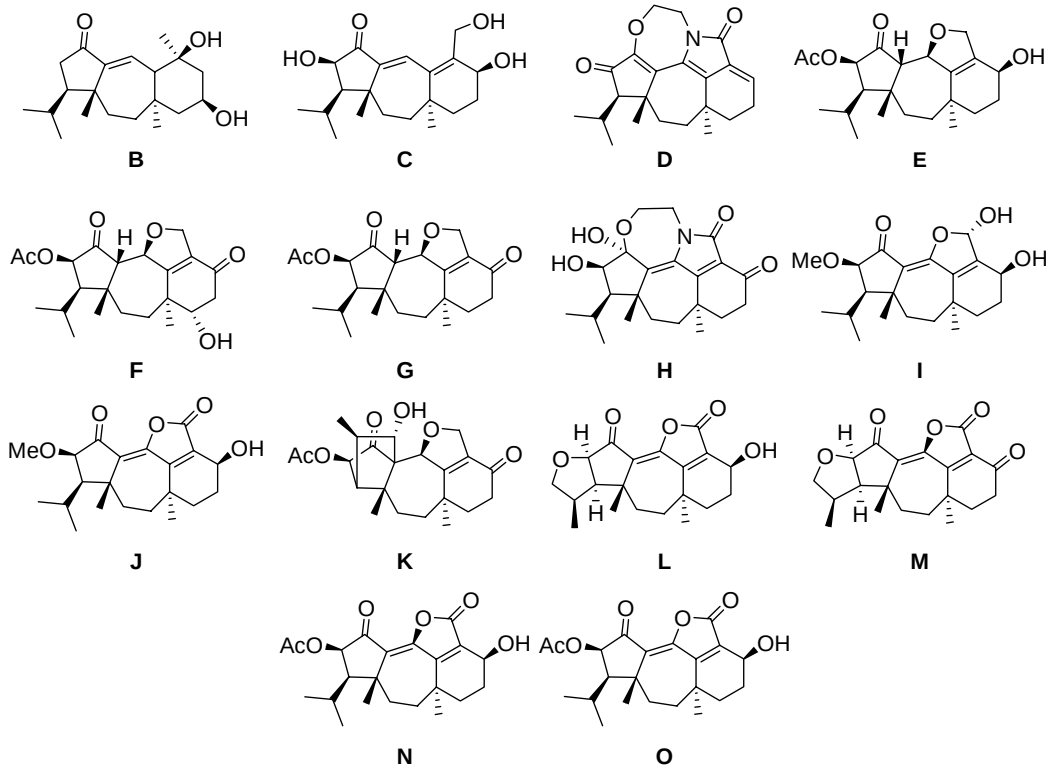
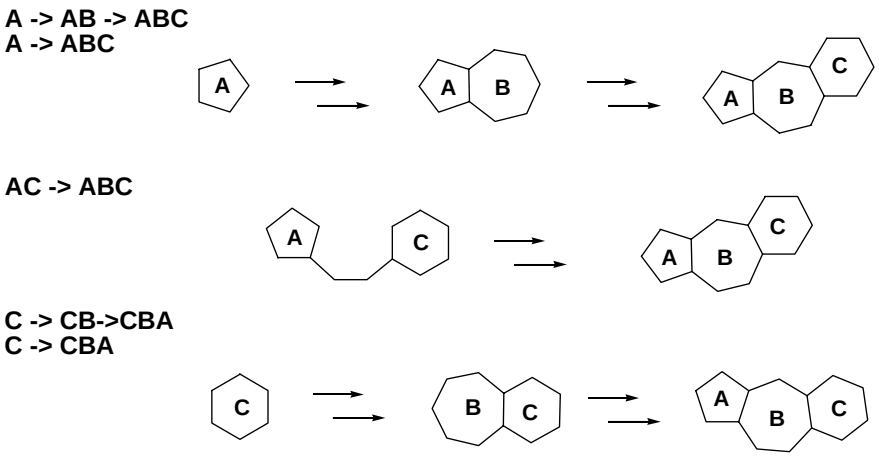


Figure 18. The guanacastepene family, guanacastepenes B-O

Unfortunately, guanacastepene A was found to lyse human red blood cells and itself cannot be a suitable antibiotic; however, analogs containing this unique carbocyclic core still have potential. For this reason guanacastepene A remains a popular target stimulating 42 current publications[67] which examine numerous unique routes to access this molecule. Danishefsky published the first total synthesis in 2002[68] followed by a route to enantiomerically pure material in 2005.[69] To date there are three formal syntheses of guanacastepene A by Snider,[70] Hannah,[67p] and Sorensen.[71] Also, four of the non-MRSA and VREF active family members have been synthesized: Guanacastepene C, (+)-E, (-)-E, C8-*epi*-O, and N by Mehta, [72] Sorensen, Trauner,[67ap] Yang,[73] and Overman,[67y] respectively.

2.2 GUANACASTEPENE A: SYNTHETIC STRATEGIES

There are three main approaches to form the [5-7-6] carbocycle. The first, as demonstrated by Danishefsky, Snider, and Hannah, forms the five membered **A**-ring and then, sequentially or in one step, forms the remaining seven membered **B**-ring and six membered **C**-ring (Scheme 36). Sorensen independently forms the **A**-ring and the **C**-ring and then connects them forming the seven-membered **B**-ring. The last approach, which has not been demonstrated thus far, forms the **C** ring first followed by formation of the **B** and the **A** rings, sequentially or in one step. This is the approach we have decided to use in our route to guanacastepene A.

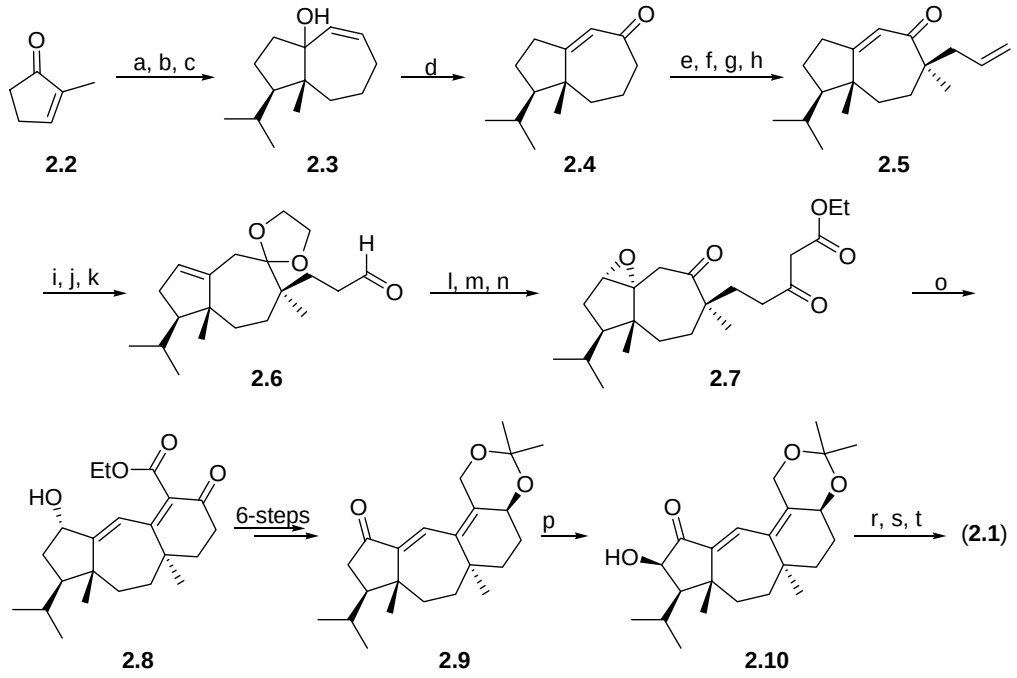


Scheme 36. Three approaches to the guanacastepenes carbocyclic core.

2.2.1 Danishefsky's Route: Exploiting a Knoevenagel Cyclization

Taking a closer look at the prior syntheses of guanacastepene A starting with Danishefsky's total synthesis; he completes the synthesis in approximately 27 linear steps in a 2.3% overall yield. His route initiates with commercially available 2-methyl-2-cyclopenten-1-one (**2.2**) and features

formation of the hydroazulenone core **2.4** via a reductive cyclization to give the tertiary alcohol **2.3**; followed by an oxidative rearrangement producing hydroazulenone **2.4** (Scheme 37).[74]



Reagents: (a) *i*-PrMgBr, CuBr DMS, TMSCl, HMPA, 94% (b) MeLi, HMPA, 5-iodopent-1-ene, 63% (c) n-BuLi, reverse addition, 62-65% (d) PCC, 71-92% (e) LHMDS, then Eschenmoser's salt (f) mCPBA, 60-70% over 2-steps (g) vinyl-MgBr, CuI, HMPA, TMSCl, 77% (h)MeLi, then HMPA, MeI, 96% (i) $(CH_2OH)_2$, *p*-TsOH, 88% (j) 9-BBN, then 3 M NaOH, 30% H_2O_2, 71% (k) Dess-Martin, 83% (l) ethyl diazoacetate, $SnCl_2$ (m) TsOH, 80% over 2-steps (n) *m*CPBA, 89% (o) NaOEt, 80% (p) Et_3SiOTf, TEA (q) DMDO/acetone, then DMS, 82-90% over 2-steps (r) Ac_2O, pyridine, DMAP, 96% (s) PPTS (t) $PhI(OAc)_2$, TEMPO, 59-65% over 2-steps.

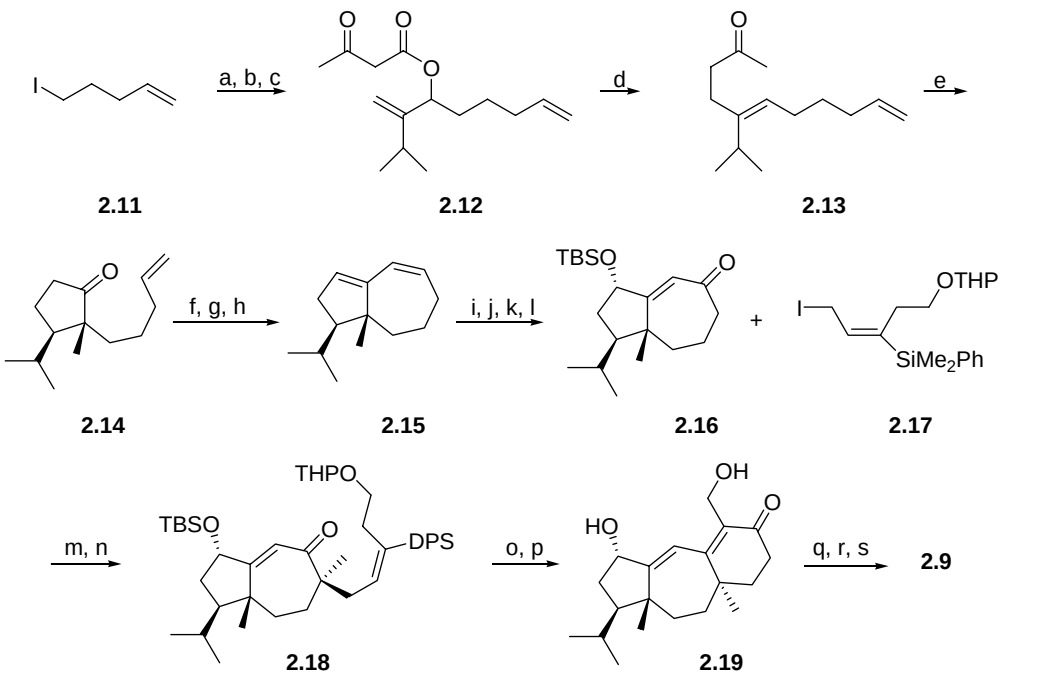
Scheme 37. Danishefsky's route to guanacastepene A

Subsequently, the hydroazulenone **2.4** is stereoselectively alkylated by a formal dialkylation process giving intermediate **2.5** as one diastereomer.[75] Acid-catalyzed protection of the carbonyl moiety promoted an isomerization of the olefin from the seven-membered ring to the five-membered ring, and a hydroboration/oxidation protocol of the monosubstituted olefin gave aldehyde **2.6**. The resulting aldehyde was transformed into the corresponding β-keto ester, and then subjected to *m*-CPBA yielding the epoxide **2.7** diastereoselectively. At this juncture Danishefsky and co-workers developed a tandem epoxide-opening β-elimination/Knoevenagel cyclization protocol; addition of NaOEt to epoxide **2.7** gives the advanced [5-7-6] carbocyclic

core **2.8** of guanacastepene A.[76] After preparation of the keto-acetonide **2.9** over six steps, a Rubottum oxidation[74,77] of **2.9** gives stereoselectively the desired diastereomer **2.10**, which is opposite of that they originally predicted. Guanacastepene A is obtained from **2.10** via acetylation of the alcohol, deprotection of the acetonide, and selective oxidation with TEMPO. In summary, Danishefsky developed an interesting tandem epoxide-opening β-elimination/Knoevenagel cyclization for the synthesis of guanacastepene. His route also gives insight into the stability and reactivity of guanacastepene intermediates as well as giving a versatile point of intersection for formal syntheses by many other groups.

2.2.2 Snider's Route: Featuring a Stork-Jung Robinson Annulation

Snider's formal synthesis of guanacastepene A intersects Danishefsky's intermediate **2.9**, after 25 steps (21 longest linear) and 0.6% overall yield. In order to accurately compare the yields of the formal syntheses to Danishefsky's total synthesis the overall yield is calculated as if the author completed the synthesis of guanacastepene A. Snider's key steps are an $EtAlCl_2$-mediated cyclization of a γ,δ-unsaturated ketone, a ring closing metathesis, and a Stork-Jung vinylsilane Robinson annulation. Snider's synthesis begins with 5-iodo-1-pentene (**2.11**), readily accessible from 5-bromo-1-pentene, which is easily transformed into the acetoacetate **2.12** in two steps (Scheme 38).



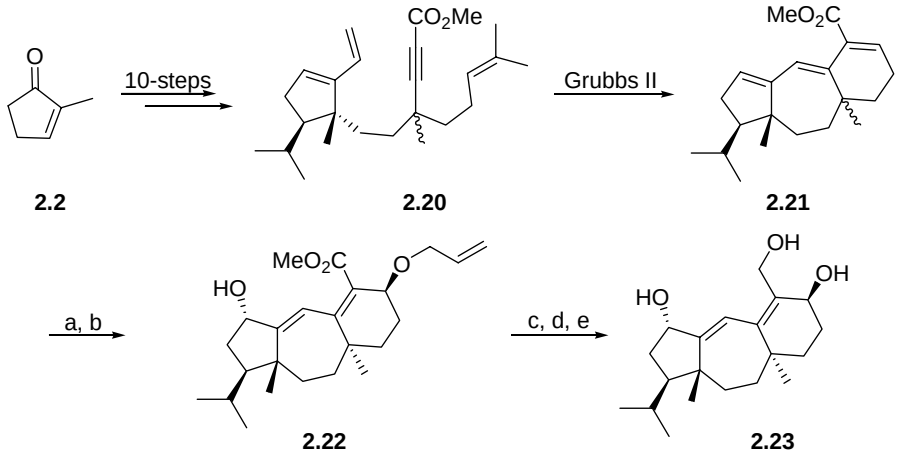
[a]Reagents: *t*-BuLi, 3-methyl-2-methylenebutanal, 89% (b) diketene, DMAP (c) LDA , reflux (d) Toluene, reflux, 67% over 3-steps (e) $EtAlCl_2$, 69% (f) Tf_2O, proton sponge, 86% (g) $H_2C{=}CHMgBr$, Pd_2dba_3, TFP, 76% (h) $(Pcy_3)_2PhCHRuCl_2$, 86% (i) mCPBA (j) Pd_2dba_3, dppb, AcOH, 51% over 2-steps (j)TBSCl, imidazole (k) K_2CO_3, $NaHCO_3$ (l) Dess-Martin, 90% over 3-steps (m) LDA, DMPU, 94% (n) LDA, DMPU, MeI (o) mCPBA, then pyr (HF)x, 64% over 2-steps (p) NaOMe, 85% (q) $LiAlH(O\text{-}t\text{-}Bu)_3$ (r) $Me_2C(OMe)_2$, PPTS, 48% over 2-steps (s) Dess-Martin, 86%

Scheme 38. Snider's formal synthesis of guanacastepene A.

This acetoacetate **2.12** underwent a Carrol rearrangement followed by decarboxylation to give the γ,δ-unsaturated ketone **2.13**. Addition of $EtAlCl_2$ promoted cyclization to give the desire cyclopentene **2.14**, which interestingly is the same intermediate formed in Danishefsky's route in two steps from 2-methyl-2-cyclopenten-1-one (**2.2**).[78] Formation of the hydroazulenone core **2.16** was acquired using ring-closing-metathesis to give **2.15** followed by an oxidative epoxide opening with $Pd(PPh_3)_4$ and AcOH. This hydroazulenone core **2.16** was then coupled with allylic iodide **2.17** yielding the functionalized hydroazulenone **2.18**.[79] After a successful regio- and stereoselective application of the Stork-Jung vinylsilane Robinson annulation reaction to give the advanced [5-7-6] carbocycle intermediate **2.19**; formation of Danishefsky's intermediate **2.9** was achieved in three steps.

2.2.3 Hanna's Route: Featuring a Tandem Ring Closing Metathesis

Hanna formal synthesis intersects Snider's route at **2.23** in 18 linear steps and a 0.7% overall yield. Hanna's route also begins with 2-methyl-2-cyclopenten-1-one (**2.2**) and features a tandem ring closing metathesis of a cyclopentadiene-yne **2.20**, which uniquely gives the [5-7-6] carbocycle **2.21** in one step (Scheme 39).[67o] After selective epoxidation of **2.21**, a concomitant ytterbium catalyzed etherification/epoxide opening gave the functionalized intermediate **2.22** in a 3 : 2 mixture of the desired product and a diastereomer, respectively. To complete the formal synthesis, the hydroxyl group was protected with a TBS group followed by a nickel(0)-catalyzed hydroalumination reaction with excess DIBAL-H. These reagents cleave the allyl ether as well as reduce the ester. Removal of TBS-protecting group to give the triol intermediate **2.23** intersects with Snider's synthesis (two steps prior to Danishefsky's intermediate **2.9**).

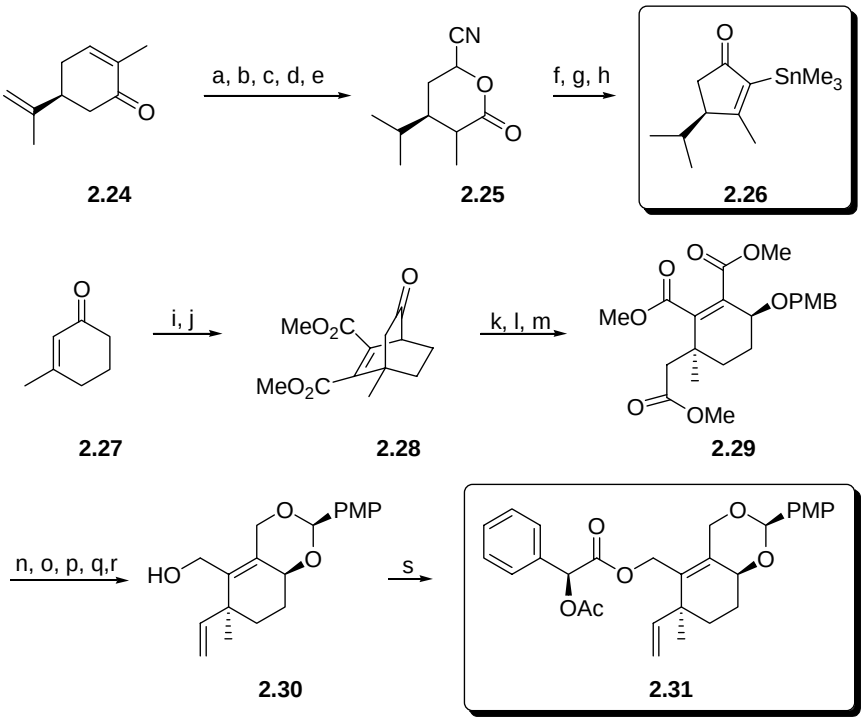


[a]Reagents: (a)*m*CPBA (b) allyl alcohol, $Yb(OTf)_3$, 56% over 2-steps, 3 : 2 diasteromeric mixture (c) TBSOTf, py, 81% (d) DIBAL-H, $[NiCl_2(dppp)]$, 71% (e)TBAF, 81%.

Scheme 39. Hanna's formal synthesis of guanacastepene A.

2.2.4 Sorensen's Route: Demonstrating an Allyl Stille Cross Coupling

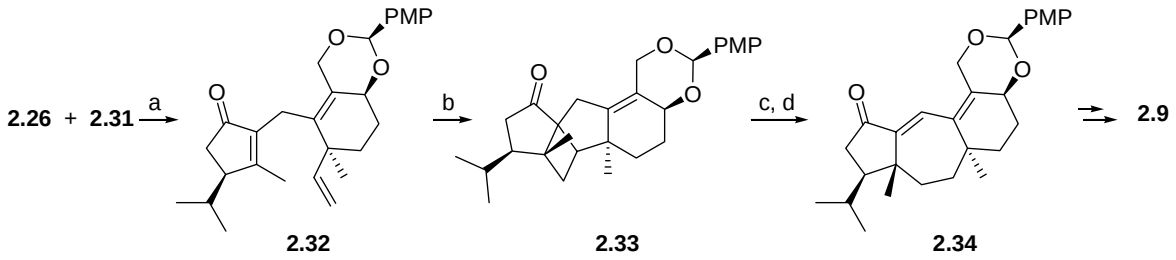
The most recent formal synthesis of guanacastepene A by Sorensen forms the core [5-7-6] carbocycle by a more convergent route where he couples the functionalized five and six membered rings together via an π-allyl Stille cross-coupling. Subsequently, he performs an intramolecular [2+2] photocycloaddition followed by a fragmentation/enolate trapping elimination.[80] He accomplished the formal synthesis in 29 total steps, 16 steps is the longest linear sequence, and in approximately a 0.7% yield of the racemic guanacastepene A and calculated 0.35% of the enantiomerically pure material. Formation of the five and six membered ring coupling partners proceeds as follows: synthesis of the enantiomerically pure cyclopentenone **2.26** initiates with (*S*)-(+)-carvone (**2.24**) (Scheme 40). (*S*)-(+)-Carvone (**2.24**) is functionalized and subjected to a ring contraction protocol, which begins with opening of the cyclohexenone via ozonolysis, conversion to the cyanohydrin, and lactonization giving lactone **2.25** as a mixture of four diastereomers. Base induced ring contraction gave the enol form of a diketone, which is then transformed into the vinyl stannane **2.26**.



Reagents: (a) PtO_2, H_2, 100% (b) LDA, MeI, 96% (c) O_3, then H_2, Pd/C, 48-54% (d) NaCN, *p*-TsOH, 99% (e) EDCI, 79% (f) LHMDS, then 1 N HCl, 50-58% (g) TEA, Nf, 94% (h) $Pd(dppf)Cl_2$, $Me_3SnSnMe_3$, NMP, 63% (i) LDA, TMSCl, 98% (j) dimethylacetylenedicarboxylate, then 1 N HCl (k) mCPBA, $NaHCO_3$, 96% (l) CSA, 100% (m) PMB-trichloroacetimidate, CSA (n) $LiAlH_4$, 87% (o) anisaldehyde dimethyl acetal, PPTS, 80% (p) 0-nitrophenylselenocyanate, n-Bu_3P, the H_2O_2, i-Pr_2EtN, 71% (q) PPTS, 85% (r) DDQ, 69% (s)O-acetyl (S)-(+)-mandelic acid, DMAP, DCC, 98%

Scheme 40. Sorenson's synthesis of guanacastepene A, formation of coupling partners 2.26 and 2.31

Construction of the coupling partner **2.31** begins with cyclohexenone **2.27**. After formation of the silylenolether, the resulting diene underwent a Diels-Alder reaction with dimethylacetylenedicarboxylate to give the bicyclic ketone **2.28**. Baeyer-Villiger oxidation and acid-catalyzed methanolysis of the newly formed bridged lactone gave the highly functionalized cyclohexene **2.29** after PMB protection of the alcohol. The three methyl esters were reduced in one step; two were then selectively protected and the third was transformed into the desired olefin in one step. Transposition of the protecting groups gave the allylic alcohol **2.30** that was esterified with (S)-(+)-mandelic acid and the diastereomers were separated.



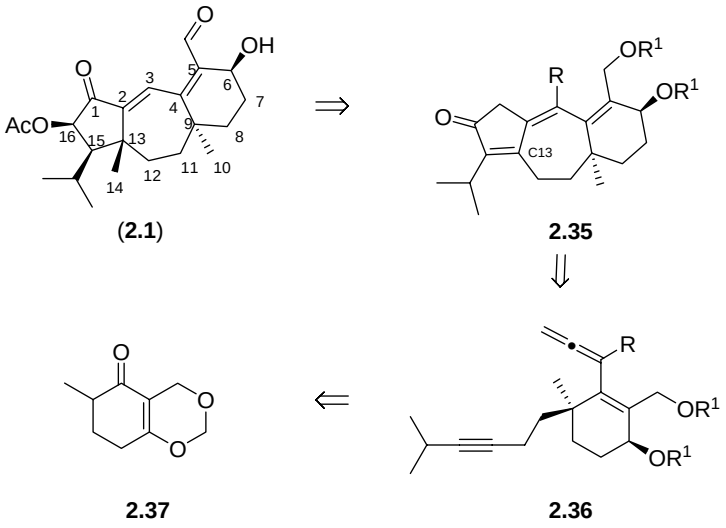
Reagents: (a) LiCl, CuCl, $Pd(PPh_3)_4$, 78% (b) hv, i-Pr_2NEt, 82% (c) SmI_2, HMPA, then PhSeBr, 50% (d) *m*CPBA, 86%

Scheme 41. Completion of Sorenson's formal route to guanacastepene A

Coupling of the allylic mandelic ester **2.31** and the vinyl stannane **2.26** with π-allyl Stille cross-coupling conditions gave intermediate **2.32** (Scheme 41). Subjection of enone **2.32** to a photocyclization protocol gave the [2+2] product **2.33** which underwent reductive fragmentation by addition of SmI_2. Finally, formation of the enone **2.34** was obtained by a selenoxide elimination protocol. Changing the diol protecting group from the benzyl to dimethyl gave Danishefsky's intermediate **2.9**.

In summary, each route to guanacastepene A demonstrates the utility of powerful synthetic methods. The Knoevenagel cyclization, Robinson annulation, tandem ring closing metathesis, and allyl Stille cross-coupling each provide key intermediates that lead to the synthesis of guanacastepene A. These syntheses all exhibit how synthetically challenging the synthesis of guanacastepene is since each route is >20 synthetic steps.

2.2.5 Retrosynthetic Analysis: Brummond / McCabe Approach Utilizing an Allenic Cyclocarbonylation Reaction



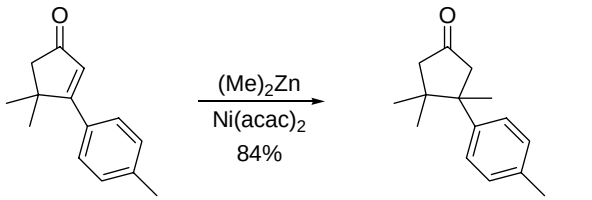
Scheme 42. Brummond/McCabe retrosynthetic analysis of guanacastepene A

Our retrosynthetic analysis of guanacastepene A (**2.1**) utilizes the allenic cyclocarbonylation reaction developed in our group[81] and is outlined in Scheme 42. It was envisioned that the [5-7-6] carbocyclic core **2.35** could arise via the [2+2+1] cycloaddition reaction of alkynyl allene **2.36**. This strategy differs from those previously reported in that the carbocyclic core is assembled possessing fully functionalized six- and seven-membered rings and a five-membered ring poised for conversion to guanacastepene A.

For example, it is predicted that the angular methyl group at C13 can be installed in a stereoselective manner by a conjugate addition to the enone from the less sterically hindered β-face. This prediction was reinforced using a lowest energy conformer search for the 4-alkylidene cyclopentenone **2.35**, where R = H and R^1 = Me. While it was recognized that the installation of this angular methyl group may be problematic, there are many protocols in the literature for

introducing methyl groups at sterically hindered sites. Kuwajima[82] has shown that addition of TMSCl and HMPA accelerate conjugated additions during cuprate reactions. Using these conditions to enhance the reactivity of a cuprate reagent was an option, but if unsuccessful a variety of alternatives exist. For example, the solvent used during a cuprate reaction has been shown to have an effect on its reactivity. Namely, $Me_2CuLi{\cdot}LiI$ is more reactive in diethyl ether than THF.[83] Also, several Lewis acids accelerate cuprate reagents in THF[84] namely: $BF_3{\cdot}Et_2O$,[85] TMSI, TMSOTf, and TMSCl.[86] Furthermore, additives such as DMS and LiBr are known to accelerate cuprate reagents.[87] Lastly, 'higher order' cuprates, where $Me_2CuLi{\cdot}LiCN$, are more reactive in some cases than lower order cuprates like $Me_2CuLi{\cdot}LiI$.[88]

While cuprates, developed in the 1960's, are the traditional nucleophiles used to undergo a conjugate addition to an enone, nickel catalyzed reactions are also known to affect this type of transformation. In fact $Ni(acac)_2$ with either trimethyl aluminum (TMA)[89] or dimethyl zinc ($(Me)_2Zn$)[90] have been found to be superior in conjugate addition with sterically hindered substrates, and have been used in many natural product syntheses.[91] For instance, in the synthesis of β-cuparenone, enone **2.38** easily undergoes conjugate addition by addition of $(Me)_2Zn$ and $Ni(acac)_2$ to give β-cuparenone (**2.39**) (Scheme 43). The use of standard cuprates to affect this transformation did not give any of the addition product **2.39**.

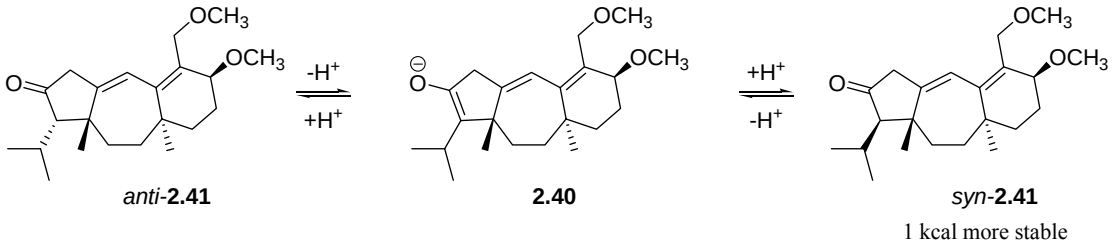


2.38 **β-cuparenone (2.39)**

Scheme 43. An example of $Ni(acac)_2$ used as a catalyst for a conjugate addition reaction

Upon installation of the methyl group at C13, molecular modeling studies indicate that the

ketone *syn*-**2.41** where the isopropyl moiety on the top face is ~1 kcal/mol more stable than *anti*-**2.41** (Scheme 44). Therefore, the thermodynamic equilibration of the resulting enolate **2.40** after the conjugate addition should afford the correct stereochemistry of the isopropyl moiety *syn*-**2.41**.



Scheme 44. Proposed equilibrium for the isopropyl group stereochemistry of 2.41

Next, α-hydroxylation of ketone **2.41** will be accomplished by using either Rubottom[92] or Davis oxidation[93] protocols. It is proposed that the resulting α-hydroxy ketone **2.42** will equilibrate under the reaction conditions to give enone **2.43** (Figure 19). It is predicted that the equilibrium will favor **2.43** since the carbonyl is now in conjugation with the double bond. This type of isomerization has been seen by other groups; however, as an undesired transformation.[94],[67aa]

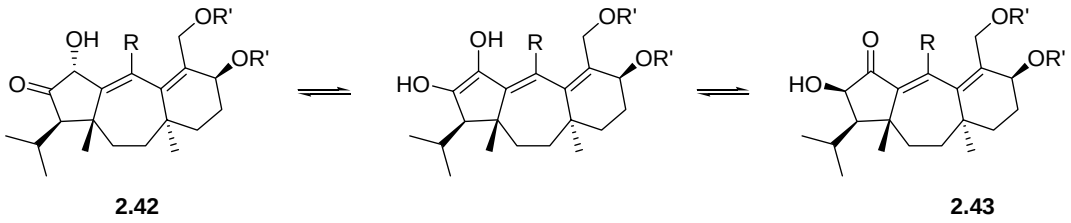
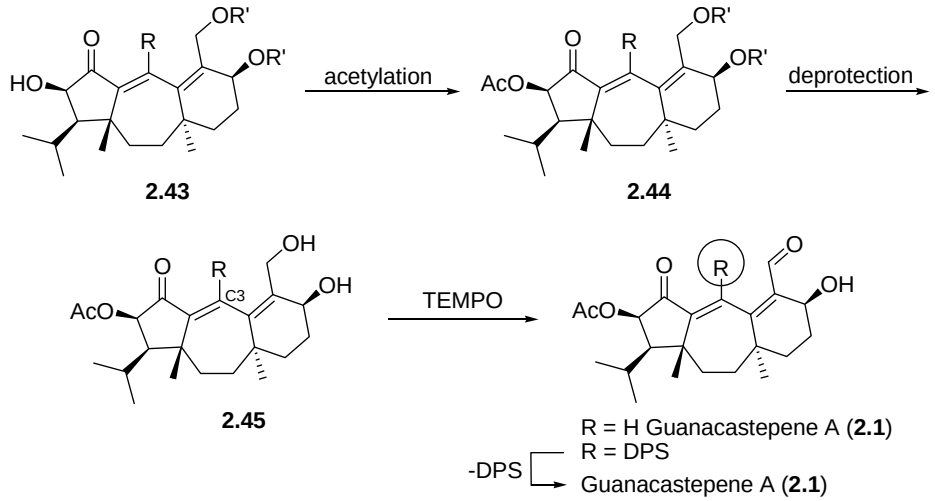


Figure 19. Equilibration of the α-hydroxy ketone 2.42→2.43

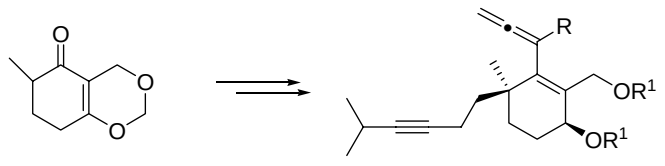
Completion of guanacastepene A, where R = H, entails acetylation of the secondary alcohol of **2.43**, deprotection of the diol protecting group, and selective oxidation of the primary

alcohol with TEMPO (Scheme 45). Danishefsky reports that diol **2.45**, where R = H is extremely unstable due to facile conjugate addition of the primary alcohol at C3. Consequently, this leads to a low yield for the oxidation step. Alternatively, we propose that the [5-7-6]-carbocycle **2.45** (where R = DPS) will effectively block the undesired addition and increase the yield of the TEMPO oxidation. Subsequently, removal of the DPS group would give guanacastepene A.



Scheme 45. The Brummond/McCabe proposed route to complete guanacastepene A

It is also advantageous to obtain guanacastepene A via the allenic cyclocarbonylation reaction since the allenyne precursor **2.37** is a functionalized cyclohexenol. There is an abundance of known protocols to synthesize cyclohexanones efficiently and stereoselectively; therefore, a variety of options for their preparation are available. It is proposed that functionalization of Smith's methylated enone[95] **2.37** will give the desired allenyne **2.36** with good diastereoselectivity (Scheme 46).



2.37 **2.36**

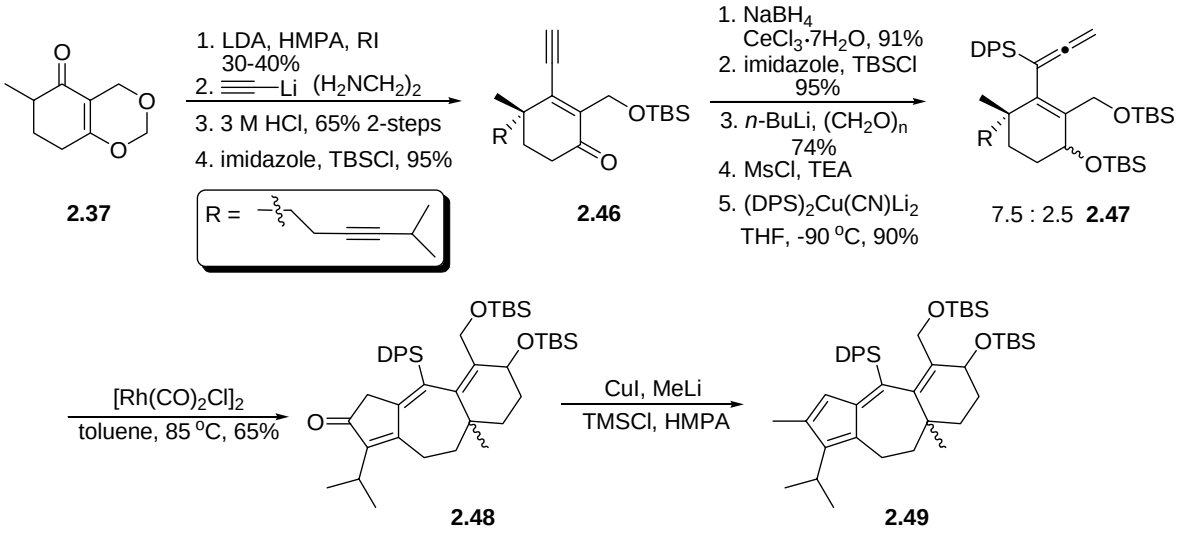
Scheme 46. Functionalization of enone 2.37 to give allenyne 2.36

As outlined a short, efficient, and stereoselective route to guanacastepene A via a Rh(I)-catalyzed cyclocarbonylation reaction is proposed. If the synthesis of guanacastepene A is completed as proposed the total synthesis could arise after 16 synthetic steps. This is dramatically less than any of the other previous syntheses; Hanna's being the next shortest with 24 synthetic steps to guanacastepene A.

2.3 BRUMMOND AND COWORKERS' APPROACHES TO GUANACASTEPENE A

2.3.1 First Generation Approach: Cyclocarbonylation of Allenyne 2.47

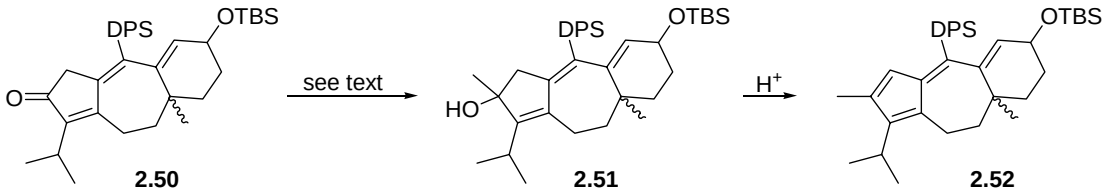
A former graduate student in the Brummond group, Dong Gao, worked on the synthesis of guanacastepene A and his results are briefly summarized.[96] His important contributions were completing the synthesis of the highly functionalized allenyne **2.47** and demonstrating that the cyclocarbonylation reaction indeed gives the desired [5-7-6] carbocycle **2.48** in a 65% yield. Formation of the carbocycle **2.48** starts with a problematic alkylation on methylated Smith's enone **2.37** with 1-iodo-5-methyl-3-butyne, which produces 30%-40% yields of dialkylated product regardless of the order of introduction of the methyl and alkynyl groups (Scheme 47).



Scheme 47. Gao's route to the carbocyclic core 2.48

Addition of lithium acetylene ethylene diamine complex to the enone forms the unstable tertiary alcohol, which under acid conditions hydrolyzes to give the desired enynone in a 65% yield over two steps (Scheme 47). The newly formed primary alcohol is protected with a TBS-group to give enone **2.46** and then the enone is reduced with the Luche reduction protocol[52] to give a 7.5 : 2.5 diastereomeric mixture of the corresponding allylic alcohol in a 91% yield. At this time it was not determined if the major diastereomer possessed the correct stereochemistry for the synthesis of guanacastepene A. The mixture of diastereomeric alcohols were protected with a TBS-group and then subjected to *n*-BuLi and paraformaldehyde giving the respective propargylic alcohol in a 74% yield. The alcohol was converted to a mesylate (MsCl and TEA) and added crude to the preformed silylcuprate [$(DPS)_2Cu(CN)Li_2$] to give the desired allenyne **2.47** in a 90% yield. After successful application of the Rh(I)-catalyzed allenyne cyclocarbonylation reaction, the [5-7-6] carbocycle **2.48** was subjected to activated cuprate conditions,[82] which gave fulvene **2.49**, via a 1,2-addition/elimination pathway, and recovered starting material. Furthermore, subjection of a similar carbocycle, enone **2.50**, to Me_2CuLi;

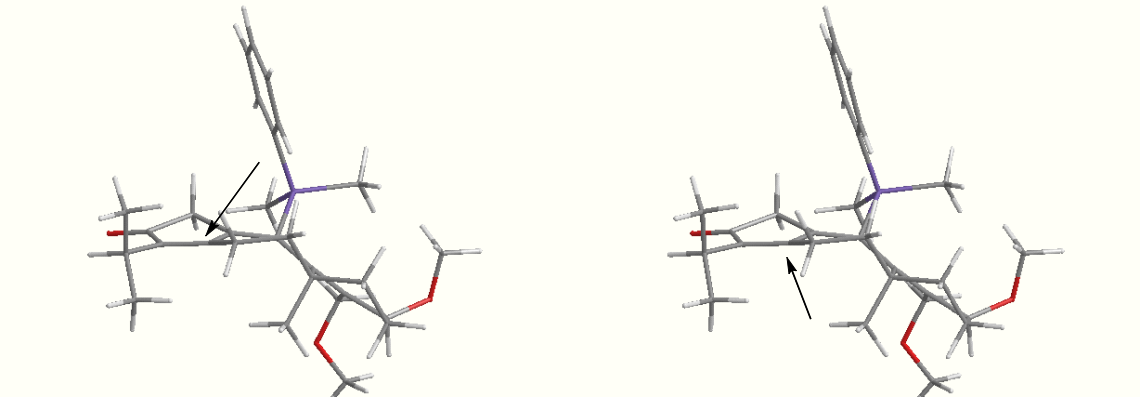
MeMgBr·DMS, TMSCl, HMPA; TMA and $Ni(acac)_2$; or Me_2Zn and $Ni(acac)_2$ all gave 1,2-addition product **2.51**, which subsequently formed the fulvene **2.52** (Scheme 48).



Scheme 48. Attempts to affect a 1,4-addition on enone 2.50

2.3.2 Second Generation Approach: Cyclocarbonylation of Alkyne and Des-silyl Allene

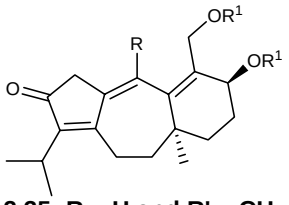
We subsequently reevaluated the first generation approach to guanacastepene A. Dong Gao's work gave us an abundant amount of information for which we used to develop our second generation approach to guanacastepene A. In reference to Gao's problems with conjugate addition to enone **2.48**, computational analysis of **2.48** (with TBS groups = methyl) revealed that the bulky DPS group distorted the [5-7-6] carbocyclic ring system in such a way that effectively both faces of the enone were blocked (Figure 20).



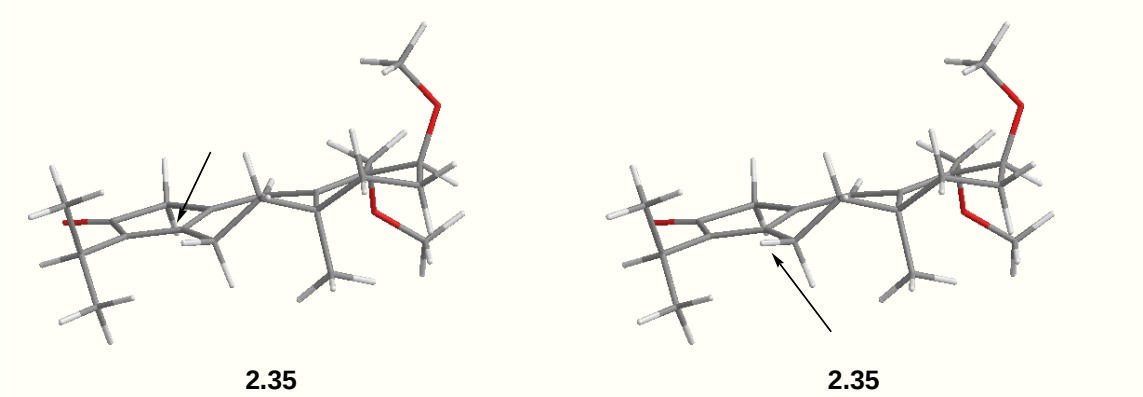
2.48 **2.48**

Figure 20. Lowest energy conformer for 2.48 (the TBS groups have been replaced with Me groups for computational ease): conformational search performed in Macspartan using MM2

As shown in figure 20, the DPS group on intermediate **2.48** blocks the top face of the enone while the six-membered ring blocks the other face of the enone preventing the conjugate addition at C13. To remedy this problem, we envisioned the formation of tricycle **2.35**, where R = H (Scheme 42, page 92). As depicted in figure 21, conformational analysis of the [5-7-6]-carbocycle **2.35**, where R = H and R^1 = methyl, reveals flattening of the ring system. This flattening of carbocycle makes the C13 position more accessible than with the DPS group; allowing for the conjugated addition of the nucleophile to occur from the β-face.



2.35; R = H and R' = CH_3

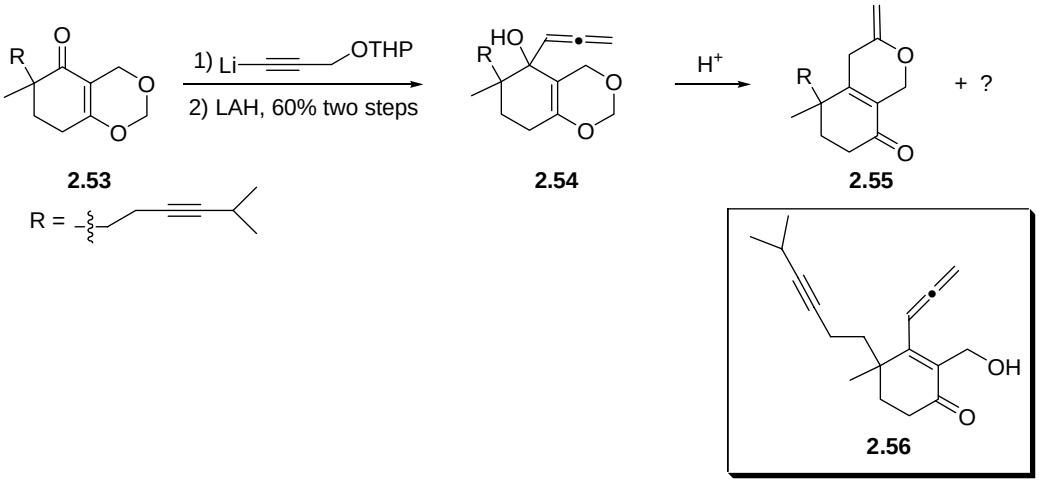


2.35 **2.35**

Figure 21. Lowest energy conformer for 2.35, where R = H and R^1 = methyl: conformational search performed in Cache using MM2

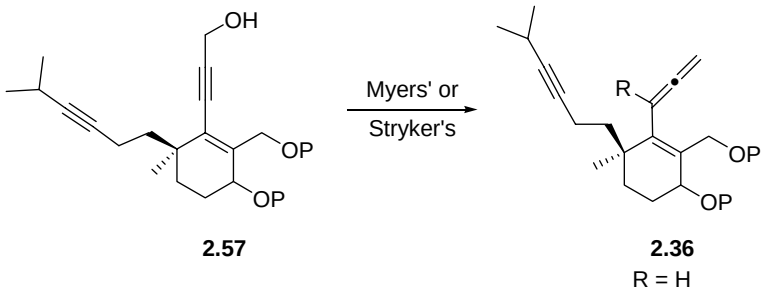
The options for synthesizing tricycle **2.35** were: formation of allenyne **2.36**, where R = H, or removal of the DPS group from **2.35**, where R = DPS, which would require changing the TBS protecting groups. However, the formation of an allenyne without the DPS functionality had

briefly been explored by Gao. Addition of the lithium anion of THP-protected propargyl alcohol to enone **2.53** gave the corresponding tertiary alcohol. This alcohol was then subjected to LAH initiating an S_N2' addition of hydride giving the allene **2.54** in a 60% yields over two steps.[97] Unfortunately, all attempts to hydrolyze allenyne **2.54** gave none of the desired ene-allene **2.56**, but a 1 : 1 mixture of by-product **2.55** and an unknown product (Scheme 49).



Scheme 49. Hydrolysis of allene-ene 2.54

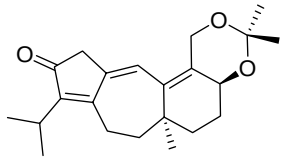
To avoid this problem, an alternative route to allenyne **2.35**, where R = H, was proposed that circumvents the hydrolysis of allenyne **2.54** (Scheme 50). It was reasoned that the mono-substituted allene of **2.36** could be obtained by either subjecting the homo-propargylic alcohol **2.57** to a sigmatropic rearrangement using Myers' protocol[98] or alternatively conversion of the alcohol to an acetate and then effect an S_N2' addition with Stryker's reagent.[99]



2.57 **2.36**
R = H

Scheme 50. Using Myers' or Stryker's reagents for access to allenyne 2.36

In the event that this pathway did not yield allenyne **2.36**, where R = H, the DPS functionality would be removed from enone **2.48** after the cyclocarbonylation reaction. This alternative also required that the diol protecting groups be changed from TBS ethers to an acetonide. Fortunately, Danishefsky demonstrated that the acetonide protecting group can be carried through to the completion of the synthesis of guanacastepene A.



2.58

Figure 22. [5-7-6]-carbocycle 2.58β

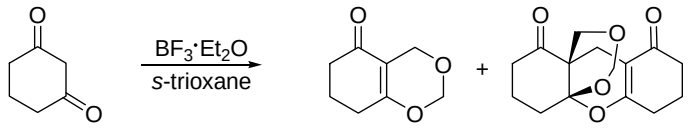
Therefore, carbocycle **2.58** was our new target, and only minor modifications in the synthesis of the alkynyl allene starting material were necessary (Figure 22). This allowed us to utilize many of the same reactions in the second generation approach. Also, it provided an opportunity to re-examine some of the steps in the first generation synthesis and to determine the stereoselectivity of the carbonyl reduction of cyclohexenone **2.46** (Scheme 47, page 99).

2.4 AN EFFICIENT SYNTHESIS OF THE CYCLOCARBONYLATION PRECURSOR 2.77 AND 2.86

2.4.1 Optimization of the Synthesis of Smith's Enone 2.60 and the Alkylation of Enone 2.37

Our proposed route to guanacastepene A has the potential to be the shortest route currently in the literature. However, efficient synthetic reactions, readily available and inexpensive starting materials and practical and convenient conditions all contribute to the success of a synthesis. Low yields or inconvenient conditions in the beginning stages of a synthesis can foil the best of synthetic strategies if key-step precursors cannot be accessed in sufficient quantities. Therefore, our focus first turned to the optimization of burdensome or low yielding steps exposed in Gao's route to guanacastepene A.

The synthesis of Smith's enone **2.60**, while well precedented in the literature, was an inconvenient reaction based on the very dilute reaction conditions (0.019M). While these conditions were necessary to prevent the formation of **2.61**, which results from oligomerization of **2.60**, this made large scale reactions difficult due to the large quantities of dichloromethane that were required (102 mL to prepare 260 mg of product) (Scheme 51).[95]

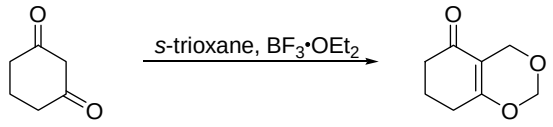


Scheme 51. Formation of Smith's Enone 2.60

Typically, the concentration of the reaction is kept low by diluting the *s*-trioxane and

$BF_3{\cdot}OEt_2$ in CH_2Cl_2 to 0.12 M, then 0.019 molarity is achieved by the addition of a 1 M solution of 1,3-cyclohexanedione in CH_2Cl_2. It was reasoned that lowering the concentration of the 1,3-cyclohexanedione during addition to the solution of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 would limit the amount of non-reacted 1,3-cyclohexanedione in solution; thus, prevent oligomerization. Once enone **2.60** is formed, it cannot oligomerize. To determine if changing the concentration of the reaction would in fact prevent oligomerization, three small scale reactions were performed and the results are shown in Table 6. It was found that lowering the concentration of the 1,3-cyclohexanedione solution to 0.16 M and increasing the concentration of the *s*-trioxane solution to 0.35 M gave the best yields on small scale and with the overall lowest solvent volume (compare Entry 2 to Entries 3 & 4, Table 6). While the yield of this reaction was lower than the published yield of 84%, the total amount of solvent used was decreased to half the original volume (compare Entries 1 and 2, Table 6). Fortunately, when the reaction scale was increased from 200 mg to 5 g, a 99% yield of **2.60** was obtained making these conditions superior to those previously published (Entry 5, Table 6).

Table 6. [a]Optimization of condensation reaction conditions to prepare enone 2.60



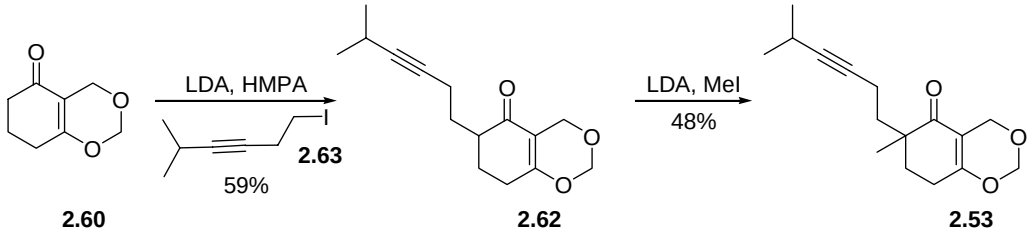
2.59 **2.60**

Entry	[**2.59**] M	[trioxane] M	Yield of **2.60**	Solvent Volume[d]
1	1.0 M	0.12	84%[b]	40 mL
2	0.16 M	0.35	67%	20 mL
3	1.0 M	0.24	57%	24 mL
4	0.08 M	0.18	60%	40 mL
5	0.16 M	0.35	99%[c]	20 mL

[a.] All reactions were run with 1 eq of diketone (200 mg), 6 eq of trioxane, and 3 eq of BF_3 OEt_2 at rt. [b.] Yield from reference **XX**. [c.] Reaction ran on 5 g scale.[d.] Total volume of solvent per 100 mg of diketone **2.59**

Next, we were motivated to increase the yield of the alkylation reaction of **2.37** with 1-

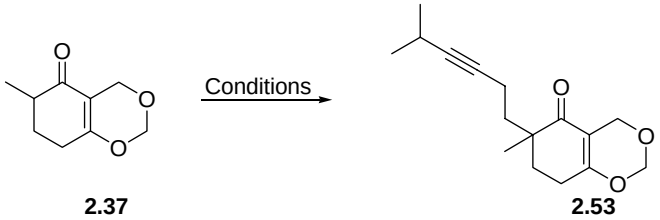
iodo-5-methylhex-3-yne (**2.63**) (Scheme 47, page 99). While it is not uncommon for an alkylation using homopropargylic electrophiles to be low yielding,[100] a 30-40% yield in the second step of this reaction sequence was a serious setback by limiting the amount of material for later steps in the synthesis. Gao briefly investigated this low yielding process by reversing the order in which the electrophiles were added so that the more reactive methyl iodide was added after the alkynyl iodide **2.63** (Scheme 52). Addition of 1-iodo-5-methylhex-3-yne (**2.63**) to enone and LDA gave enone **2.62** in a 59% yield. Subsequent deprotonation of enone **2.62** with LDA followed by addition of methyl iodide gave the dialkylated product **2.53** in a 48% yield. Unfortunately, the overall yield for this two step process is approximately the same as previously reported.



Scheme 52. Gao's alkylation results: reversing the order of electrophile addition to Smith's enone

Thus, a systematic study to increase the yields of the alkylation of enone **2.37** was performed and the results are summarized. First, the base used for the deprotonation step was altered. Unfortunately, KHMDS, NaHMDS, and KH gave either recovered starting material or decomposition; LDA was the only base that gave enone **2.53**. Therefore, using LDA as the base, the equivalents (equiv) of base relative to the enone **2.37** and iodide **2.63** were investigated (in all cases, enone equivalent equals one) (Table 7).

Table 7. [a]Optimization of alkylation reaction conditions for the synthesis of enone 2.53

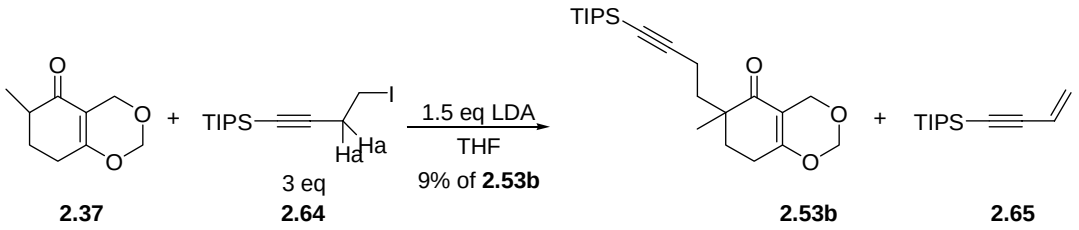


2.37 **2.53**

Entry	Base (eq.)	Additive (eq.)	eq. of **2.63**	**2.53** yield	**2.37** yield
1	LDA (1.2)	none	2	42%	31%
2	LDA (3)	none	3	32%	23%
3	LDA (1.5)	none	3	58%[b]	41%
4	LDA (1.5)	DMPU (2)	3	55%	25%
5	LDA (1.5)	HMPA (3)	3	53%	24%

[a]Reaction done on 0.5-1.0 mmol scale [b]Reaction done on 7 mmol scale.

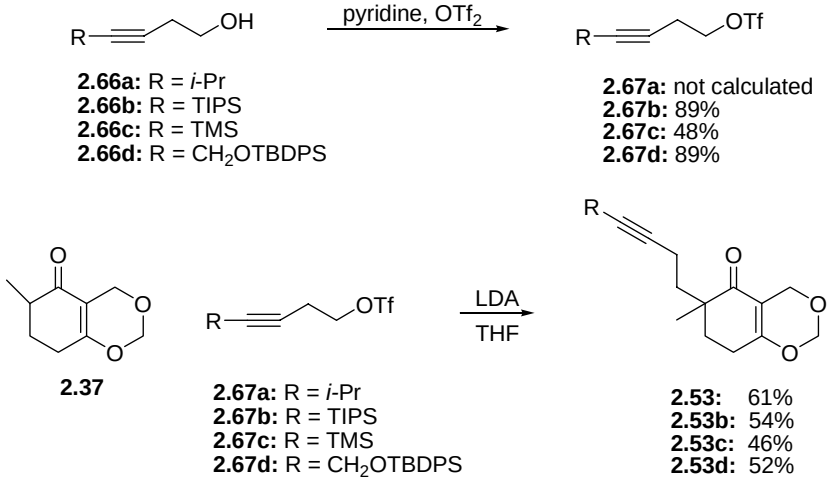
Typically a 42% yield of **2.53** could be obtained using 1.2 equiv of LDA and 2 equiv of iodide **2.63**. Increasing the amount of both base and electrophile to 3 equiv gave a lower yield (32%) of **2.53**. However, when 1.5 equiv of LDA and 3 equiv of iodide **2.63** were used the yield of **2.53** increased to 58% (Entry 3, Table 7). Polar additives such as HMPA and DMPU have been shown to increase the yields in alkylation reactions.[101] However, addition of HMPA or DMPU did not promote an increased yield of enone **2.63** (compare Entry 3 to Entries 4 and 5, Table 7). While altering the equivalents of LDA and iodide increased the yield of enone **2.53** from 30-40% to 50-60%, synthesis of iodide **2.63** was inconvenient on large scale. The formation of large, pure quantities of iodide **2.63** from alcohol **2.66a** was a two-step Finkelstein type process that took approximately 2 days.[102] Furthermore, when the isopropyl moiety on iodide **2.64** is replaced by a TIPS group a substantial amount of enyne **2.65** is formed under the alkylation reaction conditions (Scheme 53).



Scheme 53. Alkylation of enone 2.37 with electrophile 2.64

Determined to make the synthesis of Guanacastepene A as efficient, convenient and general as possible, we searched for better reaction conditions. A possible alternative was the use of a triflate moiety in place of the iodide. It has been demonstrated that a triflate moiety is a better leaving group in an S_N2 reaction than the corresponding iodides; therefore, it is proposed that alkylation could occur prior to deprotonation of Ha which leads to the elimination product **2.65** (Scheme 53).[103]

The alkylation of enone **2.37** using triflate **2.67a** was investigated. Addition of alcohol **2.66a** to a solution of pyridine and triflic anhydride at -78 ˚C gave triflate **2.67a** after approximately 1 hour; the yield was not calculated at this time (Scheme 54). Subsequent addition of triflate **2.67a** to the enolate of enone **2.37** gave a 61% yield of the alkylation product **2.53**.

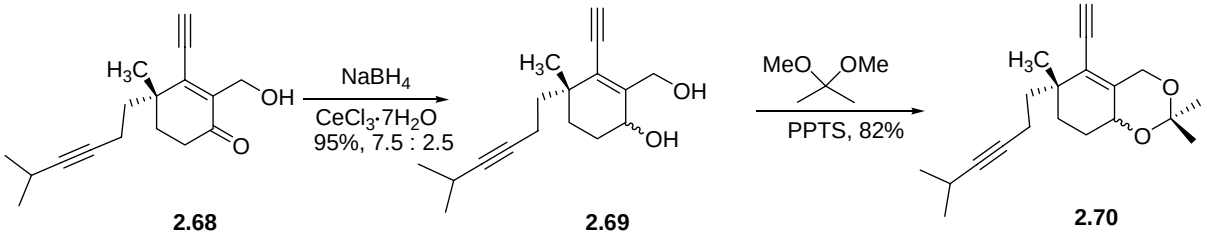


Scheme 54. Synthesis of enone 2.53b-2.53d and 2.53

Using the triflate moiety in place of the iodide gave a higher yield of enone **2.53** and decreased the lab time needed to synthesize the electrophile (48 h to 1 h). Moreover, no solvent was used to form the triflate **2.67a** from alcohol **2.66a**; therefore this reaction was more economical than the formation of the iodide. Also, the triflate moiety has been found to be very general and promotes alkylations that had been problematic. For example, 4-(triisopropylsilyl)but-3-ynyl triflate (**2.67b**), 4-(trimethylsilyl)but-3-ynyl triflate (**2.67c**) and 5-(*tert*-butyldiphenylsilyloxy)pent-3-ynyl triflate (**2.67d**) all undergo the alkylation reaction smoothly to give enone **2.53b** , **2.53c** and **2.53d** in 54%, 46% and 52% yield, respectively (Scheme 54).

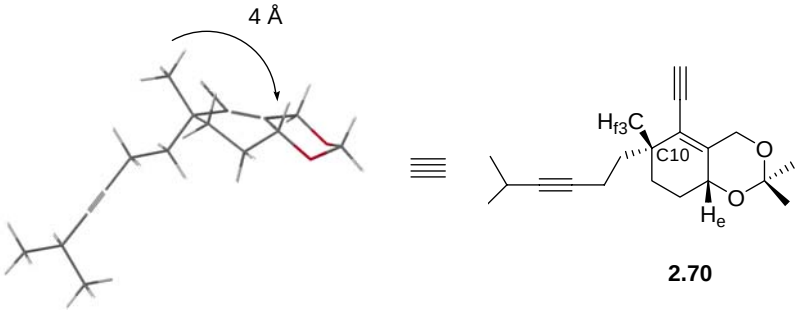
2.4.2 Exploring Conditions to Attain a Stereoselective Reduction of Enone 2.77 or 2.86

Continuing on our quest to attain the most efficient route to the allenyne precursor **2.77** or **2.86**, the stereoselectivity of the carbonyl reduction of cyclohexenone **2.68** was examined. Following Gao's procedure, subjection of enone **2.68** to Luche reduction conditions gave the allylic diol **2.69** in a 95% yield as a 7.5 : 2.5 diastereomeric ratio as determined by analysis of the ^{1}H NMR spectrum (Scheme 55). The diastereomeric mixture of diol **2.69** was conformationally fixed by synthesizing acetal **2.70** and then the diastereomers were separated and analyzed via NOESY NMR.



Scheme 55. Synthesis of propargylic alcohol 2.70

The NOESY experiment was performed on acetonide **2.70β**; the minor diastereomer from the Luche reduction. As depicted in figure 23 there is a strong correlation between the Hf protons on the quaternary methyl group at C9 and the He protons; signifying that they are *syn* to one another.



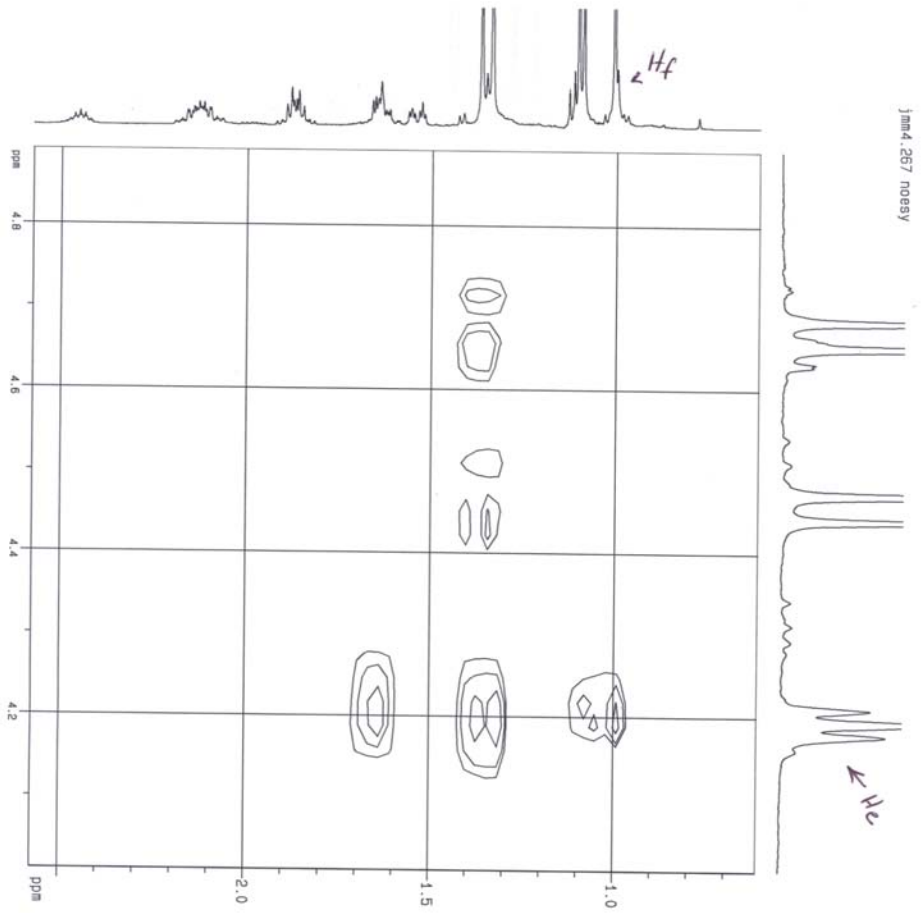
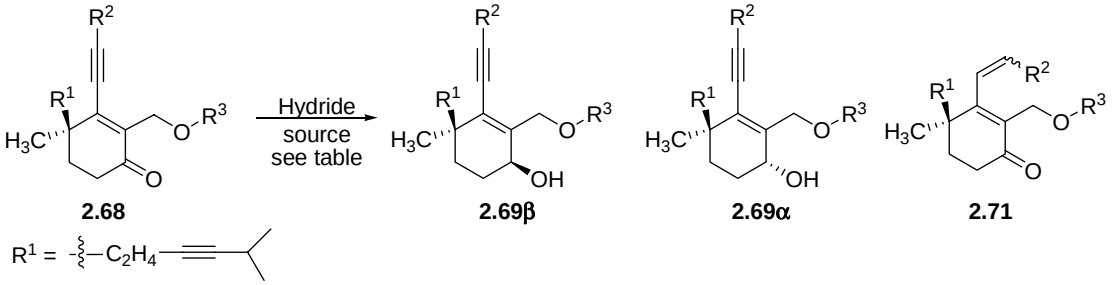


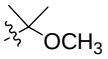
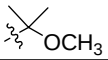
Figure 23. NOESY spectrum of enyne 2.70β

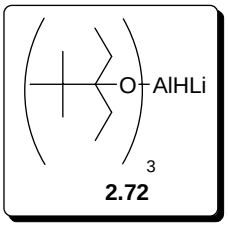
Based upon the stereochemical assignments, the Luche reduction protocol gave a 2.5 : 7.5 ratio of **2.69β** : **2.69α** in a 95% yield; in favor of the wrong diastereomer for the synthesis of guanacastepene A (Entry 1, Table 8). Reduction protocols to give a predominance of the desired diastereomer were investigated. Using $NaBH_4$ resulted in lower selectivity, but still favored the **2.69α** isomer (Entry 2, Table 8). Because the smaller hydride source favored formation of **2.69α**, a bulkier hydride source was examined. Addition of L-selectride to enone **2.68** gave a reversal in the selectivity affording a 7 : 3 ratio of **2.69β : 2.69α** (Entry 3, Table 8). To further increase the selectively, tri[(3-tert-butyl-3-pentyl)oxy] aluminum hydride (**2.72**), a reductant reported to give

the same facial selectivity as L-selectride,[104] was used. Subjection of enone **2.68** to hydride **2.72** gave a 5.7 : 1.9 ratio of **2.69β** : **2.69α** in a 79% yield; but unfortunately, a substantial amount of the diene **2.71** was obtained, as determined by analysis of the ^{1}H NMR spectrum.

Table 8. Reversal of diastereoselectivity in the reduction of 2.68

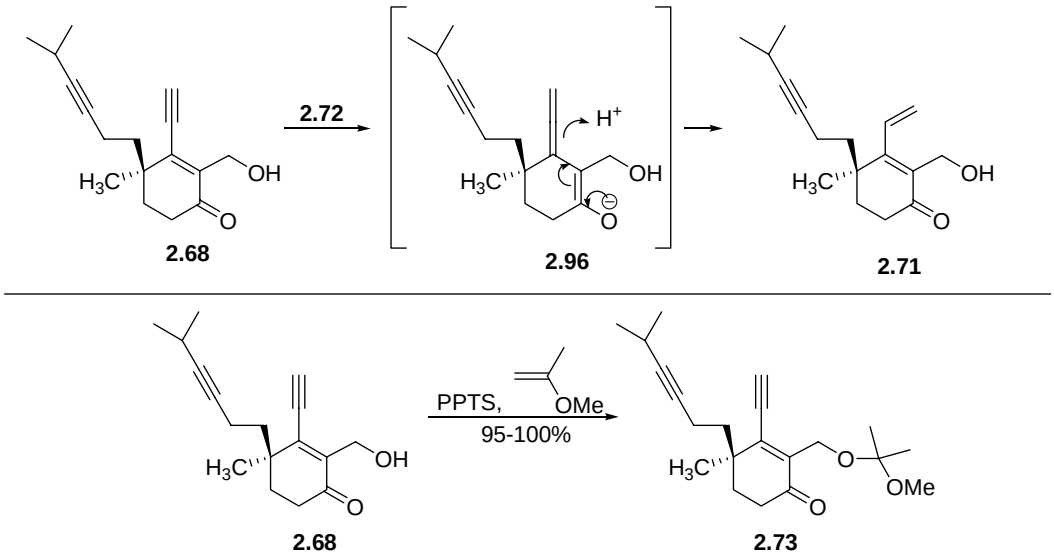


Entry	SM	R^2	R^3	Hydride Source	Yield (%)[a]	**2.69β : 2.69α : 2.71**
1	**2.68**	H	H	$NaBH_4$ / $CeCl_3$	95	2.5 : 7.5 : 0
2	**2.68**	H	H	$NaBH_4$	76	3 : 7 : 0
3	**2.68**	H	H	L-selectride	82	7 : 3 : 0
4	**2.68**	H	H	**2.72**	79	5.7 : 1.9 : 2.4
5	**2.73**	H		**2.72**	60	6.3 : 1.2 : 2.5
6	**2.74**	TMS	H	**2.72**	88	7.5 : 2.5 : 0
7	**2.75**	TMS		**2.72**	45	8.2 : 1.8 : 0



[a] Yield of the product mixture

Diene **2.71** arises from a preferential 1,6-conjugate addition onto the alkyne. This type of addition has been observed by Krause,[105] who performs 1,6-additions onto 2-en-4-ynoates using cuprate reagents. It is predicted that hydride **2.72** effects a conjugate addition to en-ynone **2.68** to give allene **2.96** (Scheme 56). Allene **2.96** then undergoes an isomerization to give the more stable diene **2.71**.

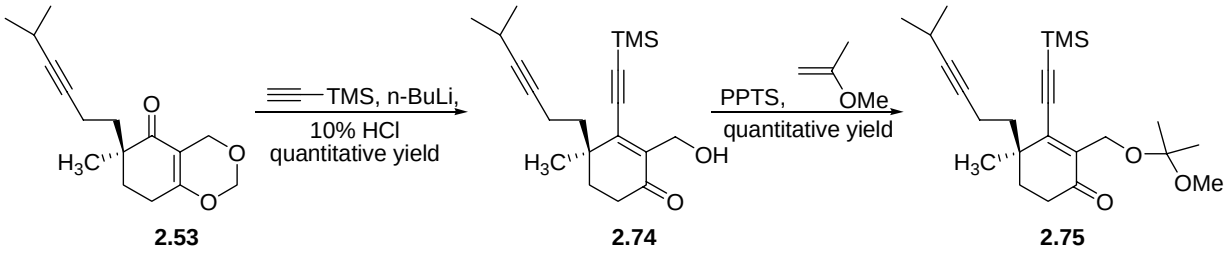


Scheme 56. Formation of diene 2.71 and acetal 2.73

It was thought that formation of diene **2.71** could be prevented by protection of the primary alcohol; because it was envisioned that the free alcohol could be directing the reduction of the alkyne. The alcohol **2.68** was protected as the mono-acetal **2.73** using PPTS and 2-methoxyprop-1-ene. This protecting group was used because it could eventually be transformed into our desired acetonide (Scheme 56). Addition of hydride **2.72** to **2.73** gave an improved diastereoselectivity of 6.3 : 1.2; however, diene formation was still observed and only a 60% combined yield was obtained (Entry 5, Table 8).

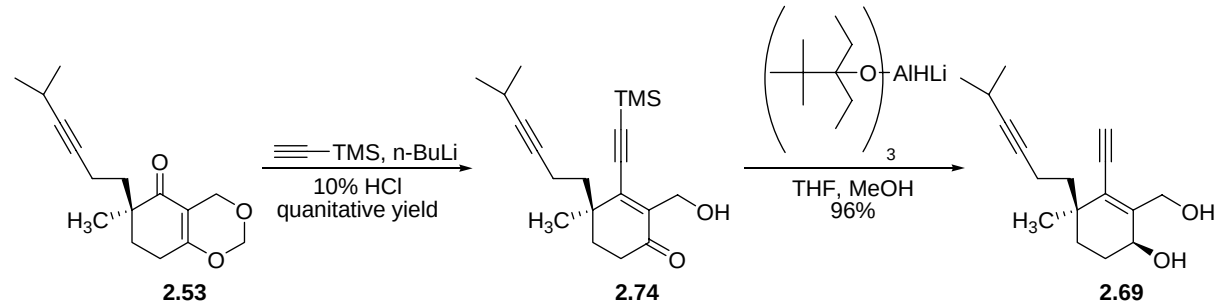
Alternatively, the terminus of the alkyne of enone **2.68** was protected with a bulky TMS group. Enone **2.74** was prepared by addition of ((trimethylsilyl)ethynyl)lithium to enone **2.53**, followed by acid hydrolysis of the respective tertiary alcohol (Scheme 57). Reduction of enone **2.74** with hydride **2.72** gave a 7.5 : 2.5 diastereomeric ratio of **2.69β : 2.69α** in an 88% yield with no evidence of diene formation (Entry 6, Table 8). In an effort to ascertain whether this selectivity could be further enhanced, the primary alcohol of **2.74** was protected to give enone

2.75.



Scheme 57. Synthesis of enone 2.75

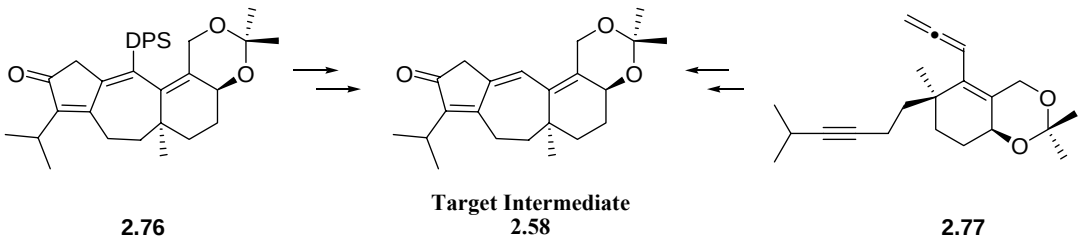
Addition of tri[(3-tert-butyl-3-pentyl)oxy] aluminum hydride (**2.72**) to **2.75** revealed an 8.2 : 1.8 ratio of diastereomers of **2.69β : 2.69α**; however, in a low 45% yield (Entry 7, Table 8). Even though the diastereomeric ratio obtained from the reduction of enone **2.75** was better than **2.74**, the low yield limited its usefulness. Therefore, enone **2.74** was chosen as the optimal substrate for the reduction and the reducing agent tri[(3-tert-butyl-3-pentyl)oxy] aluminum hydride (**2.72**) gave the highest diastereoselectivity. Fortunately, diol **2.69β** can be synthesized in the same number of steps as previously shown (Scheme 47, page 99), since the TMS group is cleaved during the workup of the carbonyl reduction by quenching with MeOH (Scheme 58).



Scheme 58. Synthesis of diol 2.69 with correct stereochemistry

2.4.3 Functionalization of Guanacastepene A's C-Ring Leading to Allenyne 2.77 or 2.86

Having developed a sequence that efficiently formed guanacastepene A's C-ring, diol **2.69**; our efforts now turned towards further functionalization of the C-ring that would ultimately lead to the formation of allenyne **2.77**; the precursor to guanacastepene A's carbocyclic core. The results obtained in Gao's route concluded that an effective synthesis of an alternative target, **2.58**, was necessary to complete the synthesis of guanacastepene A. Two synthetic sequences could lead to the formation of the A, B and C-tricycle **2.58** (Scheme 59). Synthesis of allenyne **2.77**, a system that does not contain a DPS group, and subsequent cyclocarbonylation would give the triene **2.58** directly. Alternatively, triene **2.58** could be formed by desilylating enone **2.76**. The first option was more efficient, having fewer synthetic steps, and also more practical given that removal of vinyl silanes can be difficult;[106] therefore, a sequence to form allenyne **2.77** was pursued.

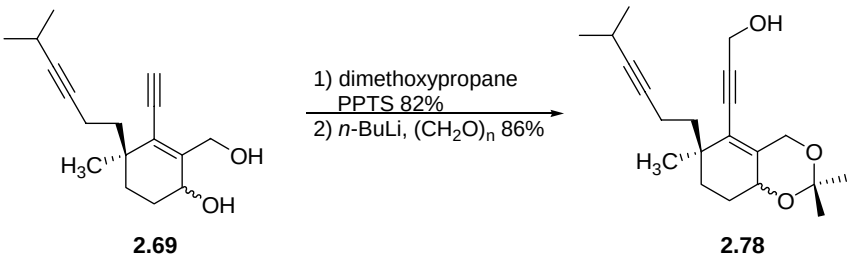


2.76 **Target Intermediate 2.58** **2.77**

Scheme 59. Pathways that could lead to the target intermediate 2.58

Diol **2.69**, taken on as a 7.5 : 2.5 mixture of diastereomers, was protected as the acetonide and then subjected to *n*-BuLi and paraformaldehyde yielding homopropargylic alcohol **2.78** in a 86% yield (Scheme 60). At this stage the diastereomers could be separated using a Biotage apparatus eluting with 5-25% (5% *t*-BuOH/THF solution) / pentanes solvent system. The fractions were analyzed by GC using method hc-200-15 giving a retention time of 11.5 min for

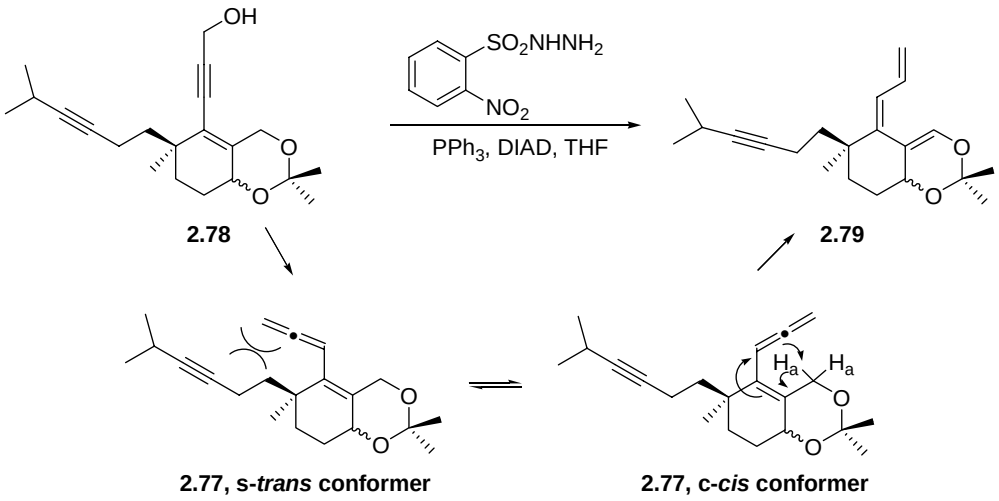
2.78α and 12.2 min for **2.78β**.



2.69 **2.78**

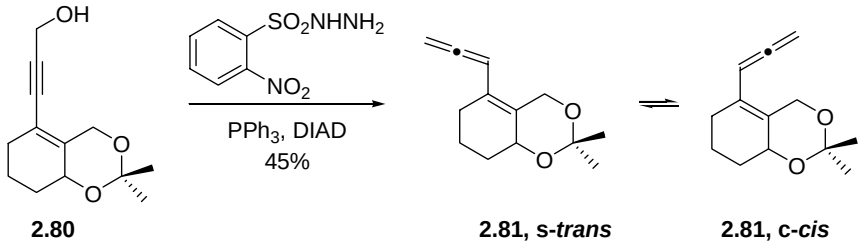
Scheme 60. Formation of alcohol 2.78

The propargylic alcohol **2.78** was subjected to Myers' hydrazine protocol,[98,107] which initially gave the desired product **2.77**, as observed by analysis of the ^{1}H NMR spectrum (Scheme 61). The allene **2.77** stained pink on TLC using *para*-anisaldehyde (PAA) stain and was the only product seen on TLC after aqueous workup of the reaction mixture. However, after silica gel chromatography a second spot appeared which was slightly less polar and stained blue on TLC with PAA stain. This new less polar material was fully characterized as triene **2.79**. This mixture of allene **2.677** and triene **2.79,** obtained after silica gel chromatography, eventually all converted to triene **2.79** in an NMR tube diluted with $CDCl_3$ to give approximately a 30% overall yield of triene **2.79**.



Scheme 61. Myers' rearrangement protocol to convert alcohol 2.78 to allene 2.77

It is presumed that upon formation of the allene-ene **2.77**, a 1,5-sigmatropic hydrogen shift occurs giving the conjugated triene **2.79**. This type of rearrangement has been previously observed by Okamura[108] in 1980, and then he published a more in depth study on the rearrangement in 1990.[109] In both publications, heat was required to promote rearrangement.



Scheme 62. Myers' rearrangement to convert alcohol 2.80 to allene 2.81

To probe deeper into why allenyne **2.77** was readily undergoing this rearrangement, a model system **2.80** was formed and subjected to the Myers protocol. In this case allene **2.81** was formed in a 45% yield and no subsequent rearrangement was observed (Scheme 62). It was concluded that the favored conformation of **2.81** is the conformer in which the allene is in the s-*trans* conformation; therefore hampering rearrangement. Thus, it is reasoned that the steric bulk

of the α-substituents on **2.77** favor the c-*cis* conformation thereby affording the rearrangement (Figure 24). Conformational analysis of allene-ene **2.77** confirms this conclusion. As depicted in figure 24 the lowest calculated energy conformation shows the allene and alkene moieties existing virtually in the same plane.

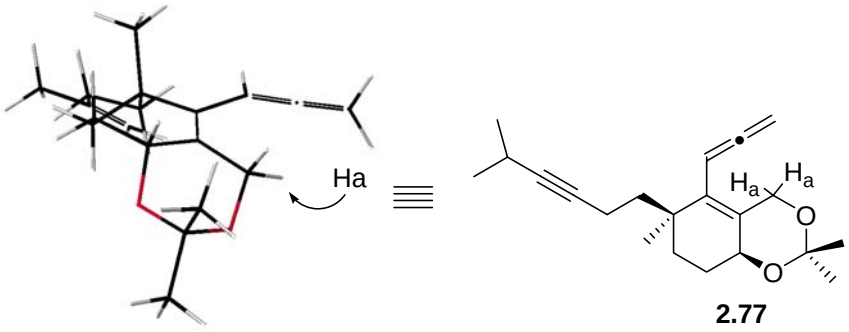
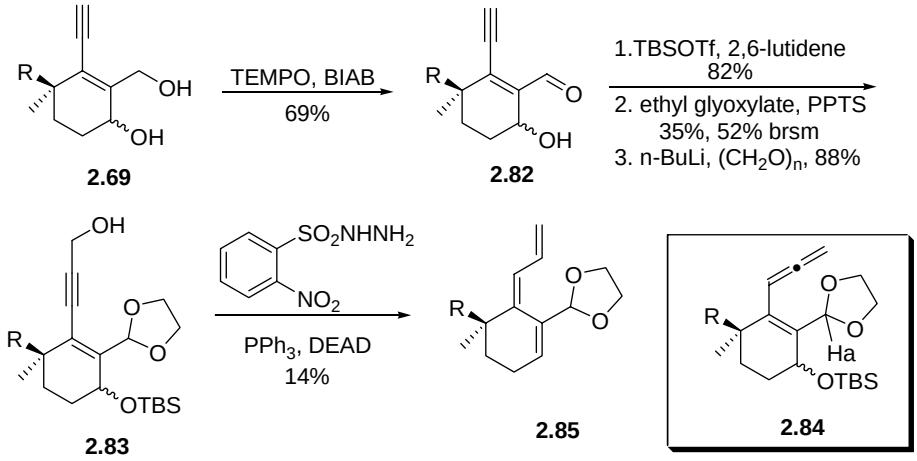


Figure 24. Lowest energy conformation for 2.77β: conformational search performed in Cache using MM2

There are two methods that could potentially prevent this isomerization: one method would alter the reaction conditions such that isomerization is less favorable. Alternatively, the functionality on the starting material could be changed in such a way that the preferred conformation of the allene would not favor rearrangement. Unfortunately, the Myers reaction is very sensitive to temperature in that cooling the reaction below -15 ˚C leads to the formation of betaine, which gives inferior results;[110] therefore, decreasing the reaction temperature in order to potentially prevent isomerization was not an option. Hence, changing the functionality on enyne **2.70** was the only method that could be used to prevent the rearrangement.

To this end, enyne **2.83** was synthesized with hypothesis that Ha of ene-allene **2.84** would be too sterically hindered to undergo the sigmatropic rearrangement (Scheme 63). Subjection of diol **2.69** to TEMPO oxidation conditions gave aldehyde **2.82** in a 69% yield. The

secondary alcohol was then protected with a TBS-group in an 82% yield and the aldehyde was protected as the acetal in a 35% yield, 52% based on recovered starting material (brsm). Subjection of the respective enyne to *n*-BuLi and paraformaldehyde gave the propargylic alcohol **2.83** in an 88% yield. To our surprise, this propargylic alcohol under the Myers' reaction conditions gave a 14% of a triene **2.85** and none of the desired allene-ene **2.84**.



Scheme 63. Synthesis of allene 2.84

Even though it is not understandable how triene **2.85** is formed, the spectral data undoubtedly supports its formation. It is clear from analysis of the ^{1}H NMR spectrum that triene **2.85** does not contain a TBS group and it contains five olefinic resonances, which possess coupling constant expected for triene **2.85**. The ^{13}C NMR spectrum of triene **2.85** contains six olefinic carbon resonances as well as the acetal carbon at 102 ppm. Lastly, the mass spectroscopy spectrum showed a $[M]^{+}$ peak at 300, which is the calculated molecular weight of triene **2.85**.

In lieu of these results, an alternative approach to prevent rearrangement was necessary. For a sigmatropic rearrangement to occur the allene and alkene must be in the same plane. Furthermore, it was known that allene-ene **2.47** does not undergo this rearrangement (see

Scheme 47, page 98), therefore, it was concluded that the DPS moiety rotates the allene out of the plane with the alkene inhibiting rearrangement.

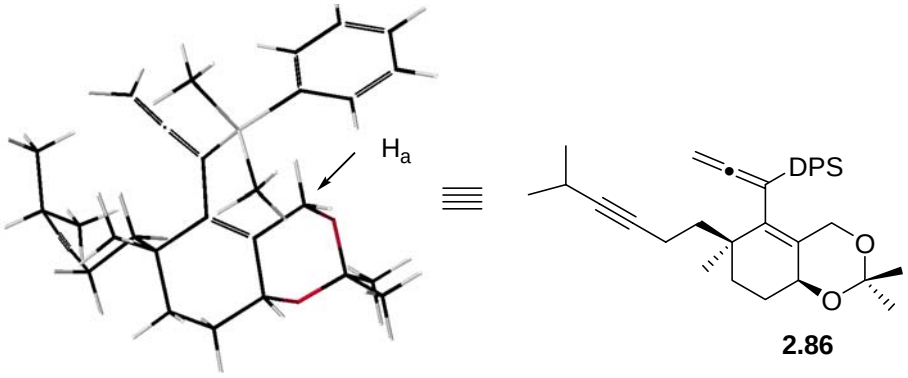
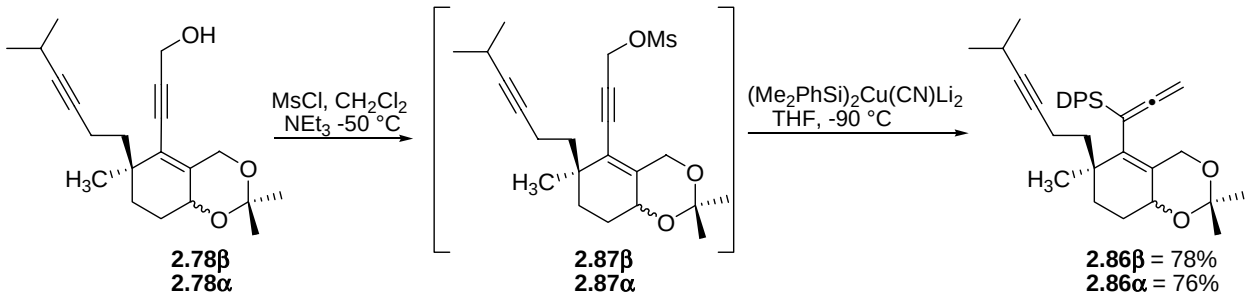


Figure 25. Conformational representation of allene 2.86: conformational search performed in Cache using MM2

As shown in figure 25, the allene moiety in **2.86** is nearly perpendicular from the H_a methylene protons; therefore, rearrangement cannot occur. A large steric interaction between the DPS group and alkyl substituents most likely prevents alignment of the allene moiety with the methylene protons.

It was clear that formation of an allenyne that did not posses a DPS group was not a viable route to obtain triene **2.58** due to its capability to undergo rearrangement. Therefore, our attention was turned to the synthesis of enone **2.76** and subsequent removal of the DPS group. The propargylic alcohols **2.78β** and **2.78α** were converted to mesylates **2.87β** and **2.87α**, respectively. The crude mesylates were subjected to a solution of $DPS_2Cu(CN)Li_2$ to give allene-enes **2.86** in a 78% yield via an S_N2' reaction (Scheme 64).[111]



Scheme 64. Synthesis of allenynes 2.86β and 2.86α

2.4.4 Summary and Conclusions for the Route to Allenyne 2.86: The Cyclocarbonylation Precursor

In this section diol **2.69β** was prepared in 5 steps and in a 64% overall yield; a dramatic enhancement from the previous sequence (5 steps and ≈18% overall yield). Besides the increased yields acquired for Smith's enone **2.60** and enone **2.53** each synthetic operation was made more practical and convenient. Furthermore, the use of a triflate moiety as a leaving group in an alkylation reaction is seldom seen in the literature and was found to be a very general and advantageous method to alkylate our vinylogous ester.

It was critical for the success of this route to guanacastepene A to determine and improve the diastereoselectivity obtained in the reduction step of enone **2.68**. Using a relatively unknown hydride source (tri[(3-tert-butyl-3-pentyl)oxy] aluminum hydride (**2.72**)), not only produced enhanced selectivity favoring our desired diastereomer **2.69β**, but also broadened our understanding of 1,6-conjugate additions on this substrate. Increasing the size of the hydride source promoted 1,6-addition to the ene-ynone **2.68**; a processes typically only observed under cuprate reaction conditions.

Also, the work presented in this section demonstrated that allenyne **2.86β** could be efficiently formed from diol **2.69**. While the synthesis of allenyne **2.77** was attempted (Scheme 61), it revealed the remarkable propensity for ene allene **2.77** to undergo a 1,5-sigmatropic rearrangement. To our knowledge this was the first example of this type of rearrangement to occur at low temperatures. This result exaggerated the importance of the DPS-moiety on allenyne **2.68** in that it was essential for the inhibition of the rearrangement.

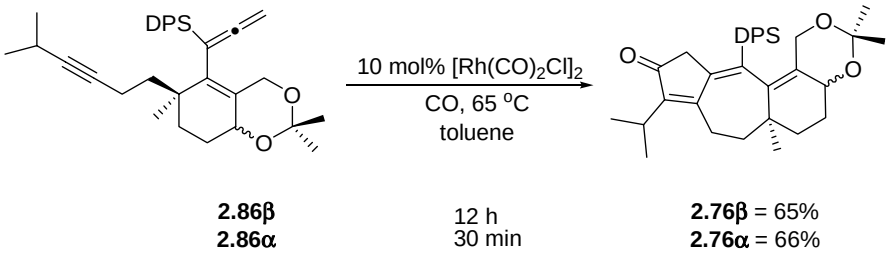
Lastly, as stated previously, a convenient route to the cyclocarbonylation precursor to guanacastepene A is an important attribute to any synthetic sequence. Hence, the development of a solvent system that was able to separate diastereomers **2.78α** and **2.78β** was a significant stride to this goal. It allowed for quick access to diastereomerically pure or enhanced material, which otherwise could only be obtained by separation on a HPLC instrumentation. The next section continues to develop the most efficient and effective route to guanacastepene A.

2.5 PROGRESS TOWARDS THE SYNTHESIS OF GUANACASTEPENE A: A 1,4-CONJUGATE ADDITION APPROACH TO INSTALL THE ANGULAR METHYL GROUP AT C13

2.5.1 Synthesis of Guanacastepene A's Carbocyclic Core via Allenyne 2.86

In section 2.4 an efficient synthesis of the cyclocarbonylation precursor, allenyne **2.86**, was developed. Upon formation of enone **2.58α** and **2.58β** from allenyne **2.86**, we will focus on the installation of the angular methyl group at C13. Subjection of the allenyne **2.86β** to rhodium biscarbonyl chloride dimer ($[Rh(CO)_2Cl]_2$) at 65 ˚C after 12 h gave the [5-7-6]-carbocycle **2.76β**

in a 65% yield. On the other hand, subjection of allenyne **2.86α** to $[Rh(CO)_2Cl]_2$ at 65 ºC gave the [5-7-6]-carbocycle **2.76α** in a 66% yield after only 30 min (Scheme 65).

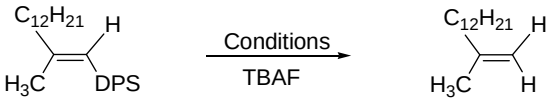


Scheme 65. Synthesis of trienone 2.76

It is unclear why there is such a large difference in the reaction times between the two diastereomers. It was proposed that this was a result of a large conformational difference in the lowest energy conformation for each allenyne diastereomer, because the oxidative addition step is considered to be the rate-limiting step for the Rh(I)-catalyzed carbocyclization.[15]

Attempts to desilylate the trienone **2.76** ensued and the results are summarized in Table 9. Following Oshima's[95] protocol the trienone **2.76** was subjected to TBAF in a THF : DMSO solvent system at room temperature (rt) (Entry 1, Table 9). Usually high temperatures are required (85 ˚C) for the removal of silyl groups from vinyl silanes; however, upon addition of the TBAF to **2.76** at rt the solution turned black and the TLC showed no starting material; only a large streak indicating decomposition. Similar results were seen using HMPA as the co-solvent (Entry 2, Table 9). Removal of all co-solvent yielded a trace amount of the desired product at rt even though all the starting material was consumed, as observed on TLC (Entry 3, Table 9). It was surprising that cleavage of the DPS group was so facile since typically high temperatures and polar additives are required. For example, Oshima reports addition of TBAF to olefin **2.88** in THF : HMPA at 80 ˚C gave a 91% yield of the desilylated product **2.89**; however, when their reaction was carried out without the HMPA co-solvent decreased yields and prolonged reaction

times were observed (Scheme 66)



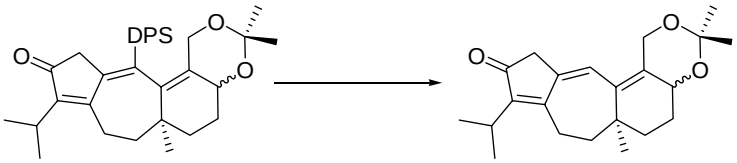
2.80 **2.81**

Conditions:
A. THF : HMPA (1 : 2), 80 ^{o}C, 0.5 h, 91%
B. THF, 80 ^{o}C, 10 h, 66% (28% recovered SM)

Scheme 66. Example of desilylation protocols of a vinyl silane

Thus, it is possible that the removal of the DPS group on intermediate **2.76** is facilitated by the release of steric strain and that milder reaction conditions are necessary for removal of the DPS group of **2.76**.

Table 9. Removal of the DPS group from 2.76



2.76 **2.58**

entry	F- source	solvent (eq)	co-solvent (eq)	temp	yield **2.58**
1	TBAF	THF (1)	DMSO (2)	rt	--
2	TBAF	THF (1)	HMPA (2)	rt	--
3	TBAF	THF		rt	trace
4	TBAF	THF		-12	45%
5	BTAF	THF (2)	DMSO (1)	rt	59%
6	BTAF	THF (3)	DMSO (1)	rt	81%

For this reason the reaction was carried out at a cooler temperature, -12 ˚C, and as anticipated, the desilylated enone **2.58** was obtained in 45% yield (Entry 4, Table 9). In an attempt to further increase the yield, the fluoride source was switched from TBAF to BTAF (benyltrimethyl ammonium fluoride) and performed in a THF : DMSO (2 : 1) solvent system to

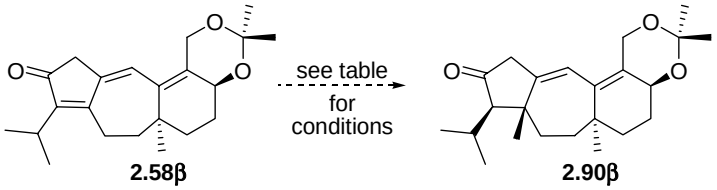
give a 59% yield of enone **2.58** (Entry 5, Table 9). Further yield enhancement was observed by decreasing the amount of DMSO in the reaction mixture which gave an 81% yield of enone **2.58** (Entry 6, Table 9). However, subjection diastereomerically pure **2.76β** gave a 73% yield of the desilylated enone **2.58β**, consistently.

2.5.2 1,4-Conjugate Addition Approach to Install the Angular Methyl Group on Enone 2.58β

Having developed a highly efficient synthesis of enone **2.58α** and **2.58β**, our focus now turned towards the installation of the angular methyl group at C13. Conjugate addition reaction conditions especially designed for the generation of quaternary carbons were performed using the accelerated or nickel catalyzed procedures described in section 2.2.5.

Subjection of enone **2.58β** to standard non-accelerated cuprate conditions in diethyl ether did not give any of the desired ketone **2.90β**; only starting material (SM) was recovered (Entry 1, Table 10).

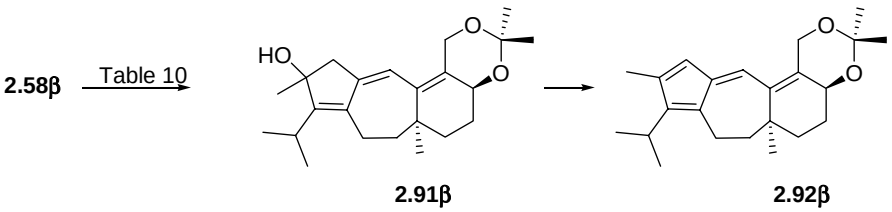
Table 10. Attempts to install an angular methyl group on enone 2.58β



2.58β **2.90β**

Entry	conditions	solvent	results
1	CuI, MeLi	Et_2O	SM
2	MeMgBr, CuBr DMS, TMSCl, HMPA	THF	SM and fulvene
3	CuI, MeLi LiBr, TMSCl, HMPA	Et_2O	SM
4	Cu, MeLi LiBr	"	SM
5	CuI, MeLi, TMSI	"	SM, 1,2-add, fulvene
6	CuI, MeLi, BF_3 Et_2O	"	decomp., SM, and cleaved acetonide
7	CuI, MeLi LiBr, TMSOTf	"	decomp. SM, and cleaved acetonide
8	CuCN, PBu_3, MeMgBr	"	SM, 1,2-addition

Enone **2.58β** was then added to Kuwajima's conditions,[82] MeMgBr/CuBr·DMS/ TMSCl/HMPA; and fulvene **2.92β**, which arises from an elimination reaction of the 1,2-addition product **2.91β**, and recovered starting material were observed by TLC and analysis of the crude ^{1}H NMR spectrum (Scheme 69, and Entry 2, Table 10). Furthermore, using LiBr as an additive in the reaction did not promote any addition to the starting material (Entries 3, 4, and 7, Table 10).

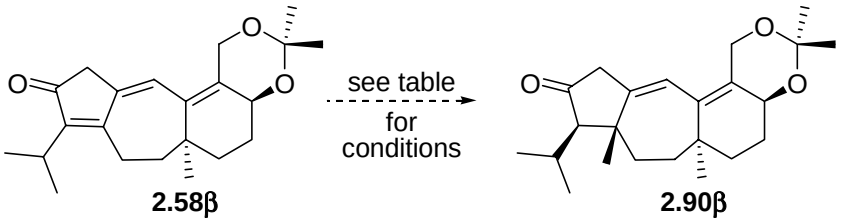


2.91β **2.92β**

Scheme 67. 1,2-Addition product 2.91β and fulvene 2.92β from conjugate addition reactions

Next, a variety of Lewis acids were added to the cuprate reaction to see if any addition product could be obtained. When TMSI was used as the Lewis acid, the 1,2-addition product **2.91β** and fulvene **2.92β** were obtained; however, addition of $BF_3{\cdot}Et_2O$ or TMSOTf cleaved the acetonide moiety. This product was isolated after silica gel chromatography and verified by analysis of the ^1H NMR spectrum. Also, a significant decomposition was observed via TLC (Entries 5, 6, and 7, Table 10). Furthermore, higher order cuprates did not give any of the desired ketone **2.90β** (Entry 8, Table 10).

Table 11. Attempts to install an angular methyl group at C13 using nickel

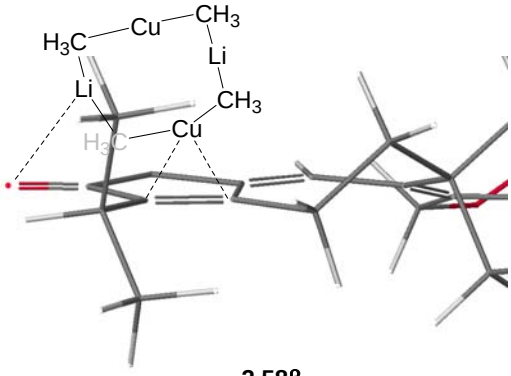


2.58β **2.90β**

Entry	conditions	solvent	results
1	Me_2Zn, $Ni(acac)_2$	Et_2O	SM, 1,2-addition
2	Me_2Zn, $Ni(acac)_2$, heat	"	SM, 1,2-addition
3	Me_2Zn, $Ni(acac)_2$, TMSCl, TEA	"	SM, 1,2-addition
4	TMA, $Ni(acac)_2$	THF	SM, 1,2-product, unknown product

Lastly, the Ni-catalyzed conjugate addition protocols were investigated. Subjection of enone **2.58β** to $Ni(acac)_2$ and $(Me)_2Zn$ at rt, 40 ˚C, or in combination with TMSCl/TEA gave the 1,2-addition product **2.91β** in all cases and the starting material was recovered (Entries 1-3, Table 11). Changing the methyl source to TMA gave similar results (starting material and 1,2-addition product **2.91β**) and a small amount of an undetermined product (Entry 4, Table 11). Unfortunately, none of these conditions produced ketone **2.90β**.

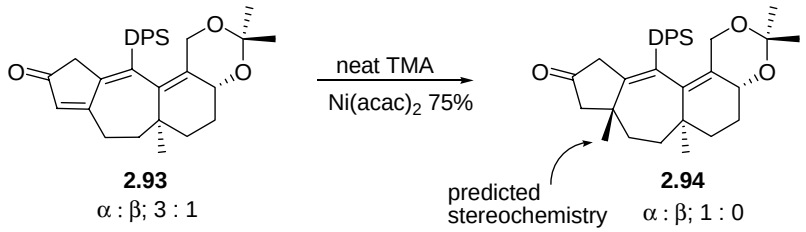
It is rationalized that the isopropyl group at the 3-position was sterically preventing addition. As depicted in figure 26 coordination the proposed copper cluster would be confronted with steric congestion caused by the isopropyl moiety.[112] While rotation of the isopropyl moiety would alleviate congestion, this would result in a highly unfavorable $A_{1,3}$ interaction of the methyl group on the isopropyl moiety with the methylene group on the seven membered ring. The presumption that sufficient enhancement of the reactivity of the cuprate reagent would overcome this steric hurdle was inaccurate. Therefore, an enone that lacks the isopropyl moiety should undergo conjugate addition at C13.



2.58β

Figure 26. Steric congestion on compound 2.58β arising from isopropyl group and copper cluster

To test this theory, enone **2.93** was synthesized using a route completely analogous to the synthesis of enone **2.76**. Addition of neat TMA and $Ni(acac)_2$ to **2.93α** , as a 3 : 1 diastereomeric ratio, produced ketone **2.94α** in a 75% yield and as a single diastereomer (Scheme 68). Based upon the ^1H NMR spectrum only one diastereomer was obtained in this reaction. Unfortunately, the stereochemistry of the methyl group at C13 was not determined at this time; however, it is predicted that the methyl group would be delivered to the top face of enone **2.93α**.

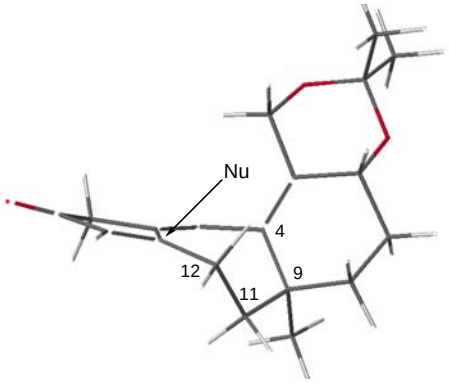


2.93
α : β; 3 : 1

2.94
α : β; 1 : 0

Scheme 68. Synthesis of ketone 2.94

This prediction arises from the conformational analysis of enone **2.93α**, which reveals a convex shape of C12-C11-C9-C4 in the seven membered ring, promoting addition from the β-face (Figure 27). For visual clarity the DPS moiety has been deleted from figure 27 after the conformational calculations were performed.



2.93α

Figure 27. Conformational analysis of enone 2.93α: conformational search performed in Cache using MM2

The results discussed in this section demonstrated that enone **2.58β** could be efficiently formed from allenyne **2.86β**. The desilylation process described in this sequence was achieved under very mild conditions; not typical for the desilylation of vinyl silanes. This suggests that the DPS moiety imposes a significant conformational strain, which is released upon its removal.

Also, the potential of the 1,4-conjugate addition approach to install the angular methyl

group at C13 was demonstrated. It was clear that a conjugate addition on enone **2.58** was sterically inhibited by the isopropyl moiety at C15 as demonstrated by the successful conjugate addition on enone **2.93**. Critical for the completion of guanacastepene A, is the installation of the angular methyl group at C13 in the most practical and concise manner. While enone **2.93** has the potential to eventually yield guanacastepene A, a sequence that could generate the angular methyl group in the presence of the isopropyl moiety was preferred. The following sections will discuss two different approaches designed to accomplish this goal.

2.6 A REDUCTIVE RING OPENING APPROACH TO INSTALL AN ANGULAR METHYL GROUP: THE SYNTHESIS OF A BIOLOGICALLY ACTIVE INTERMEDIATE

As highlighted in section 2.5.2, difficulties arose during the installation of an angular methyl group on enone **2.58** via a conjugate addition approach. An alternative approach, that could install the methyl group at C13 in the presence of the isopropyl moiety at C15, was to form the cyclopropyl ketone **2.95** and then reductively open the electron deficient cyclopropane ring (Figure 28).

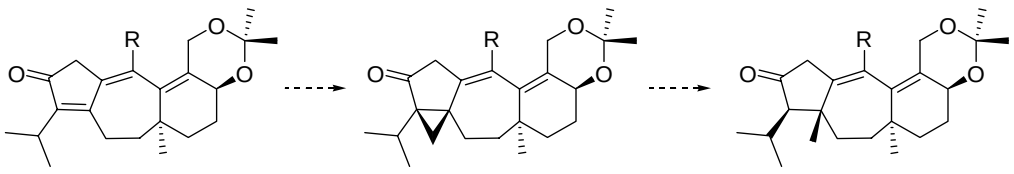
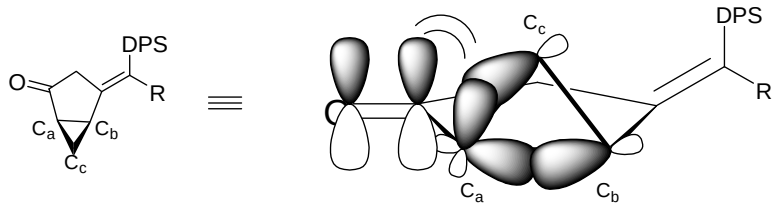


Figure 28. Proposed sequence to give ketone 2.90 or 2.97 via a cyclopropyl ring opening

There are a number of ways to open an electron deficient cyclopropane ring; electron transfer process, nucleophilic attack or hydrogenation. Focusing first on the electron transfer method, this protocol has been highlighted in a number of natural product syntheses that faced problems with the installation of an angular methyl group.[113] It is known that the selective reduction of cyclopropyl ketones is governed by the C-C bond processing better overlap with the π-system of the adjacent carbonyl group.[114] For most bicyclo[3.1.0]hexanes, i.e. **2.98**, it is predicted from the orbital overlap in the cyclopropyl ring with the ketone that the breaking of Ca-Cc bond should be kinetically favored over the breaking of Ca-Cb bond (Figure 29).



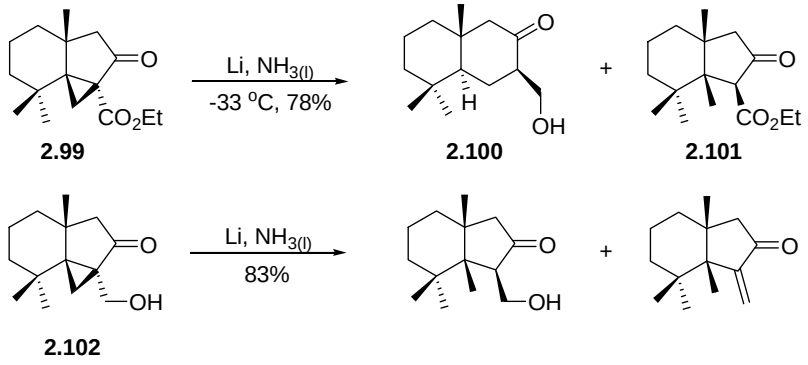
2.98

Figure 29. Orbital overlap of cyclopropyl ring and carbonyl group of 2.98

As this depiction shows, orbital overlap of Ca-Cb bond to give the 6-membered ring seems nearly impossible; and there are a number of examples that demonstrate this selectivity. Corey, in his synthesis of limonoid systems obtains an angular methyl group via a selective reduction of the cyclopropyl ketone shown in scheme 69.[115]

Scheme 69. Example of a reductive ring opening reaction of a cyclopropyl ketone

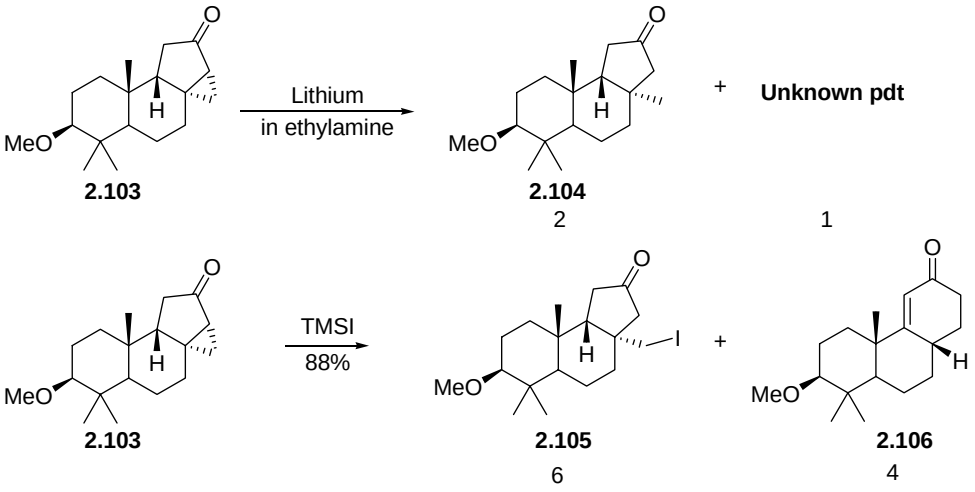
However, it is possible to obtain the ring expanded product from a bicyclo[3.1.0]hexane. For the most part, an additional carbonyl substituent is necessary to donate electrons that can sufficiently overlap with the Ca-Cb bond. As shown in scheme 70, an ethylester substituent at the α-position of ketone **2.99** gives a mixture of the ring expanded product **2.100** and five membered ring **2.101** in a 4 : 3 ratio, respectively.[116] It follows that subjection of ketone **2.102** to the same reaction conditions gives the five membered ring selectively. Alternatively, the ring expansion process can be achieved if the conformation of molecule provides sufficient overlap of the Ca-Cb bond.



Scheme 70. Reversing the selectivity of the C-C cleavage by altering the group α to the carbonyl

One example by Heissler,[117] suggests that a mixture of a cyclopentanone and a cyclohexanone in a 2 : 1 ratio may have been obtained from an electron transfer reaction on cyclopropyl ketone **2.103**; however, they report that only one of the products is thought to be the ketone **2.104** (Scheme 71). When they subject **2.103** to a nucleophilic ring opening reaction they obtain a mixture of cyclopentanone **2.107** and cyclohexanone **2.106** in an 88% yield. There are not many examples in the literature documenting a ring expanded process for systems that do not have an additional carbonyl substituent. This could be because it is a rare occurrence or the ring expanded products are not the desired product, and therefore, the results were never published. In

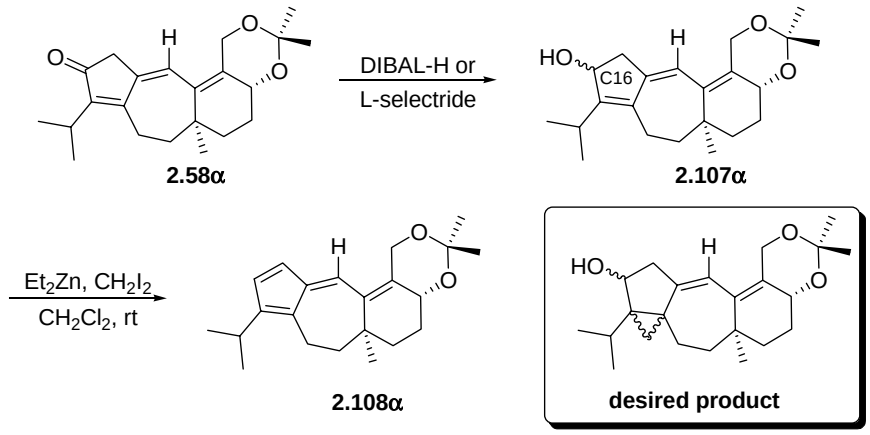
the absence of an additional carbonyl substituent, we predict that we should selectively obtain the cyclopentanone **2.90**.



Scheme 71. Example of reductive opening to give a ring expansion product

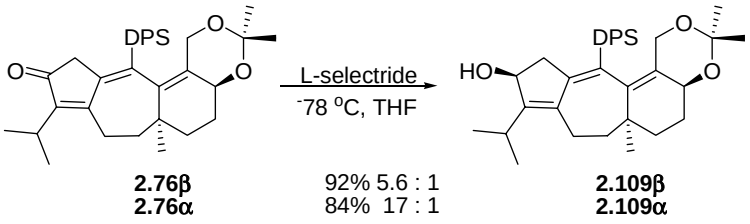
2.6.1 The Development of a Stereoselective Route to Ketone 2.113

As described is section 2.5.1, a concise route to enone **2.58** had been developed; therefore, synthesis of the cyclopropyl ketone **2.95** from enone **2.58** was desired. To this end, subjection of enone **2.58α** to DIBAL-H at -78 ˚C gave a 73% yield of alcohol **2.107α** in a 1 : 1 diastereomeric ratio at C16, as determined by analysis of the ^{1}H NMR spectrum (Scheme 72). It was noted that upon concentration of alcohol **2.107** the solution started to turn a yellow/orange color and the TLC of this material showed a new additional non-polar product. After addition of Et_2Zn and I_2CH_2 to the mixture in DCM, all of the material converted to the non-polar product that was fully characterized as fulvene **2.108α** (Scheme 72). The same result was obtained whether the reaction was performed at room temperature or 0 ˚C.



Scheme 72. Attempt to synthesize fulvene 2.108

Alcohol **2.107** readily eliminated to give this undesired fulvene product **2.108**, making subsequent transformations unfeasible. It was anticipated that reduction of enone **2.76** would not undergo this elimination process. To this end both enones **2.76β** and **2.76α** were reduced with L-selectride to give a separable 5.6 : 1 or 17 : 1 diastereomeric mixture, respectively, of alcohols **2.109β** and **2.109α** in yields of 92% or 84%, respectively (Scheme 70). The diastereomeric ratios were determined by milligrams of isolated material.



Scheme 73. Reduction of enone 2.76 with L-selectride

It is predicted that the stereoisomer at C16 for both **2.109β** and **2.109α** is the product shown in scheme 73. As depicted in figure 30 the hydride should come from the more accessible α-face of enone **2.76β**, which places the alcohol on the β- face of the molecule.

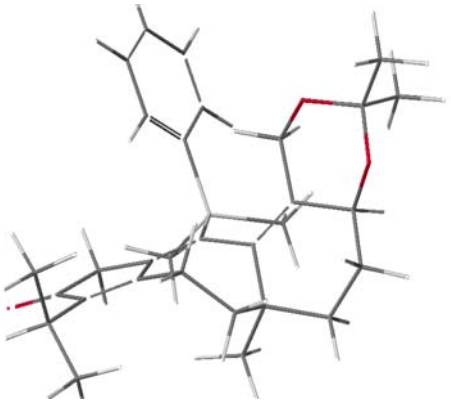


Figure 30. Lowest energy conformation for 2.76β: conformational search performed in Cache using MM2

Better selectivity is obtained for the reduction of **2.76α** compared to **2.76β**. Based upon conformational analysis of diastereomer **2.76α**, it is apparent that the concave core of **2.76α** is more pronounced leading to high diastereoselectivity in the reduction of the ketone; while the conformation of enone **2.76β** is more flattened leading to decreased selectivity in the reduction (Figure 31).

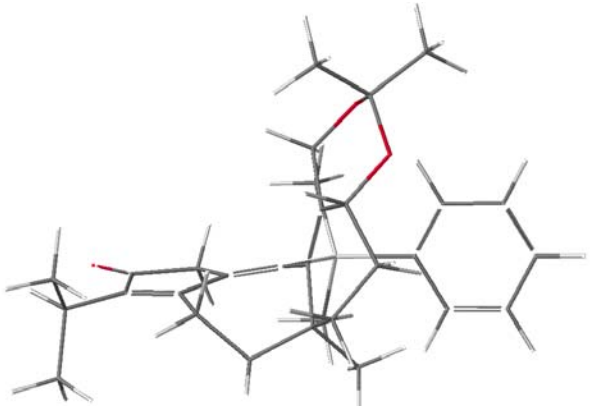
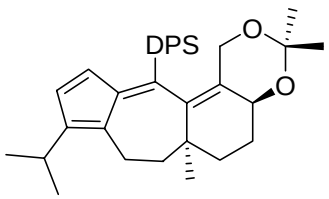


Figure 31. Lowest energy conformation for 2.76α: conformational search performed in Cache using MM2

The diastereoselectivity in the reduction of enone **2.76** was essential for establishing the

stereochemistry for the remainder of the synthesis of cyclopropyl ketone **2.113**. Using the Simmons-Smith cyclopropanation,[118] the alcohol of **2.109** will be used to direct the methylene to the neighboring alkene giving chemo- and stereo-control in the cyclopropanation reaction.

Similar to alcohol **2.107**, alcohol **2.109** needed to be carefully handled, since trace acid would cause the compound to turn yellow/orange and reveal the appearance of olefinic peaks in the ^{1}H NMR spectrum. It was hypothesized, from the previous results, that alcohol **2.109** was undergoing an elimination process forming fulvene **2.110**; however, this material easily decomposed preventing full characterization. While alcohol **2.109** was showing signs of fulvene formation, it was more stable than alcohol **2.107** and could be stored for 24-48 h in a benzene solution.

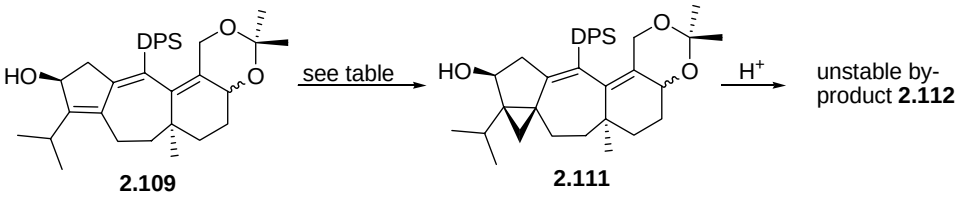


2.110

Figure 32. Proposed by-product: fulvene 2.110

This allylic alcohol's sensitivity to acids made the cyclopropanation reaction challenging because acidic by-products are often formed. Initially, using Simmons-Smith's cyclopropanation conditions, subjection of alcohol **2.109α** to 2 equivalents of Et_2Zn and 4 equivalents of diiodomethane (I_2CH_2) in CH_2Cl_2 at 0 ˚C gave a small amount of the desired product **2.111α** and a significant amount of a very non-polar by-product **2.112α** (Entries 1 and 3, Table 12).

Table 12. Formation of the cyclopropane 2.111

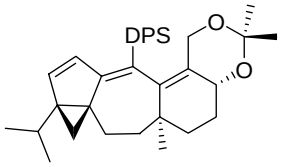


2.109 **2.111**

Entry	SM	Equiv. of Et_2Zn	Equiv. of I_2CH_2	Temp (^{o} C)	Results
1	**2.109α**	2	4	0	10% **2.111α**, 90% **2.112**
2	**2.109α**	2	2	0	**2.111α** and **2.112**[a]
3	**2.109α**	2	2	20	**2.111α** in 84% crude yield
4	**2.109β**	2	2	20	**2.111β** in 90% crude yield[b]

[a] Subjected to TPAP oxidation conditions immediately.[b] Messy TLC; not pure material

This by-product was assumed to be an elimination product of the starting material fulvene **2.110** (Figure 32) or elimination of the cyclopropanated product **2.112** (Figure 33). However, due to the instability of this material, a conclusive ^{1}H NMR spectrum could not be obtained, only speculation derived from the R_f value and the color of the material (yellow/orange).

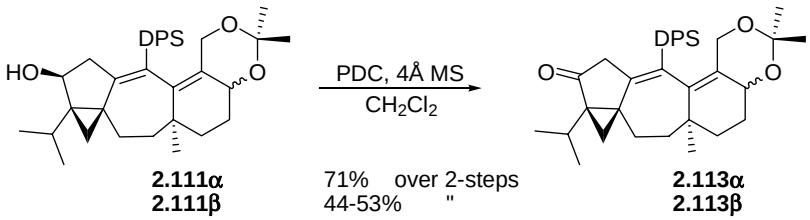


2.112

Figure 33. Suspected by-product of the cyclopropanation reaction of 2.109, vinylcyclopropane 2.112

To prevent the formation of this unknown product that was suspected to result from adventitious acid, the stoichiometry of the Et_2Zn and I_2CH_2 was changed from 2 : 4 to 2 : 2, which minimizes formation of ZnI_2.[119] Addition of alcohol **2.109α** to equal amounts of Et_2Zn and I_2CH_2 at 0 ˚C in DCE did not promote any reaction by TLC; only starting material was recovered (Entry 2, Table 12). However, repeating the experiment in CH_2Cl_2 at 0 ˚C promoted cyclopropanation. Initially by TLC only starting material and product formation were seen;

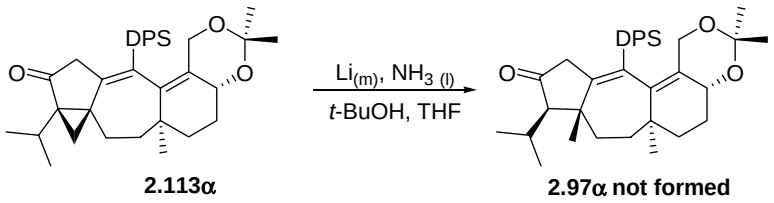
however, by the time all of the starting material was consumed, formation of the non-polar by-product was observed by TLC (Entry 4, Table 12). From this observation, it was reasoned that adventitious acid was causing the decomposition of the newly formed product over time; therefore it was decided to increase the reaction rate by increasing the reaction temperature. This in turn should limit the exposure of **2.111** to the reaction media. Also, as an added precaution, we decided to quench the reaction with an aqueous buffer. As predicted, running the reaction at room temperature and quenching with a pH 7.0 phosphate buffer gave **2.111** in high yields as a single diastereomer (Entry 5 and 6, Table 12). Due to the instability of this product after aqueous workup the crude material was immediately oxidized with PDC and cyclopropyl ketone **2.113α** and **2.113β** could be obtained in a 71% or 44-53% yield over two steps, respectively (Scheme 74).



Scheme 74. PDC oxidation of 2.108 to give 2.113

Cyclopropyl ketone **2.113** was then subjected to a variety of dissolving metal electron transfer conditions to promote cyclopropyl ring opening and the results are summarized below. When $Li_{(m)}/NH_{3(l)}$ was used as the reducing agent, multiple compounds including starting material were seen by TLC (Scheme 75). The newly formed products were more polar on TLC than the starting material and crude ^1H NMR spectrum did not give any evidence supporting formation of ketone **2.97**. This was later confirmed when the desired ketone **2.97** was obtained and its spectrum was compared (Table 13, page 139). Failure of this reaction is attributed to

technical difficulties associated with performing $Li_{(m)}/NH_{3(l)}$ reduction on a 5 mg scale.

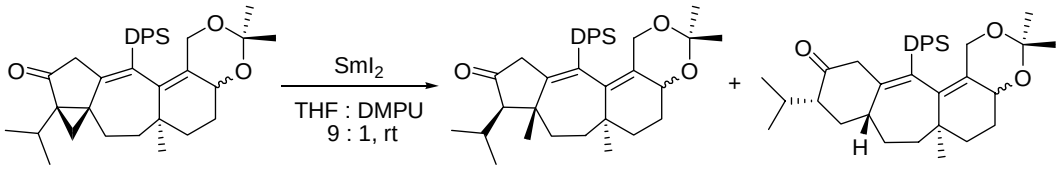


2.113α **2.97α not formed**

Scheme 75. Reductive ring opening of cyclopropyl ketone 2.113 using $Li_{(m)}/NH_{3(l)}$

Another common electron transfer reagent used to open cyclopropyl ketones is samarium diiodide (SmI_2).[120] Using SmI_2 on small scale reactions is advantageous since a large batch of SmI_2 can be formed and then transferred to the reaction flask via cannula or gas-tight syringe. The results using SmI_2 as an electron transfer reagent are summarized in the following sections. Subjection of cyclopropyl ketone **2.113α** to approximately 5 equivalents SmI_2 in THF/DMPU (9 /1) at room temperature gave a trace amount of the cyclopentanone **2.97α** as identified by the ^1H NMR spectrum (Trial 1, Table 13). Repeating this experiment but this time adding approximately 20 equivalents of SmI_2 caused complete decomposition of all material as evidenced by a streak on TLC (Trial 2, Table 13).

Table 13. Reductive ring opening of ketone 2.113 using SmI_2/THF/DMPU



2.113 **2.97** **2.114**

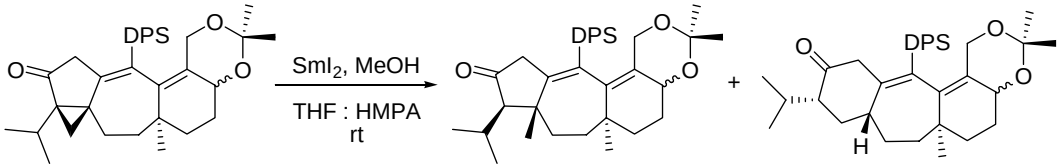
Trial	SM	**2.97α**	**2.114α**
1	**2.113α**	trace	0
2	**2.113α**	decomposition	
3	**2.113β**	0	trace

Because ketone **2.113** and cyclopentanone **2.97** moved the same on TLC and using

excess reducing agent was detrimental to our substrates, we decided to monitor the reaction by HPLC. Differentiation of starting material and product could be observed by HPLC using the Pursuit C^8 column eluting with 30% to 0% (H_2O / acetonitrile) over 10 min and then 100% acetonitrile. The retention time for the starting material was 9.5 min and 10.3 min for the product, using a flow rate of 1 mL/min. Ketone **2.113β** was subjected to SmI_2 and by HPLC analysis a trace of the cyclohexanone **2.114β** was obtained, which was characterized by analysis of the ^1H NMR spectrum (Trial 3, Table 13). This was quite an interesting result and suggests that possibly the conformation of ketone **2.113β** favors the ring expansion product cyclohexanone **2.114β**, while the conformation of ketone **2.113α** favors the cyclopentanone **2.97α** (compare Entries 1 and 3, Table 13). However, only trace amounts of material were obtained in both reactions making it unclear whether the reduction was selective or if the both **2.97** and **2.114** were formed initially and then subsequently decomposed giving trace amounts of one or the other. In an attempt to increase the yield, we decided to change the solvent system to that which was use by Kuwajima in his route to Taxol.[118]

This involved changing the solvent system to THF/HMPA and adding a proton source such as MeOH. This reaction was performed at room temperature and was much cleaner, as evidenced by TLC. As shown in table 14, while products **2.97** and **2.114** were obtained cleanly, it was evident that the major product in all cases was the ring expansion product **2.114**, as observed by analysis of the ^1H NMR spectrum. Also, it was evident that the product ratios were independent of starting material diastereomer; both diastereomers **2.113α** and **2.113β** favored the ring expansion product **2.114** (compare Trials 1-3 to 4-6, Table 14).

Table 14.[a,b]Reductive ring opening of cyclopropyl ketone 2.113 using SmI_2/THF/HMPA/MeOH



2.113 **2.97** **2.114**

Trial	SM	**2.97**	**2.114**
1	**2.113α**	1	4.5
2	**2.113β**[c]	1	3
3	**2.113β**[d]	1	2
4	**2.113β**	1	2

[a.] All reactions were run under the same reaction conditions and the product ratios were determined by crude ^{1}H NMR [b] Reactions were monitored by HPLC: **2.113α** = 9.5 min, **2.114α** = 10.0 min, **2.97α** = 10.5 min.[c.] Ratio of starting material **2.113β** : **2.113α** = 2 : 1 [d.] Ratio of starting material **2.113β** : **2.113α** = 1 : 1.

2.6.1.1 Altering the Electron Transfer Conditions to Obtain Ketone 2.97 Preferentially

In each case formation of cyclohexanone **2.114** was favored suggesting two possible scenarios: either the conformation of cyclopropyl ketone **2.113** embodies better orbital overlap of the Ca-Cb bond with the carbonyl moiety than the Ca-Cc bond or the reductive ring opening is reversible allowing equilibration to the thermodynamic cyclohexanone **2.114**. Conformational analysis of cyclopropyl ketone **2.113** does not support the premise that the orbital overlap of the Ca-Cb bond with the carbonyl moiety is better than the overlap of the Ca-Cc bond with the carbonyl moiety (Figure 34).

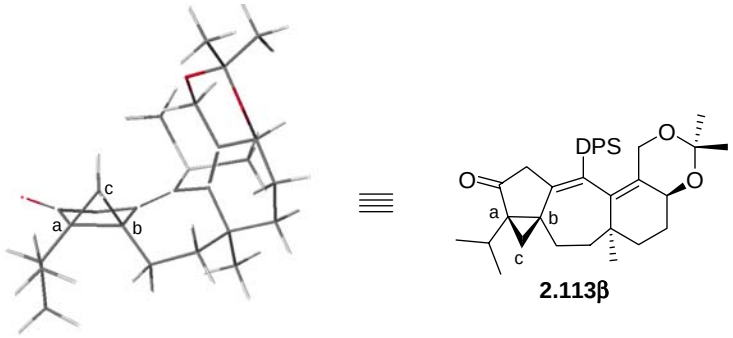
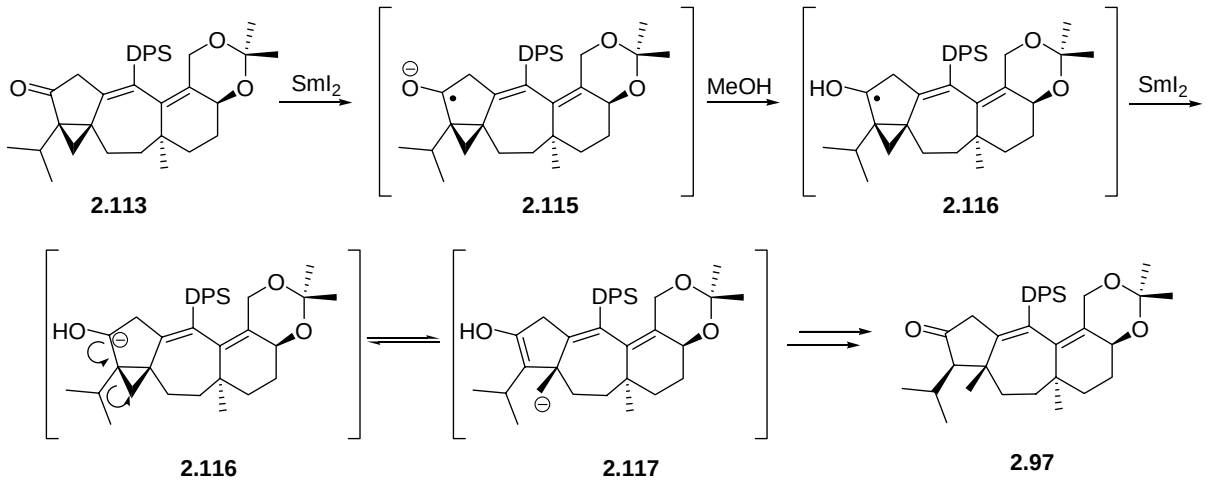


Figure 34. Lowest energy conformation of 2.113β using Cache MM2; phenyl moiety removed after calculations for visual purposes

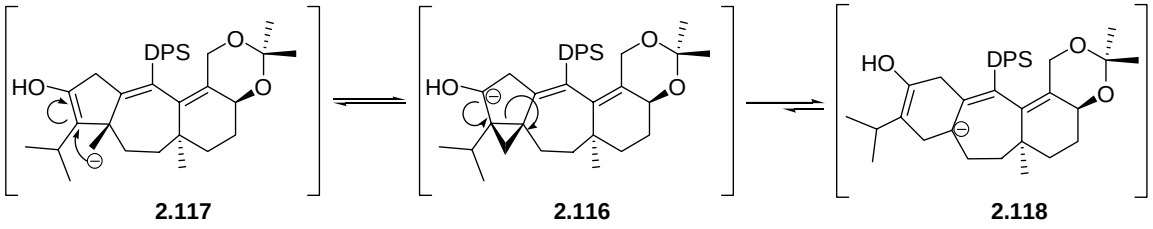
As depicted in figure 34 the Ca-Cb bond is parallel to the carbonyl moiety making orbital overlap unattainable; however, it is experimentally proven that proper overlap of the Ca-Cb bond is attainable. It is possible that the reductive ring opening is reversible by considering the mechanism of SmI_2 in the presence of methanol (Scheme 76).[121]



Scheme 76. Mechanism of the SmI_2 induced reduction of cyclopropyl ketone 2.113 in the presence of methanol

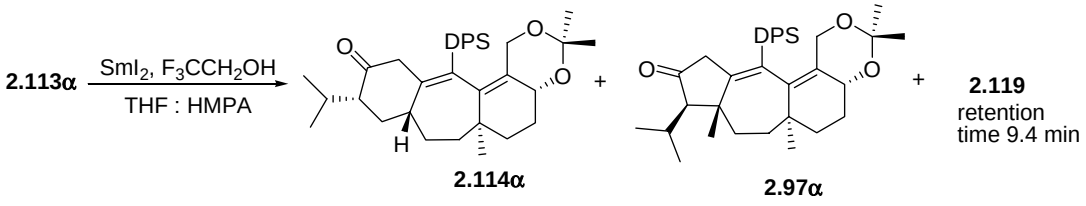
Subjection of SmI_2 to the cyclopropyl ketone **2.113** forms ketyl **2.115** via an electron transfer

process. The ketyl **2.115** is rapidly protonated by methanol to give radical **2.116**. A second electron is transferred by another equivalent of SmI_2 producing a carbanion that initiates the ring opening of the cyclopropane. It is predicted that opening to the cyclopentanone **2.117** is kinetically favored; however, the intermediate at this stage can either undergo tautomerization and protonation to give cyclopentanone **2.97** or, if protonation is slow, recycles forming intermediate **2.116** (Scheme 77). Intermediate **2.116** can then reopen to give either the cyclohexanone **2.118** or the cyclopentanone **2.117**. If the cyclohexanone **2.118** is formed, it is predicted that protonation would be faster than recyclization to give the cyclohexanone **2.114**.



Scheme 77. Proposed equilibrium process between 2.117 and 2.118

Our focus now turned to retarding the equilibrium process between intermediate **2.117** and **2.118**. It was proposed that changing the proton source from methanol a more acidic reagent, trifluroethanol, would protonate the methyl anion faster than methanol inhibiting the recyclization of the cyclopropane ring. These reactions were monitored by HPLC so that product ratios (**2.97** vs. **2.114**) could be easily determined.

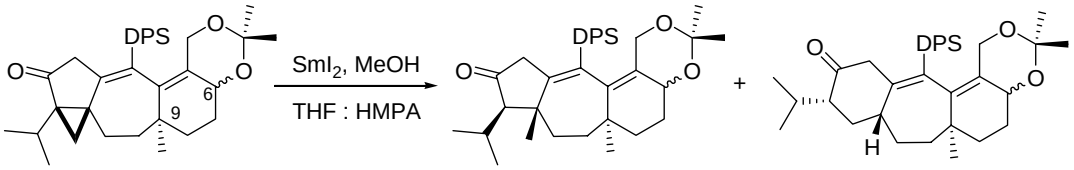


Scheme 78. Electron transfer reactions of 2.113α in the presence of trifluroethanol

Addition of SmI_2 to a solution of **2.113α**/THF/F_3CCH_2OH/HMPA revealed a 1.4 : 1 ratio of **2.114α** : **2.97α** as calculated by integration of the HLPC peaks; however, there was also another peak with a retention time of 9.4 min (**2.119**) (Scheme 78). Upon complete consumption of the starting material the reaction was quenched, extracted, and chromatographed. The fractions from the column were then resubjected to HLPC analysis. To our surprise, the peak (R_T = 10.5 min) attributed to compound **2.97α** was absent leaving only **2.114α** (R_T = 10.0 min) and the known by-product **2.119**. This was also confirmed by analysis of the ^1H NMR spectrum; however, we were unable to determine the structure of the **2.119**. The mass spectrum of the by-product **2.119** shows a $[M\text{-}CH_3]^+$ peak at 477, which is expected for a reduced substrate; however, it did not correlate with the **2.114α** or **2.972α** spectra or with the reduced carbonyl of **2.113α** that would contain a secondary alcohol.

Alternatively, the temperature of the reaction was decreased in an attempt to alter the product ratios. These reactions were performed on 3-5 mg of **2.113** and monitored by HPLC; therefore, the yields for these reactions were not calculated. Subjecting ketone **2.113** to SmI_2/MeOH/HMPA/THF at -78 ˚C gave a 1 : 1 ratio of **2.97** : **2.114** (Trial 1, Table 15). This result was repeated twice with a diastereomeric mixture of ketone **2.113** and diastereomerically pure **2.113β** (Trial 3, Table 15).

Table 15. [a]Reaction of cyclopropyl ketone 2.113 with SmI_2/MeOH/THF/HMPA



2.113 **2.97** **2.114**

Trial	SM	temp (°C)	**2.97**	**2.114**
1	**2.113**[b]	-78	1	1
2	**2.113**[b]	-90	0	1
3	**2.113β**	-78	1	1
4	**2.113β**	-78	decomposition[c]	
5	**2.113**[b]	-78[d]	0	0
6[e]	**2.113α**	-78	0	1
7[e]	**2.113β**	-78	0	1

[a] Product ratios determined by ^1H NMR and SmI_2 synthesized from $Sm_{(m)}$ and CH_2I_2. [b] Starting material diastereomeric ratio 1 : 1; C6-C9. [c] Reaction was scaled up from 5 mg to 18 mg. [d] no HMPA added [e] SmI_2 was synthesied from $Sm_{(m)}$ and I_2

Decreasing of the reaction temperature to -90 ˚C gave exclusively the ketone **2.114**; and increasing the reaction scale gave decomposition of all materials (Trials 2 & 4, Table 15, respectively). Removal of HMPA as a co-solvent completely inhibited any product formation (Trial 5, Table 15).[122] Cooling the SmI_2 to -78 ˚C and then adding it to a solution of ketone **2.113β** at -78 ˚C formed an inseparable by-product; therefore, the exact product ratios could not be determined by analysis of the ^1H NMR spectrum.

Numerous attempts to obtain selective formation of cyclopentanone **2.97** did not prove fruitful giving at best a 1 : 1 ratio of cyclohexanone **2.114** and cyclopentanone **2.97**. Altering the process used to form SmI_2, however, did provide the selective formation of cyclohexanone **2.114**. When SmI_2 was formed by addition of I_2 to samarium metal in THF and subsequently added to ketone **2.113α** or **2.113β**, only cyclohexanone **2.114α** or **2.114β** was formed, respectively (Trials 6 & 7, Table 15).[123]

As discussed previously, the selective formation of a ring expansion product is an uncommon result for cyclic cyclopropyl ketones that do not have an additional carbonyl group.

In an attempt to capitalize on the selective formation of cyclohexanone **2.114β**, it was tested against nine key indicator Gram-positive and –negative bacterial pathogens: *S. aureus* oxacillin-susceptible, *S. aureus* oxacillin-resistant, *Enterococcus spp.* vancomycin-susceptible, *Enterococcus spp.* vancomycin-resistant, *S. pneumoniae* penicillin-intermediate, *S. pneumoniae* penicillin-resistant, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *Acinetobacter baumanii*.

The testing results revealed that **2.114β** displayed activity against *Enterococcus spp.* vancomycin-susceptible, *Enterococcus spp.* vancomycin-resistant bacteria at the screening concentration 32 μg/ml. Subsequent testing provided a minimal inhibitory concentration (MIC) values of 64 μg/ml; a moderately high MIC value considering susceptible MIC values are considered ≤8 μg/ml.[124] Nevertheless, this data provides a starting point for further analysis of cyclohexanone **2.114β**.

2.6.1.2 Attempts to Reduce Cyclopropyl Ketone 2.113 using Hydrogenation Conditions

The difficulties encountered using dissolving metals to open the cyclopropane ring ordered an alternative method that did not proceed via an anionic pathway. Although not used often, Pd/C in the presence of hydrogen can cleave cyclopropyl rings;[125] and has been used in natural product synthesis and in the synthesis of interesting carbocycles.[126] Mechanistic studies reveal that selectivity of the C-C bond cleavage arises from electronic and sterics factors (Figure 35). If R is an electron withdrawing group, cleavage of the Ca-Cb or Ca-Cc bond is favored; however if R is an electron donating group, steric factors prevail and the Cb-Cc bond is cleaved.

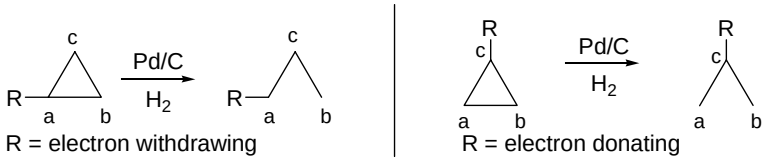
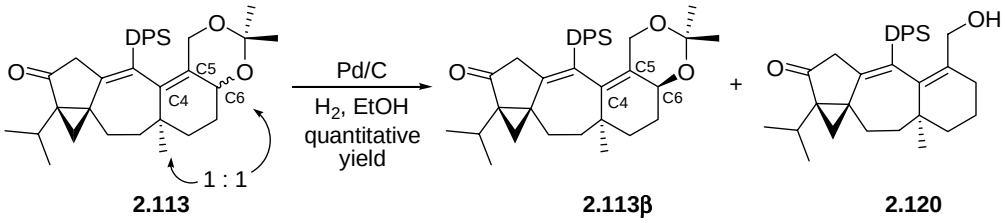


Figure 35. Selectivity of hydrogenation of substituted cyclopropanes

Addition of 10% by weight of Pd/C to ketone **2.113** under a H_2 atmosphere gave recovered starting material. When cyclopropyl ketone **2.113** was subjected to an excess of Pd/C, a new compound was formed along with recovered starting material (Scheme 79). More forcing conditions (60 psi of H_2) did not appear to change the ratio of these compounds by TLC. The new compound was subsequently characterized as alcohol **2.120** resulting from hydrogenolysis of **2.113**. Interestingly, the ^{1}H NMR spectrum of the recovered starting material revealed that it was a single diastereomer and that of **2.113β**. Thus, the hydrogenolysis was selective for only isomer **2.113α**.

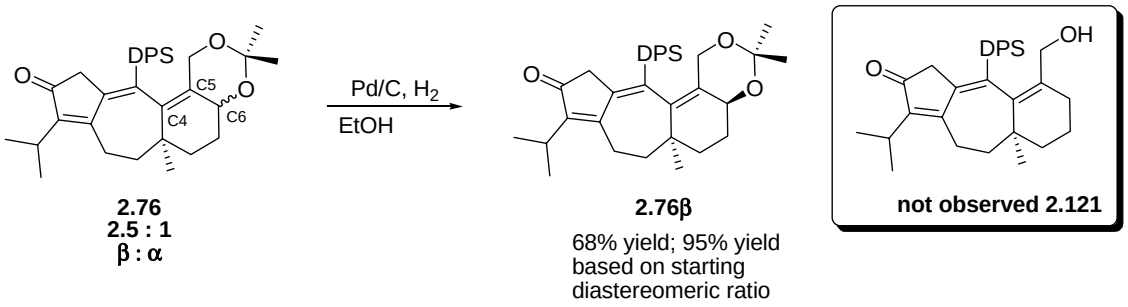


Scheme 79. Subjection of cyclopropyl ketone 2.113 to Pd/C and H_2

This selectivity is thought to arise from overlap of the C4-C5 π-bond with C6-O σ-bond in ketone **2.113α** and because only **2.113α** reacts it is predicted that there is not substantial overlap of the C4-C5 π-bond with C6-O σ-bond of **2.113β**. Unfortunately, comparing the lowest energy conformations of **2.113α** or **2.113β**, calculated using Cache, does not reveal any differences in the overlap of the C4-C5 π-bond with C6-O σ-bond that would justify this selectivity.

The unique diastereo-discrimination seen in this hydrogenation reaction exposed an opportunity for a purification protocol. If this hydrogenolysis of the α-isomer was applicable to other guanacastepene A intermediates, it could prove very useful for obtaining

diastereomerically pure material. To this end, subjection of a 2.5 : 1 diastereomeric mixture of enone **2.76α/β** to Pd/C gives diastereomerically pure **2.76β** in a 68% yield, but the hydrogenolysis product **2.121** was not observed (Scheme 80). The calculated quantitative yield, based on the starting diastereomeric material, is 71%; therefore, a 95% yield of the **2.76β** was produced. It is proposed that this diastereoselective enrichment is a result of the hydrogenolysis of the **2.76α**, as seen previously; however, without isolation of **2.121** its formation can only be speculated.



2.76
2.5 : 1
β : α

2.76β
68% yield; 95% yield based on starting diastereomeric ratio

Scheme 80. Hydrogenolysis of trienone 2.76

While the purification protocol was advantageous for the synthesis of guanacastepene A, installation of the angular methyl group at C13 was still needed. Various attempts at hydrogenating the cyclopropane ring; however, either resulted in no reaction or in a reduction of the aromatic ring on the DPS-group. The sluggish reactivity of the cyclopropane ring in the hydrogenation reduction could be attributed to steric congestion encompassing the cyclopropane ring.

2.6.2 Summary and Conclusions for the Reductive Ring Opening Approach to Guanacastepene A

The work presented in this section demonstrated the potential of the reductive cyclopropyl ring opening approach to install an angular methyl group at C13. The synthesis of the cyclopropyl ketone **2.113α** or **2.113β** was achieved with high diastereoselective initiated by a highly diastereoselective carbonyl reduction of enone **2.76α or 2.76β** using L-selectride. When using an electron transfer protocol to open the cyclopropane ring, it was discovered that selectivity in the C-C bond breaking of the cyclopropyl ring could be influenced by the reaction temperature, and in turn a 1 : 1 ratio of cyclopentanone **2.97** and cyclohexanone **2.114** was achieved. Furthermore, under certain reaction conditions, exclusive formation of cyclohexanone **2.114** could be obtained.

The selectively formation of cyclohexanone **2.114** discloses that the conformation of cyclopropyl ketone **2.113** acquires efficient overlap of the Ca-Cb bond with the carbonyl. Thus, this was a rare example where a bicylo[3.1.0]hexane's conformation, which did not posses a second carbonyl moiety, favored the formation of the ring expanded product. Furthermore, the cyclohexanone **2.114β**, which can be formed efficiently and selectively, was found to be biologically active against *Enterococcus spp.* vancomycin-susceptible, *Enterococcus spp.* vancomycin-resistant bacteria. The biological activity that cyclohexanone **2.114β** possesses makes this formerly 'undesired product' a significant result.

This section also briefly explores using hydrogenation protocols to open the cyclopropane ring. While the hydrogenation protocol did not produce the cyclopentanone **2.97**, it did provide an efficient and general purification protocol. Furthermore, C-O cleavage of allyl

ethers (R_2C=CH-OR) is most commonly observed when an allyl ether is used as a protecting group.[127] However, Pd/C does not affect C-O cleavage in most allyl ethers unless catalytic TsOH or $HClO_4$ are added as well.[128] It is proposed that the conformation a **2.113α** embodies ideal overlap of C4-C5 π-bond with C6-O σ-bond such at hydrogenolysis occurs under unprecedented mild reaction conditions (room temperature and 1 atmosphere of H_2).

The difficulties encountered during the opening of the cyclopropyl ketone **2.113** indicated that an alternative strategy to install the angular methyl group was necessary. The formation of the cyclopropyl ketone **2.113** did demonstrate that, unlike the methyl cuprate, a methylene could be added to the sterically congested enone **2.76**. The development of a synthetic strategy that capitalizes on this result is detailed in the next section.

2.7 A RADIAL CYCLIZATION APPROACH TO GIVE THE ANGULAR METHYL GROUP AT C13

As discussed in section 2.6.1, a synthetic sequence was developed that introduced a methylene carbon at C13, but was unable to subsequently yield ketone **2.97**. An alternative method that could subsequently provide ketone **2.97** was sought. Temporary silicon tethers convert an intermolecular process into an intramolecular process which can give an increase in reactivity, regioselectivity, and diastereoselectivity and they can subsequently be transformed into a number of functional groups.[129] Therefore, an approach using a silicon tether to install the methyl group at C13 was investigated.

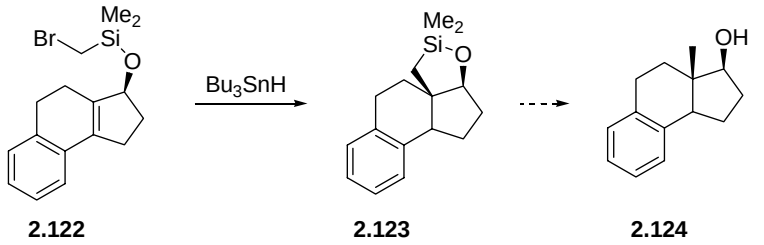


Figure 36. Example of using bromo-silanes to install angular methyl groups

In the past our group has benefited from this process by development of silicon tethered Pauson-Khand reaction, which lead to the synthesis PGJ_2.[130] Furthermore, Stork demonstrated that bromo-silicon intermediate **2.122** can undergo a radical cyclization to give the cyclic siloxane **2.123** (Figure 36).[131] The siloxane moiety on **2.123** was subsequently removed with TBAF to give an angular methyl group (alcohol **2.124**). It is proposed that the low sensitivity of radials to steric hindrance, the ultimate contributor to the failure of the 1,4-conjugate addition reaction on **2.58**, allows for the addition of an angular group where cuprate reactions fail.

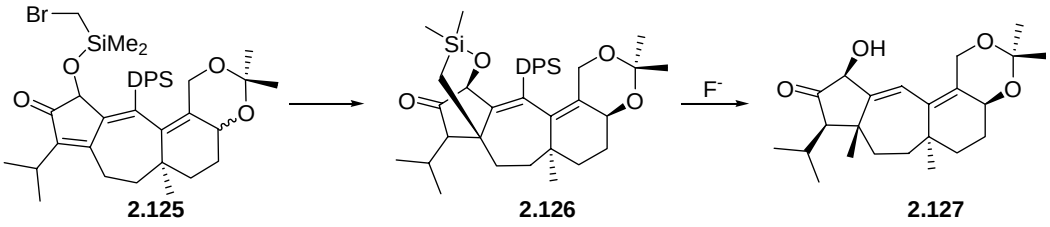


Figure 37. Cyclization of bromo-silane 2.125 to obtain 2.127

Using a silicon tether approach in the synthesis of guanacastepene A mandated formation of bromo-silane **2.125**, which would subsequently be subjected to radical cyclization to give cyclic siloxane **2.126**. This cyclic siloxane could then be subjected to F^- to give ketone **2.127** (Figure 37). However, one concern with this strategy was the regioselectivity of the radical cyclization, because there are two olefins susceptible to cyclization and four possibilities for

reaction (Figure 38).

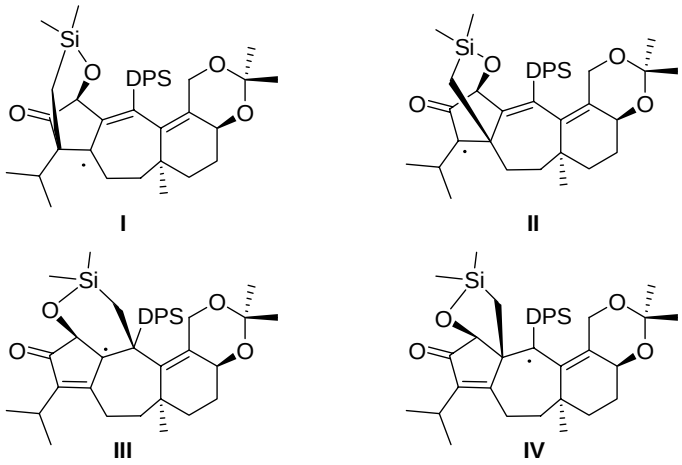


Figure 38. Four possible siloxane cyclization intermediates

Each cyclization is favored by Baldwin's rules;[132] however, differentiation between the olefins could be attained based upon their electronics. Typically radical cyclizations to form five-membered rings are known to be faster than six-membered; however, α-silyl radicals have been found to reverse this preference; thus, intermediates I – III would be favored.[133] Also, regioselectivity of this cyclization can be influenced by electronics, as demonstrated by Lallemand (Figure 39).[134] When bromo-silane **2.128** is subjected to Bu_3SnH and AIBN cyclization occurs quantitatively giving only siloxane **2.129**. Electronically altering the olefin by addition of an α-carbonyl moiety reverses the regioselectivity as evidenced by **2.130** cyclizing to give only the angular addition product **2.131**. This experimental evidence suggests ketone **II** will be formed preferentially.

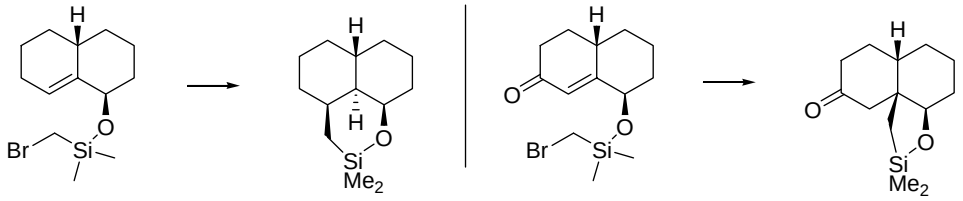
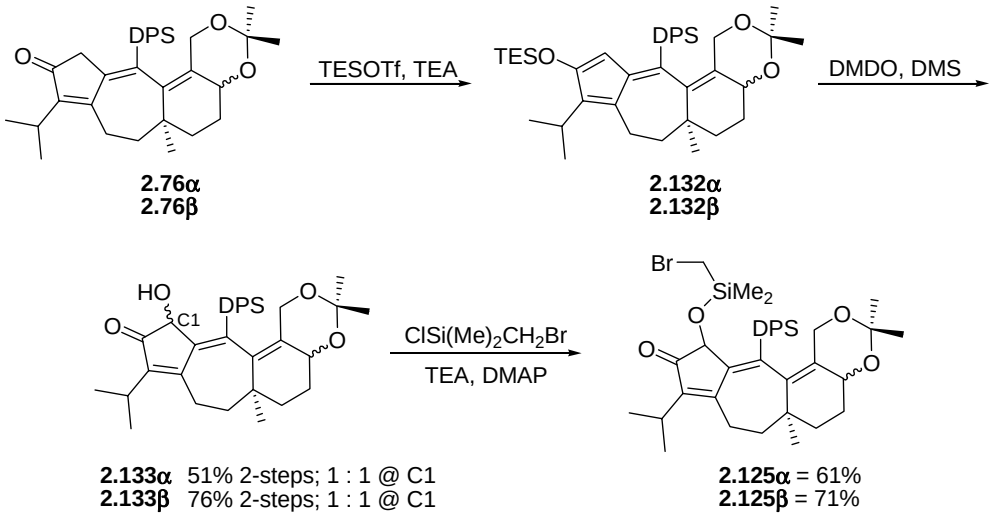


Figure 39. Evidence for electronic influence on radical cyclization

2.7.1 Synthesis of Bromo-silane 2.125 and Cyclization Attempts

After determining that the radical cyclization of bromo-silane **2.125** should afford syloxane **2.126**, we began a synthetic sequence proposed to give bromo-silane **2.125**. Addition of TESOTf and TEA to enone **2.76** promoted formation of the silyl enol ether **2.132** in quantitative yield (Scheme 81).[68] These fulvenes **2.132** were yellow in color and the crude material was characterized by analysis of the ^{1}H NMR spectrum taken in C_6D_6. A selective epoxidation of the crude silyl enol ether **2.132** with DMDO gave the α-hydroxy ketone as a 1 : 1 diastereomeric mixture at C16 of **2.133α** and **2.133β** in a 51% and 76% overall yield, respectively. The diagnostic carbon resonance for C1 appears at 70.4 ppm and the O-H stretch in the IR appears at 3366 cm^{-1} supporting the formation of ketone **2.133**, which was later confirmed by a crystal structure (see Appendix A).



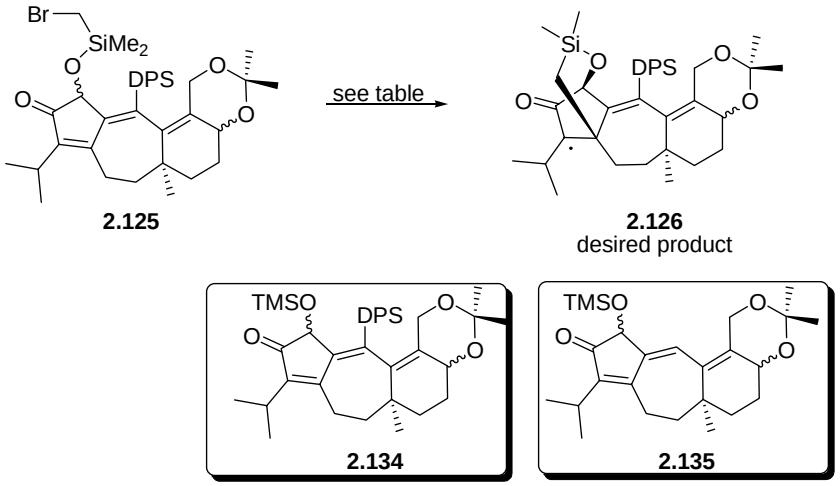
Scheme 81. Synthesis of bromo-silyloxanes 2.125β and 2.125α

The diastereomers at C16 were partially separable upon careful silica gel chromatography. When the diastereomeric mixture at C1 was used in the radical reaction the letter (m) is placed before the number. The letter (f) before the number indicates the faster moving diastereomer on TLC, R_f = 0.22 (20% EtOAc/hexanes), while the letter (s) indicates the slower moving diastereomer on TLC, R_f = 0.18 (20% EtOAc/hexanes). Subjection of alcohol **2.133α** or **2.133β** to $ClSi(Me)_2CH_2Br$, TEA, and DMAP afforded the bromo-silane **2.125α** or **2.125β** in a 61% or 71% yield, respectively (Scheme 81).

Next, **2.125α** and **2.125β** were subjected to radical cyclization protocols and the results are summarized in Table 16. Addition of Bu_3SnH and AIBN to a refluxing solution of bromo-silane **m-2.125α** (as a 1 : 1 diastereomeric mixture at C16) gave a small amount of the reduced product **2.134α** and recovered starting material, as observed by analysis of the ^1H NMR spectrum (Entry 1, Table 16). Also, analysis of the mass spectroscopy spectrum showed a $[M-CH_3]^+$ peak at 549 supporting the conclusion that the bromo-silane was reduced to a TMS moiety. Changing the rate of addition from 3 h to 1.5 h gave the reduced silane **2.134α** with

some impurities (Entry 2, Table 16). At least it was clear from these experiments that we were forming the desired radical; unfortunately, it was being quenched prior to cyclization. For this reason we extended the rate of addition to 6 h, and after concentration of the reaction it was added directly to a KF impregnated silica gel column to assist in the removal of excess tin reagent (Entry 3, Table 16). Surprisingly, this workup cleaved off the DPS group while the TMS-alcohol remained unaffected giving the reduced intermediate **2.135**, as evidenced from analysis of the ^{1}H NMR spectrum and mass spectrometry spectrum.

Table 16. Radical cyclization of bromo-silane 2.125



2.125 **2.126** desired product **2.134** **2.135**

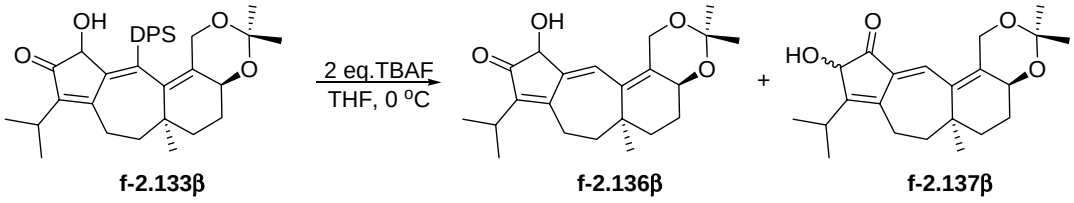
Entry	Substrate[a]	Bu_3SnH (eq)	AIBN (eq)	addition (h)	reflux (h)	results
1	**m-2.125α**	4.1	0.9	3	0	SM + **m-2.134α**
2	**m-2.125α**	4.1	0.9	1.5	0	**m-2.134α**
3	**m-2.125α**	4.1	0.9	6	0	**m-2.135α**
4	**f-2.125β**	1.2	0.1	4	0	SM
5	**s-2.125β**	1.2	0.1	4	0	SM
6	**f-2.125β**	2	0.1	2	5	59% of **f-2.134β**
7	**f-2.125β**	3	0.1	2	5	**f-2.134β**
8	**s-2.125β**	3	0.1	2	5	**f-2.134β**
9	**s-2.125β**	3	0.4	2	5	decomp.[b]

[a] m = 1 : 1 mixture of diastereomers at C1, f = one diastereomer R_f = 0.22 (20% EtOAc/ hexanes), s = one diastereomer R_f = 0.18 (20% EtOAc/hexanes). [b] Toluene was used as the solvent

Due to the probability that one diastereomer at C1 will cyclize faster than the other, the diastereomers were separated and then subjected to the reaction conditions. Reducing the

equivalents of the Bu_3SnH and initiator (AIBN) to 1.2 and 0.1, respectively, gave only recovered starting material (Entries 4 & 5, Table 16). Increasing the equivalents of Bu_3SnH and reducing the addition time to 2 h, but allowing for the reaction to reflux for 5 h after the addition was complete gave the reduced product **2.134β** (Entries 6-8, Table 16). Changing the reaction solvent to toluene so that higher refluxing temperatures could be reached gave some of the reduced product **2.134β** and multiple by-products as detected by HPLC (Entry 9, Table 16).

We concluded that the DPS-group on bromo-silane **2.125** was causing too much conformational strain to allow for cyclization. Therefore, we attempted to remove DPS group from α-hydroxy ketone **2.133β** using TBAF. Subjection of α-hydroxy ketone **2.133β** to TBAF gave a 91% yield of a 1 : 1 separable mixture of **f-2.136β** : **f-2.137β** in 5 min at 0 ˚C. The ratio of the products was calculated by the amount of material isolated (Scheme 82).



f-2.133β **f-2.136β** **f-2.137β**

Scheme 82. Addition of TBAF to f-2.133β

The ^1H NMR spectrum for the isomerized product shows a significant downfield shift of the resonance for the olefinic proton from 6.2 to 6.9, which is expected for this enone moiety. Also, this is approximately the same chemical shift reported for the olefinic proton resonance of a guanacastepene A intermediate **2.138α** by Danishefsky (Figure 40).[67j]

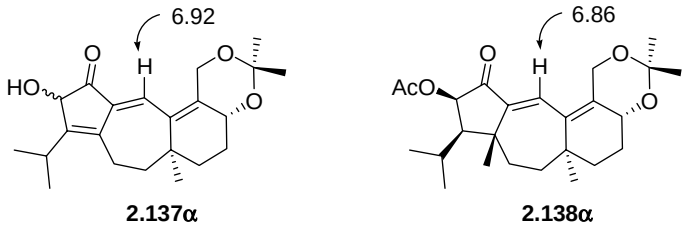


Figure 40. Comparison of the ^{1}H NMR resonances for 2.137α and 2.138α

Unfortunately, full data was not obtained on this compound because the material decomposed before a ^{13}C NMR spectrum could be obtained. However, the IR spectrum reveals a carbonyl stretch for **2.137α** at 1717 cm^{-1}. This stretch is a significantly higher than the carbonyl stretch given by **2.136α** , which has a carbonyl stretch of 1685 cm^{-1}, and approximately the same (1716 cm^{-1}) as the carbonyl stretch reported for the guanacastepene A intermediate **2.139α** (Figure 41).[67x]

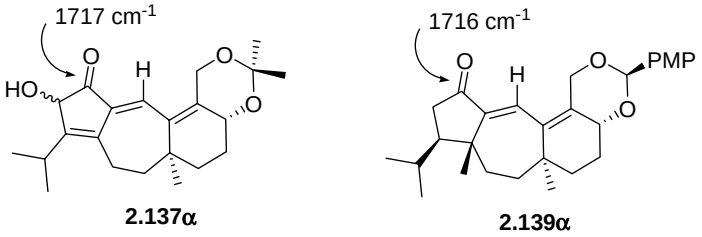
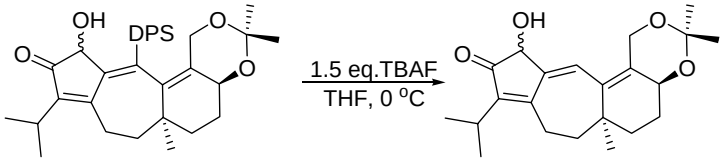


Figure 41. Comparison of the IR stretches for 2.137α and 2.139α

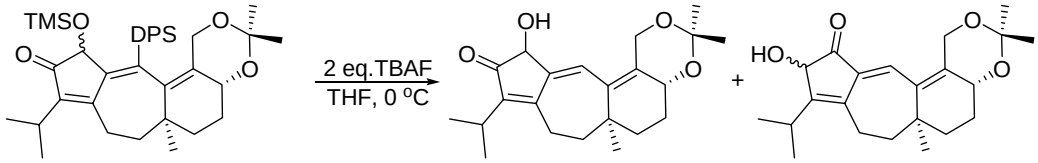
This result was a pleasant surprise since we propose this type of isomerization in the final steps to guanacastepene A (Figure 19, page 96). For this example both products are α-hydroxy enones, which would not be the case for the completion of the synthesis; therefore, it was not a surprise that there was an equal mixture of **2.136β** and **2.137β**.



m-2.133β **m-2.136β**

Scheme 83. Subjection of m-2.133β to TBAF

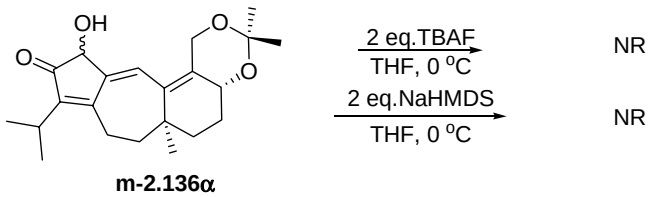
Taking a closer look at this isomerization process, addition of 1.5 equivalents of TBAF gave only desilylated product **2.136β** (Scheme 83). However, when reduced product **m-2.134α** was exposed 2 equivalents of TBAF again approximately a 1 : 1 ratio of **m-2.136α** and **m-2.137α** was obtained (Scheme 84). Thus far it seemed that at least 2 equivalents of TBAF were necessary to effect isomerization.



m-2.134α **m-2.136α** **m-2.137α**

Scheme 84. Subjection of m-2.134α to TBAF

To test whether this was a base-promoted isomerization of the enone, addition of TBAF and, in a separate run, NaHMDS to α-hydroxy-enone **m-2.136α** did not promote any isomerization (Scheme 85). From these results it seems that isomerization only occurs by using an excess of TBAF and during a desilylation process.



m-2.136α

Scheme 85. Subjection of m-2.136α to TBAF or NaHMDS

2.7.2 Summary and Conclusions of the Radical Cyclization Approach

The work presented in this section demonstrated that the α-hydroxy ketones **2.133α** and **2.133β** and bromo-silanes **2.125α** and **2.125β** can be assembled in high yields. Furthermore, the α-hydroxy ketone **2.133α** crystallized confirming the stereochemical assignments of C6 previously attained by analysis of NOESY spectra (Appendix A). More importantly, however, the α-hydroxylation and isomerization reactions, which were proposed in section 2.2.5 to lead to guanacastepene A, were verified (Figure 19, page 96). These results strengthen our hypothesis, that upon successful installation of the angular methyl group at C13, C1 can be oxidized to the alcohol and then isomerized to give enone **2.43**.

2.8 EXPERIMENTAL SECTION

2.8.1 General

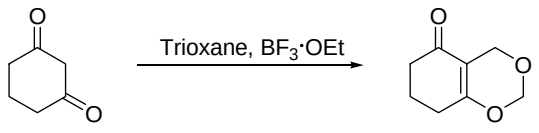
All reactions were performed using syringe-septum cap techniques under a nitrogen atmosphere and glassware was flame dried prior to use. All commercially available compounds were purchased from Aldrich Chemical Co., GFS Chemicals, Strem Chemicals, and Acros Organics and used as received, unless otherwise specified. Tetrahydrofuran (THF), diethyl ether (Et_2O), and dichloromethane (DCM) were purified with alumina using the Sol-Tek ST-002 solvent purification system. Benzene was freshly distilled from Na(m) and benzophenone. Toluene and triethylamine (TEA) were freshly distilled from CaH_2 prior to use. Triethylsilyl trifluoromethanesulfonate (TESOTf) was distilled under vacuum (4 torr) and stored in septum

capped flask on bench top. Copper iodide (CuI) was purified by following the procedure in *Purification of Laboratory Chemicals* by D.D. Perrin and W. L. F. Armarego. Anhydrous MeOH was purchased from Aldrich in 100 mL bottles.

Purification of the products by flash chromatography was performed using silica gel (32-63 μm particle size, 60 Å pore size) purchased from SAI. TLC analyses were performed on EM Science Silica Gel 60 F254 plates (250 μm thickness). HPLC purification was performed on a Varian-Prostar 210 instrument using a Varian Microsorb Dynamax 100-5 Si column (5 μm packing, 250 mm x 10 mm) or Varian Pursuit C8 column (5μ packing, 250 mm x 10mm).

All ^{1}H and ^{13}C spectra were obtained on Bruker Avance 300 MHz, Bruker Avance DRX 500 MHz instrument, or Bruker UltraShield 600 MHz instrument and chemical shifts (δ) reported relative to residual peak $CHCl_3$ or toluene. All NMR spectra were obtained at room temperature unless otherwise specified and are tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet), coupling constant(s), number of protons. IR spectra were obtained using a Nicolet Avatar E.S.P. 360 FT-IR. EI mass spectrometry was performed on a Micromass Autospec high resolution mass spectrometer. ES low resolution mass spectrometry was performed on a HPMSD 1100 LCMS and high resolution was performed on ESI Biosystem time of flight mass spectrometer.

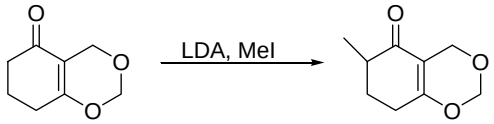
2.8.2 Experimental procedures



2.59 **2.60**

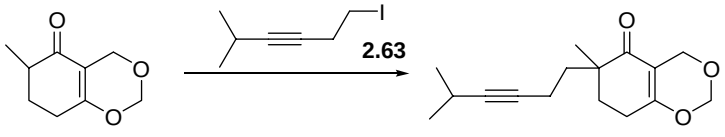
7,8-Dihydro-4H-benzo[d][1,3]dioxin-5(6H)-one (Smith's enone 2.60): The protocol reported

by Smith[95] was followed with slight deviations that resulted in higher yields using less solvent. To a solution of s-trioxane (24.1 g, 0.268 mol) and $BF_3{\cdot}OEt_2$ (19.0 g, 0.134 mol) in 760 mL of CH_2Cl_2 at ambient temperature was added a solution of 1,3-cyclohexadione (4.90 g, 44.6 mmol) in 280 mL of CH_2Cl_2 over 3 h via cannulation. The reaction mixture was maintained at ambient temperature for another 15 h after which time it was quenched by addition of a sat. aqueous $NaHCO_3$ solution. The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2. The combined organics were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 20-40% EtOAc / hexanes to afford Smith's enone **2.60** (6.70 g, 99% yield) as a colorless oil. R_f = 0.1 (20% EtOAc / hexanes). All spectroscopic data matched literature findings.



2.60 **2.37**

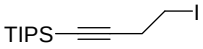
7,8-Dihydro-6-methyl-4H-benzo[d][1,3]dioxin-5(6H)-one 2.37: Followed the procedure reported by Smith, enone **2.60** (2.34 g, 15.2 mmol), LDA (1.2 eq), CH_3I (4.73 mL, 76.0 mmol), afforded enone **2.37** (2.24 g, 88% yield). All spectroscopic data matched literature findings.



2.37 **2.53**

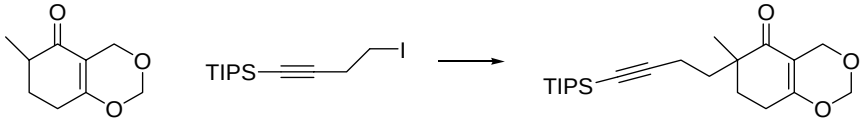
7,8-Dihydro-6-methyl-6-(5-methylhex-3-ynyl)-4H-benzo[d][1,3]dioxin-5(6H)-one (2.53): To a solution of LDA at -78 ˚C [prepared from diisopropylamine (0.17 mL, 1.2 mmol) in 1 mL of THF and *n*-butyllithium (0.70 mL of a 1.6 M hexanes solution, 1.1 mmol) at 0 ˚C for 30 min] was added a solution of enone **2.37** (0.13 g, 0.75 mmol) in 1.5 mL of THF dropwise via cannulation. After an additional 1.5 h at -78 ˚C, 1-iodo-5-methylhex-3-yne (**2.63**, 0.50 g, 2.2

mmol) was added. The reaction mixture was allowed to slowly warm to ambient temperature overnight and then was quenched by the addition of a sat. aqueous NH_4Cl solution. The mixture was diluted with H_2O and extracted with ether several times. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 10-20% EtOAc / hexanes to afford enone **2.53** (119 mg, 61% yield) as a colorless oil. R_f = 0.36 (20% EtOAc / hexanes). All spectroscopic data matched literature findings: Brummond, K. M.; Gao, D. *Org. Lett.* **2003**, *5*, 3491.



2.64

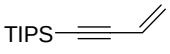
(4-Iodobut-1-ynyl)triisopropylsilane (2.64). ^1H NMR (300 MHz, $CDCl_3$): δ 1.04-1.12 (m, 21H), 2.84 (t, *J* = 7.3 Hz, 2H), 3.25 (t, *J* = 7.3 Hz, 2H).



2.37 **2.64** **2.53b**

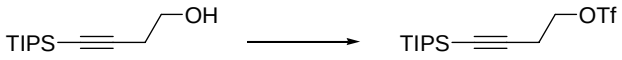
6-Methyl-6-(4-(triisopropylsilyl)but-3-ynyl)-7,8-dihydro-4H-benzo[d][1,3]dioxin-5(6H)-one (2.53b). To a solution of LDA at -78 ˚C [prepared from diisopropylamine (0.23 mL, 1.7 mmol) in 2 mL of THF and *n*-butyllithium (1.00 mL of a 1.6 M hexanes solution, 1.6 mmol) at 0 ˚C for 30 min] was added a solution of enone **2.37** (0.18 g, 1.0 mmol) in 0.5 mL of THF dropwise via cannulation. After an additional 1.5 h at -78 ˚C, (4-iodobut-1-ynyl)-triisopropylsilane (**2.64**, 0.8 g, 2.4 mmol) was added. The reaction mixture was allowed to slowly warm to ambient temperature overnight and then was quenched by the addition of a sat. aqueous NH_4Cl solution. The mixture was diluted with H_2O and extracted with ether several times. The

combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 10-20% EtOAc / hexanes to afford enone **2.53b** (106 mg, 23% yield). R_f = 0.3 (20% EtOAc / hexanes); ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.03 (s, 18H), 1.04 (s, 3H), 1.10 (s, 3H), 1.70-1.86 (m, 3H), 2.00 (ddd, *J* = 6.7 Hz, *J* = 6.7 Hz, *J* = 13.2 Hz, 1H), 2.14-2.27 (m, 2H), 2.45 (qt, *J* = 5.7 Hz, *J* = 19.4 Hz, 2H), 4.30-4.45 (m, 2H), 5.12 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 11.2 (3), 15.1, 18.5 (6), 22.0, 24.5, 31.3, 35.9, 43.0, 63.0, 80.2, 91.3, 108.8, 110.0, 168.3, 199.9; MS (GC/MS) *m/e* (relative intensity) 333 ([M-$(CH_3)_2CH]^+$, 30), 303 (100); HRMS calcd for $C_{19}H_{29}O_3Si$: 333.1886 [M-$(CH_3)_2CH]^+$; found: 333.1882 [M-$(CH_3)_2CH]^+$.



2.65

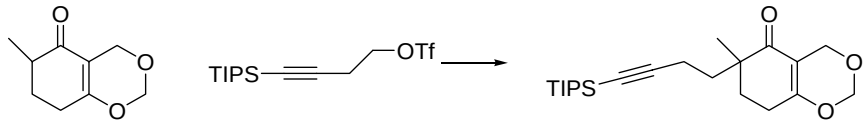
But-3-en-1-ynyltriisopropylsilane (2.65). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10 (s, 21H), 5.49 (dd, *J* = 2.5 Hz, *J* = 10.9 Hz, 1H), 5.68 (dd, *J* = 2.5 Hz, *J* = 17.6 Hz, 1H), 5.85 (dd, *J* = 10.9 Hz, *J* = 17.6 Hz, 1H).



2.66b **2.67b**

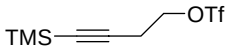
General procedure for synthesis of triflates 2.67a-d. 4-(Triisopropylsilyl)but-3-ynyl trifluoromethanesulfonate (2.67b): To a solution of pyridine (1.00 g, 12.7 mmol) in 13 mL of CH_2Cl_2 at -78 ˚C was added Tf_2O (3.00 g, 10.6 mmol) dropwise. After 20 min the reaction mixture solidified and alcohol **2.67b** (2.4 g, 11 mmol) was added. The reaction was left at -78 ˚C and allowed to slowly warm to -40 ˚C; stirring vigorously. Once all solids dissolved the reaction was complete by TLC. The reaction mixture was diluted with CH_2Cl_2 and 10% HCl solution was added. The aqueous layer was removed and the organic layer was dried with Na_2SO_4, filtered, and concentrated under reduced pressure keeping the rotovap bath temperature at 24 ˚C. The

crude residue was quickly flushed through a pad of silica gel with 10% ether / pentanes and the material was concentrated under reduced pressure (3.4 g, 89% crude yield) and used immediately in the next step.



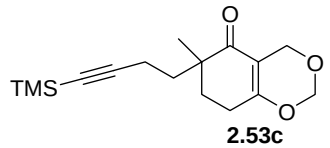
2.37 **2.67b** **2.53b**

General procedure for alkylation of 2.37 with various triflates. 6-Methyl-6-(4-(triisopropylsilyl)but-3-ynyl)-7,8-dihydro-4H-benzo[d][1,3]dioxin-5(6H)-one (2.53). To a solution of LDA at -78 ˚C [prepared from diisopropylamine (1.0 mL, 7.3 mmol) in 7 mL of THF and *n*-butyllithium (4.2 mL of a 1.6 M hexanes solution, 6.7 mmol) at 0 ˚C for 30 min] was added a solution of enone **2.37** (0.94 g, 5.59 mmol) in 33 mL of THF dropwise via cannulation. After an additional 1.5 h at -78 ˚C, a solution of 5-methylhex-3-ynyl trifluoromethanesulfonate (**2.67b**, 3.30 g, 9.20 mmol) in 9 mL of THF at -78 ˚C was added dropwise via cannulation. The reaction mixture was kept at -78 ˚C for 1 h and then was quenched by the addition of a sat. aqueous NH_4Cl solution at -78 ˚C and then allowed to warm to ambient temperature.[135] Once at ambient temperature and reaction was diluted with some H_2O and extracted with ether several times. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 10-20% EtOAc / hexanes to afford enone **2.53b** (1.13 g, 54% yield) as a colorless oil.



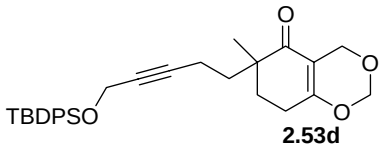
2.67c

4-(Trimethylsilyl)but-3-ynyl trifluoromethanesulfonate (2.67c). R_f = 0.75 (20% EtOAc / hexanes); ^1H NMR (300 MHz, $CDCl_3$): δ 0.16 (s, 9H), 2.77 (t, *J* = 6.8 Hz, 2H), 4.57 (t, *J* = 6.8 Hz, 2H).



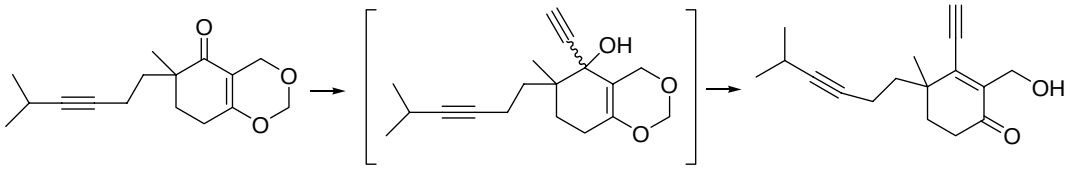
2.53c

6-Methyl-6-(4-(trimethylsilyl)but-3-ynyl)-7,8-dihydro-4H-benzo[d][1,3]dioxin-5(6H)-one (2.53c). R_f = 0.75 (20% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.11 (s, 9H), 1.06 (s, 3H), 1.66-1.85 (m, 3H), 1.86-2.00 (dt, *J* = 6.4 Hz, *J* = 13.7 Hz, 1H), 2.01-2.28 (dt, *J* = 6.1 Hz, *J* = 9.5 Hz, 2H), 2.30-2.56 (m, 2H), 4.33 (dt, *J* = 2.0 Hz, *J* = 16.7 Hz, 1H), 4.40 (dt, *J* = 2.1 Hz, *J* = 16.6 Hz, 1H), 5.07(dd, *J* = 5.5 Hz, *J* = 10.3 Hz, 1H), 5.17 (dd, *J* = 2.2 Hz, *J* = 18.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.0 (3), 15.0, 21.8, 24.4, 31.4, 35.7, 42.9, 63.0, 84.5, 91.2, 107.2, 109.9, 168.1, 200.0; IR (neat) 2959, 2174, 1637 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 292 ([M]$^+$, 1), 247 (6), 138 (100); HRMS calcd for $C_{16}H_{24}O_3Si$: 292.1495 [M]$^+$; found: 292.1499 [M]$^+$.



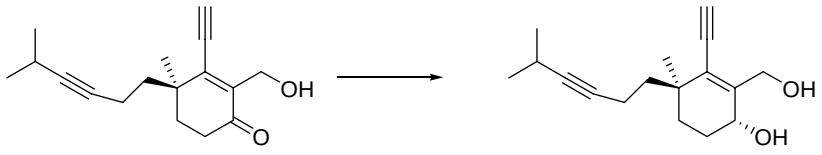
2.53d

6-(5-(tert-Butyldiphenylsilyloxy)pent-3-ynyl)-6-methyl-7,8-dihydro-4H-benzo[d][1,3]dioxin-5(6H)-one (2.53d). R_f = 0.32 (20% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.07 (s, 9H), 1.10 (s, 3H), 1.62-1.83 (m, 3H), 1.94 (dt, *J* = 6.0 Hz, *J* = 13.7 Hz, 1H), 2.00-2.23 (m, 2H), 2.34-2.60 (m, 2H), 4.32 (app s, 2H), 4.35-4.50 (m, 2H), 5.09 (dd, *J* = 5.5 Hz, *J* = 11.7 Hz, 1H), 5.16 (dd, J = 5.5 Hz, J = 10.8 Hz, 1H), 7.36-7.48 (m, 6H), 7.70-7.77 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 19.1, 21.8, 24.4, 26.6 (3), 31.4, 35.5, 42.9, 52.8, 63.0, 78.5, 85.5, 91.2, 109.9, 127.5 (4), 129.6 (2), 133.2 (2), 135.5 (4), 168.1, 199.7; IR (neat) 2931, 2858, 1636 cm^{-1}; MS (API-ES) *m/e* (relative intensity) 511 ([M+Na]$^+$, 40); HRMS calcd for $C_{30}H_{36}O_4SiNa$: 511.2281 [M+Na]$^+$; found: 511.2260 [M+Na]$^+$.



2.53 **2.68**

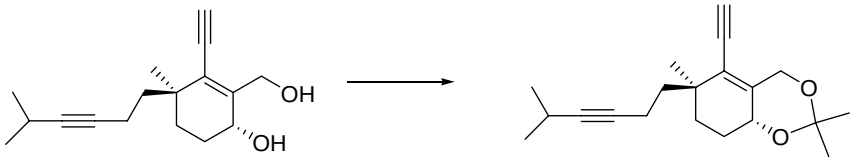
3-Ethynyl-2-(hydroxymethyl)-4-methyl-4-(5-methylhex-3-ynyl)cyclohex-2-enone (2.68). To a suspension of lithium acetylide ethylenediamine complex (1.92 g, 20.8 mmol) in 26 mL of THF at 0 ˚C was added a solution of enone **2.53** (1.09 g, 4.17 mmol) in 7 mL of THF, dropwise via cannula. The mixture was allowed to warm to ambient temperature and was maintained at that temperature for 2 h after which time complete consumption of starting material was observed by TLC (R_f = 0.5; 30% EtOAc / hexanes). Then, 2 mL of water was added followed by 30 mL of 10% HCl. After 15 min complete hydrolysis was observed by TLC (R_f = 0.25; 30% EtOAc / hexanes, for **2.68**) and the layers were separated. The aqueous layer was extracted with ether, and the combined organics were washed a sat. aqueous $NaHCO_3$ solution, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 20-40% EtOAc / hexanes to afford enyne **2.68** (972 mg, 90% yield) as a colorless oil. R_f = 0.2 (20% EtOAc / hexanes). All spectroscopic data matched literature findings: Brummond, K. M.; Gao, D. *Org. Lett.* **2003**, *5*, 3491.



2.68 **2.69α** 7.5 : 2.5

(1R*,4R*)-3-Ethynyl-2-(hydroxymethyl)-4-methyl-4-(5-methylhex-3-ynyl)cyclohex-2-enol (2.69α). The ketone **2.68** (0.97 g, 3.8 mmol) was diluted with a solution of $CeCl_3 \cdot 7H_2O$ (12 mL of a 0.4 M solution in methanol, 4.9 mmol), cooled to -30 ˚C, and $NaBH_4$ (0.19 g, 4.9 mmol) was added in one portion. The mixture was kept at -30 ˚C and after 30 min complete consumption of

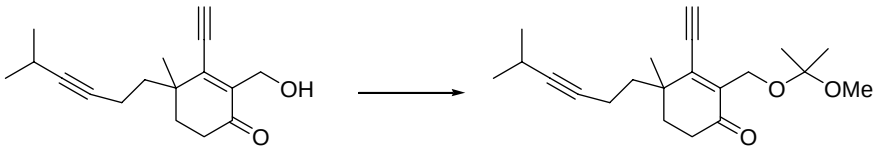
starting material was observed by TLC. The solution was quenched with slow addition of H_2O, and the aqueous layer was separated and washed with Et_2O (3x). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 40% EtOAc / hexanes to the afford alcohol **2.69** (980 mg, 100%) as a 7.5 : 2.5 diastereomeric mixture of **2.69α : 2.69β** as determined by ^{1}H NMR; however, pure **2.69β** was obtained by HPLC for spectroscopic purposes (Varian Microsorb Dynamax 100-5 Si column, 250mmx10mm, 50 μL, 23 ˚C, EtOAc / hexanes = 30%, flow rate = 3 mL/min. R_f = 0.16 (40% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08 (s, 3H), 1.13 (d, *J* = 6.8 Hz, 6H), 1.65-2.00 (m, 7H), 2.04-2.27 (m, 3H), 2.44-2.57 (m, 1H), 3.23 (s, 1H), 4.36 (t, *J* = 4.1 Hz, 1H), 4.40 (A of an ABq, *J* = 12.7 Hz, 1H), 4.68 (B of ABq, *J* = 12.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) : δ 14.1, 20.5, 23.4 (2), 25.5, 27.1, 28.2, 37.4, 39.9, 64.7, 66.3, 79.5, 79.6, 84.4, 86.0, 127.7, 145.0; IR (neat) 3287, 2966, 2936, 2870 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 260 ([M]$^+$, 5), 199 (40), 91 (100): HRMS calcd for $C_{17}H_{24}O_2$: 260.1776 [M]$^+$; found: 260.1792 [M]$^+$.



2.69 7.5 : 2.5 **2.70** 8 : 2

(6R*,8aR*)-5-Ethynyl-2,2,6-trimethyl-6-(5-methylhex-3-ynyl)-6,7,8,8a-tetrahydro-4H-benzo[d][1,3]dioxine (2.70). To a solution of diol **2.69** (0.98 g, 3.8 mmol) in 94 mL of CH_2Cl_2 at 0 ˚C was added 2,2-dimethoxypropane (9.3 mL, 75 mmol) and then PPTS (0.19 g, 0.75 mmol). The reaction flask was kept at 0 ˚C and after 1.5 h the reaction was quenched by the addition of a sat. aqueous $NaHCO_3$ solution and the aqueous layer was separated and extracted with CH_2Cl_2 (2x). The combined organic layers were dried with $MgSO_4$, filtered, and

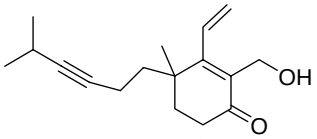
concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 5-10% EtOAc / hexanes to afford enyne **2.70** (920 mg, 82% yield) as a 8 : 2 diastereomeric ratio as determined by ^{13}C NMR; however, ratios could also be calculated using ^{1}H NMR when C_6D_6 was used as the solvent). *designates major diastereomer where peaks were resolved. R_f = 0.86 (50% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) (major diastereomer) **2.70α**: δ 1.04* (s, 3H), 1.09 (d, *J* = 6.7 Hz, 6H), 1.10 (s, 3H), 1.34 (s, 3H), 1.41 (s, 3H), 1.45-1.65 (m, 4H), 1.66-1.90 (m, 2H), 2.02 (dt, *J* = 7.1 Hz, *J* = 1.9 Hz, 2H), 2.06-2.24 (m, 1H), 2.47 (sept, *J* = 6.8 Hz, 1H), 3.16 (s, 1H), 4.25-4.30 (m, 1H), 4.36 (A of an ABq, *J* = 15.8 Hz, 1H), 4.48 (B of an ABq, *J* = 15.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.7, 14.3*, 20.4, 22.3*, 22.4, 23.3, 25.0, 25.9, 26.1*, 26.2, 26.6, 30.4, 31.1*, 36.7*, 37.5, 38.3, 40.7, 61.5, 61.7*, 67.0, 78.7, 79.1*, 79.2*, 79.3, 84.0, 84.1*, 85.7, 85.8*, 99.3, 120.1, 121.5*, 143.2*, 144.3; IR (neat) 3278, 2966, 2870, 2089, 1452 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 285 ($[M\text{-}CH_3]^+$, 0.5), 171 (100): HRMS calcd for $C_{19}H_{25}O_2$: 285.1855 $[M\text{-}CH_3]^+$; found: 285.1843 $[M\text{-}CH_3]^+$. ^{1}H NMR (500 MHz, C_6D_6) (minor diastereomer) **2.70β**: δ 1.01 (s, 3H), 1.10 (d, *J* = 6.8 Hz, 6H), 1.34 (s, 3H), 1.37 (s, 3H), 1.54 (dt, *J* = 3.7 Hz and *J* = 14.1 Hz, 1H), 1.61-1.68 (m, 3H), 1.82-1.94 (m, 2H), 2.05-2.20 (m, 2H), 2.40-2.51 (m, 1H), 2.69 (s, 1H), 4.19 (t, *J* = 8.2 Hz, 1H), 4.46 (A of an ABq, *J* = 15.6 Hz, 1H), 4.66 (B of an ABq, dd, *J* = 15.6 Hz, *J* = 1.6 Hz, 1H).



2.68 **2.73**

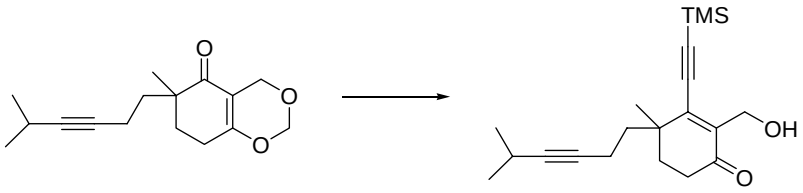
3-Ethynyl-2-((2-methoxypropan-2-yloxy)methyl)-4-methyl-4-(5-methylhex-3-ynyl)cyclohex-2-enone (2.73). To a solution of enone **2.68** (0.05 g, 0.17 mmol) in 0.2 mL of 2-methoxyprop-1-ene at 0 ˚C was added PPTS (4 μmol). After 15 min the mixture was quenched by the addition of

a sat. aqueous $NaHCO_3$ solution and ether. The organic layer was washed with H_2O, dried with Na_2SO_4, filtered, and concentrated under reduced pressure and the residue (55 mg, 98% yield of monoacetal **2.73**) was used without further purification. R_f = 0.7 (20% EtOAc / hexanes on alumina TLC plate); ^{1}H NMR (300 MHz, C_6D_6): δ 0.87 (s, 3H), 1.08 (d, *J* = 6.8 Hz, 6H), 1.40 (s, 6H), 1.65 (ddd, *J* = 6.7 Hz, *J* = 9.5 Hz, *J* = 13.6 Hz, 2H), 1.75-1.87 9 (m, 2H), 1.96-2.05 (m, 2H), 2.06-2.16 (m, 2H), 2.43 (tsep, *J* = 2.1 Hz, *J* = 6.8 Hz, 1H), 3.05 (s, 1H), 3.36 (s, 3H), 4.46 (A of an ABq, *J* = 8.7 Hz, 1H), 4.52 (B of an ABq, *J* = 8.7 Hz, 1H).



2.71

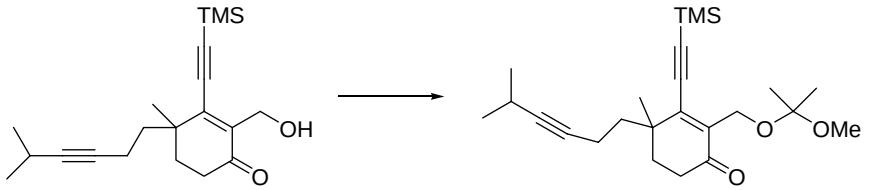
2-(Hydroxymethyl)-4-methyl-4-(5-methylhex-3-ynyl)-3-vinylcyclohex-2-enone (2.71, Table 8, Entry 4). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13 (d, *J* = 6.9 Hz, 6H), 1.18 (s, 3H), 1.60-1.92 (m, 4H), 2.01-2.22 (m, 3H), 2.52-2.60 (m, 2H), 2.85 (t, *J* = 6.9 Hz, 1H), 4.36 (d, *J* = 6.8 Hz, 2H), 5.35 (dd, *J* = 1.9 Hz, *J* = 17.5 Hz, 1H), 5.56 (dd, *J* = 1.9 Hz, 11.7 Hz, 1H), 6.35 (dd, *J* = 11.7 Hz, *J* = 17.5 Hz, 1H).



2.53 **2.74**

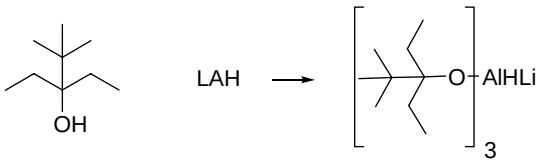
2-(Hydroxymethyl)-4-methyl-4-(5-methylhex-3-ynyl)-3-(2-(trimethylsilyl)ethynyl) cyclohex-2-enone (2.74). To a solution of trimethylsilylacetylene (2.1 g, 15 mmol) in 40 mL of THF at -78 ˚C was added n-butyllithium (8.4 mL of a 1.6 M hexanes solution, 14 mmol). After 1 h at -78 ˚C a solution of enone **2.53** (2.2 g, 8.4 mmol) in 40 mL of THF was added via cannulation. The reaction was allowed to warm to ambient temperature at which time the reaction was deemed

complete based upon consumption of the starting material as seen on TLC. Then, 10% HCl was added to the reaction mixture and after 45 min complete hydrolysis was seen by TLC. The reaction mixture was extracted with ether and the combined organic layers were washed with a sat. aqueous $NaHCO_3$ solution, dried with $MgSO_4$, filtered, and concentrated under reduced pressure to afford enone **2.74** (2.8 g, quantitative yield) as a colorless oil. R_f = 0.4 (30% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.19 (s, 9H), 1.05 (d, *J* = 6.9 Hz, 6H), 1.19 (s, 3H), 1.60-1.78 (m, 2H), 1.88 (ddd, *J* = 6.4 Hz, *J* = 9.3 Hz, *J* = 13.8 Hz, 1H), 1.96-2.20 (m, 3H), 2.35-2.51 (m, 3H), 3.00 (t, *J* = 6.4 Hz, 1H), 4.43 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ -0.6 (3), 14.0, 20.3, 23.1 (2), 25.0, 31.7, 33.8, 38.2, 39.2, 60.4, 78.6, 86.2, 99.6, 113.5, 140.2, 146.8, 199.3; IR (neat) 3448, 2964, 2932, 1663 cm^{-1}.



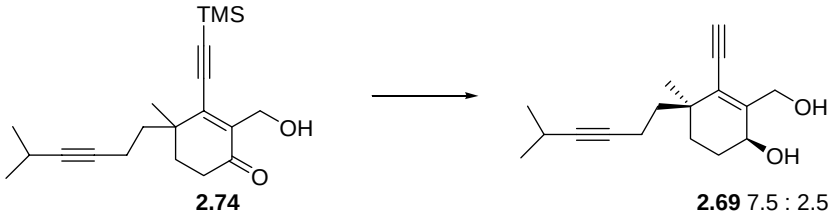
2.74 **2.75**

2-((2-Methoxypropan-2-yloxy)methyl)-4-methyl-4-(5-methylhex-3-ynyl)-3-((trimethylsilyl)ethynyl)cyclohex-2-enone (2.75). To a solution of enone **2.74** (0.05 g, 0.15 mmol) in 0.15 mL of 2-methoxyprop-1-ene at 0 ˚C was added PPTS (3 μmol). After 15 min the mixture was quenched by the addition of a sat. aqueous $NaHCO_3$ solution and ether. The organic layer was washed with H_2O, dried with Na_2SO_4, filtered, and concentrated under reduced pressure and the residue (62 mg, quantitative yield of monoacetal **2.75**) was used without further purification. R_f = 0.3 (30% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.15 (s, 9H), 0.94 (s, 3H), 1.08 (d, *J* = 6.8 Hz, 6H), 1.42 (s, 6H), 1.45-1.55 (m, 2H), 1.61-1.72 (m, 1H), 1.85-2.00 (m, 1H), 2.01-2.08 (m, 2H), 2.10-2.18 (m, 2H), 2.43 (tsep, *J* = 2.1 Hz, *J* = 6.8 Hz, 1H), 3.41 (s, 3H), 4.52 (A of an ABq, *J* = 8.7 Hz, 1H), 4.58 (B of an ABq, *J* = 8.7 Hz, 1H).



2.72

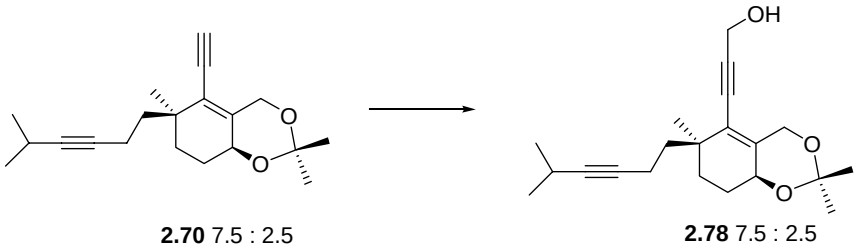
Lithium tris [(3-tert-butyl-3-pentyl)oxy] aluminum hydride (2.72): To a solution of LAH (22 mL of a 1.0 M THF solution, 38 mmol) at ambient temperature was added 3-ethyl-2,2-dimethylpentan-3-ol (0.18 mL , 0.04 mol) dropwise. After the addition was complete, the reaction mixture was refluxed for 2 h. The mixture was then cooled to ambient temperature and used immediately in the following reaction. This procedure gave an estimated 0.5 M solution of hydride **2.72** in THF.



2.74 **2.69** 7.5 : 2.5

(1S*,4R*)-3-Ethynyl-2-(hydroxymethyl)-4-methyl-4-(5-methylhex-3-ynyl)cyclohex-2-enol (2.69β). To a solution of enone **2.74** (2.2 g, 6.4 mmol) in 50 mL of THF at -78 ˚C was added hydride **2.86** (26 mL of a 0.5 M THF solution, 13 mmol) with a syringe pump at a rate of 13 mL/h. After the addition was complete, the reaction was left for 1 h and then quenched by the addition of MeOH. The reaction flask was then allowed to warm to ambient temperature overnight and then the organic layer was evaporated under reduced pressure to approximately ¼ original volume. The organic layers were taken up in ether and water and then the organic layer was removed and the aqueous layer was extract with ether. The combined organics were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 20-30% EtOAc / hexanes to afford alcohol **2.69β** (1.6 g, 96% yield) as a 7.5 : 2.5 diastereomeric ratio as determined by ^{1}H NMR). R_f = 0.3 (40% EtOAc /

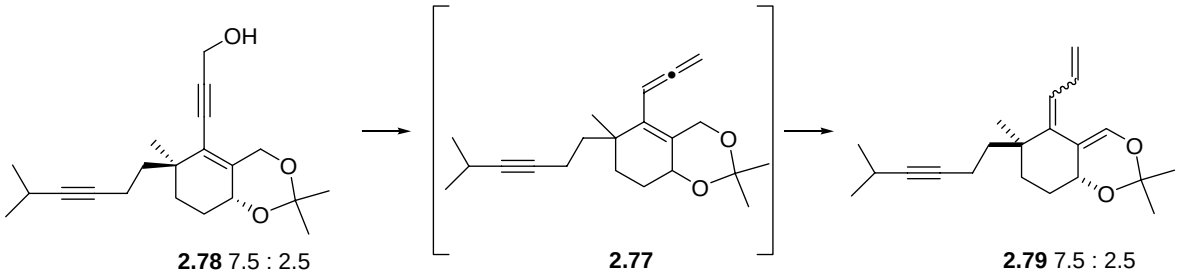
hexanes). All spectroscopic data matched for **2.69β** and **2.69α**.



2.70 7.5 : 2.5 **2.78** 7.5 : 2.5

3-((6S*,8aR*)-2,2,6-Trimethyl-6-(5-methylhex-3-ynyl)-6,7,8,8a-tetrahydro-4H-benzo[d][1,3]dioxin-5-yl)prop-2-yn-1-ol (2.78). To a solution of alkyne **2.70** (1.2 g, 4.0 mmol) in 15 mL of THF at -78 °C was added *n*-butyllithium (3.1 mL of a 1.6 M hexanes solution, 4.8 mmol) dropwise. After 30 min at -78 °C paraformaldehyde (0.96 g, 32 mmol) was added in one portion. The reaction mixture was allowed to slowly warm to ambient temperature overnight and then was quenched by the addition of a sat. aqueous NH_4Cl solution. The mixture was diluted with H_2O and extracted with ether several times. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 5-10% EtOAc / hexanes to afford alcohol **2.78** (1.13 g, 86% yield) as a 3 : 1 diastereomeric ratio based upon integration of peaks in the GC trace; however, diastereomerically enhanced material (9 : 1) could be obtained using Biotage apparatus eluting with 5-25% (5% t-BuOH/THF solution) / pentanes. Fractions were analyzed by GC using method hc-200-15 giving a retention time of 11.5 min for **2.78α** and 12.2 for **2.78β**. R_f = 0.14 (20% EtOAc / hexanes); ^{1}H NMR (300 MHz, C_6D_6) (minor diastereomer) **2.78β**: δ 1.03 (s, 3H), 1.10 (d, *J* = 6.6 Hz, 6H), 1.37 (s, 3H), 1.41 (s, 3H), 1.55 (dt, *J* = 3.4 Hz, *J* = 14.1 Hz, 1H), 1.60-1.75 (m, 2H), 1.85-1.98 (m, 2H), 2.07-2.25 (m, 3H), 2.35-2.52 (m, 1H), 3.87 (s, 2H), 4.24 (t, *J* = 8.0 Hz, 1H), 4.46 (A of an ABq, *J* = 15.4 Hz, 1H), 4.70 (B of an ABq, *J* = 15.4 Hz, 1H); ^{13}C

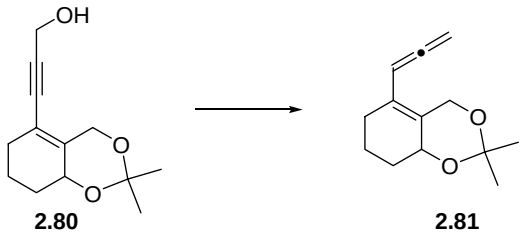
NMR (75 MHz, C_6D_6): δ 14.8, 21.0, 22.5, 23.6, 25.7, 23.6, 25.7, 26.5, 27.1, 31.3, 37.2, 39.1, 51.1, 62.1, 67.4, 80.0, 80.9, 86.1, 95.5, 99.5, 122.2, 142.4; IR (neat) 3446, 2966, 2869, 1457 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 315 ($[M]^+$, 0.2), 272 (20), 91 (100): HRMS calcd for $C_{20}H_{27}O_3$: 315.1960 $[M]^+$; found: 315.1961 $[M]^+$.



2.78 7.5 : 2.5 **2.77** **2.79** 7.5 : 2.5

(6R*,8aR*)-5-Allylidene-2,2,6-trimethyl-6-(5-methylhex-3-ynyl)-6,7,8,8a-tetrahydro-5H-benzo[d][1,3]dioxine (2.79). To a solution of triphenylphosphine (0.19 g, 0.72 mmol) in 1.5 mL of THF at 0 °C was added diisopropylazodicarboxylate (DIAD) (0.14 mL, 0.69 mmol). Immediately afterwards, a solution of alcohol **2.78** (0.20 g, 0.60 mmol) in 0.6 mL of THF was added via cannula followed by the dropwise addition of a solution of 2-nitrobenzenesulfonohydrazide (0.16 g, 0.72 mmol) in 1 mL of THF. The reaction flask was kept at 0 °C for 1 h and then allowed to warm to ambient temperature and after 2 h the reaction was diluted with pentanes (R_f = 0.74; 20% EtOAc / hexanes, TLC showed one pink (subsequently determined to be allene **2.77**) spot with PAA stain). The organic layer was washed four times with H_2O and then the organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 5% EtOAc / hexanes to afford triene **2.79** (44 mg, 23% yield) (TLC showed one pink and one blue spot (triene **2.79**) with PAA stain, then after ^1H NMR only blue spot) as a 3 : 1 diastereomeric ratio as determined by ^1H NMR. R_f = 0.65 (20% EtOAc / hexanes); ^1H NMR (300 MHz, $CDCl_3$): δ 1.05 (s, 3H), 1.16 (d, *J* = 6.8 Hz, 6H), 1.40-1.47 (m, 1H), 1.50 (s, 3H), 1.54 (s, 3H), 1.56-1.85 (m,

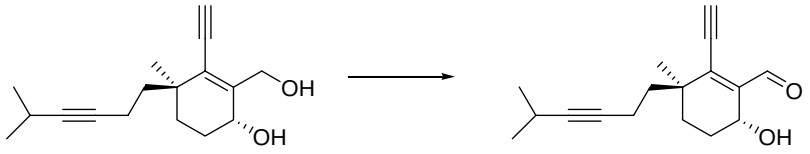
3H), 1.86-2.05 (m, 2H), 2.10-2.30 (m, 2H) 2.44-2.61 (m, 1H), 4.10 (ddd, J = 1.2 Hz, J = 5.8 Hz, J = 10.7 Hz, 1H), 5.00 (dd, J = 1.2 Hz, J = 10.1 Hz, 1H), 5.23 (dd, J = 1.4 Hz, J = 16.9 Hz, 1H), 5.97 (d, J = 10.4 Hz, 1H), 6.26 (d, J = 1.3 Hz, 1H), 6.71 (dt, J = 10.4 Hz, J = 16.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.7, 20.5, 21.2, 23.4 (2), 25.6, 27.6, 27.9, 32.8, 38.7, 40.1, 69.0, 79.7, 85.9, 98.9, 112.2, 115.9, 123.5, 134.6, 139.9, 143.5; IR (neat) 2966, 2870, 1643 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 256 ($[M\text{-}C(CH_3)_2O]^+$,10), 185 (100), 91 (97): HRMS calcd for $C_{21}H_{30}O_2$: 256.1827 $[M\text{-}C(CH_3)_2O]^+$; found: 256.1839 $[M\text{-}C(CH_3)_2O]^+$.



2.80 **2.81**

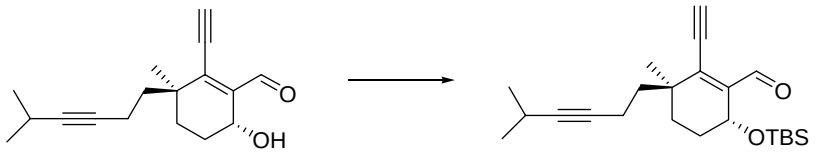
2,2-Dimethyl-5-(propa-1,2-dienyl)-6,7,8,8a-tetrahydro-4H-benzo[d][1,3]dioxine (2.81). To a solution of triphenylphosphine (0.19 g, 0.72 mmol) in 1.5 mL of THF at -15 ˚C was added diisopropylazodicarboxylate (DIAD) (0.12 mL, 0.62 mmol). Immediately afterwards, a solution of alcohol **2.80** (0.12 g, 0.54 mmol) in 0.4 mL of THF was added via cannula followed by the dropwise addition of a solution of 2-nitrobenzenesulfonohydrazide (0.14 g, 0.65 mmol) in 1 mL of THF. The reaction flask was kept at ˉ15-ˉ10 ˚C for 45 min and then allowed to warm to ambient temperature and after 45 min the reaction was diluted with pentanes. The organic layer was washed four times with H_2O and then the organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 5-10% EtOAc / hexanes to afford allene **2.81** (49 mg, 44% yield). R_f = 0.64 (20% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (s, 3H), 1.47 (s, 3H), 1.51-1.65 (m, 2H), 1.75-1.90 (m, 2H), 1.95-2.05 (m, 2H), 4.26-4.53 (m, 3H), 4.90-5.00 (m, 2H), 5.89 (t, J = 6.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.9, 22.4, 26.3, 26.7, 28.9, 59.8, 67.6, 78.0, 90.4, 99.2,

123.6, 131.3, 210.7.



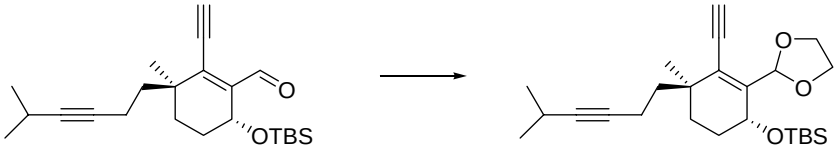
2.69 7.5 : 2.5 **2.82**

(3R*,6R*)-2-Ethynyl-6-hydroxy-3-methyl-3-(5-methylhex-3-ynyl)cyclohex-1-enecarbaldehyde (2.82). To a solution of diol **2.69** (0.30 g, 1.15 mmol) in 1.2 mL of CH_2Cl_2 at 0 ˚C was added tetramethylpiperdinyloxy free radical (TEMPO) (18 mg, 0.12 mmol) and then bis(acetoxy)iodobenzene (BIAB) (0.41 g, 1.27 mmol). The reaction flask was then allowed to warm to ambient temperature and after an additional 2 h TEMPO (10 mg, 0.06 mmol) was added. The reaction was left overnight and then was diluted with CH_2Cl_2 and a sat. aqueous $Na_2S_2O_3$ solution. The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 several times. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 20% EtOAc / hexanes to afford aldehyde **2.82** (206 mg, 69% yield) the diastereomeric ratio was not determined at this point; but diastereomerically enhanced material was obtained by ^{1}H NMR analysis of one fraction from silica gel column. R_f = 0.68 (50% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12 (d, *J* = 6.8 Hz, 6H), 1.26 (s, 3H), 1.60-2.02 (m, 6H), 2.04-2.28 (m, 2H), 2.50 (tsept, *J* = 3.1 Hz, *J* = 6.8 Hz, 1H), 3.45 (d, *J* = 2.0 Hz, 1H), 3.64 (s, 1H), 4.59 (t, *J* = 5.1 Hz, 1H), 10.17 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 20.5, 23.3 (2), 26.6, 26.7, 28.8, 38.8, 39.6, 61.8, 63.8, 78.6, 86.5, 90.7, 144.4, 149.0, 195.5; IR (neat) 3264, 2966, 2086, 1671 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 258 ([M]$^+$, 3), 243 (100), 91 (98): HRMS calcd for $C_{17}H_{22}O_2$: 258. 1620 [M]$^+$; found: 258.1612 [M]$^+$.



2.82 **2.140**

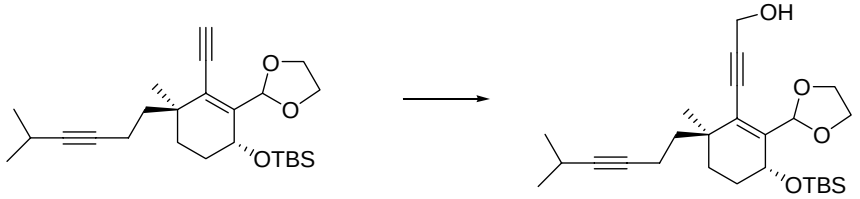
(3R*,6R*)-6-(tert-Butyldimethylsilyloxy)-2-ethynyl-3-methyl-3-(5-methylhex-3-ynyl)cyclohex-1-enecarbaldehyde (2.140). To a solution of alcohol **2.82** (0.28 g, 1.1 mmol) in 4 mL of CH_2Cl_2 at 0 °C was added 2,6-lutidene (0.25 mL, 2.1 mmol) and then TBSOTf (0.37 mL, 1.6 mmol). After 10 min complete consumption of starting material was observed on TLC and the reaction was quenched by addition of a sat. aqueous $NaHCO_3$ solution. The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 several times. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 5% EtOAc / hexanes to afford the aldehyde **2.140** (327 mg, 82% yield) as a 3 : 1 diastereomeric ratio as determined by ^{13}C NMR. R_f = 0.58 (20% EtOAc / hexanes); IR (neat) 2931, 2856, 1681 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 372 ($[M]^+$, 1.5), 315 (70), 91 (100): HRMS calcd for $C_{23}H_{36}O_2Si$: 372.2485 $[M]^+$; found: 372.2494 $[M]^+$.



2.140 **2.141**

((1R*,4R*)-2-(1,3-Dioxolan-2-yl)-3-ethynyl-4-methyl-4-(5-methylhex-3-ynyl)cyclohex-2-enyloxy)(tert-butyl)dimethylsilane(2.141). To a solution of aldehyde **2.140** (0.33 g, 0.88 mmol) in 11 mL of benzene was added ethylene glycol (0.55 mg, 9.0 mmol) and PPTS (0.04 g, 0.18 mmol). The reaction flask was then brought to reflux for 24 h after which time the mixture was cooled to ambient temperature and then concentrated under reduced pressure. The resulting

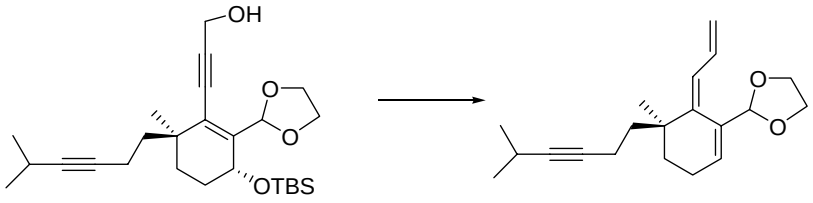
residue was diluted with ether. The organic solution was washed with a sat. aqueous $NaHCO_3$ solution and brine. The combined aqueous layers were then extracted with ether several times. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 3% EtOAc / hexanes to afford acetal **2.141** (128 mg, 35% yield) as a 3 : 1 diastereomeric ratio as determined by ^1H NMR. R_f = 0.48 (20% EtOAc / hexanes); ^1H NMR (300 MHz, $CDCl_3$): δ 0.06 (bs, 6H), 0.88 (s, 9H), 1.12 (d, *J* = 6.8 Hz, 6H), 1.16 (s, 3H), 1.48-1.85 (m, 6H), 1.86-2.23 (m, 2H), 2.50 (tsept, *J* = 2.2 Hz, *J* = 6.8 Hz, 1H), 3.25 (s, 1H), 3.80-4.15 (m, 4H), 4.37 (t, *J* = 2.8 Hz, 1), 5.78 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ -4.6, -4.5, 14.3, 18.1, 20.5, 23.4 (2), 25.9 (3), 26.7, 27.4, 28.6, 37.5, 38.2, 61.9, 64.9, 65.0, 79.4, 79.6, 85.2, 85.8, 102.9, 133.0, 142.0; IR (neat) 2930, 1463 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 416 ($[M]^+$, 0.1), 343 (9), 75 (100): HRMS calcd for $C_{25}H_{40}O_3Si$: 416.2747 $[M]^+$; found: 416.2740 $[M]^+$.



2.141 **2.83** 7.5 : 2.5

3-((3R*,6R*)-3-(tert-Butyldimethylsilyloxy)-2-(1,3-dioxolan-2-yl)-6-methyl-6-(5-methylhex-3-ynyl)cyclohex-1-enyl)prop-2-yn-1-ol (2.83). To a solution of alkyne **2.141** (0.13 g, 0.31 mmol) in 3 mL of THF at -78 °C was added *n*-butyllithium (0.29 mL of a 1.6 M hexanes solution, 0.46 mmol) dropwise. After 30 min at -78 °C paraformaldehyde (0.05 g, 1.5 mmol) was added in one portion. The reaction mixture was allowed to slowly warm to ambient temperature overnight and then was quenched by the addition of a sat. aqueous NH_4Cl solution. The mixture was diluted with some H_2O and extracted with ether several times. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was

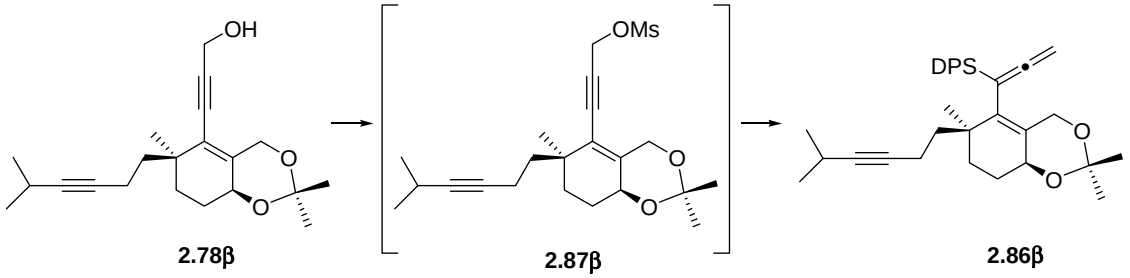
purified by silica gel chromatography to afford alcohol **2.83** (120 mg, 88% yield) as a 4 : 1 diastereomeric ratio as determined by ^{1}H NMR. R_f = 0.14 (20% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.04 (s, 3H), 0.05 (s, 3H), 0.86 (s, 9H), 1.12 (d, *J* = 7.1 Hz, 6H), 1.13 (s, 3H), 1.50-1.80 (m, 6H), 2.00-2.20 (m, 3H), 2.41-2.53 (m, 1H), 3.81-4.11 (m, 4H), 4.32-4.38 (m, 1H), 4.42 (d, *J* = 6.0 Hz, 2H), 5.74 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ -4.6, -4.5, 14.2, 18.0, 20.4, 23.3 (2), 25.8 (3), 26.8, 27.4, 28.6, 37.6, 38.2, 51.6, 61.8, 64.8, 65.0, 79.4, 81.7, 85.9, 95.2, 103.0, 133.0, 140.6; IR (neat) 3423, 2931 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 446 ([M]$^+$, 0.4), 75 (100): HRMS calcd for $C_{26}H_{42}O_4Si$: 446.2852 [M]$^+$; found: 446.2851 [M]$^+$.



2.83 7.5 : 2.5 **2.85**

(Z)-2-(6-Allylidene-5-methyl-5-(5-methylhex-3-ynyl)cyclohex-1-enyl)-1,3-dioxolane (2.85). To a solution of triphenylphosphine (0.04 g, 0.15 mmol) in 1 mL of THF at -15 ˚C was added diethylazodicarboxylate (DEAD) (24 μL, 0.15 mmol). After 5 min a solution of alcohol **2.83** (0.05 g, 0.12 mmol) in 0.3 mL of THF was added and then after 10 min a solution of 2-nitrobenzenesulfonohydrazide (34 mg, 0.16 mmol) in 0.3 mL of THF was added to the mixture. The reaction flask was kept at ˉ15-ˉ10 ˚C for 45 min and then allowed to warm to ambient temperature and after 24 h the reaction was diluted with pentanes. The organic layer was washed four times with H_2O and then the organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 3-5% EtOAc / hexanes to afford triene **2.85** (5 mg, 14% yield). R_f = 0.17 (20% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.11 (d, *J* = 6.8 Hz, 6H), 1.13 (s, 3H), 1.45 (ddd. *J* = 5.7 Hz, *J* = 10.9 Hz, *J* = 13.4 Hz, 1H), 1.55-1.62 (m, 2H), 1.74 (ddd, *J* = 5.5 Hz, *J* =

11.1, *J* = 13.5 Hz, 1H), 2.02 (m, 3H), 2.15-2.40 (m, 2H), 2.50 (tsep, *J* = 2.5 Hz, *J* = 6.8 Hz, 1H), 3.68-4.00 (m, 2H), 4.01-4.13 (m, 2H), 5.12 (dd, *J* = 2.0 Hz, *J* = 10.1 Hz, 1H), 5.22 (dd, *J* = 2.0 Hz, *J* = 16.5 Hz, 1H), 5.46 (s, 1H), 5.95 (d, *J* = 11.2 Hz, 1H), 6.38 (t, *J* = 3.6 Hz, 1H), 6.94 (td, *J* = 10.1 Hz, *J* = 16.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3, 20.5, 23.1, 23.4 (2), 35.4, 36.7, 38.3, 64.7, 65.0, 79.8, 85.6, 102.5, 118.0, 124.0, 132.0, 133.3, 134.6, 141.1; IR (neat) 2964, 2924 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 300 ($[M]^+$, 2), 257 (30), 73 (100): HRMS calcd for $C_{20}H_{28}O_2$: 300.2089 $[M]^+$; found: 300.2091 $[M]^+$.

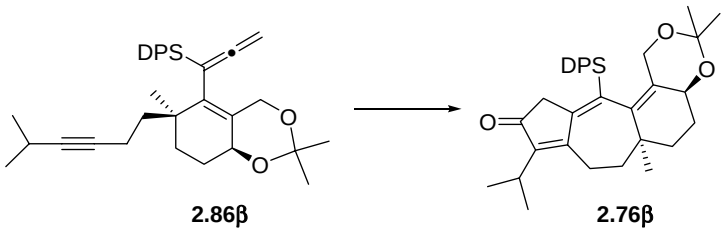


2.78β **2.87β** **2.86β**

Dimethyl(phenyl)(1-((6R*,8aS*)-2,2,6-trimethyl-6-(5-methylhex-3-ynyl)-6,7,8,8a-tetrahydro-4H-benzo[d][1,3]dioxin-5-yl)propa-1,2-dienyl)silane (2.86β). To a solution of alcohol **2.78β** (0.74 g, 2.24 mmol) in 11 mL of CH_2Cl_2 was added TEA (0.44 mL, 3.1 mmol) and the solution was cooled to ˉ50 ˚C. Then methanesulfonyl chloride (0.21 mL, 2.7 mmol) was added and after 30 min at ˉ50 ˚C the reaction was diluted with pentanes at ˉ50 ˚C. The suspension was then filtered through a sintered glass funnel of medium porosity packed with celite and the resulting filtrate was washed with a sat. aqueous $NaHCO_3$ solution and brine. The organic layer were dried over $MgSO_4$, filtered, and concentrated under reduced pressure and the residue (840 mg of propargyl mesylate **2.87β**, 92% crude yield) was used immediately without further purification.

To a suspension of lithium foil cut with into 2x2 mm pieces (0.141 g, 20.2 mmol, washed with hexanes (3x) and dried with a stream of N_2 introduced with a needle) in 16 mL of THF at 0 ˚C

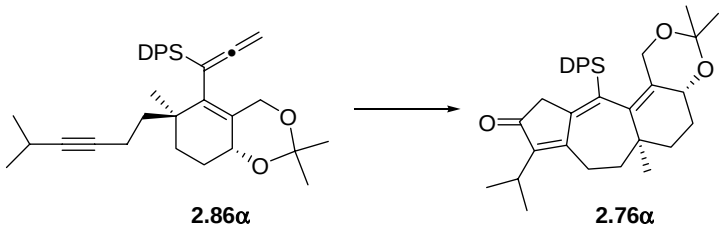
was added dimethylphenylsilyl chloride (0.81 mL, 4.8 mmol) dropwise. The mixture was stirred vigorously and allowed to warm to ambient temperature. After 12-18 h, the dark red solution was cooled to 0 ˚C and added dropwise, with a Teflon cannula, to a suspension of unpurified CuCN (0.22 g, 2.4 mmol) in 24 mL THF at -10 ˚C, and the mixture was stirred at 0 ˚C for 30 min. (The reaction must remain dark red at all times! If it turns purple, start over.) The red mixture was then cooled to -90 ˚C and a solution of mesylate **2.87** (0.84 g, 2.0 mmol) in 7 mL of THF at -78 ˚C was added dropwise with a Teflon cannula. After 1 h the reaction was quenched by the addition of AcOH and was left at -90 ˚C until mixture turned black in color and then was warmed to ambient temperature. Once at ambient temperature, H_2O and a sat. aqueous $NaHCO_3$ solution were added and the organic layer separated. The aqueous layer was then extracted with ether several times. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 2-5% EtOAc / hexanes to afford allene **2.86β** (790 mg, 78%) as a colorless oil. R_f = 0.8 (20% EtOAc / hexanes); ^{1}H NMR (500 MHz, C_6D_6, 60 ˚C): δ 0.46 (s, 3H), 0.47 (s, 3H), 0.84 (s, 3H), 1.09 (d, *J* = 7.0 Hz, 6H), 1.39 (s, 3H), 1.41 (s, 3H), 1.62-1.76 (m, 5H), 1.82 (ddd, *J* = 6.5 Hz, *J* = 9.0 Hz, *J* = 14.0 Hz, 1H), 1.95-2.10 (m, 2H), 2.44 (tsept, *J* = 2.0 Hz, *J* = 7.0 Hz, 1H), 4.20 (A of an ABq, *J* = 11.5 Hz, 1H), 4.24 (A of an ABq, d, *J* = 0.5 Hz, *J* = 15.0 Hz, 1H), 4.26 (B of an ABq, *J* = 12.0 Hz, 1H), 4.32 (t, *J* = 8.5 Hz, 1H), 4.41 (B of an ABq, d, *J* = 1.0 Hz, *J* = 14.5 Hz, 1H), 7.16-7.25 (m, 3H), 7.60-7.62 (m, 2H); ^{13}C NMR (75 MHz, C_6D_6, 60 ˚C): δ -1.8 (2), 14.6, 21.0, 22.5, 23.6 (2), 26.3, 26.9, 27.0, 32.2, 38.6, 39.3, 62.3, 67.6, 68.0, 80.2, 86.0, 93.2, 99.2, 128.3 (2), 129.4, 130.9, 134.4 (2), 134.7, 138.7, 210.4; IR (neat) 2964, 2870, 1922 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 448 ($[M]^+$, 0.3), 135 (100): HRMS calcd for $C_{29}H_{40}O_2Si$: 448.2798; found: 448.2780.



2.86β **2.76β**

4-(Dimethylsilyl)-6-hydroxy-5-hydroxymethyl-1-isopropyl-8a-methyl-6,7,8,8a,9,10-hexahydro-3H-benzo[*f*]azulen-2-oneacetonide (2.76β). To a flame dried 16 x 150 mm test tube was added allene **2.86β** (0.30 g, 0.66 mmol) and the tests tube was sealed with a 19/22 rubber septum. Next, benzene (≈0.5 mL) was added and subsequently removed under vacuum (3x), by insertion an 18 gauge needle connected to a vac-line (7 mm Hg) into the septum. Once the benzene was evaporated the test tube was charged with CO(g). The residue was then dilute with 7 mL of toluene and the test tube was evacuated under vacuum and charged with CO three times. Then, $[Rh(CO)_2Cl]_2$ (0.02 g, 0.07 mmol) was added at ambient temperature and the system was evacuated and charged with CO once more. The test tube was placed in a 53 ˚C oil bath under a CO balloon and after 24 h the test tube was removed from the oil bath and cooled to room temperature. The solution was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 5-10% EtOAc / hexanes to afford [5-7-6]-carbocyce **2.76β** (200 mg, 64%). R_f = 0.4 (20% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.41 (s, 3H) 0.46 (s, 3H), 1.12 (s, 3H), 1.17 (d, *J* = 5.8 Hz, 3H), 1.19 (d, *J* = 5.9 Hz, 3H), 1.37 (s, 3H), 1.46 (s, 3H), 1.49-1.78 (m, 5H), 1.87-1.97 (m, 2H), 2.58 (t, *J* = 13.1 Hz, 1H), 2.72-2.86 (m, 3H), 4.25 (A of an ABq, d, *J* = 15.0 Hz, *J* = 1.0 Hz, 1H), 4.31 (B of an ABq, d, *J* = 15.0 Hz, *J* = 1.0 Hz, 1H), 4.41 (t, *J* = 6.4 Hz, 1H), 7.32-7.40 (m, 3H), 7.53-7.60 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ =1.0, -0.9, 20.3, 20.6, 22.0, 24.8, 25.3, 26.8, 28.8, 30.6, 37.3, 39.6, 40.6, 40.8, 62.2, 66.8, 99.2, 128.0 (2), 129.2, 129.8, 134.3 (2), 137.1, 137.2, 138.1, 146.8, 147.5, 168.2, 204.5; IR (neat) 2957, 2870, 1694 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 476 ($[M]^+$, 0.1),

418 (90), 135 (100): HRMS calcd for $C_{30}H_{40}O_3Si$: 476.2747 $[M]^+$; found: 476.2732 $[M]^+$.

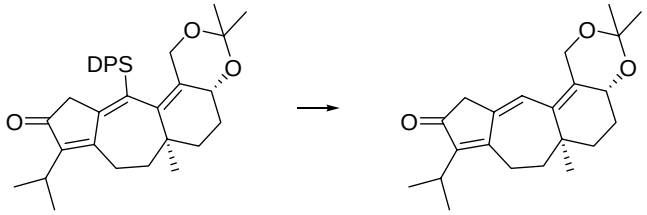


2.86α **2.76α**

[5-7-6]-Carbocycle (2.76α). To a flame dried 13 x 100 mm test tube was added allene **2.86α** (36 mg, 0.08 mmol) and the tests tube was sealed with a #17 SUBA·SEAL® rubber septum. Next, benzene (≈0.1 mL) was added and subsequently removed under vacuum (3x), by insertion an 18 gauge needle connected to a vac-line (7 mm Hg) into the septum. Once the benzene was evaporated the test tube was charged with CO(g). The residue was then dilute with 1 mL of toluene and the test tube was evacuated under vacuum and charged with CO three times. Then, $[Rh(CO)_2Cl]_2$ (4.4 mg, 11 μmol) was added at ambient temperature and the system was evacuated and charged with CO once more. The test tube was placed in a 65 ˚C oil bath under a CO balloon and after 1.5 h the test tube was removed from the oil bath and cooled to room temperature. The solution was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 5-10% EtOAc / hexanes to afford [5-7-6]-carbocyce **2.76α** (21 mg, 55%). R_f = 0.4 (20% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) (**2.76α** matches Dong Gao's spectra): δ 0.46 (s, 3H), 0.58 (s, 3H), 1.16 (d, *J* = 7.0 Hz, 3H), 1.17 (s, 3H), 1.18 (d, *J* = 7.0 Hz, 3H), 1.42 (s, 3H), 1.50 (s, 3H), 1.52-1.62 (m, 5H), 1.85-1.98 (m, 1H), 2.20 (dd, *J* = 11.6 Hz, *J* = 15.7 Hz, 1H), 2.64-2.90 (m, 4H), 4.17 (A of an ABq, *J* = 14.8 Hz, 1H), 4.32 (B of an ABq, *J* = 14.8 Hz, 1H), 4.35-4.46 (m, 1H), 7.32-7.41 (m, 3H), 7.55-7.62 (m, 2H).

General modified procedure for cyclocarbonylation. To a flame dried test tube was added allene and the tests tube was sealed with a rubber septum. Next, benzene (≈0.1 mL) was added and subsequently removed under vacuum (3x), by insertion an 18 gauge needle connected to a

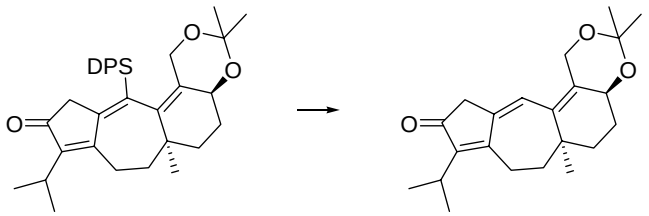
vac-line (7 mm Hg) into the septum. Once the benzene was evaporated the test tube was charged with CO(g).To a flame dried test tube was added allene which was then azeotroped under vacuum with benzene and charged with CO (3x). The residue was then dilute with toluene (0.1 M) and the test tube was evacuated under vacuum and charged with CO three times. Then, 10 mol% of $[Rh(CO)_2Cl]_2$ was added at ambient temperature and the system was evacuated and charged with CO once more. The test tube was placed in a 65 ˚C oil bath under a CO balloon and monitored by TLC. Once all starting material was consumed as observed by TLC the test tube was removed from the oil bath and cooled to ambient temperature. Approximately 5-10 equivalents (based on Rh(I)-catalyst) of triphenylphosphine polymer bond cross-linked with 1% DVB ≈ 1.6 mmol/g resin was added that the mixture was left to stir for 1-2 h after which time the mixture was filtered thru a pad of celite; rinsing with pentanes. The solution was concentrated under reduced pressure. The residue was purified by silica gel chromatography.



2.76α **2.58α**

[5-7-6]-Carbocycle (2.58α). To a solution of enone **2.76α** (0.26 g, 0.54 mmol) in 6.7 mL of THF at room temperature was added 2.2 mL of DMSO and then benzyltrimethyl ammonium fluoride (BTAF) (0.14 g, 0.81 mmol).[136] The mixture was left at room temperature for 75 min after which time complete consumption of starting material was observed by TLC. The reaction was quenched by the addition of a sat. aqueous NH_4Cl solution and ether. The organic layer was removed and the aqueous layer was extracted with ether several times. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 7% EtOAc / hexanes to afford enone

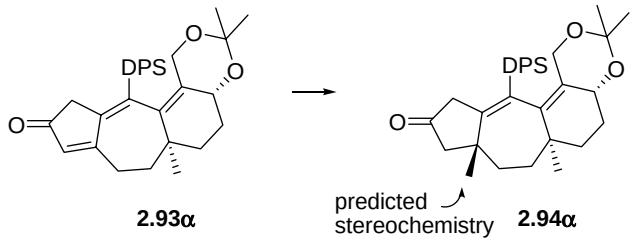
2.58α (150 mg, 81% yield). R_f = 0.47 (30% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.11 (s, 3H), 1.20 (d, *J* = 7.0 Hz, 6H), 1.39 (s, 3H), 1.44 (s, 3H), 1.44-1.80 (m, 5H), 1.82-1.94 (m, 1H), 2.55-2.90 (m, 3H), 2.97 (app s, 2H), 4.32-4.49 (m, 1H), 4.38 (A of an ABq, *J* = 15.5 Hz, 1H), 4.53 (B of an ABq, d, *J* = 2.1 Hz, *J* = 15.5 Hz, 1H), 5.96 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.9 (2), 23.8, 24.2, 24.9, 25.0, 25.2, 25.4, 36.7, 37.8, 38.5, 42.7, 60.5, 67.3, 99.6, 120.0, 134.8, 135.9, 1316.0, 149.1, 165.0, 203.9; IR (neat) 2936, 1691 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 342 ($[M]^+$, 5), 284 (100): HRMS calcd for $C_{22}H_{30}O_3$: 342.2195 $[M]^+$; found:342.2189 $[M]^+$.



2.76β **2.58β**

[5-7-6]-Carbocycle (2.58β). To a solution of enone **2.76β** (0.16 g, 0.33 mmol) in 4 mL of THF at ambient temperature was added 1.4 mL of DMSO and then benzyltrimethyl ammonium fluoride (BTAF) (0.08 g, 0.49 mmol).[136] The mixture was left at ambient temperature for 1 h after which time complete consumption of starting material was observed by TLC. The reaction was quenched by the addition of a sat. aqueous NH_4Cl solution and ether. The organic layer was removed and the aqueous layer was extracted with ether several times. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 7% EtOAc / hexanes to afford enone **2.58β** (81 mg, 73% yield). R_f = 0.41 (20% EtOAc / hexanes); ^{1}H NMR (500 MHz, C_6D_6) : δ 0.82 (s, 3H), 1.12-1.21 (m, 2H), 1.28 (d, *J* = 7.1 Hz, 3H), 1.30 (d, *J* = 7.1 Hz, 3H), 1.40 (s, 3H), 1.44 (s, 3H), 1.58-1.74 (m, 2H), 1.75-1.85 (m, 1H), 2.20 (ddd, *J* = 4.4 Hz, *J* = 8.4 Hz, *J* = 16.3 Hz,

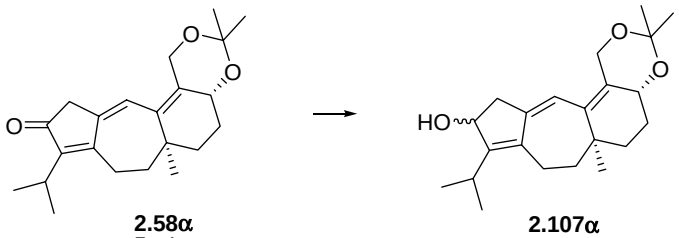
1H), 2.25-2.37 (m, 1H), 2.37 (ddd, *J* = 4.2 Hz, *J* = 8.4 Hz, *J* = 16.4 Hz, 1H), 2.65-2.76 (m, 3H), 4.26 (s, 2H), 4.29-4.40 (m, 1H), 5.49 (s, 1H); ^{13}C NMR (125 MHz, C_6D_6): δ 20.4, 20.5, 24.0, 25.4, 25.5, 25.8, 26.1, 27.9, 37.7, 38.6, 38.8, 41.7, 61.0, 67.1, 99.8, 120.3, 134.8, 136.4, 137.6, 149.0, 164.0, 202.5; IR (neat) 2935, 2869, 1691 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 342 ([M]$^+$, 0.1), 284 (100).



2.93α **2.94α**

Ketone (2.94α). To a solution of enone **2.93α** (5.0 mg, 11 μL) in 0.6 mL of THF was added $Ni(acac)_2$ (1.1 μmol) and the solution was degassed by bubbling N_2 throughout solution for 5 min. The reaction flask was then cooled to 0 ˚C and trimethylaluminum (1 drop from a 25μL gas-tight Hamilton syringe, 2.2 μL, 0.02 mmol) was added. After 25 min complete consumption of the starting material was observed by TLC and the reaction flask was diluted with hexanes and a sat. aqueous NH_4Cl solution. The organic layer was removed and the aqueous layer was extracted with hexanes several times. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 5% EtOAc / hexanes to afford ketone **2.94α** (3.7 mg, 75% yield). R_f = 0.3 (20% EtOAc / hexanes). ^{1}H NMR 600 MHz, $CDCl_3$): δ 0.44 (s, 3H), 0.45 (s, 3H), 1.09 (s, 3H), 1.15 (s, 3H), 1.40 (s, 3H), 1.42-1.44 (m, 1H), 1.53 (s, 3H), 1.52-1.65 (m, 6H), 1.85-1.92 (m, 1H), 2.03 (A of an ABq, *J* = 17.4 Hz, 1H), 2.48 (B of an ABq, *J* = 17.4 Hz, 1H), 2.90 (A of an ABq, d, *J* = 22.7 Hz, *J* = 1.9 Hz, 1H), 3.03 (B of an ABq, *J* = 22.7 Hz, 1H), 4.24 (A of an ABq, d, *J* = 14.4 Hz, *J* = 1.2 Hz, 1H), 4.28 (B of an ABq, d, *J* = 14.4 Hz, *J* = 1.2 Hz, 1H), 4.41-4.48 (m, 1H), 7.34-7.38 (m, 3H), 7.55-7.58 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ -1.1, -0.7,

21.1, 25.9, 27.0, 27.7, 28.8, 32.0, 33.7, 36.1, 40.1, 42.2, 48.1, 54.0, 61.4, 68.1, 98.7, 128.1 (2), 129.1, 129.6, 130.8, 134.2 (2), 137.3, 137.4, 155.2, 215.1; IR (neat) 2934, 2859, 1741 cm^{-1}; MS (API-ES) *m/e* (relative intensity) 511 ($[M+Na]^+$, 40); HRMS calcd for $C_{30}H_{36}O_4SiNa$: 511.2281 $[M+Na]^+$; found: 511.2260 $[M+Na]^+$.

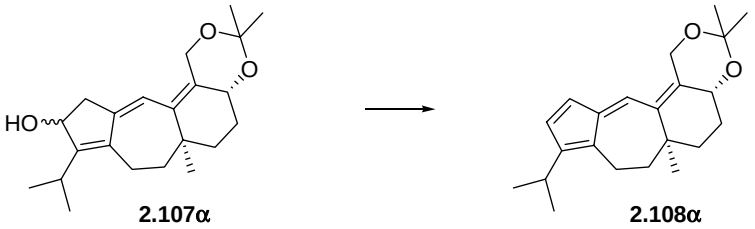


2.58α
5 : 1

2.107α
5 : 1 @ C6
1 : 1 @ C16

Allylic Alcohol (2.107α). To a solution of enone **2.58α** (0.09 g, 0.25 mmol) in 1.6 mL of THF at -78 ˚C was added DIBAL-H (0.38 mL of a 1.0 M hexanes solution, 0.38 mmol) dropwise. After 30 min at -78 ˚C complete consumption of the starting material was observed by TLC and the reaction was quenched by the addition of H_2O and 10% HCl. The aqueous layer was then extracted with ether several times. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 10% EtOAc / hexanes to afford alcohol **2.107α** (64 mg, 73% yield) in a 1 : 1 mixture at C16 and a 5 : 1 ratio at C6 as determined by ^1H NMR. R_f = 0.5 (30% EtOAc / hexanes); ^1H NMR (300 MHz, $CDCl_3$) of diastereomeric mixture: δ 1.07 (d, *J* = 10.1 Hz, 3H), 1.10-1.23 (m, 6H), 1.38 (s, 3H), 1.40-1.70 (m, 8H), 1.78-1.90 (m, 1H), 2.30-2.51 (m, 4H), 2.75 (sept, *J* = 6.5 Hz, 1H), 2.90 (dt, *J* = 6.0 Hz, *J* = 16.6 Hz, 1H), 4.33 (A of an ABq, d, *J* = 15.2 Hz, *J* = 3.1 Hz, 1H), 4.25-4.40 (m, 1H), 4.50 (B of an ABq, *J* = 15.3 Hz, 1H), 4.79 (t, *J* = 5.7 Hz, 1H), 5.60 (s, 0.5H), 5.63 (s, 0.5H); ^{13}C NMR (75 MHz, $CDCl_3$) of diastereomeric mixture (double the number of carbons): δ19.9, 20.2, 22.4, 22.5, 22.9 (2), 23.8, 23.9, 24.3, 24.4, 25.0, 25.1, 25.3 (2), 27.3, 27.5, 37.0 (2), 37.9, 38.2, 39.1, 39.3, 43.0 (2), 60.7 (2), 67.4 (2), 73.7, 73.9,

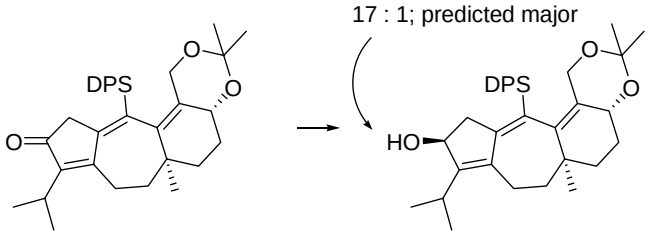
99.3, 99.4, 113.5, 114.1, 130.9, 131.1, 135.3, 135.4, 140.0, 140.1, 143.8, 144.2, 153.4, 153.5; IR (neat) 3452, 2937, 2870, 1748 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 360 ($[M-H_2O]^+$, 10), 268 (75), 121 (100); HRMS calcd for $C_{22}H_{32}O_3$: 326.2246 $[M-H_2O]^+$; found: 326.2236 $[M-H_2O]^+$.



2.107α **2.108α**

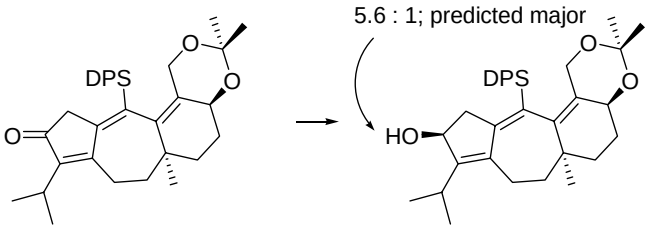
Fulvene (2.108α). A solution of alcohol **2.107α** (8.5 mg, 0.03 mmol) in 0.2 mL of CH_2Cl_2 at ambient temperature was degassed by bubbling N_2 throughout the solution for 5 min, and then Et_2Zn (0.05 mL of a 1.0 M hexanes solution, 0.05 mmol) followed by I_2CH_2 (4.0 μL, 0.05 mmol) were added. After 20 min at ambient temperature the reaction mixture was quenched by the addition of a pH 7.38 phosphate buffer and diluted with CH_2Cl_2. The organic layer was removed and the aqueous layer was extract with CH_2Cl_2 several times. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 5% EtOAc / hexanes to afford fulvene **2.108α** as a by-product. R_f = 0.8 (20% EtOAc / hexanes); ^1H NMR (300 MHz, $CDCl_3$) with trace impurity: δ 1.11 (d, *J* = 6.8 Hz, 6H), 1.15 (s, 3H), 1.42 (s, 3H), 1.45 (s, 3H), 1.62-1.82 (m, 4H), 1.83-1.96 (m, 2H), 2.63 (dd, *J* = 4.3 Hz, *J* = 6.2 Hz, 2H), 2.81 (qn, *J* = 6.8 Hz, 1H), 4.45 (t, *J* = 8.1 Hz, 1H), 4.53 (A of an ABq, d, *J* = 1.3 Hz, *J* = 16.1 Hz, 1H), 4.68 (B of an ABq, d, *J* = 2.4 Hz, *J* = 16.0 Hz, 1H), 6.01 (d, *J* = 5.4 Hz, 1H), 6.40 (d, *J* = 5.4 Hz, 1H), 6.46 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.8 (2), 22.5, 22.6, 24.2, 24.5, 24.7, 26.5, 37.2, 37.6, 39.9, 60.7, 67.6, 99.0, 125.5, 126.4, 128.8, 129.8, 136.0, 142.0, 146.0, 151.0; IR (neat) 2931, 2870 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 326 ($[M]^+$, 15), 268 (100); HRMS calcd for $C_{22}H_{30}O_2$: 326.2246 $[M]^+$;

found: 326.2249 $[M]^+$.



2.76α **2.109α**

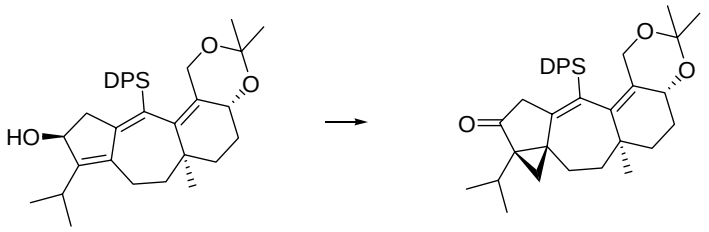
Allylic Alcohol (2.109α). To a solution of enone **2.76α** (0.13 g, 0.27 mmol) in 2 mL of THF at -78 °C was added L-selectride (0.54 mL of a 1.0 M solution in THF solution, 0.54 mmol) dropwise. After 1 h at -78 °C complete consumption of the starting material was observed by TLC and the reaction flask was placed in an ice bath and 0.04 mL of H_2O was added followed sequentially by 0.2 mL of 3 M NaOH and 0.2 mL of 30% H_2O_2. The reaction flask was then allowed to warm to ambient temperature and stirred for 30 min. The organic layer was removed and the aqueous layer was extract with EtOAc several times. The combined organics were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford alcohol **2.109α** (108 mg, 84% yield) as a 17 : 1 diastereomeric ratio based upon isolation of material. R_f = 0.4 (20% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.39 (s, 3H), 0.52 (s, 3H), 1.13 (s, 3H), 1.16 (d, *J* = 6.8 Hz, 6H), 1.39 (s, 3H), 1.47 (s, 3H), 1.47-1.70 (m, 5H), 1.80-2.00 (m, 3H), 2.05 (dd, *J* = 3.8 Hz, *J* = 16.1 Hz, 1H), 2.25-2.37 (m, 1H), 2.62-2.82 (m, 1H), 2.90 (dd, *J* = 6.5 Hz, *J* = 16.1 Hz, 1H), 4.16 (A of an ABq, *J* = 15.1 Hz, 1H), 4.30 (B of an ABq, d, *J* = 1.1 Hz, *J* = 14.6 Hz, 1H), 4.33-4.40 (m, 1H), 4.78 (bs, 1H), 7.31-7.42 (m, 3H), 7.58-7.68 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ -0.7, -0.6, 19.8, 21.4, 22.2, 23.1, 25.7, 26.6, 27.1, 27.3, 34.7, 40.0, 41.4, 42.5, 61.5, 68.1, 75.7, 99.0, 124.4, 127.8 (2), 128.6, 131.0, 134.4 (2), 137.7, 138.8, 143.8, 152.1, 156.0.



2.76β **2.109β**

Allylic Alcohol (2.109β). To a solution of enone **2.76β** (0.09 g, 0.18 mmol) in 1.4 mL of THF at -78 °C was added L-selectride (0.36 mL of a 1.0 M solution in THF solution, 0.36 mmol) dropwise. After 1 h at -78 °C complete consumption of starting material was observed by TLC and the reaction flask was placed in an ice bath and 0.1 mL of H_2O was added. The reaction flask was then allowed to warm to ambient temperature and stirred for 30 min. The organic layer was removed and the aqueous layer was extract with EtOAc several times. The combined organics were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford alcohol **2.109β** (67 mg of one diastereomer with R_f = 0.5 and 12 mg of diastereomer with R_f = 0.3 (20% EtOAc / hexanes), 92% yield) to give a 5.6 : 1 separable diastereomeric ratio based upon isolation of material. R_f = 0.5 (20% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) contains trace amount of **2.109α**: δ 0.45 (s, 3H), 0.47 (s, 3H), 1.11 (d, *J* = 6.9 Hz, 3H), 1.17 (s, 3H), 1.19 (d, *J* = 7.1 Hz, 3H), 1.40-1.54 (m, 9H), 1.59-1.78 (m, 2H), 1.89-2.00 (m, 2H), 2.17 (dd, *J* = 2.9 Hz, *J* = 16.5 Hz, 1H), 2.34 (dd, *J* = 4.1 Hz, *J* = 14.6 Hz, 1H), 2.45-2.57 (m, 1H), 2.64 (quin, *J* = 7.0 Hz, 1H), 2.78 (dd, *J* = 6.7 Hz, *J* = 16.4 Hz, 1H), 4.48 (A of an ABq, *J* = 13.1 Hz, 1H), 4.45-4.60 (m, 2H), 4.65 (B of an ABq, *J* = 14.0, 1H), 7.22-7.30 (m, 3H), 7.69-7.75 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) contains trace amount of **2.109β** minor diastereomer at C16 *denotes minor isomer where resolved: δ -0.7, -0.3, 19.8, 22.6, 23.6, 24.8, 25.0*, 26.0, 27.2, 27.4, 30.7, 37.8, 40.9*, 41.1 (2), 42.2, 62.7, 67.2, 75.2, 77.7*, 99.2, 122.3*, 125.6, 128.3 (2), 129.1, 129.4*, 130.3, 131.1*, 134.7*, 134.8 (2), 138.4, 139.1,

141.7*, 143.7, 148.2*, 152.7, 156.7.

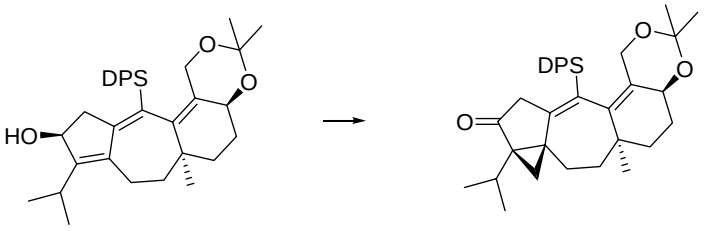


2.109α **2.113α**

Cyclopropyl Ketone (2.113α). A solution of alcohol **2.109α** (0.02 g, 0.05 mmol) in 0.5 mL of CH_2Cl_2 at ambient temperature was degassed by bubbling N_2 throughout the solution for 5 min, and then Et_2Zn (0.09 mL of a 1.0 M hexanes solution, 0.09 mmol) followed by I_2CH_2 (8.0 μL, 92 μmol) were added. Both reagents were added with a gas-tight Hamilton syringe. After 35 min at ambient temperature the reaction mixture was quenched by the addition of a pH 7.38 phosphate buffer and diluted with ether. The organic layer was removed and the aqueous layer was extract with ether several times. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure and the residue (quantitative yield of cyclopropyl alcohol **2.111α**) was used immediately without further purification; however, for characterization purposes **2.111α** was purified once by silica gel chromatography. R_f = 0.35 (20% EtOAc / hexanes); ^{1}H NMR (300 MHz, C_6D_6): δ -0.07 (d, *J* = 4.1 Hz, 1H), 0.47 (s, 3H), 0.65 (s, 3H), 0.90 (d, *J* = 6.2 Hz, 3H), 1.03 (d, *J* = 3.0 Hz, 1H), 1.12-1.18 (m, 3H), 1.19 (s, 3H), 1.22-1.38 (m, 3H), 1.39 (s, 3H), 1.46 (s, 3H), 1.48-1.58 (m, 3H), 1.74 (ddt, *J* = 3.3 Hz, *J* = 7.2 Hz, *J* = 10.0 Hz, 2H), 1.83-2.00 (m, 3H), 2.46 (dd, *J* = 7.6 Hz, *J* = 15.0 Hz, 1H), 4.18-4.28 (m, 2H), 4.27 (A of an ABq, *J* = 14.3 Hz, 1H), 4.65 (B of an ABq, *J* = 14.8 Hz, 1H), 7.16-7.28 (m, 3H), 7.68-7.74 (m, 2H); ^{13}C NMR (75 MHz, C_6D_6): δ -0.2, 0.4, 19.8, 21.2, 21.4, 22.4, 26.2, 26.4, 28.2, 28.8, 30.2, 30.9, 36.3, 38.6, 40.7, 42.1, 44.7, 45.7, 62.1, 67.6, 72.0, 99.1, 126.7, 129.0 (2), 131.1, 134.7 (2), 138.1, 140.0, 157.3. IR (neat) 3448, 2955, 2866, 1590 cm^{-1}; MS (API-ES) *m/e* (relative

intensity) 434 ([M-C$(CH_3)_2$O]$^+$, 25), 135 (100); HRMS calcd for $C_{31}H_{44}O_3SiNa$: 515.2957 [M+Na]$^+$; found: 515.2964 [M+Na]$^+$.

To a solution of crude alcohol **2.111α** (≈0.05 mmol) in 0.32 mL of CH_2Cl_2 was added 4 Å molecular sieves (28 mg) and PDC (0.03 g, 0.08 mmol). After 3 h complete consumption of the starting material was observed on TLC and the reaction was diluted with CH_2Cl_2, filtered through a pad of celite; rinsing with CH_2Cl_2, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford ketone **2.113α** (16 mg, 71% yield). R_f = 0.57 (20% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.36 (s, 3H), 0.57 (s, 3H), 0.87 (d, *J* = 4.2 Hz, 1H), 1.03 (d, *J* = 6.9 Hz, 3H), 1.22 (d, *J* = 7.1 Hz, 3H), 1.23 (s, 3H), 1.24-1.28 (m, 3H), 1.40 (s, 3H), 1.51 (s, 3H), 1.59-1.70 (m, 4H), 1.81 (ddd, *J* = 2.2 Hz, *J* = 6.0 Hz, *J* = 13.6 Hz, 1H), 1.92-2.05 (m, 1H), 2.16 (bt, *J* = 13.4 Hz, 1H), 2.45 (app s, 2H), 4.20 (A of an ABq, *J* = 14.2 Hz, 1H), 4.30-4.36 (m, 1H), 4.40 (B of an ABq, *J* = 14.2 Hz, 1H), 7.28-7.38 (m, 3H), 7.48-7.60 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ -1.0, -0.5, 19.5, 19.7, 21.6, 25.4, 26.2, 27.4, 28.4, 28.6, 29.1, 29.7, 35.8, 40.2, 41.2, 41.8, 49.3, 52.4, 61.9, 66.9, 99.3, 127.9 (2), 128.8, 131.2, 134.2 (2), 137.4, 138.8, 150.9, 209.8; IR (neat) 2926, 2851, 1727 cm^{-1}; MS (API-ES) *m/e* (relative intensity) 513 ([M+Na]$^+$, 100); HRMS calcd for $C_{31}H_{42}O_3SiNa$: 513.2801 [M+Na]$^+$; found: 513.2802 [M+Na]$^+$.



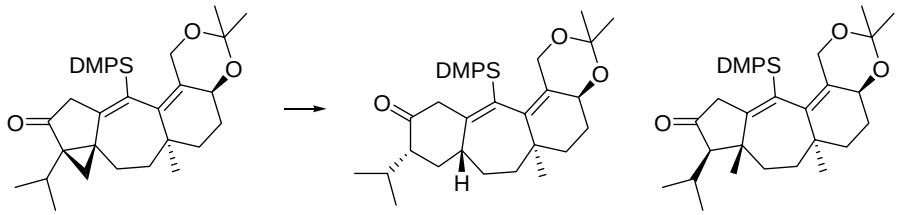
2.109β **2.113β**

Cyclopropyl Ketone (2.113β). A solution of alcohol **2.109β** (0.03 g, 0.07 mmol) in 1 mL of CH_2Cl_2 at ambient temperature was degassed by bubbling N_2 throughout the solution for 5 min,

and then Et_2Zn (0.13 mL of a 1.0 M hexanes solution, 0.13 mmol) followed by I_2CH_2 (11.0 μL, 0.13 mmol) were added. Both reagents were using a gas-tight Hamilton syringe. After 40 min at ambient temperature the reaction mixture was quenched by the addition of a pH 7.38 phosphate buffer and diluted with ether. The organic layer was removed and the aqueous layer was extract with ether several times. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure and the residue **2.111β** was used immediately without further purification. R_f = 0.36 (20% EtOAc / hexanes).

To a solution of crude alcohol **2.111β** (≈0.07 mmol) in 0.4 mL of CH_2Cl_2 was added 4 Å molecular sieves (37 mg) and PDC (0.04 g, 0.10 mmol). After 3 h complete consumption of starting material was observed on TLC and the reaction was diluted with CH_2Cl_2, filtered through a pad of celite; rinsing with CH_2Cl_2 and concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford ketone **2.113β** (14 mg, 44% yield). R_f = 0.57 (20% EtOAc / hexanes); ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.29 (s, 3H), 0.45 (s, 3H), 0.93 (d, *J* = 4.4 Hz, 1H), 1.06 (d, *J* = 6.8 Hz, 3H), 1.15 (dt, *J* = 3.6 Hz, 14.0 Hz, 1H), 1.20 (dd, *J* = 1.6 Hz, *J* = 4.4 Hz, 1H), 1.23 (s, 3H), 1.25 (d, *J* = 7.0 Hz, 3H),1.32-1.36 (m, 1H), 1.38 (s, 3H), 1.42 (s, 3H), 1.46 (dt, *J* = 3.4 Hz, *J* = 11.1 Hz, 1H), 1.59-1.66 (m, 2H), 1.73-1.82 (m, 1H), 1.90 (dddd, *J* = 3.2 Hz, *J* = 3.4 Hz, *J* = 6.3 Hz, *J* = 13.0 Hz, 1H), 2.00 (dt, *J* = 3.7 Hz, *J* = 13.6 Hz, 1H), 2.47 (tdd, *J* = 1.4 Hz, *J* = 3.6 Hz, *J* = 13.4 Hz, 1H), 2.50 (app s, 2H), 4.26 (A of an ABq, d, *J* = 14.4 Hz *J* = 1.2 Hz, 1H), 4.34 (B of an ABq, d, *J* = 14.4 Hz *J* = 1.5 Hz, 1H), 4.36-4.40 (m, 1H), 7.30-7.35 (m, 3H), 7.47-7.53 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ -1.0, -0.7, 19.4, 19.6, 21.9, 25.3, 26.7, 27.2, 27.4, 28.9, 31.5, 37.8, 40.7, 41.06, 41.1, 48.1, 51.4, 62.3, 67.7, 99.0, 127.8 (2), 128.9, 129.0, 130.5, 134.1 (2), 136.6, 138.4, 151.1, 210.2; IR (neat) 2936, 2851, 1726 cm^{-1}; MS (API-ES) *m/e* (relative intensity) 513 ($[M+Na]^+$, 100); HRMS calcd for $C_{31}H_{42}O_3SiNa$: 513.2801

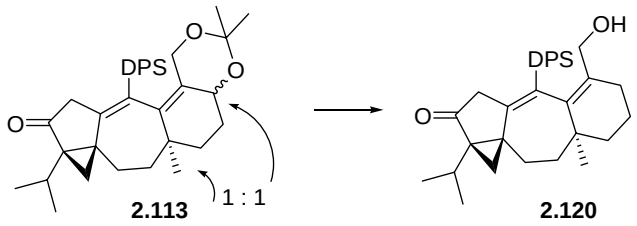
$[M+Na]^+$; found: 513.2806 $[M+Na]^+$.



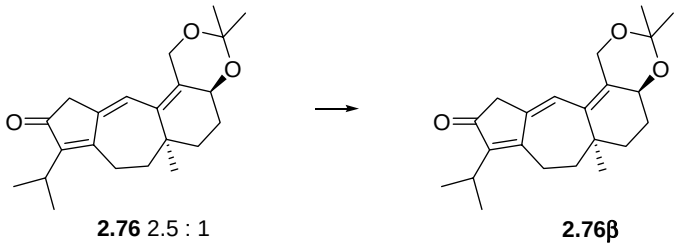
2.113β **2.114β** **2.97β**

Cyclohexanone (2.114β) and Cyclopentanone (2.97β). A solution of enone **2.113β** (9.00 mg, 0.02 mmol), MeOH (3.00 μL, 0.07 mmol), and HMPA (0.06 mL, 0.37 mmol) in 1 mL of THF was degassed by bubbling N_2 throughout the solution for 5 min and cooled to -78 ˚C. Then a solution of SmI_2 (0.5 - 1.0 mL of a 0.1 M THF solution)[prepared by charging a flame dried round bottom equipped with a new stir bar with samarium powder (0.07 g, 0.47 mmol). The flask was then flame dried again and cooled using a flow of N_2. Then 4.2 mL of THF followed by CH_2I_2 (34.0 μL, 0.42 mmol) were added and the reaction flask was left at ambient temperature and stirred vigorously for 3 h, upon which time the solution should turn a cobalt blue] was added to the reaction mixture until the solution remained a deep blue color. After 3 h at -78 ˚C the color of the reaction mixture was yellow and the reaction was quenched by the addition of a sat. aqueous NH_4Cl solution and ether. The organic layer was removed and the aqueous layer was extracted with ether several times. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 5% EtOAc / hexanes to afford ketones **2.114β** and **2.97β** (3 mg, 34% yield) in a 1 : 1 mixture as determined by ^1H NMR; however, pure **2.114β** and **2.97β** was obtained by HPLC for spectroscopic purposes (Varian Pursuit C8 5μ column, 250mm x 100mm, 50 μL, 23 ˚C, H_2O / acetonitrile = 30-0%, flow rate = 3 mL/min. R_f = 0.7 (20% EtOAc / hexanes); ^1H NMR (600 MHz, $CDCl_3$) **2.114β**: δ 0.25 (s, 3H), 0.49 (s, 3H), 0.84 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.6 Hz,

3H), 1.10 (s, 3H), 1.38 (s, 3H), 1.45 (s, 3H), 1.30-1.35 (m, 2H), 1.56-1.63 (m, 4H), 1.64-1.73 (m, 2H), 1.97 (ddd, *J* = 3.6 Hz, *J* = 6.1 Hz, *J* = 13.0 Hz, 1H), 2.18-2.27 (m, 2H), 2.44-2.50 (m, 1H), 2.86 (A of an ABq, *J* = 14.3 Hz, 1H), 3.33 (B of an ABq, *J* = 14.3 Hz, 1H), 4.17-4.24 (m, 2H), 4.34 (t, *J* = 6.3 Hz, 1H), 7.31-7.35 (m, 3H), 7.51-7.55 (m, 2H).; ^{13}C NMR (150 MHz, $CDCl_3$): δ 0.2, 1.2, 18.4, 20.9, 23.1, 25.2, 26.2, 26.6, 29.2, 29.4, 33.8, 36.5, 39.6, 40.2, 49.6, 54.1, 56.0, 62.7, 66.3, 99.3, 127.8 (2), 128.9, 129.1, 131.6, 134.3 (2), 137.9, 138.6 149.6, 209.0; IR (neat) 2931, 2856, 1712 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 477 ($[M-CH_3]^+$, 0.5), 356 (30), 135 (100); HRMS calcd for $C_{31}H_{44}O_3Si$: 477.2825 $[M-CH_3]^+$; found: 477.2810 $[M-CH_3]^+$. ^{1}H NMR (500 MHz, $CDCl_3$) **2.114α**: δ 0.34 (s, 3H), 0.59 (s, 3H), 0.81 (d, *J* = 6.6 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H), 1.12-1.22 (m, 1H), 1.38 (s, 3H), 1.40-1.47 (m, 4H), 1.49 (s, 3H), 1.55 (s, 3H), 1.52-1.70 (m, 3H), 1.80-1.87 (m, 1H), 1.90-1.99 (m, 1H), 2.15-2.25 (m, 2H), 2.46-2.57 (m, 1H), 2.83 (A of an ABq, *J* = 14.2 Hz, 1H), 3.30 (B of an ABq, *J* = 14.2 Hz, 1H), 4.10 (A of an ABq, *J* = 14.7 Hz, 1H), 4.26 (B of an ABq, *J* = 14.7 Hz, 1H), 4.32-4.29 (m, 1H), 7.30-7.39 (m, 3H), 7.53-7.60 (m, 2H). ^{1}H NMR (500 MHz, $CDCl_3$) **2.97β** (5-membered with trace silyl impurity): δ 0.26 (s, 3H), 0.48 (s, 3H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 1.13 (s, 3H), 1.32 (s, 3H), 1.38 (s, 3H), 1.43 (s, 3H), 1.50-1.70 (m, 5H), 1.76 (t, *J* = 13.1 Hz, 1H), 1.80-1.91 (m, 1H), 2.15-2.30 (m, 2H), 2.32-2.41 (m, 1H), 3.14 (A of an ABq, *J* = 15.6 Hz, 1H), 3.23 (B of an ABq, *J* = 15.6 Hz, 1H), 4.23 (s, 2H), 4.33 (t, *J* = 7.8 Hz, 1H), 7.31-7.38 (m, 3H), 7.47-7.52 (m, 2H); IR (neat) 2934, 1714 cm^{-1};MS (API-ES) *m/e* (relative intensity) 493 ($[M+H]^+$, 75), 413 (100); HRMS calcd for $C_{31}H_{45}O_3Si$: 493.3138 $[M+H]^+$; found: 493.3149 $[M+H]^+$.

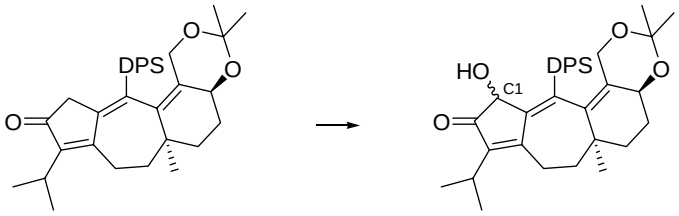


Alcohol (2.120). To a solution of ketone **2.113** (1.5 mg, 3.0 μmol), as a mixture of diastereomers, in 0.5 mL of EtOH was added Pd/C (≈2.0 mg). The flask was evacuated under vacuum, by insertion an 18 gauge needle connected to a vac-line (7 mm Hg) into the septum, and charged with H_2 three times. The reaction was then left under H_2 at ambient temperature for 24 h; after which time the reaction was filtered through a pad of celite; rinsing with EtOH and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 5%-10% EtOAc / hexanes to afford alcohol **2.120** (≈ 0.5 mg) and ketone **2.113β** (≈1.2 mg, quantitative yield). R_f = of **2.120** 0.4 (20% EtOAc / hexanes); ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.33 (s, 3H), 0.42 (s, 3H), 0.92 (d, *J* = 4.5 Hz, 1H), 1.03 (d, *J* = 6.9 Hz, 3H), 1.12 (dt, *J* = 3.4 Hz, *J* = 13.8 Hz, 1H), 1.21-1.26 (m, 2H), 1.24 (3, 3H), 1.26 (d, *J* = 6.9 Hz, 3H), 1.35 (quartet, *J* = 7.0 Hz, 2H), 1.41 (dt, *J* = 3.4 Hz, *J* = 13.8 Hz, 1H), 1.52 (dt, *J* = 3.8 Hz, *J* = 12.8 Hz, 1H), 1.68-1.85 (m, 2H), 1.90 (dt, *J* = 3.6 Hz, *J* = 13.4 Hz, 1H), 2.05 (ddd, *J* = 7.4 Hz, *J* = 10.6 Hz, *J* = 18.0 Hz, 1H), 2.18 (dd, *J* = 5.2 Hz, *J* = 17.5 Hz, 1H), 2.30-2.40 (m, 1H), 2.58 (app s, 2H), 3.96 (A of an ABq, *J* = 12.0 Hz, 1H), 4.16 (B of an ABq, *J* = 12.0 Hz, 1H), 7.30-7.35 (m, 3H), 7.52-7.56 (m, 2H).



[5-7-6]-Carbocycle (2.76) (purification). To a solution of enone **2.76**, as a 2.5 : 1

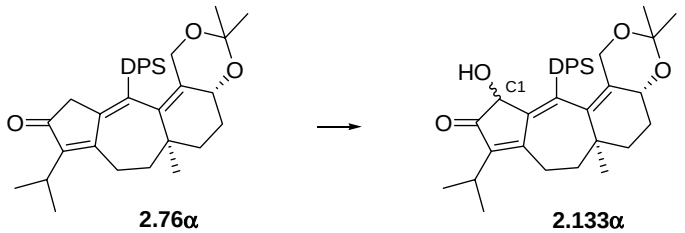
diastereomeric ratio, (7.2 mg, 0.02 mmol) in 0.3 mL of EtOH was added Pd/C (7.0 mg, 1 equivalent by weight). The flask was evacuated under vacuum, by insertion an 18 gauge needle connected to a vac-line (7 mm Hg) into the septum, and charged with H_2 three times. The reaction was then left under H_2 at ambient temperature for 1.5 h; after which time the reaction was filtered through a pad of celite; rinsing with EtOH and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 5%-10% EtOAc / hexanes to afford enone **2.76β** (3.5 mg, 68% yield).



2.76β **2.133β**
1 : 1 @ C1

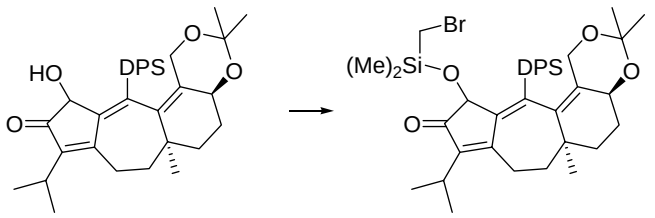
α-Hydroxy Enone (2.133β). To a solution of enone **2.76β** (0.07 g, 0.15 mmol) in 7 mL of CH_2Cl_2 at ambient temperature was added TEA (0.20 mL, 1.5 mmol) and then freshly distilled TESOTf (0.17 mL, 0.76 mmol) dropwise. After 10 min the reaction mixture was quenched by addition of 35 mL of EtOAc and 7 mL of a sat. aqueous $NaHCO_3$ solution. The organic layer was removed and dried with Na_2SO_2, filtered, and concentrated under reduced pressure and the residue was used immediately without further purification. The crude material was azeotroped with benzene 3 times and then taken up in 15 mL of CH_2Cl_2. The reaction mixture was cooled to -78 ˚C and DMDO (2.7 mL of a 0.8 M acetone solution, 0.22 mmol) was added dropwise. After 10 min at -78 ˚C complete consumption of the starting material was observed by TLC and DMS (0.16 mL, 2.2 mmol) was added. After 5 min at -78 ˚C the reaction mixture was allowed to warm to ambient temperature and then concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 10% EtOAc / hexanes to afford alcohol **2.133β** (48

mg, 67% yield) in a 1 : 1 mixture at C_1 as determined by ^{1}H NMR; however, careful silica gel chromatography afforded pure material. R_f = 0.22 (20% EtOAc / hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) **f2.133β**: δ 0.39 (s, 3H), 0.66 (s, 3H), 1.17 (d, *J* = 7.0 Hz, 3H), 1.19 (d, *J* = 7.9 Hz, 3H), 1.20 (s, 3H), 1.35 (s, 3H), 1.37 (s, 3H), 1.60-1.65 (m, 4H), 1.86-2.00 (m, 2H), 2.39 (d *J* = 3.0 Hz, 1H), 2.63 (t, *J* = 12.8 Hz, 1H), 2.78 (qn, *J* = 7.0 Hz, 1H), 2.82 (dd, *J* = 3.8 Hz, *J* = 14.5 Hz, 1H), 4.02 (d, *J* = 2.8 Hz, 1H), 4.04 (A of an ABq, *J* = 14.2 Hz, 1H), 4.20 (B of an ABq, *J* = 13.9 Hz, 1H), 4.29 (t, *J* = 8.2 Hz, 1H), 7.32-7.40 (m, 3H), 7.64-7.68 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ -1.0, 0.7, 19.9, 20.9, 21.4, 25.0, 25.5, 27.2, 27.5, 30.9, 37.8, 39.6, 40.6, 61.9, 66.9, 70.4, 99.1, 109.6, 127.7 (2), 129.2, 129.4, 134.6 (2), 138.1, 141.9, 144.0, 148.0, 169.8, 205.5.



α-Hydroxy Enone (2.133α). To a solution of enone **2.76α** (0.04 g, 0.08 mmol) in 4 mL of CH_2Cl_2 at ambient temperature was added TEA (0.1 mL, 0.8 mmol) and then freshly distilled TESOTf (0.09 mL, 0.38 mmol) dropwise. After 10 min the reaction mixture was quenched by addition of EtOAc and of a sat. aqueous $NaHCO_3$ solution. The organic layer was removed and dried with Na_2SO_2, filtered, and concentrated under reduced pressure and the residue was used immediately without further purification. The crude material was azeotroped with benzene 3 times and then taken up in 8 mL of CH_2Cl_2. The reaction mixture was cooled to -78 ˚C and DMDO (0.81 mL of a 0.14 M acetone solution, 0.11 mmol) was added dropwise. After 10 min at -78 ˚C complete consumption of the starting material was observed by TLC and DMS (0.08 mL, 1.1 mmol) was added. After 5 min at -78 ˚C the reaction mixture was allowed to warm to

ambient temperature and then concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 10% EtOAc / hexanes to afford alcohol **2.133α** (48 mg, 67% yield) in a 1 : 1 mixture at C1 as determined by ^{1}H NMR. R_f = 0.2 (20% EtOAc / hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) 1 : 1 diastereomeric mixture as determined by ^{1}H NMR: δ 0.45 (s, 3H), 0.54 (s, 3H), 0.64 (s, 3H), 0.76 (s, 3H), 1.08 (s, 3H), 1.14 (d, *J* = 7.0 Hz, 6H), 1.17 (d, *J* = 7.1 Hz, 3H), 1.18 (d, *J* = 7.1 Hz, 3H), 1.23 (s, 3H), 1.42 (s, 3H), 1.44 (s, 3H), 1.51 (s, 3H), 1.52 (s, 3H), 1.55-1.70 (m, 10H), 1.85-2.00 (m, 2H), 2.16 (d, *J* = 3.0 Hz, 1H), 2.16-2.24 (m, 2H), 2.44 (d, *J* = 3.9 Hz, 1H), 2.64-2.76 (m, 4H), 3.91 (A of an ABq, *J* = 3.1 Hz, 1H), 3.94 (B of an ABq, *J* = 2.9 Hz, 1H), 4.14 (A of an ABq, *J* = 10.6 Hz, 1H), 4.16 (B of an ABq, *J* = 10.4 Hz, 1H), 4.34-4.44 (m, 4H), 7.34-7.40 (m, 6H), 7.70-7.78 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$): δ -0.4, 0.1, 0.3, 1.2, 19.8, 20.1, 20.4, 20.5, 21.3, 21.7, 23.4, 24.0, 25.0, 25.2, 25.6, 25.7, 26.8, 27.0, 27.5, 27.7, 29.7, 34.3, 34.5, 39.1, 40.9, 41.4, 61.0, 61.2, 68.2, 68.3, 69.7, 72.7, 98.9, 99.2, 127.7 (2), 128.0 (2), 128.9, 129.4, 131.1, 132.5, 134.5 (4), 136.6, 137.4, 137.8, 138.0, 138.8, 140.8, 144.0, 144.7, 149.3, 150.0, 167.7, 171.0, 204.4, 204.8; IR (neat) 3400, 2924, 2853, 1686 cm^{-1}.

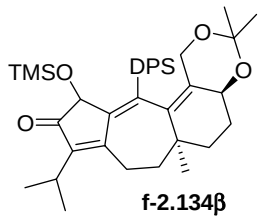


f-2.133β
faster diastereomer

f-2.125β
faster diastereomer

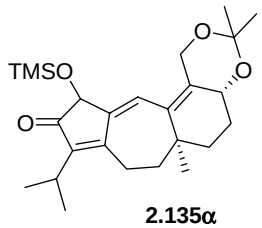
Bromo-silane (f-2.125β). To a solution of alcohol **f-2.133β** (0.01 g, 0.02 mmol) in 0.2 mL of CH_2Cl_2 at ambient temperature was added DMAP (3.0 mg, 0.02 mmol). The reaction mixture was cooled to 0 ˚C and TEA (8.5 μL, 61 μmol) and then $BrCH_2Si(Me)_2Cl$ (6.0 μL, 41 μmol) were added. Both reagents were added via a Hamilton gas-tight syringe. After 5 min complete consumption of the starting material was observed by TLC and the reaction was quenched by the

addition of a sat. aqueous $NaHCO_3$ solution and EtOAc. The organic layer was removed and the aqueous layer was extracted with EtOAc several times. The combined organic layers were dried with Na_2SO_2, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 5% EtOAc / hexanes to afford bromo silane **f-2.125β** (9.5 mg, 74% yield). R_f = 0.7 (20% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.15 (s, 3H), 0.16 (s, 3H), 0.34 (s, 3H), 0.59 (s, 3H), 1.17 (d, *J* = 3.1 Hz, 3H), 1.18 (s, 3H), 1.20 (d, *J* = 3.4 Hz, 3H), 1.33 (s, 3H), 1.34 (s, 3H), 1.58-1.72 (m, 4H), 1.85-1.95 (m, 2H), 2.40 (A of an ABq, *J* = 12.7 Hz, 1H), 2.47 (B of an ABq, *J* = 12.7 Hz, 1H), 2.61 (dt, *J* = 2.0 Hz, J = 14.3 Hz, 1H), 2.72-2.85 (m, 2H), 4.00 (A of an ABq, *J* = 14.2 Hz, 1H), 4.15 (B of an ABq, d, *J* = 1.0 Hz, *J* = 14.2 Hz, 1H), 4.22-4.30 (m, 1H), 4.35 (s, 1H), 7.32-7.40 (m, 3H), 7.56-7.62 (m, 2H); IR (neat) 2957, 1701 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 584 ([M-(C(CH$_3$)$_2$O)]$^+$, 7), 432 (7), 135 (100); HRMS calcd for $C_{33}H_{47}BrO_4Si_2$: 584.1778 [M-(C(CH$_3$)$_2$O)]$^+$; found: 584.1710 [M-(C(CH$_3$)$_2$O)]$^+$.



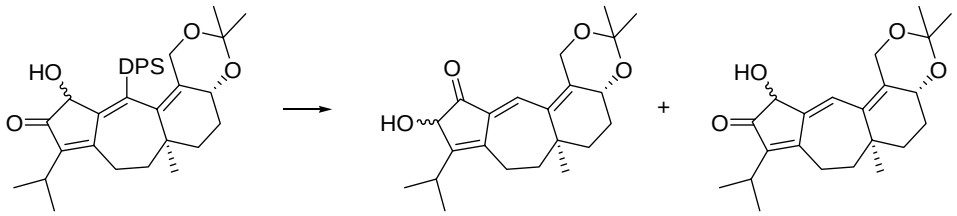
f-2.134β

(Table 16, Entry 6, f-2.134β). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.04 (s, 9H), 0.34 (s, 3H), 0.61 (s, 3H), 1.18 (d, *J* = 3.7 Hz, 3H), 1.19 (s, 3H), 1.20 (d, *J* = 3.8 Hz, 3H), 1.25-1.40 (m, 4H), 1.32 (s, 6H), 1.75-1.90 (m, 2H), 2.60 (t, *J* = 13.0 Hz, 1H), 2.73-2.90 (m, 2H), 3.93 (A of an ABq, *J* = 14.1 Hz, 1H), 4.13 (B of an ABq, *J* = 14.1 Hz, 1H), 4.19-4.26 (m, 1H), 4.32 (s, 1H), 7.30.7.38 (m, 3H), 7.56-7.63 (m, 2H); MS (GC/MS) *m/e* (relative intensity) 549 ([M-CH$_3$]$^+$, 2.5), 135 (100).



2.135α

(Table 16, Entry 3, 2.135α). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.25 (s, 9H), 1.15 (s, 3H), 1.20 (d, *J* = 3.8 Hz, 3H), 1.21 (d, *J* = 3.8 Hz, 3H), 1.42 (s, 3H), 1.46 (s, 3H), 1.68-1.77 (m, 5H), 1.90-1.96 (m, 2H), 2.70-2.76 (m, 2H), 2.80 (sept, *J* = 7.0 Hz, 1H), 4.35-4.45 (m, 1H), 4.43 (A of an ABq, *J* = 14.8 Hz, 1H) 4.58 (B of an ABq, d, *J* = 2.0 Hz, *J* = 15.8 Hz, 1H), 6.10 (s, 1H); MS (GC/MS) *m/e* (relative intensity) 372 ([M-(C(CH$_3$)$_2$O)]$^+$, 23), 69 (100); HRMS calcd for $C_{25}H_{38}O_4Si$: 372.2121 [M-(C(CH$_3$)$_2$O)]$^+$; found: 372.2113 [M-(C(CH$_3$)$_2$O)]$^+$.



f2.133α **2.137α** **2.136α**

α-Hydroxyl Enones (2.136α & 2.137α). To a solution of α-hydroxy enone **f-2.133α** (0.012 g, 0.024 mmol) in THF at 0 ˚C was added TBAF (0.05 mL of a 1.0 M THF solution, 0.05 mmol). After 5 min at 0 ˚C complete consumption of the starting material was observed by TLC and the reaction was quenched by the addition of a sat. aqueous NH_4Cl solution and ether. The organic layer was removed and the aqueous layer was extracted with ether several times. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 10-20% EtOAc / hexanes to afford enone **2.136α** (4 mg) and **2.137α** (4mg) for a combined yield of 91% yield. R_f of **2.136α** = 0.1 (20% EtOAc / hexanes); R_f of **2.137α** = 0.3 (20% EtOAc / hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) **2.137α** (as a 1 : 1 mixture of diastereomers at C16): δ 1.03 (s, 3H), 1.30 (d, *J* = 4.4 Hz,

3H), 1.33 (d, J = 4.4 Hz, 3H), 1.41 (s, 3H), 1.45 (s, 3H), 1.65-1.80 (m, 5H), 1.90-2.00 (m, 1H), 2.20 (dd, J = 8.5 Hz, J = 17.4 Hz, 1H), 2.42 (dd, J = 1.0 Hz, J = 17.2 Hz, 1H), 2.88 (sept, J = 7.1 Hz, 1H), 4.30-4.45 (m, 1H), 4.60 (A of an ABq, J = 16.0 Hz, 1H), 4.76 (B of an ABq, J = 16.3 Hz, 1H), 5.78 (s, 1H), 5.89 (d, J = 2.6 Hz, 1/2H), 5.91 (d, J = 2.4 Hz, 1/2H), 6.92 (s, 1H); IR (neat) 3422, 2923, 1717 cm^{-1}. **2.136α** as a 1.3 : 1 diastereomeric mixture at C1; ^1H NMR (300 MHz, $CDCl_3$): δ 1.08 (s, 3H), 1.15 (s, 3H), 1.18-1.28 (m, 12H), 1.40 (s, 6H), 1.44 (s, 6H), 1.50-1.98 (m, 12H), 2.63-2.89 (m, 8H), 4.27-4.70 (m, 8H), 6.19 (s, 1H), 6.26 (s, 1H); IR (neat) 3426, 2936, 1684 cm^{-1}; MS (API-ES) *m/e* (relative intensity) 381 ($[M+Na]^+$, 100); HRMS calcd for $C_{22}H_{30}O_4Na$: 381.2042 $[M+Na]^+$; found: 381.2119 $[M+Na]^+$

APPENDIX A

CRYSTALLOGRAPHIC DATA TABLES

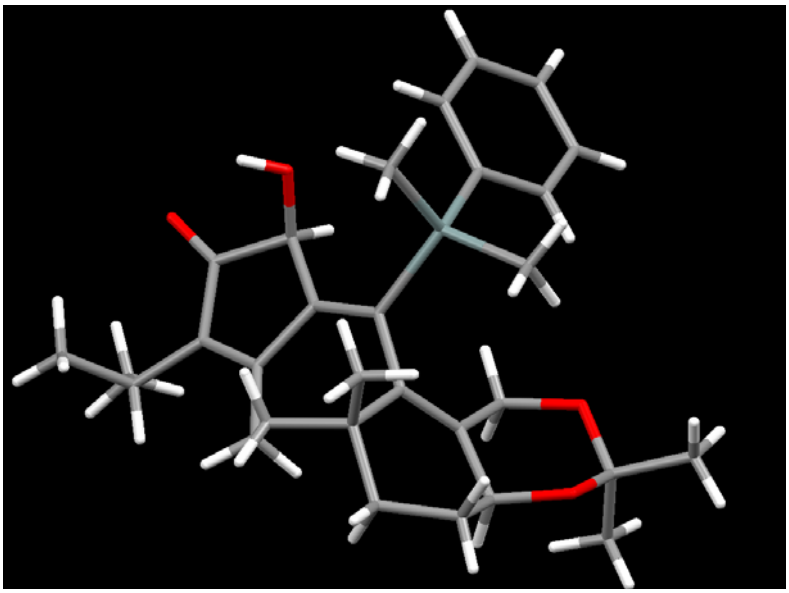


Figure 42. Crystal structure of 2.138α

Table 1. Crystal data and structure refinement for alcohol **2.138α**.

Identification code	jamie1	
Empirical formula	C30 H40 O4 Si	
Formula weight	492.71	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pbca	
Unit cell dimensions	a = 15.262(3) Å	a= 90°.
	b = 18.986(4) Å	b= 90°.

	c = 19.463(4) Å g = 90°.
Volume	5640(2) $Å^3$
Z	8
Density (calculated)	1.161 Mg/m^3
Absorption coefficient	0.115 mm^{-1}
F(000)	2128
Crystal size	0.17 x 0.08 x 0.08 mm^3
Theta range for data collection	2.01 to 23.00°.
Index ranges	-16<=h<=16, -20<=k<=20, -21<=l<=21
Reflections collected	35645
Independent reflections	3926 [R(int) = 0.3807]
Completeness to theta = 23.00°	100.0 %
Absorption correction	None
Max. and min. transmission	0.9909 and 0.9807
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3926 / 0 / 323
Goodness-of-fit on F^2	0.996
Final R indices [I>2sigma(I)]	R1 = 0.1138, wR2 = 0.2238
R indices (all data)	R1 = 0.2289, wR2 = 0.2719
Largest diff. peak and hole	0.324 and -0.374 $e.Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for **2.138α**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Si	7682(2)	10928(1)	4941(1)	40(1)
C(1)	7809(5)	9923(4)	4855(4)	35(2)
O(1)	7917(4)	10496(3)	3373(3)	65(2)
C(2)	8036(5)	9605(4)	4269(4)	32(2)
O(2)	8732(4)	9398(3)	2534(3)	55(2)
O(3)	8156(3)	9584(3)	7244(3)	46(2)
C(3)	8431(6)	9944(4)	3638(4)	40(2)
O(4)	9222(3)	10179(3)	6610(3)	43(2)
C(4)	8542(5)	9328(4)	3141(4)	41(2)
C(5)	8350(6)	8681(4)	3508(4)	47(2)
C(6)	8028(5)	8829(4)	4136(4)	38(2)
C(7)	7570(6)	8322(4)	4612(4)	52(2)
C(8)	6676(6)	8613(4)	4823(5)	56(3)
C(9)	6712(5)	9075(4)	5483(4)	40(2)
C(10)	6658(6)	8591(4)	6105(4)	49(2)
C(11)	6952(5)	8941(4)	6763(4)	49(2)
C(12)	7920(5)	9116(4)	6691(4)	39(2)
C(13)	9026(5)	9841(5)	7245(4)	43(2)
C(14)	9035(5)	9770(4)	6008(4)	42(2)
C(15)	8128(5)	9456(4)	6025(4)	33(2)
C(16)	7573(5)	9496(4)	5487(4)	32(2)
C(17)	8452(9)	7949(4)	3172(5)	73(3)
C(18)	9387(10)	7862(6)	2895(7)	134(6)
C(19)	7775(10)	7853(6)	2618(6)	115(5)
C(20)	5926(6)	9576(5)	5472(5)	70(3)
C(21)	9684(5)	9250(5)	7400(4)	56(3)
C(22)	9062(7)	10427(5)	7787(5)	76(3)
C(23)	7468(6)	11152(4)	5857(4)	61(3)
C(24)	6714(5)	11227(5)	4432(5)	60(3)
C(25)	9355(6)	11571(4)	5170(5)	51(2)

C(26)	10078(6)	11978(5)	5018(6)	68(3)
C(27)	10153(7)	12266(5)	4370(7)	73(3)
C(28)	9517(8)	12160(5)	3889(6)	66(3)
C(29)	8795(6)	11762(4)	4035(5)	51(2)
C(30)	8699(5)	11448(4)	4695(4)	37(2)

Table 3. Bond lengths [Å] and angles [°] for **2.138α**.

Si-C(23)	1.863(8)
Si-C(24)	1.866(8)
Si-C(30)	1.900(8)
Si-C(1)	1.925(8)
C(1)-C(2)	1.337(10)
C(1)-C(16)	1.515(10)
O(1)-C(3)	1.406(9)
O(1)-H(1A)	0.8400
C(2)-C(6)	1.495(10)
C(2)-C(3)	1.513(10)
O(2)-C(4)	1.225(8)
O(3)-C(13)	1.415(9)
O(3)-C(12)	1.442(9)
C(3)-C(4)	1.526(11)
C(3)-H(3)	1.0000
O(4)-C(13)	1.423(9)
O(4)-C(14)	1.435(9)
C(4)-C(5)	1.450(11)
C(5)-C(6)	1.348(10)
C(5)-C(17)	1.544(11)
C(6)-C(7)	1.507(10)
C(7)-C(8)	1.527(11)
C(7)-H(7A)	0.9900
C(7)-H(7B)	0.9900
C(8)-C(9)	1.558(11)
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(9)-C(10)	1.521(10)
C(9)-C(20)	1.530(11)
C(9)-C(16)	1.539(10)
C(10)-C(11)	1.512(10)
C(10)-H(10A)	0.9900
C(10)-H(10B)	0.9900
C(11)-C(12)	1.520(10)

C(11)-H(11A)	0.9900
C(11)-H(11B)	0.9900
C(12)-C(15)	1.484(10)
C(12)-H(12)	1.0000
C(13)-C(22)	1.534(11)
C(13)-C(21)	1.536(11)
C(14)-C(15)	1.508(11)
C(14)-H(14A)	0.9900
C(14)-H(14B)	0.9900
C(15)-C(16)	1.348(10)
C(17)-C(19)	1.505(14)
C(17)-C(18)	1.535(15)
C(17)-H(17)	1.0000
C(18)-H(18A)	0.9800
C(18)-H(18B)	0.9800
C(18)-H(18C)	0.9800
C(19)-H(19A)	0.9800
C(19)-H(19B)	0.9800
C(19)-H(19C)	0.9800
C(20)-H(20A)	0.9800
C(20)-H(20B)	0.9800
C(20)-H(20C)	0.9800
C(21)-H(21A)	0.9800
C(21)-H(21B)	0.9800
C(21)-H(21C)	0.9800
C(22)-H(22A)	0.9800
C(22)-H(22B)	0.9800
C(22)-H(22C)	0.9800
C(23)-H(23A)	0.9800
C(23)-H(23B)	0.9800
C(23)-H(23C)	0.9800
C(24)-H(24A)	0.9800
C(24)-H(24B)	0.9800
C(24)-H(24C)	0.9800
C(25)-C(26)	1.379(12)
C(25)-C(30)	1.383(11)

C(25)-H(25)	0.9500
C(26)-C(27)	1.380(13)
C(26)-H(26)	0.9500
C(27)-C(28)	1.364(13)
C(27)-H(27)	0.9500
C(28)-C(29)	1.366(12)
C(28)-H(28)	0.9500
C(29)-C(30)	1.424(11)
C(29)-H(29)	0.9500

C(23)-Si-C(24)	107.5(4)
C(23)-Si-C(30)	105.4(4)
C(24)-Si-C(30)	110.8(4)
C(23)-Si-C(1)	109.0(4)
C(24)-Si-C(1)	109.6(4)
C(30)-Si-C(1)	114.3(3)
C(2)-C(1)-C(16)	120.8(7)
C(2)-C(1)-Si	123.2(6)
C(16)-C(1)-Si	115.9(5)
C(3)-O(1)-H(1A)	109.5
C(1)-C(2)-C(6)	126.2(7)
C(1)-C(2)-C(3)	127.1(7)
C(6)-C(2)-C(3)	106.4(7)
C(13)-O(3)-C(12)	116.7(6)
O(1)-C(3)-C(2)	113.1(6)
O(1)-C(3)-C(4)	113.6(6)
C(2)-C(3)-C(4)	103.4(6)
O(1)-C(3)-H(3)	108.9
C(2)-C(3)-H(3)	108.9
C(4)-C(3)-H(3)	108.9
C(13)-O(4)-C(14)	115.0(6)
O(2)-C(4)-C(5)	127.9(8)
O(2)-C(4)-C(3)	123.6(7)
C(5)-C(4)-C(3)	108.4(7)
C(6)-C(5)-C(4)	110.1(7)
C(6)-C(5)-C(17)	127.4(7)

C(4)-C(5)-C(17)	122.3(7)
C(5)-C(6)-C(2)	111.0(7)
C(5)-C(6)-C(7)	126.4(7)
C(2)-C(6)-C(7)	121.8(7)
C(6)-C(7)-C(8)	110.4(7)
C(6)-C(7)-H(7A)	109.6
C(8)-C(7)-H(7A)	109.6
C(6)-C(7)-H(7B)	109.6
C(8)-C(7)-H(7B)	109.6
H(7A)-C(7)-H(7B)	108.1
C(7)-C(8)-C(9)	113.3(7)
C(7)-C(8)-H(8A)	108.9
C(9)-C(8)-H(8A)	108.9
C(7)-C(8)-H(8B)	108.9
C(9)-C(8)-H(8B)	108.9
H(8A)-C(8)-H(8B)	107.7
C(10)-C(9)-C(20)	110.2(7)
C(10)-C(9)-C(16)	110.9(6)
C(20)-C(9)-C(16)	110.3(7)
C(10)-C(9)-C(8)	108.3(7)
C(20)-C(9)-C(8)	108.1(7)
C(16)-C(9)-C(8)	109.0(6)
C(11)-C(10)-C(9)	113.1(7)
C(11)-C(10)-H(10A)	109.0
C(9)-C(10)-H(10A)	109.0
C(11)-C(10)-H(10B)	109.0
C(9)-C(10)-H(10B)	109.0
H(10A)-C(10)-H(10B)	107.8
C(10)-C(11)-C(12)	107.9(7)
C(10)-C(11)-H(11A)	110.1
C(12)-C(11)-H(11A)	110.1
C(10)-C(11)-H(11B)	110.1
C(12)-C(11)-H(11B)	110.1
H(11A)-C(11)-H(11B)	108.4
O(3)-C(12)-C(15)	109.2(6)
O(3)-C(12)-C(11)	108.0(6)

C(15)-C(12)-C(11)	112.6(7)
O(3)-C(12)-H(12)	109.0
C(15)-C(12)-H(12)	109.0
C(11)-C(12)-H(12)	109.0
O(3)-C(13)-O(4)	110.6(6)
O(3)-C(13)-C(22)	106.6(7)
O(4)-C(13)-C(22)	105.2(7)
O(3)-C(13)-C(21)	111.2(7)
O(4)-C(13)-C(21)	111.2(6)
C(22)-C(13)-C(21)	111.8(7)
O(4)-C(14)-C(15)	112.3(6)
O(4)-C(14)-H(14A)	109.1
C(15)-C(14)-H(14A)	109.1
O(4)-C(14)-H(14B)	109.1
C(15)-C(14)-H(14B)	109.1
H(14A)-C(14)-H(14B)	107.9
C(16)-C(15)-C(12)	124.7(7)
C(16)-C(15)-C(14)	122.5(7)
C(12)-C(15)-C(14)	112.8(7)
C(15)-C(16)-C(1)	120.7(7)
C(15)-C(16)-C(9)	120.7(7)
C(1)-C(16)-C(9)	118.5(6)
C(19)-C(17)-C(18)	111.9(10)
C(19)-C(17)-C(5)	110.1(9)
C(18)-C(17)-C(5)	109.8(9)
C(19)-C(17)-H(17)	108.3
C(18)-C(17)-H(17)	108.3
C(5)-C(17)-H(17)	108.3
C(17)-C(18)-H(18A)	109.5
C(17)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18B)	109.5
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H(18A)-C(18)-H(18C)	109.5
H(18B)-C(18)-H(18C)	109.5
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C(17)-C(19)-H(19B)	109.5

H(19A)-C(19)-H(19B)	109.5
C(17)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5
C(9)-C(20)-H(20A)	109.5
C(9)-C(20)-H(20B)	109.5
H(20A)-C(20)-H(20B)	109.5
C(9)-C(20)-H(20C)	109.5
H(20A)-C(20)-H(20C)	109.5
H(20B)-C(20)-H(20C)	109.5
C(13)-C(21)-H(21A)	109.5
C(13)-C(21)-H(21B)	109.5
H(21A)-C(21)-H(21B)	109.5
C(13)-C(21)-H(21C)	109.5
H(21A)-C(21)-H(21C)	109.5
H(21B)-C(21)-H(21C)	109.5
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H(22A)-C(22)-H(22B)	109.5
C(13)-C(22)-H(22C)	109.5
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H(22B)-C(22)-H(22C)	109.5
Si-C(23)-H(23A)	109.5
Si-C(23)-H(23B)	109.5
H(23A)-C(23)-H(23B)	109.5
Si-C(23)-H(23C)	109.5
H(23A)-C(23)-H(23C)	109.5
H(23B)-C(23)-H(23C)	109.5
Si-C(24)-H(24A)	109.5
Si-C(24)-H(24B)	109.5
H(24A)-C(24)-H(24B)	109.5
Si-C(24)-H(24C)	109.5
H(24A)-C(24)-H(24C)	109.5
H(24B)-C(24)-H(24C)	109.5
C(26)-C(25)-C(30)	122.0(9)
C(26)-C(25)-H(25)	119.0

C(30)-C(25)-H(25)	119.0
C(25)-C(26)-C(27)	119.0(10)
C(25)-C(26)-H(26)	120.5
C(27)-C(26)-H(26)	120.5
C(28)-C(27)-C(26)	120.6(10)
C(28)-C(27)-H(27)	119.7
C(26)-C(27)-H(27)	119.7
C(27)-C(28)-C(29)	120.9(10)
C(27)-C(28)-H(28)	119.6
C(29)-C(28)-H(28)	119.6
C(28)-C(29)-C(30)	120.2(9)
C(28)-C(29)-H(29)	119.9
C(30)-C(29)-H(29)	119.9
C(25)-C(30)-C(29)	117.3(8)
C(25)-C(30)-Si	120.7(6)
C(29)-C(30)-Si	121.9(6)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **2.138α**. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Si	45(1)	20(1)	54(2)	3(1)	2(1)	0(1)
C(1)	34(5)	25(4)	45(5)	6(4)	-12(4)	-1(4)
O(1)	117(5)	41(4)	37(3)	-2(3)	-6(4)	7(4)
C(2)	25(4)	24(4)	47(5)	5(4)	-5(4)	4(4)
O(2)	83(5)	44(4)	37(3)	0(3)	10(3)	-7(3)
O(3)	43(4)	55(4)	42(3)	-7(3)	7(3)	-8(3)
C(3)	58(6)	24(5)	38(5)	15(4)	-7(4)	11(4)
O(4)	43(3)	40(3)	47(3)	2(3)	1(3)	-11(3)
C(4)	50(5)	34(5)	39(5)	5(4)	7(4)	-3(4)
C(5)	83(7)	20(4)	37(5)	-2(4)	4(5)	8(5)
C(6)	61(6)	18(4)	35(5)	3(4)	2(4)	-3(4)
C(7)	82(7)	26(5)	49(5)	4(4)	3(5)	-10(5)
C(8)	54(6)	38(5)	75(7)	11(5)	-8(5)	-11(5)
C(9)	41(5)	41(5)	36(5)	9(4)	1(4)	-1(4)
C(10)	60(6)	35(5)	51(5)	1(5)	0(5)	-9(5)
C(11)	43(5)	44(5)	60(6)	7(5)	18(5)	-5(4)
C(12)	42(5)	29(5)	47(5)	5(4)	-2(4)	5(4)
C(13)	32(5)	59(6)	38(5)	13(5)	4(4)	-3(5)
C(14)	50(6)	37(5)	40(5)	0(4)	1(4)	14(4)
C(15)	29(5)	30(5)	41(5)	1(4)	7(4)	6(4)
C(16)	28(4)	18(4)	51(5)	2(4)	3(4)	4(4)
C(17)	157(11)	17(5)	44(6)	-2(4)	26(7)	0(6)
C(18)	206(16)	45(7)	152(13)	-37(8)	84(12)	20(9)
C(19)	206(15)	55(7)	85(9)	-28(7)	-13(10)	-34(9)
C(20)	58(6)	57(7)	94(8)	10(6)	-3(6)	3(5)
C(21)	39(5)	61(6)	68(6)	11(5)	-6(5)	-3(5)
C(22)	94(8)	78(8)	55(6)	-36(6)	9(6)	-8(6)
C(23)	92(8)	35(5)	55(6)	0(5)	27(6)	9(5)
C(24)	41(5)	50(6)	89(7)	12(5)	-2(5)	2(5)
C(25)	44(6)	35(5)	74(7)	3(5)	-8(5)	-7(4)
C(26)	44(6)	60(7)	101(9)	-2(7)	-8(6)	-6(5)

C(27)	51(7)	46(7)	123(11)	-18(7)	22(8)	-9(5)
C(28)	79(8)	46(7)	73(8)	-11(6)	25(7)	-5(6)
C(29)	62(6)	36(5)	54(6)	-12(5)	14(5)	-1(5)
C(30)	37(5)	27(4)	48(5)	-7(4)	4(4)	0(4)

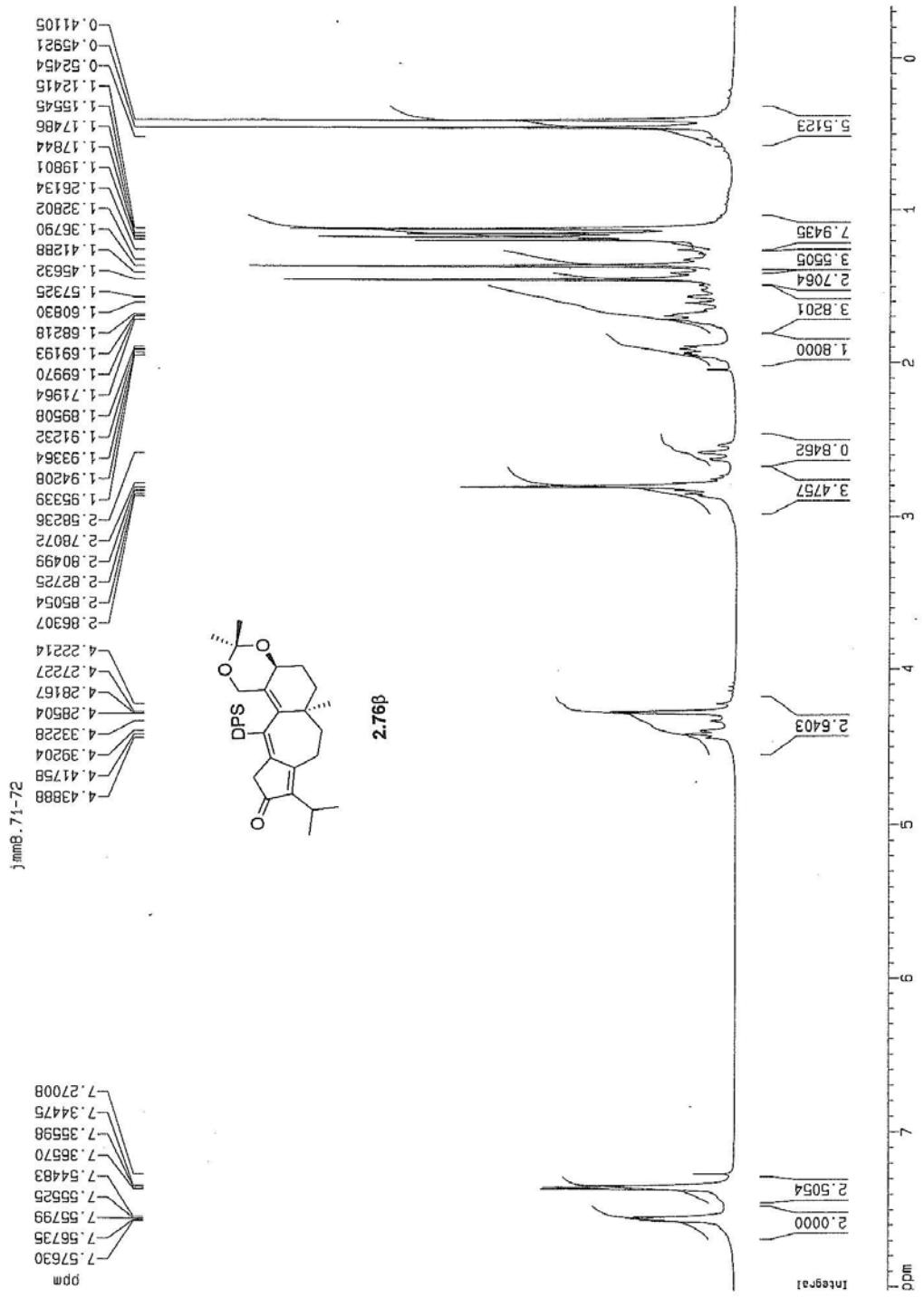
Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **2.138α**.

	x	y	z	U(eq)
H(1A)	7643	10353	3025	97
H(3)	9023	10133	3758	48
H(7A)	7933	8244	5026	63
H(7B)	7492	7863	4377	63
H(8A)	6270	8215	4901	67
H(8B)	6438	8899	4440	67
H(10A)	6045	8429	6160	58
H(10B)	7027	8171	6021	58
H(11A)	6860	8620	7157	58
H(11B)	6610	9376	6843	58
H(12)	8268	8672	6733	47
H(14A)	9471	9386	5969	51
H(14B)	9093	10073	5597	51
H(17)	8352	7583	3533	87
H(18A)	9478	7372	2752	201
H(18B)	9809	7984	3255	201
H(18C)	9471	8174	2499	201
H(19A)	7817	8241	2288	173
H(19B)	7189	7850	2824	173
H(19C)	7877	7405	2381	173
H(20A)	5943	9879	5879	104
H(20B)	5382	9302	5472	104
H(20C)	5951	9868	5057	104
H(21A)	9543	9035	7844	84
H(21B)	10278	9446	7416	84
H(21C)	9652	8892	7038	84
H(22A)	8563	10745	7724	114
H(22B)	9609	10693	7735	114
H(22C)	9038	10218	8247	114
H(23A)	7434	11664	5909	91

H(23B)	7944	10968	6144	91
H(23C)	6912	10940	6002	91
H(24A)	6179	11024	4628	90
H(24B)	6778	11071	3954	90
H(24C)	6678	11742	4446	90
H(25)	9306	11370	5615	61
H(26)	10518	12058	5355	82
H(27)	10654	12540	4257	88
H(28)	9576	12366	3447	79
H(29)	8356	11695	3695	61

APPENDIX B

^{1}H AND ^{13}C NMR DATA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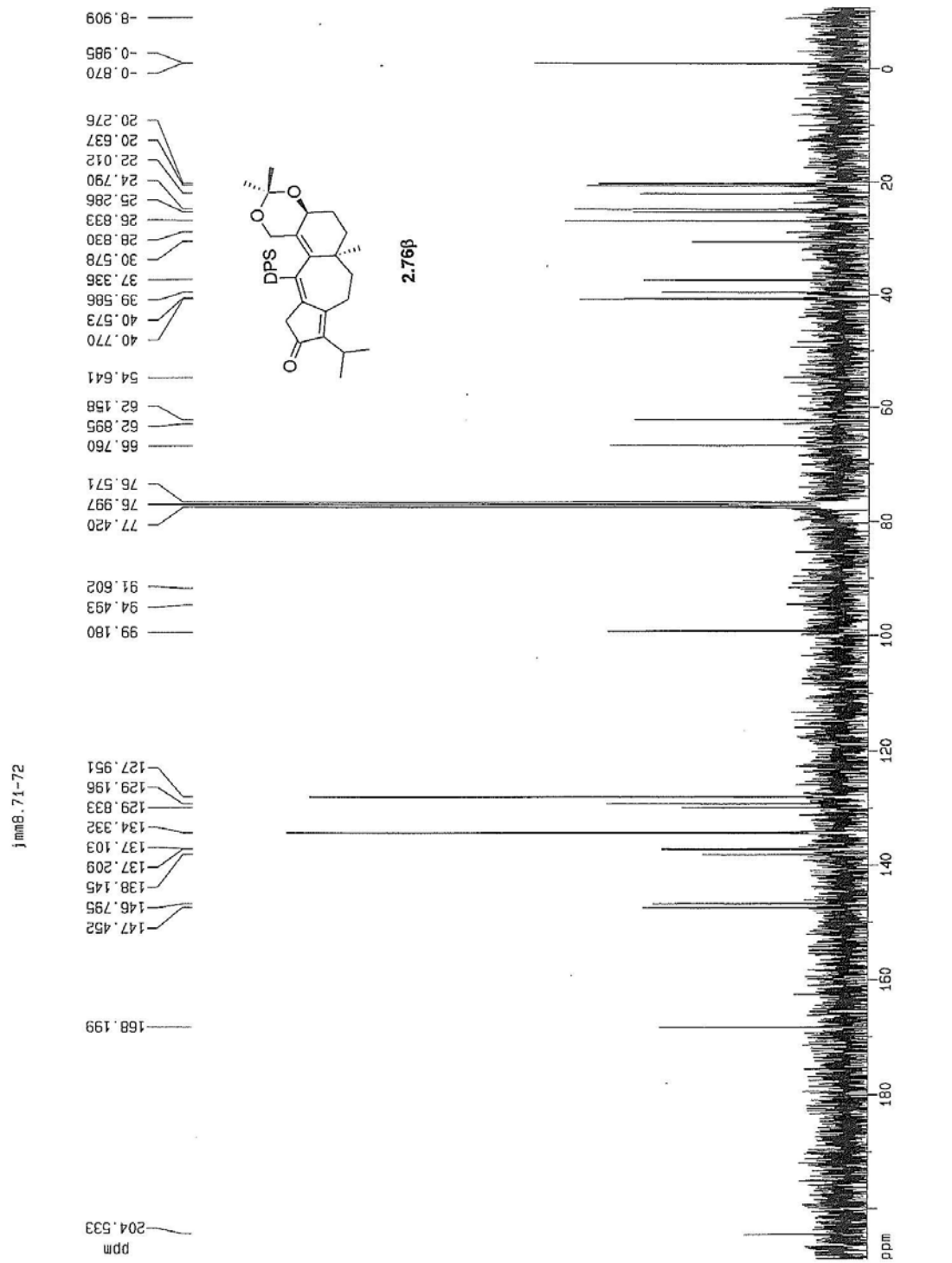
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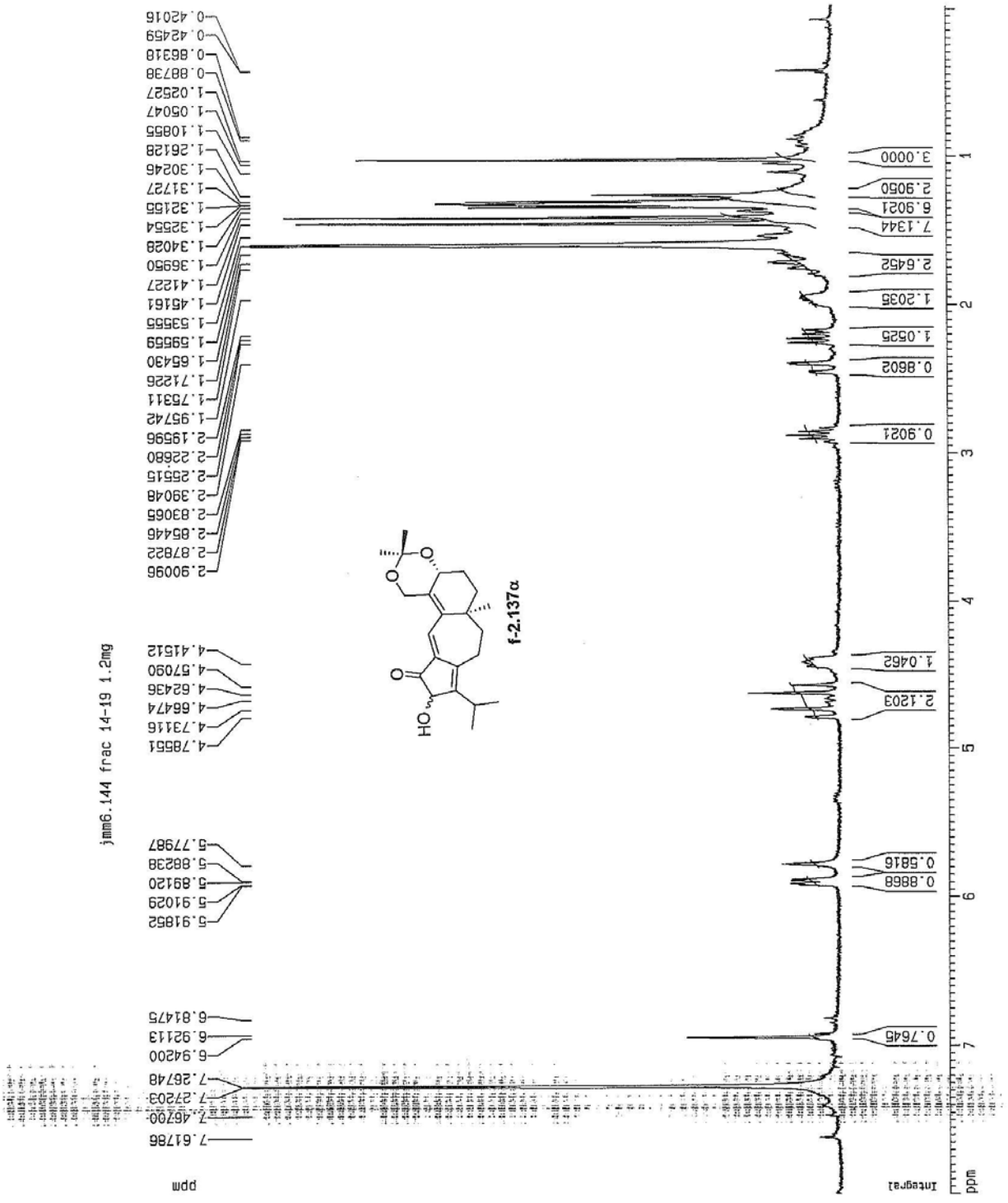
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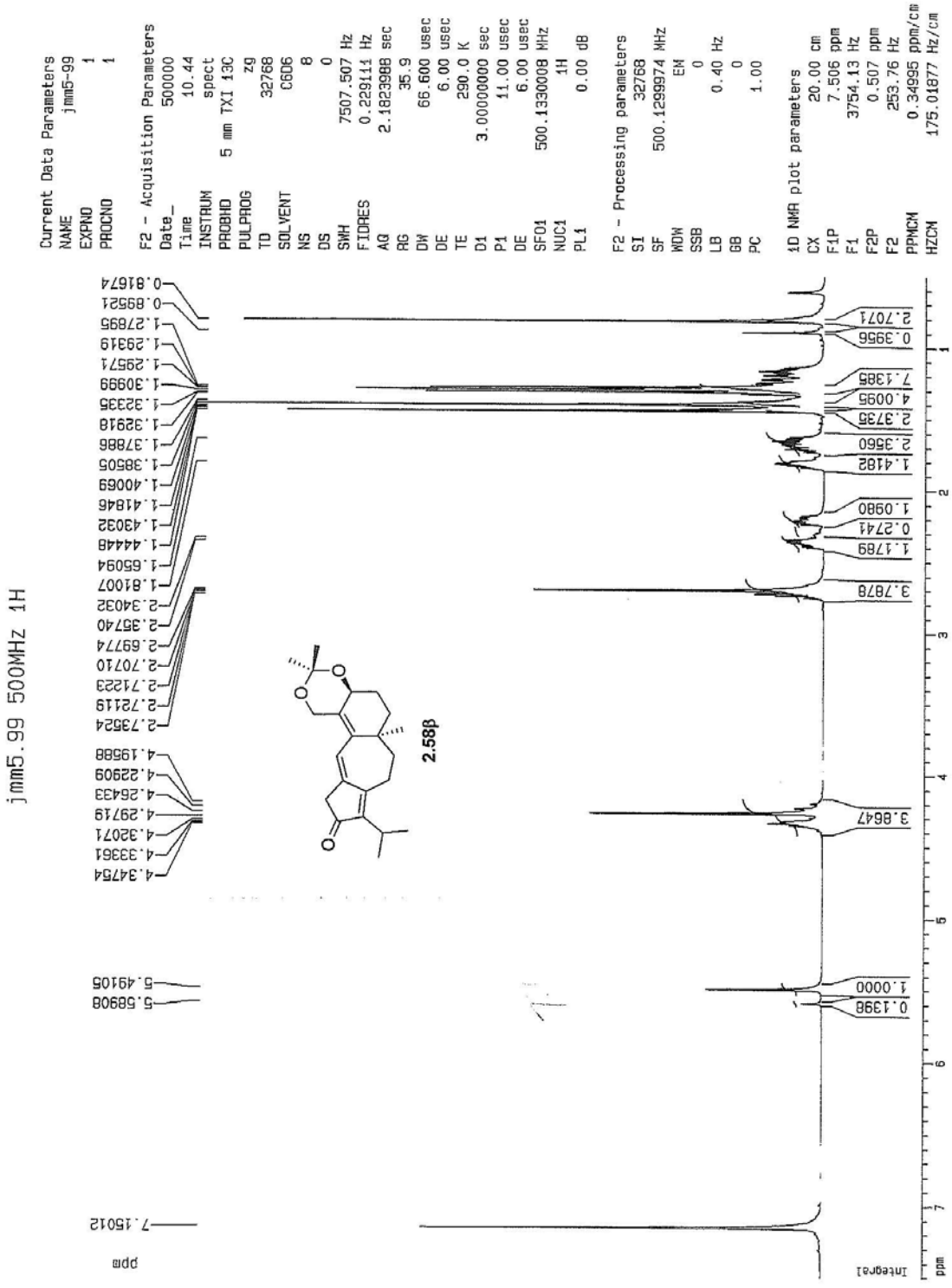
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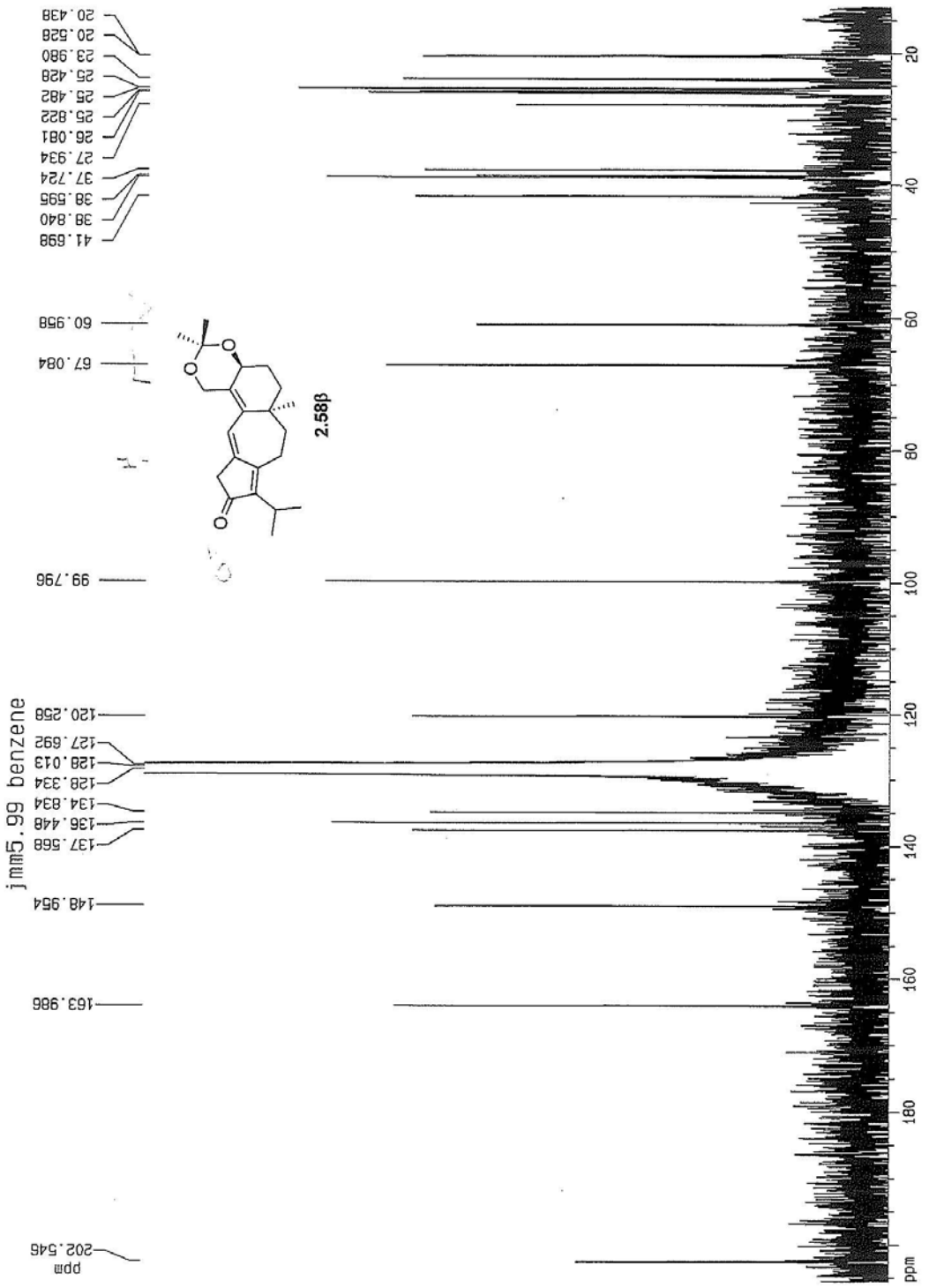
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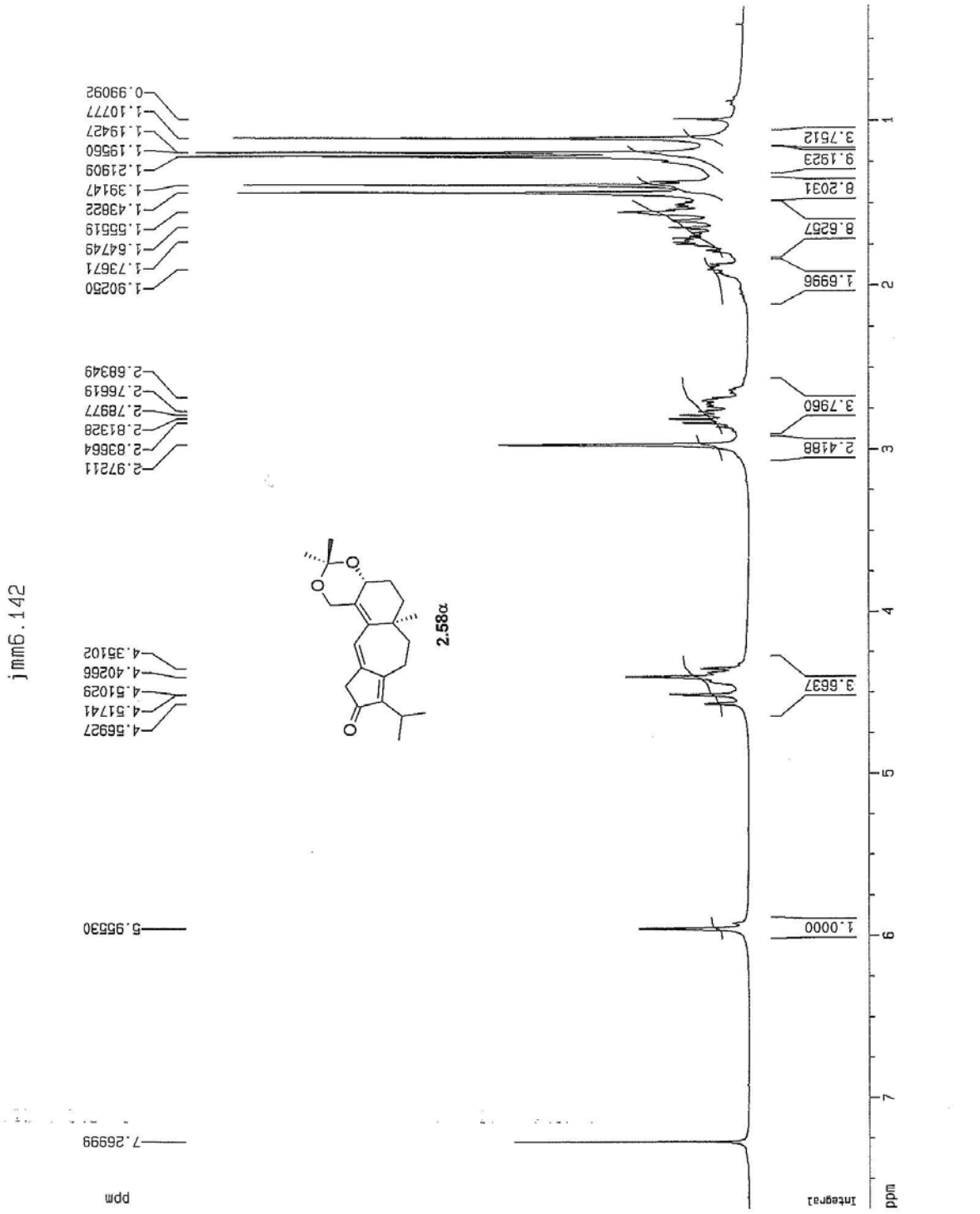
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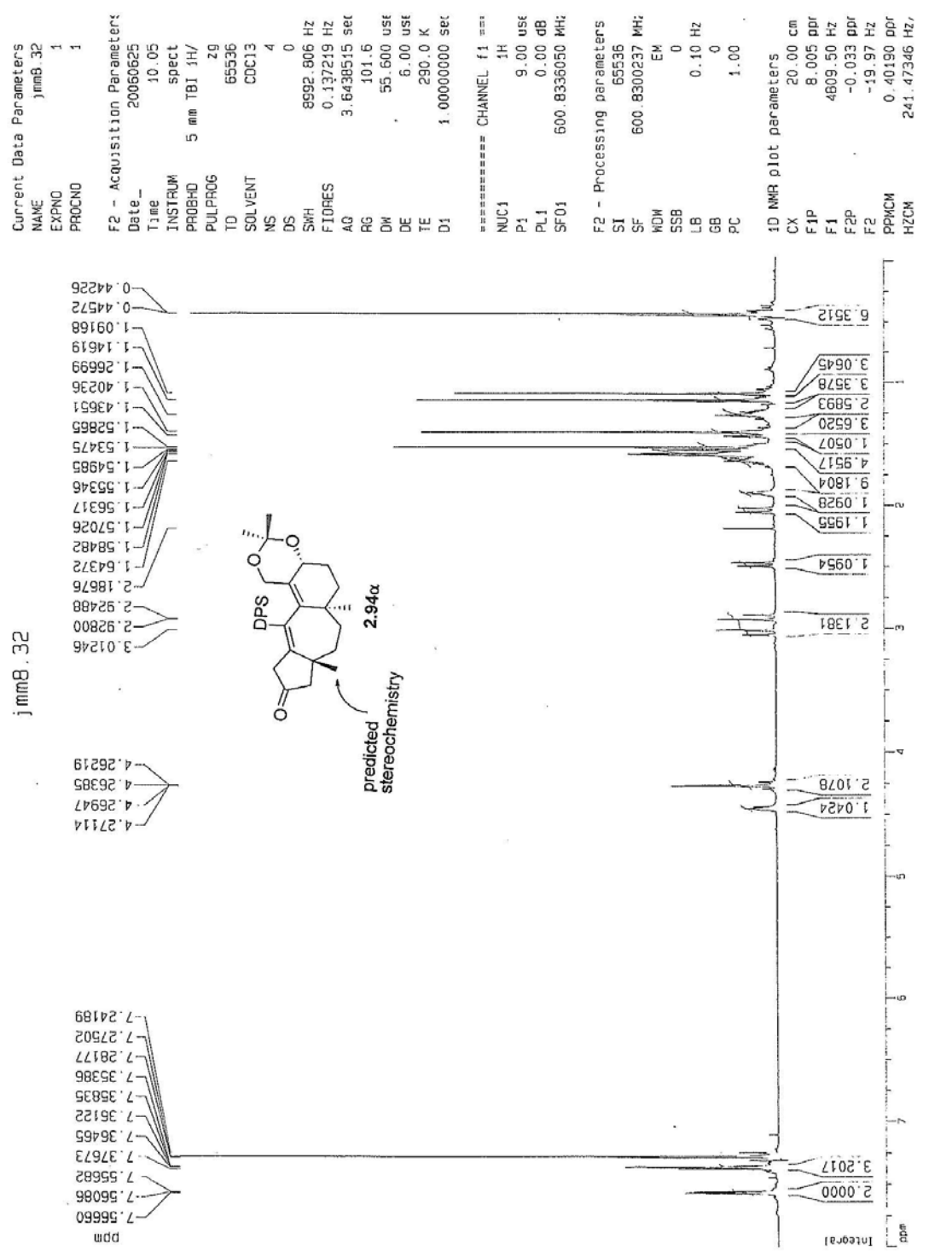
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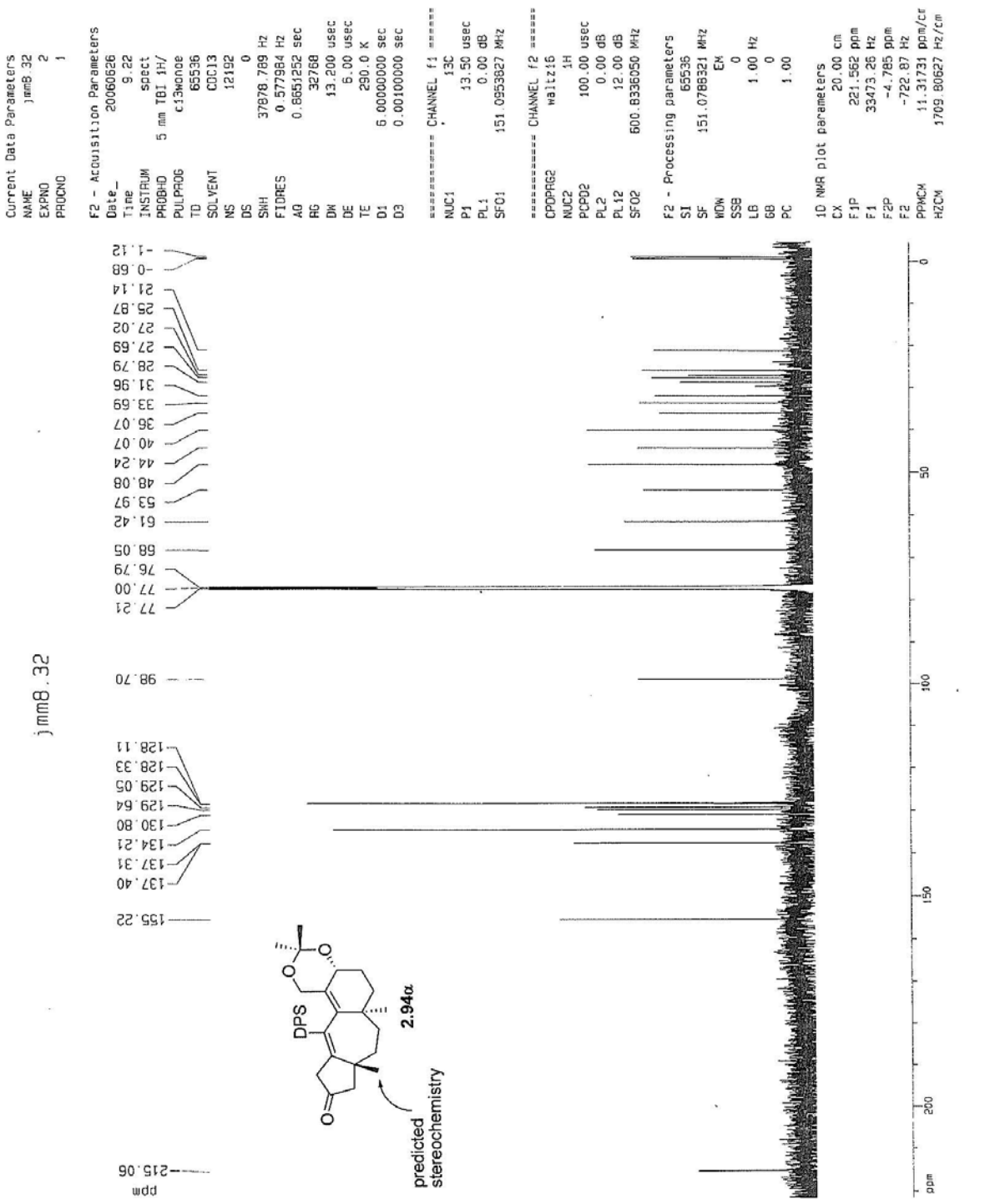
DPS
2.94α
predicted
stereochemistry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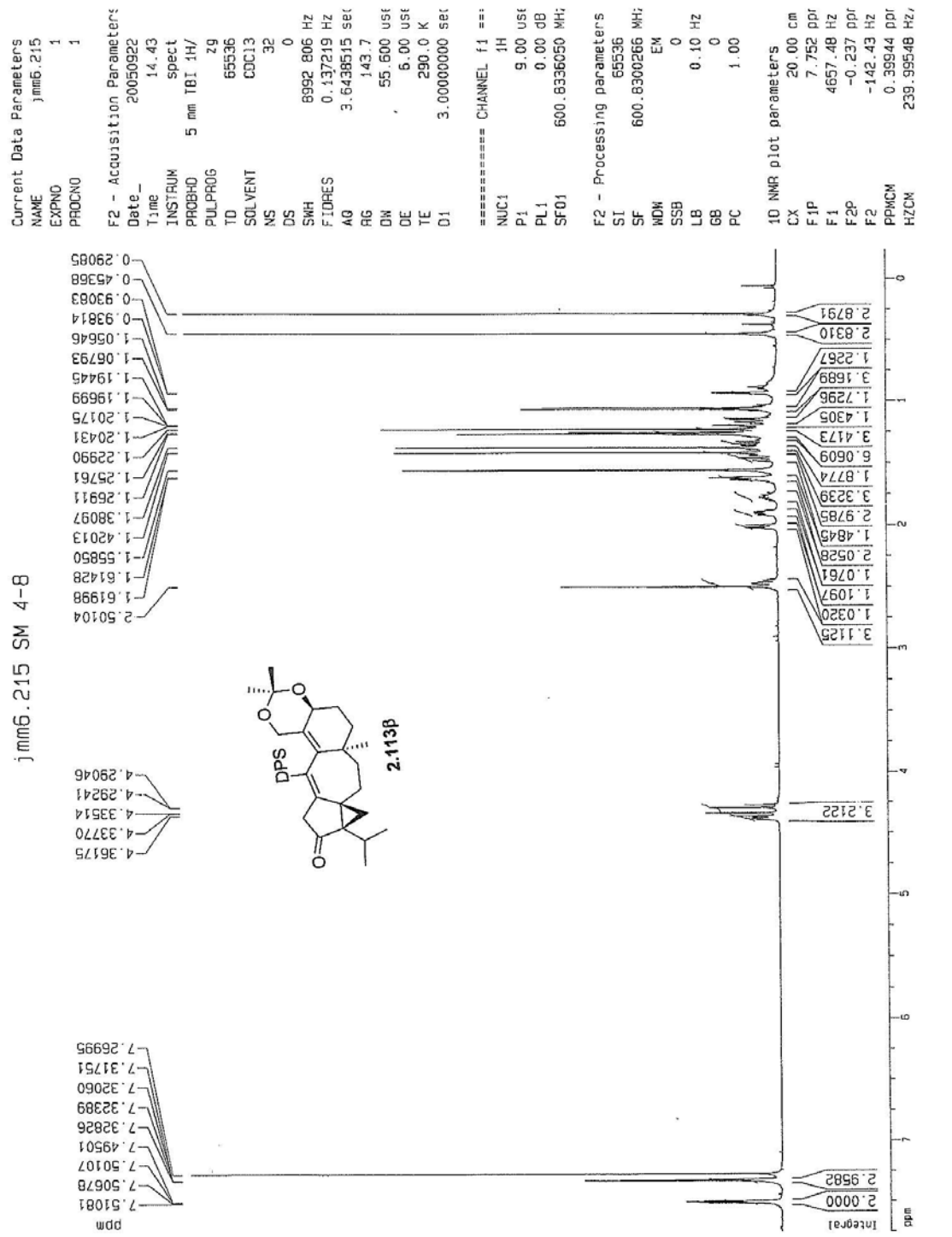
predicted
stereochemistry
ppm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EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
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Time 14.43
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PULPROG zg
TD 65536
SOLVENT CDCl3
NS 32
DS 0
SWH 8992.806 Hz
FIDRES 0.137219 Hz
AQ 3.6438515 se
RG 143.7
DW 55.600 us
DE 6.00 us
TE 290.0 K
D1 3.00000000 se
CHANNEL f1
NUC1 1H
P1 9.00 us
PL1 0.00 dB
SFO1 600.8336050 MH
F2 - Processing parameters
SI 65536
SF 600.8300266 MH
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 7.752 pp
F1 4657.48 Hz
F2P -0.237 pp
F2 -142.43 Hz
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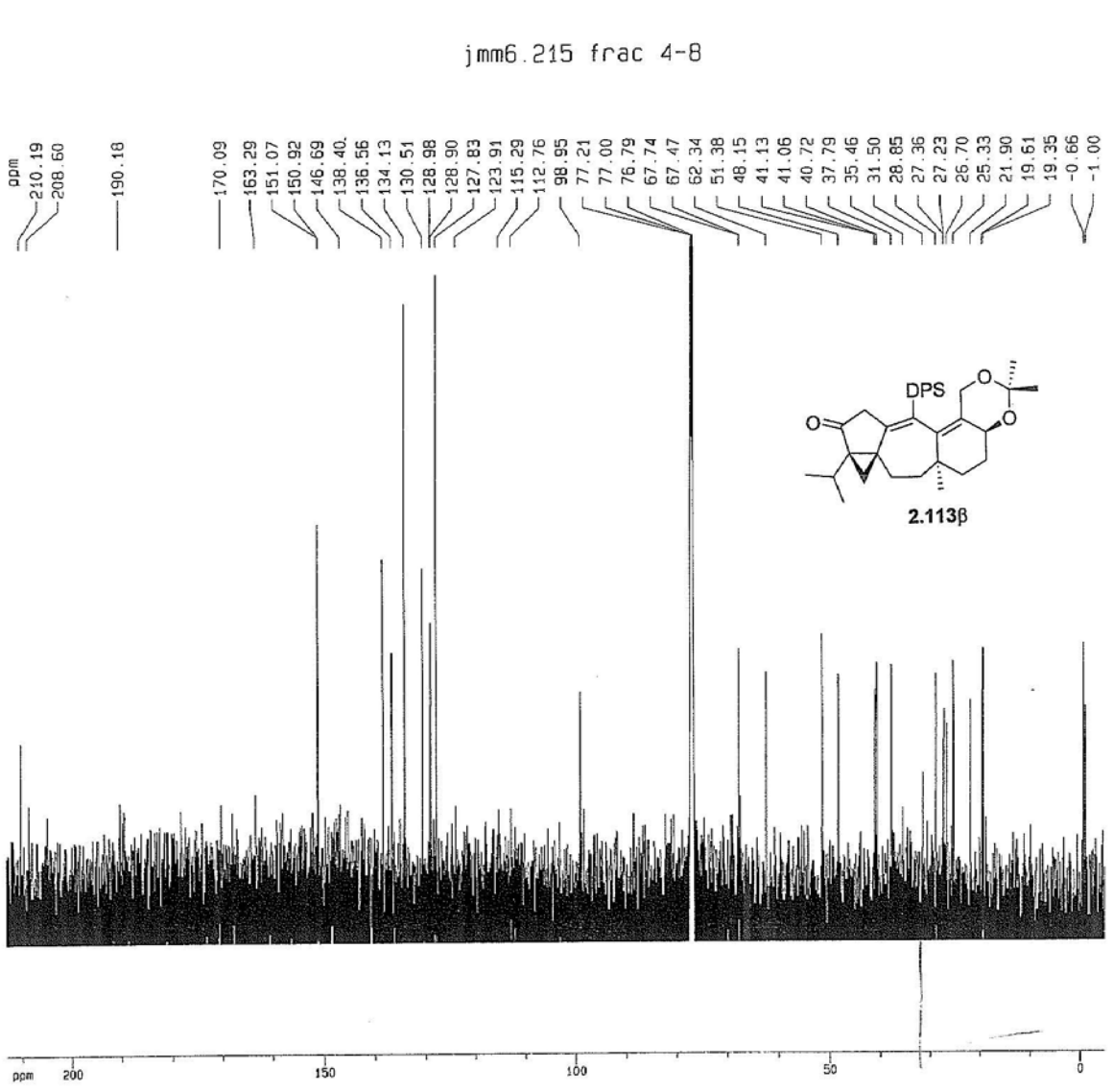
ppm
Integral

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PROCNO                       1

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PULPROG                c13monoe
TD                        65536
SOLVENT                   CDCl3
NS                         1654
DS                            0
SWH                37878.789 Hz
FIDRES             0.577984 Hz
AQ                 0.8651252 sec
RG                        32768
DW                    13.200 usec
DE                     6.00 usec
TE                     290.0 K
D1                 6.00000000 sec
D3                 0.00100000 sec

============ CHANNEL f1 ======
NUC1                       13C
P1                    13.00 usec
PL1                    0.00 dB
SFO1              151.0953827 MHz

============ CHANNEL f2 ======
CPDPRG2                waltz16
NUC2                       1H
PCPD2                100.00 usec
PL2                    0.00 dB
PL12                  12.00 dB
SFO2              600.8336050 MHz

F2 - Processing parameters
SI                        65536
SF                151.0788309 MHz
WDW                          EM
SSB                           0
LB                     1.00 Hz
GB                            0
PC                         1.00

1D NMR plot parameters
CX                     20.00 cm
F1P                  213.115 ppm
F1                  32197.30 Hz
F2P                   -4.903 ppm
F2                  -740.77 Hz
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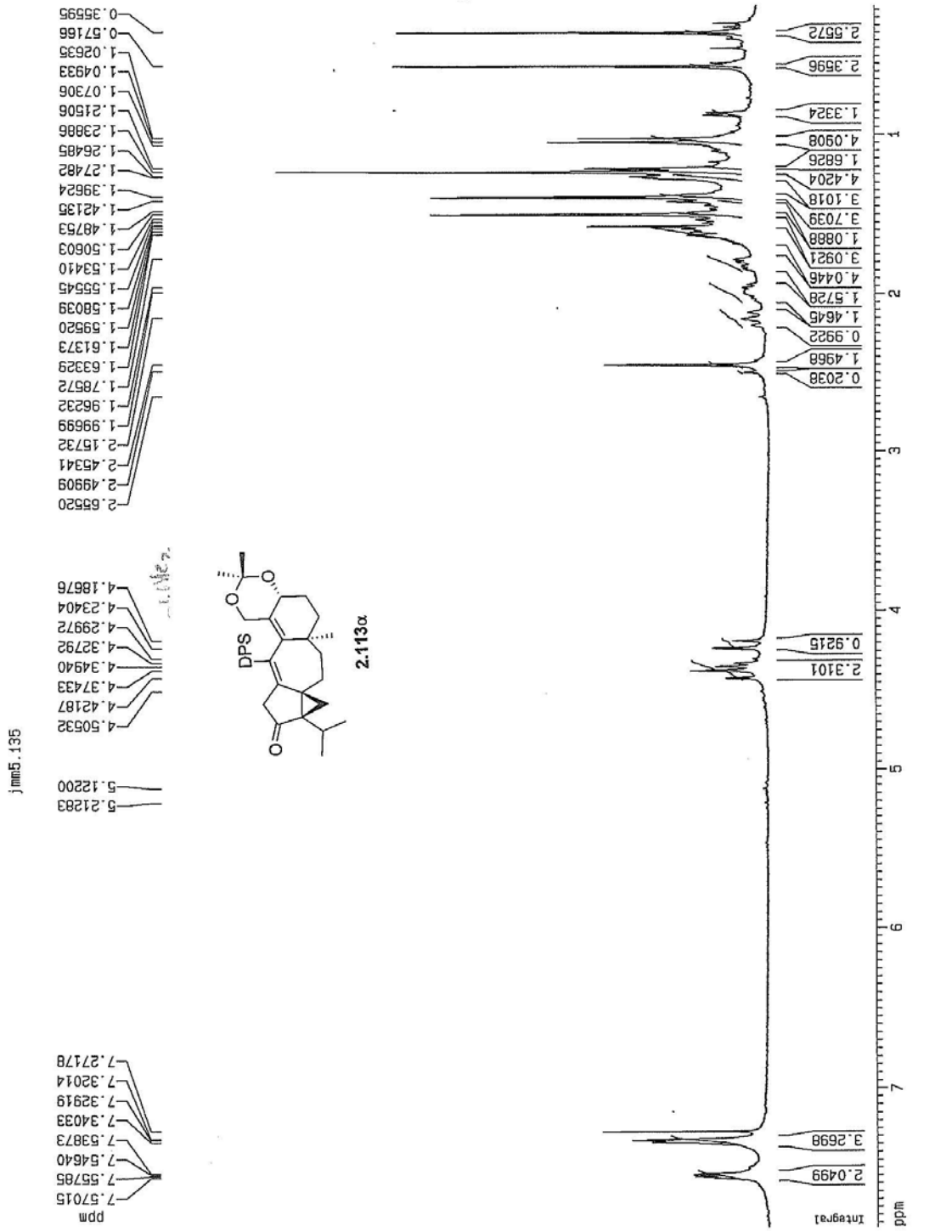
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2.113α
ppm
Integral

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19.513
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22.689
25.459
26.201
27.410
28.447
28.573
29.059
29.706
31.532
35.825
36.124
40.218
41.208
41.833
49.263
52.393
60.135
61.870
66.924
73.027
76.583
77.007
77.431
79.078
99.300
106.988
122.080
127.874
128.271
128.824
129.410
130.053
131.172
134.188
137.395
138.761
150.853
175.009
204.106
209.786
ppm
DPS
2.113α
20
40
60
80
100
120
140
160
180
200
ppm

jmm5.287 minor
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PROCNO 1
F2 - Acquisition Parameters
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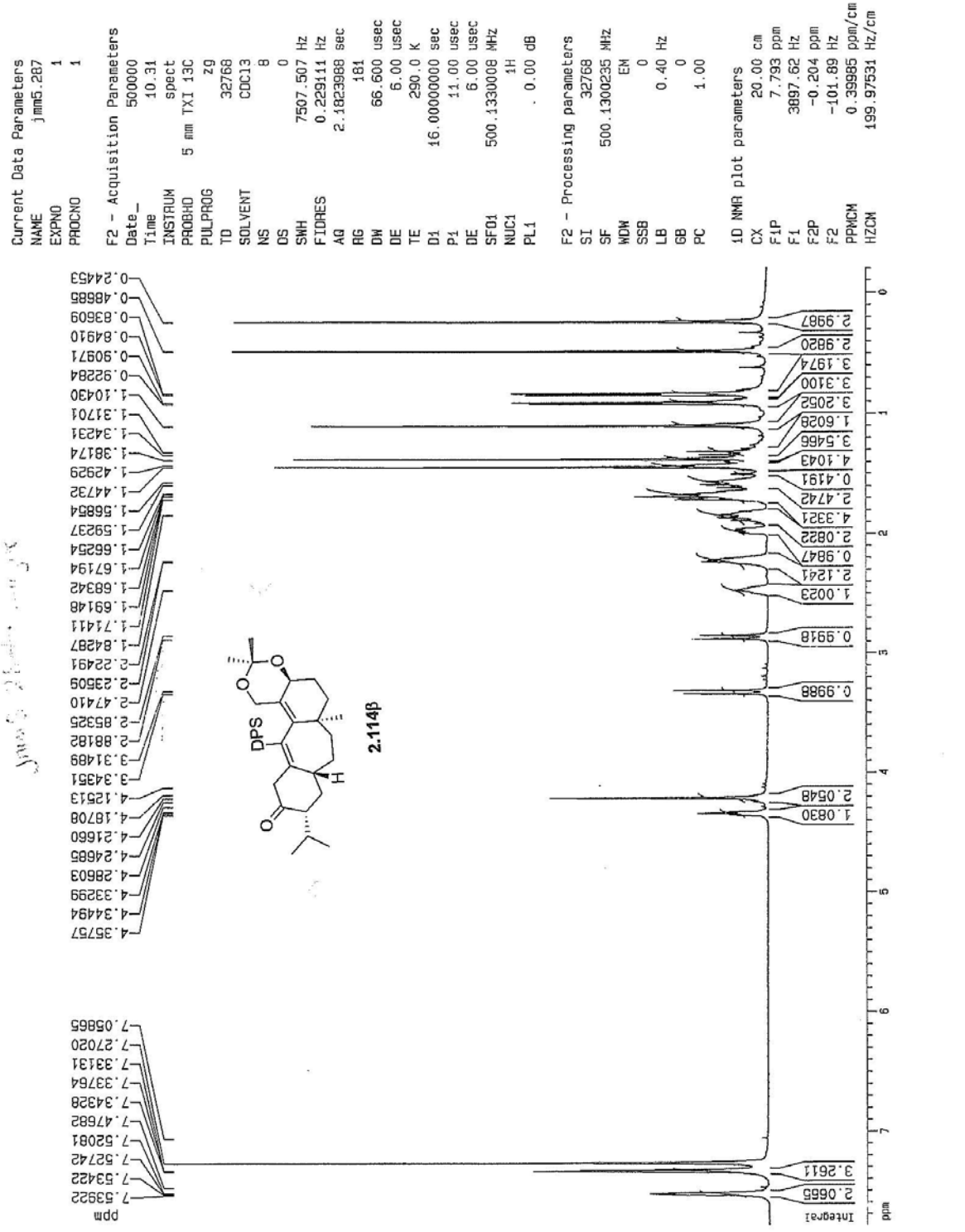
TD 32768
SOLVENT CDCl3
NS 16
DS 0
SWH 7507.507 Hz
FIDRES 0.229111 Hz
AQ 2.1823988 sec
RG 362
DW 66.600 usec
DE 6.00 usec
TE 290.0 K
D1 16.00000000 sec
P1 11.00 usec
DE 6.00 usec
SFO1 500.1330008 MHz
NUC1 1H
PL1 0.00 dB
F2 - Processing parameters
SI 32768
SF 500.1300235 MHz
WDW EM
SSB 0
LB 0.40 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 7.870 ppm
F1 3936.17 Hz
F2P -0.165 ppm
F2 -82.61 Hz
PPMCM 0.40177 ppm/cm
HZCM 200.93904 Hz/cm
DPS
2.97β
ppm
Integral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DS 0
SWH 7507.507 Hz
FIDRES 0.229111 Hz
AQ 2.1823988 sec
RG 181
DW 66.600 usec
DE 6.00 usec
TE 290.0 K
D1 16.00000000 sec
P1 11.00 usec
DE 6.00 usec
SFO1 500.1330008 MHz
NUC1 1H
PL1 0.00 dB
F2 - Processing parameters
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SF 500.1300235 MHz
WDW EM
SSB 0
LB 0.40 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 7.793 ppm
F1 3897.62 Hz
F2P -0.204 ppm
F2 -101.89 Hz
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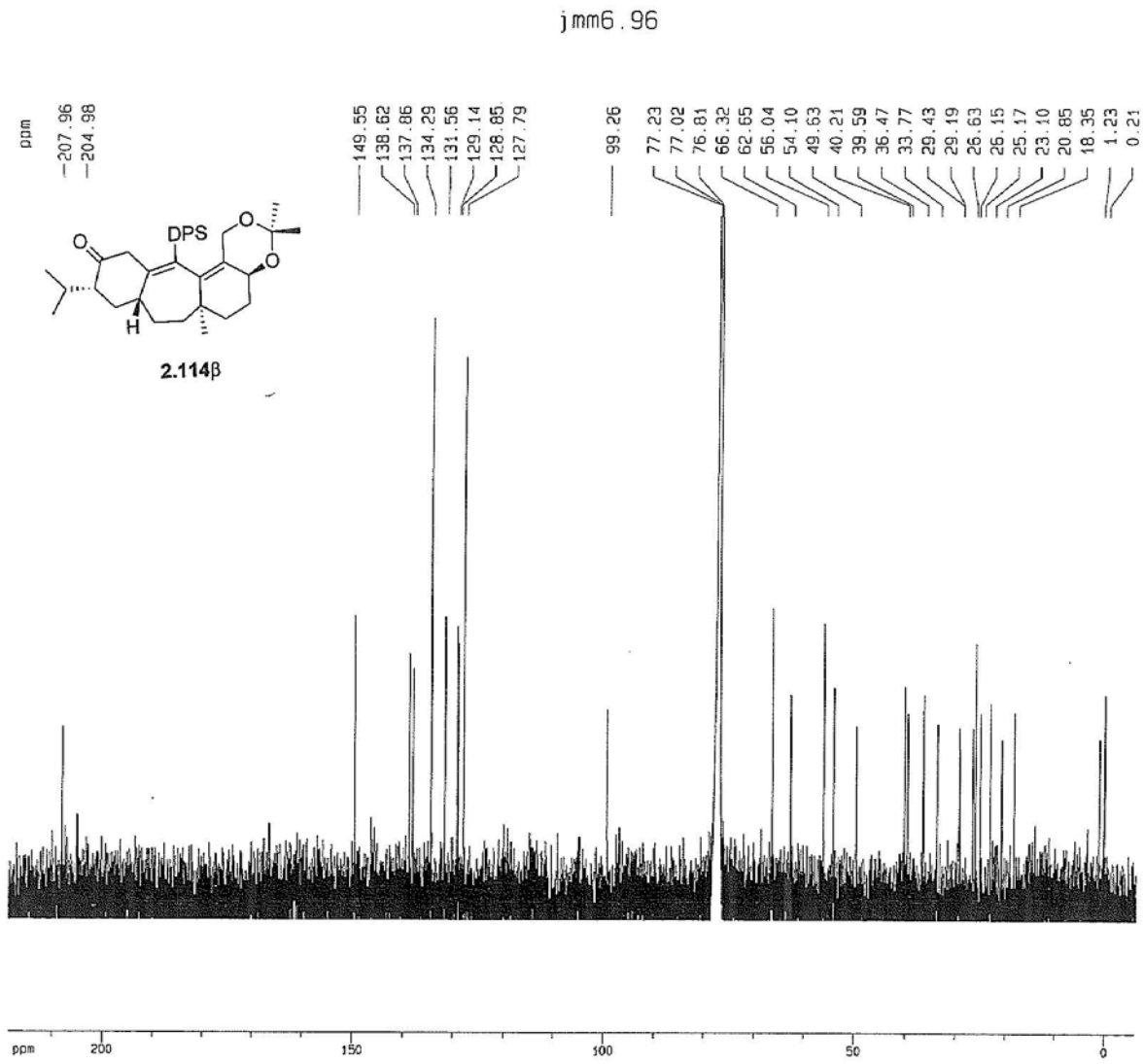
DPS
2.114β
ppm
Integral



Current Data Parameters

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EXPNO	2
PROCNO	1

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TD	65536
SOLVENT	CDCl3
NS	8996
DS	0
SWH	37878.789 Hz
FIDRES	0.577984 Hz
AQ	0.8651252 sec
RG	32768
DW	13.200 usec
DE	6.00 usec
TE	290.0 K
D1	6.00000000 sec
D3	0.00100000 sec

========== CHANNEL f1 ======

NUC1	13C
P1	12.60 usec
PL1	0.00 dB
SFO1	151.0953827 MHz

========== CHANNEL f2 ======

CPDPRG2	waltz16
NUC2	1H
PCPD2	100.00 usec
PL2	0.00 dB
PL12	12.00 dB
SFO2	600.8336050 MHz

F2 - Processing parameters

SI	65536
SF	151.0788269 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	218.676 ppm
F1	33037.37 Hz
F2P	-6.208 ppm
F2	-937.88 Hz
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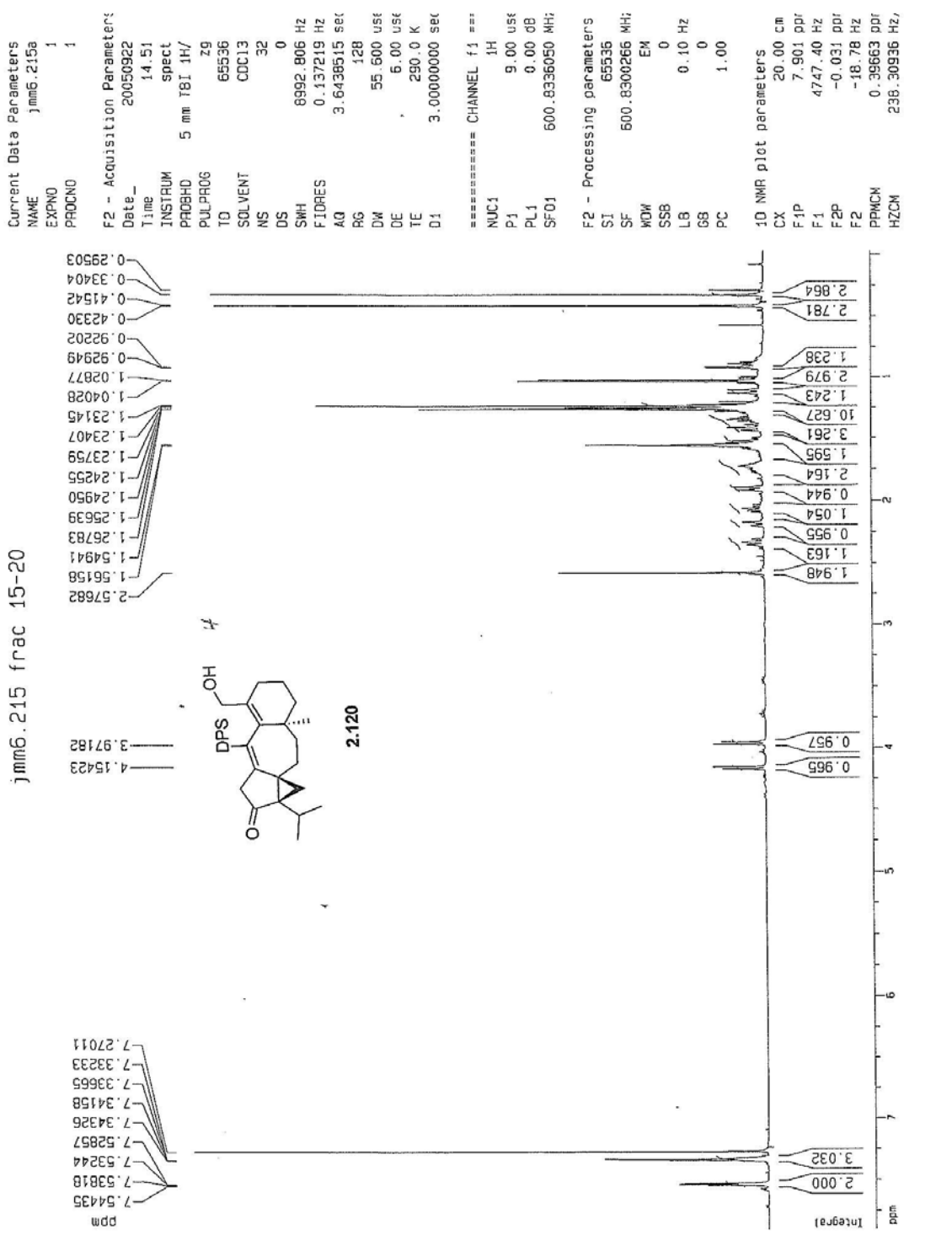
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2.120
DPS
OH
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PROCNO 1
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PULPROG zg
TD 65536
SOLVENT CDCl3
NS 32
DS 0
SWH 8992.806 Hz
FIDRES 0.137219 Hz
AQ 3.6438515 se
RG 128
DW 55.600 us
DE 6.00 us
TE 290.0 K
D1 3.00000000 se
======== CHANNEL f1 ==
NUC1 1H
P1 9.00 us
PL1 0.00 dB
SFO1 600.8336050 MH
F2 - Processing parameters
SI 65536
SF 600.8300266 MH
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 7.901 pp
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F2P -0.031 pp
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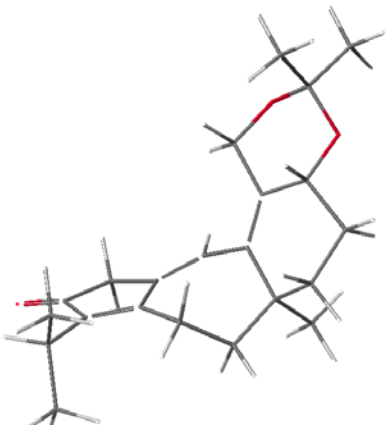
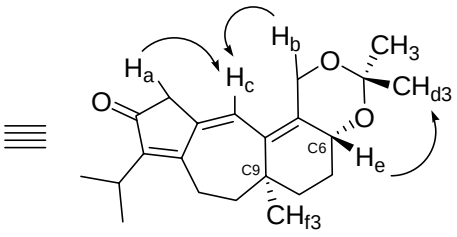
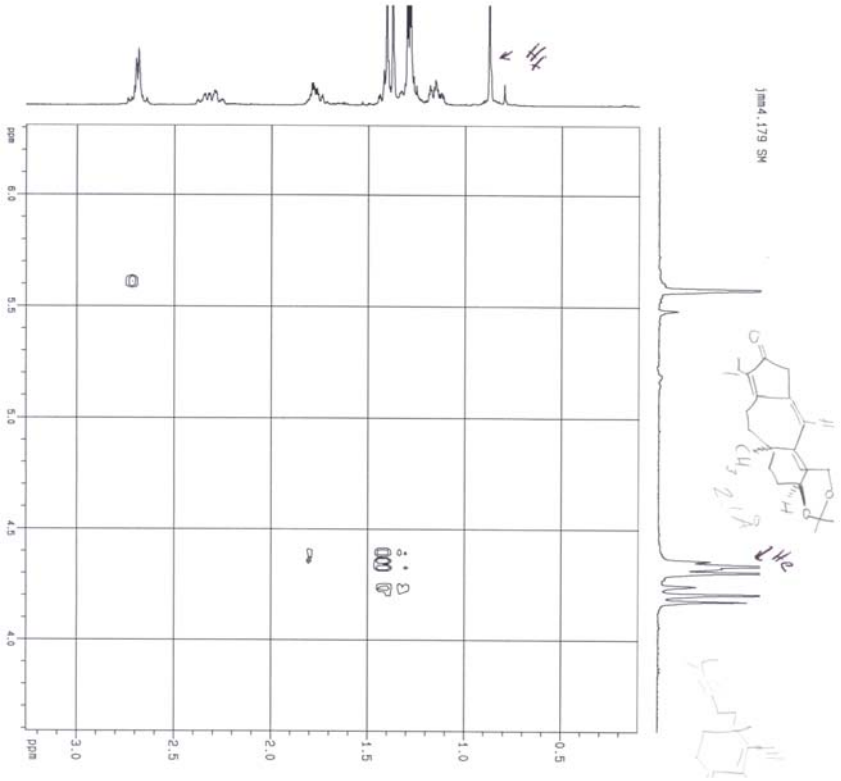
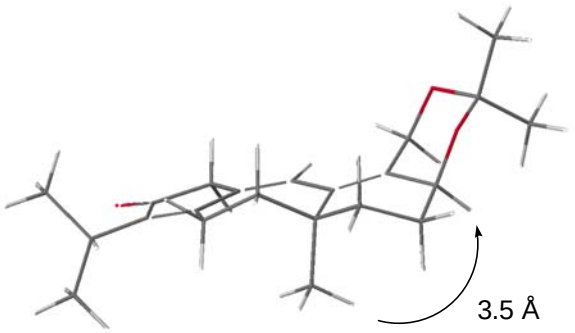
ppm
Integral

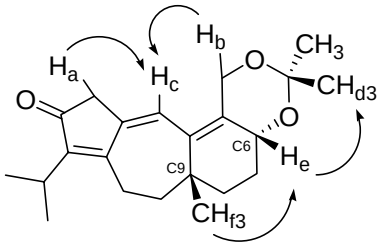



Ha
Hb
Hc
O
O
O
CH3
CHd3
C6
C9
He
CHf3

2.58α


jmm4.179 SM
ppm
6.0
5.5
5.0
4.5
4.0
3.0
2.5
2.0
1.5
1.0
0.5


3.5 Å


Ha
Hb
Hc
O
O
CH3
CHd3
O
C6
C9
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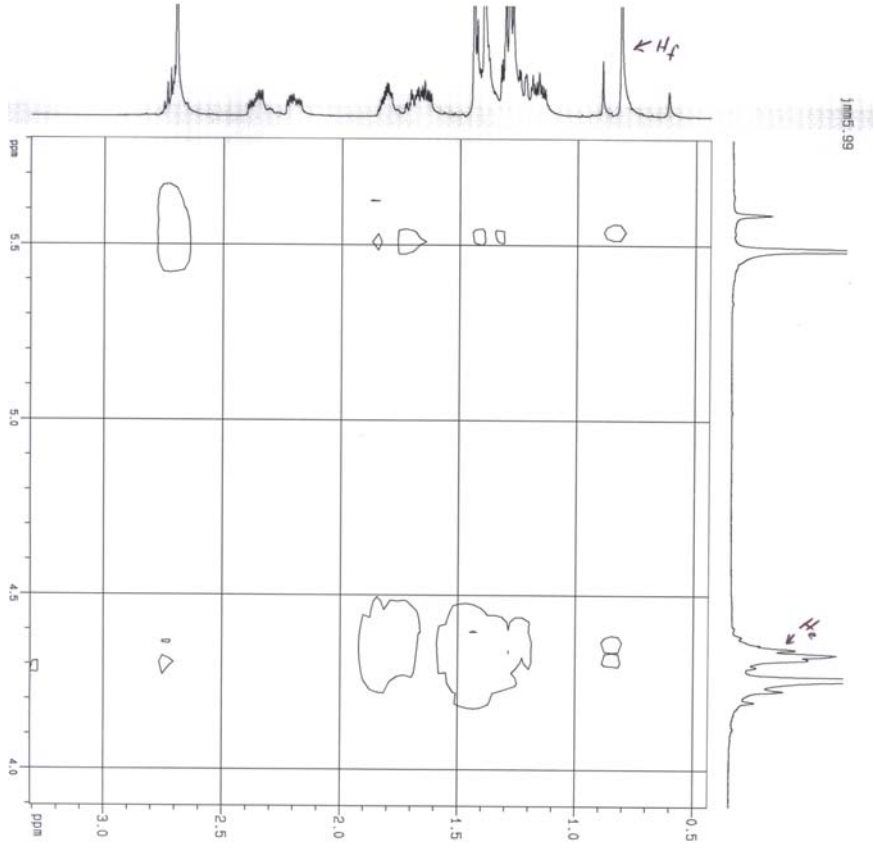
CHf3

2.58β


Hf
ppm
5.5
5.0
4.5
4.0
ppm
3.0
2.5
2.0
1.5
1.0
0.5
He

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[135] Do not warm reaction flask to ambient temperature prior to quench otherwise polymerization of THF occurs to give a thick gooey substance.

[136] Several months after this reaction was preformed we started storing the BTAF in the glove box.